DISSERTATION

SELECTIVE FUNCTIONALIZATION OF AZINES VIA PHOSPHONIUM SALTS

Submitted by

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ABSTRACT

SELECTIVE FUNCTIONALIZATION OF AZINES VIA PHOSPHONIUM SALTS

Pyridines and diazines are ubiquitous in pharmaceuticals, agrochemicals, and materials. Therefore, methods to functionalize these structural motifs are increasingly valuable. We have shown that phosphonium salts can be formed on a range of azines, including complex biologically-active compounds. Additionally, these azinyl phosphonium salts serve as a general functional handle to facilitate a variety of bond formations.

Chapter 2 focuses on a method to incorporate deuterium and tritium atoms onto azines and pharmaceuticals using azinyl phosphonium salts. Deuteration is commonly used as a means to deter unwanted oxidative metabolism on drugs, and tritium is installed as a radiolabel for metabolic studies in the pharmaceutical industry. The protocol of the reaction is simple, and it functions on a wide range of building blocks and complex molecules. Additionally, the tritiation protocol was effectively applied on a selection of drug molecules through a collaborative effort with Merck.

In chapter 3, a pyridine-pyridine coupling reaction is discussed using azinyl phosphonium salts as radical precursors. The reaction functions through a radical-radical coupling mechanism using B_2pin_2 and 4-cyanopyridine as an electron-transfer reagent for reduction of the phosphonium salt. Azinyl phosphonium salts were found to be the only radical precursor amenable to the reaction, and the process functions as an alternative to the Minisci reaction to form bipyridine products.

ACKNOWLEDGEMENTS

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I want to thank my undergraduate research advisor, Paul Bonvallet, for his patience, knowledge, and perseverance with me throughout my least motivated times. I also want to thank my mentor, Nicholas Shaw, for helping me find my passion, believing in me, and continuing to be a teacher throughout my life. If it were not for his friendship and advice, I would not have ever pursued a career in chemistry.

I want to thank my wife, Caitie, for going through this journey with me. There have been trying times for me throughout graduate school, and I am unbelievably blessed that I had her to lean on. Her strength, trust, intelligence, and immense love continue to inspire me every day. I am also incredibly grateful for my family and the support they have given me throughout my life. Importantly, I give God all the credit for these accomplishments as He continues to lead my life.

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CHAPTER ONE

HETEROCYCLIC PHOSPHONIUM SALTS AND THEIR SYNTHETIC APPLICATIONS

1.1 Introduction to Pyridines and Diazines

Nitrogen heterocycles are ubiquitous in biologically active molecules and are present in 59% of FDA-approved pharmaceuticals.[1,2] Within this structurally diverse set of heterocycles, 6-membered aromatic nitrogen heterocycles are especially prevalent. Pyridine is the most common azine found within FDA-approved pharmaceuticals, and pyridine-containing molecules are well known to be biologically active across a number of disease areas (Figure 1.1).

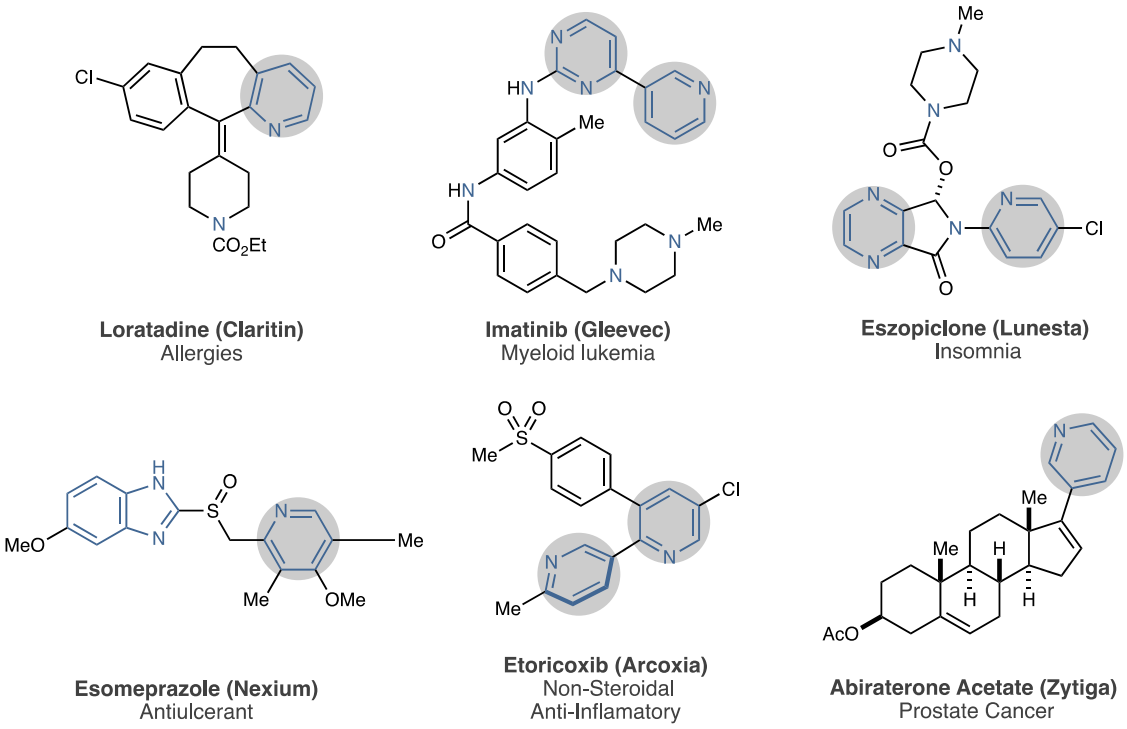

Figure 1.1. Examples of Azines in Pharmaceuticals, Agrochemicals, and Materials

The prevalence of azaarenes in pharmaceuticals, and pyridines in particular, is largely due to their critical features. Azines often play a significant role in the binding of pharmaceuticals to their

intended targets, but they also impart valuable medicinal chemistry properties onto the drug. These properties include increased aqueous solubility, polarity, and, importantly, resistance to oxidative metabolism by cytochrome P-450 (CPY-450) enzymes. In addition to pyridines, diazines, such as pyrimidines and pyrazines, are also frequently found in biologically active compounds. Outside of pharmaceuticals, pyridines and diazines are commonly observed in agrochemicals, allowing us to feed the world's growing population, and are also encountered in material sciences as well as ligands for coordination compounds.[3–5] As a result of their importance in medicinal chemistry, as well as these other areas, developing methods to functionalize pyridines and diazines is increasingly essential to our society.

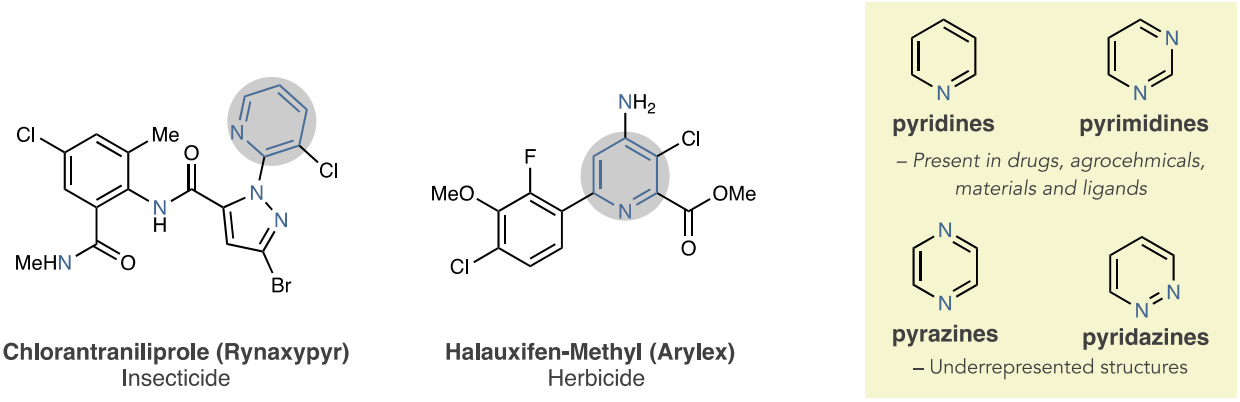

Figure 1.2. Azines Are Also Prominent in Agrochemicals, Materials, and Ligands

1.2 Overview of Current Synthetic Methods for Pyridines and Diazines

Direct functionalization of azines from their corresponding C-H bonds has been of considerable interest and challenging when compared to their benzo-derivative counterparts.[6,7] Traditional methods to functionalize azines include electrophilic aromatic substitution (EAS) reactions, such as halogenation (Figure 1.3). However, it is often challenging to use EAS on these azines due to their decreased pi-nucleophilicity. Therefore, these reactions often require harsh conditions, such as elevated temperatures and Brønsted or Lewis acid activation, resulting in poor

functional group tolerance and often produce mixtures of regioisomers. Additionally, the Lewis-basic nitrogen atom can ligate to transition-metal catalysts and adversely affect transition metal-mediated processes. The nitrogen can also easily undergo undesired oxidation forming the *N*-oxide byproduct.

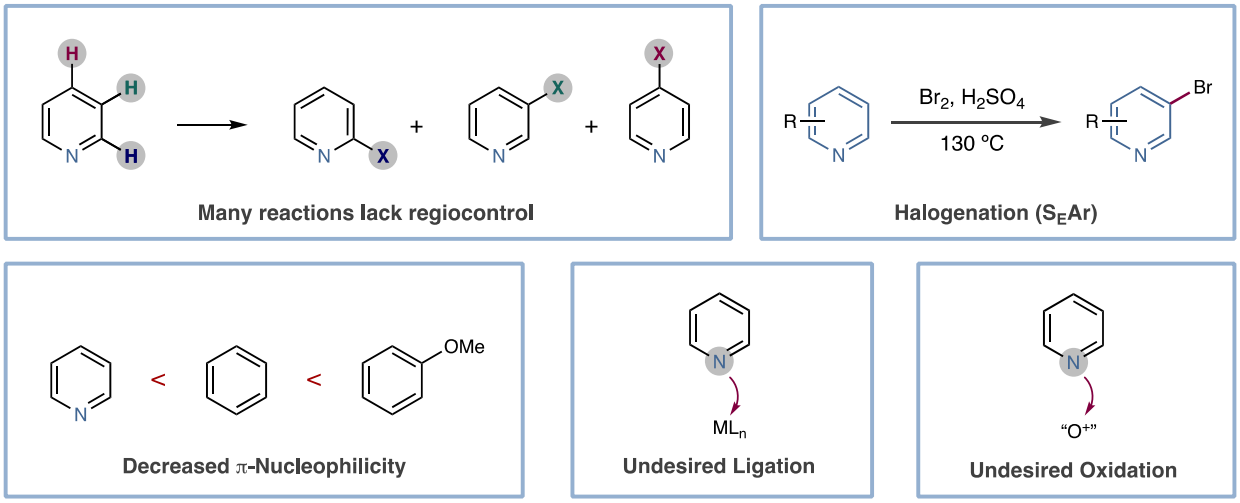

Figure 1.3. Challenges to Functionalizing Azines via Traditional Methods

Other classical methods to functionalize pyridines include the Chichibabin reaction, which uses the strongly basic and nucleophilic $NaNH_2$ for 2-position amination (Figure 1.4).[8] Lithiation-trapping sequences can also be performed, but often require a directing group to be preinstalled on the molecule to control regioselectivity and are limited in scope by using a strong lithium or magnesium base.[9,10] The Minisci reaction is a useful way to install carbon fragments onto pyridines and diazines through a radical pathway.[11,12] These reactions are commonly promoted by acid to increase the regioselectivity for the 2-position, but often still produce mixtures of regioisomers. The recent emergence of photoredox has led to modern variations of the Minisci reaction using milder conditions, however regioselectivity of the reaction remains problematic.[13,14] Hartwig's 2-position fluorination reaction using AgF_2 facilitates the installation of a useful fluoride handle enabling further transformations via nucleophilic aromatic substitution reactions (S_NAr).[15,16]

Various transition metal-catalyzed C-H activation strategies to functionalize the 2- and 3-position of pyridines have been developed, with iridium-catalyzed borylation being one of the most powerful approaches.[17–23]

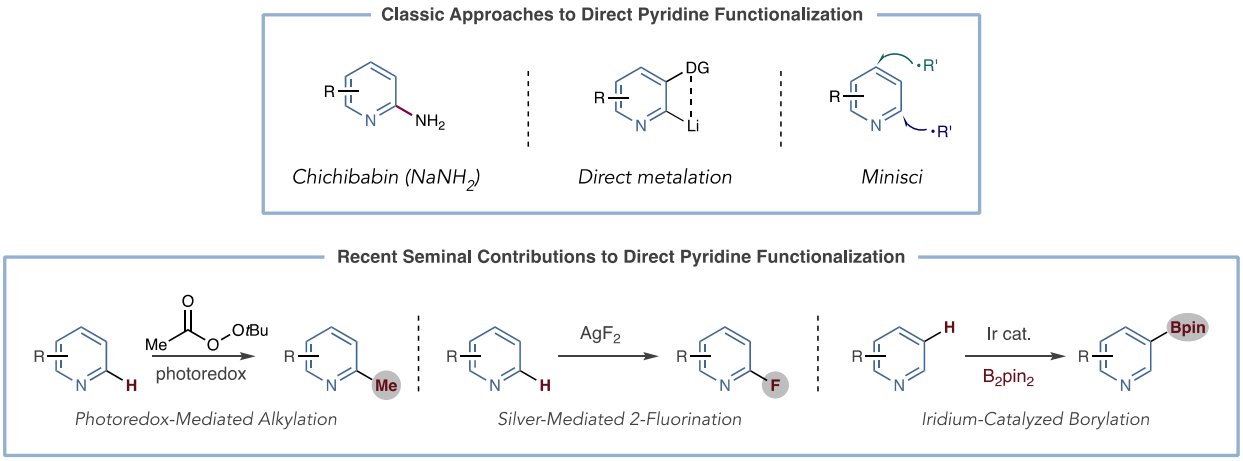

Figure 1.4. Classic and Modern Approaches to Direct Pyridine Functionalization

Despite the interest in pyridine functionalization, methods to directly and selectively functionalize the 4-position of pyridines remain challenging and are limited to a few examples (Figure 1.5).[24–27] In recent literature, Kanai has shown that bulky Lewis acids can coordinate to the nitrogen atom and direct the functionalization to the 4-position.[28] This method uses preformed bulky borane Lewis acid-pyridine Lewis base adducts that can undergo trifluoromethylation with a nucleophilic "CF_3^-" that adds to the 4-position. The resulting dearomatized trifluoromethylated pyridine product must then be oxidized in a separate step. While this method is effective on simple pyridine derivatives, as the complexity of the substrates increases, it begins reacting at the 2-position leading to a mixture of regioisomers (**1**). Nakao has also developed a method, based on the same principle, where a bulky Yamamoto-type Lewis acid directs a nickel catalyst to the 4-position of the pyridine, which then undergoes C-H activation and produces alkylated and alkenylated pyridines.[29]

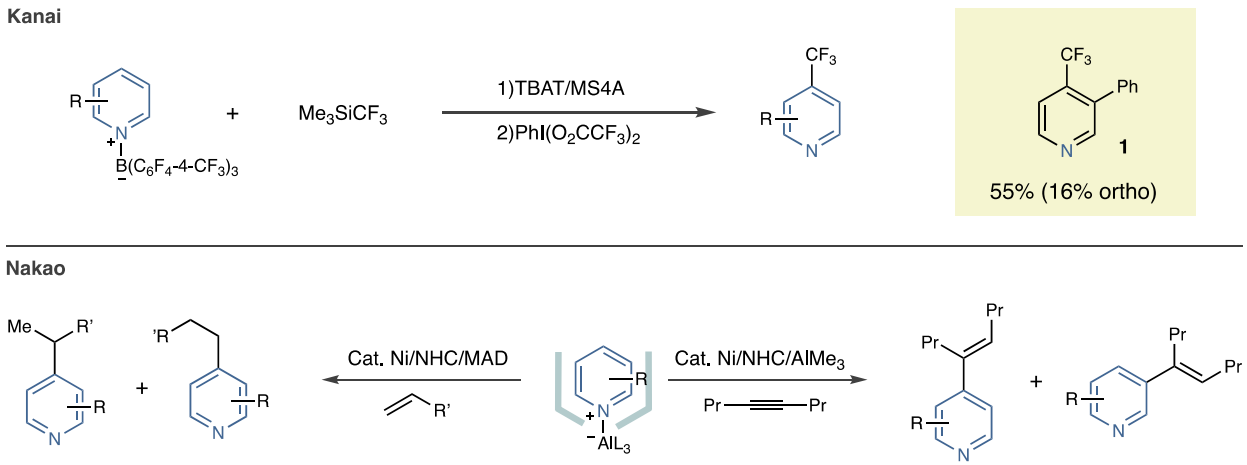

Figure 1.5. Examples of Methods for 4-Position Selective Pyridine Functionalization

1.3 Introduction to Heterocyclic Phosphonium Salts

Understanding the limitations of functionalizing pyridines and diazines, our lab set out to develop a strategy to transform azines with high selectivity for the 4-position. Our initial goal was not to target the selective introduction of one functionality, but instead to install a functional handle that could be transformed further. Therefore, the key to our strategy was the nature of the functional group that we aimed to install.[30] We wanted this functional group to directly and regioselectively add to the 4-position of pyridines, but we also needed the group to be a versatile handle that would enable a wide range of subsequent transformations, allowing chemists to synthesize a variety of pyridine and diazine derivatives efficiently (Figure 1.6).

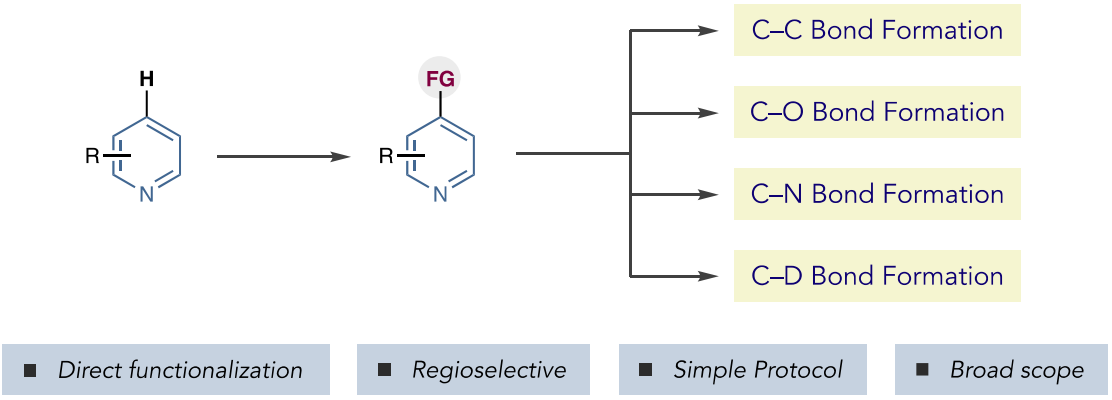

Figure 1.6. Installing a Functional Handle Could Enable Various Bond Constructions.

We also wanted the reaction to be simple in terms of the reagents used, and broad in terms of the applicable scope, in particular towards complex derivatives. Most synthetic chemistry methodology development is targeted towards building block molecules, which are relatively simple starting materials for a drug development process. However, we wanted our chemistry to have application on more complex drug fragments, as well as bioactive compounds and pharmaceuticals (Figure 1.7). As the complexity of your substrates increases, applying a new chemical transformation becomes increasingly more difficult due to issues arising from lack of selectivity, and from the excess of polar functionality within the molecule. For these reasons, most new synthetic methodology falls short of being truly broadly applicable, especially at the later stages of the drug discovery process.

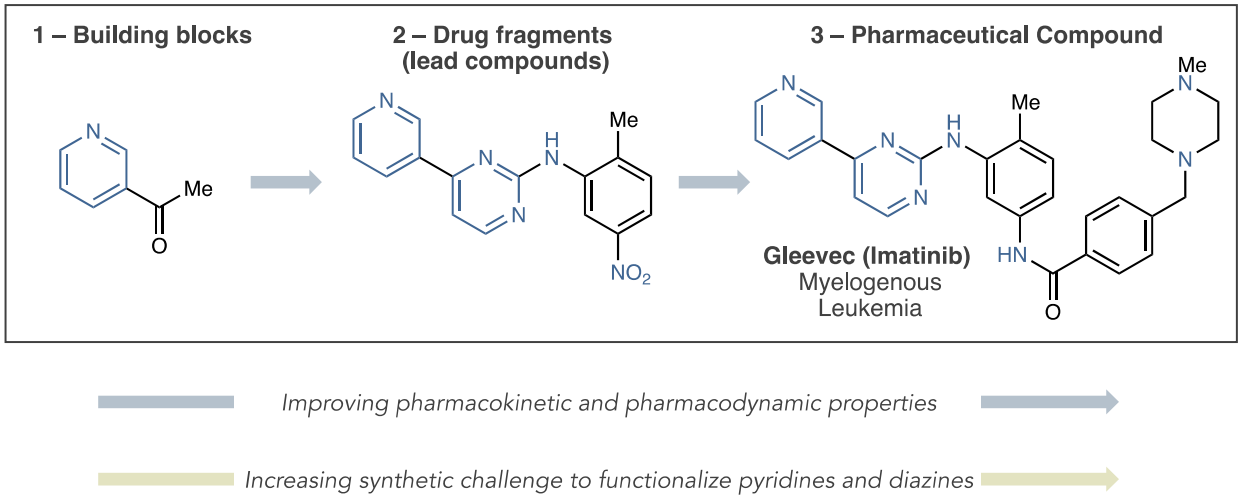

Figure 1.7. Reaction Development in the Drug Discovery Process

While investigating methods to selectively install a functional handle to the 4-position on pyridines, we found that reacting a pyridine with trifluoromethanesulfonic (triflic) anhydride first formed the *N*-triflyl pyridinium triflate (Figure 1.8, **2**). Next, a nucleophile then adds to the pyridine, leading to an intermediate dearomatized pyridyl salt (**3**). During our investigation, we

found that phosphines were particularly adept at this transformation, and importantly the nucleophilic addition was completely 4-position selective. This dearomatized species is then deprotonated by an organic base, such as NEt_3, to rearomatize the pyridine ring and produce a pyridyl triphenylphosphonium salt (**4**). In the literature, we found that these phosphonium salts were initially reported in the 1980s by Anders; however, the scope of the reaction remained limited, and subsequent transformations using these species were not thoroughly pursued.[31–37]

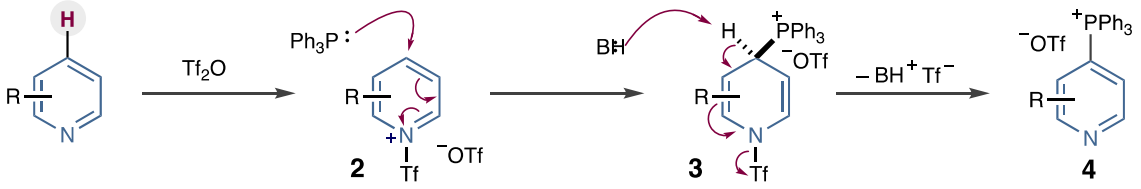

Figure 1.8. Proposed Mechanism for Phosphonium Salt Formation

After developing our reaction protocol, we found that activation of the pyridine with triflic anhydride in CH_2Cl_2 at −78 C and addition of triphenylphosphine, followed by deprotonating the dearomatized intermediate with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) or NEt_3 was operationally effective (Figure 1.9). The resulting heteroaryl phosphonium salts are then isolated by precipitation from diethyl ether, completely eliminating the need for chromatography. Importantly, the reaction is completely selective for the 4-position of the pyridine in the vast majority of examples explored. Pyridines with 2,3- and 2,5-disubstitution undergo the reaction and form the phosphonium salt in good yield (**5-9**). Related heterocycles, such as azaindoles, work under the reaction conditions, and even sterically hindered 3,5-disubstituted pyridines also give reasonable yields (**10-12**). When the 4-position of the pyridine is blocked by a substituent, the phosphonium will selectively add to the 2-position (**13-14**). Other azines are able to react through

these conditions as well with pyrimidines (**15-17**), pyrazines (**18**), quinoxalines (**19**), and phthalazines (**20**) all giving reasonable yields. Outside of substitution patterns, a range of functional groups can be tolerated. The reaction is compatible with aryl halides (**7, 11, 13, 16-18**) and trifluoromethyl groups (**8**), and also tolerates other heterocycles (**5**).

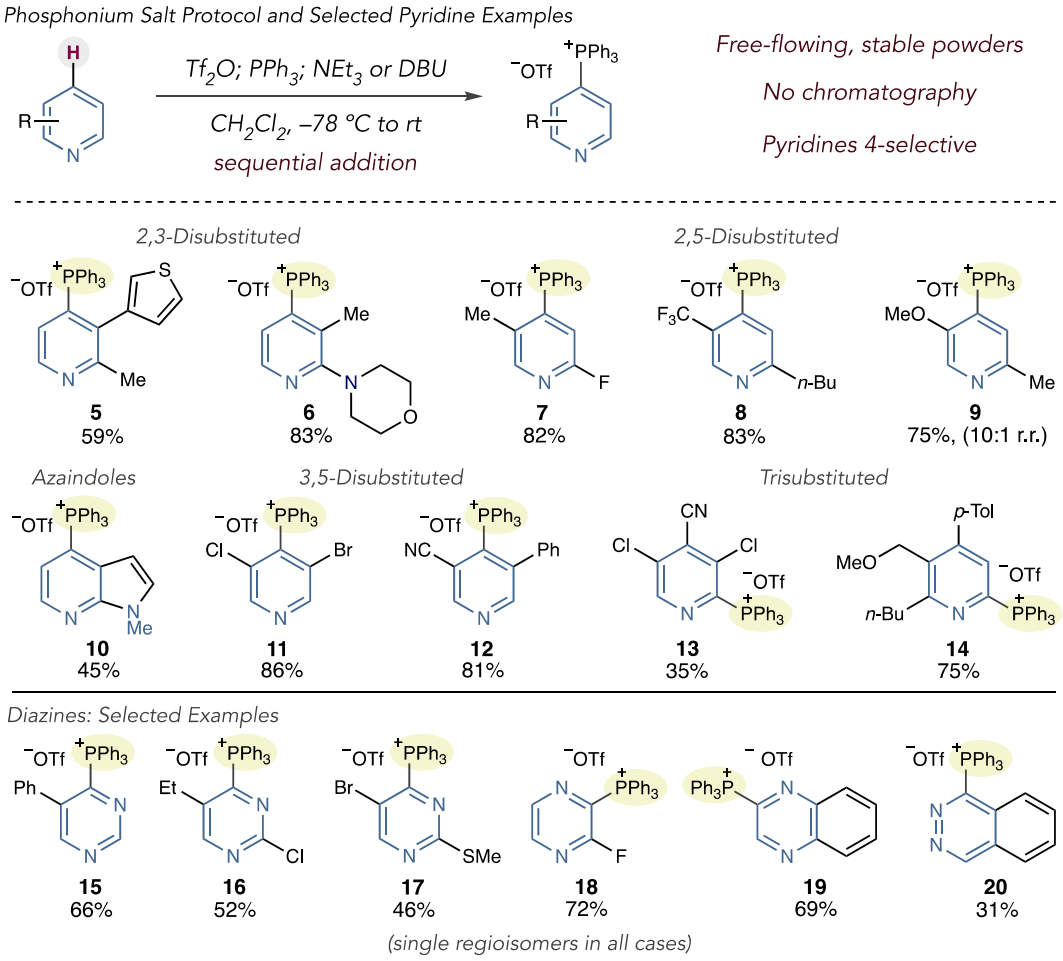

Figure 1.9. Phosphonium Salt Protocol and Application to Azines

Next, we considered whether our phosphonium salt reaction protocol would be applicable beyond simple azine building blocks. We applied the reaction conditions to larger, more complex substrates, similar to drug fragment-type molecules seen in the pharmaceutical industry, and found

that the reaction operated effectively (**21-24**). Lastly, we applied our reaction protocol to a set of complex bioactive molecules and pharmaceuticals. Despite the excess of polar functionality and multiple reactive sites, the reaction functions well and produces the desired phosphonium salt products in good yields (**25-29**). Additionally, **30-32** highlight a significant feature of this reaction manifold. Not only does the reaction exhibit excellent regioselectivity with these molecules but also remarkable site selectivity on substrates where more than one pyridine or diazine is present within the structure.

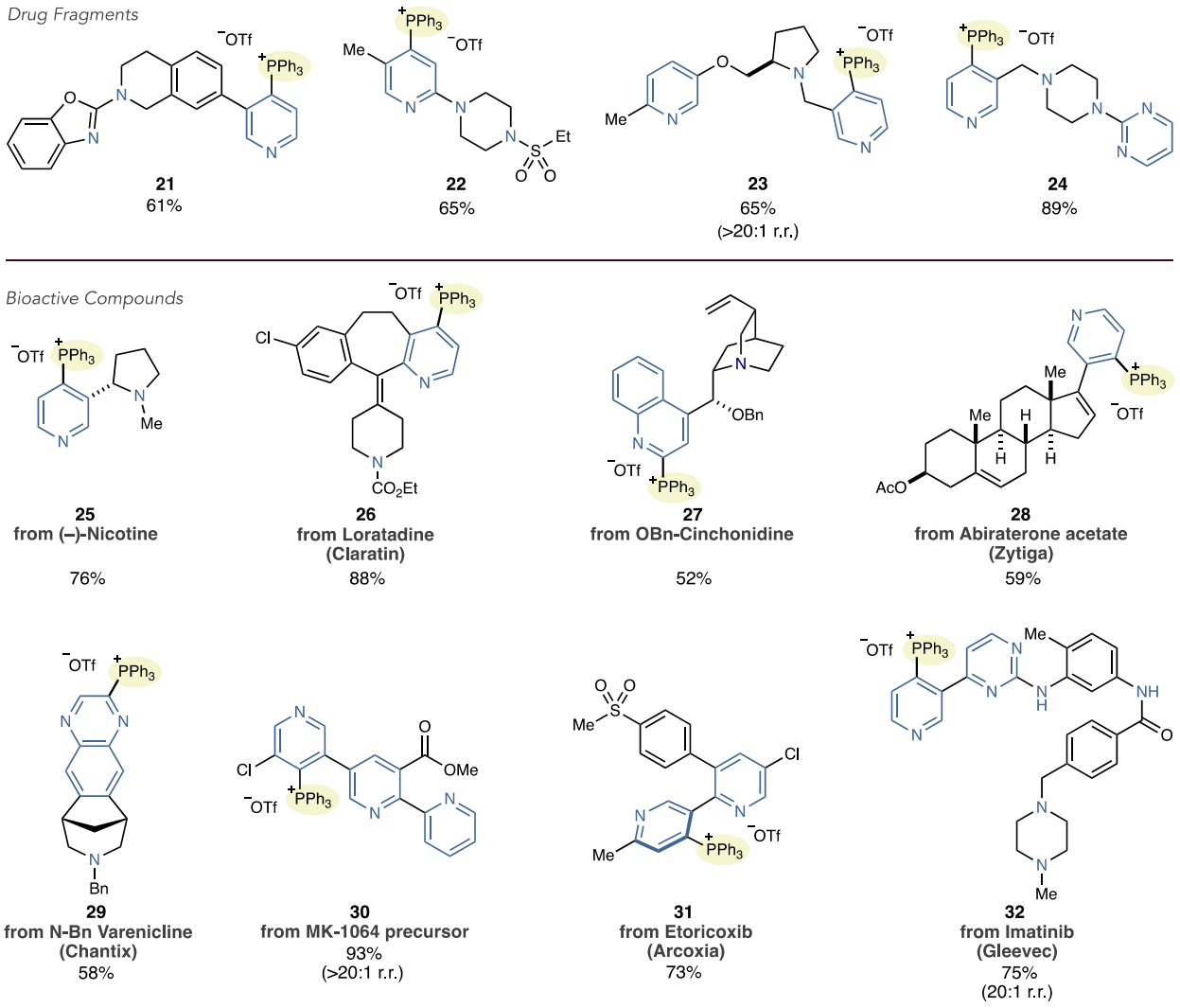

Figure 1.10. Phosphonium Salt Formation on Drug-Like Fragments and Bioactive Molecules

1.4 Nucleophilic Additions to Heterocyclic Phosphonium Salts

After developing a reliable protocol to make a variety of *N*-heterocyclic phosphonium salts, our group next investigated their abilities to act as electrophiles under S*N*Ar type conditions with nucleophiles.[38] We reasoned that these nucleophiles could add to the pyridine through two distinct mechanisms (Figure 1.11). Path A, S*N*Ar, shows a mechanistic possibility where the nucleophile first adds to the *ipso* carbon of the phosphonium salt, forming a Meisenheimer complex and eliminating off triphenylphosphine. In path B, conversely, the nucleophile first adds to the phosphorus atom, forming a P(V) phosphorane intermediate, and then undergoes a shift to the ipso carbon of the pyridine through an asynchronous ligand coupling process. Through a computational collaboration with Professor Robert Paton, we believe that path B is operative due to a near barrierless addition to the phosphorus, subsequent ligand coupling, and expulsion of PPh3.[39,40]

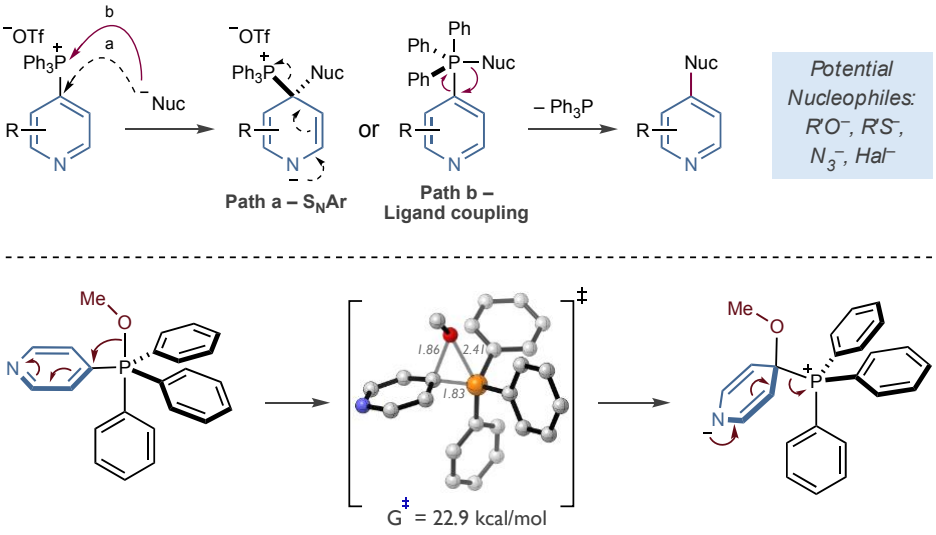

Figure 1.11. Proposed Mechanism for Nucleophilic Additions to Pyridyl Phosphonium Salts

Using this reaction manifold, Hilton and Dolewski first examined alkoxide nucleophiles as coupling partners with the heterocyclic phosphonium salts to form heteroaryl ethers.[38] They found that running the reactions in THF at 0 °C served as an effective protocol, with a range of different alkoxides and azinyl phosphonium salts being amendable (**33-36**). They also found that phosphonium salts derived from pharmaceuticals worked well under the reaction conditions (**37-39**). Furthermore, Anderson extended this reaction platform to include thiolate nucleophiles, as well as a range of various exocyclic and endocyclic aromatic nucleophiles after slight modifications of the reaction conditions.[41,42]

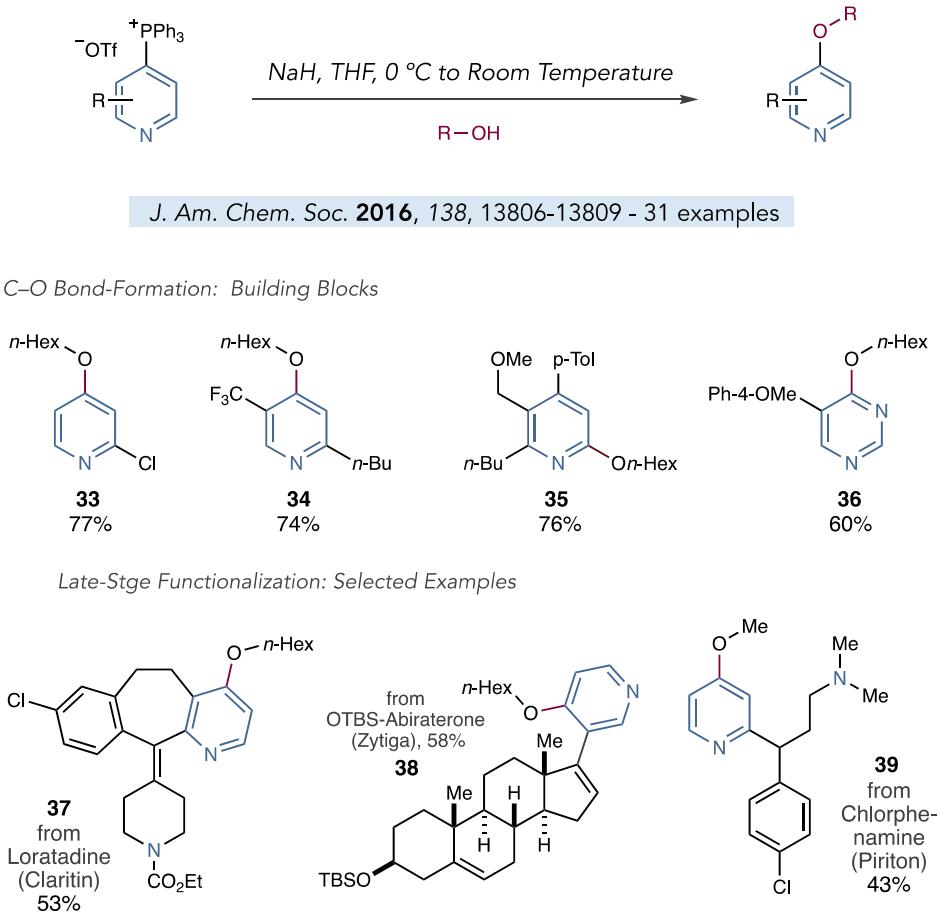

Figure 1.12. Reacting Alkoxide Nucleophiles with Pyridyl Phosphonium Salts

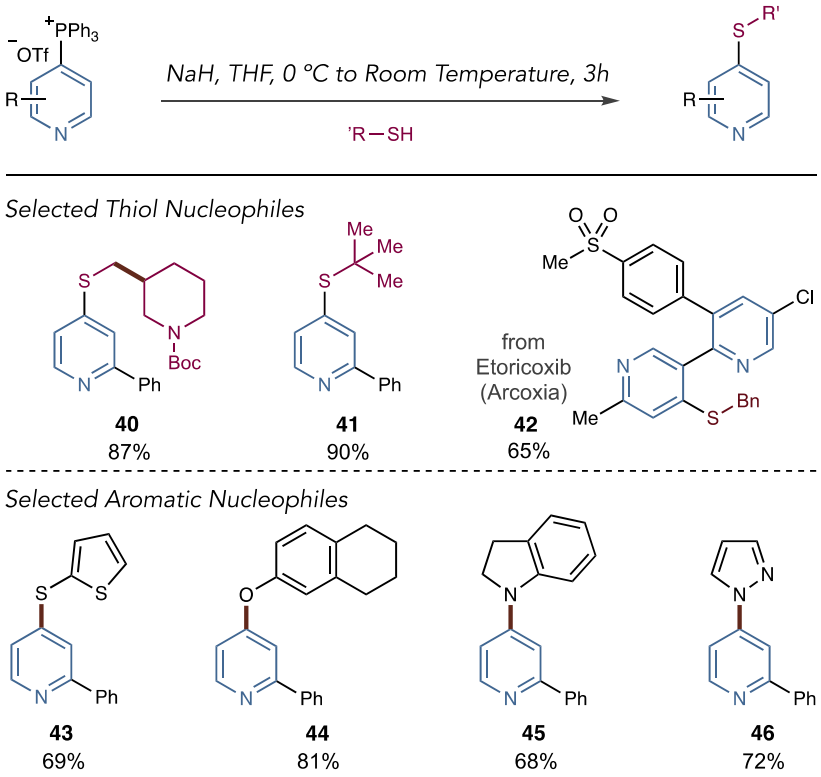

Figure 1.13. Thiol, Exocyclic, and Endocyclic Aromatic Nucleophiles with Azinyl Phosphonium Salts

As we continued our investigation of useful nucleophiles to add to our phosphonium salts, Patel et al. used sodium azide to form iminophosphoranes (Figure 1.14).[43] These reactions are suggested to proceed through a classical S*N*Ar-type mechanism to first form an organoazide intermediate, followed by a Staudinger rearrangement (**47**-**49**). These iminophosphorane products can then readily be transformed into other useful functional groups, such as amines and isothiocyanates (**50**-**52**).

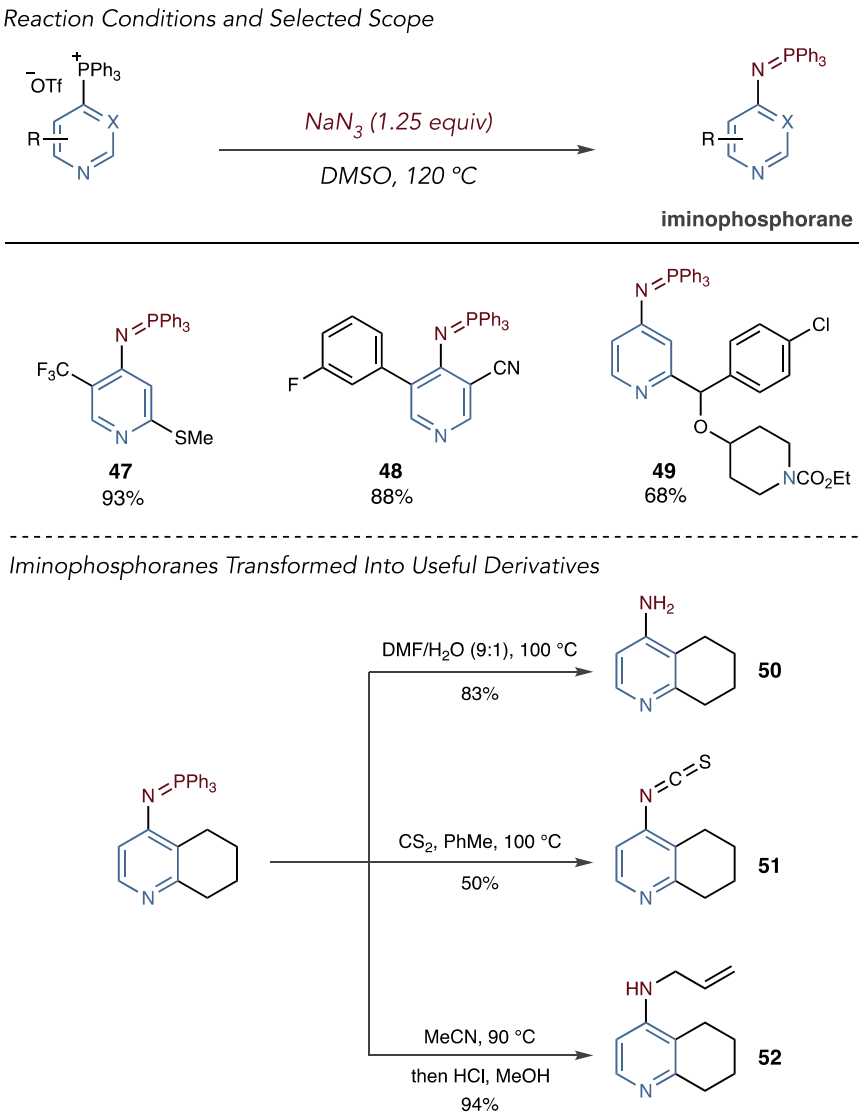

Figure 1.14. Sodium Azide as a Nucleophile to Form C-N Bonds

1.5 Carbon-Carbon Cross-Coupling via Heterocyclic Phosphonium Salts

Transition metal-catalyzed aryl-aryl cross-couplings are some of the most commonly used reactions in the pharmaceutical industry.[44–46] These reactions typically use a (hetero)aryl halide as one of the reactive partners; however, the preparation of the (hetero)aryl halide remains a significant challenge on pyridines and diazines *vide supra*. Therefore, we reasoned whether heterocyclic phosphonium salts could serve as a valuable pseudo-halide in these types of reactions due to the ease of preparation from the corresponding C-H precursor. Zhang then showed that azinyl phosphonium salts were able to participate in Suzuki-Miyaura reactions using a nickel catalyst and an NHC ligand.[47] This catalyst system suppressed undesired phenyl transfer and promoted selective pyridyl transfer to form aryl-heteroaryl C-C bonds. The reaction proved to be broad in scope and encouraged our group to think further about other transition metal systems that would be amendable to azinyl phosphonium salts.

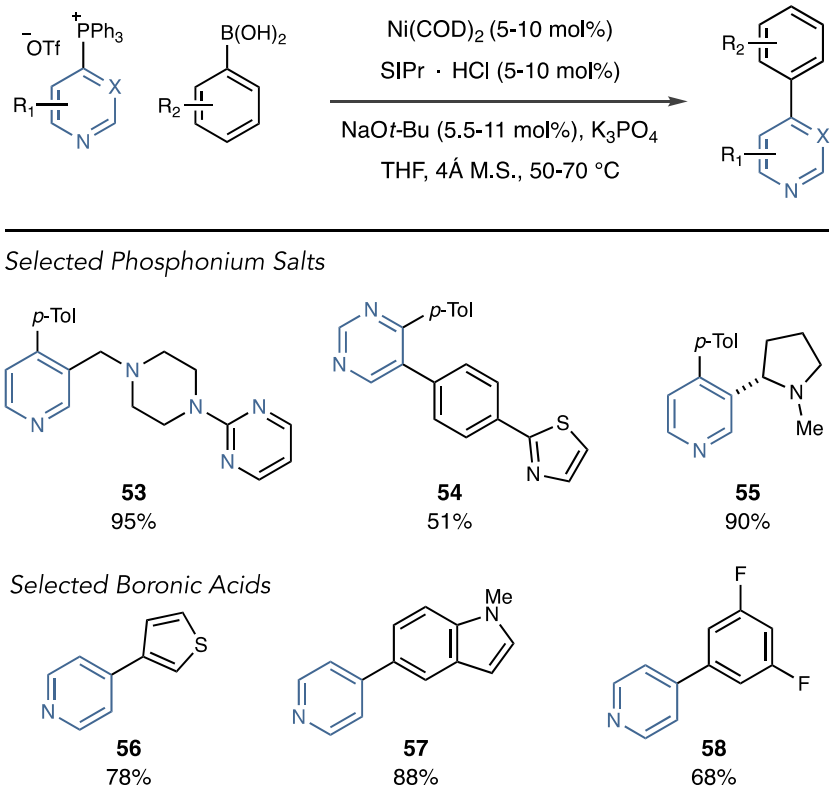

Figure 1.15. Nickel-Catalyzed Suzuki-Miyaura Reaction Using Azinyl Phosphonium Salts

1.6 Heteroaryl Alkylation via Heterocyclic Phosphonium Salts

Alkylated pyridines and diazines are another class of important molecules in the drug industry (Figure 1.16). During the pharmaceutical design process, structure-activity relationship (SAR) studies are commonly used to determine the optimum drug structure for the desired binding properties. During SAR studies, small changes are made to the drug structure, commonly including alkylations of various positions. In the context of pharmaceuticals, alkyl groups are common functional groups on azines and can affect the binding properties of the Lewis basic nitrogen atom, as well as improve binding in a hydrophobic pocket of the target. Methods to install these alkyl groups on azines include the Minisci reaction and metal-catalyzed cross-couplings. While these approaches are widely employed, each reaction has its own set of drawbacks associated with it. The Minisci reaction can give regioisomeric mixtures of alkylated products, often complicating isolation procedures, but is widely used in the pharmaceutical industry. Cross-coupling is another prevalent way to form Csp^2-Csp^3 bonds using heteroaryl halides as the coupling handle.[48,49] However, the heteroaryl halide must be commercially available or synthetically accessible in order to take advantage of these cross-coupling methods. As the molecular complexity of the substrate increases, methods to selectively install halides on an azine become extraordinarily rare. Therefore,

methods that can install a halide or pseudohalide on azines selectively from the C-H bond and can undergo alkylation are valuable.

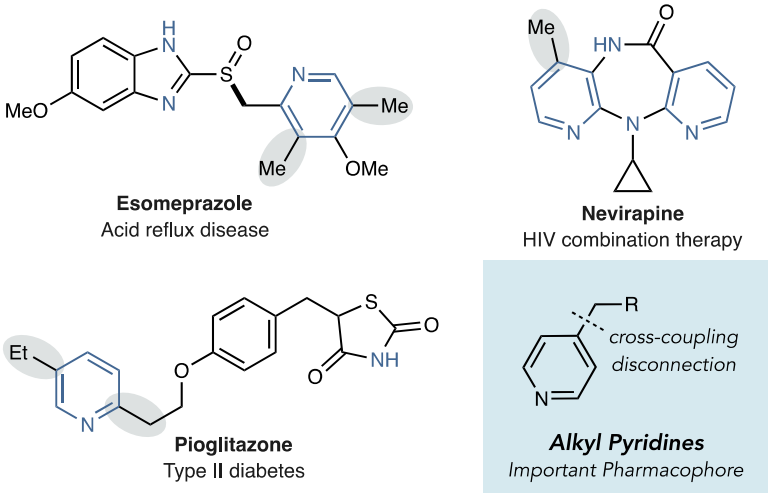

Figure 1.16. Examples of Alkylated Pyridines Within Pharmaceutical Compounds

Building on our success with Csp^2-Csp^2 cross-couplings via nickel catalysis, Zhang was able to show that azinyl phosphonium salts were also amendable to Csp^2-Csp^3 cross-couplings (Figure 1.17).[50] Using cobalt(acac)$_3$ and a 2,2'-bipyridine ligand as the catalytic system, the phosphonium salts undergo a Negishi reaction with a range of alkyl zinc reagents (**59-61**) and phosphonium salts (**62-64**). Significantly, this method also demonstrates the ability to selectively methylate the 4-positon of pyridines, an important transformation for SAR studies, through this two-step process (**65**).

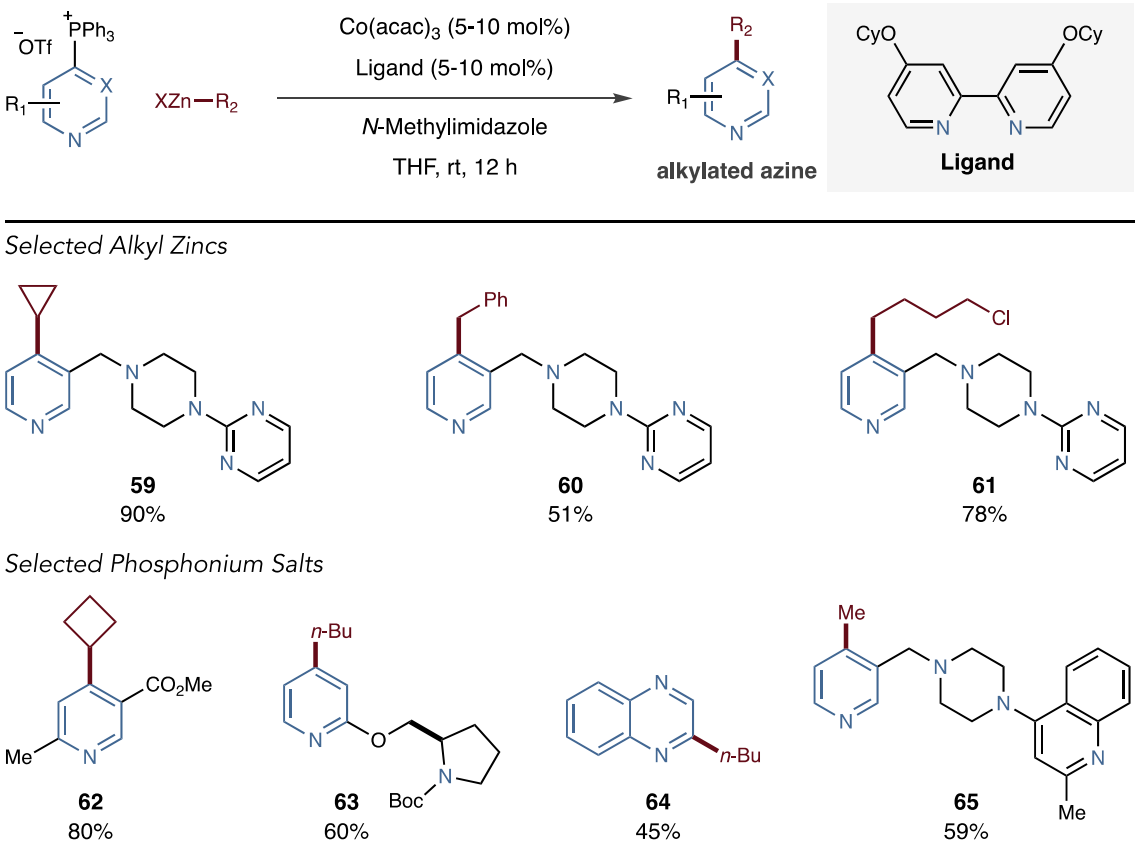

Figure 1.17. Cobalt Catalyzed Csp^3-Csp^2 Cross-Coupling and Selected Scope

1.7 Heterobiaryl Formation via Bis-Heterocyclic Phosphonium Salts

Heterobiaryls are a notable group of molecules in the pharmaceutical industry. In this class of molecules, joined 6-membered azines are commonly observed in pharmaceuticals, such as the drugs etoricoxib and imatinib, spanning a wide range of disease areas (Figure 1.18).[51–53] The most prevalent method to synthesize biaryl fragments is the Suzuki-Miyaura reaction; however, pyridine-pyridine and pyridine-diazine couplings remain a notable challenge. The lack of commercially available halide coupling partners significantly limits the reaction scope, and there are no general methods to halogenate pyridines directly. Additionally, only a moderate range of

azinyl boronic acid coupling partners are available commercially, and they are known to often protodeboronate under the reaction conditions, decomposing the starting material.

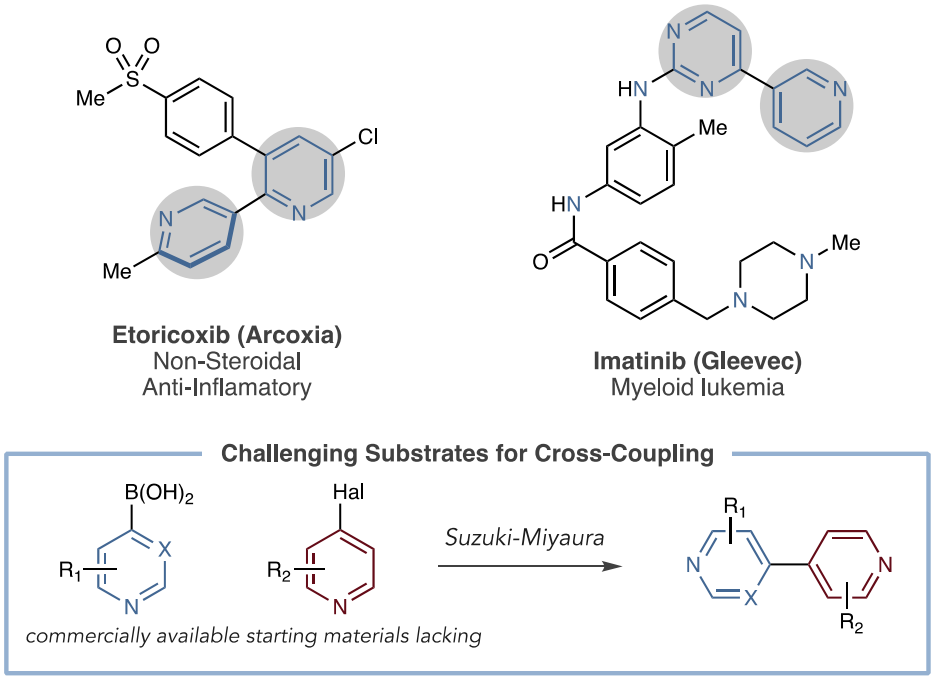

Figure 1.18. Examples of Heterobiaryls in Drugs, and Challenges to Synthesize This Motif

Our lab has developed a method to synthesize heterobiaryls using a phosphorus ligand-coupling approach (Figure 1.19).[39] Hilton et al. have shown that azinyl phosphines can be made through our phosphonium-forming protocol using fragmentable phosphine nucleophile **66** (easily prepared from diphenylphosphine and methyl acrylate). Adding an extra equivalent of the base in the reaction leads to the elimination of the heteroaryl phosphine **67**. Next, this phosphine is used to form the phosphonium salt on another azine. The resultant bis-heteroaryl phosphonium salt **68** is then reacted with a nucleophilic trigger, such as ethanol, in the presence of 2 equivalents of HCl promoting C-C bond formation of the two azine substituents to form the heterobiaryl product **69**. This approach to heterobiaryl synthesis is extremely broad in terms of the reaction scope and

tolerates diverse functional groups that are often observed in the drug-discovery process (**70-75**). The reagents are all commercially available, and the protocol can be readily applied by medicinal chemists.

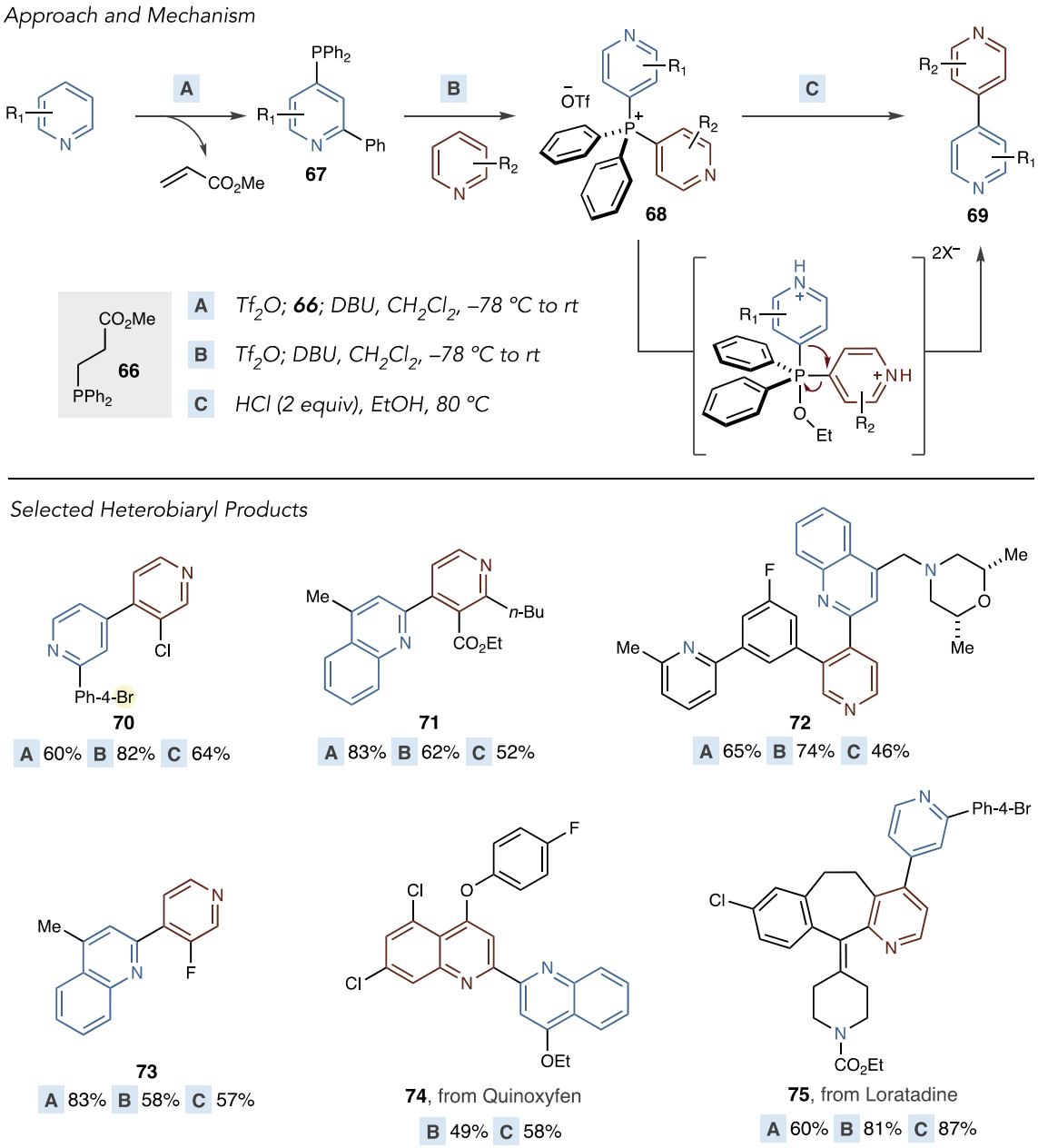

Figure 1.19. A Method to Form Heterobiaryls Using a Phosphorus Ligand-Coupling Approach

In cases when the azinyl chlorides are commercially available, Boyle et al. have shown that they are effective substrates for heterobiaryl synthesis through a modified version of the ligand-coupling protocol (Figure 1.20).[54] This method, using two heteroaryl chloride coupling partners, circumvents using azinyl boronic acids that often decompose under Suzuki cross-coupling conditions. For this protocol, the first chloroazine **76** and diphenylphosphine undergo an S*N*Ar reaction to form a pyridyl phosphine **77**. Next, the pyridyl phosphine reacts with another chloroazine **78** to form a phosphonium salt intermediate. Similar to our previous phosphorus ligand-coupling method, acid activates the phosphonium salt, and C-C bond formation occurs, forming the bipyridine product **79**. The reaction has broad scope, allowing a range of heterobiaryls to be readily made (**80**-**83**), including valuable 2,2'-bipyridine products (**84**-**87**).

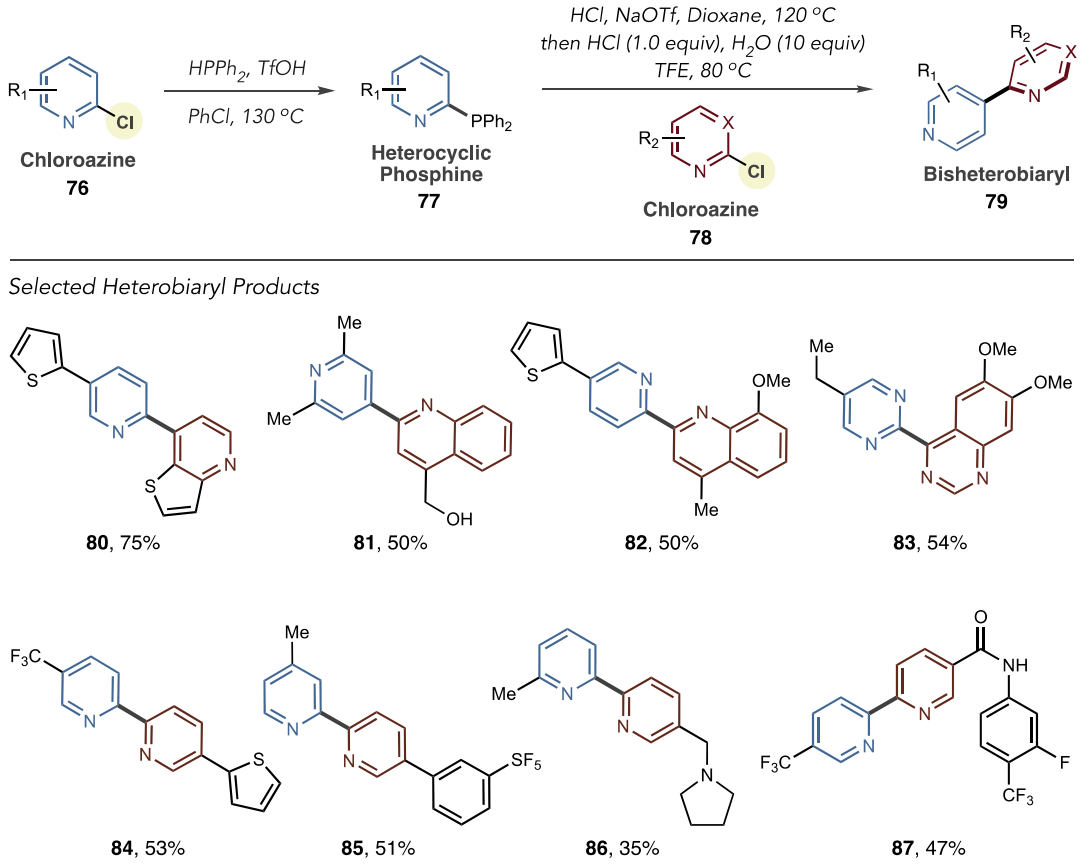

Figure 1.20. Tandem S*N*Ar-Ligand Coupling Reaction to Form Heterobiaryls. Yields are reaction of **77** with **78**, then ligand coupling to form **79**.

1.8 Azine Halogenation via Heterocyclic Phosphonium Salts

Recently, our lab demonstrated that heteroaryl phosphonium salts are suitable functional handles for halogenation, including iodination, bromination, and chlorination (Figure 1.21).[55] This reaction is a significant advancement, as there are no general methods to halogenate the 4-position of pyridines directly. This protocol is simple in terms of reagents and protocol, producing useful azinyl halide products. The success of this strategy centered on using specially designed phosphines when forming the phosphonium salt. Using pyridyl phosphines **91** or **92** to form the phosphonium salt makes the azinyl phosphonium more electron-deficient and activated towards nucleophilic attack from the halide. A range of azine building blocks, as well as bioactive molecules, were amendable to the reaction conditions yielding useful halogenated products (**93-107**).

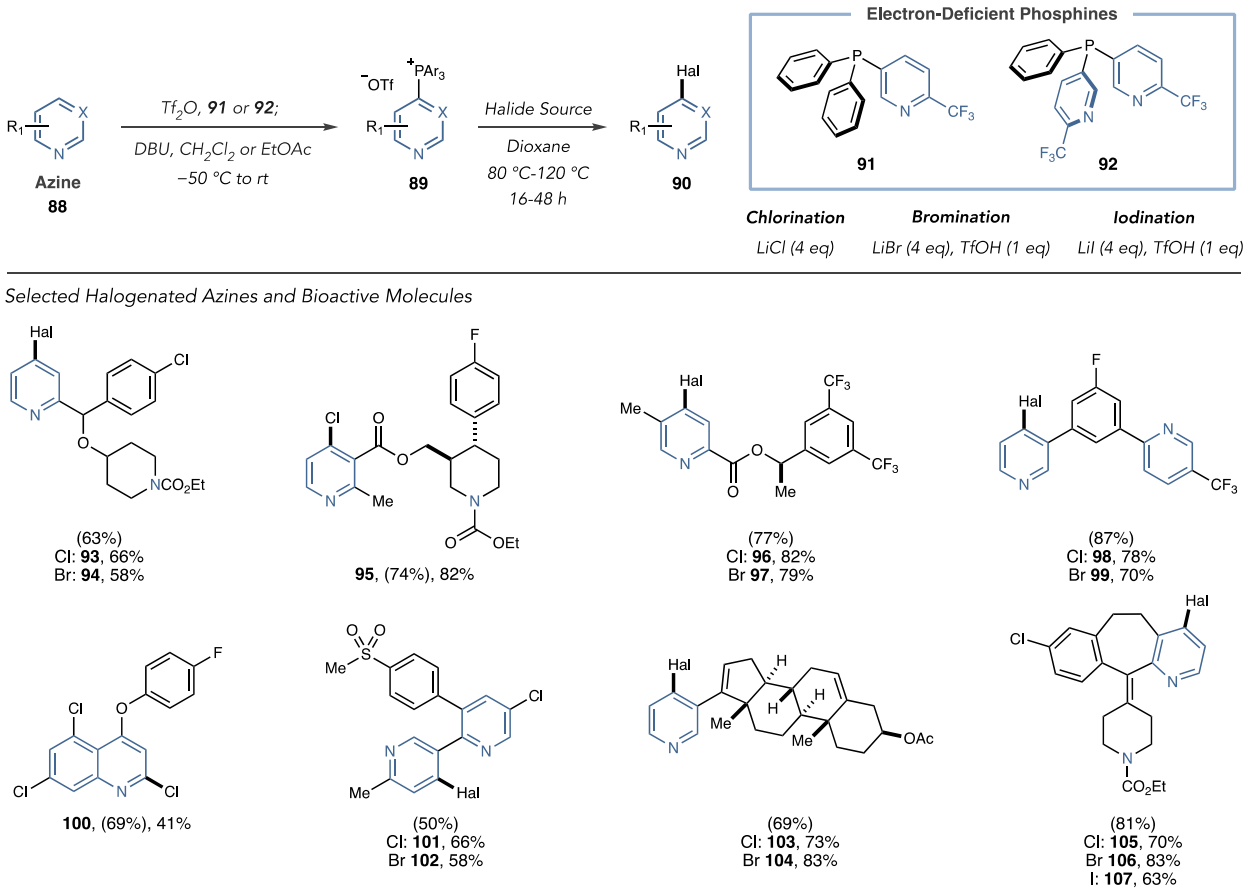

Figure 1.21. Halogenation of Azines via Heterocyclic Phosphonium Salts

1.9 Conclusion

This section serves as an introduction to the preparation of pyridines and diazines, their importance across disciplines, and current challenges in methods to functionalize these motifs. It also highlights the work the McNally lab has accomplished regarding synthesizing azinyl phosphonium salts and the development of their applications. Azinyl phosphonium ions are prepared through simple protocol using common organic reagents, and they prove to be versatile functional handles that allow for a broad range of subsequent transformations.

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CHAPTER TWO

DEUTERATION AND TRITIATION OF PYRIDINES, DIAZINES, AND PHARMACEUTICALS VIA HETEROCYCLIC PHOSPHONIUM SALTS

2.1 Introduction to Deuteration

Isotopic labeling of bioactive molecules plays a crucial role in drug discovery and design, mechanistic elucidation, pharmacokinetic/pharmacodynamic (PK/PD) studies of drug compounds, and nuclear imaging.[1–9] The most common isotopes used in industry are ^{125}I, ^{15}N, ^{14}C, ^{2}H, and ^{3}H. Incorporating deuterium into drug molecules has made a recent resurgence in the pharmaceutical industry as a method to identify new clinical candidates through improving the PK/PD profile of a compound.[10–15] A significant challenge in the drug discovery process is combating oxidative metabolism by cytochrome-P450 (CYP450) enzymes. These enzymes are responsible for oxidatively metabolizing and clearing many of the active pharmaceutical ingredients (APIs) from the body, often decreasing the half-life of the drug. Therefore, approaches to mitigate this oxidative metabolic pathway are in high demand.

Attaching deuterium atoms onto a scaffold does not affect the binding selectivity or potency of the drug, but often can increase many beneficial metabolic attributes. The carbon-deuterium bond strength is greater than the carbon-hydrogen bond; therefore, hydrogen atoms at metabolically-active locations, such as adjacent to heteroatoms, on electron-rich aromatic rings, or benzylic positions, are often replaced with deuterium atoms. The stronger C-D bond can increase resistance to oxidation by CYP450s and improve the metabolic stability of the drug. This increased stability can have a profound impact on lowering the rate of systemic and pre-systemic clearance of the drug from the body, increasing the dosing efficacy, and allowing less of the drug to be metabolized before reaching the intended target. Deutetrabenazine, a treatment for symptoms of

Huntington's disease and the first FDA-approved deuteration drug, deters undesired metabolism by including strong C-D bonds at metabolically active sites, which results in increased bioavailability and decreased adverse side effects (Figure 2.1).[16] Additionally, this increased bioavailability decreases the necessary dosing of a pharmaceutical, which can have a profound impact in reducing the build-up of toxic metabolites within the body. Substituting a metabolically-active hydrogen for a deuterium atom can also cause the drug to be metabolized at a different position than would have been observed with the non-deuterated API. This "metabolic switching" effect can again reduce the production of toxic metabolites within the body, and further increase the safety profile of a drug candidate in patients.

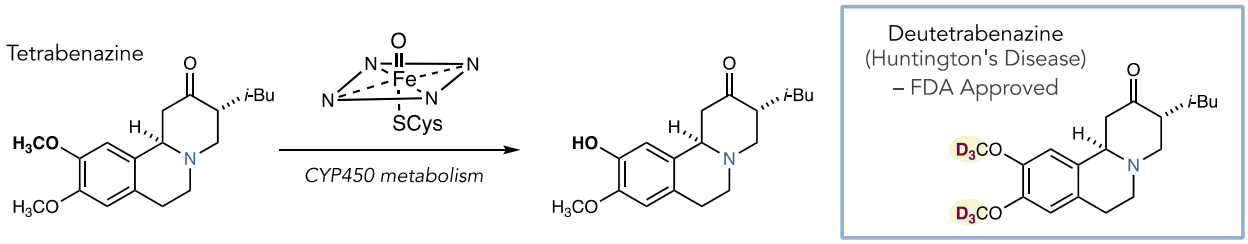


Figure 2.1. Oxidative Metabolism of Tetrabenazine by CYP450 Enzyme and Deutetrabenazine

As discussed, the oxidative metabolism of pharmaceuticals is most frequently accomplished by CYP-450 enzymes.[17] This iron heme-containing class of enzymes target the weak C-H bonds at electron-rich positions on molecules, such as electron-rich aromatics, benzylic C-H bonds, and C-H bonds adjacent to heteroatoms. Additionally, these enzymes catalyze oxidation through the demasking of polar functional groups, such as the dealkylation of ethers or alkyl amines, to form free hydroxyls and amines. Once oxidation has occurred, the molecules have greater polarity, increasing the water solubility, and allowing the liver and kidneys to clear the metabolized drug from the system.

In the drug discovery process, oxidation of electron-rich aromatic systems by CYP450 enzymes is addressed by decreasing the electron density of the ring. Changing the electronics of these systems can be accomplished by installing electron-withdrawing groups, or instead by replacing the aromatic ring with an electron-deficient aromatic variant, such as pyridines and diazines. In this way, CYP450 oxidation can be limited; however, the oxidative metabolism of pyridines and diazines has been found to frequently occur by molybdenum-containing enzymes such as aldehyde-oxidases (AOs) (Figure 2.2).[18–22] The molybdenum cofactor (MoCo) serves as the active nucleophile that attacks the electron-deficient azine (**108**) at either the 2- or 4-position.[23] Following hydride transfer to the cofactor, water attacks the activated position to release the reduced MoCo and the hydroxylated azine (**109**).

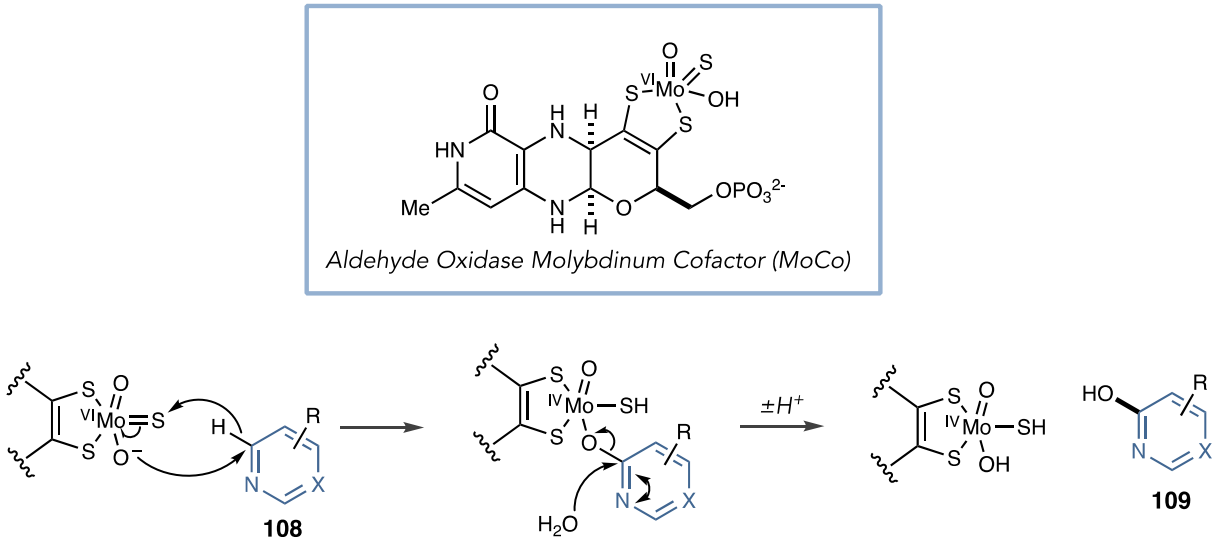


Figure 2.2. Aldehyde Oxidase Cofactor and Mechanism of Azine Oxidation

To deter this metabolic pathway, pharmaceutical companies have begun to install deuterium atoms at these metabolically active positions. The deuterated clinical trial candidate, VX-984, was developed by Vertex Pharmaceuticals due to undesired AO oxidation of the pyrimidine ring,

rescuing a previously non-viable drug candidate (Figure 2.3).[10] While oxidation of the C-H bonds adjacent to the nitrogen atom is common, it is often unpredictable where this metabolism will occur on the scaffold. Therefore, there must be methods available to easily access these deuterated azines.

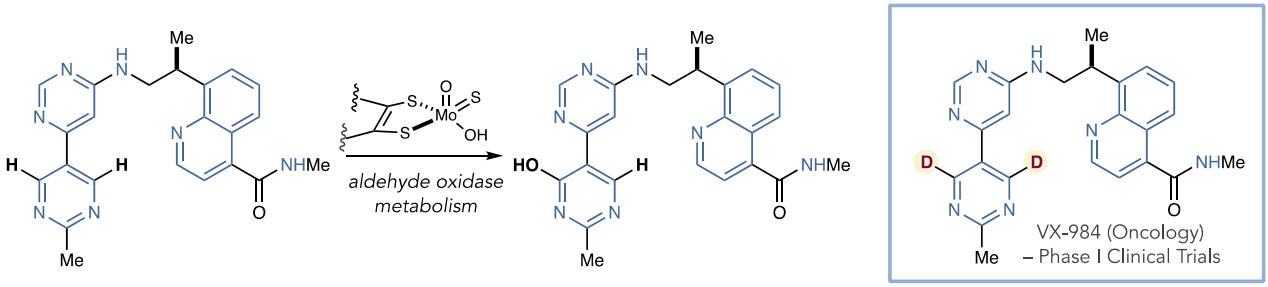


Figure 2.3. Solving Undesired Oxidation of VX-984 Through Deuteration of Azine

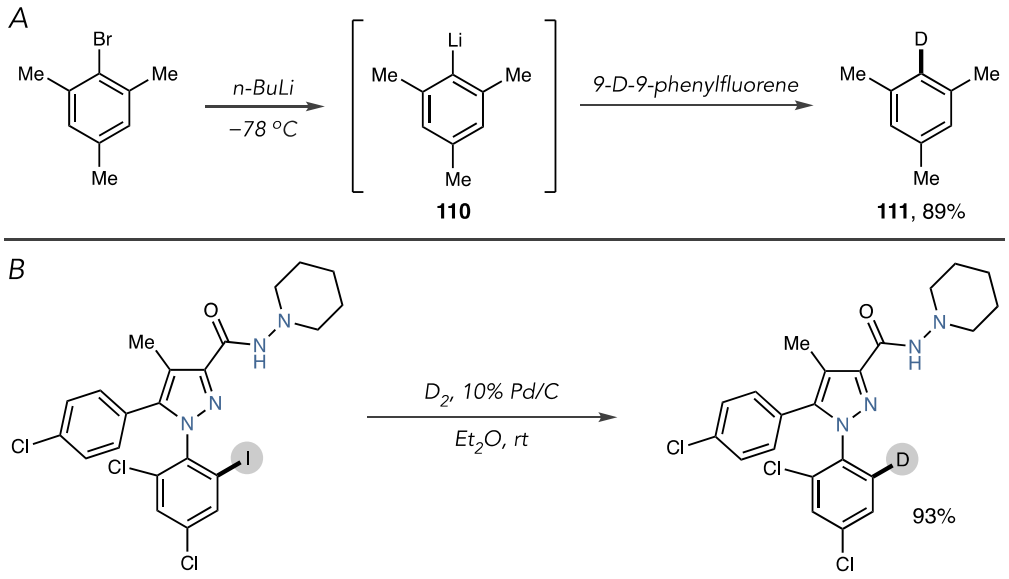


Figure 2.4. Deuteration of Arenes Using A) Lithium Halogen Exchange – Electrophilic Trapping, and B) Transition Metal-Catalyzed Deuterodehalogenation

Current methods to install deuterium onto (hetero)arenes fall into one of two general categories, modifying an existing functional handle to incorporate the deuterium atom, or directly exchanging a C-H bond for a C-D bond. In the former category, installing deuterium through a deuterodehalogenation process using (hetero)aryl halides is a general strategy (Figure 2.4, A).[24,25]

These methods use a metal, often lithium or magnesium, to form the organometallic intermediate (**110**), which then attacks an electrophilic deuterium source to give the deuterated product (**111**). Additionally, transition-metals, most commonly palladium, can catalyze the deuterodehalogenation process using D_2 gas as the deuterium source (Figure 2.4, B). Both of these dehalogenative approaches are widely used in the pharmaceutical industry; however, the functional group tolerance is limited, and they both necessitate pre-installing the aryl halide.

Direct metalation and trapping sequences are also used to deuterate azines (Figure 2.5).[26–29] After metalation of the (hetero)arene (**112**), commonly accomplished using organolithium or organomagnesium reagents, an electrophilic source of deuterium is added, such as D_2O, to give the deuterated product (**113**). However, for this approach to be practical, the molecule of interest must have a directing group ortho to the desired position of deuteration to control the regioselectivity of the metalation. Therefore, this method tends to be less commonly used due to these inherent substrate limitations.

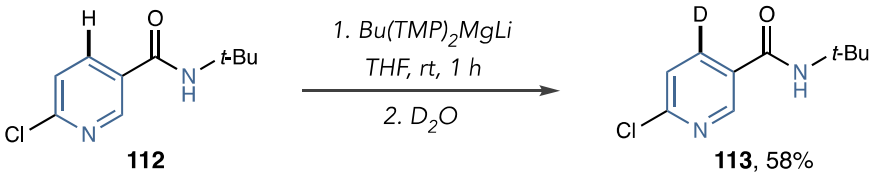
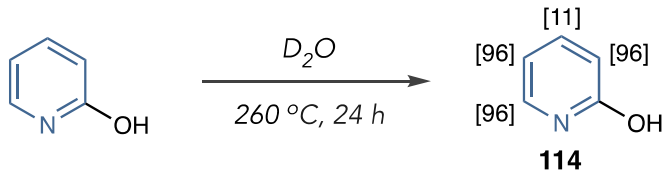


Figure 2.5. Deuteration Through Direct Metalation-Trapping

Direct substitution of a C-H bond for a C-D bond, deemed hydrogen isotope exchange (HIE), has made a significant impact on the deuteration field in recent years.[30–33] These methods are highly valuable, as they do not require pre-installing a functional handle before they undergo deuteration. Therefore, fully functionalized drug candidates or late-stage intermediates can be deuterated without any prior synthesis, often using D_2 or D_2O as convenient and readily available

deuterium sources. These types of reactions can be accomplished on azines using neutral, acidic, or basic conditions under elevated temperatures using D_2O, but typically do not give quantitative deuterium incorporation at every reactive site (Figure 2.6).[34] Instead, these types of conditions install deuterium atoms non-regioselectively at various sites within the scaffold.



114

Figure 2.6. HIE Deuteration with D_2O Under Neutral Conditions

Homogeneous metal-catalyzed HIE is a more popular strategy for deuteration due to the mild conditions, functional group tolerance, and a higher degree of site selectivity. A transition-metal catalyst, most commonly an iridium complex such as Crabtree's catalyst [(COD)Ir(py)- PCy_3][PF_6] (COD = 1,5-cyclooctadiene) or contemporary alternatives developed by Kerr and others are used to mediate the isotope exchange typically using D_2 or D_2O as the deuterium source (Figure 2.7).[35–38] A directing group positions the iridium catalyst in proximity to insert into a C-H bond, which then undergoes exchange with D_2 gas to generate the respective products, predominantly favoring ortho-selectivity. These methods tend to be exhaustive, incorporating deuterium atoms at various positions throughout the molecule with differing percentages of incorporation at each site. Dichloromethane (DCM) is the only solvent that is well tolerated; however, drug solubility in DCM is frequently limited. Additionally, iridium-phosphine complexes can often have functional group incompatibilities, such as undesired reduction of alkenes.[39]

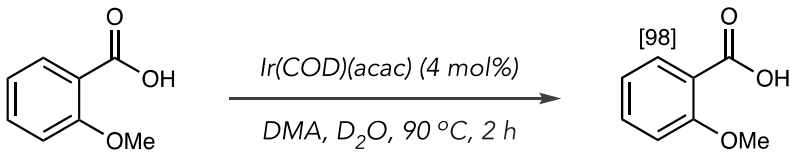


Figure 2.7. Iridium-Catalyzed HIE for Deuteration of Arenes

Chirik has recently developed an iron complex (**115**) that catalyzes deuteration through an HIE pathway (Figure 2.8).[31] Complimentary to existing metal-catalyzed methods that rely on directing groups to guide the catalyst, this protocol's selectivity is based on the most sterically accessible positions (**116**). Additionally, electron-deficient positions of the substrate react at faster rates than electron-rich positions; therefore, this method effectively deuterates electron-deficient azines selectively over electron-neutral or rich aromatics (**121**-**122**). Chirik's catalyst performs well in a wide variety of solvents, allowing for broader substrate compatibility. However, the azine is deuterated at a multitude of positions in many examples shown, and regioselectivity is not entirely predictable (**123**). Furthermore, deuterium incorporation is often below quantitative, which can be problematic when attempting to synthesize, isolate, and test a discreet drug candidate. However, this method is tolerant of various functional groups found in FDA-approved drugs and allows for the late-stage deuteration of complex molecules.

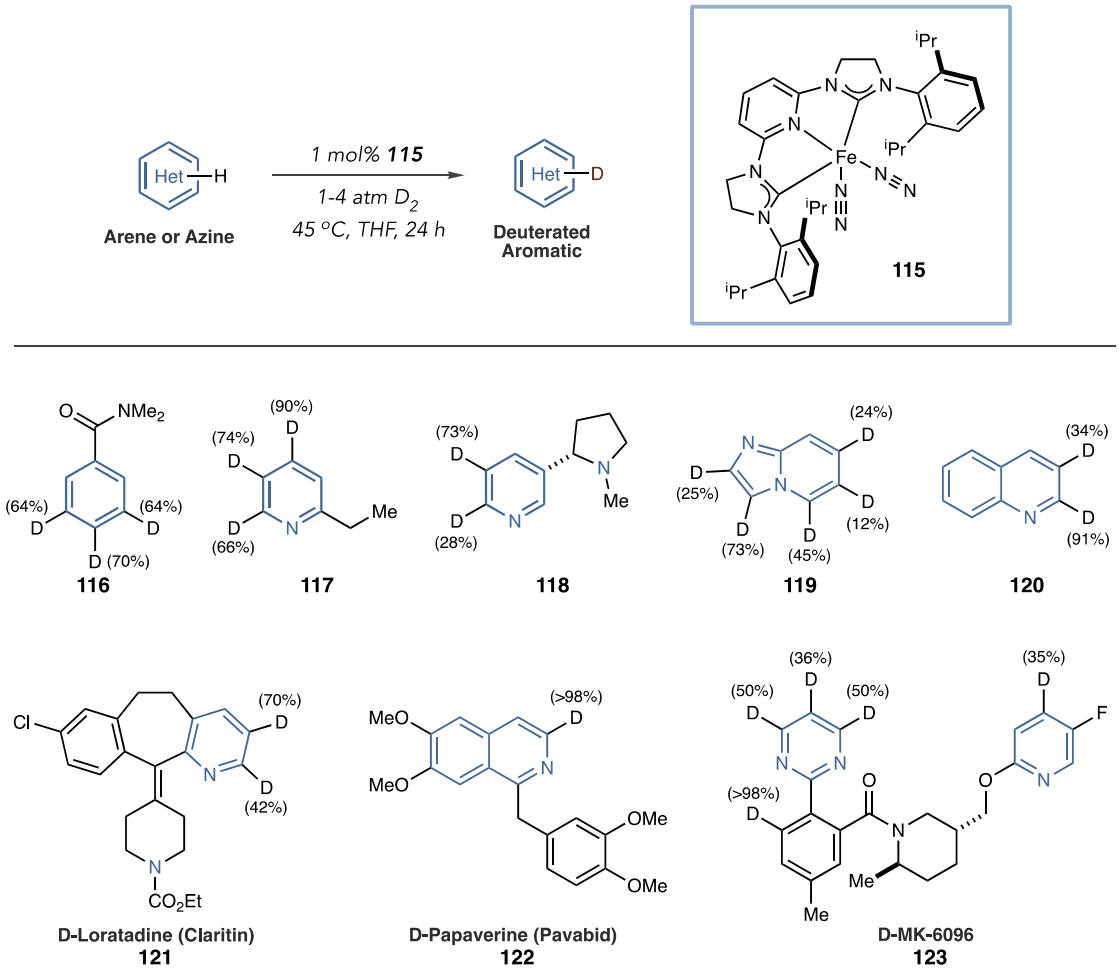


Figure 2.8. Selected Scope of Chirik's Fe-Catalyzed HIE Deuteration

The Chirik group continued their work and developed a new class of dimeric nickel catalysts (**124**-**125**) for hydrogen isotope exchange reactions (Figure 2.9).[40,41] Again, these catalysts operated in mild reaction conditions using D_2 gas as the deuterium source in a range of solvents. The first-generation catalyst was selective for azine deuteration (**126**-**129**), while the second-generation catalyst also reacted on electron-rich positions of arenes in addition to azines (**130**-**133**). The second-generation catalyst was found to be more active, producing higher isotopic enrichment than the first-generation catalyst in the majority of substrates.

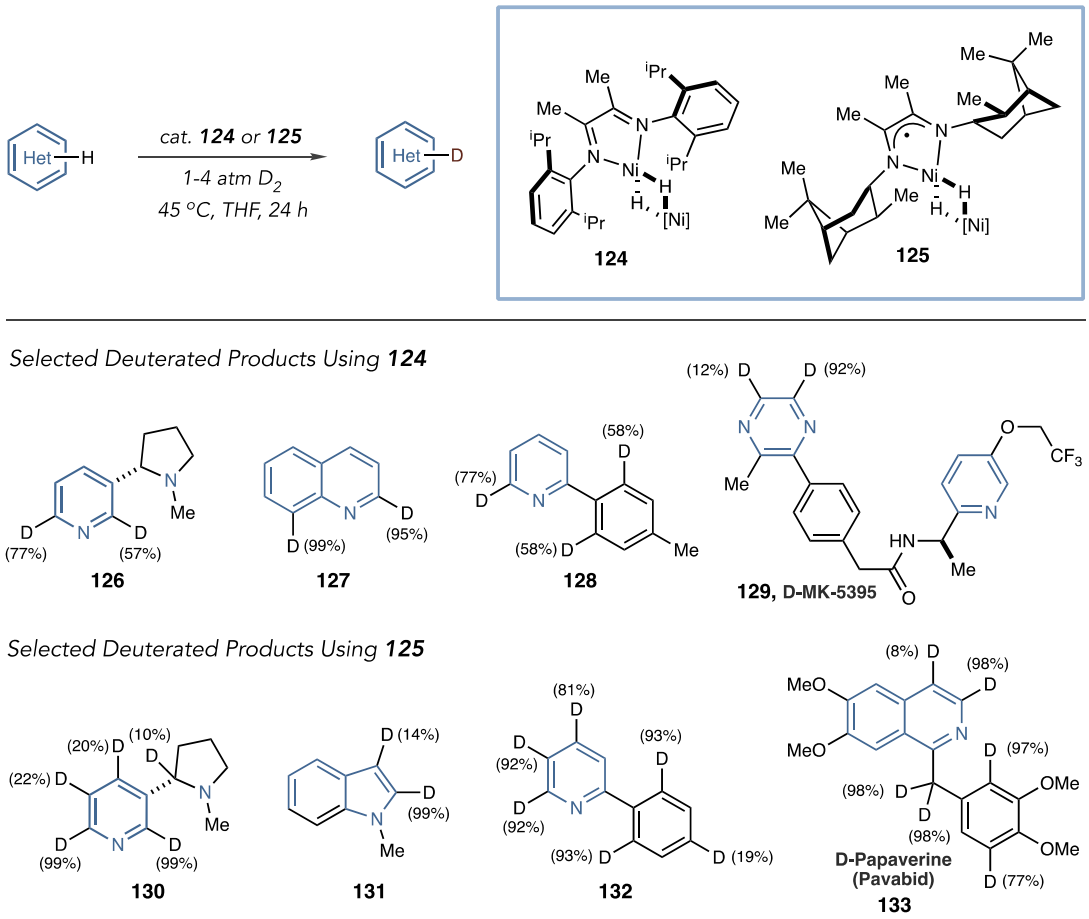


Figure 2.9. Examples of Chirik's Nickel-Catalyzed HIE Deuteration

In 2017 MacMillan and coworkers disclosed a photoredox-mediated radical deuteration protocol using D_2O as the deuterium source (Figure 2.10).[42] This reaction uses a mild set of reaction conditions to catalyze HIE at positions adjacent to aliphatic nitrogen atoms and at benzylic positions on a range of pharmaceuticals.

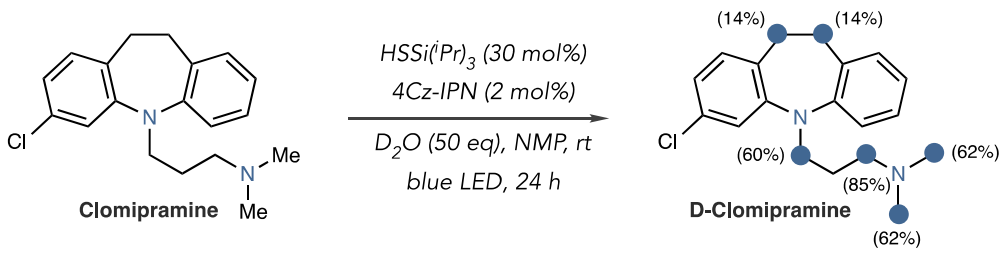


Figure 2.10. MacMillan's Photoredox-Mediated Deuteration of Pharmaceuticals

2.2 Development of Deuteration

Complimentary to reactions developed by our group using azinyl phosphonium salts, we were aware of a fragmentation pathway that could prove useful (Figure 2.11).[43–45] Nucleophiles can add to the phosphonium salt and form a five-valent phosphorane species, leading to unique reactivity. Using carbonate nucleophiles, the resultant phosphorane decomposes into CO_2, triphenylphosphine oxide, and drives the formation of a nucleophilic azinyl anion equivalent that can react with electrophiles. By including an electrophilic deuterium source in the reaction, such as *d*4-methanol, we proposed that we could devise a site-selective and straightforward method to install a deuterium atom on azinyl building blocks and pharmaceuticals.[46]

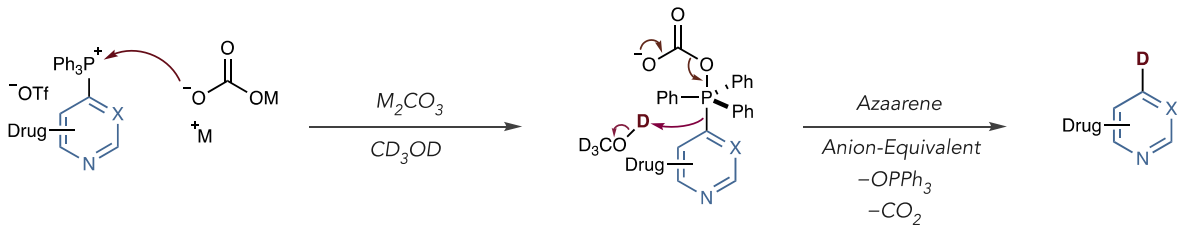
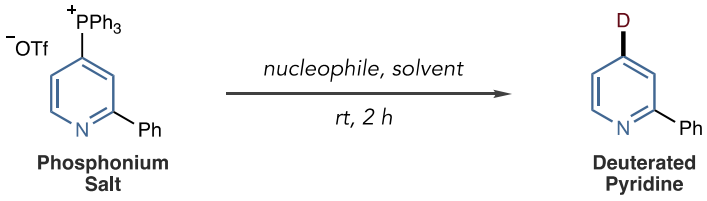


Figure 2.11. Deuteration Strategy Using Azinyl Phosphonium Salt Precursors

We began our investigation by determining reaction conditions for azine deuteration using phosphonium salt precursors (Table 2.1). We concluded that carbonate nucleophiles would function effectively due to the entropic gain associated with forming CO_2 and triphenylphosphine oxide following addition to the phosphonium salt. Using the 2-phenylpyridine triphenylphosphonium salt to begin the screen with deuterated *d*4-methanol (CD_3OD) as the solvent, we examined the influence of the carbonate nucleophile. Sodium carbonate (Na_2CO_3) gave a moderate yield of the deuterated pyridine (entry 1); however, cesium carbonate (Cs_2CO_3) in CD_3OD increased the reaction efficiency further (entry 2). Swapping to potassium carbonate

(K_2CO_3) produced the deuterated pyridine in the highest yield (entry 3), while lowering the amount of K_2CO_3 to 3 equivalents improved the efficiency of the reaction (entry 4). Changing the solvent to a mixture of CD_3OD:DMF (1:9) gave the desired deuterated product in good yield when the reaction time was extended out to 12 hours (entry 5), which is a notable set of conditions for molecules that are not readily soluble in methanol. Entry 5 conditions lead to a heterogeneous mixture due to the insolubility of the K_2CO_3 in CD_3OD. Therefore, a mixture of CD_3OD:D_2O (9:1) was examined and found to improve the solubility of the K_2CO_3, increasing the reaction consistency and rate even when the equivalents of the carbonate nucleophile were reduced (entry 5-6). Overall, we were pleased to find that this reaction uses commercial reagents and a simple protocol to produce valuable azinyl products.

Table 2.1. Optimization of Pyridyl Phosphonium Deuteration Conditions

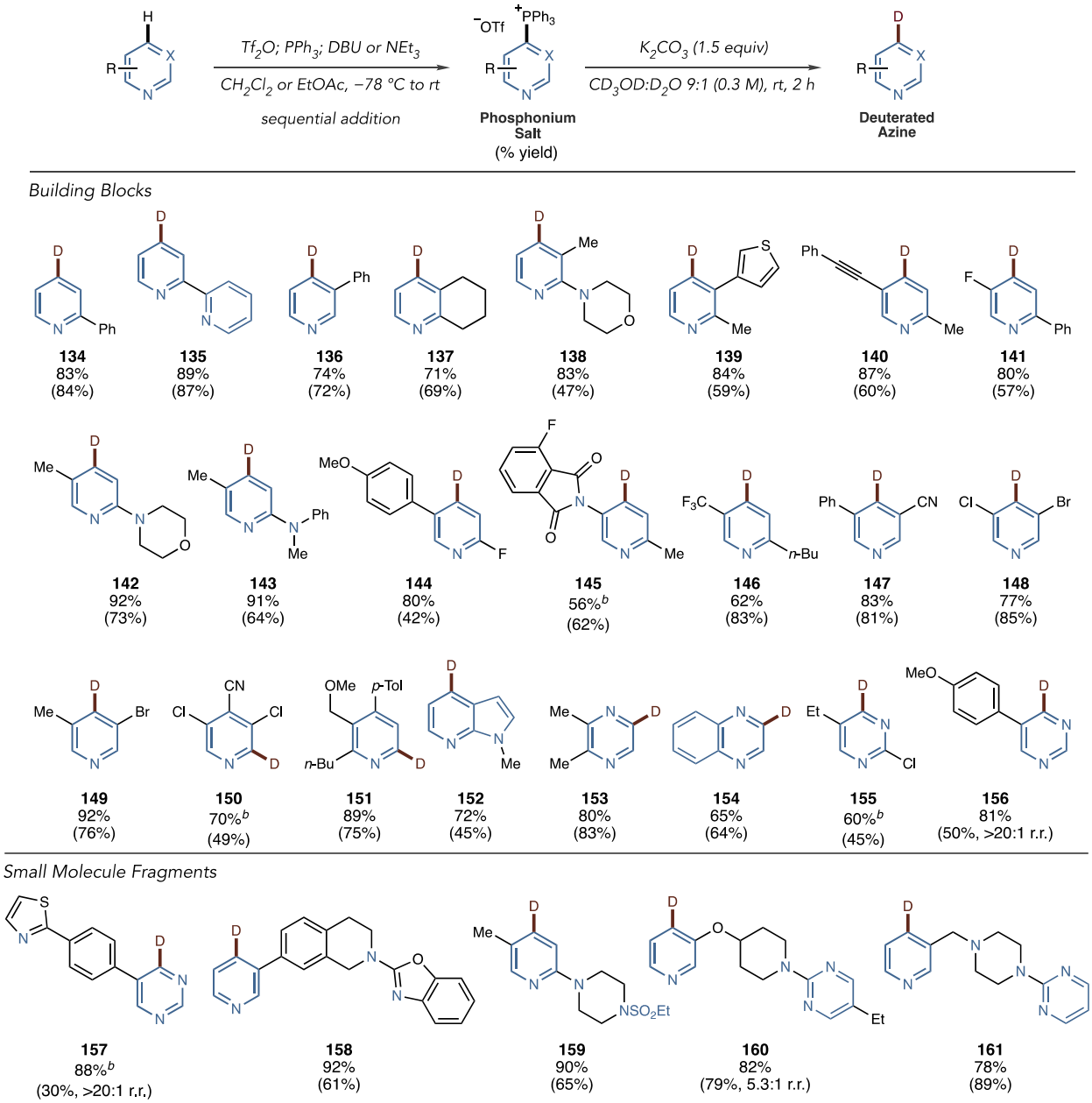


Entry	Nucleophile	Equivalents of Base	Solvent[a]	% Yield
1	Na_2CO_3	5	CD_3OD	38
2	Cs_2CO_3	5	CD_3OD	64
3	K_2CO_3	5	CD_3OD	76
4	K_2CO_3	3	CD_3OD	90
5	K_2CO_3	3	CD_3OD : D_2O 9:1	93
6[b]	K_2CO_3	1.5	CD_3OD : D_2O 9:1	94

[a]0.2 M concentration. [b]0.3 M concentration.

2.3 Deuteration Reaction Scope

With the optimized deuteration conditions in hand, we began to investigate the scope of the reaction on pyridyl building blocks. We found that monosubstituted, as well as 2,3- and 2,5-disubstituted pyridyl phosphonium salts worked well under these reaction conditions, giving exclusive 4-position deuteration with only traces of the C-H byproduct observed by ^{1}H NMR (**134-144**). We discovered that our reaction conditions using deuterated methanol were not suitable for substrates that could easily undergo transesterification. Therefore, we found that an alternative solvent mixture using D_2O:DMF 1:9 gave comparable yields for the deuterated pyridine when the reaction time was extended to 12 hours (**145**). Additionally, 3,5-disubstituted pyridines undergo the reaction protocol, including substrates containing halides, without forming a possible pyridyne intermediate (**147-149**). When the 4-position of the pyridine is blocked, the phosphonium is installed at the 2-position, leading to effective deuteration adjacent to the nitrogen atom (**150-151**). We also found that other azines building blocks were amendable to the reaction sequence, including azaindoles, pyrimidines, and pyrazines (**152-156**).



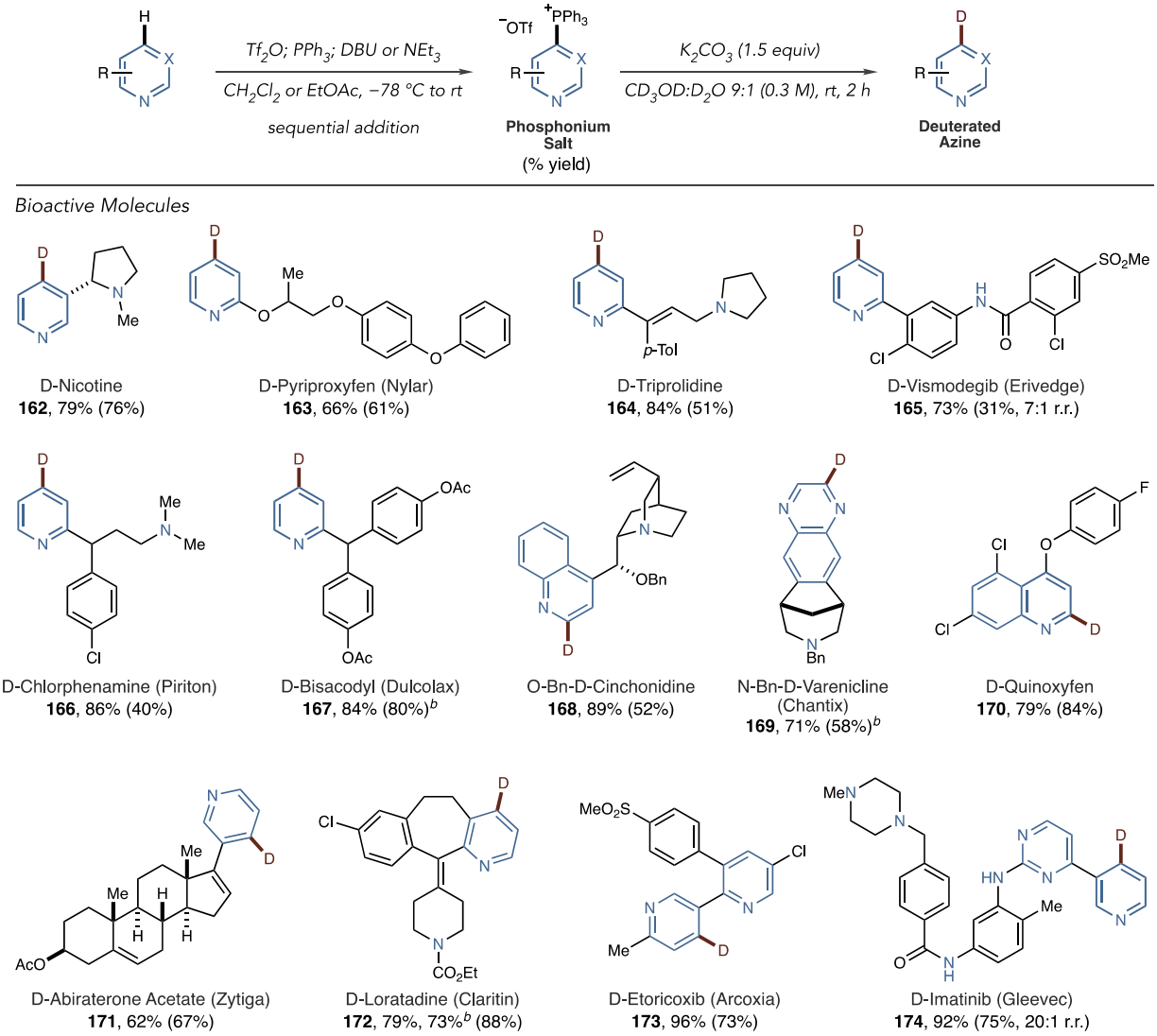
[a]Isolated yields of single regioisomers (unless stated) shown with yields of phosphonium salts in parentheses. [b]Run with K_2CO_3 (1.5 equiv), DMF:D_2O (9:1, 0.3 M).

Figure 2.12. Substrate Scope of the Azine Deuteration Protocol*a*

Small molecule fragments containing multiple reactive heterocycles and functional groups are common lead compounds in drug discovery. These substrates present a greater challenge due to their additional reactive functionality, especially for the phosphonium salt-forming step of the

protocol. Piperazines, thiazoles, and benzoxazoles were tolerated in the reaction sequence (**157**-**159**), and pyridines were selectively deuterated in the presence of 2-amino pyrimidines (**160**-**161**).

We then focused our efforts on applying the deuteration protocol to bioactive molecules, such as pharmaceuticals and agrochemicals (Figure 2.13). Deuteration reactions that can function on late-stage molecules are particularly attractive due to the ability to quickly and efficiently synthesize deuterated analogs directly from the parent drug.[47] These pharmaceutical and agrochemical molecules highlight the functional group tolerance and generality of the deuteration protocol due to their sophisticated structural motifs and adverse physical properties, notably decreased solubility in organic solvents. Nicotine, pyriproxyfen, triprolidine, vismodegib, and chlorphenamine function effectively in the deuteration protocol, installing the isotope at the 4-position of the pyridine with exclusive regioselectivity (**162**-**166**). Bisacodyl was deuterated by changing the reaction solvent to DMF:D_2O 9:1 to avoid methanolysis of the phenolic acetates, and the reaction time was extended to 12 h (**167**). Quinoxyfen and benzyl-protected cinchonidine and varenicline react effectively under the protocol with the deuterium introduced at the 2-position of the azine (**168**-**170**), and abiraterone acetate also gives the desired product in good yield (**171**). In Chirik's Fe-catalyzed HIE reaction, loratadine is deuterated at the 2- and 3- positions of the pyridine and highlights the unique 4-position selectivity observed using our protocol (**172**).[31] Etoricoxib and imatinib again highlight the unique selectivity of our protocol due to the heterobiaryl motifs in their structures. With etoricoxib, the reaction occurs on the 2,5-disubstituted pyridine exclusively (**173**), and imatinib is deuterated at the pyridyl 4-position with 20:1 selectivity over the pyrimidine (**174**).



[a]Isolated yields of single regioisomers (unless stated) shown with yields of phosphonium salts in parentheses. [b]Run with K_2CO_3 (1.5 equiv), DMF:D_2O (9:1, 0.3 M).

Figure 2.13. Bioactive Molecule Substrate Scope for the Deuteration Protocol*a*

The site-selectivity of our azine deuteration protocol is a beneficial aspect for drug discovery. Many current state-of-the-art HIE deuteration methods that are employed on complex molecules install multiple deuterium atoms, lack regiocontrol, and isotope incorporation varies. For producing the deuterated mass spectrometry standards frequently needed in metabolic studies, requiring greater than four deuterium atoms per molecule, these methods represent the benchmark

for useful protocol. However, designing a specific drug target using these methods is often problematic due to the imprecise nature of these types of reactions. Using a functional handle such as a halide to install the deuterium atom via deuterodehalogenation gives much more control over the regioselectivity and the isotope incorporation; however, installing a halide on a late-stage drug candidate can frequently prove impossible due to the sensitive functional groups present on drugs or drug candidates. Our method addresses these limitations by first installing the phosphonium salt regioselectively through a simple and mild protocol. Next, the phosphonium salt deuteration uses incredibly mild reaction conditions, exemplified by the broad functional group tolerance and general applicability to a range of complex pharmaceuticals in addition to building block molecules. Notably, deuterium incorporation is quantitative in all examples, providing a robust method to precisely synthesize a desired deuterated drug target.

2.4 Introduction to Tritiation

Tritium (^3H) is a radioactive hydrogen isotope and is routinely used in the pharmaceutical industry as a radiolabel (Figure 2.14).[2] Drug candidates are often tritiated to study the potency of the drug towards a specific target using radioligand binding assays. Additionally, before each drug becomes FDA-approved, it must also undergo comprehensive preclinical and clinical adsorption, distribution, metabolism, and excretion (ADME) studies. Tritium-labeled drug candidates are regularly used in ADME studies to assess the bioaccumulation, metabolism, metabolite production, toxicity profile, and covalent binding affinity. These labeled drug candidates are also used in ADME/mass balance (ADME/MB) studies to determine that complete drug excretion from the body is achieved. Lastly, radiolabeled drug candidates are essential tools for quantitative whole-

body autoradiography (QWBA), an imaging technique that determines the in situ locations of drugs in laboratory animals.

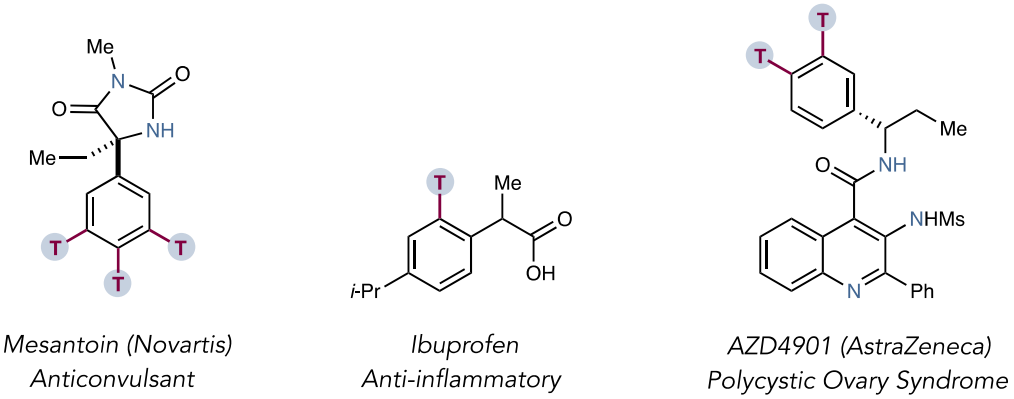


Figure 2.14. Examples of Tritiated Pharmaceuticals for ADME Studies

Tritium is installed through many of the same methods as deuterium, such as transition metal-catalyzed tritiodehalogenation and HIE reactions. Tritiated water (THO) stock solutions can be used as a tritium source; however, tritiated water solutions are heavily diluted by H_2O and, therefore, contain low isotopic purity. This decreased isotopic purity could then be transferred to the desired tritiated product when using this isotope source. Tritium gas (T_2) is the preferred source in industry due to high isotopic purity, safer handling, and the ability to reclaim unused tritium when the reaction is completed.[1,48] In Chirik's HIE protocol, switching D_2 for T_2 gas results in efficient tritiation of a range of bioactive molecules, delivering the high specific activities that are needed for practical use in industry (Figure 2.15, A). Macmillan's deuteration method, using D_2O as the isotope source, is not directly applicable to tritiation due to the lack of commercially available T_2O solution.[42] To address this limitation, they prepared stock solutions of T_2O from reacting T_2 gas and PtO_2 in *N*-Methyl-2-pyrrolidone (NMP) and used this high concentration T_2O solution in their protocol to access tritiated drug molecules (Figure 2.15, B). Similar to their

deuterium counterparts, tritiation by HIE reactions label the molecule at numerous positions and is often not predictable. However, the position of the tritium atom on the scaffold can be important for the purposed of an ADME study when tracking a metabolite through the body.[2,49] Additionally, the tritium atom should be placed at a non-metabolically active position, reducing the chance that the radiolabel is oxidized off of the drug. However, it is often impossible to predict the location of oxidation from drug to drug. Therefore, a protocol to install tritium radiolabels regioselectively at new positions not often achieved by current methods would be an important advancement in the area.

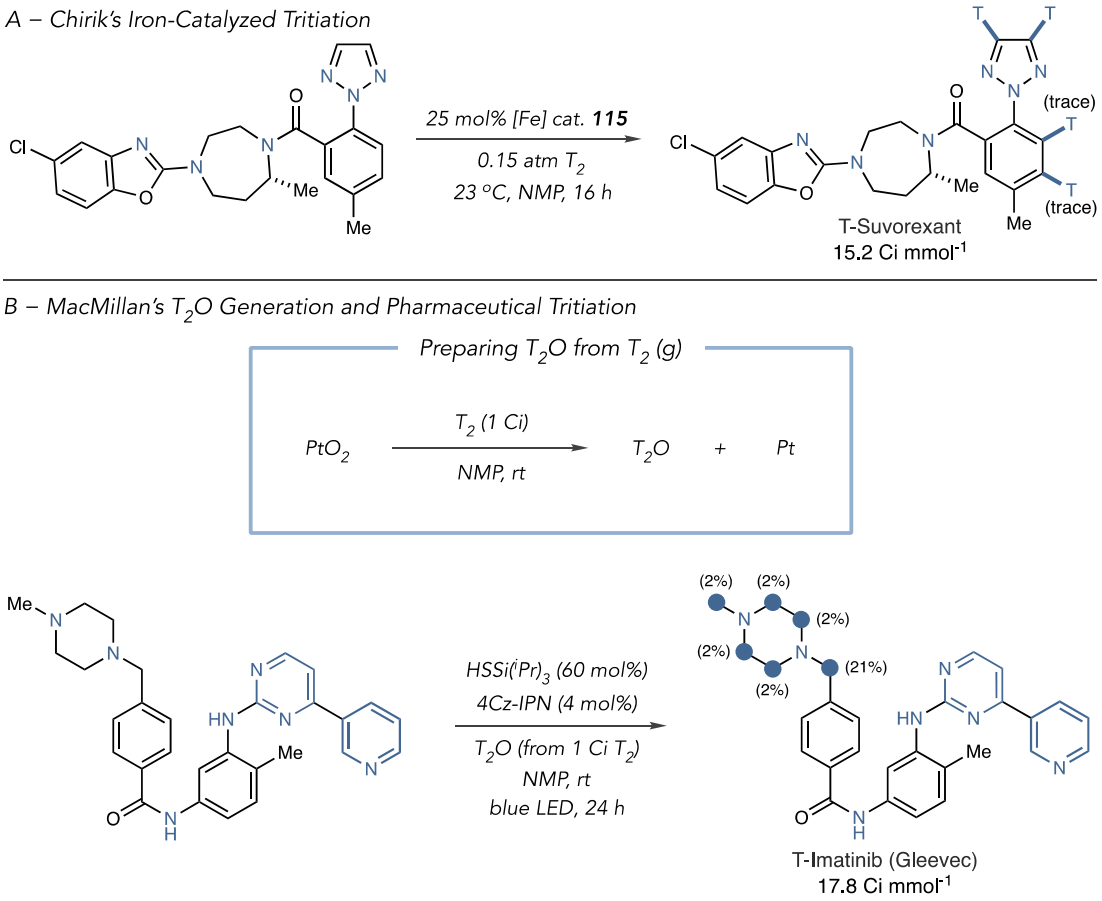


Figure 2.15. Tritiation of Pharmaceuticals Using HIE Protocol with T_2

2.4 Development of Tritiation Protocol

We began investigating whether phosphonium salts could be used to tritiate azines and pharmaceuticals using tritium gas as the isotope source. Due to the specialized equipment and additional safety requirements needed to handle tritium gas, however, we chose to use D_2 gas as a surrogate to screen the reaction conditions. We began by examining heterogeneous catalysis to install the deuterium atom, and all efforts to deuterate through the hydrogenolysis of the phosphonium salts using D_2 failed to form the desired product.

We then began focusing on our original fragmentation pathway to determine if it could be used to install tritium atoms. The difficulty in using this pathway, however, is that a mildly-acidic isotope source is needed in the reaction (Figure 2.16, A). Unlike deuterated methanol, tritiated methanol is not commercially available, so we began considering a method by which high concentration MeOT could be synthesized using a transition metal-catalyzed HIE reaction between MeOH and T_2 (Figure 2.16, B).

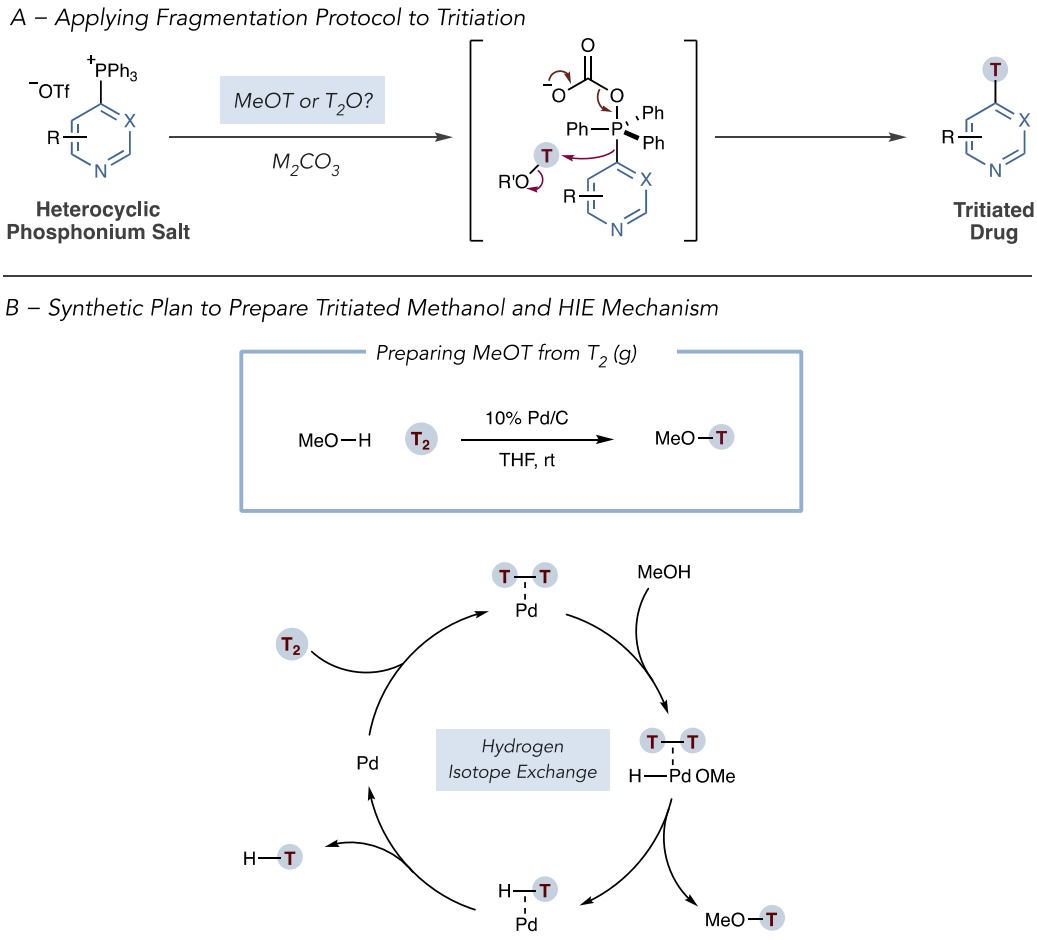


Figure 2.16. Synthetic Approach to Translate Fragmentation Pathway to Tritiation

Using D_2 gas as a surrogate for T_2, we found that stirring MeOH in THF with 10% Pd/C under 1 atmosphere of D_2 produced the desired MeOD product as a high concentration solution in THF (Figure 2.17).[50] We took this MeOD solution forward into a slightly modified set of fragmentation conditions and observed modest yields and deuterium incorporation onto the azine product (**175**).

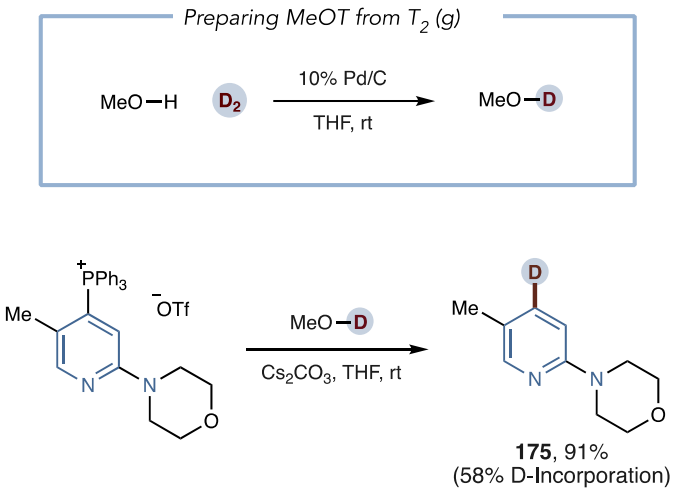


Figure 2.17. HIE Reaction Forming MeOD and Subsequent Deuteration of Phosphonium Salt

2.5 Tritiation Reaction Scope

Through a collaboration with Merck, we began testing our tritiation protocol using T_2 gas in order to show that this method would function effectively in a radiolabeling laboratory. A marked difference to using D_2 is that the pressure of T_2 gas within the reaction flask is lowered to 0.17 atmospheres; therefore, we considered it essential to show that our HIE procedure performed well under these conditions. Experimentally, we found that stirring MeOH with Pd/C in THF under 0.17 atmospheres of T_2 at room temperature for 12 hours worked well as a general procedure (Figure 2.18). The Pd/C catalyst was then filtered off, and the phosphonium salt and carbonate nucleophile were added to the solution to efficiently produce a tritiated product.

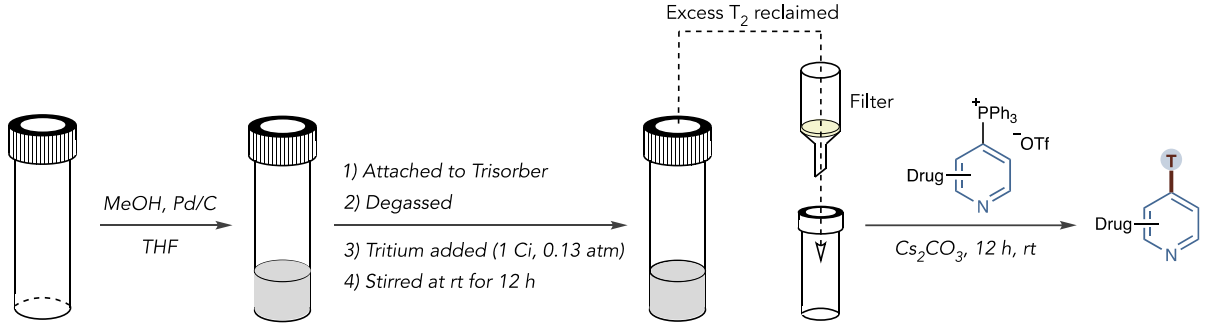
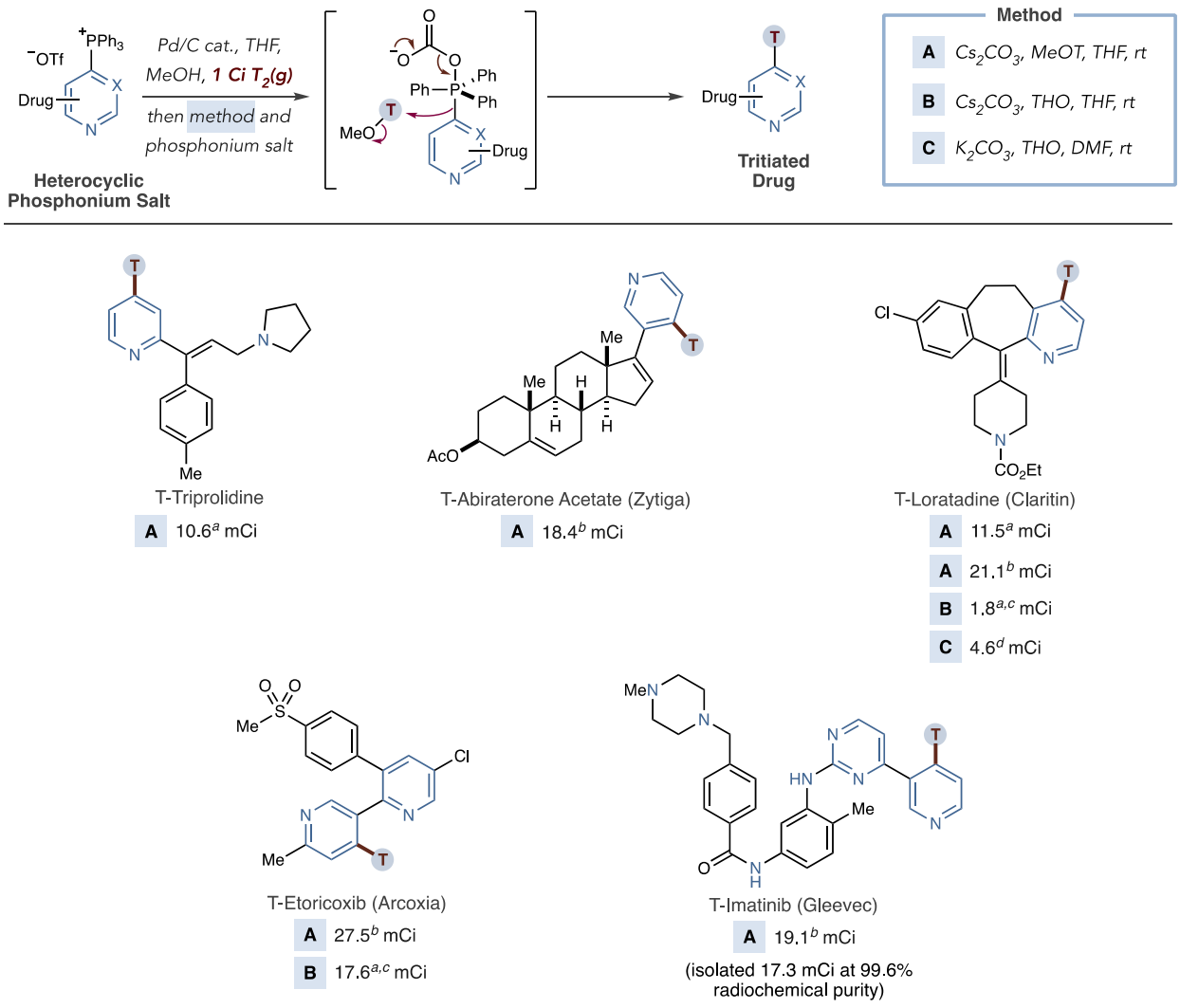


Figure 2.18. General Workflow for Pharmaceutical Tritiation Protocol

We chose to apply these reaction conditions to a range of phosphonium derivatives of pharmaceuticals containing representative structures that a medicinal chemist might encounter. Our general protocol produced tritiated drug molecules with radiochemical yields and specific activities well within the range needed for ADME studies (Figure 2.19). Triprolidine and abiraterone acetate were tritiated using the MeOT solution generated from our HIE procedure, giving respectable radiochemical yields (Method A). The loratadine phosphonium salt was tritiated using benchtop Cs_2CO_3; a new bottle of Cs_2CO_3 was also used and found to give a higher radiochemical yield than Cs_2CO_3 stored on the benchtop, likely due residual water content. A stock solution of THO was also successful in tritiating loratadine in DMF, albeit in lower radiochemical yield, providing an additional set of conditions for molecules that are poorly soluble in THF (Method C). Additionally, the etoricoxib phosphonium salt was tritiated in high radiochemical yield using THO in THF, confirming that using stock solutions of THO in our optimized protocol can be a highly effective tritiation strategy (Method B). Lastly, a 20:1 mixture of imatinib phosphonium salt regioisomers were tritiated using the MeOT protocol, with the radiochemical yield closely matching an isolated sample of the radiopure product. These results show that azinyl phosphonium salts can be applied to tritiate pharmaceuticals in radioisotope laboratories under mild conditions using THO stock solutions or T_2 gas for applications that warrant more significant specific activity.



MeOH HIE protocol: MeOH (10 µL), 6.5 mg Pd/C, 1.0 Ci T_2 (0.13 atm). 8.3–29.1 mg of phosphonium salts used in this study. Reported mCi values calculated from the crude mCi corrected for radiochemical purity. [a]Benchtop Cs_2CO_3 used. [b]Fresh bottle of Cs_2CO_3 used. [c]Using 500 mCi THO at 50 Ci/cc. [d]Using 150 mCi THO at 50 Ci/cc.

Figure 2.19. Substrate Scope for the Tritiation of Pharmaceuticals via Azinyl Phosphonium Salts

2.6 Conclusion

In this chapter, the current state-of-the-art deuteration and tritiation methods are discussed, and a new approach using azinyl phosphonium salts for hydrogen isotope incorporation is presented. Our protocol uses the C-H bond precursors, installing a phosphonium salt directly and regioselectively, and is then subjected to fragmentation conditions to provide the deuteration or tritiated product. Additionally, we have developed an HIE method to synthesize high concentration MeOT directly from T_2 gas and methanol using Pd/C as the catalyst. This method may prove useful in future applications requiring generation of high concentration MeOT or T_2O.

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CHAPTER THREE

PYRIDINE-PYRIDINE CROSS-COUPLING VIA DEAROMATIZED RADICAL INTERMEDIATES

3.1 Introduction

Methodology for forming new C–C bonds, in particular directly from the C–H precursor, are exceptionally important reactions for synthetic chemists. The Minisci reaction is a popular reaction for achieving these bond constructions on heteroarenes.[1–6] These reactions couple a variety of carbon-centered radicals, produced from convenient and readily-accessible radical precursors, to a range of heteroarenes directly from their C–H bonds without the need for pre-functionalization (Figure 3.1).

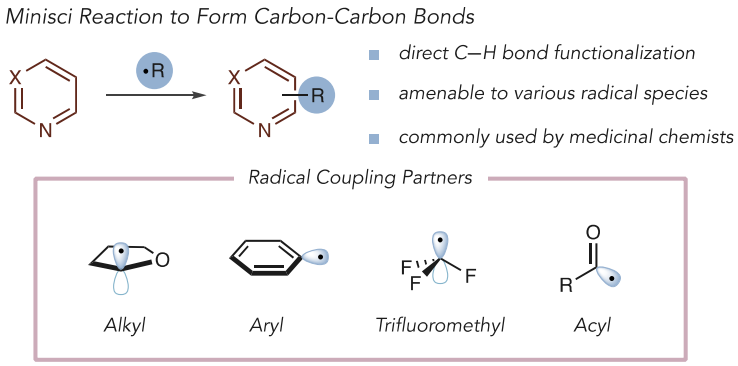


Figure 3.1. The Minisci Reaction to Form Carbon-Carbon Bonds and Common Radical Species

Adding radical species to electron-deficient heteroarenes was initially investigated by Lynch and other groups in the 1960s (refs from phipps review), where they found that phenylation of pyridines gave regioisomeric mixtures of products (Figure 3.2, A).[7,8] In these initial studies, a preference for C-2 addition was observed when the reaction was run in the presence of acetic acid due to favorable radical addition to a pyridinium intermediate.[9] In 1968, Minisci and co-workers

reported the addition of alkyl radicals to the 2- and 4-position of pyridines and quinolines in good yields under acidic conditions with no 3-position regioisomer formed.[10] In the years following, Minisci published a series of papers outlining a protocol that is now commonly referred to as "the Minisci reaction", using a silver catalyst and persulfate to facilitate radical decarboxylation and form alkyl radicals that add to heteroaromatic bases (Figure 3.2, B).[11,12] Due to the ability to functionalize directly from the C–H bond, considerable effort has been devoted to increasing the regioselectivity of the reaction, as well as expanding the radical precursors amenable to the synthetic approach.

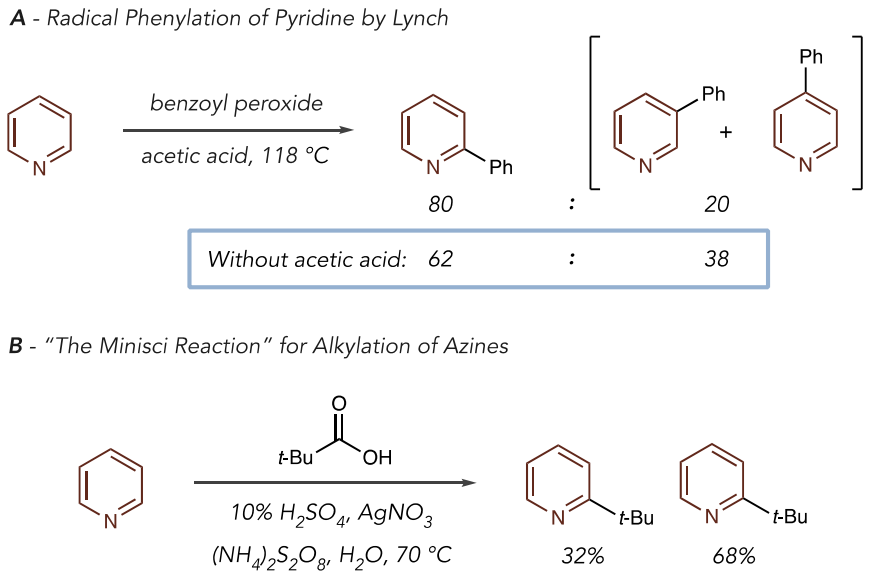


Figure 3.2. Seminal Discoveries of Radical Additions to Azines by Lynch and Minisci

In modern chemistry, the Minisci reaction has been widely adopted by medicinal chemists since the reaction can be applied directly to pharmaceutically-relevant scaffolds.[2] Notably, the reaction functions effectively on molecules containing Lewis-basic atoms, such as azines, contrasting transition metal-catalyzed cross-coupling methods, where azines can often coordinate to the metal and interfere with catalytic processes.[13–18] Additionally, protecting groups are not

regularly needed due to the fast rate of radical attack on the heteroarene compared to the rate of potential side-reactions. While a proven and versatile reaction, there are several recognized deficiencies in the Minisci reaction, most notably production of regioisomers, low yields, and incomplete conversions. The regioisomeric mixture is dependent on the azine and is also contingent on the radical species that is being added. Production of regioisomeric mixtures presents a challenge in the purification process due to similar physical properties, especially when applying the protocol on complex scaffolds. Nevertheless, rapid access to valuable scaffolds directly through C–H functionalization of the heteroarene precursor frequently outweighs these downfalls.

Due to the Minisci reaction's ability to be applied at a range of stages of the drug discovery process, it is commonly used by medicinal chemists to introduce a variety of alkyl groups onto azines on biologically-active molecules. Using an aldehyde as an alkyl radical precursor, Sawada and co-workers used a Minisci reaction to install an ethyl group at the 4-position of the quinoline of camptothecin en route to the anti-cancer agent, Irinotecan (Figure 3.3) (pg1138 Duncton).[19] Sawada then used the Minisci strategy to further elaborate camptothecin with a variety of carbon centered radical species to rapidly access a range of quinoline scaffolds and conduct structure-activity relationship (SAR) studies of the analogs.[20,21]

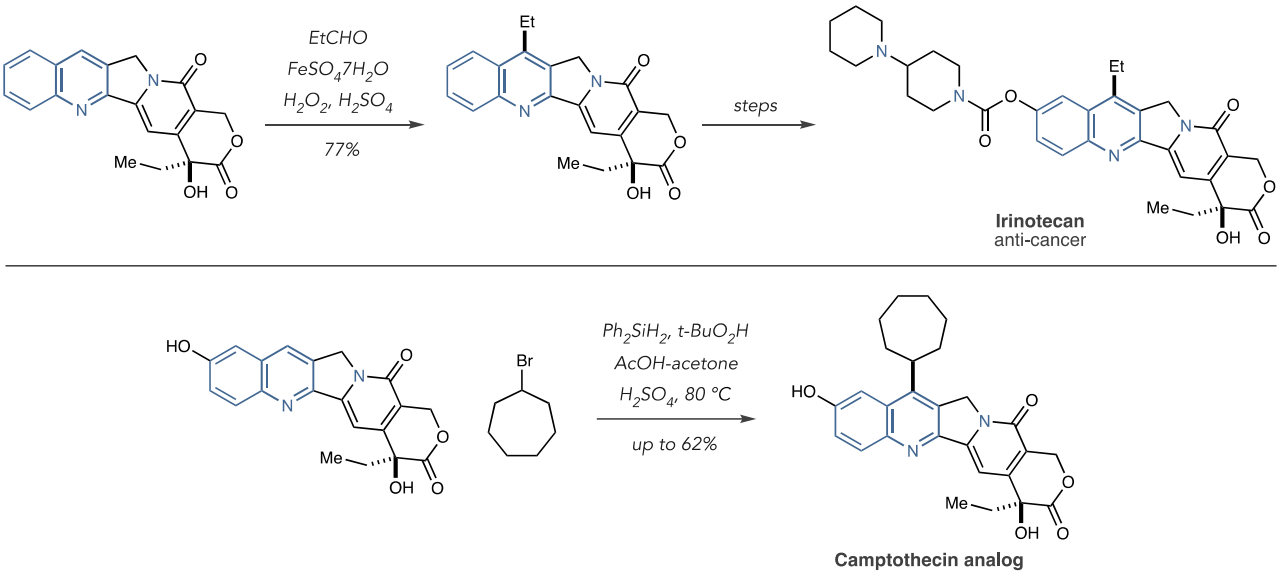


Figure 3.3. Minisci Reactions to Derivatize Camptothecin

As one of the previously mentioned deficits of the Minisci protocol, these types of reactions can produce multiple regioisomers due to multiple reactive positions on the scaffold. However, this non-selective feature can also prove beneficial to medicinal chemists. Jain and co-workers used the Minisci reaction to develop new quinoline-containing molecules with anti-tuberculosis activity.[22–25] Alkylating lepidine through a classical Minisci protocol, using a cycloalkyl carboxylic acid radical precursor, resulted in forming a mixture of the desired 2-alkyl product along with the di-addition 2,8-disubstituted quinoline (Figure 3.3). In this study, (**176**) showed an increased biological profile compared to the mono-addition lepidine analog (**177**), leading to a serendipitous outcome. In many cases, however, separating multiple regioisomers is not always possible, and this selectivity problem leads to decreased yields for the desired isomer.

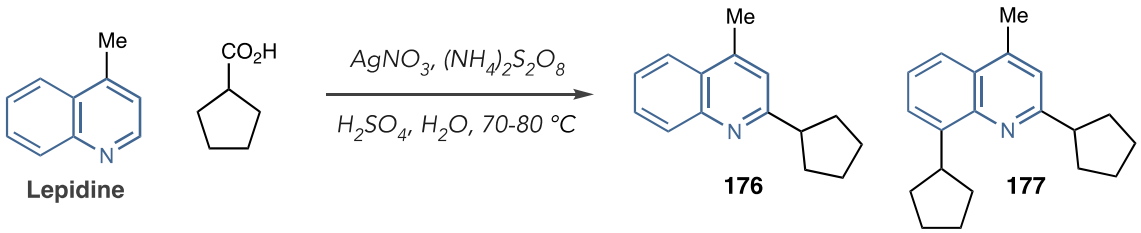


Figure 3.3. Alkylation of Lepidine and Resulting Di- and Tri-Substituted Analogs

Besides simple alkyl groups, the Minisci reaction can also install fluoroalkyl groups, a valuable motif for medical chemists.[26–28] Installing these groups onto biologically-active molecules can often have profound effects on a drug's physical and chemical properties. The fluorine atoms induce a change in metabolic stability, solubility, and biological activity of drug molecules. A number of trifluoromethylation strategies have emerged in recent years including a report by Yamakawa and co-workers.[29] They have developed trifluoromethylation procedures based on the Minisci strategy to install trifluoromethyl groups on pyridines, pyrimidines, and pyrazines (Figure 3.4).

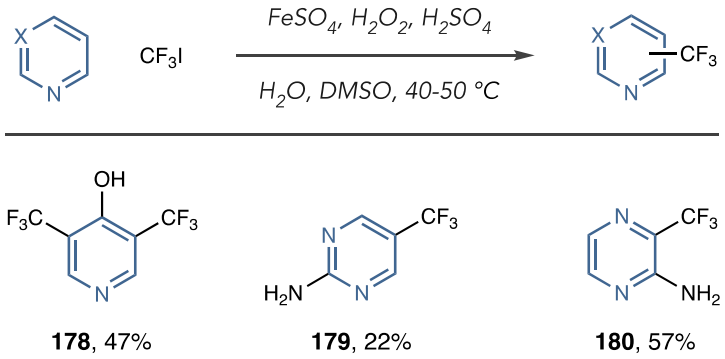


Figure 3.4. Azine Trifluoromethylation Reaction Developed by Yamakawa

While the traditional Minisci reaction relied on carboxylic acids are the radical precursors, several new precursors have been developed. The Molander group has developed conditions to alkylate heteroarenes using alkyl trifluoroborates as radical precursors through a Minisci reaction. This protocol proceeds under mild conditions, using $Mn(OAc)_3$ to catalyze radical formation (Figure 3.5).[30]

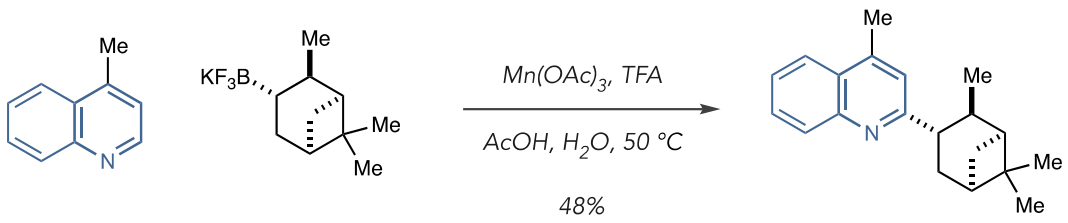


Figure 3.5. Minisci Reaction Using Alkyl-BF_3K Salts as Radical Precursors

The emergence of photoredox catalysis has led to the recent development of the photocatalytic generation of carbon radicals under mild conditions (Figure 3.6, A). MacMillan and others have shown that generating alkyl radicals via photoredox catalysis and using them in a Minisci reaction is an effective strategy for elaborating azines.[31–34] The benefits of these protocol include using mild reaction conditions and C–H precursors for generating the radical species. Outside of simple alkyl radicals, MacMillan has expanded the scope with CF_3I as a radical precursor allowing for trifluoromethylation under mild photoredox conditions (Figure 3.6, B).[35] Furthermore, Dirocco and co-workers disclosed a Minisci reaction for late-stage C–H functionalization using *t*-butylperacetate to form methyl radicals which add to azines and produce valuable methylated products, such as a trifluoromethylated camptothecin analog (**185**) (Figure 3.6, C).[36]

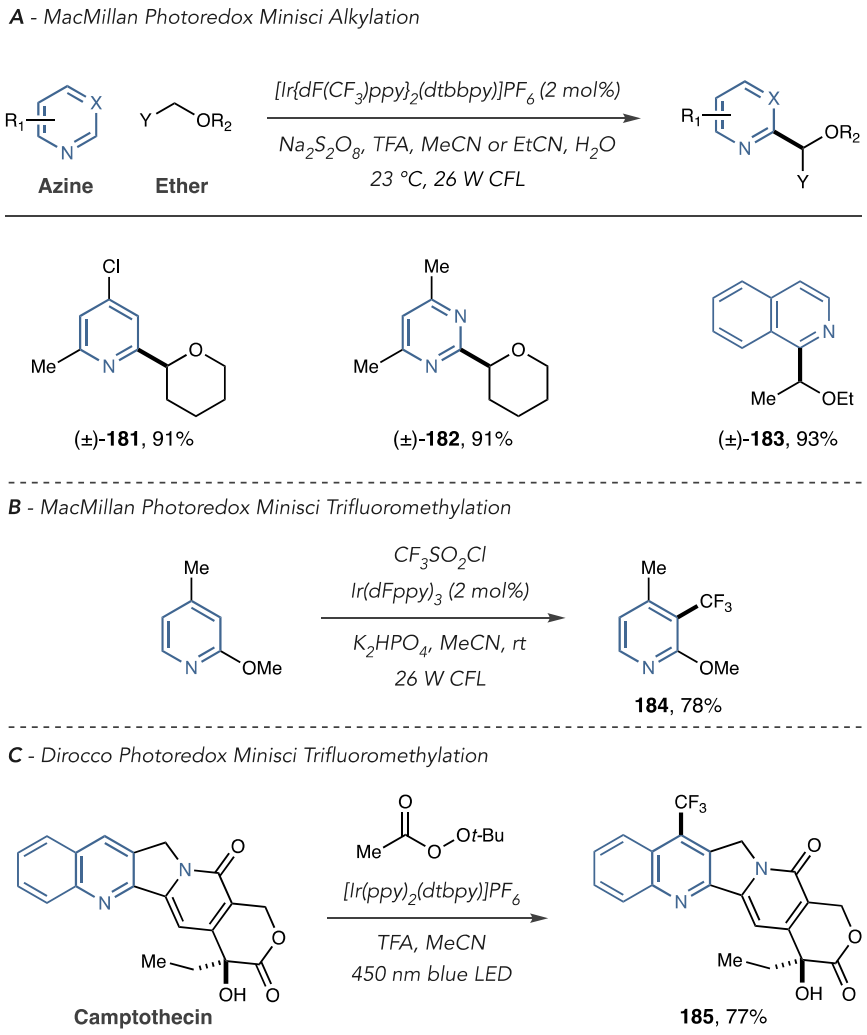


Figure 3.6. Examples of Photoredox-Mediated Minisci Reactions

The Minisci reaction is typically associated with the addition of alkyl radicals to the heteroarene, while the addition of sp^2 radicals has proven more difficult through traditional Minisci conditions. Therefore, synthesizing biaryl products through the Minisci reaction using aryl radicals has drawn substantial interest in the field. Employing aryl carboxylic acids, Minisci's oxidative decarboxylation conditions fail to produce desired pyridine **186** (Figure 3.7).[37] In 2015, Su and co-workers established modified conditions for Minisci-type arylation of pyridines using aryl

carboxylic acids as the radical precursors; however, elevated temperatures and a significant excess of TFA and azine are needed in order to promote radical addition.[38] Additionally, mixtures of 2-, 3-, and 4-position regioisomers are often produced through these methods (**187-189**).

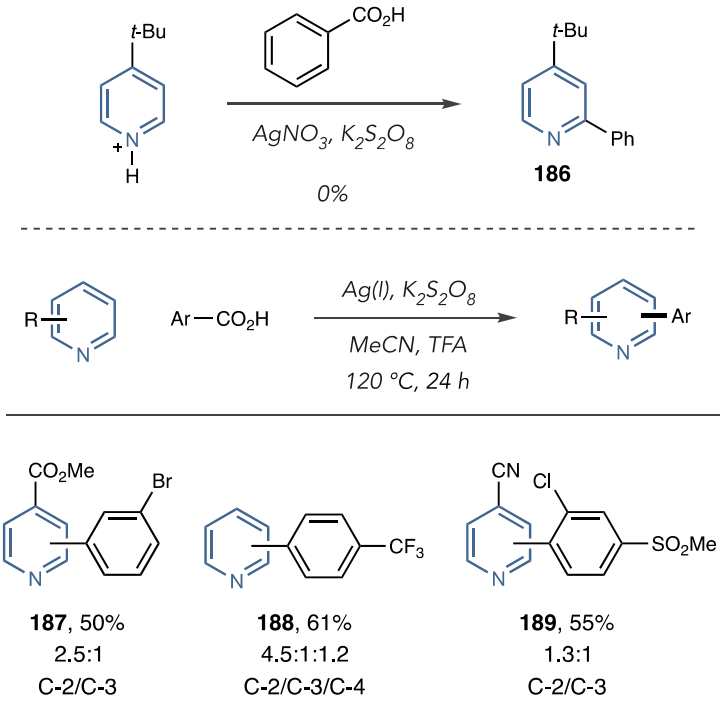


Figure 3.7. Azine Arylation through a Minisci Reaction

A significant advancement in aryl Minisci chemistry was Baran's development of a mild method using boronic acids to generate aryl radicals in the presence of silver nitrate, trifluoroacetic acid (TFA), and potassium persulfate oxidant (Figure 3.8).[37] This reaction efficiently arylates a range of azines, including pyridines, quinolines, and diazines using aryl boronic acids as the coupling partner (pg17 phipps). However, the reaction produces mixtures of regioisomers, a recurring downfall for the Minisci protocol (**190-191**).

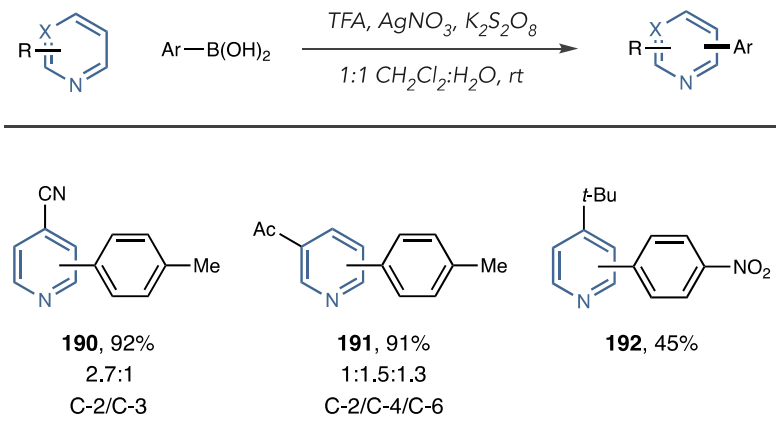


Figure 3.8. Baran's Azine Arylation Using Boronic Acid Radical Precursors

Despite the prevalence of both the Minisci reaction as well as bis-azines in the pharmaceutical industry and in academic research, no pyridine-pyridine couplings have been reported using the Minisci manifold. In fact, Baran's report did not show azinyl boronic acid radical precursors, and using electron-deficient aryl boronic acids resulted in decreased yields (**192**). Additionally, Xue and co-workers disclosed a photoredox procedure using aryl diazonium salts as radical precursors to arylate azines; however, this protocol was not amendable to azinyl diazonium salts.[39] Various factors can justify the unfavorable nature of a pyridine-pyridine Minisci reaction; first, the electron-deficient character of the pyridyl radical is electronically mismatched with the electron-deficient π-system of the acceptor pyridine, making the reaction kinetically unfavorable. Additionally, Minisci reactions are often promoted through Brønsted acid activation forming a more reactive pyridinium ion, only increasing the electronic incompatibility of the donor and acceptor pyridines (Figure 3.9, A). Second, obtaining successful cross-selectivity in the reaction would also be a significant challenge because pyridyl radicals could react with their radical

precursor at rates comparable to adding to the desired acceptor pyridine (Figure 3.9, B). These challenges have thus far not been addressed to allow heterobiaryl synthesis through Minisci reactions, and the development of such a methodology would be valuable.

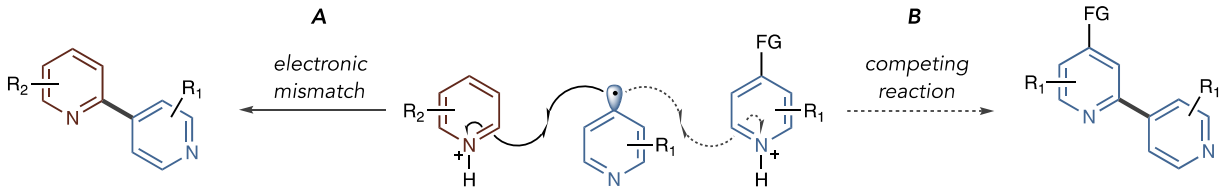


Figure 3.9. Challenges in Achieving a Pyridine-Pyridine Minisci Coupling

In summary, the Minisci reaction is a valuable synthetic process for constructing C–C bonds via a carbon-centered radicals and C–H precursors. However, the reaction commonly produces mixtures of *ortho*-, *meta*-, and *para*-regioisomers particularly on electron-deficient pyridine acceptors, severely complicating the purification process and yield. Additionally, azinyl radical precursors are not amenable to the reaction protocol, which limits the construction of valuable heterobiaryl scaffolds. Therefore, alternatives to the Minisci reaction to address these limitations could have a significant impact on the field.

3.2 Development of Cross-Coupling

Our group became interested in accessing single-electron pathways of pyridyl phosphonium salts. We had previously shown that phosphonium salts could perform as pseudohalides for transition-metal catalyzed cross-couplings, so we began our study by considering if the phosphonium ion could also behave similarly to pyridyl halides concerning single-electron reduction to form pyridyl radical intermediates (Figure 3.10, A).[40,41] We hypothesized that single-

electron transfer (SET) to a phosphonium salt would produce a pyridyl radical (**193**) that could be intercepted by a borylation reagent to furnish valuable, borylated pyridine **194**. The Li and Jiao groups hypothesized that a persistent boryl radical (**195**) forms when 4-cyanopyridine and diboron reagents, such as bis(pinacolato)diboron (B_2pin_2), react (Figure 3.10, B).[42,43] Jiao then showed that aryl radicals can then react with this persistent boryl radical to produce borylated arenes (**196**) (Figure 3.10, C).

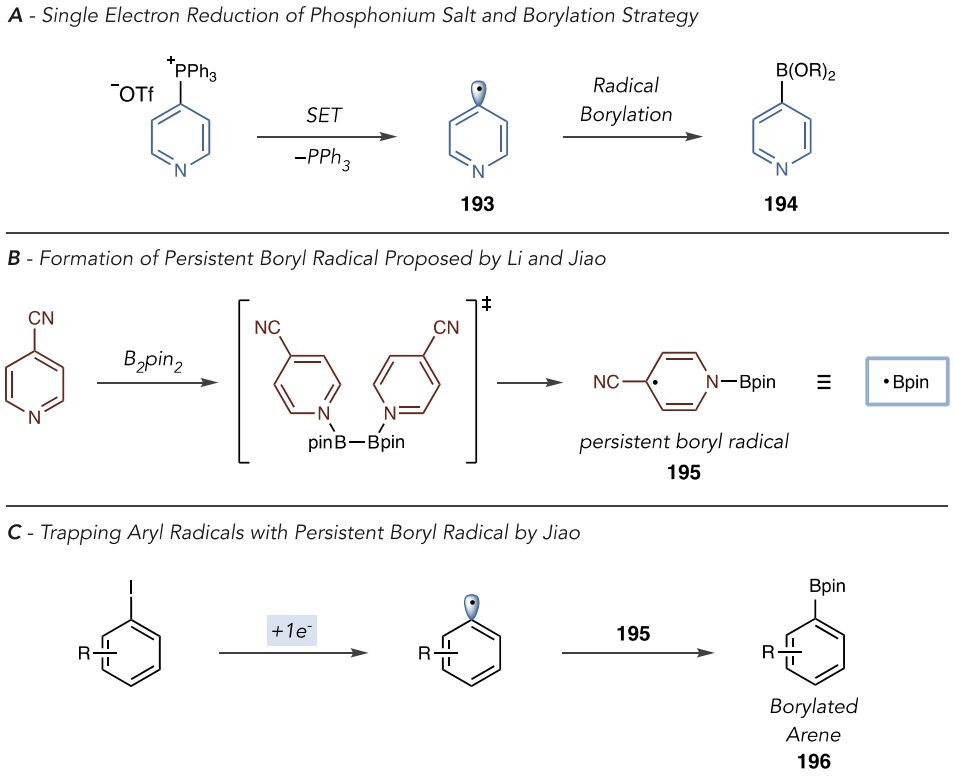


Figure 3.10. Proposed Borylation Strategy Using Persistent Boryl Radical Intermediate

With the idea of using persistent boryl radical **195** as a borylating reagent, the reduction potential of 2-phenylpyridine triphenylphosphonium salt **197** was measured to be $E_{redp/2}$ = –1.51 V vs. SCE, well within the reduction range of conventional photoredox catalysts such as Ir(ppy)$_3$ ($E_{1/2}$ = –1.71 V vs. SCE) using *i*Pr$_2$EtN as a sacrificial reductant (Figure 3.11). We proposed that

following single electron reduction and expulsion of PPh_3, pyridyl radical **198** could react with the putative persistent boryl radical forming a borylated pyridine (**199**). When running this reaction, however, no borylated products were detected; instead, the 2,4'-bipyridine product (**202**) formed with exclusive regioselectivity. Surprisingly, based on our proposed catalytic cycle, running the reaction in the absence of photocatalyst, or the absence of photocatalyst and light did not affect the formation of **202**. Shortly after this discovery, the Jiao group revised the identity of the **195** from a boryl radical to a delocalized radical that predominantly resides in the pyridine ring of the 4-cyanopyridine-Bpin species.[44] They also suggested that this species may be able to undergo single electron transfer, and the Li group showed a variety of transformations using these intermediates for carbon-carbon bond formation on cyanopyridines.[45–47] We hypothesized that 4-cyanopyridine-Bpin species **195** might be capable of reducing the pyridyl phosphonium salt to pyridyl radical **198** that could then react with activated pyridinium **201** in a Minisci-type radical addition process, forming the 2,4'-bipyridine product **202**.

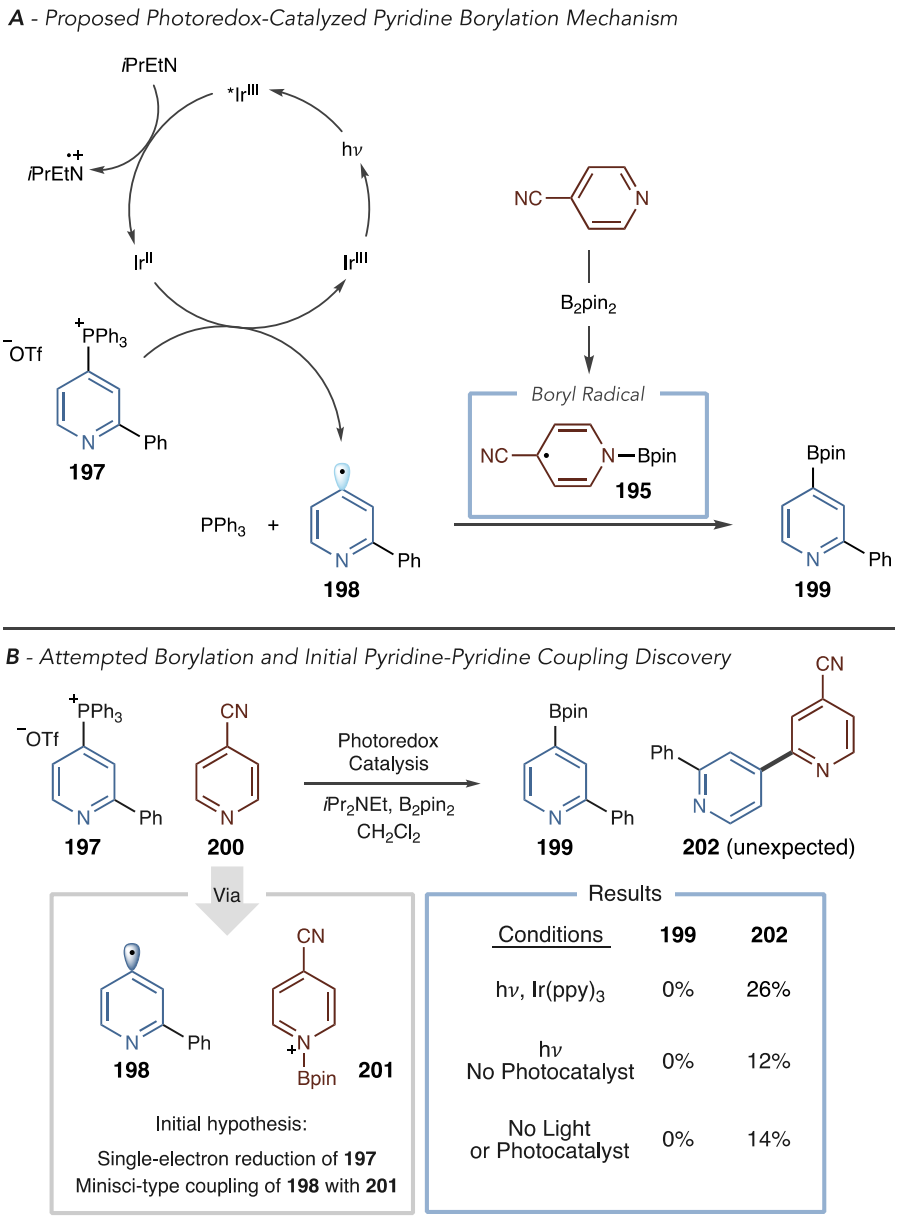


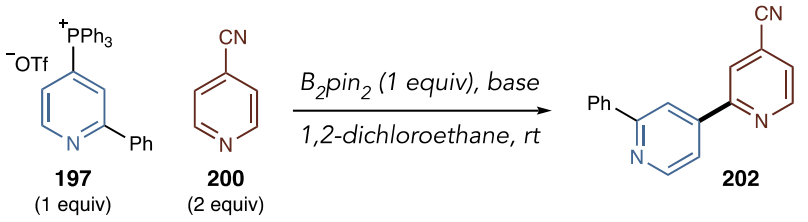
Figure 3.11. (**A**) Proposed Mechanism for Pyridyl Borylation. (**B**) Initial Results for Pyridine-Pyridine Coupling

3.3 Reaction Optimization

After this serendipitous discovery, we began optimizing the reaction conditions using the 2-phenylpyridine phosphonium salt **197** and 4-cyanopyridine **200** as the coupling partners (Table 3.1). Raising the reaction concentration to 0.2 M and extending the reaction time to 36 hours both

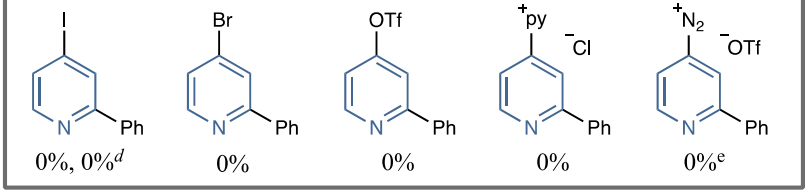
led to slight increases in yield (entry 1-3). The reaction does not function in the absence of B_2pin_2, leaving unreacted phosphonium salt and cyanopyridine (entry 4). More sterically hindered bases, such as tetramethylpiperidine (TMP), also work in the reaction, albeit in lower yield (entry 5). Most notably, changing the base to NEt_3 increased the reaction yield to near quantitative (entry 6), and the efficiency decreases significantly when no base is present (entry 7). Lastly, reducing the equivalents of NEt_3 to 1.25 did not have a negative impact on the product yield (entry 8). With these optimized conditions, we investigated whether other common radical precursors were amenable to the reaction. Pyridyl halides, triflates, and pyridiniums failed to produce the desired product, and the pyridyl diazonium salt rapidly decomposed under the reaction conditions. Surprisingly, none of the desired product formed even when photoredox conditions known to reduce pyridyl iodides to the pyridyl radicals were applied to the system, further highlighting the unique reactivity of phosphonium salts as the coupling partners.[48,49]

Table 3.1. Pyridine-Pyridine Coupling Reaction Optimization



entry	base (equiv)	time (h)	concentration (M)	% **202**[a]
1	*i*Pr$_2$NEt (2.5)	8	0.1	14
2	*i*Pr$_2$NEt (2.5)	8	0.2	26
3	*i*Pr$_2$NEt (2.5)	36	0.2	34
4[b]	*i*Pr$_2$NEt (2.5)	36	0.2	0
5	TMP (2.5)	36	0.2	16
6	NEt$_3$ (2.5)	36	0.2	99
7	none	36	0.2	26
8	NEt$_3$ (1.25)	36	0.2	97

Other radical precursors[c]



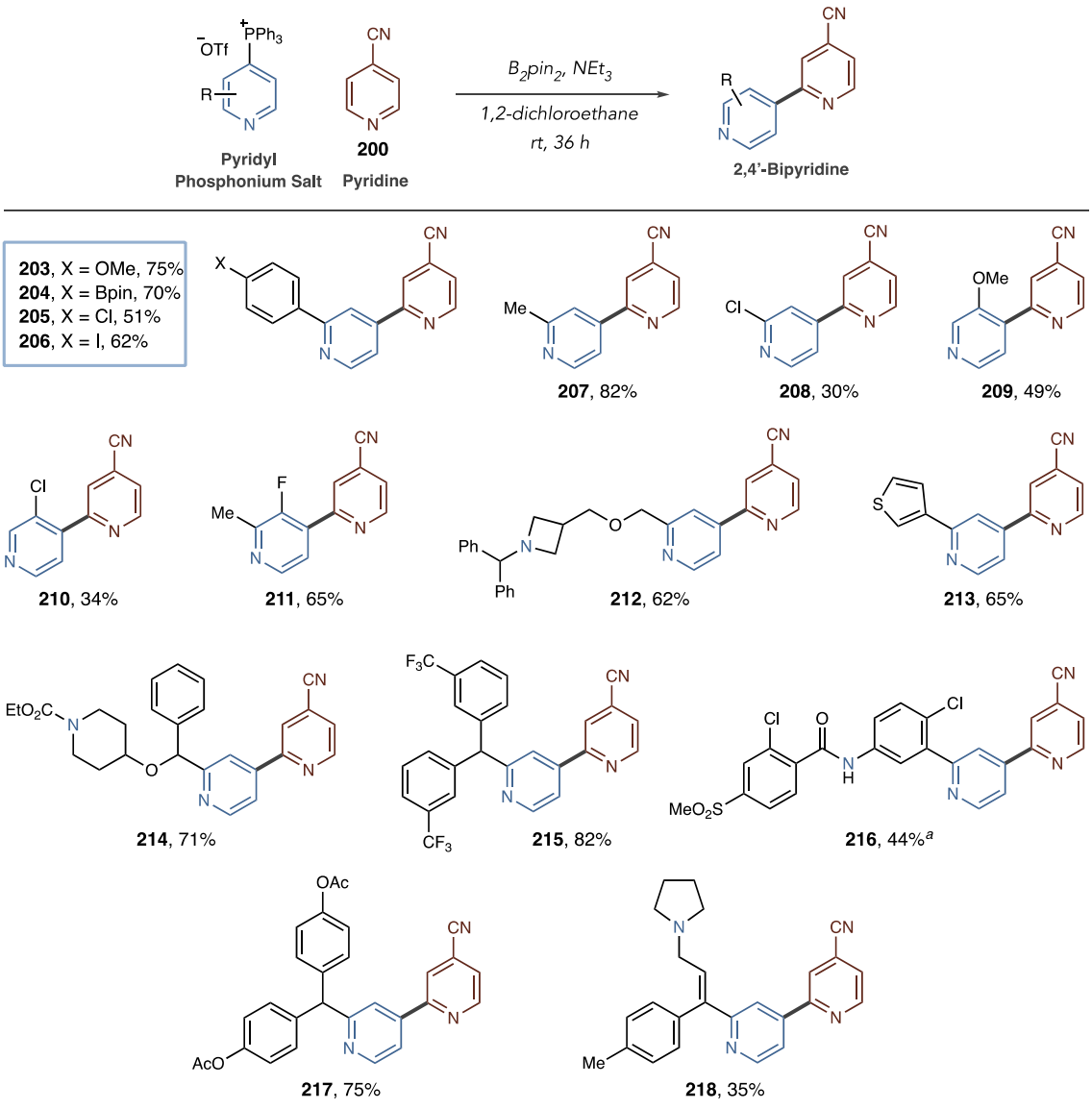
0%, 0%[d] | 0% | 0% | 0% | 0%[e]

[a]Yields Determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [b]B$_2$pin$_2$ omitted from the reaction. [c]Radical precursors (1 equiv) used in place of phosphonium **1a**. [d]Reaction conditions: Ir(ppy)$_3$ (1 mol%), iodopyridine (1.0 equiv), **2** (2.0 equiv), B$_2$pin$_2$ (1 equiv), NEt (1.25 equiv), 1,2-dichlorethane (0.2 M), 34-W Kessil blue LED, rt, 36 h. [e]Diazo decomposed under entry 7 conditions.

3.4 Reaction Scope

We next began investigating the scope of the coupling protocol (Figure 3.12). Beginning with the heteroaryl phosphonium salt scope, a variety of 2-aryl substituents on the phosphonium salt functioned effectively, as well as a 2-methyl group (**203**-**207**). A 2-chloro substituent also worked, albeit in a lower yield (**208**). Functional groups in the 3-position also gave the bipyridine product in moderate yields, including a 2,3-disubstituted fluoropyridine (**209**-**211**). However, bulky 3-position substituents and diazine-derived phosphonium salts did not work in the reaction to give the heterobiaryl product. Azetidine and heterocyclic groups are tolerated in the reaction without

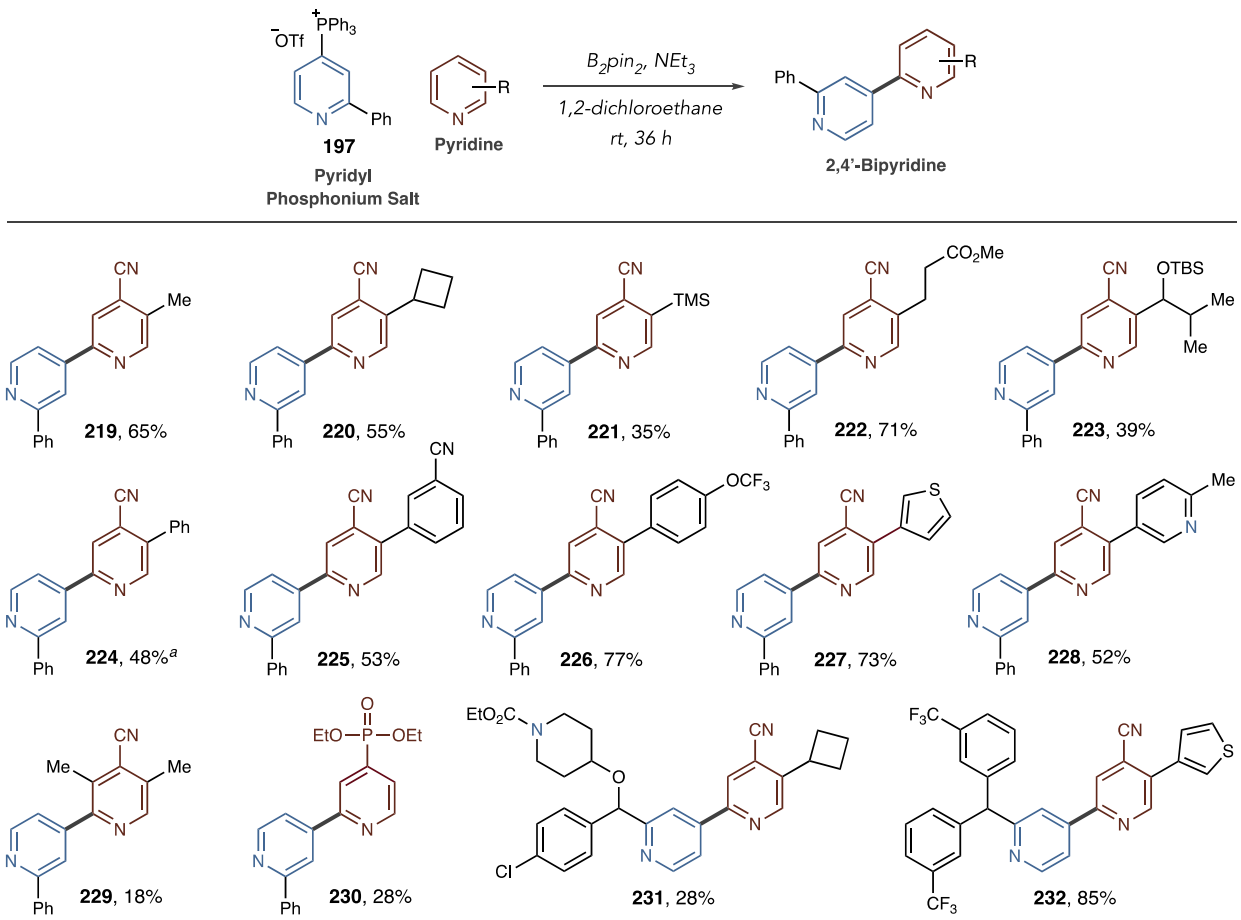
issue (**212-213**), and phosphonium salts derived from pharmaceuticals and drug analogs provide the bipyridine products in good yield, demonstrating the functional group compatibility of the reaction and its ability to function on complex structures (**214-218**).



Isolated yields of single regioisomers. Conditions: phosphonium (1.0 equiv), **200** (2.0 equiv), B_2pin_2 (1.0 equiv), NEt_3 (1.25 equiv), 1,2-dichloroethane (0.2 M), rt, 36 h. [a]Yield determined by ^1H NMR analysis.

Figure 3.12. Phosphonium Substrate Scope for Pyridine-Pyridine Coupling Reaction

After investigating the phosphonium salt scope, we began focusing on the scope of the 4-cyanopyridine (Figure 3.13). Substituents at the 3-position are tolerated, including alkyl and silyl groups (**219**-**221**). Interestingly, each of the examples produced a single regioisomer, apart from one example, despite the presence of multiple reactive sites. The observed 2-position selectivity is unique when compared to typical Minisci reactions that would give a mixture of 2- and 3-position regioisomers on 4-cyanopyridine. In addition, we did not detect any dimerization-type products of either the cyanopyridine or phosphonium salt, giving the reaction exclusive cross-selectivity. Esters and protected alcohols function within the reaction (**222**-**223**), and triaryl systems are readily synthesized using the protocol (**224**-**227**). Bipyridine **228** highlights the regioselectivity of the reaction, where C–C bond formation occurs on the cyano-substituted pyridine over the alkyl pyridine. A 3,4,5-trisubstituted pyridine also worked under the reaction conditions in lower yield (**229**), and a phosphonate ester at the 4-position also functions (**230**). Lastly, complex pyridyl phosphonium salts and acceptor pyridines were effective in the protocol (**231**-**232**). Aryl groups at the 4-position, which are known to stabilize similar radical intermediates, do not give any of the desired product, but a 4-ethyl ester pyridine produced the bipyridine in low yield. Inductively withdrawing groups at the 4-position, such as trifluoromethyl or halides, are not capable of undergoing the reaction, further suggesting a pyridyl radical intermediate as part of the mechanism.



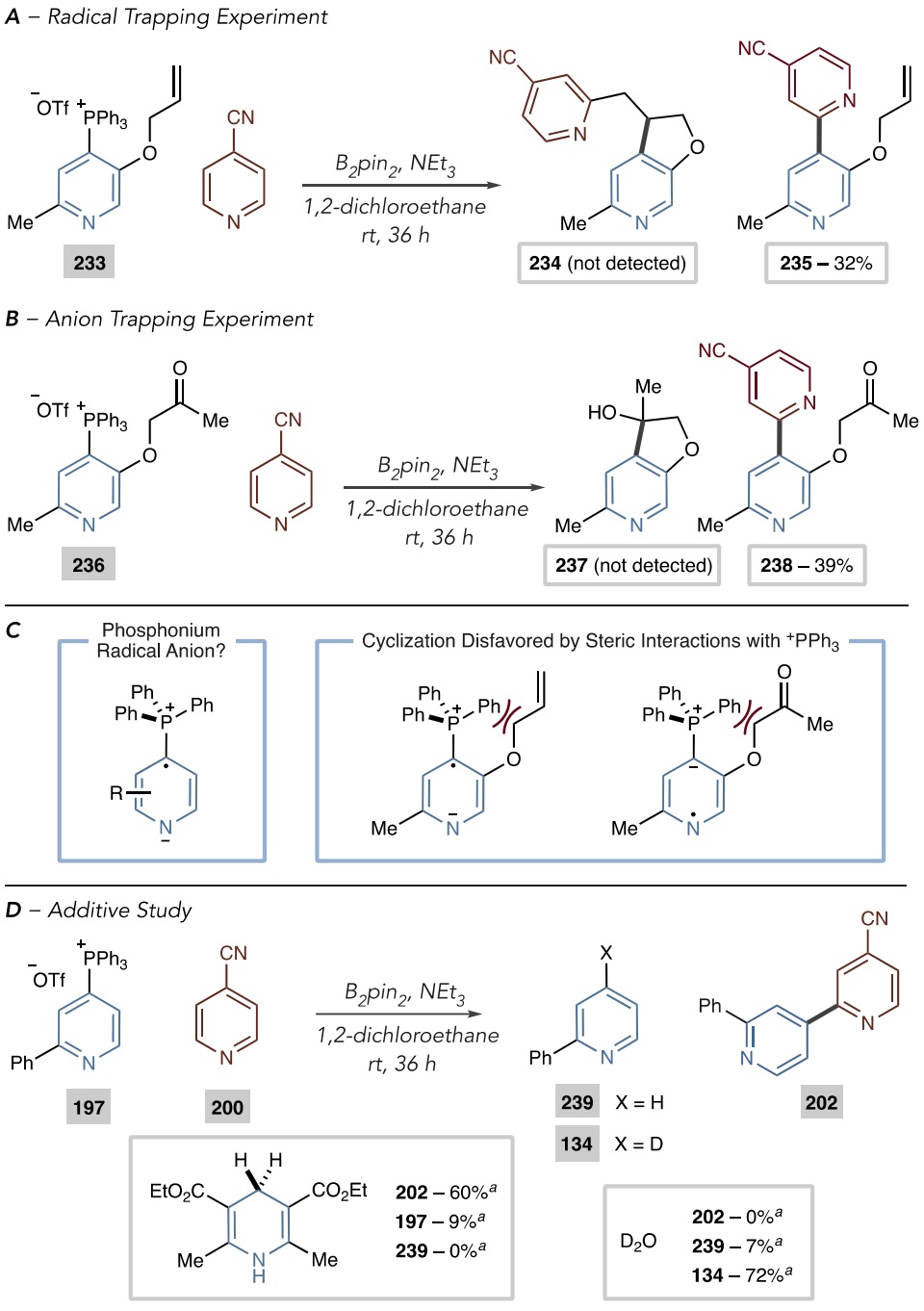
Isolated yields of single regioisomers. Conditions: phosphonium **197** (1.0 equiv), (2.0 equiv), B_2pin_2 (1.0 equiv), NEt_3 (1.25 equiv), 1,2-dichloroethane (0.2 M), rt, 36 h. [a]17:1 regiomeric ratio.

Figure 3.13. Pyridine Acceptor Substrate Scope for Pyridine-Pyridine Coupling Reaction

3.5 Mechanistic Investigation

After examining the reaction scope, we were intrigued by the reaction mechanism for the transformation. Traditional Minisci-type reactions suffer from mixtures of regioisomers, and our ability to achieve exclusive cross-selectivity would be extraordinary for a pyridine-pyridine Minisci. In order to probe the mechanism, we performed a series of experiments. We synthesized a phosphonium salt (**233**) containing a 3-allyloxy substituent to probe the intermediacy of a free radical species (Figure 3.14, A). A rapid 5-exo-trig cyclization should occur if a discreet 4-position

radical is forming in the reaction (rates for similar systems: 7.87 x 10^7 to 9.6 x 10^9 s^{-1}).[50–52] However, we did not detect any cyclized product **234** when **233** was subjected to the reaction conditions and instead bipyridine **235** was formed in 32% yield, suggesting that a discrete pyridyl radical was not operative. We next considered the possibility that a 4-position pyridyl radical could undergo a second electron transfer event, further reducing the radical to a pyridyl anion before C–C bond formation (Figure 3.14, B). We constructed an alkyl-tethered ketone (**236**) as the cyclization probe for the two-electron pathway and subjected it to the reaction conditions. None of the desired cyclized tertiary alcohol **237** was detected, and bipyridine **238** had formed as the major product. In light of these results, we speculated whether C–C bond formation could be taking place through a pyridyl phosphonium radical anion intermediate, where the bulky phosphonium ion prevents cyclization in both mechanistic probe substrates (Figure 3.14, C). We also ran an additive study using Hantzsch ester and D_2O as hydrogen atom and deuteron sources, respectively (Figure 3.14, D). When Hantzsch ester was added to the reaction, bipyridine **202** was still produced in high yield, and C–H abstraction had not occurred. When D_2O was added to the reaction, however, 4-position deuteration was observed, while no bipyridine formed. Although these mechanistic experiments provide evidence towards a possible phosphonium radical anion intermediate, the unusual nature of this species warranted additional investigation through computation studies.



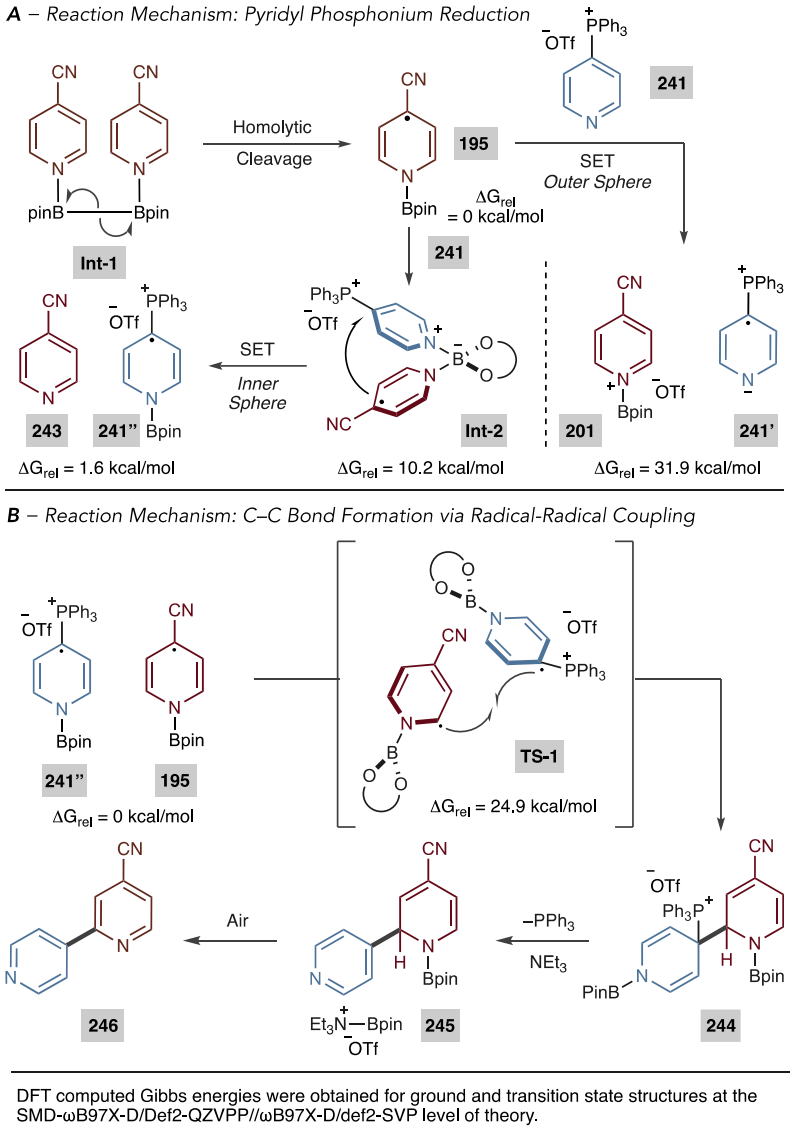
[a]Yield calculated by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

Figure 3.14. Experimental Mechanistic Probes for Pyridine-Pyridine Coupling Reaction

3.6 Computational Insight

Collaborating with the Paton group, we examined the reaction mechanism computationally (Figure 3.15). We began by exploring how the phosphonium salt is reduced in the system. Li and Jiao proposed that two equivalents of 4-cyanopyridine coordinate with a molecule of B_2pin_2, forming a Lewis acid-Lewis base adduct (**Int-1**).[42–47] From there, homolytic B–B bond cleavage occurs forming two equivalents of a boryl 4-cyanopyridine radical (**195**). This radical species could undergo outer sphere single-electron transfer with phosphonium salt **241** to make pyridinium **201** and pyridyl phosphonium radical anion **241'**. However, the process is endergonic by 32 kcal/mol and, therefore, thermodynamically unlikely at room temperature. Another possibility, similar to mechanistic proposals by Li, is that the nitrogen atom of the pyridyl phosphonium salt coordinates to the boron of **195**, which then facilitates intramolecular inner sphere electron transfer.[42,46,47] This process is endergonic by 10 kcal/mol due to the entropic penalty of forming **Int-2**, but the electron transfer is spontaneous forming 4-cyanopyridine and boryl pyridyl radical **241''**. The spin density was calculated to reside primarily at the 2- and 4-position, and we modeled C–C bond formation of **241''** with **243**, or **241'** with **201**; however, these mechanistic pathways had excessively high energy barriers of 42 kcal/mol and 43 kcal/mol, respectively. Alternately, the most favorable pathway was the radical-radical coupling of boryl pyridyl radical **241''** with boryl-cyanopyridine radical **195** to form intermediate **244**. This reactivity is complimentary to typical radical-radical couplings involving 4-cyanopyridine, where the 4-cyanopyridine radical reacts through the 4-position of the pyridine ring. However, this pathway is endergonic by 25 kcal/mol, a transition-state energy readily achieved at room temperature. The process is made irreversible following C–C bond formation by loss of PPh_3 and forming dearomatized intermediate **245**. These intermediates were observed by ^1H NMR and LCMS when the samples were kept under an inert

atmosphere. When the reaction mixture is exposed to air, however, a rapid color change is observed indicating oxidation and rearomatization to form bipyridine **246**.



DFT computed Gibbs energies were obtained for ground and transition state structures at the SMD-ωB97X-D/Def2-QZVPP//ωB97X-D/def2-SVP level of theory.

Figure 3.15. Proposed Reaction Mechanism and Computed Energy Values

Additionally, we have found that the production of **241''** and **195** could occur through homolytic B–B bond cleavage of other diboron Lewis acid-Lewis base complexes (Figure 3.16). In the case where the phosphonium salt does not contain a 2-position substituent, the process is

similar in energy to the homolysis of **Int-1**. As 2-position substituents, such as methyl groups, are introduced on the phosphonium salt, this mechanism becomes less energetically favorable due to the presumed steric destabilization of **Int-4**; however, we cannot rule out this mechanistic possibility.

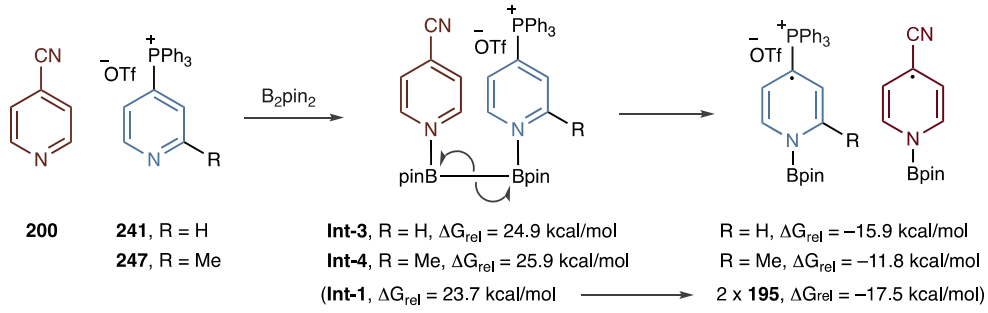


Figure 3.16. Alternative Mechanism to Form the Radical Coupling Pair

3.7 Conclusion

This chapter functions to outline Minisci-type methods to derivatize pyridines through radical addition processes. Through all the advancements made on the Minisci reaction, however, no examples of pyridine-pyridine couplings are reported. Using pyridyl phosphonium salts as the radical precursors, we have demonstrated a useful alternative to the Minisci reaction, forming 2,4'-bipyridine products through a unique mechanism and, importantly, with exclusive regioselectivity. Computational studies and experimental investigation suggest that the reaction proceeds through an unusual boryl pyridyl radical intermediate rather than a discreet pyridyl radical in the C–C bond-forming step. This unusual mechanism shows potential to be exploited in other radical based methods, and is exclusive for phosphonium salts compared with other radical precursors.

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APPENDIX ONE

DEUTERATION AND TRITIATION OF PYRIDINES, DIAZINES, AND PHARMACEUTICALS VIA HETEROCYCLIC PHOSPHONIUM SALTS: EXPERIMENTAL

A1.1 General Information and Materials

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (400 MHz) 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, proton assignment). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity was reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (100 MHz) 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 $CDCl_3$ (77.00 ppm), C_6D_6 (128.06 ppm), $(CD_3)_2SO$ (39.51 ppm), CD_3OD (49.00 ppm) or CD_3CN (1.32 ppm). DEPT135, NOE experiments and 2-dimensional experiments (COSY, HMBC and HSQC) were used to support assignments where appropriate.

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) or foil-backed basic aluminum oxide plates (Baker-flex 4467). Flash column chromatography was undertaken on Fluka or Material Harvest silica gel (230–400 mesh) or Sigma-Aldrich aluminum oxide (activated, basic) under a positive pressure of air. Preparative thin layer chromatography was performed using pre-coated Silicycle glass-backed silica gel plates (Siliaplate 60Å, 20 cm×20 cm, 2000 μm, TLG–R10011B–353). Visualization was achieved using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or basic potassium permanganate solutions as appropriate.

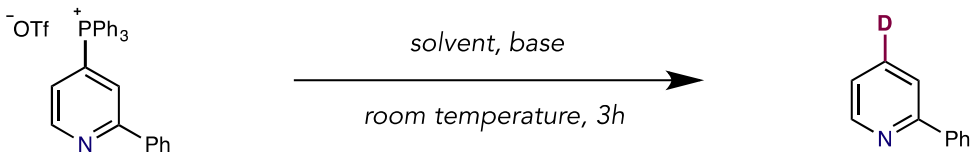
Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] 1,2-Dichloroethane (DCE), 1,4-dioxane, chloroform, chlorobenzene and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest 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.

PPh_3 (99%) was purchased from Oakwood Chemical and is most effective when crushed to a powder before use. Tf_2O (99%) was purchased from Oakwood Chemical and used without further purification and was routinely stored in a –20 ºC fridge. NEt_3 and DBU were distilled before use. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and were used without further purification. K_2CO_3 was purchased from Sigma Aldrich chemical company, stored in a desiccator, and is most effective when crushed to a powder before use. Cs_2CO_3 was purchased from Sigma Aldrich chemical company and was stored inside a glovebox.

Tritiations were run on a Lablogic Trisorber® manifold. Liquid scintillation counting was performed on a Perkin Elmer Tricarb 4910TR scintillation counter. High performance liquid chromatography (HPLC) analysis was performed on a Waters 2695 Alliance HPLC with a Waters 2996 PDA detector and a Packard C150TR radioactivity flow detector. Mass spectrometry was obtained on an Agilent 1260 infinity HPLC with an Agilent 6130 mass detector.

A1.2 Optimization of Reaction Conditions

Table A1.1 Optimization of Deuteration Reaction Conditions

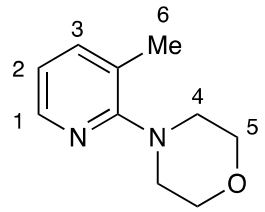


entry	*base*	*equivalents of base*	*solvent*[a]	*% yield*[b]
1	Na_2CO_3	5	CD_3OD	38
2	Cs_2CO_3	5	CD_3OD	64
3	K_2CO_3	5	CD_3OD	76
4	K_2CO_3	3	CD_3OD	90
5	K_2CO_3	3	CD_3OD : MeCN 1:9	14
6	K_2CO_3	3	CD_3OD : DMF 1:9	39
7	K_2CO_3	3	CD_3OD : DMF 1:9	94[c]
8	K_2CO_3	3	CD_3OD : D_2O 9:1	93
9	K_2CO_3	1.5	CD_3OD : D_2O 9:1	94
10	K_2CO_3	1.5	CD_3OD : D_2O 9:1	93[d]

[a]0.2 M concentration. [b]GC yields using 1,3,5-trimethoxybenzene as an internal standard. [c]Ran for 15 h. [d]Ran at 0.3 M concentration

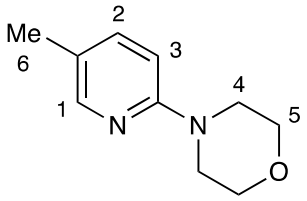
A1.3 Preparation of Heterocyclic Phosphonium Salt Precursors

4-(3-Methylpyridin-2-yl)morpholine



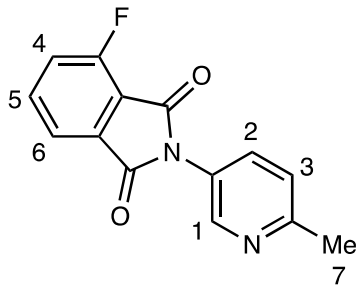
An oven dried 100 mL round bottom flask was flushed with nitrogen and charged with morpholine (1.49 mL, 17.0 mmol) and THF (15 mL). *N*–butyl lithium (6.8 mL, 17.0 mmol, 2.5 M in hexane) was added dropwise at 0 °C and the reaction was warmed to room temperature for 15 minutes. The mixture was cooled to 0 °C and 2-fluoro-3-methylpyridine (850 μL, 8.4 mmol) in THF (2 mL) was added dropwise. After 1 hour, the reaction was quenched with H_2O (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 25% EtOAc in hexanes) to provide the title compound as a colorless oil (1.35 g, 7.56 mmol, 90% yield). IR ν_{max}/cm^{-1} (film): 2953, 2834, 1568, 1409, 1385, 1240, 1110, 943, 857, 729, 633, 529; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.16 (1H, d, J = 4.7 Hz, H_1), 7.40 (1H, d, J = 7.3 Hz, H_2), 6.86 (1H, dd, J = 7.2, 4.9 Hz, H_2), 3.84 (4H, t, J = 4.6 Hz, H_5), 3.14 (4H, t, J = 4.6 Hz, H_4), 2.27 (3H, s, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.36, 145.35, 139.33, 124.77, 118.08, 67.16, 50.05, 18.28. *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 179.1, $C_{10}H_{15}N_2O^+$ requires 179.1.

4-(5-Methylpyridin-2-yl)morpholine



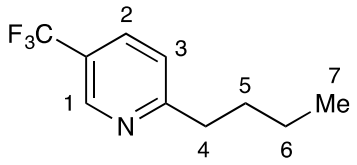
An oven dried 100 mL round bottom flask was flushed with nitrogen and charged with morpholine (1.75 mL, 20.0 mmol) and THF (15 mL). *N*–butyl lithium (12.5 mL, 20.0 mmol, 1.6 M in hexane) was added dropwise at 0 °C and the reaction was warmed to room temperature for 15 minutes. The mixture was cooled to 0 °C and 2-fluoro-5-methylpyridine (1.04 mL, 10.0 mmol) in THF (5 mL) was added dropwise. After 1 hour the reaction was quenched with H_2O (5 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (4 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a yellow oil (1.73 g, 9.70 mmol, 97% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.99 (1H, d, J = 2.4 Hz, H_1), 7.28 (1H, dd, J = 8.6, 2.4 Hz, H_2), 6.52 (1H, d, J = 8.6 Hz, H_3), 3.79-3.75 (4H, m, H_5), 3.41-3.36 (4H, m, H_4), 2.16 (3H, s, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.93, 147.48, 138.15, 122.56, 106.58, 66.55, 45.88, 17.11. The spectroscopic data is in agreement with a reported synthesis.[2]

4-Fluoro-2-(6-methylpyridin-3-yl)isoindoline-1,3-dione



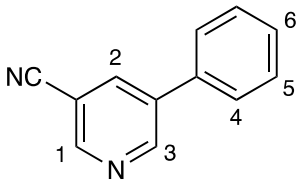
To a mixture of 4-fluoroisobenzofuran-1,3-dione (2.49 g, 15.0 mmol) and 6-methylpyridin-3-amine (1.62 g, 15.0 mmol) was added AcOH (30 mL). The mixture was stirred at 130 °C for 4 hours under nitrogen. After cooling to room temperature, the reaction mixture was partitioned between a saturated aqueous solution of Na_2CO_3 (100 mL) and CH_2Cl_2 (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were then washed with H_2O (50 mL), a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was used without need for further purification as a tan solid (3.30 g, 12.9 mmol, 86% yield). mp 215-218 °C; IR ν_{max}/cm^{-1} (film): 3087, 3036, 1771, 1714, 1614, 1495, 1480, 1439, 1378, 1251, 1097, 967, 877, 741, 724, 630; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.61 (1H, d, *J* = 2.5 Hz, H_1), 7.85-7.76 (2H, m, H_5, H_4 or H_6), 7.67 (1H, dd, *J* = 8.3, 2.5 Hz, H_2), 7.50-7.44 (1H, m, H_4 or H_6), 7.31 (1H, d, *J* = 8.3 Hz, H_3), 2.63 (3H, s, H_7) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.73 (d, *J* = 3.0 Hz), 165.51 (d, *J* = 1.3 Hz), 158.30, 157.92 (d, *J* = 267.2 Hz), 146.62, 137.19 (d, *J* = 7.6 Hz), 133.95, 133.72, 125.69, 123.34, 122.83 (d, *J* = 19.8 Hz), 120.10 (d, *J* = 3.8 Hz), 117.46 (d, *J* = 12.2 Hz), 24.22; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –111.77-(–111.83) (m); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 257.1, $C_{14}H_{10}FN_2O_2^+$ requires 257.1.

2-Butyl-5-(trifluoromethyl)pyridine



Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$): 8.77 (1H, s, H_1), 7.79 (1H, dd, J = 8.2, 1.8 Hz, H_2), 7.29-7.21 (1H, m, H_3), 2.84 (2H, t, J = 7.5 Hz, H_4), 1.71 (2H, qn, J = 7.5 Hz, H_5), 1.37 (2H, sext, J = 7.5 Hz, H_6), 0.92 (3H, t, J = 7.6 Hz, H_7); ^{13}C NMR (100 MHz, $CDCl_3$): 166.60, 146.12 (q, J = 4.1 Hz), 133.23 (q, J = 3.5 Hz), 123.99 (q, J = 32.8 Hz), 123.77 (q, J = 271.2 Hz), 122.36, 38.08, 31.70, 22.37, 12.82; ^{19}F NMR (365 MHz, $CDCl_3$): –62.32. The spectroscopic data is in agreement with our reported synthesis.[3]

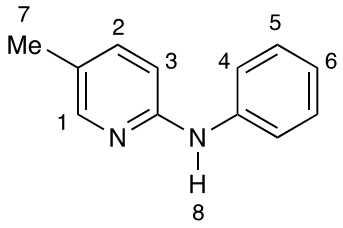
5-Phenylnicotinonitrile



Prepared according to a method adapted from Thomas.[4] An oven dried 200 mL round bottom flask was flushed with nitrogen and charged with dioxane (30 mL), EtOH (30 mL), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (460 mg, 2.00 mmol), bromobenzene (315 µL, 3.00 mmol), $Pd(PPh_3)_4$ (116 mg, 0.10 mmol), and aq. Na_2CO_3 (1.50 mL, 10.1 mmol, 0.067 M). The reaction was heated to 85 °C for 19 hours and then cooled to room temperature. The reaction mixture was partitioned between H_2O (30 mL) and EtOAc (30 mL) and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by

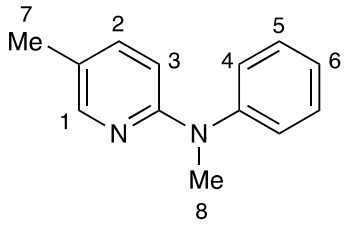
flash chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 15% EtOAc in hexanes) to provide the title compound as a white solid (208 mg, 1.16 mmol, 58% yield). mp 73-74 ºC; IR ν_{max}/cm^{-1} (film): 3035, 2231, 1579, 1561, 1459, 1430, 1411, 1022, 898, 765, 697, 603, 557; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.01 (1H, s, H_1), 8.83 (1H, s, H_2), 8.10 (1H, s, H_3), 7.58-7.43 (5H, m, H_4, H_5, and H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.37, 150.55, 137.08, 136.78, 135.25, 129.33, 129.13, 127.02, 116.43, 109.95. *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 181.1, $C_{12}H_9N_2^+$ requires 181.1.

5-Methyl-*N*-phenylpyridin-2-amine



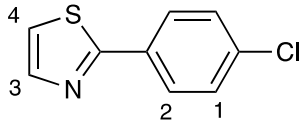
Prepared according to the method of Wang on a 10.00 mmol scale.[5] The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) followed by a second flash column (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) to provide the title compound as a yellow oil (218 mg, 1.20 mmol, 12% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (1H, s, H_1), 7.35-7.27 (5H, m, H_4, H_5, and H_6), 7.04-6.98 (1H, m, H_2), 6.84 (1H, d, J = 8.4 Hz, H_3), 6.65 (1H, s, H_8), 2.23 (3H, s, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.85, 147.99, 140.98, 138.52, 129.22, 124.07, 122.21, 119.62, 108.15, 17.51. The spectroscopic data is in agreement with a reported synthesis.[5]

_N_,5-Dimethyl-_N_-phenylpyridin-2-amine



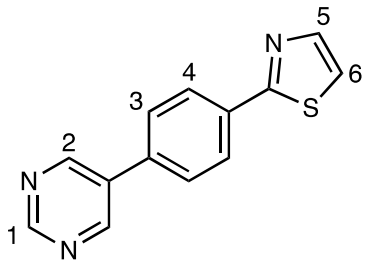
An oven dried 25 mL round bottom flask was charged with 5-methyl-*N*-phenylpyridin-2-amine (645 mg, 3.50 mmol), NaH (60% dispersion in mineral oil, 154 mg, 3.85 mmol), flushed with nitrogen, DMF (7 mL), and iodomethane (240 μL, 3.85 mmol). The reaction was stirred at room temperature for 2 hours and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes) to provide the title compound as a yellow oil (671 mg, 3.40 mmol, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (1H, s, H_1), 7.36 (2H, t, J = 7.7 Hz, H_5), 7.23 (2H, d, J = 8.3 Hz, H_4), 7.18-7.12 (2H, m, H_2 and H_6), 6.53 (1H, d, J = 8.6 Hz, H_3), 3.45 (3H, s, H_8), 2.18 (3H, s, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.10, 147.33, 147.24, 137.59, 129.46, 125.49, 124.66, 122.16, 109.36, 38.33, 17.31. The spectroscopic data is in agreement with a reported synthesis.[6]

2-(4-Chlorophenyl)-thiazole



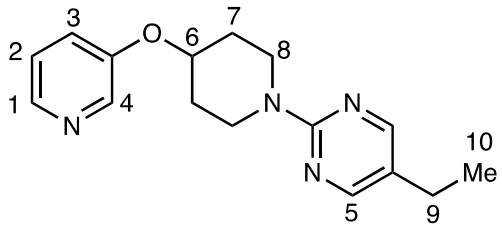
Prepared according to a previous report.[7] ^{1}H NMR (400 MHz, $CDCl_3$): 7.88 (2H, d, J = 8.4 Hz, H_1), 7.84 (1H, d, J = 3.2 Hz, H_3), 7.39 (2H, d, J = 8.4 Hz, H_2), 7.31 (1H, d, J = 2.8 Hz, H_4); ^{13}C NMR (100 MHz, $CDCl_3$): 166.73, 143.61, 135.66, 131.85, 128.94, 127.53, 118.94. The spectroscopic data is in agreement with a reported synthesis.[7]

2-(4-(Pyrimidin-5-yl)phenyl)thiazole



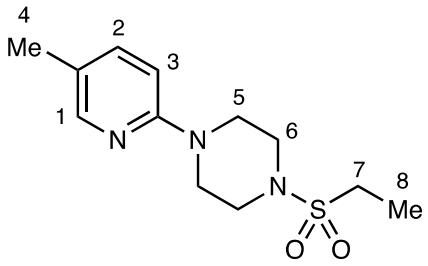
To a mixture of pyrimidine-5ylboronic acid (1.07 g, 8.66 mmol), 2-(4-chlorophenyl)thiazole (1.54 g, 7.87 mmol), $Pd_2(dba)_3$ (216 mg, 0.24 mmol) and PCy_3 (159 mg, 0.57 mmol) was added a degassed mixture of 1,4-dioxane (21 mL) and a 1.27 M aqueous solution of K_3PO_4 (11 mL). The mixture was stirred at 100 °C for 12 hours under nitrogen. After cooling to room temperature, the reaction mixture was partitioned between H_2O (100 mL) and EtOAc (30 mL) and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in CH_2Cl_2) to provide the title compound as a white solid (1.60 g, 6.69 mmol, 85% yield). mp 173-174 °C; IR ν_{max}/cm^{-1} (film): 3086, 3069, 1569, 1483, 1411, 1396, 1355, 1147; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.24 (1H, s, H_1), 9.01 (2H, s, H_2), 8.13 (2H, d, J = 8.0 Hz, H_3), 7.92 (1H, d, J = 2.8 Hz, H_5), 7.68 (2H, d, J = 8.0 Hz, H_4), 7.40 (1H, d, J = 2.8 Hz, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.16, 157.79, 154.78, 143.97, 135.62, 134.15, 133.49, 127.55, 127.49, 119.42; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 240.1, $C_{13}H_{10}N_3S^+$ requires 240.1.

5-Ethyl-2-(4-(pyridin-3-yloxy)piperidin-1-yl)pyrimidine



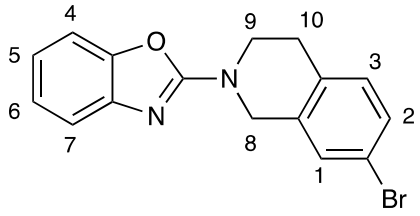
An oven dried 25 mL flask was charged with 3-(piperidin-4-yloxy)pyridine (332 mg, 1.86 mmol), 2-chloro-5-ethylpyrimidine (265 mg, 1.86 mmol), K_2CO_3 (771 mg, 5.58 mmol), DMF (3.8 mL, and stirred at 130 °C for 3 hours. After cooling to room temperature, the reaction mixture was partitioned between H_2O (50 mL) and EtOAc (50 mL) and the aqueous layer was extracted with EtOAc (3 × 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: 20% EtOAc in hexanes) to provide the title compound as a yellow oil (445 mg, 1.57 mmol, 84%). IR ν_{max}/cm^{-1} (film): 2961, 2930, 2860, 1603, 1496, 1453, 1422, 1257, 1225, 1025; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.35-8.34 (1H, m, H_4), 8.24-8.22 (1H, m, H_1), 8.19 (2H, s, H_5, 7.26-7.24 (2H, m, H_2 and H_3), 4.59 (1H, sept, J = 4.0 Hz, H_6), 4.21-4.15 (2H, m, H_8), 3.68-3.62 (2H, m, H_8), 2.47 (2H, d, J = 7.6 Hz, H_9), 2.06-2.00 (2H, m, H_7), 1.87-1.79 (2H, m, H_7), 1.19 (3H, t, J = 7.6 Hz, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.60, 157.02, 153.56, 142.05, 139.26, 124.41, 123.87, 122.72, 73.52, 40.89, 30.24, 22.59, 15.49; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 285.2, $C_{16}H_{21}N_4O^+$ requires 285.2.

1-(Ethylsulfonyl)-4-(5-methylpyridin-2-yl)piperazine



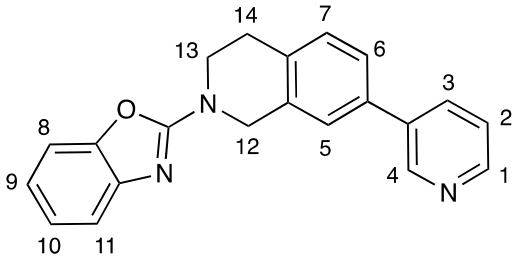
An oven dried 250 mL round bottom flask was charged with 1-(ethylsulfonyl)piperazine (900 mg, 5.05 mmol. The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of 2-fluoro-5-methylpyridine (0.52 mL, 5.00 mmol), EtN(Pr-*i*)$_2$ (1.16 mL, 6.65 mmol), and NMP (2.5 mL). The mixture was heated at 180 °C for 72 hours, cooled to room temperature and diluted with CH_2Cl_2 and H_2O. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were washed with a saturated aqueous solution of NaCl and were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 20% Et_2O in CH_2Cl_2) to provide the title compound as a crystalline white solid (610 mg, 2.25 mmol, 45% yield). mp 133-135 ºC. IR ν_{max}/cm^{-1} (film): 3000, 2983, 2909, 2855, 1609, 1492, 1324, 1144, 1116; ^{1}H NMR (400 MHz, $CDCl_3$): 8.02 (1H, s, H_1), 7.35 (1H, d, J = 8.8 Hz, H_2), 6.61 (1H, d, J = 8.4 Hz, H_3), 3.59 (4H, t, J = 4.8 Hz, H_5 and H_6), 3.40 (4H, t, J = 4.8 Hz, H_5 and H_6), 2.97 (2H, q, J = 7.2 Hz, H_7), 2.21 (3H, s, H_4), 1.38 (3H, t, J = 7.2 Hz, H_8); ^{13}C NMR (100 MHz, $CDCl_3$): 157.10, 147.34, 138.92, 123.31, 107.47, 45.98, 45.50, 43.83, 17.28, 7.75; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 270.1, $C_{12}H_{20}N_3O_2S^+$ requires 270.1.

2-(7-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)benzo[*d*]oxazole



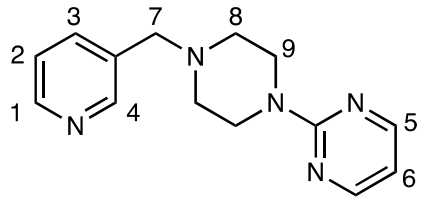
An oven dried 50 mL round bottom flask was charged with 7-bromo-1,2,3,4-tetrahydroisoquinoline (1.27 g, 6.00 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of 2-chlorobenzo[*d*]oxazole (0.82 mL, 7.2 mmol), NEt_3 (1.51 mL, 10.8 mmol), and THF (20 mL). The mixture was heated at 70 °C for 6 hours, cooled to room temperature and diluted with CH_2Cl_2 and H_2O. The organic layer was separated and washed with H_2O (2 x 20 mL). The organic layers were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 10% hexanes in CH_2Cl_2 followed by 100% CH_2Cl_2) to provide the title compound as a white solid (1.39 g, 4.20 mmol, 70% yield). mp 117-120 ºC. IR ν_{max}/cm^{-1} (film): 2936, 2848, 1635, 1568, 1458, 1242, 739; ^1H NMR (400 MHz, $CDCl_3$): 7.38 (1H, br d, J = 7.6 Hz, H_4), 7.29-7.26 (3H, m, H_1, H_5, and H_7), 7.15 (1H, br t, J = 7.2 Hz, H_6), 7.03-6.96 (2H, m, H_2 and H_3), 4.74 (2H, s, H_8), 3.89 (2H, br t, H_9), 2.87 (2H, br t, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$): 161.78, 148.75, 142.92, 134.47, 132.93, 130.44, 129.90, 129.16, 124.05, 120.73, 120.02, 116.33, 108.77, 46.75, 42.92, 27.90; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 329.1, $C_{16}H_{14}BrN_2O^+$ requires 329.0.

2-(7-(Pyridin-3-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzo[*d*]oxazole



An oven dried 50 mL round bottom flask was charged with 2-(7-bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)benzo[*d*]oxazole (988 mg, 3.00 mmol), pyridin-3-ylboronic acid (553 mg, 4.5 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol), and K_2CO_3 (2.07 g, 15 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of dioxane (38 mL) and H_2O (7.5 mL). The mixture was heated at 100 °C for 21.5 hours, cooled to room temperature and diluted with CH_2Cl_2 and H_2O. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 2% MeOH in CH_2Cl_2 followed by 3% MeOH in CH_2Cl_2) and then was washed with cold Et_2O (–20 ºC) on a frit to provide the title compound as a light yellow solid (805 mg, 2.46 mmol, 82% yield). mp 189- 191 ºC. IR ν_{max}/cm^{-1} (film): 3031, 2933, 2833, 1645, 1574, 1453, 1238; ^{1}H NMR (400 MHz, $CDCl_3$): 8.84 (1H, s, H_4), 8.61 (1H, d, J = 4.4 Hz, H_1), 7.87 (1H, d, J = 8.0 Hz, H_3), 7.44-7.37 (4H, m, H_2, H_5, H_8, and H_{11}), 7.31-7.29 (2H, m, H_6 and H_7), 7.18 (1H, t, J = 7.6 Hz, H_9), 7.04 (1H, t, J = 7.6 Hz, H_{10}), 4.94 (2H, s, H_{12}), 4.01 (2H, t, J = 6.0 Hz, H_{13}), 3.07 (2H, t, J = 5.6 Hz, H_{14}); ^{13}C NMR (100 MHz, $CDCl_3$): 161.93, 148.78, 148.48, 148.11, 143.08, 136.19, 136.05, 134.13, 134.06, 133.22, 129.59, 125.57, 124.91, 123.99, 123.53, 120.61, 116.29, 108.73, 47.24, 43.05, 28.13; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 328.2, $C_{21}H_{18}N_3O^+$ requires 328.1.

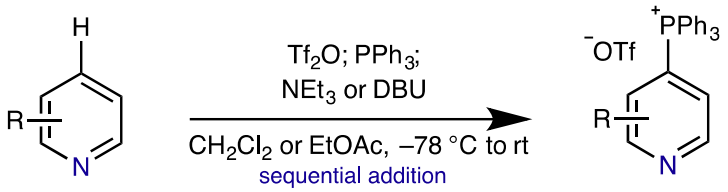
2-(4-(Pyridin-3-ylmethyl)piperazin-1-yl)pyrimidine



To a warm (50 °C) solution of 2-(piperazin-1-yl)pyrimidine (1.42 mL, 10.00 mmol) and NEt_3 (2.09 mL, 15.00 mmol) in EtOH (180 mL) was added dropwise 3-(chloromethyl)pyridine (2.17 g, 17.00 mmol) in EtOH (20 mL), and then the reaction mixture was allowed to stir at 60 °C for 24 hours. After cooling to room temperature, the solvent was removed under vacuum. The residue was treated with water (50 mL) and extracted with CH_2Cl_2 (3 × 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: EtOAc to 5% NEt_3 in EtOAc) to provide the title compound as a white solid (2.07 g, 8.10 mmol, 81% yield). mp 104-106 °C; IR ν_{max}/cm^{-1} (film): 2942, 2901, 2871, 2828, 2803, 2764, 1585, 1541, 1513, 1479, 1458, 1446, 1423, 1394, 1353, 1309, 1300, 1277, 1259, 1218, 1184, 1139, 1128, 1098, 1083, 1029, 1000, 951, 839, 810, 790, 768, 715; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.57 (1H, d, *J* = 1.3 Hz, H_4), 8.53 (1H, dd, *J* = 4.8, 1.3 Hz, H_1), 8.30 (2H, d, *J* = 4.7 Hz, H_5), 7.70 (1H, d, *J* = 7.7 Hz, H_3), 7.28 (1H, dd, *J* = 7.7, 4.8 Hz, H_2), 6.47 (1H, t, *J* = 4.7 Hz, H_6), 3.82 (4H, t, *J* = 5.o Hz, H_9), 3.55 (2H, s, H_7), 2.50 (4H, t, *J* = 5.0 Hz, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.56, 157.60, 150.41, 148.65, 136.60, 133.38, 123.27, 109.77, 60.23, 52.86, 43.56; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 256.2, $C_{28}H_{28}N_2OP^+$ requires 256.2.

A1.4 Preparation of Heterocyclic Phosphonium Salts

General Procedure A



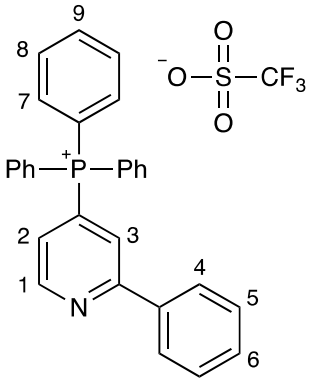
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) or EtOAc (0.4 M) was added, the reaction vessel cooled to –78 ºC, and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before PPh_3 (1.1 equiv) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 minutes at –78 ºC. The stated organic base (NEt_3 or 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 15-30 minutes). The reaction mixture was quenched with H_2O (approximately the same volume as CH_2Cl_2) and the mixture was transferred to a separatory funnel. The mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Approximately 2-10 mL (depending on the scale of the reaction) of CH_2Cl_2 was added to reaction mixture and was then added dropwise to an excess of chilled Et_2O (0 ºC). The flask was then placed in a –20 ºC refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 ºC),

and dried *in vacuo* to provide the pure phosphonium salt.

Notes.

1) PPh_3 was crushed into a powder prior to use.
2) Certain substrates require longer periods for the precipitation step and specific cases are indicated below.
3) In a small number of cases, residual CH_2Cl_2 can become trapped in the phosphonium salt products. In these cases, heating the salts under vacuum (50-100 ºC) removed the solvent.
4) In order to evaluate regioselectivity from the crude reaction mixtures, a duplicate reaction was performed and aliquots taken after addition of the organic base and warming to room temperature. These aliquots were concentrated *in vacuo* and analyzed by ^1H and ^{31}P NMR.

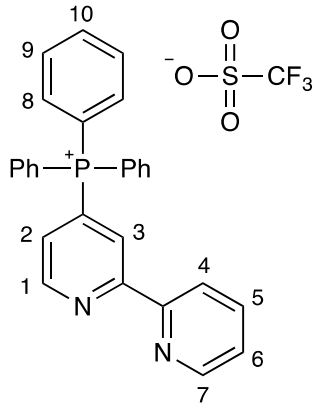
Triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate



Prepared according to our previous report.[3] ^1H NMR (400 MHz, $CDCl_3$) δ: 9.01 (1H, app t, *J* = 5.1 Hz, H_1), 7.93-7.54 (18H, m, H_3, H_7, H_8, H_9, and H_4), 7.50 (1H, ddd, *J* = 17.8, 5.1, 1.1 Hz, H_2), 7.42-7.36 (3H, m, H_5 and H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: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,

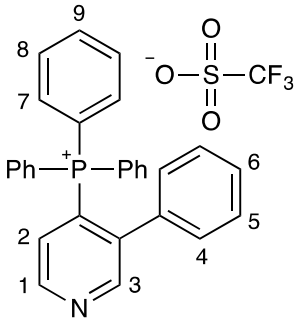
J = 8.4 Hz), 120.68 (q, *J* = 321.1 Hz), 115.49 (d, *J* = 89.1 Hz).

[2,2'-Bipyridin]-4-yltriphenylphosphonium trifluoromethanesulfonate



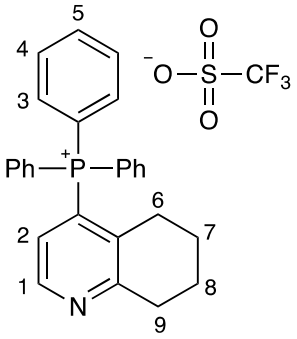
Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.06 (1H, app t, *J* = 5.1 Hz, H_1), 8.65 (1H, d, *J* = 13.8 Hz, H_3), 8.55 (1H, d, *J* = 4.4 Hz, H_7), 8.46 (1H, d, *J* = 7.9 Hz, H_4), 7.96-7.88 (3H, m, H_{10}), 7.87-7.74 (7H, m, H_9 and H_5), 7.72-7.55 (7H, m, H_2 and H_8), 7.35 (1H, dd, *J* = 7.7, 4.5 Hz, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.80 (d, *J* = 9.9 Hz), 153.36 (d, *J* = 2.3 Hz), 151.37 (d, *J* = 10.7 Hz), 149.34, 137.34, 136.17 (d, *J* = 3.1 Hz), 134.42 (d, *J* = 9.9 Hz), 130.97 (d, *J* = 13.0 Hz), 129.29 (d, *J* = 83.9 Hz), 126.91 (d, *J* = 8.4 Hz), 125.08, 123.89 (d, *J* = 9.2 Hz), 121.65, 120.80 (q, *J* = 321.2 Hz), 115.75 (d, *J* = 89.3 Hz).

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



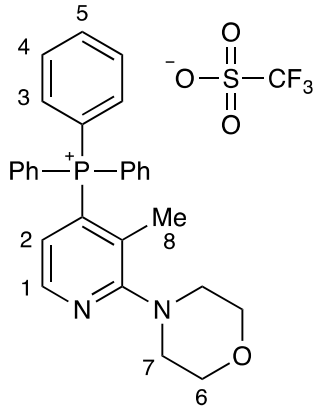
Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.95 (1H, app t, J = 4.7 Hz, H_1), 8.74 (1H, d, J = 6.8 Hz, H_3), 7.85-7.73 (3H, m, H_9), 7.73-7.40 (13H, m, H_2, H_7, and H_8), 7.11 (1H, t, J = 7.6 Hz, H_6), 6.91 (2H, app t, J = 7.6 Hz, H_5), 6.71 (2H, d, J = 7.5 Hz, H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 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).

Triphenyl(5,6,7,8-tetrahydroquinolin-4-yl)phosphonium trifluoromethanesulfonate



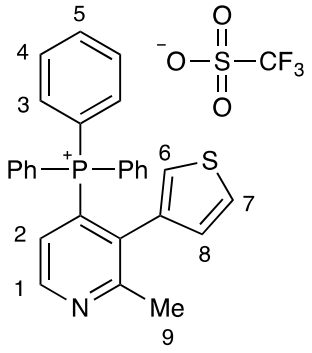
Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.74 (1H, app t, J = 5.1 Hz, H_1), 8.07-7.93 (3H, m, H_5), 7.92-7.71 (12H, m, H_3 and H_4), 6.94 (1H, dd, J = 15.3, 5.1 Hz, H_2), 3.12-2.97 (2H, m, H_9), 2.21-2.04 (2H, m, H_6), 1.84-1.71(2H, m, H_8), 1.60-1.44 (2H, m, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.25 (d, J = 8.4 Hz), 148.20 (d, J = 11.4 Hz), 135.48 (d, J = 7.6 Hz), 135.27 (d, J = 3.1 Hz), 134.06 (d, J = 10.7 Hz), 130.50 (d, J = 13.0 Hz), 126.18 (d, J = 9.9 Hz), 125.51 (d, J = 82.4 Hz), 120.40 (q, J = 322.0 Hz), 116.34 (d, J = 87.7 Hz), 32.01 (d, J = 2.3 Hz), 29.66 (d, J = 5.3 Hz), 21.03, 20.54.

(3-Methyl-2-morpholinopyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



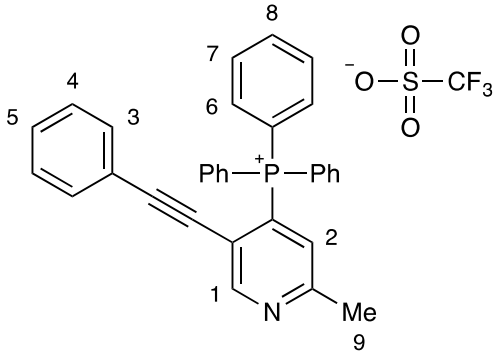
Prepared according to general procedure A using 4-(3-methylpyridin-2-yl)morpholine (1.35 g, 7.59 mmol), Tf_2O (1.27 mL, 7.59 mmol), PPh_3 (2.19 g, 8.35 mmol), DBU (1.14 mL, 7.59 mmol) and CH_2Cl_2 (76 mL). After the purification procedure, the title compound was isolated as a yellow solid (2.10 g, 3.57 mmol, 47% yield). mp 181-184 ºC; IR ν_{max}/cm^{-1} (film): 2971, 2841, 1649, 1559, 1441, 1404, 1260, 1222, 1191, 1027, 689, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.44 (1H, app t, *J* = 5.1 Hz, H_1), 7.94-7.63 (15H, m, H_3, H_4, and H_5), 6.68 (1H, dd, *J* = 14.5, 5.1 Hz, H_2), 3.84-3.79 (4H, m, H_6), 3.23-3.18 (4H, m, H_7), 1.96 (3H, s, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.50 (d, *J* = 12.3 Hz), 147.21 (d, *J* = 13.6 Hz), 135.70 (d, *J* = 3.0 Hz), 133.84 (d, *J* = 10.4 Hz), 130.92 (d, *J* = 13.0 Hz), 128.41 (d, *J* = 7.5 Hz), 128.02 (d, *J* = 83.3 Hz), 121.81 (d, *J* = 10.6 Hz), 120.66 (q, *J* = 321.4 Hz), 116.52 (d, *J* = 88.4 Hz), 66.52, 50.01, 19.45 (d, *J* = 6.5 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.79; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 439.2, $C_{28}H_{28}N_2OP^+$ requires 439.2.

(2-Methyl-3-(thiophen-3-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (1H, app t, *J* = 5.0 Hz, H_1), 7.86-7.77 (3H, m, H_5), 7.75-7.65 (6H, m, H_4), 7.63-7.52 (6H, m, H_3), 7.28-7.18 (1H, m, H_2), 6.85 (1H, dd, *J* = 5.1, 2.9 Hz, H_8), 6.58 (1H, dd, *J* = 2.9, 1.1 Hz, H_6), 6.20 (1H, dd, *J* = 5.1, 1.2 Hz, H_7), 2.31 (3H, s, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.95 (d, J = 8.1 Hz), 149.44 (d, *J* = 10.8 Hz), 135.84 (d, *J* = 7.6 Hz), 135.21 (d, *J* = 3.0 Hz), 134.56 (d, *J* = 5.3 Hz), 133.80 (d, *J* = 9.9 Hz), 130.49 (d, *J* = 12.9 Hz), 128.05, 127.68 (d, *J* = 84.8 Hz), 126.48, 125.97, 125.86 (d, *J* = 9.6 Hz), 120.69 (q, *J* = 320.9 Hz), 117.16 (d, *J* = 89.6 Hz), 23.54 (d, *J* = 2.3 Hz).

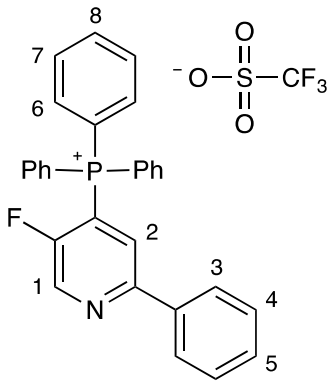
(2-Methyl-5-(phenylethynyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, d, *J* = 2.8 Hz, H_1), 7.86 (3H, m, H_8), 7.80-7.68 (13H, m, H_7, H_6, and H_5), 7.17 (2H, app t, *J* = 7.7 Hz,

H_4), 7.09 (1H, d, J = 15.1 Hz, H_2), 6.66 (2H, d, J = 7.4 Hz, H_3), 2.66 (3H, s, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.40 (d, J = 10.4 Hz), 154.04 (d, J = 7.1 Hz), 135.72 (d, J = 3.0 Hz), 134.22 (d, J = 10.5 Hz), 130.83, 130.67 (d, J = 13.2 Hz), 129.87, 128.65 (d, J = 85.9 Hz), 128.32, 128.11 (d, J = 8.8 Hz), 120.75 (q, J = 321.2 Hz), 120.37 (d, J = 4.5 Hz), 119.90, 115.82 (d, J = 90.3 Hz), 103.30, 83.97 (d, J = 6.1 Hz), 24.83.

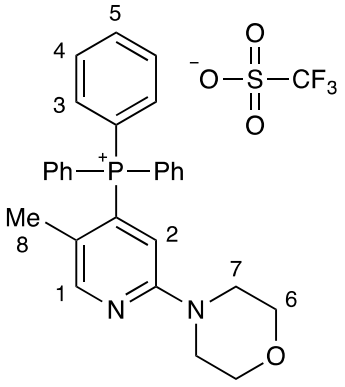
(5-Fluoro-2-phenylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 5-fluoro-2-phenylpyridine (520 mg, 3.00 mmol), Tf_2O (504 μL, 3.00 mmol), PPh_3 (866 mg, 3.30 mmol), NEt_3 (620 μL, 3.00 mmol) and CH_2Cl_2 (30 mL). After the purification procedure, the title compound was isolated as a light yellow solid (998 mg, 1.71 mmol, 57% yield). mp 83-86 ºC; IR ν_{max}/cm^{-1} (film): 3062, 1467, 1438, 1259, 1146, 1106, 1102, 634; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, d, J = 6.4 Hz, H_1), 7.96-7.93 (3H, m, H_8), 7.86-7.74 (14H, m, H_3, H_6 and H_7), 7.53 (1H, dd, J = 14.8, 4.4 Hz, H_2), 7.46-7.44 (3H, m, H_4 and H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.72 (d, J = 263.5 Hz), 156.25 (dd, J = 10.0, 4.7 Hz), 140.14 (dd, J = 24.1, 4.5 Hz), 136.38 (d, J = 3.0 Hz), 136.17, 134.16 (d, J = 11.0 Hz), 131.10 (d, J = 13.5 Hz), 130.26, 129.12, 127.05, 124.57 (d, J = 6.2 Hz), 120.79 (q, J = 319.5 Hz), 117.29 (dd, J = 84.0, 14.4 Hz), 115.03 (d, J = 90.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –

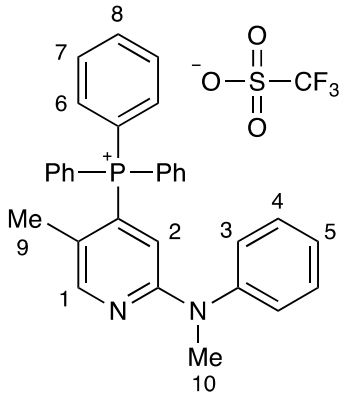
78.19, –113.93; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.80; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 434.2, $C_{29}H_{22}FNP^+$ requires 434.2.

(5-Methyl-2-morpholinopyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 4-(5-methylpyridin-2-yl)morpholine (1.73 g, 9.71 mmol), Tf_2O (1.63 mL, 9.71 mmol), PPh_3 (2.81 g, 10.68 mmol), DBU (1.45 mL, 9.71 mmol) and CH_2Cl_2 (97 mL). After the purification procedure, the title compound was isolated as a yellow solid (4.18 g, 7.10 mmol, 73% yield). mp 231-233 ºC; IR ν_{max}/cm^{-1} (film): 2850, 1587, 1494, 1439, 1403, 1340, 1266, 1223, 1107, 1030, 764, 727, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (1H, d, *J* = 7.7 Hz, H_1), 7.88-7.57 (15H, m, H_3, H_4, and H_5), 6.19 (1H, d, *J* = 17.9 Hz, H_2), 3.68-3.61 (4H, m, H_6), 3.29-3.22 (4H, m, H_7), 1.74 (3H, s, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.86 (d, *J* = 13.6 Hz), 152.21 (d, *J* = 10.4 Hz), 135.71 (d, *J* = 3.0 Hz), 133.89 (d, *J* = 10.5 Hz), 130.80 (d, *J* = 13.0 Hz), 127.08 (d, *J* = 82.7 Hz), 122.50 (d, *J* = 7.0 Hz), 120.67 (q, *J* = 321.2 Hz), 116.18 (d, *J* = 88.5 Hz), 111.50 (d, *J* = 12.5 Hz), 66.04, 44.39, 18.25; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.09; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.21; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 439.2, $C_{28}H_{28}N_2OP^+$ requires 439.2.

(5-Methyl-2-(methyl(phenyl)amino)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate

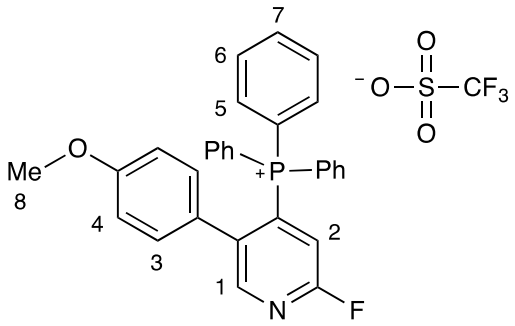


Prepared according to general procedure A using *N*,5-dimethyl-*N*-phenylpyridin-2-amine (44 mg, 0.22 mmol), Tf_2O (38 μL, 0.22 mmol), PPh_3 (65 mg, 0.25 mmol), DBU (33 μL, 0.23 mmol) and CH_2Cl_2 (2.0 mL). After the purification procedure,‡ the title compound was isolated as a yellow solid (86 mg, 0.14 mmol, 64% yield). mp 169-174 ºC; IR ν_{max}/cm^{-1} (film): 3063, 2238, 2164, 1585, 1496, 1438, 1371, 1264, 1221, 1134, 1106, 721, 690, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.32 (1H, d, *J* = 7.5 Hz, H_1), 7.85-7.52 (15H, m, H_6, H_7, and H_8), 7.28-7.22 (2H, m, H_3), 7.17 (2H, t, *J* = 7.3 Hz, H_4), 7.03 (1H, d, *J* = 7.3 Hz, H_5), 6.02 (1H, d, *J* = 18.3 Hz, H_2), 3.45 (3H, s, H_{10}), 1.79 (3H, s, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.72 (d, *J* = 13.6 Hz), 151.81 (d, *J* = 10.1 Hz), 144.35, 135.68 (d, *J* = 3.0 Hz), 133.99 (d, *J* = 10.3 Hz), 130.89 (d, *J* = 13.0 Hz), 130.27, 127.05 (d, *J* = 82.6 Hz), 126.92, 126.50, 121.29 (d, *J* = 7.3 Hz), 120.95 (q, *J* = 321.3 Hz), 116.26 (d, *J* = 88.7 Hz), 114.67 (d, *J* = 13.1 Hz), 38.2, 18.33 (d, *J* = 4.0 Hz); ^{19}F NMR (365 MHz,

‡ The solid was redissolved in approximately 3 mL of CH_2Cl_2 and was precipitated a second time. The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt.

$CDCl_3$) δ: –78.12; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.15; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 459.2, $C_{31}H_{28}N_2P^+$ requires 459.2.

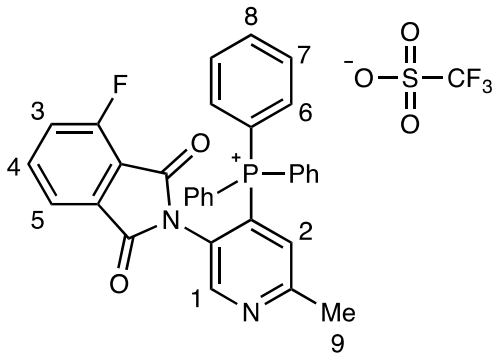
(2-Fluoro-5-(4-methoxyphenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A (except that the stirring time after addition of Tf_2O was 1 hour instead of 30 minutes) using 2-fluoro-5-(4-methoxyphenyl)pyridine (203 mg, 1.00 mmol), Tf_2O (169 μL, 1.00 mmol), PPh_3 (289 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After the purification procedure, the title compound was isolated as a light tan solid (256 mg, 0.42 mmol, 42% yield). mp 177-180 ºC; IR ν_{max}/cm^{-1} (film): 3061, 1608, 1579, 1462, 1440, 1337, 1266, 1142, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.29 (1H, d, *J* = 6.8 Hz, H_1), 7.79-7.58 (15H, m, H_5, H_6, and H_7), 6.99 (1H, d, *J* = 14.8 Hz, H_2), 6.61 (2H, d, *J* = 7.6 Hz, H_3), 6.37 (2H, d, *J* = 7.6 Hz, H_4), 3.66 (3H, s, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.65 (dd, *J* = 244.6, 17.3 Hz), 159.85, 152.61 (dd, *J* = 13.5, 10.1 Hz), 139.76 (dd, *J* = 7.4, 6.0 Hz), 135.57 (d, *J* = 3.1 Hz), 134.27 (d, *J* = 10.4 Hz), 132.30 (dd, *J* = 83.8, 6.6 Hz), 130.94, 130.68 (d, *J* = 13.0 Hz), 125.35 (d, *J* = 3.8 Hz), 120.79 (q, *J* = 319.6 Hz), 116.49 (d, *J* = 88.9 Hz), 115.52 (dd, *J* = 40.1, 11.7 Hz), 113.75, 55.30; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –65.12 (d, *J* = 8.4 Hz), –78.19; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.28 (d, *J* = 9.2 Hz) ; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 464.2,

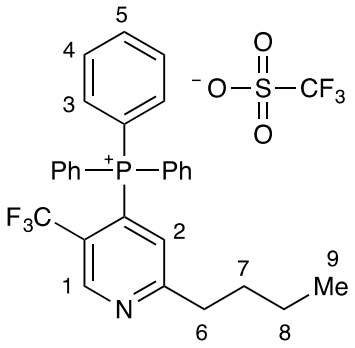
$C_{30}H_{24}FNOP^+$ requires 464.2.

(5-(4-Fluoro-1,3-dioxoisoindolin-2-yl)-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



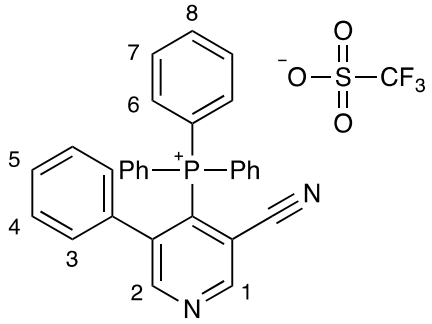
Prepared according to general procedure A using 4-fluoro-2-(6-methylpyridin-3-yl)isoindoline-1,3-dione (1.53 g, 6.00 mmol), Tf_2O (1.01 mL, 6.00 mmol), PPh_3 (1.73 g, 6.60 mmol), DBU (897 μL, 6.00 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a white solid (2.49 g, 3.72 mmol, 62% yield). mp 281-284 ºC; IR ν_{max}/cm^{-1} (film): 3093, 1786, 1727, 1612, 1586, 1483, 1442, 1384, 1263, 1223, 1142, 1096, 1031, 969, 869, 741, 687, 662, 555; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, d, *J* = 6.9 Hz, H_1), 7.83 (1H, dt, *J* = 7.9, 4.2 Hz, H_4), 7.72-7.57 (15H, m, H_6, H_7, and H_8), 7.52-7.38 (3H, m, H_2, H_3, and H_5), 2.73 (3H, s, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.26 (d, *J* = 3.0 Hz), 163.21, 162.12 (d, *J* = 10.0 Hz), 157.27 (d, *J* = 268.0 Hz), 152.66 (d, *J* = 6.2 Hz), 138.64 (d, *J* = 7.7 Hz), 135.68 (d, *J* = 3.1 Hz), 134.43 (d, *J* = 10.6 Hz), 132.36, 130.59 (d, *J* = 13.2 Hz), 128.99 (d, *J* = 7.5 Hz), 127.97 (d, *J* = 84.7 Hz), 127.57, 123.56 (d, *J* = 19.2 Hz), 120.76 (q, *J* = 321.2 Hz), 120.38 (d, *J* = 3.5 Hz), 116.30 (d, *J* = 12.8 Hz), 116.21 (d, *J* = 89.2 Hz), 24.65; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.13, 110.95 (q, *J* = 4.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.46; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 517.2, $C_{32}H_{23}FN_2O_2P^+$ requires 517.1.

(2-Butyl-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$): 9.16 (1H, d, J = 6.8 Hz, H_1), 7.92–7.87 (3H, m, H_5), 7.80–7.76 (6H, m, H_4), 7.73–7.67 (6H, m, H_3), 7.18 (1H, d, J = 17.2 Hz, H_2), 2.93 (2H, t, J = 7.6 Hz, H_6), 1.69–1.62 (2H, m, H_7), 1.37–1.27 (2H, m, H_8), 0.88 (3H, t, J = 7.2 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$): 169.99 (d, J = 9.7 Hz), 150.06 (m), 135.96 (d, J = 3.1 Hz), 134.41 (d, J = 10.4 Hz), 130.74 (d, J = 13.0 Hz), 129.77 (d, J = 8.5 Hz), 125.90 (d, J = 80.1, 1.0 Hz), 124.42 (qd, J = 33.1, 4.0 Hz), 122.49 (qd, J = 275.1, 2.9 Hz), 120.76 (q, J = 321.2 Hz), 116.40 (d, J = 90.4 Hz), 37.93, 30.35, 22.11, 13.63; ^{19}F NMR (365 MHz, $CDCl_3$): –78.27, –53.55; ^{31}P NMR (162 MHz, $CDCl_3$): 27.4 (d, J = 2.3 Hz). The spectroscopic data is in agreement with our reported synthesis.[3]

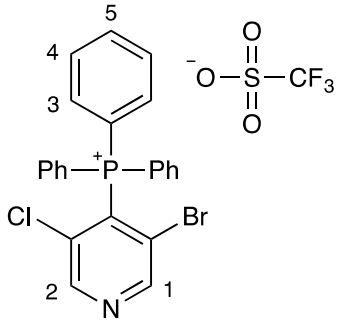
(3-Cyano-5-phenylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 5-phenylnicotinonitrile (991 mg, 5.50

mmol), Tf_2O (930 μL, 5.50 mmol), PPh_3 (1.587 g, 6.05 mmol), DBU (820 μL, 5.50 mmol) and CH_2Cl_2 (55 mL). After the purification procedure, the title compound was isolated as a tan solid (2.51 g, 4.46 mmol, 81% yield). mp 209-214 ºC; IR ν_{max}/cm^{-1} (film): 3067, 2224, 1585, 1482, 1440, 1261, 1140, 1101, 1030, 636, 548; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.10 (1H, d, *J* = 5.0 Hz, H_1), 8.86 (1H, d, *J* = 5.6 Hz, H_2), 7.78-7.58 (15H, m, H_6, H_7, and H_8), 7.15-7.07 (1H, m, H_5), 6.98-6.91 (4H, m, H_3 and H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.60 (d, *J* = 7.1 Hz), 154.24 (d, *J* = 5.8 Hz), 145.10 (d, *J* = 6.1 Hz), 135.45 (d, *J* = 3.0 Hz), 134.49 (d, *J* = 10.6 Hz), 133.77 (d, *J* = 4.6 Hz), 130.58 (d, *J* = 13.5 Hz), 129.49, 129.41, 128.62, 128.00 (d, *J* = 83.2 Hz), 120.79 (q, *J* = 321.3 Hz), 116.58 (d, *J* = 88.9 Hz), 113.69 (d, *J* = 6.0 Hz), 113.16 (d, *J* = 4.6 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.10; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.14; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 441.2, $C_{30}H_{22}N_2P^+$ requires 441.2.

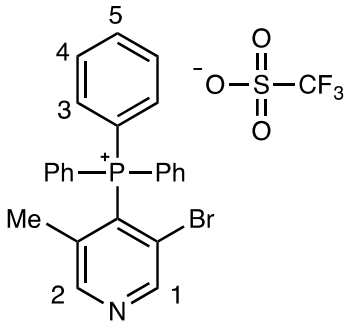
(3-Bromo-5-chloropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 3-bromo-5-chloropyridine (577 mg, 3.00 mmol), Tf_2O (507 μL, 3.00 mmol), PPh_3 (865 mg, 3.30 mmol), DBU (449 μL, 3.00 mmol) and CH_2Cl_2 (30 mL). After the purification procedure, the title compound was isolated as a white solid (1.54 g, 2.55 mmol, 85% yield). mp 186-187 ºC; IR ν_{max}/cm^{-1} (film): 3091, 3059, 3025, 1584, 1500, 1437, 1383, 1161, 1101, 1027, 998, 632; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.79 (1H, d, *J* =

4.7 Hz, H_2), 8.76 (1H, d, J = 5.0 Hz, H_1), 7.83-7.66 (15H, m, H_3, H_4, and H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.56 (d, J = 5.6 Hz), 151.35 (d, J = 4.7 Hz), 137.03 (d, J = 2.5 Hz), 135.66 (d, J = 3.1 Hz), 134.03 (d, J = 10.6 Hz), 130.69 (d, J = 13.4 Hz), 125.87 (d, J = 3.0 Hz), 125.64 (d, J = 91.4 Hz), 120.55 (q, J = 321.3 Hz), 117.01 (d, J = 90.1 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.09; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 23.28; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 452.0, $C_{23}H_{17}BrClNP^+$ requires 452.0.

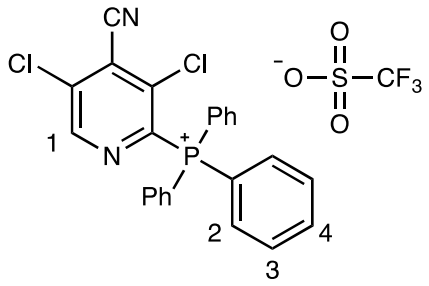
(3-Bromo-5-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 4-(3-methylpyridin-2-yl)morpholine (116 μL, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), PPh_3 (288 mg, 1.10 mmol), DBU (149 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After the purification procedure, the title compound was isolated as a white solid (442 mg, 0.76 mmol, 76% yield). mp 180-182 ºC; IR ν_{max}/cm^{-1} (film): 3056, 3030, 1584, 1510, 1439, 1260, 1221, 1149, 1102, 1028, 763, 633; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.82 (1H, d, J = 5.4 Hz, H_1), 8.64 (1H, d, J = 5.6 Hz, H_2), 7.90-7.72 (15H, m, H_3, H_4, and H_5), 1.86 (3H, s, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.60 (d, J = 8.3 Hz), 153.05 (d, J = 5.6 Hz), 141.86 (d, J = 6.7 Hz), 135.69 (d, J = 3.1 Hz), 134.27 (d, J = 10.3 Hz), 130.90 (d, J = 13.2 Hz), 126.05 (d, J = 87.8 Hz), 125.47 (d, J = 4.0 Hz), 120.77 (q, J = 321.2 Hz), 118.22 (d, J = 89.0 Hz), 20.38; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.17; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.45; *m/z* LRMS (ESI + APCI)

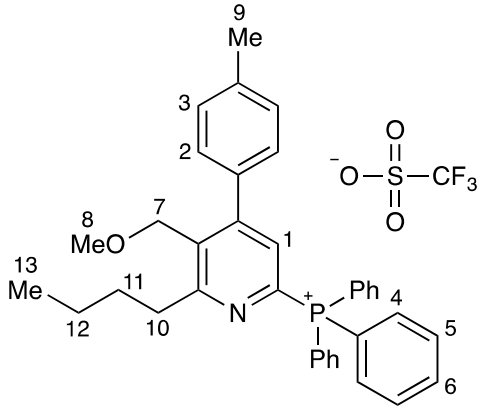
found $[M–OTf]^+$ 432.1, $C_{24}H_{20}BrNP^+$ requires 432.1.

(3,5-Dichloro-4-cyanopyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate



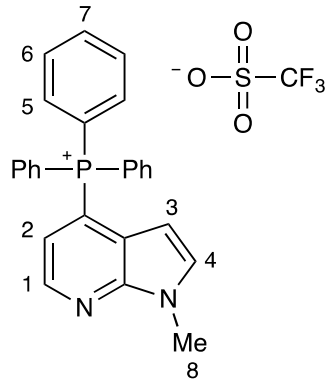
Prepared according to general procedure A (except that the stirring time after Tf_2O addition was 4 hours instead of 30 minutes, the stirring time after PPh_3 addition was 1 hour instead of 30 minutes, and the stirring time after DBU addition was 2 hours) using 3,5-dichloroisonicotinonitrile (650 mg, 3.76 mmol), Tf_2O (0.63 mL, 3.76 mmol), PPh_3 (1.08 g, 4.13 mmol), DBU (0.57 mL, 3.76 mmol) and CH_2Cl_2 (38 mL). After the purification procedure [except that the organic layer was washed with brine (2 x 40 mL)], the title compound was isolated as a yellow solid (1.08 g, 1.84 mmol, 49% yield). mp 190-192 ºC; IR ν_{max}/cm^{-1} (film): 3063, 1438, 1334, 1260, 1149, 1107, 1029, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, s, H_1), 7.84-7.74 (15H, m, H_2, H_3, H_4); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.88 (d, J = 19.9 Hz), 140.67 (d, J = 3.4 Hz), 140.61 (d, J = 64.4 Hz), 140.08 (d, J = 86.7 Hz), 135.70 (d, J = 3.0 Hz), 134.57 (d, J = 10.5 Hz), 130.59 (d, J = 13.2 Hz), 125.34 (d, J = 9.0 Hz), 120.64 (q, J = 319.4 Hz), 115.78 (d, J = 90.2 Hz), 110.49 (d, J = 2.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.98; *m/z* TOF LC/MS found $[M–OTf]^+$ 433.0441, $C_{24}H_{16}Cl_2N_2P^+$ requires 433.04.

(6-Butyl-5-(methoxymethyl)-4-(p-tolyl)pyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate



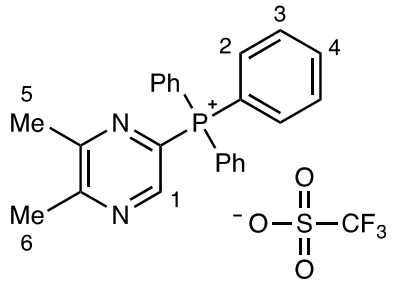
Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91-7.82 (3H, m, H_6), 7.78- 7.62 (12H, m, H_5 and H_4), 7.35 (1H, d, J = 6.4 Hz, H_1), 7.26-7.23 (4H, m, H_3 and H_2), 4.35 (2H, s, H_7), 3.38 (3H, s, H_8), 3.06 (2H, t, J = 7.7 Hz, H_{10}), 2.35 (3H, s, H_9), 1.71 (2H, qn, J = 7.7 Hz, H_{11}), 1.33 (2H, sext, J = 7.6 Hz, H_{12}), 0.87 (3H, t, J = 7.5 Hz, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.00 (d, J = 19.1 Hz), 152.58 (d, J = 11.4 Hz), 143.18, 141.99, 139.39, 135.63 (d, J = 3.1 Hz), 134.47 (d, J = 10.7 Hz), 133.60 (d, J = 1.5 Hz), 133.19 (d, J = 3.8 Hz), 130.42 (d, J = 13.0 Hz), 129.91 (d, J = 25.2 Hz), 129.04 (d, J = 84.7 Hz), 120.83 (q, J = 321.2 Hz), 117.07 (d, J = 89.3 Hz), 67.93, 58.68, 34.27, 30.58, 22.31, 21.08, 13.83.

(1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



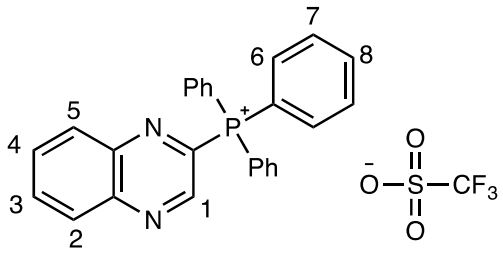
Prepared according to general procedure A using 1-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (388 mg, 2.94 mmol), Tf_2O (500 μL, 2.94 mmol), PPh_3 (847 mg, 3.23 mmol), DBU (440 μL, 2.94 mmol) and CH_2Cl_2 (30 mL). After the purification procedure, the title compound was isolated as a yellow solid (734 mg, 1.32 mmol, 45% yield). mp 182-185 ºC; IR ν_{max}/cm^{-1} (film): 3147, 3068, 1505, 1439, 1261, 1146, 1107, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.56 (1H, t, *J* = 4.4 Hz, H_1), 7.90 (3H, t, *J* = 7.6 Hz, H_7), 7.78-7.73 (6H, m, H_6), 7.67-7.62 (6H, m, H_5), 7.51 (1H, d, *J* = 3.2 Hz, H_4), 7.05 (1H, dd, *J* = 14.8, 4.8 Hz, H_2), 5.64 (1H, d, *J* = 3.2 Hz, H_3), 4.02 (3H, s, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.56 (d, *J* = 12.0 Hz), 142.56 (d, *J* = 11.3 Hz), 135.78 (d, *J* = 3.0 Hz), 134.41, 134.08 (d, *J* = 10.5 Hz), 130.67 (d, *J* = 12.9 Hz), 121.39 (d, *J* = 8.7 Hz), 120.80 (d, *J* = 9.0 Hz), 120.75 (q, *J* = 319.3 Hz), 116.43 (d, *J* = 89.0 Hz), 116.28 (d, *J* = 86.4 Hz), 99.10 (d, *J* = 2.9 Hz), 31.65; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.14; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.22; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 393.2, $C_{26}H_{22}N_2P^+$ requires 393.2.

(5,6-Dimethylpyrazin-2-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 2,3-dimethylpyrazine (1.07 mL, 10.00 mmol), Tf_2O (1.68 mL, 10.00 mmol), PPh_3 (2.89 g, 11.00 mmol), NEt_3 (1.39 mL, 10.00 mmol) and CH_2Cl_2 (100 mL). After the purification procedure, the title compound was isolated as a brown solid (4.30 g, 8.30 mmol, 83% yield). mp 179-181 ºC; IR ν_{max}/cm^{-1} (film): 3062, 2998, 1436, 1260, 1144, 1108, 1029, 634; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.41 (1H, s, H_1), 7.88 (3H, t, J = 7.6 Hz, H_4), 7.76-7.72 (6H, m, H_3), 7.69-7.64 (6H, m, H_2), 2.69 (6H, s, H_5 and H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.65 (d, J = 3.6 Hz), 156.64 (d, J = 15.2 Hz), 146.87 (d, J = 24.6 Hz), 136.30 (d, J = 117.5 Hz), 135.86 (d, J = 3.0 Hz), 134.47 (d, J = 10.5 Hz), 130.60 (d, J = 6.4 Hz), 120.78 (q, J = 319.5 Hz), 116.37 (d, J = 89.0 Hz), 22.78 (d, J = 2.8 Hz), 22.49; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 12.94; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 369.2, $C_{24}H_{22}N_2P^+$ requires 369.2.

Triphenyl(quinoxalin-2-yl)phosphonium trifluoromethanesulfonate

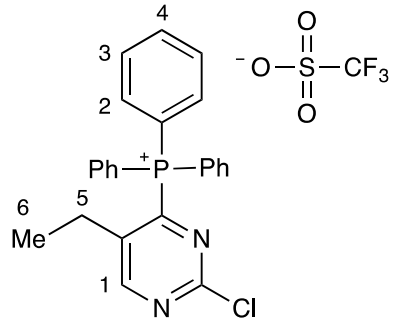


Prepared according to general procedure A (except that NaOAc was added simultaneously

with PPh_3. Additionally, the reaction mixture was heated to 40 ºC for 1 hour after the addition of PPh_3 and NaOAc, was then cooled to room temperature before DBU was added, and was then heated to 40 ºC for 1 hour) using quinoxaline (52 mg, 0.40 mmol), Tf_2O (67 μL, 0.40 mmol), PPh_3 (113 mg, 0.44 mmol), NaOAc (50 mg, 0.6 mmol), DBU (60 μL, 0.40 mmol) and CH_2Cl_2 (4 mL). After the purification procedure,‡‡ the title compound was isolated as a brown solid (138 mg, 0.26 mmol, 64% yield). mp 130-132 ºC; IR ν_{max}/cm^{-1} (film): 3063, 2360, 1484, 1438, 1262, 1109, 1030, 634; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, s, H_1), 8.27-8.22 (2H, m, H_3 and H_4), 8.09-8.01 (2H, m, H_2 and H_5), 7.93-7.90 (3H, m, H_8), 7.79-7.72 (12H, m, H_6 and H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.86 (d, *J* = 25.4 Hz), 143.38 (d, *J* = 2.8 Hz), 142.70 (d, *J* = 17.3 Hz), 140.83 (d, *J* = 111.6 Hz), 136.16 (d, *J* = 3.1 Hz), 134.98, 134.66 (d, *J* = 10.5 Hz), 133.08, 130.86 (d, *J* = 13.0 Hz), 130.19 (d, *J* = 2.0 Hz), 129.85 (d, *J* = 2.3 Hz), 120.76 (q, *J* = 319.5 Hz), 116.03 (d, *J* = 88.1 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.17; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 13.54; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 391.2, $C_{39}H_{31}N_3OP^+$ requires 391.1.

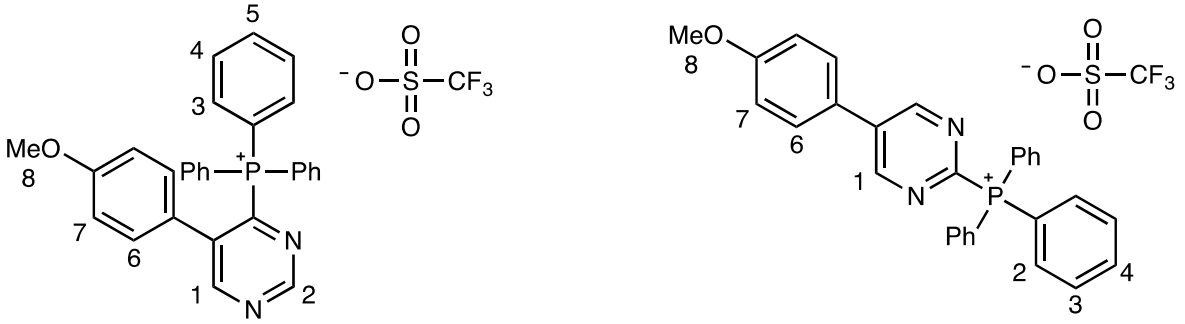
‡‡ The product was precipitated a second time using the same protocol and the product suspension was placed in a –20 °C refrigerator for 12 hours instead of 1 hour.

(2-Chloro-5-ethylpyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A (except that the stirring time Tf_2O addition was 1 hour instead of 30 minutes, EtOAc (0.4 M) was used as the solvent, and the reaction was quenched after 30 minutes at –78 ºC with H_2O) using 2-chloro-5-ethylpyrimidine (0.61 mL, 5.00 mmol), Tf_2O (0.84 mL, 5.00 mmol), PPh_3 (1.44 g, 5.50 mmol), NEt_3 (0.70 mL, 5.00 mmol) and EtOAc (12.5 mL). The solvent was switched to CH_2Cl_2 to follow the purification procedure and the title compound was isolated as a white solid (1.25 g, 2.25 mmol, 45% yield). mp 149-151 ºC; IR ν_{max}/cm^{-1} (film): 3067, 2980,1437, 1396, 1262, 1151, 1107, 1030, 724, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.97 (1H, d, J = 8.4 Hz, H_1), 7.89-7.67 (15H, m, H_2, H_3, and H_4), 2.48 (2H, br q, J = 7.6 Hz, H_5), 0.81 (3H, br t, J = 7.6 Hz, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.59 (d, J = 6.1 Hz), 159.58 (d, J = 20.6 Hz), 152.17 (d, J = 112.3 Hz), 142.42 (d, J = 19.0 Hz), 136.01 (d, J = 3.0 Hz), 134.59 (d, J = 10.4 Hz), 130.83 (d, J = 13.1 Hz), 120.78 (q, J = 319.7 Hz), 115.89 (d, J = 88.1 Hz), 23.91, 13.18; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.18; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.53; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 403.1, $C_{24}H_{21}ClN_2P^+$ requires 403.1.

(5-(4-Methoxyphenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate and (5-(4-methoxyphenyl)pyrimidin-2-yl)triphenylphosphonium trifluoromethanesulfonate

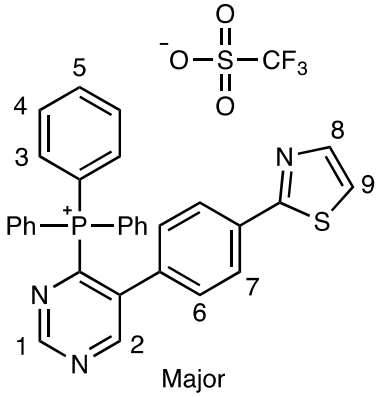


Major Minor

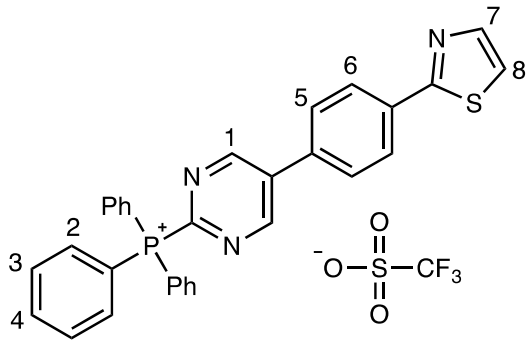
24:1 Mixture of Regioisomers

Prepared according to our previous report.[3] Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.44 (1H, s, H_2), 8.98 (1H, d, J = 9.0 Hz, H_1), 7.80-7.70 (3H, m, H_5), 7.67-7.56 (12H, m, H_3 and H_4), 6.91 (2H, d, J = 8.7 Hz, H_6), 6.55 (2H, d, J = 8.7 Hz, H_7), 3.72 (3H, s, H_8); Minor isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.23 (2H, s, H_1), 7.80-7.70 (3H, m, H_4), 7.70 (2H, d, J = 8.7 Hz, H_5), 7.67-7.56 (12H, m, H_2 and H_3), 7.09 (2H, d, J = 8.6 Hz, H_6), 3.88 (3H, s, H_7); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.84 (d, J = 5.3 Hz), 160.53, 156.97 (d, J = 16.8 Hz), 149.74 (d, J = 114.5 Hz), 142.72 (d, J = 19.2 Hz), 135.22 (d, J = 3.1 Hz), 134.67 (d, J = 10.2 Hz), 130.60, 130.25 (d, J = 13.1 Hz), 123.61, 120.82 (q, J = 321.3 Hz), 117.10 (d, J = 88.6 Hz), 114.37, 55.42; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.01; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ; 17.84; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 447.2, $C_{29}H_{24}N_2OP^+$ requires 447.2.

Triphenyl(5-(4-(thiazol-2-yl)phenyl)pyrimidin-4-yl)phosphonium trifluoromethanesulfonate and Triphenyl(5-(4-(thiazol-2-yl)phenyl)pyrimidin-2-yl)phosphonium trifluoromethanesulfonate



Major



Minor

>20:1 Mixture of Regioisomers

Prepared according to general procedure A (expect that CH_2Cl_2/EtOAc = 1:1 was used as the solvent and NaOAc was added simultaneously with PPh_3) using 2-(4-(pyrimidin-5-yl)phenyl)thiazole (96 mg, 0.40 mmol), Tf_2O (67 μL, 0.40 mmol), PPh_3 (115 mg, 0.44 mmol), NaOAc (36 mg, 0.44 mmol), DBU (60 μL, 0.40 mmol) and CH_2Cl_2/EtOAc (2 mL/2 mL). After the purification procedure,†† the title compound was isolated as a light yellow solid (78 mg, 0.12

†† An excess of chilled Et_2O (0 °C) was added to the concentrated CH_2Cl_2 solution (5 mL) of crude product that was then placed in a –20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit and the solid was washed four times with chilled Et_2O (0 °C). The solid was redissolved in 20 mL of CH_2Cl_2 and washed four times with H_2O and three times with brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to approximately 5 mL. An excess of chilled Et_2O (0 °C) was added to the concentrated solution that was then placed in a –20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit,

mmol, 30% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3060, 1482, 1437, 1397, 1261, 1145, 1106, 1029, 635; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.47 (1H, s, H_1), 8.97 (1H, d, *J* = 7.4 Hz, H_2), 7.84-7.39 (19H, m, H_3, H_4, H_5, H_7, H_8, and H_9), 7.08 (2H, d, *J* = 7.1 Hz, H_6); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.17, 161.36 (d, *J* = 5.3 Hz), 157.42 (d, *J* = 16.8 Hz), 150.16 (d, *J* = 114.0 Hz), 143.92, 142.03 (d, *J* = 19.4 Hz), 135.19 (d, *J* = 3.0 Hz), 134.68 (d, *J* = 10.2 Hz), 134.28, 132.98, 130.23 (d, *J* = 13.0 Hz), 129.89, 126.41, 120.68 (q, *J* = 319.5 Hz), 120.06, 116.79 (d, *J* = 88.2 Hz); Major isomer, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.16ij; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ; 17.96; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 500.2, $C_{31}H_{23}N_3PS^+$ requires 500.1.

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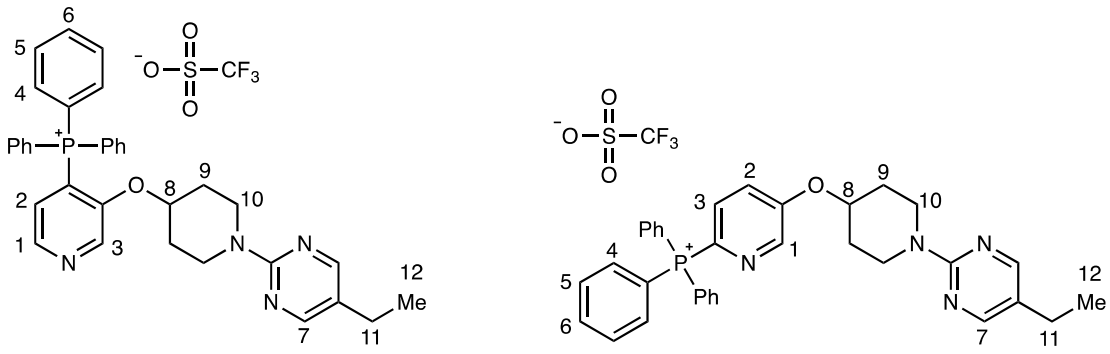
the solid washed with chilled Et_2O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt.

(3-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate and (5-((1-(5-Ethylpyrimidin-2-yl)piperidin-4-yl)oxy)pyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate

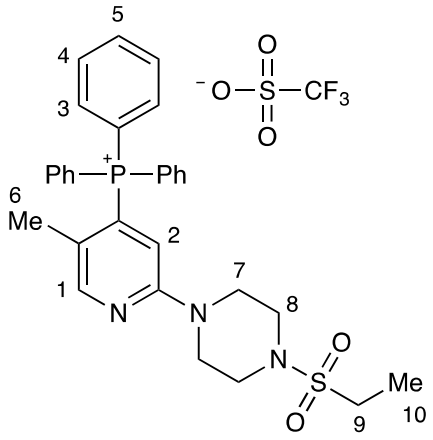


5.3:1 Mixture of Regioisomers

Prepared according to general procedure A using 5-ethyl-2-(4-(pyridin-3-yloxy)piperidin-1-yl)pyrimidine (445 mg, 1.57 mmol), Tf_2O (263 μL, 1.57 mmol), PPh_3 (452 mg, 1.72 mmol), DBU (235 μL, 1.57 mmol) and CH_2Cl_2 (16 mL). After the purification procedure, the title compound was isolated as a white solid (859 mg, 1.24 mmol, 79% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3064, 2940, 2862, 1479, 1437, 1260, 1153, 1030; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, d, *J* = 6.8 Hz, H_3), 8.51 (1H, app t, *J* = 4.3 Hz, H_1), 8.11 (2H, s, H_7), 7.82-7.79 (3H, m, H_6), 7.73-7.68 (6H, m, H_5), 7.65-7.60 (6H, m, H_4), 7.06 (1H, dd, *J* = 15.0, 4.9 Hz, H_2), 4.89 (1H, sept, *J* = 3.7 Hz, H_8), 3.57-3.51 (2H, m, H_{10}), 3.36-3.30 (2H, m, H_{10}), 2.45 (2H, q, *J* = 7.6 Hz, H_{11}), 1.72-1.67 (2H, m, H_9), 1.17 (3H, t, *J* = 7.6 Hz, H_{12}), 1.03-0.95 (2H, m, H_9); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.12, 156.90, 154.11, 143.32 (d, *J* = 11.1 Hz), 136.76 (d, *J* = 4.6 Hz), 135.55 (d, *J* = 3.0 Hz), 133.89 (d, *J* = 10.6 Hz), 130.58 (d, *J* = 13.2 Hz), 128.46 (d, *J* = 7.2 Hz), 124.75, 120.76 (q, *J* = 319.6 Hz), 116.43 (d, *J* = 90.9 Hz), 114.95 (d, *J* = 87.0 Hz), 76.08, 40.51, 29.39, 22.51, 15.46; Major isomer, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.19; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ; 21.48; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$

545.3, $C_{34}H_{34}N_4OP^+$ requires 545.2.

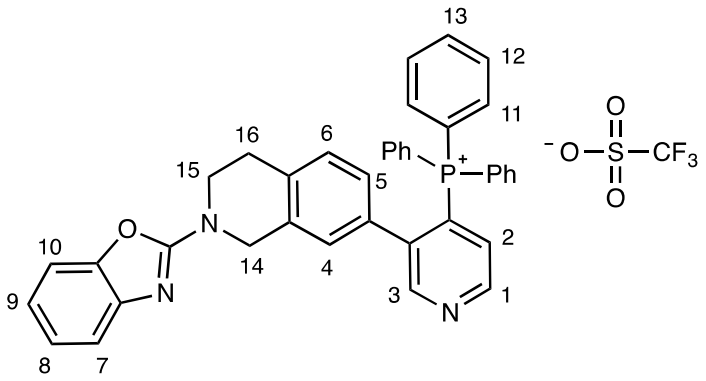
(2-(4-(Ethylsulfonyl)piperazin-1-yl)-5-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A (except that the stirring time PPh_3 addition was 1 hour instead of 30 minutes) using 1-(ethylsulfonyl)-4-(5-methylpyridin-2-yl)piperazine (269 mg, 1.00 mmol), Tf_2O (169 μL, 1.00 mmol), PPh_3 (289 mg, 1.10 mmol), DBU (152 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After the purification procedure, the title compound was isolated as a light yellow solid (440 mg, 0.65 mmol, 65% yield). mp 190-192 ºC; IR ν_{max}/cm^{-1} (film): 3063, 2988, 2927, 2860, 1587, 1438, 1261, 1141, 1029, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.25 (1H, d, J = 7.6 Hz, H_1), 7.89 (3H, t, J = 7.6 Hz, H_5), 7.78-7.69 (12H, m, H_3 and H_4), 6.35 (1H, d, J = 18.0 Hz, H_2), 3.50 (4H, app t, H_7 and H_8), 3.34 (4H, app t, H_7 and H_8), 2.98 (2H, q, J = 7.2 Hz, H_9), 1.77 (3H, s, H_6), 1.33 (3H, t, J = 7.2 Hz, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.41 (d, J = 13.6 Hz), 152.22 (d, J = 10.5 Hz), 135.73 (d, J = 3.0 Hz), 134.15 (d, J = 10.4 Hz), 130.88 (d, J = 12.9 Hz), 127.25 (d, J = 82.5 Hz), 122.58 (d, J = 7.1 Hz), 120.78 (q, J = 319.6 Hz), 116.42 (d, J = 88.1 Hz), 112.48 (d, J = 12.4 Hz), 44.99, 44.53, 43.79, 18.33 (d, J = 4.0 Hz), 7.56; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.25; *m/z* LRMS (ESI + APCI) found [M–

OTf]+ 530.2, $C_{30}H_{33}N_3O_2PS^+$ requires 530.2.

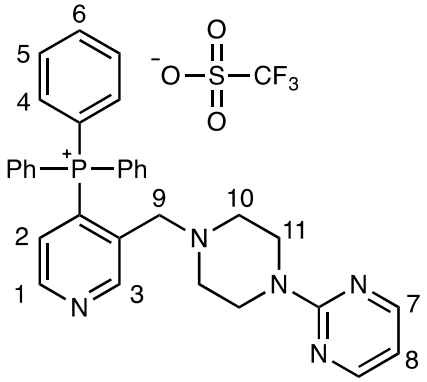
(3-(2-(Benzo[*d*]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A (except that the workup involved six H_2O washes instead of three) using 2-(7-(pyridin-3-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzo[*d*]oxazole (133 mg, 0.41 mmol), Tf_2O (68 μL, 0.41 mmol), PPh_3 (117 mg, 0.45 mmol), DBU (60 μL, 0.41 mmol) and CH_2Cl_2 (4 mL). After the purification procedure, the title compound was dried at 60 ºC under vacuum and isolated as a white solid (185 mg, 0.25 mmol, 61% yield). mp 132-134 ºC; IR ν_{max}/cm^{-1} (film): 3060, 2927, 1635, 1571, 1459, 1437, 1261, 1146, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.92 (1H, app t, *J* = 4.8 Hz, H_1), 8.70 (1H, br d, *J* = 5.6 Hz, H_3), 7.72-7.53 (15H, m, H_{11}, H_{12}, and H_{13}), 7.43 (1H, dd, *J* = 14.8, 4.8 Hz, H_2), 7.33-7.26 (2H, m, H_5 and H_6), 7.13 (1H, t, *J* = 7.6 Hz, H_9), 7.00 (1H, t, *J* = 7.2 Hz, H_8), 6.75 (1H, d, *J* = 7.6 Hz, H_7), 6.63 (1H, d, *J* = 7.6 Hz, H_{10}), 6.43 (1H, s, H_4), 4.35 (2H, s, H_{14}), 3.82 (2H, br t, *J* = 4.8 Hz, H_{15}), 2.82 (2H, app t, *J* = 4.8 Hz, H_{16}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.35, 153.18 (d, *J* = 8.0 Hz), 149.83 (d, *J* = 10.3 Hz), 148.40, 142.49, 140.99 (d, *J* = 6.9 Hz), 135.12 (d, *J* = 2.7 Hz), 135.04, 134.00 (d, *J* = 10.2 Hz), 132.48 (d, *J* = 4.2 Hz), 132.31, 130.28 (d, *J* = 12.9 Hz), 128.56, 128.06 (d, *J* = 8.5 Hz), 127.61, 127.12, 126.45

(d, J = 83.0 Hz), 123.78, 120.63 (q, J = 319.8 Hz), 120.57, 116.74 (d, J = 88.5 Hz), 115.86, 108.68, 46.36, 42.57, 27.49; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.06; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.12; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 588.2, $C_{39}H_{31}N_3OP^+$ requires 588.2.

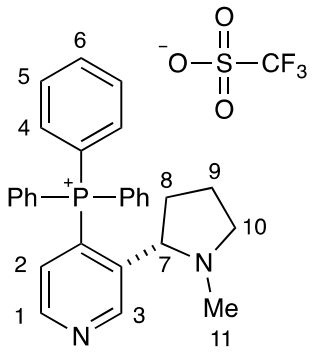
Triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate



Prepared according to general procedure A (expect that after PPh_3 was added, the reaction mixture was stirred for 30 minutes at –50 °C then cooled to –78 °C) using 2-(4-(pyridin-3-ylmethyl)piperazin-1-yl)pyrimidine (510 mg, 2.00 mmol), Tf_2O (336 μL, 2.00 mmol), PPh_3 (577 mg, 2.20 mmol), DBU (300 μL, 2.00 mmol) and CH_2Cl_2 (20 mL). After the purification procedure, the title compound was isolated as a white solid (1.18 g, 1.78 mmol, 89% yield). mp 108-110 ºC; IR ν_{max}/cm^{-1} (film): 2824, 1584, 1547, 1484, 1439, 1357, 1259, 1222, 1145, 1107, 1029, 982, 754, 717; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15 (1H, d, J = 6.7 Hz, H_3), 8.85 (1H, app t, J = 4.5 Hz, H_1), 8.23 (2H, d, J = 4.7 Hz, H_7), 7.89-7.86 (3H, m, H_6), 7.81-7.69 (12H, m, H_4 and H_5), 7.22 (1H, dd, J = 5.1, 15.8 Hz, H_2), 6.45 (1H, t, J = 4.7 Hz, H_8), 3.42 (4H, s, H_{11}), 3.17 (2H, s, H_9), 1.93 (4H, r, J = 4.7 Hz, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.17, 157.49, 153.37 (d, J = 8.2 Hz), 150.76 (d, J = 10.6 Hz), 136.99 (d, J = 5.8 Hz), 135.72 (d, J = 3.0 Hz), 133.99 (d, J = 10.2 Hz),

130.89 (d, J = 13.0 Hz), 129.06 (d, J = 9.7 Hz), 126.61 (d, J = 82.4 Hz), 120.72 (q, J = 319.5 Hz), 116.86 (d, J = 88.9 Hz), 110.07, 59.13 (d, J = 3.0 Hz), 52.47, 42.81; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.16, -115.20; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.19; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 516.3, $C_{32}H_{31}N_5P^+$ requires 516.2.

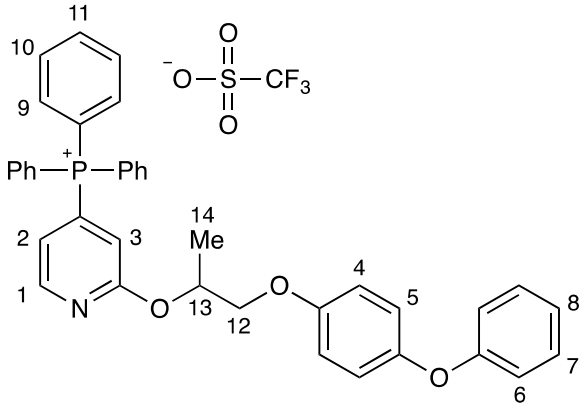
(*S*)-(3-(1-Methylpyrrolidin-2-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.37 (1H, d, J = 6.9 Hz, H_3), 8.79 (1H, app t, J = 4.6 Hz, H_1), 7.96-7.62 (15H, m, H_4, H_5, and H_6), 7.12 (1H, dd, J = 15.5, 5.1 Hz, H_2), 3.10-2.93 (2H, m, H_7 and H_{10}), 1.99 (1H, app q, J = 8.5 Hz, H_{10}), 1.87-1.67 (4H, m, H_9 and H_{11}), 1.49-1.23 (2H, m, H_8 and H_9), 1.01-0.83 (1H, m, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.01 (d, J = 8.1 Hz), 149.96 (d, J = 10.6 Hz), 144.24 (d, J = 6.7 Hz), 135.99 (d, J = 3.0 Hz), 134.39 (d, J = 10.2 Hz), 131.05 (d, J = 13.0 Hz), 127.53 (d, J = 9.9 Hz), 126.24 (d, J = 81.6 Hz), 120.83 (q, J = 321.3 Hz), 116.74 (d, J = 88.5 Hz), 66.03 (d, J = 4.9 Hz), 55.97, 39.39, 35.43, 22.93.

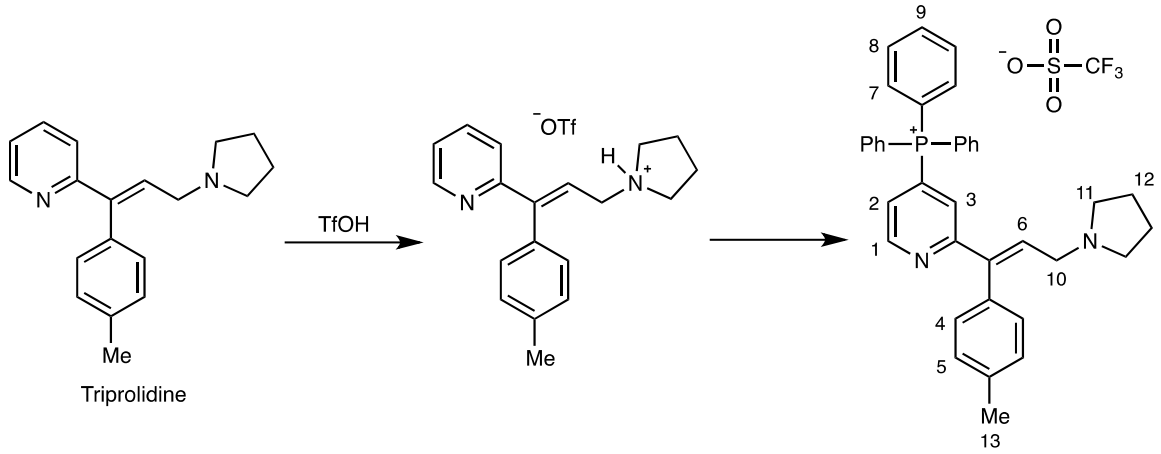
(2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridin-4-yl)triphenylphosphonium

trifluoromethanesulfonate



Prepared according to general procedure A using 2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine (1.91 g, 5.95 mmol), Tf_2O (1.00 mL, 5.95 mmol), PPh_3 (1.73 g, 6.58 mmol), DBU (0.89 mL, 5.95 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a white solid (1.90 g, 3.64 mmol, 61% yield). mp 68-70 ºC; IR ν_{max}/cm^{-1} (film): 3063, 2984, 2936, 2877, 1586, 1541, 1503, 1486, 1438, 1398, 1262, 1218, 1147, 1107, 1029, 996, 725, 689, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, app t, J = 5.3 Hz, H_1), 7.93-7.87 (3H, m, H_{11}), 7.82-7.74 (6H, m, H_{10}), 7.67-7.59 (6H, m, H_9), 7.30-7.23 (2H, m, H_7), 7.13 (1H, ddd, J = 11.7, 5.3, 1.2 Hz, H_2), 7.02 (1H, t, J = 7.4 Hz, H_8), 6.94-6.77 (7H, m, H_3, H_4, H_5, and H_6), 5.66 (1H, sext, J = 5.3 Hz, H_{13}), 4.18-4.07 (2H, m, H_{12}), 1.48 (3H, d, J = 6.4 Hz, H_{14}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.72 (d, J = 15.9 Hz), 158.13, 154.71, 150.29, 149.77 (d, J = 12.1 Hz), 136.11 (d, J = 3.0 Hz), 134.32 (d, J = 10.6 Hz), 130.91 (d, J = 13.0 Hz), 130.78 (d, J = 84.2 Hz), 129.50, 122.43, 120.78 (q, J = 321.2 Hz), 120.56, 119.08 (d, J = 8.1 Hz), 117.47, 116.55 (d, J = 10.0 Hz), 115.62 (d, J = 89.4 Hz), 115.61, 71.50, 70.49, 16.41; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.11; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.28; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 582.3, $C_{38}H_{33}NO_3P^+$ requires 582.2.

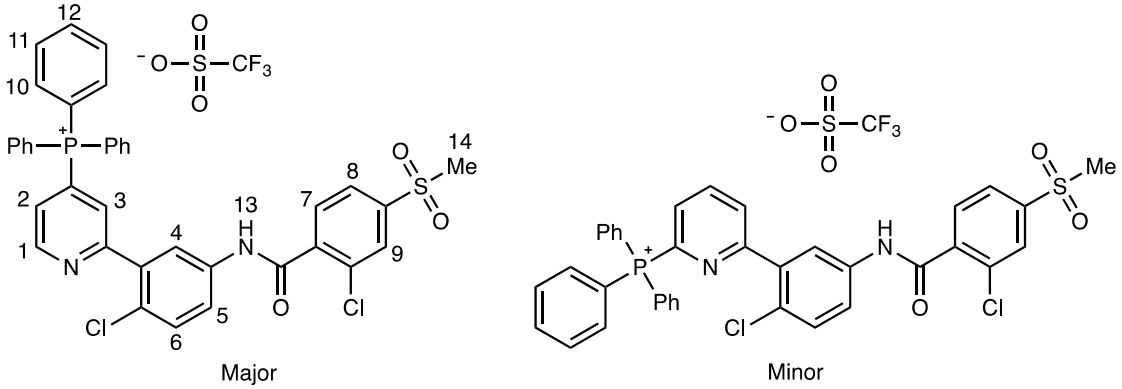
(*E*)-Triphenyl(2-(3-(pyrrolidin-1-yl)-1-(*p*-tolyl)prop-1-en-1-yl)pyridin-4-yl)phosphonium



Triprolidine (651 mg, 2.34 mmol) was dissolved in Et_2O (10 mL) and cooled to 0 °C. Trifluoromethanesulfonic acid (206 μL, 2.34 mmol) was added dropwise, the ice bath was removed, and the solution was stirred for 10 minutes at room temperature. The solution was concentrated *in vacuo* and the resulting acid salt was subjected to general procedure A (except that the product was precipitated a second time using the same protocol and the product suspension was placed in a –20 °C refrigerator for 12 hours instead of 1) using (*E*)-2-(3-(pyrrolidin-1-yl)-1-(*p*-tolyl)prop-1-en-1-yl)pyridine (1.00 g, 2.34 mmol), Tf_2O (393 μL, 2.34 mmol), PPh_3 (673 mg, 2.57 mmol), DBU (699 μL, 4.68 mmol) and EtOAc (23 mL). After the purification procedure, the title compound was isolated as an orange solid (820 mg, 1.19 mmol, 51% yield). mp 81-85 ºC; IR ν_{max}/cm^{-1} (film): 3057, 1709, 1578, 1536, 1485, 1439, 1260, 1108, 1028, 921, 844, 745, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.93 (1H, app t, J = 5.3 Hz, H_1), 7.92-7.56 (15H, m, H_7, H_8, and H_9), 7.38 (1H, dd, J = 12.3, 4.8 Hz, H_2), 7.26 (1H, d, J = 14.3 Hz, H_3), 7.18-6.98 (5H, m, H_4, H_5, and H_6), 3.71 (2H, d, J = 6.9 Hz, H_{10}), 3.13 (4H, br s, H_{11}), 2.37 (3H, s, H_{13}), 1.99 (4H, br s, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.35 (d, J = 10.1 Hz), 150.91 (d, J = 10.5 Hz), 144.24, 138.20, 135.98 (d, J = 3.0 Hz), 134.35 (d, J = 10.6 Hz), 132.33, 130.86 (d, J = 13.1 Hz), 129.74, 129.13, 128.85 (d, J = 84.7 Hz), 126.31, 125.58 (d, J = 9.2 Hz), 125.33 (d, J = 8.0 Hz), 120.56 (q, J =

320.4 Hz), 115.58 (d, J = 89.6 Hz), 53.99, 53.75, 23.03, 21.21; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.05; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.34; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 539.3, $C_{37}H_{36}N_2P^+$ requires 539.3.

(2-(2-Chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate and (6-(2-chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate

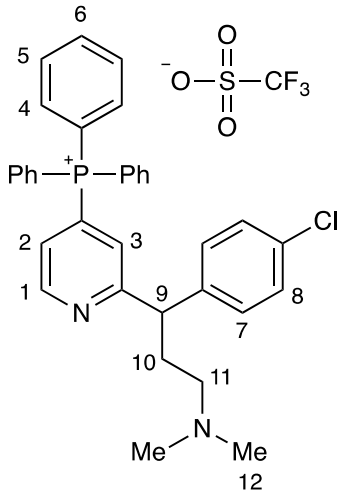


7:1 Mixture of Regioisomers

Prepared according to general procedure A using 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (632 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), PPh_3 (433 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol) and CH_2Cl_2 (15 mL). After the purification procedure, the compound was purified by flash column chromatography (silica gel, gradient elution: 5% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2 followed by a second silica gel column: 3% MeOH in CH_2Cl_2) affording the title compound as a yellow solid with a 2.8% unknown impurity (387 mg, 0.47 mmol, 31% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3061, 2925, 1681, 1537, 1314, 1247, 1151, 1049, 725, 635; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.98 (1H, s, H_{13}), 8.98 (1H, app t, J = 4.9 Hz, H_1), 8.15-7.33 (23H, m, H_2, H_3, H_4, H_5, H_6, H_7,

H_8, H_9, H_{10}, H_{11}, and H_{12}), 3.01 (3H, s, H_{14}); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.47, 158.46 (d, *J* = 10.8 Hz), 151.22 (d, *J* = 10.9 Hz), 142.27, 140.45, 137.91, 136.76, 136.21 (d, *J* = 2.9 Hz), 134.44 (d, *J* = 10.5 Hz), 132.47, 130.94 (d, *J* = 13.1 Hz), 130.55, 130.02, 128.68, 128.54 (d, *J* = 84.4 Hz), 128.12 (d, *J* = 8.8 Hz), 126.44, 125.78, 125.45 (d, *J* = 8.4 Hz), 123.22, 122.62, 120.39 (q, *J* = 320.6 Hz), 115.58 (d, *J* = 89.6 Hz), 44.34; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.34; Both isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.60 (major), 17.95 (minor); ; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 681.1, $C_{37}H_{28}Cl_2N_2O_3PS^+$ requires 681.1.

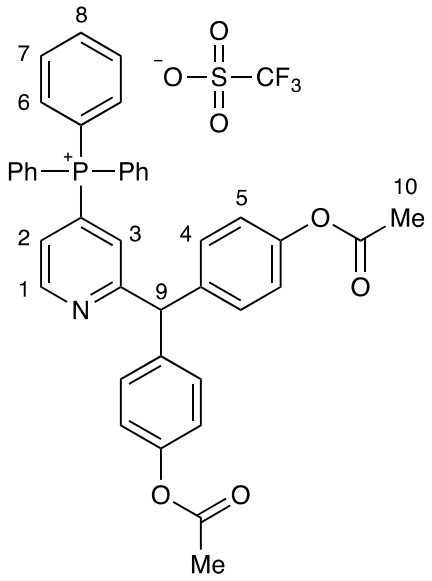
(2-(1-(4-Chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[3] ^1H NMR (400 MHz, $CDCl_3$) δ: 8.97 (1H, app t, *J* = 5.1 Hz, H_1), 7.93-7.86 (3H, m, H_6), 7.80-7.70 (6H, m, H_5), 7.61-7.50 (6H, m, H_4), 7.39 (1H, ddd, *J* = 12.8, 5.1, 1.5 Hz, H_2), 7.25-7.16 (5H, m, H_3, H_7, and H_8), 4.28 (1H, app t, *J* = 6.8 Hz, H_9), 2.56-2.43 (1H, m, H_{10}), 2.32-2.11 (9H, m, H_{10}, H_{11}, and H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.55 (d, *J* = 9.9 Hz), 150.97 (d, *J* = 9.9 Hz), 140.26, 135.82 (d, *J* = 3.1 Hz), 134.02 (d, *J* = 10.7 Hz), 132.25, 130.61 (d, *J* = 13.0 Hz), 128.92 (d, *J* = 85.5 Hz), 128.75, 127.92, 126.26 (d, *J* = 8.4

Hz), 124.42 (d, J = 7.6 Hz), 120.46 (q, J = 321.2 Hz), 115.31 (d, J = 89.3 Hz), 56.73, 49.77, 44.88, 31.99.

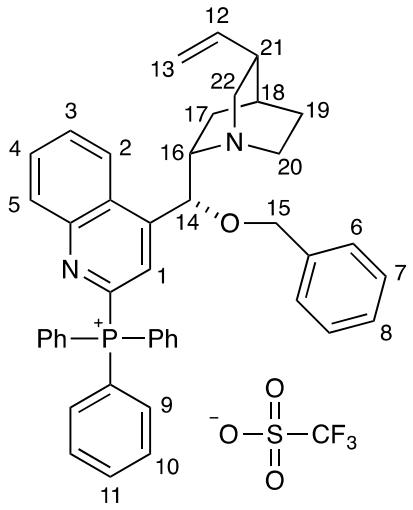
(2-(Bis(4-acetoxyphenyl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using (pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate (181 mg, 0.50 mmol), Tf_2O (84 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), NEt_3 (70 μL, 0.50 mmol) and CH_2Cl_2 (5 mL). After the purification procedure, the title compound was isolated as a white solid (309 mg, 0.40 mmol, 80% yield). mp 97-100 ºC; IR ν_{max}/cm^{-1} (film): 3060, 1752, 1576, 1503, 1438, 1369, 1262, 1149, 1108, 1029, 910, 725, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, app t, J = 5.1 Hz, H_1), 7.86-7.80 (3H, m, H_8), 7.73-7.66 (6H, m, H_7), 7.56-7.39 (7H, m, H_2 and H_6), 7.18 (1H, d, J = 13.7 Hz, H_3), 7.13-7.08 (4H, m, H_4), 6.97–6.91 (4H, m, H_5), 5.72 (1H, s, H_9), 2.21 (6H, s, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.12, 164.99 (d, J = 9.4 Hz), 151.19 (d, J = 10.4 Hz), 149.33, 138.40, 135.95 (d, J = 3.0 Hz), 134.11 (d, J = 10.6 Hz), 130.73 (d, J = 13.0 Hz), 129.91, 129.02 (d, J = 83.8 Hz), 126.64 (d, J = 8.7 Hz), 124.91 (d, J =

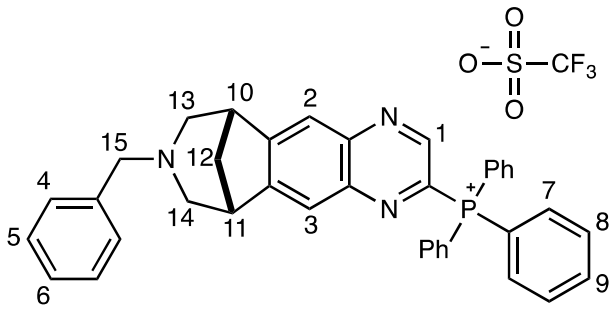
7.9 Hz), 121.55, 120.62 (q, J = 321.2 Hz), 115.26 (d, J = 89.4 Hz), 57.36, 20.85; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.05; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.34; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 622.2, $C_{40}H_{33}NO_4P^+$ requires 622.2.

(4-((*R*)-(Benzyloxy)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate



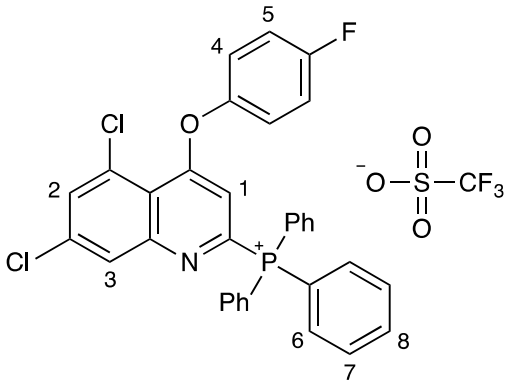
Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, J = 8.1 Hz, H_5), 8.26 (1H, d, J = 8.6 Hz, H_2), 7.94 (1H, t, J = 7.2 Hz, H_3), 7.91-7.60 (17H, m, H_1, H_4, H_9, H_{10}, and H_{11}), 7.29-7.02 (3H, m, H_7 and H_8), 7.14-7.02 (2H, m, H_6), 5.83-5.45 (2H, m, H_{12} and H_{14}), 5.07-4.89 (2H, m, H_{13}), 4.60 (1H, d, J = 11.4 Hz, H_{15}), 4.33 (1H, d, J = 11.4 Hz, H_{15}), 3.52-3.06 (3H, m, H_{16}, H_{20}, and H_{22}), 2.84-2.62 (2H, m, H_{20} and H_{22}), 2.49-2.33 (1H, br s, H_{21}), 2.06-1.47 (5H, m, H_{17}, H_{18}, H_{19}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.20 (d, J = 22.1 Hz), 148.45, 145.10, 143.93, 139.54, 136.58, 135.68 (d, J = 3.0 Hz), 134.53 (d, J = 10.0 Hz), 131.99-131.79 (3C, m), 131.23, 130.44 (d, J = 13.2 Hz), 128.40, 127.89, 127.22, 126.71 (d, J = 3.1 Hz), 126.08, 123.78, 120.64 (q, J = 320.3 Hz), 116.99 (d, J = 87.7 Hz), 115.55, 71.81, 60.71, 55.61, 43.04, 38.32, 26.89, 25.83.

((6*S*,10*R*)-8-Benzyl-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxalin-2-yl)triphenylphosphonium



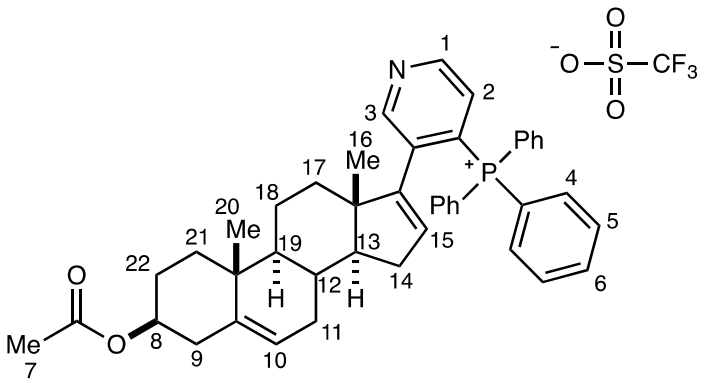
Prepared according to our previous report.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.09 (1H, s, H_1), 8.10-7.72 (17H, m, H_2, H_3, H_7, H_8, and H_9), 7.20-7.05 (3H, m, H_5 and H_6), 6.92-6.80 (2H, m, H_4), 3.55-3.27 (4H, m, H_{15}, H_{10}, and H_{11}), 3.03-2.87 (2H, m, H_{13} or H_{14}), 2.66-2.42 (2H, m, H_{13} or H_{14}), 2.29-2.15 (1H, m, H_{12}), 1.87 (1H, d, J = 10.8 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$)[§§] δ: 144.90 (d, J = 23.5 Hz), 144.21, 143.45 (d, J = 16.9 Hz), 137.51 (br s), 136.00 (d, J = 2.9 Hz), 134.55 (d, J = 10.9 Hz), 130.72 (d, J = 13.0 Hz), 129.20-126.21 (3C, m,), 120.69 (br s), 120.67 (q, J = 321.5 Hz), 116.42 (d, J = 88.3 Hz), 61.29, 57.90-56.06 (2C, m), 43.14-40.43 (3C, m). The spectroscopic data is in agreement with our reported synthesis.[3]

(5,7-Dichloro-4-(4-fluorophenoxy)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 5,7-dichloro-4-(4-fluorophenoxy)quinoline-2-*d* (308 mg, 1.00 mmol), Tf_2O (168 μL, 1.00 mmol), PPh_3 (288 mg, 1.10 mmol), DBU (150 μL, 1.00 mmol) and EtOAc (10 mL). After the purification procedure, the title compound was isolated as a white solid (605 mg, 0.84 mmol, 84% yield). mp 159-160 ºC; IR ν_{max}/cm^{-1} (film): 3045, 2919, 2849, 1595, 1556, 1499, 1371, 1295, 1147, 1107, 866, 748, 726, 687; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.09 (1H, d, *J* = 1.8 Hz, H_3), 7.86 (3H, m, H_8), 7.76 (1H, d, *J* = 1.8 Hz, H_2), 7.72-7.64 (12H, m, H_6 and H_7), 7.16-7.06 (4H, m, H_4 and H_5), 6.54 (1H, d, *J* = 6.6 Hz, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.79 (d, *J* = 13.7 Hz), 160.44 (d, *J* = 246.0 Hz), 152.01 (d, *J* = 24.8 Hz), 148.45 (d, *J* = 83.2 Hz), 147.85 (d, *J* = 32.0 Hz), 137.33, 135.66 (d, *J* = 3.0 Hz), 134.49 (d, *J* = 10.3 Hz), 132.40, 131.16 (d, *J* = 1.4 Hz), 130.49 (d, *J* = 13.0 Hz), 128.11, 122.81 (d, *J* = 8.6 Hz), 120.71 (q, *J* = 321.3 Hz), 117.94 (d, *J* = 2.2 Hz), 117.35 (d, *J* = 23.7 Hz), 116.18 (d, *J* = 88.4 Hz), 110.10 (d, *J* = 29.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.21, –115.20; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.39; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 568.1, $C_{32}H_{23}FN_2O_2P^+$ requires 568.1.

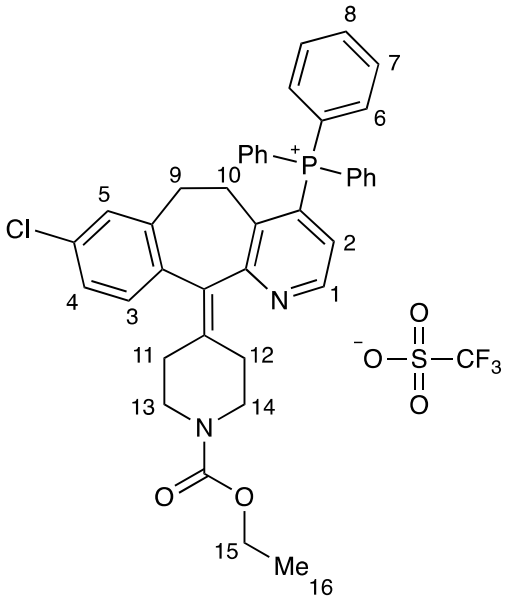
(3-((3*S*,9*S*,10*R*,13*S*,14*S*)-3-Acetoxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



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-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (930 mg, 2.37 mmol), Tf_2O (398 μL, 2.37 mmol), PPh_3 (685 mg, 2.61 mmol), DBU (354 μL, 2.37 mmol) and CH_2Cl_2 (24 mL). After the purification procedure, the title compound was isolated as a white solid (1.28 g, 1.60 mmol, 67% yield). mp 162-169 ºC; IR ν_{max}/cm^{-1} (film): 3060, 2925, 2852, 1727, 1437, 1374, 1222, 1147, 1100, 1029, 718, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, d, *J* = 7.2 Hz), 8.72 (1H, app t, *J* = 4.1 Hz), 7.88-7.59 (15H, m), 7.27 (1H, dd, *J* = 15.7, 5.2 Hz), 5.55 (1H, s), 5.28 (1H, d, *J* = 3.4 Hz), 4.58 (1H, m), 2.33-2.18 (2H, m), 1.99 (3H, s), 1.87-1.30 (10H, m), 1.24-1.01 (5H, m), 0.94 (3H, s), 0.79 (1H, td, *J* = 12.1, 3.7 Hz), 0.57 (1H, td, *J* = 11.2, 3.9 Hz), –0.22 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.37, 150.59 (d, *J* = 7.5 Hz), 149.00 (d, *J* = 4.2 Hz), 148.68 (d, *J* = 10.8 Hz), 139.88, 139.11, 137.35 (d, *J* = 6.1 Hz), 135.54 (d, *J* = 2.9 Hz), 134.22 (d, *J* = 9.9 Hz), 130.83 (d, *J* = 13.0 Hz), 129.95 (d, *J* = 10.5 Hz), 125.23 (d, *J* = 83.7 Hz), 121.56, 120.74 (q, *J* = 321.2 Hz), 117.96 (d, *J* = 89.6 Hz), 73.46, 55.28, 49.70, 48.71, 37.88, 36.76, 36.42, 33.51, 32.43, 30.97, 29.74, 27.50, 21.27, 20.25, 18.95, 18.64; ^{19}F NMR (365

MHz, $CDCl_3$) δ: –78.12; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.76; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 652.4, $C_{44}H_{47}NO_2P^+$ requires 652.3.

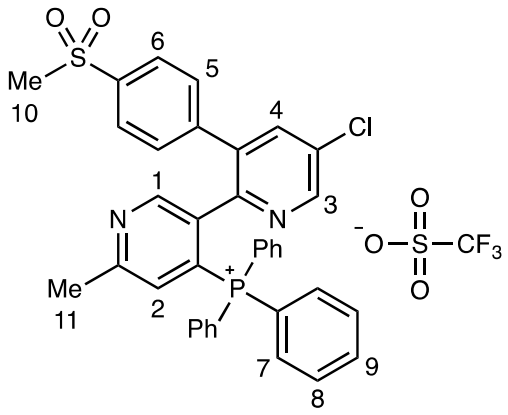
(8-Chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5Hbenzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[3] ^1H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, app t, *J* = 5.0 Hz, H_1), 7.97-7.87 (3H, m, H_8), 7.86-7.74 (6H, m, H_7), 7.73-7.60 (6H, m, H_6), 7.16-7.01 (3H, m, H_2, H_3, and H_4), 6.71 (1H, s, H_5), 4.14 (2H, q, *J* = 7.0 Hz, H_{15}), 3.84-3.61 (2H, m, H_{13} or H_{14}), 3.45- 3.20 (3H, m, H_{10} and H_{13} or H_{14}), 2.75 (1H, dt, *J* = 17.4, 4.7 Hz, H_9), 2.58 (1H, dt, *J* = 14.9, 4.7 Hz, H_{10}), 2.53-2.30 (3H, m, H_{11} or H_{12}), 2.26-2.09 (1H, m, H_{11} or H_{12}), 1.60-1.43 (1H, m, H_9), 1.25 (3H, t, *J* = 7.2 Hz, H_{16}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.64 (d, *J* = 8.3 Hz), 155.37, 149.08 (d, *J* = 11.4 Hz), 139.23, 136.84, 136.66 (d, *J* = 6.8 Hz), 136.06 (d, *J* = 3.1 Hz), 134.21 (d, *J* = 10.7 Hz), 133.95, 133.57, 132.37, 131.58, 131.13 (d, *J* = 13.0 Hz), 129.85, 127.22 (d, *J* = 10.0 Hz), 127.01 (d, *J* = 82.2 Hz), 126.43, 120.78 (q, *J* = 321.3 Hz), 116.42 (d, *J* = 88.5 Hz), 61.39,

44.65, 44.41, 30.74, 30.46, 30.39, 29.39, 14.59.

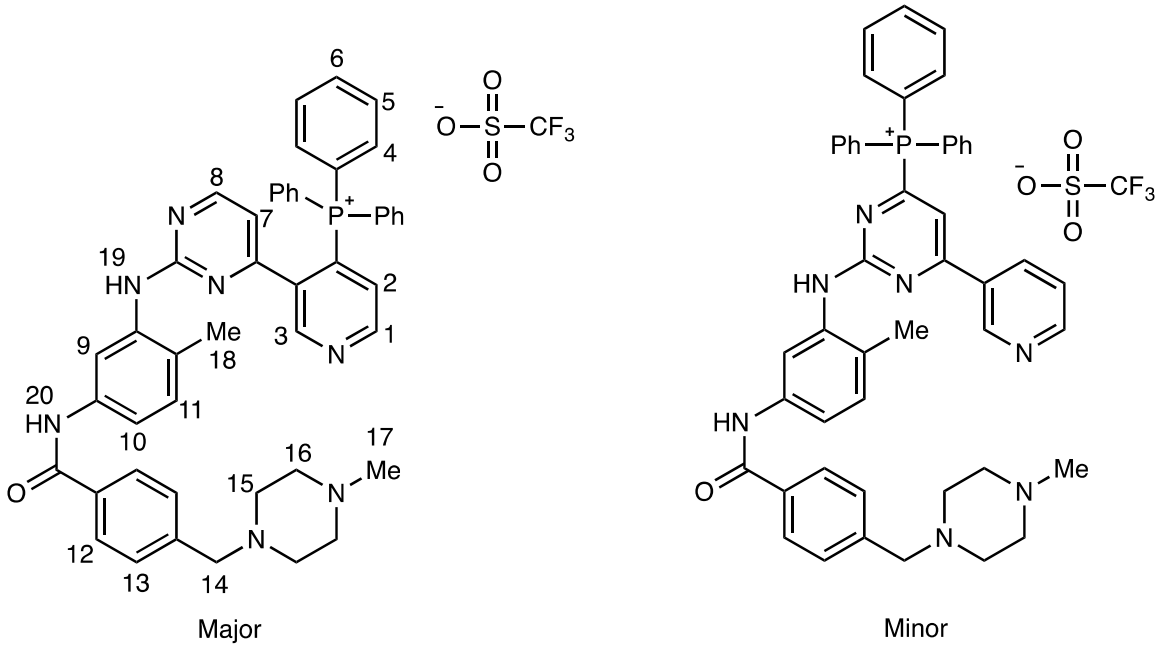
(5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A (except that NaOAc was added simultaneously with PPh_3) using 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (384 mg, 1.07 mmol), Tf_2O (180 μL, 1.07 mmol), PPh_3 (309 mg, 1.18 mmol), NaOAc (88 mg, 1.07 mmol), DBU (160 μL, 1.07 mmol) and CH_2Cl_2 (11 mL). After the purification procedure, the title compound was isolated as a white solid (603 mg, 0.78 mmol, 73% yield). mp 157-163 ºC; IR ν_{max}/cm^{-1} (film): 3062, 1709, 1577, 1542, 1485, 1436, 1311, 1261, 1223, 1150, 1101, 1030, 921, 888, 715, 690, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.28 (1H, d, *J* = 7.1 Hz, H_1), 8.10 (2H, d, *J* = 8.2 Hz, H_6), 7.86-7.62 (16H, m, H_4, H_7, H_8, and H_9), 7.51-7.45 (3H, m, H_3 and H_5), 7.20 (1H, d, *J* = 16.5 Hz, H_2), 3.14 (3H, s, H_{10}), 2.54 (3H, s, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.84 (d, *J* = 11.2 Hz), 152.42 (d, *J* = 7.3 Hz), 147.53 (d, *J* = 2.2 Hz), 146.09, 141.53, 141.02, 138.92, 135.62, 134.84 (d, *J* = 2.9 Hz), 134.17 (d, *J* = 10.0 Hz), 133.29 (d, *J* = 3.6 Hz), 132.10, 130.76 (d, *J* = 10.2 Hz), 130.03 (d, *J* = 13.1 Hz), 129.86, 128.55, 128.19 (d, *J* = 86.2 Hz), 120.77 (q, *J* = 321.1 Hz), 119.34 (d, *J* = 91.8 Hz), 43.96, 24.55; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.14; ^{31}P NMR (162 MHz,

$CDCl_3$) δ: 25.54; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 619.2, $C_{36}H_{29}ClN_2O_2PS^+$ requires 619.1.

(3-(2-((2-Methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate and (2-((2-Methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)-6-(pyridin-3-yl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate



20:1 Mixture of Regioisomers

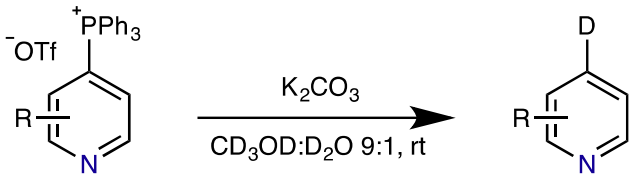
Prepared according to general procedure A† using Imatinib (*N*-(4-methyl-3-((4-(pyridin-3-

† Imatinib was dissolved in 6.3 mL of CH_2Cl_2 by gentle heating with a heat gun. After adding Tf_2O, the mixture was stirred for 2 hours at –78 ºC instead of 30 minutes. After adding PPh_3 at –78 ºC the mixture was warmed to –50 ºC and stirred for 1 hour. DBU was added at –50 ºC and allowed to stir for 2 hours before quenching at –50 ºC with H_2O (2 mL).

yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide) (123 mg, 0.25 mmol), Tf_2O (42 μL, 0.25 mmol), PPh_3 (72 mg, 0.28 mmol), DBU (38 μL, 0.25 mmol) and CH_2Cl_2 (6.3 mL). After the purification procedure, the title compound was isolated as a yellow solid (170 mg, 0.19 mmol, 75% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3421, 3301, 3067, 2797, 1662, 1570, 1527, 1441, 1402, 1308, 1223, 1143, 1103, 1029, 748, 635; Major isomer, ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.14 (1H, s, H_{20}), 9.55 (1H, d, J = 6.7 Hz, H_3), 9.09 (1H, app t, J = 4.6 Hz, H_1), 8.31 (1H, d, J = 5.1 Hz, H_8), 8.00-7.55 (18H, m, H_4, H_5, H_6, H_9, and H_{12}), 7.52-7.20 (5H, m, H_2, H_7, H_{10}, and H_{13}), 7.08 (1H, d, J = 8.3 Hz, H_{11}), 6.10 (1H, br, H_{19}), 3.55 (2H, s, H_{14}), 2.70-2.13 (11H, m, H_{15}, H_{16}, and H_{18}), 1.74 (3H, s, H_{17}); Major isomer, ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.15, 159.79, 159.72 (d, J = 2.0 Hz), 158.29, 152.67 (d, J = 11.4 Hz), 151.77 (d, J = 6.8 Hz), 141.14 (br), 137.28, 136.16, 135.81 (d, J = 3.8 Hz), 134.70 (d, J = 2.3 Hz), 133.91 (d, J = 10.0 Hz), 130.75 (d, J = 10.2 Hz), 129.96, 129.95 (d, J = 13.4 Hz), 128.74, 127.70, 125.67 (d, J = 86.2 Hz), 125.48, 120.67 (q, J = 322.8 Hz), 119.54 (d, J = 92.3 Hz), 117.03, 117.00, 115.56, 110.34, 60.65, 53.15, 50.09, 43.09, 16.99; Both isomers ^{19}F NMR (365 MHz, DMSO-d_6) δ: –77.75; Both isomers, ^{31}P NMR (162 MHz, DMSO-d_6) δ: 25.92 (major), 21.57 (minor); *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 754.4, $C_{47}H_{45}N_7OP^+$ requires 754.3.

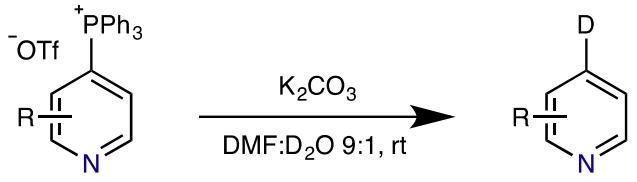
A1.5 Preparation of Deuterated Azines

General procedure B



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 phosphonium salt (1.0 equiv), K_2CO_3 (1.5 equiv), and placed under a nitrogen atmosphere. CD_3OD:D_2O 9:1 (0.3 M) was added at room temperature and the reaction was stirred for 2 hours. The reaction mixture was diluted with CH_2Cl_2 (approximately the same volume as CD_3OD:D_2O) and the mixture was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography under the stated conditions to provide the deuterated azaarene product.

General procedure C

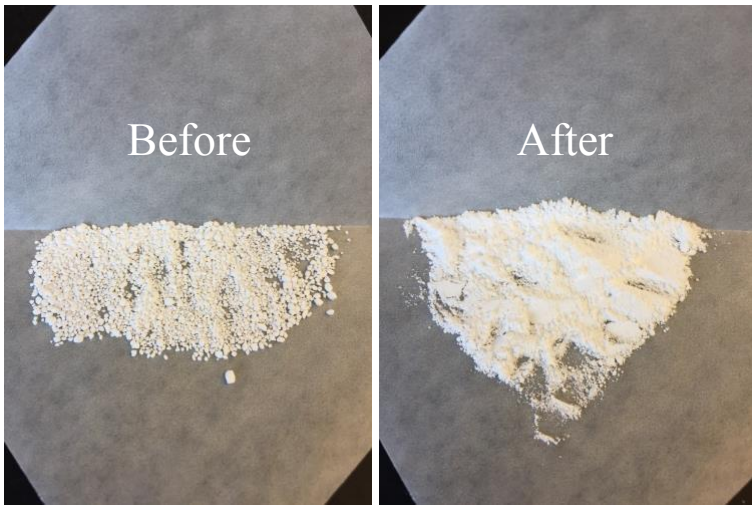


An oven-dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the phosphonium salt (1.0 equiv), K_2CO_3 (1.5 equiv),

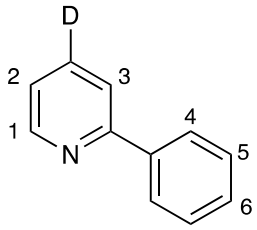
and placed under a nitrogen atmosphere. DMF:D_2O 9:1 (0.3 M) was added at room temperature and the reaction was stirred for 15 hours. The reaction mixture was diluted with H_2O (approximately double the volume as DMF:D_2O used) and the aqueous layer was separated and extracted with EtOAc (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography under the stated conditions to provide the deuterated azaarene product.

Notes.

1) Certain substrates require longer reaction times and specific cases are indicated below.
2) K_2CO_3 (1.00 g) was crushed into a fine powder prior to use by mortar and pestle for approximately one minute.

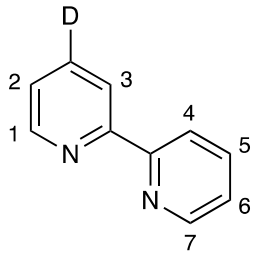


2-Phenylpyridine-4-*d* (134)



Prepared according to general procedure B using (2-phenylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (282 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a light yellow oil (65 mg, 0.42 mmol, 83% yield). IR ν_{max}/cm^{-1} (film): 3059, 2996, 2924, 1572, 1551, 1464, 1444, 1388; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, d, J = 4.8 Hz, H_1), 8.01 (2H, d, J = 8.4 Hz, H_4), 7.73 (1H, s, H_3), 7.50-7.40 (3H, m, H_5 and H_6), 7.22 (1H, d, J = 4.4 Hz, H_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.39, 149.60, 139.33, 136.37 (t, J = 24.4 Hz), 128.88, 128.68, 126.85, 121.92, 120.38; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 157.1, $C_{11}H_9DN^+$ requires 157.1.

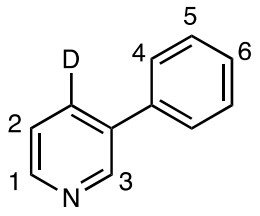
2,2'-Bipyridine-4-*d* (135)



Prepared according to general procedure B using [2,2'-bipyridin]-4-yltriphenylphosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel flushed with NEt_3 eluting with hexane: 10% EtOAc in hexanes, and the reaction mixture was dry loaded onto the column) afforded the

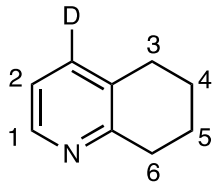
title compound as a white solid (70 mg, 0.45 mmol, 89% yield). mp 64-68 ºC; IR ν_{max}/cm^{-1} (film): 3083, 3075, 2918, 2849, 2360, 2341, 1966, 1565, 1550, 1448, 1384, 1031, 991, 879, 801, 743, 682; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (2H, d, *J* = 4.7 Hz, H_1 and H_7), 8.41-8.37 (2H, m, H_3 and H_4), 7.78 (1H, td, *J* = 7.7, 1.2 Hz, H_5), 7.29-7.25 (2H, m, H_2 and H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.01 (2C), 149.04 (2C), 136.74, 136.44 (t, *J* = 24.9 Hz), 123.55, 123.45, 120.91, 120.81; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 158.1, $C_{10}H_8DN_2^+$ requires 158.1.

3-Phenylpyridine-4-*d* (136)



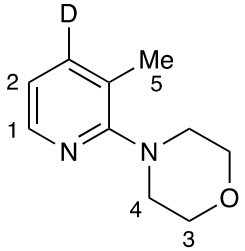
Prepared according to general procedure B using triphenyl(3-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 25% EtOAc in hexanes) afforded the title compound as a clear oil (58 mg, 0.37 mmol, 74% yield). IR ν_{max}/cm^{-1} (film): 3031, 2922, 2850, 2268, 1948, 1709, 1580, 1444, 1258, 1075, 1004, 915, 860, 790, 746, 695, 651; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.89 (1H, br, H_3), 8.62 (1H, br, H_1), 7.57 (2H, d, *J* = 7.4 Hz, H_4), 7.52-7.31 (4H, m, H_2, H_5, and H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.32, 148.18, 137.72, 136.63, 133.95 (t, *J* = 24.7 Hz), 129.00, 128.02, 127.06, 123.51; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 157.2, $C_{11}H_9DN^+$ requires 157.1.

5,6,7,8-Tetrahydroquinoline-4-*d* (137)



Prepared according to general procedure B (except that the reaction was run for 12 hours) using triphenyl(5,6,7,8-tetrahydroquinolin-4-yl)phosphonium trifluoromethanesulfonate (272 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography by dissolving in MeOH and dry loading (silica gel: 30% EtOAc in hexanes) afforded the title compound as a colorless oil (48 mg, 0.35 mmol, 71% yield). IR ν_{max}/cm^{-1} (film): 3094, 2931.2857, 1734, 1689, 1568, 1451, 1433, 1411, 1254, 1143, 1080, 862, 813, 746, 701, 674, 620; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.33 (1H, d, J = 4.5 Hz, H_1), 7.01 (1H, d, J = 4.5 Hz, H_2), 2.92 (2H, t, J = 6.3 Hz, H_6), 2.75 (2H, t, J = 6.3 Hz, H_3), 1.93-1.75 (4H, m, H_4 and H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.26, 146.57, 136.47 (t, J = 24.2 Hz), 132.21, 120.73, 32.35, 28.64, 22.98, 22.61; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 135.2, $C_9H_{11}DN^+$ requires 135.1.

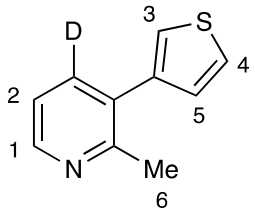
4-(3-Methylpyridin-2-yl-4-*d*)morpholine (138)



Prepared according to general procedure B (except that the reaction was ran for 12 hours) using (3-methyl-2-morpholinopyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (294 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column

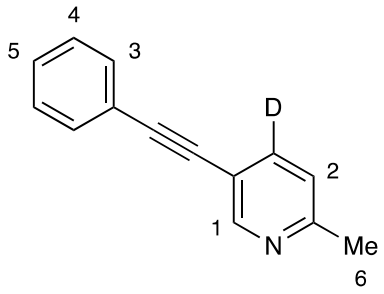
chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a colorless oil (74 mg, 0.41 mmol, 83% yield). IR ν_{max}/cm^{-1} (film): 2956, 2914, 2890, 2848, 1572, 1412, 1264, 1115, 943, 725, 630; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (1H, d, J = 4.9 Hz, H_1), 6.83 (1H, d, J = 4.9 Hz, H_2), 3.84-3.79 (4H, m, H_3), 3.13-3.09 (4H, m, H_4), 2.24 (3H, s, H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.26, 145.25, 138.90 (t, J = 24.3 Hz), 124.57, 117.89, 67.05, 49.95, 18.12; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 180.1, $C_{10}H_{14}DN_2O^+$ requires 180.1.

2-Methyl-3-(thiophen-3-yl)pyridine-4-*d* (139)



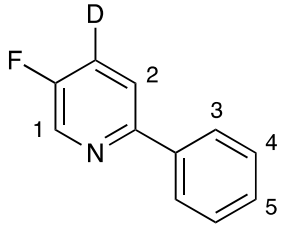
Prepared according to general procedure B using (2-methyl-3-(thiophen-3-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (285 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 20% EtOAc and 1% NEt_3 in hexanes) afforded the title compound as a yellow oil (74 mg, 0.42 mmol, 84% yield). IR ν_{max}/cm^{-1} (film): 3101, 3038, 2958, 2922, 2850, 1562, 1422, 1382, 1191, 860, 797, 765, 671; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45 (1H, d, J = 2.9 Hz, H_1), 7.37 (1H, dd, J = 4.8, 3.0 Hz, H_5), 7.24-7.21 (1H, m, H_3), 7.15-7.10 (2H, m, H_2 and H_4), 2.25 (3H, s, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.84, 147.64, 139.87, 136.61 (t, J = 24.6 Hz), 131.66, 128.29, 125.56, 123.23, 120.79, 23.52; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 177.1, $C_{10}H_9DNS^+$ requires 177.1.

2-Methyl-5-(phenylethynyl)pyridine-4-*d* (140)



Prepared according to general procedure B using (2-methyl-5-(phenylethynyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (302 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a white solid (85 mg, 0.44 mmol, 87% yield). mp 69-72 ºC; IR ν_{max}/cm^{-1} (film): 3049, 2919, 2849, 2271, 2217, 1959, 1574, 1496, 1476, 1441, 1337, 1035, 906, 755, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (1H, s, H_1), 7.55-7.49 (2H, m, H_3), 7.36-7.30 (3H, m, H_4 and H_5), 7.11 (1H, s, H_2), 2.56 (3H, s, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.57, 151.43, 138.18 (t, J = 25.2 Hz), 131.46, 128.44, 128.26, 122.60, 122.43, 117.08, 91.75, 86.07, 24.36; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 195.1, $C_{14}H_{11}DN^+$ requires 195.1.

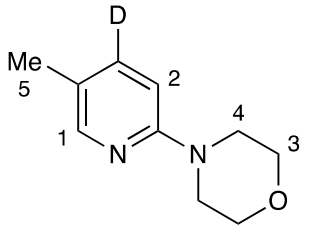
5-Fluoro-2-phenylpyridine-4-*d* (141)



Prepared according to general procedure B (except that the reaction was run for 11 hours) using (5-fluoro-2-phenylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (233 mg, 0.40 mmol), K_2CO_3 (83 mg, 0.60 mmol), and CD_3OD:D_2O 9:1 (1.20 mL:0.13 mL). Flash column

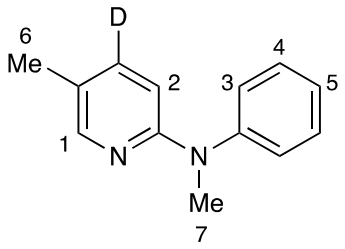
chromatography (silica gel: 3% EtOAc in hexanes) afforded the title compound as a white solid (56 mg, 0.32 mmol, 80% yield). mp 42-44 ºC; IR ν_{max}/cm^{-1} (film): 3051, 2919, 2849, 1462, 1445, 1353, 1217, 902, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, s, H_1), 7.94 (2H, d, *J* = 8.0 Hz, H_3), 7.70 (1H, d, *J* = 4.0 Hz, H_2), 7.49-7.40 (3H, m, H_4 and H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.73 (d, *J* = 254.9 Hz), 153.68 (d, *J* = 3.8 Hz), 138.35, 137.67 (d, *J* = 23.4 Hz), 128.82, 128.73, 126.70, 123.17 (td, *J* = 25.5, 18.5 Hz), 121.12 (d, *J* = 4.5 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –130.09; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 175.1, $C_{11}H_8DFN^+$ requires 175.1.

4-(5-Methylpyridin-2-yl-4-*d*)morpholine (142)



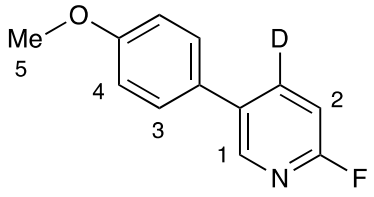
Prepared according to general procedure B (except that the reaction was run for 12 hours) using (5-methyl-2-morpholinopyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (295 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the title compound as a yellow oil (82 mg, 0.46 mmol, 92% yield). IR ν_{max}/cm^{-1} (film): 2999, 2976, 2913, 2861, 2731, 2246, 1603, 1550, 1487, 1466, 1385, 1329, 1240, 1111, 942, 872, 727, 640, 598; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (1H, s, H_1), 6.53 (1H, s, H_2), 3.77 (4H, t, *J* = 4.9 Hz, H_3), 3.38 (4H, t, *J* = 4.9, H_4), 2.15 (3H, s, H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.97, 147.52, 137.91 (t, *J* = 24.1 Hz), 122.58, 106.56, 66.60, 45.92, 17.11; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 180.1, $C_{10}H_{14}DN_2O^+$ requires 180.1.

_N_,5-Dimethyl-_N_-phenylpyridin-2-amine-4-_d_ (143)



Prepared according to general procedure B (except that the reaction was run for 24 hours) using (5-methyl-2-(methyl(phenyl)amino)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (304 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the title compound as a yellow oil (90 mg, 0.46 mmol, 91% yield). IR ν_{max}/cm^{-1} (film): 3085, 3059, 3035, 2995, 2920, 2863, 2815, 2255, 1604, 1590, 1549, 1483, 1361, 1249, 1125, 1022, 747, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (1H, s, H_1), 7.35 (2H, t, J = 7.4 Hz, H_4), 7.23 (2H, d, J = 7.4 Hz, H_3), 7.15 (1H, t, J = 7.4 Hz, H_5), 6.53 (1H, s, H_2), 3.46 (3H, s, H_7), 2.18 (3H, s, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.03, 147.29, 147.18, 137.19 (t, J = 24.1 Hz), 129.40, 125.41, 124.59, 122.00, 109.17, 38.25, 17.19; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 200.1, $C_{13}H_{14}DN_2^+$ requires 200.1.

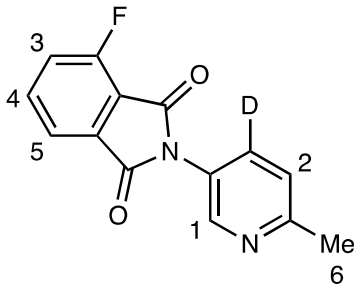
2-Fluoro-5-(4-methoxyphenyl)pyridine-4-_d_ (144)



Prepared according to general procedure B (except that the reaction was run for 4.5 hours) using (2-fluoro-5-(4-methoxyphenyl)pyridin-4-yl)triphenylphosphonium

trifluoromethanesulfonate (222 mg, 0.36 mmol), K_2CO_3 (75 mg, 0.54 mmol), and CD_3OD:D_2O 9:1 (1.20 mL). Flash column chromatography (silica gel: CH_2Cl_2) afforded the title compound as a white solid (59 mg, 0.29 mmol, 80% yield). mp 64-66 ºC. IR ν_{max}/cm^{-1} (film): 3023, 2967, 2923, 2846, 1586, 1456, 1247, 1182, 842, 775; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (1H, s, H_1), 7.46 (2H, d, J = 8.8 Hz, H_3), 7.00 (2H, d, J = 8.8 Hz, H_4), 6.97 (1H, d, J = 1.5 Hz, H_2), 3.86 (3H, s, H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.65 (d, J = 237.3 Hz), 159.68, 145.20 (d, J = 14.6 Hz), 138.84 (td, J = 24.6, 8.0 Hz), 134.31 (d, J = 4.6 Hz), 128.97, 128.01, 114.50, 109.10 (d, J = 37.4 Hz), 55.27; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –71.50; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 205.1, $C_{12}H_{10}DFNO^+$ requires 205.1.

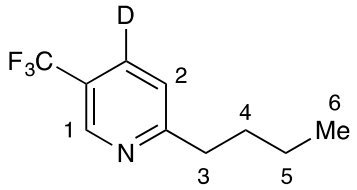
4-Fluoro-2-(6-methylpyridin-3-yl-4-*d*)isoindoline-1,3-dione (145)



Prepared according to general procedure B (except that the reaction was run for 12 hours) using (5-(4-fluoro-1,3-dioxoisoindolin-2-yl)-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (200 mg, 0.30 mmol), K_2CO_3 (62 mg, 0.45 mmol), and DMF:D_2O 9:1 (1.00 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 30% EtOAc in hexanes) afforded the title compound as a white solid (43 mg, 0.17 mmol, 52% yield). mp 213-214 ºC. IR ν_{max}/cm^{-1} (film): 3133, 2930, 1730, 1687, 1567, 1464, 1379, 1261, 1014, 968, 740; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.61 (1H, br s, H_1), 7.84-7.75 (2H, m, H_3 and H_5), 7.49-7.42

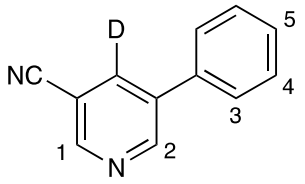
(1H, m, H_4), 7.30 (1H, s, H_2), 2.62 (3H, s, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.66 (d, *J* = 2.9 Hz), 163.46 (d, *J* = 1.2 Hz), 158.22, 157.85 (d, *J* = 267.1 Hz), 146.52, 137.16 (d, *J* = 7.6 Hz), 133.65, 133.57 (t, *J* = 25.3 Hz), 125.59, 123.18, 122.87 (d, *J* = 19.7 Hz), 120.04 (d, *J* = 3.8 Hz), 117.38 (d, *J* = 12.3 Hz), 24.18; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –111.79 (m); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 258.1, $C_{14}H_9DFN_2O_2^+$ requires 258.1.

2-Butyl-5-(trifluoromethyl)pyridine-4-*d* (146)



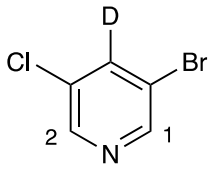
Prepared according to general procedure B using (2-butyl-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (307 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.50 mL:0.17 mL). Flash column chromatography (silica gel: CH_2Cl_2) afforded the title compound as a clear oil (63 mg, 0.31 mmol, 62% yield). IR ν_{max}/cm^{-1} (film): 2951, 2925, 2854, 2360, 1726, 1596, 1438, 1263, 1151, 721; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.78 (1H, s, H_1), 7.26 (1H, s, H_2), 2.86 (2H, t, *J* = 7.6 Hz, H_3), 1.72 (2H, qn, *J* = 7.6 Hz, H_4), 1.38 (2H, sext, *J* = 7.6 Hz, H_5), 0.94 (3H, t, *J* = 7.6 Hz, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.56, 146.02 (d, *J* = 3.7 Hz), 133.00 (m), 123.74 (q, *J* = 270.5 Hz), 123.94 (q, *J* = 32.5 Hz), 122.27, 38.02, 31.67, 22.35, 13.78; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.29; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 205.1, $C_{10}H_{12}DF_3N^+$ requires 205.1.

5-Phenylnicotinonitrile-4-*d* (147)



Prepared according to general procedure B (except the reaction was run for 21 hours and Na_2CO_3 was used in place of K_2CO_3) using (3-cyano-5-phenylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (295 mg, 0.50 mmol), Na_2CO_3 (80 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a white solid (75 mg, 0.42 mmol, 83% yield). mp 73-74 ºC; IR ν_{max}/cm^{-1} (film): 3058, 3040, 2924, 2269, 2234, 1582, 1566, 1420, 1403, 1313, 1164, 1006, 903, 752, 693, 653, 603; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00 (1H, s, H_1), 8.82 (1H, s, H_2), 7.59-7.42 (5H, m, H_3, H_4, and H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.29, 150.50, 136.73 (t, J = 25.7 Hz), 136.63, 135.20, 129.30, 129.09, 126.98, 116.40, 109.82; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 182.1, $C_{12}H_8DN_2^+$ requires 182.1.

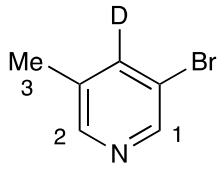
3-Bromo-5-chloropyridine-4-*d* (148)



Prepared according to general procedure B (except that the reaction was run for 12 hours) using (3-bromo-5-chloropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (301 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 3% EtOAc in hexanes) afforded the title compound as a white solid

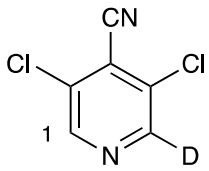
(75 mg, 0.39 mmol, 77% yield). mp 80-81 ºC; IR ν_{max}/cm^{-1} (film): 3045, 3017, 2923, 2852, 2254, 1811, 1534, 1401, 1384, 1237, 1102, 881, 779, 651; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, s, H_2), 8.45 (1H, s, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.62, 146.84, 137.71 (t, J = 26.4 Hz), 132.08, 120.20; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 192.9, $C_5H_3DBrClN^+$ requires 192.9.

3-Bromo-5-methylpyridine-4-*d* (149)



Prepared according to general procedure B using (3-bromo-5-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (291 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 20% EtOAc and 1% NEt_3 in hexanes) afforded the title compound as a yellow oil (79 mg, 0.46 mmol, 92% yield). IR ν_{max}/cm^{-1} (film): 2955, 2921, 2851, 2360, 2341, 1725, 1457, 1377, 1265, 757; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (1H, s, H_1), 8.34 (1H, s, H_2), 2.31 (3H, s, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.38, 148.00, 138.67 (t, J = 25.5 Hz), 134.83, 120.33, 18.00; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 173.0, $C_6H_6DBrN^+$ requires 173.0.

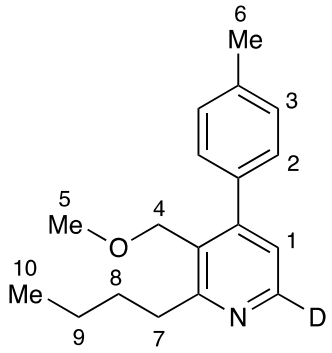
3,5-Dichloroisonicotinonitrile-2-*d* (150)



Prepared according to general procedure C (except that the reaction was run for 16.5 hours)

using (3,5-dichloro-4-cyanopyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (292 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and DMF:D_2O 9:1 (1.50 mL:0.17 mL). Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the title compound as a white solid (61 mg, 0.35 mmol, 70% yield). mp 115-116 ºC. IR ν_{max}/cm^{-1} (film): 3055, 2922, 2851, 2244, 1522, 1430, 1334, 1196, 1106; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, s, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.69, 147.36, (t, J = 29.0 Hz), 133.86, 133.74, 121.36, 111.21; *m/z* TOF LC/MS found $[M+H]^+$ 174.0, $C_6H_2DCl_2N_2^+$ requires 174.0.

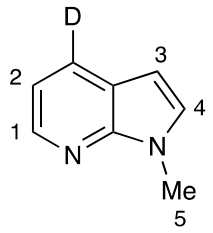
2-Butyl-3-(methoxymethyl)-4-(*p*-tolyl)pyridine-6-*d* (151)



Prepared according to general procedure B using (6-butyl-5-(methoxymethyl)-4-(*p*-tolyl)pyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (272 mg, 0.40 mmol), K_2CO_3 (83 mg, 0.60 mmol), and CD_3OD:D_2O 9:1 (1.20 mL:0.13 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a light yellow oil (96 mg, 0.36 mmol, 89% yield). IR ν_{max}/cm^{-1} (film): 2955, 2924, 2870, 2805, 1574, 1514, 1378, 1089; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29 (2H, d, J = 8.0 Hz, H_2), 7.22 (2H, d, J = 8.0 Hz, H_3), 7.00 (1H, s, H_1), 4.26 (2H, s, H_4), 3.32 (3H, s, H_5), 2.93 (2H, t, J = 8.0 Hz, H_7), 2.38 (3H, s, H_6), 1.77 (2H, qn, J = 7.6 Hz, H_8), 1.46 (2H, sext, J = 7.6 Hz, H_9), 0.96 (3H, t, J = 7.2 Hz, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.21, 151,04, 147.82 (t, J = 26.7 Hz), 137.71, 136.05, 128.81, 128.67, 127.78, 122.01,

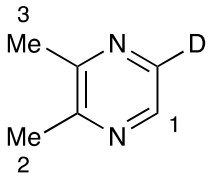
68.56, 58.02, 34.87, 32.14, 22.93, 21.05, 13.90; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 271.2, $C_{18}H_{23}DNO^+$ requires 271.2.

1-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine-4-*d* (152)



Prepared according to general procedure B (except that the reaction was run for 48 hours) using (1-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (271 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.50 mL:0.17 mL). Flash column chromatography (neutral alumina: 5% EtOAc in hexanes) afforded the title compound as an orange oil (48 mg, 0.36 mmol, 72% yield). IR ν_{max}/cm^{-1} (film): 3048, 2924, 2852, 1584, 1514, 1400, 1297; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.34 (1H, d, J = 4.4 Hz, H_1), 7.15 (1H, d, J = 3.2 Hz, H_4), 7.03 (1H, d, J = 4.4 Hz, H_2), 6.43 (1H, d, J = 3.2 Hz, H_3), 3.87 (3H, s, H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.70, 142.69, 128.90, 128.33 (t, J = 24.4 Hz), 120.35, 115.27, 99.15, 31.13; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 134.1, $C_8H_8DN_2^+$ requires 134.1.

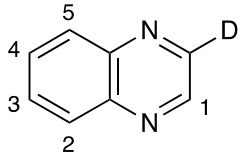
2,3-Dimethylpyrazine-*d* (153)



Prepared according to general procedure B (except that ^1H NMR and ^{13}C NMR were run on the crude reaction mixture due to volatility of the product) using (5,6-dimethylpyrazin-2-

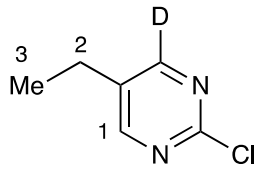
yl)triphenylphosphonium trifluoromethanesulfonate (52 mg, 0.10 mmol), K_2CO_3 (21 mg, 0.15 mmol), 1,3,5-trimethoxybenzene as an internal standard (17 mg, 0.10 mmol), and CD_3OD:D_2O 9:1 (0.33 mL) to afford the title compound (^1H NMR yield: 80%). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.27 (1H, s, H_1), 2.52 (6H, s, H_2 and H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.38, 154.34, 142.09, 141.85 (t, J = 28.0 Hz), 21.77 (2C); *m/z* TOF LC/MS found $[M+H]^+$ 110.1, $C_6H_8DN_2^+$ requires 110.1.

Quinoxaline-2-*d* (154)



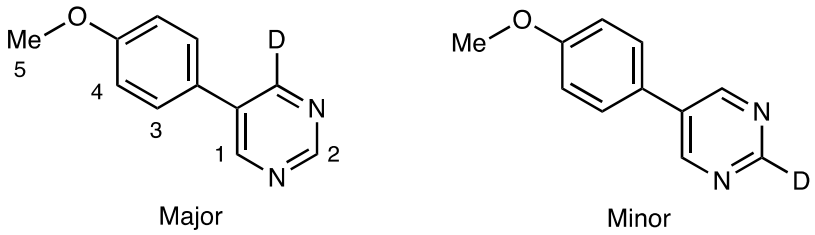
Prepared according to general procedure B (except that the reaction was run for 4.5 hours) using triphenyl(quinoxalin-2-yl)phosphonium trifluoromethanesulfonate (270 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.50 mL:0.17 mL). Flash column chromatography (silica gel: 30% Et_2O in hexanes) afforded the title compound as an orange oil (42 mg, 0.33 mmol, 65% yield). IR ν_{max}/cm^{-1} (film): 3063, 2924, 2852,2360, 1492, 1367, 1077, 955, 768; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.80 (1H, s, H_1), 8.08-8.05 (2H, m, H_3 and H_4), 7.73-7.71 (2H, m, H_2 and H_5); ^{13}C NMR (100 MHz, $CDCl_3$): 144.76, 144.47 (t, J = 27.6 Hz), 142.91, 142.84, 129.91 (2C), 129.37 (2C); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 132.1, $C_8H_6DN_2^+$ requires 132.1.

2-Chloro-5-ethylpyrimidine-*d* (155)



Prepared according to general procedure C (except that the reaction was run for 4 hours) using (2-chloro-5-ethylpyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (277 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and DMF:D_2O 9:1 (1.67 mL). Preparatory plate (silica gel: 30% Et_2O in hexanes) afforded the title compound as a clear oil (43 mg, 0.30 mmol, 60% yield). IR ν_{max}/cm^{-1} (film): 2970, 2926, 2854, 1535, 1386, 1345, 1239, 1147, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46 (1H, s, H_1), 2.64 (2H, q, J = 7.6 Hz, H_2), 1.27 (3H, t, J = 7.6 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$): 158.97, 158.57 (t, J = 27.2 Hz), 135.08, 128.52, 22.77, 14.69; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 144.1, $C_6H_7DClN_2^+$ requires 144.0.

5-(4-Methoxyphenyl)pyrimidine-4-*d* (156) and 5-(4-Methoxyphenyl)pyrimidine-2-*d* (156')

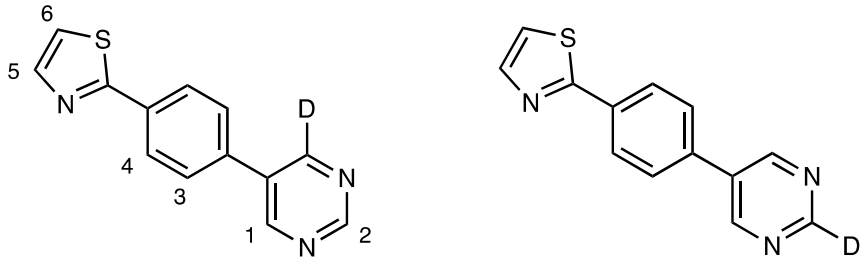


>20:1 Mixture of Regioisomers

Prepared according to general procedure B (except that the reaction was run for 8 hours) using (5-(4-methoxyphenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (298 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the title compound as a white solid (76 mg, 0.40 mmol, 81% yield). mp 108-110 ºC; IR ν_{max}/cm^{-1} (film): 3026, 2920, 2842, 1612,

1517, 1392, 1251, 1015, 834; $_1$H NMR (400 MHz, $CDCl_3$) δ: 9.11 (1H, s, H_2), 8.87 (1H, s, H_1), 7.48 (2H, d, J = 8.4 Hz, H_3), 7.00 (2H, d, J = 8.4 Hz, H_4), 3.82 (3H, s, H_5); $_{13}$C NMR (100 MHz, $CDCl_3$) δ: 160.26, 156.75, 154.26, 153.88 (t, J = 27.3 Hz), 133.64, 127.95, 126.33, 114.77, 55.26; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 188.1, $C_{11}H_{10}DN_2O^+$ requires 188.1.

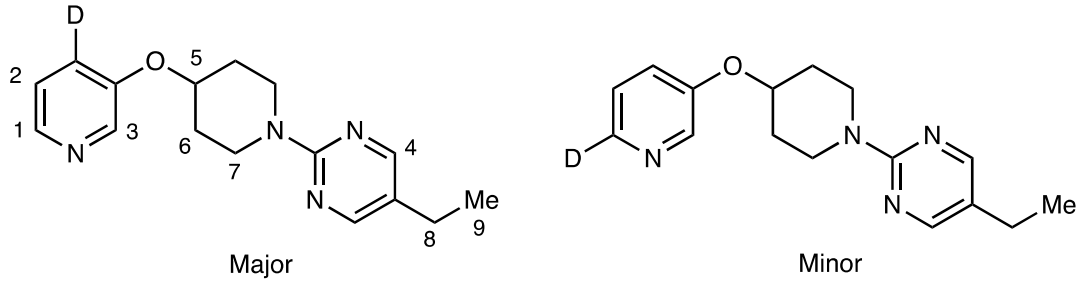
2-(4-(Pyrimidin-5-yl-4-*d*)phenyl)thiazole (157) and 2-(4-(Pyrimidin-5-yl-2-*d*)phenyl)thiazole (157')



>20:1 Mixture of Regioisomers

Prepared according to general procedure C using triphenyl(5-(4-(thiazol-2-yl)phenyl)pyrimidin-4-yl)phosphonium trifluoromethanesulfonate (325 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and DMF:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 50% Et_2O and 1% NEt_3 in toluene) afforded the title compound as light yellow solid (105 mg, 0.44 mmol, 88% yield). mp 175-176 ºC. IR ν_{max}/cm^{-1} (film): 3086, 3069, 1568, 1483, 1390, 1146, 746, 663; $_1$H NMR (400 MHz, $CDCl_3$) δ: 9.24 (1H, s, H_2), 9.01 (1H, s, H_1), 8.13 (2H, d, J = 8.4 Hz, H_3), 7.92 (1H, d, J = 3.2 Hz, H_5), 7.69 (2H, d, J = 8.0 Hz, H_4), 7.40 (1H, d, J = 3.2 Hz, H_6); $_{13}$C NMR (100 MHz, $CDCl_3$) δ: 167.03, 157.72, 154.68, 154.30 (t, J = 27.6 Hz), 143.95, 135.47, 134.08, 133.25, 127.43, 127.37, 119.34; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 241.0, $C_{13}H_9DN_3S^+$ requires 241.1.

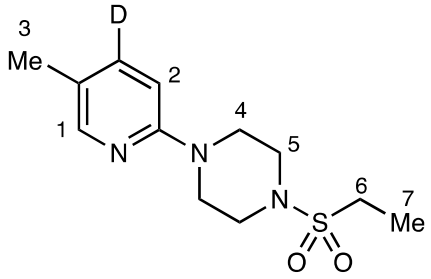
5-Ethyl-2-(4-((pyridin-3-yl-4-*d*)oxy)piperidin-1-yl)pyrimidine (160) and 5-Ethyl-2-(4-((pyridin-3-yl-6-*d*)oxy)piperidin-1-yl)pyrimidine (160')



5.3:1 Mixture of Regioisomers

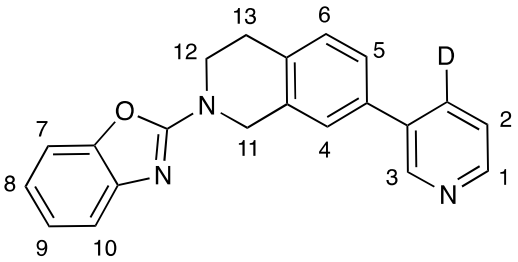
Prepared according to general procedure B (except that the reaction was run for 32 hours) using (3-((1-(5-ethylpyrimidin-2-yl)piperidin-4-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (347 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 60% EtOAc in hexanes, followed by a basic alumina column with 30% EtOAc in hexanes) afforded the title compound as an orange oil (285 mg, 0.41 mmol, 82% yield). IR ν_{max}/cm^{-1} (film): 2941, 2872, 1604, 1499, 1412, 1237, 1010; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (1H, s, H_3), 8.17 (1H, d, J = 4.8 Hz, H_1), 8.13 (2H, s, H_4), 7.18 (1H, d, J = 4.8 Hz, H_2), 4.53 (1H, app sp, J = 3.7 Hz, H_5), 4.17-4.11 (2H, m, H_7), 3.63-3.57 (2H, m, H_7), 2.41 (2H, q, J = 7.6 Hz, H_8), 2.02-1.95 (2H, m, H_6), 1.81-1.73 (2H, m, H_6), 1.14 (3H, t, J = 7.6 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$): 160.57, 156.99, 153.44, 142.11, 139.35, 124.37, 123.68, 122.29 (t, J = 24.7 Hz), 73.47, 40.87, 30.21, 22.56, 15.47; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 286.2, $C_{16}H_{20}DN_4O^+$ requires 286.2.

1-(Ethylsulfonyl)-4-(5-methylpyridin-2-yl-4-*d*)piperazine (159)



Prepared according to general procedure B (except that the reaction was run for 8 hours) using (2-(4-(ethylsulfonyl)piperazin-1-yl)-5-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (340 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 16% Et_2O in CH_2Cl_2) afforded the title compound as a white solid (122 mg, 0.45 mmol, 90% yield). mp 133-135 ºC. IR ν_{max}/cm^{-1} (film): 3001, 2987, 2922, 2852, 1598, 1487, 1323, 1144; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.03 (1H, s, H_1), 6.60 (1H, s, H_2), 3.58 (4H, app t, J = 4.8 Hz, H_4 and H_5), 3.40 (4H, app t, J = 4.8 Hz, H_4 and H_5), 2.97 (2H, q, J = 7.6 Hz, H_6), 2.21 (3H, s, H_3), 1.39 (3H, t, J = 7.6 Hz, H_7); ^{13}C NMR (100 MHz, $CDCl_3$): 157.15, 147.50, 138.11 (t, J = 24.1 Hz), 122.94, 107.05, 45.66, 45.30, 43.51, 17.06, 7.57; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 271.1, $C_{12}H_{19}DN_3O_2S^+$ requires 271.1.

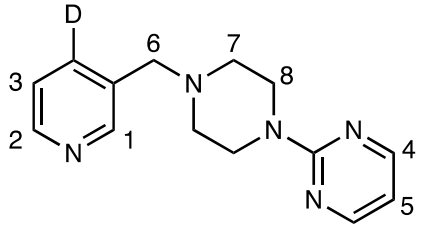
2-(7-(Pyridin-3-yl-4-*d*)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzo[*d*]oxazole (158)



Prepared according to general procedure B (except that the reaction was run for 48 hours) using (3-(2-(benzo[*d*]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinolin-7-yl)pyridin-4-

yl)triphenylphosphonium trifluoromethanesulfonate (313 mg, 0.42 mmol), K_2CO_3 (88 mg, 0.64 mmol), and CD_3OD:D_2O 9:1 (1.40 mL). Recrystallization from MeOH followed by washing on a frit with Et_2O afforded the title compound as a white solid (127 mg, 0.39 mmol, 92% yield). mp 202-204 ºC. IR ν_{max}/cm^{-1} (film): 3031, 2932, 2834, 1646, 1571, 1461, 1452, 736; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.85 (1H, s, H_3), 8.61 (1H, d, J = 2.4 Hz, H_1), 7.45-7.39 (4H, m, H_2, H_4, H_7, and H_{10}), 7.32-7.29 (2H, m, H_5 and H_6), 7.18 (1H, t, J = 7.2 Hz, H_8), 7.04 (1H, t, J = 7.6 Hz, H_9), 4.95 (2H, s, H_{11}), 4.01 (2H, t, J = 5.6 Hz, H_{12}), 3.07 (2H, t, J = 5.6 Hz, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.95, 148.80, 148.51, 148.12, 143.09, 136.18, 135.99, 134.07, 133.82 (t, J = 24.8 Hz), 133.24, 129.60, 125.58, 124.92, 124.00, 123.45, 120.62, 116.30, 108.74, 47.26, 43.06, 28.15; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 329.2, $C_{21}H_{17}DN_3O^+$ requires 329.2.

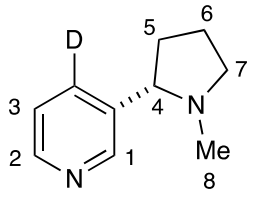
2-(4-((pyridin-3-yl-4-*d*)methyl)piperazin-1-yl)pyrimidine (161)



Prepared according to general procedure B using triphenyl(3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (200 mg, 0.30 mmol), K_2CO_3 (62 mg, 0.45 mmol), and CD_3OD:D_2O 9:1 (1.00 mL). Flash column chromatography (silica gel, gradient elution: EtOAc to 10% MeOH in EtOAc) afforded the title compound as a light yellow solid (60 mg, 0.23 mmol, 78% yield). mp 98-100 ºC. IR ν_{max}/cm^{-1} (film): 3102, 3033, 2986, 2903, 2781, 1709, 1584, 1541, 1481, 1446, 1353, 1258, 1108, 981, 952, 870, 792, 767, 659; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60-8-47 (2H, m, H_1 and H_3), 8.28 (2H, d, J = 4.7 Hz, H_4), 7.26 (1H, s, H_2),

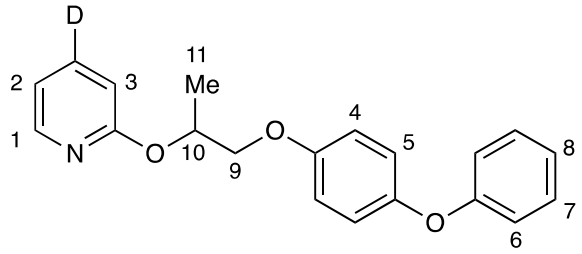
6.46 (1H, t, J = 4.7 Hz, H_5), 3.81 (4H, t, J = 5.0 Hz, H_8), 3.54 (2H, s, H_6), 2.49 (4H, t, J = 5.0 Hz, H_7); ^{13}C NMR (100 MHz, $CDCl_3$): 161.47, 157.51, 150.31, 148.55, 136.18 (t, J = 24.5 Hz), 133.28, 123.12, 109.68, 60.10, 52.78, 43.47; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 258.2, $C_{14}H_{17}DN_5^+$ requires 258.2.

(*S*)-3-(1-Methylpyrrolidin-2-yl)pyridine-4-*d* (162)



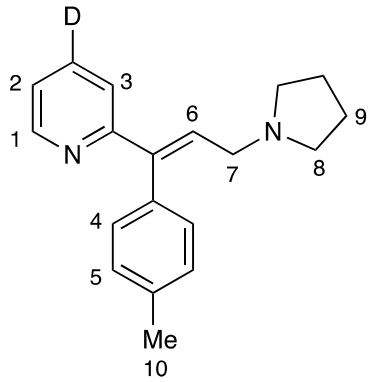
Prepared according to general procedure B using (*S*)-(3-(1-methylpyrrolidin-2-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (115 mg, 0.20 mmol), K_2CO_3 (42 mg, 0.30 mmol), and CD_3OD:D_2O 9:1 (0.67 mL). Flash column chromatography (silica gel, gradient elution: 3% MeOH in CH_2Cl_2 to 3% MeOH and 1% NEt_3 in CH_2Cl_2) afforded the title compound as yellow oil (26 mg, 0.158 mmol, 79% yield). IR ν_{max}/cm^{-1} (film): 3399, 2956, 2610, 2500, 1668, 1585, 1456, 1417, 1260, 1224, 1155, 1030, 1010, 655, 638; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49-8.38 (2H, m, H_1 and H_2), 7.17 (1H, d, J = 4.6 Hz, H_3), 3.19-3.12 (1H, m, H_7), 3.03-2.96 (1H, m, H_4), 2.27-2.05 (5H, m, H_5, H_6, and H_8), 1.95-1.58 (3H, m, H_5, H_6, and H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.41, 148.47, 138.55, 134.33 (t, J = 24.7 Hz), 123.27, 68.66, 56.85, 40.22, 35.08, 22.47; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 164.0, $C_{10}H_{14}DN_2^+$ requires 164.1.

2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)pyridine-4-*d* (163)



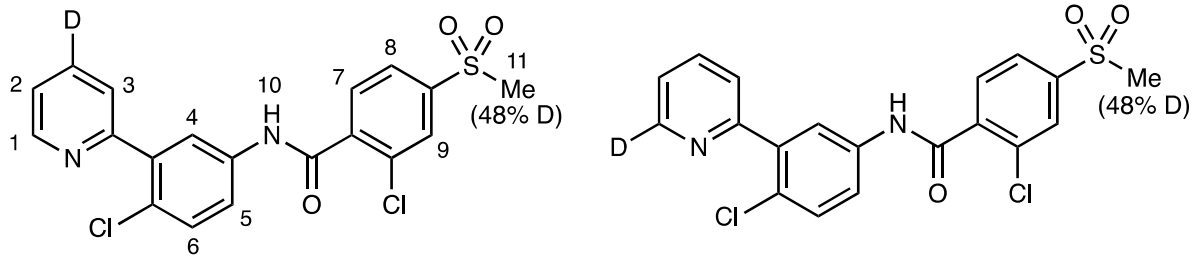
Prepared according to general procedure B using (2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (175 mg, 0.30 mmol), K_2CO_3 (62 mg, 0.45 mmol), and CD_3OD:D_2O 9:1 (1.00 mL). Flash column chromatography (silica gel: 10% MeOH in CH_2Cl_2) afforded the title compound as a white solid (64 mg, 0.20 mmol, 66% yield). mp 44-47 ºC; IR ν_{max}/cm^{-1} (film): 3080, 2967, 2923, 2871, 1584, 1562, 1489, 1406, 1218, 1155, 1041, 842, 753, 692, 644; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (1H, d, *J* = 5.0 Hz, H_1), 7.31 (2H, t, *J* = 7.3 Hz, H_7), 7.05 (1H, t, *J* = 7.3 Hz, H_8), 7.01-6.92 (6H, m, H_4, H_5, and H_6), 6.87 (1H, d, *J* = 5.0 Hz, H_2), 6.76 (1H, s, H_3), 5.62 (1H, sext, *J* = 6.4 Hz, H_{10}), 4.21 (1H, dd, *J* = 9.8, 5.3 Hz, H_9), 4.09 (1H, dd, *J* = 9.8, 5.3 Hz, H_9), 1.51 (3H, d, *J* = 6.4 Hz, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.10, 158.43, 155.16, 150.20, 146.73, 138.32 (t, *J* = 24.7 Hz), 129.54, 122.36, 120.70, 117.54, 116.59, 115.73, 111.49, 70.99, 69.20, 16.97; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 323.2, $C_{20}H_{19}DNO_3^+$ requires 323.2.

(*E*)-2-(3-(pyrrolidin-1-yl)-1-(*p*-tolyl)prop-1-en-1-yl)pyridine-4-*d* (164)



Prepared according to general procedure B (except that the reaction was run for 15 hours) using (*E*)-triphenyl(2-(3-(pyrrolidin-1-yl)-1-(*p*-tolyl)prop-1-en-1-yl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (207 mg, 0.30 mmol), K_2CO_3 (62 mg, 0.45 mmol), and CD_3OD:D_2O 9:1 (1.00 mL). Flash column chromatography (silica gel, gradient elution: EtOAc to 2% NEt_3 in EtOAc) afforded the title compound as a yellow oil (70 mg, 0.25 mmol, 84% yield). IR ν_{max}/cm^{-1} (film): 2957, 2923, 2872, 2779, 2280, 1575, 1551, 1479, 1460, 1389, 1371, 1316, 1264, 1107, 1055, 910, 863, 821, 729, 701, 603, 637; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (1H, d, *J* = 4.8 Hz, H_1), 7.20 (2H, d, *J* = 7.8 Hz, H_5), 7.11-7.07 (3H, m, H_2 and H_4), 7.00 (1H, s, H_3), 6.93 (1H, t, *J* = 6.9 Hz, H_6), 3.22 (2H, d, *J* = 6.9 Hz, H_7), 2.59-2.50 (4H, m, H_8), 2.38 (3H, s, H_{10}), 1.82-1.70 (4H, m, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.68, 149.15, 142.02, 136.84, 135.73 (t, *J* = 24.2 Hz), 135.49, 130.14, 129.68, 129.01, 121.92, 121.55, 54.65, 54.05, 23.46, 21.23; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 280.2, $C_{19}H_{22}DN_2^+$ requires 280.2.

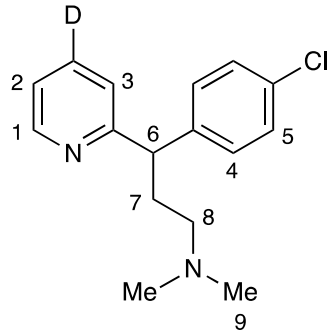
2-Chloro-*N*-(4-chloro-3-(pyridin-2-yl-4-*d*)phenyl)-4-(methylsulfonyl)benzamide (165) and 2-chloro-*N*-(4-Chloro-3-(pyridin-2-yl-6-*d*)phenyl)-4-(methylsulfonyl)benzamide (165')



7:1 Mixture of Regioisomers

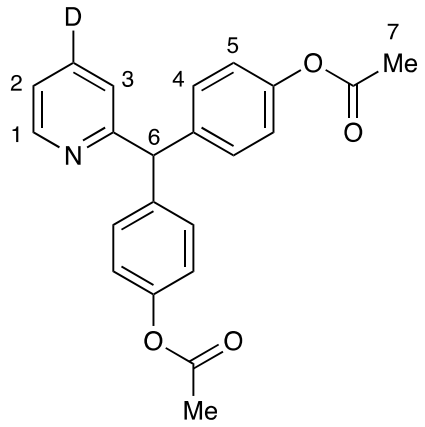
Prepared according to general procedure B using (2-(2-chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (83.2 mg, 0.10 mmol), K_2CO_3 (21 mg, 0.15 mmol), and CD_3OD:D_2O 9:1 (0.33 mL). Flash column chromatography (silica gel with EtOAc) afforded the title compound as a white solid (30.9 mg, 0.073 mmol, 73% yield). IR ν_{max}/cm^{-1} (film): 3015, 2918, 2849, 2359, 1676, 1581, 1540, 1457, 1373, 1313, 1153, 822, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.02 (1H, s, H_{10}), 8.33 (1H, d, *J* = 4.9 Hz, H_1), 8.05 (1H, dd, *J* = 8.8, 2.4 Hz, H_5), 7.82 (1H, s, H_9), 7.69-7.62 (3H, m, H_3, H_4, and H_8), 7.51-7.46 (2H, m, H_6 and H_7), 7.17 (1H, d, *J* = 4.9 Hz, H_2), 2.97 (3H [integration = 1.56, 48% deuterium], s, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.82, 155.72, 148.73, 142.46, 140.66, 138.49, 137.11, 136.09 (t, *J* = 24.4 Hz), 132.18, 130.95, 129.87, 128.75, 127.22, 125.69, 125.28, 122.72, 122.69, 121.71, 44.30; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 422.1, $C_{22}H_{23}DClN_2O_2^+$ requires 422.0.

3-(4-Chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl-4-*d*)propan-1-amine (166)



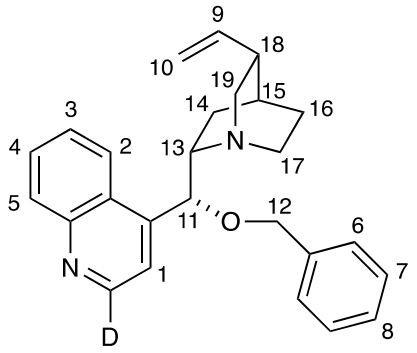
Prepared according to general procedure B using (2-(1-(4-chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (301 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then gradient elution: 3% MeOH in CH_2Cl_2 to 15% MeOH in CH_2Cl_2, followed by a basic alumina plug: 2% MeOH in CH_2Cl_2) afforded the title compound as a yellow oil (119 mg, 0.43 mmol, 86% yield). IR ν_{max}/cm^{-1} (film): 3065, 2941, 2815, 2765, 1580, 1556, 1464, 1397, 1170, 1090, 819, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, d, J = 4.8 Hz, H_1), 7.24 (2H, d, J = 8.5 Hz, H_5), 7.18 (2H, d, J = 8.5 Hz, H_4), 7.09 (1H, s, H_3), 7.01 (1H, d, J = 4.8 Hz, H_2), 4.08 (1H, t, J = 7.0 Hz, H_6), 2.43-2.28 (1H, m, H_7), 2.19-2.05 (9H, m, H_7, H_8, and H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.98, 149.24, 142.11, 135.98 (t, J = 24.7 Hz), 131.98, 129.28, 128.41, 122.53, 121.17, 57.52, 50.42, 45.37, 32.86; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 276.2, $C_{16}H_{19}DClN_2^+$ requires 276.1.

((Pyridin-2-yl-4-*d*)methylene)bis(4,1-phenylene) diacetate (167)



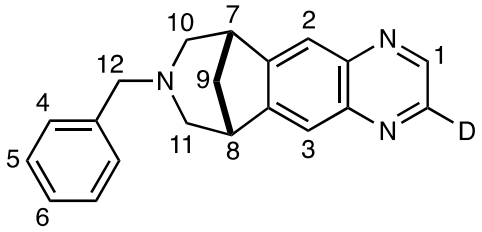
Prepared according to general procedure C (except that the reaction was run for 22 hours) using (2-(bis(4-acetoxyphenyl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (386 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and DMF:D_2O 9:1 (1.67 mL). Flash column chromatography (silica gel: 30% EtOAc and 1% NEt_3 in hexanes) afforded the title compound as a white solid (153 mg, 0.42 mmol, 84% yield). mp 132-133 ºC; IR ν_{max}/cm^{-1} (film): 3489, 3029, 2924, 2852, 1752, 1580, 1503, 1392, 1366, 1199, 1163, 912, 828, 644; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, d, J = 4.7 Hz, H_1), 7.18 (4H, d, J = 8.5 Hz, H_5), 7.12 (1H, d, J = 4.7 Hz, H_2), 7.10 (1H, s, H_3), 7.02 (4H, d, J = 8.5 Hz, H_4), 5.66 (1H, s, H_6), 2.26 (6H, s, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.15, 162.35, 149.40, 149.10, 139.82, 136.08 (t, J = 24.8 Hz), 130.04, 123.44, 121.32, 121.26, 57.89, 20.90; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 363.2, $C_{22}H_{19}DNO_4^+$ requires 363.1.

(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(benzyloxy)(quinolin-4-yl-2-*d*)methyl)-5-vinylquinuclidine (168)



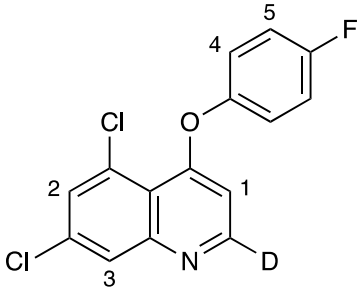
Prepared according to general procedure B (except the reaction was run for 5 hours) using (4-((*R*)-(benzyloxy)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (80 mg, 0.10 mmol), K_2CO_3 (21 mg, 0.15 mmol), and CD_3OD:D_2O 9:1 (0.33 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then gradient elution: 1% MeOH in CH_2Cl_2 to 5% MeOH CH_2Cl_2 followed by a second flash column (basic alumina: 2% MeOH in CH_2Cl_2) afforded the title compound as a yellow oil (34 mg, 0.09 mmol, 89% yield). IR ν_{max}/cm^{-1} (film): 3067, 2924, 2836, 2223, 1585, 1441, 1401, 1139, 1101, 1029, 703, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.19 (2H, m, H_2 and H_5), 7.73 (1H, t, *J* = 7.9 Hz, H_4), 7.58 (1H, t, *J* = 7.8 Hz, H_3), 7.53 (1H, s, H_1), 7.38-7.27 (5H, m, H_6, H_7, and H_8), 5.73 (1H, ddd, *J* = 17.1, 10.2, 7.7 Hz, H_9), 5.30 (1H, br s, H_{11}), 4.97-4.87 (2H, m, H_{10}), 4.47-4.38 (2H, m, H_{12}), 3.44-3.33 (1H, m, H_{17}), 3.20-3.03 (2H, m, H_{13} and H_{19}), 2.72-2.57 (2H, m, H_{17} and H_{19}), 2.29-2.21 (1H, m, H_{18}), 1.88-1.44 (5H, m, H_{14}, H_{15}, and H_{16}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.76 (d, *J* = 26.7 Hz), 148.53, 146.44, 141.89, 137.77, 130.47, 128.99, 128.35, 127.65, 127.57, 126.57, 126.49, 123.13, 118.40, 114.10, 80.94, 71.22, 60.76, 57.03, 43.07, 40.01, 27.88, 27.76, 22.53; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 386.2, $C_{26}H_{28}DN_2O^+$ requires 386.2.

(6*S*,10*R*)-8-benzyl-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxaline-2-*d* (169)



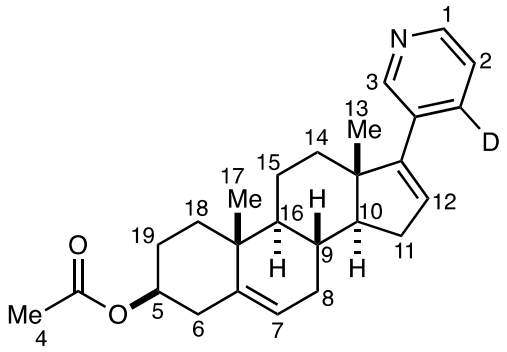
Prepared according to general procedure C using ((6*S*,10*R*)-8-benzyl-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxalin-2-yl)triphenylphosphonium trifluoromethanesulfonate (214 mg, 0.30 mmol), K_2CO_3 (62 mg, 0.45 mmol), and DMF:D_2O 9:1 (1.00 mL). Flash column chromatography (silica gel, gradient elution: 30% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as an orange oil (65 mg, 0.21 mmol, 71% yield). IR ν_{max}/cm^{-1} (film): 2943, 2787, 2749, 2255, 1719, 1672, 1467, 1454, 1355, 1283, 1264, 1083, 1052, 928, 875, 776, 733, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.77 (1H, s, H_1), 7.79 (2H, s, H_2 and H_3), 7.13-7.06 (3H, m, H_5 and H_6), 6.86-6.80 (2H, m, H_4), 3.48 (2H, s, H_{12}), 3.38-3.30 (2H, m, H_7 and H_8), 3.03-2.96 (2H, m, H_{10} and H_{11}), 2.57 (2H, d, J = 10.3 Hz, H_{10} and H_{11}), 2.37-2.29 (1H, m, H_9), 1.86 (1H, d, J = 10.7 Hz, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.87 (2C), 143.38, 143.32, 143.20, 142.93 (t, J = 28.8 Hz), 138.14, 128.25, 127.96, 126.62, 120.41 (2C), 61.49, 57.36, 43.09, 41.23; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 303.2, $C_{20}H_{19}DN_3^+$ requires 303.2.

5,7-Dichloro-4-(4-fluorophenoxy)quinoline-2-*d* (170)



Prepared according to general procedure B using (5,7-dichloro-4-(4-fluorophenoxy)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (72 mg, 0.10 mmol), K_2CO_3 (21 mg, 0.15 mmol), and CD_3OD:D_2O 9:1 (0.33 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a white solid (24 mg, 0.079 mmol, 79% yield). IR ν_{max}/cm^{-1} (film): 3044, 2918, 2849, 1726, 1600, 1575, 1555, 1500, 1473, 1371, 1294, 1196, 978, 837, 747; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (1H, d, J = 2.1 Hz, H_3), 7.58 (1H, d, J = 2.1 Hz, H_2), 7.20-7.10 (4H, m, H_4 and H_5), 6.60 (1H, s, H_1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.50, 160.09 (d, J = 244.9 Hz), 152.02 (t, J = 26.7 Hz), 151.63, 149.80 (d, J = 2.6 Hz), 135.00, 130.14, 129.58, 127.84, 122.37, 122.28, 117.08 (d, J = 25.6 Hz), 106.55; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –116.73; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 309.0, $C_{15}H_7DCl_2FNO^+$ requires 309.0.

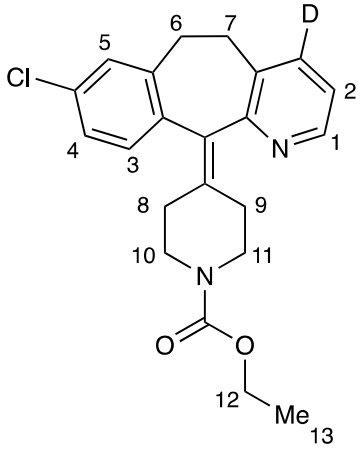
(3*S*,9*S*,10*R*,13*S*,14*S*)-10,13-Dimethyl-17-(pyridin-3-yl-4-*d*)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (171)



Prepared according to general procedure C using (3-((3*S*,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)triphenylphosphonium trifluoromethanesulfonate (80 mg, 0.10 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), and DMF:D_2O 9:1 (0.33 mL). Preparative thin layer chromatography (40% EtOAc in hexanes) afforded the title compound as a white solid (24 mg, 0.062 mmol, 62% yield).

mp 140-141 ºC; IR ν_{max}/cm^{-1} (film): 3045, 2936, 2890, 2854, 1732, 1469, 1372, 1243, 1033, 660; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.61 (1H, s), 8.45 (1H, d, *J* = 3.4 Hz), 7.20 (1H, d, *J* = 4.6 Hz), 5.99-5.96 (1H, m), 5.40 (1H, d, *J* = 5.0 Hz), 4.65-4.55 (1H, m), 2.39-2.21 (3H, m), 2.10-1.98 (6H, m), 1.90-1.81 (2H, m), 1.80-1.42 (7H, m), 1.27-1.00 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.44, 151.59, 147.88, 147.82, 139.97, 133.52, 133.03 (t, *J* = 24.5 Hz), 129.13, 122.88, 122.23, 73.79, 57.41, 50.21, 47.27, 38.09, 36.87, 36.74, 35.16, 31.74, 31.46, 30.36, 27.69, 21.38, 20.77, 19.21, 16.52; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 393.3, $C_{26}H_{33}DNO_2^+$ requires 393.3.

Ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene-4-*d*)piperidine-1-carboxylate (172)

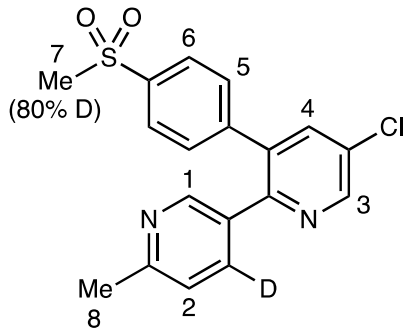


Prepared according to general procedure B using (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (396 mg, 0.50 mmol), K_2CO_3 (104 mg, 0.75 mmol), and CD_3OD:D_2O 9:1 (1.67 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 80% EtOAc in hexanes) followed by a second flash column (basic alumina: 30% EtOAc in hexanes) afforded the title compound as a yellow oil (152 mg, 0.40 mmol, 79% yield). IR ν_{max}/cm-

$_1$ (film): 2980, 2911, 2863, 1688, 1557, 1476, 1433, 1227, 1116, 995, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (1H, d, *J* = 4.8 Hz, H_1), 7.15-7.04 (4H, m, H_2, H_3, H_4, and H_5), 4.11 (2H, q, *J* = 7.1 Hz, H_{12}), 3.88-3.70 (2H, m, H_{10} and H_{11}), 3.42-3.26 (2H, m, H_6 and H_7), 3.16-3.05 (2H, m, H_{10} and H_{11}), 2.87-2.71 (2H, m, H_6 and H_7), 2.52-2.23 (4H, m, H_8 and H_9), 1.22 (3H, t, *J* = 7.1 Hz, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.96, 155.35, 146.59, 139.43, 137.57, 137.34, 137.04 (t, *J* = 24.4 Hz), 134.11, 133.12, 132.78, 130.43, 128.87, 126.03, 122.03, 61.19, 44.70, 44.67, 31.59, 31.31, 30.64, 30.42, 14.58; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 384.2, $C_{22}H_{23}DClN_2O_2^+$ requires 384.2.

Additionally prepared according to general procedure C using (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (238 mg, 0.30 mmol), K_2CO_3 (62 mg, 0.45 mmol), and DMF:D_2O 9:1 (1.00 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 80% EtOAc in hexanes) followed by a second flash column (basic alumina: 30% EtOAc in hexanes) afforded the title compound as a yellow oil (84 mg, 0.22 mmol, 73% yield). IR ν_{max}/cm^{-1} (film): 2980, 2911, 2863, 1688, 1557, 1476, 1433, 1227, 1116, 995, 750; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (1H, d, *J* = 4.6 Hz, H_1), 7.17-7.04 (4H, m, H_2, H_3, H_4, and H_5), 4.12 (2H, q, *J* = 7.1 Hz, H_{12}), 3.88-3.70 (2H, m, H_{10} and H_{11}), 3.43-3.26 (2H, m, H_6 and H_7), 3.18-3.06 (2H, m, H_{10} and H_{11}), 2.89-2.72 (2H, m, H_6 and H_7), 2.52-2.23 (4H, m, H_8 and H_9), 1.23 (3H, t, *J* = 7.1 Hz, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.00, 155.40, 146.61, 139.45, 137.59, 137.39, 137.09 (t, *J* = 24.1 Hz), 134.11, 133.16, 132.82, 130.47, 128.91, 126.07, 122.07, 61.23, 44.73, 44.70, 31.62, 31.34, 30.66, 30.45, 14.61; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 384.2, $C_{22}H_{23}DClN_2O_2^+$ requires 384.2.

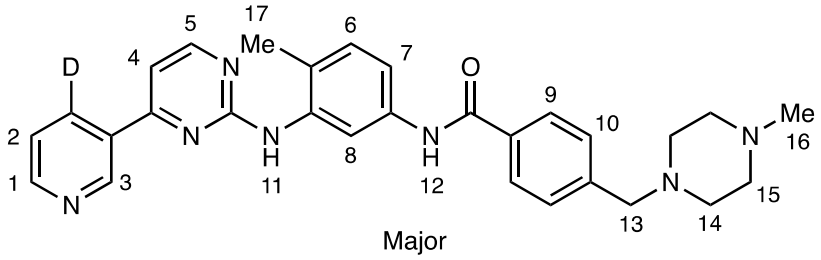
5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine-4'-*d* (173)



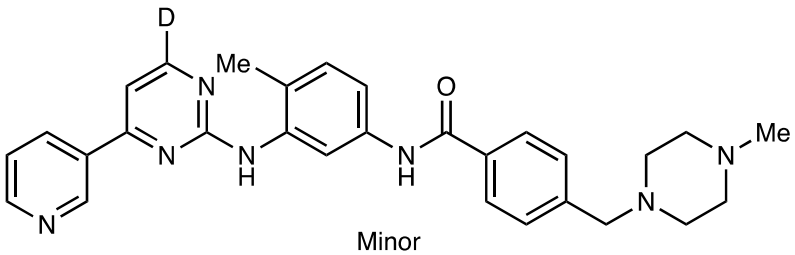
Prepared according to general procedure B (except that the reaction was run for 12 hours instead of 3) using (5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)triphenylphosphonium trifluoromethanesulfonate (154 mg, 0.20 mmol), K_2CO_3 (41 mg, 0.30 mmol), and CD_3OD:D_2O 9:1 (0.67 mL). Flash column chromatography (silica gel, gradient elution: 40% EtOAc and 3% AcOH in hexanes to EtOAc) afforded the title compound as a white solid (69 mg, 0.19 mmol, 96% yield). mp 108-113 ºC; IR ν_{max}/cm^{-1} (film): 3053, 2921, 2853, 1722, 1664, 1587, 1554, 1485, 1427, 1401, 1295, 1149, 1011, 800, 688, 578; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, d, *J* = 2.3 Hz, H_3), 8.37 (1H, s, H_1), 7.88 (2H, d, *J* = 8.2 Hz, H_6), 7.72 (1H, d, *J* = 2.3 Hz, H_4), 7.39 (2H, d, *J* = 8.2 Hz, H_5), 7.07 (1H, s, H_2), 3.04 (3H [integration = 0.59, 80% deuterium], s, H_7), 2.52 (3H, s, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.48, 152.28, 149.79, 148.32, 143.72, 140.10, 137.88, 136.89 (t, *J* = 24.9 Hz), 135.19, 131.05, 131.01, 130.29, 127.85, 122.58, 43.94 (m), 24.21; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 360.0, $C_{18}H_{15}DClN_2O_2S^+$ requires 360.1.

***N*-(4-Methyl-3-((4-(pyridin-3-yl-4-*d*)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (174) and *N*-(4-Methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl-6-*d*)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (174')**

20:1 Mixture of Regioisomers



Major



Minor

Prepared according to general procedure B (except the reaction was run for 12 hours instead of 3) using (3-(2-((2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (20:1 mixture of regioisomers) (202 mg, 0.23 mmol), K_2CO_3 (47 mg, 0.34 mmol), and CD_3OD:D_2O 9:1 (0.77 mL). Flash column chromatography (silica gel, gradient elution: EtOAc to 10% CH_3OH and 1% NEt_3 in CH_2Cl_2) and recrystallization from CH_2Cl_2 and Et_2O afforded the title compound as a yellow solid (105 mg, 0.21 mmol, 92% yield). mp 108-113 ºC; IR ν_{max}/cm^{-1} (film): 3232, 3008, 2797, 1654, 1574, 1525, 1448, 1407, 1306, 1181, 1009, 746, 646; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.23 (1H, s, H_3), 8.68 (1H, d, J = 4.8 Hz, H_1), 8.59 (1H, d, J = 1.7 Hz, H_8), 8.50 (1H, d, J = 5.1 Hz, H_5), 8.04 (1H, br s, H_{12}), 7.84 (2H, d, J = 8.1 Hz, H_9), 7.44-7.38 (3H, m, H_2 and H_{10}), 7.31 (1H, dd, J = 8.2, 1.7 Hz, H_7), 7.22-7.14 (2H, m, H_4 and H_6), 7.05

(1H, s, H_{11}), 3.58 (2H, s, H_{13}), 2.63 (8H, br s, H_{14} and H_{15}), 2.45 (3H, s, H_{16}), 2.33 (3H, s, H_{17}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.47, 162.28, 160.38, 158.76, 151.10, 148.20, 141.31, 137.43, 136.64, 134.39 (t, J = 25.0 Hz), 133.86, 132.29, 130.40, 128.88, 127.20, 124.48, 123.40, 115.78, 113.80, 107.95, 61.79, 54.30, 51.47, 44.80, 17.51; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 495.3, $C_{29}H_{31}DN_7O^+$ requires 495.3.

A1.7 Preparation of Tritiated Azaarenes

General procedure A

In a 1 mL Trisorber ultratorr reaction vessel, 10% Pd/C (1.5 mg) was suspended in THF (200 μL) and methanol (10 μL) was added. The reaction vessel was attached to the Trisorber and subjected to a single freeze thaw cycle. Tritium gas (1 Ci, 100 mm, 0.13 atmospheres) was added and the reaction vigorously stirred overnight. At the completion of the reaction after recovery of excess tritium, the suspension was passed through a 4 mm 0.2 μm Millipore nylon filter into a 0.3 mL crimp top V-vial containing the phosphonium salt (0.012-0.013 mmol) and Cs_2CO_3 (6.5 mg, 0.020 mmol). The Trisorber vessel was rinsed with an additional 100 μL of THF and this rinse was added to the V-vial by passing through the filter. The vial was crimped and vigorously stirred overnight.

At the completion of the reaction, the suspension was transferred to a RB flask in ethanol and concentrated *in vacuo*. The residue was dissolved in ethanol (10 mL) for analysis by liquid scintillation counting to determine the total radioactivity, HPLC with radioactivity flow monitoring to determine radiochemical purity, and LC/MS to determine specific activity.

General procedure B

A 0.3 mL crimp top V-vial was charged with the phosphonium salt (0.013-0.038 mmol), Cs_2CO_3 (0.020 mmol), THF (100 μL), and placed under a nitrogen atmosphere. Either 500 mCi THO at 50 Ci/cc (10 μL) or 150 mCi THO at 50 Ci/cc (3 μL) was added at room temperature, the vial was crimped, and the reaction vigorously stirred overnight.

At the completion of the reaction, the suspension was transferred to a RB flask in ethanol and concentrated *in vacuo*. The residue was dissolved in ethanol (10 mL) for analysis by liquid scintillation counting to determine the total radioactivity, HPLC with radioactivity flow monitoring to determine radiochemical purity, and LC/MS to determine specific activity.

General procedure C

A 0.3 mL crimp top V-vial was charged with the phosphonium salt (0.013 mmol), K_2CO_3 (0.020 mmol), DMF (100 μL), and placed under a nitrogen atmosphere. Either 500 mCi THO at 50 Ci/cc (10 μL) or 150 mCi THO at 50 Ci/cc (3 μL) was added at room temperature, the vial was crimped, and the reaction vigorously stirred overnight.

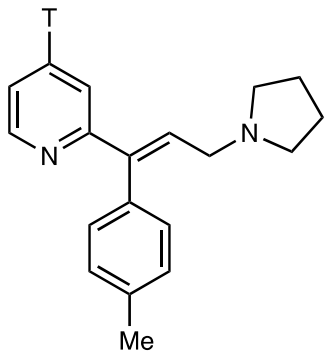
At the completion of the reaction, the suspension was transferred to a RB flask in ethanol and concentrated *in vacuo*. The residue was dissolved in ethanol (10 mL) for analysis by liquid scintillation counting to determine the total radioactivity, HPLC with radioactivity flow monitoring to determine radiochemical purity, and LC/MS to determine specific activity.

Notes.

1) Benchtop Cs_2CO_3 (exposed to air and without purification) was used for select examples and is less effective than a new bottle of Cs_2CO_3. We presume that residual H_2O content

results in lower mCi values. We recommend using a new bottle of Cs_2CO_3 and storing the base in a glovebox.

(*E*)-2-(3-(Pyrrolidin-1-yl)-1-(*p*-tolyl)prop-1-en-1-yl)pyridine-4-*t* (T-Triprolidine)



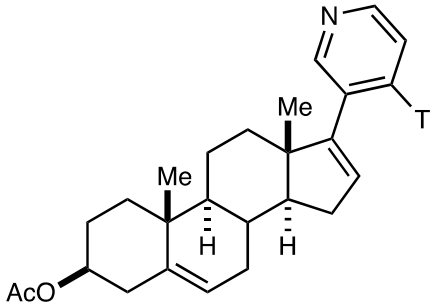
Procedure A:

Using benchtop Cs_2CO_3 stored in a desiccator.

Prepared according to General Procedure A using triprolidine phosphonium salt (8.3 mg, 0.012 mmol).

HPLC Analysis: Gemini NX C18 4.6 x 50 mm, 3 μm, 254 nm, 0.05 M pH 10 triethylammonium acetate (55:45) acetonitrile at 1 mL/min for 6 minutes followed by a step gradient to acetonitrile. 28.2 mCi was isolated at a radiochemical purity of 37.6%. Radiochemical yield 10.6 mCi.

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



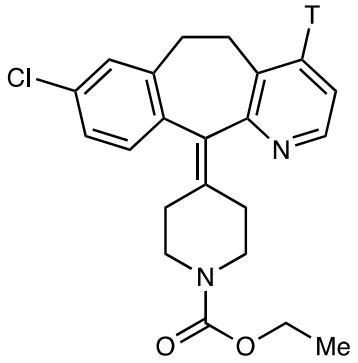
Procedure A:

Using a new bottle of Cs_2CO_3.

Prepared according to General Procedure A using (3-((3*S*,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)triphenylphosphonium trifluoromethanesulfonate (10.1 mg, 0.013 mmol).

HPLC Analysis: Gemini NX C18 4.6 x 50 mm, 3 μm, 254 nm, 0.05 M pH 4 triethylammonium acetate (25:75) acetonitrile at 1 mL/min for 6 minutes followed by a step gradient to acetonitrile. 37.4 mCi was isolated at a radiochemical purity of 49.1%. Radiochemical yield 18.4 Ci/mmol. Specific activity 2.52 mCi.

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



Procedure A:

Run 1: Benchtop Cs_2CO_3 stored in a desiccator.

Prepared according to General Procedure A using (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (9.7 mg, 0.012 mmol).

HPLC Analysis: Gemini NX C18 4.6 x 50 mm, 3 μm, 254 nm, 0.05 M pH 10 triethylammonium acetate (45:55) acetonitrile at 1 mL/min for 6 minutes followed by a step gradient to acetonitrile. 28.1 mCi was isolated at a radiochemical purity of 40.9%. Radiochemical yield 11.5 mCi.

Run 2: Using a new bottle of Cs_2CO_3.

Prepared according to General Procedure A using (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (9.7 mg, 0.012 mmol).

HPLC Analysis: Gemini NX C18 4.6 x 50 mm, 3 μm, 254 nm, 0.05 M pH 10 triethylammonium acetate (45:55) acetonitrile at 1 mL/min for 6 minutes followed by a step gradient to acetonitrile. 55.6 mCi was isolated at a radiochemical purity of 38.1%. Radiochemical

yield 21.1 mCi. Specific activity 2.24 Ci/mmol.

Procedure B:

Benchtop Cs_2CO_3 stored in a desiccator.

Prepared according to General Procedure B using (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (10.0 mg, 0.013 mmol) and THO (10 μL of a 500 mCi solution at 50 Ci/cc)

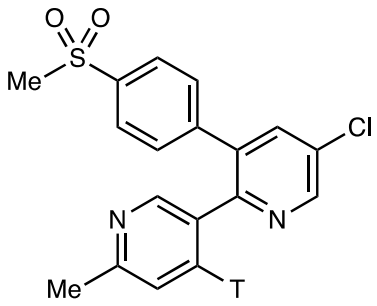
HPLC Analysis: Gemini NX C18 4.6 x 50 mm, 3 μm, 254 nm, 0.05 M pH 10 triethylammonium acetate (45:55) acetonitrile at 1 mL/min for 6 minutes followed by a step gradient to acetonitrile. 2.07 mCi was isolated at a radiochemical purity of 89.3%. Radiochemical yield 1.8 mCi.

Procedure C:

Prepared according to General Procedure C using (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (10.3 mg, 0.013 mmol) and THO (3 μL of a 150 mCi solution at 50 Ci/cc).

HPLC Analysis: Gemini NX C18 4.6 x 50 mm, 3 μm, 254 nm, 0.05 M pH 10 triethylammonium acetate (45:55) acetonitrile at 1 mL/min for 6 minutes followed by a step gradient to acetonitrile. 7.4 mCi was isolated at a radiochemical purity of 61.7%. Radiochemical yield 4.6 mCi.

5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine-4'-*t* (T-Etoricoxib)



Procedure A:

Using a new bottle of Cs_2CO_3.

Prepared according to General Procedure A using (5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)triphenylphosphonium trifluoromethanesulfonate (10.0 mg, 0.013 mmol).

HPLC Analysis: Gemini NX C18 4.6 x 50 mm, 3 μm, 254 nm, 0.05 M pH 10 triethylammonium acetate (65:35) acetonitrile at 1 mL/min for 6 minutes followed by a step gradient to acetonitrile. 55.4 mCi was isolated at a radiochemical purity of 49.7%. Specific activity 1.66 Ci/mmol. Radiochemical yield 27.5 mCi.

Procedure B:

Benchtop Cs_2CO_3 stored in a desiccator.

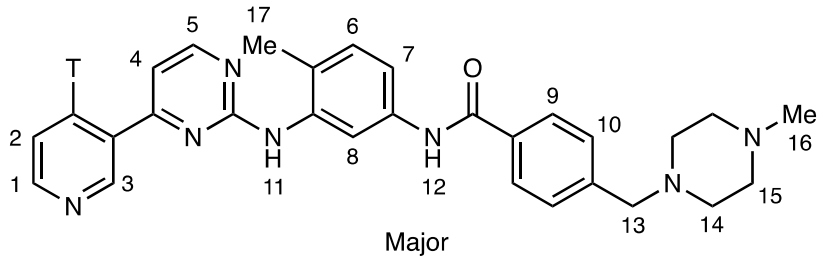
Prepared according to General Procedure B using (5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)triphenylphosphonium trifluoromethanesulfonate (29.1 mg, 0.038 mmol) and THO (10 **μ**L of a 500 mCi solution at 50 Ci/cc).

HPLC Analysis: Gemini NX C18 4.6 x 50 mm, 3 μm, 254 nm, 0.05 M pH 10 triethylammonium acetate (45:55) acetonitrile at 1 mL/min for 6 minutes followed by a step gradient to acetonitrile. 18.8 mCi was isolated at a radiochemical purity of 94.0%. Radiochemical

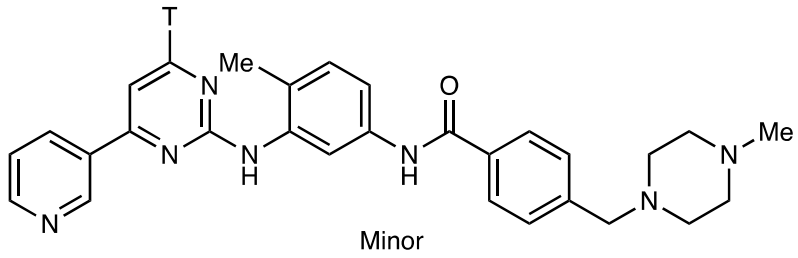
yield 17.6 mCi.

_N_-(4-Methyl-3-((4-(pyridin-3-yl-4-_t_)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide and _N_-(4-Methyl-3-((4-(pyridin-3-yl-4-_t_)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (T-Imatinib)

20:1 Mixture of Regioisomers



Major



Minor

Procedure A:

Using a new bottle of Cs_2CO_3.

Prepared according to General Procedure A using (3-(2-((2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (20:1 mixture of regioisomers) (11.7 mg, 0.013 mmol).

HPLC Analysis: Gemini NX C18 4.6 x 50 mm, 3 μm, 254 nm, 0.05 M pH 10 triethylammonium acetate (70:30) acetonitrile at 1 mL/min for 6 minutes followed by a step gradient to acetonitrile. 37.6 mCi was isolated at a radiochemical purity of 50.7%. The crude reaction was purified on a Gemini NX C18 250 mm x 10 mm semi-prep HPLC column with a

mobile phase of 0.05 M pH 10 triethylammonium acetate (70:30) acetonitrile at a flow rate of 5 mL/minute and detection at 254 nm. A total batch of 17.3 mCi was isolated at a radiochemical purity of 99.6% and a specific activity of 2.29 Ci/mmol.

REFERENCES

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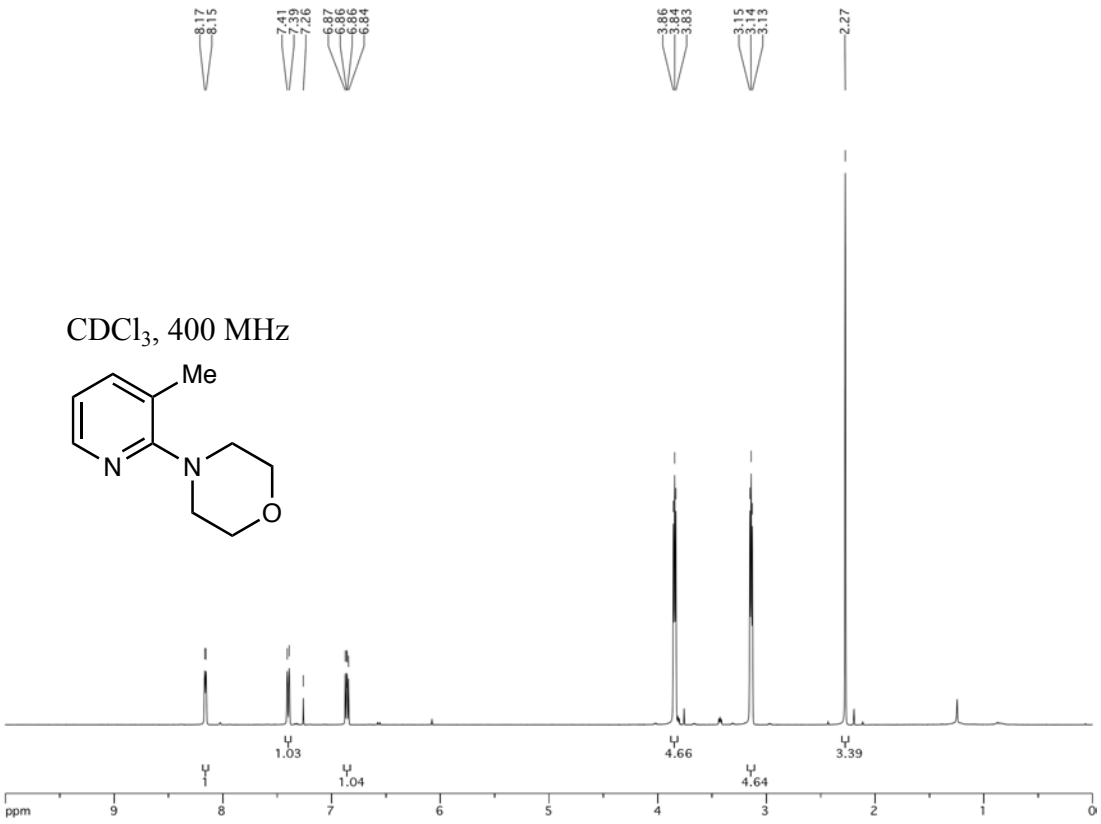
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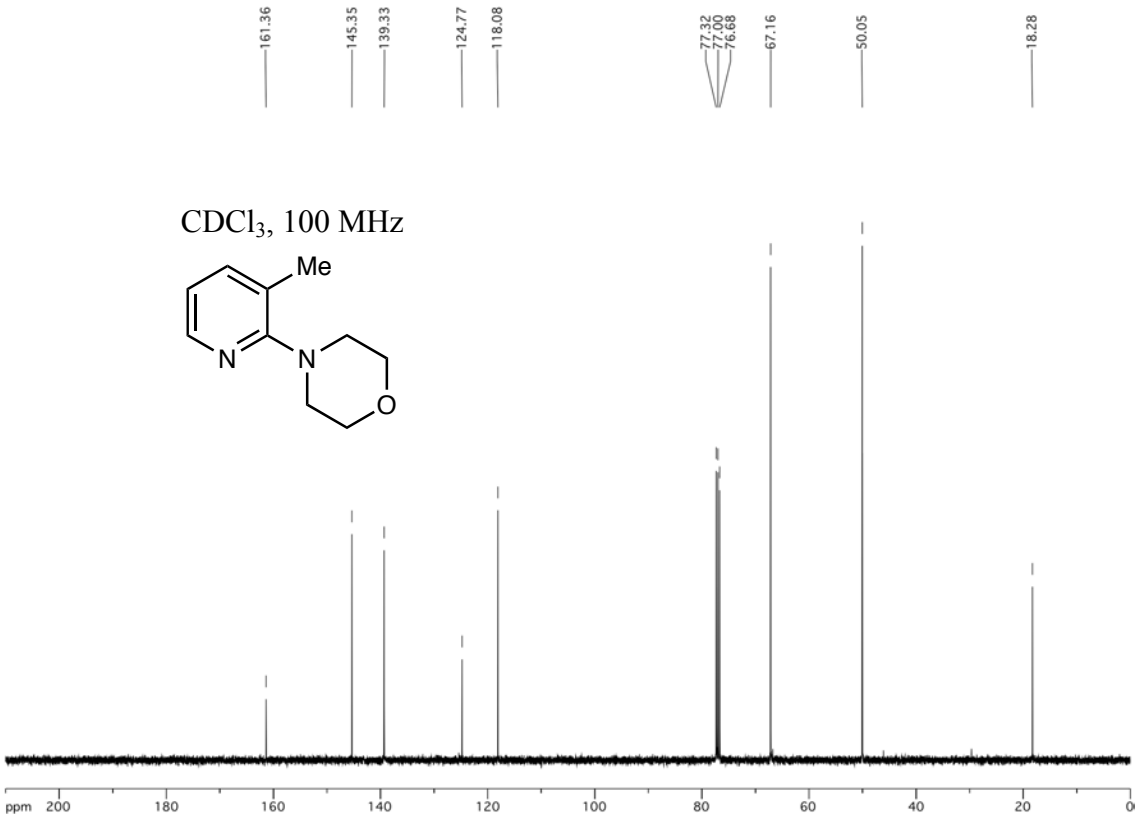
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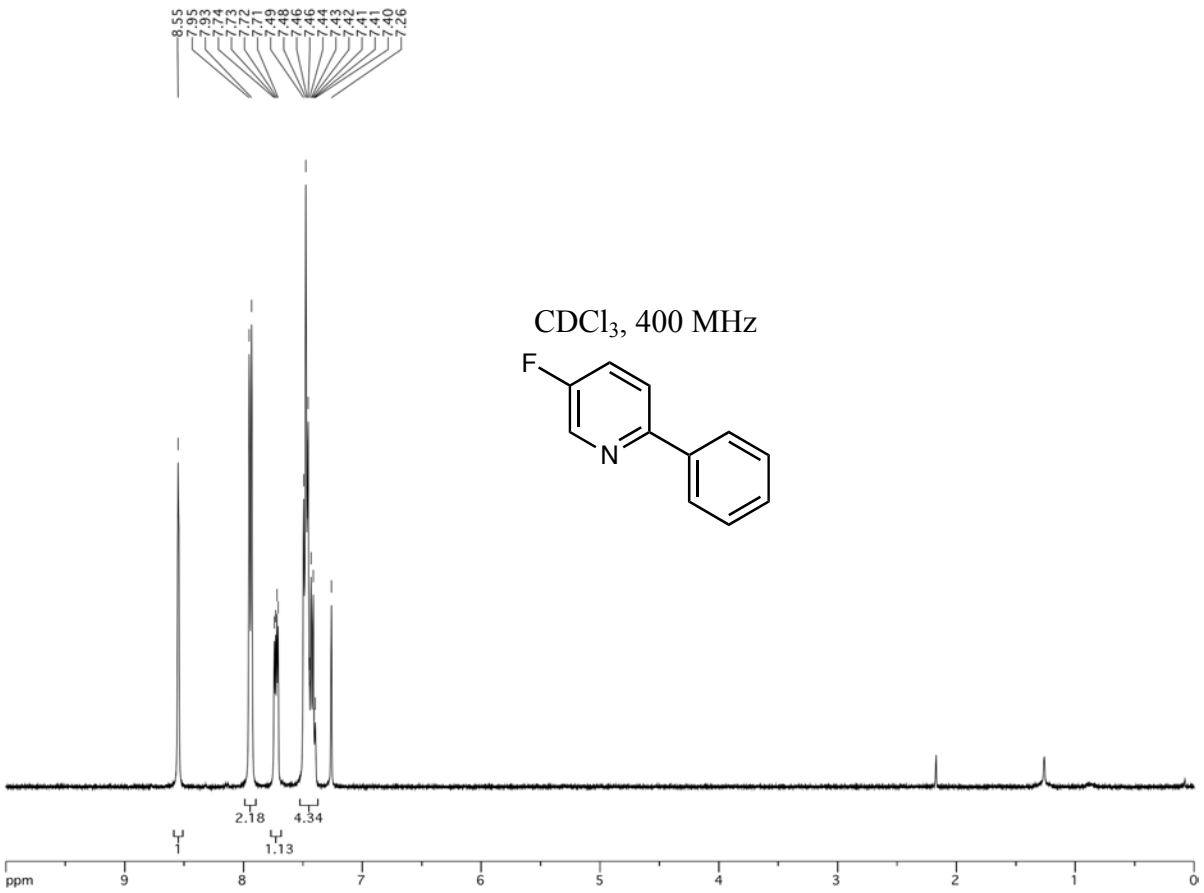
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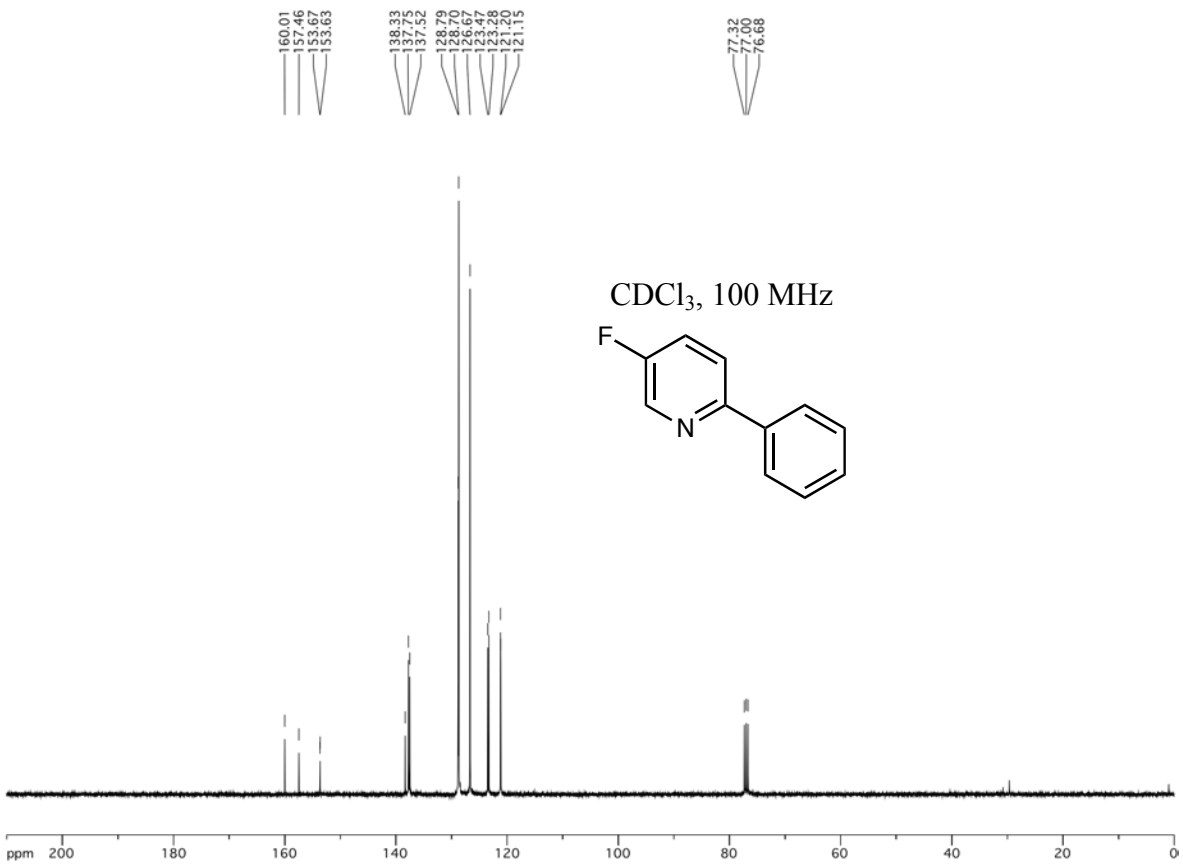
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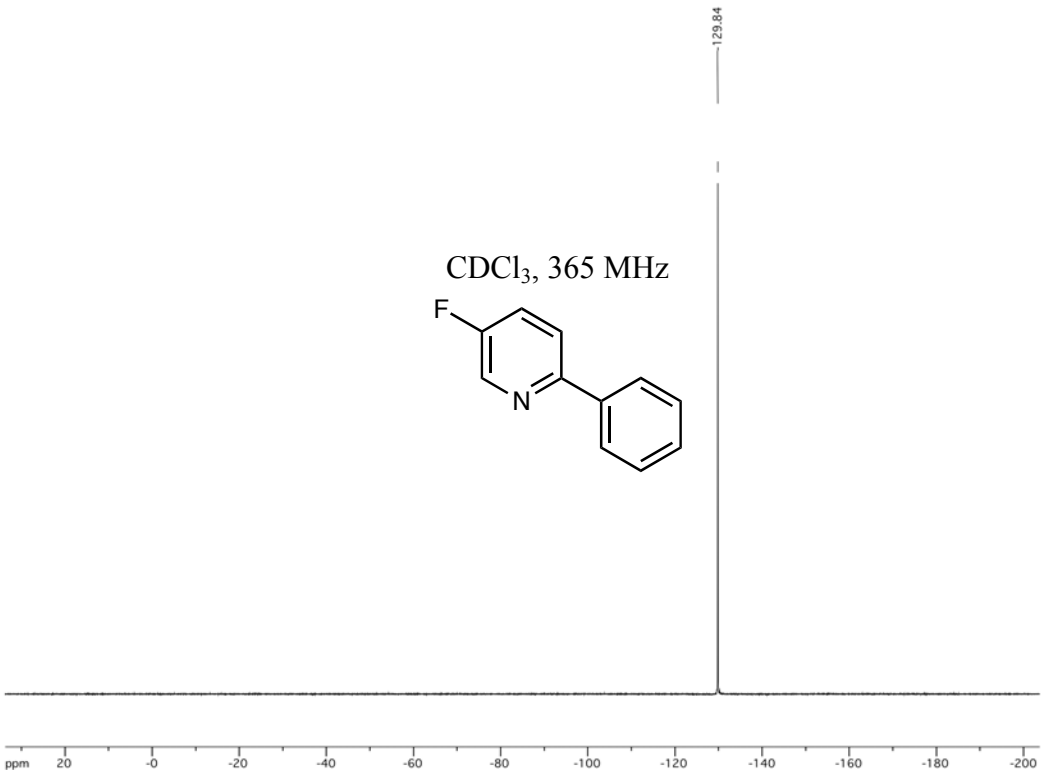
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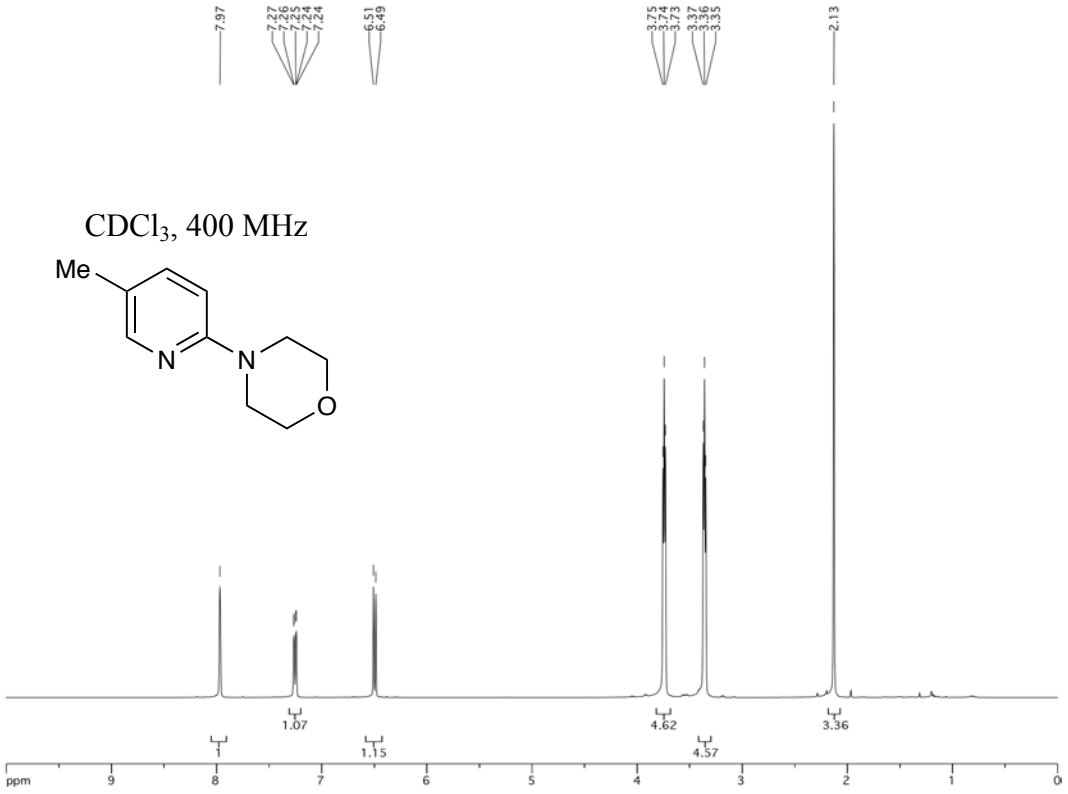
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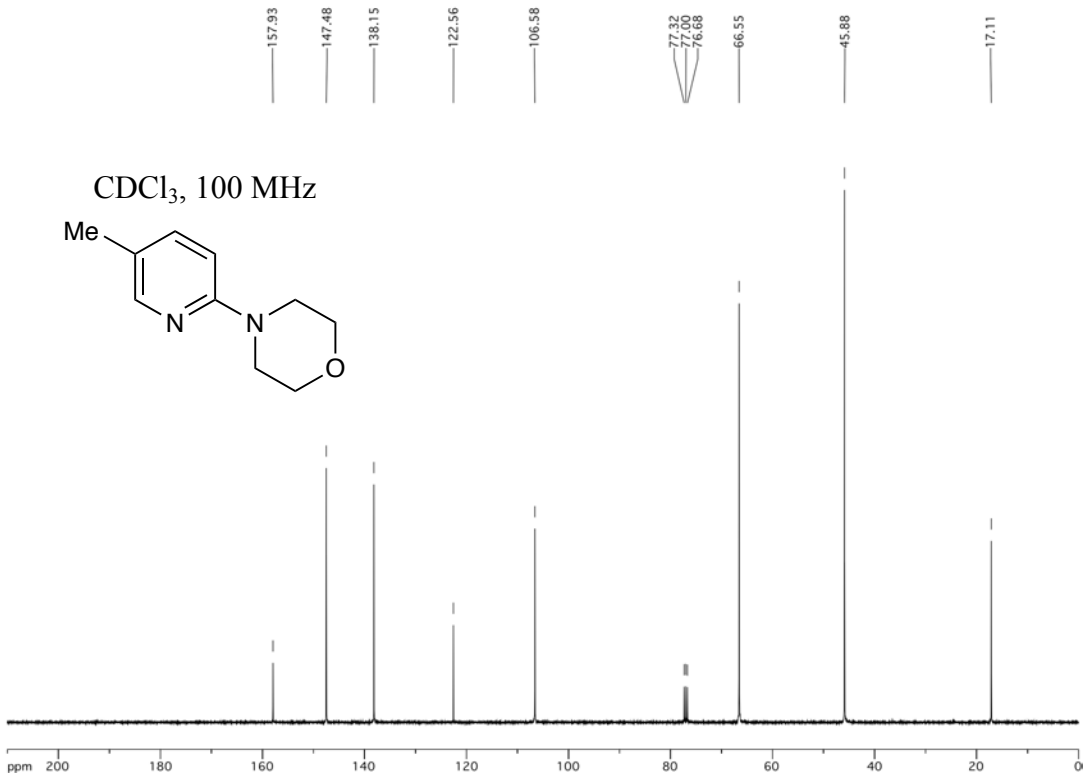
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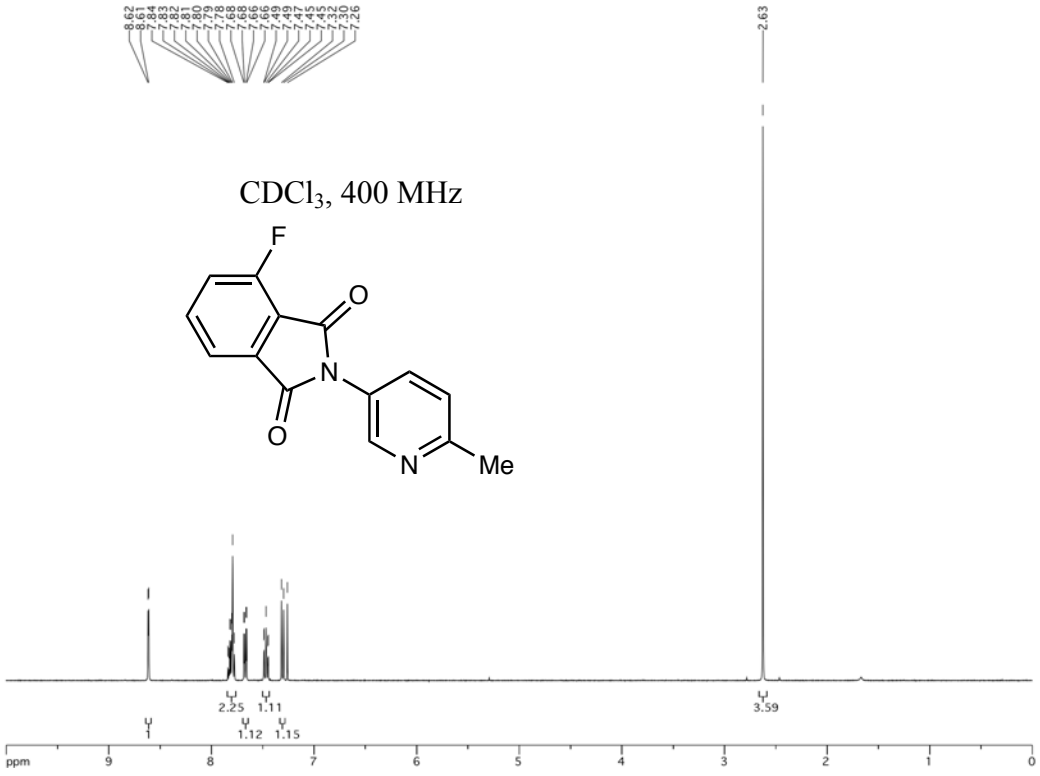
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7.45
7.32
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CDCl3, 400 MHz
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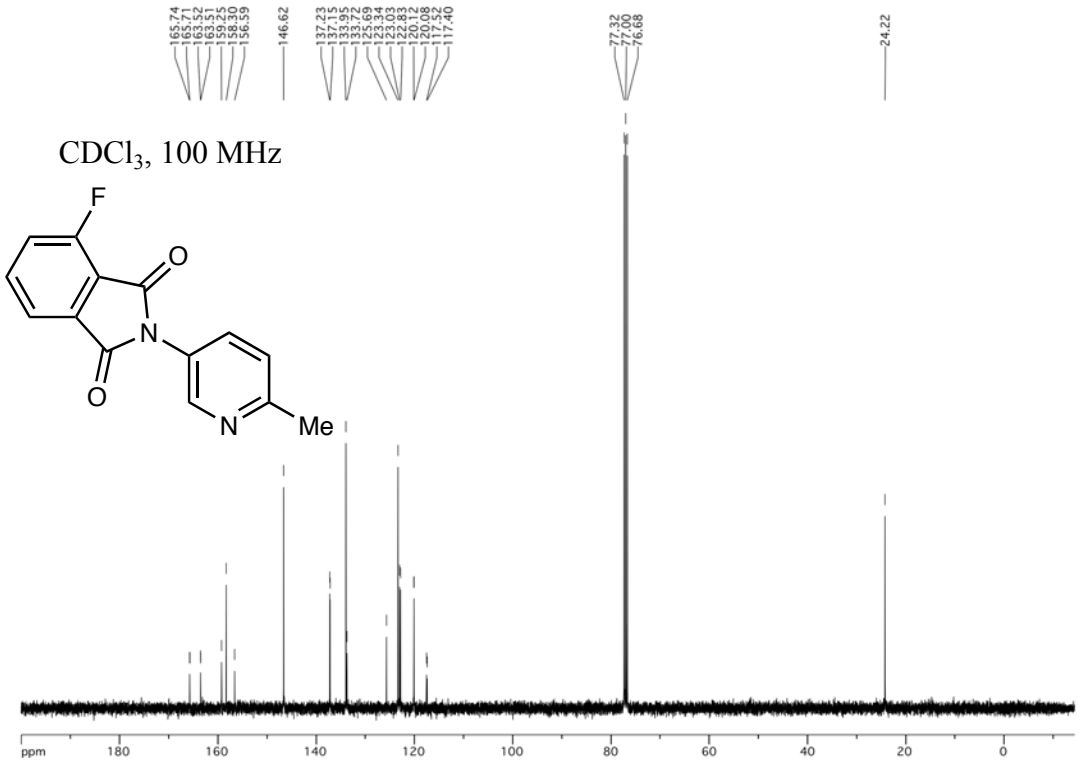
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24.22
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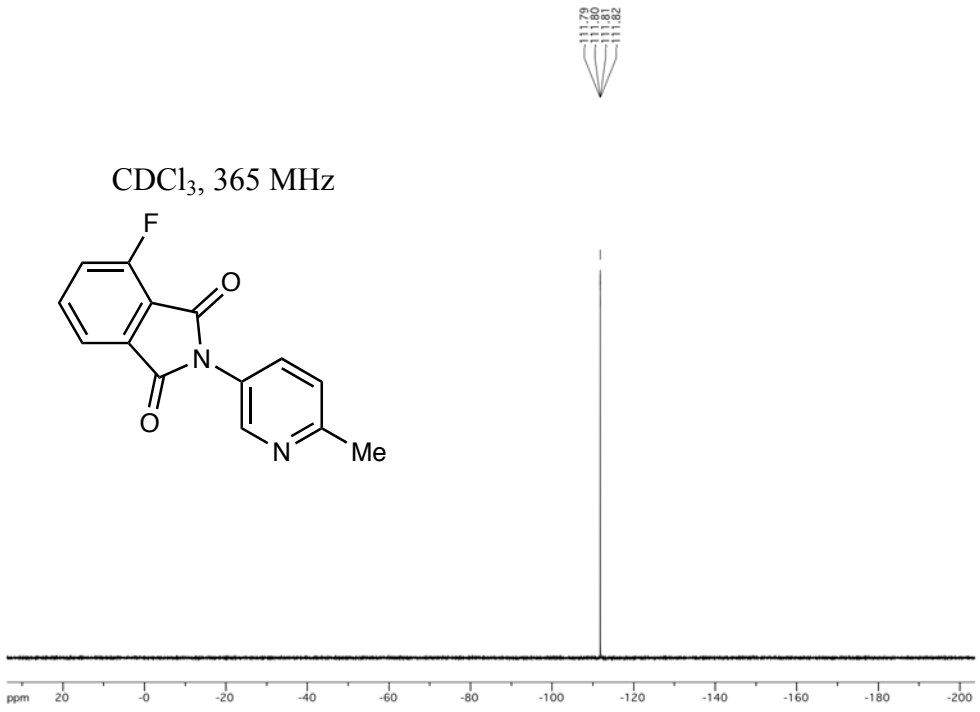
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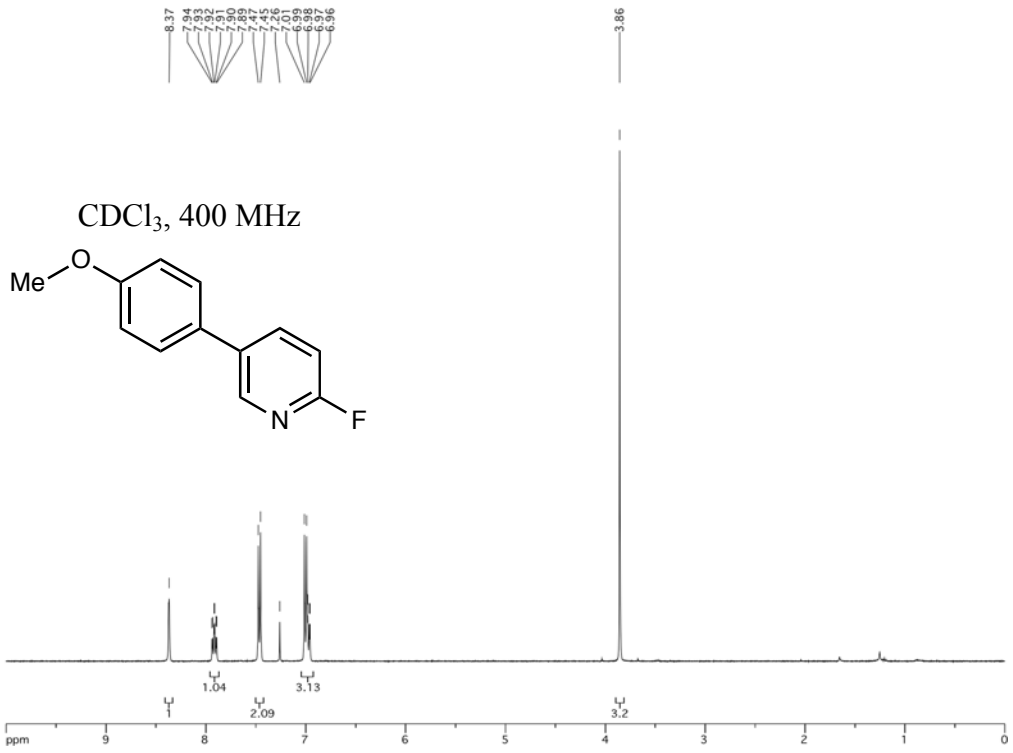
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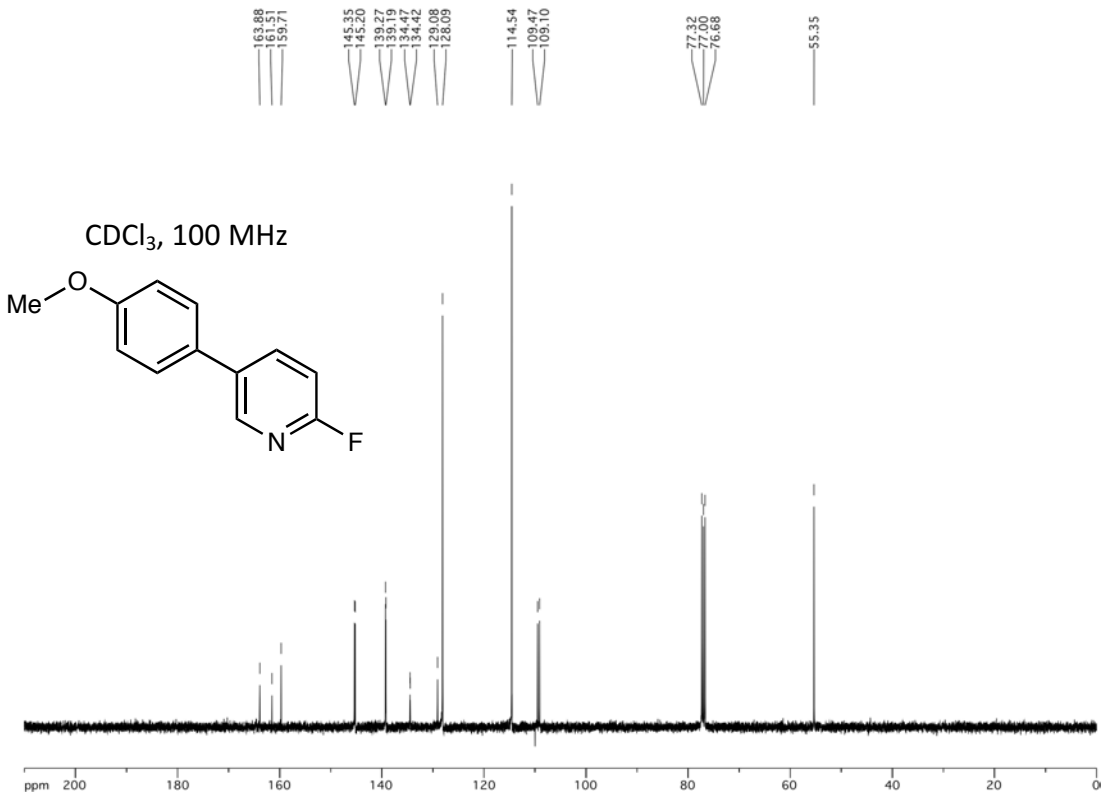
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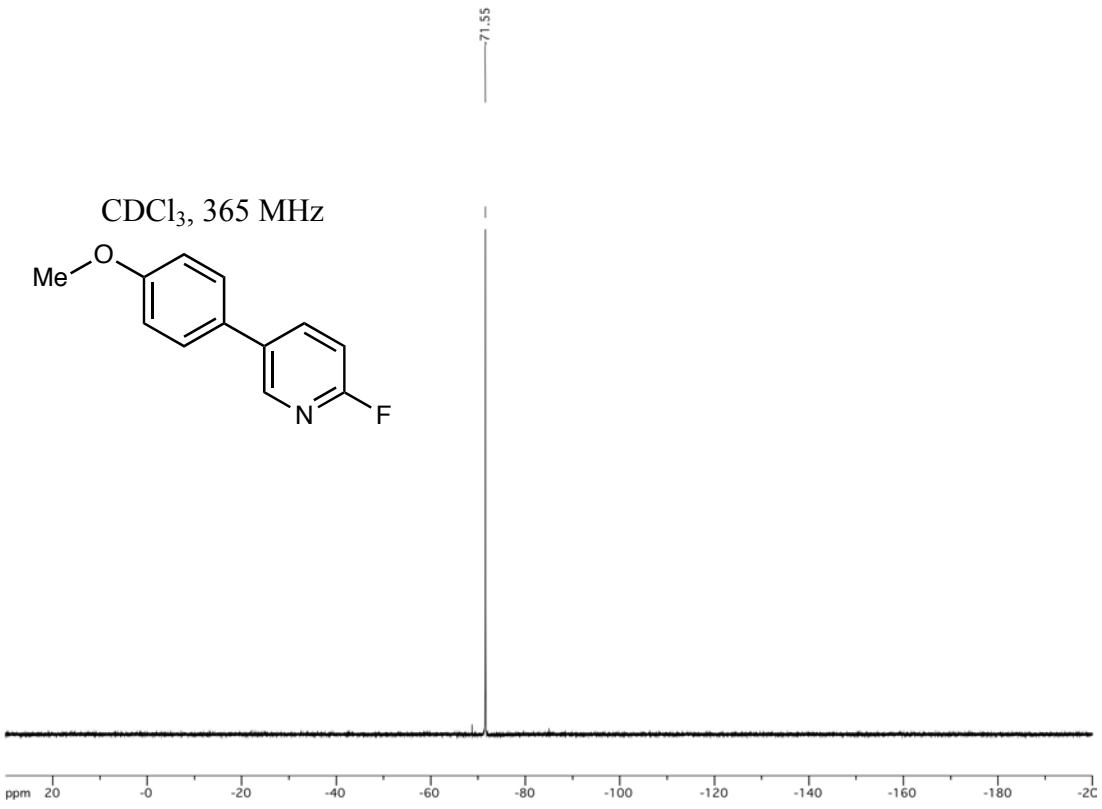
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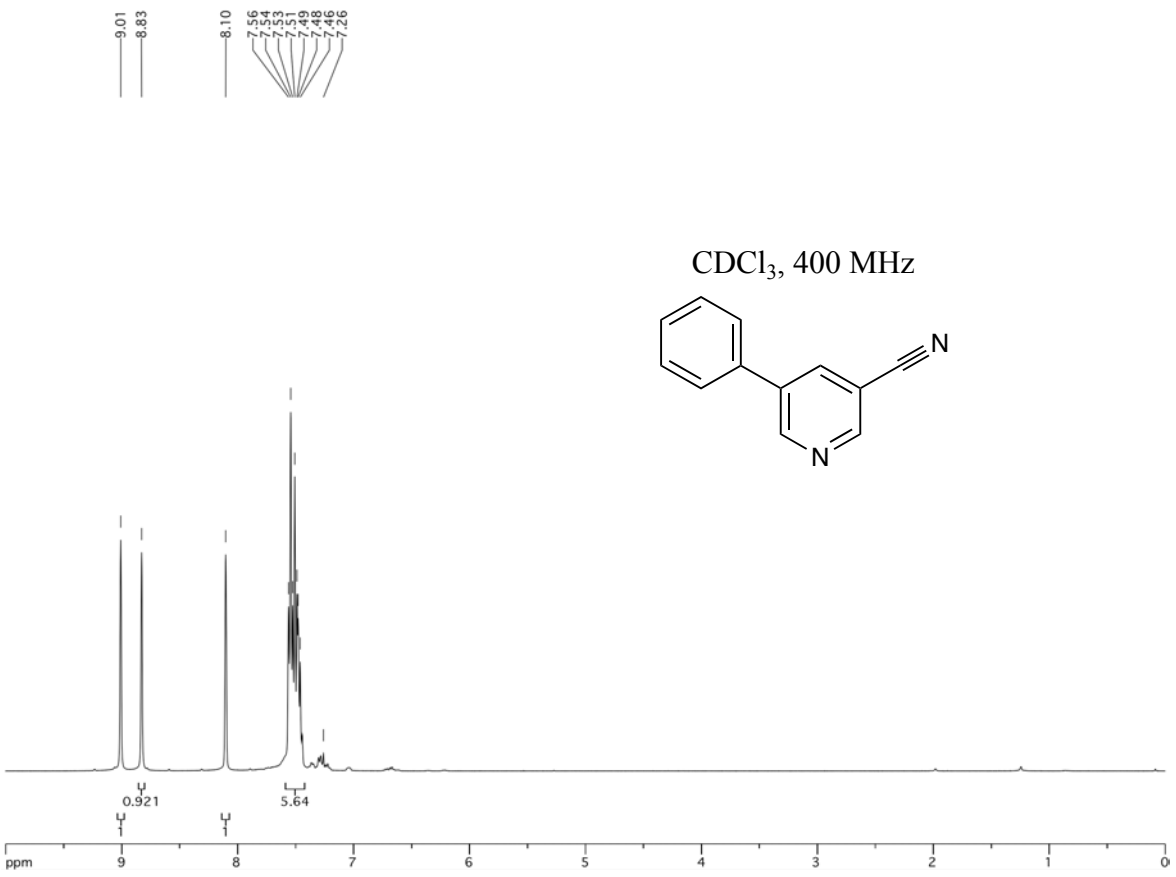
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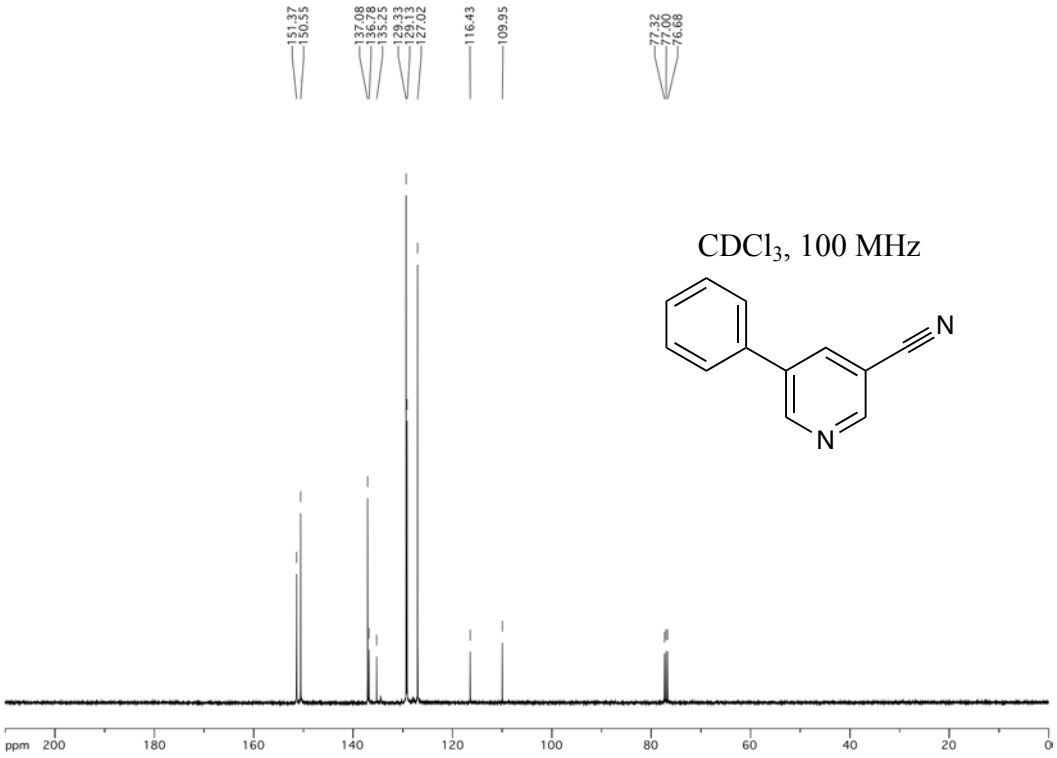
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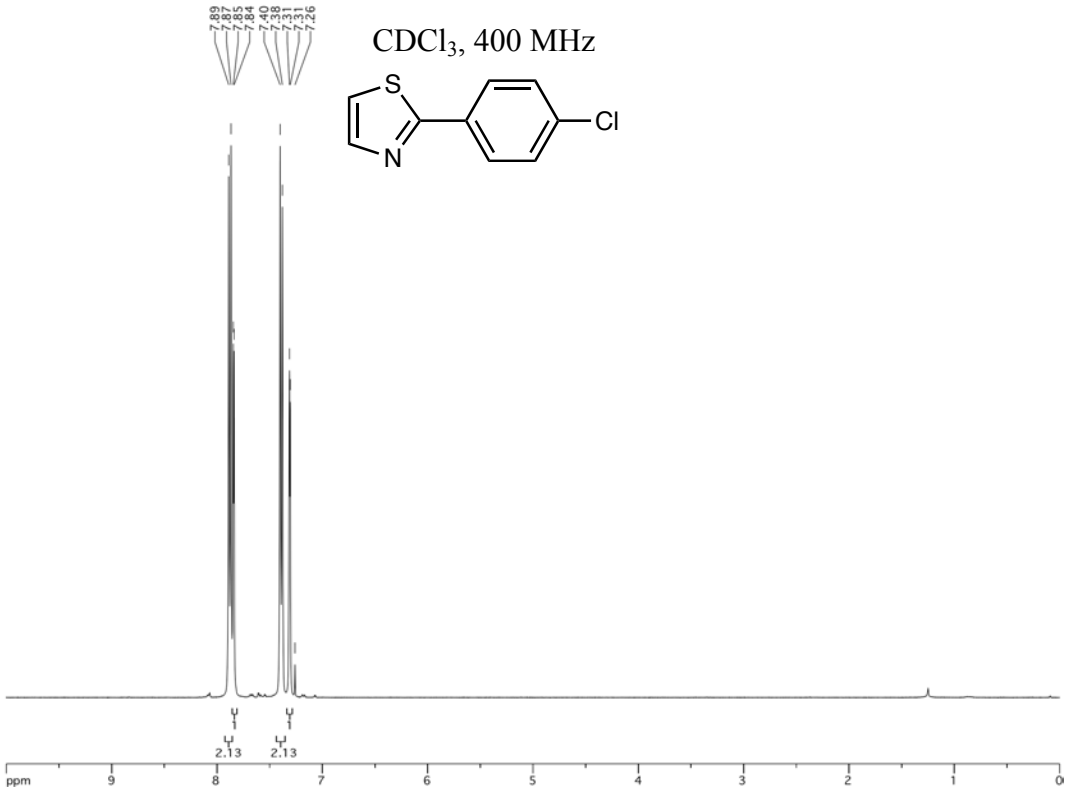
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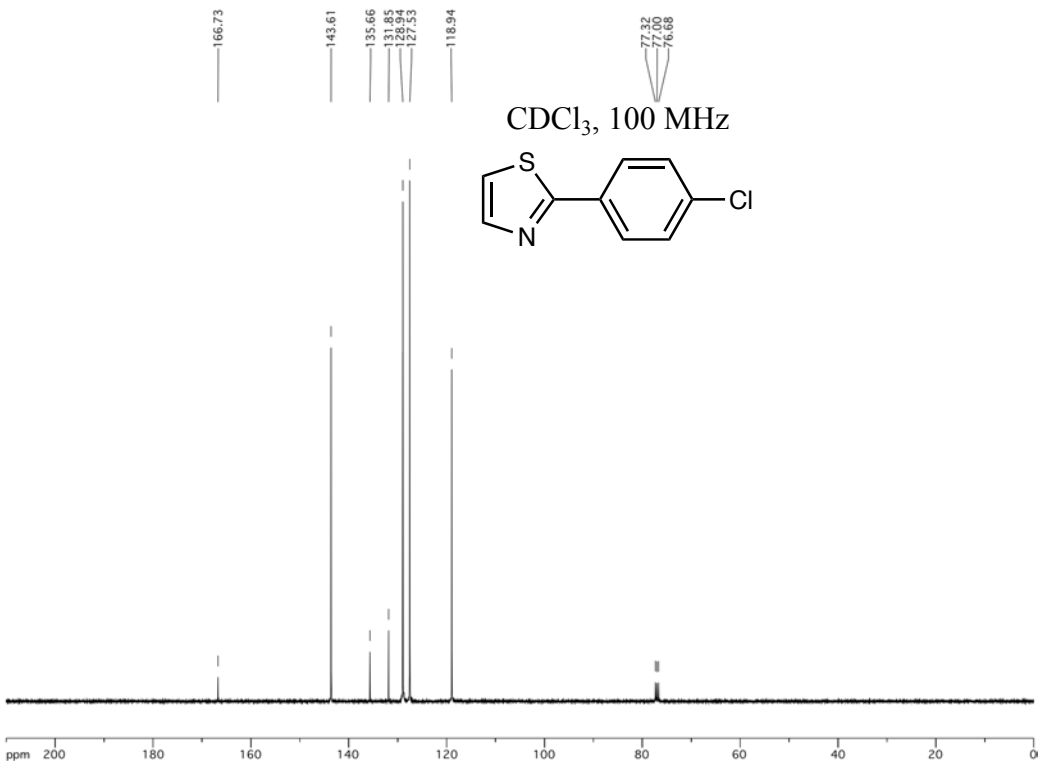
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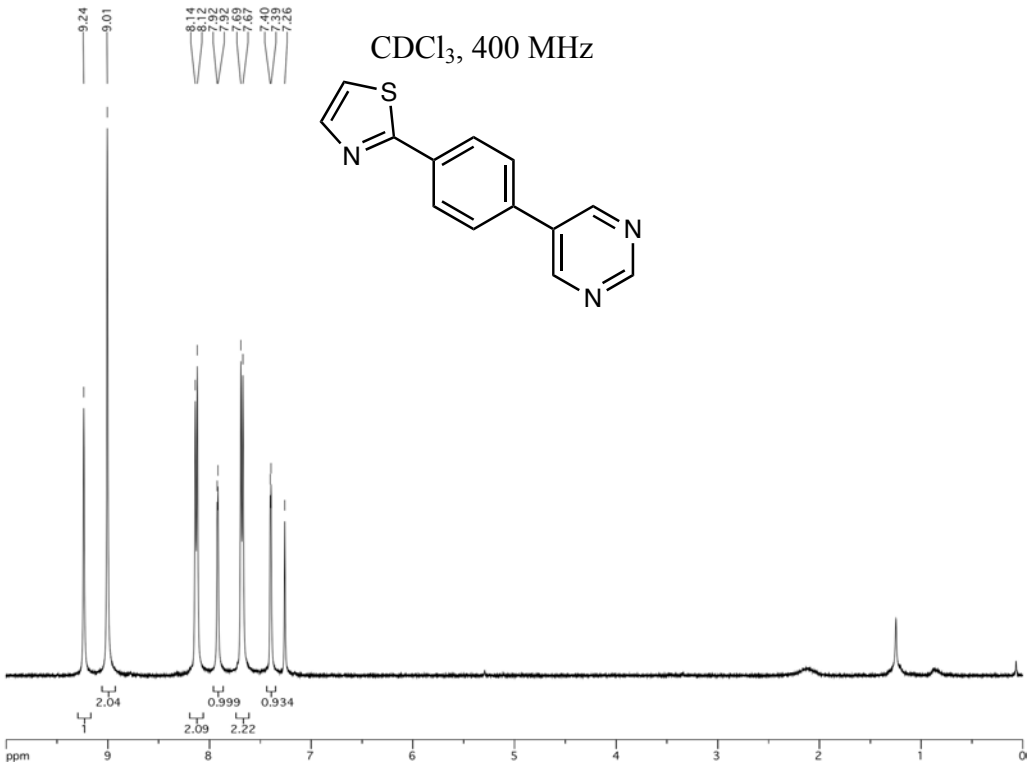
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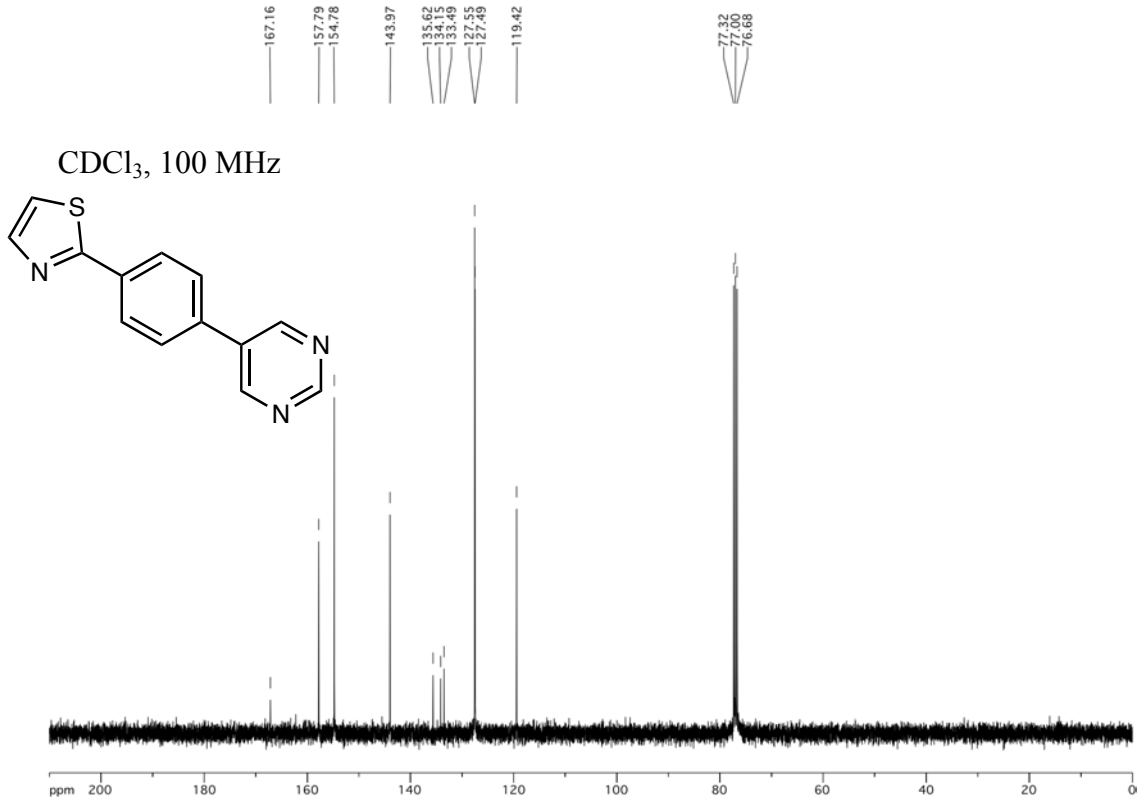
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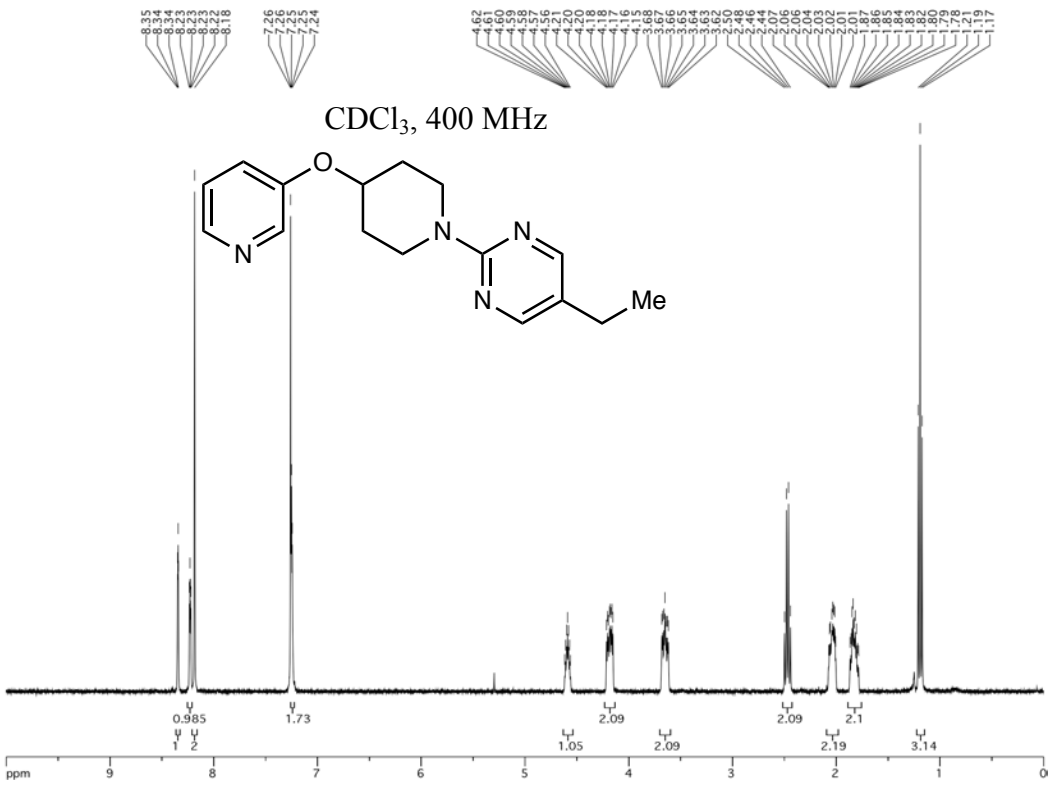
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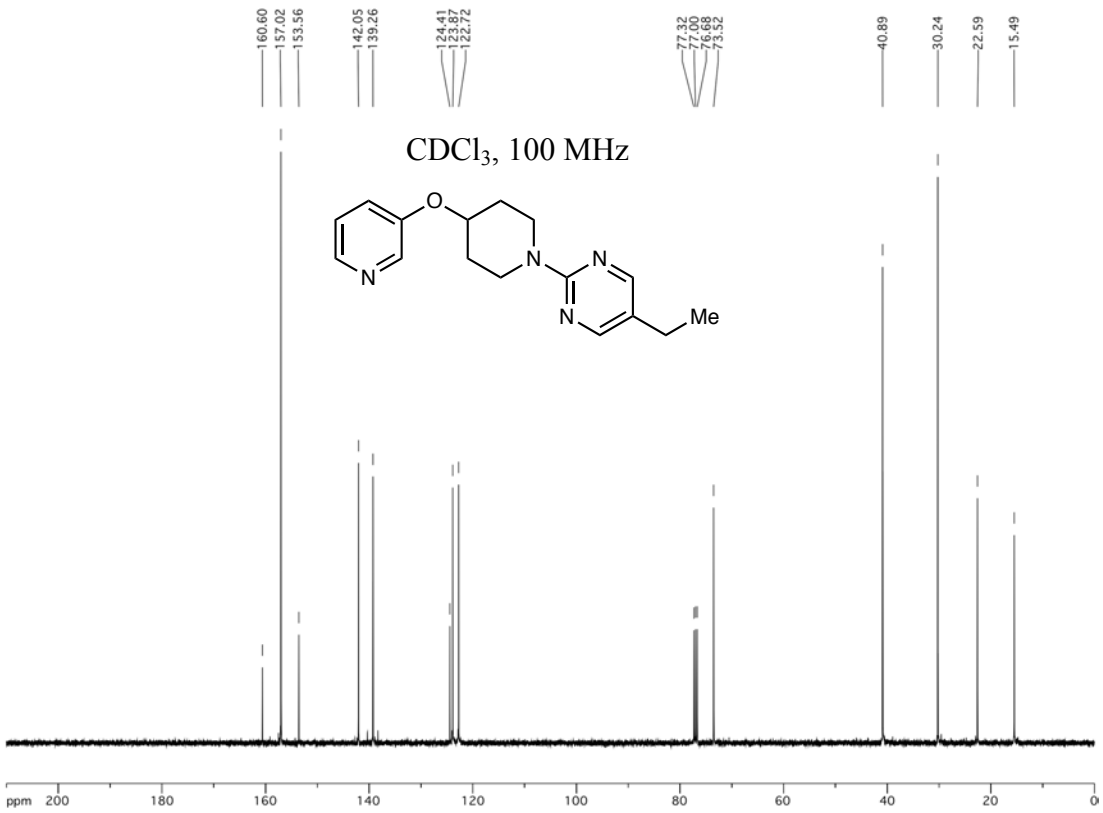
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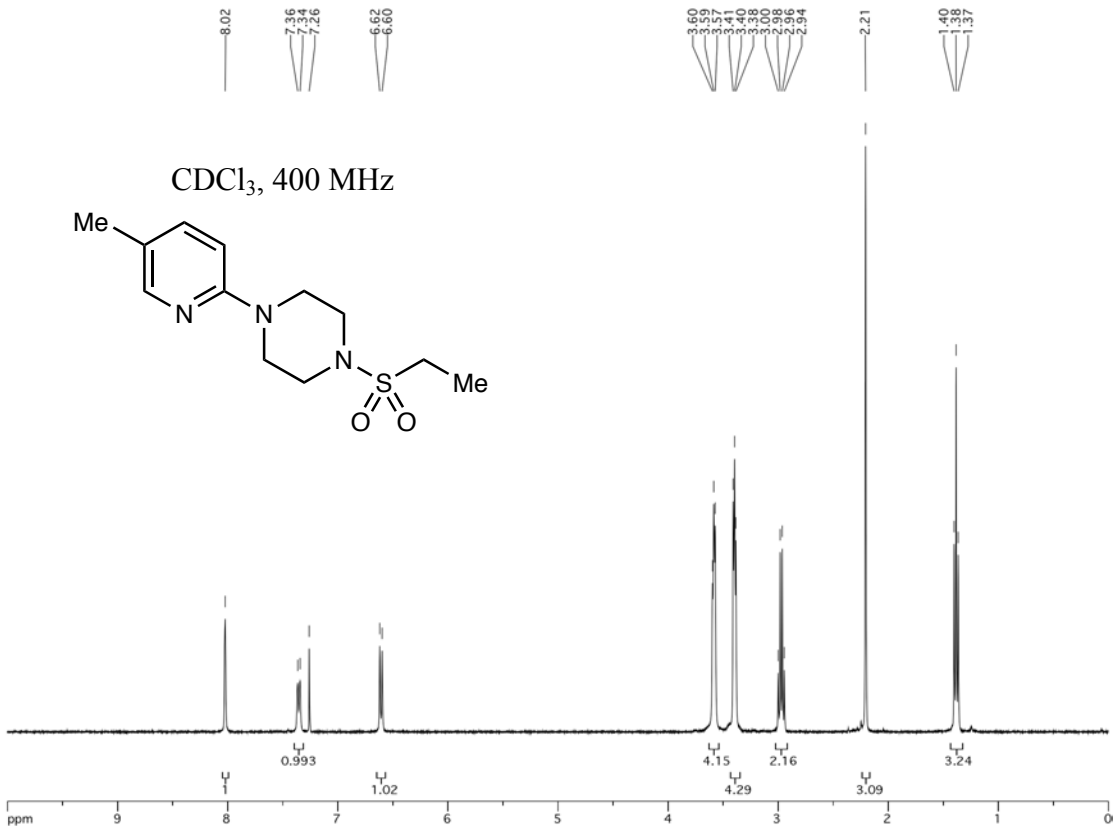
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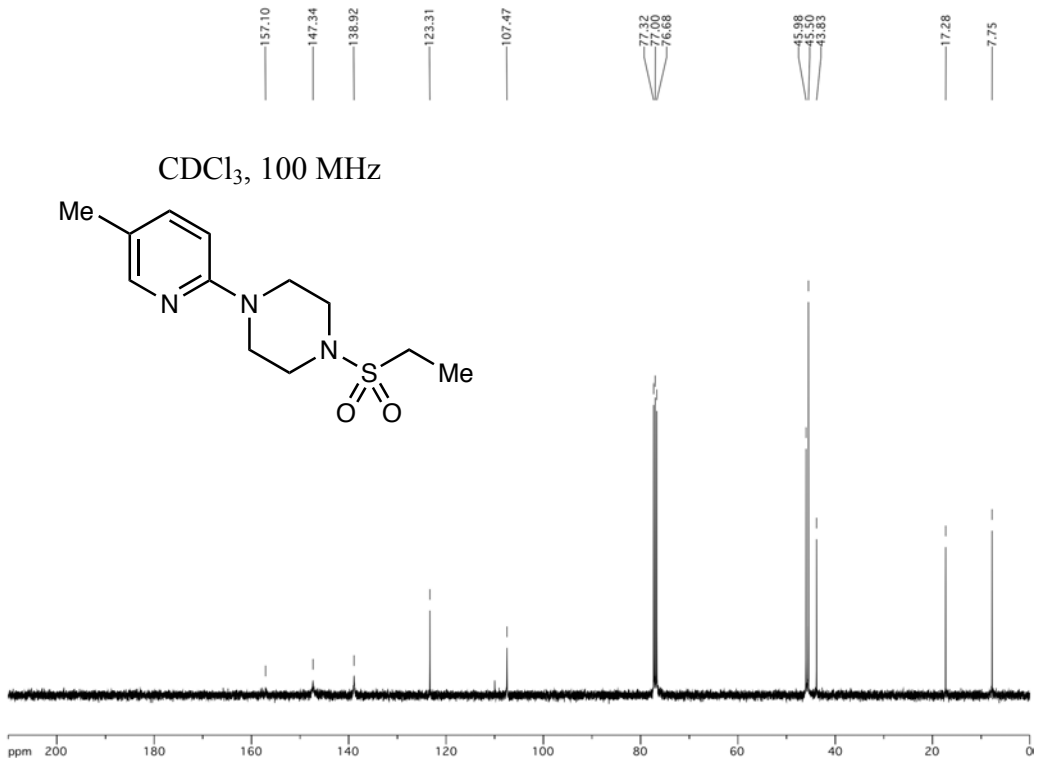
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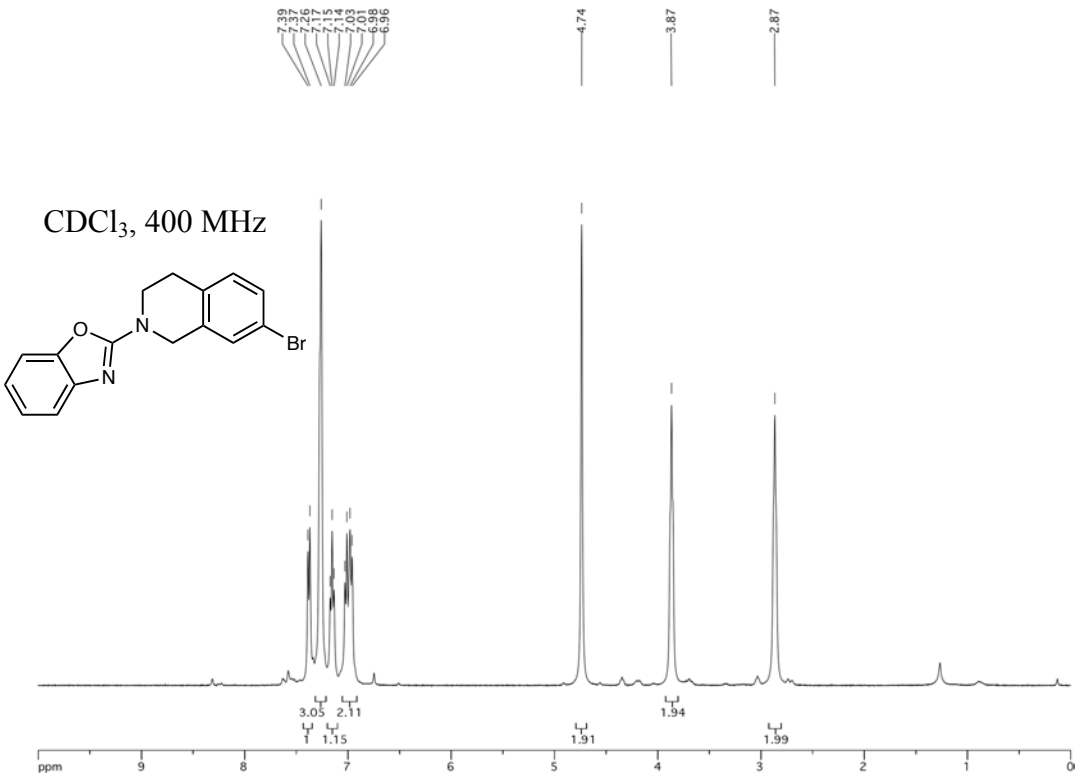
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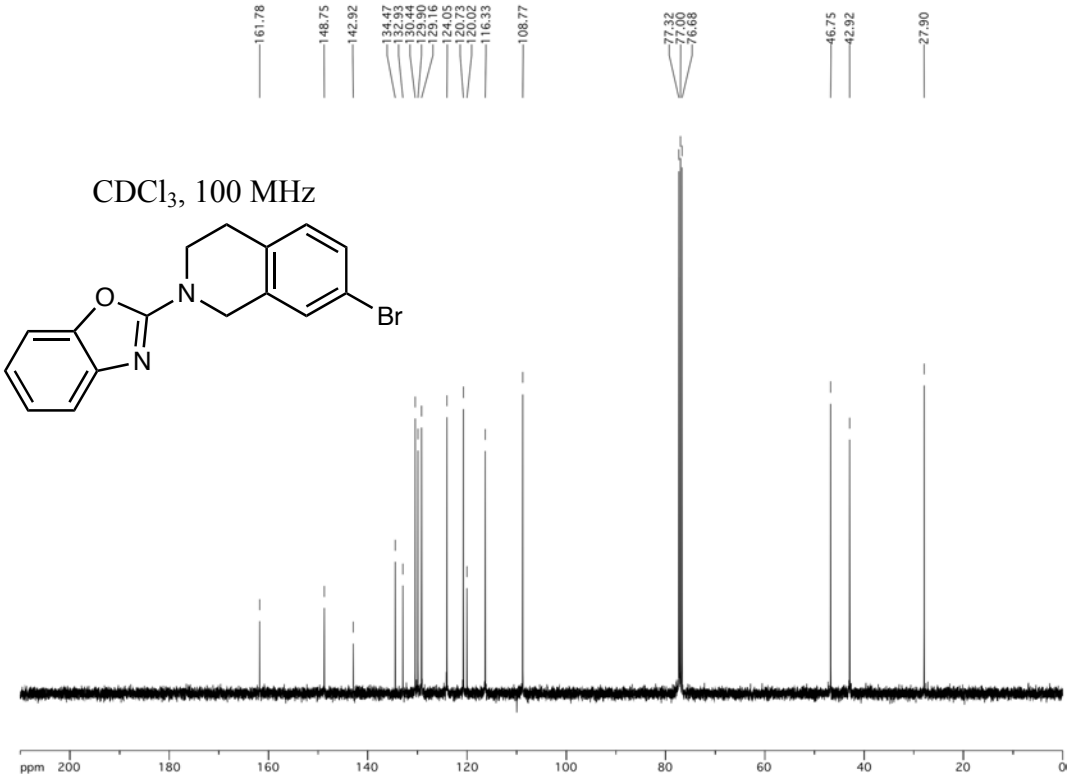
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42.92
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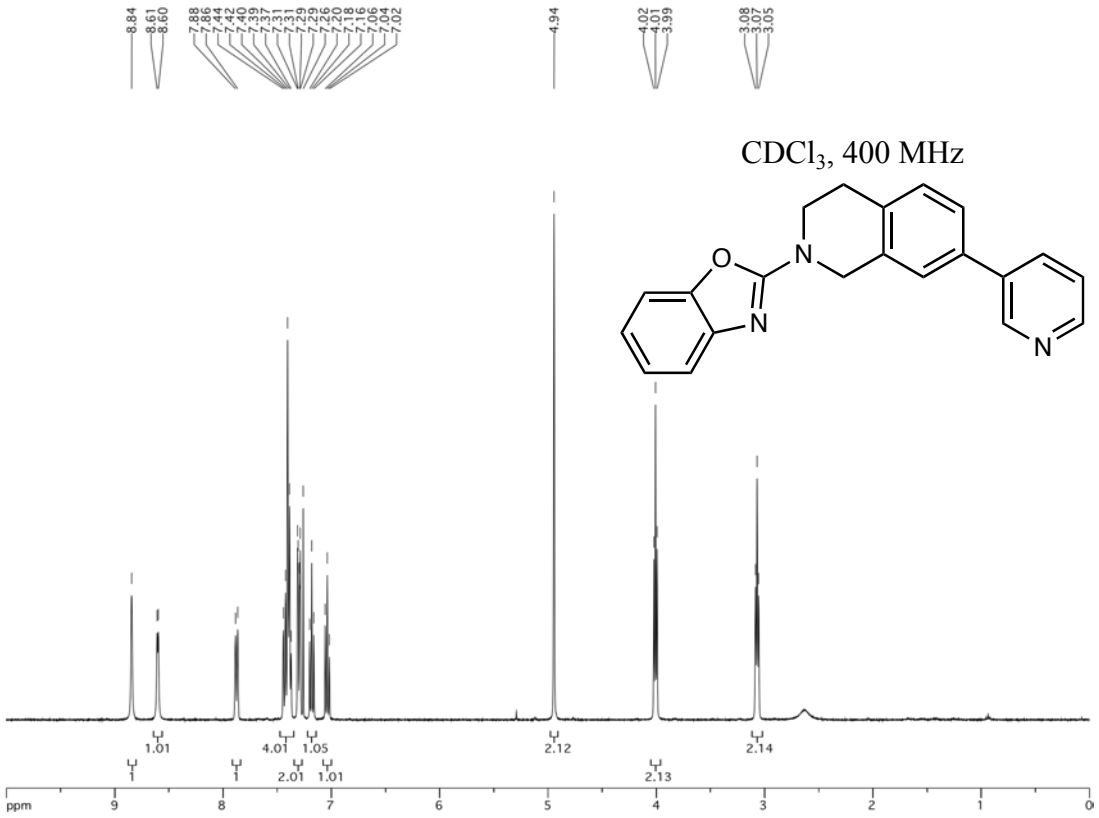
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CDCl3, 400 MHz
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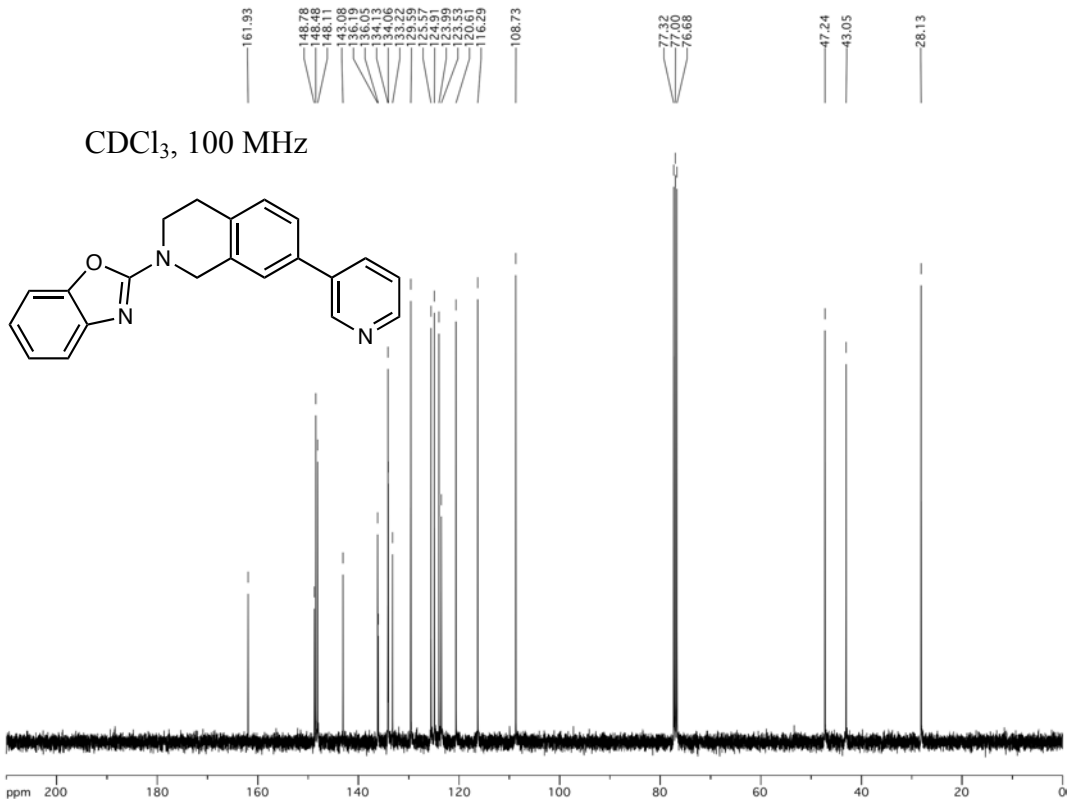
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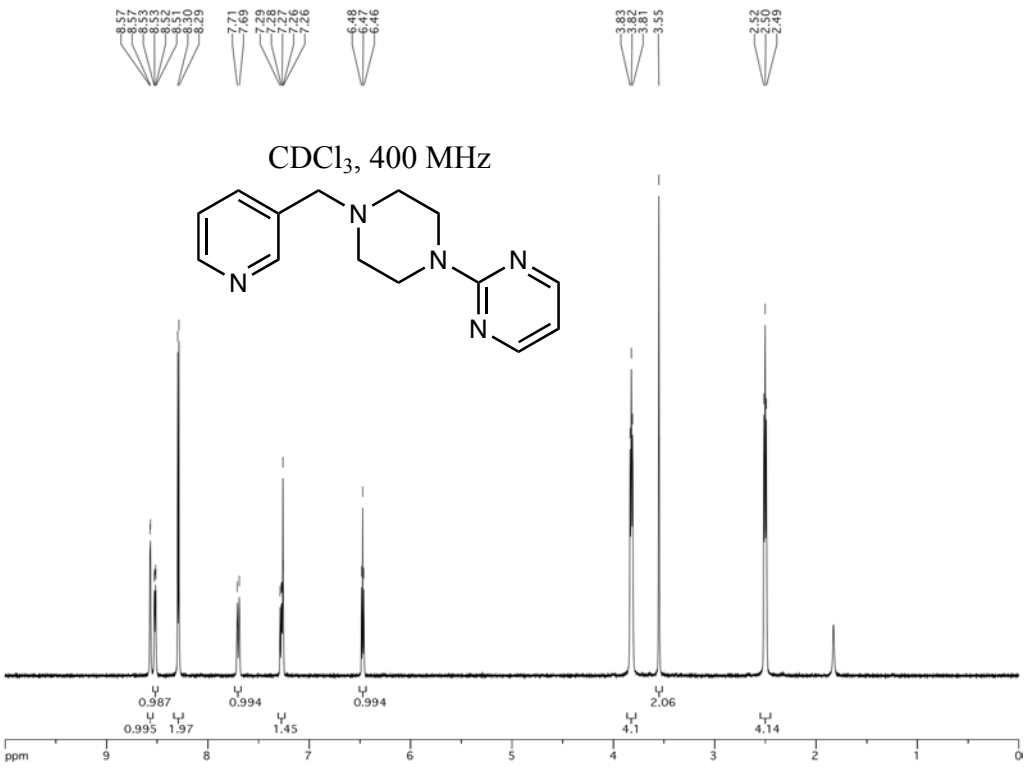
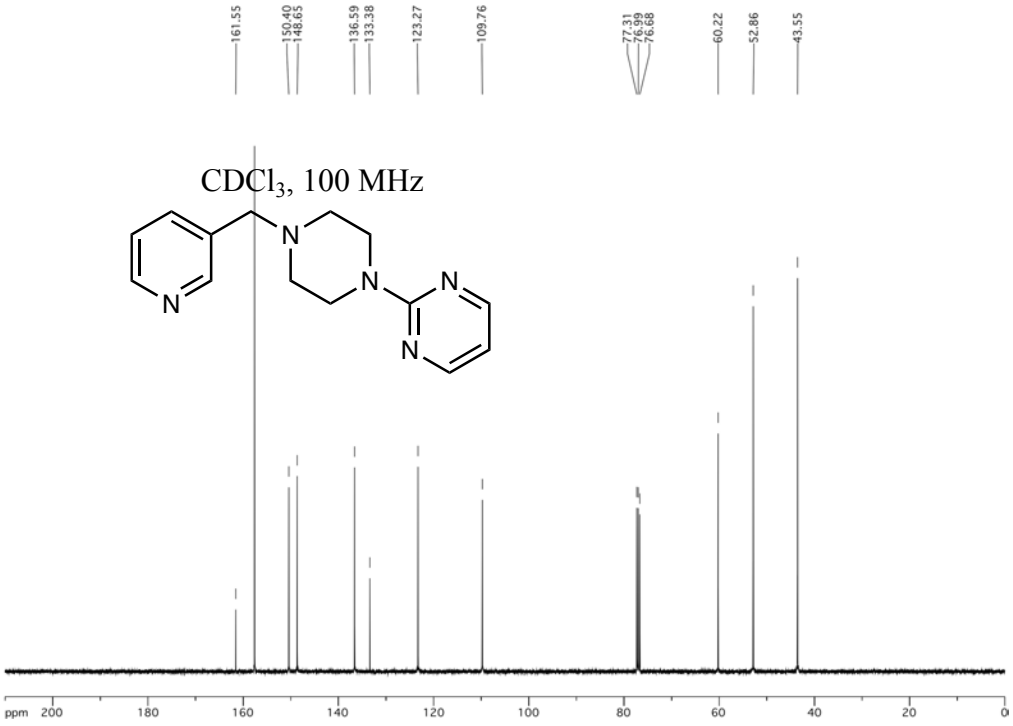
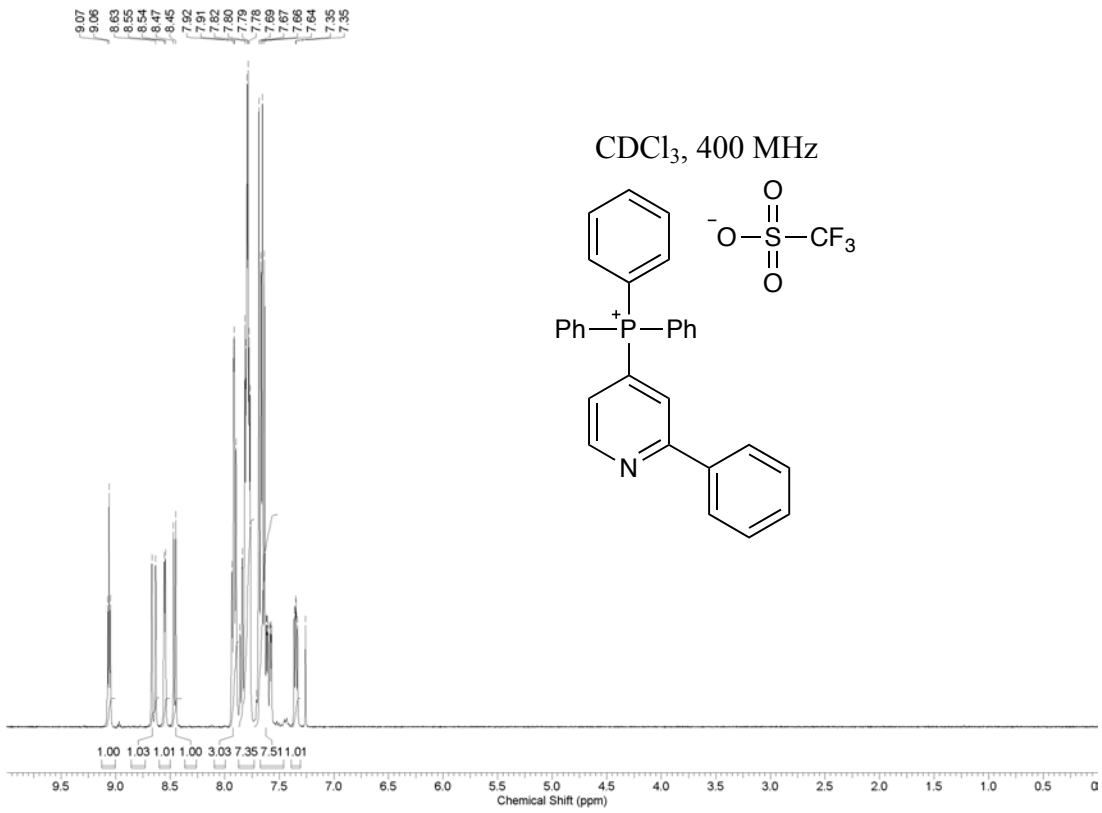
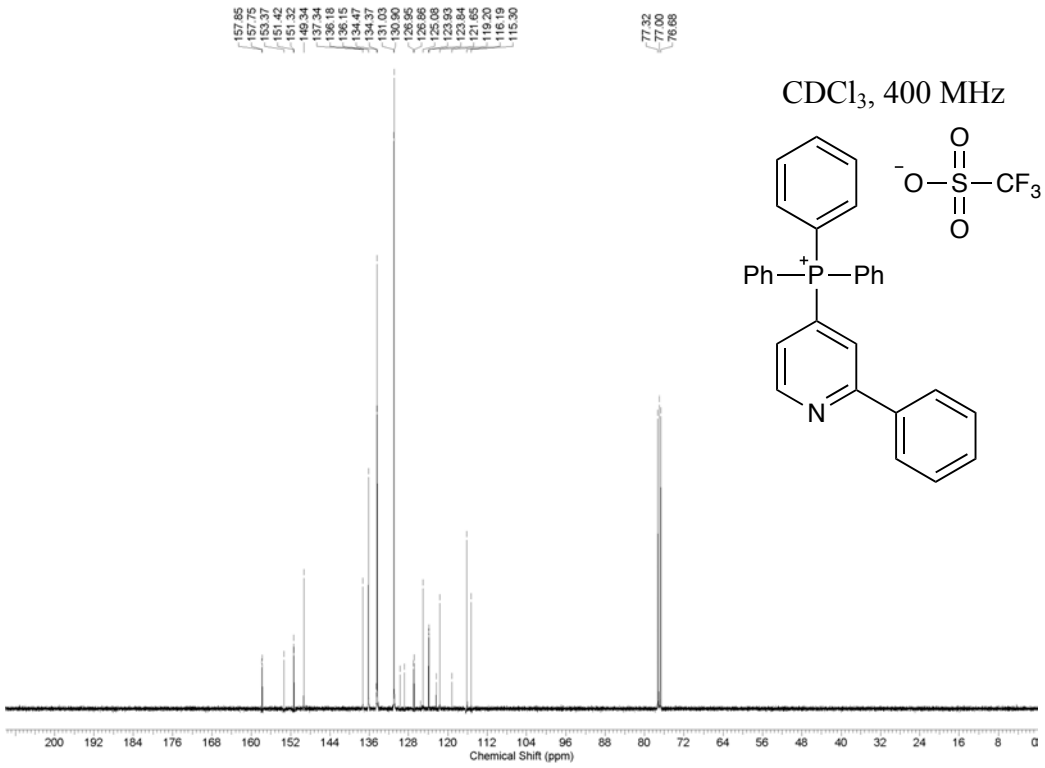
136.05
134.13
134.06
133.22
129.59
125.97
124.91
123.99
123.53
120.61
116.29
108.73
77.32
77.00
76.68
47.24
43.05
28.13
CDCl3, 100 MHz
O
N
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0

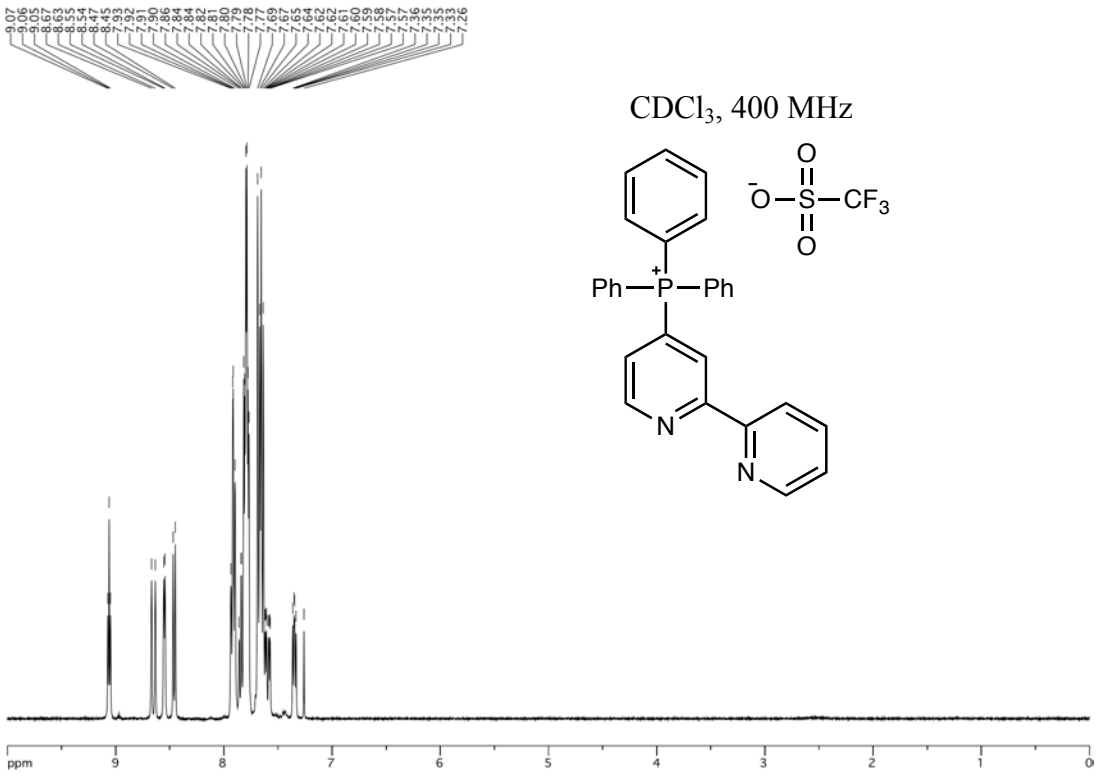

8.57
8.57
8.53
8.53
8.52
8.52
8.31
8.30
8.29
7.71
7.69
7.29
7.28
7.27
7.27
7.26
7.26
6.48
6.47
6.46
3.83
3.82
3.81
3.55
2.52
2.50
2.49
CDCl3, 400 MHz
N
N
N
N
0.987
0.995
1.97
0.994
1.45
0.994
2.06
4.1
4.14
ppm
9
8
7
6
5
4
3
2
1
0

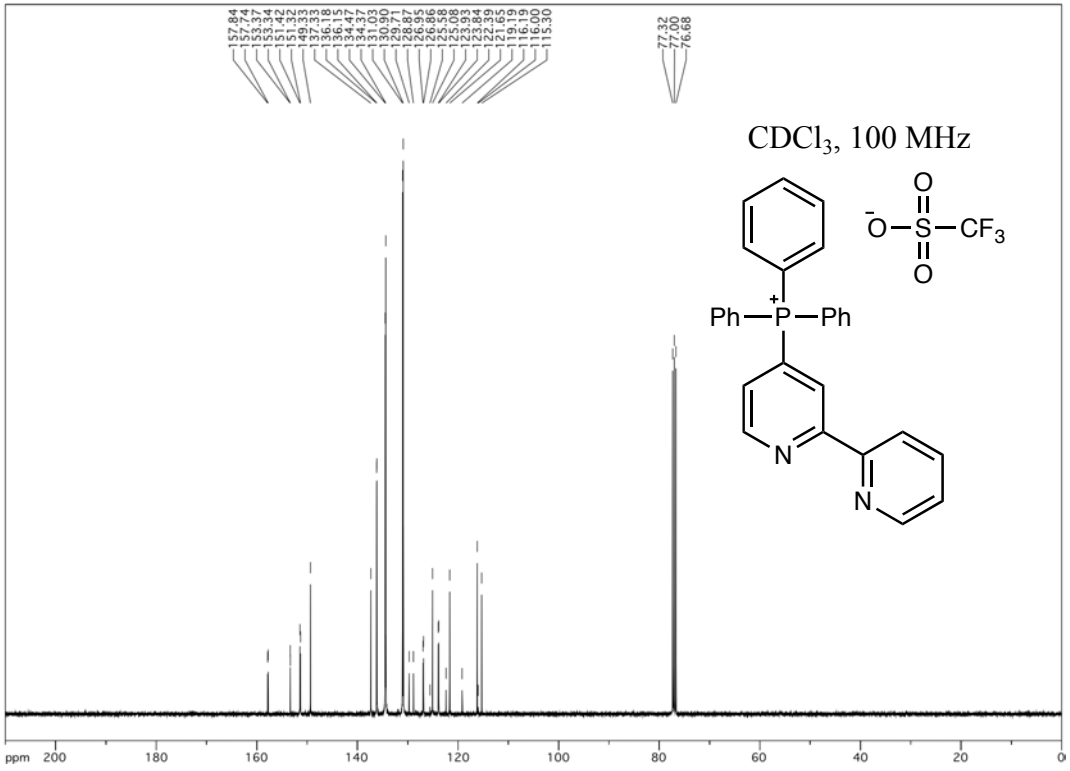

161.55
150.40
148.65
136.59
133.38
123.27
109.76
77.31
76.99
76.68
60.22
52.86
43.55
CDCl3, 100 MHz
N
N
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0

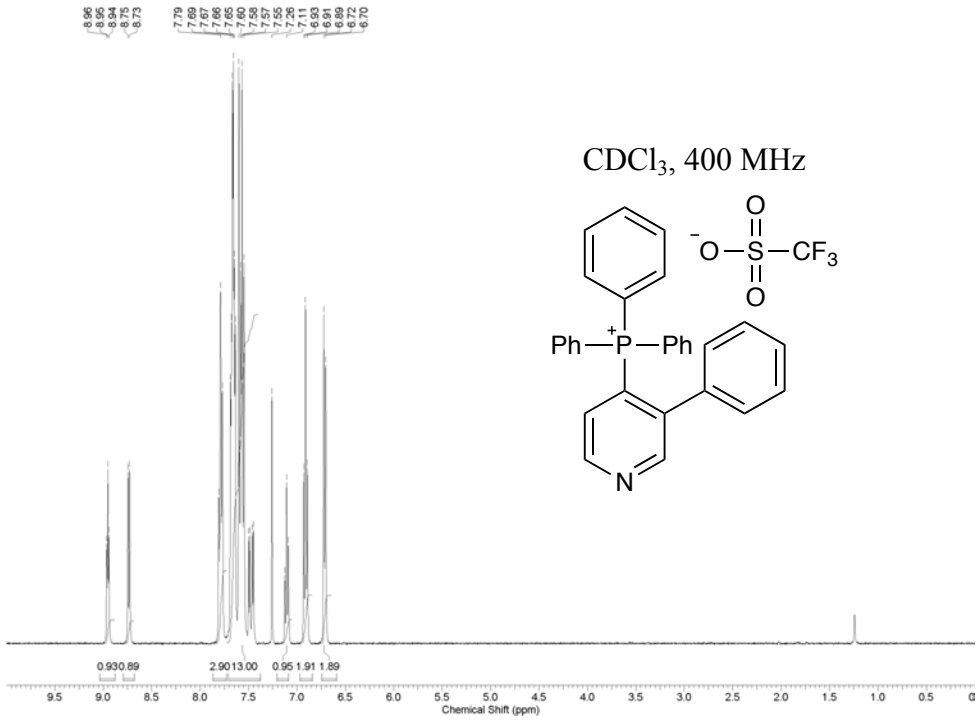


$CDCl_3$, 400 MHz

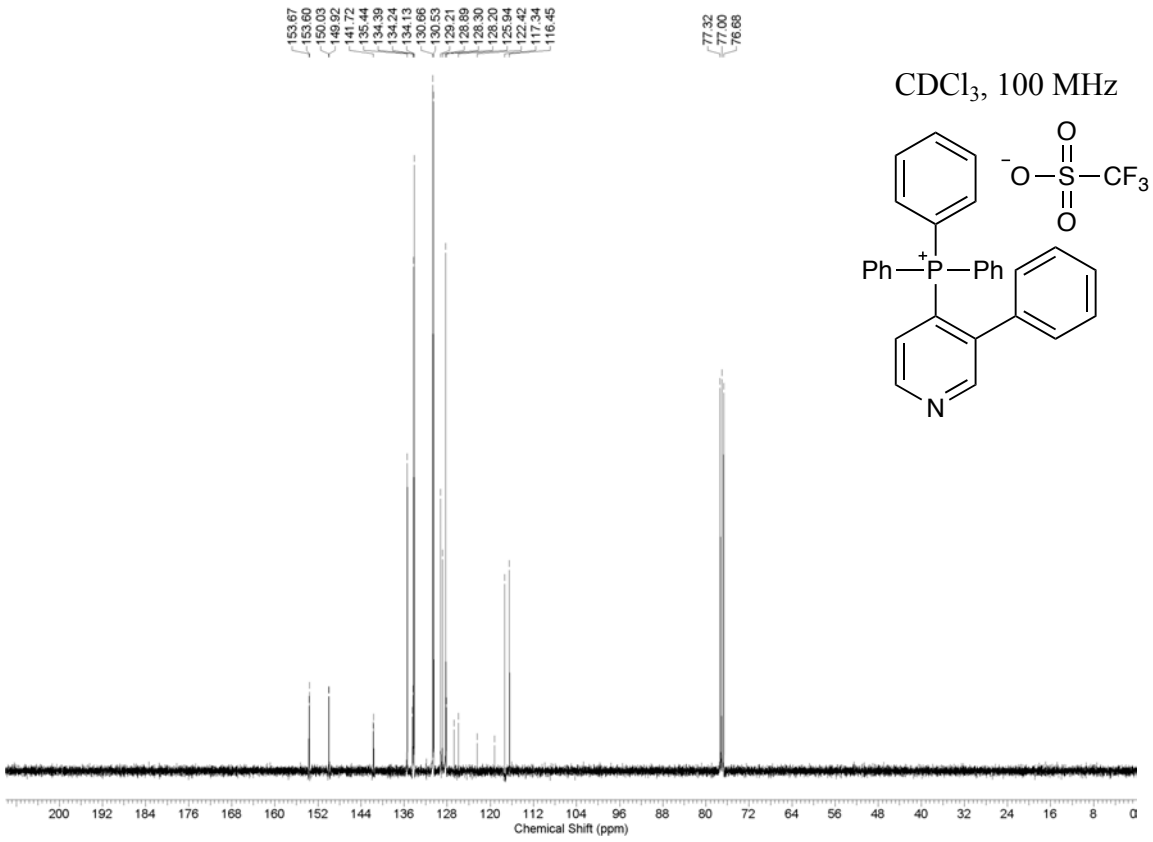

157.85
157.75
153.37
151.42
151.32
149.34
137.34
136.18
136.15
134.47
134.37
131.03
130.90
128.95
128.88
125.08
123.93
123.84
121.65
119.20
116.19
115.30
77.32
77.00
76.68
CDCl3, 400 MHz
O
-O—S—CF3
O
Ph—P+—Ph
N
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8
Chemical Shift (ppm)

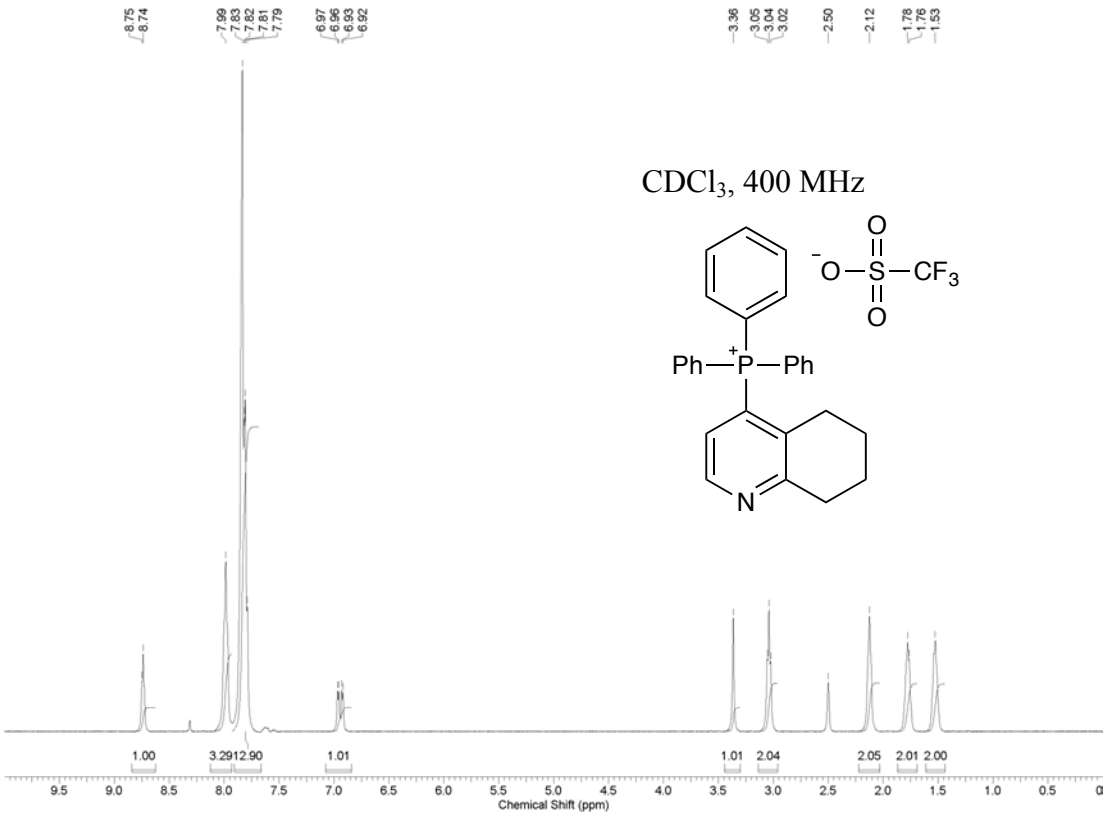

9.07
9.06
9.05
8.67
8.63
8.55
8.54
8.47
8.45
7.93
7.92
7.91
7.90
7.86
7.84
7.84
7.82
7.81
7.80
7.79
7.78
7.77
7.69
7.67
7.65
7.64
7.62
7.62
7.61
7.60
7.59
7.58
7.57
7.57
7.36
7.35
7.35
7.33
7.26
CDCl3, 400 MHz
O
O
S
CF3
O
Ph
P
Ph
N
N
ppm
9
8
7
6
5
4
3
2
1
0

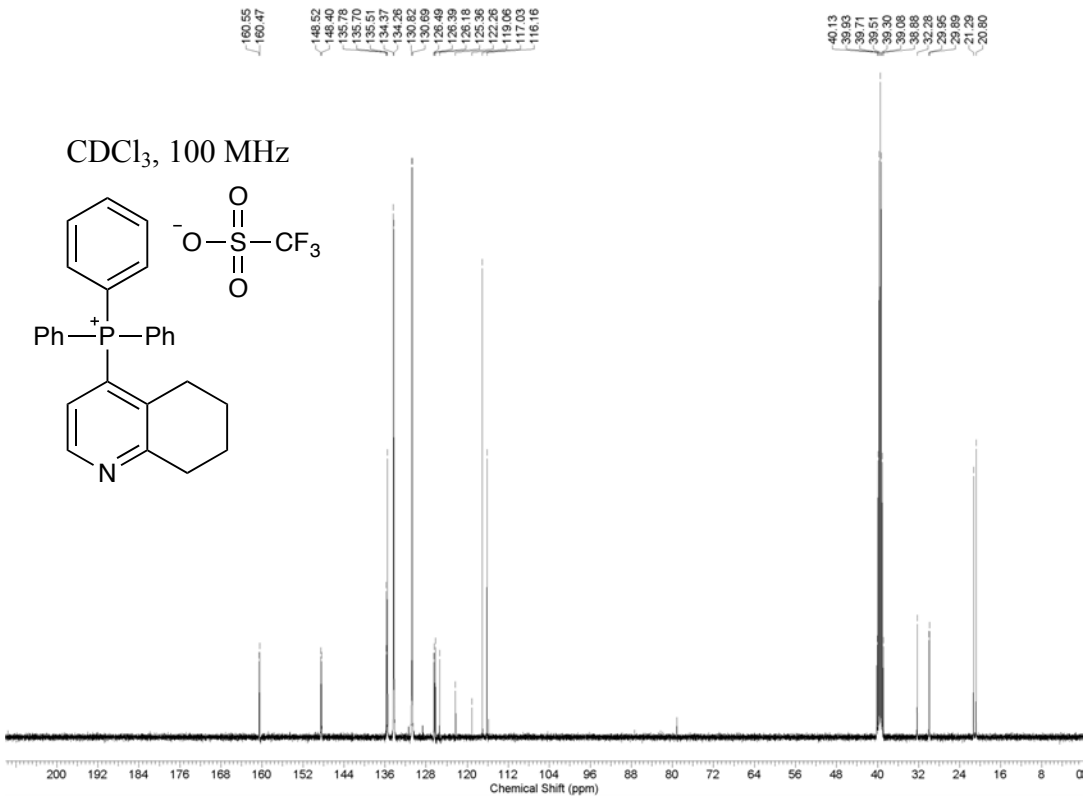

157.84
157.74
153.37
151.54
151.42
151.32
149.33
137.33
136.18
136.15
134.47
134.37
131.03
130.90
129.71
129.67
126.95
126.86
125.58
125.08
123.93
123.84
122.39
121.65
119.19
116.19
116.00
115.30
77.32
77.00
76.68
CDCl3, 100 MHz
O
O
S
O
CF3
Ph
P
Ph
N
N
ppm
200
180
160
140
120
100
80
60
40
20
0

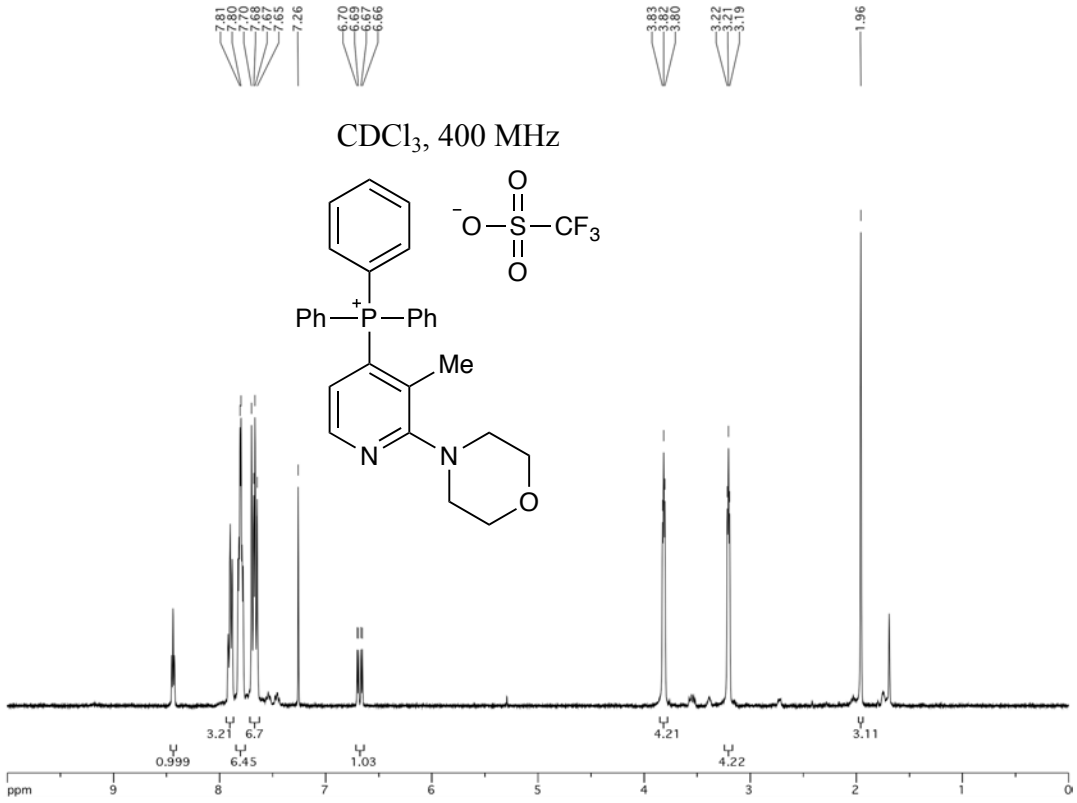


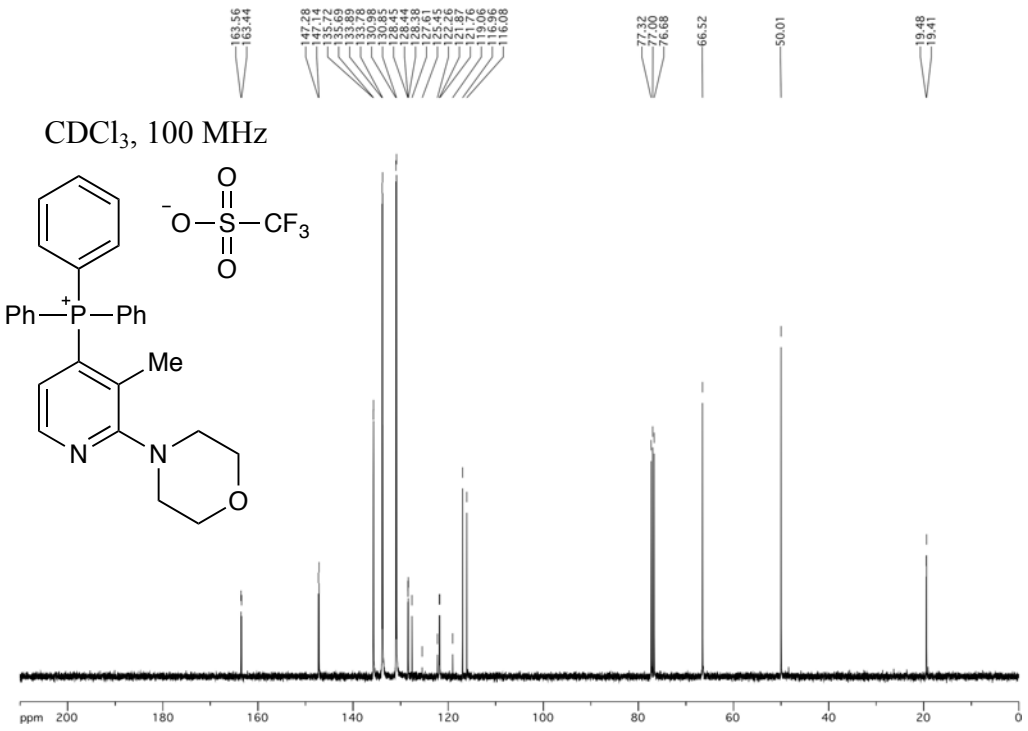
$CDCl_3$, 400 MHz


153.67
153.60
150.03
149.92
141.72
135.44
134.39
134.24
134.13
130.66
130.53
129.21
128.89
128.30
128.20
125.94
122.42
117.34
116.45
77.32
77.00
76.68
CDCl3, 100 MHz
Ph
P
Ph
O
S
CF3
N
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8
Chemical Shift (ppm)

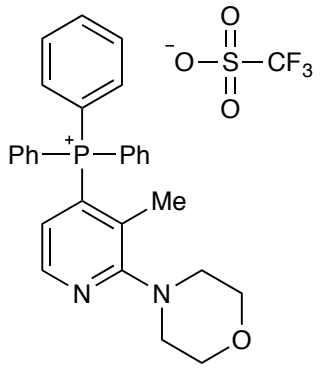

8.75
8.74
7.99
7.83
7.82
7.81
7.79
6.97
6.96
6.93
6.92
3.36
3.05
3.04
3.02
2.50
2.12
1.78
1.76
1.53
CDCl3, 400 MHz
O
O
O
S
CF3
Ph
P
Ph
N
1.00
3.29
12.90
1.01
1.01
2.04
2.05
2.01
2.00
Chemical Shift (ppm)


160.55
160.47
148.52
148.40
135.78
135.70
135.51
134.37
134.26
130.82
130.69
126.49
126.39
126.18
125.36
122.26
119.06
117.03
116.16
40.13
39.93
39.71
39.51
39.30
39.08
38.88
32.28
29.95
29.89
21.29
20.80
CDCl3, 100 MHz
O
O−S−CF3
O
Ph—P—Ph
N
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

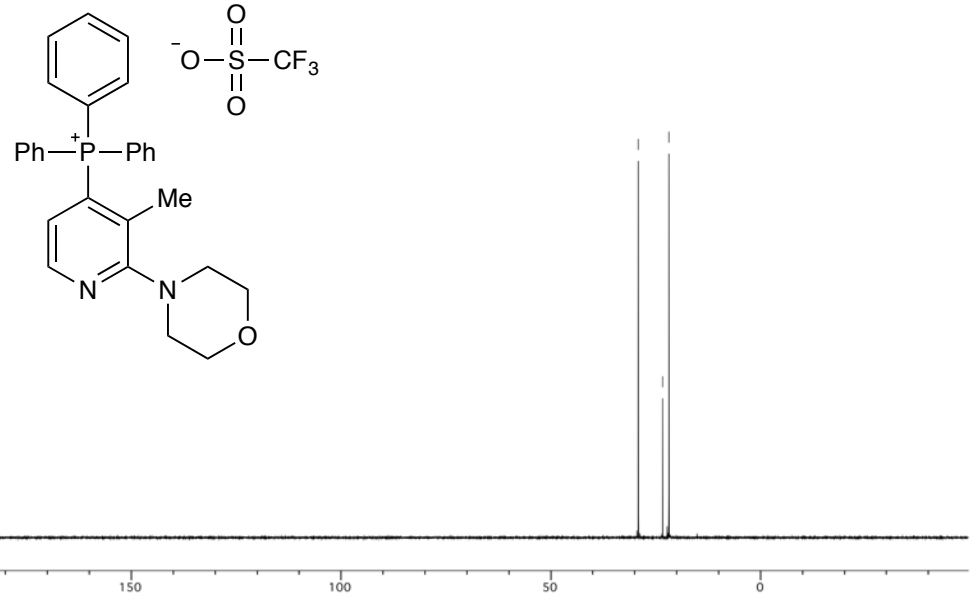

7.81
7.80
7.70
7.68
7.67
7.65
7.26
6.70
6.69
6.67
6.66
3.83
3.82
3.80
3.22
3.21
3.19
1.96
CDCl3, 400 MHz
O
O
O
CF3
Ph
P
Ph
Me
N
N
O
0.999
3.21
6.7
6.45
1.03
4.21
4.22
3.11
ppm
9
8
7
6
5
4
3
2
1
0


163.56
163.44
147.28
147.14
135.72
135.69
133.89
133.78
130.98
130.85
128.45
128.44
128.38
127.61
125.45
122.26
121.97
121.76
119.06
116.96
116.08
77.32
77.00
76.68
66.52
50.01
19.48
19.41
CDCl3, 100 MHz
Ph
P
Ph
Me
N
N
O
O
O
S
CF3
ppm 200
180
160
140
120
100
80
60
40
20
0

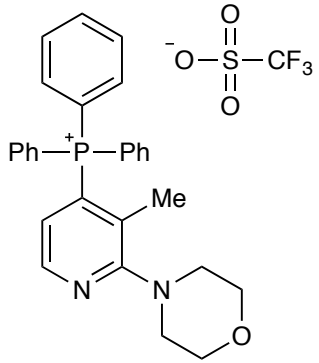
$CDCl_3$, 162 MHz

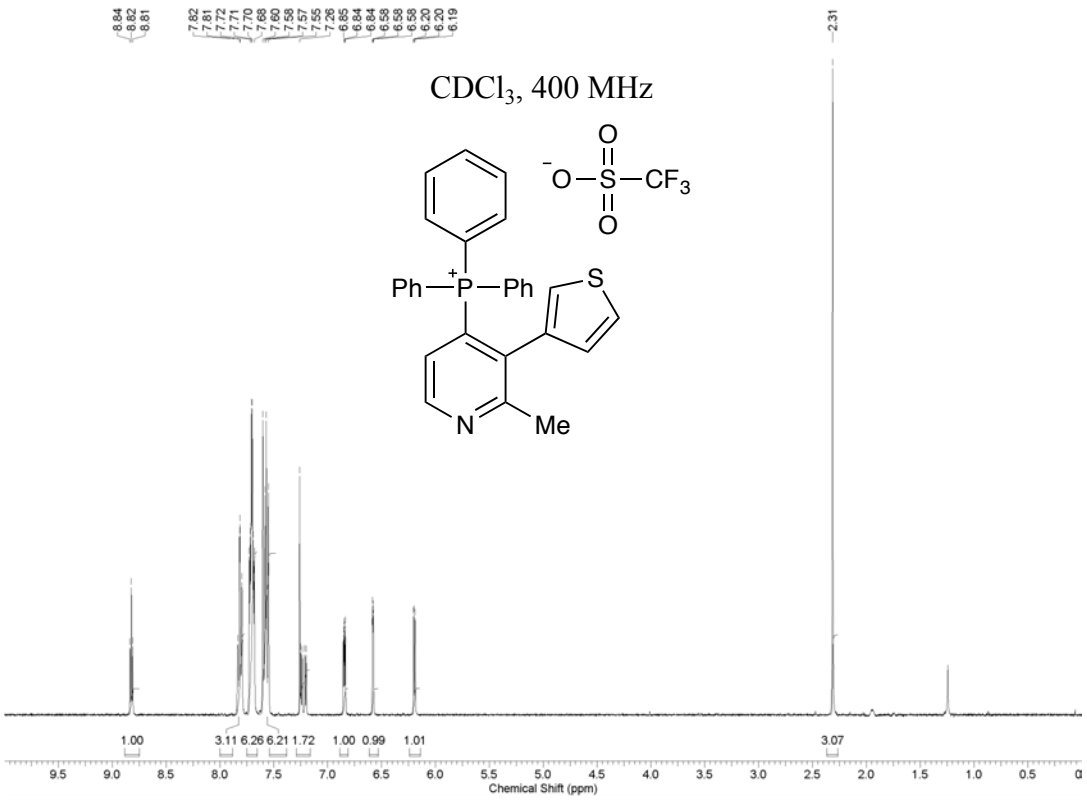


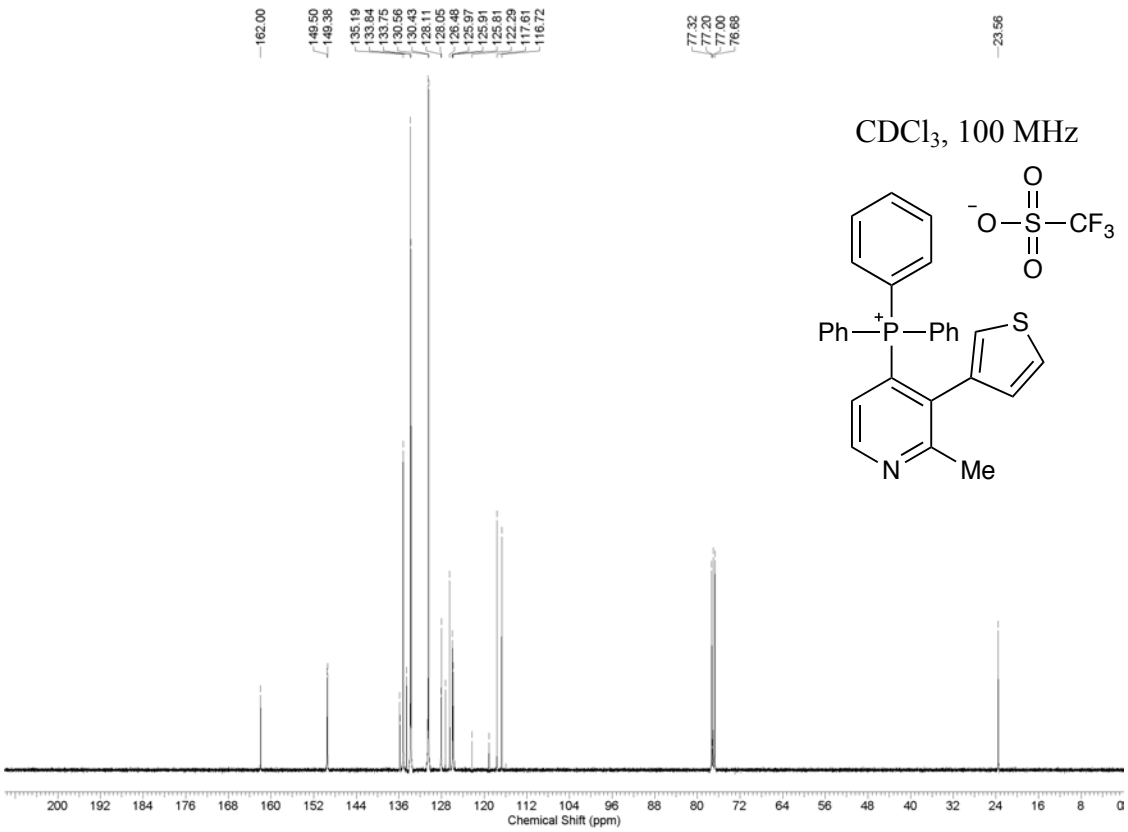
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

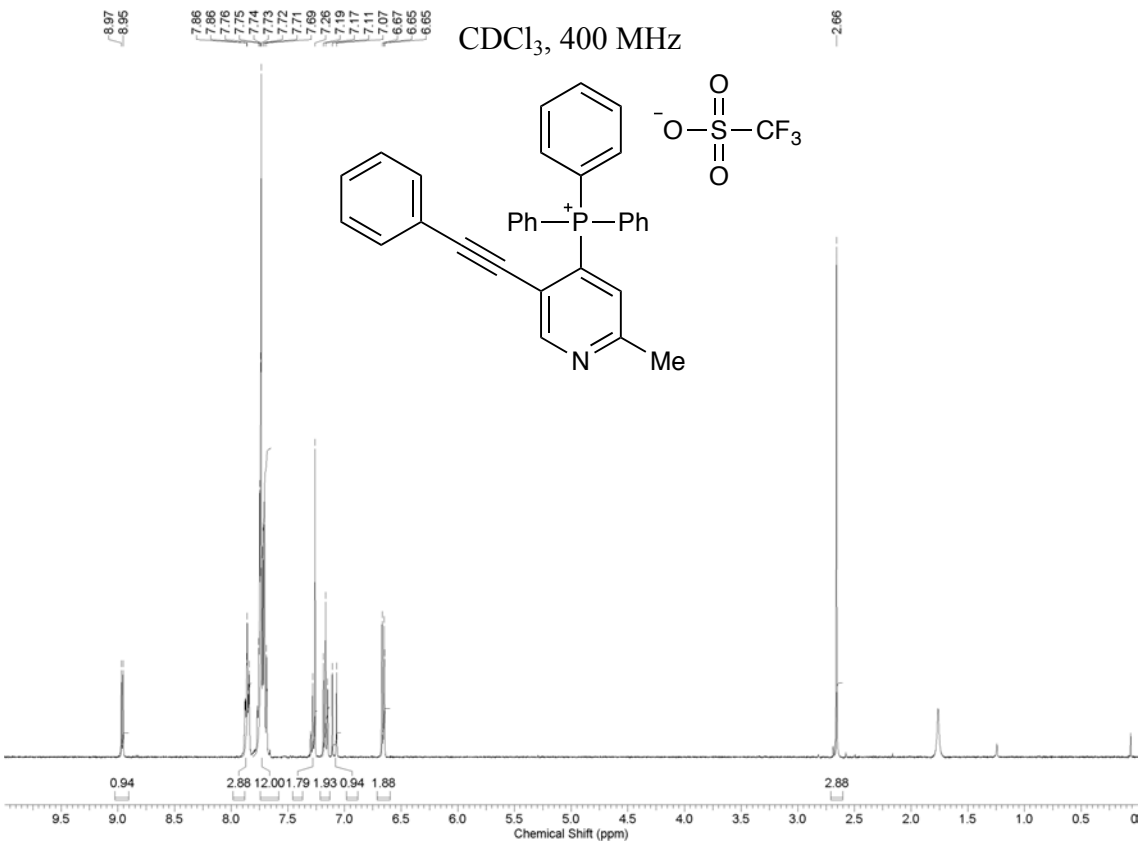


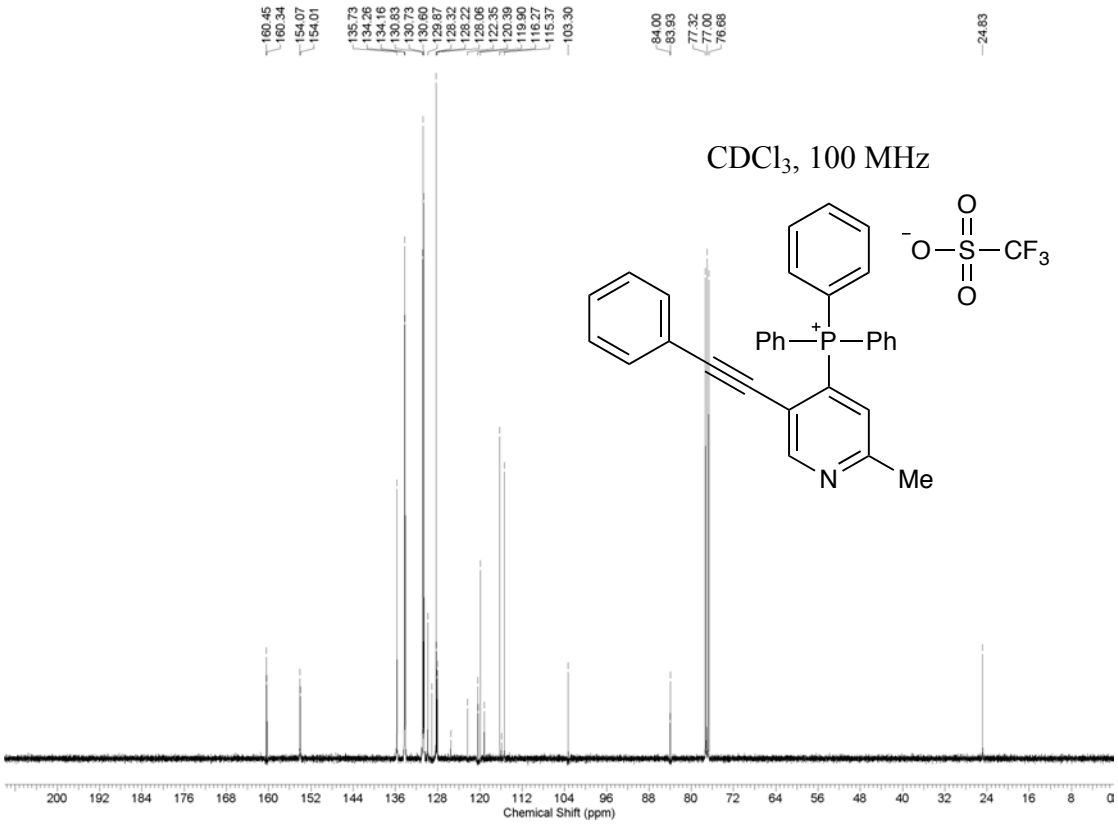
$CDCl_3$, 365 MHz

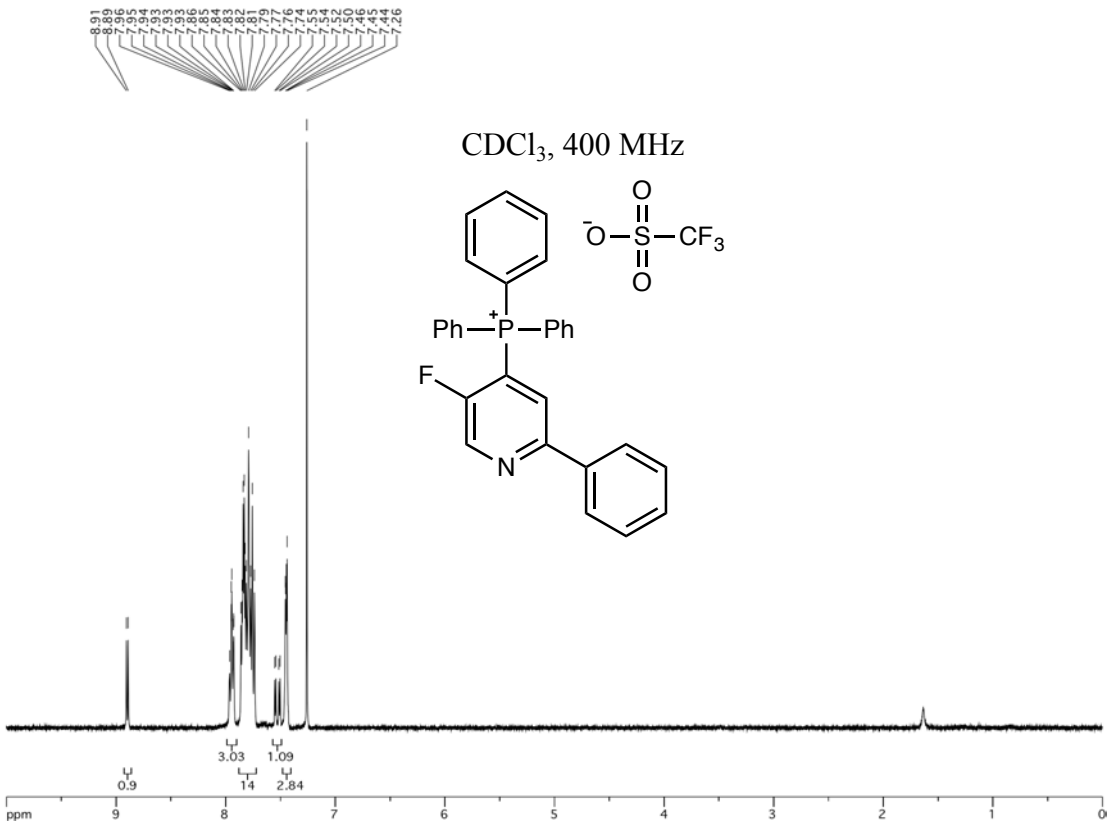


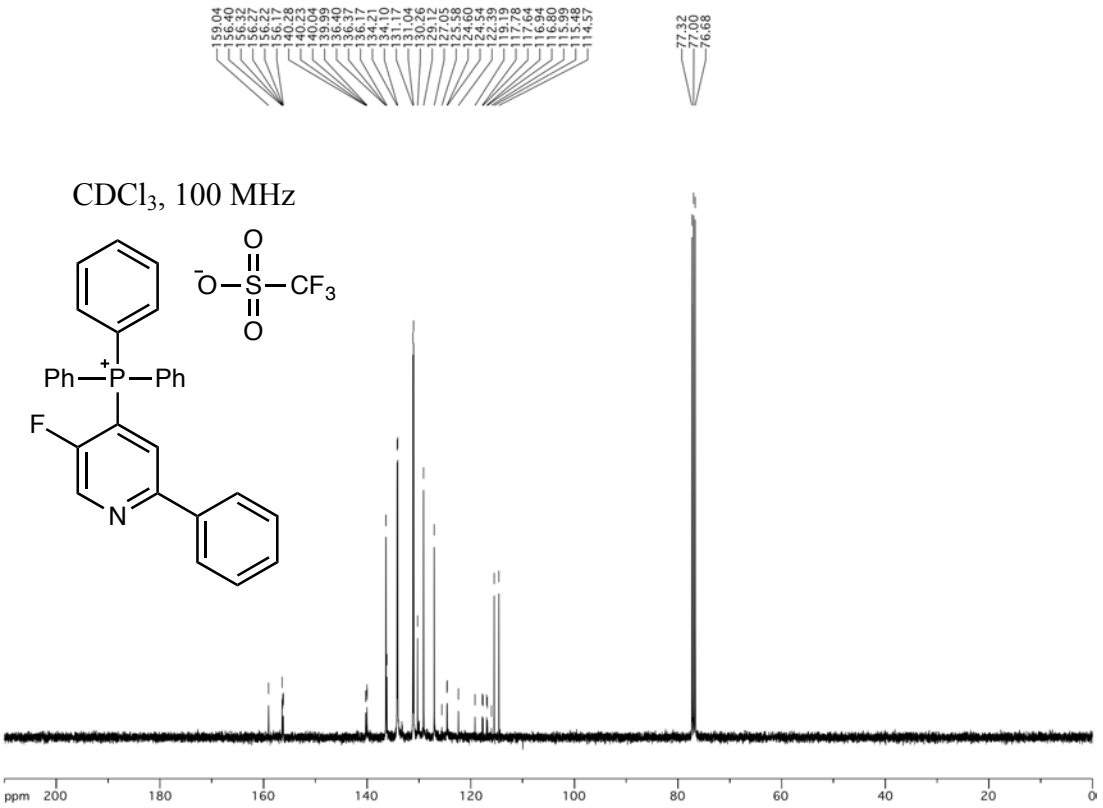

8.84
8.82
8.81
7.82
7.81
7.72
7.71
7.70
7.68
7.60
7.58
7.57
7.55
7.26
6.65
6.64
6.64
6.58
6.58
6.58
6.20
6.20
6.19
2.31
CDCl3, 400 MHz
O
O
S
CF3
O
Ph
P
Ph
S
N
Me
1.00
3.11
6.26
6.21
1.72
1.00
0.99
1.01
3.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)


162.00
149.50
149.38
135.19
133.84
133.75
130.56
130.43
128.11
128.05
128.48
125.97
125.91
125.81
122.29
117.61
116.72
77.32
77.20
77.00
76.68
23.56
CDCl3, 100 MHz
Ph
P
Ph
S
N
Me
O
O
S
O
CF3
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

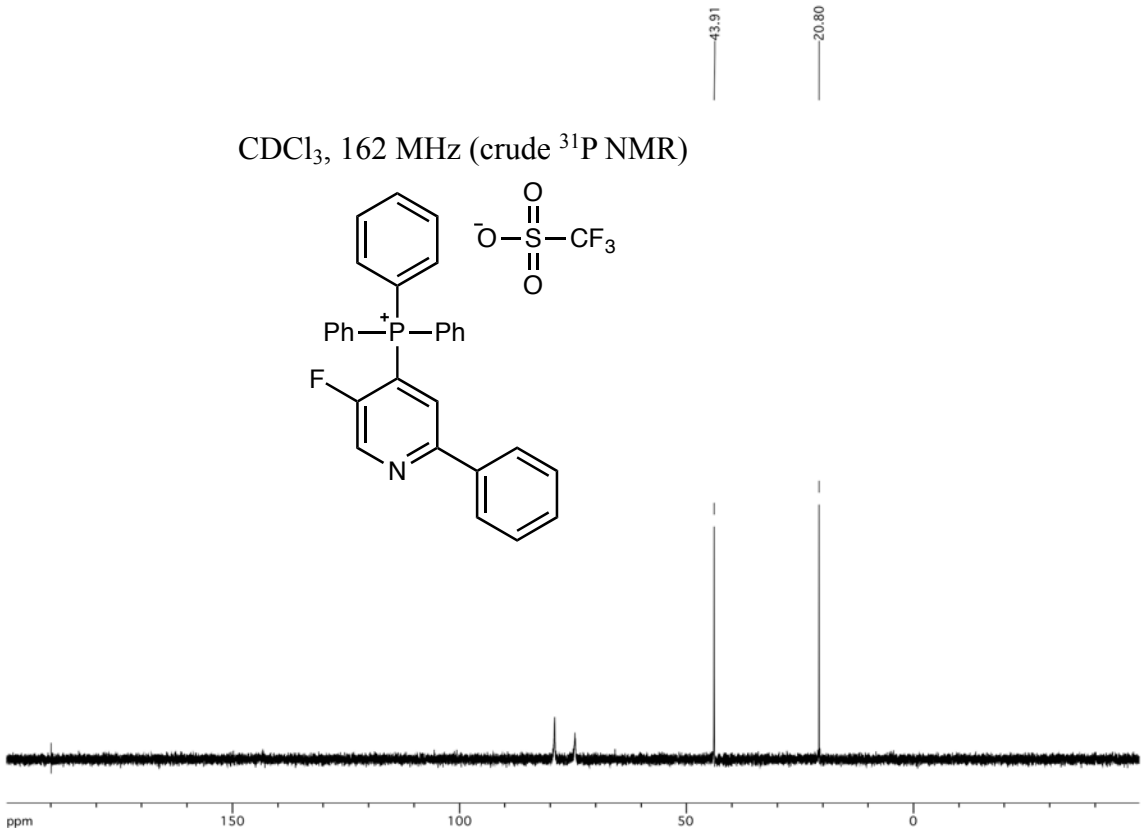

CDCl3, 400 MHz
8.97
8.95
7.86
7.86
7.76
7.75
7.74
7.73
7.72
7.71
7.69
7.26
7.19
7.17
7.11
7.07
6.67
6.65
6.65
2.66
O
O
S
O
CF3
Ph
P
Ph
N
Me
0.94
2.88
12.00
1.79
1.93
0.94
1.88
2.88
Chemical Shift (ppm)

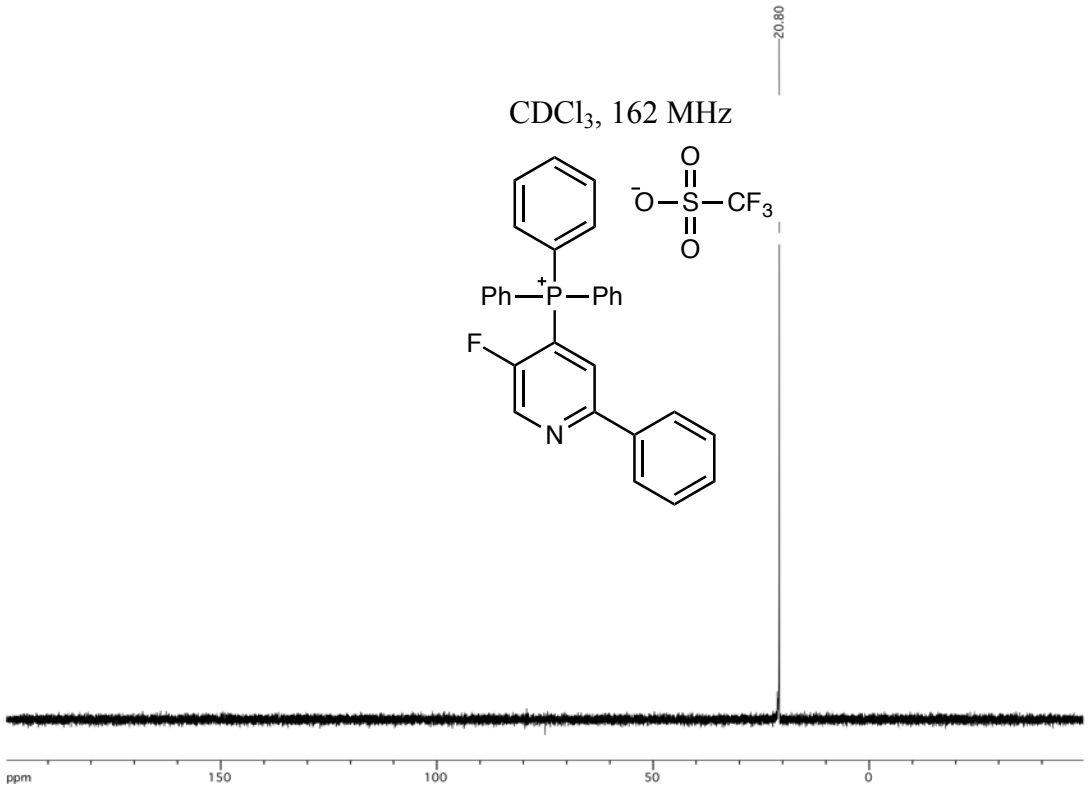

160.45
160.34
154.07
154.01
135.73
134.26
134.16
130.83
130.73
130.60
129.87
128.32
128.22
128.06
122.35
120.39
119.90
116.27
115.37
103.30
84.00
83.93
77.32
77.00
76.68
24.83
CDCl3, 100 MHz
O
O
S
CF3
O
Ph
P
Ph
N
Me
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8
Chemical Shift (ppm)


8.91
8.89
7.96
7.95
7.94
7.93
7.93
7.93
7.86
7.85
7.84
7.83
7.82
7.81
7.79
7.77
7.76
7.74
7.55
7.54
7.52
7.50
7.46
7.45
7.44
7.26
CDCl3, 400 MHz
O
O
S
CF3
O
Ph
P
Ph
F
N
3.03
1.09
0.9
1.4
2.84
ppm
9
8
7
6
5
4
3
2
1
0

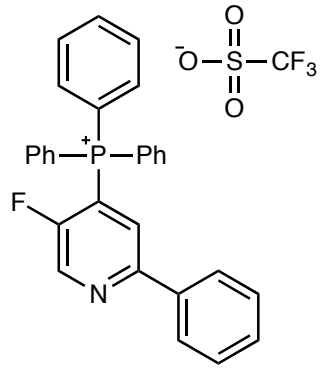

159.04
156.40
156.32
156.27
156.22
156.17
156.13
140.23
140.04
139.99
136.40
136.37
136.17
134.21
134.10
131.17
131.04
130.26
129.12
127.05
125.58
124.60
124.54
122.39
119.19
117.78
117.64
116.94
116.80
115.99
115.48
114.57
77.32
77.00
76.68
CDCl3, 100 MHz
O
O−S−CF3
O
Ph−P−Ph
F
N
ppm 200 180 160 140 120 100 80 60 40 20 0

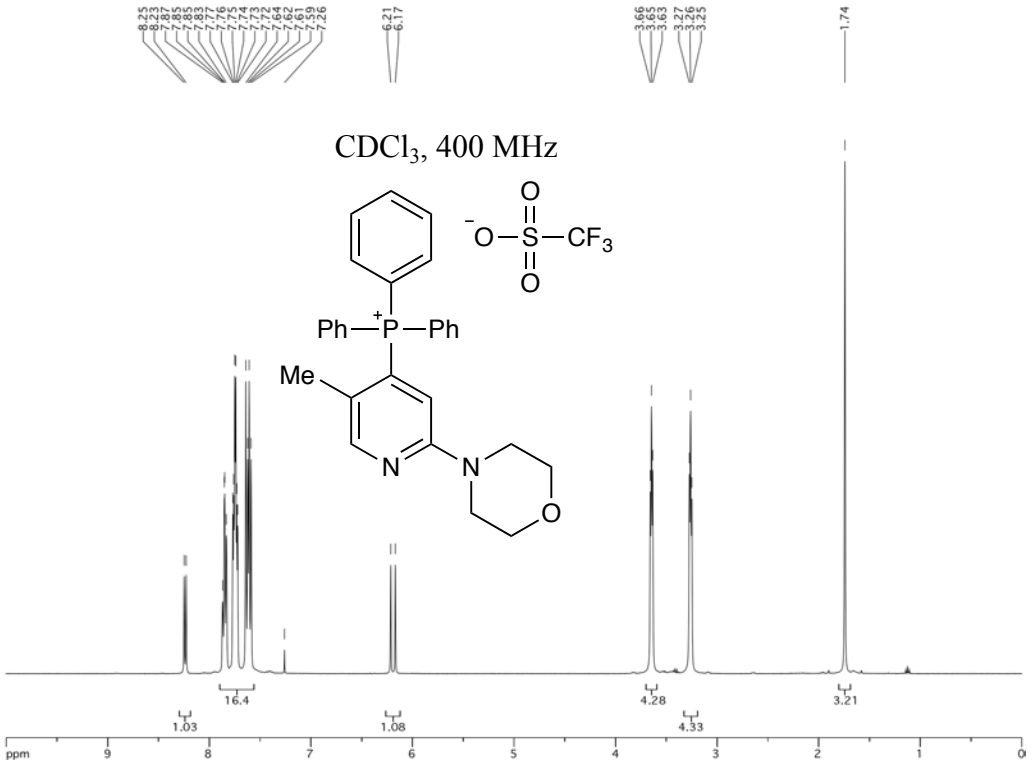
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

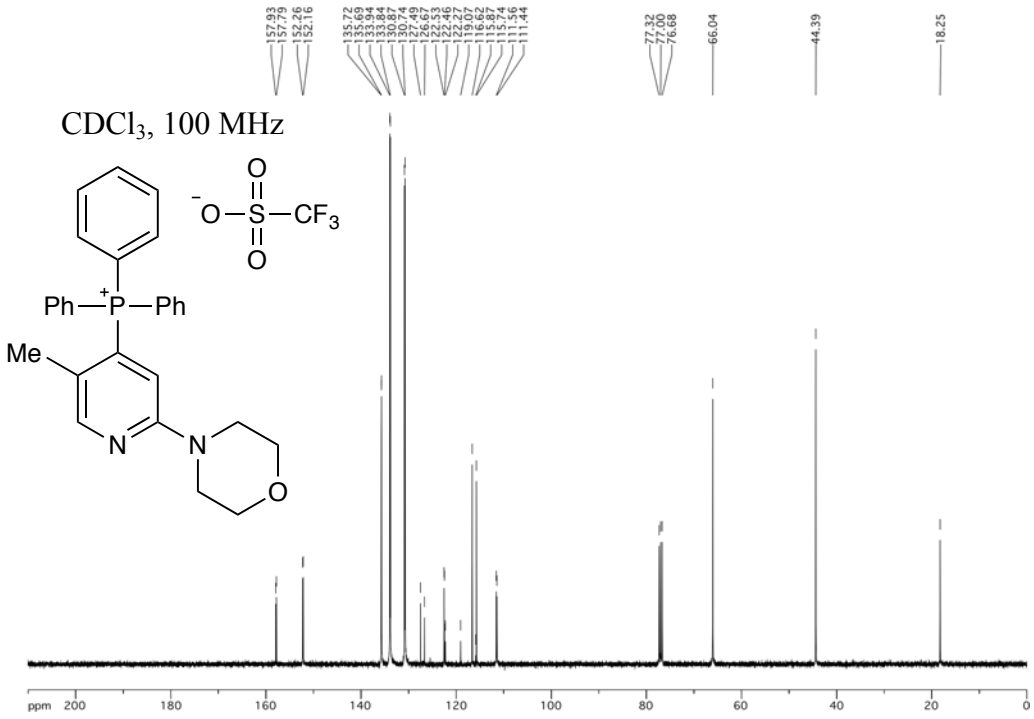



20.80
CDCl3, 162 MHz
O
O
S
CF3
O
Ph
P
Ph
F
N
ppm
150
100
50
0

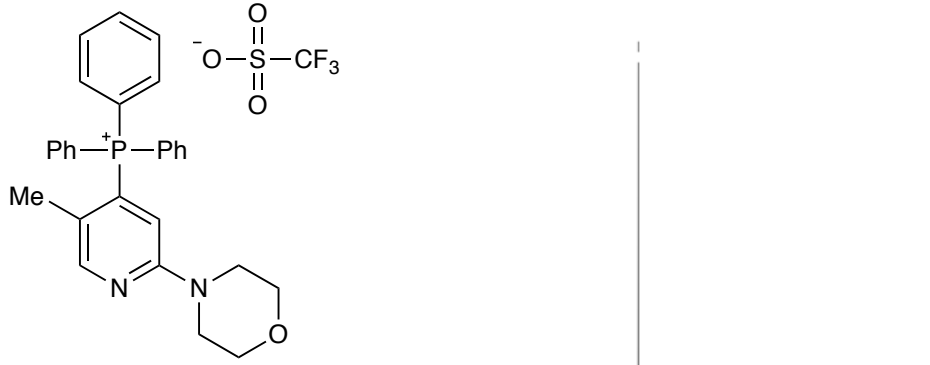
$CDCl_3$, 365 MHz



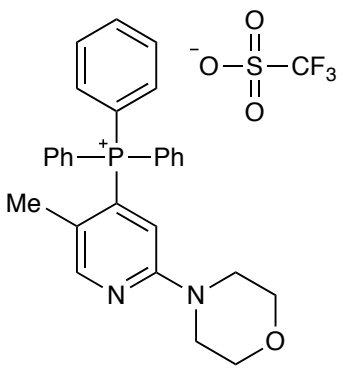

8.25
8.23
8.07
7.87
7.85
7.85
7.83
7.77
7.76
7.75
7.74
7.73
7.72
7.64
7.62
7.61
7.59
7.26
6.21
6.17
3.66
3.65
3.63
3.27
3.26
3.25
1.74
CDCl3, 400 MHz
O
O
S
O
CF3
Ph
P
Ph
Me
N
N
O
16.4
1.03
1.08
4.28
4.33
3.21
ppm
9
8
7
6
5
4
3
2
1
0

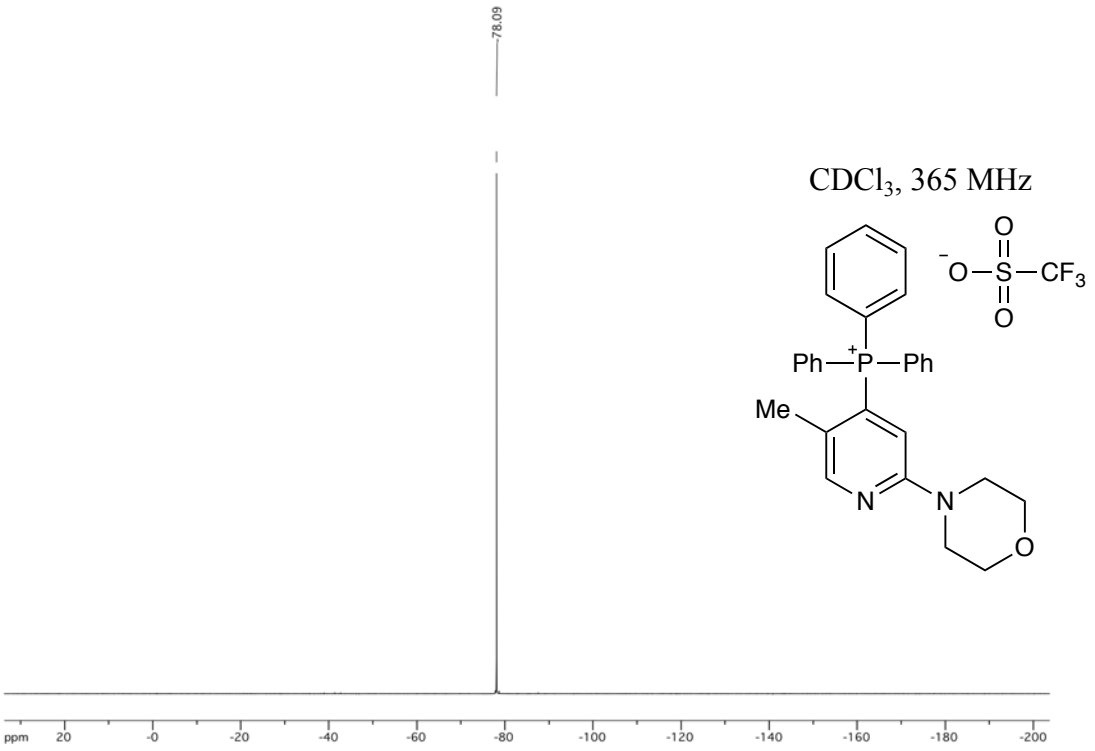

157.93
157.79
152.26
152.16
135.72
135.69
133.94
133.84
130.87
130.74
130.49
126.67
122.53
122.46
122.27
119.07
116.62
115.87
115.74
111.56
111.44
77.32
77.00
76.68
66.04
44.39
18.25
CDCl3, 100 MHz
O
O
S
CF3
Ph
P
Ph
Me
N
N
O
ppm
200
180
160
140
120
100
80
60
40
20
0

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

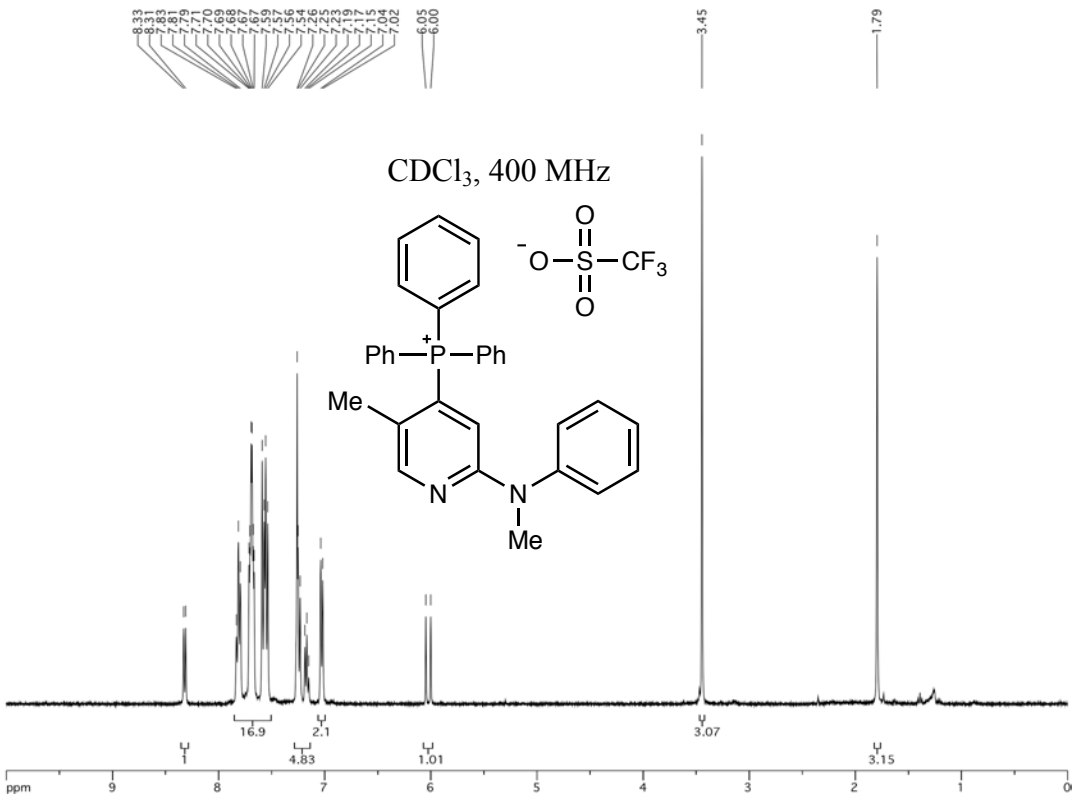


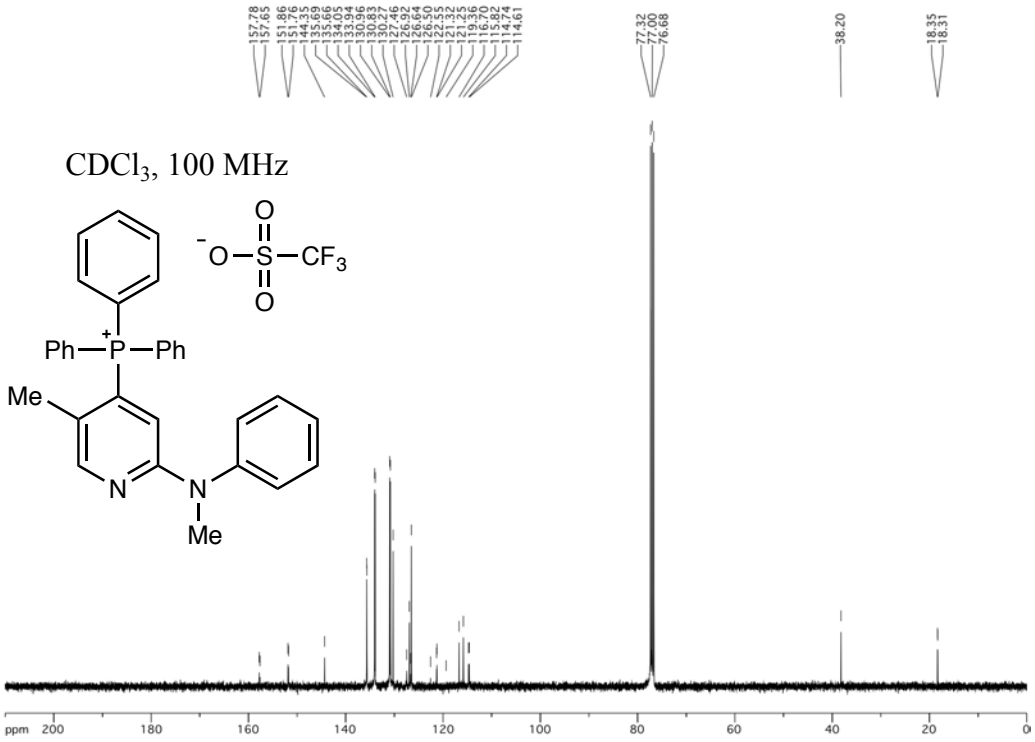
$CDCl_3$, 162 MHz



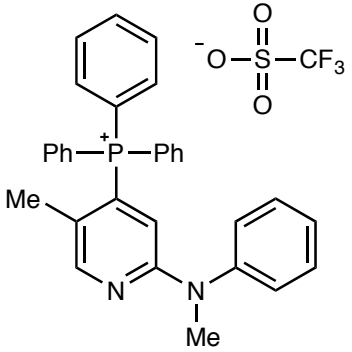


$CDCl_3$, 365 MHz

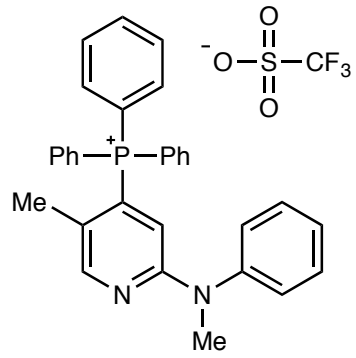

8.33
8.31
8.30
8.29
8.28
8.27
7.81
7.79
7.71
7.70
7.69
7.68
7.67
7.67
7.59
7.57
7.56
7.54
7.26
7.25
7.23
7.19
7.17
7.15
7.04
7.02
6.05
6.00
3.45
1.79
CDCl3, 400 MHz
O
O
S
O
CF3
Ph
P
Ph
Me
N
N
Me
16.9
2.1
3.07
1
4.83
1.01
3.15
ppm
9
8
7
6
5
4
3
2
1
0

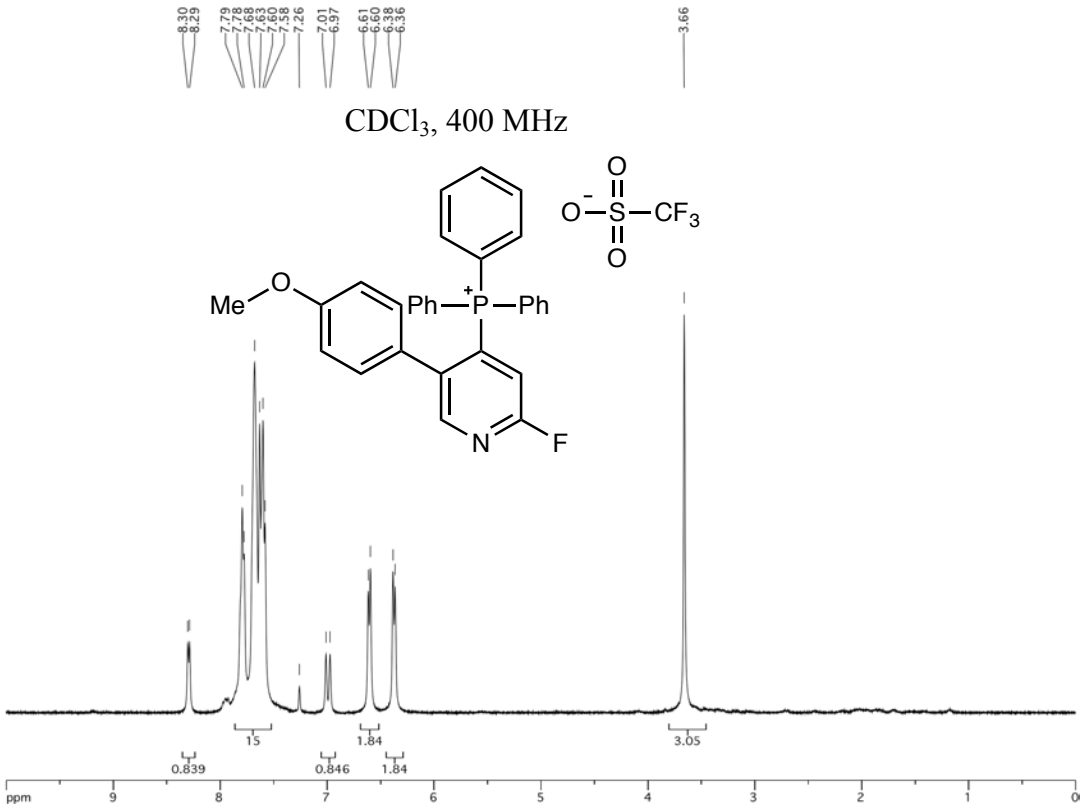

157.78
157.65
151.86
151.76
144.35
135.69
135.66
134.05
133.94
130.96
130.83
130.57
130.37
127.46
126.92
126.64
126.50
126.35
121.32
121.25
119.36
119.30
116.82
116.62
114.74
114.61
77.32
77.00
76.68
38.20
18.35
18.31
CDCl3, 100 MHz
O
-O—S—CF3
O
+
Ph—P—Ph
Me
N
N
Me
ppm 200 180 160 140 120 100 80 60 40 20 0

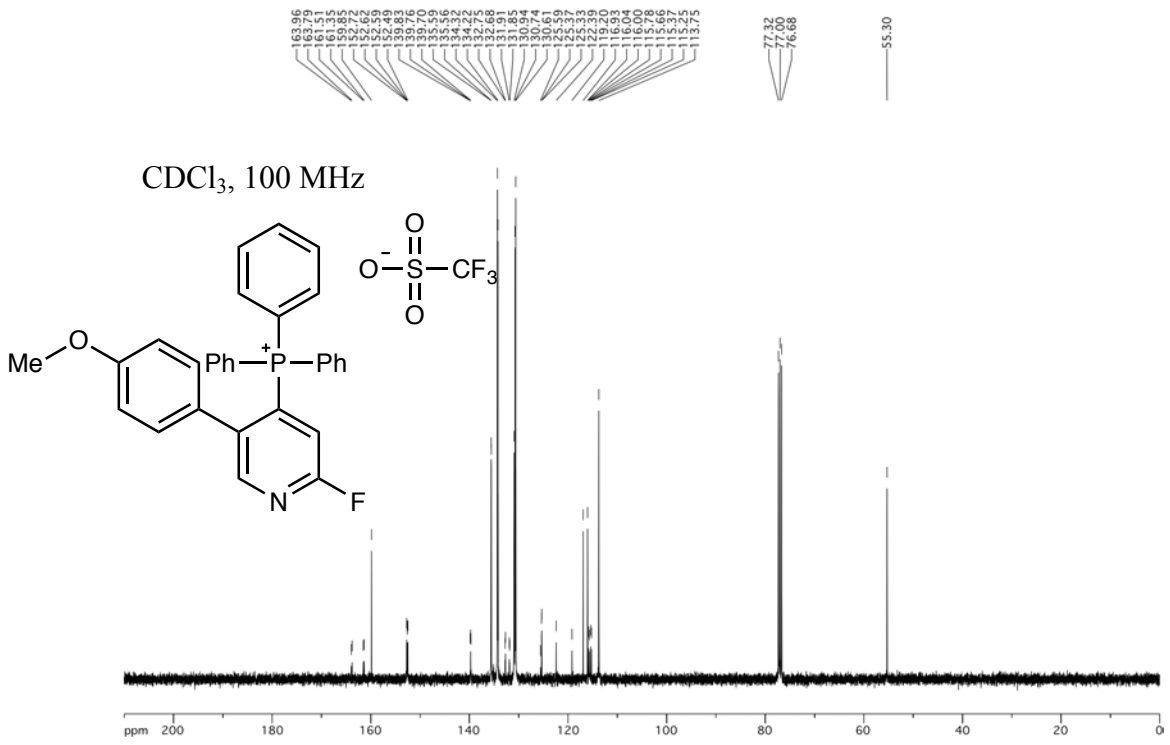
$CDCl_3$, 162 MHz



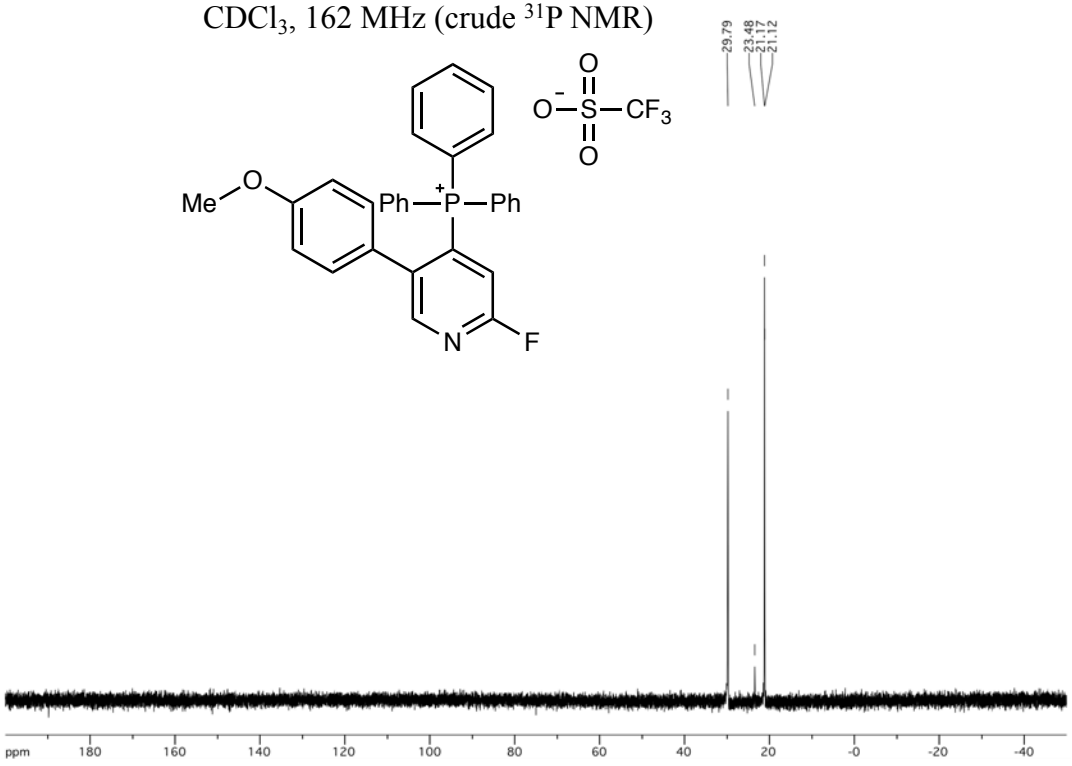
$CDCl_3$, 365 MHz



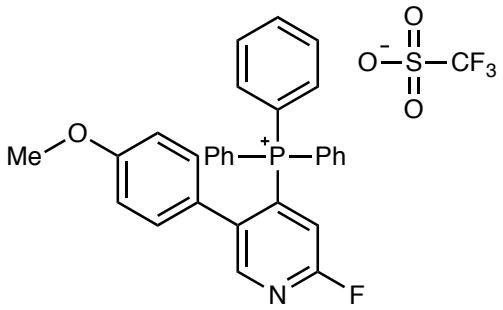

8.30
8.29
7.79
7.78
7.68
7.63
7.60
7.58
7.26
7.01
6.97
6.61
6.60
6.38
6.36
3.66
CDCl3, 400 MHz
O
O
S
CF3
Me
Ph
P
Ph
N
F
15
1.84
3.05
0.839
0.846
1.84
ppm

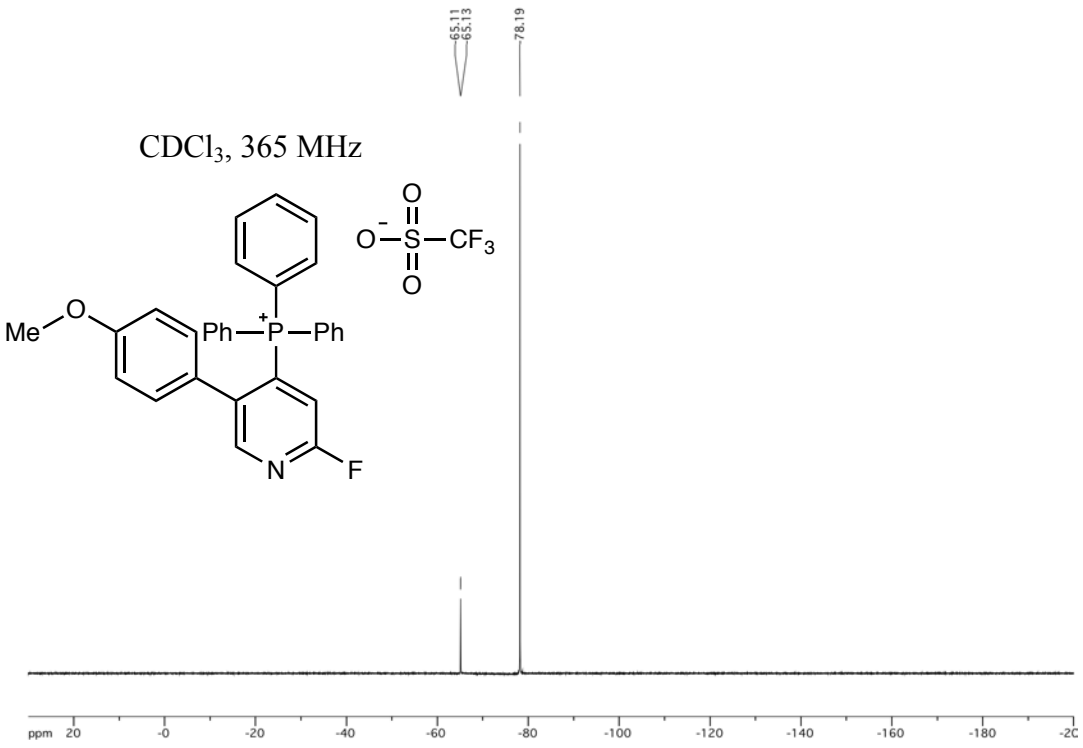

163.96
163.79
161.31
161.15
159.85
152.72
152.62
152.59
152.49
152.43
139.76
139.70
135.59
135.56
134.32
134.22
132.75
132.68
131.91
131.85
130.94
130.74
130.61
125.59
125.37
123.33
122.39
119.20
116.93
116.04
116.00
115.78
115.66
115.37
115.25
113.75
77.32
77.00
76.68
55.30
CDCl3, 100 MHz
Me
O
Ph
P
Ph
O
O
S
CF3
O
N
F
ppm
200
180
160
140
120
100
80
60
40
20
0

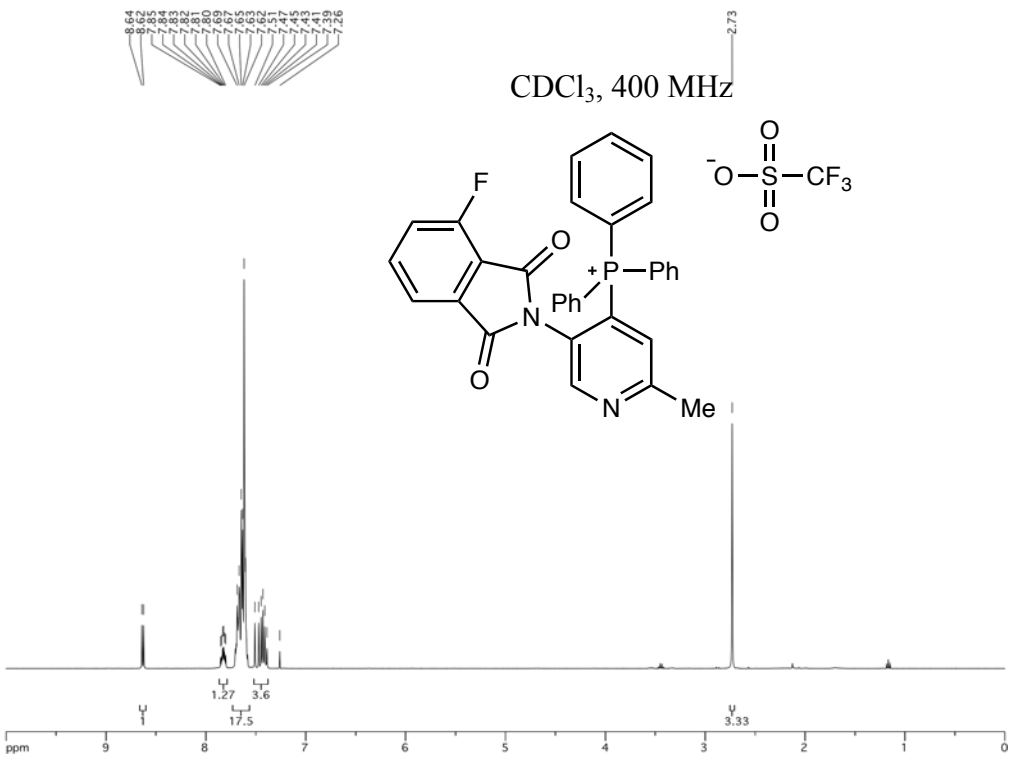
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

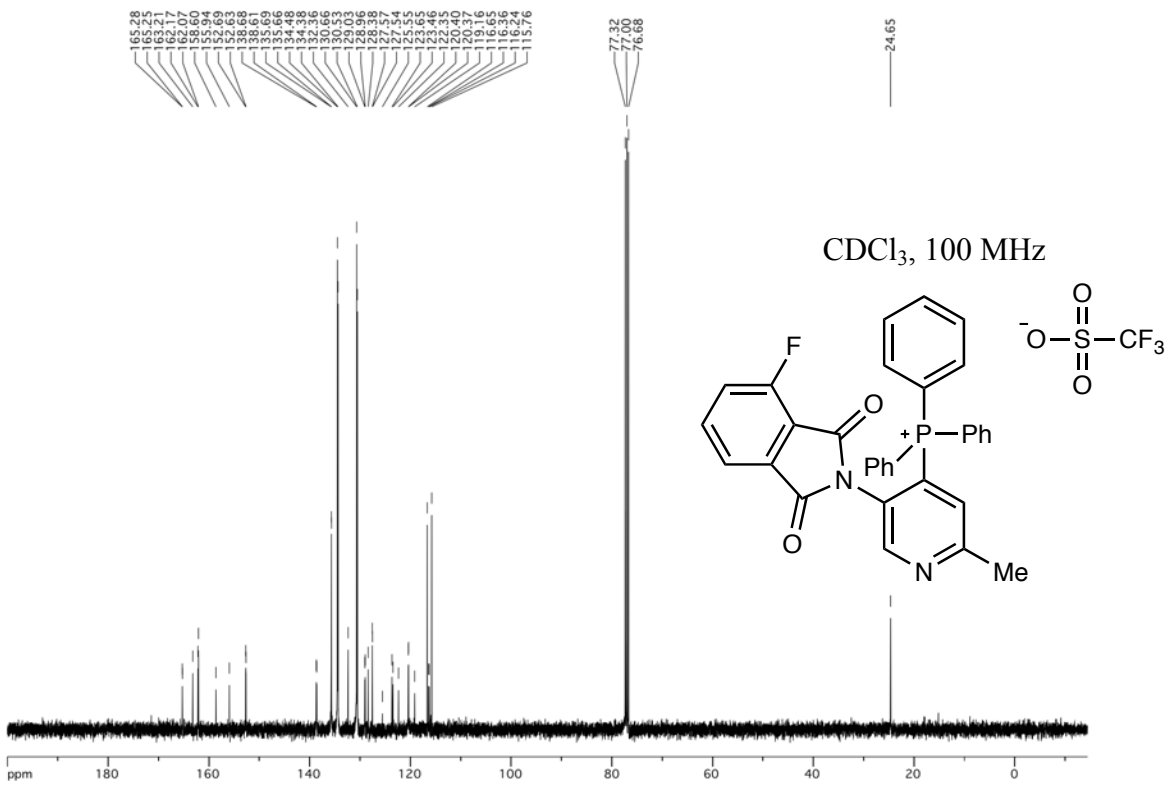


$CDCl_3$, 162 MHz

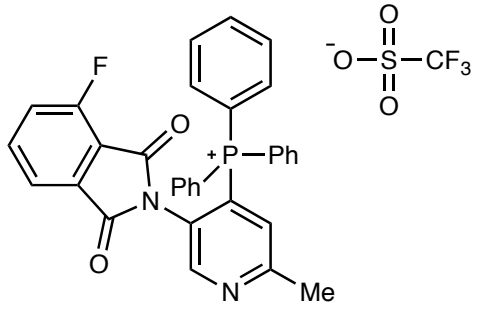



65.11
65.13
78.19
CDCl3, 365 MHz
O
O
S
CF3
O
Me
O
Ph
P
Ph
N
F
ppm
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180

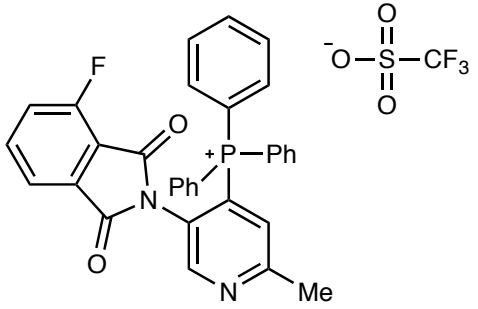

8.64
8.62
7.85
7.84
7.83
7.82
7.81
7.80
7.69
7.67
7.65
7.63
7.62
7.51
7.47
7.45
7.43
7.41
7.39
7.26
2.73
CDCl3, 400 MHz
F
O
N
O
P
Ph
Ph
O
O
S
O
CF3
N
Me
1.27
3.6
1
17.5
3.33
ppm
9
8
7
6
5
4
3
2
1
0

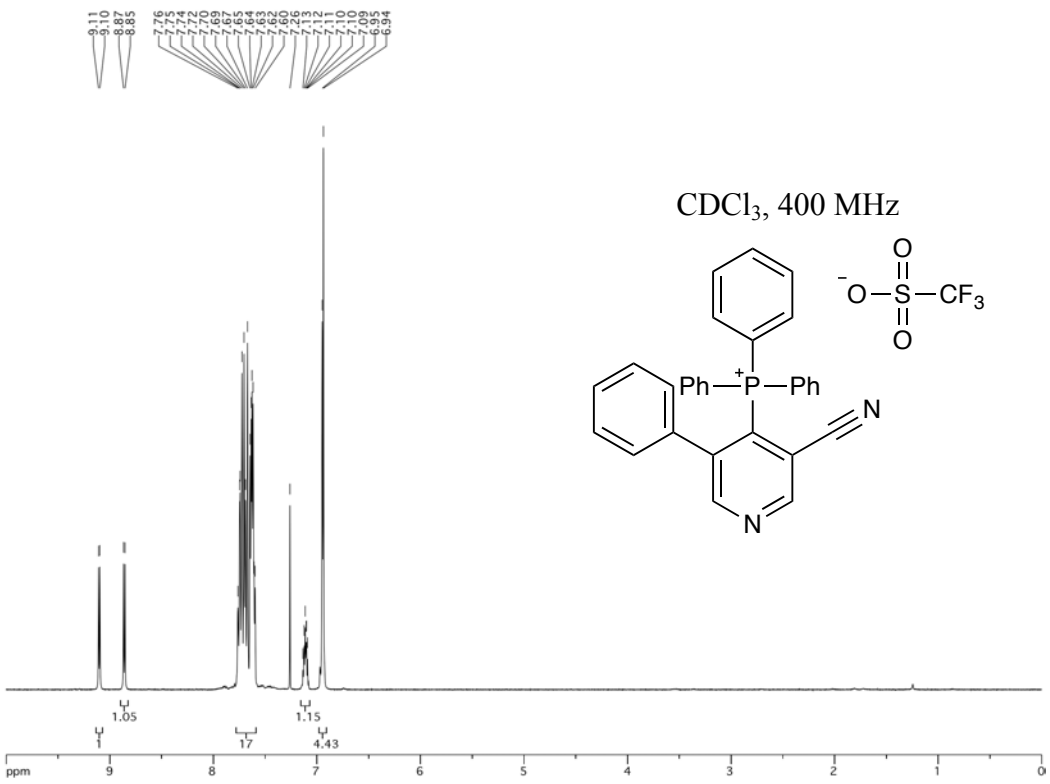

165.28
165.25
163.21
162.17
162.07
158.60
155.64
152.69
152.63
138.68
138.61
135.69
135.66
134.48
134.38
132.36
130.66
130.53
129.03
128.96
128.38
127.57
127.54
125.55
123.65
123.46
122.55
120.45
120.37
119.16
116.65
116.36
116.24
115.76
77.32
77.00
76.68
24.65
CDCl3, 100 MHz
F
O
N
O
P
Ph
Ph
O
O
S
O
CF3
N
Me
ppm
180
160
140
120
100
80
60
40
20
0

$CDCl_3$, 162 MHz

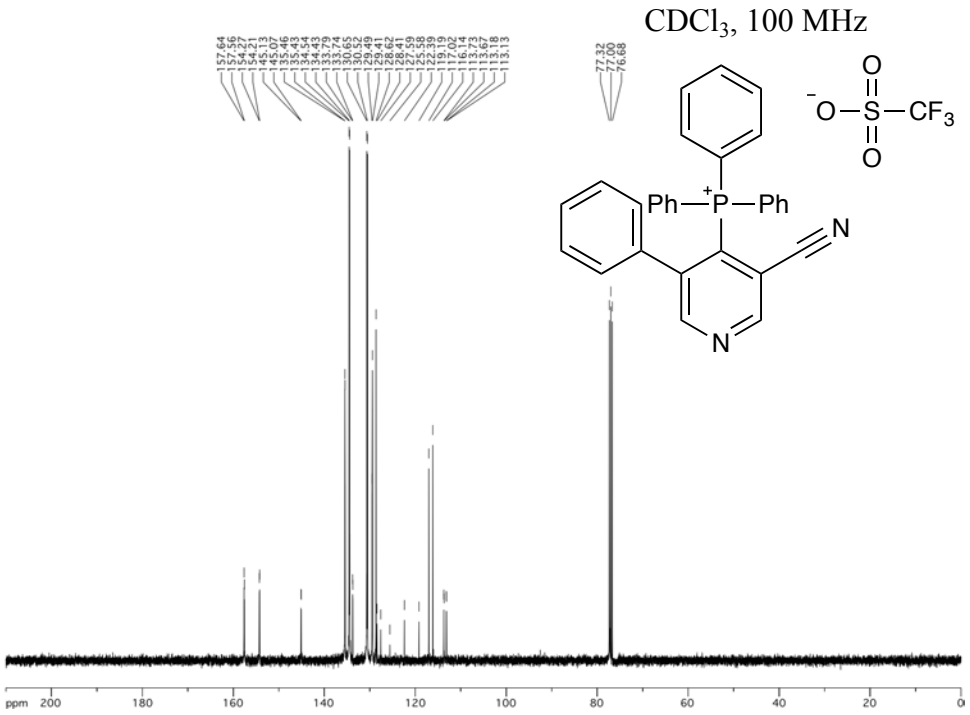


$CDCl_3$, 365 MHz

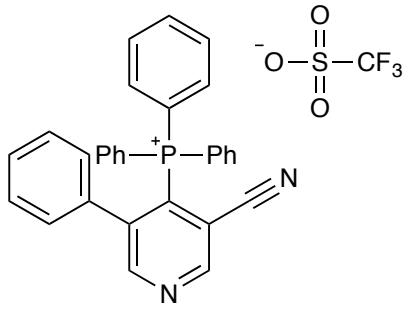


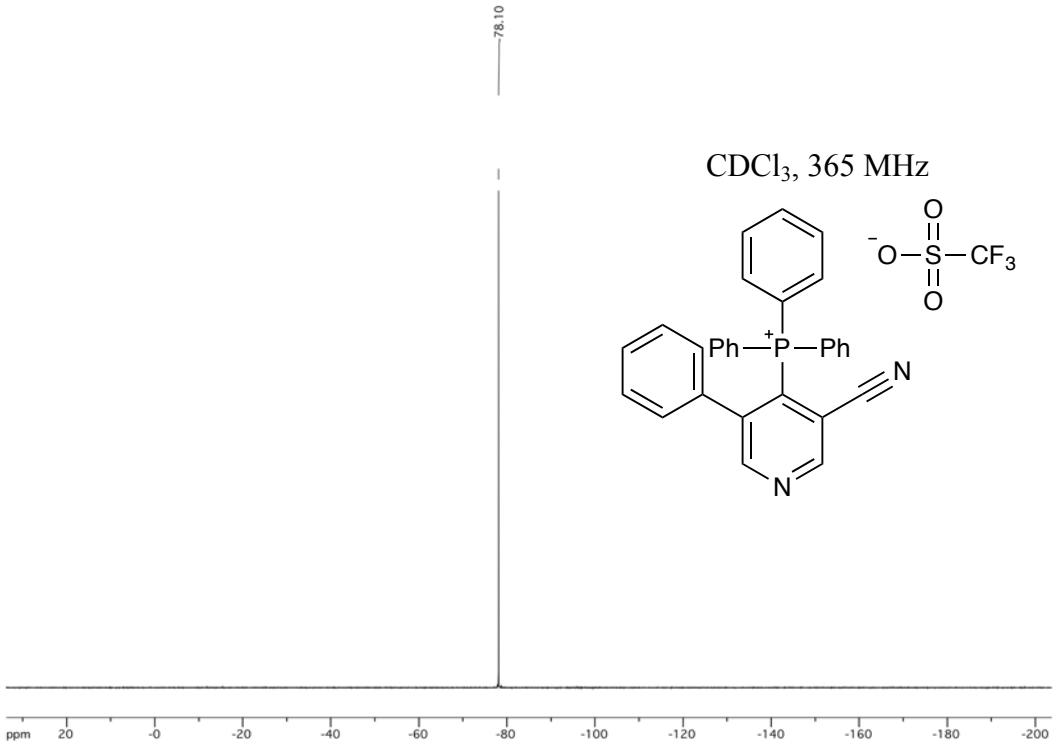


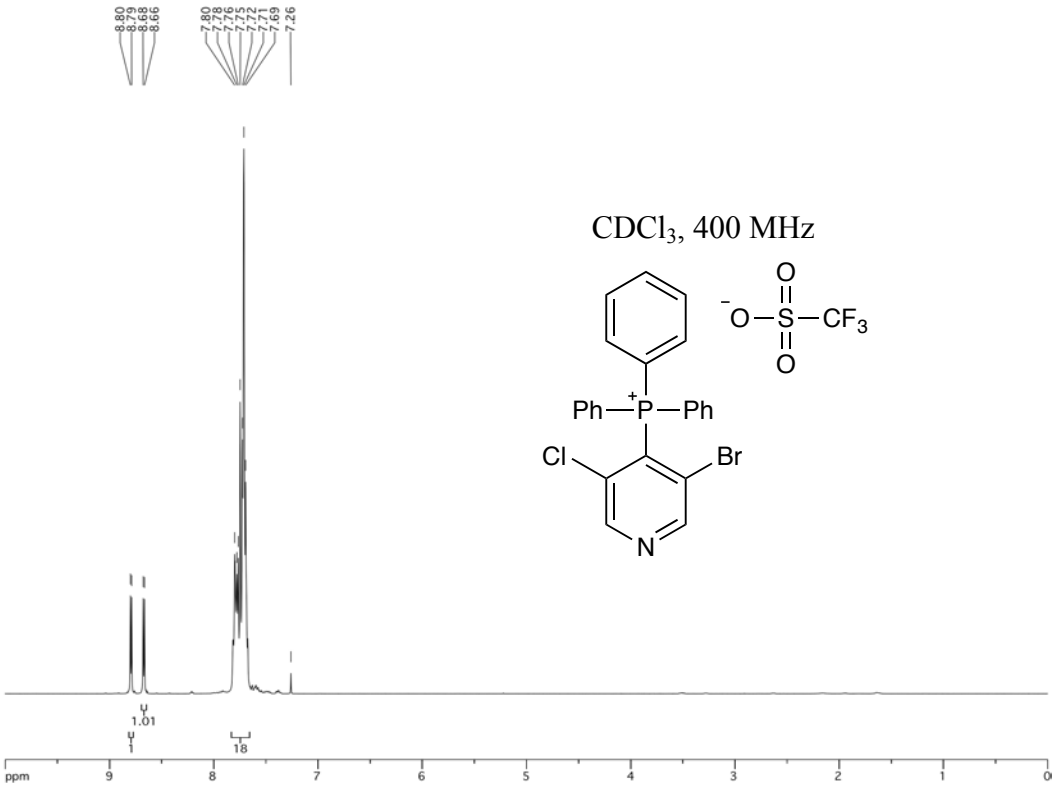
$CDCl_3$, 400 MHz


CDCl3, 100 MHz
157.64
157.56
154.27
154.21
145.13
145.07
135.46
135.43
134.54
134.43
133.79
133.74
130.65
130.52
129.49
129.41
128.62
128.41
127.59
127.38
125.39
125.38
119.19
117.02
116.64
116.73
113.67
113.18
113.13
77.32
77.00
76.68
Ph
P
Ph
N
N
O
O
S
O
CF3
ppm 200 180 160 140 120 100 80 60 40 20 0

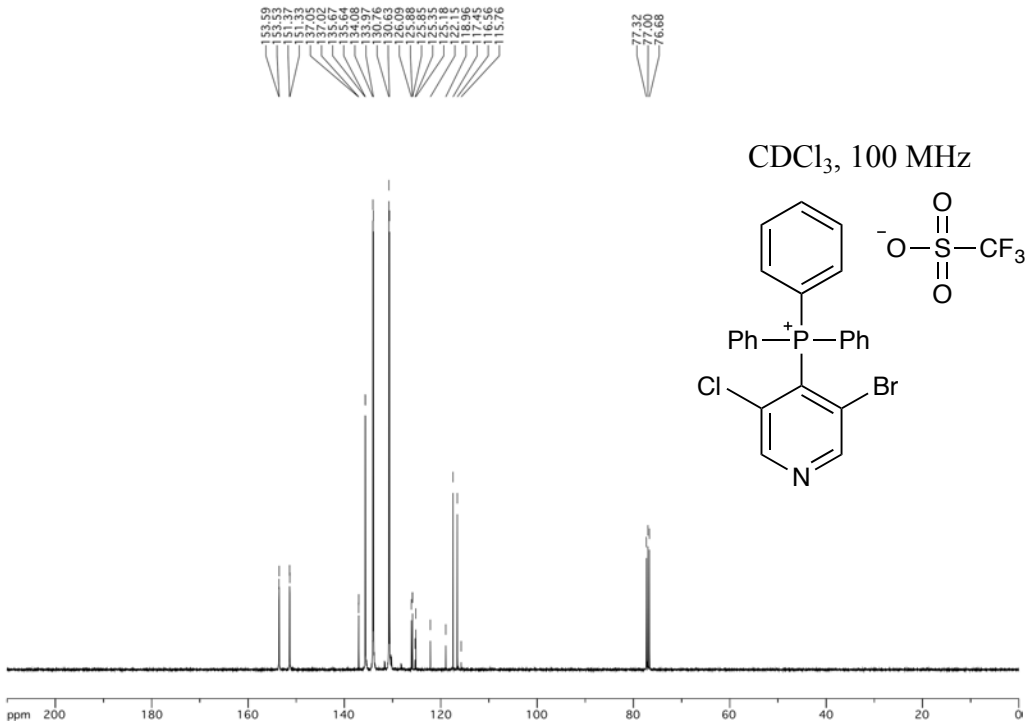
$CDCl_3$, 162 MHz



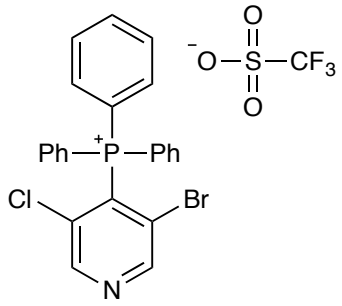

78.10
CDCl3, 365 MHz
O
O
O
S
CF3
Ph
P
Ph
N
N
ppm
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200

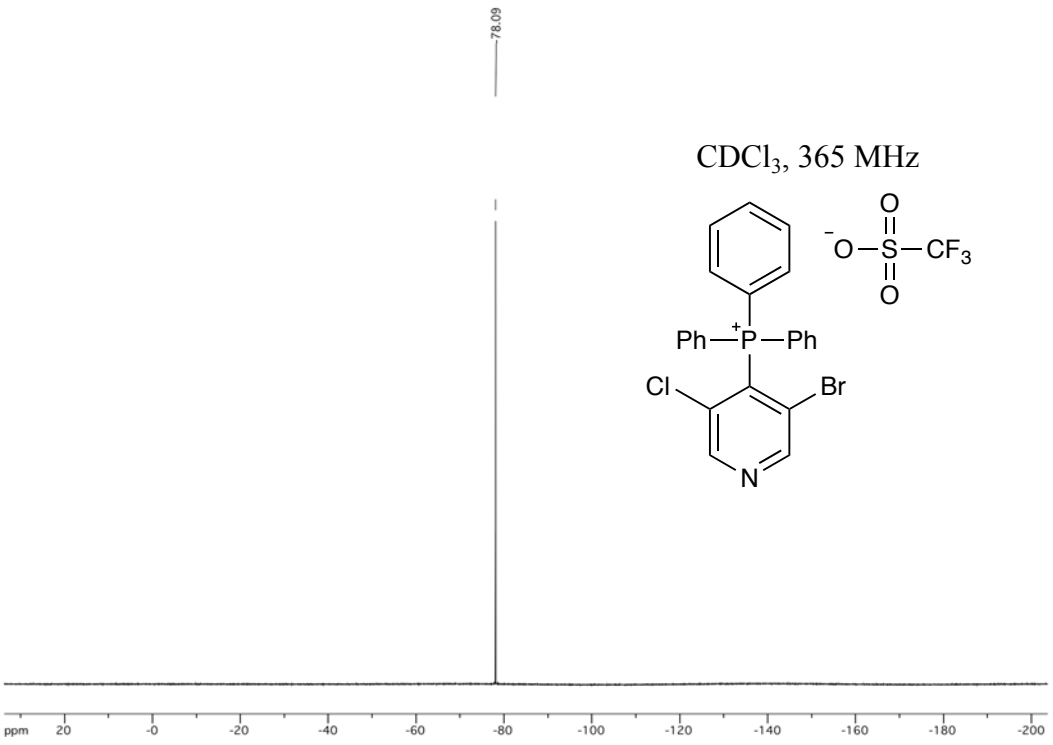


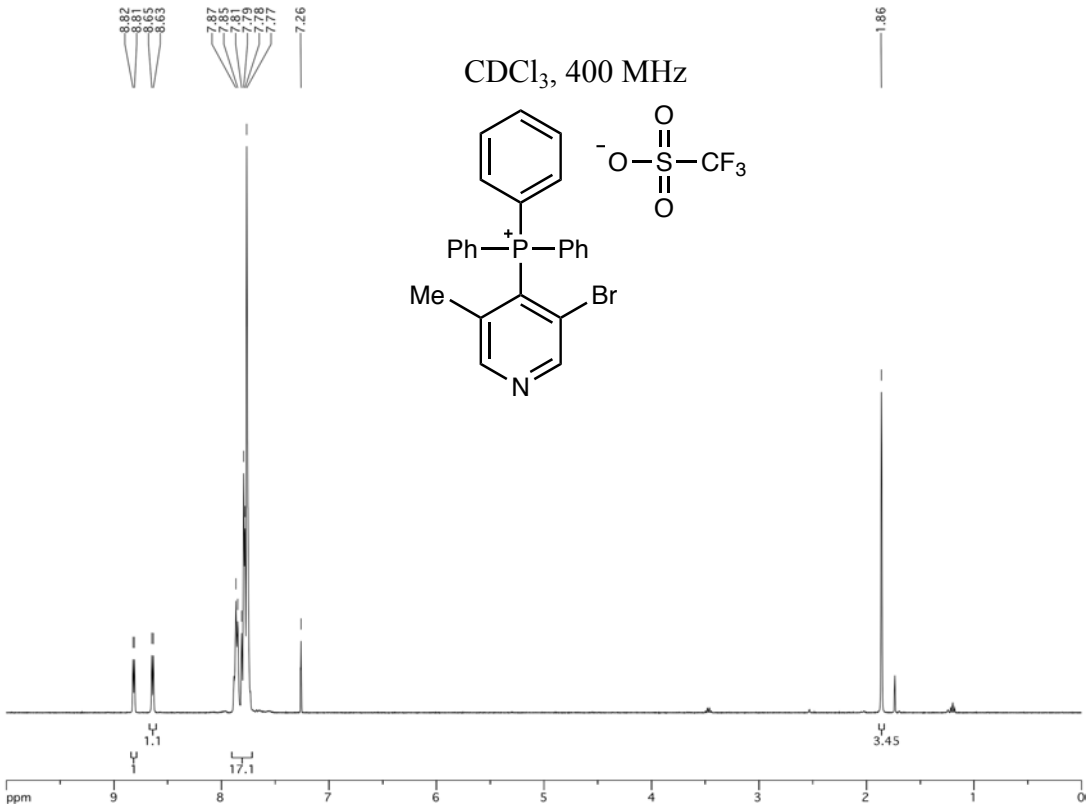
$CDCl_3$, 400 MHz

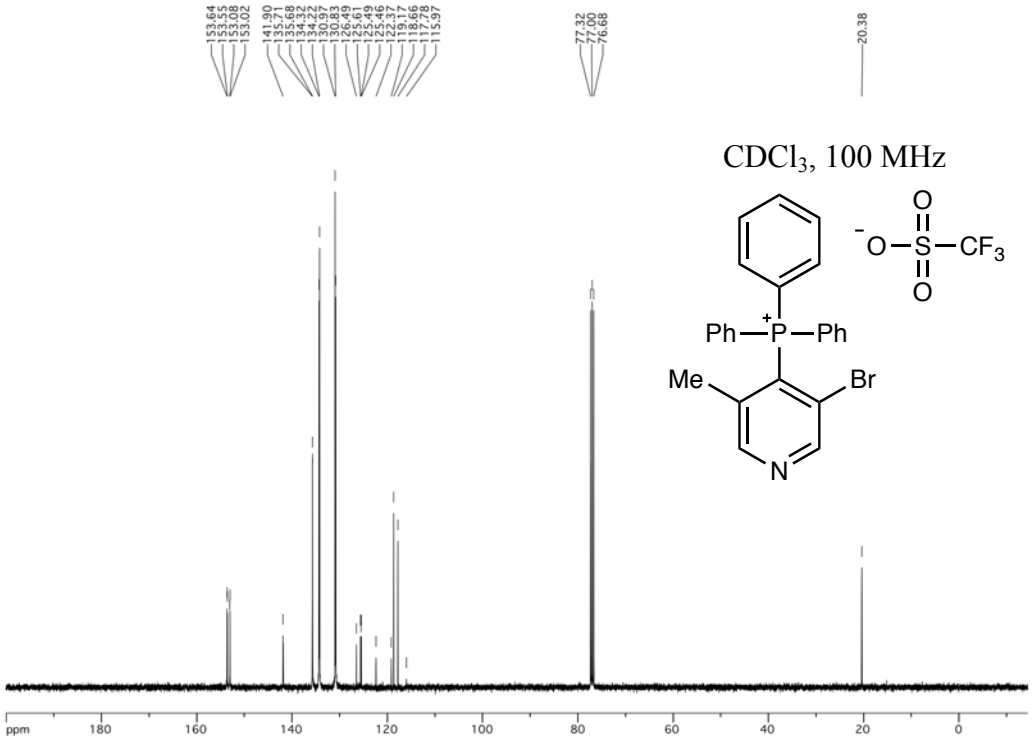

153.59
153.53
151.37
151.33
137.05
137.02
135.67
135.64
134.08
133.97
130.76
130.63
126.09
125.88
125.85
125.35
125.18
122.15
118.96
117.45
116.56
115.76
77.32
77.00
76.68
CDCl3, 100 MHz
O
O
S
CF3
O
Ph
P
Ph
Cl
Br
N
ppm
200
180
160
140
120
100
80
60
40
20

$CDCl_3$, 162 MHz

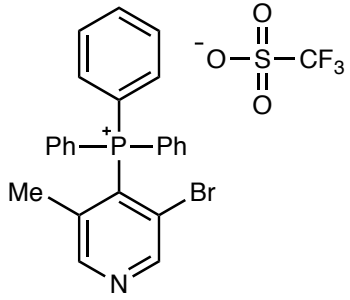



78.09
CDCl3, 365 MHz
O
O
S
CF3
O
Ph
P
Ph
Cl
Br
N
ppm
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200

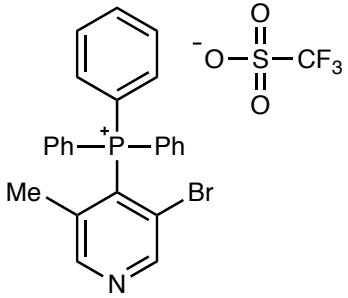

8.82
8.81
8.65
8.63
7.87
7.85
7.81
7.79
7.78
7.77
7.26
1.86
CDCl3, 400 MHz
O
O
-O—S—CF3
O
Ph—P—Ph
+
Me
Br
N
1.1
1
17.1
3.45
ppm
9
8
7
6
5
4
3
2
1
0


153.64
153.55
153.08
153.02
141.90
135.71
135.68
134.32
134.22
130.97
130.43
126.49
125.61
125.49
125.46
122.17
121.77
118.66
117.78
115.97
77.32
77.00
76.68
20.38
CDCl3, 100 MHz
O
O
S
O
CF3
Ph
P
Ph
Me
Br
N
ppm
180
160
140
120
100
80
60
40
20
0

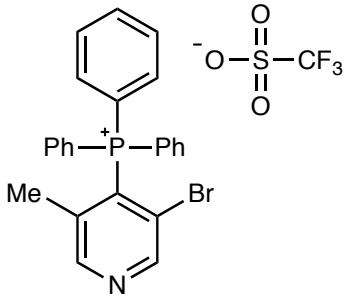
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

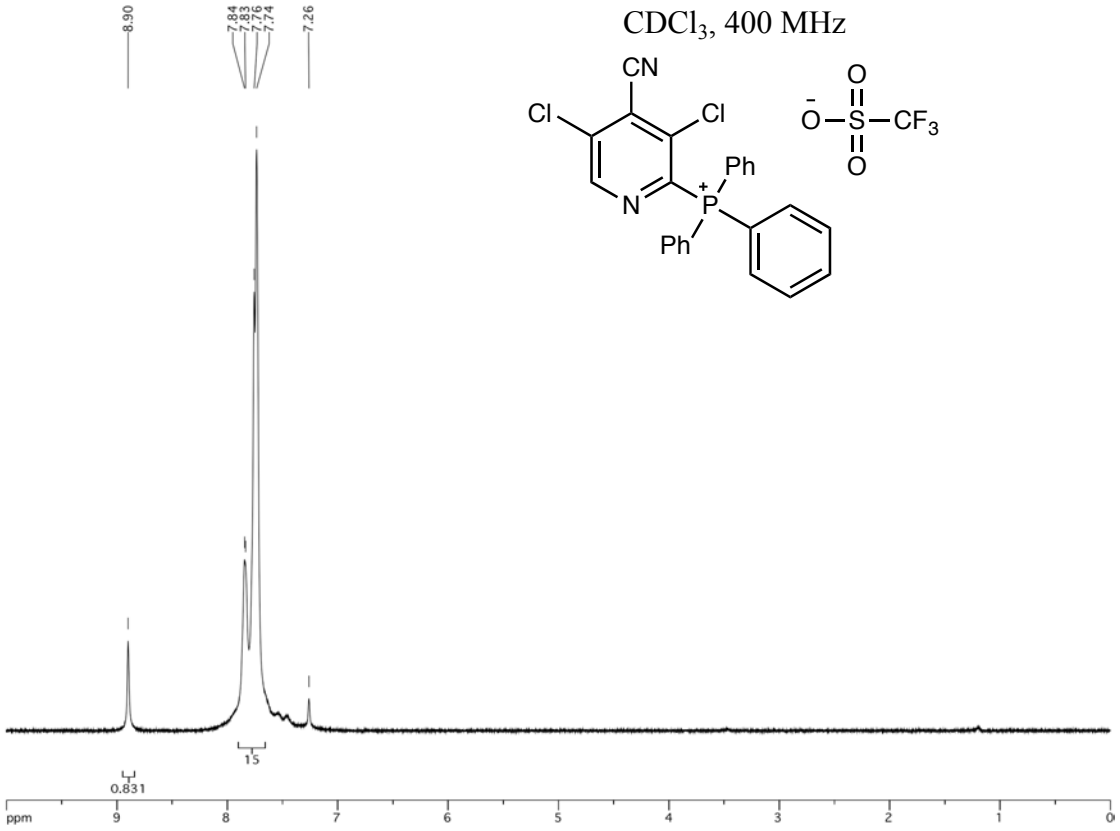


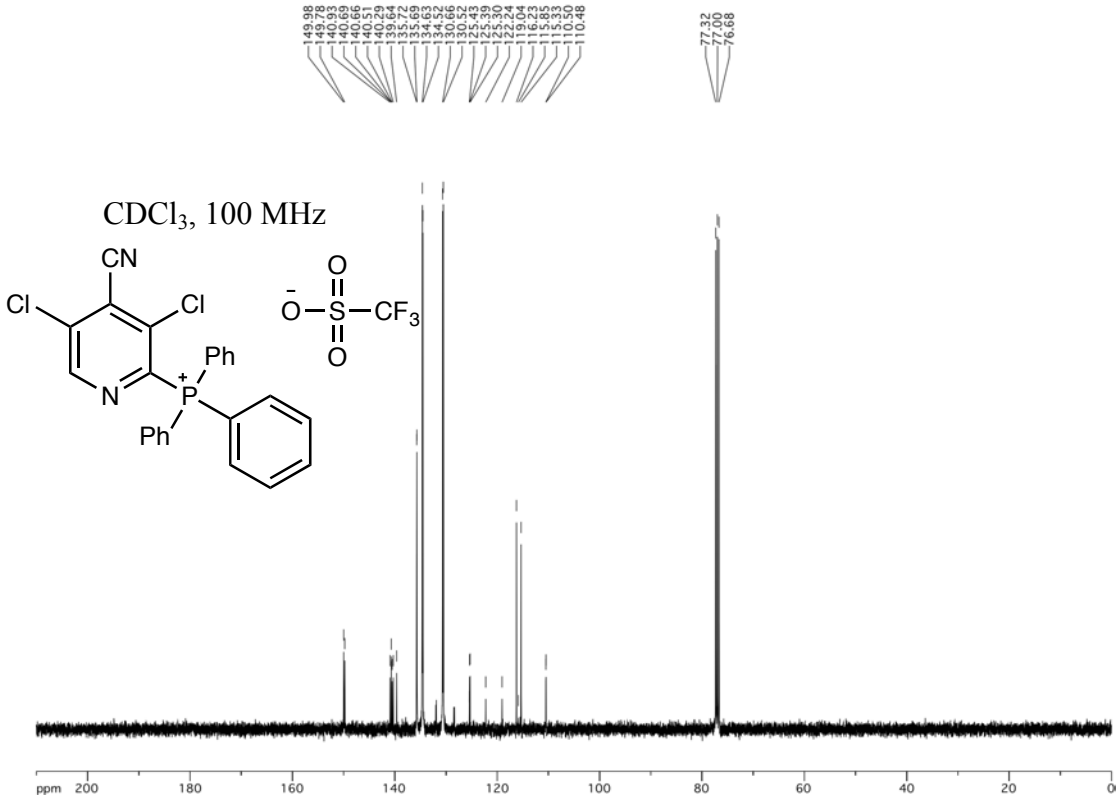
$CDCl_3$, 162 MHz



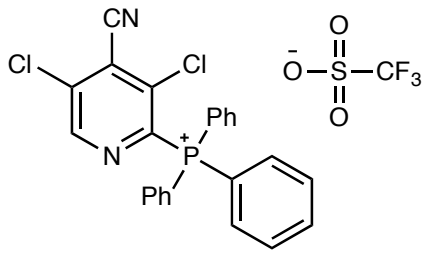
$CDCl_3$, 365 MHz



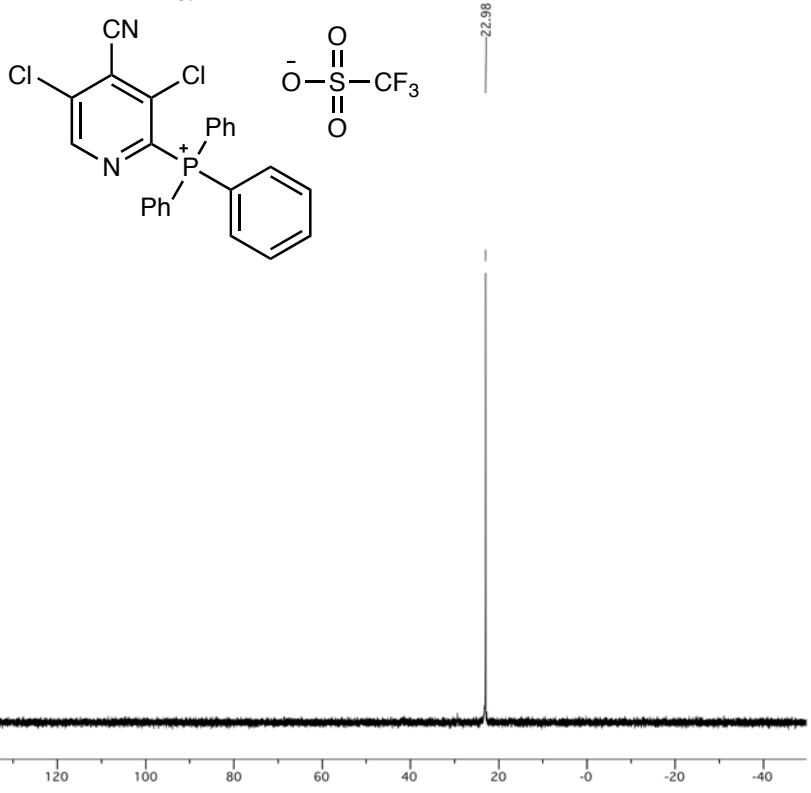

8.90
7.84
7.83
7.76
7.74
7.26
CDCl3, 400 MHz
CN
Cl
Cl
N
P
Ph
Ph
O
O
S
CF3
O
0.831
1.5
ppm
9
8
7
6
5
4
3
2
1
0


149.98
149.78
140.93
140.69
140.66
140.51
140.29
139.64
135.72
135.69
134.63
134.52
130.66
130.52
125.43
125.39
125.30
122.24
119.04
116.23
115.85
115.33
110.50
110.48
77.32
77.00
76.68
CDCl3, 100 MHz
CN
Cl
Cl
Ph
Ph
N
P
O
O
S
CF3
O
ppm 200
180
160
140
120
100
80
60
40
20

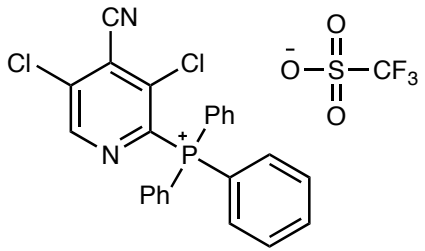
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

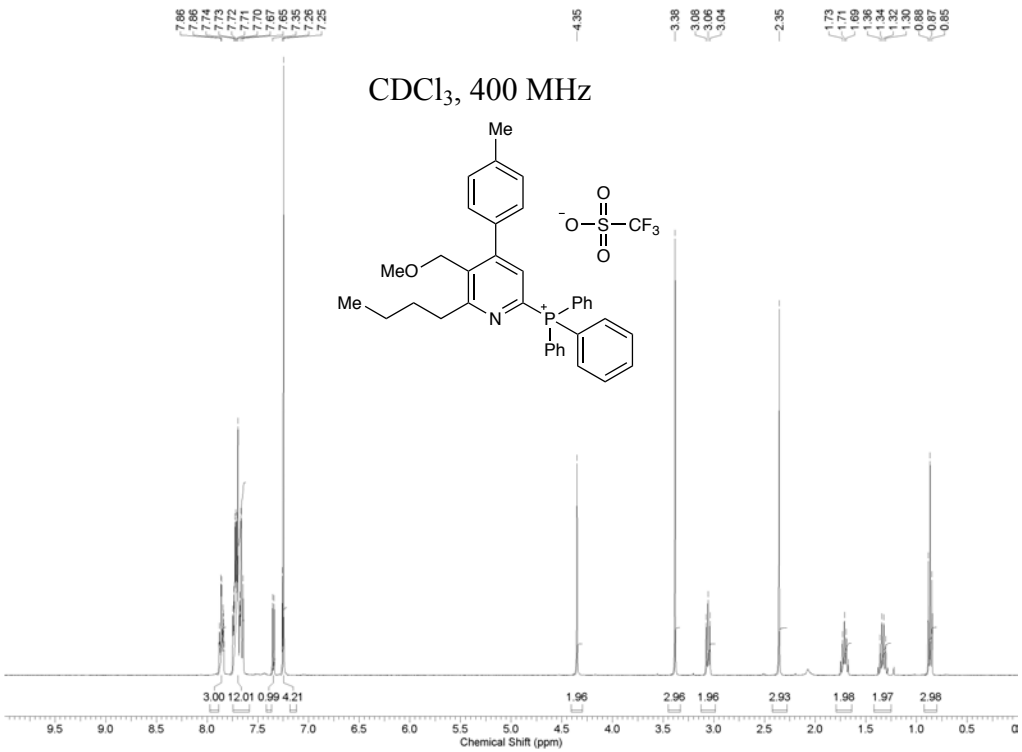


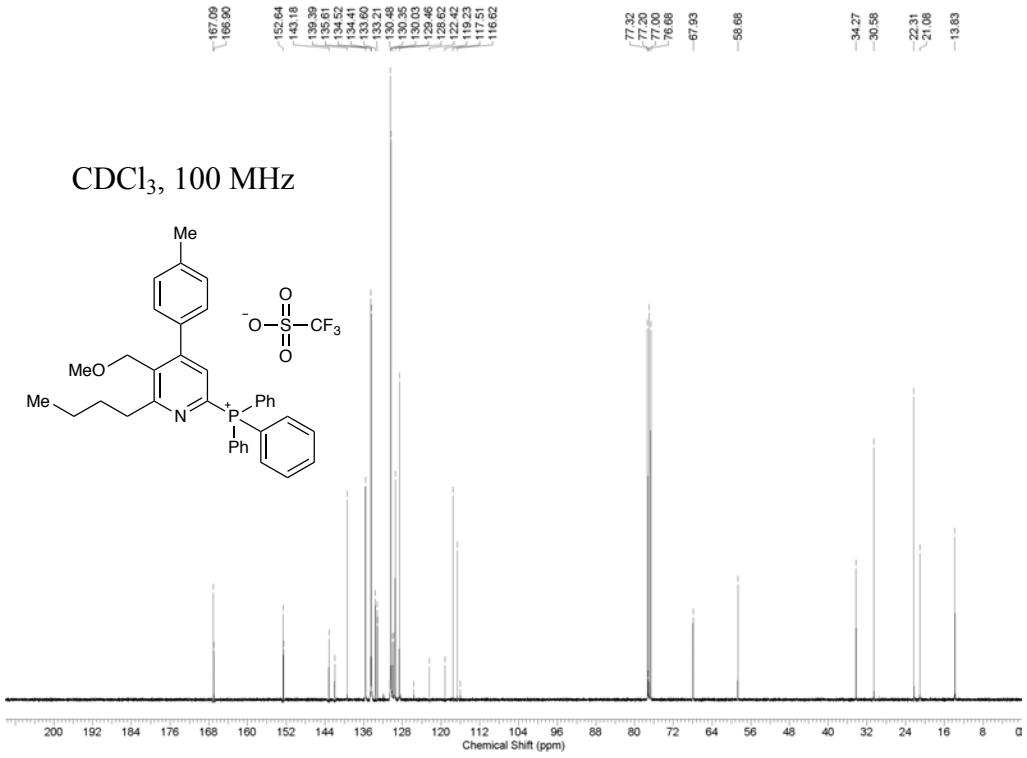
$CDCl_3$, 162 MHz

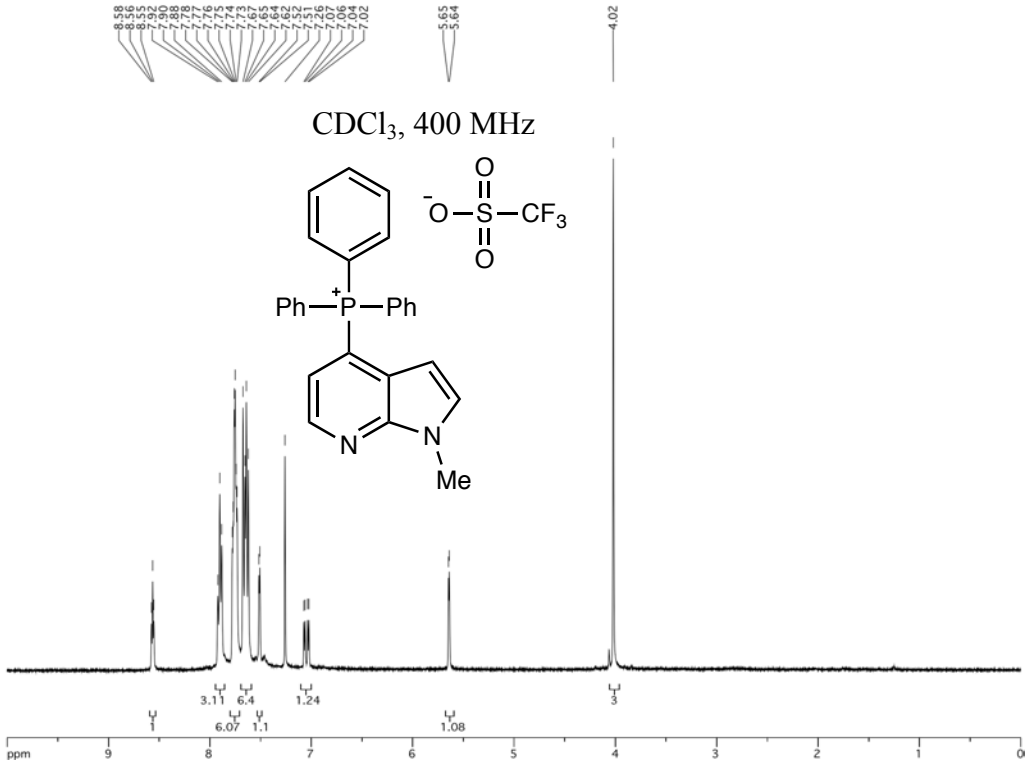


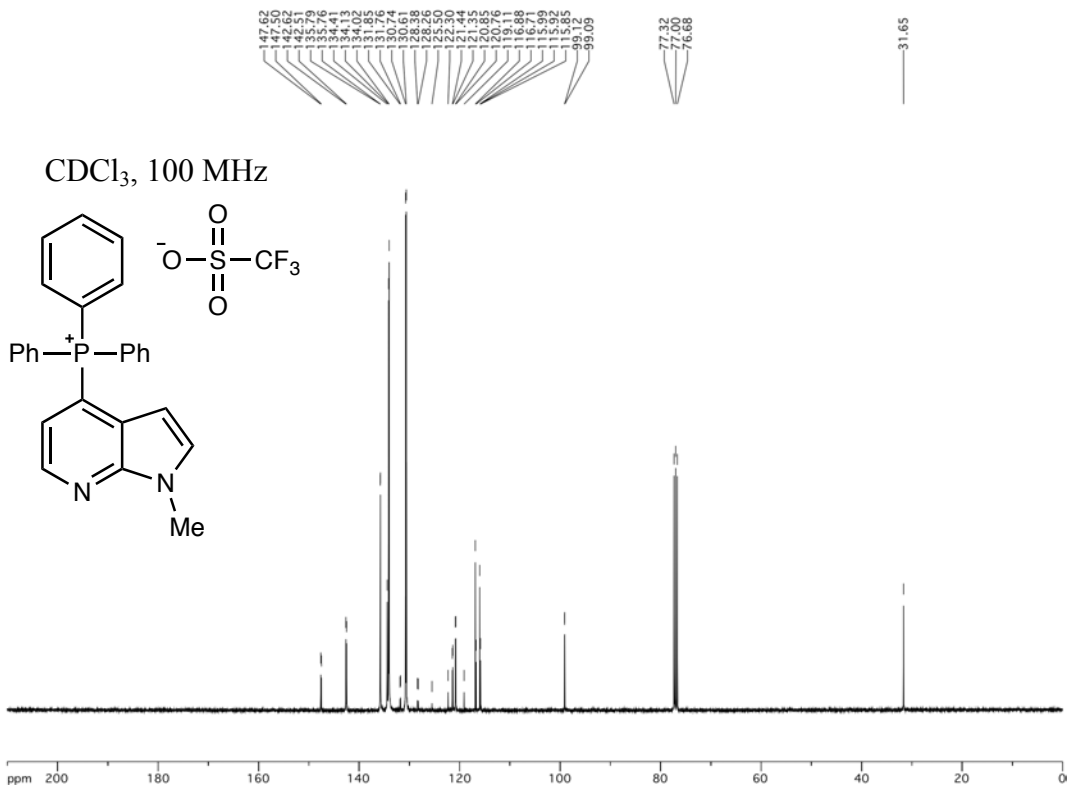
$CDCl_3$, 365 MHz



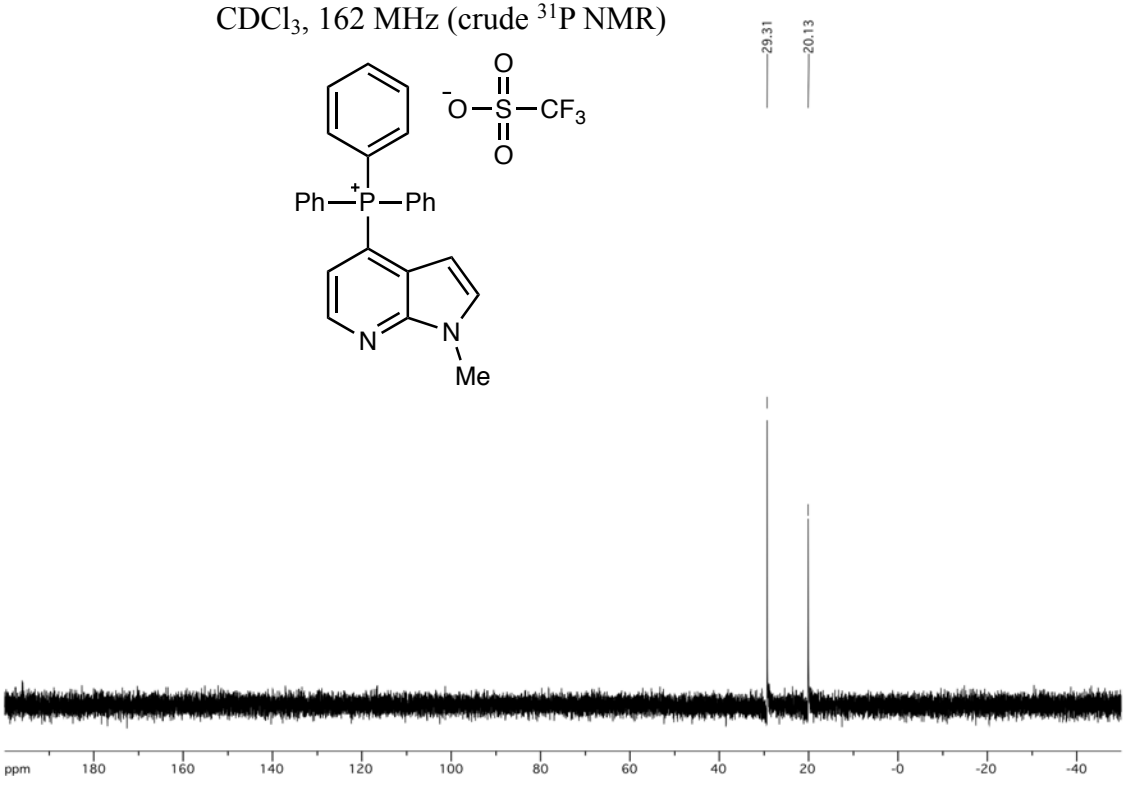

7.86
7.86
7.74
7.73
7.72
7.71
7.70
7.67
7.65
7.35
7.26
7.25
4.35
3.38
3.08
3.06
3.04
2.35
1.73
1.71
1.69
1.36
1.34
1.32
1.30
0.88
0.87
0.85
CDCl3, 400 MHz
Me
MeO
Me
N
P
Ph
Ph
O
O
O
S
CF3
3.00 12.01 0.99 4.21
1.96
2.96 1.96
2.93
1.98 1.97
2.98
Chemical Shift (ppm)


167.09
166.90
152.64
143.18
139.39
135.61
134.52
134.41
133.60
133.21
130.48
130.35
130.03
129.46
128.62
122.42
119.23
117.51
116.62
77.32
77.20
77.00
76.68
67.93
58.66
34.27
30.58
22.31
21.08
13.83
CDCl3, 100 MHz
Me
MeO
Me
N
P
Ph
Ph
O
O
S
O
CF3
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8
Chemical Shift (ppm)

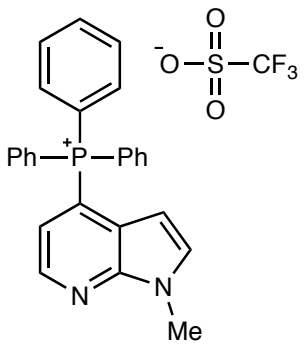

8.58
8.56
8.55
8.55
7.92
7.90
7.88
7.78
7.77
7.76
7.75
7.74
7.73
7.67
7.65
7.64
7.62
7.52
7.51
7.16
7.07
7.06
7.04
7.02
5.65
5.64
4.02
CDCl3, 400 MHz
O
O
S
CF3
O
Ph
P
Ph
N
N
Me
3.11
6.4
1.24
1
6.07
1.1
1.08
3
ppm
9
8
7
6
5
4
3
2
1
0


147.62
147.50
142.62
142.51
142.19
135.76
134.41
134.13
134.02
131.85
131.76
130.74
130.61
128.38
128.26
125.50
125.30
121.44
121.35
120.85
120.76
119.11
116.88
116.71
115.99
115.92
115.85
99.17
99.09
77.32
77.00
76.68
31.65
CDCl3, 100 MHz
O
O−S−CF3
O
Ph−P−Ph
N
N
Me
ppm 200 180 160 140 120 100 80 60 40 20 0

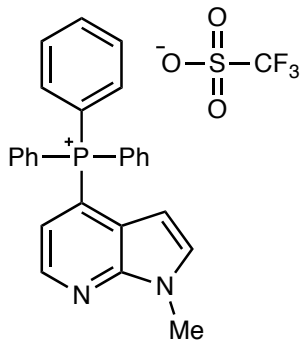
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

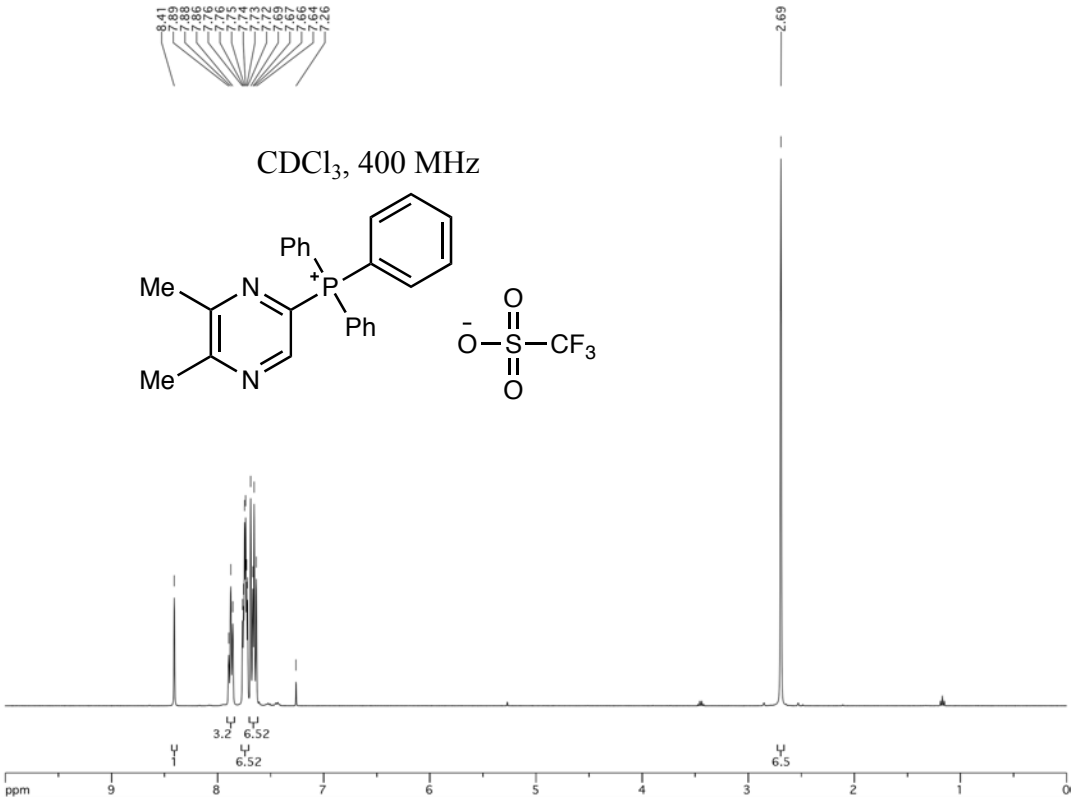


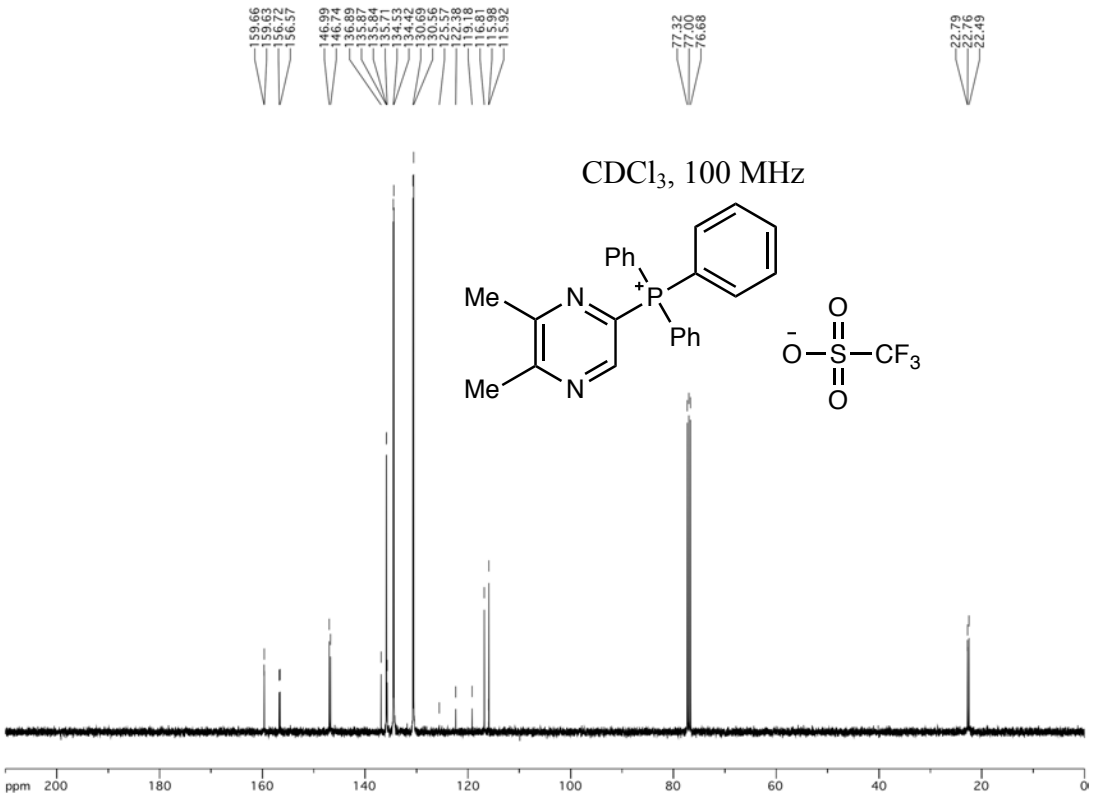
$CDCl_3$, 162 MHz

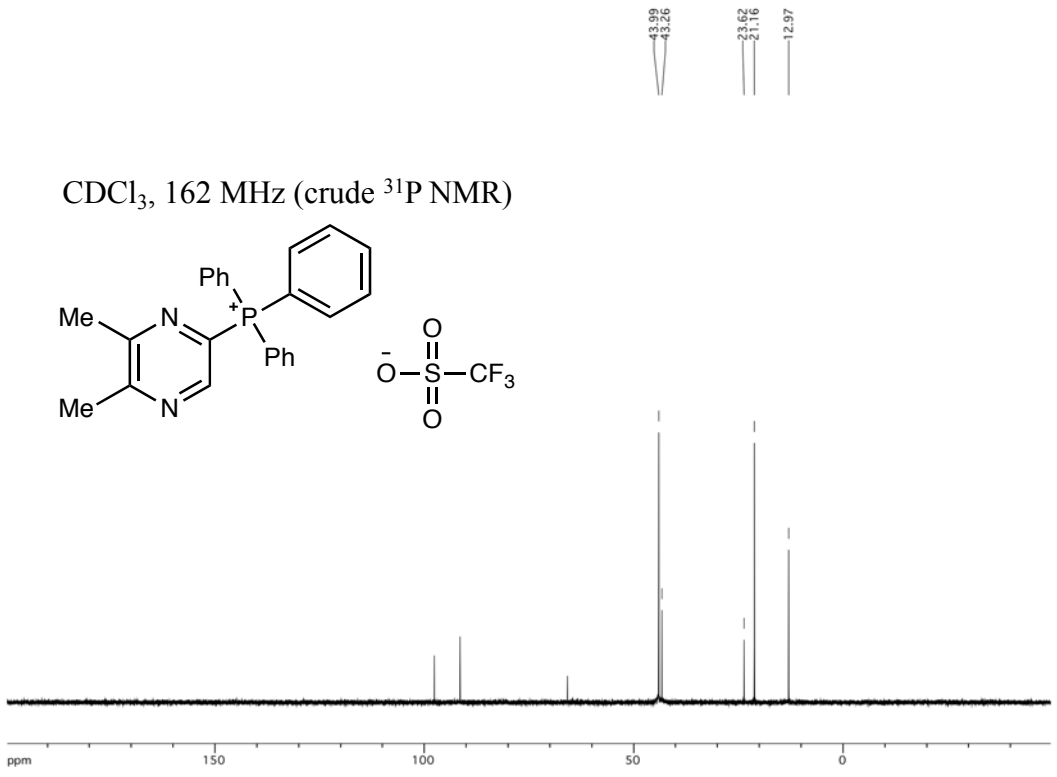


$CDCl_3$, 365 MHz



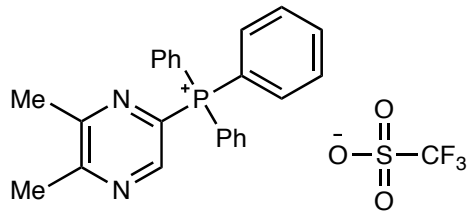

8.41
7.89
7.88
7.86
7.77
7.76
7.75
7.74
7.73
7.72
7.69
7.67
7.66
7.64
7.26
2.69
CDCl3, 400 MHz
Ph
Me
N
P
Ph
Me
N
O
O
S
CF3
O
3.2
6.52
1
6.52
6.5
ppm
9
8
7
6
5
4
3
2
1
0


159.66
157.63
156.72
156.57
146.99
146.74
145.89
135.87
135.84
135.71
134.53
134.42
130.69
130.56
125.57
122.38
119.18
116.81
115.98
115.92
77.32
77.00
76.68
22.79
22.76
22.49
CDCl3, 100 MHz
Ph
Me
N
P
Ph
Me
N
O
O
S
CF3
O
ppm 200
180
160
140
120
100
80
60
40
20
0

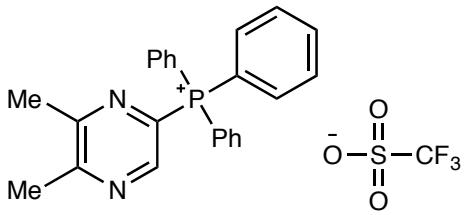


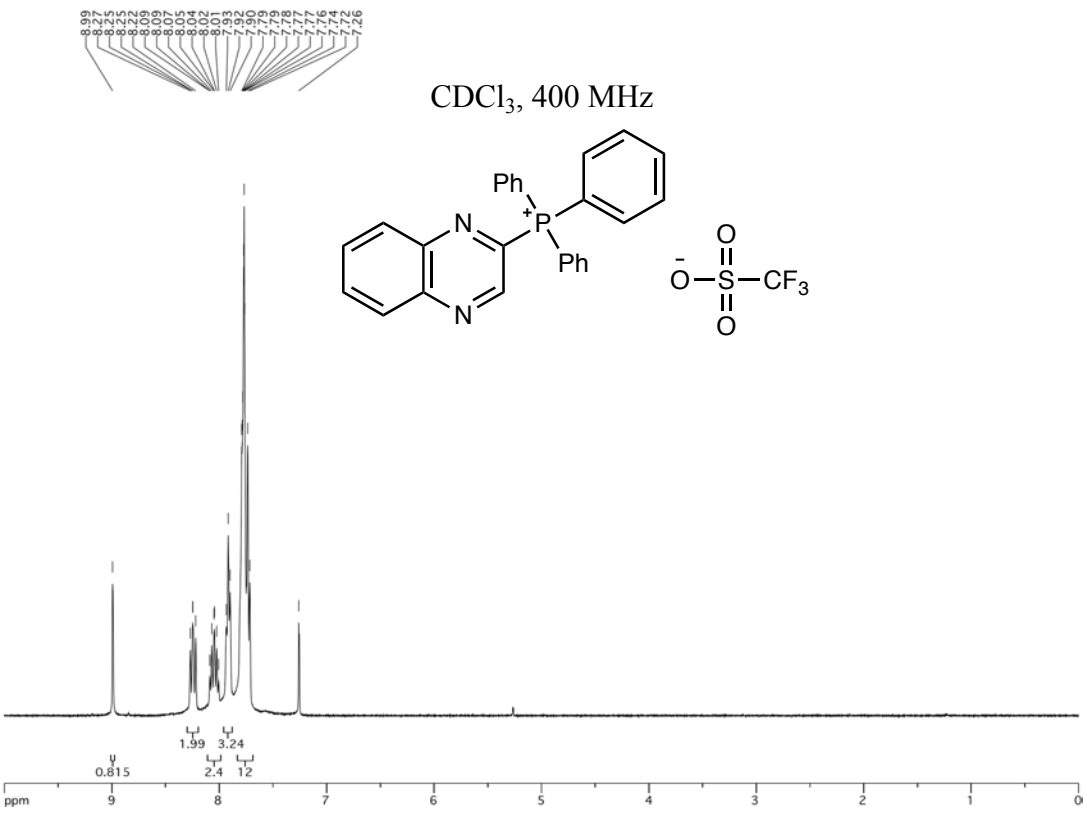
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

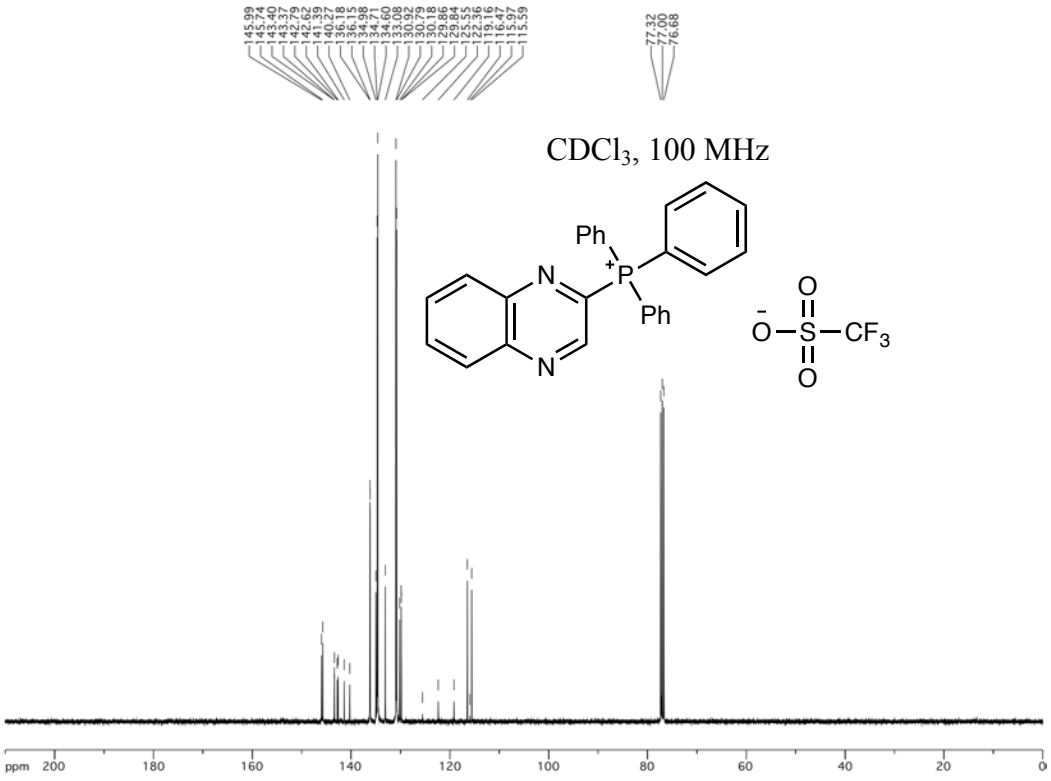
$CDCl_3$, 162 MHz



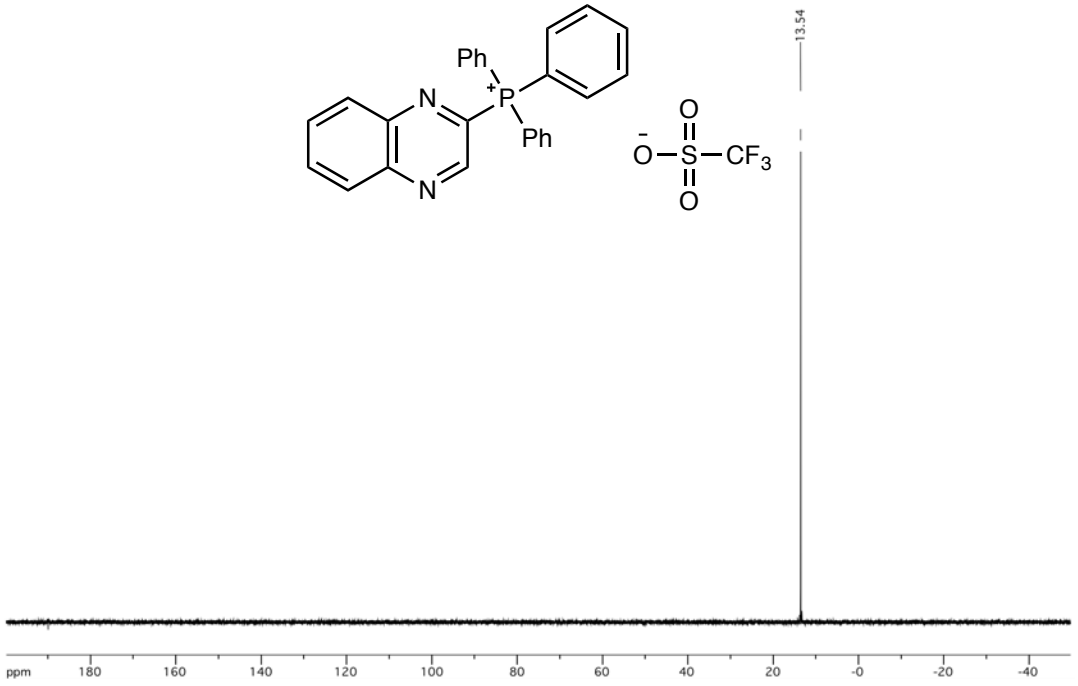
$CDCl_3$, 365 MHz

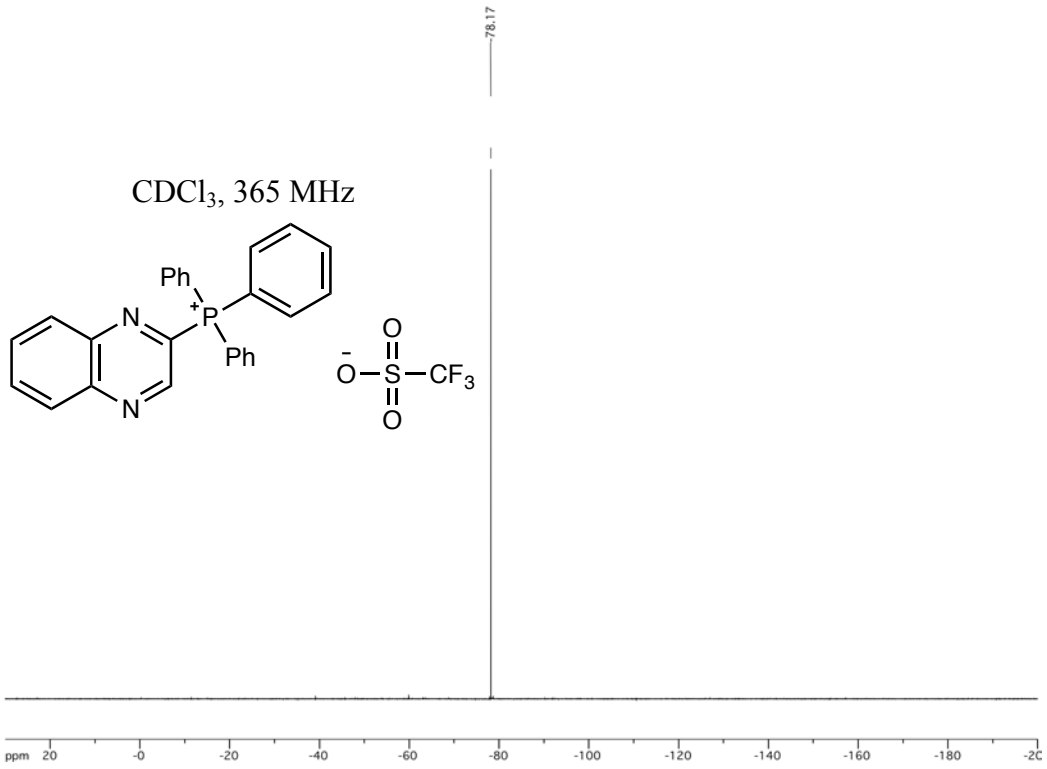


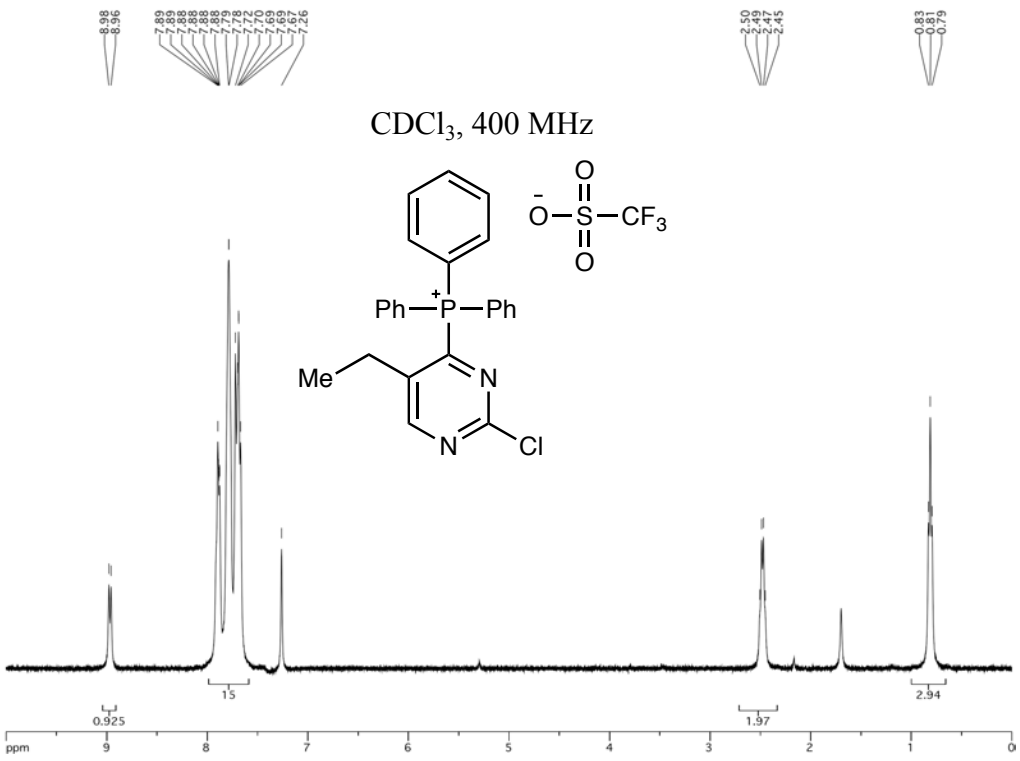

8.99
8.27
8.25
8.25
8.22
8.09
8.09
8.07
8.05
8.04
8.02
8.01
7.93
7.92
7.90
7.79
7.79
7.78
7.77
7.77
7.76
7.74
7.72
7.26
CDCl3, 400 MHz
Ph
P
Ph
N
N
O
S
CF3
O
O
1.99
3.24
0.815
2.4
12
ppm
9
8
7
6
5
4
3
2
1
0

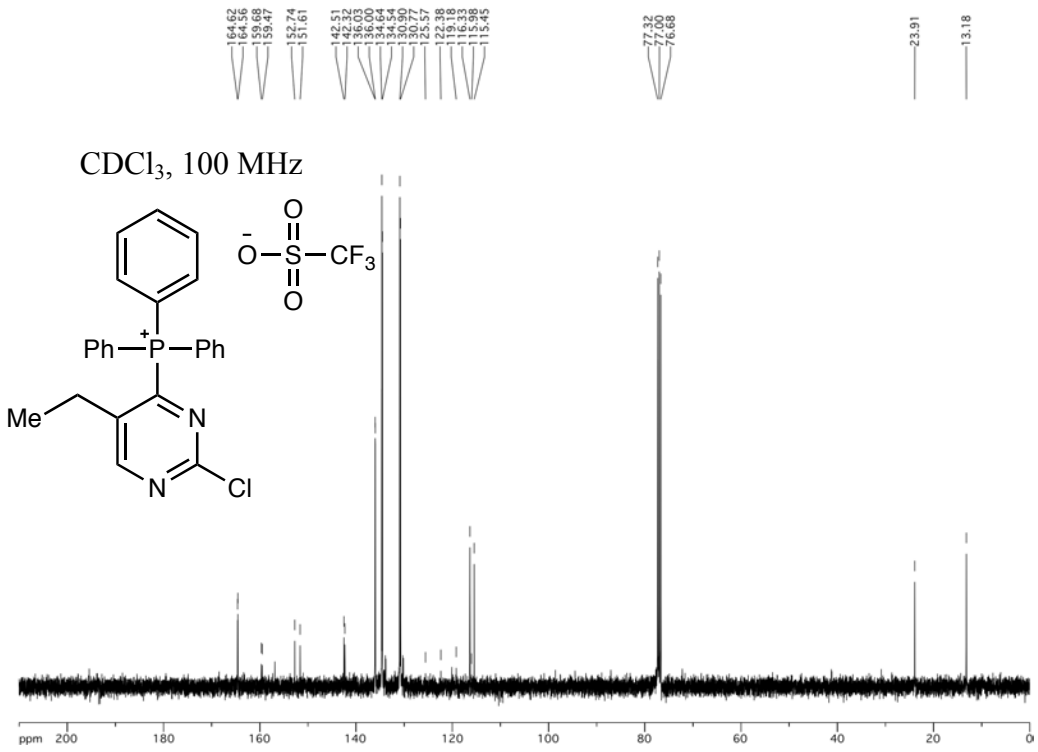

145.99
145.74
143.40
143.37
142.79
142.67
141.39
140.27
136.18
136.15
134.98
134.71
134.60
133.08
130.92
130.79
130.18
129.86
129.84
125.55
125.36
119.16
116.47
115.97
115.59
77.32
77.00
76.68
CDCl3, 100 MHz
Ph
P
Ph
N
N
O
O
S
O
CF3
ppm 200
180
160
140
120
100
80
60
40
20

$CDCl_3$, 162 MHz

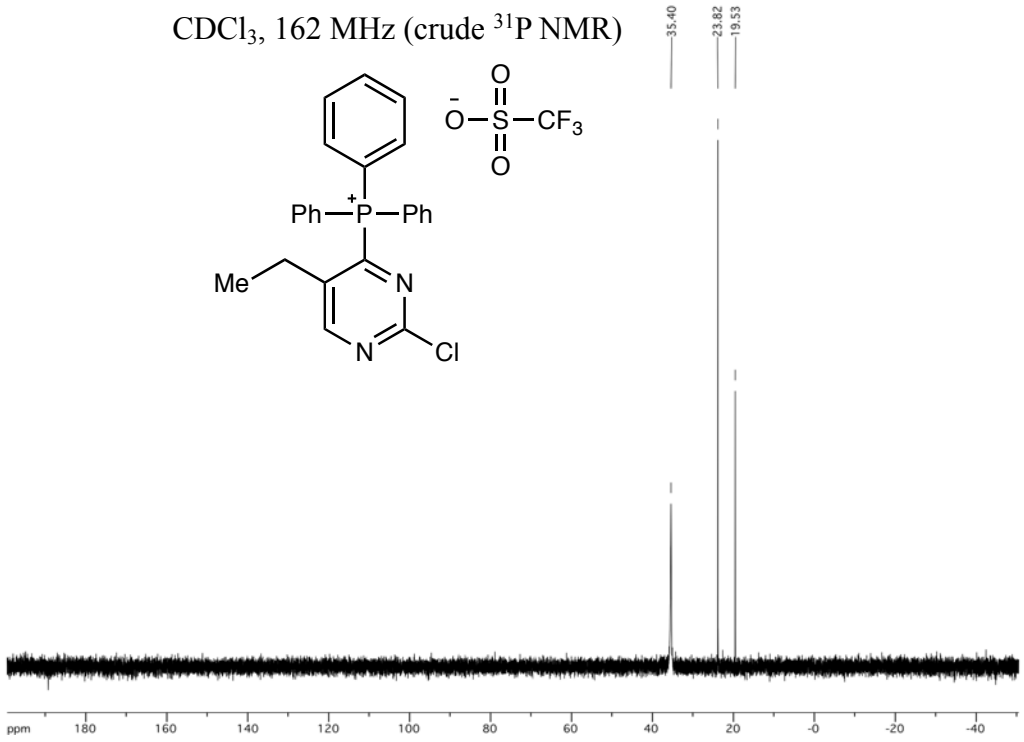



78.17
CDCl3, 365 MHz
Ph
N
P
Ph
N
O
O
S
CF3
O
ppm 20
-0
-20
-40
-60
-80
-100
-120
-140
-160
-180

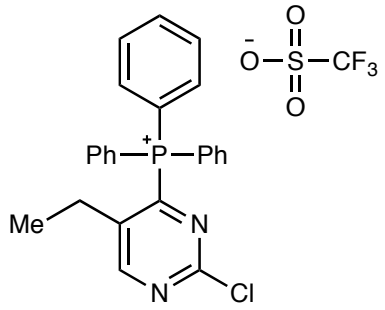

8.98
8.96
7.89
7.89
7.88
7.88
7.88
7.88
7.79
7.78
7.72
7.70
7.69
7.69
7.67
7.26
2.50
2.49
2.47
2.45
0.83
0.81
0.79
CDCl3, 400 MHz
O
O
S
CF3
Ph
P
Ph
Me
N
N
Cl
0.925
15
1.97
2.94
ppm
9
8
7
6
5
4
3
2
1
0


164.62
164.56
159.68
159.47
152.74
151.61
142.51
142.32
136.03
136.00
134.64
134.44
130.90
130.77
125.57
122.38
119.18
116.33
115.38
115.45
77.32
77.00
76.68
23.91
13.18
CDCl3, 100 MHz
O
O
S
CF3
O
Ph
P
Ph
Me
N
N
Cl
ppm 200 180 160 140 120 100 80 60 40 20 0

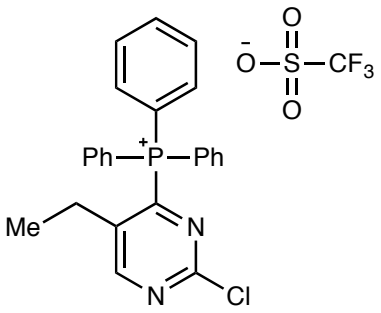
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

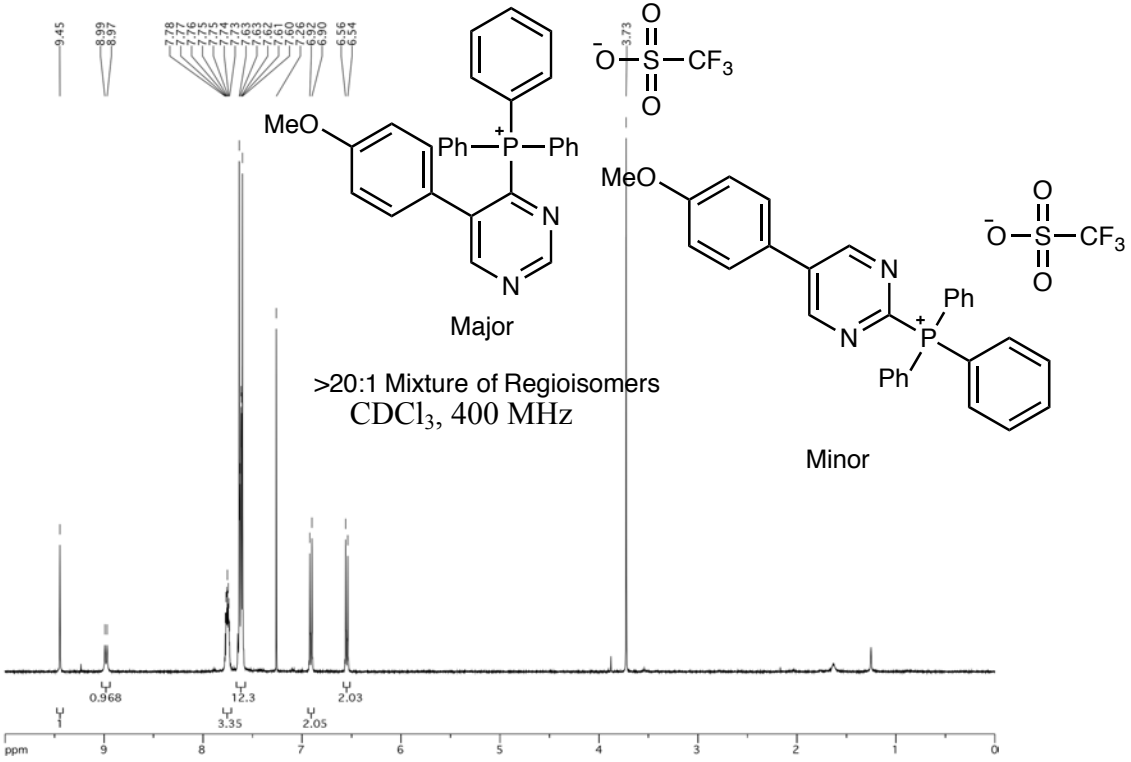


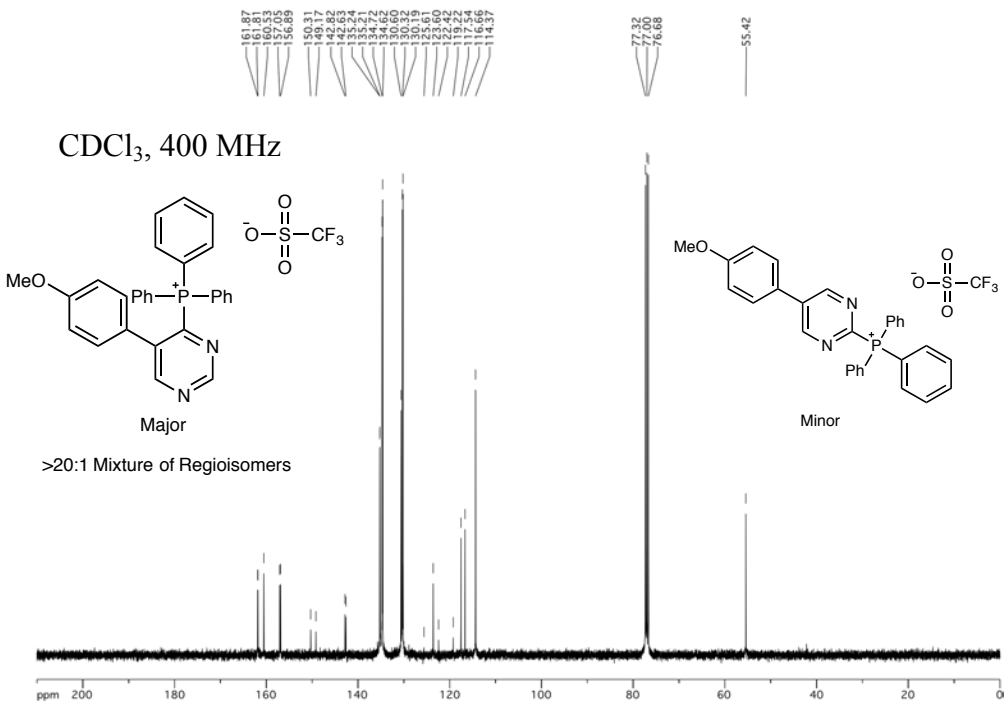
$CDCl_3$, 162 MHz

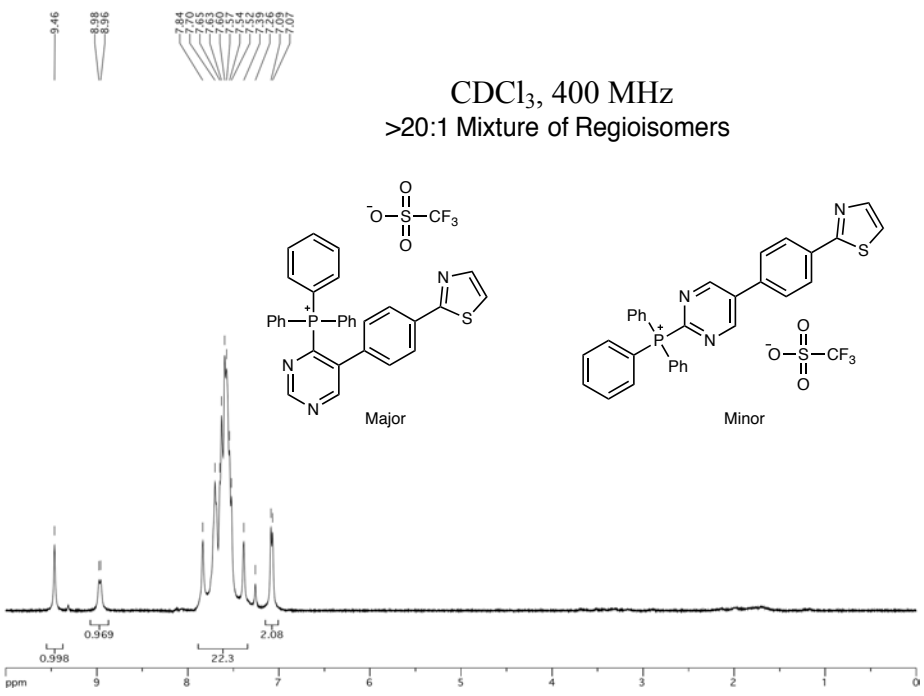


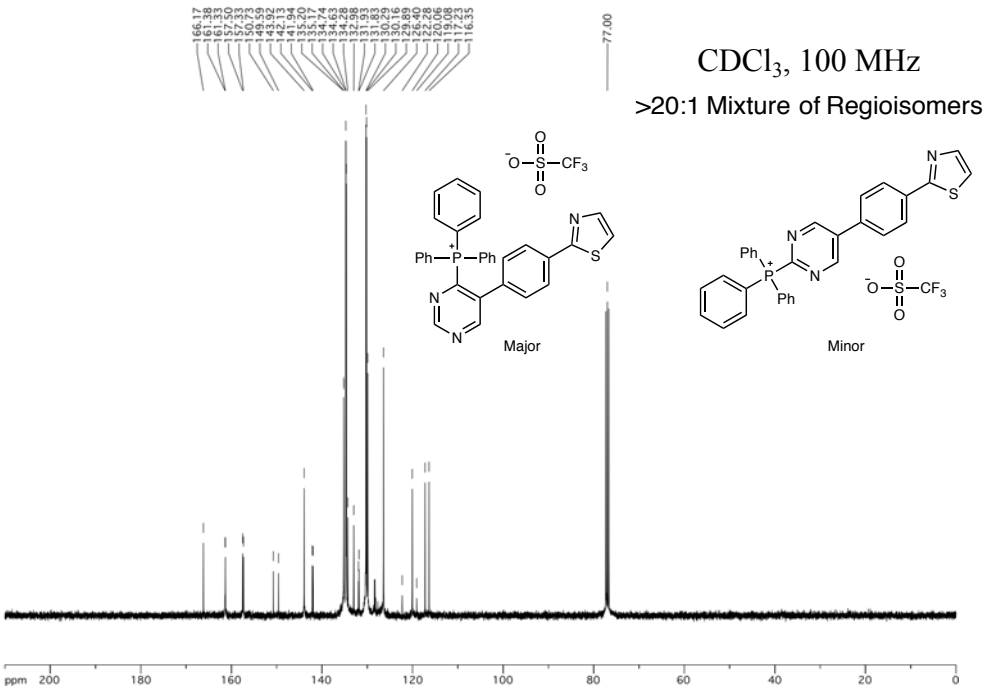
$CDCl_3$, 365 MHz




9.45
8.99
8.97
7.78
7.77
7.76
7.75
7.75
7.74
7.73
7.63
7.62
7.61
7.60
6.92
6.90
6.56
6.54
3.73
MeO
Ph
P
Ph
N
N
Major
>20:1 Mixture of Regioisomers
CDCl3, 400 MHz
MeO
N
N
Ph
P
Ph
Ph
Minor
O
S
CF3
0.968
12.3
2.03
1
3.35
2.05
ppm
9
8
7
6
5
4
3
2
1
0

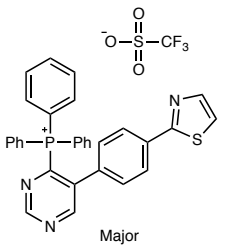

161.87
161.81
160.53
157.05
156.89
150.31
149.17
142.82
142.65
135.24
135.21
134.72
134.66
130.60
130.32
130.19
129.96
123.60
122.42
119.22
117.64
116.66
114.37
77.32
77.00
76.68
55.42
CDCl3, 400 MHz
MeO
Ph
P
Ph
N
N
O
O
S
O
CF3
Major
>20:1 Mixture of Regioisomers
MeO
N
N
Ph
P
Ph
O
O
S
O
CF3
Minor
ppm 200 180 160 140 120 100 80 60 40 20 0


9.46
8.98
8.96
7.84
7.70
7.65
7.63
7.60
7.57
7.54
7.52
7.39
7.36
7.09
7.07
CDCl3, 400 MHz
>20:1 Mixture of Regioisomers
Major
Minor
0.998
0.969
22.3
2.08
ppm

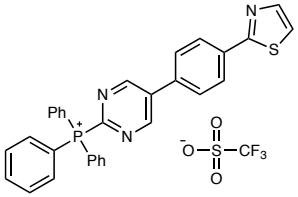

166.17
161.38
161.33
157.50
157.23
150.73
149.59
143.92
143.73
141.34
135.20
135.17
134.74
134.65
134.28
132.98
131.83
131.63
130.29
130.16
128.89
128.60
122.28
120.06
119.08
117.23
116.35
77.00
CDCl3, 100 MHz
>20:1 Mixture of Regioisomers
Major
Minor
ppm 200 180 160 140 120 100 80 60 40 20 0

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

>20:1 Mixture of Regioisomers



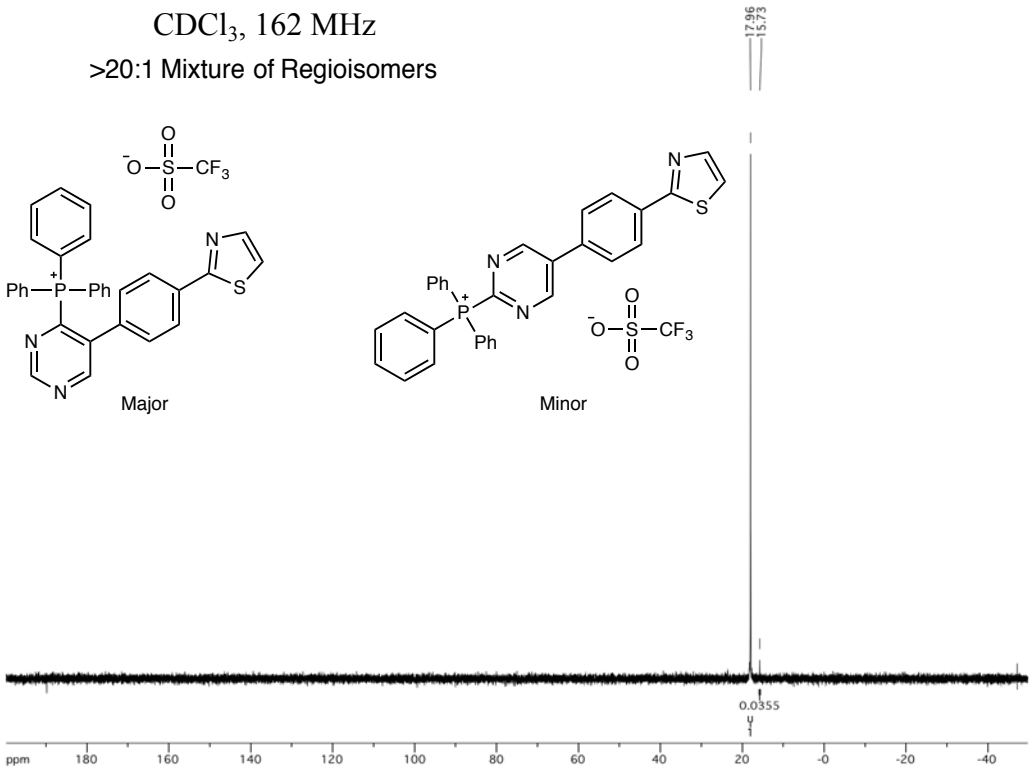
Major

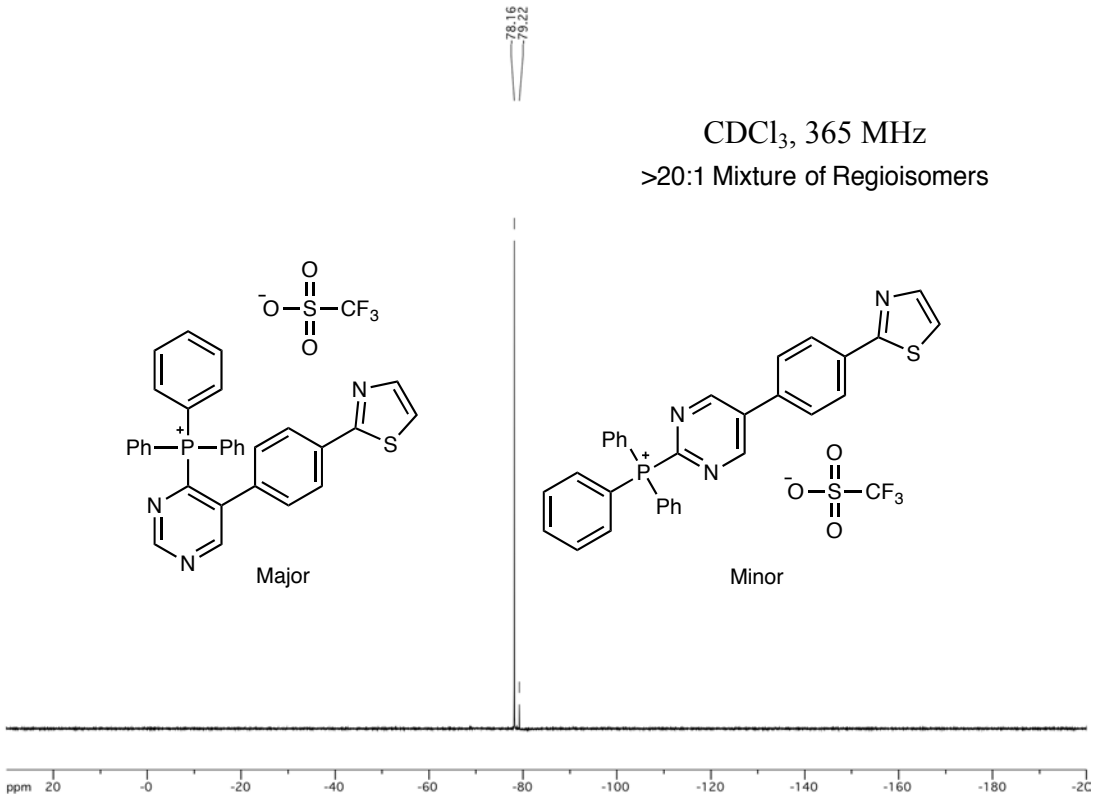


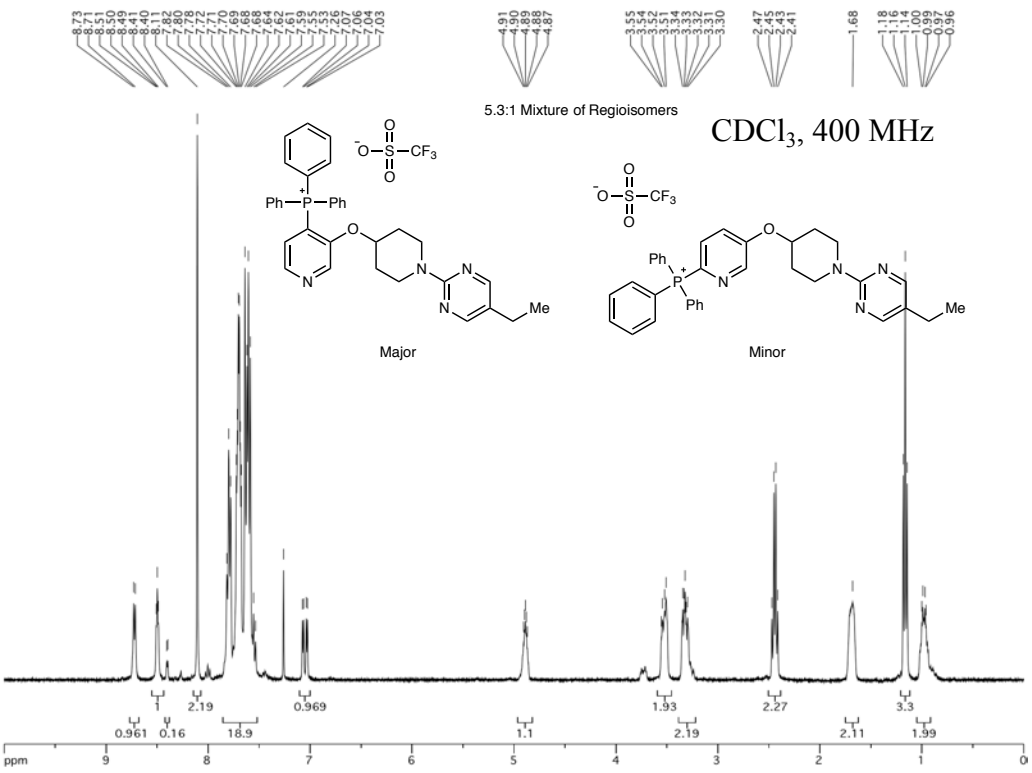
Minor

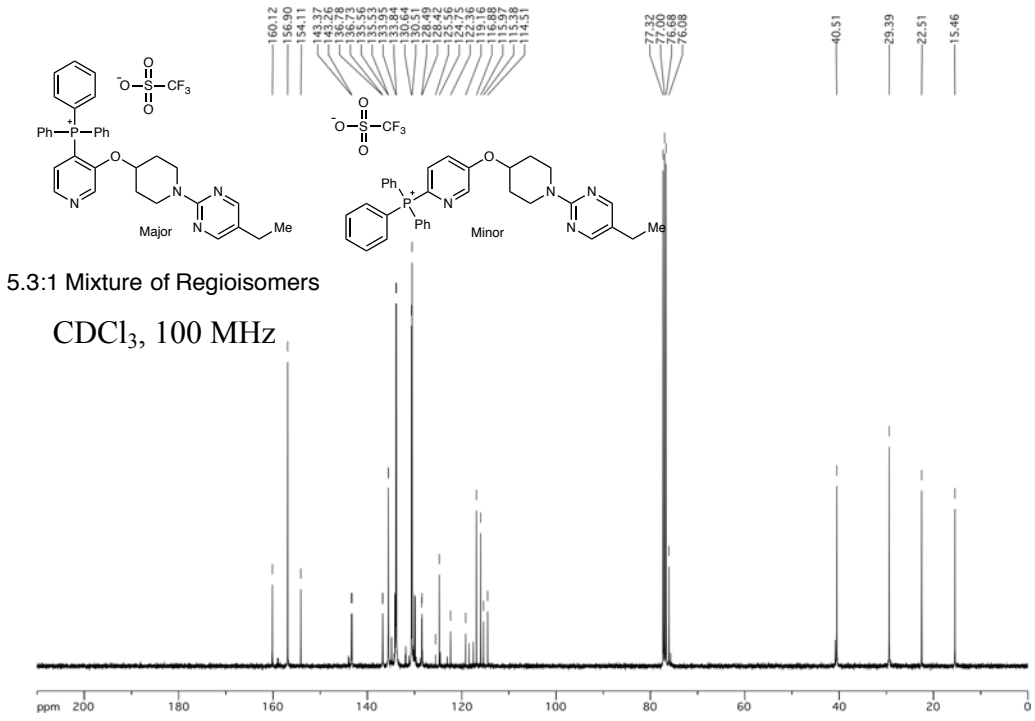
$CDCl_3$, 162 MHz

>20:1 Mixture of Regioisomers

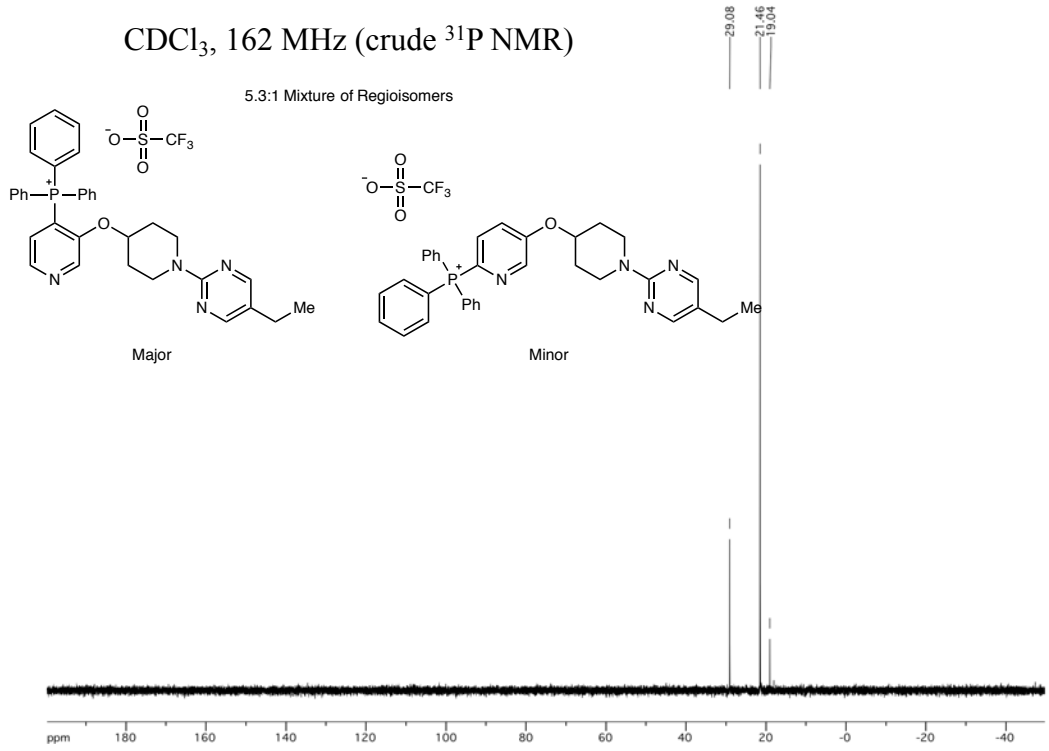


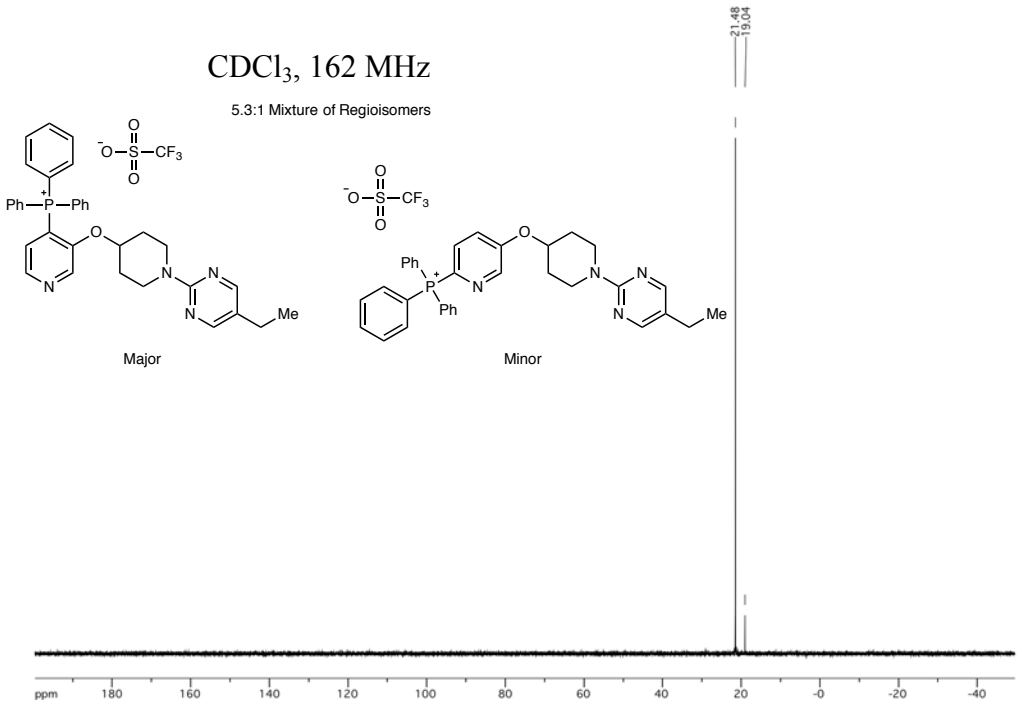

78.16
79.22
CDCl3, 365 MHz
>20:1 Mixture of Regioisomers
Major
Minor
ppm 20 -0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -20

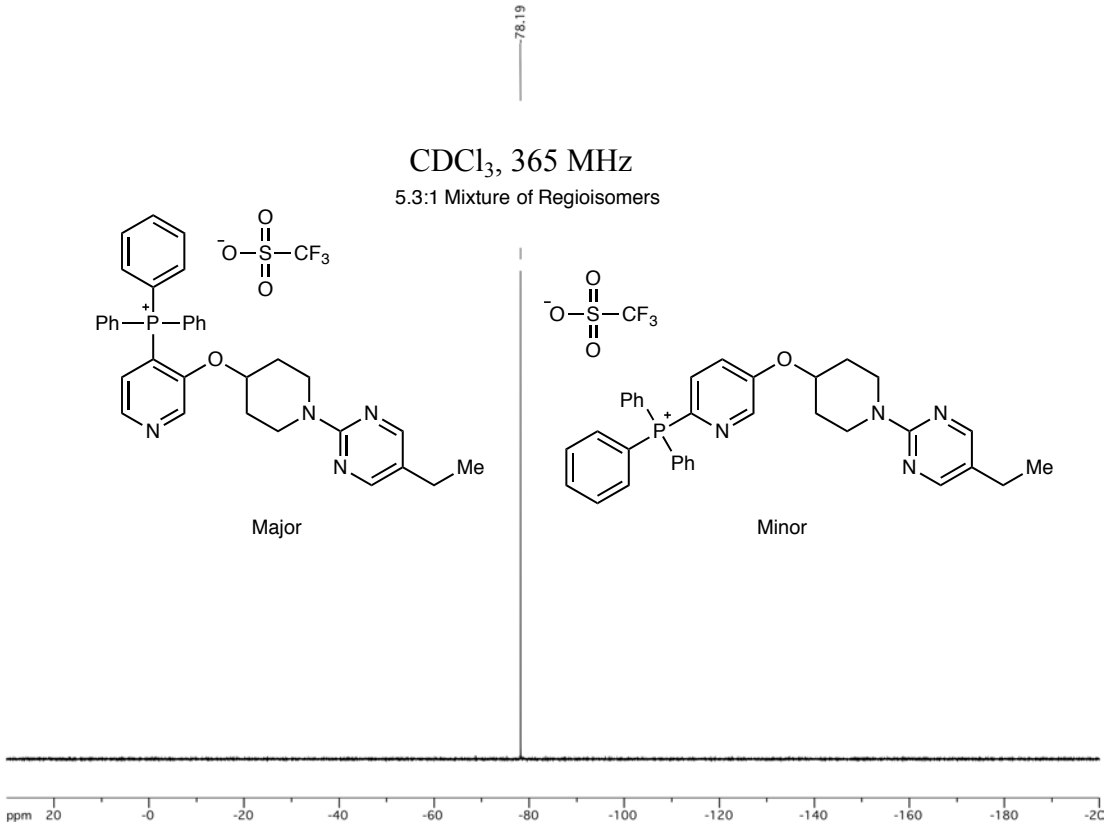

5.3:1 Mixture of Regioisomers
CDCl3, 400 MHz
Major
Minor
ppm

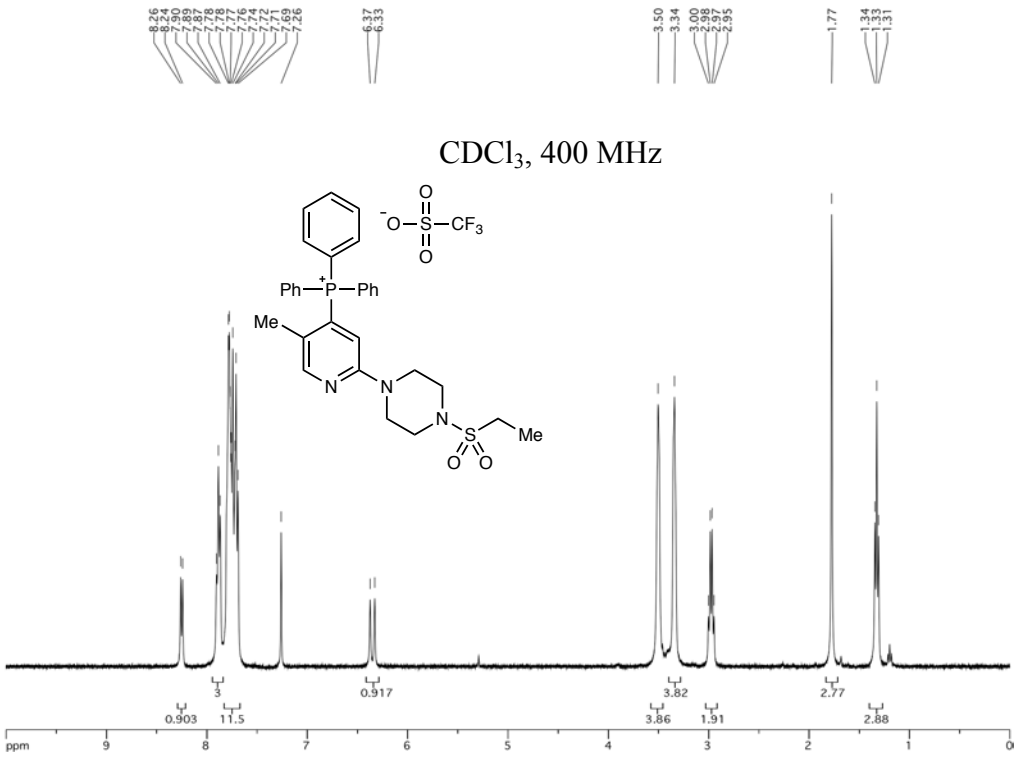

160.12
156.90
154.11
143.37
143.26
136.78
136.73
135.76
135.53
133.95
133.84
130.64
130.51
128.49
128.42
124.56
124.47
122.36
119.16
116.88
115.97
115.38
114.51
77.32
77.00
76.68
76.08
40.51
29.39
22.51
15.46
Ph
P
Ph
O
N
N
N
Me
Major
Minor
5.3:1 Mixture of Regioisomers
CDCl3, 100 MHz
ppm 200
180
160
140
120
100
80
60
40
20
0

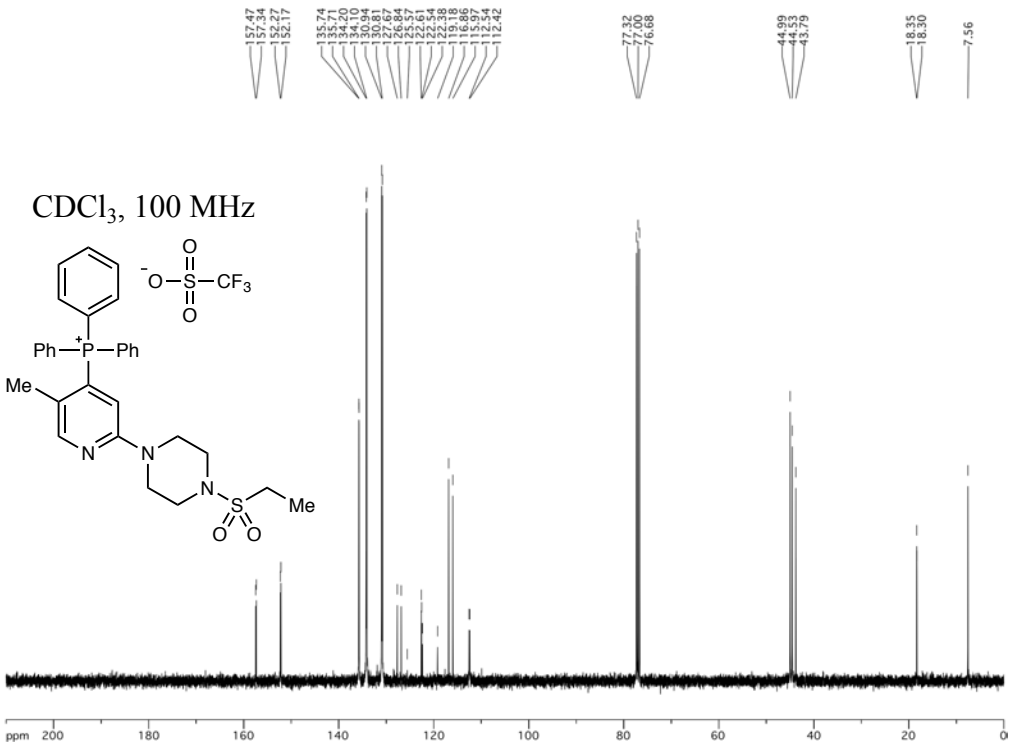
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



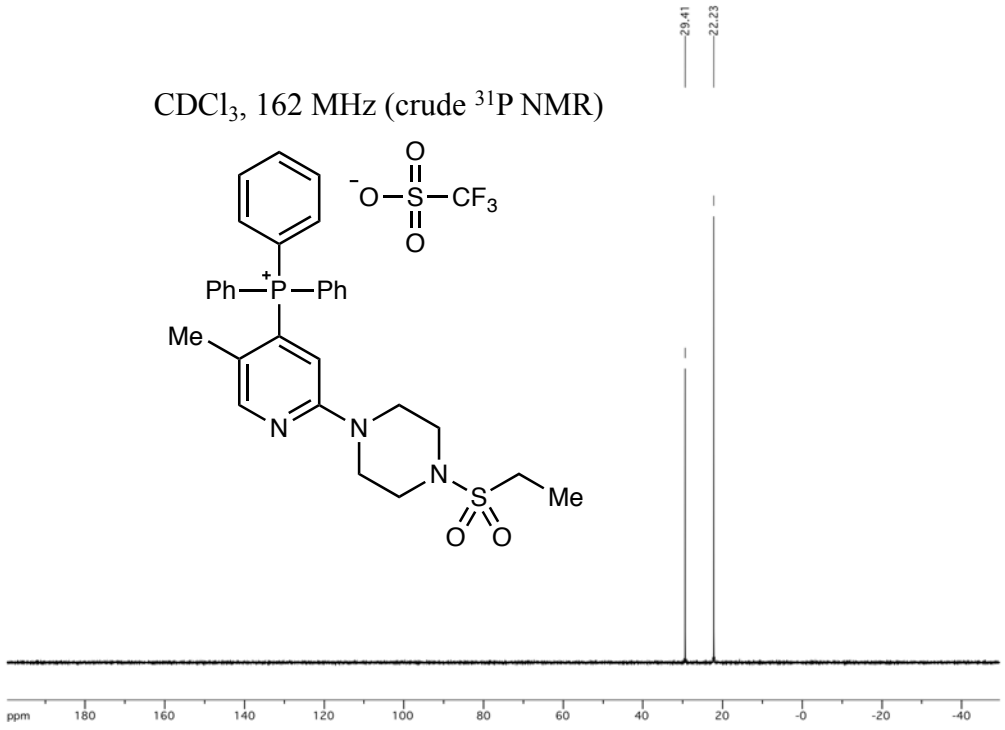

CDCl3, 162 MHz
5.3:1 Mixture of Regioisomers
Major
Minor
21.48
19.04
ppm
180
160
140
120
100
80
60
40
20
-0
-20
-40


78.19
CDCl3, 365 MHz
5.3:1 Mixture of Regioisomers
Major
Minor
ppm 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -20

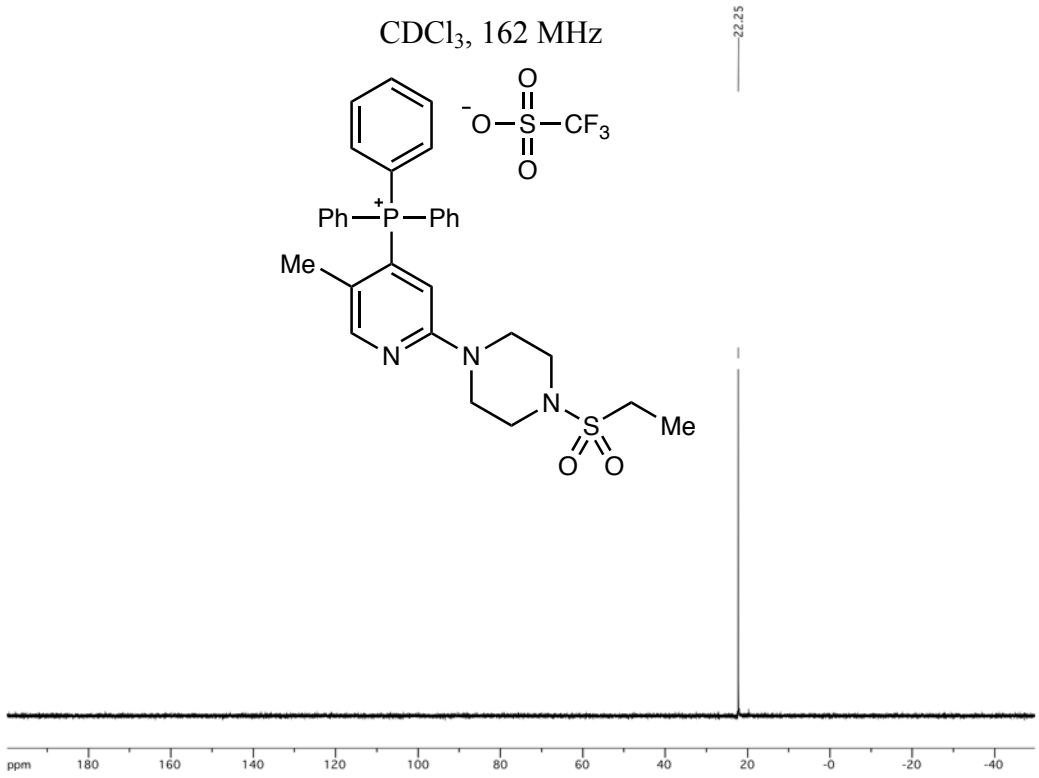

8.26
8.24
7.90
7.89
7.87
7.78
7.77
7.76
7.74
7.72
7.71
7.69
7.26
6.37
6.33
3.50
3.34
3.00
2.98
2.97
2.95
1.77
1.34
1.33
1.31
CDCl3, 400 MHz
Ph
P
Ph
Me
N
N
N
S
Me
O
O
O
O
S
CF3
3
0.903
11.5
0.917
3.82
3.86
1.91
2.77
2.88
ppm
9
8
7
6
5
4
3
2
1
0

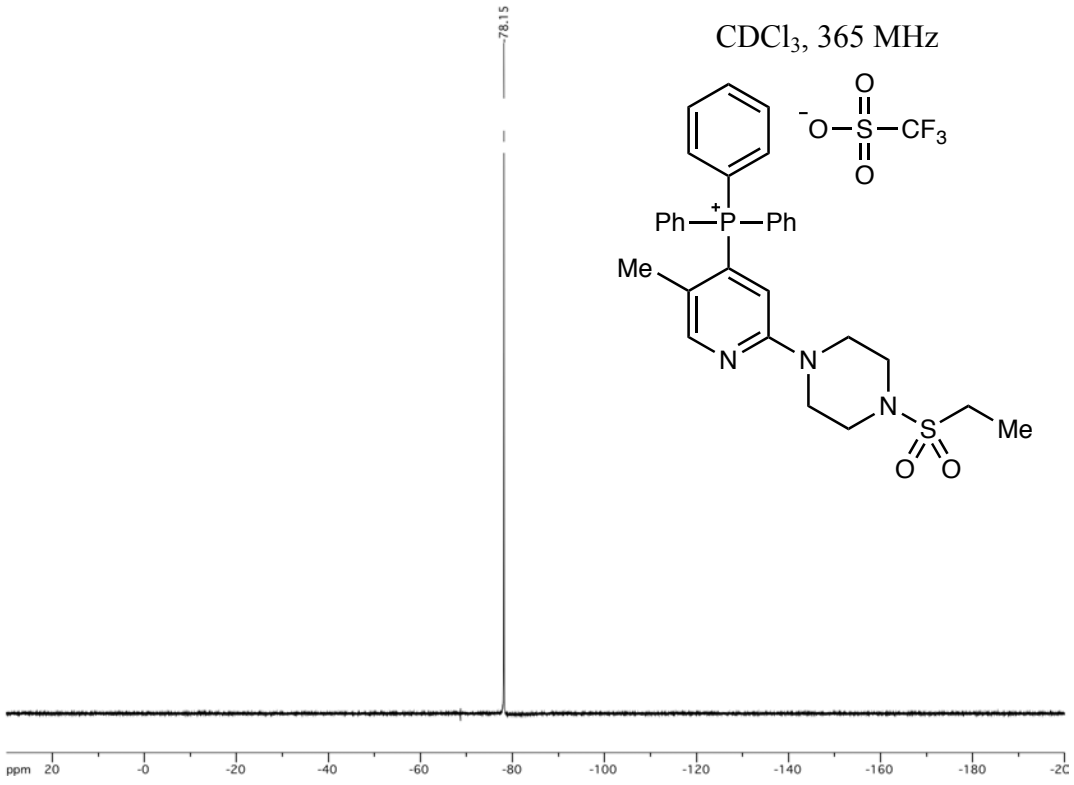

157.47
157.34
152.27
152.17
135.74
135.71
134.20
134.10
130.94
130.81
127.67
127.64
126.57
122.61
122.54
122.38
122.18
116.86
115.97
112.54
112.42
77.32
77.00
76.68
44.99
44.53
43.79
18.35
18.30
7.56
CDCl3, 100 MHz
ppm 200
180
160
140
120
100
80
60
40
20
0

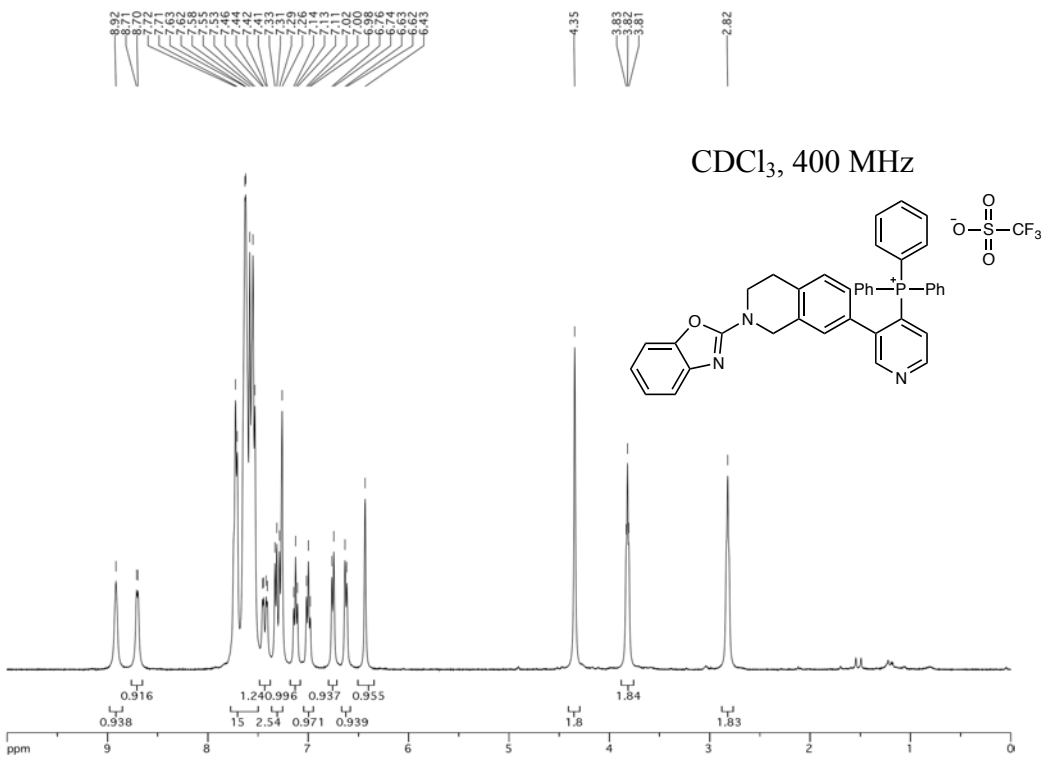
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

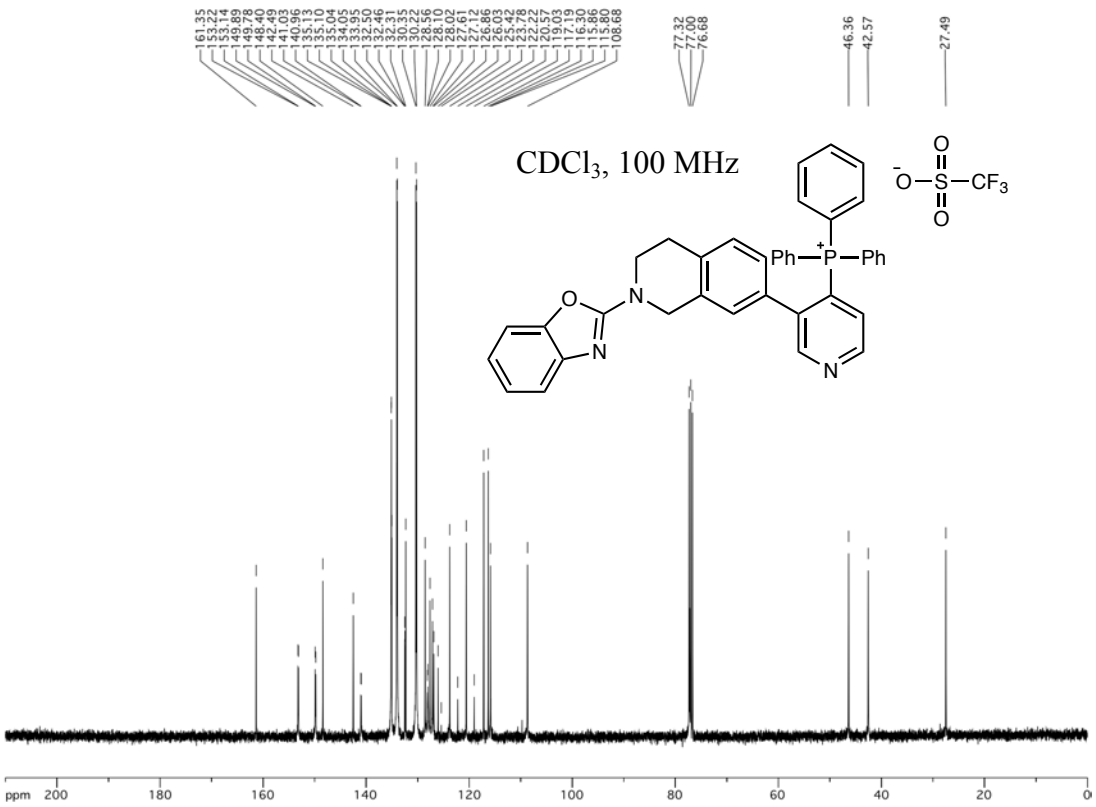


$CDCl_3$, 162 MHz

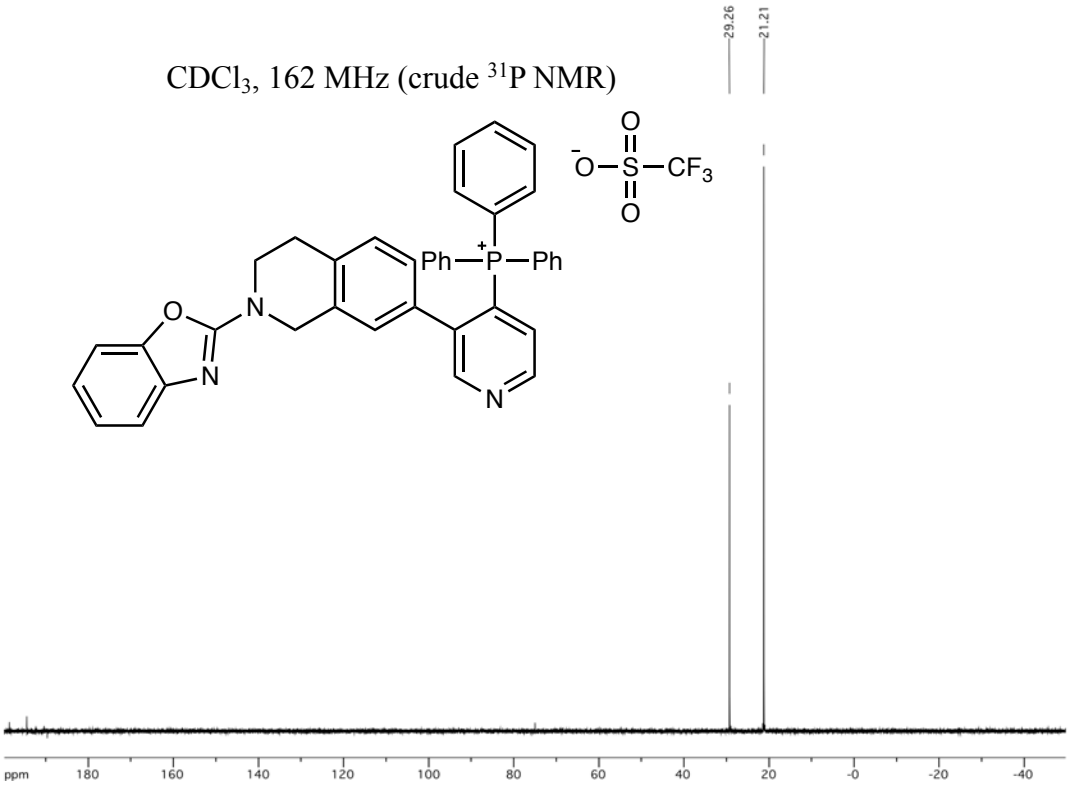



78.15
CDCl3, 365 MHz
O
O
S
CF3
O
Ph
P
Ph
Me
N
N
N
S
Me
O
O
ppm 20
-0
-20
-40
-60
-80
-100
-120
-140
-160
-180

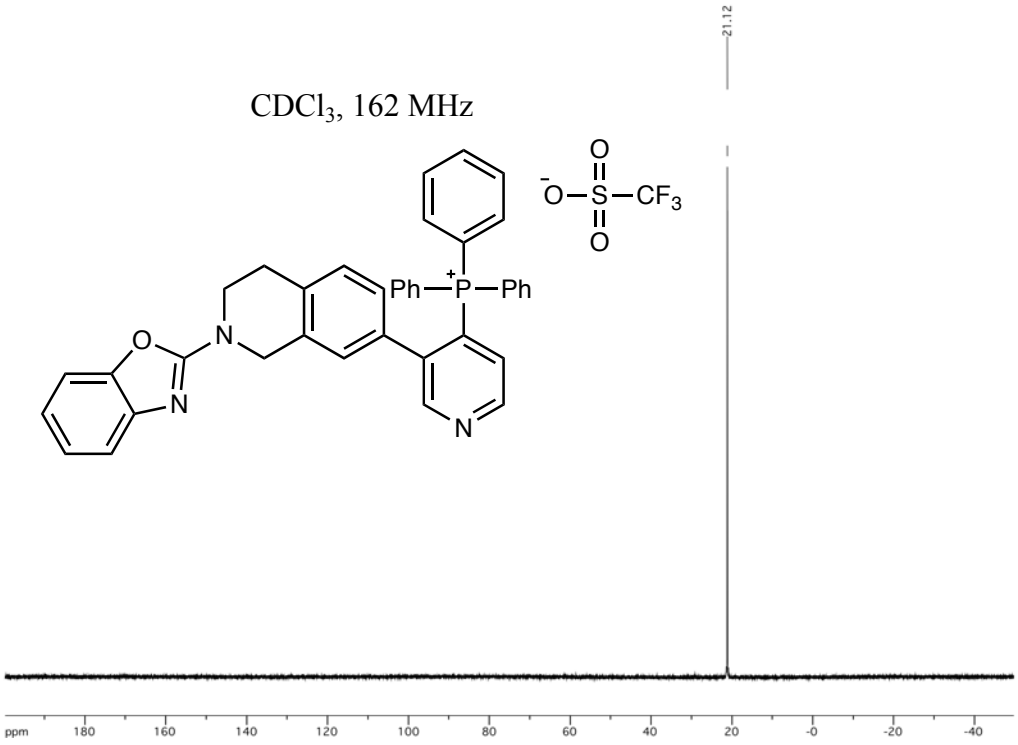

8.92
8.71
8.70
7.72
7.71
7.63
7.62
7.58
7.55
7.53
7.46
7.44
7.42
7.41
7.33
7.31
7.29
7.26
7.14
7.13
7.11
7.02
7.00
6.98
6.76
6.74
6.63
6.62
6.43
4.35
3.83
3.82
3.81
2.82
CDCl3, 400 MHz
Ph
P
Ph
O
N
O
N
N
O
S
CF3
0.916
1.24
0.996
0.937
0.955
1.84
0.938
15
2.54
0.971
0.939
1.8
1.83
ppm
9
8
7
6
5
4
3
2
1

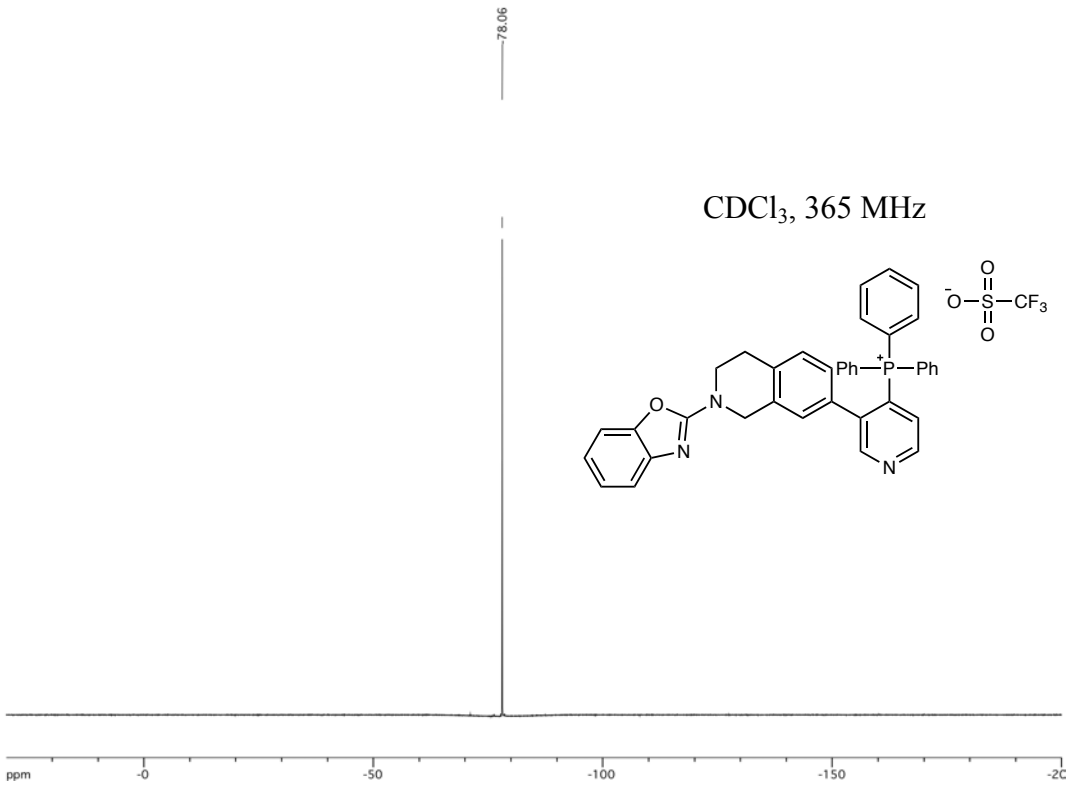

161.35
153.22
153.14
149.89
149.78
148.49
147.49
141.03
140.96
135.13
135.10
135.04
134.95
133.95
132.50
132.46
132.31
130.35
130.22
128.26
128.10
128.02
127.61
127.12
126.86
126.03
124.42
123.78
122.22
120.57
119.03
117.19
116.10
115.86
115.80
108.68
77.32
77.00
76.68
46.36
42.57
27.49
CDCl3, 100 MHz
Ph
P
Ph
O
N
O
N
N
O
S
CF3
ppm 200
180
160
140
120
100
80
60
40
20

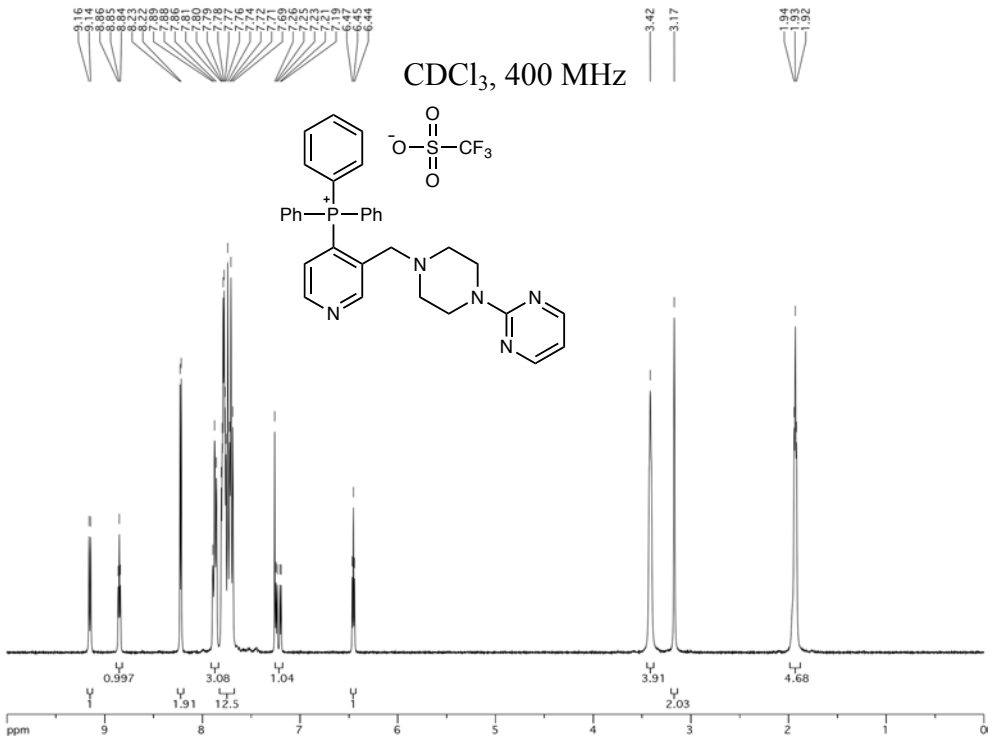
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

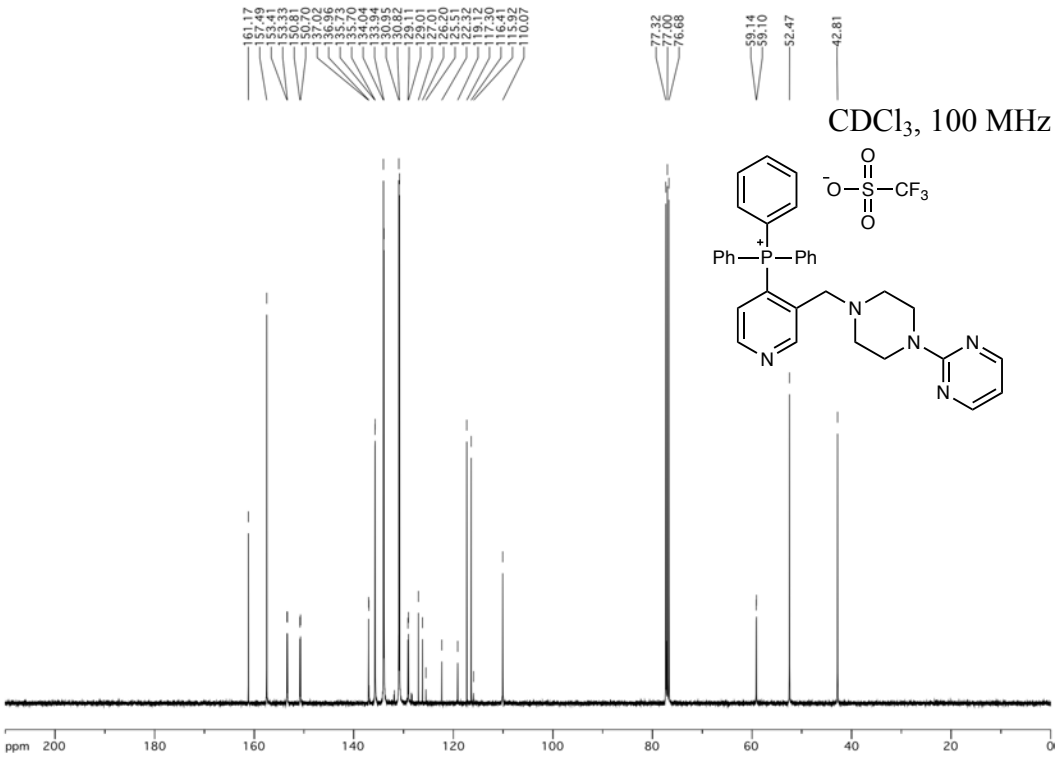


$CDCl_3$, 162 MHz

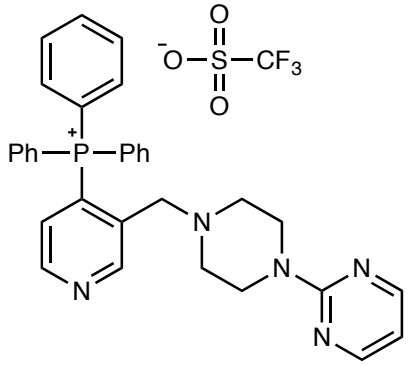



78.06
CDCl3, 365 MHz
Ph
P
Ph
O
S
CF3
O
N
N
N
ppm
-0
-50
-100
-150
-20

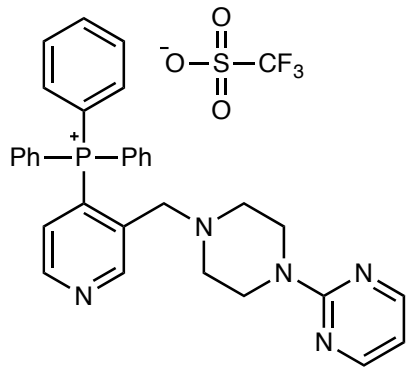

CDCl3, 400 MHz
Ph—P—Ph
O—S—CF3
0.997
3.08
1.04
3.91
4.68
1.91
12.5
2.03
ppm


161.17
157.49
153.41
153.33
150.81
150.70
137.02
136.96
135.73
135.70
134.04
134.04
130.94
130.82
129.11
129.01
127.01
127.00
126.51
122.32
119.12
117.30
116.41
116.32
110.07
77.32
77.00
76.68
59.14
59.10
52.47
42.81
CDCl3, 100 MHz
ppm 200 180 160 140 120 100 80 60 40 20 0

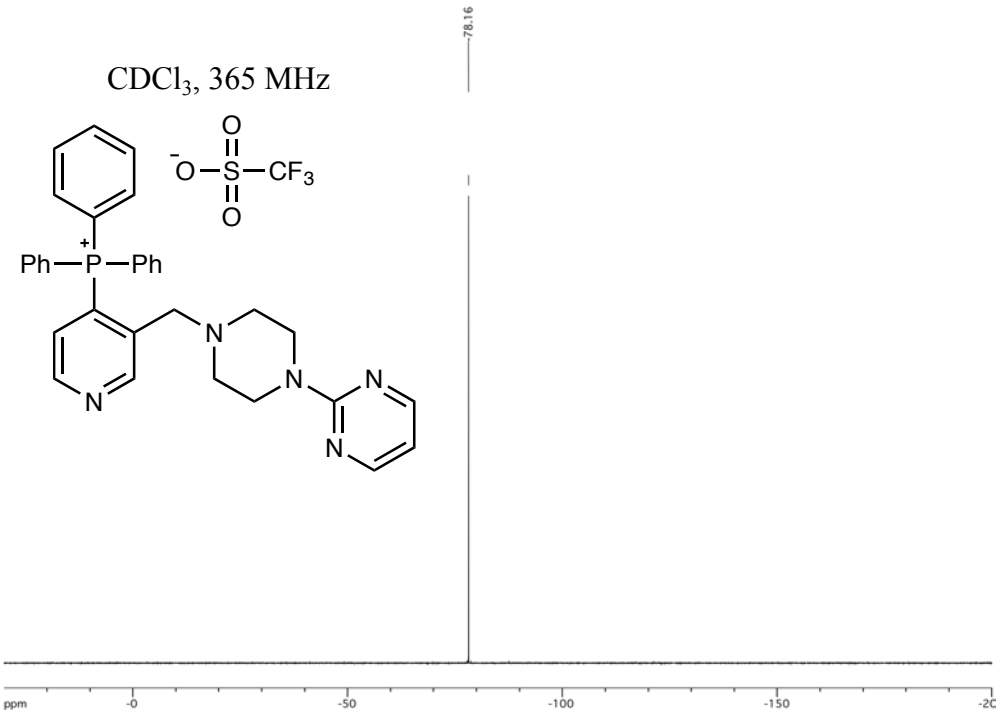
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

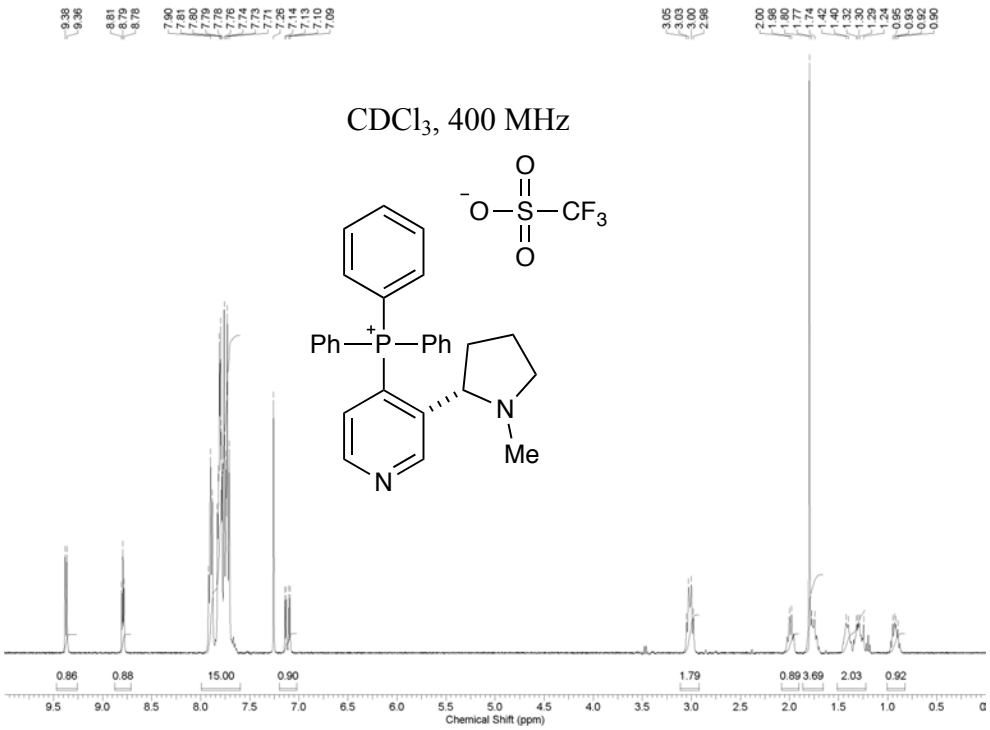


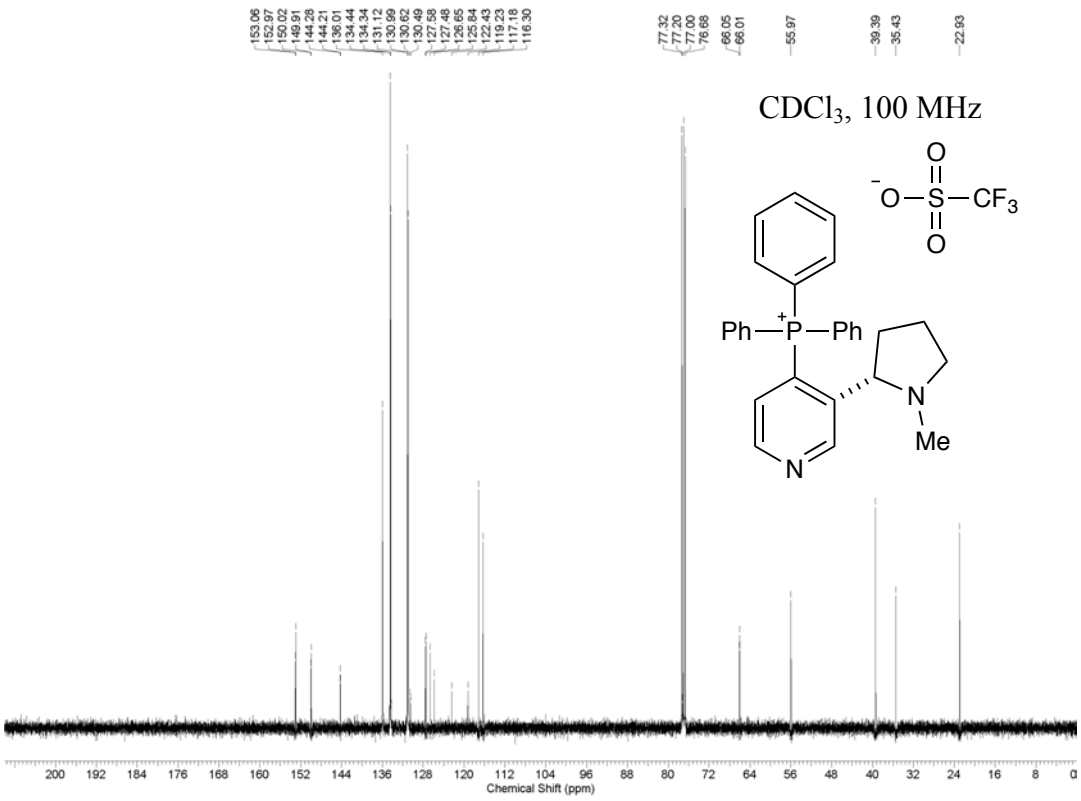
$CDCl_3$, 162 MHz

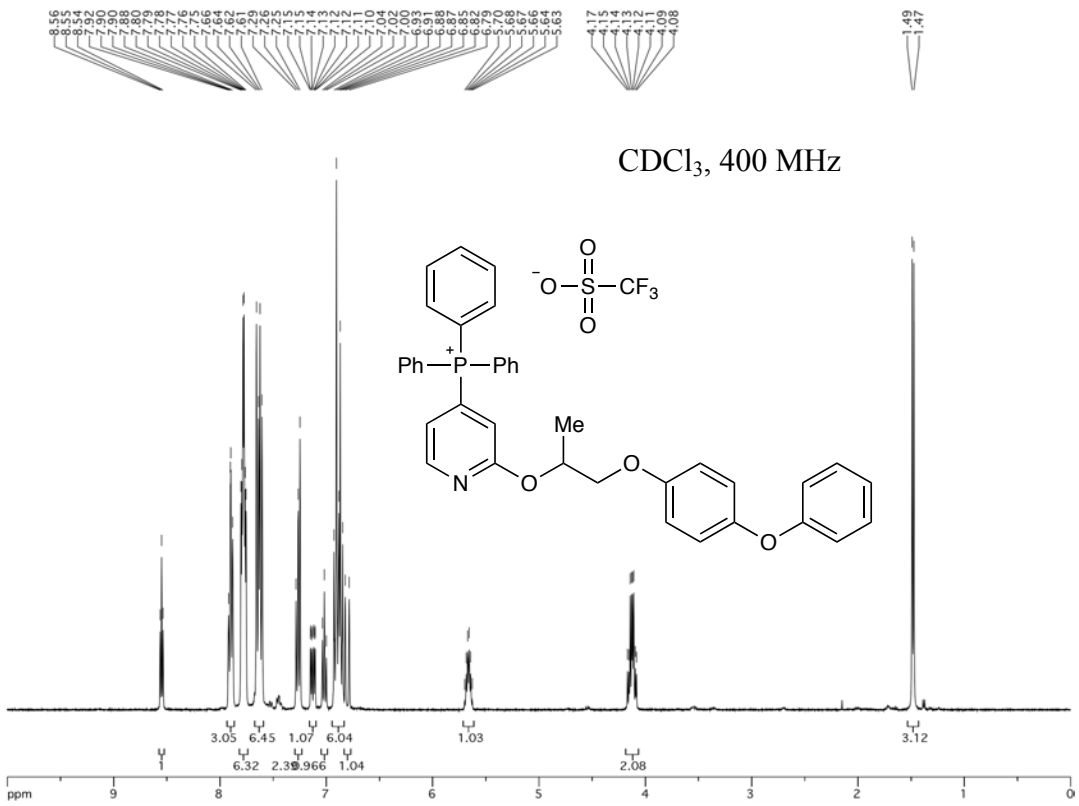


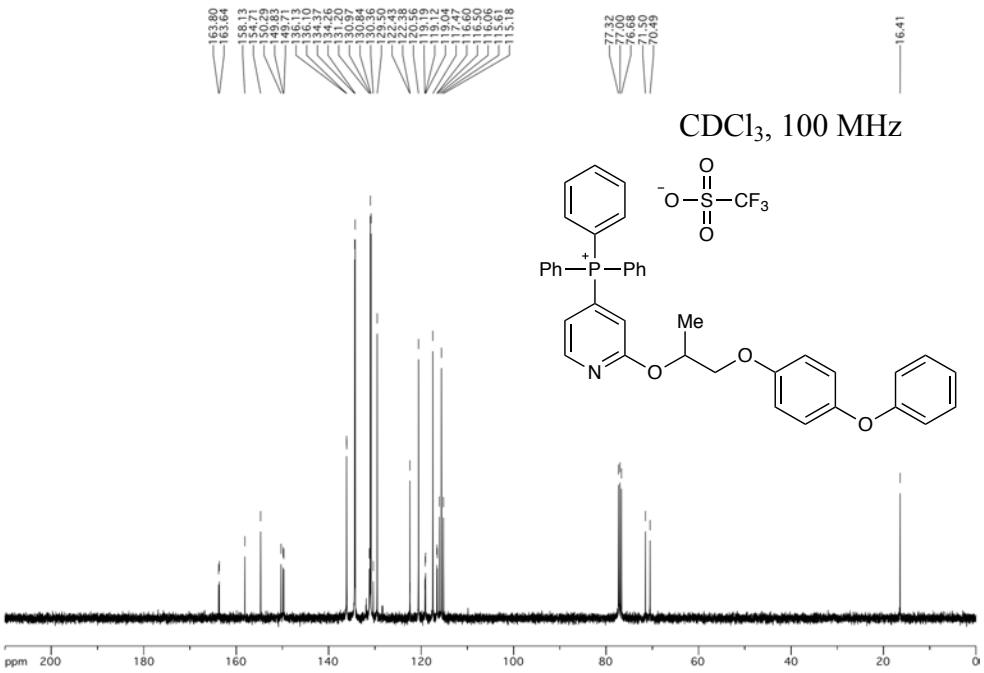
$CDCl_3$, 365 MHz



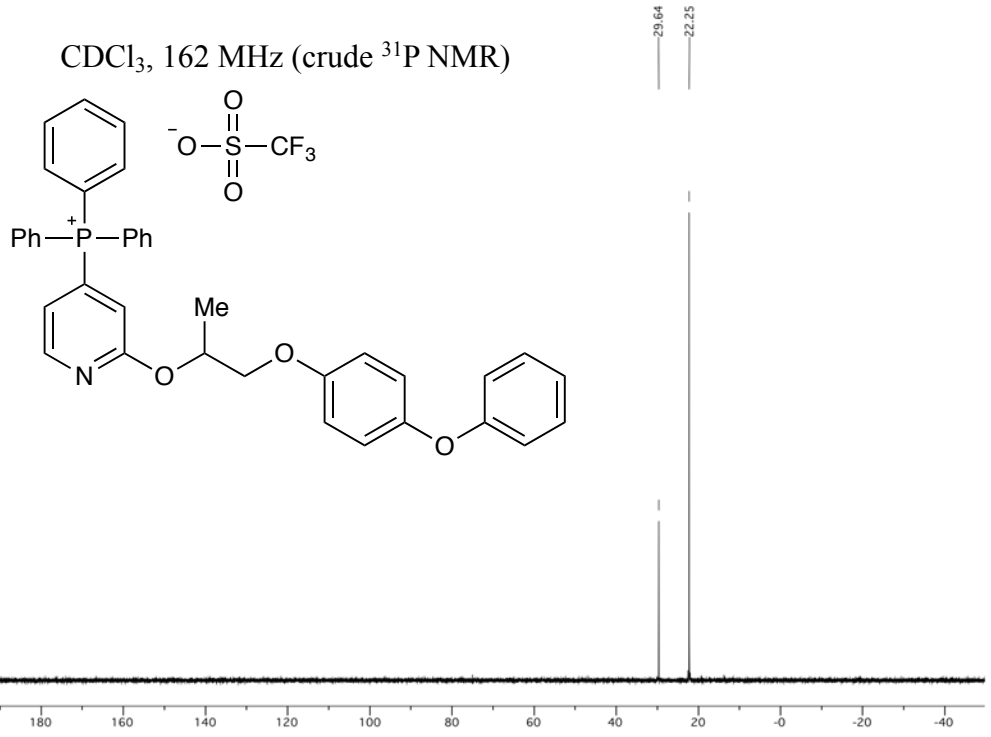

9.38
9.36
8.81
8.79
8.78
7.90
7.81
7.80
7.79
7.78
7.76
7.74
7.73
7.71
7.26
7.14
7.13
7.10
7.09
3.05
3.03
3.00
2.98
2.00
1.98
1.80
1.77
1.74
1.42
1.40
1.32
1.30
1.29
1.24
0.95
0.93
0.92
0.90
CDCl3, 400 MHz
O
O−S−CF3
O
Ph−P−Ph
N
Me
N
0.86
0.88
15.00
0.90
1.79
0.89
3.69
2.03
0.92
Chemical Shift (ppm)


153.06
152.97
150.02
149.91
144.28
144.21
136.01
134.44
134.34
131.12
130.99
130.62
130.49
127.58
127.48
126.65
125.64
122.43
119.23
117.18
116.30
77.32
77.20
77.00
76.68
66.05
66.01
55.97
39.39
35.43
22.93
CDCl3, 100 MHz
Ph
P
Ph
N
Me
N
O
S
CF3
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8
Chemical Shift (ppm)

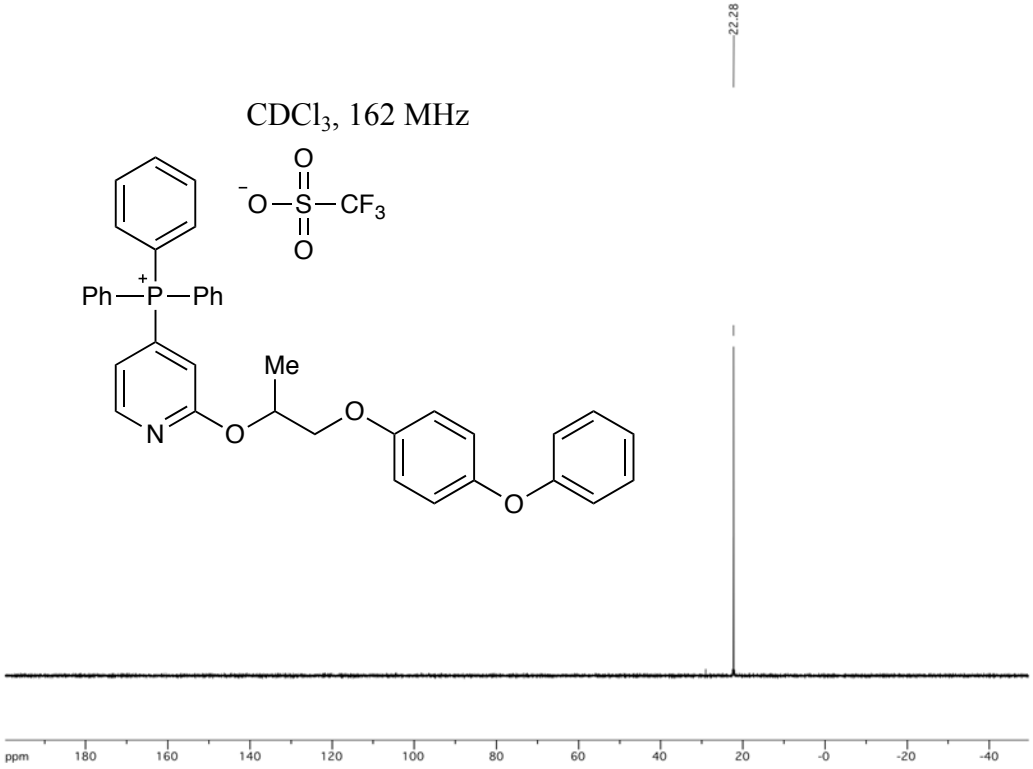

8.56 8.55 8.54 7.92 7.90 7.90 7.88 7.80 7.79 7.78 7.77 7.76 7.66 7.64 7.62 7.61 7.29 7.26 7.25 7.15 7.15 7.14 7.13 7.12 7.11 7.10 7.04 7.02 7.00 6.93 6.91 6.88 6.87 6.85 6.82 6.79 5.70 5.68 5.67 5.66 5.64 5.63
4.17 4.15 4.14 4.13 4.12 4.11 4.09 4.08
1.49 1.47
CDCl3, 400 MHz
Ph P Ph
O S CF3
Me
N O O O
3.05 6.45 1.07 6.04 1.03 3.12
1 6.32 2.39 0.966 1.04 2.08
ppm 9 8 7 6 5 4 3 2 1 0

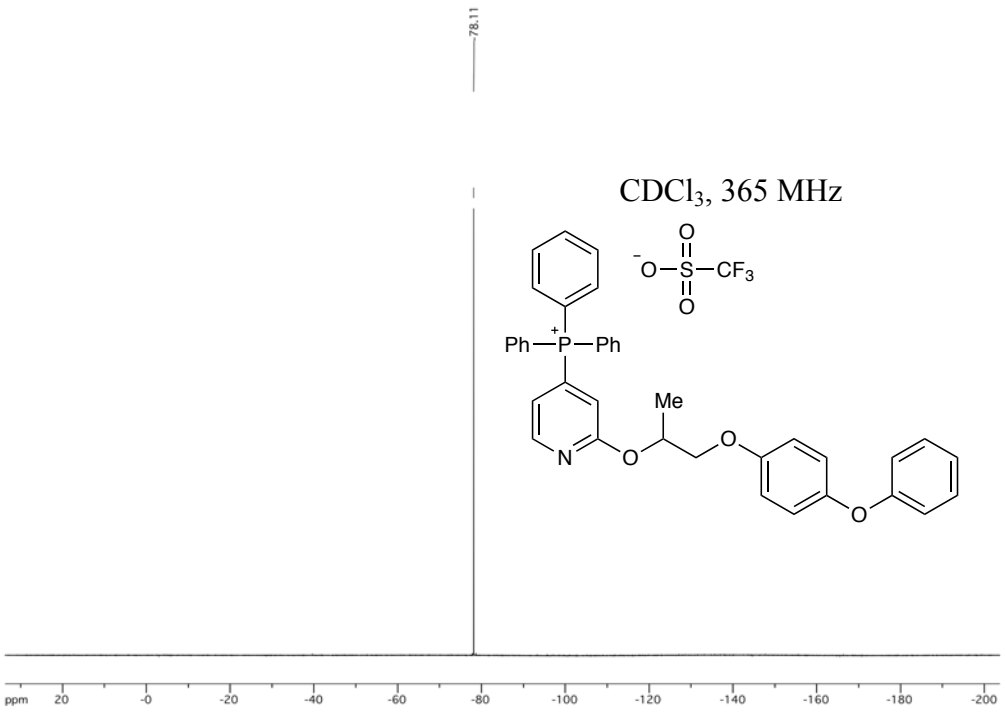

163.80
163.64
158.13
154.71
150.29
149.83
149.71
136.13
136.10
134.37
134.26
131.20
130.97
130.84
130.16
129.50
122.43
122.38
120.56
119.19
119.12
119.04
117.47
116.67
116.50
116.06
115.61
115.18
77.32
77.00
76.68
71.50
70.49
16.41
CDCl3, 100 MHz
Ph
P
Ph
Me
N
O
O
O
O
O
S
CF3
ppm 200
180
160
140
120
100
80
60
40
20

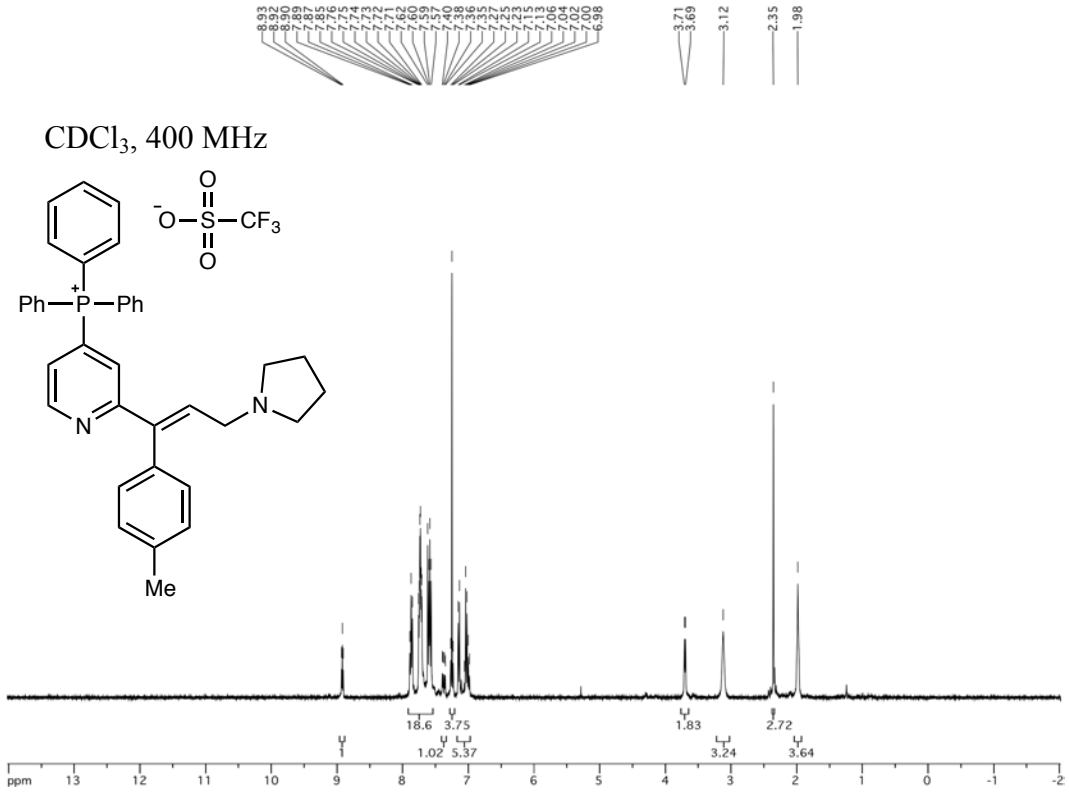
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

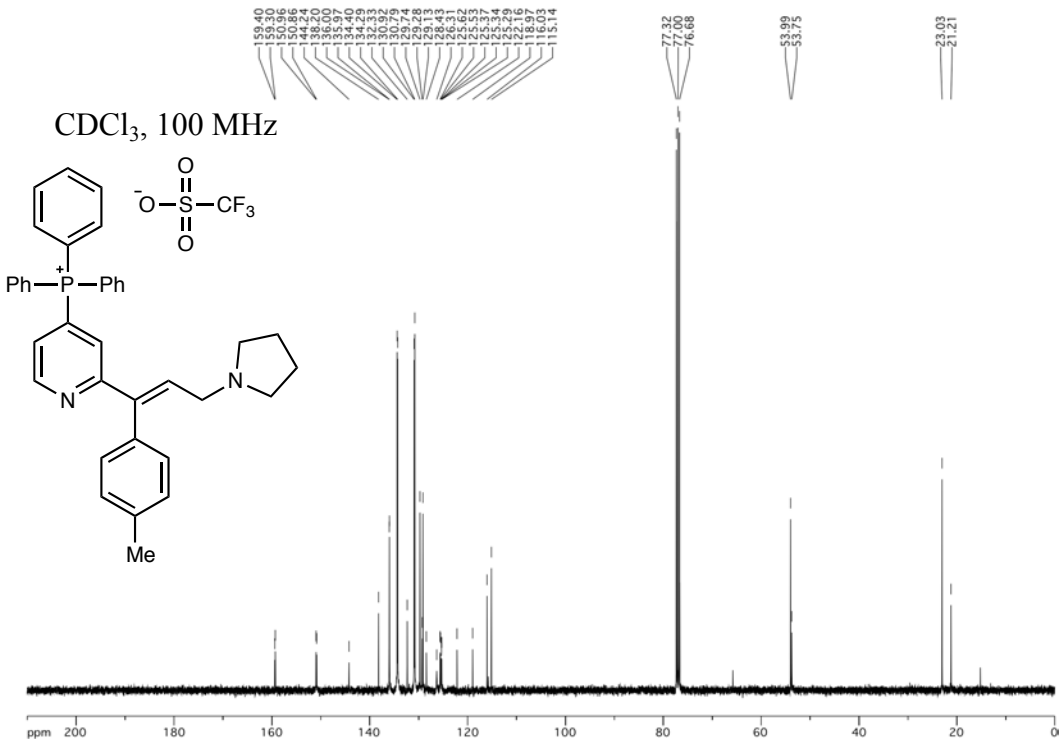


$CDCl_3$, 162 MHz

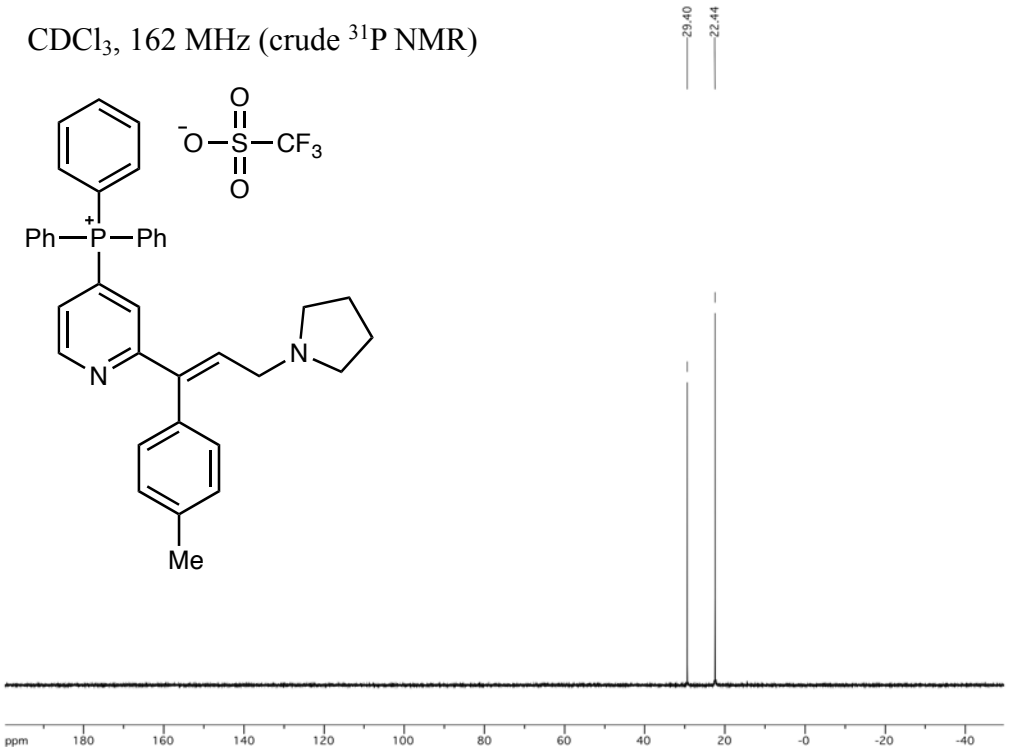



78.11
CDCl3, 365 MHz
ppm
20
-0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200

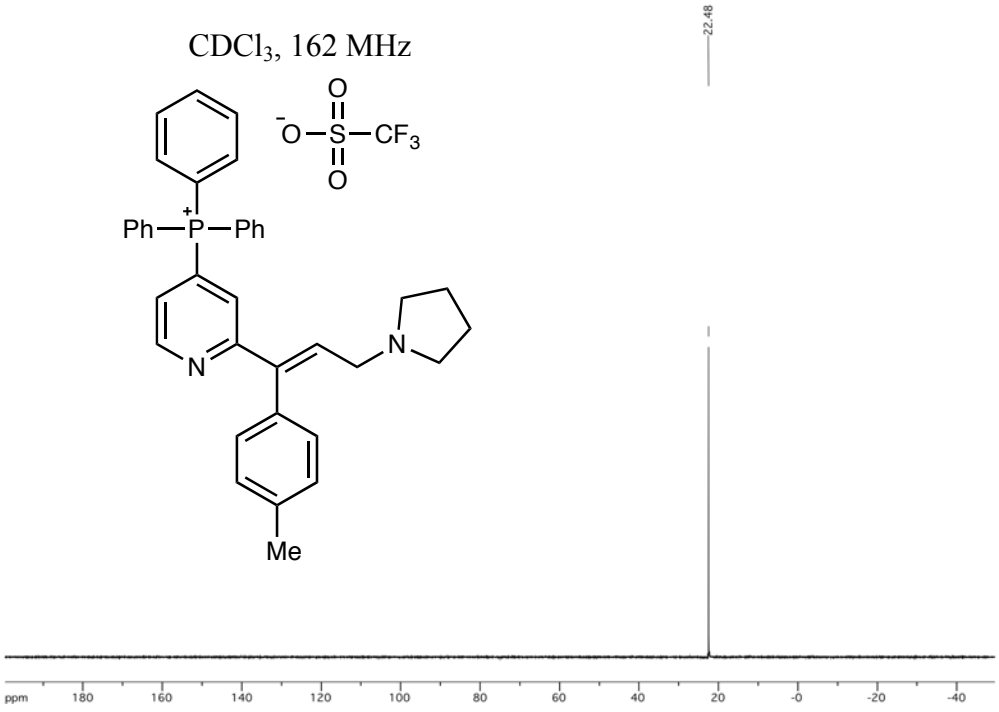

8.93
8.92
8.90
7.89
7.87
7.85
7.76
7.75
7.74
7.73
7.72
7.71
7.62
7.60
7.59
7.57
7.40
7.38
7.36
7.35
7.27
7.25
7.23
7.15
7.13
7.06
7.04
7.02
7.00
6.98
3.71
3.69
3.12
2.35
1.98
CDCl3, 400 MHz
O
O−S−CF3
O
Ph−P−Ph
N
N
Me
18.6
3.75
1.02
5.37
1.83
2.72
3.24
3.64
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2


CDCl3, 100 MHz
Ph
P
Ph
N
N
Me
O
S
CF3
159.40
159.30
150.96
150.86
144.24
138.20
136.00
135.97
134.40
134.29
132.33
131.92
130.79
129.74
129.28
129.13
128.43
126.31
125.62
125.53
125.37
125.34
125.29
122.16
118.97
116.03
115.14
77.32
77.00
76.68
53.99
53.75
23.03
21.21
ppm 200 180 160 140 120 100 80 60 40 20

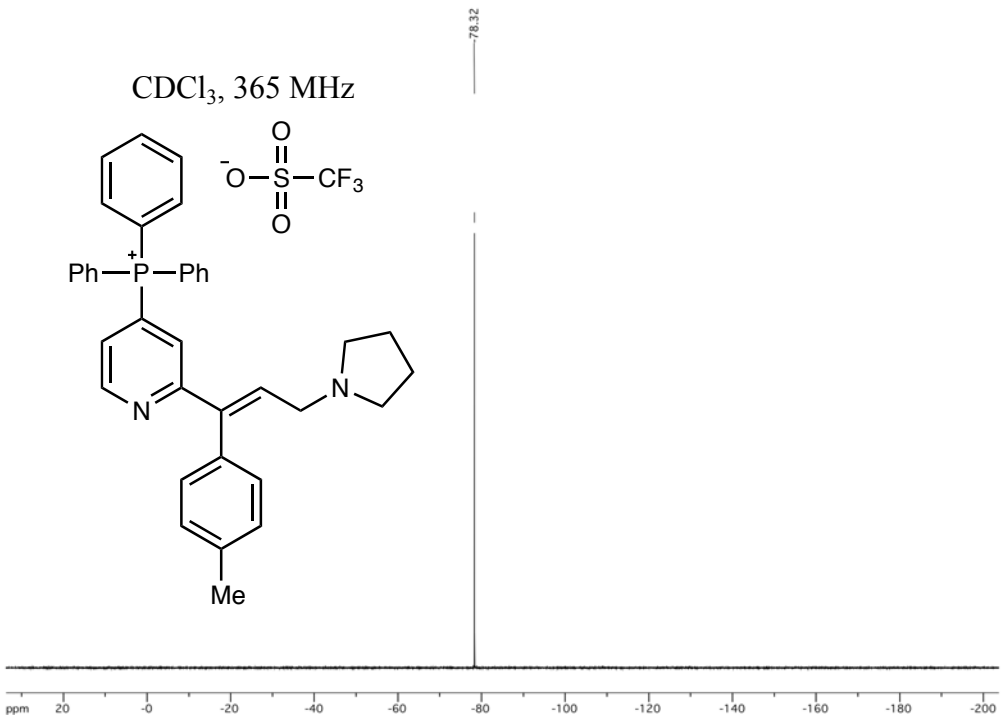
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



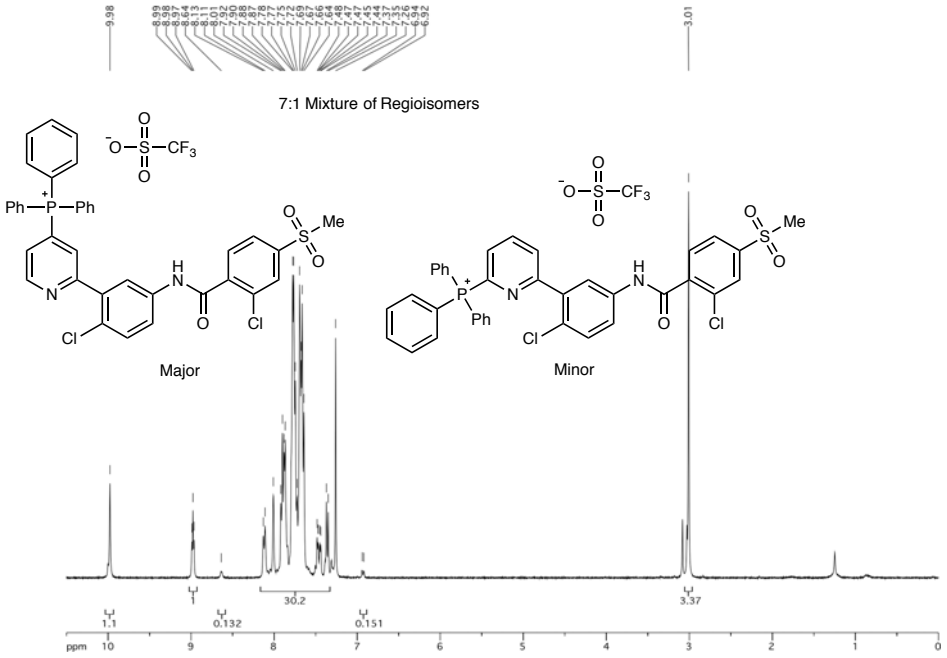
$CDCl_3$, 162 MHz

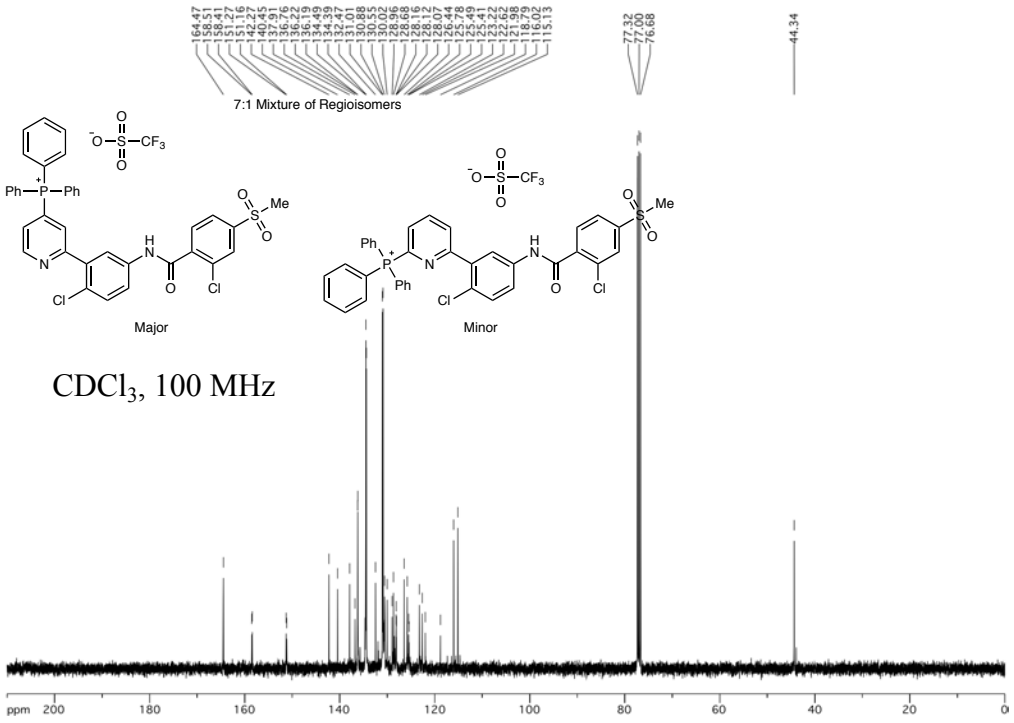


$CDCl_3$, 365 MHz

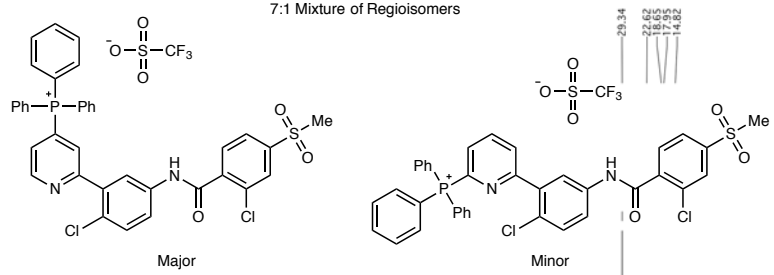


$CDCl_3$, 400 MHz

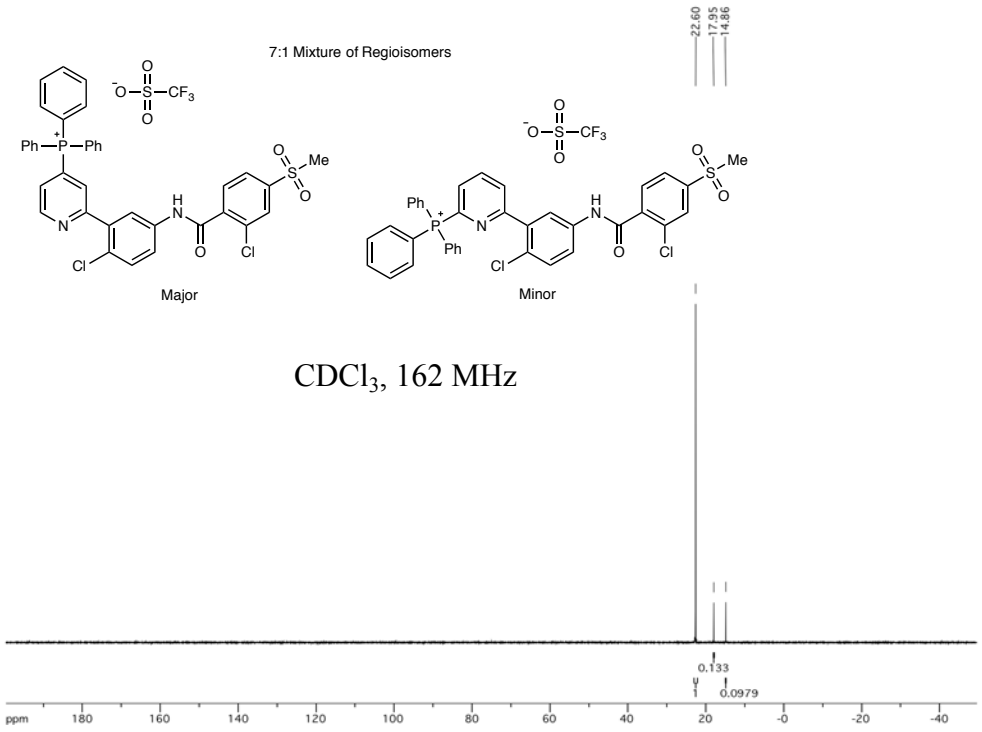



164.47
158.51
158.41
151.27
151.16
142.27
140.45
137.91
136.76
136.22
136.19
134.49
134.39
132.47
131.01
130.88
130.55
130.02
128.96
128.68
128.16
128.11
128.07
126.44
125.78
125.49
125.41
123.22
122.62
121.98
118.79
116.02
115.13
77.32
77.00
76.68
44.34
7:1 Mixture of Regioisomers
Major
Minor
CDCl3, 100 MHz
ppm 200
180
160
140
120
100
80
60
40
20

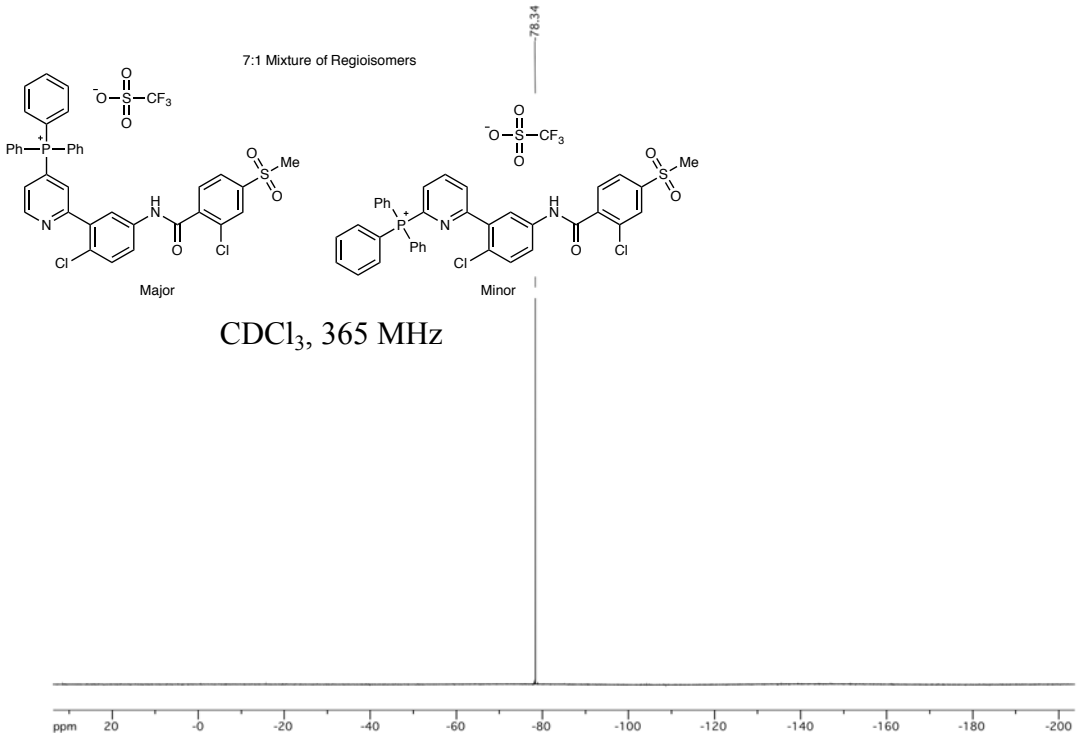
7:1 Mixture of Regioisomers

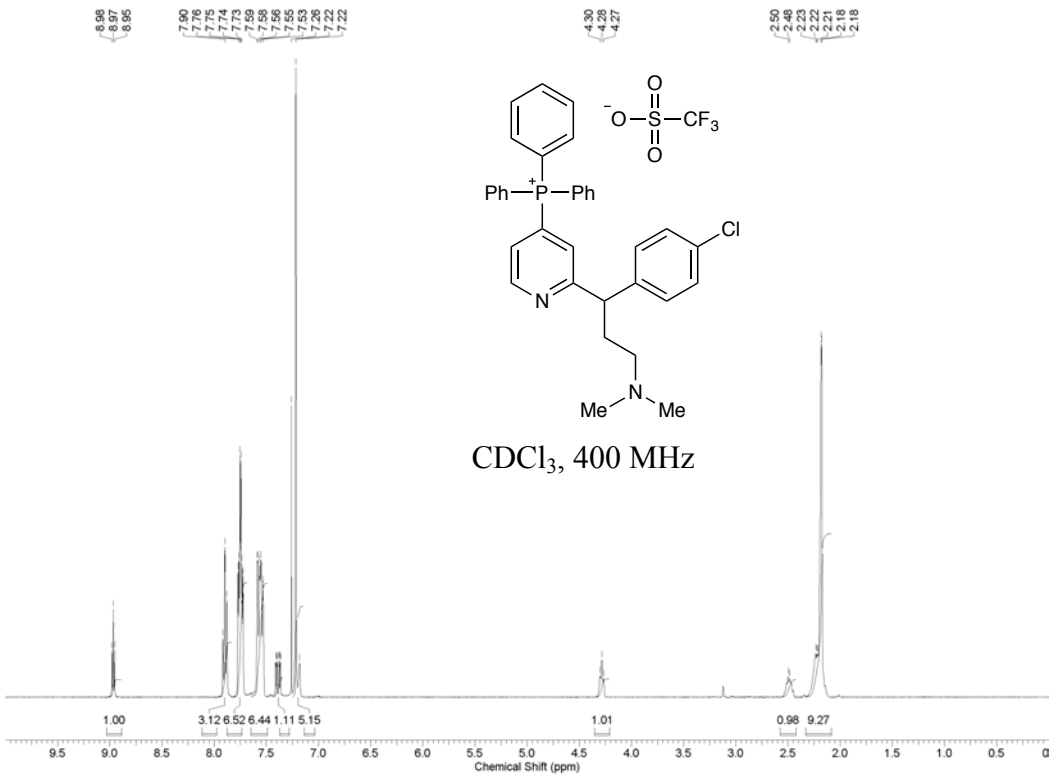


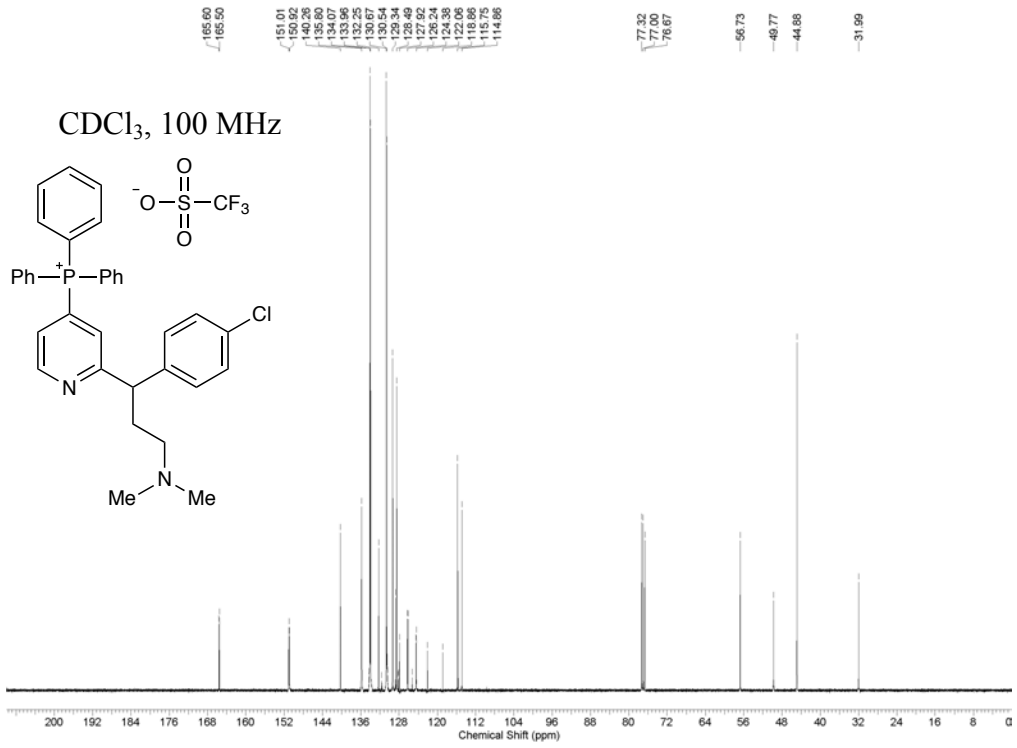
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

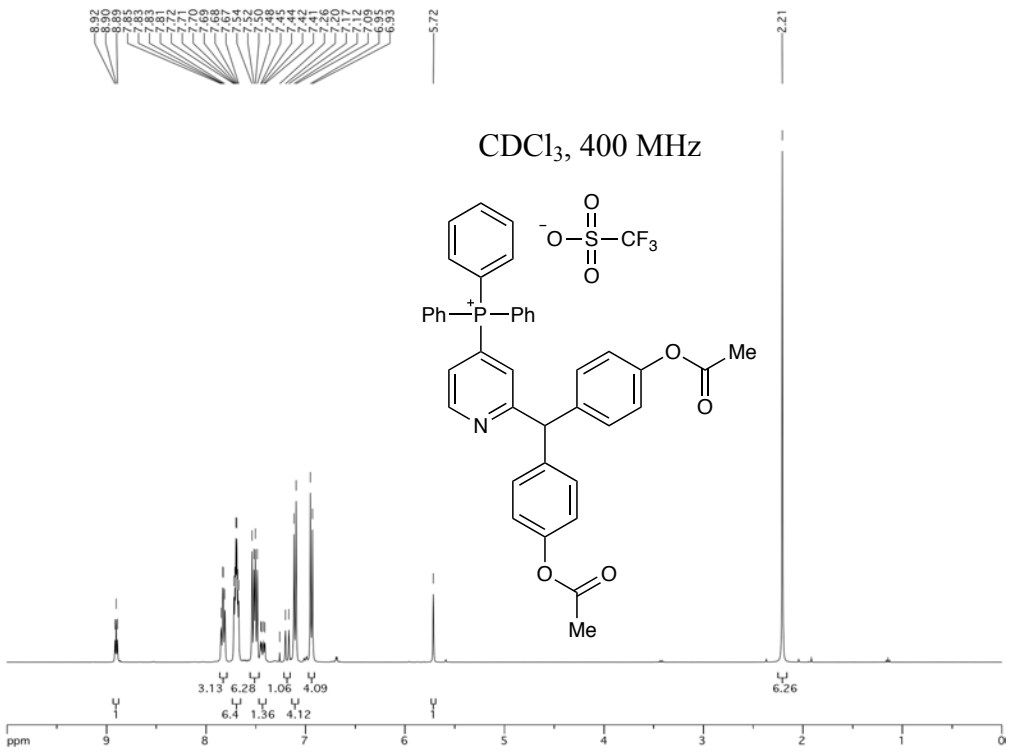


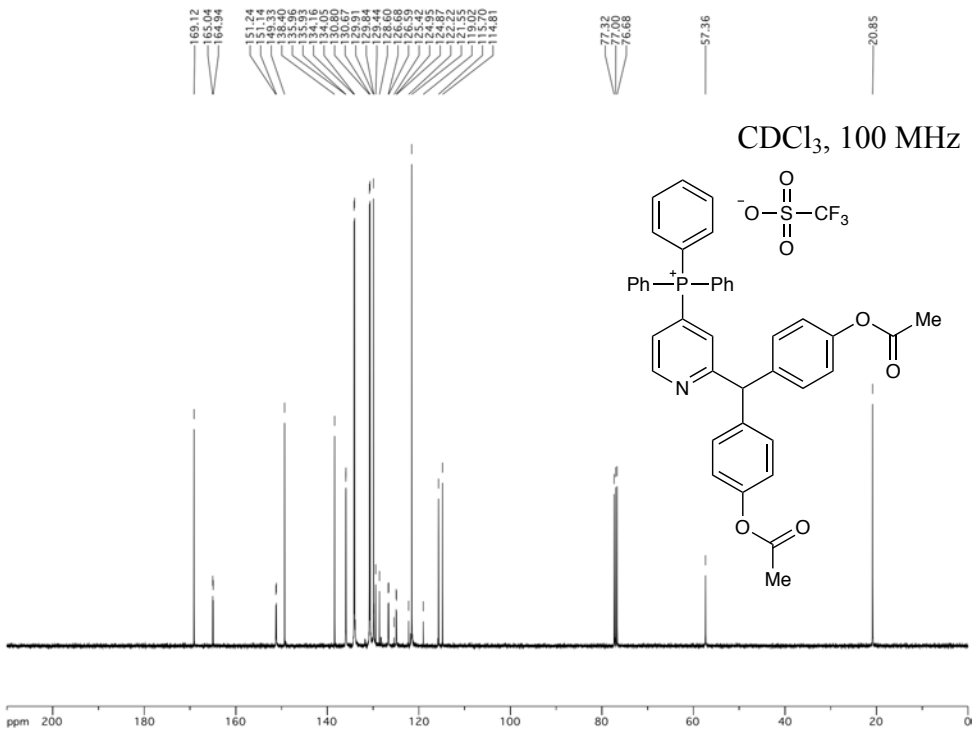
$CDCl_3$, 162 MHz


7:1 Mixture of Regioisomers
78.34
Major
Minor
CDCl3, 365 MHz
ppm
20
-0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200

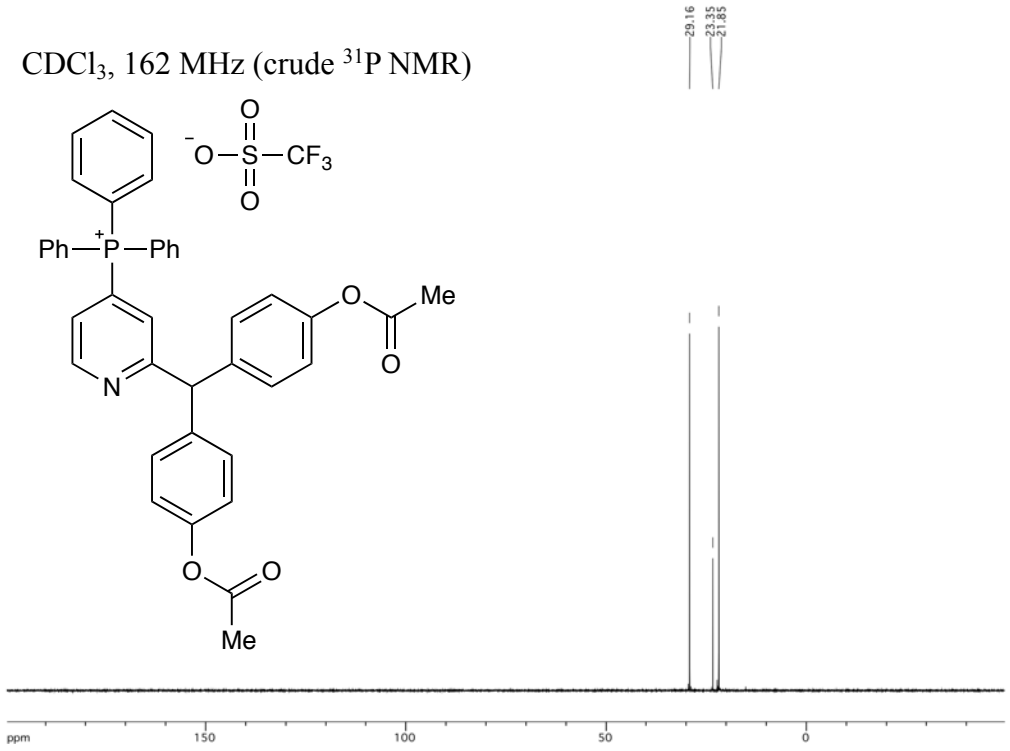

8.98
8.97
8.95
7.90
7.76
7.75
7.74
7.73
7.59
7.58
7.56
7.55
7.53
7.26
7.22
7.22
4.30
4.28
4.27
2.50
2.48
2.23
2.22
2.21
2.19
2.18
O
O
O
O
S
CF3
Ph
P
Ph
Cl
N
Me
N
Me
CDCl3, 400 MHz
1.00
3.12
6.52
6.44
1.11
5.15
1.01
0.98
9.27
Chemical Shift (ppm)


CDCl3, 100 MHz
Chemical Shift (ppm)

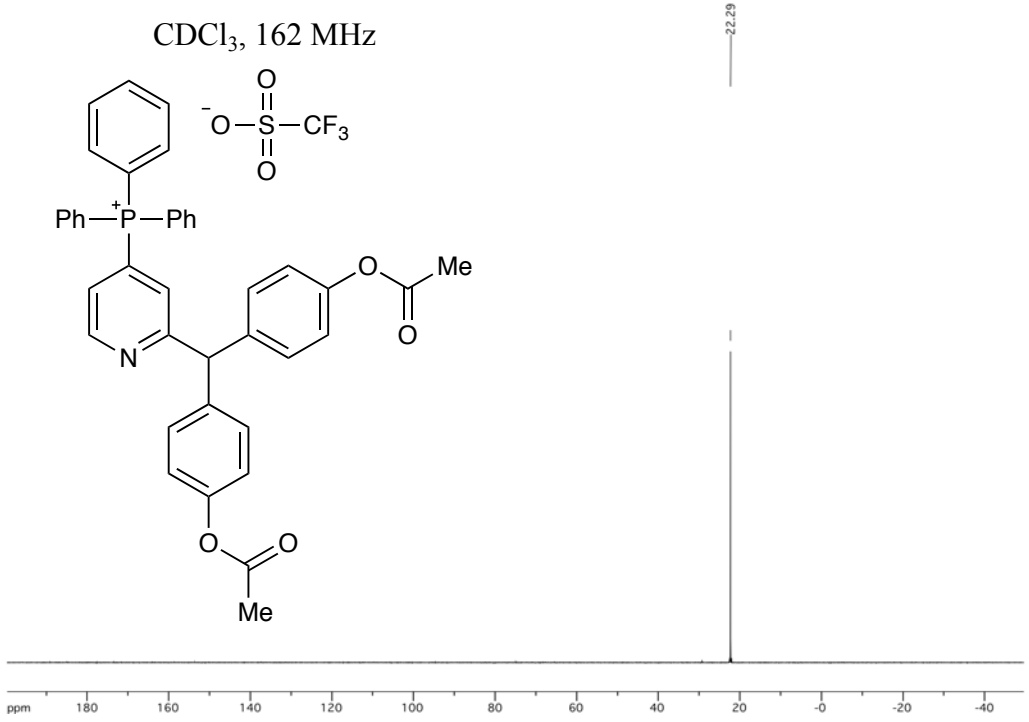

8.92
8.90
8.89
8.85
7.83
7.83
7.81
7.72
7.71
7.70
7.69
7.68
7.67
7.54
7.52
7.50
7.48
7.45
7.44
7.42
7.41
7.26
7.20
7.17
7.12
7.09
7.05
6.93
5.72
2.21
CDCl3, 400 MHz
Ph—P—Ph
O—S—CF3
O
Me
N
3.13
6.28
1.06
4.09
6.4
1.36
4.12
6.26
ppm
9
8
7
6
5
4
3
2
1
0

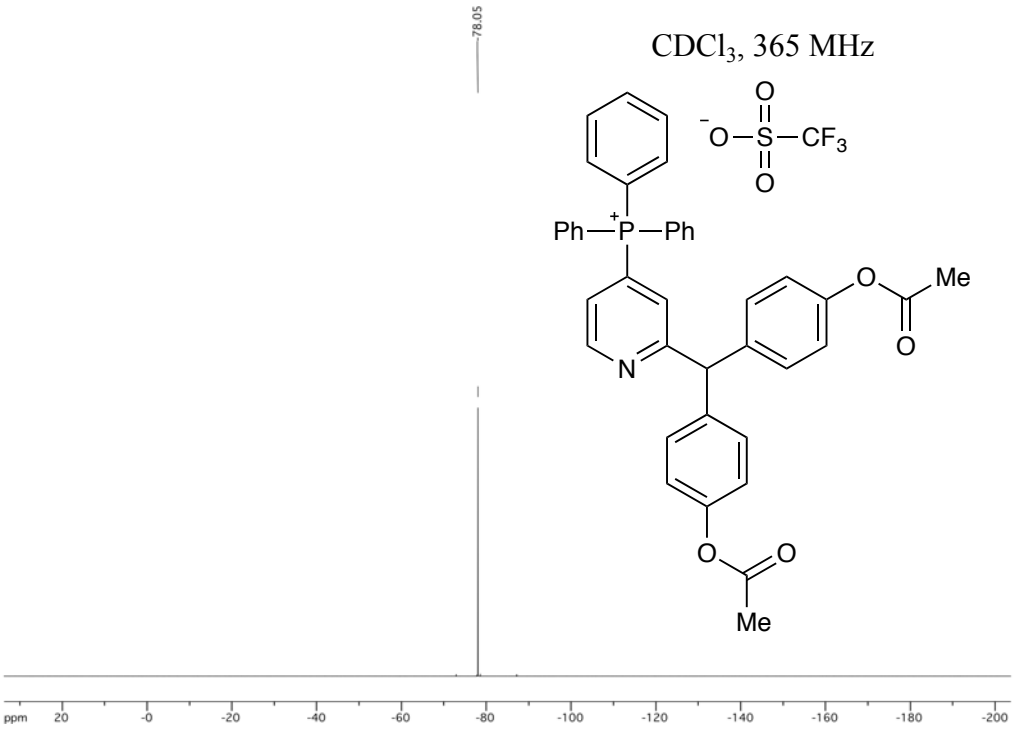

169.12
165.04
164.94
151.24
151.14
149.33
138.40
135.96
135.93
134.16
134.05
132.80
130.67
129.91
129.44
129.34
128.60
126.68
126.59
125.42
124.95
124.87
122.22
122.15
119.02
115.70
114.81
77.32
77.00
76.68
57.36
20.85
CDCl3, 100 MHz
ppm 200
180
160
140
120
100
80
60
40
20

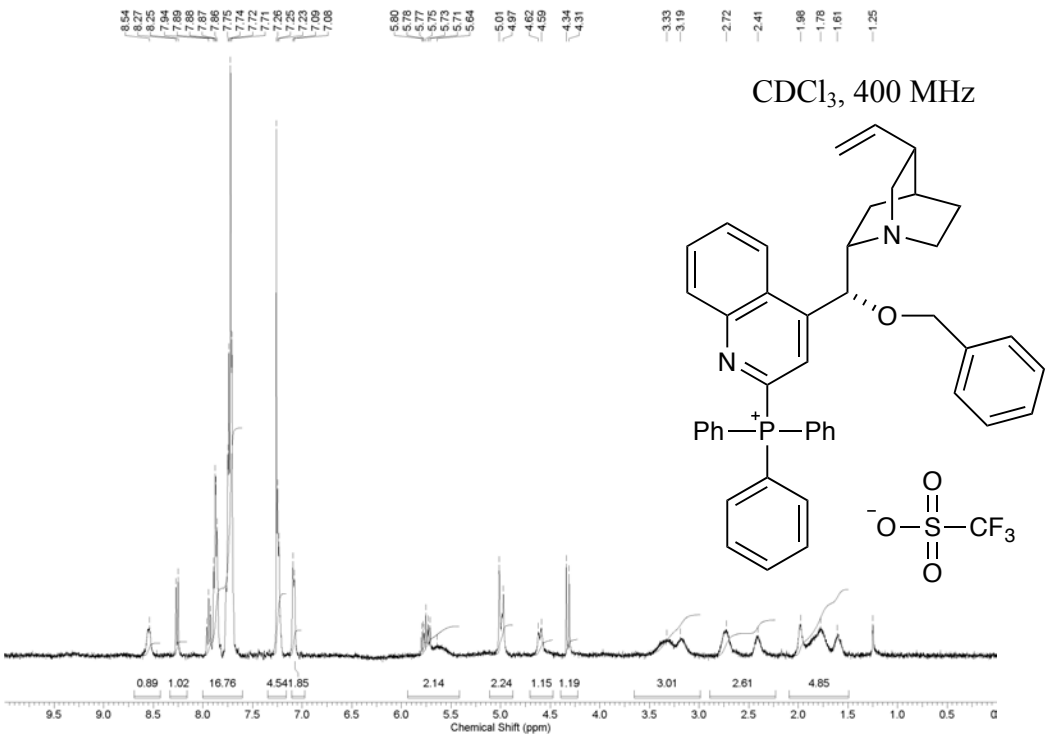
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

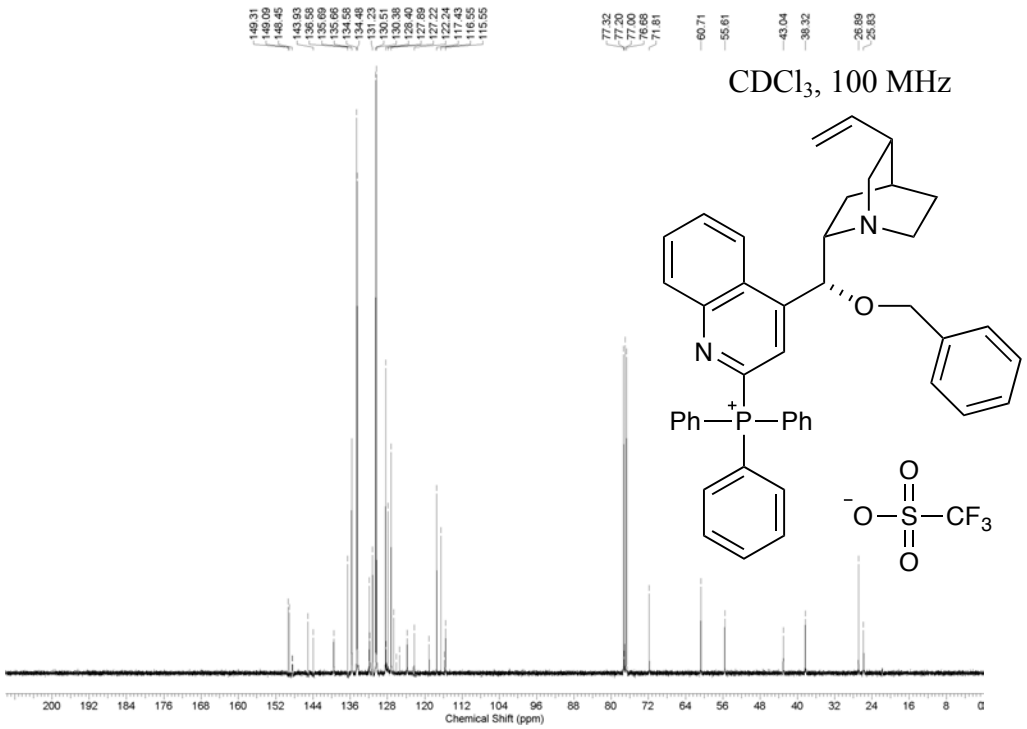


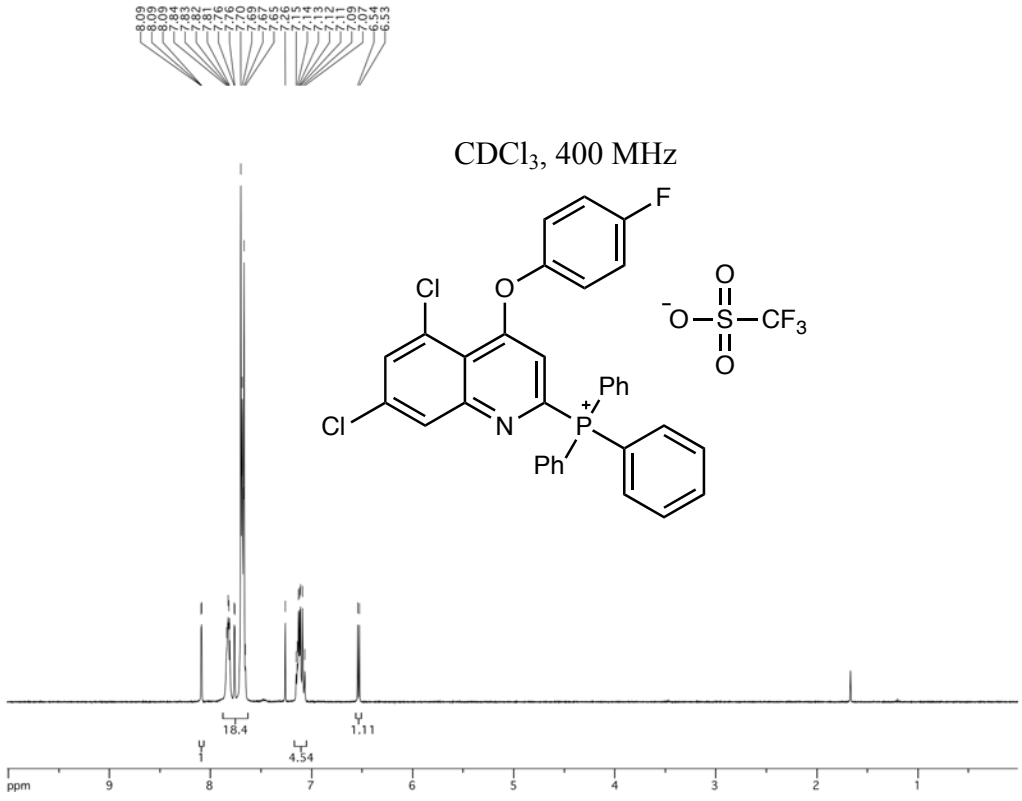
$CDCl_3$, 162 MHz

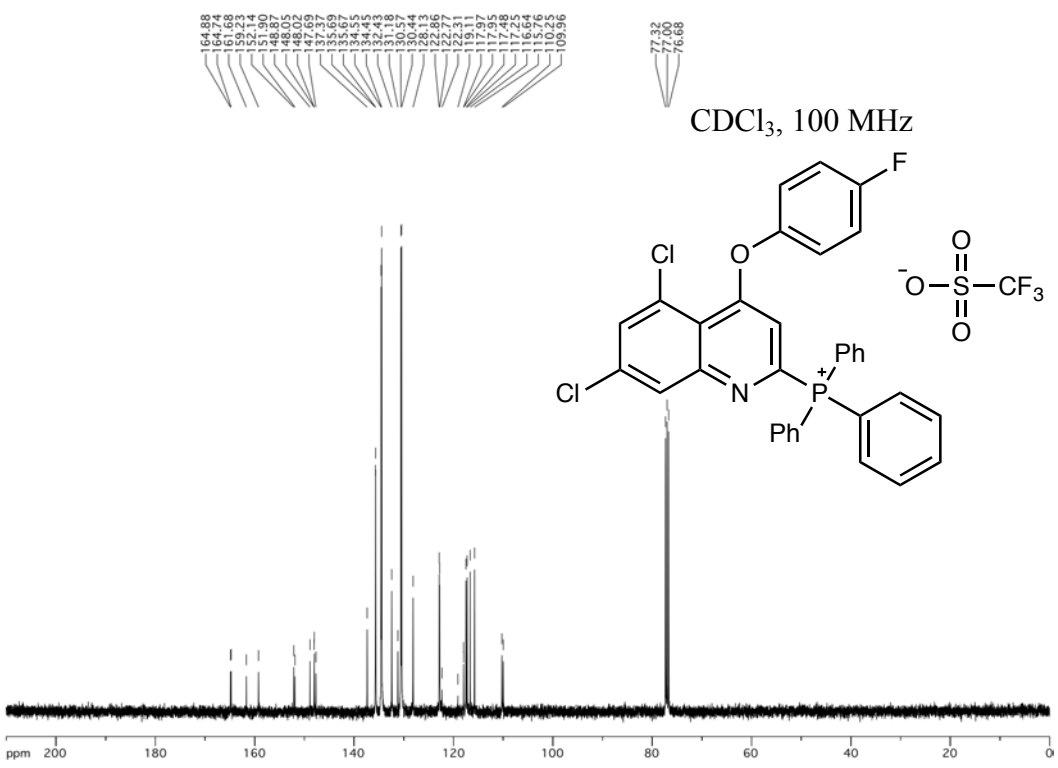



78.05
CDCl3, 365 MHz
O
O
S
O
CF3
Ph
P
Ph
N
O
Me
O
O
O
Me
ppm
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200

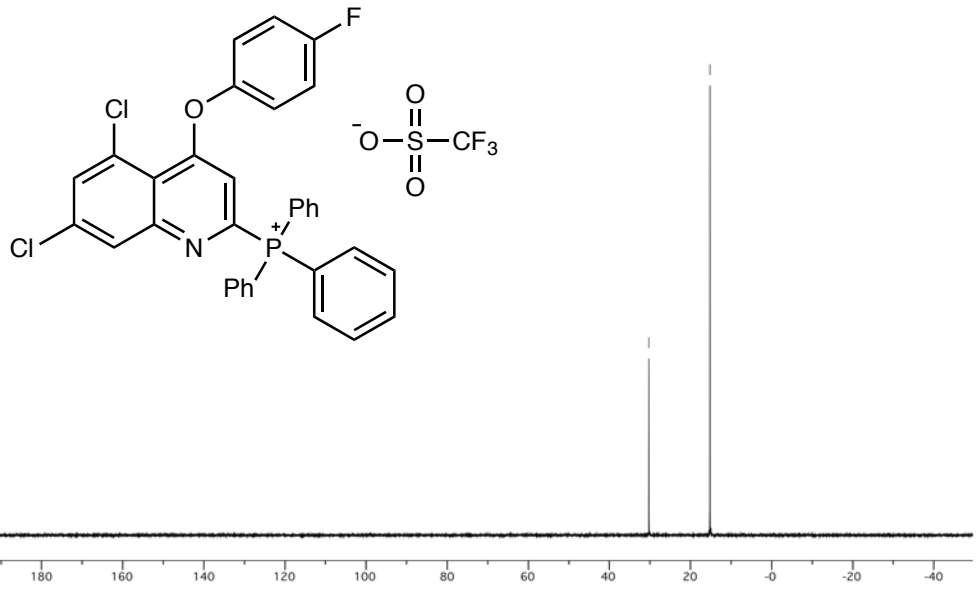

8.54
8.27
8.25
7.94
7.89
7.88
7.87
7.86
7.75
7.74
7.72
7.71
7.25
7.23
7.09
7.08
5.80
5.78
5.77
5.75
5.73
5.71
5.64
5.01
4.97
4.62
4.59
4.34
4.31
3.33
3.19
2.72
2.41
1.98
1.78
1.61
1.25
CDCl3, 400 MHz
N
O
N
Ph
P
Ph
O
O
O
S
CF3
O
0.89
1.02
16.76
4.54
1.85
2.14
2.24
1.15
1.19
3.01
2.61
4.85
9.5
9.0
8.5
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
Chemical Shift (ppm)


149.31
149.09
148.45
143.93
136.55
135.69
135.66
134.58
134.48
131.23
130.51
130.38
129.40
127.89
127.22
122.24
117.43
116.55
115.55
77.32
77.20
77.00
76.68
71.81
60.71
55.61
43.04
38.32
26.89
25.83
CDCl3, 100 MHz
N
O
N
Ph—P—Ph
O
O—S—CF3
O
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8
Chemical Shift (ppm)

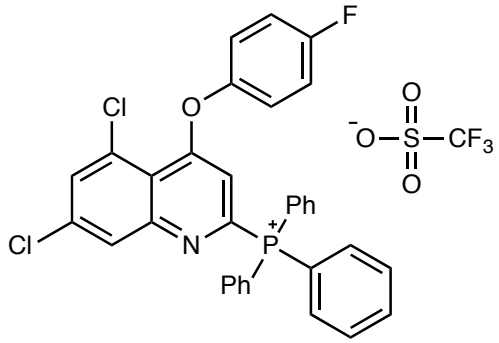

8.09
8.09
8.09
8.09
7.84
7.83
7.82
7.81
7.76
7.76
7.70
7.69
7.67
7.65
7.65
7.15
7.14
7.13
7.12
7.11
7.09
7.07
7.04
6.53
CDCl3, 400 MHz
F
O
Cl
O
S
CF3
Ph
Cl
N
P
Ph
18.4
1.11
1
4.54
ppm
9
8
7
6
5
4
3
2
1

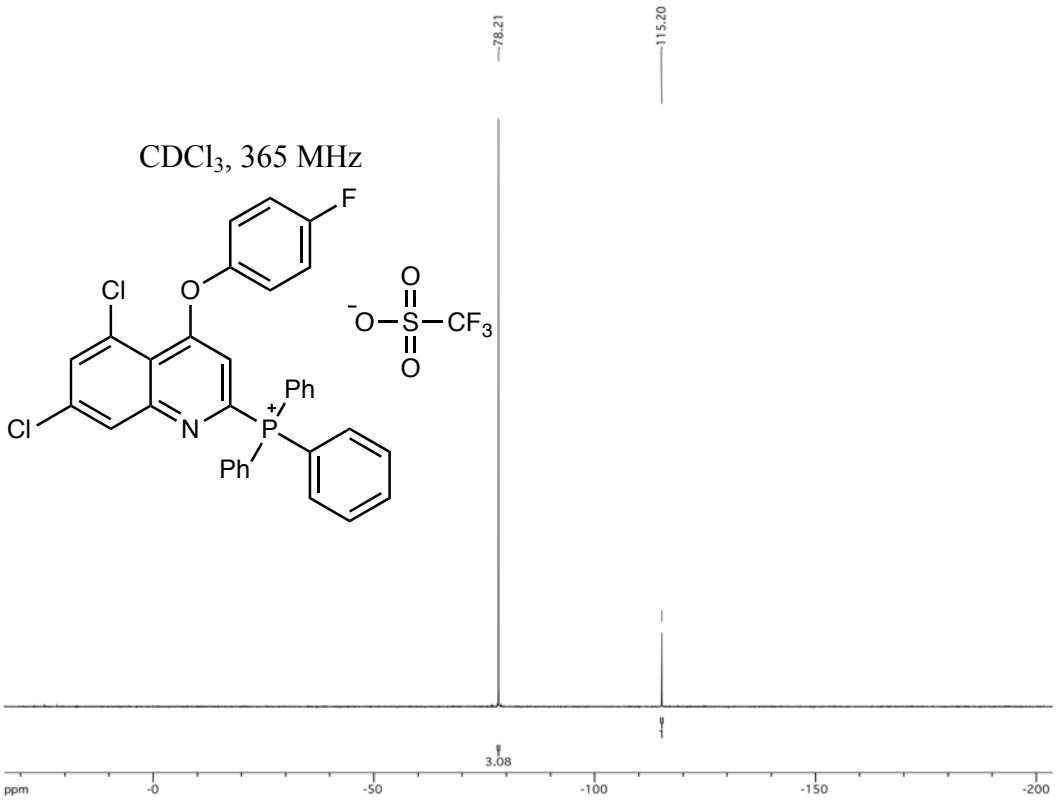

164.88
164.74
161.68
159.23
152.14
151.80
148.87
148.05
148.02
147.69
137.37
135.89
135.67
134.55
134.45
132.43
131.18
130.57
130.44
128.13
122.86
122.77
121.11
117.97
117.95
117.48
117.25
116.64
115.76
110.25
109.96
77.32
77.00
76.68
CDCl3, 100 MHz
F
O
Cl
O
S
CF3
Ph
P
Ph
Cl
N
ppm 200 180 160 140 120 100 80 60 40 20 0

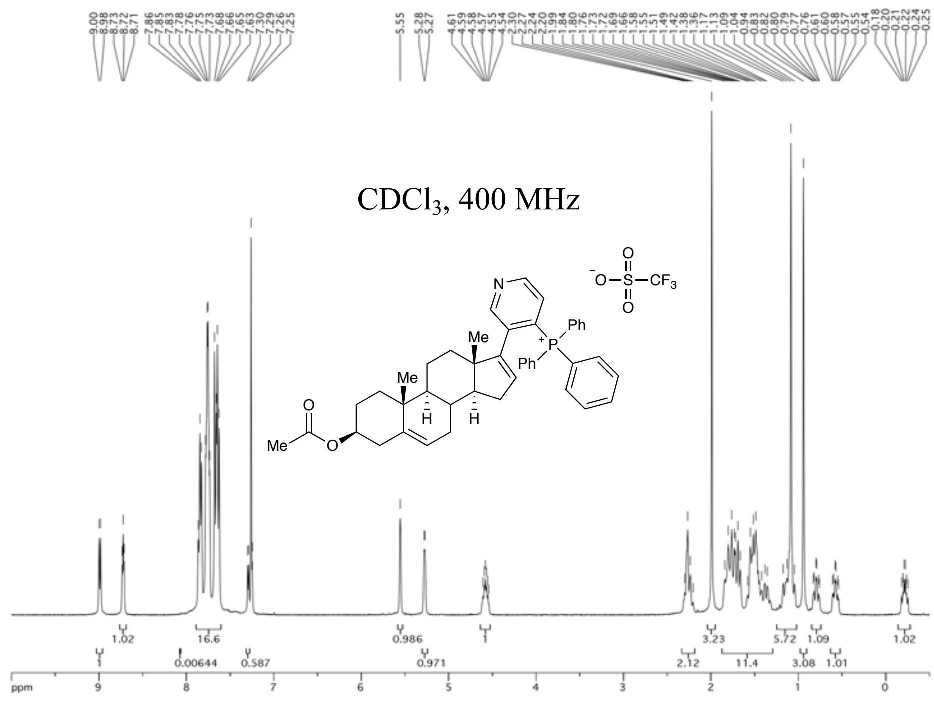
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

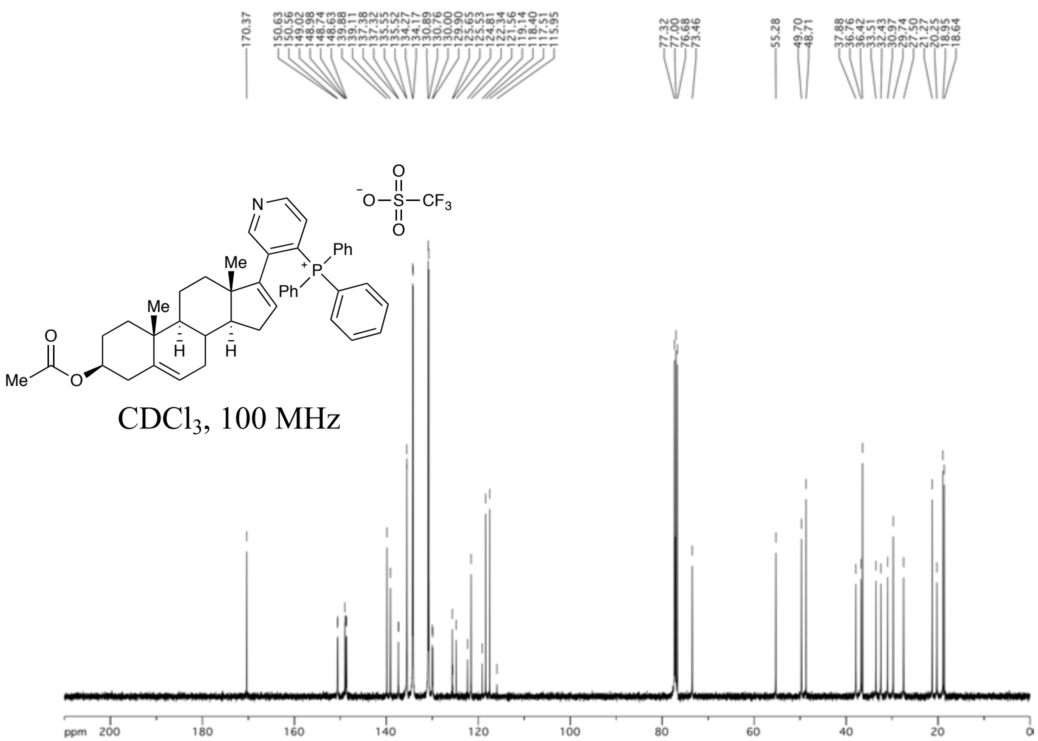


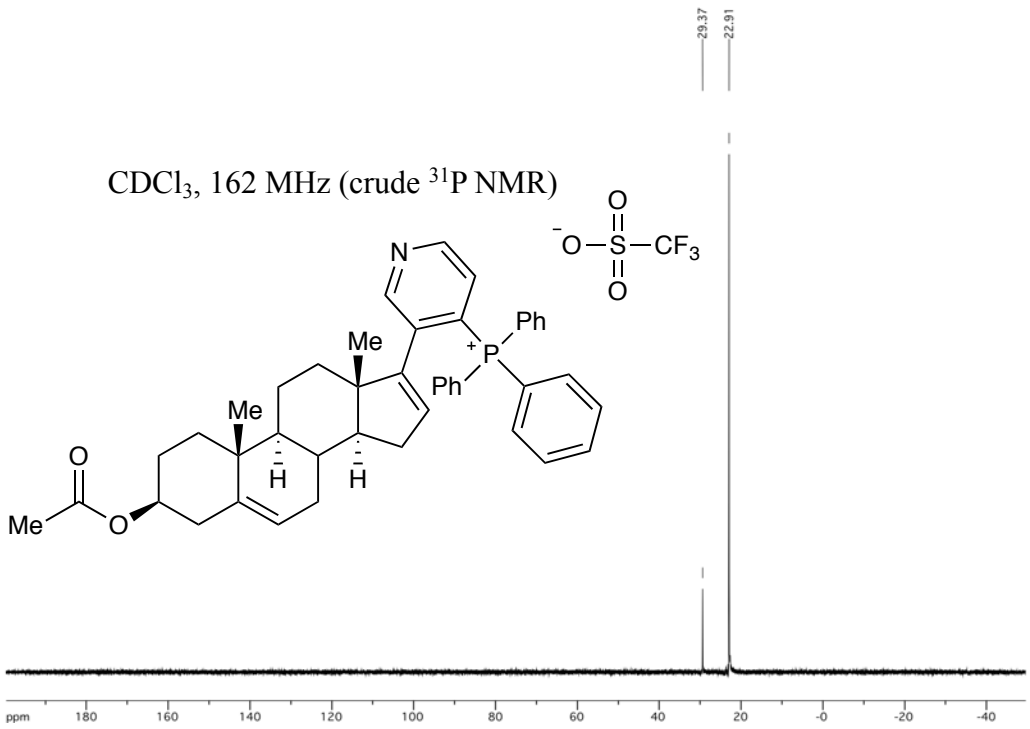
$CDCl_3$, 162 MHz

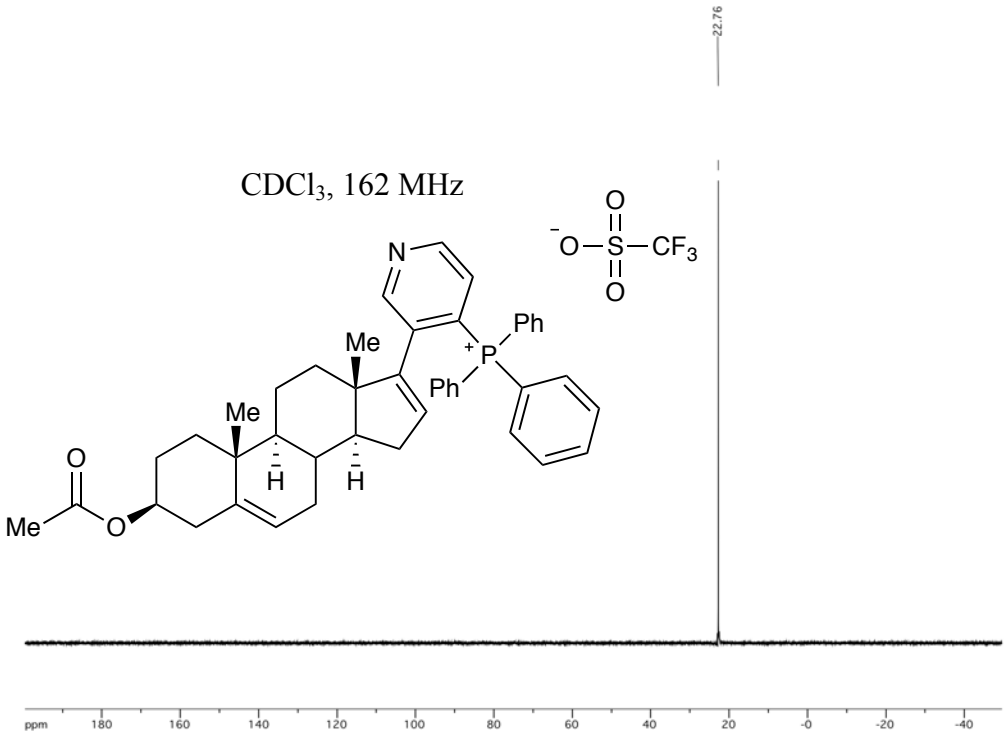


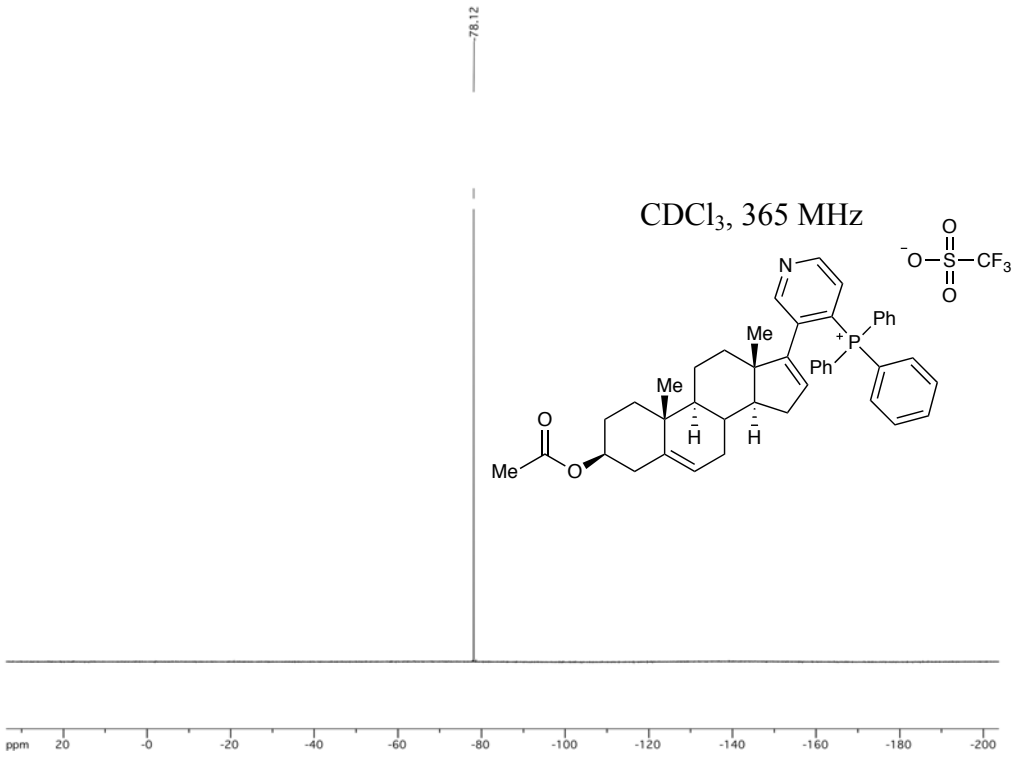

78.21
115.20
CDCl3, 365 MHz
F
Cl
O
O
O
O
S
CF3
Ph
Cl
N
P
Ph
3.08
ppm
-0
-50
-100
-150
-200

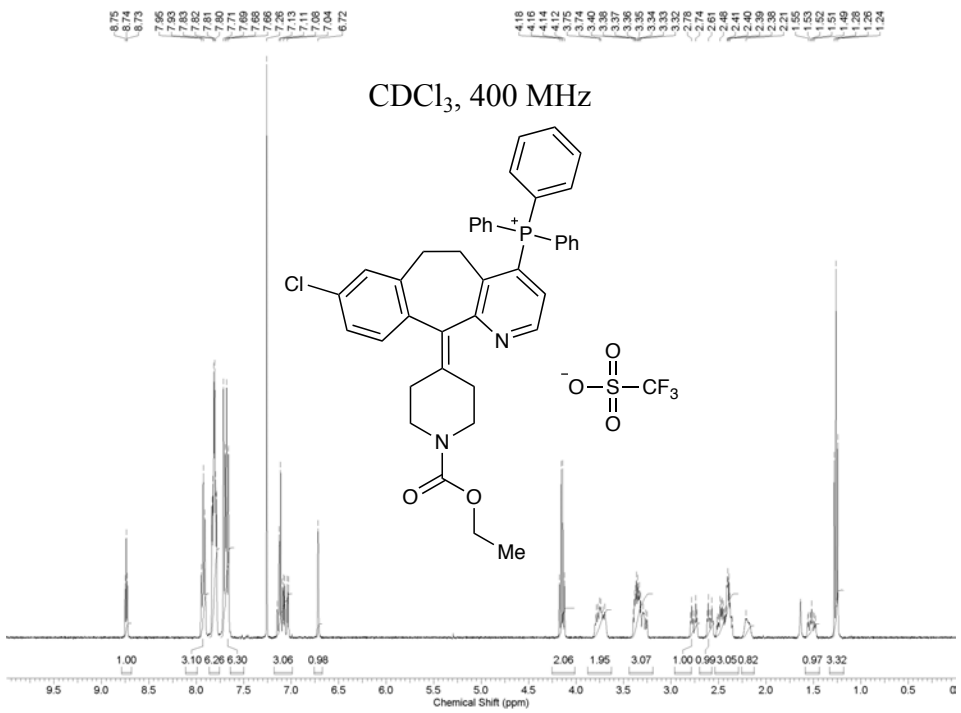

CDCl3, 400 MHz
ppm

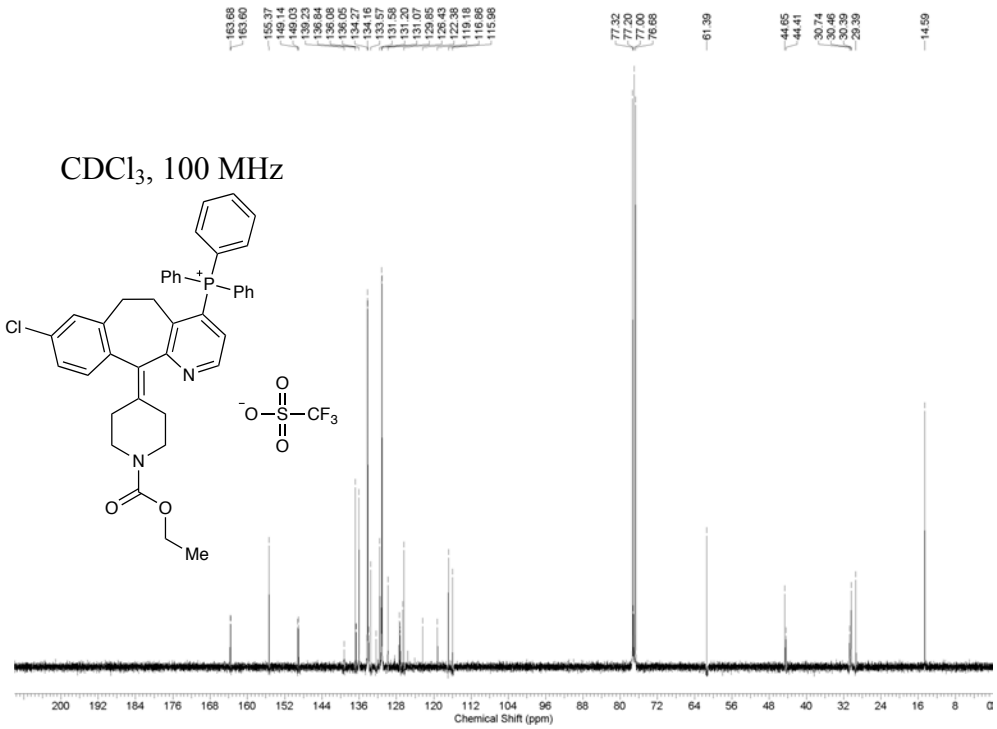

170.37
150.63
150.56
149.02
148.98
148.74
148.63
139.88
139.11
137.38
137.32
135.55
135.52
134.27
134.17
130.89
130.76
130.00
129.90
125.65
125.53
124.81
122.34
121.56
119.14
118.40
117.51
115.95
77.32
77.00
76.68
73.46
55.28
49.70
48.71
37.88
36.76
36.42
33.51
32.43
30.97
29.74
27.50
21.27
20.25
18.95
18.64
N
Me
Me
H
H
Ph
Ph
P
O
S
CF3
Me
O
O
CDCl3, 100 MHz
ppm
200
180
160
140
120
100
80
60
40
20
0

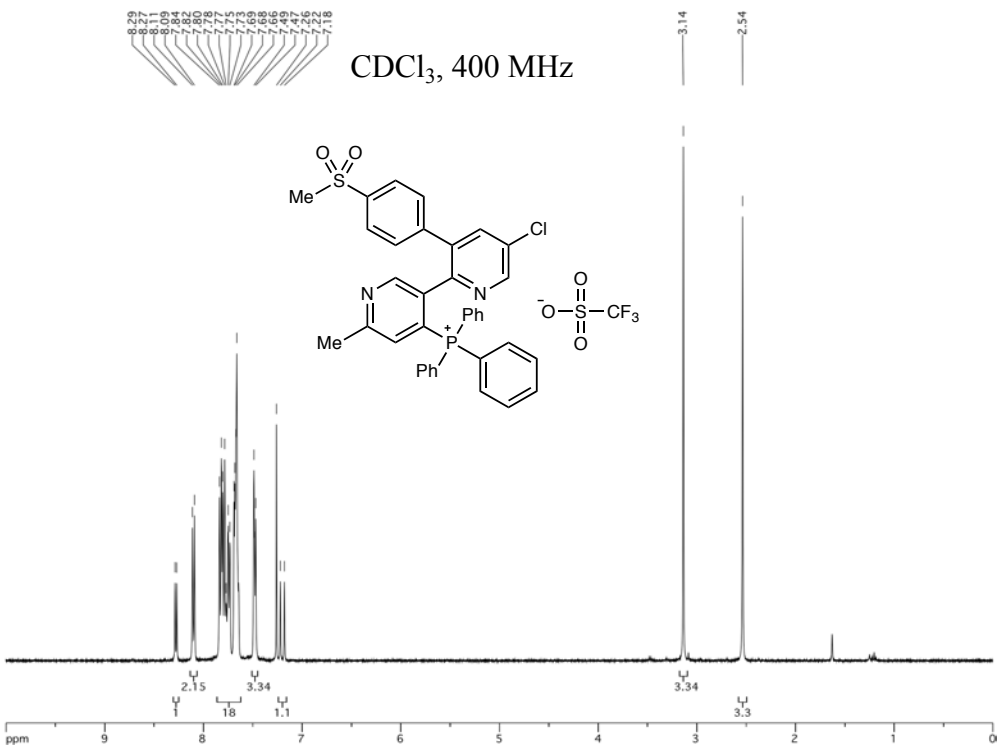

29.37
22.91
CDCl3, 162 MHz (crude 31P NMR)
O
O
-O—S—CF3
O
N
Ph
+P
Ph
Me
Me
H
H
O
Me
O
ppm
180
160
140
120
100
80
60
40
20
-0
-20
-40

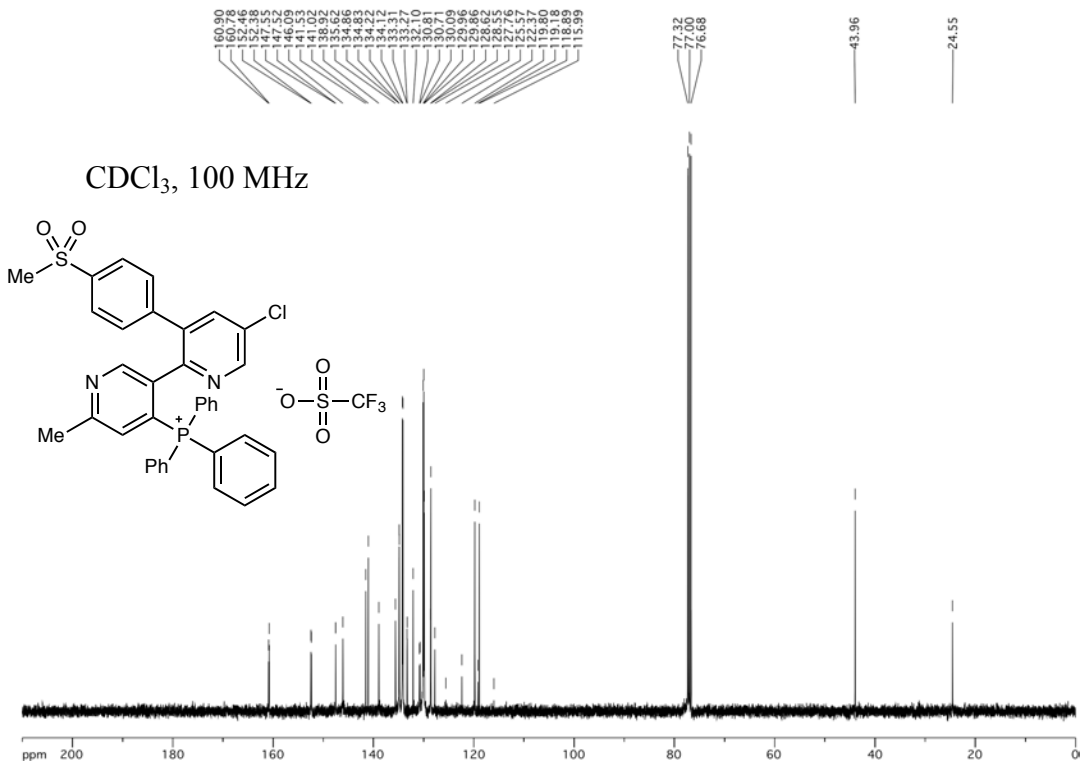

CDCl3, 162 MHz
22.76
N
Me
Ph
P
Ph
Me
O
Me
O
H
H
O
S
CF3
O
O
ppm
180
160
140
120
100
80
60
40
20
-0
-20
-40


78.12
CDCl3, 365 MHz
N
Me
Ph
P
Ph
Ph
Me
H
H
O
Me
O
O
O
S
CF3
ppm
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200

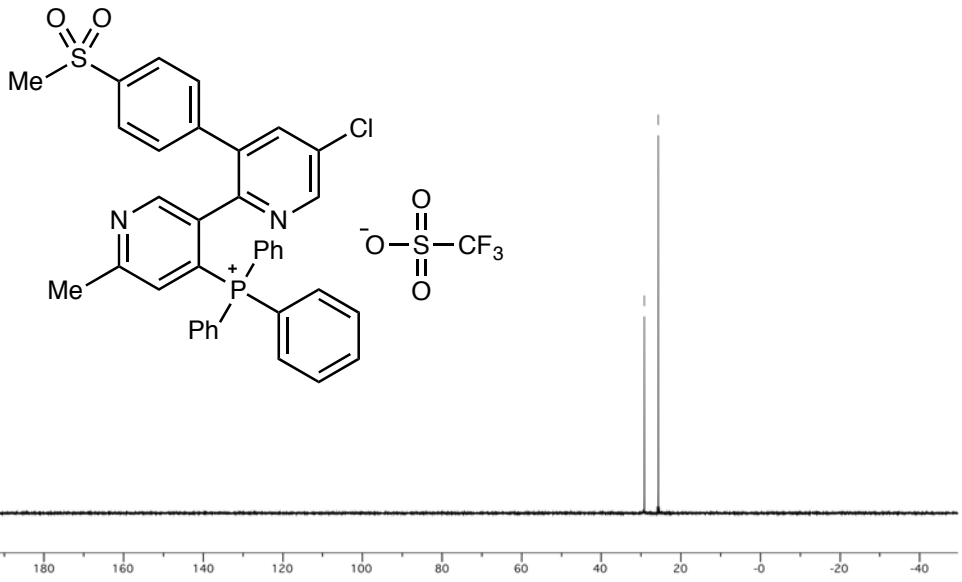

CDCl3, 400 MHz
Ph
P
Ph
Cl
N
O
O
S
CF3
O
N
O
O
Me
1.00
3.10
6.26
6.30
3.06
0.98
2.06
1.95
3.07
1.00
0.99
3.05
0.82
0.97
3.32
Chemical Shift (ppm)


163.68
163.60
155.37
149.14
148.03
139.23
136.84
136.08
136.05
134.27
134.16
133.57
131.58
131.20
131.07
129.65
126.43
122.38
119.18
116.86
115.98
77.32
77.20
77.00
76.68
61.39
44.65
44.41
30.74
30.46
30.39
29.39
14.59
CDCl3, 100 MHz
Ph
P
Ph
Cl
N
O
O
S
CF3
O
N
O
O
Me
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8
Chemical Shift (ppm)

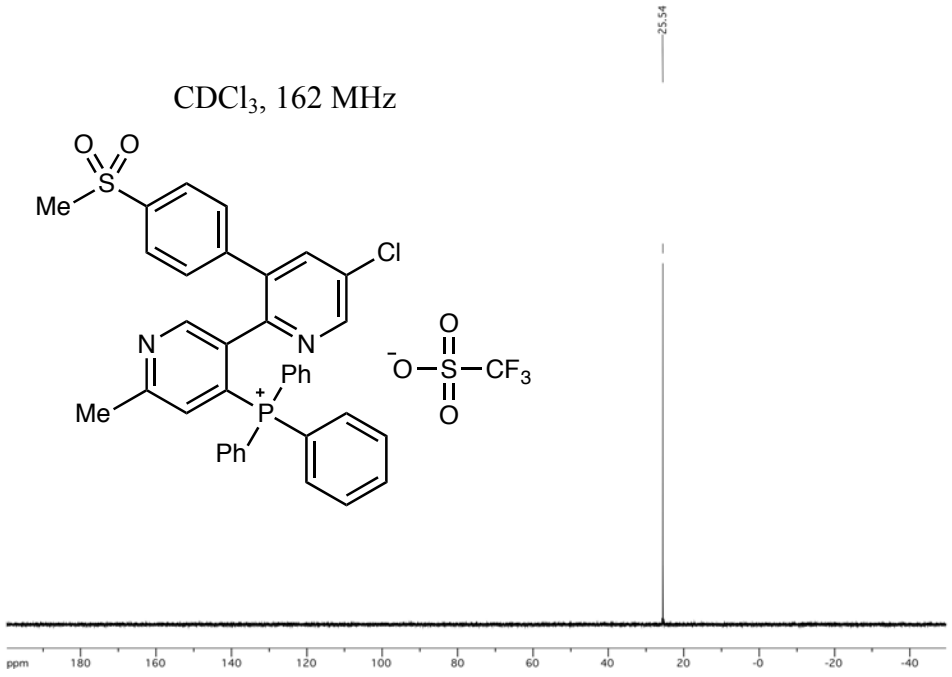

8.29
8.27
8.11
8.09
7.84
7.82
7.80
7.78
7.77
7.75
7.73
7.69
7.68
7.66
7.49
7.47
7.26
7.22
7.18
3.14
2.54
CDCl3, 400 MHz
Me
Cl
N
N
Ph
Me
P
Ph
O
S
CF3
2.15
3.34
3.34
1
1.8
1.1
3.3
ppm


160.90
160.78
152.46
147.48
147.35
147.52
146.09
141.53
141.02
140.92
135.62
134.86
134.83
134.22
134.12
133.71
133.27
132.10
130.81
130.71
130.09
129.96
128.86
128.62
128.55
127.76
125.37
119.80
119.18
118.89
115.99
77.32
77.00
76.68
43.96
24.55
CDCl3, 100 MHz
Me
S
O
O
Cl
N
N
Ph
Me
P
Ph
O
O
S
CF3
O
O
ppm 200
180
160
140
120
100
80
60
40
20
0

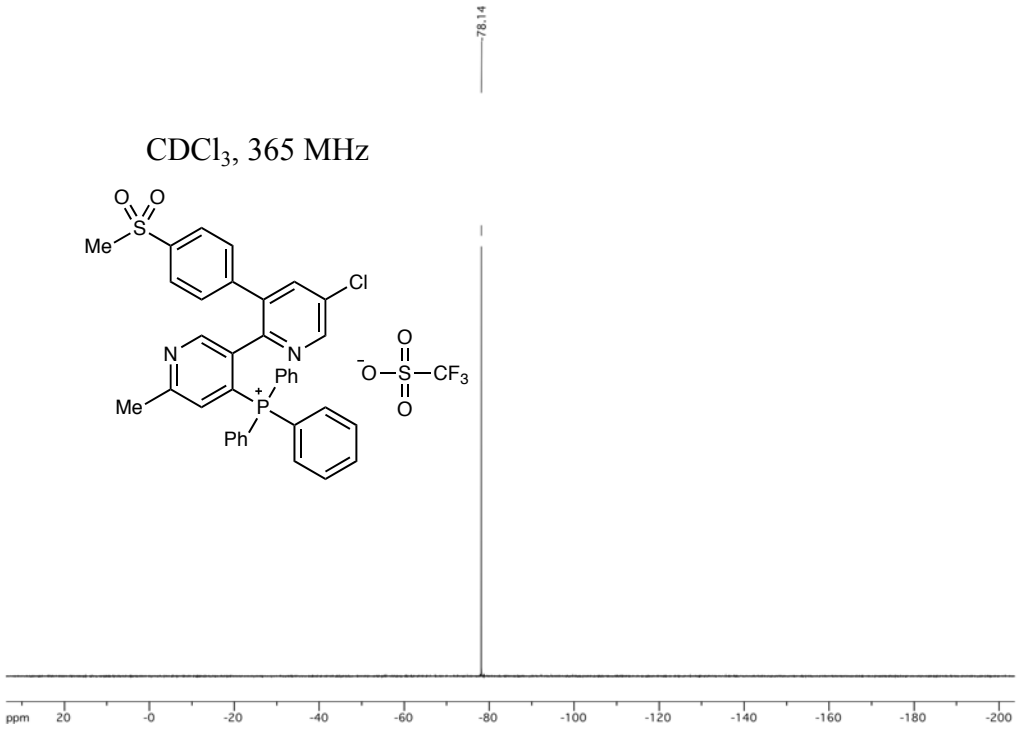
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

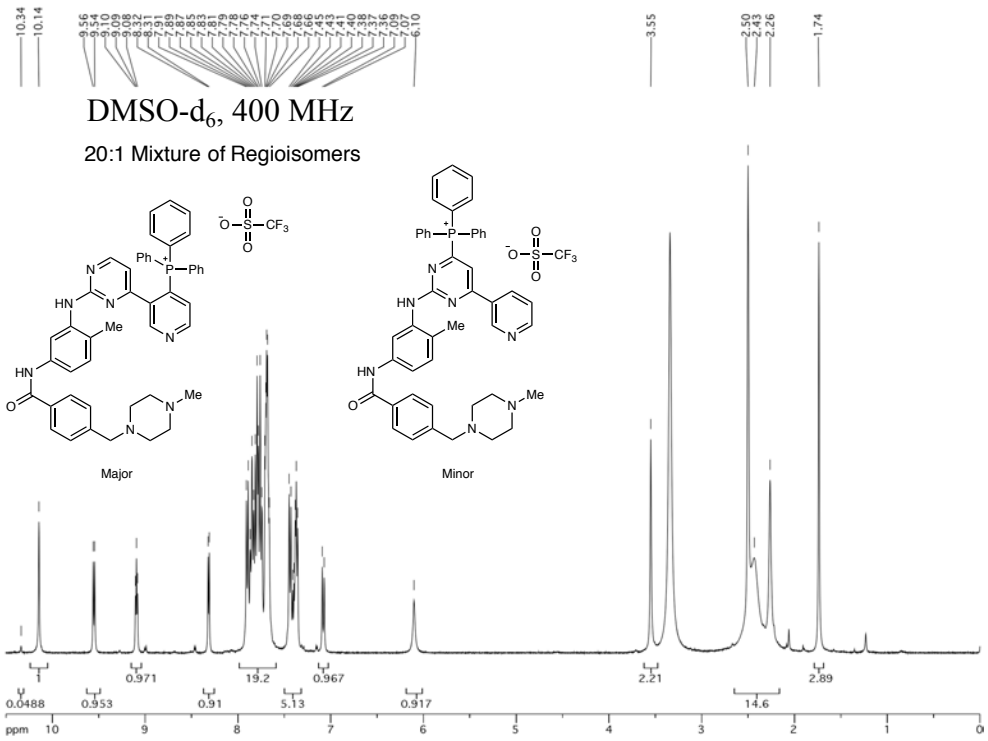


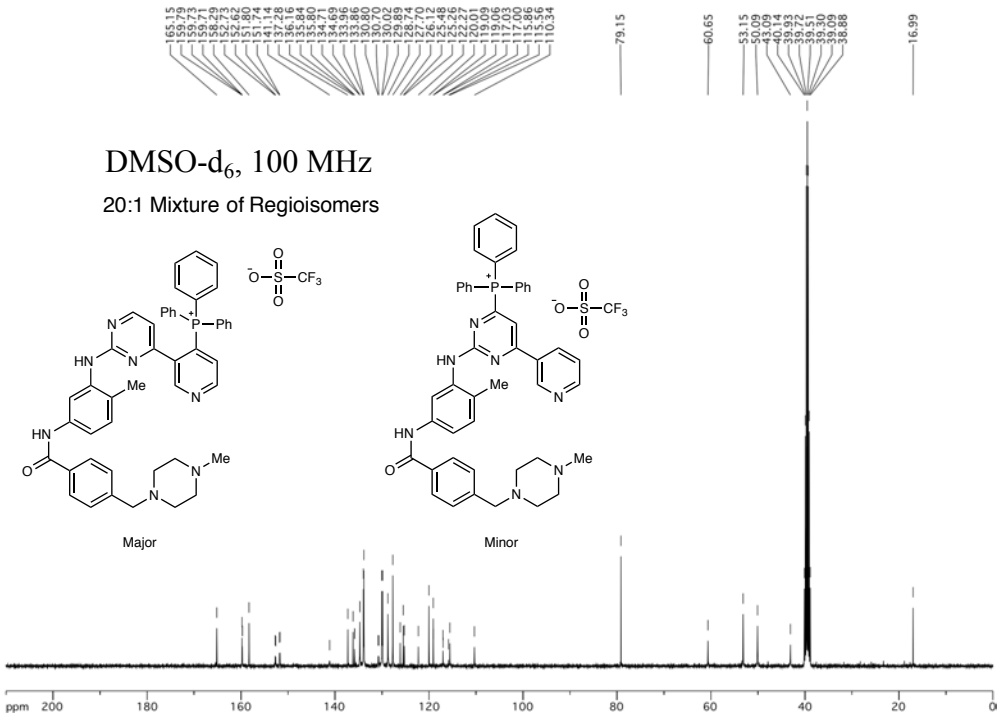
$CDCl_3$, 162 MHz



$CDCl_3$, 365 MHz

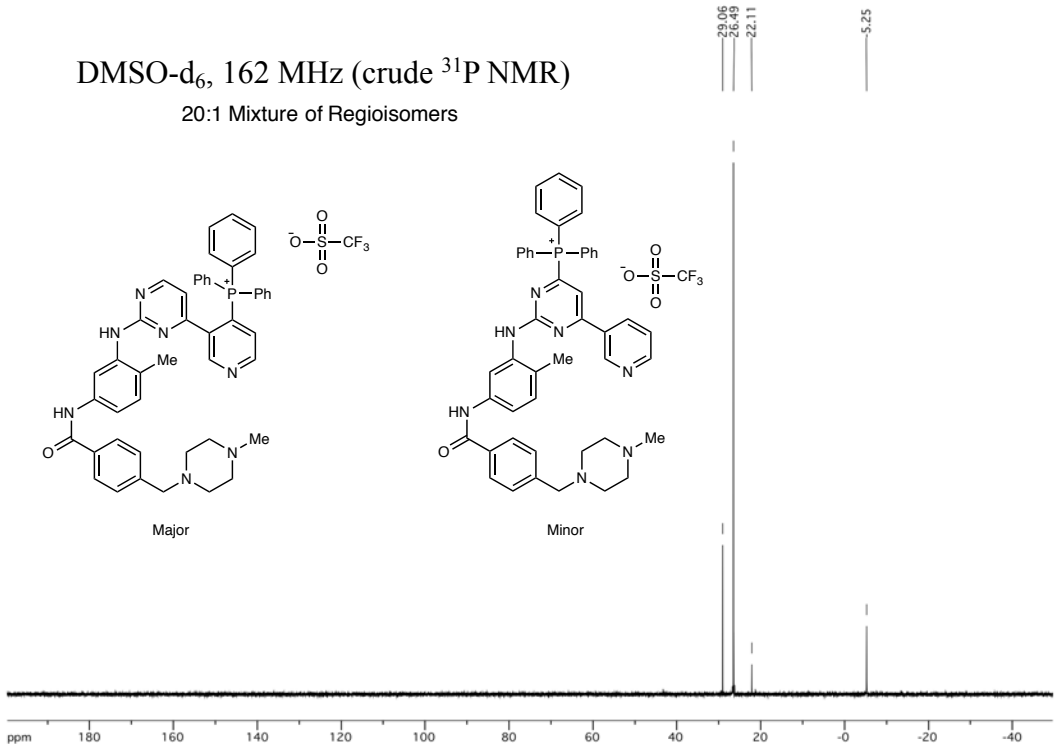


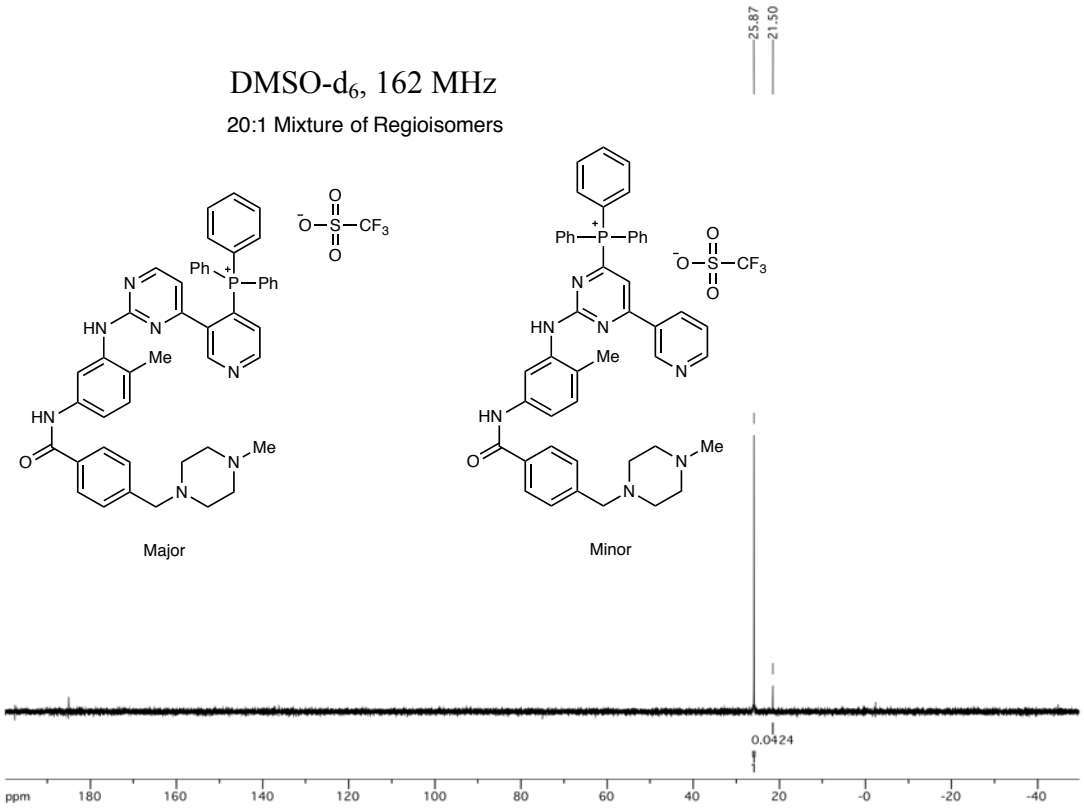

DMSO-d6, 400 MHz
20:1 Mixture of Regioisomers
Major
Minor
ppm

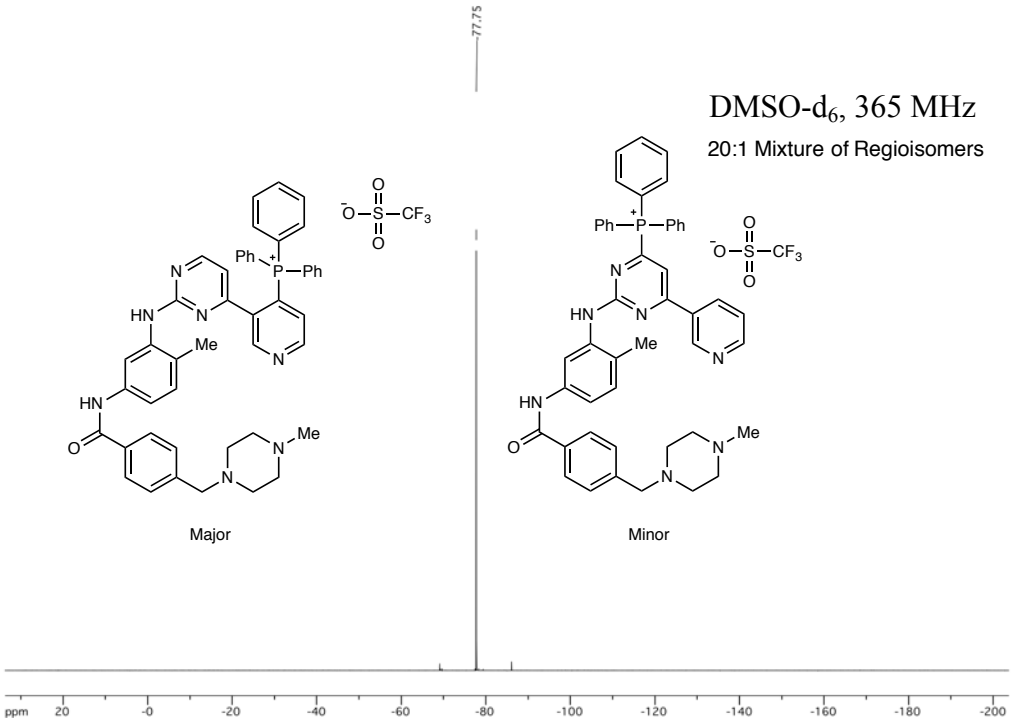

DMSO-d6, 100 MHz
20:1 Mixture of Regioisomers
Major
Minor
ppm 200 180 160 140 120 100 80 60 40 20 0

DMSO-d_6, 162 MHz (crude ^{31}P NMR)

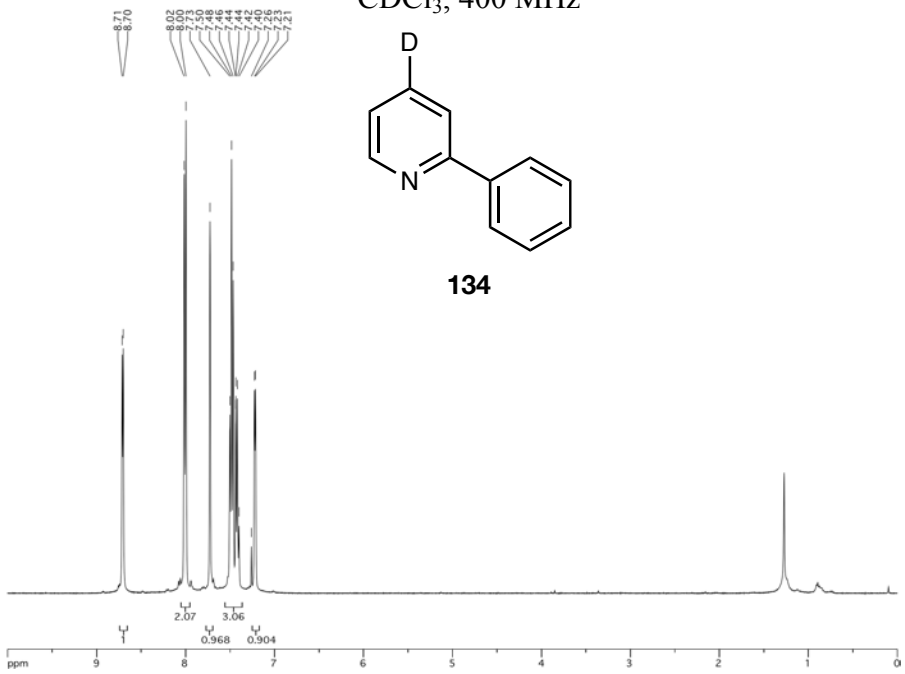
20:1 Mixture of Regioisomers



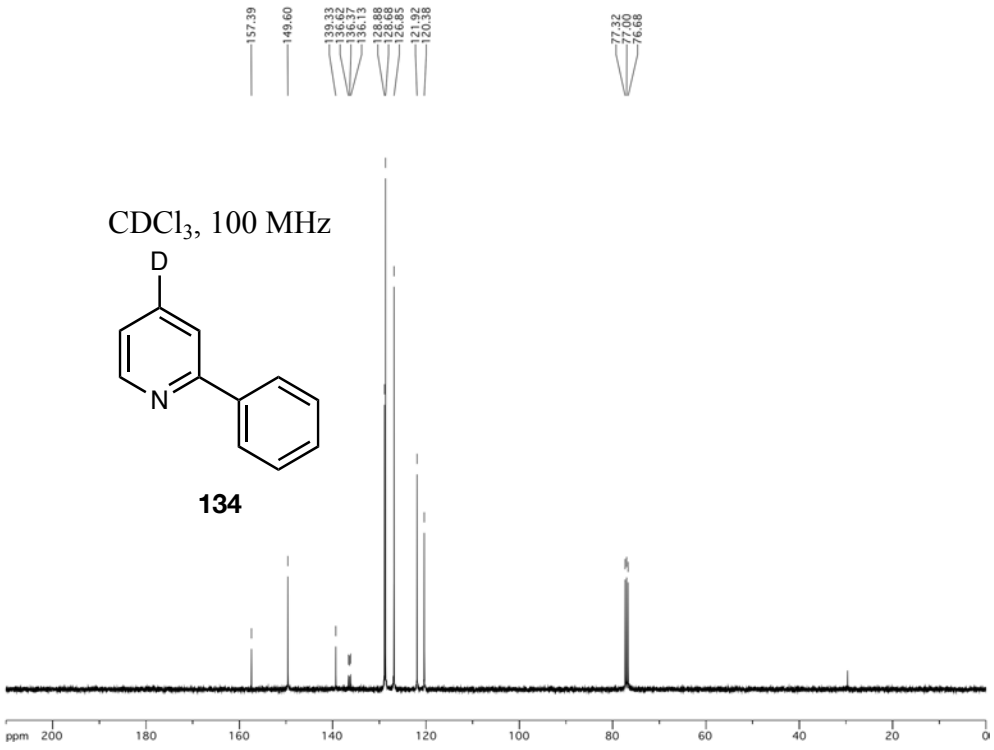

DMSO-d6, 162 MHz
20:1 Mixture of Regioisomers
25.87
21.50
Major
Minor
0.0424
ppm
180
160
140
120
100
80
60
40
20
-0
-20
-40

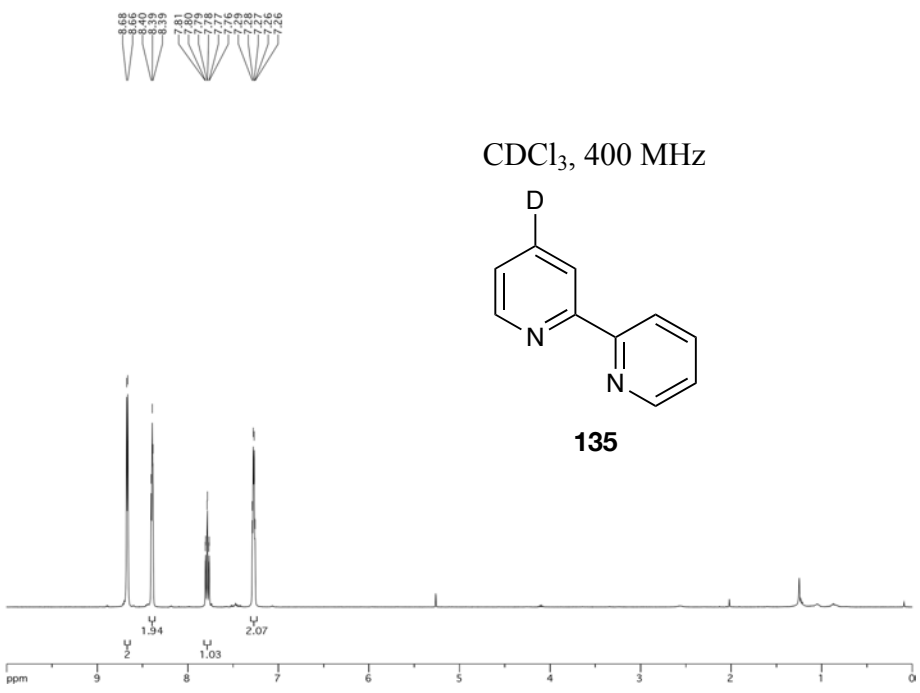

77.75
DMSO-d6, 365 MHz
20:1 Mixture of Regioisomers
Major
Minor
ppm
20
-0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200

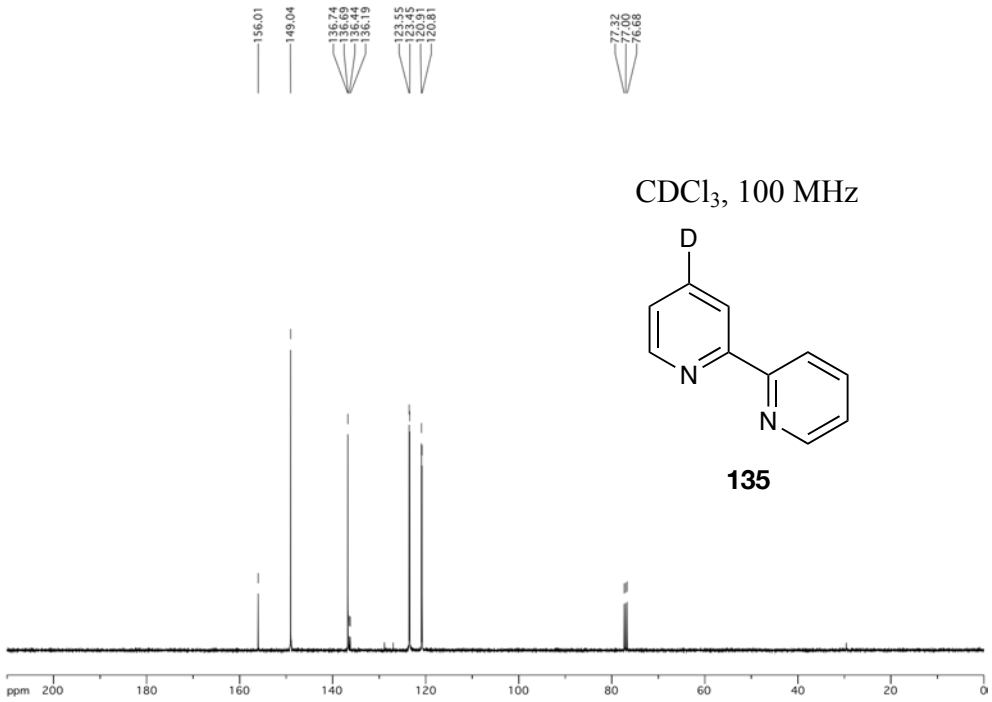
$CDCl_3$, 400 MHz

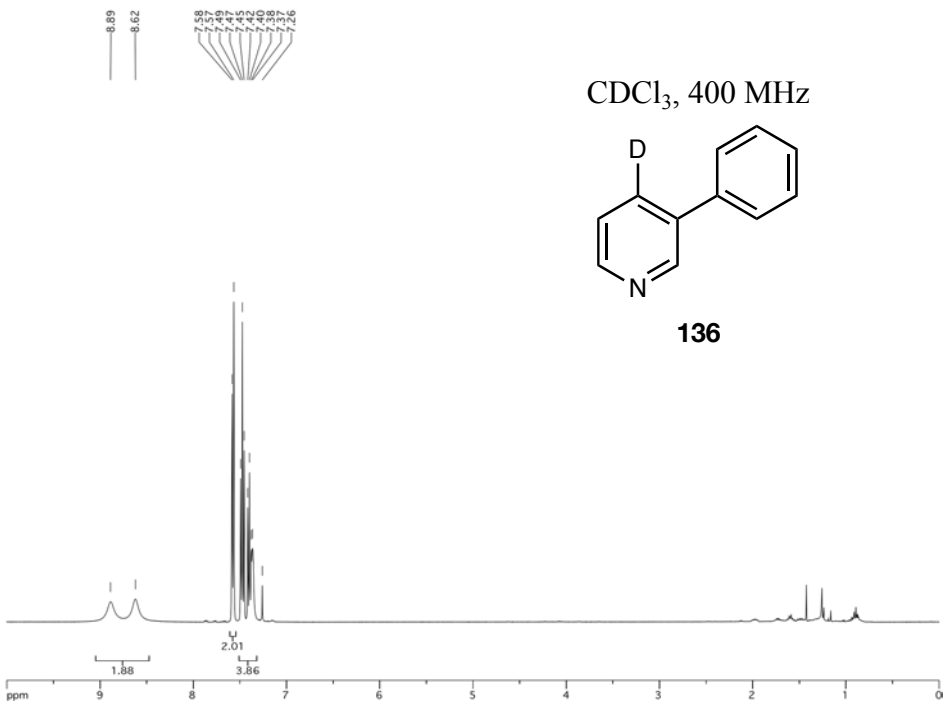


134


157.39
149.60
139.33
138.62
136.37
136.13
128.88
128.68
126.85
121.92
120.38
77.32
77.00
76.68
CDCl3, 100 MHz
D
N
134
ppm 200
180
160
140
120
100
80
60
40
20

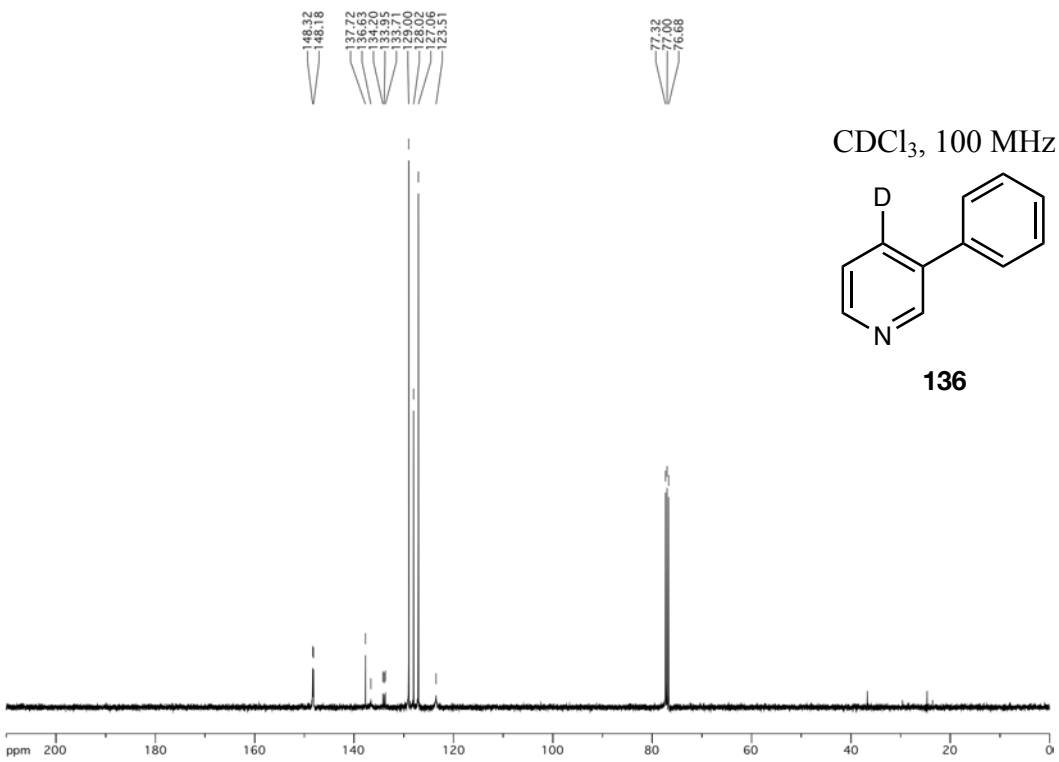

8.68
8.66
8.40
8.39
7.81
7.80
7.79
7.78
7.77
7.76
7.28
7.27
7.26
7.26
CDCl3, 400 MHz
D
N
N
135
1.94
2.07
2
1.03
ppm
9
8
7
6
5
4
3
2
1
0


156.01
149.04
136.74
136.69
136.44
136.19
123.55
123.45
120.91
120.81
77.32
77.00
76.68
CDCl3, 100 MHz
D
N
N
135
ppm 200
180
160
140
120
100
80
60
40
20



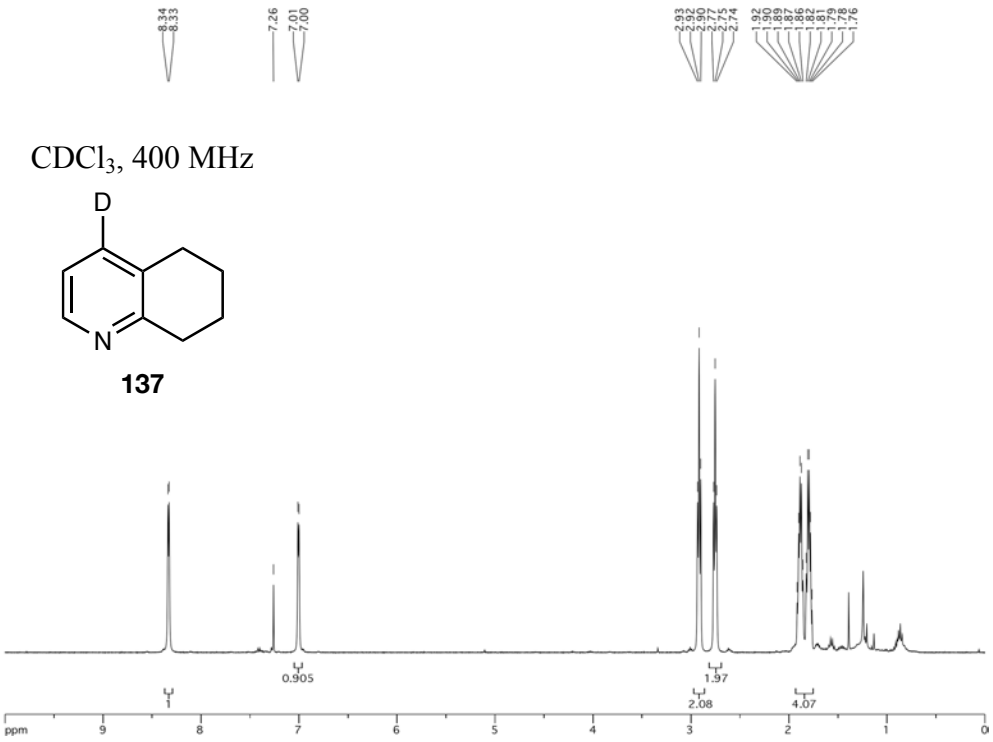
$CDCl_3$, 400 MHz

136

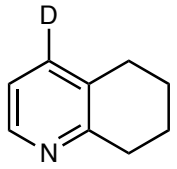


$CDCl_3$, 100 MHz

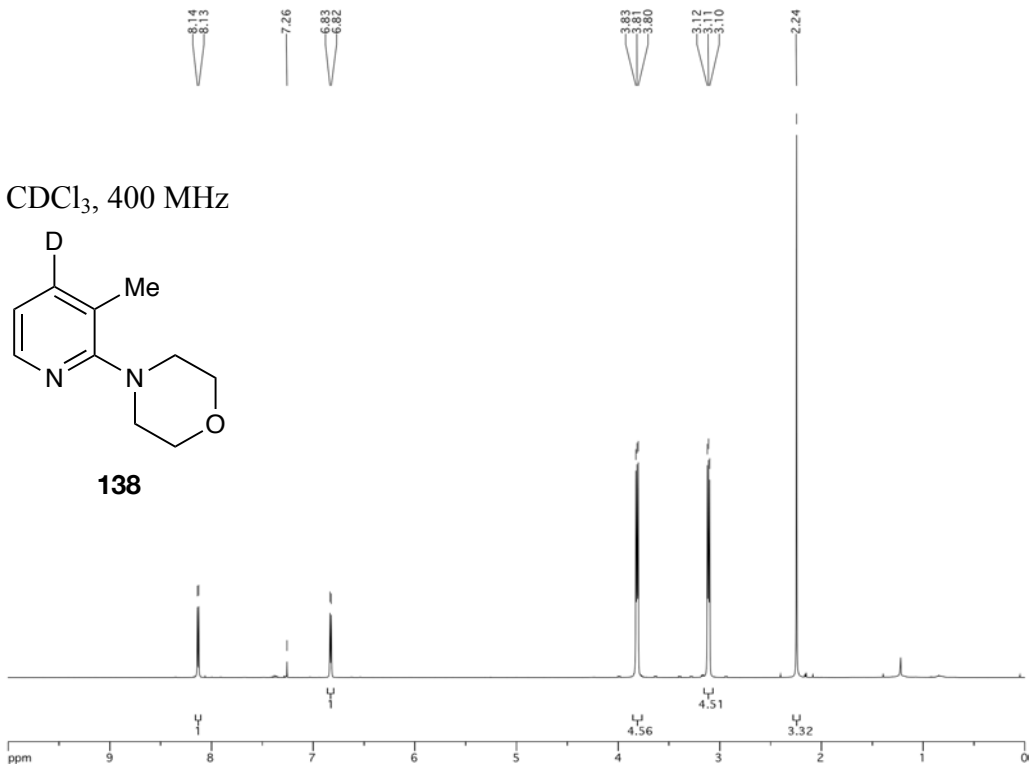
136

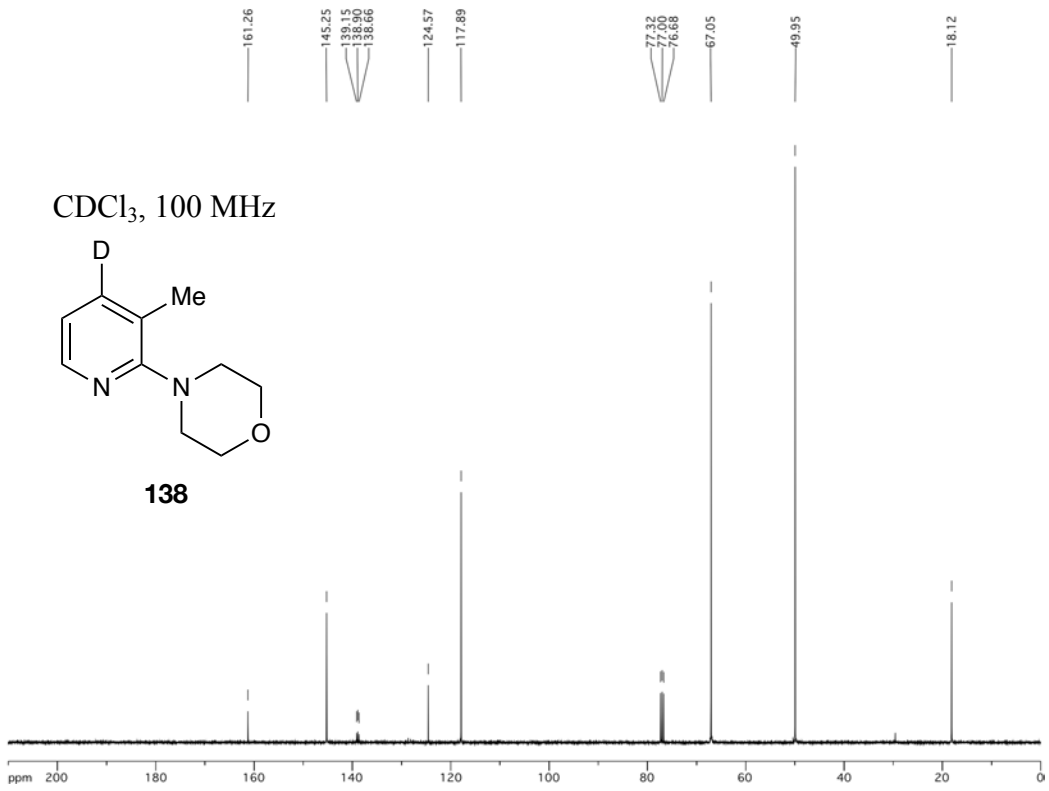

8.34
8.33
7.26
7.01
7.00
2.93
2.92
2.90
2.77
2.75
2.74
1.92
1.90
1.89
1.87
1.86
1.82
1.81
1.79
1.78
1.76
CDCl3, 400 MHz
D
N
137
0.905
1.97
1
2.08
4.07
ppm
9
8
7
6
5
4
3
2
1
0

$CDCl_3$, 100 MHz

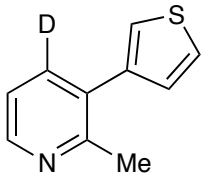


137

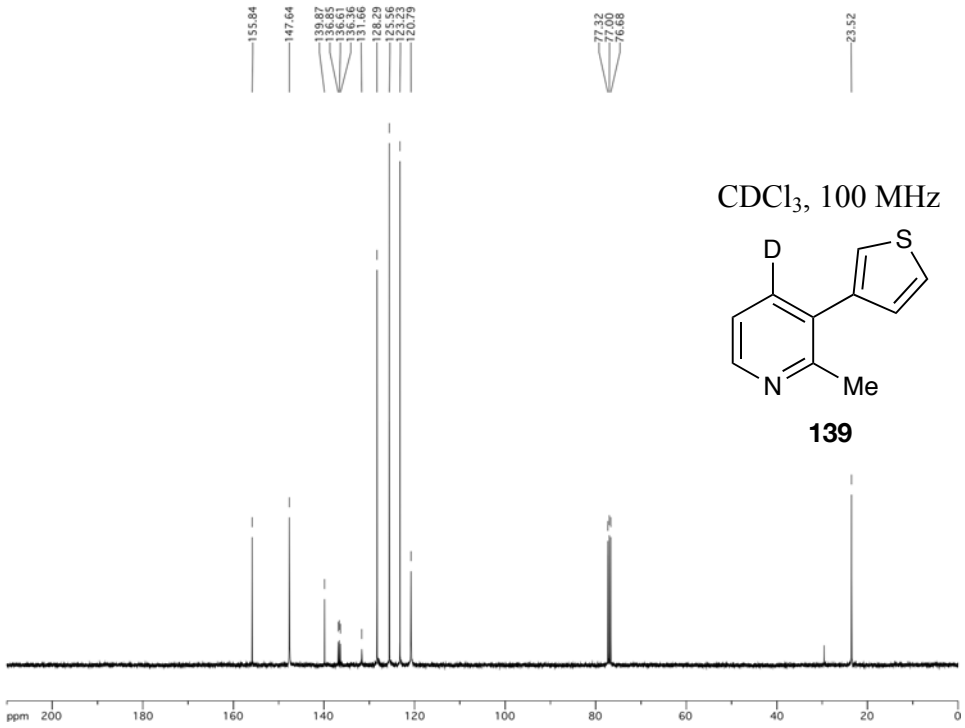

8.14
8.13
7.26
6.83
6.82
3.83
3.81
3.80
3.12
3.11
3.10
2.24
CDCl3, 400 MHz
D
Me
N
N
O
138
4.51
4.56
3.32
ppm
9
8
7
6
5
4
3
2
1
0


161.26
145.25
139.15
138.80
138.66
124.57
117.89
77.32
77.00
76.68
67.05
49.95
18.12
CDCl3, 100 MHz
D
Me
N
N
O
138
ppm 200
180
160
140
120
100
80
60
40
20
0

$CDCl_3$, 400 MHz

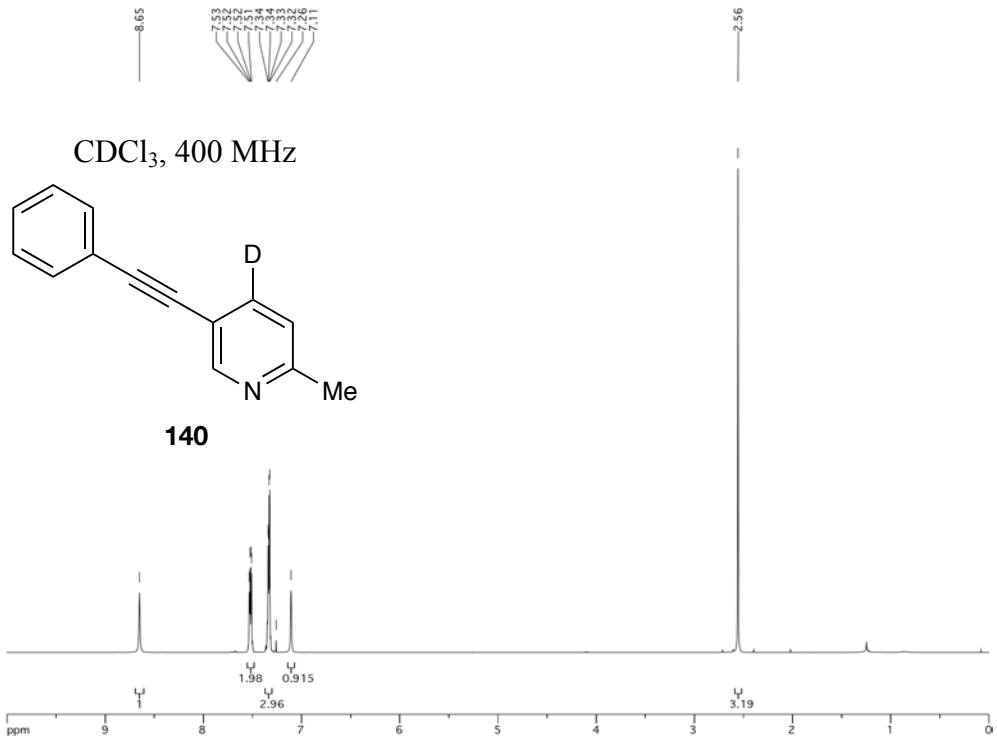


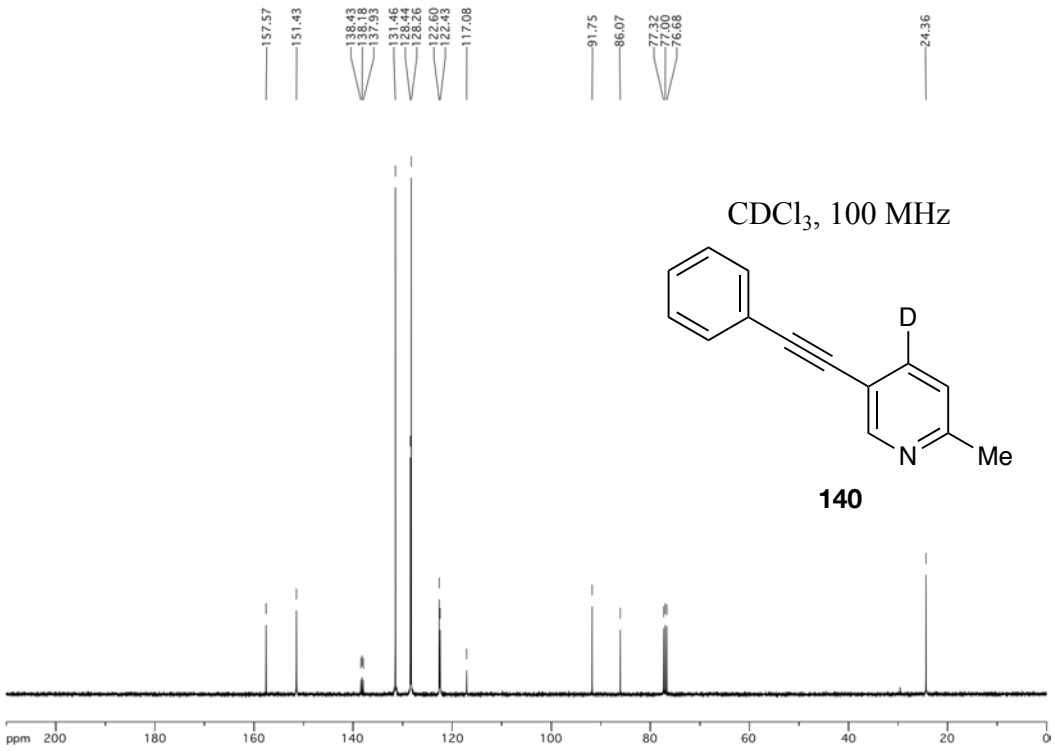
139

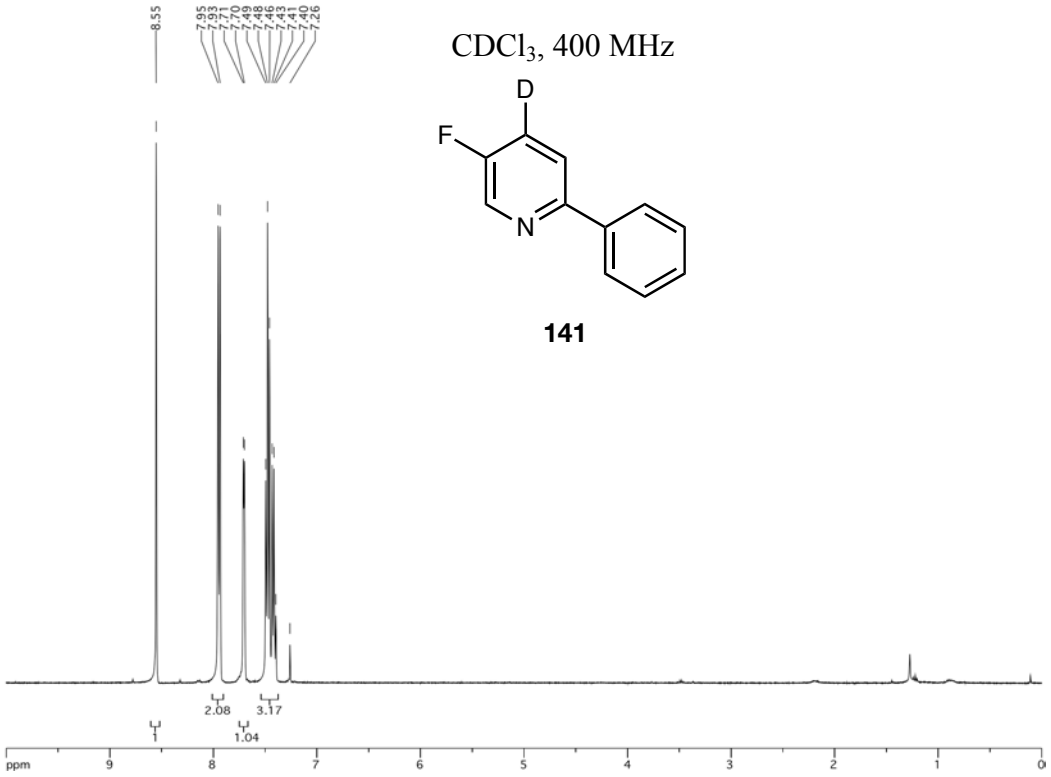


$CDCl_3$, 100 MHz

139

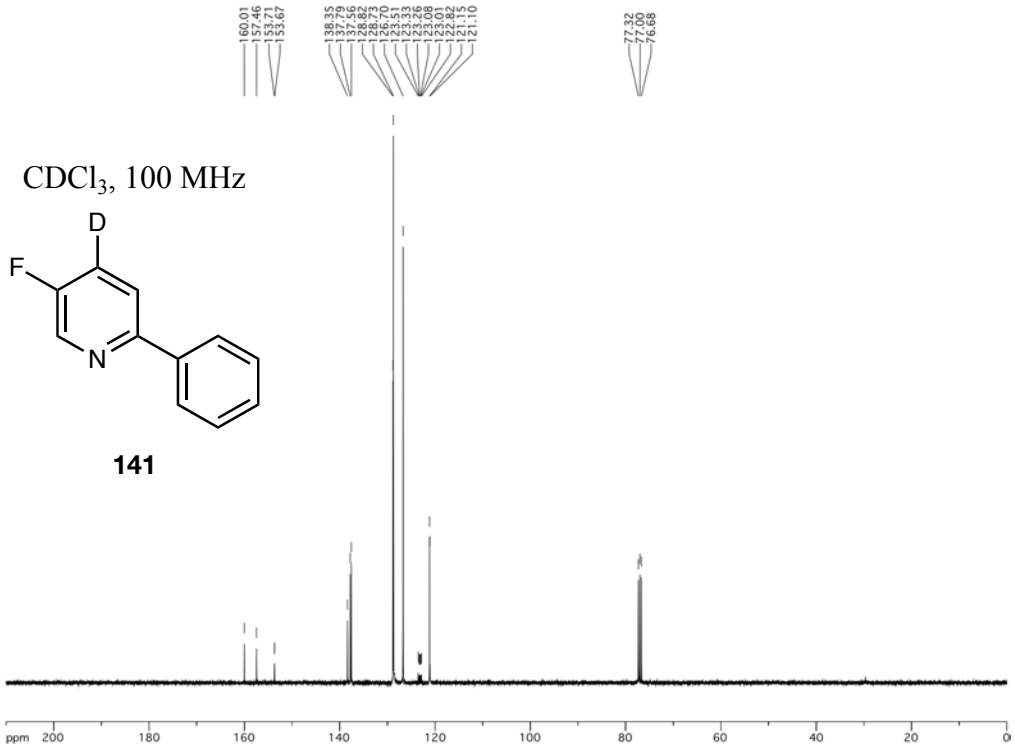

8.65
7.53
7.52
7.52
7.51
7.34
7.33
7.33
7.26
7.11
2.56
CDCl3, 400 MHz
D
N
Me
140
1.98
0.915
1
2.96
3.19
ppm
9
8
7
6
5
4
3
2
1
0


157.57
151.43
138.43
138.18
137.93
131.46
128.44
128.26
122.60
122.43
117.08
91.75
86.07
77.32
77.00
76.68
24.36
CDCl3, 100 MHz
D
N
Me
140
ppm 200
180
160
140
120
100
80
60
40
20
0

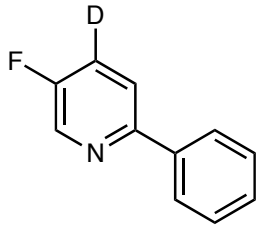


$CDCl_3$, 400 MHz

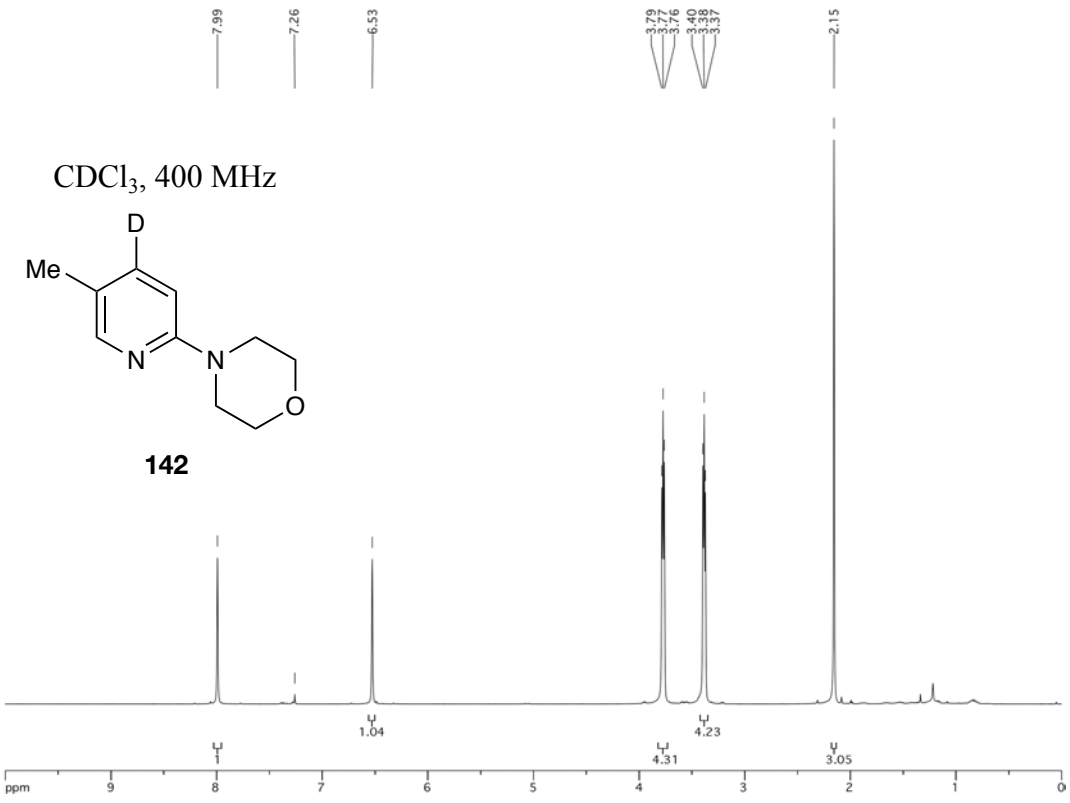
141

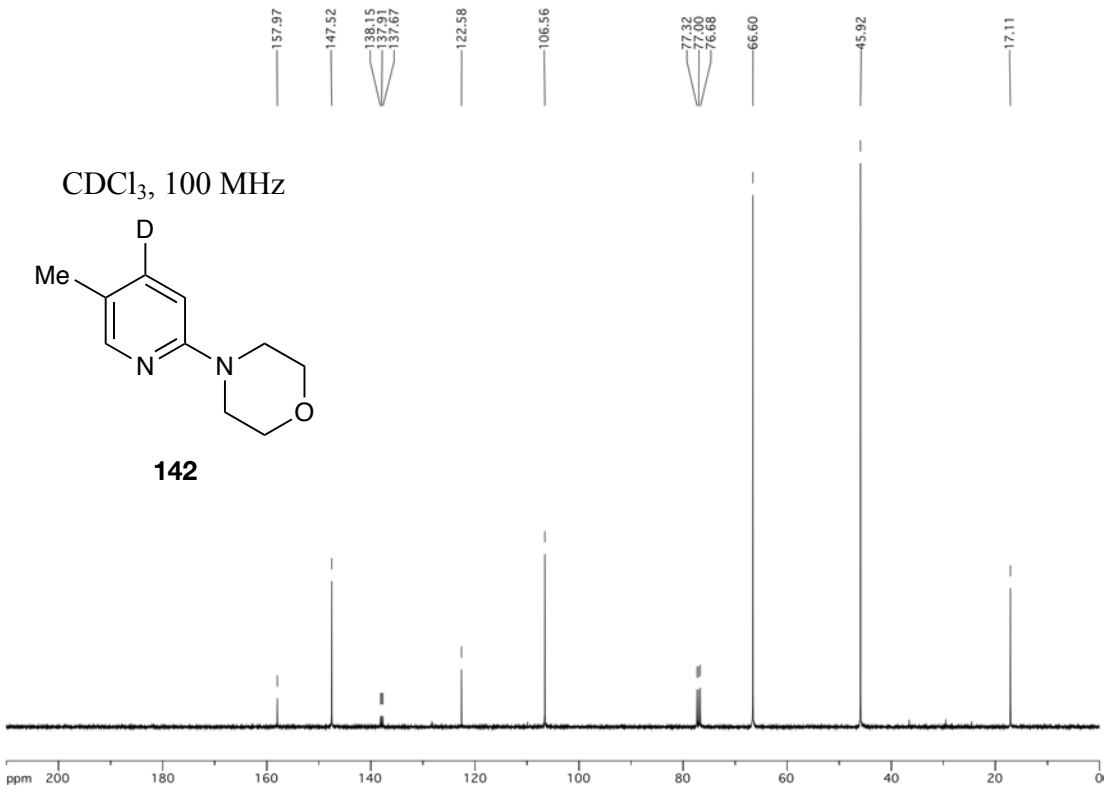

160.01
157.46
153.71
153.67
138.35
137.79
137.56
128.82
128.73
126.70
123.51
123.33
123.26
123.08
123.01
121.82
121.11
121.10
77.32
77.00
76.68
CDCl3, 100 MHz
D
F
N
141
ppm 200
180
160
140
120
100
80
60
40
20
0

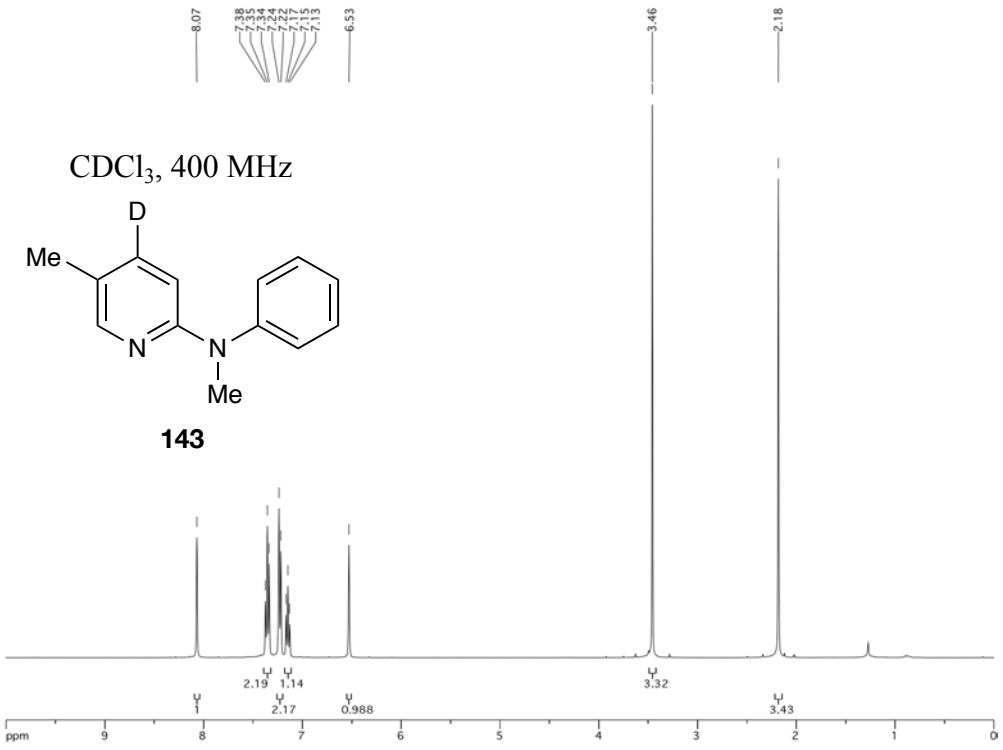
$CDCl_3$, 365 MHz

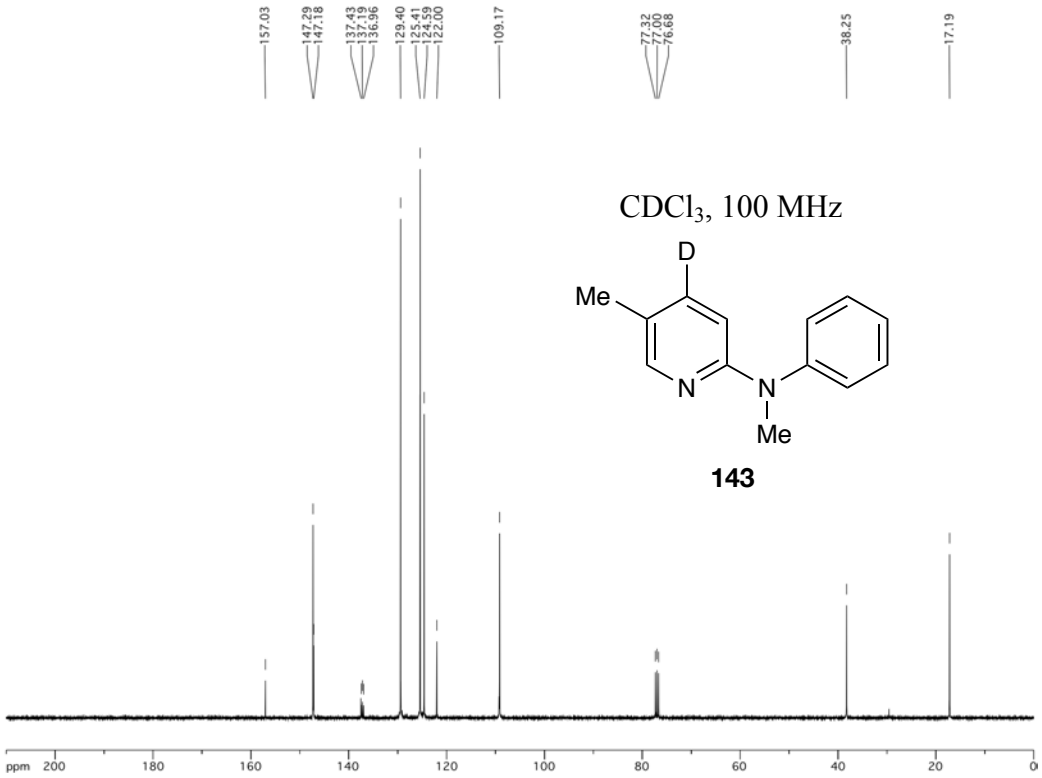


141


7.99
7.26
6.53
3.79
3.77
3.76
3.40
3.38
3.37
2.15
CDCl3, 400 MHz
D
Me
N
N
O
142
1.04
4.23
1
4.31
3.05
ppm
9
8
7
6
5
4
3
2
1
0

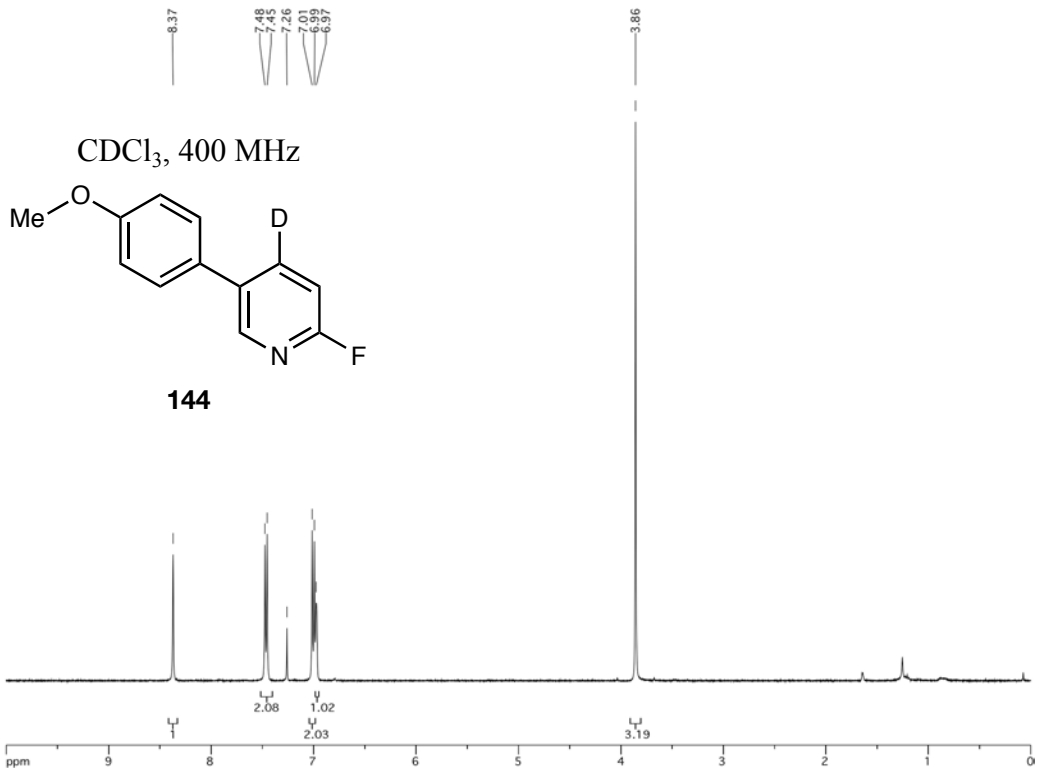

157.97
147.52
138.15
137.91
137.67
122.58
106.56
77.32
77.00
76.68
66.60
45.92
17.11
CDCl3, 100 MHz
D
Me
N
N
O
142
ppm 200
180
160
140
120
100
80
60
40
20
0

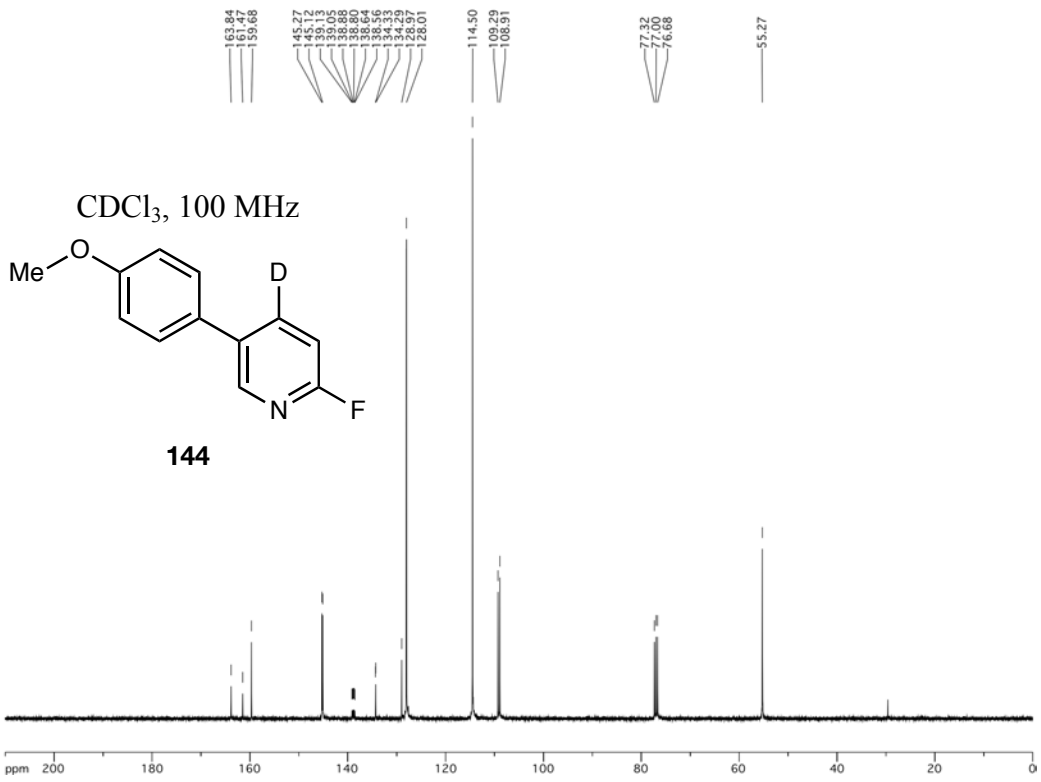

8.07
7.38
7.35
7.34
7.24
7.22
7.17
7.15
7.13
6.53
3.46
2.18
CDCl3, 400 MHz
D
Me
N
N
Me
143
2.19
1.14
3.32
1
2.17
0.988
3.43
ppm
9
8
7
6
5
4
3
2
1
0



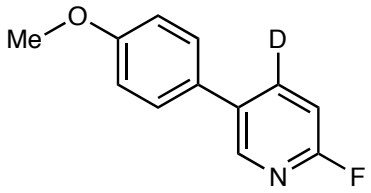
$CDCl_3$, 100 MHz

143

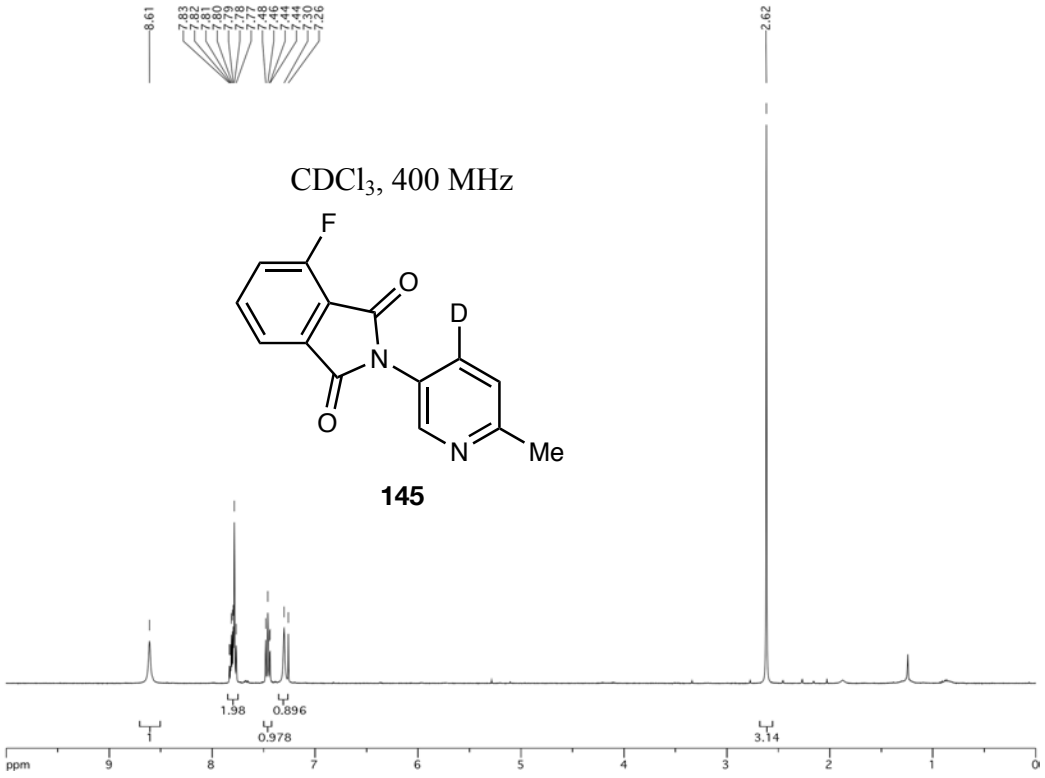

8.37
7.48
7.45
7.26
7.01
6.99
6.97
3.86
CDCl3, 400 MHz
Me
O
D
N
F
144
2.08
1.02
1
2.03
3.19
ppm
9
8
7
6
5
4
3
2
1
0

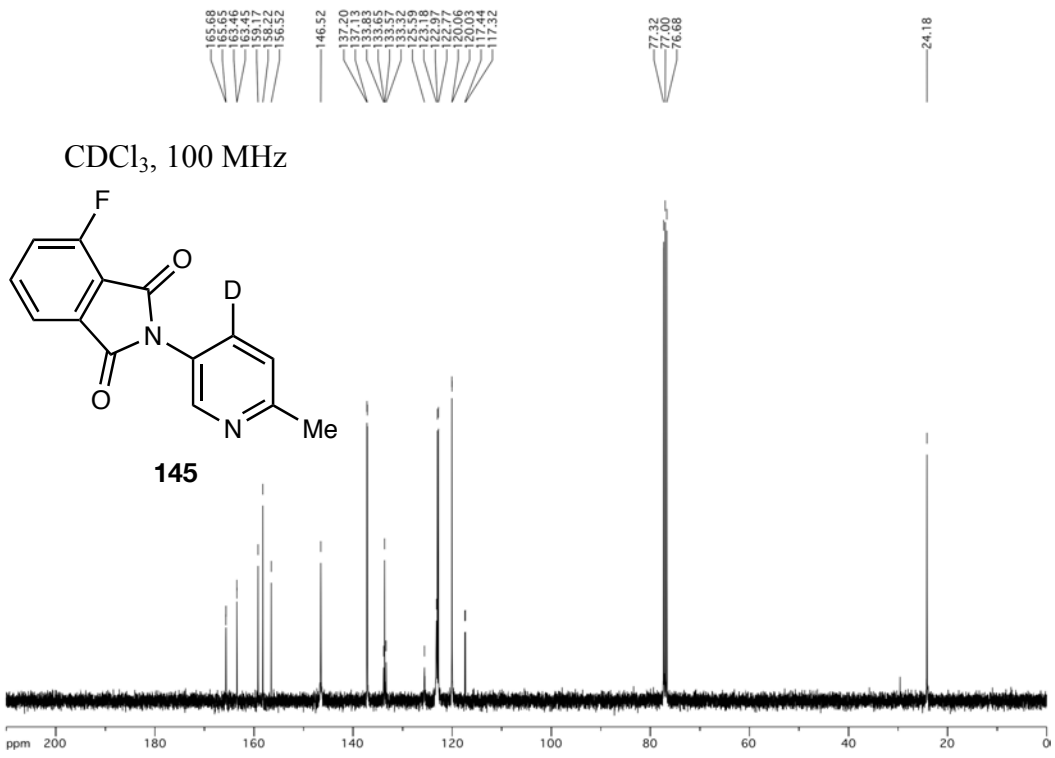

163.84
161.47
159.68
145.27
145.17
139.13
139.05
138.88
138.80
138.64
138.56
134.33
134.29
128.97
128.01
114.50
109.29
108.91
77.32
77.00
76.68
55.27
CDCl3, 100 MHz
Me
O
D
N
F
144
ppm 200 180 160 140 120 100 80 60 40 20 0

$CDCl_3$, 365 MHz

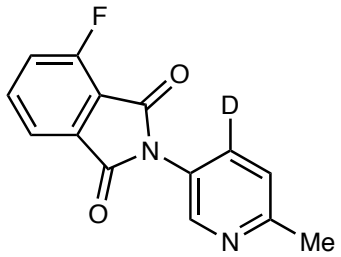


144

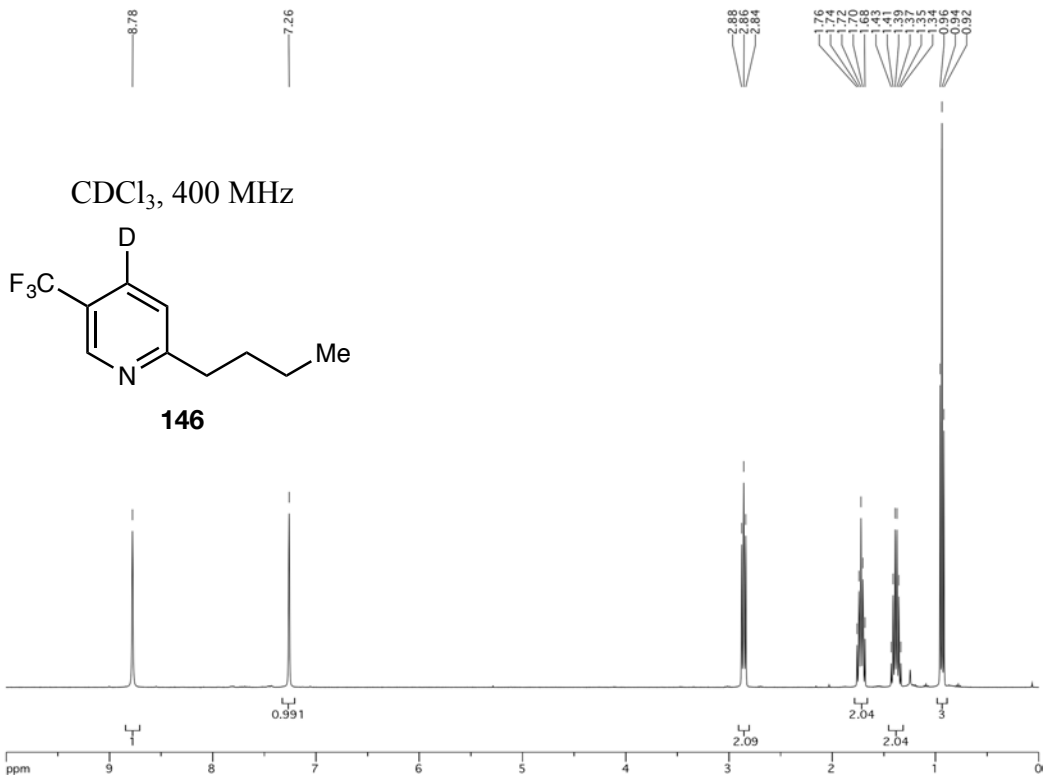

8.61
7.83
7.82
7.81
7.80
7.79
7.78
7.77
7.48
7.46
7.44
7.44
7.30
7.26
2.62
CDCl3, 400 MHz
F
O
D
N
O
N
Me
145
1.98
0.896
1
0.978
3.14
ppm
9
8
7
6
5
4
3
2
1
0

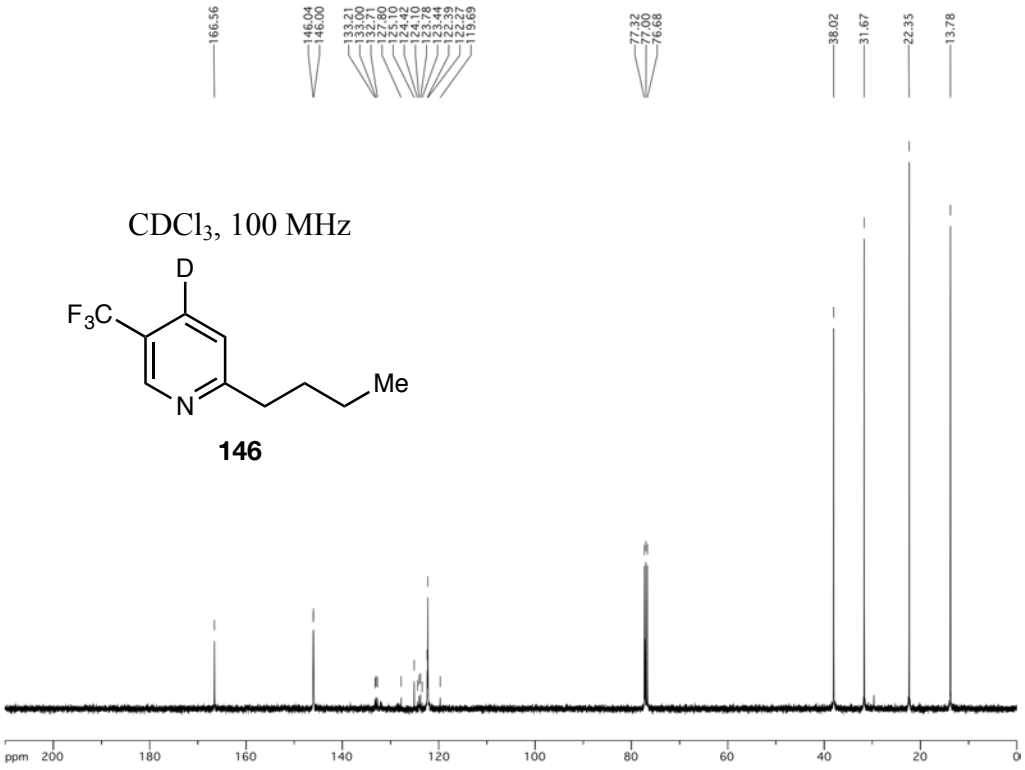

165.68
165.65
163.46
163.45
159.17
158.12
156.52
146.52
137.20
137.13
133.88
133.65
133.57
133.32
125.59
125.18
122.97
122.77
120.06
120.03
117.44
117.32
77.32
77.00
76.68
24.18
CDCl3, 100 MHz
F
O
D
N
O
N
Me
145
ppm 200 180 160 140 120 100 80 60 40 20 0

$CDCl_3$, 365 MHz

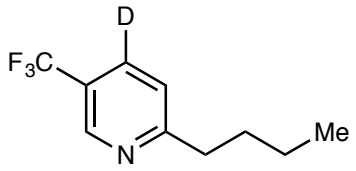


145

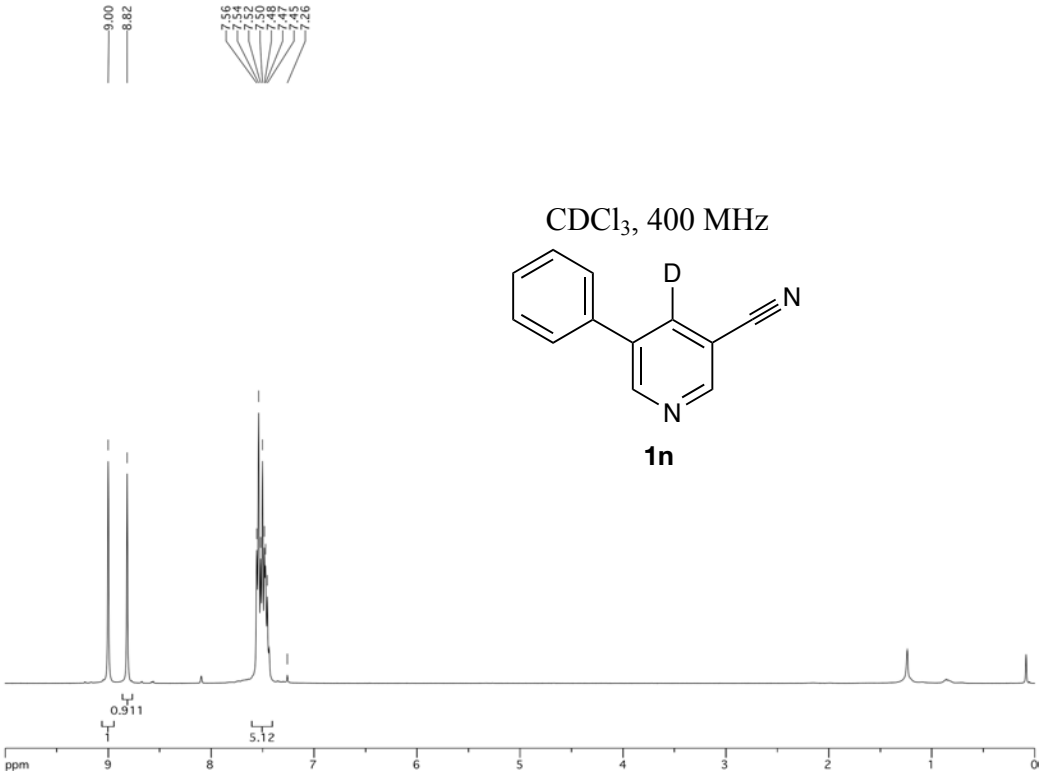

8.78
7.26
2.88
2.86
2.84
1.76
1.74
1.72
1.70
1.68
1.43
1.41
1.39
1.37
1.35
1.34
0.96
0.94
0.92
CDCl3, 400 MHz
D
F3C
N
Me
146
0.991
2.04
3
1
2.09
2.04
ppm
9
8
7
6
5
4
3
2
1
0

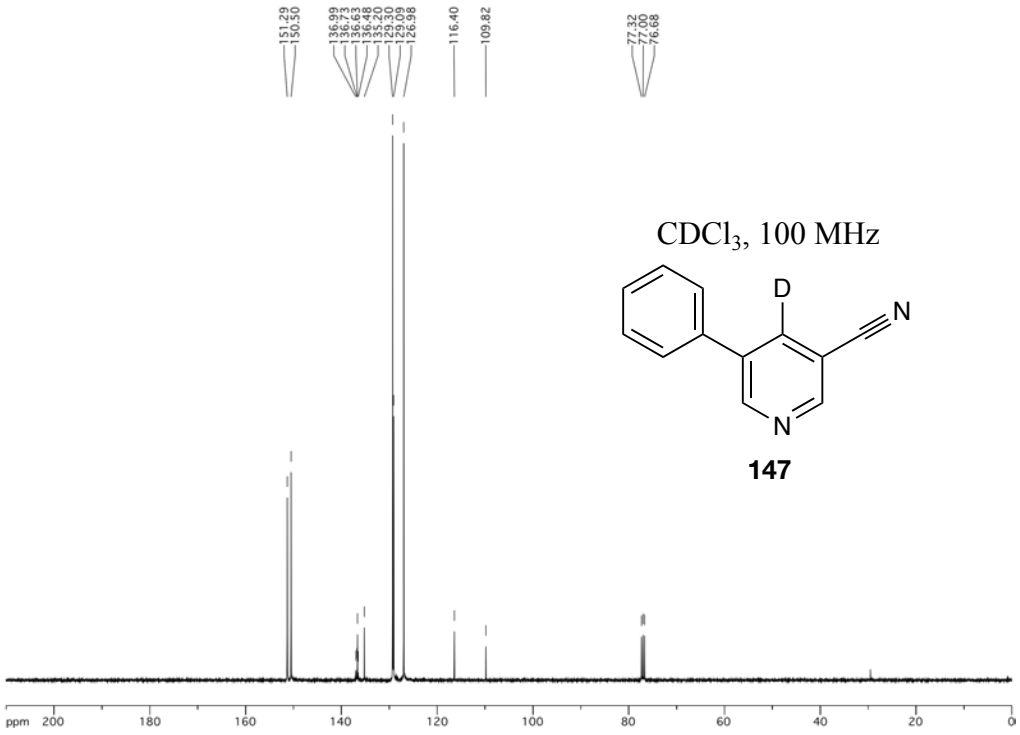

166.56
146.04
146.00
133.21
133.00
132.71
132.80
121.80
121.10
124.42
124.10
123.78
123.44
122.34
122.27
119.69
77.32
77.00
76.68
38.02
31.67
22.35
13.78
CDCl3, 100 MHz
D
F3C
N
Me
146
ppm 200
180
160
140
120
100
80
60
40
20
0

$CDCl_3$, 365 MHz



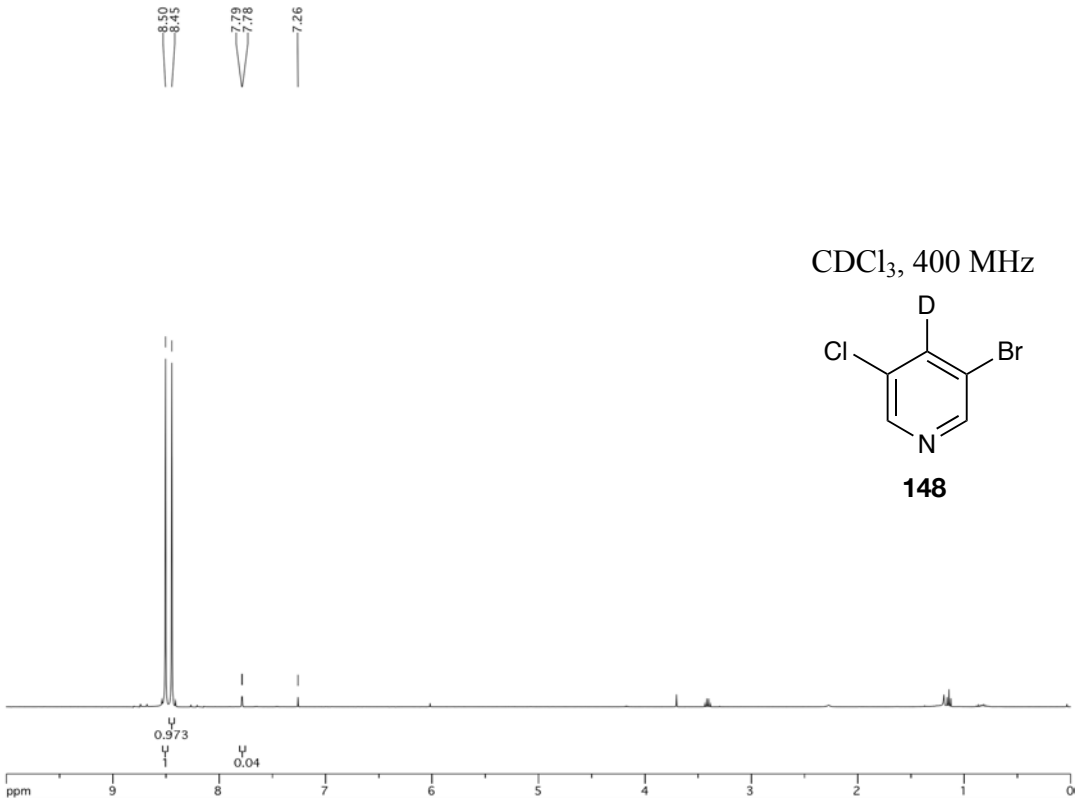
146


9.00
8.82
7.56
7.54
7.52
7.50
7.48
7.47
7.45
7.26
CDCl3, 400 MHz
D
N
N
1n
0.911
5.12
ppm
9
8
7
6
5
4
3
2
1
0



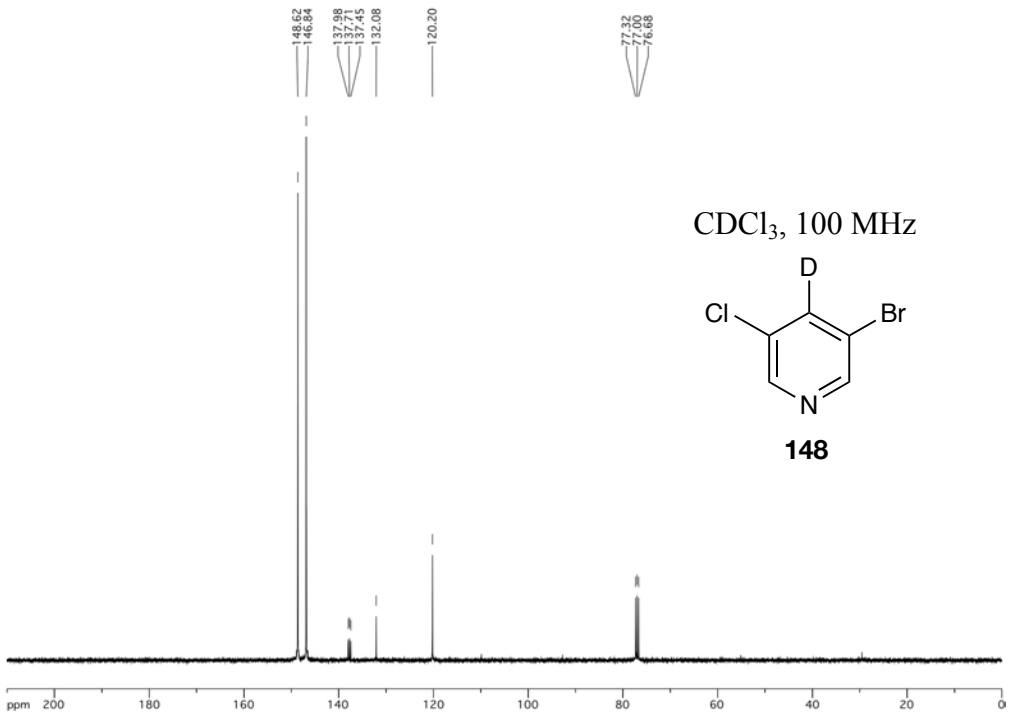
$CDCl_3$, 100 MHz

147



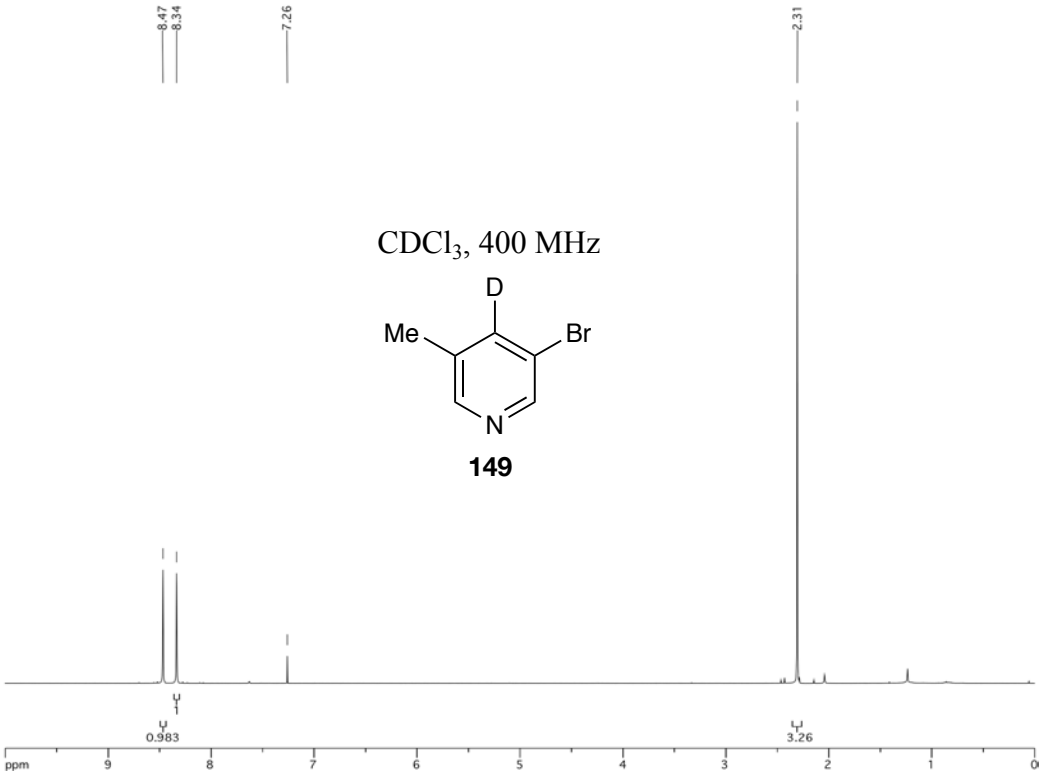
$CDCl_3$, 400 MHz

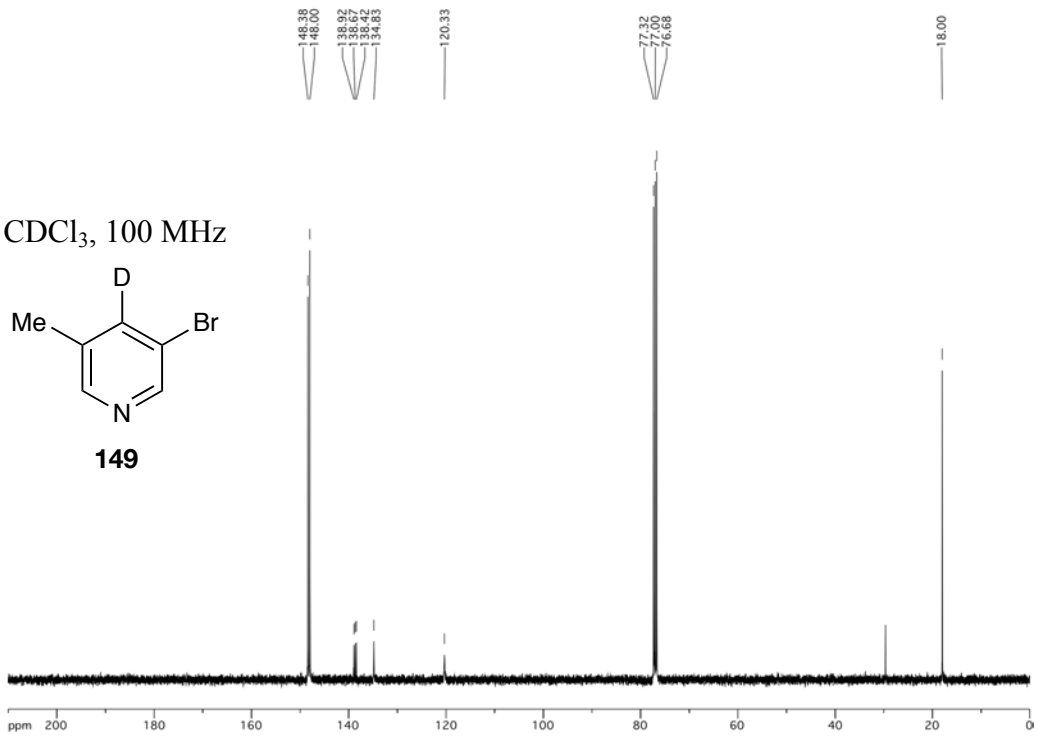
148

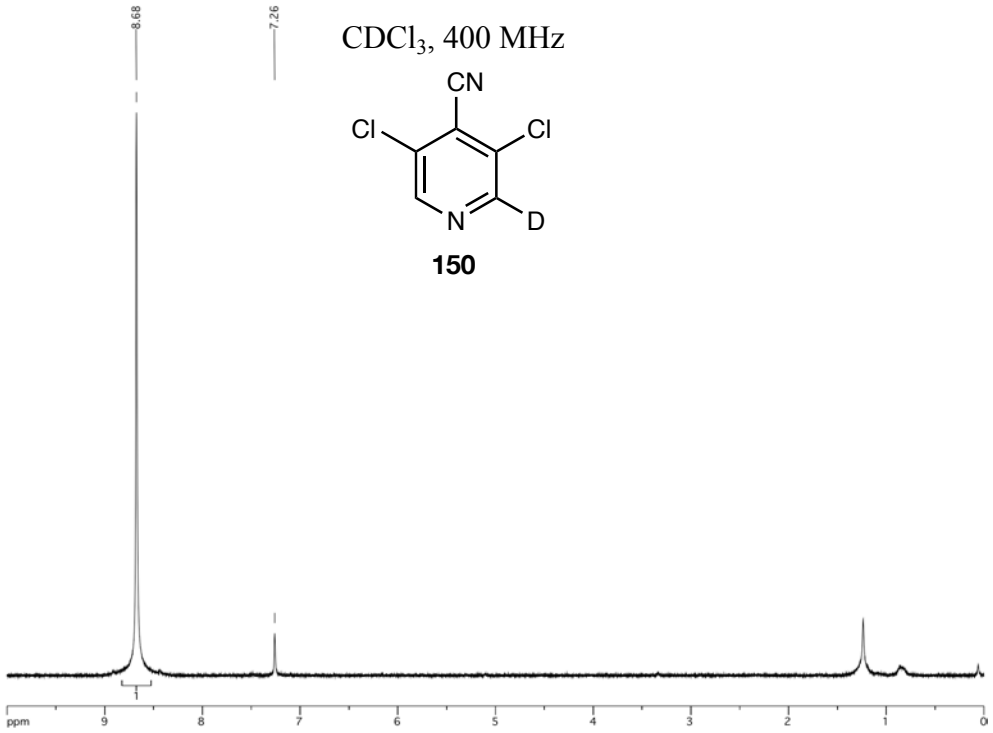


$CDCl_3$, 100 MHz

148

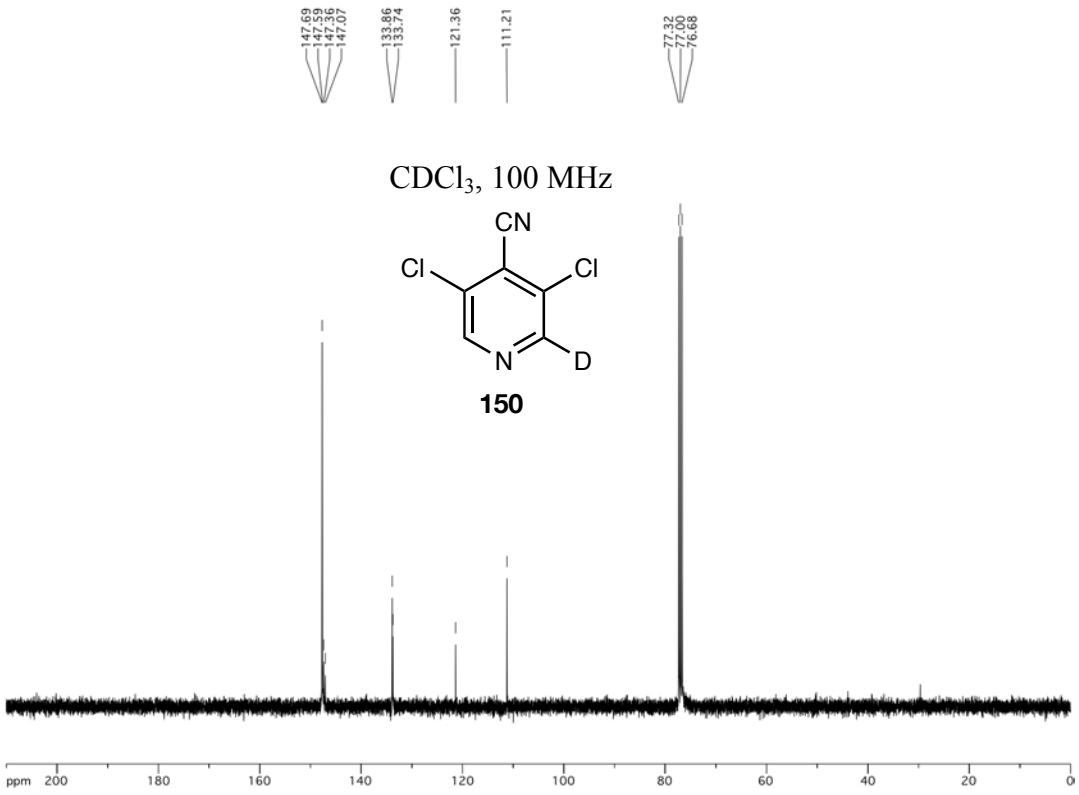

8.47
8.34
7.26
2.31
CDCl3, 400 MHz
D
Me
Br
N
149
0.983
3.26
ppm
9
8
7
6
5
4
3
2
1
0

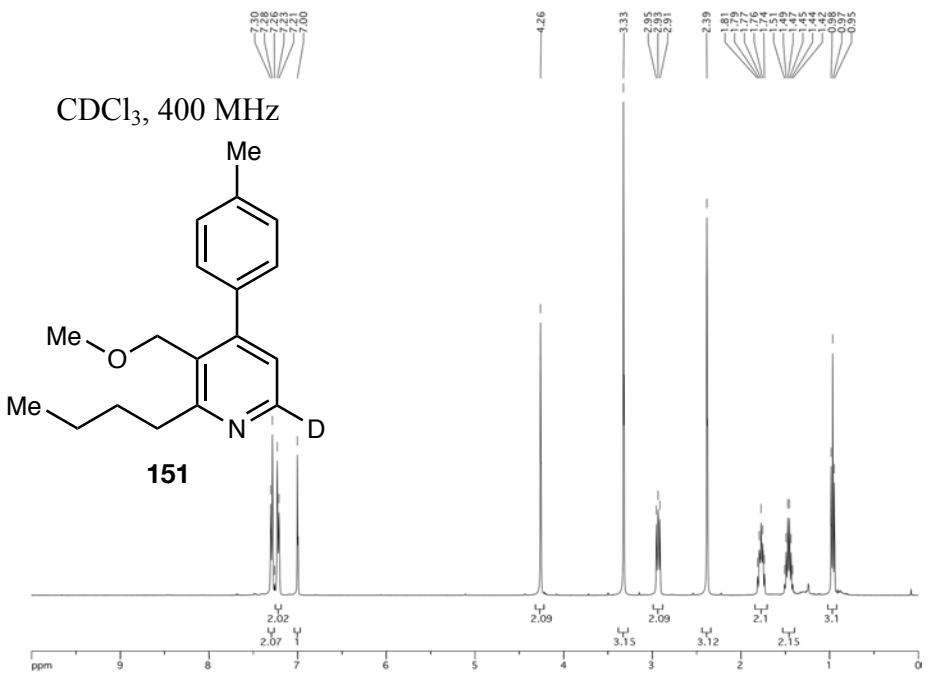

148.38
148.00
138.92
138.67
138.42
134.83
120.33
77.32
77.00
76.68
18.00
CDCl3, 100 MHz
D
Me
Br
N
149
ppm 200
180
160
140
120
100
80
60
40
20
0

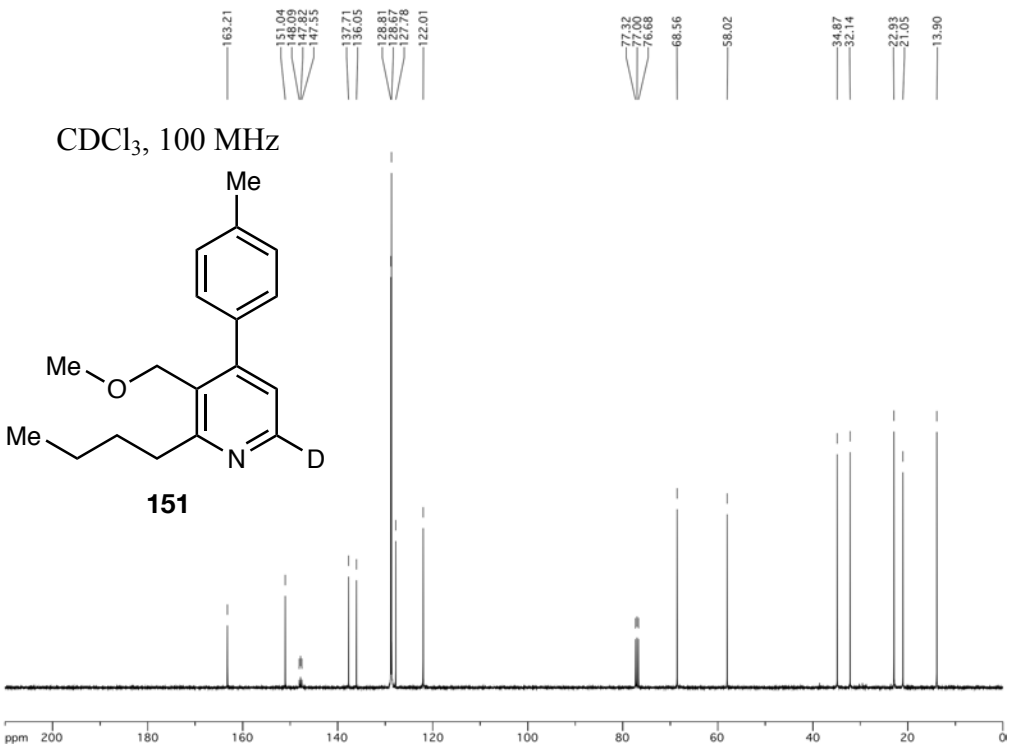


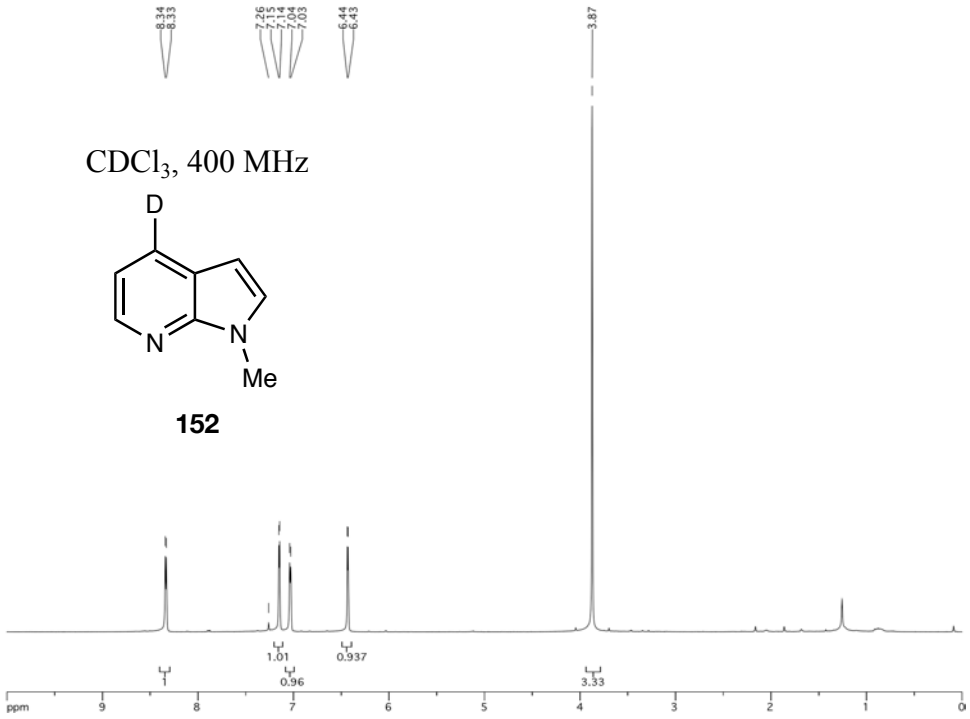
$CDCl_3$, 400 MHz

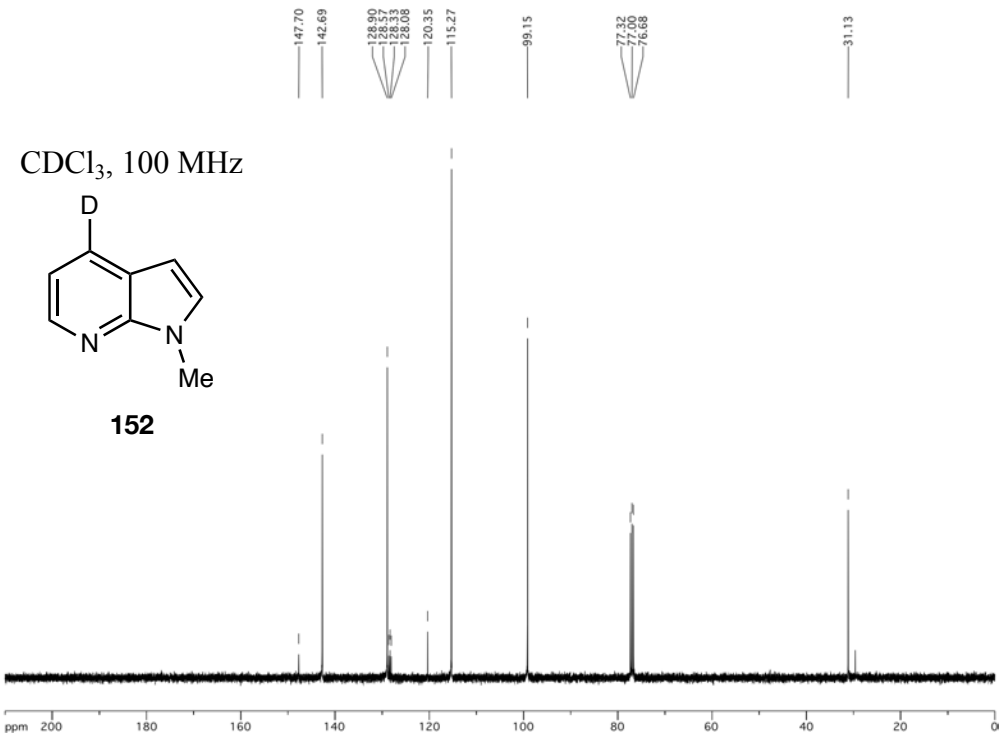
150

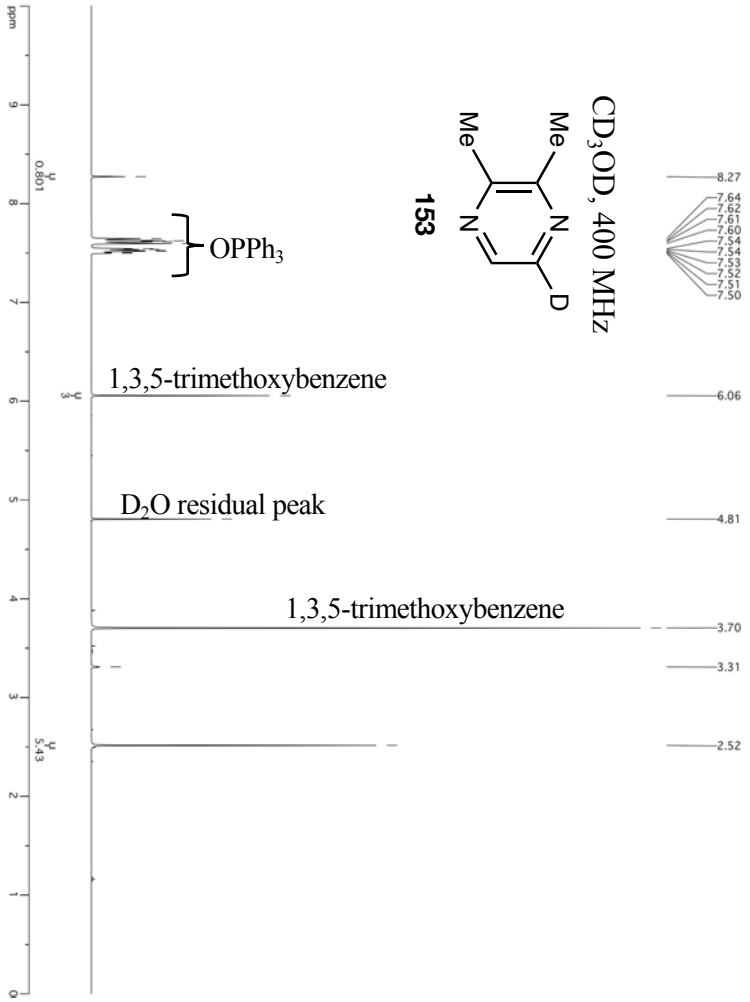

147.69
147.59
147.36
147.07
133.86
133.74
121.36
111.21
77.32
77.00
76.68
CDCl3, 100 MHz
CN
Cl
Cl
N
D
150
ppm 200
180
160
140
120
100
80
60
40
20
0

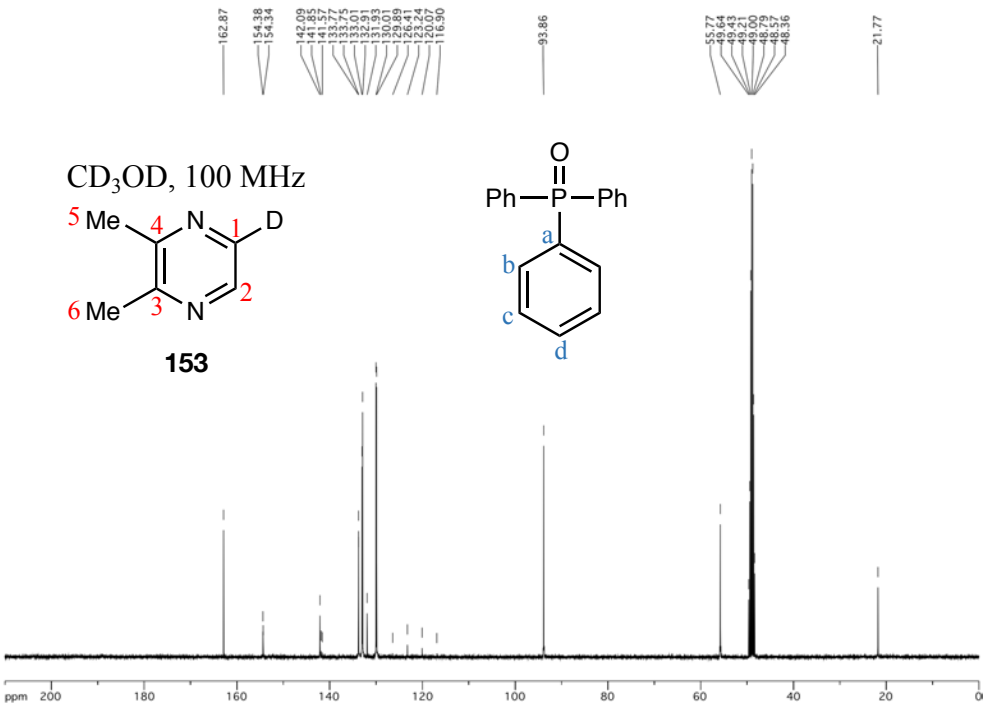

CDCl3, 400 MHz
Me
Me
O
Me
N
D
151
7.30
7.28
7.26
7.25
7.23
7.21
7.00
4.26
3.33
2.95
2.93
2.91
2.39
1.81
1.79
1.77
1.76
1.74
1.51
1.49
1.47
1.45
1.44
1.42
1.39
0.97
0.95
2.02
2.07
1
2.09
2.09
3.15
2.1
3.12
2.15
3.1
ppm
9
8
7
6
5
4
3
2
1
0

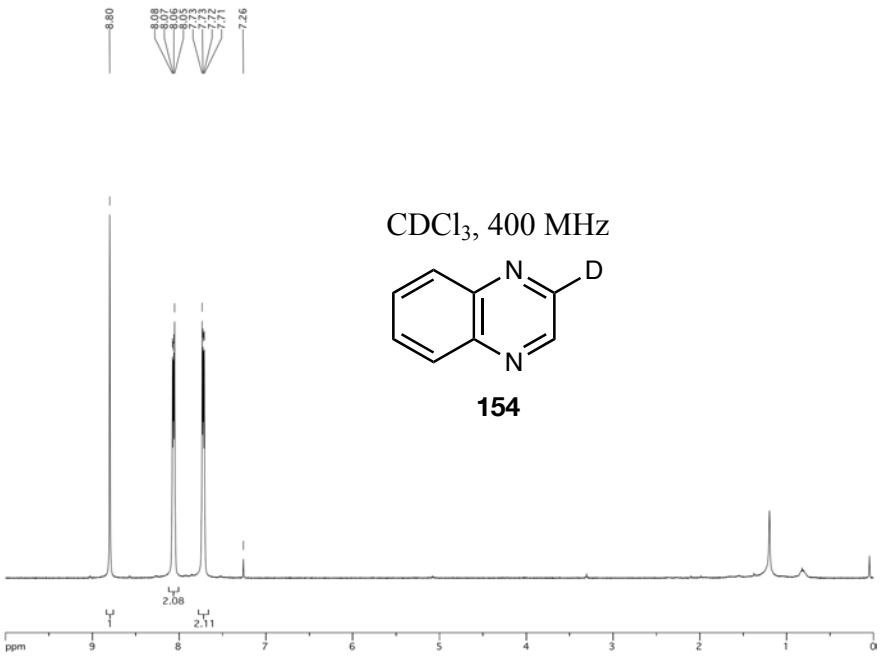

163.21
151.04
148.09
147.22
147.55
137.71
136.05
128.81
128.67
127.78
122.01
77.32
77.00
76.68
68.56
58.02
34.87
32.14
22.93
21.05
13.90
CDCl3, 100 MHz
Me
Me
O
Me
N
D
151
ppm 200
180
160
140
120
100
80
60
40
20


8.34
8.33
7.26
7.15
7.14
7.04
7.03
6.44
6.43
3.87
CDCl3, 400 MHz
D
N
N
Me
152
1.01
0.96
0.937
1
3.33
ppm
9
8
7
6
5
4
3
2
1
0


147.70
142.69
128.90
128.57
128.33
128.08
120.35
115.27
99.15
77.32
77.00
76.68
31.13
CDCl3, 100 MHz
D
N
N
Me
152
ppm 200
180
160
140
120
100
80
60
40
20

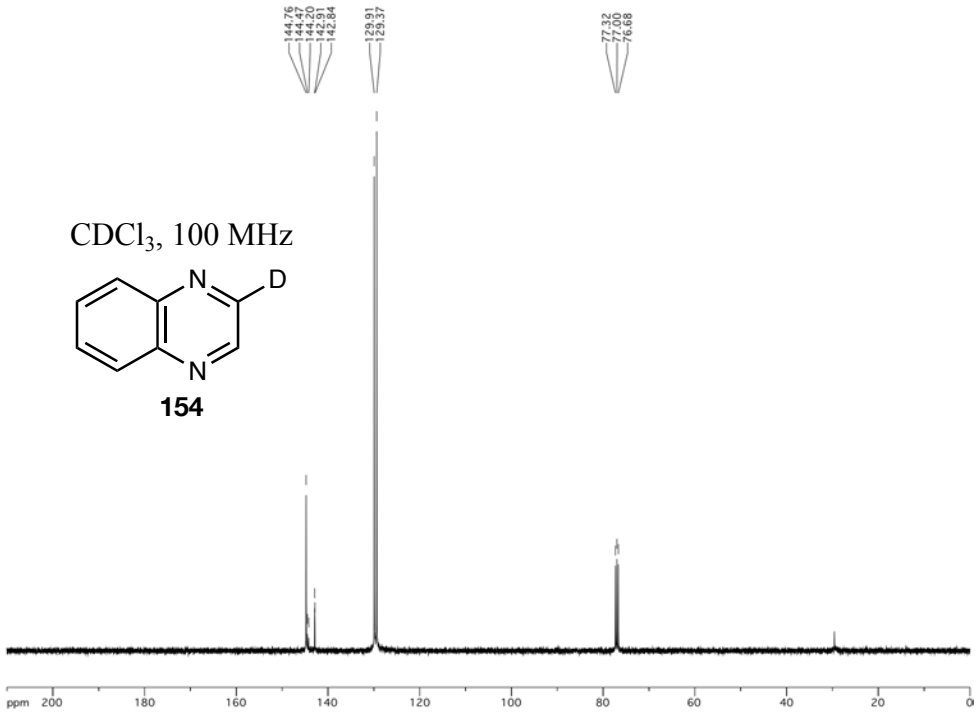

CD3OD, 400 MHz
153
Me
Me
N
N
D
OPPh3
1,3,5-trimethoxybenzene
D2O residual peak
1,3,5-trimethoxybenzene
8.27
7.64
7.62
7.61
7.60
7.54
7.54
7.53
7.52
7.51
7.50
6.06
4.81
3.70
3.31
2.52
ppm

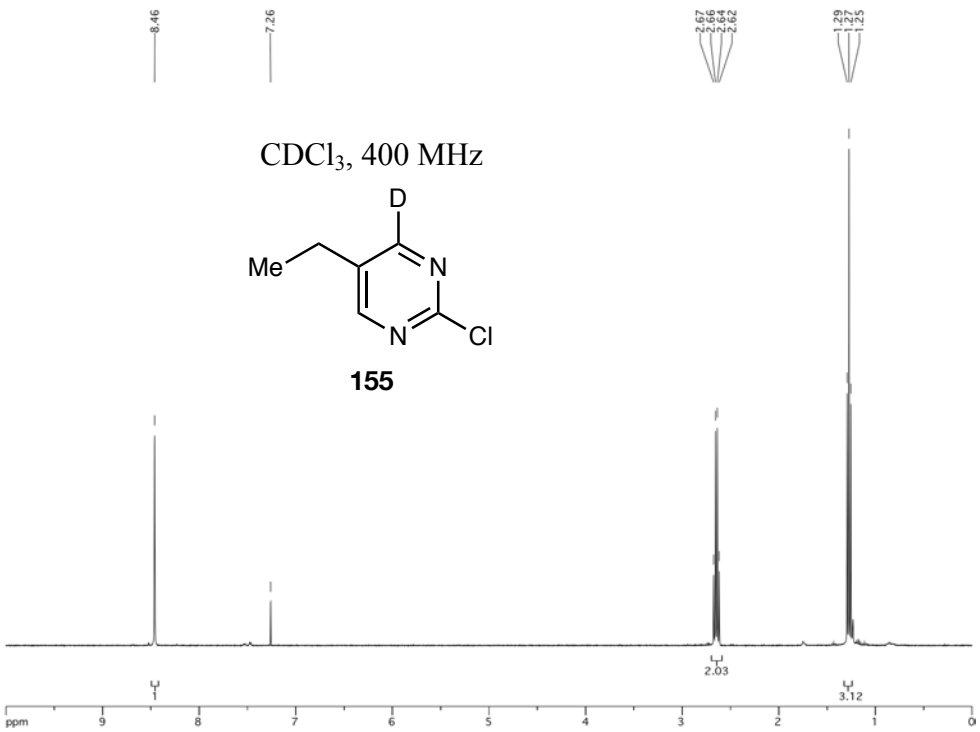

162.87
154.38
154.34
142.09
141.85
141.57
133.77
133.75
133.01
132.91
132.53
130.01
129.89
126.41
126.24
120.07
116.90
93.86
55.77
49.64
49.43
49.21
49.00
48.79
48.57
48.36
21.77
CD3OD, 100 MHz
5 Me
4
N
1
D
6 Me
3
N
2
153
O
Ph
P
Ph
a
b
c
d
ppm 200
180
160
140
120
100
80
60
40
20
0

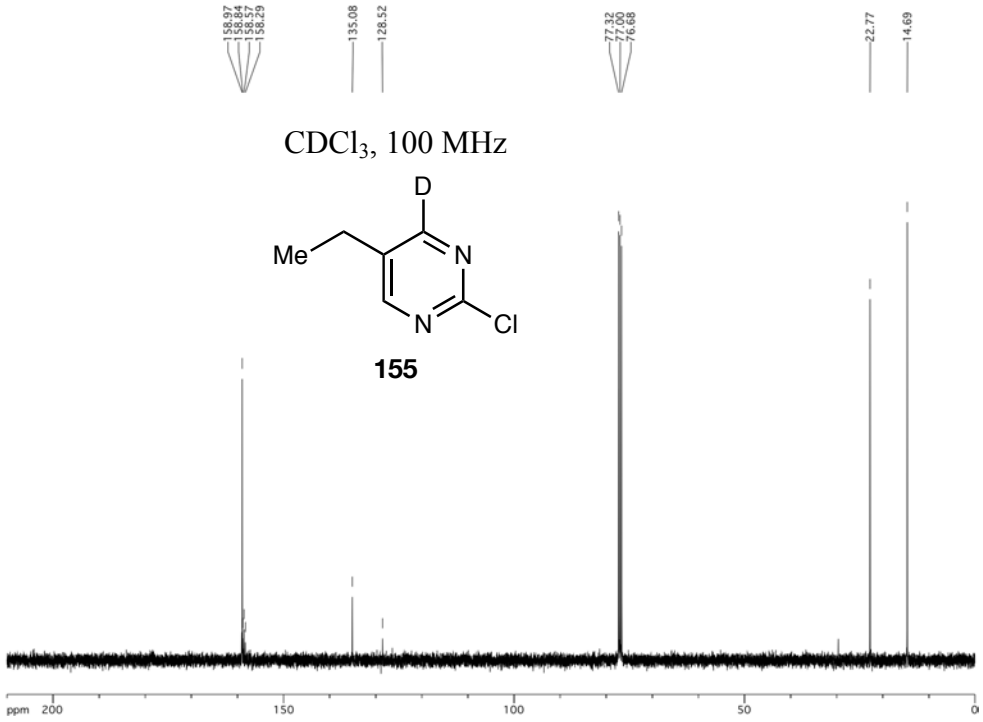


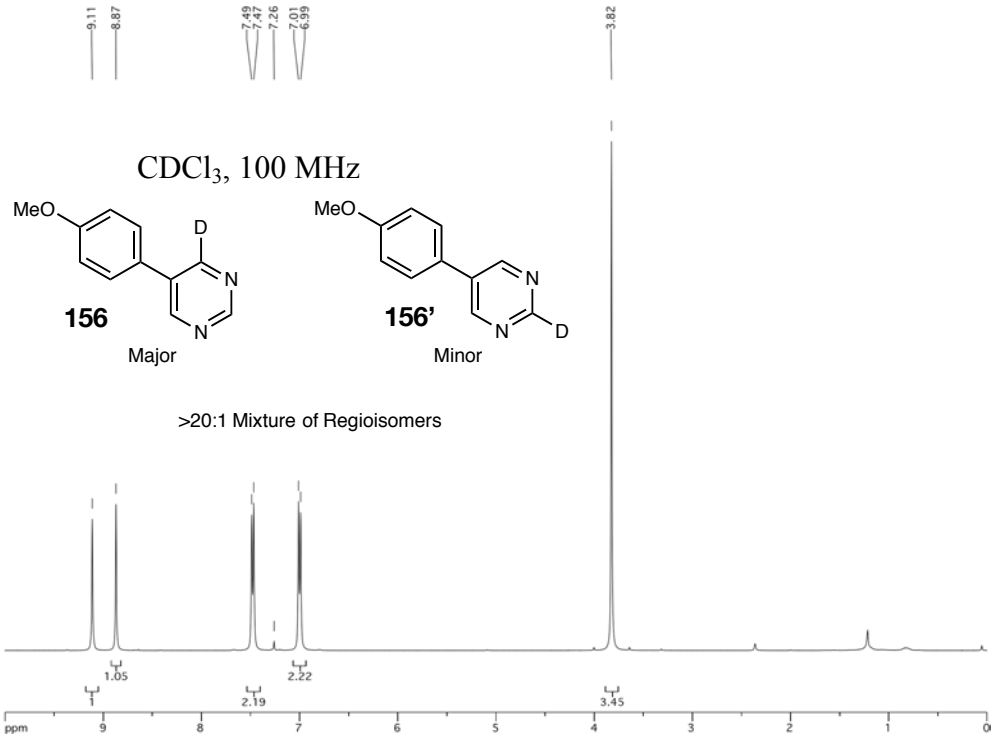
$CDCl_3$, 400 MHz

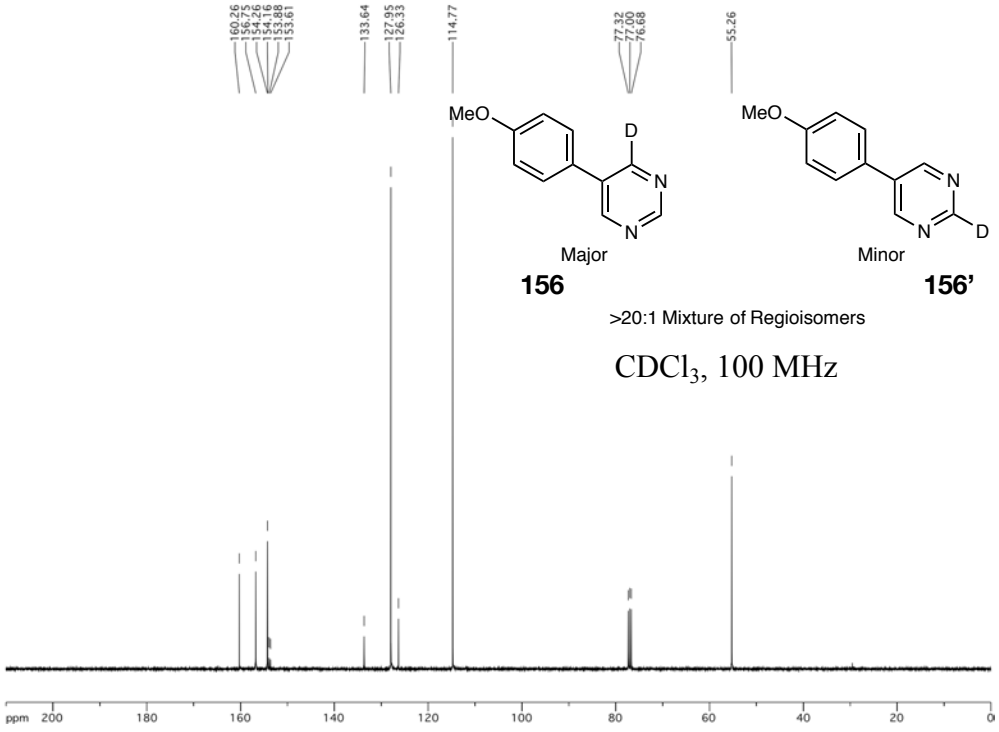
154

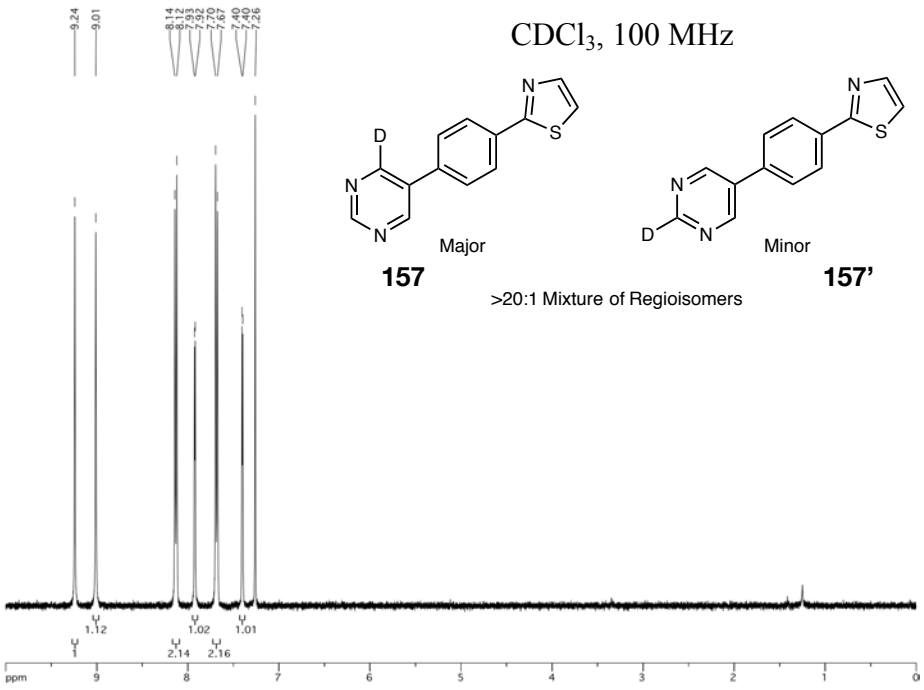

144.76
144.47
144.20
142.91
142.64
129.91
129.37
77.32
77.00
76.68
CDCl3, 100 MHz
N
D
N
154
ppm 200 180 160 140 120 100 80 60 40 20 0


8.46
7.26
2.67
2.66
2.64
2.62
1.29
1.27
1.25
CDCl3, 400 MHz
D
Me
N
N
Cl
155
2.03
3.12
ppm
9
8
7
6
5
4
3
2
1
0


158.97
158.84
158.57
158.29
135.08
128.52
77.32
77.00
76.68
22.77
14.69
CDCl3, 100 MHz
D
Me
N
N
Cl
155
ppm 200
150
100
50


9.11
8.87
7.49
7.47
7.26
7.01
6.99
3.82
CDCl3, 100 MHz
MeO
D
N
N
156
Major
MeO
N
N
D
156'
Minor
>20:1 Mixture of Regioisomers
1.05
2.22
1
2.19
3.45
ppm
9
8
7
6
5
4
3
2
1
0


160.26
156.75
154.26
154.16
153.88
153.61
133.64
127.95
126.33
114.77
77.32
77.00
76.68
55.26
MeO
D
N
N
Major
156
MeO
N
N
D
Minor
156'
>20:1 Mixture of Regioisomers
CDCl3, 100 MHz
ppm 200
180
160
140
120
100
80
60
40
20



$CDCl_3$, 100 MHz

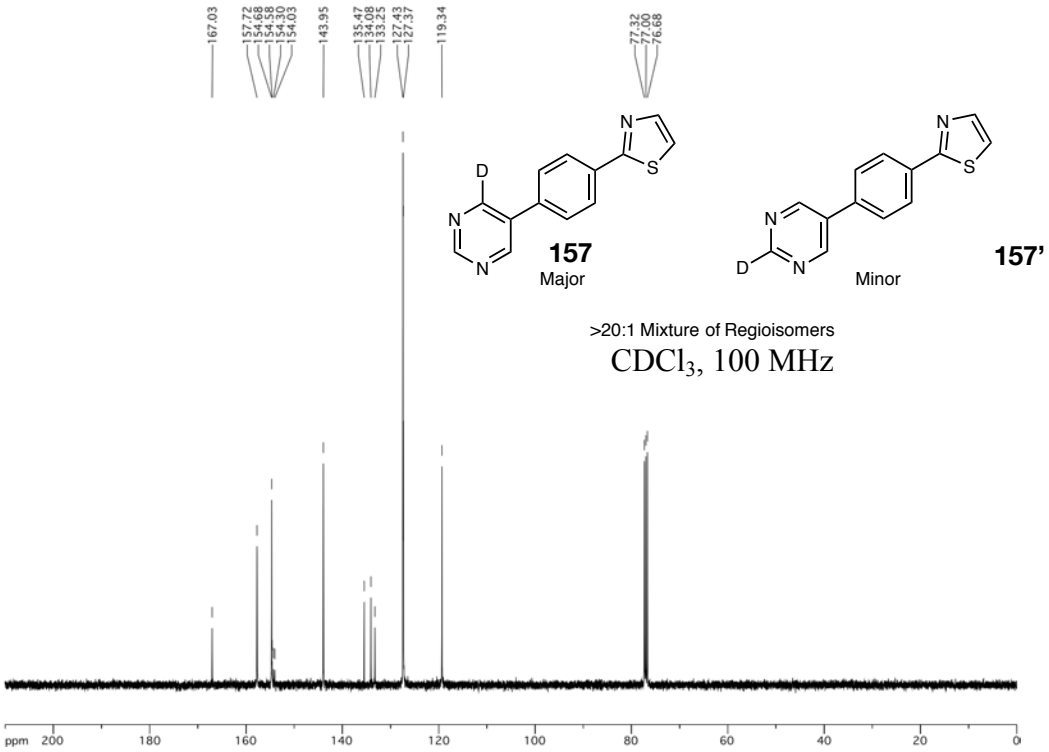
Major

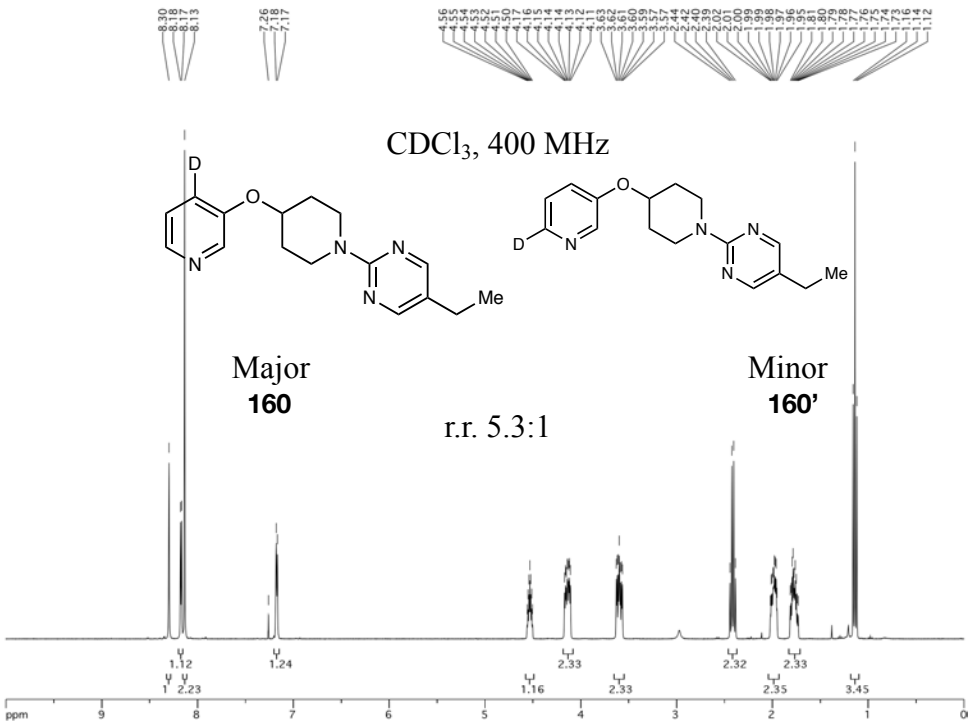
157

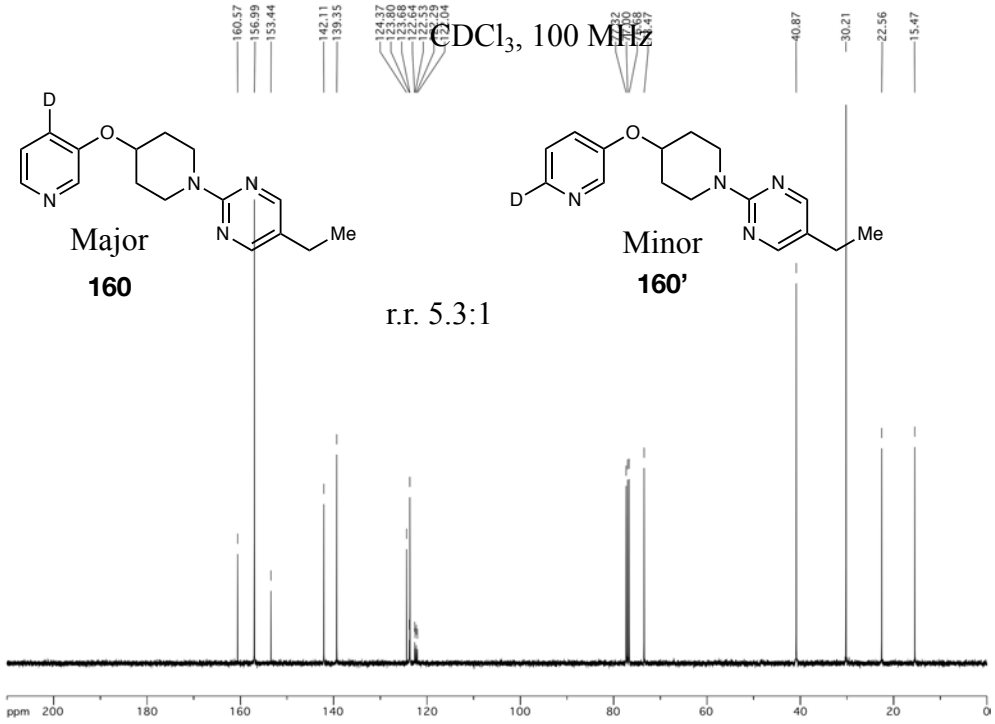
Minor

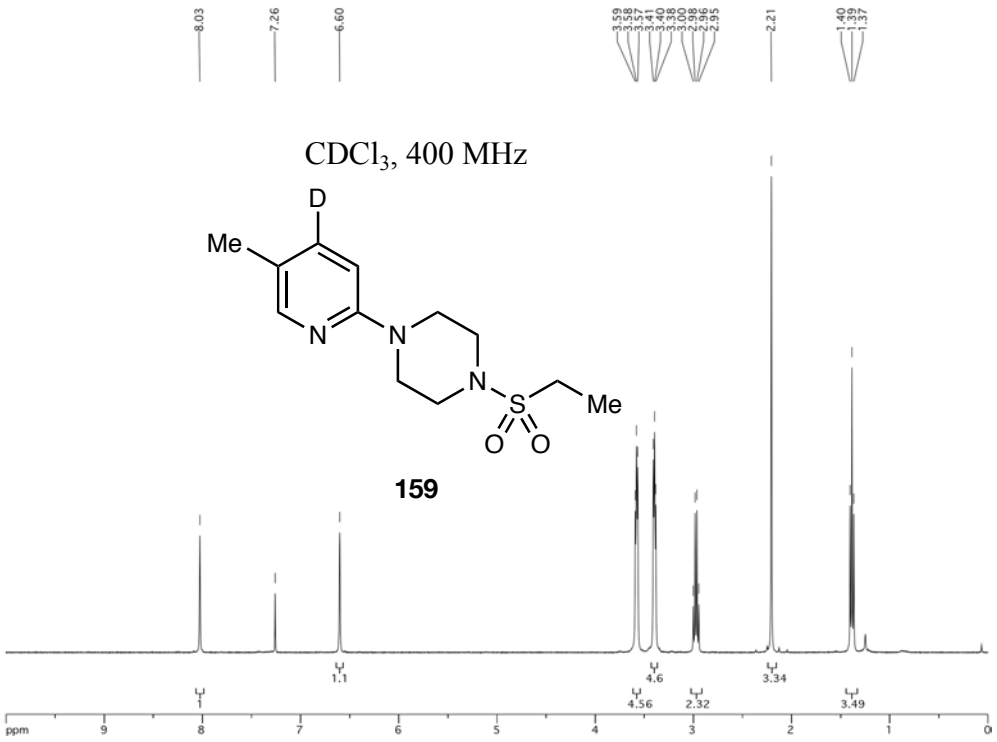
157'

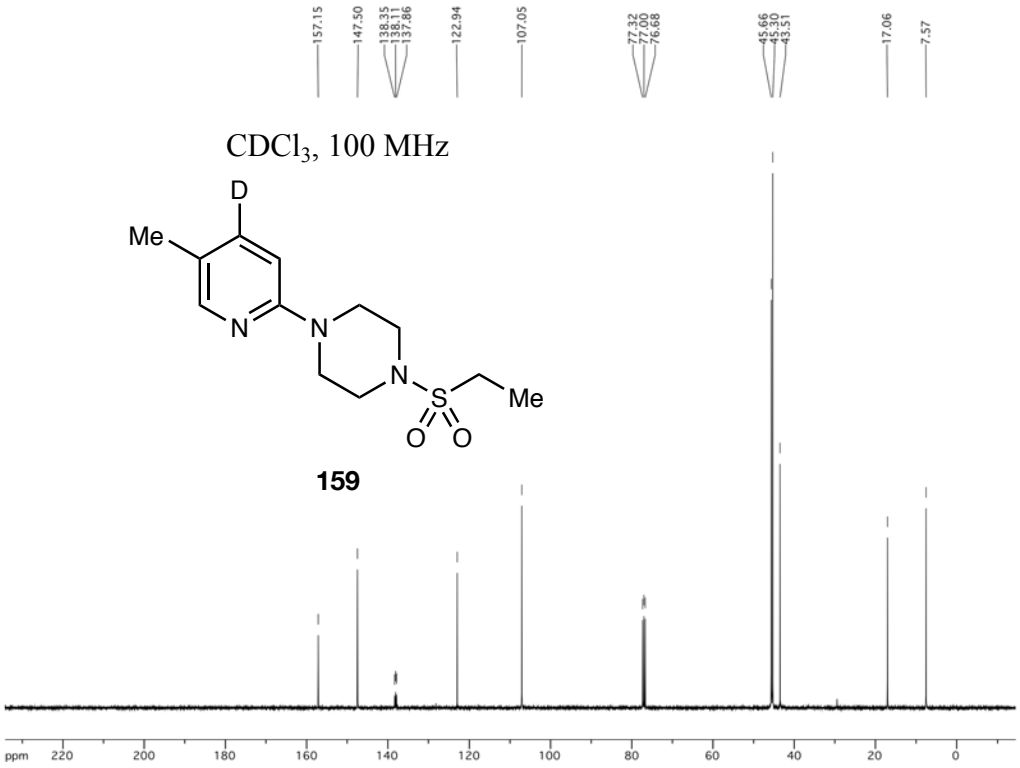
>20:1 Mixture of Regioisomers

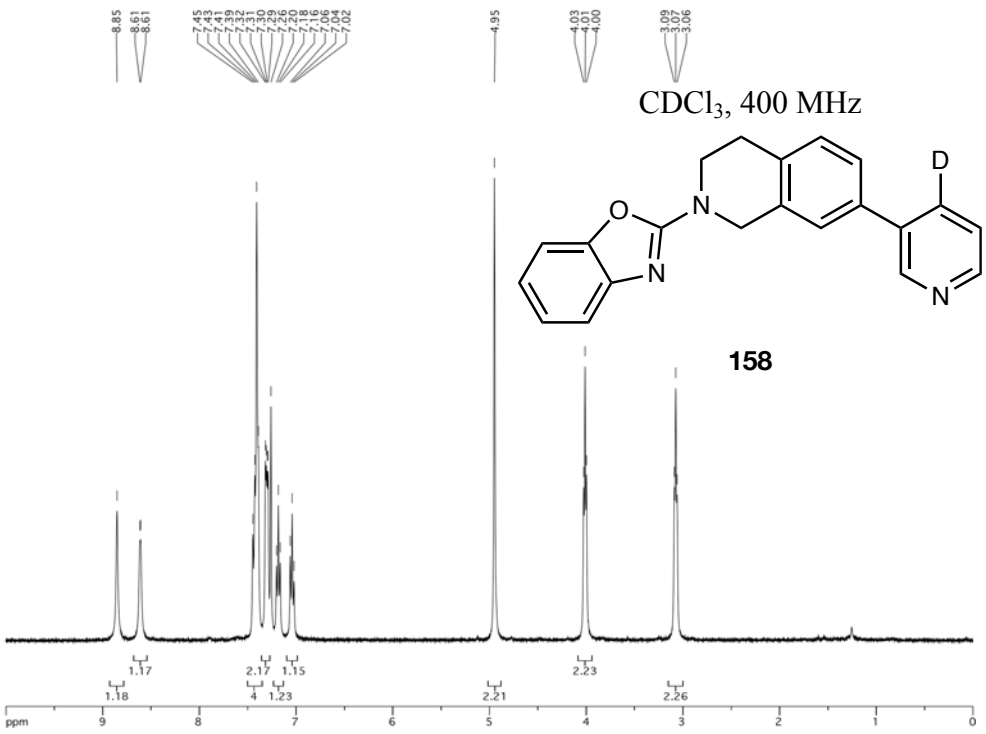

167.03
157.72
154.68
154.58
154.30
154.03
143.95
135.47
134.08
133.25
127.43
127.37
119.34
77.32
77.00
76.68
N
S
D
N
N
157
Major
N
S
N
D
N
Minor
157'
>20:1 Mixture of Regioisomers
CDCl3, 100 MHz
ppm 200
180
160
140
120
100
80
60
40
20
0

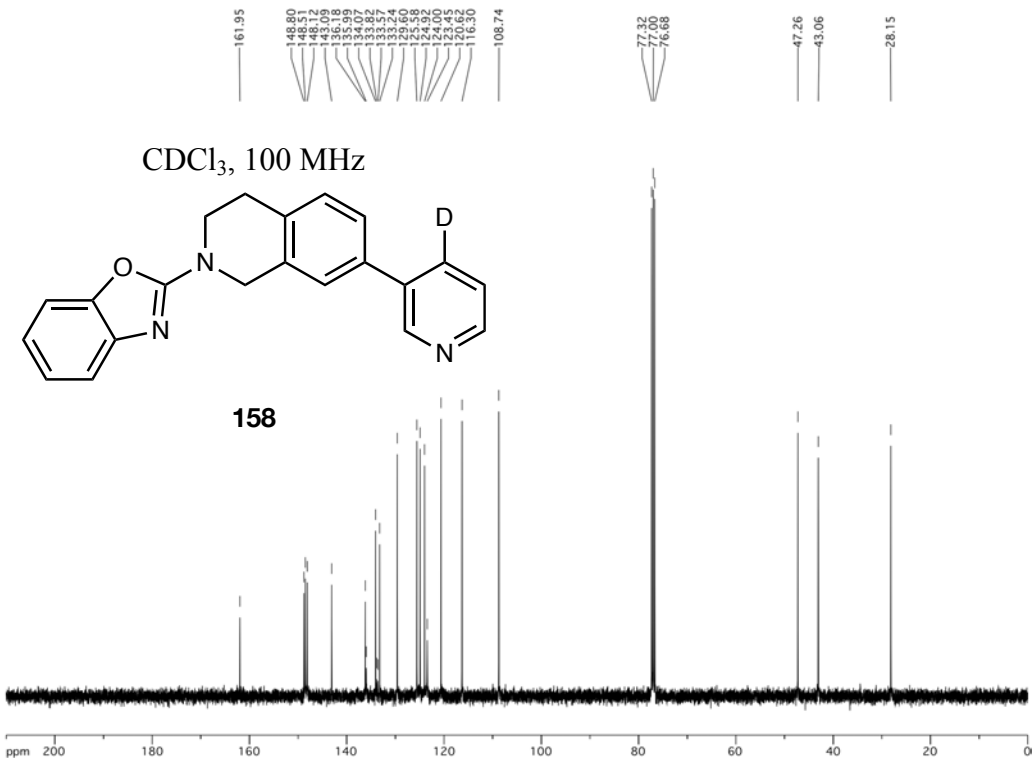

CDCl3, 400 MHz
Major
160
Minor
160'
r.r. 5.3:1
Me
Me

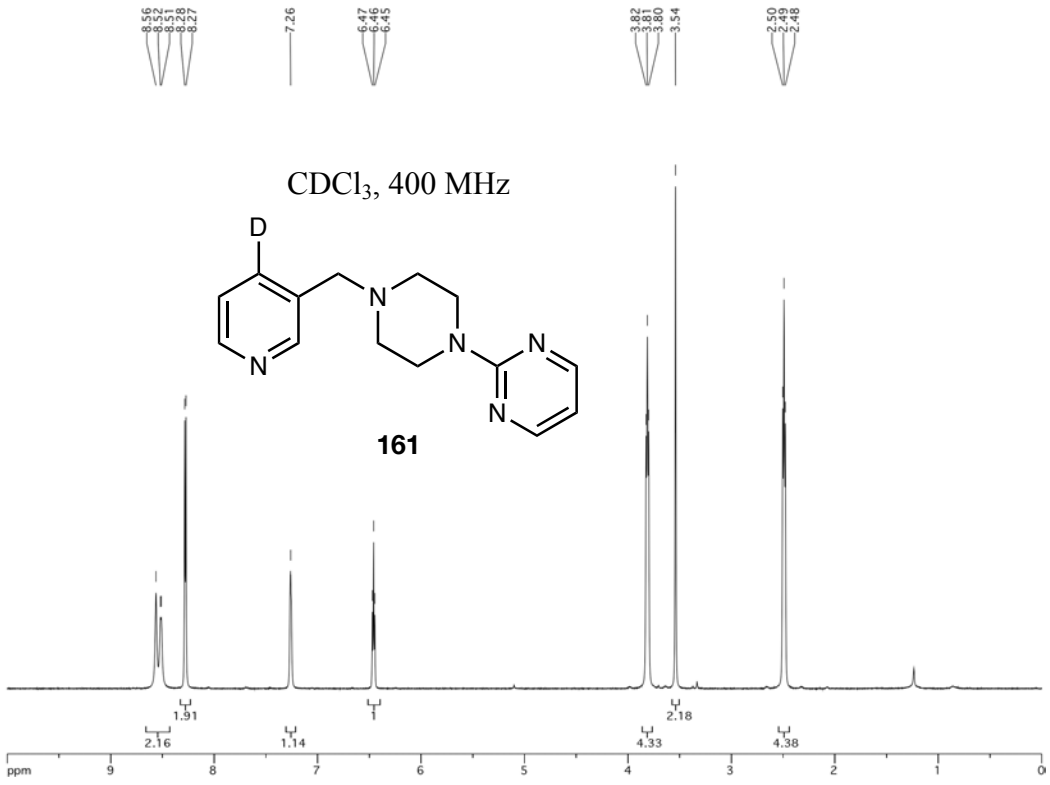

CDCl3, 100 MHz
Major
160
Minor
160'
r.r. 5.3:1
ppm 200 180 160 140 120 100 80 60 40 20 0

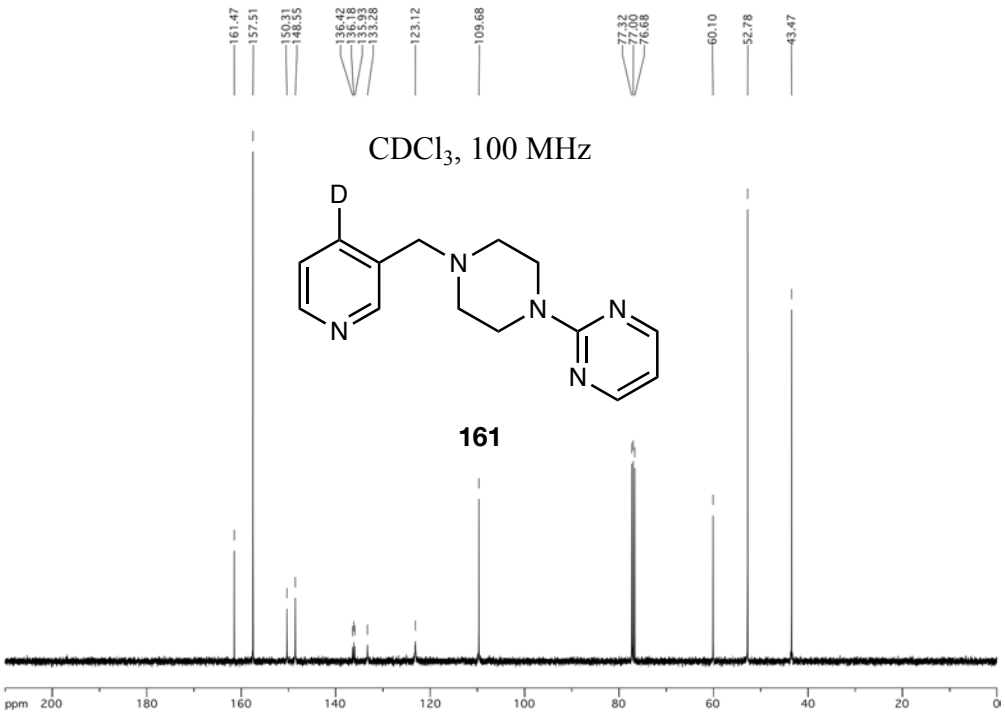

8.03
7.26
6.60
3.59
3.58
3.57
3.41
3.40
3.38
3.00
2.98
2.96
2.95
2.21
1.40
1.39
1.37
CDCl3, 400 MHz
D
Me
N
N
N
S
O
O
Me
159
1.1
4.6
3.34
1
4.56
2.32
3.49
ppm
9
8
7
6
5
4
3
2
1
0

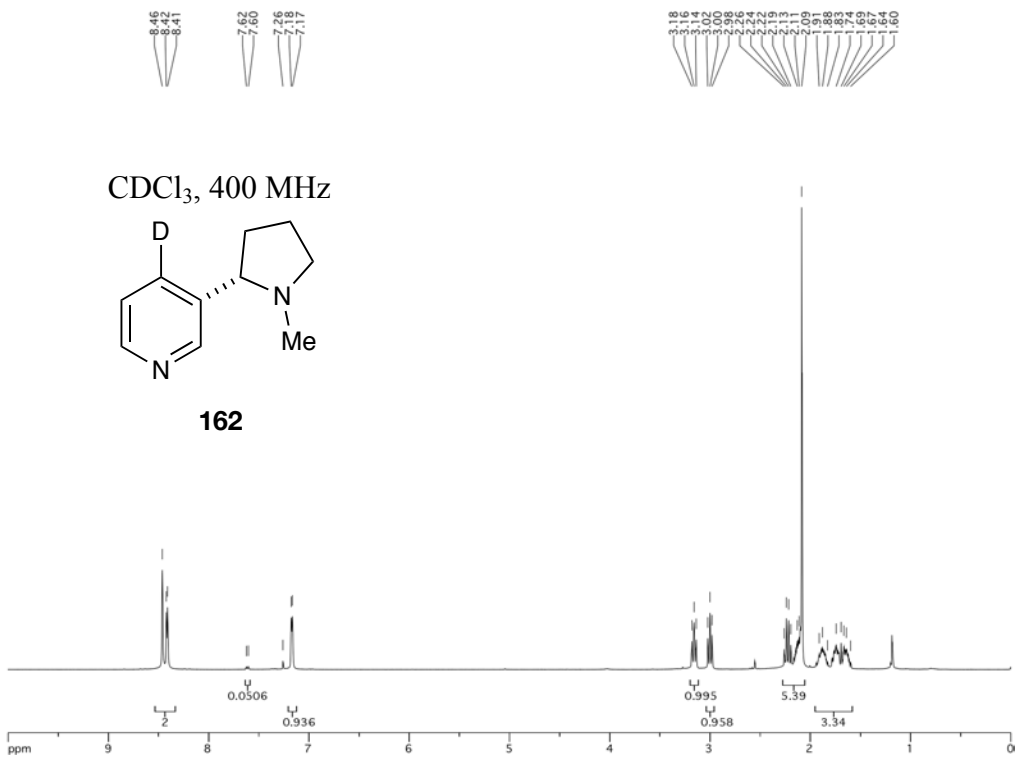

157.15
147.50
138.35
138.11
137.86
122.94
107.05
77.32
77.00
76.68
45.66
45.30
43.51
17.06
7.57
CDCl3, 100 MHz
D
Me
N
N
N
S
Me
O
O
159
ppm
220
200
180
160
140
120
100
80
60
40
20
0

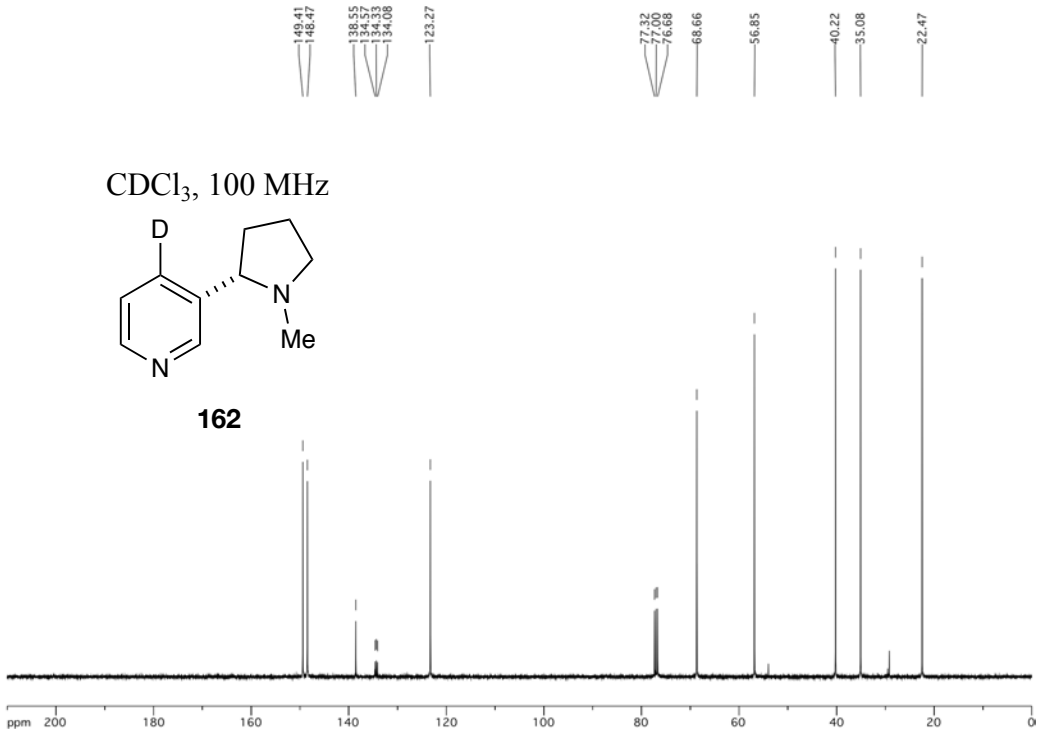

8.85
8.61
8.61
7.45
7.43
7.41
7.40
7.32
7.31
7.30
7.29
7.26
7.20
7.18
7.16
7.06
7.04
7.02
4.95
4.03
4.01
4.00
3.09
3.07
3.06
CDCl3, 400 MHz
O
N
N
N
D
158
1.17
2.17
1.15
1.18
4
1.23
2.21
2.23
2.26
ppm
9
8
7
6
5
4
3
2
1
0

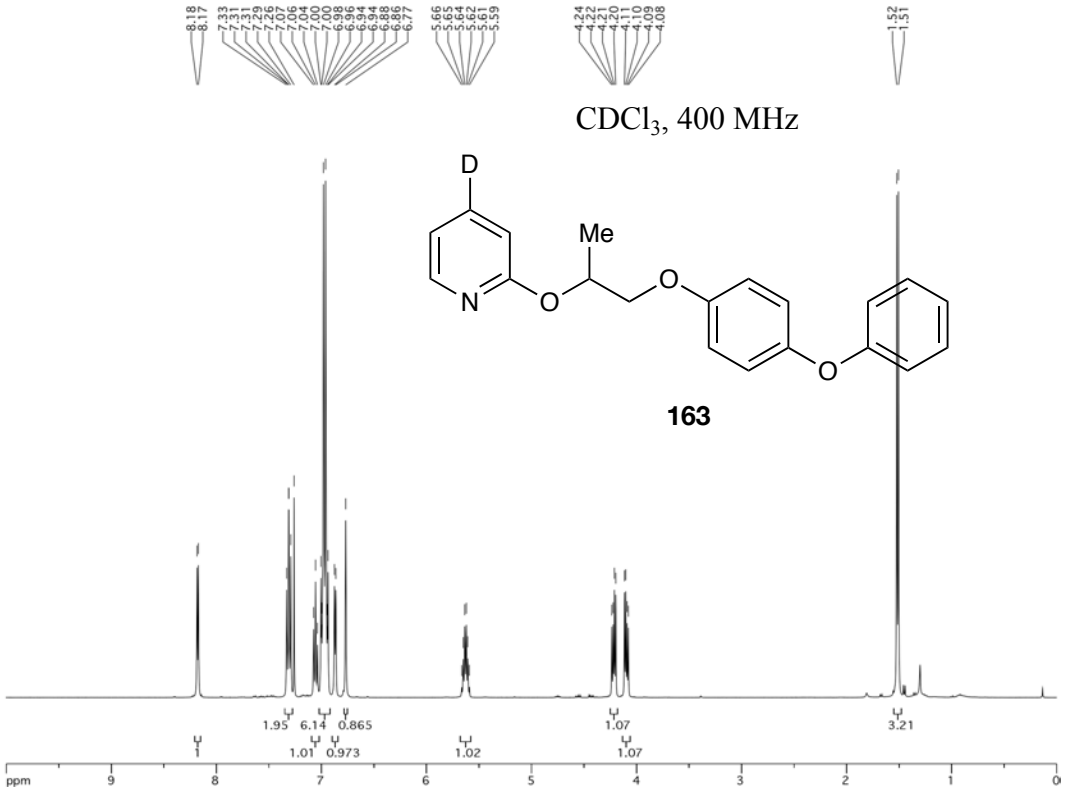

161.95
148.80
148.51
148.12
148.09
136.18
135.99
134.07
133.82
133.57
133.24
129.60
125.58
124.92
124.00
123.45
120.62
116.30
108.74
77.32
77.00
76.68
47.26
43.06
28.15
CDCl3, 100 MHz
O
N
N
D
N
158
ppm 200
180
160
140
120
100
80
60
40
20

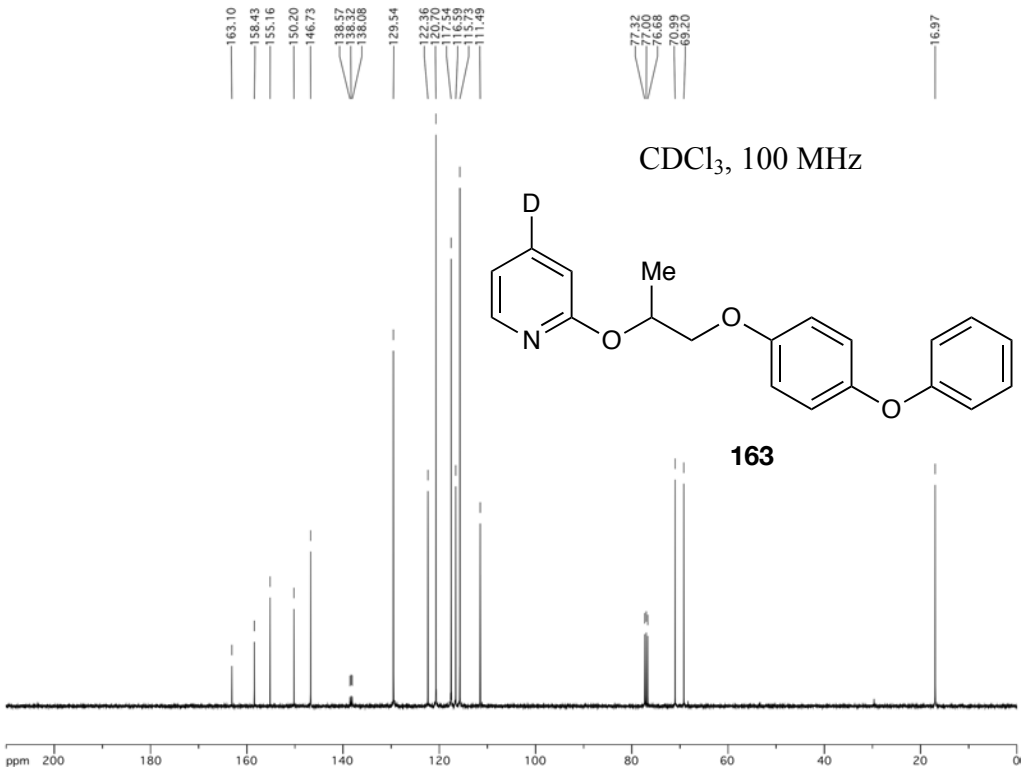

8.56
8.52
8.51
8.28
8.27
7.26
6.47
6.46
6.45
3.82
3.81
3.80
3.54
2.50
2.49
2.48
CDCl3, 400 MHz
D
N
N
N
N
161
1.91
1
2.18
2.16
1.14
4.33
4.38
ppm
9
8
7
6
5
4
3
2
1
0

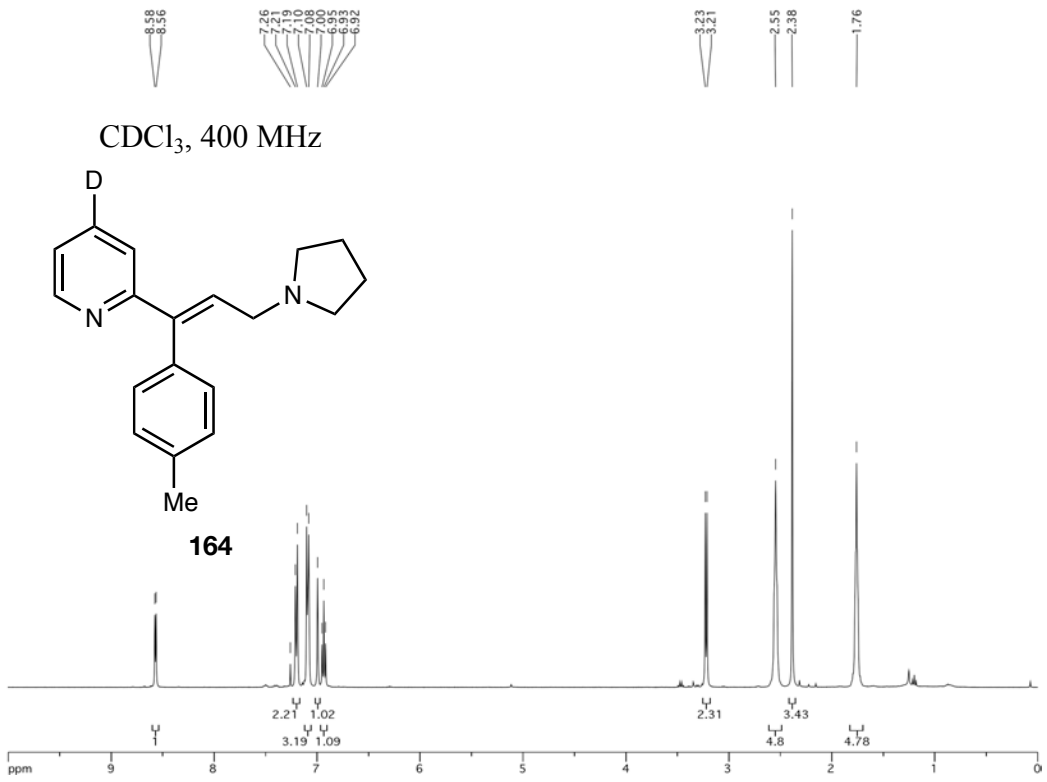

161.47
157.51
150.31
148.55
136.42
135.93
133.28
123.12
109.68
77.32
60.10
52.78
43.47
CDCl3, 100 MHz
D
N
N
N
N
161
ppm 200
180
160
140
120
100
80
60
40
20


8.46
8.42
8.41
7.62
7.60
7.26
7.18
7.17
3.18
3.16
3.14
3.02
3.00
2.98
2.26
2.24
2.22
2.19
2.13
2.11
2.09
1.91
1.88
1.83
1.74
1.69
1.67
1.64
1.60
CDCl3, 400 MHz
D
N
Me
N
162
0.0506
0.936
0.995
0.958
5.39
3.34
2
ppm
9
8
7
6
5
4
3
2
1
0


149.41
148.47
138.55
134.57
134.33
134.08
123.27
77.32
77.00
76.68
68.66
56.85
40.22
35.08
22.47
CDCl3, 100 MHz
D
N
Me
N
162
ppm 200
180
160
140
120
100
80
60
40
20

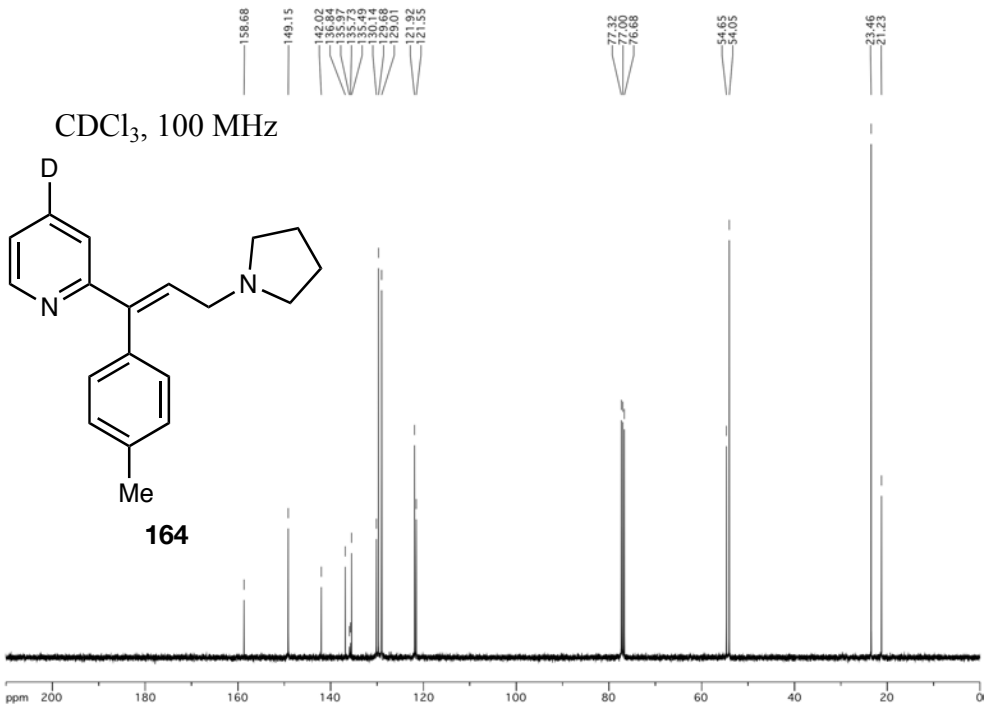

8.18
8.17
7.33
7.31
7.31
7.29
7.26
7.07
7.06
7.04
7.00
7.00
6.98
6.96
6.94
6.94
6.88
6.86
6.77
5.66
5.65
5.64
5.62
5.61
5.59
4.24
4.22
4.21
4.20
4.11
4.10
4.09
4.08
1.52
1.51
CDCl3, 400 MHz
D
Me
N
O
O
O
O
163
1.95
6.14
0.865
1.07
3.21
1
1.01
0.973
1.02
1.07
ppm
9
8
7
6
5
4
3
2
1
0


163.10
158.43
155.16
150.20
146.73
138.57
138.32
138.08
129.54
122.36
120.70
117.54
116.59
115.73
111.49
77.32
77.00
76.68
70.99
69.20
16.97
CDCl3, 100 MHz
D
Me
N
O
O
O
163
ppm 200
180
160
140
120
100
80
60
40
20

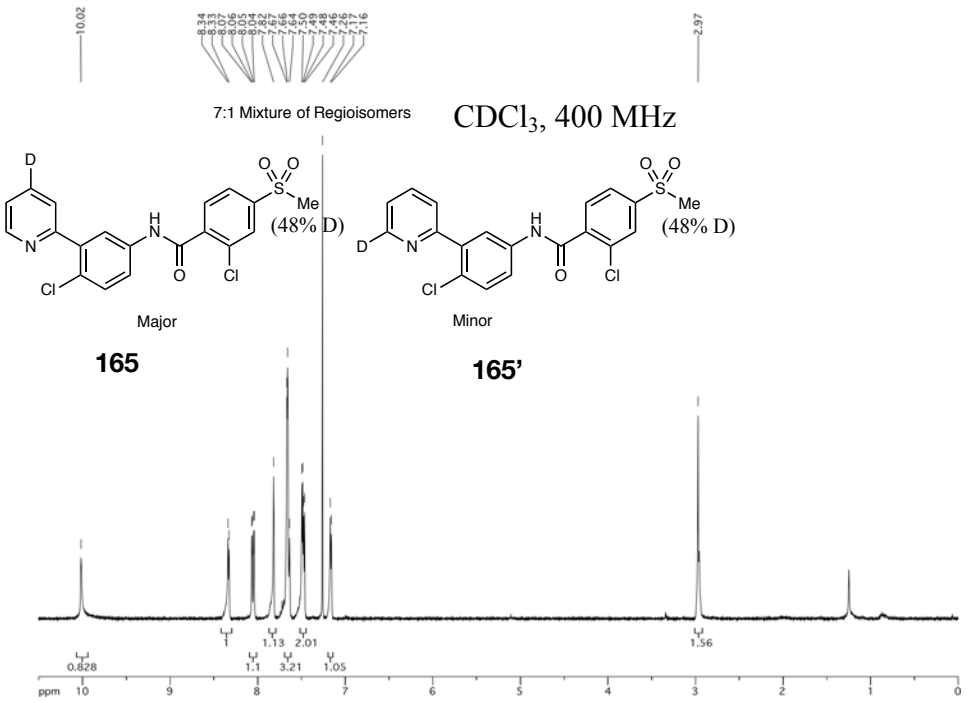


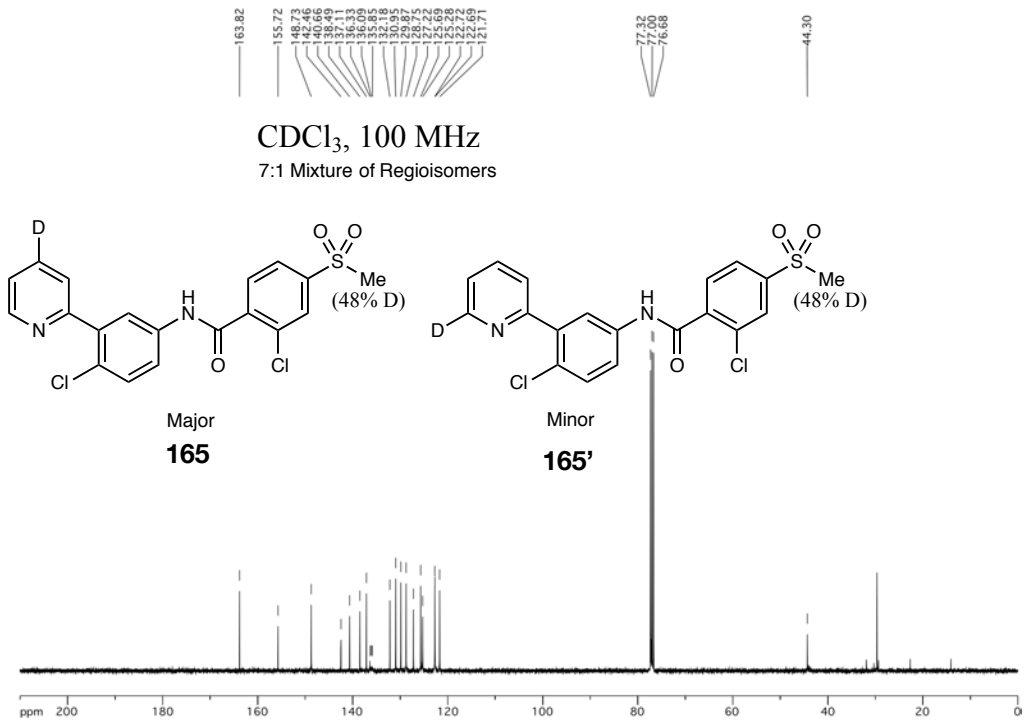
$CDCl_3$, 400 MHz

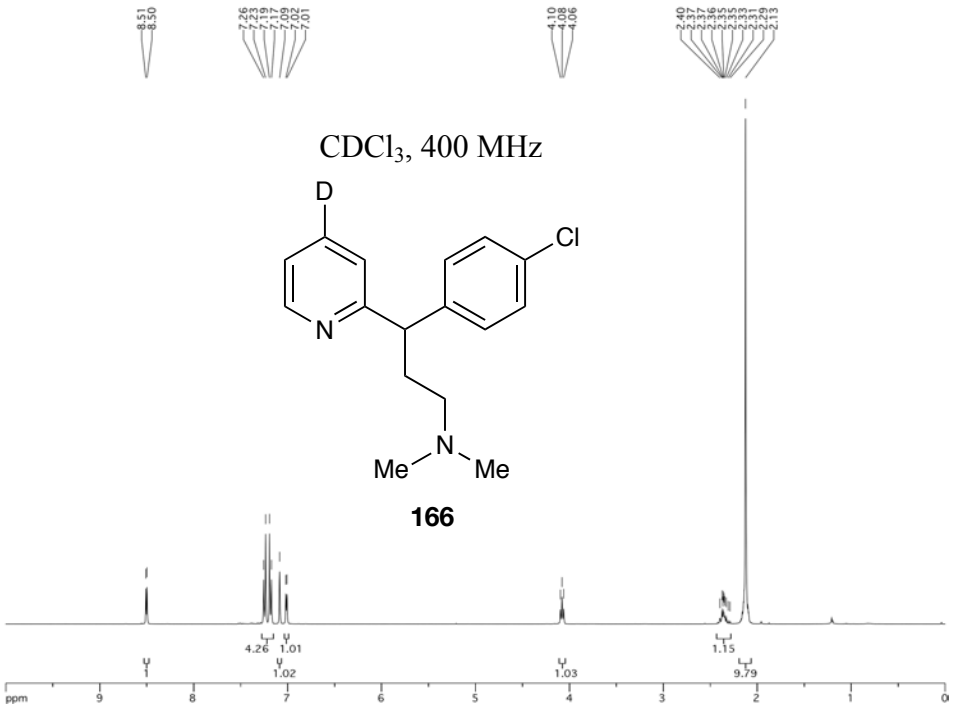
164

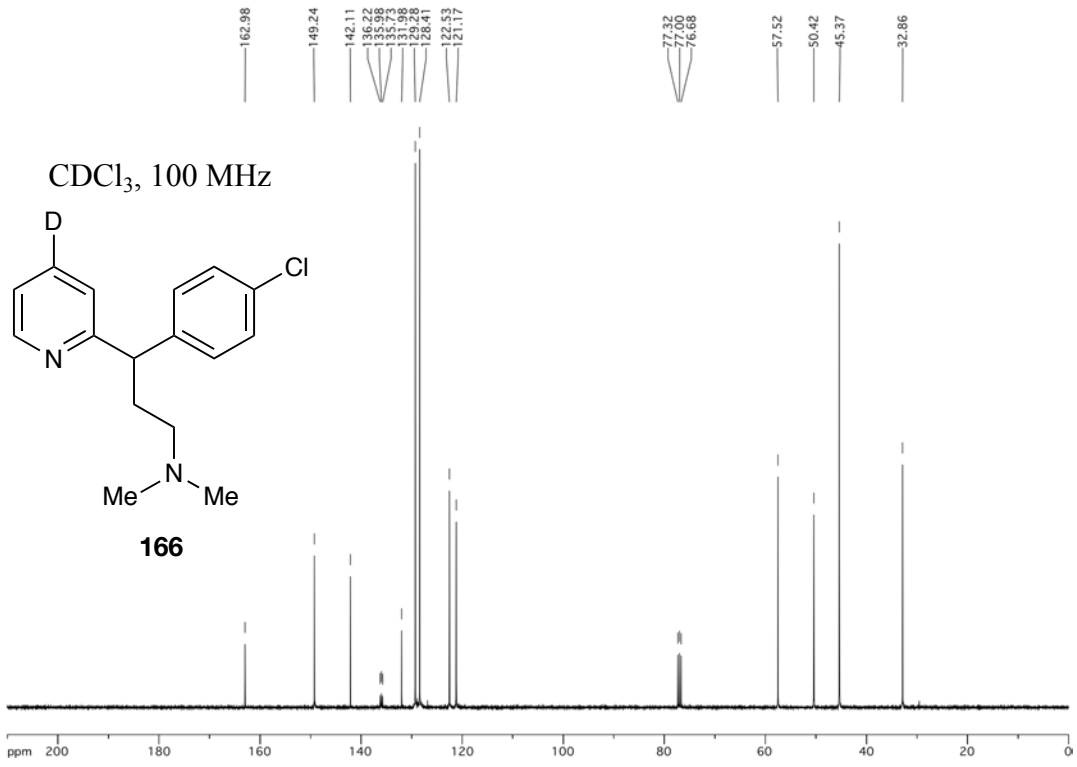

158.68
149.15
142.02
136.84
135.27
133.73
130.14
129.68
129.01
121.92
121.55
77.32
77.00
76.68
54.65
54.05
23.46
21.23
CDCl3, 100 MHz
D
N
N
Me
ppm 200
180
160
140
120
100
80
60
40
20

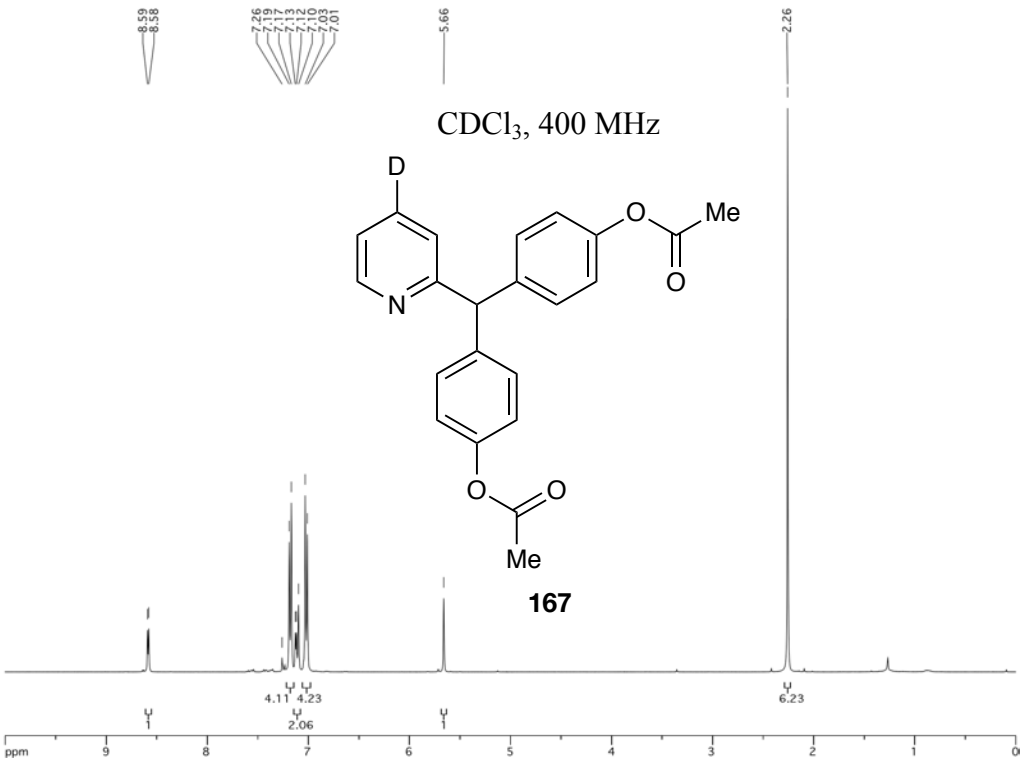
164

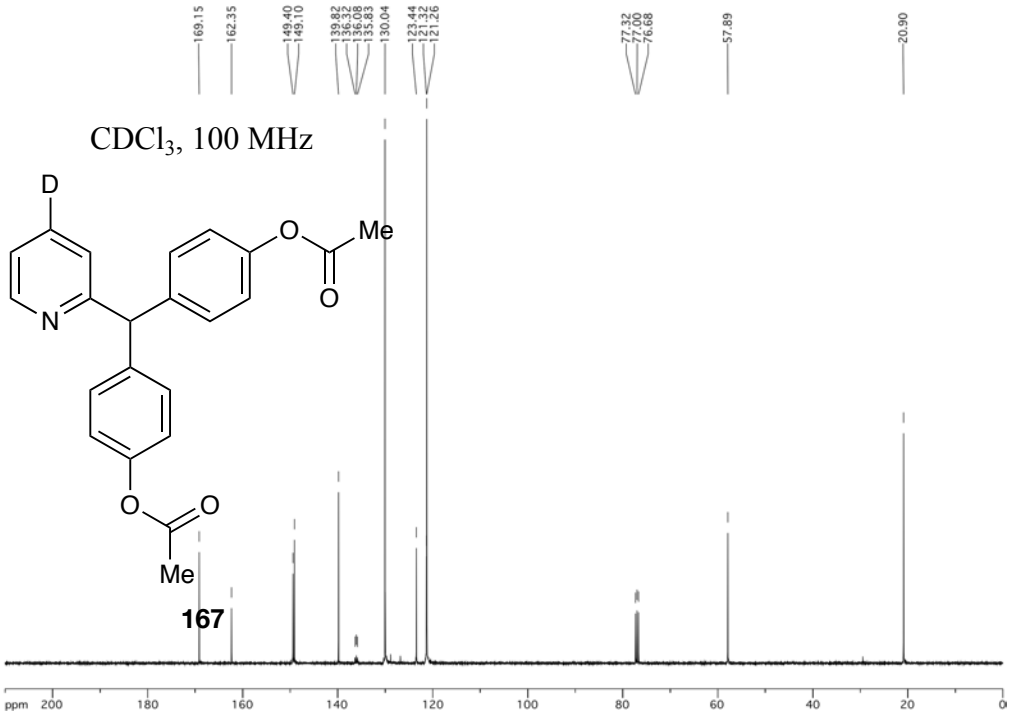

10.02
8.34
8.33
8.07
8.06
8.05
8.04
7.82
7.67
7.66
7.65
7.50
7.49
7.48
7.46
7.26
7.17
7.16
2.97
7:1 Mixture of Regioisomers
CDCl3, 400 MHz
D
N
H
N
O
O
S
O
O
Me
(48% D)
Cl
Cl
Major
165
D
N
H
N
O
O
S
O
O
Me
(48% D)
Cl
Cl
Minor
165'
0.828
1
1.13
2.01
1.56
1.1
3.21
1.05
ppm 10 9 8 7 6 5 4 3 2 1 0

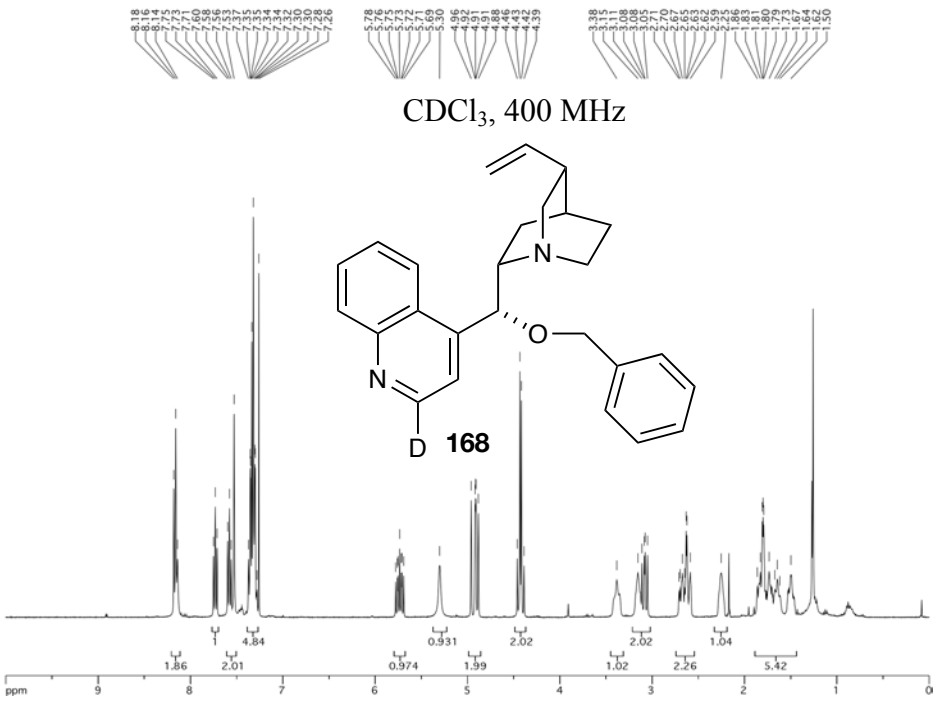

163.82
155.72
148.73
142.46
140.66
138.49
137.11
136.13
136.09
135.85
132.18
130.95
130.67
128.75
127.22
125.69
125.28
122.77
122.69
121.71
77.32
77.00
76.68
44.30
CDCl3, 100 MHz
7:1 Mixture of Regioisomers
D
N
H
N
O
O
S
O
O
Me
(48% D)
Cl
Cl
Major
165
D
N
H
N
O
O
S
O
O
Me
(48% D)
Cl
Cl
Minor
165'
ppm 200 180 160 140 120 100 80 60 40 20 0


8.51
8.50
7.26
7.25
7.19
7.17
7.09
7.02
7.01
4.10
4.08
4.06
2.40
2.37
2.37
2.36
2.35
2.35
2.33
2.31
2.29
2.13
CDCl3, 400 MHz
D
Cl
N
N
Me
Me
166
4.26
1.01
1.15
1
1.02
1.03
9.79
ppm
9
8
7
6
5
4
3
2
1
0

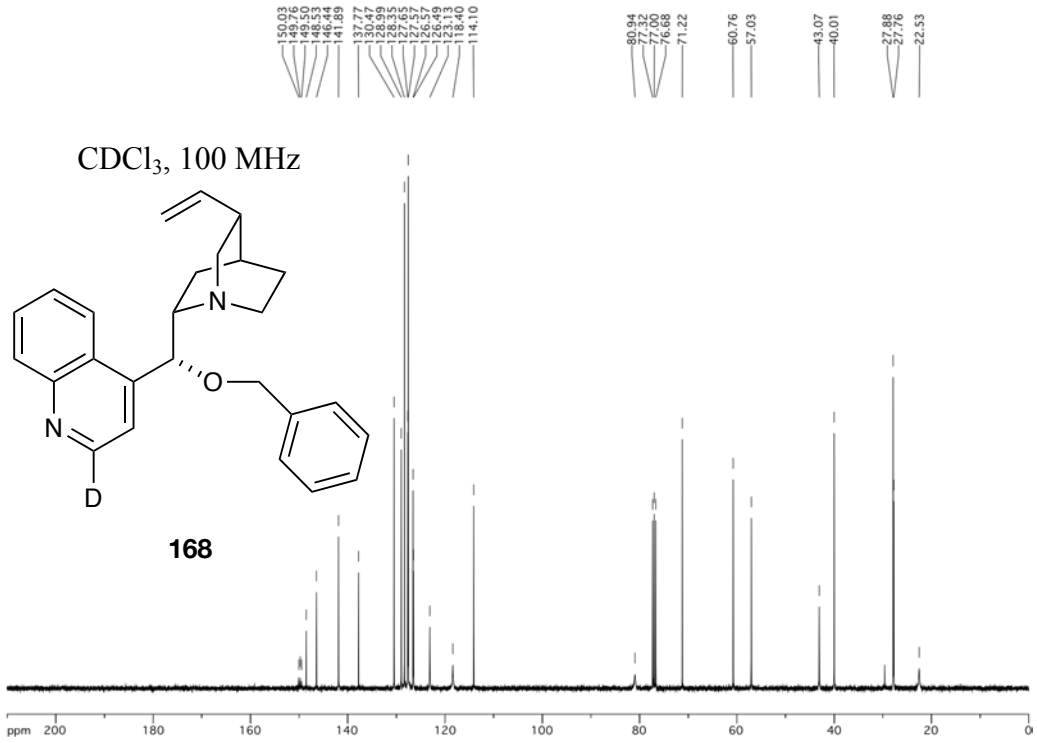

162.98
149.24
142.11
136.22
135.68
135.73
131.98
129.28
128.41
122.53
121.17
77.32
77.00
76.68
57.52
50.42
45.37
32.86
CDCl3, 100 MHz
D
Cl
N
Me
N
Me
166
ppm 200
180
160
140
120
100
80
60
40
20
0

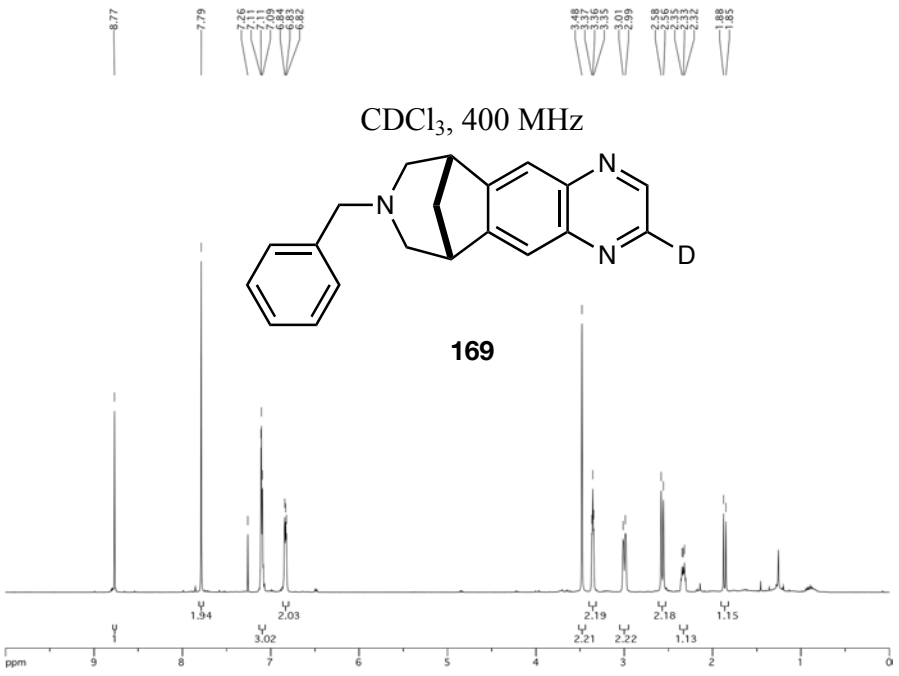

8.59
8.58
7.26
7.19
7.17
7.13
7.12
7.10
7.03
7.01
5.66
2.26
CDCl3, 400 MHz
D
N
O
Me
O
O
O
Me
167
4.11
4.23
2.06
6.23
ppm

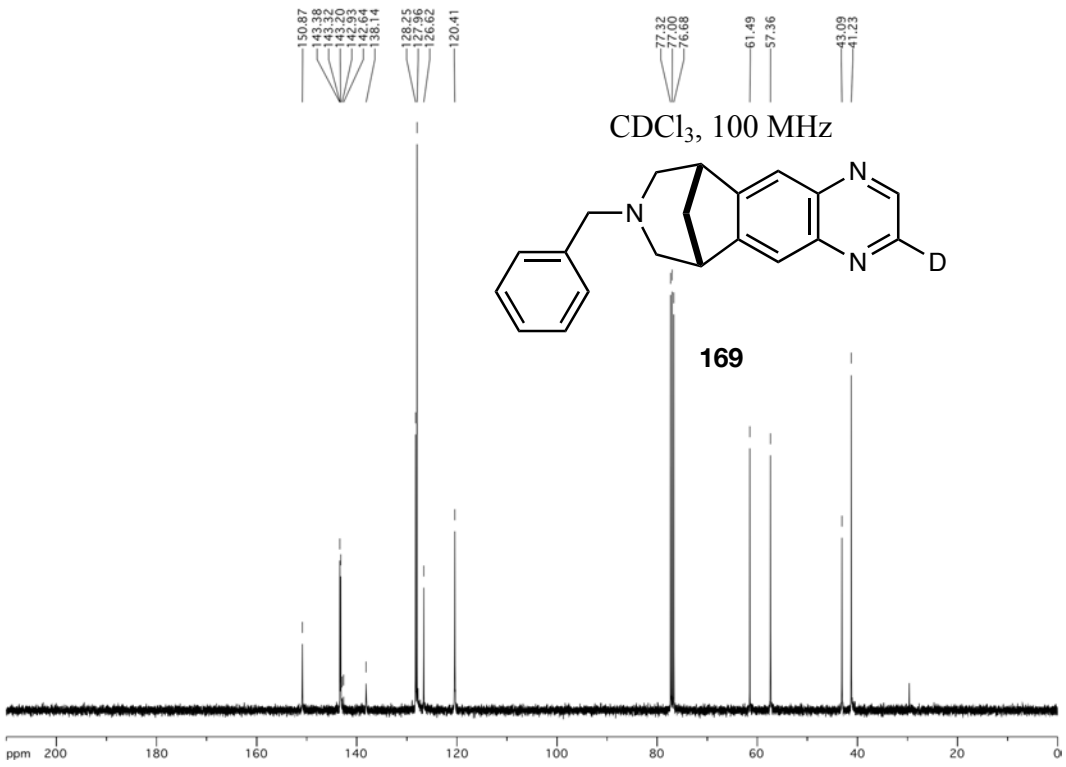

169.15
162.35
149.40
149.10
139.82
136.72
136.08
135.83
130.04
123.44
121.32
121.26
77.32
77.00
76.68
57.89
20.90
CDCl3, 100 MHz
D
N
O
Me
O
O
O
Me
167
ppm 200
180
160
140
120
100
80
60
40
20

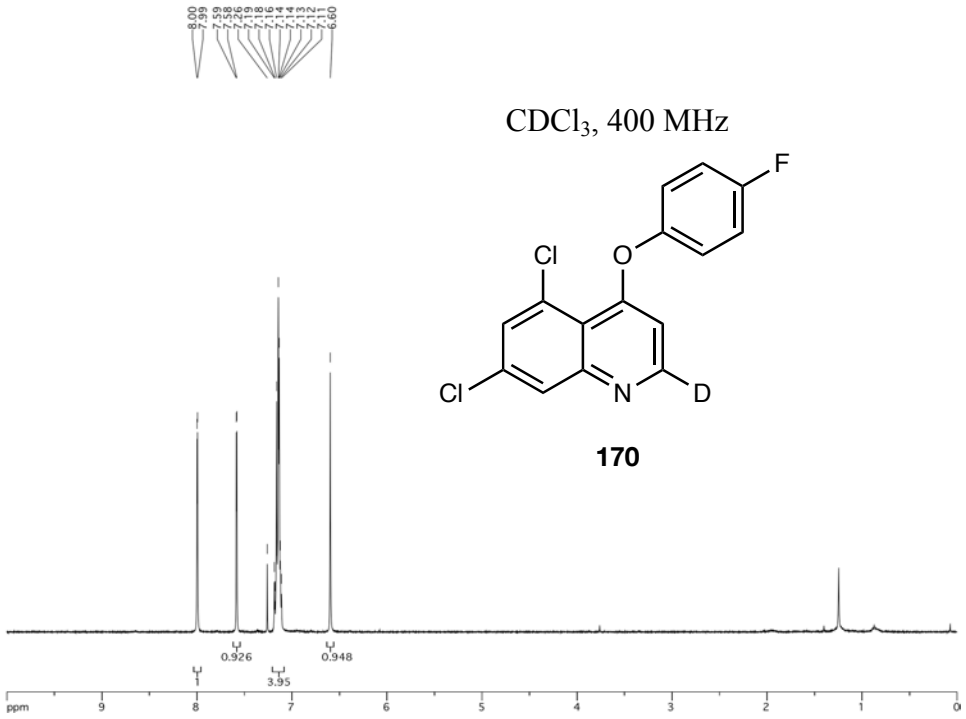


$CDCl_3$, 400 MHz

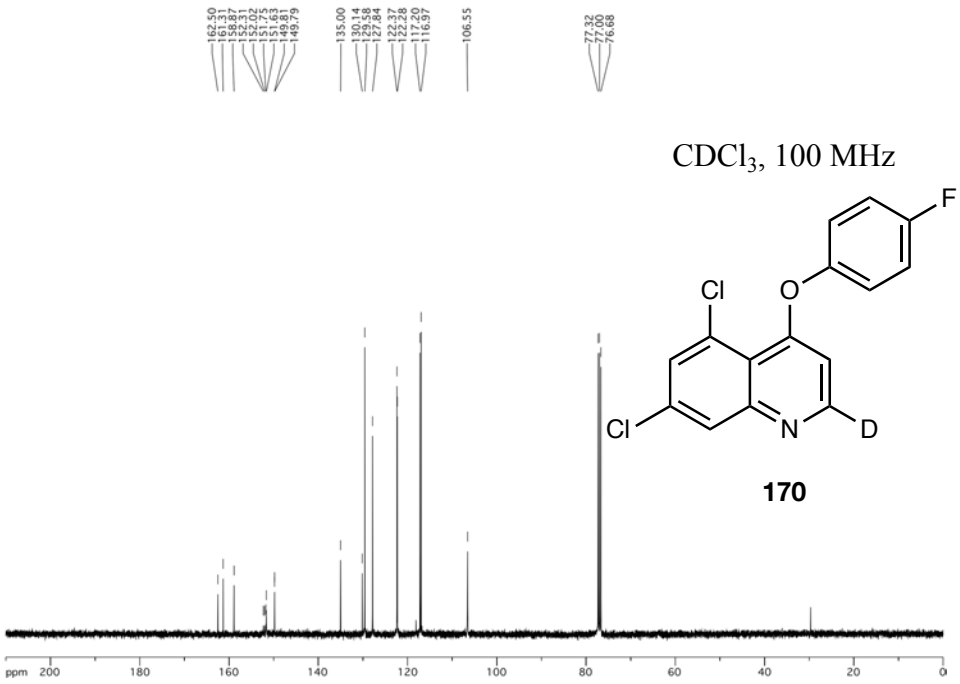

150.03
149.76
149.50
148.33
146.44
141.89
137.77
130.47
128.99
128.35
127.65
127.57
126.77
126.49
123.13
118.40
114.10
80.94
77.32
77.00
76.68
71.22
60.76
57.03
43.07
40.01
27.88
27.76
22.53
CDCl3, 100 MHz
N
O
N
D
168
ppm 200
180
160
140
120
100
80
60
40
20


8.77
7.79
7.26
7.11
7.09
6.84
6.83
6.82
3.48
3.37
3.36
3.35
3.01
2.89
2.58
2.56
2.35
2.33
2.32
1.88
1.85
CDCl3, 400 MHz
N
N
N
D
169
1.94
2.03
3.02
2.19
2.21
2.22
2.18
1.13
1.15
ppm
9
8
7
6
5
4
3
2
1
0

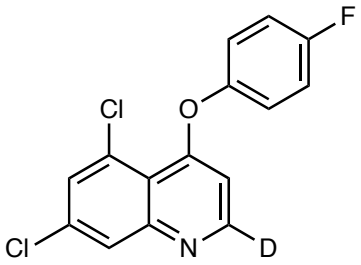

150.87
143.38
143.32
143.20
142.93
142.64
138.14
128.25
127.96
126.62
120.41
77.32
77.00
76.68
61.49
57.36
43.09
41.23
CDCl3, 100 MHz
N
N
N
D
169
ppm 200
180
160
140
120
100
80
60
40
20
0


8.00
7.99
7.59
7.58
7.26
7.18
7.16
7.14
7.13
7.12
7.11
6.60
CDCl3, 400 MHz
F
O
Cl
Cl
N
D
0.926
0.948
1
3.95
ppm
9
8
7
6
5
4
3
2
1
0

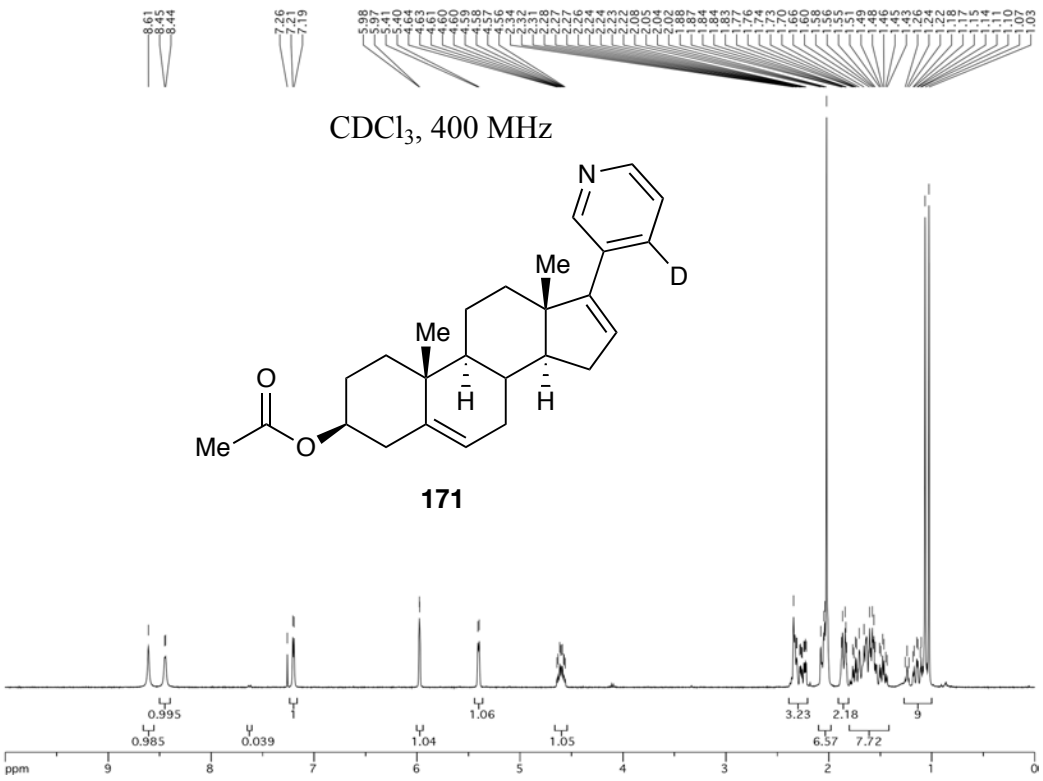
170

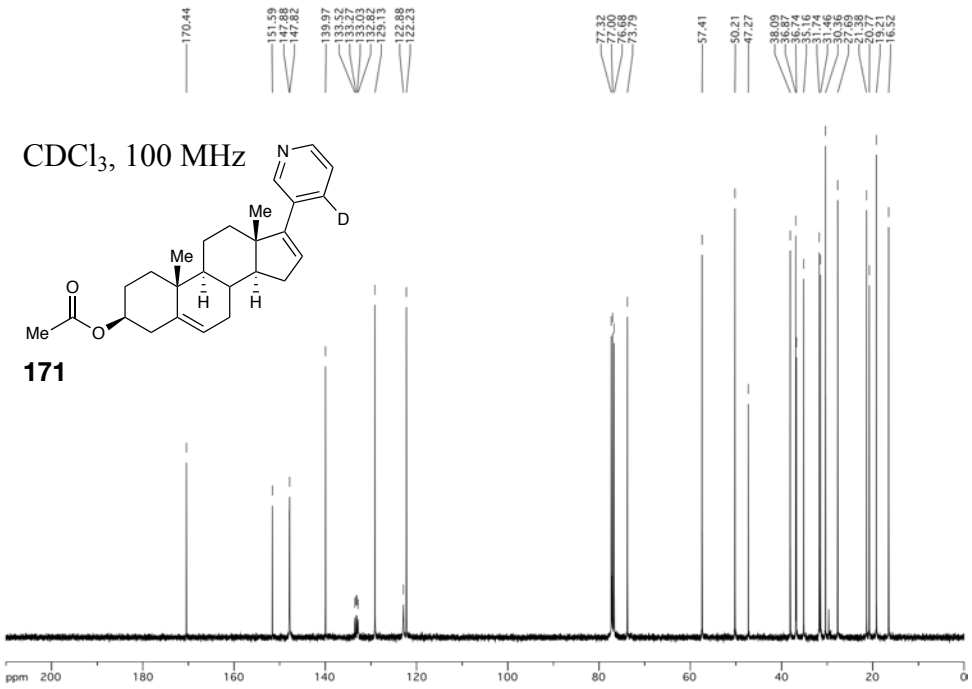

162.50
159.31
158.87
152.31
152.02
151.75
151.63
149.81
149.79
135.00
130.14
129.58
127.84
122.37
122.26
117.20
116.97
106.55
77.32
77.00
76.68
CDCl3, 100 MHz
F
O
Cl
Cl
N
D
170
ppm 200 180 160 140 120 100 80 60 40 20 0

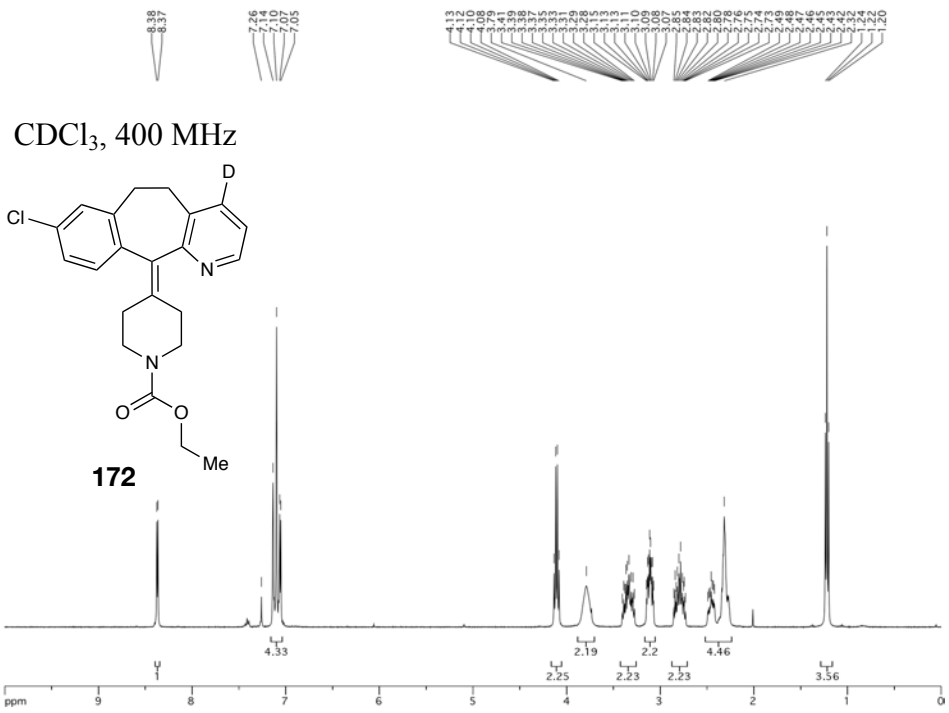
$CDCl_3$, 365 MHz

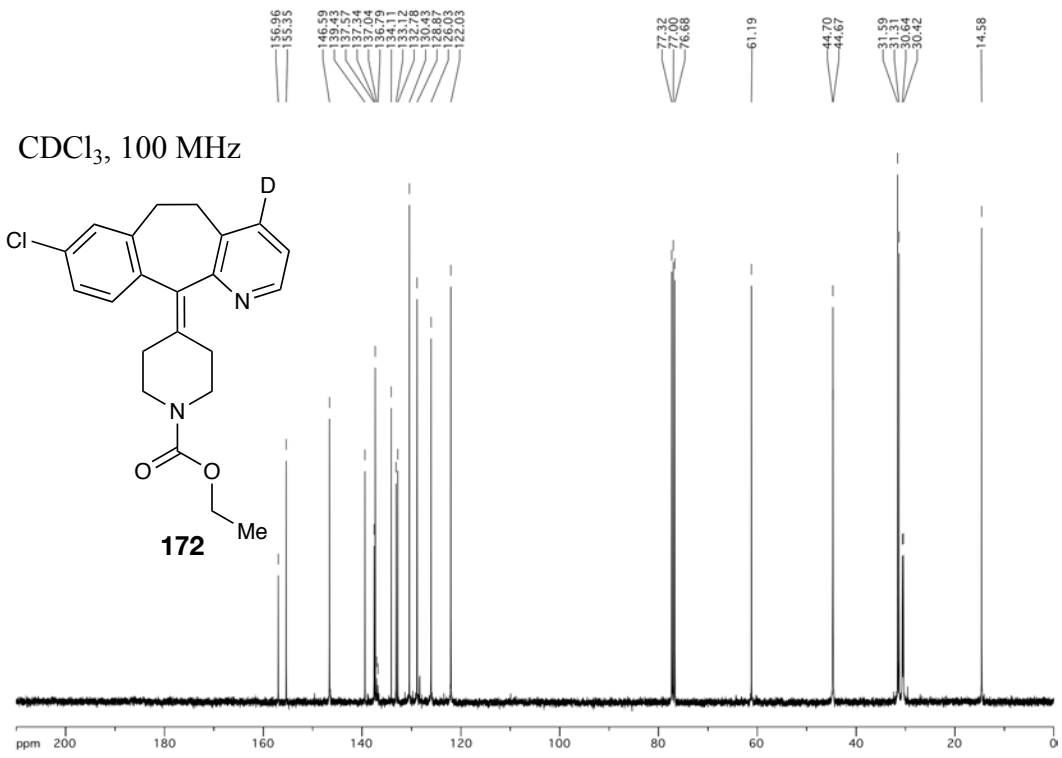


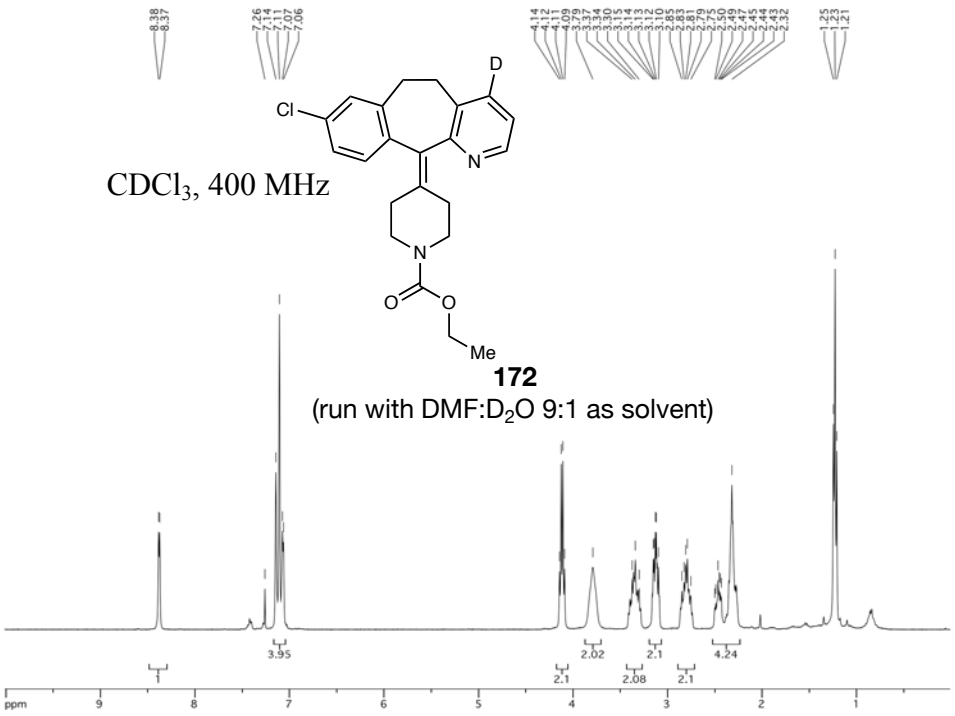
170

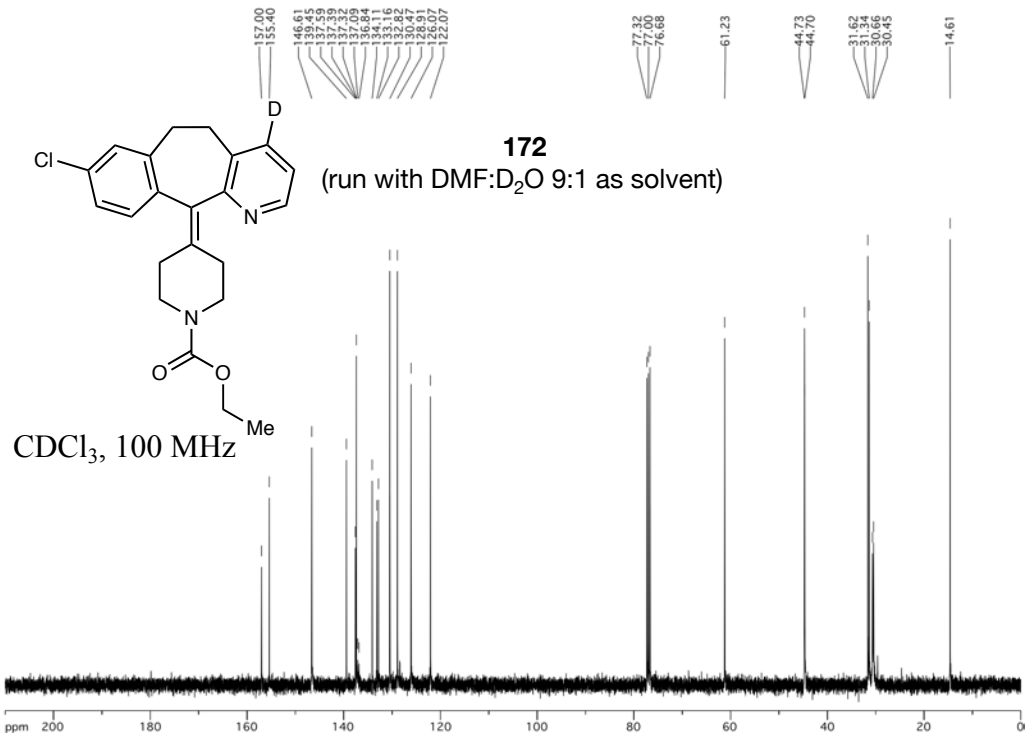

8.61
8.45
8.44
7.26
7.21
7.19
5.98
5.97
5.41
5.40
4.64
4.63
4.61
4.60
4.60
4.59
4.58
4.57
4.56
4.34
2.32
2.31
2.28
2.27
2.27
2.26
2.24
2.24
2.23
2.22
2.08
2.05
2.04
2.02
1.88
1.87
1.84
1.84
1.83
1.77
1.76
1.74
1.73
1.70
1.66
1.60
1.58
1.56
1.55
1.51
1.49
1.48
1.46
1.45
1.43
1.26
1.24
1.22
1.18
1.17
1.15
1.14
1.11
1.10
1.07
1.03
CDCl3, 400 MHz
N
D
Me
Me
O
Me
O
H
H
171
0.995
1
1.06
3.23
2.18
9
0.985
0.039
1.04
1.05
6.57
7.72
ppm
9
8
7
6
5
4
3
2
1
0


170.44
151.59
147.88
147.82
139.97
133.52
133.27
133.05
132.82
129.13
122.88
122.23
77.32
77.00
76.68
73.79
57.41
50.21
47.27
38.09
36.87
36.74
35.16
31.74
31.46
31.36
27.69
21.38
20.77
19.21
16.52
CDCl3, 100 MHz
N
D
Me
Me
H
H
O
Me
O
171
ppm 200
180
160
140
120
100
80
60
40
20
0


CDCl3, 400 MHz
D
Cl
N
N
O
O
Me
172
4.33
2.19
2.2
4.46
2.25
2.23
2.23
3.56
ppm

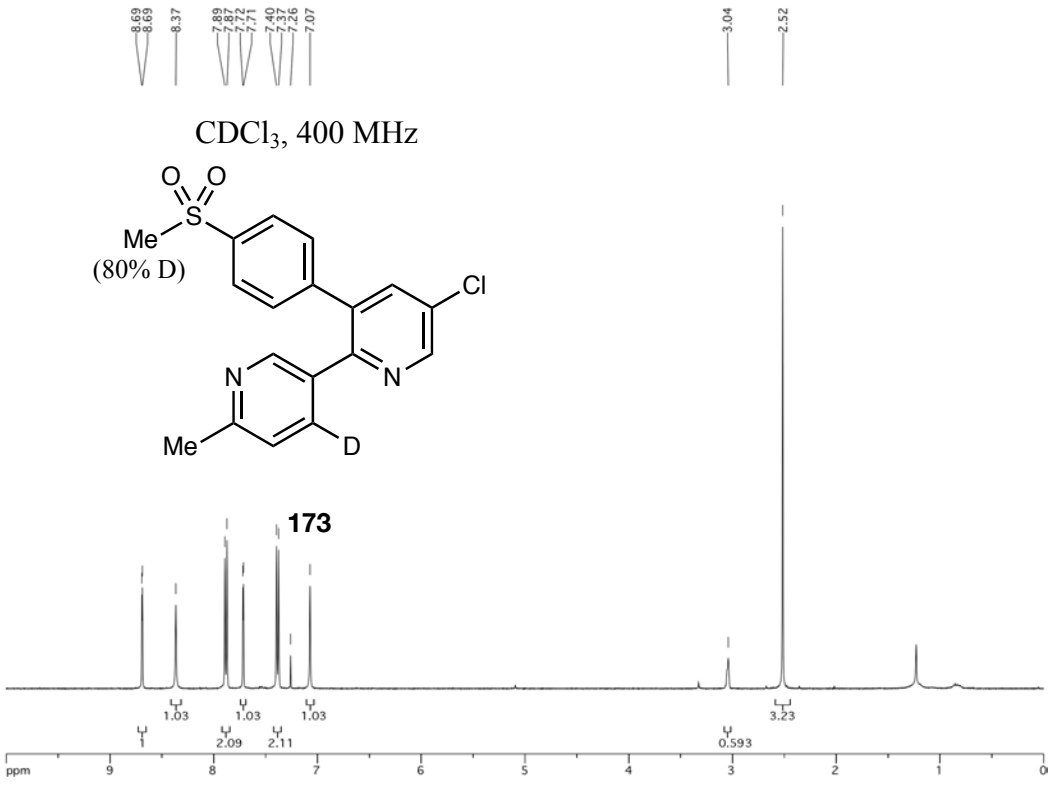

156.96
155.35
146.59
139.43
137.57
137.34
137.04
136.79
134.11
132.78
130.43
128.87
126.03
122.03
77.32
77.00
76.68
61.19
44.70
44.67
31.59
31.31
30.64
30.42
14.58
CDCl3, 100 MHz
D
Cl
N
N
O
O
Me
172
ppm 200
180
160
140
120
100
80
60
40
20
0


8.38
8.37
7.26
7.14
7.11
7.07
7.06
4.14
4.12
4.11
4.09
3.79
3.37
3.34
3.30
3.15
3.14
3.13
3.10
2.85
2.83
2.81
2.79
2.75
2.50
2.49
2.47
2.45
2.44
2.43
2.32
1.25
1.23
1.21
D
Cl
N
N
O
O
Me
CDCl3, 400 MHz
172
(run with DMF:D2O 9:1 as solvent)
3.95
2.02
2.1
4.24
1
2.1
2.08
2.1
ppm
9
8
7
6
5
4
3
2
1



172

(run with DMF:D_2O 9:1 as solvent)


8.69
8.69
8.37
7.89
7.87
7.72
7.71
7.40
7.37
7.26
7.07
3.04
2.52
CDCl3, 400 MHz
O
O
S
Me
(80% D)
Cl
N
N
Me
D
173
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ppm
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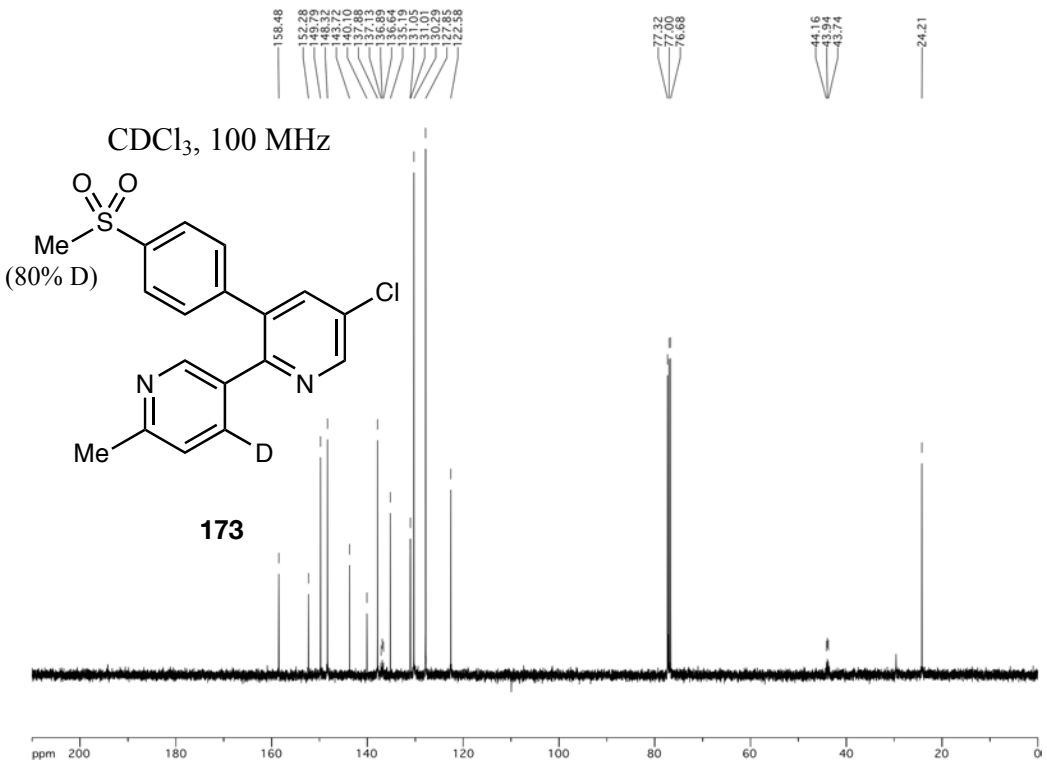
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130.29
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122.58
77.32
77.00
76.68
44.16
43.94
43.74
24.21
CDCl3, 100 MHz
O
O
S
Me
(80% D)
Cl
N
N
Me
D
173
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140
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60
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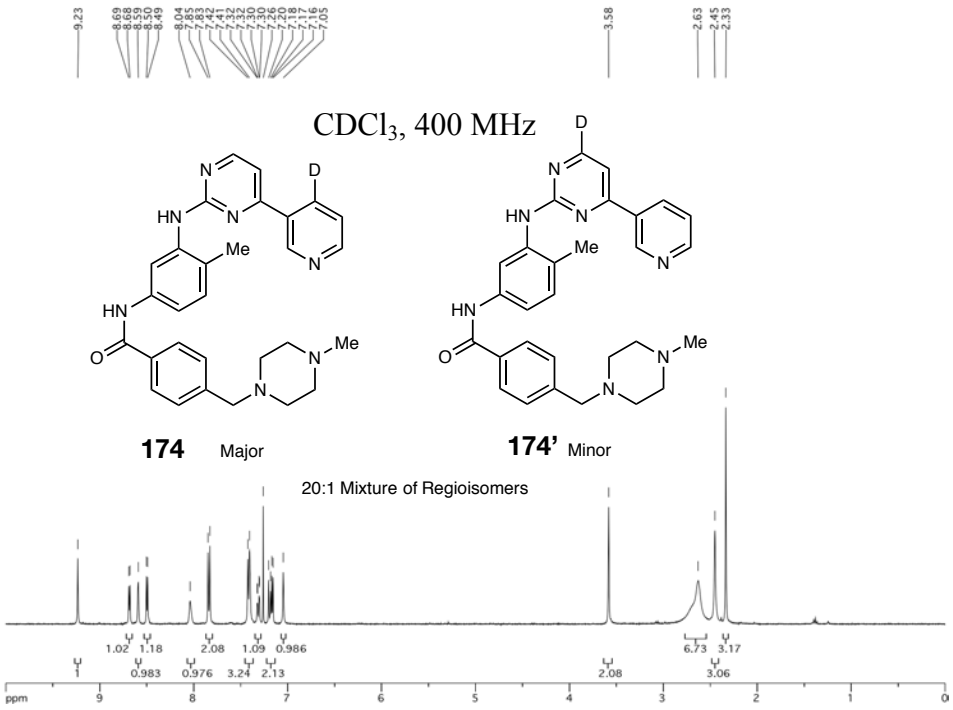
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7.30
7.26
7.20
7.18
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7.05
3.58
2.63
2.45
2.33
CDCl3, 400 MHz
D
N
HN
N
Me
N
HN
O
N
Me
174 Major
174' Minor
20:1 Mixture of Regioisomers
1.02
1.18
2.08
1.09
0.986
6.73
3.17
1
0.983
0.976
3.24
2.13
2.08
3.06
ppm
9
8
7
6
5
4
3
2
1
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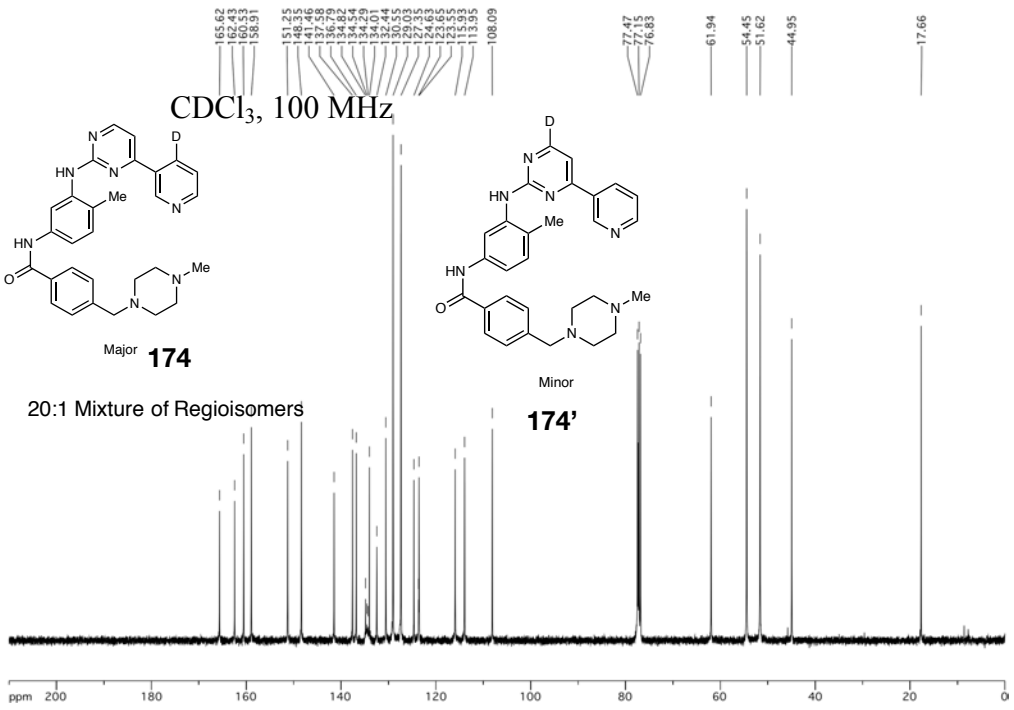

CDCl3, 100 MHz
Major
174
20:1 Mixture of Regioisomers
Minor
174'
ppm 200 180 160 140 120 100 80 60 40 20 0

APPENDIX TWO

PYRIDINE-PYRIDINE CROSS-COUPLING VIA DEAROMATIZED RADICAL INTERMEDIATES: EXPERIMENTAL

A2.1 General Information and Materials

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (400 MHz), an Agilent Inova 400 (400 MHz) spectrometer, an Agilent Inova 500 (500 MHz) spectrometer, or a Bruker AV-111 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 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, proton assignment). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity was reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, oct = octet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (100 MHz) 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). 2-dimensional experiments (COSY, HMBC and HSQC) were used to support assignments where appropriate.

Absorption spectra were obtained with a Hewlett-Packard 8453 spectrometer in quartz cuvettes with a 1 cm or 0.17 cm path length. Electrochemical experiments were performed in 0.1

M solutions of Bu_4NPF_6 in CH_2Cl_2. Cyclic voltammograms (CVs) and square-wave voltammograms (SWVs) were recorded with a CH Instruments potentiostat (Model 1230A or 660C) using a 0.25 mm glassy carbon disk working electrode, Ag^+/Ag reference electrode, and a Pt wire auxiliary electrode. Scans were collected at 100 mV/s. Reported potentials are referenced to the $[Cp2Fe]^+/[Cp2Fe]$ (Fc^+/Fc), where Cp = cyclopentadiene, redox couple, and were determined by adding ferrocene as an internal standard at the conclusion of each electrochemical experiment. The potentials in reference to SCE are estimates based on the reported of Fc^+/Fc^0 in 0.1 M solution of Bu_4NPF_6 in dichloromethane.[1]

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}).

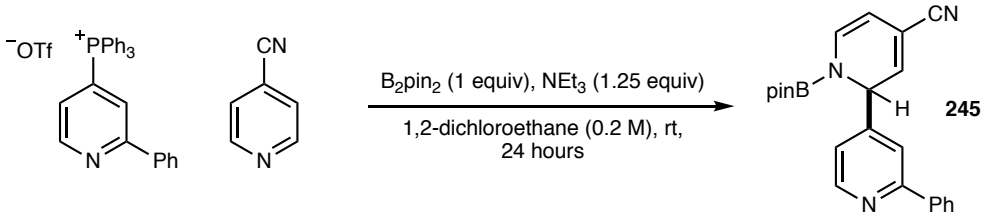
Analytical thin layer chromatography (TLC) was performed using pre-coated Merck glass-backed silica gel plates (Silicagel 60 F254) or foil-backed basic aluminum oxide plates (Baker-flex 4467). Flash column chromatography was undertaken on Fluka or Material Harvest silica gel (230–400 mesh) or Sigma-Aldrich aluminum oxide (activated, basic) under a positive pressure of air. Preparative thin layer chromatography was performed using pre-coated Silicycle glass-backed silica gel plates (Siliaplate 60Å, 20 cm×20 cm, 2000 μm, TLG–R10011B–353). 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), 1,4-dioxane, chloroform, chlorobenzene 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, ^{1}H 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.

PPh_3 (99%) was purchased from Oakwood Chemical and is most effective when crushed to a powder before use. Tf_2O (99%) was purchased from Oakwood Chemical and used without further purification and was routinely stored in a –20 ºC fridge. NEt_3 and DBU were distilled before use. 4-cyanopyridine was recrystallized from a 50:50 mixture of CH_2Cl_2:Et_2O and stored in the glovebox before use.

A2.2 Evidence of Dearomatized Species 245



Evidence of the proposed dearomatized species **245** was observed using **197** as the phosphonium salt. The standard reaction was set up and ran in a glovebox using degassed $CDCl_3$. After 24 hours, the ^{1}H NMR and MS samples were prepared in the glovebox to avoid exposure to air. By ^{1}H NMR

analysis, four protons appeared in the alkenyl region of the spectra (see below). The sample was transferred from the NMR tube to a vial and stirred open to air for thirty minutes and reanalyzed by ^{1}H NMR and LCMS. The alkenyl peaks seen before were no longer present and had converted almost completely to rearomatized product **202**. For integration values in ^{1}H NMR, 1,3,5-trimethoxybenzene was used as internal standard.

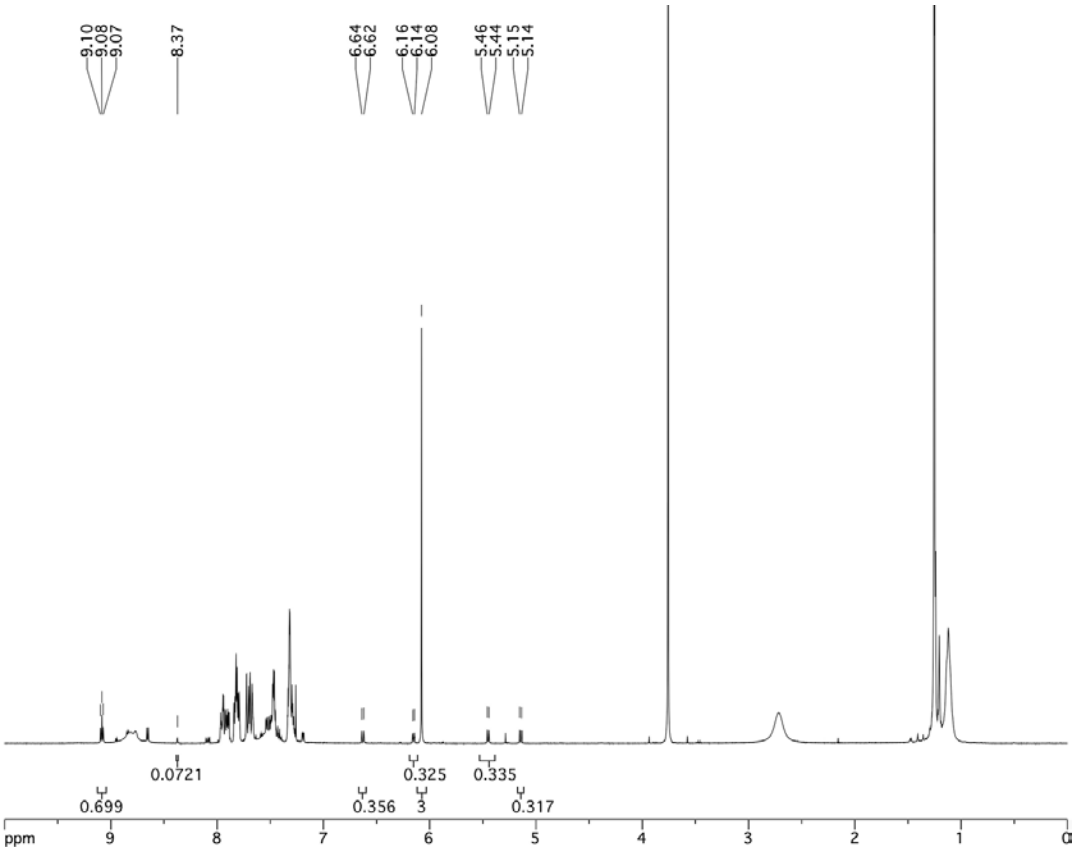


Figure A2.1. ^{1}H NMR of **245** before exposure to air.

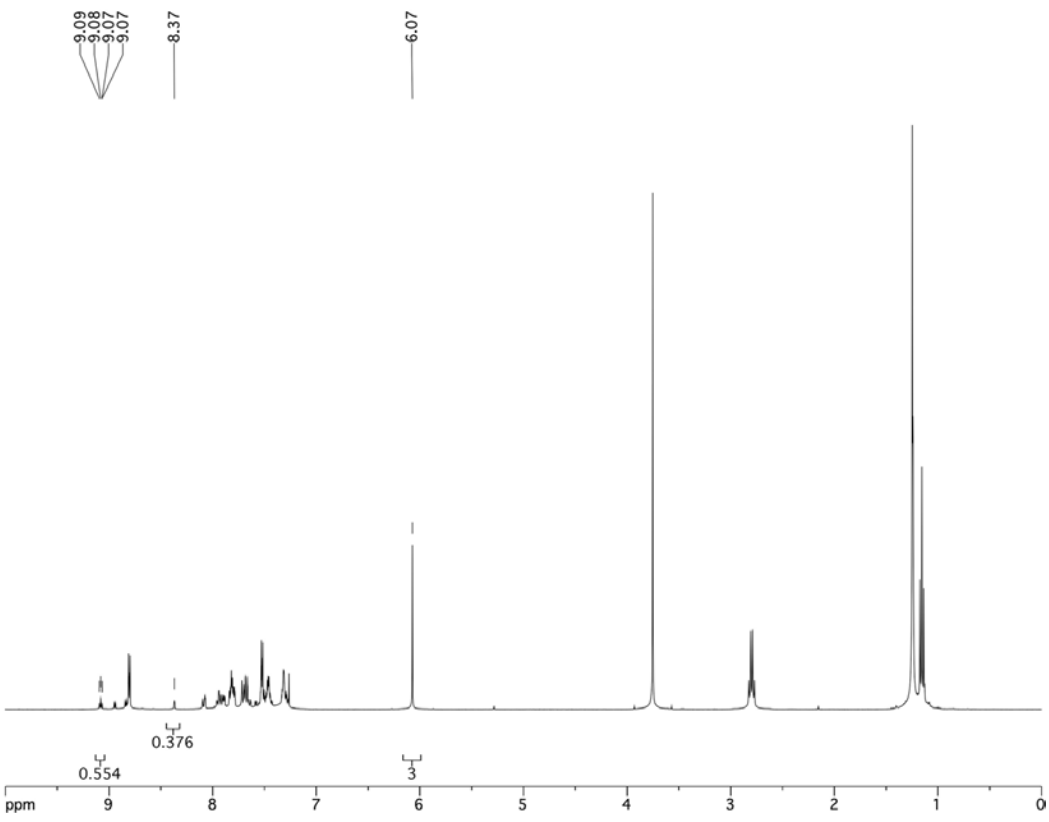
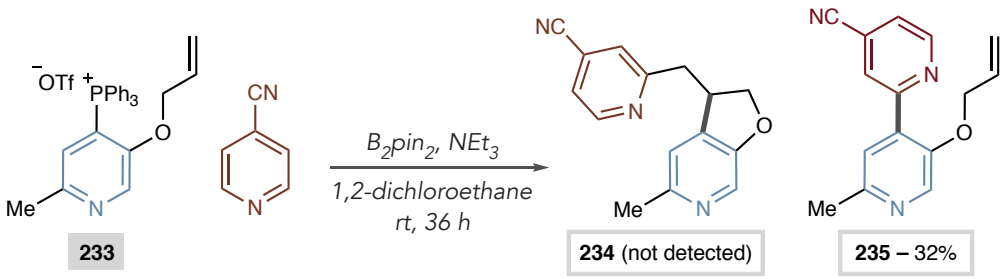
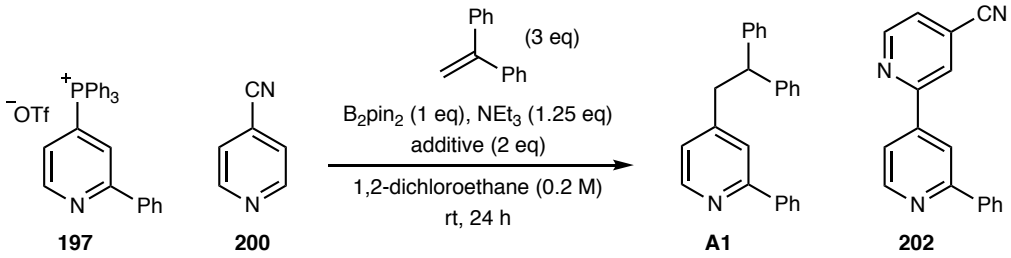


Figure A2.2. ^{1}H NMR of **245** after exposure to air for 30 minutes.

A2.3 Radical Clock Experiments



To probe the intermediacy of a free radical, we synthesized phosphonium **233**, which should be able to undergo a 5-exo-trig cyclization with the allyloxy substituent upon reduction and formation of a discrete pyridyl radical intermediate. The reaction was subjected to the standard reaction conditions at 0.1 mmol scale and analyzed after 36 hours. Through ^{1}H NMR analysis, no cyclized product **234**, nor any other cyclized products were detected. The major product formed in the reaction was coupled product **235** and isolated at 32% (see below for details).

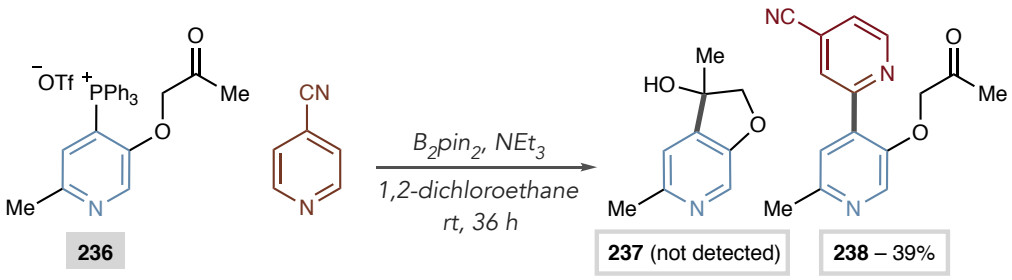


entry	additive	% **197**	% **A1**	% **202**
1	none	23	0	78
2	benzyl mercaptan	75	0	30
3	Hantzsch ester	37	0	40

Additionally, we attempted to trap the postulated pyridyl radical formed from **197** with 1,1-diphenylethylene and a hydrogen atom source (benzyl mercaptan or Hantzsch ester). The reaction

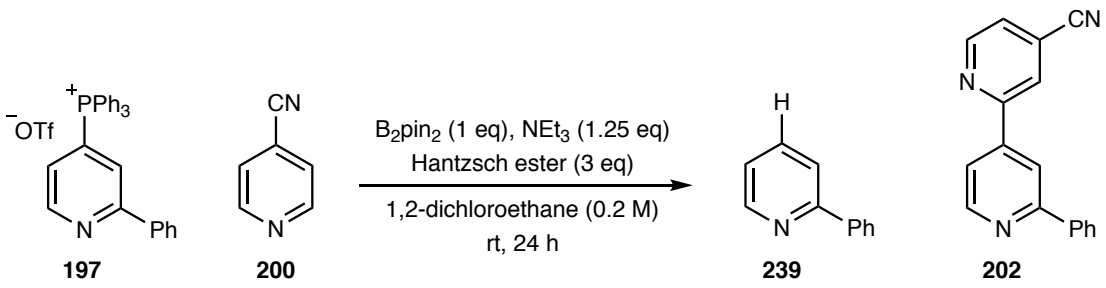
was subjected to the standard reaction conditions at 0.1 mmol scale and analyzed after 24 hours. In all cases, bipyridine **202** was the major product, none of the trapped product was observed, and unreacted starting material **197** remained.

A2.4 Anion cyclization trap experiment



To probe the intermediacy of a pyridyl anion or a pyridyl radical anion, we synthesized phosphonium **236**, which should be able to undergo a 5-exo-trig cyclization with the allyloxy substituent upon reduction and formation of a discreet pyridyl anion or a pyridyl radical anion. The reaction was subjected to the standard reaction conditions at 0.1 mmol scale and analyzed after 36 hours. Through ^{1}H NMR analysis, no cyclized product **237**, nor any other cyclized products were detected. The major product formed in the reaction was coupled product **238** and was isolated at 39% yield (see below for details).

A2.5 Inhibition Experiment with Hantzsch Ester as an H-atom Donor



We attempted to inhibit the reaction using Hantzsch Ester as an H-atom source. If a pyridyl radical was formed, we expect to see product **239** arising from H-atom abstraction. The reaction was subjected to the standard reaction conditions at 0.1 mmol scale with 3 equivalents of Hantzsch Ester and analyzed after 24 hours. The results of the reaction are shown in the figure above. 9% of phosphonium salt **197** remained, no product **239** detected, and 60% ^{1}H NMR yield of the bipyridine coupled product **202**. This suggests that the reaction is not proceeding through a discrete pyridyl-radical.

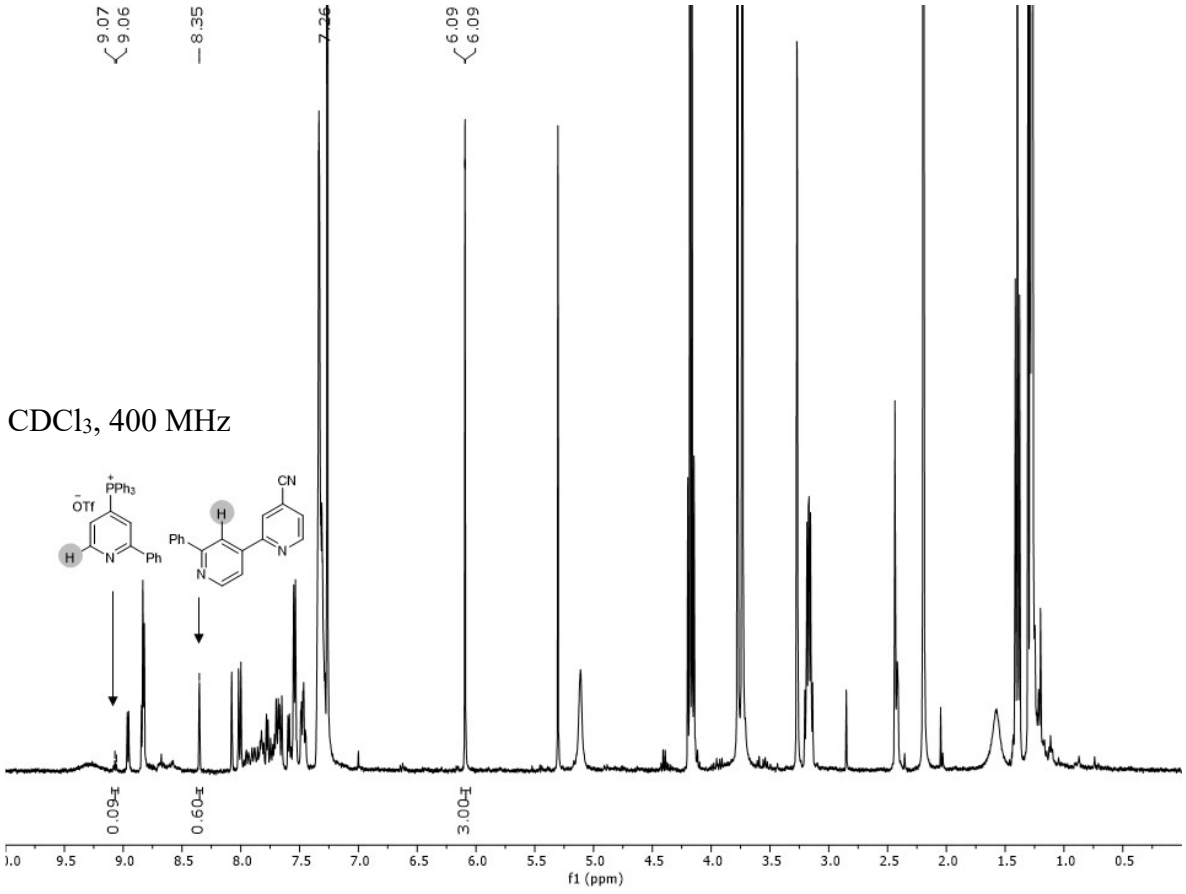
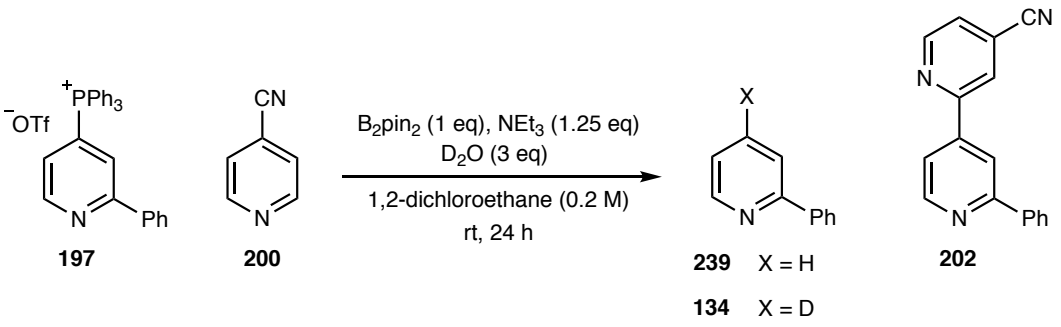


Figure A2.3. Crude ^{1}H NMR spectrum of coupling reaction using Hantzsch as H-atom donor.

A2.6 Inhibition Experiment with Deuterium Oxide (D_2O) as a Proton Donor



We attempted to trap the possible pyridyl anion using D_2O as an acidic deuterium source. If a pyridyl anion, or the proposed radical phosphonium ylide was formed, we should observe deuteration of the anion from D_2O to make product **134**. The reaction was subjected to the standard reaction conditions at 0.1 mmol scale with 3 equivalents of D_2O and analyzed after 24 hours. The results of the reaction are shown in the figure above. Phosphonium salt **197** and bipyridine product **202** were not detected, however a mixture of product **239** and **134** was isolated (silica gel plug, 30% EtOAc:hexane) giving 72% of deuterated product **134** and 7% of product **239** (79% yield overall with 91% deuterium incorporation by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard). This suggests that the reaction is proceeding either through a pyridyl anion or the proposed radical phosphonium ylide.

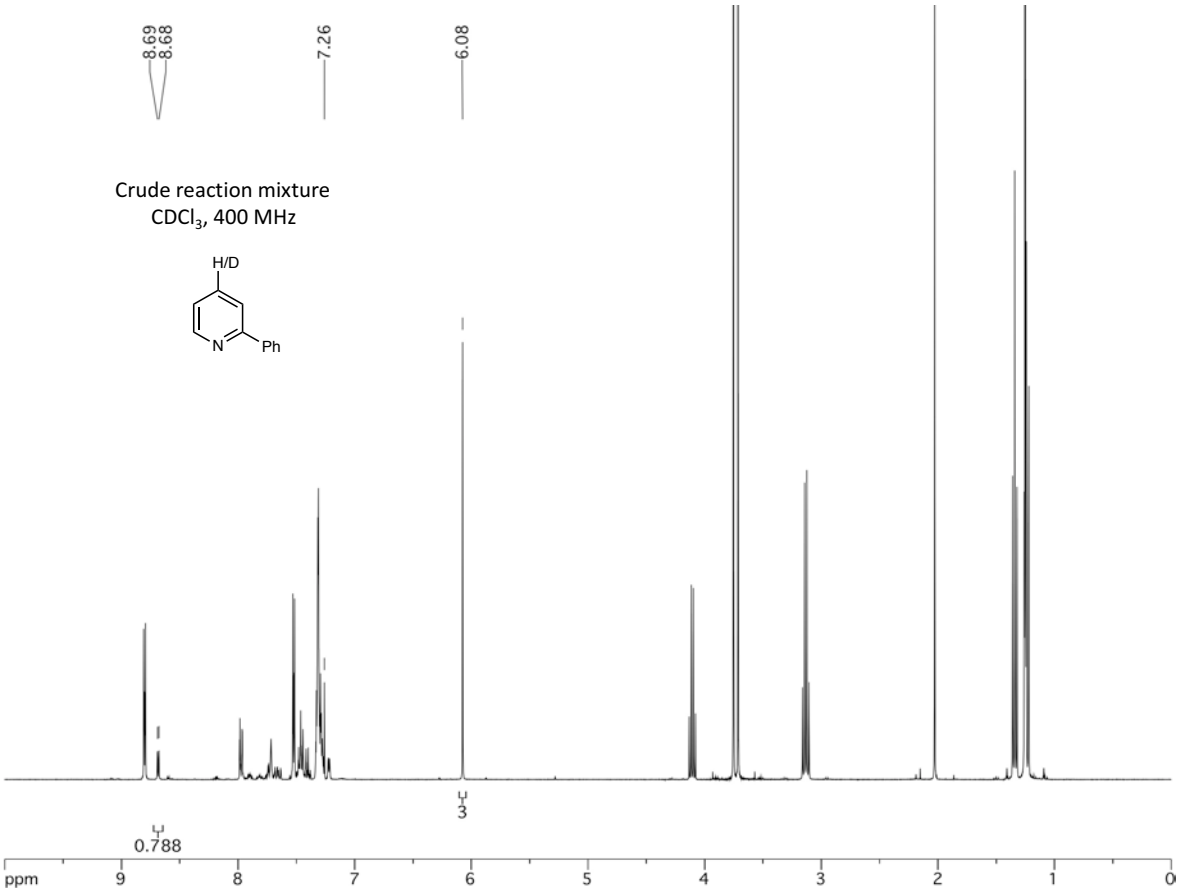


Figure A2.4. Crude ^{1}H NMR spectrum of coupling reaction using D_2O as deuteron donor.

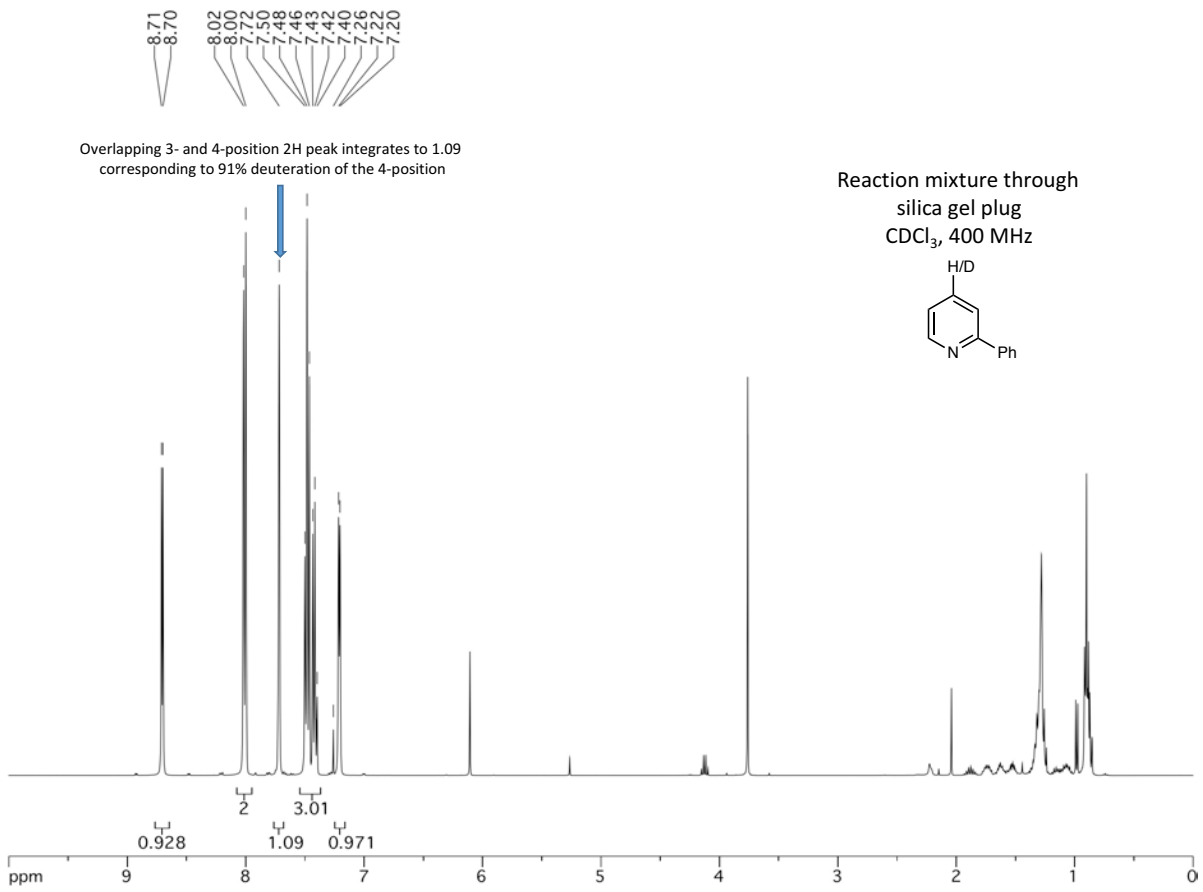


Figure A2.5. ^{1}H NMR spectrum of isolated C-H/D product reaction using D_2O as deuteron donor.

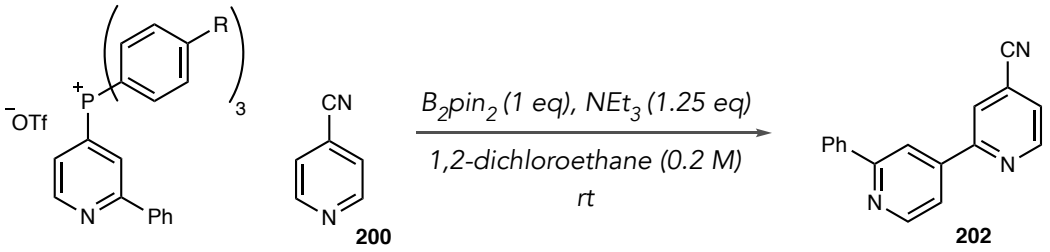
Control reaction of phosphonium in presence of D_2O and LiOD

197 **134**

To assure that a catalytic amount of LiOD was not initiating the decomposition and subsequent deuteration of **197** to produce **134** in the previous mechanistic experiment, the following study was performed. A LiOD/D_2O solution (LiOD 10 mol % relative to phosphonium salt) was prepared by adding *n*BuLi (2.3 M in hexane) (0.025 mmol, 10.9 µL) to D_2O (0.75 mmol, 13.5 µL) at 0 °C and

warmed to rt. This LiOD/D_2O solution was then added to a solution of phosphonium **197** (141 mg, 0.25 mmol), 1,2-dichloroethane (1.25 mL, 0.2 M), and let stir at rt for 24 h. Analysis by ^1H NMR and LCMS confirmed that there was no degradation of the phosphonium salt **197** to deuterated product **134**. This result suggests that LiOD in the reaction mixture does not decompose the phosphonium salt in the above reaction conditions.

A2.7 Aryl Group Substitution Study: Initial Rates



R = H (**197**), Me (**A2**), OMe (**A3**), or Cl (**A4**)

The standard reaction was monitored for 1-2 hours in duplicate and the average was used for comparison of initial rates with phosphonium salt derivatives **197**, **A2**, **A3**, and **A4**. The linear range for the standard reaction was chosen for analysis of the initial rate. Yields were determined at the given time points using ^1H NMR in $CDCl_3$ with 1,3,5-trimethoxybenzene as the internal standard. Procedure for data collection is detailed below. Each reaction performed for the kinetic analysis was carried to completion to validate method of monitoring product formation instead of starting material consumption; each reaction regardless of phosphonium salt derivative gave 84-104% yield.

Procedure for Aryl Group Substitution Study:

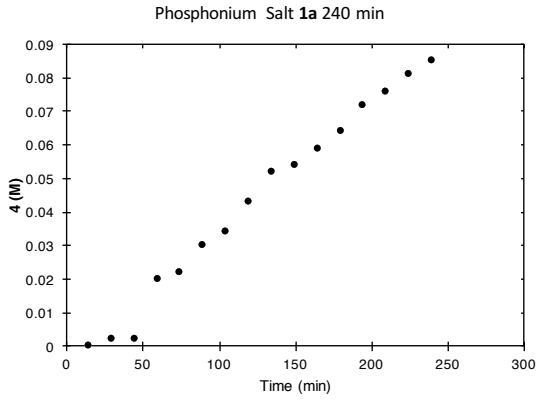
An oven dried 8 mL vial with a septa cap was charged with the phosphonium salt

(Characterization of phosphonium salts shown in Preparation of Heteroaryl Phosphonium Salt section (**197, A2**, **A3**, **A4**) (0.5 mmol), 4-cyanopyridine **200** (104 mg, 1.0 mmol), B_2pin_2 (127 mg, 0.5 mmol), NEt_3 (87 µL, 0.625 mmol), 1,3,5-trimethoxybenzene (84 mg, 0.5 mmol), 1,2-dichloroethane (2.5 mL) and sealed under a nitrogen atmosphere in a glovebox. At each time point, 100 µL of the reaction mixture was sampled via a syringe and charged to a vial open to air. EtOAc (4 mL) was then added to the vial and was allowed to stir for 30 minutes open to air. The vial was then concentrated *in vacuo* and the resulting residue was dissolved in $CDCl_3$ and ^1H NMR spectrum was obtained on the sample. The reaction was allowed to progress until the phosphonium salt was fully consumed and the final yield for the reaction was obtained via ^1H NMR in $CDCl_3$ (48 hours). Each reaction profile was performed in duplicate and the average of the two runs used for initial rate analysis.

Data:

Time (min)	Average [Product] (M)
15	0
30	0.002
45	0.002
60	0.02
75	0.022
90	0.03
105	0.034
120	0.043
135	0.052
150	0.054
165	0.059
180	0.064
195	0.072
210	0.076
225	0.081
240	0.085

Average yield after 60 h: 103%



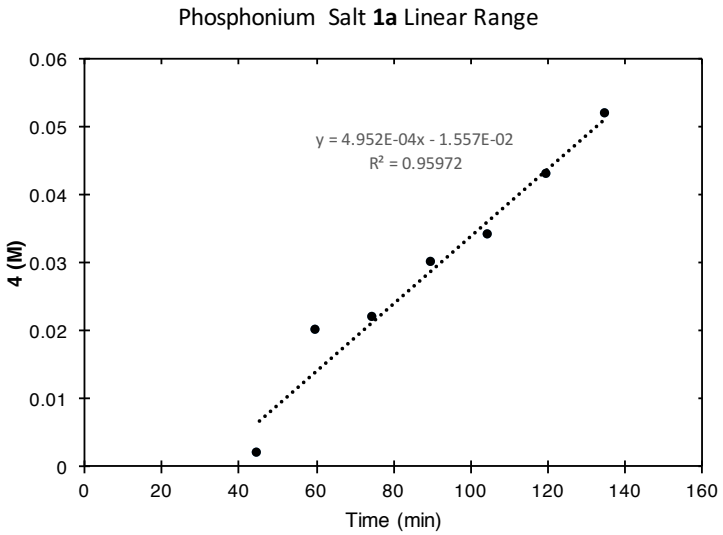
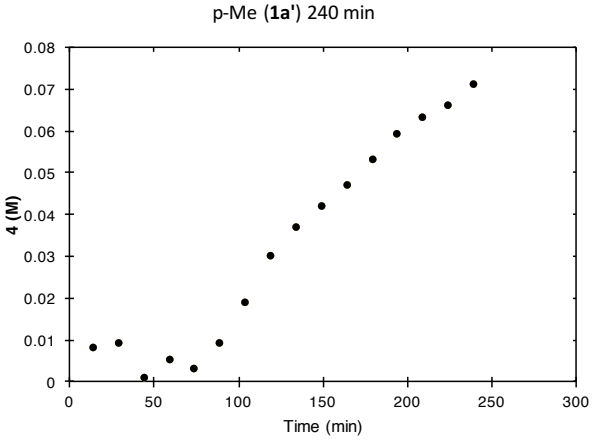


Figure A2.6. Standard reaction conditions ran with phosphonium salt **197** to obtain the initial reaction rate. Study was run in duplicate and the average yield was used. Yields were determined at the given time points using ^{1}H NMR in $CDCl_3$ with 1,3,5-trimethoxybenzene as the internal standard.

Time (min)	Average [Product] (M)
15	0.008
30	0.009
45	0.001
60	0.005
75	0.003
90	0.009
105	0.019
120	0.03
135	0.037
150	0.042
165	0.047
180	0.053
195	0.059
210	0.063
225	0.066
240	0.071

Average yield after 60 h: 93.5%

13



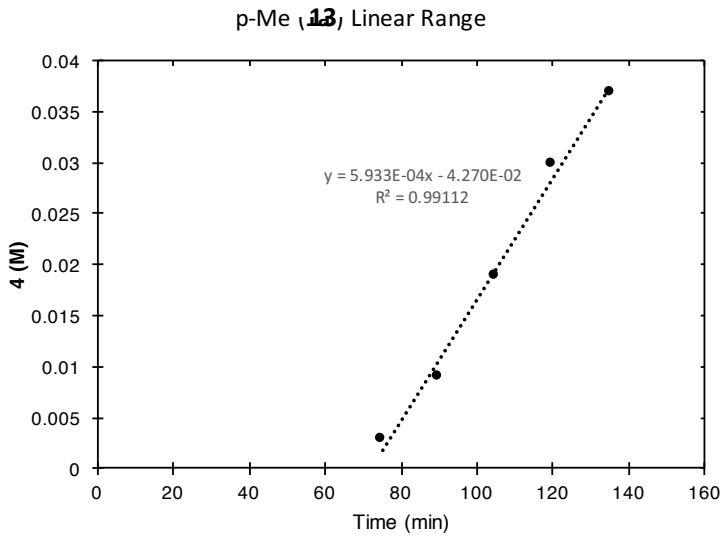
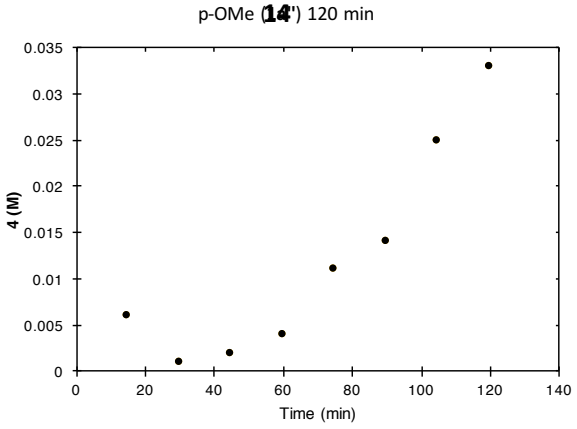


Figure A2.7. Standard reaction conditions ran with phosphonium salt **A2** to obtain the initial reaction rate. Study was run in duplicate and the average yield was used. Yields were determined at the given time points using ^{1}H NMR in $CDCl_3$ with 1,3,5-trimethoxybenzene as the internal standard.

Time (min)	Average [Product] (M)
15	0.006
30	0.001
45	0.002
60	0.004
75	0.011
90	0.014
105	0.025
120	0.033

Average yield after 60 h: 84%



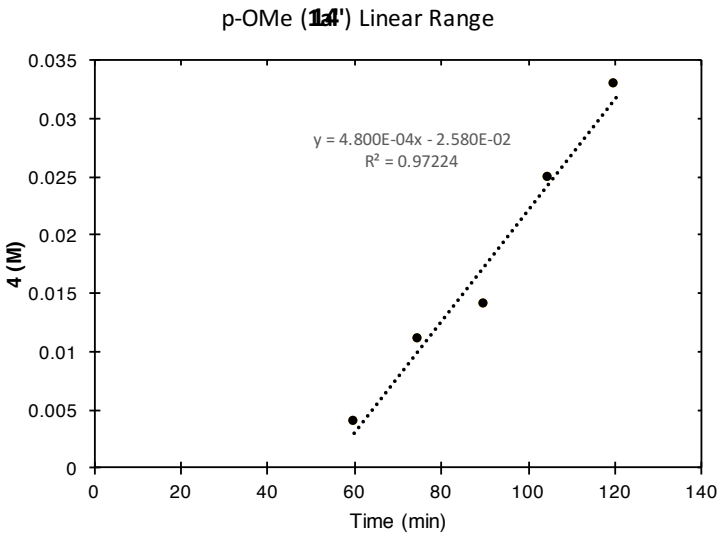
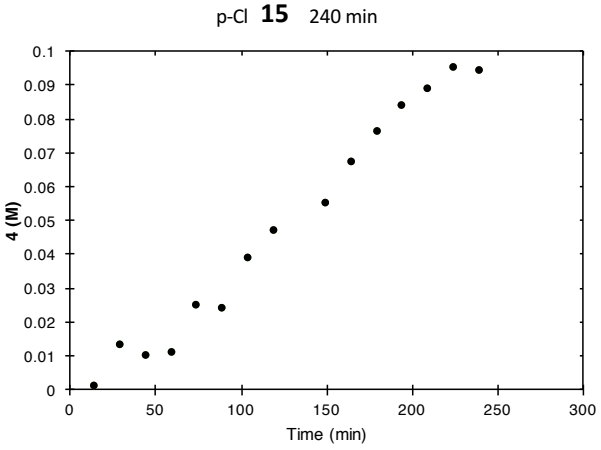


Figure A2.8. Standard reaction conditions ran with phosphonium salt **A3** to obtain the initial reaction rate. Study was run in duplicate and the average yield was used. Yields were determined at the given time points using ^{1}H NMR in $CDCl_3$ with 1,3,5-trimethoxybenzene as the internal standard.

Time (min)	Average [Product] (M)
15	0.001
30	0.013
45	0.01
60	0.011
75	0.025
90	0.024
105	0.039
120	0.047
150	0.055
165	0.067
180	0.076
195	0.084
210	0.089
225	0.095
240	0.094

Average yield after 60 h: 104%



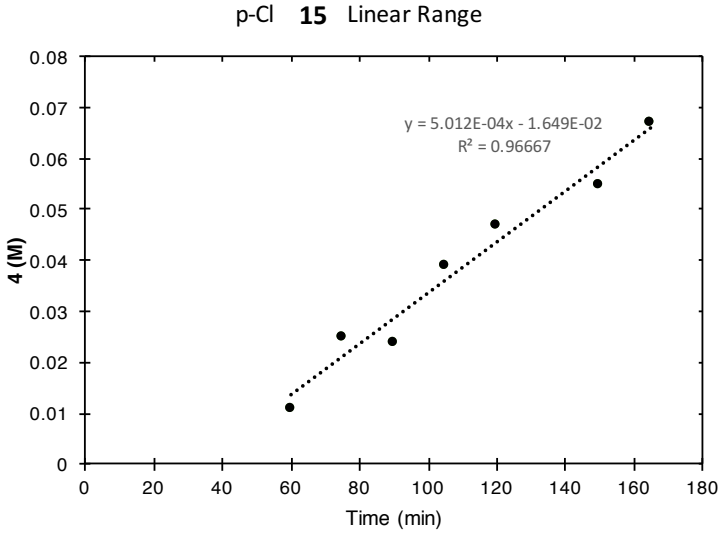


Figure A2.9. Standard reaction conditions ran with phosphonium salt **A4** to obtain the initial reaction rate. Study was run in duplicate and the average yield was used. Yields were determined at the given time points using ^{1}H NMR in $CDCl_3$ with 1,3,5-trimethoxybenzene as the internal standard.

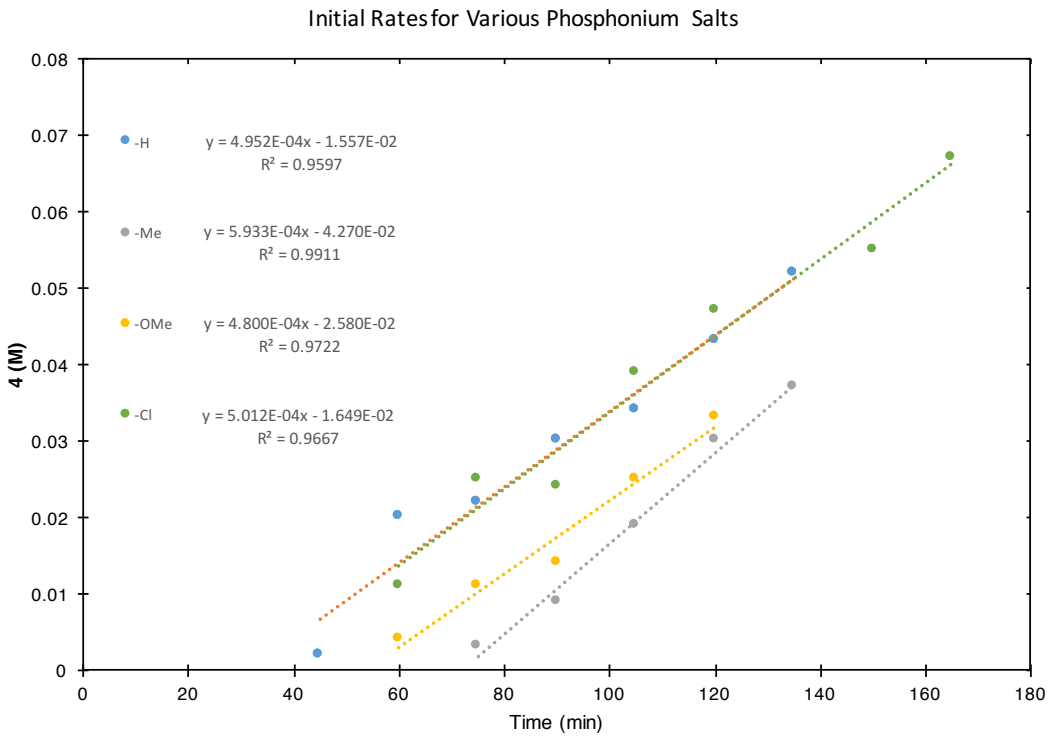


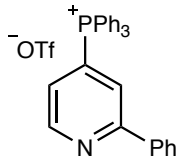
Figure A2.10. Standard reaction conditions ran with phosphonium salts **197** and **A2** through **A4** to obtain the initial reaction rates. Studies were run in duplicate and the average yield was used. Yields were determined at the given time points using ^{1}H NMR in $CDCl_3$ with 1,3,5-trimethoxybenzene as the internal standard.

Relative Rates:	
-Cl	1.01
-H	1.00
-Me	1.20
-OMe	0.97

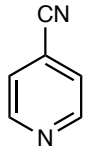
T**able S2**: Relative Initial Rates ($rate_X/rate_H$) of Phosphonium Salts **197, A2-A4** under Standard Reaction Conditions.

Analysis: The investigation into the relative initial rates for the Minisci reaction shows no apparent correlation between initial reaction rate and electrophilicity (reduction potential) at the phosphorus center.

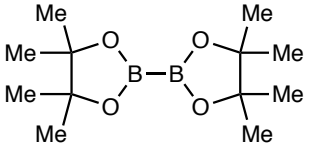
A2.8 UV-Visible Spectroscopy Study



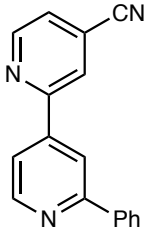
197



200



B_2Pin_2



202

Procedure: An oven dried 8 mL vial with a septa cap was charged with the reactants (0.05 mmol scale) (according to the standard equivalents for the optimized conditions if multiple reactants were added) under a nitrogen atmosphere in a glovebox. The vial was sealed and the mixture was stirred for 1-24 hours. Within a glovebox, a series of dilutions were made to achieve an absorbance between 0 and 1 a.u. (0.01 M – 0.0001 M) and the cuvette was then sealed under nitrogen.

UV-Vis Data:

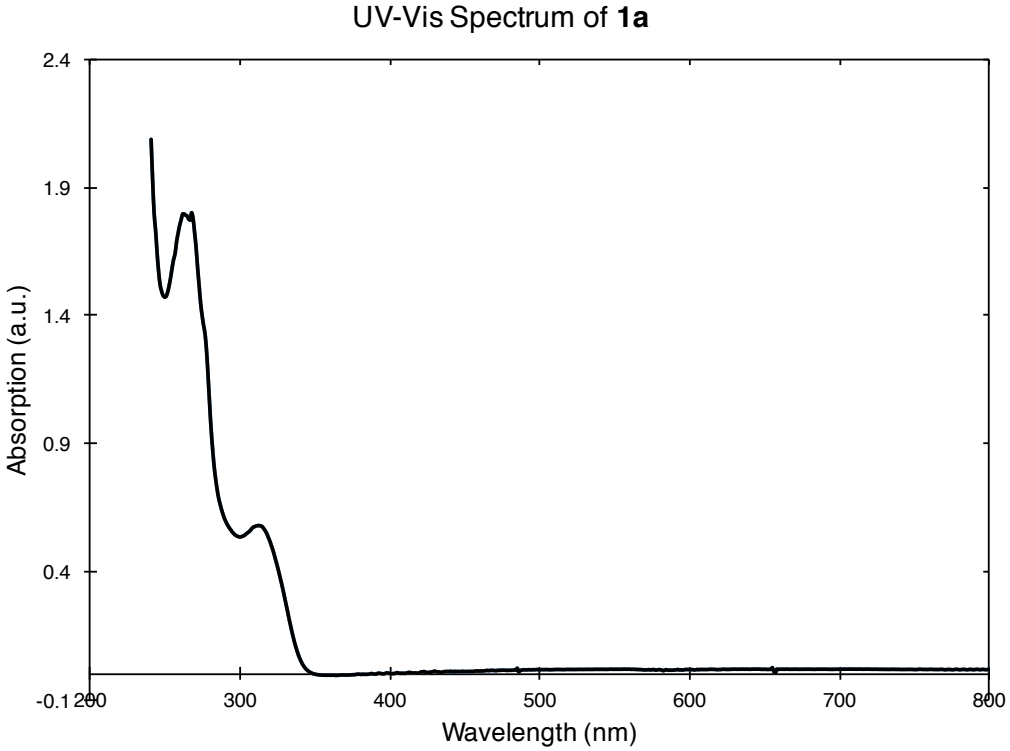


Figure A2.11. 197 (28 mg, 0.05 mmol) in 1,2-dichloroethane (250 µL) was allowed to stir under a nitrogen atmosphere for 1 hour. The sample was then diluted with 1,2-dichloroethane to 0.0001 M and sealed in a cuvette with a 1.0 cm path length under nitrogen.

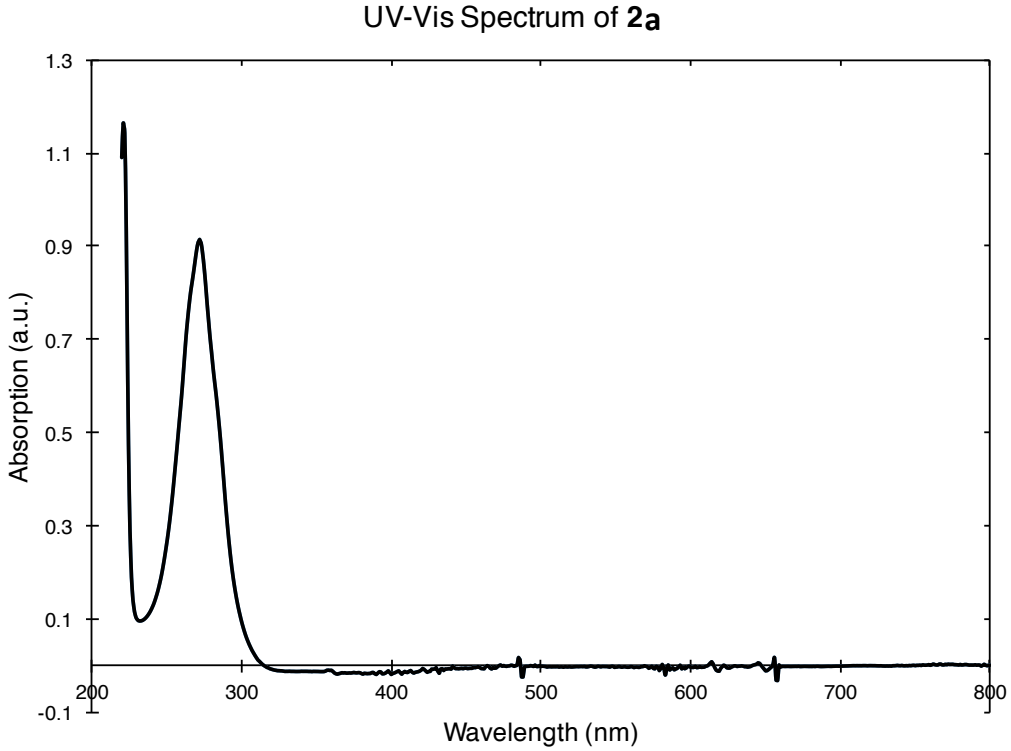


Figure A2.12. 200 (10 mg, 0.1 mmol) in 1,2-dichloroethane (250 μL) was allowed to stir under a nitrogen atmosphere for 1 hour. The sample was then diluted with 1,2-dichloroethane to 0.001 M and sealed in a cuvette with a 0.17 cm path length under nitrogen.

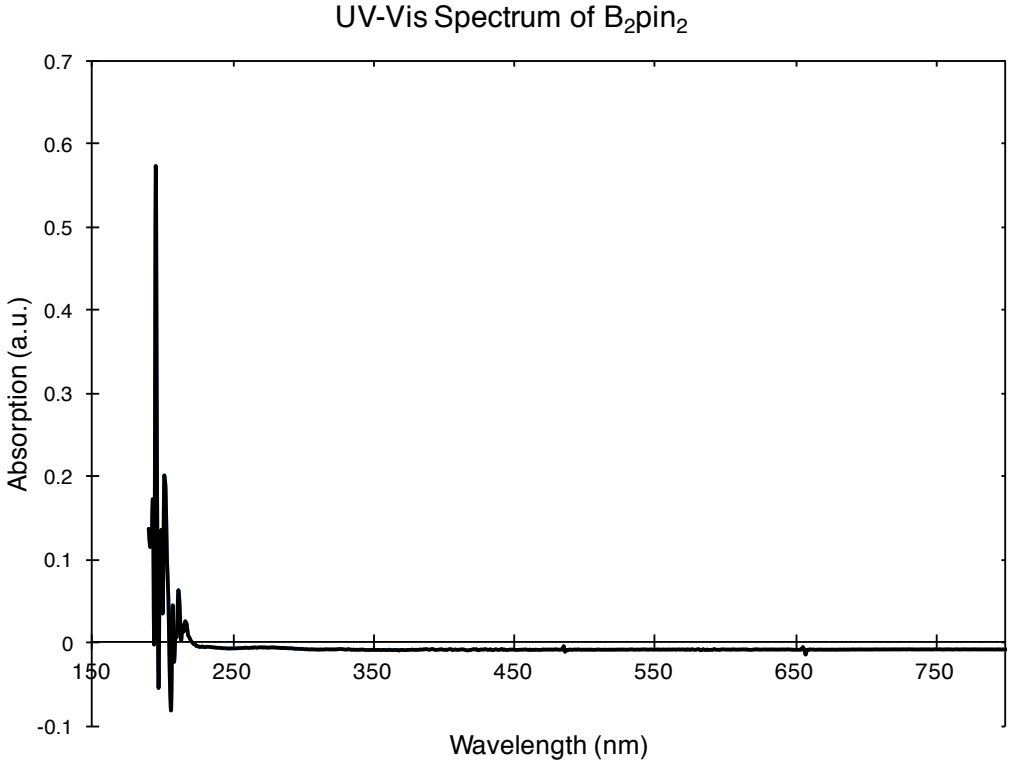


Figure A2.13. B_2pin_2 (13 mg, 0.05 mmol) in 1,2-dichloroethane (250 μL) was allowed to stir under a nitrogen atmosphere for 1 hour. The sample was then diluted with 1,2-dichloroethane to 0.01 M and sealed in a cuvette with a 0.17 cm path length under nitrogen.

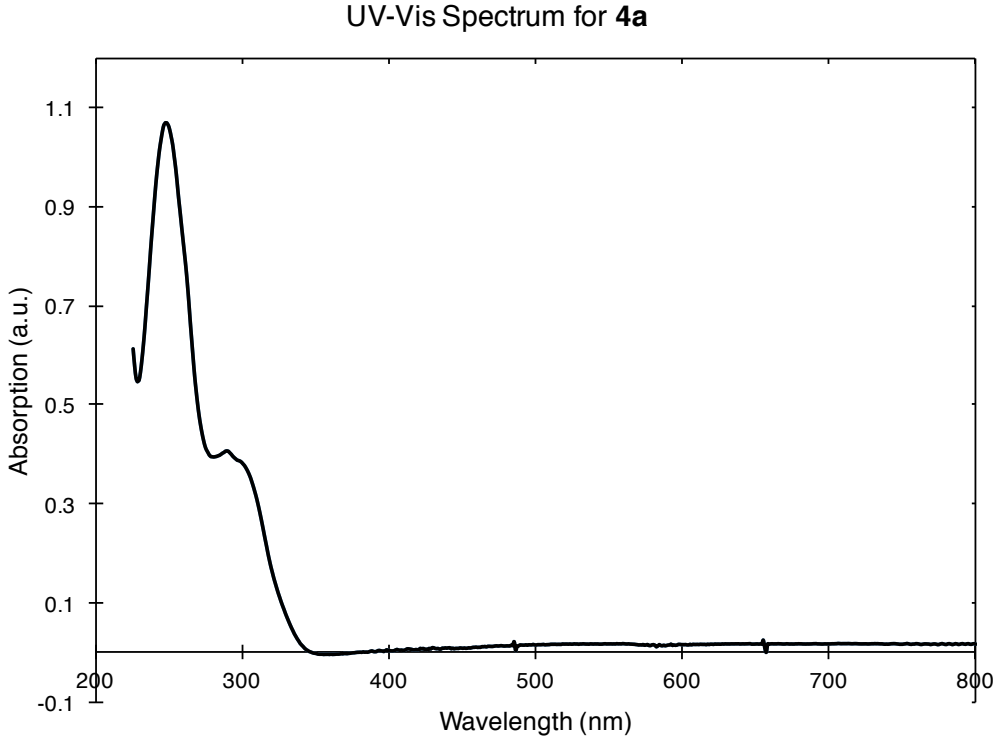


Figure A2.14. 202 (13 mg, 0.05 mmol) in 1,2-dichloroethane (250 µL) was allowed to stir under a nitrogen atmosphere for 1 hour. The sample was then diluted with 1,2-dichloroethane to 0.0002 M and sealed in a cuvette with a 0.17 cm path length under nitrogen.

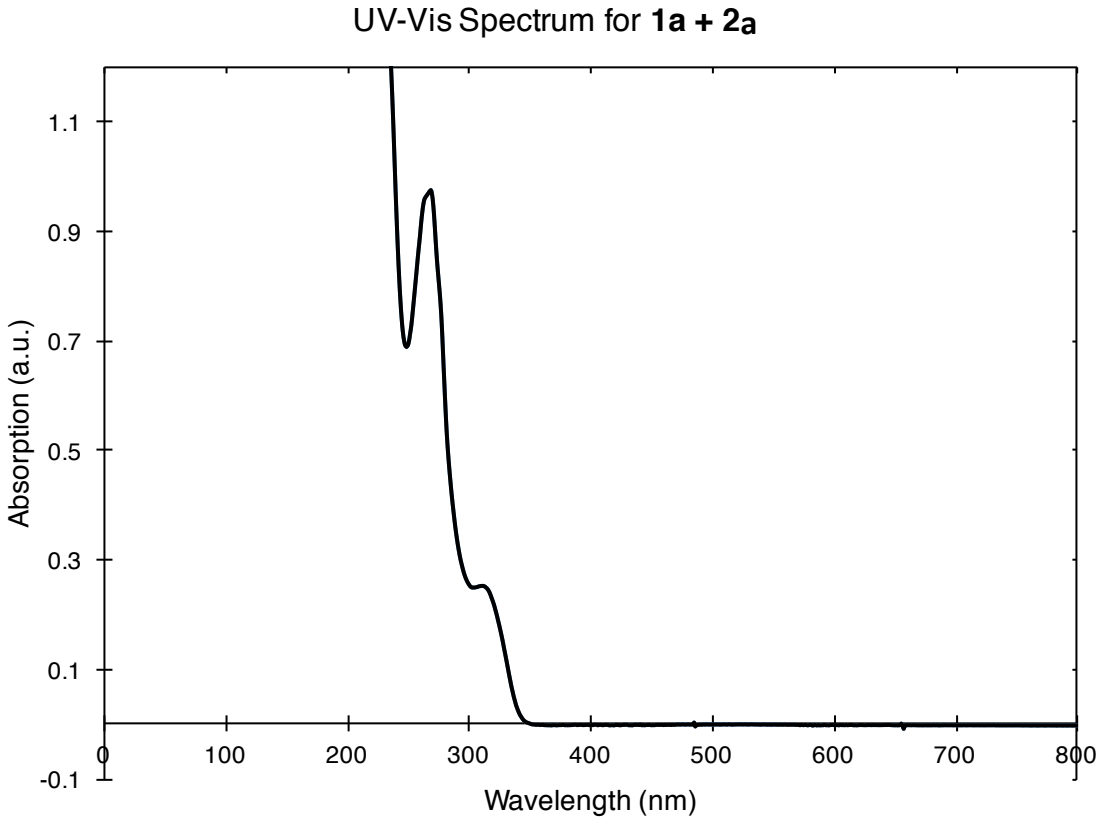


Figure A2.15. 197 (28 mg, 0.05 mmol) and **200** (10 mg, 0.1 mmol) in 1,2-dichloroethane (250 μL) were allowed to stir under a nitrogen atmosphere for 24 hours. The sample was then diluted with 1,2-dichloroethane to 0.001 M with respect to **197** and sealed in a cuvette with a 0.17 cm path length under nitrogen.

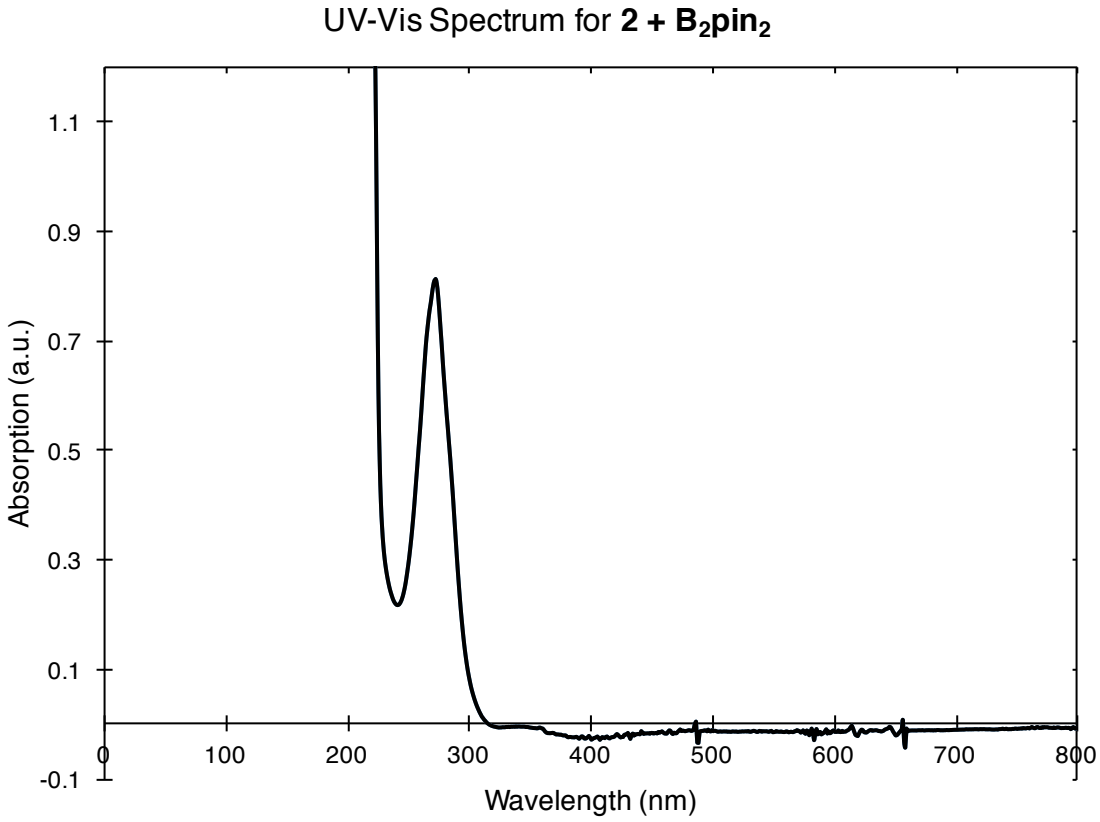


Figure A2.16. 200 (10 mg, 0.1 mmol) and B_2pin_2 (13 mg, 0.05 mmol) in 1,2-dichloroethane (250 μL) were allowed to stir under a nitrogen atmosphere for 24 hours. The sample was then diluted with 1,2-dichloroethane to 0.002 M with respect to **200** and sealed in a cuvette with a 0.17 cm path length under nitrogen.

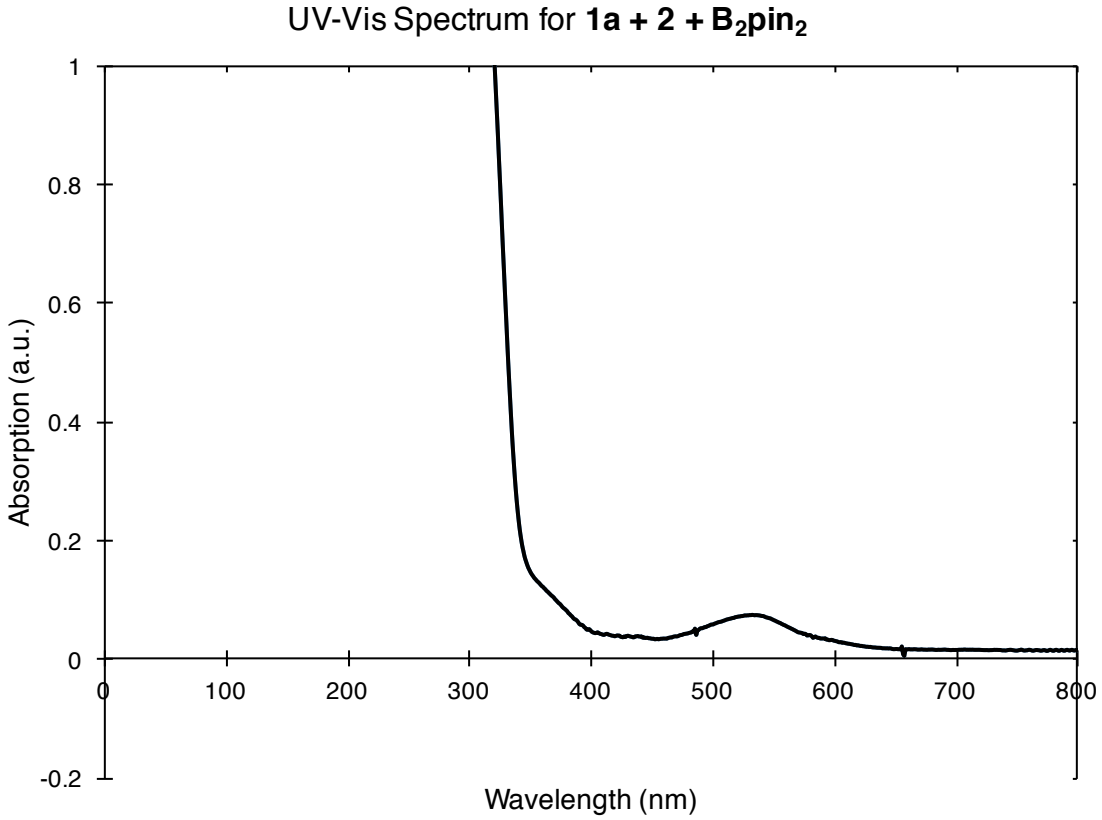


Figure A2.17. **197** (28 mg, 0.05 mmol), **200** (10 mg, 0.1 mmol), and B_2pin_2 (13 mg, 0.05 mmol) in 1,2-dichloroethane (250 μL) were allowed to stir under a nitrogen atmosphere for 24 hours. The sample was then diluted with 1,2-dichloroethane to 0.001 M with respect to **197** and sealed in a cuvette with a 0.17 cm path length under nitrogen.

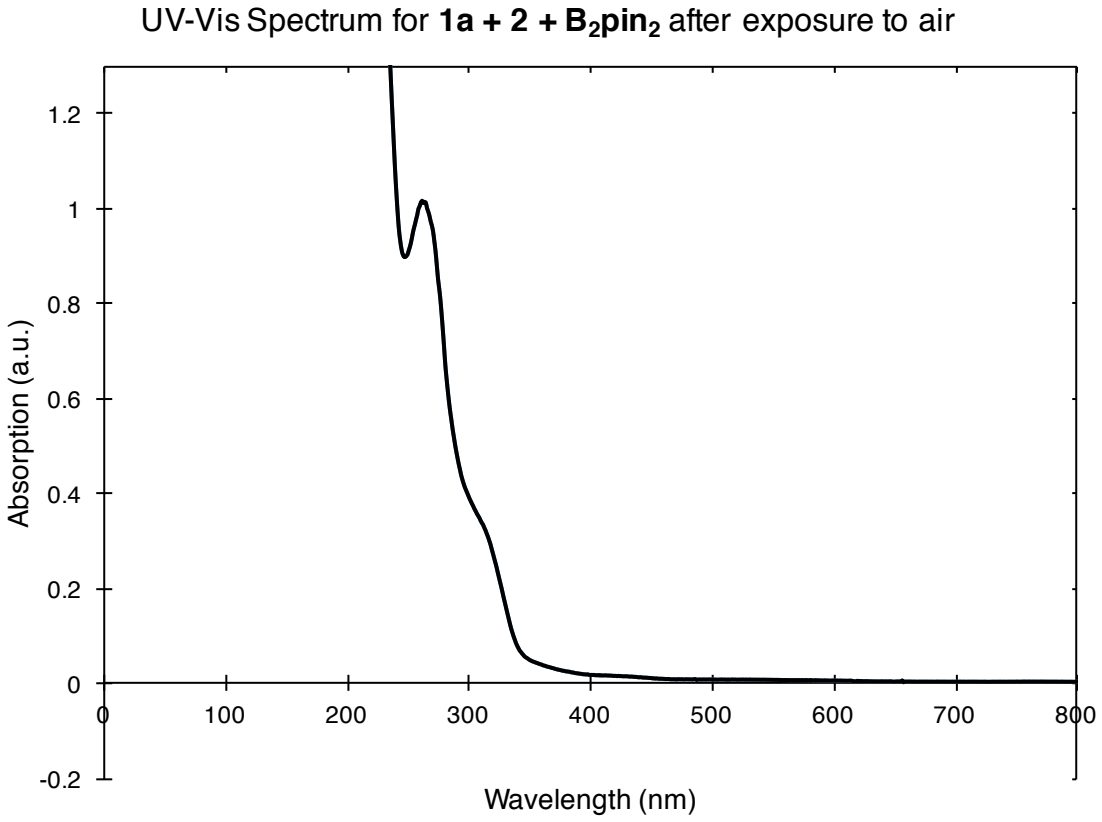


Figure A2.18. 197 (28 mg, 0.05 mmol), **200** (10 mg, 0.1 mmol), and B_2pin_2 (13 mg, 0.05 mmol) in 1,2-dichloroethane (250 μL) were allowed to stir under a nitrogen atmosphere for 24 hours. The sample was then diluted with 1,2-dichloroethane to 0.001 M with respect to **197** and opened to air for 30 minutes. The sample was then placed in a cuvette with a 0.17 cm path length.

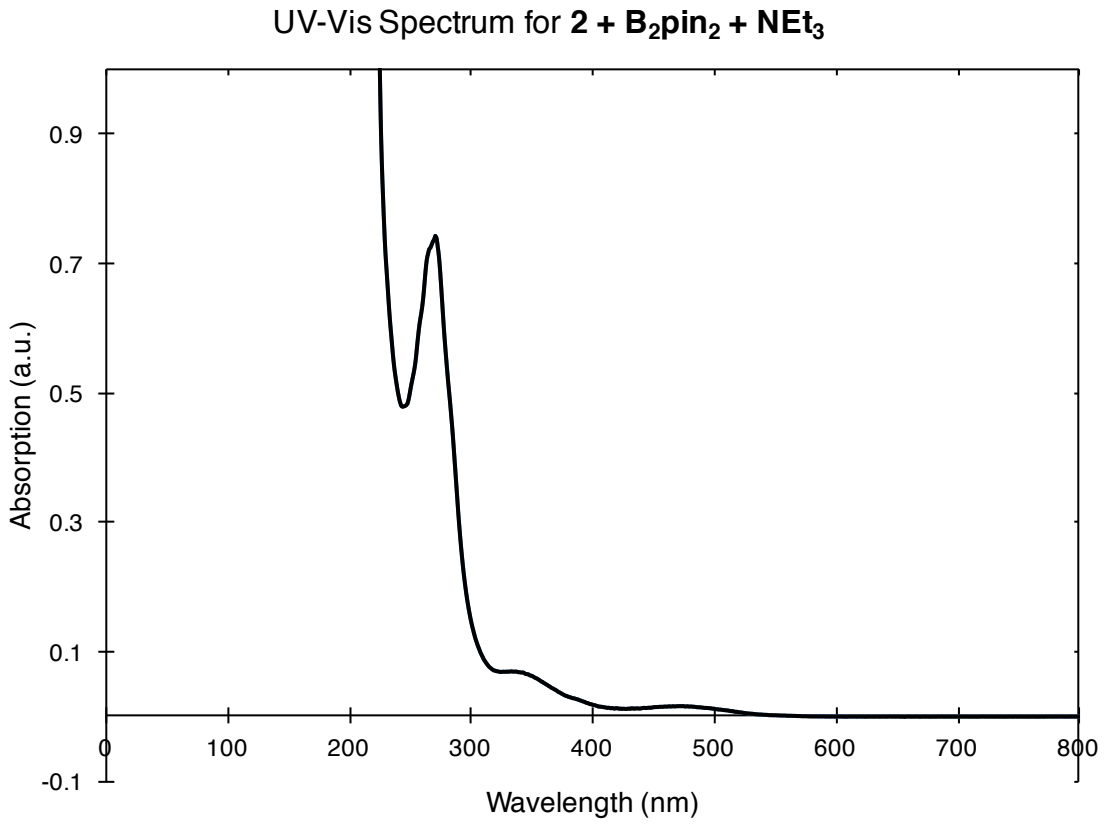


Figure A2.19. 200 (10 mg, 0.1 mmol), B_2pin_2 (13 mg, 0.05 mmol), and NEt_3 (8.7 μL, 0.0625 mmol) in 1,2-dichloroethane (250 μL) were allowed to stir under a nitrogen atmosphere for 24 hours. The sample was then diluted with 1,2-dichloroethane to 0.002 M with respect to **200** and sealed in a cuvette with a 0.17 cm path length under nitrogen.

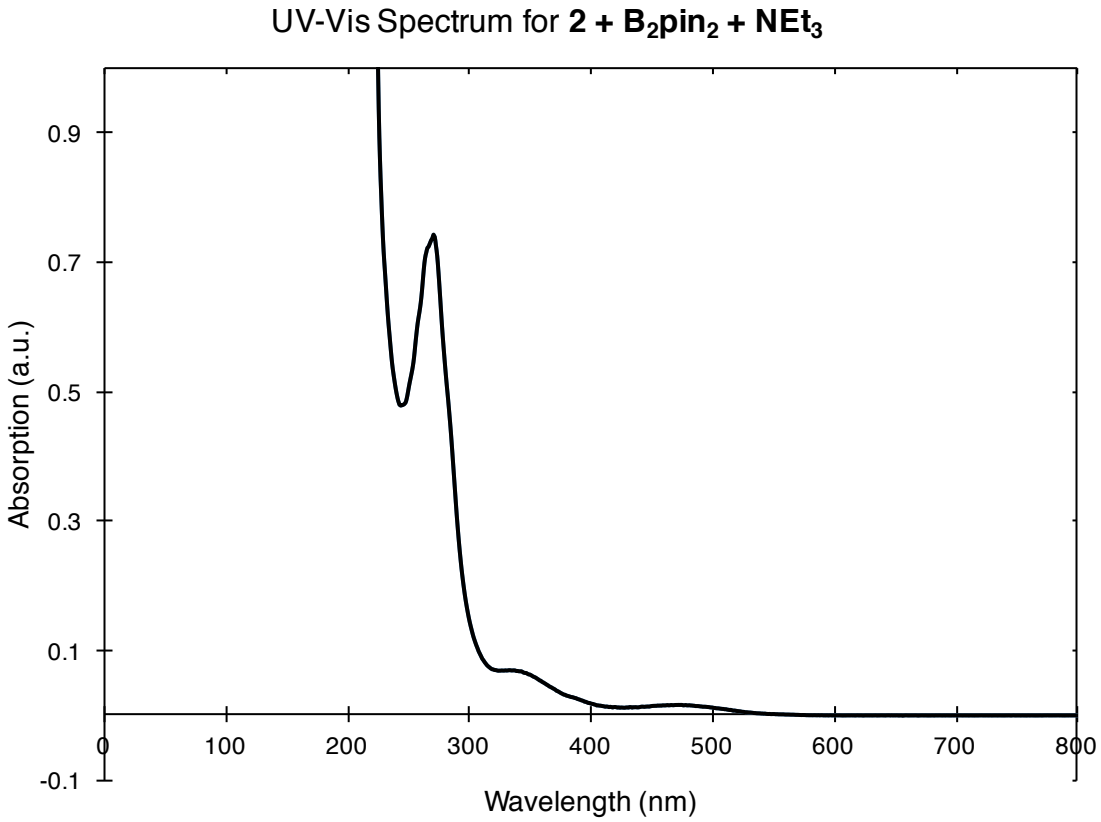


Figure A2.20. 200 (10 mg, 0.1 mmol), B_2pin_2 (13 mg, 0.05 mmol), and PPh_3 (13 mg, 0.05 mmol) in 1,2-dichloroethane (250 μL) were allowed to stir under a nitrogen atmosphere for 24 hours. The sample was then diluted with 1,2-dichloroethane to 0.002 M with respect to **200** and sealed in a cuvette with a 0.17 cm path length under nitrogen.

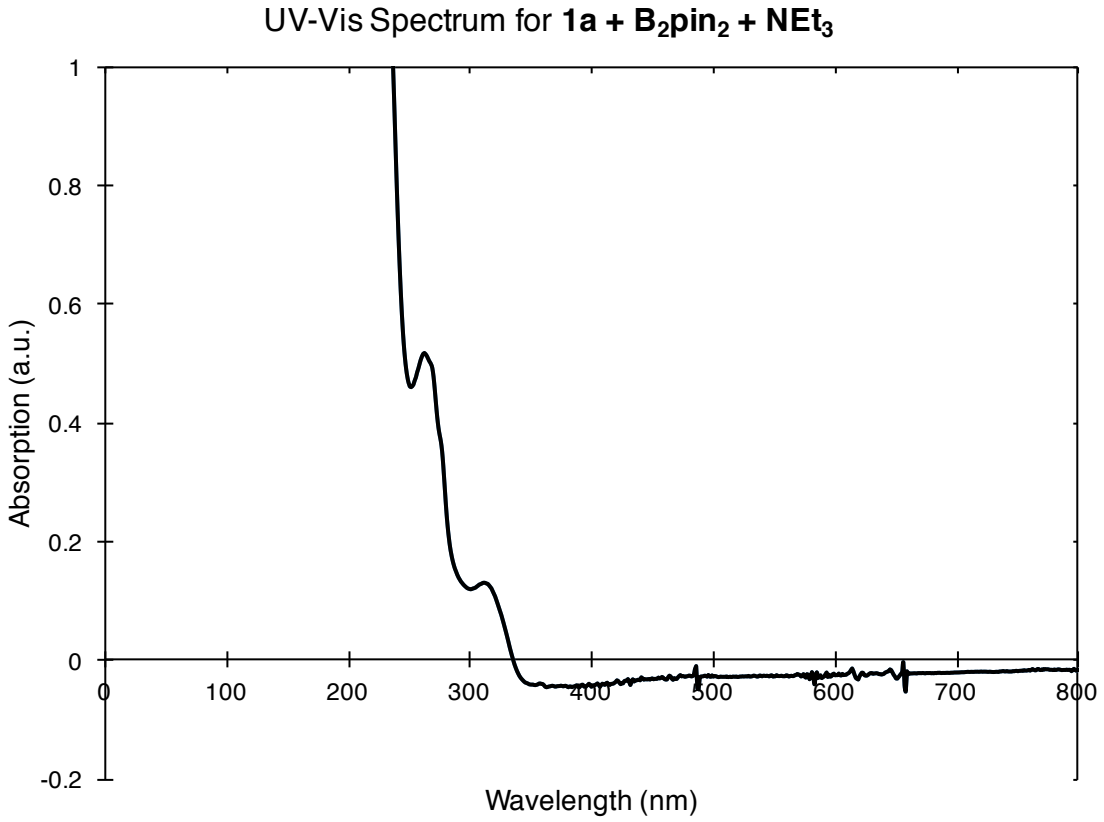


Figure A2.21. **197** (28 mg, 0.05 mmol), B_2pin_2 (13 mg, 0.05 mmol), and NEt_3 (8.7 μL, 0.0625 mmol) in 1,2-dichloroethane (250 μL) were allowed to stir under a nitrogen atmosphere for 24 hours. The sample was then diluted with 1,2-dichloroethane to 0.0005 M with respect to **197** and sealed in a cuvette with a 0.17 cm path length under nitrogen.

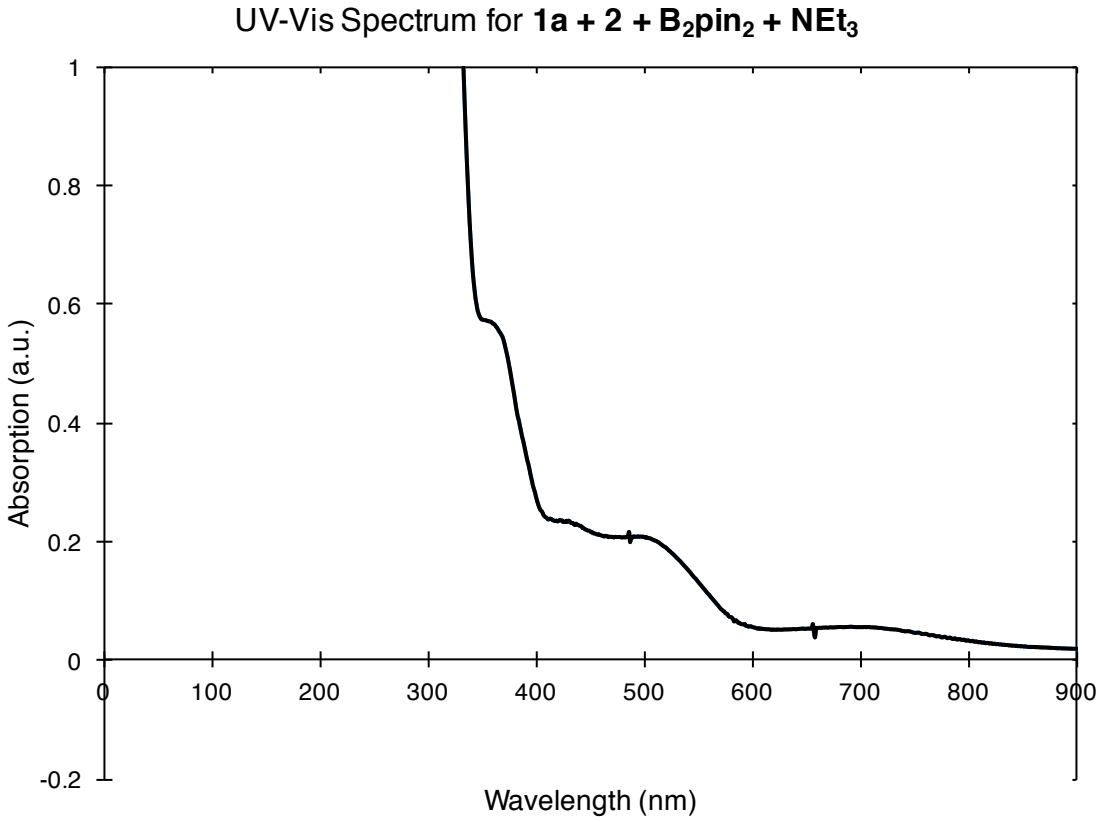


Figure A2.22. **197** (28 mg, 0.05 mmol), **200** (13 mg, 0.1 mmol), B_2pin_2 (13 mg, 0.05 mmol), and NEt_3 (8.7 μL, 0.0625 mmol) in 1,2-dichloroethane (250 μL) were allowed to stir under a nitrogen atmosphere for 24 hours. The sample was then diluted with 1,2-dichloroethane to 0.0025 M with respect to **1a** and sealed in a cuvette with a 0.17 cm path length under nitrogen.

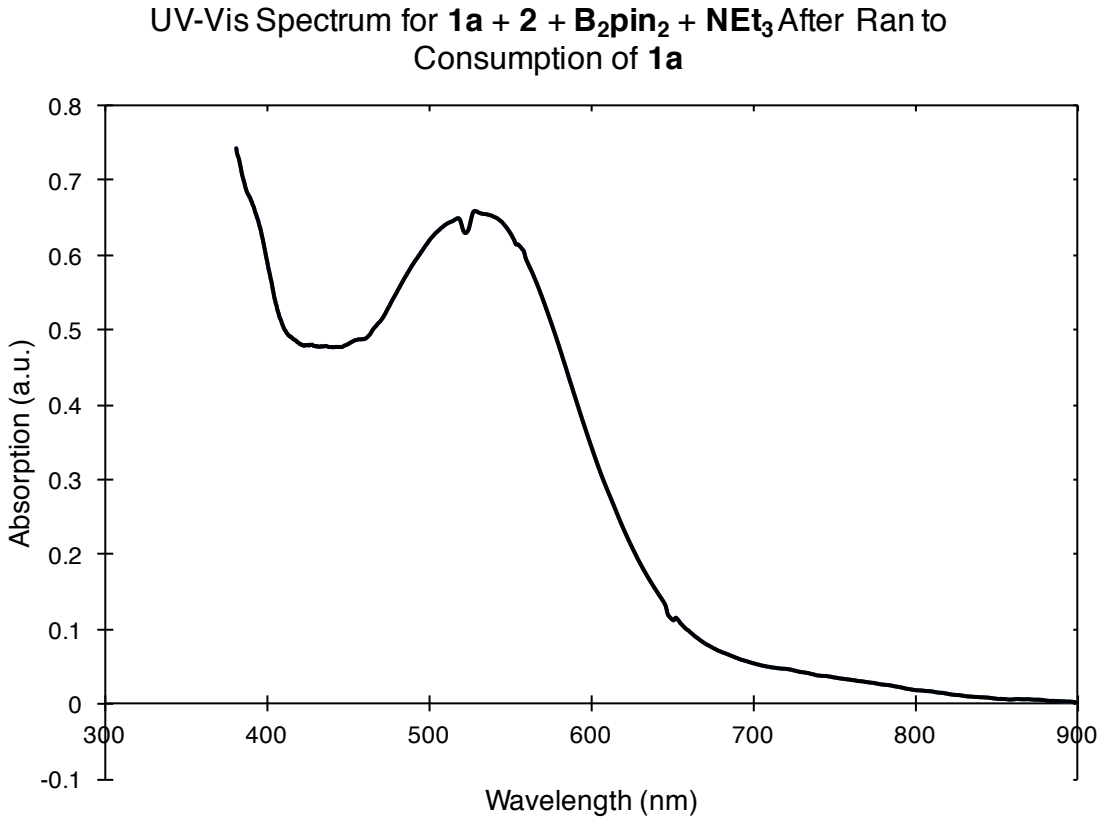


Figure A2.23. **197** (21 mg, 0.2 mmol), **200** (13 mg, 0.1 mmol), B_2pin_2 (13 mg, 0.05 mmol), and NEt_3 (8.7 μL, 0.0625 mmol) in 1,2-dichloroethane (250 μL) were allowed to stir under a nitrogen atmosphere for 48 hours. Consumption of **197** was confirmed by LCMS. The sample was then diluted with 1,2-dichloroethane to 0.0025 M with respect to **197** and sealed in a cuvette with a 0.17 cm path length under nitrogen.

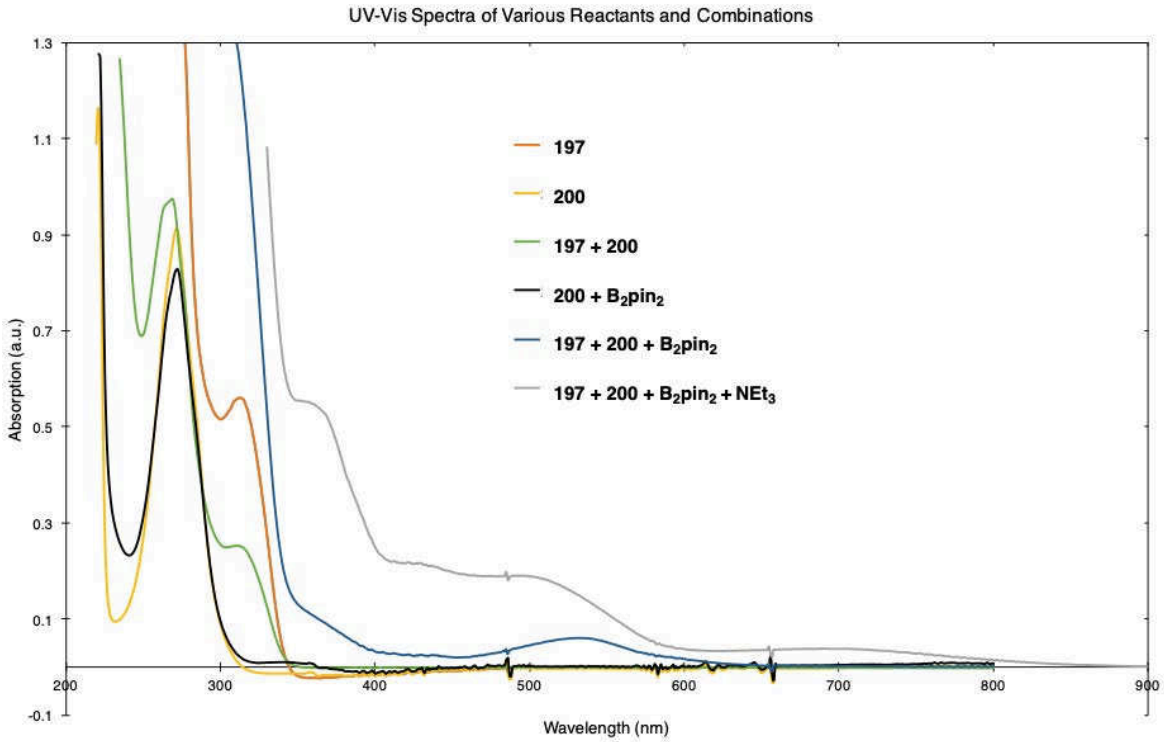


Figure A2.24. Overlaid UV-Vis spectra for various reactants and reactant combinations.

Analysis: The investigation into whether an electron donor-acceptor (EDA) complex could be observed by UV-Visible spectroscopy between the phosphonium salt **197** and the reactants was inconclusive. A new bathochromic-shifted absorption (535 nm) was observed in Figure S17, however, this can most likely be attributed to dearomatized intermediate **245**. To support this hypothesis, a UV-Vis spectrum was collected from a reaction that was ran to completion (i.e. phosphonium salt **197** was completely consumed) and the bathochromic shift was still present. At this time, an EDA complex is not supported by the UV-Vis data.

A2.9. Cyclic Voltammetry

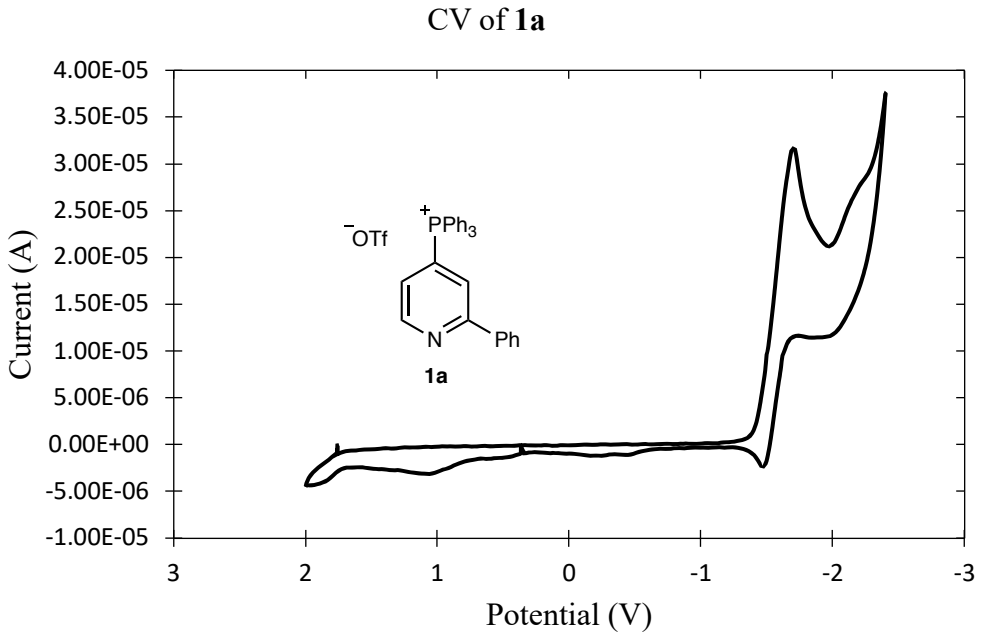


Figure A2.25. CV of **197** in a 0.1 M CH_2Cl_2 solution of Bu_4NPF_6. Sweep rate: 100 mV/sec. Carbon working electrode, Pt auxiliary electrode, Ag pseudo-reference electrode. Referenced to Fc^+/Fc. The scan was started at the rest potential of the cell and swept cathodic. $E_p^{red} = -2.13$ V vs Fc^+/Fc (−1.67 V vs SCE), $E_{p/2} = -1.97$ V vs Fc^+/Fc (−1.51 V vs SCE).

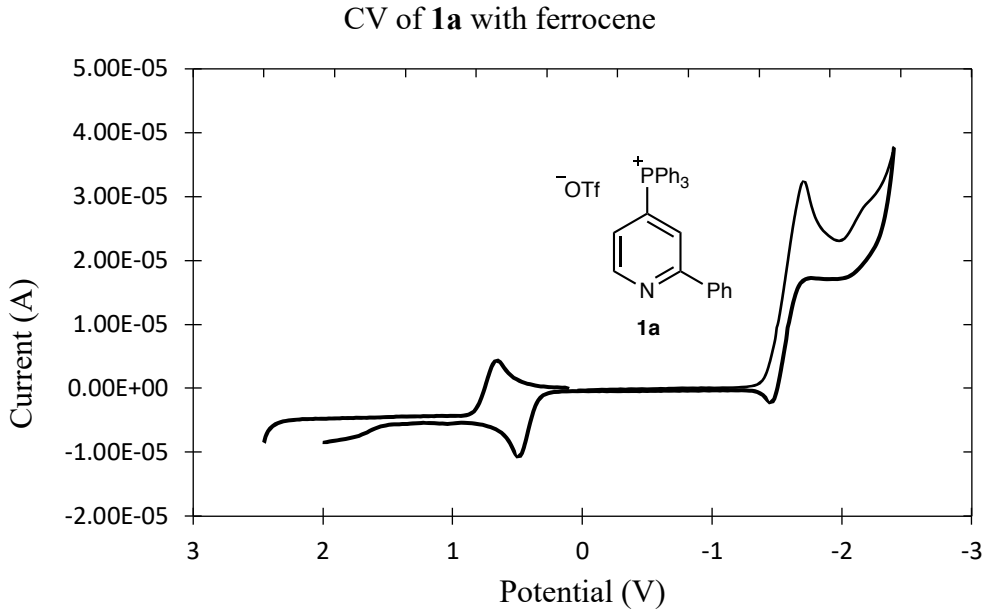


Figure A2.26. CV of **197** and ferrocene in a 0.1 M CH_2Cl_2 solution of Bu_4NPF_6. Sweep rate: 100 mV/sec. Carbon working electrode, Pt auxiliary electrode, Ag pseudo-reference electrode. The scan was started at the rest potential of the cell and swept cathodic. Ferrocene anodic and cathodic peak difference = 127 mV, **197** anodic and cathodic peak difference = 245 mV. Since **197** peak difference is not 127 mV/*n* where *n* = 2 (*n* = number of electrons), this suggests that the quasi-reversible redox peak for **197** is a single-electron event according to the Nernst equation.

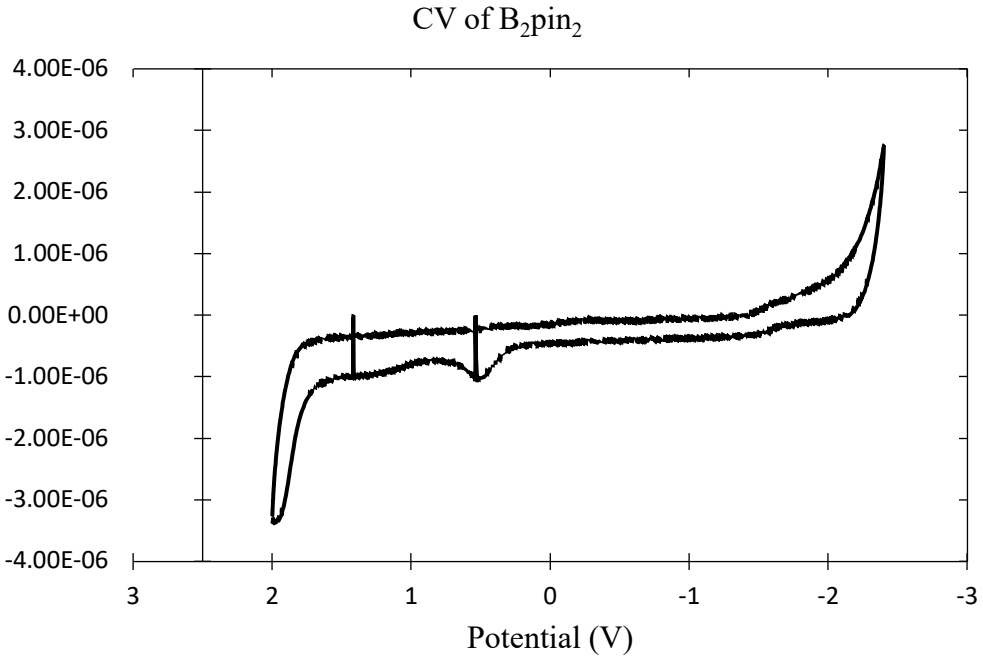


Figure A2.27. CV of B_2pin_2 in a 0.1 M CH_2Cl_2 solution of Bu_4NPF_6. Sweep rate: 100 mV/sec. Carbon working electrode, Pt auxiliary electrode, Ag pseudo-reference electrode. Referenced to Fc^+/Fc. The scan was started at the rest potential of the cell and swept cathodic. No significant redox events were observed.

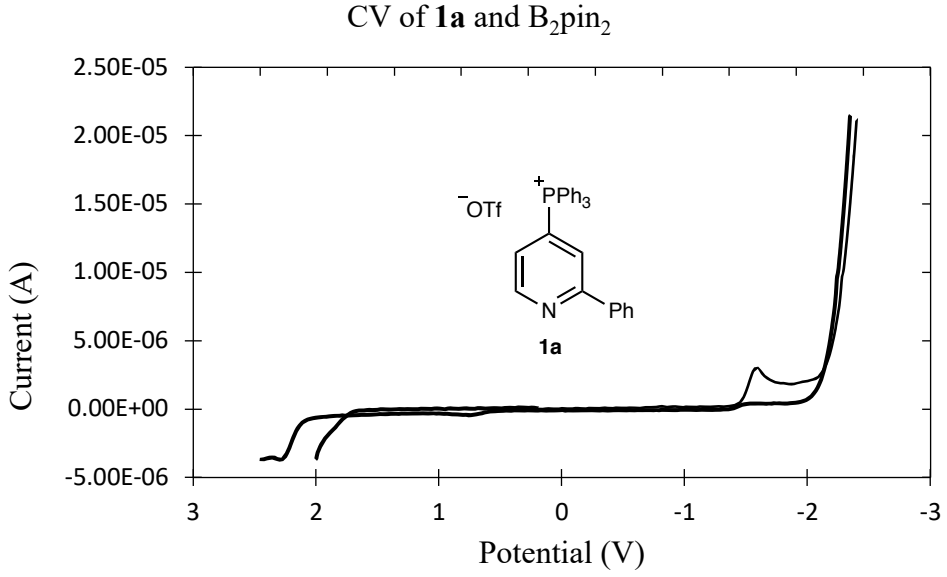


Figure A2.28. CV of **197** and B_2pin_2 (equimolar) in a 0.1 M CH_2Cl_2 solution of Bu_4NPF_6. Sweep rate: 100 mV/sec. Carbon working electrode, Pt auxiliary electrode, Ag pseudo-reference electrode. Referenced to Fc^+/Fc. The scan was started at the rest potential of the cell and swept cathodic. $E_p^{red} = -2.13$ V vs Fc^+/Fc (−1.67 V vs SCE), $E_{p/2} = -1.96$ V vs Fc^+/Fc (−1.50 V vs SCE). This result shows that there is no change in reduction potential for **197** when in the presence of an equimolar amount of B_2pin_2.

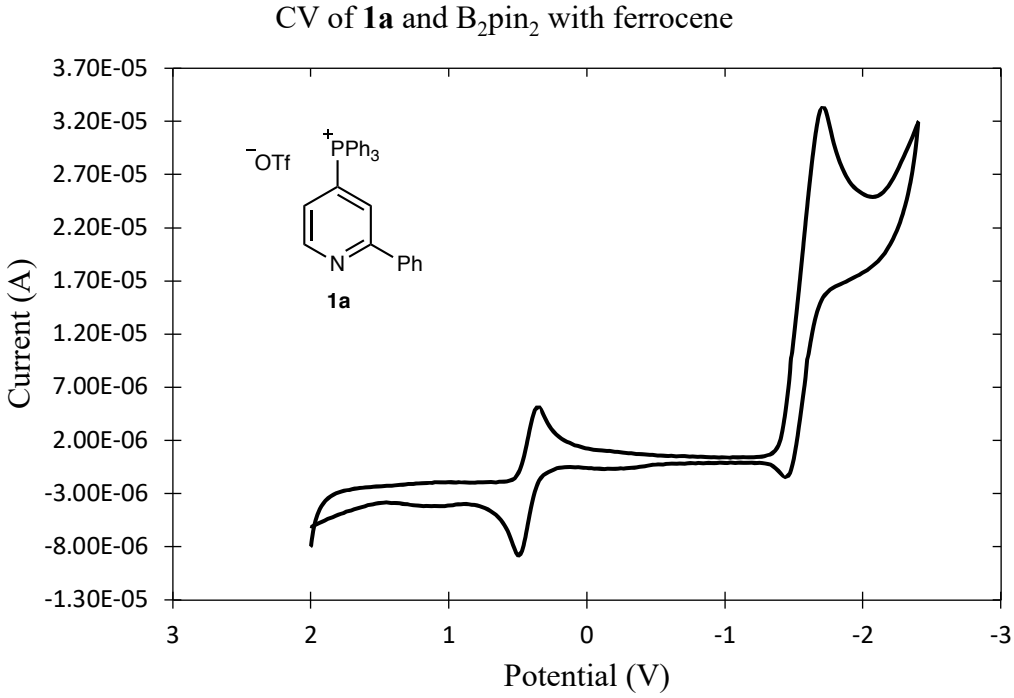


Figure A2.29. CV of **197**, B_2pin_2, and ferrocene in a 0.1 M CH_2Cl_2 solution of Bu_4NPF_6. Sweep rate: 100 mV/sec. Carbon working electrode, Pt auxiliary electrode, Ag pseudo-reference electrode. The scan was started at the rest potential of the cell and swept cathodic. Ferrocene anodic and cathodic peak difference = 140 mV, **197** anodic and cathodic peak difference = 263 mV. Since **197** peak difference is not 140 mV/*n* where *n* = 2 (*n* = number of electrons), this suggests that the quasi-reversible redox peak for **197** is a single-electron event according to the Nernst equation.

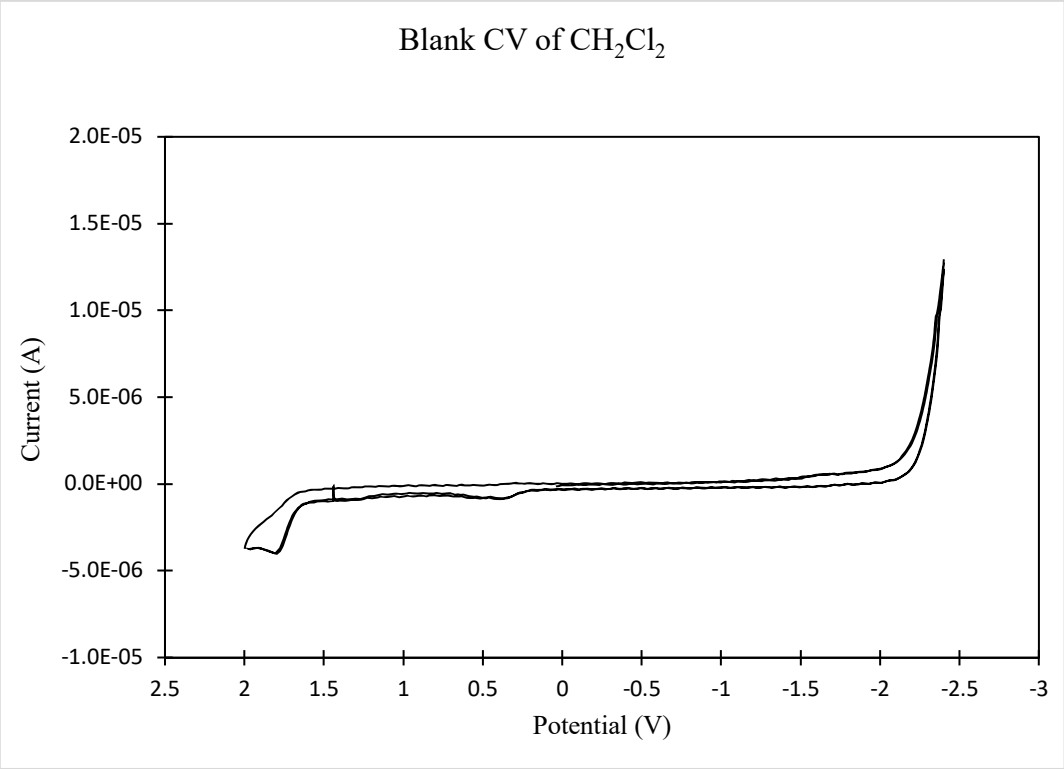


Figure A2.30. Blank CV of a 0.1 M CH_2Cl_2 solution of Bu_4NPF_6. Sweep rate: 100 mV/sec. Carbon working electrode, Pt auxiliary electrode, Ag pseudo-reference electrode. The scan was started at the rest potential of the cell and swept cathodic.

A2.10 Computational studies:

DFT calculations (ωB97X-D/def2-QZVPP with implicit solvation) were used to probe the feasibility of electron transfer. The outer sphere single electron transfer from boryl radical to a pyridyl phosphonium was found to be thermodynamically unfavorable: the reaction is endergonic by ca. 30 kcal/mol (Figure A2.31). **With such a barrier, the kinetics of outer-sphere electron transfer are also expected to be prohibitively slow**. The DFT result was corroborated by DLPNO-CCSD(T) calculations.

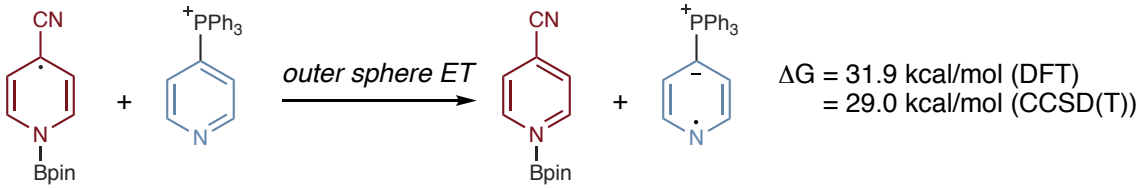


Figure A2.31. Computed thermodynamics for single-electron transfer to pyridyl phosphonium. DFT = ωB97X-D/def2-QZVPP//ωB97X-D/def2-SVP; CCSD(T) = DLPNO-CCSD(T)/cc-pV(2,3)Z//ωB97X-D/def2-SVP.

The possibility of a second single-electron reduction of putative pyridyl phosphonium radical was also examined computationally (Figure A2.32). Again, the thermodynamics of this process are extremely unfavorable such that this process can be dismissed from contention.

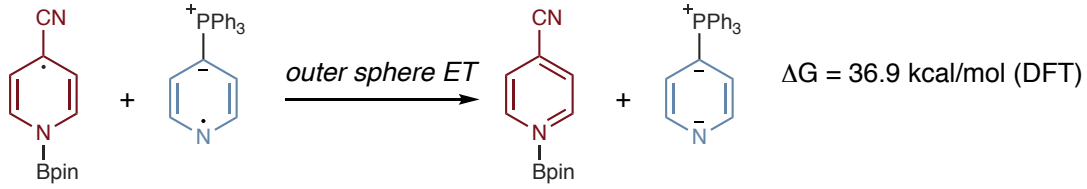


Figure A2.32. Computed thermodynamics for a second single-electron transfer to a pyridyl phosphonium radical. DFT = ωB97X-D/def2-QZVPP//ωB97X-D/def2-SVP.

In contrast, an *inner sphere* electron transfer event, mediated by the intermediacy of a boron-bridged complex was found to be much more facile (Figure A2.33). Formation of this intermediate is energetically favorable, with the overall endergonicity of this process resulting from the unfavorable entropic cost of bimolecular association. From this intermediate, release of a borylated pyridyl phosphonium and cyanopyridine can occur, with a very similar stability (i.e. within 2 kcal/mol) to the starting species. **The two borylated pyridine species are therefore expected to interchange readily and reversibly in solution**.

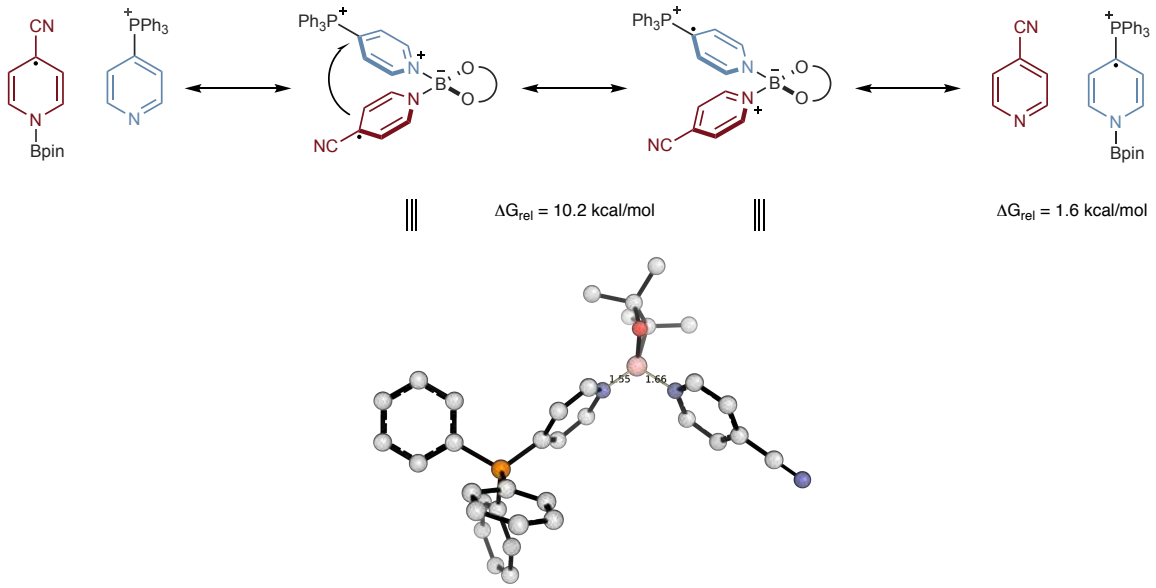


Figure A2.33. Computed thermodynamics for inner sphere single-electron transfer. DFT = ωB97X-D/def2-QZVPP//ωB97X-D/def2-SVP.

Intramolecular electron redistribution in the boron-bridged intermediate was found to occur spontaneously once the complex is formed: in the DFT optimized structure the unpaired electron resides entirely in the pyridyl phosphonium ring (spin-density plots, Figure A2.34), having migrated from the cyanopyridine ring. In each of the radical species shown below, the unpaired

electron is delocalized around the pyridine ring, with most of the spin residing at C2 and C4-positions.

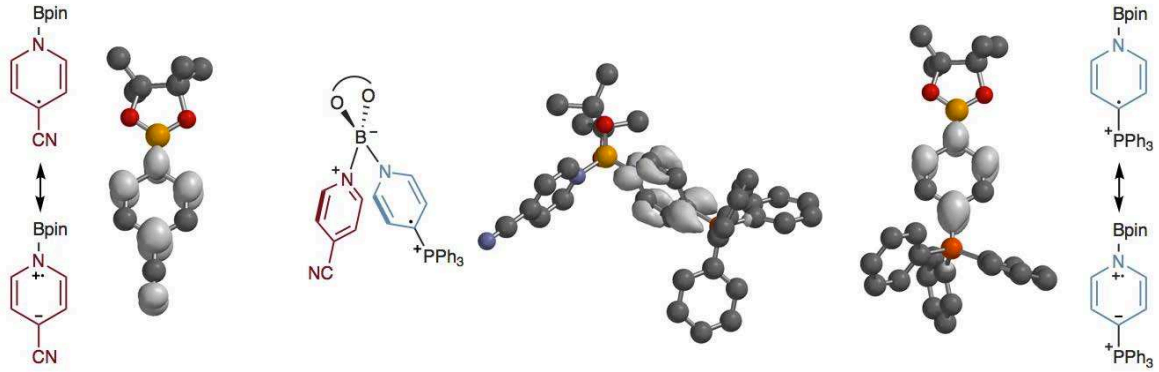


Figure A2.34. ωB97X-D Mulliken spin densities indicating localization of the unpaired electron.

Radical generation: Multiple pathways were considered to form radical pair **241''** and **195** from homolytic cleavage of heterodiboron complexes (Figure A2.35). The energy barriers are comparable in all the cases, indicating that all these events might occur in different degree to form the different pyridyl radicals. The importance of each pathway most likely varies depending on the electronic and steric properties of the aromatic substituents of the pyridyl phosphonium salts used.

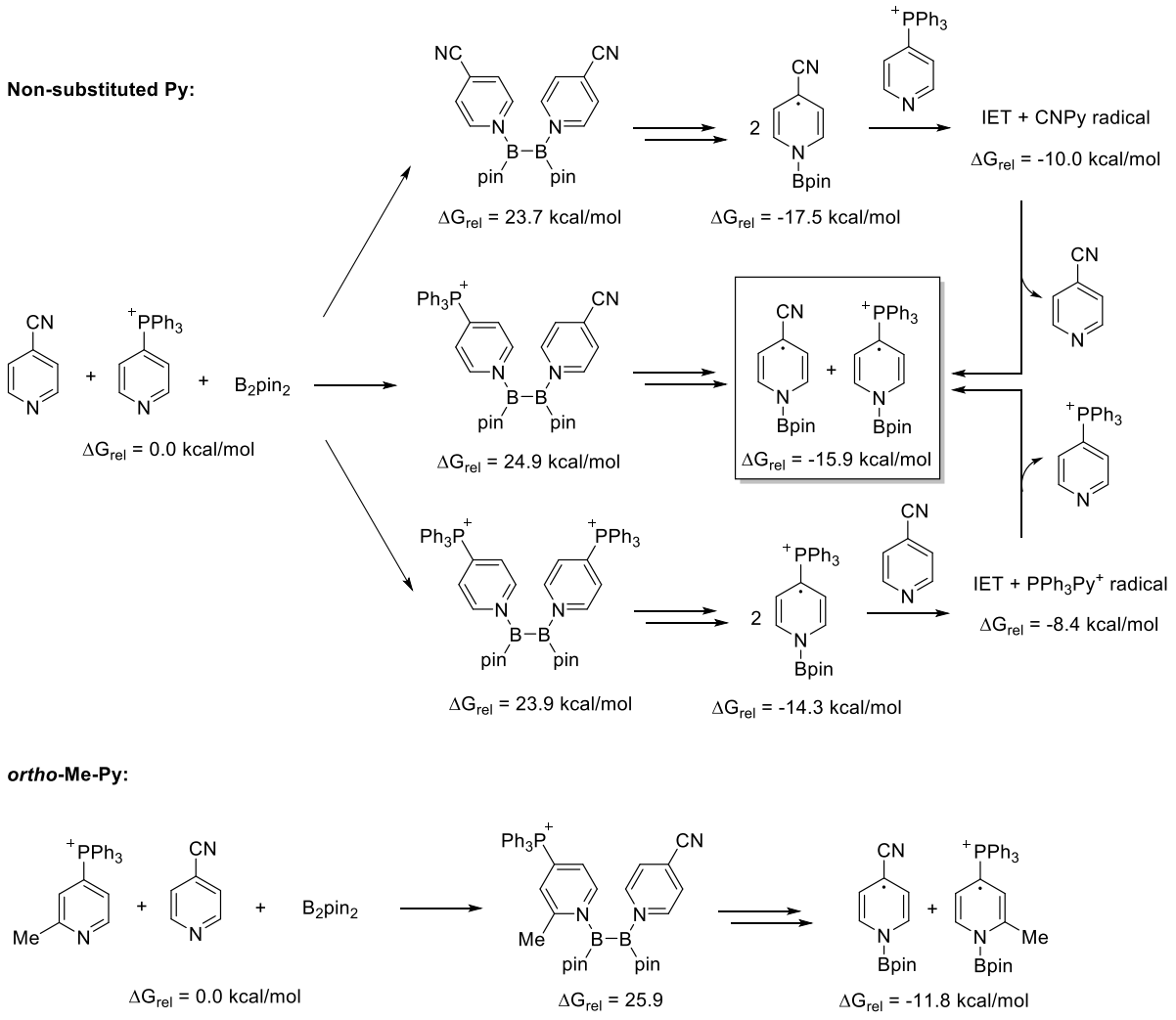


Figure A2.35. Different pathways studied to generate radical pair **241''** and 1**95**. IET = inner sphere electron transfer step.

Carbon-carbon bond formation: C-C bond formation can take place via radical recombination of a boryl pyridyl phosphonium radical and a boryl cyanopyridine radical. While the recombination of two boryl cyanopyridine radicals is thought to occur reversibly, this process (pyridyl phosphonium and cyanopyridine radical recombination) is irreversible due to the loss of triphenylphosphine. Subsequently, deborylation by an amine can also occur favorably, giving the adduct **245** that is observed by NMR spectroscopy (Figure A2.36). There is a low activation energy barrier for this C-C bond forming TS, $\Delta E^{\ddagger} = 6.6$ kcal/mol. The Gibbs energy of activation $\Delta G^{\ddagger} =$

24.9 kcal/mol is higher due to the cost of bimolecular association, but nonetheless is readily attainable at ambient temperatures. Relatively little charge-transfer (< 0.2e) occurs in this TS, indicative that this is radical-radical coupling (the total spin densities on each of the two molecules, 0.47e, are equal and opposite) as opposed to a further single-electron reduction of the pyridyl phosphonium moiety. The radical-radical coupling of the borylated pyridyl phosphonium and cyanopyridyl radicals was computed to have a barrier *ca.* 20 kcal/mol lower than the alternatives considered (discussed below) and is consistent with room temperature reactivity.

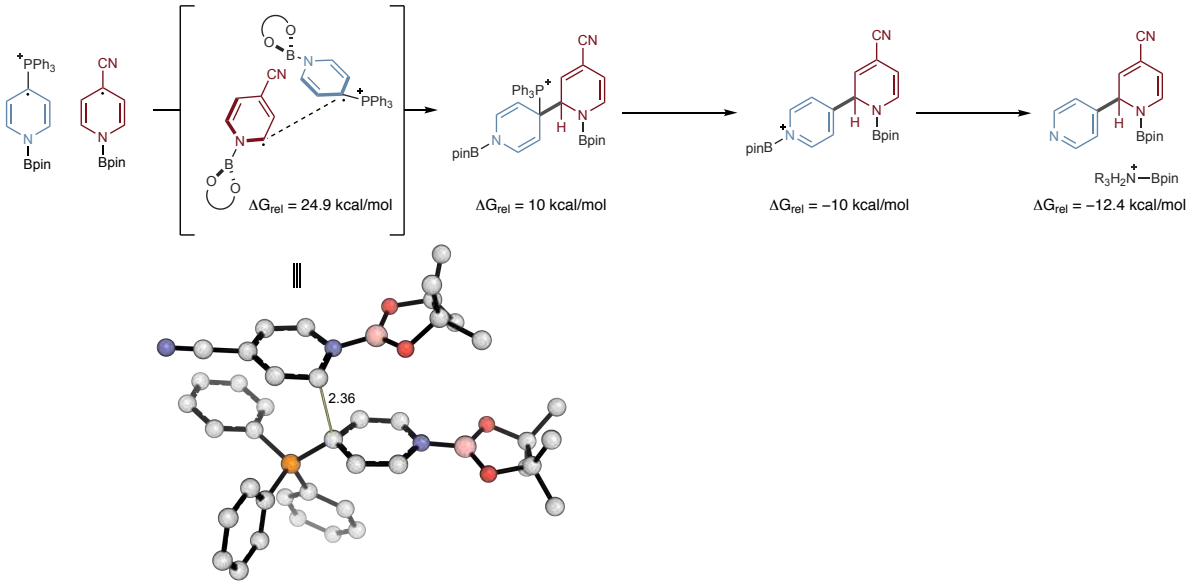


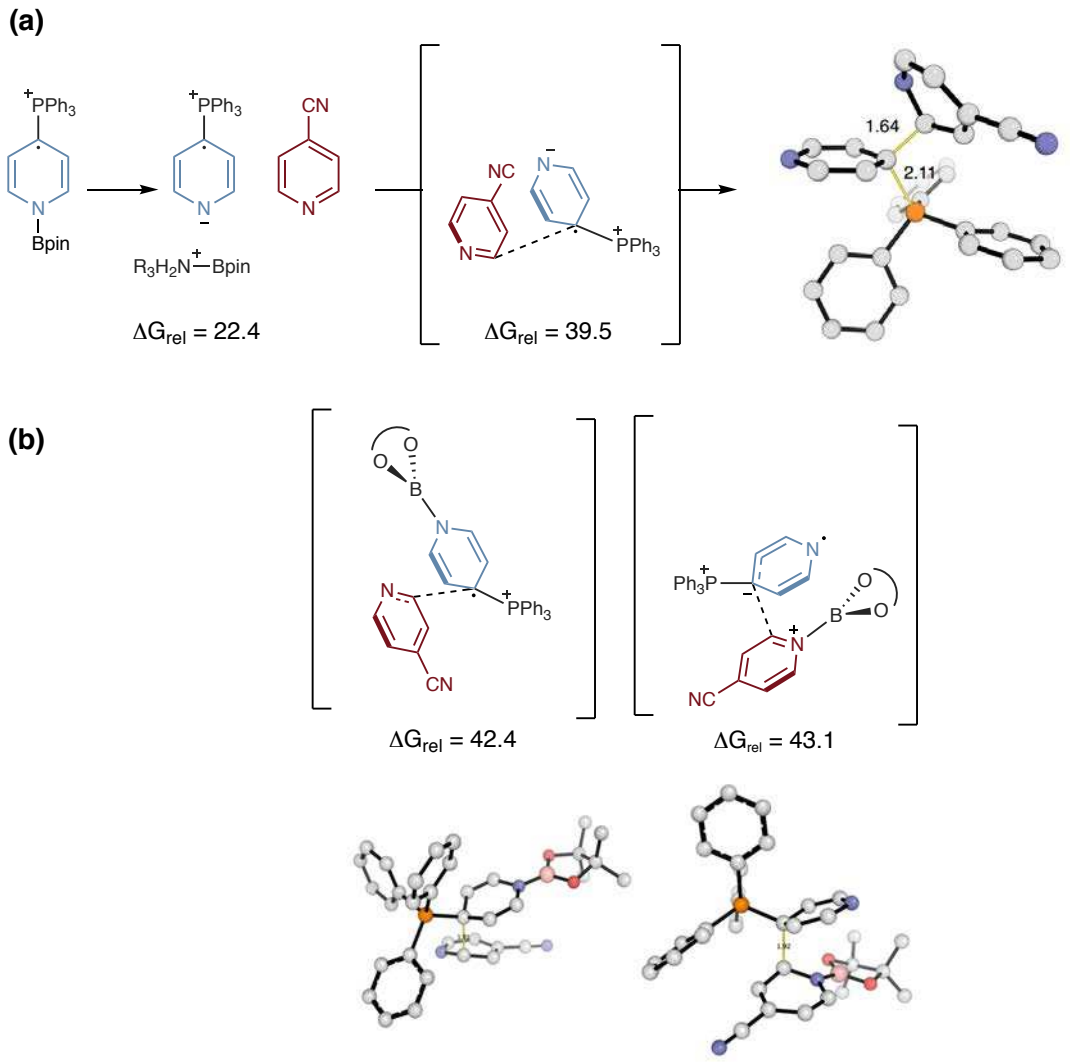
Figure A2.36. ωB97X-D computed reaction coordinate for bipyridyl formation via radical-radical coupling. Forming bond distance shown in Å, relative Gibbs energies in kcal/mol.

The alternative possibility of the pyridyl phosphonium radical reacting directly with cyanopyridine was also considered computationally (Figure A2.37). Gibbs energy barriers in excess of 40 kcal/mol were obtained with the boryl group still attached, indicative of an unfavorable reaction at room temperature (Figure A2.37b). Therefore, we considered the possibility of deborylation (for example by amine), resulting in the formation of the free pyridyl phosphonium radical anion, that

can then react with cyanopyridine. The Gibbs energy barrier for this TS, relative to these two species is a further 39.5 kcal/mol uphill, again indicative of an unfavorable coupling process at room temperature. The loss of triphenylphosphine occurs in concert with C-C bond formation via this pathway.

Figure A2.37. ωB97X-D computed reaction coordinate for bipyridyl formation via radical addition to cyanopyridine. Forming bond distance shown in Å, relative Gibbs energies in kcal/mol

Computational methods: The dispersion-corrected density functional theory (DFT) functional ωB97X-D[2,3] was used with the def2-SVP[4,5] basis set for geometry optimizations. We carried out



vibrational frequency calculations to obtain thermal corrections to Gibbs free energies (*G*) at 298.15 K (25 °C). Additionally, these frequency calculations were used to confirm that stationary points as minima or saddle points on the potential energy surface. An ultrafine pruned (99,950) grid was used for numerical integration and molecules were converted to their standard orientations before thermochemical analysis, which is expected to reduce the noise of rotational grid invariance. Additionally, quasi-harmonic entropy corrections were also applied.

In all the individual calculations, quasi-harmonic (QHA) vibrational corrections were applied to entropies using a frequency cut-off value of 100.0 cm^{-1}, as proposed by Grimme.[6] In a few cases, systems showed one persistent small imaginary frequency with $\nu_i < 20$ cm^{-1}. These imaginary frequencies were inverted to their respective positive values before the QHA entropic corrections were computed as seen in previous examples.[7] Additionally, a correction for the change in standard state from gas phase at 1 atm to a 1 M solution was applied when calculating G values. All of these thermodynamic corrections were calculated and automatically applied to the computed results by the *GoodVibes* program.[8]

All the optimization, frequency and single-point energy calculations included solvent effects obtained with the integral equation formalism variant of the polarizable continuum model (IEF-PCM) with the SMD solvation model (solvent = acetonitrile).[9-14]

Single-point energy calculations were used to refine electronic energies of optimized geometries. For this, DFT (ωB97X-D/Def2-QZVPP) was used. QHA G corrections calculated at the ωB97X-D/Def2-SVP level of theory were applied to these single point energies to obtain the final G values.

A manual conformational search was carried out in all the systems, positioning the different units in multiple interaction sites. Furthermore, for each possible interaction site, the different functional groups were rotated (see section *Thermochemical data and absolute energy values* for more information about the number of conformers used).

Gaussian 16[15] was used to perform all the DFT calculations with an "ultrafine" pruned (99,590) grid for numerical integration. Molecular graphics were generated using *PyMol*;[16] Our display settings have been made openly accessible.[17] Additionally, we used the "stable" option from Gaussian to test the stability of the wavefunctions created and detect any kind of partial or complete singlet biradical character in all the reaction steps involving singlet states.

Thermochemical data and absolute energy values: Boltzmann weighted G (G_{av}) were calculated with the *GoodVibes* program (option --pes) as:

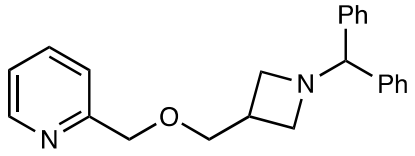
$$G_{av} = \sum_i G_i \times p_i \quad (1)$$

where G_i is the relative Gibbs free energy of the corresponding conformers of a certain system and p_i is the probability of each conformer calculated as:

$$p_i = \frac{e^{\frac{-G_i}{RT}}}{\sum_i \left(e^{\frac{-G_i}{RT}}\right)} \quad (2)$$

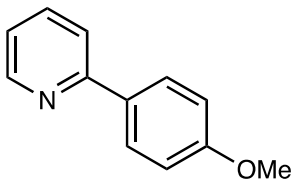
A2.11 Preparation of Heterocyclic Phosphonium Salt Precursors and Pyridines

2-(((1-Benzhydrylazetidin-3-yl)methoxy)methyl)pyridine



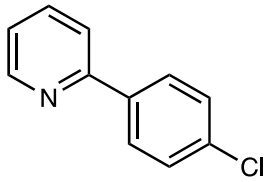
An oven dried 100 mL round bottom flask was charged with sodium hydride (60% dispersion in mineral oil, 8 equiv). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of DMF (5 mL). The mixture was cooled to 0 °C, and a mixture of (1-benzhydrylazetidin-3-yl)methanol (506 mg, 2.00 mmol) in DMF (5 mL) was added dropwise over five minutes. The mixture was warmed to room temperature and stirred for 1 hour before being cooled back down to 0 °C. A mixture of 2-(chloromethyl)pyridine hydrochloride (492 mg, 3.00 mmol) in DMF (5 mL) was added mixture, and the reaction was warmed to room temperature and stirred until the reaction was completed by TLC. The mixture was quenched with water (20 mL) and diluted with CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The crude material was purified by flash chromatography (silica gel: 50% EtOAc in hexanes) to provide the title compound as a white solid (601 mg, 1.74 mmol, 87% yield). mp 89-91 ºC. IR ν_{max}/cm^{-1} (film): 3061, 2934, 2858, 2843, 1584, 1489, 1448, 1348, 1127, 937, 758, 705; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, dq, J = 4.9, 0.9 Hz), 7.78-7.72 (1H, m), 7.50 (5H, J = 7.5 Hz), 7.38-7.32 (4H, m), 7.29-7.23 (3H, m), 4.73 (2H, s), 4.44 (1H, s), 3.81 (2H, d, J = 6.7 Hz), 3.41 (2H, t, J = 7.4 Hz), 3.03 (2H, t, J = 6.6 Hz), 2.87 (1H, sept, J = 6.8 Hz), ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.8, 149.1, 142.4, 136.6, 128.4, 127.6, 127.1, 122.4, 121.3, 78.1, 74.04, 73.7, 56.6, 29.9; m/z LRMS (ESI + APCI) found $[M+H]^+$ 345.3, $C_{23}H_{25}N_2O^+$ requires 345.2.

2-(4-Methoxyphenyl)pyridine



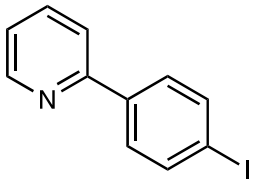
Prepared according to the method of Bao on a 5.00 mmol scale.[18] Flash chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 20% EtOAc in hexanes) afforded the title compound as a white solid (802 mg, 4.35 mmol, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, d, J = 4.8 Hz), 7.94 (2H, d, J = 8.8 Hz), 7.68–7.62 (2H, m), 7.15–7.11 (1H, m), 7.02 (2H, d, J = 8.8 Hz), 3.82 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.6, 157.2, 149.6, 136.7, 132.1, 128.2, 121.5, 119.9, 114.2, 55.4. The spectroscopic data is in agreement with a reported synthesis.[19]

2-(4-Chlorophenyl)pyridine



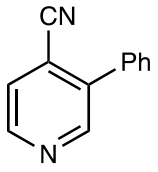
An oven-dried 100 mL round bottom flask was charged with 2-bromopyridine (0.47 mL, 5.00 mmol), (4-chlorophenyl)boronic acid (1.17 g, 7.50 mmol), $Pd(OAc)_2$ (22 mg, 0.10 mmol), and K_3PO_4 (2.12 g, 10.0 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before the addition of *i*PrOH (20 mL) and H_2O (20 mL). The reaction was heated to 80 °C using a condenser open to air, and monitored by TLC. After the reaction ran to completion, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 x 30 mL). The organic layer was washed with brine (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes, and the product was dry-loaded onto the column) to provide the title compound as a pale yellow solid (695 mg, 3.65 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, d, J = 4.0 Hz), 7.94 (2H, d, J = 8.6 Hz), 7.75 (1H, t, J = 7.6 Hz), 7.69 (1H, d, J = 7.6 Hz), 7.45 (2H, d, J = 8.6 Hz), 7.02 (1H, dd, J = 7.6 Hz, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.9, 150.4, 138.5, 137.5, 135.8, 129.6, 128.8, 123.0, 121.0. The spectroscopic data is in agreement with a reported synthesis.[20]

2-(4-Iodophenyl)pyridine



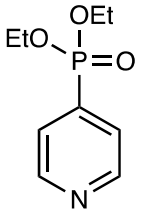
Prepared according to a method adapted from Doyle[21]. An oven-dried 100 mL round bottom flask was charged with (4-(pyridin-2-yl)phenyl)boronic acid (633 mg, 3.18 mmol), K_2CO_3 (1.097 g, 7.95 mmol), and I_2 (1.454 g, 5.23 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before the addition of MeCN (12.7 mL), then heated to 90°C. The reaction was monitored by TLC and diluted with H_2O after completion. The reaction mixture was extracted with EtOAc (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, gradient elution: hexanes to 10% EtOAc in hexanes) to provide the title compound as a pale orange solid (741 mg, 2.64 mmol, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, m), 7.82-7.66 (6H, m), 7.27-7.21 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.1, 149.7, 138.7, 137.8, 136.8, 128.6, 122.4, 120.1, 95.4. The spectroscopic data is in agreement with a reported synthesis.[22]

3-Phenylisonicotinonitrile



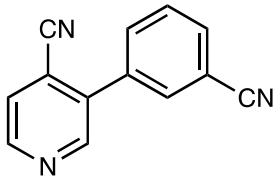
Prepared according to the method reported by Baxter on a 10.0 mmol scale.[23] The crude material was purified by flash chromatography (basic alumina, gradient elution: 15% EtOAc in hexanes to 20% EtOAc in hexanes) to provide the title compound as a pale yellow solid (406 mg, 2.30 mmol, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.86 (1H, s), 8.75 (1H, d, J = 5.0 Hz), 7.63 (1H, d, J = 5.0 Hz), 7.60-7.52 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.1, 148.8, 138.8, 134.5, 129.6, 129.2, 128.9, 126.1, 118.9, 116.4. The spectroscopic data is in agreement with a reported synthesis.[23]

Diethyl pyridin-4-ylphosphonate



Prepared according to the procedure of Lin.[24] An oven dried 100 mL round bottom flask was charged with 4-bromopyridine hydrochloride (1.95 g, 10.0 mmol) and Tetrakis(triphenylphosphine)palladium(0) (232 mg, 0.20 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of toluene (40 mL), diethyl phosphonate (1.90 mL, 15.0 mmol), and NEt_3 (3.90 mL, 28.0 mmol). The mixture was refluxed at 120°C for 36 hours, cooled to room temperature and diluted with CH_2Cl_2 and H_2O. The organic layer was separated and washed with H_2O (2 x 20 mL). The organic layers were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 3% MeOH in CH_2Cl_2) to provide the title compound as a colorless oil (667 mg, 3.10 mmol, 31% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.79-8.72 (2H, m), 7.69-7.60 (2H, m), 4.24-4.04 (4H, m), 1.36-1.29 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.2 (d, J = 12.3 Hz), 137.6 (d, J = 189.5 Hz), 125.3 (d, J = 8.3 Hz), 62.8 (d, J = 5.55 Hz), 16.4 (d, J = 6.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 14.59. The spectroscopic data is in agreement with a reported synthesis.[24]

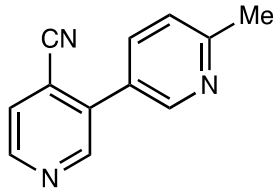
3-(3-Cyanophenyl)isonicotinonitrile



Prepared according to a method adapted from Schmidt.[25] An oven-dried 50 mL round bottom flask was charged with 3-bromoisonicotinonitrile (366 mg, 2.00 mmol), (3-cyanophenyl)boronic acid (441 mg, 3.00 mmol), $Pd(PPh_3)_4$ (69 mg, 0.06 mmol), and Na_2CO_3 (848 mg, 8.00 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before the addition of toluene (2.86 mL), EtOH (2.86 mL), and H_2O (2.86 mL) were added, and the reaction was heated to 80 °C. The reaction was monitored by TLC and diluted with H_2O after completion. The reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 50% EtOAc in hexanes, followed by recrystallization from CH_2Cl_2 and hexanes) afforded the title compound as a white solid (175 mg, 0.86 mmol, 43% yield). mp 168-170 ºC. IR ν_{max}/cm^{-1} (film): 3095, 3019, 2220, 1582, 1490, 1416, 1399, 1205, 1174, 858, 793, 691; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.82-8.86 (2H, m), 7.79-7.87 (3H, m), 7.66-7.73 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$)

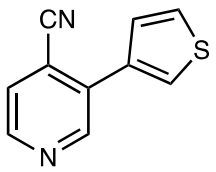
δ: 150.7, 150.1, 136.4, 135.9, 133.3, 133.1, 132.3, 130.2, 126.2, 119.2, 118.0, 115.7, 113.8; m/z LRMS (ESI + APCI) found $[M+H]^+$ 206.1, $C_{13}H_8N_3^+$ requires 206.1.

6'-Methyl-[3,3'-bipyridine]-4-carbonitrile



An oven-dried 50 mL round bottom flask was charged with 3-bromoisonicotinonitrile (366 mg, 2.00 mmol), pyridin-3-ylboronic acid (274 mg, 2.00 mmol), $Pd(PPh_3)_4$ (69 mg, 0.06 mmol), and K_2CO_3 (690 mg, 5.00 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before the addition 1,4-dioxane (3.33 mL), and the reaction was heated to 95 °C. The reaction was monitored by TLC and diluted with H_2O after completion. The reaction mixture was extracted with EtOAC (3 x 20 mL), and the combined organic extracts were washed with brine (3 x 20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, gradient elution: 80% EtOAc in hexanes to EtOAc) to provide the title compound as a white solid (135 mg, 0.68 mmol, 34% yield). mp 179-180 °C; IR ν_{max}/cm^{-1} (film): 3096, 3050, 3018, 2924, 2852, 2231, 1923, 1599, 1582, 1480, 1412, 1386, 1367, 1333, 1198, 1035, 828, 789, 584; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.85 (1H, s), 8.79 (1H, d, *J* = 5.0 Hz), 8.69 (1H, d, *J* = 2.1 Hz), 7.84 (1H, dd, *J* = 8.1, 2.4 Hz), 7.65 (1H, d, *J* = 5.0 Hz), 7.30 (1H, d, *J* = 8.1 Hz), 2.66 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.1, 150.8, 149.5, 148.6, 136.5, 135.6, 127.6, 126.2, 123.5, 119.2, 116.0, 24.5; m/z LRMS (ESI + APCI) found $[M+H]^+$ 196.1, $C_{12}H_{10}N_3^+$ requires 196.1.

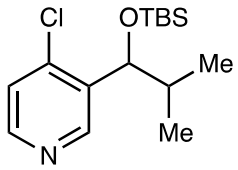
3-(Thiophen-3-yl)isonicotinonitrile



An oven-dried 50 mL round bottom flask was charged with 3-bromoisonicotinonitrile (275 mg, 1.50 mmol), thiophen-3-ylboronic acid (192 mg, 1.50 mmol), $Pd(PPh_3)_4$ (52 mg, 0.045 mmol), and K_2CO_3 (518 mg, 3.50 mmol). The flask was subjected to three cycles of vacuum/nitrogen

backfill before the addition of THF (3.80 mL) and H_2O (1.90 mL), and then the reaction was heated to 95°C. The reaction was monitored by TLC and diluted with H_2O after completion. The reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic extracts were washed with a saturated solution of brine (3 x 20 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a white solid (270 mg, 1.45 mmol, 97% yield). mp 88-89 °C; IR ν_{max}/cm^{-1} (film): 3159, 3085, 3044, 3021, 2232, 1951, 1521, 1477, 1423, 1297, 1190, 866, 802, 647, 584; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, s), 8.65 (1H, d, *J* = 5.0 Hz), 7.75 (1H, dd, *J* = 2.9, 1.4 Hz), 7.55 (1H, dd, *J* = 5.0, 0.7 Hz), 7.49-7.42 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.4, 148.3, 134.8, 133.1, 127.3, 127.0, 126.2, 125.8, 117.6, 116.6; m/z LRMS (ESI + APCI) found $[M+H]^+$ 187.1, $C_{10}H_7N_2S^+$ requires 187.0.

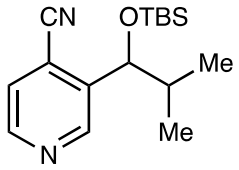
3-(1-((Tert-butyldimethylsilyl)oxy)-2-methylpropyl)-4-chloropyridine



A 50 mL round bottom flask was charged with 1-(4-chloropyridin-3-yl)-2-methylpropan-1-ol (222 mg, 1.20 mmol), and the flask was subjected to three cycles of vacuum/nitrogen backfill before the addition of DMF (2 mL). A solution of tert-butyldimethylsilyl chloride (634 mg, 4.20 mmol) in DMF (2 mL) was added at 0 °C followed by addition of a solution of imidazole (408 mg, 6.00 mmol) in DMF (2 mL) at 0 °C. The flask was warmed up to room temperature and stirred for 18 hours. After completion, the reaction was quenched with a saturated solution of sodium bicarbonate (6 mL). The reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic layers were washed with a saturated brine solution (3 x 20 mL), dried ($MgSO_4$), and concentrated *in vacuo.* The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes) to provide the title compound as a yellow oil (278 mg, 1.20 mmol, 77% yield). IR νmax/cm-1 (film): 2957, 2929, 2895, 2858, 1556, 1462, 1403, 1252, 1084, 1046, 837, 812, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, s), 8.35 (1H, d, *J* = 5.3 Hz), 7.23 (1H, d, *J* = 5.3 Hz), 4.85 (1H, d, *J* = 5.3 Hz), 1.94 (1H, oct, *J* = 6.7 Hz), 0.91 (3H, d, *J* = 1.3 Hz), 0.90 (3H, d, *J* = 1.6 Hz), 0.89 (9H, s), 0.06 (3H, s), -0.22 (3H, s); ^{13}C NMR (100 MHz, CDCl3) δ: 151.0, 148.7,

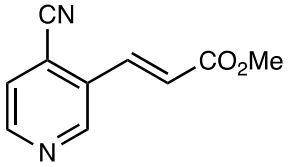
141.6, 137.9, 124.0, 74.4, 35.3, 25.9, 19.4, 18.2, 17.0, -4.6, -5.0; m/z LRMS (ESI + APCI) found $[M+H]^+$ 300.2, $C_{15}H_{27}ClNOSi^+$ requires 300.2.

3-(1-((Tert-butyldimethylsilyl)oxy)-2-methylpropyl)isonicotinonitrile



An oven dried 50 mL round bottom flask was charged with 3-(1-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)-4-chloropyridine (276 mg, 0.92 mmol), dicyanozinc (64 mg, 0.55 mmol), $Pd_2(dba)_3$ (165 mg, 0.18 mmol), 1,1'-Bis(diphenylphosphino)ferrocene (205 mg, 0.37 mmol), and zinc dust (6 mg, 0.09 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before the addition of DMA (2.0 mL). The reaction was heated to 120 °C for 12 hours before diluting with water, and extracting the mixture with CH_2Cl_2 (3 x 10 mL). After extraction, the combined organic layers were washed with a saturated solution of NH_4Cl (10 mL), 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 yellow oil (149 mg, 0.52 mmol, 56 %). IR ν_{max}/cm^{-1} (film): 2958, 2930, 2858, 1585, 1471, 1409, 1253, 1077, 1054, 836, 775; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.87 (1H, s), 8.65 (1H, d, *J* = 5.0 Hz), 7.45 (1H, d, *J* = 5.0 Hz), 4.71 (1H, d, *J* = 6.2 Hz), 2.01 (1H, oct, *J* = 6.7 Hz), 0.97 (3H, d, *J* = 6.7 Hz), 0.89 (9H, s), 0.88 (3H, d, *J* = 6.8 Hz), 0.09 (3H, s), -0.20 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.6, 148.8, 141.6, 125.0, 118.5, 115.6, 76.7, 36.5, 25.9, 19.1, 18.2, 17.7, -4.6, -5.0; m/z LRMS (ESI + APCI) found $[M+H]^+$ 291.2, $C_{16}H_{27}N_2OSi^+$ requires 291.2.

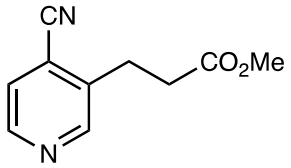
Methyl (E)-3-(4-cyanopyridin-3-yl)acrylate



An oven-dried 50 mL round bottom flask was charged with 3-bromoisonicotinonitrile (368 mg, 2.00 mmol), $Pd(OAc)_2$ (45 mg, 0.20 mmol), triphenylphosphine (105 mg, 0.40 mmol), and K_2CO_3 (552 mg, 4.00 mmol). The flask was subjected to 3 cycles of vacuum/nitrogen backfill

before being addition of DMF (20 mL), followed by addition of methyl acrylate (1.81 mL, 20.0 mmol). The reaction was heated to 110 °C and monitored by TLC until completion. The reaction mixture was diluted with water and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* Flash chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 30% EtOAc in hexanes) afforded the title compound as a white solid (149 mg, 0.80 mmol, 30% yield). mp 117-119 °C; IR ν_{max}/cm^{-1} (film): 3095, 3061, 3021, 2956, 2230, 1720, 1639, 1581, 1435, 1325, 1207, 980, 847; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.02 (1H, s), 8.75 (1H, d, *J* = 5.0 Hz), 7.88 (1H, d, *J* = 16.2 Hz), 7.57 (1H, dd, *J* = 5.0, 0.5 Hz), 6.76 (1H, d, *J* = 16.1 Hz), 3.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.5, 150.6, 148.9, 136.5, 131.0, 125.8, 124.3, 119.4, 114.9, 52.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 189.1, $C_{10}H_9N_2O_2^+$ requires 189.1.

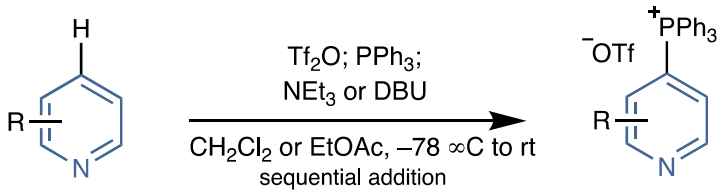
Methyl 3-(4-cyanopyridin-3-yl)propanoate



An oven-dried 50 mL round bottom flask was charged with methyl (E)-3-(4-cyanopyridin-3-yl)acrylate (123 mg, 0.65 mmol) and Pd/C(10 w%) (12 mg, 10 w%). The flask was subjected to 3 cycles of vacuum/nitrogen backfill before being addition of MeOH (6.5 mL). The reaction mixture atmosphere was exchanged with a balloon of H_2 gas, then capped with a second balloon of H_2 gas (1 atm) and stirred for 48 hours. The reaction mixture was filtered through celite, extracted with EtOAc (3 x 20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo.* Flash chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel: 30% EtOAc in hexanes) afforded the title compound as a colorless oil (73 mg, 0.39 mmol, 60% yield). IR ν_{max}/cm^{-1} (film): 3097, 2955, 2928, 2855, 2233, 1728, 1587, 1486, 1442, 1410, 1370, 1203, 1167, 847; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, s), 8.60 (1H, d, *J* = 5.0 Hz), 7.45 (1H, d, *J* = 5.0 Hz), 3.63 (3H, s), 3.13 (2H, t, *J* = 7.4 Hz), 2.71 (2H, t, *J* = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.8, 151.3, 148.5, 137.6, 125.4, 120.4, 115.4, 51.9, 34.0, 26.8; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 191.1, $C_{10}H_{11}N_2O_2^+$ requires 191.1.

A2.12 Preparation of Heterocyclic Phosphonium Salts

General Procedure A



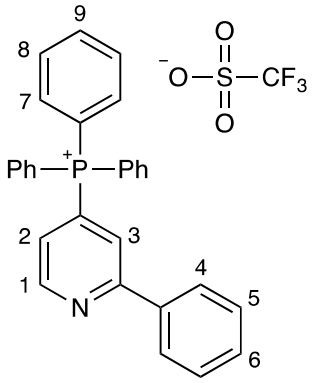
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC, and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes then warmed to –50 °C before PPh_3 (1.1 equiv) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 minutes at –78 ºC. The stated organic base (NEt_3 or 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 15-30 minutes). When the reaction mixture reached room temperature, it was then quenched with H_2O (approximately the same volume as CH_2Cl_2) and the mixture was transferred to a separatory funnel. The mixture was diluted with CH_2Cl_2 and the resulting organic layer was washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Approximately 2-10 mL (depending on the scale of the reaction) of CH_2Cl_2 was added to reaction mixture and was then added dropwise to an excess of chilled Et_2O (0 ºC). The flask was then placed in a –20 ºC refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 ºC), and dried *in vacuo* to provide the pure phosphonium salt.

Notes.

1) PPh_3 was crushed into a powder prior to use.
2) Certain substrates require longer periods for the precipitation step and specific cases are indicated below.
3) In a small number of cases, residual CH_2Cl_2 can become trapped in the phosphonium salt products. In these cases, heating the salts under vacuum (50-100 ºC) removed the solvent.

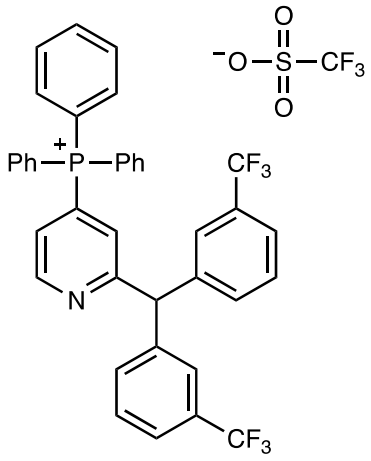
4) In order to evaluate regioselectivity from the crude reaction mixtures, a duplicate reaction was performed and aliquots taken after addition of the organic base and warming to room temperature. These aliquots were concentrated *in vacuo* and analyzed by ^{1}H and ^{31}P NMR.

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



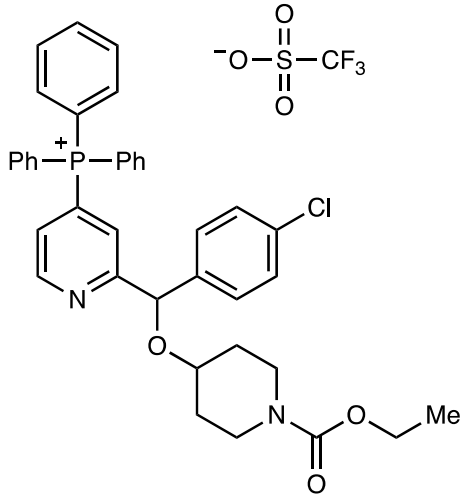
Prepared according to our previous report.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.01 (1H, app t, J = 5.1 Hz, H_1), 7.93-7.54 (18H, m, H_3, H_7, H_8, H_9, and H_4), 7.50 (1H, ddd, J = 17.8, 5.1, 1.1 Hz, H_2), 7.42-7.36 (3H, m, H_5 and H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1 (d, J = 9.9 Hz), 151.6 (d, J = 10.7 Hz), 136.7 (d, J = 1.5 Hz), 136.1 (d, J = 3.2 Hz), 134.3 (d, J = 9.8 Hz), 130.9 (d, J = 13.0 Hz), 130.3, 129.2 (d, J = 84.1 Hz), 129.0, 127.0, 125.2 (d, J = 7.8 Hz), 123.1, (d, J = 8.4 Hz), 120.7 (q, J = 321.1 Hz), 115.5 (d, J = 89.1 Hz).

(2-(Bis(3-(trifluoromethyl)phenyl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



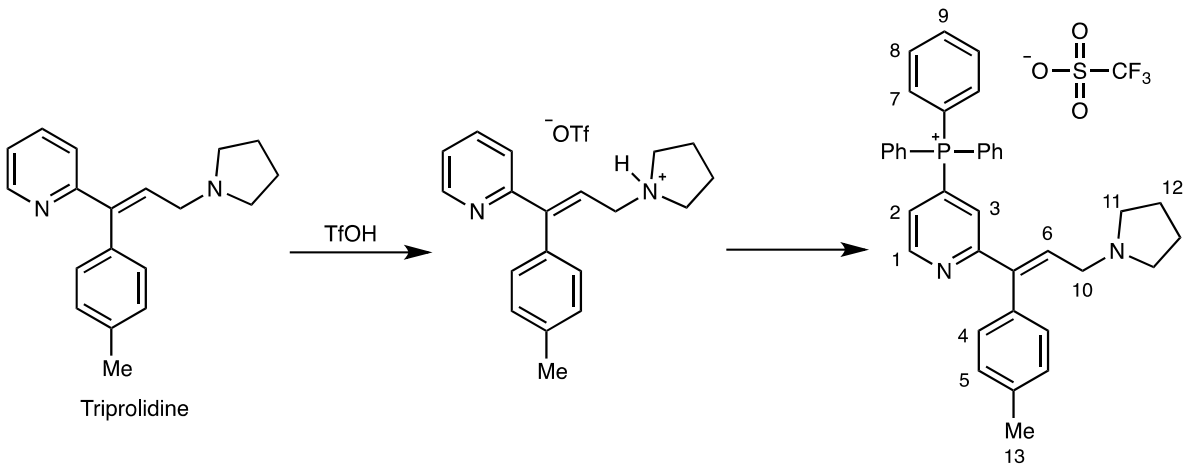
Prepared according to our previous report.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, app t, *J* = 5.1 Hz), 7.91-7.80 (3H, m), 7.78-7.66 (6H, m), 7.63-7.37 (15H, m), 7.29 (1H, d, *J* = 13.8 Hz), 5.97 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.0 (d, *J* = 9.8), 151.6 (d, *J* = 10.4 Hz), 141.7, 136.1 (d, *J* = 3.1 Hz), 134.3 (d, *J* = 10.5 Hz), 132.9 (d, *J* = 1.1 Hz), 130.9 (d, *J* = 13.1 Hz), 130.7 (q, *J* = 32.2 Hz), 130.0, 129.6 (d, *J* = 83.7 Hz), 127.0 (d, *J* = 8.7 Hz), 125.6-125.4 (2C, m), 124.0 (q, *J* = 3.8 Hz), 123.8 (q, *J* = 272.5 Hz), 120.78 (q, *J* = 321.2 Hz), 115.4 (d, *J* = 89.5 Hz), 57.7; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.46, –78.13; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.38.

(2-((4-Chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl) triphenylphosphonium trifluoromethanesulfonate



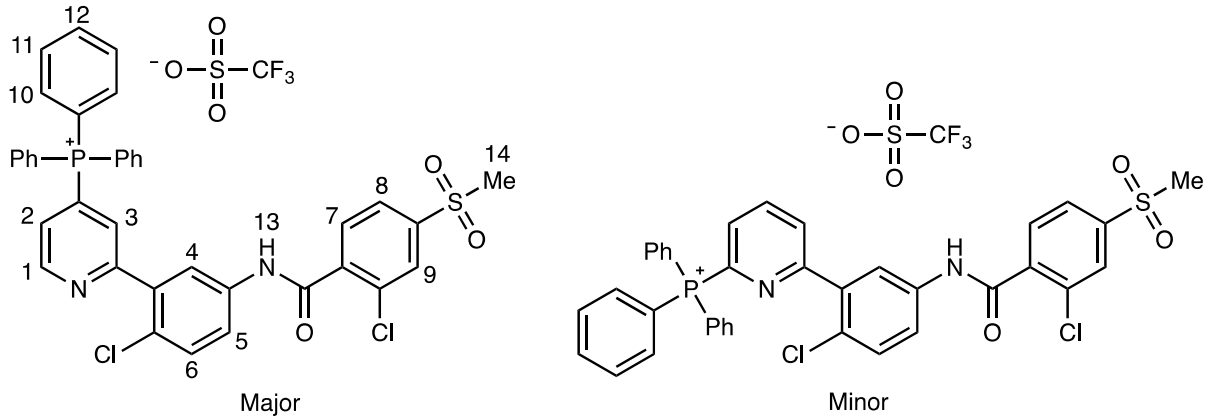
Prepared according to our previous report.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, t, *J* = 5.1 Hz), 7.94-7.86 (3H, m), 7.82-7.73 (6H, m), 7.71-7.59 (7H, m), 7.49 (1H, ddd, *J* = 12.6, 5.0, 1.1 Hz), 7.34-7.25 (4H, m), 5.71 (1H, s), 4.11 (2H, q, *J* = 7.1 Hz), 3.70-3.60 (1H, m), 3.55-3.42 (2H, m), 3.25-3.12 (2H, m), 1.79-1.56 (2H, m), 1.54-1.37 (2H, m), 1.25 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.4 (d, *J* = 9.6 Hz), 155.4, 151.1 (d, *J* =10.5 Hz), 138.7, 136.2 (d, *J* = 3.1 Hz), 134.5 (d, *J* = 10.5 Hz), 134.0, 130.9 (d, *J* = 13.1 Hz), 129.3 (d, *J* = 84.1 Hz), 128.8, 128.5, 125.9 (d, *J* = 8.4 Hz), 123.9 (d, *J* = 9.1 Hz), 120.8 (q, *J* = 321.2 Hz), 115.8 (d, *J* = 89.4 Hz), 79.9, 72.8, 61.3, 40.7 (rot), 40.7, 31.3, 30.3 (rot), 14.7; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.67.

(E)-Triphenyl(2-(3-(pyrrolidin-1-yl)-1-(p-tolyl)prop-1-en-1-yl)pyridin-4-yl)phosphonium trifluoromethanesulfonate



Prepared according to our previous report.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.93 (1H, app t, J = 5.3 Hz, H_1), 7.92-7.56 (15H, m, H_7, H_8, and H_9), 7.38 (1H, dd, J = 12.3, 4.8 Hz, H_2), 7.26 (1H, d, J = 14.3 Hz, H_3), 7.18-6.98 (5H, m, H_4, H_5, and H_6), 3.71 (2H, d, J = 6.9 Hz, H_{10}), 3.13 (4H, br s, H_{11}), 2.37 (3H, s, H_{13}), 1.99 (4H, br s, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.3 (d, J = 10.1 Hz), 150.9 (d, J = 10.5 Hz), 144.2, 138.2, 136.0 (d, J = 3.0 Hz), 134.3 (d, J = 10.6 Hz), 132.3, 130.9 (d, J = 13.1 Hz), 129.7, 129.1, 128.8 (d, J = 84.7 Hz), 126.3, 125.6 (d, J = 9.2 Hz), 125.3 (d, J = 8.0 Hz), 120.6 (q, J = 320.4 Hz), 115.6 (d, J = 89.6 Hz), 54.0, 53.7, 23.0, 21.2; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.05; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.34.

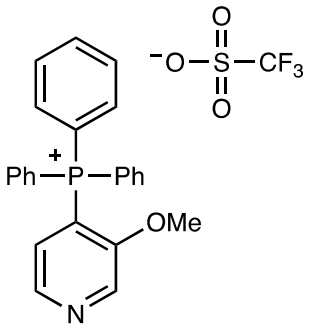
(2-(2-Chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate and (6-(2-chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate



7:1 Mixture of Regioisomers

Prepared according to our previous report.[28] Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.98 (1H, s, H_{13}), 8.98 (1H, app t, J = 4.9 Hz, H_1), 8.15-7.33 (23H, m, H_2, H_3, H_4, H_5, H_6, H_7, H_8, H_9, H_{10}, H_{11}, and H_{12}), 3.01 (3H, s, H_{14}); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.5, 158.5 (d, J = 10.8 Hz), 151.2 (d, J = 10.9 Hz), 142.3, 140.4, 137.9, 136.8, 136.2 (d, J = 2.9 Hz), 134.4 (d, J = 10.5 Hz), 132.5, 130.9 (d, J = 13.1 Hz), 130.5, 130.0, 128.7, 128.5 (d, J = 84.4 Hz), 128.1 (d, J = 8.8 Hz), 126.4, 125.8, 125.4 (d, J = 8.4 Hz), 123.2, 122.6, 120.4 (q, J = 320.6 Hz), 115.6 (d, J = 89.6 Hz), 44.3; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.34; Both isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.60 (major), 17.95 (minor).

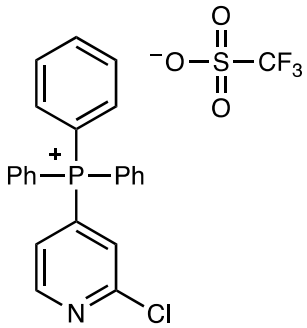
(3-Methoxypyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[29] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, d, J = 6.8 Hz), 8.58 (1H, app t, J = 3.9 Hz), 7.90–7.86 (3H, m), 7.79–7.74 (6H, m), 7.66–7.60 (6H,

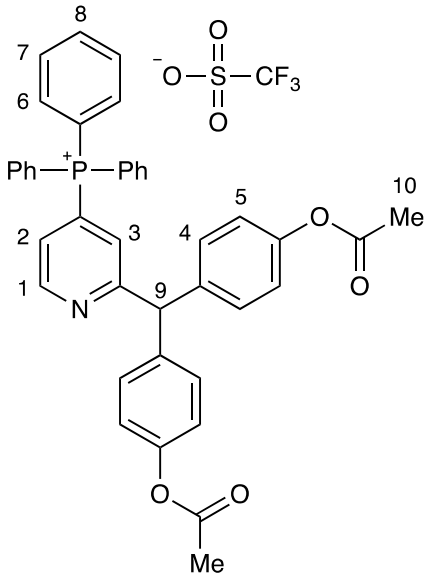
m), 7.09 (1H, dd, J = 4.9, 15.0 Hz), 3.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.8 (d, J = 0.6 Hz), 143.9 (d, J = 10.9 Hz), 136.6 (d, J = 4.6 Hz), 135.6 (d, J = 3.0 Hz), 133.8 (d, J = 10.6 Hz), 130.6 (d, J =13.2 Hz), 127.9 (d, J = 7.0 Hz), 120.7 (q, J = 319.4 Hz), 116.4 (d, J = 90.9 Hz), 115.2 (d, J = 86.4 Hz), 57.2; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.14; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.45.

(2-Chloropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



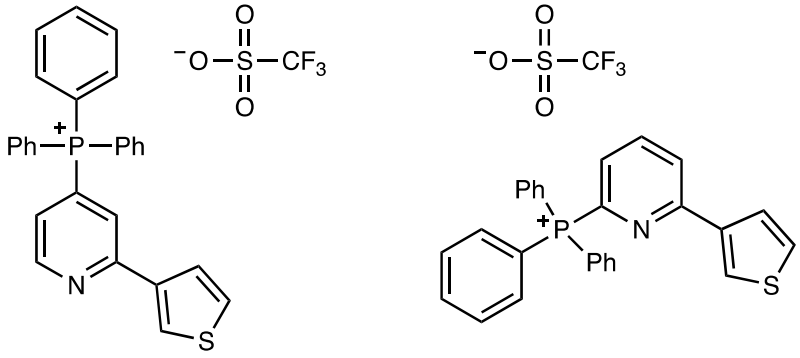
Prepared according to our previous report.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (1H, app t, J = 5.1 Hz), 7.98-7.89 (3H, m), 7.86-7.77 (6H, m), 7.75-7.62 (7H, m), 7.40 (1H, d, J = 13.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.4 (d, J = 15.1 Hz), 152.3 (d, J = 11.3 Hz), 136.4 (d, J = 3.0 Hz), 134.5 (d, J = 10.4 Hz), 132.0 (d, J = 83.2 Hz), 131.1 (d, J = 13.0 Hz), 127.4 (d, J = 9.5 Hz), 126.3 (d, J = 8.4 Hz), 120.7 (q, J = 320.4 Hz), 115.0 (d, J = 90.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.19; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.27.

(2-(Bis(4-acetoxyphenyl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to our previous report.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, app t, J = 5.1 Hz, H_1), 7.86-7.80 (3H, m, H_8), 7.73-7.66 (6H, m, H_7), 7.56-7.39 (7H, m, H_2 and H_6), 7.18 (1H, d, J = 13.7 Hz, H_3), 7.13-7.08 (4H, m, H_4), 6.97–6.91 (4H, m, H_5), 5.72 (1H, s, H_9), 2.21 (6H, s, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.1, 165.0 (d, J = 9.4 Hz), 151.2 (d, J = 10.4 Hz), 149.3, 138.4, 135.9 (d, J = 3.0 Hz), 134.1 (d, J = 10.6 Hz), 130.7 (d, J = 13.0 Hz), 129.9, 129.0 (d, J = 83.8 Hz), 126.6 (d, J = 8.7 Hz), 124.9 (d, J = 7.9 Hz), 121.5, 120.6 (q, J = 321.2 Hz), 115.3 (d, J = 89.4 Hz), 57.4, 20.8; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.05; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.34.

Triphenyl(2-(thiophen-3-yl)pyridin-4-yl)phosphonium trifluoromethanesulfonate

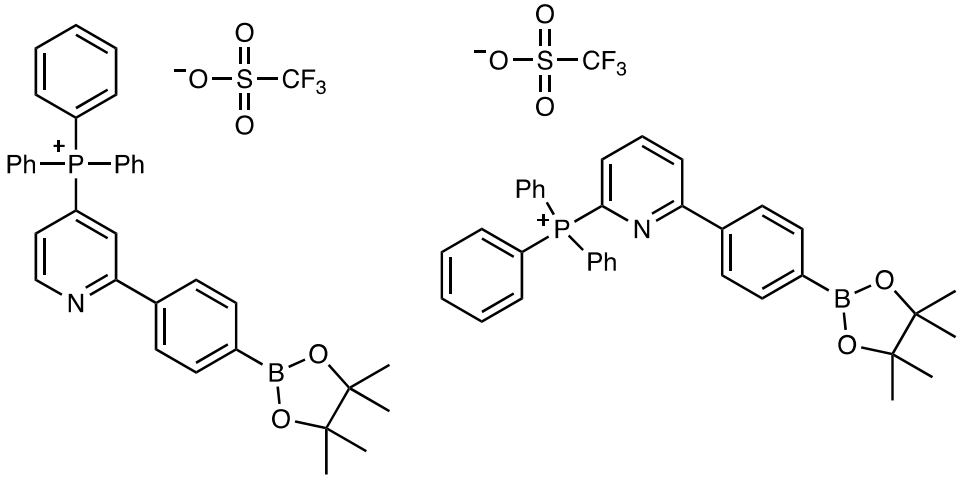


Major Minor

10:1 mixture of regioisomers

Prepared according to general procedure A (except immediately after addition of Tf_2O, the reaction was warmed up to -50 °C) using 2-(thiophen-3-yl)pyridine (460 mg, 2.86 mmol), Tf_2O (280 μL, 2.86 mmol), PPh_3 (823 mg, 3.14 mmol), DBU (427 μL, 2.86 mmol) and CH_2Cl_2 (30 mL). After the purification procedure, the title compound was isolated as a white, amorphous solid (611 mg, 1.06 mmol, 37% yield). IR ν_{max}/cm^{-1} (film): 3090, 3064, 1577, 1438, 1260, 1223, 1108, 1029, 725, 650; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, td, *J* = 5.1, 0.9 Hz), 8.00 (1H, dd, *J* = 3.0, 1.3 Hz), 7.90-7.96 (3H, m), 7.66-7.86 (13H, m), 7.55 (1H, dd, *J* = 5.1, 1.3 Hz), 7.44 (1H, dd, *J* = 5.0, 1.6 Hz), 7.38-7.42 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.1 (d, *J* = 10.9 Hz), 151.7 (d, *J* = 10.6 Hz), 139.8 (d, *J* = 1.6 Hz), 136.3 (d, *J* = 3.1 Hz), 134.4 (d, *J* = 10.3 Hz), 131.0 (d, *J* = 12.8 Hz), 129.3 (d, *J* = 84.2 Hz), 127.3, 126.4, 125.9, 124.8 (d, *J* = 8.2 Hz), 123.0 (d, *J* = 8.7 Hz), 120.8 (q, *J* = 321.1 Hz), 115.6 (d, *J* = 89.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.69; m/z LRMS (ESI + APCI) found $[M–OTf]^+$ 422.2, $C_{27}H_{21}NPS^+$ requires 422.1.

Triphenyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate

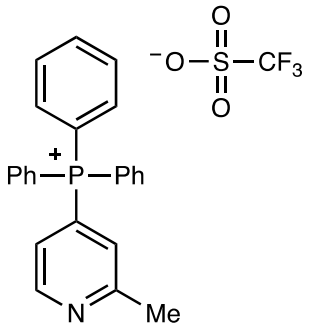


Major Minor

>20:1 mixture of regioisomers

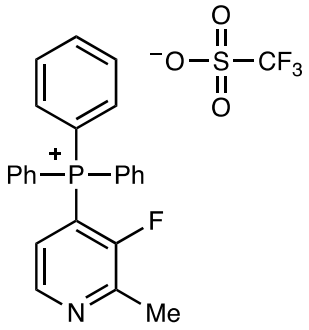
Prepared according to general procedure A (except PPh_3 was added and stirred at –30 °C) using 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine (1.615 g, 5.75 mmol), Tf_2O (0.97 mL, 5.75 mmol), PPh_3 (1.656 g, 6.32 mmol), DBU (0.86 mL, 5.75 mmol) and CH_2Cl_2 (58 mL). After the purification procedure, the title compound was isolated as a white, amorphous solid (2.84 g, 5.00 mmol, 87% yield). IR ν_{max}/cm^{-1} (film): 3062, 2978, 2929, 1578, 1439, 1357, 1260, 1142, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.10 (1H, td, J = 5.1, 0.7 Hz), 7.67-7.97 (20H, m), 7.57 (1H, ddd, J = 7.7, 5.0, 1.6 Hz), 1.34 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2 (d, J = 10.2 Hz), 152.0 (d, J = 10.5 Hz), 139.3 (d, J = 1.5 Hz), 136.4 (d, J = 3.1 Hz), 135.5, 134.5 (d, J = 10.4 Hz), 131.1 (d, J = 13.2 Hz), 130.6 (d, J = 12.7 Hz), 129.5 (d, J = 83.9 Hz), 126.3, 125.8 (d, J = 8.0 Hz), 123.6 (d, J = 8.7 Hz), 120.9 (q, J = 324.7 Hz), 115.7 (d, J = 89.4 Hz), 84.1, 24.9; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.11; ^{31}P NMR (162 MHz, CD_3CN) δ: 22.71, 16.07; m/z LRMS (ESI + APCI) found $[M–OTf]^+$ 542.3, $C_{35}H_{34}BNO_2P^+$ requires 542.2.

(2-Methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 2-methylpyridine (1.97 mL, 20.0 mmol), Tf_2O (3.36 mL, 20.0 mmol), PPh_3 (5.76 g, 22.0 mmol), NEt_3 (2.78 mL, 20.0 mmol) and CH_2Cl_2 (200 mL). After the purification procedure, the title compound was isolated as a white solid (7.47 g, 14.8 mmol, 74% yield). mp 187-189 ºC; IR ν_{max}/cm^{-1} (film): 3067, 3042, 2974, 2925, 2854, 2239, 1591, 1546, 1514, 1355, 1328, 1286, 1141, 1092, 961, 829, 774, 663; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.88 (1H, app t, J = 5.2 Hz), 7.97-7.60 (15H, m), 7.42-7.30 (2H, m), 2.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.9 (d, J = 10.0 Hz), 150.6 (d, J = 10.7 Hz), 135.7 (d, J = 2.9 Hz), 134.1 (d, J = 10.4 Hz), 130.6 (d, J = 13.0 Hz), 128.2 (d, J = 83.5 Hz), 126.2 (d, J = 7.9 Hz), 123.8 (d, J = 11.1 Hz), 120.4 (q, J = 321.3 Hz), 115.4 (d, J = 89.4 Hz), 24.4; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.14; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.39; m/z LRMS (ESI + APCI) found $[M–OTf]^+$ 354.2, $C_{24}H_{21}NP^+$ requires 354.1.

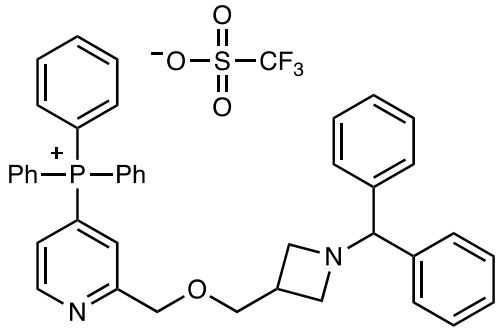
(3-Fluoro-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure using 3-fluoro-2-methylpyridine (618 μL, 6.00 mmol), Tf_2O (1.00 mL, 6.00 mmol), PPh_3 (1.73 g, 6.60 mmol), DBU (896 μL, 6.00 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a tan solid (1.41 g, 2.70 mmol, 45% yield). mp 205-209 ºC; IR ν_{max}/cm^{-1} (film): 3088, 3063, 1586, 1482,

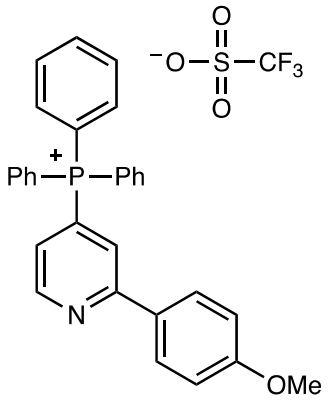
1437, 1408, 1260, 1225, 1143, 1106, 1030, 724, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (1H, app t, *J* = 4.1 Hz), 7.94-7.86 (3H, m), 7.83-7.75 (6H, m), 7.70-7.61 (6H, m), 7.09 (1H, dt, *J* = 14.0, 4.6 Hz), 2.64 (3H, d, *J* = 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.1 (d, *J* = 264.9 Hz), 150.0 (dd, *J* = 17.0, 4.4 Hz), 147.0 (dd, *J* = 11.0, 6.8 Hz), 136.2 (d, *J* = 3.1 Hz), 134.0 (d, *J* = 11.2 Hz), 131.0 (d, *J* = 13.6 Hz), 125.9 (dd, *J* = 6.0, 2.3 Hz), 120.8 (q, *J* = 321.6 Hz), 115.6 (dd, *J* = 84.1, 14.6 Hz), 115.3 (d, *J* = 91.0 Hz), 18.2 (d, *J* = 2.4 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.18, –107.41; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.66 (d, *J* = 3.7 Hz); m/z LRMS (ESI + APCI) found $[M–OTf]^+$ 372.2, $C_{24}H_{20}FNP^+$ requires 372.1.

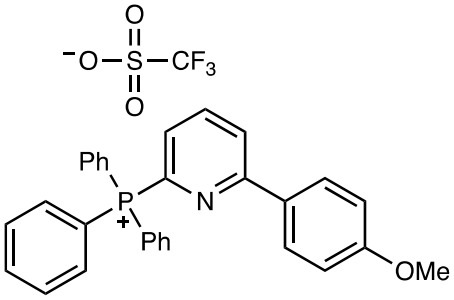
(2-(((1-Benzhydrylazetidin-3-yl)methoxy)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 2-(((1-benzhydrylazetidin-3-yl)methoxy)methyl)pyridine (962 mg, 2.79 mmol), Tf_2O (468 μL, 2.79 mmol), PPh_3 (812 mg, 3.10 mmol), DBU (416 μL, 2.79 mmol) and CH_2Cl_2 (28 mL). After the purification procedure, the title compound was isolated as a white solid (1.77 g, 2.34 mmol, 84% yield). mp 201-203 ºC; IR ν_{max}/cm^{-1} (film): 3060, 2949, 2851, 1582, 1485, 1439, 1264, 1223, 1147, 1108, 1029, 689, 636, 558; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.93 (1H, app t, *J* = 5.0 Hz), 7.82-7.11 (27H, m), 4.71 (2H, s), 4.29 (1H, br), 3.68 (2H, d, *J* = 6.9 Hz), 3.15 (2H, br), 2.93-2.49 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.5 (d, *J* = 9.9 Hz), 150.7 (d, *J* = 10.4 Hz), 141.3-140.8 (br), 135.9 (d, *J* = 2.79 Hz), 134.1 (d, *J* = 10.6 Hz), 130.6 (d, *J* = 13.0 Hz), 128.8 (d, *J* = 84.0 Hz), 128.3, 127.2, 127.1, 125.5 (d, *J* = 8.1 Hz), 123.8 (d, *J* = 9.1 Hz), 120.6 (q, *J* = 324.3 Hz), 115.8, 115.4 (d, *J* = 89.4 Hz), 78.0, 72.3, 56.0, 29.0; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.08; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.64; m/z LRMS (ESI + APCI) found $[M–OTf]^+$ 605.3, $C_{41}H_{38}N_2OP^+$ requires 605.3.

(2-(4-Methoxyphenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



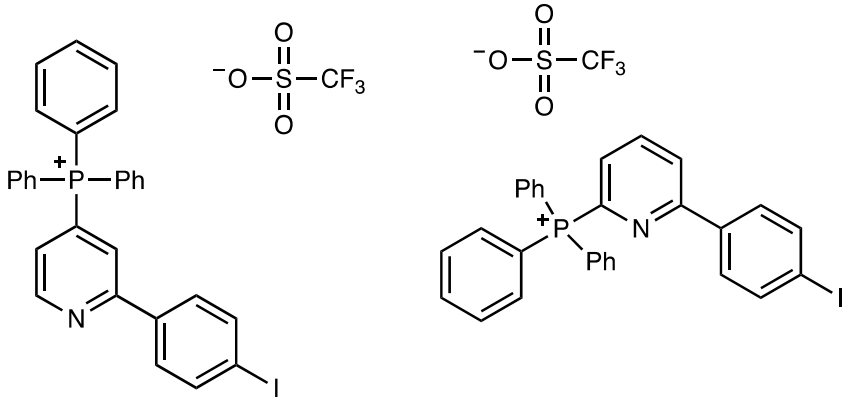


Major Minor

>20:1 mixture of regioisomers

Prepared according to general procedure A using 2-(4-methoxyphenyl)pyridine (92 mg, 0.50 mmol), Tf_2O (84 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), NEt_3 (70 μL, 0.50 mmol) and CH_2Cl_2 (5 mL). After the purification procedure, the title compound was isolated as a white solid (298 mg, 0.38 mmol, 75% yield). mp 123-125 ºC; IR ν_{max}/cm^{-1} (film): 3062, 2963, 2937, 2839, 2231, 1606, 1582, 1515, 1463, 1438, 1377, 1260, 1222, 1148, 1108, 1029, 830, 725, 689, 635; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.00 (1H, app t, J = 5.1 Hz), 7.99-7.62 (18H, m), 7.41 (1H, dd, J = 12.7, 4.9 Hz), 6.97 (2H, d, J = 8.8 Hz), 3.83 (3H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.5, 158.8 (d, J = 10.5 Hz), 151.5 (d, J = 10.8 Hz), 136.2 (d, J = 2.9 Hz), 134.3 (d, J = 10.5 Hz), 130.9 (d, J = 13.0 Hz), 129.2 (d, J = 1.3 Hz), 129.0 (d, J = 84.0 Hz), 128.5, 124.6 (d, J = 8.1 Hz), 122.4 (m), 120.7 (q, J = 323.7 Hz), 115.6 (d, J = 89.5 Hz), 114.4, 55.4; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.12; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.77, 15.16; m/z LRMS (ESI + APCI) found $[M–OTf]^+$ 446.2, $C_{30}H_{25}NOP^+$ requires 446.2.

(2-(4-Iodophenyl) pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate

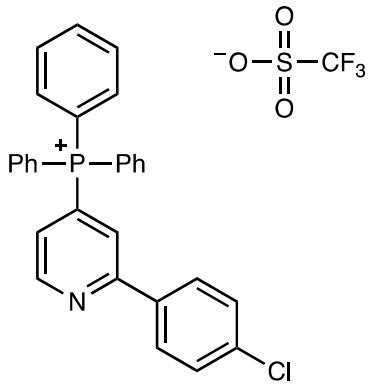


Major Minor

19:1 Mixture of Regioisomers

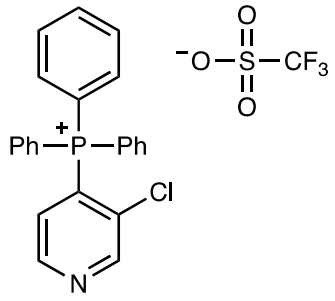
Prepared according to general procedure A (except that PPh_3 was stirred at -30 °C) 2-(4-iodophenyl)pyridine (843 mg, 3.00 mmol), Tf_2O (504 μL, 3.00 mmol), PPh_3 (865 mg, 3.30 mmol), DBU (448 μL, 3.00 mmol) and CH_2Cl_2 (30 mL). After the purification procedure, the title compound was isolated as a yellow solid (2.00 g, 2.91 mmol, 97% yield). mp 204-207 ºC; IR ν_{max}/cm^{-1} (film): 3061, 1585, 1438, 1285, 1147, 1108, 1029, 635; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.05 (1H, td, *J* = 5.1, 0.7 Hz), 7.96-7.63 (20H, m), 7.54 (1H, ddd, *J* = 12.7, 5.0, 1.6 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.4 (d, *J* = 10.6 Hz), 151.8 (d, *J* = 10.7 Hz), 138.3, 136.5 (d, *J* = 1.5 Hz), 136.3 (d, *J* = 3.0 Hz), 135.6 (d, *J* = 10.6 Hz), 131.1 (d, *J* = 13.1 Hz), 129.7 (d, *J* = 83.9 Hz), 129.0, 125.8 (d, *J* = 8.0 Hz), 123.2 (d, *J* = 8.6 Hz), 121.1 (q, *J* = 321.2 Hz), 115.7 (d, *J* = 89.4 Hz), 97.4; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.14; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.78, 15.72; m/z LRMS (ESI + APCI) found $[M–OTf]^+$ 542.1, $C_{29}H_{22}INP^+$ requires 542.1.

(2-(4-Chlorophenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 2-(4-chlorophenyl)pyridine (95 mg, 0.50 mmol), Tf_2O (84 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), NEt_3 (70 μL, 0.50 mmol) and CH_2Cl_2 (5 mL). After the purification procedure, the title compound was isolated as a white solid (300 mg, 0.35 mmol, 69% yield). mp 211-213 ºC; IR ν_{max}/cm^{-1} (film): 3060, 1582, 1439, 1373, 1260, 1223, 1148, 1108, 1029, 725, 636, 545; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.05 (1H, app t, J = 5.1 Hz), 7.97-7.63 (18H, m), 7.52 (1H, ddd, J = 12.7, 5.0, 1.6 Hz), 7.40 (2H, d, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.0 (d, J = 10.5 Hz), 151.7 (d, J = 10.7 Hz), 136.5, 136.2 (d, J = 3.0 Hz), 135.5 (d, J = 1.5 Hz), 134.5 (d, J = 10.5 Hz), 131.0 (d, J = 13.0 Hz), 129.7 (d, J = 84.1 Hz), 129.2, 128.6, 125.7 (d, J = 8.2 Hz), 123.2 (d, J = 8.6 Hz), 122.8 (q, J = 327.4 Hz), 115.6 (d, J = 89.5 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.75; m/z LRMS (ESI + APCI) found $[M–OTf]^+$ 450.2, $C_{29}H_{22}ClNP^+$ requires 450.1.

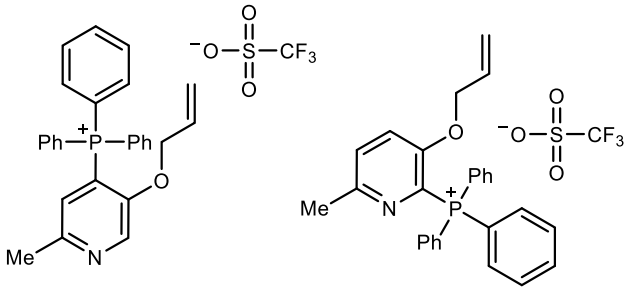
(3-Chloropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Prepared according to general procedure A using 3-chloroisonicotinonitrile (48 μL, 0.50 mmol), Tf_2O (84 μL, 0.50 mmol), PPh_3 (144 mg, 0.55 mmol), DBU (75 μL, 0.50 mmol) and CH_2Cl_2 (5 mL). After the purification procedure, the title compound was isolated as a white solid (262 mg, 0.38 mmol, 76% yield). mp 197-200 ºC; IR ν_{max}/cm^{-1} (film): 3064, 1587, 1483, 1437,

1391, 1260, 1224, 1182, 1147, 1107, 1029, 749, 701, 634, 528; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.93-8.84 (2H, m), 7.95-7.65 (15H, m), 7.31 (1H, dd, *J* = 14.6, 4.9 Hz; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.6 (d, *J* = 5.0 Hz), 149.8 (d, *J* = 9.9 Hz), 135.8 (d, *J* = 3.0 Hz), 134.5 (d, *J* = 1.5 Hz), 134.0 (d, *J* = 10.7 Hz), 130.8 (d, *J* = 13.4 Hz), 130.2 (d, *J* = 8.3 Hz), 127.1 (d, *J* = 88.4 Hz), 120.6 (q, *J* = 321.4 Hz), 115.0 (d, *J* = 90.5 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.68; *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 374.1, $C_{23}H_{18}ClNP^+$ requires 374.1.

(5-(allyloxy)-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate

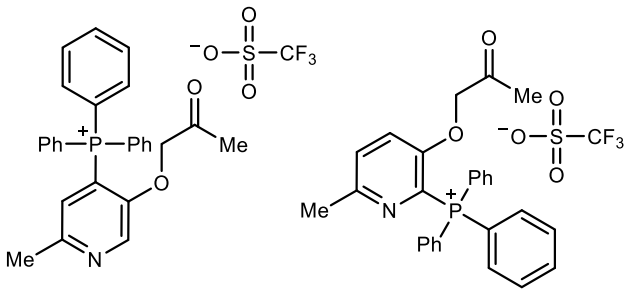


Major **Minor**

16:1 mixture of regioisomers

Prepared according to general procedure A (except PPh_3 was added and stirred at -78°C) using 5-(allyloxy)-2-methylpyridine (885 mg, 5.90 mmol), Tf_2O (0.99 mL, 5.90 mmol), PPh_3 (1.700 g, 6.49 mmol), DBU (0.88 mL, 5.90 mmol) and CH_2Cl_2 (59 mL). After the purification procedure, the title compound was isolated as a white amorphous solid (2.467 g, 4.43 mmol, 75% yield); IR ν_{max}/cm^{-1} (film): 3061, 3026, 2995, 2926, 1586, 1484, 1438, 1350, 1260, 1222, 1146, 1107, 1029, 983, 722, 689, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, J = 6.9 Hz), 7.91-7.86 (3H, m), 7.79-7.72 (6H, m), 7.68-7.60 (6H, m), 6.88 (1H, d, J = 15.1 Hz), 5.32-5.21 (1H, m), 5.01 (1H, dq, J = 10.5, 1.1 Hz), 4.91 (1H, dq, J =17.1, 1.2 Hz), 4.46 (2H, dt, J = 5.6, 1.3 Hz), 2.54 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d: 152.6, 136.0 (d, *J* = 4.7 Hz), 135.2, 133.6 (d, *J* = 10.6 Hz), 130.3 (d, *J* = 13.1 Hz), 129.6, 127.0 (d, *J* = 6.8 Hz), 120.5 (q, *J* = 321.2 Hz), 119.1, 117.7 (d, *J* = 90.9 Hz), 116.2 (d, *J* = 91.3 Hz), 115.0, 70.3, 23.3; ^{19}F NMR (365 MHz, $CDCl_3$) d: –78.18; ^{31}P NMR (162 MHz, $CDCl_3$) d: 22.46 (major), 17.78 (minor); *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 410.2, $C_{23}H_{18}ClNP^+$ requires 410.2.

(2-methyl-5-(2-oxopropoxy)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate



Major **Minor**

6:1 mixture of regioisomers

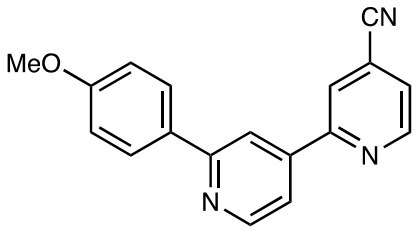
Prepared according to general procedure A using 1-((6-methylpyridin-3-yl)oxy)propan-2-one (885 mg, 5.0 mmol), Tf_2O (0.84 mL, 5.0 mmol), PPh_3 (1.441 g, 5.5 mmol), DBU (0.75 mL, 5.0 mmol) and CH_2Cl_2 (50 mL). After the purification procedure, the title compound was isolated as a brown amorphous solid (1.526 g, 2.65 mmol, 53% yield); IR ν_{max}/cm^{-1} (film): 3071, 3023, 2923, 1726, 1493, 1437, 1353, 1259, 1153, 1106, 1027, 722, 689, 635, 569; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.42 (1H, d, J = 6.8 Hz), 7.95 – 7.60 (16H, m), 6.84 (1H, d, J = 15.2 Hz), 4.80 (2H, s), 2.51 (3H, s), 2.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.1, 153.3 (d, J = 2.0 Hz), 136.0 (d, J = 3.1 Hz), 134.7 (d, J = 10.8 Hz), 131.1 (d, J = 13.3 Hz), 130.3 (d, J = 13.1 Hz), 128.2 (d, J = 7.1 Hz), 121.2 (q, J = 320.8 Hz), 118.7 (d, J = 90.4 Hz), 117.0 (d, J = 91.3 Hz), 116.5 (d, J = 85.9 Hz), 73.77, 26.3, 23.8; ^{19}F NMR (365 MHz, $CDCl_3$) δ -78.22; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.72 (Major), 17.88 (Minor). *m/z* LRMS (ESI + APCI) found $[M–OTf]^+$ 426.2, $C_{27}H_{25}NO_2P^+$ requires 426.2.

13. Synthesis of Bipyridines

General Procedure B

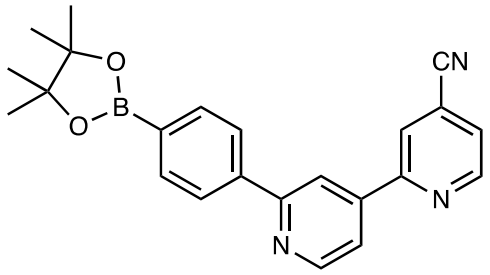
An oven-dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the phosphonium salt (1 equiv), the pyridyl coupling partner (2 equiv), B_2Pin_2 (1.0 equiv), and placed under a nitrogen atmosphere. 1,2-Dichloroethane (0.2 M) was added, followed by addition of NEt_3 (1.25 equiv) at room temperature, and the reaction was stirred for 36 hours. The reaction mixture was then opened, diluted with EtOAc (2 mL), and allowed to stir under air for 30 minutes. The crude mixture was directly concentrated *in vacuo*, and the residue was purified by flash chromatography under the stated conditions to provide the bisheterobiaryl product.

2'-(4-Methoxyphenyl)-[2,4'-bipyridine]-4-carbonitrile (203)



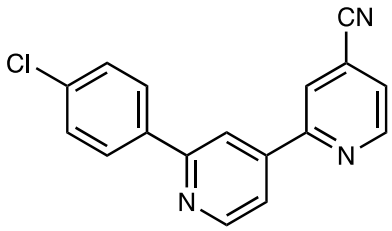
Prepared according to general procedure B using (2-(4-methoxyphenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (238 mg, 0.40 mmol), isonicotinonitrile (83 mg, 0.80 mmol), B_2Pin_2 (102 mg, 0.40 mmol), NEt_3 (70 μL, 0.50 mmol), and 1,2-dichloroethane (2.0 mL). Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the title compound as a white solid (86 mg, 0.30 mmol, 75% yield). mp 156-158 ºC; IR ν_{max}/cm^{-1} (film): 3020, 2956, 2927, 2237, 1607, 1546, 1516, 1426, 1259, 1177, 833; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.91 (1H, d, *J* = 4.8 Hz), 8.77 (1H, d, *J* = 5.0 Hz), 8.27 (1H, s), 7.98-8.10 (3H, m), 7.69 (1H, d, 5.0 Hz) 7.55 (1H, s, *J* = 4.7 Hz), 7.01 (2H, d, *J* = 8.7 Hz), 3.86 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.8, 158.2, 156.4, 151.0, 150.5, 145.0, 131.5, 128.4, 124.9, 122.4, 121.6, 118.6, 117.0, 116.4, 114.2, 55.4; m/z LRMS (ESI + APCI) found $[M+H]^+$ 288.1, $C_{18}H_{14}N_3O^+$ requires 288.1.

2'-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[2,4'-bipyridine]-4-carbonitrile (204)



Prepared according to general procedure B using triphenyl(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (346 mg, 0.50 mmol), isonicotinonitrile (104 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 μL, 1.25 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel, gradient elution: 15% EtOAc in hexanes) afforded the title compound as a white solid (135 mg, 0.35 mmol, 70% yield). mp 189-191 ºC; IR ν_{max}/cm^{-1} (film): 3067, 3042, 2974, 2925, 2854, 2239, 1608, 1546, 1355, 1328, 1286, 1141, 1093, 961, 829, 663; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.93 (1H, d, *J* = 4.9 Hz), 8.84 (1H, d, *J* = 5.1 Hz), 8.38 (1H, s), 8.10 (2H, d, *J* = 8.2 Hz), 8.06 (1H, s), 7.94 (2H, d, *J* = 8.1 Hz), 7.78 (1H, dd, *J* = 5.1, 1.5 Hz), 7.56 (1H, dd, *J* = 4.9, 1.2 Hz), 1.37 (12H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.3, 156.2, 151.0, 150.6, 145.1, 141.2, 135.3, 130.0, 126.2, 125.0, 122.5, 121.6, 119.5, 118.0, 116.3, 84.0, 25.0; m/z LRMS (ESI + APCI) found $[M+H]^+$ 384.3, $C_{23}H_{23}BN_3O_2^+$ requires 384.2.

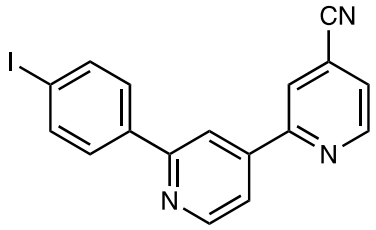
2'-(4-Chlorophenyl)-[2,4'-bipyridine]-4-carbonitrile (205)



Prepared according to general procedure B using (2-(4-chlorophenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (300 mg, 0.50 mmol), isonicotinonitrile (104 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 μL, 0.63 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography (silica gel, gradient elution: EtOAc to 1% MeOH in CH_2Cl_2, followed by 6% EtOAc in toluene) afforded the title compound as a white solid (75 mg,

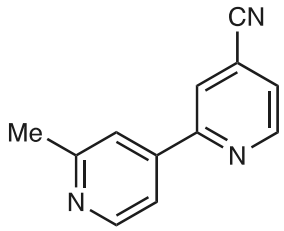
0.26 mmol, 51% yield). mp 164-166 ºC; IR νmax/cm-1 (film): 3089, 3040, 3021, 2235, 1590, 1545, 1473, 1425, 1372, 1097, 843, 829; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, d, *J* = 4.9 Hz), 8.84 (1H, d, *J* = 5.1 Hz), 8.36 (1H, s), 8.07 (3H, m), 7.80 (1H, dd, *J* = 5.1, 1.6 Hz), 7.60 (1H, dd, *J* = 4.9, 1.3 Hz), 7.48 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.6, 156.3, 151.2, 150.8, 145.4, 137.5, 135.7, 129.2, 128.5, 125.2, 122.6, 121.9, 119.6, 117.8, 116.4; m/z LRMS (ESI + APCI) found $[M+H]^+$ 292.1, $C_{17}H_{11}ClN_3^+$ requires 292.1.

2'-(4-Iodophenyl)-[2,4'-bipyridine]-4-carbonitrile (206)



Prepared according to general procedure B using (2-(4-iodophenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (276 mg, 0.40 mmol), isonicotinonitrile (83 mg, 0.80 mmol), B_2Pin_2 (102 mg, 0.40 mmol), NEt_3 (70 µL, 0.50 mmol), and 1,2-dichloroethane (2.0 mL). Flash column chromatography (silica gel: 17% EtOAc in hexanes) afforded the title compound as a white solid (95 mg, 0.25 mmol, 62% yield). mp 209-211 ºC. IR ν_{max}/cm^{-1} (film): 3138, 3091, 3020, 2958, 2923, 2852, 2236, 1592, 1544, 1462, 1423, 1368, 818, 646; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.95 (1H, dd, *J* = 4.9, 0.9 Hz), 8.84 (1H, d, *J* = 5.1 Hz), 8.36 (1H, m), 8.07 (1H, m), 7.85 (4H, s), 7.80 (1H, dd, *J* = 5.1, 1.6 Hz), 7.59 (1H, dd, *J* = 4.9, 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.7, 156.3, 151.2, 150.8, 145.4, 138.5, 138.1, 128.9, 125.2, 122.6, 121.9, 119.7, 117.7, 116.4, 96.0; m/z LRMS (ESI + APCI) found $[M+H]^+$ 384.1, $C_{17}H_{11}IN_3^+$ requires 384.0.

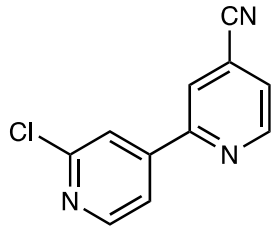
2'-Methyl-[2,4'-bipyridine]-4-carbonitrile (207)



Prepared according to general procedure B using (2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (252 mg, 0.50 mmol), isonicotinonitrile (104

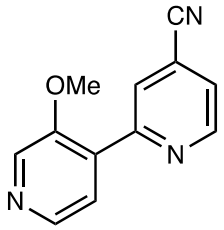
mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 μL, 0.63 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a white solid (80 mg, 0.41 mmol, 82% yield). mp 123-125 ºC; IR ν_{max}/cm^{-1} (film): 3099, 3009, 2957, 2922, 2239, 1593, 1547, 1463, 833, 644; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.89 (1H, d, *J* = 4.8 Hz), 8.63 (1H, d, *J* = 5.1 Hz), 7.98 (1H, s), 7.75 (1H, s), 7.65 (1H, d, *J* = 4.8 Hz), 7.54 (1H, d, *J* = 4.7 Hz), 2.64 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.7, 156.4, 151.0, 150.2, 144.6, 124.9, 122.5, 121.6, 120.5, 118.1, 116.3, 24.7; m/z LRMS (ESI + APCI) found $[M+H]^+$ 196.1, $C_{12}H_{10}N_3^+$ requires 196.1.

2'-Chloro-[2,4'-bipyridine]-4-carbonitrile (208)



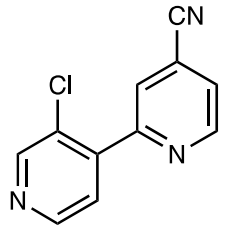
Prepared according to general procedure B using (2-chloropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (262 mg, 0.50 mmol), isonicotinonitrile (104 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), $^{44}NEt_3$ (87 μL, 0.63 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography (basic alumina: 15% EtOAc in hexanes) afforded the title compound as a white solid (33 mg, 0.15 mmol, 30% yield). mp 199-200 ºC; IR ν_{max}/cm^{-1} (film): 3097, 3064, 2240, 1590, 1540, 1403, 1364, 1098, 836, 769, 644; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.94 (1H, d, *J* = 4.8 Hz), 8.55 (1H, d, *J* = 5.1 Hz), 8.00 (2H, m), 7.82 (1H, d, *J* = 5.1 Hz), 7.61 (1H, d, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.9, 153.0, 151.4, 150.8, 147.4, 125.7, 122.6, 122.1, 121.9, 119.7, 116.1; m/z LRMS (ESI + APCI) found $[M+H]^+$ 216.1, $C_{11}H_7ClN_3^+$ requires 216.0.

3'-Methoxy-[2,4'-bipyridine]-4-carbonitrile (209)



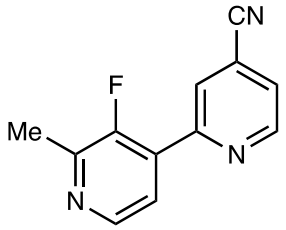
Prepared according to general procedure B using (3-methoxypyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (519 mg, 1.00 mmol), isonicotinonitrile (208 mg, 2.00 mmol), B_2Pin_2 (254 mg, 1.00 mmol), NEt_3 (254 μL, 1.25 mmol), and 1,2-dichloroethane (5.0 mL). Flash column chromatography (silica gel: 50% EtOAc in hexanes, followed by recrystallization from CH_2Cl_2 and hexanes) afforded the title compound as a white solid (103 mg, 0.49 mmol, 49% yield). mp 122-124 ºC; IR ν_{max}/cm^{-1} (film): 3054, 2948, 2943, 2236, 1752, 1592, 1556, 1494, 1424, 1230, 1055, 840, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.89 (1H, dd, *J* = 5.0, 0.9 Hz), 8.47 (1H, s), 8.40 (1H, d, *J* = 4.9 Hz), 8.27 (1H, m), 7.85 (1H, d, *J* = 4.9 Hz), 7.50 (1H, dd, *J* = 5.0, 1.5 Hz), 4.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.4, 152.6, 150.5, 143.3, 134.9, 132.8, 127.1, 124.2, 123.8, 120.6, 116.7, 56.4; m/z LRMS (ESI + APCI) found $[M+H]^+$ 212.1, $C_{12}H_{10}N_3O^+$ requires 212.1.

3'-Chloro-[2,4'-bipyridine]-4-carbonitrile (210)



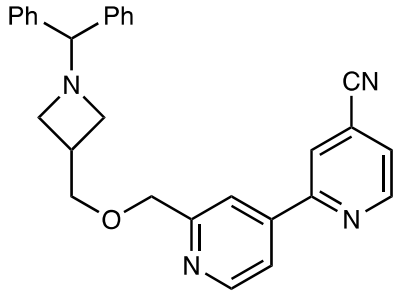
Prepared according to general procedure B (except ran for 115 hours) using (3-chloropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (262 mg, 0.50 mmol), isonicotinonitrile (104 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 μL, 0.63 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the title compound as a white solid (37 mg, 0.17 mmol, 34% yield). mp 136-138 ºC. IR ν_{max}/cm^{-1} (film): 3092, 3060, 3025, 2240, 1595, 1461, 1388, 851, 640; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, d, *J* = 4.9 Hz), 8.75 (1H, s), 8.65 (1H, d, *J* = 4.6 Hz), 8.02 (1H, s), 7.60 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.5, 151.2, 150.8, 148.5, 143.8, 129.5, 126.3, 125.2, 125.0, 121.1, 116.2; m/z LRMS (ESI + APCI) found $[M+H]^+$ 216.1, $C_{11}H_7ClN_3^+$ requires 216.0.

3'-Fluoro-2'-methyl-[2,4'-bipyridine]-4-carbonitrile (211)



Prepared according to general procedure B using triphenyl(2-(prop-1-en-2-yl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (261 mg, 0.50 mmol), isonicotinonitrile (104 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 μL, 1.25 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel, gradient elution: 15% EtOAc in toluene) afforded the title compound as a white solid (70 mg, 0.33 mmol, 65% yield). mp 102-104 ºC; IR ν_{max}/cm^{-1} (film): 3068, 2957, 2923, 2852, 2241, 1596, 1564, 1474, 1395, 1298, 1200, 1123, 850, 532; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.92 (1H, d, *J* = 4.9 Hz), 8.42 (1H, d, *J* = 5.0 Hz), 8.12 (1H, s), 7.78 (1H, t, *J* = 3.8 Hz), 7.56 (1H, d, *J* = 4.9 Hz), 2.61 (3H, d, *J* = 3.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.1 (d, *J* = 260.3 Hz), 152.5, 150.8, 148.3 (d, *J* = 18.6 Hz), 145.1 (d, *J* = 7.0 Hz), 131.3 (d, *J* = 9.5 Hz), 126.3 (d, *J* = 11.5 Hz), 124.9, 121.8, 121.3, 116.1, 18.1; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –129.52; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 214.1, $C_{12}H_9FN_3^+$ requires 214.1.

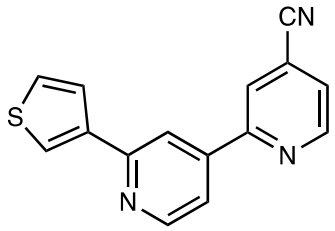
2'-(((1-Benzhydrylazetidin-3-yl)methoxy)methyl)-[2,4'-bipyridine]-4-carbonitrile (212)



Prepared according to general procedure B using (2-(((1-benzhydrylazetidin-3-yl)methoxy)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (226 mg, 0.30 mmol), isonicotinonitrile (62 mg, 0.60 mmol), B_2Pin_2 (76 mg, 0.30 mmol), NEt_3 (52 μL, 0.38 mmol), and 1,2-dichloroethane (1.5 mL). Flash column chromatography (basic alumina: 25% EtOAc in hexanes) followed by a second flash column (silica gel: 40% EtOAc in hexanes) afforded the title compound as a light yellow, amorphous solid (83 mg, 0.19 mmol, 62% yield). IR ν_{max}/cm-

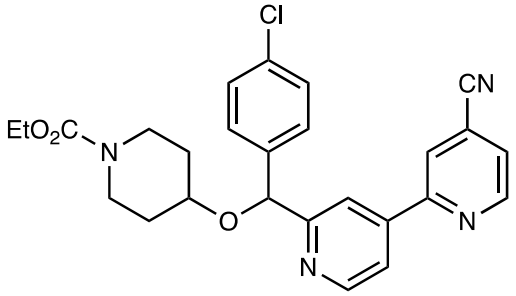
$_1$ (film): 3098, 3062, 3024, 2962, 2845, 2831, 2242, 1593, 1453, 1123, 840, 783, 706, 699, 544; $_1$H NMR (400 MHz, $CDCl_3$) δ: 8.87 (1H, d, *J* = 4.8 Hz), 8.71 (1H, d, *J* = 5.1 Hz), 8.04 (1H, s), 8.00 (1H, s), 7.79 (1H, d, *J* = 3.9 Hz), 7.54 (1H, d, *J* = 4.9 Hz), 7.40 (4H, d, *J* = 7.4 Hz), 7.13-7.29 (6H, m), 4.73 (2H, s), 4.37 (1H, s), 3.78 (2H, d, *J* = 6.6 Hz), 3.34 (2H, t, *J* = 7.5 Hz), 2.98 (2H, t, *J* = 6.6 Hz), 2.83 (1H, qn, *J* = 6.6 Hz); $_{13}$C NMR (100 MHz, $CDCl_3$) δ: 160.2, 156.4, 151.1, 150.1, 145.1, 142.4, 128.5, 127.6, 127.1, 125.0, 122.5, 121.7, 119.7, 118.6, 116.4, 78.2, 73.9, 73.9, 56.7, 29.9; m/z LRMS (ESI + APCI) found $[M+H]^+$ 447.3, $C_{29}H_{27}N_4O^+$ requires 447.2.

2'-(Thiophen-3-yl)-[2,4'-bipyridine]-4-carbonitrile (213)



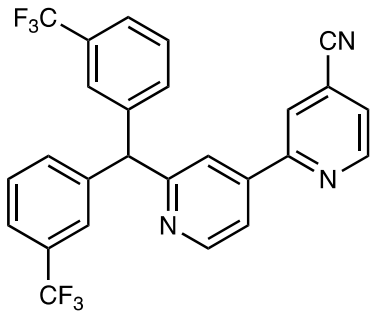
Prepared according to general procedure B using triphenyl(2-(thiophen-3-yl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (172 mg, 0.30 mmol), isonicotinonitrile (62 mg, 0.60 mmol), B_2Pin_2 (76 mg, 0.30 mmol), NEt_3 (52 μL, 0.38 mmol), and 1,2-dichloroethane (1.5 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a white solid (57 mg, 0.20 mmol, 65% yield). mp 165-166 ºC; IR ν_{max}/cm^{-1} (film): 3130, 3090, 3058, 3024, 2238, 1590, 1559, 1543, 1463, 1433, 1382, 789, 670, 526; $_1$H NMR (400 MHz, $CDCl_3$) δ: 8.94 (1H, d, *J* = 4.9 Hz), 8.77 (1H, d, *J* = 5.2 Hz), 8.25 (1H, s), 8.05 (1H, s), 8.02 (1H, d, *J* = 2.8 Hz), 7.76 (1H, d, *J* = 5.6 Hz), 7.72 (1H, dd, *J* = 5.0, 1.5 Hz), 7.58 (1H, d, *J* = 5.0 Hz), 7.44 (1H, dd, *J* = 4.9, 3.0 Hz); $_{13}$C NMR (100 MHz, $CDCl_3$) δ: 156.4, 154.8, 151.2, 150.7, 145.2, 141.9, 126.7, 126.4, 125.1, 124.3, 122.5, 121.8, 119.0, 117.7, 116.4; m/z LRMS (ESI + APCI) found $[M+H]^+$ 264.1, $C_{15}H_{10}N_3S^+$ requires 264.1.

Ethyl 4-((4-cyano-[2,4'-bipyridin]-2'-yl)(phenyl)methoxy)piperidine-1-carboxylate (214)



Prepared according to general procedure B using (2-((4-chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (393 mg, 0.30 mmol), isonicotinonitrile (62 mg, 0.60 mmol), B_2Pin_2 (76 mg, 0.30 mmol), NEt_3 (52 μL, 0.38 mmol), and 1,2-dichloroethane (1.5 mL). Flash column chromatography (silica gel: 15% EtOAc in hexanes) afforded the title compound as a tan solid (102 mg, 0.21 mmol, 71% yield). mp 46-48 ºC; IR ν_{max}/cm^{-1} (film): 3059, 2979, 2928, 2866, 2239, 1690, 1592, 1428, 1273, 1227, 1085, 833, 806, 526; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.92 (1H, d, *J* = 4.9 Hz), 8.66 (1H, d, *J* = 5.1 Hz), 8.11 (1H, s), 7.99 (1H, s), 7.77 (1H, dd, *J* = 5.1, 1.7 Hz), 7.57 (1H, dd, *J* = 4.9, 1.3 Hz), 7.42 (2H, d, *J* = 8.6 Hz), 7.30 (2H, d, *J* = 8.5 Hz), 5.71 (1H, s), 4.11 (2H, q, *J* = 7.1 Hz), 3.81 (2H, m), 3.68 (1H, sp, *J* = 3.8 Hz), 3.18 (2H, m), 1.87 (2H, m), 1.69 (2H, m), 1.25 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 156.3, 155.6, 151.2, 150.1, 145.6, 139.9, 133.7, 128.8, 128.3, 125.1, 122.6, 121.8, 120.0, 117.9, 116.4, 81.0, 73.1, 61.4, 41.3 (rot), 41.2, 31.4 (rot), 31.2, 14.8; m/z LRMS (ESI + APCI) found $[M+H]^+$ 477.2, $C_{26}H_{26}ClN_4O_3^+$ requires 477.2.

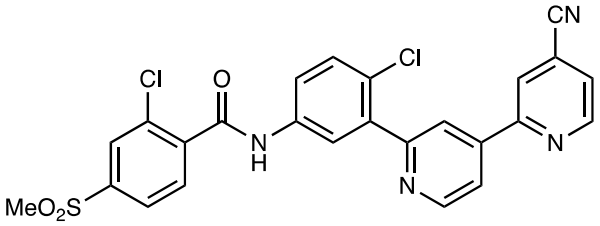
2'-(Bis(3-(trifluoromethyl)phenyl)methyl)-[2,4'-bipyridine]-4-carbonitrile (215)



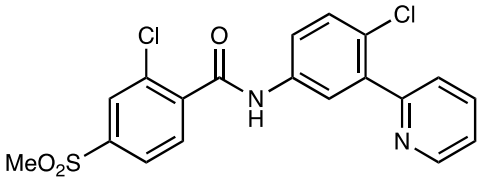
Prepared according to general procedure B using (2-(bis(3-(trifluoromethyl)phenyl)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate

(158 mg, 0.20 mmol), isonicotinonitrile (42 mg, 0.40 mmol), B_2Pin_2 (51 mg, 0.20 mmol), NEt_3 (35 μL, 0.25 mmol), and 1,2-dichloroethane (1.0 mL). Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the title compound as a light yellow solid (79 mg, 0.16 mmol, 82% yield). mp 86-89 ºC; IR ν_{max}/cm^{-1} (film): 3058, 2925, 2853, 2239, 1593, 1543, 1310, 1161, 1118, 1075, 701; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, dd, *J* = 5.0, 0.8 Hz), 8.80 (1H, d, *J* = 5.1 Hz), 7.96 (1H, app t, *J* = 1.0 Hz), 7.84 (1H, s), 7.78 (1H, dd, *J* = 5.1, 1.7 Hz), 7.41-7.55 (9H, m), 5.83 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5, 156.0, 151.2, 151.0, 145.5, 142.8, 132.7, 131.0 (q, *J* = 32.3 Hz), 129.3, 126.0 (q, *J* = 3.9 Hz), 124.1 (q, *J* = 272.5 Hz), 124.1 (q, *J* = 3.7 Hz), 122.6, 121.8, 121.2, 120.1, 119.5, 116.3, 58.8; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.54; m/z LRMS (ESI + APCI) found $[M+H]^+$ 484.2, $C_{23}H_{17}N_4^+$ requires 484.1.

2-Chloro-N-(4-chloro-3-(4-cyano-[2,4'-bipyridin]-2'-yl)phenyl)-4-(methylsulfonyl)benzamide (216)



Major

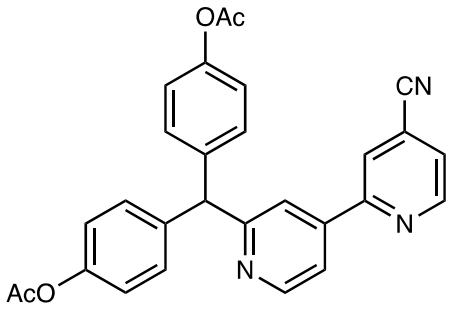


Minor

Isolated as 3.8:1 mixture of products

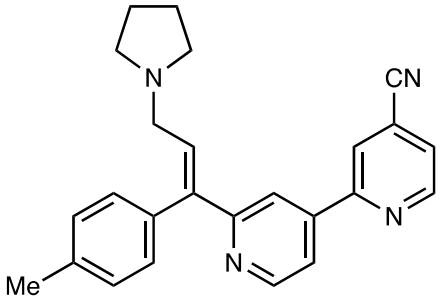
Prepared according to general procedure B (except bubbled 1 atm of O_2 through the reaction instead of opening to air and used 2 equivalents of B_2pin_2) using (2-(2-Chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (208 mg, 0.25 mmol), 3,5-dimethylisonicotinonitrile (52 mg, 0.50 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (43 μL, 0.31 mmol), and 1,2-dichloroethane (1.25 mL). Flash column chromatography (silica gel: 40% EtOAc and 1% Acetic Acid in hexanes followed by recrystallization from CH_2Cl_2 and hexanes) afforded the title compound as a 3.8:1 mixture of products as a white solid with a crude ^1H NMR yield = 44% using 1,3,5-trimethoxybenzene as an internal standard. *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 523.1, $C_{25}H_{17}Cl_2N_4O_3S^+$ requires 523.0.

((4-Cyano-[2,4'-bipyridin]-2'-yl)methylene)bis(4,1-phenylene) diacetate (217)



Prepared according to general procedure B using ((4-cyano-[2,4'-bipyridin]-2'-yl)methylene)bis(4,1 phenylene) diacetate (232 mg, 0.30 mmol), isonicotinonitrile (162 mg, 0.60 mmol), B_2Pin_2 (76 mg, 0.30 mmol), NEt_3 (52 μL, 0.38 mmol), and 1,2-dichloroethane (1.5 mL). Flash column chromatography (silica gel: 35% EtOAc in hexanes) afforded the title compound as a light brown oil (104 mg, 0.23 mmol, 75% yield). IR ν_{max}/cm^{-1} (film): 2920, 2850, 2260, 1756, 1592, 1503, 1369, 1190, 1165, 1017, 912, 834, 644; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.84 (1H, dd, J = 4.9, 0.6 Hz), 8.73 (1H, d, J = 5.1 Hz), 7.91 (1H, s), 7.78 (1H, s), 7.71 (1H, dd, J = 5.2, 1.6 Hz), 7.50 (1H, dd, J = 4.9 Hz, 1.3 Hz), 7.27-7.22 (4H, m), 7.06-7.01 (4H, m), 5.74 (1H, m), 2.26 (6H, m); ^{13}C NMR (100 MHz, CD_3CN) δ: 170.5, 164.5, 156.4, 151.9, 151.3, 150.6, 146.3, 141.4, 131.2, 126.5, 124.2, 122.7, 122.3, 121.9, 120.0, 117.5, 58.4, 21.2; m/z LRMS (ESI + APCI) found $[M+H]^+$ 464.2, $C_{28}H_{22}N_3O_4^+$ requires 464.2

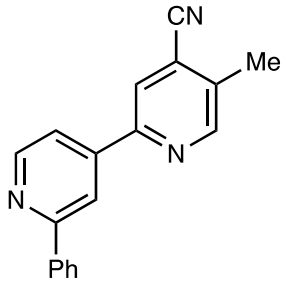
(E)-2'-(3-(Pyrrolidin-1-yl)-1-(p-tolyl)prop-1-en-1-yl)-[2,4'-bipyridine]-4-carbonitrile (218)



Prepared according to general procedure B using (E)-triphenyl(2-(3-(pyrrolidin-1-yl)-1-(p-tolyl)prop-1-en-1-yl)pyridin-4-yl)phosphonium trifluoromethanesulfonate (207 mg, 0.30 mmol), isonicotinonitrile (62 mg, 0.60 mmol), B_2Pin_2 (76 mg, 0.30 mmol), NEt_3 (52 μL, 0.38 mmol), and 1,2-dichloroethane (1.5 mL). Flash column chromatography (silica gel, gradient elution: 50% Et_2O and 1% NEt_3 in CH_2Cl_2 to 10% MeOH in CH_2Cl_2) followed by a second flash column (silica gel:

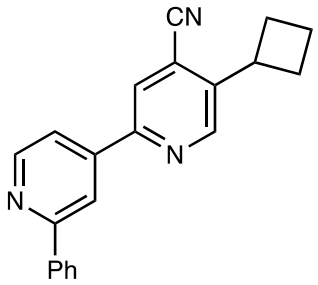
3% MeOH in CH_2Cl_2), then the product was recrystallized from CH_2Cl_2 and hexanes, collected on a frit, and washed with brine (2 x 20 mL) and a saturated solution of $NaHCO_3$ (20 mL) afforded the title compound as a white solid (40 mg, 0.11 mmol, 35% yield). mp 112-114 ºC; IR ν_{max}/cm^{-1} (film): 3045, 3000, 2960, 2926, 2909, 2874, 2787, 2238, 1586, 1419, 840, 526; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.85 (1H, d, *J* = 4.9 Hz), 8.72 (1H, d, *J* = 5.1 Hz), 7.83 (1H, s), 7.71 (1H, dd, *J* = 5.1, 1.6 Hz), 7.62 (1H, s), 7.50 (1H, dd, *J* = 4.9, 1.3 Hz), 7.23 (2H, d, *J* = 7.9 Hz), 7.13 (2H, d, *J* = 8.0 Hz), 6.99 (1H, t, *J* = 6.8 Hz), 3.25 (2H, d, *J* = 6.8 Hz), 2.58-2.51 (4H, m), 2.41 (3H, s), 1.80-1.74 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.3, 156.7, 151.0, 150.3, 144.8, 141.9, 137.3, 135.2, 131.7, 129.8, 129.4, 124.8, 122.5, 121.6, 119.3, 119.2, 116.4, 54.9, 54.3, 23.6, 21.5; m/z LRMS (ESI + APCI) found $[M+H]^+$ 381.3, $C_{25}H_{25}N_4^+$ requires 381.2.

5-Methyl-2'-phenyl-[2,4'-bipyridine]-4-carbonitrile (219)



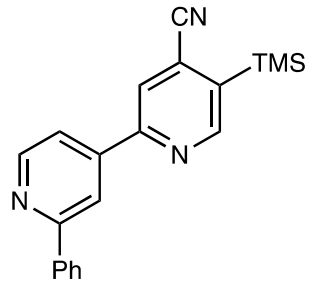
Prepared according to general procedure B using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), 3-methylisonicotinonitrile (118 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 µL, 0.63 mmol), and 1,2-dichloroethane (2.50 mL). Flash column chromatography (silica gel: 15% EtOAc in hexanes) afforded the title compound as white solid (95 mg, 0.36 mmol, 71% yield). mp 181-182 ºC; IR ν_{max}/cm^{-1} (film): 3057, 2923, 2237, 1581, 1542, 1467, 1367, 1211, 855, 780, 690; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (1H, d, *J* = 5.1 Hz), 8.79 (1H, s), 8.34 (1H, s), 8.06-8.12 (2H, m), 8.00 (1H, s), 7.76 (1H, dd, *J* = 5.1, 1.6 Hz), 7.42-7.54 (3H, m), 2.62 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.6, 153.5, 151.9, 150.6, 145.3, 139.1, 135.6, 129.4, 128.9, 127.1, 122.2, 121.9, 119.1, 117.7, 115.7, 17.4; m/z LRMS (ESI + APCI) found $[M+H]^+$ 272.1, $C_{18}H_{14}N_3^+$ requires 272.1.

5-Cyclobutyl-2'-phenyl-[2,4'-bipyridine]-4-carbonitrile (220)



Prepared according to general procedure B using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), 3-cyclobutylisonicotinonitrile (158 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 μL, 0.63 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography (silica gel: 15% EtOAc in hexanes, followed by recrystallization from CH_2Cl_2 and hexanes) afforded the title compound as a white solid (85 mg, 0.28 mmol, 55% yield). mp 160-161 ºC; IR ν_{max}/cm^{-1} (film): 2995, 2975, 2943, 2862, 2229, 1597, 1531, 1481, 1390, 1364, 1207, 864, 779, 692; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.85 (1H, s), 8.79 (1H, dd, *J* = 5.1, 0.7 Hz), 8.32 (1H, dd, *J* = 1.6, 0.7 Hz), 8.08 (2H, m), 7.95 (1H, d, *J* = 0.7 Hz), 7.74 (1H, dd, *J* = 5.1, 1.7 Hz), 7.39-7.53 (3H, m), 3.90 (1H, qn, *J* = 8.8 Hz), 2.58 (2H, m), 2.35 (2H, m), 2.18 (1H, m), 1.98 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.5, 153.3, 150.6, 149.5, 145.2, 142.5, 139.1, 129.3, 128.9, 127.1, 122.5, 120.1, 119.1, 117.7, 115.9, 36.8, 28.9, 18.7; m/z LRMS (ESI + APCI) found $[M+H]^+$ 312.2, $C_{21}H_{18}N_3^+$ requires 312.2.

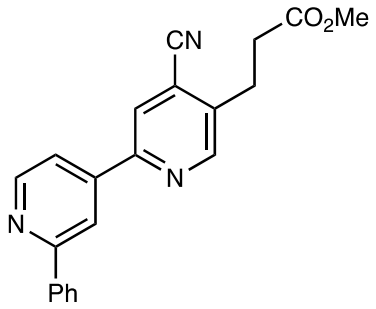
2'-Phenyl-5-(trimethylsilyl)-[2,4'-bipyridine]-4-carbonitrile (221)



Prepared according to general procedure B using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), 3-(3-cyanophenyl)isonicotinonitrile (176 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 μL, 0.63 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography (silica gel: 10% EtOAc in hexanes, followed by recrystallization from CH_2Cl_2 and hexanes) afforded the title

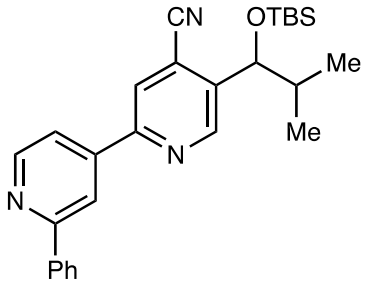
compound as a white solid (57 mg, 0.18 mmol, 35% yield). mp 128-130 ºC; IR ν_{max}/cm^{-1} (film): 3053, 2956, 2925, 2895, 2228, 1579, 1512, 1500, 1346, 1252, 1208, 820, 766, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.97 (1H, s), 8.83 (1H, d, *J* = 5.1 Hz), 8.37 (1H, s), 8.10 (2H, m), 8.05 (1H, s), 7.79 (1H, dd, *J* = 5.1, 1.4 Hz), 7.42-7.54 (3H, m), 0.52 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.7, 156.0, 155.5, 150.6, 145.3, 139.0, 137.5, 129.4, 128.9, 127.1, 126.8, 123.3, 119.3, 117.8, 117.7, 1.4; m/z LRMS (ESI + APCI) found $[M+H]^+$ 330.2, $C_{20}H_{20}N_3Si^+$ requires 330.1.

Methyl 3-(4-cyano-2'-phenyl-[2,4'-bipyridin]-5-yl)propanoate (222)



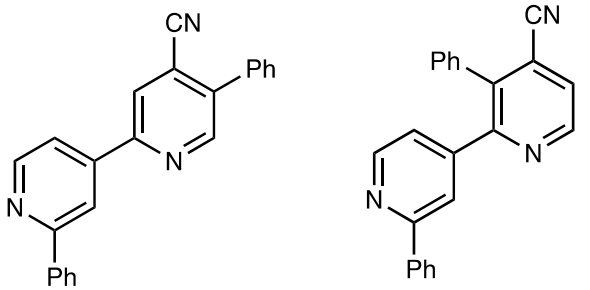
Prepared according to general procedure B using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (96 mg, 0.17 mmol), methyl 3-(4-cyanopyridin-3-yl)propanoate (67 mg, 0.35 mmol), B_2Pin_2 (43 mg, 0.17 mmol), NEt_3 (30 μL, 0.21 mmol), and 1,2-dichloroethane (0.85 mL). Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the title compound as a colorless oil (41 mg, 0.12 mmol, 71% yield). IR ν_{max}/cm^{-1} (film): 3060, 2952, 2920, 2852, 2237, 1730, 1622, 1488, 1442, 1371, 1196, 1182, 1161, 854, 691; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (1H, s), 8.81 (1H, d, *J* = 5.1 Hz), 8.33 (1H, s), 8.09 (2H, m), 8.01 (1H, s), 7.75 (1H, dd, *J* = 5.1, 1.6 Hz), 7.41-7.54 (3H, m), 3.70 (3H, s), 3.24 (2H, t, *J* = 7.4 Hz), 2.80 (2H, t, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 158.7, 154.2, 151.8, 150.6, 145.1, 139.1, 137.8, 129.4, 128.9, 127.1, 122.6, 121.7, 119.2, 117.8, 115.5, 52.1, 34.0, 26.8; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 344.2, $C_{21}H_{18}N_3O_2^+$ requires 344.1.

5-(1-((Tert-butyldimethylsilyl)oxy)-2-methylpropyl)-2'-phenyl-[2,4'-bipyridine]-4-carbonitrile (223)



Prepared according to general procedure B using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (147 mg, 0.26 mmol), 3-(1-((tert-butyldimethylsilyl)oxy)-2-methylpropyl)isonicotinonitrile (149 mg, 0.51 mmol), B_2Pin_2 (66 mg, 0.26 mmol), NEt_3 (45 μL, 0.33 mmol), and 1,2-dichloroethane (1.3 mL). Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the title compound as a colorless oil (45 mg, 0.10 mmol, 39% yield). IR ν_{max}/cm^{-1} (film): 2957, 2929, 2857, 1590, 1540, 1465, 1253, 1074, 884, 774, 693; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.01 (1H, s), 8.84 (1H, d, *J* = 5.1 Hz), 8.39 (1H, s) 8.11 (2H, d, *J* = 7.2 Hz), 8.01 (1H s), 7.80 (1H, dd, *J* = 5.1, 1.5 Hz), 7.42-7.54 (3H, m), 4.80 (1H, d, *J* = 6.0 Hz), 2.06 (1H, sext, *J* = 6.6 Hz), 1.00 (3H, d, *J* = 6.6 Hz), 0.93 (12H, m), 0.13 (3H, s), -0.14 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.8, 154.4, 150.9, 150.7, 145.2, 141.7, 139.1, 129.4, 129.0, 127.2, 122.2, 119.6, 119.2, 117.9, 115.6, 76.5, 36.6, 25.9, 19.1, 18.3, 17.6 (rot), -4.4, -4.9 (rot); m/z LRMS (ESI + APCI) found $[M+H]^+$ 444.3, $C_{27}H_{34}N_3OSi^+$ requires 444.3.

2',5-Diphenyl-[2,4'-bipyridine]-4-carbonitrile (224)



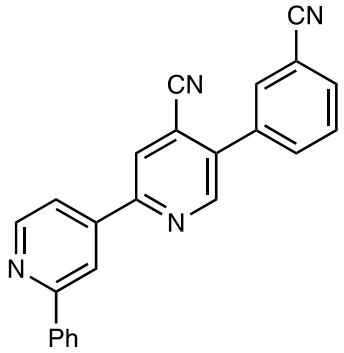
Major Minor

17:1 mixture of regioisomers

Prepared according to general procedure B using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), 3-phenylisonicotinonitrile (180

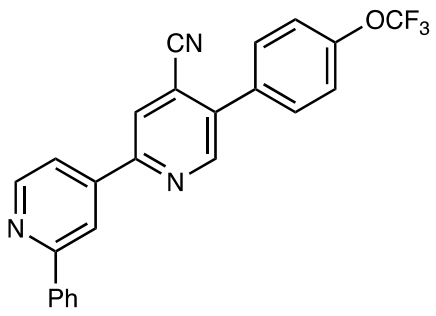
mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 μL, 0.63 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography (silica gel: 10% EtOAc in hexanes, followed by recrystallization from CH_2Cl_2 and hexanes) afforded the title compound as a white solid (80 mg, 0.24 mmol, 48% yield). mp 184-186 ºC; IR ν_{max}/cm^{-1} (film): 3057, 3037, 3026, 2238, 1959, 1624, 1537, 1470, 1443, 1365, 1212, 904, 768, 693, 532; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, m), 8.86 (1H, d, *J* = 5.1 Hz), 8.42 (1H, m), 8.09-8.17 (3H, m), 7.84 (1H, dd, *J* = 5.1, 1.6 Hz), 7.42-7.71 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.8, 154.3, 151.4, 150.7, 145.0, 139.1, 138.6, 134.1, 130.0, 129.5, 129.4, 129.0, 128.9, 127.2, 123.4, 120.0, 119.3, 117.9, 116.5; m/z LRMS (ESI + APCI) found $[M+H]^+$ 334.2, $C_{23}H_{16}N_3^+$ requires 334.1.

5-(3-Cyanophenyl)-2'-phenyl-[2,4'-bipyridine]-4-carbonitrile (225)



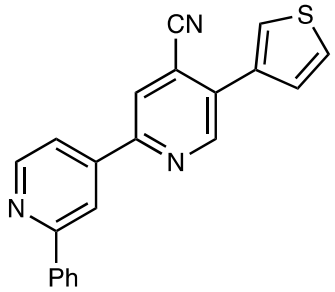
Prepared according to general procedure B except the reaction was diluted to 0.1 M. Triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (188 mg, 0.33 mmol), 3-(3-cyanophenyl)isonicotinonitrile (135 mg, 0.66 mmol), B_2Pin_2 (84 mg, 0.33 mmol), NEt_3 (58 μL, 0.41 mmol), and 1,2-dichloroethane (3.3 mL, 0.1 M) were combined in the reaction vessel. Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a white solid (63 mg, 0.18 mmol, 53% yield). mp 223-225 ºC; IR ν_{max}/cm^{-1} (film): 3063, 3013, 2235, 1601, 1588, 1535, 1469, 1448, 1366, 1215, 1182, 891, 816, 779, 692, 544; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.97 (1H, s), 8.89 (1H, d, *J* = 5.1 Hz), 8.43 (1H, m), 8.21 (1H, m), 8.12 (2H, m), 7.80-7.98 (4H, m), 7.69-7.77 (1H, m), 7.42-7.59 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.0, 155.7, 151.0, 150.9, 144.6, 139.0, 136.1, 135.5, 133.4, 133.2, 132.3, 130.4, 129.6, 129.0, 127.2, 123.4, 120.4, 119.3, 118.0, 117.9, 115.8, 114.0; m/z LRMS (ESI + APCI) found $[M+H]^+$ 359.2, $C_{24}H_{15}N_4^+$ requires 359.1.

2'-Phenyl-5-(4-(trifluoromethoxy)phenyl)-[2,4'-bipyridine]-4-carbonitrile (226)



Prepared according to general procedure B using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), 3-(4-(trifluoromethoxy)phenyl)isonicotinonitrile (264 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 μL, 0.63 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a tan solid (161 mg, 0.39 mmol, 77% yield). mp 194-196 ºC; IR ν_{max}/cm^{-1} (film): 3051, 3012, 2924, 2852, 2236, 1601, 1582, 1467, 1254, 1203, 852; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, s), 8.85 (1H, d, J = 4.9 Hz), 8.40 (1H, s), 8.15 (1H, s), 8.11 (2H, d, J = 7.3 Hz), 7.82 (1H, d, J = 4.4 Hz), 7.69 (2H, d, J = 8.6 Hz), 7.39-7.55 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.7, 154.8, 151.1, 150.7, 150.5 (m), 144.7, 139.0, 137.0, 132.6, 130.5, 129.5, 128.9, 127.1, 123.3, 121.6, 120.4 (q, J = 258.5 Hz), 120.0, 119.2, 117.8, 116.1; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –57.68; m/z LRMS (ESI + APCI) found $[M+H]^+$ 418.2, $C_{24}H_{15}F_3N_3O^+$ requires 418.1.

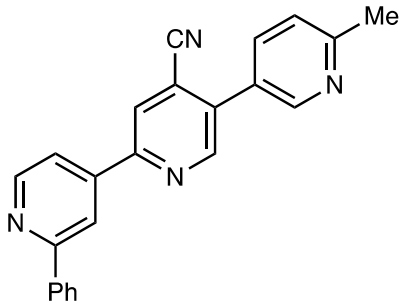
2'-Phenyl-5-(thiophen-3-yl)-[2,4'-bipyridine]-4-carbonitrile (227)



Prepared according to general procedure B using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), 3-(thiophen-3-

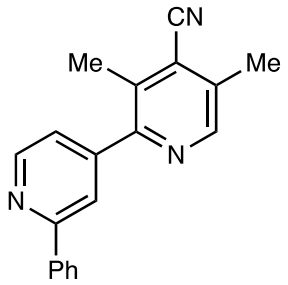
yl)isonicotinonitrile (186 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 µL, 0.63 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes, followed by silica gel, gradient elution: CH_2Cl_2 to 1% MeOH in CH_2Cl_2) afforded the title compound as a white solid (123 mg, 0.37 mmol, 73% yield). mp 195-197 ºC; IR ν_{max}/cm^{-1} (film): 3114, 3092, 3074, 2228, 1567, 1583, 1469, 1423, 1375, 1201, 782, 693, 526; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.06 (1H, d, *J* = 0.7 Hz), 8.85 (1H, dd, *J* = 5.1, 0.6 Hz), 8.39 (1H, m), 8.12 (3H, m), 7.88 (1H, m), 7.81 (1H, dd, *J* = 5.1, 1.7 Hz), 7.43-7.57 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.8, 153.8, 150.8, 150.8, 145.0, 139.1, 134.5, 133.0, 129.5, 129.0, 127.7, 127.2, 127.1, 126.3, 123.5, 119.2, 118.8, 117.8, 116.8; m/z LRMS (ESI + APCI) found $[M+H]^+$ 340.2, $C_{21}H_{14}N_3S^+$ requires 340.1.

6-Methyl-2''-phenyl-[3,3':6',4''-terpyridine]-4'-carbonitrile (228)



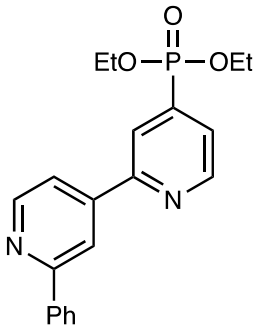
Prepared according to general procedure B using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (170 mg, 0.30 mmol), 6'-methyl-[3,3'-bipyridine]-4-carbonitrile (118 mg, 0.60 mmol), B_2Pin_2 (76 mg, 0.30 mmol), NEt_3 (52 µL, 0.38 mmol), and 1,2-dichlorethane (1.5 mL). Flash column chromatography (silica gel: 60% EtOAc in hexanes, followed by recrystallization from CH_2Cl_2 and hexanes) afforded the title compound as a white solid (55 mg, 0.16 mmol, 52% yield). mp 209-211 ºC; IR ν_{max}/cm^{-1} (film): 3061, 3027, 2920, 2851, 2230, 1596, 1468, 1383, 1037, 840, 730, 687; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.99 (1H, s), 8.87 (1H, d, *J* = 5.1 Hz), 8.77 (1H, d, *J* = 2.0 Hz), 8.42 (1H, s), 8.19 (1H, s) 8.11 (2H, d, *J* = 7.2 Hz), 7.92 (1H, dd, *J* = 8.0, 2.3 Hz) 7.84 (1H, dd, *J* = 5.1, 1.2 Hz), 7.44-7.56 (3H, m), 7.38 (1H, d, *J* = 8.0 Hz), 2.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.4, 158.9, 155.1, 151.0, 150.8, 148.6, 144.8, 139.1, 136.5, 135.4, 129.6, 129.0, 127.3, 127.2, 123.6, 123.4, 120.3, 119.3, 117.9, 116.1, 24.6; m/z LRMS (ESI + APCI) found $[M+H]^+$ 349.2, $C_{23}H_{17}N_4^+$ requires 349.1.

3,5-Dimethyl-2'-phenyl-[2,4'-bipyridine]-4-carbonitrile (229)



Prepared according to general procedure B (except used 4 equivalents of the cyanopyridine instead of 2 equivalents, 2 equivalents of B_2pin_2 instead of 1 equivalent, and ran the reaction for 48 hours instead of 36) using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (170 mg, 0.30 mmol), 3,5-dimethylisonicotinonitrile (158 mg, 1.20 mmol), B_2Pin_2 (76 mg, 0.30 mmol), NEt_3 (52 μL, 0.38 mmol), and 1,2-dichloroethane (1.5 mL). Flash column chromatography by dissolving in CH_2Cl_2 and dry loading (silica gel, gradient elution: 20% EtOAc in hexanes to 25% EtOAc in hexanes, followed by recrystallization from CH_2Cl_2) afforded the title compound as a white solid (26 mg, 0.05 mmol, 18% yield). mp 156-158 ºC; IR ν_{max}/cm^{-1} (film): 3058, 2919, 2852, 2224, 1596, 1540, 1388, 1219, 765, 694, 530; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (1H, d, J = 4.9 Hz), 8.59 (1H, s), 8.05-8.00 (2H, m), 7.84 (1H, s), 7.51-7.40 (3H, m), 7.34 (1H, dd, J = 5.0, 1.6 Hz), 2.59 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.0, 155.1, 149.9, 148.6, 147.5, 139.1, 135.4, 132.9, 129.3, 128.9, 127.1, 132.2, 122.0, 120.7, 115.0, 18.6, 17.8; m/z LRMS (ESI + APCI) found $[M+H]^+$ 286.2, $C_{19}H_{16}N_3^+$ requires 286.1.

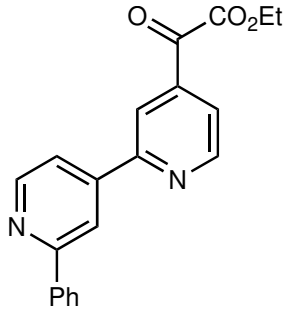
Diethyl (2'-phenyl-[2,4'-bipyridin]-4-yl)phosphonate (230)



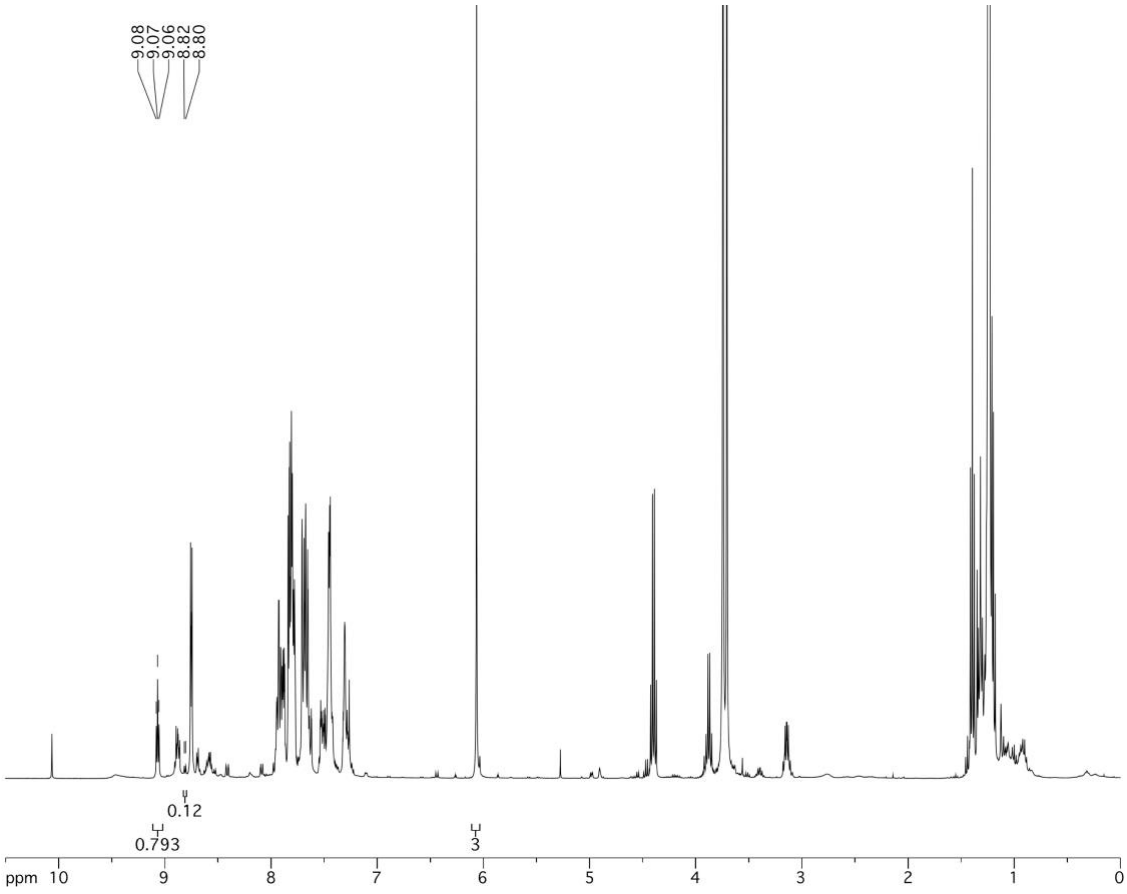
Prepared according to general procedure B (except 2 equivalents of B_2pin_2 and 4 equivalents of diethyl pyridin-4-ylphosphonate). Triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (141 mg, 0.25 mmol), diethyl pyridin-4-ylphosphonate (216 mg, 1.00

mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (44 μL, 0.31 mmol), and 1,2-dichloroethane (1.25 mL). Flash column chromatography (basic alumina: 60% EtOAc in hexanes) followed by a second flash column (silica gel: 75% EtOAc in hexanes) afforded the title compound as colorless oil (26 mg, 0.07 mmol, 28% yield; IR ν_{max}/cm^{-1} (film): 3052, 2981, 2926, 2852, 1589, 1256, 1047, 1010, 967, 776, 694, 558; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, app t, *J* = 5.1 Hz), 8.82 (1H, d, *J* = 5.1), 8.41 (1H, s), 8.22 (1H, d, *J* = 14.1 Hz), 8.10 (2H, d, *J* = 7.3 Hz), 7.86 (1H, dd, *J* = 5.1, 1.3 Hz), 7.69 (1H, dd, *J* = 13.0, 4.7 Hz), 7.48 (3H, m), 4.22 (4H, m), 1.38 (6H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.6, 155.6 (d, *J* = 15.8 Hz), 150.5, 150.5 (d, *J* = 13.1 Hz), 146.4 (d, *J* = 2.2 Hz), 139.3, 139.1 (d, *J* = 185.9), 129.3, 128.9, 127.2, 125.3 (d, *J* = 7.9 Hz), 122.7 (d, *J* = 9.3 Hz), 119.6, 118.2, 63.1 (d, *J* = 5.8 Hz), 16.5 (d, *J* = 6.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 14.38; m/z LRMS (ESI + APCI) found $[M+H]^+$ 369.2, $C_{20}H_{22}N_2O_3P^+$ requires 369.1.

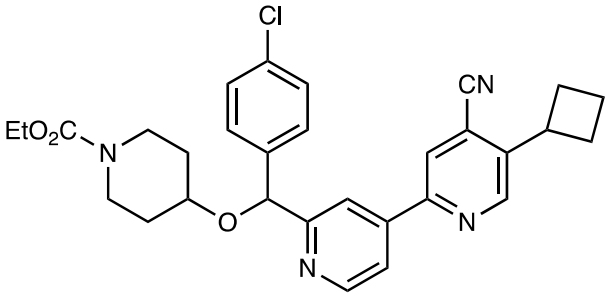
Ethyl 2'-phenyl-[2,4'-bipyridine]-4-carboxylate



Prepared according to general procedure B using triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (226 mg, 0.40 mmol), ethyl isonicotinate (120 μL, 0.80 mmol), B_2pin_2 (102 mg, 0.40 mmol), NEt_3 (70 μL, 0.50 mmol), and 1,2-dichloroethane (2.0 mL). Crude ^1H NMR spectrum of reaction suggests that the product was made in ca. 12% yield (8.81 ppm, 1H, d, *J* = 5.2 Hz).



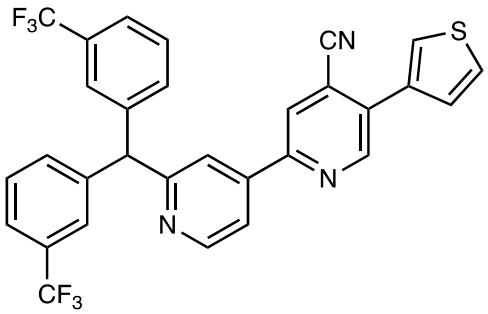
Ethyl 4-(2-(4-chlorophenyl)-2-(4-cyano-5-cyclobutyl-[2,4'-bipyridin]-2'-yl)ethyl)piperidine-1-carboxylate (231)



Prepared according to general procedure B using (2-((4-chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (196 mg, 0.25 mmol), 3-cyclobutylisonicotinonitrile (79 mg, 0.50 mmol), B_2Pin_2 (64 mg, 0.25 mmol), NEt_3 (44 μL, 0.31 mmol), and 1,2-dichloroethane (1.25 mL). Flash column chromatography (silica gel: 80% Et_2O in hexanes, then silica gel: 65% EtOAc in hexanes, then recrystallized from CH_2Cl_2 and hexanes) afforded the title compound as a colorless

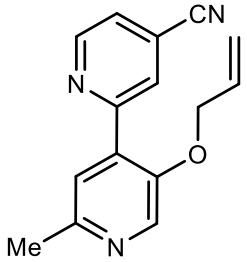
oil (37 mg, 0.07 mmol, 28% yield). IR ν_{max}/cm^{-1} (film): 2979, 2944, 2866, 2233, 1689, 1600, 1590, 1488, 1433, 1227, 1085, 728; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.87 (1H, s), 8.63, (1H, d, *J* = 5.0 Hz), 8.08 (1H, s), 7.89 (1H, s), 7.74 (1H, m), 7.42 (2H, *J* = 7.4 Hz), 7.29 (2H, d, *J* = 7.6 Hz), 5.70 (1H, s), 4.11 (2H, q, *J* = 7.0 Hz), 3.62-3.96 (4H, m), 3.10-3.24 (2H, m), 2.53-2.64 (2H, m), 2.34 (2H, qn, *J* = 9.6 Hz), 2.18 (1H, sext, *J* = 9.5 Hz), 1.93-2.04 (1H, m), 1.78-193 (2H, m), 1.59-1.78 (2H, m), 1.24 (3H, t, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2, 155.6, 153.2, 150.0, 149.6, 145.7, 142.7, 140.0, 133.7, 128.8, 128.3, 122.6, 120.2, 119.8, 117.7, 115.9, 81.1, 73.0, 61.4, 41.3 (rot), 41.2, 36.8, 31.3 (rot), 31.2, 29.0, 18.7, 14.8; m/z LRMS (ESI + APCI) found $[M+H]^+$ 531.3, $C_{30}H_{32}ClN_4O_3^+$ requires 531.2.

2'-(Bis(3-(trifluoromethyl)phenyl)methyl)-5-(thiophen-3-yl)-[2,4'-bipyridine]-4-carbonitrile (232)



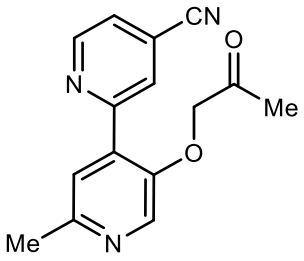
Prepared according to general procedure B using 2-(bis(3-(trifluoromethyl)phenyl)methyl)-4-(triphenyl-l4-phosphaneyl)pyridine trifluoromethanesulfonate (119 mg, 0.15 mmol), 3-(thiophen-3-yl)isonicotinonitrile (56 mg, 0.30 mmol), B_2Pin_2 (38 mg, 0.15 mmol), NEt_3 (26 μL, 0.19 mmol), and 1,2-dichloroethane (0.75 mL). Flash column chromatography (silica gel: 2% Et_2O in toluene) afforded the title compound as a white solid (72 mg, 0.13 mmol, 85% yield). mp 131-133 ºC; IR ν_{max}/cm^{-1} (film): 3059, 2924, 2852, 2232, 1596, 1528, 1469, 1449, 1320, 1159, 1118, 1074, 790, 700, 532; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.02 (1H, s), 8.80 (1H, d, *J* = 5.1 Hz), 8.01 (1H, s), 7.86 (2H, m), 7.80 (1H, dd, *J* = 5.1, 1.6 Hz), 7.40-7.58 (10H, m), 5.84 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.5, 153.3, 151.1, 150.8, 145.2, 142.8, 134.4, 133.1, 132.8, 131.1 (q, *J* = 32.3 Hz), 129.3, 127.7, 127.1, 126.4, 126.1 (q, *J* = 3.9 Hz), 124.2 (q, *J* = 272.7 Hz), 124.1 (q, *J* = 3.9 Hz), 123.6, 121.0, 119.3, 118.8, 116.7, 58.9; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –62.54; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 566.2, $C_{30}H_{18}F_6N_3S^+$ requires 566.1.

5'-(Allyloxy)-2'-methyl-[2,4'-bipyridine]-4-carbonitrile (235)



Prepared according to general procedure B using (5-(allyloxy)-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (280 mg, 0.50 mmol), isonicotinonitrile (104 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 µL, 1.25 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography (silica gel: 25% EtOAc in hexanes) afforded the title compound as a yellow solid (40.1 mg, 0.16 mmol, 32% yield). mp 157-160 ºC; IR ν_{max}/cm^{-1} (film): 3071, 3032, 2922, 2851, 2238, 1599, 1540, 1423, 1400, 1354, 1282, 1195, 894, 856, 786; ^1H NMR (400 MHz, $CDCl_3$) δ: 12.98 (1H, s), 8.77 (1H, dd, *J* = 5.2, 1.0 Hz), 8.22 (1H, t, *J* = 1.2 Hz), 7.58 (1H, dd, *J* = 5.2, 1.4 Hz), 7.26 (1H, s), 6.15 (1H, ddt, *J* = 16.8, 10.1, 6.6 Hz), 5.19 (1H, dq, *J* = 17.2, 1.7 Hz), 5.10 (1H, dq, *J* = 10.1, 1.6 Hz), 3.72 (2H, dt, *J* = 6.6, 1.6 Hz), 2.56 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.60, 151.14, 149.98, 147.56, 147.22, 134.94, 123.77, 122.61, 122.19, 121.96, 116.15, 115.91, 115.65, 37.28, 23.46; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 252.2, $C_{15}H_{14}N_3O^+$ requires 252.1.

2'-Methyl-5'-(2-oxopropoxy)-[2,4'-bipyridine]-4-carbonitrile (238)



Prepared according to general procedure B using 1-((6-methyl-4-(triphenyl-l4-phosphaneyl)pyridin-3-yl)oxy)propan-2-one trifluoromethanesulfonate (287 mg, 0.50 mmol), isonicotinonitrile (105 mg, 1.00 mmol), B_2Pin_2 (127 mg, 0.50 mmol), NEt_3 (87 µL, 1.25 mmol), and 1,2-dichloroethane (2.5 mL). Flash column chromatography (silica gel: 85% EtOAc in hexanes) afforded the title compound as a tan solid (52 mg, 0.19 mmol, 39% yield). mp 142-148 ºC; IR ν_{max}/cm^{-1} (film): 3448, 3043, 2922, 2900, 2234, 1732, 1591, 1492, 1255, 1178, 1080, 1043,

865, 644; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, d, *J* = 4.9 Hz), 8.45 (1H, s), 8.17 (1H, s), 7.73 (1H, s), 7.53 (1H, d, *J* = 4.9H z), 4.80 (2H, s), 2.58 (3H, s), 2.26 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.4, 154.5, 152.9, 150.7, 149.5, 134.8, 134.3, 127.5, 124.5, 124.0, 120.9, 116.6, 73.7, 26.5, 23.7; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 268.1, $C_{15}H_{14}N_3O_2^+$ requires 268.1.

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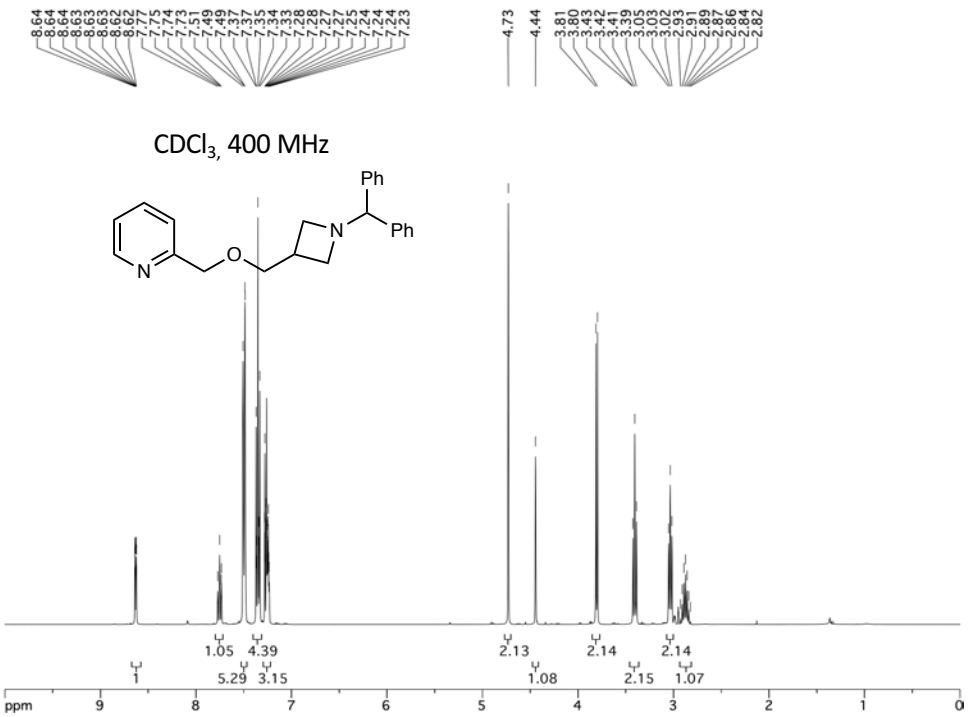
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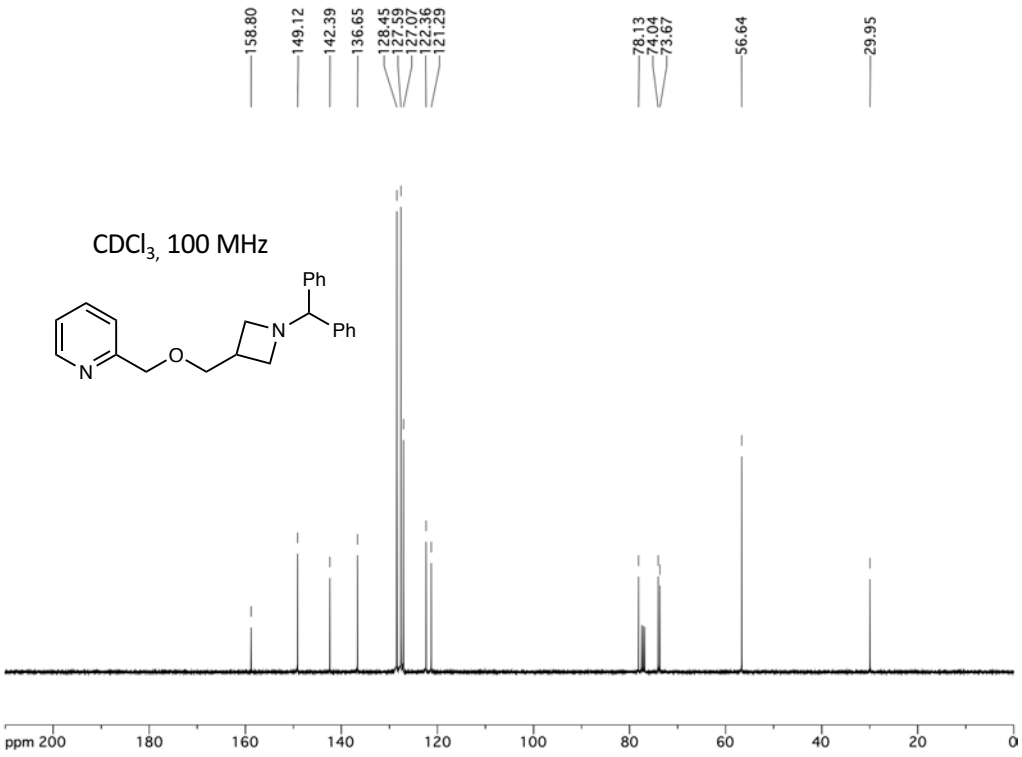
8.64
8.64
8.63
8.63
8.63
8.63
8.62
8.62
7.77
7.75
7.74
7.73
7.51
7.49
7.49
7.37
7.37
7.35
7.34
7.33
7.28
7.27
7.27
7.25
7.24
7.24
7.24
7.23
4.73
4.44
3.81
3.80
3.43
3.42
3.41
3.39
3.05
3.03
3.02
2.93
2.91
2.89
2.87
2.86
2.84
2.82
CDCl3, 400 MHz
Ph
Ph
N
O
N
1.05
4.39
2.13
2.14
2.14
1
5.29
3.15
1.08
2.15
1.07
ppm
9
8
7
6
5
4
3
2
1
0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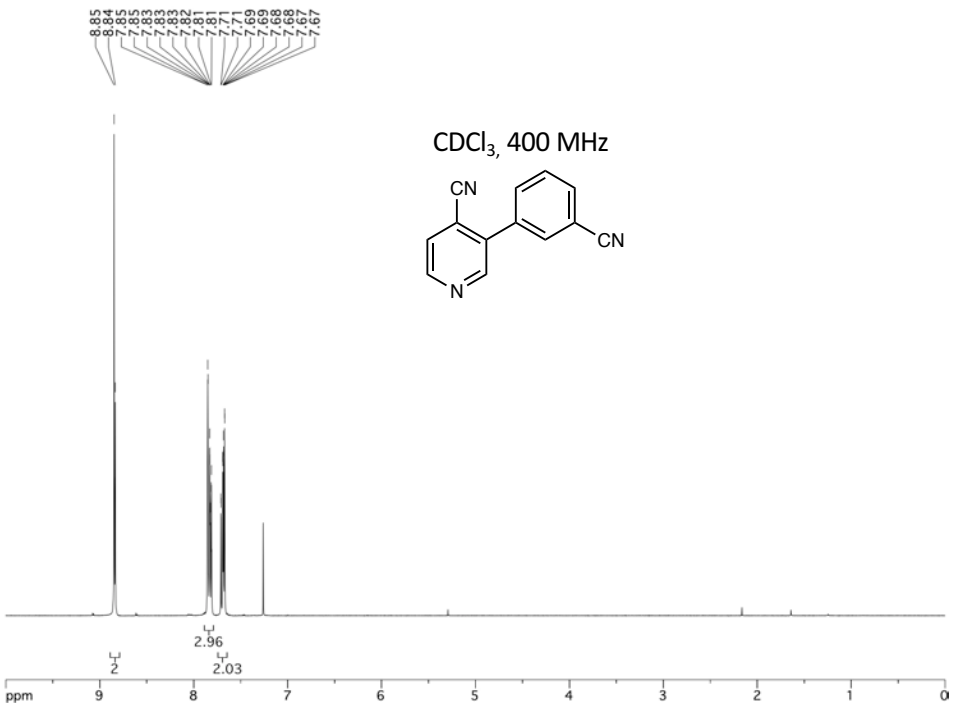
149.12
142.39
136.65
128.45
127.59
127.07
122.36
121.29
78.13
74.04
73.67
56.64
29.95
CDCl3, 100 MHz
Ph
Ph
N
O
N
ppm 200
180
160
140
120
100
80
60
40
20
0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8.84
7.85
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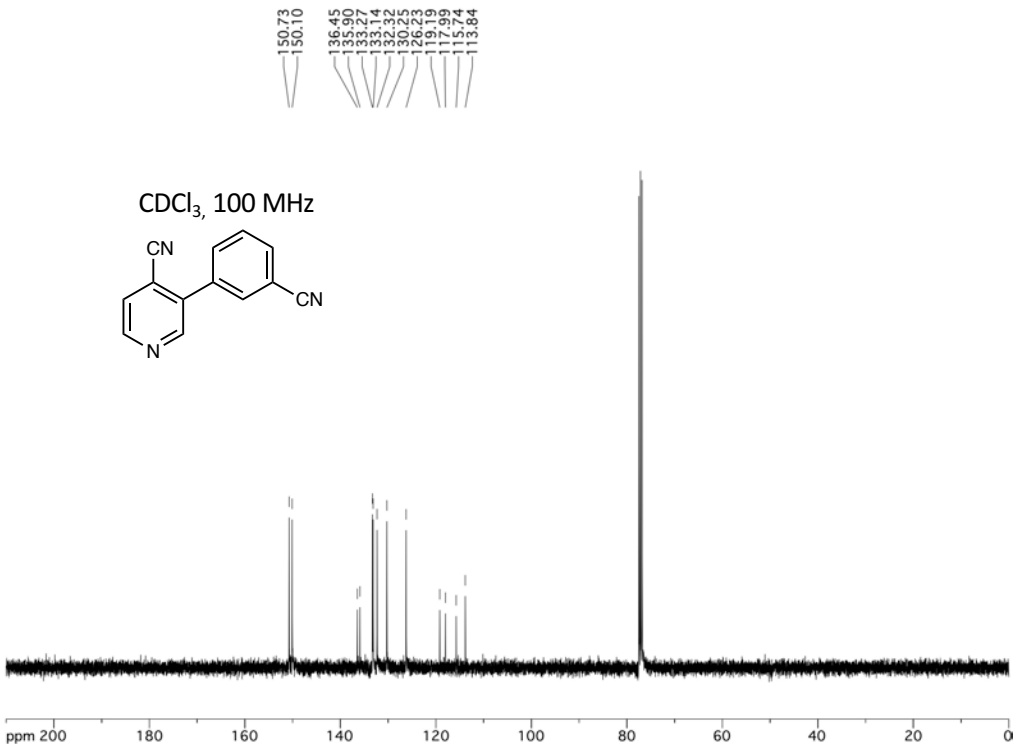
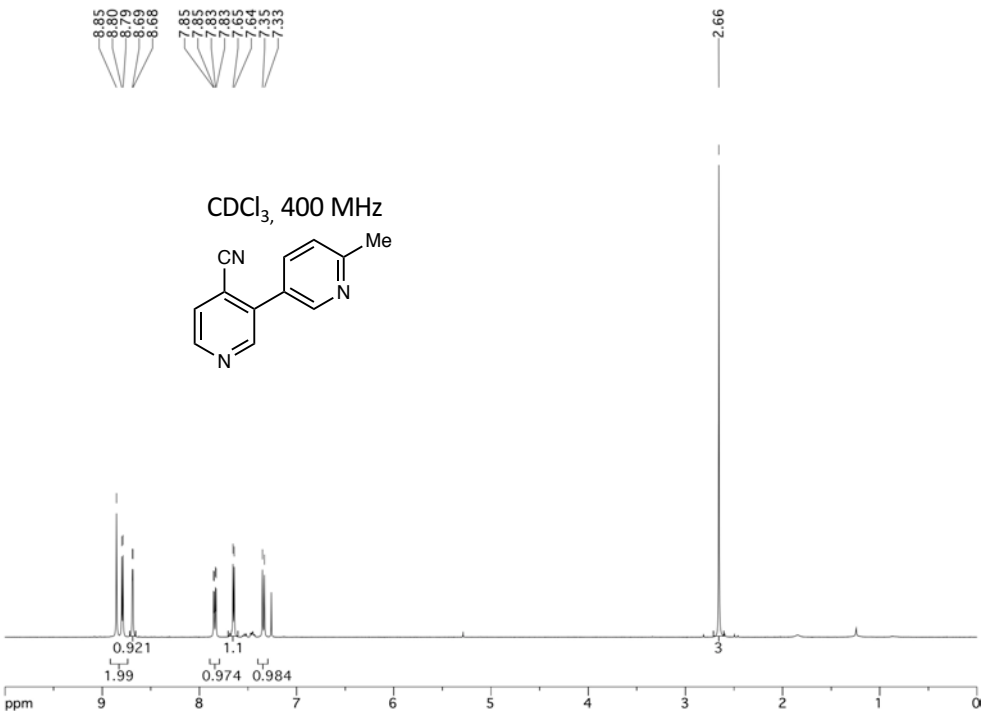
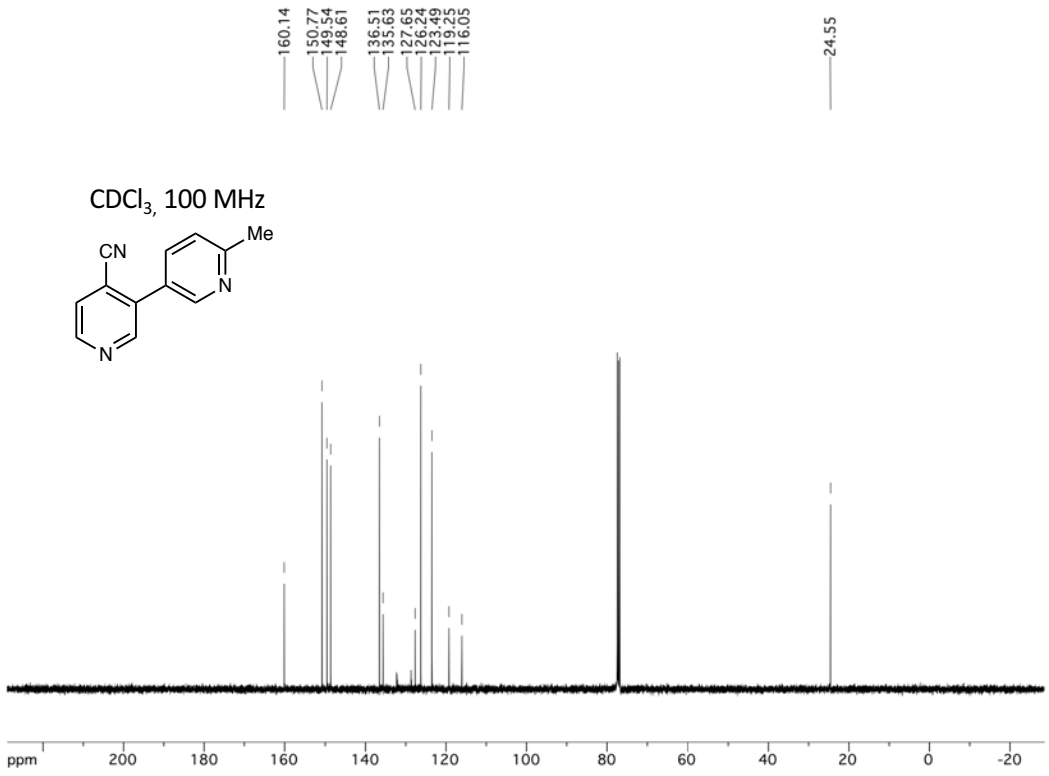
7.83
7.83
7.82
7.81
7.81
7.71
7.71
7.69
7.69
7.68
7.68
7.67
7.67
CDCl3, 400 MHz
CN
CN
N
2.96
2
2.03
ppm
9
8
7
6
5
4
3
2
1
0


150.73
150.10
136.45
135.90
133.27
133.14
132.32
130.25
126.23
119.19
117.99
115.74
113.84
CDCl3, 100 MHz
CN
CN
N
ppm 200
180
160
140
120
100
80
60
40
20
0


8.85
8.80
8.79
8.69
8.68
7.85
7.85
7.83
7.83
7.65
7.64
7.35
7.33
2.66
CDCl3, 400 MHz
CN
Me
N
N
0.921
1.1
3
1.99
0.974
0.984
ppm
9
8
7
6
5
4
3
2
1
0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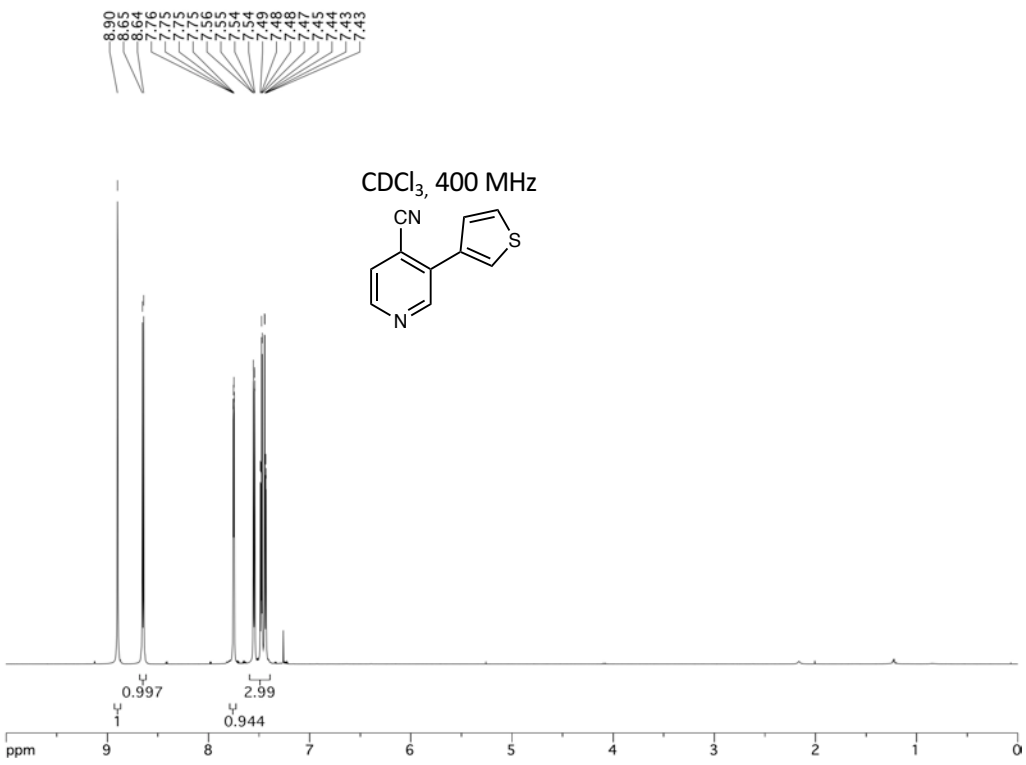
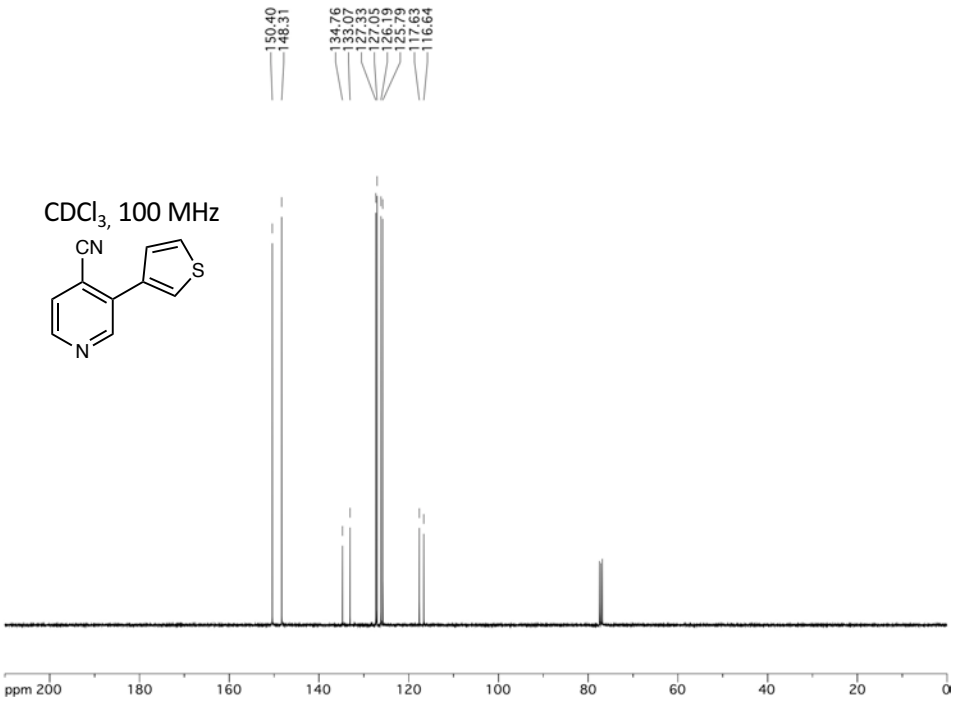
150.77
149.54
148.61
136.51
135.63
127.65
126.24
123.49
119.25
116.05
24.55
CDCl3, 100 MHz
CN
Me
N
N
ppm
200
180
160
140
120
100
80
60
40
20
0
-20


8.90
8.65
8.64
7.76
7.75
7.75
7.75
7.56
7.55
7.54
7.54
7.49
7.48
7.48
7.47
7.45
7.44
7.43
7.43
CDCl3, 400 MHz
CN
S
N
0.997
2.99
1
0.944
ppm
9
8
7
6
5
4
3
2
1
0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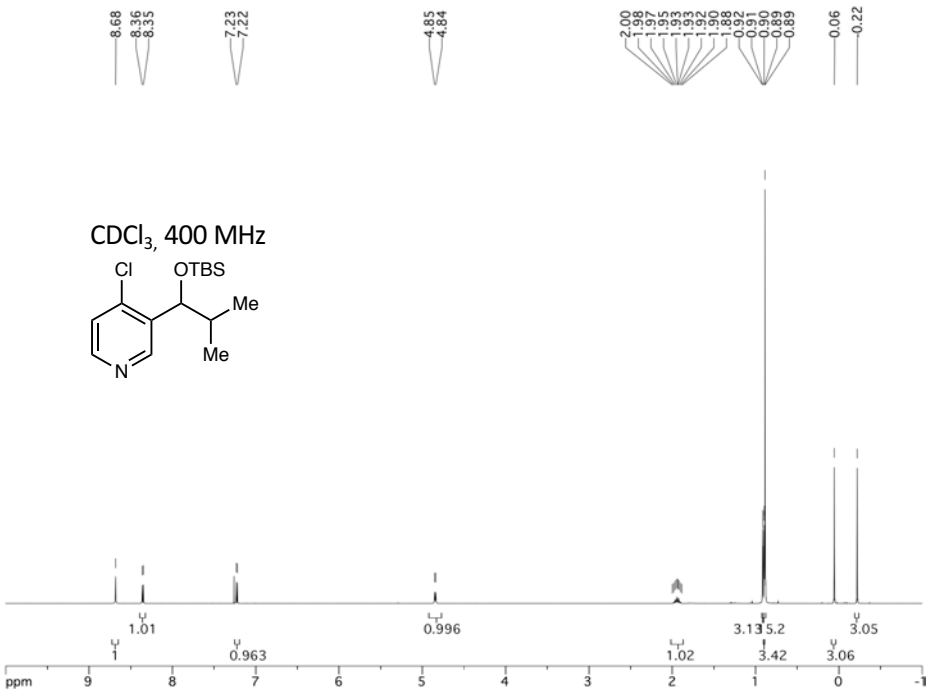
148.31
134.76
133.07
127.33
127.05
126.19
125.79
117.63
116.64
CDCl3, 100 MHz
CN
S
N
ppm 200
180
160
140
120
100
80
60
40
20
0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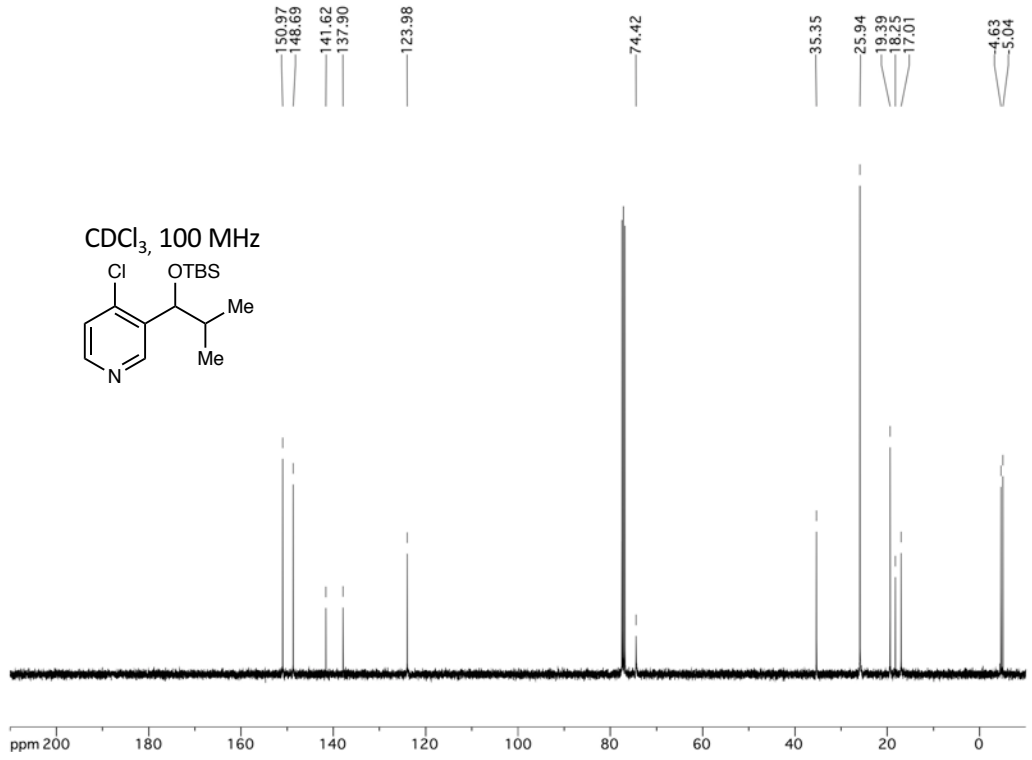
7.23
7.22
4.85
4.84
2.00
1.98
1.97
1.95
1.93
1.93
1.92
1.90
1.88
0.92
0.91
0.90
0.89
0.89
0.06
0.22
CDCl3, 400 MHz
Cl
OTBS
Me
Me
N
1.01
0.996
3.13
5.2
3.05
1
0.963
1.02
3.42
3.06
ppm
9
8
7
6
5
4
3
2
1
0
-1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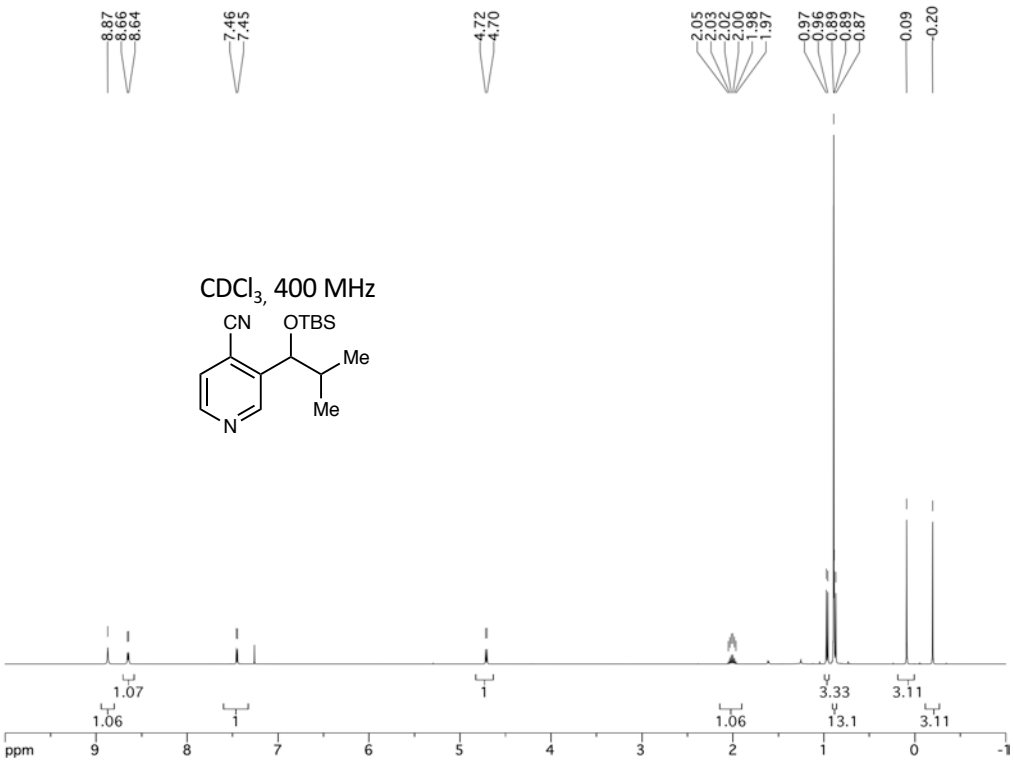
141.62
137.90
123.98
74.42
35.35
25.94
19.39
18.25
17.01
4.63
-5.04
CDCl3, 100 MHz
Cl
OTBS
Me
Me
N
ppm 200
180
160
140
120
100
80
60
40
20
0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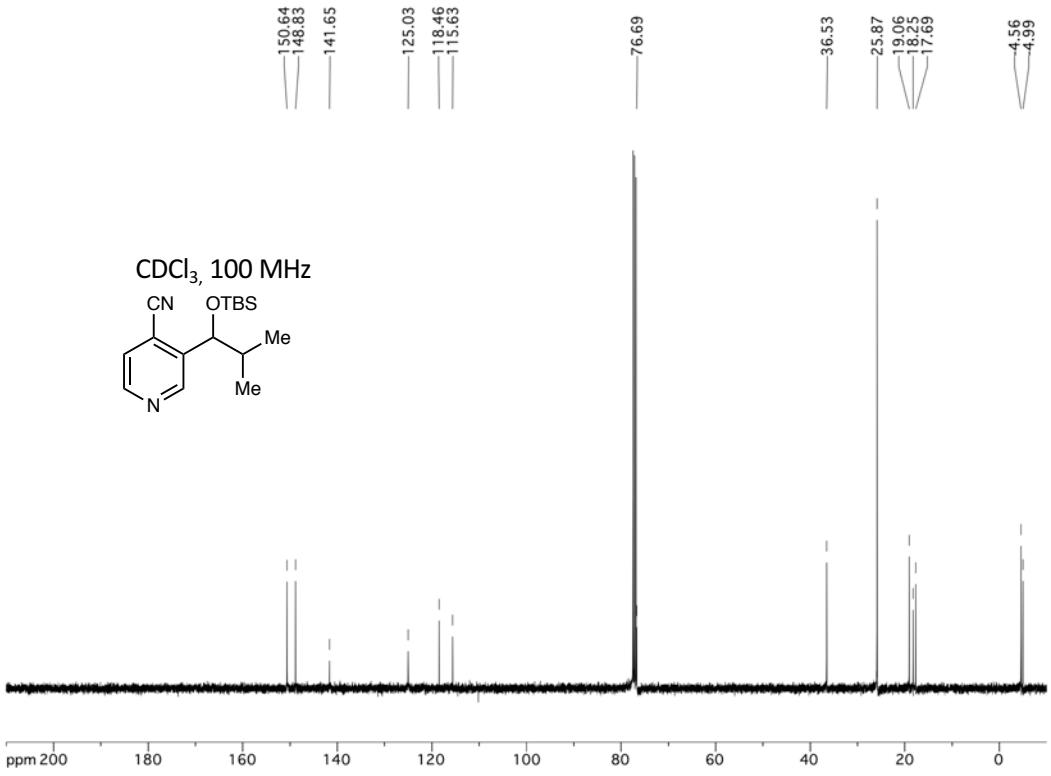
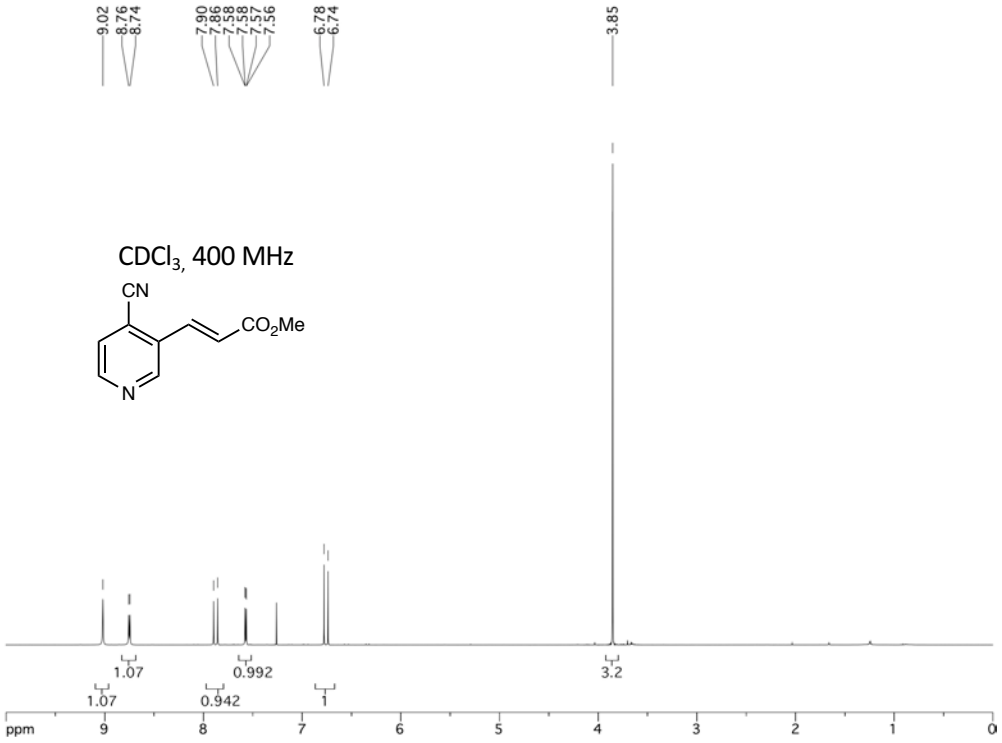
8.64
7.46
7.45
4.72
4.70
2.05
2.03
2.02
2.00
1.98
1.97
0.97
0.96
0.89
0.89
0.87
0.09
0.20
CDCl3, 400 MHz
CN
OTBS
Me
Me
N
1.07
1
3.33
3.11
1.06
1
1.06
13.1
3.11
ppm
9
8
7
6
5
4
3
2
1
0
-1


150.64
148.83
141.65
125.03
118.46
115.63
76.69
36.53
25.87
19.06
18.25
17.69
4.56
4.99
CDCl3, 100 MHz
CN
OTBS
Me
Me
N
ppm 200
180
160
140
120
100
80
60
40
20
0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8.76
8.74
7.90
7.86
7.58
7.58
7.57
7.56
6.78
6.74
3.85
CDCl3, 400 MHz
CN
CO2Me
N
1.07
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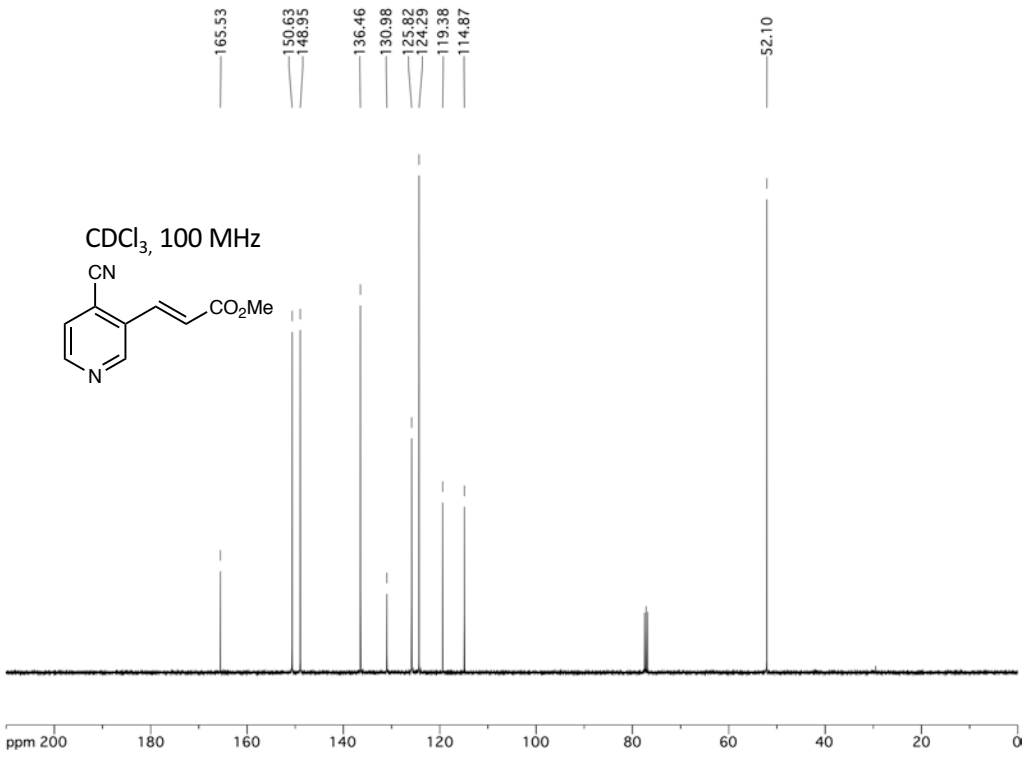
3.2
1.07
0.942
1
ppm
9
8
7
6
5
4
3
2
1
0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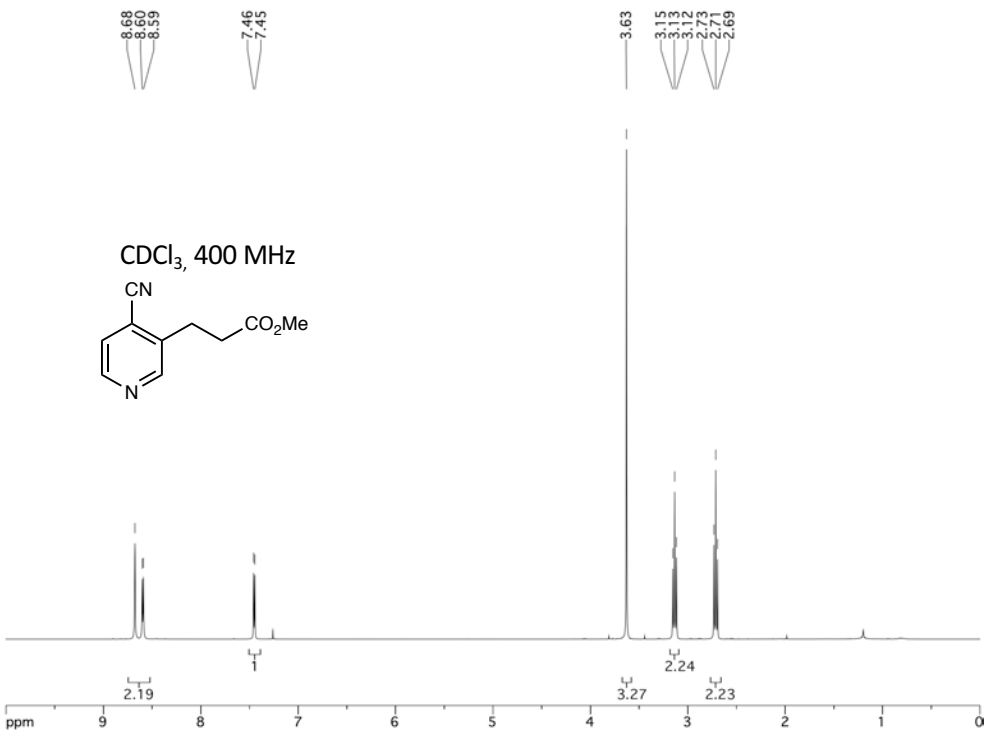
150.63
148.95
136.46
130.98
125.82
124.29
119.38
114.87
52.10
CDCl3, 100 MHz
CN
CO2Me
N
ppm 200
180
160
140
120
100
80
60
40
20
0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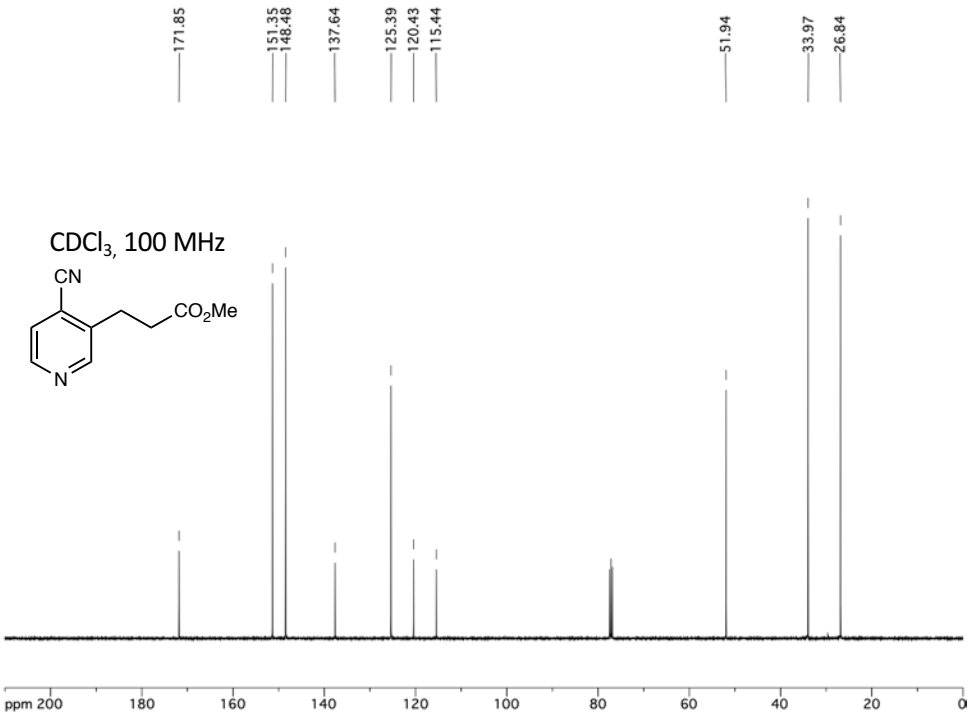
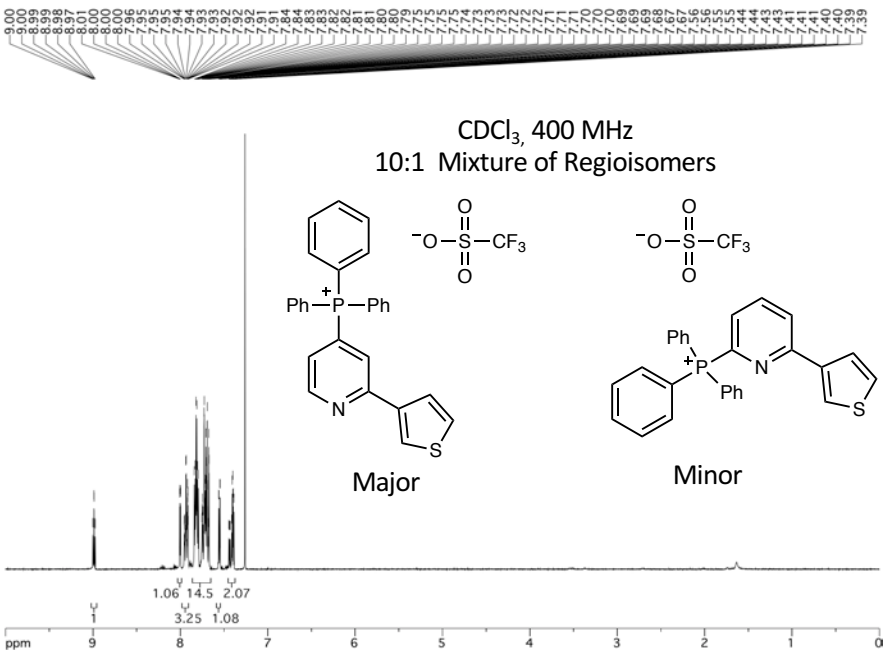
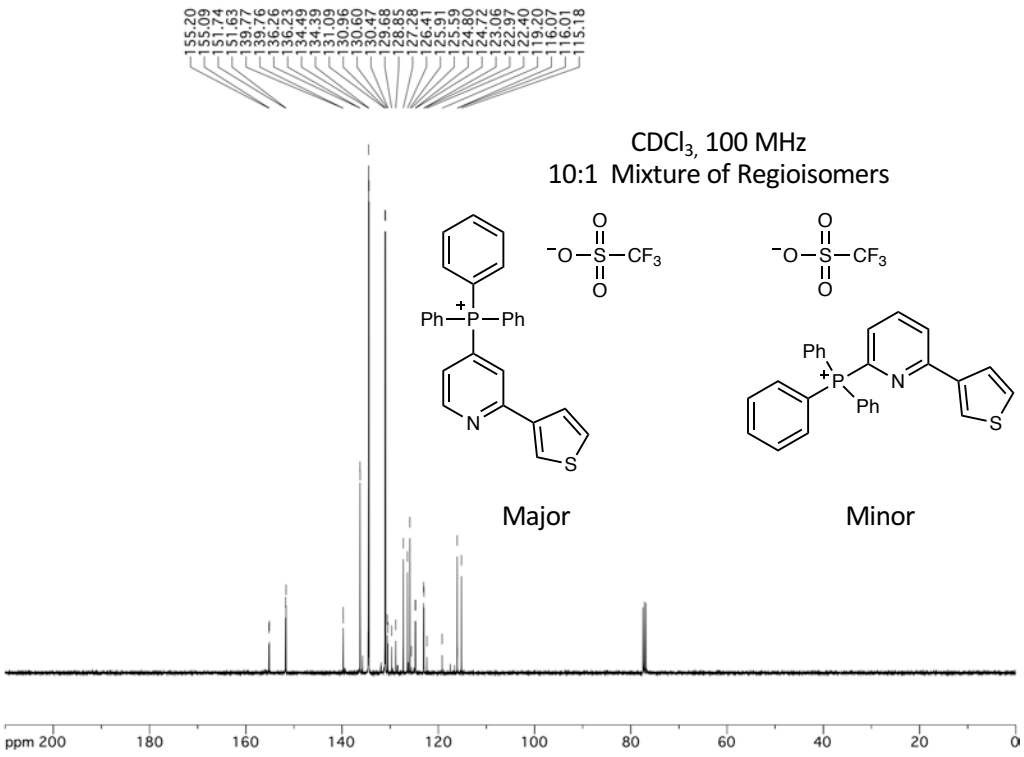
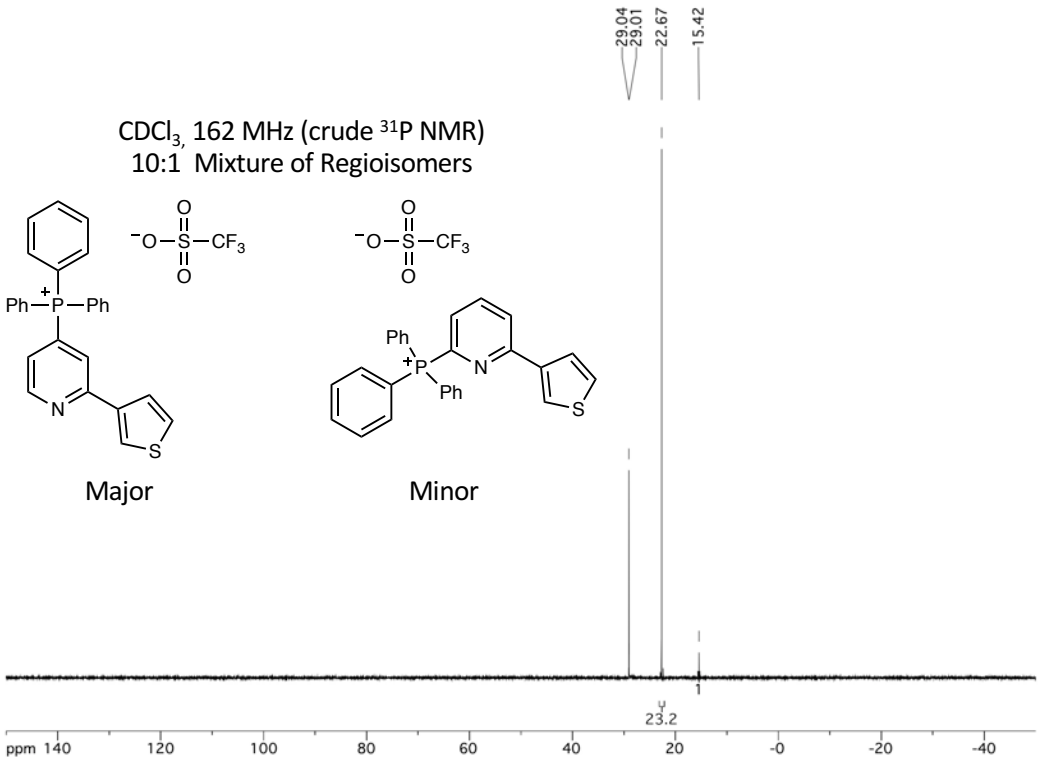
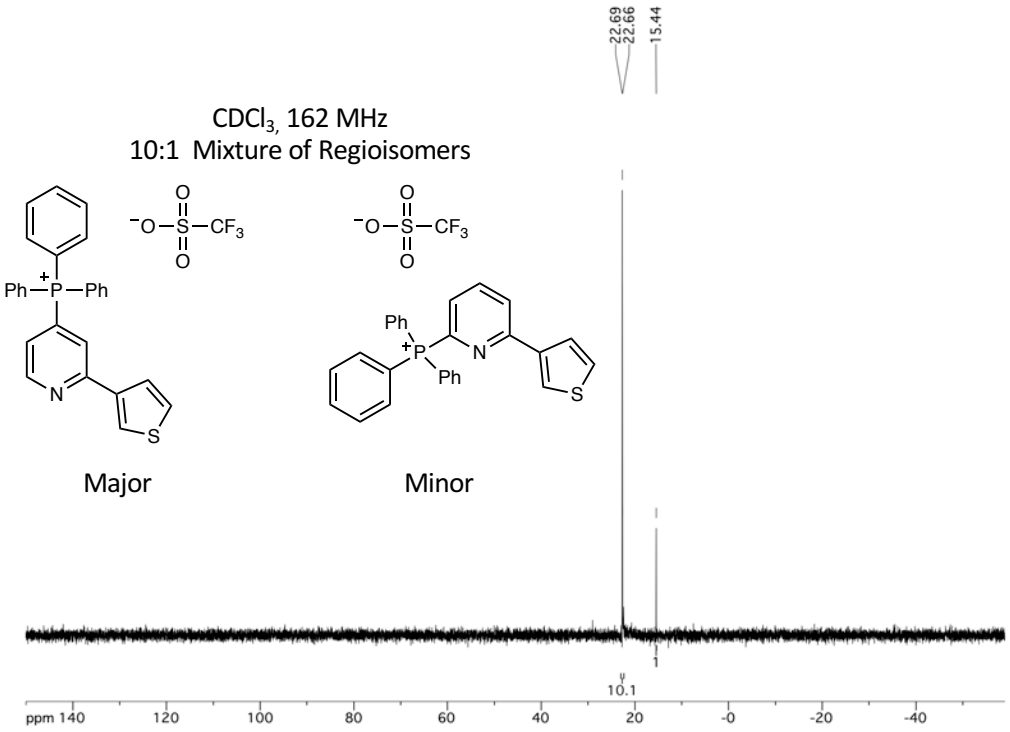
8.60
8.59
7.46
7.45
3.63
3.15
3.13
3.12
2.73
2.71
2.69
CDCl3, 400 MHz
CN
CO2Me
N
2.19
1
3.27
2.24
2.23
ppm
9
8
7
6
5
4
3
2
1
0

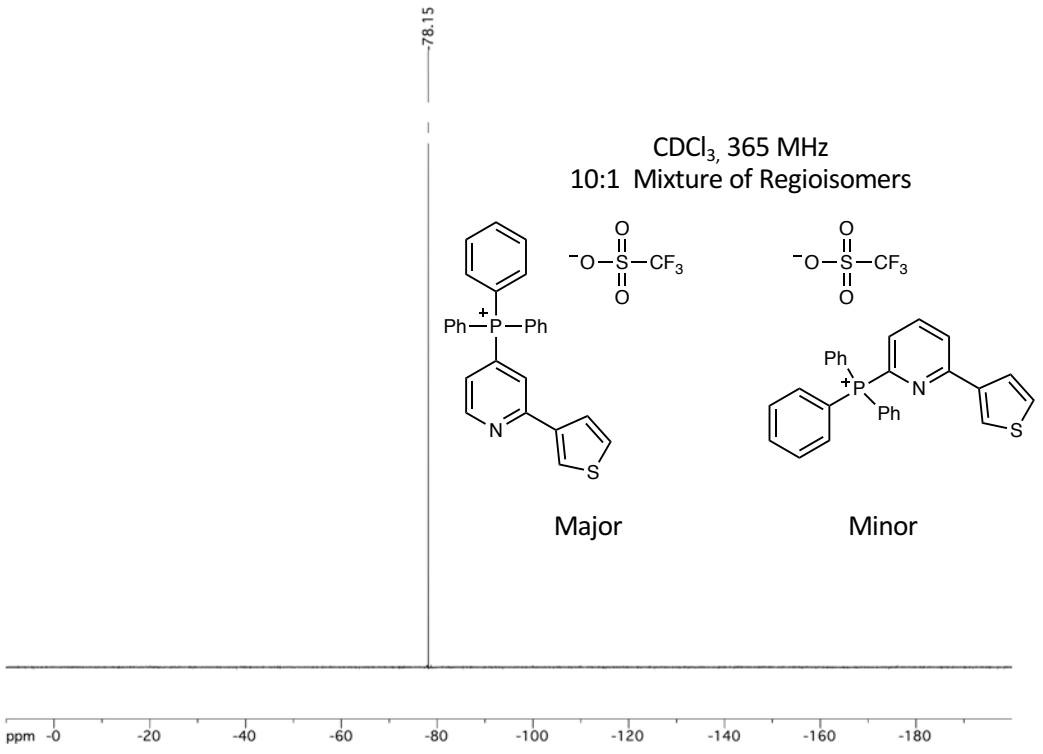

171.85
151.35
148.48
137.64
125.39
120.43
115.44
51.94
33.97
26.84
CDCl3, 100 MHz
CN
CO2Me
N
ppm 200
180
160
140
120
100
80
60
40
20
0

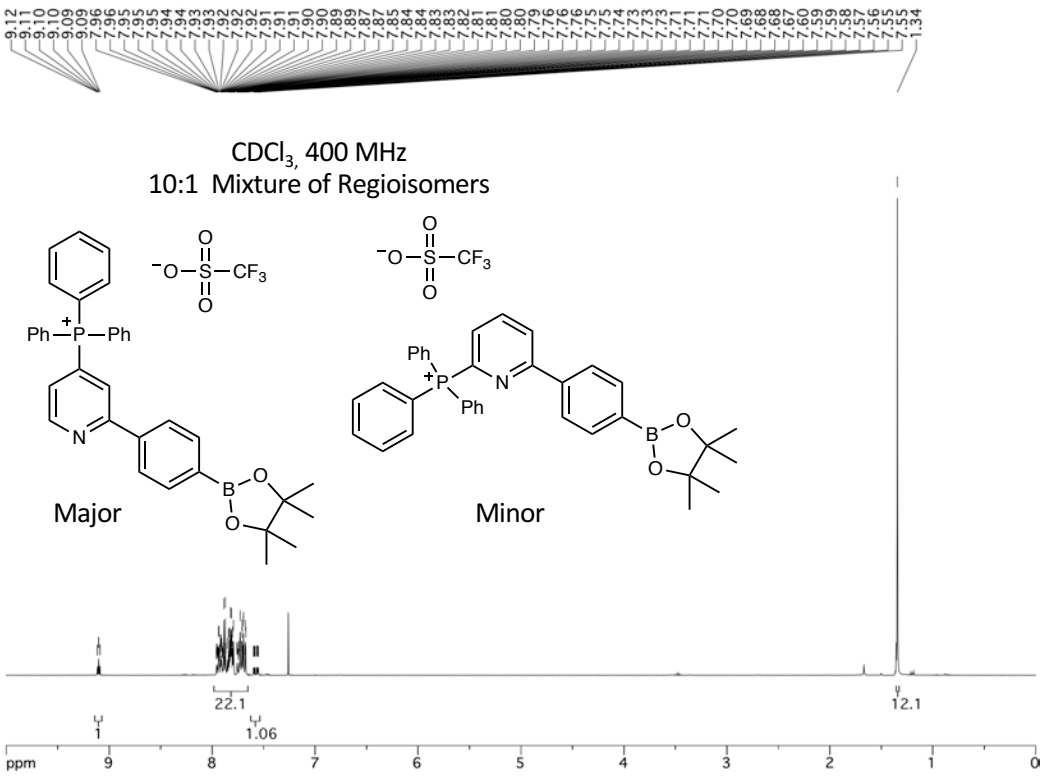

CDCl3, 400 MHz
10:1 Mixture of Regioisomers
Major
Minor
1.06 14.5 2.07
1 3.25 1.08
ppm

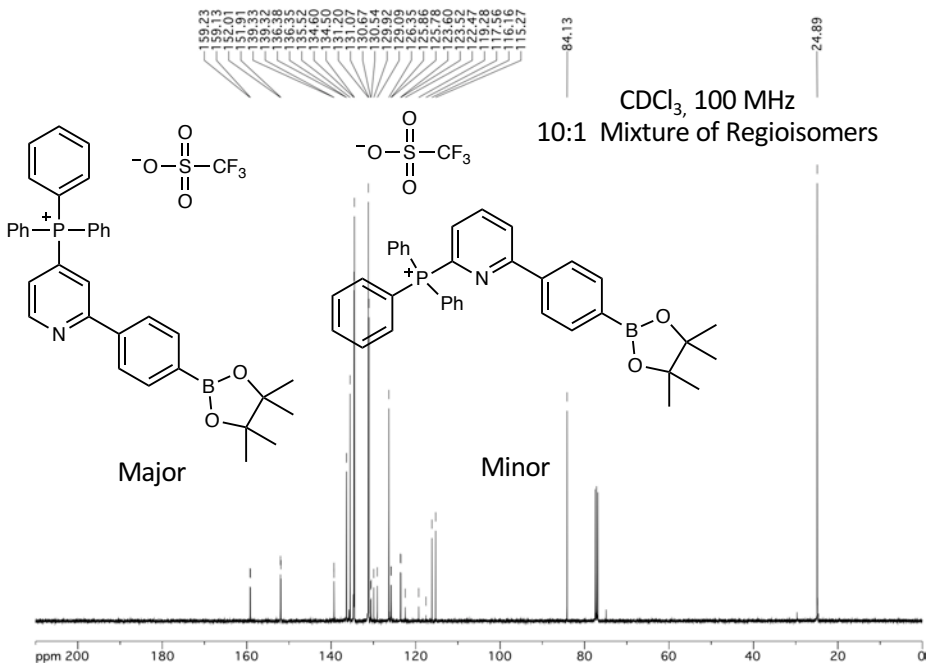

155.20
155.09
151.74
151.63
139.77
139.76
136.26
136.23
134.49
134.39
131.09
130.96
130.60
130.47
129.68
128.85
127.28
126.41
125.91
125.59
124.80
124.72
123.06
122.97
122.40
119.20
116.07
116.01
115.18
CDCl3, 100 MHz
10:1 Mixture of Regioisomers
Major
Minor
ppm 200
180
160
140
120
100
80
60
40
20
0

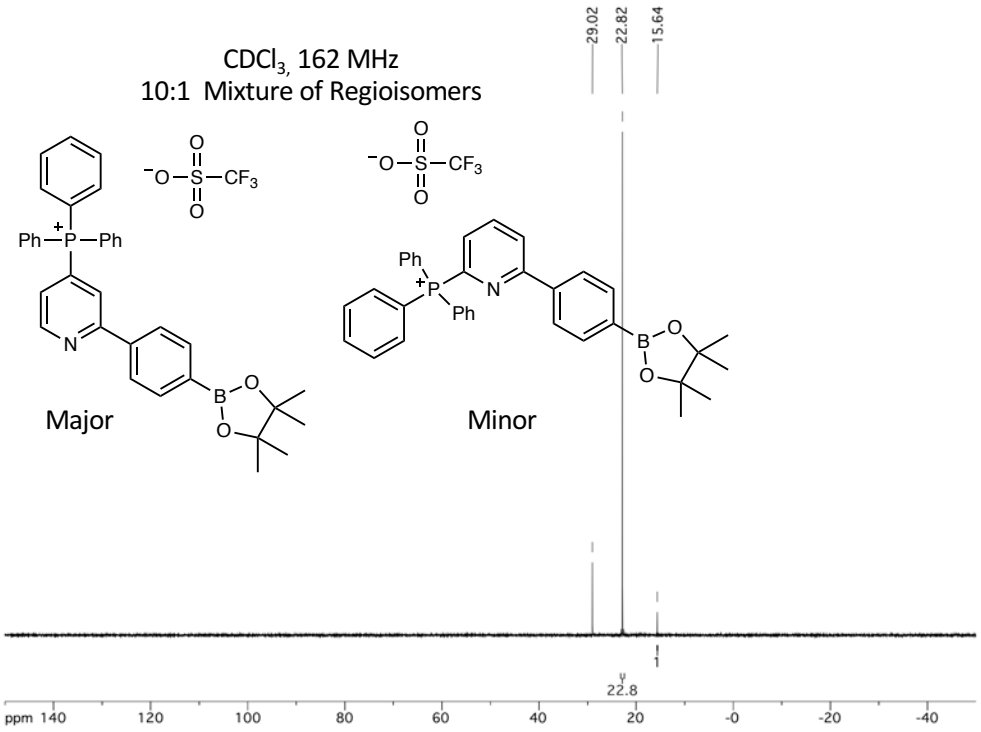

29.04
29.01
22.67
15.42
CDCl3, 162 MHz (crude 31P NMR)
10:1 Mixture of Regioisomers
Major
Minor
23.2
ppm 140
120
100
80
60
40
20
-0
-20
-40

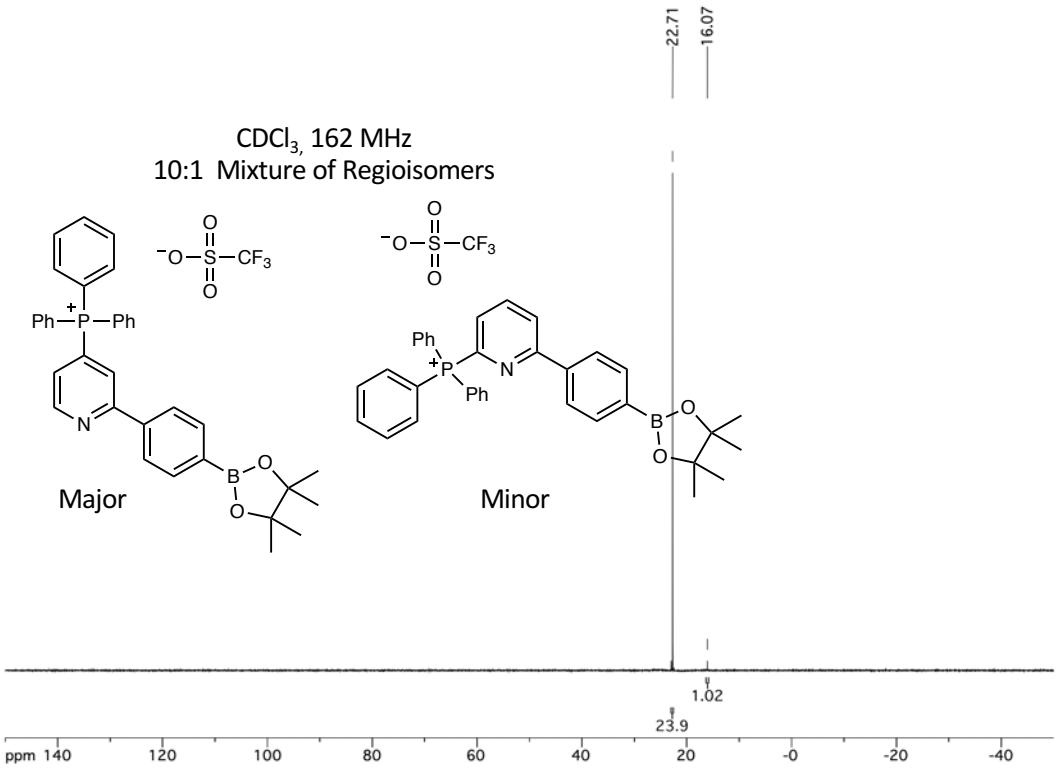

22.69
22.66
15.44
CDCl3, 162 MHz
10:1 Mixture of Regioisomers
Major
Minor
10.1
ppm 140
120
100
80
60
40
20
-0
-20
-40

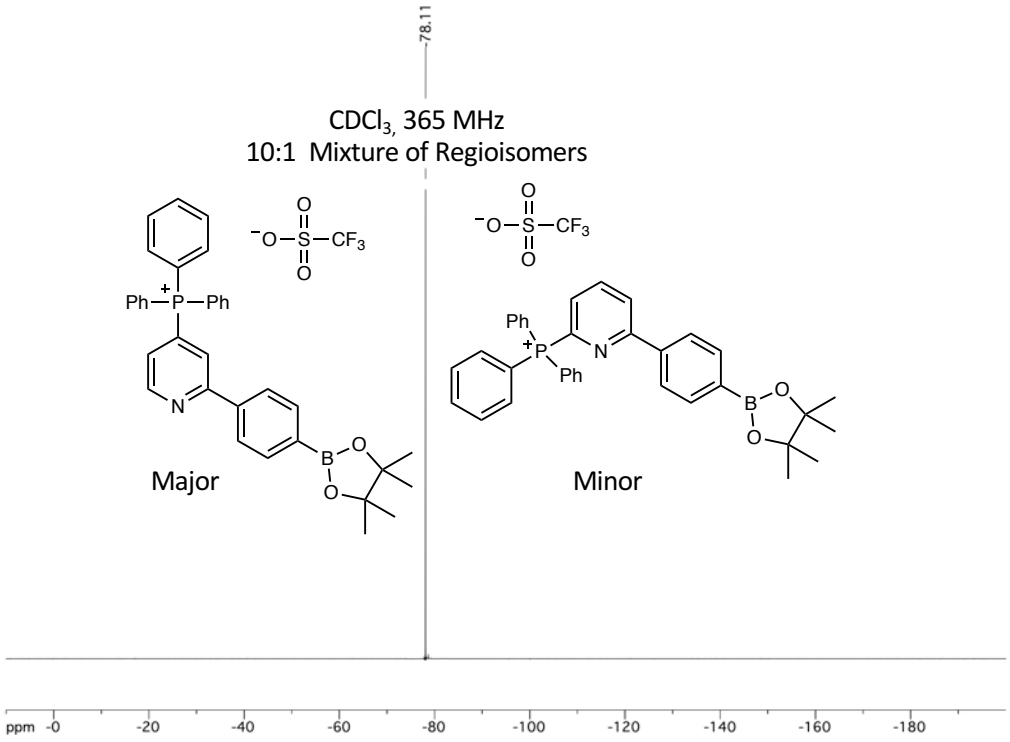

-78.15
CDCl3, 365 MHz
10:1 Mixture of Regioisomers
Major
Minor
ppm -0 -20 -40 -60 -80 -100 -120 -140 -160 -180

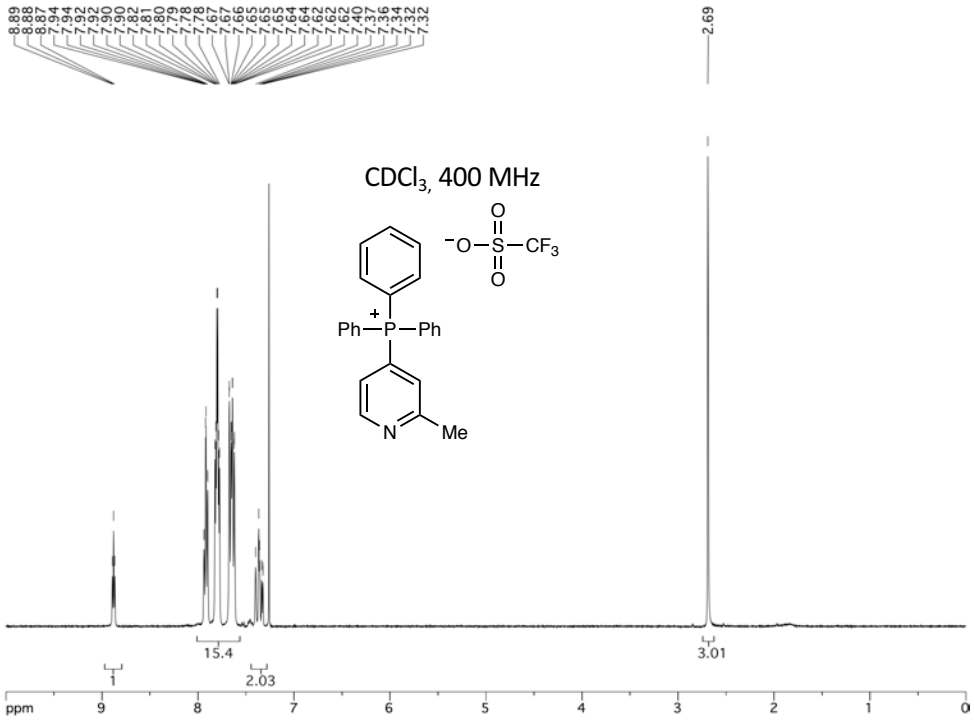

CDCl3, 400 MHz
10:1 Mixture of Regioisomers
Major
Minor
22.1
1.06
1
12.1
ppm

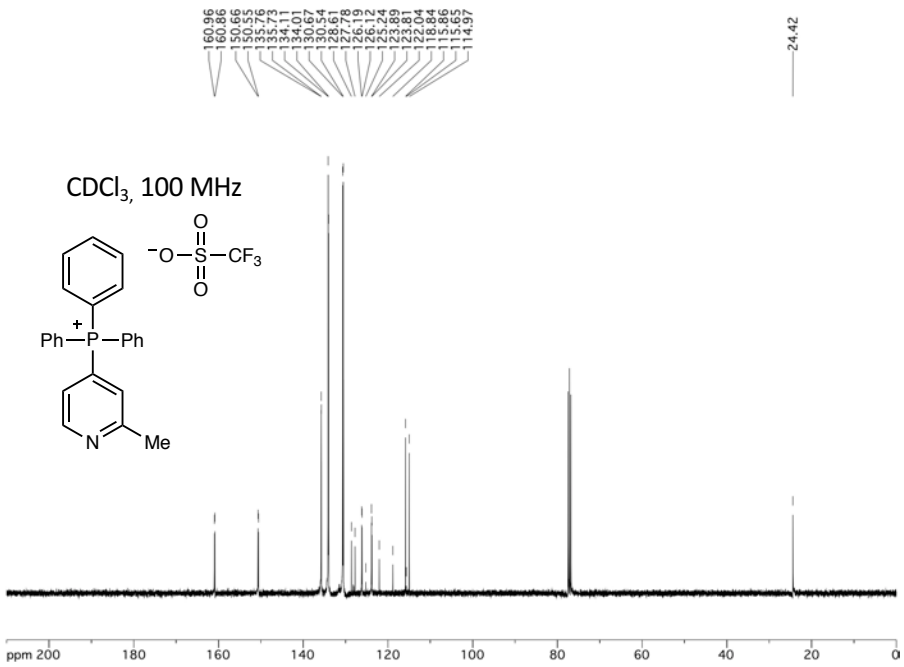

159.23
159.13
152.01
151.91
139.33
139.32
136.38
136.35
135.32
134.60
134.50
131.20
131.07
130.67
130.54
129.92
129.09
126.35
125.86
125.78
123.60
123.52
122.47
122.38
17.56
16.16
15.27
84.13
24.89
CDCl3, 100 MHz
10:1 Mixture of Regioisomers
Major
Minor
ppm 200
180
160
140
120
100
80
60
40
20
0


CDCl3, 162 MHz
10:1 Mixture of Regioisomers
29.02
22.82
15.64
Major
Minor
22.8
ppm 140
120
100
80
60
40
20
-0
-20
-40

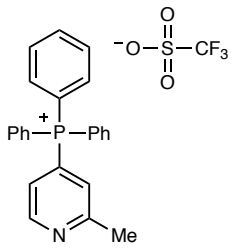

22.71
16.07
CDCl3, 162 MHz
10:1 Mixture of Regioisomers
Major
Minor
1.02
23.9
ppm 140
120
100
80
60
40
20
-0
-20
-40

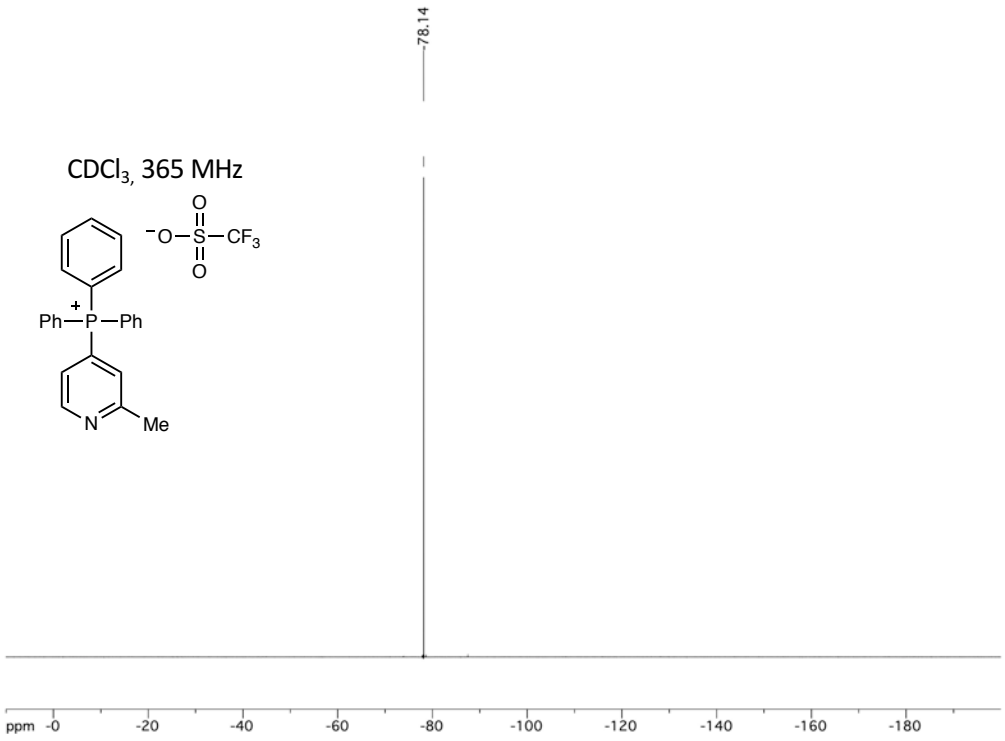

-78.11
CDCl3, 365 MHz
10:1 Mixture of Regioisomers
Major
Minor
ppm -0 -20 -40 -60 -80 -100 -120 -140 -160 -180

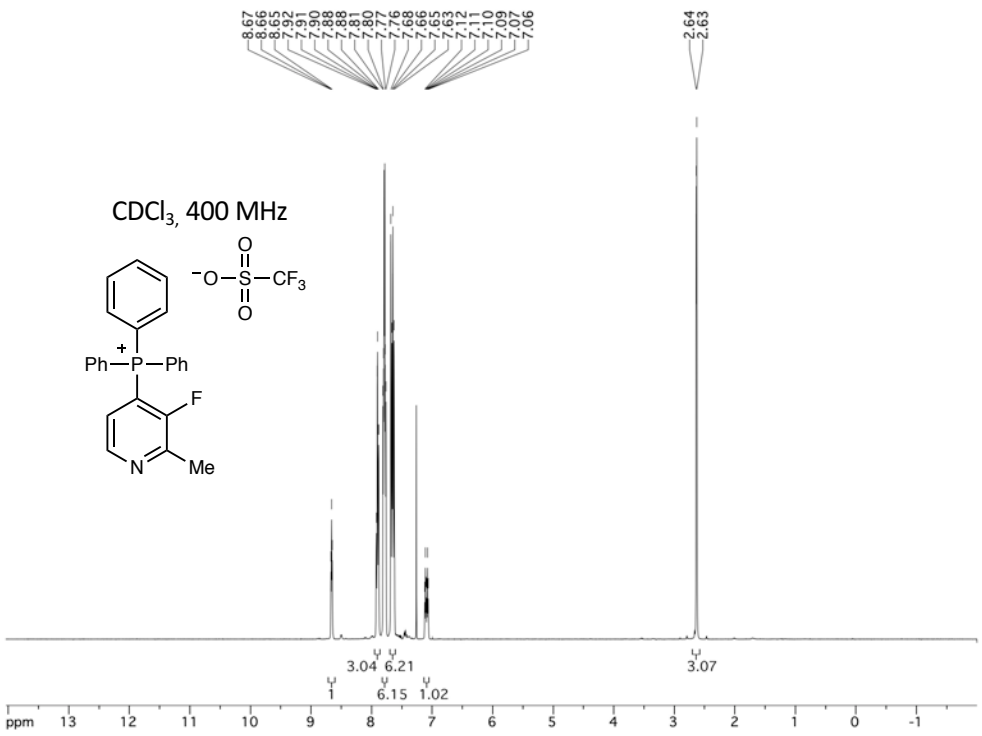

8.89
8.88
8.87
7.94
7.94
7.92
7.92
7.90
7.90
7.82
7.81
7.80
7.79
7.78
7.78
7.67
7.66
7.65
7.65
7.64
7.64
7.62
7.62
7.62
7.40
7.37
7.36
7.34
7.32
7.32
2.69
CDCl3, 400 MHz
O
O−S−CF3
O
Ph−P−Ph
N
Me
15.4
3.01
1
2.03
ppm
9
8
7
6
5
4
3
2
1
0

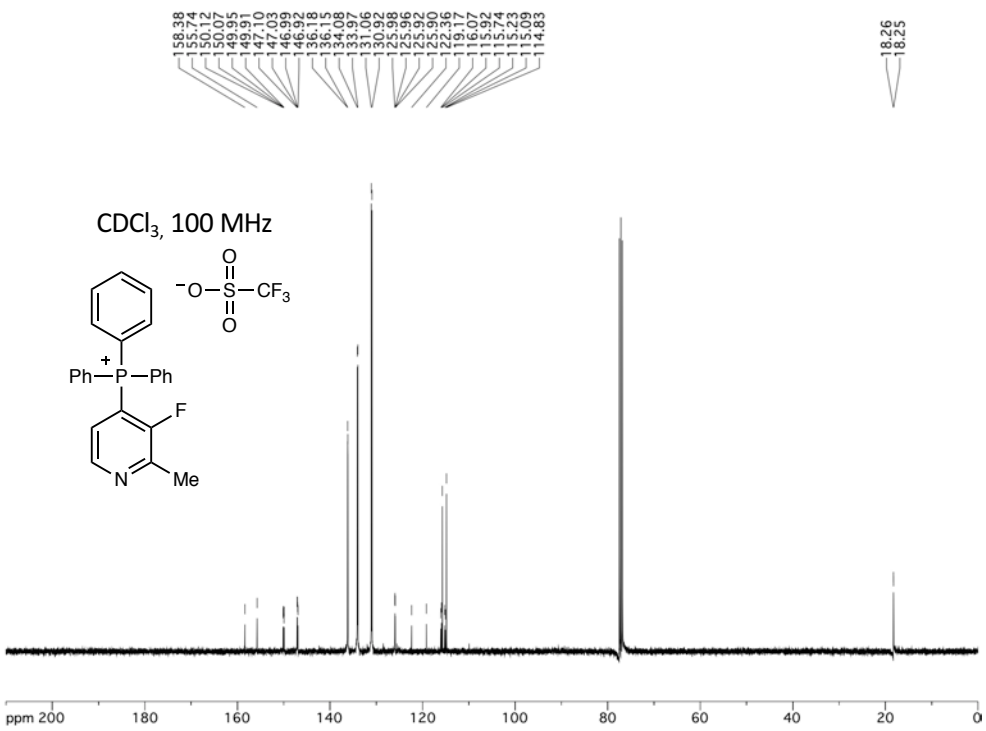

160.96
160.86
150.66
150.55
135.75
135.73
134.11
134.01
130.67
130.54
128.61
127.78
126.19
126.12
125.24
123.89
123.81
122.04
118.84
115.86
115.65
114.97
24.42
CDCl3, 100 MHz
O
⁻O—S—CF3
O
+
Ph—P—Ph
N
Me
ppm 200
180
160
140
120
100
80
60
40
20
0

$CDCl_3$, 162 MHz

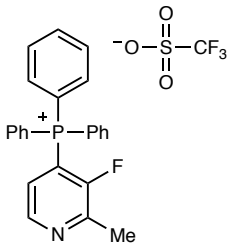


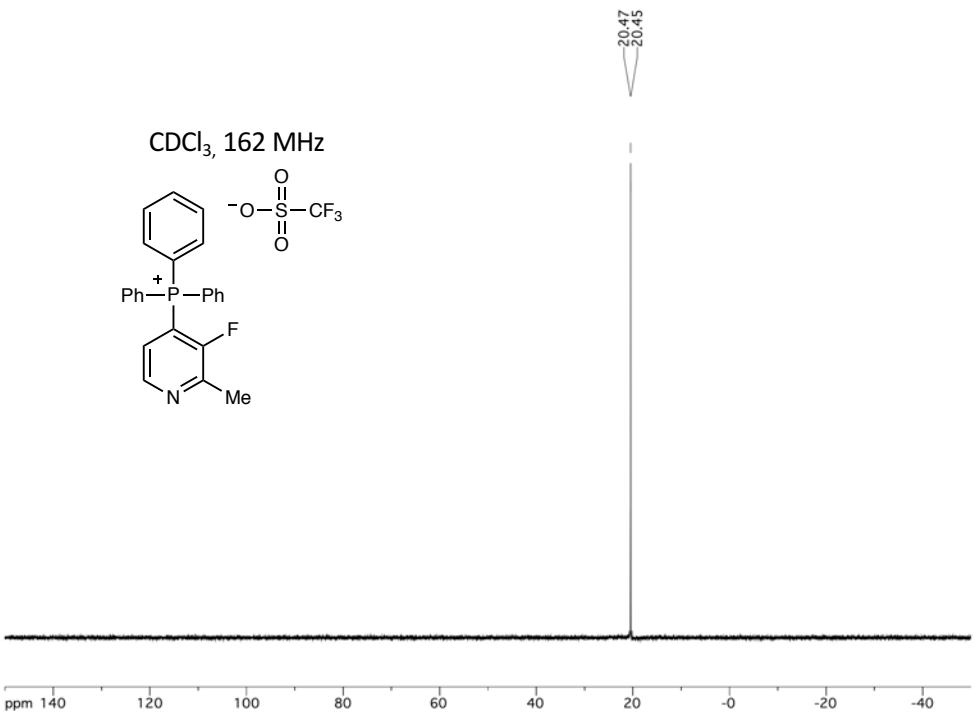

-78.14
CDCl3, 365 MHz
O
⁻O—S—CF3
O
+
Ph—P—Ph
N
Me
ppm -0
-20
-40
-60
-80
-100
-120
-140
-160
-180

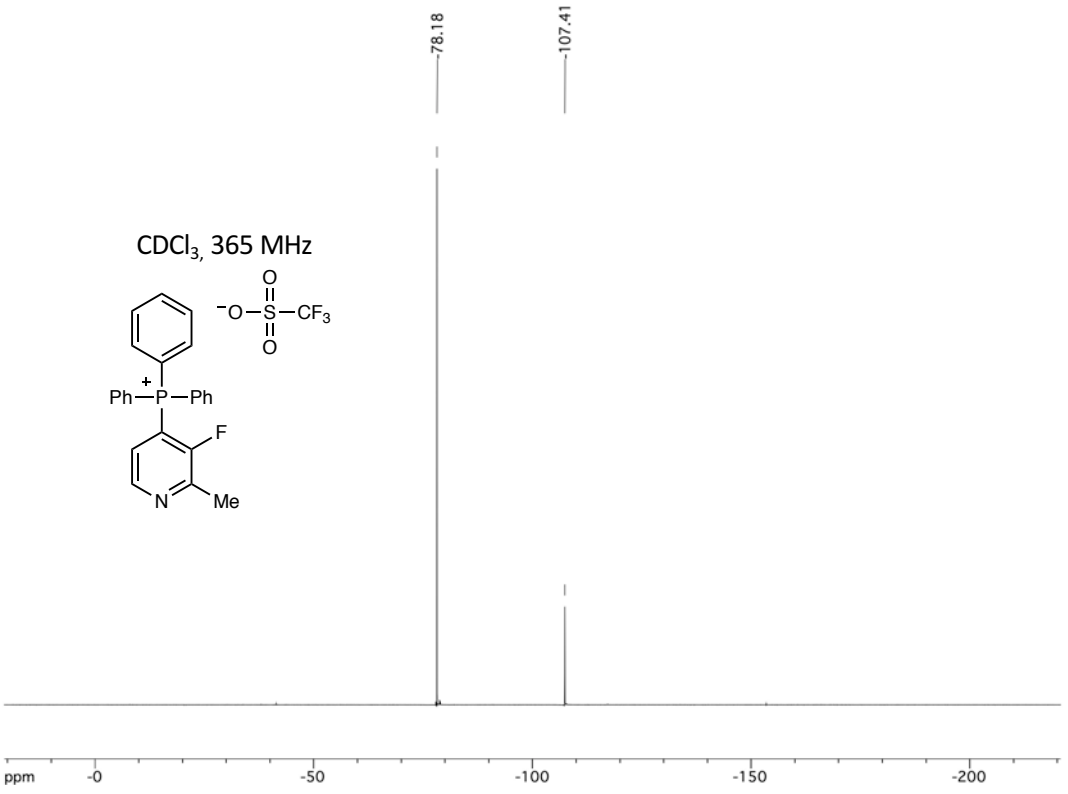

8.67
8.66
8.65
7.92
7.91
7.90
7.88
7.88
7.81
7.80
7.77
7.76
7.68
7.66
7.65
7.63
7.12
7.11
7.10
7.09
7.07
7.06
2.64
2.63
CDCl3, 400 MHz
O
⁻O—S—CF3
O
Ph—P—Ph
+
F
N
Me
3.04
6.21
3.07
1
6.15
1.02
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1

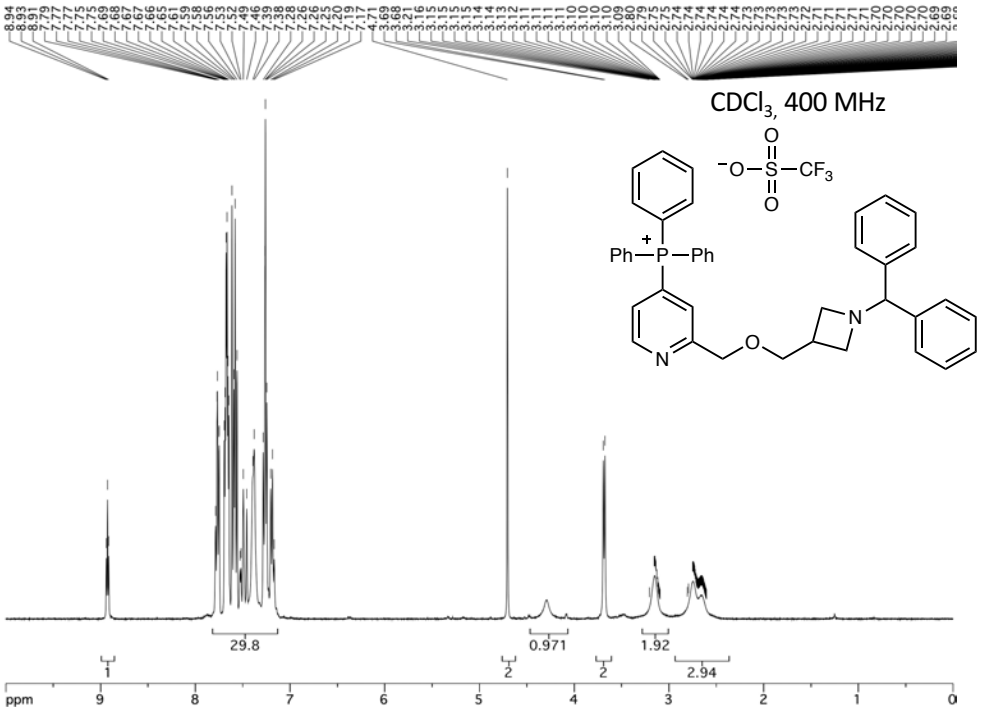

158.38
155.74
150.12
150.07
149.95
149.91
147.10
147.03
146.99
146.92
136.18
136.15
134.08
133.97
131.06
130.92
125.98
125.96
125.92
125.90
122.36
122.17
116.07
115.92
115.74
115.23
115.09
114.83
18.26
18.25
CDCl3, 100 MHz
O
⁻O—S—CF3
O
+
Ph—P—Ph
F
N
Me
ppm 200
180
160
140
120
100
80
60
40
20
0

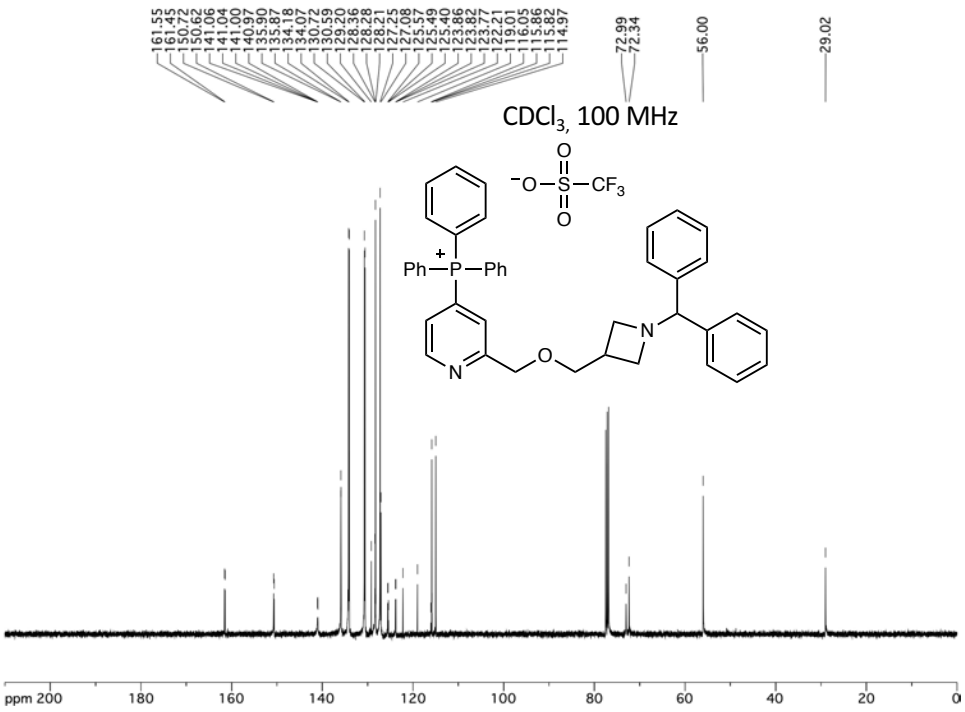
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



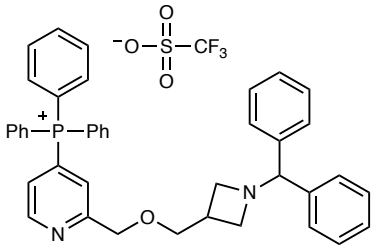

20.47
20.45
CDCl3, 162 MHz
O
⁻O—S—CF3
O
+
Ph—P—Ph
F
N
Me
ppm 140
120
100
80
60
40
20
-0
-20
-40

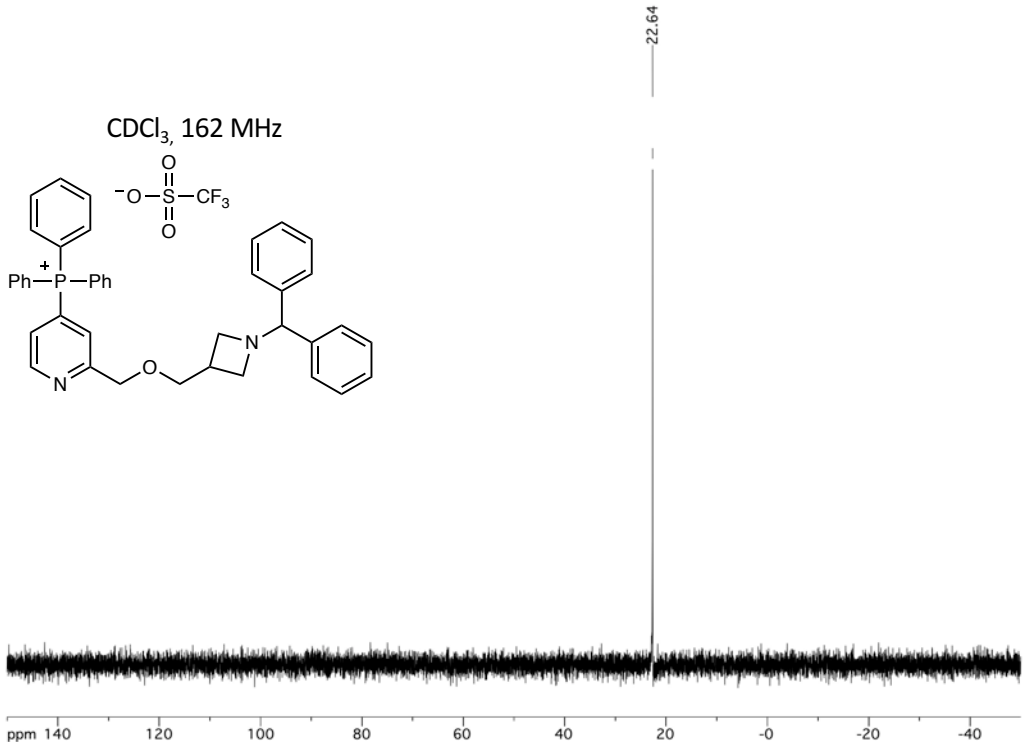

78.18
107.41
CDCl3, 365 MHz
O
⁻O—S—CF3
O
Ph—P—Ph
+
F
N
Me
ppm
-0
-50
-100
-150
-200

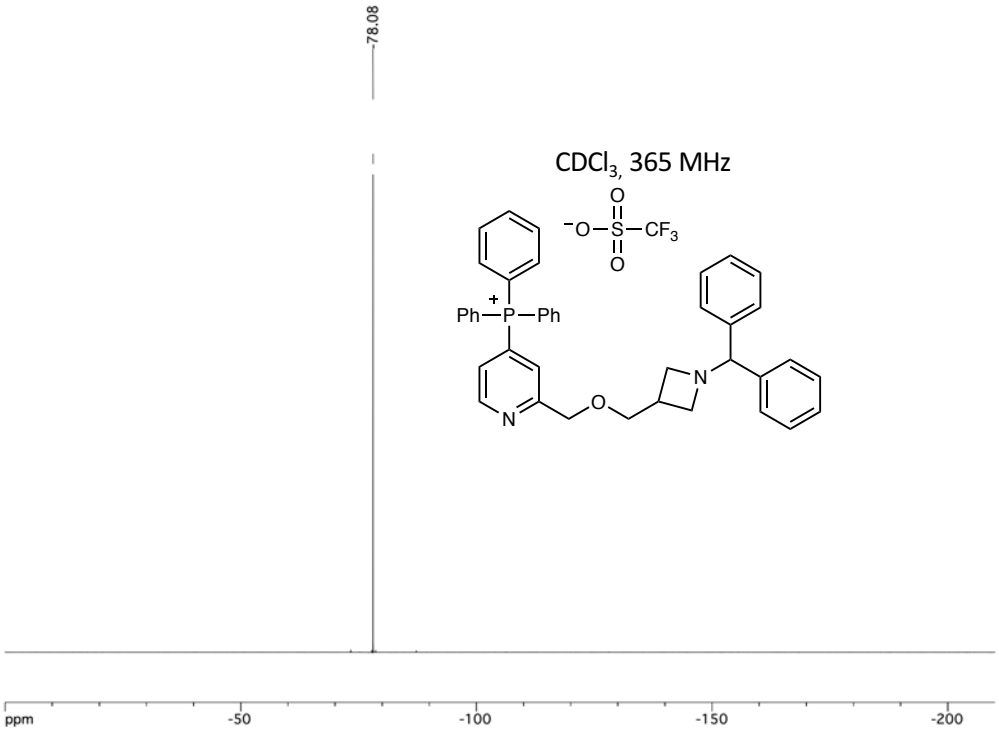

CDCl3, 400 MHz
29.8
0.971
1.92
2.94
1
2
2
ppm

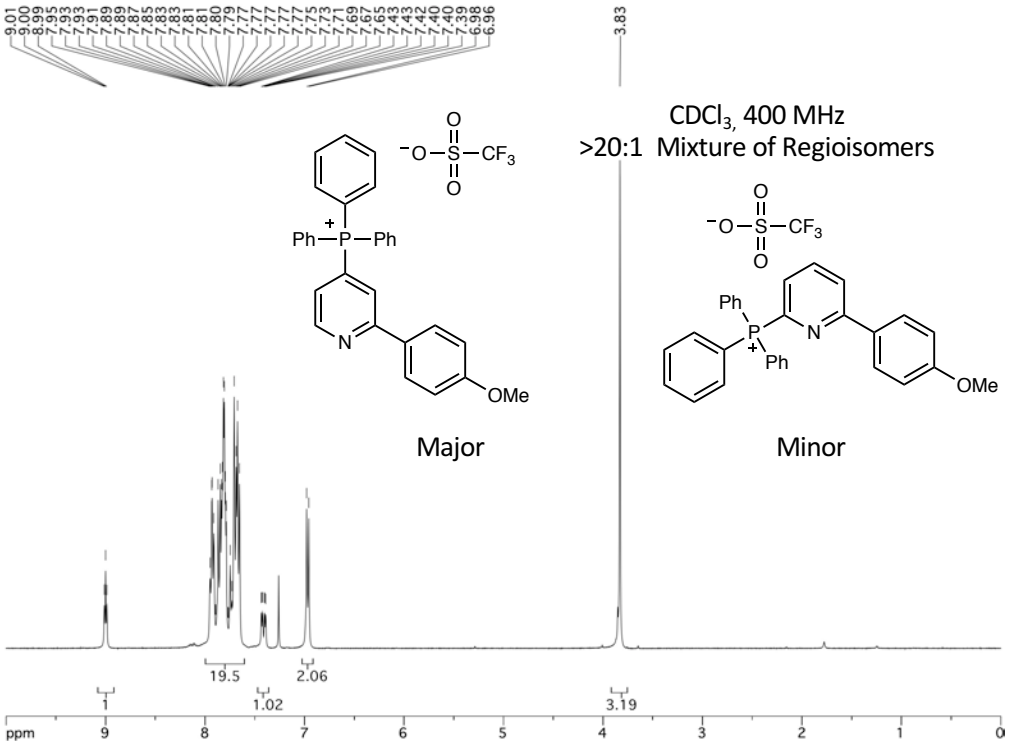

161.55
161.45
150.72
150.62
141.06
141.04
141.00
140.97
135.90
135.87
134.18
134.07
130.72
130.59
129.20
128.36
128.28
128.21
127.25
127.08
125.49
125.40
123.86
123.82
123.77
122.21
119.01
116.05
115.86
115.82
114.97
72.99
72.34
56.00
29.02
CDCl3, 100 MHz
ppm 200
180
160
140
120
100
80
60
40
20
0

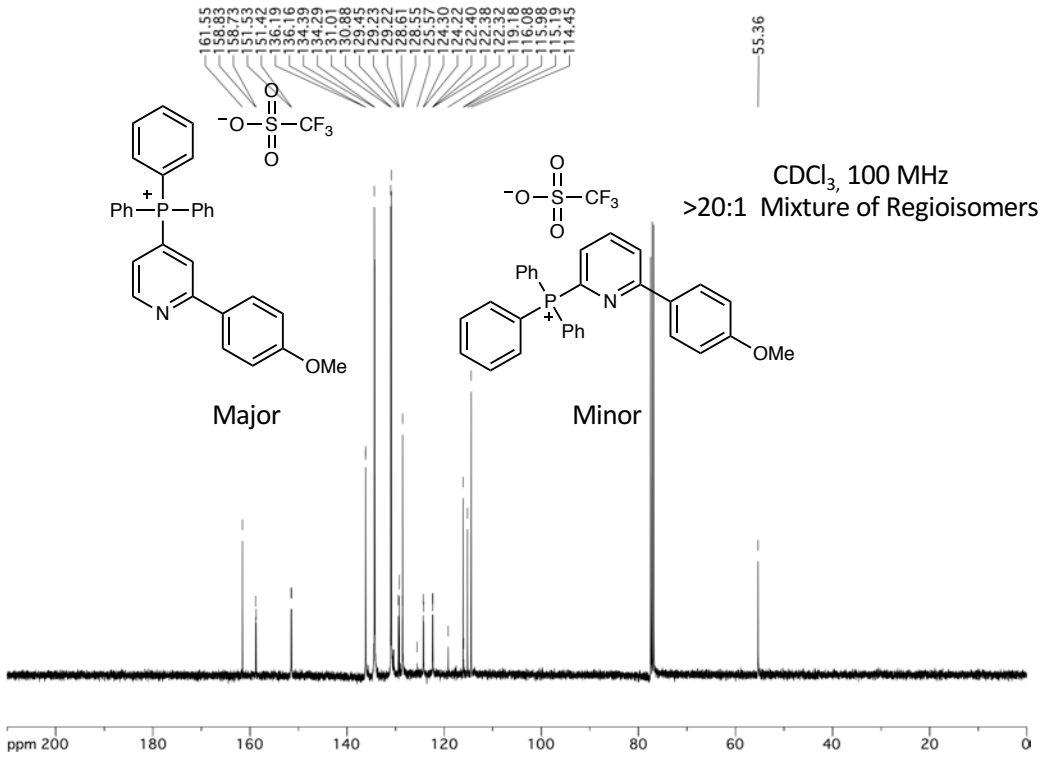
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

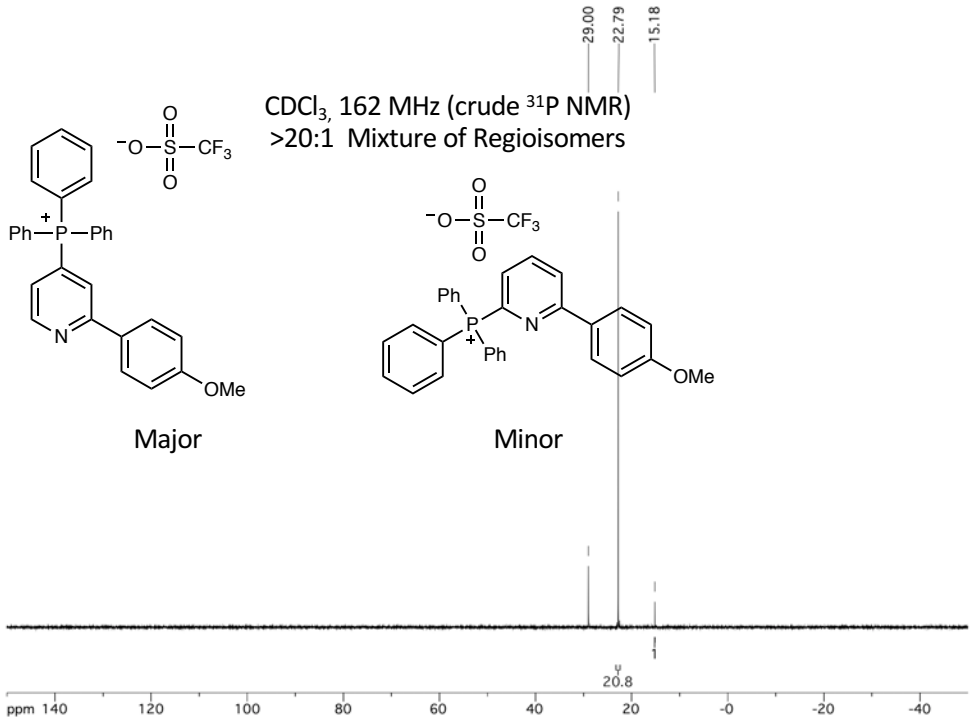


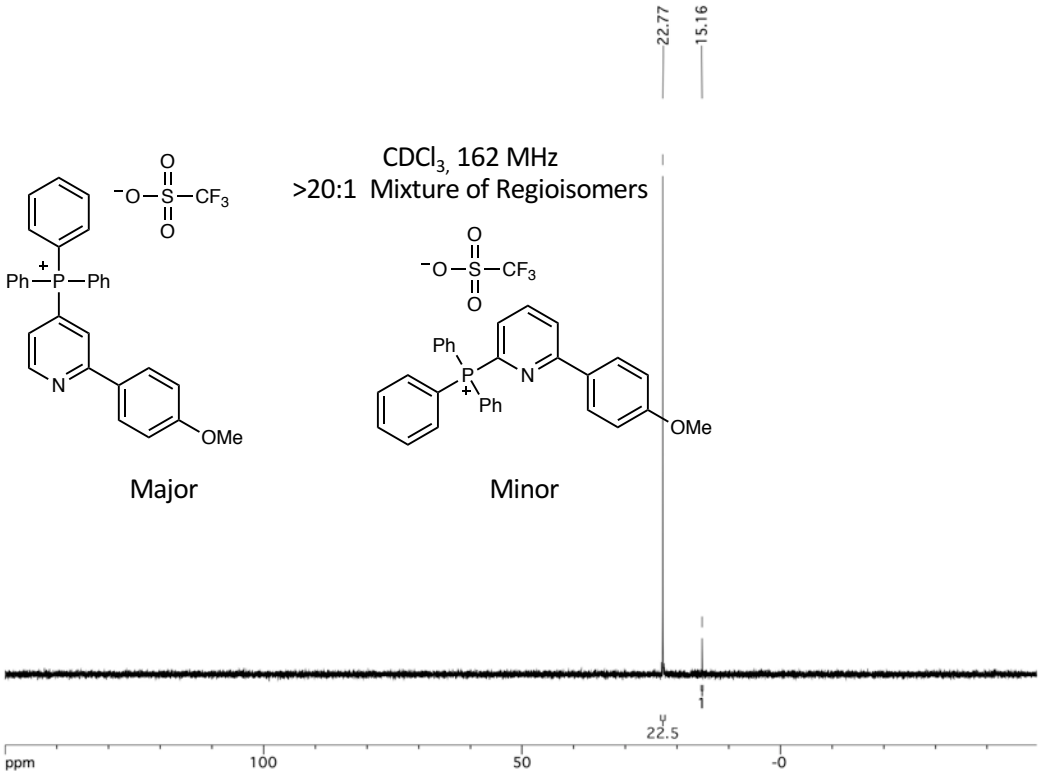

22.64
CDCl3, 162 MHz
O
⁻O—S—CF3
O
Ph—P—Ph
+
N
O
N
ppm 140
120
100
80
60
40
20
-0
-20
-40

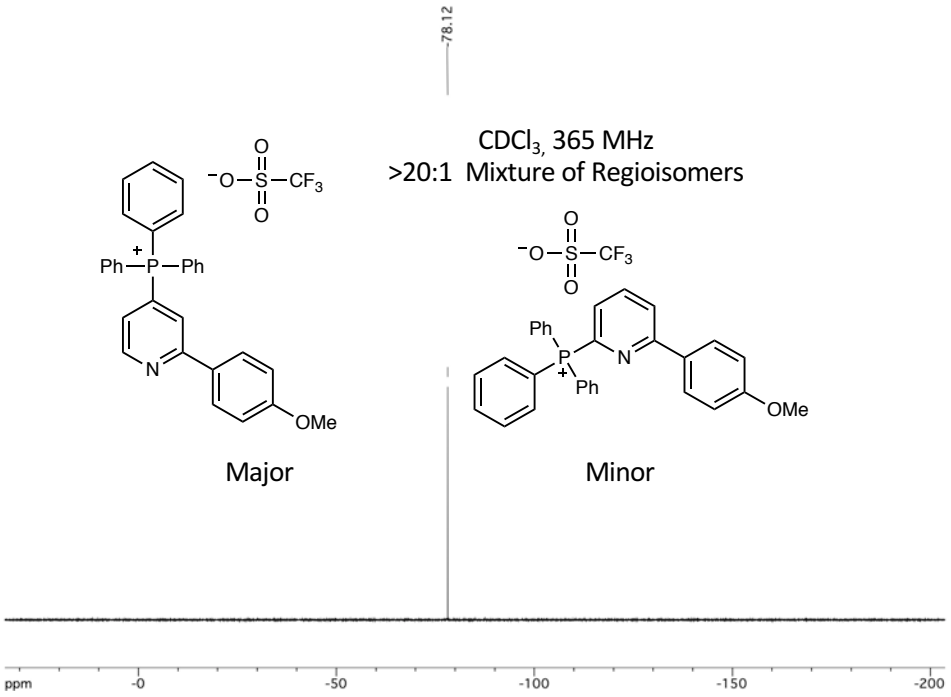

78.08
CDCl3, 365 MHz
O
⁻O—S—CF3
O
+
Ph—P—Ph
N
O
N
ppm
-50
-100
-150
-200

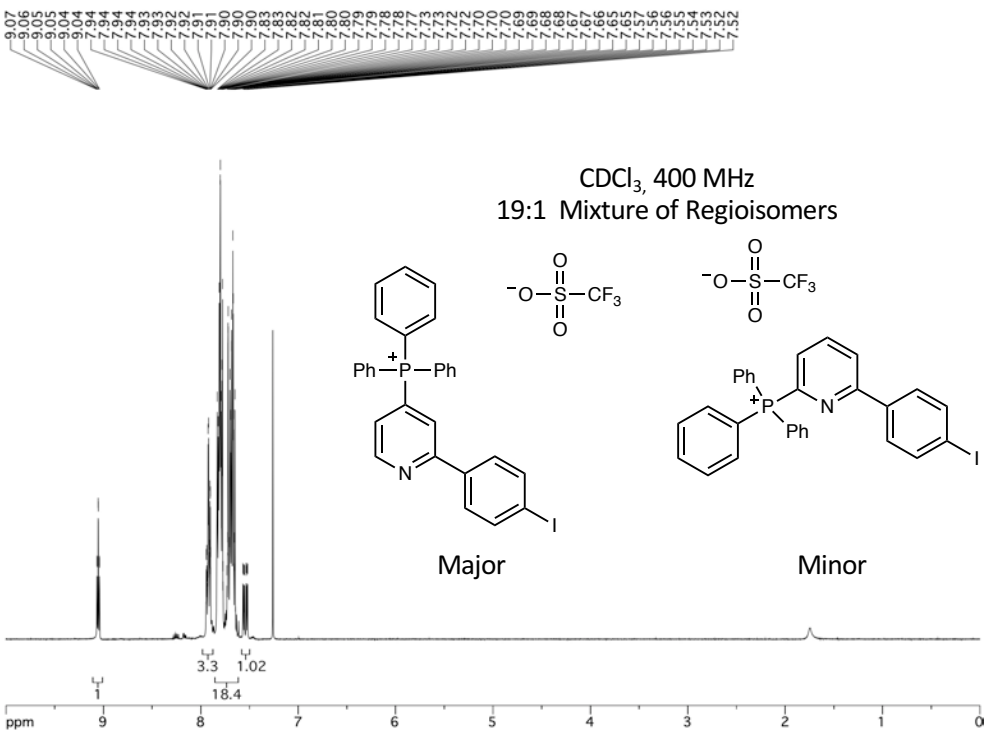

9.01
9.00
8.99
7.95
7.93
7.93
7.91
7.89
7.89
7.87
7.85
7.83
7.83
7.81
7.81
7.80
7.79
7.77
7.77
7.77
7.77
7.77
7.75
7.73
7.71
7.69
7.67
7.65
7.43
7.43
7.42
7.40
7.40
7.39
6.98
6.96
3.83
CDCl3, 400 MHz
>20:1 Mixture of Regioisomers
Major
Minor
19.5
2.06
1.02
3.19
ppm

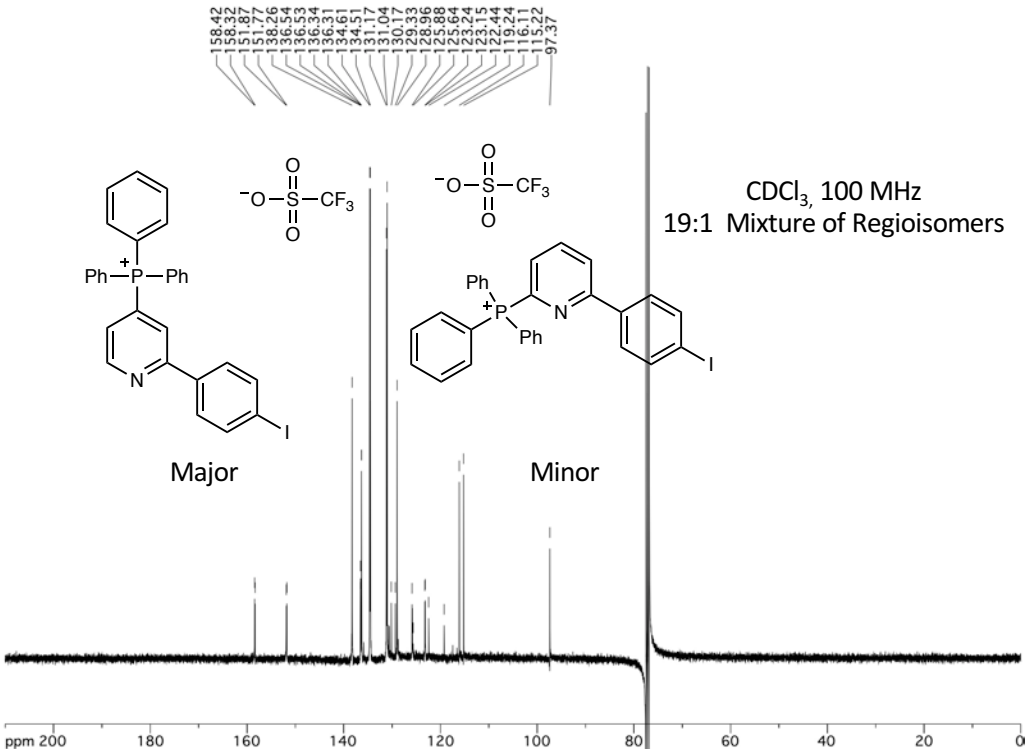

161.55
158.83
158.73
151.53
151.42
136.19
136.16
134.39
134.29
131.01
130.88
129.45
129.23
129.22
128.61
128.55
125.57
124.30
124.22
122.40
122.38
122.32
119.18
116.08
115.98
115.19
114.45
55.36
CDCl3, 100 MHz
>20:1 Mixture of Regioisomers
Major
Minor
ppm 200
180
160
140
120
100
80
60
40
20
0

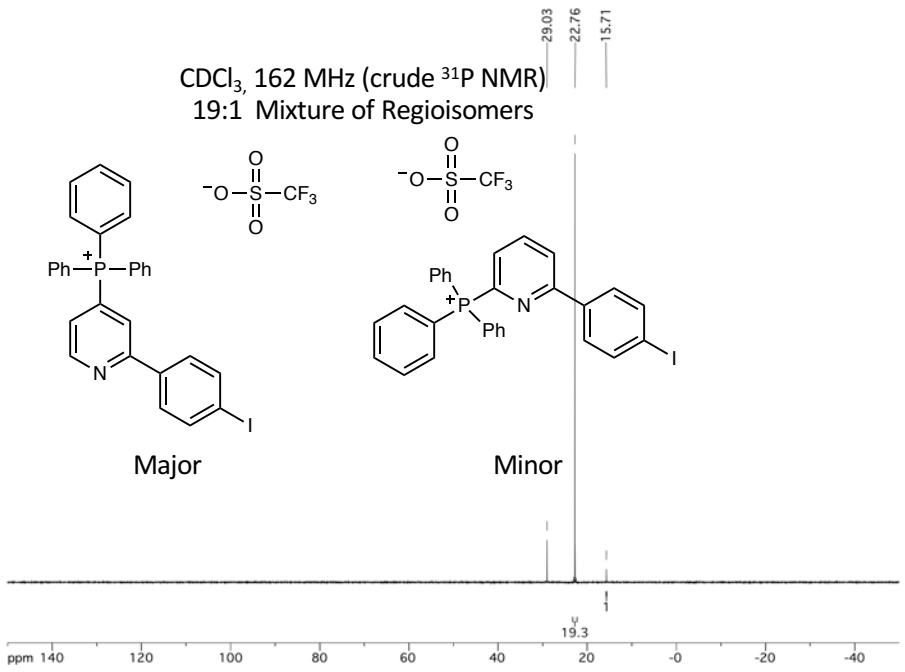

29.00
22.79
15.18
CDCl3, 162 MHz (crude 31P NMR)
>20:1 Mixture of Regioisomers
Major
Minor
20.8
ppm 140
120
100
80
60
40
20
-0
-20
-40

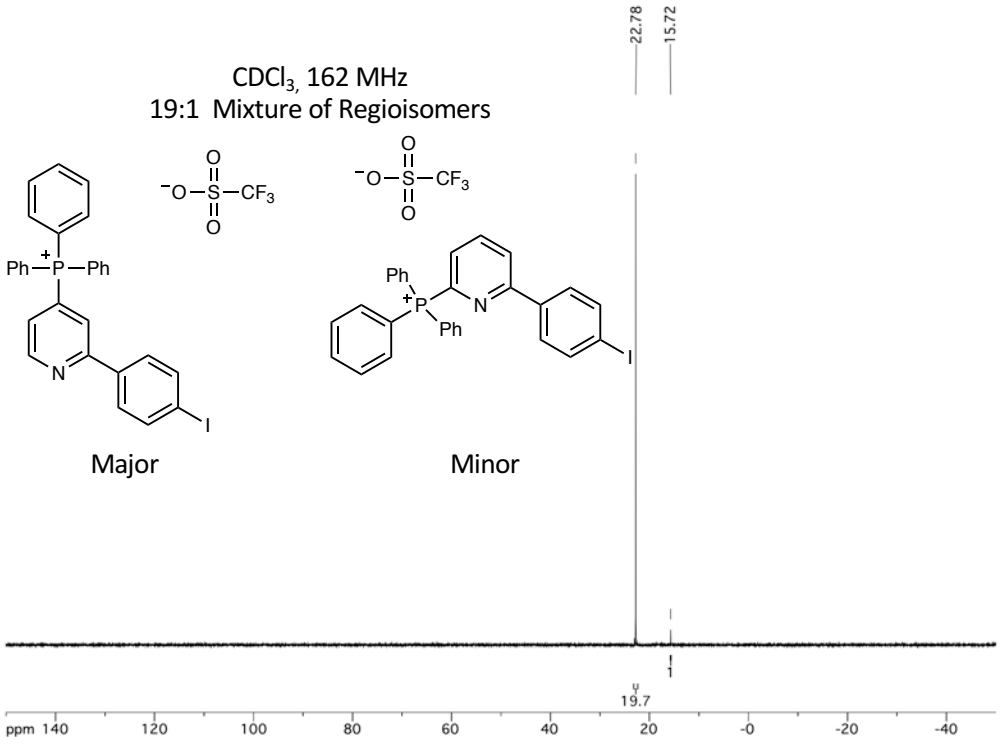

22.77
15.16
CDCl3, 162 MHz
>20:1 Mixture of Regioisomers
Major
Minor
22.5
ppm
100
50
-0

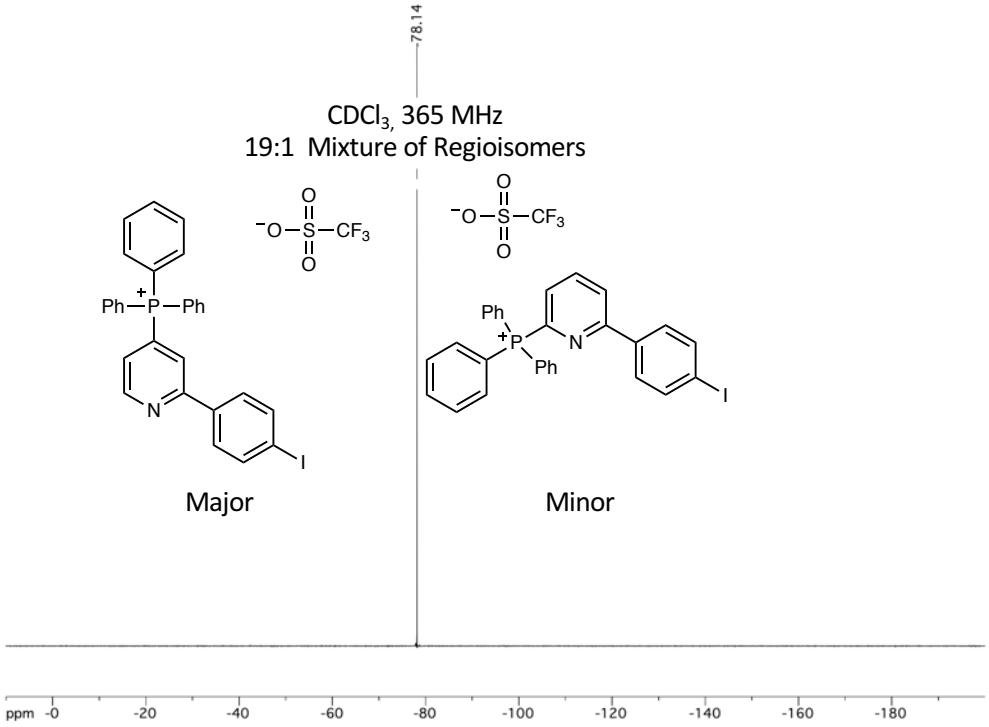

78.12
CDCl3, 365 MHz
>20:1 Mixture of Regioisomers
Major
Minor
ppm
-0
-50
-100
-150
-200

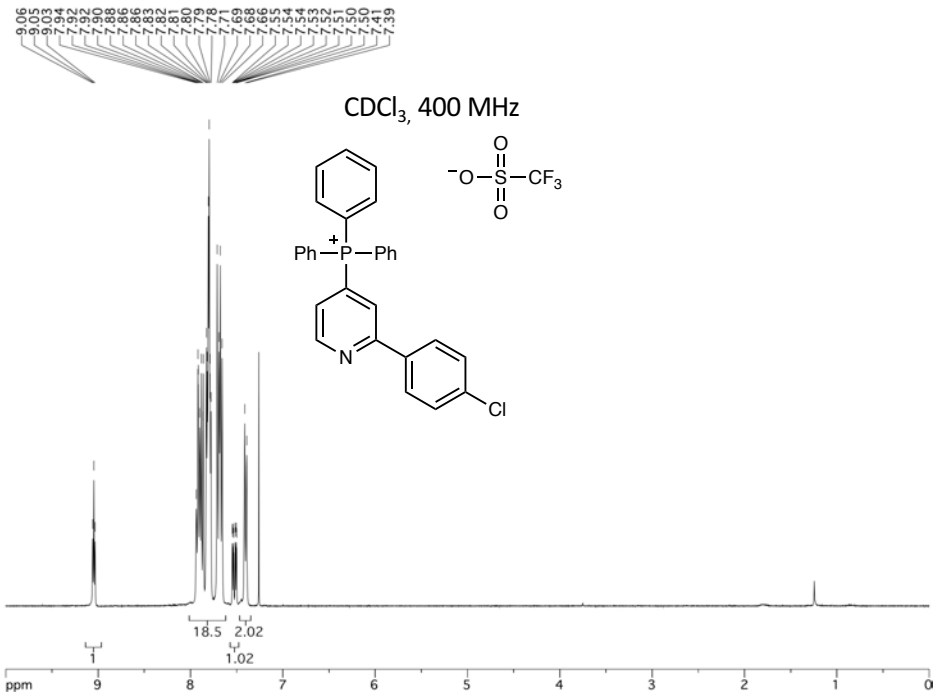

9.07 9.06 9.05 9.05 9.04 9.04 7.94 7.94 7.94 7.93 7.93 7.92 7.92 7.91 7.91 7.90 7.90 7.90 7.83 7.83 7.82 7.82 7.81 7.80 7.80 7.79 7.79 7.78 7.78 7.77 7.73 7.72 7.72 7.70 7.70 7.70 7.69 7.69 7.68 7.68 7.67 7.67 7.66 7.65 7.65 7.57 7.56 7.56 7.55 7.54 7.53 7.52 7.52
CDCl3, 400 MHz
19:1 Mixture of Regioisomers
Major
Minor
3.3
1.02
1
18.4
ppm

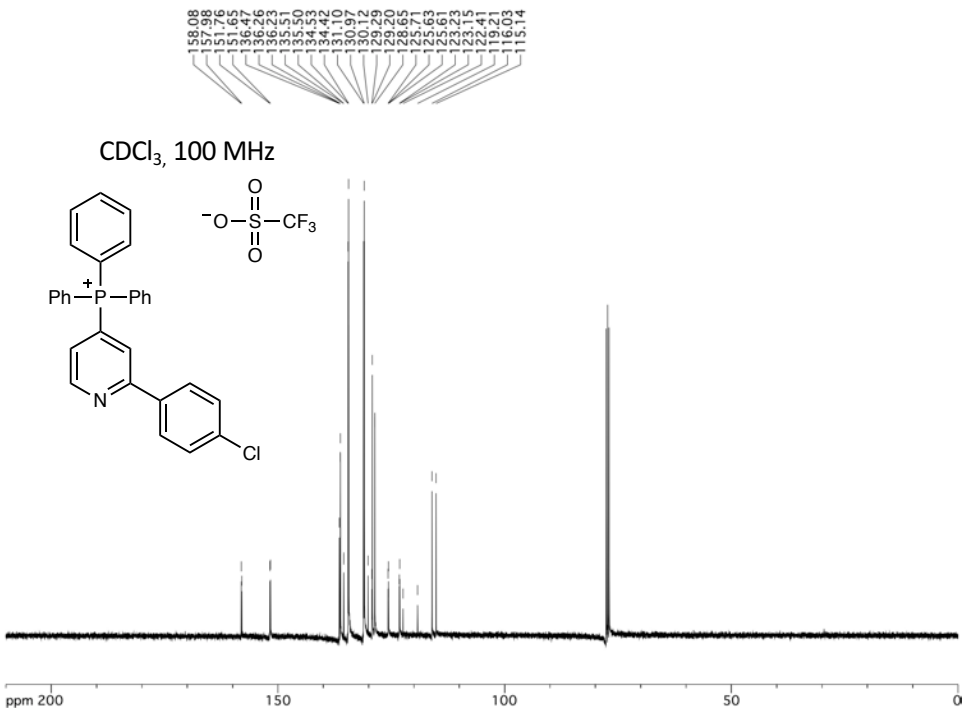

158.42
158.32
158.32
151.97
151.77
138.26
136.64
136.53
136.34
136.31
136.11
134.61
134.51
131.17
131.04
130.17
129.33
128.96
125.88
125.64
123.24
123.15
122.44
116.24
116.11
115.22
97.37
CDCl3, 100 MHz
19:1 Mixture of Regioisomers
Major
Minor
ppm 200
180
160
140
120
100
80
60
40
20
0

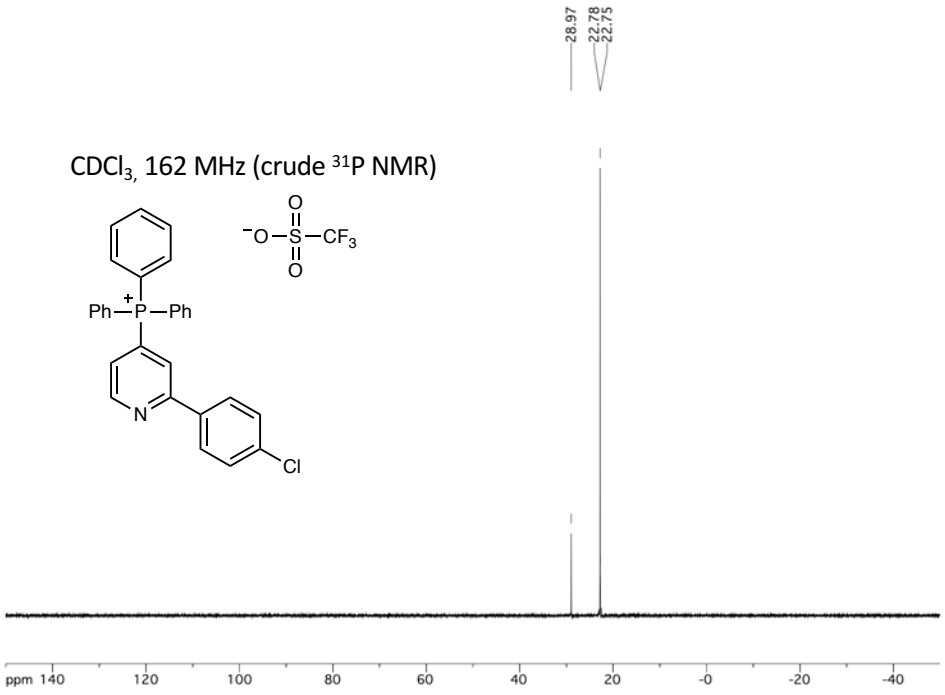

29.03
22.76
15.71
CDCl3, 162 MHz (crude 31P NMR)
19:1 Mixture of Regioisomers
Major
Minor
19.3
ppm 140
120
100
80
60
40
20
-0
-20
-40

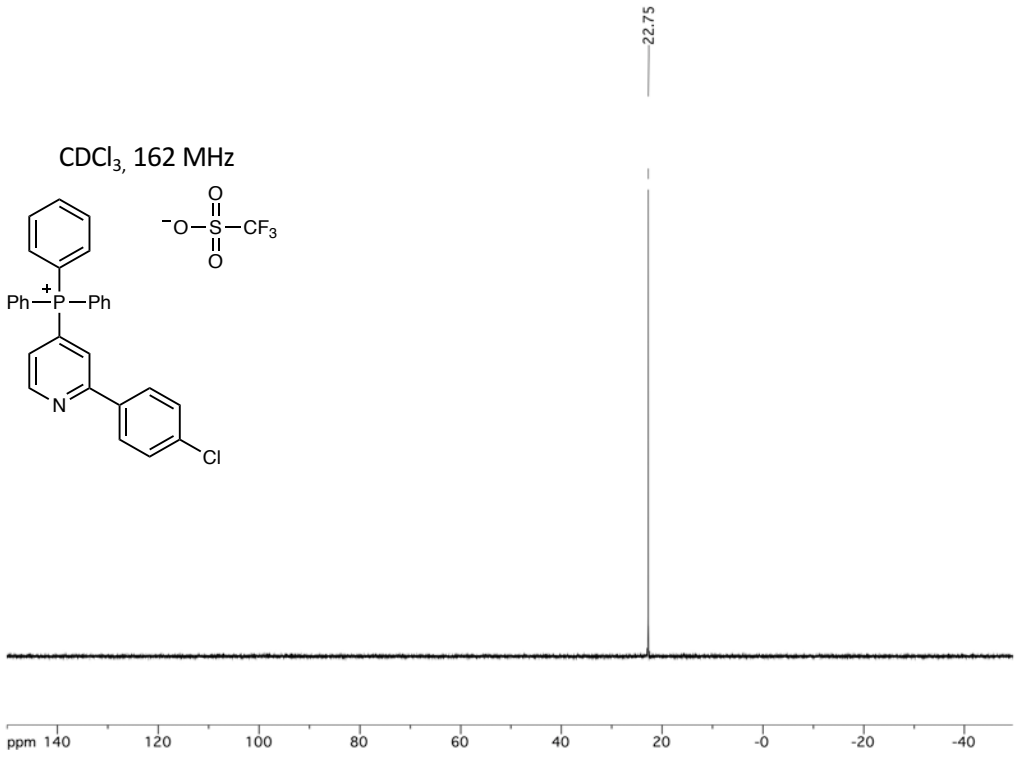

22.78
15.72
CDCl3, 162 MHz
19:1 Mixture of Regioisomers
Major
Minor
19.7
ppm 140
120
100
80
60
40
20
-0
-20
-40

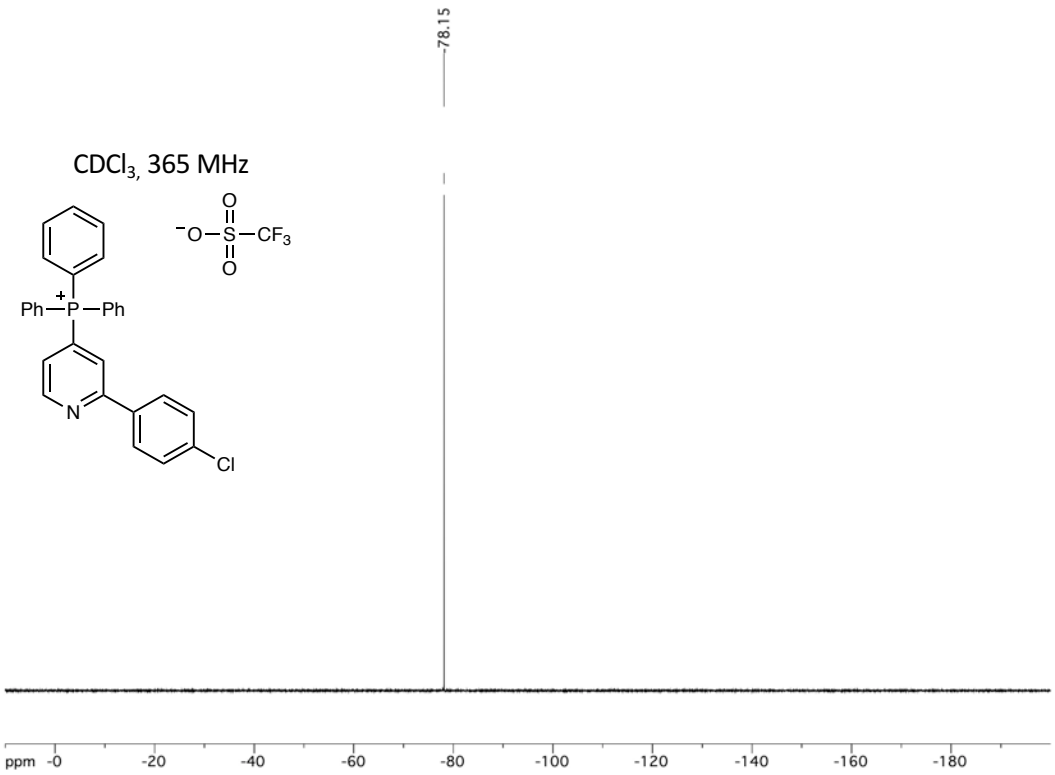

78.14
CDCl3, 365 MHz
19:1 Mixture of Regioisomers
Major
Minor
ppm -0 -20 -40 -60 -80 -100 -120 -140 -160 -180

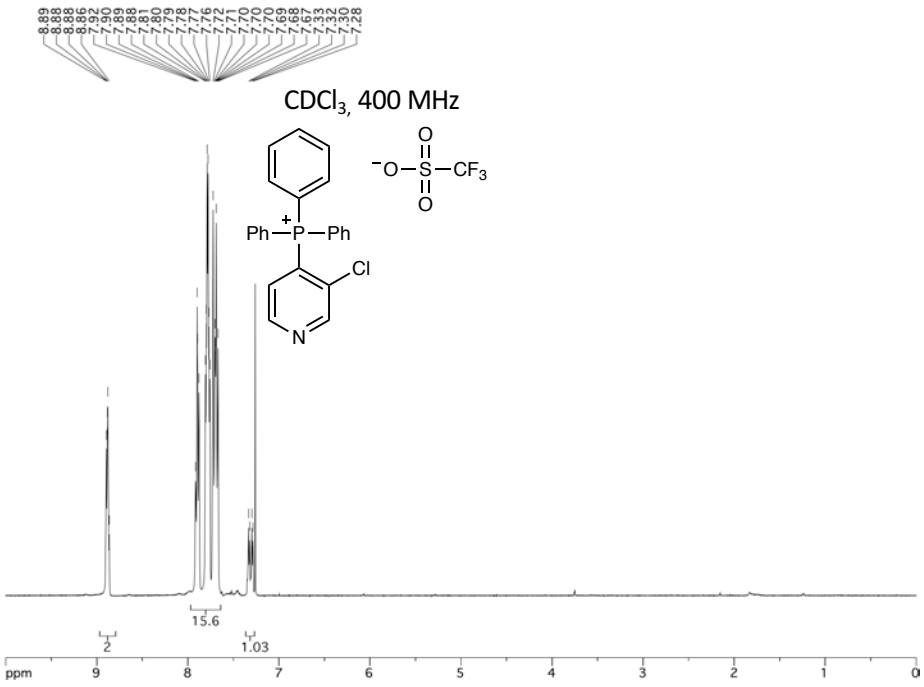

9.06
9.05
9.03
7.94
7.92
7.92
7.90
7.88
7.86
7.86
7.83
7.82
7.81
7.80
7.79
7.78
7.71
7.69
7.68
7.66
7.55
7.54
7.54
7.53
7.52
7.51
7.50
7.50
7.41
7.39
CDCl3, 400 MHz
O
O−S−CF3
O
Ph−P−Ph
N
Cl
18.5
2.02
1
1.02
ppm
9
8
7
6
5
4
3
2
1
0

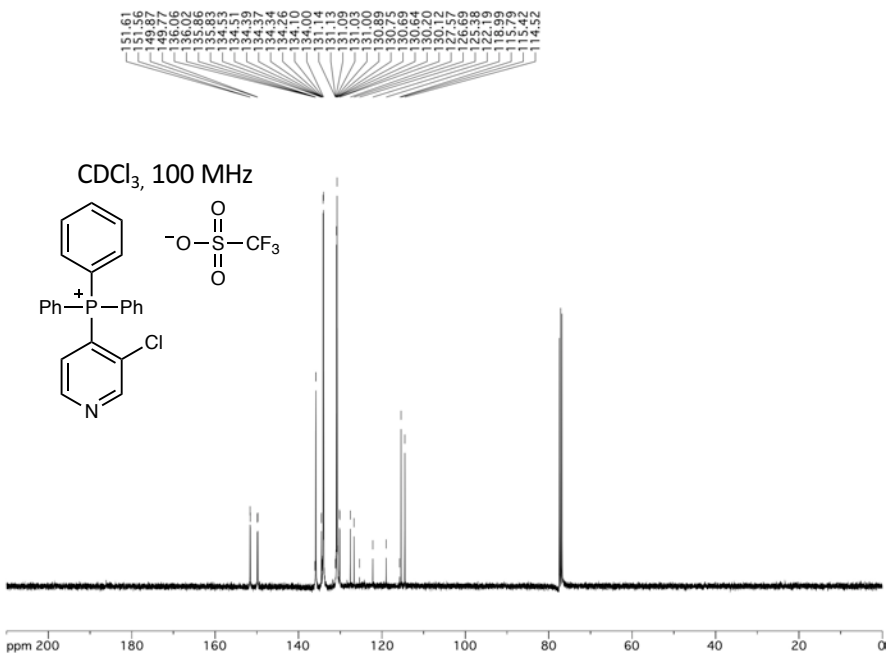

158.08
157.98
151.76
151.65
136.47
136.26
136.23
135.51
135.50
134.53
134.42
131.10
130.97
130.12
129.29
129.20
128.65
125.71
125.63
125.61
123.23
123.15
122.41
119.21
116.03
115.14
CDCl3, 100 MHz
Ph
P
Ph
N
Cl
O
S
CF3
ppm 200
150
100
50
0


28.97
22.78
22.75
CDCl3, 162 MHz (crude 31P NMR)
O
−O—S—CF3
O
Ph—P—Ph
+
N
Cl
ppm 140
120
100
80
60
40
20
-0
-20
-40

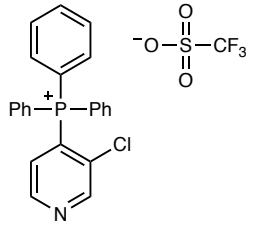

22.75
CDCl3, 162 MHz
O
⁻O—S—CF3
O
Ph—P—Ph
+
N
Cl
ppm 140
120
100
80
60
40
20
-0
-20
-40

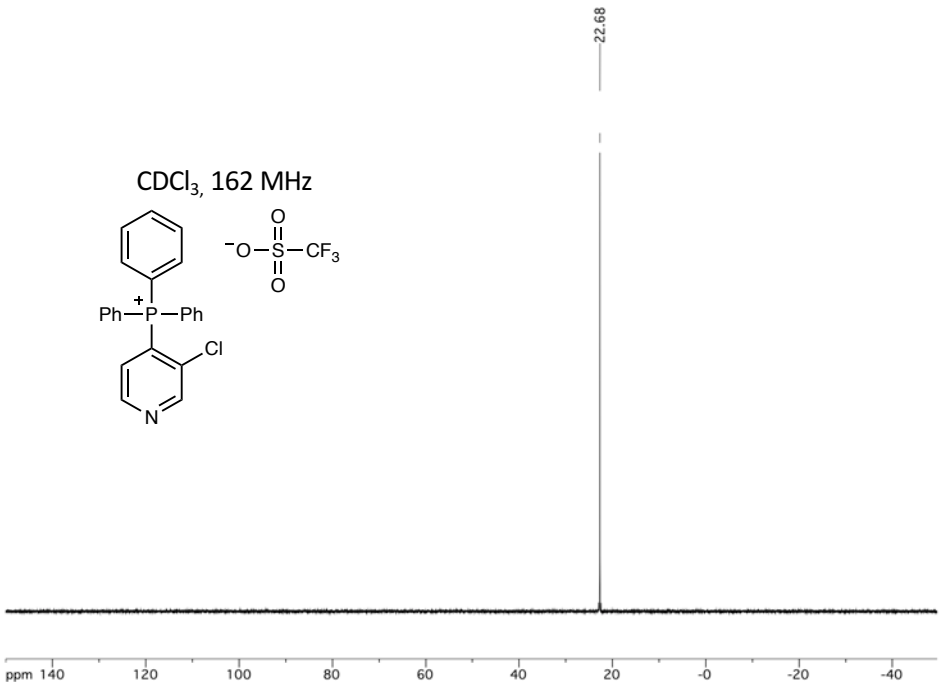

-78.15
CDCl3, 365 MHz
O
⁻O—S—CF3
O
+
Ph—P—Ph
N
Cl
ppm -0 -20 -40 -60 -80 -100 -120 -140 -160 -180

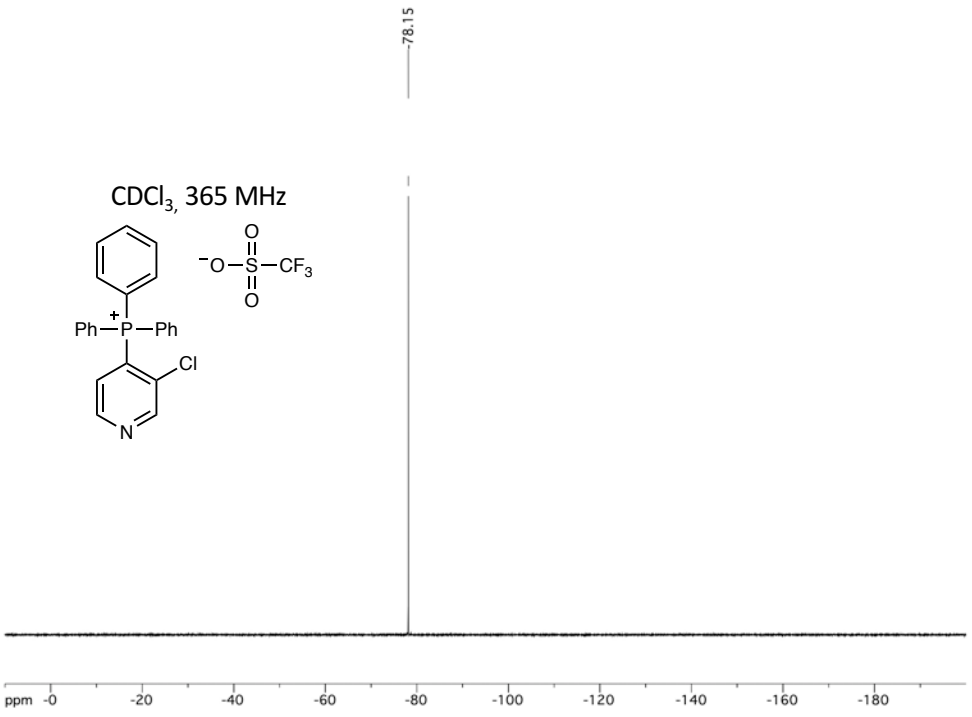

8.89
8.88
8.88
8.88
8.86
7.92
7.90
7.89
7.88
7.81
7.80
7.79
7.78
7.77
7.76
7.72
7.71
7.70
7.70
7.70
7.69
7.68
7.67
7.33
7.32
7.30
7.28
CDCl3, 400 MHz
Ph
P
Ph
Cl
N
O
O
S
CF3
15.6
2
1.03
ppm
9
8
7
6
5
4
3
2
1
0

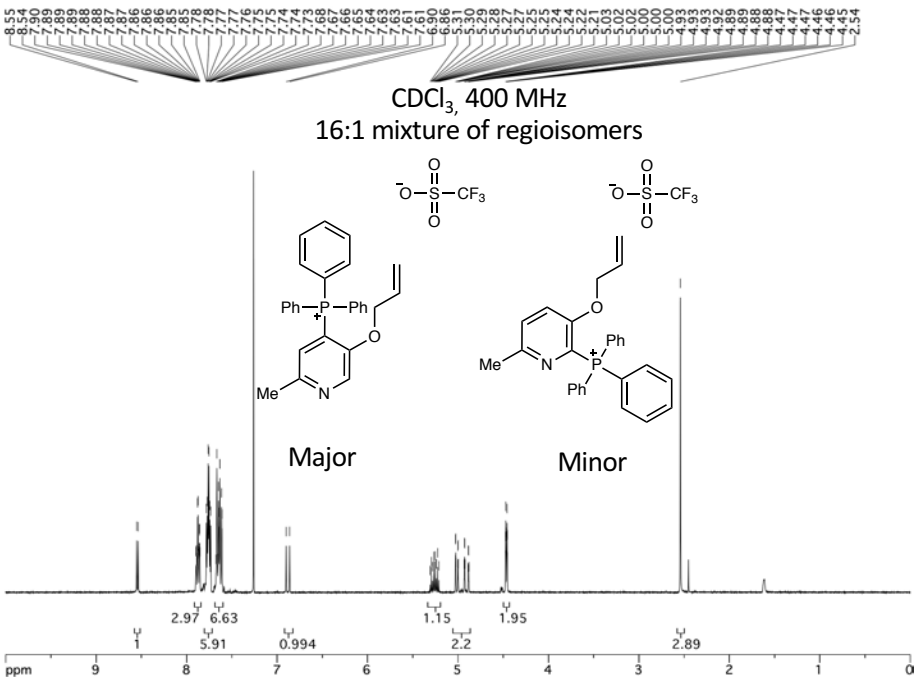

151.61
151.56
149.87
149.77
136.06
135.92
135.86
135.83
134.53
134.51
134.39
134.37
134.34
134.26
134.10
134.00
131.14
131.13
131.09
131.03
131.00
130.89
130.75
130.69
130.64
130.20
130.12
127.17
126.69
125.38
122.19
118.99
115.79
115.42
114.32
CDCl3, 100 MHz
O
O−S−CF3
O
Ph−P−Ph
Cl
N
ppm 200
180
160
140
120
100
80
60
40
20
0

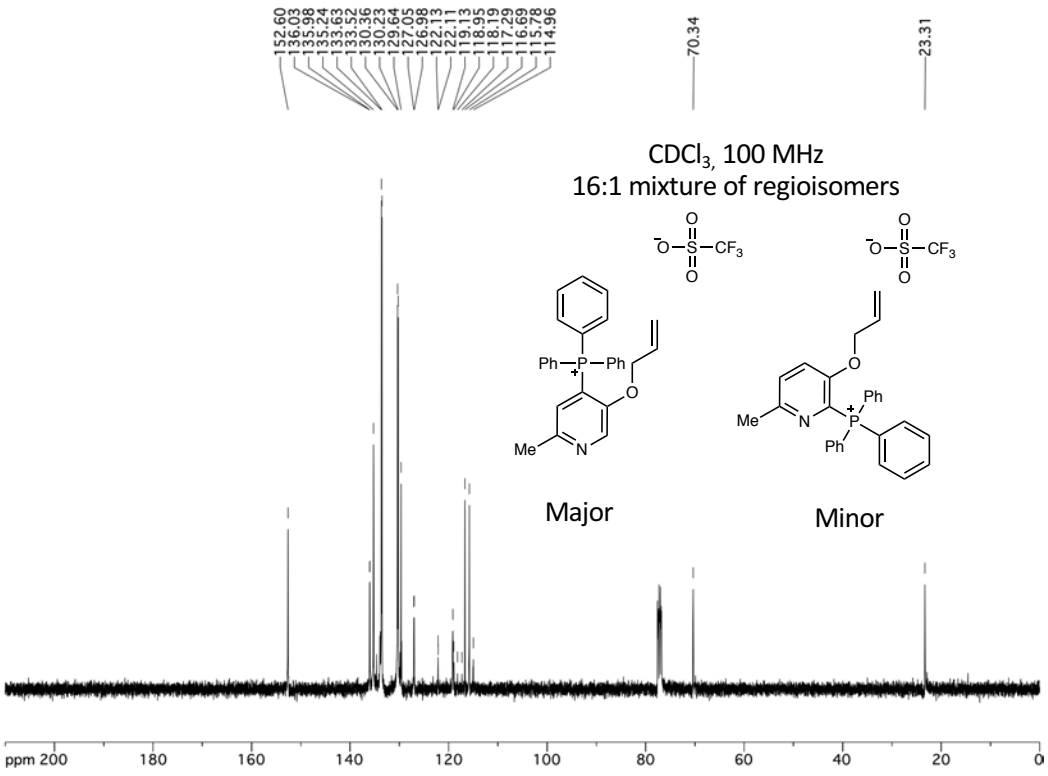
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

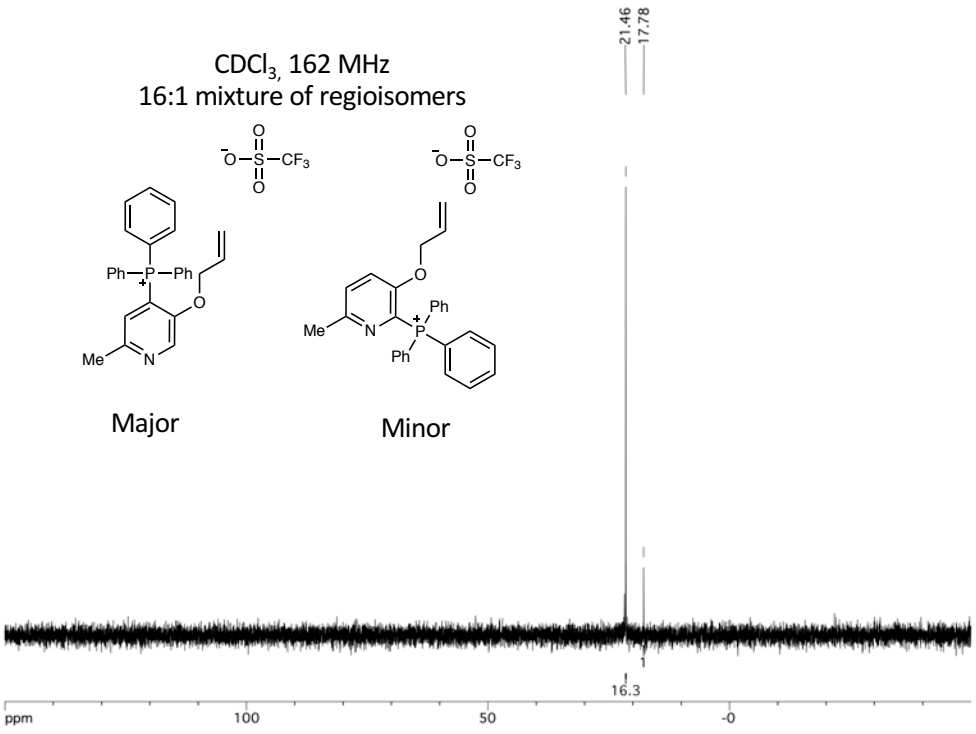


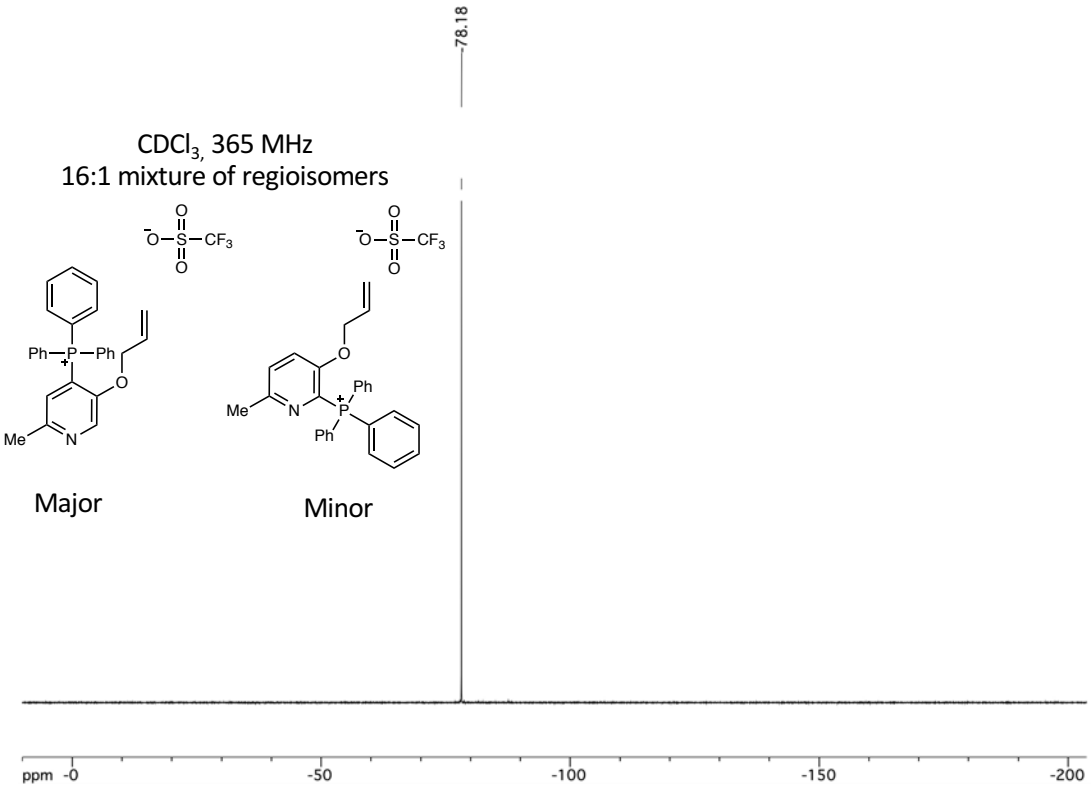

22.68
CDCl3, 162 MHz
Ph
P
Ph
Cl
N
O
S
CF3
ppm 140
120
100
80
60
40
20
-0
-20
-40

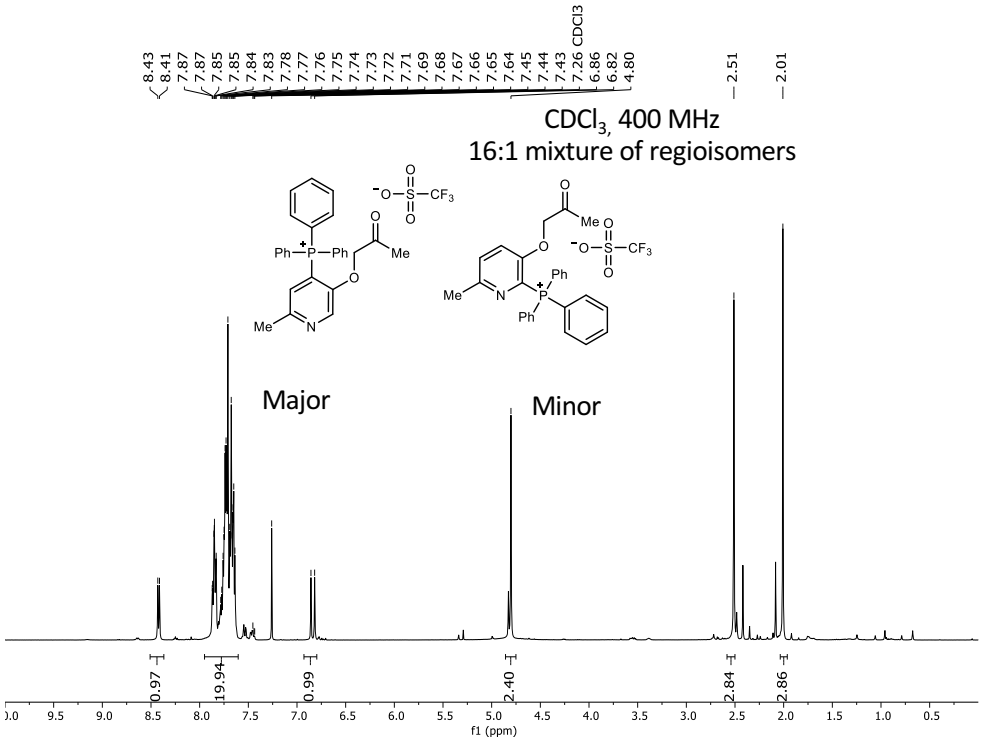

78.15
CDCl3, 365 MHz
O
⁻O—S—CF3
O
Ph—P—Ph
+
Cl
N
ppm -0 -20 -40 -60 -80 -100 -120 -140 -160 -180

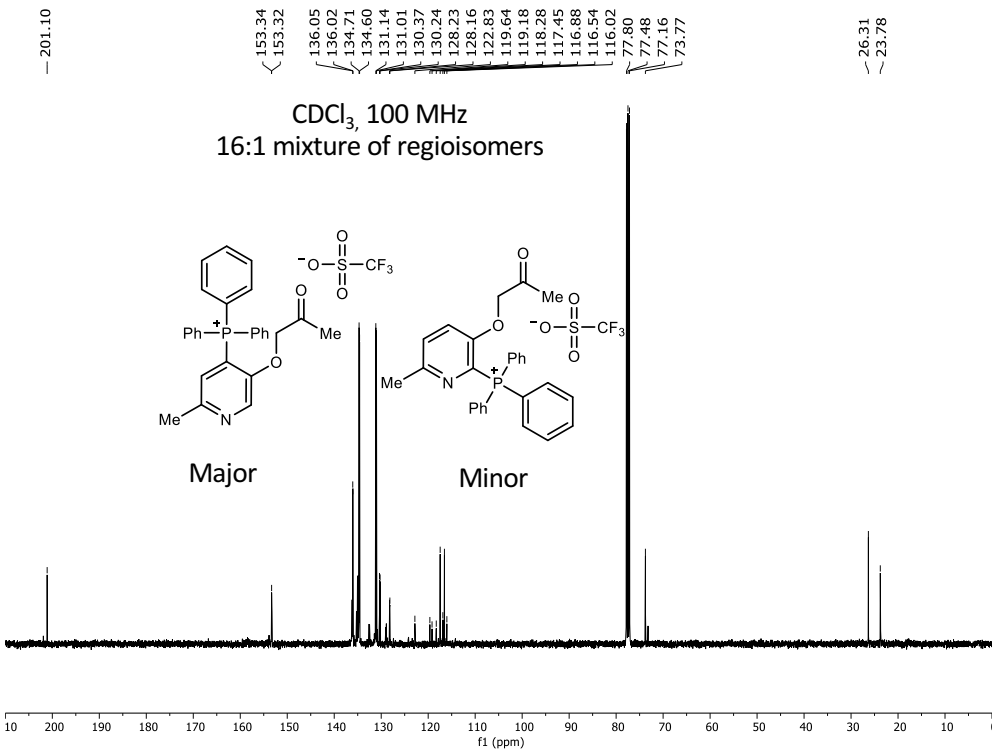

CDCl3, 400 MHz
16:1 mixture of regioisomers
Major
Minor
2.97
6.63
1.15
1.95
1
5.91
0.994
2.2
2.89
ppm

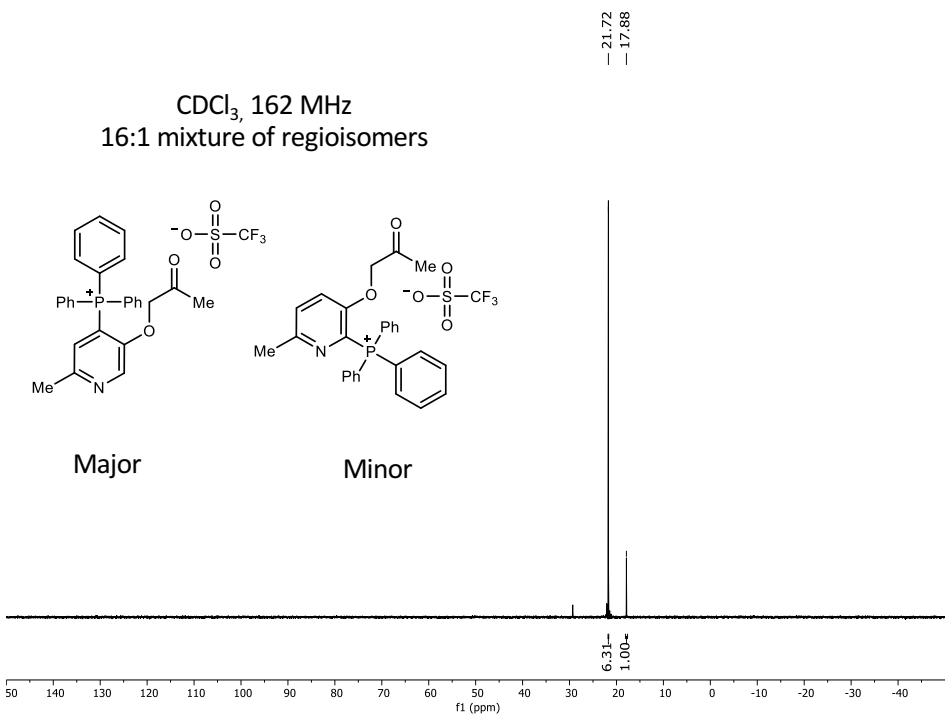

152.60
136.03
135.98
135.24
133.63
133.52
130.36
130.23
129.64
127.05
126.98
122.13
122.11
119.13
118.95
118.19
117.29
116.69
115.78
114.96
70.34
23.31
CDCl3, 100 MHz
16:1 mixture of regioisomers
Major
Minor
ppm 200
180
160
140
120
100
80
60
40
20
0

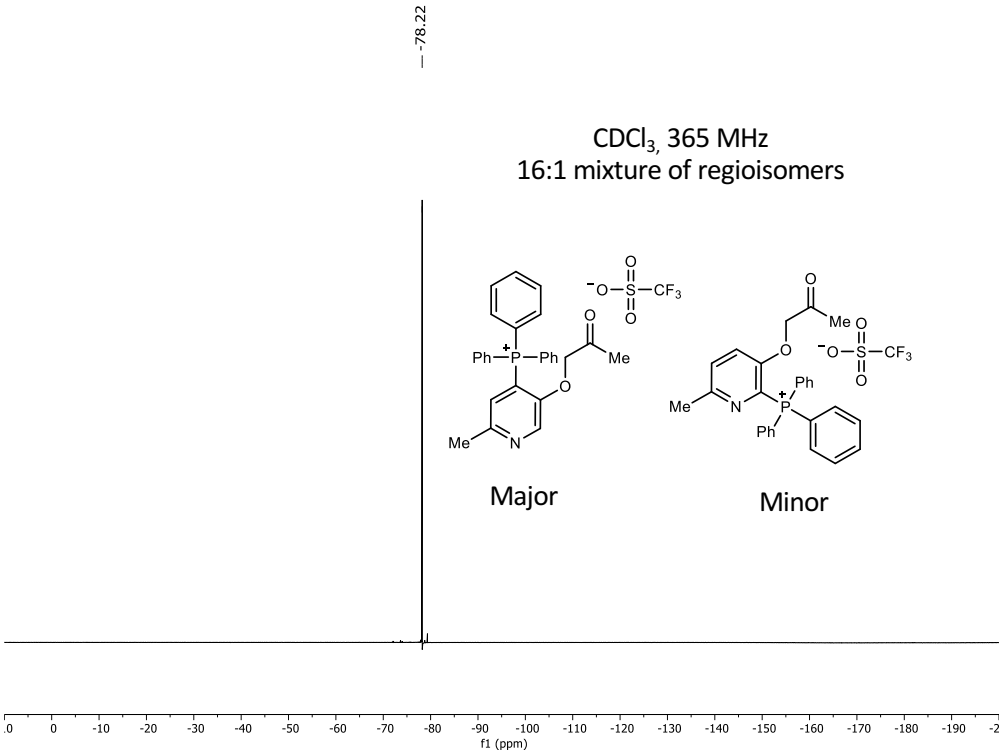

CDCl3, 162 MHz
16:1 mixture of regioisomers
Major
Minor
21.46
17.78
16.3
ppm
100
50
-0

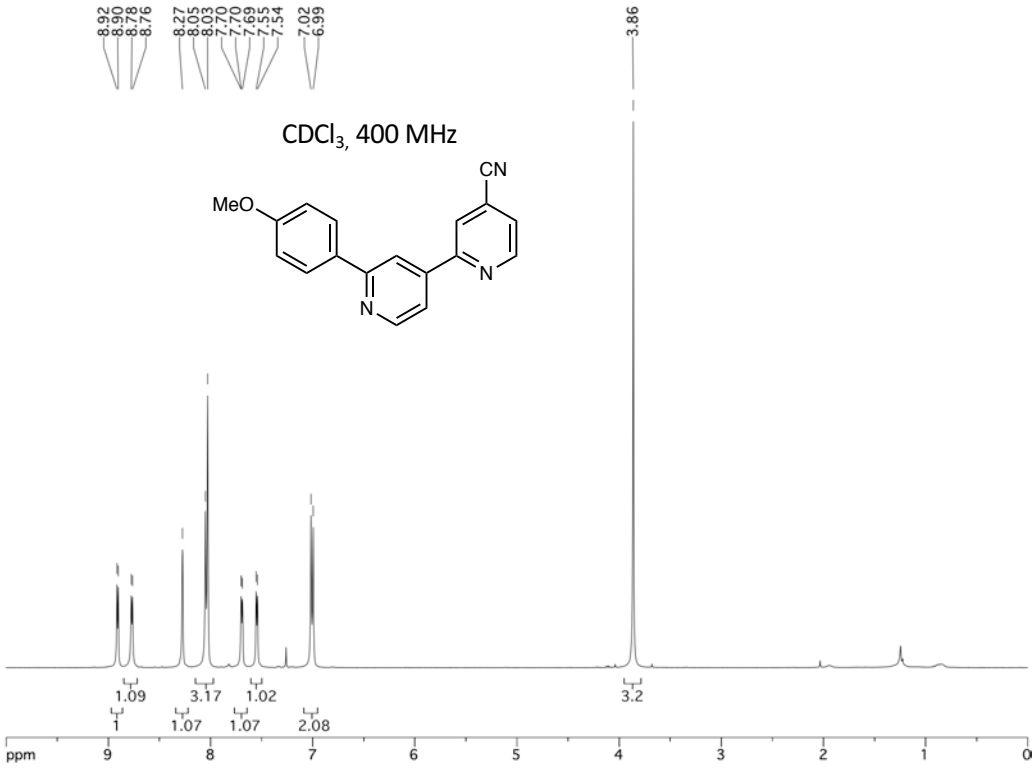

78.18
CDCl3, 365 MHz
16:1 mixture of regioisomers
Major
Minor
ppm -0
-50
-100
-150
-200

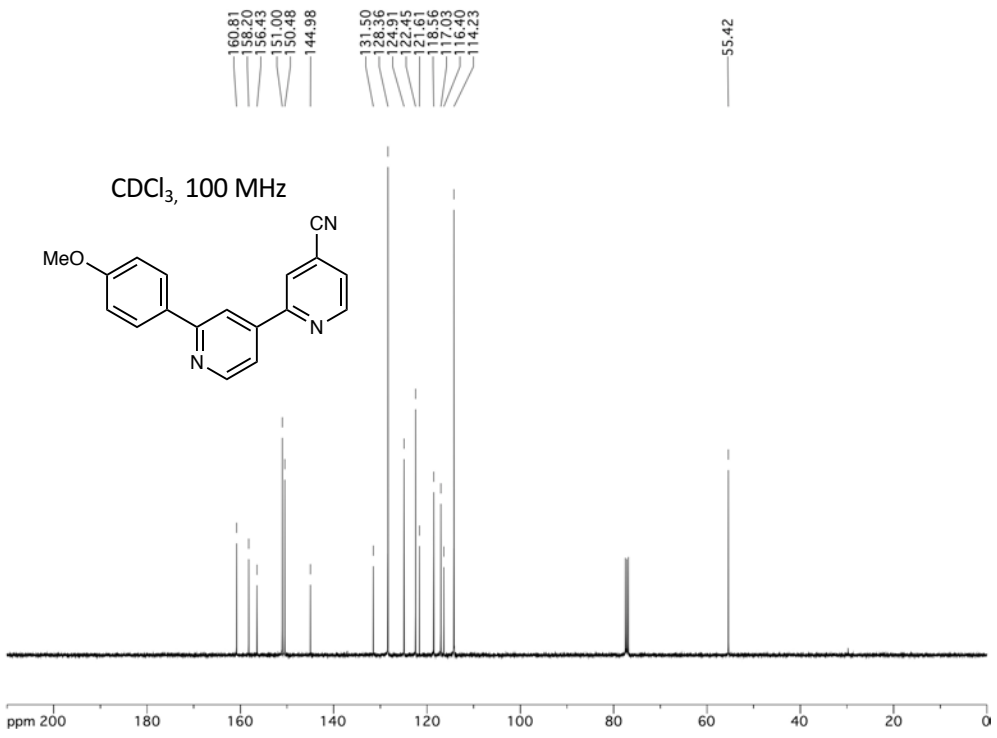

8.43
8.41
7.87
7.87
7.85
7.85
7.84
7.83
7.78
7.77
7.76
7.75
7.74
7.73
7.72
7.71
7.69
7.68
7.67
7.66
7.65
7.64
7.45
7.44
7.43
7.26 CDCl3
6.86
6.82
4.80
2.51
2.01
CDCl3, 400 MHz
16:1 mixture of regioisomers
Major
Minor
0.97
19.94
0.99
2.40
2.84
2.86
f1 (ppm)

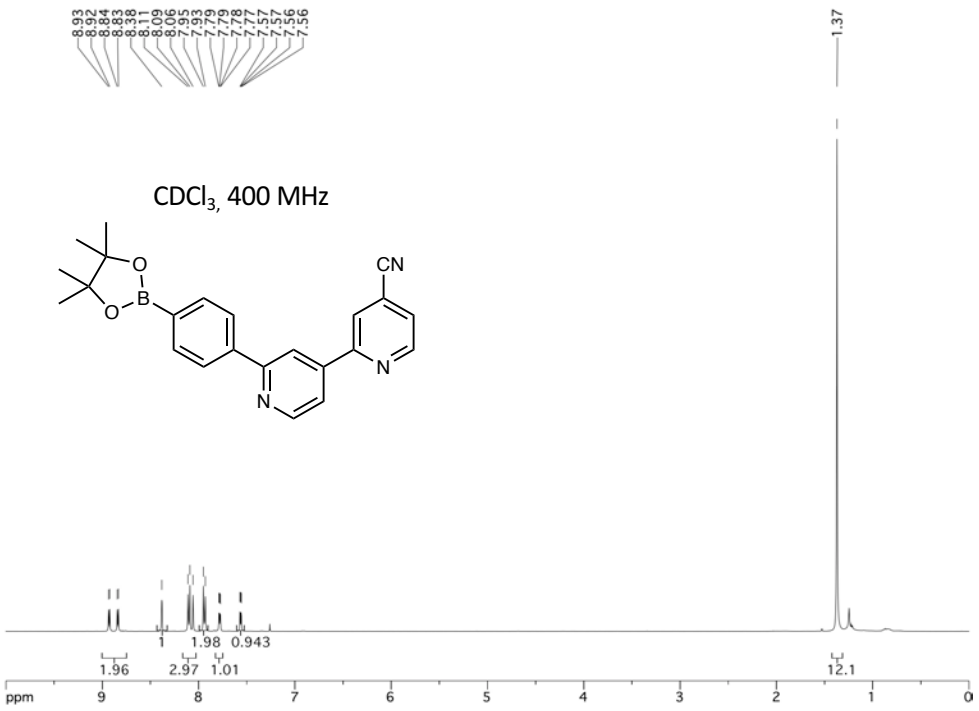

201.10
153.34
153.32
136.05
136.02
134.71
134.60
131.14
131.01
130.37
130.24
128.23
128.16
122.83
119.64
119.18
118.28
117.45
116.88
116.54
116.02
77.80
77.48
77.16
73.77
26.31
23.78
CDCl3, 100 MHz
16:1 mixture of regioisomers
Major
Minor
f1 (ppm)

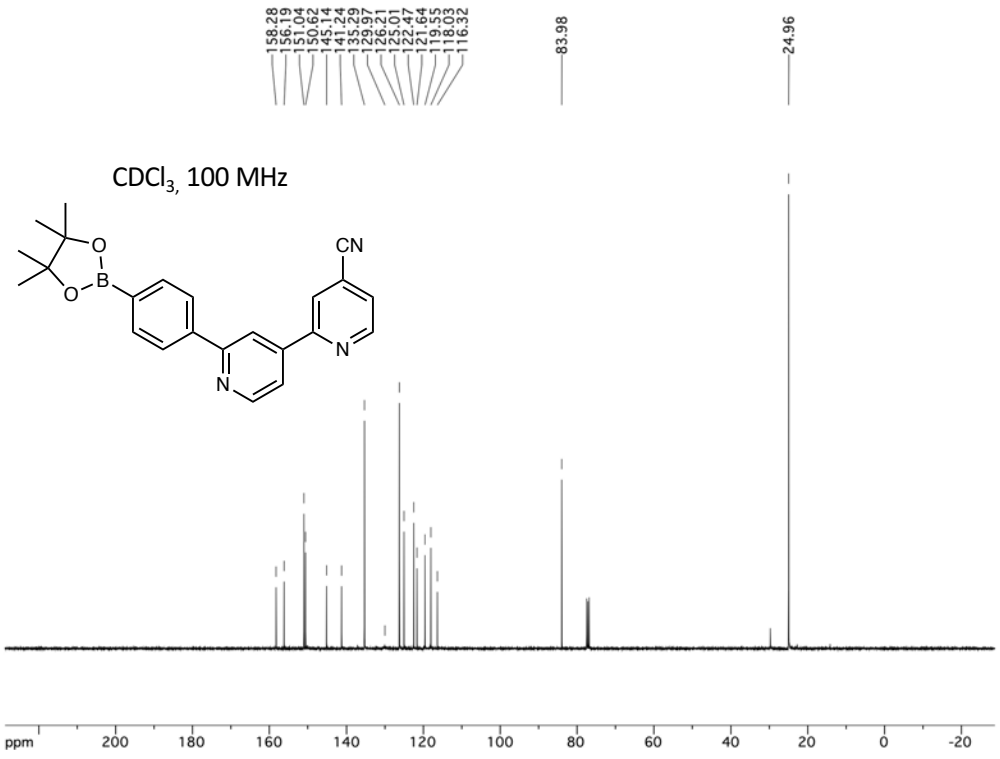

21.72
17.88
CDCl3, 162 MHz
16:1 mixture of regioisomers
Major
Minor
6.31
1.00
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

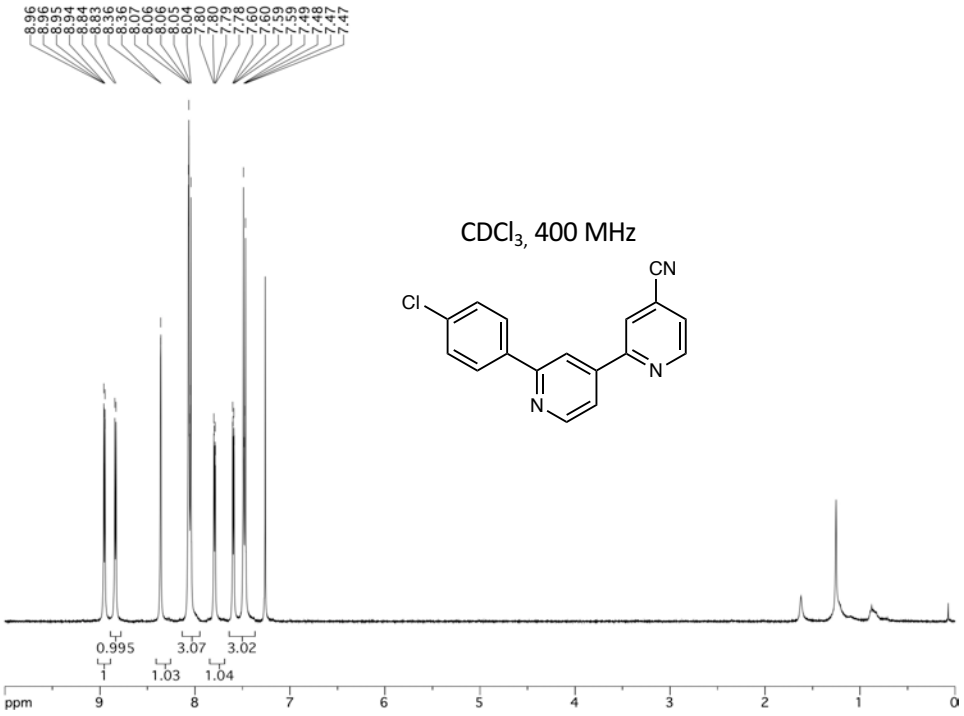

-78.22
CDCl3, 365 MHz
16:1 mixture of regioisomers
Major
Minor
f1 (ppm)

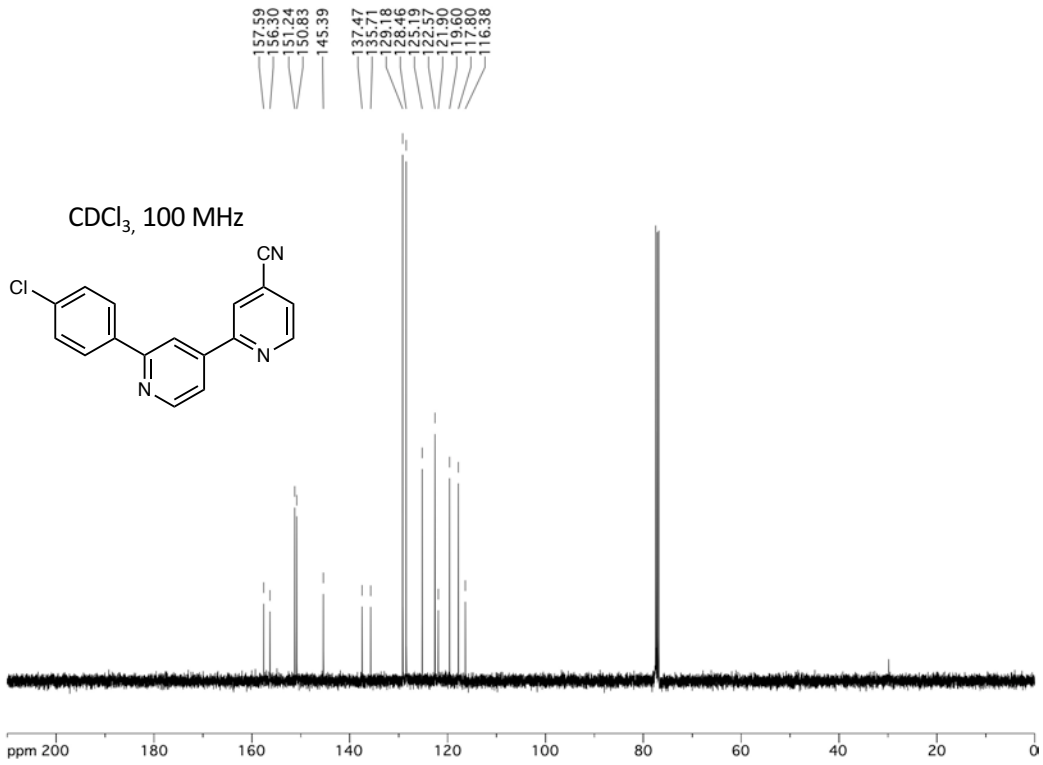

8.92
8.90
8.78
8.76
8.27
8.05
8.03
7.70
7.70
7.69
7.55
7.54
7.02
6.99
3.86
CDCl3, 400 MHz
CN
MeO
N
N
1.09
3.17
1.02
3.2
1
1.07
1.07
2.08
ppm
9
8
7
6
5
4
3
2
1
0

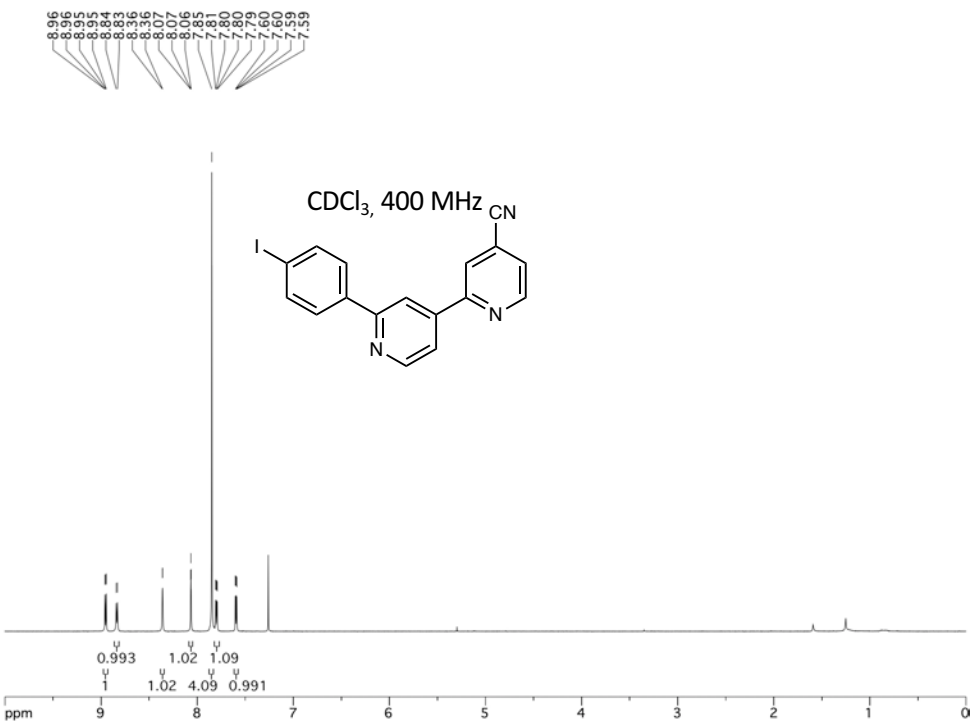

160.81
158.20
156.43
151.00
150.48
144.98
131.50
128.36
124.91
122.45
121.61
118.56
117.03
116.40
114.23
55.42
CDCl3, 100 MHz
CN
MeO
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0

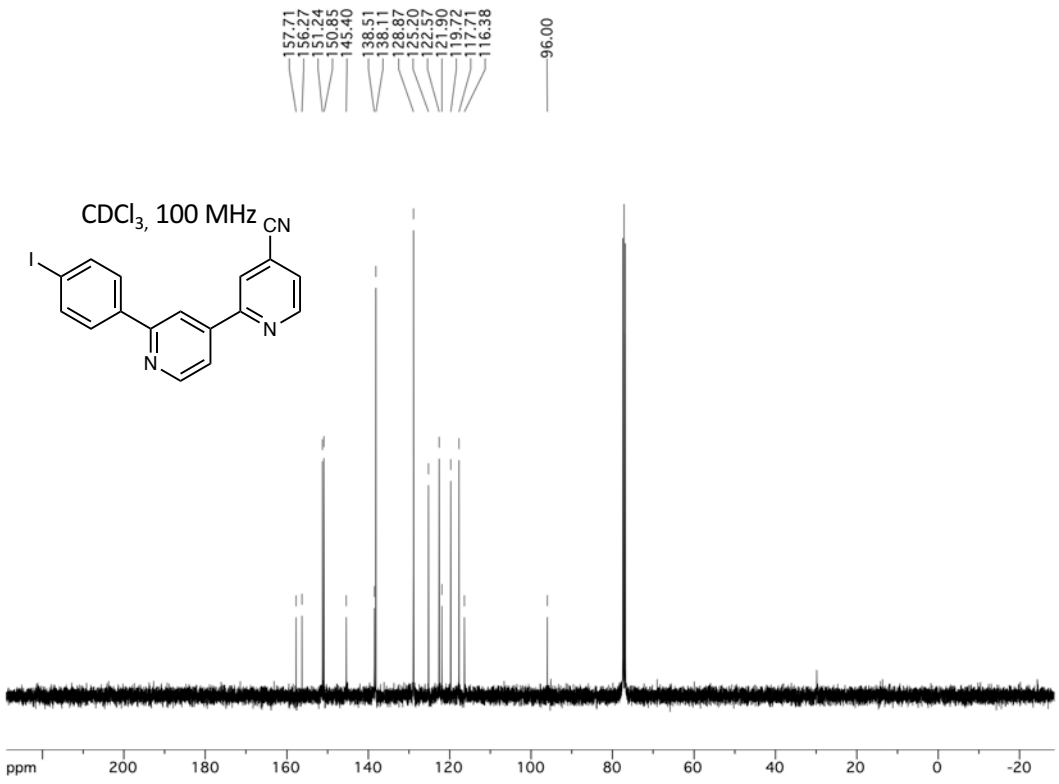

8.93
8.92
8.84
8.83
8.38
8.11
8.09
8.06
7.95
7.93
7.79
7.78
7.77
7.57
7.56
7.56
1.37
CDCl3, 400 MHz
O
B
O
CN
N
N
1
1.98
0.943
1.96
2.97
1.01
12.1
ppm
9
8
7
6
5
4
3
2
1
0

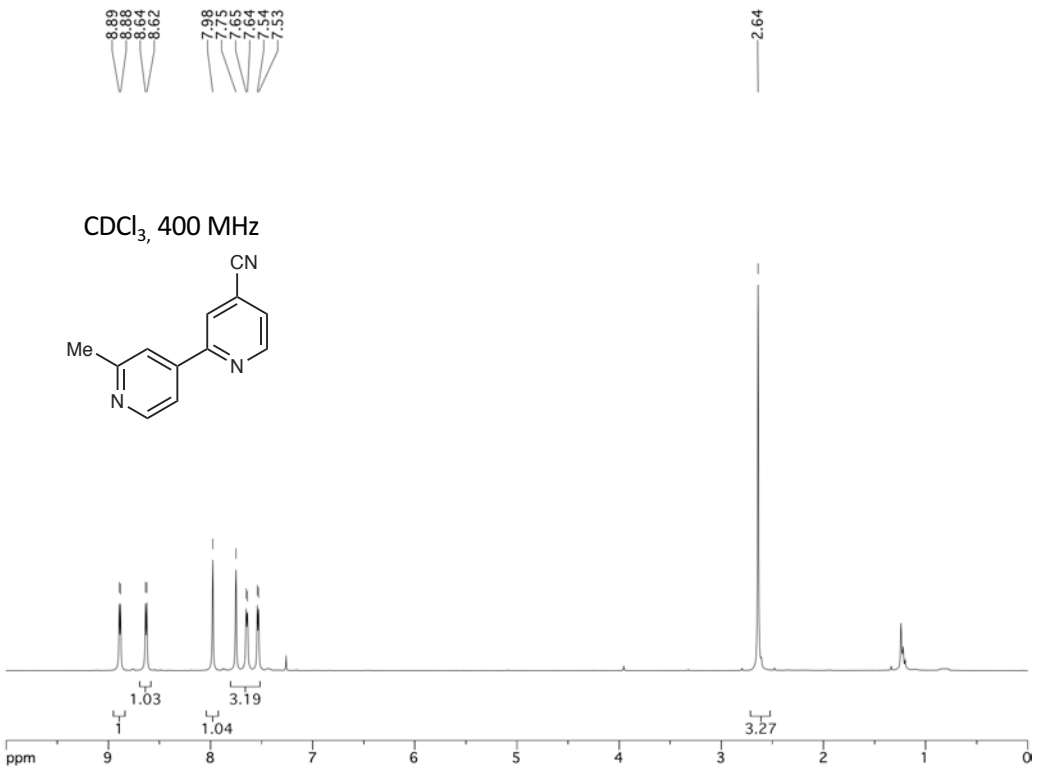

158.28
156.19
151.04
150.62
145.14
141.24
135.29
129.97
126.21
125.01
122.47
121.64
119.55
118.03
116.32
83.98
24.96
CDCl3, 100 MHz
O
B
O
CN
N
N
ppm
200
180
160
140
120
100
80
60
40
20
0
-20

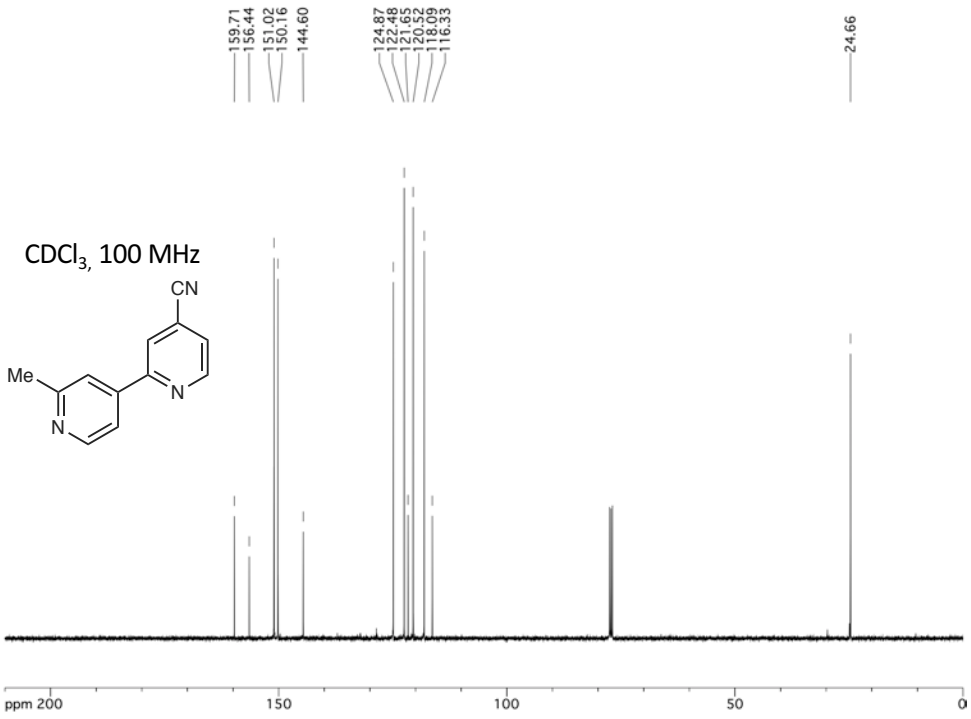

8.96
8.96
8.95
8.95
8.84
8.84
8.83
8.36
8.36
8.07
8.06
8.06
8.05
8.04
7.80
7.79
7.78
7.60
7.59
7.59
7.49
7.48
7.47
7.47
CDCl3, 400 MHz
Cl
N
N
CN
0.995
3.07
3.02
1
1.03
1.04
ppm
9
8
7
6
5
4
3
2
1
0

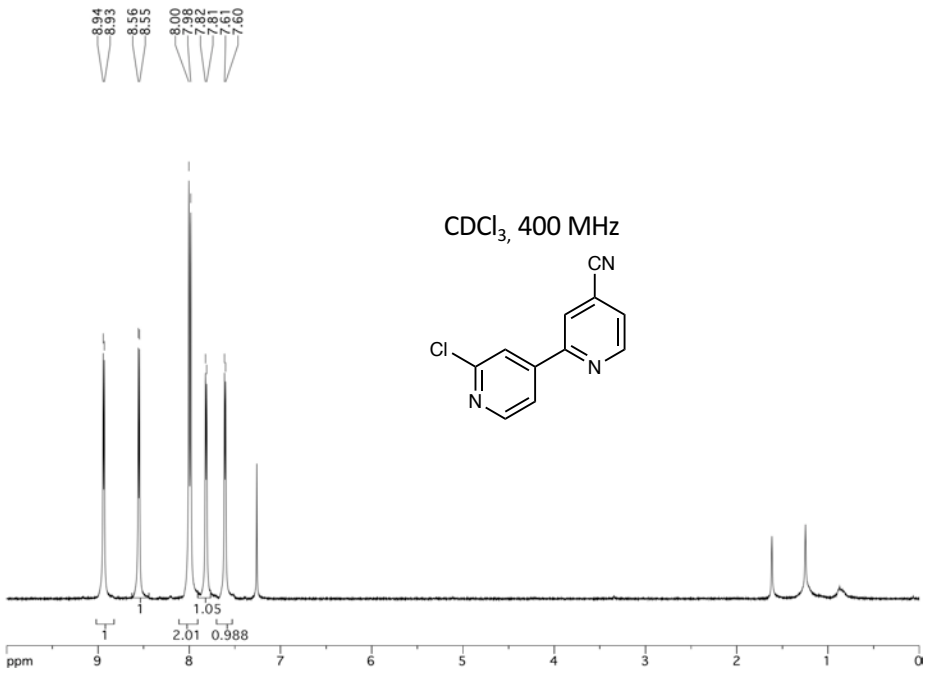

157.59
156.30
151.24
150.83
145.39
137.47
135.71
129.18
128.46
125.19
122.57
121.90
119.60
117.80
116.38
CDCl3, 100 MHz
CN
Cl
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0

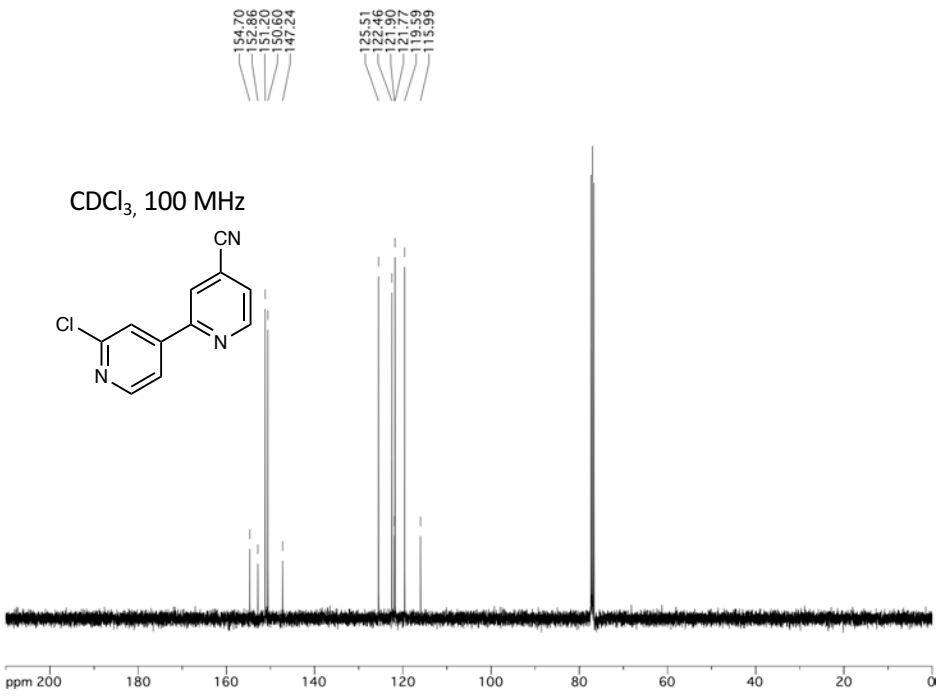

8.96
8.96
8.95
8.95
8.84
8.83
8.36
8.36
8.07
8.07
8.06
7.85
7.81
7.80
7.80
7.79
7.60
7.60
7.59
7.59
CDCl3, 400 MHz
CN
I
N
N
0.993
1.02
1.09
1
1.02
4.09
0.991
ppm
9
8
7
6
5
4
3
2
1
0

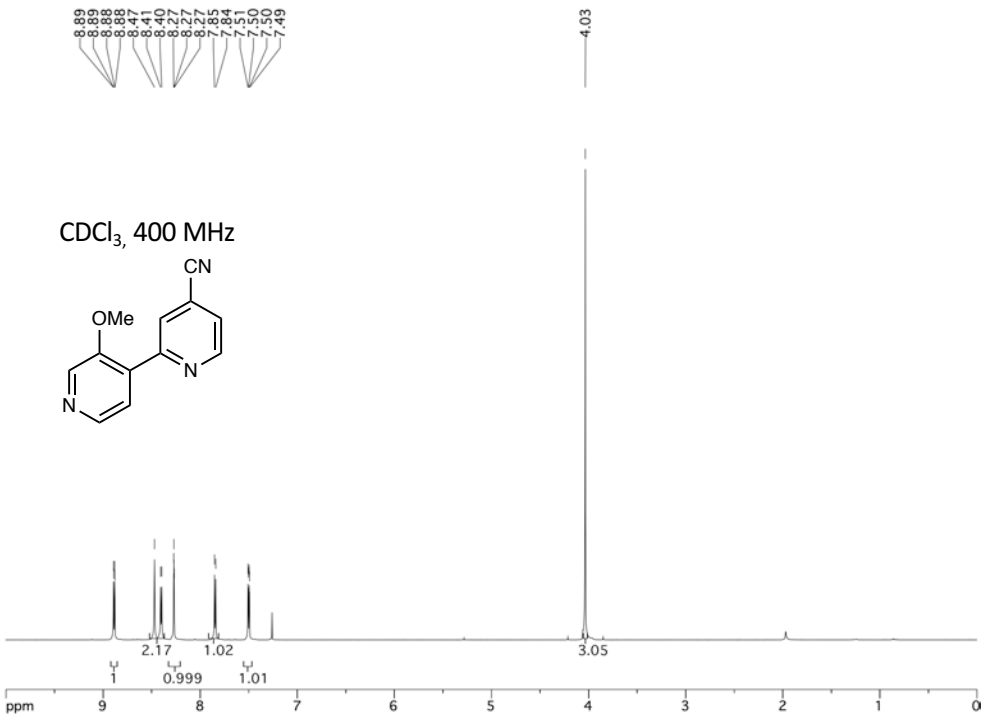

157.71
156.27
151.24
150.85
145.40
138.51
138.11
128.87
125.20
122.57
121.90
119.72
117.71
116.38
96.00
CDCl3, 100 MHz
CN
I
N
N
ppm
200
180
160
140
120
100
80
60
40
20
0
-20

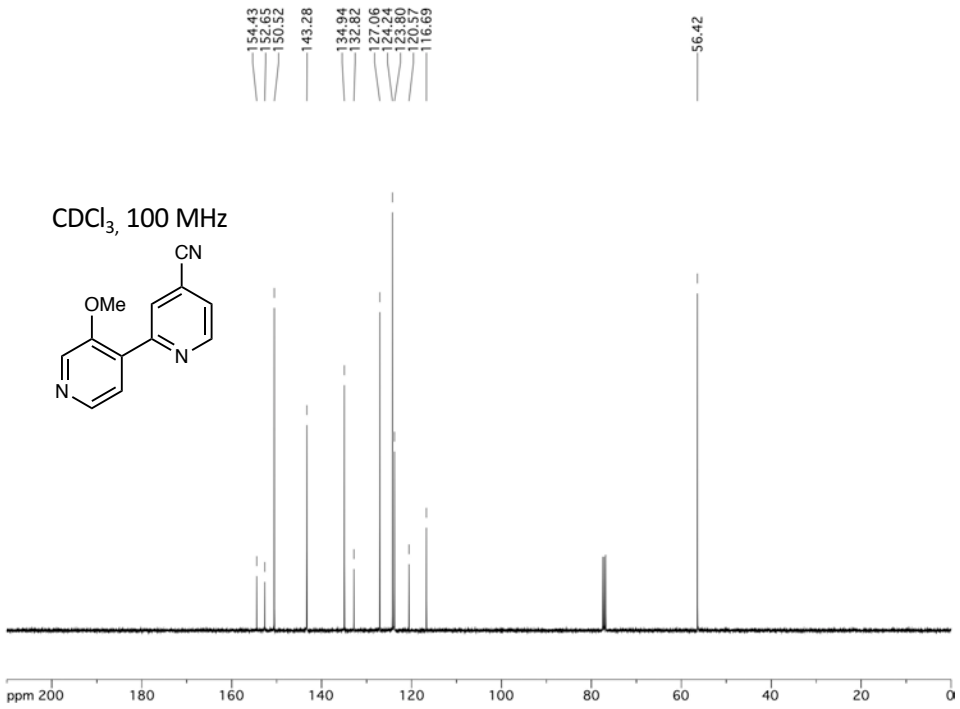

8.89
8.88
8.64
8.62
7.98
7.75
7.65
7.64
7.54
7.53
2.64
CDCl3, 400 MHz
CN
Me
N
N
1.03
3.19
1
1.04
3.27
ppm
9
8
7
6
5
4
3
2
1
0

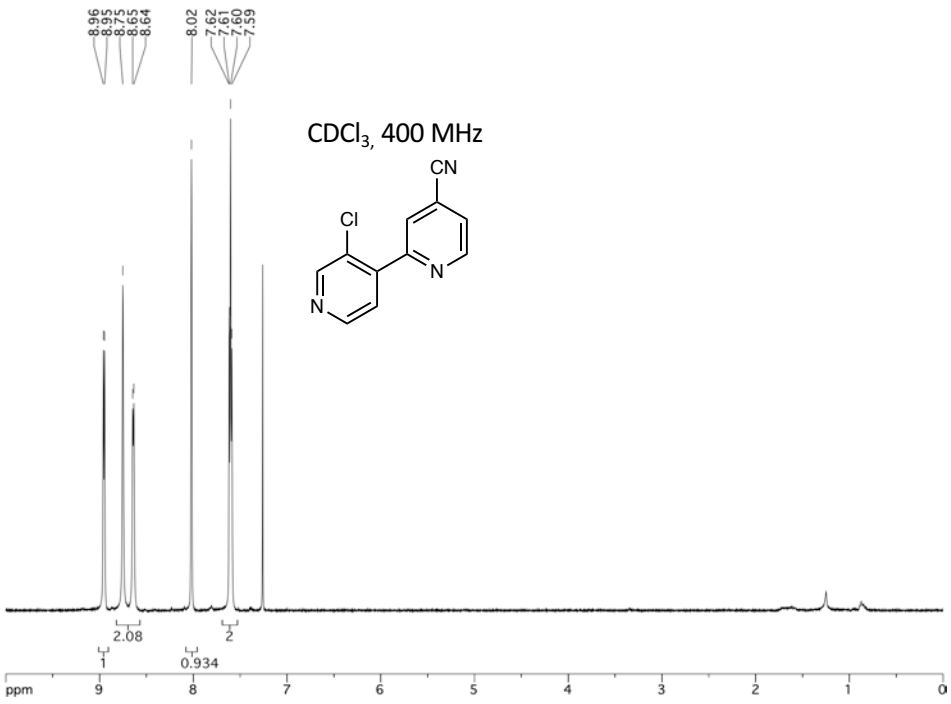

159.71
156.44
151.02
150.16
144.60
124.87
122.48
121.65
120.52
118.09
116.33
24.66
CDCl3, 100 MHz
CN
Me
N
N
ppm 200
150
100
50
0

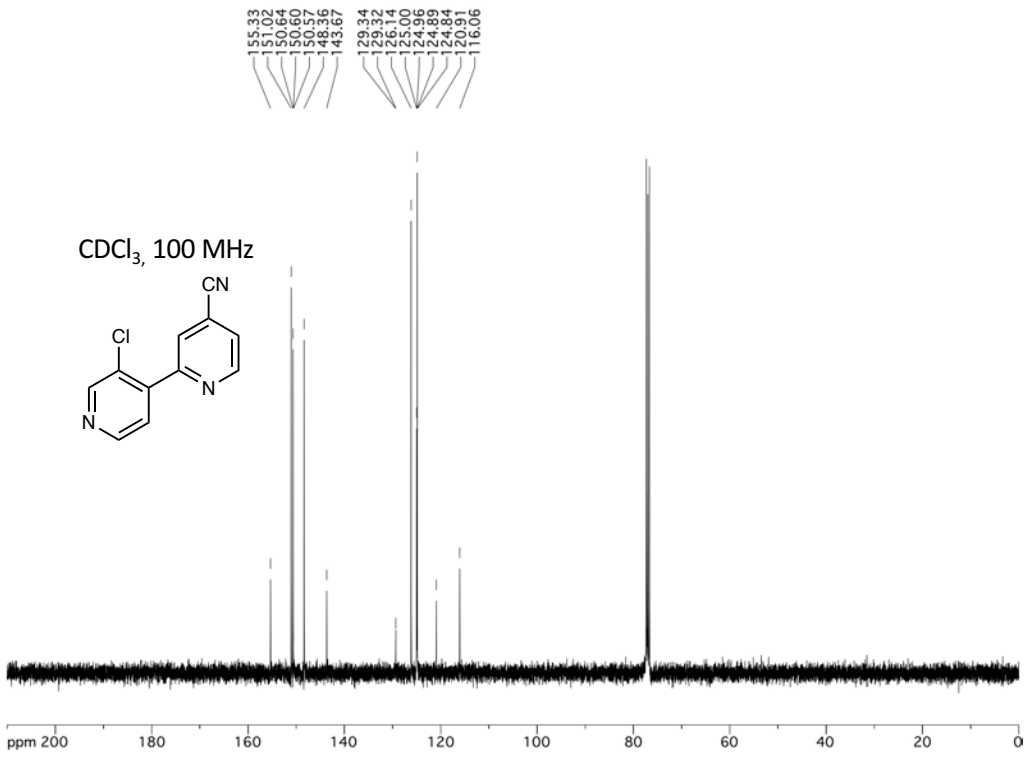

8.94
8.93
8.56
8.55
8.00
7.98
7.82
7.81
7.61
7.60
CDCl3, 400 MHz
CN
Cl
N
N
1
1
1.05
1
2.01
0.988
ppm
9
8
7
6
5
4
3
2
1
0

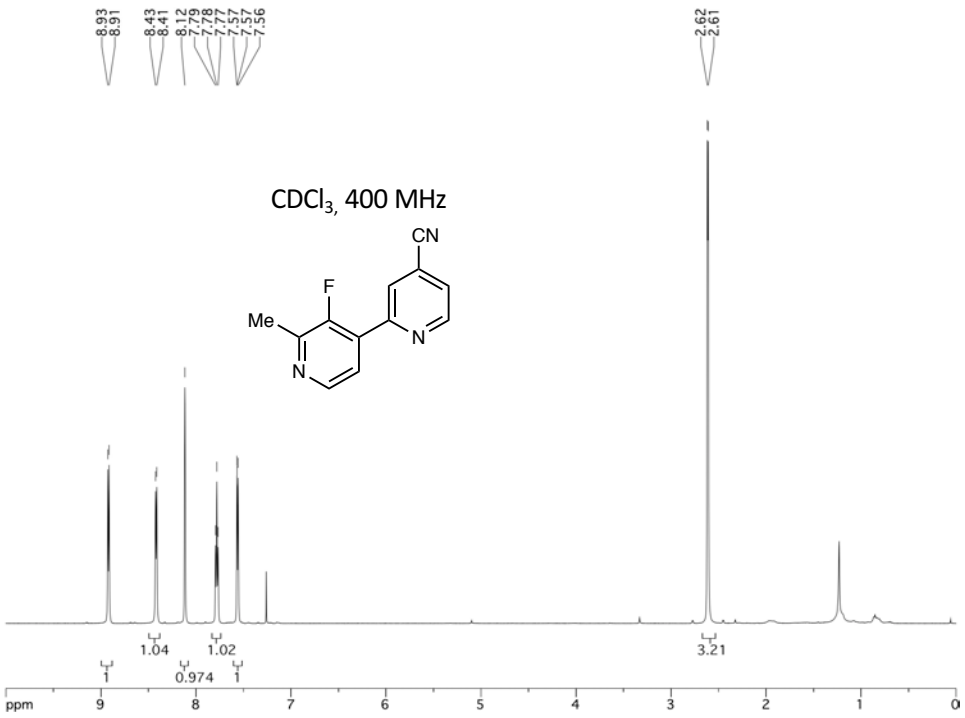

154.70
152.86
151.20
150.60
147.24
125.51
122.46
121.90
121.77
119.59
115.99
CDCl3, 100 MHz
CN
Cl
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0

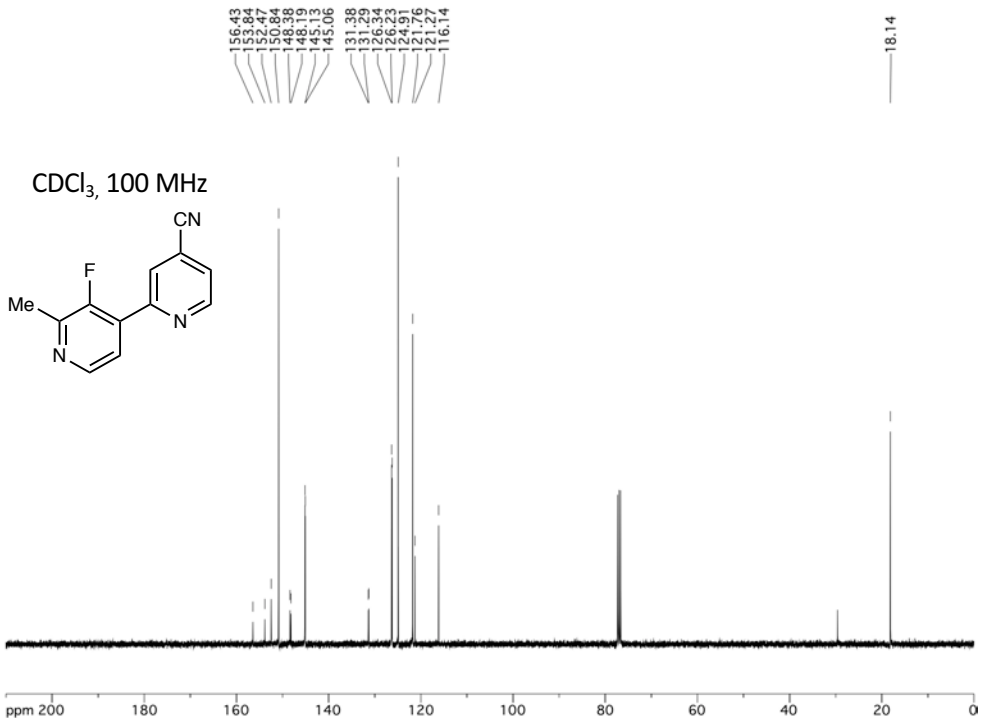

8.89
8.89
8.88
8.88
8.47
8.41
8.40
8.27
8.27
8.27
7.85
7.84
7.51
7.50
7.50
7.49
4.03
CDCl3, 400 MHz
CN
OMe
N
N
2.17
1.02
3.05
1
0.999
1.01
ppm
9
8
7
6
5
4
3
2
1
0

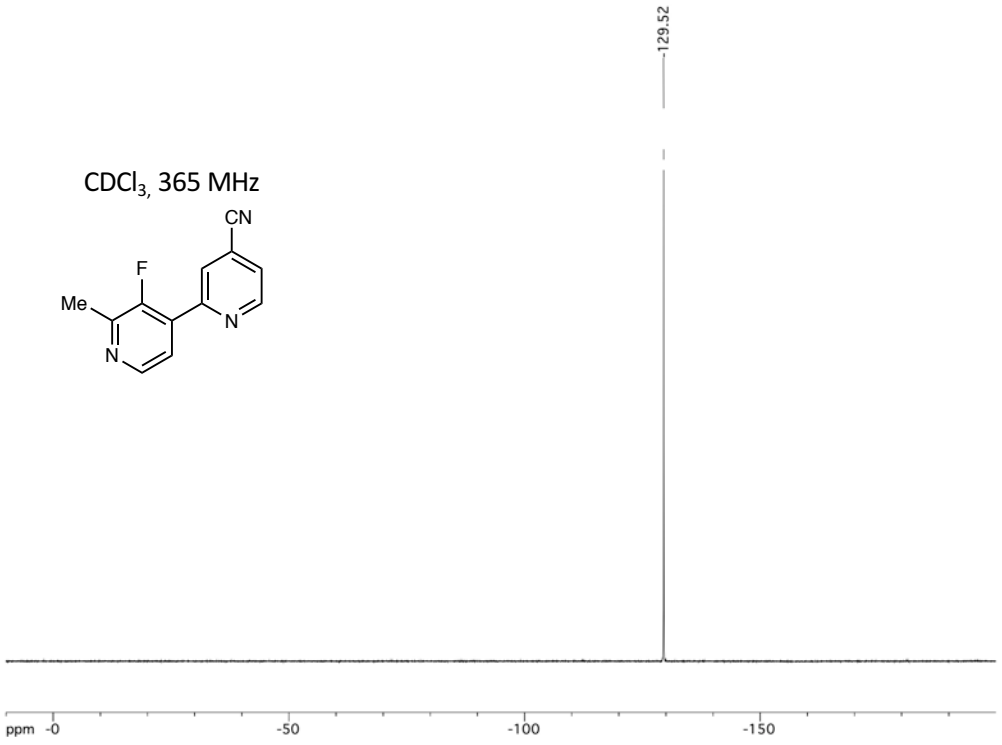

154.43
152.65
150.52
143.28
134.94
132.82
127.06
124.24
123.80
120.57
116.69
56.42
CDCl3, 100 MHz
CN
OMe
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0

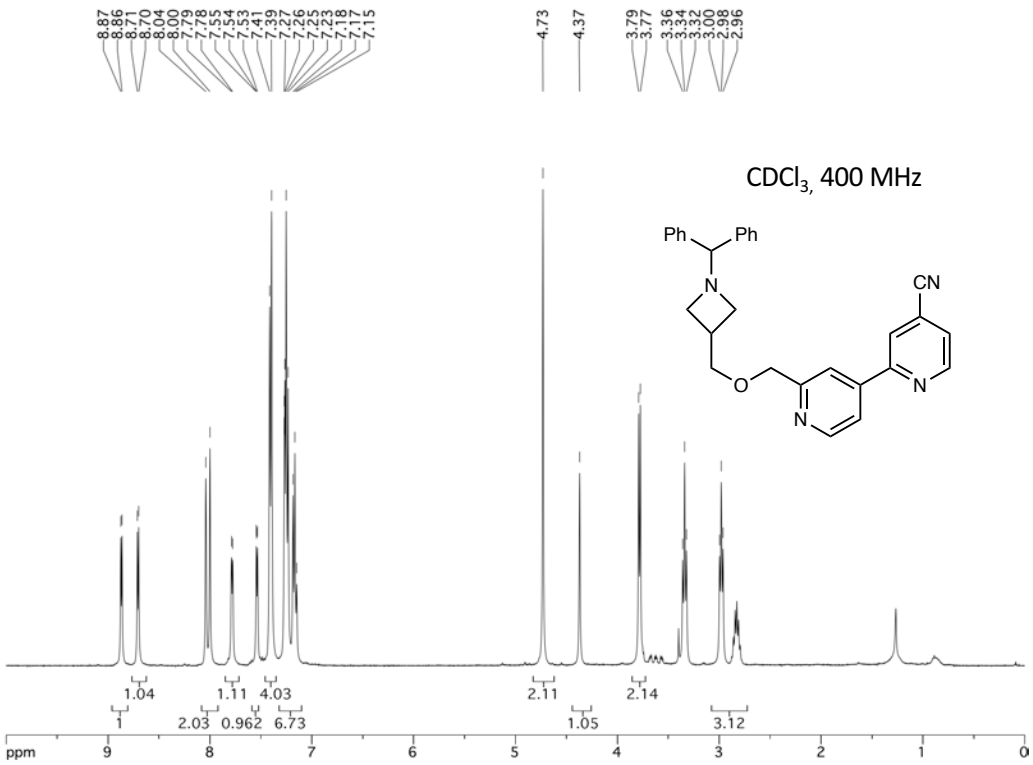

8.96
8.95
8.75
8.65
8.64
8.02
7.62
7.61
7.60
7.59
CDCl3, 400 MHz
CN
Cl
N
N
2.08
2
1
0.934
ppm
9
8
7
6
5
4
3
2
1
0

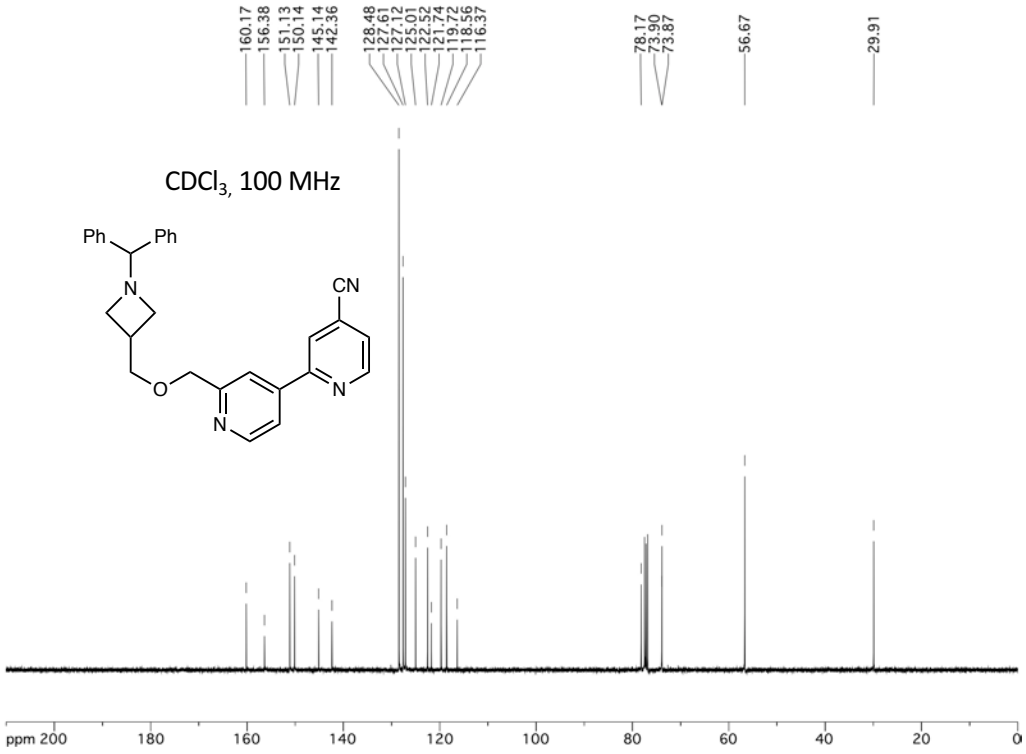

155.33
151.02
150.64
150.60
150.57
148.36
143.67
129.34
129.32
126.14
125.00
124.96
124.89
124.84
120.91
116.06
CDCl3, 100 MHz
CN
Cl
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0


8.93
8.91
8.43
8.41
8.12
7.79
7.78
7.77
7.57
7.57
7.56
2.62
2.61
CDCl3, 400 MHz
CN
F
Me
N
N
1.04
1.02
3.21
1
0.974
1
ppm
9
8
7
6
5
4
3
2
1
0

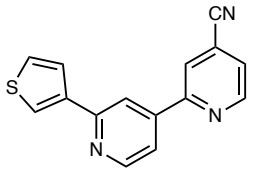

156.43
153.84
152.47
150.84
148.38
148.19
145.13
145.06
131.38
131.29
126.34
126.23
124.91
121.76
121.27
116.14
18.14
CDCl3, 100 MHz
CN
F
Me
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0

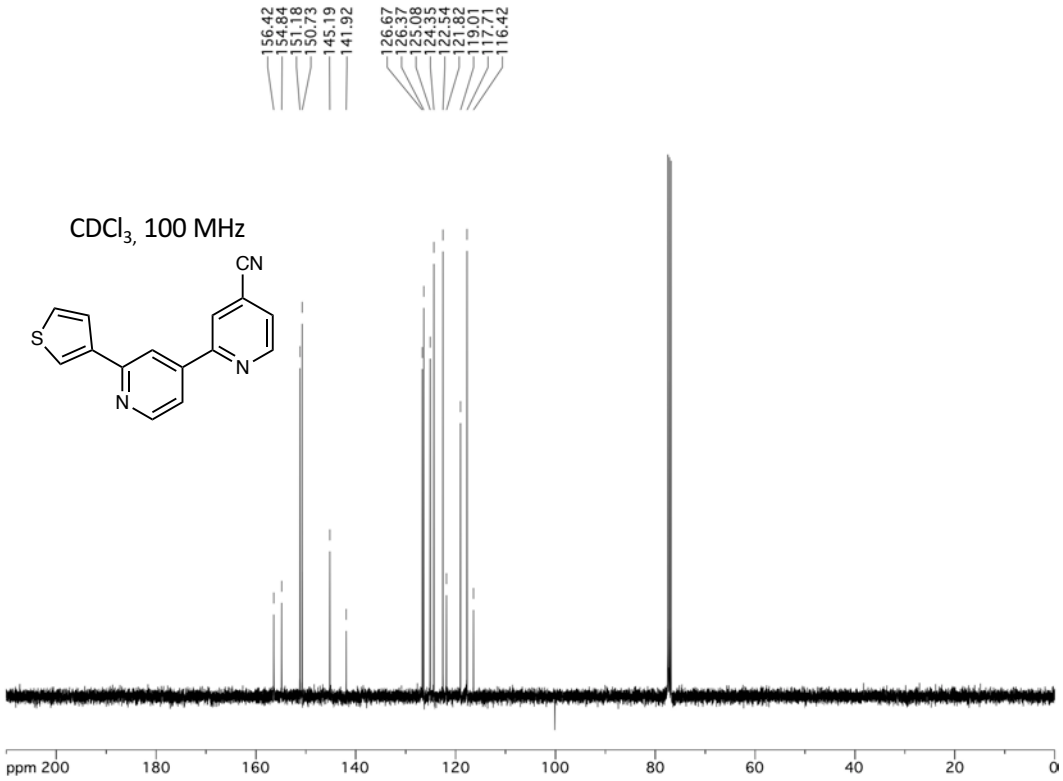

129.52
CDCl3, 365 MHz
CN
F
Me
N
N
ppm -0
-50
-100
-150

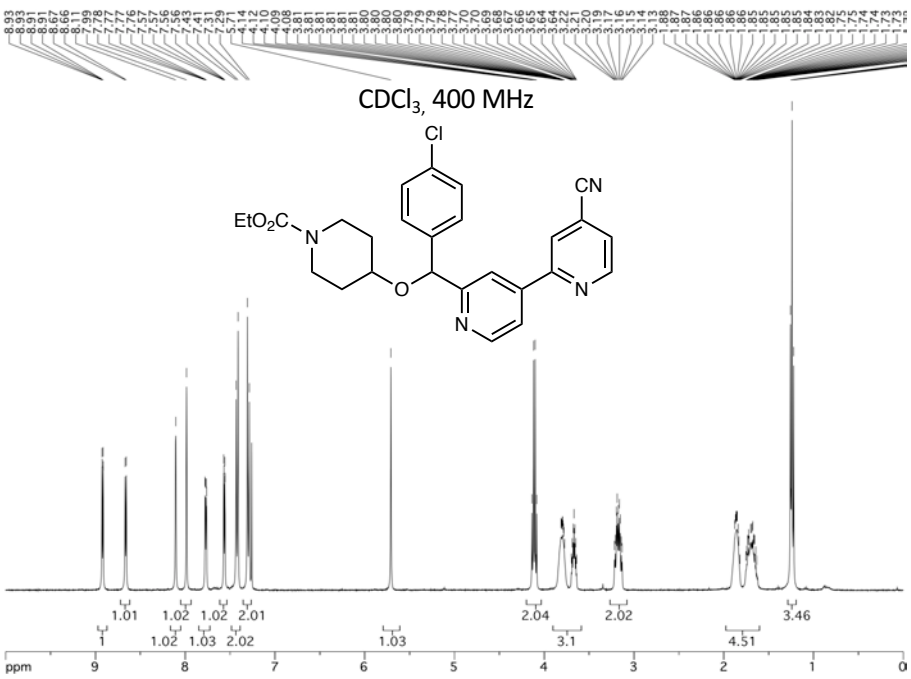

8.87
8.86
8.71
8.70
8.04
8.00
7.79
7.78
7.55
7.54
7.53
7.41
7.39
7.27
7.26
7.25
7.23
7.18
7.17
7.15
4.73
4.37
3.79
3.77
3.36
3.34
3.32
3.00
2.98
2.96
CDCl3, 400 MHz
Ph
Ph
N
CN
O
N
N
1.04
1.11
4.03
2.11
2.14
1
2.03
0.962
6.73
1.05
3.12
ppm
9
8
7
6
5
4
3
2
1
0

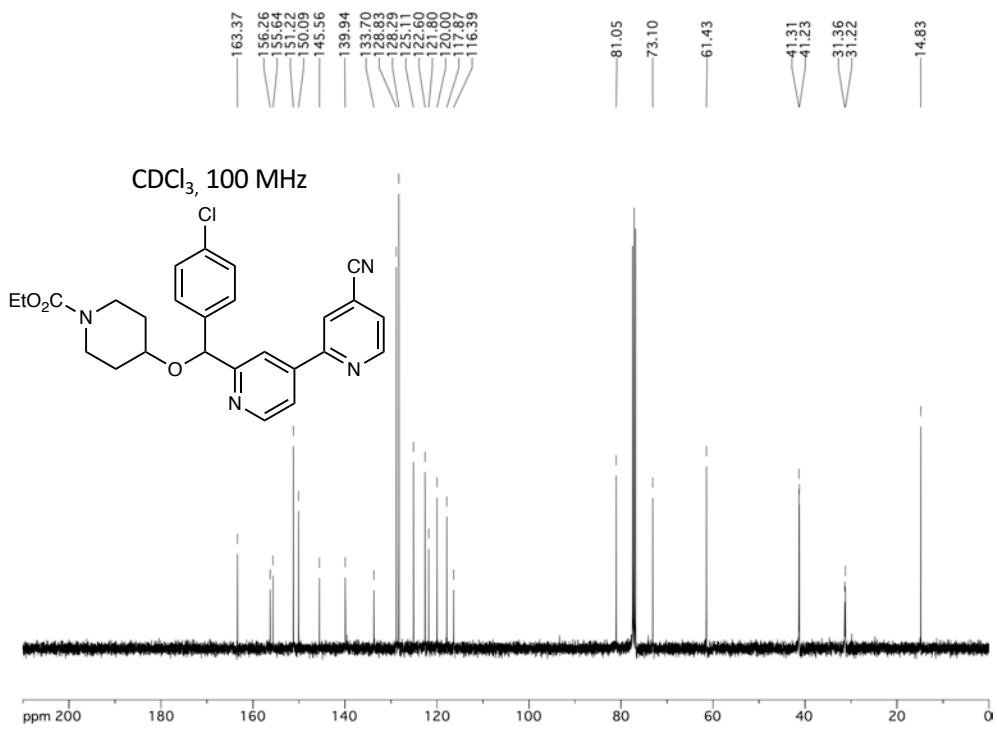

160.17
156.38
151.13
150.14
145.14
142.36
128.48
127.61
127.12
125.01
122.52
121.74
119.72
118.56
116.37
78.17
73.90
73.87
56.67
29.91
CDCl3, 100 MHz
Ph
Ph
N
O
N
N
CN
ppm 200
180
160
140
120
100
80
60
40
20
0

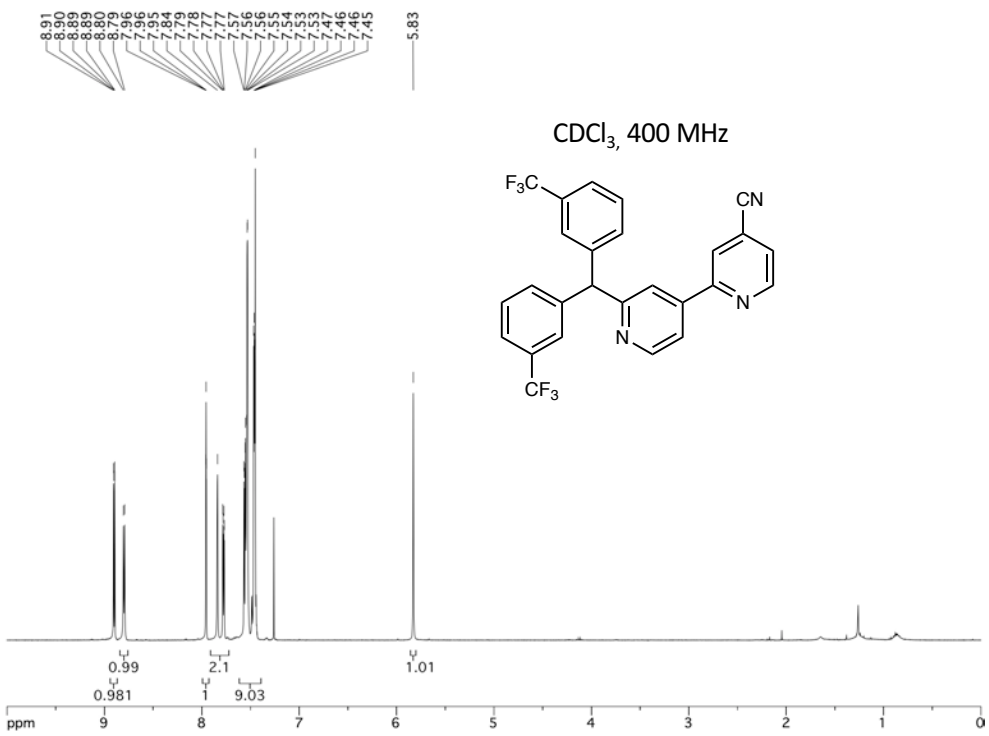
$CDCl_3$, 400 MHz

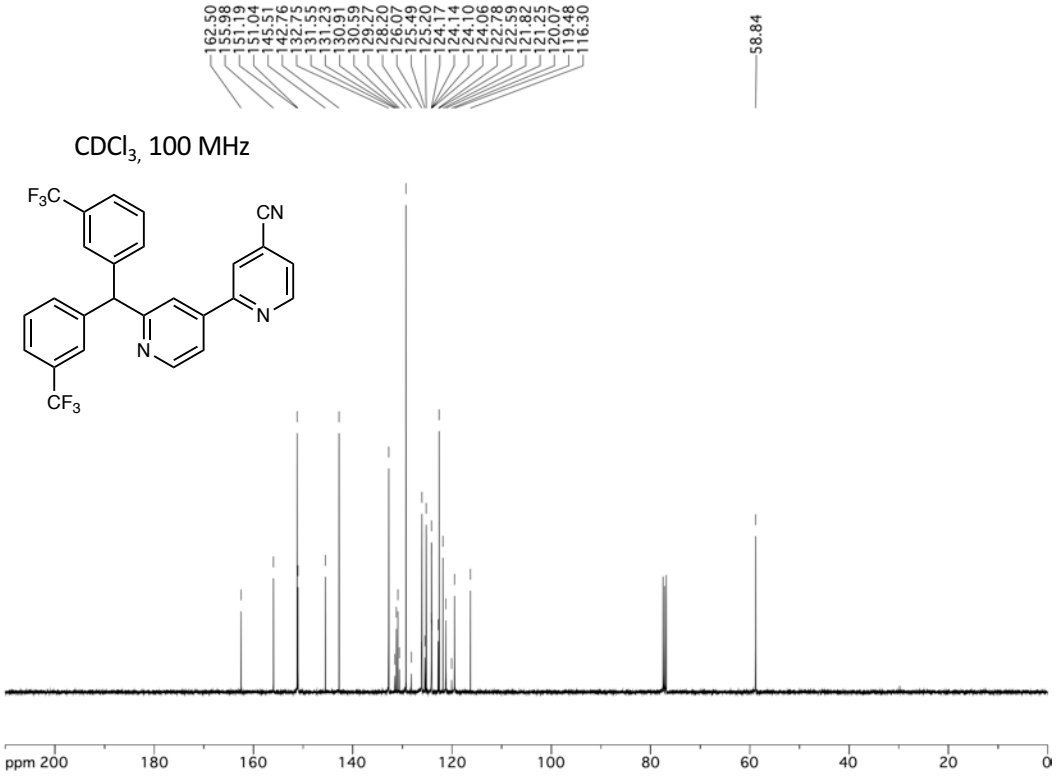


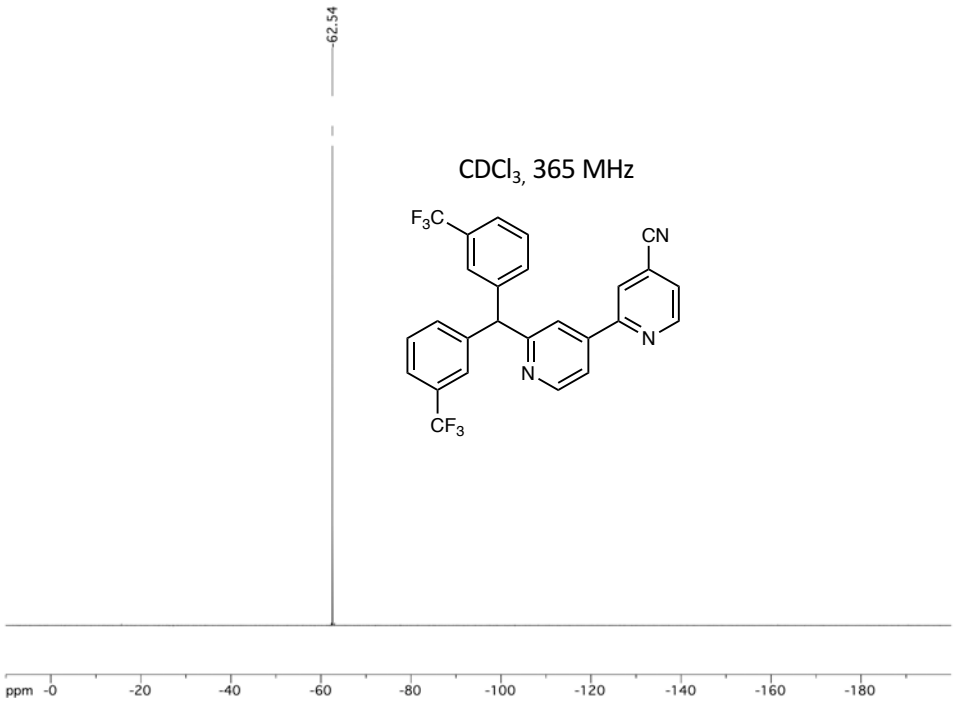

156.42
154.84
151.18
150.73
145.19
141.92
126.67
126.37
125.08
124.35
122.54
121.82
119.01
117.71
116.42
CDCl3, 100 MHz
CN
S
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0

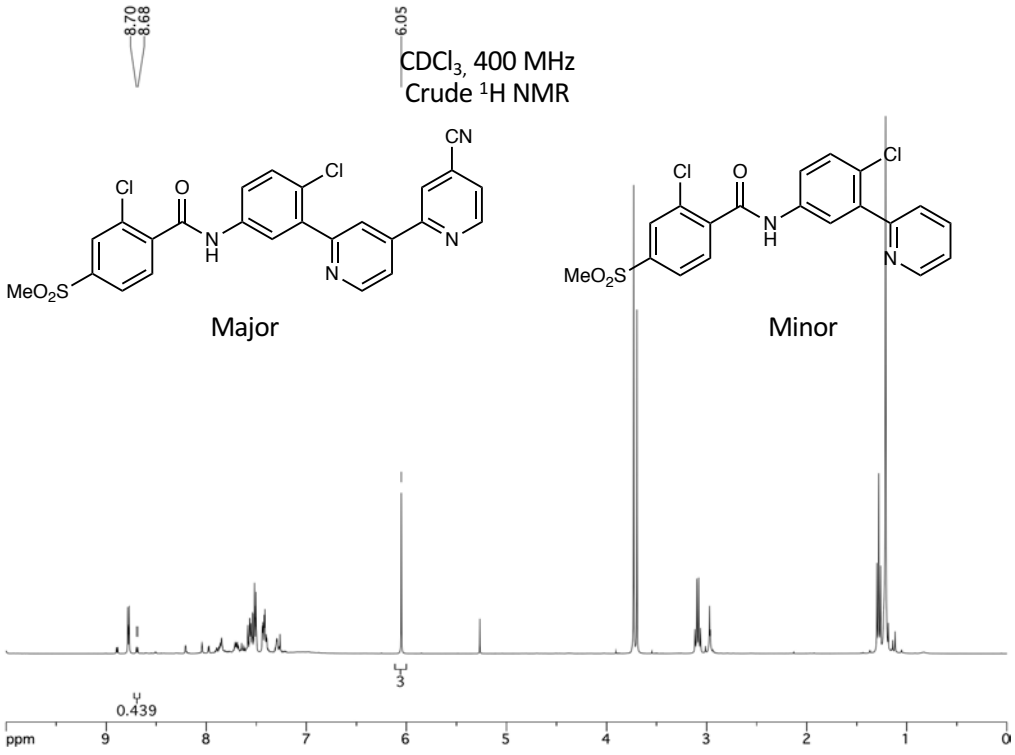

CDCl3, 400 MHz
Cl
CN
EtO2C
N
O
N
N
1.01
1.02
1.02
2.01
2.04
2.02
3.46
1
1.02
1.03
2.02
1.03
3.1
4.51
ppm
9
8
7
6
5
4
3
2
1
0

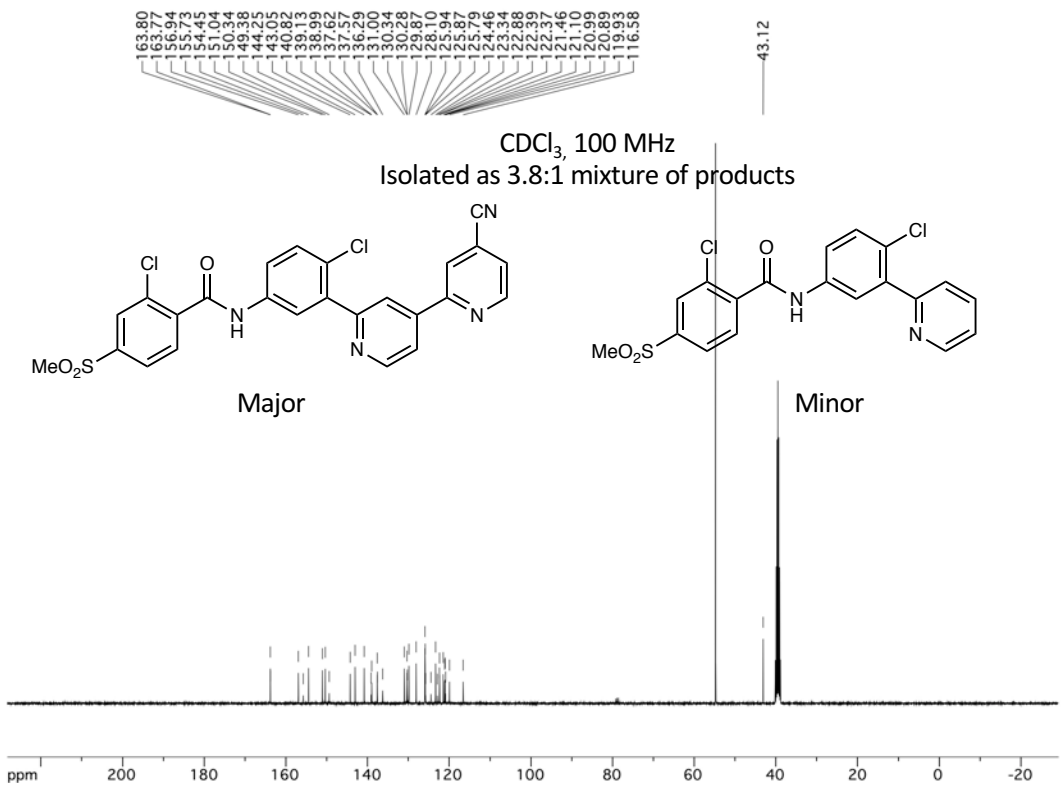

163.37
156.26
155.64
151.22
150.09
145.56
139.94
133.70
128.83
128.29
125.11
122.60
121.80
120.00
117.87
116.39
81.05
73.10
61.43
41.31
41.23
31.36
31.22
14.83
CDCl3, 100 MHz
Cl
CN
EtO2C
N
O
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0

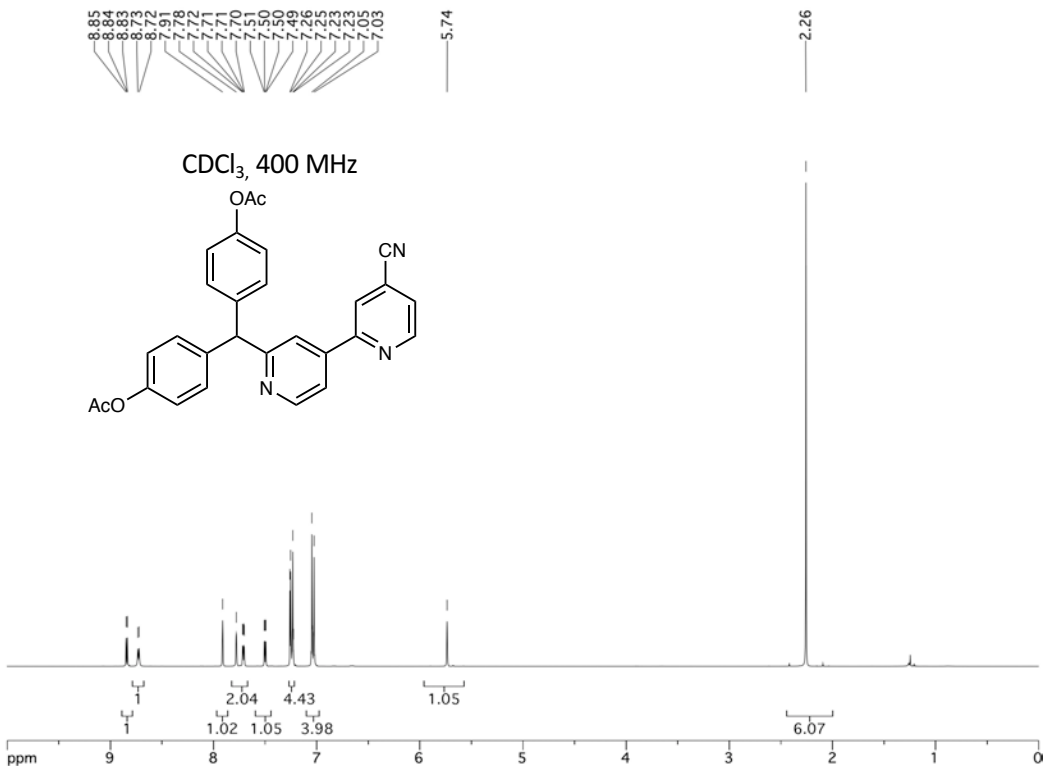

8.91
8.90
8.89
8.89
8.80
8.79
7.96
7.95
7.84
7.79
7.78
7.77
7.77
7.57
7.56
7.56
7.55
7.54
7.53
7.53
7.47
7.46
7.46
7.45
5.83
CDCl3, 400 MHz
F3C
CN
N
N
CF3
0.99
2.1
1.01
0.981
1
9.03
ppm
9
8
7
6
5
4
3
2
1
0

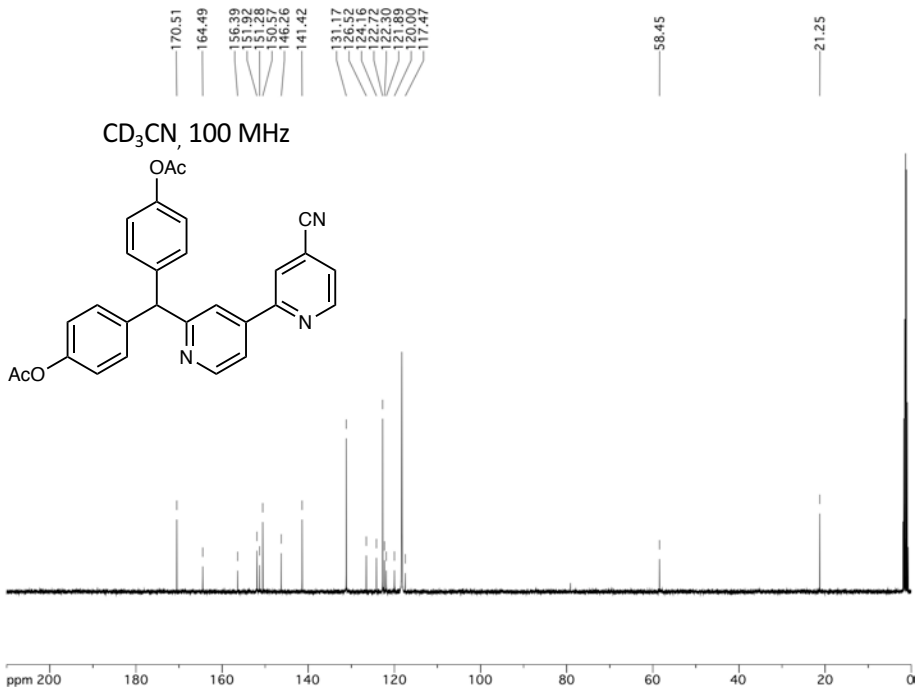

162.50
155.98
151.19
151.04
145.51
142.76
132.75
131.55
131.23
130.91
130.59
129.27
128.20
126.07
125.49
125.20
124.17
124.14
124.10
124.06
122.78
122.59
121.82
121.25
120.07
119.48
116.30
58.84
CDCl3, 100 MHz
F3C
CN
N
N
CF3
ppm 200
180
160
140
120
100
80
60
40
20
0

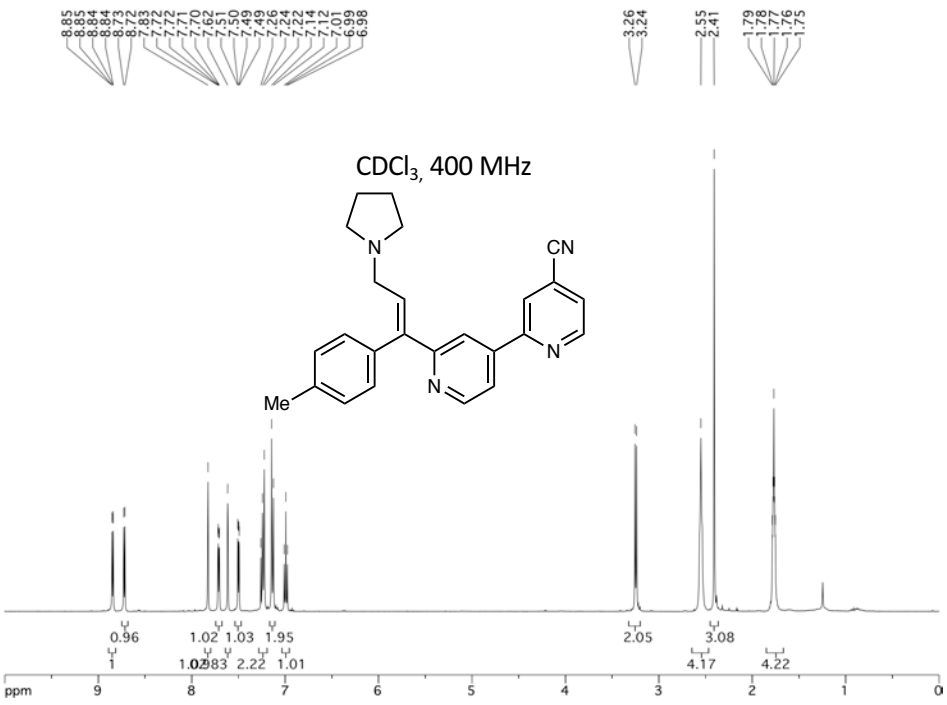

62.54
CDCl3, 365 MHz
F3C
CN
N
N
CF3
ppm -0 -20 -40 -60 -80 -100 -120 -140 -160 -180

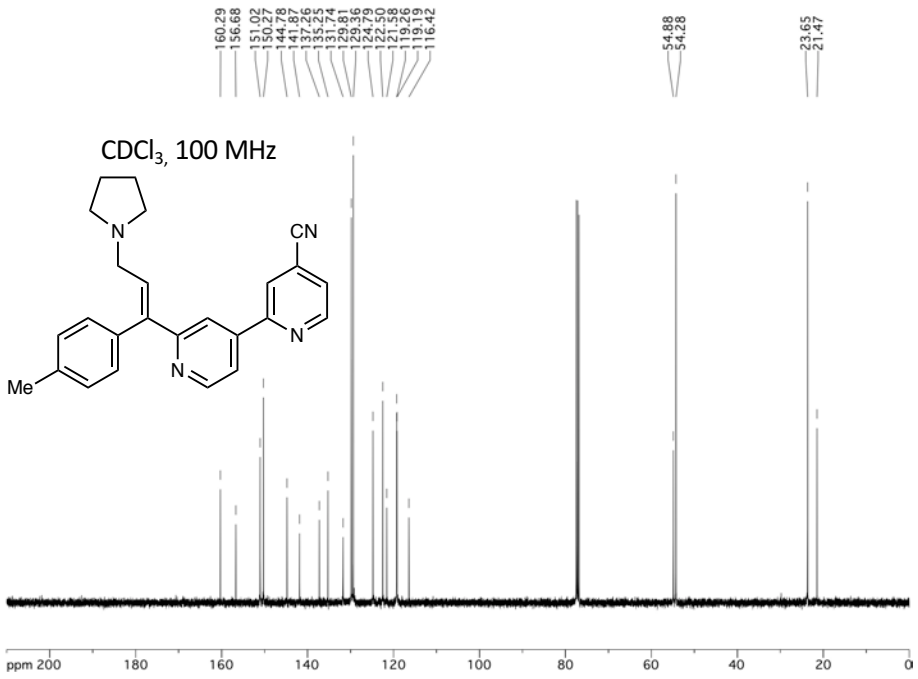

8.70
8.68
6.05
CDCl3, 400 MHz
Crude 1H NMR
Cl
O
N
H
Cl
CN
N
N
MeO2S
Major
Cl
O
N
H
Cl
N
MeO2S
Minor
3
0.439
ppm
9
8
7
6
5
4
3
2
1
0

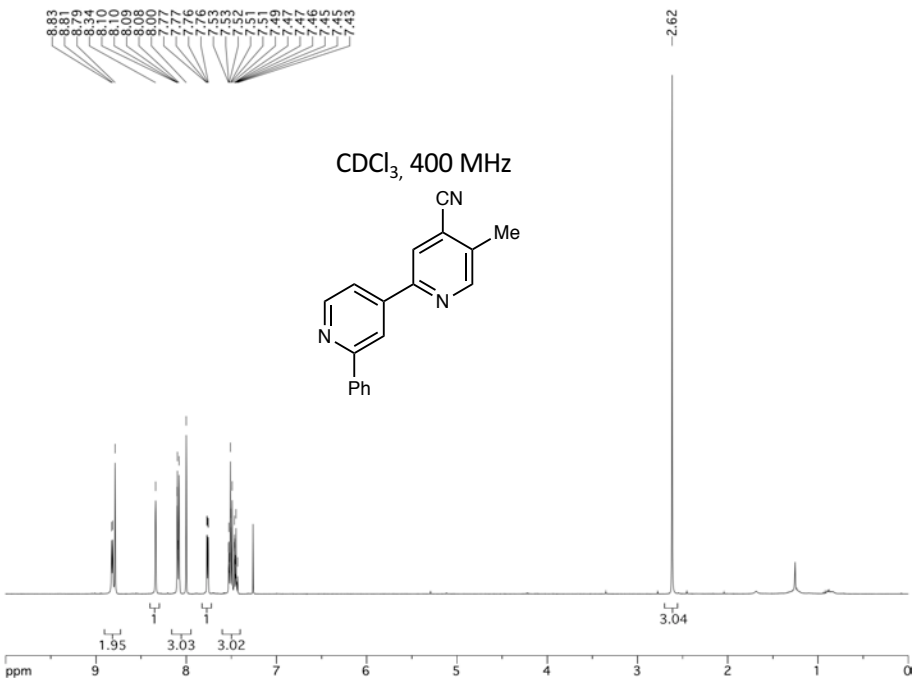

163.80
163.77
156.94
155.73
154.45
151.04
150.34
149.38
144.25
143.05
140.82
139.13
138.99
137.62
137.57
136.29
131.00
130.34
130.28
129.87
128.10
125.94
125.87
125.79
124.46
123.34
122.88
122.39
122.37
121.46
121.10
120.99
120.89
119.93
116.58
43.12
CDCl3, 100 MHz
Isolated as 3.8:1 mixture of products
Major
Minor
ppm
200
180
160
140
120
100
80
60
40
20
0
-20

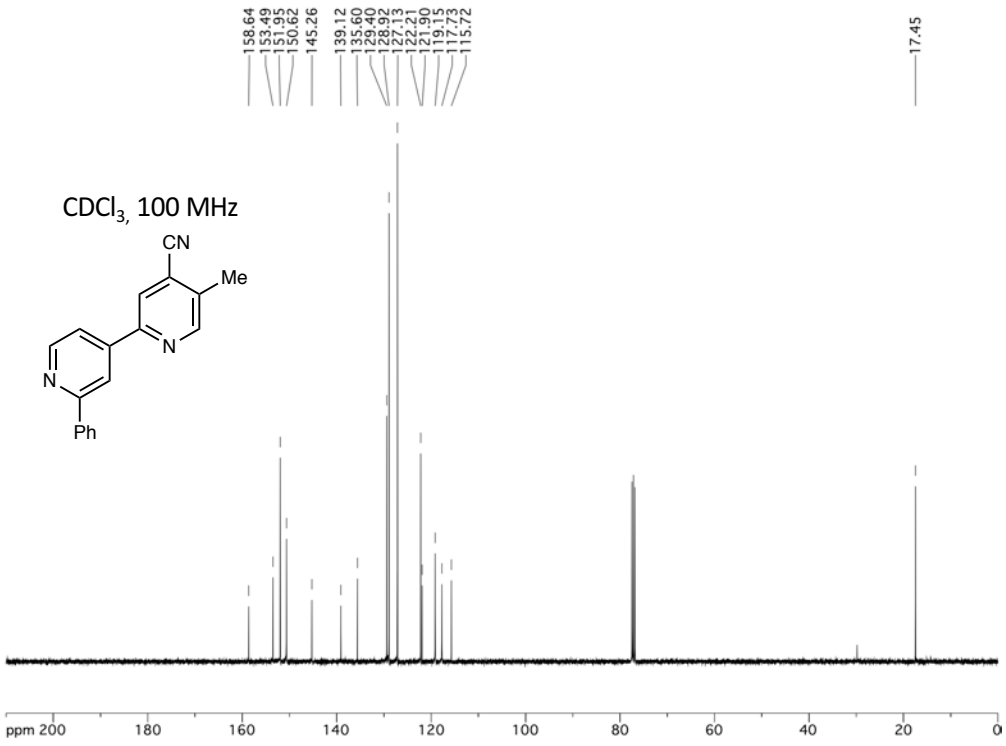

8.85
8.84
8.83
8.73
8.72
7.91
7.78
7.72
7.71
7.70
7.51
7.50
7.49
7.26
7.25
7.23
7.23
7.05
7.03
5.74
2.26
CDCl3, 400 MHz
OAc
CN
N
N
AcO
1
2.04
4.43
1.05
1
1.02
1.05
3.98
6.07
ppm
9
8
7
6
5
4
3
2
1
0

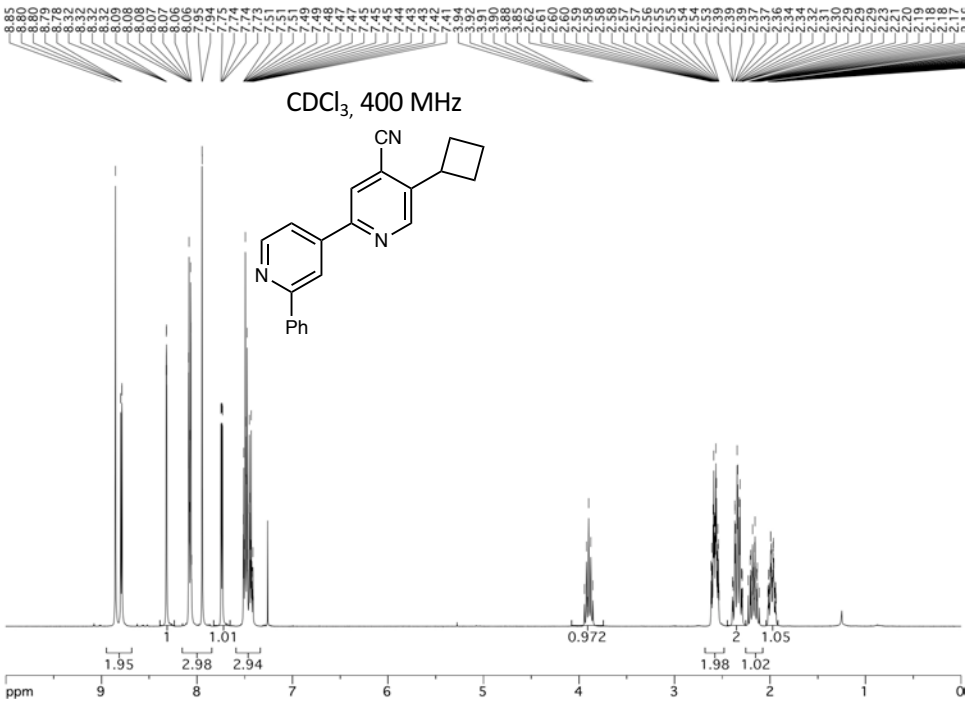

170.51
164.49
156.39
151.22
151.28
150.57
146.26
141.42
131.17
126.52
124.16
122.72
122.30
121.89
120.00
117.47
58.45
21.25
CD3CN, 100 MHz
OAc
CN
AcO
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0

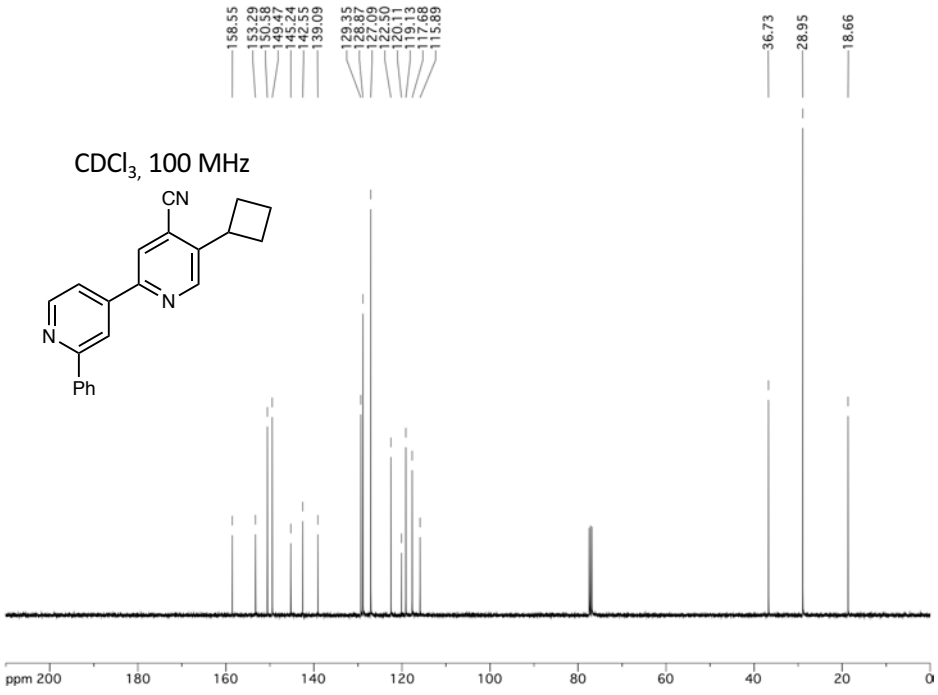

8.85
8.85
8.84
8.84
8.73
8.72
7.83
7.72
7.71
7.71
7.70
7.62
7.51
7.50
7.49
7.49
7.26
7.24
7.22
7.14
7.12
7.01
6.99
6.98
3.26
3.24
2.55
2.41
1.79
1.78
1.77
1.76
1.75
CDCl3, 400 MHz
N
CN
N
N
Me
0.96
1.02
1.03
1.95
2.05
3.08
1
1.02
0.83
2.22
1.01
4.17
4.22
ppm
9
8
7
6
5
4
3
2
1
0

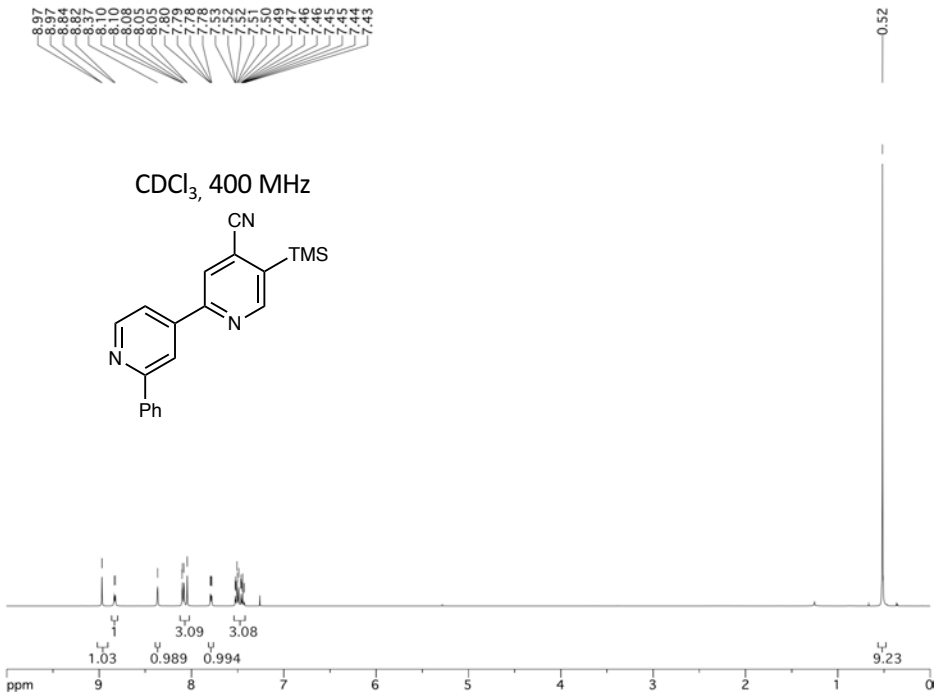

160.29
156.68
151.02
150.27
144.78
141.87
137.26
135.25
131.74
129.81
129.36
124.79
122.50
121.58
119.26
119.19
116.42
54.88
54.28
23.65
21.47
CDCl3, 100 MHz
N
CN
N
N
Me
ppm 200
180
160
140
120
100
80
60
40
20
0

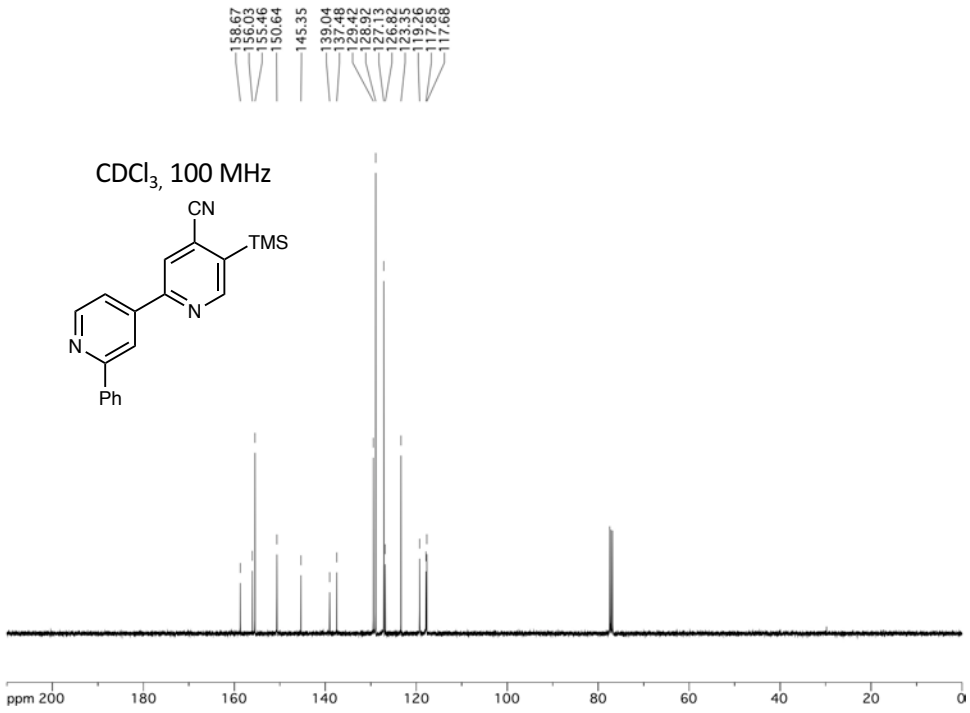

8.83
8.81
8.79
8.34
8.10
8.10
8.09
8.08
8.00
7.77
7.77
7.76
7.76
7.53
7.53
7.52
7.51
7.51
7.49
7.47
7.47
7.46
7.45
7.45
7.43
2.62
CDCl3, 400 MHz
CN
Me
N
N
Ph
1
1
1.95
3.03
3.02
3.04
ppm
9
8
7
6
5
4
3
2
1
0

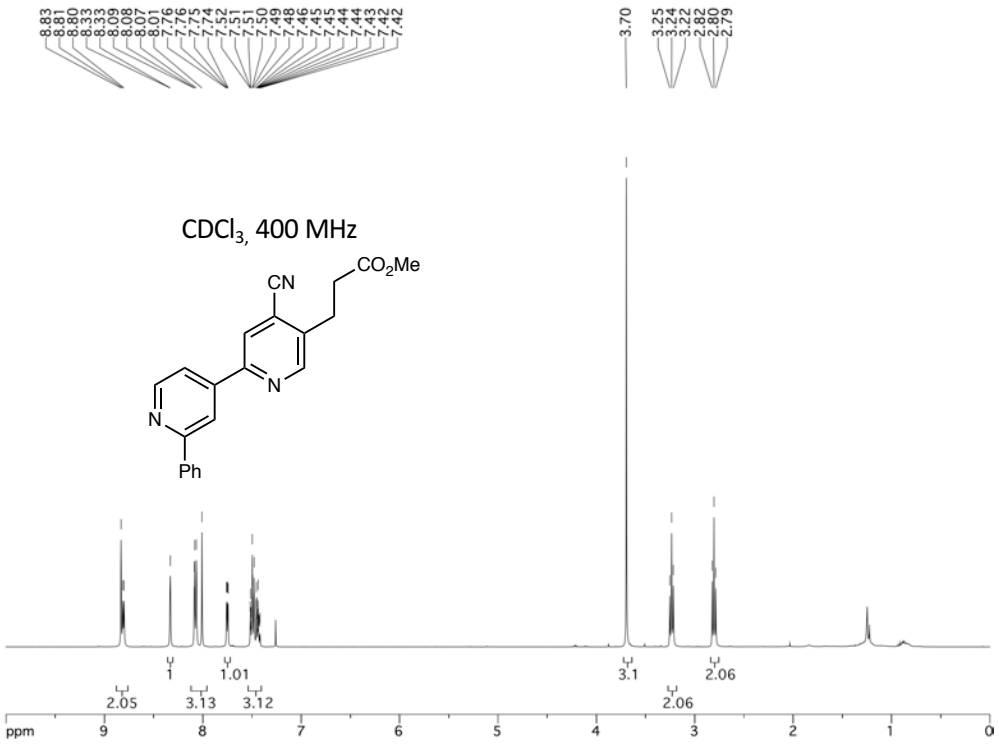

158.64
153.49
151.95
150.62
145.26
139.12
135.60
129.40
128.92
127.13
122.21
121.90
119.15
117.73
115.72
17.45
CDCl3, 100 MHz
CN
Me
N
N
Ph
ppm 200
180
160
140
120
100
80
60
40
20
0

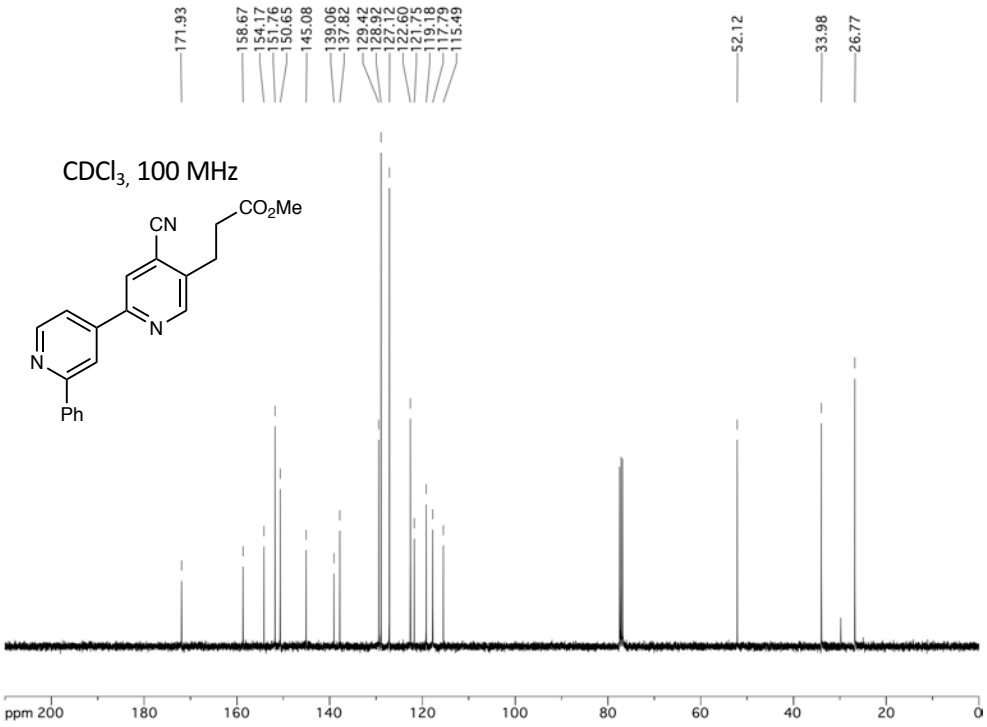

CDCl3, 400 MHz
CN
N
N
Ph
1
1.01
0.972
2
1.05
1.95
2.98
2.94
1.98
1.02
ppm
9
8
7
6
5
4
3
2
1
0

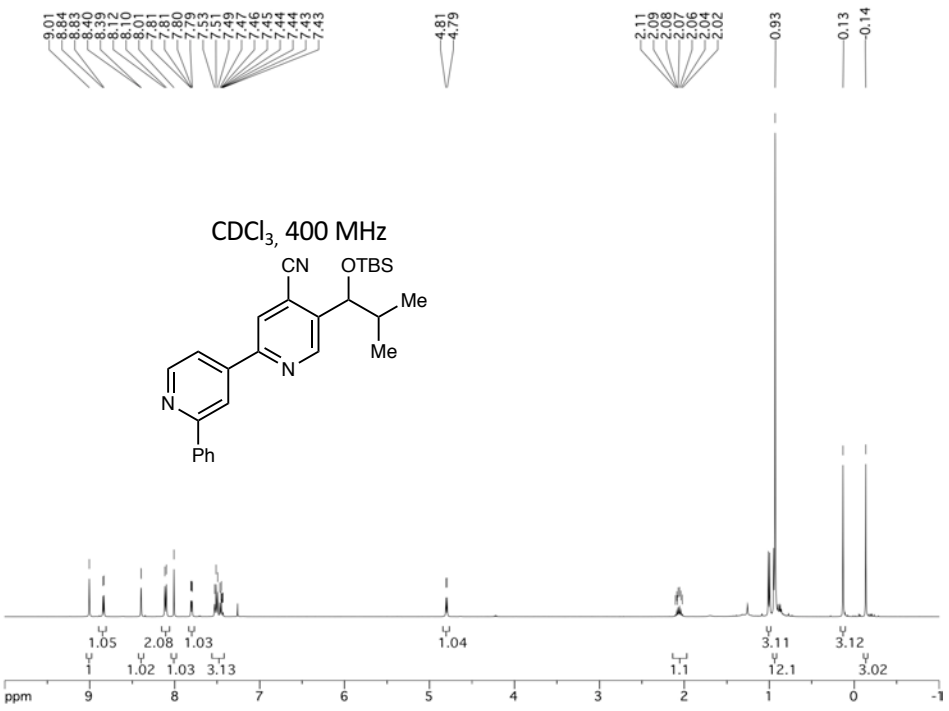

158.55
153.29
150.58
149.47
145.24
142.55
139.09
129.35
128.87
127.09
122.50
120.11
119.13
117.68
115.89
36.73
28.95
18.66
CDCl3, 100 MHz
CN
N
N
Ph
ppm 200
180
160
140
120
100
80
60
40
20
0

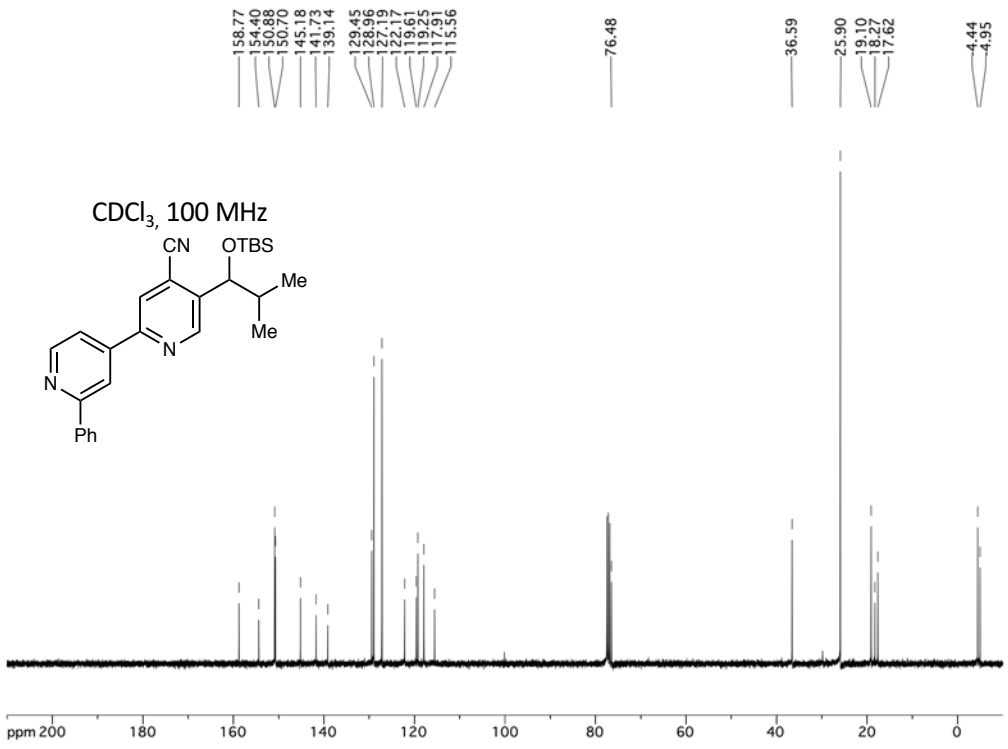

8.97
8.97
8.84
8.82
8.37
8.10
8.08
8.05
7.90
7.79
7.78
7.53
7.52
7.51
7.50
7.49
7.47
7.46
7.45
7.45
7.44
7.43
0.52
CDCl3, 400 MHz
CN
TMS
N
N
Ph
1
3.09
3.08
1.03
0.989
0.994
9.23
ppm
9
8
7
6
5
4
3
2
1
0

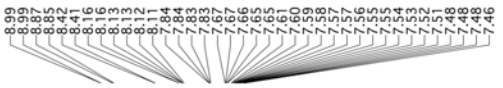

158.67
156.03
155.46
150.64
145.35
139.04
137.48
128.42
128.92
127.13
126.82
123.35
119.26
117.85
117.68
CDCl3, 100 MHz
CN
TMS
N
N
Ph
ppm 200
180
160
140
120
100
80
60
40
20
0


8.83
8.81
8.80
8.33
8.09
8.08
8.07
8.01
7.76
7.76
7.75
7.74
7.52
7.51
7.51
7.50
7.49
7.48
7.46
7.45
7.45
7.44
7.43
7.42
7.42
3.70
3.25
3.24
3.22
2.82
2.80
2.79
CDCl3, 400 MHz
CO2Me
CN
N
N
Ph
1
1.01
3.1
2.06
2.05
3.13
3.12
2.06
ppm
9
8
7
6
5
4
3
2
1
0

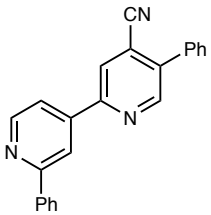

171.93
158.67
154.17
151.76
150.65
145.08
139.06
137.82
129.42
128.92
127.12
122.60
121.75
119.18
117.78
115.49
52.12
33.98
26.77
CDCl3, 100 MHz
CO2Me
CN
N
N
Ph
ppm 200
180
160
140
120
100
80
60
40
20
0


9.01
8.84
8.83
8.40
8.39
8.12
8.10
8.01
7.81
7.81
7.80
7.79
7.53
7.51
7.49
7.47
7.46
7.45
7.44
7.44
7.43
7.43
4.81
4.79
2.11
2.09
2.08
2.07
2.06
2.04
2.02
0.93
0.13
0.14
CDCl3, 400 MHz
CN
OTBS
Me
Me
N
N
Ph
1.05
2.08
1.03
1.04
3.11
3.12
1
1.02
1.03
3.13
1.1
12.1
3.02
ppm
9
8
7
6
5
4
3
2
1
0
-1

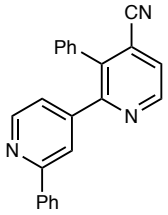

158.77
154.40
150.88
150.70
145.18
141.73
139.14
129.45
128.96
127.19
122.17
119.61
119.25
117.91
115.56
76.48
36.59
25.90
19.10
18.27
17.62
-4.44
-4.95
CDCl3, 100 MHz
CN
OTBS
Me
Me
N
N
Ph
ppm 200
180
160
140
120
100
80
60
40
20
0



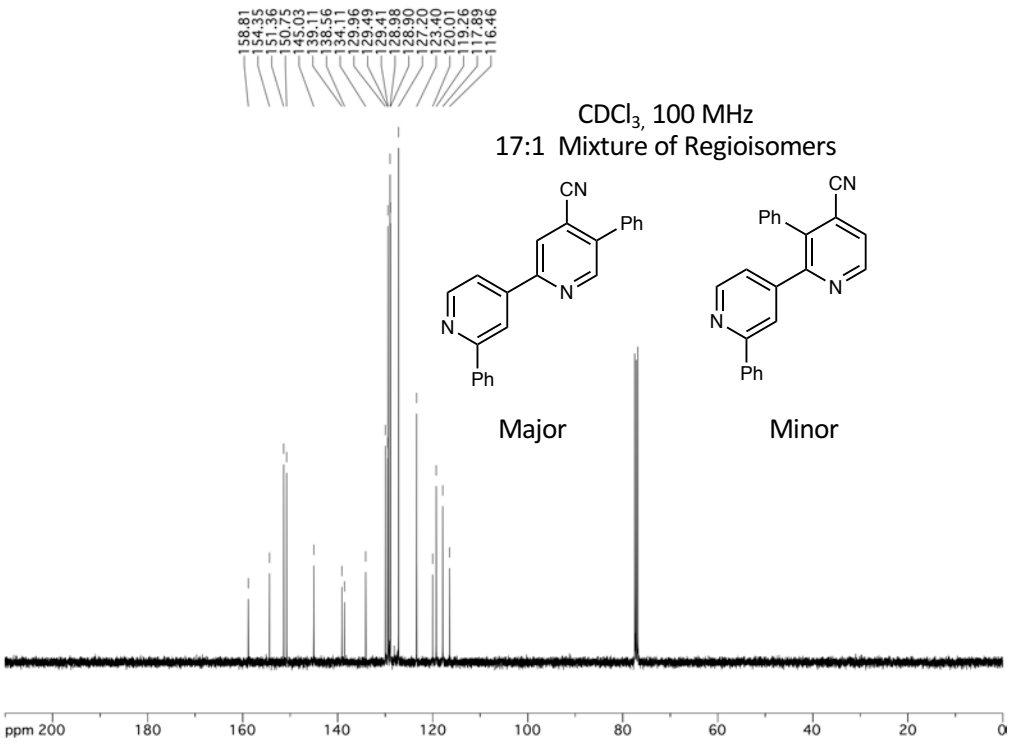
$CDCl_3$, 400 MHz
17:1 Mixture of Regioisomers

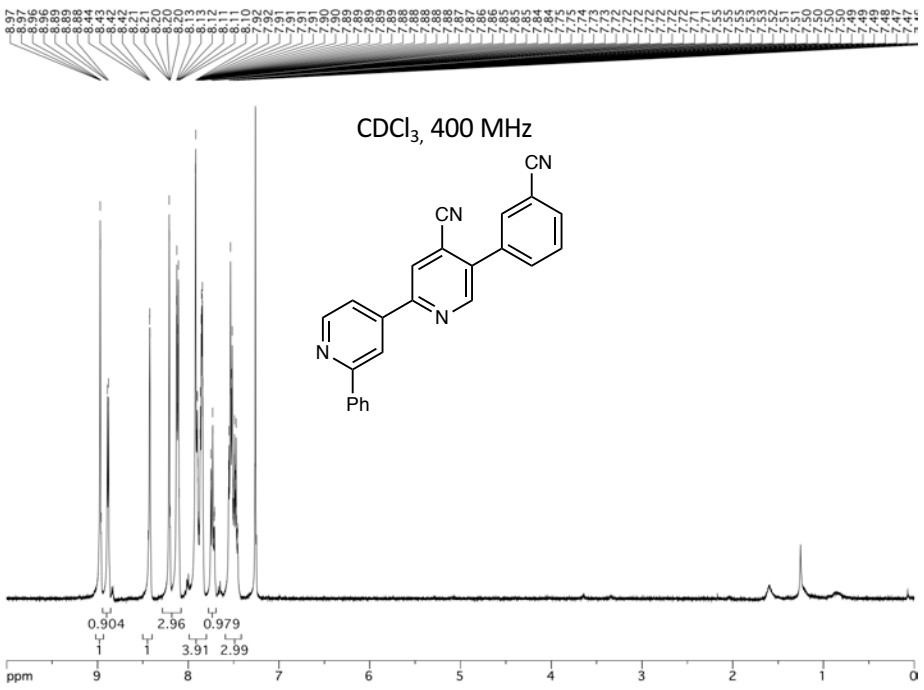


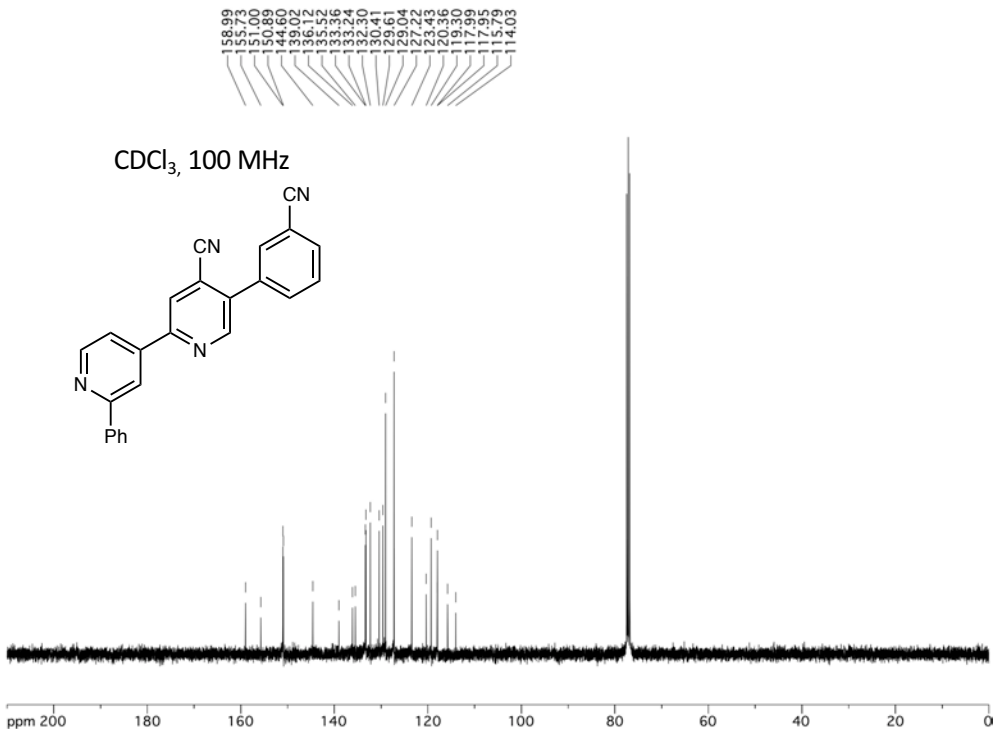
Major

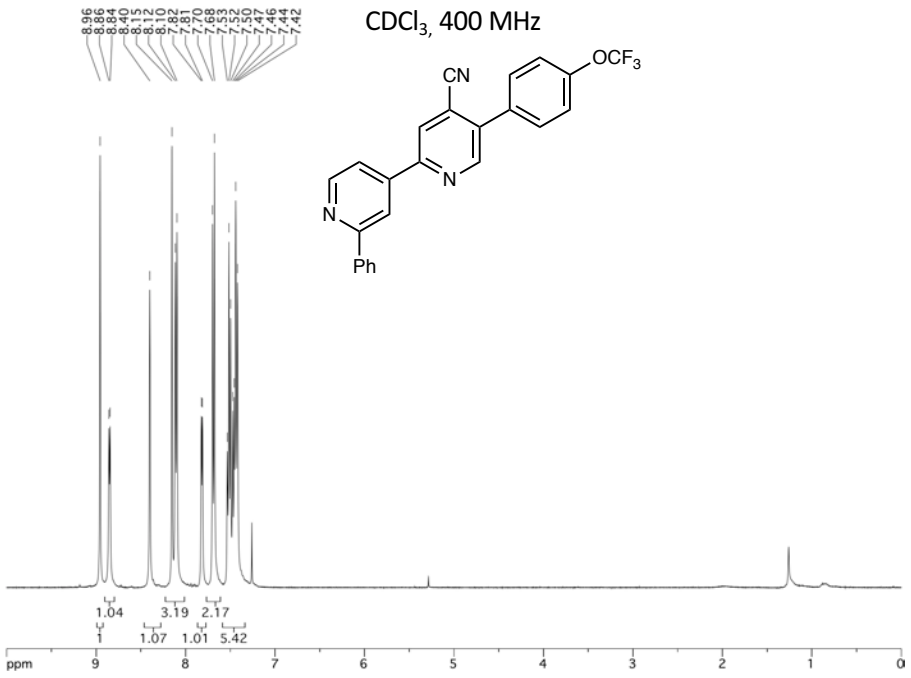


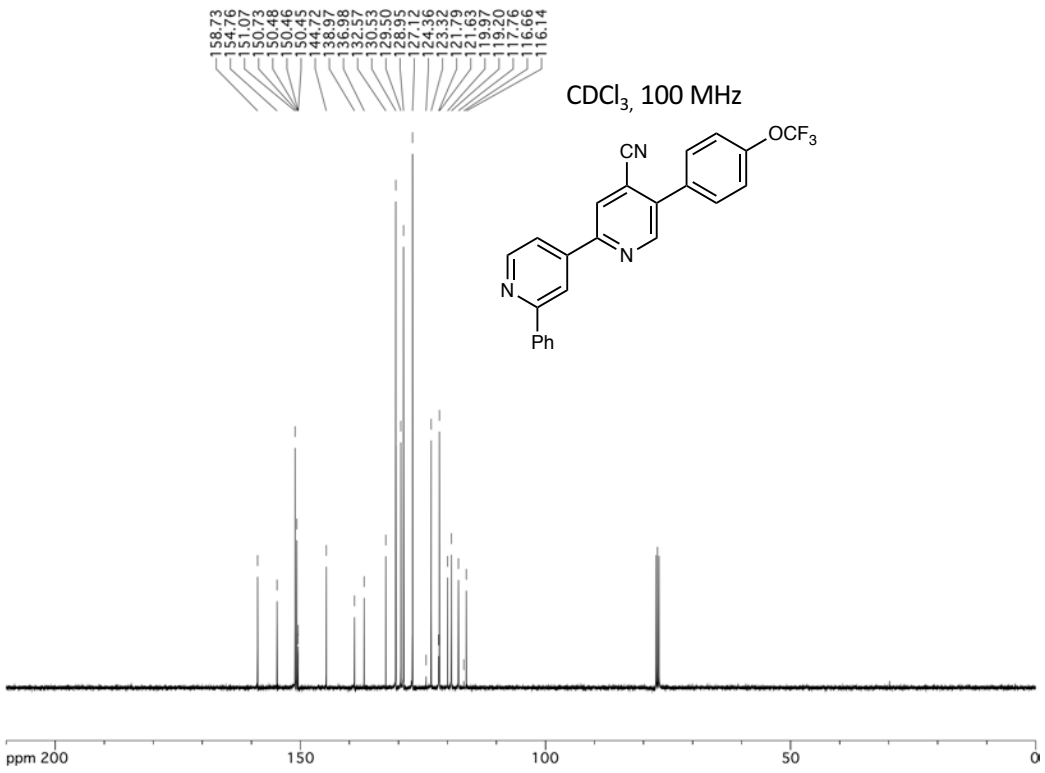
Minor

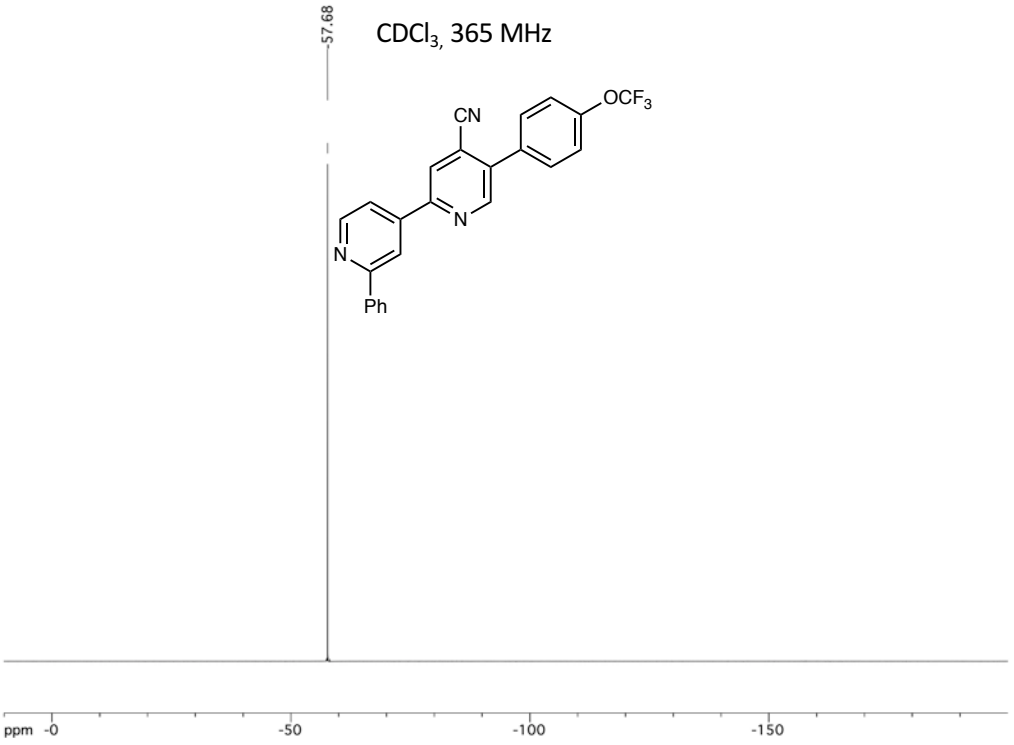

158.81
154.35
151.36
150.75
145.03
139.11
138.56
134.11
129.96
129.49
129.41
128.98
128.90
127.20
123.40
120.01
119.26
117.89
116.46
CDCl3, 100 MHz
17:1 Mixture of Regioisomers
CN
Ph
N
N
Ph
Major
CN
Ph
N
N
Ph
Minor
ppm 200
180
160
140
120
100
80
60
40
20
0

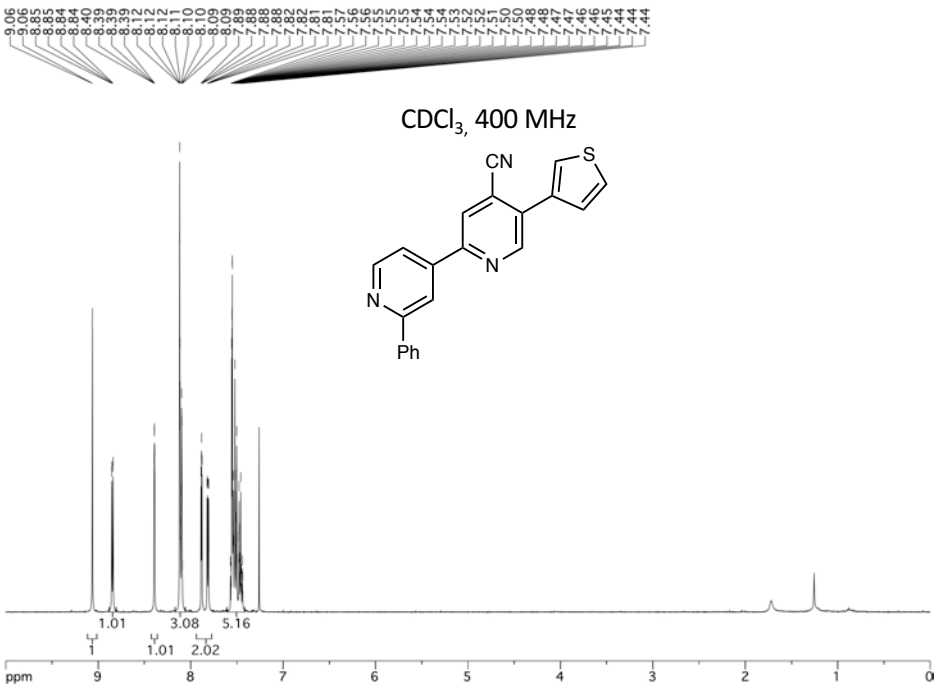

CDCl3, 400 MHz
CN
CN
N
N
Ph
0.904
2.96
0.979
1
1
3.91
2.99
ppm
9
8
7
6
5
4
3
2
1
0

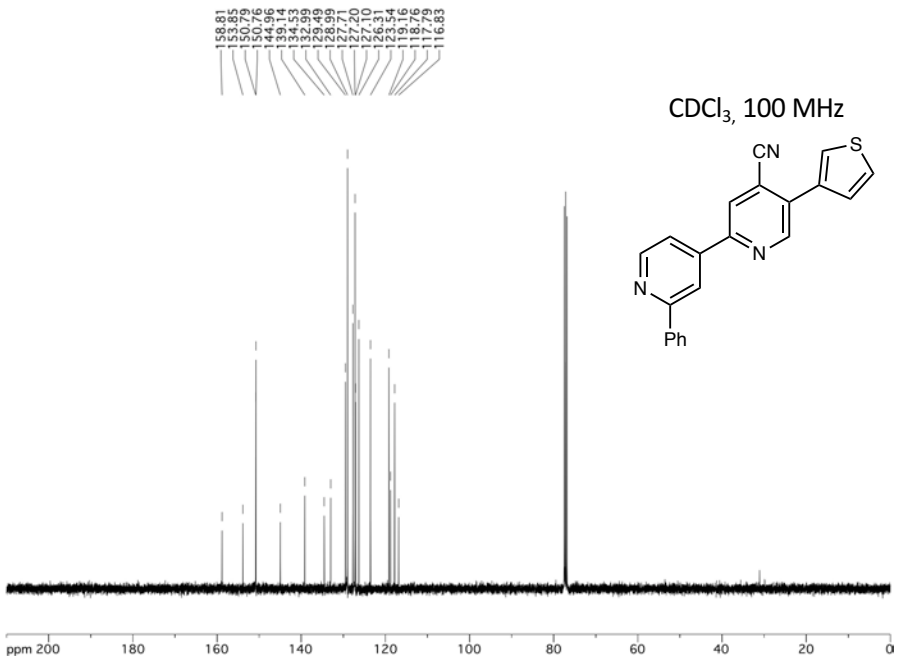

158.99
155.73
151.00
150.89
144.60
138.02
136.12
135.52
133.36
133.24
132.30
130.41
129.61
129.04
127.22
123.43
120.36
119.30
117.99
117.95
115.79
114.03
CDCl3, 100 MHz
CN
CN
N
N
Ph
ppm 200
180
160
140
120
100
80
60
40
20
0

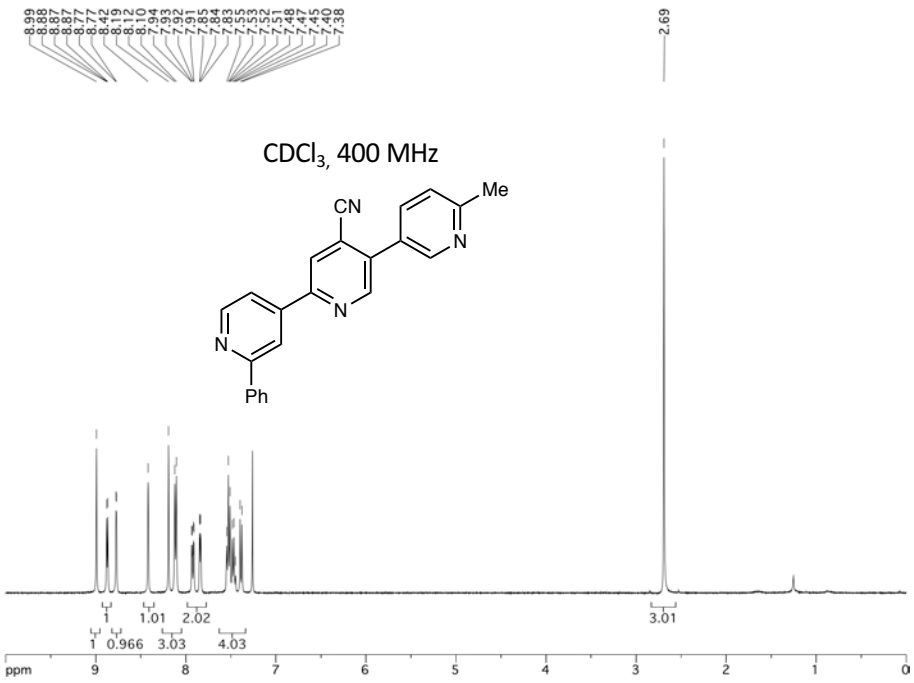

8.96
8.86
8.84
8.40
8.15
8.12
8.10
7.82
7.81
7.70
7.68
7.53
7.52
7.50
7.47
7.46
7.44
7.42
CDCl3, 400 MHz
CN
OCF3
N
N
Ph
1.04
3.19
2.17
1
1.07
1.01
5.42
ppm
9
8
7
6
5
4
3
2
1
0

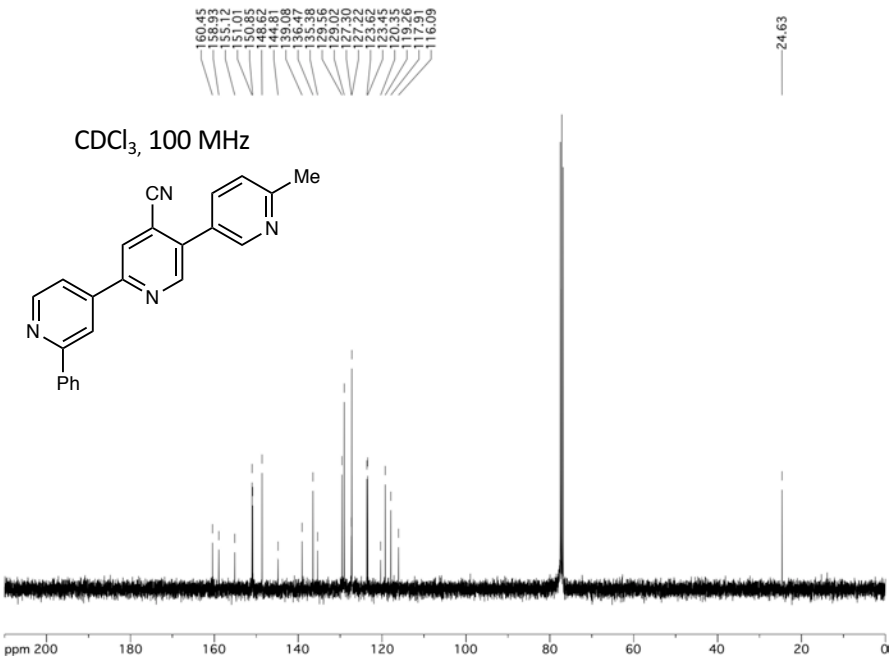

158.73
154.76
151.07
150.73
150.48
150.46
150.45
144.72
138.97
136.98
132.57
130.53
129.50
128.95
127.12
124.36
123.32
121.79
121.63
119.97
119.20
117.76
116.66
116.14
CDCl3, 100 MHz
CN
OCF3
N
N
Ph
ppm 200
150
100
50
0

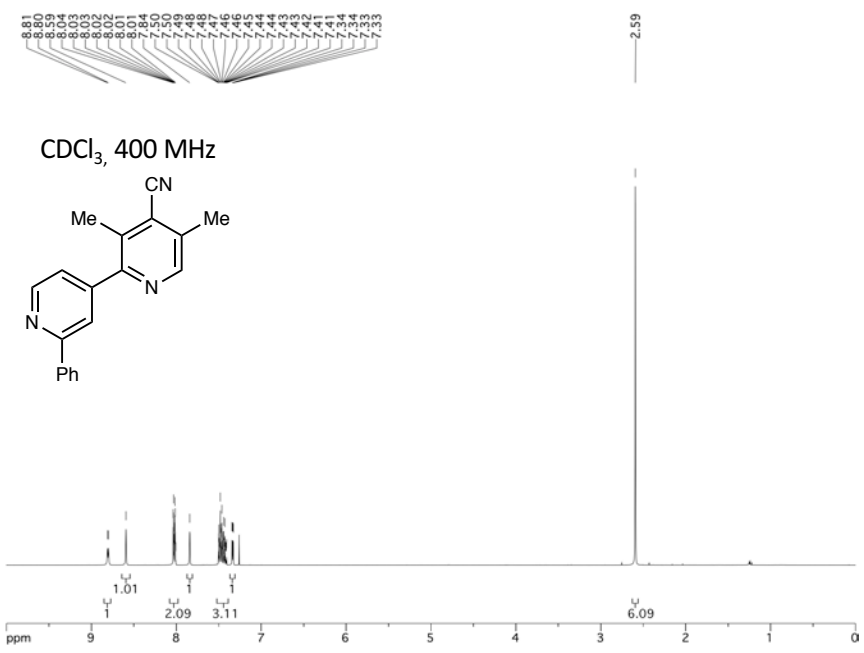

-57.68
CDCl3, 365 MHz
CN
OCF3
N
N
Ph
ppm -0
-50
-100
-150

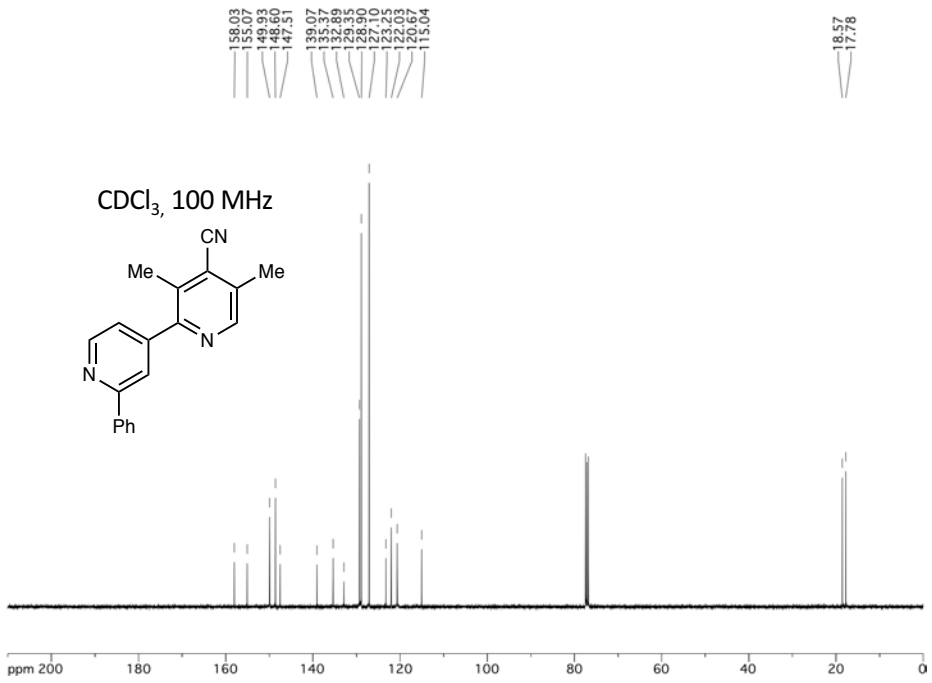

9.06
9.06
8.85
8.85
8.84
8.84
8.40
8.39
8.39
8.12
8.12
8.11
8.10
8.10
8.09
8.09
7.89
7.88
7.88
7.82
7.82
7.81
7.81
7.57
7.56
7.56
7.55
7.55
7.55
7.54
7.54
7.54
7.53
7.52
7.52
7.51
7.50
7.48
7.48
7.47
7.47
7.46
7.46
7.45
7.44
7.44
7.44
CDCl3, 400 MHz
CN
S
N
N
Ph
1.01
3.08
5.16
1
1.01
2.02
ppm
9
8
7
6
5
4
3
2
1
0

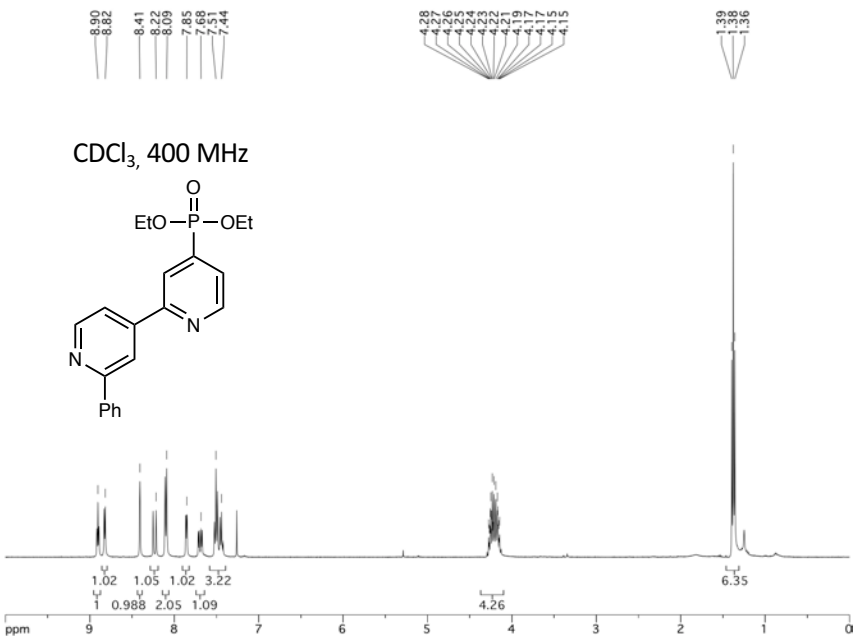

158.81
153.85
150.79
150.76
144.96
139.14
134.53
132.99
129.49
128.99
127.71
127.70
127.10
126.31
123.54
119.16
118.76
117.79
116.83
CDCl3, 100 MHz
CN
S
N
N
Ph
ppm 200
180
160
140
120
100
80
60
40
20
0

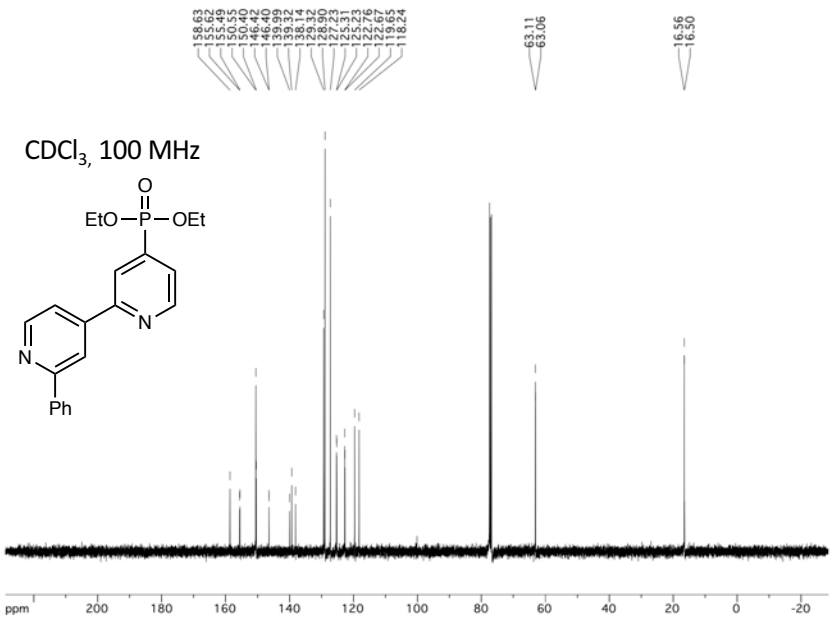

8.99
8.88
8.87
8.87
8.77
8.77
8.42
8.19
8.12
8.10
7.94
7.93
7.92
7.91
7.85
7.84
7.83
7.55
7.53
7.52
7.51
7.48
7.47
7.45
7.40
7.38
2.69
CDCl3, 400 MHz
CN
Me
N
N
N
Ph
1
1.01
2.02
3.01
1
0.966
3.03
4.03
ppm
9
8
7
6
5
4
3
2
1
0

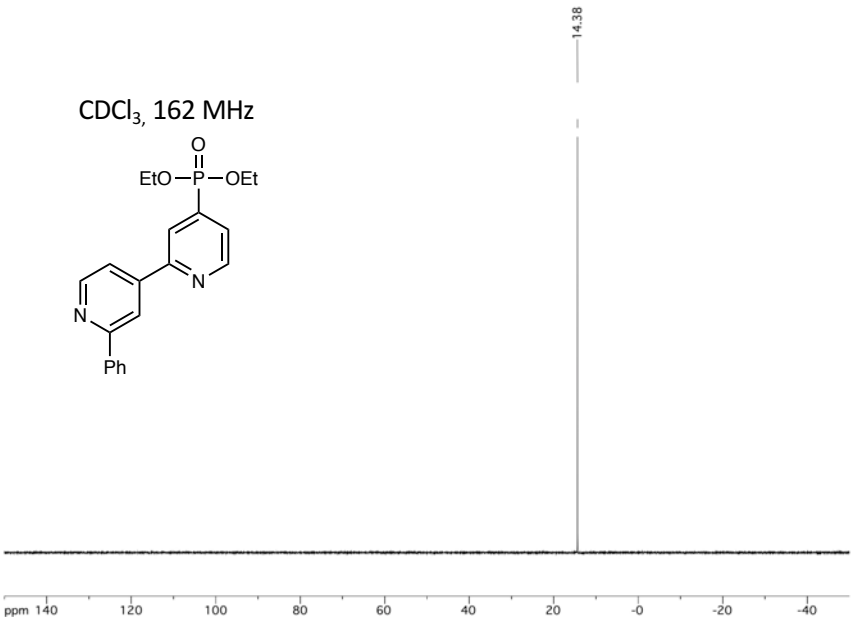

160.45
158.93
155.12
151.01
150.65
148.82
144.81
139.08
136.47
135.38
129.56
129.02
127.30
127.22
123.62
123.45
120.35
119.26
117.91
116.09
24.63
CDCl3, 100 MHz
CN
Me
N
N
N
Ph
ppm 200
180
160
140
120
100
80
60
40
20
0

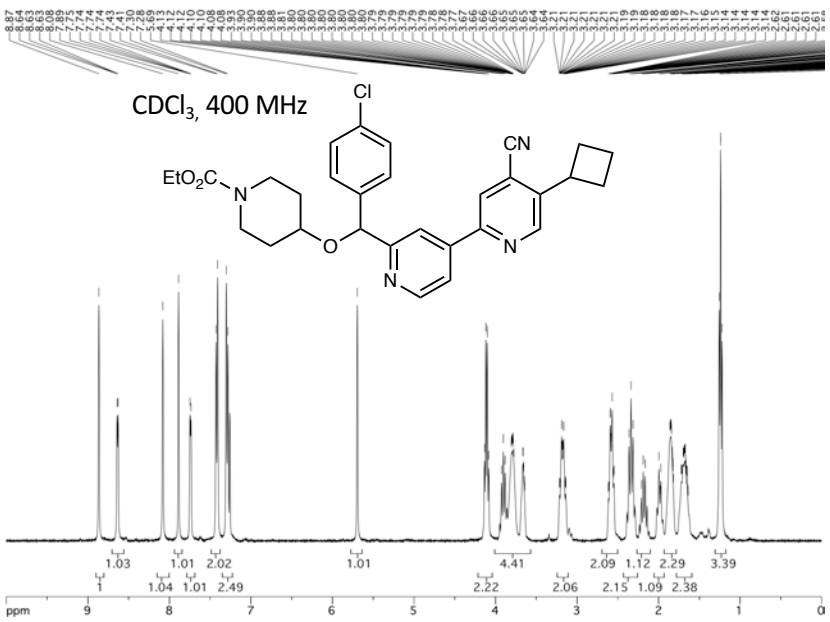

8.81
8.80
8.59
8.04
8.03
8.03
8.02
8.02
8.01
8.01
7.84
7.50
7.50
7.49
7.48
7.48
7.47
7.46
7.46
7.45
7.44
7.44
7.43
7.43
7.42
7.41
7.41
7.34
7.34
7.33
7.33
2.59
CDCl3, 400 MHz
CN
Me
Me
N
N
Ph
1.01
1
1
1
2.09
3.11
6.09
ppm
9
8
7
6
5
4
3
2
1
0

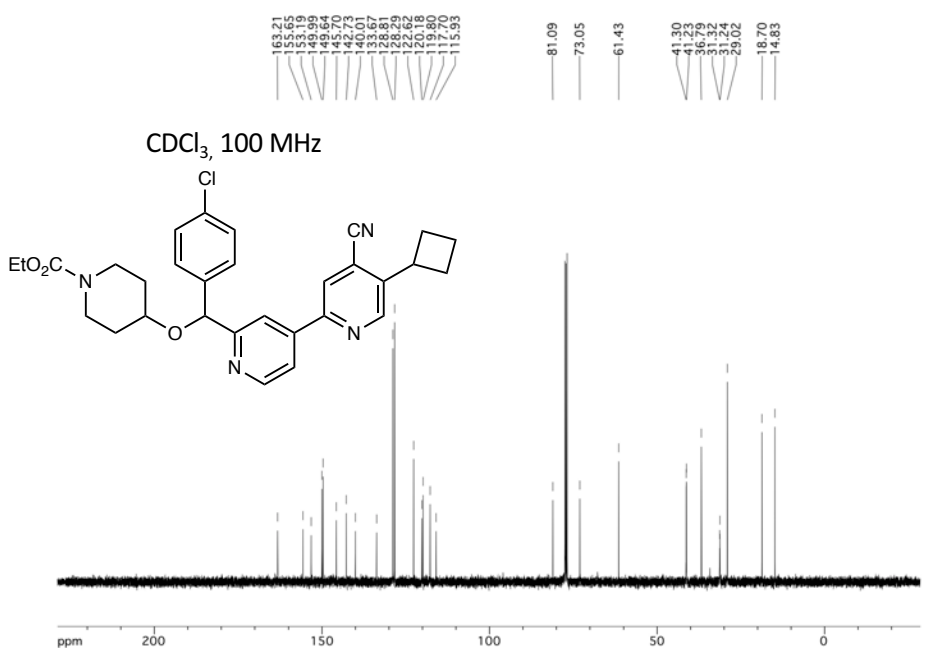

158.03
155.07
149.33
148.60
147.51
139.07
135.37
132.89
129.35
128.90
127.10
123.15
122.03
120.67
115.04
18.57
17.78
CDCl3, 100 MHz
CN
Me
Me
N
N
Ph
ppm 200
180
160
140
120
100
80
60
40
20
0

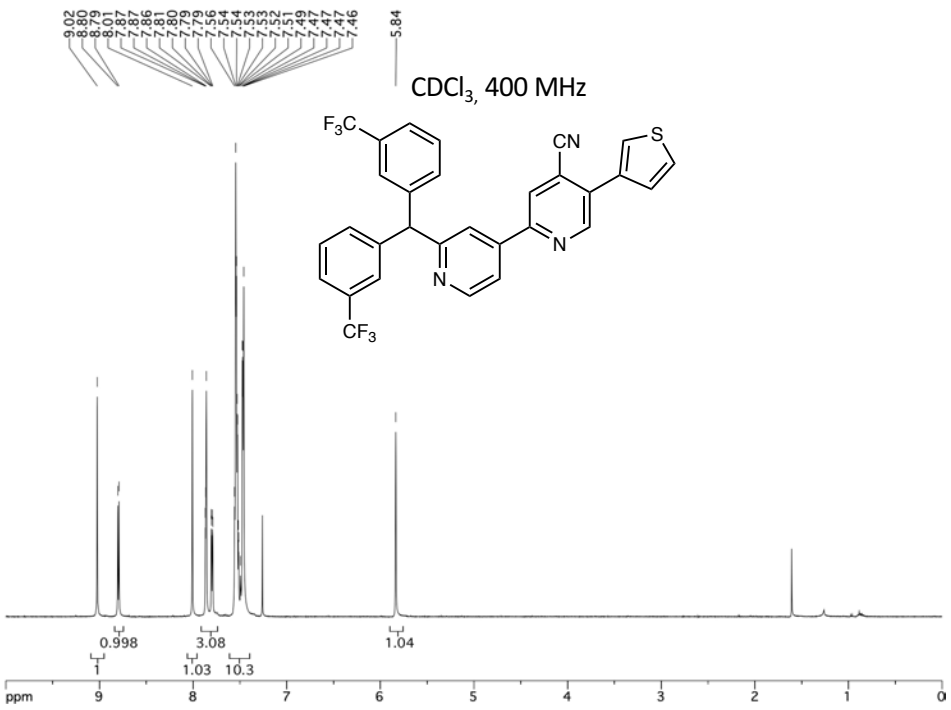

8.90
8.82
8.41
8.22
8.09
7.85
7.68
7.51
7.44
4.28
4.27
4.26
4.25
4.24
4.23
4.22
4.21
4.19
4.17
4.17
4.15
4.15
1.39
1.38
1.38
1.36
CDCl3, 400 MHz
O
EtO—P—OEt
N
N
Ph
1.02
1.05
1.02
3.22
6.35
1
0.988
2.05
1.09
4.26
ppm
9
8
7
6
5
4
3
2
1
0

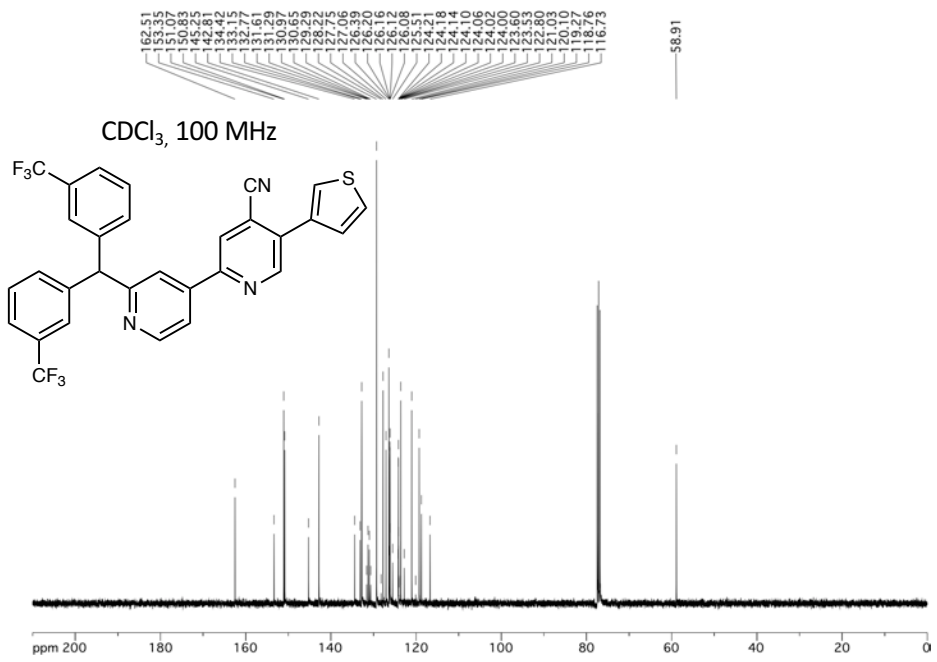

158.63
155.62
155.49
150.35
150.40
146.42
146.40
139.99
139.32
138.14
129.32
128.90
127.23
125.31
122.73
122.76
122.67
119.65
118.24
63.11
63.06
16.56
16.50
CDCl3, 100 MHz
O
EtO—P—OEt
N
N
Ph
ppm
200
180
160
140
120
100
80
60
40
20
0
-20

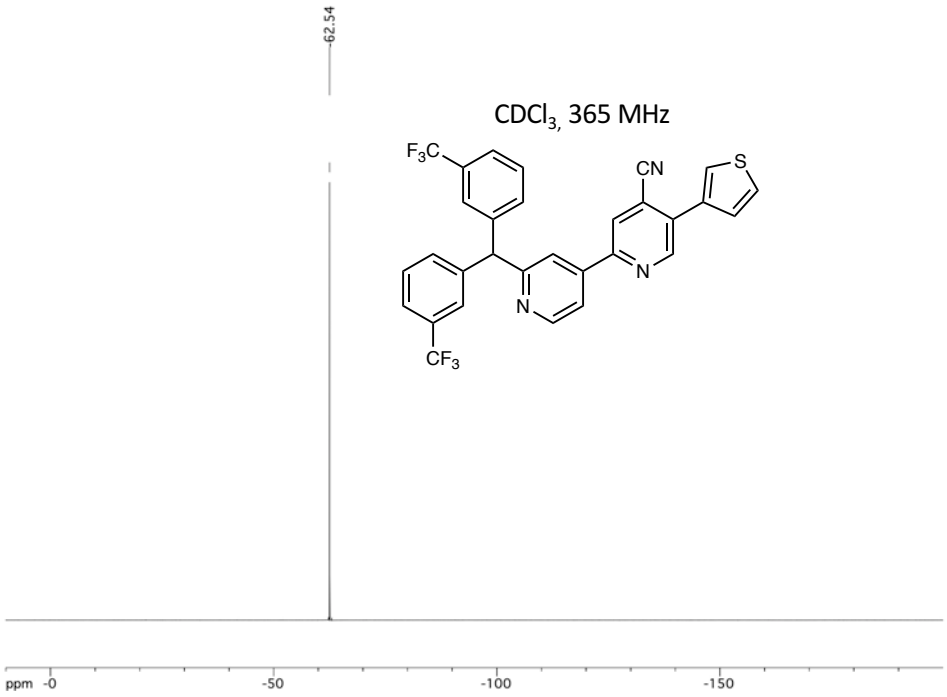

14.38
CDCl3, 162 MHz
O
EtO
P
OEt
N
N
Ph
ppm 140
120
100
80
60
40
20
-0
-20
-40

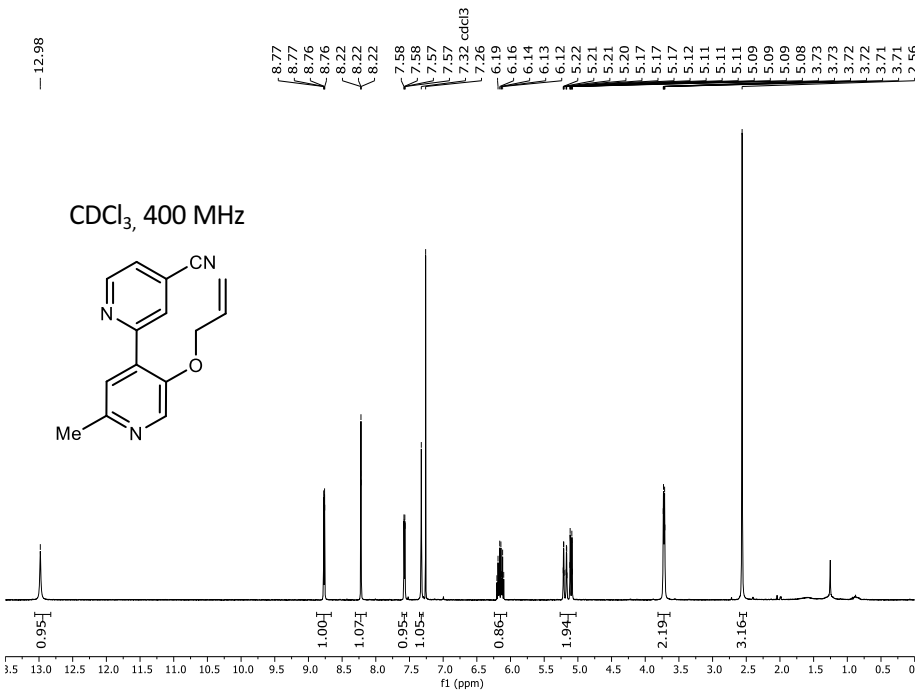

CDCl3, 400 MHz
Cl
CN
EtO2C
N
O
N
N
1.03
1.01
2.02
1.01
4.41
2.09
1.12
2.29
3.39
1
1.04
1.01
2.49
2.22
2.06
2.15
1.09
2.38
ppm
9
8
7
6
5
4
3
2
1
0

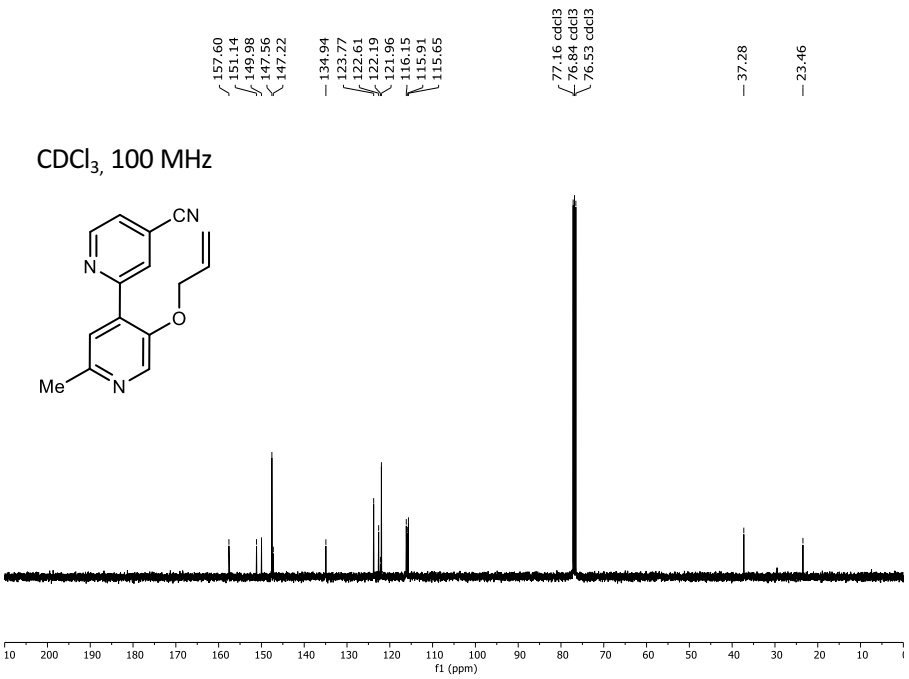

163.21
155.65
153.19
149.99
149.64
145.70
142.73
140.01
133.67
128.81
128.79
122.62
120.18
119.80
117.70
115.93
81.09
73.05
61.43
41.30
41.23
36.79
31.32
31.24
29.02
18.70
14.83
CDCl3, 100 MHz
Cl
CN
EtO2C
N
O
N
N
ppm
200
150
100
50
0

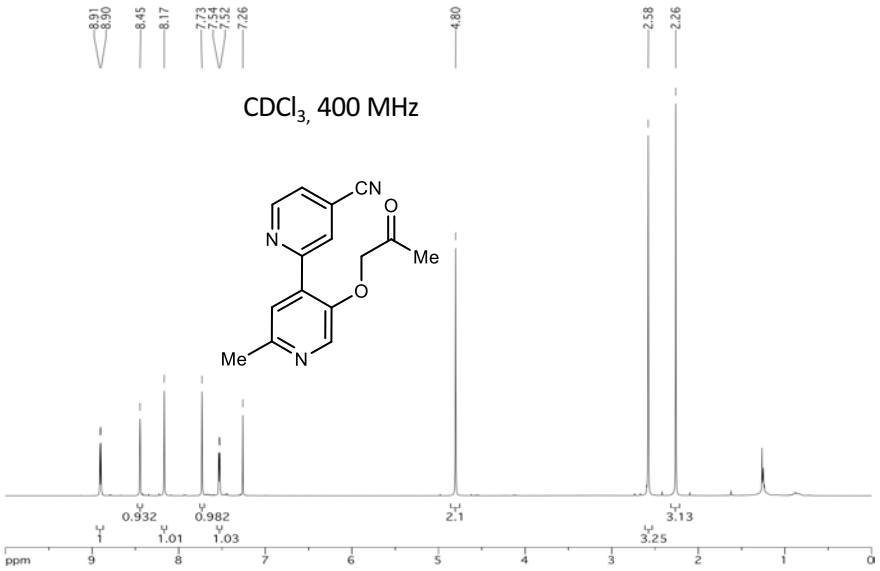

8.02
8.80
8.79
8.01
7.87
7.87
7.86
7.81
7.80
7.79
7.79
7.56
7.54
7.54
7.53
7.53
7.52
7.51
7.49
7.47
7.47
7.47
7.46
5.84
CDCl3, 400 MHz
F3C
CF3
CN
S
N
N
0.998
3.08
1.04
1
1.03
10.3
ppm
9
8
7
6
5
4
3
2
1
0

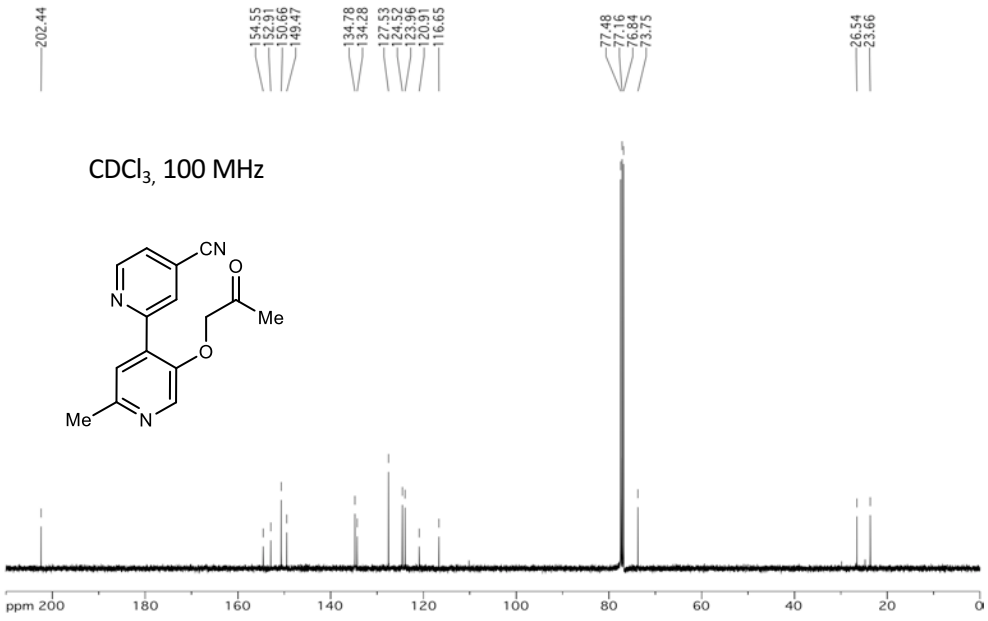

162.51
153.35
151.07
150.83
145.25
142.81
134.42
134.15
132.77
131.61
131.29
130.97
130.65
129.29
128.22
127.95
127.06
126.39
126.20
126.16
126.12
126.08
125.51
124.21
124.18
124.14
124.10
124.06
124.02
124.00
123.60
123.53
122.80
121.03
120.10
119.27
118.76
116.73
58.91
CDCl3, 100 MHz
F3C
CF3
CN
S
N
N
ppm 200
180
160
140
120
100
80
60
40
20
0


62.54
CDCl3, 365 MHz
F3C
CF3
CN
S
N
N
ppm -0
-50
-100
-150


12.98
8.77
8.77
8.76
8.76
8.22
8.22
8.22
7.58
7.58
7.57
7.57
7.32 cdcl3
7.26
6.19
6.16
6.14
6.13
6.12
5.22
5.21
5.21
5.20
5.17
5.17
5.12
5.11
5.11
5.11
5.09
5.09
5.09
5.08
3.73
3.73
3.72
3.72
3.71
3.71
CDCl3, 400 MHz
CN
N
O
Me
N
0.95
1.00
1.07
0.95
1.05
0.86
1.94
2.19
3.16
f1 (ppm)


157.60
151.14
149.98
147.56
147.22
134.94
123.77
122.61
122.19
121.96
116.15
115.91
115.65
77.16 cdcl3
76.84 cdcl3
76.53 cdcl3
37.28
23.46
CDCl3, 100 MHz
CN
N
O
Me
N
f1 (ppm)


8.91
8.90
8.45
8.17
7.73
7.54
7.52
7.26
4.80
2.58
2.26
CDCl3, 400 MHz
CN
O
N
Me
O
Me
N
0.932
0.982
2.1
3.13
1
1.01
1.03
3.25
ppm
9
8
7
6
5
4
3
2
1
0


202.44
154.55
152.91
150.66
149.47
134.78
134.28
127.53
124.52
123.96
120.91
116.65
77.48
77.16
76.84
73.75
26.54
23.66
CDCl3, 100 MHz
CN
O
N
Me
O
Me
N
ppm 200
180
160
140
120
100
80
60
40
20
0