DISSERTATION

NEW STRATEGIES TO SYNTHESIZE COMPLEX PYRIDINES AND TETRAHYDROPYRIDINES USING MAIN GROUP CHEMISTRY

Submitted by

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ABSTRACT

NEW STRATEGIES TO SYNTHESIZE COMPLEX PYRIDINES AND TETRAHYDROPYRIDINES USING MAIN GROUP CHEMISTRY

Pyridine and piperidine are important molecular scaffolds in small molecule drug development in medicinal chemistry research. Because of their importance, methods to synthesize complex pyridines and piperidines are highly desirable. Chapter one discusses the importance of these scaffolds in the pharmaceutical industry along with the history of pyridine and piperidine synthesis and the challenges that still remain.

Chapter two discusses the switching strategies for selective installation of phosphonium salts on polyazines. The methods include an acylation, base-mediate, phosphine mediate, and order-of-reagent addition strategies. Additionally, we demonstrate how these methods can be applied to medicinal chemistry research during structure-activity relationship studies by derivatizing the phosphonium salts.

Chapter three presents a new strategy for selective pyridine alkylation at the 4-position of the pyridine ring. Using a triazine chloride activating group allows for 4-selective phosphonium ylide formation inside the pyridine ring. A Wittig olefination-rearomatization sequence with an aldehyde then furnishes the alkylated pyridine. This method offers an alternative strategy to conventionally used metal-catalyzed cross coupling and Minisci-type reactions.

Chapter four describes a stepwise reduction method for the synthesis of dihydropyridine and tetrahydropyridine. Using *N*-Tf activation allows for a selective hydride reduction to the dihydropyridine, which can subsequently undergo hydrogenation to the tetrahydropyridine.

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CHAPTER ONE

INTRODUCTION TO PYRIDINE AND PIPERIDINE AND METHODS FOR THEIR FUNCTIONALIZATION

1.1 Six Membered Nitrogen-containing Heterocycles and Their Importance in Pharmaceuticals

Pyridine and Piperidines are the two most commonly found nitrogen-containing heterocycles in FDA-approved pharmaceuticals.[1–4] A 2014 survey showed that 72 approved pharmaceuticals contain piperidine, and 62 contained pyridine (**Figure 11**).[1] The authors also found other closely related six-membered heterocycles in high frequency, suc/h as piperazine (59), pyrimidine (16), 1,4-dihydropyridine (10), and quinazoline (9). Overall, two of the five top-selling pharmaceuticals in 2013 contain at least one azaarene, and 27% of approved pharmaceuticals had a non-aromatic six-membered heterocycle.

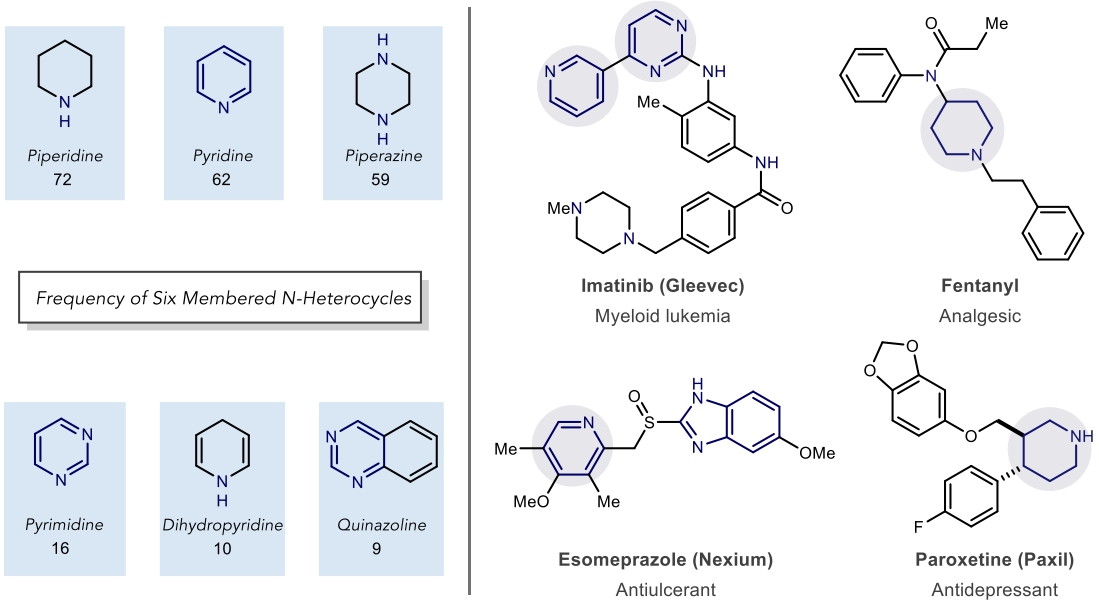

Figure 1.1 Frequency of *N*-heterocycles in pharmaceuticals and examples.

The popularity of these six-membered heterocycles in pharmaceuticals is due to the beneficial biological and physical properties they attribute to the molecule.[1,4–7] Pyridine has a basic nitrogen atom in the aromatic system, making it significantly different than its all-carbon counterpart, benzene.[5,6] The electronegativity of the nitrogen atom polarizes the aromatic ring and can increase hydrophilicity and solubility within biological systems. This increased solubility results in a higher concentration of the drug in the bloodstream, thus allowing for lower drug dosage. Piperidine contributes similar effects, and both heterocycles are often incorporated into pharmaceutical scaffolds to modulate these properties in beneficial ways.[8–10]

The nitrogen atom of pyridine and piperidine also has an electron lone pair, allowing it to hydrogen bond to target enzymes or receptors and increase the drug's binding affinity. An informative example demonstrating these advantages pyridine attributes to a drug is Motesanib, a therapeutic known to bind to vascular endothelial growth factor receptor-2 (VEGFR-2), inhibiting cellular proliferation (**Figure 1.2**).[11] The nitrogen atom of pyridine **A** has a vital hydrogen bonding interaction with amino acid residue Cys 919.[11] Additionally, pyridine **B** has a cation-π interaction with the ammonium side chain of Lys 868.[11] Both interactions are critical in the molecular recognition and binding of Motesanib in VEGFR-2.[11] The pyridine rings also provide a scaffold for incorporating other important interactions, such as the hydrogen bonding between the Glu 885 and the appending amide on pyridine **B**.[11]

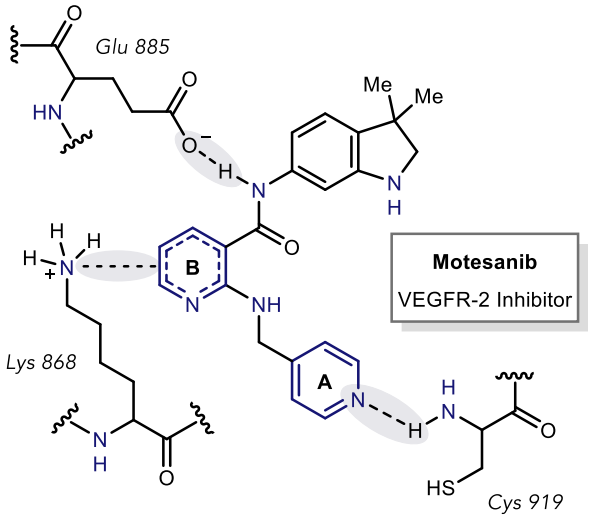

Figure 1.2. Binding interactions between Motesanib and amino acid residues of VEGFR-2.

A common way to metabolize pharmaceuticals is the oxidation of electron-rich aromatics using CYP450 enzymes.[12,13] The enzyme installs a hydroxyl group onto the aromatic ring, increasing aqueous solubility and ease of excretion from the body. While this process is facile on electron-rich aromatics, it is considerably slower on pyridine and other related heteroarenes.[14] This resistance to CYP450 metabolism has led medicinal chemists to target these azaarenes to regulate the metabolic stability of drugs.[15]

1.2 Functionalization of Pyridine

1.2.1 Classical Methods for Direct Pyridine Functionalization

Considering pyridine's importance to the pharmaceutical industry, methods to directly functionalize them are greatly desired. However, some inherent challenges come with direct pyridine C-H functionalization.[5,6] The electronegativity of the nitrogen atom makes the aromatic ring less π-nucleophilic; thus, electrophilic aromatic substitution (EAS) reactions become significantly more challenging to accomplish compared to its benzene counterpart. For instance,

the bromination of pyridine requires the use of oleum and elemental bromine at elevated temperatures (**Figure 1.3A**).[5,6,16] In contrast, electron-rich arenes react under more moderate conditions, using mild halogenating reagents at room temperature. The harsh conditions to accomplish EAS reactivity on pyridine severely limit its functional group tolerance and applicability.

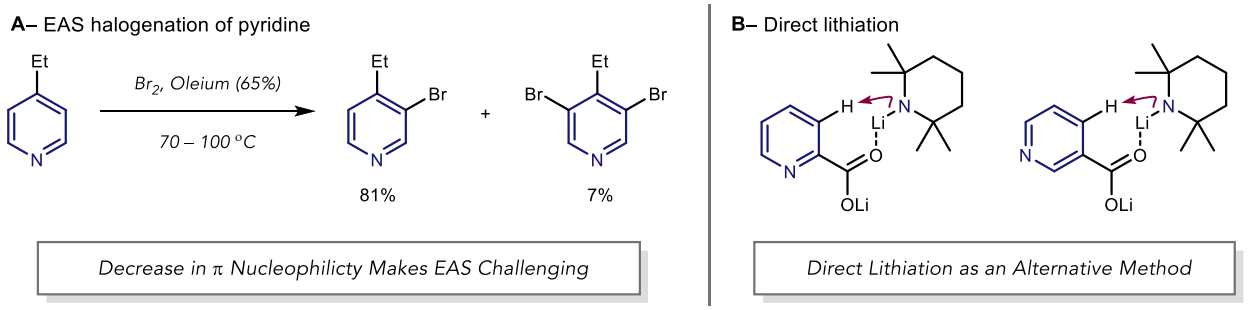

Figure 1.3. Bromination of pyridine via EAS and direct lithiation with selectivity being determined by the substituents.

An alternative method to react pyridine with electrophiles is through direct metalation (**Figure 1.3B**).[17,18] Lithium or magnesium bases are used to generate the pyridine metalate *in-situ*, which is then subsequently trapped with an electrophile. Selectivity of this process is typically dictated by the substituents on the ring and their respective position.[17] The directing group coordinates with the incoming metal base to bring it within proximity of a single proton, resulting in selective deprotonation.

On the other hand, incorporating the nitrogen atom into the aromatic system of pyridine makes it electrophilic and susceptible to reactions with nucleophiles.[5,6] Nucleophiles preferentially add to the *ortho* or *para* positions of the ring due to the nitrogen's electronegativity and ability to stabilize the negative charge of the dearomatized intermediate (**Figure 1.4**). The Chichibabin reaction is an example of this type of reaction, resulting in selective amination of the 2-position on

pyridine.[19,20] Sodium amide selectively adds *ortho* onto the pyridine ring, yielding a Meisenheimer intermediate. Subsequent hydride elimination results in the rearomatized aminated product.

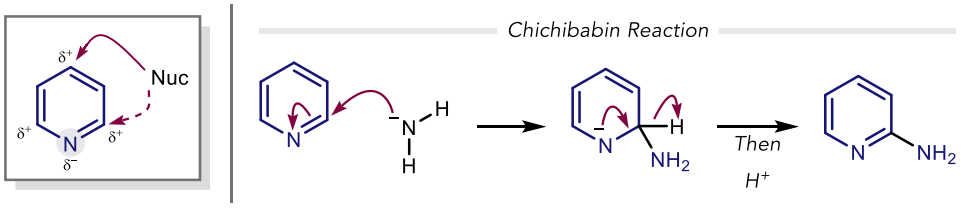

Figure 1.4. Chichibabin reaction as an example for direct nucleophilic addition to pyridine

Activating the aromatic systems via pyridinium formation can also aid nucleophilic addition into pyridine (**Figure 1.5**).[21–23] Common activating groups include acyl chlorides, chloroformates, chlorosilanes, and alkyl halides. Following nucleophilic addition, rearomatization occurs via the addition of an external oxidant.[21] Regioselectivity between the 2- and 4-position is often dictated by the substituents located on the aromatic ring. This activation-addition-rearomatization sequence is particularly amenable to, although not exclusive to, carbon nucleophiles such as Grignard reagents, organo-cuprates, and cyanide.[21–23]

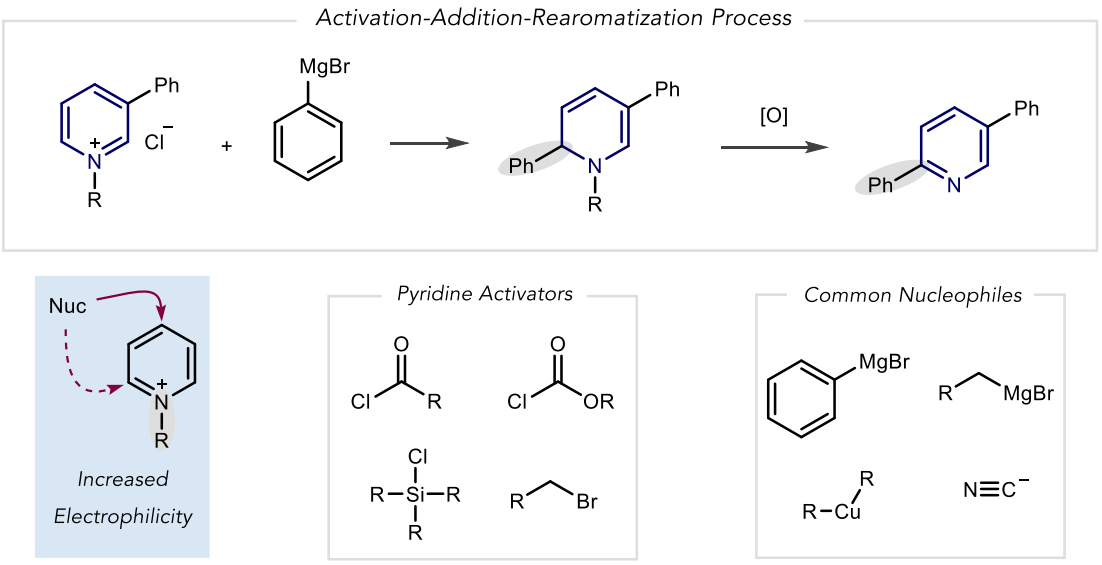

Figure 1.5. Common activators and nucleophiles in Activation-Addition-Rearomatization processes.

Pyridine is also commonly functionalized via radical addition processes. The Minisci reaction uses this approach to install carbon-bearing groups onto the azine (**Figure 1.6**).[24–26] Single-electron oxidation of carboxylic acids generates alkyl and aryl radicals with catalytic amounts of $AgNO_3$ and $K_2S_2O_8$.[27] The generated radical adds into protonated pyridine, yielding a stabilized radical cation, which is subsequently oxidized and deprotonated to produce the functionalized pyridine ring. The reaction is generally unselective, resulting in a mixture of products at the 2-, 3-, and 4-position of the azine; however, the addition of acid can bias the reaction towards the 2-position. An example from the Su group is demonstrated along with the proposed mechanism.[27] Broad availability of the carboxylic acid starting material and simplicity of generating the radical has made this a practical approach for medicinal chemists for pyridine functionalization.

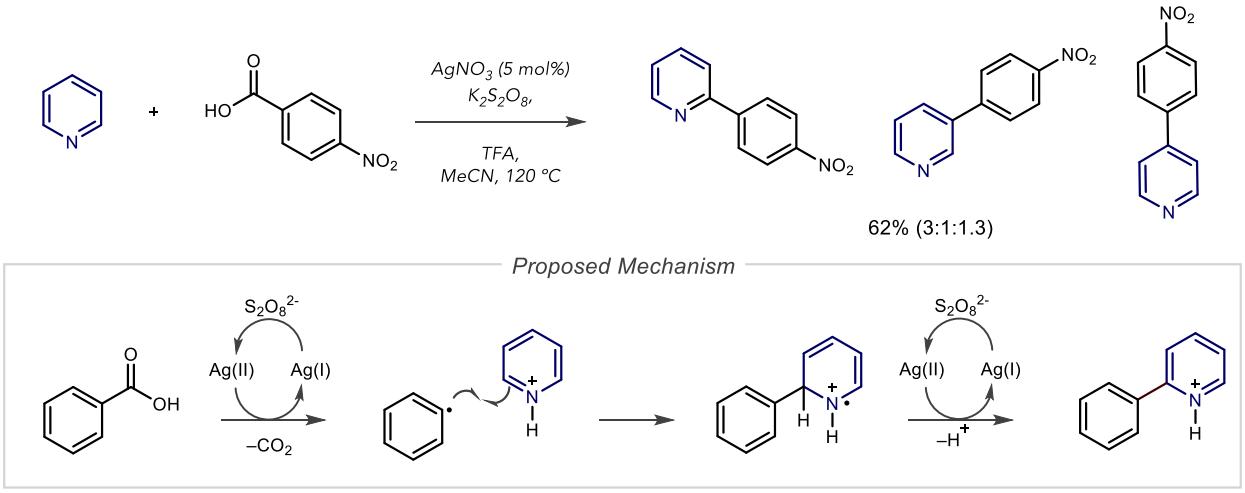

Figure 1.6. Example of the Minisci reaction with proposed mechanism.

1.2.2 Modern Approaches to Pyridine Functionalization

The classical approaches to direct pyridine functionalization have laid the groundwork for pyridine functionalization and have inspired several modern methods. The Chichibabin reaction has been a model for advancements in *ortho*-selective pyridine functionalization.[20,28–30] The protocol inspired Hartwig and coworkers to develop a fluorination reaction using AgF_2, thus installing the valuable functional handle selectively to the 2-position.[28,29] The proposed mechanism has an equivalent of the AgF_2 coordinate to the nitrogen atom of the pyridine ring. Internal delivery of fluoride into the π-system of the aromatic ring occurs, resulting in dearomatized intermediate **I**. Hydrogen atom abstraction follows next, yielding the functionalized product (**Figure 1.7**). The authors also demonstrated a one-pot approach for tandem fluorination-nucleophilic substitution leading to C-O and C-S bond construction on pharmaceutically relevant examples, such as a Pirenzepine precursor [29]

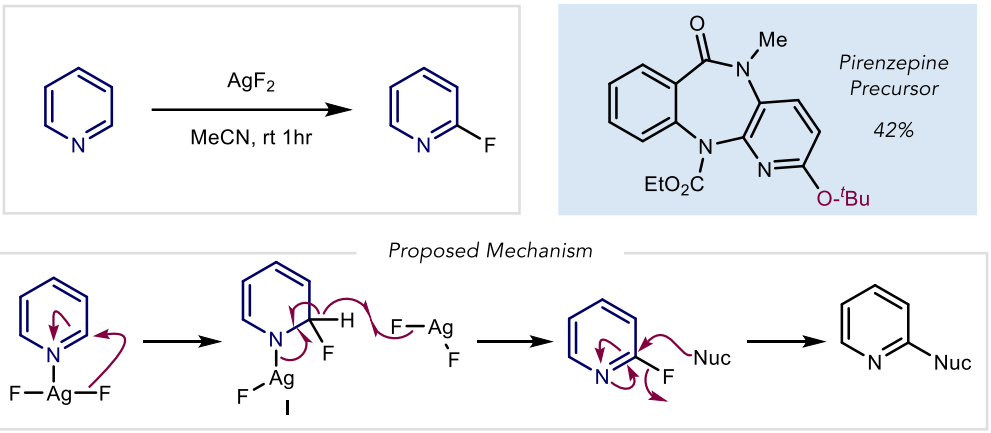

Figure 1.7. Hartwig's tandem fluorination/nucleophilic addition for selective *ortho* functionalization

Several groups have developed new variations of the Minisci reaction with the advancement of photoredox catalysis.[25–27,31–40] A notable example includes MacMillan's trifluoromethylation of arenes (**Figure 1.8**). In the procedure, a Ruthenium photocatalyst is excited with white light from Ru(II) to Ru(II)*, which subsequently reduces trifluoromethanesulfonyl chloride, forming trifluoromethyl radical with SO_2 gas and chloride byproducts.[36] The radical adds to the azine, and oxidation of the dearomatized intermediate regenerates the photocatalyst. Aromatization to the final trifluoromethylated product occurs following deprotonation with dibasic potassium phosphate (K_2HPO_4). Although the conditions are milder than the original Minisci report, this procedure can still result in a mixture of alkylated products. This example only shows functionalization of simple azine precursors, although several other methods have been developed and demonstrated on medicinally relevant compounds, including examples from DiRocco, Baran, Stephenson, Molander, and follow up reports from MacMillan.[31–35,37,38,40]

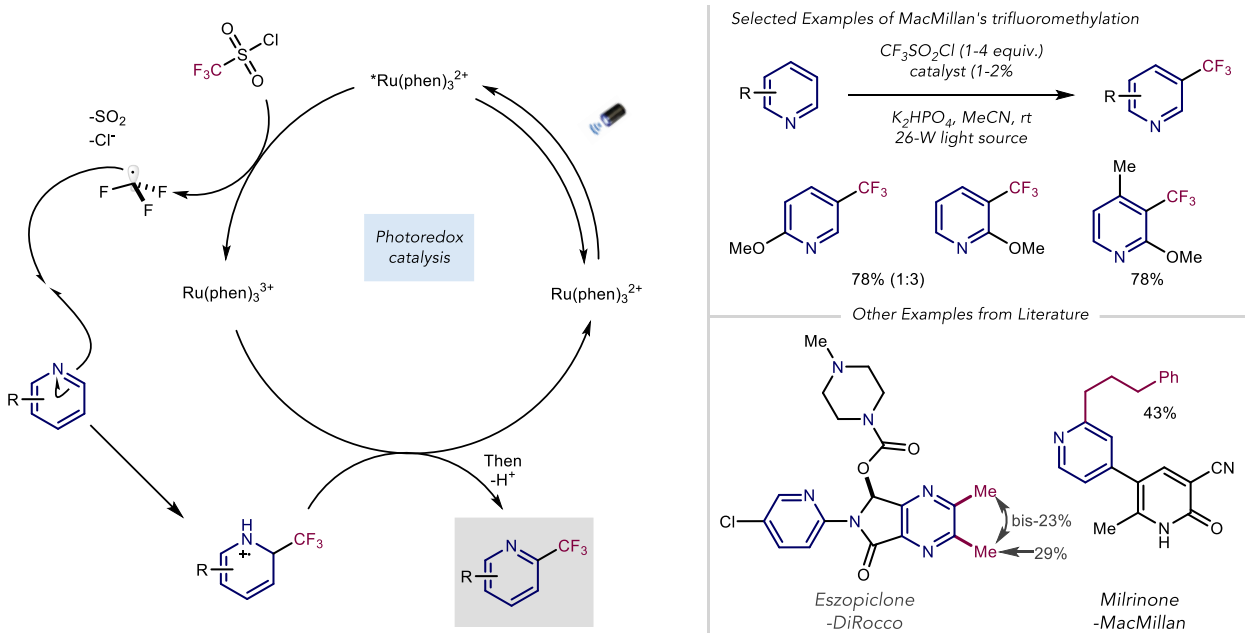

Figure 1.8. Mechanism of MacMillan's trifluoromethylation via Minisci reaction. Examples of the trifluoromethylation are shown, as well as other developed Minisci reactions.

Modern approaches have also followed the activation-addition-rearomatization process as well.[21–23,41–43] Fier has demonstrated two methods using designed activating groups that allow for selective *ortho* functionalization of pyridines.[41,42] In his first report, the author created a bifunctional reagent, α-chloro *O*-methanesulfonyl aldoxime, to activate the pyridine for nucleophilic addition and to easily be removed via elimination (**Figure 1.9**).[41] Pyridine is first activated at elevated temperatures with the **II** and a sodium triflate (NaOTf) additive, then the addition of sodium cyanide (NaCN) selectively occurs to the 2-position of the pyridinium salt. Deprotonating the *ipso* proton with sodium carbonate (Na_2CO_3) eliminates and decomposes the activating group to acetonitrile and mesylate, resulting in selective cyanation of pyridine. The functionalization of a mixed progesterone agonist/antagonist is shown as a representative example. In a subsequent paper, Fier designed a pyrazine-based pyridine activator that selectively aminates the 2-position via internal delivery of the Boc protected amine.[42]

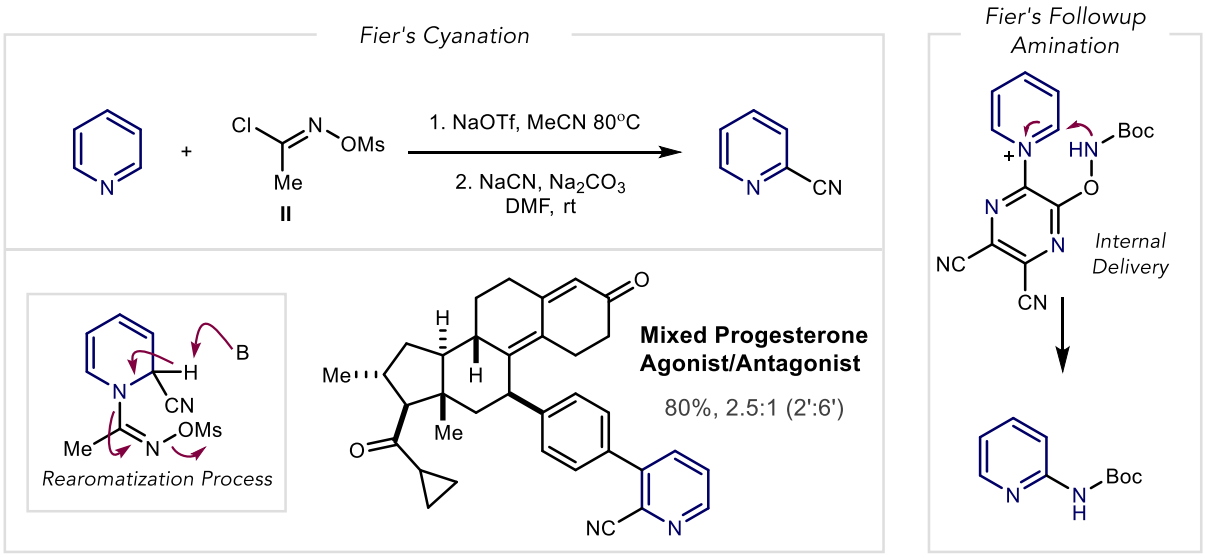

Figure 1.9. Fier's Activation-Addition-Rearomatization reactions for pyridine cyanation and amination.

Transition metal protocols for direct C-H functionalization have been developed and typically are 2- or 3-selective.[44–55] A challenge to using this approach is the Lewis basic nature of

the lone pair on the nitrogen atom. The electrons can coordinate with the metal, thus poisoning the catalyst or leading to undesired C-H activation elsewhere on the substrate.[56] However, examples overcoming this issue have been reported, including a direct arylation reports from Yu[47,48] and Sames,[50] borylation from Hartwig,[45,46,57] and alkenylation from Nakao (**Figure 1.10**).[53] Several different transition metals have also been demonstrated to accomplish direct pyridine C-H functionalization, such as palladium,[47,48,50] iron,[49] iridium,[45,46,57] rhodium,[51] nickel,[53] and rare earth metals.[55]

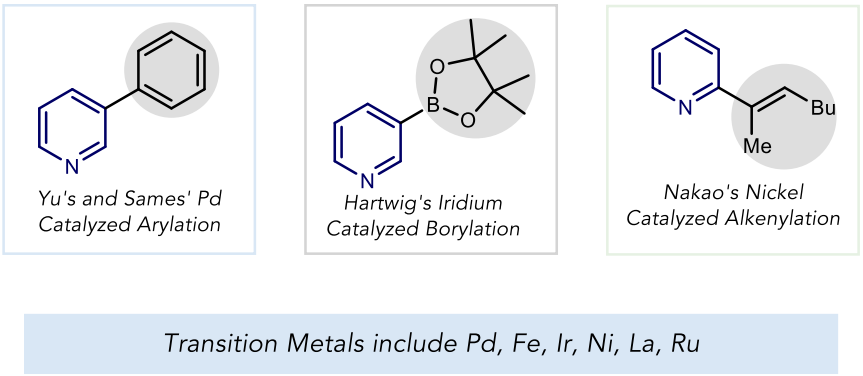

Figure 1.10. Transition metal catalysis used for direct pyridine functionalization.

1.2.3 Modern Approaches for 4-Selective Pyridine Functionalization

Relative to 2- and 3-selective processes, direct 4-selective pyridine functionalization methods are rare. Alkylations have been achieved via activation-addition-rearomatization processes, including an example from Kanai where he accomplishes perfluoroalkylation of pyridines and quinolines (**Figure 1.11**).[58] The authors use a bulky Lewis acid borane as an activating group in this case, thus sterically blocking the *ortho* and *meta* positions of the pyridine ring. Tetrabutyl ammonium difluorotriphenylsilicate (TBAT) then reacts with

trimethyl(trifluoromethyl)silane (Me_3SiCF_3), generating a trifluoromethyl anion that selectively adds to the 4-position of the azine to make intermediate **III**. Oxidation using hypervalent iodine furnishes the trifluoromethylated arene. While the reaction is 4-selective, regioisomers begin to appear when adding substituents to the 3-position of the pyridine ring. Comins has also demonstrated alkylation through a similar reaction pathway, adding organo cuprates to *N*-acyl pyridinium salts.[59]

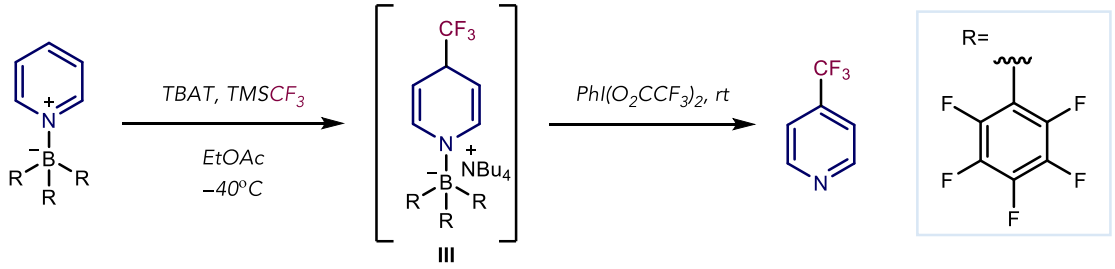

Figure 1.11. Kanai's 4-selective perfluoroalkylation using a borane activating group.

Strategies using bulky Lewis acids to block the 2- and 3-position of pyridine and selectively functionalize the 4-position have been applied to transition metal-catalyzed C-H activation.[60,61] Nakao used methylaluminum bis (2, 6-di-t-butyl-4-methylphenoxide) (MAD) to coordinate to the pyridine nitrogen (**IV**), then an NHC ligated nickel catalyst would oxidatively add to the 4-position C-H bond (**V**).[60] Migratory insertion across an alkene to intermediate **VI** followed by reductive elimination yields the alkylated pyridine (**Figure 1.12**). The authors also observed minor amounts of the secondary alkylated pyridine in this transformation. Nakao and coworkers also demonstrated alkenylation using an alkyne coupling partner, although regioselectivity became a problem, as they reported significant amounts of the 3-substituted product.

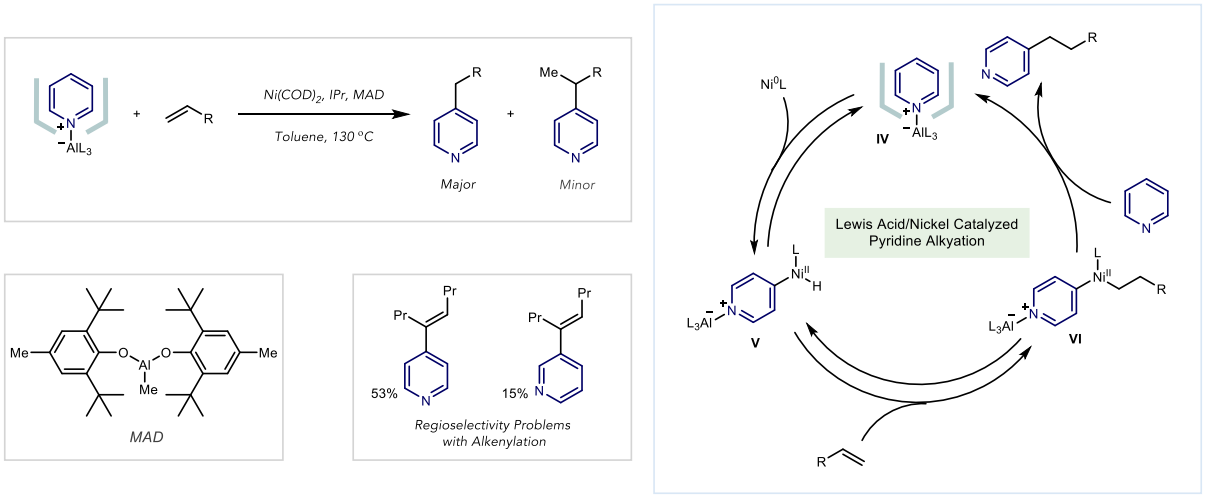

Figure 1.12. Nakao's nickel catalyzed direct alkylation using a bulky Lewis acid to control regioselectivity.

Hong and coworkers have made advancements in Minisci-type reactions by selectively obtaining 4-substituted products by using a *N*-amidopyridinium salt with alkyl bromide coupling partners.[62] The proposed mechanism shows the pyridinium salt forms an electron-donor-acceptor (EDA) complex with a bromide anion and undergoes a single electron transfer (SET) upon excitation with light to generate bromine radical (**Figure 1.13**). That radical abstracts a hydrogen atom from $(TMS)_3SiH$ to generate **VII** and starts the catalytic cycle. The silyl radical will react with the alkyl bromide, making an alkyl radical (**VIII**) which will add directly to the 4-position of the pyridinium salt. Deprotonation of **IX** with sodium acetate (NaOAc) forms the alkylated pyridine along with an amidyl radical **X**. This radical will abstract a hydrogen atom from another equivalent of silane, completing the catalytic cycle. Alkylation of Etorcoxib is shown as a representative example. Hong has also demonstrated similar reactions for pyridine acylation and sulfination, as well as using other alkyl precursors.[63–65]

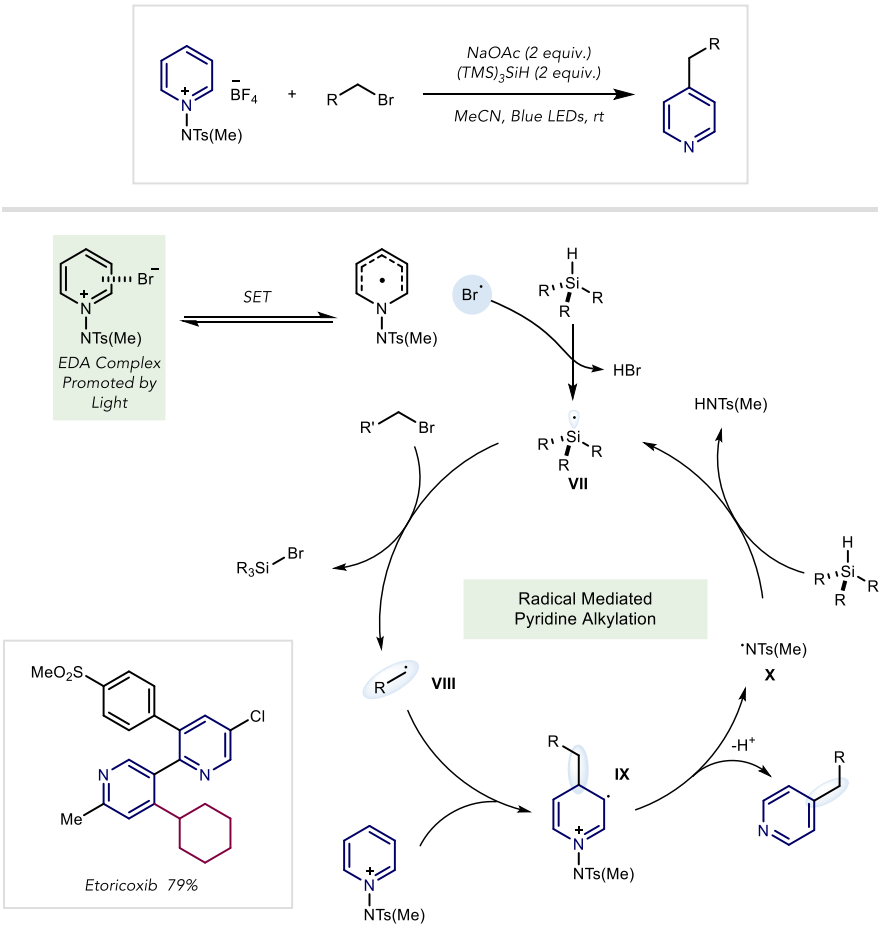

Figure 1.13. Hong's radical approach for selective alkylation of the 4-position of pyridines.

McNally and coworkers have significantly expanded the use of heterocyclic phosphonium salts for selective pyridine functionalization.[43,66–76] Through a sequential addition of trifluoromethanesulfonic anhydride (Tf_2O), triphenylphosphine (PPh_3), and an organic base (Et_3N or DBU) to pyridine at low temperatures, a phosphonium salt is selectively installed to the 4-position of the arene.[43,69] A steric interaction between the triflyl activating group and the incoming phosphine nucleophile dictates the regioselectivity. The steric interaction pushes the phosphine to the *para* position, resulting in a completely selective reaction in most cases. The group has demonstrated the ability to install these reagents on both building block pyridines and numerous pharmaceuticals and drug fragments. Additionally, they have shown the salts can undergo various

reaction pathways for subsequent functionalization, including nucleophilic substitution, ligand-coupling, fragmentation, metal-insertion, and single-electron reduction.

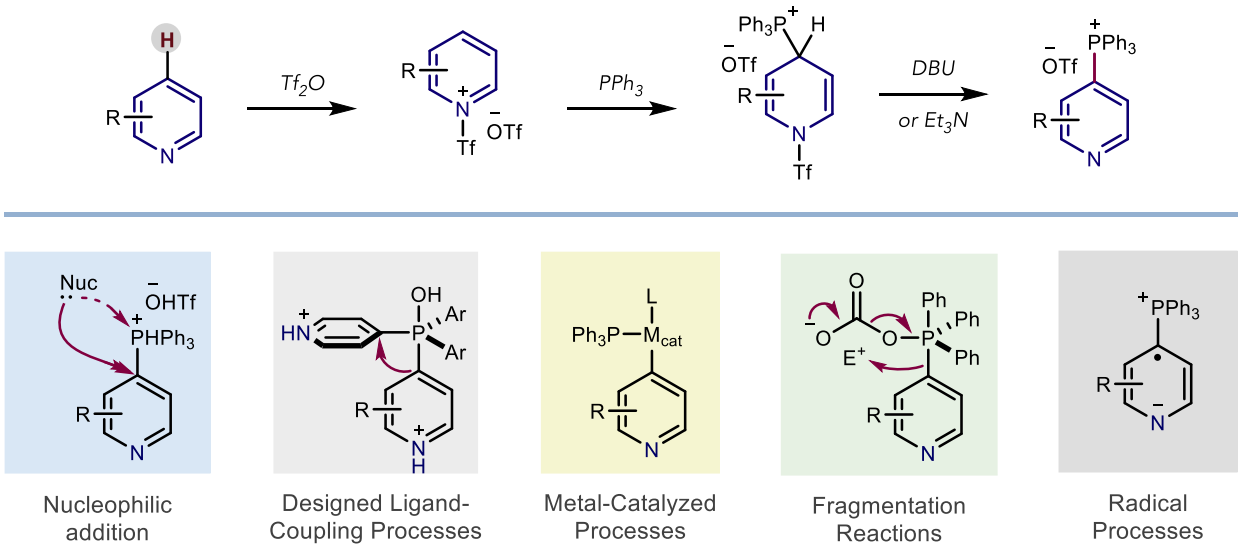

Figure 1.14. The synthesis of heterocyclic phosphonium salts and the different reaction processes they undergo for pyridine functionalization.

The heterocyclic phosphonium salts allow for different bond constructions onto the pyridine ring through the various reaction processes described above. Nucleophilic addition reactions have allowed for C-Halogen,[72] C-S,[67,68] C-O,[43,68] and C-N[73] bond formation directly from the salt (**Figure 1.15**). They have also been used as halide surrogates in metal catalysis, resulting in Suzuki cross-couplings with nickel catalysis and Negishi reactions with cobalt.[66,75] Fragmentation of the phosphonium in deuterated or tritiated solvents gives 4-selective isotopic labeling of the azine.[71] They have also been shown to undergo single electron reduction and couple with cyanopyridine for the formation of bipyridine scaffolds.[76]

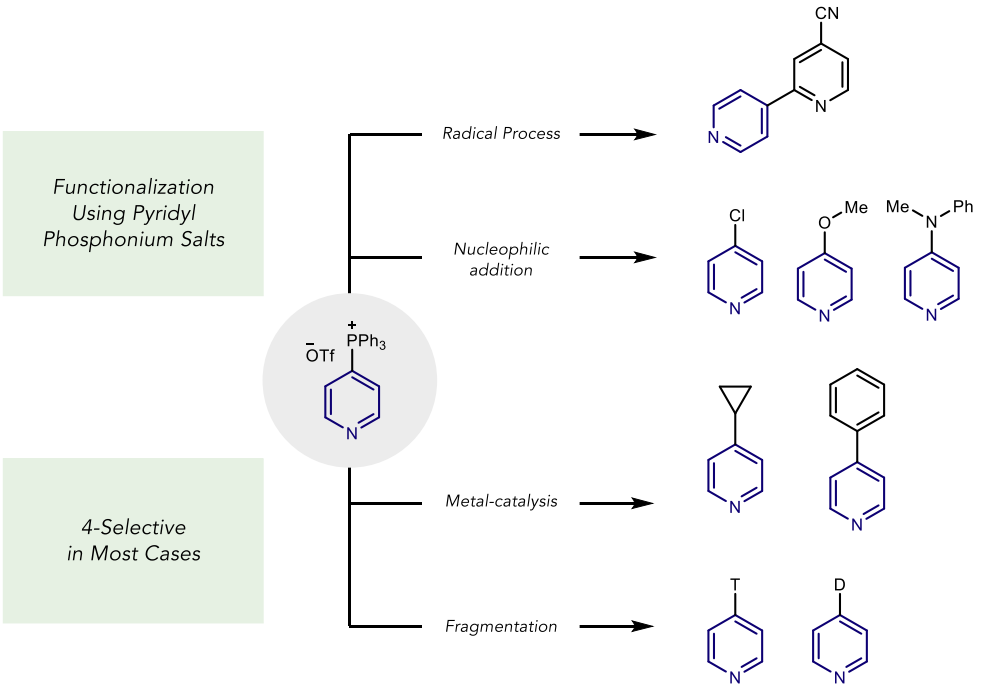

Figure 1.15. Transformations available from the heterocyclic phosphonium salts

The phosphonium installation is not limited to PPh_3. Various designed phosphines are amenable to the process, allowing for ligand-coupling reactions for pyridine functionalization. Pyridyl phosphines can be installed via the standard salt protocol to yield bis-heteroarylphosphonium salts.[70] Adding acid and a nucleophilic trigger such as water produces a P(V) intermediate, which undergoes an asynchronous ligand-coupling process to deliver the bishetero-biaryl product. Chlorphenamine is shown as a representative example. McNally and coworkers recently exploited this reaction pathway for trifluoromethylation and difluoromethylation.[74] Using designed fluoroalkyl diarylphosphines, the salt is installed in the same manner and subsequently triggered for ligand-coupling in a one-pot process. The group demonstrated the protocol on 13 pharmaceuticals or agrochemicals and over 60 total examples.

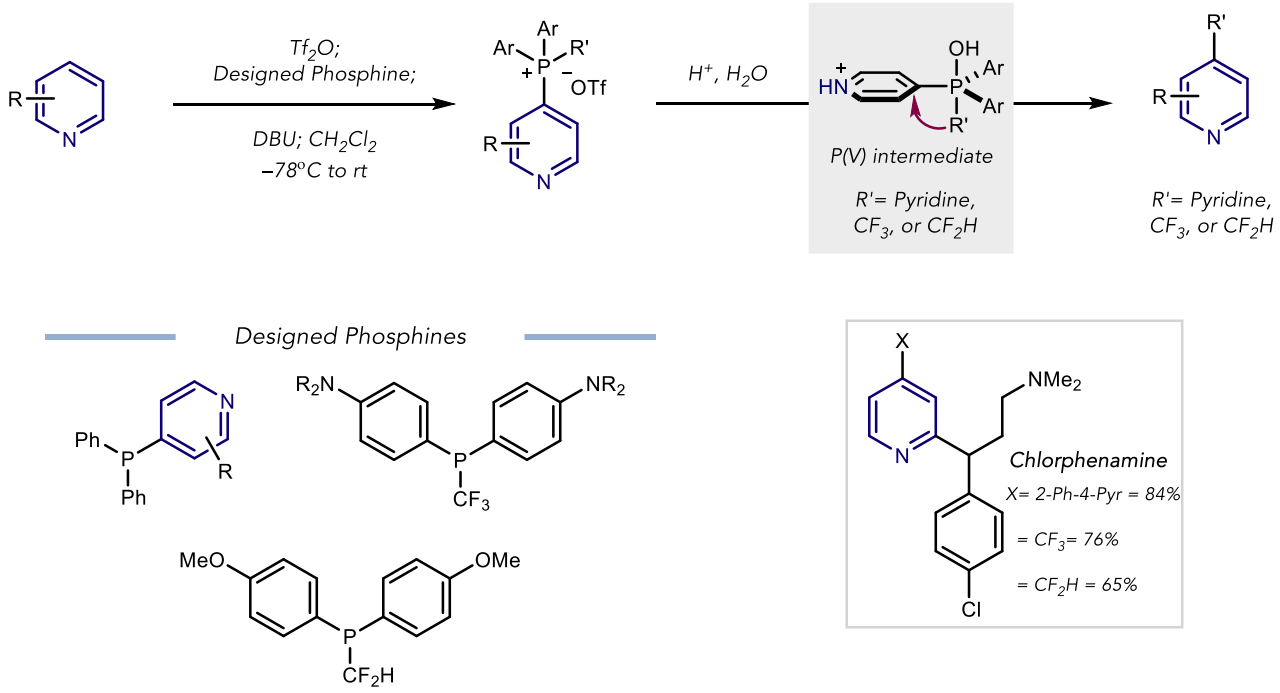

Figure 1.16. Ligand-coupling process for pyridine functionalization. Chlorphenamine is shown as a representative example.

1.3 Introduction to Hydrogenation Methods for Piperidine Synthesis

As piperidines are more frequently found that pyridine scaffolds in pharmaceuticals, it can be argued that they are more important of a heterocycle. Because it is fully saturated, the piperidine ring offers a more complex molecular scaffold, allowing for exploration into different chemical space without significantly increasing the molecular weight.[77] The incorporation of all sp^3 centers introduces chirality to the substrate, resulting in more isomers to be examined. As with pyridine, there are inherent issues when it comes to functionalizing piperidines. Like its aromatic counterpart, the lone pair on the nitrogen atom can cause undesired metal ligation and poison catalytic cycles.[56,78,79] In contrast to pyridine, the fully saturated nature of piperidines make them

more challenging to functionalize. For this reason, hydrogenation of pyridines has become one of the most appealing strategies for piperidine synthesis. An in-depth introduction to pyridine hydrogenation will be given in the introduction to chapter 4 (vide infra).

1.4 Conclusion

This chapter serves as an introduction to pyridines and piperidines and their importance in the design of pharmaceuticals. Additionally, methods to derivatize pyridine are discussed along with their challenges. Classical methods and more recent advances tend to be 2- or 3-selective processes, and 4-selective methods are comparatively rare. Recent advancements using heterocyclic phosphonium salts have expanded the access to more diverse 4-functionalized pyridines.

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CHAPTER TWO

SITE-SELECTIVE SWITCHING PROTOCOLS FOR POLYAZINE FUNCTIONALIZATION

2.1 Introduction to Site-Selectivity

Site-selective reactions are transformations which differentiate between repeating functional groups with variations in chemical environment.[1,2] Accomplishing selectivity between the two repeating functional groups is difficult as they exhibit near identical reactivity and tend to undergo the same transformation under a given set of conditions. Slight variations in steric or electronic effects may be used to control reactivity. This approach allows for expediated drug discovery timelines by avoiding *de novo* synthesis and provides an efficient route to valuable derivatives of pharmaceutically relevant compounds.[3,4] Despite these advantages, methods to control site-selectivity are rare.

Significant advancements have been made in site-selective modifications of poly-hydroxylated compounds,[5–7] polyenes,[8,9] and polyarenes,[10,11] taking advantage of slight variations in steric or electronic properties of the repeating functionality. Each are an important class of molecules, often found in either carbohydrates, nucleic acids, essential oils, or acting as antioxidants.[5,12,13] The ability to selectively control which repeating functional group is derivatized allows for analysis of the structure-activity relationship (SAR).[3,4] This leads to a deeper understanding of how the pharmaceutical interacts with biological systems and can result in new derivatives and therapeutics. Miller and coworkers have demonstrated this extensively using

peptide catalysis for selective functionalization of polyhydroxylated compounds, including Erythromycin A,[5] Teicoplanin,[6] and Vancomycin.[11]

Erythromycin A is an antibiotic discovered in the 1950s and has been used to treat several bacterial infections.[5,14] Miller demonstrated that controlling the acylation of three distinct hydroxyl groups in the drug requires modified reaction conditions unique to each group (**Figure 2.1**).[5] The authors first showed that the most reactive alcohol at the C2' could be acylated simply by using one equivalent of acetic anhydride and catalytic amounts of *N*-methylimidazole. Selectivity changes to the C4'' by increasing acetic anhydride to two equivalences, generating the C2'/C4'' diacetate. Quenching the reaction with methanol selectively hydrolyzes the C2' acetate, yielding a switched site-selective acylation. By increasing the equivalence of acetic anhydride and prolonging the reaction time, the authors also found the C11 hydroxyl group is also acylated. However, three days of reacting are required, and it only achieves 30% conversion with poor site-selectivity (4:1; C4'':C11). To overcome this synthetic challenge, The authors implemented a small-molecule peptide catalysis and discovered the use of catalyst **1** switches the preferred reactivity to the C11 alcohol. The peptide binds explicitly to Erythromycin A via hydrogen bonding interaction, allowing for controlled reactivity. Upon acylation of the C11 alcohol, Miller et al. discovered that the structural basis of the antibiotic changes, as a hemiketal is generated from the C9 carbonyl and C12 alcohol.

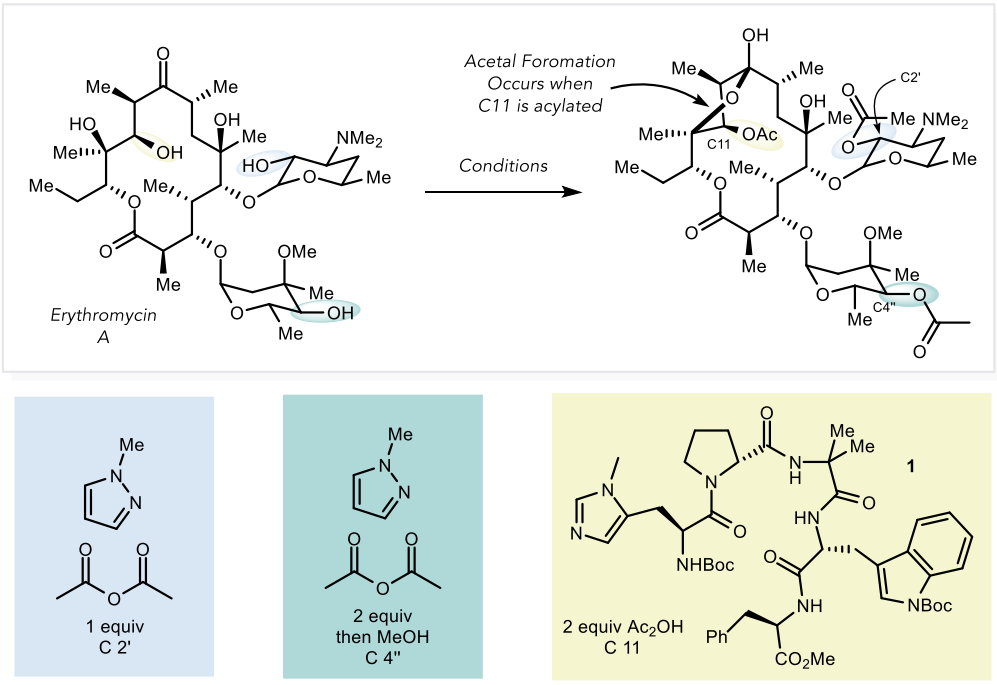


Figure 2.1. Miller's switchable site-selective acylation of Erythromycin A[5]

Miller has also demonstrated switchable site-selective functionalization using peptide catalysis on polyene substrates.[9] Small-molecule catalysis has enabled stereoselective oxidation of terminal olefins of polyenes and allylic olefins.[15–20] Miller's approach accomplishes not only enantioselective, but also site-selective epoxidation using designed peptide catalysts (**Figure 2.2**). The authors demonstrate the ability to generate the 2,3-epoxy derivative of Farnesol, an ingredient in several essential oils and perfumes, using resin-bound peptide catalyst **2** with 1-hydroxybenzotriazole (HOtB), *N,N'*-diisopropylcarbodiimide (DIC), *N,N*-dimethylaminopyridine (DMAP), and H_2O_2. The DIC activates the side chain of an aspartic acid residue, allowing for the formation of the peroxy acid. The peptide then binds to the substrate selectively, which provides enantio- and site-selective epoxidation. To switch the site-selectivity, the authors employed catalyst **3**, resulting in the 6,7-epoxy Farnesol. These catalysts additionally underwent the reaction on several other polyenes, including Geranylgeraniol.[9]

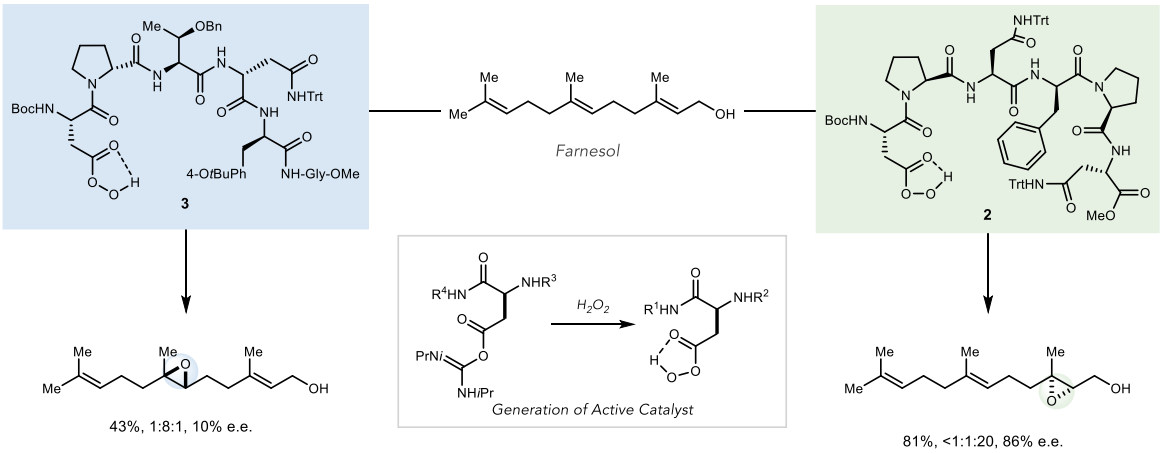


Figure 2.2. Miller's site-selective epoxidation via peptide catalysis

There have also been developments in the site-selective functionalization of polyphenols.[10,11] These compounds are typically found in fruits, vegetables, and legumes and have several health benefits, including acting as antioxidants.[13] Snyder and coworkers have developed a reagent-controlled site-selective bromination of polyphenols, allowing them to switch the reactive position simply by changing their halogenation source (**Figure 2.3**).[10] In the functionalization of ampelopsin F, the halogenation reagent can distinguish between four electronically equivalent aromatic protons. By using NBS, or several other bromine sources, the authors selectively halogenate H_a, which they attribute to the innate reactivity of the substrate. To switch the selectivity, BDSD was employed, resulting in bromination of H_c 78% yield. However, the origin of site-selectivity has yet to be determined.

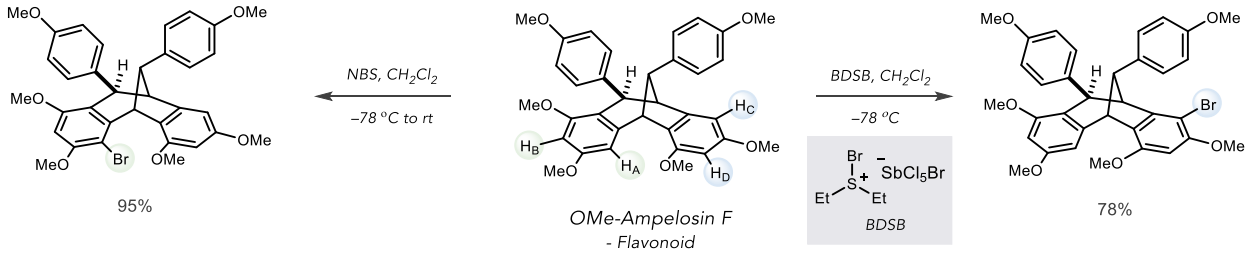


Figure 2.3. Snyder's site-selective halogenation of Ampelosin F. Adapted from reference 10.

2.2 Introduction to Switchable Site-Selective Polyazine Functionalization via Phosphonium Salts

Despite the growing examples of switchable site-selective reactions in organic synthesis, there have yet to be general strategies that focus on systems that contain multiple pyridines or diazines.[21–24] These systems, named polyazines, frequently occur in lead compounds and pharmaceuticals.[25,26] Bipyridine examples include etoricoxib, a non-steroidal anti-inflammatory drug, and nevirapine, an HIV treatment. There are also occurrences of polyazines having one pyridine and one diazine, such as the Leukemia drug imatinib or eszopicione, which treats insomnia (**Figure 2.4**). Given their ubiquity in the pharmaceutical industry, methods to selectively functionalize polyazines are highly sought-after.[27,28] A method is disclosed for site-selective installation of heterocyclic phosphonium salts.[29]

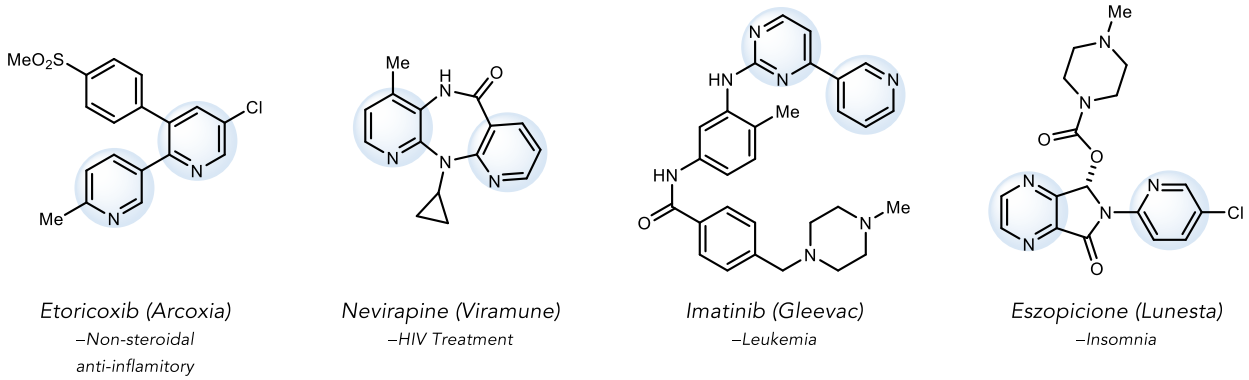


Figure 2.4. Pharmaceuticals containing polyazine scaffolds.

As mentioned in section **1.2.3**, the phosphonium salts are used to functionalize selectively the 4-position of pyridine rings.[30–36] In addition to regioselective installation of the salt, studies run by McNally and coworkers also found polyazines achieve excellent site-selectivity (**Figure 2.5**). The reasoning behind this was not understood initially and therefore led us to investigate the factors controlling selectivity.[29,37,38] Our goal was to systematically analyze how substitution

patterns, steric, and electron considerations influence the inherent selectivity of the phosphonium installation. Upon understanding each of those factors, we can hypothesize methods for switching the site-selectivity to the other azine.

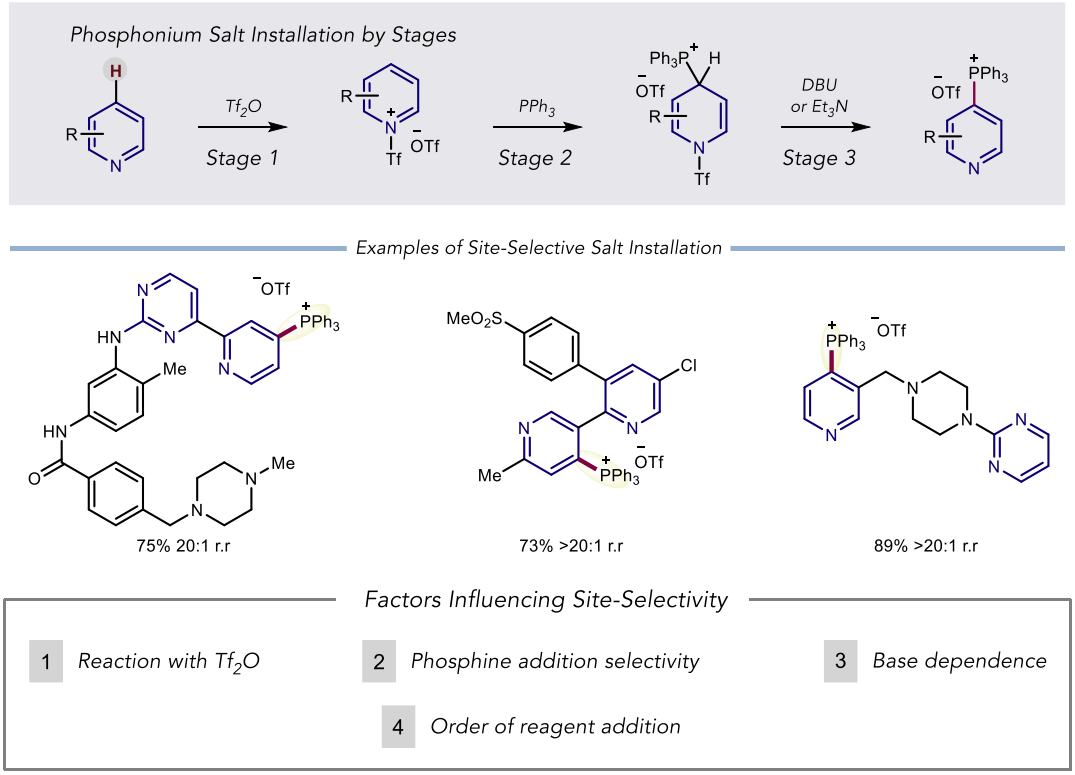


Figure 2.5. Phosphonium salt installation broken down by stages and examples of site-selective substrates.

To understand how to control inherent selectivity was, we divided the mechanism into three separate stages: activation of the azine with Tf_2O, phosphine addition into the *N*-triflylpyridinium, and organic base-mediated aromatization (**Figure 2.5**).[30] We hypothesized each of these stages influences site-selectivity, as well as external factors, such as the order of addition of reagents. To probe how each of these factors impacted reactivity, we devised intermolecular competition reactions where two different azines were in the same vessel. The two substrates varied in either substitution pattern, electronics, or steric effects and subjected to the standard phosphonium salt protocol. That procedure is first, activation with trifluoromethanesulfonic anhydride (Tf_2O) in

CH_2Cl_2 at −78°C for 30 minutes. Next, triphenylphosphine (PPh_3) is added and stirred for an additional 30 minutes, followed by deprotonation with an organic base (DBU or Et_3N), and warming to room temperature.[30] Then, using ^1H NMR and ^{31}P NMR analysis of the reactions reveals the selectivity of the salt formation. From these results, we can make hypotheses on the origin of site-selectivity, leading to experiments designed to switch the site of reactivity. Upon establishing rules for inherent selectivity and developing methods to change it, polyazine systems would be synthesized and used for switchable site-selective phosphonium installation.

2.3 Acylation Switching Strategy

Early into our investigation of the intermolecular competition reactions, we discovered a clear bias for phosphonium installation in regard to substitution pattern.[29] In the competition between 2-methoxypyridine and 3-methoxypyridine, the salt preferred to form on the 3-substituted azine in 83% yield with a 19:1 selectivity (**Figure 2.6 A**). We hypothesized that the selectivity determining step occurs during the activation of the pyridine ring. The nitrogen atom of the 3-substituted pyridine ring is sterically more accessible than its 2-substituted counterpart; therefore, Tf_2O preferentially reacts with that azine. This leads to selective phosphine addition only into the activated pyridine, thus generating one phosphonium isomer.

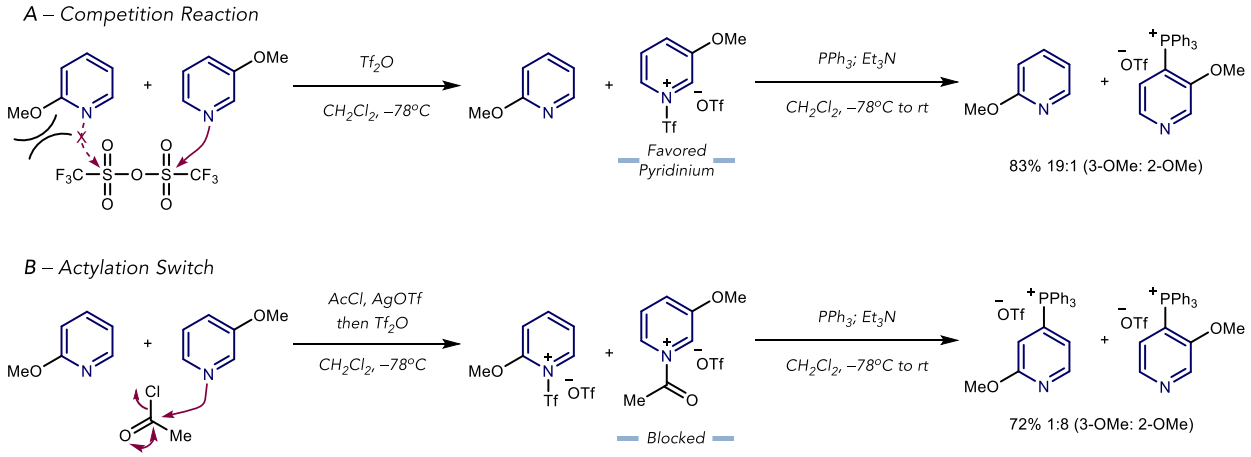


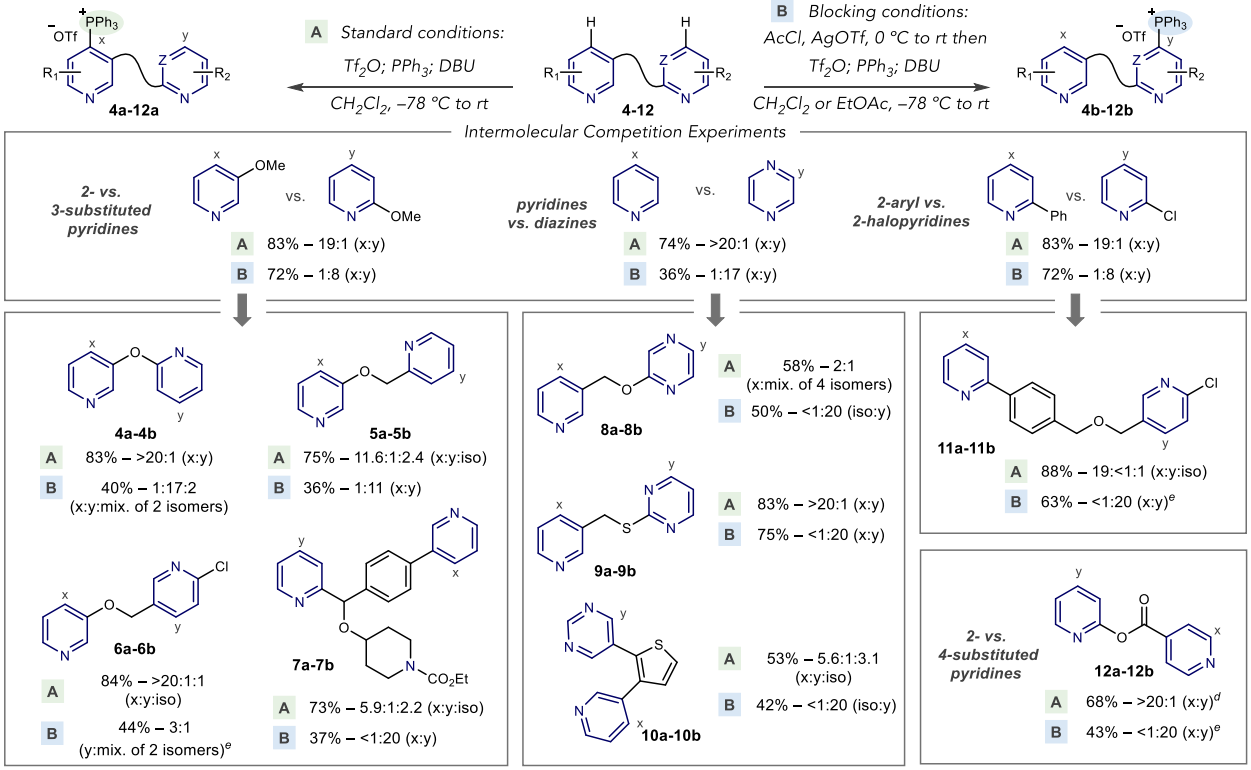
Figure 2.6. Intermolecular competition between 2-OMe and 3-OMe pyridine and its acylation switch.[29]

Since selective activation leads to selective phosphonium formation, we envisioned an acylation blocking strategy to switch reactivity. First, acetyl chloride (AcCl) and silver triflate (AgOTf) are pre-stirred with the two azines at room temperature, allowing the more nucleophilic pyridine to be acylated. Then, the reaction mixture undergoes the standard salt protocol; however, the triflyl activation would now occur on the non-acylated 2-substituted pyridine, thus switching the phosphonium selectivity. Using this strategy on the 3-methoxy versus 2-methoxypyridine competition, the salt selectivity changes in favor of the 2-methoxypyridine in 72% yield with an 8:1 ratio in favor of the 2-substituted azine (**Figure 2.6 B**).

To test if the rules for inherent selectivity and see if the acylation switching protocol applies to polyazine systems, we synthesized 2-(pyridin-3-yloxy)pyridine (**4**) (**Table 2.1**). In agreement with the intermolecular competition, the standard phosphonium protocol (A) generates the phosphonium on the 3-oxypyridine in 83% yield with >20:1 selectivity (**4a**). Next, the acylation switching conditions (B) generates the phosphonium salt on the 2-substituted azine (**4b**) in 40% in a 17:1:2 ratio of 2-oxy: 3-oxy: mixture of isomers. Following the moderate success of the polyazine experiments, we demonstrated several other substitutionally biased polyazines. 2-((pyridin-3-

yloxy)methyl)pyridine (**5**) observed similar reactivity trends. The more sterically accessible 3-oxypyridne preferentially forms the salt under conditions A in 75% yield (**5a**). Using conditions B switches the selectivity and converts the 2-alkylpyridine to the phosphonium ion (**5b**) in 36% yield in 11:1 selectivity. For substrate **6**, the chlorine atom at the 2-position blocks triflyl activation from occurring under the standard protocol, yielding the phosphonium on the 3-oxy pyridine (**6a**) in 84% yield. The acylation switch changes the salt formation site; however, lower selectivity is achieved (**6b**). A bepotastine precursor (**7**) is also amenable to this process. Under conditions A, the salt forms preferentially on the 3-aryl azine (**7a**), albeit in low selectivity. Conditions B switch the selectivity for the 2-alkylpyridine in 37% yield (**7b**) with complete selectivity. This example demonstrates the ability to use this strategy late stage on drug-like fragments where site-selectivity is often difficult to achieve.[39]

Table 2.1. Scope of Acylation Switching Strategy for Polyazine Systems [a,b,c,d,e,f]



[a]Isolated yields of salt mixtures are reported.[29] [b]Ratios were calculated from crude ^{1}H or ^{31}P NMR spectra. Ratios of isolated products can differ from the crude reaction mixture. [c]Iso refers to an unidentified phosphonium salt isomer. [d]Yields calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [e]P(*p*-OMePh)$_3$ used. [f] Adapted from reference 29

We also applied this process to other systems with differing electronics of the azine (**Table 2.1**). For instance, in an intermolecular competition between pyridine and pyrazine, the diazine is more electron-deficient due to the additional electronegative nitrogen atom in the ring. This electron deficiency lowers the nucleophilicity of the azine. Therefore, *N*-triflyl activation occurs selectively on pyridine, leading to selective phosphonium salt formation on that ring in 74% yield with complete selectivity. Using the same logic as the previous examples, we can use the acylation blocking conditions to switch the selectivity in favor of the pyrazine in 37% yield and a 17:1 ratio. Adapting this competition to polyazine **8** results in low selectivity for the standard protocol, 2:1 in favor of the pyridine (**8a**); however, the acylation blocking protocol gives better selectivity, yielding phosphonium **8b** in 50% with >20:1 ratio. Other electronically biased systems such as polyazine **9** and **10** both work in the inherent selectivity reaction. However, we observed differing degrees of selectivity, where polyazine **9** is completely selective for the pyridine ring in 83% yield (**9a**), and **10** gives a mixture of products (**10a**). Conditions B work well in both examples, resulting in one salt isomer on the diazine in each case (**9b**, **10b**). We can extend the electronic bias to more subtle examples, such as 2-phenyl versus 2-chloropyridine. In the intermolecular competition, the salt is first generated on the 2-phenylpyridine under conditions A. The acylation switch changes the bias towards the 2-chloropyridine in 72% yield with an 8:1 selectivity. Polyazine **11** mimics this competition and similar reactivity trends occurred. These protocols were also applied to 4,2' linked systems, such as the ester-linked polyazine **12**. Under standard conditions, the salt preferentially forms at the ortho position of the 4-substituted azine in 68% yield and one isomer

(**12a**). The acylation switch generates the phosphonium on the 2-oxypyridine in 43% yield using $(p\text{-}OMePh)_3P$ as the phosphine, again with one isomer (**12b**).

2.4 Base-mediated Switching Strategy

Stage 3 of the salt formation reaction can also dictate site-selectivity. In cases where there are minor steric or electronic differences, tuning the base for aromatization can be used to impact selectivity significantly. We derived this base-mediate strategy from observations made during the optimization of the phosphonium salt installation protocol. The two optimal bases are DBU and Et_3N, where the latter was found to work well on pyridine and 3-methoxypyridine but is unreactive towards 3-alkyl or 3-arylpyridine (**Figure 2.7**), and the former works well for all these cases. We hypothesize that this is due to the electronegativity differences between the pyridines. In 3-methoxypyridine, the electronegativity of the oxygen atom lowers the pK_a enough to allow Et_3N to react, where the carbon-bearing groups do not, thus requiring a stronger base like DBU. Additionally, there could be a steric interaction between the base and the appending substituent that is enhanced between the alkyl substituents of intermediate **I** and Et_3N. This steric interaction is avoided with the heteroatom in intermediate **II**.

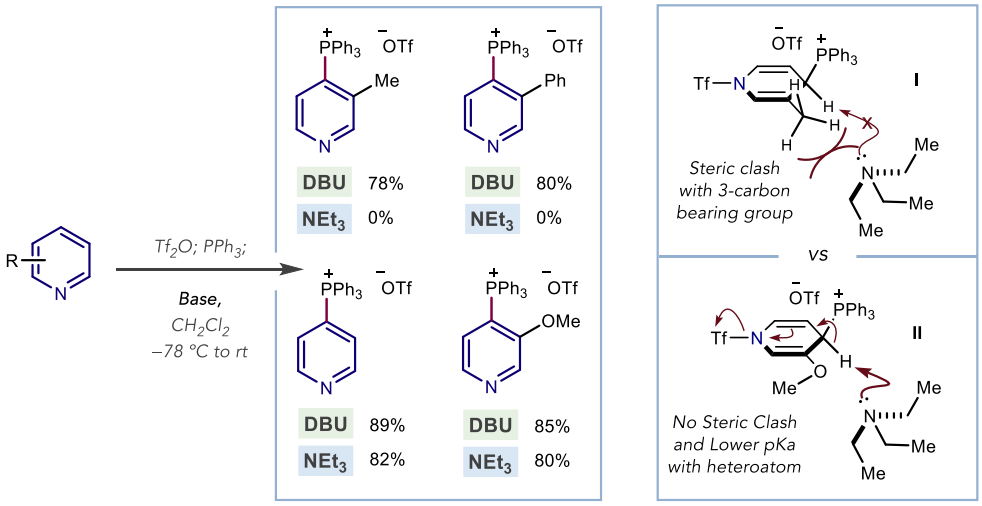


Figure 2.7. Observations made with base screen during phosphonium formation optimization and hypothesis for reactivity of triethylamine.[29]

We envisioned using this observation for the development of a base-mediated switching strategy. In this method, we exploit the binary nature of the base to aromatize one phosphonium salt intermediate over another selectively. To do so, we synthesized 3,3'-methylene ether-linked polyazine **13**. In this case, there is no clear steric or electron bias for *N*-Tf activation; therefore, when performing the standard phosphonium protocol, a mixture of products is observed (**Figure 2.8**). Since there is no clear activation bias, the acylation switching strategy cannot be applied in this case. To overcome this problem, we hypothesized that a modification to the reaction protocol would allow the base addition to dictate the site-selectivity. We found that adding two equivalences of Tf_2O at –78 °C followed by two equivalences of PPh_3 to the polyazine generates the doubly-dearomatized bisphosphonium salt **III**. This intermediate is observed using variable temperature (VT) ^{31}P NMR studies at –80 °C, giving two major resonances at 21.93 ppm and 19.53 ppm. Upon addition to the reaction, Et_3N should only react with the 3-oxypyridine, leaving the 3-alkyl unreacted, thus forcing selectivity onto one pyridine ring. During an aqueous workup, the unreacted 3-carbon bearing dearomatized intermediate will decompose. Indeed, a selective

phosphonium installation occurs, yielding the phosphonium salt product in 69% yield in >20:1 selectivity for the oxypyridine (**13b**).

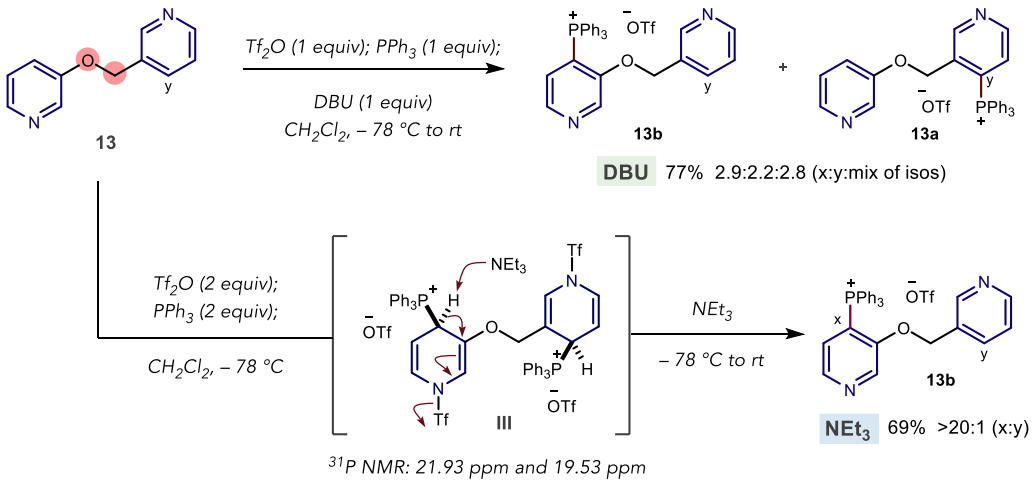
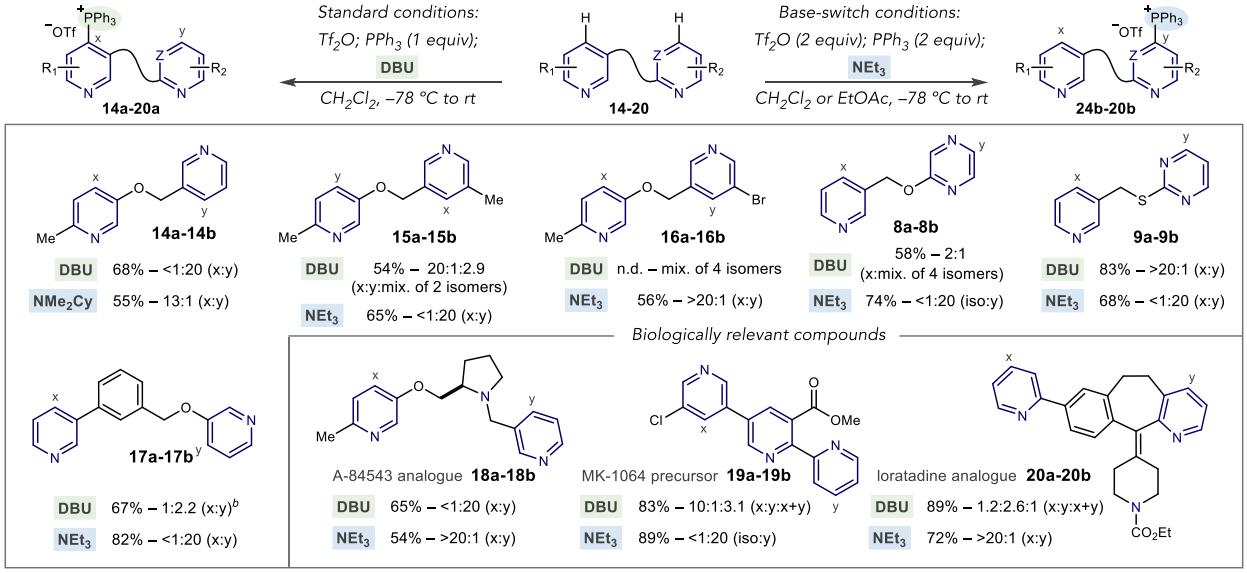


Figure 2.8. Base-mediated switching strategy for selective phosphonium installation.[29]

We next tested the generality of this base-mediate switching protocol by synthesizing several polyazines that contained one pyridine that had a 3-carbon bearing group and one that was 3-heteroatom or unsubstituted (**Table 2.2**). In the standard phosphonium protocol, the salt formed preferentially on the 3-substituted or 3,5-disubstituted azine over the 2-5-substituted pyridine (**14a**-**16a**). In each case, the inherent selectivity had a 3-carbon bearing group; therefore, we can apply the base switch protocol. In the case of **14b,** NMe_2Cy was found to outperform Et_3N, giving a better selectivity and a slight boost in yield. In the following two examples, Et_3N works well, providing 65% and 56% for **15b** and **16b**, respectively, both with >20:1 selectivity. In **8** and **9**, Tf_2O activates the pyridine first, giving preferred reactivity for that ring. In **8a**, again, the selectivity is low, but only one isomer is obtained for **9a**. Using the base switch protocol gives complete selectivity for the diazine in both examples (**8b**, **9b**). Polyazine **17** is similar to **13**, where there is no clear steric or electronic bias, resulting in a 2.2:1 mixture of products under the standard protocol. However, one of the pyridines is 3-aryl substituted and the other is 3-oxy; thus, we can employ the base switch to obtain one phosphonium product in 82% yield (**17b**).

Table 2.2. Scope of Base-mediate Switch Strategy on Polyazines [a,b,c]



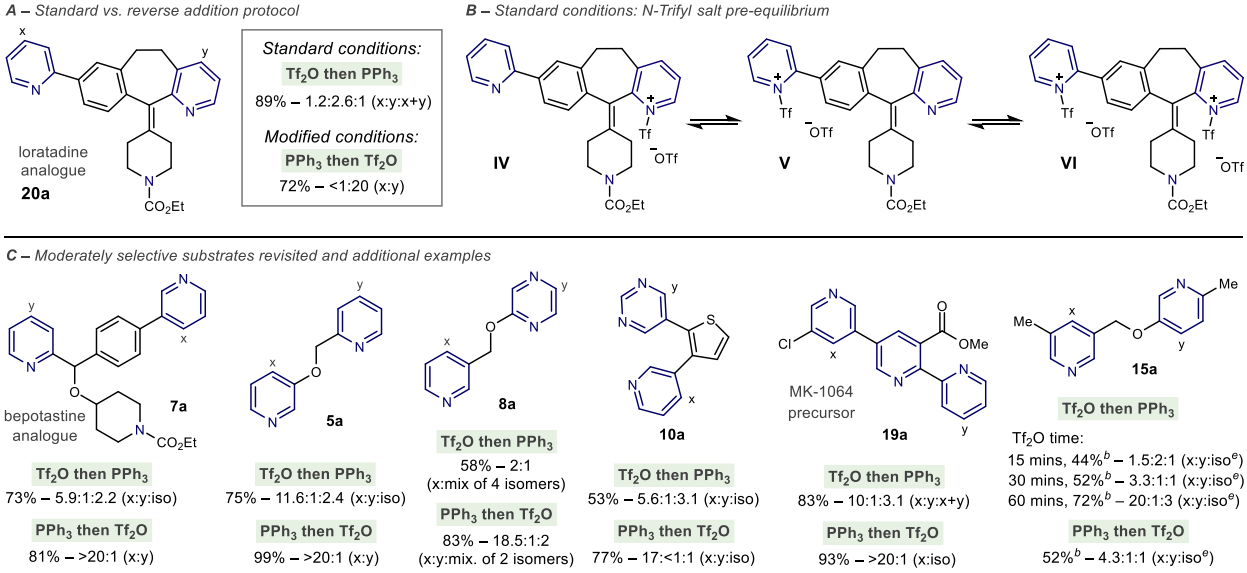
[a]Yields and ratios reported as in **Table 2.1**. [b]Yield calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]x + y represents a bis-phosphonium salt. Figure adapted from reference 29.

We also demonstrated the base-switch protocol on three biologically relevant examples to illustrate how medicinal chemists can use this strategy late-stage in a drug discovery program. First, an A-84543 analog, a nicotinic acetylcholine receptor agonist (**18**), was shown to form the salt selectively on the 3-alkyl pyridine in a 65% yield (**18a**).[40] Using Et_3N in the base switch generates the salt on the 2,5-substituted pyridine in 54% yield in >20:1 selectivity (**18b**). Next, an MK-1064 precursor (**19**) was tested for inherent selectivity. The phosphonium preferentially formed on the 3-chloro-5-arylpyridine, albeit in lower selectivity (19a, 10:1.3:1, x:y:x+y). However, employing the base switch yields the salt on the 2-aryl pyridine in 89% yield with a >20:1 selectivity (**19b**). Lastly, we synthesized a Loratadine analog by coupling a 2-stannyl pyridine with the chloroarene (**20**). Although the inherent selectivity gave an unselective mixture of phosphonium products, the base switch strategy yielded the 2-arylpyridine phosphonium ion in 72% yield and >20:1 selectivity (**20b**).

2.5 Order of Reagent Addition

Several examples from **Table 2.1** and **2.2** exhibited very low inherent selectivity using the standard phosphonium protocol. We hypothesized that this is because an equilibrium of different *N*-Tf pyridinium salts is forming in the first step of the procedure.[29] Therefore, when adding PPh_3 to the reaction, multiple dearomatized intermediates are formed and subsequently converted to the heteroarylphosphonium salt. Experimental evidence for this hypothesis was obtained using VT ^1H NMR. After stirring **20** for 30 minutes with Tf_2O at −80°C in CD_2Cl_2, the analysis showed each pyridine proton peak was shifted downfield and broadened compared to the unreacted ^1H NMR spectrum of **20**. This broadening and downfield shift are due to the rapid equilibrium of the different *N*-Tf pyridinium salts (intermediates **IV**, **V**, **VI**). To combat this synthetic challenge, we hypothesized the order in which the reagents are added would drastically affect this equilibrium. For example, in the case of Loratadine derivative **20a**, if we add PPh_3 first, then Tf_2O, the reaction produces the phosphonium salt on the 2,3-disubstituted pyridine in 72% yield in >20:1 selectivity. We hypothesize that this is due to the kinetic pyridinium formation occurring first and immediately reacting irreversibly with PPh_3, thus preventing the equilibrium of pyridinium salts. Therefore, only one dearomatized intermediate is formed, which ultimately yields only one phosphonium product.

Table 2.3. Alternation of the standard phosphonium protocol and its effect on inherent selectivity[a,b,c,d,e]



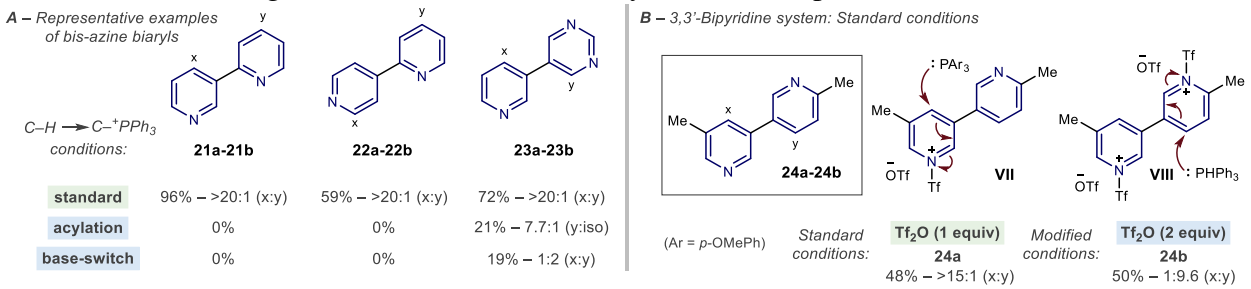
[a]Yields and ratios reported as in **Table 2.1**.[29] [b]Yield calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]x + y represents a bis-phosphonium salt. [d]Iso refers to an unidentified phosphonium salt isomer. [e]Mixture of two unidentified isomers. Figure adapted from reference 29.

We tested this order of addition modification on other polyazines that exhibited low inherent selectivity (**Table 2.3**). The phosphonium salt selectivity on the bepotastine analog increased to >20:1 in 81% yield, and **5a**'s result increased to 99% with just one isomer obtained. Similarly, **8a** and **10a** see an increase in reaction efficiency and selectivity. Under the standard procedure, MK-1064 precursor yields a 10:1:3.1 (x:y:x+y) mixture of products, but under the modified conditions, it yields **19a** in 93% yield in a >20:1 ratio (x:iso). Conversely, polyazine **15**'s inherent selectivity was worse when employing the new order of addition procedure. We found that the optimal time to stir the Tf_2O with the polyazine before adding PPh_3 was one hour. This result presumably indicates that *N*-Tf formation needed additional time to equilibrate over to the more stable pyridinium salt, and thus we cannot assume that the new protocol is the optimal procedure for all polyazines.

2.6 Investigations into Bishetero-biaryls

Bishetero-biaryls comprised of pyridines or diazines are frequently found in pharmaceutically relevant compounds, including Etoricoxib and Gleevac (**Figure 2.4**).[41] Due to their importance, we decided to examine several examples from this class of compounds in our phosphonium switching protocols. Under the standard salt-forming procedure, each example obtains excellent selectivity in good to great yields.[29] However, employing both the acylation and base-mediated switch gives very little to no product. For **23b**, the desired salt is observed, albeit in low yield and poor selectivity. We hypothesized this is because, with the increase in electrophilicity of the neighboring pyridinium, the site of PPh_3 reactivity is altered, making the attack at the sulfur atom the most favorable. We proposed a new switching strategy via stage 2 of the salt installation mechanism to overcome this problem. In the case of substrates like **24**, a phosphine addition can mediate the site-selectivity. Under standard conditions, (*p*-OMePh)$_3$P adds selectively to the 3,5-disubstituted pyridinium salt **VII**. Similar to the other bisazine-biaryls, we cannot obtain any switch product using the acylation or base-mediated strategies. However, the steric bulk surrounding the 4-position of the 3,5-disubstituted pyridine can force the phosphine to the other pyridine ring. The addition of two equivalences Tf_2O forms bispyridinium **VIII**; thus, allowing the phosphine to add to the sterically more accessible 2,5-substituted pyridine reacts first, switching the phosphonium selectivity (**24b**).

Table 2.4. Switching Protocols on Bisazine-biaryls and a Phosphine Mediated Switch [a,b,c]



[a]Yields and ratios reported as in **Table 2.1**.[29] [b]Yields calculated by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Figure adapted from reference 29.

2.7 Derivatization Reactions of Polyazines

Having created multiple protocols for influencing site-selectivity, we next demonstrated various transformations that our lab has developed with the phosphonium salts.[30,31,42,43] This showcases how medicinal chemists can adapt these strategies into their research for rapidly synthesizing analogs of polyazine lead compounds. We used Pyridine-diazine **9** as a representative example (**Figure 2.9**) and isolated the pyridyl phosphonium ion in 83% yield under the standard salt protocol, with excellent selectivity.

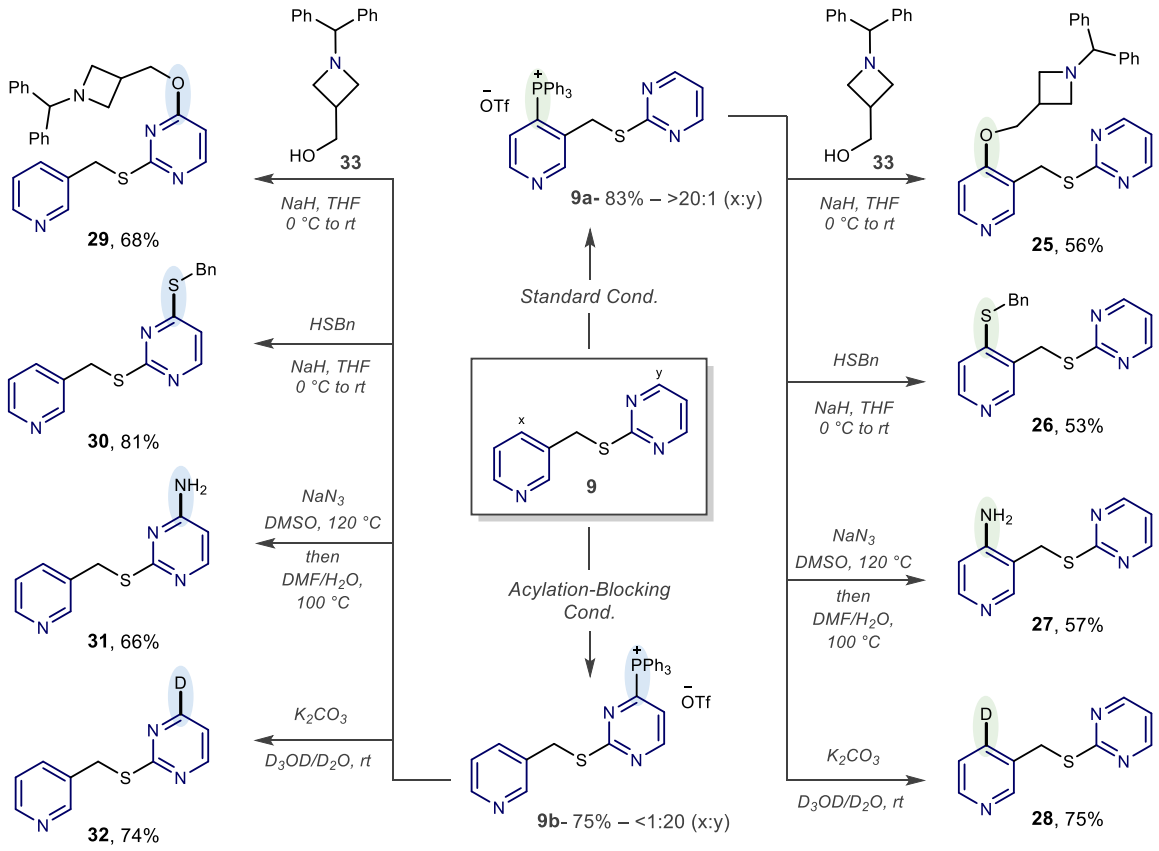


Figure 2.9. Derivatizations from phosphonium salts 9a and 9b. Ratio reported as in Table 1. Adapted from reference 29

We subjected the salt to an azetidine containing alcohol **33** and sodium hydride in THF, yielding pyridyl ether **25** in 56%.[30] Under similar conditions but using benzyl mercaptan, the reaction gives thioether **26** in 53% yield.[42] Heating the salt in DMSO with sodium azide followed by heating in a DMF/water solution generates a 4-aminopyridine in good yield.[43] Lastly, decomposition of the salt with a carbonate base in a deuterated methanol/water mixture isotopically labels the 4-position of the pyridine ring.[31] Following these derivatives, we next synthesized a distinctly new set of analogs. Using the acylation switching strategy, we obtained the phosphonium on the pyrimidine ring and subsequently performed the same transformations, giving products **29**-**32**.

In addition to PPh_3, we demonstrated that designed phosphines are amenable to the switching protocols. For instance, our group devised trifluoroalkyl phosphine **34** to undergo selective trifluoromethylation of pyridines via a ligand coupling process.[36] Employing it on Loratadine analog **20**, the standard protocol installs the CF_3 on the carbocycle-fused pyridine ring in 71% yield with a 15:1 selectivity (**Figure 2.10**). However, despite a drastic change in the steric and electronic environment of the phosphine, the base-mediated switching protocol still occurs with excellent selectivity and great yield. Similar results were obtained using a designed pyridyl phosphine meant for halogenation of pyridine.[44]

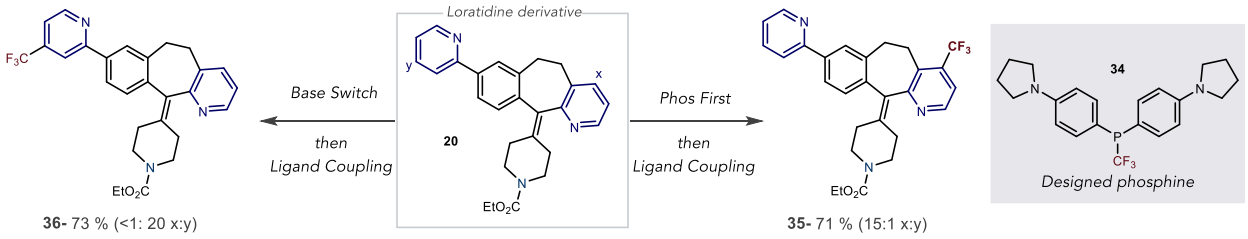


Figure 2.10. Designed phosphines used in the switch protocols.[36]

2.8 Conclusion

In conclusion, we investigated several factors for controlling the site-selectivity of the phosphonium salt installation. Substitution patterns and electronic effects coming off the pyridine or diazine dictate the inherent selectivity. Examining the mechanism for phosphonium installation led to the discovery of three distinct switching protocols, acylation blocking strategy, base-mediated switching strategy, and selective phosphine addition. Additionally, we developed a procedure to increase inherent selectivity by altering the order in which PPh3 and Tf2O are added

to the reaction vessel. The salts were shown to undergo several transformations to demonstrate how medicinal chemists can apply these methods for analog synthesis in a medicinal chemistry program. Lastly, the switching protocols were demonstrated to apply to other designed phosphines with significant differences in the steric and electronic environment.

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CHAPTER THREE

4-SELECTIVE PYRIDINE ALKYLATION VIA WITTIG OLEFINATION OF DEAROMATIZED PYRIDYL PHOSPHONIUM YLIDES

3.1 Introduction to Pyridine Alkylation

Alkylated pyridines are a common motif found in pharmaceutically relevant compounds, as well as agrochemicals, materials, and ligands (**Figure 3.1**). [1–5] In the context of pharmaceuticals, alkyl groups can impact the pharmacokinetic and pharmacodynamic properties of a drug. They can alter the Lewis basicity of the pyridyl nitrogen, occupy hydrophobic pockets in a binding site, prevent oxidative metabolism, help increase solubility inside the body by disrupting intramolecular hydrogen bonding networks, or increase lipophilicity.[1,2,6] These properties make alkylation a common SAR strategy when optimizing pyridine-containing lead compounds.[7] Their importance in this field of research has made new methods for alkylation of pyridine scaffolds highly desirable.

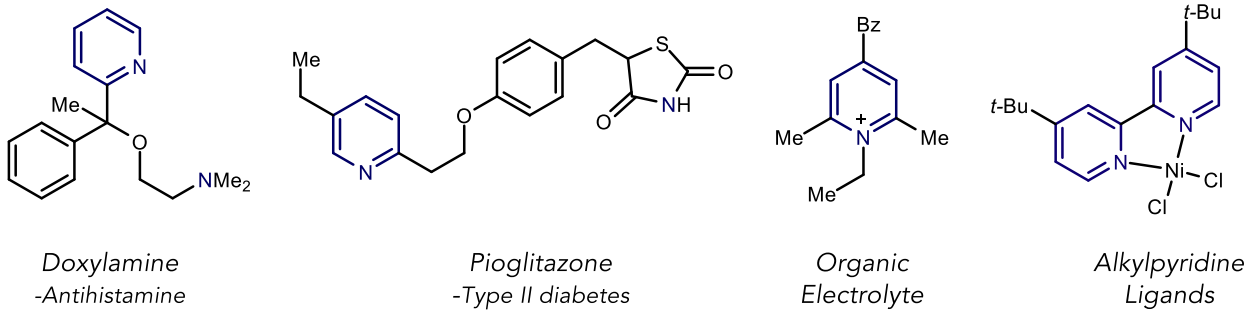


Figure 3.1. Alkylpyridines in pharmaceuticals, materials, and ligands.

Two of the most common strategies for installing alkyl groups directly onto pyridine from the C-H bond are the Minisci-type and metal-catalyzed coupling reactions (see section **1.2**). [8–30] These reactions have been heavily developed and have become the state-of-the-art method for

furnishing alkylated pyridines. However, they often give regioisomer products that are difficult to separate or are limited in the type of pyridines that are amenable to these processes. For instance, Hong's 4-selective Minisci reaction does an excellent job controlling regioselectivity using *N*-tosyl 1-aminopyridinium salts (**Figure 3.2** and see **section 1.2.3**)[12] However, making the *N*-aminopyridinium salt requires three steps, and their application to complex pyridines is limited. On the other hand, methods like DiRocco's photoredox catalyzed methylation do not require a preinstallation of an activating group or functional handle, but the reaction is unselective, giving a mixture of products.[22]

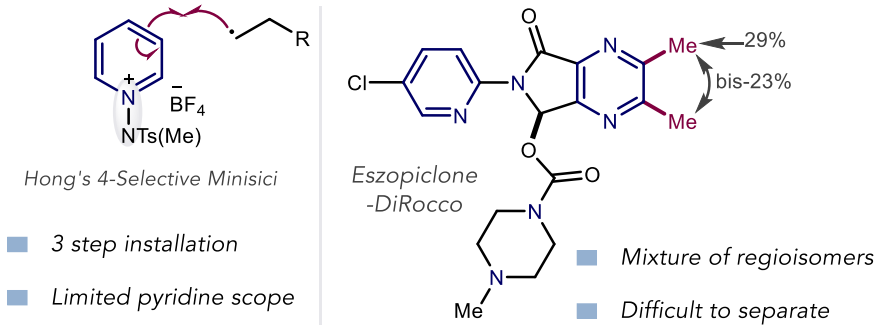


Figure 3.2. Limitations of current methods for azine alkylation.

Alternative strategies have been investigated to try and overcome some of these issues. One method for accomplishing this is using an alkene coupling partner with a metal hydride to generate an alkyl metal complex **I** (**Figure 3.3**).[31-36] This complex undergoes a 1,4 addition to pyridine to yield dearomatized intermediate **II**. Depending on reaction conditions, different strategies are used for aromatization and furnishing the alkylated pyridine. Depending on reaction conditions, different strategies are used for aromatization and furnishing the alkylated pyridine. Reports in the literature show that cobalt,[31,32] chromium,[33] and boron[34] are amenable to this process. Additionally, Buchwald and Gribble demonstrated an impressive asymmetric example using copper hydrides.[35,36] Although these reactions exhibit great regiocontrol, they are still

relatively limited to 3-substituted pyridines and only show styrene-derived coupling partners. Therefore, new methods for achieving these transformations would be highly desirable.

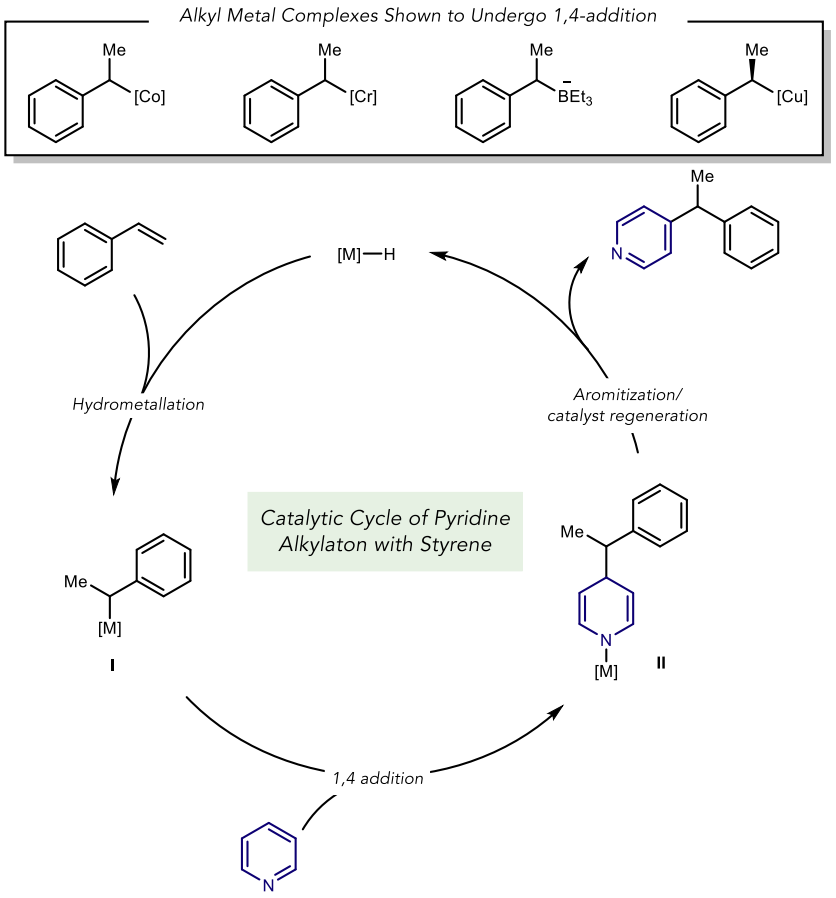


Figure 3.3. General catalytic cycle of pyridine alkylation with styrene and metal hydrides.

3.2 Dearomatized Pyridyl Phosphonium Ylides as Intermediates for Pyridine Alkylation

We report an alternative method using dearomatized pyridyl phosphonium ylides for pyridine alkylation via an olefination-rearomatization sequence. The Wittig olefination is one of the most widely used reactions for carbon-carbon bond construction.[37–40] The reaction typically uses sp^3 hybridized phosphonium salts as a coupling partner with a wide variety of aldehydes and

ketones; however, an extension of the Wittig strategy to aromatic rings is relatively unexplored. This is because installing the phosphonium precursor is no longer trivial since the addition to an arene comes with an energetic penalty of breaking the 6π-electron system of an aromatic ring (**Figure 3.4**). Alternatively, as mentioned in section **1.2**, pyridinium salts can generate stable dearomatized intermediates and are known to make dearomatized pyridyl phosphonium ions.[10,41,42] Therefore, following phosphonium formation, the intermediate can be deprotonated to form an ylide, and a subsequently undergo an olefination-rearomatization sequence to furnish the alkylated pyridine ring. We are able to accomplish this transformation for a 4-selective C-H alkylation, thus providing a valuable alternative to Minisci-type reactions and metal-catalyzed processes.

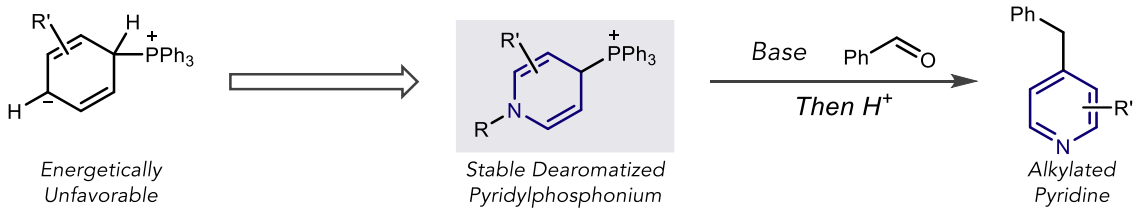


Figure 3.4. Design plan of Wittig olefination for pyridine alkylation.

The key to accomplishing the alkylation is identifying an effective *N*-activating group, which must fulfill three specific criteria. First, it must sufficiently activate the pyridine to allow efficient and selective phosphine addition to generate intermediate **III**. Next, the activating group must allow for ylide formation (**IV**), specifically, avoid an elimination-rearomatization process to form the pyridylphosphonium salt.[43,44] Finally, the activator must be reasonably tolerant of 2-substituted pyridines. This final criterion is essential, as many common activators, such as acyl or alkyl halides fail to accomplish it.[10,41,42] These activating groups often require harsh conditions and give low yields when employing them onto 2-substituted pyridines. This severely inhibits the generality of the transformations, as 2,3-, 2,4-, and 2,5-substituted azines will also have limited activation.

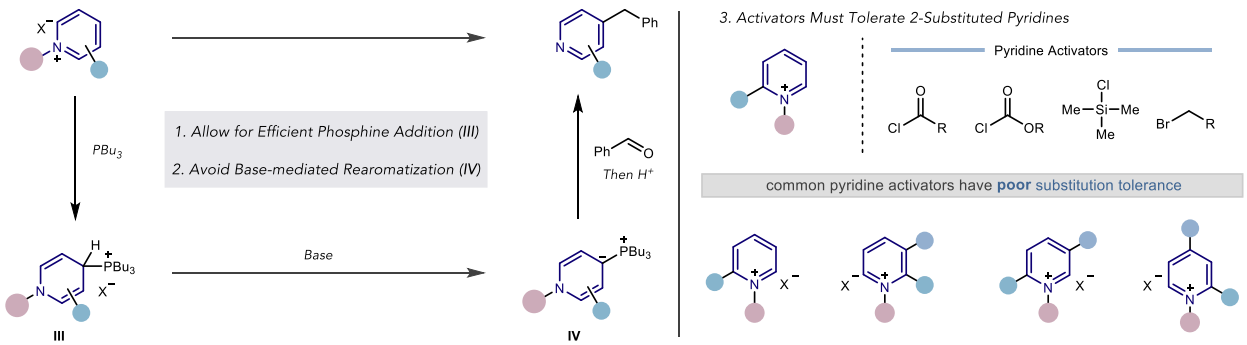


Figure 3.5. Key factors the activating group must accomplish for the Wittig protocol.

In a previous report, Lee and coworkers demonstrated that an olefination-rearomatization sequence could occur via dearomatized pyridylphosphonate esters (**Figure 3.6**).[45] They generated the dearomatized intermediate via nucleophilic addition of tri-isopropylphosphite to *N*-acyl pyridinium salt (**V**). Isolation via distillation was required to undergo the subsequent transformations. Next, LDA generates a phosphonate anion which then adds into an aldehyde giving **VI**. Again, isolation of the intermediate **VI** was necessary before subjecting it to *t*-butoxide to furnish the alkylated pyridine. The reaction worked well, but the pyridine substrate scope appeared limited, presumably due to the need for *N*-acyl activation that does not tolerate 2-position substituents well.[10,41,42] Additionally, the entire process requires three separate isolations to obtain the final alkylated product, thus rendering this method impractical for medicinal chemists. We discovered that chlorotriazines could accomplish all three criteria required and enable a one-pot and two-pot protocol, thus allowing for a practical alkylation of pyridines.

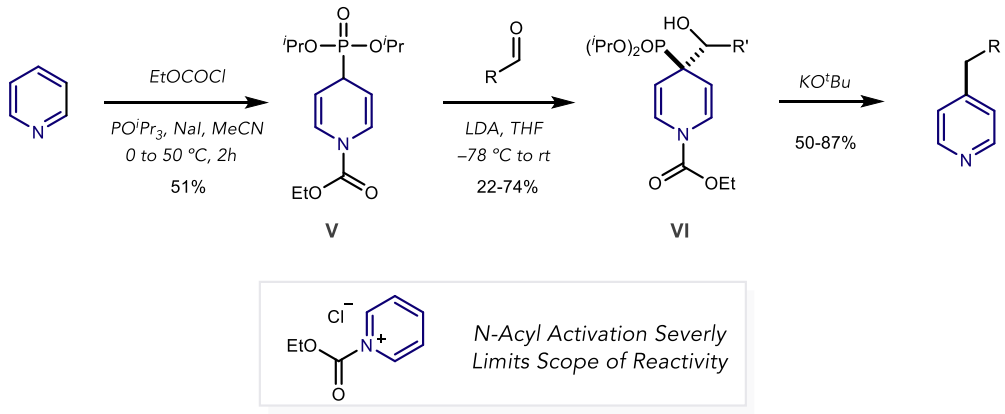
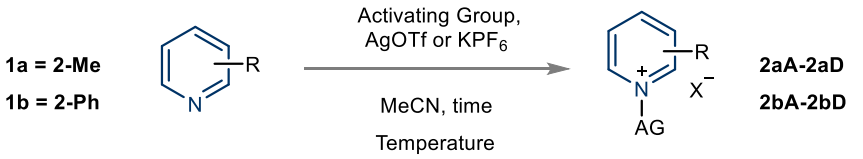


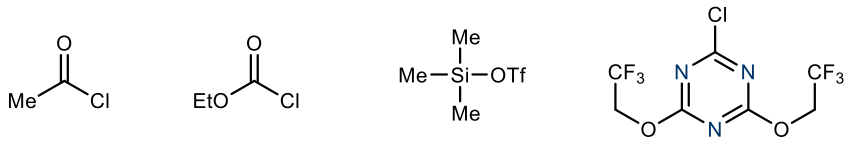
Figure 3.6. Lee's alkylation via Horner-Wadsworth-Emmons reaction.

We began our study with the activation of 2-methyl and 2-phenylpyridine using acetyl chloride (**A**), ethyl chloroformate (**B**), TMS-OTf (**C**), and chlorotriazine **D** in acetonitrile (**Table 3.1**). We chose methyl and phenyl groups to demonstrate how changes at the 2-position substituent affect activation. First, examining 2-methyl pyridine, acetyl chloride at room temperature gave little conversion to the pyridinium salt. Alternatively, **B** and **C** both made their respective salt in good yields (entries 2 and 3). The chlorotriazine gave moderate yield at room temperature over prolonged times; however, sufficient activation occurs when increasing the temperature to 50 °C and running for four hours (entries 4 and 5). Switching to 2-phenylpyridine, acetyl chloride gave no pyridinium formation at room temperature or 100 °C (entries 6 and 7). Ethyl chloroformate gave no product at room temperature, and when heated to 100 °C, the reaction yielded 22% (entries 8 and 9). Unfortunately, upon longer reaction times, decomposition was observed (entry 10). TMS-OTf sufficiently generates the pyridinium salts at room temperature (entry 11). **D** did not form any product at room temperature, but upon heating to 100 °C for one hour, the reaction achieved 24% (entries 12 and 13). Extending the reaction time to 6 hours resulted in moderate amounts of pyridinium product (entry 14).

Table 3.1. Optimization of pyridine activation on 2-substituted pyridines. [a,b,c,d]



Activating Groups



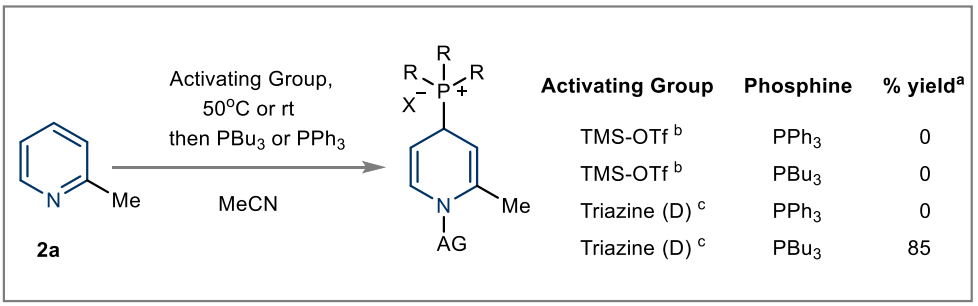
A **B** **C** **D**

Entry	R	Activating Group	Time	T (°C)	% Yield
1.	2-Me	A	1 h	rt	22
2.	2-Me	B	1 h	rt	83
3.	2-Me	C	1 h	rt	99
4.	2-Me	D	8 h	rt	64
5.	2-Me	D	4 h	50	88(88)
6.	2-Ph	A	1 h	rt	0
7.	2-Ph	A	1 h	100	0
8.	2-Ph	B	1 h	rt	0
9.	2-Ph	B	1 h	100	22
10.	2-Ph	B	6 h	100	0[c]
11.	2-Ph	C	1 h	rt	97
12.	2-Ph	D	1 h	rt	0
13.	2-Ph	D	1 h	100	24
14.	2-Ph	D	6 h	100	65[d] (52)

[a] Yields are calculated by ^{1}H NMR using p-xylene as internal standard. Number in parenthesis are isolated yields. [b] All reactions using 3-Me were run at 0.5 M and all reactions using 2-Ph were run at 2.0 M. [c] Decomposition observed. [d] Triphenylmethane used as internal standard.

Based on the results in **Table 3.1**, we chose TMS-OTf (**C**) and chlorotriazine **D** to test the phosphine addition into the 2-methylpyridinium salt (**Figure 3.7**). First, we formed the pyridinium salts according to their optimized conditions from **Table 3.1**, then added 1.1 equivalents of phosphine to the reaction at room temperature. The reaction gave no product using *N*-silyl pyridinium salt with either PPh_3 or PBu_3. Using the chlorotriazine with PPh_3 also did not yield

product but switching to PBu_3 resulted in an 85% yield of the dearomatized *N*-triazinyl pyridylphosphonium salt.

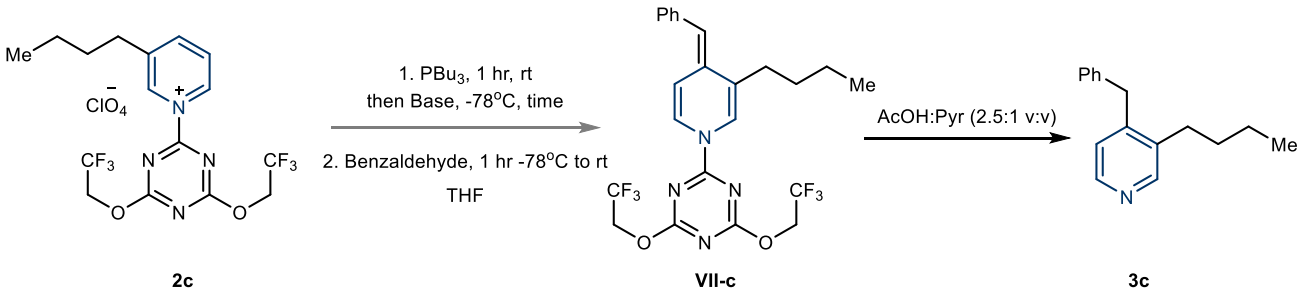


Activating Group	Phosphine	% yield[a]
TMS-OTf [b]	PPh_3	0
TMS-OTf [b]	PBu_3	0
Triazine (D) [c]	PPh_3	0
Triazine (D) [c]	PBu_3	85

Figure 3.7. Optimization of pyridinium salts dearomatization using different phosphines. [a] Yields are calculated using 1H NMR with *p*-Xylenes as internal standard. [b] Activation run at room temperature. [c] Activation run at 50 °C.

With conditions for generating the dearomatized pyridylphosphonium ions in hand, we next looked to optimize the olefination processes between 3-butylpyridinium salt 2c and benzaldehyde. We found that the most critical factor was the choice in base (**Table 3.2**). Sodium hydride gave no product; however, switching to potassium hexamethyldisilazide (KHMDS) for 1 hour gave 42% of pyridine anhydrobase **VII-c** (entries 1 and 2). Shortening the time the base stirred with the dearomatized intermediate to 30 minutes increased the yield to 66% (entry 3). Changing the cation of the disilazide did not help the reaction (entries 4 and 5). Switching to LDA lowered the product amount to 37% (entry 6). A significant increase in yield occurred when switching to alkyl and aryl lithium bases. Both phenyl lithium and butyl lithium gave good yields after stirring for one hour (entries 7 and 8). Methyl lithium gave the optimal result, providing the anhydrobase in 81% yield (entry 9). We found that stirring the base for only 15 minutes bore the same results, and thus giving us our optimized olefination reaction (entry 10). The addition of a 2.5:1 v:v mixture of AcOH: pyridine following the olefination rearomatizes the pyridine and removes the triazine, thus furnishing the alkylated product.

Table 3.2. Base optimization of olefination process.[a]



2c **VII-c** **3c**

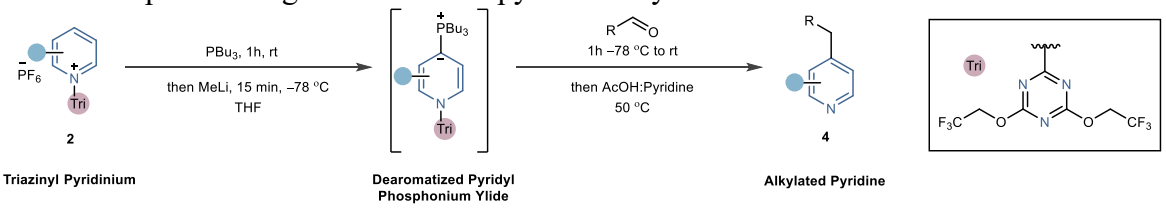
Entry	Base	%VII-c (3c)
1.	NaH (1 hr)	0
2.	KHMDS (1 hr)	42
3.	KHMDS (30 min)	66
4.	NaHMDS (30 min)	42
5.	LiHMDS (30 min)	66
6.	LDA (1hr)	37
7.	PhLi (1 hr)	75
8.	BuLi (1 hr)	77
9.	MeLi (1 hr)	81
10.	MeLi (15 min)	81(70)

[a] Yields calculated using ^{1}H NMR with triphenylmethane internal standard. Yield in parenthesis is isolated product.

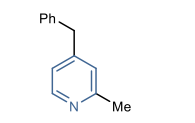
With the optimized conditions in hand, we first looked to discover the generality of the Wittig protocol using benzaldehyde as our alkyl coupling partner with the isolated pyridinium salts. We first examined a series of 3-substituted pyridines, including 3-methyl, 3-phenyl, 3-methoxy, and 3-chloropyridine, each giving good yields (**3d-3g**) (**Figure 3.7**). Polyazines **2h**, **2i**, and **2q** are site-selectively benzylated. These examples highlight an advantage of this strategy over Minisci-type reactions, as the radical approach often result in a mixture of products. Substituents at the 2-position of the pyridine ring are well tolerated and can also incorporate different functionalities such as methyl, phenyl, amino, and isoxazolyl groups (**3a, 3b, 3j, 3k**). The two-step process also alkylated 3,5-, 2,5-, and 2,3-disubstituted pyridines in very good yields (**3l-3o**). Furo[2,3-*b*]pyridine is benzylated smoothly in the 69% yield (**3p**), as is 3-sulfonate pyridine **1r**.

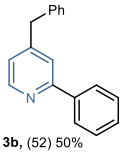
We next applied the Wittig approach to a range of different aldehydes using pyridinium salt **2d**. Benzaldehyde derivatives containing methoxy, trifluoromethyl, chloro, fluoro, and trifluoromethoxy substituents provide products **3s**-**3w** in good to excellent yields. Heteroaromatic carboxaldehydes, such as pyridyl, isoxazolyl, thiophenyl, and quinolinyl work well; the latter case reacted with the 3-butylpyridinium (**3x-3z, 3ae**). Alkyl aldehydes are amenable for this protocol, including examples with azetidine, cyclopropyl, and *N*-boc pyrrolidine functionalities (**3aa**- **3ac**). 3-methoxypyridinium was coupled with cyclopropyl carboxaldehyde and butyraldehyde in 51% and 46%, respectively (**3af, 3ag**).

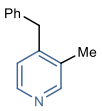
Table 3.3. Scope of Wittig olefination for pyridine alkylation [a,b]

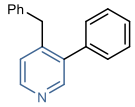


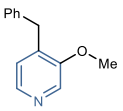
Pyridine Scope

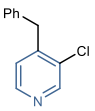

3a, (88) 88%

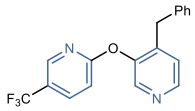

3b, (52) 50%

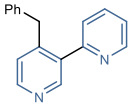

3d, (92) 95%

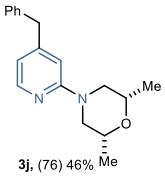

3e, (75) 81%

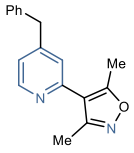

3f, (89) 87%

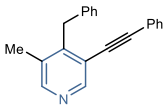

3g, (90) 70%

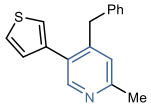

3h, (93) 55%

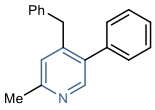

3i, (90) 82%

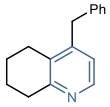

3j, (76) 46%

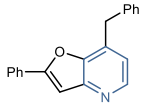

3k, (78) 33%

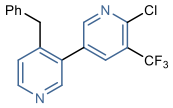

3l, (81) 79%

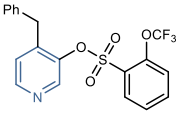

3m, (97) 76%[b]


3n, (86) 71%[c]

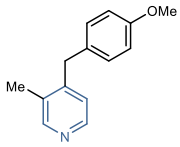

3o, (89) 59%

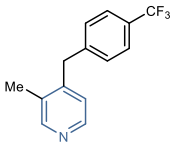

3p, (91) 69%

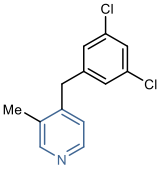

3q, (55) 77%

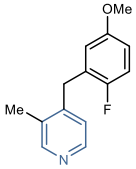

3r, (83) 72%

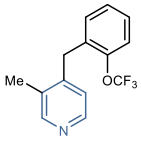
Aldehyde Scope

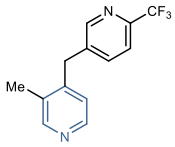

3s, 77%

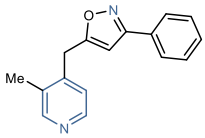

3t, 97%

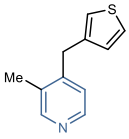

3u, 77%

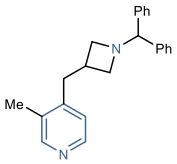

3v, 72%

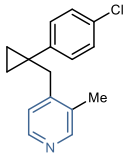

3w, 86%

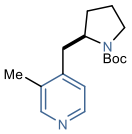

3x, 50%

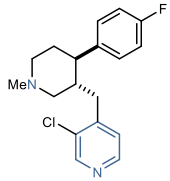

3y, 58%

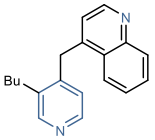

3z, 74%

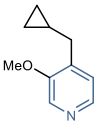

3aa, 40%

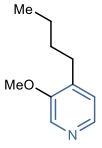

3ab, 60%

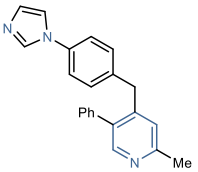

3ac, 36%

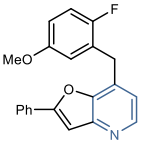

3ad, 37%

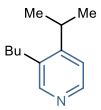

3ae, 76%


3af, 51%


3ag, 46%


3ah, 55%


3ai, 92%


3aj Not detected

[a]Yields of isolated products shown. Numbers in parenthesis are isolated yields of pyridinium salts. [b]Product isolated with 6% impurity. [c] ^{1}H NMR yield reported using triphenylmethane as internal standard.

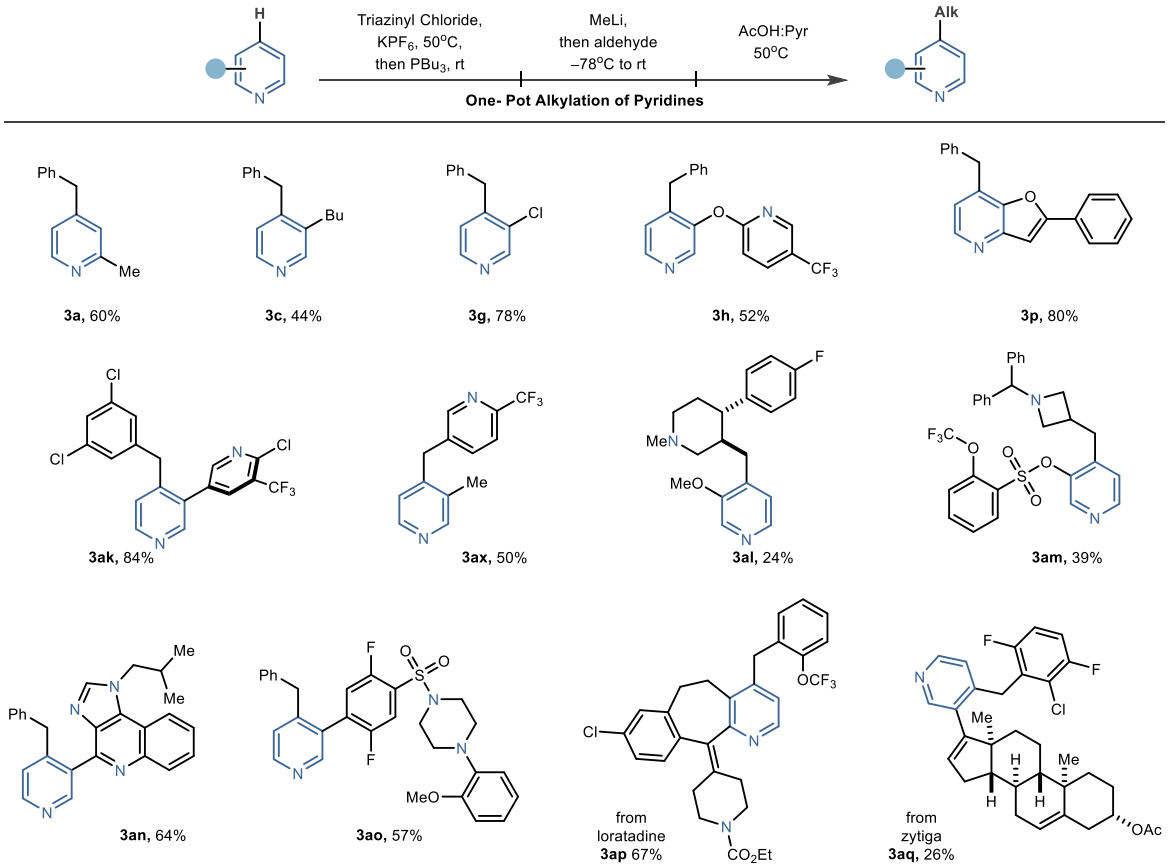
We used different pyridine building blocks with various complex aldehydes to demonstrate how this Wittig method could be used for rapid pyridine fragment synthesis. We installed a 4-imidazolylbenzyl group onto 2-methyl-5-phenylpyridine in good yield (3**ah**). Next, 2-Fluoro-5-methoxy benzaldehyde reacted well with the phosphonium ylide generated on furo[2,3-*b*]pyridine, giving 92% yield (**4ai**). Finally, 3-chloropyridinium was alkylated with an *N*-methyl paroxetine precursor to yield the piperidine-containing fragment in 30% yield (**3ad**). Analysis of the ^{1}H NMR of the Wittig protocol using acetone with 3-butylpyridinium showed a mixture of products, with no desired product detected.

3.3 Methylation and One-pot Alkylation of Pyridines

We next looked to streamline the alkylation protocol by avoiding the isolation of the pyridinium salts and complete the transformation in a one-pot process. We performed one-pot benzylations on 2-methylpyridine (**3a**), 3-butyl and 3-chloropyridine (**3c, 3g**), polyazine **3h**, and fused heteroaromatic **3p**. Chlorine-containing bipyridine **1ak** was alkylated with 3,5-dichlorobenzylaldehyde to give **3ak** in 84% yield. We coupled 2-trifluoromethyl-5-pyridylcarboxaldehyde with 3-methylpyridine in 50% yield (**3ax**). Two distinct oxy-substituted pyridines were coupled with different heterocyclic carboxaldehydes, giving piperidine fragment **4al** in 30% yield and the azetidine containing product 3**am** in 39%. Representative pyridine-comprising lead compounds, such as an Imiquimod precursor **1an** and sulfonamide containing fragment **1ao**, were benzylated in good yields, showing how this method can be used for late-stage functionalization. A benefit to the one-pot approach is the ability to alkylate different

pyridine precursors that may be unstable to isolate as the triazinyl pyridinium salt. For instance, we can now alkylate antihistamine Loratadine (**3ap**) and prostate cancer drug Abiraterone acetate (**3aq**) in 67% and 26% yield, respectively.

Table 3.4. Scope of One-pot alkylation process [a]

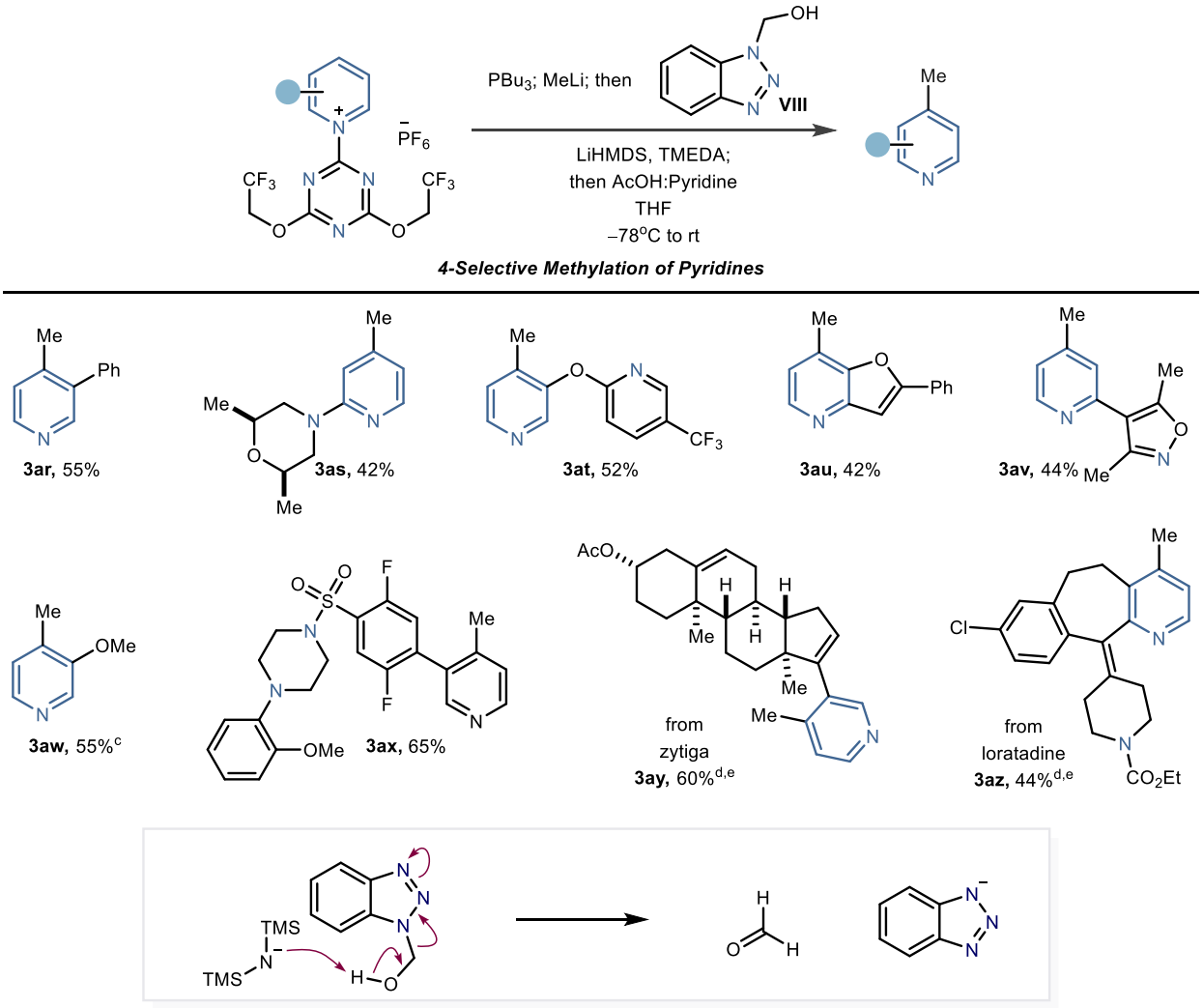


[a] Yields of isolated products shown.

Methylation of pyridine is an essential transformation as it can profoundly affect the substrate's biological properties.[6,46] Due to the methyl group's ability to alter a pharmaceutical's pharmaco-kinetic and pharmaco-dynamic properties, protocols to install them selectively are highly desirable.[47] We found that 4-selective methylation of pyridine can occur using our Wittig alkylation protocol. By pre-stirring 1-(hydroxymethyl)benzotriazole (**VIII**) with LiHMDS and TMEDA, we can generate formaldehyde in-situ and subsequently use it to methylated the 4-

position of the pyridine ring via the dearomatized ylide (**Table 5**). We show that the procedure can work on several different pyridine building blocks (**3ar-3aw**). Substrate **3ax** demonstrates the ability to apply the methylation late-stage on drug fragments, as do the pharmaceuticals Loratadine and Abiraterone acetate (**3ay, 3az**). The one-pot protocol was conducted on the last two cases directly from the pyridine precursors.

Table 3.5. Scope of the methylation protocol via Wittig olefination-rearomatization sequence [a,b]



[a] Yields of isolated products shown.[b] For pyridines with 2-substituents, formaldehyde was added at –78 ºC and stirred at –78 ºC for 2 hours. For pyridines without 2-substituents formaldehyde was added at –78 ºC and stirred at room temperature for 2 hours. [c] ^{1}H NMR yield reported due to

volatility. [d] ^{1}H NMR yield reported as compounds were inseparable from residual amounts of the C–H precursor. [e] One-pot procedure used.

Lastly, we explored different transformations from the pyridine anhydrobase. During our studies, we found these anhydrobases, although not stable enough to isolate, were able to be concentrated down and subjected to further derivatization.[48–52] Using anhydrobase **VII-e**, we first showed that deuterium incorporation could occur at the benzylic methylene carbon by changing the proton source to deuterium. A 20:1 selectivity for bis-deuteration to mono is observed (**4**). Employing the correct fluorinating reagents controls the ability to mono and bis-fluorinate.[53–55] Using *N*-fluoropyridinium with a pyridine base, we can isolate the mono fluorinated product in a 68% yield (**5**). Switching to NFSI and NaOAc, the reaction furnishes selective bis-fluorination in a 45% yield (**6**). Lastly, we show that adding iminium salts, such as Eschenmoser's salt, directly to the reaction mixture can give aza-phenethylamine derivative **7** in moderate yield.

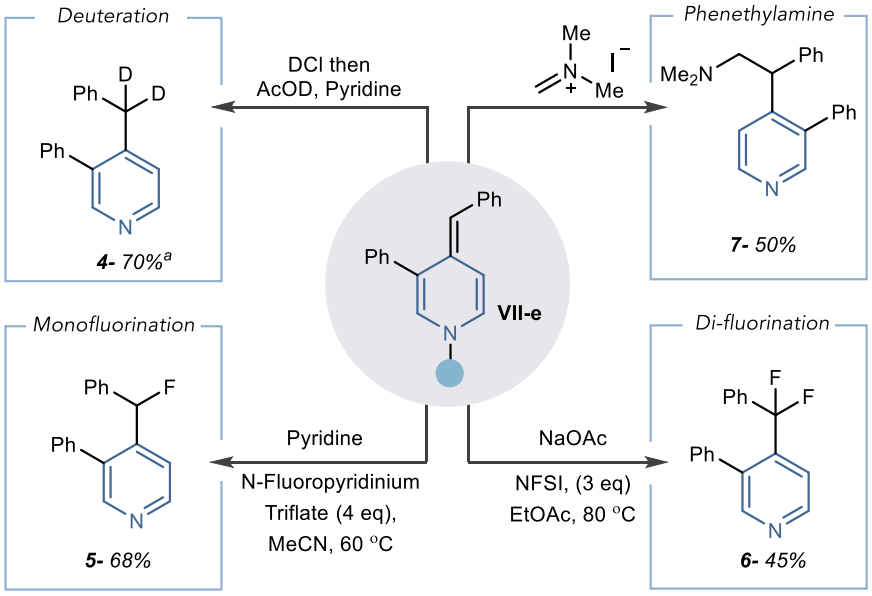


Figure 3.7. Derivatizations of the pyridine anhydrobase. Yields of isolated products shown. [a]20:1 Di- to monodeuteration.

3.4 Conclusion

A new strategy for selective pyridine alkylation via dearomatized pyridylphosphonium ylides is discussed. The procedure uses a triazine activating group that allows for 2-substituted pyridines in addition to 3-substituted. Building blocks, fragments, and pharmaceuticals are amenable to the transformations. A variety of building blocks are first transformed into the pyridinium salt and isolated, subsequently undergoing the olefination-rearomatization sequence. A one-pot approach can expand the scope to other pyridines that are too unstable to isolate as a pyridinium, including pharmaceuticals such as Loratadine and Abiraterone acetate. Next, a methylation protocol is disclosed on both building blocks and drugs using a formaldehyde surrogate. Finally, we include transformations from the pyridine anhydrobase, allowing for fluorination, deuteration, and methylamination.

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CHAPTER FOUR

STEPWISE SELECTIVE REDUCTIONS OF COMPLEX PYRIDINES TO DIHYDRO- AND TETRAHYDROPYRIDINES

4.1 Introduction to Pyridine Hydrogenation

Piperidines are key building blocks in pharmaceuticals and natural products[1–3] and often play a vital role in the drug-target interactions inside the body (**Figure 4.1A**).[4,5] Due to the degree of saturation, they offer increased complexity compared to their aromatic counterpart, pyridine.[5] This allows for the introduction of chirality, which, in turn, offers further exploration of chemical space, as well as beneficial pharmacokinetic and pharmacodynamic properties such as an increase of lipophilicity in biological systems.[5] Therefore, new methods to synthesize piperidines are highly desirable. As mentioned in section **1.3**, the hydrogenation of pyridine is the most appealing strategy for the synthesis of piperidines. Because of the difficulty of directly functionalizing a piperidine C-H bond, an alternative method is to derivatized pyridine first, then subsequently hydrogenate it to the saturated ring. Due to pyridine's π-systems, it is easier to access one position of the ring for functionalization. Following that derivatization, the arene can be hydrogenated to the fully saturated heterocycle, thus giving the functionalized piperidine (**Figure 4.1B**).

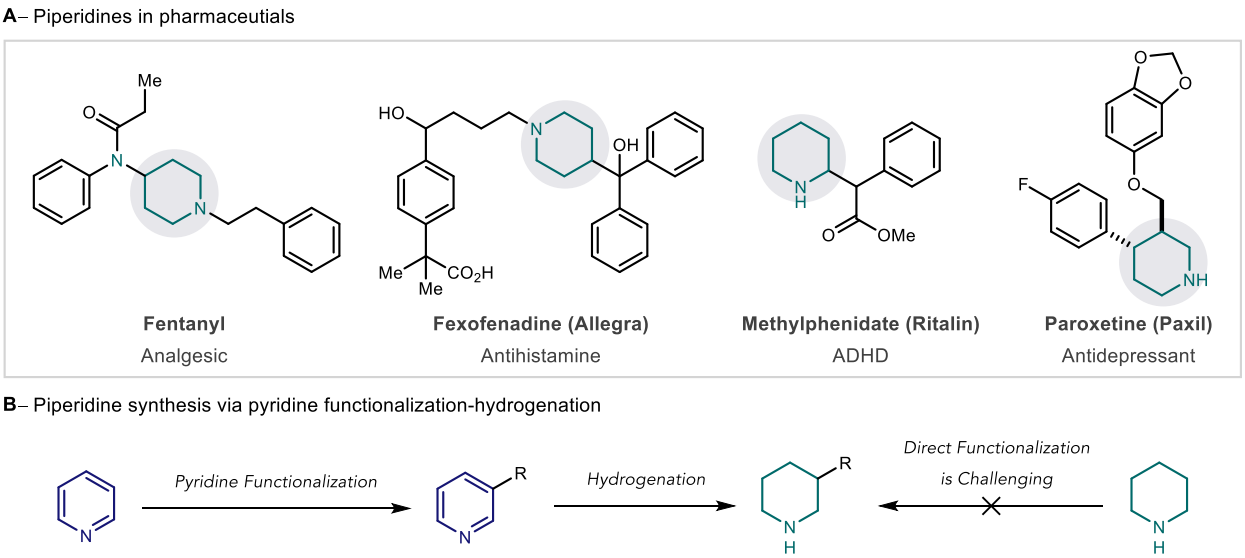


Figure 4.1. Piperidines in pharmaceuticals and a strategy for synthesizing them via pyridine hydrogenation.

There are three main strategies for the hydrogenation of heteroaromatics: catalyst activation, substrate activation, and relay catalysis (**Figure 4.2**).[6,7] The first method involves the addition of reagents to form a more active catalyst, such as halides in iridium catalysis (**Figure 4.2A**).[8–10] Second is substrate activation, which typically involves alkylation or protonation of the heteroatom ring first to overcome the high stability of the aromatic system and make it more susceptible to reduction (**Figure 4.2B**).[11–15] Relay catalysis is the third, and involves two or more catalytic systems for the full of the azine. For instance, to hydrogenate ethylnicotinic acetate asymmetrically, Zhang and coworkers used a palladium catalyst to reduce nicotinic acid to the tetrahydropyridine, then they employ a chiral rhodium complex for the final step to obtain the enantio enriched product (**Figure 4.2C**).[16] These distinct strategies have allowed for a significant expansion of heteroaromatic hydrogenation.

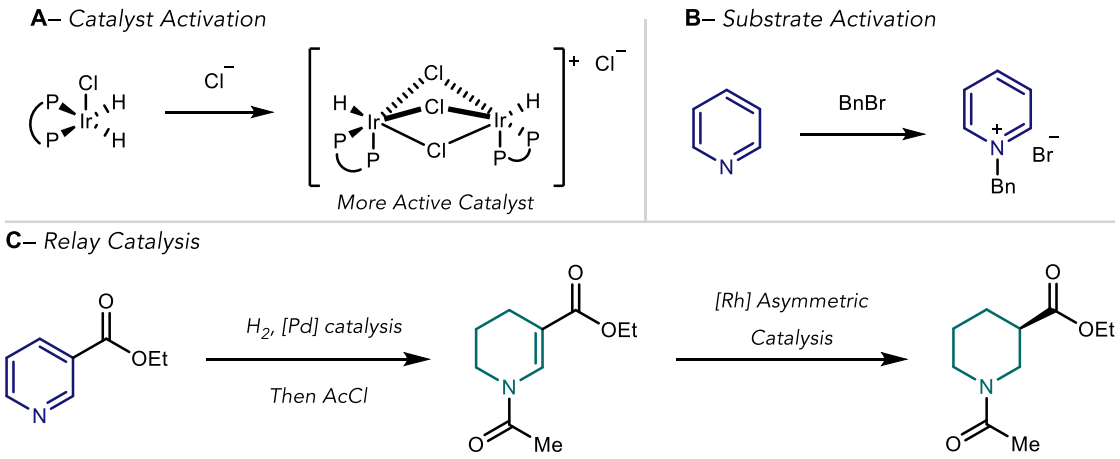


Figure 4.2. Three strategies for heteroaromatic hydrogenation.

Transition metal-catalyzed heteroarene hydrogenation is also divided into two classes, homogeneous and heterogeneous catalysis. Reports have shown heterogeneous catalysis using various metals, including platinum, palladium, rhodium, nickel, and ruthenium.[6,14,17–22] When it comes to pyridine hydrogenation, these methods often undergo substrate activation due to the heterocycle's ability to poison the catalyst.[6,7,17,23,24] Challenges with heterogeneous catalysis are potential side reactions with appending functionalities, such as halides, carbonyls, and imines. These catalytic systems often require harsh conditions, resulting in limited functional group tolerance. However, recently, examples demonstrate the ability to expand the functional group tolerance in piperidine synthesis via heterogeneous catalysis.

In a recent report, Glorius and coworkers have shown the ability to hydrogenate fluorinated pyridine using $Pd(OH)_2/C$ and HCl to give access to polyfluorinated piperidines (**Figure 4.3A**).[20] The acid serves two purposes in the reaction: first, it activates the pyridine for selective hydrogenation, and second, it prevents proto-defluorination from occurring, thus keeping the valuable functional group in the product. They have yet to understand the mechanism in which acid prevents dehalogenation. Using the substrate activation with HCl, the authors obtain selective hydrogenation of fluorinated pyridines over other fluorinated arenes. In an earlier report, Glorius

also demonstrated asymmetric hydrogenation of pyridine using heterogeneous catalysis by installing a chiral auxiliary onto the azine first (**Figure 4.3B**).[19] Although these methods are significant contributions to piperidine synthesis and have expanded the functional group tolerance in heterogeneous catalysis, it is still relatively limited to building block pyridines.

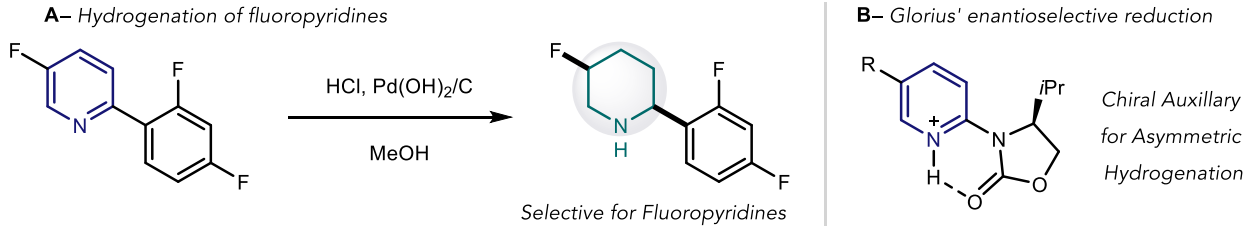


Figure 4.3. Glorius' heterogeneous catalysis for fluoropyridine hydrogenation and asymmetric hydrogenation.

To prevent undesired side reactivity during heterogeneous catalysis and expand the reaction generality, chemists have exploited homogeneous complexes for pyridine hydrogenation, with iridium, rhodium, and ruthenium the most common metal.[6,7,9,13,21,25–29] These catalysts are significantly milder than the heterogeneous counterparts and therefore permit a more comprehensive range of functionality in the substrates, including halides,[15,25,30] other heterocycles,[13] amines, and alcohols (**Figure 4.4A**).[6,7,21,31] Additionally, the use of these homogeneous systems allows for the introduction of chiral ligands to accomplish asymmetric hydrogenation of azines.

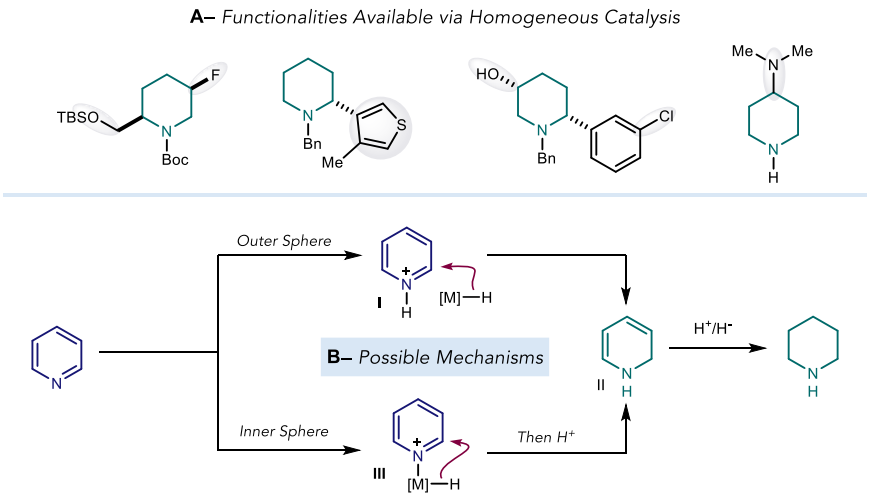


Figure 4.4. Current amenable functional groups and proposed mechanisms of homogeneous catalysis for hydrogenation of azines.

The mechanism of the hydrogenation using homogeneous catalysts typically undergoes one of two pathways (**Figure 4.4B**).[30,32,33] First is an outer-sphere pathway where a pyridinium salt is formed first via protonation, **I**. Next, the metal complex delivers a hydride either in a 1,2- or 1,4-addition to yield dearomatized intermediate **II**. From there, the dearomatized intermediate undergoes a protonation-reduction sequence to form the fully reduced heterocycle. Alternatively, an inner sphere mechanism can occur where the metal complex acts as a Lewis acid to the azine (**III**). It then delivers the hydride internally and subsequently protonates the nitrogen atom, resulting in intermediate **II**. Significant progress has been made using homogeneous catalysis, particularly in reducing (iso)quinolines and quinoxalines.[6,7,34] The ability to hydrogenate pyridine has also expanded, although it often requires activation of the azine with an alkyl group, which significantly limits the classes of pyridines available due to the difficulty of installing the activator (see **Chapter 3**).[11,13,15,26] This limitation precludes the ability to reduce pyridine to either the piperidine or tetrahydropyridine late stage in the drug discovery process or on complex azines.

4.2 Introduction to Dihydropyridine Synthesis

An alternative method to concerted hydrogenation of pyridine is a stepwise reduction to the dihydropyridine first, then successive hydrogenation to the piperidine (**Figure 4.5**).[12,25,35–40] The key to achieving generality in this reaction pathway is discovering an efficient system that yields dearomatized pyridine. The most challenging step in aromatic hydrogenation is the first reduction due to the energetic penalty that comes with disrupting aromaticity. Therefore, if a method can accomplish dearomatization first, the energy required for subsequent hydrogenation is significantly lowered. Common strategies for dihydropyridine formation are hydroboration and hydrosilylation (**Figure 5**). These protocols typically require a metal catalyst or Lewis acid to facilitate reactivity and often result in a mixture of 1,2- and 1,4-dihydropyridines.[35,37–40]

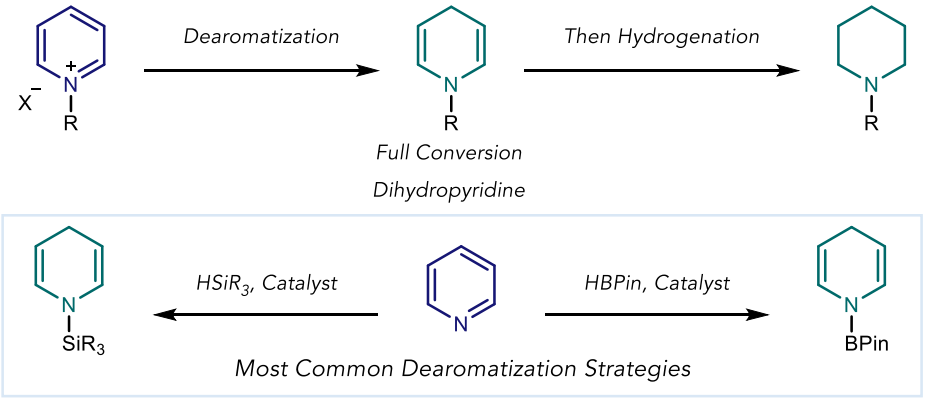


Figure 4.5. Alternative strategy for piperidine synthesis via pyridine dearomatization.

Suginome reported a hydroboration of pyridine using rhodium catalysis, which proceeds through the catalytic cycle shown in **Figure 4.6**.[41] First, the Rh^{I} will oxidatively add into a borane reagent. Pyridine will then coordinate to the metal complex (**IV**), and an internal hydride transfer gives intermediate **V**. Reductive elimination regenerates the catalyst and yields the *N*-boryl

dihydropyridine. Alternatively, Oestreich's hydrosilylation undergoes a different mechanistic pathway using ruthenium.[42] In this case, the Ru^{I} oxidatively adds to the silane, but the pyridine ring will react with the silyl cation to make **VI**. Next, the hydride is delivered externally from the ruthenium to regenerate the catalyst and yield the dearomatized product. These reactions have used several different metal catalysts to mediate the reduction, including rhodium, ruthenium, iridium, calcium, magnesium, and boron.[35,37,40,43–45] Although new methods for generating the dihydropyridine are emerging, their substrate scope is still significantly limited, particularly when it comes to substituents at the 2-position of pyridine.

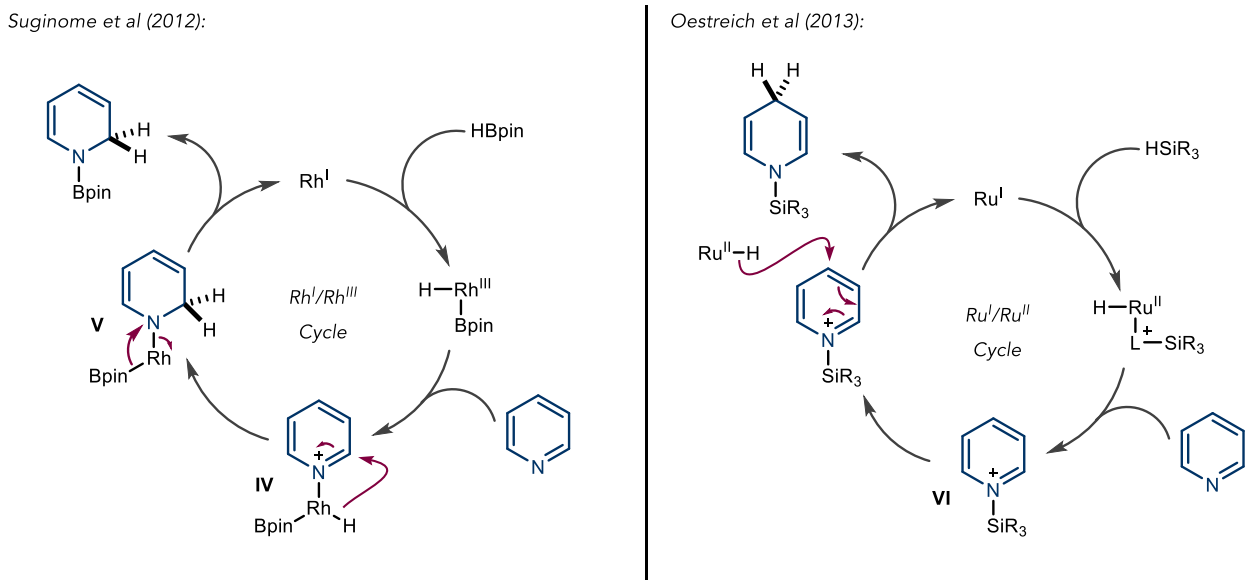


Figure 4.6. Catalytic cycle of hydroboration and hydrosilylation of pyridine.

4.3 Dihydropyridine Synthesis via *N*-Tf Pyridinium Salts

To overcome the substitutional tolerance issues with dihydropyridine formation, we envisioned a method where we first activate pyridine with trifluoromethanesulfonic anhydride (Tf_2O) at low temperatures (**VII**), then subjected to either a borohydride or silane to yield the 1,4-

dearomatized product, **VIII**, selectively (**Figure 4.7**). After concentrating the reaction, we can hydrogenate the crude material to give either the *N*-Tf piperidine or *N*-Tf tetrahydropyridine. We have shown that Tf_2O can activate a broad range of pyridines with various substitution patterns (**Section 1.2.3**),[46,47] thus allowing for a significant expansion of the reaction scope. The two main challenges to accomplishing this strategy are identifying compatible hydride sources to efficiently reduce the pyridinium salt and discovering the correct catalytic system for the subsequent hydrogenation.

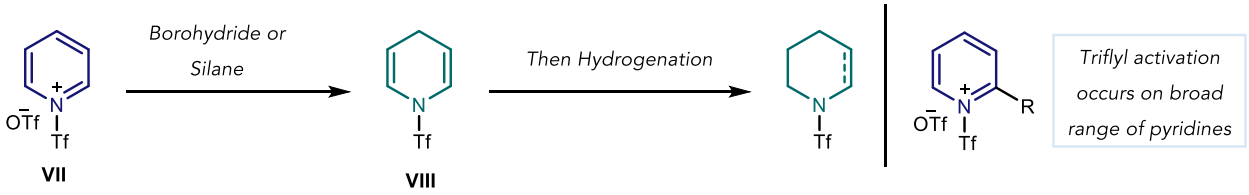
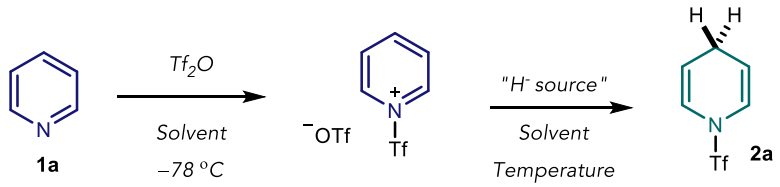


Figure 4.7. Design plan for dihydropyridine formation and overcoming substitution limitations.

We began our studies by first searching for the correct hydride source for the dihydropyridine synthesis. To do so, we generated the *N*-Tf pyridinium salt at −78°C in CH_2Cl_2 or EtOAc, then added the silane or borane and warmed to 60 °C (**Table 1**). Diphenylsilane and triethylsilane yielded the desired product after stirring overnight, albeit in low yields (entries 1 and 2). The borohydrides performed significantly worse, giving little to no product in each case (entries 3-5).

Table 4.1. Optimization of dihydropyridine formation using *N*-Tf activation. [a]



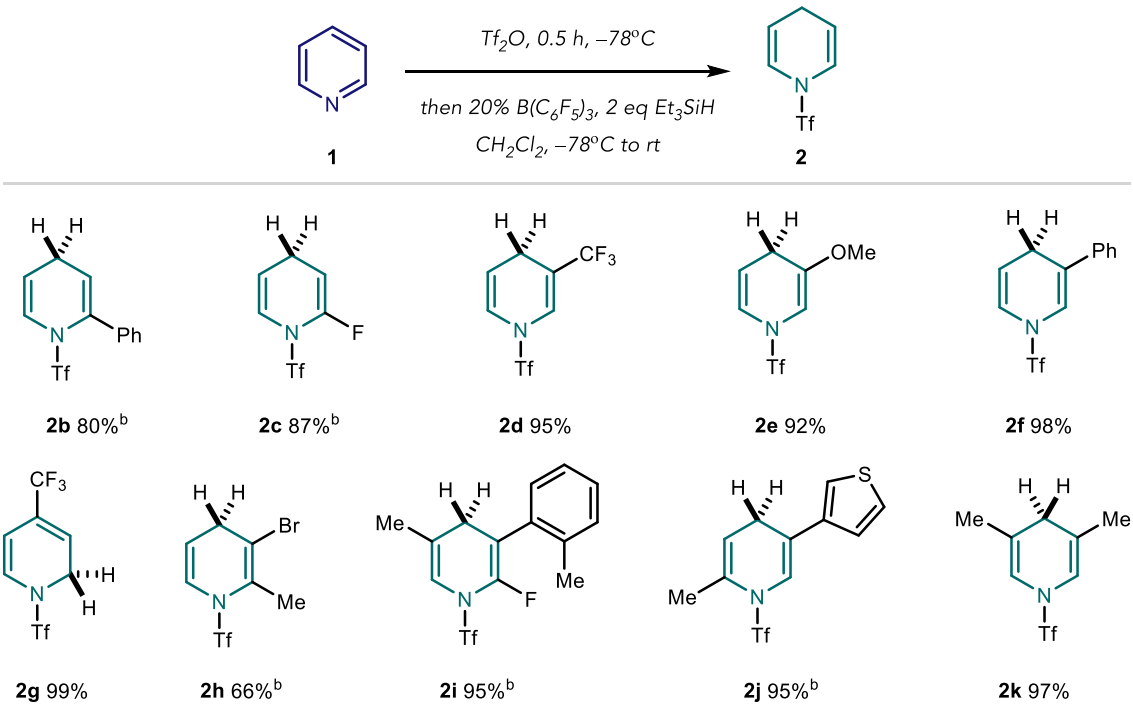
Trial	H⁻ source	T(°C)	solvent	equiv H⁻	% 2a [a]
1	Ph_2SiH_2	60 [b]	CH_2Cl_2	1.0	28
2	Et_3SiH	60 [b]	CH_2Cl_2	1.0	43
3	$NaBH_4$	60 [b]	EtOAc	1.0	0
4	$NaBH_3CN$	60 [b]	EtOAc	1.0	3
5	$NaBH(OAc)_3$	60 [b]	EtOAc	1.0	0
6	20% $B(C_6F_5)_3/Et_3SiH$	25	CH_2Cl_2	1.0	83
7	**20% $B(C_6F_5)_3/Et_3SiH$**	**25**	**CH_2Cl_2**	**2.0**	**95**
8	20% $B(C_6F_5)_3/Et_3SiH$	25	EtOAc	2.0	91
9	20% $B(C_6F_5)_3/Et_3SiH$	25	MeCN	2.0	23
10	20% $B(C_6F_5)_3/Et_3SiH$	25	THF	2.0	45
11	20% $B(C_6F_5)_3/Et_3SiH$	25	Toluene	2.0	0

[a] Yields reported after overnight stirring using ^{1}H NMR analysis with *p*-xylene as internal standard.
[b] No reaction occurred at room temperature or 40°C, so the reaction was heated to 60 °C.

We next examined using catalytic amounts of Piers' Borane[48,49] ($B(C_6F_5)_3$) combined with a silane as the hydride source. Chang and coworkers demonstrated the ability to fully reduce pyridine in toluene at 110 °C using this catalyst; however, they observed silane incorporation in their final product.[50] We hypothesized that using the *N*-Tf activation could allow for milder reaction conditions and avoid the silyl incorporation. Using 20 mol% of the borane with one equivalent of triethylsilane in CH_2Cl_2, we selective obtain the 1,4-dihydropyridine selectively in 83% (entry 6). Increasing the silane to two equivalences improves the yield to 95% (entry 7). Other solvents were also tested, including EtOAc, which gave similar results (entry 8). Acetonitrile and THF saw a drastic decrease in yield, and toluene gave no product (entries 9-11).

Moving forward with the optimized conditions in entry 7 of **Table 4.1**, we began to investigate the scope and limitations of the pyridinium reduction process (**Table 4.2**). We first examined several building-block examples, including 2-phenyl and 2-fluoropyridine, which give excellent yields (**2b, 2c**). We found that improved yields were obtained with a substituent at the 2-position if the reaction stirred at –78°C. Withdrawing groups and donating groups at the 3-position also work exceptionally well (**2d-2f**), and in each of these cases, we observe complete selectivity for the 1,4-dihydropyridine. If the 4-position is blocked, such as **2g**, the 1,2- product is formed, again in excellent yield. Increasing complexity, we began to test several poly-substituted azines. 2,3- 2,3,5- and 2-5 substituted pyridine all work well, resulting in 66%, 95%, and 95% yield, respectively (**2h-2j**). Even when there is steric hinderance around the 4-position of the azine, we still observed excellent selective for the 1,4-product, as is the case with **2i** and **2k**.

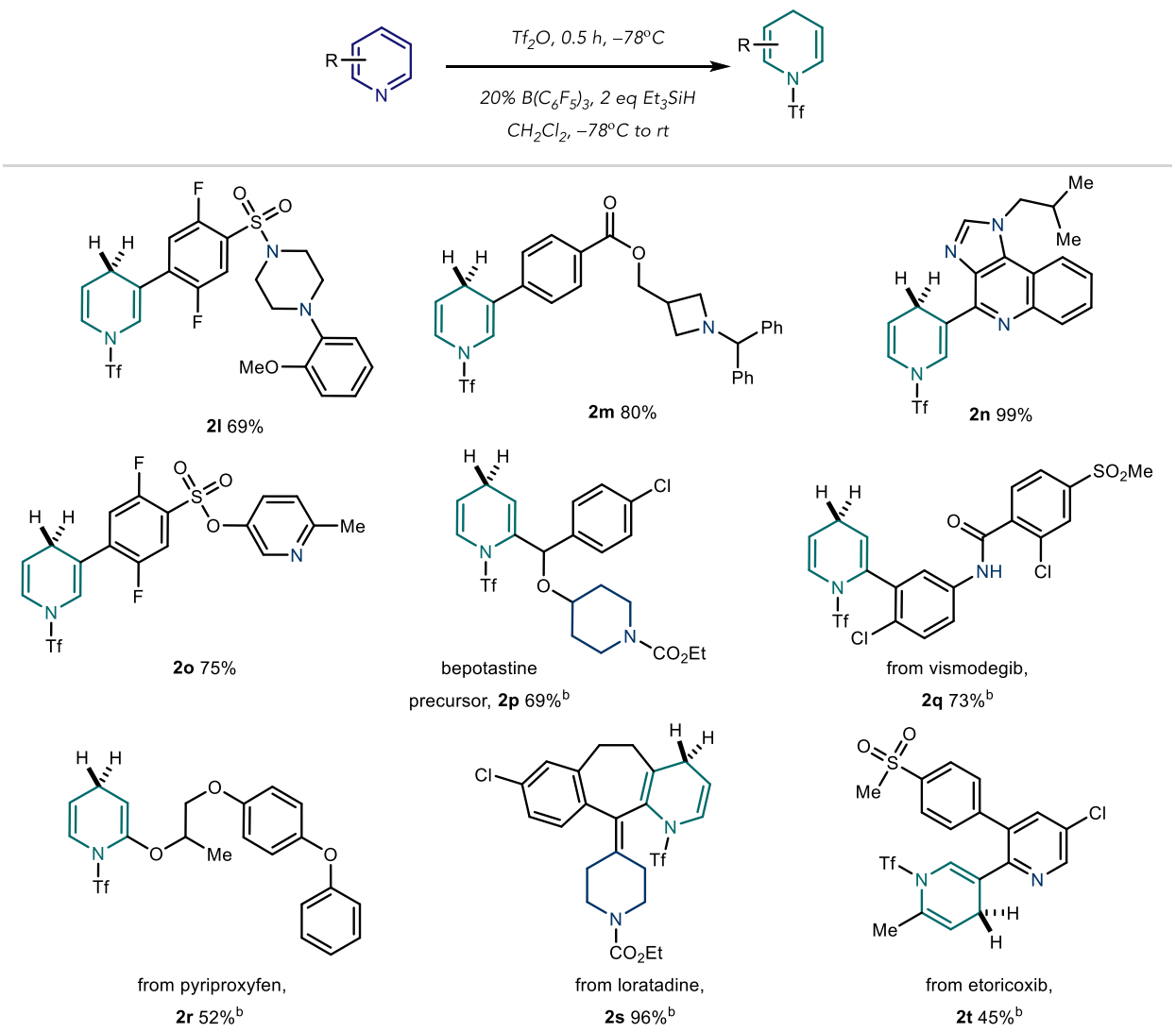
Table 4.2. Scope of building block azines for dihydropyridine formation [a]



[a] ^{1}H NMR yields reported using *p*-xylene as internal standard. [b] reduction step run at –78°C.

We next turned to drug fragments and pharmaceuticals to further test the limitations of the developed method and if it could be applied late-stage (**Table 4.3**). 3-aryl fragments incorporating sulfonamides, sulfonate esters, azetidine, and other heterocycles were tolerated, again with complete selectivity for the 1,4-dihydropyridine product (**2l- 2o**). A bepotastine precursor reacts to give the product in 69% yield (**2p**). We investigated Several drugs and agrochemicals next. The 2-aryl drug Vismodegib reduces to the 1,4-dihydropyridine product in 73% (**2q**), and agrochemical Pyriproxyfen also gives moderate yields (**2r**). This example is particularly interesting because it incorporates an oxygen linker coming directly off the 2-position of the heterocycle. Loratadine, an antihistamine, works nearly quantitatively, and Etoricoxib gives the product in 45% (**2s, 2t**). During our studies, Glorius and coworkers disclosed a similar strategy using *N*-Tf or *N*-Acyl activation with trimethylammonium borate complex as the hydride source, although in their case, they obtained a mixture of 1,2- and 1,4-products.[12] Additionally, they did not demonstrate significant yields on 2-substituted pyridines and did not show the reaction on any drugs or drug-like fragments. Because of these reasons, we decided to continue our investigation and move forward to the hydrogenation step.

Table 4.3. Scope of drug fragments and pharmaceuticals for dihydropyridine formation [a]



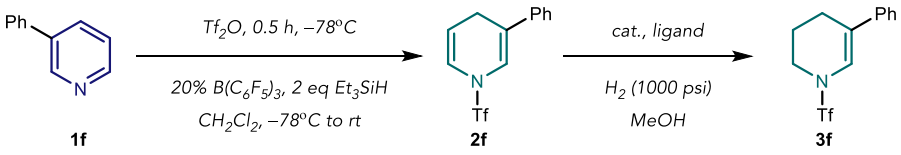
[a] ^{1}H NMR yields reported using *p*-xylene as internal standard. [b] reduction step run at –78°C.

4.4 Stepwise Reduction of Pyridines for Tetrahydropyridine Synthesis

We began our investigation of the hydrogenation step using 3-phenyl pyridine as our standard substrate. First, we would generate the dihydropyridine in CH_2Cl_2 and then concentrate the reaction and subject the crude material to the desired hydrogenation conditions. A ruthenium precatalyst was investigated first, along with several different bidentate phosphine ligands in methanol with 1,000 psi of H_2 (**Table 4.4**). Using the DPPF and BINAP ligand, we detected the

tetrahydropyridine by ^{1}H NMR in 24% and 32%, respectively. SegPhos gave no yield, and BiPHEP only gave 21% of the product. Attempting to improve the yield, we also investigated a rhodium precatalyst using the same four ligands. In each case, we did not observe any product by ^{1}H NMR. $[Ir(COD)Cl]_2$ was explored next, and using the DPPF ligand, we obtained the tetrahydropyridine product in 87% yield. Seeing the dramatic increase with iridium, we examined several other ligands, including BINAP, Segphos, BiPHEP, tetraphenylbiphosphine, and Di-PPF. Each of those examples gave significantly lower yields than DPPF, with BiPHEP resulting in the highest with 61%. Therefore, the optimized conditions are 1.1% $[Ir(COD)Cl]_2$, 2.2% DPPF, 1,000 psi H_2 in methanol.

Table 4.4. Optimization of the hydrogenation of *N*-Tf dihydropyridines. [a]

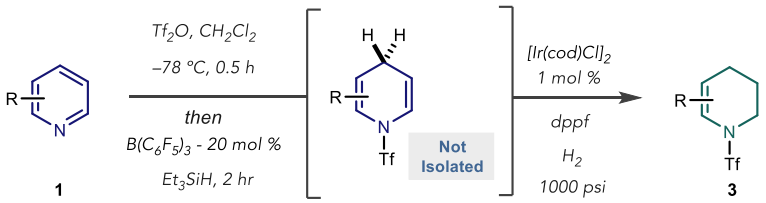


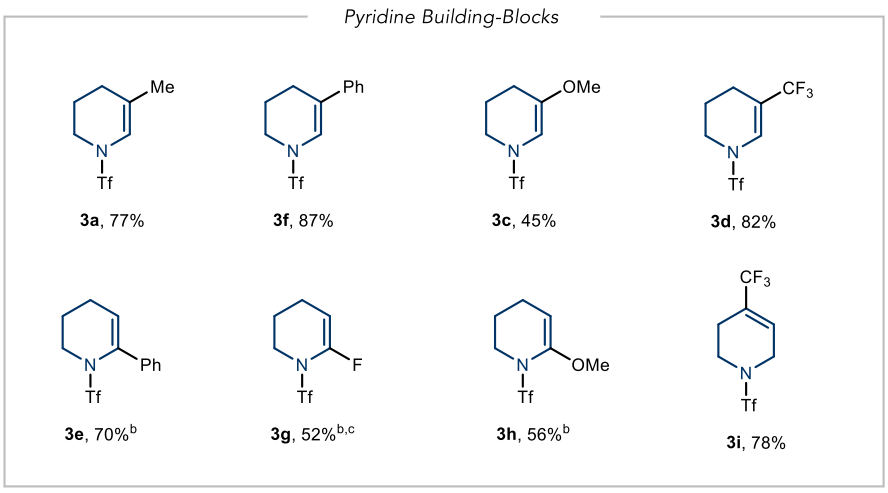
Trial	catalyst	ligand	3f[a]
1	$Ru(acac)_3$	DPPF	24
2	$Ru(acac)_3$	(R)-BINAP	32
3	$Ru(acac)_3$	(R)-SegPhos	0
4	$Ru(acac)_3$	BiPHEP	21
5	$Rh(nbd)_2BF_4$	DPPF	0
6	$Rh(nbd)_2BF_4$	(R)-BINAP	0
7	$Rh(nbd)_2BF_4$	(R)-SegPhos	0
8	$Rh(nbd)_2BF_4$	BiPHEP	0
9	**$[Ir(COD)Cl]_2$**	**DPPF**	**87**
10	$[Ir(COD)Cl]_2$	(R)-BINAP	20
11	$[Ir(COD)Cl]_2$	(R)-SegPhos	20
12	$[Ir(COD)Cl]_2$	BiPHEP	61
13	$[Ir(COD)Cl]_2$	$(Ph)_4P_2$	0
14	$[Ir(COD)Cl]_2$	Di-PPF	38

[a] ^{1}H NMR yields reported using *p*-xylenes as internal standard

Table 5 shows the results of the hydrogenation on several building block pyridines. We found that 3-substituted azines performed very well, hydrogenating 3-methyl and 3-phenyl dihydropyridine in 77% and 87%, respectively (**3a, 3f**). Withdrawing and donating groups at the 3-position give good or moderate yields (**3c, 3d**). 2-phenyl and 2-methoxypyridine work reasonably well, although 2-fluoropyridine dehalogenates under the reaction conditions (**3e, 3g, 3h**). When hydrogenating 4-substituted examples, the 1,2,5,6-tetrahydropyridine is observed (**3i**). The investigation of the hydrogenation is still in its early stages, and studies of poly-substituted building blocks are ongoing.

Table 4.5. Substrate scope of the hydrogenation of dihydropyridines [a]



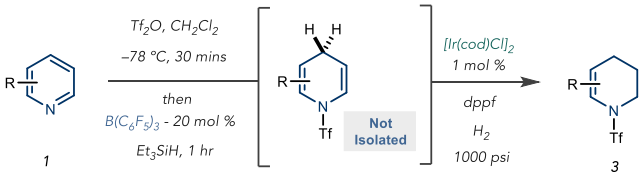


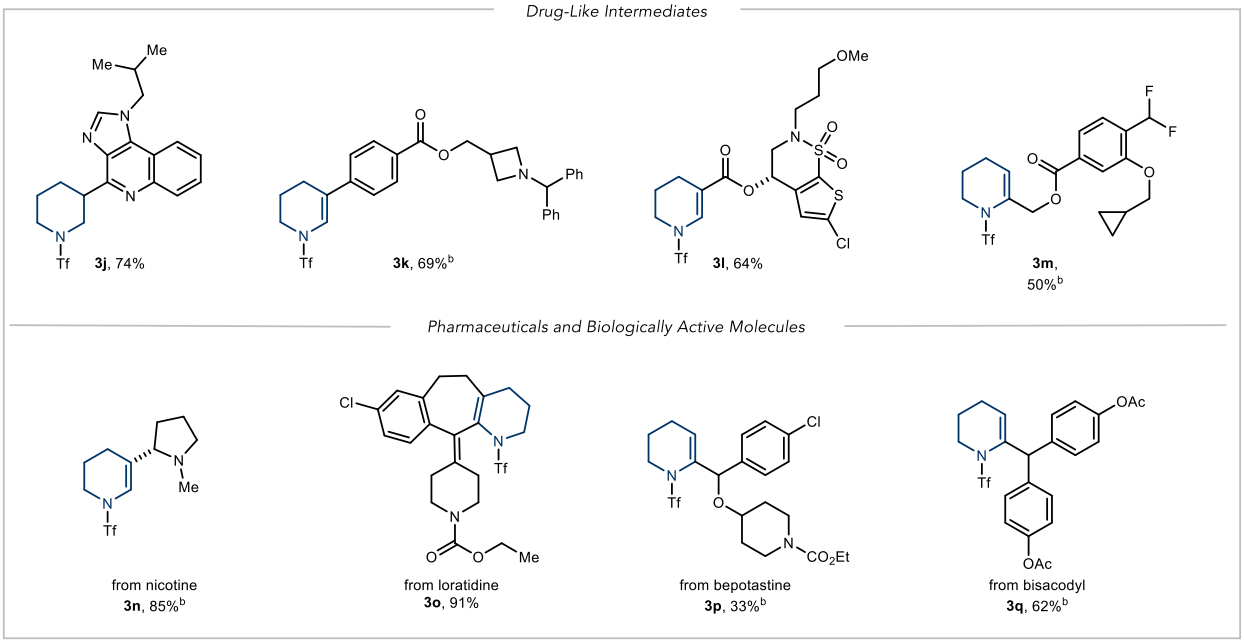
[a] ^{1}H NMR yields reported using *p*-xylene as internal standard. [b] hydride addition step stirred at –78 °C. [c] Proto-defluorination observed.

We also examined several drug fragments and pharmaceuticals in the hydrogenation (**Table 4.6**). Reduction of the 3-aryl fragment, **3j,** to the piperidine occurs in a 74% yield. This is the only example where the reaction selectively yields the piperidine over the tetrahydropyridine.

3-aryl fragments, including azetidine, sulfonamide, and ester functionalities work well in the protocol (**3k, 3l**). Difluoromethyl containing 2-substituted azine, **3m**, gave a 50% yield of the tetrahydropyridine. We investigated several biologically active molecules next. Nicotine worked in 85%, and Loratadine yielded 91% of the reduced azine (**3n, 3o**). A bepotastine precursor hydrogenated is toleratead, and bisacodyl gave 62% product (**3p, 3q**). Studies are currently ongoing in our lab to expand the scope of the reaction, and to see if we can completely reduce the heterocycles to the piperidine.

Table 4.6. Drug fragments and pharmaceutical scope of hydrogenation [a]





[a] Isolated yields shown. [b] ^{1}H NMR yield using *p*-xylene as internal standard.

4.5 Derivatizations from the Dihydropyridine Intermediate

In addition to the hydrogenation, we investigated other transformations from the dihydropyridine. 3-position functionalization occurs with dearomatized pyridines (**IX**) by reacting through the alkene with electrophiles to form intermediate **X**.[11,51] Therefore, we hypothesized a 3-selective halogenation could occur using electrophilic halogenation reagents to form intermediate **X**. This intermediate can potentially undergo two subsequent pathways; first, a base can deprotonate to give the 3-functionalized dihydropyridine, which will undergo oxidation back to the pyridine. Second, an internal nucleophile can add into the iminium, giving a difunctionalized tetrahydropyridine (**Figure 4.8**).

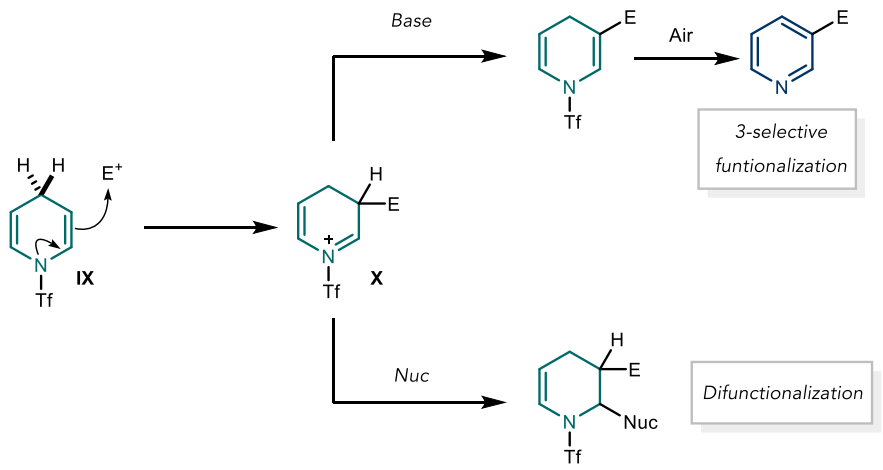
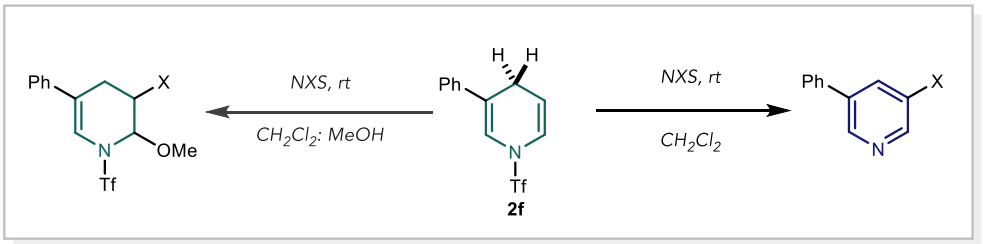


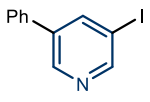
Figure 4.8. Possible functionalization pathways for dihydropyridine.

We examined different halo-succinimides first with **2f** in CH_2Cl_2. After stirring overnight then exposing it to air, the reaction gives the rearomatized halogenated products. Using NIS, 3-iodo-5-phenyl pyridine product is isolated in 22% yield (**4**). Switching to NBS gives a similar result, yielding the brominated product in 20% (**5**), and NCS also works in the protocol, producing **6** in 22%. When trying different fluorinating reagents, no halogenation occurred.

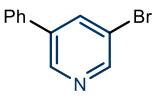
Instead, rearomatized pyridine was obtained, most likely through oxidation of the dihydropyridine with the F+ reagent. We examined a solvent mixture of CH_2Cl_2 and methanol to increase the iodination, bromination, and chlorination yield. Instead, an alternative reaction occurred where an equivalent of methanol added into the iminium intermediate, yielding the difunctionalized product. We obtained the iodinated and brominated heterocycles in good yields, resulting in 62% and 60%, respectively (**7, 8**). Chlorination also worked, albeit in a lower yield (**9**). Due to the importance of these products in pharmaceuticals and agrochemicals, studies are ongoing in the laboratory to discover the generality and limitation of the process.

Table 4.7. Derivatives from the dihydropyridine. [a]

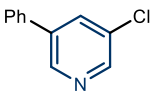




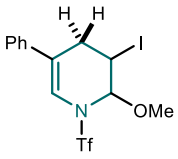
4, 22%



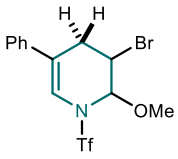
5, 20%



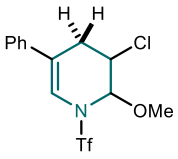
6, 22%



7, 62%



8, 60%



9, 45%

[a] Yields reported using ^{1}H NMR with *p*-xylene as internal standard.

The dihydropyridines also act as blocking groups for switchable phosphonium salt installation on bisazine biaryls. As mentioned in section **2.2**, these polyazine scaffolds are frequently found in the pharmaceutical industry. We have shown that we can selectively functionalize one of the pyridine rings with the phosphonium salt; however, we could not

accomplish the switching protocols. The reasoning was because the *N*-activation made the neighboring pyridine ring too deficient, making phosphine attack now preferential at the sulfur atom (**Figure 4.9**).[47] To evade this issue, the inherently reactive pyridine can first be transformed to the dihydropyridine, thus no longer making it a strong withdrawing group. Therefore, when performing the standard phosphonium protocol, the phosphine should now add into the arene over an attack at the sulfur. We tested this strategy on two bipyridines, **10** and **11**, which resulted in excellent site-selectivity and moderate yields in both cases.

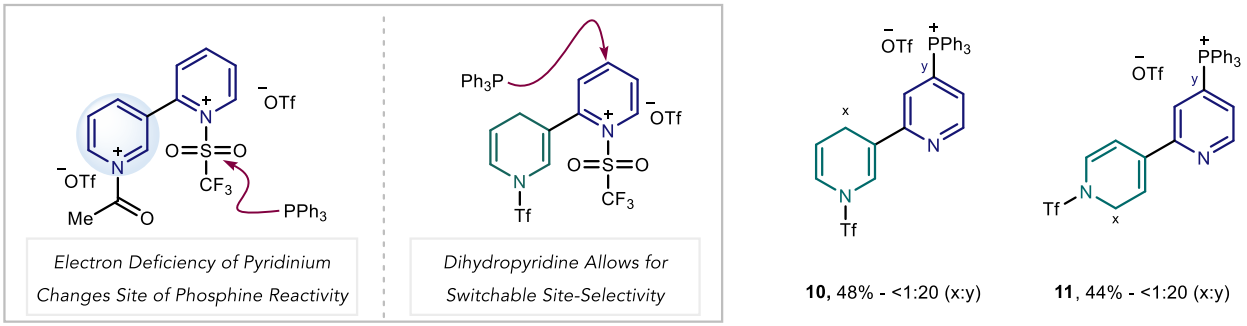


Figure 4.9. Dihydropyridines as blocking groups for switchable site-selective phosphonium installation.

4.5 Conclusion

We have demonstrated a new method for selective 1,4-dihydropyridine formation using Tf_2O activation and Piers' borane catalyst with triethyl silane. The protocol is applicable to building blocks, drug fragments, and pharmaceuticals and can subsequently undergo hydrogenation to the tetrahydropyridine. We found that Iridium catalysis using a DPPF ligand to be the optimal catalytic system for hydrogenation. In addition to further reduction, 3-selective functionalization occurs on the dihydropyridine intermediates using electrophilic halogenation reagents. They also act as blocking groups for a switching protocol for site-selective installation of phosphonium salts on bisazine biaryls.

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APPENDIX ONE

SITE-SELECTIVE SWITCHING PROTOCOLS FOR POLYAZINE FUNCTIONALIZATION

A 2.1 General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR (400 MHz) spectrometer or an Agilent Inova 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), $(CD_3)_2SO$ (2.50 ppm), CD_3OD (3.31 ppm) or CD_3CN (1.94 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR spectrometer (100 MHz) or an Agilent Inova 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual

solvent peaks in $CDCl_3$ (77.0 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. Infared (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}).

Specific optical rotation measurements were obtained from $CHCl_3$ solutions having concentrations of 10 mg/mL (example 2o) using a Rudolph Research Analytical Autopol III automatic polarimeter operating at 589 nm.

Analytical thin layer chromatography (TLC) was performed using pre–coated Merck glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Fluka or Material Harvest silica gel (230–400 mesh) under a positive pressure of air. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or basic potassium permanganate solutions as appropriate.

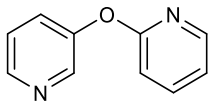
Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] Ethyl acetate (EtOAc), 1,2–Dichloroethane (DCE), 1,4–dioxane, chloroform, chlorobenzene and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents 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 but was routinely stored in a –20 ºC fridge. NEt_3 and DBU were distilled before use. Acetyl chloride (98%) was purchased from Sigma Aldrich chemical company and was used without further purification but was routinely stored in a –20 ºC fridge. Silver trifluoromethanesulfonate (>99%) was purchased from Sigma Aldrich chemical company and was stored inside a glovebox. NaH (60% in mineral oil) was purchased from Sigma Aldrich and was typically distributed into vials and stored in a desiccator. 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.

A. 2.2 Preparation of Heterocyclic Phosphonium Salt Precursors

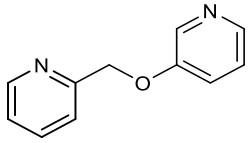
2–(pyridin–3–yloxy)pyridine (4)



An oven dried 25 mL round bottom flask was charged with 3–hydroxypyridine (476 mg, 5.00 mmol), cobalt(II) acetylacetoneate (129 mg, 0.50 mmol), copper(I) iodide (95 mg, 0.50 mmol) and cesium carbonate (3.25 g, 10.00 mmol), and NMP (15 mL). To the reaction flask, 2–bromopyridine

(477 μL, 5.00 mmol) was added and the mixture was stirred at 110 °C overnight. The reaction was cooled to room temperature, diluted with EtOAc (25 mL) and quenched with water (50 mL). The organic layer was separated, and aqueous layer was extracted with EtOAc (3 x 25 mL). The organic extracts were collected, 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 yellow oil (482 mg, 2.80 mmol, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, d, *J* = 2.7 Hz), 8.45 (1H, d, *J* = 4.6 Hz), 8.16 (1H, dd, *J* = 4.1, 0.9 Hz), 7.73 (1H, td, *J* = 8.2, 1.0 Hz), 7.53–7.50 (1H, m), 7.35 (1H, dd, *J* = 8.3, 4.7 Hz), 7.05–7.02 (1H, m), 6.98 (1H, d, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.6, 150.4, 147.2, 145.4, 143.4, 139.5, 128.4, 123.7, 118.9, 111.5. The spectroscopic data is in agreement with a reported synthesis.[2]

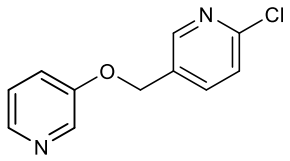
2–((pyridin–3–yloxy)methyl)pyridine (5)



An oven dried 250 mL round bottom flask was charged with sodium hydride (60% dispersion in mineral oil, 3.3 equiv). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of DMF (4 mL). The mixture was cooled to 0 °C and a mixture of 3–hydroxypyridine (523 mg, 5.50 mmol) in DMF (8 mL) was added dropwise over 5 minutes. The reaction mixture was warmed to room temperature and stirred for 30 minutes before being cooled to 0 °C. A solution of 2–(chloromethyl)pyridine hydrogen chloride (820 mg, 5.00 mmol) in DMF (13 mL) was then added dropwise to the reaction mixture over 10 minutes. The reaction mixture was warmed to room temperature and allowed to stir for 12 hours before being quenched with water (25 mL) and diluted with CH_2Cl_2 (25 mL). 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 solution of brine (5 x), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 3.5% MeOH in CH_2Cl_2) to provide title compound as a yellow solid (373 mg, 2.00 mmol, 40% yield). 29–30 ºC IR ν_{max}/cm^{-1} (film): 3056, 3013, 2921, 1591, 1573, 1475, 1434, 1429, 1272, 1225, 1188, 1050, 797, 757, 705; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.60 (1H, d, *J* = 4.8 Hz), 8.41 (1H, d, *J* = 2.8 Hz), 8.23 (1H, dd, *J* = 4.6, 1.5 Hz), 7.72 (1H, dt, *J* = 7.7, 1.7 Hz), 7.50 (1H, d, *J* = 7.8 Hz), 7.29–7.19 (3H, m), 5.24 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.3, 154.5, 149.4, 142.5, 138.5, 136.9, 123.8, 122.9, 121.3, 121.2, 70.8; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 187.1, $C_{11}H_{11}N_2O^+$ requires 187.1.

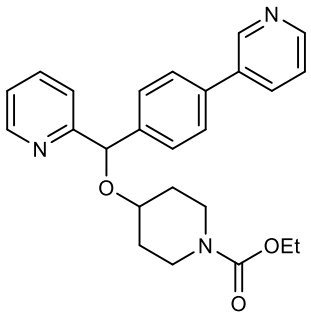
2–chloro–5–((pyridin–3–yloxy)methyl)pyridine (6)



An oven dried 1 L round bottom flask was charged with sodium hydride (60% dispersion in mineral oil, 2.1 equiv). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of DMF (67 mL) and THF (200 mL). The mixture was cooled to 0 °C and a mixture of 3–hydroxypyridine (1.90 g, 20.00 mmol) in THF (20 mL) was added dropwise over 5 minutes. The reaction mixture was warmed to room temperature and stirred for 1 hour before being cooled to 0 °C. A solution of 2–chloro–5–(chloromethyl)pyridine (3.40 g, 21.00 mmol) in DMF (20 mL) was then added dropwise to the reaction mixture over 10 minutes. The reaction mixture was warmed to room temperature and allowed to stir for 12 hours. The mixture was quenched with water (100 mL) and diluted with EtOAc (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried

($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 4% MeOH in CH_2Cl_2) to provide the title compound as a brown solid (1.97 g, 8.93 mmol, 45% yield). mp 43–45 ºC; IR n_{max}/cm^{-1} (film): 3065, 3006, 2913, 1577, 1459, 1401, 1272, 1233, 1207, 1100, 1060, 1023, 819, 792, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (1H, d, *J* = 1.8 Hz), 8.39 (1H, s), 8.29 (1H, t, *J* = 5.7 Hz), 7.76 (1H, dd, *J* = 8.2, 2.2 Hz), 7.39 (1H, d, *J* = 8.2 Hz), 7.32–7.21 (2H, m), 5.11 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.3, 151.5, 148.7, 143.0, 138.0, 130.7, 124.3, 123.9, 121.5, 67.0; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 221.1, $C_{11}H_9ClN_2O^+$ requires 221.0.

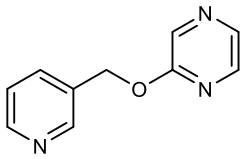
Ethyl 4–(pyridin–2–yl(4–(pyridin–3–yl)phenyl)methoxy)piperidine–1–carboxylate (7)



An oven dried 50 mL Schlenk flask was charged with ethyl 4–((4–chlorophenyl)(pyridin–2–yl)methoxy)piperidine–1–carboxylate (1.46 g, 3.50 mmol), 3–pyridylboronic acid (473 mg, 3.85 mmol), $Pd_2(dba)_3$ (64 mg, 0.07 mmol), and tricyclohexylphosphine (47 mg, 0.17 mmol). The flask was subjected to five cycles of vacuum/nitrogen backfill before the addition of 1,4–dioxane (4.69 mL) and aqueous K_3PO_4 (1.27 M, 4.69 mL, 5.95 mmol). The Schlenk flask was sealed and heated at 100 °C for 18 hours. The reaction mixture was cooled to room temperature, filtered through a pad of silica gel (washing with EtOAc) and the filtrate concentrated *in vacuo*. The aqueous residue was then extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried

($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (neutralized silica gel, gradient elution: 75% EtOAc in hexanes to 100% EtOAc) to provide the title compound as a colorless oil (1.01 g, 2.42 mmol, 69% yield). IR ν_{max}/cm^{-1} (film): 3052, 2981, 2927, 2867, 1690, 1579, 1432, 1228, 1095, 1026, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, d, *J* = 2.0 Hz), 8.56 (1H, d, *J* = 4.7 Hz), 8.53 (1H, d, *J* = 4.2 Hz), 7.82 (1H, d, *J* = 8.0 Hz), 7.70 (1H, td, *J* = 7.7, 1.4 Hz), 7.61–7.50 (5H, m), 7.33 (1H, dd, *J* = 7.9, 4.8 Hz), 7.17 (1H, m), 5.70 (1H, s), 4.11 (2H, q, *J* = 7.1 Hz), 3.78 (2H, br), 3.68 (1H, app. sept), 3.21 (2H, m), 1.86 (2H, m), 1.70 (2H, m), 1.24 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.0, 155.4, 148.9, 148.4, 148.2, 141.5, 137.0, 136.9, 136.1, 134.1, 127.4, 127.1, 123.4, 122.4, 120.6, 81.3, 72.5, 61.2, 41.0 (d, *J* = 4.6 Hz), 31.0, 14.6. *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 418.3, $C_{25}H_{28}N_3O_3^+$ requires 418.2.

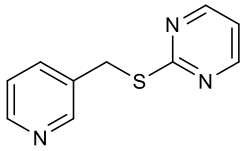
2–(pyridin–3–ylmethoxy)pyrazine (8)



An oven–dried 100 mL round bottomed flask was charged with 3–pyridylmethanol (2.92 mL, 30.00 mmol), 2–chloropyrazine (893 μL, 10.00 mmol) and DMF (15 mL). The solution was cooled to 0 °C before sodium hydride (60% dispersion in mineral oil, 3.0 equiv) was added in one portion. The reaction mixture was warmed to room temperature and allowed to stir overnight at 70 °C. The mixture was cooled to room temperature, quenched with water (20 mL) and diluted with EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (neutralized silica gel: 30% EtOAc in

hexanes) to provide the title compound as a light yellow solid (1.39 g, 7.43 mmol, 74% yield). mp 43–45 ºC; IR n_{max}/cm^{-1} (film): 3059, 2992, 1579, 1531, 1427, 1284, 1006, 711; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, d, *J* = 1.5 Hz), 8.59 (1H, dd, *J* = 4.8, 1.5 Hz), 8.28 (1H, d, *J* = 1.2), 8.16 (1H, d, *J* = 2.8 Hz), 8.10–8.07 (1H, m), 7.79 (1H, d, *J* = 7.8 Hz), 7.31 (1H, dd, *J* = 7.8, 4.9 Hz) 5.41 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.54, 149.68, 149.54, 140.36, 137.05, 135.97, 135.81, 131.90, 123.37, 65.26; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 188.1, $C_{10}H_{10}N_3O^+$ requires 188.1.

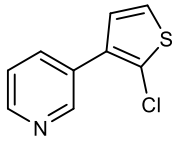
2–((pyridin–3–ylmethyl)thio)pyrimidine (9)



An oven dried 50 mL round bottom flask was charged with sodium hydride (60% dispersion in mineral oil, 1.1 equiv). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of DME (12 mL). The reaction mixture was cooled to 0 °C and a solution of pyridin–3–ylmethanethiol (814 mg, 6.50 mmol) in DME (3 mL) was added dropwise over 10 minutes. The reaction mixture stirred for 30 minutes at 0 °C before a solution of 2–chloropyrimidine (677 mg, 5.91 mmol) in DME (5 mL) was added dropwise over 10 minutes. The reaction mixture was warmed to room temperature and allowed to stir for 1 hour. The mixture was quenched with water (10 mL) and diluted with EtOAc (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (neutralized silica gel: 70% EtOAc in hexanes) to provide the title compound as a white solid (1.01 g, 4.97 mmol, 84% yield). mp 46–48 ºC; IR ν_{max}/cm^{-1} (film): 3030, 2966, 2923, 1562, 1547, 1377,

1201, 1181, 748, 711, 629; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, d, *J* = 4.9 Hz), 8.52 (2H, d, *J* = 4.8 Hz), 8.47 (1H, d, *J* = 4.6 Hz), 7.76 (1H, d, *J* = 7.8 Hz), 7.22 (1H, dd, *J* = 7.9, 4.9 Hz), 6.98 (1H, t, *J* = 4.9 Hz), 4.38 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.3, 157.3, 150.3, 148.4, 136.4, 133.7, 123.3, 116.8, 32.2; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 204.1, $C_{10}H_{10}N_3S^+$ requires 204.1.

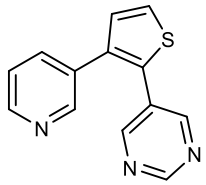
3–(2–chlorothiophen–3–yl)pyridine (10-int)



An oven dried 500 mL round bottom flask was charged with a solution of 3–bromo–2–chlorothiophene (2.73 mL, 25.00 mmol) in toluene (175 mL), followed by an aqueous solution of Na_2CO_3 (80 mL, 2.0 M) and an ethanolic solution (80 mL) of 3–pyridinylbornonic acid (4.61 g, 37.50 mmol). After 10 minutes of stirring at room temperature, $Pd(PPh_3)_4$ (1.16 g, 1.00 mmol) was added to the reaction flask. The mixture was then deoxygenated under reduced pressure and flushed with nitrogen (3 cycles) before heating under reflux overnight. After cooling to room temperature, EtOAc (100 mL) and water (100 mL) were added and the organic phase was separated. The aqueous phase was extracted with EtOAc (2 x 100 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (neutralized silica gel: 20% EtOAc in hexanes) to provide the title compound as a yellow oil (2.64 g, 13.50 mmol, 54% yield). IR ν_{max}/cm^{-1} (film): 3106, 3033, 1570, 1476, 1021, 873, 710, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, d, *J* = 1.7 Hz), 8.59 (1H, dd, *J* = 4.8, 1.6 Hz), 7.90 (1H, dt, *J* = 7.9, 2.0 Hz), 7.36 (1H, ddd, *J* = 7.9, 4.9, 0.7 Hz), 7.20 (1H, d, *J* = 5.8 Hz), 7.07 (1H, d, *J* = 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.3, 148.6, 135.5, 134.8,

130.1, 127.8, 126.2, 123.4, 123.2; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 196.1, $C_9H_7ClNS^+$ requires 196.0.

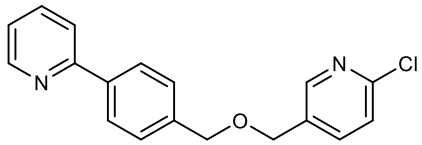
5–(3–(pyridin–3–yl)thiophen–2–yl)pyrimidine (10)



An oven dried 100 mL Schlenk flask was charged with a solution of 3–(2–chlorothiophen–3–yl)pyridine (1.37 g, 7.00 mmol), pyrimidine–5–boronic acid (1.04 g, 8.40 mmol), and $Pd(OAc)_2$ (63 mg, 0.28 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before being taken into glovebox. XPhos (160 mg, 0.34 mmol) was added, the flask then sealed and taken out of glovebox. Degassed *n*–BuOH (39 mL) was added to the flask before stirring the reaction mixture at room temperature for 15 minutes. An aqueous solution of cesium hydroxide monohydrate (1.22 M, 9.78 mL) was added to the mixture, the Schlenk flask sealed, and heated to 80 °C overnight. The reaction mixture was cooled to room temperature, filtered through a pad of silica gel (washing with EtOAc) and the filtrate concentrated *in vacuo*. The aqueous residue was then extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (neutralized silica gel: 50% EtOAc in hexanes) to provide the title compound as a white solid (919 mg, 3.84 mmol, 55% yield). mp 82–85 ºC; IR ν_{max}/cm^{-1} (film): 3029, 3032, 1548, 1440, 1379, 1188, 879, 722; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.12 (1H, s), 8.65 (2H, s), 8.61–8.53 (2H, m), 7.61–7.52 (2H, m), 7.32–7.22 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.4, 156.3, 149.7, 148.8,

137.0, 136.0, 131.6, 131.1, 130.4, 128.4, 127.2, 123.5; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 240.1, $C_{13}H_{10}N_3S^+$ requires 240.1.

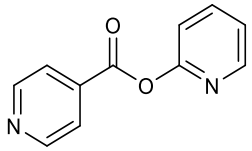
2–chloro–5–(((4–(pyridin–2–yl)benzyl)oxy)methyl)pyridine (11)



An oven dried 1 L round bottom flask was charged with sodium hydride (60% dispersion in mineral oil, 2.1 equiv). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of DMF (106 mL) and THF (318 mL). The mixture was cooled to 0 °C and a mixture of (4–(pyridin–2–yl)phenyl)methanol (5.89 g, 31.80 mmol) in THF (20 mL) was added dropwise over 5 minutes. The reaction mixture was warmed to room temperature and stirred for 1 hour before being cooled to 0 °C. A solution of 2–chloro–5–(chloromethyl)pyridine (5.41 g, 33.40 mmol) in DMF (20 mL) was then added dropwise to the reaction mixture over 10 minutes. The reaction mixture was warmed to room temperature and allowed to stir for 12 hours. The mixture was quenched with water (100 mL) and diluted with EtOAc (100 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (neutralized silica gel: 25% EtOAc in hexanes) to provide the title compound as a light yellow solid (6.91 g, 22.20 mmol, 70% yield). mp 96–98 ºC; IR ν_{max}/cm^{-1} (film): 3050, 3006, 2921, 2856, 1586, 1566, 1460, 1094, 776, 743; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, d, *J* = 4.9 Hz), 8.37 (1H, d, *J* = 2.4 Hz), 8.00 (2H, d, *J* = 8.2 Hz), 7.80–7.63 (3H, m), 7.45 (2H, d, *J* = 8.1 Hz), 7.31 (1H, d, *J* = 8.2 Hz), 7.25–7.20 (1H, m), 4.63 (2H, s), 4.55 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$)

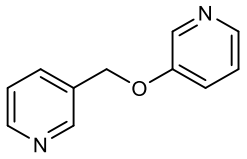
δ: 156.9, 150.7, 149.6, 148.8, 139.1, 138.2, 138.2, 136.7, 132.6, 128.1, 127.0, 124.1, 122.1, 120. 4, 72.3, 68.6; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 311.2, $C_{18}H_{16}ClN_2O^+$ requires 311.1.

Pyridin–2–yl isonicotinate (1)



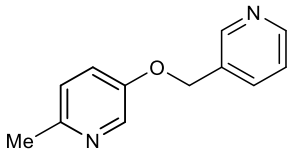
An oven dried 25 mL round bottom flask was charged with isonicotinoyl chloride hydrogen chloride (2.67 g, 15.00 mmol), 4–(dimethylamino)pyridine (660 mg, 5.40 mmol) and 2–hydroxypyridine (1.71 g, 18.00 mmol). THF (45 mL) was added to the reaction flask and triethylamine (6.3 mL, 45.00 mmol) was added dropwise over 5 minutes before heating the mixture at reflux overnight. The reaction cooled to room temperature and diluted with EtOAc (25 mL) and quenched with water (25 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified through a plug of silica eluting with 100% EtOAc to provide the title compound as a white solid (532 mg, 2.66 mmol, 18% yield). mp 86–88 ºC; IR ν_{max}/cm^{-1} (film): 3056, 3030, 1737, 1594, 1412, 1274, 1196, 1088; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.87 (2H, d, *J* = 6.0 Hz), 8.48 (1H, dd, *J* = 4.9, 1.4 Hz), 8.03 (2H, d, *J* = 6.0 Hz), 7.90–7.86 (1H, m), 7.34–7.31 (1H, m), 7.24–7.22 (1H, d, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 157.5, 150.7, 148.7, 139.7, 136.3, 123.1, 122.5, 116.2; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 201.1, $C_{11}H_9N_2O_2^+$ requires 201.1.

3–(pyridin–3–ylmethoxy)pyridine (13)



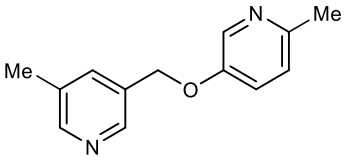
An oven dried 250 mL round bottom flask was charged with sodium hydride (60% dispersion in mineral oil, 3.3 equiv) and the flask was subjected to three cycles of vacuum/nitrogen backfill before addition of DMF (8 mL). The mixture was cooled to 0 °C and a mixture of 3–hydroxypyridine (1.14 g, 12.00 mmol) in DMF (20 mL) was added dropwise over 5 minutes. The reaction mixture was warmed to room temperature and stirred for 30 minutes before being cooled to 0 °C. A solution of 3–(chloromethyl)pyridine hydrogen chloride (1.97 g, 12.00 mmol) in DMF (32 mL) was then added dropwise to the reaction mixture over 10 minutes. The reaction mixture was warmed to room temperature and allowed to stir for 12 hours. The mixture was quenched with water (50 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with a saturated solution of brine (5 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 2.5% MeOH in CH_2Cl_2) to provide the title compound as a colorless oil (1.16 g, 6.25 mmol, 52% yield). IR ν_{max}/cm^{-1} (film): 3033, 2918, 2850, 1573, 1475, 1423, 1261, 1225, 1012; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, s), 8.61 (1H, d, *J* = 4.7 Hz), 8.40 (1H, s), 8.26 (1H, d, *J* = 4.1 Hz), 7.78 (1H, d, *J* = 7.8 Hz), 7.36–7.32 (1H, m), 7.28–7.22 (2H, m), 5.13 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.5, 149.7, 149.0, 142.8, 138.1, 135.2, 131.7, 123.9, 123.5, 121.5, 67.8; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 187.1, $C_{11}H_{11}N_2O^+$ requires 187.1.

2–methyl–5–(pyridin–3–ylmethoxy)pyridine (14)



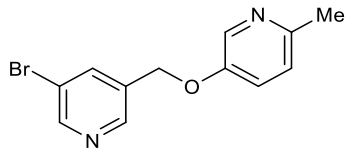
An oven dried 100 mL round bottom flask was charged with sodium hydride (60% dispersion in mineral oil, 3.3 equiv) and the flask was subjected to three cycles of vacuum/nitrogen backfill before addition of DMF (4 mL). The mixture was cooled to 0 °C and a mixture of 5–hydroxy–2–methylpyridine (798 mg, 7.32 mmol) in DMF (10 mL) was added dropwise over 5 minutes. The reaction mixture was warmed to room temperature and stirred for 30 minutes before being cooled to 0 °C. A solution of 3–(chloromethyl)pyridine hydrogen chloride (1.00 g, 6.10 mmol) in DMF (16.5 mL) was then added dropwise to the reaction mixture over 10 minutes. The reaction mixture was warmed to room temperature and allowed to stir for 12 hours. The mixture was quenched with water (50 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with a saturated solution of brine (5 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 4% MeOH in CH_2Cl_2) to provide the title compound as a white amorphous solid (714 mg, 3.57 mmol, 59% yield). IR ν_{max}/cm^{-1} (film): 3035, 2918, 2881, 1569, 1483, 1243, 1215, 1025, 1005; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.67 (1H, s), 8.59 (1H, d, *J* = 4.4 Hz), 8.26 (1H, s), 7.76 (1H, d, *J* = 7.8 Hz), 7.33–7.30 (1H, m), 7.18–7.14 (1H, m), 7.07 (1H, d, *J* = 8.6), 5.08 (2H, s), 2.48 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.4, 151.1, 149.6, 149.6, 148.9, 136.8, 135.1, 131.9, 123.4, 122.3, 67.9, 23.3; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 201.1, $C_{12}H_{13}N_2O^+$ requires 201.1.

2–methyl–5–((5–methypyridin–3–yl)methoxy)pyridine (15)



An oven dried 100 mL round bottom flask was charged with sodium hydride (60% dispersion in mineral oil, 3.3 equiv) and the flask was subjected to three cycles of vacuum/nitrogen backfill before addition of DMF (6 mL). The mixture was cooled to 0 °C and a mixture of 5–hydroxy–2–methylpyridine (1.10 g, 10.11 mmol) in DMF (14 mL) was added dropwise over 5 minutes. The reaction mixture was warmed to room temperature and stirred for 30 minutes before being cooled to 0 °C. A solution of 3–(chloromethyl)–5–methylpyridine hydrogen chloride (1.50 g, 8.42 mmol) in DMF (22.5 mL) was then added dropwise to the reaction mixture over 10 minutes. The reaction mixture was warmed to room temperature and allowed to stir for 12 hours. The mixture was quenched with water (50 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with a saturated solution of brine (5 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 6% MeOH in CH_2Cl_2) to provide the title compound as a white solid (1.37 g, 6.42 mmol, 76% yield). mp 81–83 ºC; IR ν_{max}/cm^{-1} (film): 3070, 2948, 2918, 1569, 1483, 1380, 1267, 1215, 1025; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.47 (1H, s), 8.42 (1H, s), 8.26 (1H, d, J = 2.8 Hz), 7.59 (1H, s), 7.17 (1H, dd, J = 5.7, 2.8 Hz), 7.07 (1H, d, J = 8.4 Hz), 5.05 (2H, s), 2.49 (3H, s), 2.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.5, 151.1, 150.2, 146.1, 136.9, 135.7, 133.1, 131.3, 123.3, 122.4, 67.9, 23.3, 18.3; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 215.2, $C_{13}H_{15}N_2O^+$ requires 215.1.

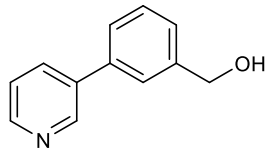
5–((5–bromopyridin–3–ly)methoxy)–2–methylpyridine (16)



An oven dried 50 mL round bottom flask was charged with 4–dimethylaminopyridine (611 mg, 5.00 mmol) and subjected to three cycles of vacuum/nitrogen backfill before addition of CH_2Cl_2 (17 mL). The mixture was then cooled to 0 °C, 5–bromo–3–pyridinemethanol (1.13 mL, 10.00 mmol) was added dropwise, followed by adding 4–toluenesulfonyl chloride (2.38 g, 12.50 mmol) portion wise over 10 minutes. Triethylamine (2.10 mL, 15.00 mmol) was then added dropwise and the reaction was allowed to stir at room temperature for 6 hours, before being diluted with CH_2Cl_2 (25 mL) and quenched with 1 M HCl (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mixture was carried onto the next reaction without further purification. An oven dried 100 mL round bottom flask was charged with sodium hydride (60% dispersion in mineral oil, 3.3 equiv). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of DMF (4 mL). The mixture was cooled to 0 °C and a mixture of 5–hydroxy–2–methylpyridine (707 mg, 6.48 mmol) in DMF (9 mL) was added dropwise over 5 minutes. The reaction mixture was warmed to room temperature and stirred for 30 minutes before being cooled to 0 °C. A solution of the crude material in DMF (14.5 mL) was then added dropwise to the reaction mixture over 10 minutes. The reaction mixture was warmed to room temperature and allowed to stir for 12 hours. The mixture was quenched with water (50 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with a saturated solution of brine (5 x 25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 4% MeOH in CH_2Cl_2) to provide the

title compound as a yellow oil (1.08 g, 3.85 mmol, 39% yield). IR ν_{max}/cm^{-1} (film): 3042, 3019, 2922, 1587,1494, 1265, 528; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (1H, d, *J* = 2.2 Hz), 8.58 (1H, d, *J* = 1.6 Hz), 8.26 (1H, d, *J* = 2.9 Hz), 7.94 (1H, t, *J* = 1.9 Hz), 7.17 (1H, dd, *J* = 8.5, 2.9 Hz), 7.09 (1H, d, *J* = 8.5 Hz), 5.08 (2H, s), 2.50 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.2, 151.5, 150.7, 146.8, 137.6, 136.7, 133.7, 123.5, 122.5, 120.9, 67.1, 23.4; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 279.0, $C_{12}H_{12}BrN_2O^+$ requires 279.0.

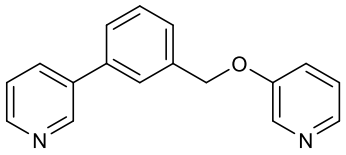
(3–(pyridin–3–yl)phenyl)methanol (17 int)



An oven dried 50 mL round bottom flask was charged with $Pd(OAc)_2$ (225 mg, 1.00 mmol), PPh_3 (682 mg, 2.60 mmol) and aq. Na_2CO_3 (14.2 mL, 28.40 mmol, 2.0 M) and subjected to three cycles of vacuum/nitrogen backfill before H_2O (10 mL) was added. A solution of 3–hydroxymethylphenylboronic acid (3.28 g, 21.60 mmol) and 3–bromopyridine (1.93 mL, 20.00 mmol) in propanol (38 mL) was added to the reaction mixture and the resulting suspension was allowed to stir at 95°C for 12 hours. The reaction mixture was diluted with EtOAc (75 mL) and quenched with water (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The organic layers were combined, washed with 1:1 saturated aqueous solution of $NaHCO_3$ (2 x 50 mL), and once with a saturated solution of brine (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 80% EtOAc in Hexanes) to provide the title compound as a clear–yellow oil (2.50 g, 13.52 mmol, 68% yield). IR ν_{max}/cm^{-1} (film): 3226, 3035, 2858, 1606, 1589, 1571, 1401, 1023; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (1H, d, *J* = 2.1 Hz),

8.59 (1H, dd, J = 4.8, 1.5 Hz), 7.88 (1H, dt, J = 8.0, 2.3 Hz), 7.60 (1H, s), 7.52–7.34 (4H, m), 4.80 (2H, s), 2.07 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.4, 147.3, 142.5, 137.1, 136.4, 134.4, 128.8, 126.4, 125.4, 125.1, 123.4, 63.9; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 186.2, $C_{12}H_{12}NO^+$ requires 186.1.

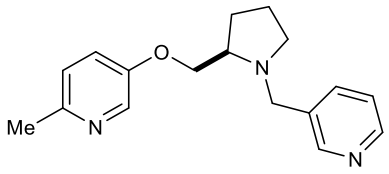
3–((3–(pyridin–3–yl)benzyl)oxy)pyridine (17)



An oven dried 50 mL round bottom flask was charged with 4–dimethylaminopyridine (99 mg, 0.81 mmol) and (3–(pyridin–3–yl)phenyl)methanol (1.50 g, 8.11 mmol) and subjected to three cycles of vacuum/nitrogen backfill, before CH_2Cl_2 (13 mL) was added. The mixture was cooled to 0 °C and 4–toluenesulfonyl chloride (2.32 g, 12.15 mmol) was added over 10 minutes. NEt_3 (2.69 mL, 12.15 mmol) was then added dropwise and the reaction was allowed to stir at room temperature for 6 hours. The mixture was diluted with CH_2Cl_2 (25 mL) and quenched with 0.3 M HCl (25 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mixture was carried onto the next reaction without further purification. An oven dried 100 mL round bottom flask was charged with sodium hydride (60% dispersion in mineral oil, 3.3 equiv). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of DMF (4 mL). The mixture was cooled to 0 °C and a mixture of 3–hydroxypyridine (585 mg, 6.15 mmol) in DMF (10 mL) was added dropwise over 5 minutes. The reaction mixture was warmed to room temperature and stirred for 30 minutes before being cooled to 0 °C. A solution of the crude material in DMF (14 mL) was then added dropwise to the reaction mixture over 10

minutes. The reaction mixture was warmed to room temperature and allowed to stir for 12 hours. The mixture was quenched with water (50 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with a saturated solution of brine (5 x 25 mL), 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 yellow oil (332 mg, 1.27 mmol, 16% yield). IR ν_{max}/cm^{-1} (film): 3032, 2923, 2873, 1572, 1473, 1424, 1259, 1226, 1021; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.85 (1H, d, *J* = 2.2 Hz), 8.61 (1H, dd, *J* = 4.8, 1.2 Hz), 8.42 (1H, d, *J* = 2.8 Hz), 8.25 (1H, d, *J* = 4.5 Hz), 7.88 (1H, dt, *J* = 7.9, 1.8 Hz), 7.65 (1H, s), 7.57–7.46 (3H, m), 7.37 (1H, dd, *J* = 7.8, 4.8 Hz), 7.30–7.21 (2H, m), 5.19 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$)δ: 154.6, 148.6, 148.2, 142.4, 138.2, 138.1, 137.0, 136.0, 134.2, 129.3, 127.0, 126.9, 126. 0, 123.7, 123.4, 121.4, 69.9; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 263.1, $C_{17}H_{15}N_2O^+$ requires 263.1.

(R)–2–methyl–5–((1–(pyridin–3–ylmethyl)pyrrolidin–2–yl)methoxy)pyridine (18)

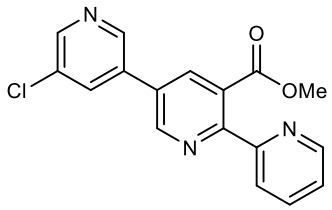


An oven dried 500 mL round bottom flask was charged with PPh_3 (12.77 g, 48.70 mmol) and a stir bar, and subjected to three cycles of vacuum/nitrogen backfill. THF (203 mL) was then added to the flask and diethyazodiethylcarboxylate (7.67 mL, 48.7 mmol) was added dropwise over 20 minutes. The solution was allowed to stir for 30 minutes before Boc–D–prolinol (6.53 g, 32.4 mmol) was added in one portion. The solution stirred for 20 minutes and then 3–hydroxypyridine

(5.31 g, 48.70 mmol) was added and the reaction mixture stirred for 36 hours. The mixture was diluted with CH_2Cl_2 (100 mL) and quenched with water (100 mL). The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 50% EtOAc in hexanes) to provide a mixture of the Boc–protected 2–methyl–5–(pyrrolidin–2–ylmethoxy)pyridine and diethyl 1,2–hydrazinedicarboxylate (10.84 g). The mixture was transferred to a 300 mL round bottom flask equipped with a stir bar and diluted with CH_2Cl_2 (112 mL). Trifluoroacetic acid (31 mL) was added dropwise over 20 minutes and the solution stirred overnight. The solution was quenched with a saturated aqueous solution of NH_4OH (20 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was washed with a saturated solution of brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The mixture was purified through flash chromatography (silica gel: 8% MeOH in CH_2Cl_2) to provide 2–methyl–5–(pyrrolidin–2–ylmethoxy)pyridine (1.52 g, 7.37 mmol, 25% yield). In a separate 50 mL round bottom flask, 3–pyridinecarboxaldehyde (675 mL, 7.19 mmol) and a stir bar were added and subjected to three cycles of vacuum/nitrogen backfills before MeOH (19 mL) and aq. acetic acid (0.96 mL, 7.20 mmol, 7.5 M) were added. The 2–methyl–5–((1–methylpyrrolidin–2–yl)methoxy)pyridine (1.52 g, 7.9 mmol) was added, followed by sodium triacetoxyborohydride (1.52 g, 7.19 mmol). The reaction was allowed to stir for 5 hours before being quenched with a saturated aqueous solution of NH_4Cl (40 mL) and diluted with CH_2Cl_2 (50 mL). The organic phase was separated from the aqueous layer and extracted with CH_2Cl_2 (3 x 50 mL). The aqueous layer was neutralized with a saturated aqueous solution of K_2CO_3 and was then extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo.* The mixture was purified by flash chromatography (silica gel: 2% MeOH

in CH_2Cl_2 to 6% MeOH in CH_2Cl_2) to provide the title compound as a yellow oil (1.07 g, 3.77 mmol, 52% yield). IR ν_{max}/cm^{-1} (film): 3025, 2960, 2920, 2072, 2788, 1572, 1494, 1483, 1424, 1266, 1240, 1211, 1026, 714; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (1H, s), 8.48 (1H, s), 8.15 (1H, d, *J* = 1.9 Hz), 7.65 (1H, d, *J* = 7.6 Hz), 7.22–7.19 (1H, m), 7.07–7.01 (2H, m), 4.13 (1H, d, *J* = 13.4 Hz), 3.96–3.84 (2H, m), 3.52 (1H, d, *J* = 13.4 Hz), 3.03–2.92 (2H, m), 2.46 (3H, s), 2.30 (1H, q, *J* = 8.5 Hz), 2.05–2.00 (1H, m), 1.76–1.73 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.0, 150.3, 150.0, 148.3, 136.6, 136.3, 134.9, 123.2 (2C), 121.8, 71.9, 62.3, 56.9, 54.5, 28.4, 23.2, 23.0; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 284.2, $C_{17}H_{22}N_3O^+$ requires 284.2; Specific Rotation $[\alpha]_D^{22}$ +53.52 (*c* 1.00, $CHCl_3$).

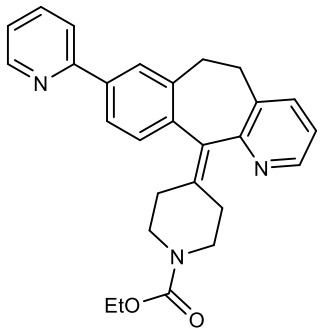
3–(2–chlorothiophen–3–yl)pyridine (19)



An oven dried 25 mL round bottom flask was charged with methyl 5',6–dichloro–[3,3'–bipyridine]–5–carboxylate (608 mg, 2.15 mmol) before the flask was subjected to three cycles of vacuum/nitrogen backfill. Degassed DMF (11 mL) was added to the flask followed by 2–(tributylstannyl)pyridine (975 μL, 3.01 mmol), cesium fluoride (980 mg, 6.45 mmol), CuI (82 mg, 0.43 mmol), $Pd(PPh_3)_4$ (248 mg, 0.22 mmol) in that order. The mixture was then deoxygenated under reduced pressure and flushed with nitrogen (3 cycles) before heating at 80 °C for 2 hours. After cooling to room temperature, the reaction mixture was diluted with EtOAc (25 mL) and filtered through a short pad of Celite. The organic filtrate was washed with water (25 mL x 5) and a saturated solution of brine (25 mL). The combined organic extracts were dried ($MgSO_4$), filtered

and concentrated *in vacuo*. The crude material was purified by flash chromatography (neutralized silica gel, gradient elution: 25% EtOAc in hexanes to 50% EtOAc in hexanes) to provide the title compound as a white solid (303 mg, 0.93 mmol, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.95 (1H, d, *J* = 2.0 Hz), 8.79 (1H, d, *J* = 1.5 Hz), 8.66 (1H, d, *J* = 2.0 Hz), 8.63 (1H, d, *J* = 4.6 Hz), 8.23 (1H, d, *J* = 7.9 Hz), 8.12 (1H, d, *J* = 2.0 Hz), 7.94 (1H, s), 7.85 (1H, t, *J* = 7.9 Hz), 7.34 (1H, dd, *J* = 7.3, 4.9 Hz), 3.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.0, 155.2, 155.1, 148.6, 148.6, 148.2, 145.7, 136.8, 135.2, 134.0, 133.4, 132.6, 131.1, 128.8, 124.0, 122.7, 52.5. The spectroscopic data is in agreement with a reported synthesis.[3]

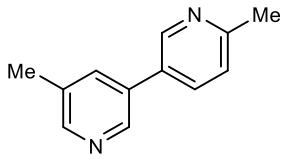
Ethyl 4–(8–(pyridin–2–yl)–5,6–dihydro–11H–benzo[5,6]cyclohepta[1,2–b]pyridin–11–ylidene)piperidine–1–carboxylate (20)



An oven dried 50 mL Schlenk flask was charged with loratadine (ethyl 4–(8–chloro–5,6–dihydro–11H–benzo[5,6]cyclohepta[1,2–b]pyridin–11–ylidene)piperidine–1–carboxylate) (766 mg, 2.00 mmol), $Pd_2(dba)_3$ (183 mg, 0.20 mmol), tri–tert–butylphosphonium tetrafluoroborate (116 mg, 0.40 mmol), and cesium fluoride (668 mg, 4.40 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before the addition of 1,4–dioxane (17 mL) and 2–(tributylstannyl)pyridine (971 µL, 3.00 mmol). The Schlenk flask was sealed and heated at 100 °C for 12 hours. The reaction mixture was cooled to room temperature and filtered through a pad of

silica gel (washing with EtOAc). The filtrate was washed with water (3 x 20 mL) and a saturated aqueous solution of brine (20 mL). The organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (neutralized silica gel: 30% EtOAc in hexanes) to provide the title compound as a white amorphous solid (660 mg, 1.55 mmol, 78% yield). IR ν_{max}/cm^{-1} (film): 3029, 2979, 2914, 2856, 1690, 1586, 1228, 1113, 996, 908, 723,; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.66 (1H, d, *J* = 4.7 Hz), 8.40 (1H, dd, *J* = 4.9, 1.4 Hz), 7.87 (1H, d, *J* = 1.5 Hz), 7.77–7.67 (3H, m), 7.44 (1H, dd, *J* = 7.6, 1.3 Hz), 7.30 (1H, d, *J* = 7.9 Hz), 7.23–7.17 (1H, m), 7.08 (1H, dd, *J* = 7.7, 4.8 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 3.82 (2H, br), 3.58–3.31 (2H , m), 3.24–3.06 (2H, m), 3.01–2.82 (2H, m), 2.60–2.27 (4H, m), 1.25, (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.2, 157.1, 155.5, 149.6, 146.6, 140.0, 138.5, 138.2, 137.4, 137.1, 136.7, 135.0, 133.6, 129.6, 127.6, 124.5, 122.1, 122.0, 120.4, 61.2, 44.8, 31.9, 31.7, 30.6 (d, *J* = 25.6 Hz), 14.6; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 426.3, $C_{27}H_{28}N_3O_2^+$ requires 426.2.

5,6'–dimethyl–3,3'–bipyridine (24)

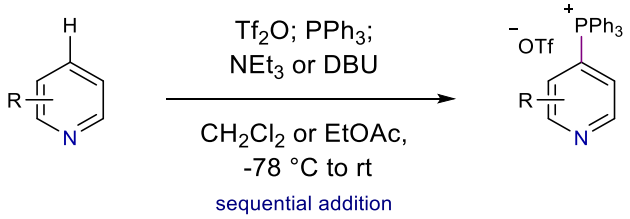


An oven dried 250 mL round bottom flask was charged with (6–methylpyrid–3–yl)boronic acid (1.00 g, 7.3 mmol) and $Pd(PPh_3)_4$ (734 mg, 0.64 mmol), before adding toluene (51 mL) and degassed ethanol (51 mL). 3–bromo–5–methylpyridine (0.74 mL, 6.40 mmol) and aq. Na_2CO_3 (6.7 mL, 13.40 mmol, 2.0 M) were added to the reaction mixture before heating to 110°C and stirring overnight. The solution was cooled to room temperature, diluted with CH_2Cl_2 (50 mL) and quenched with water (50 mL). The organic phase was separated from the aqueous layer and

extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 4% MeOH in CH_2Cl_2) to provide the title compound as a white solid (761 mg, 4.10 mmol, 65% yield); mp 69–74 ºC; IR ν_{max}/cm^{-1} (film): 3020, 2990, 2919, 1598, 1494, 1433, 1385; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.69 (1H, d, *J* = 2.2 Hz), 8.61 (1H, d, *J* = 2.0 Hz), 8.45 (1H, d, *J* = 1.3 Hz), 7.75 (1H, dd, *J* = 8.0, 2.4 Hz), 7.64 (1H, m), 7.24 (1H, d, *J* = 8.0 Hz), 2.60 (3H, s), 2.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.0, 149.5, 147.4, 145.2, 134.6, 134.6, 133.2, 133.0, 130.6, 123.2, 24.1, 13.2; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 185.2, $C_{12}H_{13}N_2^+$ requires 185.1.

2.3 Preparation of Heterocyclic Phosphonium Salts

General Procedure A



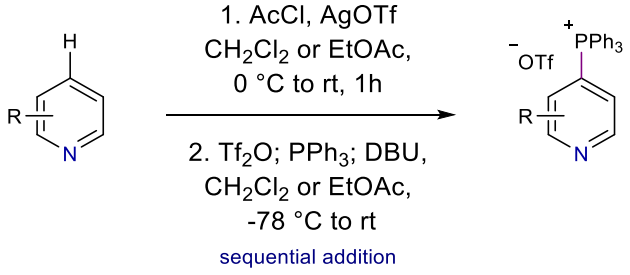
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes 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 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* to approximately 2–10 mL (depending on the scale of the reaction). An excess of chilled Et_2O (0 ºC) was added to the concentrated solution that 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.

General Procedure B (Acylation–Blocking Conditions)



An oven dried 8 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and silver trifluormethanesulfonate (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 or EtOAc (0.1 M) was added, the reaction vessel cooled to 0 ºC and acetyl chloride (1.0 equiv) was added dropwise over 5 minutes. The reaction was warmed to room temperature and stirred* for 1 hour before cooling to –78 ºC. Tf_2O (1.0 equiv) was added dropwise over 5 minutes and the reaction mixture 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. 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 pyridine (2.0 equiv) and H_2O (approximately the same volume as CH_2Cl_2) and the suspension was allowed to stir for 30 minutes before being filtered through a pad of Celite (rinsed with CH_2Cl_2). The filtrate was transferred to a separatory funnel and the organic layer was washed three times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to approximately 2–10 mL (depending on the scale of the reaction). An excess of chilled Et_2O (0 ºC) was added to the concentrated solution that 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) Silver trifluoromethanesulfonate was taken fresh from a glovebox before each reaction.
2) PPh_3 was crushed into a powder prior to use.

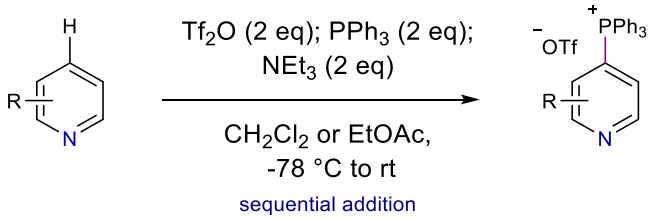
* Uniformed stirring is important for the reaction; the reaction vessel was placed directly on the middle of the stir plate and the mixture stirred at 1400–2000 rpms for the duration of the reaction.

3) Certain substrates require longer periods for the precipitation step and specific cases are indicated below.

4) 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.

5) 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.

General Procedure C (Base–Switching Conditions)



An oven dried 8 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 or EtOAc (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (2.0 equiv) was added dropwise over 5 minutes. The reaction was stirred[†] for 30 minutes before PPh_3 (2.0 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. NEt_3, (2.0 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

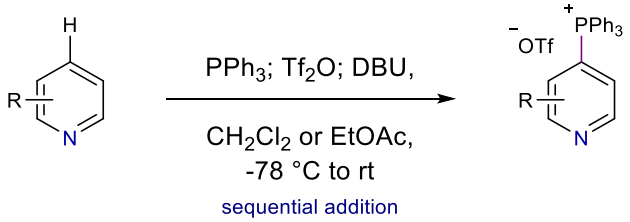
[†] Uniformed stirring is important for the reaction; the reaction vessel was placed directly on the middle of the stir plate and the mixture stirred at 1400–2000 rpms for the duration of the reaction.

to a separatory funnel. The mixture was diluted CH_2Cl_2 and the resulting organic layer was washed at least five times with H_2O. The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to approximately 2–10 mL (depending on the scale of the reaction). An excess of chilled Et_2O (0 ºC) was added to the concentrated solution that 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 contain residual protonated NEt_3 after the precipitation step. In these cases, the phosphonium salt is diluted with CH_2Cl_2 and washed with H_2O until the protonated NEt_3 disappears.
3) Certain substrates require longer periods for the precipitation step and specific cases are indicated below.
4) 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.
5) 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.

General Procedure D (Reverse Order of Reagent Addition)



An oven dried 8 mL vial (≤ 0.50 mmol scale) or a round bottom flask (> 0.50 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and PPh_3 (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 1 hour before DBU (1.0 equiv) was added dropwise via syringe, the cooling bath removed and the reaction warmed 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 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* to approximately 2–10 mL (depending on the scale of the reaction). An excess of chilled Et_2O (0 ºC) was added to the concentrated solution that 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.

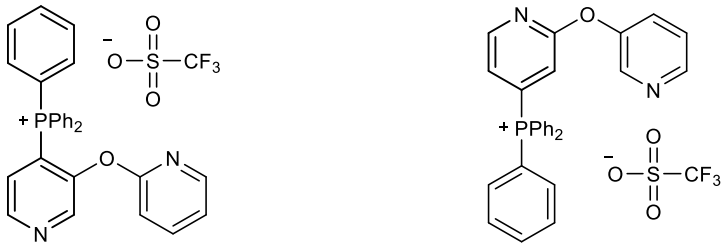
Notes.

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.

[‡] Uniformed stirring is important for the reaction; the reaction vessel was placed directly on the middle of the stir plate and the mixture stirred at 1400–2000 rpms for the duration of the reaction.

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(3–(pyridin–2–yloxy)pyridin–4–yl)phosphonium trifluoromethanesulfonate (4a)

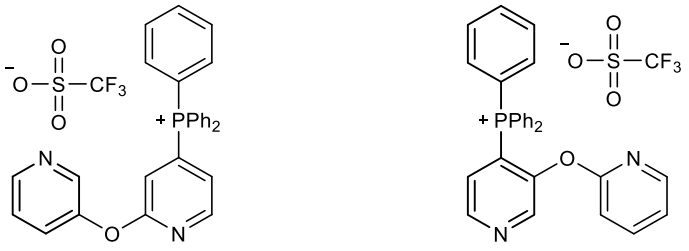


Major Minor

>20:1(Major:Minor) Mixture of Isomers

Prepared according to general procedure A using 2–(pyridin–3yloxy)pyridine (183 mg, 1.06 mmol), Tf_2O (179 μL, 1.06 mmol), PPh_3 (306 mg, 1.17 mmol), DBU (159 μL, 1.06 mmol) and CH_2Cl_2 (10.6 mL). After the purification procedure, the title compound was isolated as a white solid (498 mg, 0.85 mmol, 81% yield). mp 149–158 ºC; Both isomers, IR ν_{max}/cm^{-1} (film): 3063, 1601, 1589, 1437, 1269, 1221, 1140, 1031; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (1H, app d, J = 6.2 Hz), 8.76 (1H, app t, J = 8.8 Hz), 7.98 (1H, dd, J = 4.8, 1.8 Hz), 7.83–7.64 (15H, m), 7.55–7.51 (1H, m), 7.30 (1H, dd, J = 14.2, 5.0 Hz), 7.02 (1H, dd, J = 7.2, 5.0 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.4, 151.1, 146.6, 146.4 (d, J = 10.1 Hz), 146.3 (d, J = 4.4 Hz), 140.4, 135.6 (d, J = 3.1 Hz), 133.9 (d, J = 11.0 Hz), 130.6 (d, J = 13.4 Hz), 127.6 (d, J = 7.0 Hz), 120.9, 120.7 (q, J = 320.3 Hz), 119.6 (d, J = 86.1 Hz), 115.7 (d, J = 91.4 Hz), 111.2; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.12; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.13; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 433.2, $C_{28}H_{22}N_2OP^+$ requires 433.1.

Triphenyl(2–(pyridin–3–yloxy)pyridin–4–yl)phosphonium trifluoromethanesulfonate (4b)

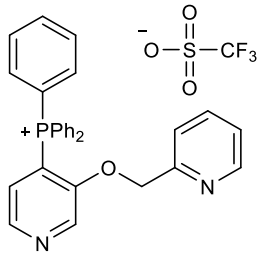


Major Minor

17:1:1:1 (Major:Minor:Undefined phosphonium isomers) Mixture of Isomers

Prepared according to general procedure B (except that the phosphine was stirred for 6 hours at –50 ºC instead of 30 minutes at –78 ºC) using 2–(pyridin–3yloxy)pyridine (86 mg, 0.50 mmol), silver trifluormethanesulfonate (129 mg, 0.50 mmol), acetyl chloride (36 μL, 0.50 mmol), Tf_2O (85 μL, 0.50 mmol), PPh_3 (145 mg, 0.55 mmol), DBU (75 μL, 0.50 mmol), pyridine (81 μL, 1.00 mmol), and EtOAc (5.0 mL). After the purification procedure, the title compound was isolated as a brown solid (113 mg, 0.19 mmol, 39% combined yield).; Both isomers, IR ν_{max}/cm^{-1} (film): 3064, 1588, 1439, 1382, 1260, 1222, 1108, 1030, 906, 734, 689, 647; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49–8.46 (3H, m), 7.93–7.62 (16H, m), 7.37 (1H, dd, *J* = 8.2, 4.7 Hz), 7.30 (1H, dd, *J* = 11.9, 5.2 Hz), 7.12 (1H, d, *J* = 14.5 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4 (d, *J* = 15.9 Hz), 149.8 (d, *J* = 12.1 Hz), 149.2, 146.4, 143.3, 136.2 (d, *J* = 3.0 Hz), 134.4 (d, *J* = 10.6 Hz), 132.2 (d, *J* = 84.5 Hz), 130.9 (d, *J* = 13.1 Hz), 126.4, 124.1, 121.6 (d, *J* = 8.3 Hz), 120.7 (q, *J* = 321.2 Hz), 116.5 (d, *J* = 10.3 Hz), 115.4 (d, *J* = 89.5 Hz); Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.12; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.39; Minor isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.97, 21.17, 21.00; *m/z* LRMS (ESI + APCI) found $[M – OTf]^+$ 433.2, $C_{28}H_{22}N_2OP^+$ requires 433.1.

Triphenyl(3–(pyridin–2–ylmethoxy)pyridin–4–yl)phosphonium trifluoromethanesulfonate (5a)

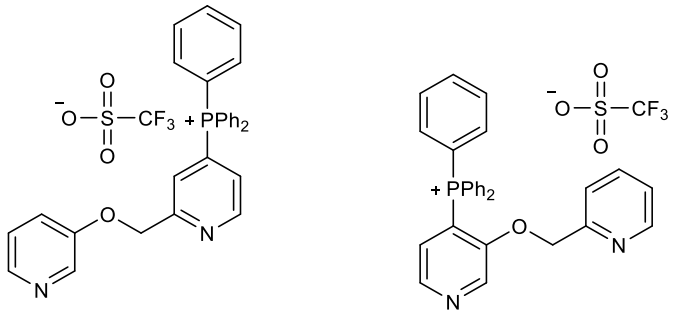


Major

>20:1 (Major:Minor) (Minor is a 2-position phosphonium isomer) Mixture of Isomers

Prepared according to general procedure D using 2–((pyridin–3–yloxy)methyl)pyridine (31 mg, 0.17 mmol), Tf_2O (29 μL, 0.17 mmol), PPh_3 (45 mg, 0.17 mmol), DBU (26 μL, 0.17 mmol), and EtOAc (1.7 mL). After the purification procedure, the title compound was isolated as a white solid (103 mg, 0.17 mmol, >99% combined yield). mp: 40–45 ºC; Both isomers, IR ν_{max}/cm^{-1} (film): 3060, 1483, 1438, 1414, 1260, 1223, 1151, 1107, 1030, 911, 722, 636; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.78 (1H, app d, *J* = 6.7 Hz), 8.52 (1H, app t, *J* = 4.4 Hz), 8.37 (1H, d, *J* = 4.4 Hz), 7.84–7.80 (3H, m), 7.71–7.66 (6H, m), 7.60–7.55 (6H, m), 7.47 (1H, td. *J* = 7.7, 1.6 Hz), 7.14 (1H, dd, *J* = 7.0, 4.9 Hz), 7.07 (1H, dd, *J* = 15.2, 4.4 Hz), 6.57 (1H, d, *J* = 7.8 Hz), 5.15 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.9, 152.9, 149.0, 143.9 (d, *J* = 10.9 Hz), 137.1 (d, *J* = 4.4 Hz), 136.8, 135.5 (d, *J* = 3.0 Hz), 133.8 (d, *J* = 10.8 Hz), 130.5 (d, *J* = 13.4 Hz), 127.9 (d, *J* = 7.0 Hz), 123.4, 122.0, 120.7 (q, *J* = 321.3 Hz), 116.1 (d, *J* = 91.4 Hz), 115.0 (d, *J* = 86.6 Hz), 72.3; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.13; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.55; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.44; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 447.2, $C_{29}H_{24}N_2OP^+$ requires 447.2.

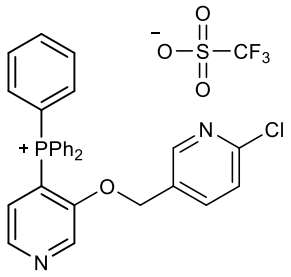
Triphenyl(2–((pyridin–3–yloxy)methyl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (5b)



11:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure B using 2–((pyridin–3–yloxy)methyl)pyridine (19 mg, 0.10 mmol), silver trifluormethanesulfonate (27 mg, 0.10 mmol), acetyl chloride (8 μL, 0.10 mmol), Tf_2O (18 μL, 0.11 mmol), PPh_3 (30 mg, 0.11 mmol), DBU (16 μL, 0.11 mmol), pyridine (17 μL, 0.20 mmol), and EtOAc (1 mL). After the purification procedure, the title compound was isolated as a brown solid (22 mg, 0.037 mmol, 37% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3062, 1585, 1575, 1439, 1260, 1224, 1154, 1108, 1030, 908, 723, 689, 635; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.03 (1H, app t, *J* = 5.0 Hz), 8.23 (2H, bs), 7.92–7.57 (17H, m), 7.23 (2H, s), 5.38 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1 (d, *J* = 10.2 Hz), 153.8, 151.6 (d, *J* = 10.4 Hz), 142.8, 138.4, 136.2 (d, *J* = 2.9 Hz), 134.5 (d, *J* = 10.4 Hz), 131.0 (d, *J* = 13.1 Hz), 129.3 (d, *J* = 84.3 Hz), 126.5 (d, *J* = 8.4 Hz), 124.5 (d, *J* = 8.9 Hz), 124.1, 121.2, 120.8 (q, *J* = 321.0 Hz), 115.6 (d, *J* = 89.5 Hz), 69.8; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.18; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.95; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.64; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 447.2, $C_{29}H_{24}N_2OP^+$ requires 447.2.

Triphenyl(3–(pyridin–2–yloxy)pyridin–4–yl)phosphonium trifluoromethanesulfonate (6a)

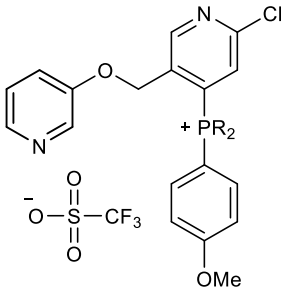


Major

20:1:1 (Major:Unidentified phosphonium isomers) Mixture of Isomers

Prepared according to general procedure A using 2–chloro–5–((pyridin–3–yloxy)methyl)pyridine (110 mg, 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 (265 mg, 0.42 mmol, 84% yield). All isomers, IR ν_{max}/cm^{-1} (film): 3059, 2924, 1570, 1438, 1414, 1261, 1105, 1029, 721, 689, 636; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.92 (1H, d, *J* = 6.7 Hz), 8.54 (1H, app t, *J* = 4.3 Hz), 7.94–7.47 (16H, m), 7.38 (1H, dd, *J* = 8.2, 2.4 Hz), 7.08 (2H, d, *J* = 8.2 Hz), 7.02 (1H, dd, *J* = 14.6, 4.9 Hz), 5.30 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.7, 151.2, 149.0, 143.9 (d, *J* = 11.0 Hz), 139.2, 137.3 (d *J* = 4.3 Hz), 135.5 (d, *J* = 2.9 Hz), 133.7 (d, *J* = 10.7 Hz), 130.9 (d, *J* = 13.0 Hz), 128.6, 127.7 (d, *J* = 6.9 Hz), 123.9, 120.7 (q, *J* = 321.1 Hz), 116.1 (d, *J* = 91.3 Hz), 114.6 (d, *J* = 87.1 Hz), 68.6; All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.18; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.54; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.22, 18.53; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 481.2, $C_{29}H_{23}ClN_2OP^+$ requires 482.1.

Triphenyl(2–(pyridin–3–yloxy)pyridin–4–yl)phosphonium trifluoromethanesulfonate (6b)

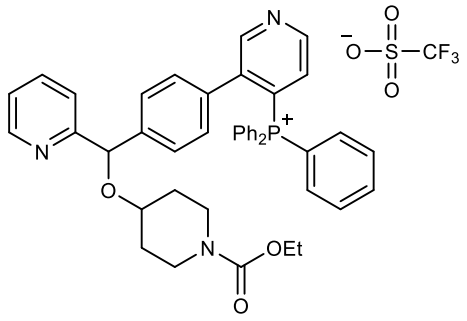


Major

12.8:2.2:2.2 (Major:Unidentified phosphonium isomers) Mixture of Isomers

Prepared according to general procedure B (except that tris(4–methoxyphenyl)phosphine was used instead of triphenylphosphine) using 2–chloro–5–((pyridin–3–yloxy)methyl)pyridine (55 mg, 0.25 mmol), silver trifluormethanesulfonate (64 mg, 0.25 mmol), acetyl chloride (18 μL, 0.25 mmol), Tf_2O (42 μL, 0.25 mmol), tris(4–methoxyphenyl)phosphine (97 mg, 0.28 mmol), DBU (37 μL, 0.25 mmol), pyridine (40 μL, 0.50 mmol), and EtOAc (2.5 mL). After the purification procedure, the title compound was isolated as a brown solid (79 mg, 0.11 mmol, 44% combined yield). All isomers, IR ν_{max}/cm^{-1} (film): 3061, 2916, 1438, 1398, 1260, 1152, 1108, 1030, 908, 722, 636; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, d, *J* = 6.3 Hz), 8.11 (1H, d, *J* = 3.8 Hz), 7.86–6.71 (16H, m), 4.80 (2H, s), 3.91 (9H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2 (d, *J* = 2.7 Hz), 153.7 (d, *J* = 9.1 Hz), 153.5 (d, *J* = 15.1 Hz), 148.9, 142.5, 137.3, 136.1 (d, *J* = 12.2 Hz), 133.2 (d, *J* = 5.6 Hz), 132.2 (d, *J* = 81.7 Hz), 129.2 (d, *J* = 11.0 Hz), 124.0 (br), 120.7 (q, *J* = 321.0 Hz), 119.1, 116.4 (d, *J* = 14.4 Hz), 106.1 (d, *J* = 98.8 Hz), 65.3 (d, *J* = 2.5 Hz), 56.0; All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.19; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.17; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.56, 19.42, 19.20; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 571.2, $C_{28}H_{22}N_2OP^+$ requires 571.2.

(3–(4–(((1–(ethoxycarbonyl)piperidin–4–yl)oxy)(pyridin–2–yl)methyl)phenyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (7a)

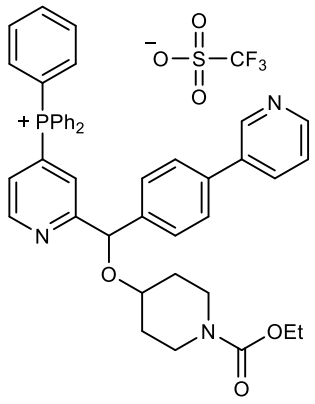


Major

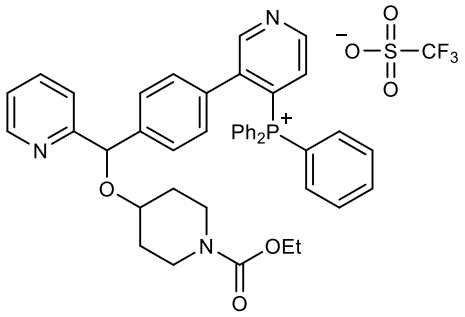
5.9:2.2:1 (Major:Unidentified phosphonium isomer) Mixture of Isomers

Prepared according to general procedure A (except that ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture) using ethyl 4–(pyridin–2–yl(4–(pyridin–3–yl)phenyl)methoxy)piperidine–1–carboxylate (42 mg, 0.10 mmol), Tf_2O (17 μL, 0.10 mmol), PPh_3 (29 mg, 0.11 mmol), DBU (15 μL, 0.10 mmol), 1,3,5-trimethoxybenzene as an internal standard (17 mg, 0.10 mmol), and CH_2Cl_2 (1 mL) to afford the title compound (combined ^{1}H NMR yield: 73%). Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99-8.89 (1H, m), 8.75 (1H, d, *J* = 6.8 Hz), 8.64 (1H, d, *J* = 5.3 Hz), 8.09-7.14 (19H, m), 7.09 (2H, d, *J* = 8.0 Hz), 6.71 (2H, d, *J* = 8.1 Hz), 5.59 (1H, s), 4.19-4.03 (2H, m), 3.84-3.66 (2H, m), 3.60-3.37 (1H, m), 3.29-3.01 (2H, m), 1.92-1.51 (4H, m), 1.33-1.15 (3H, m); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.45; Other phosphonium isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.61 (d, *J* = 19.9 Hz); *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 678.3, $C_{43}H_{41}N_3O_3P^+$ requires 678.3.

(2–(((1–(ethoxycarbonyl)piperidin–4–yl)oxy)(4–(pyridin–3–yl)phenyl)methyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (7b)



Major



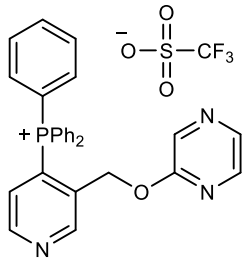
Minor

>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure B using acetyl chloride (14 μL, 0.20 mmol), silver trifluoromethanesulfonate (51 mg, 0.40 mmol), ethyl 4–(pyridin–2–yl(4–(pyridin–3–yl)phenyl)methoxy)piperidine–1–carboxylate (83 mg, 0.20 mmol), Tf_2O (34 μL, 0.20 mmol), PPh_3 (58 mg, 0.22 mmol), DBU (30 μL, 0.20 mmol) and CH_2Cl_2 (2.0 mL). After the purification procedure, the title compound was isolated as an off–white solid (62 mg, 0.075 mmol, 37% combined yield). All isomers, IR ν_{max}/cm^{-1} (film): 3009, 2930, 1685, 1437, 1264, 1225, 1108, 1030, 747; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.94 (1H, app t, *J* = 5.0 Hz), 8.82 (1H, br), 8.59 (1H, br), 7.99–7.43 (22H, m), 7.38 (1H, br s), 5.81 (1H, s), 4.13 (2H, q, *J* = 7.1 Hz), 3.83–3.62 (1H, m), 3.60–3.38 (2H, m), 3.31–3.10 (2H, m), 1.98–1.36 (4H, m), 1.26 (3H, t, *J* = 7.0 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.5 (d, *J* = 9.6 Hz), 155.4, 151.1 (d, *J* = 10.5 Hz), 148.4, 147.9, 140.0, 137.6, 136.2 (d, *J* = 2.9 Hz), 135.9, 134.4 (d, *J* = 10.5 Hz), 130.9 (d, *J* = 13.1 Hz), 130.5, 129.2 (d, *J* = 83.8 Hz), 127.8, 127.3, 125.8 (d, *J* = 8.1 Hz), 123.9–123.5 (2C, m), 120.8 (q, *J* = 321.2 Hz), 115.7 (d, *J* = 89.4 Hz), 80.2, 72.6, 61.2, 40.6 (d, *J* = 5.6 Hz), 30.7 (d, *J* = 103.8 Hz), 14.6; All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.16; Major isomer,

^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.69; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.46; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 678.3, $C_{43}H_{41}N_3O_3P^+$ requires 678.3.

Triphenyl(3–((pyrazin–2–yloxy)methyl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (8a)

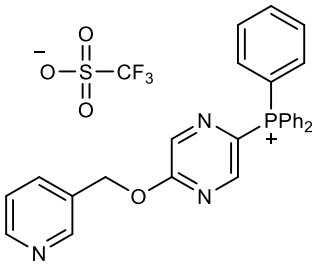


Major

10:1.4:1.2:1.2:1 (Major:Unidentified phosphonium isomer) Mixture of Isomers

Prepared according to general procedure A (except that ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture) using 2–(pyridin–3–ylmethoxy)pyrazine (19 mg, 0.10 mmol), Tf_2O (17 μL, 0.10 mmol), PPh_3 (29 mg, 0.11 mmol), DBU (15 μL, 0.10 mmol), 1,3,5-trimethoxybenzene as an internal standard (17 mg, 0.10 mmol), and CH_2Cl_2 (1 mL) to afford the title compound (combined ^{1}H NMR yield: 58%). Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.05 (1H, d, *J* = 6.6 Hz), 8.90 (1H, app t, *J* =5.6 Hz), 8.06-8.00 (1H, m), 7.86-7.30 (18H, m), 4.91 (2H, s); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.71; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.25, 21.03, 17.74, 16.72; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 448.3, $C_{28}H_{23}N_3OP^+$ requires 448.2.

Triphenyl(5–(pyridin–3–ylmethoxy)pyrazin–2–yl)phosphonium trifluoromethanesulfonate (8b)

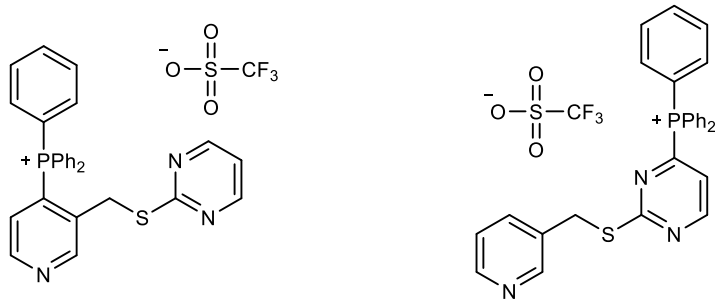


Major

>20:1:1 (Major:Unidentified phosphonium isomer) Mixture of Isomers

Prepared according to general procedure B using acetyl chloride (29 μL, 0.40 mmol), silver trifluoromethanesulfonate (103 mg, 0.40 mmol), 2–(pyridin–3–ylmethoxy)pyrazine (75 mg, 0.40 mmol), Tf_2O (68 μL, 0.40 mmol), PPh_3 (115 mg, 0.44 mmol), DBU (60 μL, 0.40 mmol) and EtOAc (4.0 mL). After the purification procedure, the title compound was isolated as an off white solid (120 mg, 0.20 mmol, 50% combined yield). All isomers, IR ν_{max}/cm^{-1} (film): 3061, 3011, 1525, 1439, 1262, 1152, 1030, 748, 636; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (1H, dd, *J* = 4.1, 2.4 Hz), 8.57 (1H, dd, *J* = 1.6, 1.2 Hz), 8.48, (1H, dd, *J* = 2.4, 1.4 Hz), 8.11 (1H, d, *J* = 1.4 Hz), 7.87–7.50 (15H, m), 7.32 (1H, dt, 7.8, 1.6 Hz), 7.16 (1H, dd, *J* = 7.7, 4.8 Hz), 5.38 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.9 (d, *J* = 17.8 Hz), 149.8 (2C), 147.7 (d, *J* = 3.4 Hz), 139.8 (d, *J* = 15.1 Hz), 136.8, 135.3 (d, *J* = 3.0 Hz), 134.2 (d, *J* = 10.5 Hz), 130.2 (d, *J* = 13.3 Hz), 129.6, 127.0 (d, *J* = 121.9 Hz), 123.4, 120.7 (q, *J* = 321.2 Hz), 116.3 (d, *J* = 90.8 Hz), 67.4; All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.12; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.23; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.04; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 448.2, $C_{28}H_{23}N_3OP^+$ requires 448.2.

Triphenyl(3–((pyrimidin–2–ylthio)methyl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (9a)

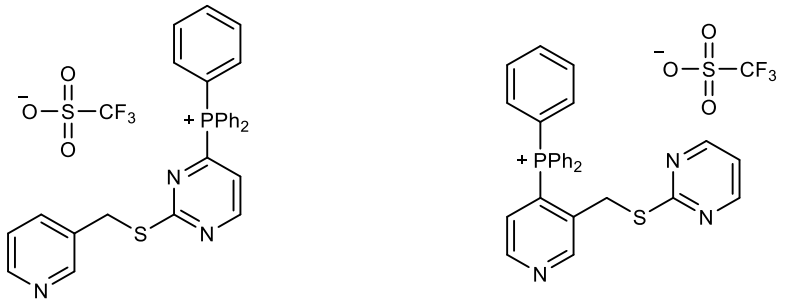


Major Minor

>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure D using 2–((pyridin–3–ylmethyl)thio)pyrimidine (102 mg, 0.50 mmol), Tf_2O (85 μL, 0.50 mmol), PPh_3 (131 mg, 0.50 mmol), DBU (75 μL, 0.50 mmol) and CH_2Cl_2 (5.0 mL). After the purification procedure, the title compound was isolated as a white solid (254 mg, 0.41 mmol, 83% combined yield). mp 75–81 ºC; Both isomers, IR ν_{max}/cm^{-1} (film): 3061, 2962, 1584, 1551, 1380, 1259, 1151, 1106, 1029, 912, 721, 689; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.18 (1H, d, *J* = 6.8 Hz), 8.84 (1H, app t, *J* = 4.4 Hz), 8.45 (2H, d, *J* = 4.8 Hz), 7.98–7.62 (15H, m), 7.17 (1H, dd, *J* = 15.2, 5.0 Hz), 7.03 (1H, t, *J* = 4.8 Hz), 4.18 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.1, 157.5, 153.7 (d, *J* = 7.4 Hz), 150.3 (d, *J* = 10.4 Hz), 137.0 (d, *J* = 5.9 Hz), 136.1 (d, *J* = 3.0 Hz), 134.2 (d, *J* = 10.6 Hz), 131.1 (d, *J* = 13.1 Hz), 128.0 (d, *J* = 9.7 Hz), 126.1 (d, *J* = 82.6 Hz), 120.7 (q, *J* = 321.2 Hz), 117.5, 115.8 (d, *J* = 88.6 Hz), 31.7 (d, *J* = 5.1 Hz); Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.10; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.42; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 464.2, $C_{28}H_{23}N_3PS^+$ requires 464.1.

Triphenyl(2–((pyridin–3–ylmethyl)thio)pyrimidin–4–yl)phosphonium trifluoromethanesulfonate (9b)

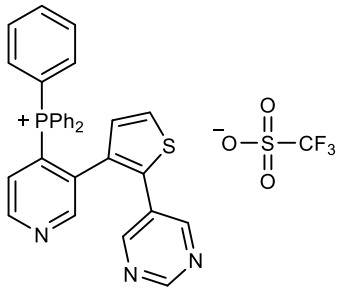


Major Minor

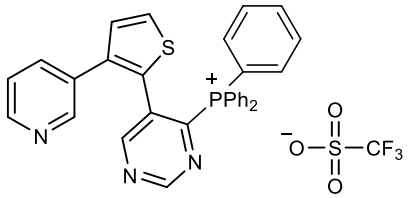
>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure B using acetyl chloride (29 μL, 0.40 mmol), silver trifluoromethanesulfonate (103 mg, 0.40 mmol), 2–((pyridin–3–ylmethyl)thio)pyrimidine (81 mg, 0.40 mmol), Tf_2O (68 μL, 0.40 mmol), PPh_3 (115 mg, 0.44 mmol), DBU (60 μL, 0.40 mmol) and EtOAc (4.0 mL). After the purification procedure, the title compound was isolated as a white solid (184 mg, 0.30 mmol, 75% yield). All isomers, IR ν_{max}/cm^{-1} (film): 3061, 3030, 2985, 1528, 1438, 1260, 1149, 1009, 1029, 911, 724; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.04 (1H, dd, *J* = 7.6, 5.0 Hz), 8.54–8.35 (2H, m), 8.03–7.57 (17H, m), 7.34–7.11 (1H, m), 4.29 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7 (d, *J* = 17.6 Hz), 160.6 (d, *J* = 7.4 Hz), 154.6 (d, *J* = 111.5 Hz), 149.6, 148.6, 136.2, 136.1 (d, *J* = 2.9 Hz), 134.6 (d, *J* = 10.3 Hz), 132.2, 130.7 (d, *J* = 13.1 Hz), 123.4, 123.1 (d, *J* = 20.3 Hz), 120.7 (q, *J* = 321.1 Hz), 114.9 (d, *J* = 88.9 Hz), 32.5; All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: −78.18; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.66; *m/z* LRMS (ESI + APCI) found $[M – OTf]^+$ 464.2, $C_{28}H_{23}N_3PS^+$ requires 464.1.

Triphenyl(3–(2–(pyrimidin–5–yl)thiophen–3–yl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (10a)



Major

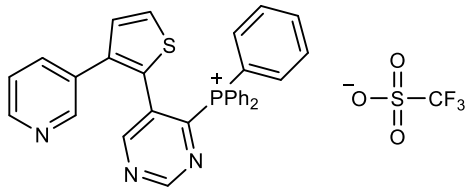


Minor

5.6:3.1:1 (Major:Unidentified phosphonium isomer:Minor) Mixture of Isomers

Prepared according to general procedure A (except that ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture) using 5–(3–(pyridin–3–yl)thiophen–2–yl)pyrimidine (72 mg, 0.30 mmol), Tf_2O (51 μL, 0.30 mmol), PPh_3 (87 mg, 0.33 mmol), DBU (45 μL, 0.30 mmol), 1,3,5-trimethoxybenzene as an internal standard (25 mg, 0.15 mmol), and CH_2Cl_2 (3 mL) to afford the title compound (combined ^{1}H NMR yield: 53%). Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.98-8.90 (2H, m), 8.70 (1H, d, J = 6.7 Hz), 8.09 (2H, s), 7.85-7.29 (16H, m), 7.10 (1H, d, J = 5.2 Hz), 6.57 (1H, d, J = 5.2 Hz); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.75; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 23.21, 20.73, 18.67; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 500.1, $C_{31}H_{23}N_3PS^+$ requires 500.1.

Triphenyl(5–(3–(pyridin–3–yl)thiophen–2–yl)pyrimidin–4–yl)phosphonium trifluoromethanesulfonate (10b)

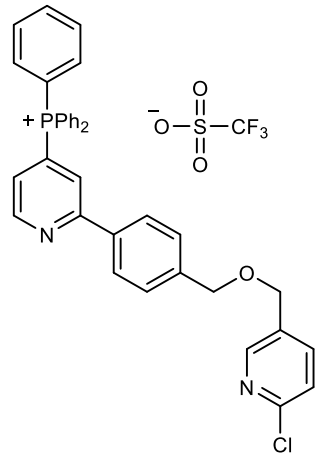


Major

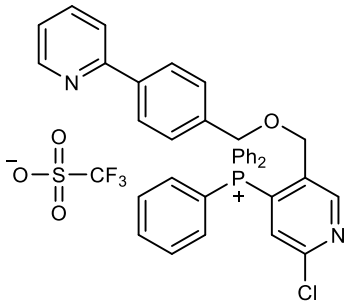
>20:1 (Major:2–position phosphonium isomer) Mixture of Isomers

Prepared according to general procedure B using acetyl chloride (11 μL, 0.15 mmol), silver trifluoromethanesulfonate (39 mg, 0.15 mmol), 5–(3–(pyridin–3–yl)thiophen–2–yl)pyrimidine (36 mg, 0.15 mmol), Tf_2O (25 μL, 0.15 mmol), PPh_3 (43 mg, 0.17 mmol), DBU (22 μL, 0.15 mmol) and CH_2Cl_2 (1.5 mL). After the purification procedure, the title compound was isolated as a yellow/orange solid (41 mg, 0.063 mmol, 42% combined yield). All isomers, IR ν_{max}/cm^{-1} (film): 3062, 1438, 1261, 1153, 1106, 1030, 912, 720, 636; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.51 (1H, s), 8.97 (1H, d, *J* = 8.7 Hz), 8.45 (1H, br s), 8.19–7.15 (19H, m), 6.98 (1H, d, *J* = 5.2 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2 (d, *J* = 5.1 Hz), 158.0 (d, *J* = 16.7 Hz), 152.6 (d, *J* = 113.3 Hz), 146.7 (2C, m), 138.8–138.2 (2C, m), 135.7, 135.5 (d, *J* = 3.1 Hz), 134.5 (d, *J* = 10.2 Hz), 132.0 (d, *J* = 9.9 Hz), 130.8, 130.3 (d, *J* = 11.9 Hz), 129.4, 128.4 (d, *J* = 11.9 Hz), 127.8, 120.7 (q, *J* = 320.5 Hz), 116.1 (d, *J* = 88.6 Hz); All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.11; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.70; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.02; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 500.1, $C_{31}H_{23}N_3PS^+$ requires 500.1.

(2–(4–(((6–chloropyridin–3–yl)methoxy)methyl)phenyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (11a)



Major



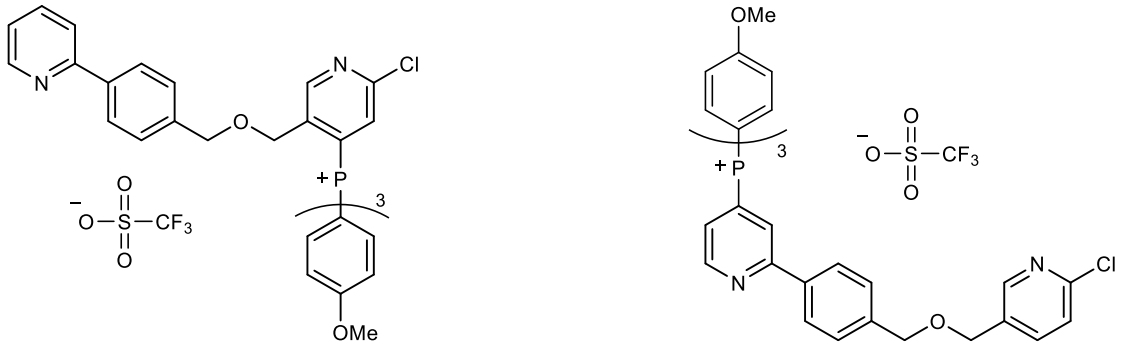
Minor

19:1:1 (Major:Minor:2-position phosphonium isomer) Mixture of Isomers

Prepared according to general procedure A using 2–chloro–5–(((4–(pyridin–2–yl)benzyl)oxy)methyl)pyridine (466 μL, 1.50 mmol), Tf_2O (253 μL, 1.50 mmol), PPh_3 (433 mg, 1.65 mmol), DBU (227 μL, 1.50 mmol) and CH_2Cl_2 (15 mL). After the purification procedure, the title compound was isolated as a white solid (957 mg, 1.33 mmol, 88% combined yield). All isomers, IR ν_{max}/cm^{-1} (film): 3060, 2851, 1584, 1438, 1260, 1148, 1107, 1029, 688; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.07 (1H, app t, *J* = 5.1 Hz), 8.33 (1H, d, *J* = 2.2 Hz), 8.06–7.62 (19H, m), 7.60–7.41 (3H, m), 7.31 (1H, d, *J* = 4.1 Hz), 4.62 (2H, s), 4.54 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.9 (d, *J* = 10.2 Hz), 151.7 (d, *J* = 10.6 Hz), 150.5, 148.7, 140.2, 138.3, 136.4 (d, *J* = 1.5 Hz), 136.2 (d, *J* = 3.0 Hz), 134.4 (d, *J* = 10.4 Hz), 132.5, 131.0 (d, *J* = 13.1 Hz), 129.3 (d, *J* = 84.1 Hz), 128.3, 127.3, 125.3 (d, *J* = 8.2 Hz), 124.0, 123.2 (d, *J* = 8.6 Hz), 120.7 (q, *J* = 321.2 Hz), 115.6 (d, *J* = 89.6 Hz), 71.9, 68.7; All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.10; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.83; Other phosphonium

isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 23.79, 15.38; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 571.2, $C_{36}H_{29}ClN_2OP^+$ requires 571.2.

(2–chloro–5–(((4–(pyridin–2–yl)benzyl)oxy)methyl)pyridin–4–yl)tris(4–methoxyphenyl)phosphonium trifluoromethanesulfonate (11b)

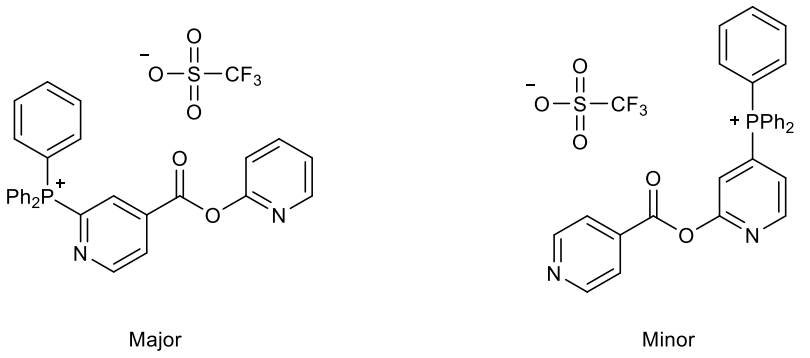


>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure B (except that the phosphine was added as a solution in CH_2Cl_2 (4.5 mL) dropwise over 30 minutes) using acetyl chloride (43 μL, 0.60 mmol), silver trifluoromethanesulfonate (154 mg, 0.60 mmol), 2–chloro–5–(((4–(pyridin–2–yl)benzyl)oxy)methyl)pyridine (186 mg, 0.60 mmol), Tf_2O (101 μL, 0.60 mmol), tris(4–methoxyphenyl)phosphine (233 mg, 0.66 mmol), DBU (91 μL, 0.60 mmol) and CH_2Cl_2 (6.0 mL). After the purification procedure, the title compound was isolated as a grey solid (308 mg, 0.38 mmol, 63%). mp 81–85 ºC; Both isomers, IR ν_{max}/cm^{-1} (film): 3093, 3010, 2975, 2944, 2843, 1591, 1262, 1106, 1018, 636; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (1H, d, *J* = 6.2 Hz), 8.67 (1H, d, *J* = 4.4 Hz), 7.86 (2H, d, *J* = 8.2 Hz), 7.82–7.70 (2H, m), 7.59–7.38 (6H, m), 7.31–7.11 (7H, m), 7.09–6.96 (3H, m), 4.10 (2H, s), 4.06 (2H, s), 3.87 (9H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.1 (d, *J* = 2.9 Hz), 156.3, 152.7 (d, *J* = 15.3 Hz), 152.7 (d, *J* = 9.3

Hz), 149.4, 138.9, 136.8, 136.5, 135.9 (d, J = 12.2 Hz), 135.2 (d, J = 5.9 Hz), 131.5 (d, J = 82.2 Hz), 128.8 (d, J = 11.2 Hz), 128.3, 126.6, 122.2, 120.8 (q, J = 321.4 Hz), 120.3, 116.4 (d, J = 14.3 Hz), 106.5 (d, J =98.9 Hz), 72.9, 67.5 (d, J = 3.6 Hz), 55.9; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.11; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.60; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 661.3, $C_{39}H_{35}ClN_2O_4P^+$ requires 661.2.

Triphenyl(4–((pyridin–2–yloxy)carbonyl)pyridin–2–yl)phosphonium trifluoromethanesulfonate (12a)

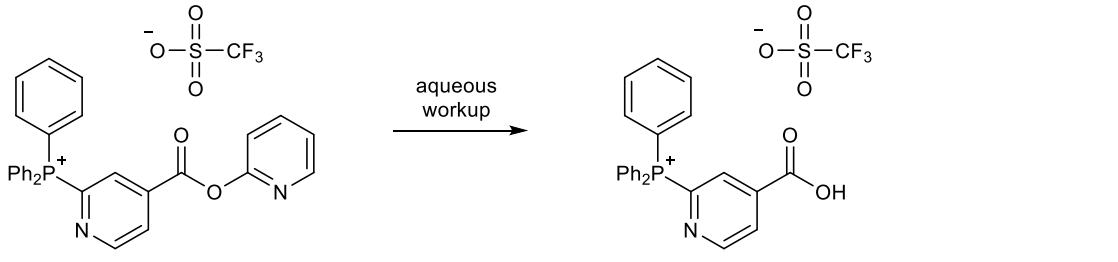


>20:1 Mixture of Isomers

Prepared according to general procedure A (except that ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture)[§] using pyridin–2–yl isonicotinate (52 mg, 0.26 mmol), Tf_2O (44 μL, 0.26

[§] ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture due to partial hydrolysis of the product during the aqueous workup.

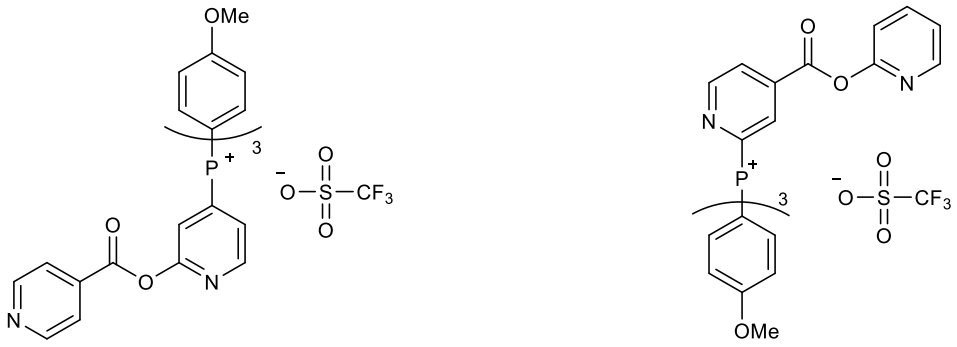
mmol), triphenylphosphine (75 mg, 0.28 mmol), DBU (39 μL, 0.26 mmol), 1,3,5-trimethoxybenzene as an internal standard (44 mg, 0.26 mmol), and CH_2Cl_2 (2.6 mL) to afford the title compound (combined ^{1}H NMR yield: 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.23 (1H, d *J* = 4.8 Hz), 8.50-8.44 (1H, m), 8.39 (1H, dd, *J* = 4.9, 1.6 Hz), 8.36 (1H, d, *J* = 6.3 Hz), 7.97-7.60 (16H, m), 7.37 (1H, d, *J* = 8.2 Hz), 7.30 (1H, dd, *J* = 7.0, 5.3 Hz); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.25; Hydrolyzed product, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.73; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 461.1, $C_{29}H_{22}N_2O_2P^+$ requires 461.1.



detected by LCMS

m/z LRMS (ESI + APCI) found [M - OTf]+ 384.1, $C_{24}H_{19}NO_2P^+$ requires 384.1

(2–(isonicotinoyloxy)pyridin–4–yl)tris(4–methoxyphenyl)phosphonium trifluoromethanesulfonate (12b)

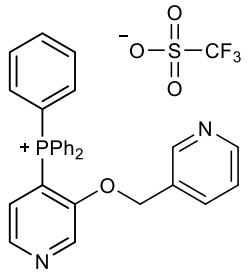


Major Minor

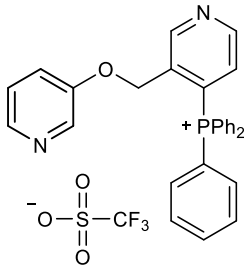
>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure B using Pyridin–2–yl isonicotinate (50 mg, 0.25 mmol), silver trifluoromethanesulfonate (64 mg, 0.25 mmol), acetyl chloride (18 μL, 0.25 mmol) Tf_2O (42 μL, 0.25 mmol), tris(4–methoxyphenyl)phosphane (97 mg, 0.28 mmol), DBU (37 μL, 0.25 mmol) and EtOAc (2.5 mL). After the purification procedure, the title compound was isolated as a brown solid (76 mg, 0.11 mmol, 43% yield). mp 70–78 ºC; Both isomers, IR ν_{max}/cm^{-1} (film): 3095, 2974, 2948, 1754, 1664, 1592, 1503, 1298, 1111, 1030; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82–8.79 (3H, m), 7.98 (2H, d, *J* = 5.8 Hz), 7.61–7.22 (14H, m), 3.92 (9H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.5 (d, *J* = 2.9 Hz), 163.0, 158.2 (d, *J* = 15.3 Hz), 151.0 (d, *J* = 12.1 Hz), 150.7, 136.3 (d, *J* = 12.3 Hz), 135.4, 134.9 (d, *J* = 85.2 Hz), 125.8 (d, *J* = 8.5 Hz), 123.2, 120.7 (q, *J* = 321.0 Hz), 120.2 (d, *J* = 9.9 Hz), 116.7 (d, *J* = 14.3 Hz), 105.7 (d, *J* = 98.9 Hz), 56.0; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.17; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.54; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 551.3, $C_{32}H_{28}N_2O_5P^+$ requires 551.2.

Triphenyl(3–(pyridin–3–ylmethoxy)pyridin–4–yl)phosphonium trifluoromethanesulfonate (13a)



Major

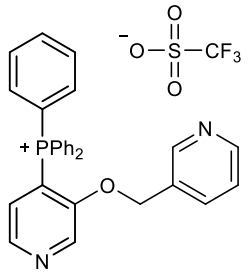


Minor

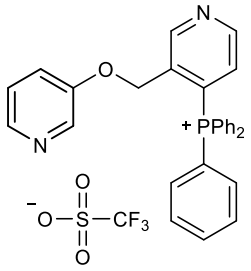
2.9:2.2:2.8 (Major:Minor:mix of 2 phosphonium isomers) Mixture of Isomers

Prepared according to general procedure A (except that ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture) using 3–(pyridin–3–ylmethoxy)pyridine (26 mg, 0.16 mmol), Tf_2O (26 μL, 0.16 mmol), PPh_3 (50 mg, 0.18 mmol), DBU (23 μL, 0.16 mmol), 1,3,5-trimethoxybenzene as an internal standard (27 mg, 0.16 mmol), and CH_2Cl_2 (1.6mL) to afford the title compound (combined ^{1}H NMR yield: 77%). Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (1H, d, J = 6.7 Hz), 8.50 (1H, app t, J = 4.3 Hz), 8.34 (1H, d, J = 2.6 Hz), 7.93-7.36 (16H, m), 7.36-6.88 (3H, m), 5.08 (2H, s); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.36; Other phosphonium isomers isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 23.84, 21.11, 20.90; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 447.2, $C_{29}H_{24}N_2OP^+$ requires 447.2.

Triphenyl(3–(pyridin–3–ylmethoxy)pyridin–4–yl)phosphonium trifluoromethanesulfonate (13b)



Major

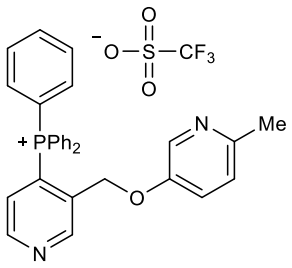


Minor

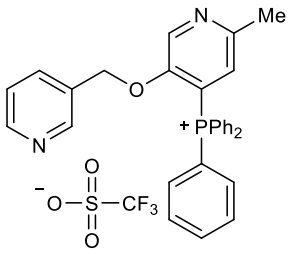
>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure C (except that the phosphine addition and stirring was conducted at –30 ºC instead of –78 ºC) using 3–(pyridin–3–ylmethoxy)pyridine (194 mg, 1.04 mmol), Tf_2O (352 μL, 2.09 mmol), PPh_3 (548 mg, 2.09 mmol), NEt_3 (291 μL, 2.09 mmol) and CH_2Cl_2 (10.4 mL). After the purification procedure, the title compound was isolated as a purple amorphous solid (408 mg, 4.08 mmol, 69% yield); Both isomers, IR ν_{max}/cm^{-1} (film): 3058, 1572, 1543, 1438, 1413, 1260, 1190, 1149,1029; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (1H, app d, *J* = 6.7 Hz), 8.59 (1H, app t, *J* = 4.4 Hz), 8.43 (1H, dd, *J* = 3.5, 1.2 Hz), 7.87–7.55 (16H, m), 7.30–7.28 (1H, m), 7.09 (1H, d, *J* = 4.9 Hz), 7.06 (1H, dd, *J*= 5.1, 4.8 Hz), 5.25 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.6, 149.4, 148.8, 143.7 (d, *J* = 11.0 Hz), 136.9 (d, *J* = 4.4 Hz), 135.9, 135.3 (d, *J* = 3.0 Hz), 133.5 (d, *J* = 10.9 Hz), 130.3 (d, *J* = 13.3 Hz), 129.1, 127.6 (d, *J* = 7.2 Hz), 123.1, 120.5 (q, *J* = 321.1 Hz), 115.9 (d, *J* = 91.5 Hz), 114.6 (d, *J* = 87.0 Hz), 69.3; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.42; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 447.2, $C_{29}H_{24}N_2OP^+$ requires 447.2.

(3–(((6–methylpyridin–3–yl)oxy)methyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (14a)



Major

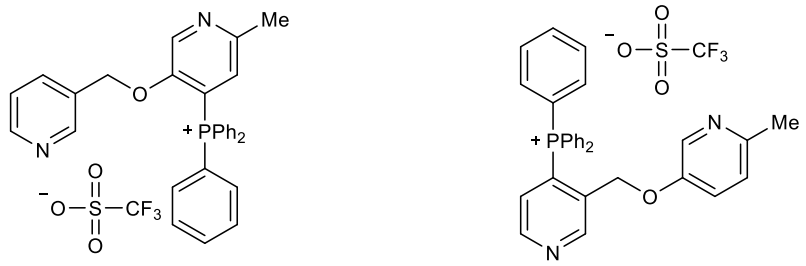


Minor

>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure A using 2–methyl–5–(pyridin–3–ylmethoxy)pyridine (111 mg, 0.55 mmol), Tf_2O (94 μL, 0.55 mmol), PPh_3 (160 mg, 0.61 mmol), DBU (83 μL, 0.55 mmol) and CH_2Cl_2 (5.6 mL). After the purification procedure, the title compound was isolated as a white solid (226 mg, 0.37 mmol, 68% yield). mp 150–160 ºC; Both isomers, IR ν_{max}/cm^{-1} (film):3059, 1586, 1573, 1484, 1438, 1259, 1153, 1105, 1029; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.11 (1H, app d, *J* = 6.4 Hz), 8.92 (1H, app t, *J* = 4.2 Hz), 7.83–7.65 (15H, m), 7.30–7.25 (1H, m), 6.94 (1H, d, *J* = 2.5 Hz), 6.84 (1H, d, *J* =8.6 Hz), 6.46 (1H, dd, *J* = 8.5, 2.5 Hz), 4.74 (2H, s), 2.36 (3H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.7 (d, *J* = 8.1 Hz), 151.9 (d, *J* = 10.8 Hz), 151.5, 150.3, 136.1, 135.7 (d, *J* = 3.1 Hz), 134.9 (d, *J* = 5.1 Hz), 134.2 (d, *J* = 10.2 Hz), 130.6 (d, *J* = 13.0 Hz), 129.2 (d, *J* = 9.7 Hz), 126.1 (d, *J* = 82.0 Hz), 123.4, 120.7 (q, *J* = 320.9 Hz), 120.3, 116.6 (d, *J* = 90.1 Hz), 66.2, 23.2; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.18; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 23.99; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 461.2, $C_{30}H_{26}N_2OP^+$ requires 461.2

(2–methyl–5–(pyridin–3–ylmethoxy)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (14b)

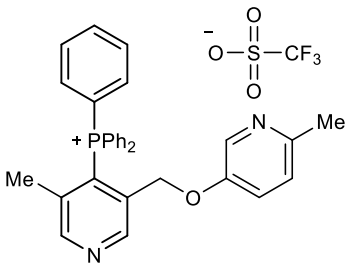


Major Minor

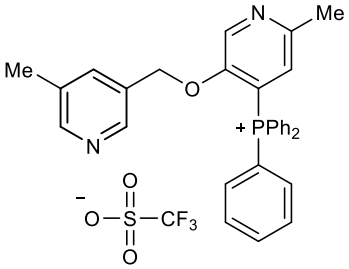
13:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure C (except the phosphine was stirred for 1 hour instead of 30 minutes) using 2–methyl–5–(pyridin–3–ylmethoxy)pyridine (41 mg, 0.21 mmol), Tf_2O (70 μL, 0.41 mmol), PPh_3 (108 mg, 0.41 mmol), *N,N*–dimethylcyclohexylamine (62 μL, 0.41 mmol) and CH_2Cl_2 (2.1 mL). After the purification procedure, the title compound was isolated as a yellow solid (69 mg, 0.11 mmol, 55% yield); Both isomers, IR ν_{max}/cm^{-1} (film): 3058, 1579, 1438, 1351, 1263, 1106, 908; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.77 (1H, app d, *J* = 6.9 Hz), 8.42 (1H, s), 7.86–7.82 (4H, m), 7.73–7.68 (6H, m), 7.58–7.53 (6H, m), 7.24–7.22 (1H, m), 7.08 (1H, dd, *J* = 7.6, 4.8 Hz), 6.82 (1H, d, *J* = 15.1 Hz), 5.18 (2H, s), 2.53 (3H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.3 (d, *J* = 10.9 Hz), 152.7, 149.7, 148.9, 136.1 (d, *J* = 5.0 Hz), 136.0, 135.3 (d, *J* = 3.0 Hz), 133.8 (d, *J* = 10.7 Hz), 130.6 (d, *J* = 13.2 Hz), 129.4, 127.1 (d, *J* = 6.9 Hz), 123.3, 120.8 (q, *J* = 321.4 Hz), 116.2 (d, *J* = 91.4 Hz), 115.3 (d, *J* = 86.4 Hz), 69.5, 23.7; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.13; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.34; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 23.91; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 461.3, $C_{30}H_{26}N_2OP^+$ requires 461.2.

(3–methyl–5–(((6–methylpyridin–3–yl)oxy)methyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (15a)



Major

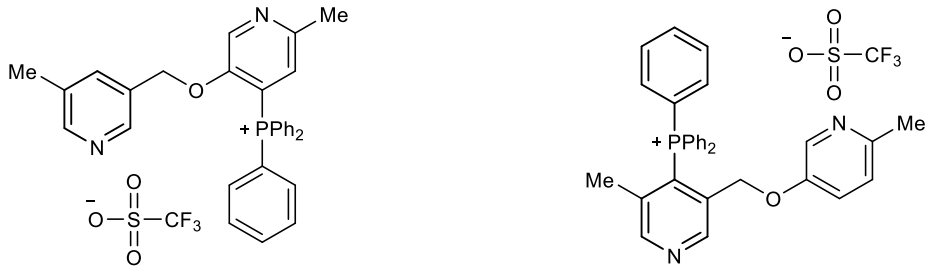


Minor

20:1:2.9 (Major:Minor:Unidentified phosphonium isomers) Mixture of Isomers

Prepared according to general procedure A (except that the Tf_2O stirred for 1 hour and phosphine stirred for 2 hours) using 2–methyl–5–((5–methylpyridin–3–yl)methoxy)pyridine (107 mg, 0.50 mmol), Tf_2O (85 μL, 0.50 mmol), PPh_3 (145 mg, 0.55 mmol), DBU (75 μL, 0.50 mmol) and CH_2Cl_2 (5.0 mL). After the purification procedure, the title compound was isolated as brown oil (169 mg, 0.27 mmol, 54% yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3058, 2958, 2923, 1572, 1482, 1438, 1261, 1030; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.84 (1H, app d, J = 6.1 Hz), 8.74 (1H, app d, J = 6.3 Hz), 7.86–7.60 (15H, m), 7.44 (1H, d, J = 3.0 Hz), 6.89 (1H, d, J = 8.5 Hz), 6.49 (1H, dd, J = 8.5, 3.0 Hz), 4.54 (2H, s), 2.42 (3H, s), 1.85 (3H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.6 (d, J = 8.6 Hz), 152.0 (d, J = 8.4 Hz), 151.1, 150.6, 138.0 (d, J = 7.2 Hz), 136.1, 136.0, 135.2 (d, J = 3.0 Hz), 133.9 (d, J = 10.3 Hz), 130.5 (d, J = 13.1 Hz), 126.7 (d, J = 80.4 Hz), 123.2, 120.6, 120.6 (q, J = 320.9 Hz), 118.1 (d, J = 87.0 Hz), 65.7 (d, J = 4.4 Hz), 23.0, 21.4 (d, J = 5.6 Hz); Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.20; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.56; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.39, 21.30, 16.43; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 475.3, $C_{31}H_{28}N_2OP^+$ requires 475.2.

(2–methyl–5–((5–methylpyridin–3–yl)methoxy)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (15b)

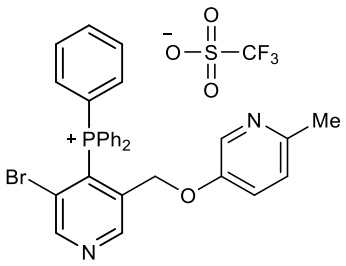


Major Minor

>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure C (except that 3 equivalents of NEt_3 were used instead of 1 equiv) using 2–methyl–5–((5–methylpyridin–3–yl)methoxy)pyridine (107 mg, 0.50 mmol), Tf_2O (169 μL, 1.00 mmol), PPh_3 (262 mg, 1.00 mmol), NEt_3 (209 μL, 1.50 mmol) and CH_2Cl_2 (5.0 mL). After the purification procedure, the title compound was isolated as a brown solid (203 mg, 0.33 mmol, 65% yield). mp 65–75 ºC; Both isomers, IR ν_{max}/cm^{-1} (film): 3058, 3026, 2924, 1584, 1438, 1260, 1149, 1029; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, app d, *J* = 6.9 Hz), 8.26 (1H, s), 7.86–7.55 (16H, m), 6.97 (1H, s), 6.86 (1H, d, *J* = 15.1 Hz), 5.09 (2H, s), 2.54 (3H, s), 2.17 (3H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.3 (d, *J* = 11.1 Hz), 152.7, 150.3, 146.0, 136.2, 136.0 (d, *J* = 5.0 Hz), 135.4 (d, *J* = 3.1 Hz), 133.8 (d, *J* = 10.9 Hz), 132.8, 130.5 (d, *J* = 13.2 Hz), 128.8, 127.2 (d, *J* = 7.2 Hz), 120.7 (q, *J* = 321.7 Hz), 116.3 (d, *J* = 91.3 Hz), 115.3 (d, *J* = 86.6 Hz), 69.4, 23.7, 18.0; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.20; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.28; *m/z* LRMS (ESI + APCI) found $[M – OTf]^+$ 475.2, $C_{31}H_{28}N_2OP^+$ requires 475.2.

(3–bromo–5–(((6–methylpyridin–3–yl)oxy)methyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (16a)

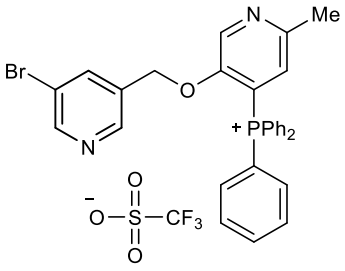


Major

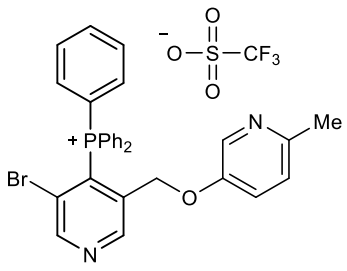
Mixture of Isomers

Prepared according to general procedure A (except that yield was not determined due to a mixture of phosphonium isomers) using 5–((5–bromopyridin–3–yl)methoxy)–2–methylpyridine (33 mg, 0.12 mmol), Tf_2O (20 μL, 0.12 mmol), PPh_3 (34 mg, 0.13 mmol), DBU (18 μL, 0.12 mmol), and CH_2Cl_2 (1.2 mL) to afford the title compound. Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.13; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.26, 21.31, 20.96; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 539.1, $C_{30}H_{25}BrN_2OP^+$ requires 539.1.

(5–((5–bromopyridin–3–yl)methoxy)–2–methylpyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (16b)



Major

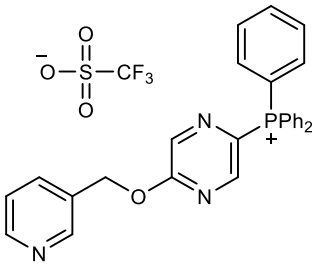


MInor

>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure C using 5–((5–bromopyridin–3–yl)methoxy)–2–methylpyridine (191 mg, 0.68 mmol), Tf_2O (231 μL, 1.37 mmol), PPh_3 (359 mg, 1.37 mmol), NEt_3 (191 μL, 1.37 mmol) and CH_2Cl_2 (6.8 mL). After the purification procedure, the title compound was isolated as a brown solid (261 mg, 0.38 mmol, 56% yield). mp 68–75 ºC; Both isomers, IR ν_{max}/cm^{-1} (film): 3058, 2923, 1585, 1484, 1351, 1260, 1106, 1029; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.77 (1H, app d, *J* = 7.0 Hz), 8.46 (1H, d, *J* = 2.1 Hz), 7.95 (1H, s), 787–7.55 (15H, m), 7.21 (1H, t, *J* = 1.8 Hz), 6.82 (1H, d, *J* = 15.2 Hz), 5.23 (2H, s), 2.53 (3H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.2 (d, *J* = 11.1 Hz), 152.4, 150.5, 147.0, 138.0, 136.2 (d, *J* = 4.8 Hz), 135.4 (d, *J* = 3.0 Hz), 133.6 (d, *J* = 10.8 Hz), 131.3, 130.5 (d, *J* = 13.4 Hz), 126.9 (d, *J* = 7.0 Hz), 120.6 (q, *J* = 321.1 Hz), 120.0, 116.1 (d, *J* = 91.3 Hz), 115.0 (d, *J* = 86.5 Hz), 68.3, 23.6; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.20; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.31; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 539.1, $C_{30}H_{25}BrN_2OP^+$ requires 539.1.

Triphenyl(5–(pyridin–3–ylmethoxy)pyrazin–2–yl)phosphonium trifluoromethanesulfonate (8b)

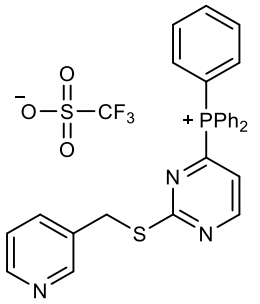


Major

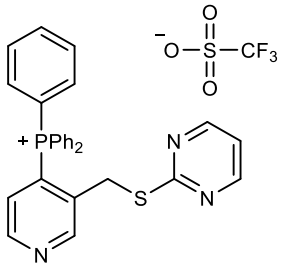
>20:1 (Major:2–position phosphonium isomer) Mixture of Isomers

Prepared according to general procedure C (except that the reaction mixture was warmed to –30 ºC prior to adding PPh_3 and remained at –30 ºC for 30 minutes before cooling down to –78 ºC for NEt_3 addition) using 2–(pyridin–3–ylmethoxy)pyrazine (75 mg, 0.40 mmol), Tf_2O (135 μL, 0.80 mmol), PPh_3 (210 mg, 0.80 mmol), NEt_3 (112 μL, 0.80 mmol) and EtOAc (4.0 mL). After the purification procedure, the title compound was isolated as a white solid (176 mg, 0.29 mmol, 74% combined yield). All isomers, IR ν_{max}/cm^{-1} (film): 3061, 2954, 1553, 1525, 1439, 1260, 1152, 1030, 723, 636; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, dd, *J* = 4.1, 2.4 Hz), 8.58 (1H, m), 8.49 (1H, d, *J* = 3.7 Hz), 8.10 (1H, s), 7.94–7.49 (15H, m), 7.42 (1H, d, *J* = 7.8 Hz), 7.17 (1H, dd, *J* = 7.7, 4.9 Hz), 5.42 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.0 (d, *J* = 17.9 Hz), 149.8 (2C), 147.7 (d, *J* = 3.4 Hz), 139.8 (d, *J* = 15.0 Hz), 136.8, 135.3 (d, *J* = 3.1 Hz), 134.2 (d, *J* = 10.6 Hz), 130.2 (d, *J* = 13.2 Hz), 130.0, 127.0 (d, *J* = 122.0 Hz), 123.4, 120.7 (q, *J* = 321.1 Hz), 116.3 (d, *J* = 90.8 Hz), 67.4; All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.12; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.22; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.91; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 448.2, $C_{28}H_{23}N_3OP^+$ requires 448.2.

1Triphenyl(2–((pyridin–3–ylmethyl)thio)pyrimidin–4–yl)phosphonium trifluoromethanesulfonate (9b)



Major

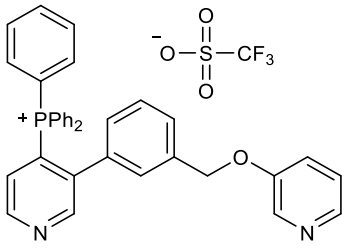


Minor

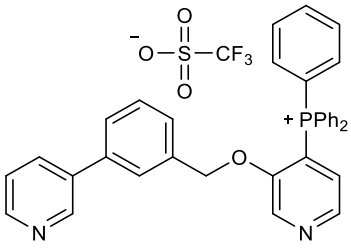
>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure C using 2–((pyridin–3–ylmethyl)thio)pyrimidine (102 mg, 0.50 mmol), Tf_2O (169 μL, 1.00 mmol), PPh_3 (262 mg, 1.00 mmol), NEt_3 (139 μL, 1.00 mmol) and CH_2Cl_2 (5.0 mL). After the purification procedure, the title compound was isolated as a white solid (210 mg, 0.34 mmol, 68% yield). mp 157–163 ºC; Both isomers, IR ν_{max}/cm^{-1} (film): 3061, 2964, 1528, 1438, 1259, 1150, 1109, 1029, 910, 724; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.03 (1H, dd, *J* = 7.6, 4.9 Hz), 8.51–8.35 (2H, m), 7.96–7.83 (3H, m), 7.82–7.58 (14H, m), 7.30–7.19 (1H, m), 4.30 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.7 (d, *J* = 17.6 Hz), 160.5 (d, *J* = 7.4 Hz), 154.6 (d, *J* = 111.6 Hz), 149.5, 148.5, 136.3, 136.1 (d, *J* = 2.9 Hz), 134.6 (d, *J* = 10.3 Hz), 132.3, 130.7 (d, *J* = 13.1 Hz), 123.5, 123.1 (d, *J* = 20.2 Hz), 120.6 (q, *J* = 321.2 Hz), 114.9 (d, *J* = 88.8 Hz), 32.5; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.23; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.61; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.19; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 464.2, $C_{28}H_{23}N_3PS^+$ requires 464.1.

Triphenyl(3–((3–(pyridin–3–yl)benzyl)oxy)pyridin–4–yl)phosphonium trifluoromethanesulfonate (17a)



Major

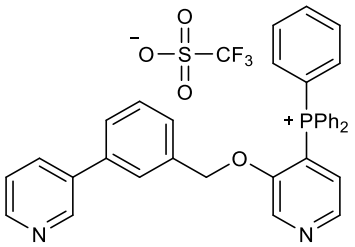


Minor

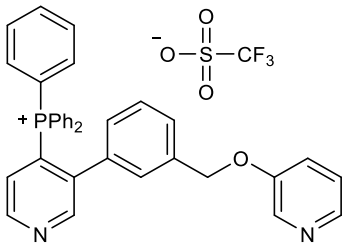
2.2:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure A (except that ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture) using 3–((3–(pyridin–3–yl)benzyl)oxy)pyridine (27 mg, 0.10 mmol), Tf_2O (18 μL, 0.10 mmol), PPh_3 (30 mg, 0.11 mmol), DBU (16 μL, 0.10 mmol), 1,3,5-trimethoxybenzene as an internal standard (19 mg, 0.10 mmol), and CH_2Cl_2 (1 mL) to afford the title compound (combined ^{1}H NMR yield: 67%). Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90-8.79 (1H, m), 8.66-8.46 (3H, m), 8.05-7.12 (19H, m), 7.05 (1H, dd, J = 14.8, 4.7 Hz), 6.90 (1H, s), 6.80 (1H, d, J = 7.5 Hz), 5.17 (2H, s); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.35; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.44; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 523.3, $C_{35}H_{28}N_2OP^+$ requires 523.3.

Triphenyl(3–((3–(pyridin–3–yl)benzyl)oxy)pyridin–4–yl)phosphonium trifluoromethanesulfonate (17b)



Major

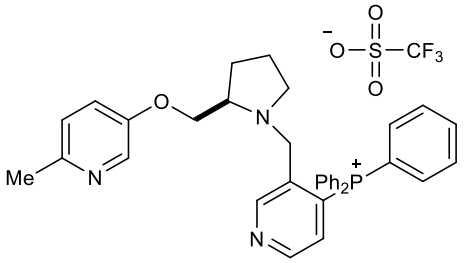


Minor

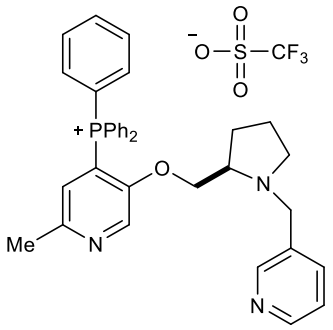
>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure C using 3–((3–(pyridin–3–yl)benzyl)oxy)pyridine (55 mg, 0.21 mmol), Tf_2O (71 μL, 0.42 mmol), PPh_3 (110 mg, 0.42 mmol), NEt_3 (59 μL, 0.42 mmol) and CH_2Cl_2 (2.1 mL). After the purification procedure, the title compound was isolated as a brown oil (115 mg, 0.17 mmol, 82% yield); Both isomers, IR ν_{max}/cm^{-1} (film): 3058, 2923, 1438, 1414, 1261, 1222, 1149, 1107, 1029, 980, 915, 721, 688, 635; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.86 (1H, app d, *J* = 6.7 Hz), 8.62 (1H, dd, *J* = 4.8, 1.4 Hz), 8.57 (1H, app t, *J* = 8.8 Hz), 8.54 (1H, d, *J* = 2.0 Hz), 7.75–7.53 (16H, m), 7.43–7.38 (2H, m), 7.25 (1H, t, *J* = 7.7 Hz), 7.09 (1H, dd, *J* = 14.8, 4.9 Hz), 6.91 (1H, s), 6.84 (1H, d, *J* = 7.6 Hz), 5.22 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.1, 148.7, 147.9, 144.0 (d, *J* = 11.0 Hz), 137.9, 137.0, 137.0, 135.7, 135.4 (d, *J* = 2.9 Hz), 134.4, 133.9 (d, *J* = 10.7 Hz), 130.5 (d, *J* = 13.2 Hz), 129.3, 128.0 (d, *J* = 7.1 Hz), 127.7, 127.3, 126.6, 123.7, 120.9 (q, *J* = 321.2 Hz), 116.2 (d, *J* = 91.4 Hz), 114.9 (d, *J* = 86.9 Hz), 71.9; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.10; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.39; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 523.3, $C_{35}H_{28}N_2OP^+$ requires 523.3.

(3–((2–(((6–methylpyridin–3–yl)oxy)methyl)pyrrolidin–1–yl)methyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (18a)



Major

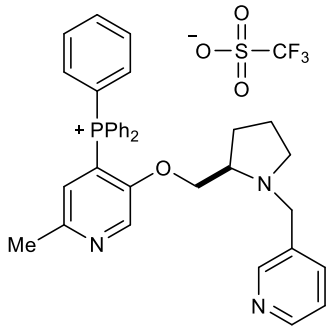


Minor

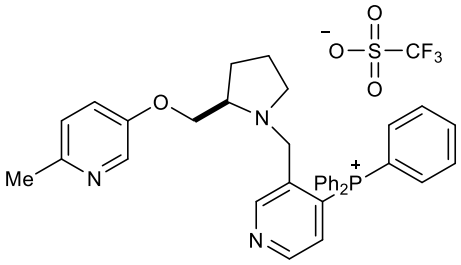
>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure A using 2–methyl–5–((1–(pyridin–3–ylmethyl)pyrrolidin–2–yl)methoxy)pyridine (150 mg, 0.53 mmol), Tf_2O (89 μL, 0.53 mmol), PPh_3 (153 mg, 0.58 mmol), DBU (80 μL, 0.53 mmol) and CH_2Cl_2 (5.3 mL). After the purification procedure, the title compound was isolated as a yellow solid (227 mg, 0.33 mmol, 65% yield). mp 55–61 ºC; Both isomers, IR ν_{max}/cm^{-1} (film): 3060, 2953, 2872, 2815, 1571, 1484, 1438, 1401, 1260, 1151, 1106, 909; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.39 (1H, app d, *J* = 6.7 Hz), 8.81 (1H, app t, *J* = 4.6 Hz), 7.91–7.60 (16H, m), 7.11 (1H, dd, *J* = 15.5, 5.1 Hz), 7.06 (1H, d, *J* = 8.6 Hz), 3.85 (1H, d, *J* = 16.0 Hz), 3.73–3.71 (2H, m), 3.31 (1H, d, *J* = 16.0 Hz), 2.76–2.65 (2H, m) 2,48 (3H, s), 1.88–1.79 (1H, m), 1.74–1.50 (4H, m); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.9 (d, *J* = 7.9 Hz), 152.5, 150.4, 150.0 (d, *J* = 10.5 Hz), 139.0 (d, *J* = 6.2 Hz), 136.6, 135.9 (d, *J* = 2.9 Hz), 133.9 (d, *J* = 10.5 Hz), 130.9, 127.7 (d, *J* = 9.7 Hz), 125.4 (d, *J* = 81.8 Hz), 123.3, 121.4, 120.7 (q, *J* = 321.2 Hz), 116.2 (d, *J* = 88.7 Hz), 71.8, 62.1, 56.3 (d, *J* = 4.8 Hz), 53.7, 27.5, 23.1, 23.1; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.12; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.83; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 544.3, $C_{35}H_{35}N_3OP^+$ requires 544.3; Specific Rotation $[\alpha]_D^{22}$ +50.88 (*c* 1.00, $CHCl_3$).

(2–methyl–5–((1–(pyridin–3–ylmethyl)pyrrolidin–2–yl)methoxy)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (18b)



Major



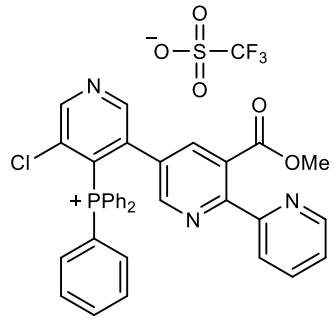
Minor

>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure C using 2–methyl–5–((1–(pyridin–3–ylmethyl)pyrrolidin–2–yl)methoxy)pyridine (147.0 mg, 0.52 mmol), Tf_2O (175 μL, 1.04 mmol), PPh_3 (272.1 mg, 1.04 mmol), Et_3N (145 μL, 1.04 mmol) and CH_2Cl_2 (5.2 mL). After the purification procedure, the title compound was isolated as a brown solid (193.9 mg, 0.28 mmol, 54% yield). mp 70–78 ºC; Both isomers, IR ν_{max}/cm^{-1} (film): 3061, 2987, 2881, 1439, 1260, 1155, 1107, 1030, 907, 723, 636; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.62 (1H, app d, *J* = 6.4 Hz), 8.47–8.46 (2H, m), 7.78–7.70 (11H, m), 7.62–7.56 (7H, m), 7.23 (1H, dd, *J* = 7.7, 4.9 Hz), 6.73 (1H, d, *J* = 15.3 Hz), 4.36 (1H, bs), 3.88 (1H, t, *J* = 7.3 Hz), 3.70 (1H, d, *J* = 12.4 Hz), 3.41 (1H, s), 2.85 (1H, s), 2.46 (5H, m), 1.54 (3H, m), 1.06 (1H, m) ; Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.3 (d, *J* = 11.0 Hz), 153.2, 149.7, 148.5, 136.4, 135.9 (d, *J* = 5.1 Hz), 135.7 (d, *J* = 3.0 Hz), 133.8 (d, *J* = 10.8 Hz), 130.7 (d, *J* = 13.2 Hz), 129.9, 127.5 (d, *J* = 7.1 Hz), 123.3, 120.8 (q, *J* = 321.3 Hz), 116.5 (d, *J* = 91.0 Hz), 115.0 (d, *J* = 86.5 Hz), 72.9, 61.7, 56.9, 54.1, 28.0, 23.7, 22.8; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; Major isomer, ^{31}P NMR

(162 MHz, $CDCl_3$) δ: 21.42; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 544.3, $C_{35}H_{35}N_3OP^+$ requires 544.3; Specific Rotation $[\alpha]_D^{22}$ +10.26 (*c* 0.85, $CHCl_3$).

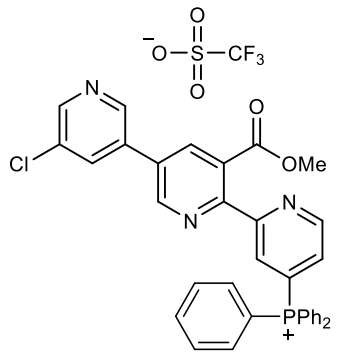
(5''–chloro–3'–(methoxycarbonyl)–[2,2':5',3''–terpyridin]–4''–yl)triphenylphosphonium trifluoromethanesulfonate (19a)



Major

10:3.1:1 (Major:Bis-phosphonium isomer:Unidentified phosphonium isomer) Mixture of Isomers Prepared according to general procedure A (except that ^1H NMR and ^{31}P NMR were run on the crude reaction mixture) using methyl–5''–chloro–[2,2':5',3''–terpyridine]–3'–carboxylate (16 mg, 0.05 mmol), Tf_2O (9 μL, 0.05 mmol), PPh_3 (14 mg, 0.06 mmol), DBU (8 μL, 0.05 mmol), 1,3,5-trimethoxybenzene as an internal standard (17 mg, 0.10 mmol), and CH_2Cl_2 (0.5 mL) to afford the title compound (combined ^1H NMR yield: 83%). Major isomer ^1H NMR (400 MHz, $CDCl_3$) δ: 8.93 (1H, d, *J* = 5.4 Hz), 8.70-8.55 (2H, m), 8.26 (1H, d, *J* = 2.0 Hz), 8.02-7.50 (18H, m), 7.40-7.30 (1H, m), 3.70 (3H, s); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.82; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.71, 22.60, 20.71, 21.67; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 586.2, $C_{35}H_{26}ClN_3O_2P^+$ requires 586.2.

(5''–chloro–3'–(methoxycarbonyl)–[2,2':5',3''–terpyridin]–4–yl)triphenylphosphonium trifluoromethanesulfonate (19b)



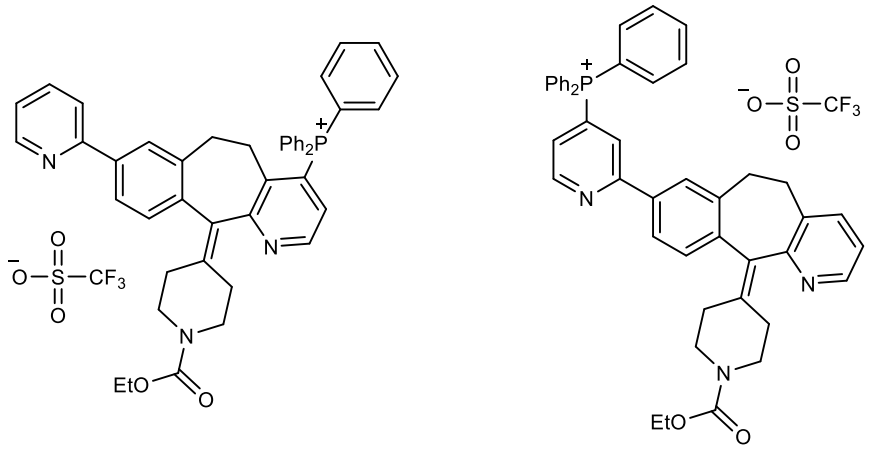
Major

>20:1 (Major:Unidentified phosphonium isomer) Mixture of Isomers

Prepared according to general procedure C (except that the reaction mixture was warmed to –50 ºC prior to adding PPh_3 and remained at –50 ºC for 1 hour before cooling down to –78 ºC for NEt_3 addition) using methyl–5''–chloro–[2,2':5',3''–terpyridine]–3'–carboxylate (65 mg, 0.20 mmol), Tf_2O (68 μL, 0.40 mmol), PPh_3 (105 mg, 0.40 mmol), NEt_3 (56 μL, 0.40 mmol) and CH_2Cl_2 (2.0 mL). After the purification procedure, the title compound was isolated as a yellow solid (132 mg, 0.18 mmol, 89% combined yield). All isomers, IR ν_{max}/cm^{-1} (film): 3059, 2951, 1728, 1439, 1259, 1107, 1030, 909, 724, 646; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.07 (1H, app t, J = 4.8 Hz), 8.88 (1H, s), 8.76 (1H, s), 8.66 (1H, s), 8.42 (1H, d, J = 13.6 Hz), 8.16 (1H, d, J = 2.2 Hz), 8.07–7.61 (17H, m), 3.90 (3H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.0, 156.9 (d, J = 10.6 Hz), 152.3 (d, J = 2.0 Hz), 150.7 (d, J = 10.3 Hz), 148.7, 148.4, 145.5, 136.2 (d, J = 2.9 Hz), 135.4, 134.4 (d , J = 10.5 Hz), 134.0, 132.8, 132.5, 132.3, 131.0 (d, J = 13.0 Hz), 129.5 (d, J = 84.2 Hz), 129.1, 127.4 (d, J = 8.4 Hz), 125.7 (d, J = 9.3 Hz), 120.7 (q, J = 321.4 Hz), 115.5 (d, J = 89.8 Hz), 52.9; All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; Major isomer, ^{31}P NMR

(162 MHz, $CDCl_3$) δ: 22.66; Other phosphonium isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.68; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 586.2, $C_{35}H_{26}ClN_3O_2P^+$ requires 586.2.

(2–(11–(1–(ethoxycarbonyl)piperidin–4–ylidene)–6,11–dihydro–5H–benzo[5,6]cyclohepta[1,2–b]pyridin–8–yl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (20a)

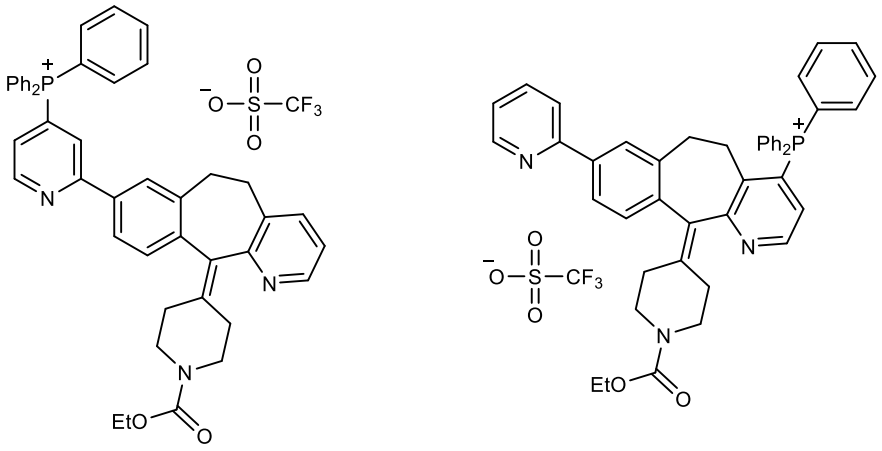


10:3.1:1 (Major:Bis-phosphonium isomer:Minor) Mixture of Isomers

Prepared according to general procedure A (except that ^1H NMR and ^{31}P NMR were run on the crude reaction mixture) using ethyl 4–(8–(pyridin–2–yl)–5,6–dihydro–11H–benzo[5,6]cyclohepta[1,2–b]pyridin–11–ylidene)piperidine–1–carboxylate (21 mg, 0.05 mmol), Tf_2O (9 μL, 0.05 mmol), PPh_3 (14 mg, 0.06 mmol), DBU (8 μL, 0.05 mmol), 1,3,5-trimethoxybenzene as an internal standard (17 mg, 0.10 mmol), and CH_2Cl_2 (0.5 mL) to afford the title compound (combined ^1H NMR yield: 89%). Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.72 (1H, app t, J = 4.8 Hz), 8.66-8.57 (1H, m), 8.01-7.33 (19H, m), 7.33-7.15 (2H, m), 7.02 (1H, dd, J = 14.8, 5.2 Hz), 4.20-4.02 (2H, m), 3.91-3.60 (2H, m), 3.42-3.20 (3H, m), 3.00-2.79 (1H, m), 2.65-2.05 (5H, m), 1.78-1.54 (1H, m) 1.36-1.07 (3H, m); Major isomer, ^{31}P NMR (162 MHz,

$CDCl_3$) δ: 21.24; Other phosphonium isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.79, 22.77, 21.13; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 686.4, $C_{45}H_{41}N_3O_2P^+$ requires 686.3.

(11–(1–(ethoxycarbonyl)piperidin–4–ylidene)–8–(pyridin–2–yl)–6,11–dihydro–5H–benzo[5,6]cyclohepta[1,2–b]pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (20b)

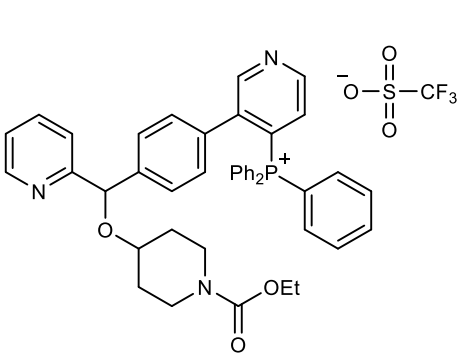


>20:1 (Major:Minor) Mixture of Isomers

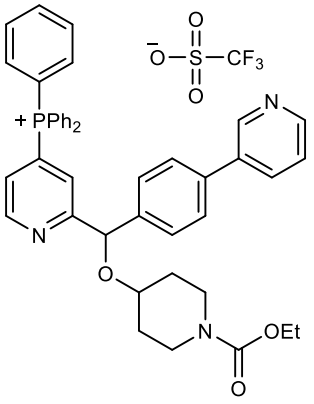
Prepared according to general procedure C using ethyl 4–(8–(pyridin–2–yl)–5,6–dihydro–11H–benzo[5,6]cyclohepta[1,2–b]pyridin–11–ylidene)piperidine–1–carboxylate (213 mg, 0.50 mmol), Tf_2O (169 μL, 1.00 mmol), PPh_3 (262 mg, 1.00 mmol), NEt_3 (139 μL, 1.00 mmol) and CH_2Cl_2 (5.0 mL). After the purification procedure, the title compound was isolated as a white solid (301 mg, 0.36 mmol, 72% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3060, 2982, 2910, 2868, 1686, 1437, 1260, 1223, 1109, 1030, 909, 724, 646; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.07 (1H, app t, *J* = 4.9 Hz), 8.39 (1H, dd, *J* = 5.0, 1.4 Hz), 7.98–7.89 (3H, m), 7.86 (1H, d, *J* = 1.5 Hz), 7.85–7.76 (7H, m), 7.75–7.65 (6H, m), 7.59 (1H, dd, *J* = 7.9, 1.8 Hz), 7.54–7.44 (2H, m), 7.29 (1H, d, *J* = 8.0 Hz), 7.11 (1H, dd, *J* = 7.7, 4.8 Hz), 4.13 (2H, q, *J* = 7.1 Hz), 3.94–3.69

(2H, m), 3.57–3.30 (2H, m), 3.23–3.03 (2H, m), 3.03–2.82 (2H, m), 2.61–2.24 (4H, m), 1.24 (3H, t, J = 7.1 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.0 (d, J = 10.3 Hz), 151.7 (d, J = 11.2 Hz), 156.4, 155.4, 146.2, 141.7, 139.0, 138.0, 137.9, 136.2 (d, J = 2.9 Hz), 136.1 (d, J = 1.5 Hz), 134.5 (d, J = 10.7 Hz), 134.2, 133.8, 131.0 (d, J = 13.1 Hz), 129.9, 129.3 (d, J = 83.6 Hz), 125.2 (d, J = 8.4 Hz), 124.7, 123.2 (d, J = 8.8 Hz), 122.4, 120.8 (q, J = 320.8 Hz), 115.7 (d, J = 89.2 Hz), 61.2, 44.7, 31.7, 31.5, 30.7, 30.5, 14.6; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.79; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.17; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 686.3, $C_{45}H_{41}N_3O_2P^+$ requires 686.3.

(3–(4–(((1–(ethoxycarbonyl)piperidin–4–yl)oxy)(pyridin–2–yl)methyl)phenyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (7a)



Major



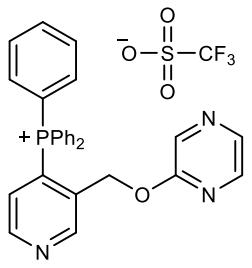
Minor

>20:1 (Major:Minor) Mixture of Isomers

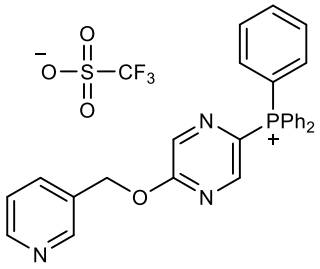
Prepared according to general procedure D (except that Tf_2O was added at –50 ºC and stirred for 1 hour instead of at –78 ºC for 1 hour) using ethyl 4–(pyridin–2–yl(4–(pyridin–3–yl)phenyl)methoxy)piperidine–1–carboxylate (104 mg, 0.25 mmol), Tf_2O (42 μL, 0.25 mmol), PPh_3 (66 mg, 0.25 mmol), DBU (37 μL, 0.25 mmol) and CH_2Cl_2 (2.5 mL). After the purification

procedure, the title compound was isolated as a light yellow solid (167 mg, 0.20 mmol, 81% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3062, 2929, 2856, 1685, 1436, 1261, 1153, 1099, 1029, 909, 724, 635; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.94 (1H, app t, *J* = 4.6 Hz), 8.72 (1H, d, *J* = 6.8 Hz), 8.58 (1H, d, *J* = 4.3 Hz), 7.93–7.17 (19H, m), 7.03 (2H, d, *J* = 8.2 Hz), 6.69 (2H, d, *J* = 8.2 Hz), 5.47 (1H, s), 4.10 (2H, q, *J* = 7.1 Hz), 3.82–3.64 (2H, m), 3.60–3.84 (1H, m), 3.27–3.07 (2H, m), 1.93–1.48 (4H, m), 1.23 (3H, t, *J* = 7.1 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.1, 155.2, 153.6 (d, *J* = 10.2 Hz), 149.8 (d, *J* = 10.2 Hz), 148.7, 142.1, 141.3 (d, *J* = 7.0 Hz), 137.0, 135.2 (d, *J* = 2.7 Hz), 134.0 (d, *J* = 10.2 Hz), 133.6 (d, *J* = 3.9 Hz), 130.3 (d, *J* = 13.0 Hz), 129.1, 128.1 (d, *J* = 9.6 Hz), 126.2, 126.1 (d, *J* = 83.2 Hz), 122.7, 120.7 (q, *J* = 321.2 Hz), 120.6, 116.6 (d, *J* = 89.0 Hz), 80.6, 72.4, 61.0, 40.7, 30.7 (d, *J* = 38.0 Hz), 14.4; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.11; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.45; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.49; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 678.3, $C_{43}H_{41}N_3O_3P^+$ requires 678.3.

Triphenyl(3–((pyrazin–2–yloxy)methyl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (8a)



Major

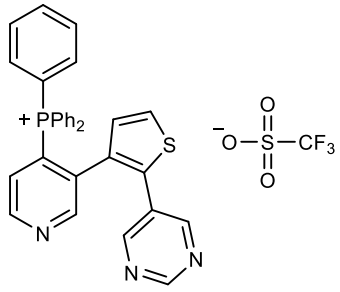


Minor

18.5:1:1:1 (Major:2–position phosphonium isomer:Minor:Unidentified phosphonium isomer) Mixture of Isomers

Prepared according to general procedure D using 2–(pyridin–3–ylmethoxy)pyrazine (94 mg, 0.50 mmol), Tf_2O (85 μL, 0.50 mmol), PPh_3 (131 mg, 0.50 mmol), DBU (75 μL, 0.50 mmol) and CH_2Cl_2 (5.0 mL). After the purification procedure, the title compound was isolated as a white solid (249 mg, 0.42 mmol, 83% combined yield). All isomers, IR ν_{max}/cm^{-1} (film): 3063, 2903, 1585, 1484, 1259, 1152, 1030, 908, 722; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.09 (1H, app d, *J* = 6.6 Hz), 8.96 (1H, app t, *J* = 4.6 Hz), 8.08 (1H, d, *J* = 2.7 Hz), 7.91–7.58 (16H, m), 7.39 (1H, d, *J* = 1.2 Hz), 7.33 (1H, dd, *J* = 15.7, 5.1 Hz), 4.96 (2H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.4, 152.8 (d, *J* = 7.8 Hz), 151.9, (d, *J* = 10.6 Hz), 140.3, 137.7, 135.9 (d, *J* = 2.9 Hz), 134.6, 134.4 (d, *J* = 5.8 Hz), 134.2 (d, *J* = 10.6 Hz), 130.7 (d, *J* = 13.1 Hz), 129.0 (d, *J* = 9.4 Hz), 126.5 (d, *J* = 81.5 Hz), 120.7 (q, *J* = 321.1 Hz), 116.1 (d, *J* = 89.2 Hz), 63.6 (d, *J* = 4.0 Hz); All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.16; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.70; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.33, 21.01, 16.64; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 448.3, $C_{28}H_{23}N_3OP^+$ requires 448.2.

Triphenyl(3–(2–(pyrimidin–5–yl)thiophen–3–yl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (10a)

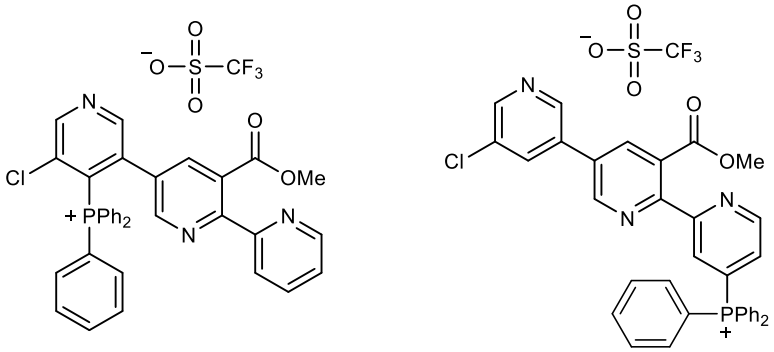


Major

17.3:1:1 (Major:Unidentified phosphonium isomer:2-position phosphonium isomer) Mixture of Isomers

Prepared according to general procedure D using 5–(3–(pyridin–3–yl)thiophen–2–yl)pyrimidine (24 mg, 0.10 mmol), Tf_2O (17 μL, 0.10 mmol), PPh_3 (27 mg, 0.10 mmol), DBU (15 μL, 0.10 mmol) and CH_2Cl_2 (1.0 mL). After the purification procedure, the title compound was isolated as a yellow solid (50 mg, 0.077 mmol, 77% combined yield). All isomers, IR ν_{max}/cm^{-1} (film): 3064, 2957, 2852, 1438, 1262, 1153, 1104, 1030, 721; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.19–8.91 (2H, m), 8.81 (1H, d, *J* = 6.7 Hz), 8.19 (2H, br s), 7.97–7.39 (16H, m), 7.15 (1H, d, *J* = 5.0 Hz), 6.74 (1H, d, *J* = 5.0 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.3, 154.2 (d, *J* = 6.5 Hz), 154.7 (2C), 150.6 (d, *J* = 10.0 Hz), 136.2 (d, *J* = 5.7 Hz), 135.7 (d, *J* = 2.9 Hz), 134.4, 134.1 (d, *J* = 10.3 Hz), 132.7 (d, *J* = 4.2 Hz), 131.9, 130.7 (d, *J* = 13.0 Hz), 129.1 (d, *J* = 8.7 Hz), 127.9, 127.2 (d, *J* = 82.7 Hz), 120.8 (q, *J* = 321.2 Hz), 116.0 (d, *J* = 88.7 Hz); All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.14; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.79; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 23.32, 15.38; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 500.1, $C_{31}H_{23}N_3PS^+$ requires 500.1.

(5''–chloro–3'–(methoxycarbonyl)–[2,2':5',3''–terpyridin]–4''–yl)triphenylphosphonium trifluoromethanesulfonate (19a)

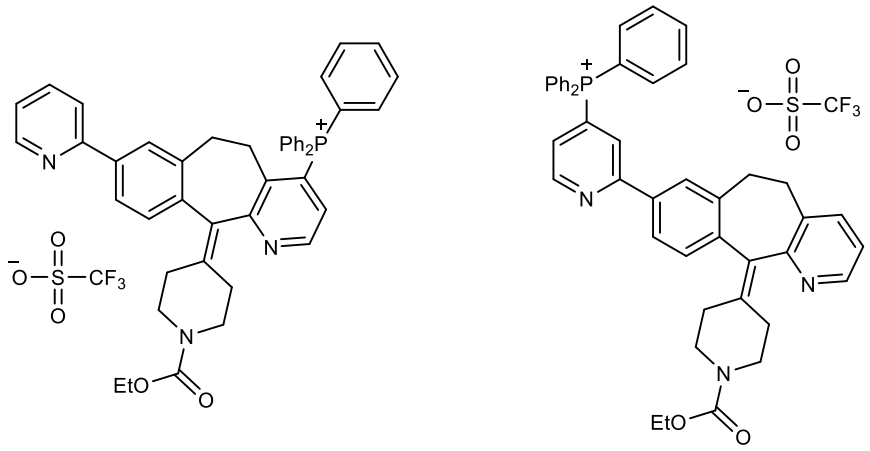


Major Minor

>20:1 (Major:Unidentified phosphonium isomer) Mixture of Isomers

Prepared according to general procedure D using methyl–5"–chloro–[2,2':5',3"–terpyridine]–3'–carboxylate (65 mg, 0.20 mmol), Tf_2O (34 μL, 0.20 mmol), PPh_3 (52 mg, 0.20 mmol), DBU (30 μL, 0.20 mmol) and CH_2Cl_2 (2.0 mL). After the purification procedure, the title compound was isolated as a tan solid (137 mg, 0.19 mmol, 93% combined yield). All isomers, IR ν_{max}/cm^{-1} (film): 3062, 2986, 1728, 1438, 1263, 1152, 1030, 912, 720, 636; Major isomer ^1H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, d, *J* = 4.5 Hz), 8.70 (1H, d, *J* = 3.1 Hz), 8.61 (1H, s), 8.28 (1H, s), 8.06–7.46 (18H, m), 7.40–7.29 (1H, m), 3.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.6, 155.3 (d, *J* = 2.2 Hz), 154.7, 152.4 (d, *J* = 7.2 Hz), 151.9 (d, *J* = 4.8 Hz), 149.6, 148.6, 140.7 (d, *J* = 5.7 Hz), 136.9 (d, *J* = 10.9 Hz), 136.8, 136.1 (d, *J* = 2.3 Hz), 135.4 (d, *J* = 2.7 Hz), 134.0 (d, *J* = 10.6 Hz), 130.7 (d, *J* = 13.6 Hz), 130.0, 127.5, 125.5 (d, *J* = 88.0 Hz), 124.1, 122.6, 120.8 (q, *J* = 321.4 Hz), 116.9 (d, *J* = 89.1 Hz), 52.3; All isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.17; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.78; Other phosphonium isomers, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.65; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 586.2, $C_{35}H_{26}ClN_3O_2P^+$ requires 586.2.

(2–(11–(1–(ethoxycarbonyl)piperidin–4–ylidene)–6,11–dihydro–5H–benzo[5,6]cyclohepta[1,2–b]pyridin–8–yl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (20a)

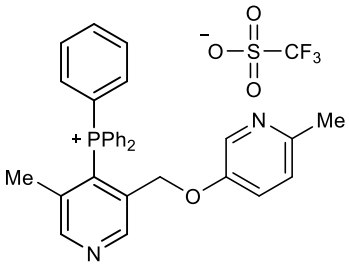


>20:1 (Major:Minor) Mixture of Isomers

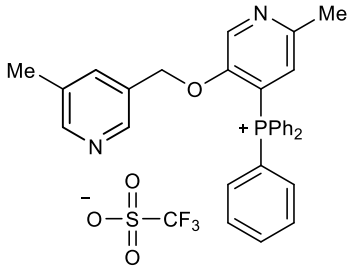
Prepared according to general procedure D using ethyl 4–(8–(pyridin–2–yl)–5,6–dihydro–11H–benzo[5,6]cyclohepta[1,2–b]pyridin–11–ylidene)piperidine–1–carboxylate (86 mg, 0.20 mmol), Tf_2O (34 μL, 0.20 mmol), PPh_3 (59 mg, 0.20 mmol), DBU (30 μL, 0.20 mmol) and CH_2Cl_2 (2.0 mL). After the purification procedure, the title compound was isolated as a yellow solid (123 mg, 0.15 mmol, 74% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3089, 2980, 1689, 1578, 1437, 1261, 1222, 1108, 1029, 726, 634; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.75 (1H, app t, *J* = 4.5 Hz), 8.67 (1H, d, *J* = 3.3 Hz), 8.06–7.56 (18H, m), 7.44 (1H, s), 7.35–7.17 (2H, m), 7.05 (1H, dd, *J* = 14.9, 5.1 Hz), 4.16 (2H, q, *J* = 7.0 Hz), 3.90–3.62 (2H, m), 3.54–3.24 (3H, m), 3.03–2.81 (1H, m), 2.74–2.35 (4H, m), 2.32–2.07 (1H, m), 1.91–1.67 (1H, m), 1.28 (3H, t, *J* = 7.0 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8 (d, *J* = 8.5 Hz), 156.2, 155.4, 149.4, 149.0 (d, *J* = 11.5 Hz), 139.1–138.7 (2C), 137.2 (d, *J* = 7.1 Hz), 136.1 (d, *J* = 2.1 Hz), 135.4, 134.2 (d, *J* = 10.5 Hz), 133.2 (d, *J* = 2.1 Hz), 131.1 (d, *J* = 13.0 Hz), 130.8, 128.6, 126.8 (d, *J* =

81.4 Hz), 127.1 (d, J = 9.8 Hz), 124.7, 122.4, 120.8 (q, J = 321.3 Hz), 120.5, 116.5 (d, J = 88.8 Hz), 61.4, 44.7, 44.8, 30.8, 30.8, 30.5, 29.8, 14.6; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.13; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.24; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.72; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 686.4, $C_{45}H_{41}N_3O_2P^+$ requires 686.3.

(3–methyl–5–(((6–methylpyridin–3–yl)oxy)methyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (15a)



Major

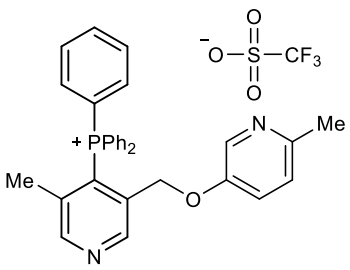


Minor

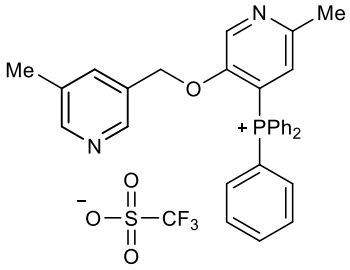
1:1.5:2 (Mixure of 2 phosphonium isomers:Major:Minor) Mixture of Isomers

Prepared according to general procedure A (except that ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture and that Tf_2O stirred for 15 minutes instead of 30 minutes) using 2–methyl–5–((5–methylpyridin–3–yl)methoxy)pyridine (22 mg, 0.10 mmol), Tf_2O (17 μL, 0.10 mmol), PPh_3 (29 mg, 0.11 mmol), DBU (15 μL, 0.10 mmol), 1,3,5-trimethoxybenzene as an internal standard (17 mg, 0.10 mmol), and CH_2Cl_2 (0.5 mL) to afford the title compound (combined ^{1}H NMR yield: 44%). Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.84 (1H, d, J = 6.0 Hz), 8.79-8.72 (1H, m), 7.94-7.33 (17H, m), 7.12-7.03 (1H, m), 6.86-6.76 (1H, m), 4.63 (1H, s), 2.22 (3H, s), 1.86 (3H, s); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.53; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.86, 21.33, 16.43; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 475.3, $C_{31}H_{28}N_2OP^+$ requires 475.2.

(3–methyl–5–(((6–methylpyridin–3–yl)oxy)methyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (15a)



Major

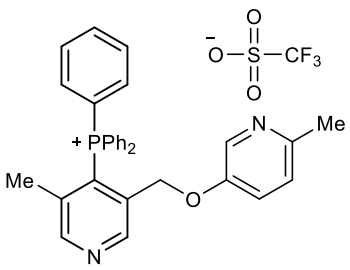


Minor

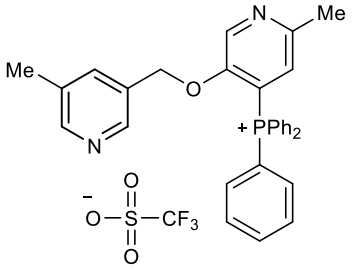
3.3:1:1 (Major:Minor:Mixture of 2 phosphonium isomers) Mixture of Isomers

Prepared according to general procedure A (except that ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture) using 2–methyl–5–((5–methylpyridin–3–yl)methoxy)pyridine (22 mg, 0.10 mmol), Tf_2O (17 μL, 0.10 mmol), PPh_3 (29 mg, 0.11 mmol), DBU (15 μL, 0.10 mmol), 1,3,5-trimethoxybenzene as an internal standard (17 mg, 0.10 mmol), and CH_2Cl_2 (0.5 mL) to afford the title compound (combined ^{1}H NMR yield: 52%). Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, d, *J* = 6.0 Hz), 8.75 (1H, d, *J* = 6.2 Hz), 7.88-7.37 (16H, m), 7.03-6.92 (1H, m), 6.59 (1H, dd, *J* = 8.7, 3.0 Hz), 4.49 (2H, s), 2.43 (3H, s), 1.85 (3H, s); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.57; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.96, 21.29, 16.41; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 475.3, $C_{31}H_{28}N_2OP^+$ requires 475.2.

(3–methyl–5–(((6–methylpyridin–3–yl)oxy)methyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (15b)



Major

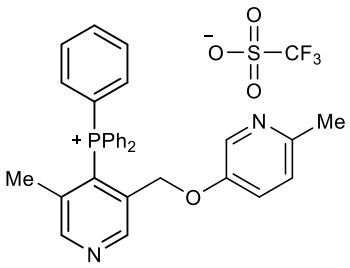


Minor

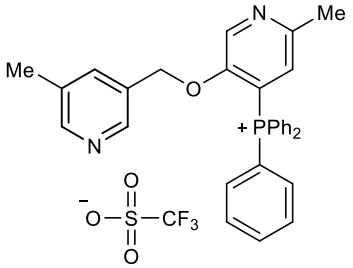
20:1:2.9 (Major:Minor:Mixture of 2 phosphonium isomers) Mixture of Isomers

Prepared according to general procedure A (except that ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture that Tf_2O stirred for 60 minutes instead of 30 minutes) using 2–methyl–5–((5–methylpyridin–3–yl)methoxy)pyridine (22 mg, 0.10 mmol), Tf_2O (17 μL, 0.10 mmol), PPh_3 (29 mg, 0.11 mmol), DBU (15 μL, 0.10 mmol), 1,3,5-trimethoxybenzene as an internal standard (17 mg, 0.10 mmol), and CH_2Cl_2 (0.5 mL) to afford the title compound (combined ^{1}H NMR yield: 72%). Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, d, J = 6.0 Hz), 8.74 (1H, d, J = 6.2 Hz), 7.92-7.33 (16H, m), 6.88 (1H, d, J = 8.6 Hz), 6.44 (1H, dd, J = 8.6, 3.0 Hz), 4.45 (2H, s), 2.40 (3H, s), 1.85 (3H, s); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.58; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.90, 21.28, 16.42; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 475.3, $C_{31}H_{28}N_2OP^+$ requires 475.2.

(3–methyl–5–(((6–methylpyridin–3–yl)oxy)methyl)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (15b)



Major

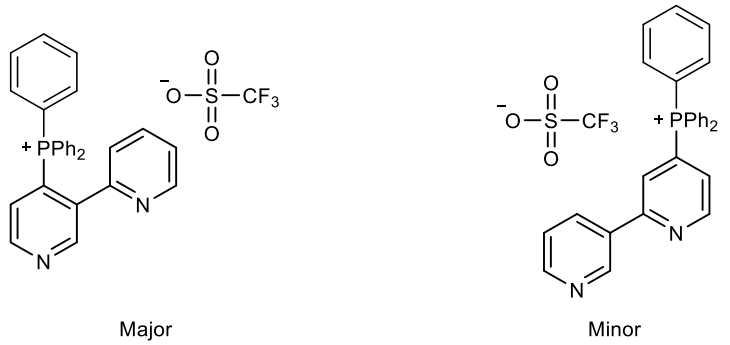


Minor

4.3:1:1.1 (Major:Minor:Mixture of 2 phosphonium isomers) Mixture of Isomers

Prepared according to general procedure D (except that ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture) using 2–methyl–5–((5–methylpyridin–3–yl)methoxy)pyridine (50 mg, 0.23 mmol), Tf_2O (39 μL, 0.23 mmol), PPh_3 (60 mg, 0.23 mmol), DBU (35 μL, 0.23 mmol), 1,3,5-trimethoxybenzene as an internal standard (39 mg, 0.23 mmol), and CH_2Cl_2 (2.3 mL) to afford the title compound (combined ^{1}H NMR yield: 52%). Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (1H, d, *J* = 6.0 Hz), 8.70 (1H, d, *J* = 6.2 Hz), 8.08-7.17 (16H, m), 7.06-7.00 (1H, m), 6.47-6.35 (1H, m), 4.41 (2H, s), 2.31 (3H, s), 1.81 (3H, s); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.57; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.81, 21.27, 16.39; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 475.3, $C_{31}H_{28}N_2OP^+$ requires 475.2.

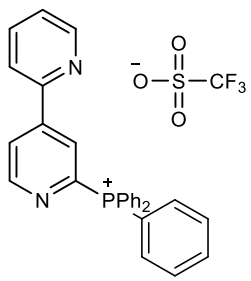
[2,3'–bipyridin]–4'–yltriphenylphosphonium trifluoromethanesulfonate (21a)



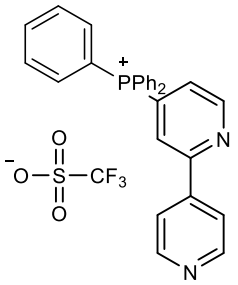
>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure A using 2,3'–bipyridine (156 mg, 1.00 mmol), Tf_2O (169 μL, 1.00 mmol), PPh_3 (288 mg, 1.10 mmol), DBU (150 μL, 1.00 mmol) and CH_2Cl_2 (10 mL). After the purification procedure, the title compound was isolated as a white amorphous solid (542 mg, 0.96 mmol, 96% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3072, 3029, 1591, 1438, 1275, 1257, 1223, 1166, 1109, 1029, 739, 659, 569; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.60 (1H, d, *J* = 6.6 Hz), 8.94 (1H, app t, *J* = 4.8 Hz), 8.06 (1H, d, *J* = 8.1 Hz), 7.85–7.46 (17H, m), 7.21 (1H, dd, *J* = 15.9, 5.1 Hz), 7.04 (1H, dd, *J* = 7.6, 5.1 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.8 (d, *J* = 11.6 Hz), 150.0 (d, *J* = 6.6 Hz), 148.3, 146.4, 138.5, 136.3, 134.2 (d, *J* = 2.9 Hz), 132.9 (d, *J* = 9.7 Hz), 131.2 (d, *J* = 10.8 Hz), 130.1 (d, *J* = 13.3 Hz), 125.3 (d, *J* = 91.6 Hz), 125.0, 122.1 (d, *J* = 95.9 Hz), 121.4, 120.9 (q, *J* = 321.2 Hz); Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.05; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 26.26; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 417.2, $C_{28}H_{22}N_2P^+$ requires 417.2.

[2,4'–bipyridin]–2'–yltriphenylphosphonium trifluoromethanesulfonate (22a)



Major

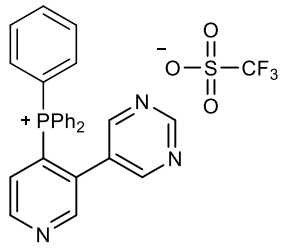


Minor

>20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure D using 2,4'–bipyridine (39 mg, 0.25 mmol), Tf_2O (42 μL, 0.25 mmol), PPh_3 (66 mg, 0.25 mmol), DBU (37 μL, 0.25 mmol) and EtOAc (2.5 mL). After the purification procedure, the title compound was isolated as a grey amorphous solid (83 mg, 0.17 mmol, 59% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3064, 1583, 1437, 1261, 1150, 1030, 723, 634; Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.12 (1H, d, *J* = 4.9 Hz), 8.68–8.62 (1H, m), 8.49–8.36 (2H, m), 8.08 (1H, d, *J* = 8.0 Hz), 7.97–7.85 (4H, m), 7.84–7.68 (12H, m), 7.37 (1H, ddd, *J* = 7.7, 4.8, 1.0 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.2 (d, *J* = 20.2 Hz), 151.6 (d, *J* = 2.0 Hz), 150.1, 148.6 (d, *J* = 10.8 Hz), 145.2 (d, *J* = 120.6 Hz), 137.9, 135.7 (d, *J* = 2.9 Hz), 134.5 (d, *J* = 10.1 Hz), 130.5 (d, *J* = 13.0 Hz), 128.7 (d, *J* = 25.8 Hz), 125.4 (d, *J* = 3.4 Hz), 125.0, 120.8 (q, *J* = 321.1 Hz), 116.9 (d, *J* = 89.0 Hz); Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.09; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.79; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 417.2, $C_{28}H_{22}N_2P^+$ requires 417.2.

Triphenyl(3–(pyrimidin–5–yl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (23a)

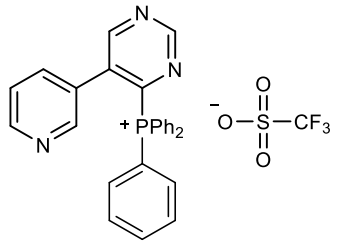


Major

>20:1 (Major:2-position phosphonium isomer) Mixture of Isomers

Prepared according to general procedure D using 5–(pyridin–3–yl)pyrimidine (157 mg, 1.00 mmol), Tf_2O (169 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 yellow amorphous solid (410 mg, 0.72 mmol, 72% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3061, 1551, 1439, 1261, 1149, 1102, 1029, 720, 636; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.07 (1H, dd, *J* = 5.2, 4.2 Hz), 8.88 (1H, s), 8.73 (1H, d, *J* = 6.8 Hz), 8.21 (2H, s), 7.89–7.79 (3H, m), 7.83–7.65 (12H, m), 7.59 (1H, dd, *J* = 15.2, 5.0 Hz); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.0, 156.0, 153.3 (d, *J* = 7.4 Hz), 151.6 (d, *J* = 10.2 Hz), 135.9 (d, *J* = 2.9 Hz), 134.4 (d, *J* = 10.4 Hz), 134.1 (d, *J* = 6.2 Hz), 130.9 (d, *J* = 13.1 Hz), 129.6 (d, *J* = 3.9 Hz), 128.9 (d, *J* = 9.1 Hz), 127.3 (d, *J* = 82.9 Hz), 120.6 (q, *J* = 321.1 Hz), 116.3 (d, *J* = 88.6 Hz); Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.18; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.08; Other phosphonium isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.75; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 418.2, $C_{27}H_{21}N_3P^+$ requires 418.2.

Triphenyl(5–(pyridin–3–yl)pyrimidin–4–yl)phosphonium trifluoromethanesulfonate (23b)

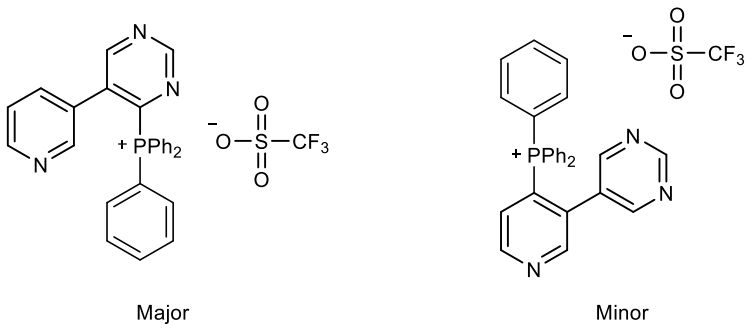


Major

7.7:1 (Major:2-position phosphonium isomer) Mixture of Isomers

Prepared according to general procedure B (except that Tf_2O was added at –30 ºC and stirred for 1 hour instead of at –78 ºC for 1 hour) using 5–(pyridin–3–yl)pyrimidine (79 mg, 0.50 mmol), silver trifluormethanesulfonate (128 mg, 0.50 mmol), acetyl chloride (36 μL, 0.50 mmol), Tf_2O (85 μL, 0.50 mmol), PPh_3 (44 mg, 0.55 mmol), DBU (75 μL, 0.50 mmol) and EtOAc (5 mL). After the purification procedure, the title compound was isolated as a yellow solid (59 mg, 0.01 mmol, 21% combined yield. Both isomers, IR ν_{max}/cm^{-1} (film): 3093, 3011, 2976, 2946, 2843, 1591, 1567, 1502, 1259, 1184, 1105, 1029, 1018, 803, 636; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.52 (1H, s), 8.96 (1H, d, *J* = 8.9 Hz), 8.35 (1H, d, *J* = 3.9 Hz), 8.10 (1H,s), 8.00–7.47 (16H, m), 7.10–7.00 (1H, m); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.8 (d, *J* = 5.1 Hz), 157.7 (d, *J* = 16.8 Hz), 156.4 (d, *J* = 16.0 Hz), 150.4 (d, *J* = 114.7 Hz), 150.3, 148.5, 139.5 (d, *J* = 19.4 Hz), 136.9, 135.3 (d, *J* = 2.9 Hz), 134.7 (d, *J* = 10.2 Hz), 130.3 (d, *J* = 13.1 Hz), 123.6, 120.6 (q, *J* = 321.1 Hz), 116.6 (d, *J* = 88.5 Hz); Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.25; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.87; Other phosphonium isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.96; *m/z* LRMS (ESI + APCI) found $[M – OTf]^+$ 418.2, $C_{33}H_{22}N_2O_3P^+$ requires 418.2.

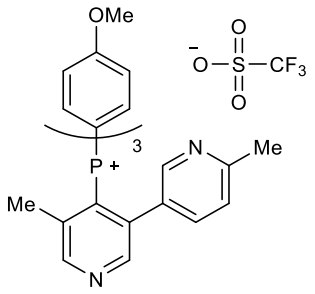
Triphenyl(5–(pyridin–3–yl)pyrimidin–4–yl)phosphonium trifluoromethanesulfonate (23b)



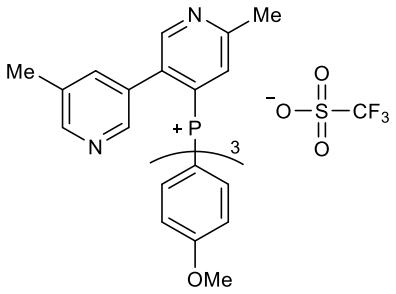
2:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure C using except that ^{1}H NMR and ^{31}P NMR were run on the crude reaction mixture) using 5–(pyridin–3–yl)pyrimidine (16 mg, 0.10 mmol), Tf_2O (34 μL, 0.20 mmol), PPh_3 (59 mg, 0.22 mmol), DBU (30 μL, 0.20 mmol), 1,3,5-trimethoxybenzene as an internal standard (39 mg, 0.23 mmol), and EtOAc (1 mL) to afford the title compound (combined ^{1}H NMR yield: 19%). Major isomer, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.42 (1H, s), 8.87 (1H, d, *J* = 8.9 Hz), 8.39-8.25 (1H, m), 7.97-7.12 (17H, m), 6.98 (1H, dd, *J* = 8.0, 4.9 Hz); Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.73; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.47; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 418.2, $C_{33}H_{22}N_2O_3P^+$ requires 418.2.

(5,6'–dimethyl–[3,3'–bipyridin]–4–yl)tris(4–methoxyphenyl)phosphonium trifluoromethanesulfonate (24a)



Major

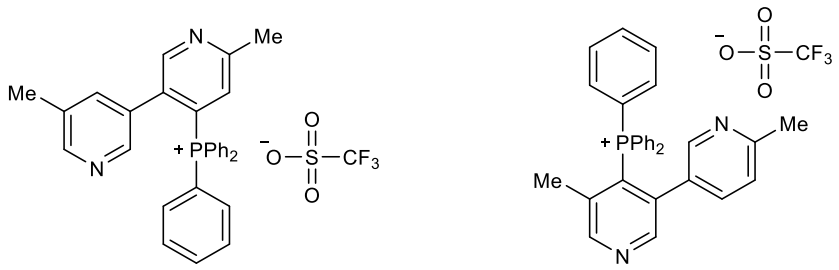


Minor

15:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure D using 5,6'–dimethyl–3,3'–bipyridine (47 mg, 0.26 mmol), Tf_2O (43 μL, 0.26 mmol), tris(4–methoxyphenyl)phosphine (92 mg, 0.26 mmol), DBU (39 μL, 0.26 mmol) and CH_2Cl_2 (2.6 mL). After the purification procedure, the title compound was isolated as a brown solid (83 mg, 0.12 mmol, 48% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3095, 3014, 2973, 2947, 2843, 1591, 1566, 1501, 1261, 1183, 1102, 1029; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, app d, *J* = 5.9 Hz), 8.45 (1H, app d, *J* = 5.7 Hz), 7.87 (1H, s), 7.47–7.42 (6H, m), 7.26–7.25 (1H, m), 7.09–7.06 (6H, m), 6.75 (1H, d, *J* = 8.0 Hz), 3.90 (9H, s), 2.41 (3H, s), 1.93 (3H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1 (d, *J* = 2.9 Hz), 158.4, 153.2 (d, *J* = 8.2 Hz), 151.9 (d, *J* = 7.5 Hz), 148.2, 139.6 (d, *J* = 7.6 Hz), 137.4 (d, *J* = 7.4 Hz), 136.3, 135.6 (d, *J* = 12.0 Hz), 129.2 (d, *J* = 4.7 Hz), 127.2 (d, *J* = 83.4 Hz), 122.9, 120.8 (q, *J* = 321.2 Hz) 116.3 (d, *J* = 14.3 Hz), 108.5 (d, *J* = 96.7 Hz), 55.9, 23.9, 21.3 (d, *J* = 5.4 Hz); Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.17; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.85; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 19.68; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 535.3, $C_{33}H_{22}N_2O_3P^+$ requires 535.2.

(5',6–dimethyl–[3,3'–bipyridin]–4–yl)triphenylphosphonium trifluoromethanesulfonate (24b)

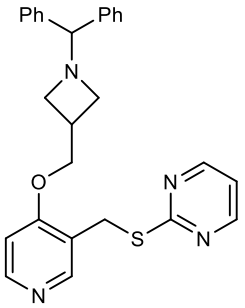


10:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure A (except that 1.75 equivalent of PPh_3 and 2 equivalents of Tf_2O and DBU were used instead of 1 equivalent of each) using 5,6'–dimethyl–3,3'–bipyridine (37 mg, 0.20 mmol), Tf_2O (68 μL, 0.40 mmol), PPh_3 (93 mg, 0.35 mmol), DBU (61 μL, 0.40 mmol) and CH_2Cl_2 (2.0 mL). After the purification procedure, the title compound was isolated as a brown solid (60 mg, 0.10 mmol, 50% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3060, 3026, 2923, 1572, 1438, 1260, 1151, 1103, 1029; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 8.59 (1H, app d, J = 7.1 Hz), 8.12 (1H, s), 7.81–7.63 (16H, m), 7.27 (1H, d, J = 15.6 Hz), 6.90 (1H, s), 2.70 (3H, s), 1.98 (3H, s); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.6 (d, J = 10.3 Hz), 153.0 (d, J = 8.3 Hz), 150.3, 146.0, 137.2, 135.4 (d, J = 3.0 Hz), 134.9 (d, J = 6.7 Hz), 134.3 (d, J = 10.2 Hz), 133.9 (d, J = 10.4 Hz), 130.8, 130.6 (d, J = 13.0 Hz), 127.9 (d, J = 9.4 Hz), 127.0 (d, J = 82.9 Hz), 120.8 (q, J = 321.1 Hz), 116.8 (d, J = 88.7 Hz), 24.6, 17.8; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.15; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.23; Minor isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 18.78; *m/z* LRMS (ESI + APCI) found $[M – OTf]^+$ 445.3, $C_{30}H_{26}N_2P^+$ requires 445.2.

A. 2.5. Preparation of Derivatized Polyazaarenes

2–(((4–((1–benzhydrylazetidin–3–yl)methoxy)pyridin–3–yl)methyl)thio)pyrimidine (25)

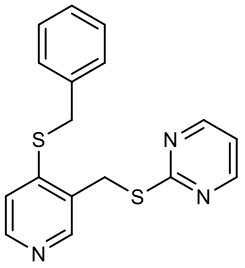


An oven dried 8 mL vial with a stir bar and septa cap was charged with sodium hydride (60% dispersion in mineral oil, 15 mg, 1.5 equiv) and placed under a nitrogen atmosphere. THF (250 μL) was added, the suspension was cooled to 0 ºC and a solution of (1–benzhydrylazetidin–3–yl)methanol (95 mg, 0.38 mmol) in THF (250 μL) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before the septa cap was briefly removed and triphenyl(3–((pyrimidin–2–ylthio)methyl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (153 mg, 0.25 mmol) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill[**], the ice bath removed and the reaction stirred for 12 hours while warming to room temperature. The reaction was quenched with H_2O (2.0 mL), the aqueous layer was separated and extracted with EtOAc (3 x 10 mL). 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 column chromatography (neutralized silica gel: 70% EtOAc in hexanes) to afford the title compound as a yellow solid (64 mg, 0.14 mmol, 56% yield). mp 142–144 ºC; IR ν_{max}/cm^{-1} (film): 3027, 2924, 2852, 1564, 1492, 1380, 1287, 1197, 705; ^1H NMR (400

[**] Vacuum was applied very briefly (less than a second) using a Schlenk manifold so that negligible solvent loss occurs.

MHz, $CDCl_3$) δ: 8.61 (1H, s), 8.51 (2H, d, *J* = 4.8 Hz), 8.38 (1H, d, *J* = 5.7 Hz), 7.49–7.12 (10H, m), 6.95 (1H, t, *J* = 4.8 Hz), 6.77 (1H, d, *J* = 5.7 Hz), 4.41 (3H, s), 4.20 (2H, d, *J* = 5.9 Hz), 3.34 (2H, t, *J* = 7.6 Hz), 3.13 (2H, t, *J* = 6.6 Hz), 3.04–2.88 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 162.8, 157.2, 151.1, 150.6, 142.0, 128.4, 127.4, 127.1, 122.3, 116.5, 106.6, 77.9, 69.3, 55.6, 29.1, 27.4; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 455.2, $C_{27}H_{27}N_4OS^+$ requires 455.2.

2–(((4–(benzylthio)pyridin–3–yl)methyl)thio)pyrimidine (26)

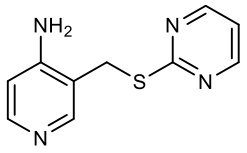


An oven dried 8 mL vial with a stir bar and septa cap was charged with sodium hydride (60% dispersion in mineral oil, 15 mg, 1.5 equiv) and placed under a nitrogen atmosphere. THF (1.0 mL) was added, the suspension was cooled to 0 ºC and benzyl mercaptan (32 μL, 0.38 mmol) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before the septa cap was briefly removed and triphenyl(3–((pyrimidin–2–ylthio)methyl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (153 mg, 0.25 mmol) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill[††], the ice bath removed and the reaction stirred for 12 hours while warming to room temperature. The reaction was quenched with H_2O (2.0 mL), the aqueous layer was separated and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered

[††] Vacuum was applied very briefly (less than a second) using a Schlenk manifold so that negligible solvent loss occurs.

and concentrated *in vacuo*. The residue was purified by flash column chromatography (neutralized silica gel: 50% EtOAc in hexanes) followed by flash chromatography (silica gel, gradient elution: 50% EtOAc/hexanes with 1% AcOH to 100% EtOAc with 3% NEt_3) to afford the title compound as a yellow oil (43 mg, 0.13 mmol, 53% yield). IR ν_{max}/cm^{-1} (film): 3029, 2924, 1563, 1547, 1378, 1193, 1181, 713; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.56 (1H, br), 8.44 (2H, d, J = 4.8 Hz), 8.22 (1H, br), 7.39–7.15 (5H, m), 7.06 (1H, d, J = 5.0 Hz), 6.88 (1H, t, J = 4.8 Hz), 4.36 (2H, s), 4.16 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.4, 157.2, 149.9, 148.3, 148.1, 135.2, 130.5, 128.8, 128.7, 127.7, 119.9, 116.6, 36.3, 30.5; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 325.1, $C_{17}H_{16}N_3S_2^+$ requires 326.1.

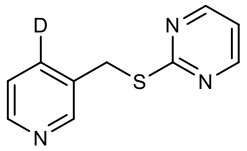
3–((pyrimidin–2–ylthio)methyl)pyridin–4–amine (2)



An oven dried 8 mL vial with a stir bar and septa cap was charged with triphenyl(3–((pyrimidin–2–ylthio)methyl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (153 mg, 0.25 mmol), sodium azide (20 mg, 0.31 mmol), and placed under a nitrogen atmosphere. DMSO (167 μL) was added, the cap was wrapped with parafilm and the reaction mixture was heated overnight at 120 ºC. The reaction was cooled to room temperature, diluted with EtOAc (2 mL), and a saturated aqueous solution of $NaHCO_3$ (2 mL). The aqueous layer was extracted a further three times with EtOAc (2 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* into an oven dried 8 mL vial equipped with a stir bar. The residue was subjected to three cycles of vacuum/nitrogen backfill before addition of a 9:1 solution of DMF and H_2O (250 μL). The reaction mixture was stirred at 100 ºC overnight before being cooled to room temperature and

concentrated *in vacuo*. The residue was purified by flash column chromatography (neutralized silica gel, gradient elution: 3% MeOH in CH_2Cl_2 to 7.5% MeOH in CH_2Cl_2) followed by filtration through a plug of basic alumina eluting with 100% EtOAc and then 10% MeOH in CH_2Cl_2 to afford the title compound as a yellow oil (31 mg, 0.14 mmol, 57% yield). IR ν_{max}/cm^{-1} (film): 3339, 3207, 3034, 2927, 1598, 1584, 1548, 1379, 1183, 906, 727; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (2H, d, *J* = 4.8 Hz), 8.26 (1H, s), 8.11 (1H, d, *J* = 5.6 Hz), 7.01 (1H, t, *J* = 4.9 Hz), 6.50 (1H, d, *J* = 5.6 Hz), 4.89 (2H, br), 4.37 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.9, 157.3, 151.7, 150.9, 149.0, 116.8, 116.6, 109.9, 29.7; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 219.1, $C_{10}H_{11}N_4S^+$ requires 219.1.

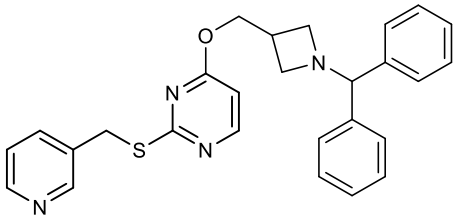
2–(((pyridin–3–yl–4–d)methyl)thio)pyrimidine (28)



An oven–dried 8 mL vial equipped with a stir bar was charged with the triphenyl(3–((pyrimidin–2–ylthio)methyl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (153 mg, 0.25 mmol), K_2CO_3 (52 mg, 0.38 mmol), and placed under a nitrogen atmosphere. CD_3OD:D_2O 9:1 (750 μL) was added at room temperature and the reaction was stirred for 12 hours. The reaction mixture was diluted with CH_2Cl_2 (2 mL) and the mixture was dried (MgSO4), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, gradient elution: 50% EtOAc in hexanes with 1% AcOH to 75% EtOAc in hexanes with 3% NEt_3) to afford the title compound as a colorless oil (38 mg, 0.19 mmol, 75% yield). IR ν_{max}/cm^{-1} (film): 3659, 3589, 3034, 2956, 2921, 1564, 1548, 1381, 1203, 651; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, br),

8.60–8.43 (3H, m), 7.33–7.18 (1H, m), 6.99 (1H, t, J = 4.9 Hz), 4.41–4.35 (0.58H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.3, 157.3, 150.3, 148.4, 136.1 (t, J = 25.3 Hz), 133.8, 123.3, 116.8, 32.2; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 207.1, $C_{10}H_9DN_3S^+$ requires 205.1

4–((1–benzhydrylazetidin–3–yl)methoxy)–2–((pyridin–3–ylmethyl)thio)pyrimidine (29)

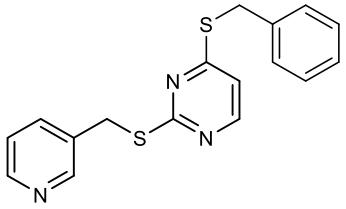


An oven dried 8 mL vial with a stir bar and septa cap was charged with sodium hydride (60% dispersion in mineral oil, 1.5 equiv) and placed under a nitrogen atmosphere. THF (250 μL) was added, the suspension was cooled to 0 ºC and a solution of (1–benzhydrylazetidin–3–yl)methanol (95 mg, 0.38 mmol) in THF (250 μL) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before the septa cap was briefly removed and triphenyl(2–((pyridin–3–ylmethyl)thio)pyrimidin–4–yl)phosphonium trifluoromethanesulfonate (153 mg, 0.25 mmol) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill[‡‡], the ice bath removed, and the reaction stirred for 12 hours while warming to room temperature. The reaction was quenched with H_2O (2.0 mL), the aqueous layer was separated and extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered and concentrated *in vacuo.* The crude material was purified by flash chromatography (neutralized silica gel: 50% EtOAc in Hexanes to 60% EtOAc in hexanes) to provide title compound as a yellow oil (77 mg, 0.17 mmol, 68% yield); IR

[‡‡] Vacuum was applied very briefly (less than a second) using a Schlenk manifold so that negligible solvent loss occurs.

ν_{max}/cm^{-1} (film): 3058, 3026, 2951, 2831, 1710, 1551, 1440, 1316, 1230; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.69–8.68 (1H, d, *J* = 1.7 Hz), 8.49 (1H, dd *J* = 4.7, 1.2 Hz), 8.21 (1H, d, *J* = 5.7 Hz), 7.77 (1H, dt, *J* = 7.8, 3.7 Hz), 7.41–7.39 (4H, m), 7.28–7.16 (7H, m), 6.37 (1H, d, *J* = 5.7 Hz), 4.46 (2H, d, *J* = 7.0 Hz), 4.37–4.34 (3H, m), 3.29 (2H, t, *J* = 7.5 Hz), 2.97 (2H, t, *J* = 13.1 Hz), 2.87–2.79 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 168.6, 157.1, 150.0, 148.3, 141.9, 136.2, 133.8, 128.3, 127.3, 127.0, 123.2, 104.2, 77.8, 68.6, 56.0, 32.2, 28.7; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 455.2, $C_{27}H_{27}N_4OS^+$ requires 455.2.

4–(benzylthio)–2–((pyridin–3–ylmethyl)thio)pyrimidine (30)

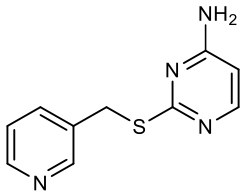


An oven dried 8 mL vial with a stir bar and septa cap was charged with sodium hydride (60% dispersion in mineral oil, 1.1 eq) and placed under a nitrogen atmosphere. THF (1.0 mL) was added, the suspension was cooled to 0 ºC and benzyl mercaptan (32 μL, 0.28 mmol) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before the septa cap was briefly removed and triphenyl(2–((pyridin–3–ylmethyl)thio)pyrimidin–4–yl)phosphonium trifluoromethanesulfonate (153 mg, 0.25 mmol) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill[§§], the ice bath was removed and the reaction stirred for 12 hours while warming to room temperature. The reaction was quenched with H_2O (2.0 mL), the aqueous layer was separated and extracted with EtOAc (3 x 10 mL). The

[§§] Vacuum was applied very briefly (less than a second) using a Schlenk manifold so that negligible solvent loss occurs.

combined organic extracts were washed with a saturated aqueous solution of brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel: 50% EtOAc in Hexanes) to provide title compound as a yellow oil (66 mg, 0.20 mmol, 81% yield). IR ν_{max}/cm^{-1} (film): 3031, 2929, 1548, 1516, 1314, 904; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.66 (1H, s), 8.48 (1H, d *J* = 3.7 Hz), 8.14 (1H, d, *J* = 5.4 Hz), 7.74–7.72 (1H, m), 7.36–7.21 (6H, m), 6.82 (1H, d, *J* = 3.7 Hz), 4.38 (2H, s), 4.36 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.5, 169.9, 154.5, 150.1, 148.5, 136.5, 136.3, 133.5, 128.8, 128.6, 127.4, 123.3, 114.4, 33.5, 32.2; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 326.1, $C_{17}H_{16}N_3S_2^+$ requires 326.1.

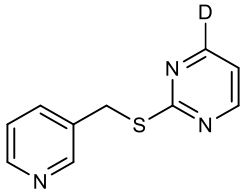
4–((1–benzhydrylazetidin–3–yl)methoxy)–2–((pyridin–3–ylmethyl)thio)pyrimidine (31)



An oven dried 8 mL vial with a stir bar and septa cap was charged with triphenyl(2–((pyridin–3–ylmethyl)thio)pyrimidin–4–yl)phosphonium trifluoromethanesulfonate (153 mg, 0.25 mmol) and sodium azide (13 mg, 0.31 mmol), and placed under a nitrogen atmosphere. DMSO (167 μL) was added, the cap was wrapped with parafilm and the reaction mixture was heated overnight at 120 ºC. The reaction was cooled to room temperature, diluted with EtOAc (2 mL), and quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL). The aqueous layer was extracted a further three times with EtOAc (2 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* into an oven dried 8 mL vial equipped with a stir bar. The residue was subjected to three cycles of vacuum/nitrogen backfill before addition of a 9:1 solution of DMF and H_2O (250 μL). The reaction mixture was stirred at 100 ºC for 44 hours before being cooled to room

temperature and concentrated *in vacuo*. The solution was purified by flash chromatography (silica gel: 6% MeOH in CH_2Cl_2) to provide title compound as a white solid (36 mg, 0.16 mmol, 66% yield). mp 114–116 ºC; IR ν_{max}/cm^{-1} (film): 3303, 3147, 3029, 1641, 1580, 1540, 1478, 1354, 904; ^{1}H NMR (400 MHz, CDCl3) δ: 8.67 (1H, s), 8.46 (1H, d, *J* = 3.6 Hz), 8.04 (1H, d, *J* = 5.8 Hz), 7.75 (1H, dt, *J* = 7.9, 3.7 Hz), 7.22 (1H, dd, *J* = 7.8, 4.8 Hz), 6.12 (1H, d, *J* = 5.8 Hz), 4.93 (2H, br), 4.33 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.2, 162.4, 156.0, 150.2, 148.2, 136.4, 134.3, 123.3, 101.2, 32.0; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 219.1, $C_{10}H_{11}N_4S^+$ requires 219.1.

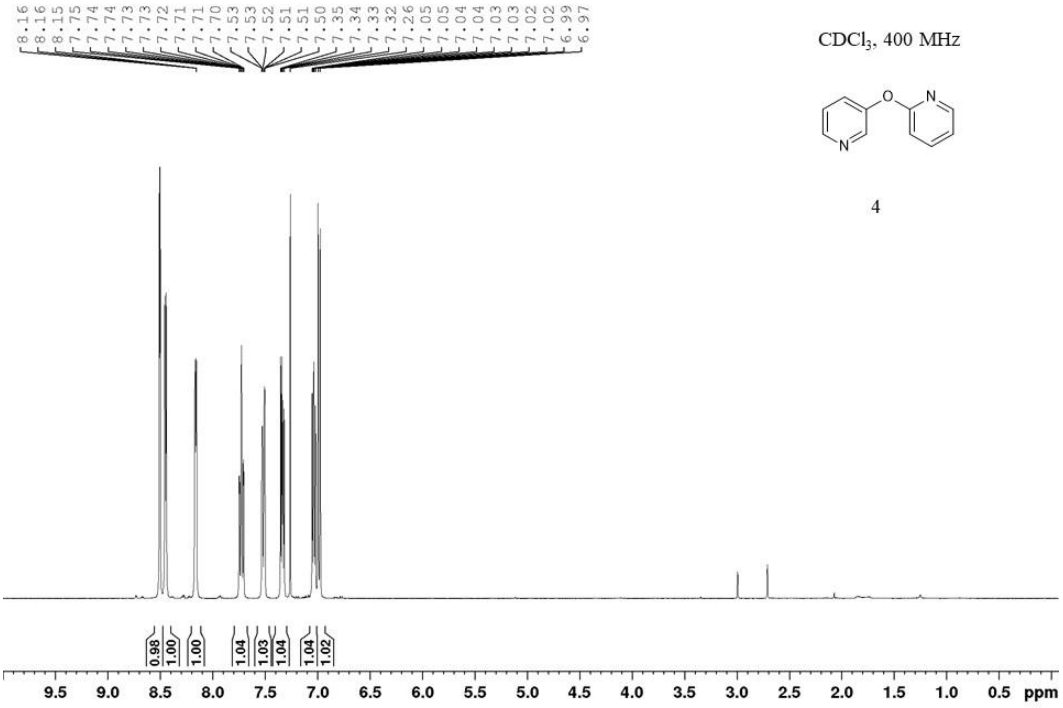
2–((pyridin–3–ylmethyl)thio)pyrimidine–4–d (32)



An oven dried 8 mL vial was charged with K_2CO_3 (52 mg, 0.38 mmol) and triphenyl(2–((pyridin–3–ylmethyl)thio)pyrimidin–4–yl)phosphonium trifluoromethanesulfonate (153 mg, 0.25 mmol) and subjected to three rapid vacuum/nitrogen backfills. CD_3OD:D_2O 9:1 (750 μL) was added at room temperature and the reaction was stirred for 12 hours. The solution was then diluted with CH_2Cl_2 (2 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (neutralized silica gel: 50% EtOAc in Hexanes) to provide title compound as a yellow oil (37.6 mg, 0.19 mmol, 74% yield); IR ν_{max}/cm^{-1} (film): 3385, 3029, 2923, 1730, 1534, 1403, 1329, 1205; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (1H, s), 8.53 (1H, d, *J* = 4.8 Hz), 8.47 (1H, d, *J* = 4.2 Hz), 7.77 (1H, d, *J* = 7.8 Hz), 7.23 (1H, dd, *J* = 7.8, 4.8 Hz), 6.98 (1H, d, *J* = 4.8 Hz), 4.38 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.2, 157.2, 159.9 (t, *J* = 27.9 Hz),

150.3, 148.3, 136.3, 133.7, 123.2, 116.6, 32.2; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 205.1, $C_{10}H_9DN_3S^+$ requires 205.1.

A 2.4 ^{1}H, ^{13}C, ^{31}P,^{10}F NMR Spectra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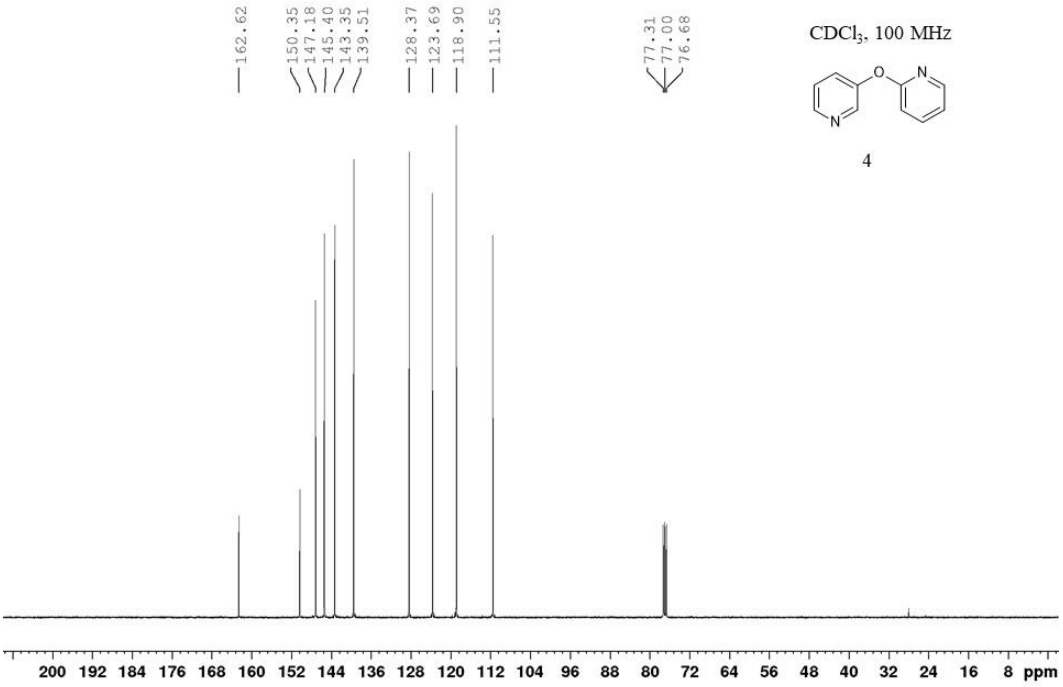
8.16
8.15
7.75
7.74
7.74
7.73
7.73
7.72
7.71
7.71
7.70
7.53
7.53
7.52
7.51
7.51
7.50
7.35
7.34
7.33
7.32
7.26
7.05
7.05
7.04
7.04
7.03
7.03
7.02
7.02
6.99
6.97
CDCl3, 400 MHz
O
N
N
4
0.98
1.00
1.00
1.04
1.03
1.04
1.04
1.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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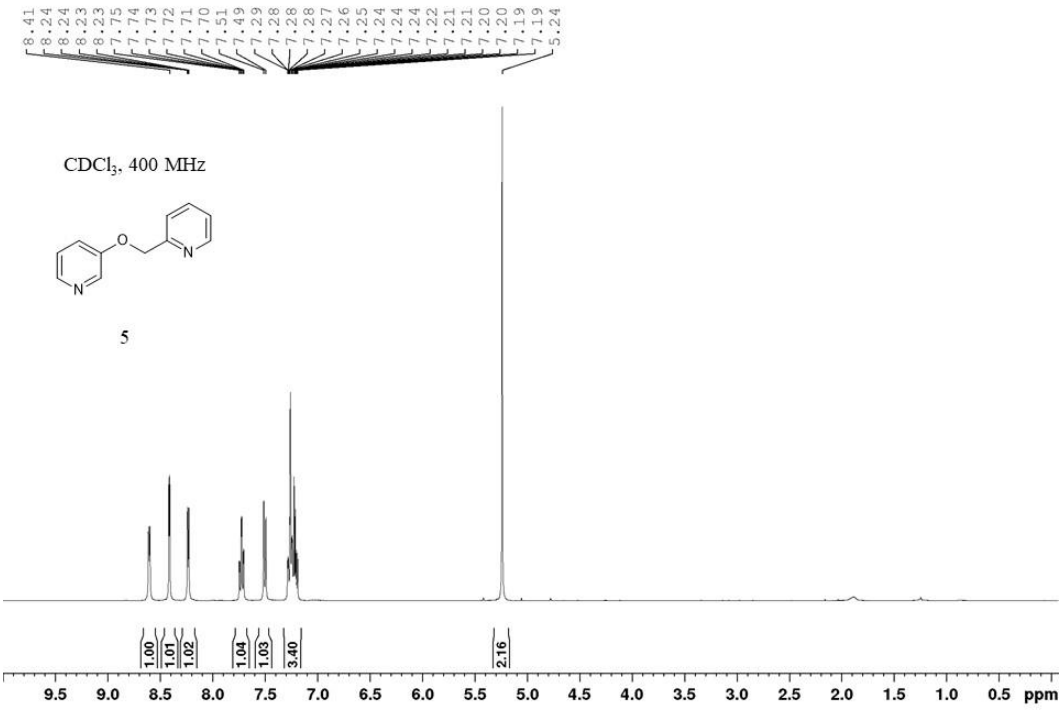
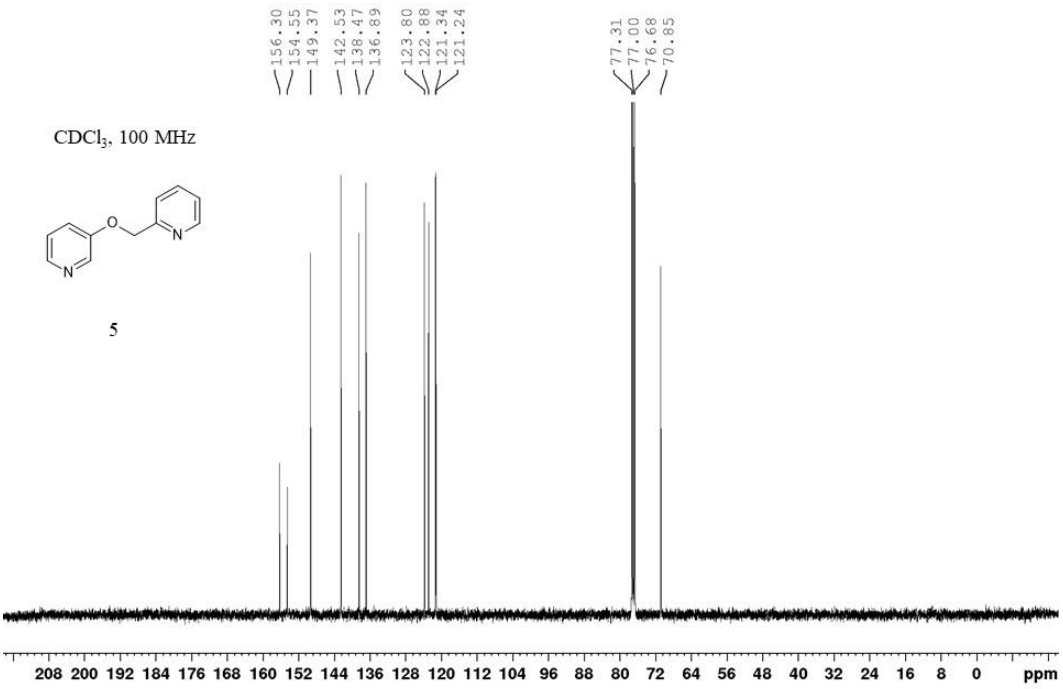
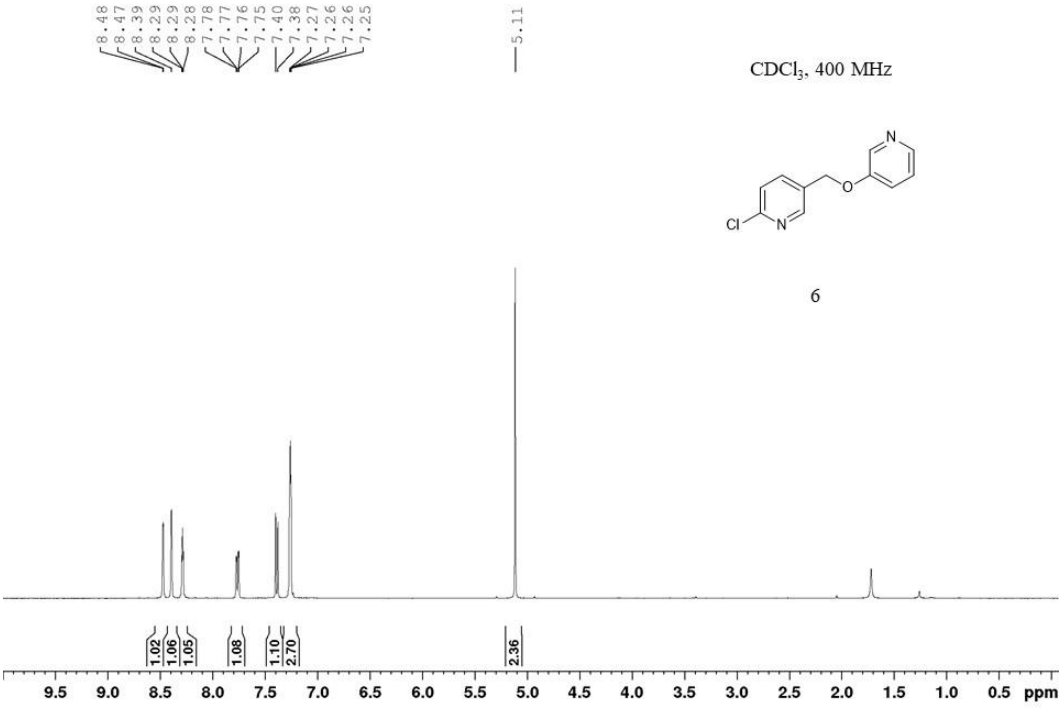
150.35
147.18
145.40
143.35
139.51
128.37
123.69
118.90
111.55
77.31
77.00
76.68
CDCl3, 100 MHz
O
N
N
4
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm


8.41
8.24
8.24
8.23
8.23
7.75
7.74
7.73
7.72
7.71
7.70
7.51
7.49
7.29
7.28
7.28
7.28
7.27
7.26
7.25
7.24
7.24
7.24
7.22
7.21
7.21
7.20
7.20
7.19
7.19
5.24
CDCl3, 400 MHz
O
N
N
5
1.00
1.01
1.02
1.04
1.03
3.40
2.16
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 ppm


156.30
154.55
149.37
142.53
138.47
136.89
123.80
122.88
121.34
121.24
77.31
77.00
76.68
70.85
CDCl3, 100 MHz
O
N
N
5
208 200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 ppm


8.48
8.47
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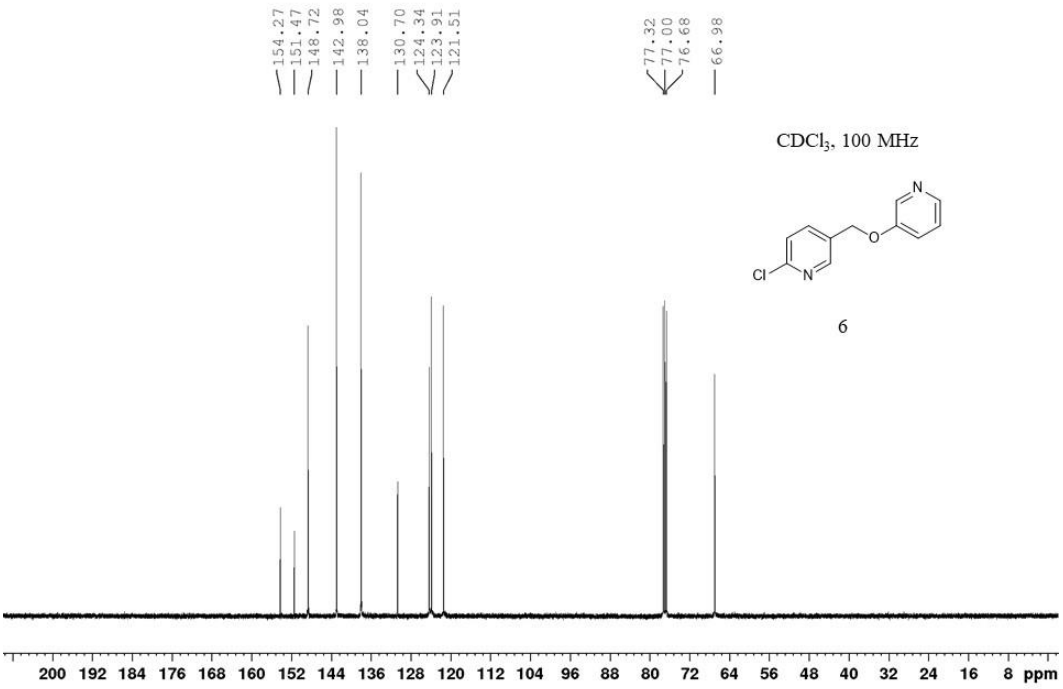
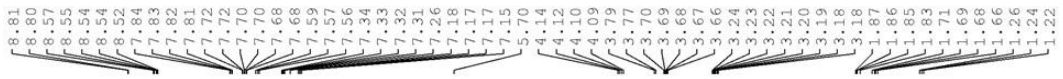
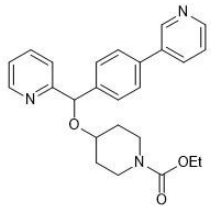
8.29
8.29
8.28
7.78
7.77
7.76
7.75
7.40
7.38
7.27
7.26
7.26
7.25
5.11
CDCl3, 400 MHz
N
O
Cl
N
6
1.02
1.06
1.05
1.08
1.10
2.70
2.36
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


154.27
151.47
148.72
142.98
138.04
130.70
124.34
123.91
121.51
77.32
77.00
76.68
66.98
CDCl3, 100 MHz
N
O
Cl
N
6
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 ppm

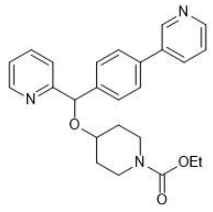


$CDCl_3$, 400 MHz

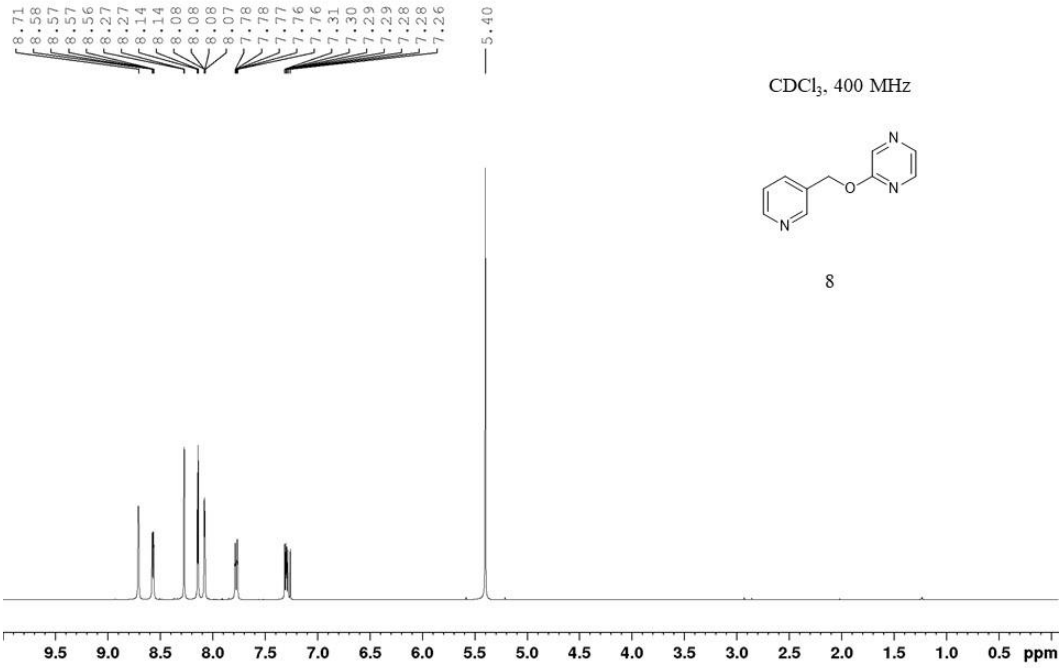


7

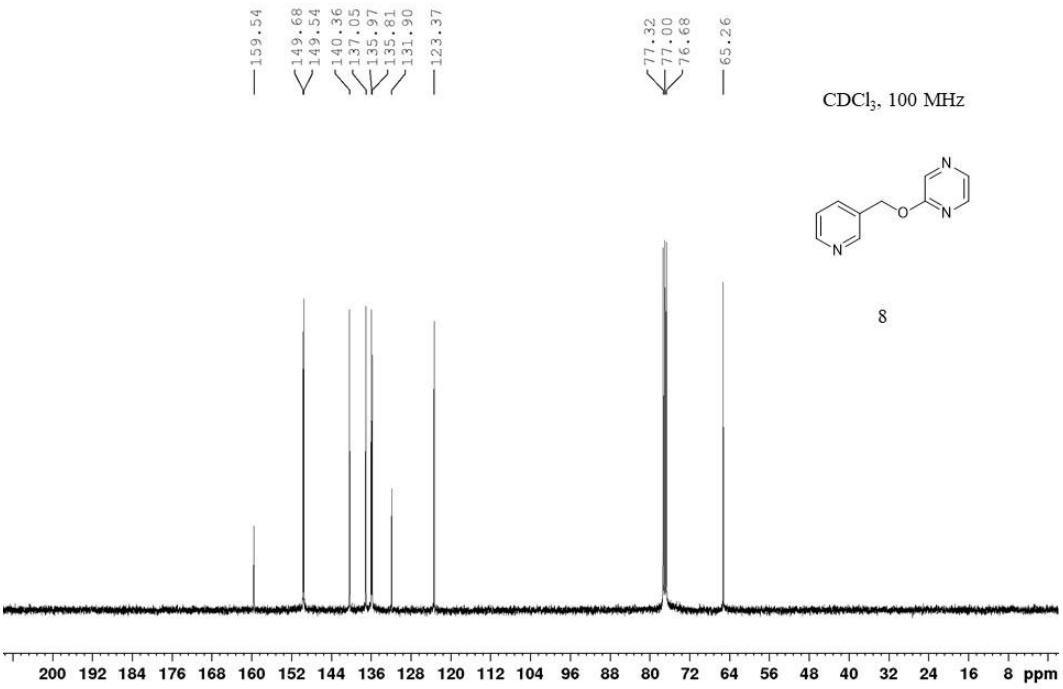
$CDCl_3$, 100 MHz



7


8.71
8.58
8.57
8.57
8.56
8.27
8.27
8.14
8.14
8.08
8.08
8.08
8.07
7.78
7.78
7.77
7.76
7.76
7.31
7.30
7.29
7.29
7.28
7.28
7.26
5.40
CDCl3, 400 MHz
N
N
O
N
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 ppm

8


159.54
149.68
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140.36
137.05
135.97
135.81
131.90
123.37
77.32
77.00
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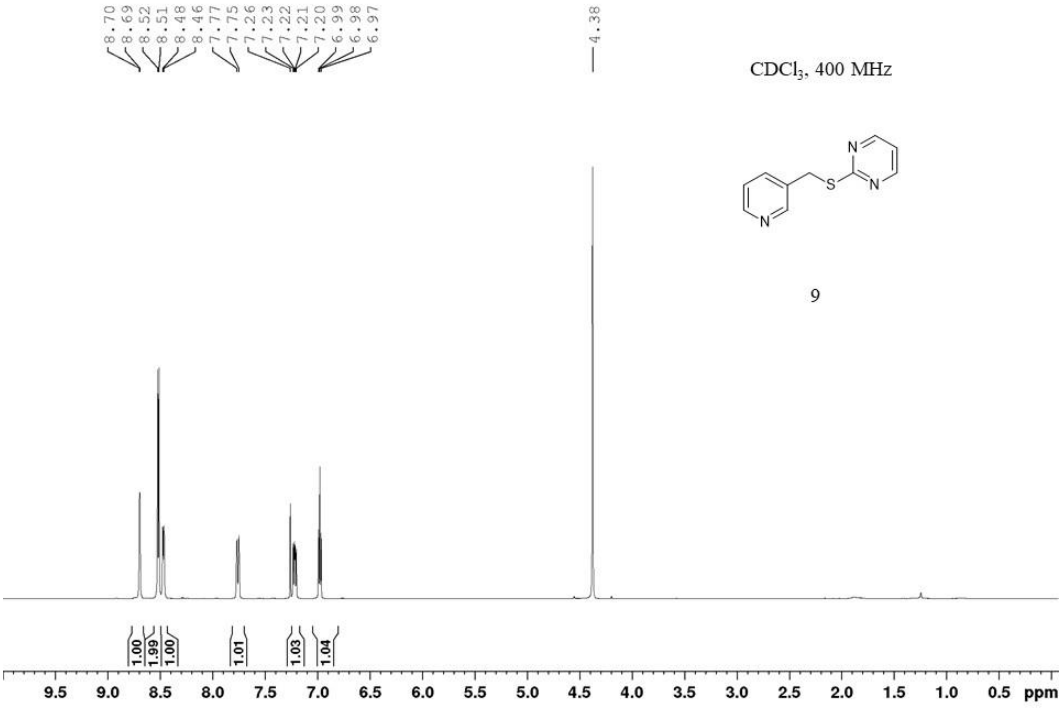
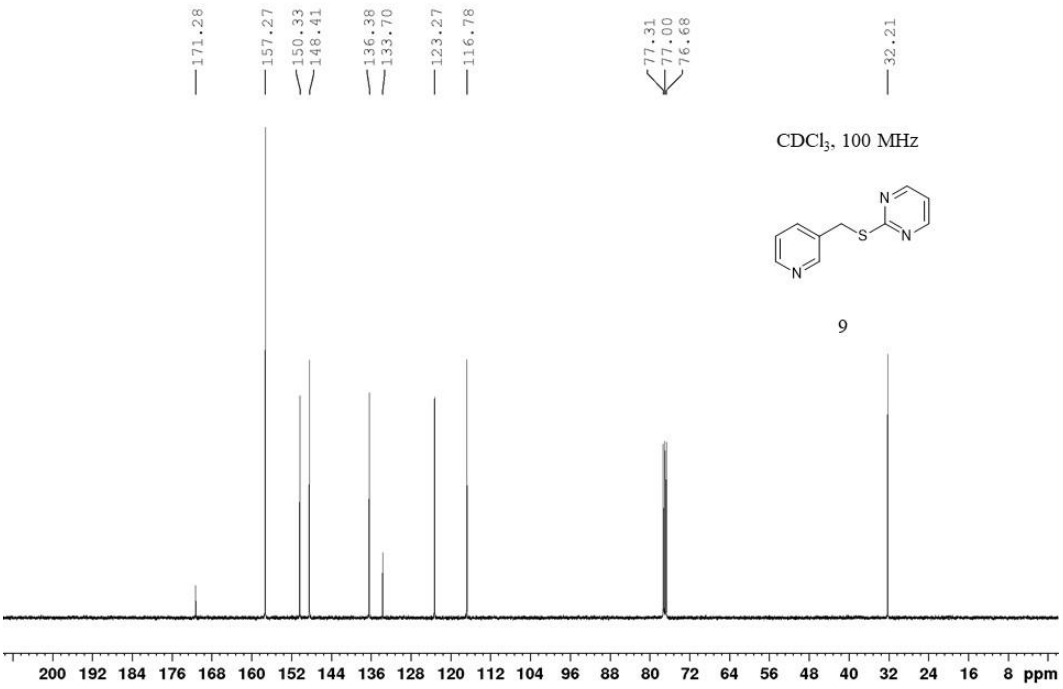
65.26
CDCl3, 100 MHz
N
N
O
N
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

8



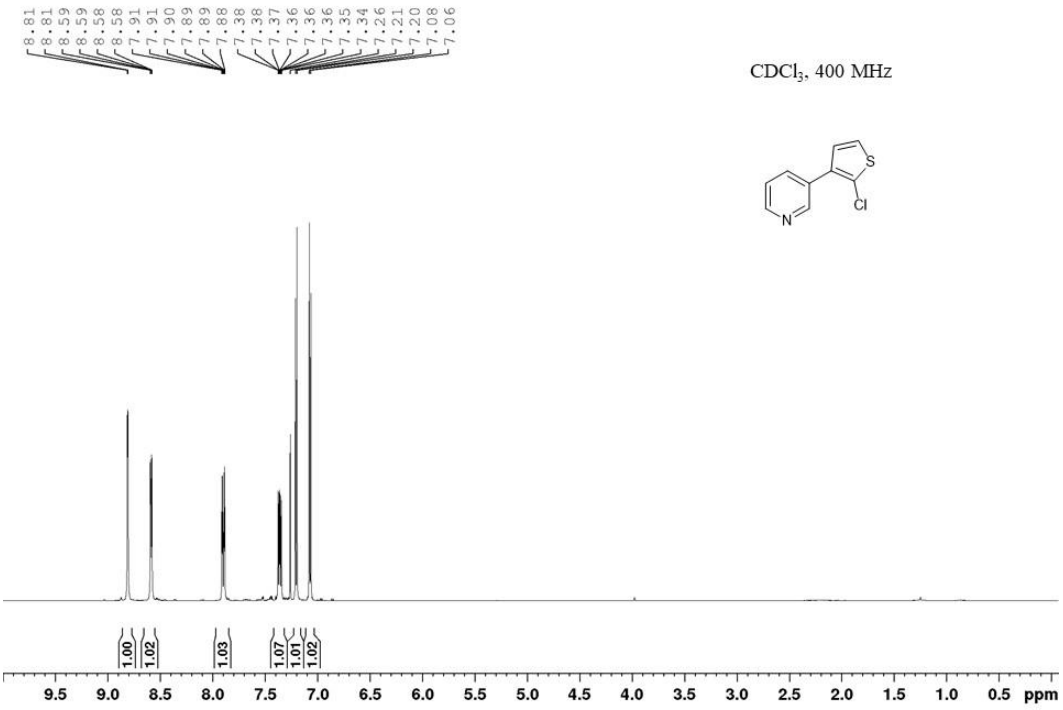
$CDCl_3$, 400 MHz

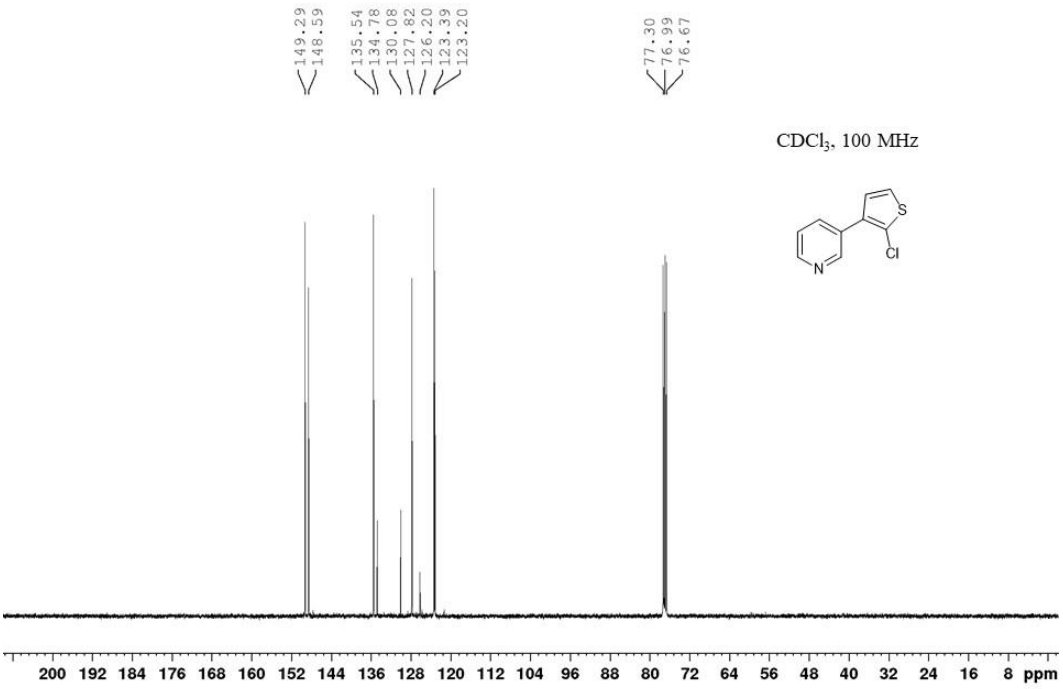
9

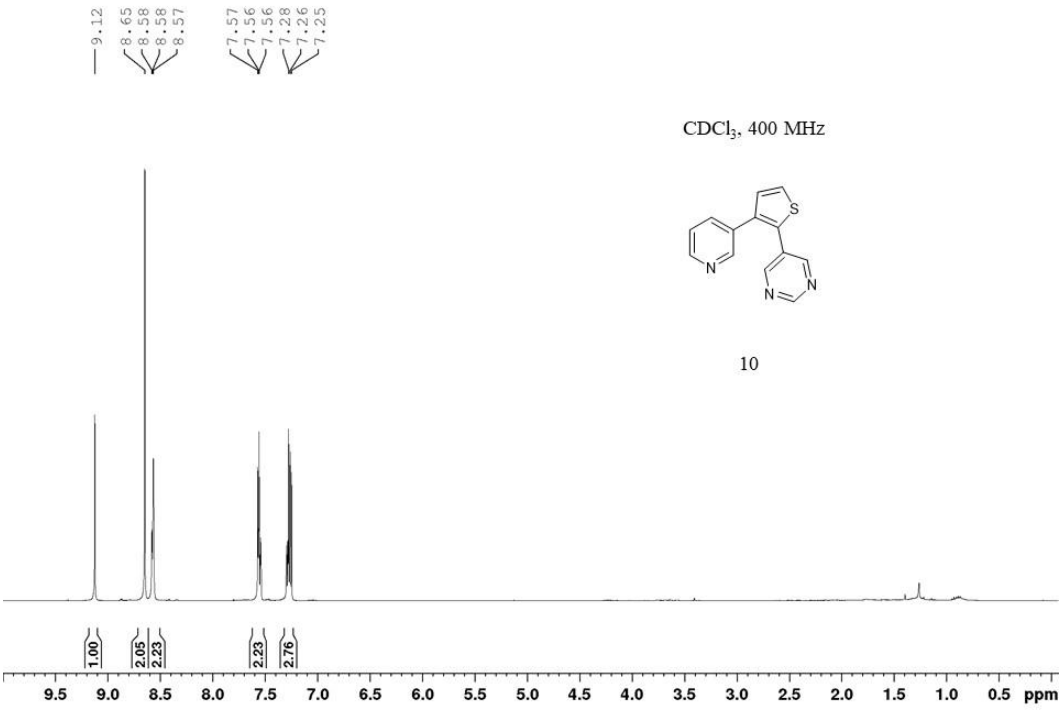


$CDCl_3$, 100 MHz

9

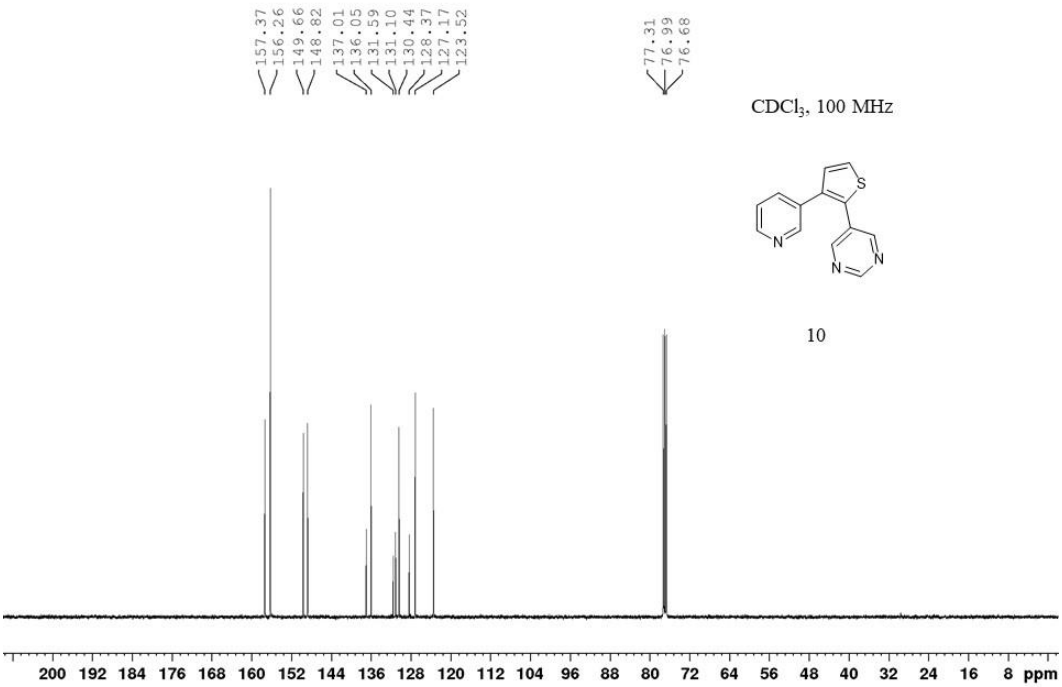

8.81
8.81
8.59
8.59
8.58
8.58
7.91
7.91
7.90
7.89
7.89
7.88
7.38
7.38
7.37
7.36
7.36
7.36
7.35
7.34
7.26
7.21
7.20
7.08
7.06
CDCl3, 400 MHz
S
Cl
N
1.00
1.02
1.03
1.07
1.01
1.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


149.29
148.59
135.54
134.78
130.08
127.82
126.20
123.39
123.20
77.30
76.99
76.67
CDCl3, 100 MHz
S
Cl
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 ppm



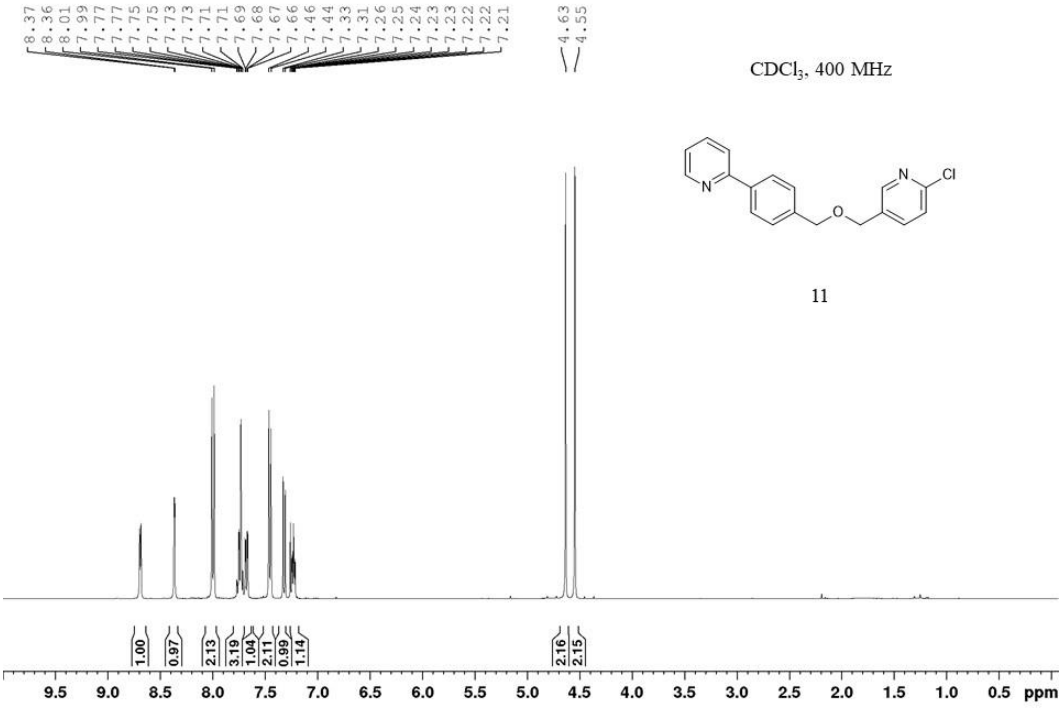
$CDCl_3$, 400 MHz

10

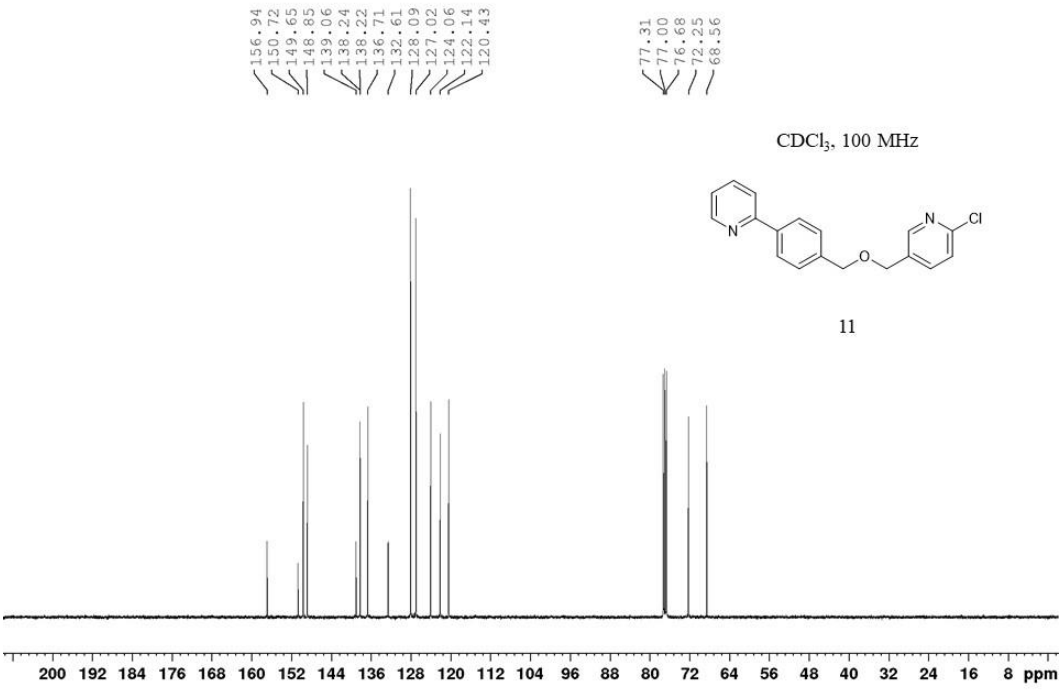


$CDCl_3$, 100 MHz

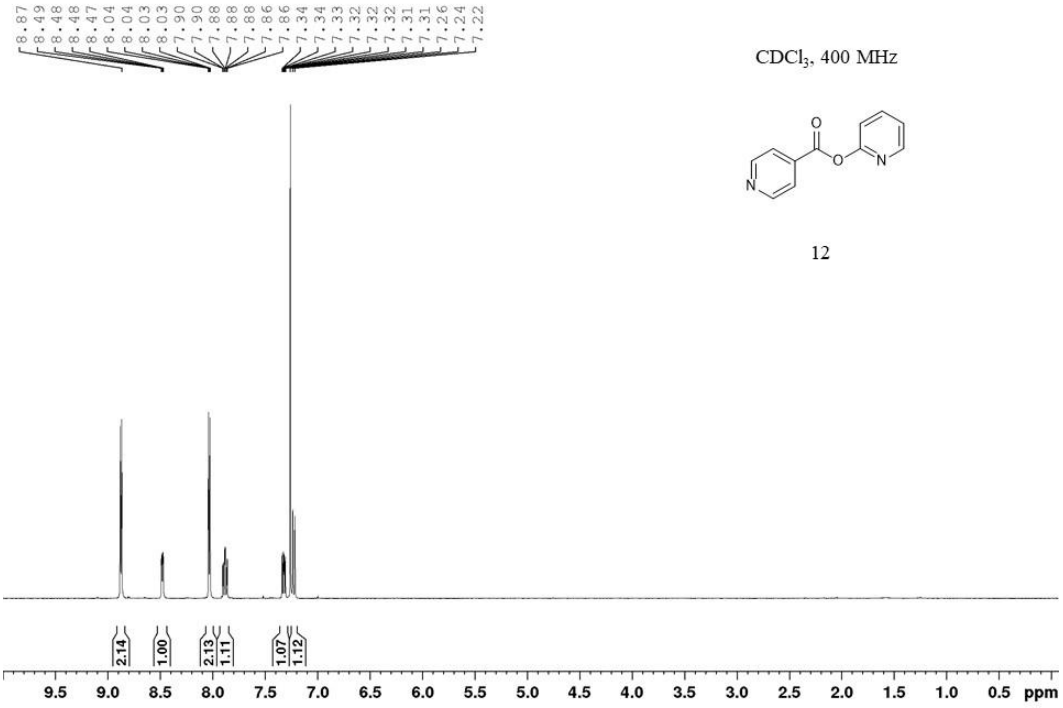
10

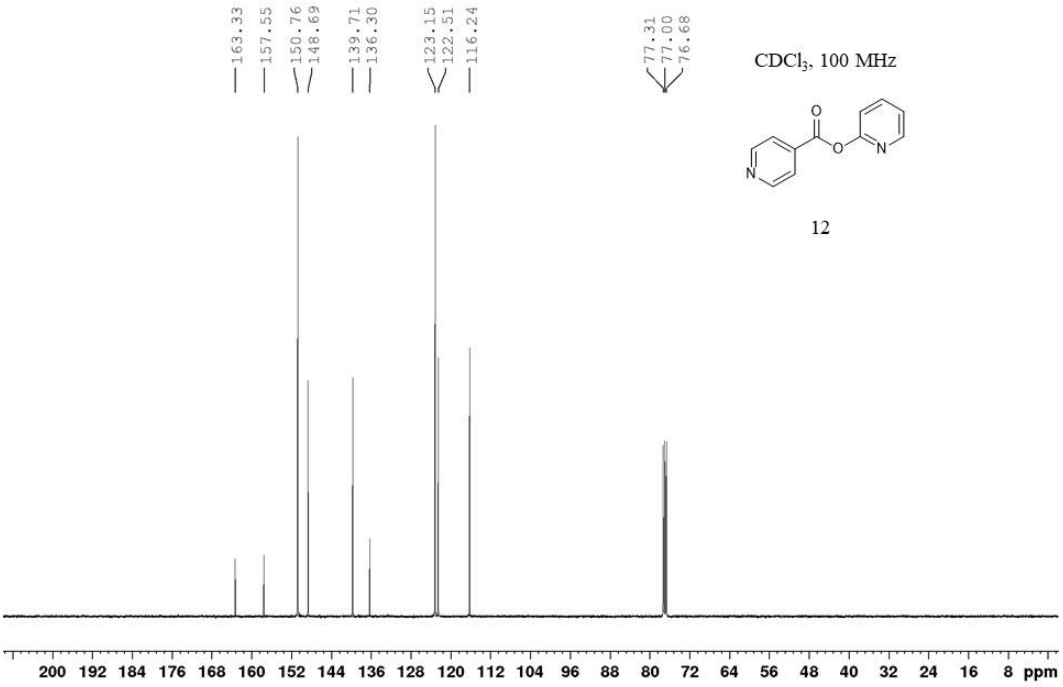

8.37
8.36
8.01
7.99
7.77
7.77
7.75
7.75
7.73
7.73
7.71
7.71
7.69
7.68
7.67
7.66
7.46
7.44
7.33
7.31
7.26
7.25
7.24
7.23
7.23
7.22
7.22
7.21
4.63
4.55
CDCl3, 400 MHz
N
Cl
O
1.00
0.97
2.13
3.19
1.04
2.11
0.99
1.14
2.16
2.15
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

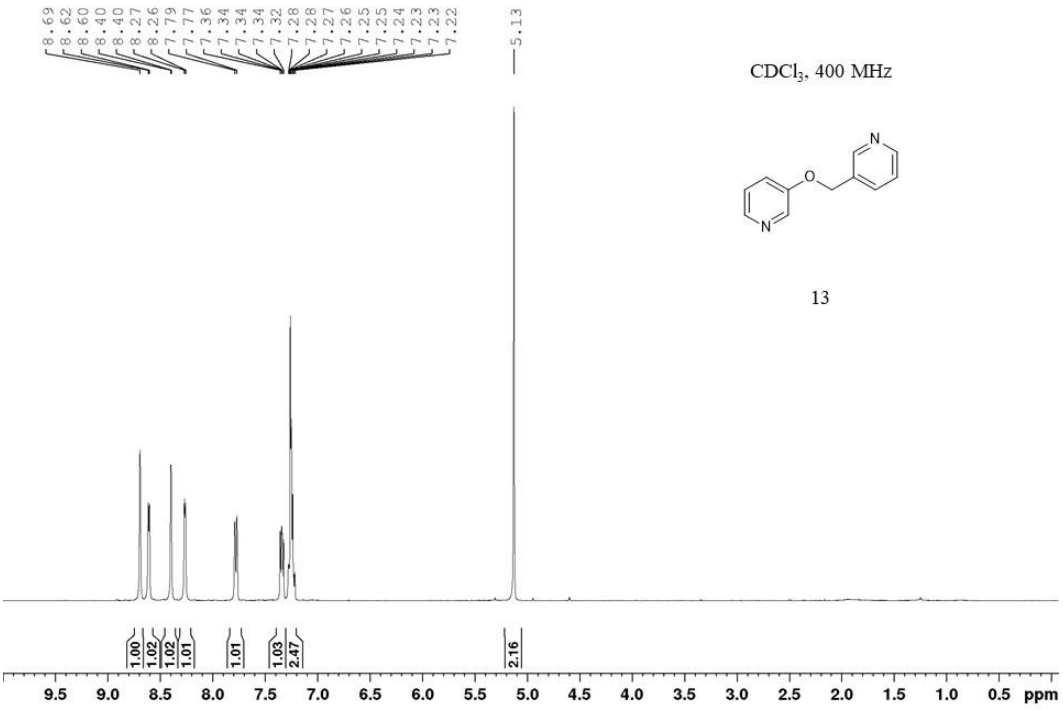
11


156.94
150.72
149.65
148.85
139.06
138.24
138.22
136.71
132.61
128.09
127.02
124.06
122.14
120.43
77.31
77.00
76.68
72.25
68.56
CDCl3, 100 MHz
N
Cl
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 ppm

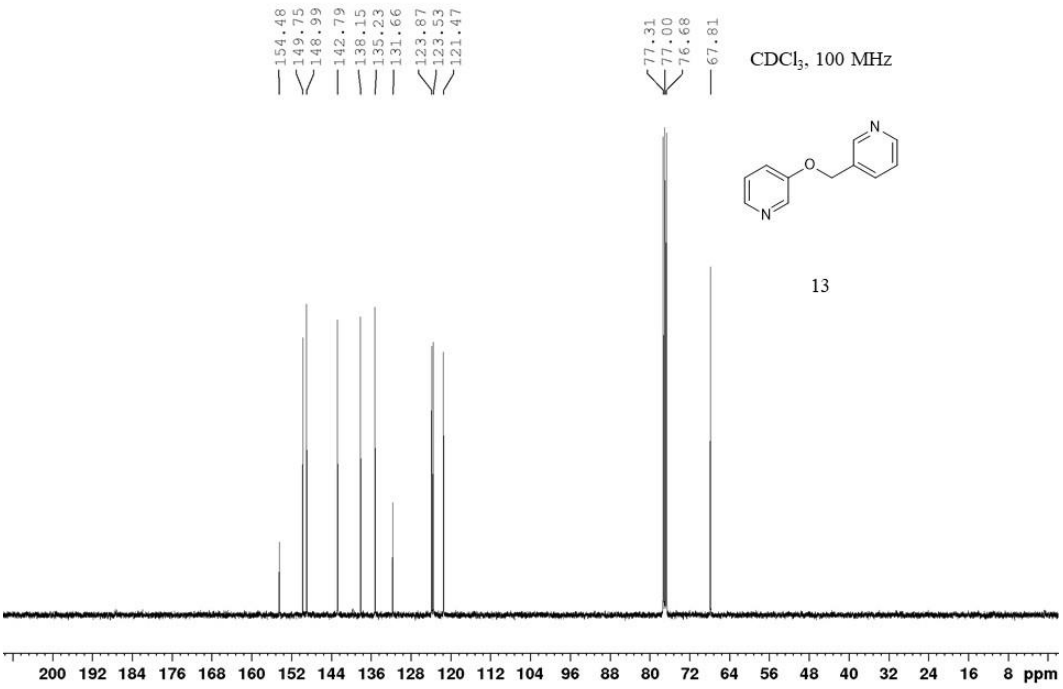
11


8.87
8.49
8.48
8.48
8.47
8.04
8.03
8.03
7.90
7.88
7.88
7.86
7.86
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.26
7.24
7.22
CDCl3, 400 MHz
O
O
N
N
12
2.14
1.00
2.13
1.11
1.07
1.12
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 ppm

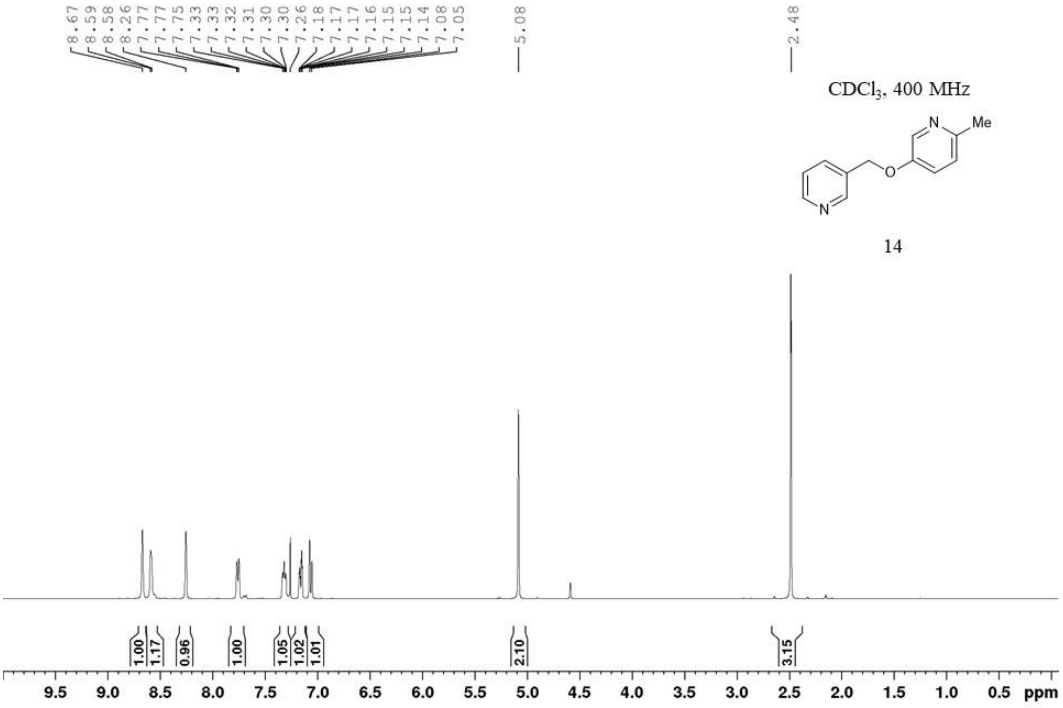

163.33
157.55
150.76
148.69
139.71
136.30
123.15
122.51
116.24
77.31
77.00
76.68
CDCl3, 100 MHz
O
O
N
N
12
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

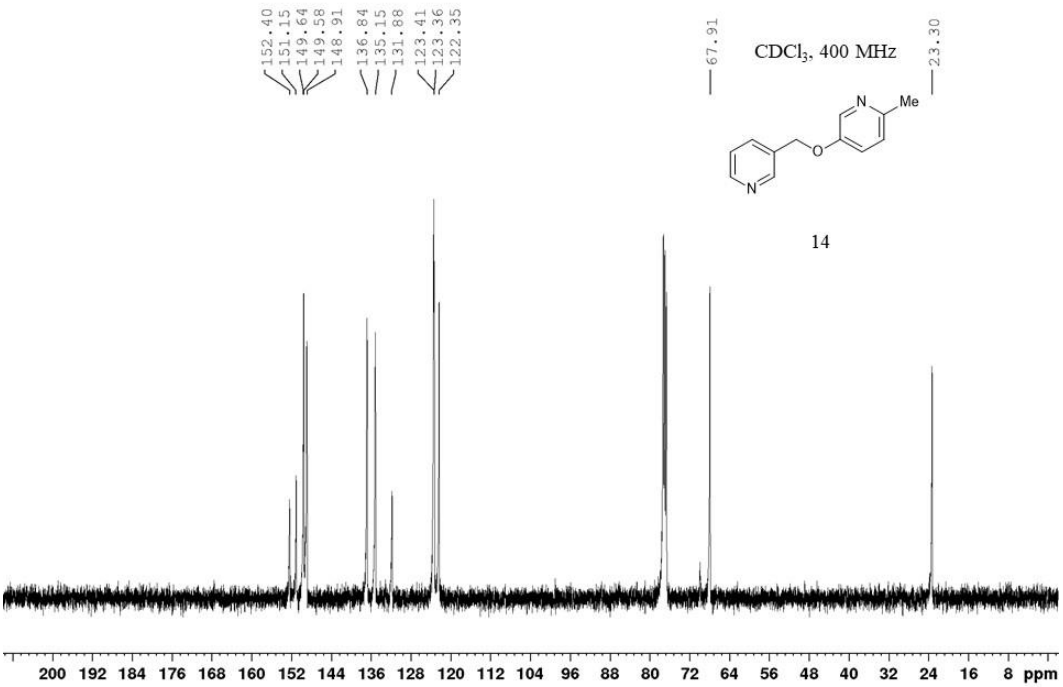

8.69
8.62
8.60
8.40
8.40
8.27
8.26
7.79
7.77
7.36
7.34
7.34
7.32
7.28
7.28
7.27
7.26
7.25
7.25
7.24
7.23
7.23
7.22
5.13
CDCl3, 400 MHz
1.00
1.02
1.02
1.01
1.01
1.03
2.47
2.16
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

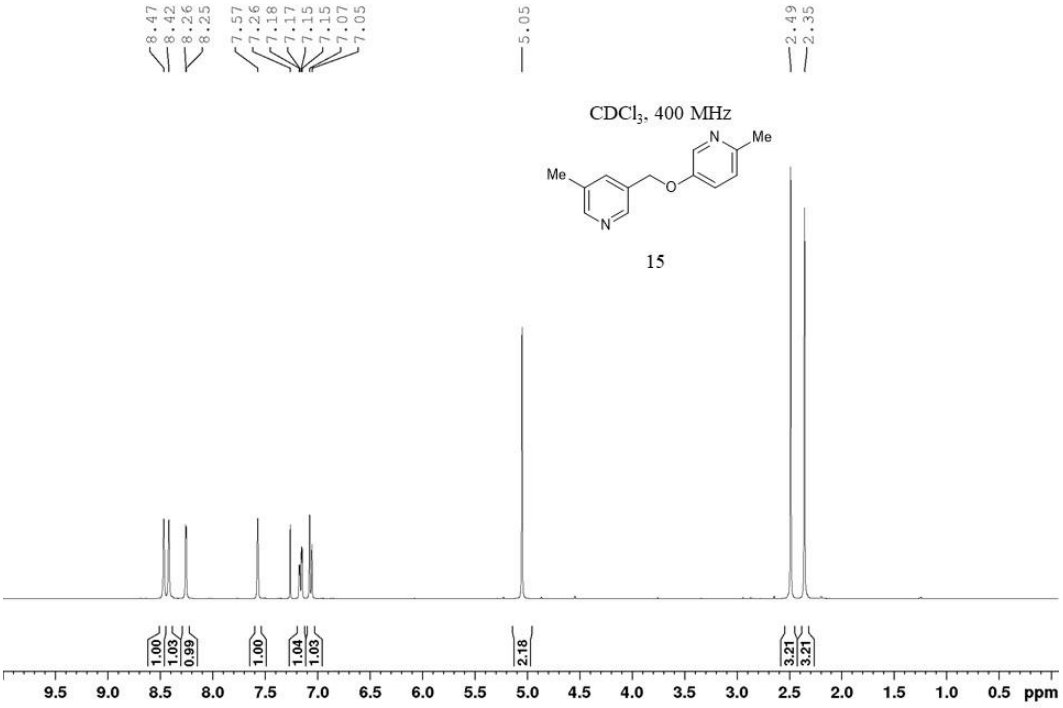
13

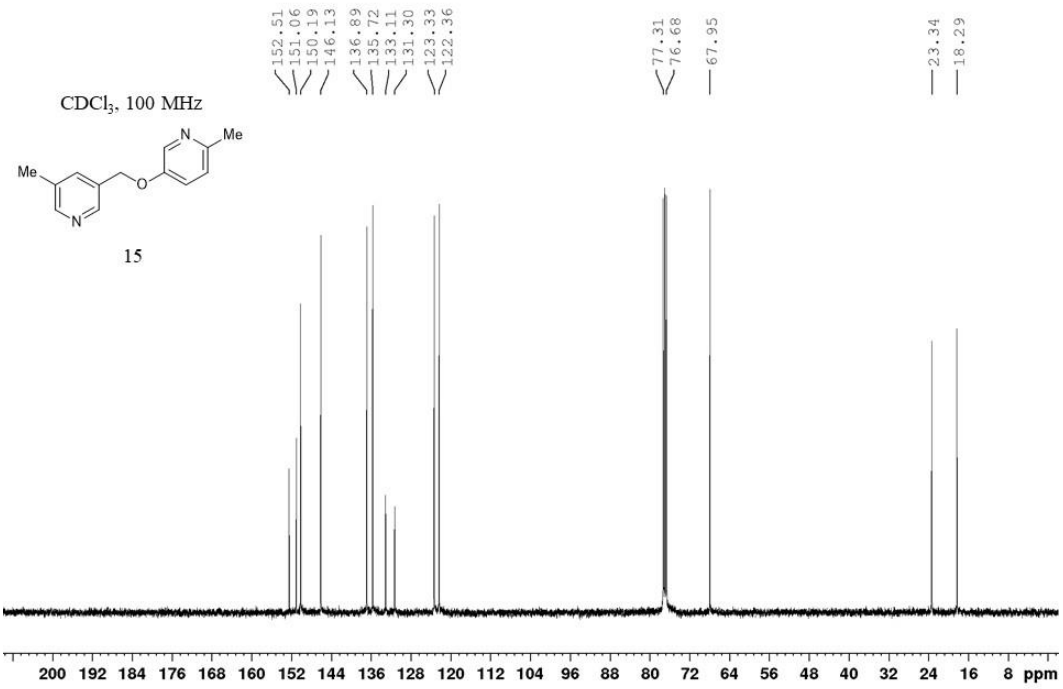

154.48
149.75
148.99
142.79
138.15
135.23
131.66
123.87
123.53
121.47
77.31
77.00
76.68
67.81
CDCl3, 100 MHz
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

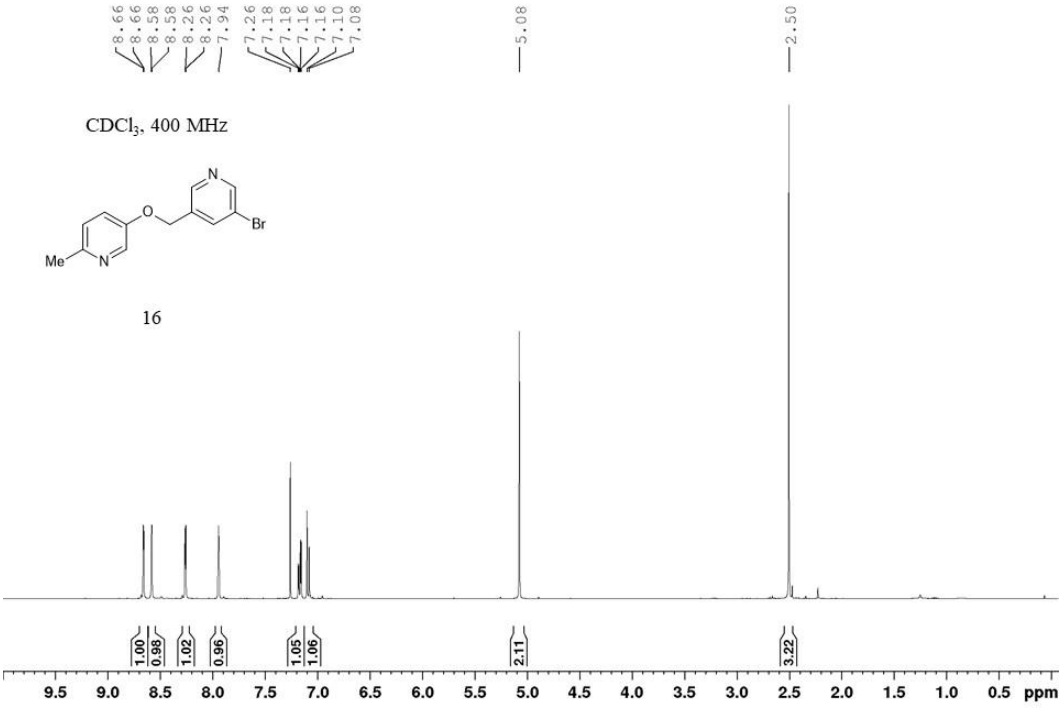
13

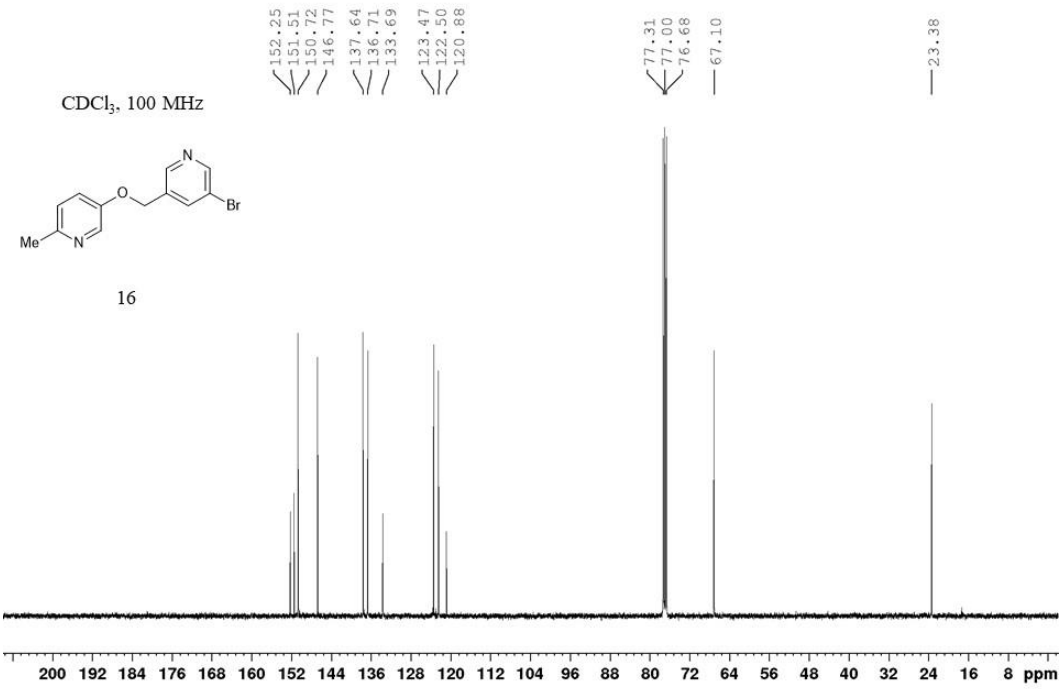

8.67
8.59
8.58
8.26
7.77
7.77
7.75
7.33
7.32
7.31
7.30
7.30
7.26
7.18
7.17
7.17
7.16
7.15
7.14
7.08
7.05
5.08
2.48
CDCl3, 400 MHz
Me
N
O
N
14
1.00
1.17
0.96
1.00
1.05
1.02
1.01
2.10
3.15
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

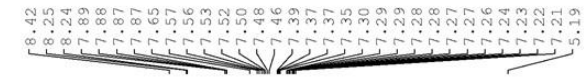

152.40
151.15
149.64
149.58
148.91
136.84
135.15
131.88
123.41
123.36
122.35
67.91
23.30
CDCl3, 400 MHz
Me
N
O
N
14
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm


8.47
8.42
8.26
8.25
7.57
7.26
7.18
7.17
7.15
7.15
7.07
7.05
5.05
2.49
2.35
CDCl3, 400 MHz
Me
Me
N
O
N
15
1.00
1.03
0.99
1.00
1.04
1.03
2.18
3.21
3.21
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 ppm

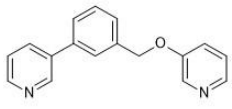

152.51
151.06
150.19
146.13
136.89
135.72
133.11
131.30
123.33
122.36
77.31
76.68
67.95
23.34
18.29
CDCl3, 100 MHz
Me
Me
N
O
N
15
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm


8.66
8.66
8.58
8.58
8.26
8.26
7.94
7.26
7.18
7.18
7.16
7.16
7.10
7.08
5.08
2.50
CDCl3, 400 MHz
N
O
Br
Me
N
16
1.00
0.98
1.02
0.96
1.05
1.06
2.11
3.22
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 ppm

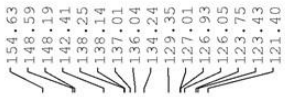

152.25
151.51
150.72
146.77
137.64
136.71
133.69
123.47
122.50
120.88
77.31
77.00
76.68
67.10
23.38
CDCl3, 100 MHz
N
O
Br
Me
N
16
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm



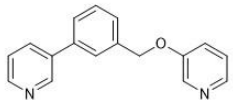
$CDCl_3$, 400 MHz



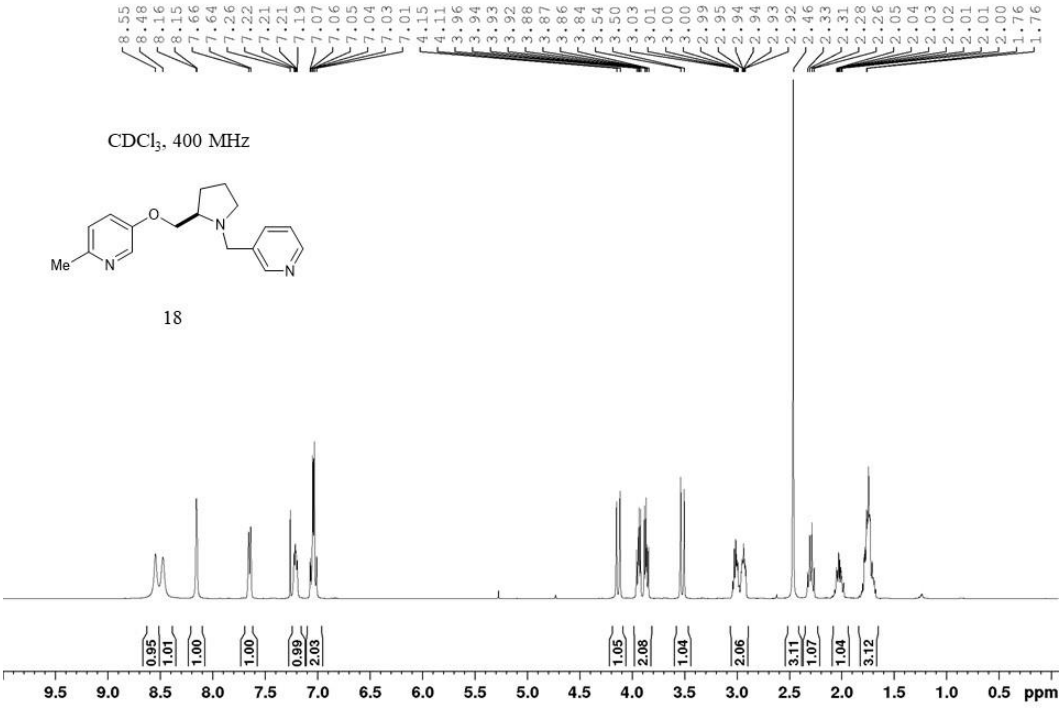
17

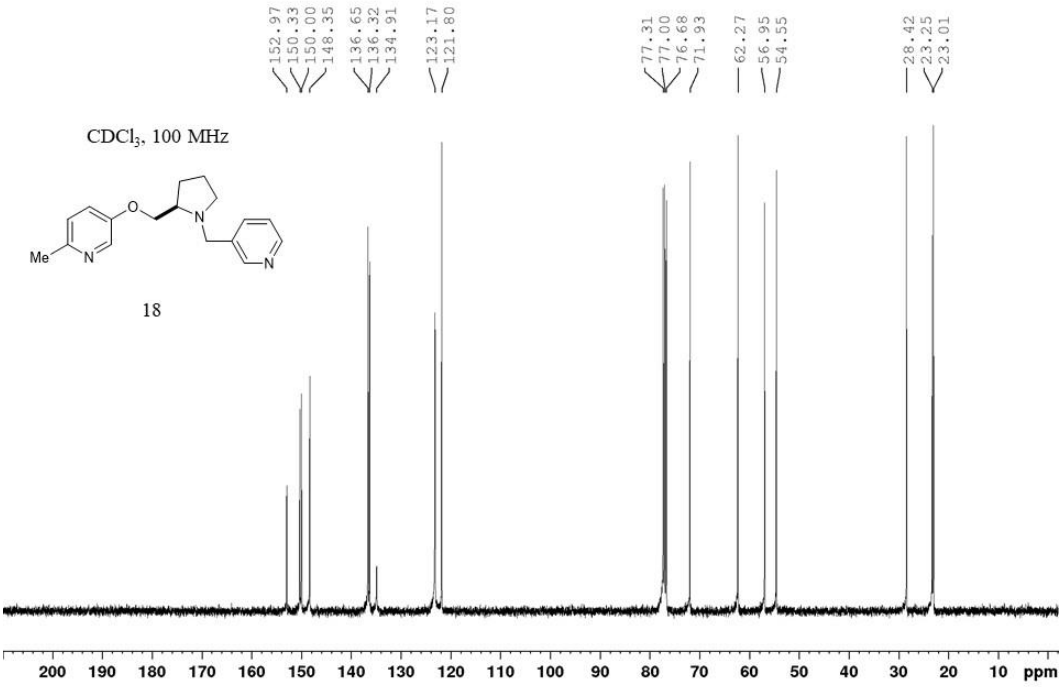


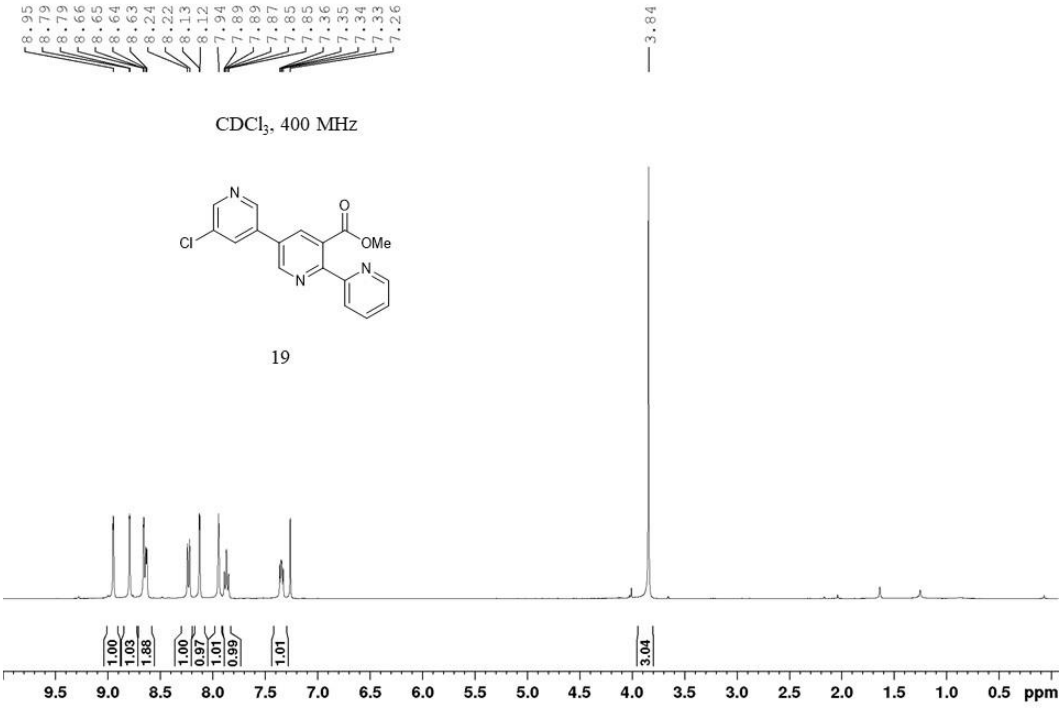
$CDCl_3$, 100 MHz

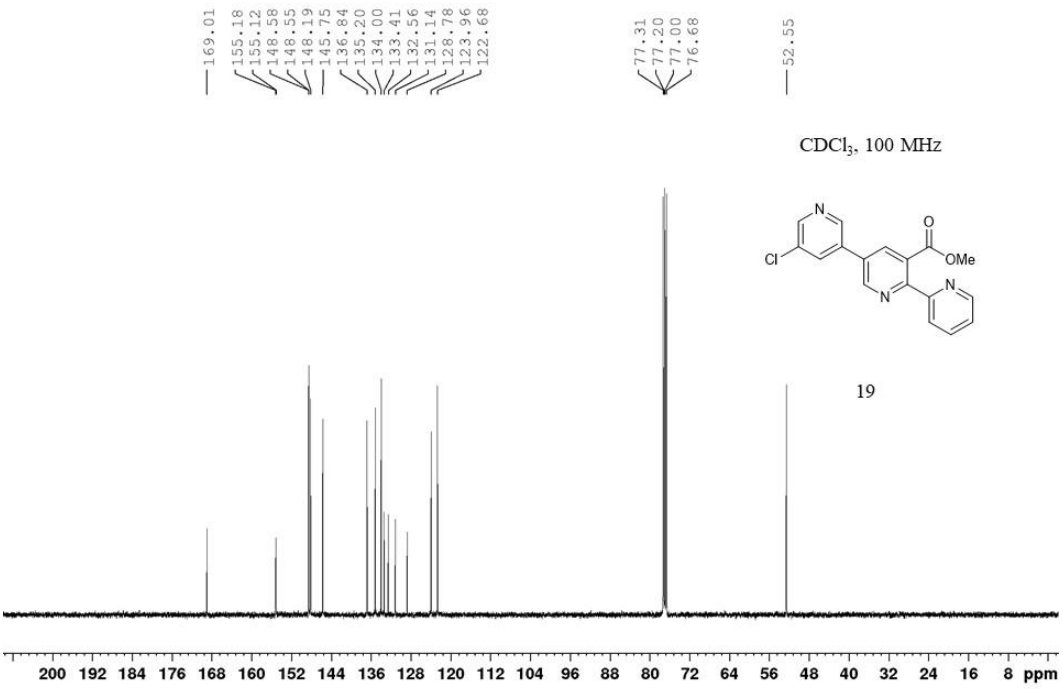


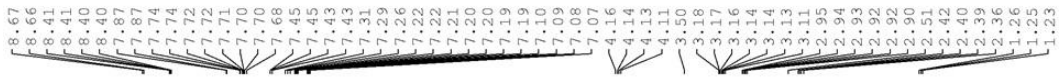
17


8.55
8.48
8.16
8.15
7.66
7.64
7.26
7.22
7.21
7.21
7.19
7.07
7.06
7.05
7.04
7.03
7.01
4.15
4.11
3.96
3.94
3.93
3.92
3.88
3.87
3.86
3.84
3.54
3.50
3.03
3.01
3.00
3.00
2.99
2.95
2.94
2.94
2.93
2.92
2.46
2.33
2.31
2.28
2.26
2.05
2.04
2.03
2.02
2.01
2.01
2.00
1.76
1.76
CDCl3, 400 MHz
Me
N
O
N
N
18
0.95
1.01
1.00
1.00
0.99
2.03
1.05
2.08
1.04
2.06
3.11
1.07
1.04
3.12
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 ppm

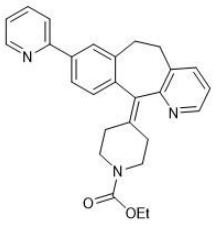

152.97
150.33
150.00
148.35
136.65
136.32
134.91
123.17
121.80
77.31
77.00
76.68
71.93
62.27
56.95
54.55
28.42
23.25
23.01
CDCl3, 100 MHz
Me
N
O
N
N
18
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


8.95
8.79
8.79
8.66
8.65
8.64
8.63
8.24
8.22
8.13
8.12
7.94
7.89
7.89
7.87
7.85
7.85
7.36
7.35
7.34
7.33
7.26
3.84
CDCl3, 400 MHz
Cl
N
O
OMe
N
N
19
1.00
1.03
1.88
1.00
0.97
1.01
0.99
1.01
3.04
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 ppm


169.01
155.18
155.12
148.58
148.55
148.19
145.75
136.84
135.20
134.00
133.41
132.56
131.14
128.78
123.96
122.68
77.31
77.20
77.00
76.68
52.55
CDCl3, 100 MHz
Cl
N
O
OMe
N
N
19
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 ppm

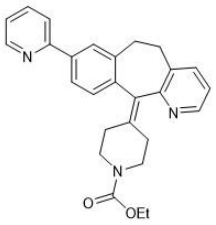


$CDCl_3$, 400 MHz

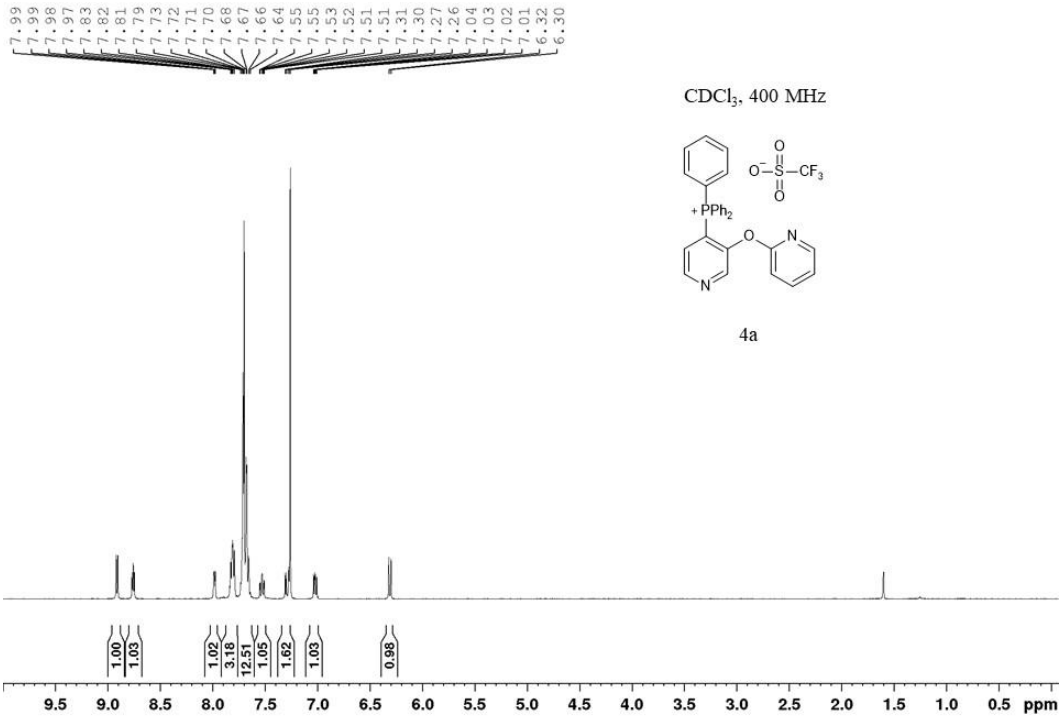


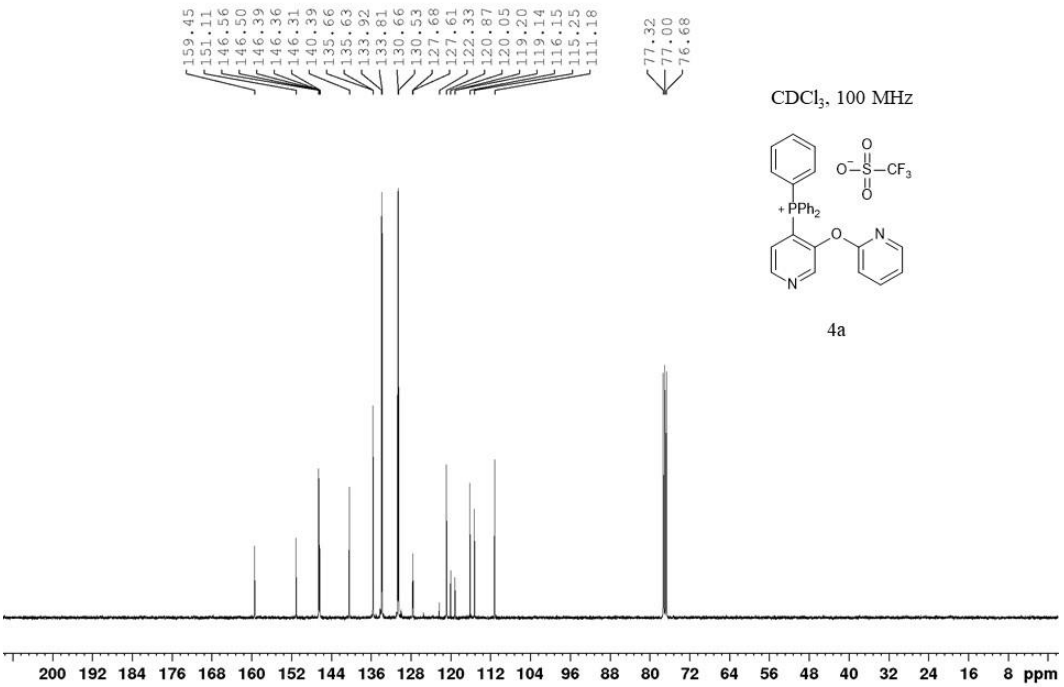
20

$CDCl_3$, 100 MHz

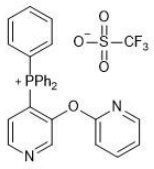


20


7.99
7.99
7.98
7.97
7.83
7.82
7.81
7.79
7.73
7.72
7.71
7.70
7.68
7.67
7.66
7.64
7.55
7.55
7.53
7.52
7.51
7.51
7.31
7.30
7.27
7.26
7.04
7.03
7.02
7.01
6.32
6.30
CDCl3, 400 MHz
4a
1.00
1.03
1.02
3.18
12.51
1.05
1.62
1.03
0.98
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 ppm

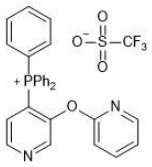

159.45
151.11
146.56
146.50
146.39
146.36
146.31
140.39
135.66
135.63
133.92
133.81
130.66
130.53
127.68
127.61
122.33
120.87
120.05
119.20
119.14
116.15
115.25
111.18
77.32
77.00
76.68
CDCl3, 100 MHz
4a
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz



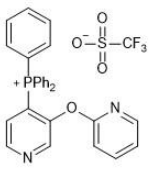
4a

$CDCl_3$, 162 MHz

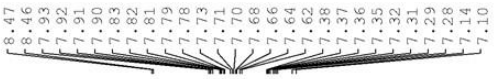


4a

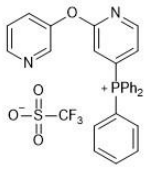
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)



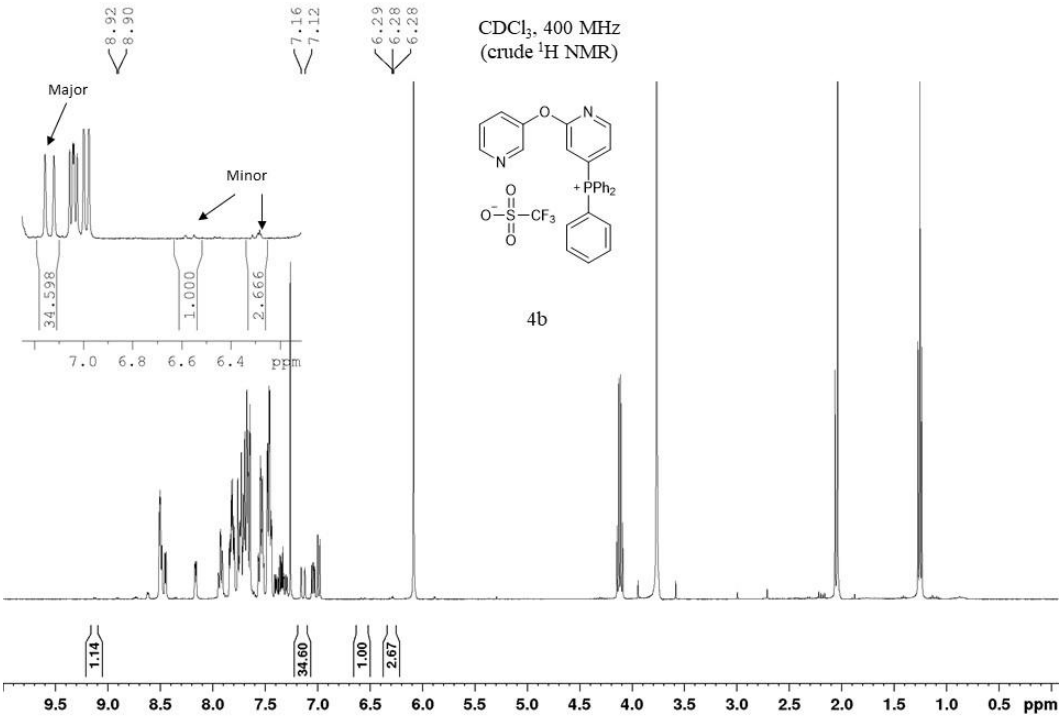
4a

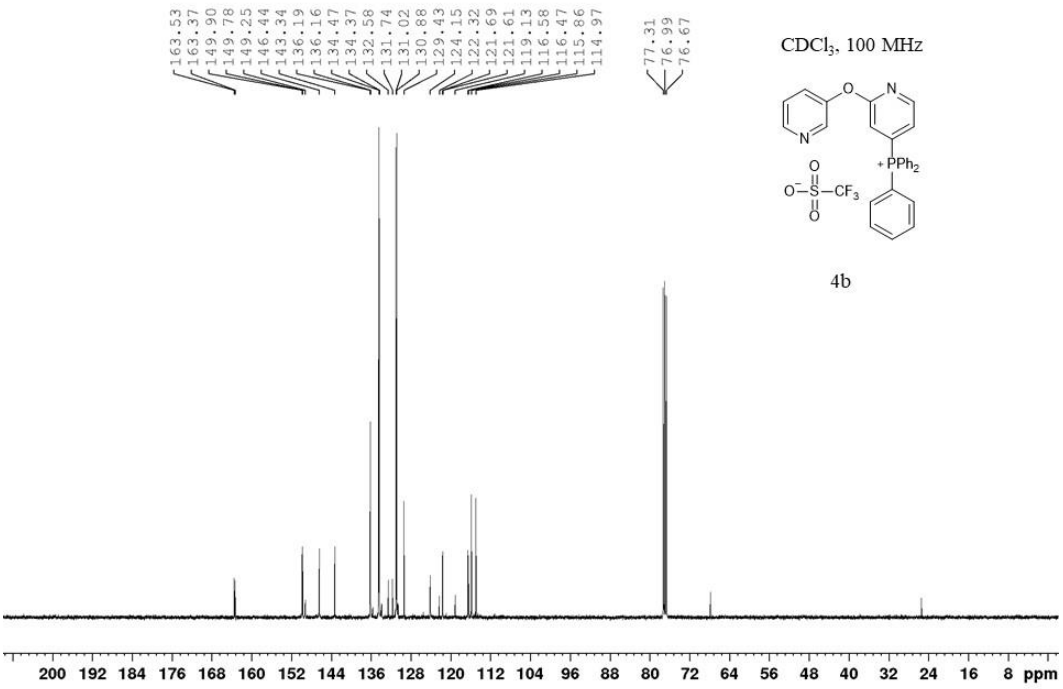


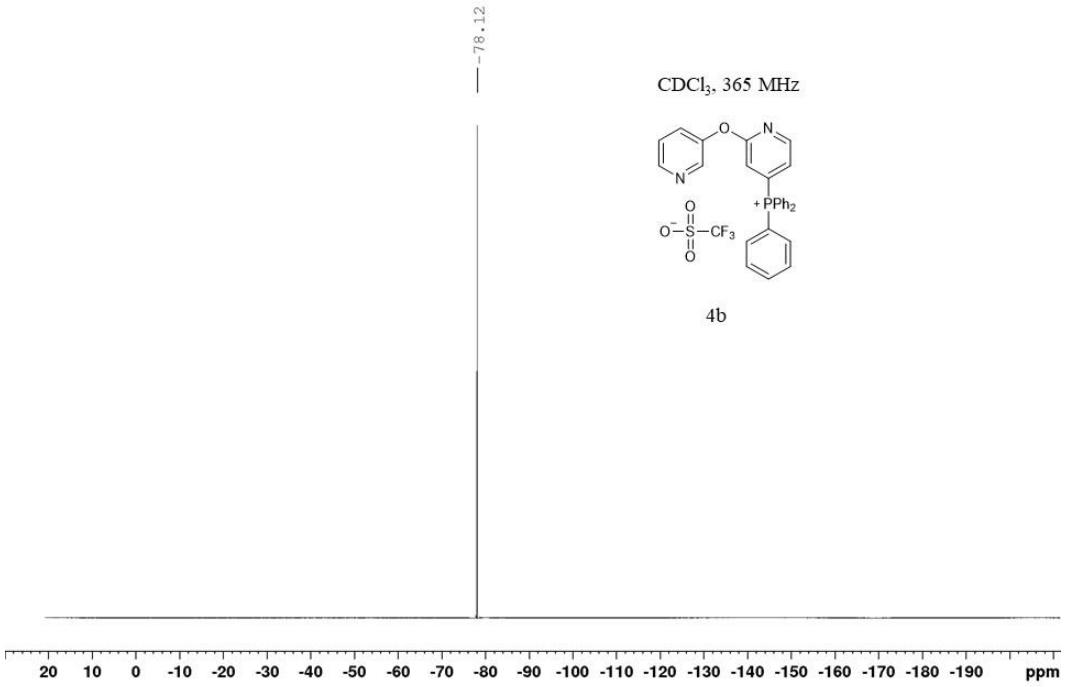
$CDCl_3$, 400 MHz

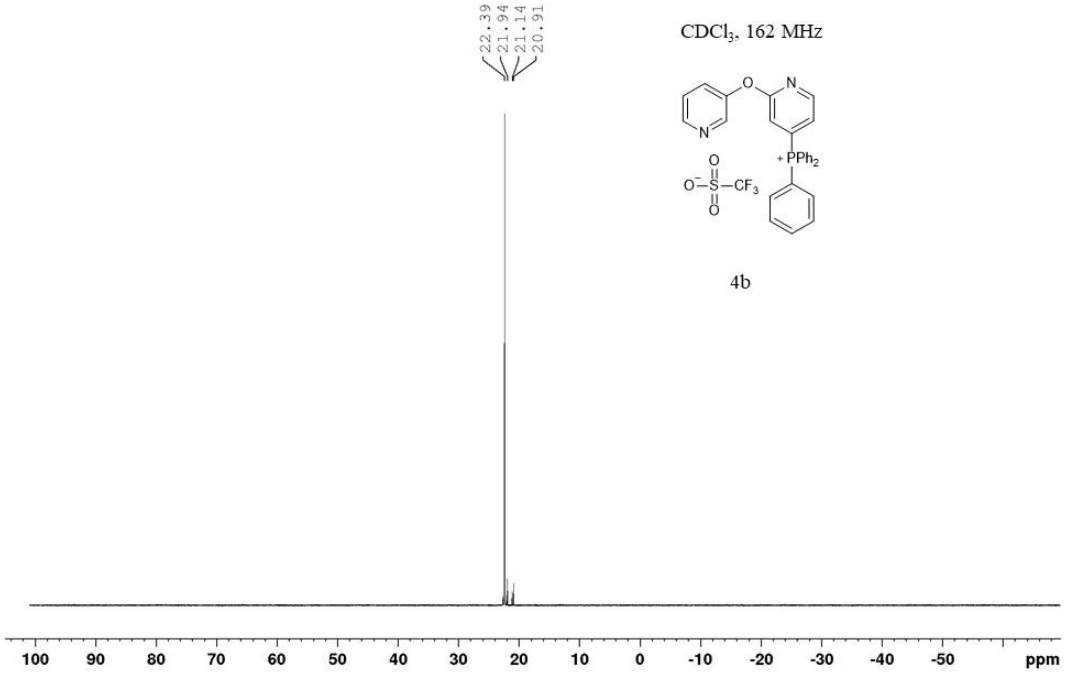


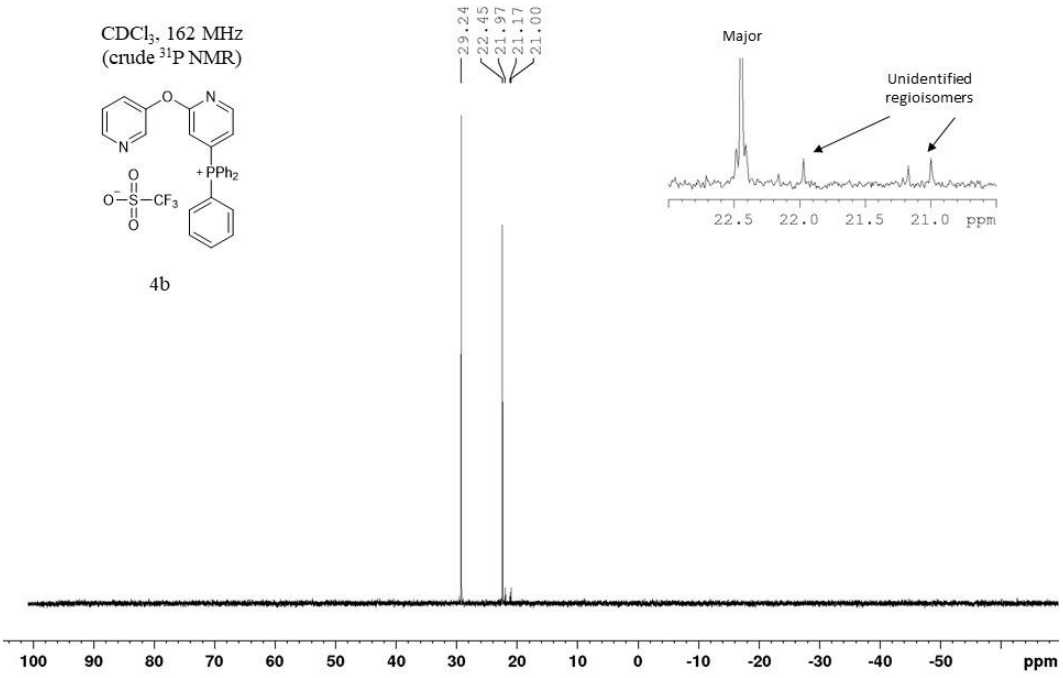
4b

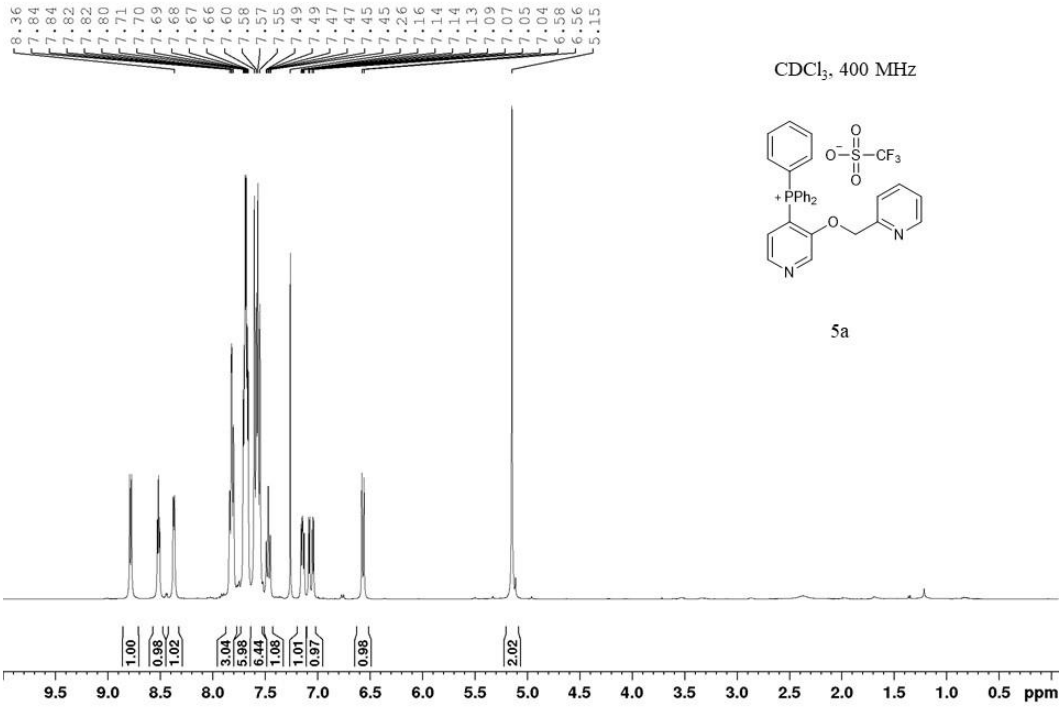

8.92
8.90
7.16
7.12
6.29
6.28
6.28
CDCl3, 400 MHz
(crude 1H NMR)
Major
Minor
34.598
1.000
2.666
7.0 6.8 6.6 6.4 ppm
4b
1.14
34.60
1.00
2.67
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

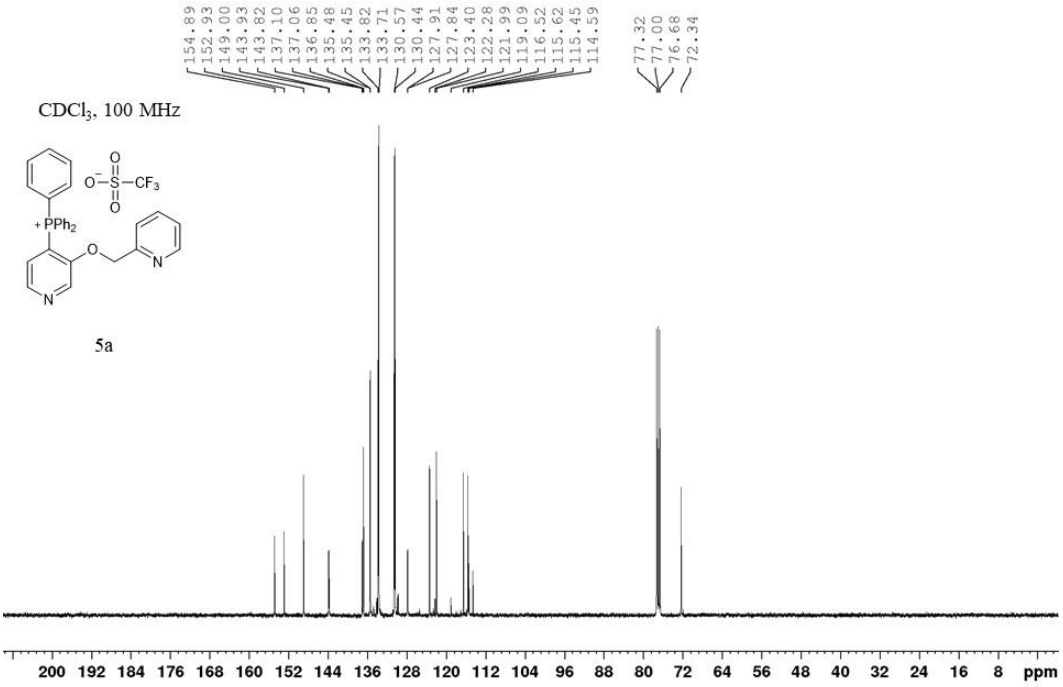

163.53
163.37
149.90
149.78
149.25
146.44
143.34
136.19
136.16
134.47
134.37
132.58
131.74
131.02
130.88
129.43
124.15
122.32
121.69
121.61
119.13
116.58
116.47
115.86
114.97
77.31
76.99
76.67
CDCl3, 100 MHz
4b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

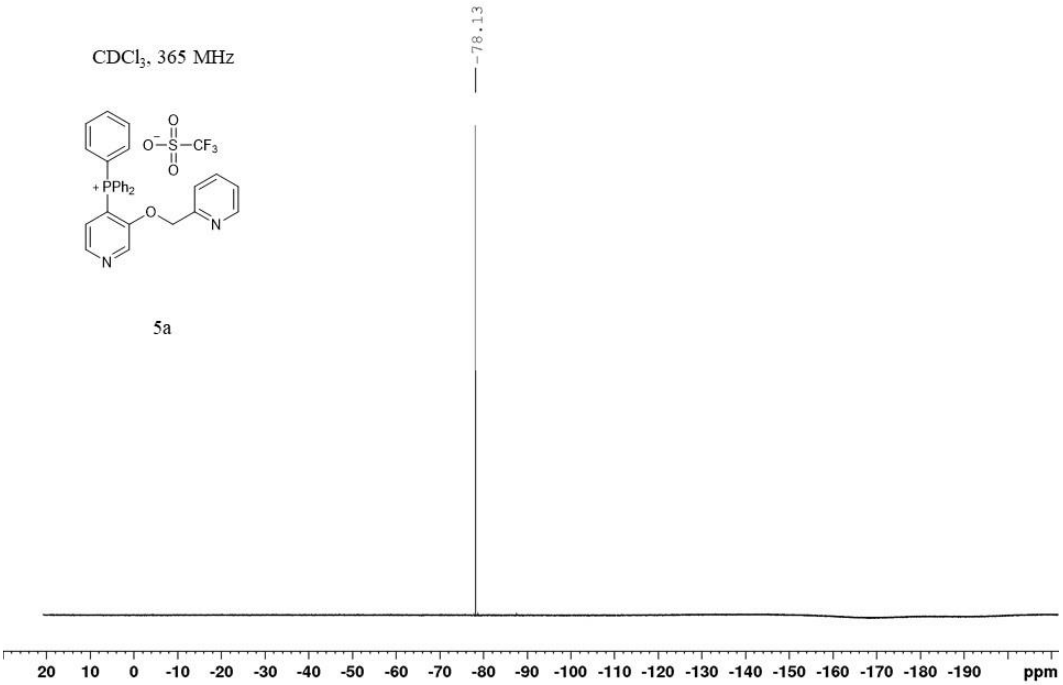

78.12
CDCl3, 365 MHz
4b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm


22.39
21.94
21.14
20.91
CDCl3, 162 MHz
4b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

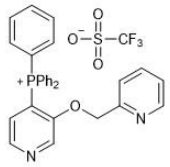

CDCl3, 162 MHz
(crude 31P NMR)
4b
29.24
22.45
21.97
21.17
21.00
Major
Unidentified
regioisomers
22.5 22.0 21.5 21.0 ppm
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm


8.36
7.84
7.84
7.82
7.82
7.80
7.71
7.70
7.69
7.68
7.67
7.66
7.60
7.58
7.57
7.55
7.49
7.49
7.47
7.47
7.45
7.45
7.26
7.16
7.14
7.14
7.13
7.09
7.07
7.05
7.04
6.58
6.56
5.15
CDCl3, 400 MHz
5a
1.00
0.98
1.02
3.04
5.98
6.44
1.08
1.01
0.97
0.98
2.02
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 ppm


154.89
152.93
149.00
143.93
143.82
137.10
137.06
136.85
135.48
135.45
133.82
133.71
130.57
130.44
127.91
127.84
123.40
122.28
121.99
119.09
116.52
115.62
115.45
114.59
77.32
77.00
76.68
72.34
CDCl3, 100 MHz
5a
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 ppm

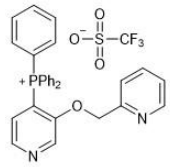

-78.13
CDCl3, 365 MHz
5a
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

$CDCl_3$, 162 MHz

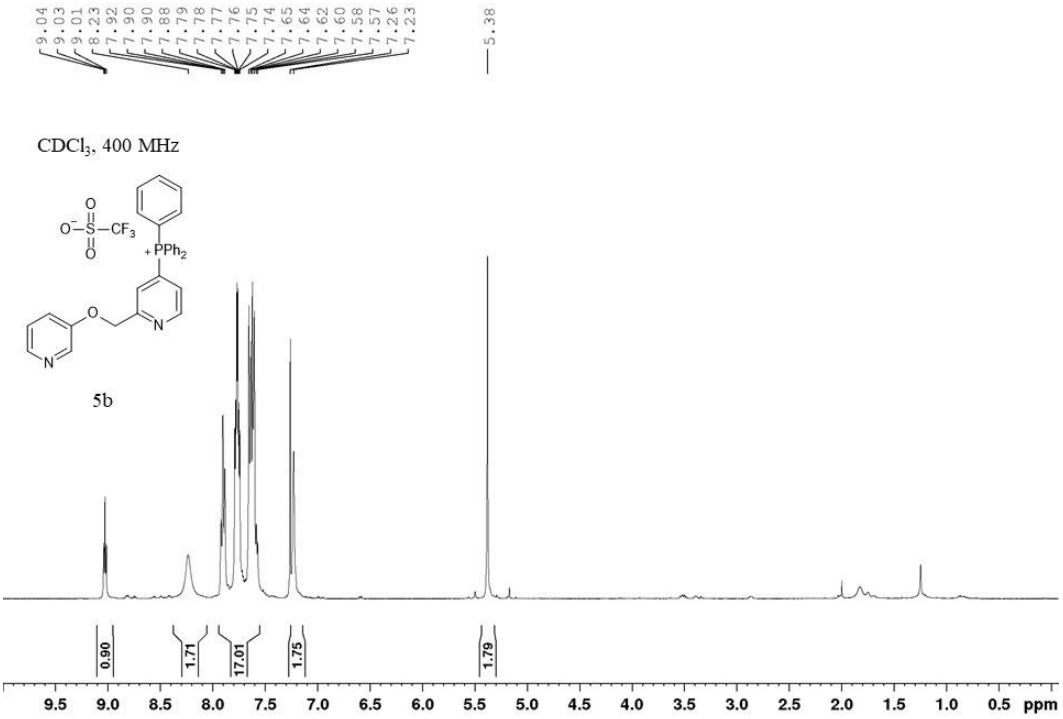


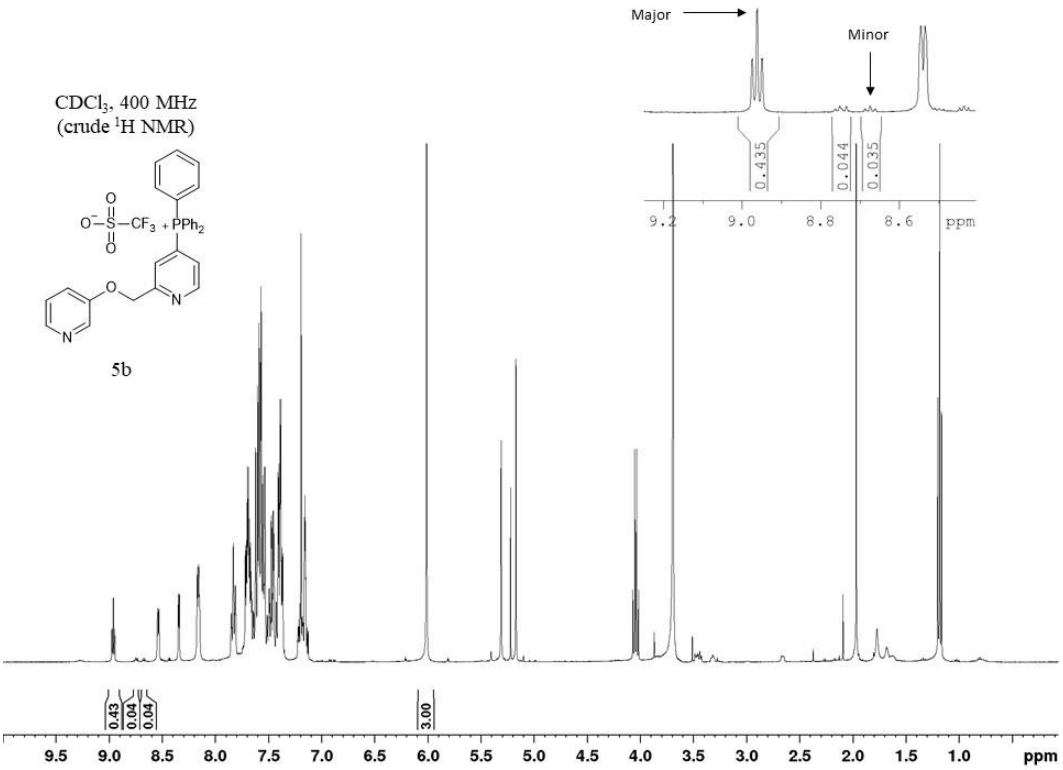
5a

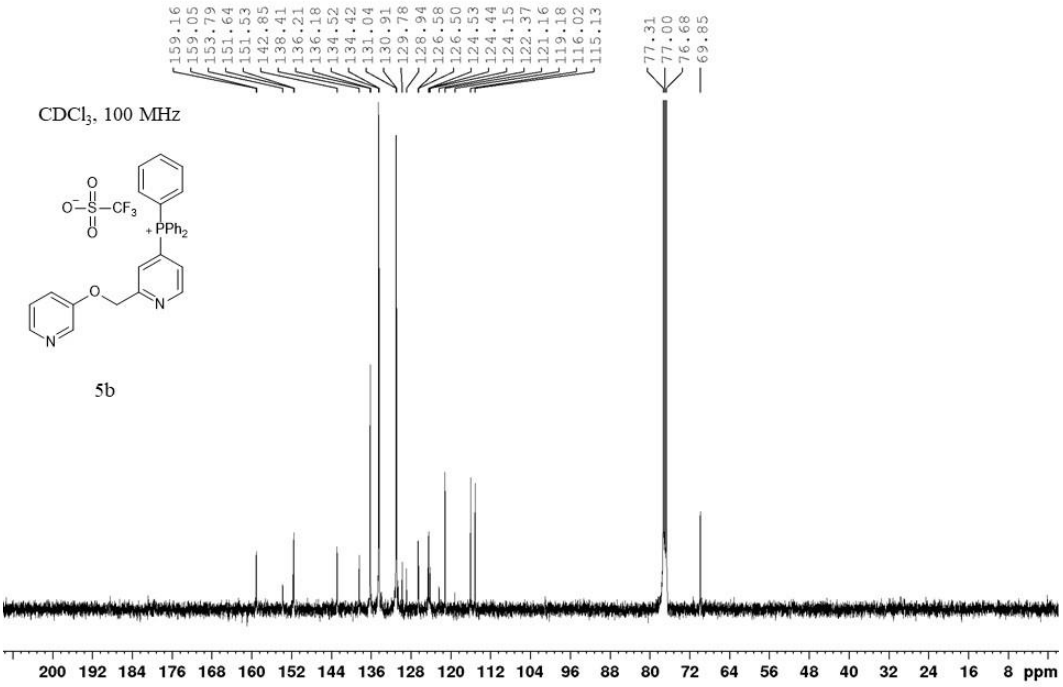
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)

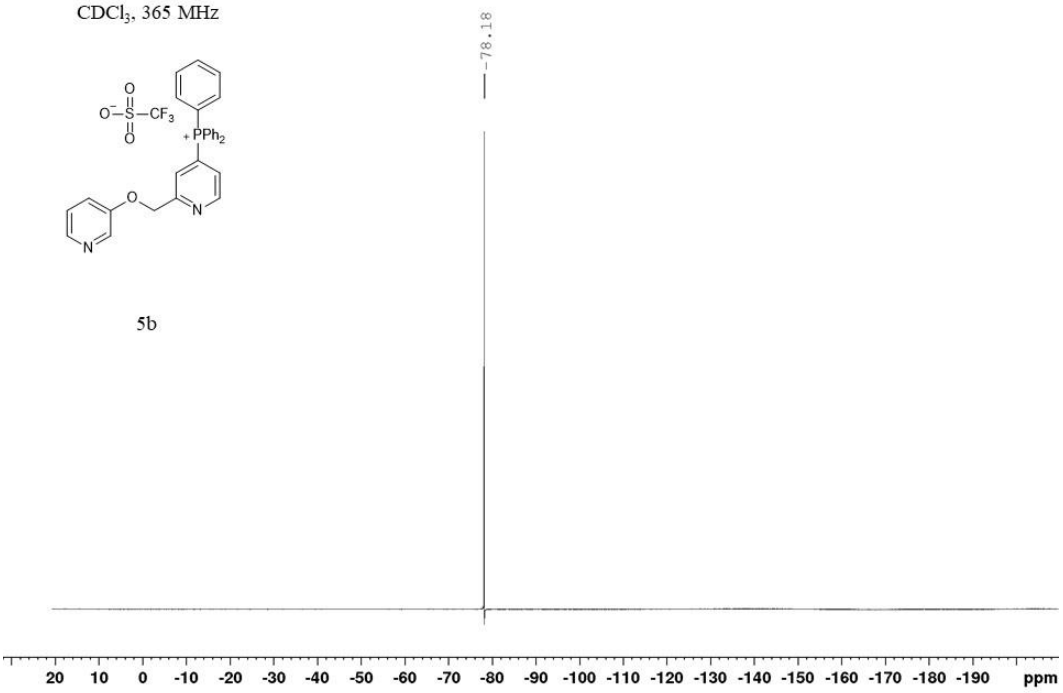


5a

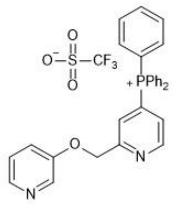

9.04
9.03
9.01
8.23
7.92
7.90
7.90
7.88
7.79
7.78
7.77
7.76
7.75
7.74
7.65
7.64
7.62
7.60
7.58
7.57
7.26
7.23
5.38
CDCl3, 400 MHz
5b
0.90
1.71
17.01
1.75
1.79
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


CDCl3, 400 MHz
(crude 1H NMR)
5b
Major
Minor
0.435
0.044
0.035
9.2 9.0 8.8 8.6 ppm
0.43
0.04
0.04
3.00
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 ppm


159.16
159.05
153.79
151.64
151.53
142.85
138.41
136.21
136.18
134.52
134.42
131.04
130.91
129.78
128.94
126.58
126.50
124.53
124.44
124.15
122.37
121.16
119.18
116.02
115.13
77.31
77.00
76.68
69.85
CDCl3, 100 MHz
5b
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 ppm

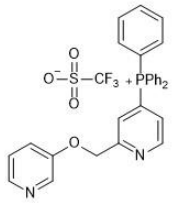

CDCl3, 365 MHz
-78.18
5b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

$CDCl_3$, 162 MHz

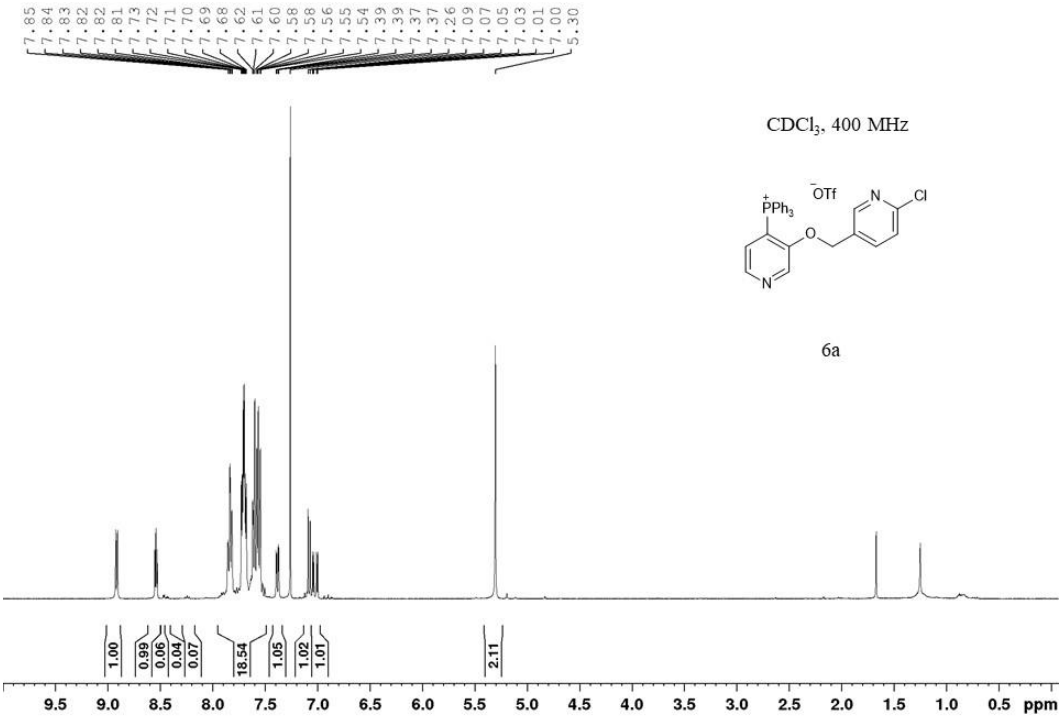


5b

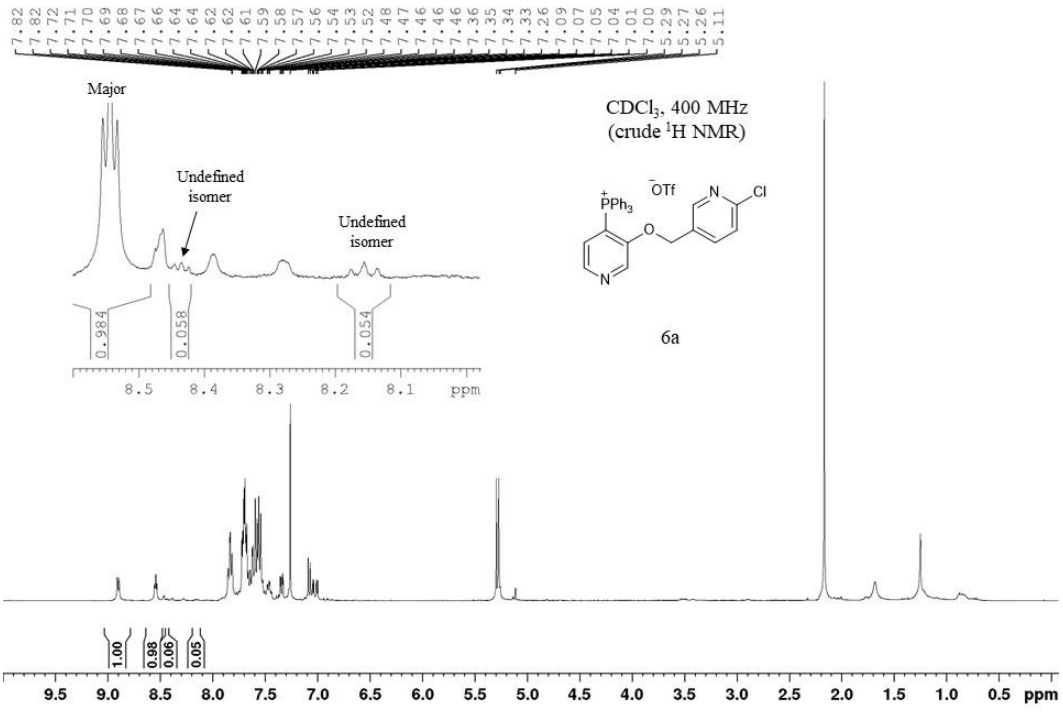
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)



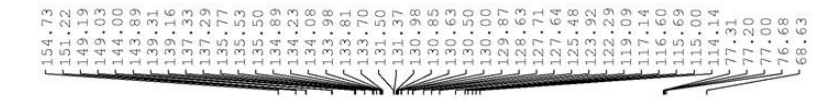
5b


7.85 7.84 7.83 7.82 7.82 7.81 7.73 7.72 7.71 7.70 7.69 7.68 7.62 7.61 7.60 7.58 7.58 7.56 7.55 7.54 7.39 7.39 7.37 7.37 7.26 7.09 7.07 7.05 7.03 7.01 7.00 5.30
CDCl3, 400 MHz
OTf
PPh3
N
Cl
O
N
1.00 0.99 0.06 0.04 0.07 18.54 1.05 1.02 1.01 2.11
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 ppm

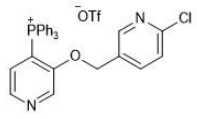
6a


7.82 7.82 7.72 7.71 7.70 7.69 7.68 7.67 7.66 7.64 7.64 7.62 7.61 7.59 7.58 7.57 7.56 7.54 7.53 7.52 7.48 7.47 7.46 7.46 7.46 7.36 7.35 7.34 7.33 7.26 7.09 7.07 7.05 7.04 7.01 7.00 5.29 5.27 5.26 5.11
Major
Undefined isomer
Undefined isomer
0.984 0.058 0.054
8.5 8.4 8.3 8.2 8.1 ppm
CDCl3, 400 MHz
(crude 1H NMR)
OTf
PPh3
N
Cl
O
N
1.00 0.98 0.06 0.05
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 ppm

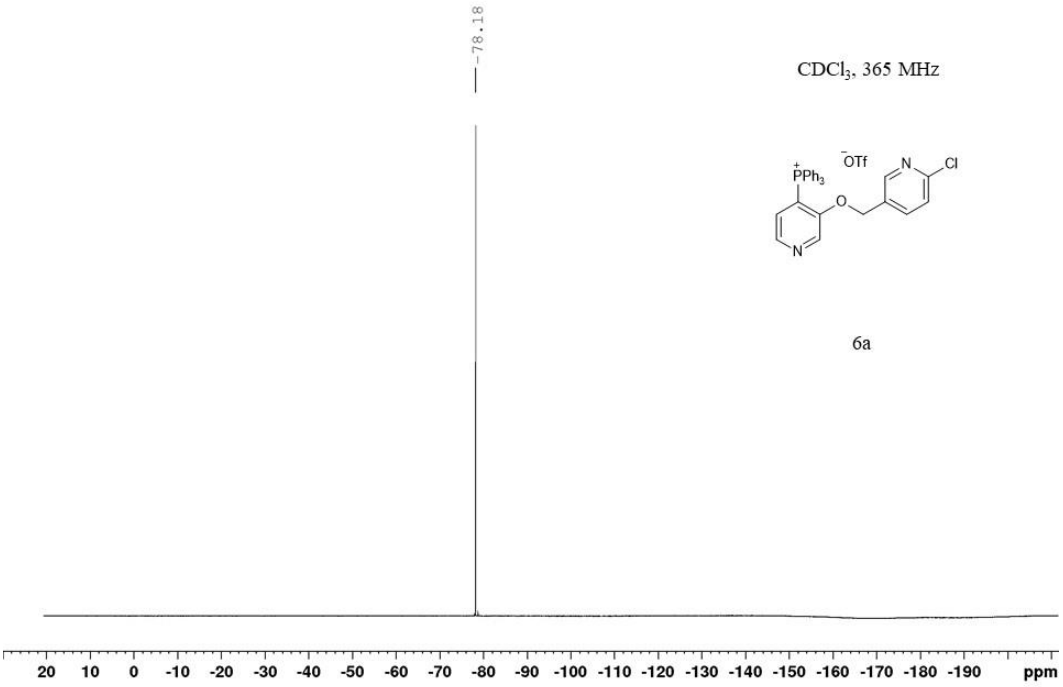
6a



$CDCl_3$, 100 MHz

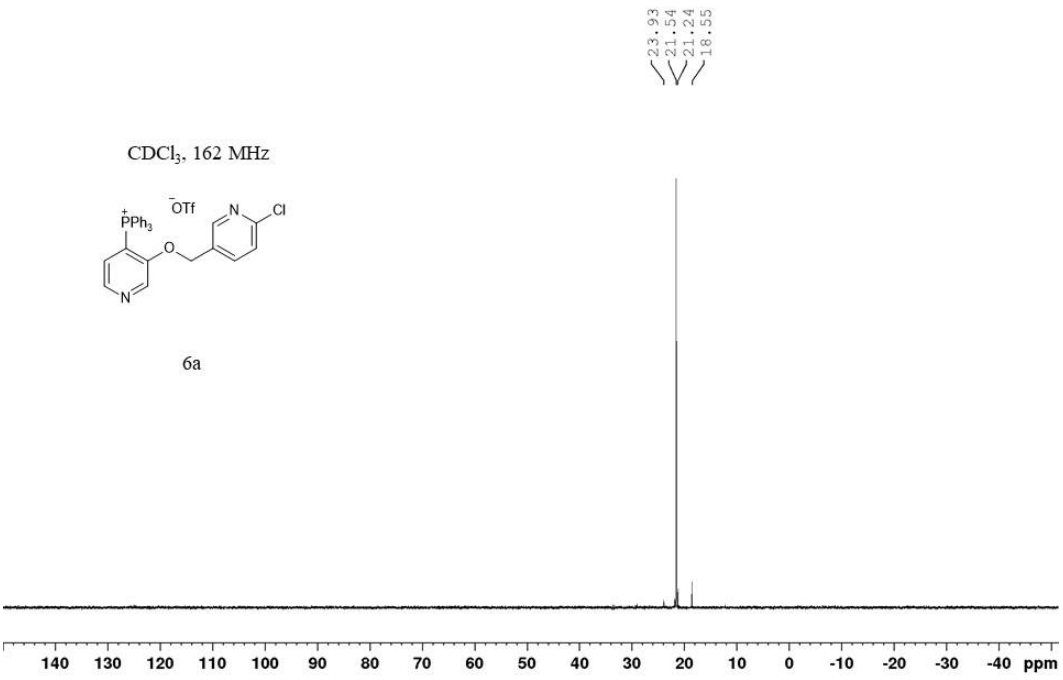


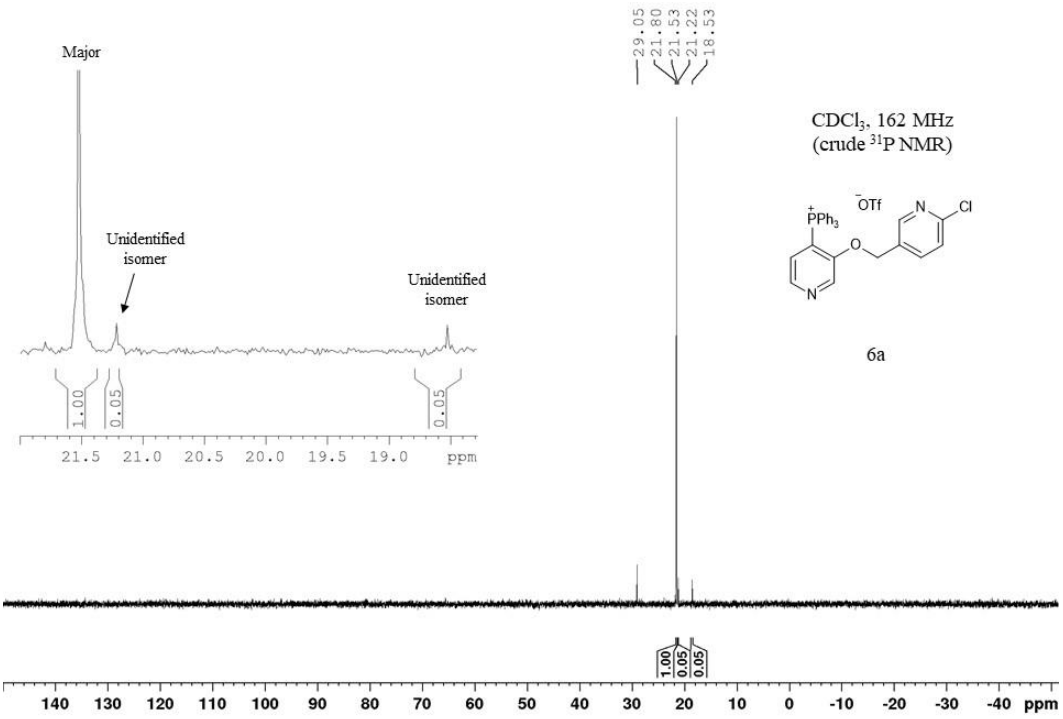
6a

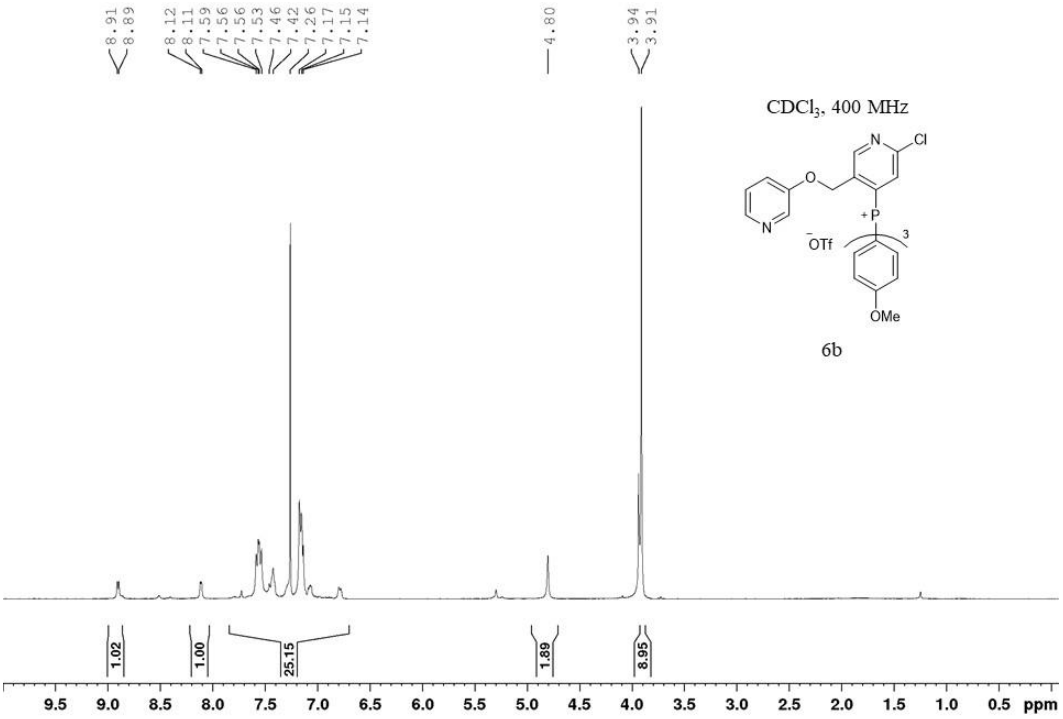


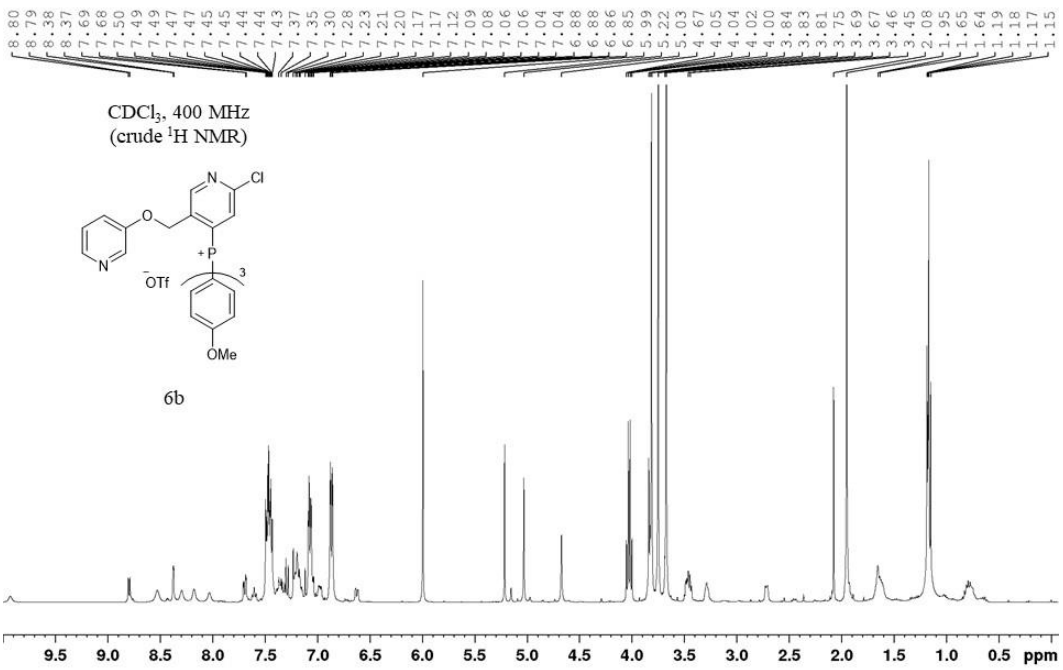
$CDCl_3$, 365 MHz

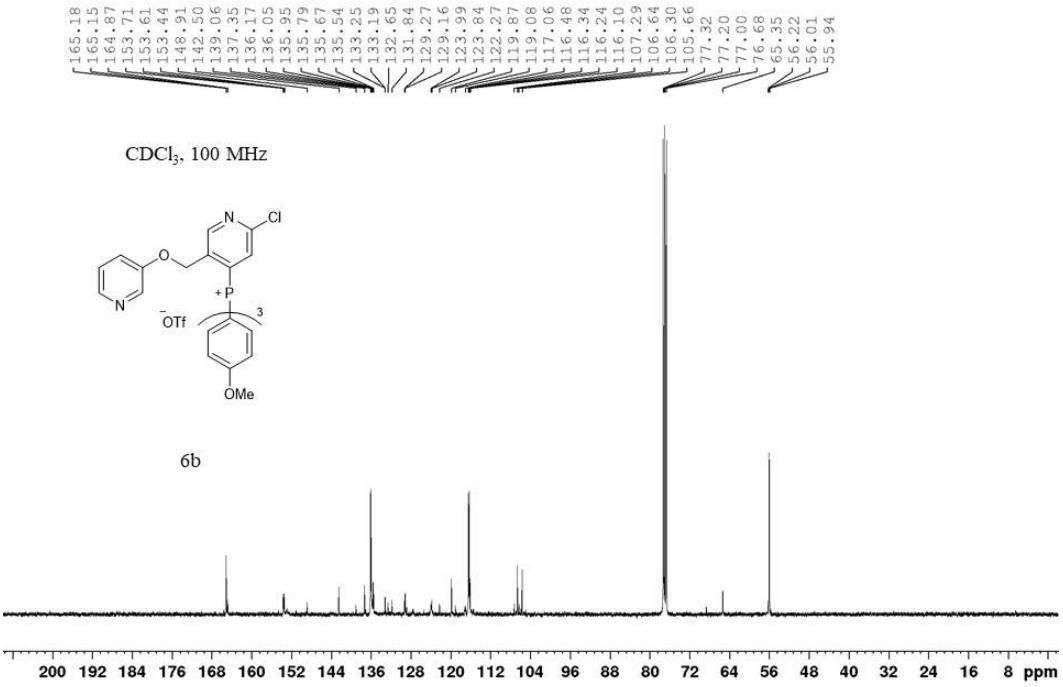
6a

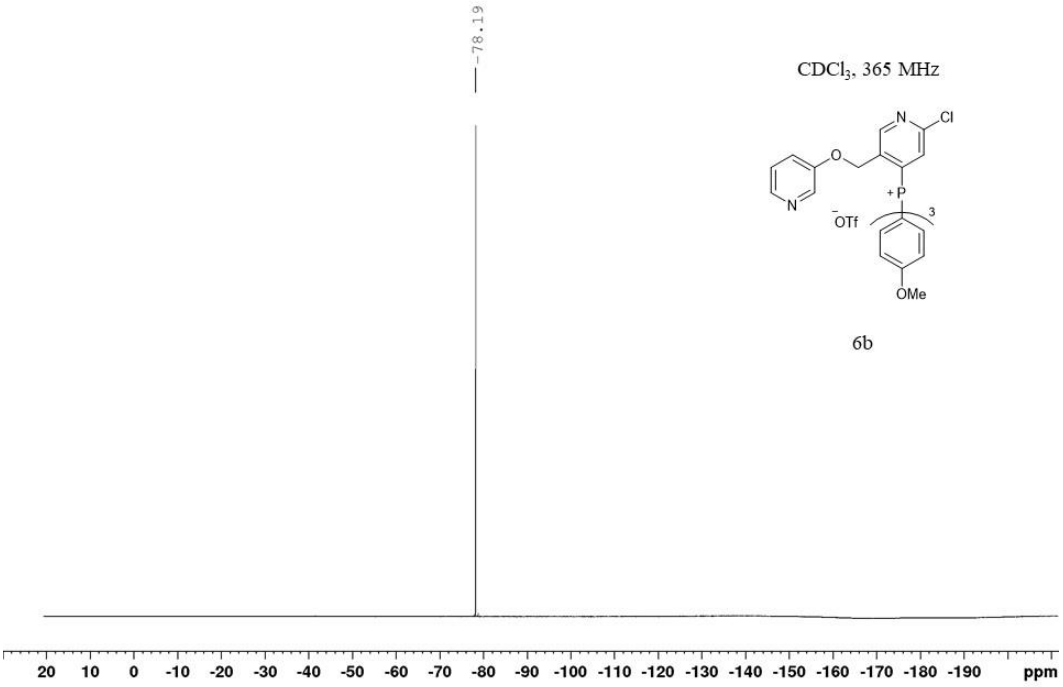

23.93
21.54
21.24
18.55
CDCl3, 162 MHz
PPh3
OTf
N
Cl
O
N
6a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

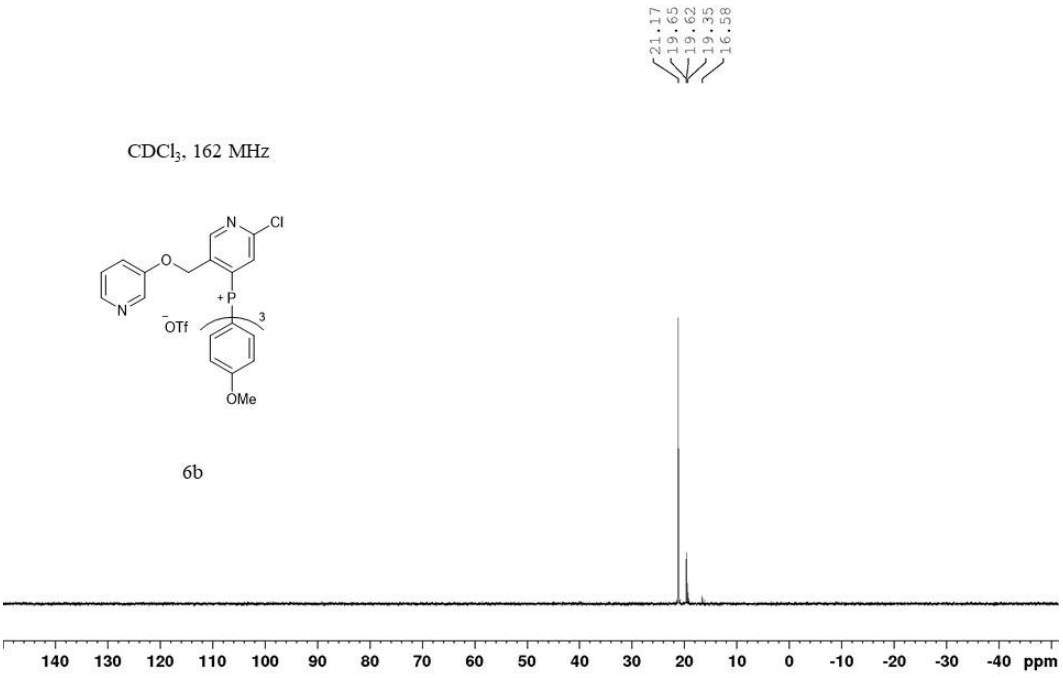

29.05
21.80
21.53
21.22
18.53
Major
Unidentified isomer
Unidentified isomer
1.00
0.05
0.05
21.5 21.0 20.5 20.0 19.5 19.0 ppm
CDCl3, 162 MHz
(crude 31P NMR)
PPh3
OTf
N
Cl
O
N
6a
1.00
0.05
0.05
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

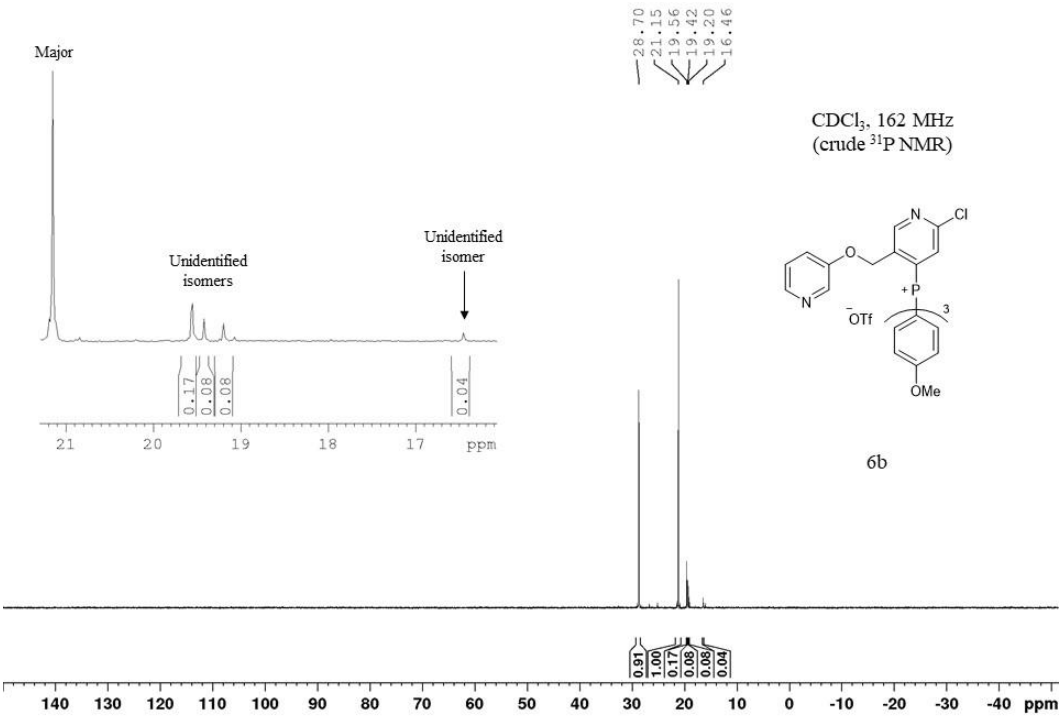

8.91
8.89
8.12
8.11
7.59
7.56
7.56
7.53
7.46
7.42
7.26
7.17
7.15
7.14
4.80
3.94
3.91
CDCl3, 400 MHz
N
Cl
O
N
+P
OTf
3
OMe
6b
1.02
1.00
25.15
1.89
8.95
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

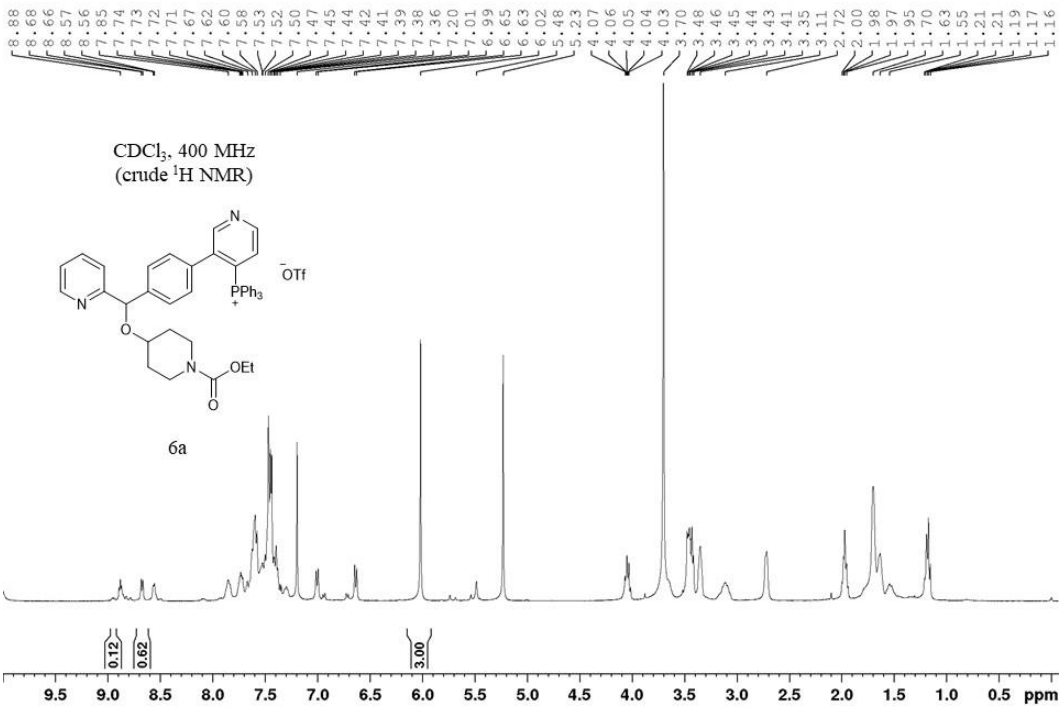

8.80
8.79
8.38
8.37
7.69
7.68
7.50
7.49
7.49
7.47
7.47
7.45
7.45
7.44
7.44
7.43
7.37
7.35
7.30
7.28
7.23
7.21
7.20
7.17
7.17
7.12
7.09
7.08
7.06
7.06
7.04
7.04
6.88
6.88
6.86
6.85
5.99
5.22
5.03
4.67
4.05
4.04
4.02
4.00
3.84
3.83
3.81
3.75
3.69
3.67
3.46
3.45
2.08
1.95
1.65
1.64
1.19
1.18
1.17
1.15
CDCl3, 400 MHz
(crude 1H NMR)
N
Cl
O
N
+P
OTf
3
OMe
6b
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 ppm

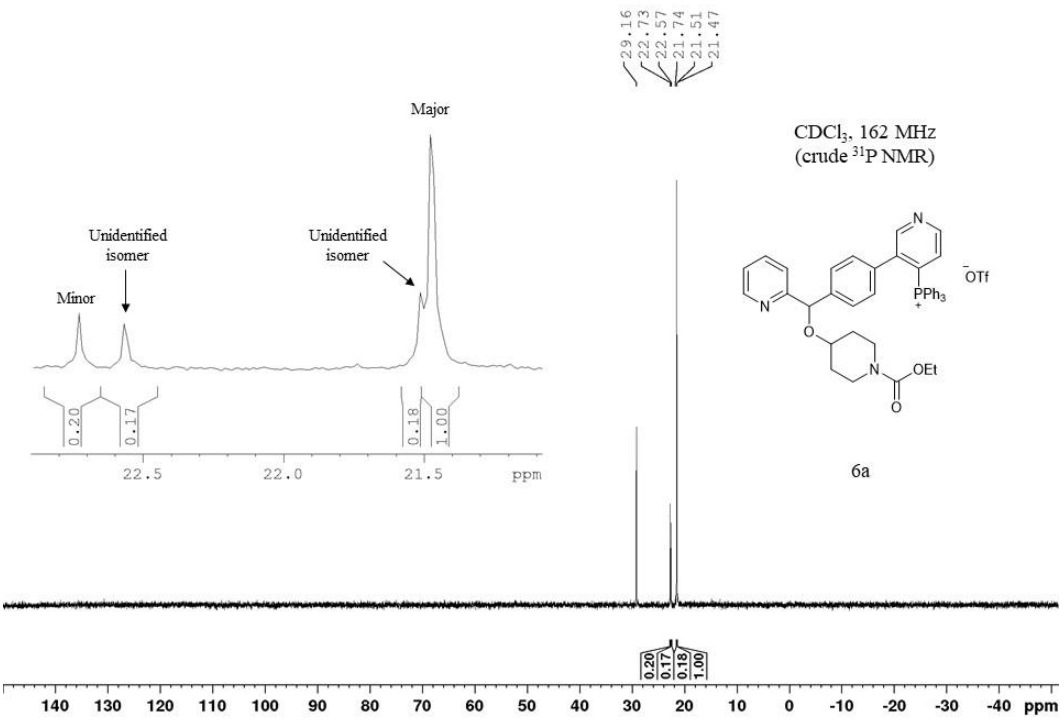

165.18
165.15
164.87
153.71
153.61
153.44
148.91
142.50
139.06
137.35
136.17
136.05
135.95
135.79
135.67
135.54
133.25
133.19
132.65
131.84
129.27
129.16
123.99
123.84
122.27
119.87
119.08
117.06
116.48
116.34
116.24
116.10
107.29
106.64
106.30
105.66
77.32
77.20
77.00
76.68
65.35
56.22
56.01
55.94
CDCl3, 100 MHz
N
Cl
O
N
+P
3
OTf
OMe
6b
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 ppm

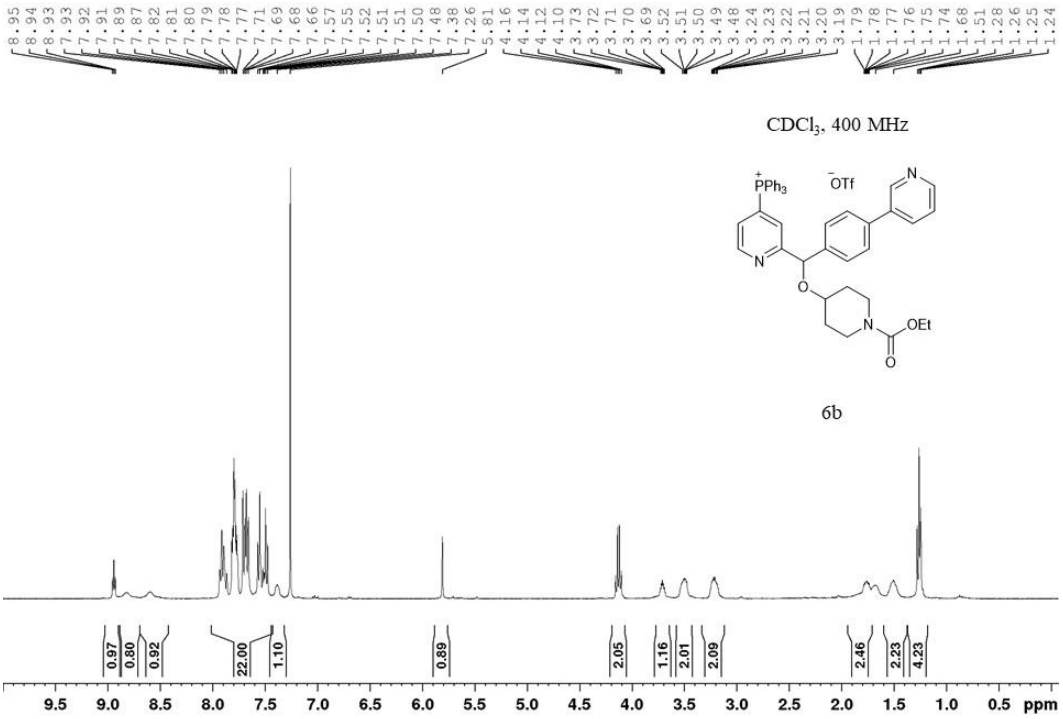

-78.19
CDCl3, 365 MHz
N
Cl
O
N
+P
3
OTf
OMe
6b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

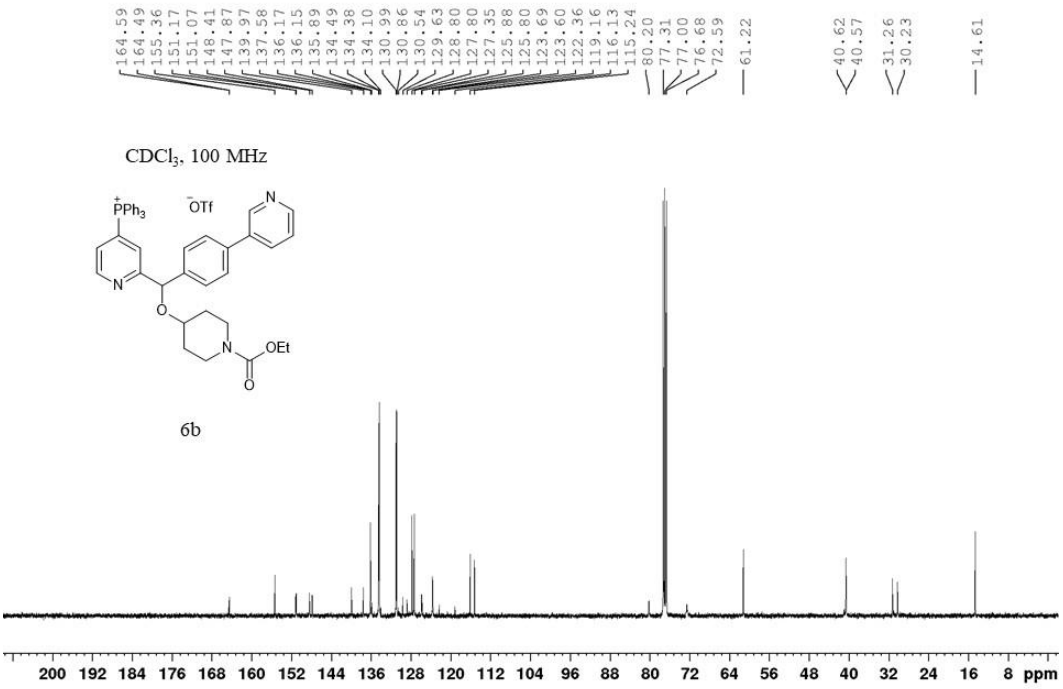

21.17
19.65
19.62
19.35
16.58
CDCl3, 162 MHz
N
Cl
O
N
+P
OTf
3
OMe
6b
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

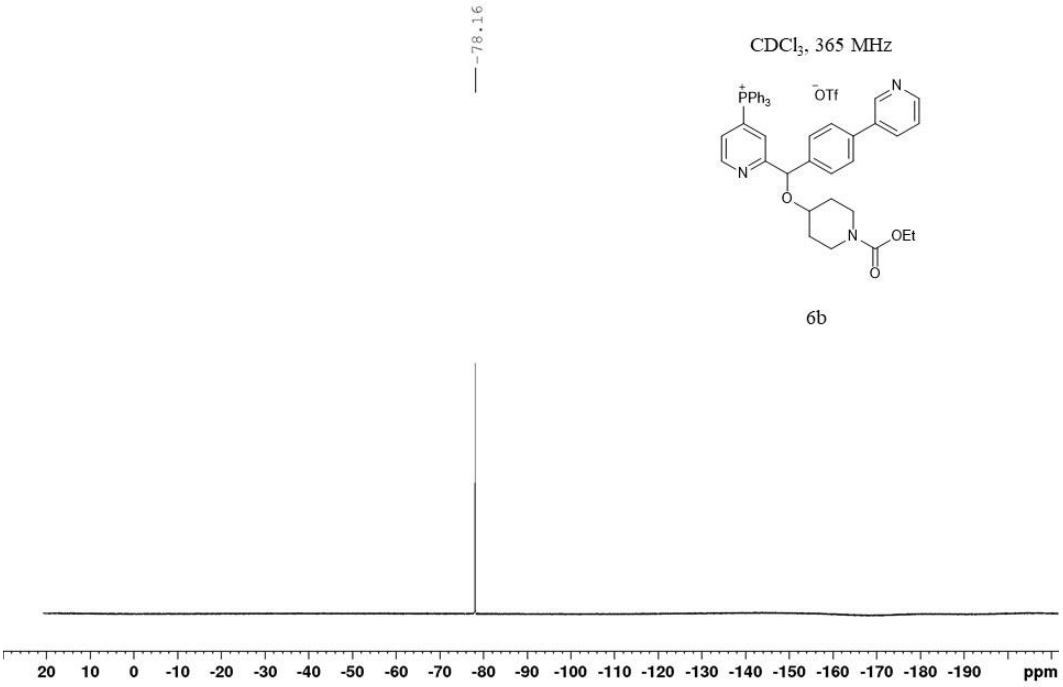

28.70
21.15
19.56
19.42
19.20
16.46
Major
Unidentified isomers
Unidentified isomer
0.17
0.08
0.08
0.04
21 20 19 18 17 ppm
CDCl3, 162 MHz
(crude 31P NMR)
N
Cl
O
N
+P
OTf
3
OMe
6b
0.91
1.00
0.17
0.08
0.08
0.04
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

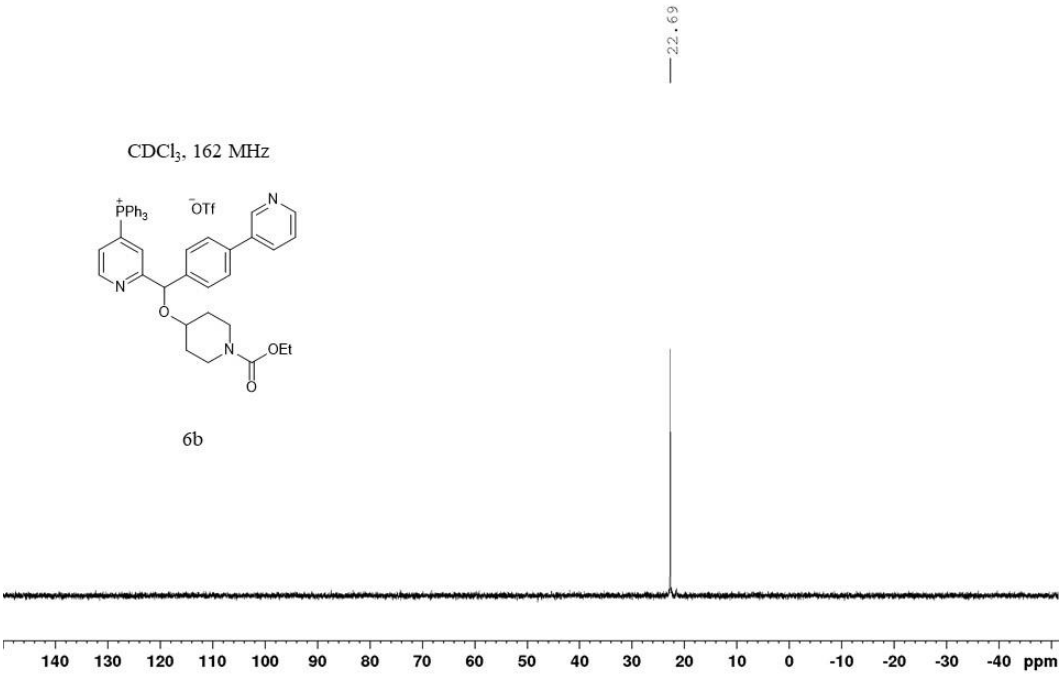

8.88
8.68
8.66
8.57
8.56
7.85
7.74
7.73
7.72
7.71
7.67
7.62
7.60
7.58
7.53
7.52
7.50
7.47
7.45
7.44
7.42
7.41
7.39
7.38
7.36
7.20
7.01
6.99
6.65
6.63
6.02
5.48
5.23
4.07
4.06
4.05
4.04
4.03
3.70
3.48
3.46
3.45
3.44
3.43
3.41
3.35
3.11
2.72
2.00
1.98
1.97
1.95
1.70
1.63
1.55
1.21
1.21
1.19
1.17
1.16
CDCl3, 400 MHz
(crude 1H NMR)
PPh3
OTf
OEt
6a
0.12
0.62
3.00
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 ppm

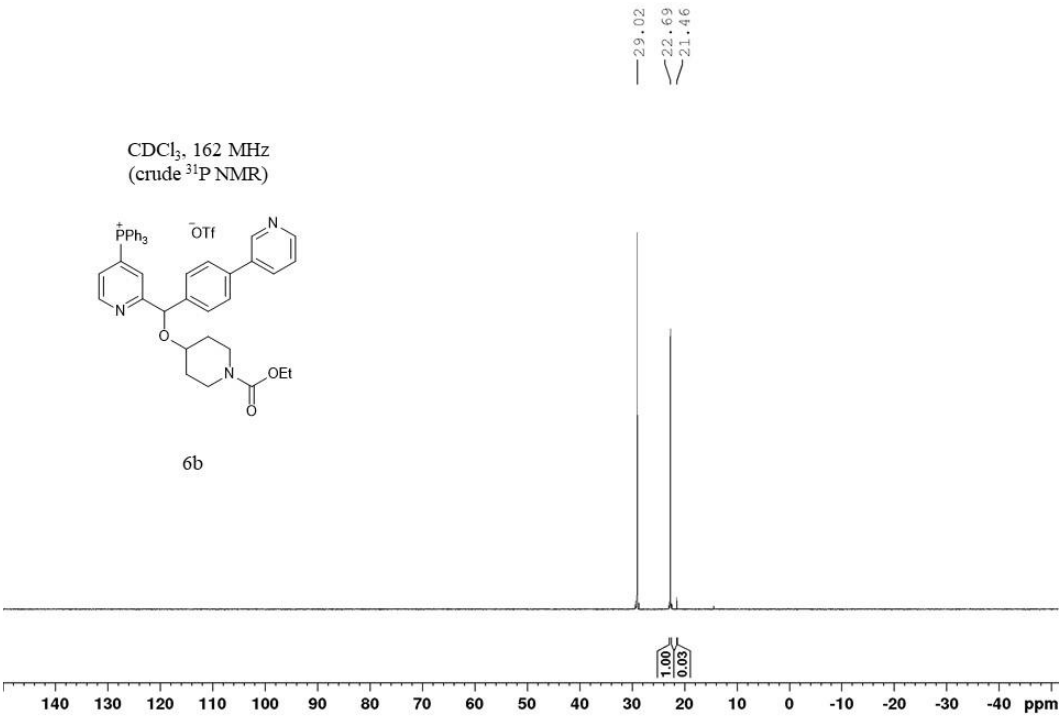

29.16
22.73
22.57
21.74
21.51
21.47
Major
Unidentified
isomer
Unidentified
isomer
Minor
0.20
0.17
0.18
1.00
22.5
22.0
21.5
ppm
CDCl3, 162 MHz
(crude 31P NMR)
PPh3
OTf
OEt
6a
0.20
0.17
0.18
1.00
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

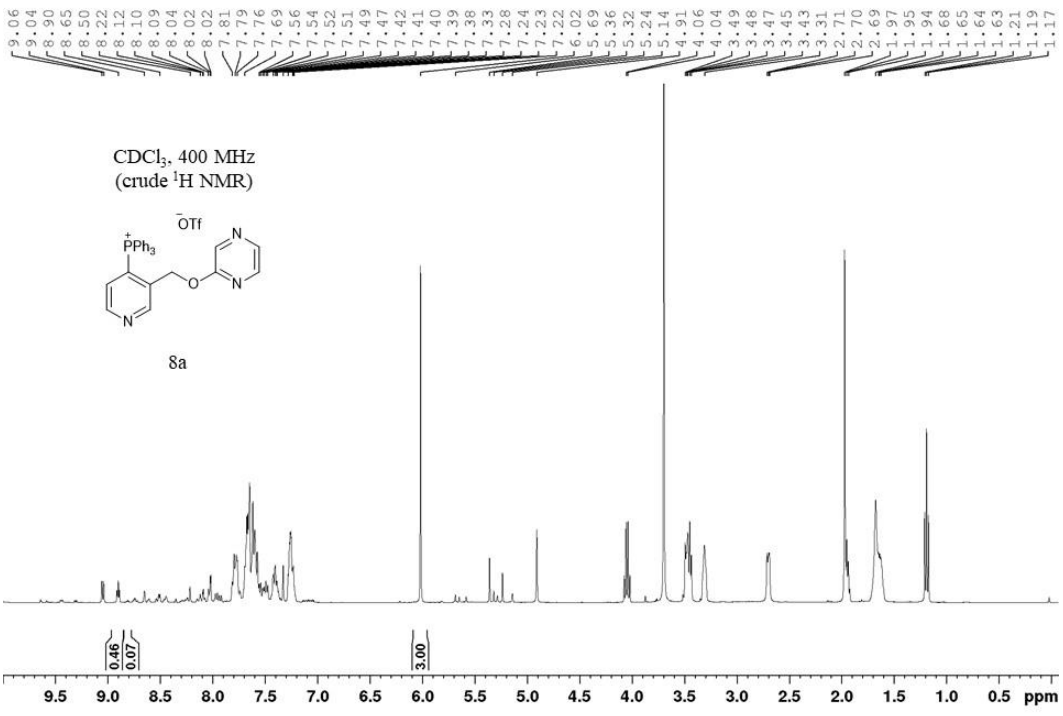

8.95 8.94 8.93 8.93 7.92 7.91 7.89 7.87 7.82 7.81 7.80 7.79 7.78 7.77 7.71 7.69 7.68 7.66 7.57 7.55 7.52 7.51 7.50 7.48 7.38 7.26 5.81 4.16 4.14 4.12 4.10 3.73 3.72 3.71 3.70 3.69 3.52 3.51 3.50 3.49 3.48 3.24 3.23 3.22 3.21 3.20 3.19 1.79 1.78 1.77 1.76 1.75 1.74 1.68 1.51 1.28 1.26 1.25 1.24
CDCl3, 400 MHz
PPh3
OTf
N
O
N
OEt
O
6b
0.97 0.80 0.92 22.00 1.10 0.89 2.05 1.16 2.01 2.09 2.46 2.23 4.23
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 ppm

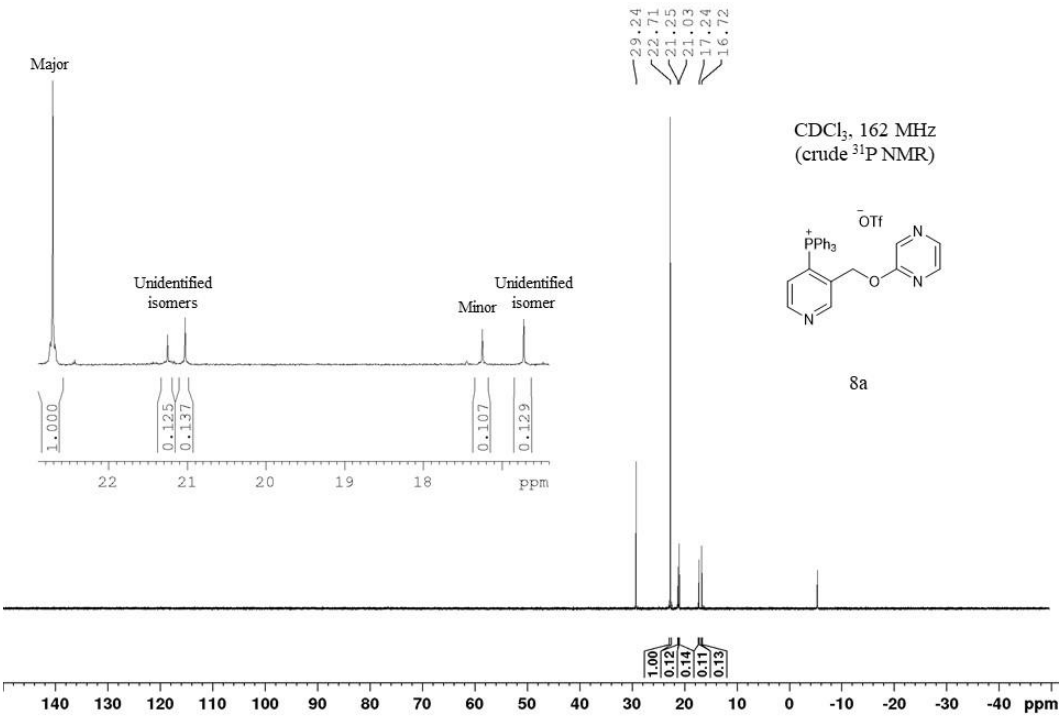

164.59 164.49 155.36 151.17 151.07 148.41 147.87 139.97 137.58 136.17 136.15 135.89 134.49 134.38 134.10 130.99 130.86 130.54 129.63 128.80 127.80 127.35 125.88 125.80 123.69 123.60 122.36 119.16 116.13 115.24 80.20 77.31 77.00 76.68 72.59 61.22 40.62 40.57 31.26 30.23 14.61
CDCl3, 100 MHz
PPh3
OTf
N
O
N
OEt
O
6b
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 ppm

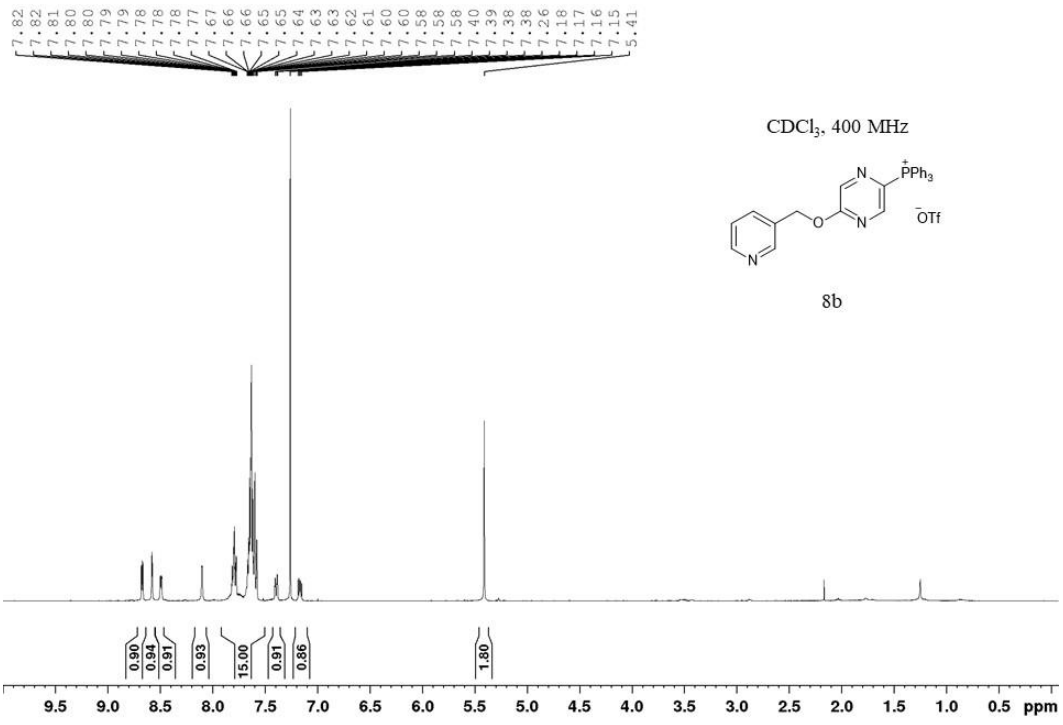

78.16
CDCl3, 365 MHz
PPh3
OTf
N
O
N
OEt
O
6b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

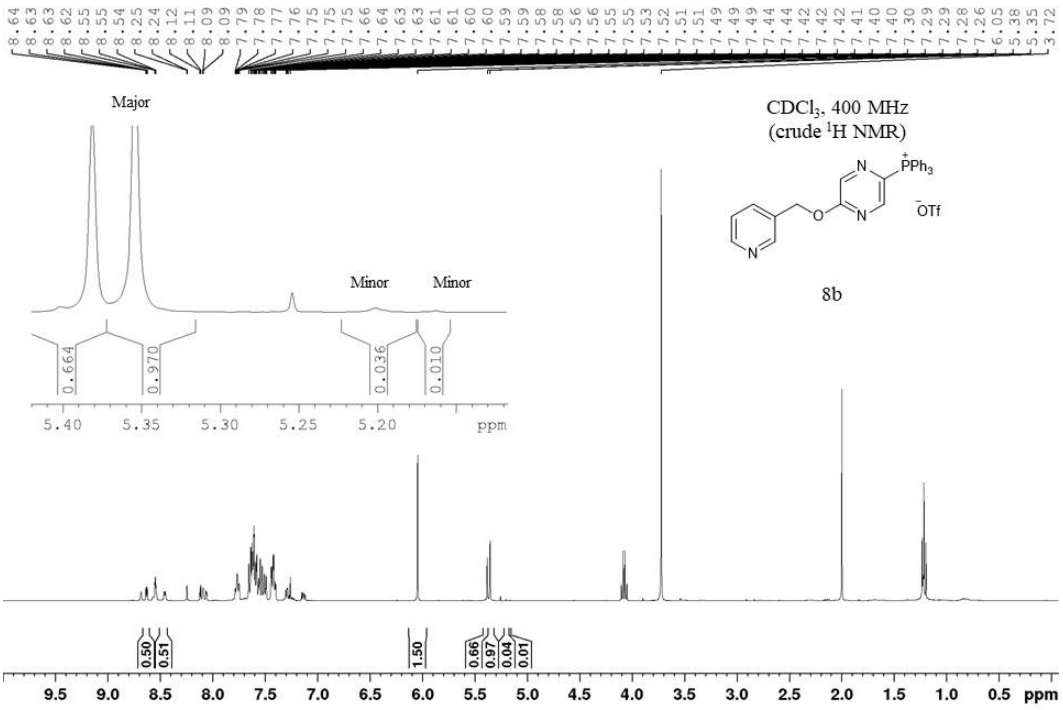

22.69
CDCl3, 162 MHz
PPh3
OTf
N
O
N
OEt
O
6b
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

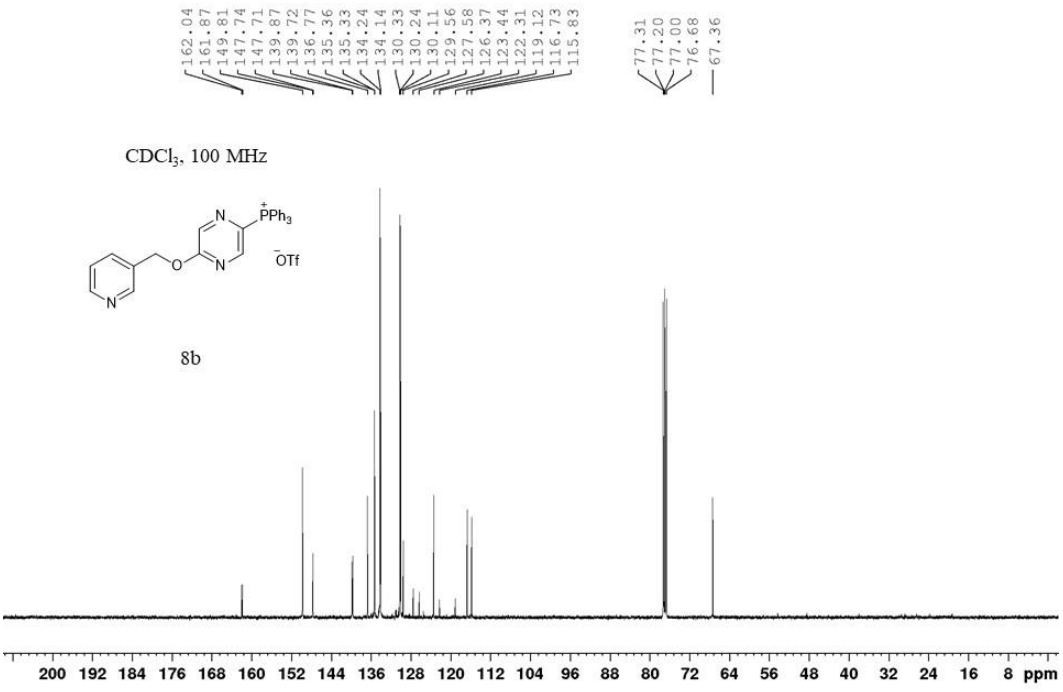

29.02
22.69
21.46
CDCl3, 162 MHz
(crude 31P NMR)
PPh3
OTf
OEt
6b
1.00
0.03
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

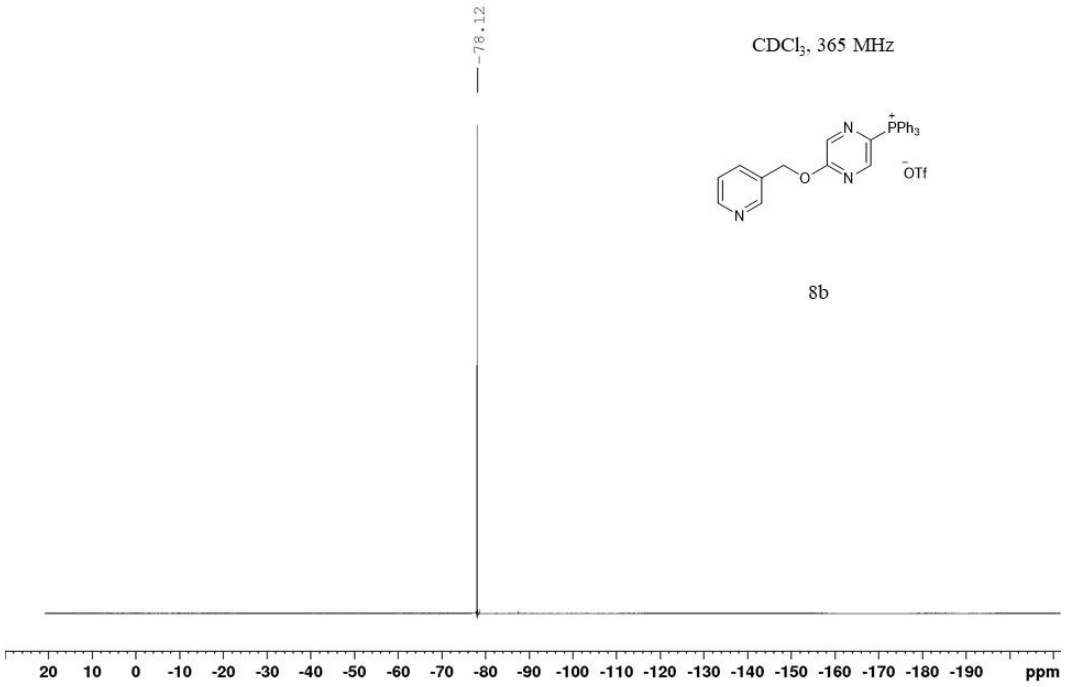

9.06
9.04
8.90
8.65
8.50
8.22
8.12
8.10
8.09
8.04
8.02
8.02
7.81
7.79
7.76
7.69
7.56
7.54
7.52
7.51
7.49
7.47
7.42
7.41
7.40
7.39
7.38
7.33
7.28
7.24
7.23
7.22
6.02
5.69
5.36
5.32
5.24
5.14
4.91
4.06
4.04
3.49
3.48
3.47
3.45
3.43
3.31
2.71
2.70
2.69
1.97
1.95
1.94
1.68
1.65
1.64
1.63
1.21
1.19
1.17
CDCl3, 400 MHz
(crude 1H NMR)
PPh3
OTf
8a
0.46
0.07
3.00
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 ppm

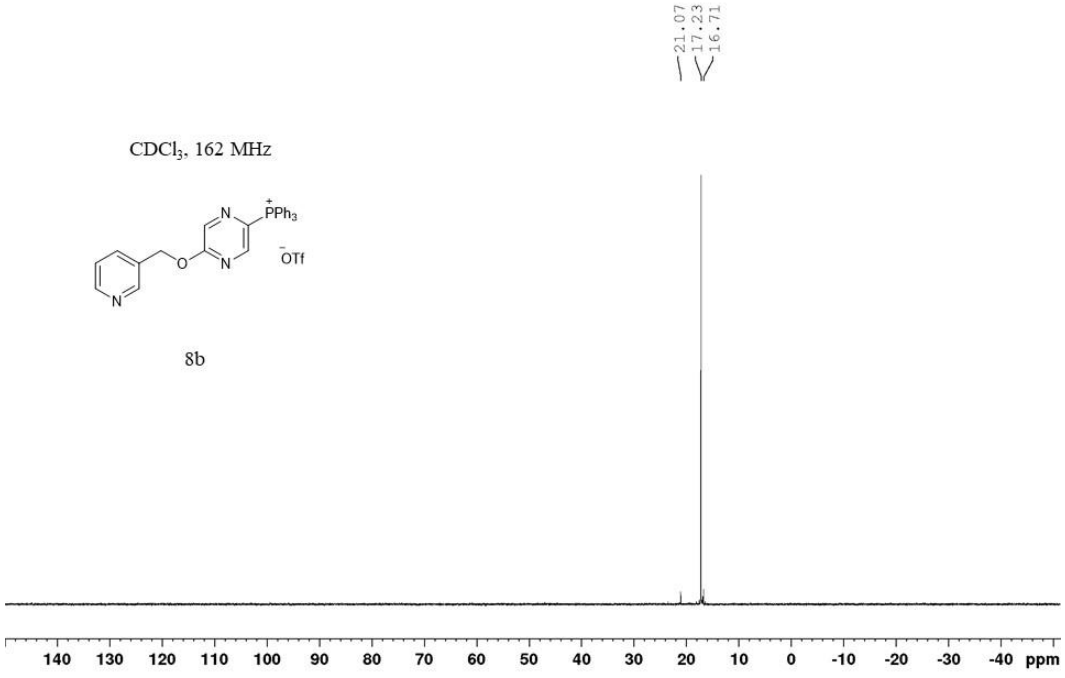

29.24
22.71
21.25
21.03
17.24
16.72
Major
Unidentified isomers
Minor
Unidentified isomer
1.000
0.125
0.137
0.107
0.129
22
21
20
19
18
ppm
CDCl3, 162 MHz
(crude 31P NMR)
OTf
PPh3
8a
1.00
0.12
0.14
0.11
0.13
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

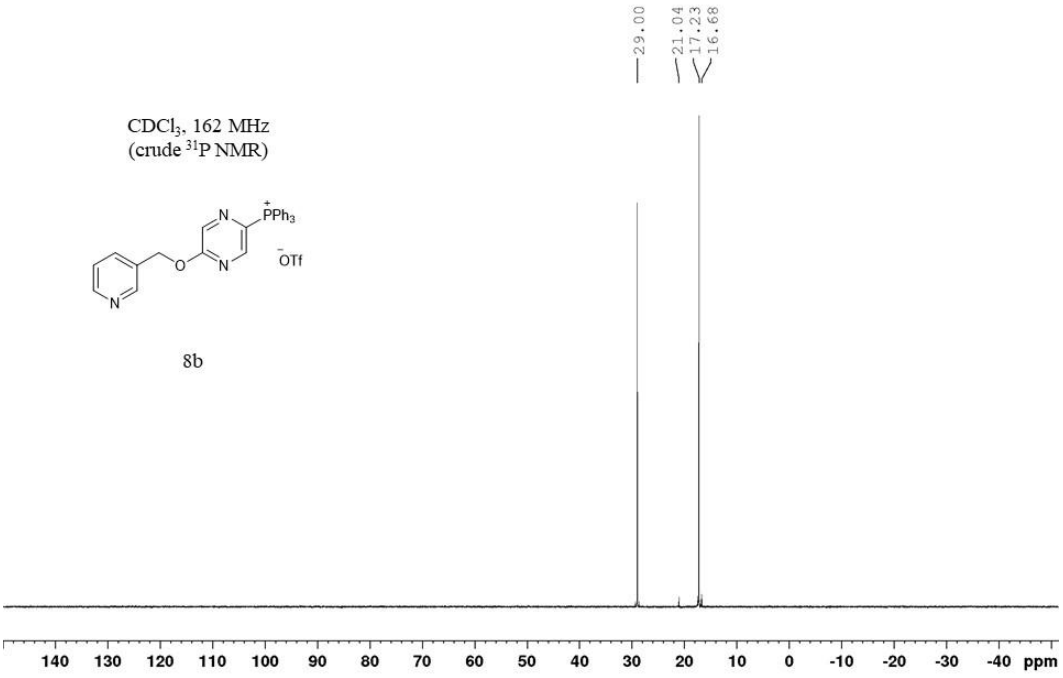

7.82
7.82
7.81
7.80
7.80
7.79
7.79
7.78
7.78
7.78
7.77
7.67
7.66
7.66
7.65
7.65
7.64
7.63
7.63
7.62
7.61
7.60
7.60
7.58
7.58
7.58
7.40
7.39
7.38
7.38
7.26
7.18
7.17
7.16
7.15
5.41
CDCl3, 400 MHz
PPh3
OTf
8b
0.90
0.94
0.91
0.93
15.00
0.91
0.86
1.80
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

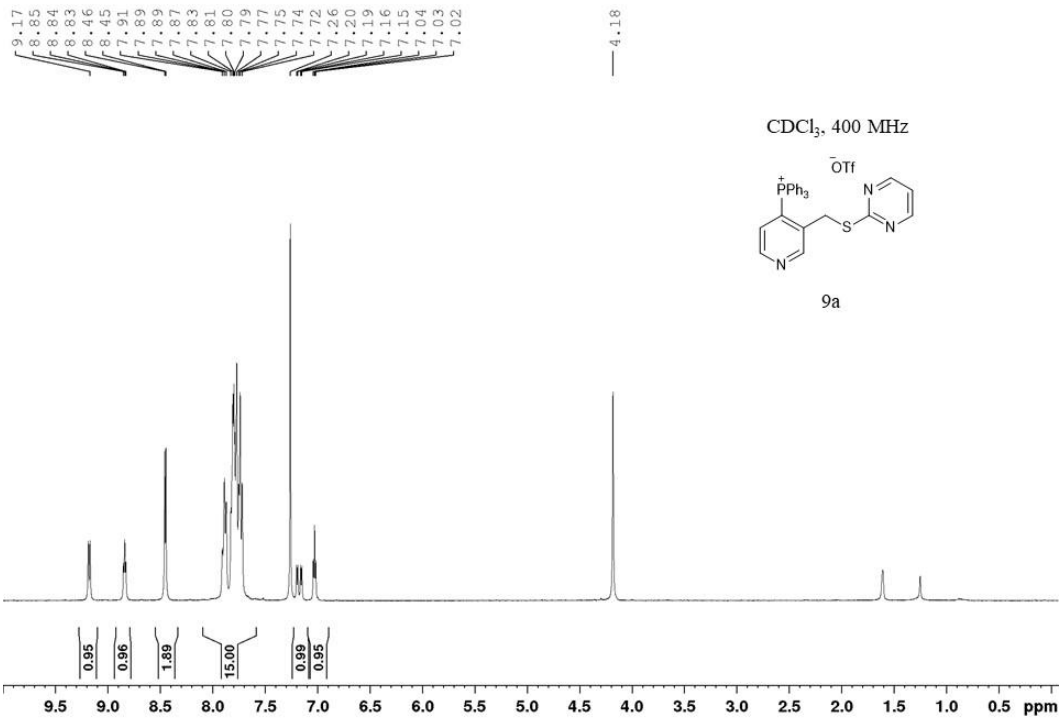

Major
Minor
Minor
0.664
0.970
0.036
0.010
5.40
5.35
5.30
5.25
5.20
ppm
CDCl3, 400 MHz
(crude 1H NMR)
PPh3
OTf
8b
0.50
0.51
1.50
0.66
0.97
0.04
0.01
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

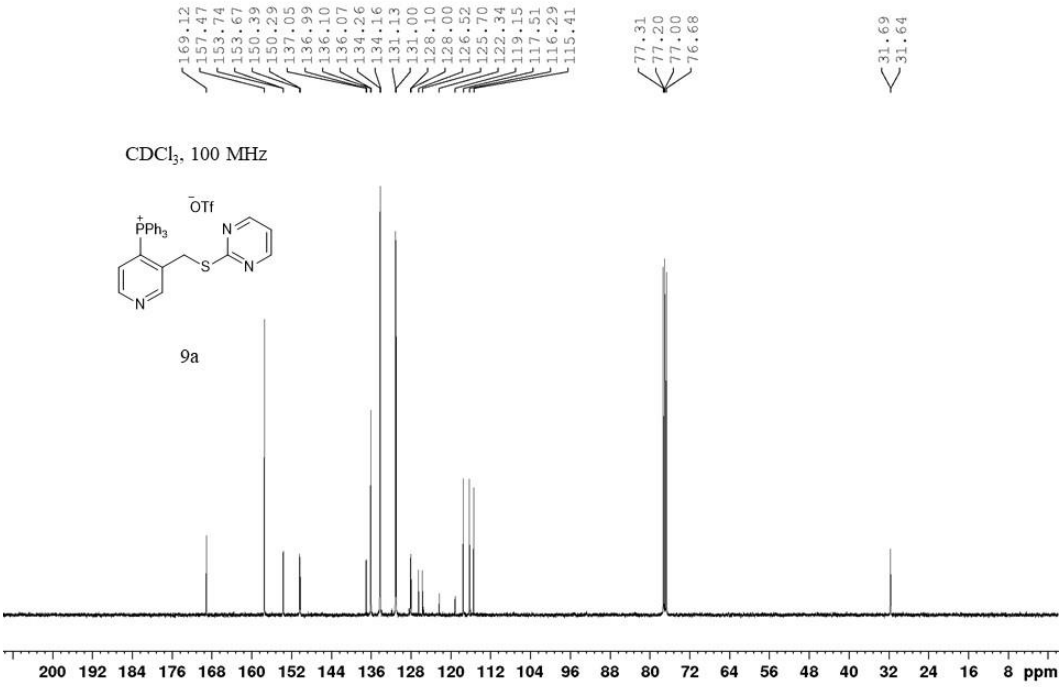

CDCl3, 100 MHz
PPh3
OTf
8b
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
ppm

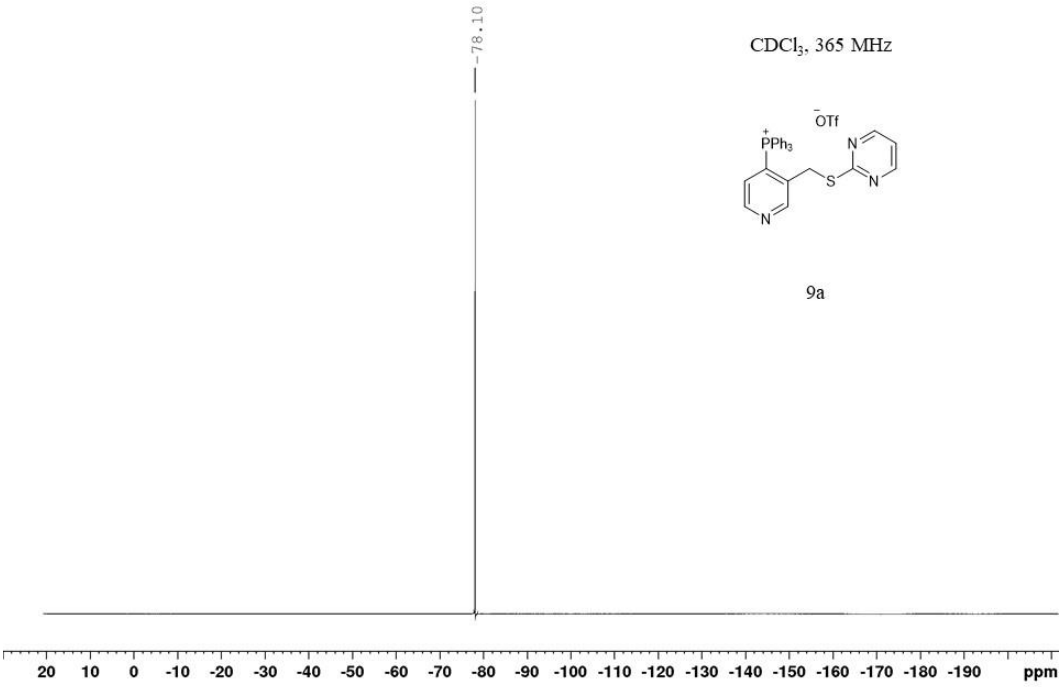

78.12
CDCl3, 365 MHz
PPh3
OTf
8b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm


21.07
17.23
16.71
CDCl3, 162 MHz
PPh3
OTf
8b
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


29.00
21.04
17.23
16.68
CDCl3, 162 MHz
(crude 31P NMR)
PPh3
OTf
8b
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

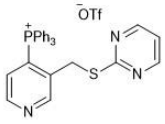

9.17
8.85
8.84
8.83
8.46
8.45
7.91
7.89
7.89
7.87
7.83
7.81
7.80
7.79
7.77
7.75
7.74
7.72
7.26
7.20
7.19
7.16
7.15
7.04
7.03
7.02
4.18
CDCl3, 400 MHz
OTf
PPh3
9a
0.95
0.96
1.89
15.00
0.99
0.95
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


169.12
157.47
153.74
153.67
150.39
150.29
137.05
136.99
136.10
136.07
134.26
134.16
131.13
131.00
128.10
128.00
126.52
125.70
122.34
119.15
117.51
116.29
115.41
77.31
77.20
77.00
76.68
31.69
31.64
CDCl3, 100 MHz
OTf
PPh3
N
S
N
N
9a
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 ppm

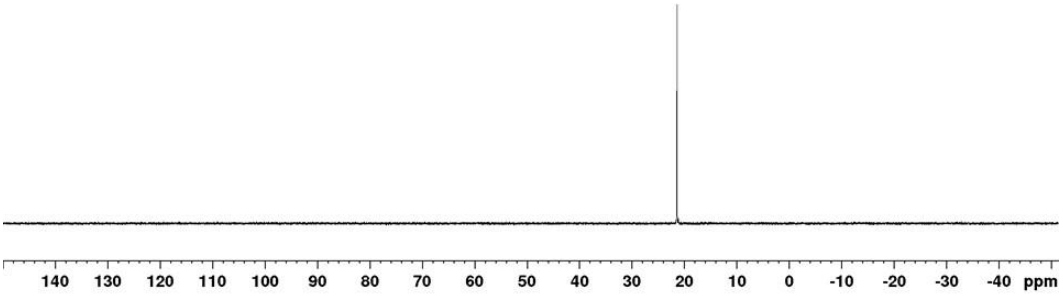

-78.10
CDCl3, 365 MHz
OTf
PPh3
N
S
N
N
9a
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

21.42

$CDCl_3$, 162 MHz

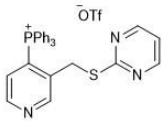


9a

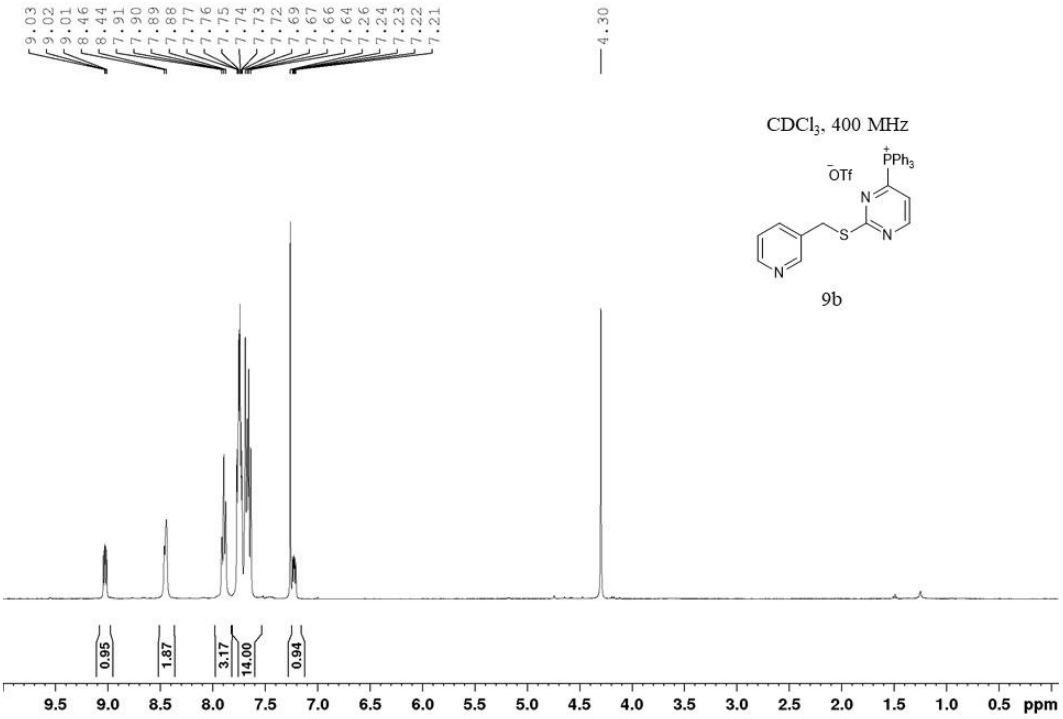


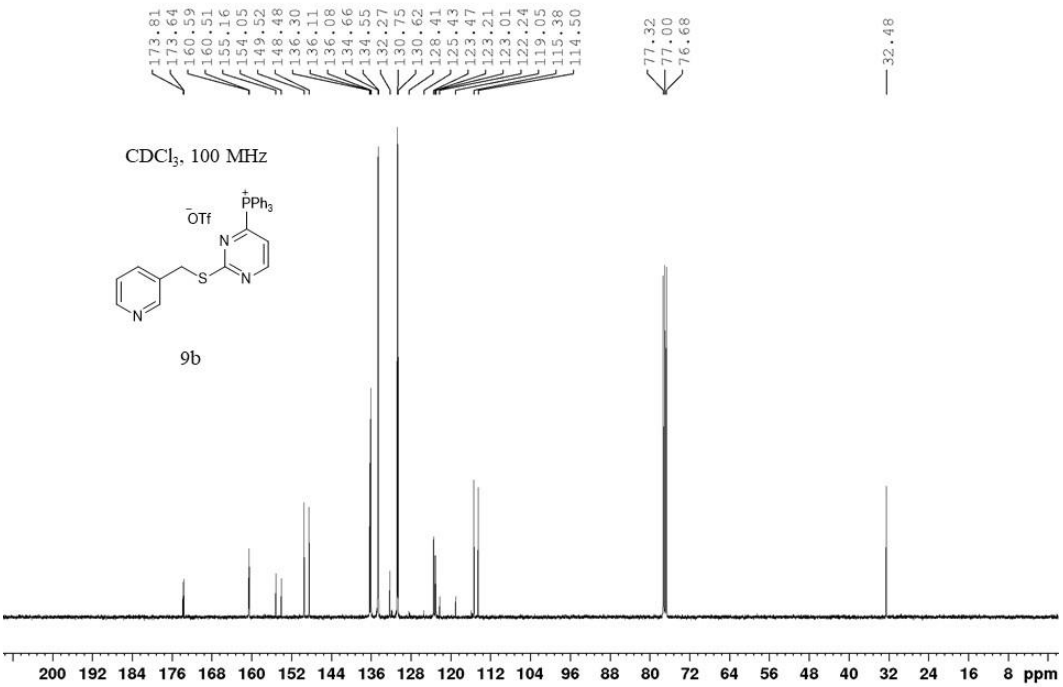
29.05
21.38
16.36

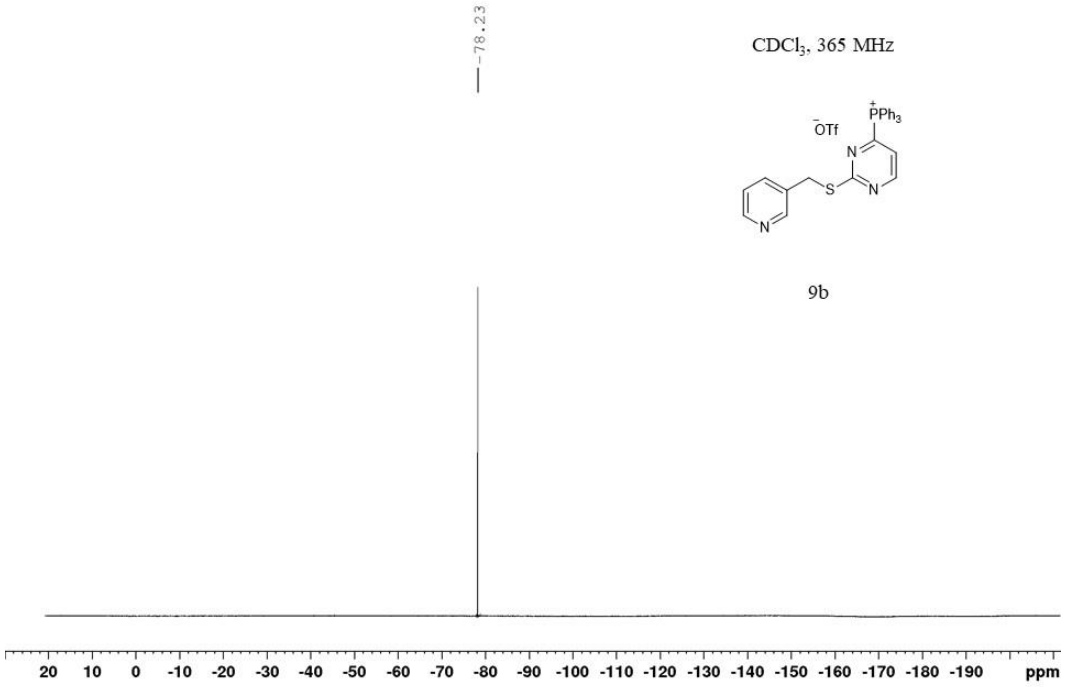
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)

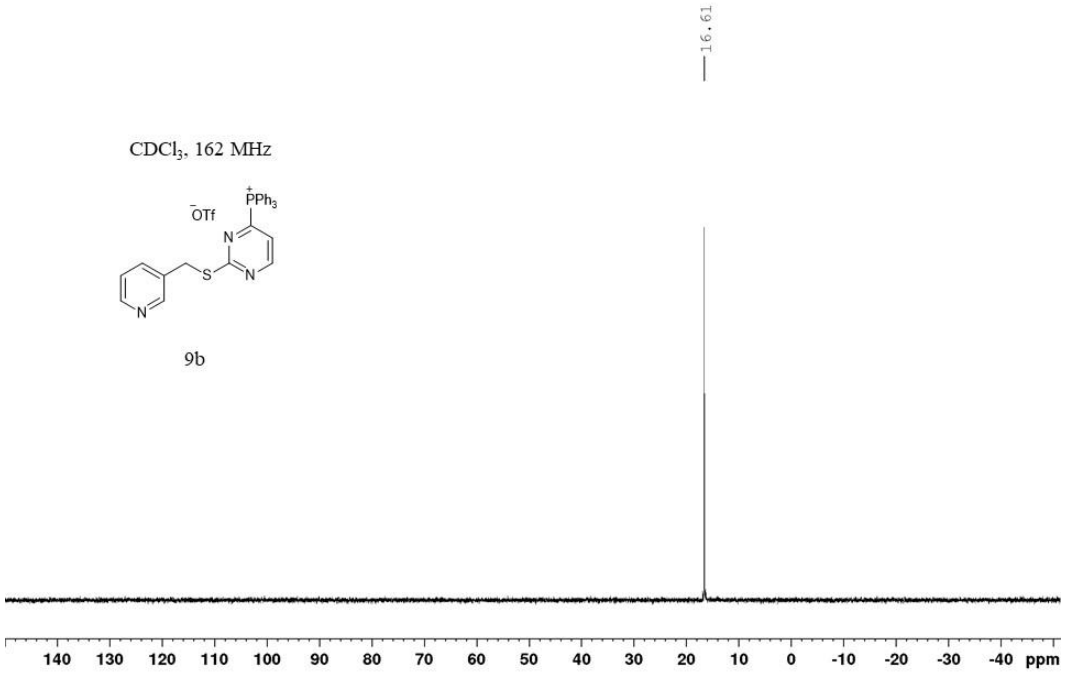


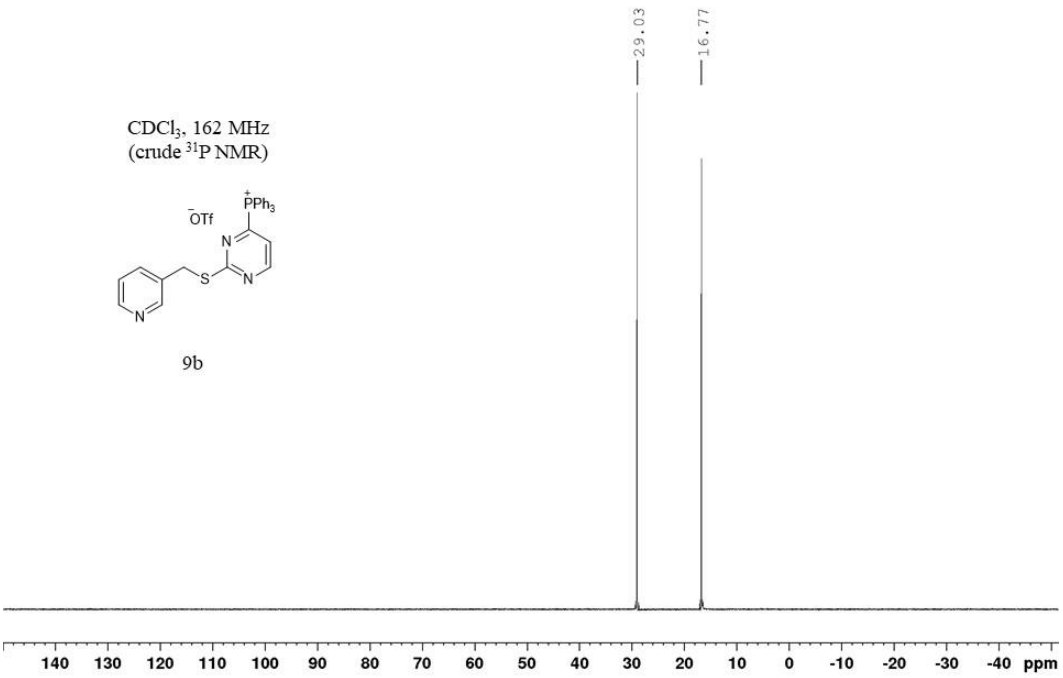
9a


9.03
9.02
9.01
8.46
8.44
7.91
7.90
7.89
7.88
7.77
7.76
7.75
7.74
7.73
7.72
7.69
7.67
7.66
7.64
7.26
7.24
7.23
7.22
7.21
4.30
CDCl3, 400 MHz
OTf
PPh3
N
S
N
N
9b
0.95
1.87
3.17
14.00
0.94
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 ppm

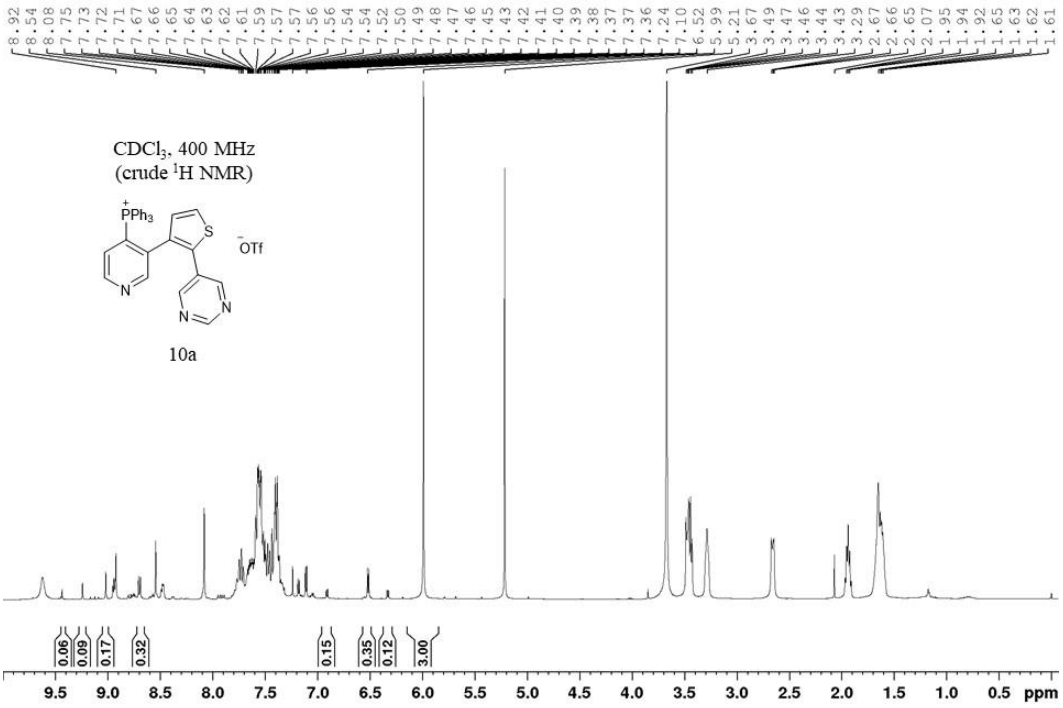

173.81
173.64
160.59
160.51
155.16
154.05
149.52
148.48
136.30
136.11
136.08
134.66
134.55
132.27
130.75
130.62
128.41
125.43
123.47
123.21
123.01
122.24
119.05
115.38
114.50
77.32
77.00
76.68
32.48
CDCl3, 100 MHz
OTf
PPh3
N
S
N
N
9b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm


78.23
CDCl3, 365 MHz
OTf
PPh3
N
S
N
N
9b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

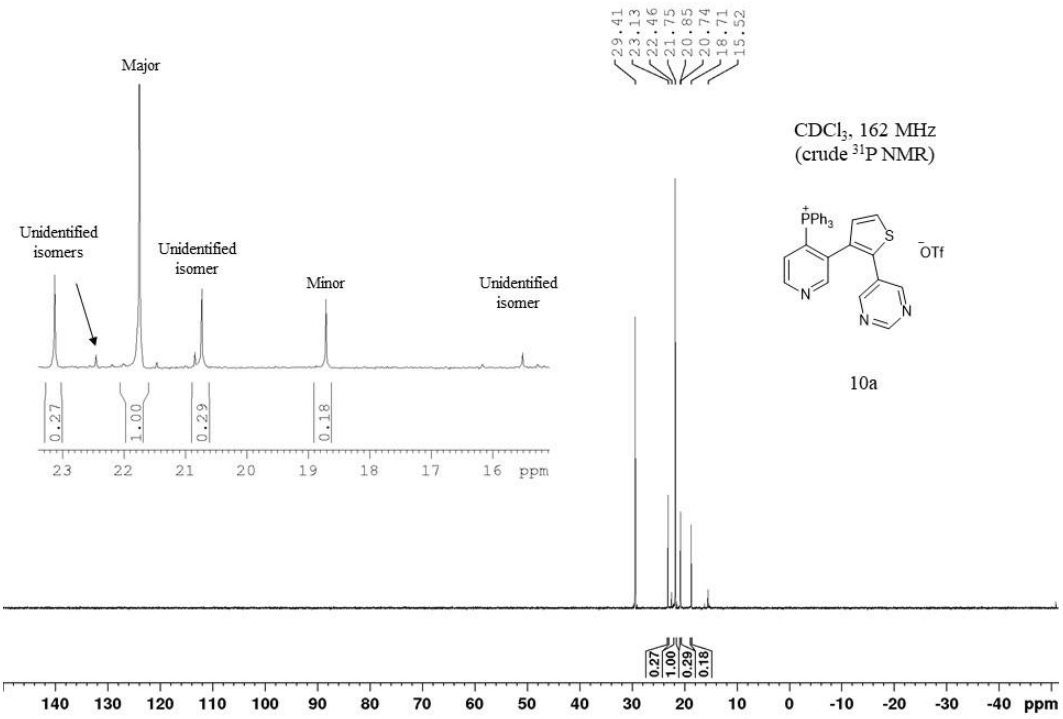

16.61
CDCl3, 162 MHz
OTf
PPh3
N
S
N
N
9b
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

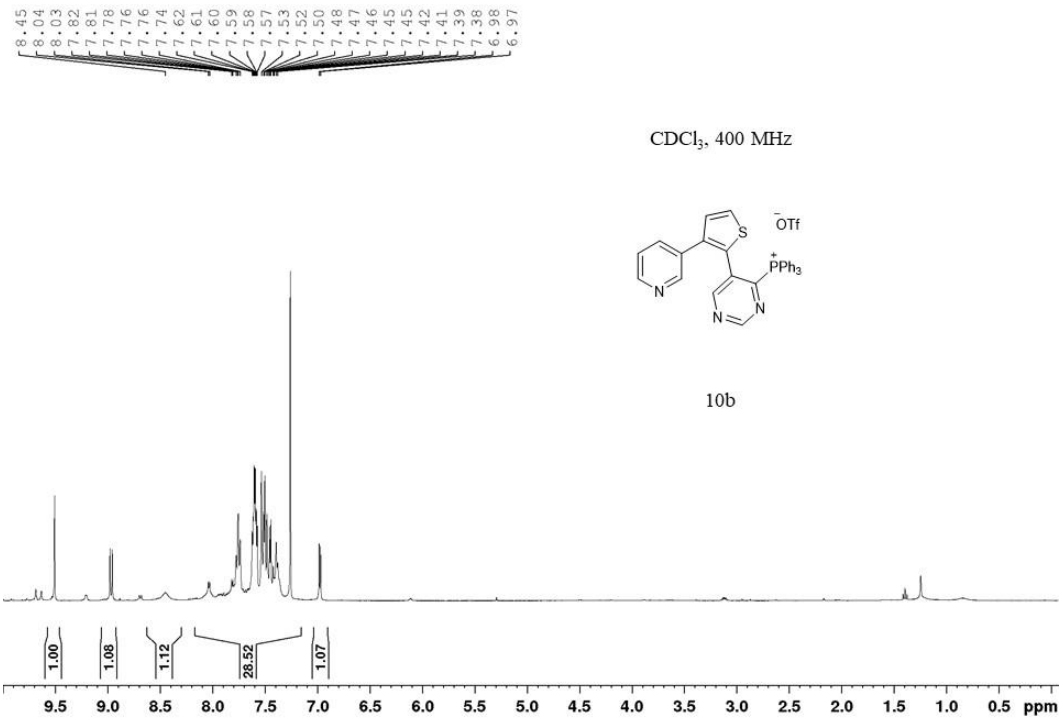

29.03
16.77
CDCl3, 162 MHz
(crude 31P NMR)
OTf
PPh3
N
S
N
N
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

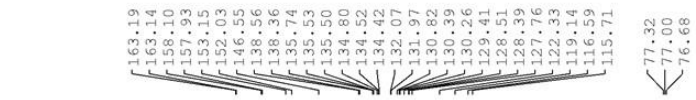
9b


8.92
8.54
8.08
7.75
7.73
7.72
7.71
7.67
7.66
7.65
7.64
7.63
7.62
7.61
7.59
7.57
7.57
7.56
7.56
7.54
7.54
7.52
7.50
7.49
7.48
7.47
7.46
7.45
7.43
7.42
7.41
7.40
7.39
7.38
7.37
7.37
7.36
7.24
7.10
6.52
5.99
5.21
3.67
3.49
3.47
3.46
3.44
3.43
3.29
2.67
2.66
2.65
2.07
1.95
1.94
1.92
1.65
1.63
1.62
1.61
CDCl3, 400 MHz
(crude 1H NMR)
PPh3
S
OTf
N
N
N
0.06
0.09
0.17
0.32
0.15
0.35
0.12
3.00
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 ppm

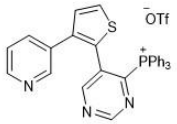
10a


29.41
23.13
22.46
21.75
20.85
20.74
18.71
15.52
Major
Unidentified isomers
Unidentified isomer
Minor
Unidentified isomer
0.27
1.00
0.29
0.18
23 22 21 20 19 18 17 16 ppm
CDCl3, 162 MHz
(crude 31P NMR)
PPh3
S
OTf
N
N
N
10a
0.27
1.00
0.29
0.16
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


8.45
8.04
8.03
7.82
7.81
7.78
7.76
7.76
7.74
7.62
7.61
7.60
7.59
7.58
7.57
7.53
7.52
7.50
7.48
7.47
7.46
7.45
7.45
7.42
7.41
7.39
7.38
6.98
6.97
CDCl3, 400 MHz
OTf
S
PPh3
N
N
N
10b
1.00
1.08
1.12
28.52
1.07
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 ppm

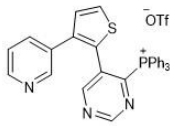


$CDCl_3$, 100 MHz

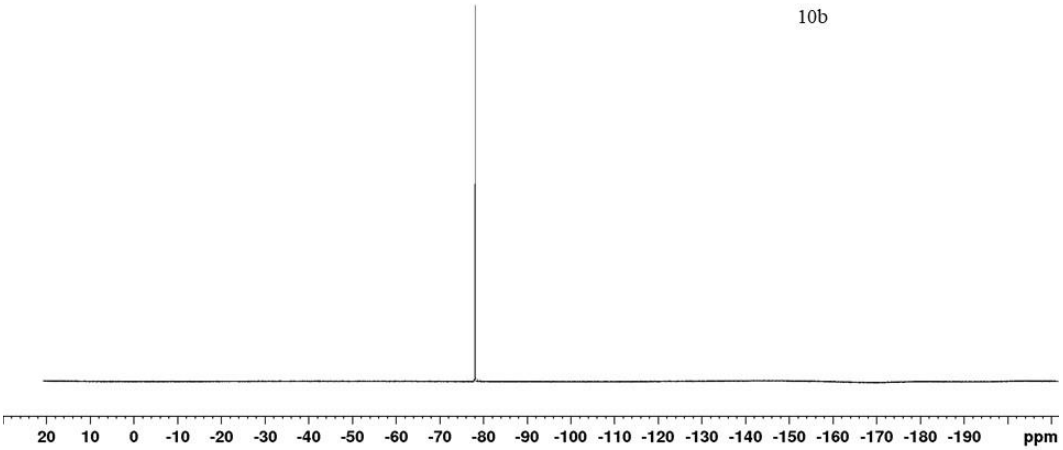


10b

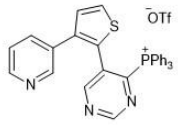
$CDCl_3$, 365 MHz



10b

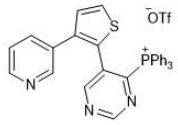


$CDCl_3$, 162 MHz

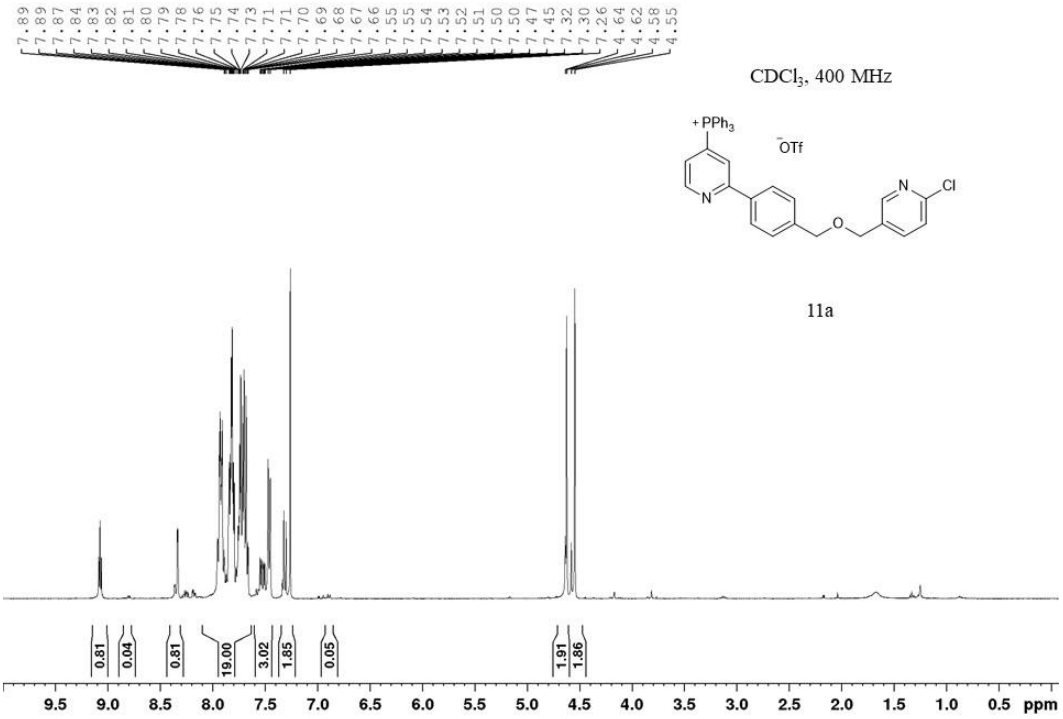


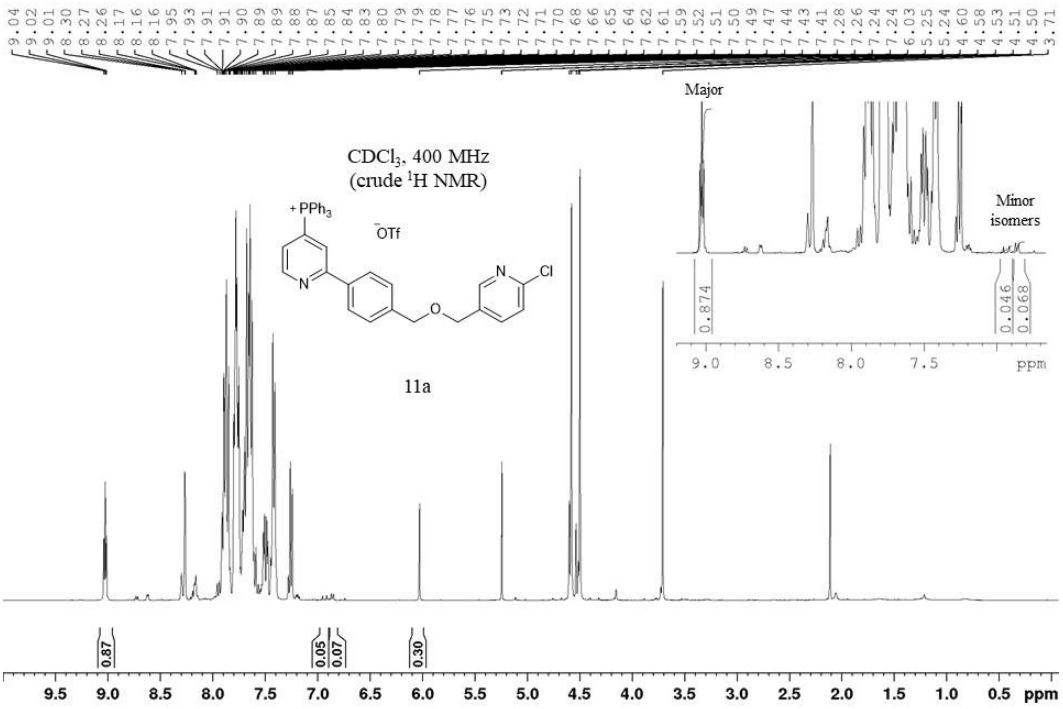
10b

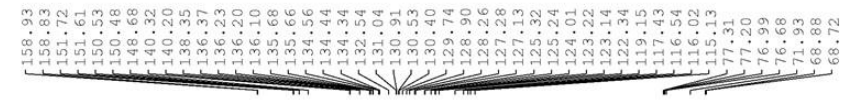
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)



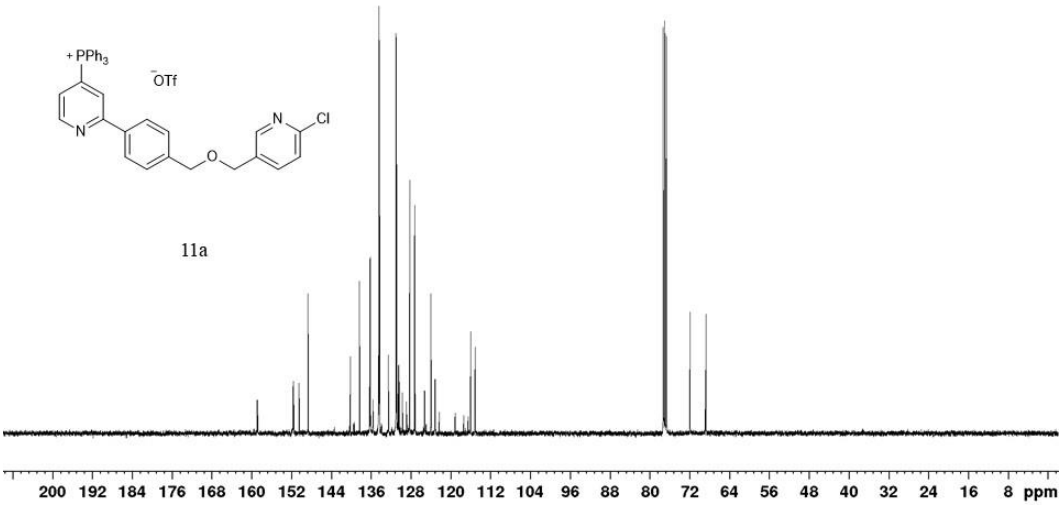
10b


CDCl3, 400 MHz
+PPh3
OTf
N
Cl
O
11a
0.81
0.04
0.81
19.00
3.02
1.85
0.05
1.91
1.86
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 ppm


CDCl3, 400 MHz
(crude 1H NMR)
+PPh3
OTf
N
Cl
O
11a
Major
Minor
isomers
0.874
0.046
0.068
9.0 8.5 8.0 7.5 ppm
0.87
0.05
0.07
0.30
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 ppm

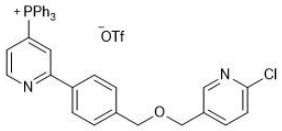


$CDCl_3$, 100 MHz

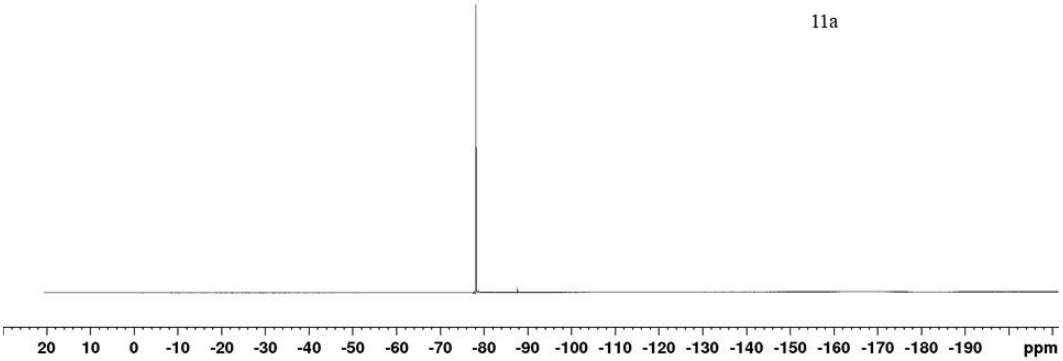


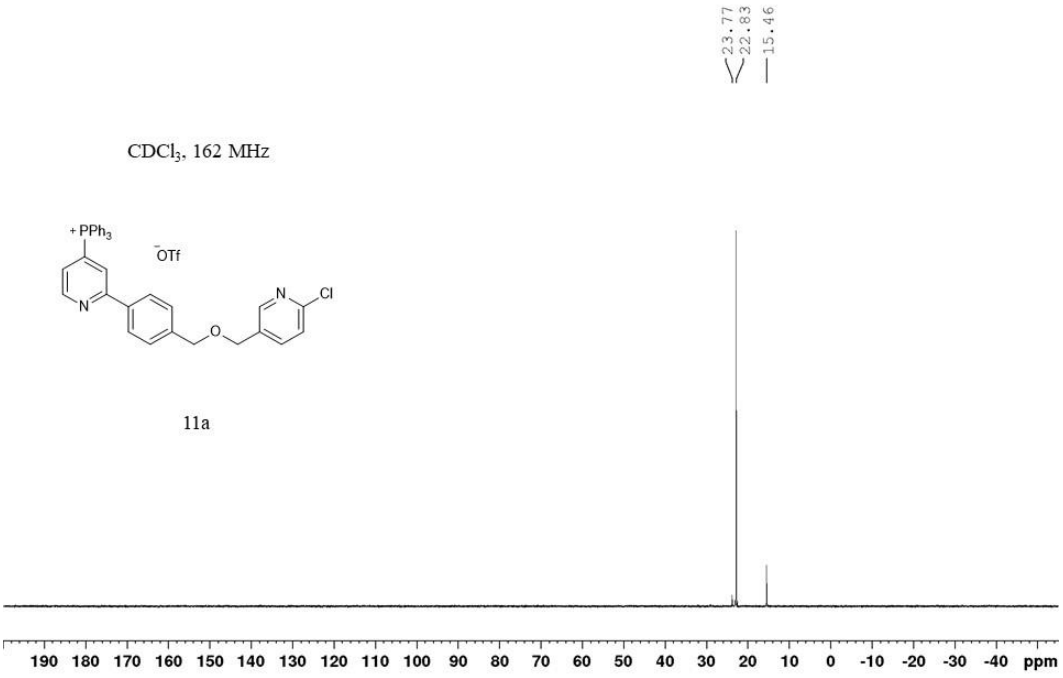
11a

$CDCl_3$, 365 MHz



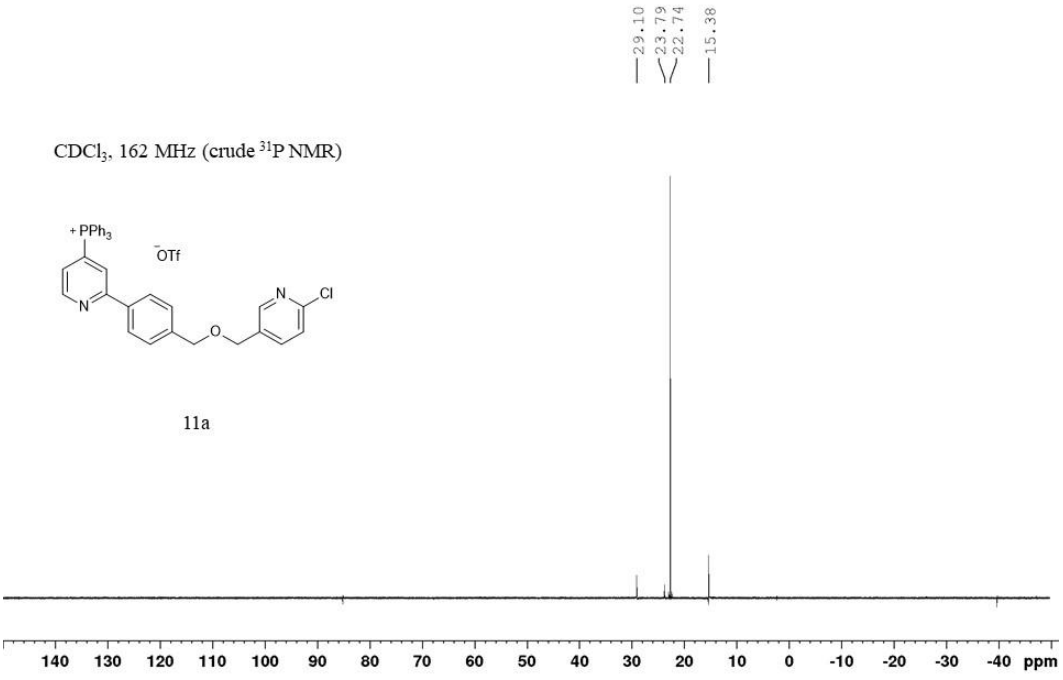
11a





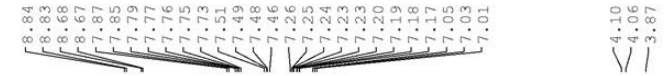
$CDCl_3$, 162 MHz

11a

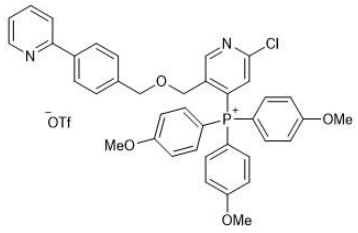


$CDCl_3$, 162 MHz (crude ^{31}P NMR)

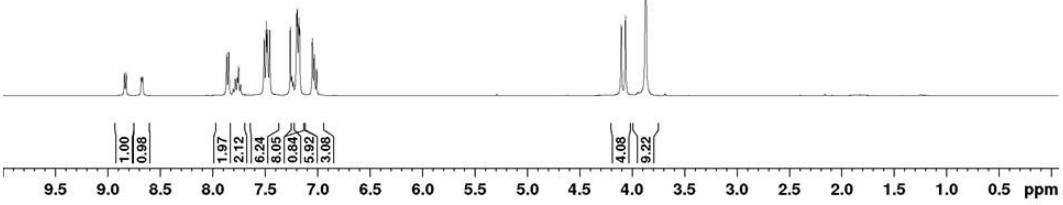
11a

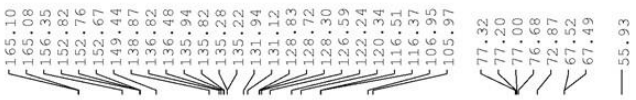


$CDCl_3$, 400 MHz

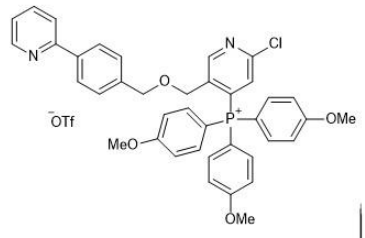


11b

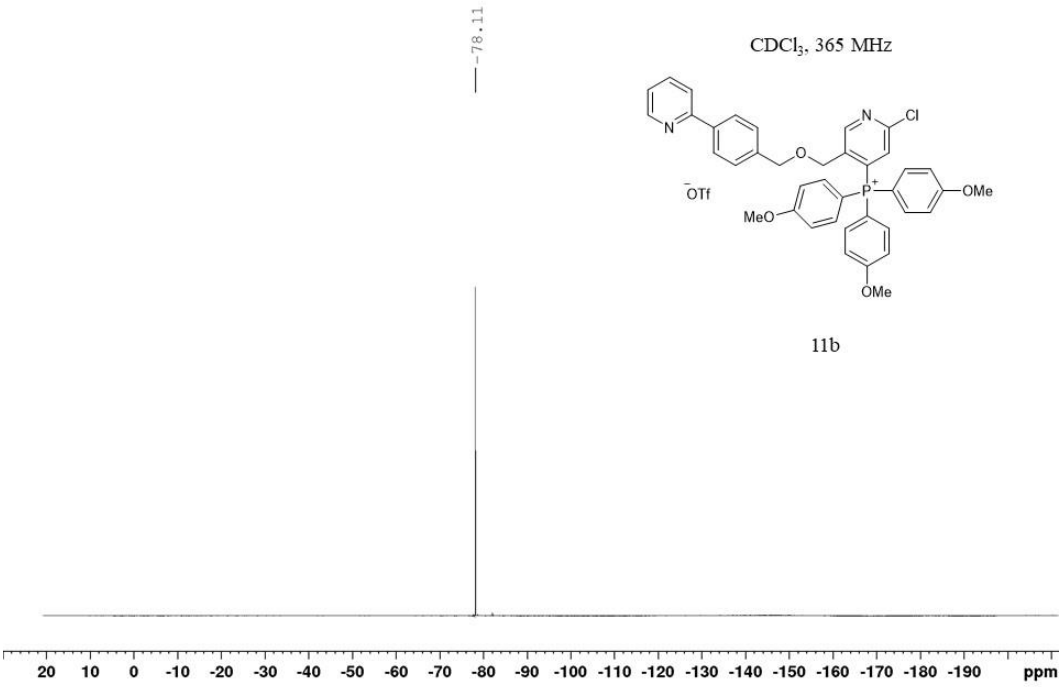




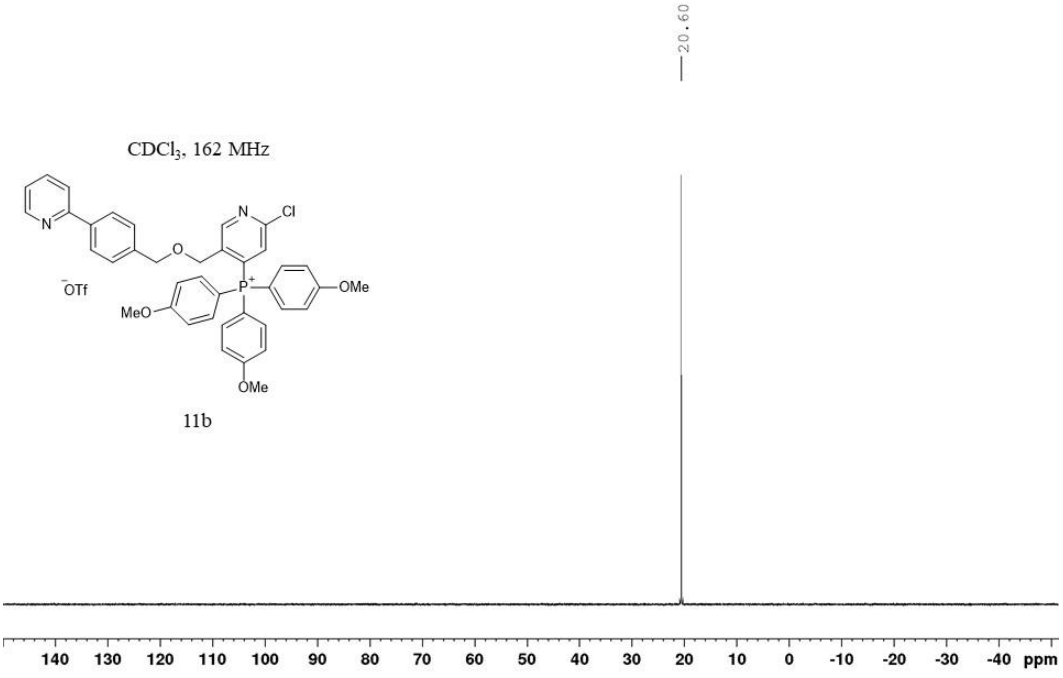
$CDCl_3$, 100 MHz



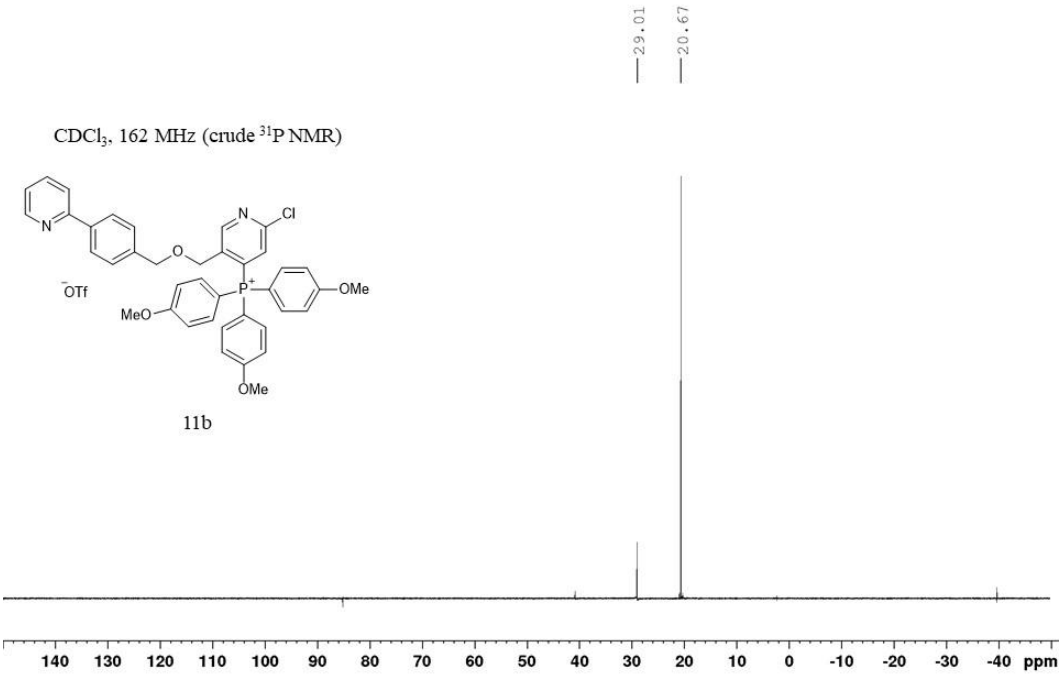
11b

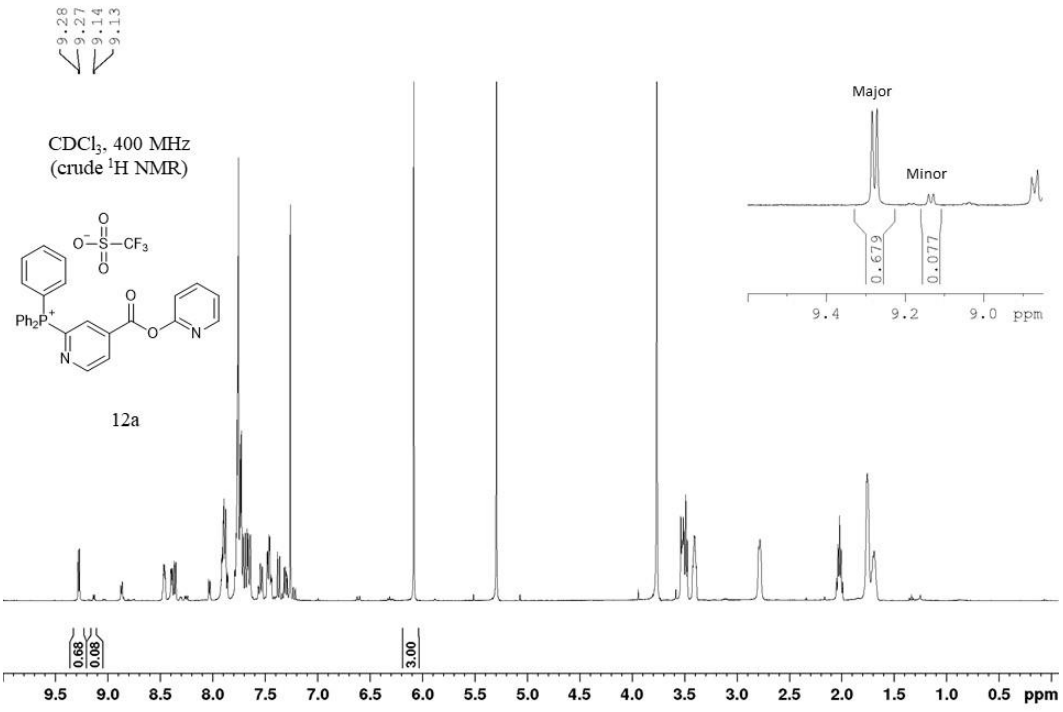

78.11
CDCl3, 365 MHz
N
Cl
O
OTf
P+
MeO
OMe
OMe
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

11b

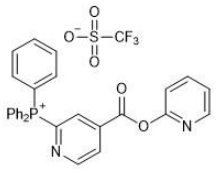

20.60
CDCl3, 162 MHz
N
Cl
O
OTf
P+
MeO
OMe
OMe
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

11b

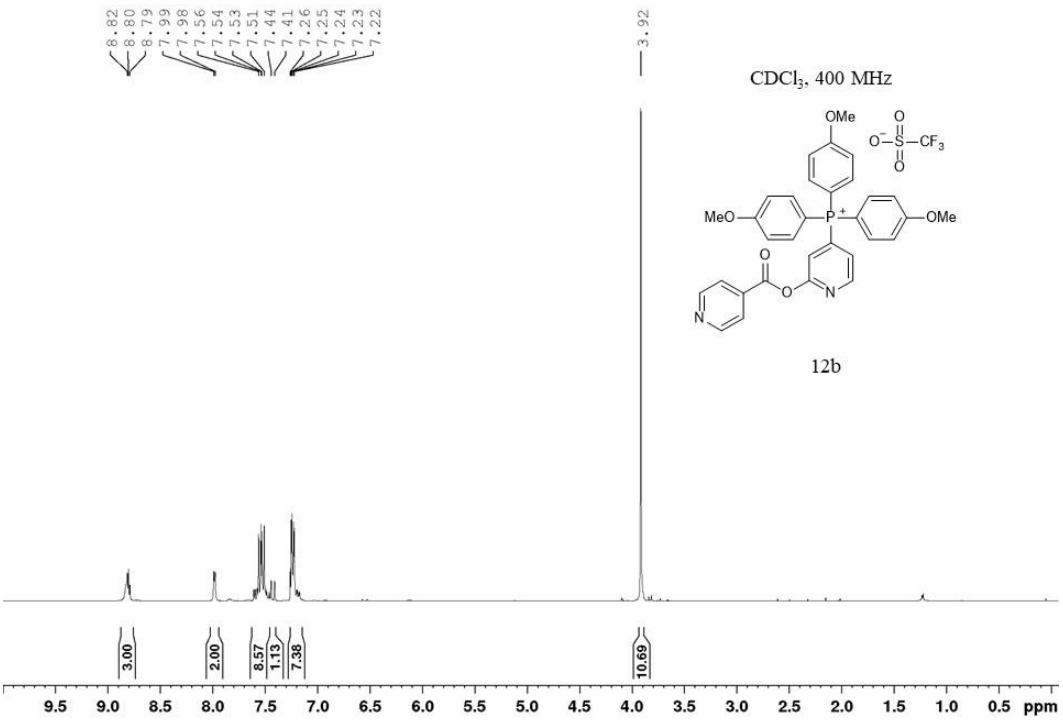

29.01
20.67
CDCl3, 162 MHz (crude 31P NMR)
OTf
MeO
OMe
OMe
Cl
11b
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


9.28
9.27
9.14
9.13
CDCl3, 400 MHz
(crude 1H NMR)
Ph2P
CF3
12a
Major
Minor
0.679
0.077
9.4 9.2 9.0 ppm
0.68
0.08
3.00
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 ppm

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

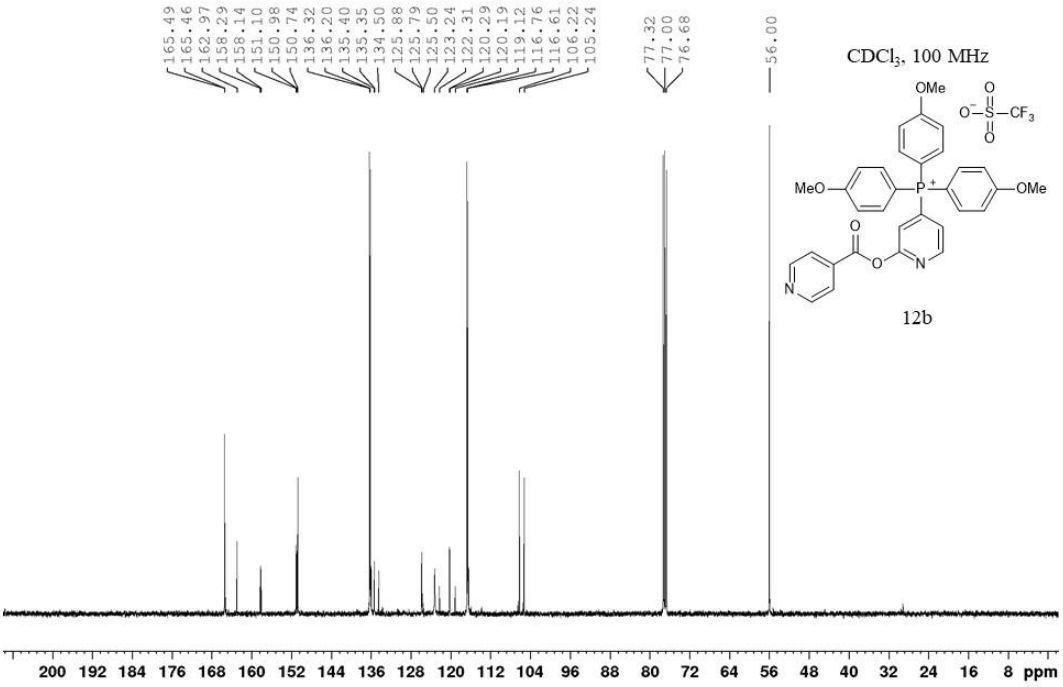


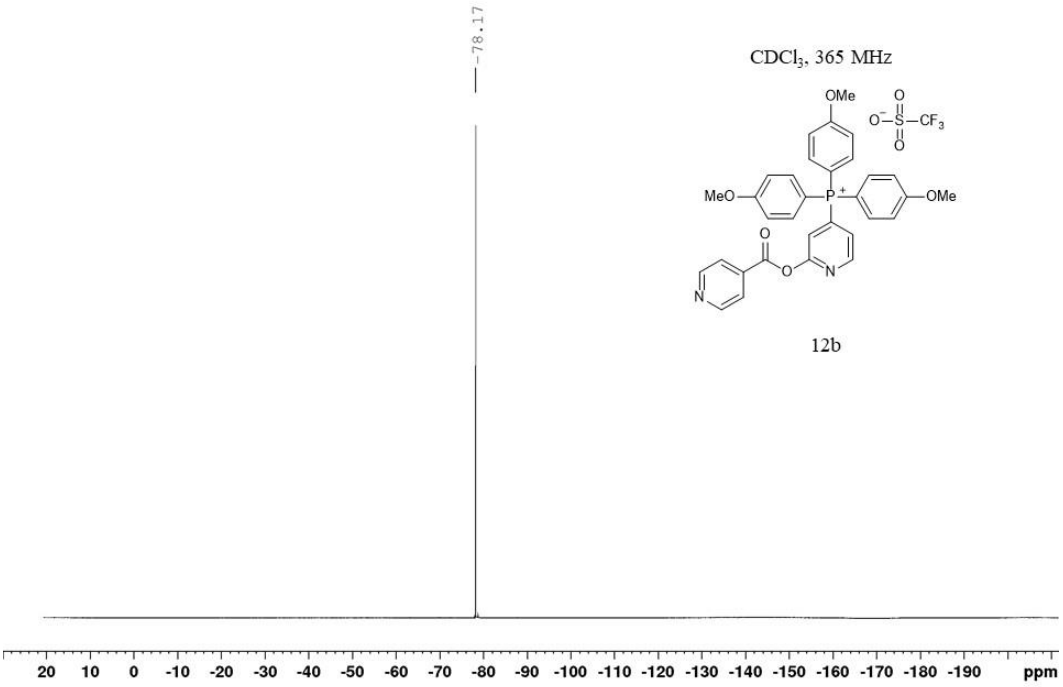
12a

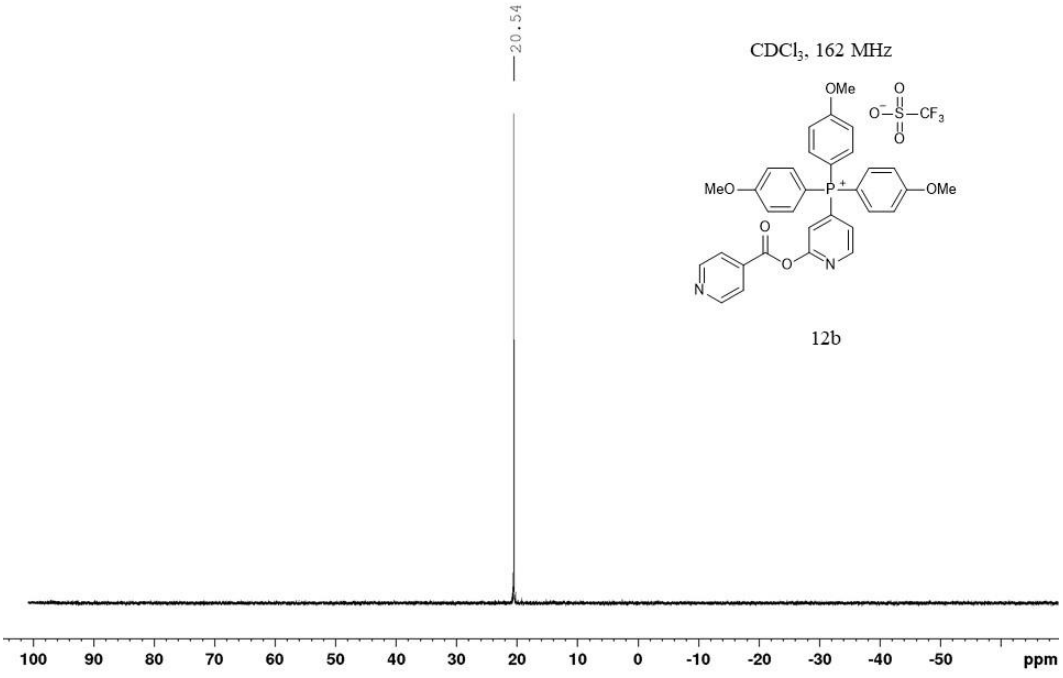


$CDCl_3$, 400 MHz

12b

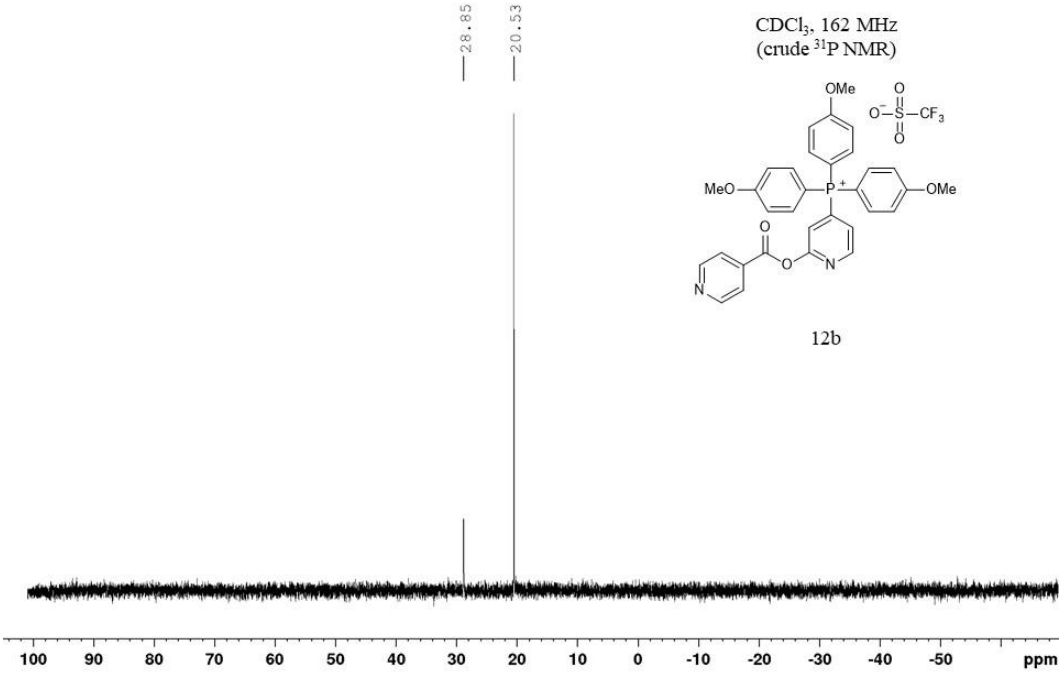

165.49
165.46
162.97
158.29
158.14
151.10
150.98
150.74
136.32
136.20
135.40
135.35
134.50
125.88
125.79
125.50
123.24
122.31
120.29
120.19
119.12
116.76
116.61
106.22
105.24
77.32
77.00
76.68
56.00
CDCl3, 100 MHz
OMe
MeO
OMe
12b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm


-78.17
CDCl3, 365 MHz
OMe
MeO
OMe
12b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm



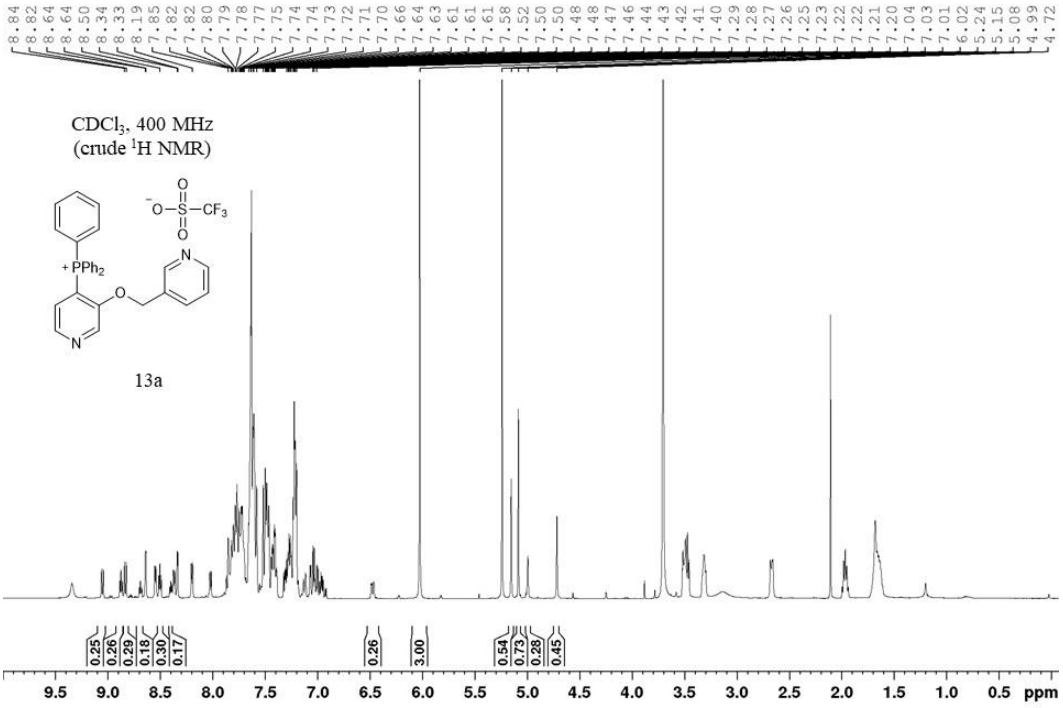
$CDCl_3$, 162 MHz

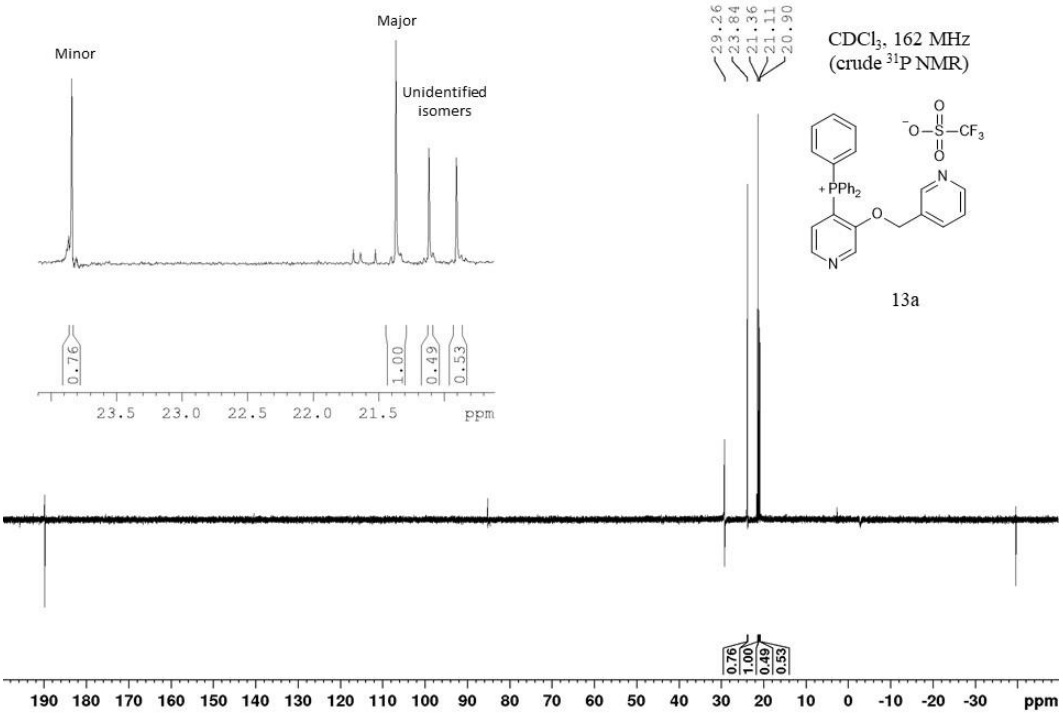
12b

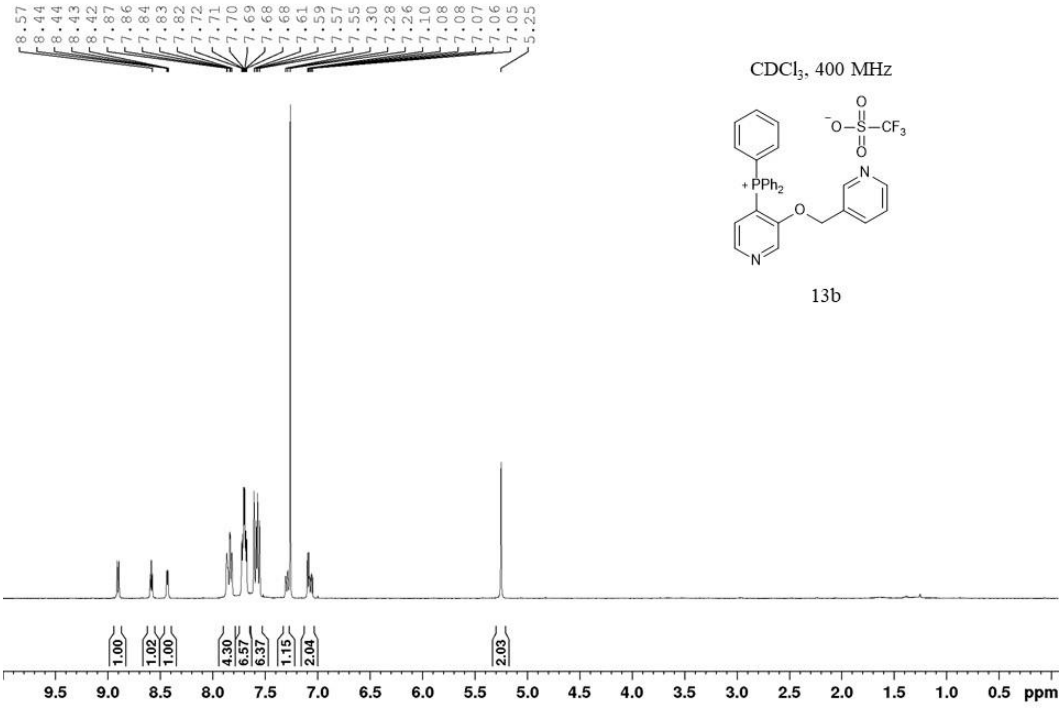


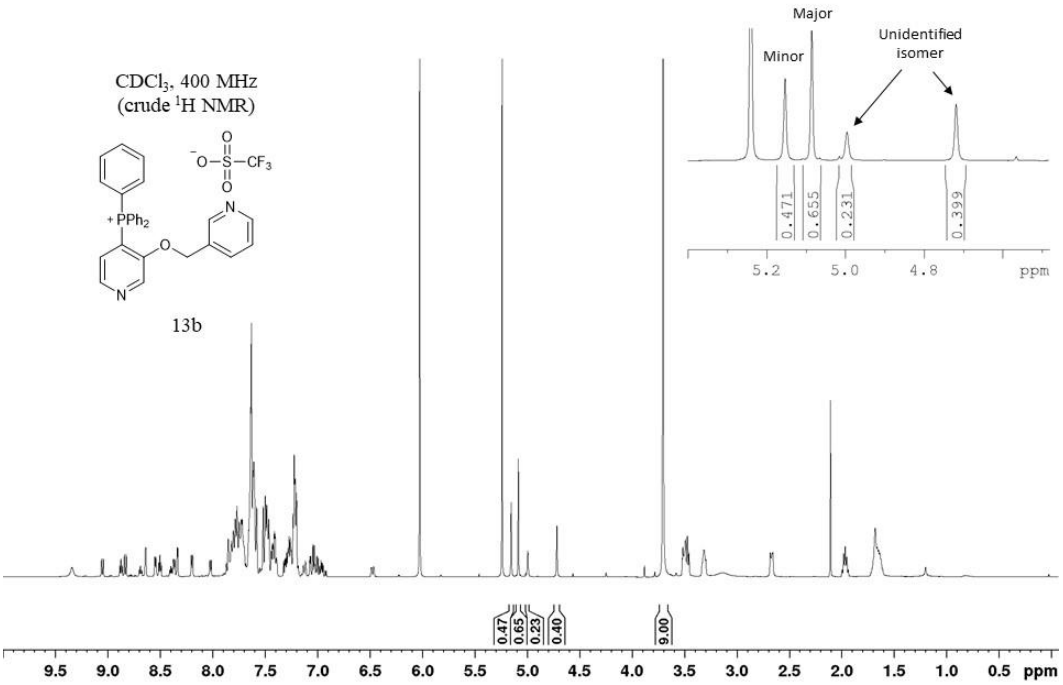
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)

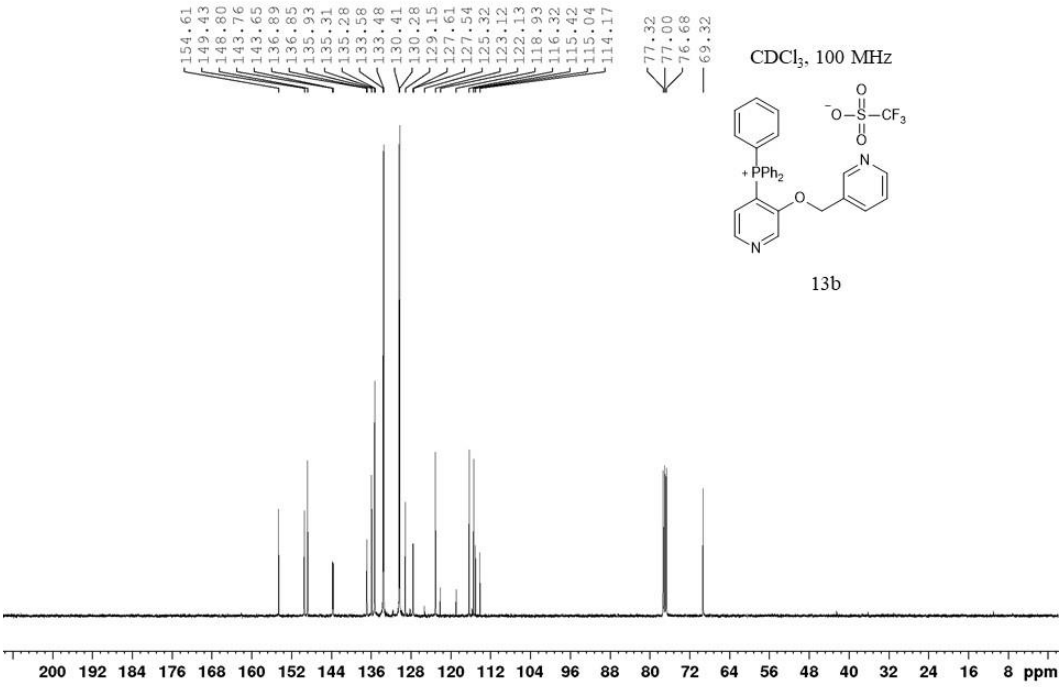
12b

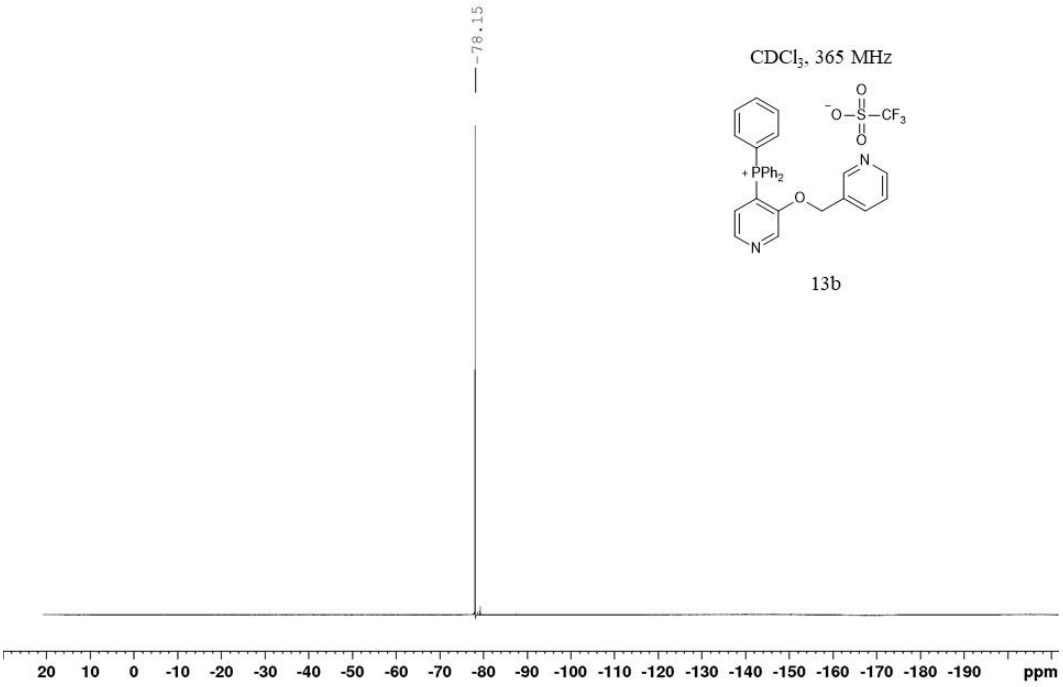

CDCl3, 400 MHz
(crude 1H NMR)
13a
ppm

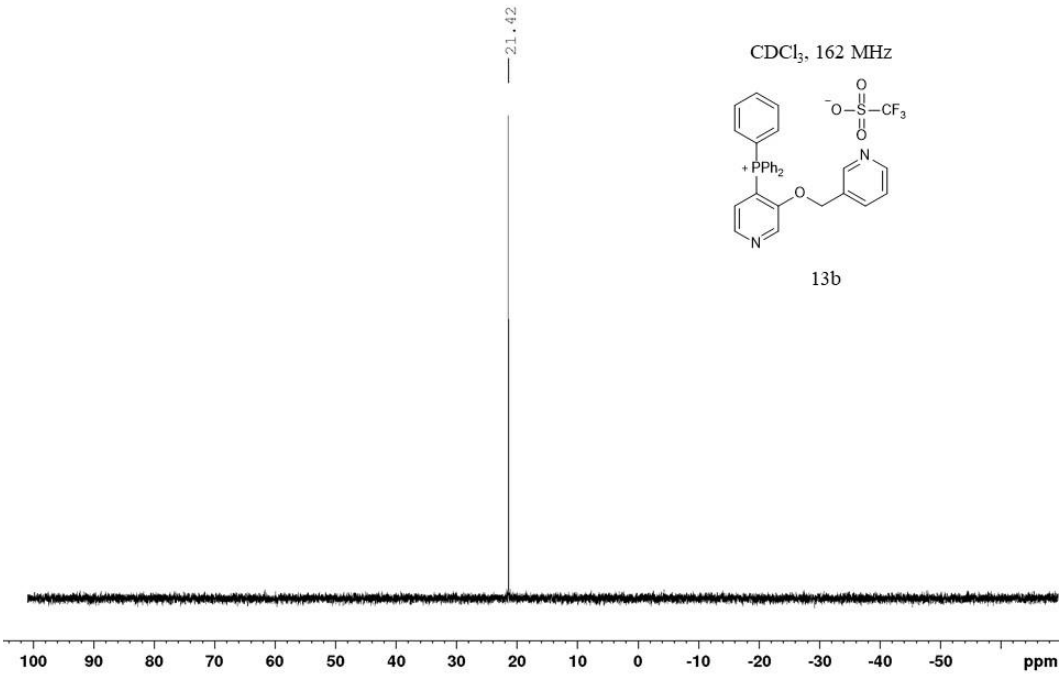

Minor
Major
Unidentified isomers
CDCl3, 162 MHz
(crude 31P NMR)
13a
ppm

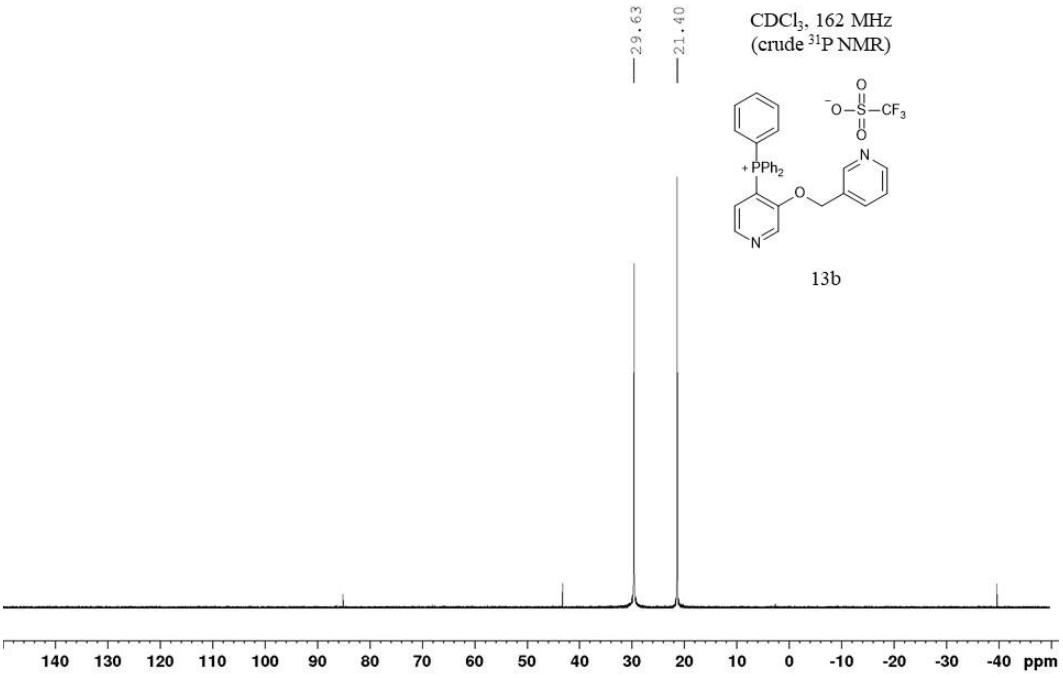

8.57
8.44
8.44
8.43
8.42
7.87
7.86
7.84
7.83
7.82
7.72
7.71
7.70
7.69
7.68
7.68
7.61
7.59
7.57
7.55
7.30
7.28
7.26
7.10
7.08
7.08
7.07
7.06
7.05
5.25
CDCl3, 400 MHz
13b
1.00
1.02
1.00
4.30
6.57
6.37
1.15
2.04
2.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

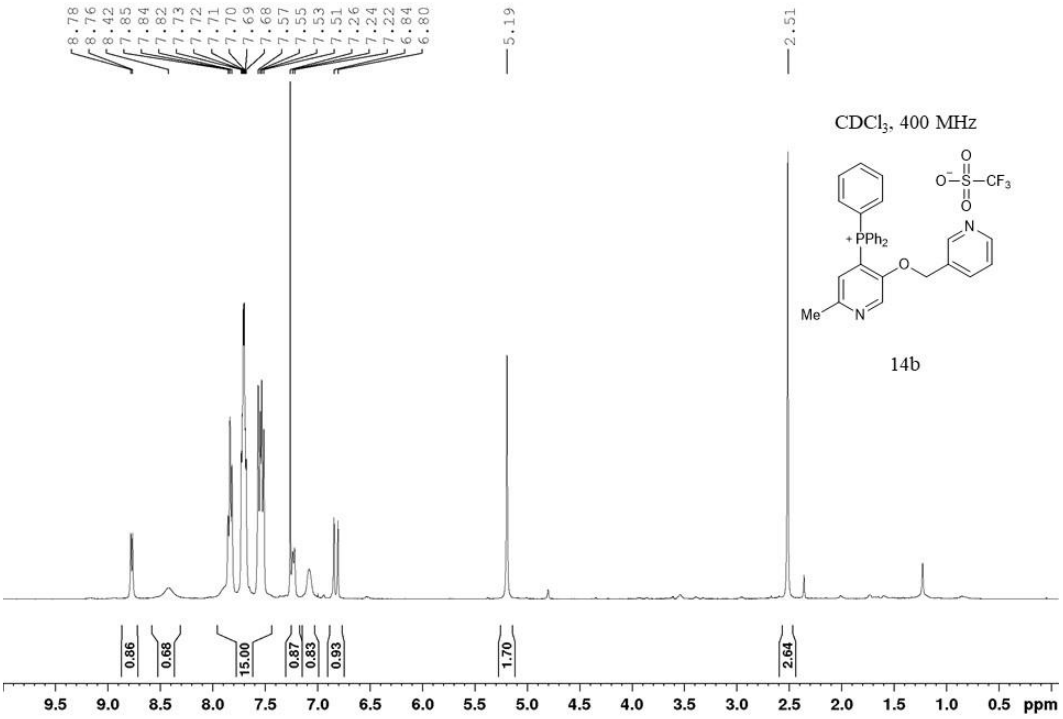

CDCl3, 400 MHz
(crude 1H NMR)
13b
Major
Minor
Unidentified isomer
0.471
0.655
0.231
0.399
5.2 5.0 4.8 ppm
0.47
0.65
0.23
0.40
9.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

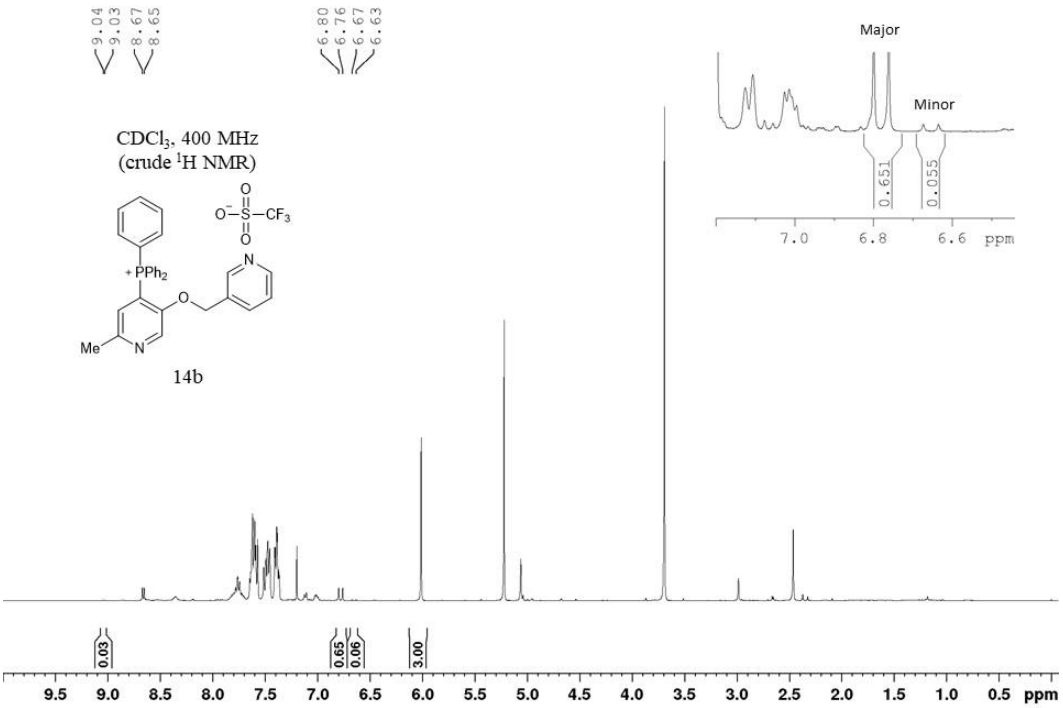

154.61
149.43
148.80
143.76
143.65
136.89
136.85
135.93
135.31
135.28
133.58
133.48
130.41
130.28
129.15
127.61
127.54
125.32
123.12
122.13
118.93
116.32
115.42
115.04
114.17
77.32
77.00
76.68
69.32
CDCl3, 100 MHz
13b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

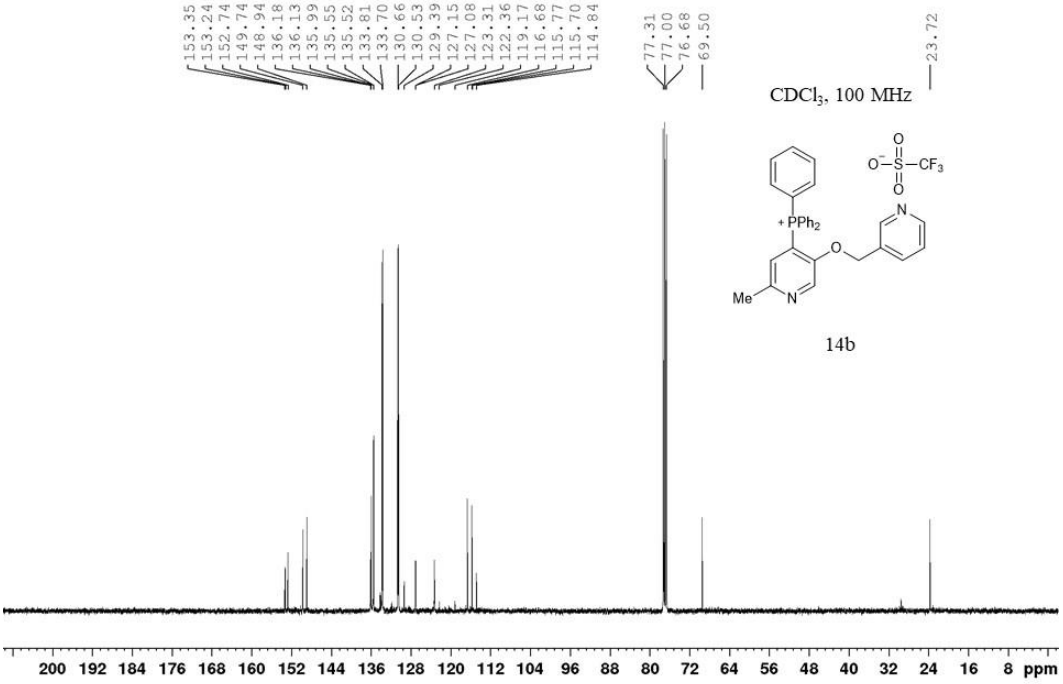

-78.15
CDCl3, 365 MHz
13b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm


21.42
CDCl3, 162 MHz
13b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

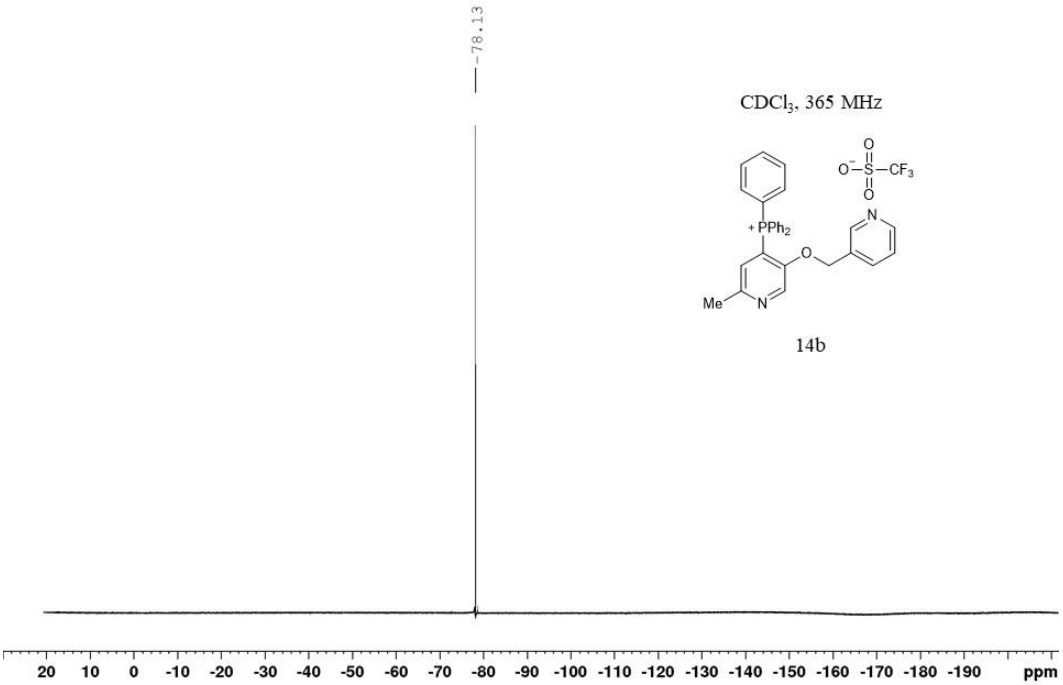

29.63
21.40
CDCl3, 162 MHz
(crude 31P NMR)
13b
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


8.78
8.76
8.42
7.85
7.84
7.82
7.73
7.72
7.71
7.70
7.69
7.68
7.57
7.55
7.53
7.51
7.26
7.24
7.22
6.84
6.80
5.19
2.51
CDCl3, 400 MHz
14b
0.86
0.68
15.00
0.87
0.83
0.93
1.70
2.64
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 ppm

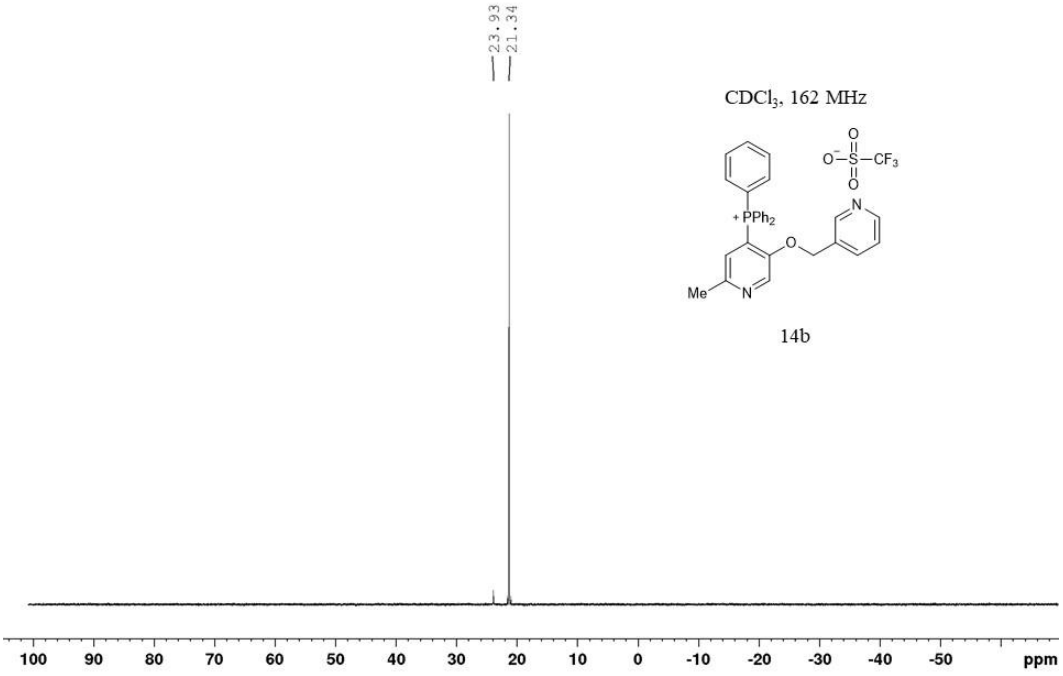

9.04
9.03
8.67
8.65
6.80
6.76
6.67
6.63
CDCl3, 400 MHz
(crude 1H NMR)
14b
Major
Minor
0.651
0.055
7.0 6.8 6.6 ppm
0.03
0.65
0.06
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

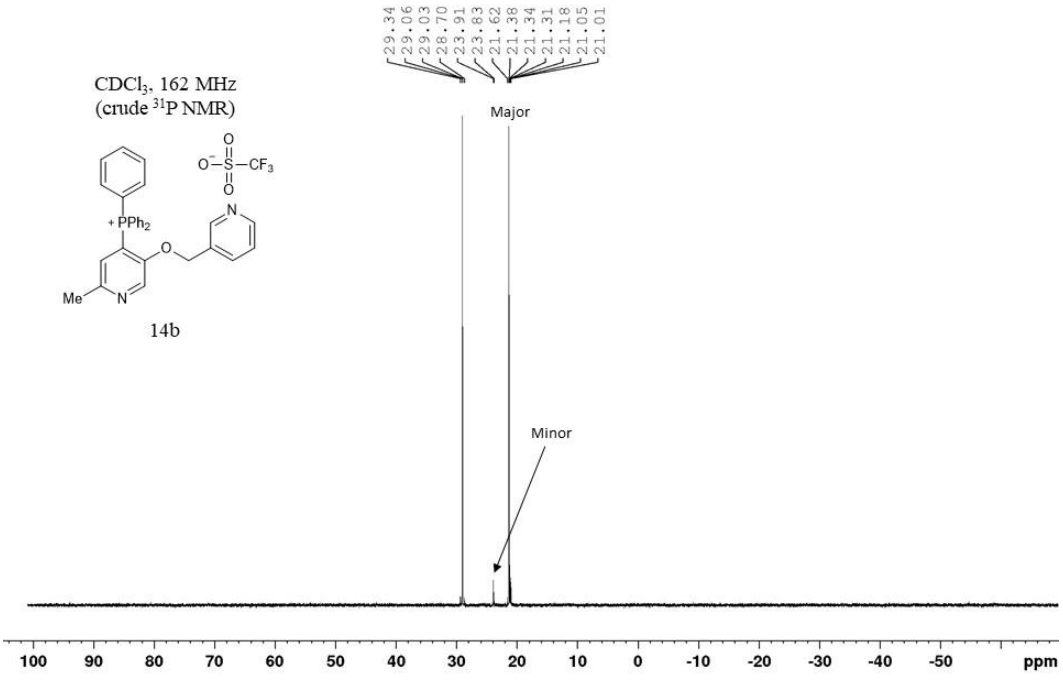

153.35
153.24
152.74
149.74
148.94
136.18
136.13
135.99
135.55
135.52
133.81
133.70
130.66
130.53
129.39
127.15
127.08
123.31
122.36
119.17
116.68
115.77
115.70
114.84
77.31
77.00
76.68
69.50
23.72
CDCl3, 100 MHz
+PPh2
O
O−S−CF3
N
Me
N
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

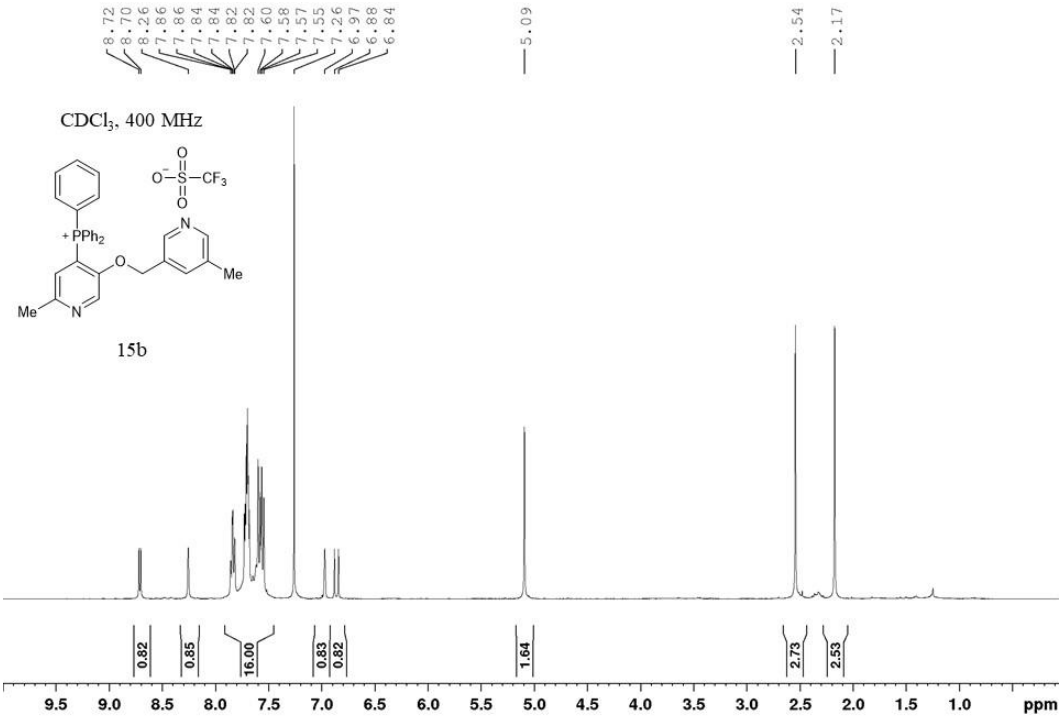
14b

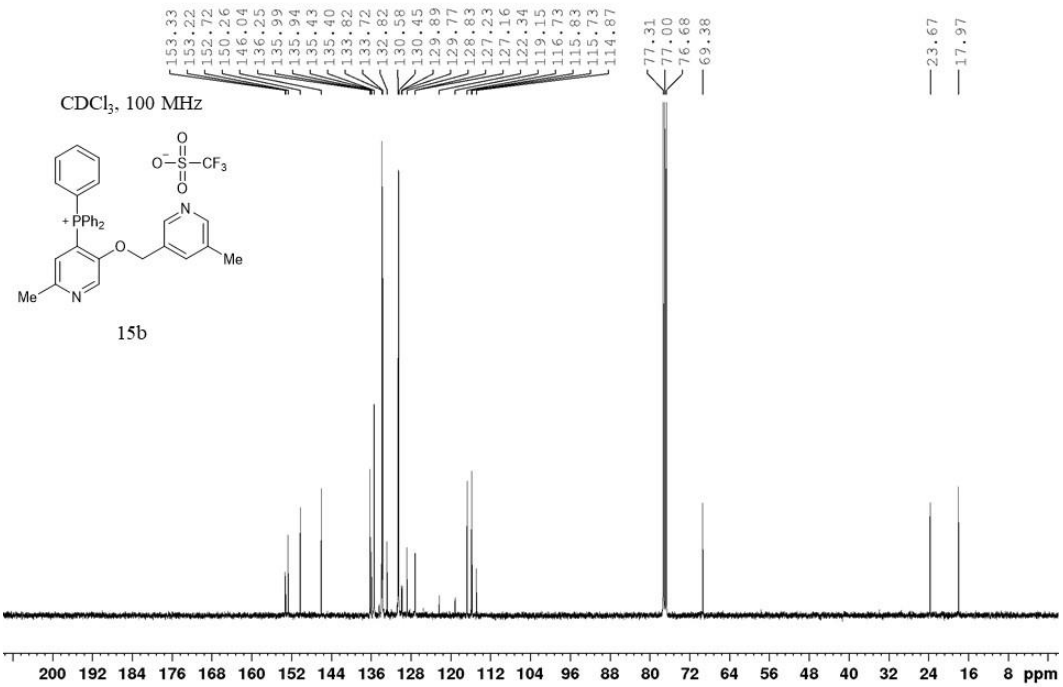

-78.13
CDCl3, 365 MHz
+PPh2
O
O−S−CF3
N
Me
N
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

14b

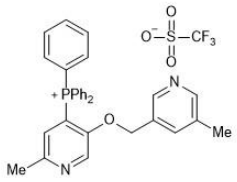

23.93
21.34
CDCl3, 162 MHz
14b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm


29.34
29.06
29.03
28.70
23.91
23.63
21.62
21.38
21.34
21.31
21.18
21.05
21.01
CDCl3, 162 MHz
(crude 31P NMR)
Major
Minor
14b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm


8.72
8.70
8.26
7.86
7.86
7.84
7.84
7.82
7.82
7.60
7.58
7.57
7.55
7.26
6.97
6.88
6.84
5.09
2.54
2.17
CDCl3, 400 MHz
15b
0.82
0.85
16.00
0.83
0.82
1.64
2.73
2.53
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 ppm

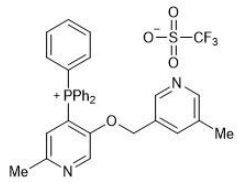

153.33
153.22
152.72
150.26
146.04
136.25
135.99
135.94
135.43
135.40
133.82
133.72
132.82
130.58
130.45
129.89
129.77
128.83
127.23
127.16
122.34
119.15
116.73
115.83
115.73
114.87
77.31
77.00
76.68
69.38
23.67
17.97
CDCl3, 100 MHz
15b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz

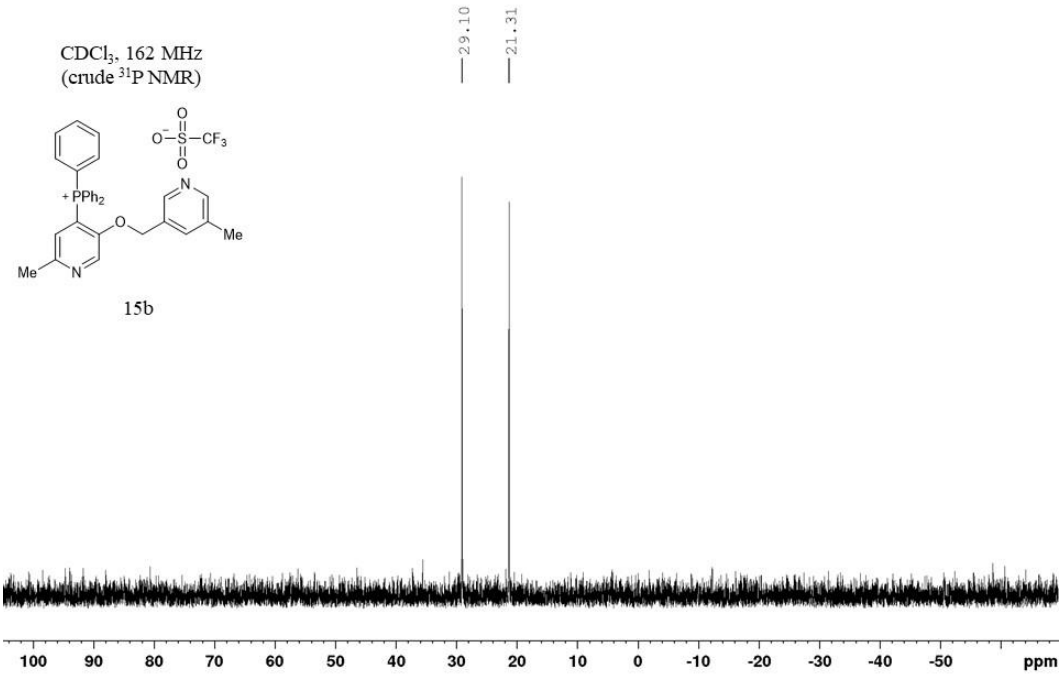


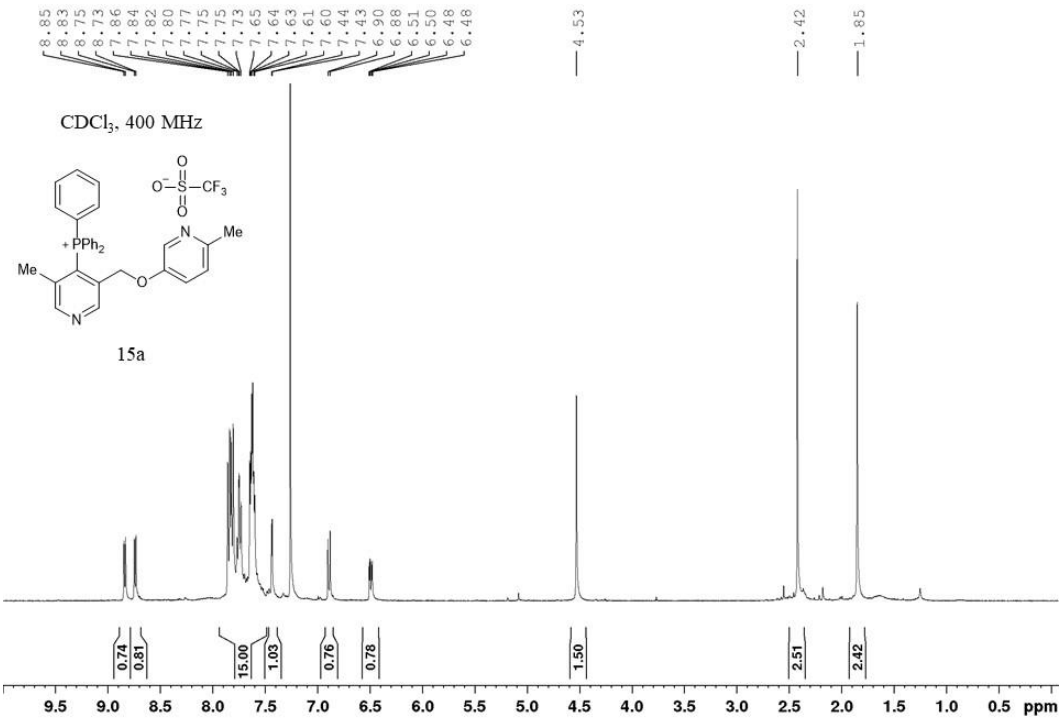
15b

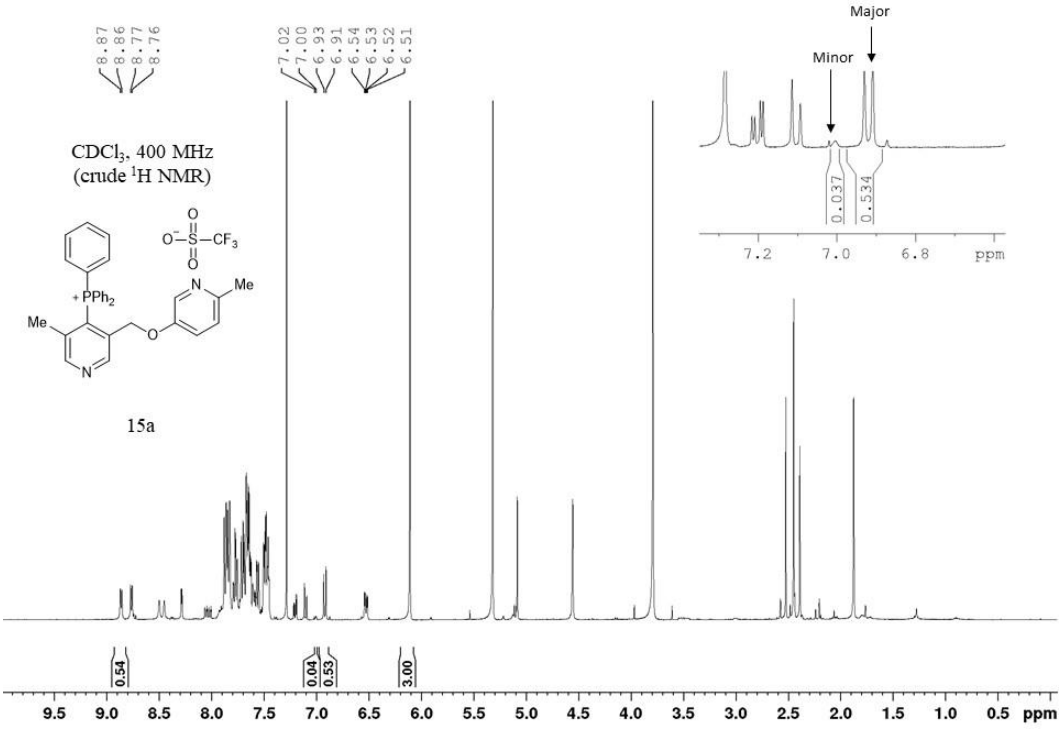
$CDCl_3$, 162 MHz

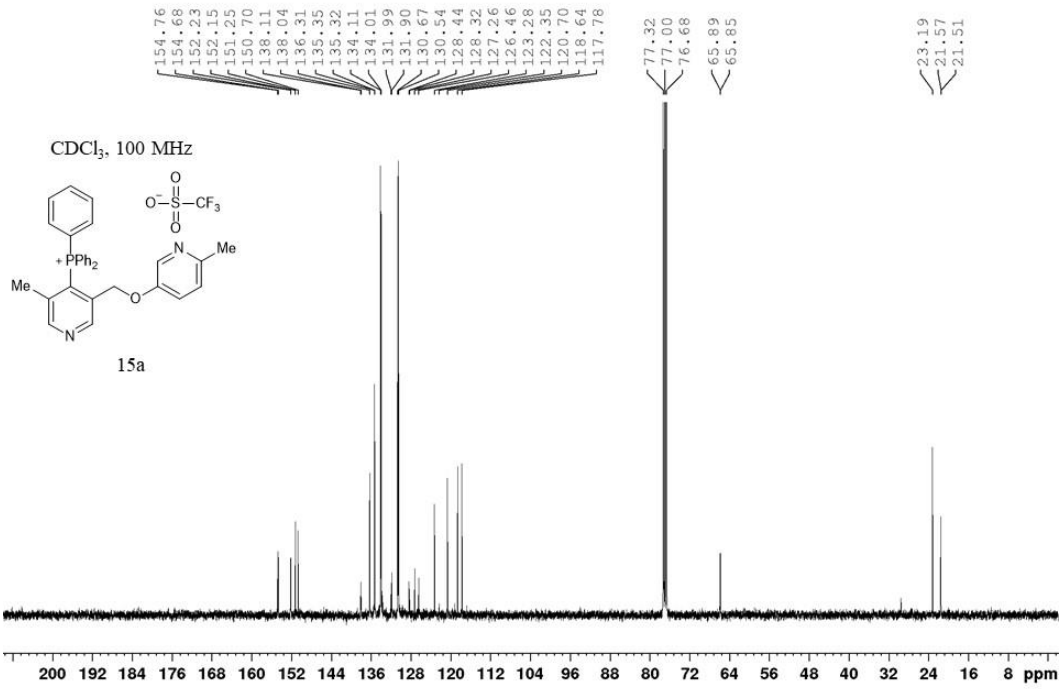


15b

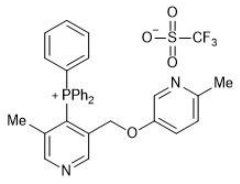

CDCl3, 162 MHz
(crude 31P NMR)
29.10
21.31
15b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm


8.85 8.83 8.75 8.73 7.86 7.84 7.82 7.80 7.77 7.75 7.75 7.73 7.65 7.64 7.63 7.61 7.60 7.44 7.43 6.90 6.88 6.51 6.50 6.48 6.48
4.53
2.42
1.85
CDCl3, 400 MHz
15a
0.74 0.81 15.00 1.03 0.76 0.78 1.50 2.51 2.42
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 ppm


8.87
8.86
8.77
8.76
7.02
7.00
6.93
6.91
6.54
6.53
6.52
6.51
Major
Minor
0.037
0.534
7.2
7.0
6.8
ppm
CDCl3, 400 MHz
(crude 1H NMR)
15a
0.54
0.04
0.53
3.00
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 ppm

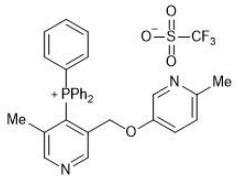

154.76
154.68
152.23
152.15
151.25
150.70
138.11
138.04
136.31
135.35
135.32
134.11
134.01
131.99
131.90
130.67
130.54
128.44
128.32
127.26
126.46
123.28
122.35
120.70
118.64
117.78
77.32
77.00
76.68
65.89
65.85
23.19
21.57
21.51
CDCl3, 100 MHz
15a
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz

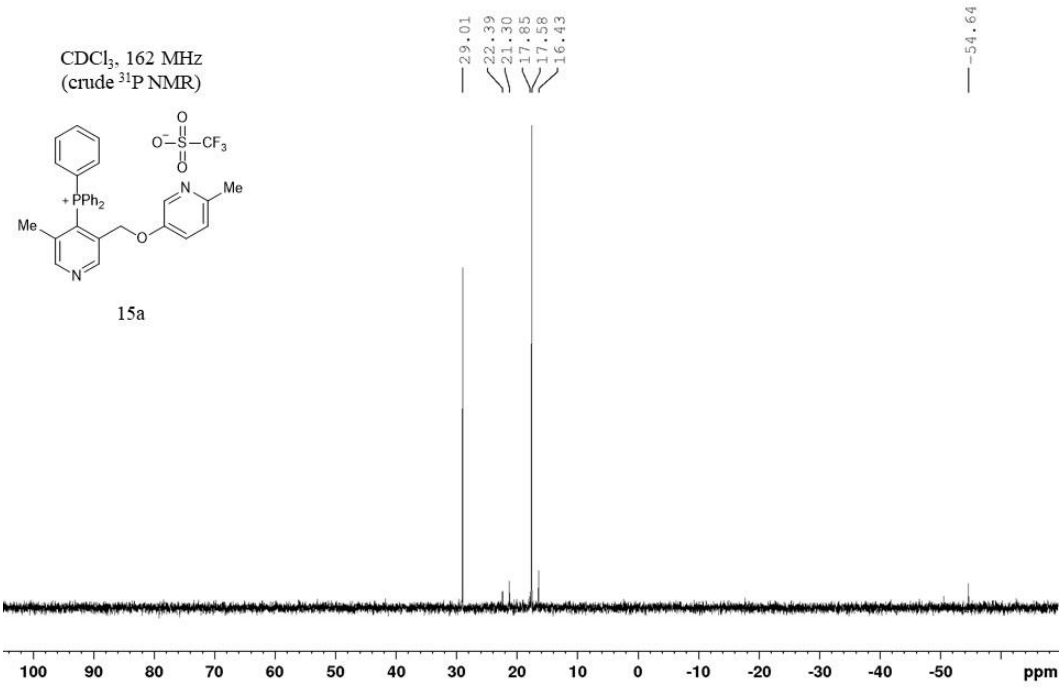


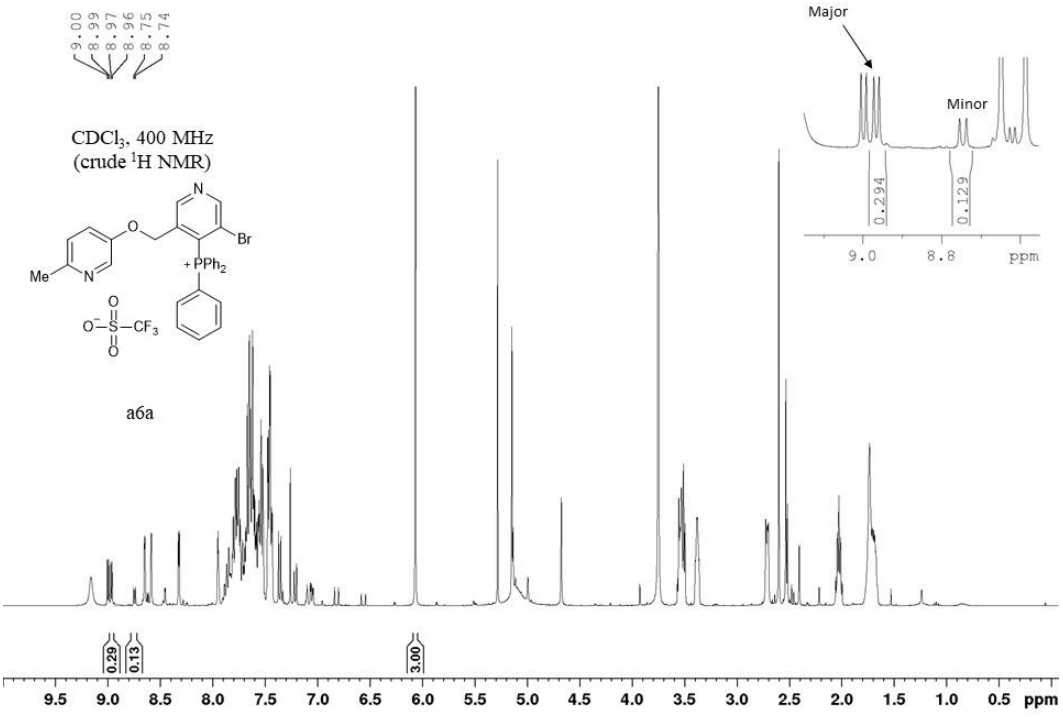
15a

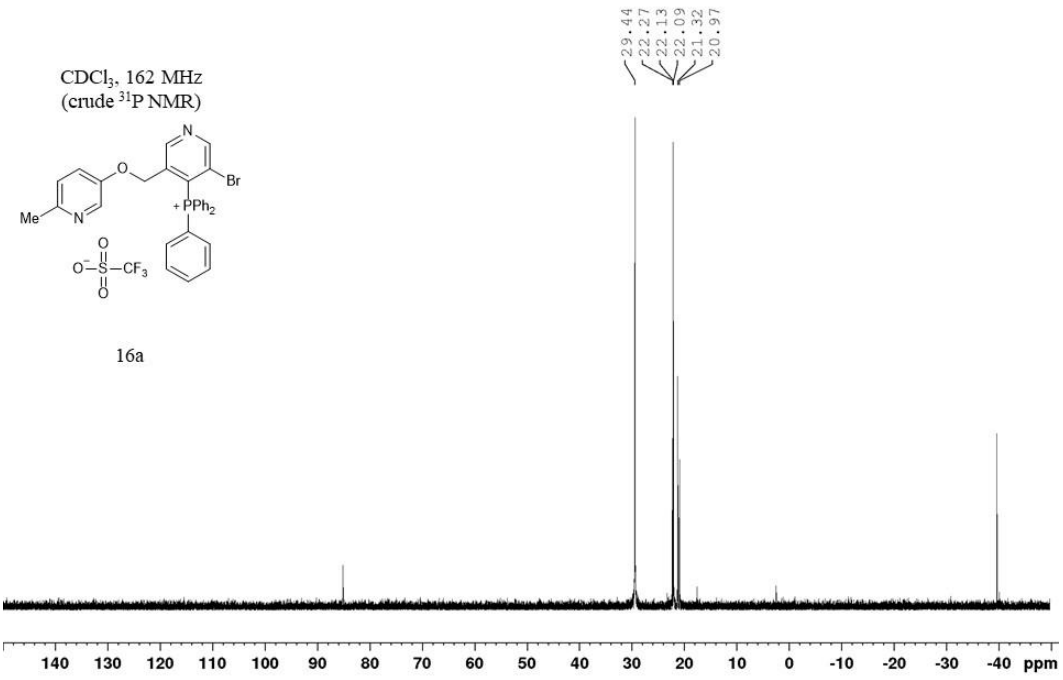
$CDCl_3$, 162 MHz

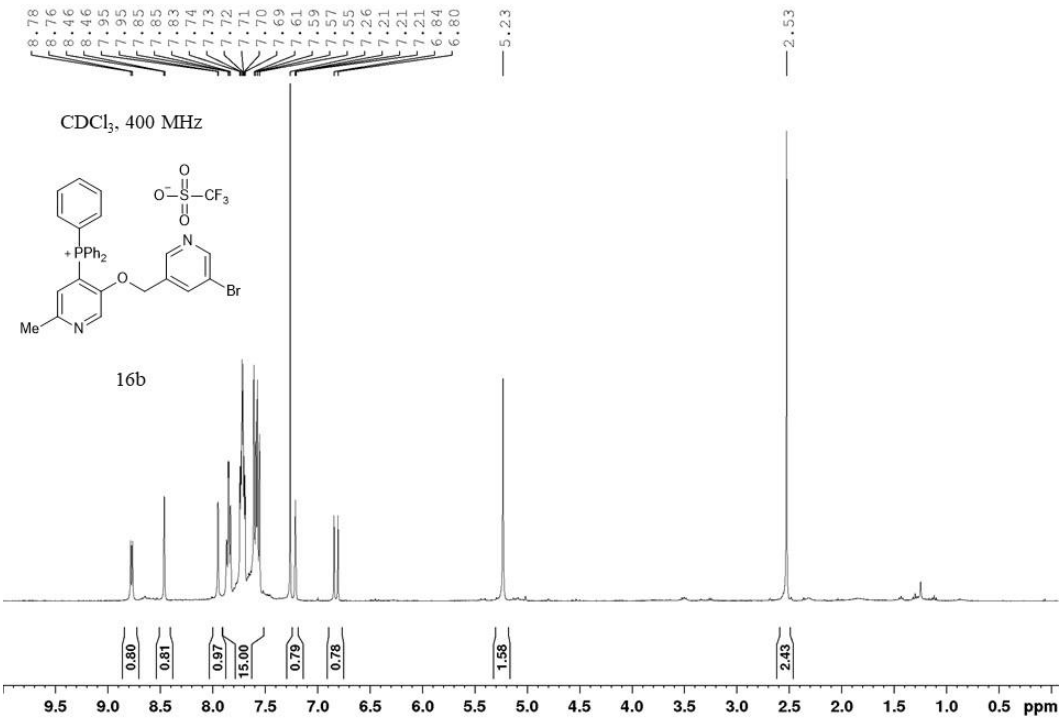


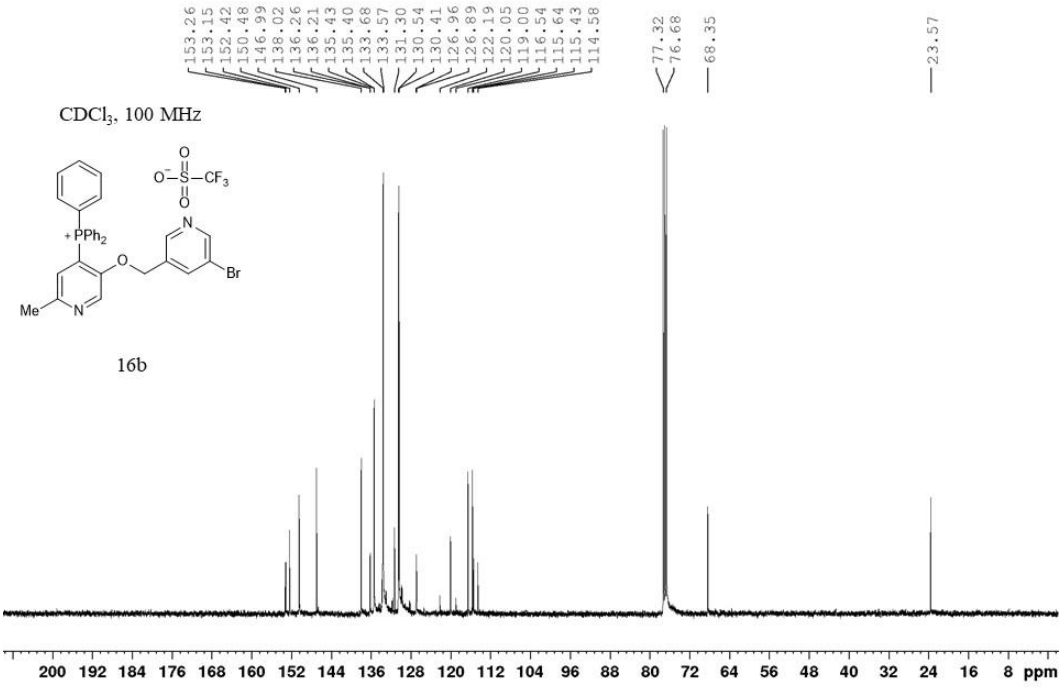
15a

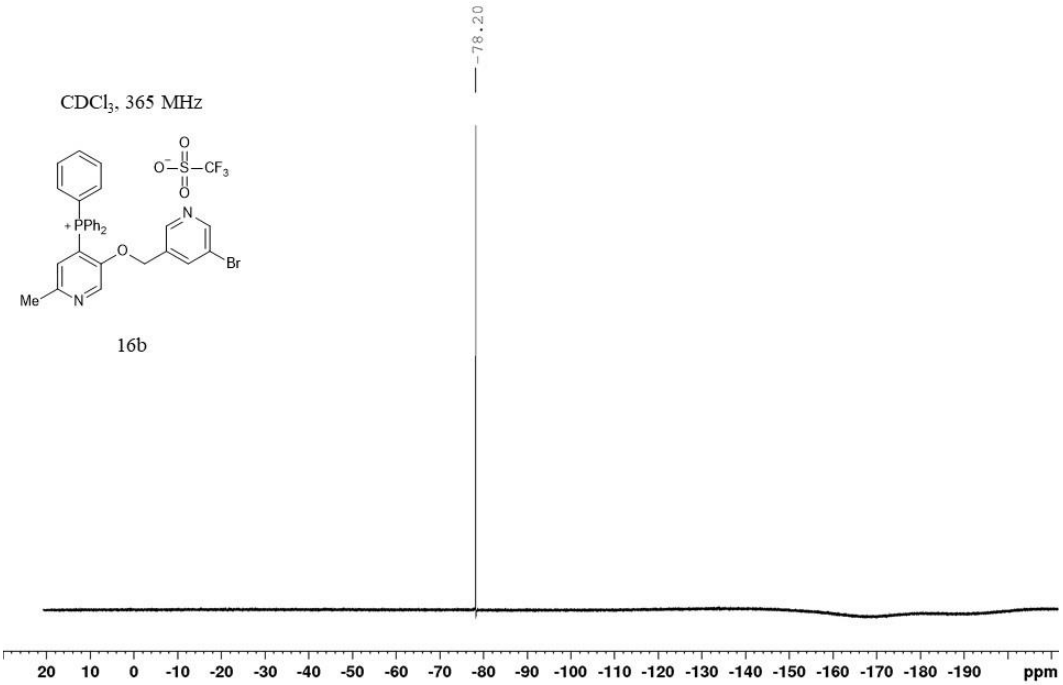

CDCl3, 162 MHz
(crude 31P NMR)
29.01
22.39
21.30
17.85
17.58
16.43
-54.64
15a
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm


9.00
8.99
8.97
8.96
8.75
8.74
CDCl3, 400 MHz
(crude 1H NMR)
Major
Minor
0.294
0.129
9.0
8.8
ppm
аба
0.29
0.13
3.00
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 ppm

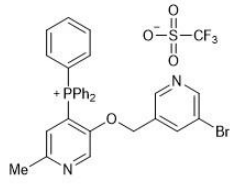

CDCl3, 162 MHz
(crude 31P NMR)
16a
29.44
22.27
22.13
22.09
21.32
20.97
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


8.78
8.76
8.46
8.46
7.95
7.85
7.85
7.83
7.74
7.73
7.72
7.71
7.70
7.69
7.61
7.59
7.57
7.55
7.26
7.21
7.21
7.21
6.84
6.80
5.23
2.53
CDCl3, 400 MHz
16b
0.80
0.81
0.97
15.00
0.79
0.78
1.58
2.43
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 ppm


153.26
153.15
152.42
150.48
146.99
138.02
136.26
136.21
135.43
135.40
133.68
133.57
131.30
130.54
130.41
126.96
126.89
122.19
120.05
119.00
116.54
115.64
115.43
114.58
77.32
76.68
68.35
23.57
CDCl3, 100 MHz
16b
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 ppm

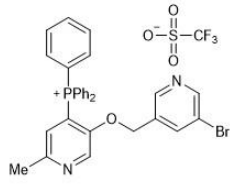

-78.20
CDCl3, 365 MHz
16b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

$CDCl_3$, 162 MHz



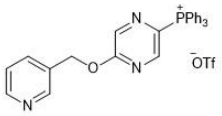
16b

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

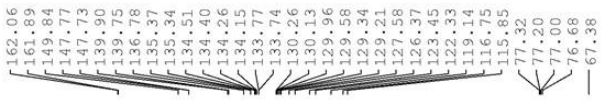


16b

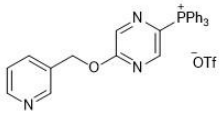
$CDCl_3$, 400 MHz



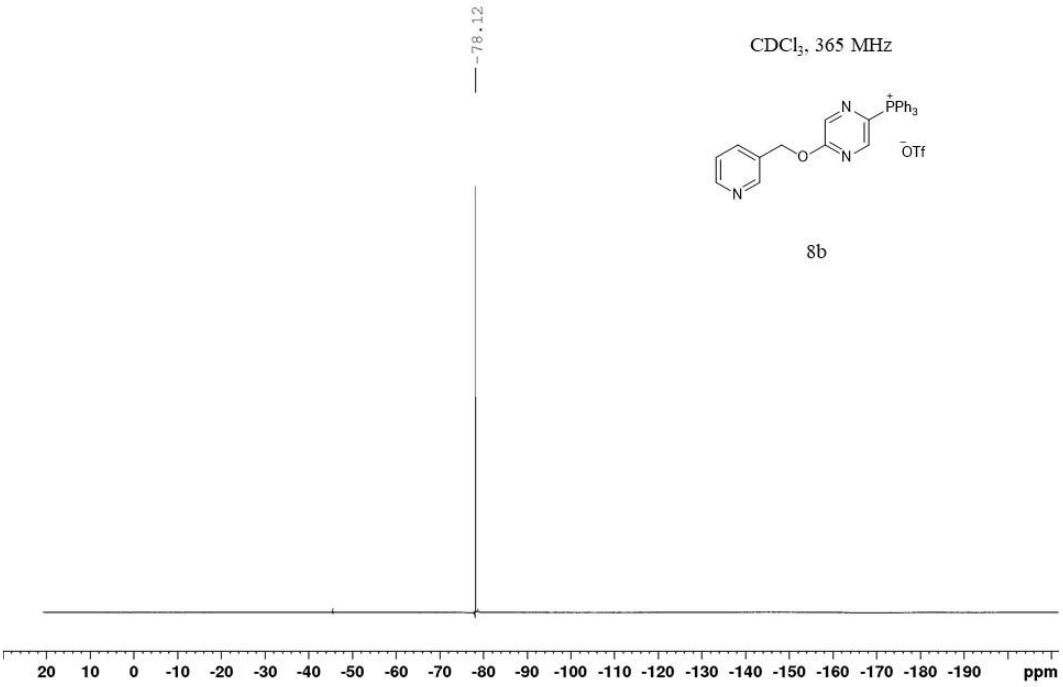
8b

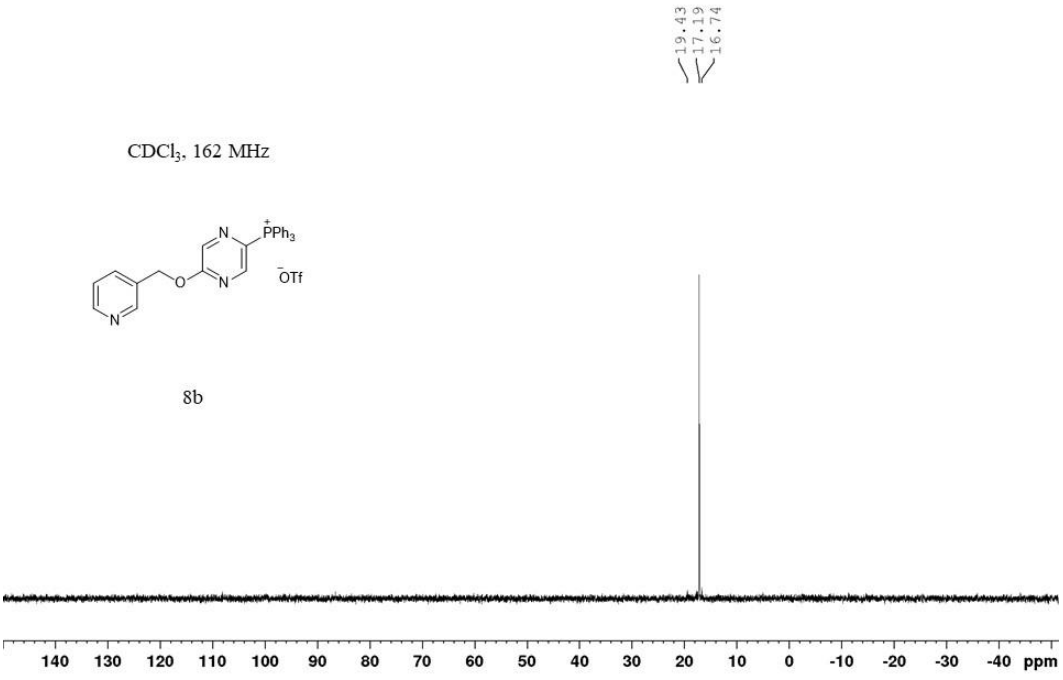


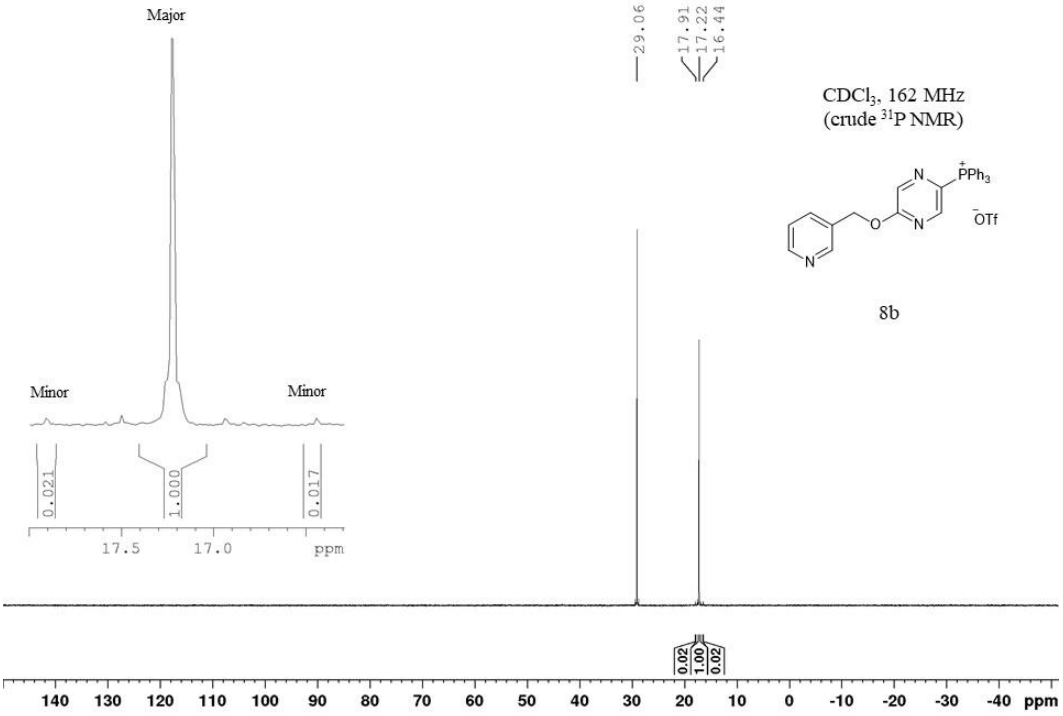
$CDCl_3$, 100 MHz



8b

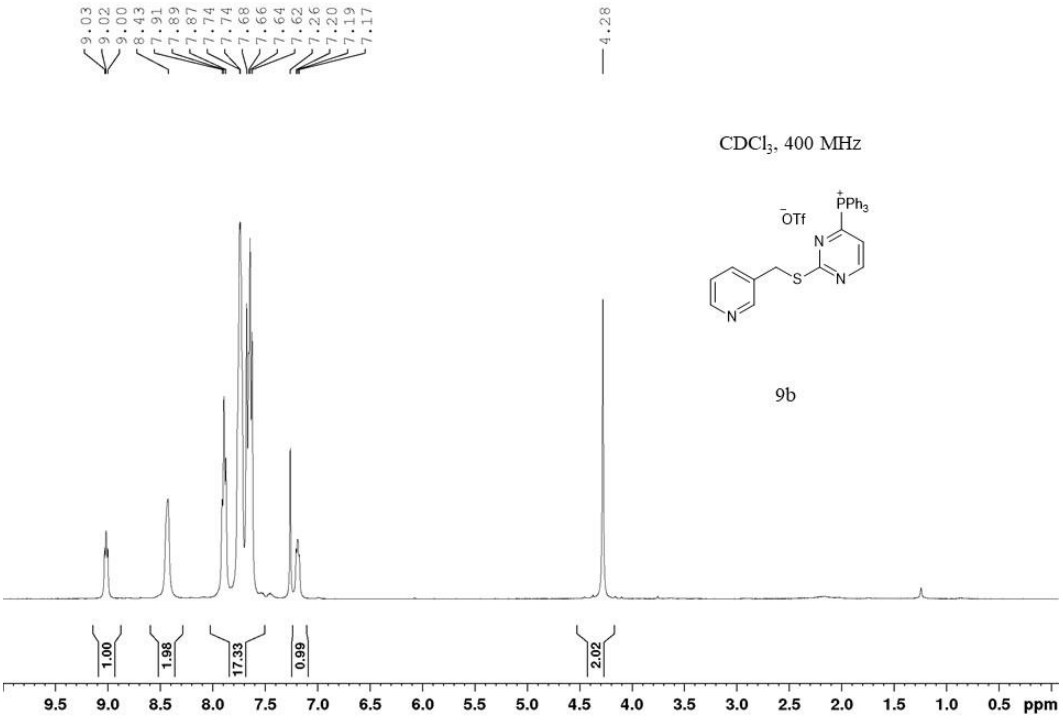

78.12
CDCl3, 365 MHz
PPh3
OTf
8b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm


19.43
17.19
16.74
CDCl3, 162 MHz
PPh3
OTf
8b
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm



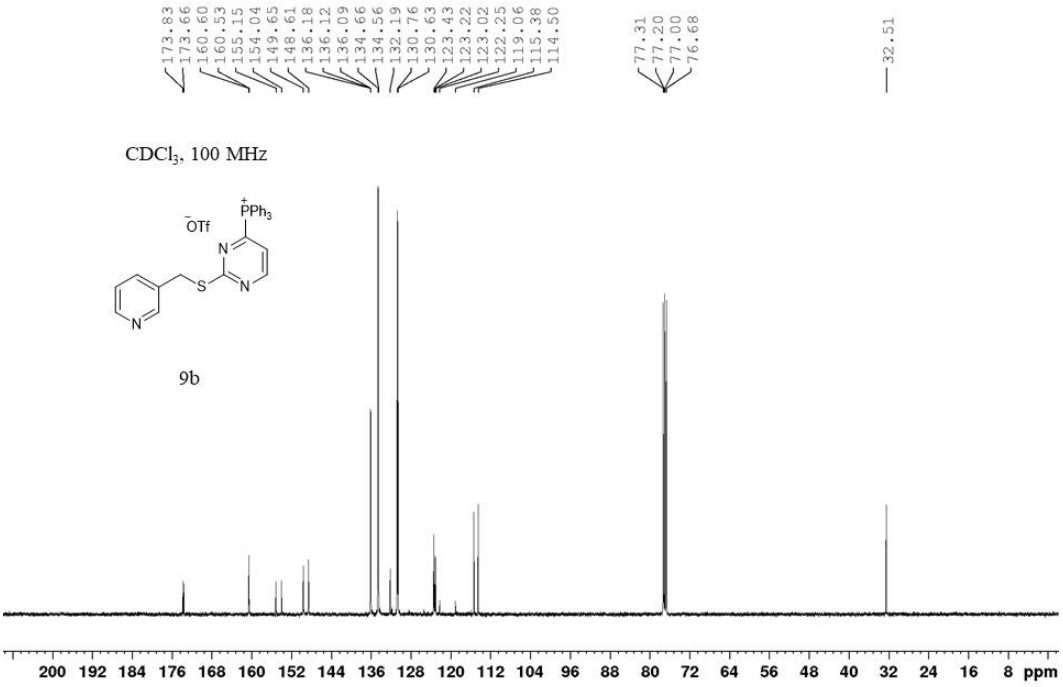
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)

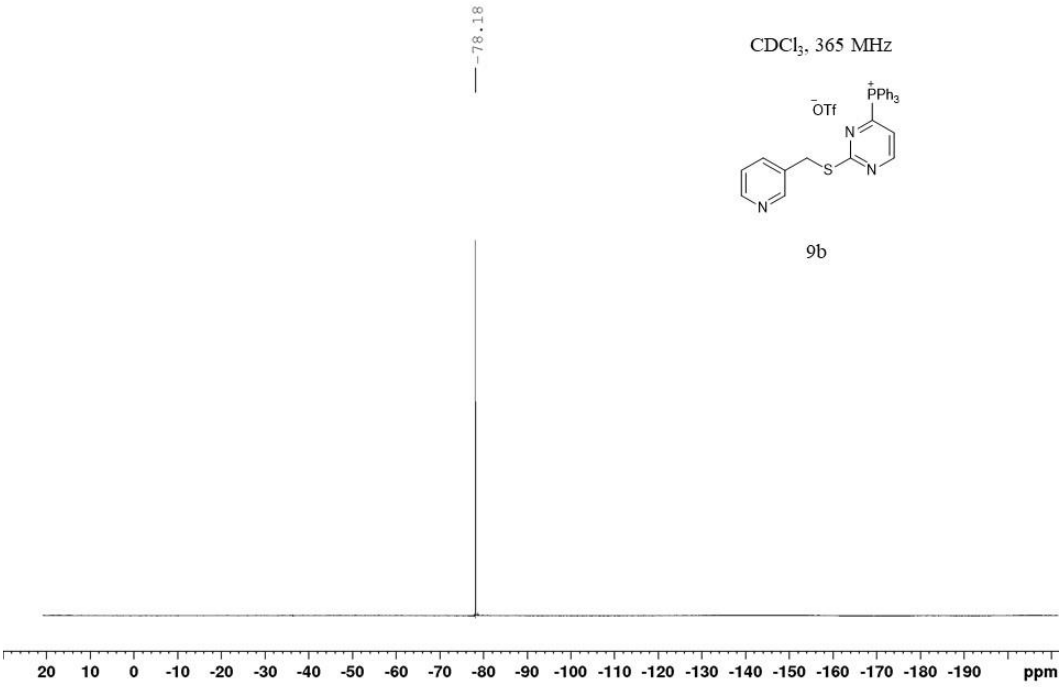
8b

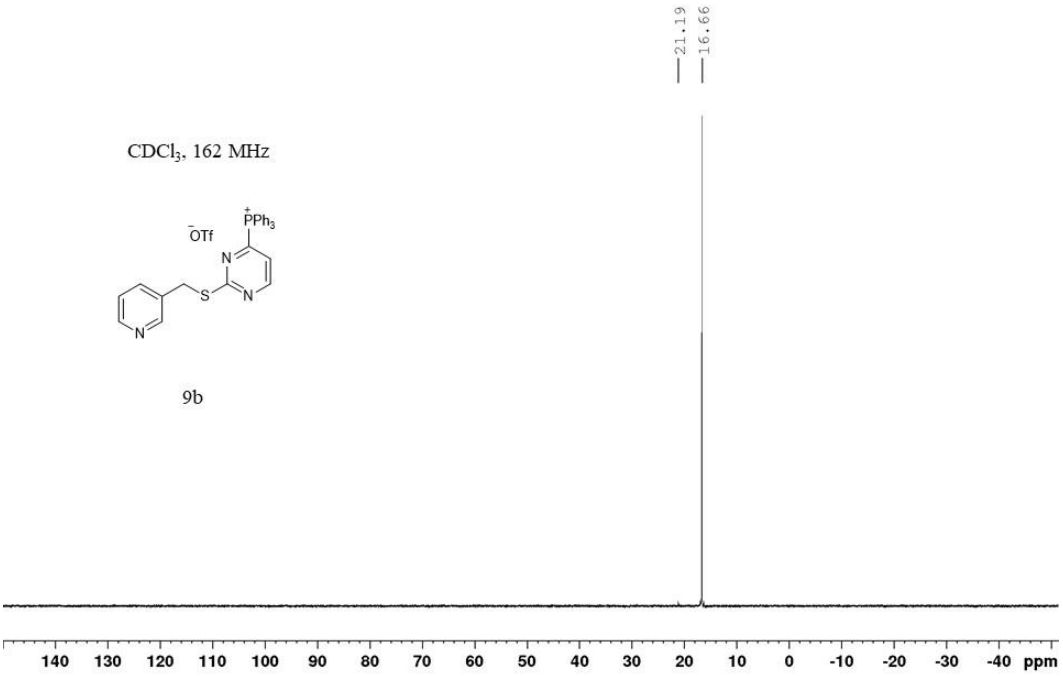


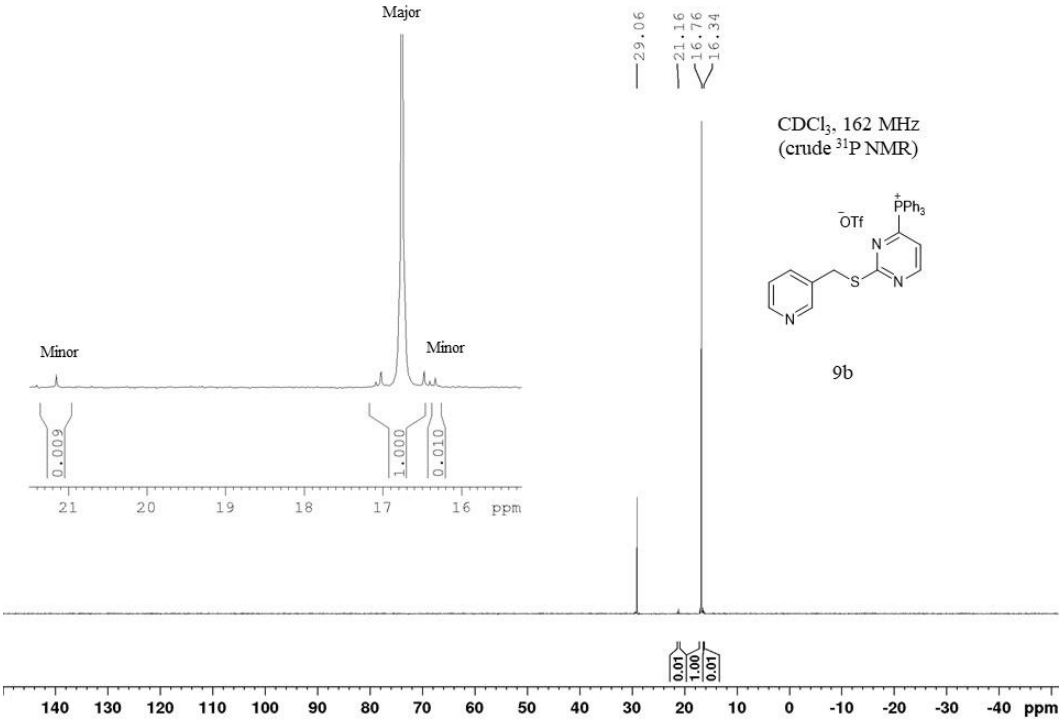
$CDCl_3$, 400 MHz

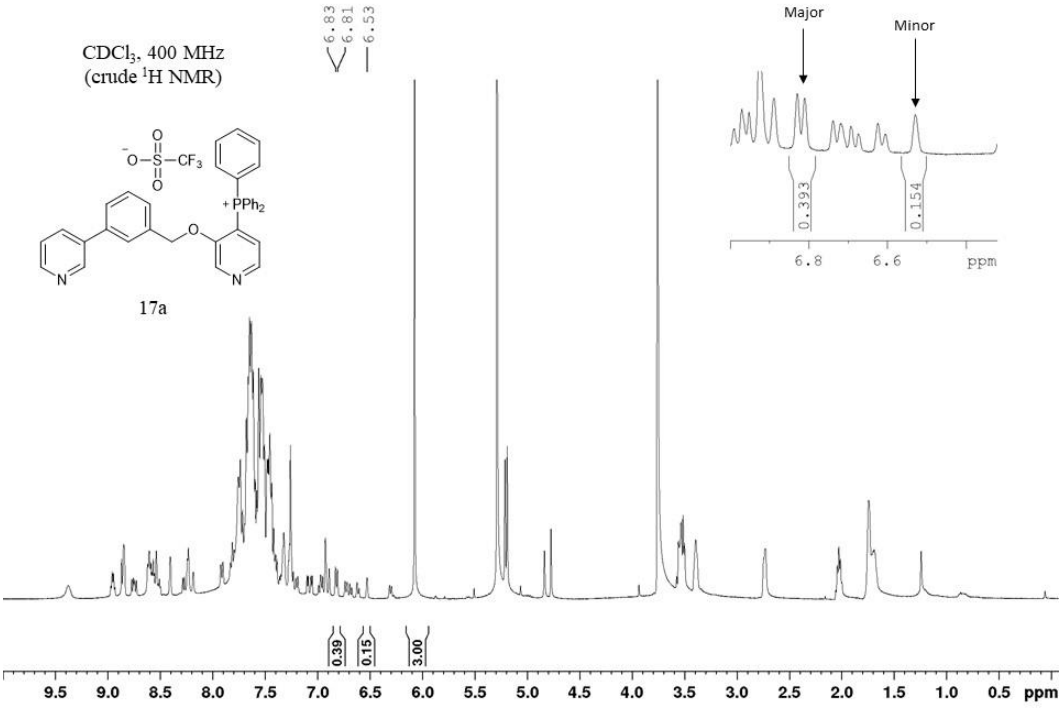
9b

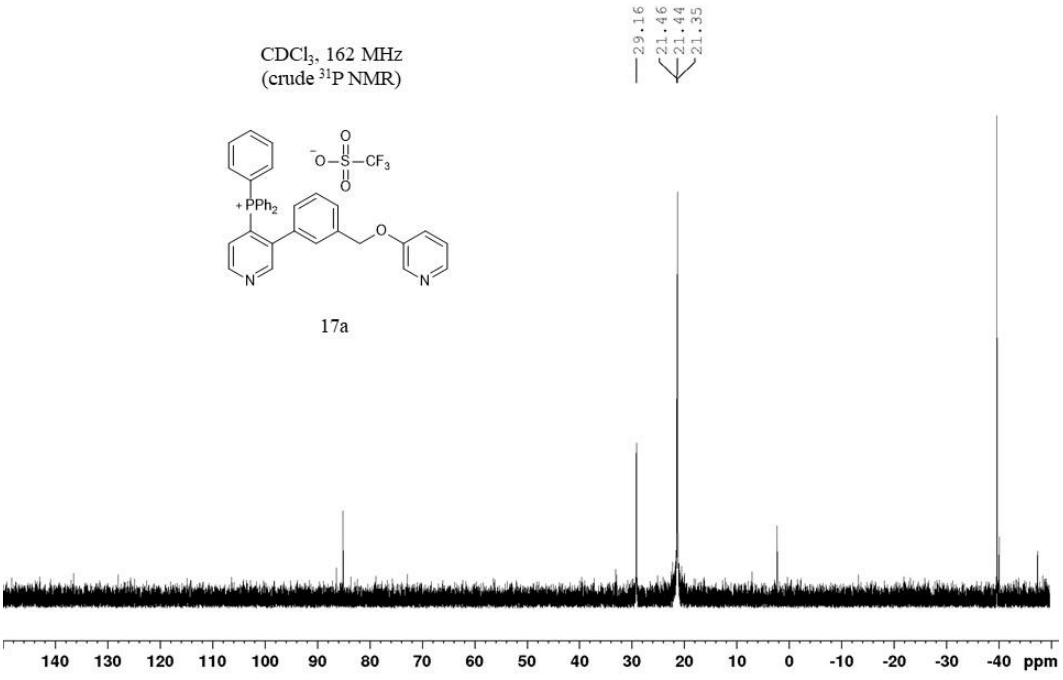

173.83
173.66
160.60
160.53
155.15
154.04
149.65
148.61
136.18
136.12
136.09
134.66
134.56
132.19
130.76
130.63
123.43
123.22
123.02
122.25
119.06
115.38
114.50
77.31
77.20
77.00
76.68
32.51
CDCl3, 100 MHz
OTf
PPh3
N
S
N
N
9b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

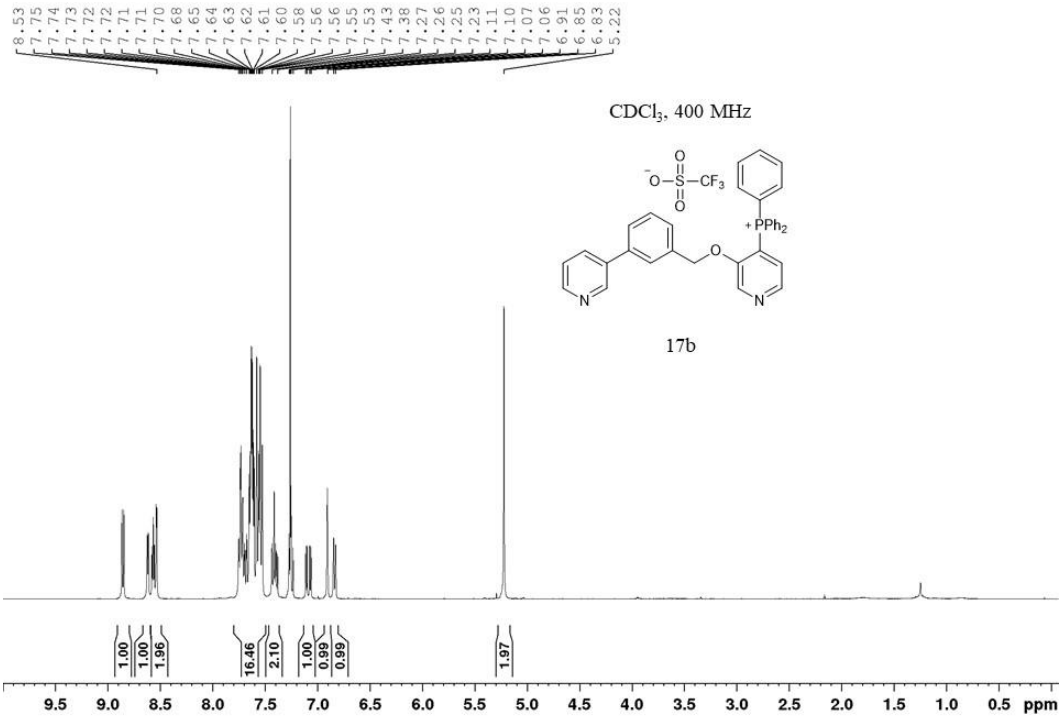

-78.18
CDCl3, 365 MHz
OTf
PPh3
N
S
N
N
9b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

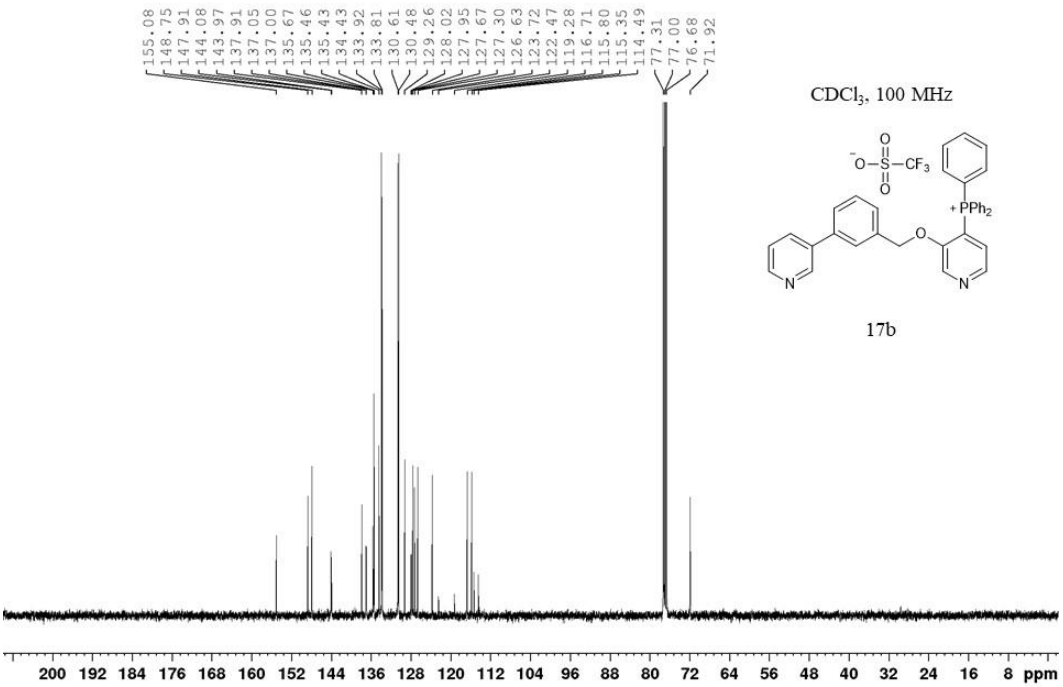

21.19
16.66
CDCl3, 162 MHz
OTf
PPh3
9b
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

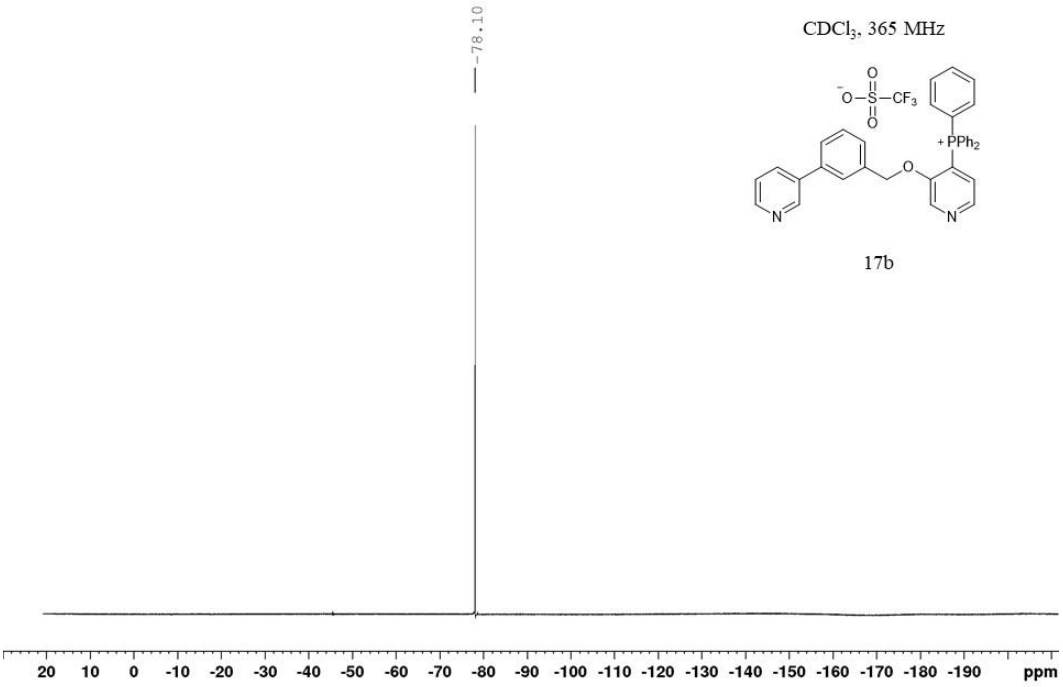

Major
Minor
Minor
0.009
1.000
0.010
21 20 19 18 17 16 ppm
29.06
21.16
16.76
16.34
CDCl3, 162 MHz
(crude 31P NMR)
OTf
PPh3
9b
0.01
1.00
0.01
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


CDCl3, 400 MHz
(crude 1H NMR)
6.83
6.81
6.53
Major
Minor
0.393
0.154
6.8
6.6
ppm
17a
0.39
0.15
3.00
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 ppm


CDCl3, 162 MHz
(crude 31P NMR)
29.16
21.46
21.44
21.35
17a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

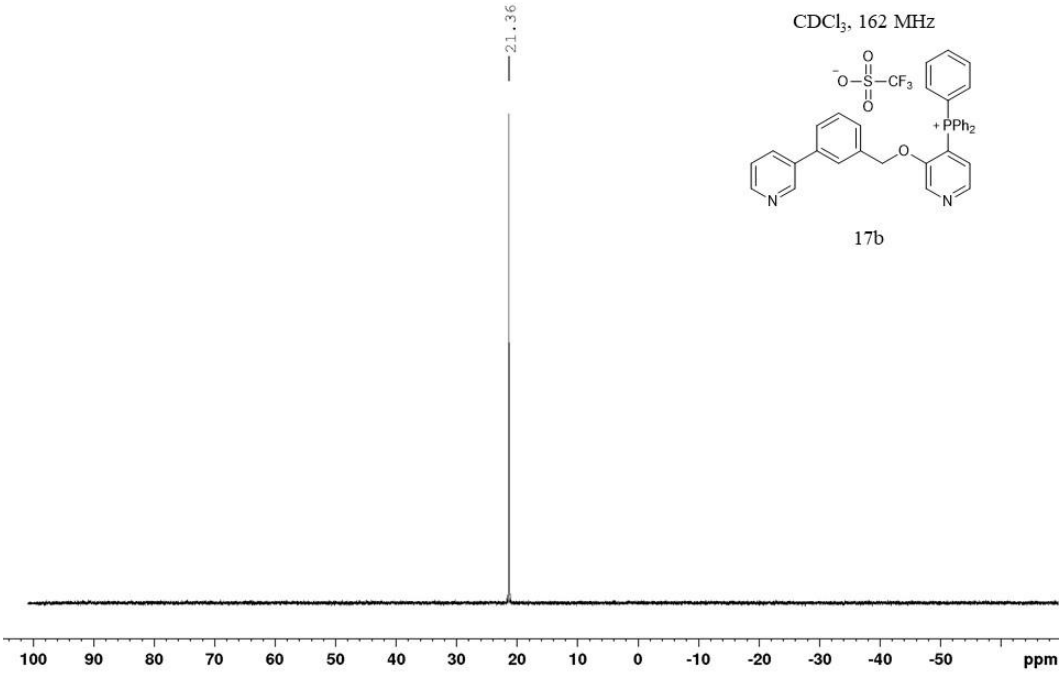

8.53
7.75
7.74
7.73
7.72
7.72
7.71
7.71
7.70
7.68
7.65
7.64
7.63
7.62
7.61
7.60
7.58
7.56
7.56
7.55
7.53
7.43
7.38
7.27
7.26
7.25
7.23
7.11
7.10
7.07
7.06
6.91
6.85
6.83
5.22
CDCl3, 400 MHz
17b
1.00
1.00
1.96
16.46
2.10
1.00
0.99
0.99
1.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


155.08
148.75
147.91
144.08
143.97
137.91
137.05
137.00
135.67
135.46
135.43
134.43
133.92
133.81
130.61
130.48
129.26
128.02
127.95
127.67
127.30
126.63
123.72
122.47
119.28
116.71
115.80
115.35
114.49
77.31
77.00
76.68
71.92
CDCl3, 100 MHz
17b
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 ppm



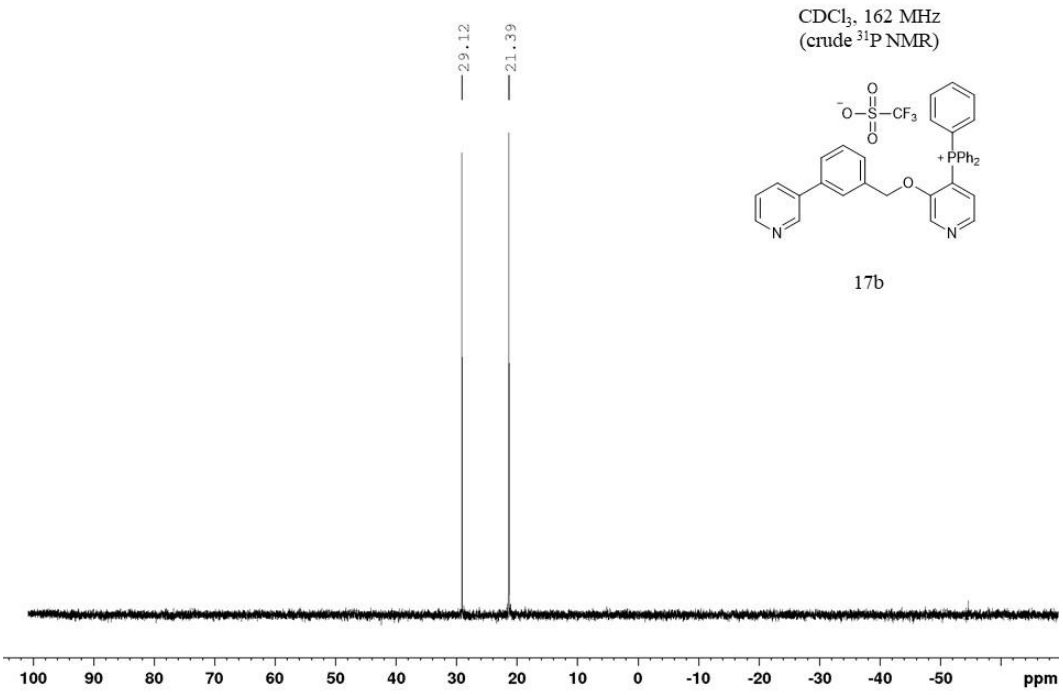
$CDCl_3$, 365 MHz

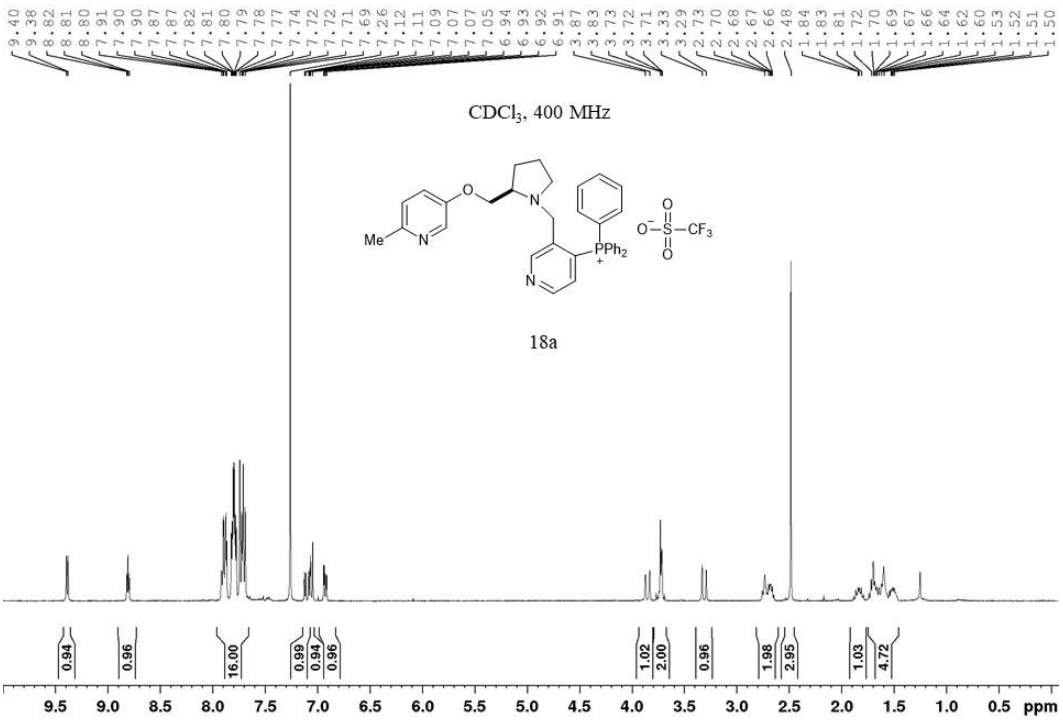
17b

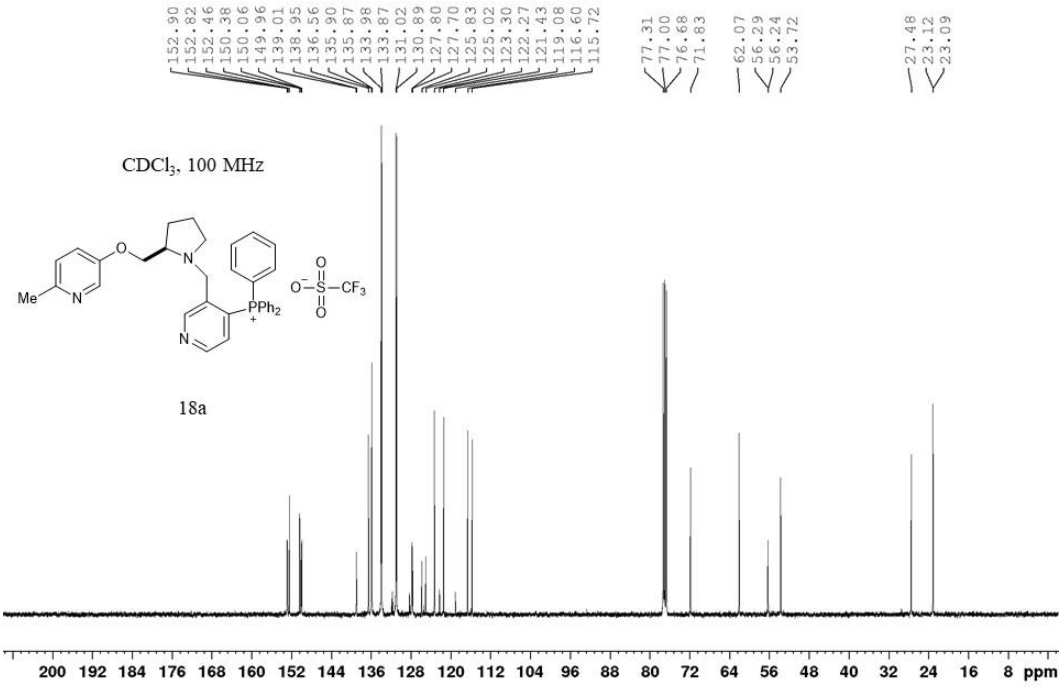


$CDCl_3$, 162 MHz

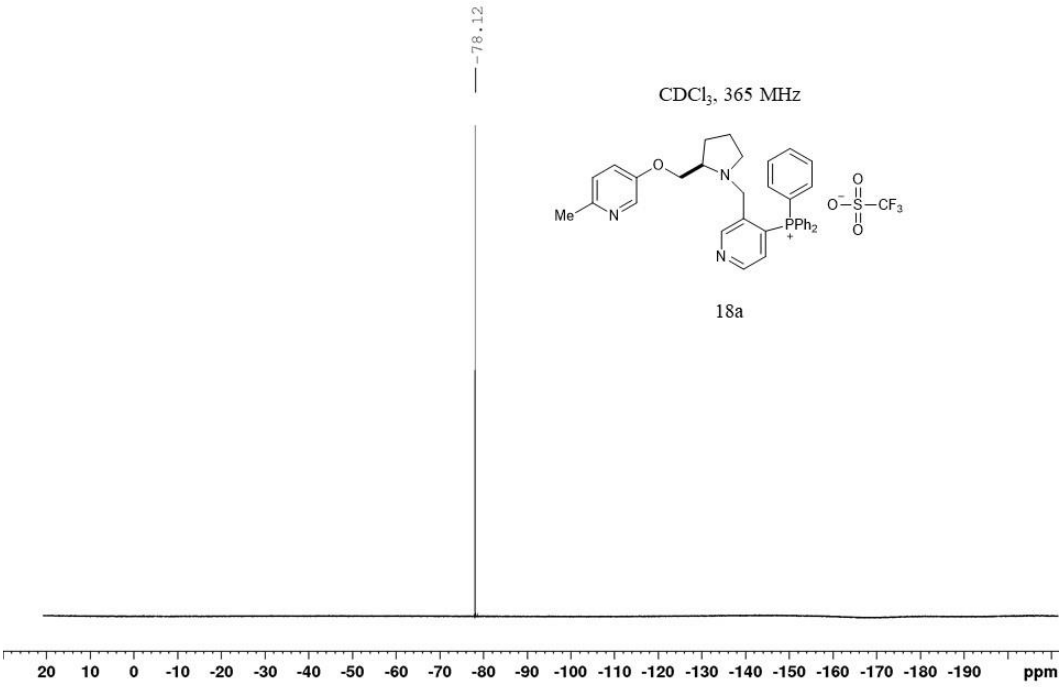
17b


CDCl3, 162 MHz
(crude 31P NMR)
29.12
21.39
17b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

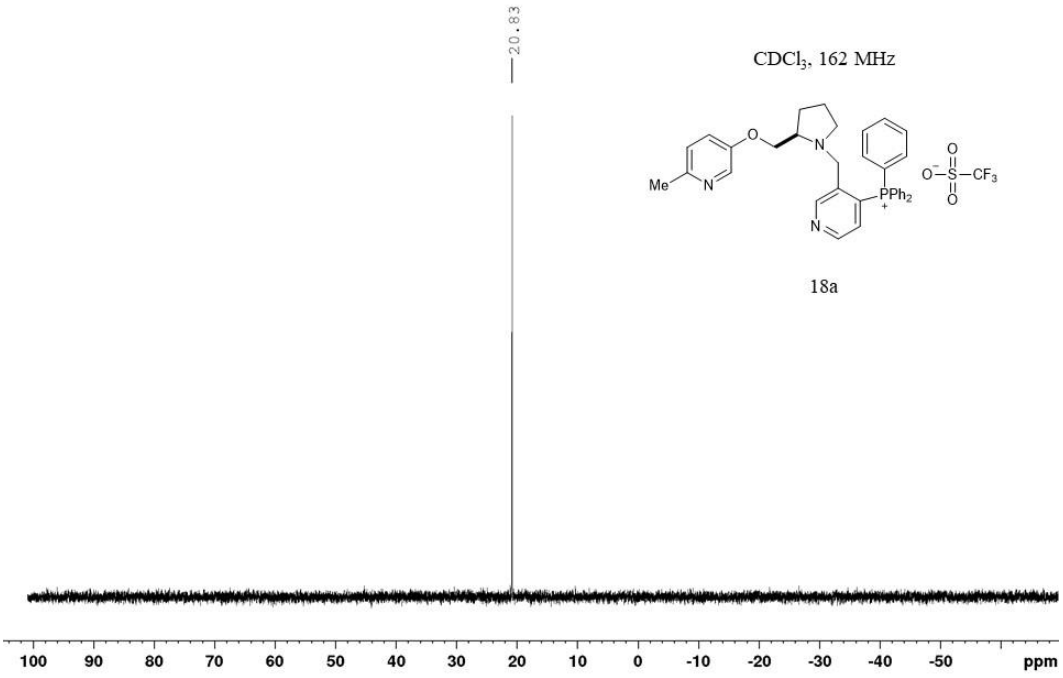

CDCl3, 400 MHz
18a
0.94 0.96 16.00 0.99 0.94 0.96 1.02 2.00 0.96 1.98 2.95 1.03 4.72
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


152.90
152.82
152.46
150.38
150.06
149.96
139.01
138.95
136.56
135.90
135.87
133.98
133.87
131.02
130.89
127.80
127.70
125.83
125.02
123.30
122.27
121.43
119.08
116.60
115.72
77.31
77.00
76.68
71.83
62.07
56.29
56.24
53.72
27.48
23.12
23.09
CDCl3, 100 MHz
Me
N
O
N
PPh2
+
O
O
S
CF3
O
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 ppm

18a

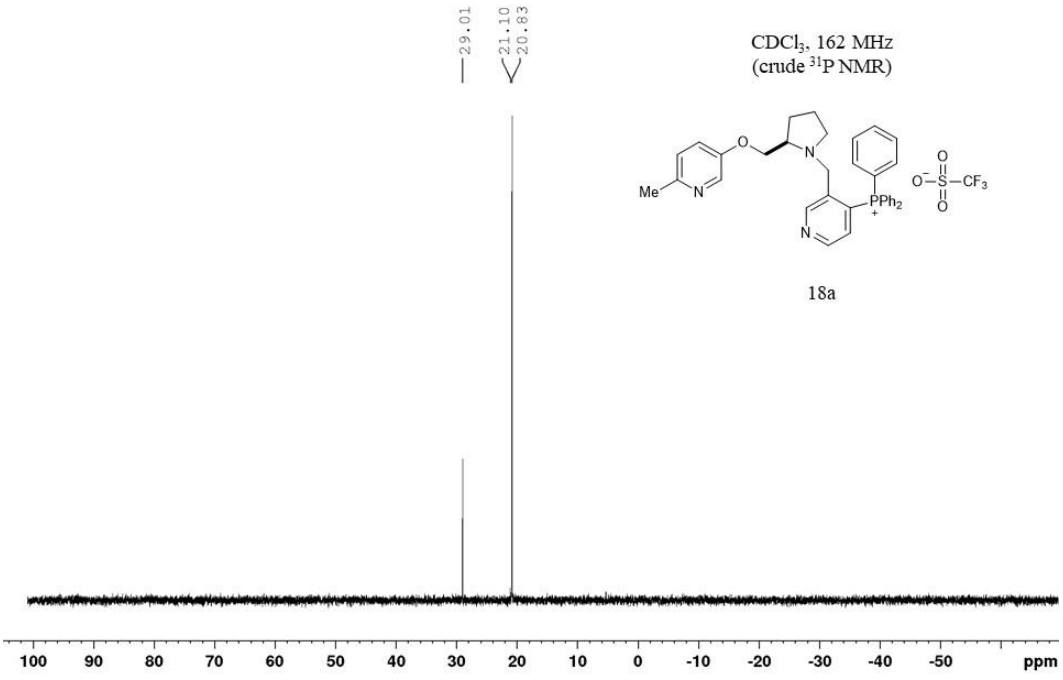

-78.12
CDCl3, 365 MHz
Me
N
O
N
PPh2
+
O
O
S
CF3
O
N
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

18a



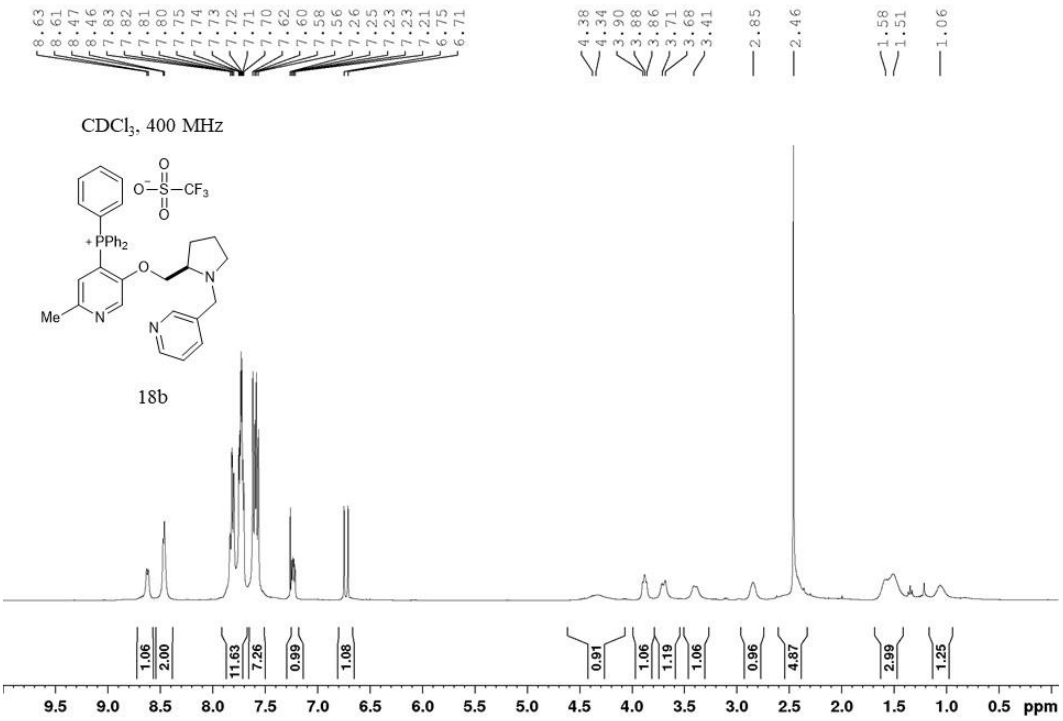
$CDCl_3$, 162 MHz

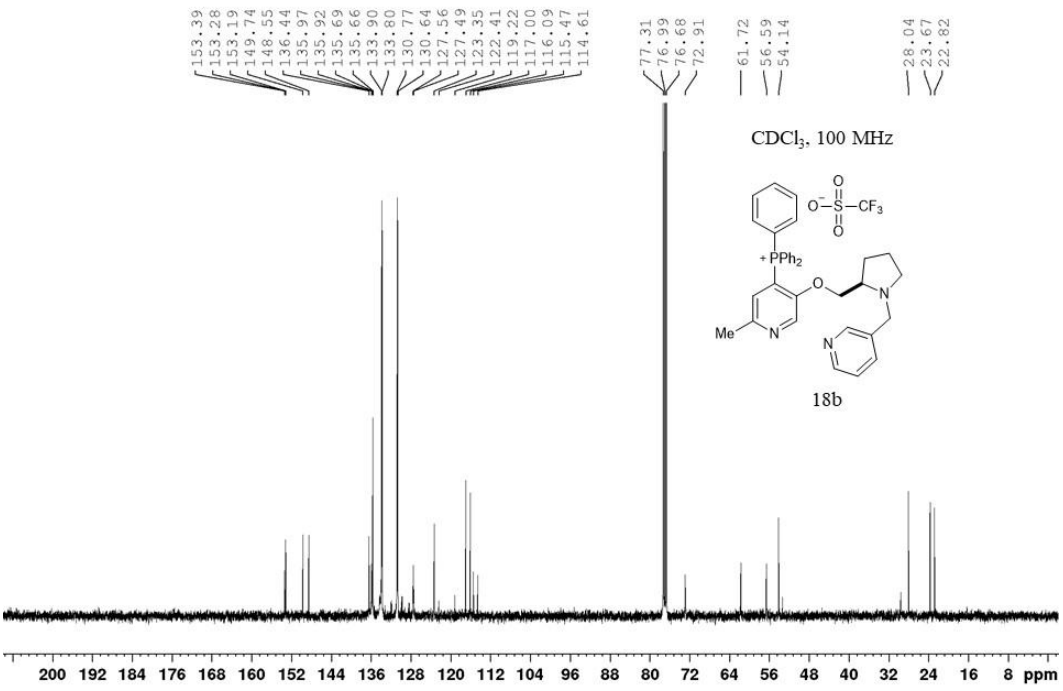
18a

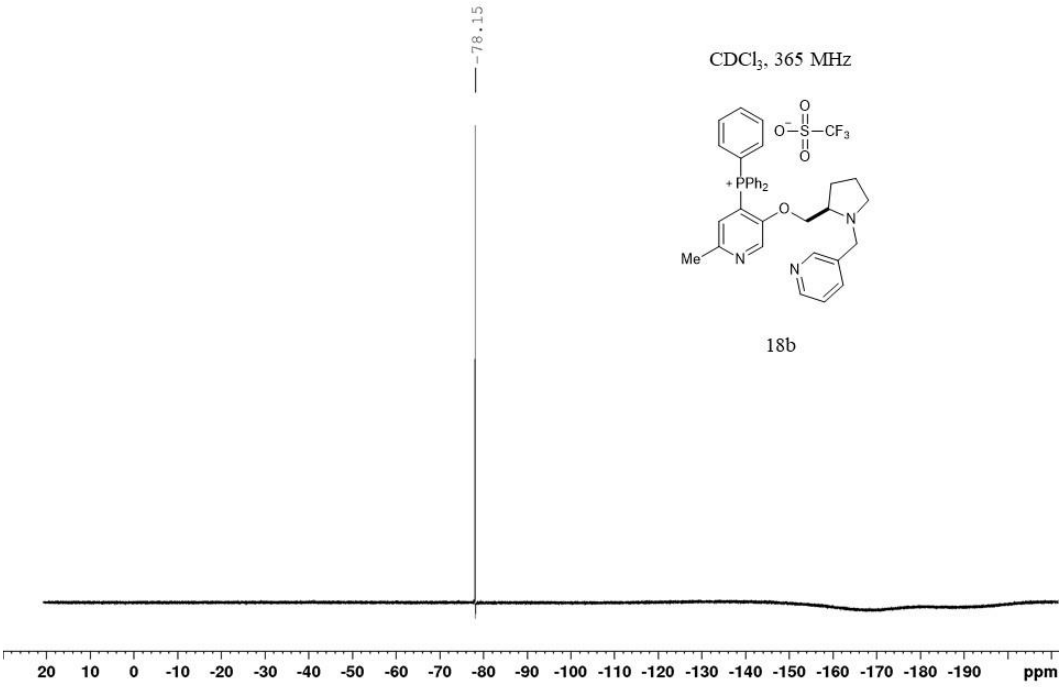


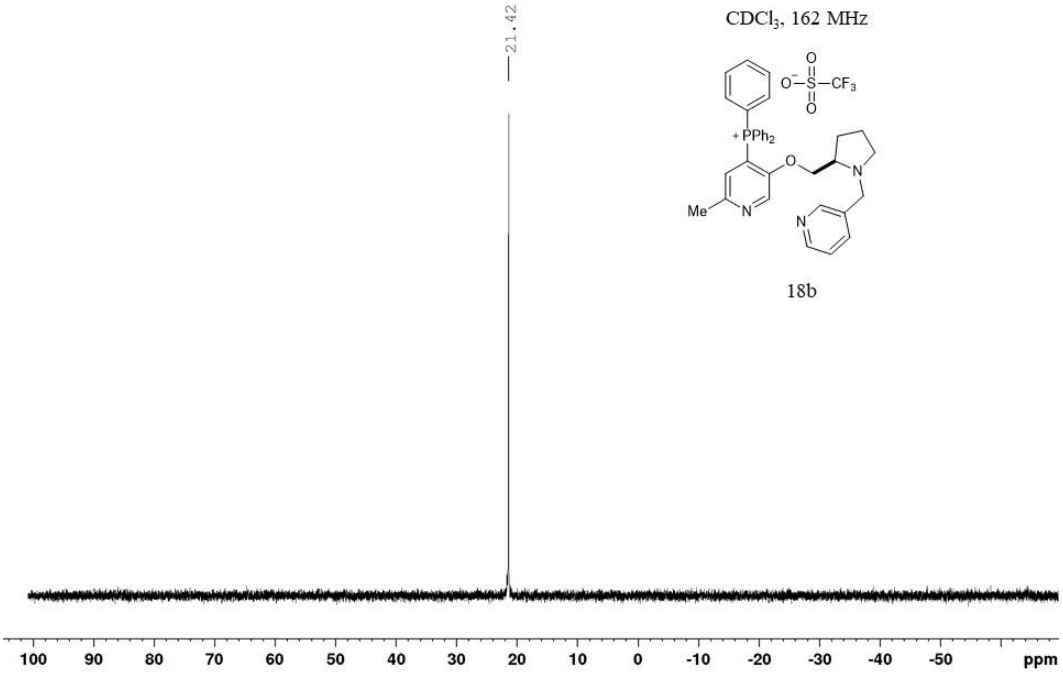
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)

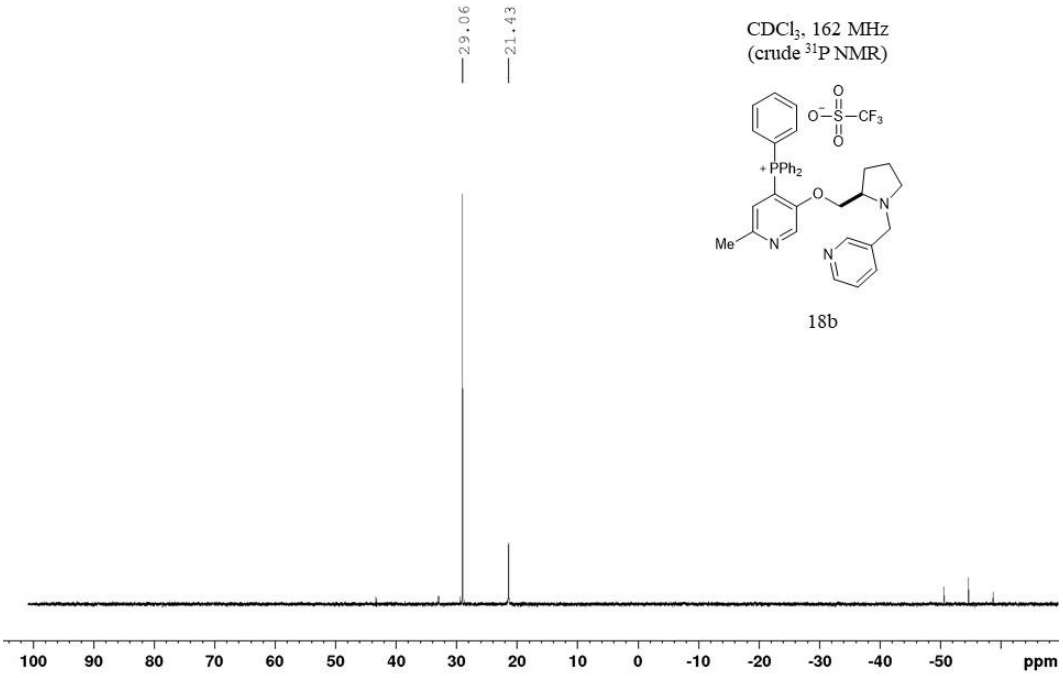
18a

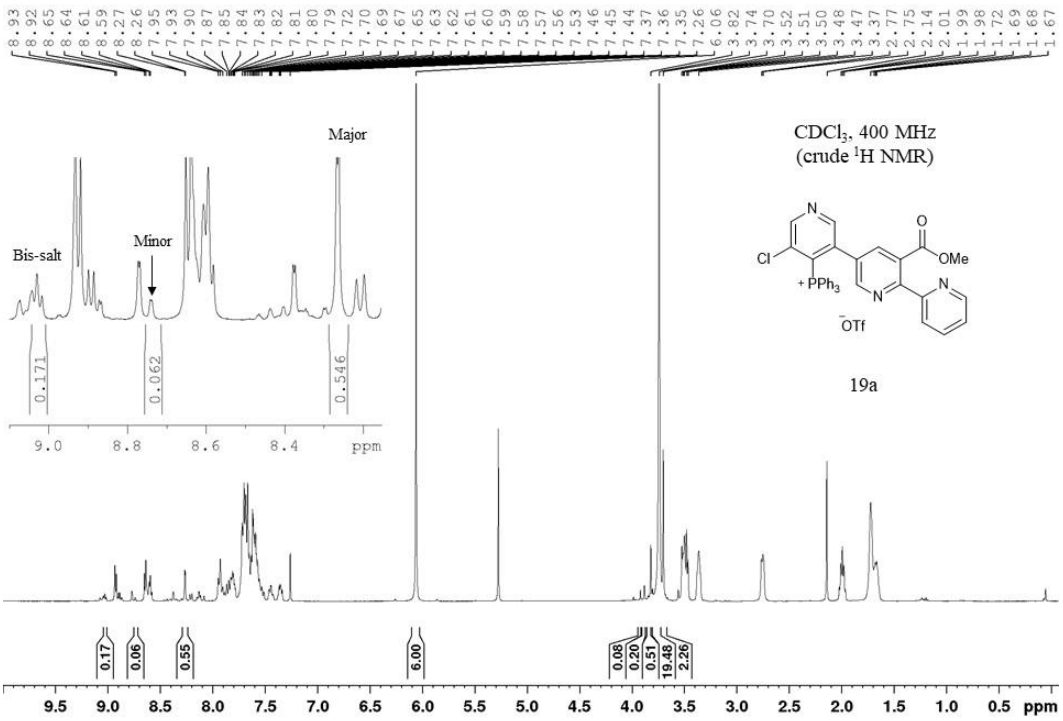

8.63
8.61
8.47
8.46
7.83
7.82
7.81
7.80
7.75
7.74
7.73
7.72
7.71
7.70
7.62
7.60
7.58
7.56
7.26
7.25
7.23
7.23
7.21
6.75
6.71
4.38
4.34
3.90
3.88
3.86
3.71
3.68
3.41
2.85
2.46
1.58
1.51
1.06
CDCl3, 400 MHz
18b
1.06
2.00
11.63
7.26
0.99
1.08
0.91
1.06
1.19
1.06
0.96
4.87
2.99
1.25
9.5 9.0 8.5 8.0 7.5 7.0 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 ppm

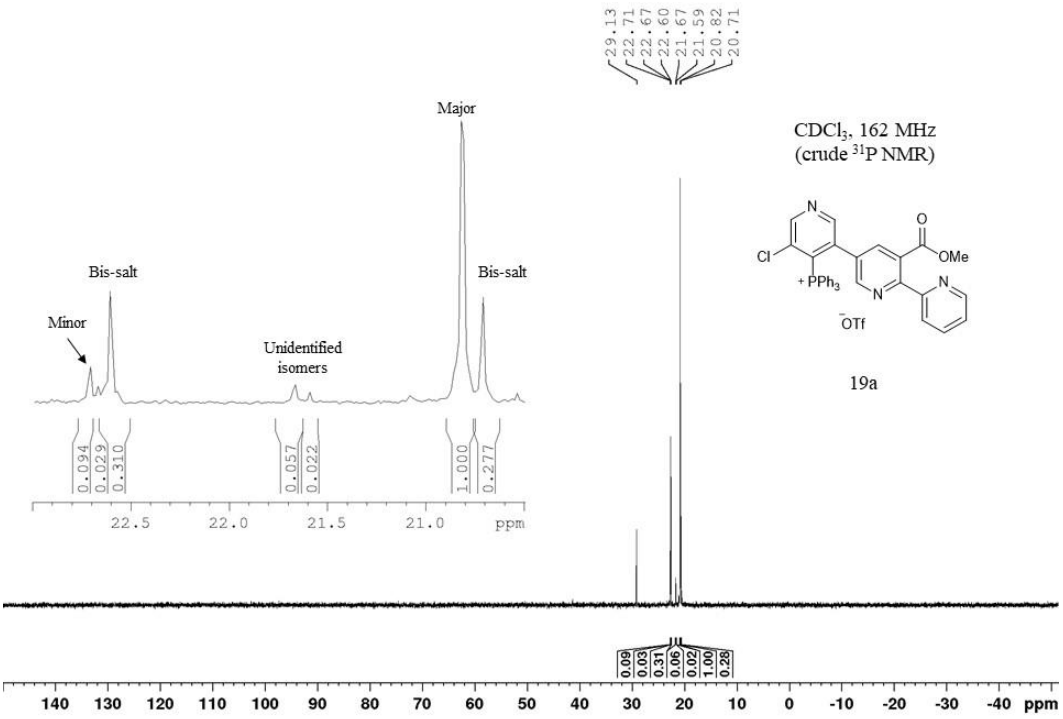

153.39
153.28
153.19
149.74
148.55
136.44
135.97
135.92
135.69
135.66
133.90
133.80
130.77
130.64
127.56
127.49
123.35
122.41
119.22
117.00
116.09
115.47
114.61
77.31
76.99
76.68
72.91
61.72
56.59
54.14
28.04
23.67
22.82
CDCl3, 100 MHz
18b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm


78.15
CDCl3, 365 MHz
18b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm


21.42
CDCl3, 162 MHz
18b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

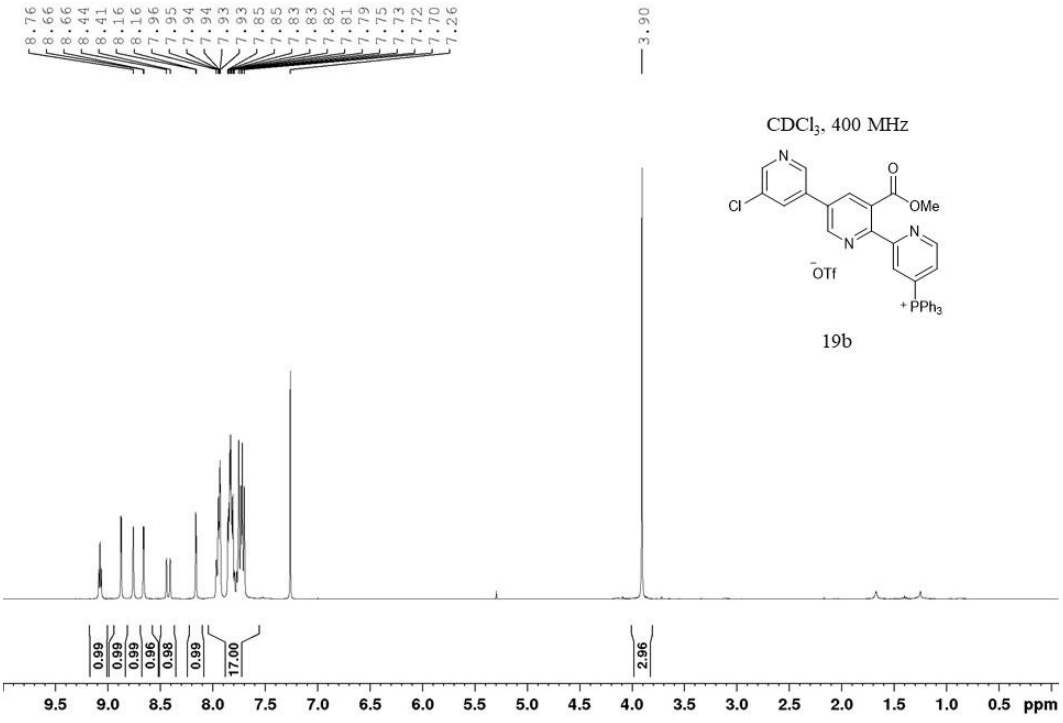

29.06
21.43
CDCl3, 162 MHz
(crude 31P NMR)
18b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm


Major
Bis-salt
Minor
0.171
0.062
0.546
9.0 8.8 8.6 8.4 ppm
CDCl3, 400 MHz
(crude 1H NMR)
19a
0.17
0.06
0.55
6.00
0.08
0.20
0.51
19.48
2.26
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 ppm



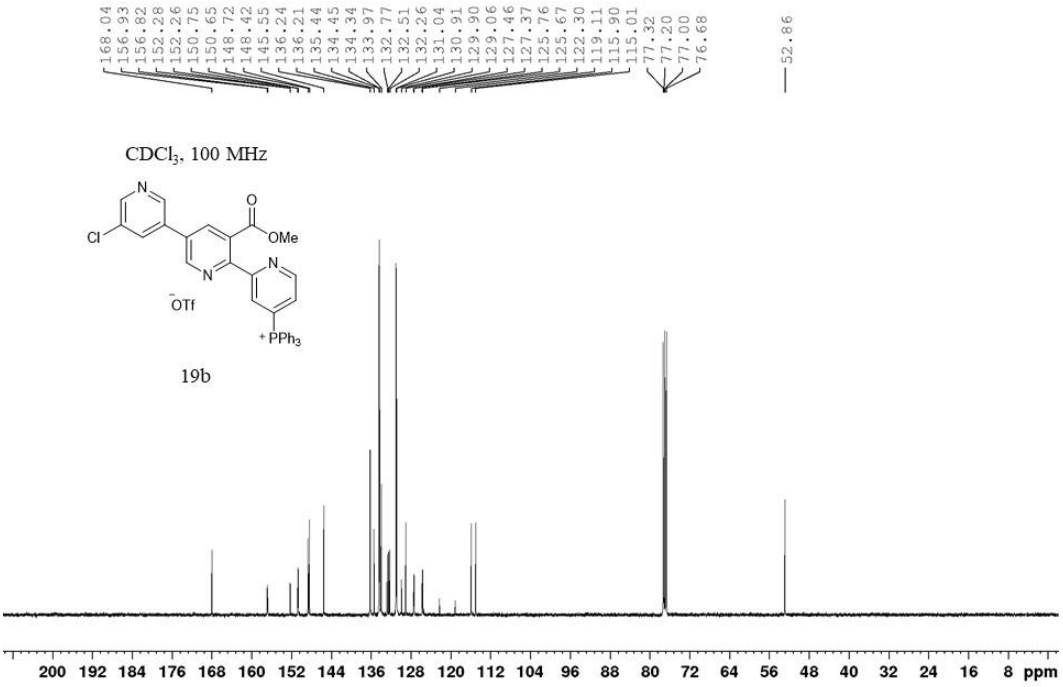
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)

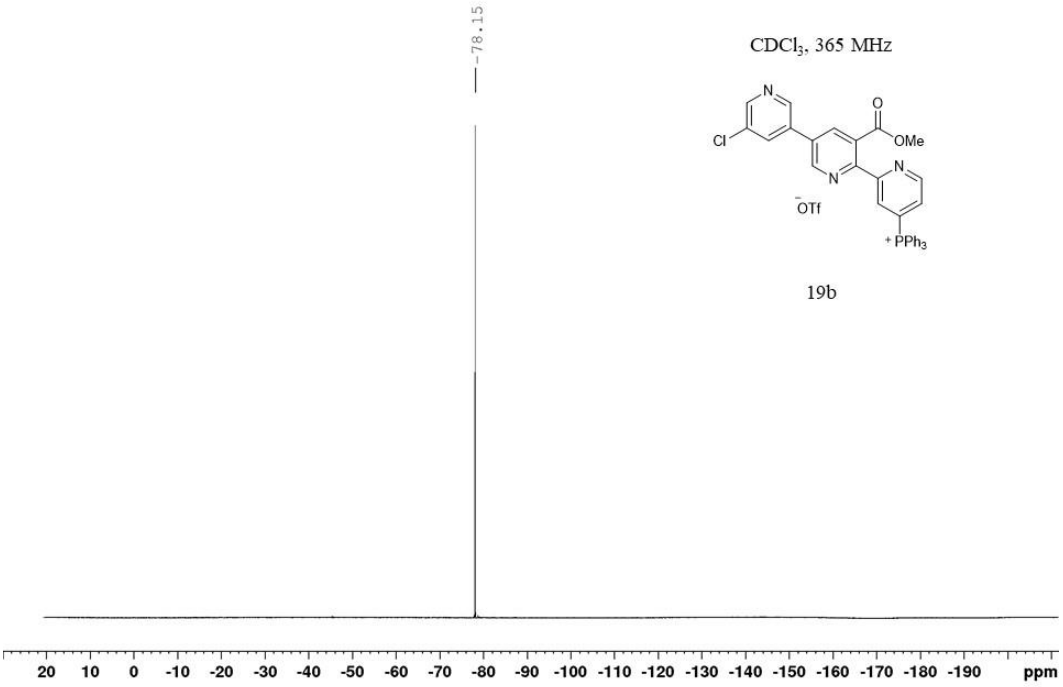
19a

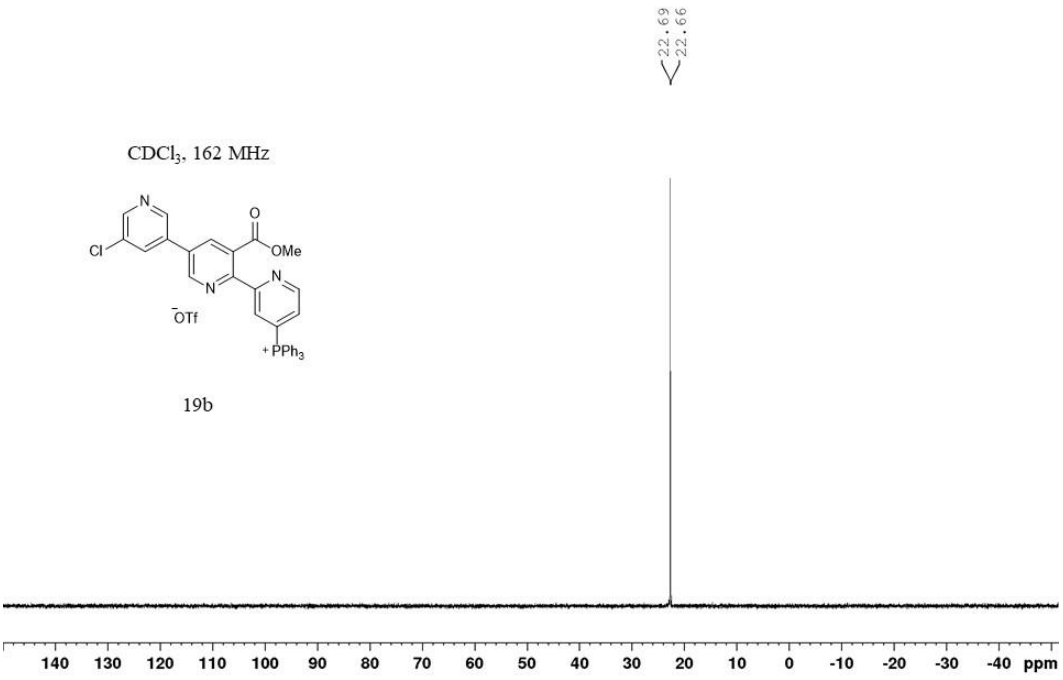


$CDCl_3$, 400 MHz

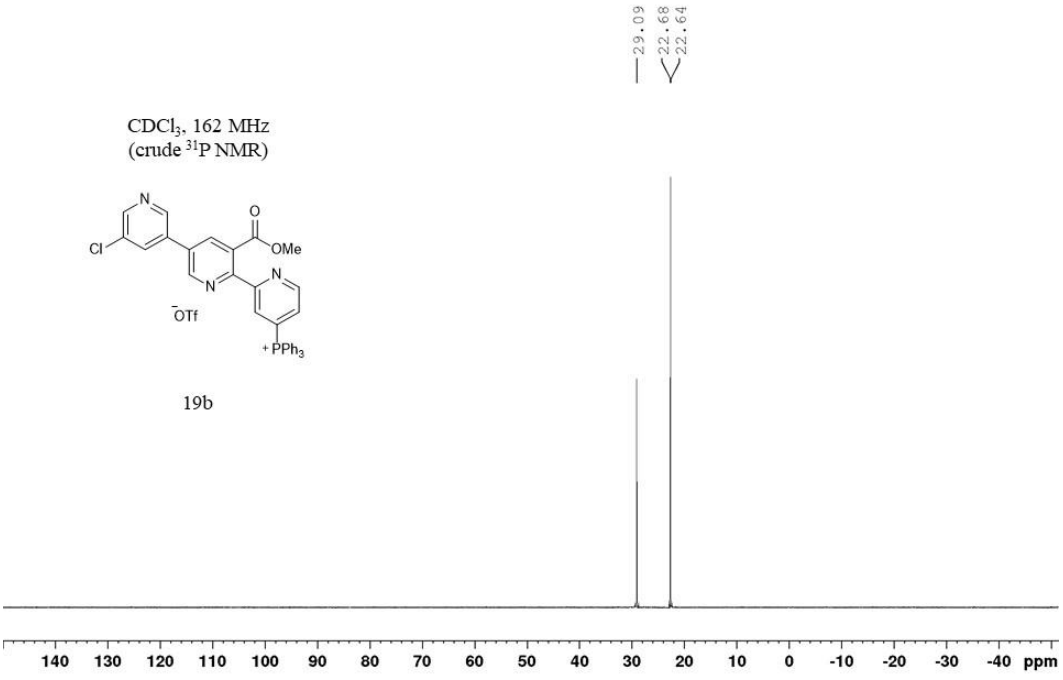
19b


168.04
156.93
156.82
152.28
152.26
150.75
150.65
148.72
148.42
145.55
136.24
136.21
135.44
134.45
134.34
133.97
132.77
132.51
132.26
131.04
130.91
129.90
129.06
127.46
127.37
125.76
125.67
122.30
119.11
115.90
115.01
77.32
77.20
77.00
76.68
52.86
CDCl3, 100 MHz
Cl
N
O
OMe
N
N
OTf
+PPh3
19b
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 ppm

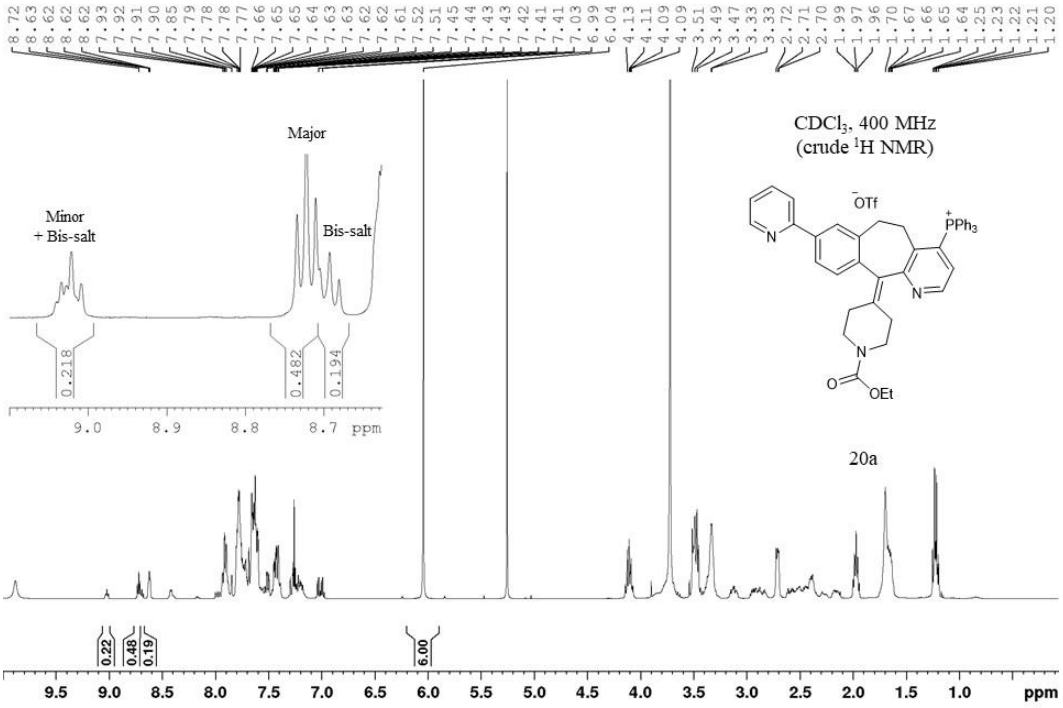

-78.15
CDCl3, 365 MHz
Cl
N
O
OMe
N
N
OTf
+PPh3
19b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

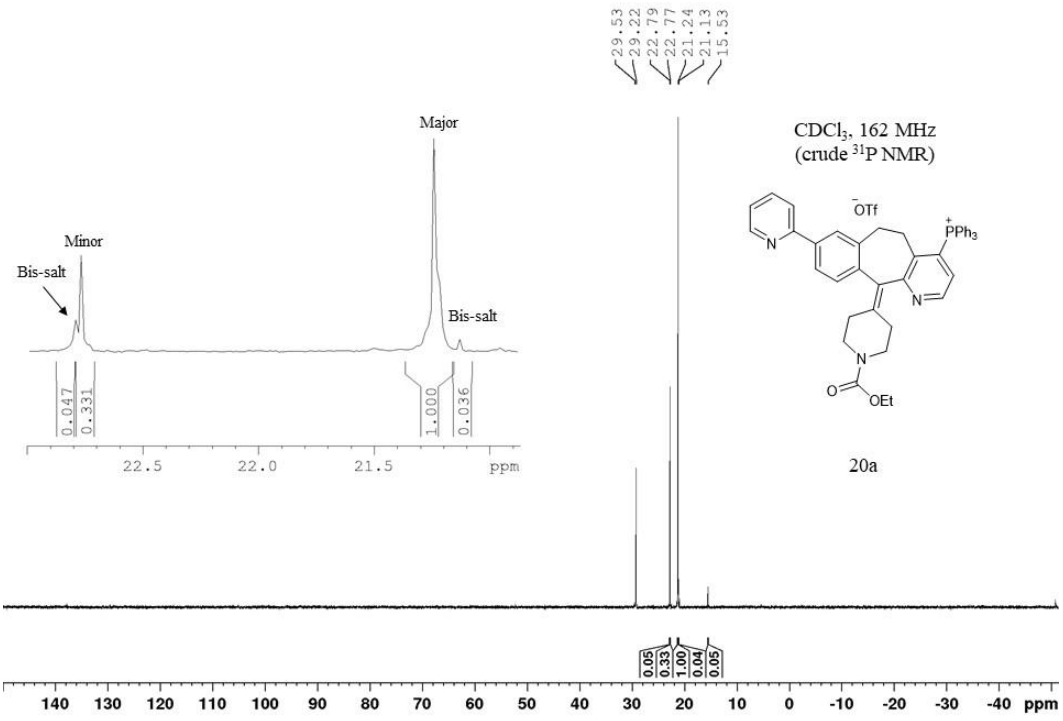

22.69
22.66
CDCl3, 162 MHz
Cl
N
O
OMe
N
N
OTf
+PPh3
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

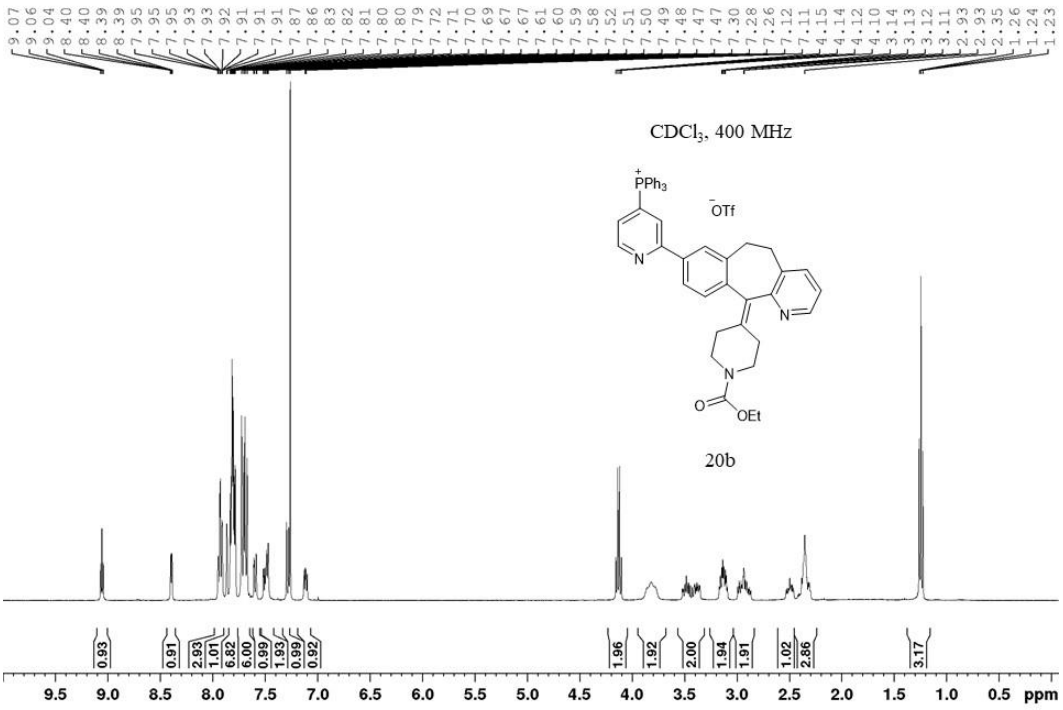
19b

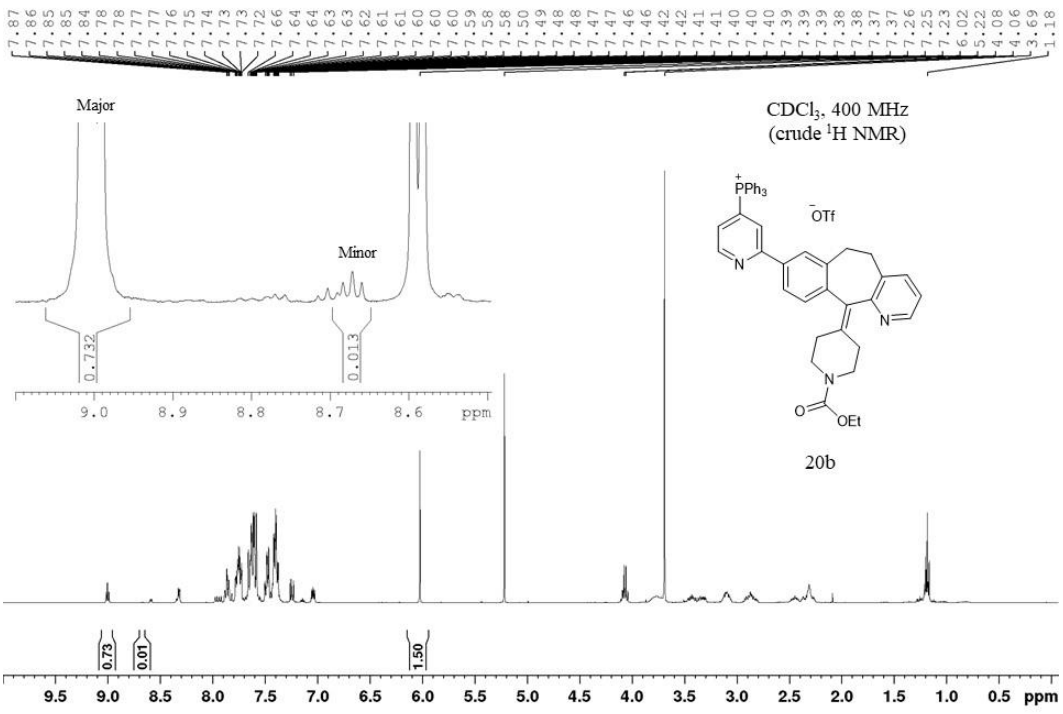

29.09
22.68
22.64
CDCl3, 162 MHz
(crude 31P NMR)
Cl
N
O
OMe
N
N
OTf
+PPh3
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

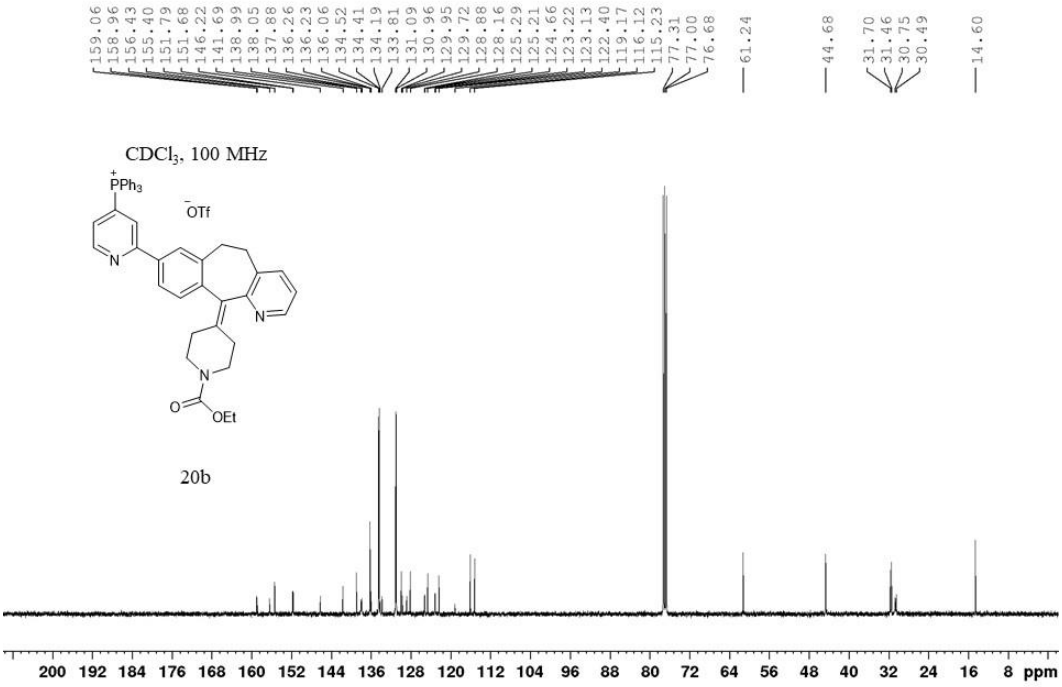
19b

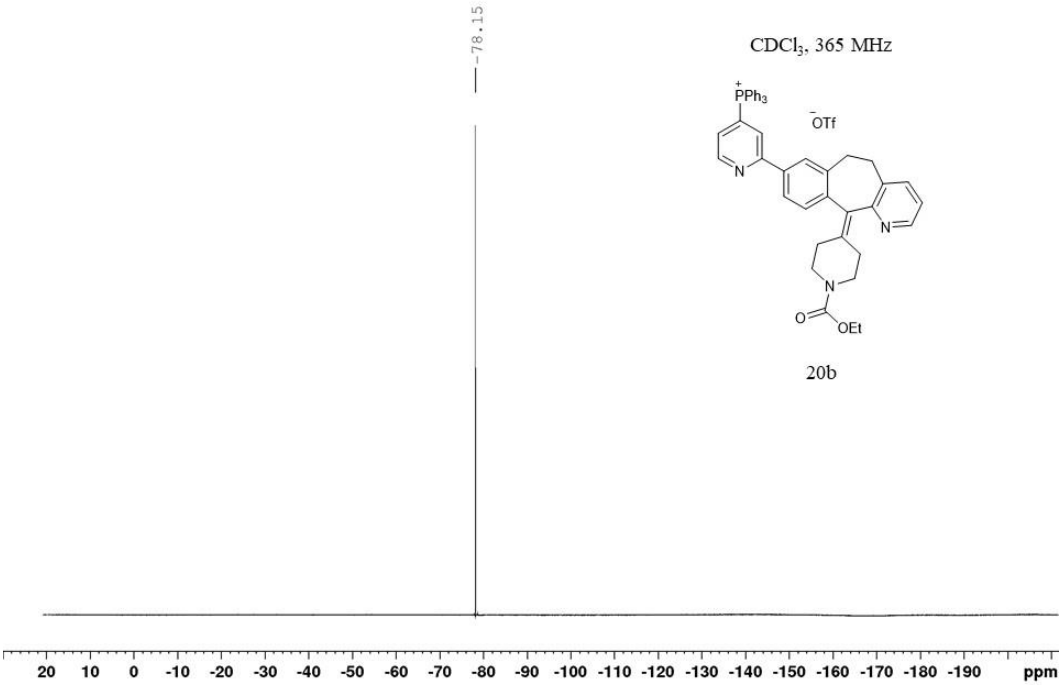

Major
Minor
+ Bis-salt
Bis-salt
0.218
0.482
0.194
9.0
8.9
8.8
8.7 ppm
CDCl3, 400 MHz
(crude 1H NMR)
OTf
PPh3
N
O
OEt
20a
0.22
0.48
0.19
6.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm


Major
Minor
Bis-salt
Bis-salt
0.047
0.331
1.000
0.036
22.5
22.0
21.5
ppm
CDCl3, 162 MHz
(crude 31P NMR)
OTf
PPh3
N
O
OEt
20a
0.05
0.33
1.00
0.04
0.05
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

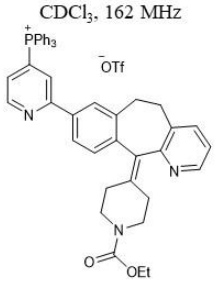

CDCl3, 400 MHz
PPh3
OTf
N
N
O
OEt
20b
0.93
0.91
2.93
1.01
6.82
6.00
0.99
1.93
0.99
0.92
1.96
1.92
2.00
1.94
1.91
1.02
2.86
3.17
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


Major
Minor
0.732
0.013
9.0 8.9 8.8 8.7 8.6 ppm
CDCl3, 400 MHz
(crude 1H NMR)
PPh3
OTf
N
N
O
OEt
20b
0.73
0.01
1.50
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 ppm


159.06
158.96
156.43
155.40
151.79
151.68
146.22
141.69
138.99
138.05
137.88
136.26
136.23
136.06
134.52
134.41
134.19
133.81
131.09
130.96
129.95
129.72
128.88
128.16
125.29
125.21
124.66
123.22
123.13
122.40
119.17
116.12
115.23
77.31
77.00
76.68
61.24
44.68
31.70
31.46
30.75
30.49
14.60
CDCl3, 100 MHz
PPh3
OTf
N
N
N
O
OEt
20b
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 ppm

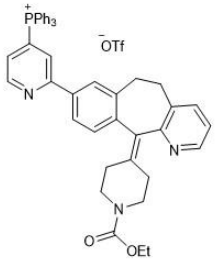

-78.15
CDCl3, 365 MHz
PPh3
OTf
N
N
N
O
OEt
20b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

$CDCl_3$, 162 MHz

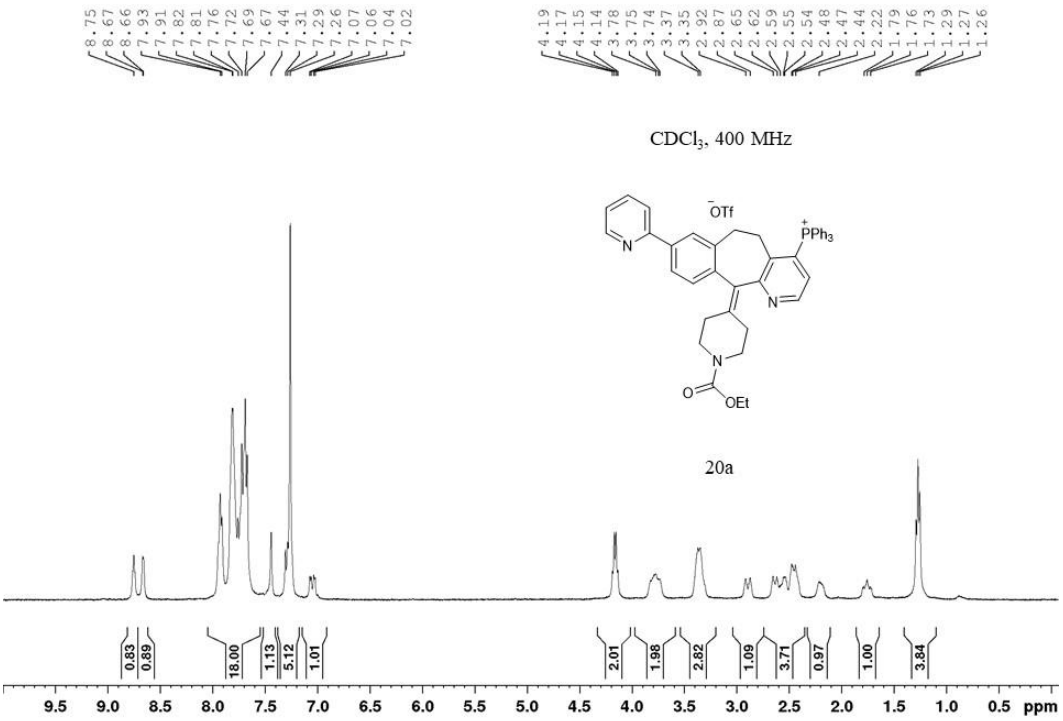


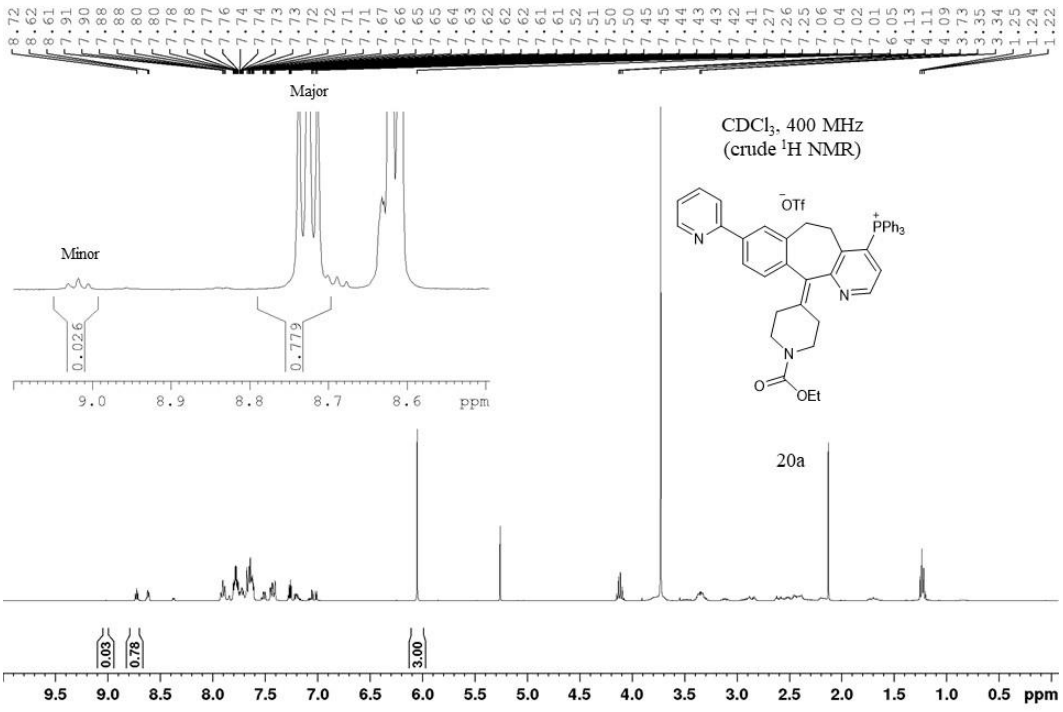
20b

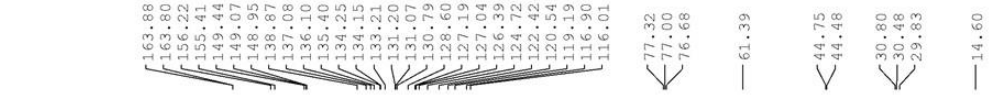
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)



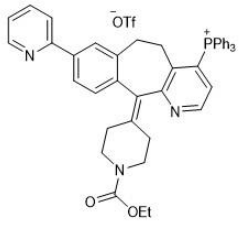
20b


8.75 8.67 8.66 7.93 7.91 7.82 7.81 7.76 7.72 7.69 7.67 7.44 7.31 7.29 7.26 7.07 7.06 7.04 7.02
4.19 4.17 4.15 4.14 3.78 3.75 3.74 3.37 3.35 2.92 2.87 2.65 2.62 2.59 2.55 2.54 2.48 2.47 2.44 2.22 1.79 1.76 1.73 1.29 1.27 1.26
CDCl3, 400 MHz
OTf
PPh3
N
O
OEt
20a
0.83 0.89 18.00 1.13 5.12 1.01 2.01 1.98 2.82 1.09 3.71 0.97 1.00 3.84
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 ppm

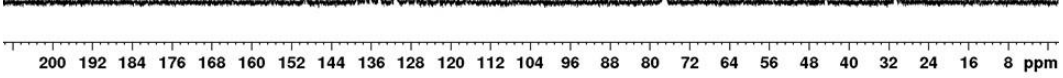

8.72 8.62 8.61 7.91 7.90 7.88 7.88 7.80 7.80 7.78 7.78 7.77 7.76 7.74 7.74 7.73 7.73 7.72 7.72 7.71 7.71 7.67 7.66 7.65 7.65 7.64 7.63 7.62 7.62 7.62 7.61 7.61 7.52 7.51 7.50 7.50 7.45 7.45 7.44 7.43 7.42 7.41 7.27 7.26 7.25 7.06 7.04 7.02 7.01 6.05 4.13 4.11 4.09 3.73 3.35 3.34 1.25 1.24 1.22
Major
Minor
0.026 0.779
9.0 8.9 8.8 8.7 8.6 ppm
CDCl3, 400 MHz
(crude 1H NMR)
OTf
PPh3
N
O
OEt
20a
0.03 0.78 3.00
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 ppm



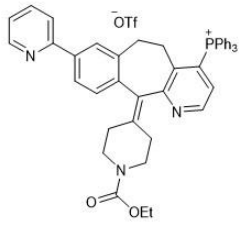
$CDCl_3$, 100 MHz



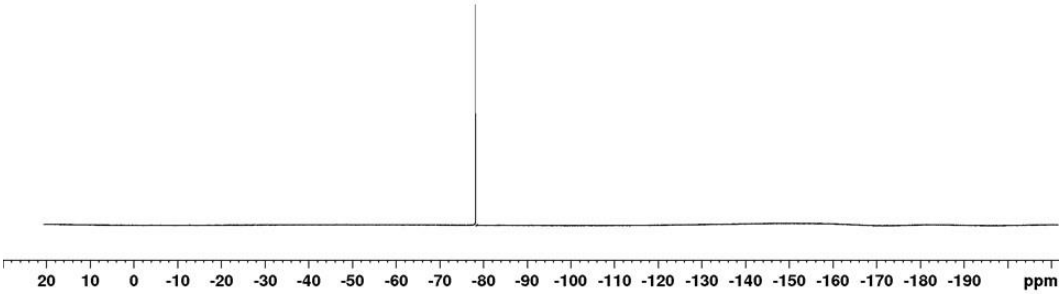
20a



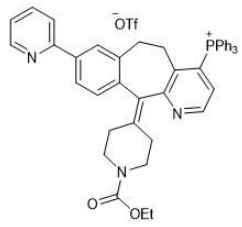
$CDCl_3$, 365 MHz



20a

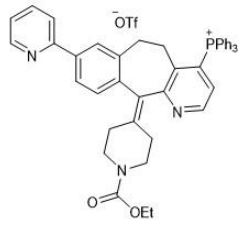


$CDCl_3$, 162 MHz

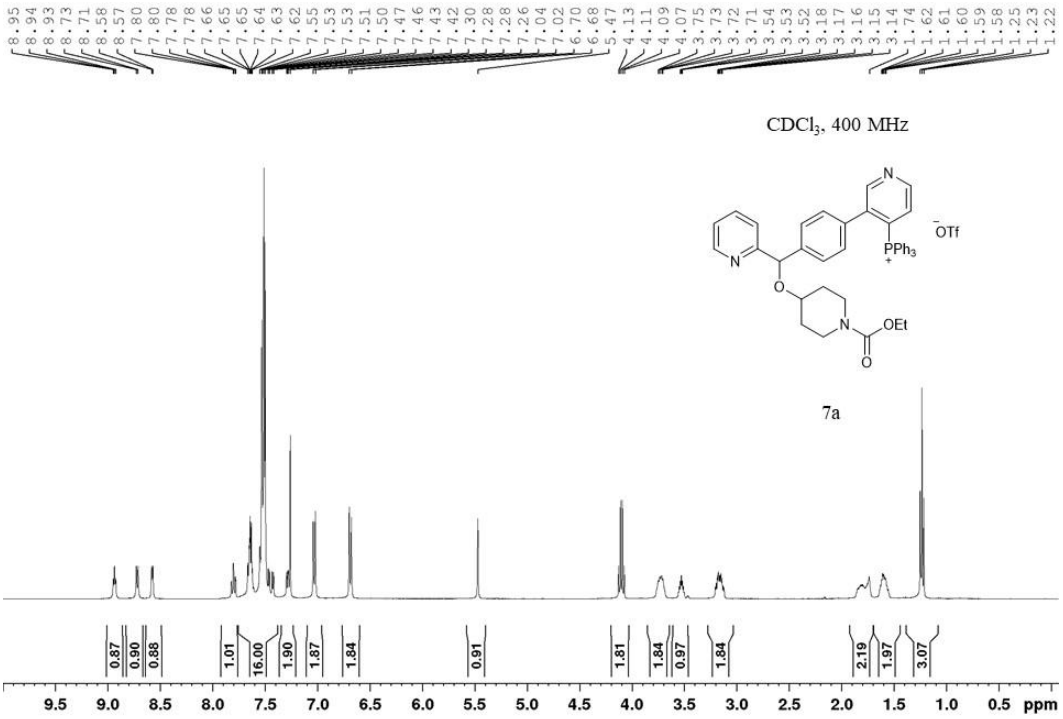


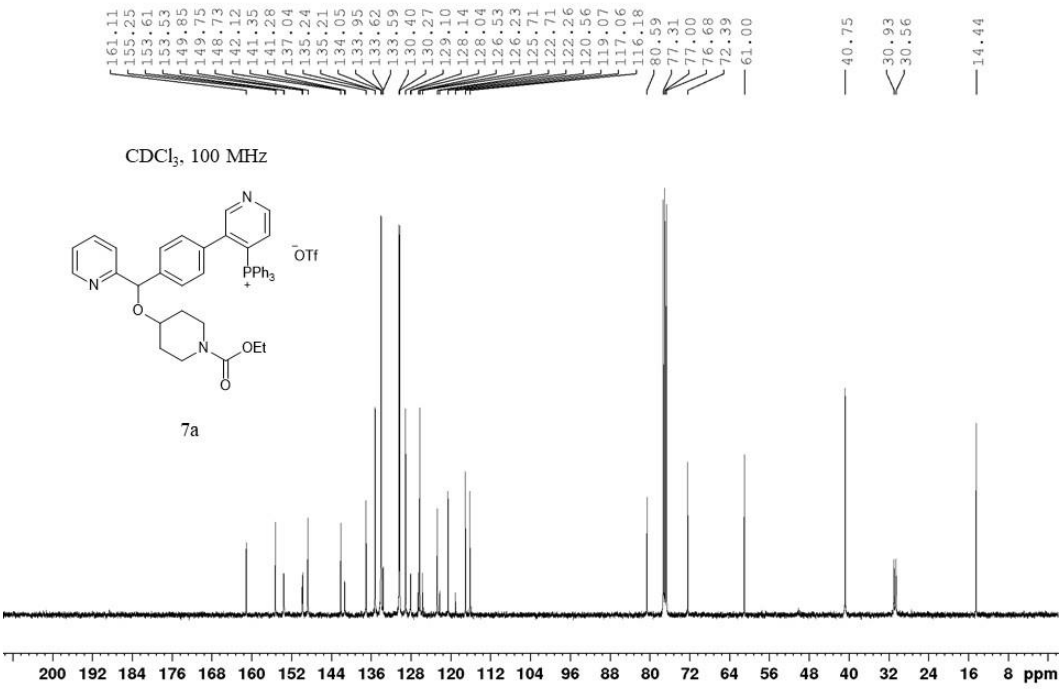
20a

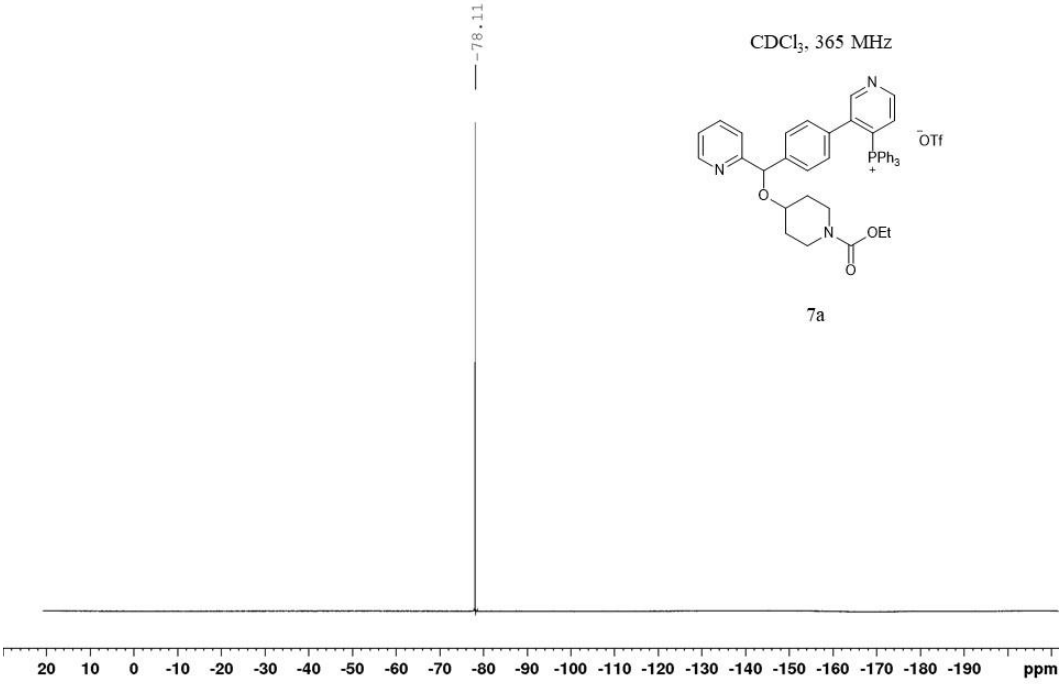
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)



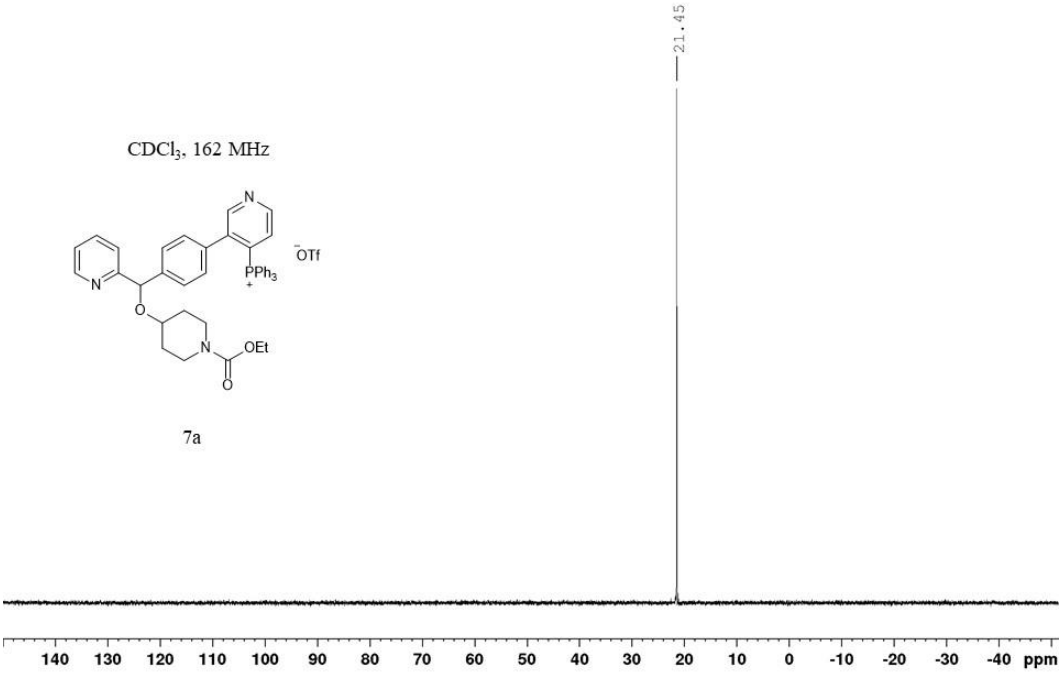
20a


8.95 8.94 8.93 8.73 8.71 8.58 8.57 7.80 7.80 7.78 7.78 7.66 7.65 7.65 7.64 7.63 7.62 7.55 7.53 7.53 7.51 7.50 7.47 7.46 7.43 7.42 7.30 7.28 7.28 7.26 7.04 7.02 6.70 6.68 5.47 4.13 4.11 4.09 4.07 3.75 3.73 3.72 3.71 3.54 3.53 3.52 3.18 3.17 3.16 3.15 3.14 1.74 1.62 1.61 1.60 1.59 1.58 1.25 1.23 1.22
CDCl3, 400 MHz
OTf
PPh3
OEt
7a
0.87 0.90 0.88 1.01 16.00 1.90 1.87 1.84 0.91 1.81 1.84 0.97 1.84 2.19 1.97 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 ppm

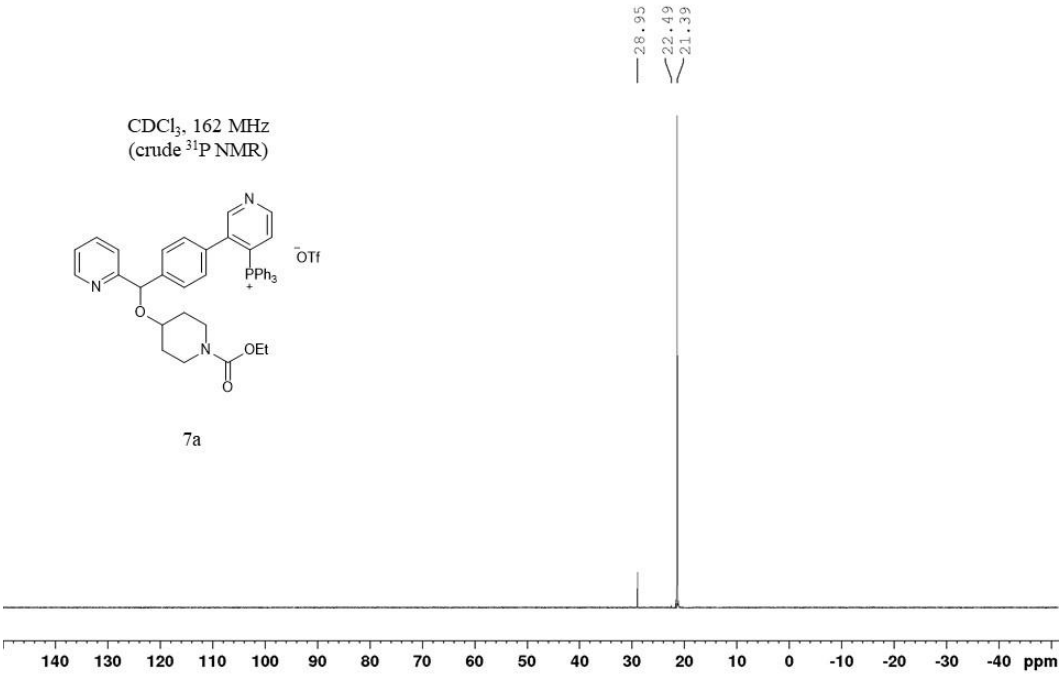

161.11 155.25 153.61 153.53 149.85 149.75 148.73 142.12 141.35 141.28 137.04 135.24 135.21 134.05 133.95 133.62 133.59 130.40 130.27 129.10 128.14 128.04 126.53 126.23 125.71 122.71 122.26 120.56 119.07 117.06 116.18 80.59 77.31 77.00 76.68 72.39 61.00 40.75 30.93 30.56 14.44
CDCl3, 100 MHz
OTf
PPh3
OEt
7a
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 ppm

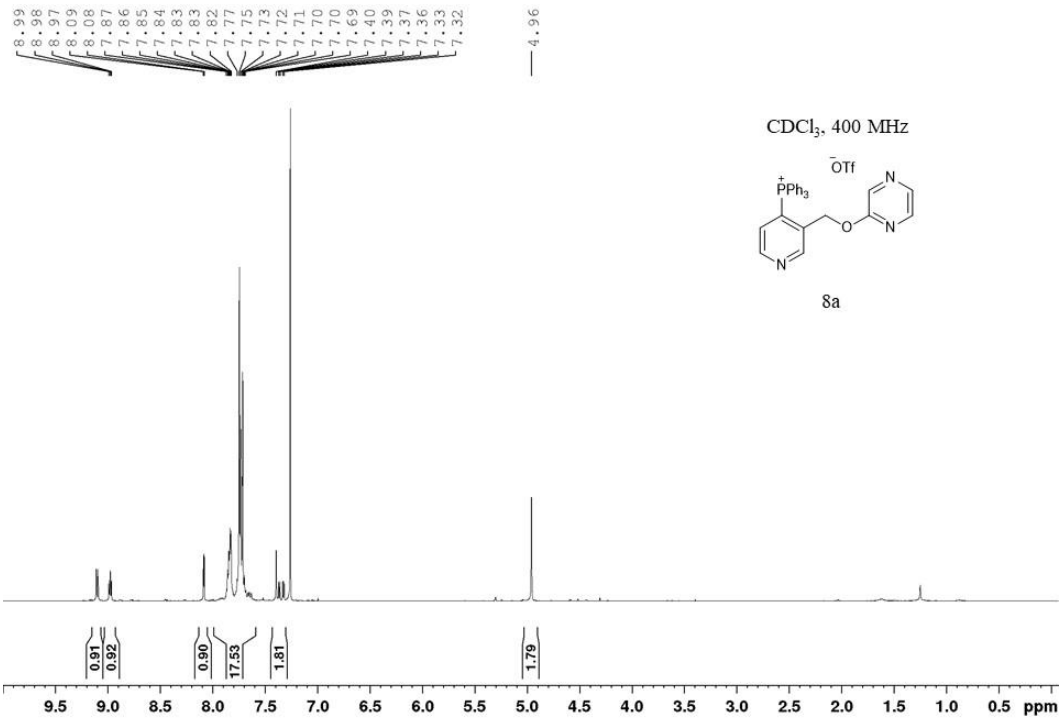

78.11
CDCl3, 365 MHz
N
OTf
PPh3
O
N
OEt
O
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

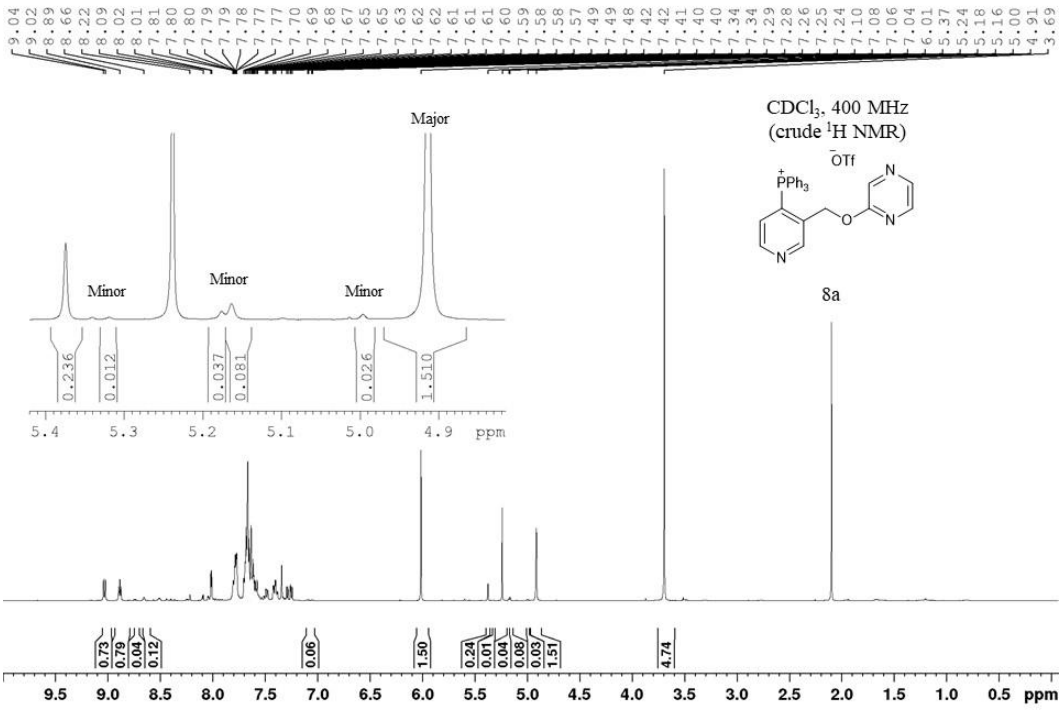
7a

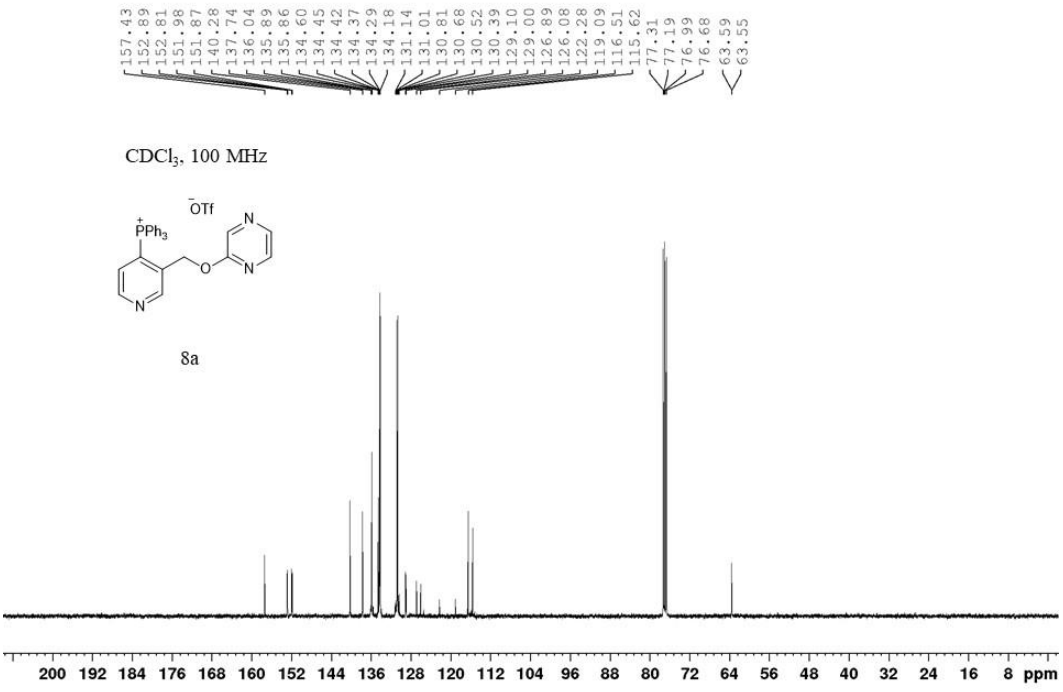

21.45
CDCl3, 162 MHz
N
OTf
PPh3
O
N
OEt
O
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

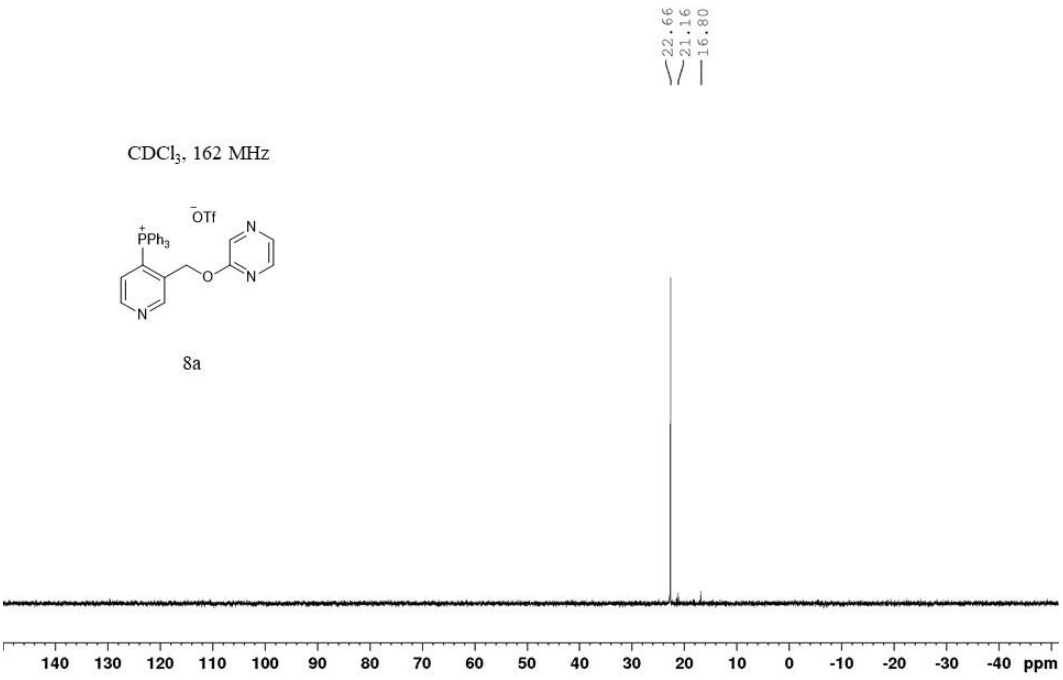
7a

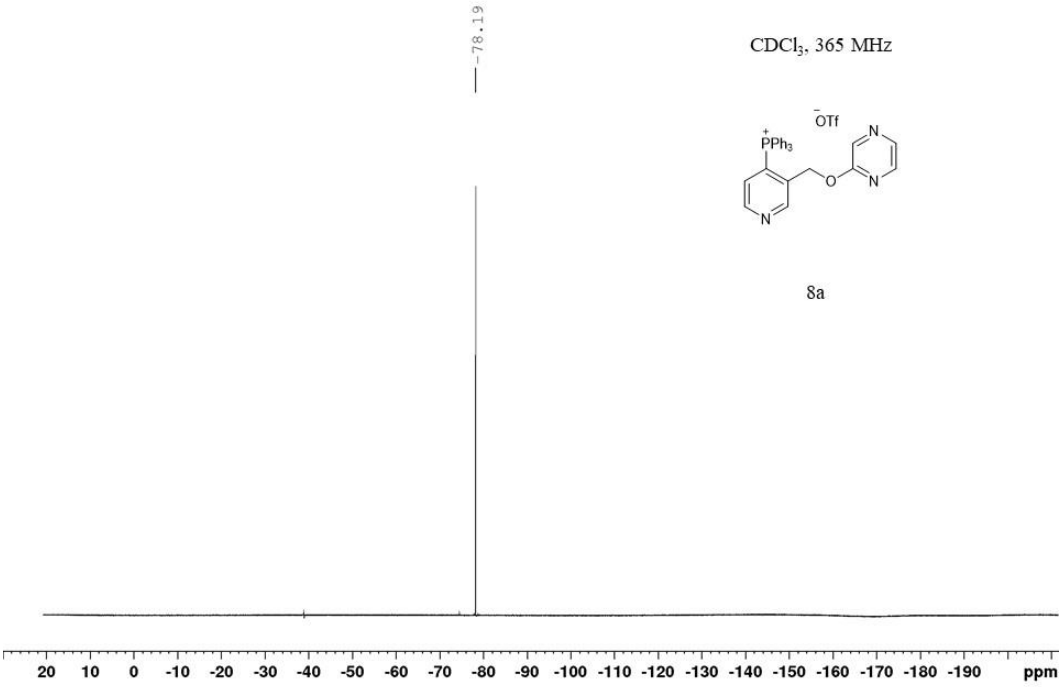

28.95
22.49
21.39
CDCl3, 162 MHz
(crude 31P NMR)
OTf
PPh3
OEt
7a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

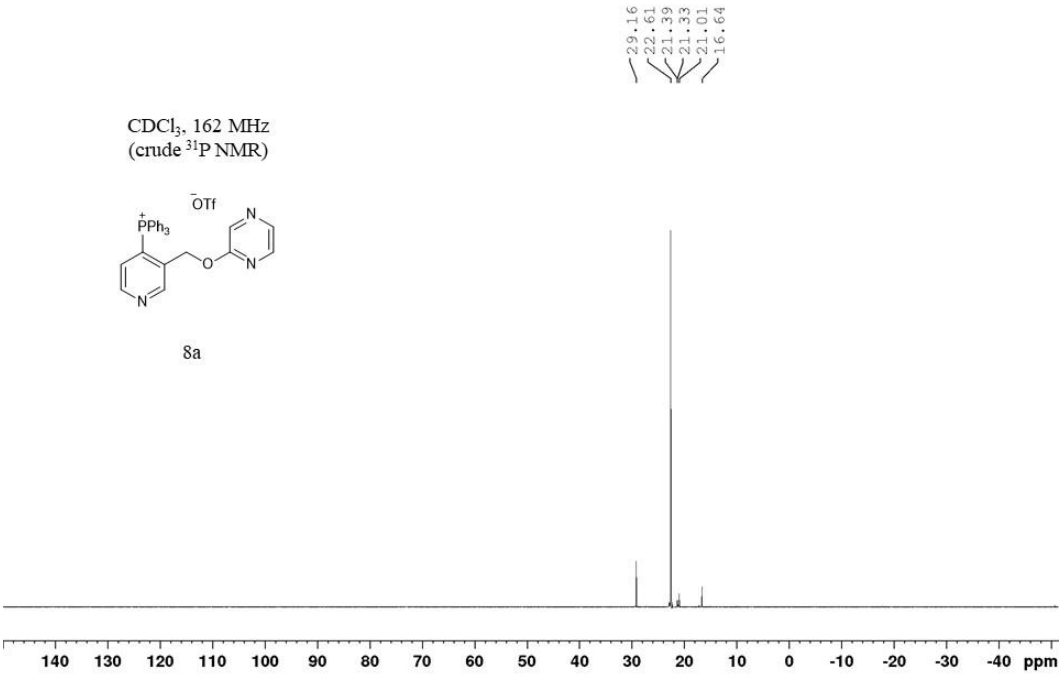

8.99
8.98
8.97
8.09
8.08
7.87
7.86
7.85
7.84
7.83
7.83
7.82
7.77
7.75
7.73
7.72
7.71
7.70
7.70
7.69
7.40
7.39
7.37
7.36
7.33
7.32
4.96
CDCl3, 400 MHz
OTf
PPh3
8a
0.91
0.92
0.90
17.53
1.81
1.79
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

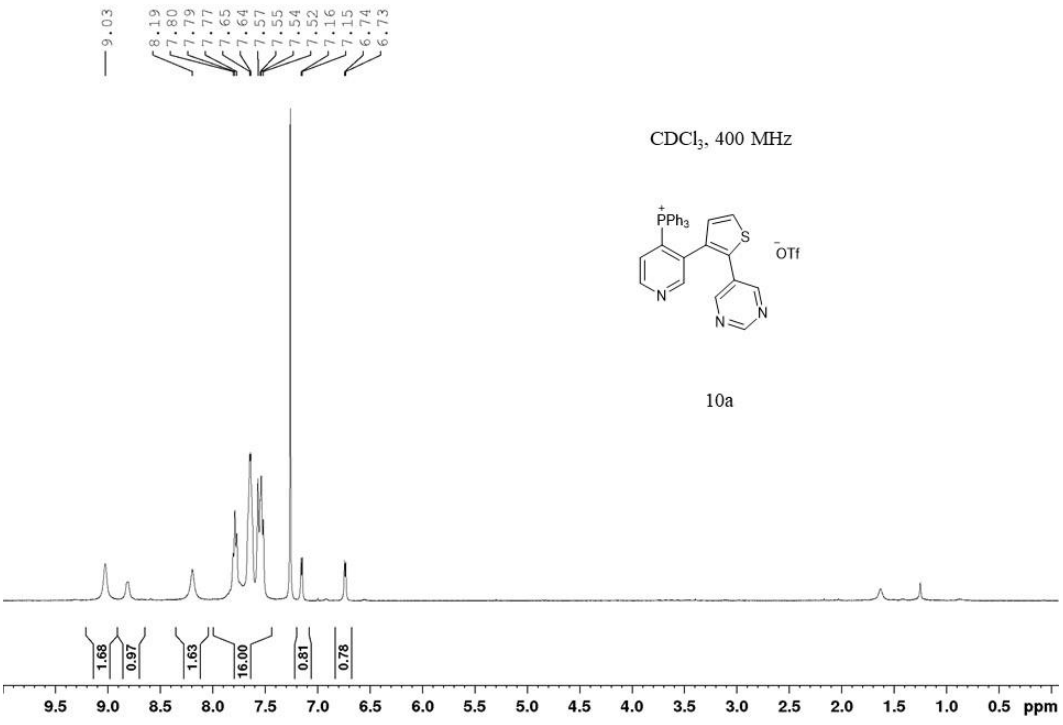

CDCl3, 400 MHz
(crude 1H NMR)
OTf
PPh3
8a
Major
Minor
Minor
Minor
0.236
0.012
0.037
0.081
0.026
1.510
0.73
0.79
0.04
0.12
0.06
1.50
0.24
0.01
0.04
0.08
0.03
1.51
4.74
ppm

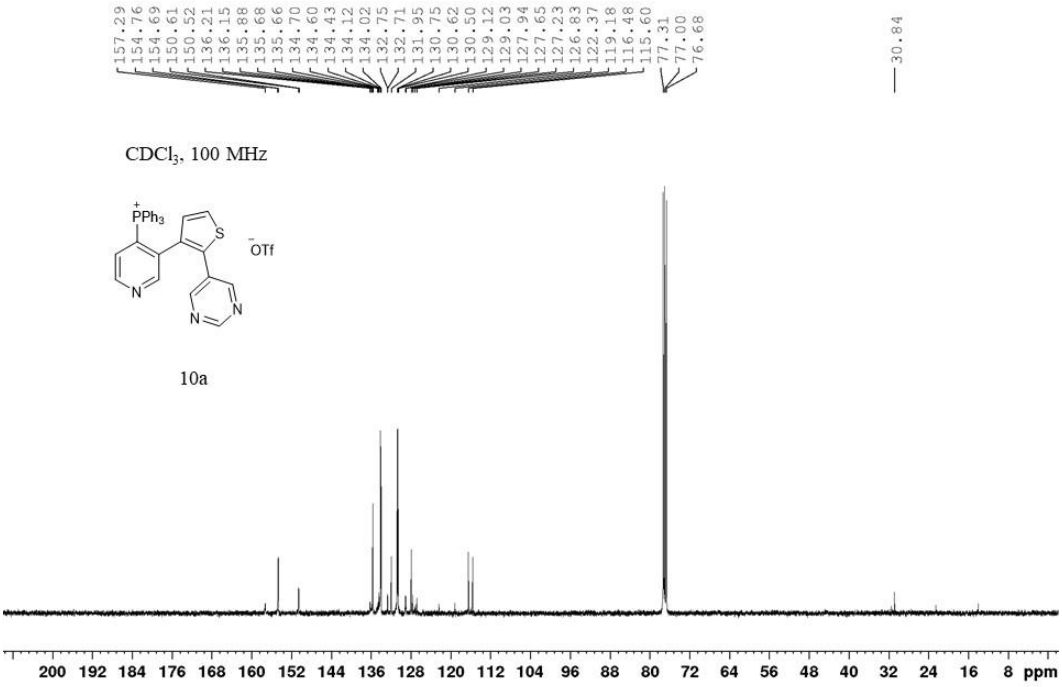

CDCl3, 100 MHz
OTf
PPh3
8a
ppm

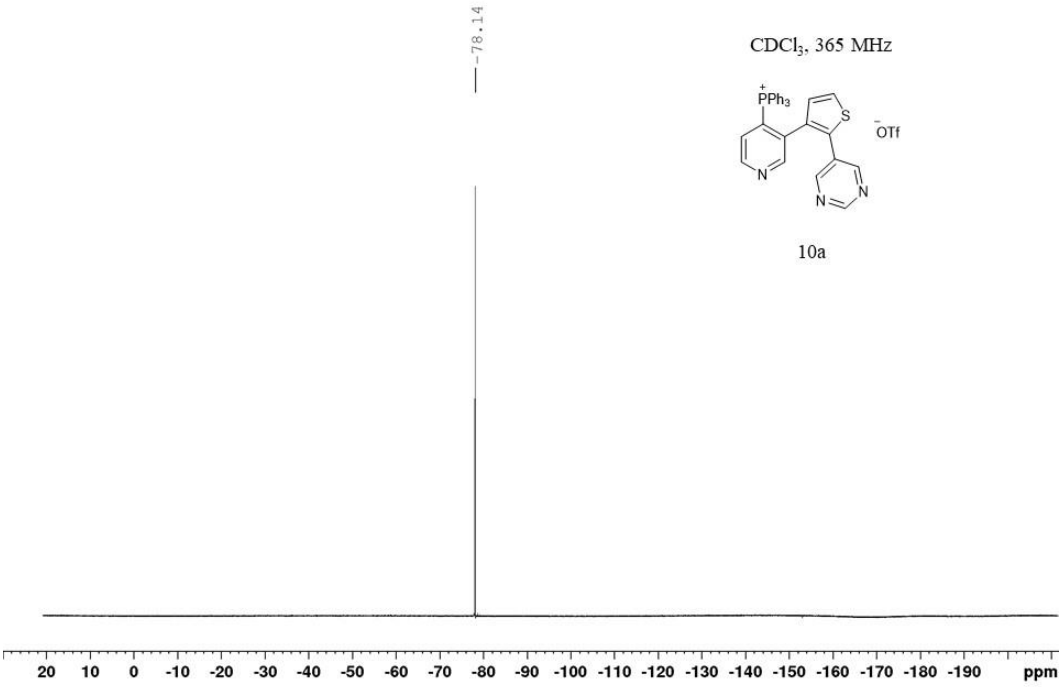

22.66
21.16
16.80
CDCl3, 162 MHz
OTf
PPh3
N
N
O
N
8a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

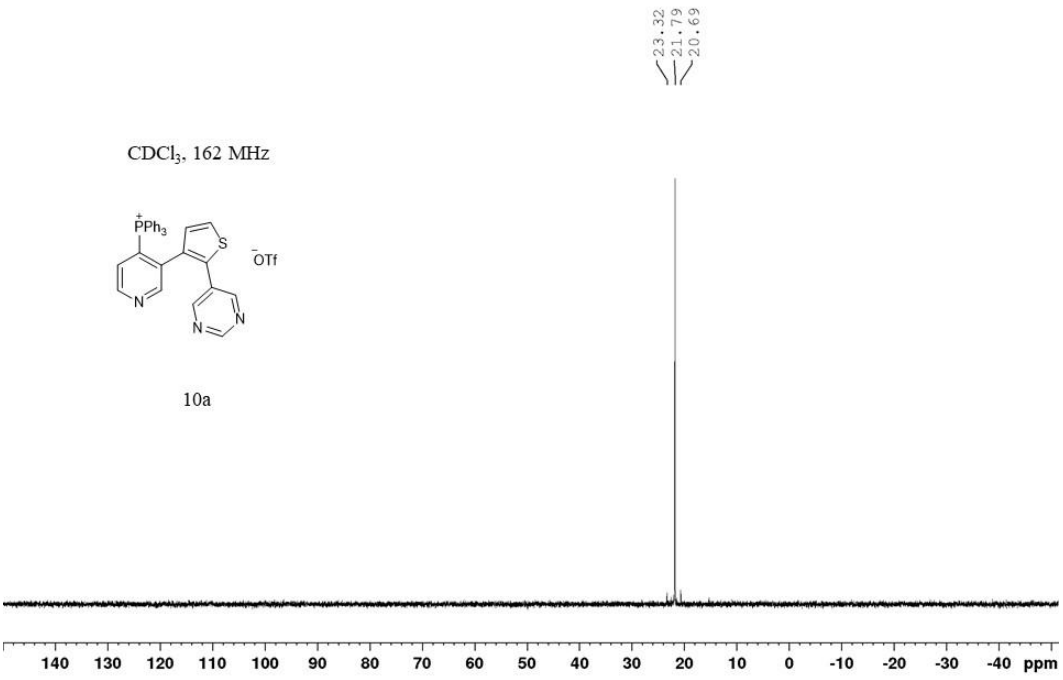

-78.19
CDCl3, 365 MHz
OTf
PPh3
N
N
O
N
8a
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

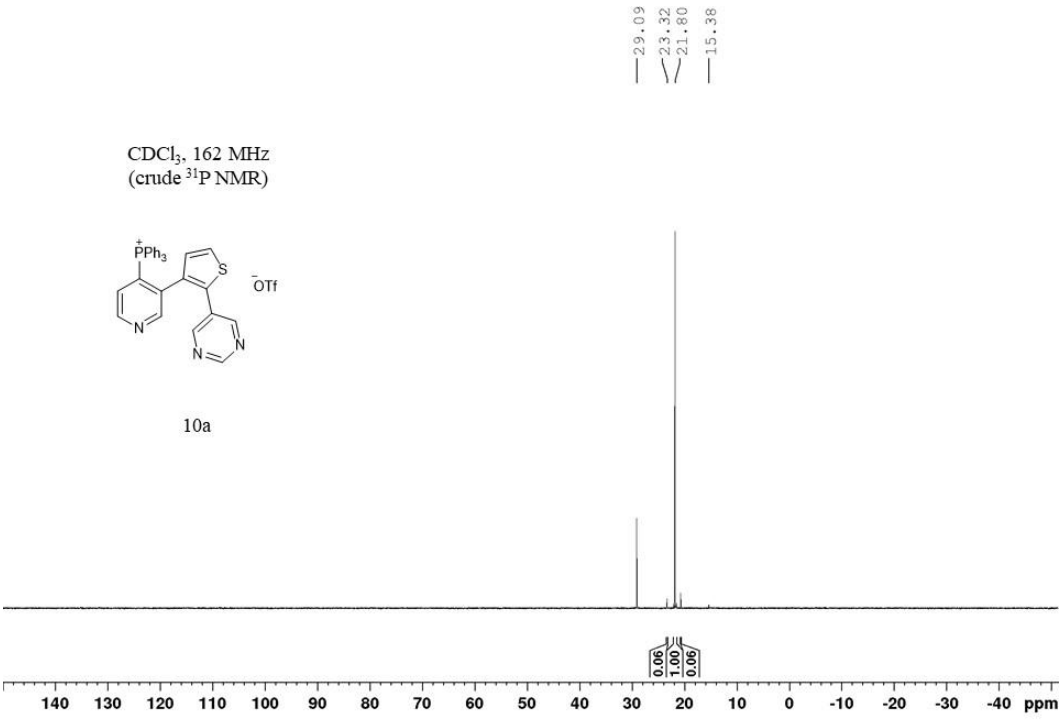

29.16
22.61
21.39
21.33
21.01
16.64
CDCl3, 162 MHz
(crude 31P NMR)
OTf
PPh3
8a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

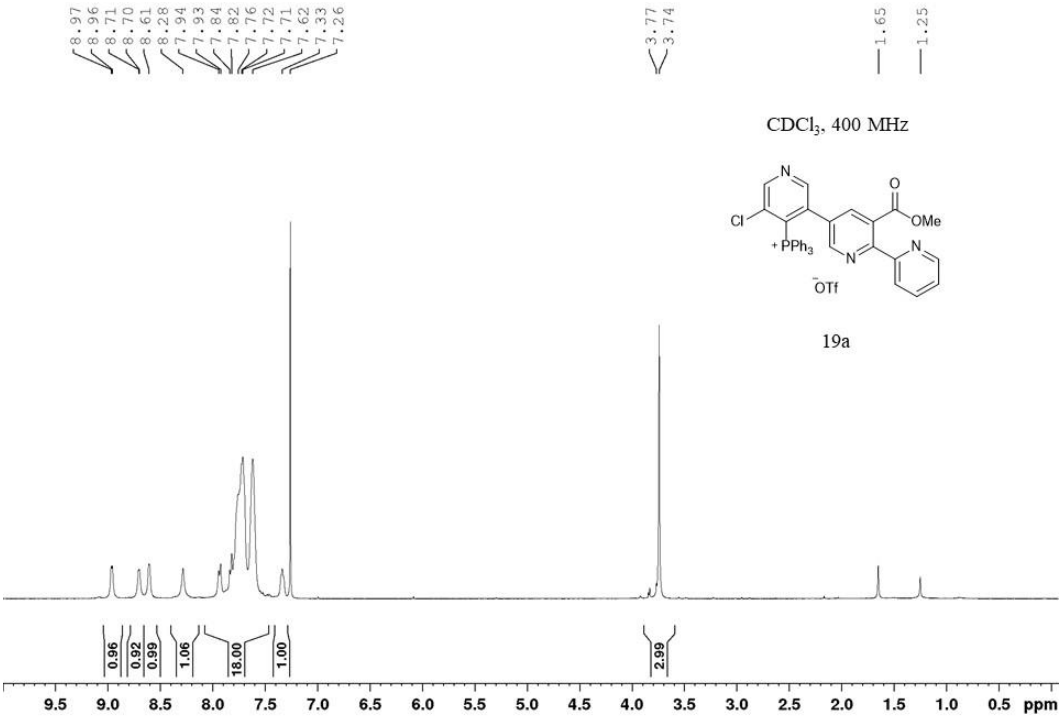

9.03
8.19
7.80
7.79
7.77
7.65
7.64
7.57
7.55
7.54
7.52
7.16
7.15
6.74
6.73
CDCl3, 400 MHz
PPh3
OTf
10a
1.68
0.97
1.63
16.00
0.81
0.78
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


157.29
154.76
154.69
150.61
150.52
136.21
136.15
135.88
135.68
135.66
134.70
134.60
134.43
134.12
134.02
132.75
132.71
131.95
130.75
130.62
130.50
129.12
129.03
127.94
127.65
127.23
126.83
122.37
119.18
116.48
115.60
77.31
77.00
76.68
30.84
CDCl3, 100 MHz
PPh3
OTf
S
N
N
10a
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 ppm


-78.14
CDCl3, 365 MHz
PPh3
OTf
S
N
N
10a
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

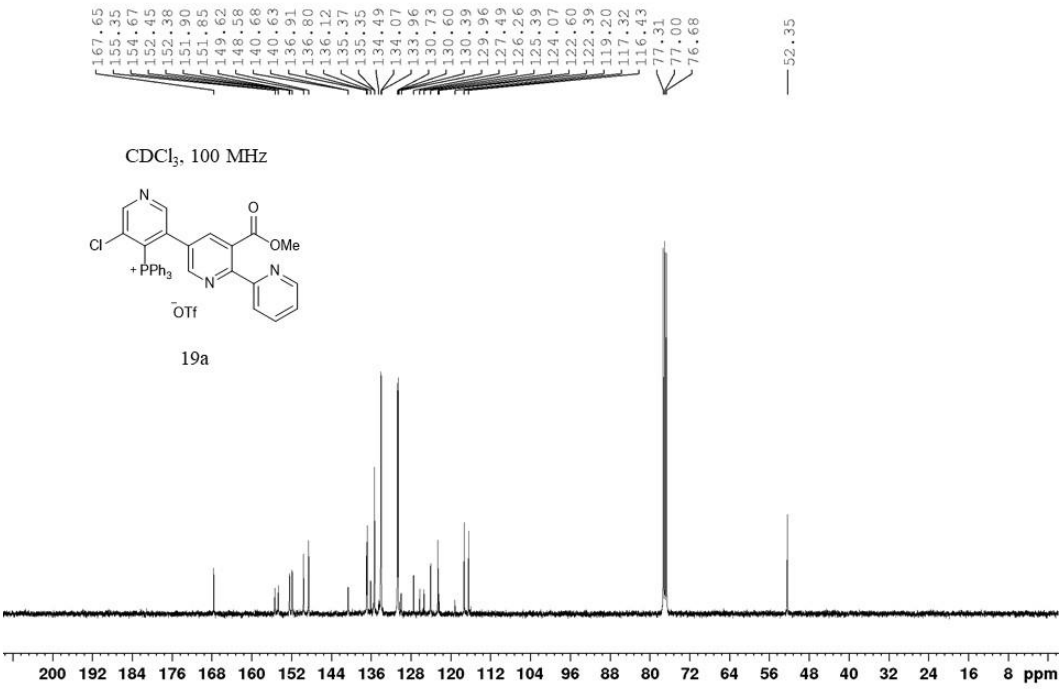

23.32
21.79
20.69
CDCl3, 162 MHz
PPh3
OTf
10a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


29.09
23.32
21.80
15.38
CDCl3, 162 MHz
(crude 31P NMR)
PPh3
OTf
10a
0.06
1.00
0.06
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm



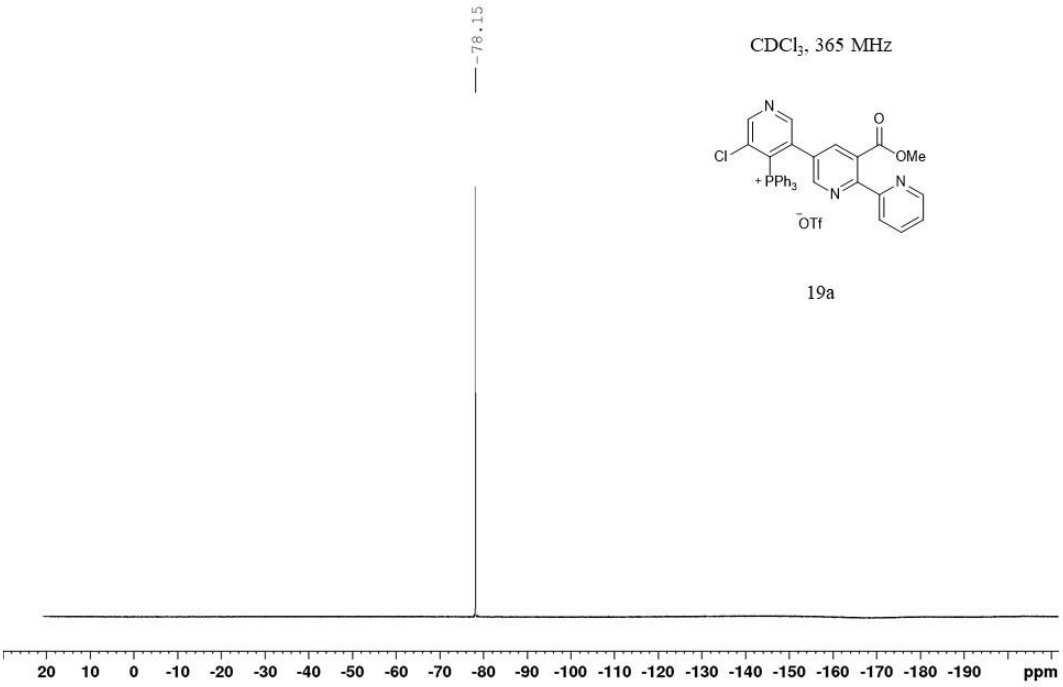
$CDCl_3$, 400 MHz

19a



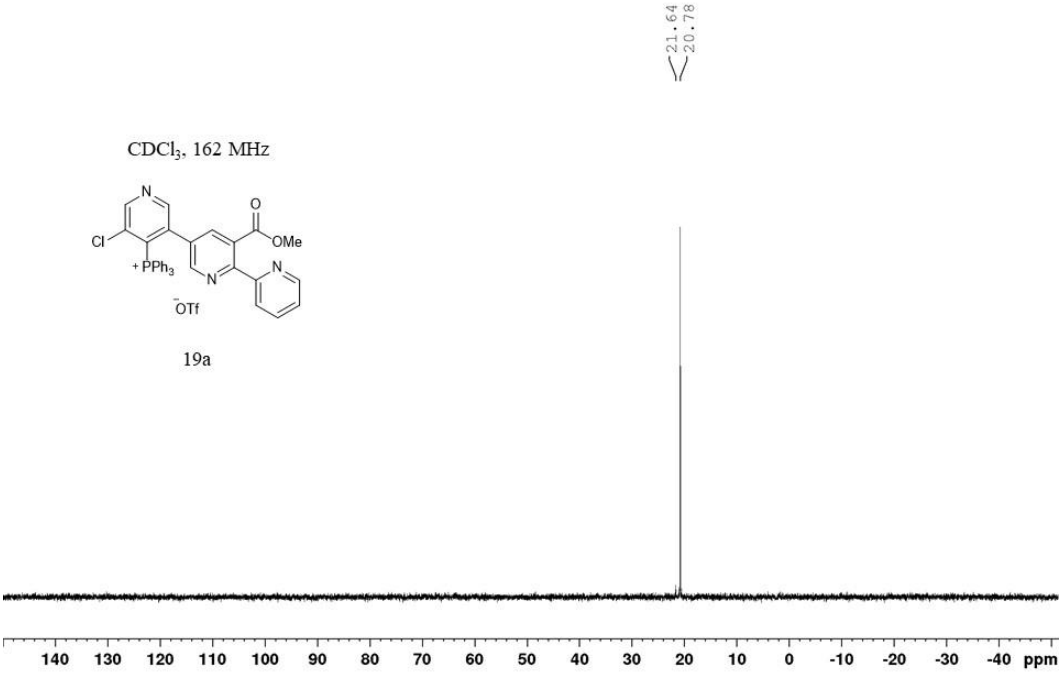
$CDCl_3$, 100 MHz

19a



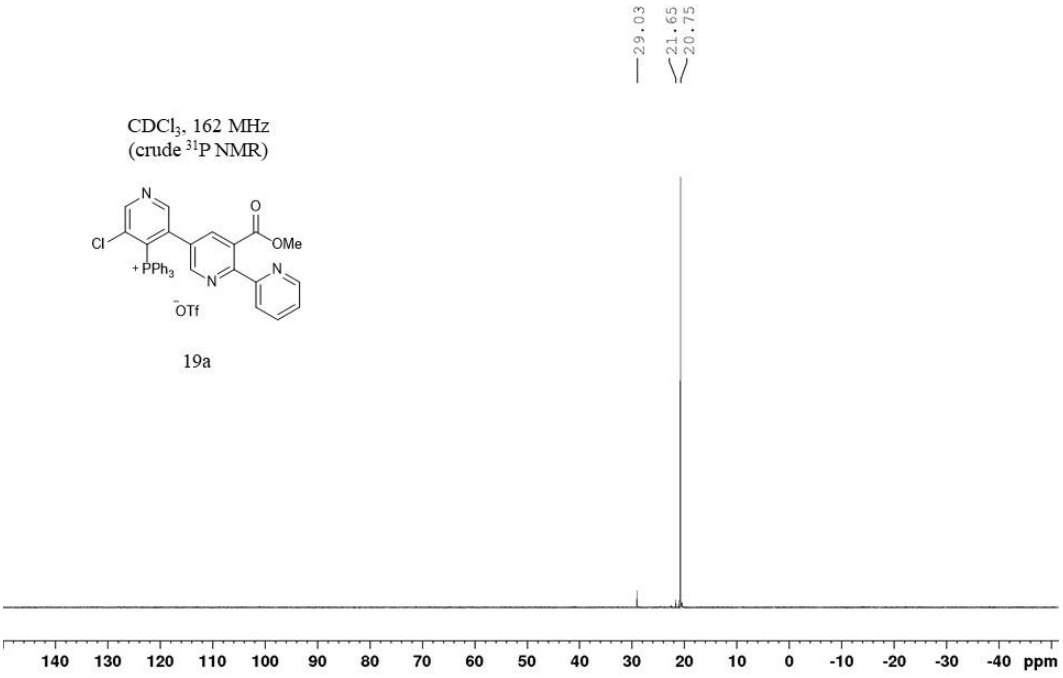
$CDCl_3$, 365 MHz

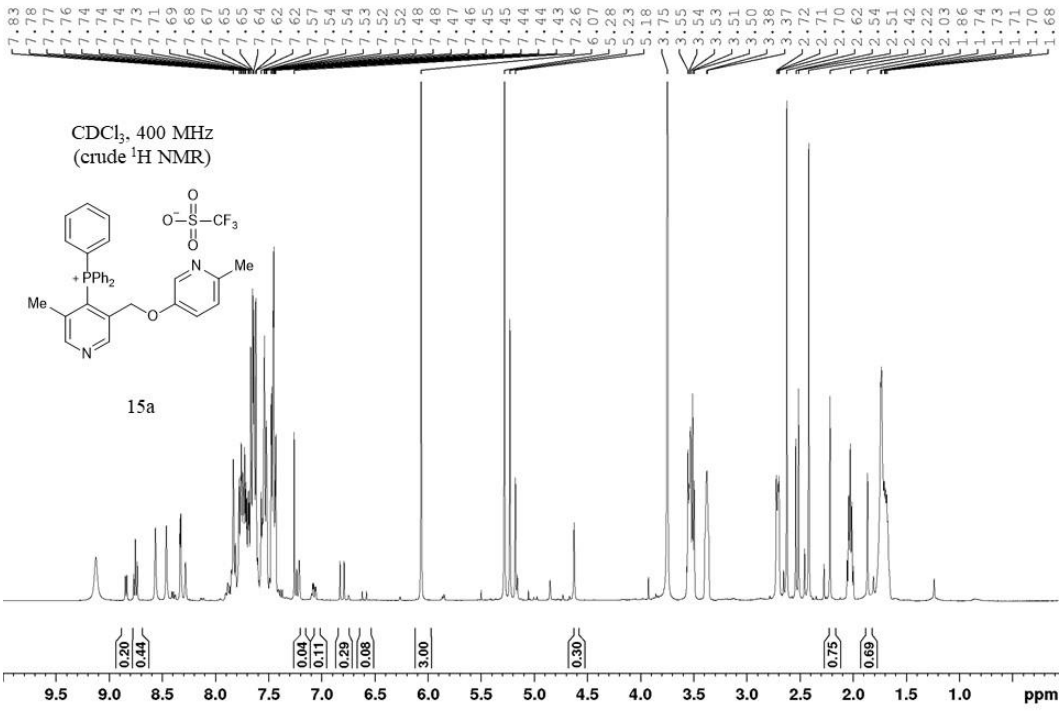
19a

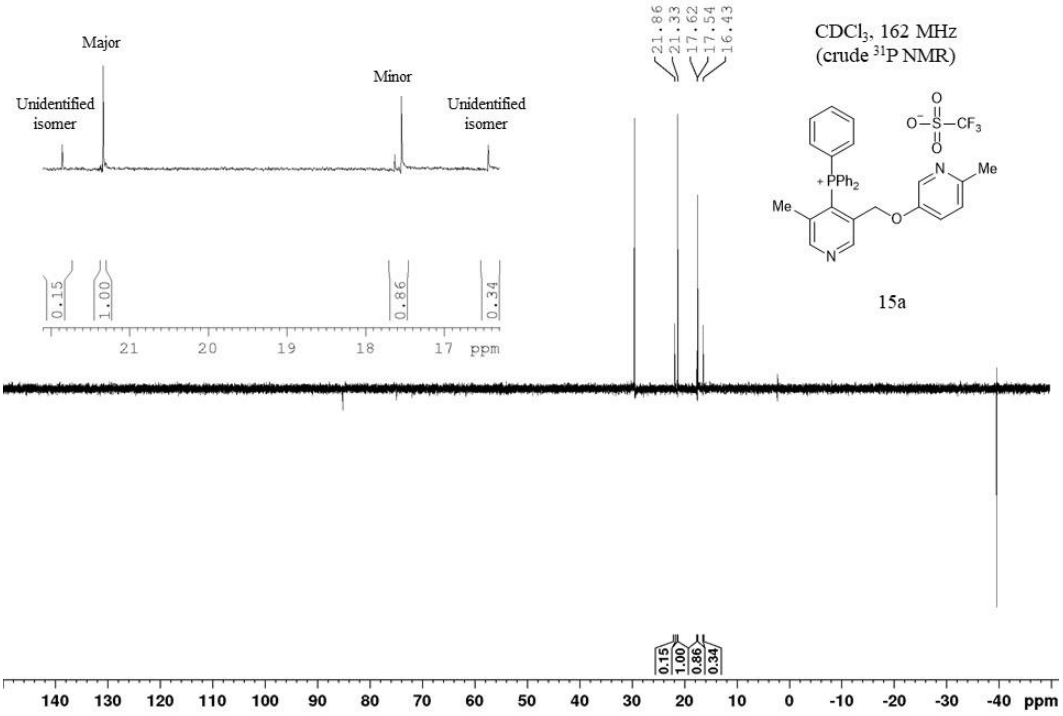


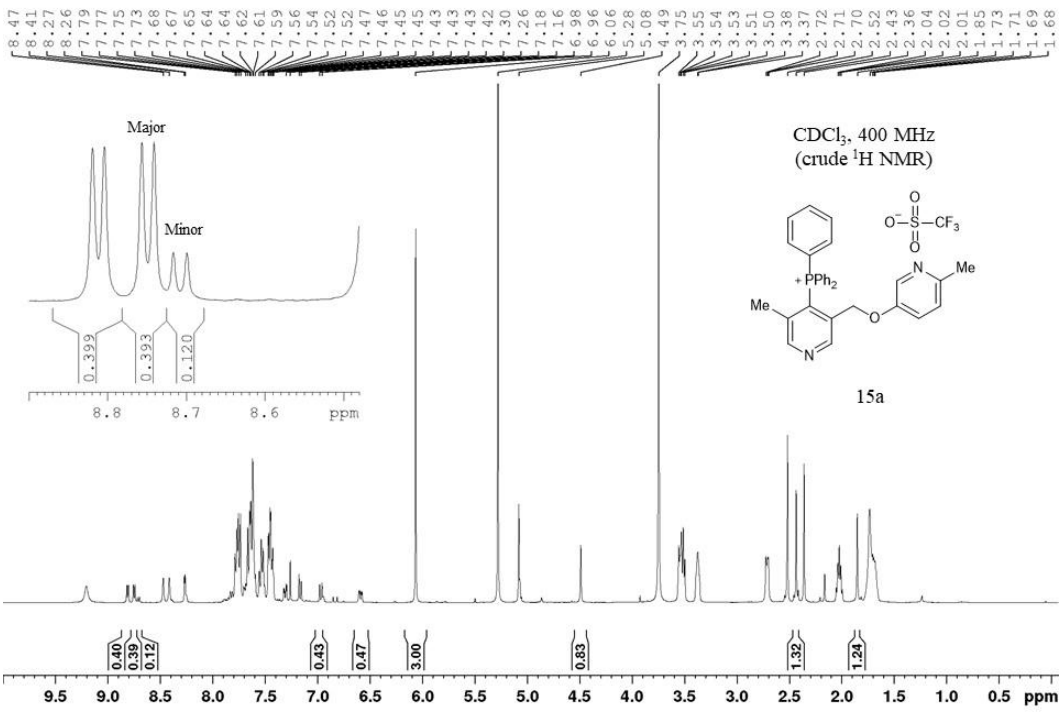
$CDCl_3$, 162 MHz

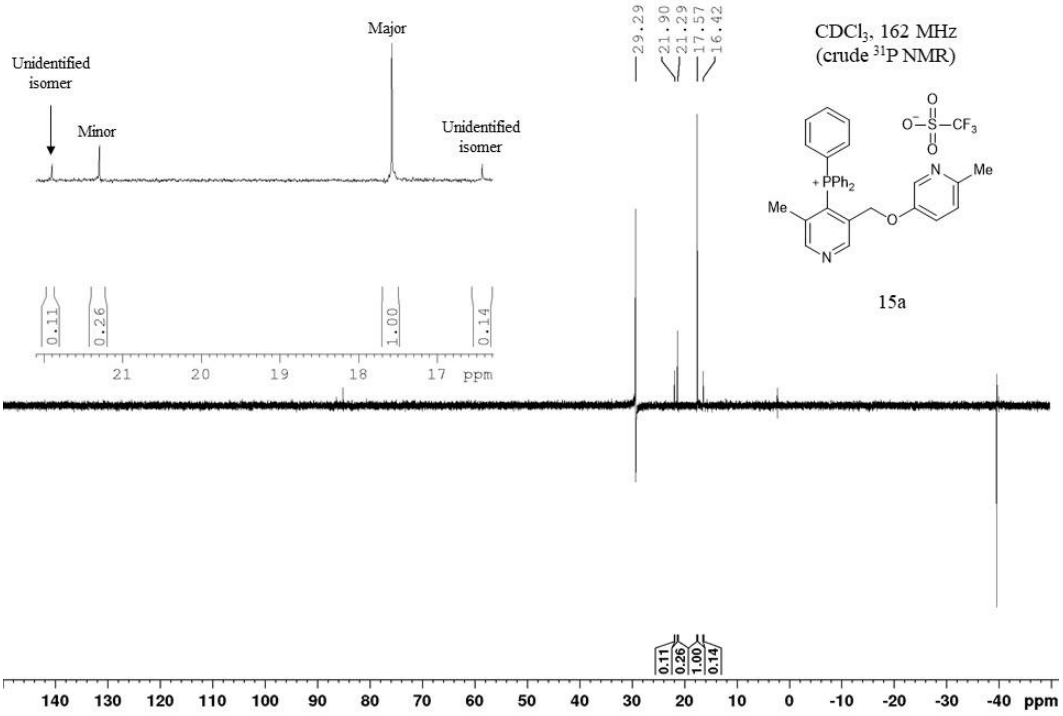
19a

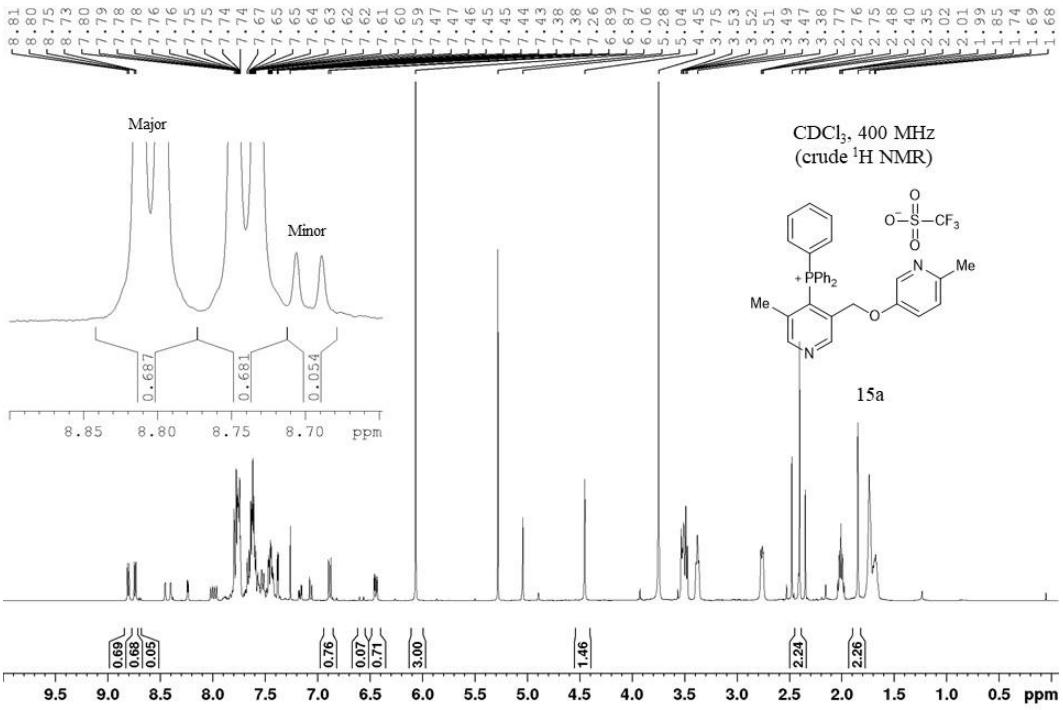

29.03
21.65
20.75
CDCl3, 162 MHz
(crude 31P NMR)
Cl
+PPh3
OTf
O
OMe
N
N
N
19a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

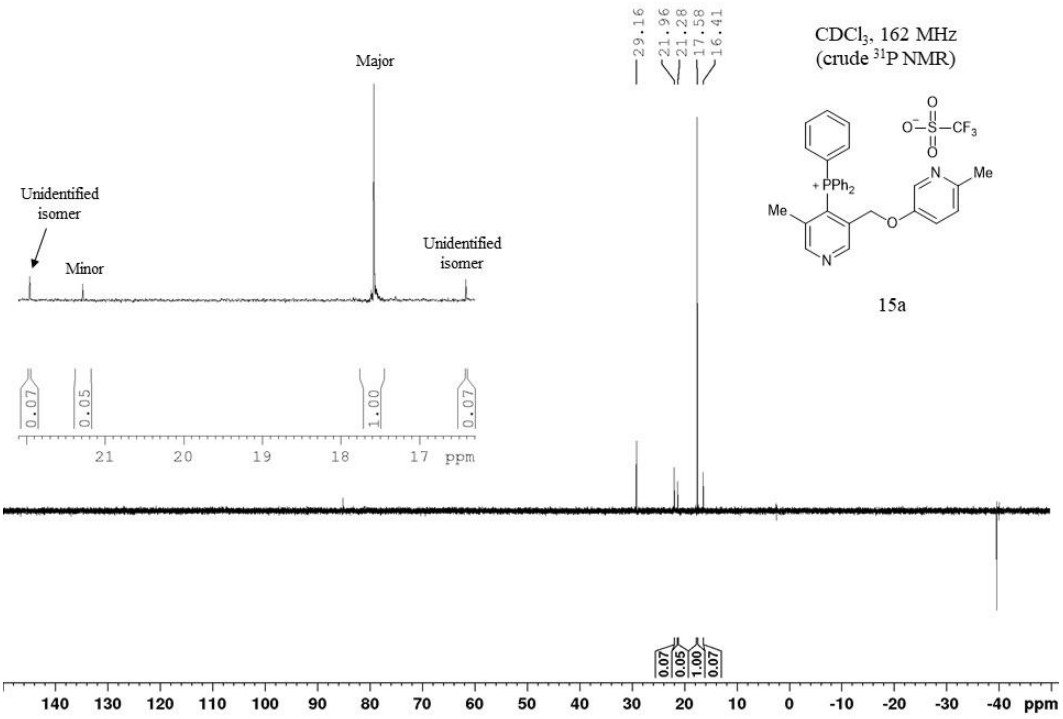

CDCl3, 400 MHz
(crude 1H NMR)
+PPh2
Me
O
O−S−CF3
N
Me
15a
0.20
0.44
0.04
0.11
0.29
0.08
3.00
0.30
0.75
0.69
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

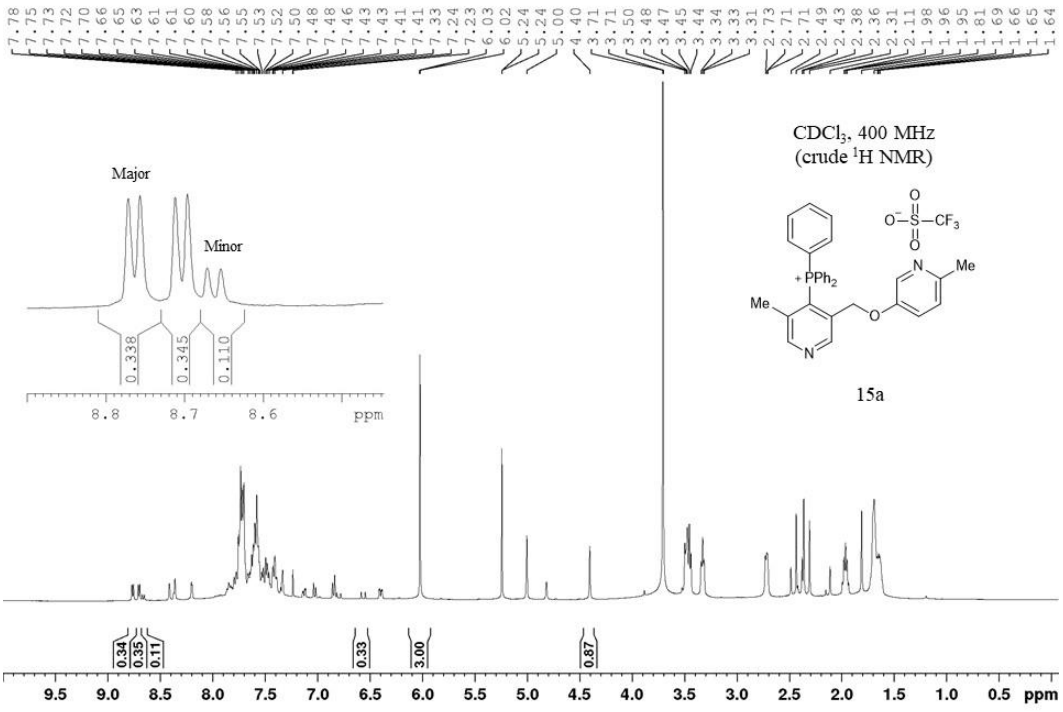

Major
Minor
Unidentified isomer
Unidentified isomer
21.86
21.33
17.62
17.54
16.43
CDCl3, 162 MHz
(crude 31P NMR)
15a
0.15
1.00
0.86
0.34
21 20 19 18 17 ppm
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

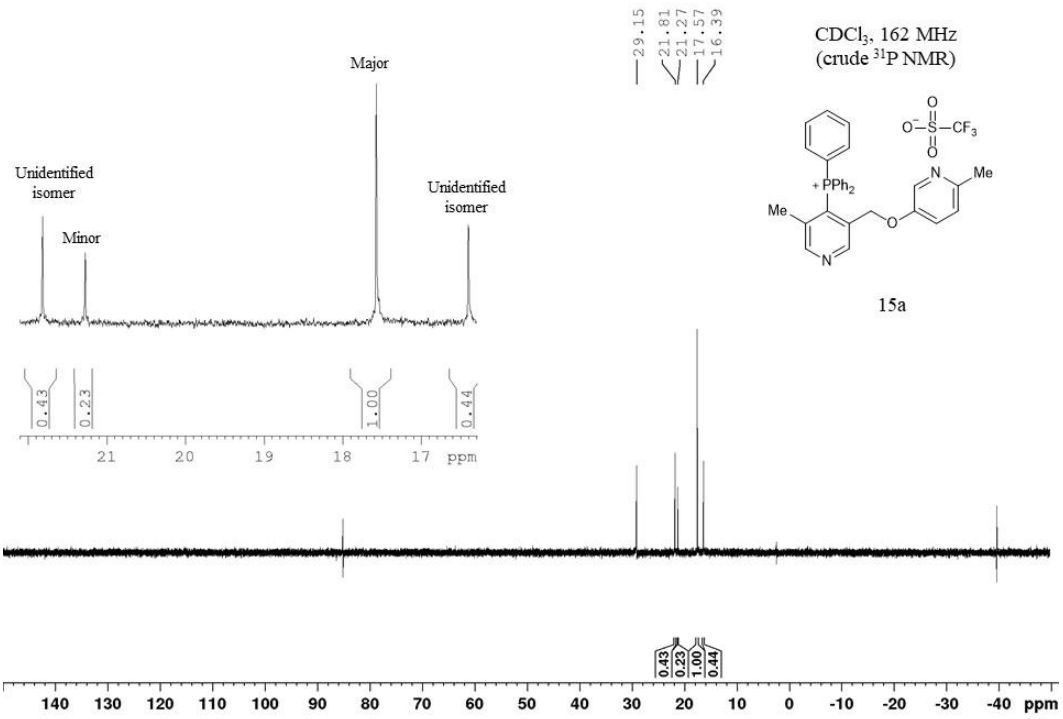

Major
Minor
CDCl3, 400 MHz
(crude 1H NMR)
15a
0.399
0.393
0.120
8.8 8.7 8.6 ppm
0.40
0.39
0.12
0.43
0.47
3.00
0.83
1.32
1.24
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


Unidentified isomer
Minor
Major
Unidentified isomer
29.29
21.90
21.29
17.57
16.42
CDCl3, 162 MHz
(crude 31P NMR)
15a
0.11
0.26
1.00
0.14
21 20 19 18 17 ppm
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


Major
Minor
CDCl3, 400 MHz
(crude 1H NMR)
15a
0.687
0.681
0.054
8.85 8.80 8.75 8.70 ppm
0.69
0.68
0.05
0.76
0.07
0.71
3.00
1.46
2.24
2.26
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 ppm


29.16
21.96
21.28
17.58
16.41
CDCl3, 162 MHz
(crude 31P NMR)
Major
Unidentified isomer
Minor
Unidentified isomer
15a
0.07
0.05
1.00
0.07
21 20 19 18 17 ppm
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

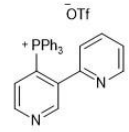

CDCl3, 400 MHz
(crude 1H NMR)
Major
Minor
15a
0.338
0.345
0.110
8.8 8.7 8.6 ppm
0.34
0.35
0.11
0.33
3.00
0.87
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm



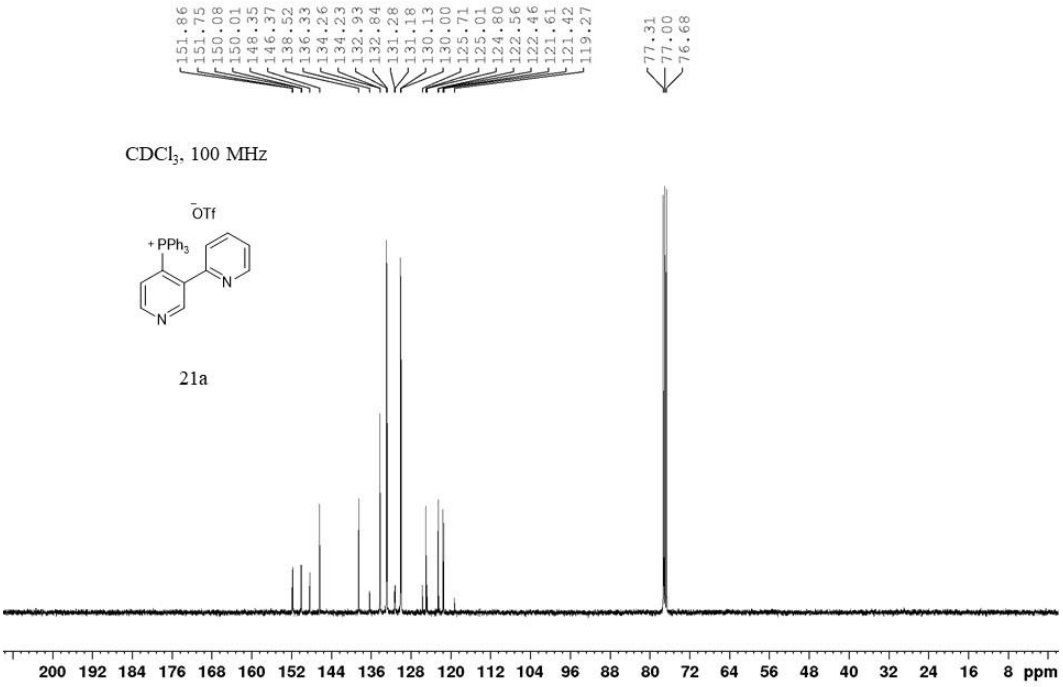
$CDCl_3$, 162 MHz
(crude ^{31}P NMR)

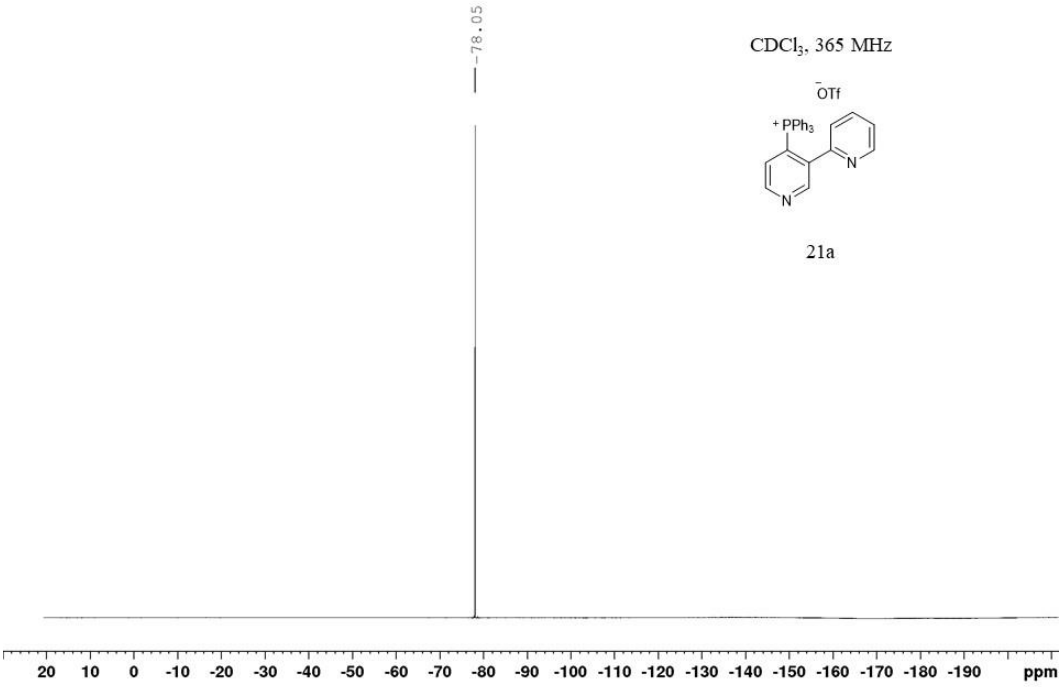
15a

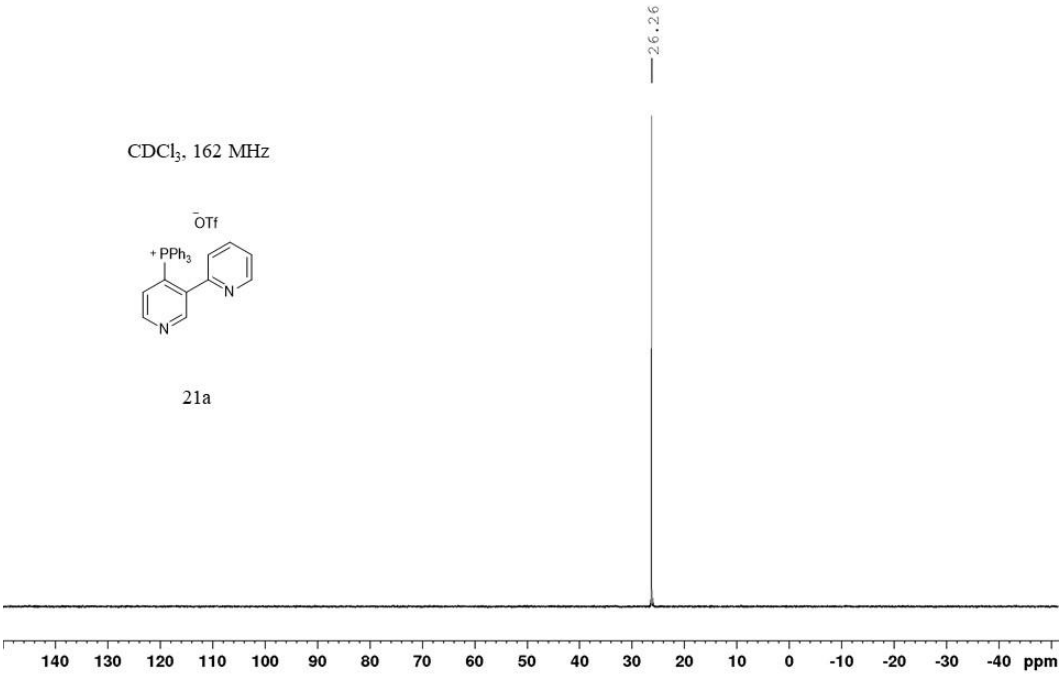
$CDCl_3$, 400 MHz

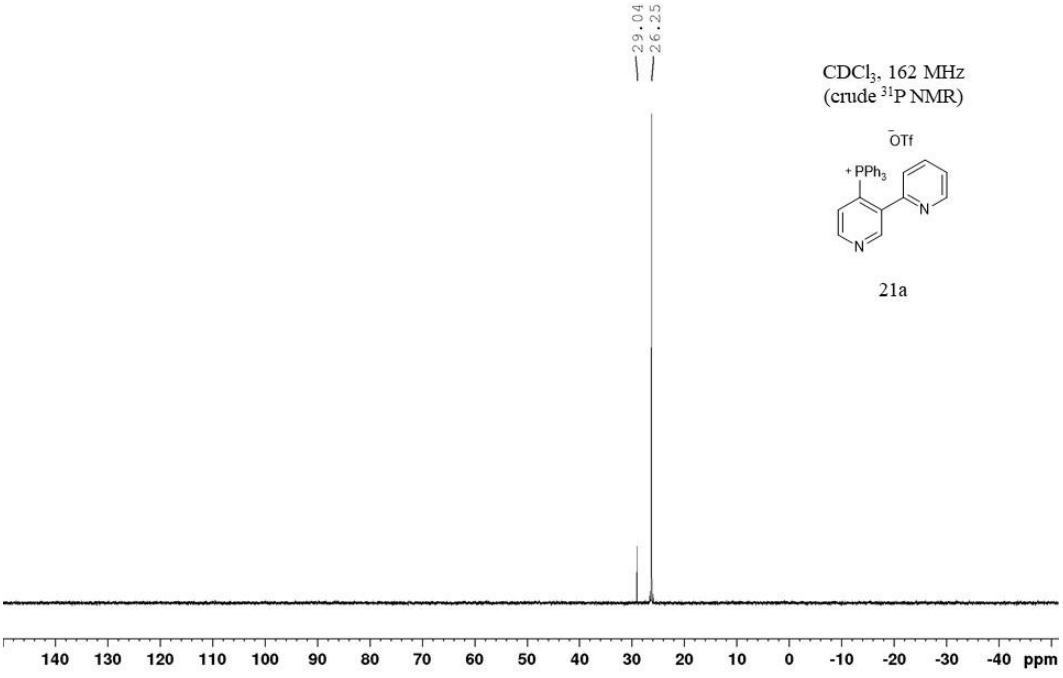


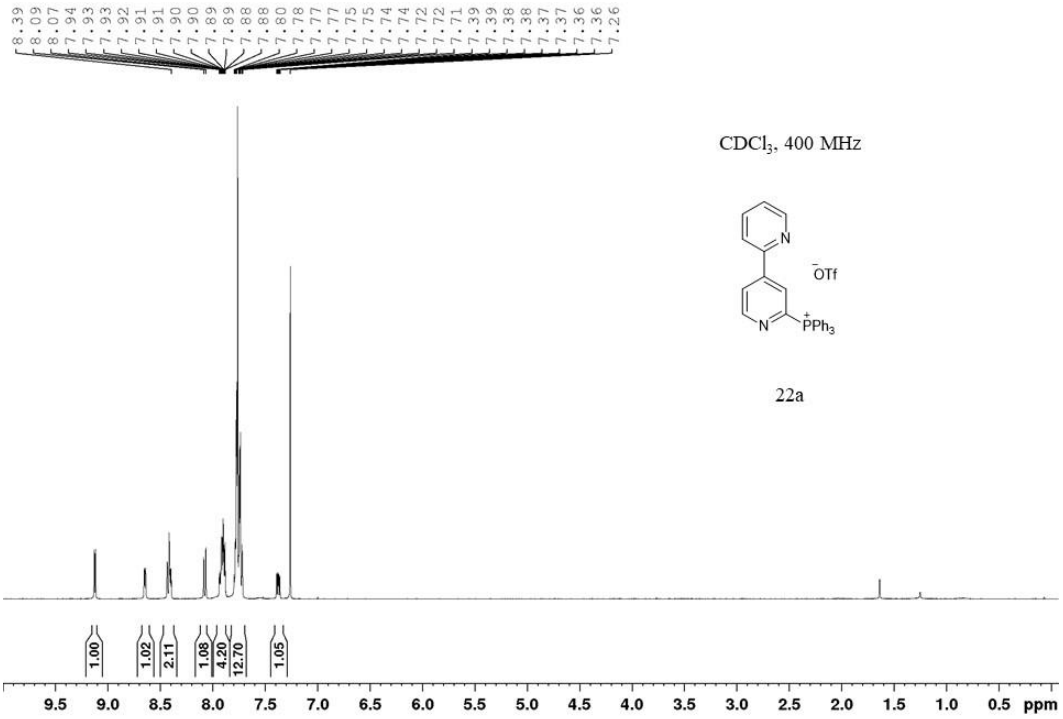
21a

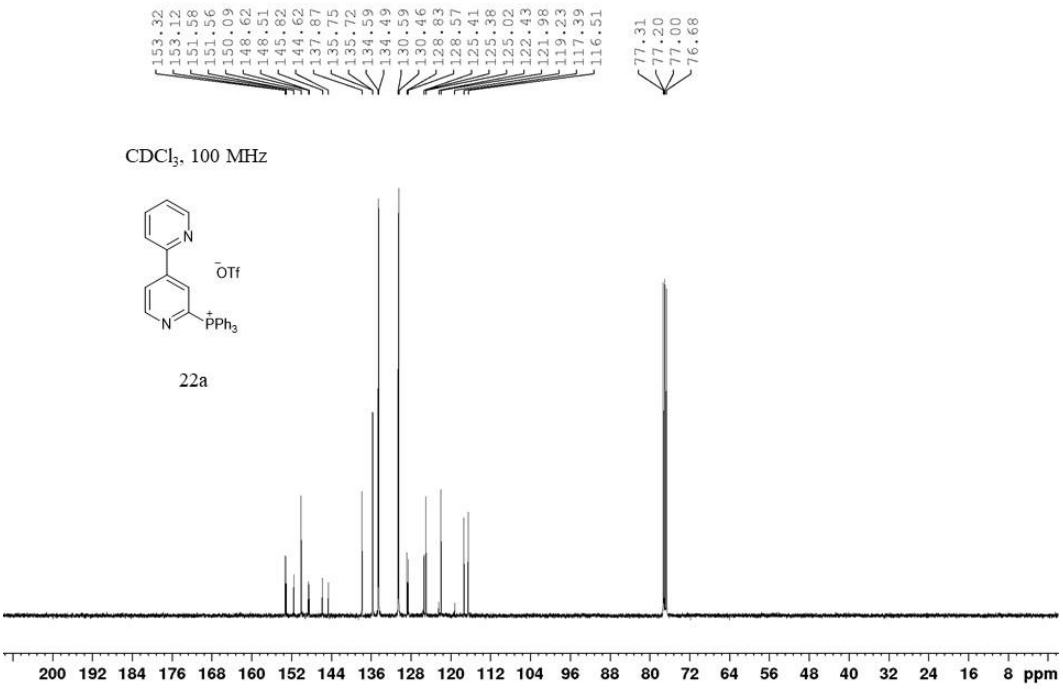

151.86
151.75
150.08
150.01
148.35
146.37
138.52
136.33
134.26
134.23
132.93
132.84
131.28
131.18
130.13
130.00
125.71
125.01
124.80
122.56
122.46
121.61
121.42
119.27
77.31
77.00
76.68
CDCl3, 100 MHz
OTf
+PPh3
N
N
21a
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

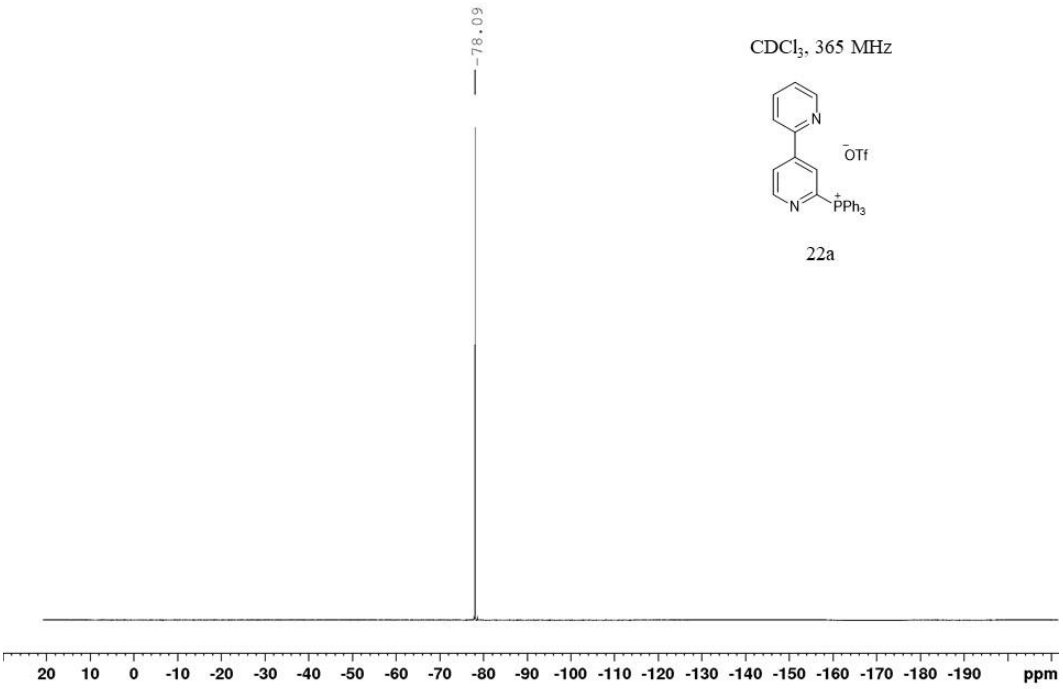

-78.05
CDCl3, 365 MHz
OTf
+PPh3
N
N
21a
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

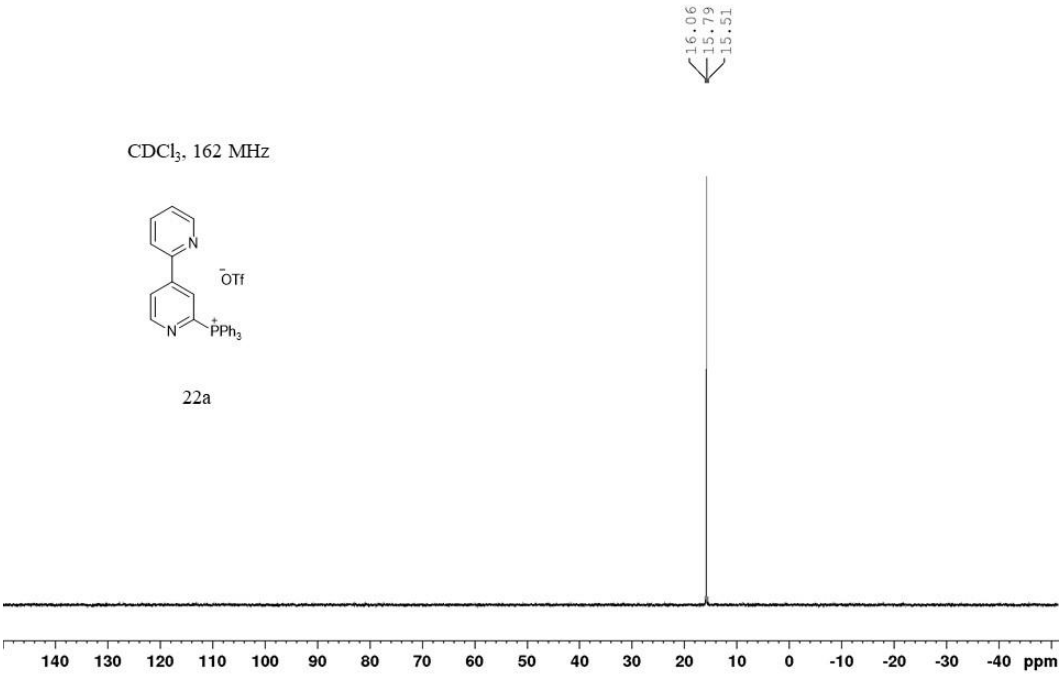

26.26
CDCl3, 162 MHz
OTf
+PPh3
N
N
21a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

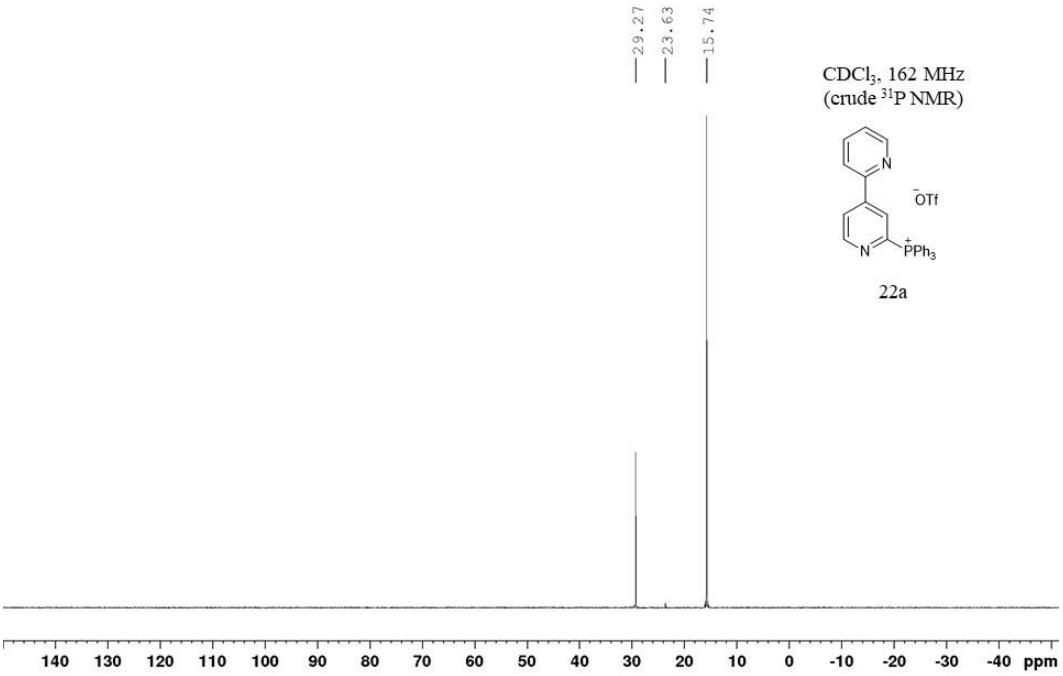

29.04
26.25
CDCl3, 162 MHz
(crude 31P NMR)
OTf
+PPh3
N
N
21a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

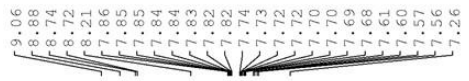

8.39
8.09
8.07
7.94
7.93
7.93
7.92
7.91
7.91
7.90
7.90
7.89
7.89
7.88
7.88
7.80
7.78
7.77
7.77
7.75
7.75
7.74
7.74
7.72
7.72
7.71
7.39
7.39
7.38
7.38
7.37
7.37
7.36
7.36
7.26
CDCl3, 400 MHz
OTf
PPh3
22a
1.00
1.02
2.11
1.08
4.20
12.70
1.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

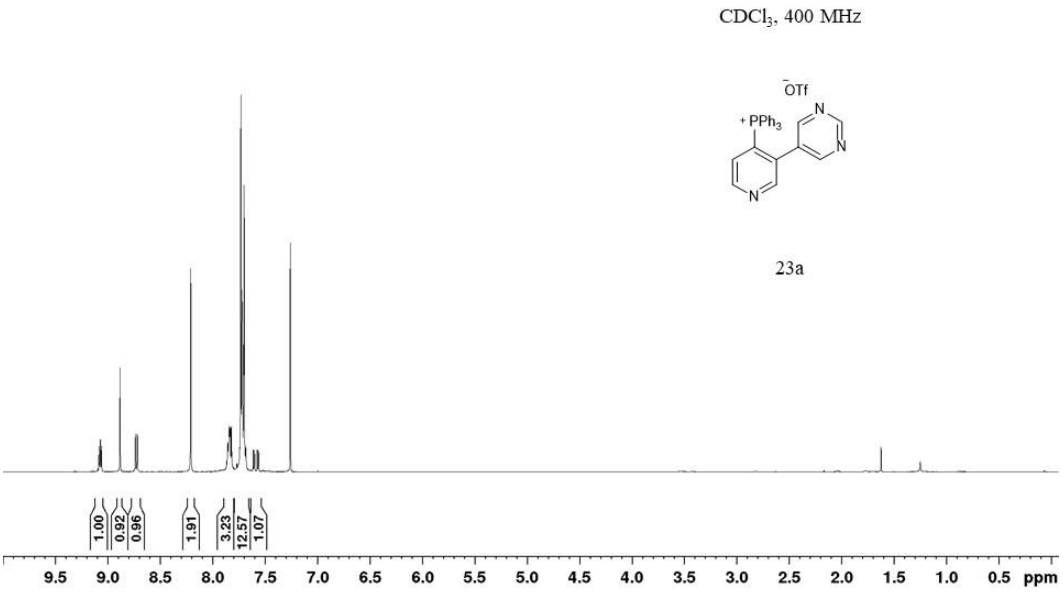

153.32
153.12
151.58
151.56
150.09
148.62
148.51
145.82
144.62
137.87
135.75
135.72
134.59
134.49
130.59
130.46
128.83
128.57
125.41
125.38
125.02
122.43
121.98
119.23
117.39
116.51
77.31
77.20
77.00
76.68
CDCl3, 100 MHz
OTf
PPh3
22a
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

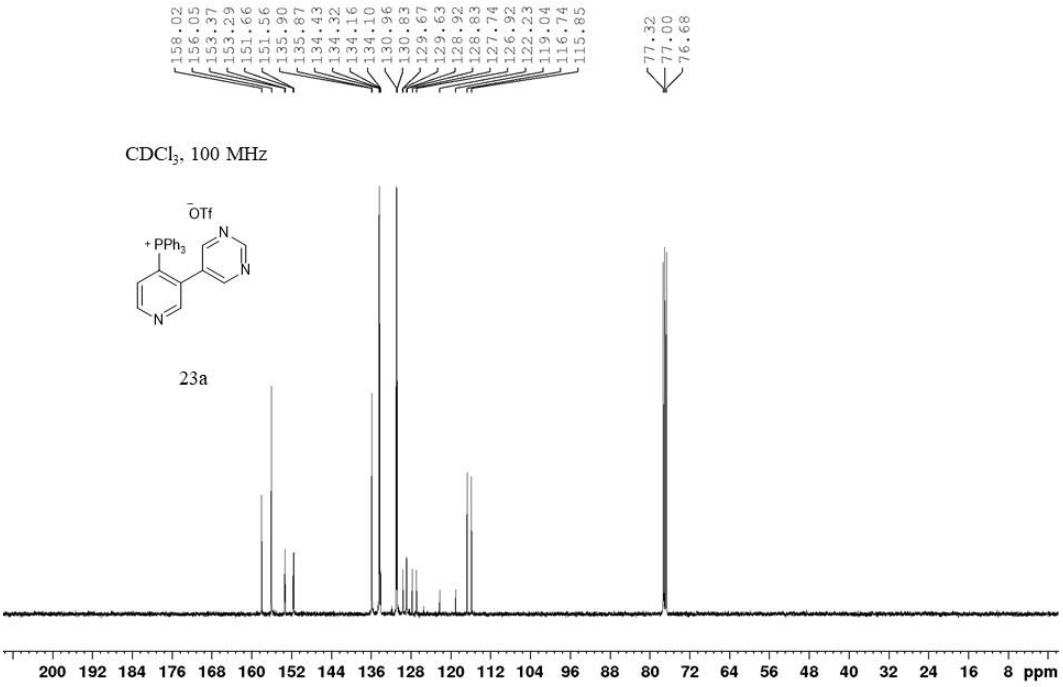

78.09
CDCl3, 365 MHz
N
OTf
N
PPh3
22a
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

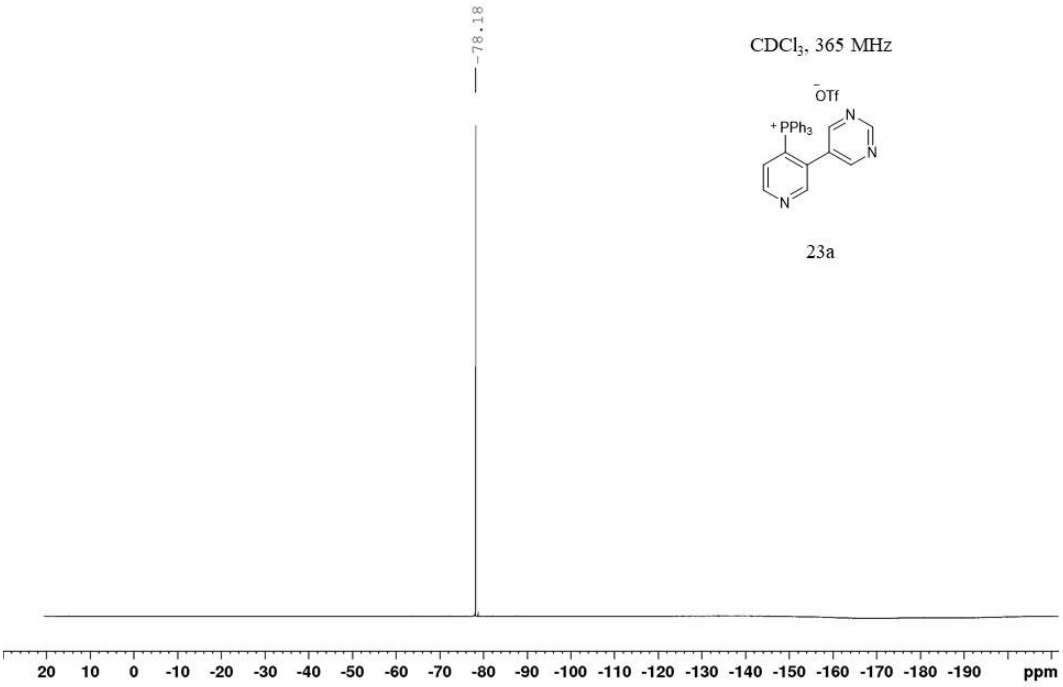

16.06
15.79
15.51
CDCl3, 162 MHz
N
OTf
N
PPh3
22a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

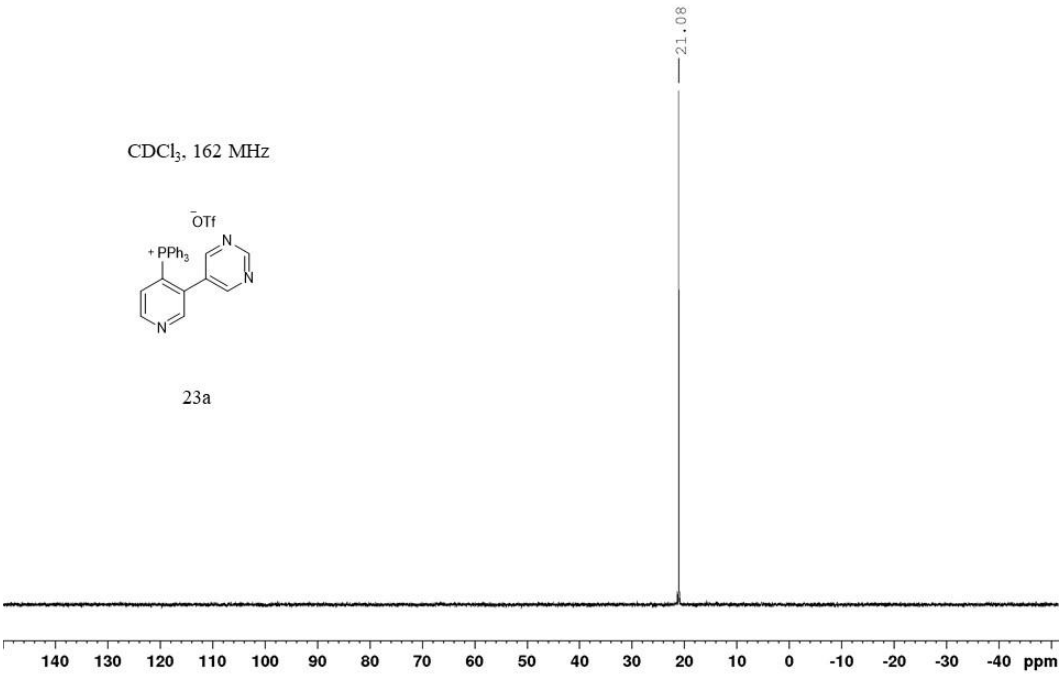

29.27
23.63
15.74
CDCl3, 162 MHz
(crude 31P NMR)
OTf
PPh3
22a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

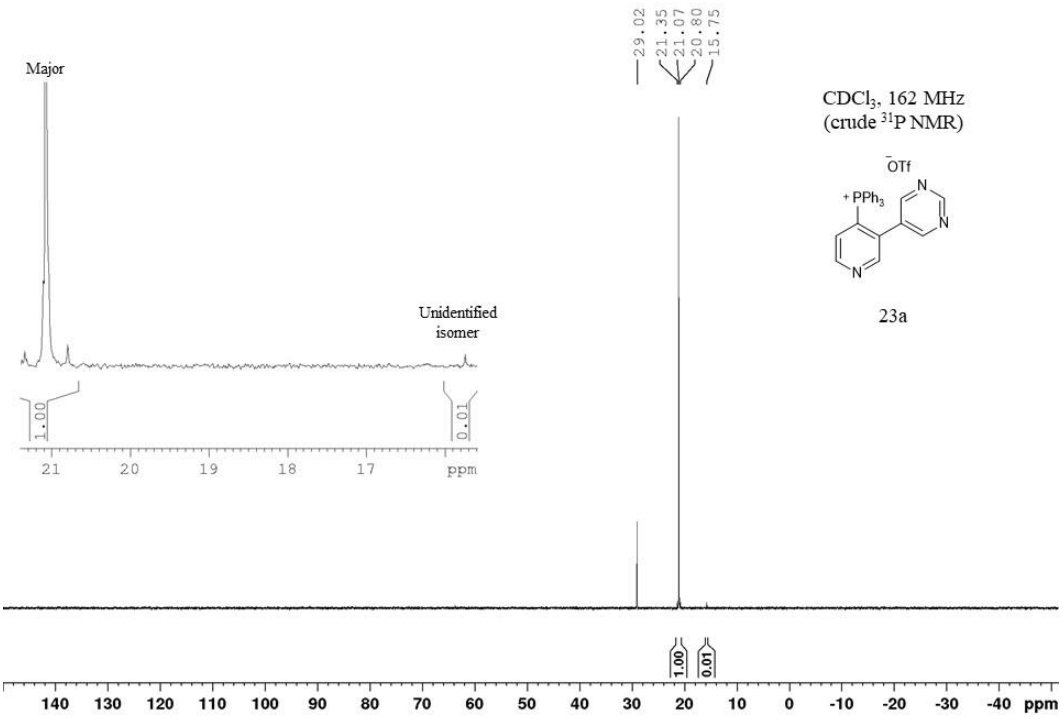

9.06
8.88
8.74
8.72
8.21
7.86
7.85
7.85
7.84
7.84
7.83
7.82
7.82
7.74
7.73
7.72
7.72
7.70
7.70
7.69
7.68
7.61
7.60
7.57
7.56
7.26

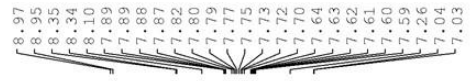

CDCl3, 400 MHz
OTf
+PPh3
23a
1.00
0.92
0.96
1.91
3.23
12.57
1.07
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


158.02
156.05
153.37
153.29
151.66
151.56
135.90
135.87
134.43
134.32
134.16
134.10
130.96
130.83
129.67
129.63
128.92
128.83
127.74
126.92
122.23
119.04
116.74
115.85
77.32
77.00
76.68
CDCl3, 100 MHz
OTf
+PPh3
N
N
N
23a
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 ppm

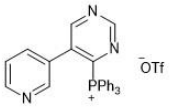

-78.18
CDCl3, 365 MHz
OTf
+PPh3
N
N
N
23a
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm


21.08
CDCl3, 162 MHz
OTf
+PPh3
N
N
N
23a
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

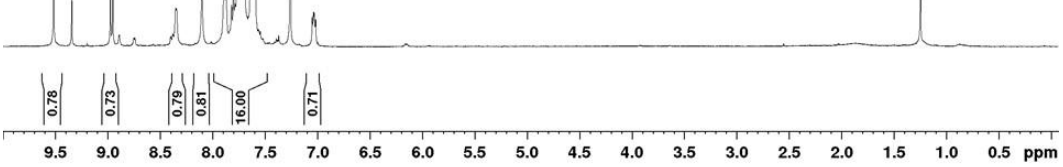

29.02
21.35
21.07
20.80
15.75
Major
Unidentified isomer
1.00
0.01
21 20 19 18 17 ppm
CDCl3, 162 MHz
(crude 31P NMR)
OTf
+PPh3
N
N
N
23a
1.00
0.01
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

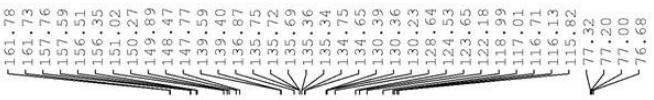


$CDCl_3$, 400 MHz

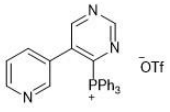


23b

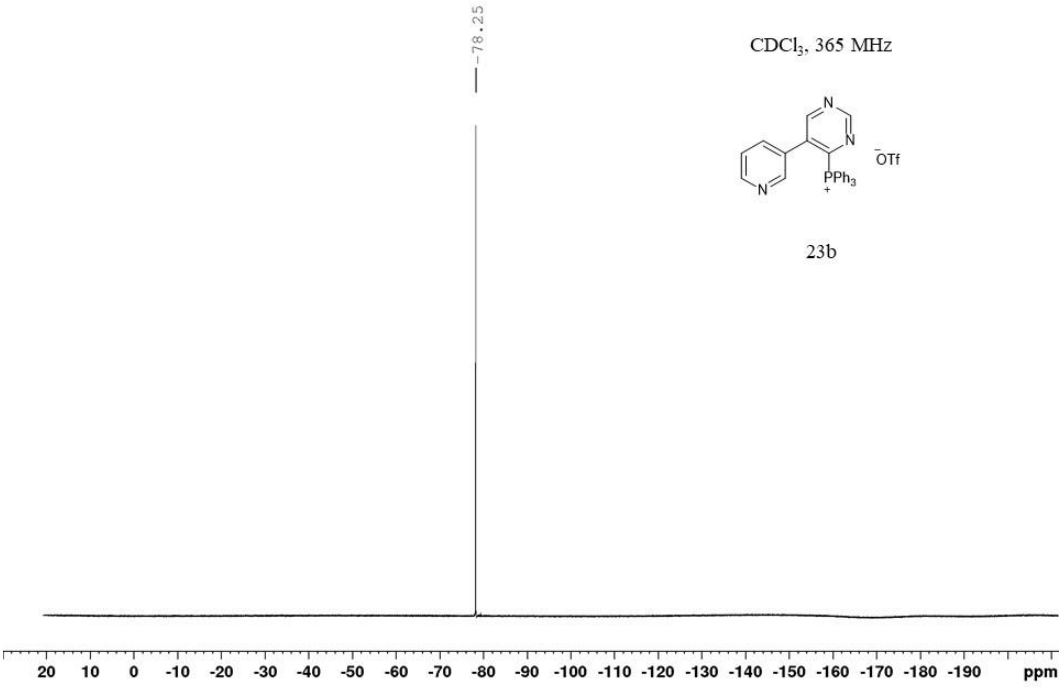




$CDCl_3$, 100 MHz

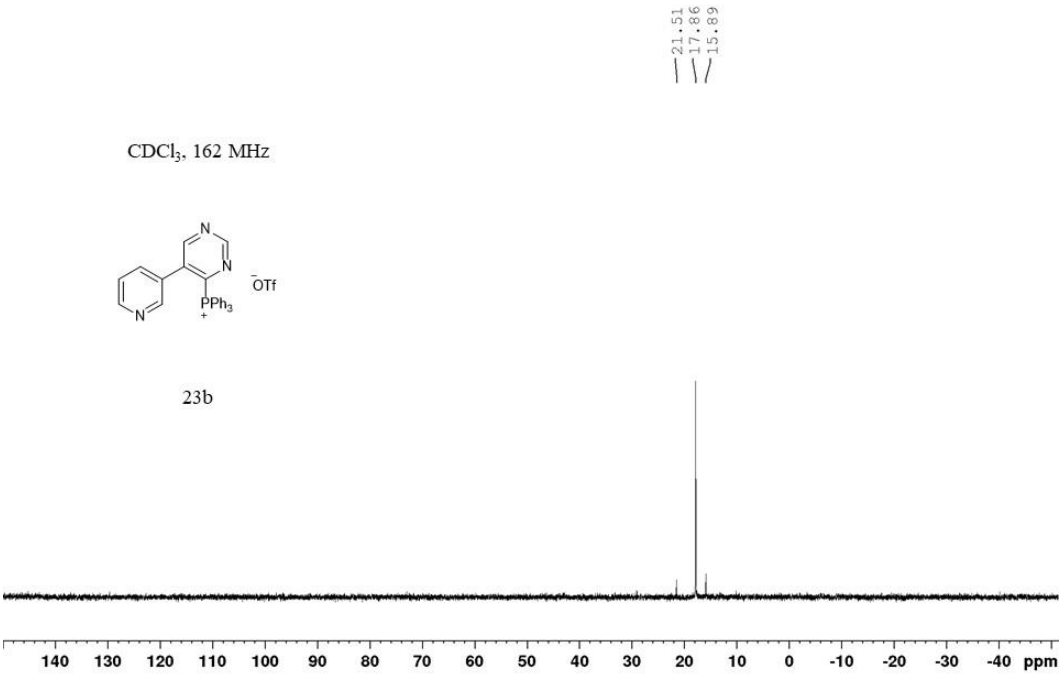


23b



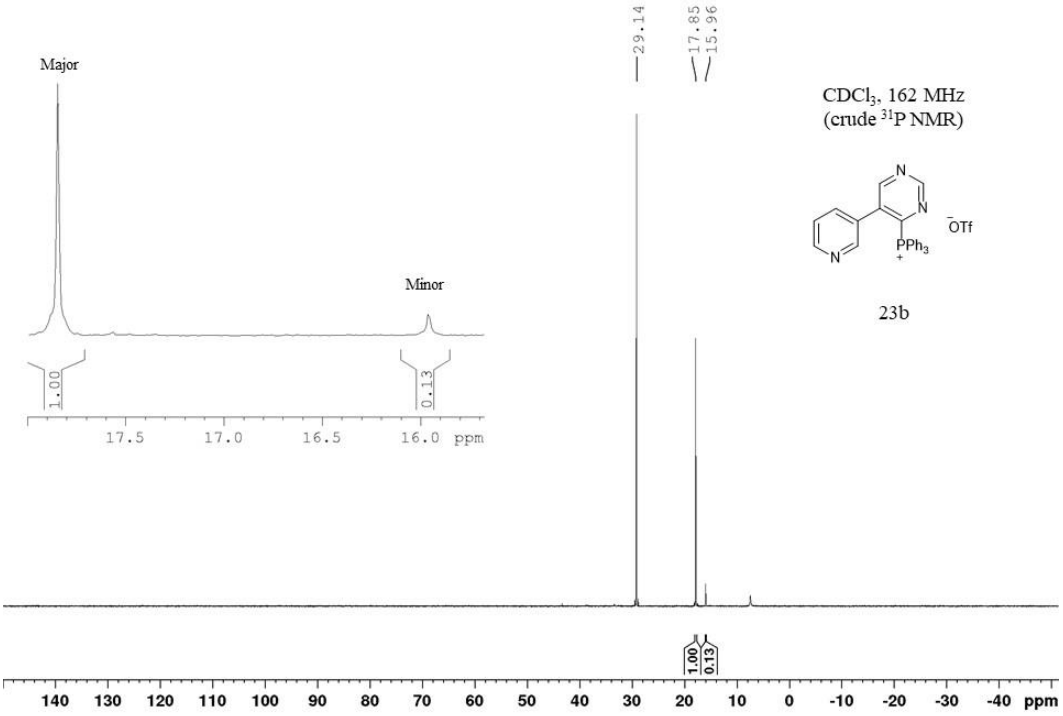
$CDCl_3$, 365 MHz

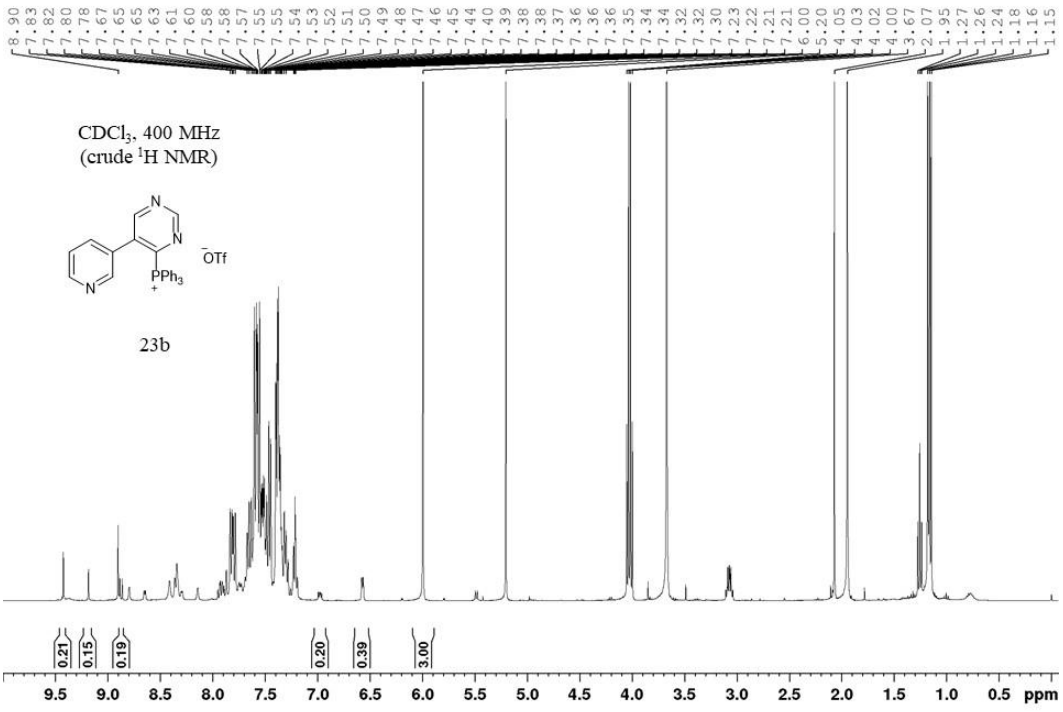
23b

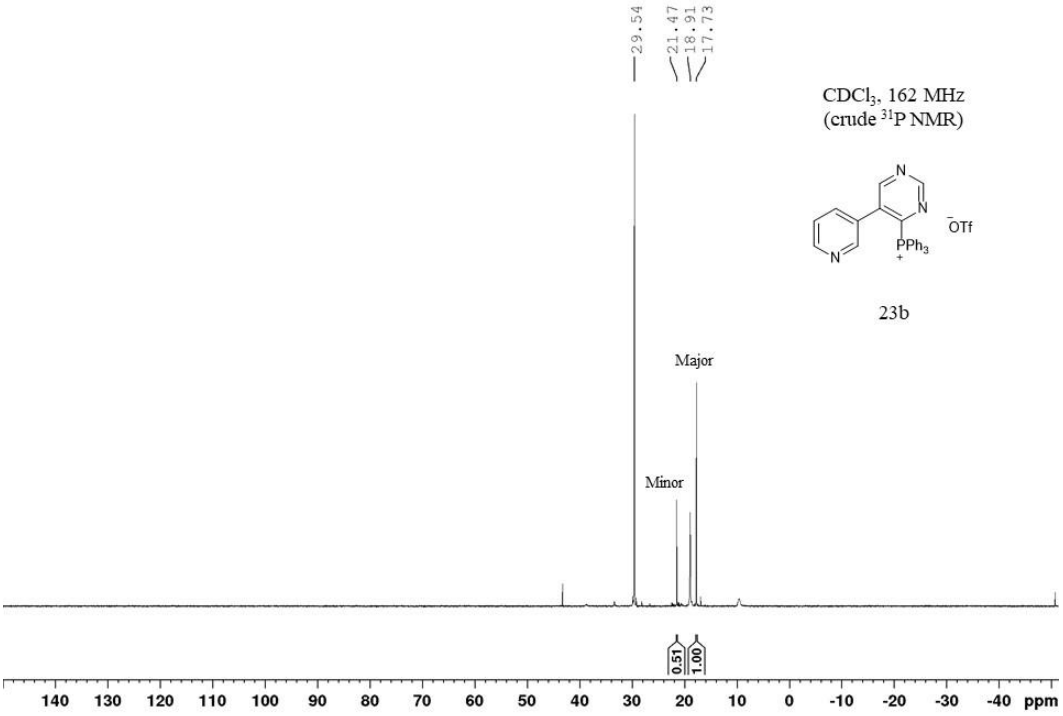


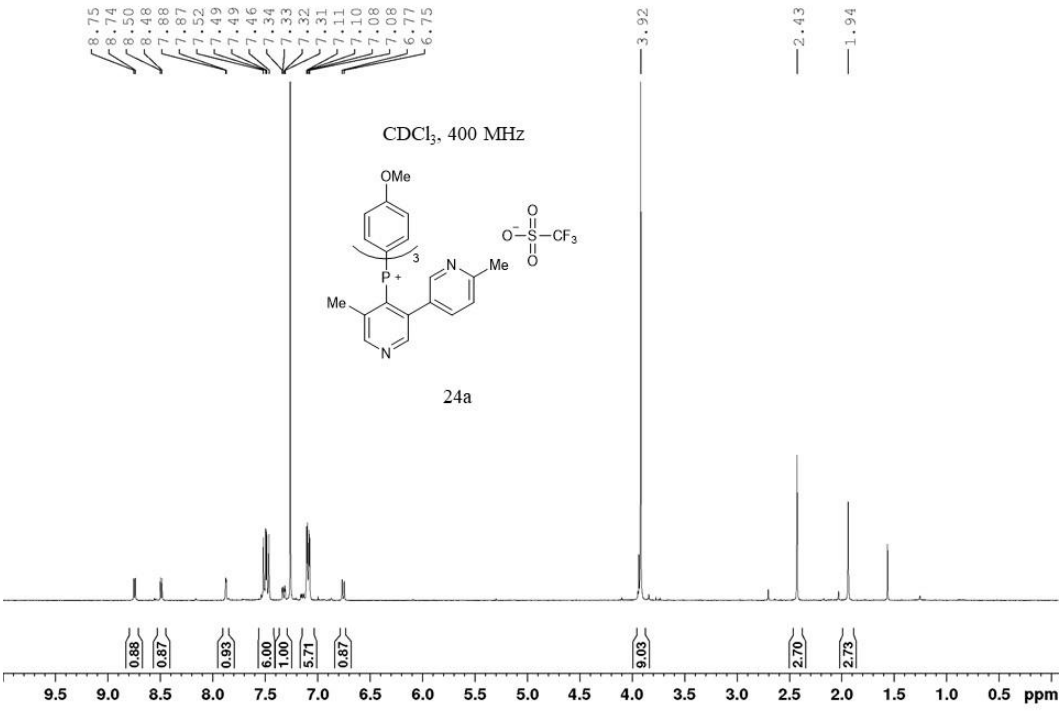
$CDCl_3$, 162 MHz

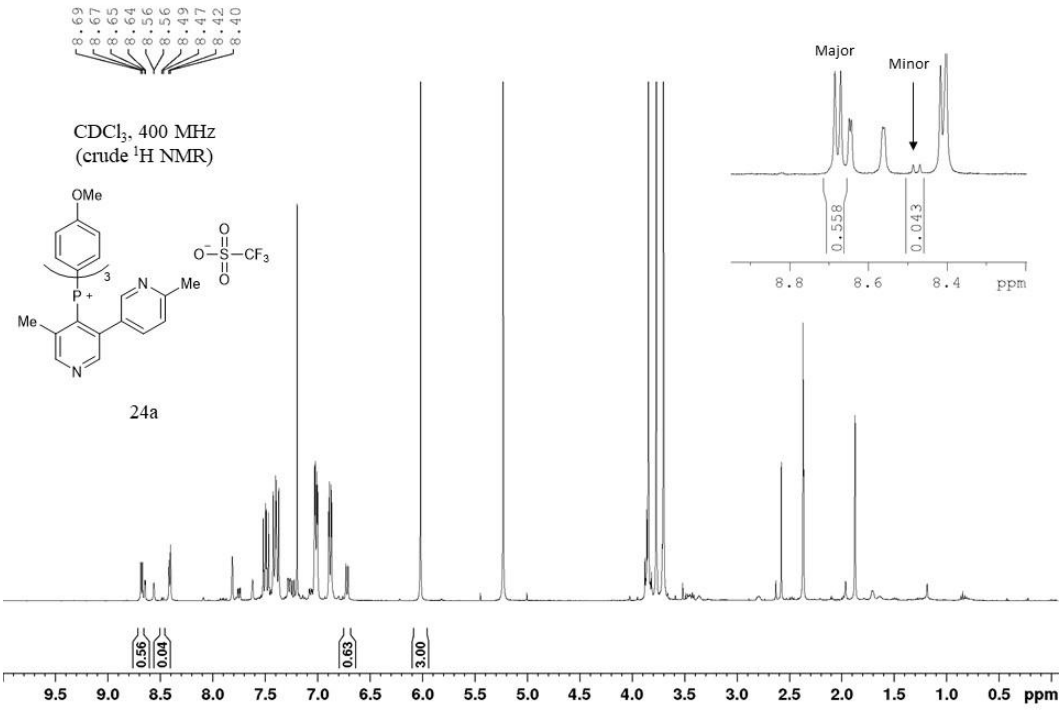
23b

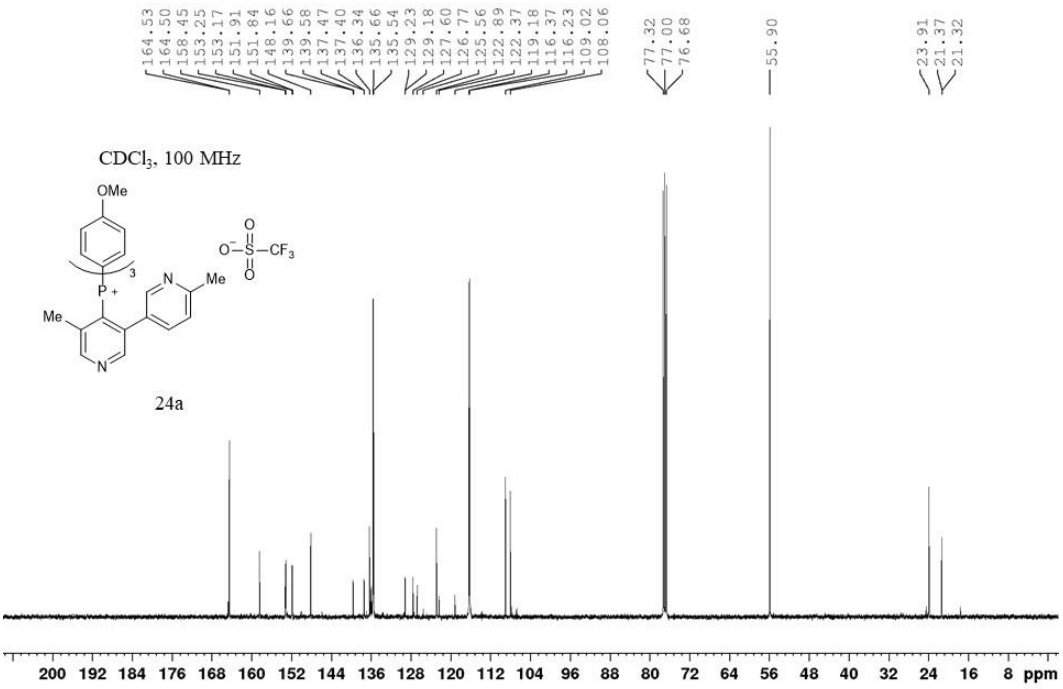

Major
Minor
1.00
0.13
17.5
17.0
16.5
16.0 ppm
29.14
17.85
15.96
CDCl3, 162 MHz
(crude 31P NMR)
OTf
PPh3
23b
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


CDCl3, 400 MHz
(crude 1H NMR)
OTf
PPh3
23b
0.21
0.15
0.19
0.20
0.39
3.00
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 ppm

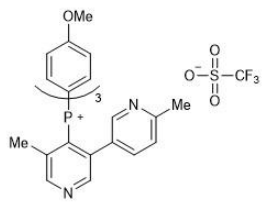

29.54
21.47
18.91
17.73
CDCl3, 162 MHz
(crude 31P NMR)
OTf
PPh3
23b
Major
Minor
0.51
1.00
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


8.75
8.74
8.50
8.48
7.88
7.87
7.52
7.49
7.49
7.46
7.34
7.33
7.32
7.31
7.11
7.10
7.08
7.08
6.77
6.75
3.92
2.43
1.94
CDCl3, 400 MHz
OMe
Me
Me
24a
0.88
0.87
0.93
6.00
1.00
5.71
0.87
9.03
2.70
2.73
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 ppm


8.69
8.67
8.65
8.64
8.56
8.56
8.49
8.47
8.42
8.40
CDCl3, 400 MHz
(crude 1H NMR)
OMe
O
O−S−CF3
O
3
P+
N
Me
Me
N
24a
Major
Minor
0.558
0.043
8.8
8.6
8.4
ppm
0.56
0.04
0.63
3.00
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 ppm

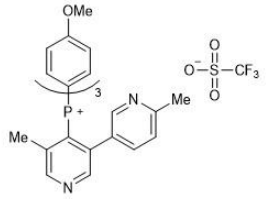

164.53
164.50
158.45
153.25
153.17
151.91
151.84
148.16
139.66
139.58
137.47
137.40
136.34
135.66
135.54
129.23
129.18
127.60
126.77
125.56
122.89
122.37
119.18
116.37
116.23
109.02
108.06
77.32
77.00
76.68
55.90
23.91
21.37
21.32
CDCl3, 100 MHz
OMe
O
O−S−CF3
O
3
P+
N
Me
Me
N
24a
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz

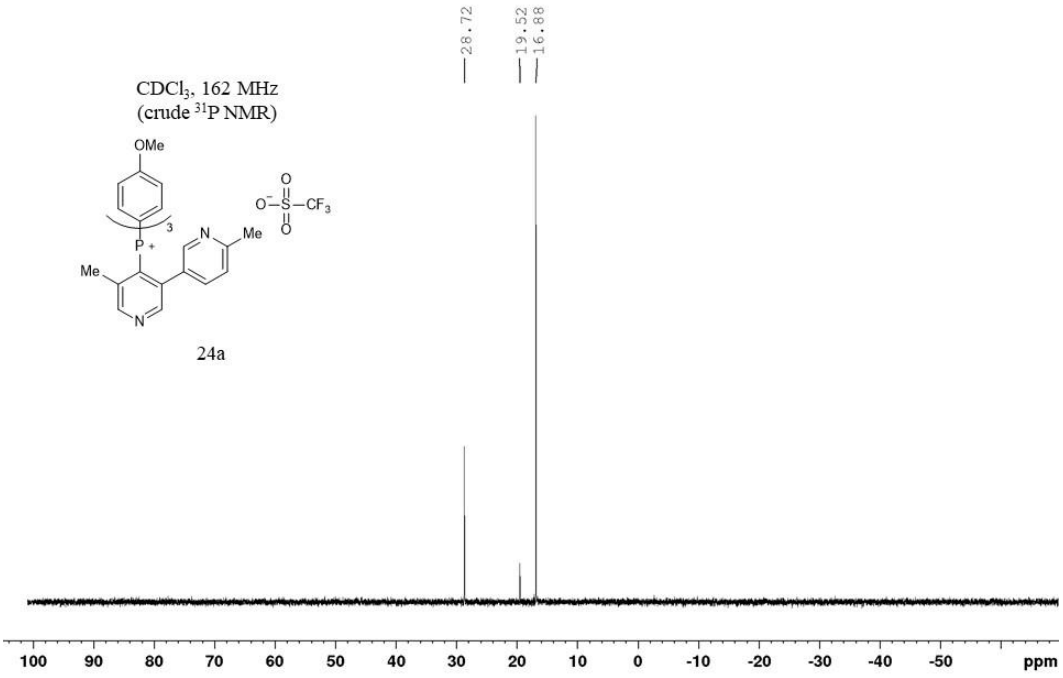


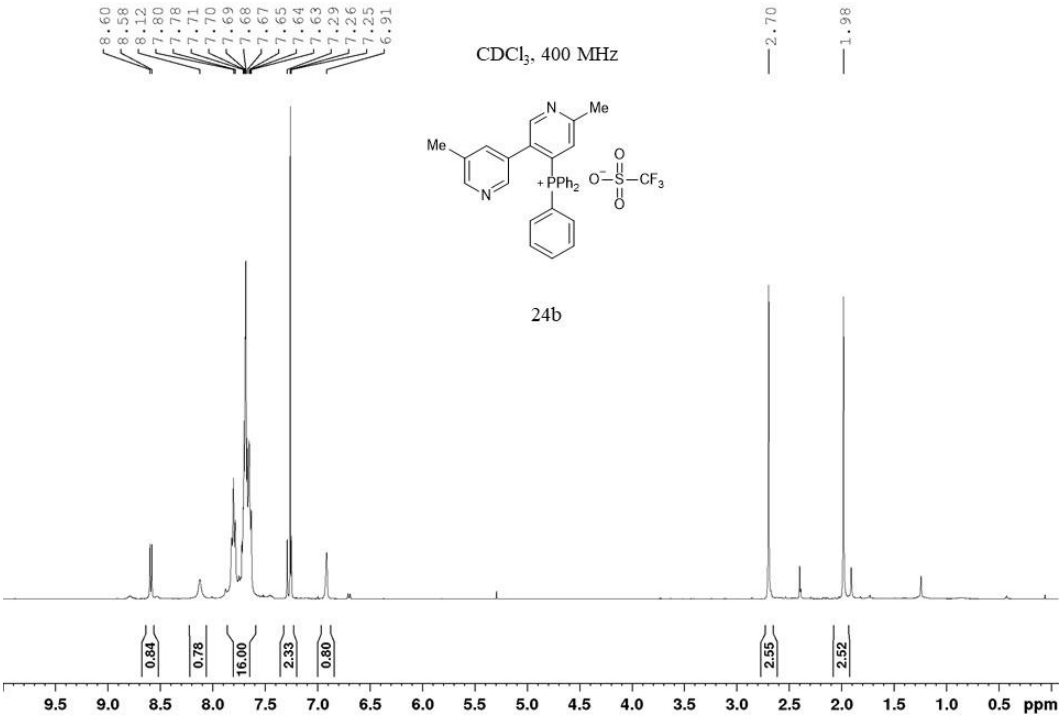
24a

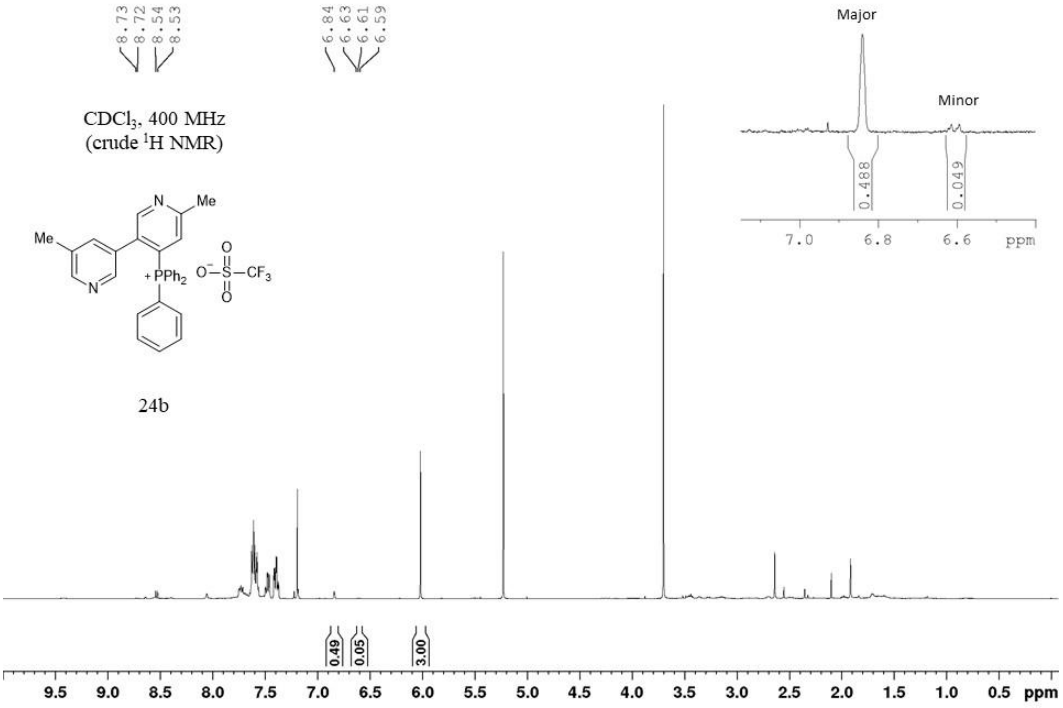
$CDCl_3$, 162 MHz

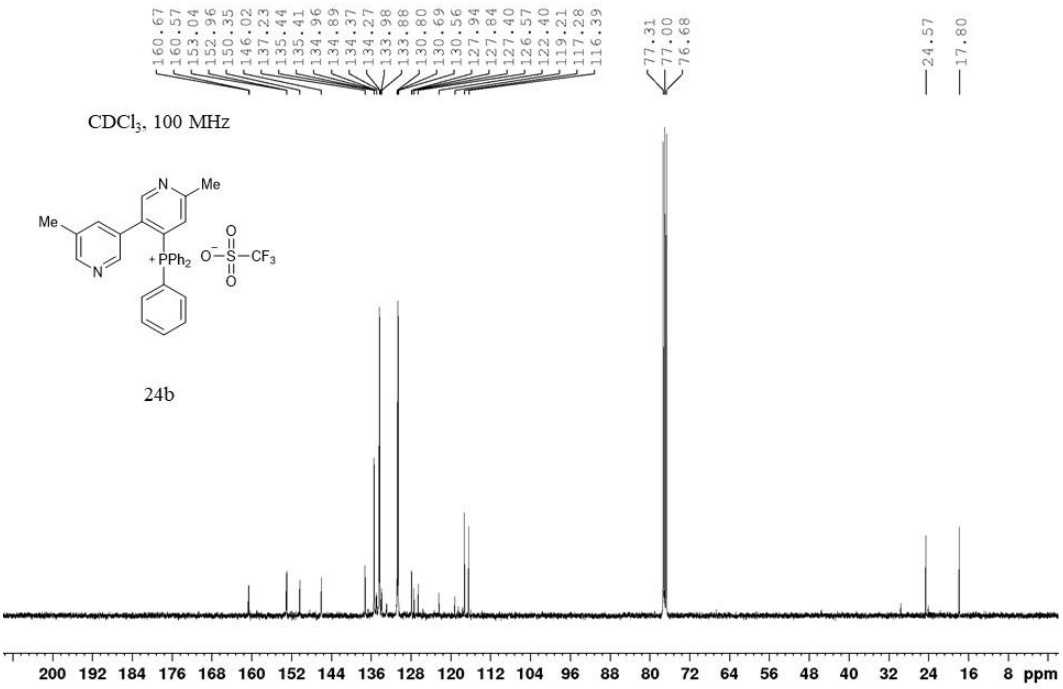


24a

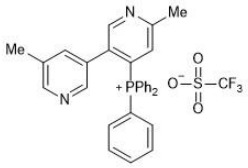

28.72
19.52
16.88
CDCl3, 162 MHz
(crude 31P NMR)
OMe
Me
Me
N
P +
3
O
O⁻S—CF3
O
24a
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm


8.60
8.58
8.12
7.80
7.78
7.71
7.70
7.69
7.68
7.67
7.65
7.64
7.63
7.29
7.26
7.25
6.91
CDCl3, 400 MHz
2.70
1.98
Me
N
Me
+PPh2
O⁻S—CF3
O
24b
0.84
0.78
16.00
2.33
0.80
2.55
2.52
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 ppm


8.73
8.72
8.54
8.53
6.84
6.63
6.61
6.59
CDCl3, 400 MHz
(crude 1H NMR)
Major
Minor
0.488
0.049
7.0
6.8
6.6
ppm
Me
N
Me
+PPh2
O
S
CF3
24b
0.49
0.05
3.00
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 ppm

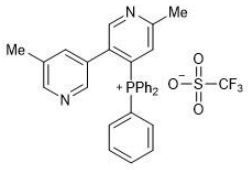

160.67
160.57
153.04
152.96
150.35
146.02
137.23
135.44
135.41
134.96
134.89
134.37
134.27
133.98
133.88
130.80
130.69
130.56
127.94
127.84
127.40
126.57
122.40
119.21
117.28
116.39
77.31
77.00
76.68
24.57
17.80
CDCl3, 100 MHz
Me
N
Me
+PPh2
O
S
CF3
24b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz

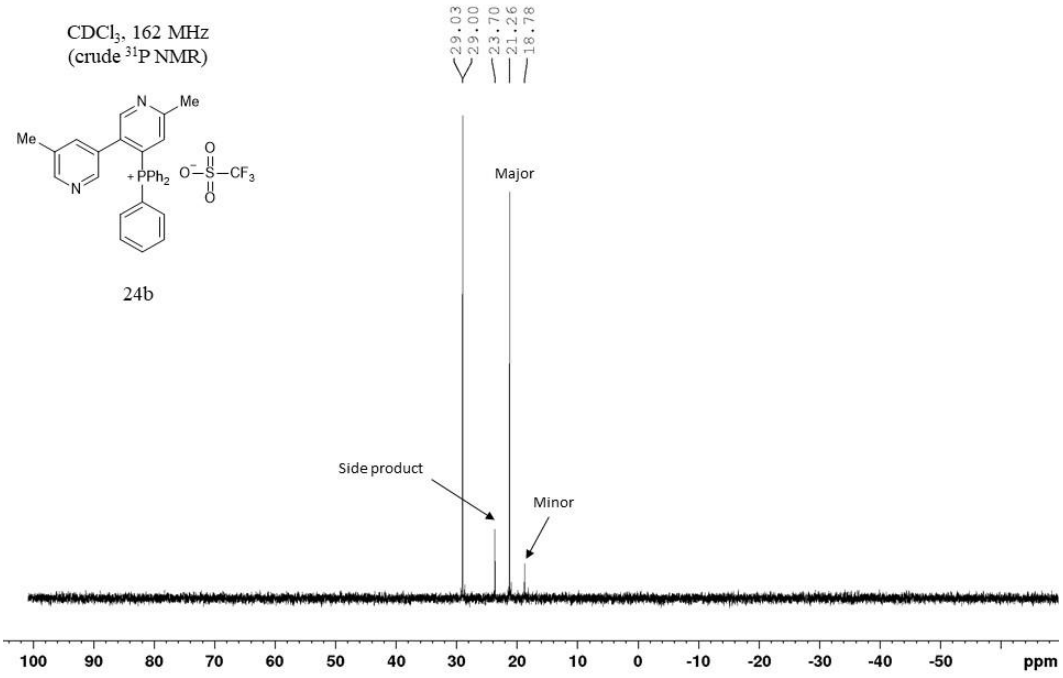


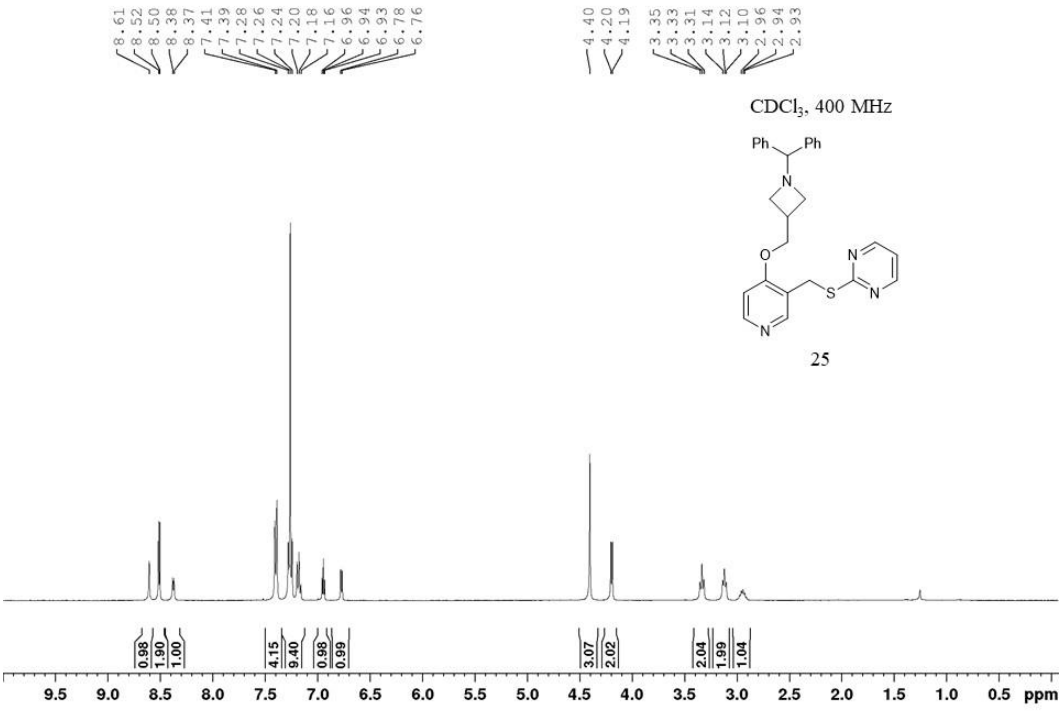
24b

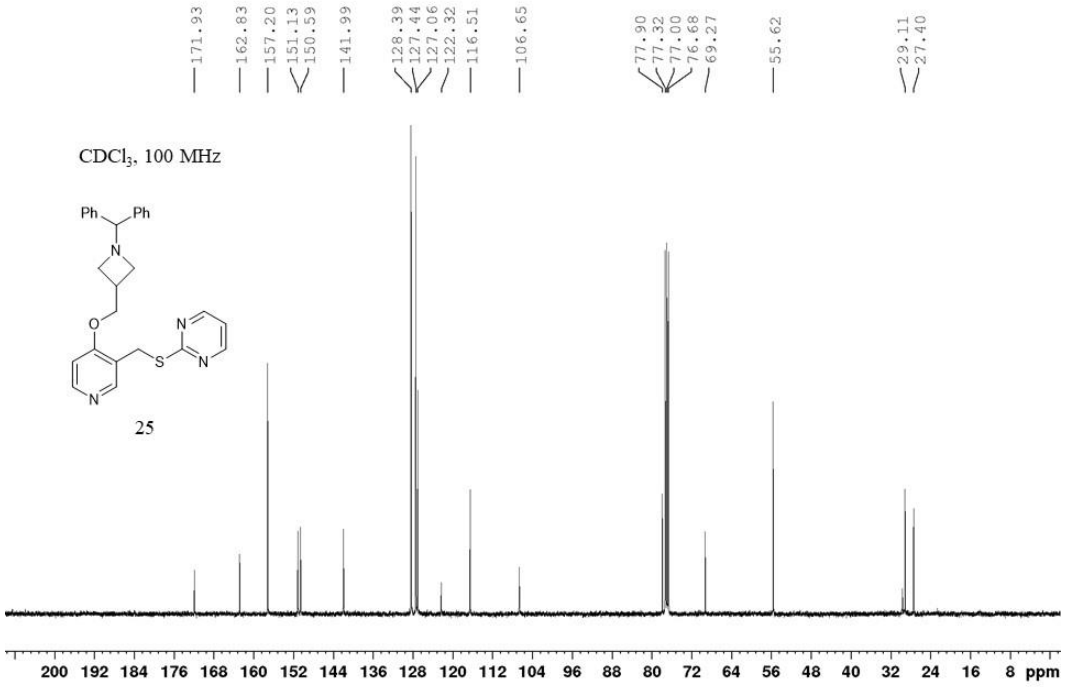
$CDCl_3$, 162 MHz



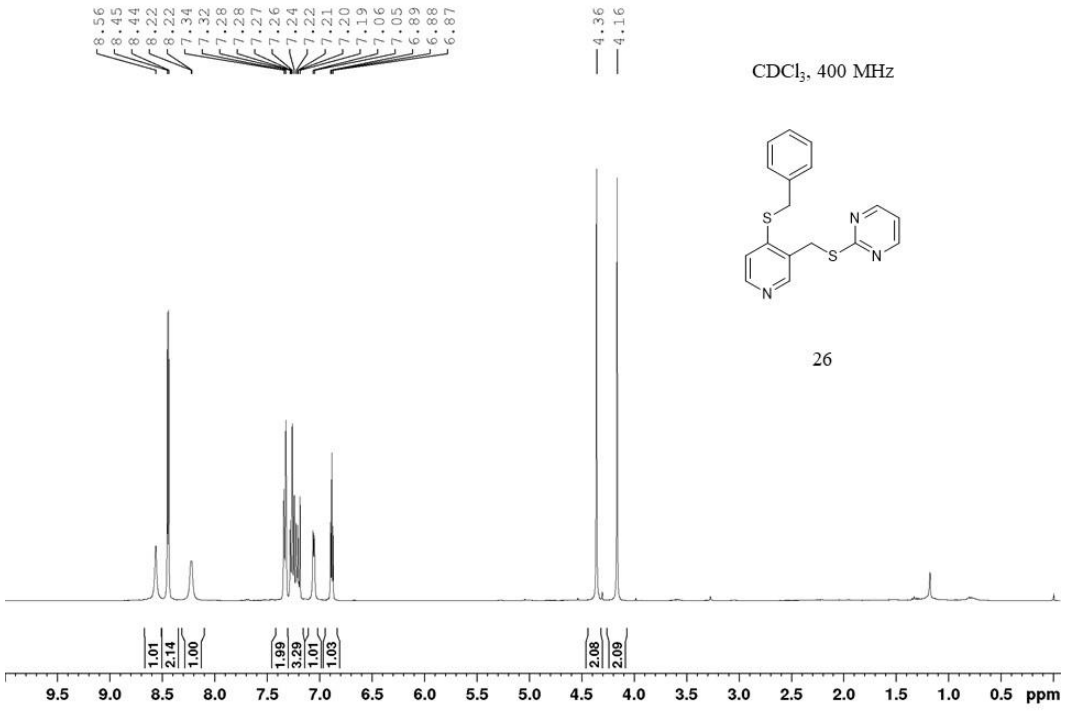
24b


CDCl3, 162 MHz
(crude 31P NMR)
29.03
29.00
23.70
21.26
18.78
Major
Side product
Minor
24b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

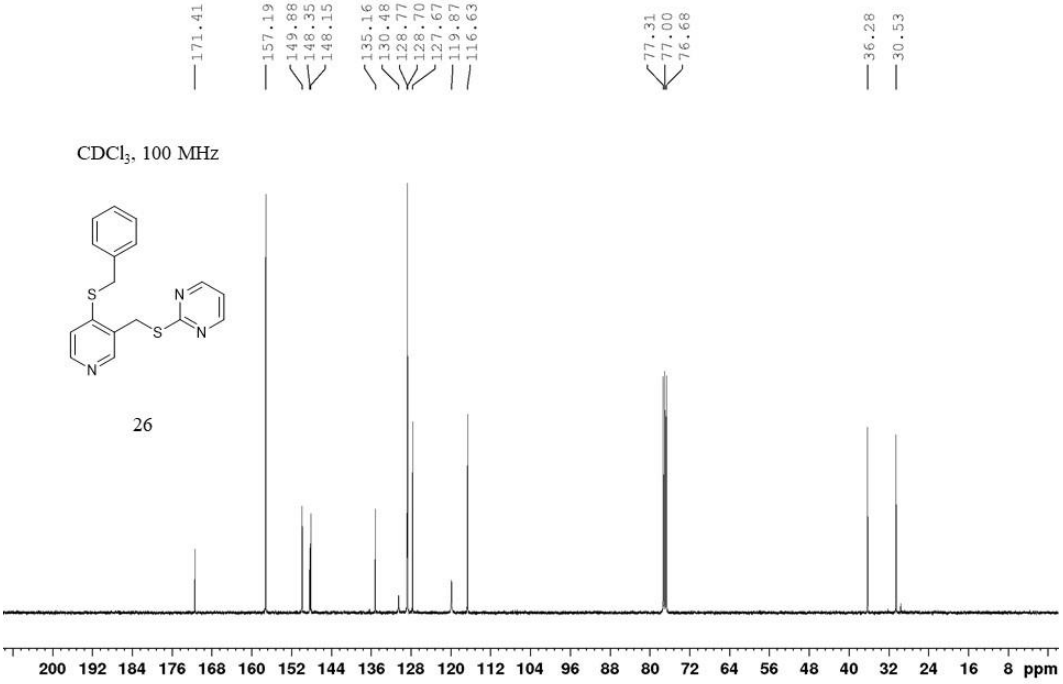

8.61
8.52
8.50
8.38
8.37
7.41
7.39
7.28
7.26
7.24
7.20
7.18
7.16
6.96
6.94
6.93
6.78
6.76
4.40
4.20
4.19
3.35
3.33
3.31
3.14
3.12
3.10
2.96
2.94
2.93
CDCl3, 400 MHz
25
0.98
1.90
1.00
4.15
9.40
0.98
0.99
3.07
2.02
2.04
1.99
1.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


171.93
162.83
157.20
151.13
150.59
141.99
128.39
127.44
127.06
122.32
116.51
106.65
77.90
77.32
77.00
76.68
69.27
55.62
29.11
27.40
CDCl3, 100 MHz
Ph
Ph
N
O
N
S
N
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 ppm

25

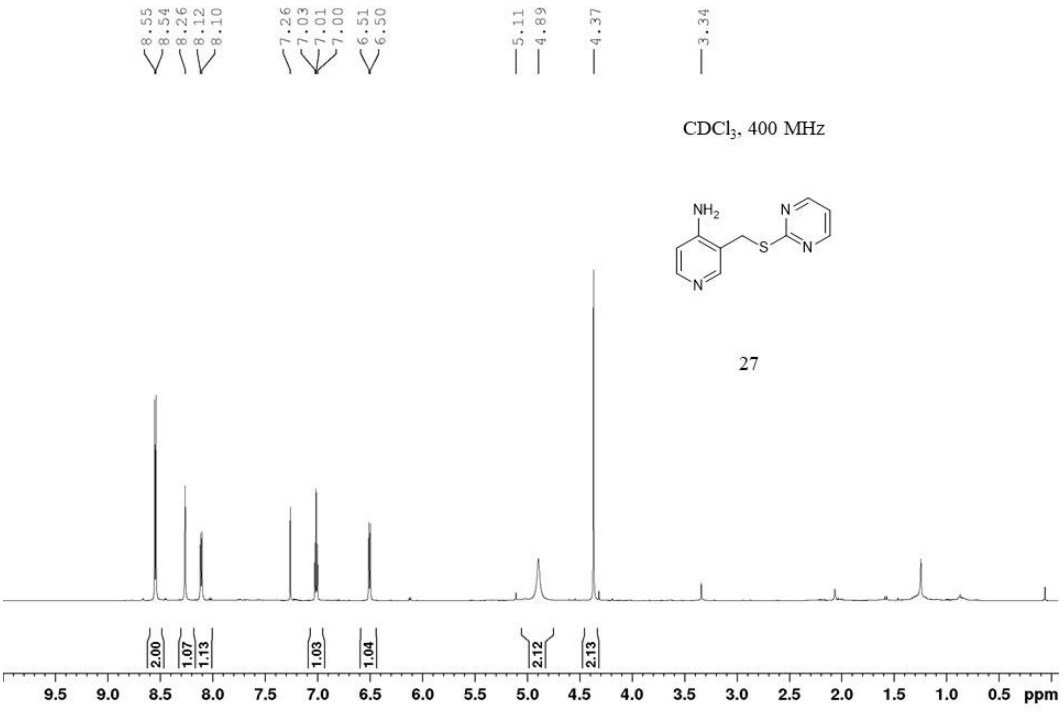

8.56
8.45
8.44
8.22
8.22
7.34
7.32
7.28
7.28
7.27
7.26
7.24
7.22
7.21
7.20
7.19
7.06
7.05
6.89
6.88
6.87
4.36
4.16
CDCl3, 400 MHz
S
N
S
N
N
1.01
2.14
1.00
1.99
3.29
1.01
1.03
2.08
2.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

26



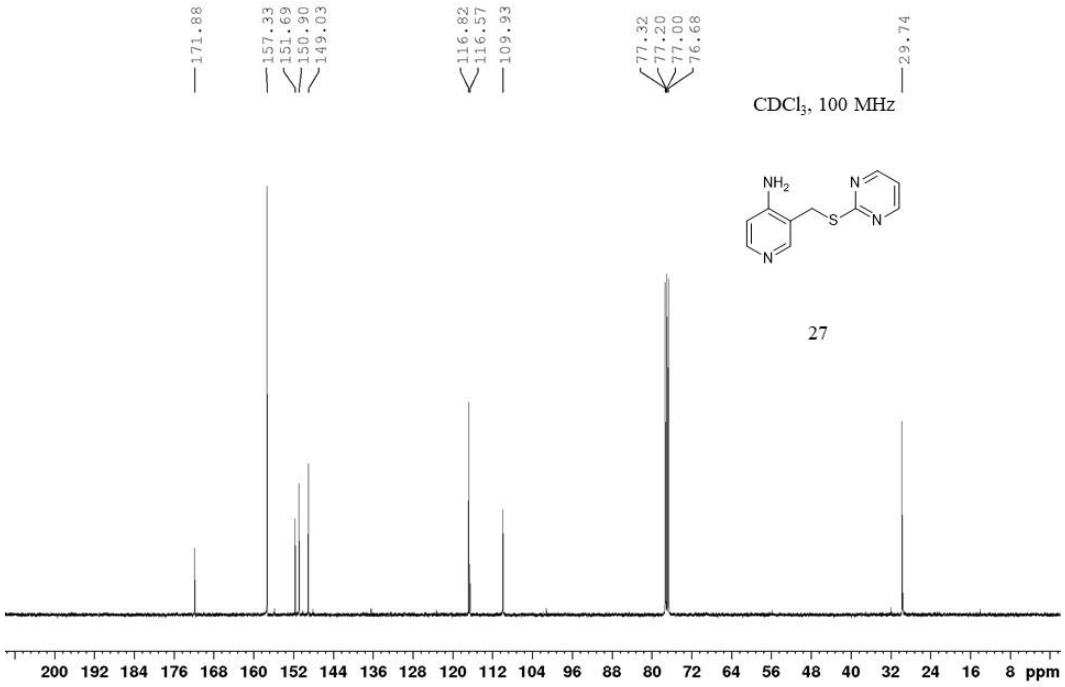
$CDCl_3$, 100 MHz

26

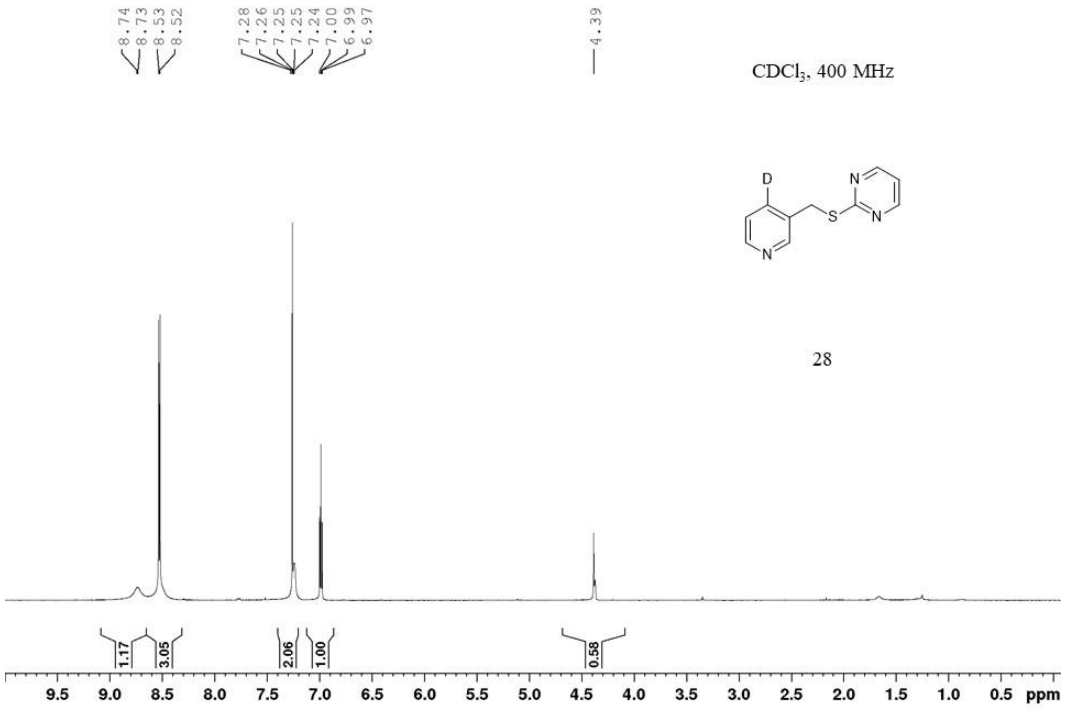


$CDCl_3$, 400 MHz

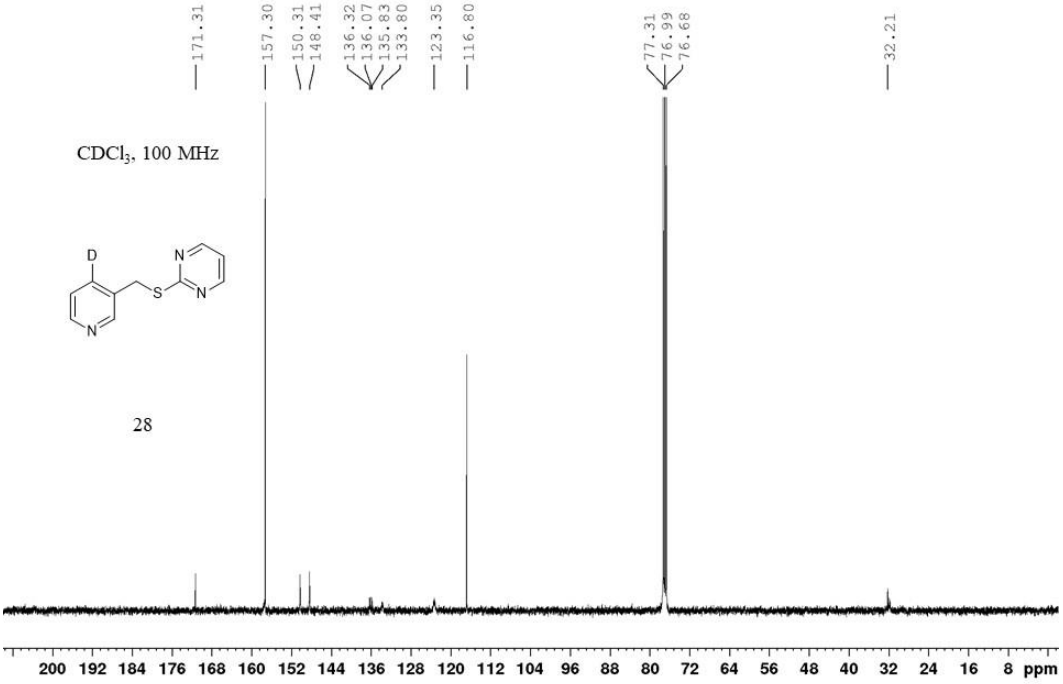
27


171.88
157.33
151.69
150.90
149.03
116.82
116.57
109.93
77.32
77.20
77.00
76.68
29.74
CDCl3, 100 MHz
NH2
N
S
N
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 ppm

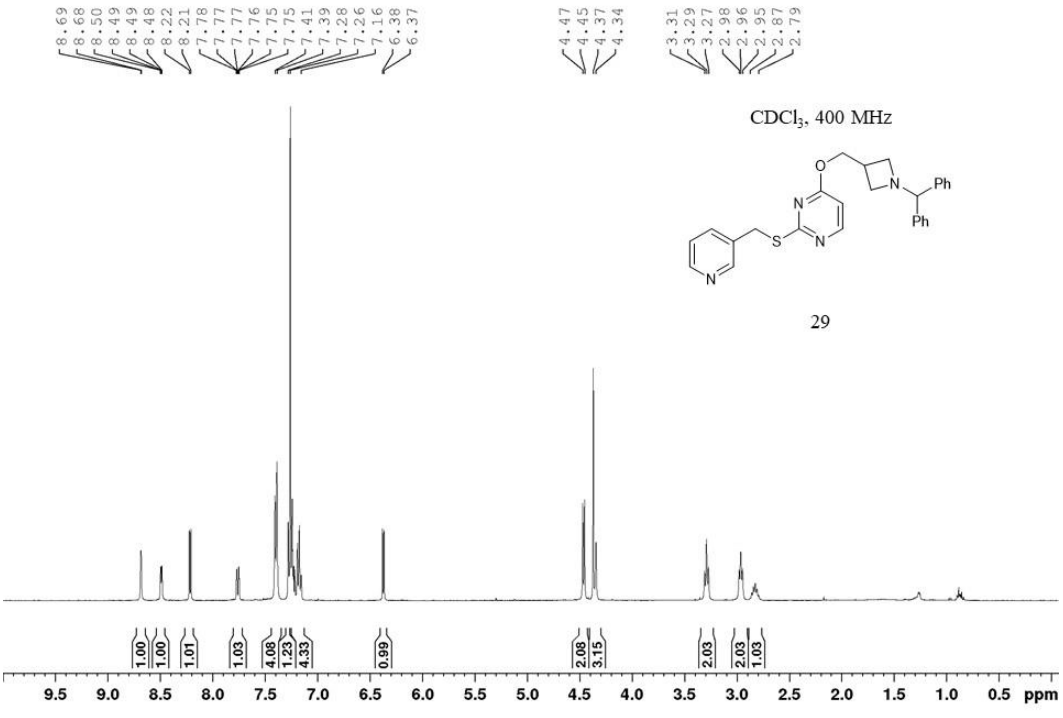
27


8.74
8.73
8.53
8.52
7.28
7.26
7.25
7.25
7.24
7.00
6.99
6.97
4.39
CDCl3, 400 MHz
D
N
S
N
N
1.17
3.05
2.06
1.00
0.58
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 ppm

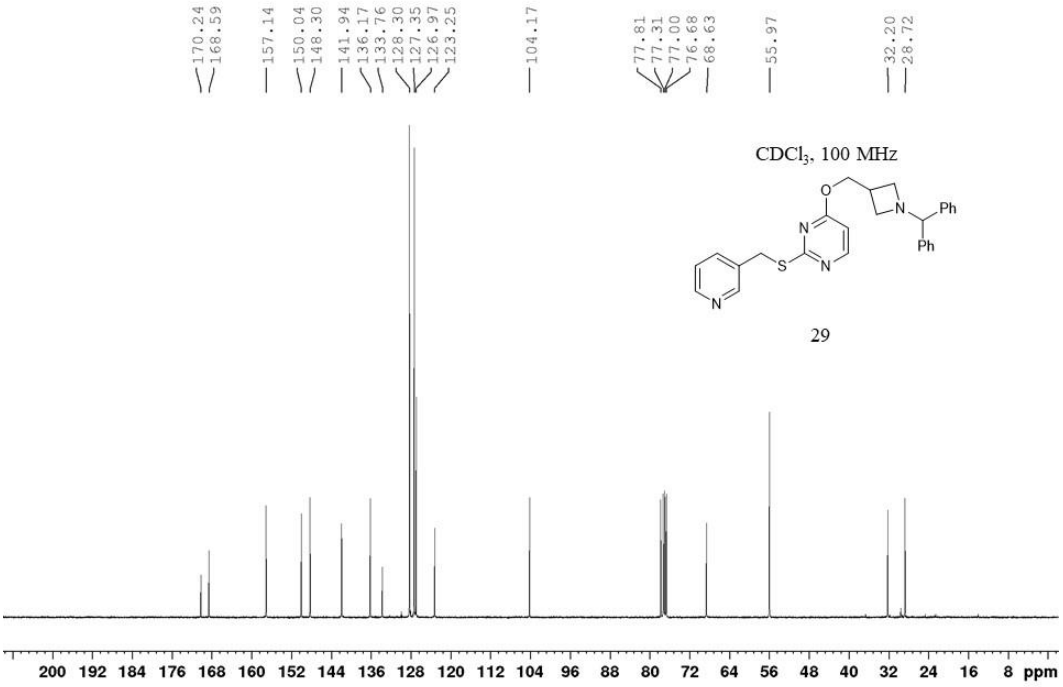
28


171.31
157.30
150.31
148.41
136.32
136.07
135.83
133.80
123.35
116.80
77.31
76.99
76.68
32.21
CDCl3, 100 MHz
D
N
S
N
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 ppm

28

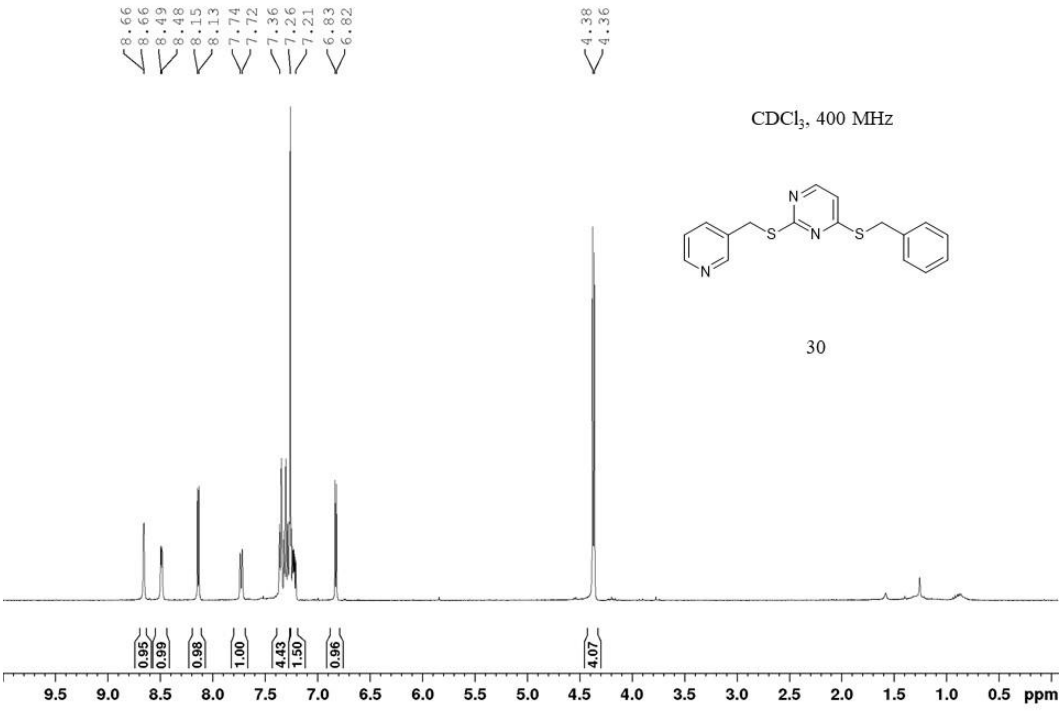

8.69
8.68
8.50
8.49
8.49
8.48
8.22
8.21
7.78
7.77
7.77
7.76
7.75
7.75
7.41
7.39
7.28
7.26
7.16
6.38
6.37
4.47
4.45
4.37
4.34
3.31
3.29
3.27
2.98
2.96
2.95
2.87
2.79
CDCl3, 400 MHz
O
N
N
Ph
Ph
S
N
N
1.00
1.00
1.01
1.03
4.08
1.23
4.33
0.99
2.08
3.15
2.03
2.03
1.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

29



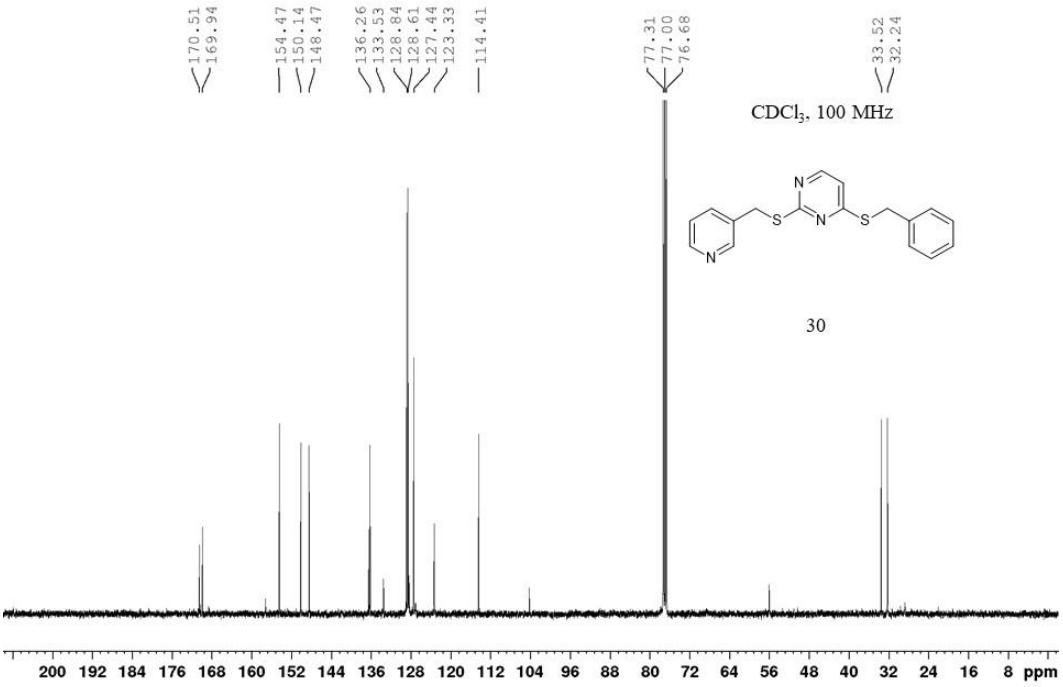
$CDCl_3$, 100 MHz

29

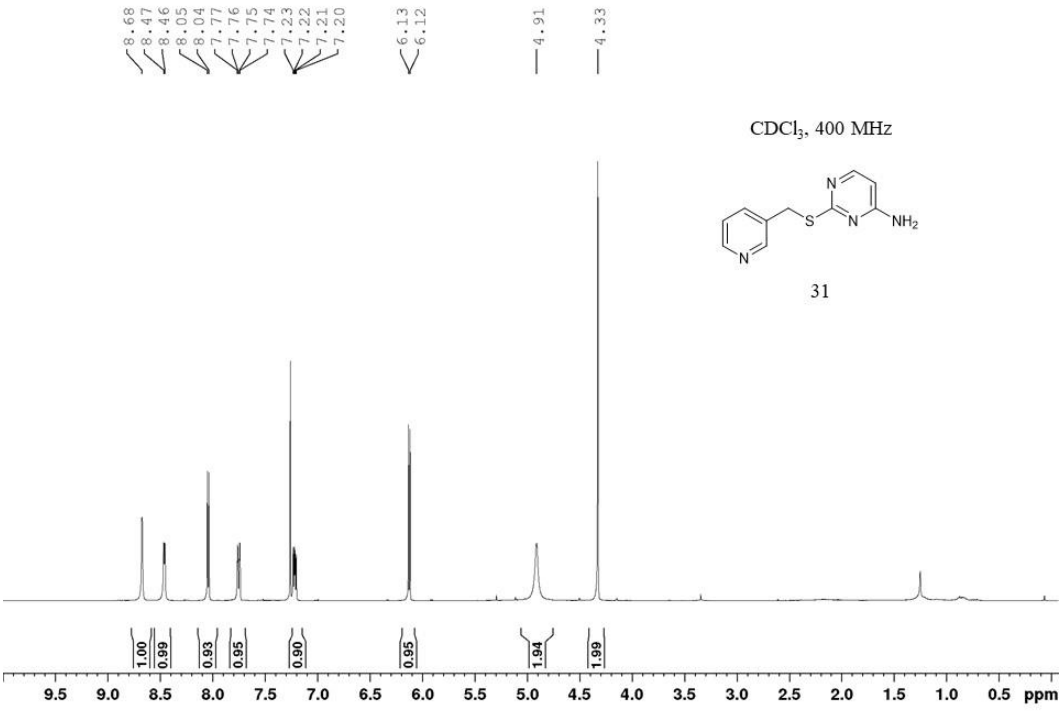


$CDCl_3$, 400 MHz

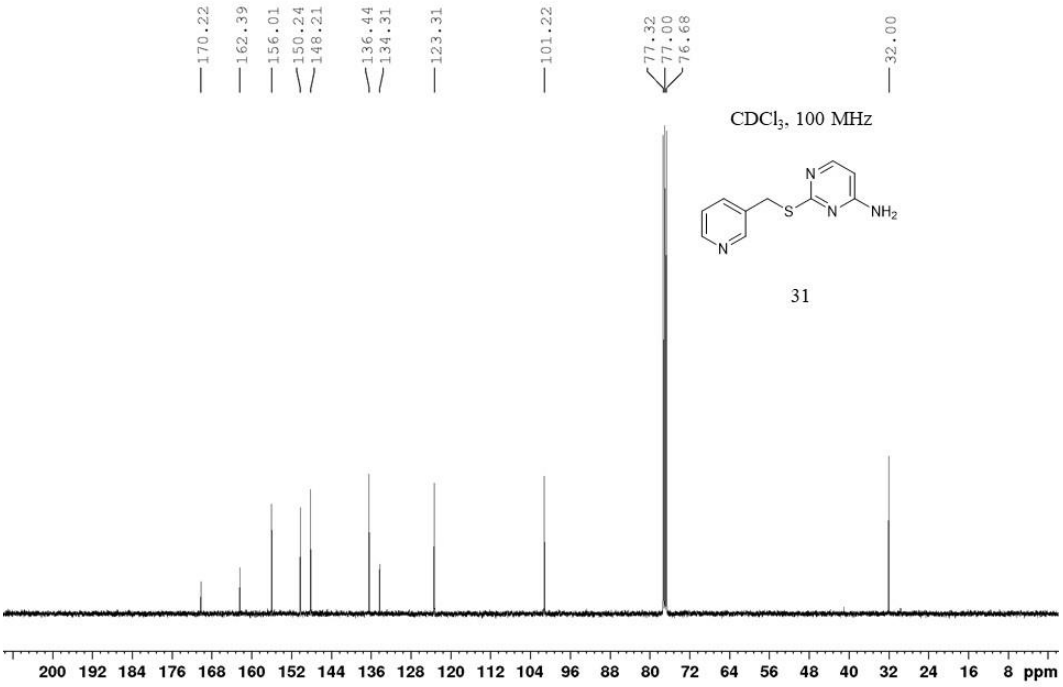
30


170.51
169.94
154.47
150.14
148.47
136.26
133.53
128.84
128.61
127.44
123.33
114.41
77.31
77.00
76.68
33.52
32.24
CDCl3, 100 MHz
N
S
N
S
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 ppm

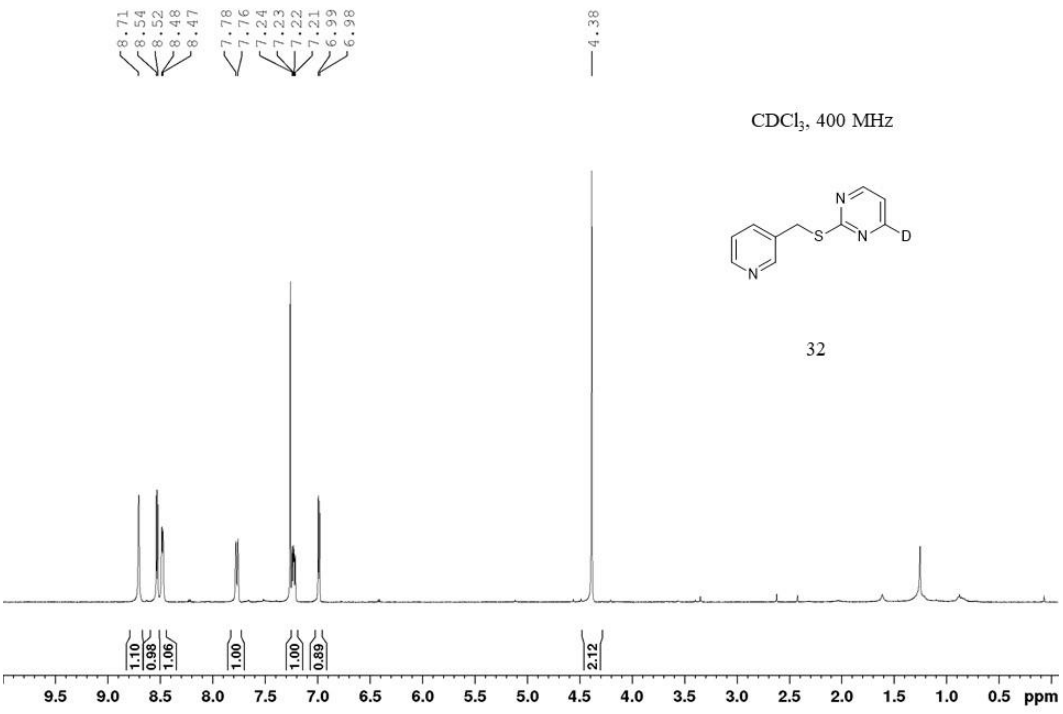
30


8.68
8.47
8.46
8.05
8.04
7.77
7.76
7.75
7.74
7.23
7.22
7.21
7.20
6.13
6.12
4.91
4.33
CDCl3, 400 MHz
N
S
N
NH2
N
1.00
0.99
0.93
0.95
0.90
0.95
1.94
1.99
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 ppm

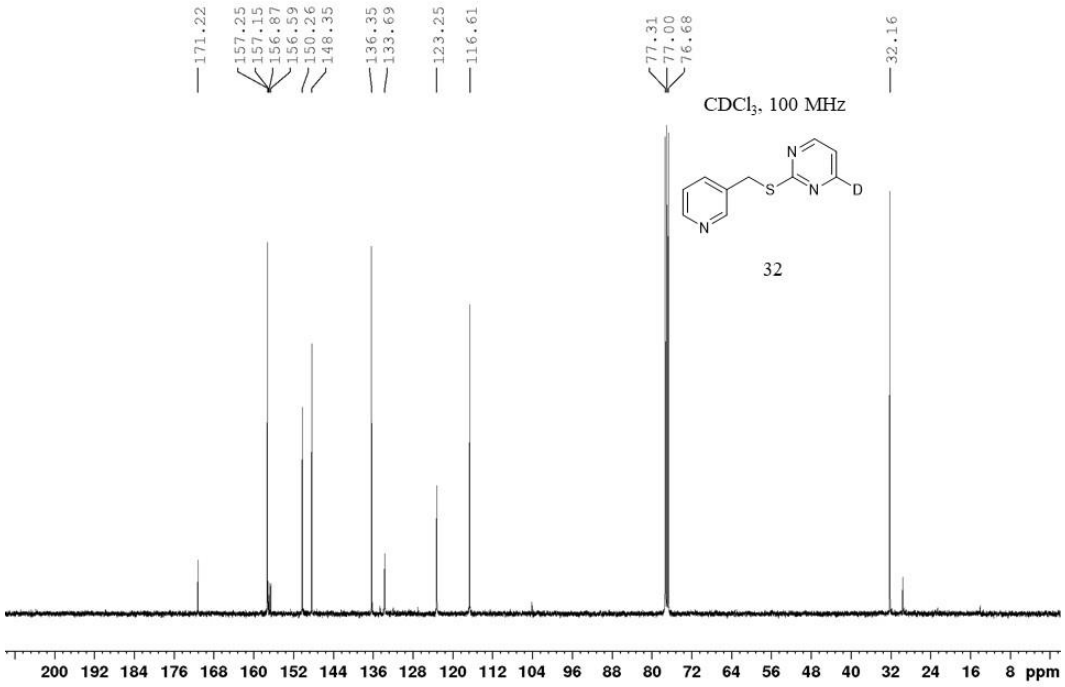
31


170.22
162.39
156.01
150.24
148.21
136.44
134.31
123.31
101.22
77.32
77.00
76.68
32.00
CDCl3, 100 MHz
N
S
N
NH2
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 ppm

31


8.71
8.54
8.52
8.48
8.47
7.78
7.76
7.24
7.23
7.22
7.21
6.99
6.98
4.38
CDCl3, 400 MHz
N
S
N
D
N
1.10
0.98
1.06
1.00
1.00
0.89
2.12
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 ppm

32


171.22
157.25
157.15
156.87
156.59
150.26
148.35
136.35
133.69
123.25
116.61
77.31
77.00
76.68
32.16
CDCl3, 100 MHz
N
S
N
D
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 ppm

32

Appendix Two

4-SELECTIVE PYRIDINE ALKYLATION VIA WITTIG OLEFINATION OF DEAROMATIZED PYRIDYL PHOSPHONIUM YLIDES

A 2.1. General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR (400 MHz) spectrometer or an Agilent Inova 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), $(CD_3)_2SO$ (2.50 ppm), CD_3OD (3.31 ppm) or CD_3CN (1.94 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR spectrometer (100 MHz) or an Agilent Inova 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in $CDCl_3$ (77.16 ppm), C_6D_6 (128.06 ppm), $(CD_3)_2SO$ (39.51 ppm), CD_3OD (49.00 ppm) or CD_3CN (1.32

ppm). 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 glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Silicycle silica gel (230–400 mesh) under a positive pressure of air. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or basic potassium permanganate solutions as appropriate.

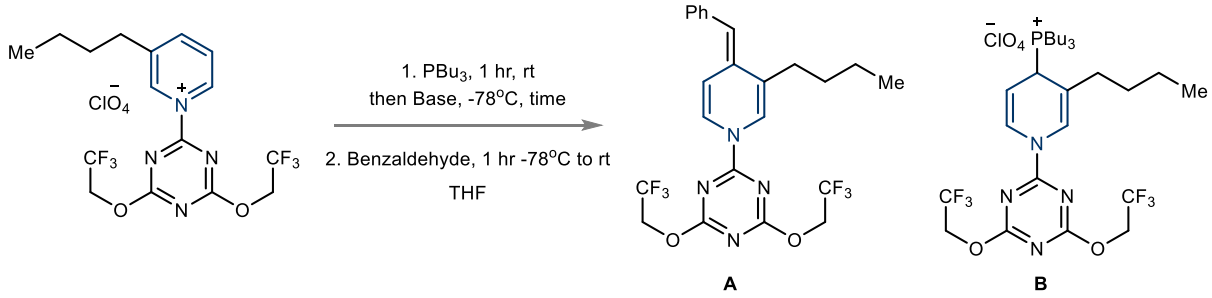
Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] Ethyl acetate (EtOAc), 1,2–Dichloroethane (DCE), 1,4–dioxane, chloroform, chlorobenzene and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents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

Methyl lithium (1.6 M sol in diethyl ether) was purchased from Acros Organics and stored in a -20^{o}C refrigerator. (2,2,2)-Trifluoroethanol (TFE) was purchased from Oakwood Chemicals and used without further purification. Cyanuric Chloride was purchased from TCI chemical company and used without further purification and stored in a –20 ^{o}C refrigerator. KPF_6 (>99%) was purchased from Sigma Aldrich chemical company and used without further purification and was stored in the glove box, but routinely small portions were taken out and stored in a desiccator.

A 2.2. Optimization Studies

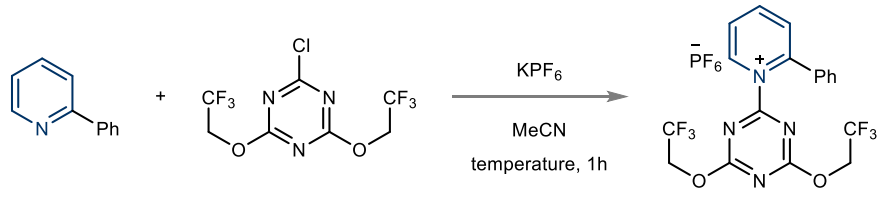
Table 1. Base Optimization[a]



Entry	Base	Starting Material	A	B
1.	KHMDS (1 hr)	5	42	0
2.	KHMDS (30 min)	4	66	0
3.	NaHMDS (30 min)	0	42	0
4.	LiHMDS (30 min)	6	66	0
5.	LDA (1hr)	5	37	38
6.	PhLi (1 hr)	2	75	0
7.	BuLi (1 hr)	2	77	3
8.	MeLi (1 hr)	2	81	0
9.	**MeLi (15 min)**	**2**	**81**	**6**

(a) Reactions were run with 0.1 mmol pyridinium, 0.11 mmol PBu_3, 0.11 mmol base, and 0.14 mmol benzaldehyde. After stirring for one hour at room temperature following the aldehyde addition, the reactions were concentrated down and analyzed by ^{1}HNMR using triphenylmethane as internal standard.

Table 2. Pyridinium Optimization on 2-Phenyl Pyridine- Concentration and Temp study[a]

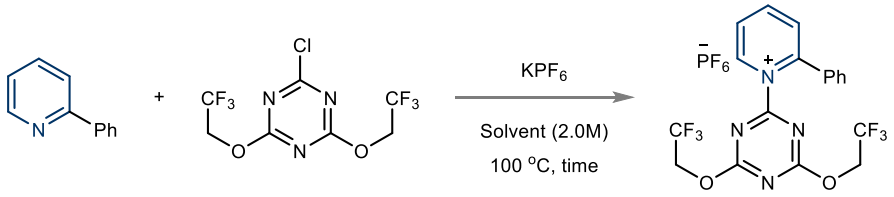


A

Entry	Concentration	Tempertaure (°C)	B
1.	1.0 M	40	0
2.	1.5 M	40	0
3.	2.0 M	40	0
4.	1.0 M	60	0
5.	1.5 M	60	0
6.	2.0 M	60	0
7.	1.0 M	80	2
8.	1.5 M	80	2
9.	2.0 M	80	3
10.	1.0 M	100	16
11.	1.5 M	100	20
12.	2.0 M	100	24

(a) Reactions were run with 0.3 mmol pyridine, 0.33 triazine, 0.33 KPF_6. After stirring for one hour at the designated temperature, the reactions were cooled to room temperature, diluted with MeCN-d_3 and analyzed by ^1H NMR using triphenylmethane as internal standard.

Table 3. Pyridinium Optimization on 2-Phenyl Pyridine- Time Study[a]

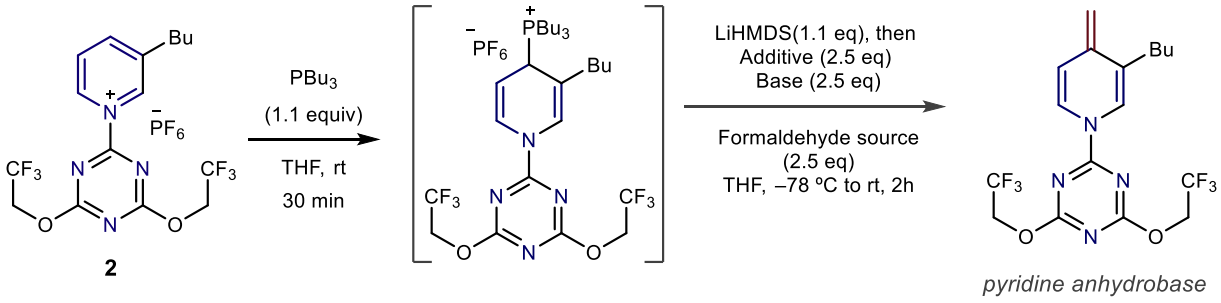


A

Entry	Solvent	Time	A
1.	MeCN	1 h	24
2.	MeCN	4 h	53
3.	**MeCN**	**6 h**	**64**
4.	MeCN	18 h	60
5.	BuCN (1.0 M)	1 h	7
6.	BuCN (2.0 M)	1 h	11

(a) Reactions were run with 0.3 mmol pyridine, 0.33 triazine, 0.33 KPF_6. After stirring for one hour at the designated temperature, the reactions were cooled to room temperature, diluted with MeCN-d_3 and analyzed by ^{1}H NMR using triphenylmethane as internal standard.

Table 4. Optimization of the methylation protocol [a,b]

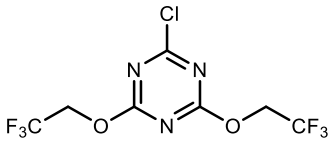


Entry	Formaldehyde Source	Base	Additive	% Yield
1	paraformaldehyde	MeLi	-	11
2	1-(hydroxymethyl)benzotriazole	MeLi	-	54
3	1-(hydroxymethyl)benzotriazole	LiHMDS	-	61
4	1-(hydroxymethyl)benzotriazole	LiHMDS	HMPA	73
5	1-(hydroxymethyl)benzotriazole	LiHMDS	DMPU	68
6	1-(hydroxymethyl)benzotriazole	LiHMDS	DMEDA	0
7	**1-(hydroxymethyl)benzotriazole**	**LiHMDS**	**TMEDA**	**84**

a) Reactions were run with 0.1 mmol pyridinium, 0.11 mmol PBu_3, 0.11 mmol MeLi, and 0.25 mmol formaldehyde source, 0.25 mmol additive, and 0.25 mmol LiHMDS. After stirring for two hours at room temperature following the aldehyde addition, the reactions were concentrated down and analyzed by ^{1}HNMR using triphenylmethane as internal standard. B) Additive screen was tested before MeLi was found to be optimal base for ylide generation, therefore the study was conducted with LiHMDS to form the ylide.

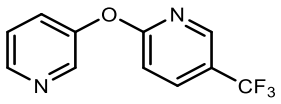
A 2.3. Preparation of Starting Materials

2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine



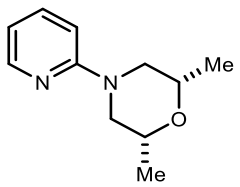
An oven-dried 500 mL round bottom flask equipped with a stir bar was charged with sodium hydride (60% dispersion in mineral oil, 4.40 g, 110 mmol) and subjected to three vacuum/nitrogen backfills before adding THF (62.5 mL). In a separate oven-dried 500 mL charged with cyanuric chloride (9.22 g, 50 mmol) and subjected to three vacuum/nitrogen backfills before adding THF (62.5 mL). The cyanuric chloride solution was transferred to the sodium hydride via cannula. The solution was then cooled to 0 °C. trifluoroethanol (8.0 mL, 110 mmol) was added dropwise over 1 hour. Two needles were inserted to the septum to vent the generated gas. The reaction was left to stir overnight as the 0 °C ice bath was allowed to slowly warm to room temperature. The reaction was then quenched with water at 0 °C, and the aqueous layer was extracted with ethyl acetate (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 column chromatography (silica gel: 4% EtOAc in hexanes) affording the title compound as a colorless oil (7.0 g, 22.4 mmol, 45% yield). IR ν_{max}/cm^{-1} (film): 2977, 1545, 1377, 1261, 1161, 1120, 1072, 958, 814, 611; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.85 (q, *J* = 8.0 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.84, 171.45, 122.41 (q, *J* = 277.5 Hz), 64.66 (q, *J* = 37.5 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -73.67 (t, *J* = 8.0 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 193.2, $C_{11}H_{17}N_2O^+$ requires 193.1.

2-(pyridin-3-yloxy)-5-(trifluoromethyl)pyridine (1h)



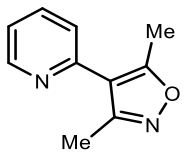
An oven-dried 25 mL shlenk flask equippied with a stir bar was charged with potassium carbonate (1.45 g, 10.5 mmol) and subjected to 3 vacuum/nitrogen backfills. A solution of 3-hydroxypyridine (630 mg, 6.6 mmol) in DMF (12.5 mL) was added dropwise and stirred for 30 minutes. Then a solution of 2-chloro-5-(trifluoromethyl)pyridine (1.09 g, 6.0 mmol) in DMF (12.5 mL) was added and the reaction was heated to 100 °C overnight. The heating bath was then removed, and the reaction was quenched with water. The aqueous layer was then 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 column chromatography under the stated conditions to provide the title compound. Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a yellow oil (1.25 g, 5.2 mmol, 87% yield). IR ν_{max}/cm^{-1} (film): 2985, 2906, 1609, 1576, 1473, 1325, 1259, 1152, 1076, 832; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.58 – 8.47 (m, 2H), 8.48 – 8.38 (m, 1H), 7.94 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.54 (ddd, *J* = 8.4, 2.8, 1.4 Hz, 1H), 7.38 (dd, *J* = 8.3, 4.7 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 165.09 (d, *J* = 1.5 Hz), 149.81, 146.62, 145.33 (q, *J* = 4.4 Hz), 143.92, 137.14 (q, *J* = 3.2 Hz), 129.23, 124.17, 123.68 (q, *J* = 271.5 Hz), 122.38 (q, *J* = 33.4 Hz), 111.80; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -61.77; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 241.2, $C_{11}H_8F_3N_2O^+$ requires 241.1.

(2R,6S)-2,6-dimethyl-4-(pyridin-2-yl)morpholine (1j)



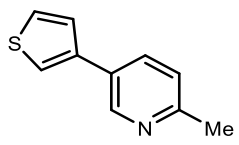
An oven-dried 50 mL round bottom flask equipped with a stir bar was subjected to three vacuum/nitrogen backfills before adding THF (20 mL) and (2R,6S)-2,6-dimethylmorpholine (1.2 mL, 9.6 mmol). The flask was cool to -78 ºC and Butyl lithium (3.9 mL, 2.5 M) was added dropwise over 15 minutes and stirred for an additional 30 minutes. Then 2-fluoropyridine (0.69 mL, 8.0 mmol) was added dropwise and the cooling bath was removed. The reaction was heated to 60 ºC for 4 hours. The heating bath was removed and the reaction was quenched with water at room temperature. The aqueous layer was extracted with ethyl acetate (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 column chromatography under the stated conditions to provide the heterocycle. Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the title compound as a yellow oil (1.52 g, 7.9 mmol, 99% yield). IR ν_{max}/cm^{-1} (film): 1727, 1679, 1590, 1479, 1437, 1248, 1086, 769, 729; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.23 – 8.17 (m, 1H), 7.48 (ddd, *J* = 9.0, 7.5, 2.0 Hz, 1H), 6.64-6.61 (m, 2H), 4.03 (dd, *J* = 13.2, 2.2 Hz, 2H), 3.71 (dtd, *J* = 12.6, 6.3, 2.5 Hz, 2H), 2.51 (dd, *J* = 12.6, 10.5 Hz, 2H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 159.38, 148.04, 137.64, 113.62, 107.14, 71.71, 50.94, 19.12; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 193.2, $C_{11}H_{17}N_2O^+$ requires 193.1.

3,5-dimethyl-4-(pyridin-2-yl)isoxazole (1k)



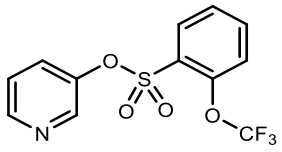
An oven-dried 100 mL pressure tube equipped with a stir bar was charged with 2-bromopyridine (0.78 mL, 8.0 mmol), (3,5-dimethylisoxazol-4-yl)boronic acid (1.24 g, 8.8 mmol), $Pd_{2(}dba)_3$ (147 mg, 0.16 mmol), PCy_3 (107 mg, 0.38 mmol), and K_3PO_4 (2.82 g, 13.6 mmol). The pressure tube was capped with a septum and subjected to three rapid vacuum/nitrogen backfills before adding degassed 1,4-Dioxane (22 mL) and degassed water (11 mL). The septum was replaced with the correct screw cap and the reaction was heated to 100 ^oC overnight. The heating bath was then removed, and the reaction was quenched with water 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 column chromatography to provide the title compound. Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a yellow oil (1.11 g, 6.4 mmol, 80% yield). IR ν_{max}/cm^{-1} (film): 1727, 1679, 1590, 1479, 1437, 1248, 1086, 769, 729; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.68 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.74 (td, *J* = 7.7, 1.9 Hz, 1H), 7.32 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.22 (ddd, *J* = 7.6, 4.9, 1.1 Hz, 1H), 2.57 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 167.48, 158.80, 150.92, 150.03, 136.59, 123.02, 121.85, 116.21, 12.45, 11.57; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 175.2, $C_{10}H_{11}N_2O^+$ requires 175.1.

2-methyl-5-(thiophen-3-yl)pyridine (1m)



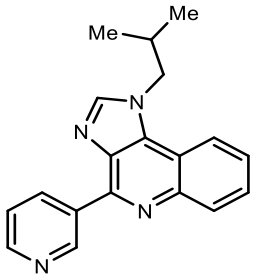
An oven-dried 300 mL round bottom flask equipped with a stir bar was charged with 5-bromo-2-methylpyridine (1.72 g, 10.0 mmol), thiophen-3-ylboronic acid (1.43 g, 11.5 mmol), and $Pd(PPh_3)_4$ (690 mg, 0.60 mmol). The flask was subjected to three rapid vacuum/nitrogen backfills before adding degassed toluene (60 mL), degassed ethanol (60 mL), and a 2 M solution of aqueous sodium carbonate (11 mL). The septum was replaced with a condenser and the reaction was heated to 110 °C overnight. The heating bath was then removed, and the reaction was quenched with water 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 column chromatography to provide the title compound. Flash column chromatography (silica gel: 30% EtOAc in hexanes) afforded the title compound as a brown solide (0.94 g, 5.4 mmol, 54% yield). mp 43-48 °C; IR ν_{max}/cm^{-1} (film): 1727, 1679, 1590, 1479, 1437, 1248, 1086, 769, 729; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.75 (d, *J* = 2.4 Hz, 1H), 7.76 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.47 (dd, *J* = 2.9, 1.4 Hz, 1H), 7.43 (dd, *J* = 5.0, 2.9 Hz, 1H), 7.37 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.13, 147.08, 139.08, 134.10, 128.87, 126.93, 126.06, 123.32, 120.90, 24.28.; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 176.2, $C_{10}H_{10}NS^+$ requires 176.1.

pyridin-3-yl 2-(trifluoromethoxy)benzenesulfonate (1r)



An oven-dried 50 mL round bottom flask equipped with a stir bar was charged with 2-(trifluoromethoxy)benzenesulfonyl chloride (3.1 g, 12 mmol). The flask was subjected to three rapid vacuum/nitrogen backfills before adding CH_2Cl_2 (12.5 mL) and cooling to 0 °C. A solution of 3-hydroxypyridine (0.95 g, 10 mmol) in 12.5 mL CH_2Cl_2 was added dropwise over 5 minutes. Then Et_3N (2.8 mL, 20 mmol) was added dropwise over 5 minutes. The ice bath was removed and allowed to stir at room temperature. The reaction was monitored by thin layer chromatography and LCMS to determine when it was finished. The reaction was diluted with CH_2Cl_2 and quenched was water. The aqueous layer was extracted with CH_2Cl_2 (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 column chromatography to provide the title compound. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a yellow oil (3.0 g, 9.4 mmol, 94% yield). IR ν_{max}/cm^{-1} (film): 3120, 2960, 1601, 1598, 1478, 1390, 1161, 856, 733, 702; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.52 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.34 (d, *J* = 2.8 Hz, 1H), 7.94 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.82 – 7.65 (m, 1H), 7.65 – 7.49 (m, 2H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.32 (dd, *J* = 8.4, 4.7 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.61, 146.91 (q, *J* = 1.8 Hz), 146.26, 143.69, 136.70, 132.16, 129.96, 127.40, 126.84, 124.44, 120.83 (q, *J* = 2.0 Hz), 120.29 (q, *J* = 261.6 Hz).; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -56.38; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 320.1, $C_{12}H_9F_3NO_4S^+$ requires 320.0.

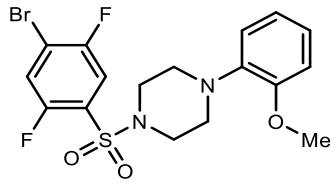
1-isobutyl-4-(pyridin-3-yl)-1H-imidazo[4,5-c]quinoline (3an)



An oven-dried 100 mL pressure tube equipped with a stir bar was charged with pyridin-3-ylboronic acid (1.08 g, 8.8 mmol), 4-chloro-1-isobutyl-1H-imidazo[4,5-c]quinoline (1.85 g, 8.0 mmol), $Pd_{2(}dba)_3$ (147 mg, 0.16 mmol), PCy_3 (107 mg, 0.38 mmol), and K_3PO_4 (2.82 g, 13.6 mmol). The pressure tube was capped with a septum and subjected to three rapid vacuum/nitrogen backfills before adding degassed 1,4-Dioxane (22 mL) and degassed water (11 mL). The septum was replaced with the correct screw cap and the reaction was heated to 100 °C overnight. The heating bath was then removed, and the reaction was quenched with water 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 column chromatography to provide the title compound. Flash column chromatography (silica gel: 2% MeOH in CH_2Cl_2) afforded the title compound as a yellow solid (2.03 g, 6.7 mmol, 84% yield). mp 98-103 °C; IR ν_{max}/cm^{-1} (film): 2943, 2856, 1592, 1520, 1357, 1099, 924, 752, 714, 638; ^1H NMR (400 MHz, Chloroform-*d*) δ 9.87 (d, *J* = 2.1 Hz, 1H), 9.00 (d, *J* = 8.0 Hz, 1H), 8.72 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.34 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.94 (s, 1H), 7.79 – 7.67 (m, 1H), 7.67 – 7.55 (m, 1H), 7.48 (dd, *J* = 8.0, 4.8 Hz, 1H), 4.37 (d, *J* = 7.3 Hz, 2H), 2.38 (dp, *J* = 13.7, 6.8 Hz, 1H), 1.04 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.10, 150.21, 149.22, 144.66, 143.92, 137.21, 136.62, 133.80, 133.66, 131.33, 127.55, 126.66, 123.25,

119.98, 117.78, 55.28, 28.85, 19.91; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 303.2, $C_{19}H_{19}N_4^+$ requires 303.2.

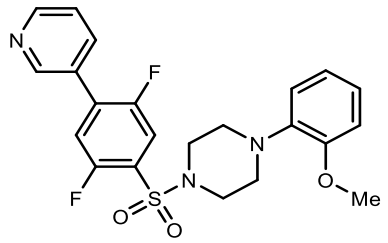
1-((4-bromo-2,5-difluorophenyl)sulfonyl)-4-(2-methoxyphenyl)piperazine (1ao-int)



An oven-dried 100 mL round bottom flask equipped with a stir bar was charged with 4-bromo-2,5-difluorobenzenesulfonyl chloride (3.5 g, 12 mmol). The flask was subjected to three rapid vacuum/nitrogen backfills before adding CH_2Cl_2 (12.5 mL) and cooling to 0 °C. A solution of 1-(2-methoxyphenyl)piperazine (1.92 g, 10 mmol) in 12.5 mL CH_2Cl_2 was added dropwise over 5 minutes. Then Et_3N (2.8 mL, 20 mmol) was added dropwise over 5 minutes. The ice bath was removed and allowed to stir at room temperature. The reaction was monitored by thin layer chromatography and LCMS to determine when it was finished. The reaction was diluted with CH_2Cl_2 and quenched was water. The aqueous layer was extracted with CH_2Cl_2 (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 column chromatography to provide the title compound. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a white crystalline solid (3.39 g, 7.6 mmol, 76% yield). mp 110-115 °C; IR ν_{max}/cm^{-1} (film): 3015, 2905, 2224, 1669, 1592, 1212, 1185, 1066, 815, 709; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.62 (dd, *J* = 7.4, 5.6 Hz, 1H), 7.49 (dd, *J* = 8.5, 5.1 Hz, 1H), 7.04 (ddd, *J* = 8.6, 6.7, 2.5 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.90 – 6.83 (m, 1H), 3.84 (s, 3H), 3.39 (t, *J* =

4.5 Hz, 4H), 3.21 – 3.04 (m, 4H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.12 (dd, *J* = 60.6, 3.1 Hz), 153.61 (dd, *J* = 67.8, 3.2 Hz), 152.26, 140.29, 125.62 (dd, *J* = 17.6, 5.5 Hz), 123.98, 122.63 (d, *J* = 27.4 Hz), 121.20, 118.69, 118.28 (dd, *J* = 27.3, 1.8 Hz), 115.53 (dd, *J* = 23.7, 9.4 Hz), 111.36, 55.53, 50.30, 46.28 (d, *J* = 1.9 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -108.94 – -109.92 (m), -110.94 (dt, *J* = 15.5, 7.1 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 447.1, $C_{17}H_{18}BrF_2N_2O_3S^+$ requires 447.0.

1-((2,5-difluoro-4-(pyridin-3-yl)phenyl)sulfonyl)-4-(2-methoxyphenyl)piperazine (1ao)

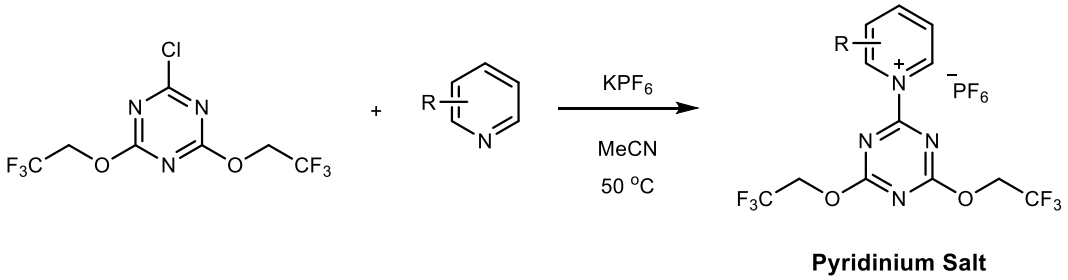


An oven-dried 100 mL pressure tube equipped with a stir bar was charged with pyridin-3-ylboronic acid (0.81 g, 6.6 mmol), 1-((4-bromo-2,5-difluorophenyl)sulfonyl)-4-(2-methoxyphenyl)piperazine (2.68 g, 6.0 mmol), $Pd(OAc)_2$ (67 mg, 0.30 mmol), and PPh_3 (315 mg, 1.20 mmol). The pressure tube was capped with a septum and subjected to three rapid vacuum/nitrogen backfills before adding degassed Dimethoxyethane (30 mL) and a 1 M aqueous solution of potassium carbonate (12 mL). The septum was replaced with the correct screw cap and the reaction was heated to 100 °C overnight. The heating bath was then removed and the reaction was quenched with water 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 column chromatography to provide the title compound.

Flash column chromatography (silica gel: 60% EtOAc in hexanes) afforded the title compound as a gray crystalline solid (2.33 g, 5.2 mmol, 87% yield). mp 109-113 °C; IR ν_{max}/cm^{-1} (film): 3055, 2991, 2878, 2834, 1769, 1592, 1504, 1389, 1169, 949, 741, 629; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.81 (s, 1H), 8.71 (dd, J = 4.8, 1.6 Hz, 1H), 7.89 (dd, J = 8.0, 2.0 Hz, 1H), 7.69 (dd, J = 9.2, 5.4 Hz, 1H), 7.45 (dd, J = 7.9, 4.8 Hz, 1H), 7.33 (dd, J = 9.6, 5.7 Hz, 1H), 7.04 (ddd, J = 8.5, 5.3, 3.7 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.86 (d, J = 8.1 Hz, 1H), 3.83 (s, 3H), 3.43 (t, J = 4.9 Hz, 4H), 3.16 (t, J = 5.0 Hz, 4H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.36 (dd, *J* = 13.9, 2.8 Hz), 153.85 (dd, *J* = 10.4, 2.7 Hz), 152.23, 150.48, 149.52 (d, *J* = 3.6 Hz), 140.30, 136.33 (d, *J* = 3.7 Hz), 132.41 (dd, *J* = 16.2, 8.1 Hz), 129.25, 125.50 (dd, *J* = 17.6, 6.7 Hz), 123.98, 123.71, 121.20, 119.16 (dd, *J* = 11.8, 2.5 Hz), 118.89 (dd, *J* = 9.3, 2.5 Hz), 118.66, 111.30, 55.52, 50.31, 46.35 (d, *J* = 1.9 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) -111.90 (ddd, *J* = 16.7, 9.6, 5.7 Hz), -120.30 (dt, *J* = 17.4, 7.5 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 446.1, $C_{22}H_{22}F_2N_3O_3S^+$ requires 446.1.

A 2.4. Preparation of *N*-triazinyl pyridinium salts

General Procedure A (pyridinium formation)

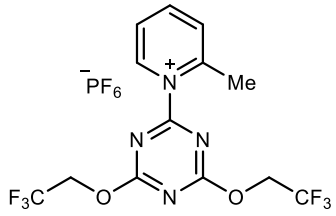


Pyridinium Salt

An oven-dried 8 mL vial equipped with a stir bar was charged with the triazine (1.1 equiv) and potassium hexafluorophosphate (1.1 equiv). The vial was subjected to three rapid cycles of

vacuum/nitrogen backfill, then acetonitrile (0.5-2.0 M) was added. The reaction was heated to 50 ºC for stated time. The reaction was diluted to 4-10 mL (depending on the scale of the reaction) with CH_2Cl_2 and added dropwise to excess chilled diethyl ether (0 ºC) and placed in a -20 ºC freezer for approximately 1 hour. The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 ºC). The solid was then dissolved in acetone and leaving behind KCl on the frit. The solution was concentrated *in vacuo* to provide the pure pyridinium salt. The pyridinium salts were be stored in a desiccator for short term use (1-2 weeks) and in the glove box for long term storage.

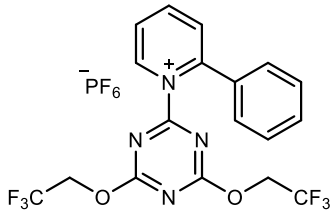
1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-methylpyridin-1-ium hexafluorophosphate(V) (2aD)



Prepared according to general procedure A using freshly distilled 2-methylpyridine (0.25 mL, 2.50 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (857 mg, 2.75 mmol), potassium hexafluorophosphate (506 mg, 2.75 mmol), and acetonitrile (2.5 mL) at 50 ºC for 4 hours. After purification, the title compound was isolated as a red solid (1.13 g, 2.10 mmol, 88% yield. IR ν_{max}/cm^{-1} (film): 3083, 2996, 1618, 1545, 1360, 1171, 827, 663; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.91 (ddd, J = 6.4, 1.5, 0.6 Hz, 1H), 8.66 (td, J = 7.9, 1.6 Hz, 1H), 8.18 – 8.03 (m, 2H), 5.12 (q, J = 8.4 Hz, 4H), 2.90 (s, 3H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 173.60, 168.84, 157.24, 150.58, 144.83, 132.01, 126.95, 123.89 (q, J = 276.6 Hz), 66.04 (q, J = 36.8 Hz), 22.08; ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -72.97 (d, J= 706.6 Hz), -74.39 (t, J = 8.3 Hz); ^{31}P

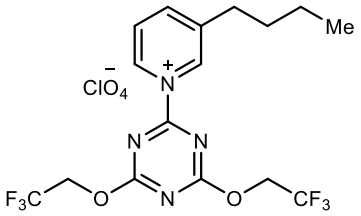
NMR (162 MHz, Acetonitrile-d_3) δ -144.64 (sp, J = 706.6 Hz); *m/z* LRMS (ESI + APCI) found $[M–PF_6]^+$ 369.1, $C_{13}H_{11}F_6N_4O_2^+$ requires 369.1.

1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-phenylpyridin-1-ium hexafluorophosphate(V) (2b)



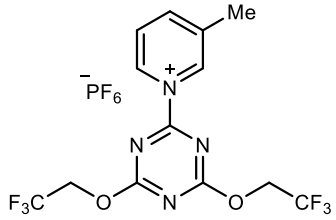
Prepared according to general procedure A using 2-phenylpyridine (0.43 mL, 3.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (1.03 g, 3.30 mmol), potassium hexafluorophosphate (608 mg, 3.30 mmol), and acetonitrile (1.5 mL) at 100 ºC for 6 hours. After purification, the title compound was isolated as a brown amorphous solid (894 mg, 1.55 mmol, 52% yield. IR ν_{max}/cm^{-1} (film): 3069, 2927, 1713, 1677, 1598, 1421, 1055, 1081, 841; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.14 (ddd, J = 6.4, 1.5, 0.6 Hz, 1H), 8.84 (td, J = 7.9, 1.5 Hz, 1H), 8.32 – 8.22 (m, 2H), 7.65 – 7.58 (m, 1H), 7.56 – 7.44 (m, 4H), 4.85 (q, J = 8.3 Hz, 4H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) 173.34, 169.67, 156.10, 151.24, 145.90, 132.87, 132.76, 132.33, 130.49, 130.28, 127.96, 123.71 (q, J = 276.6 Hz), 65.82 (q, J = 36.9 Hz); ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -72.95 (d, J = 706.3 Hz), -74.47 (t, J = 8.3 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.64 (sp, J = 706.3 Hz); *m/z* LRMS (ESI + APCI) found $[M–PF_6]^+$ 431.1, $C_{18}H_{13}F_6N_4O_2^+$ requires 431.1.

1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-butylpyridin-1-ium perchlorate (2c)



Prepared according to general procedure A using 3-butylpyridine (0.30 mL, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), sodium perchlorate (269 mg, 2.20 mmol), and acetonitrile (4.0 mL) at 50 ºC for 2 hours. After purification, the title compound was isolated as a yellow amorphous solid (0.92 g, 1.80 mmol, 90% yield); IR ν_{max}/cm^{-1} (film): 3128, 3072, 2960, 2878, 2256, 1618, 1551, 1267, 1080, 810, 623; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.79 (d, J = 6.4 Hz, 1H), 9.74 (s, 1H), 8.77 (d, J = 8.0 Hz, 1H), 8.36 – 8.05 (m, 1H), 5.19 (q, J = 8.4 Hz, 4H), 3.14 – 2.92 (m, 2H), 1.84 – 1.63 (m, 2H), 1.43 (dq, J = 14.6, 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H).; ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 173.49, 166.54, 153.90, 145.80, 141.10, 139.93, 129.03, 123.99 (q, J = 276.5 Hz), 66.18 (q, J = 36.7 Hz), 33.35, 32.95, 22.75, 14.05; ^{19}F NMR (377 MHz, Acetonitrile-d_3) δ -74.05 – -74.47 (m); *m/z* LRMS (ESI + APCI) found $[M–ClO_4]^+$ 411.2, $C_{16}H_{17}F_6N_4O_2^+$ requires 411.1.

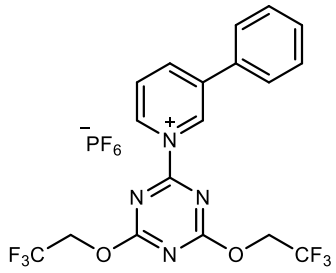
1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (2d)



Prepared according to general procedure A using 3-methylpyridine (0.20 mL, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium

hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (4.0 mL) at 50 ºC for 2 hours. After purification, the title compound was isolated as a purple solid (950 mg, 1.84 mmol, 92% yield). mp 138-140 ^{o}C; IR ν_{max}/cm^{-1} (film): 3083, 2996, 1618, 1545, 1269, 1134, 837, 661; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.77-9.75 (m, 2H), 8.74 (d, J = 7.9 Hz, 1H), 8.32 – 8.04 (m, 1H), 5.18 (q, J = 8.4 Hz, 4H), 2.69 (s, 3H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 173.54, 166.45, 154.71, 141.75, 141.21, 139.57, 128.85, 123.95 (q, J = 276.5 Hz), 66.15 (q, J = 36.8 Hz), 18.83.; ^{19}F NMR (377 MHz, Acetonitrile-d_3) δ -72.98 (d, J = 706.6 Hz), -74.38 (t, J = 8.4 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.67 (sp, J = 706.5 Hz); *m/z* LRMS (ESI + APCI) found $[M–PF_6]^+$ 369.1, $C_{13}H_{11}F_6N_4O_2^+$ requires 369.1.

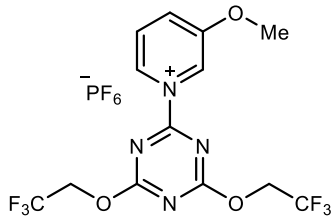
1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-phenylpyridin-1-ium hexafluorophosphate(V) (2e)



Prepared according to general procedure A using 3-phenylpyridine (0.29 mL, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (4.0 mL) at 50 ºC for 2 hours. After purification, the title compound was isolated as an orange solid (840 mg, 1.5 mmol, 75% yield). mp 74-82 ^{o}C; IR ν_{max}/cm^{-1} (film): 3075, 2923, 2360, 1618, 1556, 1271, 1147, 835, 810; ^{1}H NMR

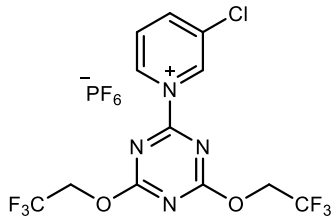
(400 MHz, Acetonitrile-d_3) δ 9.99 (t, J = 1.6 Hz, 1H), 9.88 (dt, J = 6.5, 1.4 Hz, 1H), 9.12 (ddd, J = 8.1, 2.0, 1.2 Hz, 1H), 8.36 (dd, J = 8.0, 6.5 Hz, 1H), 7.90 – 7.78 (m, 2H), 7.76 – 7.57 (m, 3H), 5.20 (q, J = 8.4 Hz, 4H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 173.56, 166.55, 151.82, 142.86, 140.45, 139.68, 133.83, 131.84, 130.81, 129.61, 128.97, 123.94 (q, J = 276.5 Hz), 66.24 (q, J = 36.8 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.69 (sept, J = 706.7 Hz); *m/z* LRMS (ESI + APCI) found $[M–PF_6]^+$ 431.1, $C_{18}H_{13}F_6N_4O_2^+$ requires 431.1.

1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methoxypyridin-1-ium hexafluorophosphate(V) (2f)



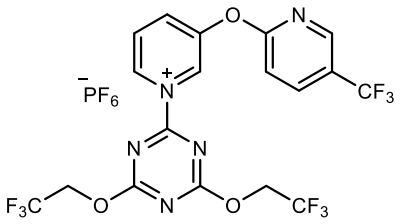
Prepared according to general procedure A using 3-methoxypyridine (0.20 mL, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (4.0 mL) at 50 ºC for 2 hours. After purification, the title compound was isolated as a green solid (1.04 g, 1.96 mmol, 98% yield). mp 105-112 ^{o}C; IR ν_{max}/cm^{-1} (film): 3133, 3069, 1623, 1581, 1265, 1147, 837, 810; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.58 (d, J = 6.3 Hz, 1H), 9.52 – 9.45 (t, J = 2.6 Hz, 1H), 8.46 (dd, J = 8.7, 2.6 Hz, 1H), 8.20 (dd, J = 8.7, 6.3 Hz, 1H), 5.18 (q, J = 8.4 Hz, 4H), 4.14 (s, 3H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 173.51, 166.34, 160.43, 138.65, 134.72, 129.92, 129.18, 123.91 (q, J = 276.4 Hz), 66.19 (q, J = 36.8 Hz), 58.92; ^{19}F NMR (377 MHz, Acetonitrile-d_3) δ -73.00 (d, J = 706.5 Hz), -74.35 (t, J = 8.4 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.68 (sept, J = 706.5 Hz); *m/z* LRMS (ESI + APCI) found $[M–PF_6]^+$ 385.1, $C_{13}H_{11}F_6N_4O_3^+$ requires 385.1.

1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-chloropyridin-1-ium hexafluorophosphate(V) (2g)



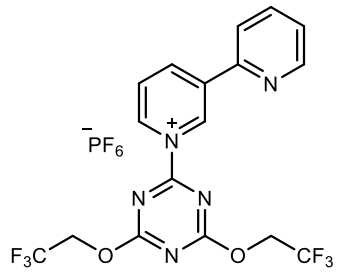
Prepared according to general procedure A using 3-chloropyridine (0.19 mL, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (4.0 mL) at 50 ºC for 2 hours. After purification, the title compound was isolated as a yellow solid (968 mg, 1.81 mmol, 90% yield). mp 124-129 °C; IR ν_{max}/cm^{-1} (film): 3133, 2991, 1719, 1640, 1553, 1363, 1157, 968, 831; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.99 (t, J = 1.7 Hz, 1H), 9.90 (d, J = 6.4 Hz, 1H), 8.96 – 8.91 (m, 1H), 8.30 (dd, J = 8.4, 6.4 Hz, 1H), 5.18 (t, J = 8.4 Hz, 4H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) 173.55, 165.78, 153.74, 141.16 (d, J = 4.3 Hz), 137.76, 130.28, 123.88 (q, J = 276.5 Hz), 66.28 (q, J = 36.9 Hz); ^{19}F NMR (377 MHz, Acetonitrile-d_3) δ -73.01 (d, J = 706.6 Hz), -74.36 (t, J = 8.3 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.70 (sept, J = 706.6 Hz); *m/z* LRMS (ESI + APCI) found $[M–PF_6]^+$ 389.0, $C_{12}H_8ClF_6N_4O_2^+$ requires 389.0.

1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-((5-(trifluoromethyl)pyridin-2-yl)oxy)pyridin-1-ium hexafluorophosphate(V) (2h)



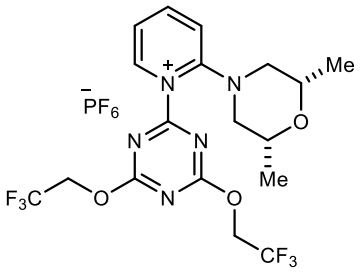
Prepared according to general procedure A using 2-(pyridin-3-yloxy)-5-(trifluoromethyl)pyridine (480 mg, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (4.0 mL) at 50 ºC for 2 hours. Purification required as 1:1 mixture of chilled hexanes: diethyl ether. The title compound was isolated as a white solid (1.23 g, 1.9 mmol, 93% yield). mp 66- 72 ^{o}C; IR ν_{max}/cm^{-1} (film): 3075, 2822, 2111, 1761, 1556, 1414, 1257, 1076, 751; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 10.03 – 9.98 (m, 1H), 9.85 (dt, *J* = 6.5, 1.4 Hz, 1H), 8.86 (dd, *J* = 8.1, 2.3 Hz, 1H), 8.52 (s, 1H), 8.36 (dd, *J* = 8.6, 6.4 Hz, 1H), 8.27 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 5.18 (q, *J* = 8.4 Hz, 4H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 173.57, 166.07, 164.36, 153.82, 147.27, 145.57 (q, *J* = 4.5 Hz), 139.64 (q, *J* = 3.2 Hz), 139.04, 136.18, 130.13, 124.69 (q, *J* = 271.1 Hz), 124.59 (q, *J* = 33.5 Hz), 123.89 (q, *J* = 276.5 Hz),113.85, 66.23 (q, *J* = 36.8 Hz); ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -62.38, -72.98 (d, *J* = 706.2 Hz), -74.36 (t, *J* = 8.5 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.650 (sp, *J* = 706.0 Hz) *m/z* LRMS (ESI + APCI) found $[M-PF_6]^+$ 516.2, $C_{18}H_{11}F_9N_5O_3^+$ requires 516.1.

1'-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-[2,3'-bipyridin]-1'-ium hexafluorophosphate(V) (2i)



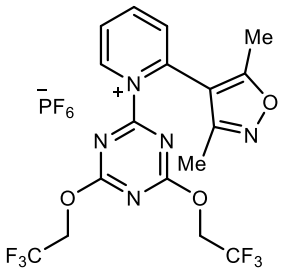
Prepared according to general procedure A using 2,3'-bipyridine (312 mg, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (4.0 mL) at 50 ºC for 2 hours. After purification, the title compound was isolated as a white solid (1.04 g, 1.80 mmol, 90% yield). mp 138-142 ^{o}C; IR ν_{max}/cm^{-1} (film): 3133, 3077, 1637, 1550, 1267, 1138, 837, 802; ^{1}H NMR (400 MHz, Acetonitrile-d_3) 10.50 (t, J = 1.6 Hz, 1H), 9.93 (dt, J = 6.4, 1.4 Hz, 1H), 9.46 (ddd, J = 8.1, 1.8, 1.3 Hz, 1H), 8.86 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.40 (dd, J = 8.0, 6.6 Hz, 1H), 8.18 (dt, J = 8.0, 1.0 Hz, 1H), 8.07 (td, J = 7.8, 1.8 Hz, 1H), 7.60 (ddd, J = 7.6, 4.8, 1.0 Hz, 1H), 5.21 (q, J = 8.4 Hz, 4H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 173.54, 166.56, 151.72, 150.56, 150.08, 141.32, 140.88, 140.22, 139.25, 129.68, 126.74, 123.91 (q, J = 276.5 Hz) 123.07, 66.21 (q, J = 36.8 Hz); ^{19}F NMR (377 MHz, Acetonitrile-d_3) δ -72.96 (d, J = 706.6 Hz), -74.33 (t, J = 8.3 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.66 (sept, J = 706.6 Hz); *m/z* LRMS (ESI + APCI) found $[M–PF_6]^+$ 432.1, $C_{17}H_{12}F_6N_5O_2^+$ requires 432.1.

1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-((2R,6S)-2,6-dimethylmorpholino)pyridin-1-ium hexafluorophosphate(V) (2j)



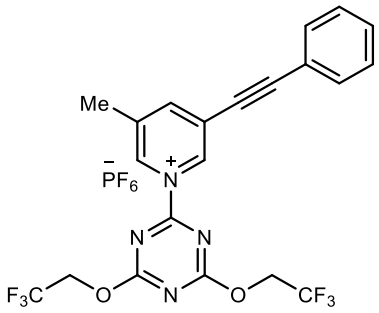
Prepared according to general procedure A using (2R,6S)-2,6-dimethyl-4-(pyridin-2-yl)morpholine (577 mg, 3.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (1.03 mg, 3.30 mmol), potassium hexafluorophosphate (608 mg, 3.30 mmol), and acetonitrile (1.5 mL) at 100 ºC for 6 hours. After purification, the title compound was isolated as a green solid (1.39 g, 2.27 mmol, 76% yield). mp 184-187 ^{o}C; IR ν_{max}/cm^{-1} (film): 3125, 2993, 2360, 1648, 1595, 1433, 1267, 1161, 831, 734; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.41 (dd, J = 7.0, 1.7 Hz, 1H), 8.05 (ddd, J = 9.1, 6.9, 1.7 Hz, 1H), 7.63 (d, J = 9.4 Hz, 1H), 7.12 (t, J = 6.9 Hz, 1H), 5.09 (q, J = 8.4 Hz, 4H), 3.75 (dtd, J = 12.5, 6.2, 2.1 Hz, 2H), 3.57 (d, J = 13.6 Hz, 2H), 2.95 (dd, J = 13.5, 10.4 Hz, 2H), 1.14 (d, J = 6.2 Hz, 6H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 173.79, 169.46, 155.78, 145.69, 139.76, 123.97 (q, J = 276.4 Hz), 119.72, 115.68, 72.08, 65.78 (q, J = 36.7 Hz), 56.84, 18.53; ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -72.89 (d, J = 706.4 Hz), -74.32 (t, J = 8.5 Hz) ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.63 (sp, J = 706.6 Hz); *m/z* LRMS (ESI + APCI) found $[M-PF_6]^+$ 468.2, $C_{18}H_{20}F_6N_5O_3^+$ requires 468.1.

1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-(3,5-dimethylisoxazol-4-yl)pyridin-1-ium hexafluorophosphate(V) (2k)



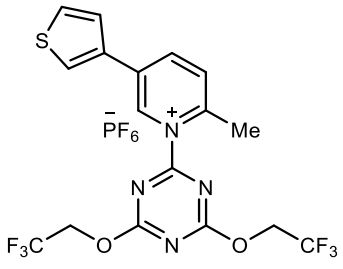
Prepared according to general procedure A using 3,5-dimethyl-4-(pyridin-2-yl)isoxazole (348 mg, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (1.0 mL) at 100 ºC for 6 hours. After purification, the title compound was isolated as a brown solid (933 mg, 1.57 mmol, 78% yield). mp: 205-209 ºC; IR ν_{max}/cm^{-1} (film): 3025, 2988, 2342, 1688, 1590, 1399, 1247, 1100, 831, 730; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.22 – 9.11 (m, 1H), 8.88 (td, J = 7.9, 1.5 Hz, 1H), 8.33 (ddd, J = 7.9, 6.4, 1.5 Hz, 1H), 8.21 (ddd, J = 8.0, 1.5, 0.6 Hz, 1H), 5.01 (q, J = 8.3 Hz, 4H), 2.25 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 173.38, 171.57, 169.08, 159.63, 151.91, 147.07, 145.69, 134.02, 129.45, 123.78 (q, J = 276.5 Hz), 110.07, 65.97 (q, J = 36.9 Hz), 12.17, 10.68; ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -72.97 (d, J = 706.3 Hz), -74.42 (t, J = 8.3 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.64 (sp, J = 706.3 Hz); *m/z* LRMS (ESI + APCI) found $[M–PF_6]^+$ 468.2, $C_{18}H_{20}F_6N_5O_3^+$ requires 468.1

1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methyl-5-(phenylethynyl)pyridin-1-ium hexafluorophosphate(V) (2l)



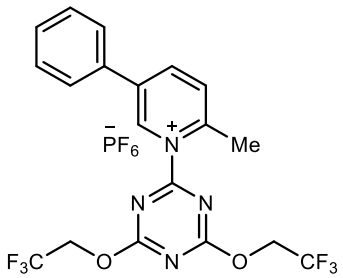
Prepared according to general procedure A using 3-methyl-5-(phenylethynyl)pyridine (386 mg, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (4.0 mL) at 50 ºC for 2 hours. After purification, the title compound was isolated as a white solid (994 mg, 1.62 mmol, 81% yield). mp 188-191 ºC; IR ν_{max}/cm^{-1} (film): 3108, 3066, 2217, 1707, 1620, 1539, 1248, 1132, 838; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.88 (s, 1H), 9.73 (s, 1H), 8.79 (s, 1H), 8.31 – 7.64 (m, 2H), 7.52 (qd, J = 8.8, 7.9, 3.7 Hz, 3H), 5.21 (q, J = 8.3 Hz, 4H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, Acetonitrile-d_3) δ 173.54, 166.10, 155.48, 155.32, 141.75, 140.98, 133.10, 131.60, 130.02, 125.71, 123.92 (q, J = 276.5 Hz),121.59, 98.68, 82.33, 66.24 (q, J = 36.8 Hz), 18.75; ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -72.98 (d, J = 706.6 Hz), -74.35 (t, J = 8.3 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.68 (sp, J = 706.7 Hz); *m/z* LRMS (ESI + APCI) found $[M–PF_6]^+$ 469.2, $C_{21}H_{15}F_6N_4O_2^+$ requires 469.1.

1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-methyl-5-(thiophen-3-yl)pyridin-1-ium hexafluorophosphate(V) (2m)



Prepared according to general procedure A using 2-methyl-5-(thiophen-3-yl)pyridine (438 mg, 2.50 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (857 mg, 2.75 mmol), potassium hexafluorophosphate (506 mg, 2.75 mmol), and acetonitrile (2.5 mL) at 50 ºC for 4 hours. After purification, the title compound was isolated as a brown solid (1.44 g, 2.42 mmol, 97% yield). mp 208-213 ºC; IR ν_{max}/cm^{-1} (film): 3094, 2864, 2341, 1601, 1556, 1265, 1161, 837, 795;^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.09 (d, J = 2.1 Hz, 1H), 8.87 (dd, J = 8.5, 2.2 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 8.03 (dd, J = 3.0, 1.4 Hz, 1H), 7.69 (dd, J = 5.1, 2.9 Hz, 1H), 7.56 (dd, J = 5.1, 1.5 Hz, 1H), 5.14 (q, J = 8.3 Hz, 4H), 2.88 (s, 3H); ^{13}C NMR (100 MHz, Acetonitrile-d_3) δ 173.63, 168.83, 154.54, 146.98, 141.38, 134.85, 134.42, 131.91, 129.99, 127.24, 126.55, 123.88 (q, J = 276.5 Hz), 66.09 (q, J = 36.9 Hz), 21.46; ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -72.97 (d, J = 706.4 Hz), -74.36 (t, J = 8.3 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.64 (sp, J = 706.4 Hz); *m/z* LRMS (ESI + APCI) found $[M-PF_6]^+$ 451.1, $C_{17}H_{13}F_6N_4O_2S^+$ requires 451.1.

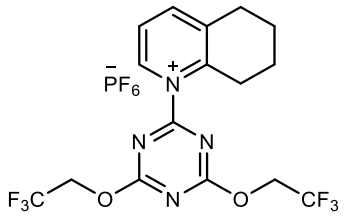
1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-methyl-5-phenylpyridin-1-ium hexafluorophosphate(V) (2n)



Prepared according to general procedure A using 2-methyl-5-phenylpyridine (423 mg, 2.50 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (857 mg, 2.75 mmol), potassium hexafluorophosphate (506 mg, 2.75 mmol), and acetonitrile (2.5 mL) at 50 ºC for 4 hours. After purification, the title compound was isolated as a white solid (1.26 g, 2.14 mmol, 86% yield). mp

215-218 ºC; IR ν_{max}/cm^{-1} (film): 3114, 3082, 2895, 2481, 1611, 1554, 1259, 1162, 834; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.09 (d, J = 2.1 Hz, 1H), 8.88 (dd, J = 8.5, 2.1 Hz, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.82 – 7.74 (m, 2H), 7.66 – 7.59 (m, 3H), 5.14 (q, J = 8.4 Hz, 4H), 2.92 (s, 3H); ^{13}C NMR (100 MHz, Acetonitrile-d_3) δ 173.63, 168.89, 155.16, 148.15, 142.28, 139.93, 133.57, 131.94, 131.61, 130.79, 128.46, 123.88 (q, J = 276.5 Hz), 66.09 (q, J = 36.8 Hz), 21.54.; ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -72.98 (d, J = 706.2 Hz), -74.36 (t, J = 8.3 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.64 (sp, J = 706.4 Hz);*m/z* LRMS (ESI + APCI) found $[M–PF_6]^+$ 445.1, $C_{19}H_{15}F_6N_4O_2^+$ requires 445.1.

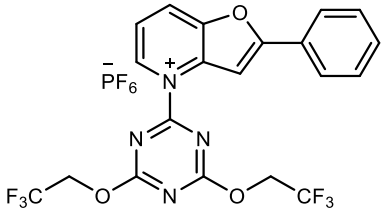
1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-5,6,7,8-tetrahydroquinolin-1-ium hexafluorophosphate(V) (2o)



Prepared according to general procedure A using 5,6,7,8-tetrahydroquinoline (0.26 mL, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (2.0 mL) at 50 ºC for 4 hours. After purification, the title compound was isolated as a red solid (1.24 g, 2.20 mmol, 89% yield). mp 73-80 ºC; IR ν_{max}/cm^{-1} (film): 3119, 2960, 1601, 1548, 1269, 1167, 1051, 839; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.67 (d, J = 6.6 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 7.95 (dd, J = 7.8, 6.4 Hz, 1H), 5.10 (q, J = 8.4 Hz, 4H), 3.08 (d, J = 12.6 Hz, 4H), 1.90 (p, J = 3.4 Hz, 4H).; ^{13}C NMR (100 MHz, Acetonitrile-d_3) δ 173.59, 168.84, 155.63, 150.72, 142.57, 141.74, 125.77, 122.89 (q, J = 276.5 Hz), 66.02 (q, J = 36.8 Hz), 29.60, 29.05, 21.65, 21.11.; ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -

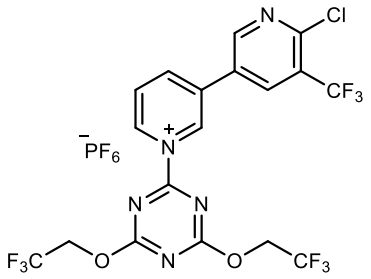
72.97 (d, J = 706.2 Hz), -74.40 (t, J = 8.4 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.64 (sp, J = 706.2 Hz); *m/z* LRMS (ESI + APCI) found $[M-PF_6]^+$ 409.2, $C_{16}H_{15}F_6N_4O_2^+$ requires 409.1.

4-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-phenylfuro[3,2-b]pyridin-4-ium hexafluorophosphate(V) (2p)



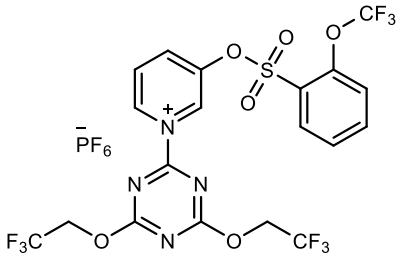
Prepared according to general procedure A using 2-phenylfuro[3,2-b]pyridine (390 mg, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (4.0 mL) at 50 ºC for 3 hours. After purification, the title compound was isolated as a green solid (1.13 g, 1.82 mmol, 91% yield). mp 208-215 ºC; IR ν_{max}/cm^{-1} (film): 3125, 1702, 1620, 1536, 1369, 1248, 1129, 835; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 9.61 (d, J = 6.9 Hz, 1H), 8.82 (d, J = 8.1 Hz, 1H), 8.37 (s, 1H), 8.22 (dd, J = 7.9, 1.6 Hz, 2H), 7.96 (dd, J = 8.1, 6.8 Hz, 1H), 7.84 – 7.56 (m, 3H), 5.21 (q, J = 8.4 Hz, 4H); ^{13}C NMR (100 MHz, Acetonitrile-d_3) δ 173.37, 169.90, 167.62, 153.12, 143.46, 137.29, 134.66, 131.57, 130.78, 128.65, 127.59, 123.98 (q, J = 276.6 Hz), 121.14, 102.07, 66.05 (q, J = 36.8 Hz); ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -72.97 (d, J = 706.0 Hz), -74.23 (d, J = 8.3 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.64 (sp, J = 706.0 Hz); *m/z* LRMS (ESI + APCI) found $[M-PF_6]^+$ 471.1, $C_{20}H_{13}F_6N_4O_3^+$ requires 471.1.

1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-6'-chloro-5'-(trifluoromethyl)-[3,3'-bipyridin]-1-ium hexafluorophosphate(V) (2q)



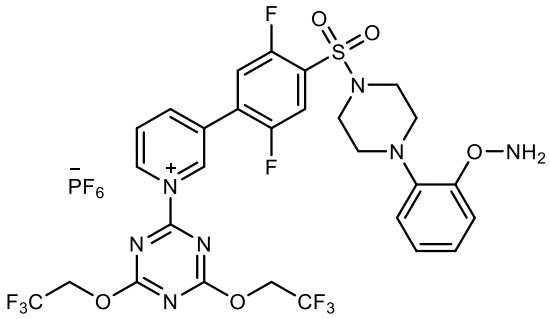
Prepared according to general procedure A using 6-chloro-5-(trifluoromethyl)-3,3'-bipyridine (517 mg, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (2.0 mL) at 50 ºC for 2 hours. After purification, the title compound was isolated as a white amorphous solid (745 mg, 1.10 mmol, 55% yield); IR ν_{max}/cm^{-1} (film): 3133, 3077, 1637, 1550, 1250, 866, 730, 541; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 10.10 (t, J = 1.6 Hz, 1H), 10.00 (d, J = 6.5 Hz, 1H), 9.15 (dt, J = 8.1, 1.4 Hz, 1H), 9.01 (d, J = 2.4 Hz, 1H), 8.57 (d, J = 2.4 Hz, 1H), 8.44 (dd, J = 8.0, 6.5 Hz, 1H), 5.21 (q, J = 8.4 Hz, 4H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 173.58, 166.35, 152.87, 152.69, 150.93 (d, J = 1.8 Hz), 142.08, 140.60, 138.43 (q, J = 4.9 Hz), 137.76, 129.93, 129.67, 125.94 (q, J = 33.6 Hz), 123.93 (q, J = 276.5 Hz), 123.29 (q, J = 272.3 Hz), 66.28 (q, J = 36.8 Hz); ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -64.24, -72.98 (d, J = 706.3 Hz), -74.33 (t, J = 8.4 Hz), -74.36 (t, J = 8.5 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) -144.65 (sp, J = 706.4 Hz); *m/z* LRMS (ESI + APCI) found $[M–PF_6]^+$ 534.1, $C_{18}H_{10}ClF_9N_5O_2^+$ requires 534.0.

1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-(((2-(trifluoromethoxy)phenyl)sulfonyl)oxy)pyridin-1-ium hexafluorophosphate(V) (2r)



Prepared according to general procedure A using pyridin-3-yl 2-(trifluoromethoxy)benzenesulfonate (639 mg, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (4.0 mL) at 50 ºC for 2 hours. Purification required a 1:1 mixture of chilled hexanes: diethyl ether, the title compound was isolated as an amorphous solid (1.22 g, 1.65 mmol, 83% yield). IR νmax/cm-1 (film): 3133, 3086, 2264, 2111, 1623, 1560, 1255, 1178, 841; 1H NMR (400 MHz, Acetonitrile-d3) 9.94 (d, J = 6.4 Hz, 1H), 9.85 (s, 1H), 9.02 – 8.59 (m, 1H), 8.35 (dd, J = 8.7, 6.4 Hz, 1H), 8.17 – 8.05 (m, 1H), 8.04 – 7.85 (m, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 5.19 (q, J = 8.3 Hz, 4H); 13C NMR (101 MHz, Acetonitrile-d3) δ 173.60, 165.78, 149.82, 147.49 (q, J = 1.9 Hz), 147.41, 141.64, 139.73, 136.90, 133.71, 131.16, 129.13, 126.74 123.94 (q, J = 277.8 Hz), 122.90 (q, J = 1.9 Hz), 119.98, 66.33 (q, J = 36.9 Hz); 19F NMR (377 MHz, Acetonitrile-d3) δ -57.20 (d, J = 1.8 Hz), -72.99 (d, J = 706.7 Hz), -74.36 (t, J = 8.3 Hz); 31P NMR (162 MHz, Acetonitrile-d3) δ -144.65 (sept, J = 706.7 Hz); m/z LRMS (ESI + APCI) found $[M-PF_6]+$ 595.1, $C_{19}H_{12}F_9N_4O_6S+$ requires 595.0.

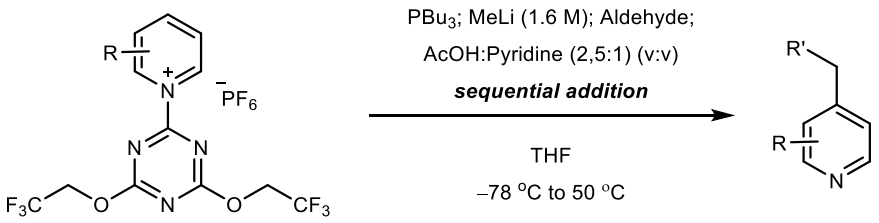
3-(4-((4-(2-(aminooxy)phenyl)piperazin-1-yl)sulfonyl)-2,5-difluorophenyl)-1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)pyridin-1-ium hexafluorophosphate(V) (2ax)



Prepared according to general procedure A using 1-((2,5-difluoro-4-(pyridin-3-yl)phenyl)sulfonyl)-4-(2-methoxyphenyl)piperazine (891 mg, 2.00 mmol), 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (685 mg, 2.20 mmol), potassium hexafluorophosphate (405 mg, 2.20 mmol), and acetonitrile (2.0 mL) at 50 ºC for 2 hours. After purification, the title compound was isolated as a white solid (1.44 g, 1.66 mmol, 83% yield). mp 188-191 ºC; IR ν_{max}/cm^{-1} (film): 3108, 3066, 2217, 1707, 1620, 1539, 1248, 1132, 838; ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 10.06 (d, *J* = 1.8 Hz, 1H), 10.00 (dt, *J* = 6.5, 1.4 Hz, 1H), 9.14 – 9.02 (m, 1H), 8.45 (dd, *J* = 8.1, 6.5 Hz, 1H), 7.85 (dd, *J* = 9.3, 5.4 Hz, 1H), 7.75 (dd, *J* = 9.7, 5.8 Hz, 1H), 7.02 (td, *J* = 7.6, 6.8, 1.9 Hz, 1H), 6.92 (qd, *J* = 7.9, 6.9, 5.4 Hz, 3H), 5.20 (q, *J* = 8.4 Hz, 4H), 3.78 (s, 3H), 3.38 (t, *J* = 4.6 Hz, 4H), 3.14 (t, *J* = 4.9 Hz, 4H); ^{13}C NMR (100 MHz, Acetonitrile-d_3) δ 173.55, 166.26, 157.33 (dd, *J* = 26.3, 2.9 Hz), 154.83 (dd, *J* = 28.2, 2.8 Hz), 153.80 (d, *J* = 2.8 Hz), 153.26, 142.19, 141.66 (d, *J* = 4.7 Hz), 140.87, 135.27, 129.93, 128.84 (dd, *J* = 17.7, 7.0 Hz), 128.24 (dd, *J* = 15.8, 8.8 Hz), 124.93, 123.89 (q, *J* = 276.5 Hz), 121.97, 121.36 (dd, *J* = 27.3, 2.1 Hz), 120.04 (d, *J* = 1.4 Hz), 119.64, 112.84, 66.25 (q, *J* = 36.8 Hz), 55.98, 51.09, 47.11 (d, *J* = 1.7 Hz); ^{19}F NMR (376 MHz, Acetonitrile-d_3) δ -72.98 (d, *J* = 706.7 Hz), -74.34 (t, *J* = 8.3 Hz), -112.98 (dt, *J* = 16.0, 8.3 Hz), -121.44 (ddd, *J* = 18.9, 9.3, 5.7 Hz); ^{31}P NMR (162 MHz, Acetonitrile-d_3) δ -144.68 (sp, *J* = 706.6 Hz); *m/z* LRMS (ESI + APCI) found $[M-PF_6]^+$ 722.2, $C_{28}H_{24}F_8N_7O_5S^+$ requires 722.1.

A 2.5. Preparation of Alkylated Pyridines

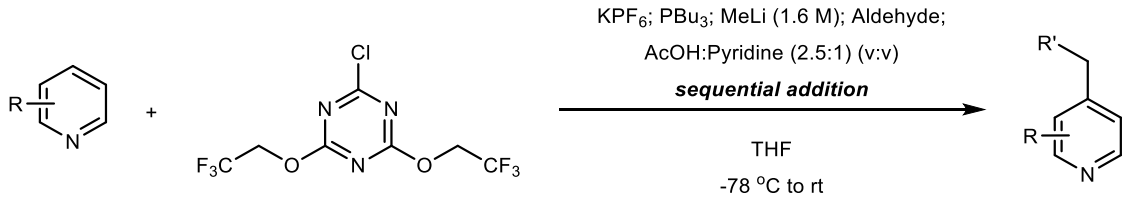
General Procedure B (Pyridine Alkylation)



An oven-dried 16 mL vial equipped with a stir bar was charged with the pyridinium salt (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, THF (0.083 M) was added, followed by tri-*n*-butylphosphine (1.1 equiv). The reaction was allowed to stir at room temperature for 1 hour, then cooled to -78 ºC. Methyl lithium (1.1 equiv, 1.6 M) was added dropwise via syringe and allowed to stir for 15 minutes before the aldehyde (1.4 equiv) was added. The cooling bath was removed and the reaction was allowed to warm to room temperature and stir for one hour. A 2.5:1 (v:v) AcOH:Pyridine mixture (2-5 mL depending on scale of reaction) was added and heated to 50 ºC overnight*. The reaction was diluted with ethyl acetate and quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (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 column chromatography under the stated conditions to provide the alkylated heterocycle.

* Not all reactions required overnight stirring. Monitoring by LCMS the disappearance of the pyridinium can allow for shorter reaction times.

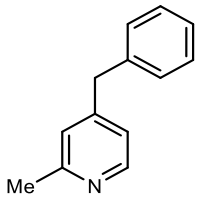
General Procedure C (One-pot protocol)



An oven-dried 16 mL vial equipped with a stir bar was charged with the triazine (1.1 equiv) and potassium hexafluorophosphate (1.1 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, and THF (1.0 M) was added, followed by the heterocycle. The reaction was heated to the stated temperature and stirred for the stated time. The reaction was cooled to room temperature and diluted with THF to 0.083 M. Tri-*n*-Butylphosphine (1.1 equiv) was added and stirred for one hour. The reaction was cooled to -78 °C and methyl lithium (1.6 M, 1.1 equiv) was added dropwise via syringe and stirred for 15 minutes before the aldehyde (1.4 equiv) was added. The cooling bath was removed, and the reaction was allowed to warm to room temperature and stir for one hour. A 2.5:1 (v:v) mixture of AcOH:pyridine (2-5 mL depending on reaction scale) was added and was heated to 50 °C overnight*. The reaction was diluted with ethyl acetate and quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (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 column chromatography under the stated conditions to provide the alkylated heterocycle.

* Not all reactions required overnight stirring. Monitoring by LCMS the disappearance of the pyridinium can allow for shorter reaction times.

4-benzyl-2-methylpyridine (3a)



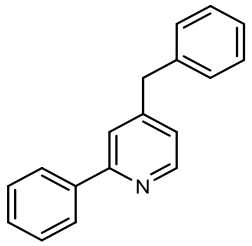
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel, gradient elution: 20% EtOAc in CH_2Cl_2) afforded the title compound as a yellow oil (81 mg, 0.44 mmol, 88% yield). IR ν_{max}/cm^{-1} (film3026, 2914, 2841, 1600, 1450, 1284, 739, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 4.9 Hz, 1H), 7.38 – 7.28 (m, 2H), 7.27 – 7.20 (m, 1H), 7.22 – 7.13 (m, 2H), 6.97 (s, 1H), 6.92 (dd, *J* = 5.1, 1.7 Hz, 1H), 3.92 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.53, 150.37, 149.22, 139.19, 129.11, 128.79, 126.70, 123.79, 121.44, 41.33, 24.44; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 184.1, $C_{13}H_{14}N^+$ requires 184.1.

One Pot:

Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), 2-methylpyridine (49 mL, 0.50 mmol) at 50 °C for 6 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 mL 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica

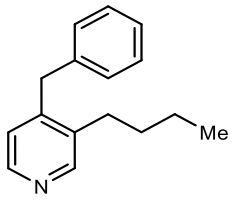
gel: 70% Et_2O in hexanes) afforded the title compound as a yellow oil (55 mg, 0.30 mmol, 60% yield).

4-benzyl-2-phenylpyridine (3b)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-phenylpyridin-1-ium hexafluorophosphate(V) (273 mg, 0.47 mmol), tri-*n*-butylphosphine (0.13 mL, 0.52 mmol), methyl lithium (325 μL, 0.52 mmol), benzaldehyde (67 μL, 0.66 mmol), AcOH:pyridine (4 mL), and THF (5.7 mL). Flash column chromatography (silica gel: 15% Et_2O in hexanes) afforded the title compound as a yellow powder (58 mg, 0.24 mmol, 50% yield). IR ν_{max}/cm^{-1} (film): 3061, 2912, 1668, 1509, 1444, 1404, 910, 729, 695; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 5.0 Hz, 1H), 8.04 – 7.88 (m, 2H), 7.55 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.51 – 7.37 (m, 3H), 7.36 – 7.29 (m, 2H), 7.29 – 7.10 (m, 3H), 7.06 (dd, *J* = 5.1, 1.6 Hz, 1H), 4.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.75, 150.83, 149.83, 139.53, 139.07, 129.14, 129.00, 128.86, 128.79, 127.08, 126.79, 122.83, 121.22, 41.57; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 246.2, $C_{18}H_{16}N^+$ requires 246.1.

4-benzyl-3-butylpyridine (3c)



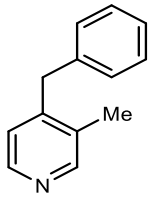
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-butylpyridin-1-ium perchlorate (255 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 10% EtOAc in CH_2Cl_2) afforded the title compound as a yellow oil (78 mg, 0.35 mmol, 69% yield). IR ν_{max}/cm^{-1} (film): 3021, 2960, 2920, 2850, 1674, 1590, 195, 1408, 729, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.34 (d, *J* = 4.7 Hz, 1H), 7.41 – 7.16 (m, 3H), 7.11 (dq, *J* = 7.3, 0.7 Hz, 2H), 6.95 (d, *J* = 5.0 Hz, 1H), 4.00 (s, 2H), 2.77 – 2.54 (m, 2H), 1.64 – 1.43 (m, 2H), 1.43 – 1.30 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.64, 147.51, 147.37, 138.99, 136.56, 128.98, 128.72, 126.58, 124.85, 38.11, 32.81, 30.06, 22.74, 13.96; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 226.2, $C_{16}H_{20}N^+$ requires 226.2.

One-Pot:

Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), sodium perchlorate (67 mg, 0.55 mmol), 3-butylpyridine (74 μL, 0.50 mmol) at 50 °C for 3 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (basic alumina: 30%

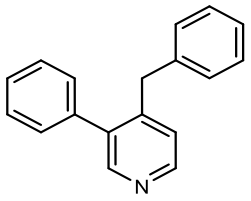
diethyl ether in hexanes) afforded the title compound as a yellow oil (48 mg, 0.213 mmol, 44% yield).

4-benzyl-3-methylpyridine (3d)



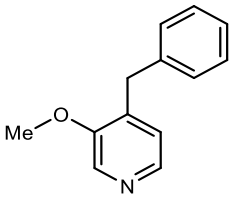
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a yellow oil (88 mg, 0.48 mmol, 96% yield). IR ν_{max}/cm^{-1} (film): 3024, 2915, 2360, 1634, 1597, 1452, 912, 841, 731, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.36 (d, *J* = 5.0 Hz, 1H), 7.41 – 7.27 (m, 2H), 7.26 – 7.19 (m, 1H), 7.12 (ddt, *J* = 7.4, 1.4, 0.7 Hz, 2H), 6.98 (d, *J* = 5.0 Hz, 1H), 3.96 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 151.87, 149.73, 148.78, 140.25, 133.61, 130.24, 129.97, 127.73, 125.57, 39.36, 16.87; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 184.2, $C_{13}H_{14}N^+$ requires 184.1.

4-benzyl-3-phenylpyridine (3e)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-phenylpyridin-1-ium hexafluorophosphate(V) (288 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 60% Et_2O in hexanes) afforded the title compound as a yellow oil (100 mg, 0.41 mmol, 82% yield); IR ν_{max}/cm^{-1} (film): 3027, 3949 2895, 1604, 1495, 1009, 768, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (m, 2H), 7.52 – 7.34 (m, 3H), 7.34 – 7.16 (m, 5H), 7.10 (dd, *J* = 5.1, 0.7 Hz, 1H), 6.98 (m, 2H), 3.96 (s, 2H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.43, 148.71, 147.39, 139.42, 137.95, 137.74, 129.56, 129.07, 128.66, 128.56, 127.89, 126.52, 124.82, 38.56; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 246.2, $C_{18}H_{16}N^+$ requires 246.1.

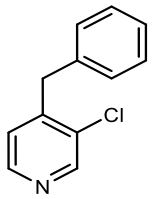
4-benzyl-3-methoxypyridine (3f)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methoxypyridin-1-ium hexafluorophosphate(V) (265 mg, 0.50 mmol), tri-*n*-

butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 20% EtOAc in CH_2Cl_2) afforded the title compound as a clear oil (87 mg, 0.44 mmol, 88% yield). IR ν_{max}/cm^{-1} (film): 3024, 2918, 2842, 2360, 1668, 1590, 1497, 1257, 1022, 837, 698, 625; ^1H NMR (400 MHz, Acetonitrile-d_3) δ 8.27 (s, 1H), 8.12 (d, J = 4.7 Hz, 1H), 7.38 – 7.28 (m, 2H), 7.27 – 7.19 (m, 3H), 7.07 (dd, J = 4.7, 0.7 Hz, 1H), 3.97 (s, 2H), 3.93 (s, 3H); ^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 155.12, 143.82, 140.86, 139.43, 134.71, 130.26, 129.87, 127.65, 125.89, 57.20, 35.99; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 200.1, $C_{13}H_{14}NO^+$ requires 200.1.

4-benzyl-3-chloropyridine (3g)



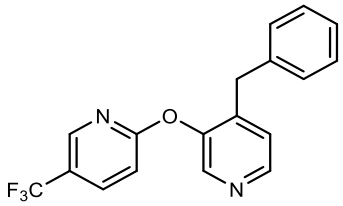
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-chloropyridin-1-ium hexafluorophosphate(V) (267 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 10% EtOAc in CH_2Cl_2) afforded the title compound as a clear oil (72 mg, 0.35 mmol, 70% yield). IR ν_{max}/cm^{-1} (film): 3030, 2926, 2848, 1674, 1581, 1396, 1032, 696, 619; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.36 (d, J = 5.0 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.29 – 7.21 (m, 1H),

7.22 – 7.14 (m, 2H), 7.02 (d, J = 5.0 Hz, 1H), 4.09 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.45, 147.89, 147.62, 137.42, 132.29, 129.23, 128.89, 126.99, 125.32, 38.60; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 204.1, $C_{12}H_{11}ClN^+$ requires 204.1.

One Pot:

Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), 3-chloropyridine (48 μL, 0.50 mmol) at 50 °C for 3 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 30% Et_2O in hexanes) afforded the title compound as a clear oil (80 mg, 0.39 mmol, 78% yield).

2-((4-benzylpyridin-3-yl)oxy)-5-(trifluoromethyl)pyridine (3h)



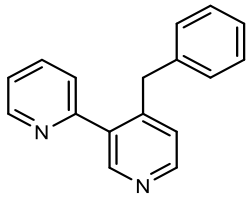
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-((5-(trifluoromethyl)pyridin-2-yl)oxy)pyridin-1-ium hexafluorophosphate(V) (331 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column

chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a colorless oil (87 mg, 0.26 mmol, 52% yield). IR ν_{max}/cm^{-1} (film): 3055, 2932, 1612, 1487, 1327, 1268, 1121, 1078, 837; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 5.0 Hz, 1H), 8.40 (s, 1H), 8.34 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.90 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.29 – 7.16 (m, 3H), 7.16 – 7.14 (m, 1H), 7.13 – 7.06 (m, 2H), 7.03 (dt, *J* = 8.7, 0.8 Hz, 1H), 3.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.15, 148.30, 147.06, 145.40 (q, *J* = 4.4 Hz), 144.58, 142.81, 137.78, 137.00 (q, *J* = 3.2 Hz), 129.18, 128.71, 126.76, 125.44, 123.68 (q, *J* = 271.6 Hz), 122.08 (q, *J* = 33.3 Hz),111.10, 35.7; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -61.74; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 331.1, $C_{18}H_{14}F_3N_2O^+$ requires 331.1.

One Pot:

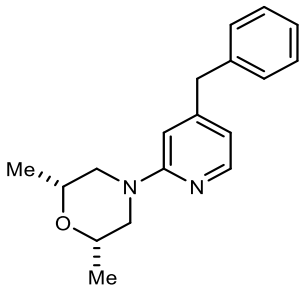
Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), 2-(pyridin-3-yloxy)-5-(trifluoromethyl)pyridine (120 mg, 0.50 mmol) at 50 °C for 3 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 mL 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a colorless oil (86 mg, 0.26 mmol, 52% yield).

4'-benzyl-2,3'-bipyridine (3i)



Prepared according to general procedure B using 1'-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-[2,3'-bipyridin]-1'-ium hexafluorophosphate(V) (289 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 2% MeOH in CH2Cl2. 2nd column, silica gel: 100% Et2O) afforded the title compound as a yellow oil (101 mg, 0.41 mmol, 82% yield). IR ν_{max}/cm-1 (film): 3019, 2923, 2845, 1679, 1584, 1427, 1020, 785, 733, 696; 1H NMR (400 MHz, CDCl3) □ 8.74 (ddd, J = 4.9, 1.9, 1.0 Hz, 1H), 8.60 (s, 1H), 8.52 (d, J = 5.1 Hz, 1H), 7.75 (td, J = 7.7, 1.8 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.24 – 7.08 (m, 4H), 7.07 – 6.94 (m, 2H), 4.17 (s, 2H); 13C NMR (100 MHz, CDCl3) δ 156.77, 150.23, 149.55 (s, 2C), 148.28, 139.25, 136.70, 136.22, 129.10, 128.51, 126.37, 125.04, 124.34, 122.49, 38.2; m/z; LRMS (ESI + APCI) found [M+H]+ 247.2, $C_{17}H_{15}N_2^+$ requires 247.1.

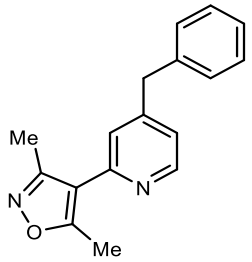
(2R,6S)-4-(4-benzylpyridin-2-yl)-2,6-dimethylmorpholine (3j)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-((2S,6R)-2,6-dimethylmorpholino)pyridin-1-ium hexafluorophosphate(V) (307 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column

chromatography (basic alumina: 10% Et_2O in hexanes) afforded the title compound as a clear oil (64 mg, 0.23 mmol, 46% yield). IR ν_{max}/cm^{-1} (film): 2968, 2904, 2834, 1727, 1598, 1435, 1254, 1086, 729, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, *J* = 5.1, 0.8 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.25 – 7.20 (m, 1H), 7.20 – 7.15 (m, 2H), 6.51 – 6.47 (m, 1H), 6.46 (s, 1H), 4.01 (dd, *J* = 13.1, 2.1 Hz, 2H), 3.88 (s, 2H), 3.71 (dqd, *J* = 10.4, 6.2, 2.5 Hz, 2H), 2.49 (dd, *J* = 12.6, 10.5 Hz, 2H), 1.26 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.80, 151.46, 148.02, 139.55, 129.03, 128.70, 126.58, 114.80, 107.34, 71.73, 50.99, 41.87, 19.1; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 283.3, $C_{18}H_{23}N_2O^+$ requires 283.2.

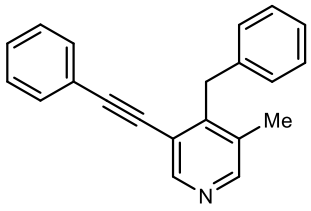
4-(4-benzylpyridin-2-yl)-3,5-dimethylisoxazole (3k)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-(3,5-dimethylisoxazol-4-yl)pyridin-1-ium hexafluorophosphate(V) (298 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 10% EtOAc in CH_2Cl_2. 2nd column, basic alumina: 30% Et_2O in hexanes) afforded the title compound as a yellow oil (44 mg, 0.17 mmol, 34% yield). IR ν_{max}/cm^{-1} (film): 3055, 3024, 2920, 2848, 1621, 1552, 1427, 1252, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 5.1, 0.9 Hz, 1H), 7.45 – 7.31 (m, 2H), 7.33 – 7.23 (m, 1H), 7.24 – 7.14 (m, 2H), 7.08 (d, *J* = 0.8 Hz, 1H), 7.07 – 7.04 (m, 1H), 4.02 (s, 2H), 2.51 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz,

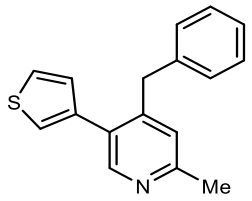
$CDCl_3$) δ 167.49, 158.83, 151.04, 150.84, 150.04, 138.75, 129.19, 128.97, 122.40, 116.22, 41.39, 12.45, 11.55; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 265.2, $C_{17}H_{17}N_2O^+$ requires 265.1.

4-benzyl-3-methyl-5-(phenylethynyl)pyridine (3l)



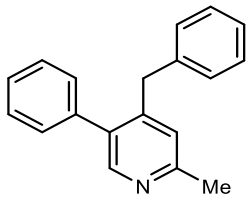
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methyl-5-(phenylethynyl)pyridin-1-ium hexafluorophosphate(V) (307 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 20% Et_2O in hexanes) afforded the title compound as a white powder (112 mg, 0.39 mmol, 79% yield). mp 74-78 ºC; IR ν_{max}/cm^{-1} (film): 3030, 2915, 2212, 1604, 1572, 1491, 756, 733, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.32 (s, 1H), 7.60 – 7.38 (m, 2H), 7.39 – 7.31 (m, 3H), 7.31 – 7.22 (m, 2H), 7.23 – 7.01 (m, 3H), 4.29 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.88, 150.17, 149.12, 138.12, 132.33, 131.72, 128.77, 128.67, 128.56, 128.50, 126.47, 122.83, 95.41, 85.79, 36.98, 16.81; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 284.1, $C_{18}H_{17}NP^+$ requires 284.1.

4-benzyl-2-methyl-5-(thiophen-3-yl)pyridine (3m)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-methyl-5-(thiophen-3-yl)pyridin-1-ium hexafluorophosphate(V) (298 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 5% EtOAc in CH_2Cl_2) afforded the title compound with a 6% impurity (101 mg, 0.38 mmol, 76% yield). IR ν_{max}/cm^{-1} (film): 3091, 2915, 2209, 1668, 1599, 1493, 920, 791, 723; ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.38 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.34 – 7.24 (m, 2H), 7.23 – 7.13 (m, 2H), 7.06 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.07 – 6.99 (m, 2H), 6.97 (s, 1H), 3.98 (s, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.29, 149.51, 147.98, 139.49, 137.89, 130.25, 128.93, 128.91, 128.73, 126.55, 125.95, 124.63, 123.87, 38.82, 24.08; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 266.1, $C_{17}H_{16}NS^+$ requires 266.1.

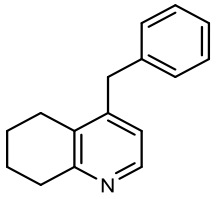
4-benzyl-2-methyl-5-phenylpyridine (3n)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-methyl-5-phenylpyridin-1-ium hexafluorophosphate(V) (236 mg, 0.40 mmol), tri-

n-butylphosphine (0.11 mL, 0.11 mmol), methyl lithium (275 μL, 0.44 mmol), benzaldehyde (57 mL, 0.56 mmol), AcOH:pyridine (5 mL), and THF (4.8 mL). ^{1}H NMR (400 MHz, $CDCl_3$) yield reported is 71% with triphenylmethane as internal standard. Flash column chromatography (silica gel: 30% Et_2O in hexanes) afforded the title compound with a 28% impurity ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.43-7.37 (m, 3H), 7.28 – 7.17 (m, 6H), 6.99-6.97 (m, 2H), 3.92 (s, 2H), 2.53 (s, 3H); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 260.1, $C_{19}H_{18}N^+$ requires 260.1.

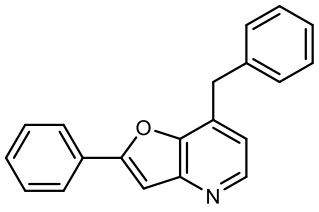
4-benzyl-5,6,7,8-tetrahydroquinoline (3o)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-5,6,7,8-tetrahydroquinolin-1-ium hexafluorophosphate(V) (277 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (basic alumina: 20% Et_2O in hexanes) afforded the title compound as a yellow oil (67 mg, 0.30 mmol, 60% yield). IR ν_{max}/cm^{-1} (film): 3024, 2926, 2845, 2663, 1727, 1578, 1435, 1408, 731, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 8.28 (d, J = 5.0 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.19 (m, 1H), 7.15 – 7.01 (m, 2H), 6.81 (d, J = 4.9 Hz, 1H), 3.91 (s, 2H), 2.94 (t, J = 6.2 Hz, 2H), 2.65 (t, J = 6.2 Hz, 2H), 2.16 – 1.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.41, 147.97, 146.61, 138.60,

131.05, 128.99, 128.72, 126.52, 122.47, 38.44, 33.21, 25.74, 22.88 (2C); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 224.1, $C_{16}H_{18}N^+$ requires 224.1.

7-benzyl-2-phenylfuro[3,2-b]pyridine (3p)



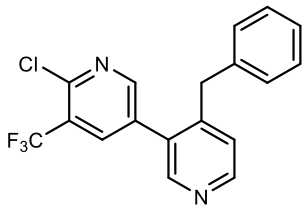
Prepared according to general procedure B using 4-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-phenylfuro[3,2-b]pyridin-4-ium hexafluorophosphate(V) (308 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (basic alumina: 55% Et_2O in hexanes. Second column, silica gel: 50% EtOAc in hexanes) afforded the title compound as a white powder (99 mg, 0.35 mmol, 70% yield). mp 66-68 ºC; IR ν_{max}/cm^{-1} (film): 3047, 3019, 2915, 2825, 1749, 1620, 1570, 1389, 1014, 908, 750, 685; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.27 (m, 1H), 7.88 – 7.75 (m, 2H), 7.47 – 7.37 (m, 2H), 7.37 – 7.29 (m, 1H), 7.26 – 7.08 (m, 6H), 6.88 (d, *J* = 4.9 Hz, 1H), 4.23 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.26, 148.80, 147.15, 146.50, 138.30, 132.55, 129.97, 129.57, 129.22, 129.02, 128.82, 126.85, 125.38, 119.50, 102.78, 35.40; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 286.2, $C_{20}H_{16}NO^+$ requires 286.1.

One Pot:

Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), 2-

phenylfuro[3,2-b]pyridine (98 mg, 0.50 mmol) at 50 ºC for 3 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 mL 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (basic alumina: 75% Et_2O in hexanes) afforded the title compound as a white powder (115 mg, 0.40 mmol, 80% yield).

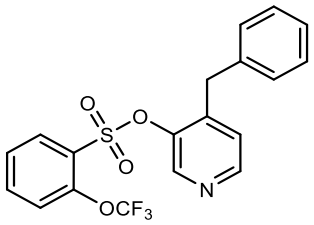
4-benzyl-6'-chloro-5'-(trifluoromethyl)-3,3'-bipyridine (3q)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-6'-chloro-5'-(trifluoromethyl)-[3,3'-bipyridin]-1-ium hexafluorophosphate(V) (340 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel, gradient elution: 10% EtOAc in CH_2Cl_2 to 30% EtOAc in CH_2Cl_2) afforded the title compound as a white powder (134 mg, 0.34 mmol, 77% yield). mp 80-85 ºC; IR ν_{max}/cm^{-1} (film): 3055, 3021, 2920, 2845, 1668, 1587, 1435, 1140, 1051, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.1 Hz, 1H), 8.45 (s, 1H), 8.44 – 8.38 (m, 1H), 7.70 (dd, *J* = 2.4, 0.6 Hz, 1H), 7.32 – 7.14 (m, 4H), 6.96 – 6.82 (m, 2H), 3.92 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.98, 150.57, 150.22, 148.46 (d, *J* = 1.7 Hz), 147.89, 138.11, 137.30 (q, *J* = 4.9 Hz), 132.53, 131.98, 128.92, 128.71, 127.03, 125.51, 124.99 (q, *J* = 33.3 Hz), 121.96 (q, *J* = 273.2 Hz), 39.11; ^{19}F NMR

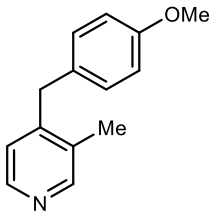
(376 MHz, Chloroform-*d*) δ -63.73; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 349.2, $C_{18}H_{13}ClF_3N_2^+$ requires 349.1.

4-benzylpyridin-3-yl 2-(trifluoromethoxy)benzenesulfonate (3r)



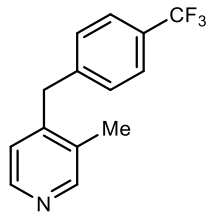
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-(((2-(trifluoromethoxy)phenyl)sulfonyl)oxy)pyridin-1-ium hexafluorophosphate(V) (370 mg, 0.50 mmol), tri-n-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), benzaldehyde (72 mL , 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a colorless oil (147 mg, 0.36 mmol, 72% yield). IR νmax/cm-1 (film): 3075, 3023, 2930, 1715, 1593, 1390, 1182, 1074; 1H NMR (400 MHz, CDCl3) □ 8.35 (d, J = 5.0 Hz, 1H), 8.19 (s, 1H), 8.03 (dd, J = 7.9, 1.7 Hz, 1H), 7.79 (ddd, J = 8.5, 7.5, 1.7 Hz, 1H), 7.55 (dt, J = 8.5, 1.4 Hz, 1H), 7.47 (td, J = 7.7, 1.1 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.28 – 7.22 (m, 1H), 7.20 – 7.12 (m, 2H), 7.05 – 6.97 (m, 1H), 4.09 (s, 2H) ; 13C NMR (100 MHz, CDCl3) □ □148.35, 146.93 (q, J = 1.9 Hz), 145.06, 144.29, 143.40, 137.33, 136.68, 131.87, 129.38, 128.84, 128.10, 126.97, 126.93, 125.64, 120.98 (q, J = 1.9 Hz), 120.29 (q, J = 261.6 Hz), 35.15; 19F NMR (376 MHz, Chloroform-d) δ -56.35; m/z LRMS (ESI + APCI) found [M+H]+ 410.1, $C_{19}H_{15}F_3NO_4S^+$ requires 410.1.

4-(4-methoxybenzyl)-3-methylpyridine (3s)



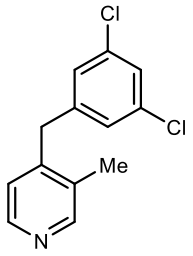
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 4-methoxybenzaldehyde (85 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 90% Et_2O in hexanes) afforded the title compound as a yellow oil (83 mg, 0.39 mmol, 77% yield). IR ν_{max}/cm^{-1} (film): 3032, 2929, 2825, 1665, 1615, 1512, 1248, 1176, 1034, 816; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.30 (m, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 5.0 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 3.89 (s, 2H), 3.79 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.37, 150.88, 148.39, 147.86, 132.09, 130.34, 129.98, 124.27, 114.19, 55.39, 37.96, 16.48; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 214.1, $C_{14}H_{16}NO^+$ requires 214.1.

3-methyl-4-(4-(trifluoromethyl)benzyl)pyridine (3t)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 4-(trifluoromethyl)benzaldehyde (96 mL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 90% Et_2O in hexanes) afforded the title compound as a colorless oil (122 mg, 0.49 mmol, 97% yield). IR ν_{max}/cm^{-1} (film): 3025, 2924, 2847, 1713, 1621, 1593, 1325, 1163, 1124, 1066; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 – 8.36 (m, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 5.0 Hz, 1H), 4.02 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.02, 147.91, 146.91, 142.48, 132.20, 129.27, 129.01 (q, *J* = 32.5 Hz), 125.74 (q, *J* = 3.7 Hz), 124.44, 124.26 (q, *J* = 272.0 Hz), 38.63, 16.49; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -62.51. *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 252.1, $C_{18}H_{17}NP^+$ requires 252.1.

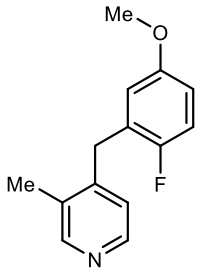
4-(3,5-dichlorobenzyl)-3-methylpyridine (3u)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 3,5-dichlorobenzaldehyde (123 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 90% Et_2O in hexanes) afforded the title compound as a white

powder (97 mg, 0.39 mmol, 77% yield). mp 116-120 ºC; IR ν_{max}/cm^{-1} (film): 3029, 2928, 2858, 1742, 1583, 1566, 1429, 1101; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.9 Hz, 2H), 7.24 (s, 1H), 7.07 – 6.11 (m, 3H), 3.91 (s, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.19, 148.07, 146.13, 141.77, 135.33, 132.09, 127.37, 127.05, 124.42, 38.19, 16.50; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 252.1, $C_{13}H_{12}Cl_2N^+$ requires 252.0.

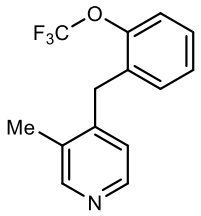
4-(2-fluoro-5-methoxybenzyl)-3-methylpyridine (3v)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 2-fluoro-5-methoxybenzaldehyde (87 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 50% Et_2O in hexanes to 95% Et_2O in hexanes) afforded the title compound as a colorless oil (83 mg, 0.36 mmol, 72% yield). IR ν_{max}/cm^{-1} (film): 3007, 2926, 2834, 1599, 1500, 1217, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.35 (d, *J* = 5.1 Hz, 1H), 6.99 (t, *J* = 9.1 Hz, 1H), 6.95 (d, *J* = 5.0 Hz, 1H), 6.74 (dt, *J* = 8.9, 3.5 Hz, 1H), 6.51 (dd, *J* = 6.1, 3.1 Hz, 1H), 3.92 (s, 2H), 3.72 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.68, 155.82 (d, *J* = 2.0 Hz), 154.31, 149.21 (d, *J* = 298.1 Hz), 146.71, 132.08, 126.05 (d, *J* = 17.7 Hz),

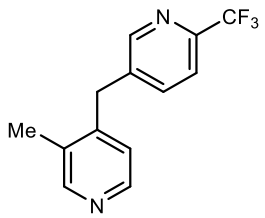
123.97, 116.15 (d, J = 4.0 Hz), 115.89 (d, J = 23.8 Hz), 112.79 (d, J = 8.0 Hz), 55.72, 31.83 (d, J = 2.8 Hz), 16.32; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -128.19 *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 232.1, $C_{14}H_{15}FNO^+$ requires 232.1.

3-methyl-4-(2-(trifluoromethoxy)benzyl)pyridine (3w)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (206 mg, 0.40 mmol), tri-*n*-butylphosphine (0.11 mL, 0.44 mmol), methyl lithium (275 μL, 0.44 mmol), 2-(trifluoromethoxy)benzaldehyde (80 μL, 0.68 mmol), AcOH:pyridine (4 mL), and THF (4.8 mL). Flash column chromatography (silica gel: 90% Et_2O in hexanes) afforded the title compound as a yellow oil (92 mg, 0.34 mmol, 86% yield). IR ν_{max}/cm^{-1} (film): 3027, 2826, 1616, 1525, 1248, 1010, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.36 (d, J = 5.0 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.21 (ddd, J = 7.6, 5.7, 2.9 Hz, 1H), 7.03 – 6.97 (m, 1H), 6.90 (d, J = 5.0 Hz, 1H), 4.00 (s, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.99, 147.91, 147.80 (d, J = 1.6 Hz), 146.51, 132.20, 131.09, 130.90, 128.33, 127.10, 120.77 (q, J = 1.6 Hz), 120.76 (q, J = 257.7 Hz), 32.66, 16.32; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -57.09 *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 268.1, $C_{14}H_{13}F_3NO^+$ requires 268.1.

5-((3-methylpyridin-4-yl)methyl)-2-(trifluoromethyl)pyridine (3x)



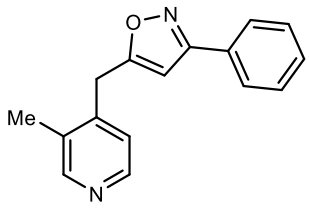
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 6-(trifluoromethyl)nicotinaldehyde (123 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (basic alumina: 80% Et_2O in CH_2Cl_2) afforded the title compound as a yellow oil (88 mg, 0.35 mmol, 70% yield). IR ν_{max}/cm^{-1} (film): 3052, 2920, 1668, 1592, 1336, 1132, 1084, 822, 733; ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.1 Hz, 1H), 8.44 (s, 1H), 8.42 (d, *J* = 5.0 Hz, 1H), 7.63 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.58 – 7.53 (m, 1H), 6.97 (d, *J* = 5.0 Hz, 1H), 4.05 (s, 2H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.31, 150.50, 148.15, 146.86 (q, *J* = 34.9 Hz), 145.60, 137.47, 137.38, 132.00, 124.24, 121.63 (q, *J* = 273.9 Hz), 120.56 (q, *J* = 2.8 Hz), 35.81, 16.49; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -67.87 *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 253.1, $C_{13}H_{12}F_3N_2^+$ requires 253.1.

One Pot:

Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), 3-methylpyridine (49 μL, 0.50 mmol) at 50 °C for 3 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 6-(trifluoromethyl)nicotinaldehyde (123 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0

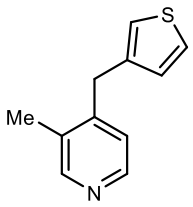
mL). Flash column chromatography (silica gel: 15% Acetone in CH_2Cl_2) afforded the title compound as a yellow oil (63 mg, 0.25 mmol, 50% yield).

5-((3-methylpyridin-4-yl)methyl)-3-phenylisoxazole (3y)



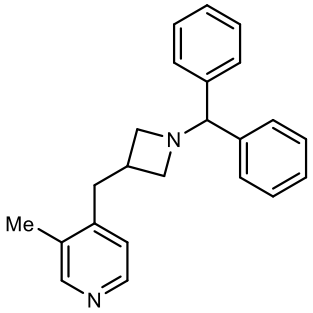
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 4-phenylfuran-2-carbaldehyde (121 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (basic alumina, gradient elution: 15% EtOAc in hexanes to 50% EtOAc in hexanes. 2nd column, silica gel: 90% Et_2O in hexanes) afforded the title compound as a colorless oil (73 mg, 0.29 mmol, 58% yield). IR ν_{max}/cm^{-1} (film): 2963, 2912, 2842, 1677, 1597, 1444, 1406, 769, 694; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.44 (d, *J* = 5.0 Hz, 1H), 7.75 (dd, *J* = 6.7, 3.1 Hz, 2H), 7.47 – 7.39 (m, 3H), 7.15 (d, *J* = 5.0 Hz, 1H), 6.21 (s, 1H), 4.13 (s, 2H), 2.35 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.17, 162.67, 151.25, 148.11, 143.19, 132.01, 130.16, 128.99, 128.92, 126.82, 124.14, 100.54, 30.44, 16.28; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 251.1, $C_{16}H_{15}N_2O^+$ requires 251.1.

3-methyl-4-(thiophen-3-ylmethyl)pyridine (3z)



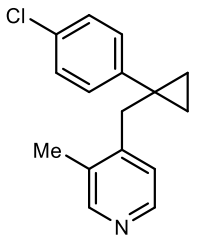
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), thiophene-3-carbaldehyde (61 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 25% EtOAc in hexanes) afforded the title compound as a yellow oil (70 mg, 0.37 mmol, 74% yield). IR ν_{max}/cm^{-1} (film): 3097, 3052, 2963, 2915, 1747, 1674, 1593, 1406, 825, 762; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 – 8.23 (m, 2H), 7.28 (dd, J = 4.9, 3.0 Hz, 1H), 7.00 (d, J = 5.0 Hz, 1H), 6.92 – 6.77 (m, 2H), 3.94 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 150.96, 147.96, 147.63, 138.57, 131.97, 128.32, 126.16, 124.08, 121.92, 33.64, 16.31; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 190.1, $C_{11}H_{12}NS^+$ requires 190.1.

4-((1-benzhydrylazetidin-3-yl)methyl)-3-methylpyridine (3aa)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 1-benzhydrylazetidine-3-carbaldehyde (176 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 75% EtOAc in hexanes) afforded the title compound as a colorless oil (67 mg, 0.21 mmol, 41% yield). IR ν_{max}/cm^{-1} (film): 3017, 2943, 2821, 1587, 1452, 904, 707, 644; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.28 (d, *J* = 5.1 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 4H), 7.30 – 7.19 (m, 5H), 7.17 (t, *J* = 7.3 Hz, 2H), 6.91 (d, *J* = 5.0 Hz, 1H), 4.32 (s, 1H), 3.36 (d, *J* = 7.2 Hz, 2H), 2.91 – 2.72 (m, 5H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.75, 147.67, 147.42, 142.24, 131.73, 128.56, 127.57, 127.23, 122.93, 78.40, 59.45, 36.78, 29.09, 16.35; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 329.2, $C_{23}H_{25}N_2^+$ requires 329.2.

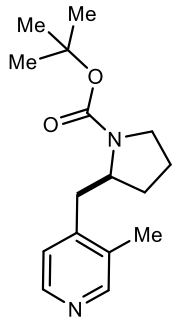
4-((1-(4-chlorophenyl)cyclopropyl)methyl)-3-methylpyridine (3ab)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 1-(4-chlorophenyl)cyclopropane-1-carbaldehyde (126 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (basic alumina, gradient elution: 75% Et_2O in

hexanes to 100% Et_2O) afforded the title compound as a yellow oil (81 mg, 0.31 mmol, 63% yield). Product rapidly decomposes. IR ν_{max}/cm^{-1} (film): 3077, 2920, 3845, 1917, 1595, 1495, 1099, 833; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.28 (s, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.08 – 6.99 (m, 3H), 2.91 (s, 2H), 2.17 (s, 3H), 2.02 (s, 3H), 1.03 – 0.33 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.61, 147.12, 146.85, 143.07, 132.41, 132.07, 130.00, 128.45, 124.53, 41.02, 24.39, 16.42, 13.55; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 258.1, $C_{16}H_{17}ClN^+$ requires 258.1.

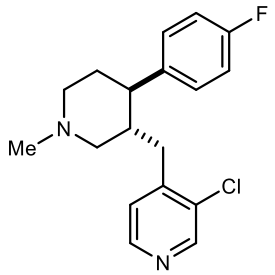
tert-butyl (S)-2-((3-methylpyridin-4-yl)methyl)pyrrolidine-1-carboxylate (3ac)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methylpyridin-1-ium hexafluorophosphate(V) (257 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), tert-butyl (S)-2-formylpyrrolidine-1-carboxylate (140 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (basic alumina, gradient elution: 85% Et_2O in hexanes to 100% Et_2O) afforded the title compound as a colorless oil (49 mg, 0.18 mmol, 36% yield). IR ν_{max}/cm^{-1} (film): 2979, 2932, 2363, 1691, 1590, 1396, 1169, 1115, 731; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37-8.34 (m, 2H), 7.03 (d, *J* = 19.0 Hz, 1H), 4.07 (s, 1H), 3.42-3.35 (m, 2H), 3.13 (dd, *J* = 75.3, 13.3 Hz, 1H), 2.54 (dd, *J* = 13.2, 9.4 Hz, 1H), 2.42 – 2.12 (m, 3H), 1.93-1.74 (m, 3H), 1.62 (s, 1H),

1.54 – 1.34 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.58, 150.94, 147.42, 146.79, 132.71, 125.09, 79.76, 56.80, 46.79, 37.26, 30.09, 28.64, 23.64, 16.61; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 277.3, $C_{16}H_{25}N_2O_2^+$ requires 277.2.

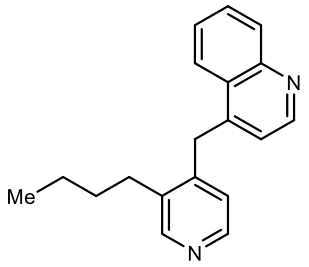
3-chloro-4-(((3S,4R)-4-(4-fluorophenyl)-1-methylpiperidin-3-yl)methyl)pyridine (3ad)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-chloropyridin-1-ium hexafluorophosphate(V) (267 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), (3S,4R)-4-(4-fluorophenyl)-1-methylpiperidine-3-carbaldehyde (155 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (neutralized silica: 10% MeOH in CH_2Cl_2) afforded the title compound as a yellow oil (58 mg, 0.19 mmol, 37% yield). IR ν_{max}/cm^{-1} (film): 3077, 2920, 3845, 1917, 1595, 1495, 1099, 833; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.32 (d, *J* = 4.9 Hz, 1H), 7.43 – 7.13 (m, 2H), 7.02 (t, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 4.9 Hz, 1H), 3.19 (d, *J* = 10.6 Hz, 1H), 2.93 (d, *J* = 10.8 Hz, 1H), 2.60 (dd, *J* = 14.2, 3.4 Hz, 1H), 2.52 – 2.22 (m, 5H), 2.21 – 2.05 (m, 2H), 1.90 (dd, *J* = 13.5, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.19, 160.75, 149.63, 147.74, 145.87, 132.27, 129.22 (d, *J* = 8.0 Hz), 125.40, 115.79 (d, *J* = 21.3 Hz),

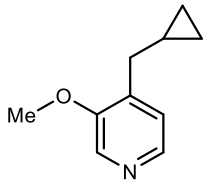
59.86, 55.76, 47.57, 45.39, 40.55, 34.92, 29.80; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -115.54; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 319.2, $C_{18}H_{21}ClFN_2^+$ requires 319.1.

4-((3-butylpyridin-4-yl)methyl)quinoline (3ae)



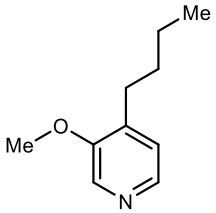
Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-butylpyridin-1-ium perchlorate (255 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), quinoline-4-carbaldehyde (110 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 75% EtOAc in CH_2Cl_2. 2nd column: 3% MeOH in CH_2Cl_2) afforded the title compound as a yellow oil (105 mg, 0.38 mmol, 76% yield). IR ν_{max}/cm^{-1} (film): 2951, 2859, 1705, 1590, 1400, 1227, 1041, 760, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 4.4 Hz, 1H), 8.49 (s, 1H), 8.32 (d, *J* = 5.1 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.90 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.74 (ddd, *J* = 8.3, 6.8, 1.4 Hz, 1H), 7.57 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 6.96 (d, *J* = 4.4 Hz, 1H), 6.80 (d, *J* = 5.0 Hz, 1H), 4.44 (s, 2H), 2.93 – 2.48 (m, 2H), 1.60 (tt, *J* = 8.0, 6.3 Hz, 2H), 1.38 (h, *J* = 7.3 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.66, 150.40, 148.39, 147.76, 145.38, 144.73, 136.61, 130.53, 129.60, 127.51, 127.09, 124.59, 123.43, 121.69, 34.40, 32.74, 30.21, 22.74, 13.98; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 277.2, $C_{18}H_{17}NP^+$ requires 277.2

4-(cyclopropylmethyl)-3-methoxypyridine (3af)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methoxypyridin-1-ium hexafluorophosphate(V) (265 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), cyclopropanecarbaldehyde (52 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel, gradient elution: 50% Et_2O in hexanes to 75% Et_2O in hexanes) afforded the title compound as a yellow oil (42 mg, 0.26 mmol, 51% yield). IR ν_{max}/cm^{-1} (film): 3055, 3008, 2955, 1661, 1576, 1443, 1094, 796, 754, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 2H), 7.25 (s, 1H), 3.91 (s, 3H), 2.53 (d, *J* = 7.0 Hz, 2H), 0.65 – 0.47 (m, 2H), 0.19 (dt, *J* = 5.9, 4.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.04, 142.43, 139.70, 132.20, 124.02, 55.96, 33.64, 9.58, 4.78.; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 164.2, $C_{10}H_{14}NO^+$ requires 164.1.

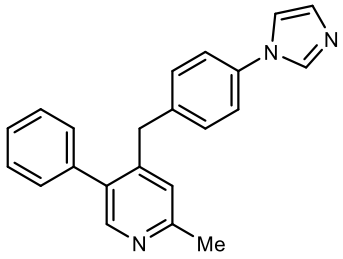
4-butyl-3-methoxypyridine (3ag)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methoxypyridin-1-ium hexafluorophosphate(V) (265 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), butyraldehyde (63

μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL) Flash column chromatography (silica gel, gradient elution: 50% Et_2O in hexanes to 90% Et_2O in hexanes) afforded the title compound as a yellow oil (38 mg, 0.23 mmol, 46% yield). IR ν_{max}/cm^{-1} (film): 3028, 2969, 1656, 1505, 1424, 1024, 864, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.16 (s, 1H), 7.06 (d, *J* = 4.7 Hz, 1H), 3.91 (s, 3H), 2.69 – 2.55 (m, 2H), 1.64 – 1.52 (m, 2H), 1.43 – 1.31 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.62, 140.14, 132.75 (2C), 124.40, 56.03, 31.12, 29.15, 22.67, 14.05; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 166.2, $C_{10}H_{16}NO^+$ requires 166.1.

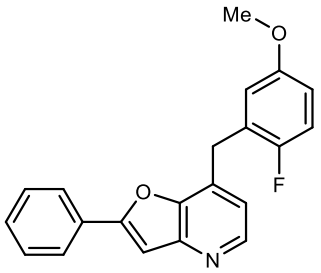
4-(4-(1H-imidazol-1-yl)benzyl)-2-methyl-5-phenylpyridine (3ah)



Prepared according to general procedure B using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-methyl-5-phenylpyridin-1-ium hexafluorophosphate(V) (295 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 4-(1H-imidazol-1-yl)benzaldehyde (121 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography basic alumina: 75% Et_2O in hexanes; 2nd column, silica gel: 40% Acetone: CH_2Cl_2) afforded the title compound as a white powder (90 mg, 0.28 mmol, 55% yield). mp 79-82 ºC; IR ν_{max}/cm^{-1} (film): 3119, 2922, 1689, 1601, 1520, 1306, 964; ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.84 (s, 1H), 7.59 – 7.39 (m, 3H), 7.33 – 7.25 (m, 5H), 7.21 (s, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.01 (s, 1H), 3.99 (s, 2H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.63, 149.95,

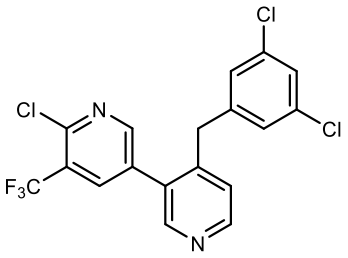
146.88, 139.09, 137.71, 135.85, 135.67, 135.17, 130.56, 130.39, 129.61, 128.62, 127.85, 124.14, 121.63, 118.31, 38.08, 24.27; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 326.2, $C_{22}H_{20}N_3^+$ requires 326.2.

7-(2-fluoro-5-methoxybenzyl)-2-phenylfuro[3,2-b]pyridine (3ai)



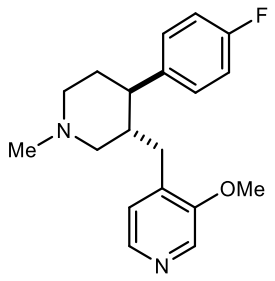
Prepared according to general procedure B using 4-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-phenylfuro[3,2-b]pyridin-4-ium hexafluorophosphate(V) (308 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 2-fluoro-5-methoxybenzaldehyde (87 μL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 75% Et_2O in hexanes) afforded the title compound as a white powder (153 mg, 0.46 mmol, 92% yield). mp 80-82 ºC; IR ν_{max}/cm^{-1} (film): 3099, 2926, 2834, 1884, 1718, 1601, 1498, 1385, 1207, 1038; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 5.0 Hz, 1H), 7.90 (dd, *J* = 7.3, 1.4 Hz, 2H), 7.48 (td, *J* = 6.9, 6.0, 1.2 Hz, 2H), 7.45 – 7.34 (m, 1H), 7.21 (d, *J* = 1.0 Hz, 1H), 7.11 – 6.94 (m, 2H), 6.84 (dd, *J* = 6.1, 3.1 Hz, 1H), 6.79 – 6.69 (m, 1H), 4.30 (s, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.33, 156.82, 155.83, 154.45, 148.86, 147.09, 146.53, 130.56 (d, *J* = 120.0 Hz), 129.64, 129.05, 125.92 (d, *J* = 17.7 Hz), 125.41, 119.39, 116.56 (d, *J* = 4.0 Hz), 116.08 (d, *J* = 23.8 Hz), 113.33 (d, *J* = 7.9 Hz), 102.76, 55.84, 28.74 (d, *J* = 3.0 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ: -128.26; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 334.2, $C_{21}H_{17}FNO_2^+$ requires 334.1.

6'-chloro-4-(3,5-dichlorobenzyl)-5'-(trifluoromethyl)-3,3'-bipyridine (3ak)



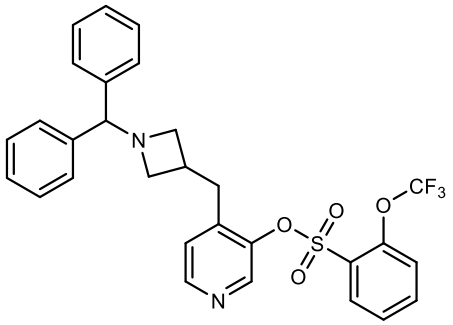
Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), 6-chloro-5-(trifluoromethyl)-3,3'-bipyridine (207 mg, 0.50 mmol) at 50 °C for 3 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 µL, 0.55 mmol), 3,5-dichlorobenzaldehyde (123 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 90% Et_2O in hexanes; 2nd column, silica gel: 20% EtOAc in CH_2Cl_2) afforded the title compound as a white amorphous solide (177 mg, 0.42 mmol, 84% yield).IR ν_{max}/cm^{-1} (film): 3051, 2917, 2851, 1704, 1570, 1431, 1147, 1051, 1022; ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 5.1 Hz, 1H), 8.49 (s, 1H), 8.43 (d, *J* = 2.3 Hz, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.27 – 7.15 (m, 2H), 6.77 (d, *J* = 1.8 Hz, 2H), 3.87 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.92, 150.92, 150.48, 148.91 (d, *J* = 1.6 Hz), 146.11, 141.31, 137.17 (q, *J* = 4.9 Hz), 135.60, 132.14, 131.85, 127.40, 127.24, 125.27 (q, *J* = 33.5 Hz), 121.92 (q, *J* = 273.3 Hz), 38.38; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -63.76 *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 417.1, $C_{18}H_{11}Cl_3F_3N_2^+$ requires 417.0.

4-(((3S,4R)-4-(4-fluorophenyl)-1-methylpiperidin-3-yl)methyl)-3-methoxypyridine (3al)



Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), 3-methoxypyridine (50 μL, 0.50 mmol) at 50 °C for 3 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), (3S,4R)-4-(4-fluorophenyl)-1-methylpiperidine-3-carbaldehyde (155 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (neutralized silica gel: 8% MeOH in CH_2Cl_2), then washed with saturated aqueous $NaHS_2O_3$ then $NaHCO_3$ and extracted with EtOAc to afford the title compound as a yellow oil (38 mg, 0.12 mmol, 24% yield). IR ν_{max}/cm^{-1} (film): 3038, 2943, 2850, 2772, 1721, 1510, 1416, 1263, 1225, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 8.01 (d, *J* = 4.7 Hz, 1H), 7.15 (dd, *J* = 8.5, 5.6 Hz, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 4.7 Hz, 1H), 3.75 (s, 3H), 2.88 (s, 1H), 2.68 (d, *J* = 11.6 Hz, 1H), 2.45 (dd, *J* = 13.3, 2.8 Hz, 1H), 2.26 – 2.12 (m, 5H), 2.01 (dd, *J* = 13.3, 10.1 Hz, 2H), 1.76-1.65 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.92, 160.50, 154.07, 142.48, 137.30, 132.90, 129.25 (d, *J* = 7.5 Hz), 125.18, 115.36 (d, *J* = 21.1 Hz), 61.18, 56.37, 55.76, 48.42, 46.38, 40.91, 32.44, 29.85; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -116.78 *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 315.2, $C_{19}H_{24}FN_2O^+$ requires 315.2.

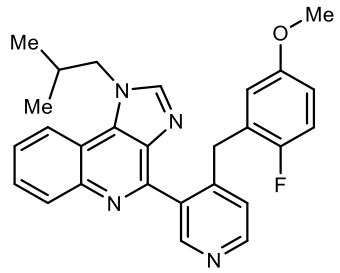
4-((1-benzhydrylazetidin-3-yl)methyl)pyridin-3-yl 2-(trifluoromethoxy)benzenesulfonate (3am)



Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), pyridin-3-yl 2-(trifluoromethoxy)benzenesulfonate (160 mg, 0.50 mmol) at 50 °C for 3 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 µL, 0.55 mmol1-benzhydrylazetidine-3-carbaldehyde (176 mg, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 50% EtOAc in CH_2Cl_2) afforded the title compound as a brown amorphous solid (109 mg, 0.20 mmol, 39% yield). IR ν_{max}/cm^{-1} (film): 3063.9, 2943.4, 2820.1, 2360.6, 1592.9; ^1H NMR (400 MHz, CD_3CN) δ 8.36 (d, *J* = 5.0 Hz, 1H), 8.16 (s, 1H), 8.01 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.93 (ddd, *J* = 8.4, 7.5, 1.7 Hz, 1H), 7.77 – 7.65 (m, 1H), 7.59 (td, *J* = 7.8, 1.0 Hz, 1H), 7.45 – 7.34 (m, 4H), 7.35 – 7.23 (m, 4H), 7.23 – 7.07 (m, 3H), 4.33 (s, 1H), 3.19 (t, *J* = 7.2 Hz, 2H), 2.85 (d, *J* = 7.5 Hz, 2H), 2.72 (dd, *J* = 7.2, 6.0 Hz, 2H), 2.68 – 2.53 (m, 1H); ^{13}C NMR (100 MHz, CD_3CN) δ 149.50, 147.35 (q, *J* = 1.9 Hz), 146.27, 144.34, 143.86, 143.74, 138.52, 132.83, 129.42, 128.76, 128.73, 128.22, 128.03, 126.08, 122.61 (q, *J* = 1.9 Hz), 121.25 (q, *J* = 259.7 Hz),78.42, 59.29, 33.94, 30.04; ^{19}F NMR

(376 MHz, CD_3CN) δ -57.11 *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 555.2, $C_{29}H_{26}F_3N_2O_4S^+$ requires 555.1.

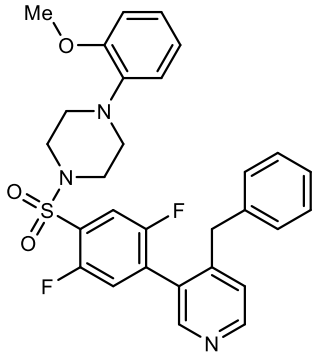
4-(4-(2-fluoro-5-methoxybenzyl)pyridin-3-yl)-1-isobutyl-1H-imidazo[4,5-c]quinoline (3an)



Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), 1-isobutyl-4-(pyridin-3-yl)-1H-imidazo[4,5-c]quinoline (151 mg, 0.50 mmol) at 50 °C for 3 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 2-fluoro-5-methoxybenzaldehyde (87 mL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (neutralized silica gel: 90% EtOAc in CH_2Cl_2; 2nd column, silica gel, gradient elution: 2% MeOH in CH_2Cl_2 to 4% MeOH in CH_2Cl_2) afforded the title compound as a white powder (140 mg, 0.32 mmol, 64% yield). mp 48-52 ºC; IR ν_{max}/cm^{-1} (film): 2957, 2908, 2865, 1626, 1498, 1209, 1039, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.59 (d, *J* = 5.2 Hz, 1H), 8.32 (d, *J* = 8.1 Hz, 1H), 8.24 – 8.10 (m, 1H), 7.92 (s, 1H), 7.82 – 7.58 (m, 2H), 7.20 (d, *J* = 5.2 Hz, 1H), 6.79 (t, *J* = 9.0 Hz, 1H), 6.56 (dt, *J* = 8.8, 3.6 Hz, 1H), 6.46 (dd, *J* = 6.1, 3.2 Hz, 1H), 4.40 (d, *J* = 7.4 Hz, 2H), 4.21 (s, 2H), 3.52 (s, 3H), 2.42 (sp, *J* = 6.8 Hz, 1H), 1.08 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.58, 155.40 (d, *J* = 2.0 Hz), 154.21, 151.55, 151.12, 149.81, 148.04, 144.49, 144.22, 137.38, 133.39, 133.28, 129.35 (d, *J* =

360.5 Hz), 126.82, 126.66 (d, J = 17.6 Hz), 124.58, 120.06, 117.78, 115.80 (d, J = 4.1 Hz), 115.60 (d, J = 24.0 Hz), 113.44 (d, J = 7.9 Hz), 55.49, 55.21, 32.19 (d, J = 2.4 Hz), 28.90, 19.91; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -128.13 *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 441.3, $C_{27}H_{26}FN_4O^+$ requires 441.2.

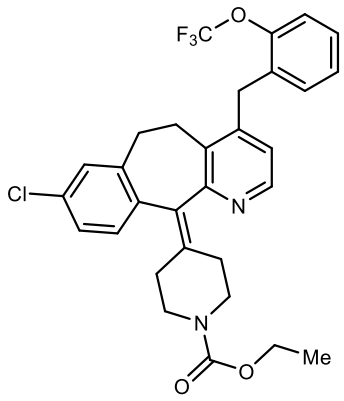
1-((4-(4-benzylpyridin-3-yl)-2,5-difluorophenyl)sulfonyl)-4-(2-methoxyphenyl)piperazine (3ao)



Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), 1-((2,5-difluoro-4-(pyridin-3-yl)phenyl)sulfonyl)-4-(2-methoxyphenyl)piperazine (223 mg, 0.50 mmol) at 50 ºC for 3 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 µL, 0.55 mmol), benzaldehyde (72 mL, 0.70 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (basic alumina: 80% Et_2O in hexanes; 2nd column, silica gel: 50% EtOAc in hexanes) afforded the title compound as a brown powder (152 mg, 0.28 mmol, 57% yield). mp 65-72 ºC; IR ν_{max}/cm^{-1} (film): 3049, 2919, 2819, 1624, 1589,

1500, 1394, 1242, 1165, 949; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.66 (d, *J* = 5.1 Hz, 1H), 8.52 (s, 1H), 7.70 (dd, *J* = 8.1, 5.3 Hz, 1H), 7.48 – 7.22 (m, 4H), 7.10 (ddd, *J* = 15.1, 8.8, 4.9 Hz, 2H), 7.04 – 6.95 (m, 4H), 6.94 (d, *J* = 8.0 Hz, 1H), 3.97 (s, 2H), 3.91 (s, 3H), 3.50 (t, *J* = 4.8 Hz, 4H), 3.24 (t, *J* = 4.9 Hz, 4H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 156.20 (dd, *J* = 40.3, 2.6 Hz), 153.70 (dd, *J* = 46.6, 2.4 Hz), 152.28, 150.56, 149.98, 148.85, 140.30, 138.05, 132.31 (dd, *J* = 19.5, 8.2 Hz), 129.04, 128.85, 126.94, 125.94 (dd, *J* = 17.4, 6.5 Hz), 124.95, 123.99, 121.19, 120.35 (dd, *J* = 25.2, 3.1 Hz), 118.70, 118.48, 118.20, 111.31, 55.50, 50.33, 46.30, 39.08 (d, *J* = 2.2 Hz).; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.17 (ddd, *J* = 18.6, 9.4, 5.7 Hz), -116.45 (ddd, *J* = 18.5, 8.0, 5.4 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 536.2, $C_{29}H_{28}F_2N_3O_3S^+$ requires 536.2.

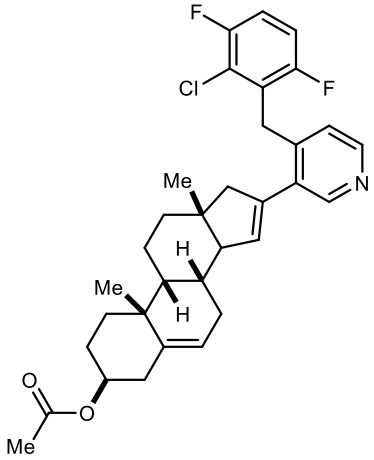
ethyl 4-(8-chloro-4-(2-(trifluoromethoxy)benzyl)-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (3ap)



Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), loratadine (191 mg, 0.50 mmol) at 50 ºC for 3 hours. The procedure continues with tri-*n*-

butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 2-(trifluoromethoxy)benzaldehyde (100 mL, 0.7 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 50% EtOAc in CH_2Cl_2) afforded the title compound as a white powder (186 mg, 0.33 mmol, 67% yield). mp 55-62 ºC; IR ν_{max}/cm^{-1} (film): 3042, 2978, 2917, 2848, 1688, 1437, 1225, 1167, 910; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 5.0 Hz, 1H), 7.31 (d, *J* = 6.0 Hz, 2H), 7.20 (td, *J* = 6.8, 5.8, 2.7 Hz, 1H), 7.12 (s, 2H), 7.07 (s, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.84 (d, *J* = 5.1 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.02 (d, *J* = 3.8 Hz, 2H), 3.81 (s, 2H), 3.42 – 3.04 (m, 4H), 2.86 (ddd, *J* = 15.6, 7.8, 4.4 Hz, 1H), 2.58 (ddd, *J* = 14.9, 9.8, 4.4 Hz, 1H), 2.52 – 2.30 (m, 3H), 2.23 (dt, *J* = 14.3, 4.8 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.75, 155.60, 147.60, 146.83, 139.22, 137.04, 136.86, 134.58, 133.00, 132.11, 131.25, 130.98 (d, *J* = 2.2 Hz), 129.39, 128.47, 127.17, 126.17, 123.89, 120.81 (d, *J* = 1.7 Hz), 120.72 (q, *J* = 258.7 Hz), 61.43, 44.87, 44.74, 32.64, 31.37, 30.75, 30.70, 27.09, 14.78; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -57.03 *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 557.3, $C_{30}H_{29}ClF_3N_2O_3^+$ requires 557.2.

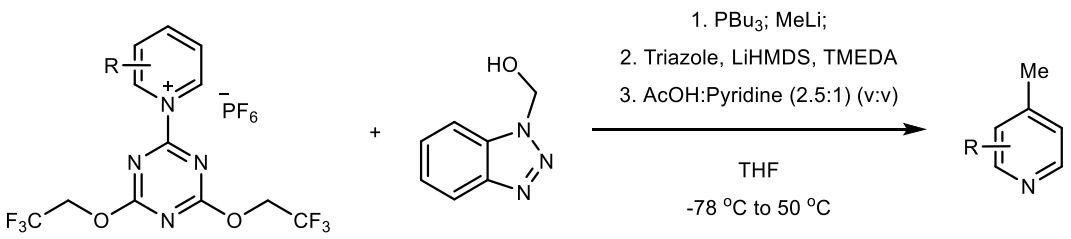
(3S,8R,9R,10R,13R)-16-(4-(2-chloro-3,6-difluorobenzyl)pyridin-3-yl)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (3aq)



Prepared according to general procedure C stirring 2-chloro-4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazine (171 mg, 0.55 mmol), potassium hexafluorophosphate (101 mg, 0.55 mmol), abiraterone acetate (196 mg, 0.50 mmol) at 50 °C for 3 hours. The procedure continues with tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 μL, 0.55 mmol), 2-chloro-3,6-difluorobenzaldehyde (88 mg, 0.7 mmol), AcOH:pyridine (5 mL), and THF (6.0 mL). Flash column chromatography (silica gel: 10% EtOAc in toluene; 2nd column, silica gel: 50% Et_2O in hexanes) afforded the title compound as a white powder (71 mg, 0.13 mmol, 26% yield). mp 172-176 ºC; IR ν_{max}/cm^{-1} (film): 3038, 293, 2847, 1724, 1477, 1238, 1032, 953; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.30 (s, 1H), 7.20 – 7.07 (m, 1H), 7.01 (td, *J* = 8.7, 4.2 Hz, 1H), 6.65 (s, 1H), 5.96 – 5.77 (m, 1H), 5.43 (d, *J* = 5.0 Hz, 1H), 4.77 – 4.46 (m, 1H), 4.34 – 4.05 (m, 2H), 2.52 – 2.29 (m, 3H), 2.25 – 2.06 (m, 2H), 2.04 (s, 3H), 1.91 – 1.83 (m, 2H), 1.83 – 1.47 (m, 8H), 1.16 (td, *J* = 14.5, 13.9, 5.0 Hz, 2H), 1.08 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.65, 160.96 (dd, *J*= 235.4, 3.7 Hz), 155.02 (dd, *J*= 240.6, 5.1 Hz), 150.27, 149.22, 148.14, 145.53, 140.20, 131.67, 127.11, 126.91, 122.92 (dd, *J* = 19.3, 6.4 Hz), 122.40, 122.19, 115.44 (dd, *J* = 23.7, 9.6 Hz), 114.49 (dd, *J* = 24.9, 8.1 Hz), 73.97, 57.33, 50.57, 49.87, 38.27, 37.07, 36.98, 35.14, 32.51, 27.87, 21.56, 20.87, 19.38, 16.76.; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -117.35 (d, *J* = 7.6 Hz). *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 552.3, $C_{33}H_{37}ClF_2NO_2^+$ requires 552.2.

A 2.6. Preparation of Methylated Pyridines

General Procedure D (Methylation)

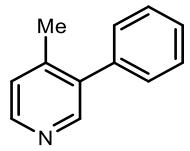


An oven-dried 16 mL vial equipped with a stir bar was charged with the pyridinium (1.0 equiv) and subjected to three rapid cycles of vacuum/nitrogen backfill before THF (0.083 M) was added. Tri-*n*-butylphosphine (1.1 equiv) was added dropwise and stirred for one hour. The reaction was then cooled to -78 °C and methyl lithium (1.6 M, 1.1 equiv) was added dropwise and stirred for 15 minutes. In a separate oven-dried 16 mL equipped with a stir bar was charged LiHMDS (2.5 equiv). THF (1.0 M) was added followed by TMEDA (2.5 equiv). The LiHMDS solution was cooled to -78 °C and a 0.25 M solution of 1*H*-benzotriazole-1-methanol (2.5 equiv) in THF was added dropwise over 15 minutes‡ and stirred for 20 minutes. The generated formaldehyde solution was then added in one portion via syringe to the ylide and stirred for 2 hours at the stated temperature. Then a 2.5:1 (v:v) mixture of AcOH:pyridine (2-4 mL depending on the scale) was added at room temperature and then heated to 50 °C overnight*. The reaction was diluted with ethyl acetate and quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (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 column chromatography under the stated conditions to provide the methylated heterocycle.

‡ Slow addition over 15 minutes is important for the reaction.

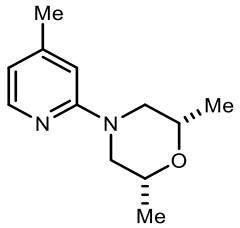
* Not all reactions required overnight stirring. Monitoring by LCMS the disappearance of the pyridinium can allow for shorter reaction times.

4-methyl-3-phenylpyridine (3ar)



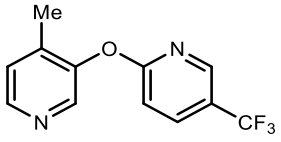
Prepared according to general procedure D using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-phenylpyridin-1-ium hexafluorophosphate(V) (231 mg, 0.4 mmol), tri-*n*-butylphosphine (110 μL, 0.44 mmol), methyl lithium (275 μL, 0.44 mmol), 1*H*-benzotriazole-1-methanol (149 mg, 1.0 mmol), LiHMDS (167 mg, 1.0 mmol), TMEDA (150 μL, 1.0 mmol), AcOH:pyridine (3 mL), and THF (4.8 mL). The olefination step was warmed to room temperature. Flash column chromatography (silica gel: 2% MeOH in CH_2Cl_2; 2nd column, silica gel: 90% Et_2O in hexanes) afforded the title compound as a yellow oil (37 mg, 0.22 mmol, 55% yield). IR ν_{max}/cm^{-1} (film): 3047, 3016, 2912, 1714, 1591, 1402, 1325, 1263, 1132, 1076, 1007; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.47 (app br s, 2H), 7.52 – 7.37 (m, 3H), 7.36 – 7.29 (m, 2H), 7.21 (d, *J* = 4.9 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.93, 148.25, 144.70, 137.96, 129.36, 128.52, 127.73, 125.39 (2C), 19.93; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 170.1, $C_{12}H_{12}N^+$ requires 170.1.

(2R,6S)-2,6-dimethyl-4-(4-methylpyridin-2-yl)morpholine (3as)



Prepared according to general procedure D using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-((2R,6S)-2,6-dimethylmorpholino)pyridin-1-ium hexafluorophosphate(V) (245 mg, 0.40 mmol), tri-*n*-butylphosphine (0.11 mL, 0.44 mmol), methyl lithium (275 μL, 0.44 mmol), 1*H*-benzotriazole-1-methanol (149 mg, 1.0 mmol), LiHMDS (167 mg, 1.0 mmol), TMEDA (0.15 mL, 1.0 mmol), AcOH:pyridine (4 mL), and THF (4.8 mL). The olefination step was run at -78 ^{o}C. Flash column chromatography (silica gel: 30% Et_2O in hexanes) afforded the title compound as a yellow oil (35 mg, 0.17 mmol, 42% yield). IR ν_{max}/cm^{-1} (film): 2971, 2928, 2848, 1600, 1448, 1173, 1078, 870; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (dd, *J* = 5.1, 0.8 Hz, 1H), 6.49 (d, *J* = 5.1 Hz, 1H), 6.45 (s, 1H), 4.03 (dd, *J* = 13.2, 2.1 Hz, 2H), 3.73 (ddd, *J* = 10.5, 6.4, 2.5 Hz, 2H), 2.50 (dd, *J* = 12.5, 10.5 Hz, 2H), 2.27 (s, 3H), 1.27 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.65, 148.73, 147.59, 115.24, 107.66, 71.76, 51.11, 21.57, 19.14; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 207.2, $C_{12}H_{19}N_2O^+$ requires 207.1.

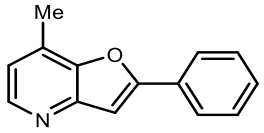
2-((4-methylpyridin-3-yl)oxy)-5-(trifluoromethyl)pyridine (3at)



Prepared according to general procedure D using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-((5-(trifluoromethyl)pyridin-2-yl)oxy)pyridin-1-ium hexafluorophosphate(V) (264

mg, 0.40 mmol), tri-*n*-butylphosphine (0.11 mL, 0.44 mmol), methyl lithium (275 µL, 0.44 mmol), 1*H*-benzotriazole-1-methanol (149 mg, 1.0 mmol), LiHMDS (167 mg, 1.0 mmol), TMEDA (0.15 mL, 1.0 mmol), AcOH:pyridine (4 mL), and THF (4.8 mL). The olefination step was warmed to room temperature. Flash column chromatography (neutralized silica gel: 70% Et_2O in hexanes) afforded the title compound as a white crystalline solid (54 mg, 0.21 mmol, 53% yield). IR ν_{max}/cm^{-1} (film): 3054, 2912, 2843, 1681, 1610, 1327, 1261, 1124, 1078, 1012; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 – 8.33 (m, 3H), 7.94 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.26 – 7.25 (m, 1H), 7.10 (dd, *J* = 8.7, 0.8 Hz, 1H), 2.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.12, 148.90, 146.70, 145.52 (q, *J* = 4.4 Hz), 143.89, 140.40, 137.14 (q, *J* = 3.2 Hz), 126.22, 123.71 (q, *J* = 271.5 Hz), 122.09 (q, *J* = 33.3 Hz), 111.11, 16.09; ^{19}F NMR (376 MHz, Chloroform-*d*) δ -61.71; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 255.1, $C_{12}H_{10}F_3N_2O^+$ requires 255.1.

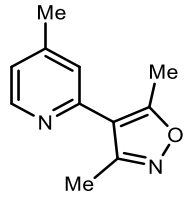
7-methyl-2-phenylfuro[3,2-b]pyridine (3au)



Prepared according to general procedure D using 4-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-phenylfuro[3,2-b]pyridin-4-ium hexafluorophosphate(V) (247 mg, 0.40 mmol), tri-*n*-butylphosphine (0.11 mL, 0.44 mmol), methyl lithium (275 µL, 0.44 mmol), 1*H*-benzotriazole-1-methanol (149 mg, 1.0 mmol), LiHMDS (167 mg, 1.0 mmol), TMEDA (0.15 mL, 1.0 mmol), AcOH:pyridine (4 mL), and THF (4.8 mL). The olefination step was run at -78 °C. Flash column chromatography (neutralized silica gel: 70% Et_2O in hexanes) afforded the title compound as a

white powder (35 mg, 0.17 mmol, 42% yield). mp 58-61 ºC; IR ν_{max}/cm^{-1} (film): 3097, 3049, 2914, 2848, 1723, 1624, 1572, 1387, 1257, 1213, 1016, 906, 866; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.39 (d, *J* = 4.9 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.48 (app t, *J* = 7.7 Hz, 2H), 7.44 – 7.33 (m, 1H), 7.20 (s, 1H), 7.02 (d, *J* = 4.8 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.11, 148.35, 146.11, 130.08, 129.68, 129.56, 129.03, 125.41, 120.54 (2C), 102.74, 14.82; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 210.5, $C_{14}H_{12}NO^+$ requires 210.1.

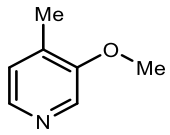
3,5-dimethyl-4-(4-methylpyridin-2-yl)isoxazole (3av)



Prepared according to general procedure D using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-2-(3,5-dimethylisoxazol-4-yl)pyridin-1-ium hexafluorophosphate(V) (238 mg, 0.40 mmol), tri-*n*-butylphosphine (0.11 mL, 0.44 mmol), methyl lithium (275 µL, 0.44 mmol), 1*H*-benzotriazole-1-methanol (149 mg, 1.0 mmol), LiHMDS (167 mg, 1.0 mmol), TMEDA (0.15 mL, 1.0 mmol), AcOH:pyridine (4 mL), and THF (4.8 mL). The olefination step was run at -78 ºC. Flash column chromatography (neutralized silica gel: 60% Et_2O in hexanes; 2nd column, silica gel: 10% EtOAc in CH_2Cl_2) afforded the title compound as a yellow oil (33 mg, 0.18 mmol, 44% yield). IR ν_{max}/cm^{-1} (film): 3007, 2924, 2848, 1624, 1605, 1429, 1254, 1066, 854; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.53 (d, *J* = 5.0 Hz, 1H), 7.13 (s, 1H), 7.06 (d, *J* = 5.0 Hz, 1H), 2.56 (s, 3H), 2.41 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.37, 158.87, 150.74, 149.77,

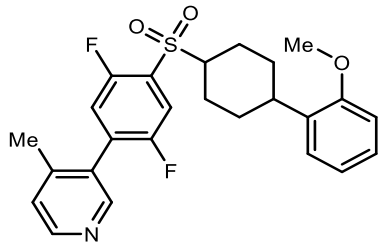
147.79, 124.06, 122.97, 116.26, 21.29, 12.44, 11.55.; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 189.1, $C_{11}H_{13}N_2O^+$ requires 189.1.

3-methoxy-4-methylpyridine (3aw)



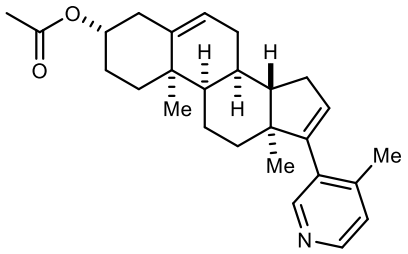
Prepared according to general procedure D using 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-methoxy-4-methylpyridin-1-ium hexafluorophosphate(V) (265 mg, 0.50 mmol), tri-*n*-butylphosphine (0.14 mL, 0.55 mmol), methyl lithium (343 µL, 0.455 mmol), 1*H*-benzotriazole-1-methanol (186 mg, 1.25 mmol), LiHMDS (209 mg, 1.25 mmol), TMEDA (0.19 mL, 1.25 mmol), AcOH:pyridine (4 mL), and THF (6.0 mL). The olefination step was run was warmed to room temperature. The product was made in 55% HNMR yield with triphenylmethane as internal standard. The olefination step was run was warmed to room temperature. The product was made in 55% ^{1}H NMR yield with triphenylmethane as internal standard. Flash column chromatography (Basic alumina: 10% EtOAc in CH_2Cl_2). The product was volatile, so no isolated yield was calculated. The purified product matched reported values for ^{1}H NMR and LRMS; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.14 (d, *J* = 4.7 Hz, 2H), 7.08 (d, *J* = 4.8 Hz, 2H), 3.92 (s, 6H), 2.24 (s, 3H); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 124.1, $C_7H_{10}NO^+$ requires 124.

3-(2,5-difluoro-4-((4-(2-methoxyphenyl)cyclohexyl)sulfonyl)phenyl)-4-methylpyridine (3ax)



Prepared according to general procedure D 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-(2,5-difluoro-4-((4-(2-methoxyphenyl)piperazin-1-yl)sulfonyl)phenyl)pyridin-1-ium hexafluorophosphate(V) (347 mg, 0.40 mmol), tri-*n*-butylphosphine (0.11 mL, 0.44 mmol), methyl lithium (275 μL, 0.44 mmol), 1*H*-benzotriazole-1-methanol (149 mg, 1.0 mmol), LiHMDS (167 mg, 1.0 mmol), TMEDA (0.15 mL, 1.0 mmol), AcOH:pyridine (4 mL), and THF (4.8 mL). The olefination step was warmed to room temperature. Flash column chromatography (silica gel, gradient eluent: 85% Et_2OAc in hexanes to 100% Et_2O) afforded the title compound as a white powder (119 mg, 0.26 mmol, 65% yield). mp 48-55 ºC; IR ν_{max}/cm^{-1} (film): 3049, 2909, 2822, 1619, 1500, 134, 1244, 1163, 955, 912; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.56 (d, *J* = 5.1 Hz, 1H), 8.44 (s, 1H), 7.68 (dd, *J* = 8.3, 5.4 Hz, 1H), 7.28 (s, 1H), 7.18 (dd, *J* = 9.3, 5.4 Hz, 1H), 7.05 (dt, *J* = 7.8, 4.5 Hz, 1H), 6.94 (d, *J* = 4.6 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 1H), 3.85 (s, 3H), 3.46 (t, *J* = 4.8 Hz, 4H), 3.17 (t, *J* = 4.8 Hz, 4H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.26 (dd, *J* = 31.6, 2.7 Hz), 153.76 (dd, *J* = 37.0, 2.8 Hz), 152.20, 150.18, 149.65, 145.97, 140.24, 132.48 (dd, *J* = 19.4, 8.2 Hz), 129.73, 125.94 (dd, *J* = 17.6, 6.6 Hz), 125.30, 124.01, 121.19, 120.20 (dd, *J* = 25.0, 3.3 Hz), 118.66, 118.46 (dd, *J* = 28.0, 1.3 Hz), 111.27, 55.51, 50.34, 46.31 (d, *J* = 1.9 Hz), 19.57 (d, *J* = 3.2 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.05 (ddd, *J* = 17.9, 9.2, 5.5 Hz), -116.54 (dt, *J* = 18.6, 6.8 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 458.3, $C_{25}H_{26}F_2NO_3S^+$ requires 458.2.

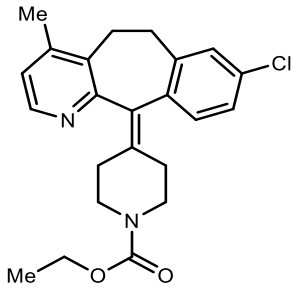
(3S,8R,9R,10R,13S,14S)-10,13-dimethyl-17-(4-methylpyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate (3ay)



An oven-dried 16 mL vial equipped with a stir bar was charged with the triazine (137 mg, 0.44 mmol), potassium hexafluorophosphate (81 mg, 0.44 mmol) and abiraterone acetate (157 mg, 0.4 mmol) and subjected to three rapid cycles of vacuum/nitrogen backfill before THF (1.0 M) was added. The reaction was heated to 50 °C for 4 hours. The reaction was then cooled to room temperature and diluted with THF to 0.083M. Tri-*n*-butylphosphine (0.11 mL, 0.44) was added dropwise and stirred for one hour. The reaction was then cooled to -78 °C and 1.6 M solution of methyl lithium (275 μL, 0.44 mmol) was added dropwise and stirred for 15 minutes. In a separate oven-dried 16 mL equipped with a stir bar was charged LiHMDS (167 mg, 1.0 mmol). THF (1.0 mL) was added followed by TMEDA (0.15 mL, 1.0 mmol). The LiHMDS solution was cooled to -78 °C and a 0.25 M solution of 1*H*-benzotriazole-1-methanol (149 mg, 1.0 mmol) in THF was added dropwise over 15 minutes‡ and stirred for 20 minutes. The generated formaldehyde solution was then added in one portion via syringe to the ylide and stirred for 2 hours at −78 °C. Then a 2.5:1 (v:v) mixture of AcOH:pyridine (3 mL) was added and heated to 50 °C and monitored by LCMS until completion. The reaction was diluted with ethyl acetate and quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (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 column chromatography under the stated conditions to provide the methylated heterocycle. ^{1}H NMR yield is reported using *p*-xylene as internal standard due to inability to separate from starting material. Flash column chromatography (neutralized silica gel: 20% EtOAc in Hexanes) afforded the title compound as a mixture with 44% starting materials. (60% ^{1}H NMR yield). ^{1}H NMR (400 MHz, Chloroform-*d*) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 7.12 (d, *J* = 5.0 Hz, 1H), 5.66 (dd, *J* = 3.1, 1.6 Hz, 1H), 5.42 (m, 1H), 4.67 – 4.52 (m, 1H), 2.45 – 2.30 (m, 2H), 2.29 (s, 3H), 2.20 – 2.05 (m, 2H), 2.03 (s, 3H), 1.48-1.88 (m, 10H) 1.30 – 1.06 (m, 10H), 0.94 (s, 3H); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 406.3, $C_{27}H_{36}NO_2^+$ requires 406.3.

ethyl 4-(8-chloro-4-methyl-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (3az)

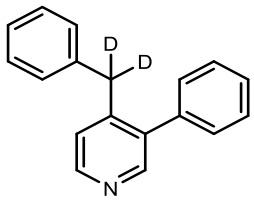


An oven-dried 16 mL vial equipped with a stir bar was charged with the triazine (137 mg, 0.44 mmol), potassium hexafluorophosphate (81 mg, 0.44 mmol) and loratadine (153 mg, 0.4 mmol) subjected to three rapid cycles of vacuum/nitrogen backfill before THF (1.0 M) was added. The reaction was heated to 80 °C for 8 hours. The reaction was then cooled to room temperature and diluted with THF to 0.083M. Tri-*n*-butylphosphine (0.11 mL, 0.44) was added dropwise and

stirred for one hour. The reaction was then cooled to -78 °C and 1.6 M solution of methyl lithium (275 μL, 0.44 mmol) was added dropwise and stirred for 15 minutes. In a separate oven-dried 16 mL equipped with a stir bar was charged LiHMDS (167 mg, 1.0 mmol). THF (1.0 mL) was added followed by TMEDA (0.15 mL, 1.0 mmol). The LiHMDS solution was cooled to -78 °C and a 0.25 M solution of 1*H*-benzotriazole-1-methanol (149 mg, 1.0 mmol) in THF was added dropwise over 15 minutes[‡] and stirred for 20 minutes. The generated formaldehyde solution was then added in one portion via syringe to the ylide and stirred for 2 hours at -78 °C. Then a 2.5:1 (v:v) mixture of AcOH:pyridine (2-4 mL depending on the scale) was added and heated to 50 °C overnight. The reaction was diluted with ethyl acetate and quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (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 column chromatography under the stated conditions to provide the methylated heterocycle. Flash column chromatography (silica gel: 100% Et_2O) afforded the title compound as a white powder with a 5% impurity (69 mg, 0.18 mmol, 44% yield). IR ν_{max}/cm^{-1} (film): 2983, 2928, 2850, 1681, 1435, 1232, 1120, 904; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.27 (d, *J* = 5.0 Hz, 1H), 7.17 (s, 1H), 7.13 (d, *J* = 2.3 Hz, 2H), 6.97 (d, *J* = 5.1 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 2H), 3.41 (td, *J* = 9.6, 4.1 Hz, 1H), 3.13 (ddd, *J* = 13.1, 8.9, 4.3 Hz, 3H), 2.82 (tdd, *J* = 12.9, 8.8, 4.4 Hz, 2H), 2.48 (ddd, *J* = 14.3, 9.4, 4.6 Hz, 1H), 2.33 (d, *J* = 4.8 Hz, 3H), 2.26 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.67, 155.62, 146.24, 139.70, 138.12, 137.65, 137.25, 132.98, 132.16, 130.42, 128.84, 126.32, 124.38, 122.40, 61.43, 44.86, 31.28, 30.83, 30.71, 29.81, 28.39, 19.61, 14.80; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 397.3, $C_{23}H_{26}ClN_2O_2^+$ requires 397.2.

A 2.7. Derivatization from Pyridine Anhydrobase

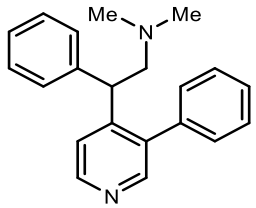
3-phenyl-4-(phenylmethyl-d2)pyridine (4)



An oven-dried 16 mL vial equipped with a stir bar was charged with 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-phenylpyridin-1-ium hexafluorophosphate(V) (153 mg, 0.27 mmol). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, THF (3.2 mL) was added, followed by tri-*n*-butylphosphine (73 μL, 0.29 mmol). The reaction was allowed to stir for 1 hour, then cooled to -78 ºC. A 1.6 M solution of Methyl lithium (183 μL, 0.29 mmol) was added dropwise via syringe and allowed to stir for 15 minutes before benzaldehyde (38 μL, 0.37 mmol) was added. The cooling bath was removed, and the reaction was allowed to warm to room temperature and stir for one hour. In a separate vial, acetyl chloride (19 μL, 027 mmol) is added dropwise to methanol-d_4 (265 μL) at 0 ºC. The generated DCl is then transferred to the anhydrobase and stirred for 30 minutes. Then a 2.5:1 (v:v) AcOH-d_4:Pyridine mixture (2 mL) was added and heated to 50 ºC overnight. The reaction was diluted with ethyl acetate and quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate (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 column chromatography under the stated conditions to provide the product. Flash column chromatography (silica gel: 60% Et_2O in hexanes; 2nd column, silica gel: 20% EtOAc in CH_2Cl_2) afforded the title

compound as a colorless oil (39 mg, 0.16 mmol, 60% yield). IR ν_{max}/cm^{-1} (film): 3027, 3949 2895, 1604, 1380, 1222, 1200, 1016, 916, 806; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49-8.48 (3, 2H), 7.45-7.38 (m, 3H), 7.34 – 7.16 (m, 5H), 7.11 (d, *J* = 5.1 Hz, 1H), 7.02 – 6.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.40, 148.67, 147.29, 139.31, 137.92, 137.71, 129.53, 129.02, 128.63, 128.54, 127.86, 126.50, 124.79, 38.87 (t, *J* = 19.1 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 248.2, $C_{18}H_{14}D_2N^+$ requires 248.1.

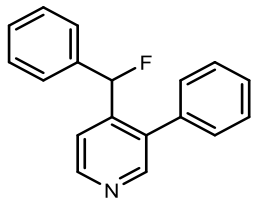
N,N-dimethyl-2-phenyl-2-(3-phenylpyridin-4-yl)ethan-1-amine (5)



An oven-dried 8 mL vial equipped with a stir bar was charged with 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-phenylpyridin-1-ium hexafluorophosphate(V) (115 mg, 0.20 mmol). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, THF (2.4 mL) was added, followed by tri-*n*-butylphosphine (55 μL, 0.22 mmol). The reaction was allowed to stir for 1 hour, then cooled to -78 ºC. A 1.6 M solution of Methyl lithium (137 μL, 0.22 mmol) was added dropwise via syringe and allowed to stir for 15 minutes before benzaldehyde (28 μL, 0.28 mmol) was added. The cooling bath was removed, and the reaction was allowed to warm to room temperature and stir for one hour. *N,N*-dimethylmethyleneiminium iodide (111 mg, 0.6 mmol) was added and allowed to stir overnight. Then a 2.5:1 (v:v) mixture of AcOH: pyridine (1.5 mL) and stirred for 6 hours. The reaction was then diluted with ethyl acetate and quenched with

water. The aqueous layer was extracted with ethyl acetate (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 column chromatography under the stated conditions to provide the product. Flash column chromatography (silica gel, gradient elution: 2% MeOH in CH_2Cl_2 to 6% MeOH in CH_2Cl_2) afforded the title compound as a colorless oil (31 mg, 0.10 mmol, 50% yield). IR ν_{max}/cm^{-1} (film): 3158, 3061, 2850, 1712, 1622, 1548, 1442, 1112, 1068, 877, 765; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, *J* = 5.3 Hz, 1H), 8.33 (s, 1H), 7.40 – 7.28 (m, 3H), 7.21 (d, *J* = 5.3 Hz, 1H), 7.15 – 7.02 (m, 5H), 7.00 – 6.86 (m, 2H), 4.25 (t, *J* = 7.8 Hz, 1H), 2.94 – 2.67 (m, 2H), 2.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.59, 149.21, 148.88, 141.45, 138.16, 137.71, 129.73, 128.73, 128.47, 128.26, 128.00, 126.96, 122.42, 64.10, 45.33, 44.36; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 303.3, $C_{21}H_{23}N_2^+$ requires 303.2.

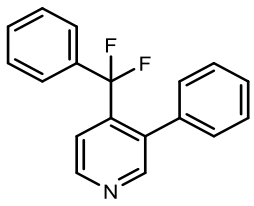
4-(fluoro(phenyl)methyl)-3-phenylpyridine (6)



An oven-dried 8 mL vial equipped with a stir bar was charged with 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-phenylpyridin-1-ium hexafluorophosphate(V) (115 mg, 0.20 mmol). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, THF (2.4 mL) was added, followed by tri-*n*-butylphosphine (55 μL, 0.22 mmol). The reaction was allowed to stir for 1 hour, then cooled to -78 ºC. A 1.6 M solution of Methyl lithium (138 μL, 0.22 mmol)

was added dropwise via syringe and allowed to stir for 15 minutes before benzaldehyde (28 μL, 0.28 mmol) was added. The cooling bath was removed, and the reaction was allowed to warm to room temperature and stir for one hour. The reaction was then concentrated *in vacuo*. 1-fluoropyridinium triflate (198 mg, 0.8 mmol) was added to the crude material and then dissolved in acetonitrile (0.8 mL). Pyridine (48 μL, 0.6 mmol) was added and the reaction was heated to 60 ^{o}C overnight. The reaction was diluted with ethyl acetate and quenched with water. The aqueous layer was extracted with ethyl acetate (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 column chromatography under the stated conditions to provide the product. Flash column chromatography (silica gel: 40% Et_2O in hexanes) afforded the title compound as a yellow oil (36 mg, 0.14 mmol, 68% yield). IR ν_{max}/cm^{-1} (film): 3072, 3033, 2954, 2912, 1400, 1228, 995, 700; ^{1}H NMR (400 MHz, Chloroform-*d*) 8.69 (d, *J* = 5.2 Hz, 1H), 8.53 (s, 1H), 7.56 (d, *J* = 5.2 Hz, 1H), 7.52 – 7.34 (m, 3H), 7.33 – 7.23 (m, 3H), 7.20 – 7.12 (m, 2H), 7.10 – 6.99 (m, 2H), 6.50 (d, *J* = 47.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.62, 149.22, 145.73 (d, *J* = 22.4 Hz), 138.21 (d, *J* = 21.6 Hz), 136.40, 136.15, 129.51, 128.97 (d, *J* = 2.7 Hz), 128.69, 128.62, 128.33, 127.18 (d, *J* = 5.7 Hz), 120.85 (d, *J* = 7.9 Hz), 90.71 (d, *J* = 173.0 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -167.00 (d, *J* = 47.1 Hz); *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 264.2, $C_{18}H_{15}FN^+$ requires 264.1.

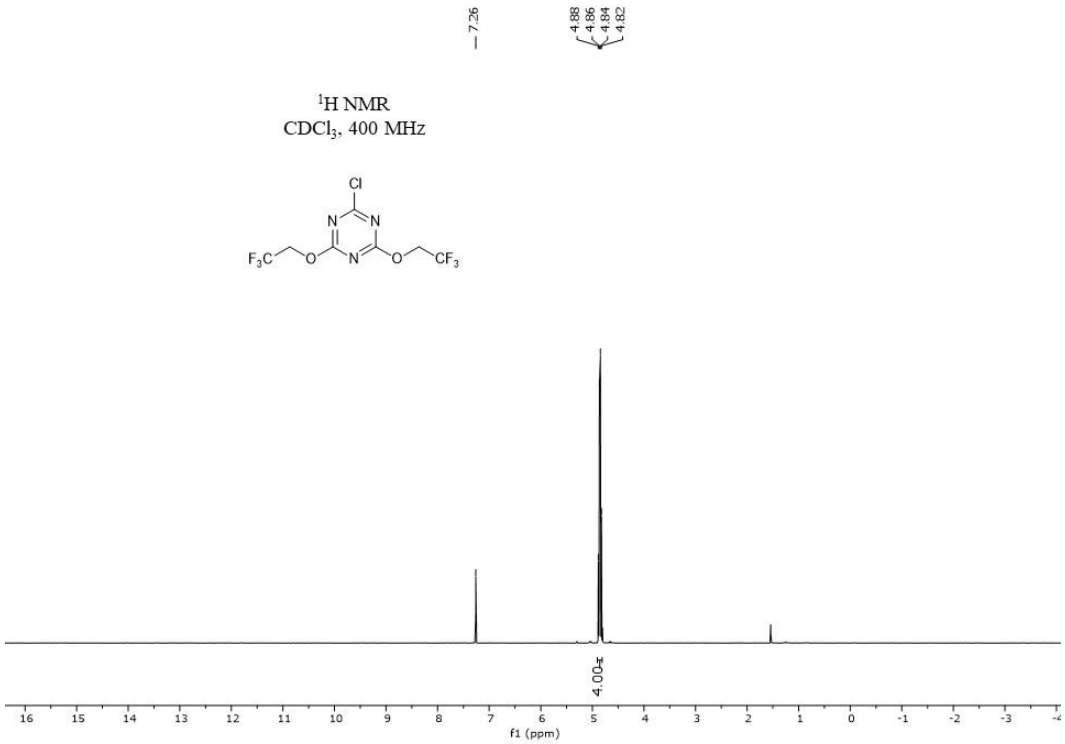
4-(difluoro(phenyl)methyl)-3-phenylpyridine (7)



An oven-dried 16 mL vial equipped with a stir bar was charged with 1-(4,6-bis(2,2,2-trifluoroethoxy)-1,3,5-triazin-2-yl)-3-phenylpyridin-1-ium hexafluorophosphate(V) (231 mg, 0.40 mmol). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, THF (4.8 mL) was added, followed by tri-*n*-butylphosphine (110 mL, 0.44 mmol). The reaction was allowed to stir for 1 hour, then cooled to -78 ºC. A 1.6 M solution of Methyl lithium (275 mL, 0.44 mmol) was added dropwise via syringe and allowed to stir for 15 minutes before benzaldehyde (28 mL, 0.28 mmol) was added. The cooling bath was removed, and the reaction was allowed to warm to room temperature and stir for one hour. The reaction was then concentrated *in vacuo*. *N*-Fluorobenzenesulfonimide (505 mg, 1.6 mmol) and Sodium acetate (33 mg, 0.4 mmol) were added to the crude material and then dissolved in ethyl acetate (2.0 mL) and heated to 80 ºC overnight. The heating bath was removed and diluted with ethyl acetate and quenched with water. The aqueous layer was extracted with ethyl acetate (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 column chromatography under the stated conditions to provide the product. Flash column chromatography (silica gel: 40% Et_2O in hexanes; 2nd column, silica gel: 5% Et_2O in CH_2Cl_2) afforded the title compound as a yellow oil (52 mg, 0.19 mmol, 46% yield). IR ν_{max}/cm^{-1} (film): 3061, 2918, 2850, 1758, 1609, 1520, 1455, 1222, 1010, 812, 689; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.85 (d, *J* = 5.3 Hz, 1H), 8.56 (s, 1H), 7.83 (d, *J* = 5.2 Hz, 1H), 7.50 – 7.30 (m, 2H), 7.26 (td, *J* = 7.7, 2.4 Hz, 4H), 7.08 (d, *J* = 7.7 Hz, 2H), 6.99 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.36, 149.22, 143.33 (t, *J* = 27.8 Hz), 136.57 (t, *J* = 13.4 Hz), 136.40, 136.18, 129.87 (t, *J* = 1.9 Hz), 129.80 (d, *J* = 1.7 Hz), 128.10, 127.78, 127.51, 125.56 (t,

J = 5.6 Hz), 119.72 (t, *J* = 7.2 Hz), 119.46 (t, *J* = 244.3 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) δ -87.30; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 282.2, $C_{18}H_{14}F_2N^+$ requires 282.1.

A 2.8. ^{1}H, ^{13}C, and ^{19}F Spectra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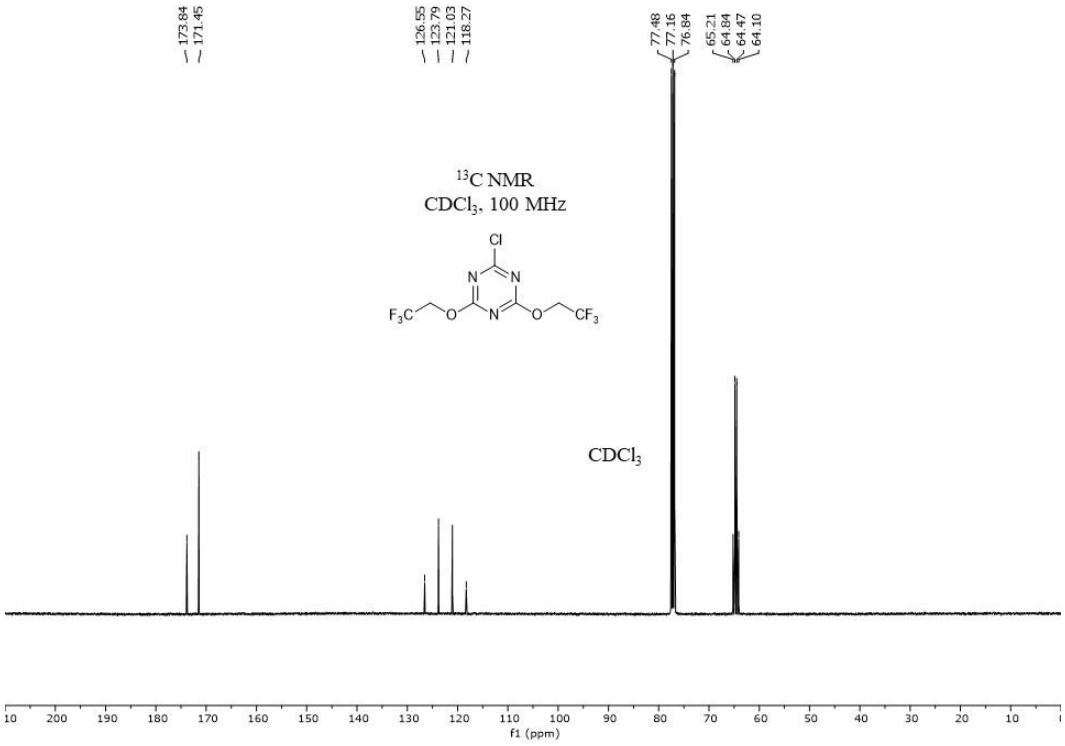
f1 (ppm)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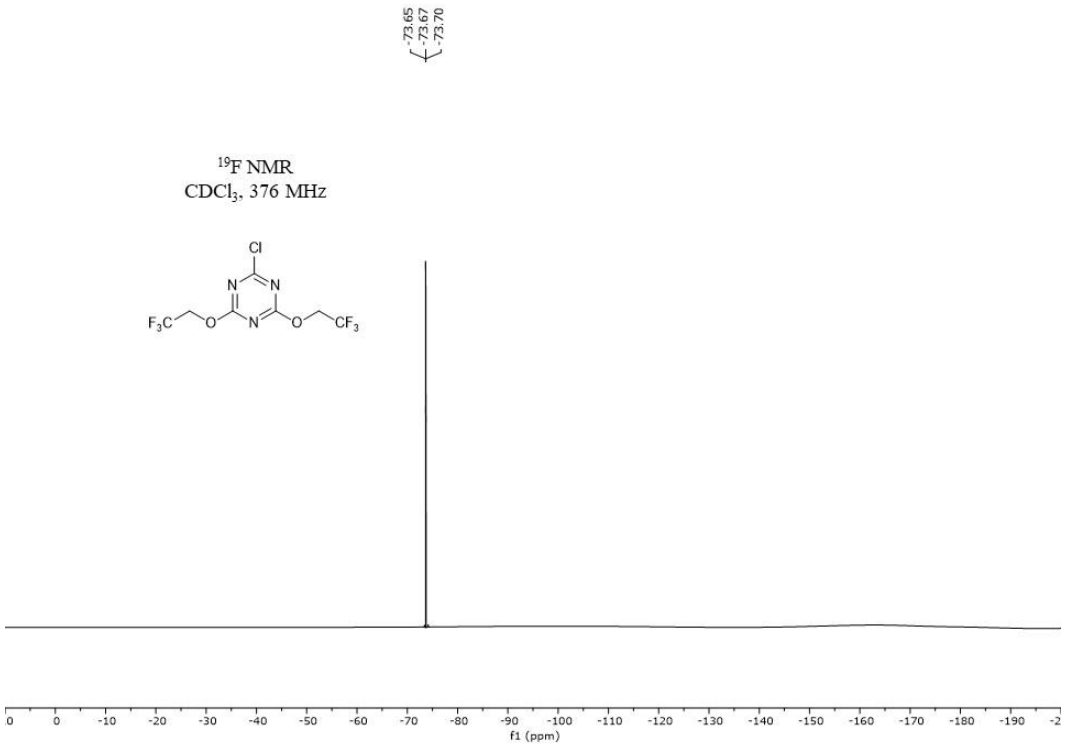
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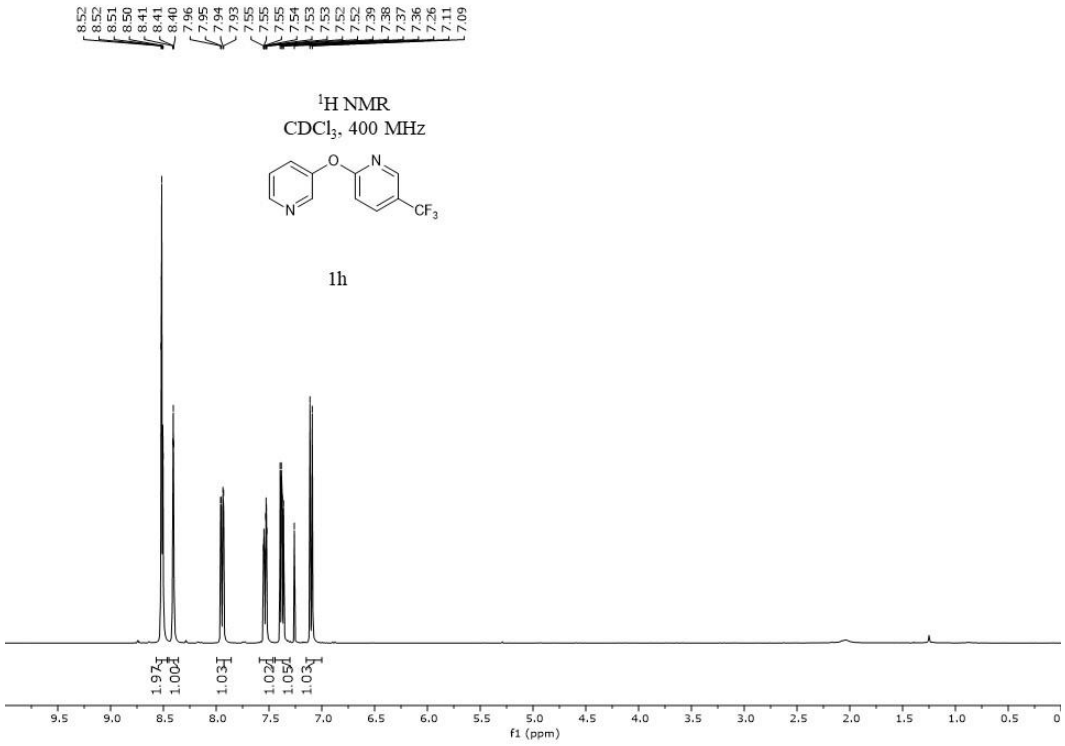
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)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8.52
8.51
8.50
8.41
8.41
8.40
7.96
7.95
7.94
7.93
7.55
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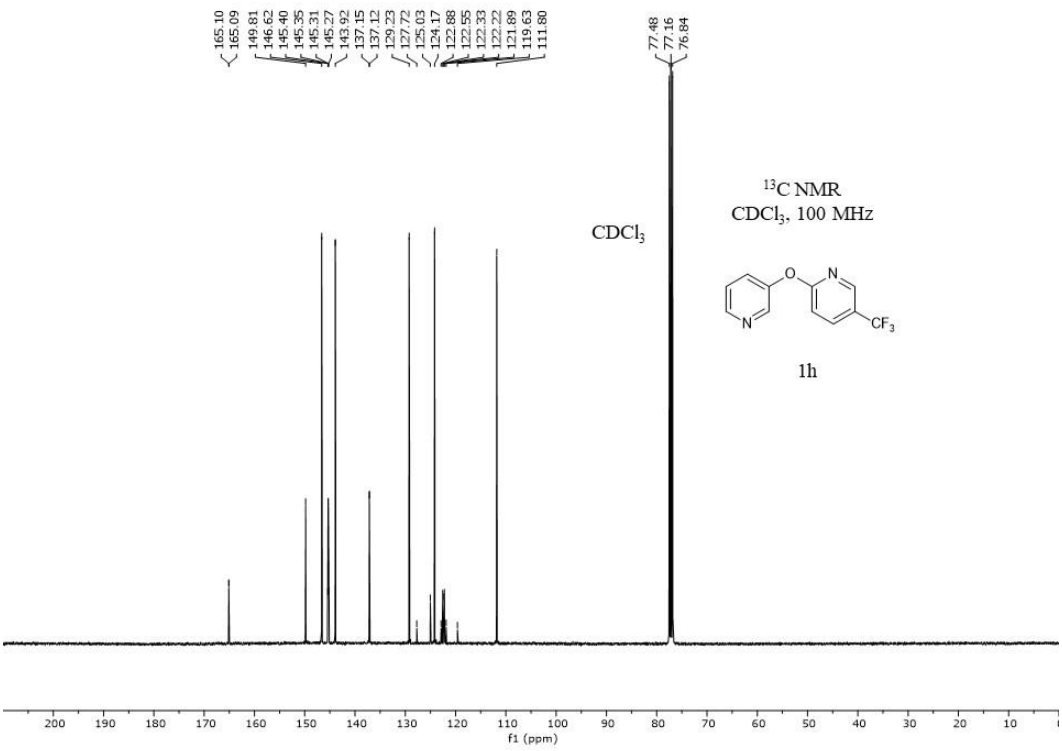
7.55
7.54
7.53
7.53
7.52
7.52
7.39
7.38
7.37
7.36
7.26
7.11
7.09
1H NMR
CDCl3, 400 MHz
O
N
N
CF3
1h
1.97
1.00
1.03
1.02
1.05
1.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
f1 (ppm)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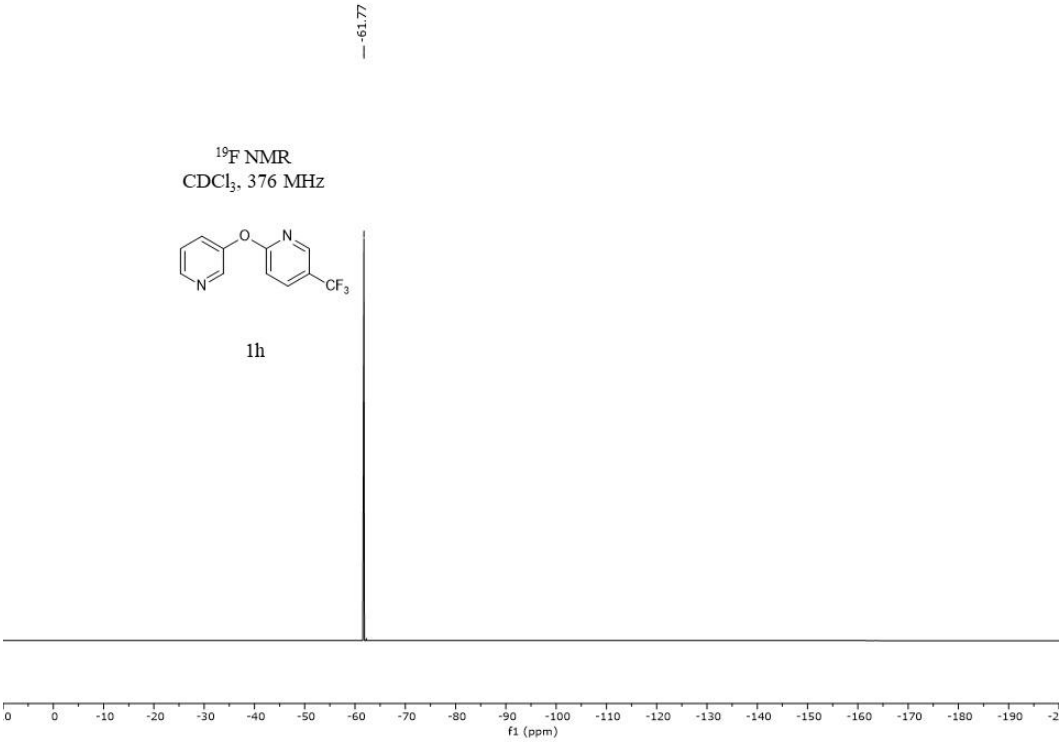
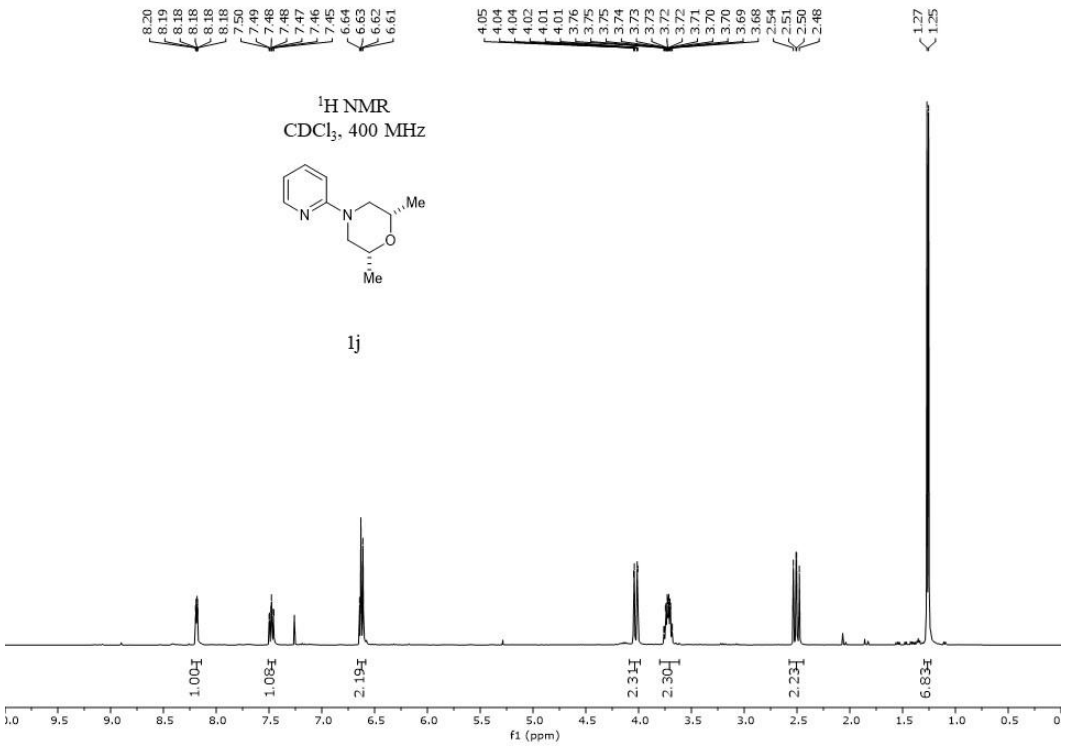
165.09
149.81
146.62
145.40
145.35
145.31
145.27
143.92
137.15
137.12
129.23
127.72
125.03
124.17
122.88
122.55
122.33
122.22
121.89
119.63
111.80
77.48
77.16
76.84
CDCl3
13C NMR
CDCl3, 100 MHz
O
N
N
CF3
1h
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-61.77
19F NMR
CDCl3, 376 MHz
O
N
N
CF3
1h
0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)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8.19
8.18
8.18
8.18
8.18
7.50
7.49
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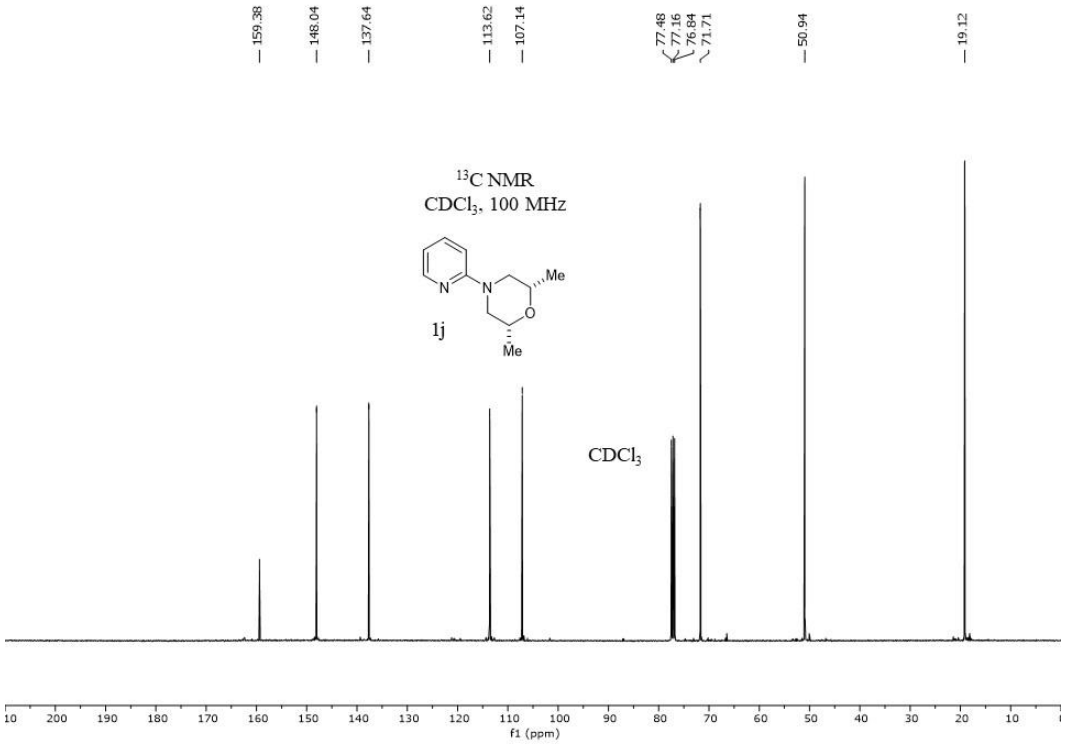
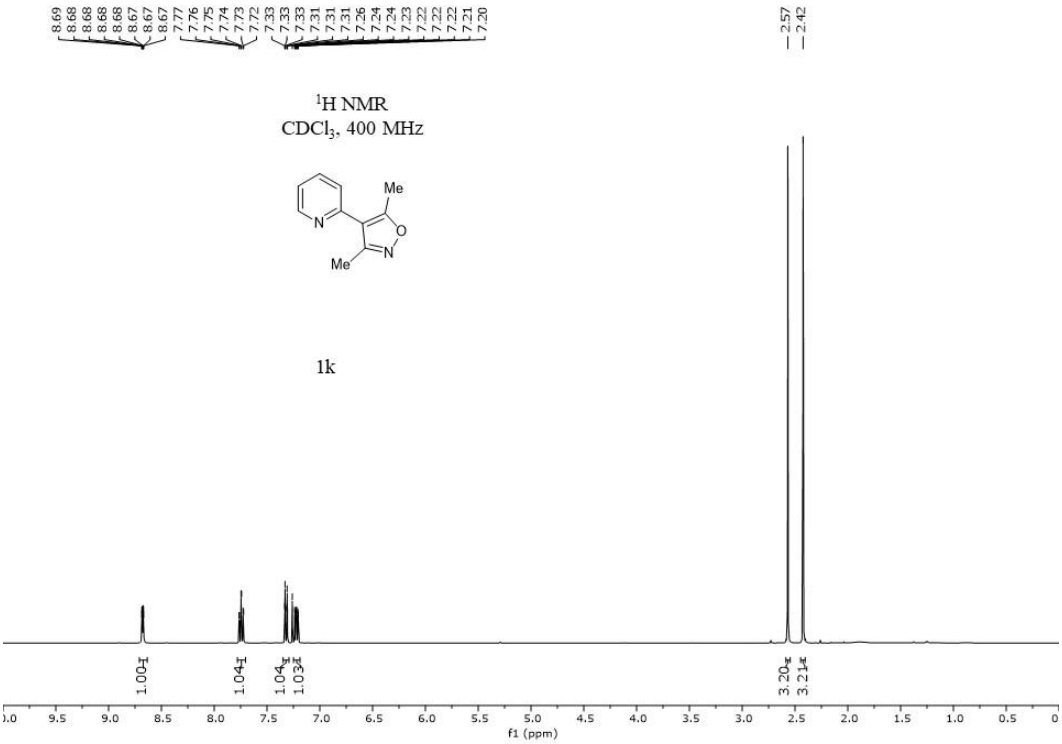
7.48
7.47
7.46
7.45
6.64
6.63
6.62
6.61
4.05
4.04
4.04
4.02
4.01
4.01
3.76
3.75
3.75
3.74
3.73
3.73
3.72
3.72
3.71
3.70
3.70
3.69
3.68
2.54
2.51
2.50
2.48
1.27
1.25
1H NMR
CDCl3, 400 MHz
Me
N
N
O
Me
1j
1.00
1.08
2.19
2.31
2.30
2.23
6.83
f1 (ppm)


159.38
148.04
137.64
113.62
107.14
77.48
77.16
76.84
71.71
50.94
19.12
13C NMR
CDCl3, 100 MHz
Me
N
N
O
Me
1j
CDCl3
f1 (ppm)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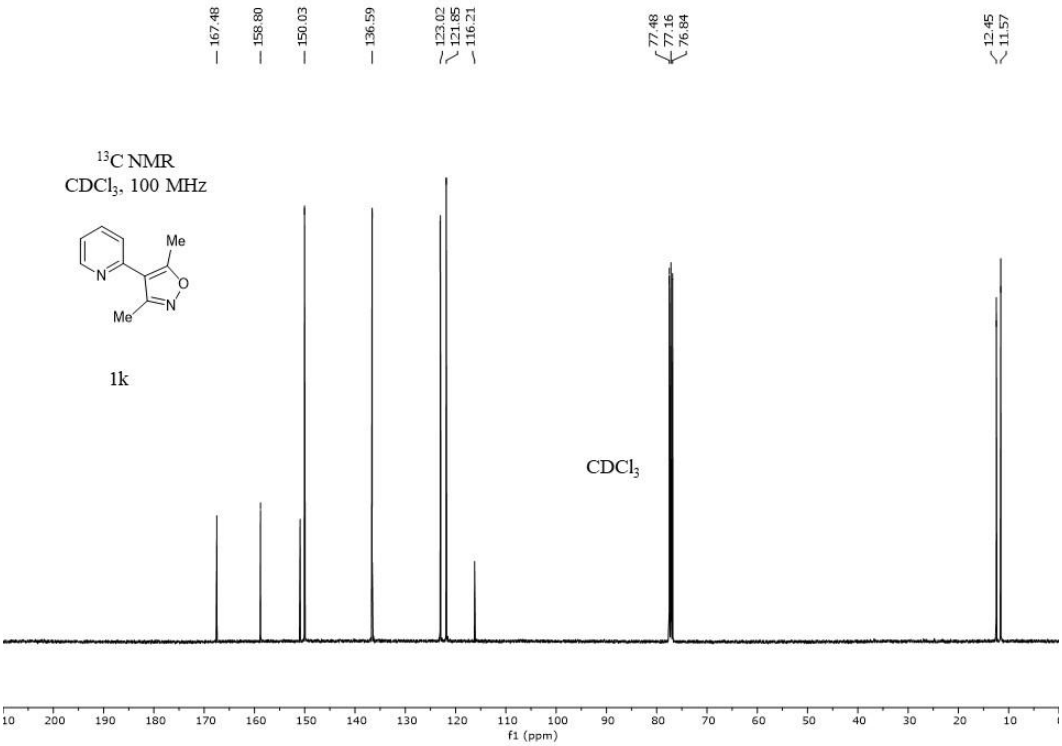
8.68
8.68
8.68
8.67
8.67
7.77
7.76
7.75
7.74
7.73
7.72
7.33
7.33
7.31
7.31
7.26
7.24
7.23
7.22
7.22
7.21
7.20
2.57
2.42
1H NMR
CDCl3, 400 MHz
Me
N
O
N
Me
1k
1.00
1.04
1.04
1.03
3.20
3.21
f1 (ppm)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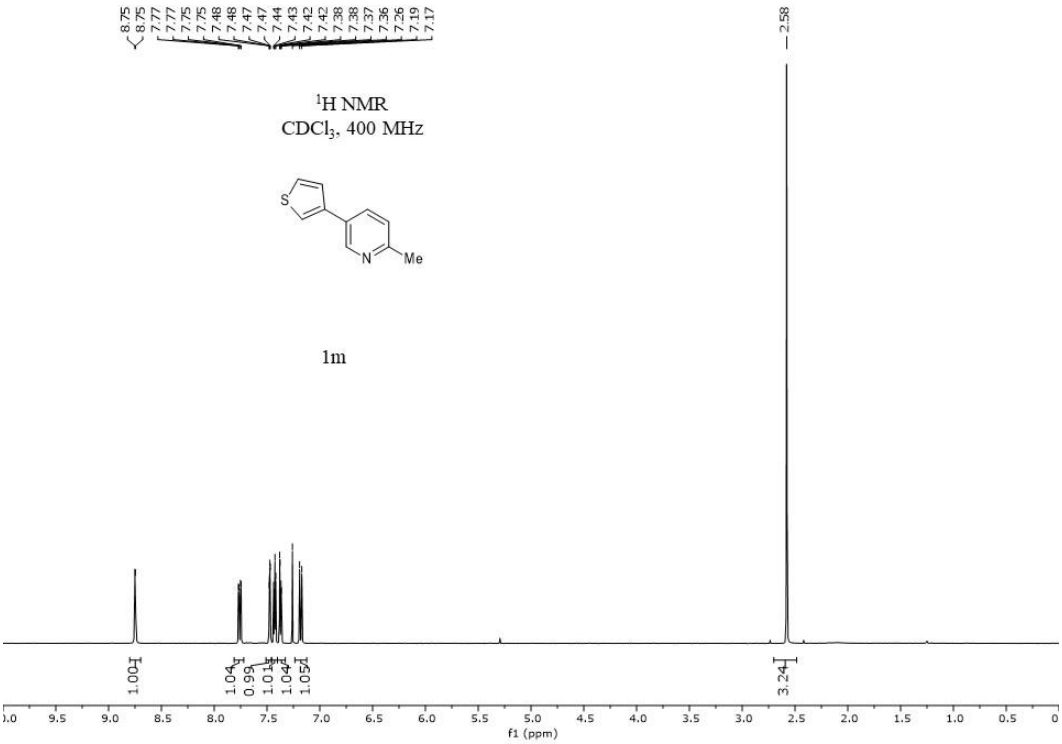
158.80
150.03
136.59
123.02
121.85
116.21
77.48
77.16
76.84
12.45
11.57
13C NMR
CDCl3, 100 MHz
Me
N
O
N
Me
1k
CDCl3
f1 (ppm)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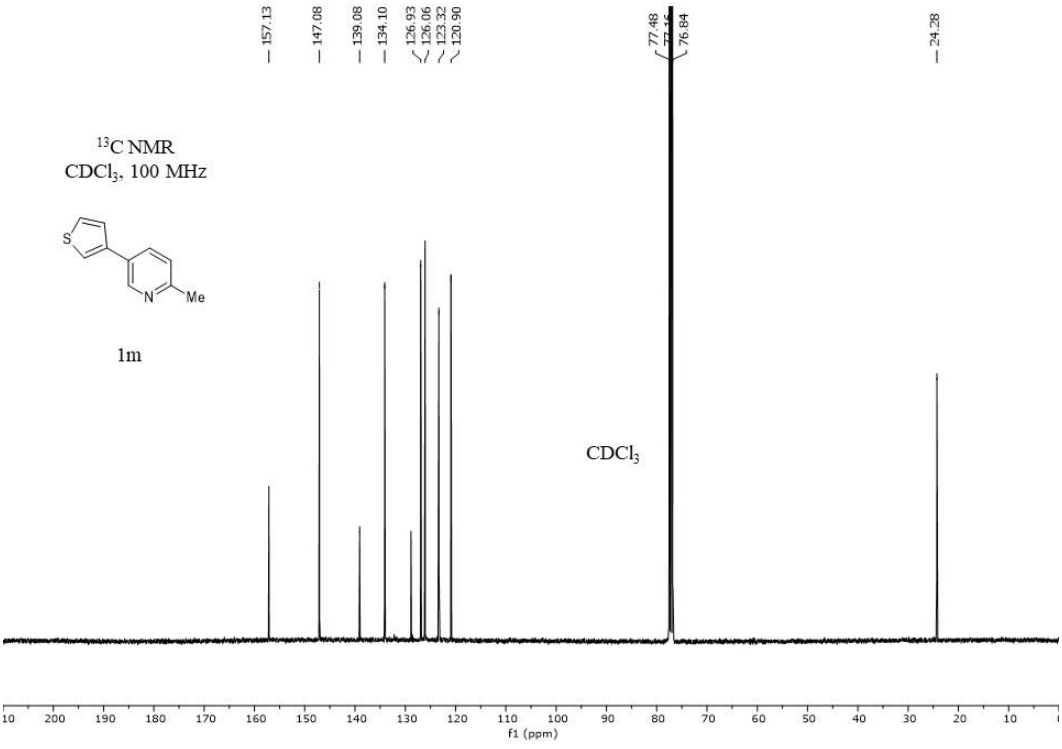
8.75
7.77
7.77
7.75
7.75
7.48
7.48
7.47
7.47
7.44
7.43
7.42
7.42
7.38
7.37
7.36
7.26
7.19
7.17
2.58
1H NMR
CDCl3, 400 MHz
S
N
Me
1m
1.00
1.04
0.99
1.01
1.04
1.05
3.24
f1 (ppm)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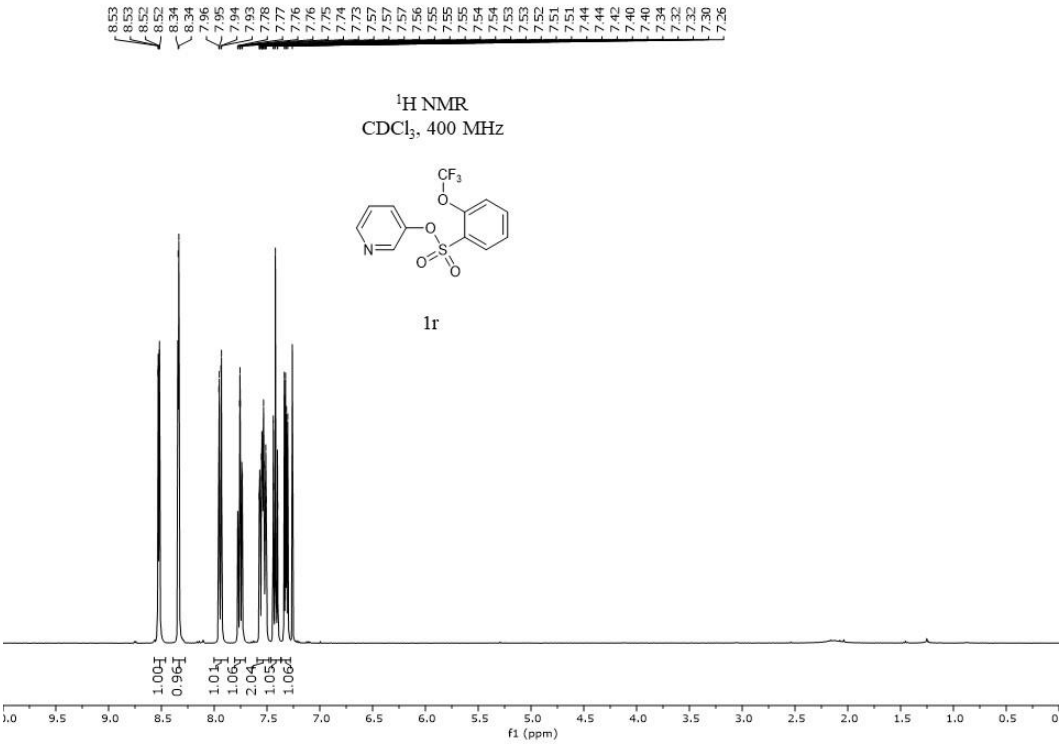
147.08
139.08
134.10
126.93
126.06
123.32
120.90
77.48
77.16
76.84
24.28
13C NMR
CDCl3, 100 MHz
S
N
Me
1m
CDCl3
f1 (ppm)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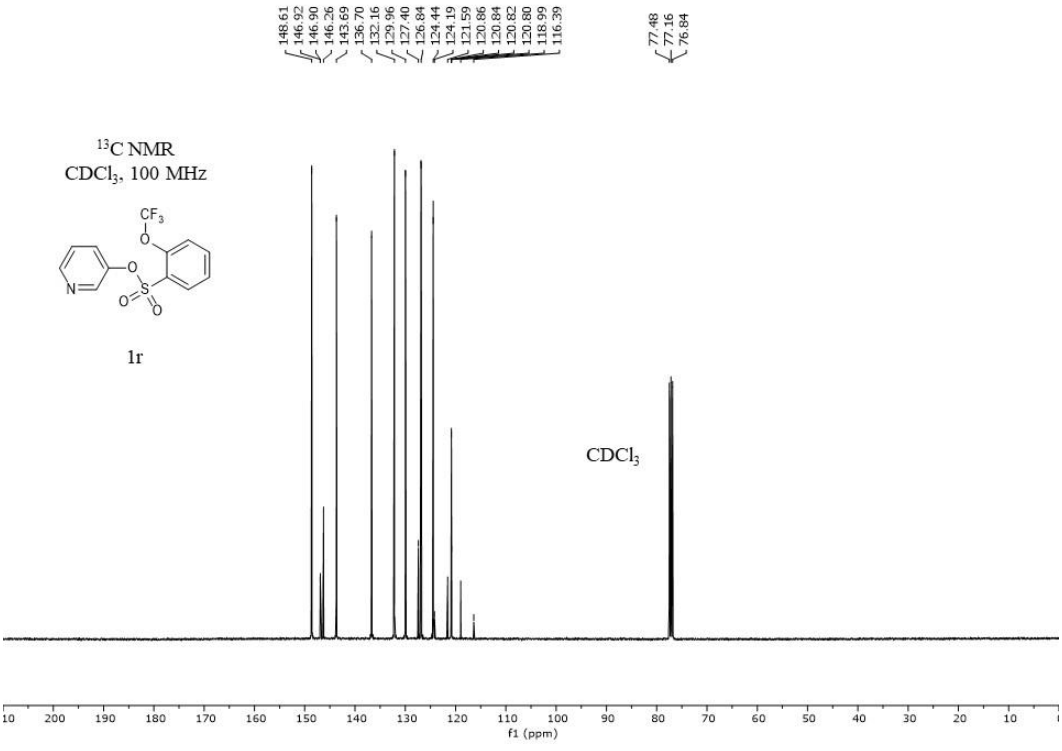
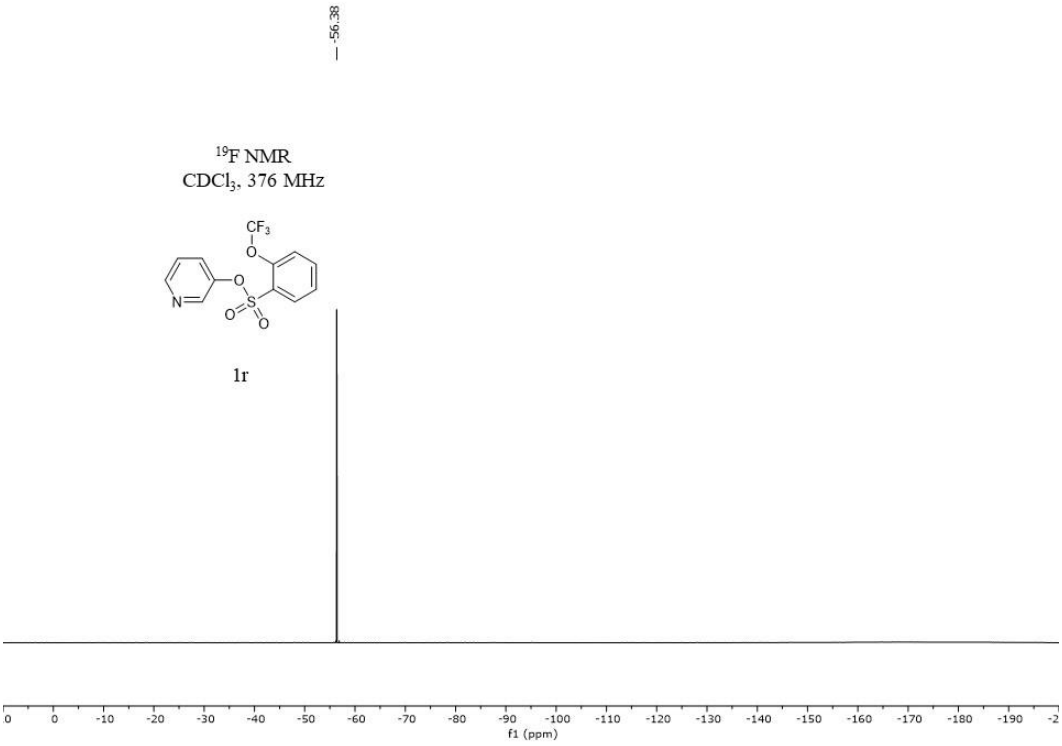
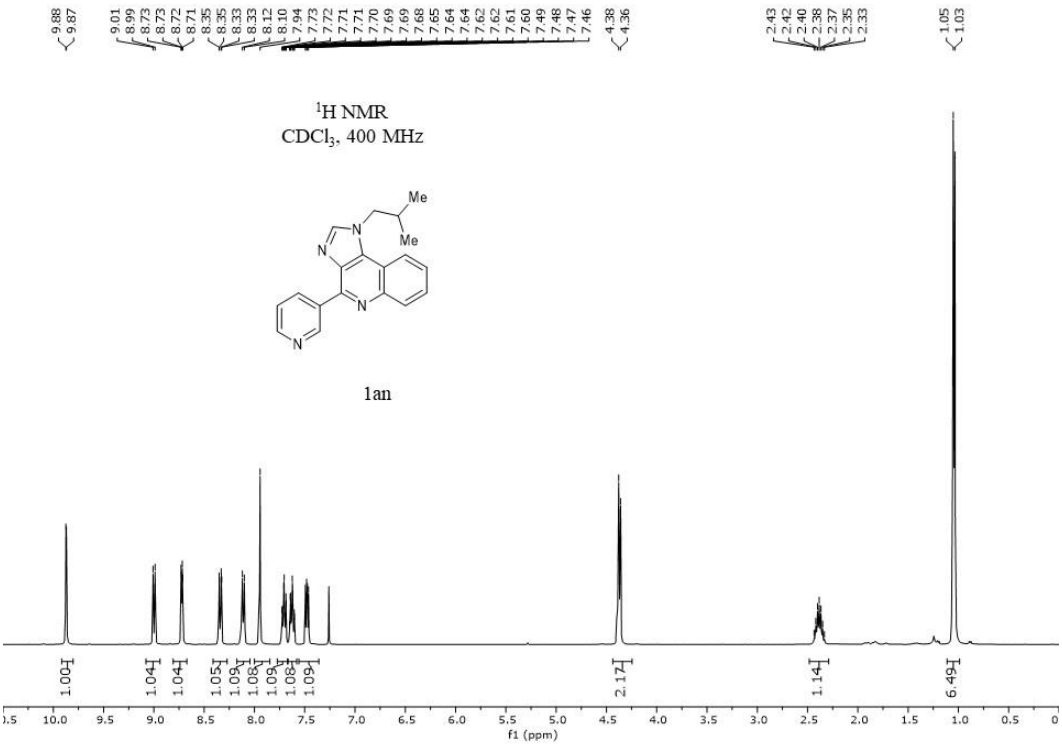
8.53
8.52
8.52
8.34
8.34
7.96
7.95
7.94
7.93
7.78
7.77
7.76
7.76
7.75
7.74
7.73
7.57
7.57
7.56
7.55
7.55
7.55
7.54
7.54
7.53
7.53
7.52
7.51
7.51
7.44
7.44
7.42
7.40
7.40
7.34
7.32
7.30
7.26
1H NMR
CDCl3, 400 MHz
CF3
O
N
O
S
O
O
1r
1.00
0.96
1.01
1.06
2.04
1.05
1.06
f1 (ppm)


148.61
146.92
146.90
146.26
143.69
136.70
132.16
129.96
127.40
126.84
124.44
124.19
121.59
120.86
120.84
120.82
120.80
118.99
116.39
77.48
77.16
76.84
13C NMR
CDCl3, 100 MHz
CF3
O
N
O
S
O
O
1r
CDCl3
f1 (ppm)



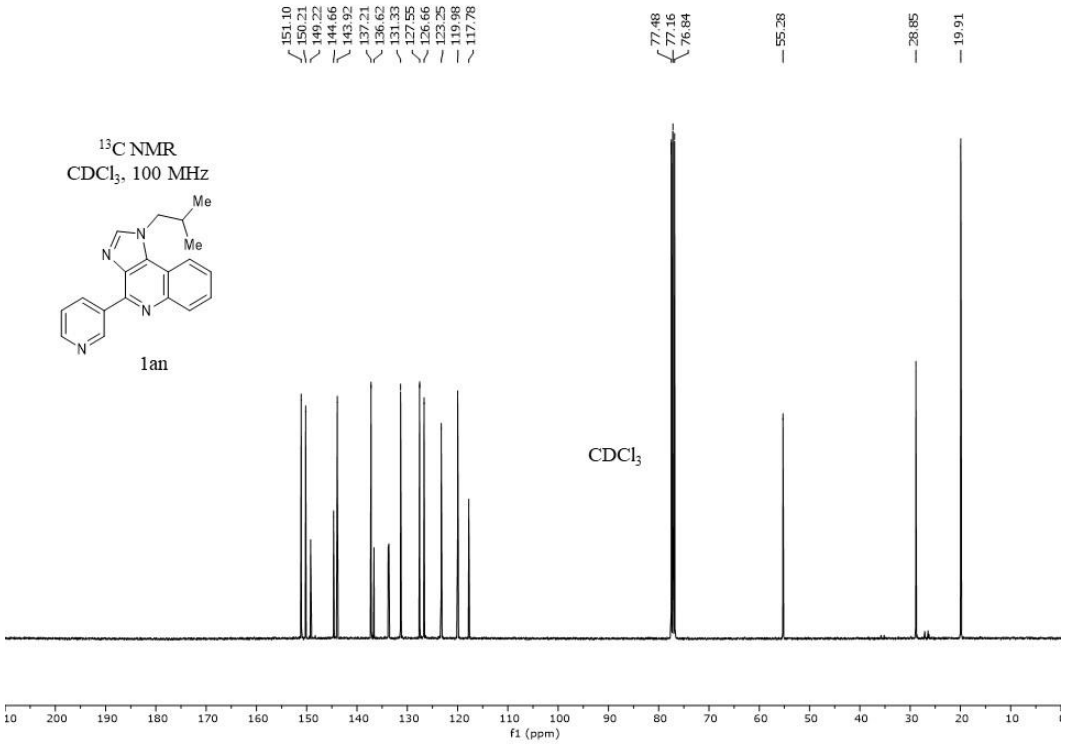
^{19}F NMR
$CDCl_3$, 376 MHz

1r



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

1an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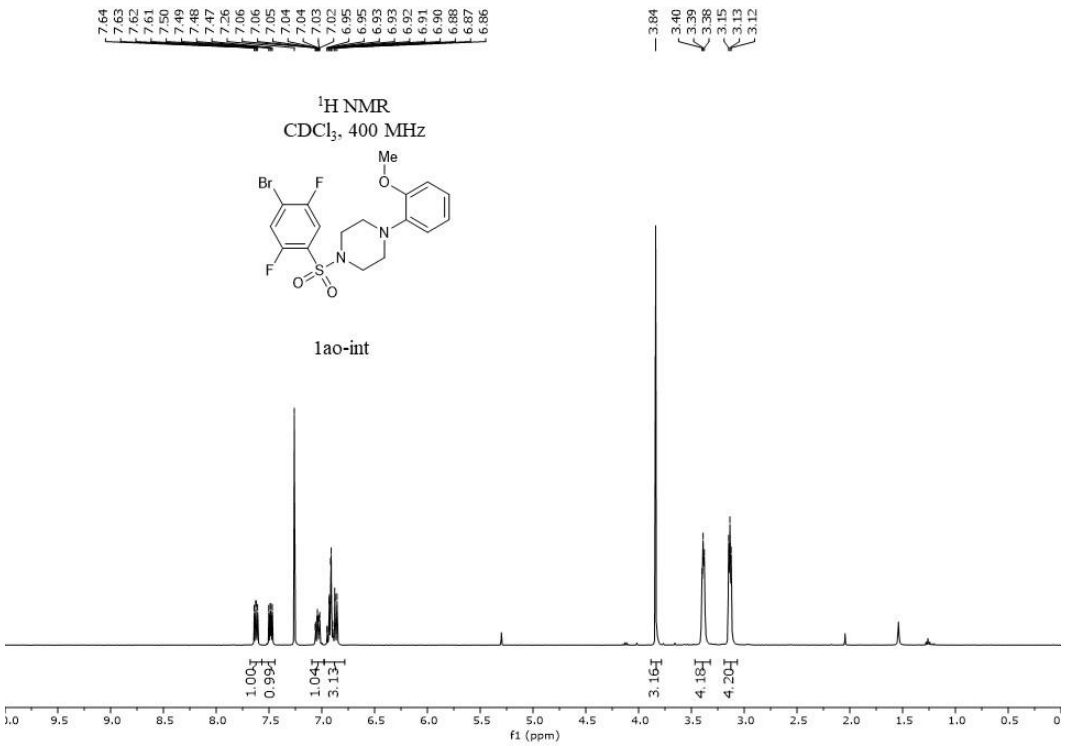
149.22
144.66
143.92
137.21
136.62
131.33
127.55
126.66
123.25
119.98
117.78
77.48
77.16
76.84
55.28
28.85
19.91
13C NMR
CDCl3, 100 MHz
Me
Me
N
N
N
1an
CDCl3
f1 (ppm)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7.47
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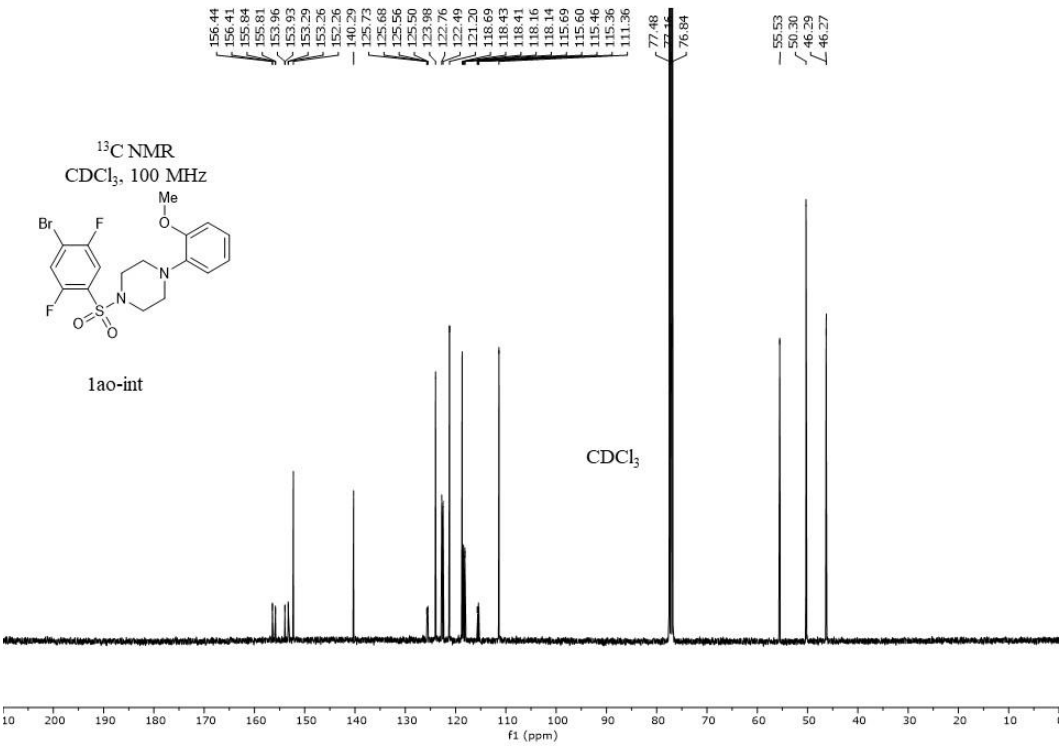
7.06
7.06
7.05
7.04
7.04
7.03
7.02
6.95
6.93
6.93
6.92
6.91
6.90
6.88
6.87
6.86
3.84
3.40
3.39
3.38
3.15
3.13
3.12
1H NMR
CDCl3, 400 MHz
Me
O
Br
F
F
N
N
S
O
O
1ao-int
1.00
0.99
1.04
3.13
3.16
4.18
4.20
f1 (ppm)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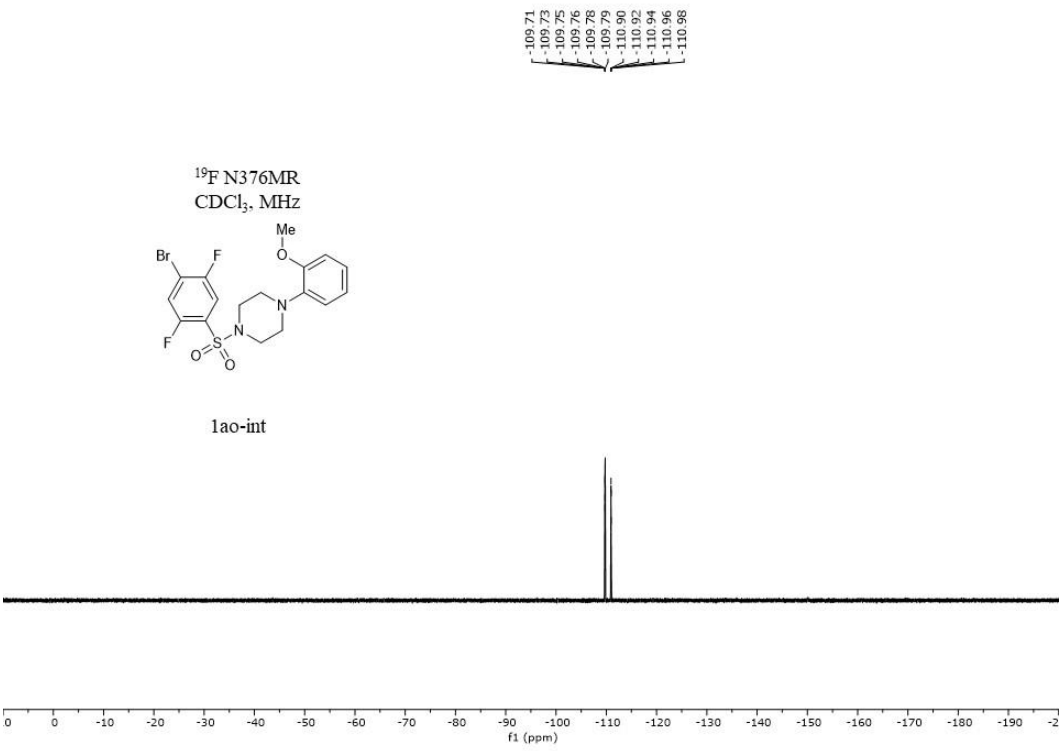
155.81
153.96
153.93
153.29
153.26
152.26
140.29
125.73
125.68
125.56
125.50
123.98
122.76
122.49
121.20
118.69
118.43
118.41
118.16
118.14
115.69
115.60
115.46
115.36
111.36
77.48
77.16
76.84
55.53
50.30
46.29
46.27
^{13}C NMR
$CDCl_3$, 100 MHz
Me
O
Br
F
F
N
S
O
O
1ao-int
$CDCl_3$
f1 (ppm)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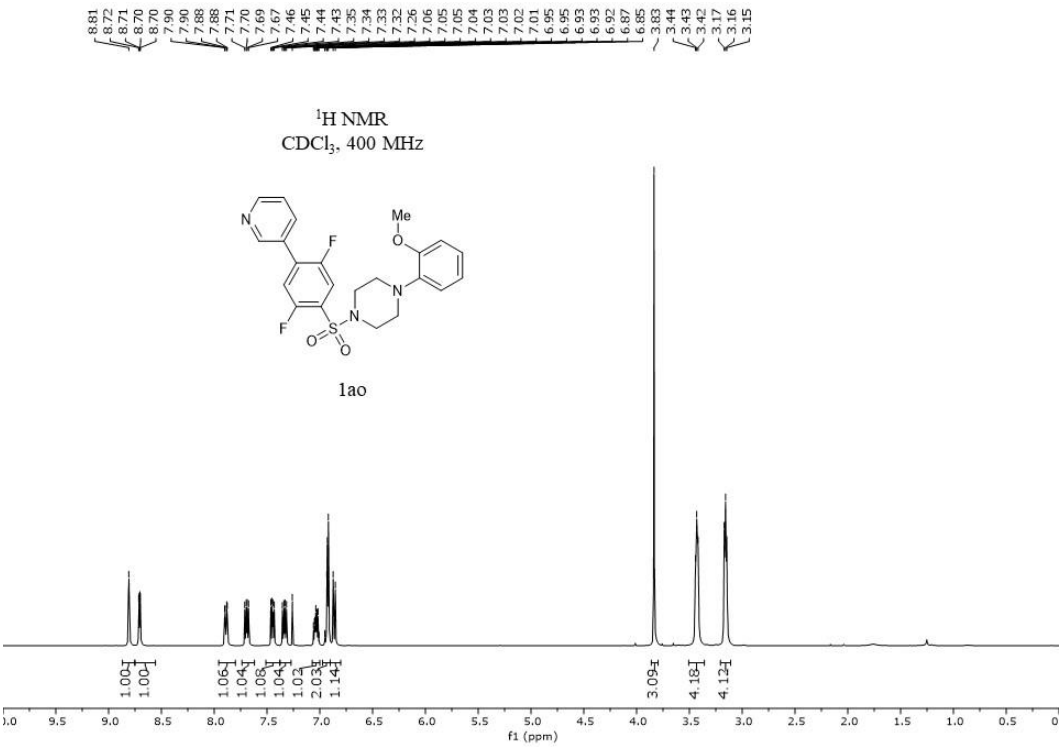
-109.73
-109.75
-109.76
-109.78
-109.79
-110.90
-110.92
-110.94
-110.96
-110.98
^{19}F N376MR
$CDCl_3$, MHz
Me
O
Br
F
F
N
S
O
O
1ao-int
f1 (ppm)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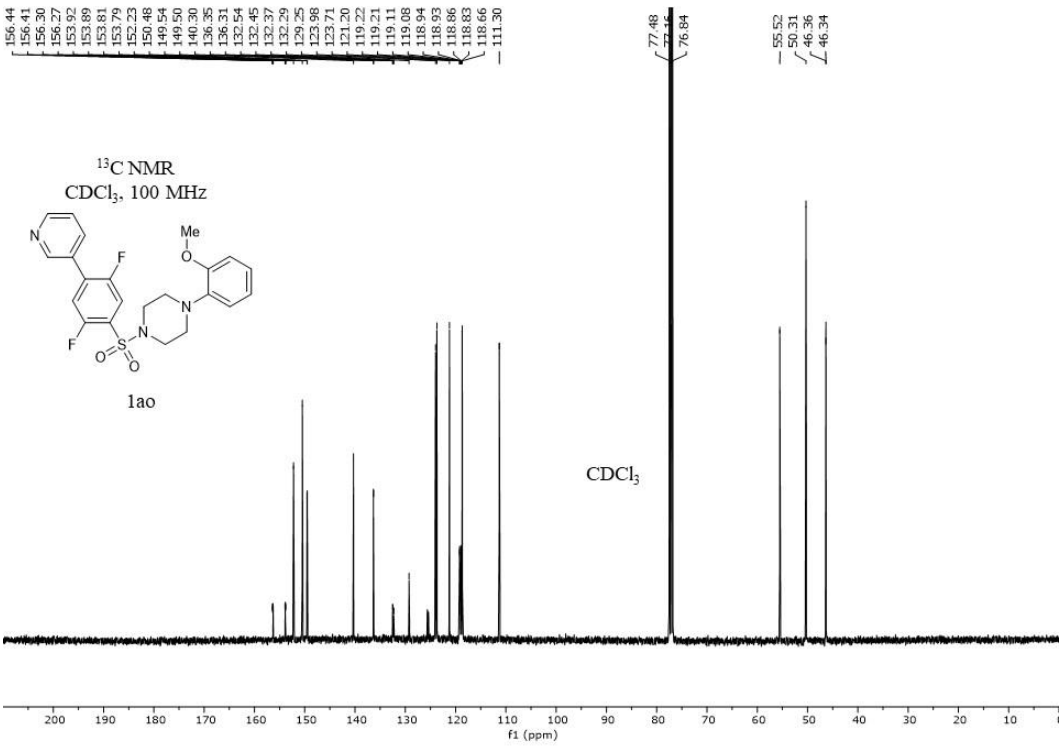
7.90
7.88
7.88
7.71
7.70
7.69
7.67
7.46
7.45
7.44
7.43
7.35
7.34
7.33
7.32
7.26
7.06
7.05
7.05
7.04
7.03
7.03
7.02
7.01
6.95
6.95
6.93
6.93
6.92
6.87
6.85
3.83
3.44
3.43
3.42
3.17
3.16
3.15
1H NMR
CDCl3, 400 MHz
Me
O
N
F
F
N
S
O
O
1ao
1.00
1.00
1.06
1.04
1.08
1.04
1.03
2.03
1.14
3.09
4.18
4.12
f1 (ppm)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150.48
149.54
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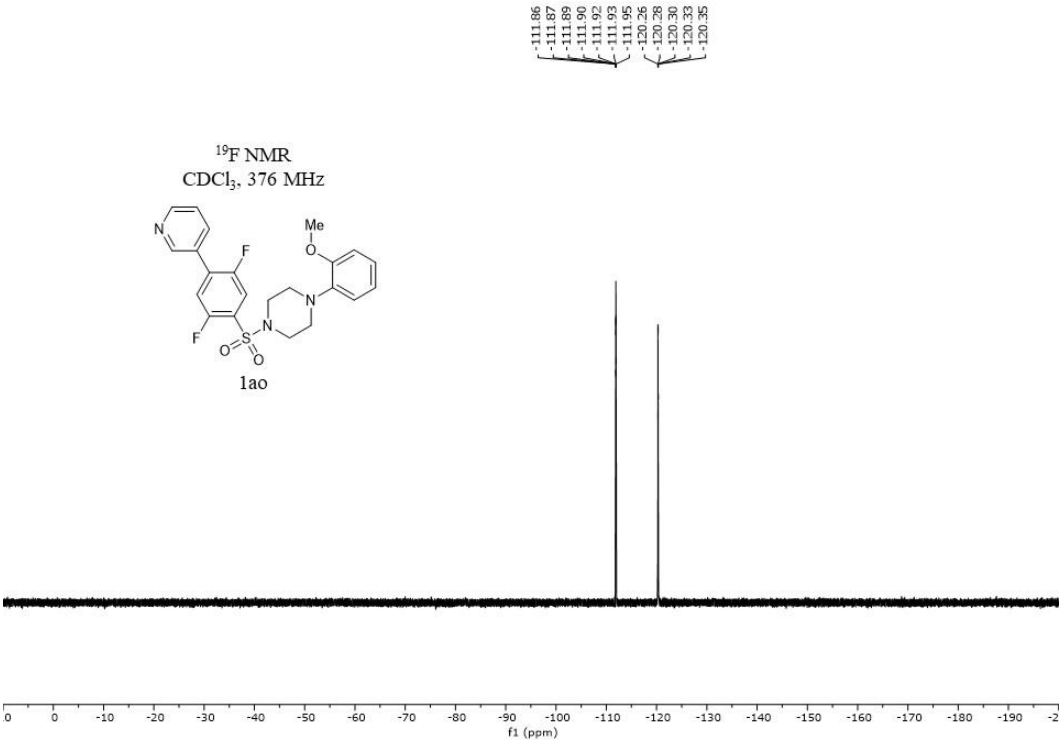
140.30
136.35
136.31
132.54
132.45
132.37
132.29
129.25
123.98
123.71
121.20
119.22
119.21
119.11
119.08
118.94
118.93
118.86
118.83
118.66
111.30
77.48
77.16
76.84
55.52
50.31
46.36
46.34
13C NMR
CDCl3, 100 MHz
Me
O
N
F
F
N
S
O
O
1ao
CDCl3
f1 (ppm)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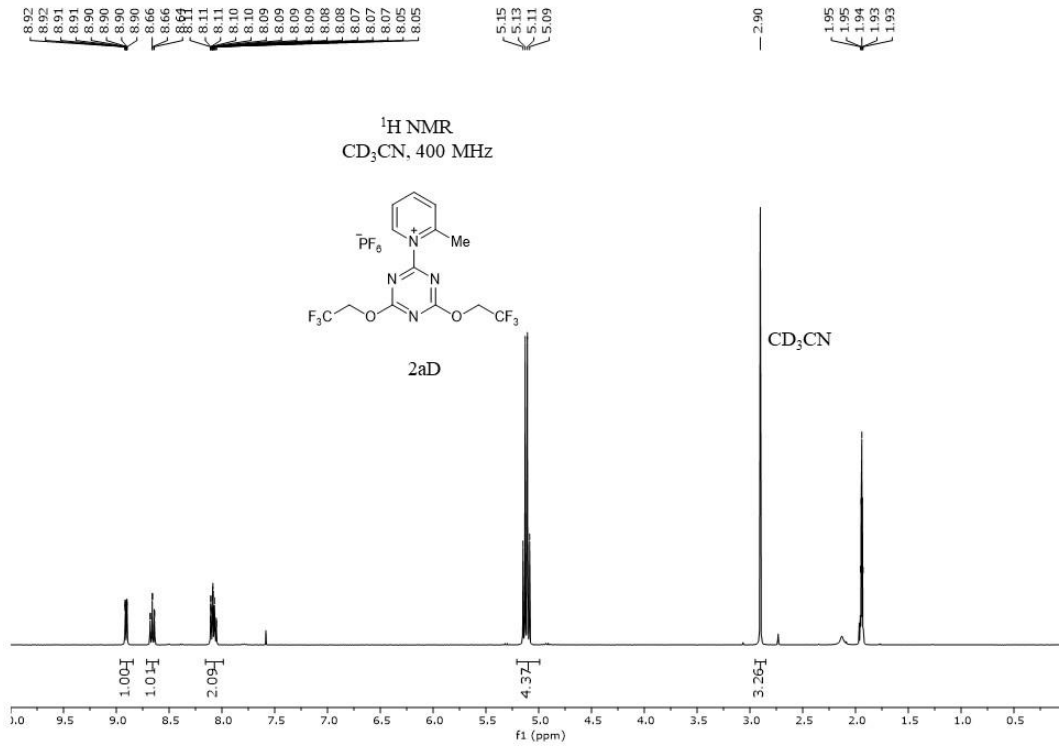
-111.87
-111.89
-111.90
-111.92
-111.93
-111.95
-120.26
-120.28
-120.30
-120.33
-120.35
19F NMR
CDCl3, 376 MHz
Me
O
N
F
F
S
O
O
1ao
f1 (ppm)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8.91
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8.90
8.90
8.90
8.90
8.66
8.66
8.11
8.11
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8.10
8.09
8.09
8.09
8.09
8.08
8.08
8.07
8.07
8.07
8.05
8.05
5.15
5.13
5.11
5.09
2.90
1.95
1.95
1.94
1.93
1.93
1H NMR
CD3CN, 400 MHz
PF6
Me
N
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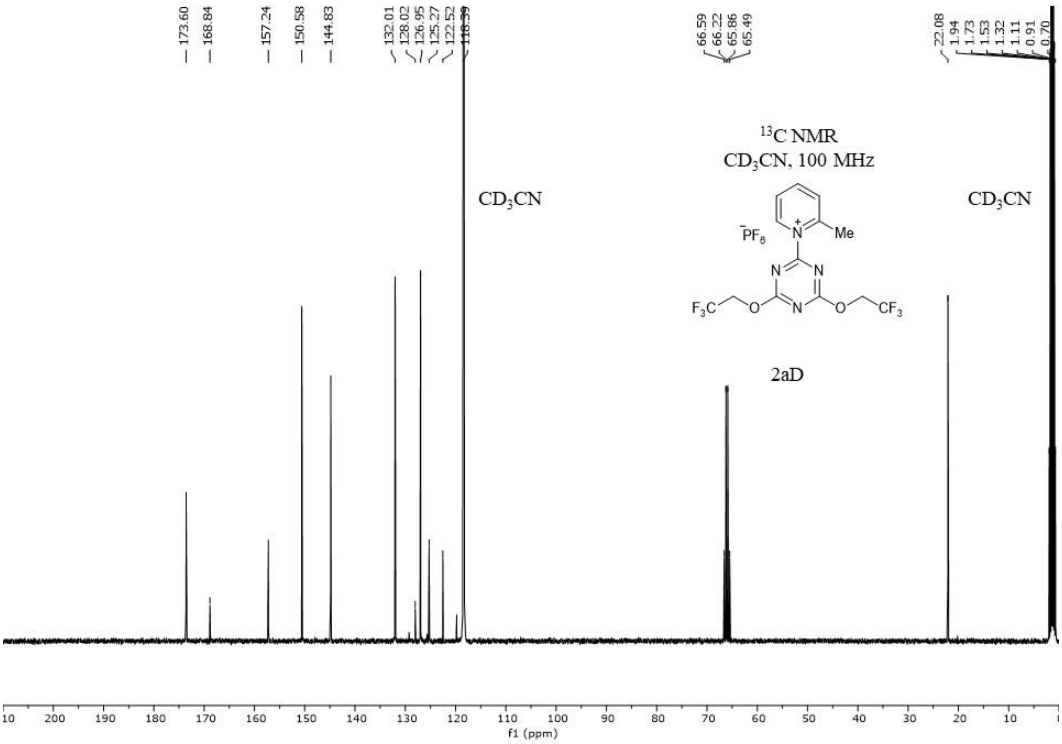
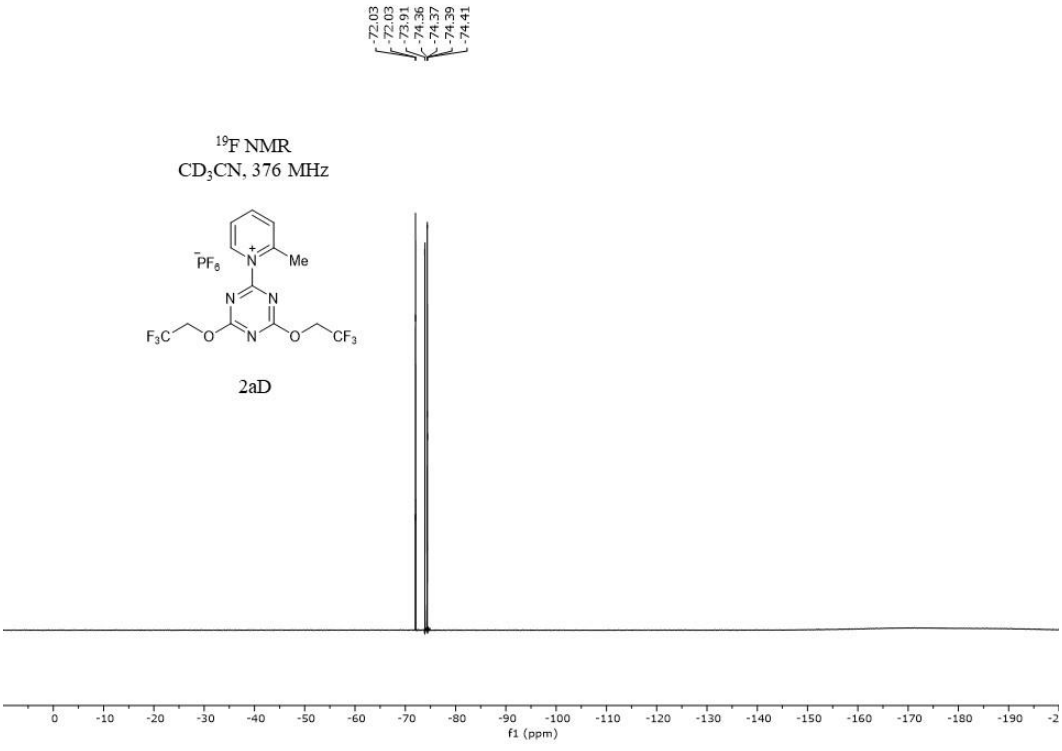
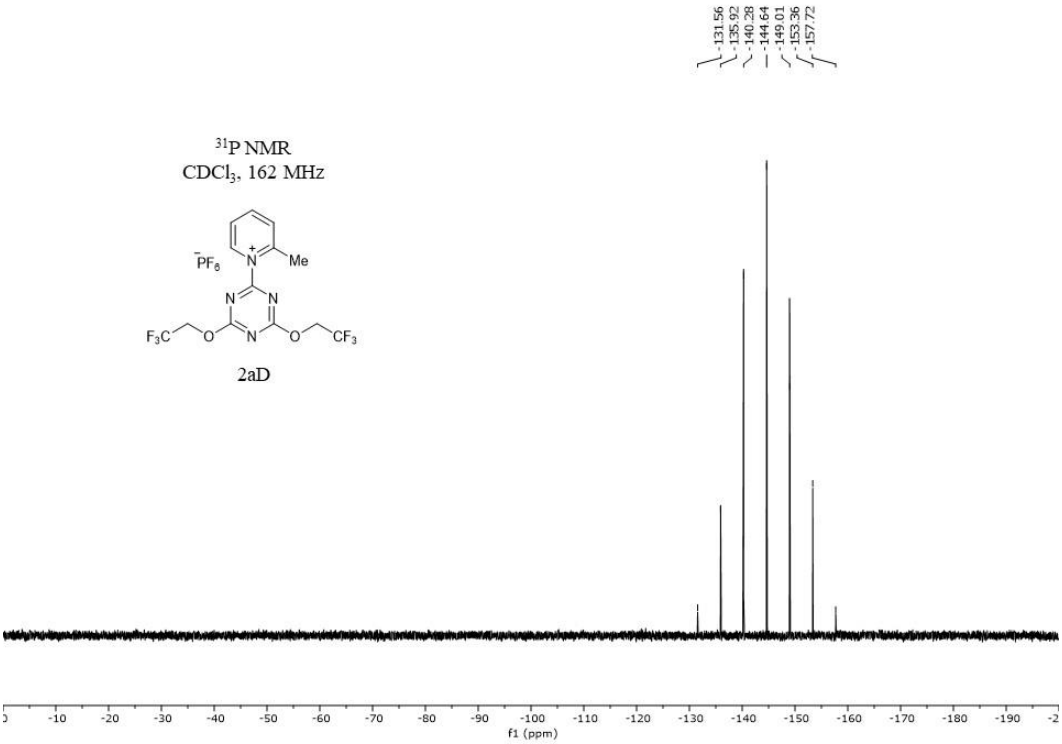
1.01
2.09
4.37
3.26
f1 (ppm)


173.60
168.84
157.24
150.58
144.83
132.01
128.02
126.95
125.27
122.52
118.39
66.59
66.22
65.86
65.49
22.08
1.94
1.73
1.53
1.32
1.11
0.91
0.70
CD3CN
CD3CN
13C NMR
CD3CN, 100 MHz
2aD
f1 (ppm)


-72.03
-72.03
-73.91
-74.36
-74.37
-74.39
-74.41
19F NMR
CD3CN, 376 MHz
2aD
f1 (ppm)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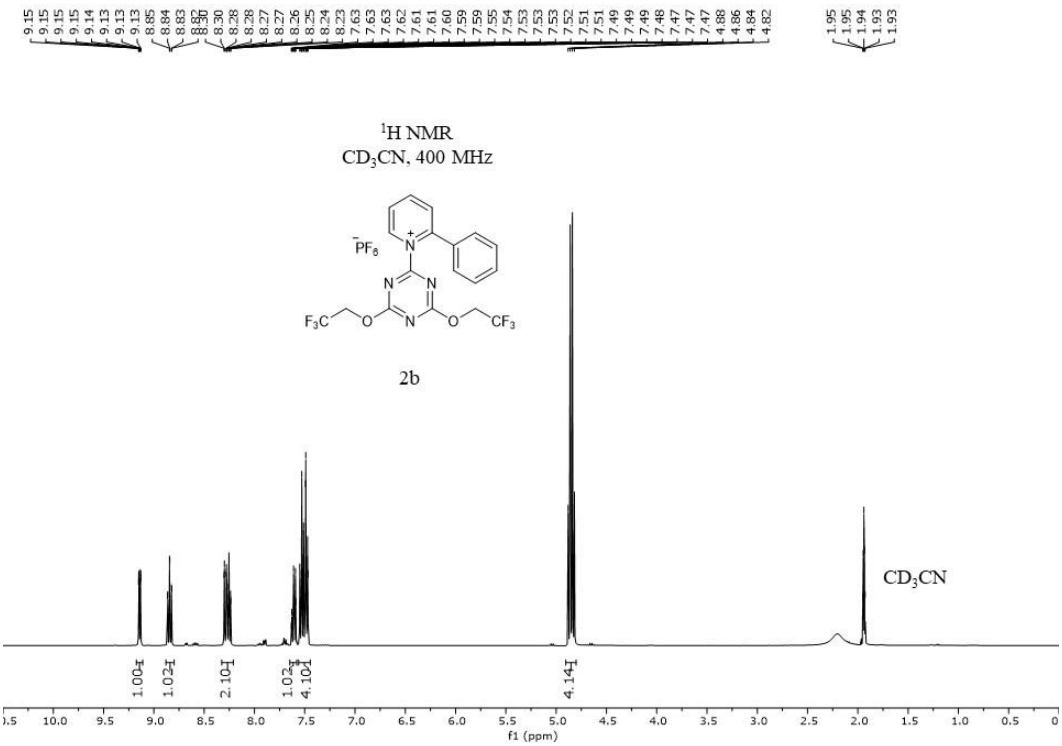
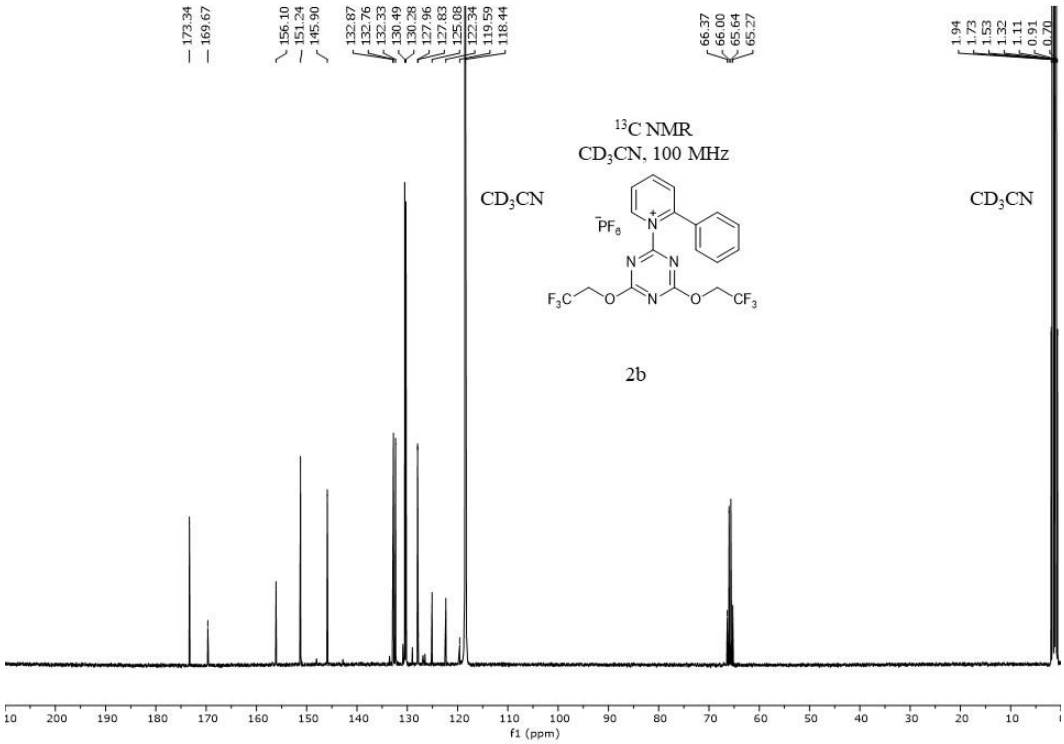
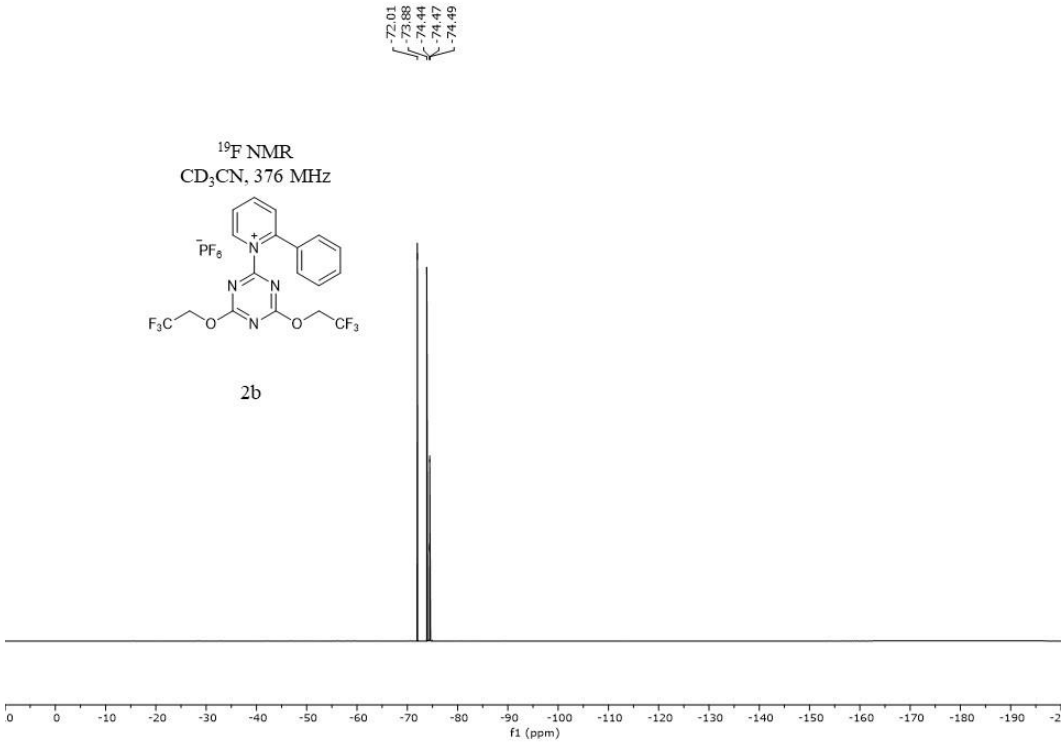
-135.92
-140.28
-144.64
-149.01
-153.36
-157.72
31P NMR
CDCl3, 162 MHz
PF6
Me
F3C
O
N
O
CF3
2aD
f1 (ppm)


1H NMR
CD3CN, 400 MHz
PF6
F3C
O
N
O
CF3
2b
CD3CN
1.00
1.02
2.10
1.02
4.10
4.14
f1 (ppm)


173.34
169.67
156.10
151.24
145.90
132.87
132.76
132.33
130.49
130.28
127.96
127.83
125.08
122.34
119.59
118.44
66.37
66.00
65.64
65.27
1.94
1.73
1.53
1.32
1.11
0.91
0.70
^{13}C NMR
CD_3CN, 100 MHz
CD_3CN
CD_3CN
$^-PF_6$
F_3C
CF_3
2b
f1 (ppm)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-73.88
-74.44
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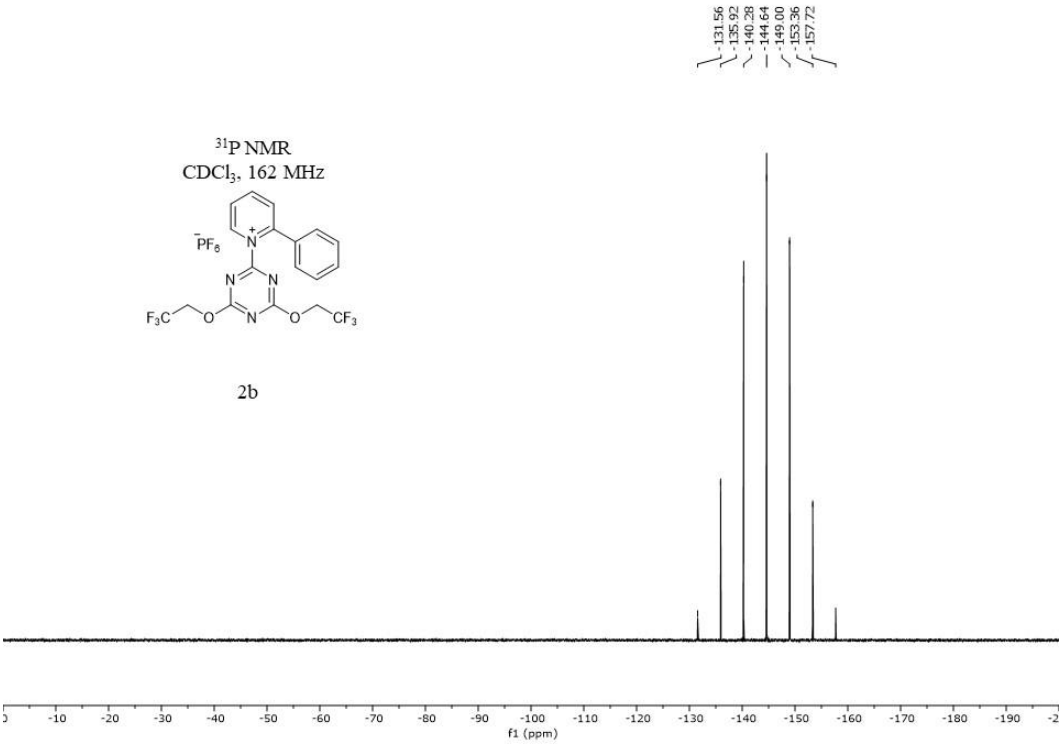
^{19}F NMR
CD_3CN, 376 MHz
$^-PF_6$
F_3C
CF_3
2b
f1 (ppm)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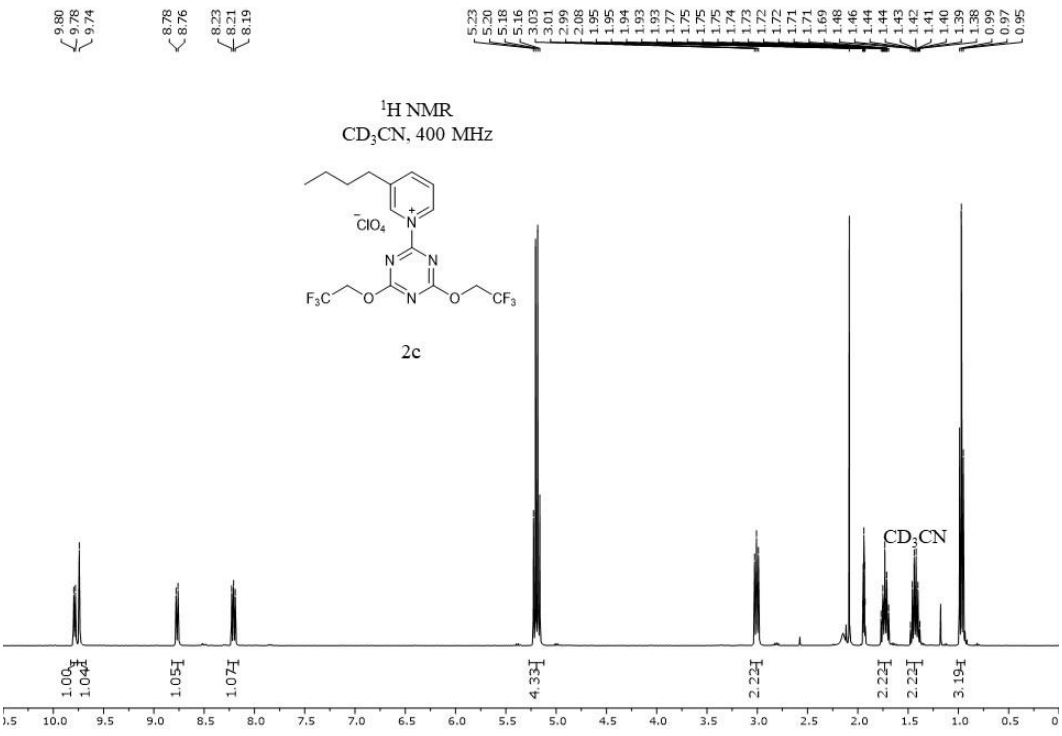
-135.92
-140.28
-144.64
-149.00
-153.36
-157.72
31P NMR
CDCl3, 162 MHz
PF6
F3C
O
N
O
CF3
2b
f1 (ppm)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5.16
3.03
3.01
2.99
2.08
1.95
1.95
1.94
1.93
1.93
1.77
1.75
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1.72
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1.71
1.69
1.48
1.46
1.44
1.44
1.43
1.42
1.41
1.40
1.39
1.38
0.99
0.97
0.95
1H NMR
CD3CN, 400 MHz
ClO4
F3C
O
N
O
CF3
2c
CD3CN
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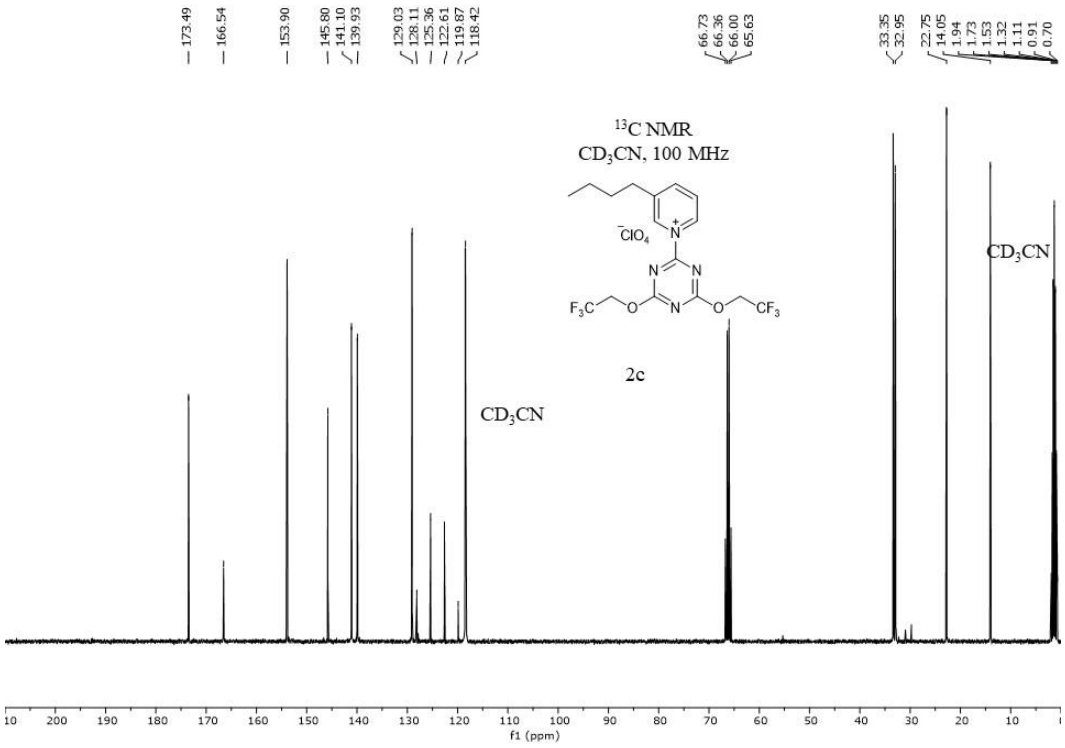
1.05
1.07
4.33
2.23
2.23
2.23
3.19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122.61
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118.42
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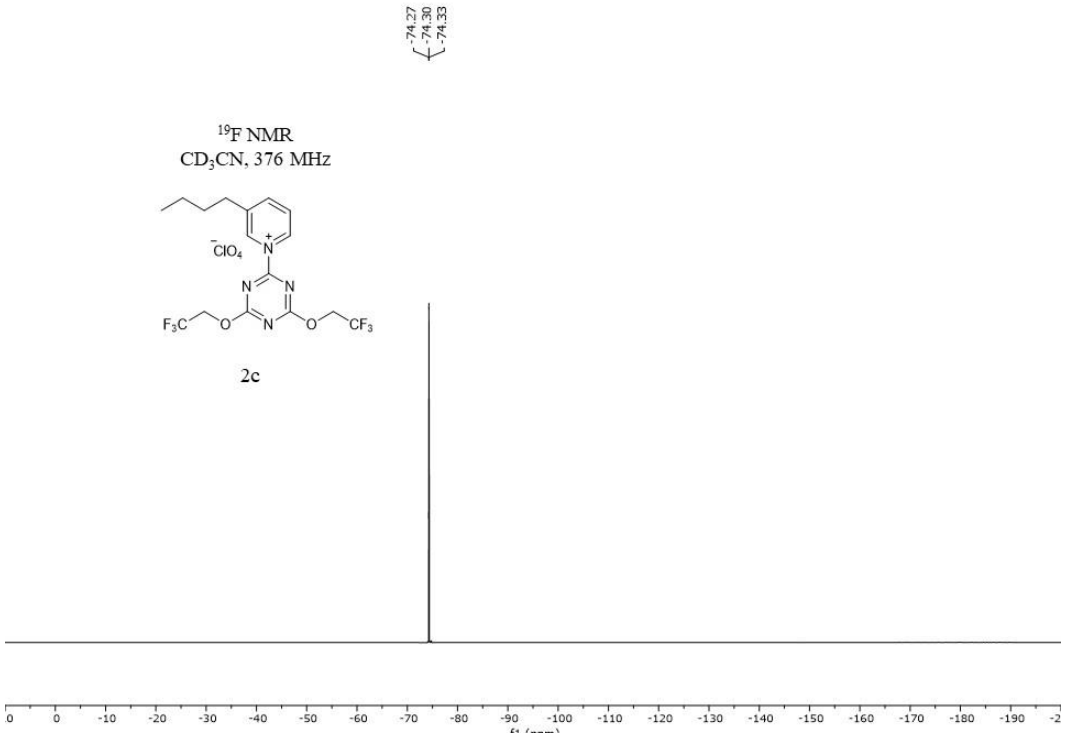
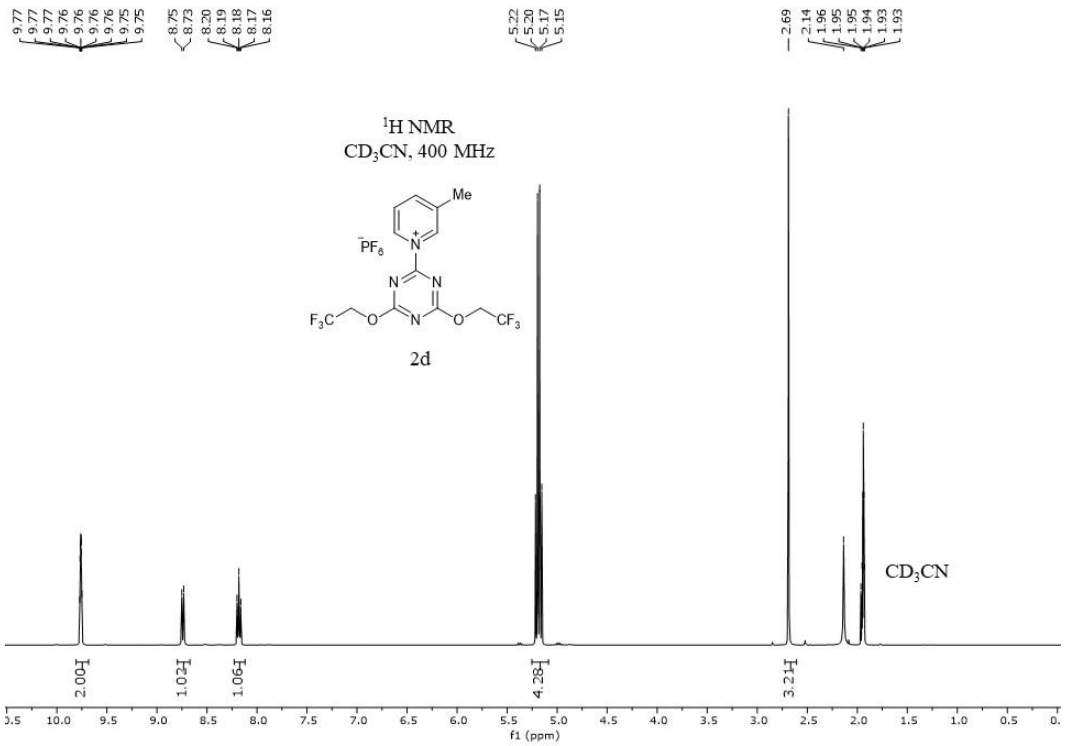
66.36
66.00
65.63
33.35
32.95
22.75
14.05
1.94
1.73
1.53
1.32
1.11
0.91
0.70
13C NMR
CD3CN, 100 MHz
CD3CN
CD3CN
2c
f1 (ppm)


-74.27
-74.30
-74.33
19F NMR
CD3CN, 376 MHz
2c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9.77
9.77
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9.76
9.76
9.75
9.75
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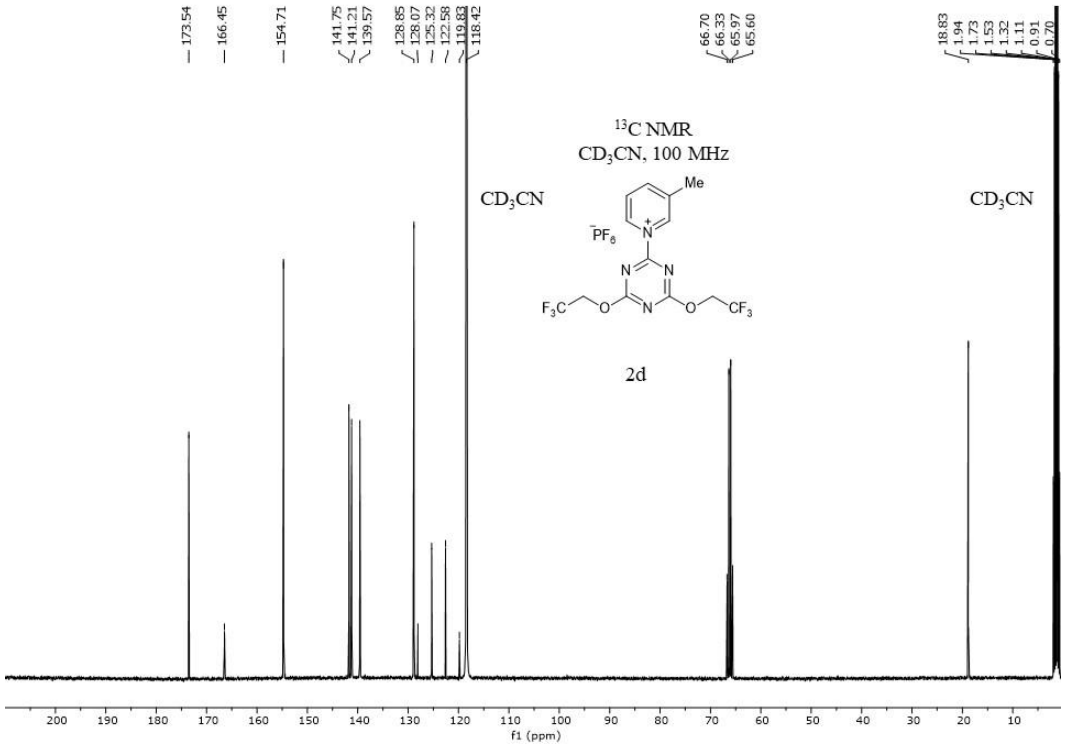
8.73
8.20
8.19
8.18
8.17
8.16
5.22
5.20
5.17
5.15
2.69
2.14
1.96
1.95
1.95
1.94
1.93
1.93
^{1}H NMR
CD_3CN, 400 MHz
Me
PF_6^-
F_3C
CF_3
2d
CD_3CN
2.00
1.02
1.06
4.28
3.21
f1 (ppm)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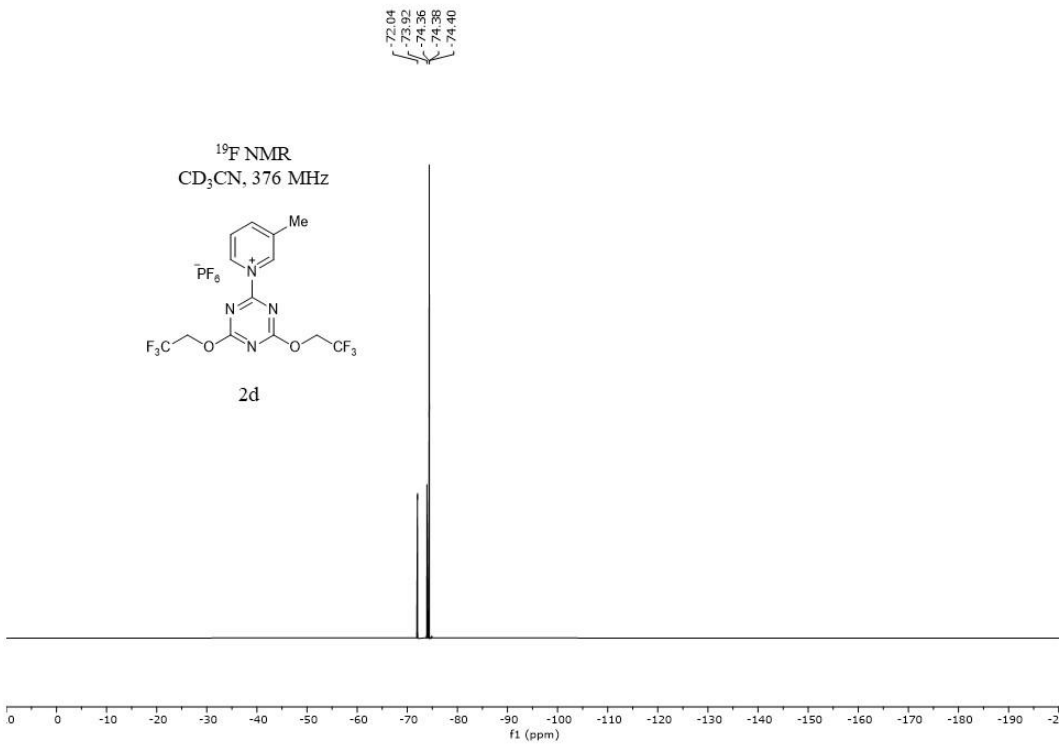
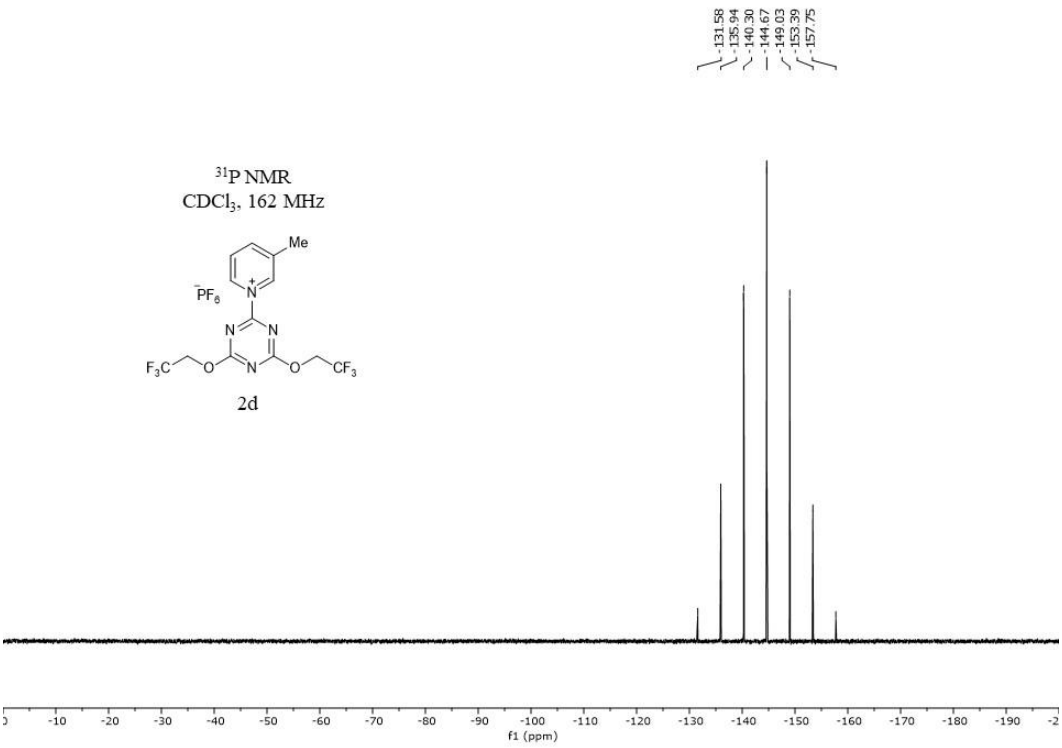
66.33
65.97
65.60
18.83
1.94
1.73
1.53
1.32
1.11
0.91
0.70
^{13}C NMR
CD_3CN, 100 MHz
CD_3CN
CD_3CN
Me
PF_6^-
F_3C
CF_3
2d
f1 (ppm)


-72.04
-73.92
-74.36
-74.38
-74.40
19F NMR
CD3CN, 376 MHz
Me
PF6
F3C
O
N
CF3
2d
f1 (ppm)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135.94
140.30
144.67
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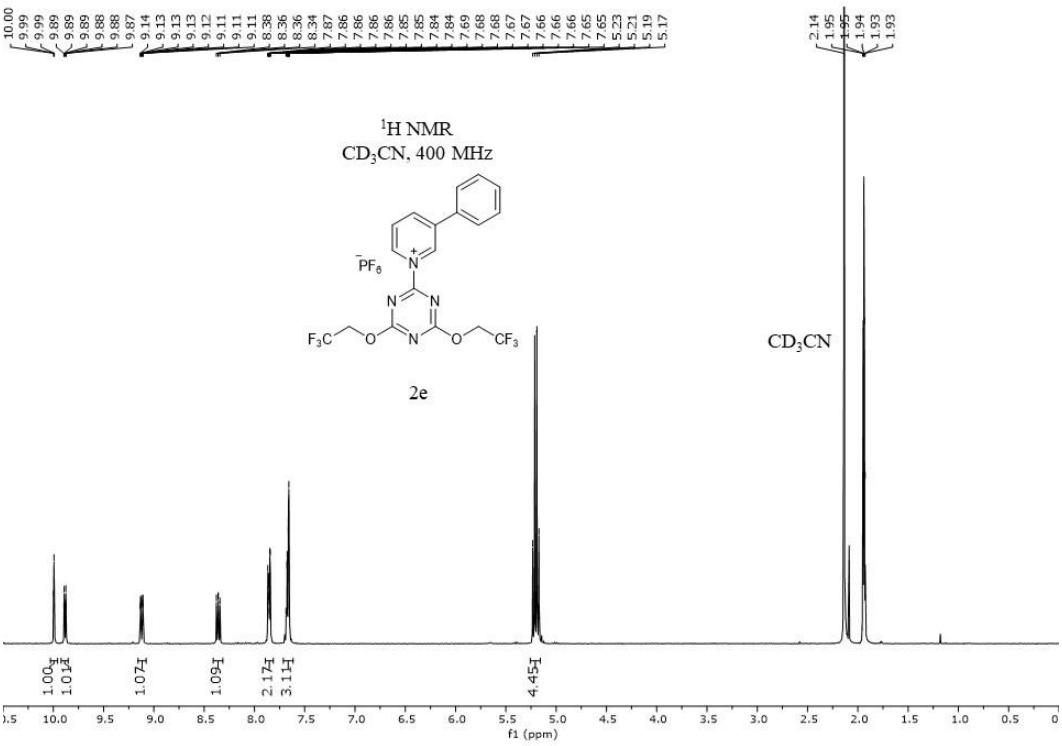
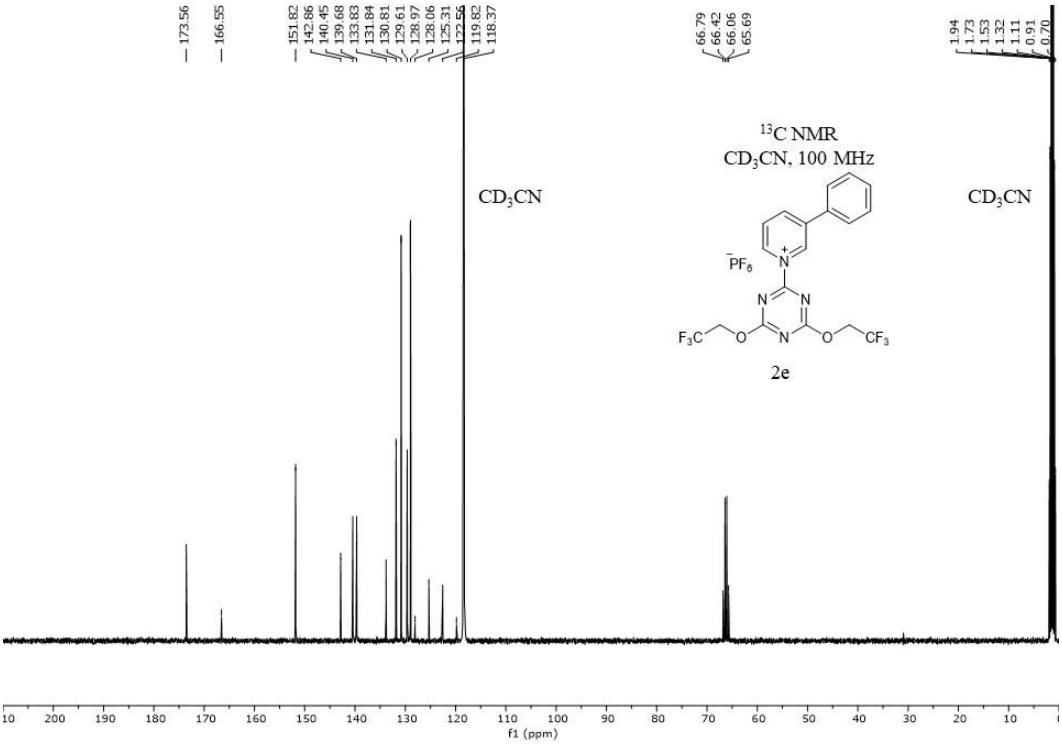
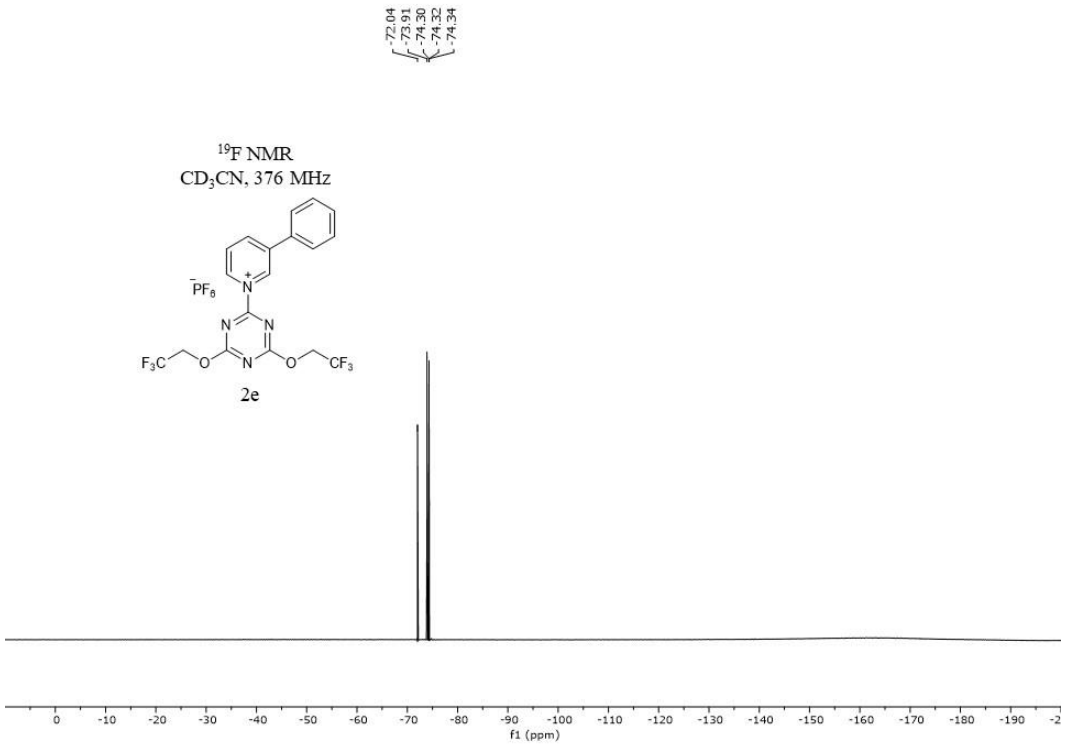
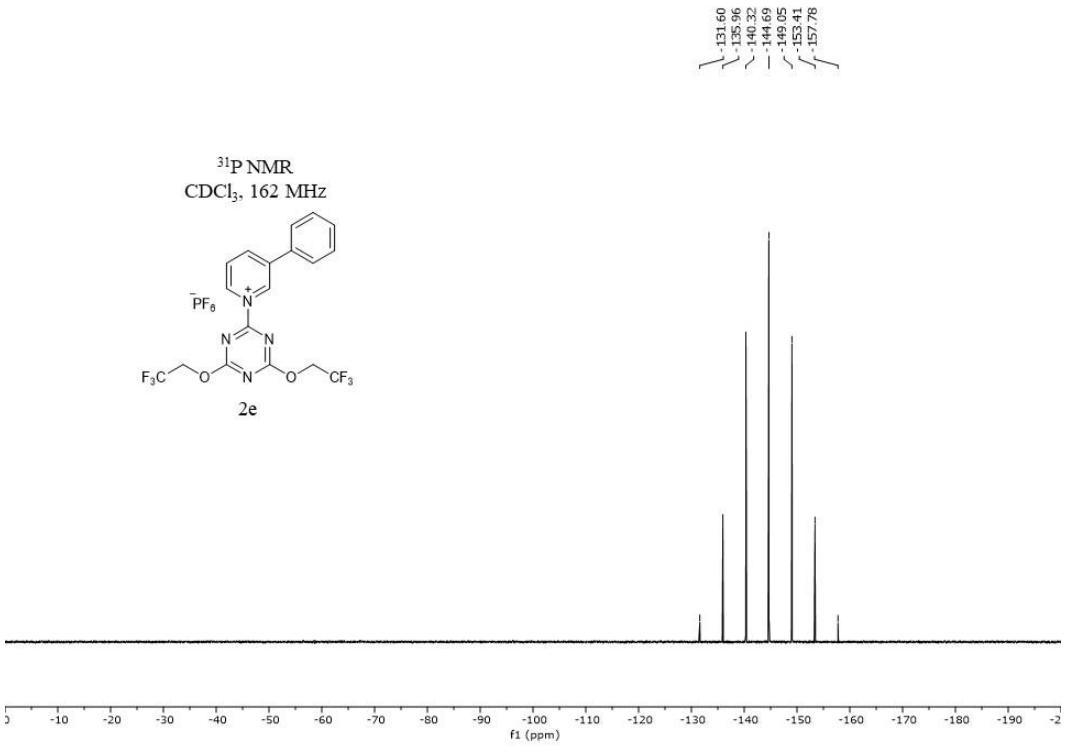
157.75
31P NMR
CDCl3, 162 MHz
Me
PF6
F3C
O
N
CF3
2d
f1 (ppm)


^{1}H NMR
CD_3CN, 400 MHz
PF_6^-
F_3C
CF_3
2e
CD_3CN
f1 (ppm)


^{13}C NMR
CD_3CN, 100 MHz
CD_3CN
CD_3CN
PF_6^-
F_3C
CF_3
2e
f1 (ppm)


-72.04
-73.91
-74.30
-74.32
-74.34
19F NMR
CD3CN, 376 MHz
PF6
F3C
CF3
2e
f1 (ppm)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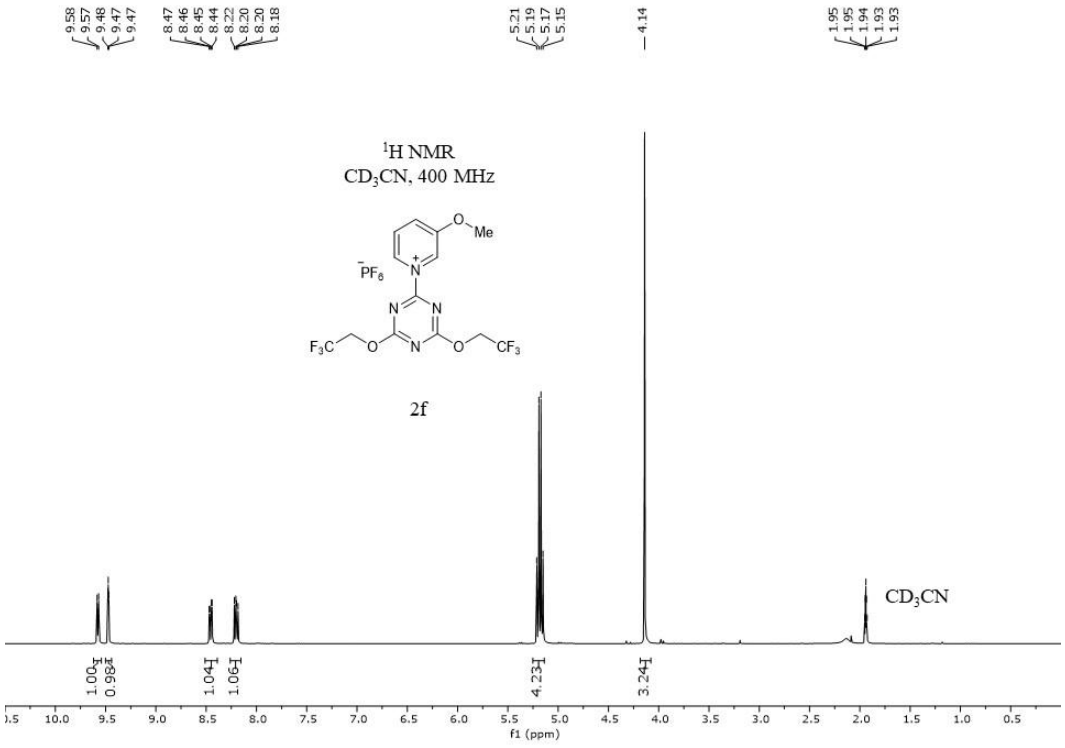
-157.78
31P NMR
CDCl3, 162 MHz
PF6
F3C
CF3
2e
f1 (ppm)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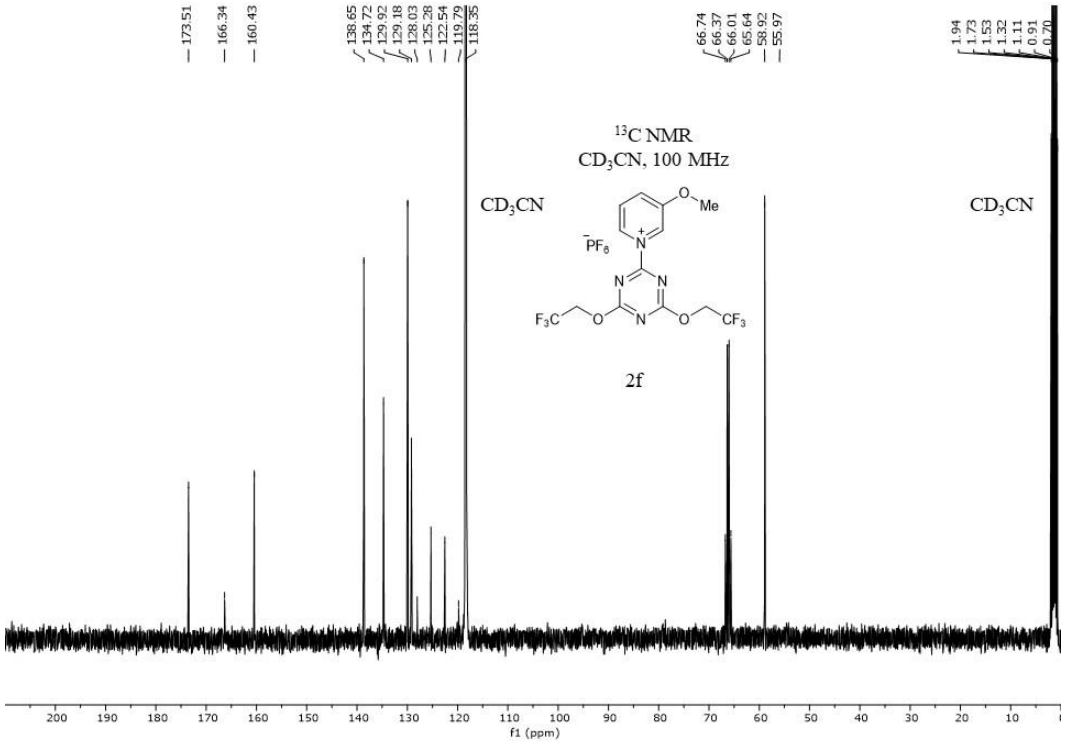
8.22
8.20
8.20
8.18
5.21
5.19
5.17
5.15
4.14
1.95
1.95
1.94
1.93
1.93
^{1}H NMR
CD_3CN, 400 MHz
Me
PF_6^-
F_3C
CF_3
2f
CD_3CN
1.00
0.98
1.04
1.06
4.23
3.24
f1 (ppm)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129.18
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119.79
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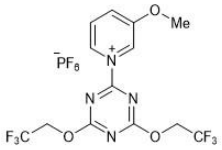
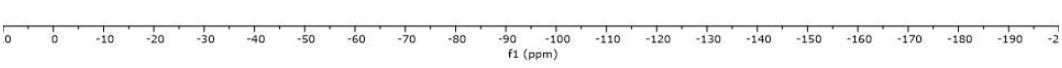
66.74
66.37
66.01
65.64
58.92
55.97
1.94
1.73
1.53
1.32
1.11
0.91
0.70
^{13}C NMR
CD_3CN, 100 MHz
CD_3CN
CD_3CN
Me
PF_6^-
F_3C
CF_3
2f
f1 (ppm)

-72.06
-73.94
-74.32
-74.35
-74.37

^{19}F NMR
CD_3CN, 376 MHz



2f



-131.59
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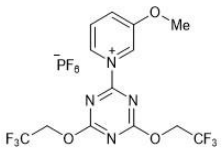
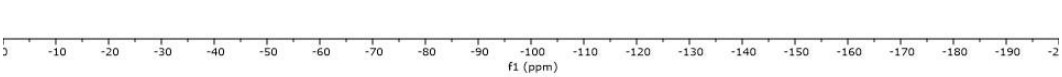
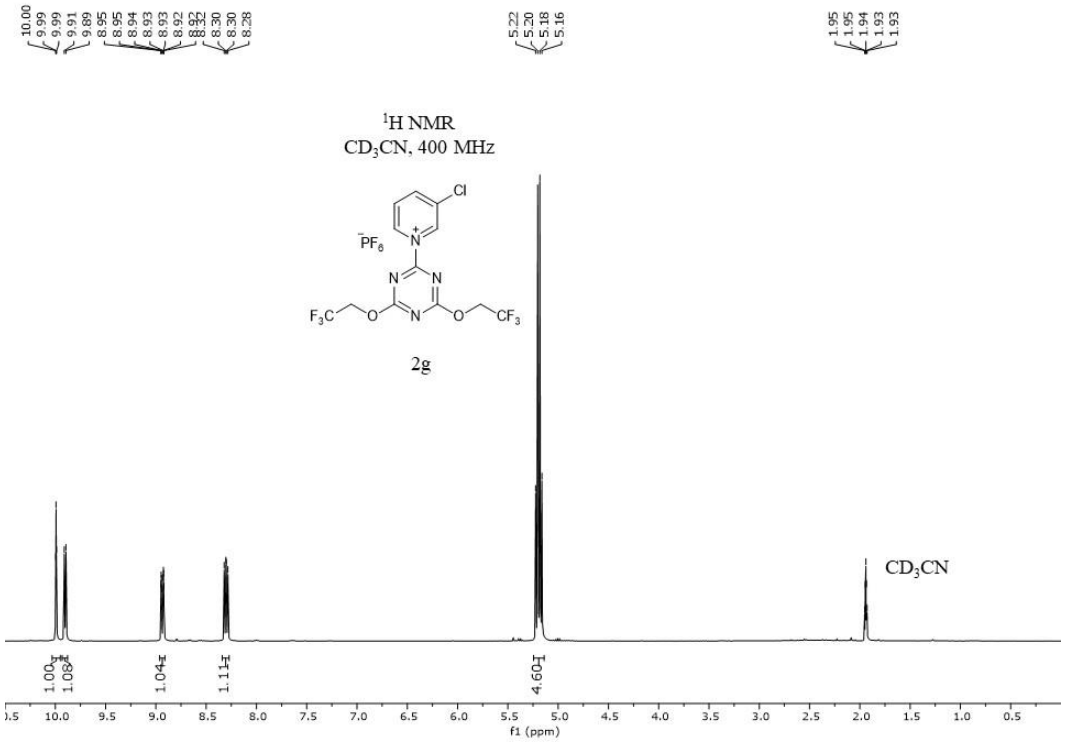
-149.04
-153.40
-157.76

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



2f

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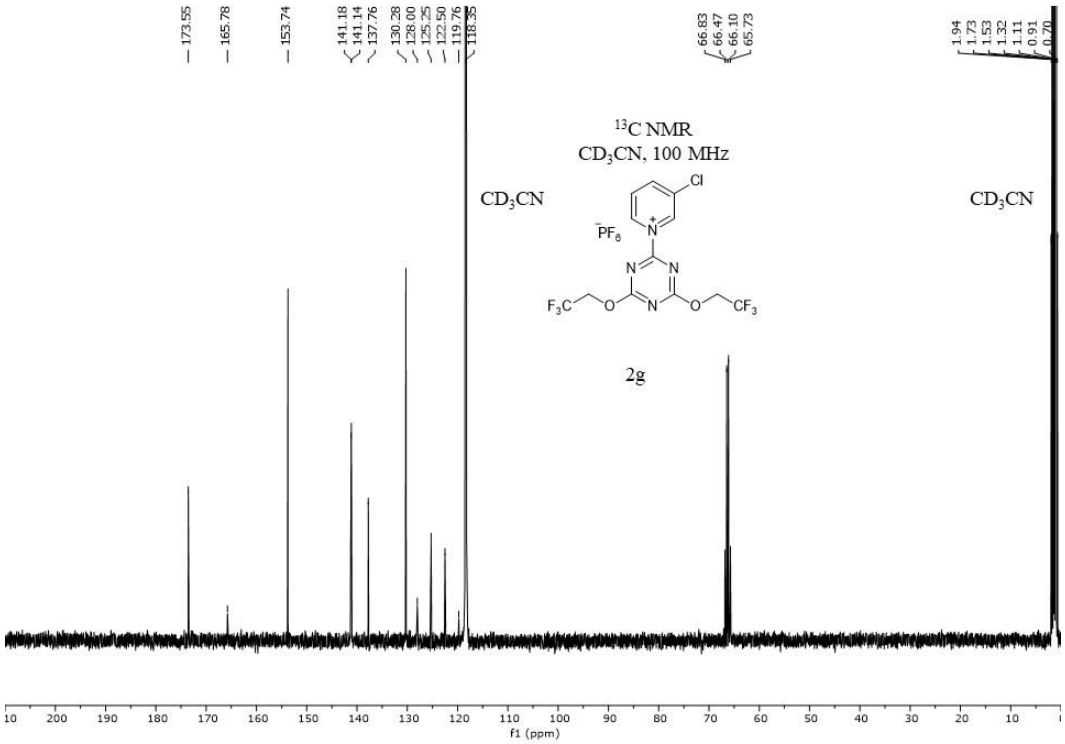
8.94
8.93
8.93
8.92
8.32
8.30
8.30
8.28
5.22
5.20
5.18
5.16
1.95
1.95
1.94
1.93
1.93
1H NMR
CD3CN, 400 MHz
Cl
PF6
N
N
N
F3C
O
O
CF3
2g
CD3CN
1.00
1.08
1.04
1.11
4.60
f1 (ppm)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66.83
66.47
66.10
65.73
1.94
1.73
1.53
1.32
1.11
0.91
0.70
13C NMR
CD3CN, 100 MHz
CD3CN
CD3CN
Cl
PF6
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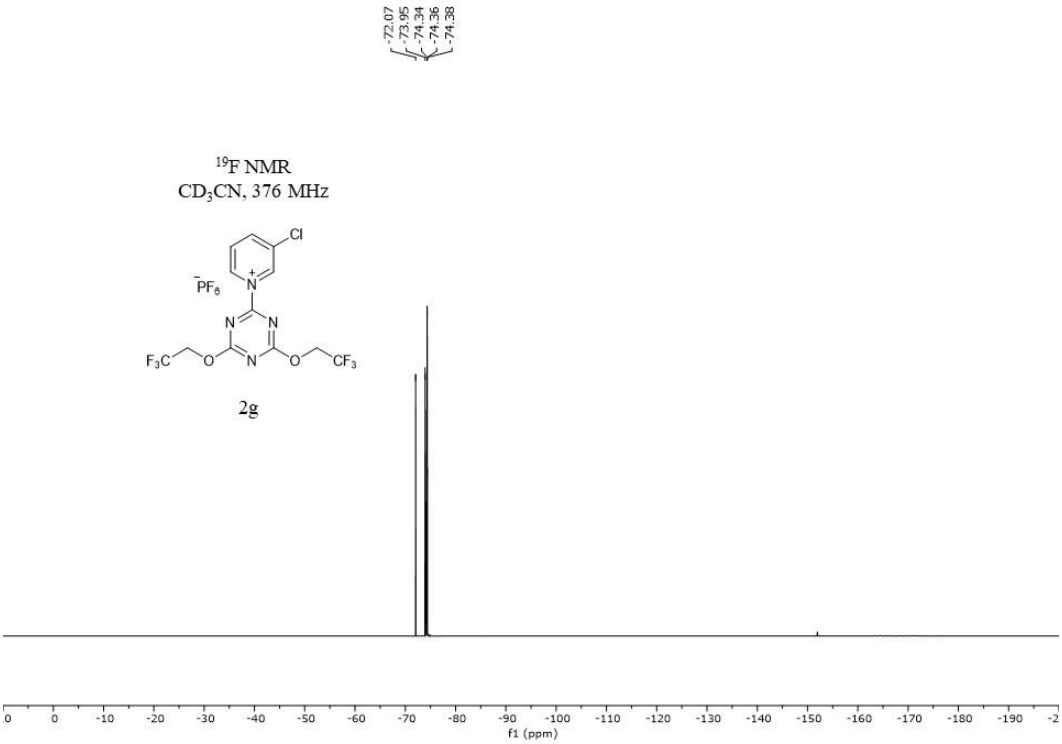
N
N
F3C
O
O
CF3
2g
f1 (ppm)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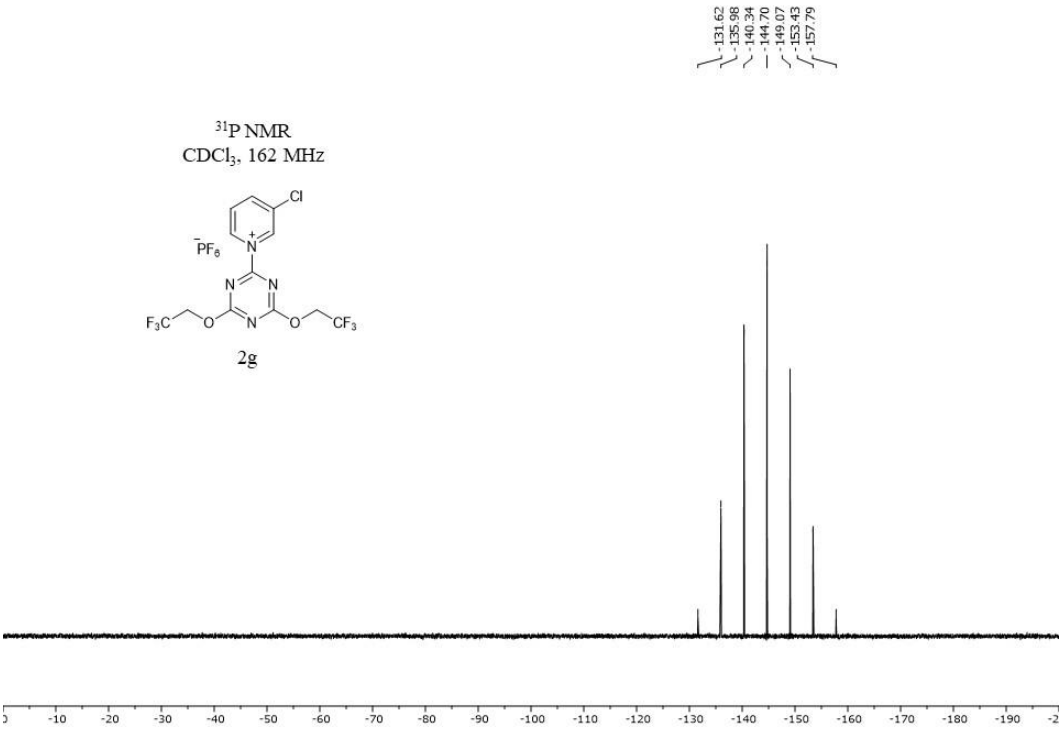
-73.95
-74.34
-74.36
-74.38
19F NMR
CD3CN, 376 MHz
Cl
PF6
N
N
N
F3C
O
O
CF3
2g
f1 (ppm)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31P NMR
CDCl3, 162 MHz
Cl
PF6
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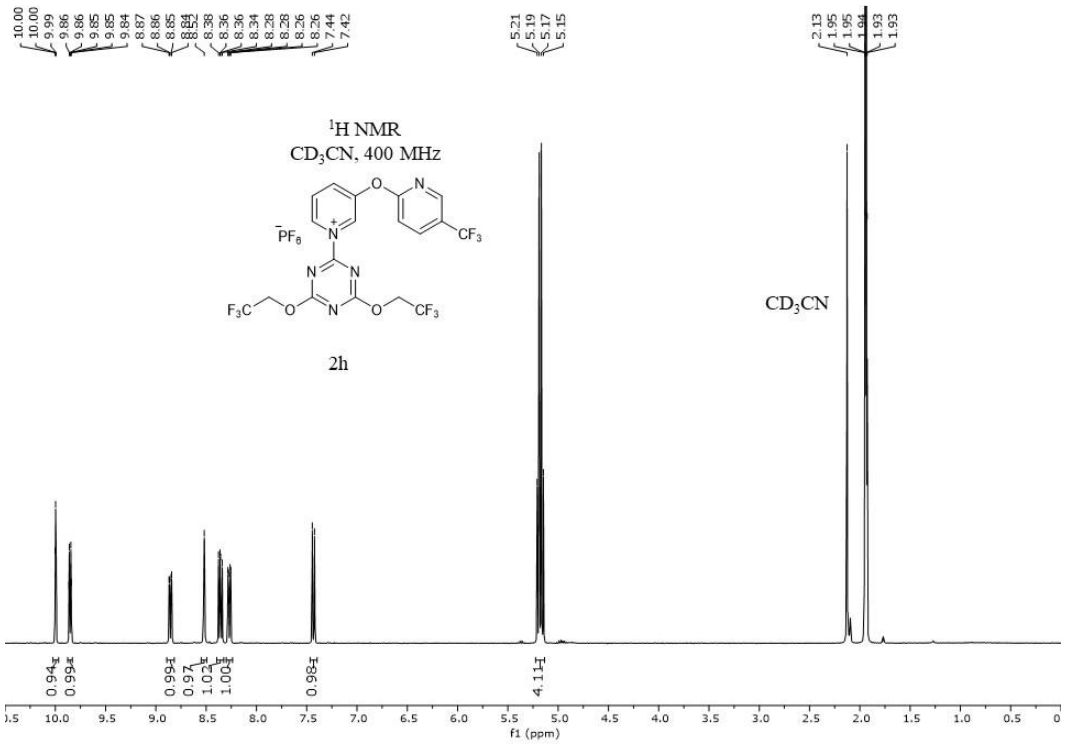
N
N
F3C
O
O
CF3
2g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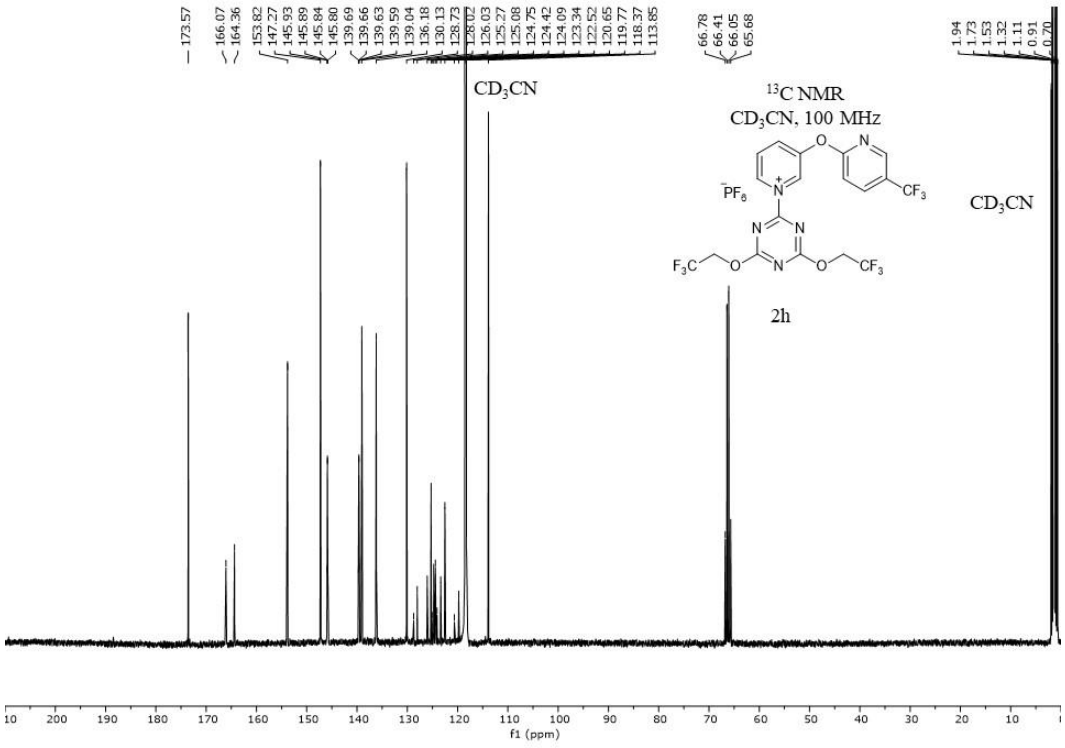
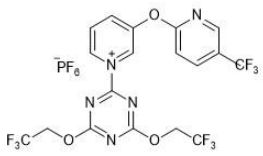
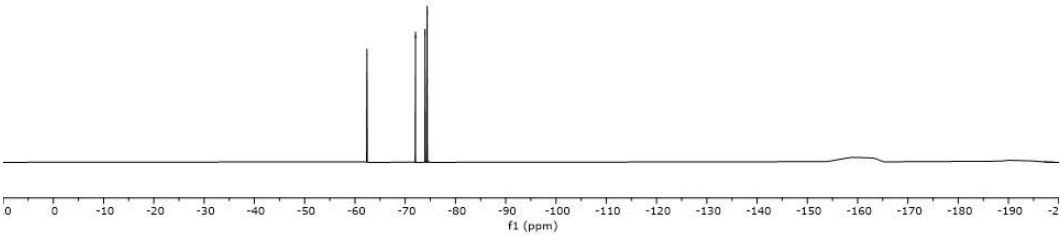
CD_3CN, 400 MHz
2h
CD_3CN
f1 (ppm)


^{13}C NMR
CD_3CN, 100 MHz
2h
CD_3CN
CD_3CN
f1 (ppm)

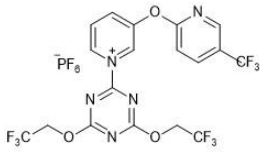
^{19}F NMR
CD_3CN, 376 MHz



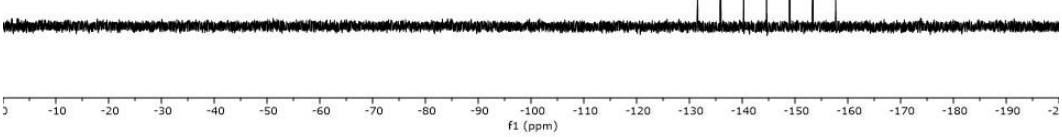
2h

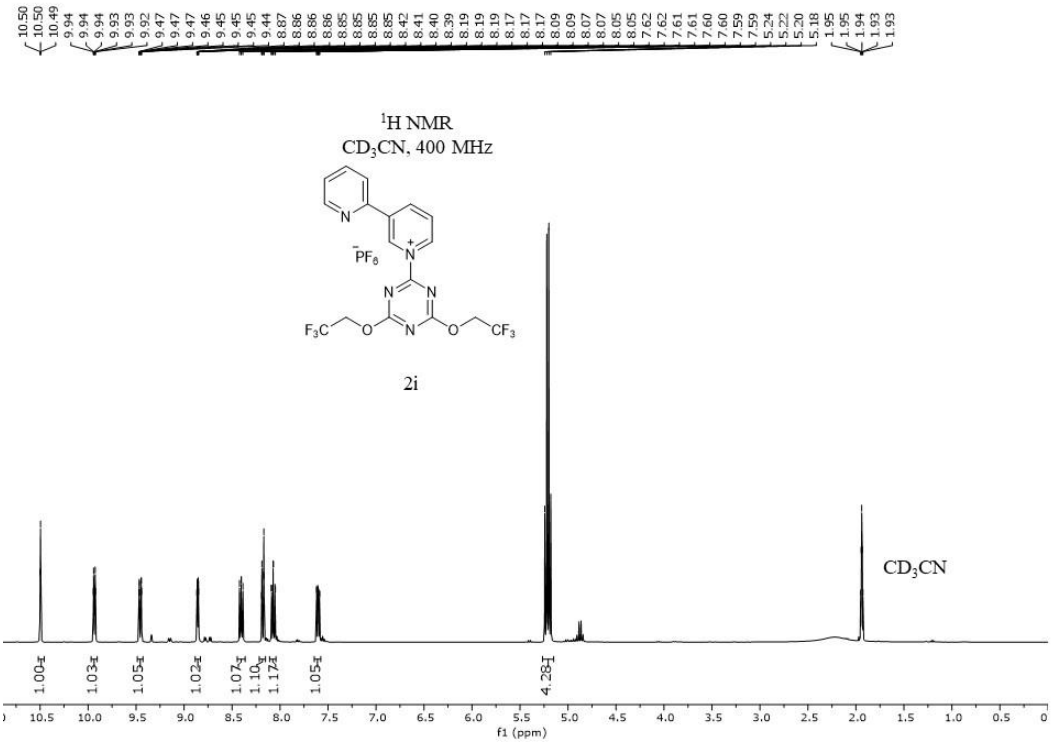


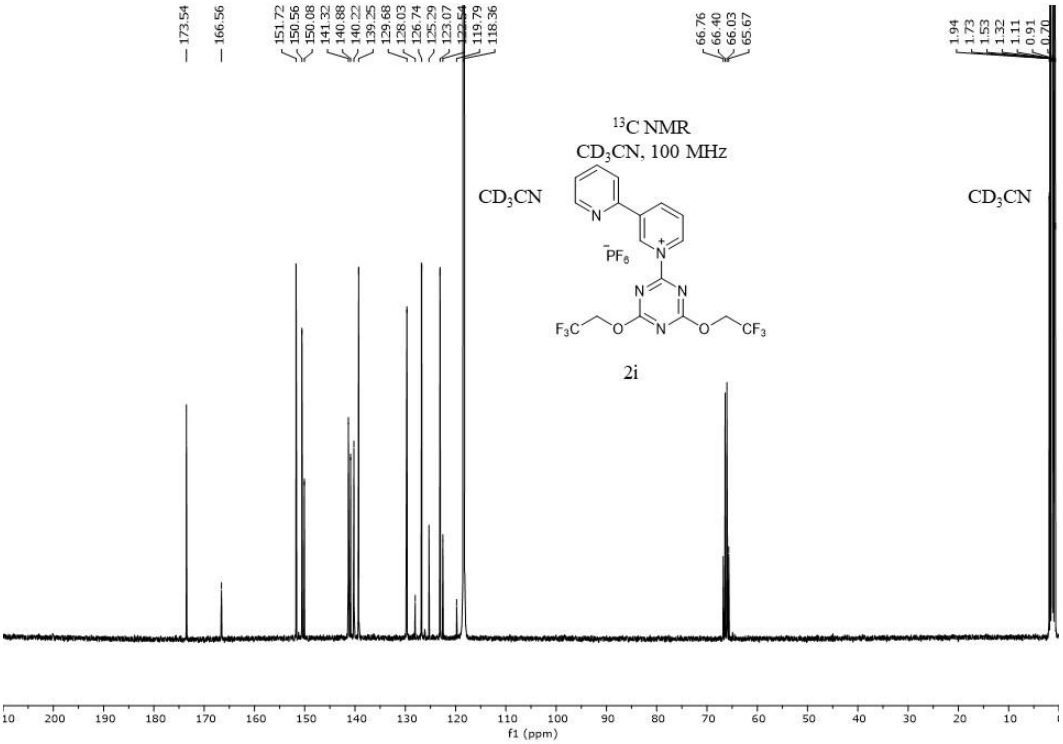
^{31}P NMR
$CDCl_3$, 162 MHz

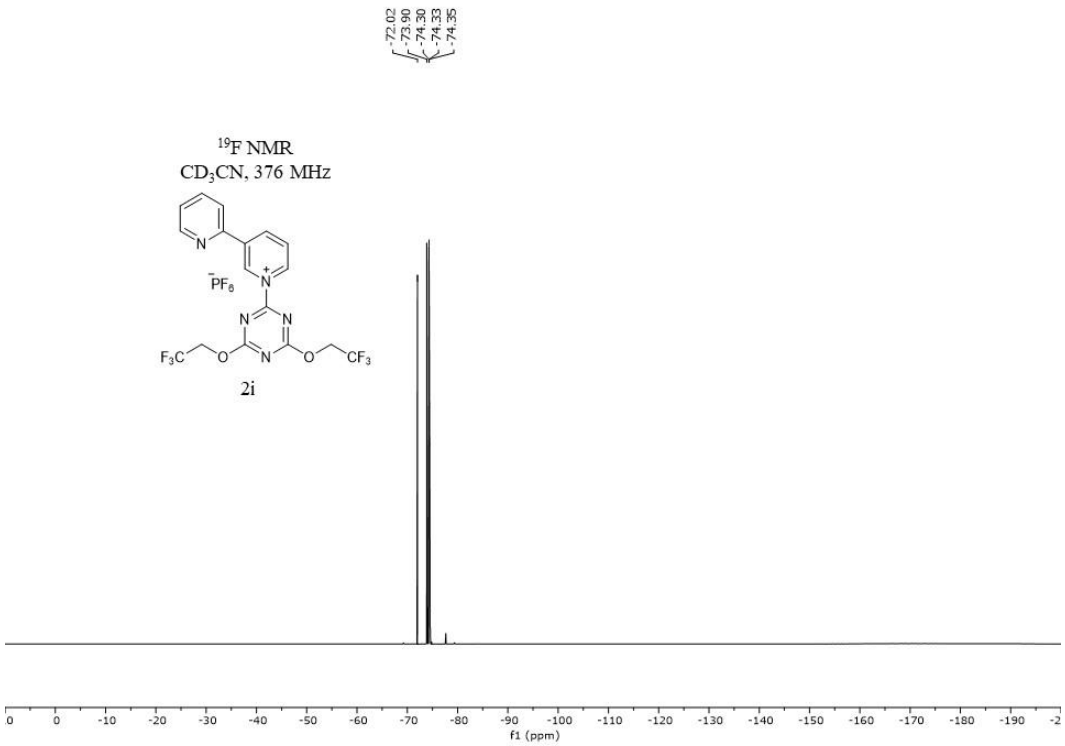


2h




^{1}H NMR
CD_3CN, 400 MHz
2i
CD_3CN
f1 (ppm)


^{13}C NMR
CD_3CN, 100 MHz
2i
CD_3CN
CD_3CN
f1 (ppm)


-72.02
-73.90
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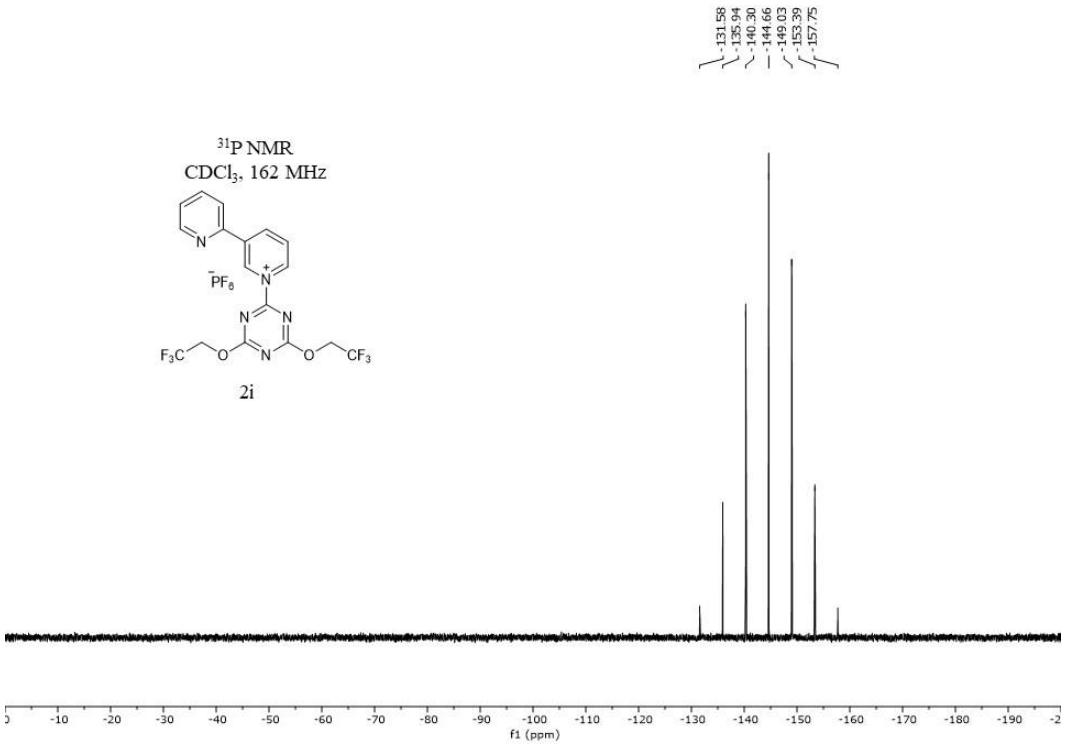
-74.35
19F NMR
CD3CN, 376 MHz
PF6
F3C
O
N
CF3
2i
f1 (ppm)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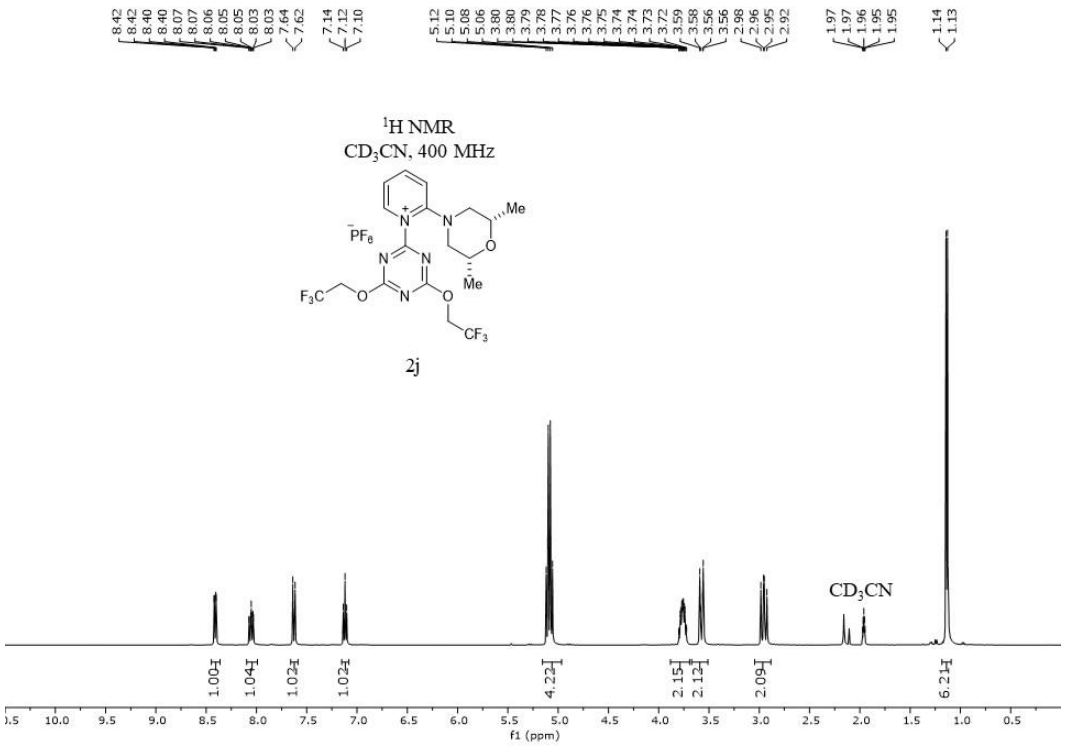
CDCl3, 162 MHz
PF6
F3C
O
N
CF3
2i
f1 (ppm)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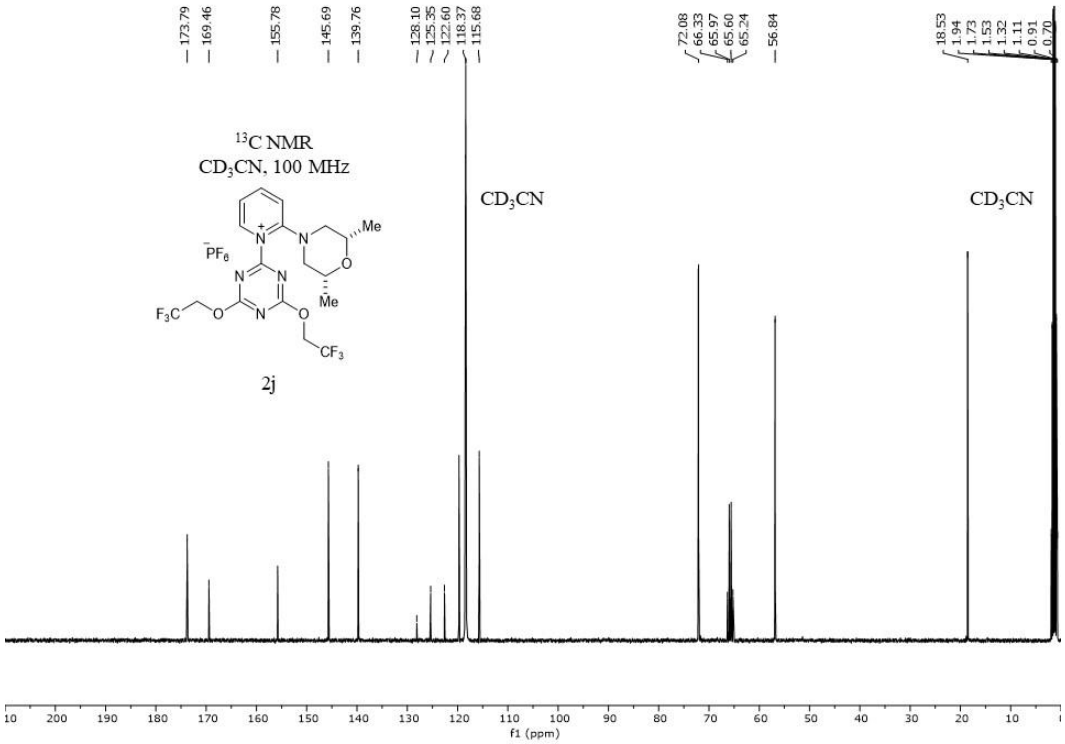
2.95
2.92
1.97
1.97
1.96
1.95
1.95
1.14
1.13
1H NMR
CD3CN, 400 MHz
Me
PF6
Me
F3C
CF3
2j
CD3CN
1.00
1.04
1.03
1.02
4.22
2.15
2.13
2.09
6.21
f1 (ppm)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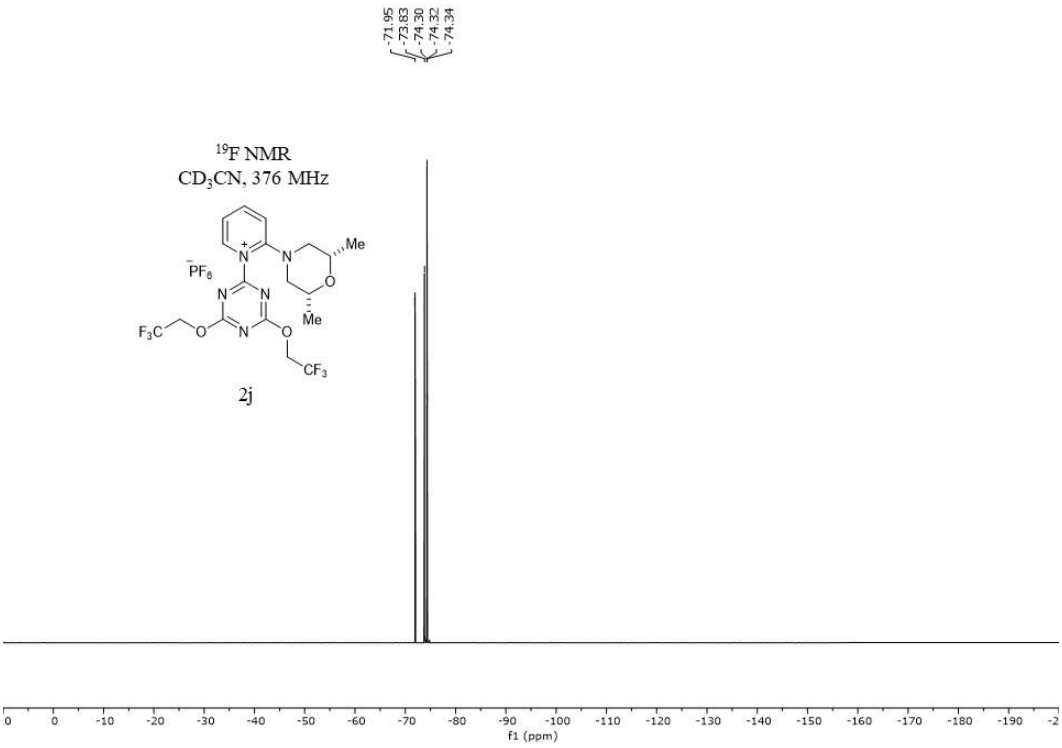
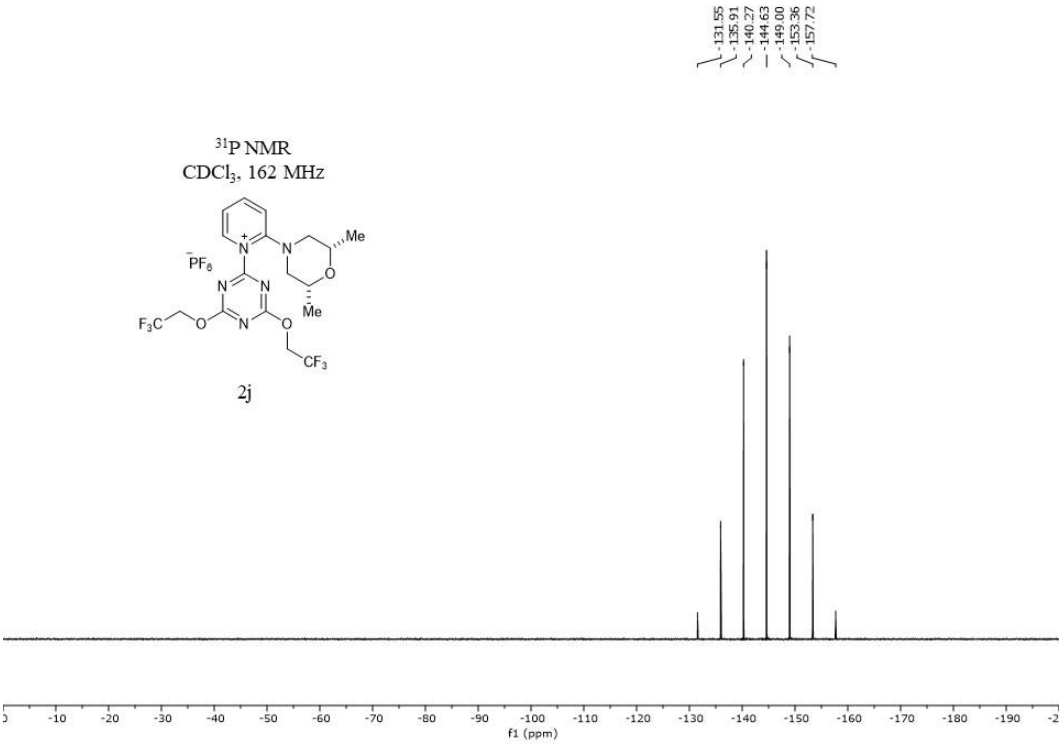
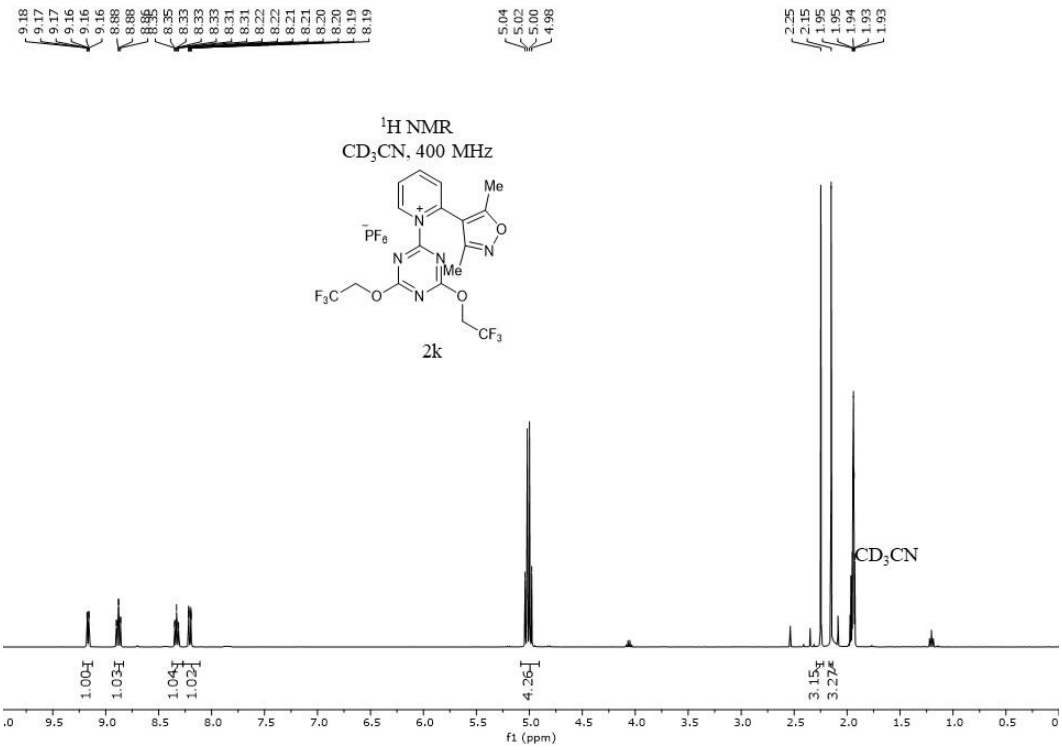
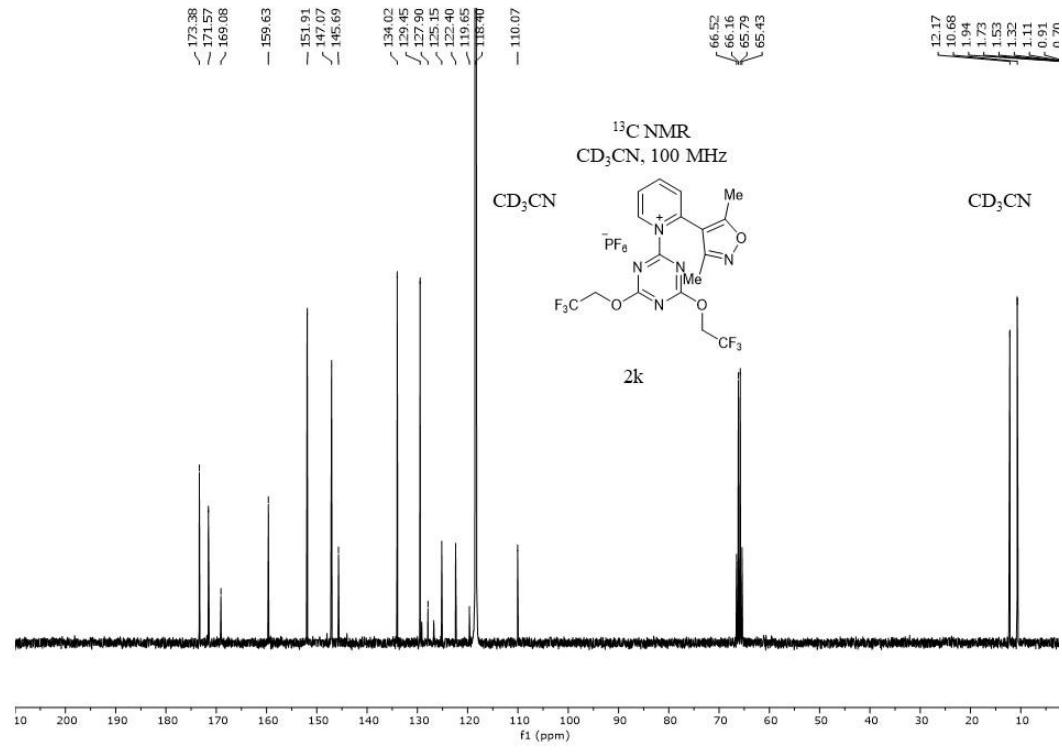
169.46
155.78
145.69
139.76
128.10
125.35
122.60
118.37
115.68
72.08
66.33
65.97
65.60
65.24
56.84
18.53
1.94
1.73
1.53
1.32
1.11
0.91
0.70
13C NMR
CD3CN, 100 MHz
Me
PF6
Me
F3C
CF3
2j
CD3CN
CD3CN
f1 (ppm)


-71.95
-73.83
-74.30
-74.32
-74.34
19F NMR
CD3CN, 376 MHz
Me
Me
F3C
CF3
2j
f1 (ppm)

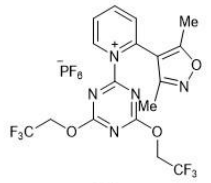

-131.55
-135.91
-140.27
-144.63
-149.00
-153.36
-157.72
31P NMR
CDCl3, 162 MHz
Me
Me
F3C
CF3
2j
f1 (ppm)


^{1}H NMR
CD_3CN, 400 MHz
2k
CD_3CN
f1 (ppm)

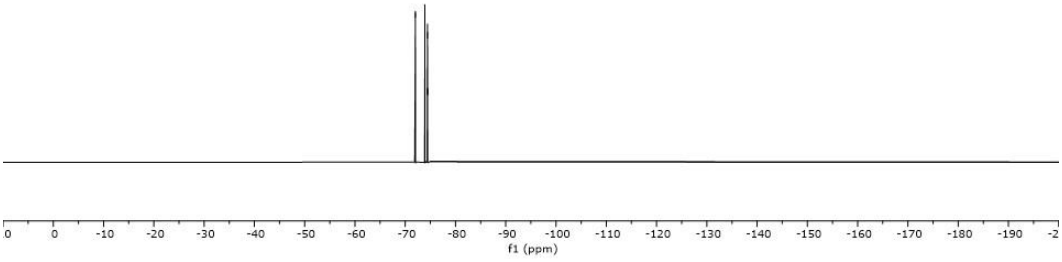

^{13}C NMR
CD_3CN, 100 MHz
CD_3CN
CD_3CN
2k
f1 (ppm)

-72.03
-73.91
-74.40
-74.42
-74.45

^{19}F NMR
CD_3CN, 376 MHz

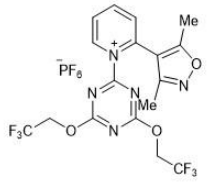


2k

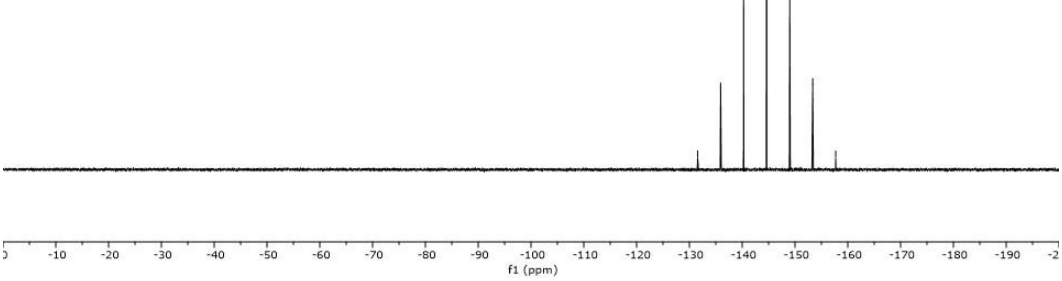


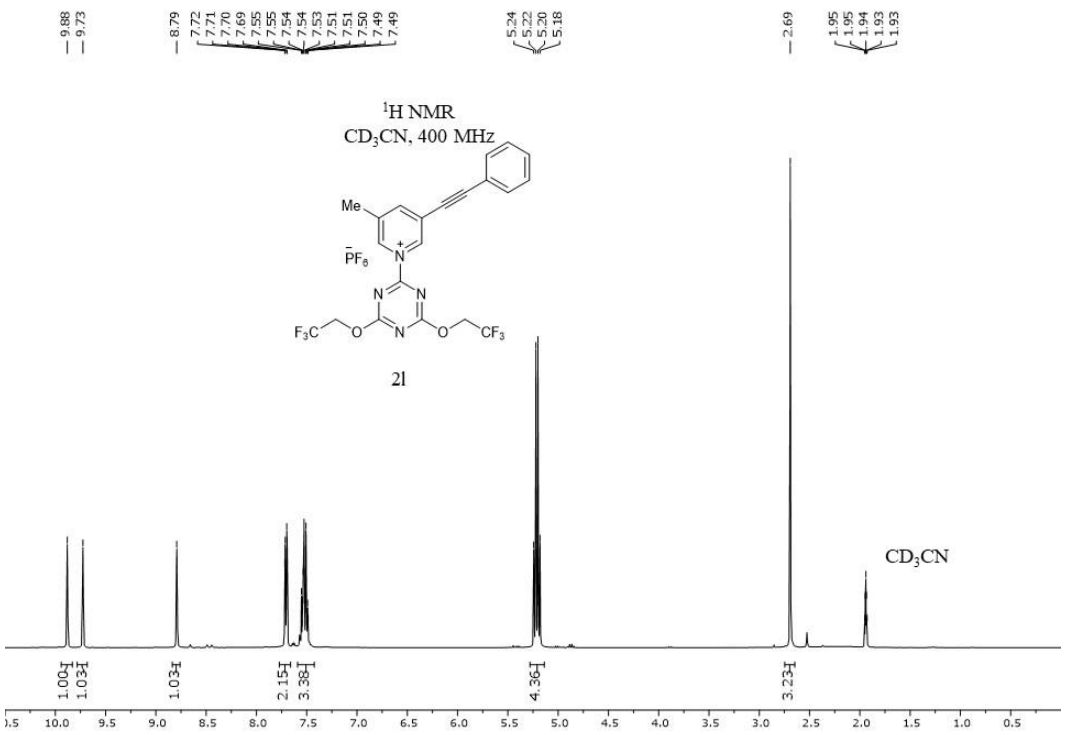
-131.56
-135.92
-140.28
-144.64
-149.00
-153.36
-157.72

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



2k

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7.72
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7.70
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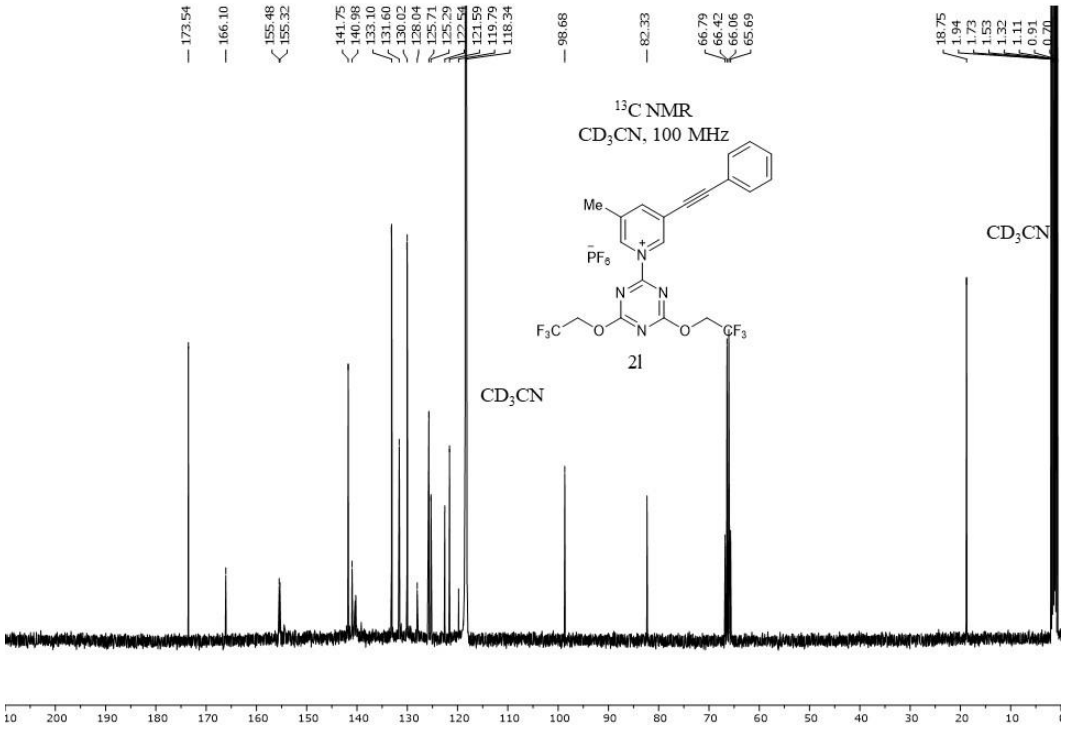
7.55
7.55
7.54
7.54
7.53
7.51
7.51
7.50
7.49
7.49
5.24
5.22
5.20
5.18
2.69
1.95
1.95
1.94
1.93
1.93
1H NMR
CD3CN, 400 MHz
Me
PF6
F3C
O
N
O
CF3
21
CD3CN
1.00
1.03
1.03
2.15
3.38
4.36
3.23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166.10
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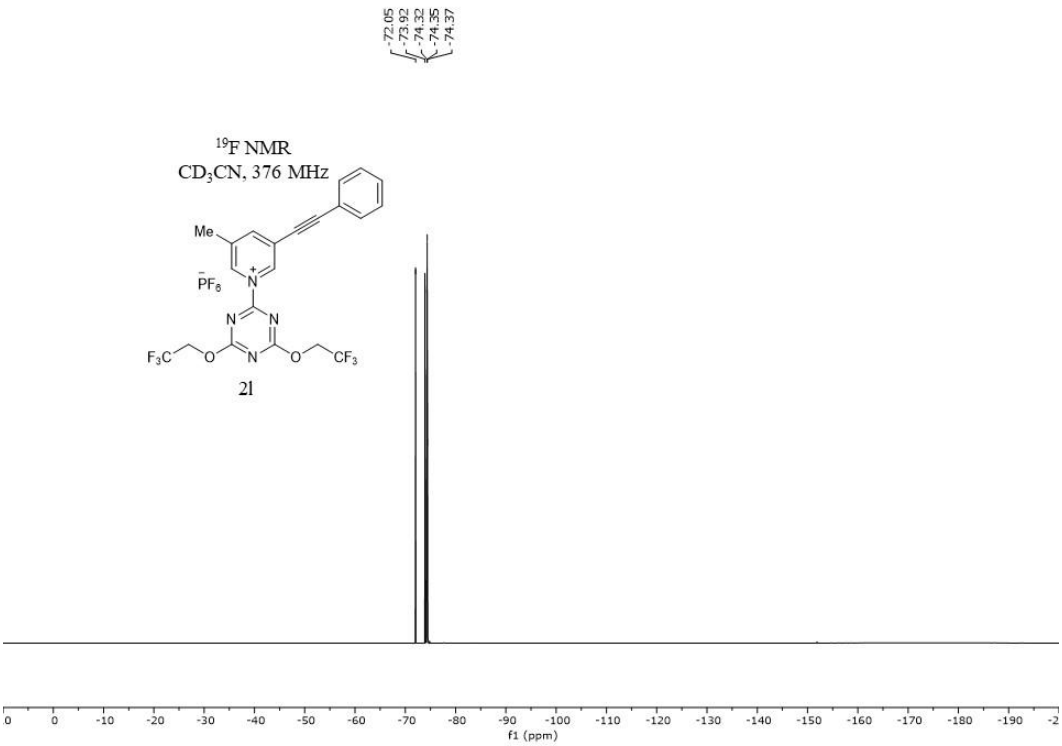
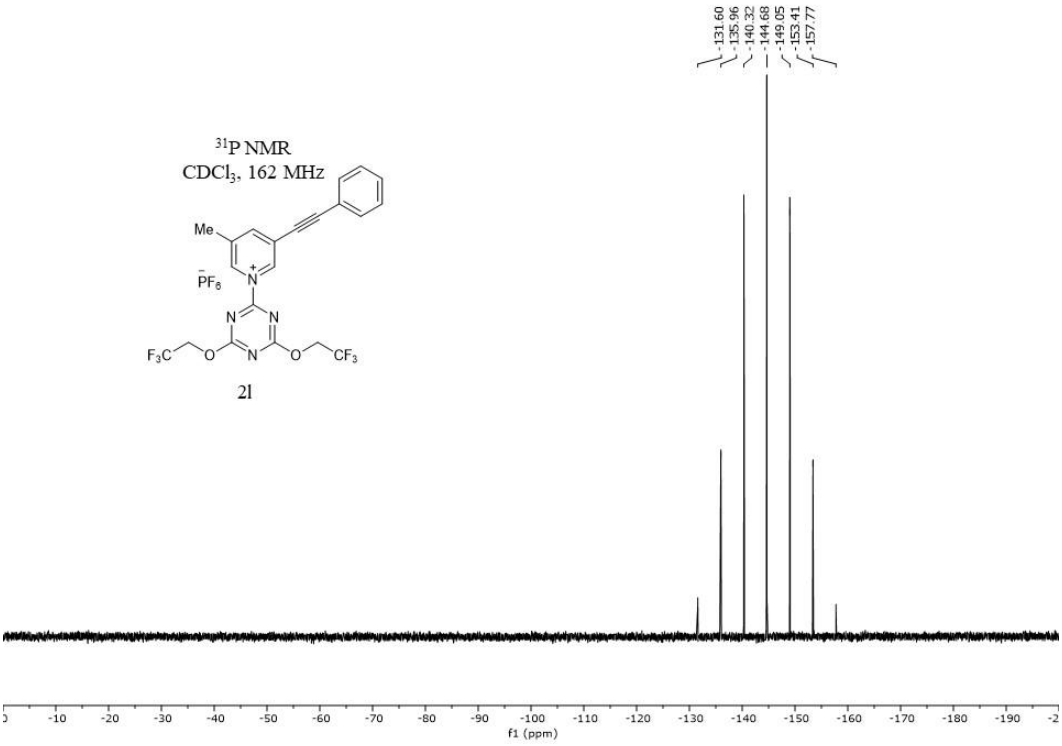
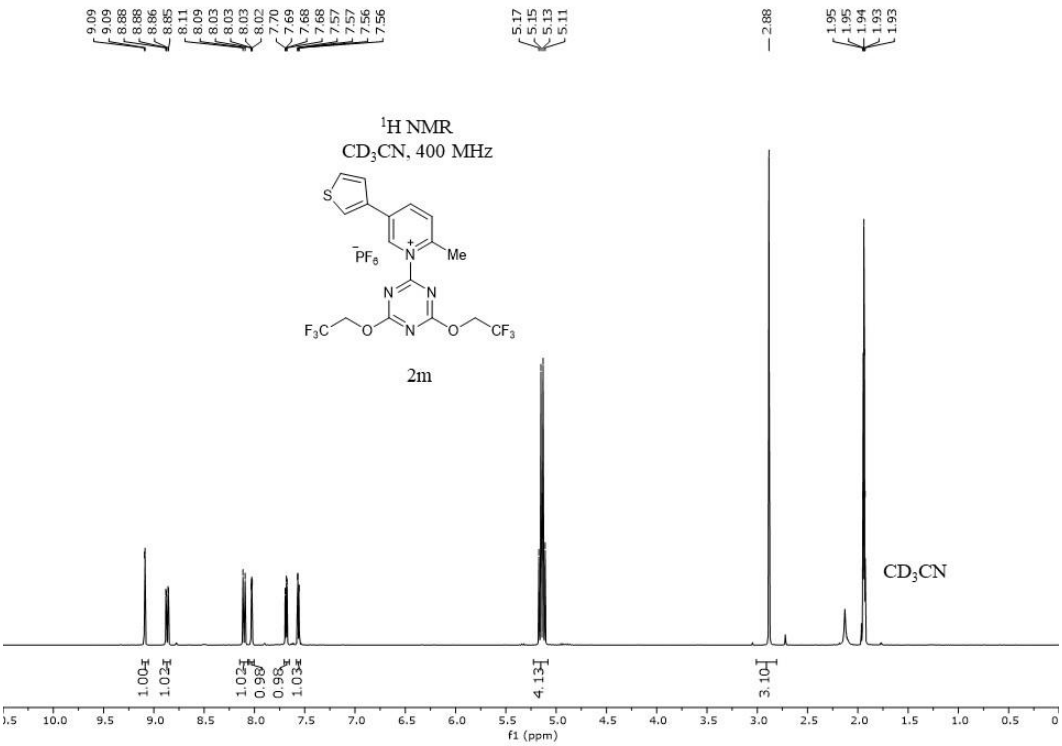
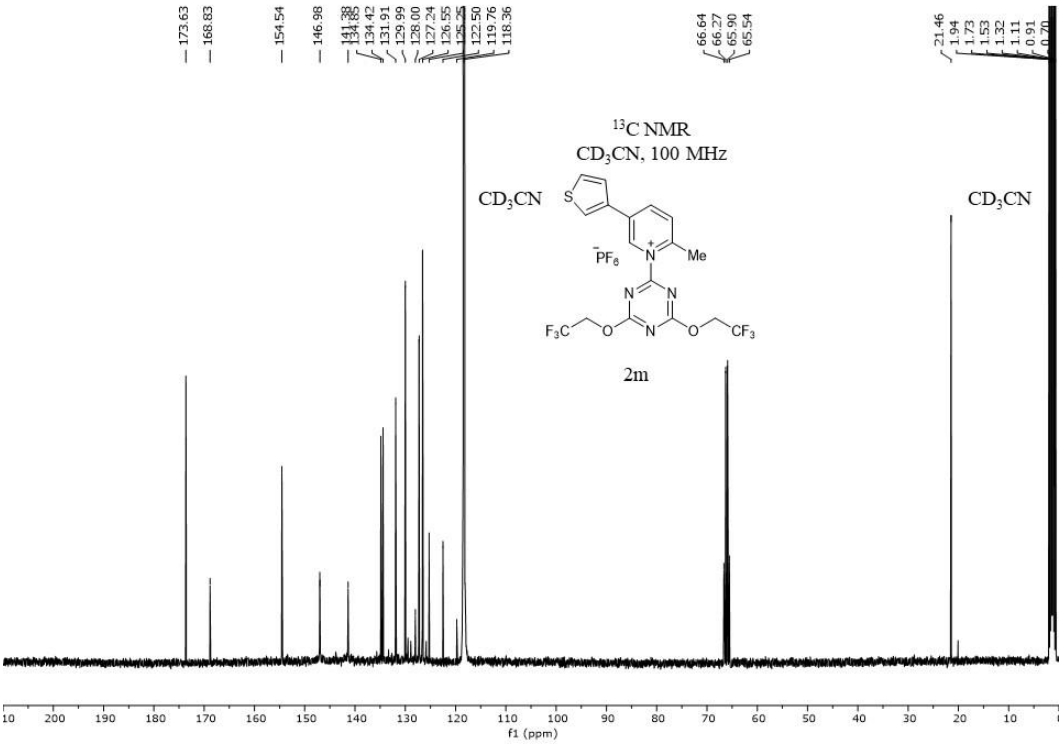
155.32
141.75
140.98
133.10
131.60
130.02
128.04
125.71
125.29
122.54
121.59
119.79
118.34
98.68
82.33
66.79
66.42
66.06
65.69
18.75
1.94
1.73
1.53
1.32
1.11
0.91
0.70
13C NMR
CD3CN, 100 MHz
Me
PF6
F3C
O
N
O
CF3
21
CD3CN
CD3CN


-72.05
-73.92
-74.32
-74.35
-74.37
19F NMR
CD3CN, 376 MHz
Me
PF6
F3C
O
N
CF3
21
f1 (ppm)

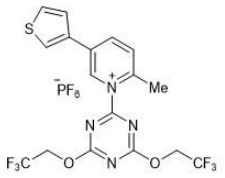

-131.60
-135.96
-140.32
-144.68
-149.05
-153.41
-157.77
31P NMR
CDCl3, 162 MHz
Me
PF6
F3C
O
N
CF3
21
f1 (ppm)


^{1}H NMR
CD_3CN, 400 MHz
2m
CD_3CN
f1 (ppm)

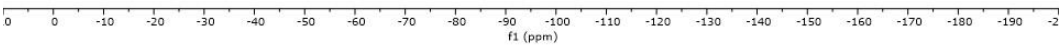

^{13}C NMR
CD_3CN, 100 MHz
CD_3CN
CD_3CN
2m
f1 (ppm)

-70.60
-72.03
-73.91
-74.33
-74.36
-74.38

^{19}F NMR
CD_3CN, 376 MHz

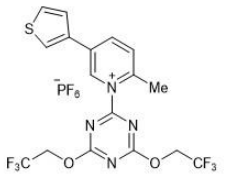


2m

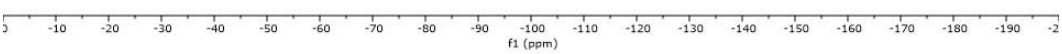


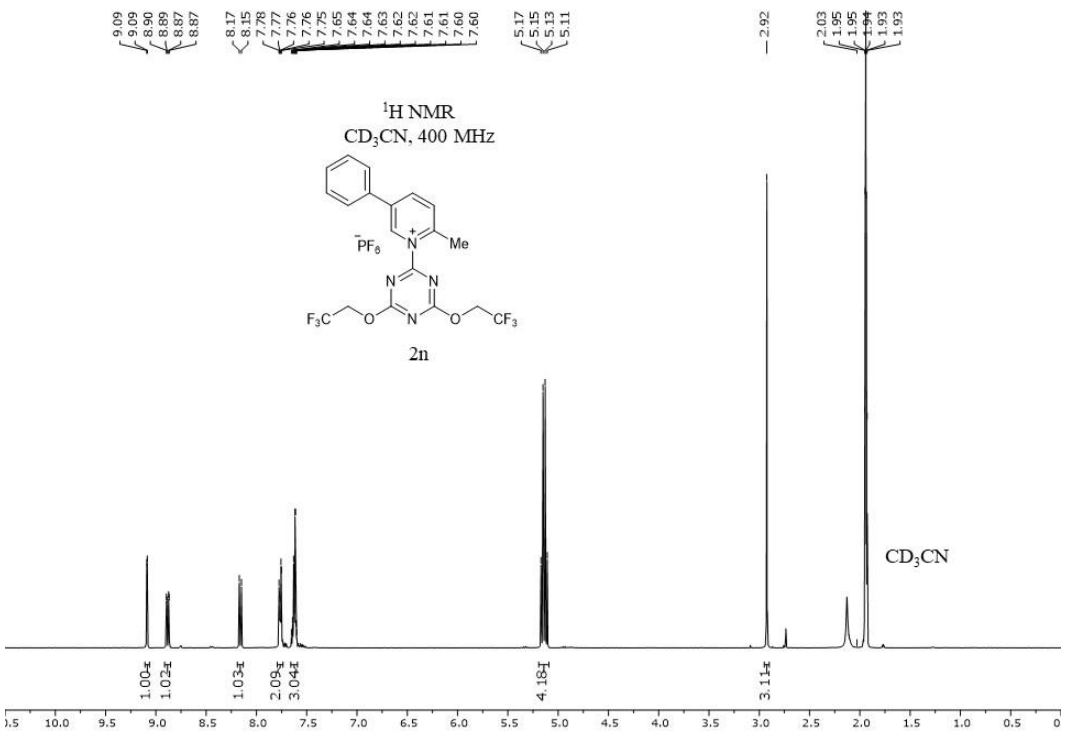
-131.56
-135.92
-140.28
-144.64
-149.00
-153.37
-157.73

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



2m

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8.87
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8.15
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7.76
7.76
7.75
7.65
7.64
7.64
7.63
7.62
7.62
7.61
7.61
7.60
7.60
5.17
5.15
5.13
5.11
2.92
2.03
1.95
1.95
1.94
1.93
1.93
1H NMR
CD3CN, 400 MHz
PF6
Me
F3C
O
N
O
CF3
2n
CD3CN
1.00
1.02
1.03
2.09
3.04
4.18
3.11
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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3.5
3.0
2.5
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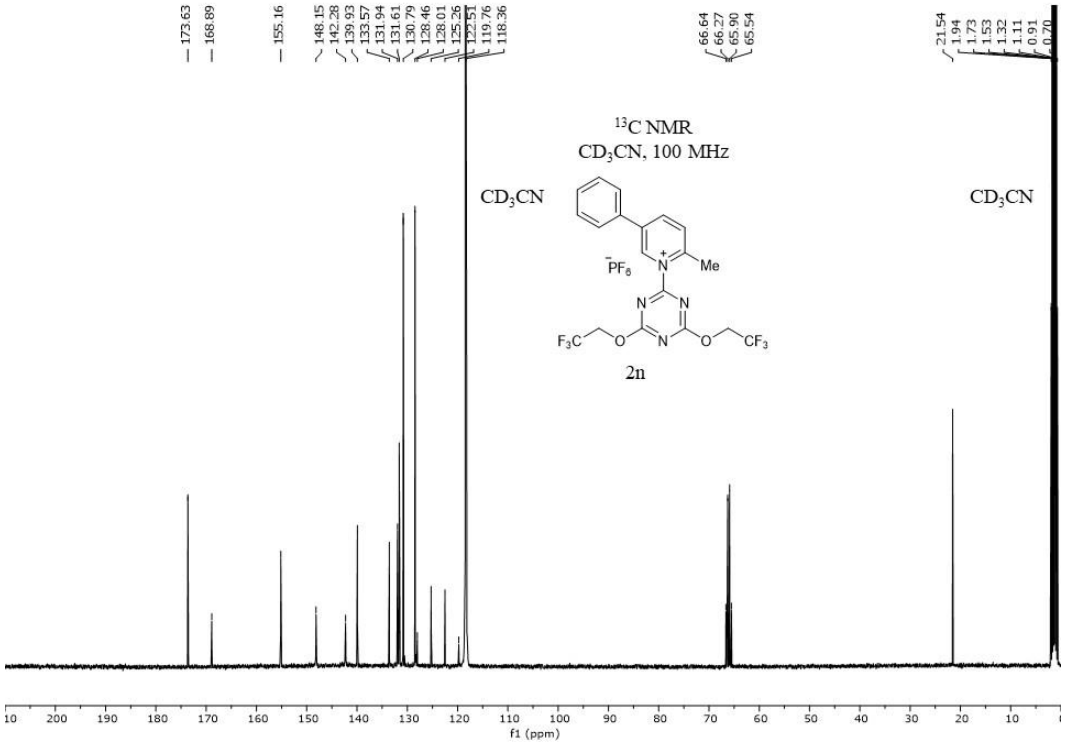
1.5
1.0
0.5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139.93
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131.94
131.61
130.79
128.46
128.01
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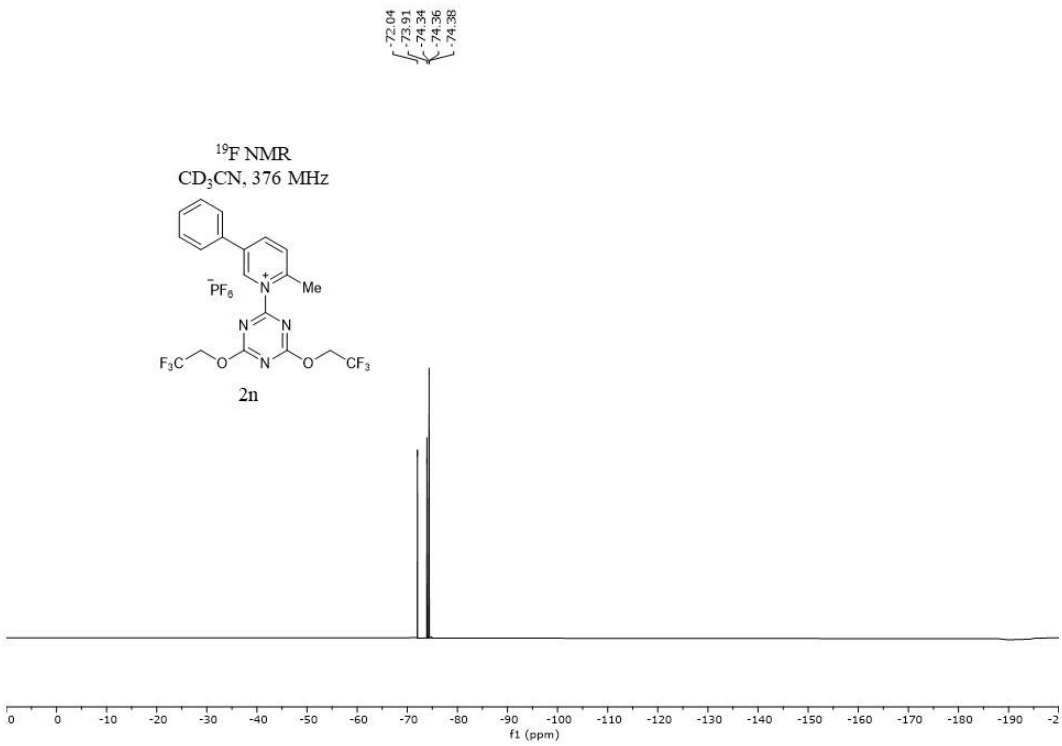
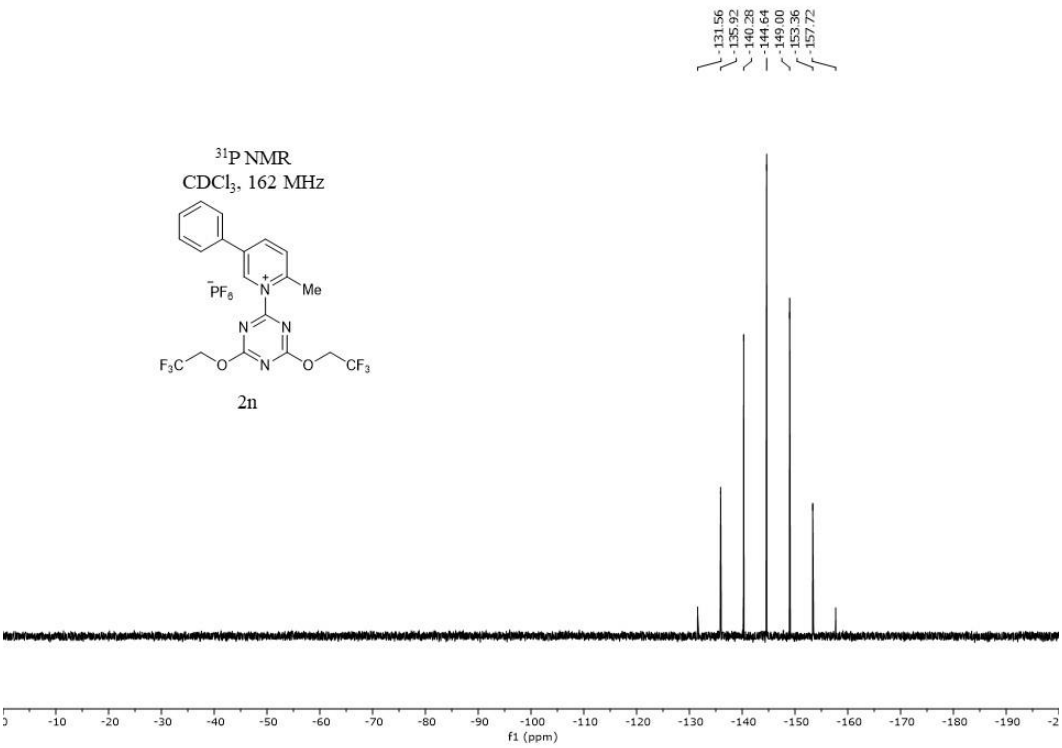
122.51
119.76
118.36
66.64
66.27
65.90
65.54
21.54
1.94
1.73
1.53
1.32
1.11
0.91
13C NMR
CD3CN, 100 MHz
CD3CN
CD3CN
PF6
Me
F3C
O
N
O
CF3
2n
f1 (ppm)



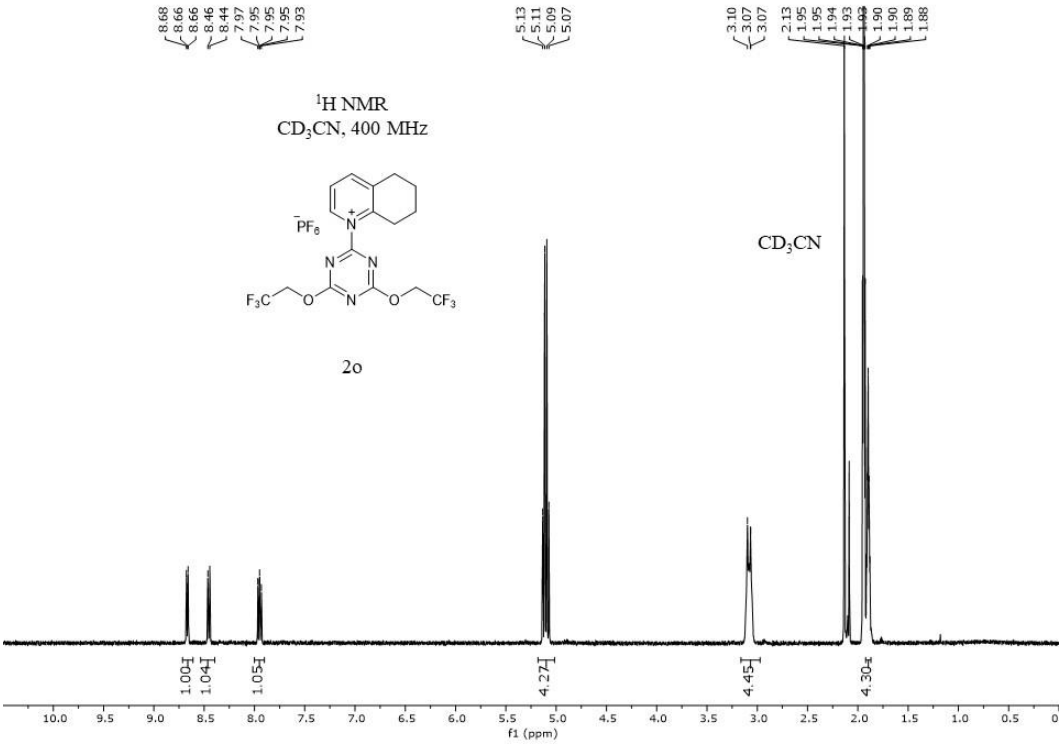
^{19}F NMR
CD_3CN, 376 MHz

2n



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

2n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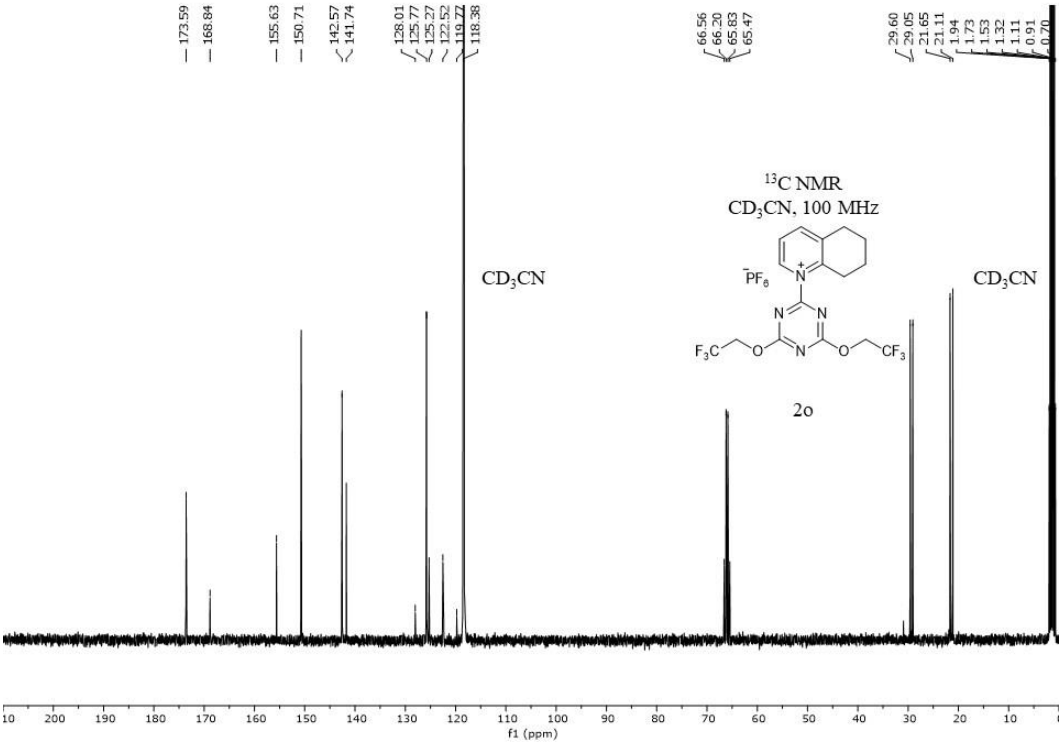
8.44
7.97
7.95
7.95
7.95
7.93
5.13
5.11
5.09
5.07
3.10
3.07
3.07
2.13
1.95
1.95
1.94
1.93
1.90
1.90
1.89
1.88
1H NMR
CD3CN, 400 MHz
CD3CN
2o
1.00
1.04
1.05
4.27
4.45
4.30
f1 (ppm)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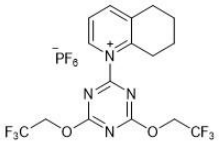
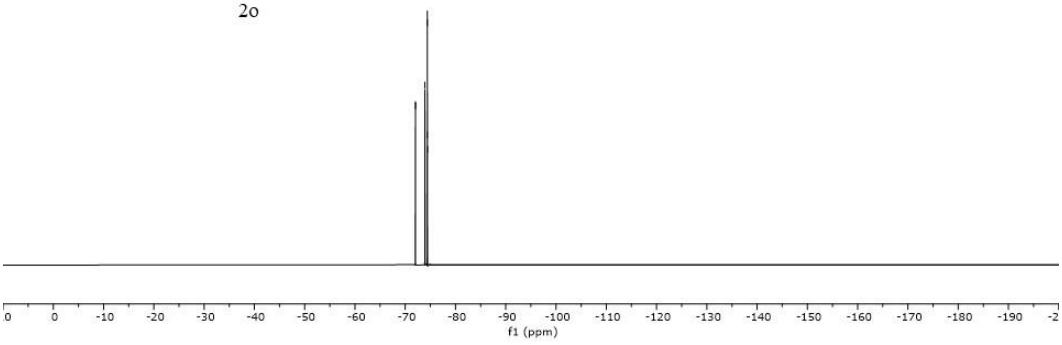
150.71
142.57
141.74
128.01
125.77
125.27
122.52
119.22
118.38
66.56
66.20
65.83
65.47
29.60
29.05
21.65
21.11
1.94
1.73
1.53
1.32
1.11
0.91
13C NMR
CD3CN, 100 MHz
CD3CN
CD3CN
2o
f1 (ppm)

-72.04
-73.91
-74.37
-74.40
-74.42

^{19}F NMR
CD_3CN, 376 MHz

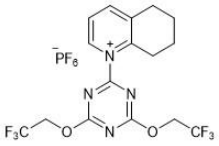


2o

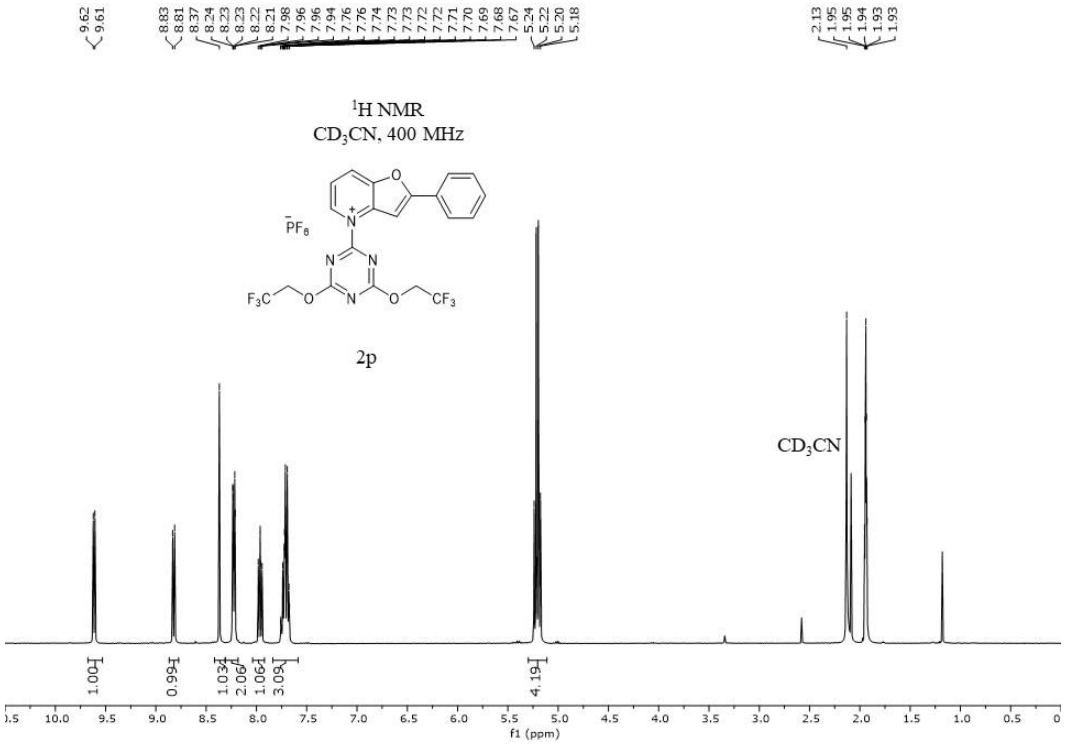


-131.56
-135.92
-140.28
-144.65
-149.00
-153.37
-157.73

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



2o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8.24
8.23
8.23
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8.21
7.98
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7.94
7.76
7.76
7.74
7.73
7.73
7.72
7.72
7.71
7.70
7.69
7.68
7.67
5.24
5.22
5.20
5.18
2.13
1.95
1.95
1.94
1.93
1.93
1H NMR
CD3CN, 400 MHz
PF6
F3C
O
N
N
O
CF3
2p
CD3CN
1.00
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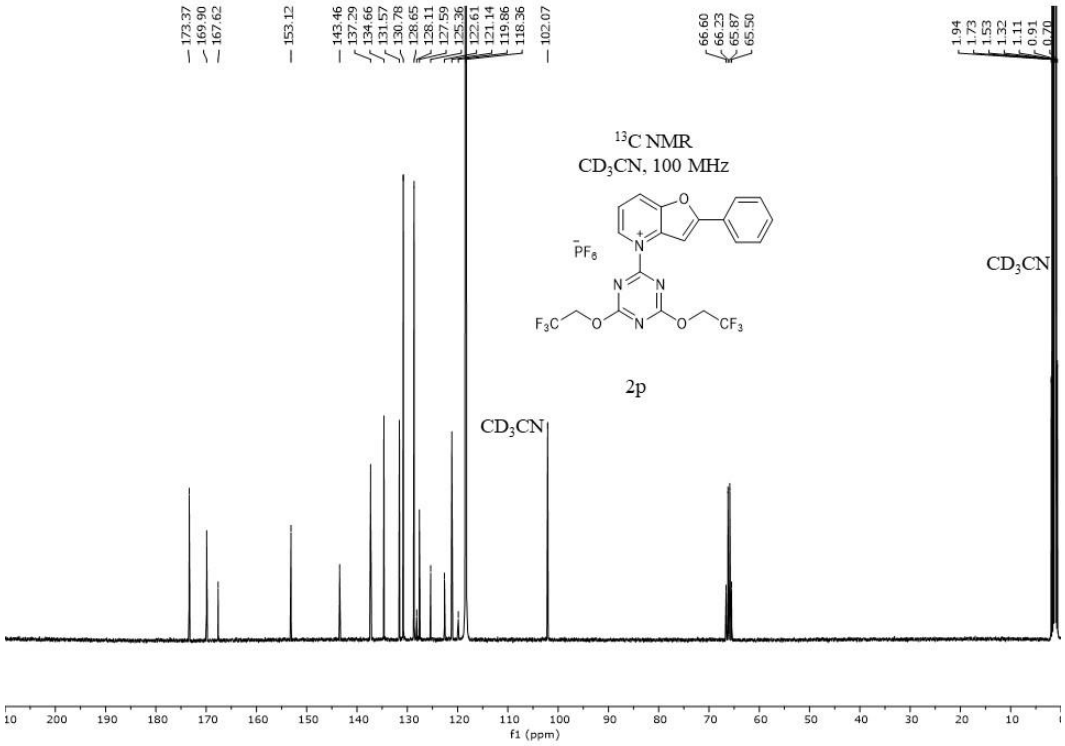
1.03
2.06
1.06
3.09
4.19
f1 (ppm)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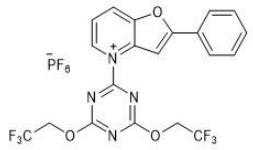
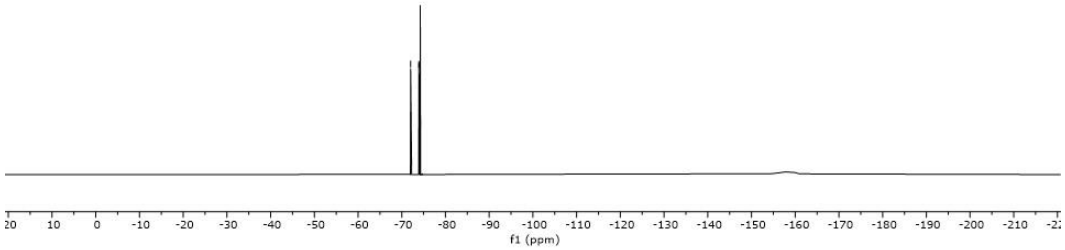
169.90
167.62
153.12
143.46
137.29
134.66
131.57
130.78
128.65
128.11
127.59
125.36
122.61
121.14
119.86
118.36
102.07
66.60
66.23
65.87
65.50
1.94
1.73
1.53
1.32
1.11
0.91
0.70
13C NMR
CD3CN, 100 MHz
PF6
F3C
O
N
N
O
CF3
2p
CD3CN
CD3CN
f1 (ppm)

-72.03
-73.91
-74.22
-74.24
-74.26

^{19}F NMR
CD_3CN, 376 MHz

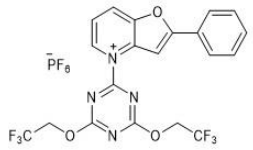


2p

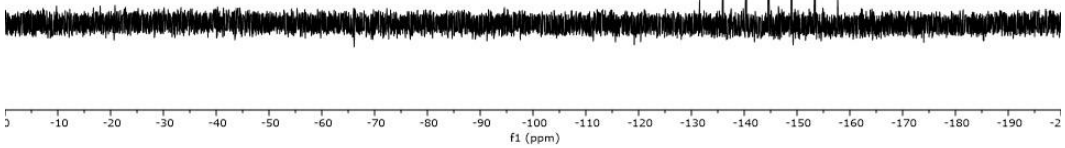


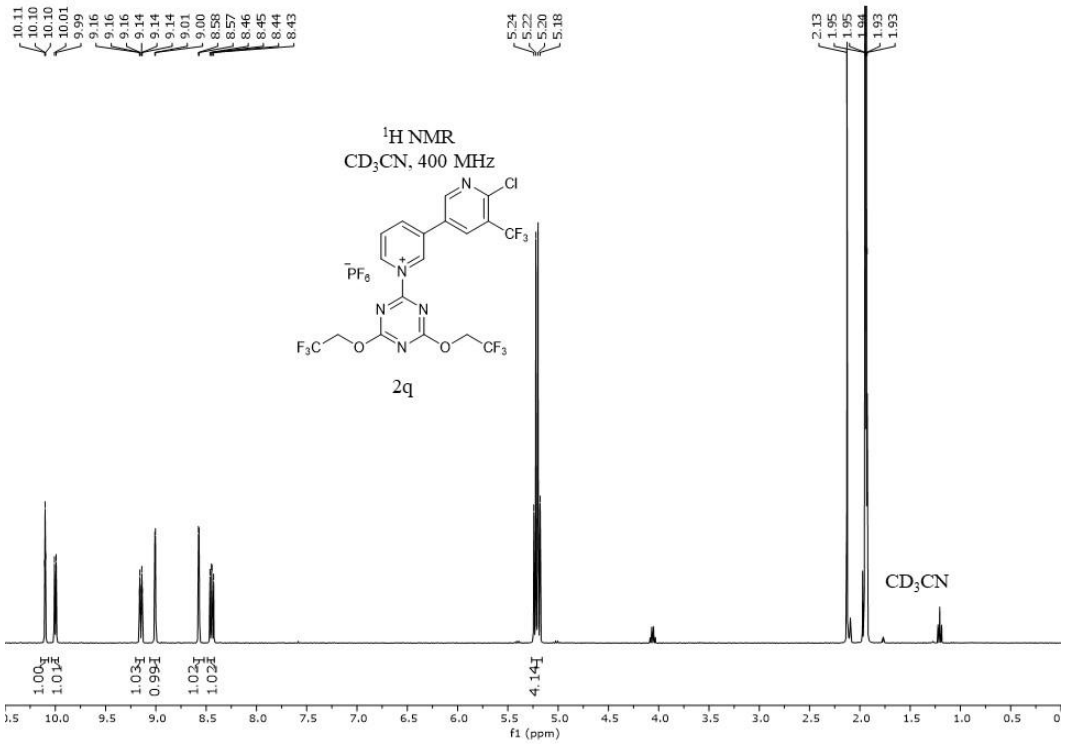
-131.56
-135.92
-140.28
-144.64
-149.00
-153.36
-157.72

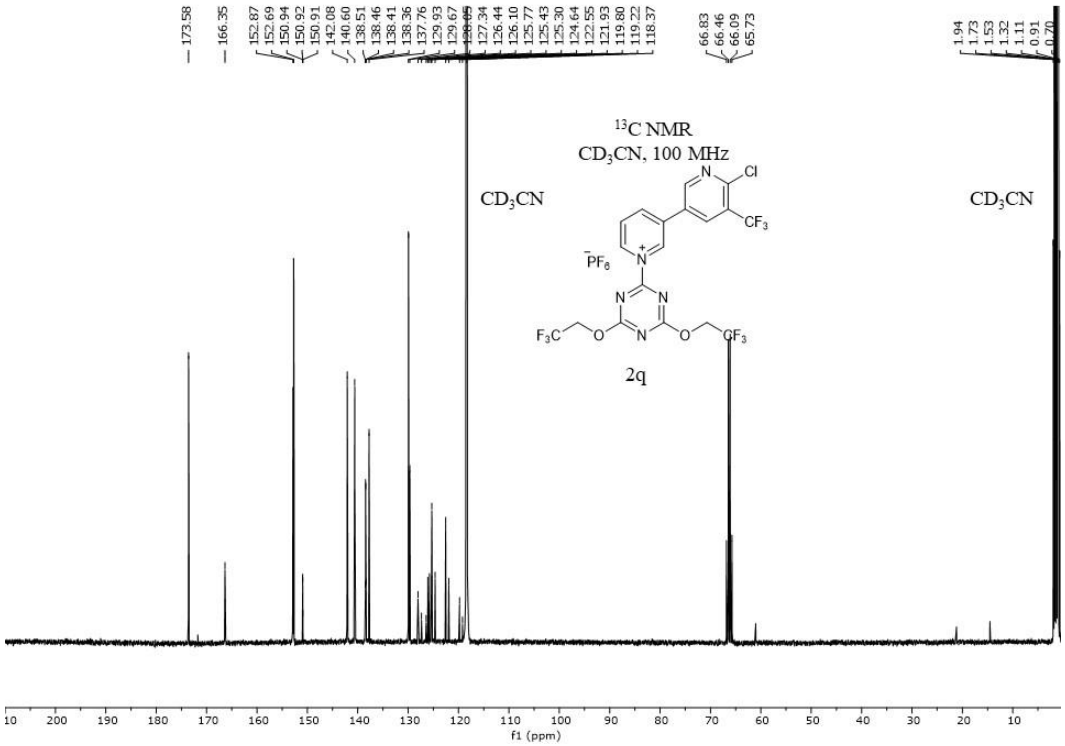
^{31}P NMR
$CDCl_3$, 162 MHz

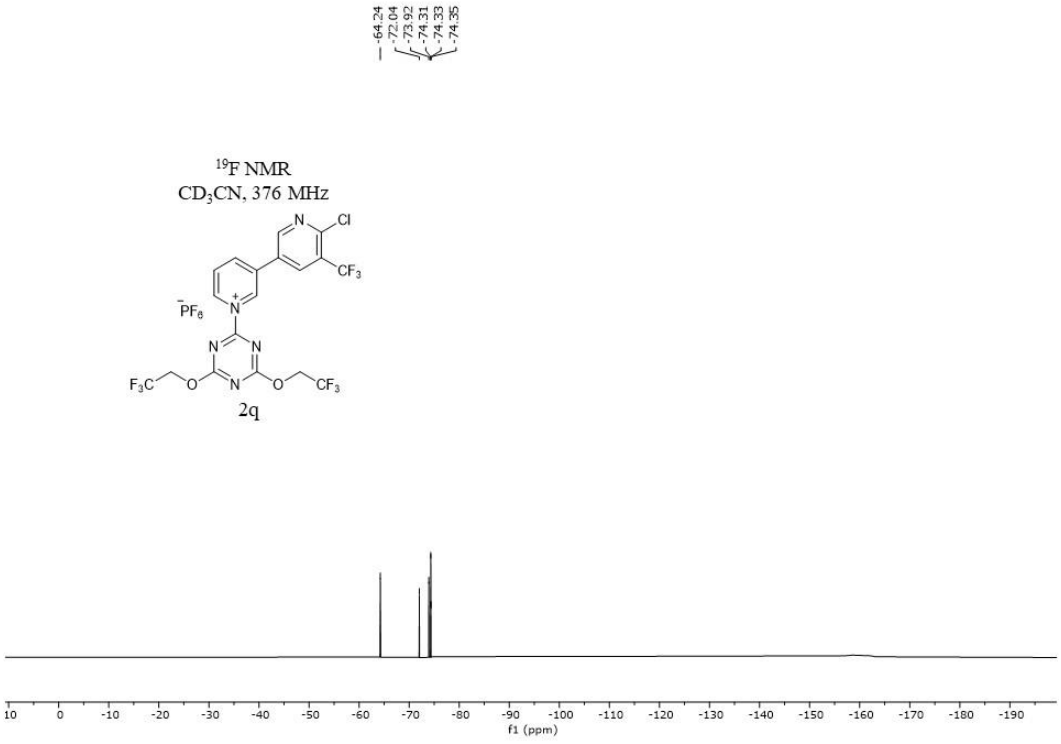


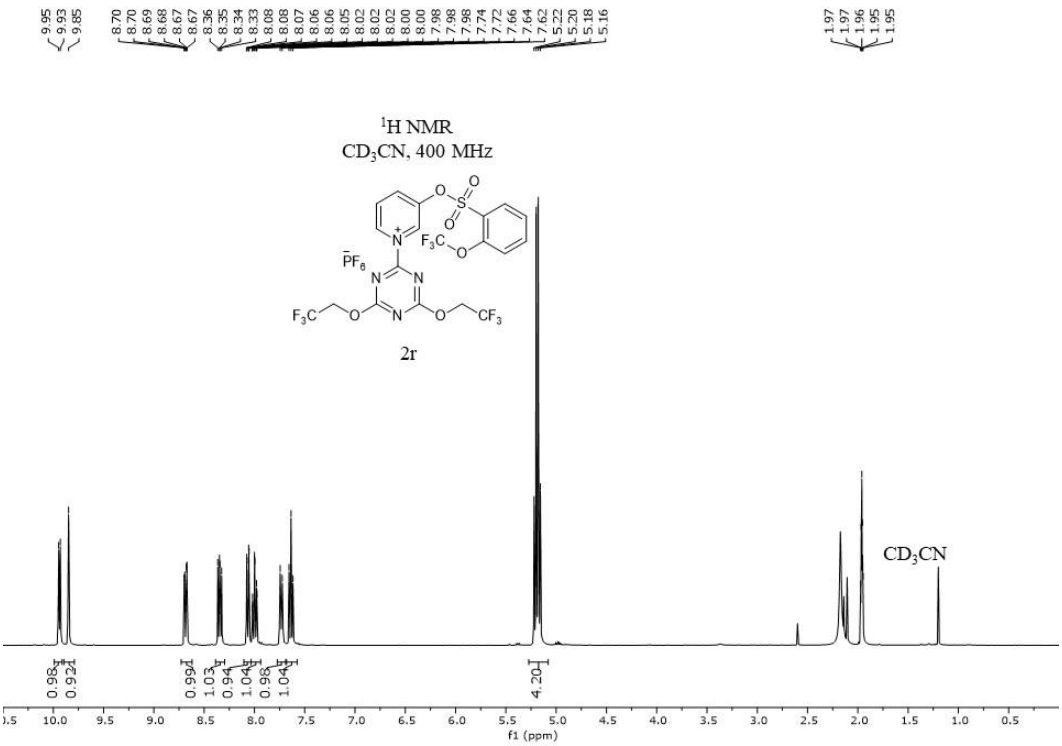
2p




^{1}H NMR
CD_3CN, 400 MHz
2q
CD_3CN
f1 (ppm)


^{13}C NMR
CD_3CN, 100 MHz
2q
CD_3CN
CD_3CN
f1 (ppm)


-64.24
-72.04
-73.92
-74.31
-74.33
-74.35
19F NMR
CD3CN, 376 MHz
2q
f1 (ppm)
-131.57
-135.93
-140.29
-144.65
-149.01
-153.37
-157.74
31P NMR
CDCl3, 162 MHz
2q
f1 (ppm)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9.93
9.85
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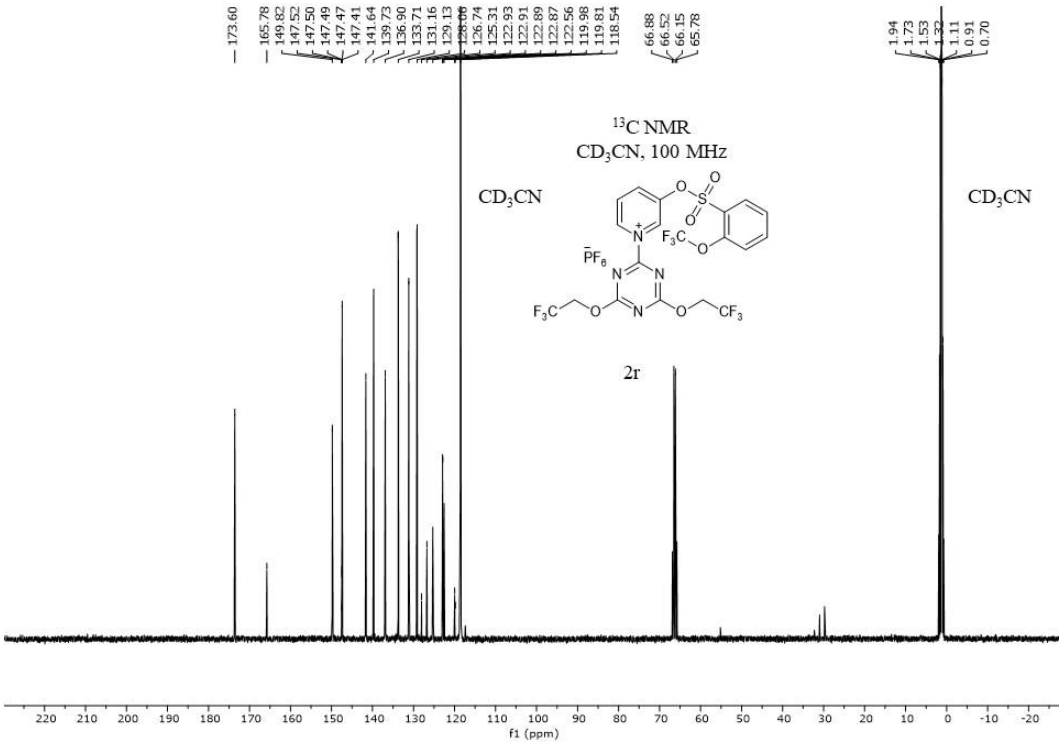
8.69
8.68
8.67
8.67
8.36
8.35
8.34
8.33
8.08
8.08
8.07
8.06
8.06
8.05
8.02
8.02
8.00
8.00
7.98
7.98
7.98
7.74
7.72
7.66
7.64
7.62
5.22
5.20
5.18
5.16
1.97
1.97
1.96
1.95
1.95
1H NMR
CD3CN, 400 MHz
2r
CD3CN
0.98
0.92
0.99
1.03
0.94
1.04
0.98
1.04
4.20
f1 (ppm)


173.60
165.78
149.82
147.52
147.50
147.49
147.47
147.41
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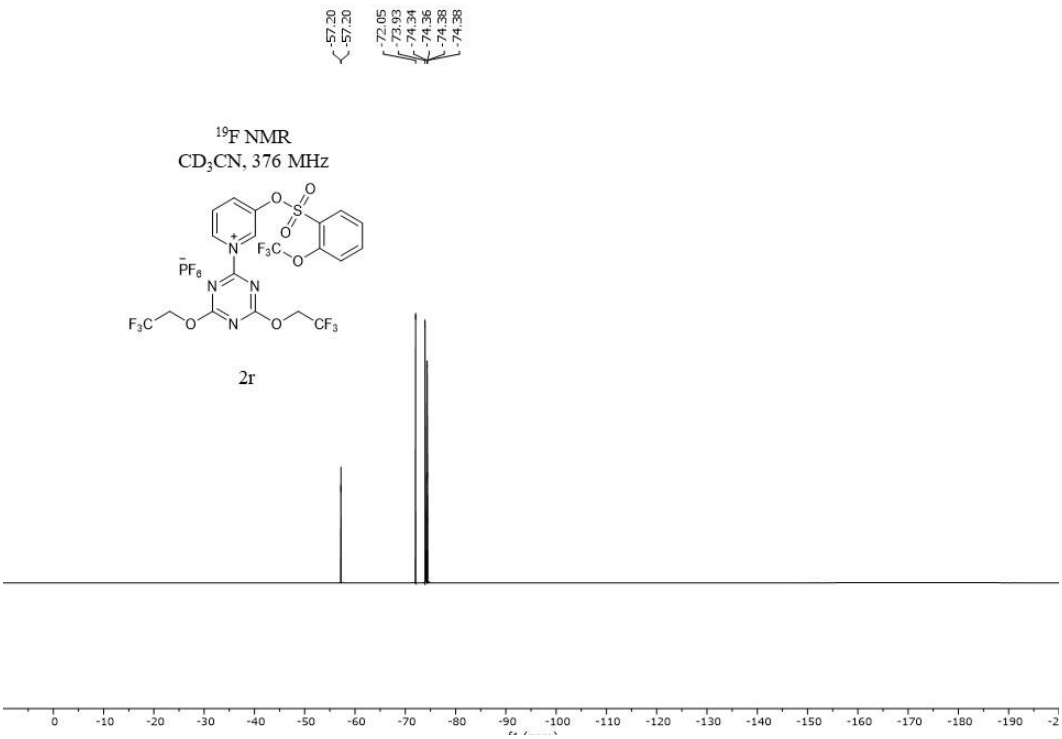
139.73
136.90
133.71
131.16
129.13
126.74
125.31
122.93
122.91
122.89
122.87
122.56
119.98
119.81
118.54
66.88
66.52
66.15
65.78
1.94
1.73
1.53
1.32
1.11
0.91
0.70
13C NMR
CD3CN, 100 MHz
CD3CN
CD3CN
2r
f1 (ppm)


-57.20
-57.20
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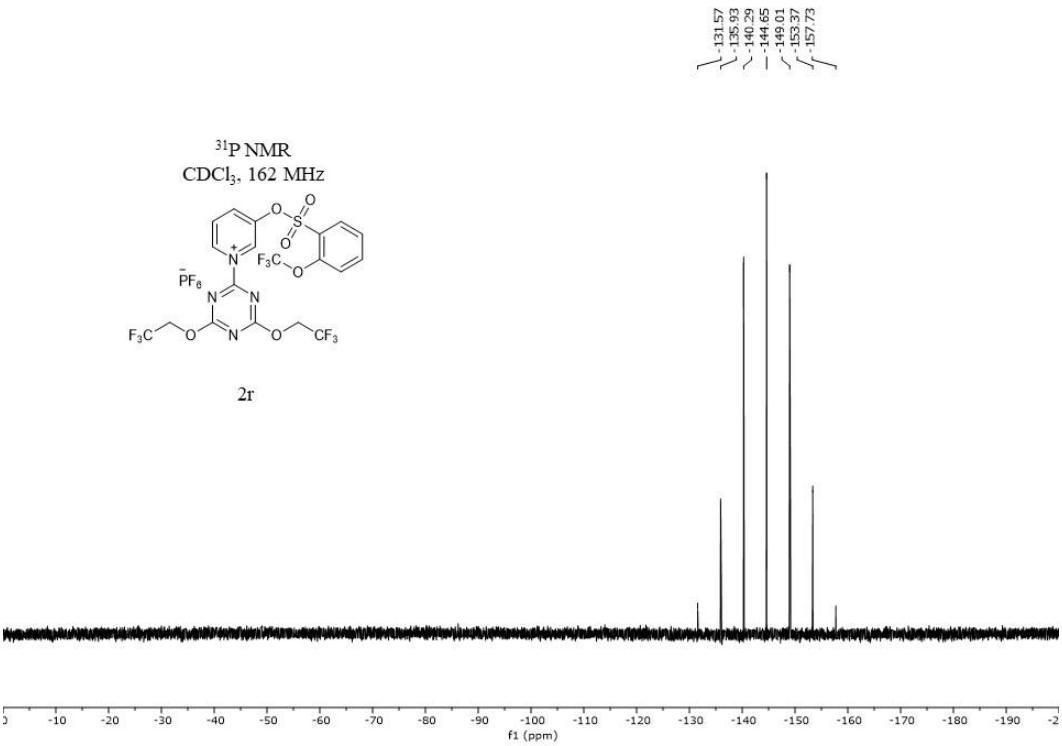
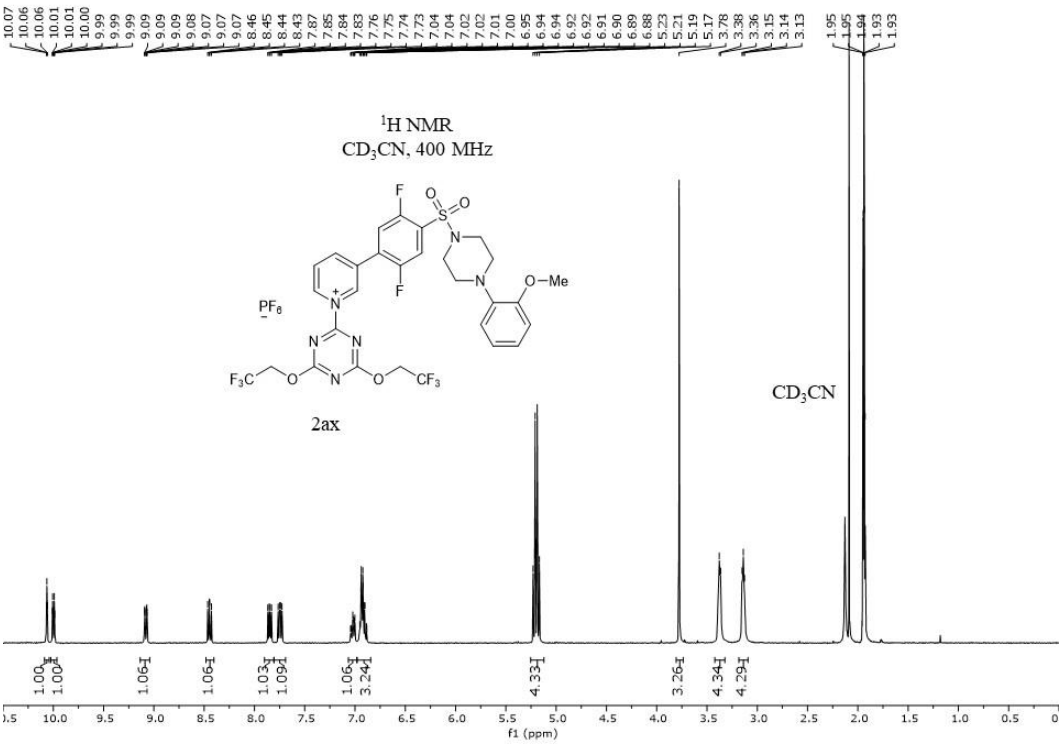
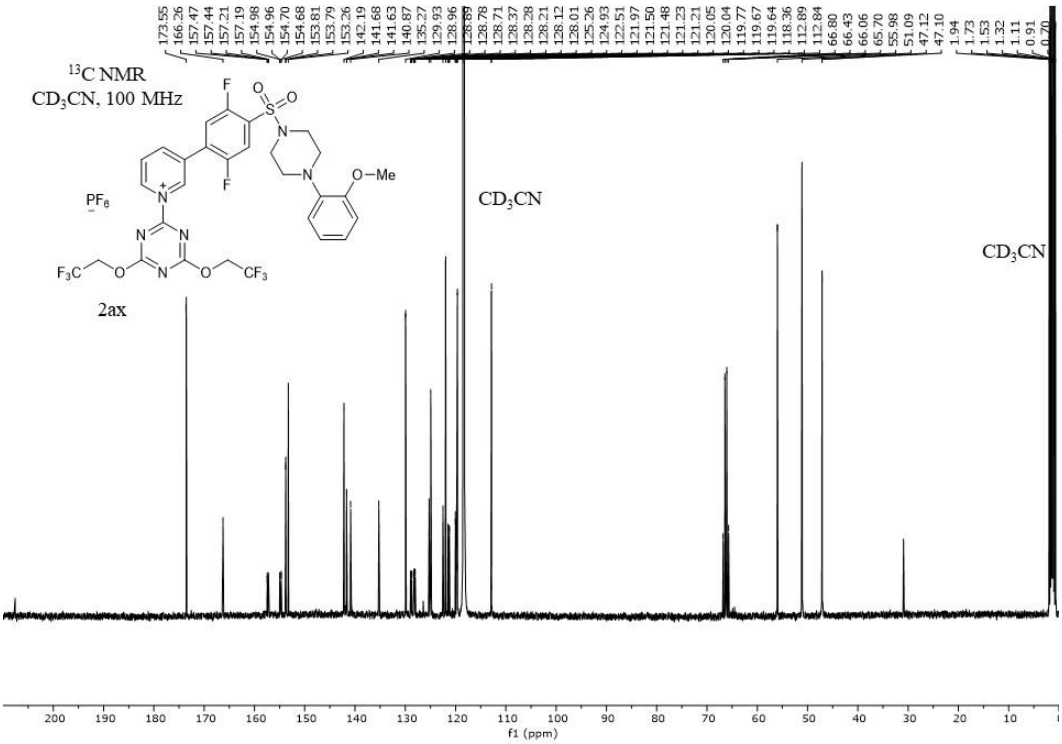
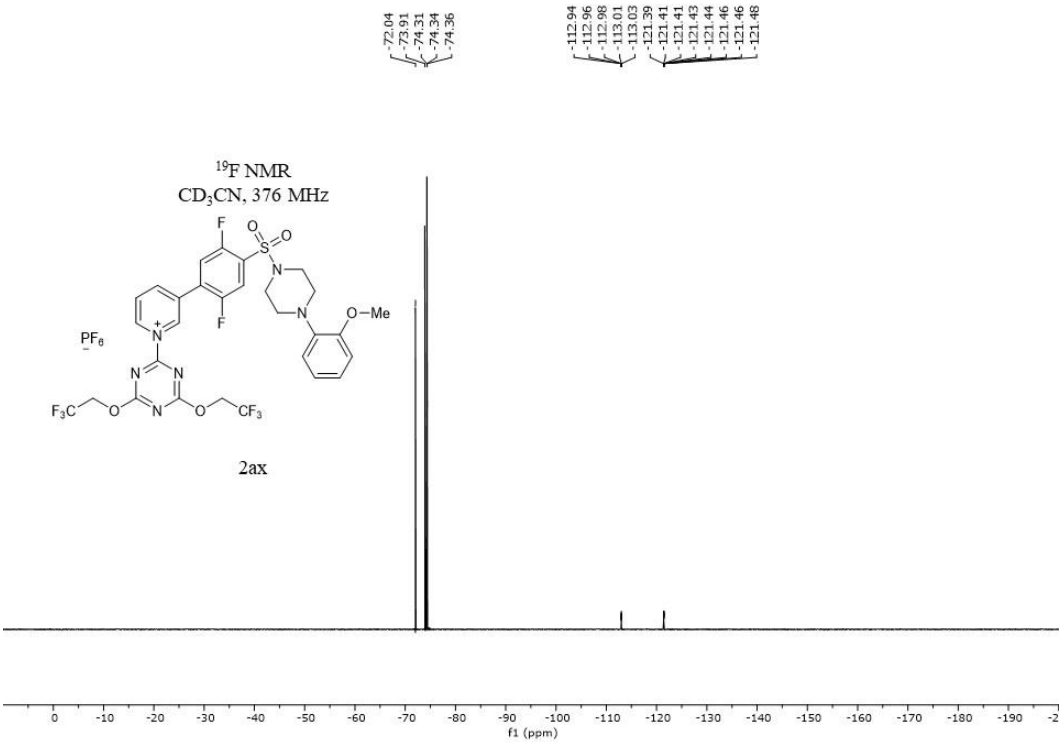
-73.93
-74.34
-74.36
-74.38
-74.38
19F NMR
CD3CN, 376 MHz
2r


-131.57
-135.93
-140.29
-144.65
-149.01
-153.37
-157.73
31P NMR
CDCl3, 162 MHz
2r
f1 (ppm)


^{1}H NMR
CD_3CN, 400 MHz
2ax
CD_3CN
f1 (ppm)


^{13}C NMR
CD_3CN, 100 MHz
2ax
CD_3CN
CD_3CN
f1 (ppm)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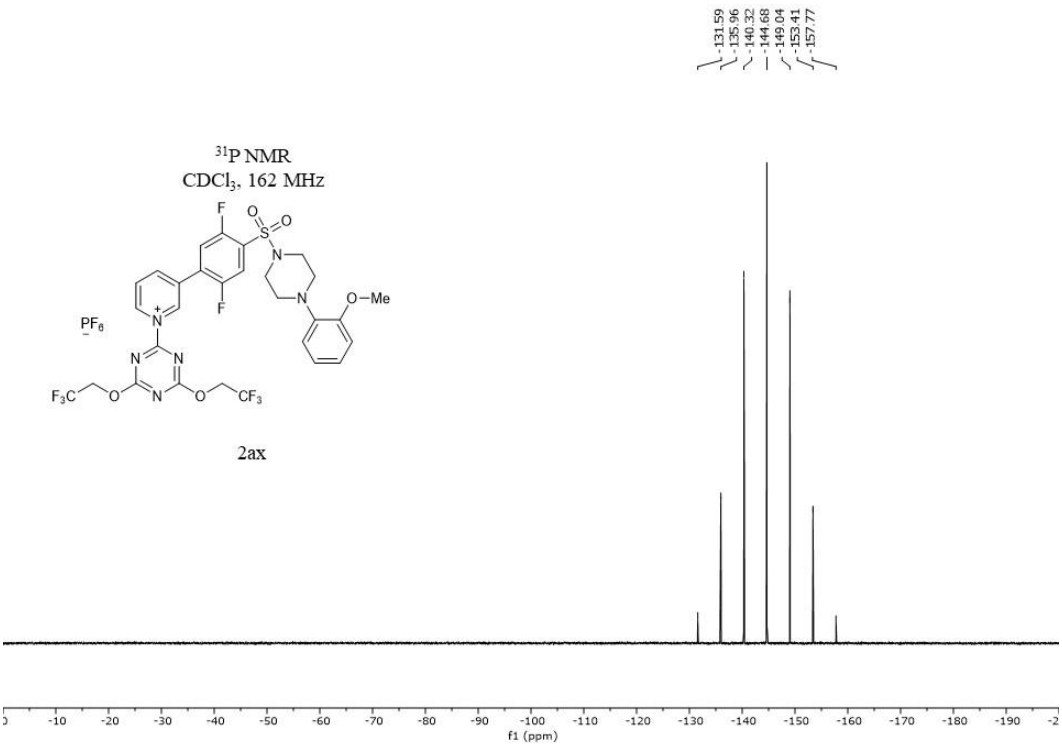
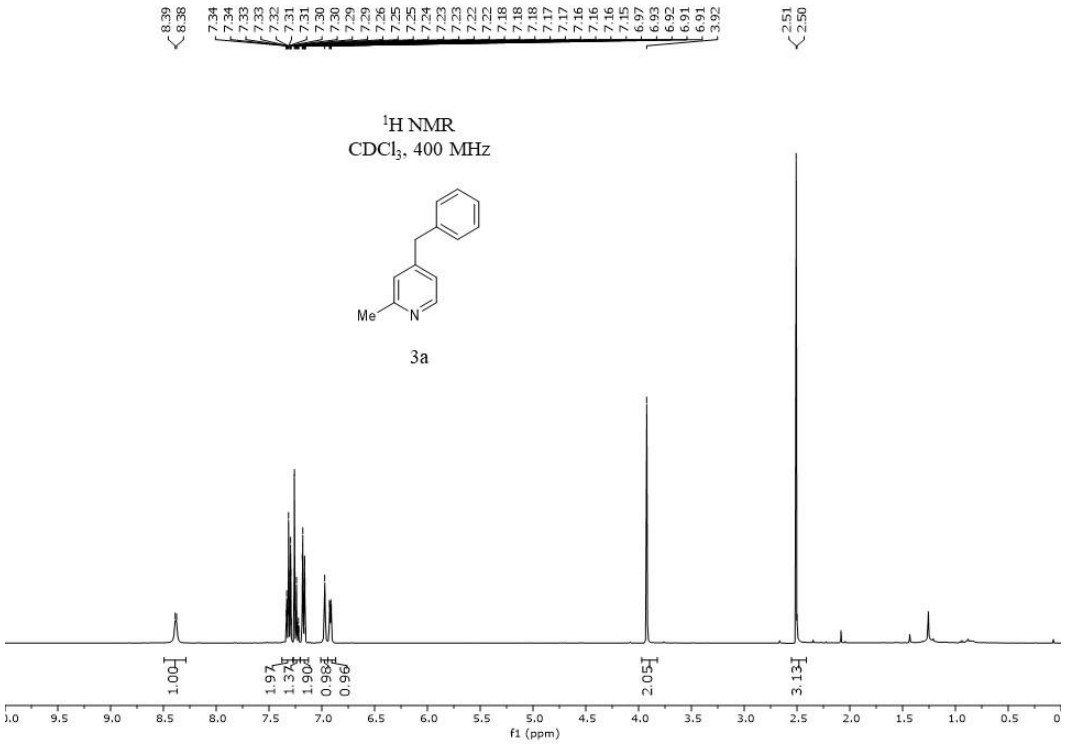
-73.91
-74.31
-74.34
-74.36
-112.94
-112.96
-112.98
-113.01
-113.03
-121.39
-121.41
-121.41
-121.43
-121.44
-121.46
-121.46
-121.48
19F NMR
CD3CN, 376 MHz
F
O
S
O
N
N
O–Me
F
PF6
N
N
N
F3C
O
O
CF3
2ax
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


-131.59
-135.96
-140.32
-144.68
-149.04
-153.41
-157.77
31P NMR
CDCl3, 162 MHz
F
O
S
O
N
N
O–Me
F
PF6
N
N
N
F3C
O
O
CF3
2ax
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)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7.31
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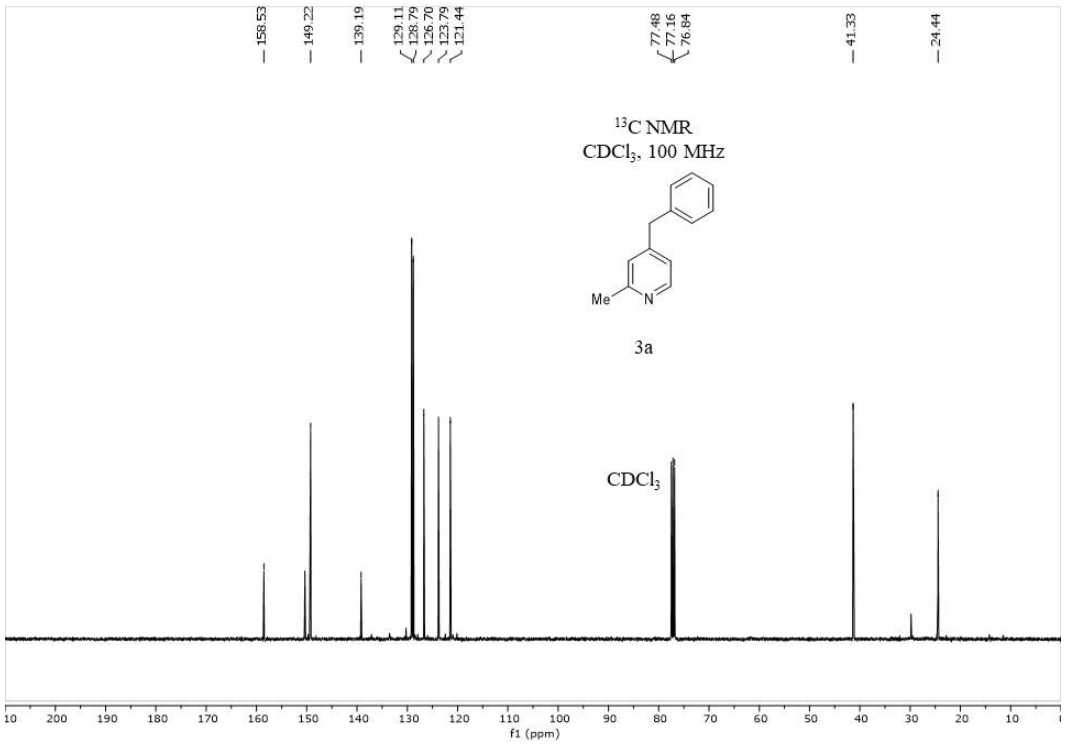
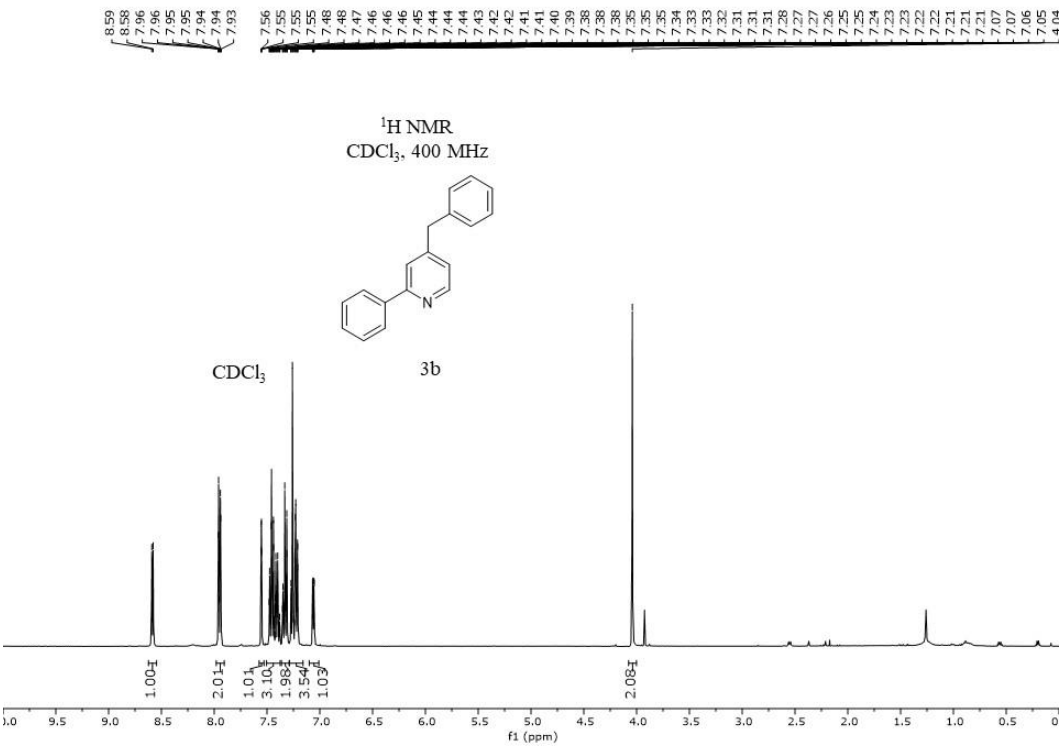
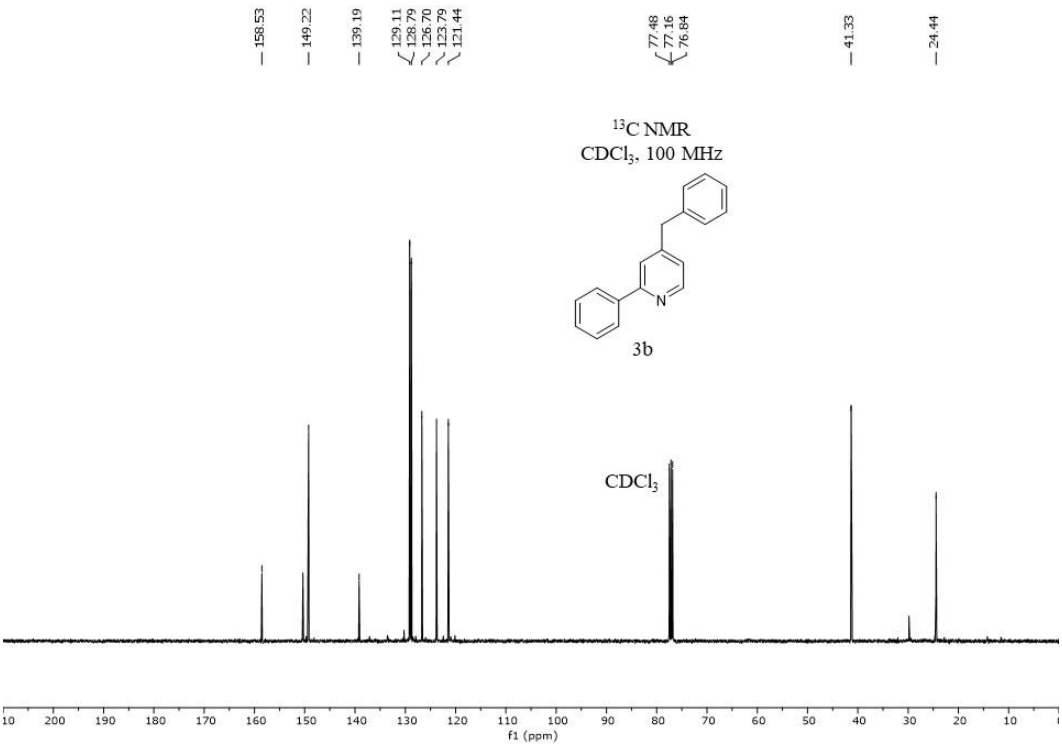
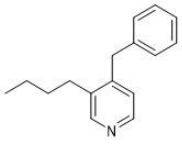
7.30
7.29
7.29
7.26
7.25
7.25
7.24
7.23
7.23
7.22
7.22
7.18
7.18
7.17
7.17
7.16
7.16
7.15
6.97
6.93
6.92
6.91
6.91
3.92
2.51
2.50
1H NMR
CDCl3, 400 MHz
Me
N
3a
1.00
1.97
1.37
1.90
0.98
0.96
2.05
3.13
f1 (ppm)


158.53
149.22
139.19
129.11
128.79
126.70
123.79
121.44
77.48
77.16
76.84
41.33
24.44
13C NMR
CDCl3, 100 MHz
Me
N
3a
CDCl3
f1 (ppm)


8.59 8.58 7.96 7.96 7.95 7.95 7.94 7.94 7.93
7.56 7.55 7.55 7.55 7.48 7.48 7.47 7.46 7.46 7.46 7.45 7.44 7.44 7.44 7.43 7.42 7.42 7.41 7.41 7.40 7.39 7.38 7.38 7.38 7.35 7.35 7.35 7.34 7.33 7.33 7.32 7.31 7.31 7.28 7.27 7.27 7.26 7.25 7.25 7.24 7.23 7.23 7.22 7.22 7.21 7.21 7.21 7.07 7.06 7.05
1H NMR
CDCl3, 400 MHz
N
3b
CDCl3
1.00 2.01 1.01 3.10 1.98 3.54 1.03 2.08
f1 (ppm)

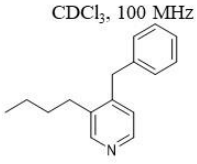

158.53 149.22 139.19 129.11 128.79 126.70 123.79 121.44 77.48 77.16 76.84 41.33 24.44
13C NMR
CDCl3, 100 MHz
N
3b
CDCl3
f1 (ppm)

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

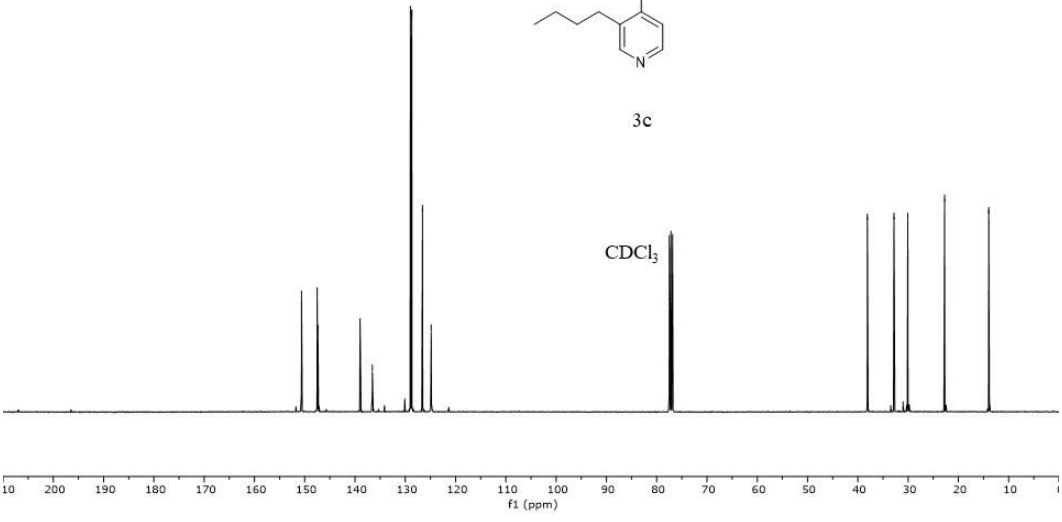


3c

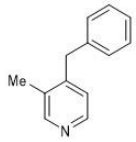
^{13}C NMR
$CDCl_3$, 100 MHz



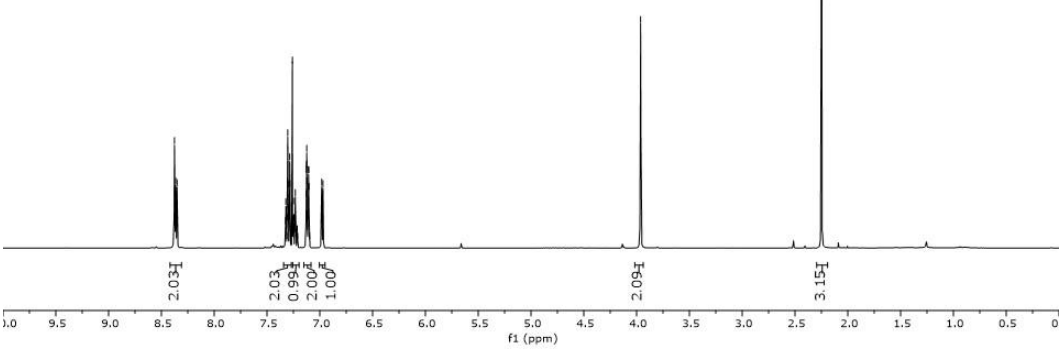
3c

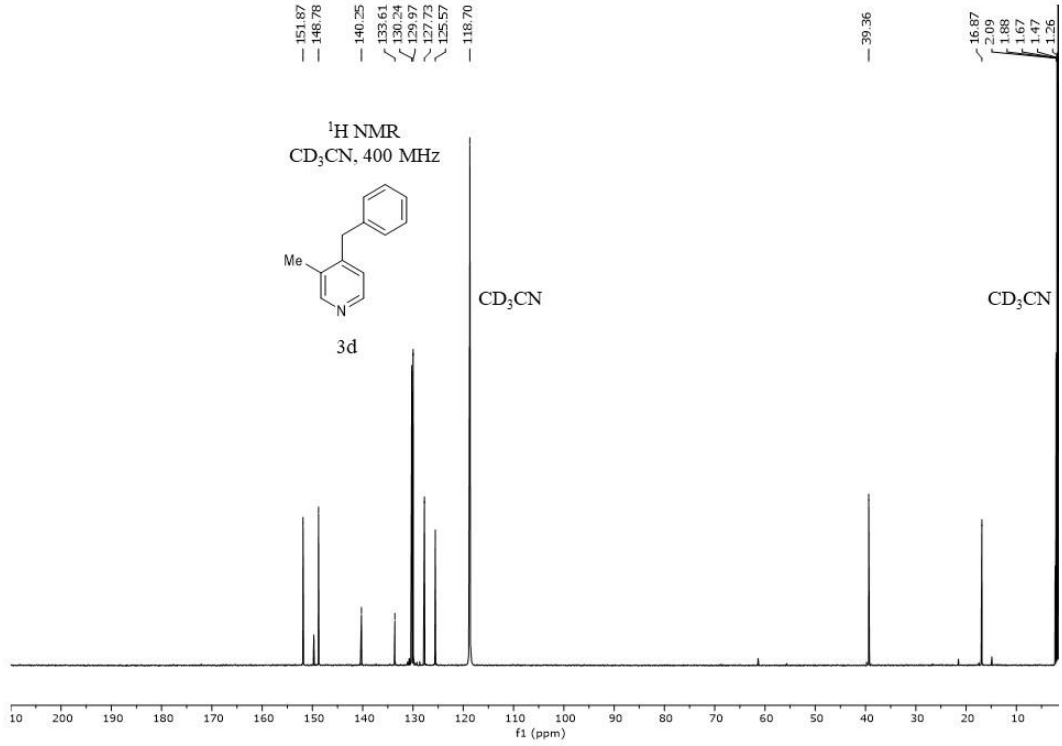


^{1}H NMR
$CDCl_3$, 400 MHz



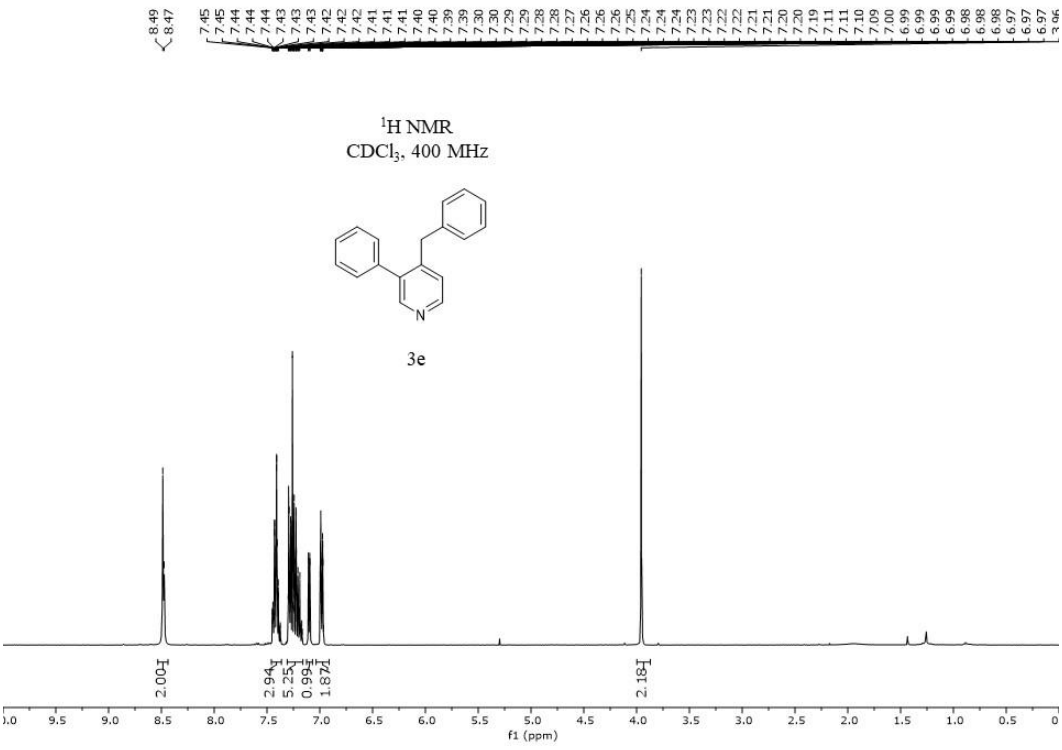
3d





^{1}H NMR
CD_3CN, 400 MHz

3d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7.40
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7.29
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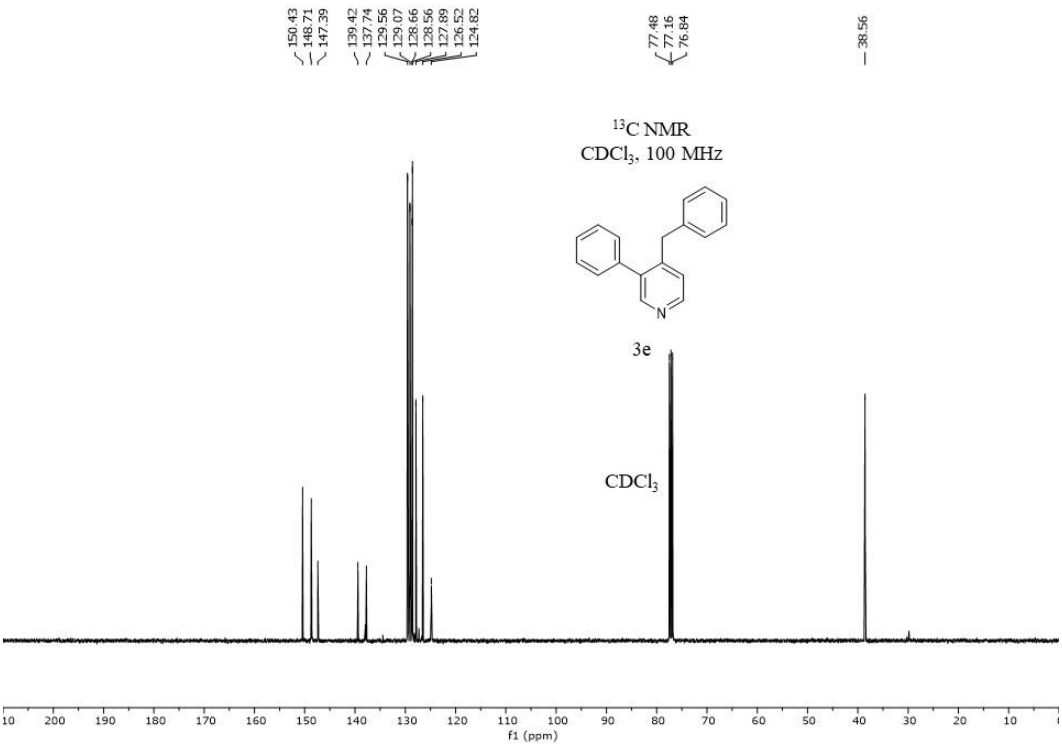
7.21
7.20
7.20
7.19
7.11
7.10
7.09
7.00
6.99
6.99
6.99
6.98
6.98
6.98
6.97
6.97
6.97
1H NMR
CDCl3, 400 MHz
3e
2.00
2.94
5.25
0.99
1.87
2.18
f1 (ppm)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148.71
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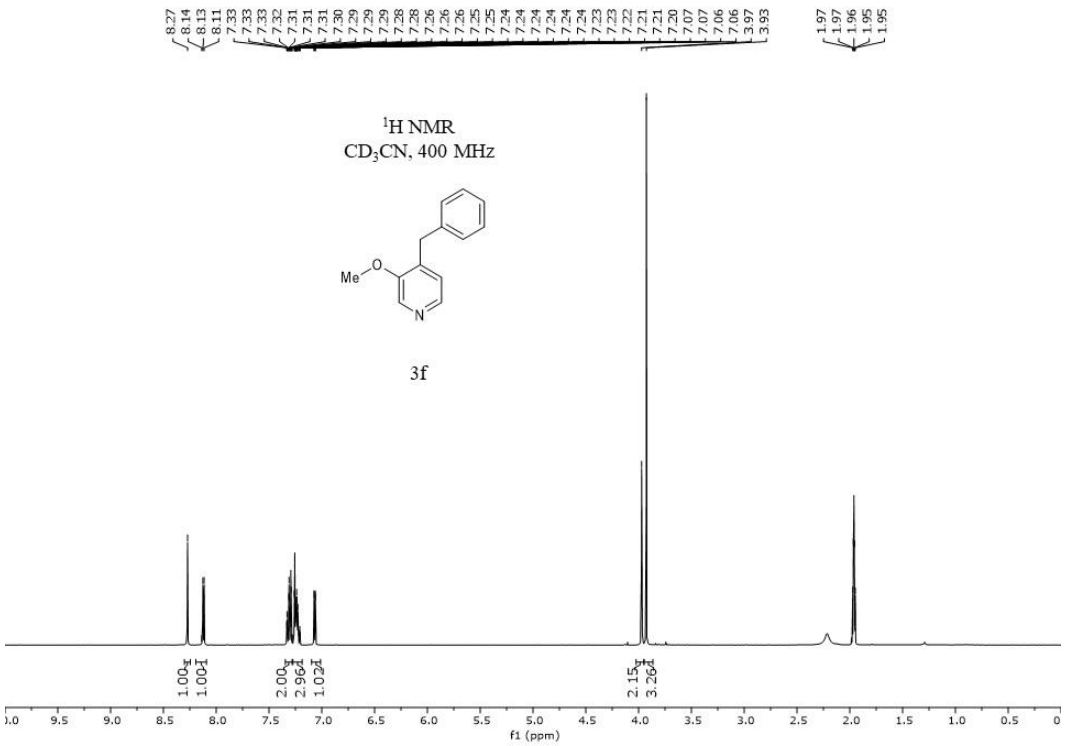
139.42
137.74
129.56
129.07
128.66
128.56
127.89
126.52
124.82
77.48
77.16
76.84
38.56
13C NMR
CDCl3, 100 MHz
3e
CDCl3
f1 (ppm)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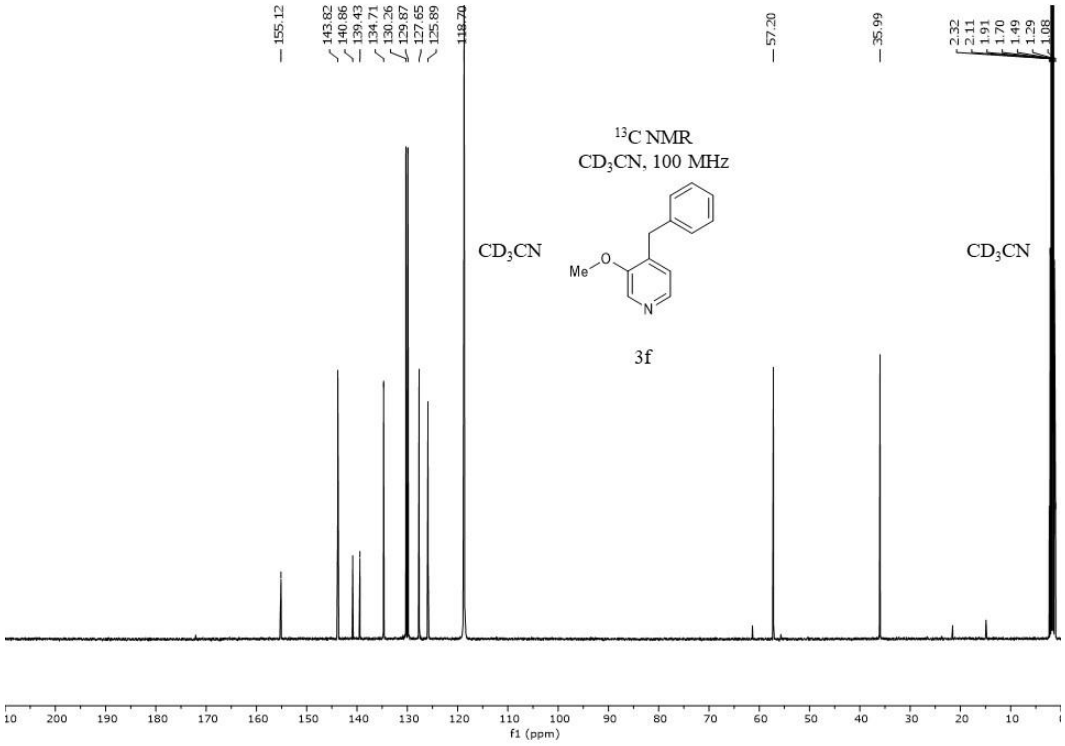
7.23
7.23
7.22
7.21
7.21
7.20
7.07
7.07
7.06
7.06
3.97
3.93
1.97
1.97
1.96
1.95
1.95
^{1}H NMR
CD_3CN, 400 MHz
Me
O
N
3f
1.00
1.00
2.00
2.96
1.02
2.15
3.26
f1 (ppm)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143.82
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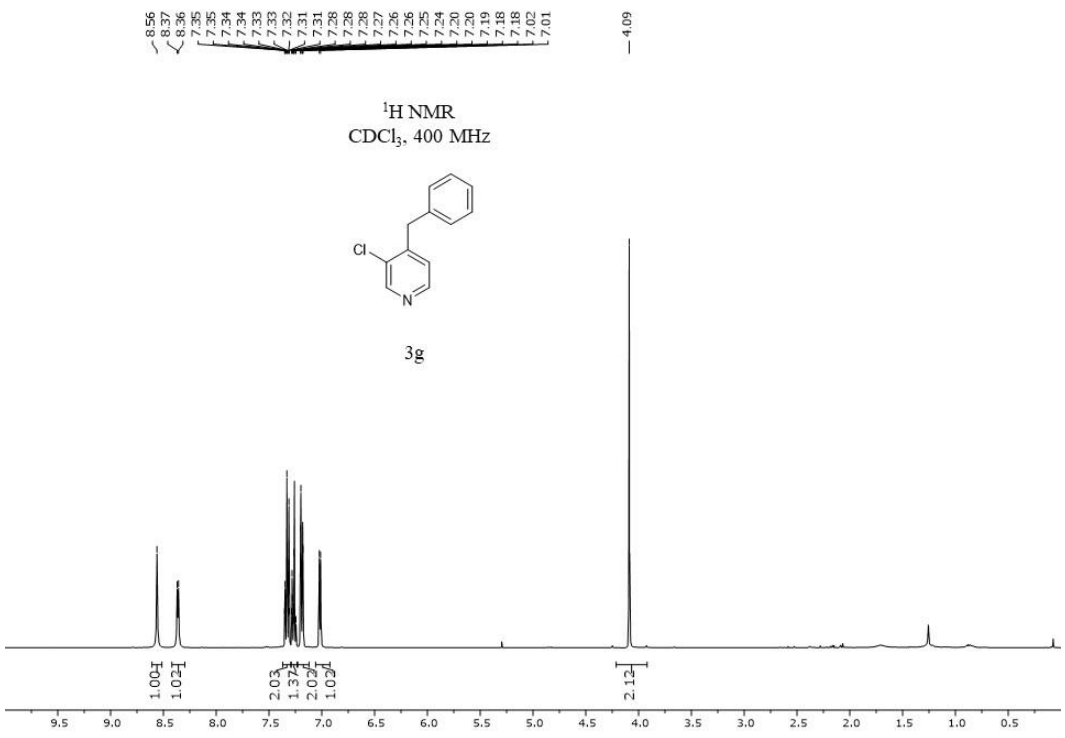
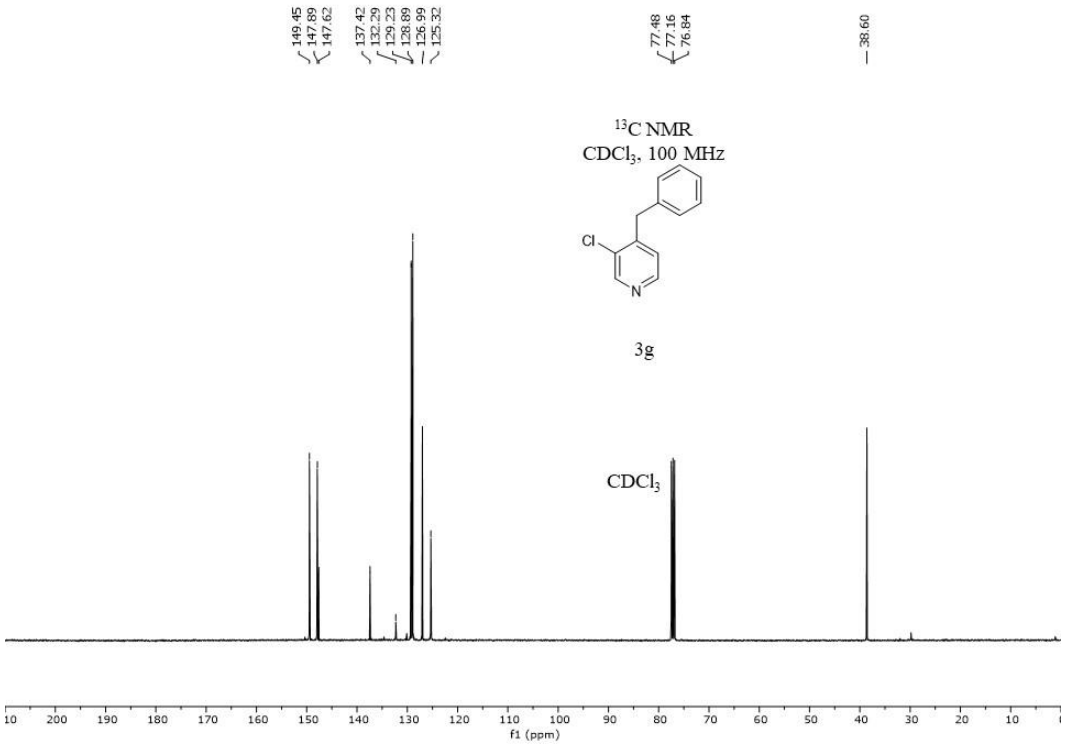
134.71
130.26
129.87
127.65
125.89
118.70
57.20
35.99
2.32
2.11
1.91
1.70
1.49
1.29
1.08
^{13}C NMR
CD_3CN, 100 MHz
CD_3CN
CD_3CN
Me
O
N
3f
f1 (ppm)



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

3g

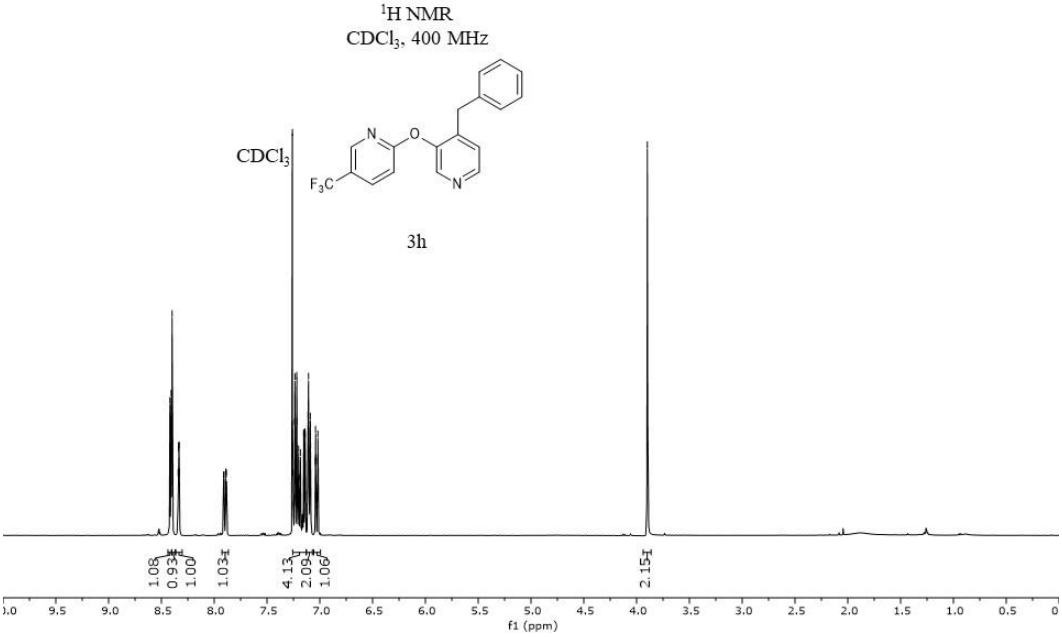


^{13}C NMR
$CDCl_3$, 100 MHz

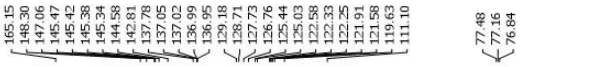
3g

$CDCl_3$

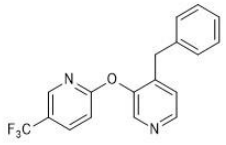
^{1}H NMR
$CDCl_3$, 400 MHz



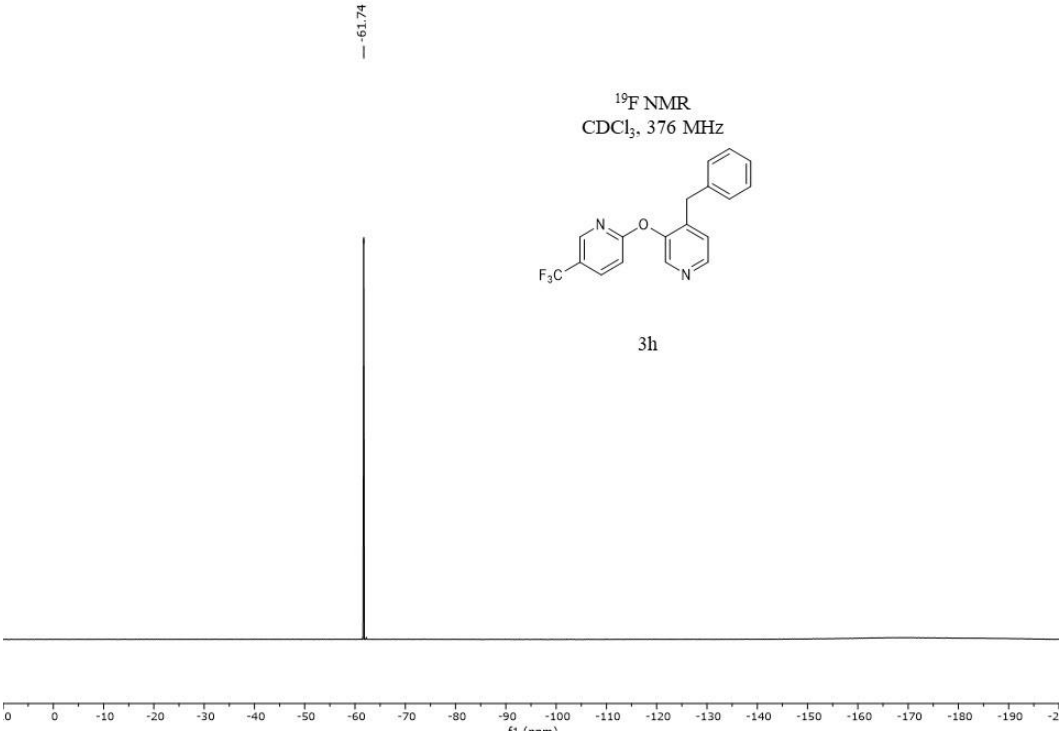
3h



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



3h


-61.74
19F NMR
CDCl3, 376 MHz
N
O
F3C
N
3h
8.75
8.75
8.74
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8.74
8.73
8.73
8.73
8.60
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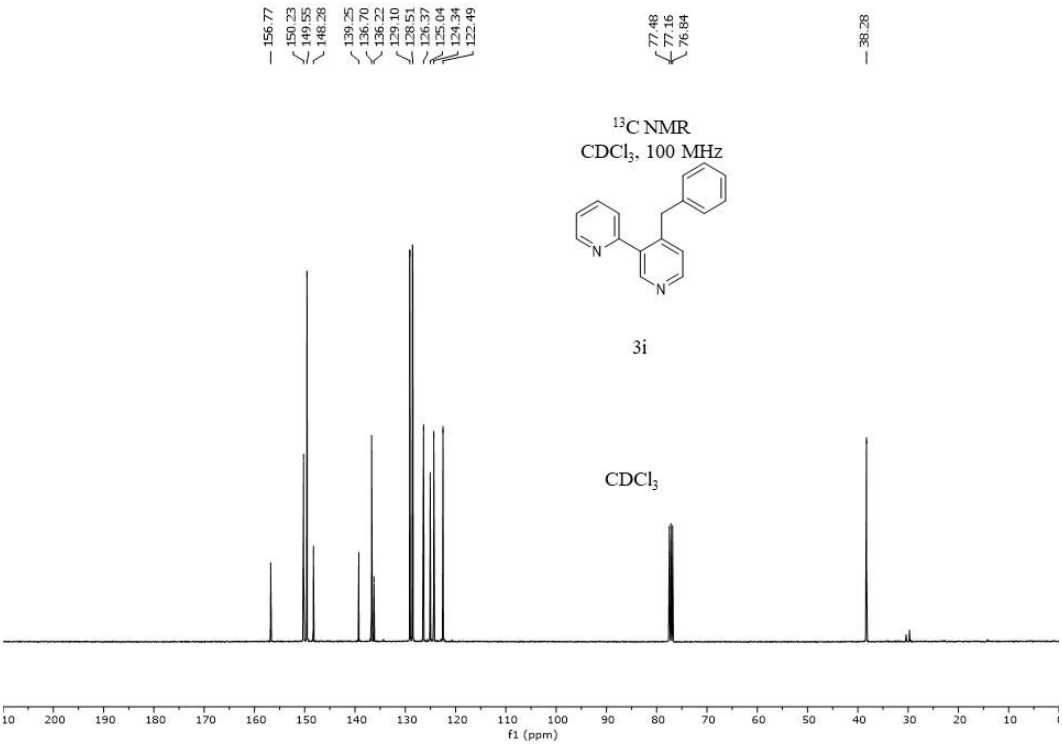
7.18
7.17
7.17
7.16
7.15
7.14
7.14
7.14
7.12
7.00
7.00
6.99
6.98
6.98
4.17
1H NMR
CDCl3, 400 MHz
N
N
3i
1.00
1.01
1.00
1.02
2.13
4.05
2.02
2.13
f1 (ppm)


156.77
150.23
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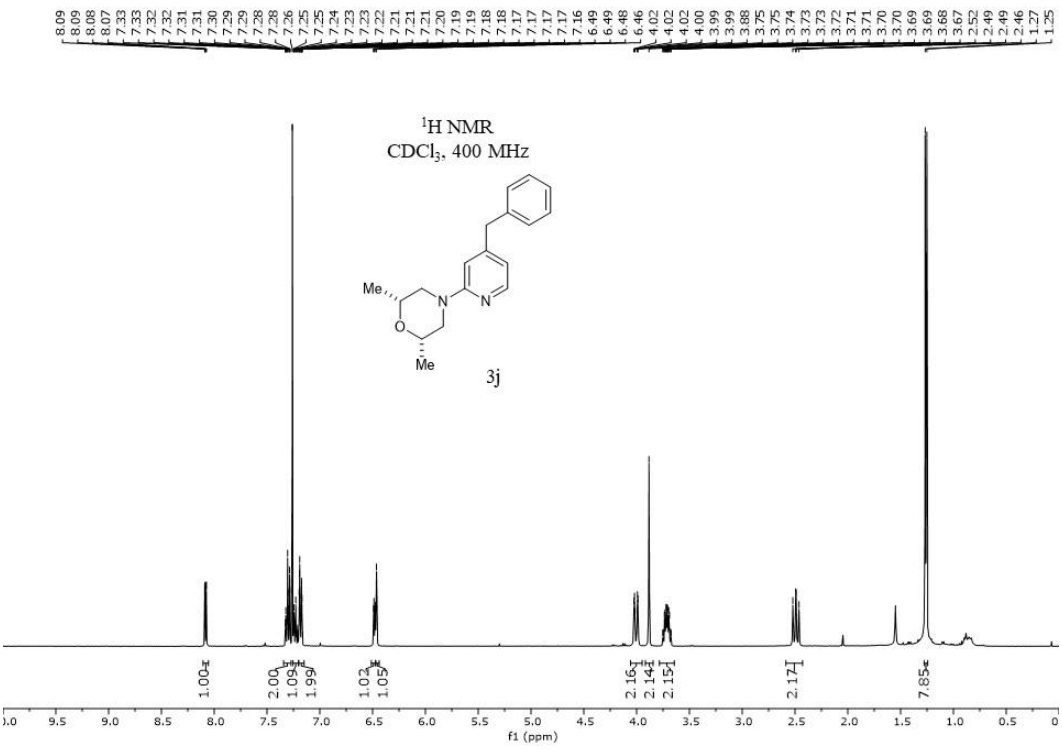
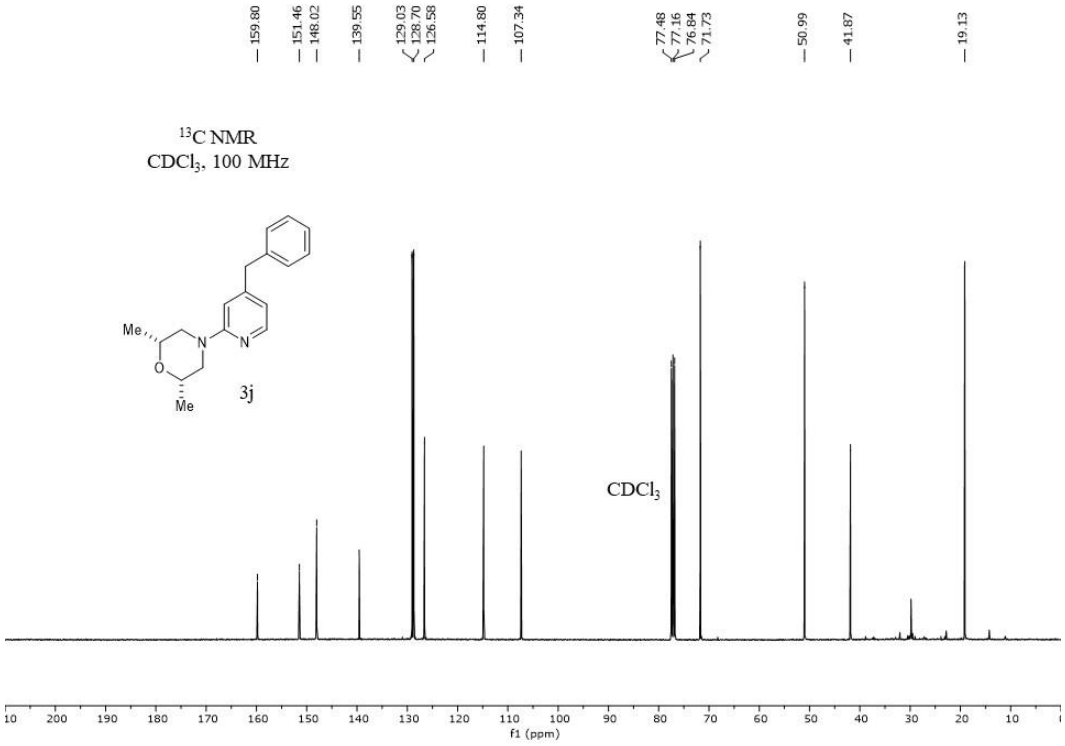
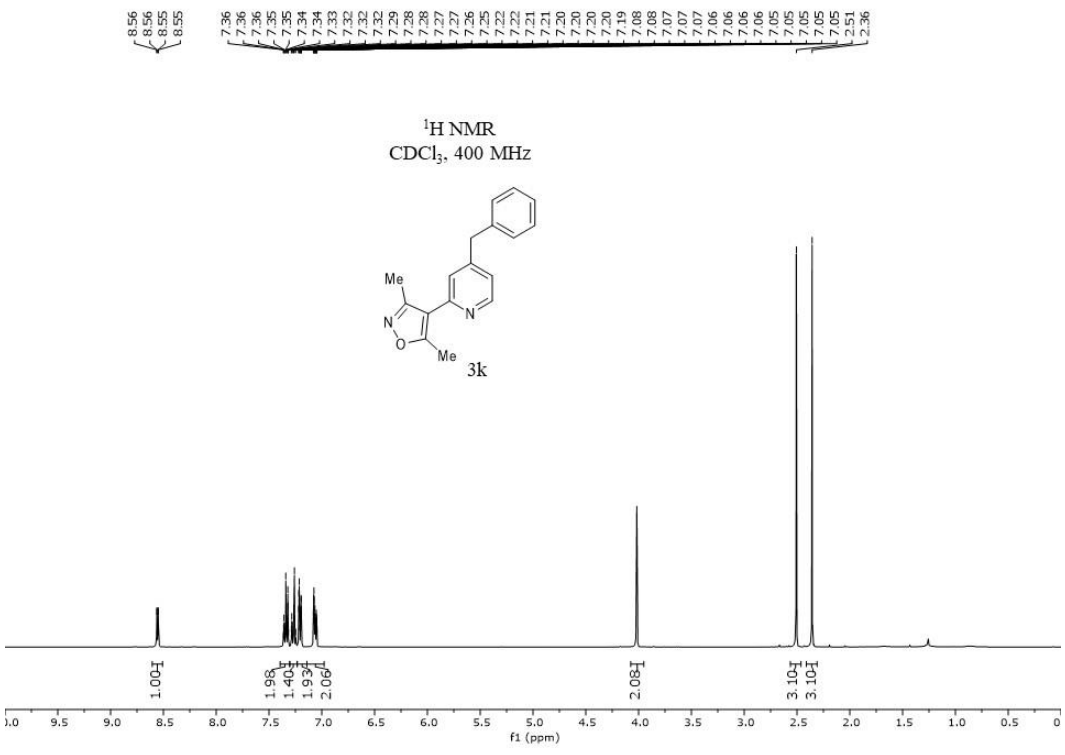
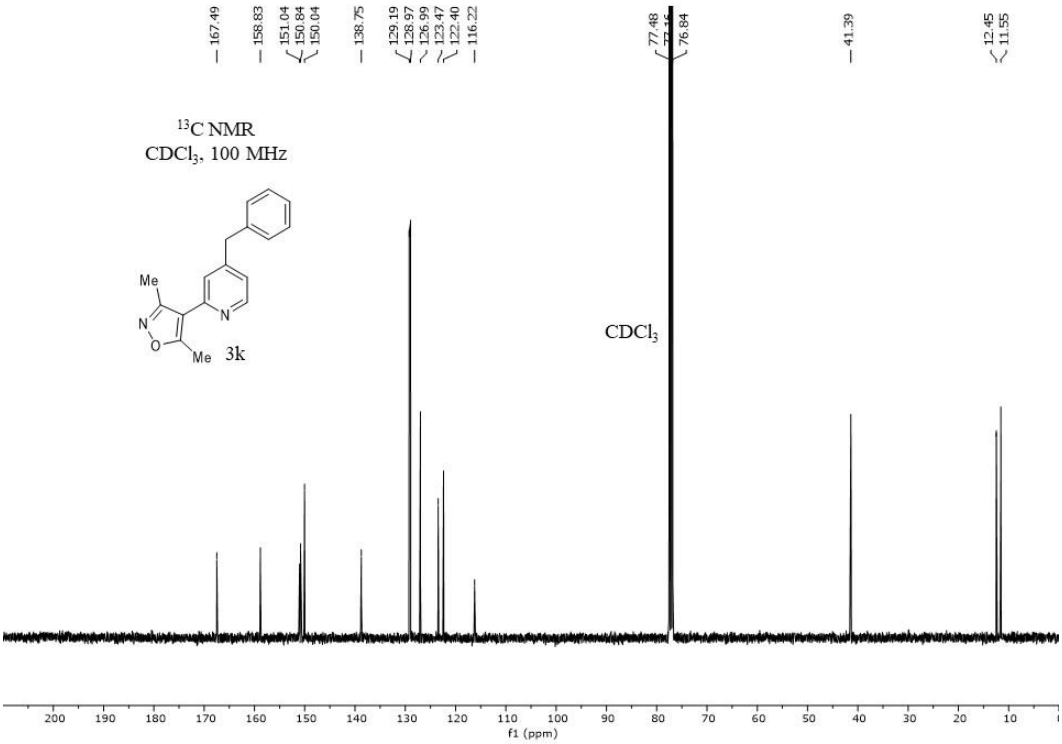
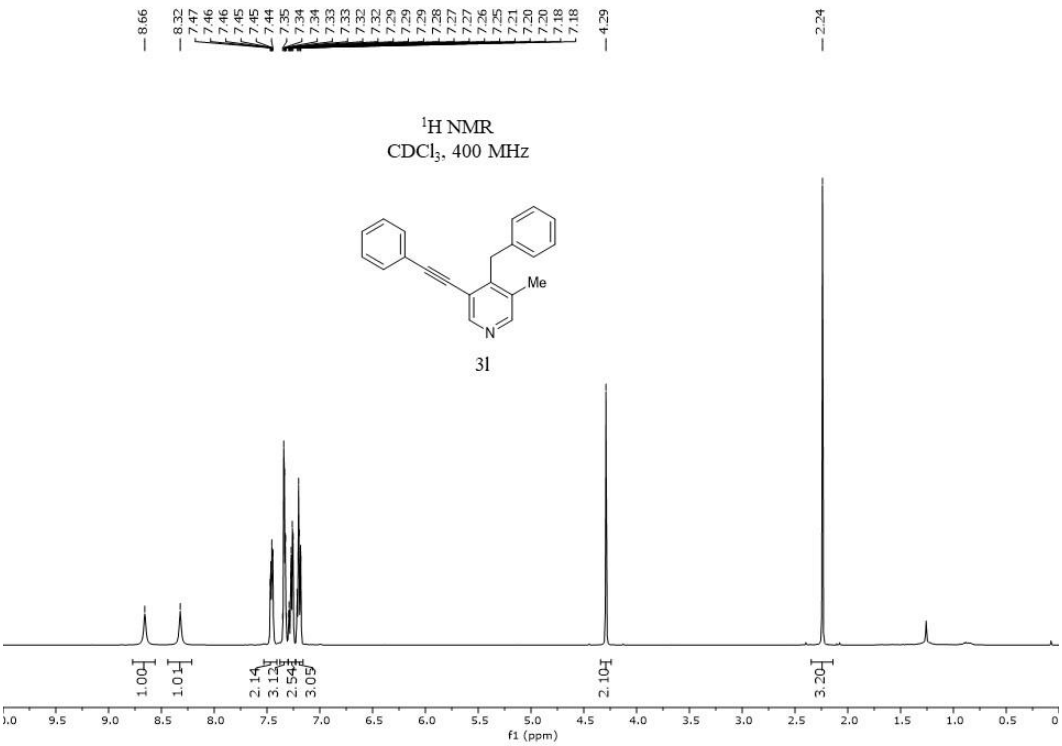
148.28
139.25
136.70
136.22
129.10
128.51
126.37
125.04
124.34
122.49
77.48
77.16
76.84
38.28
13C NMR
CDCl3, 100 MHz
3i
CDCl3
f1 (ppm)

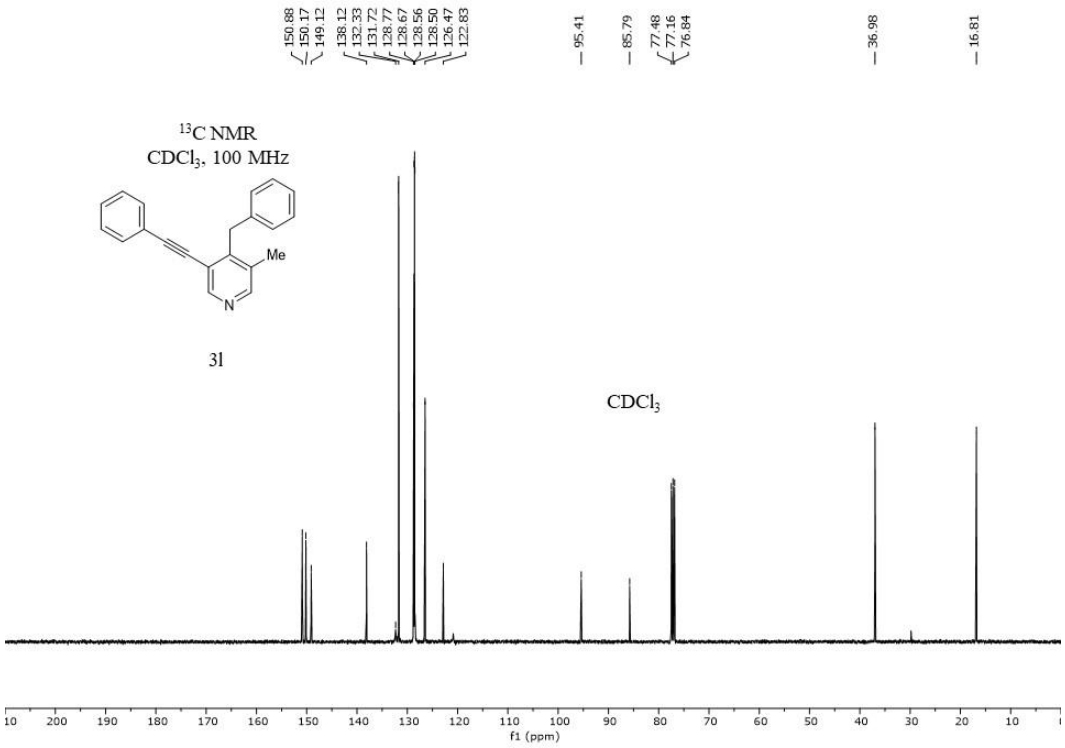

1H NMR
CDCl3, 400 MHz
Me
Me
3j
1.00
2.00
1.09
1.99
1.02
1.05
2.16
2.14
2.15
2.17
7.85
f1 (ppm)

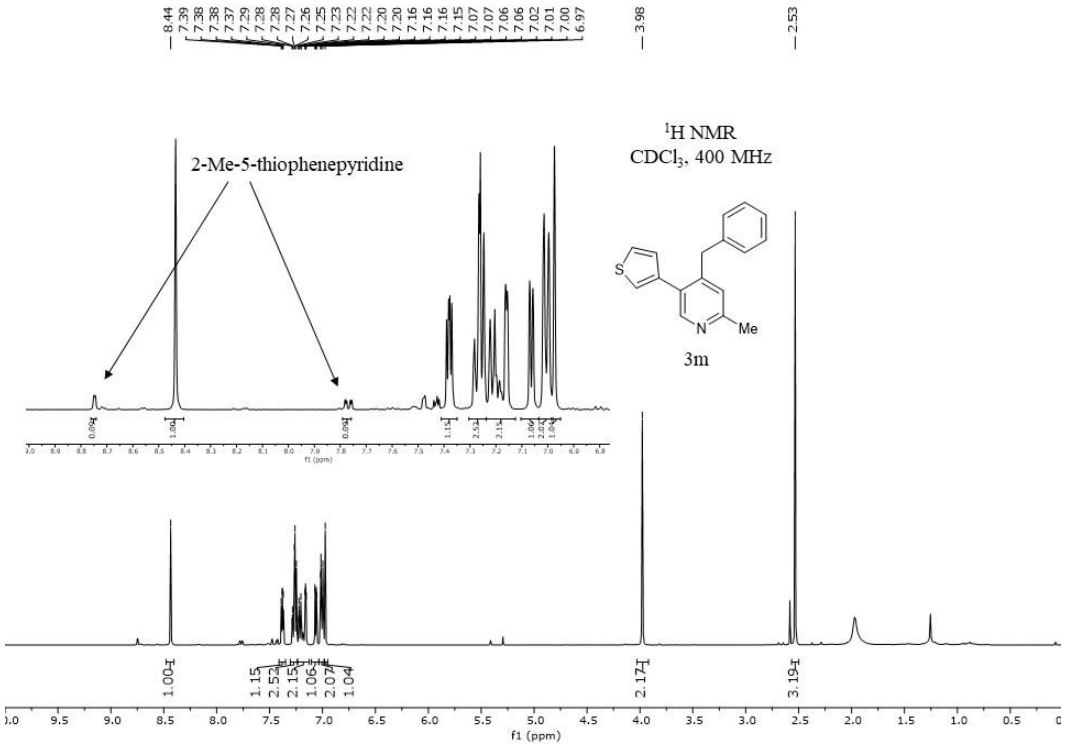

159.80
151.46
148.02
139.55
129.03
128.70
126.58
114.80
107.34
77.48
77.16
76.84
71.73
50.99
41.87
19.13
13C NMR
CDCl3, 100 MHz
Me
N
O
N
Me
3j
CDCl3
f1 (ppm)

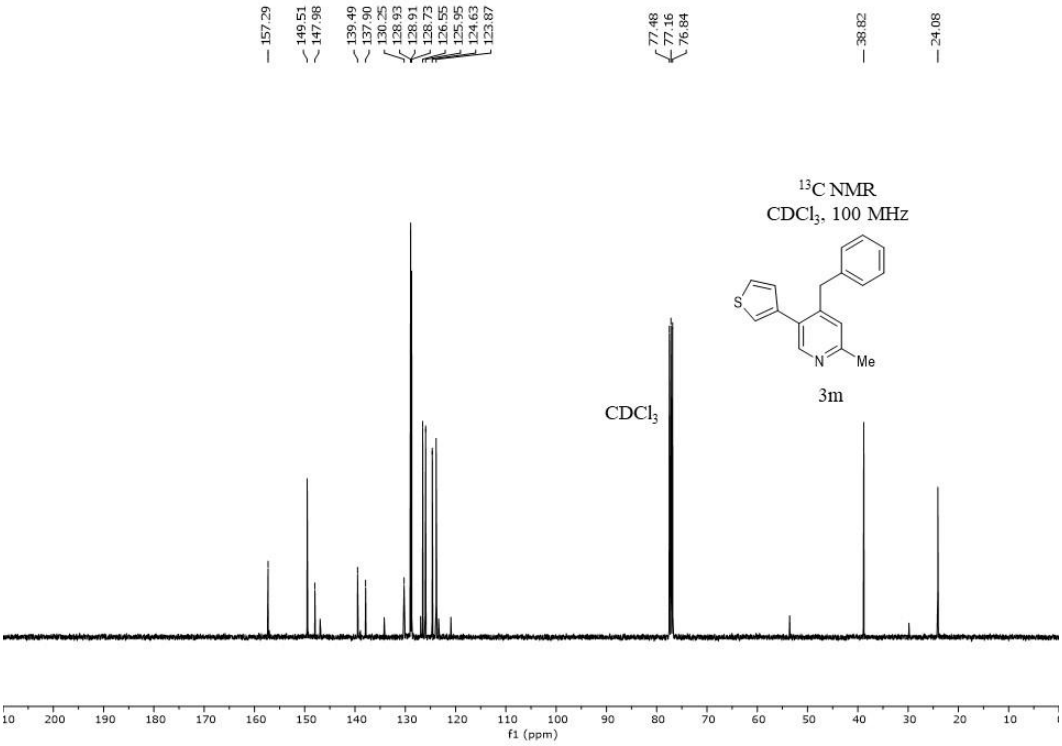

8.56
8.56
8.55
8.55
7.36
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.32
7.32
7.32
7.29
7.28
7.28
7.27
7.27
7.26
7.25
7.22
7.22
7.21
7.21
7.20
7.20
7.20
7.20
7.19
7.08
7.08
7.07
7.07
7.07
7.06
7.06
7.06
7.06
7.05
7.05
7.05
7.05
7.05
2.51
2.36
1H NMR
CDCl3, 400 MHz
Me
N
O
Me
3k
1.00
1.98
1.40
1.93
2.06
2.08
3.10
3.10
f1 (ppm)

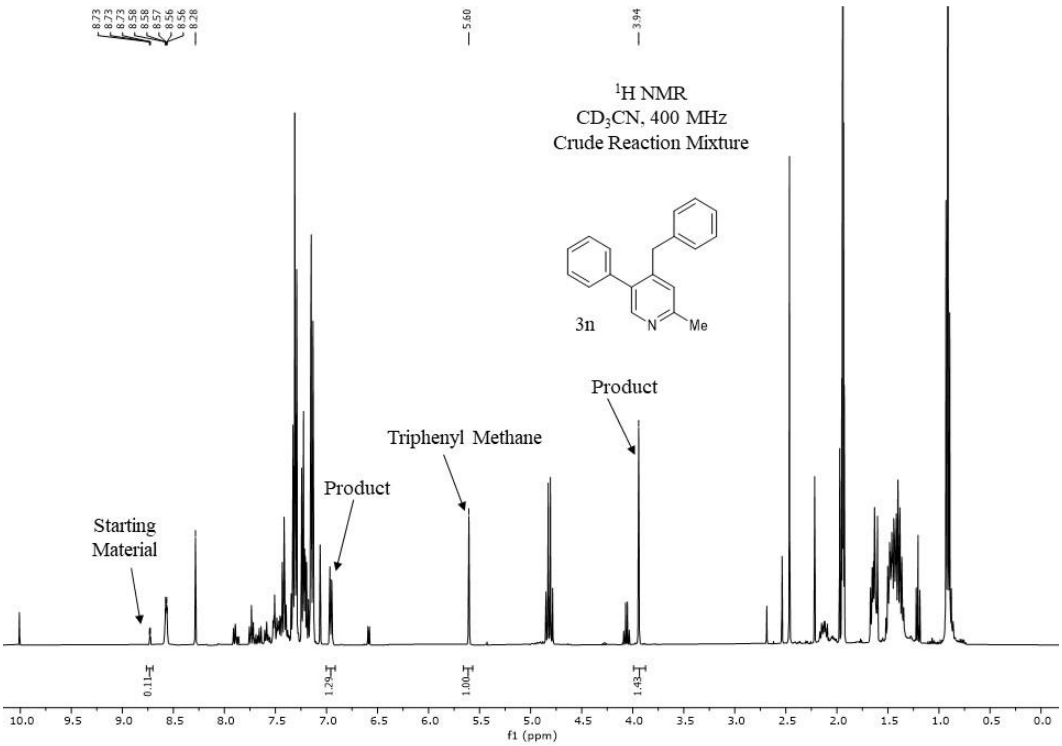

167.49
158.83
151.04
150.84
150.04
138.75
129.19
128.97
126.99
123.47
122.40
116.22
77.48
76.84
41.39
12.45
11.55
^{13}C NMR
$CDCl_3$, 100 MHz
Me
N
O
Me
3k
$CDCl_3$
f1 (ppm)

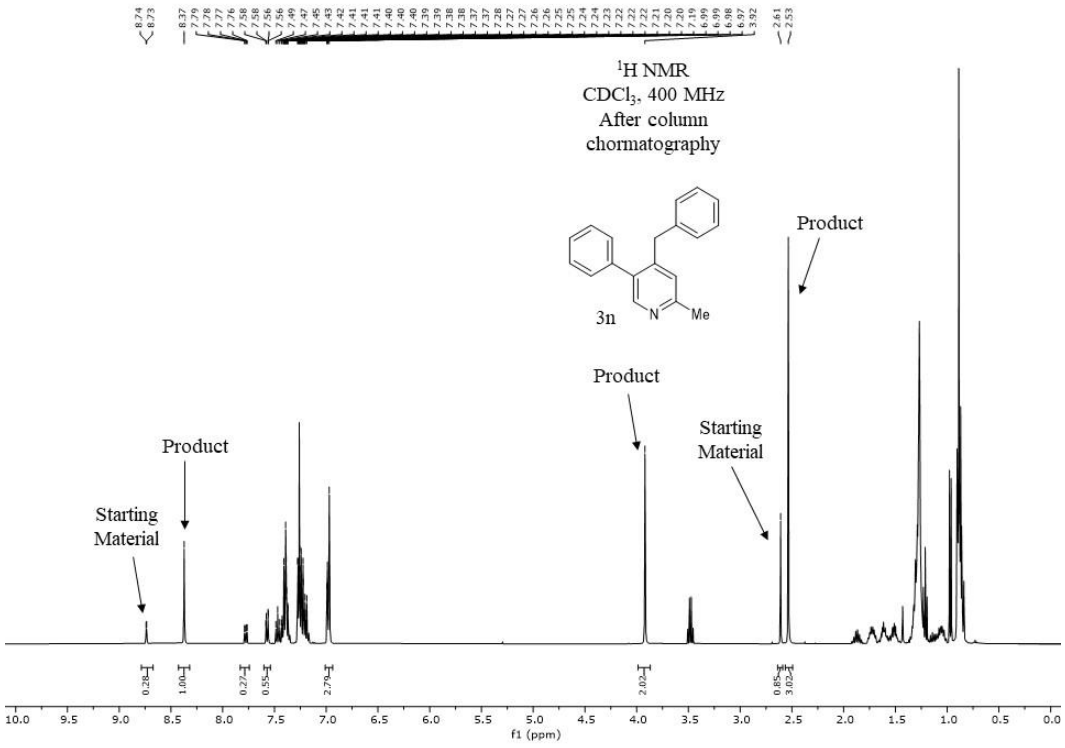

8.66
8.32
7.47
7.46
7.46
7.45
7.45
7.44
7.35
7.34
7.34
7.33
7.33
7.32
7.32
7.29
7.29
7.29
7.28
7.27
7.27
7.26
7.25
7.21
7.20
7.20
7.18
7.18
4.29
2.24
^{1}H NMR
$CDCl_3$, 400 MHz
Me
N
3l
1.00
1.01
2.14
3.12
2.54
3.05
2.10
3.20
f1 (ppm)

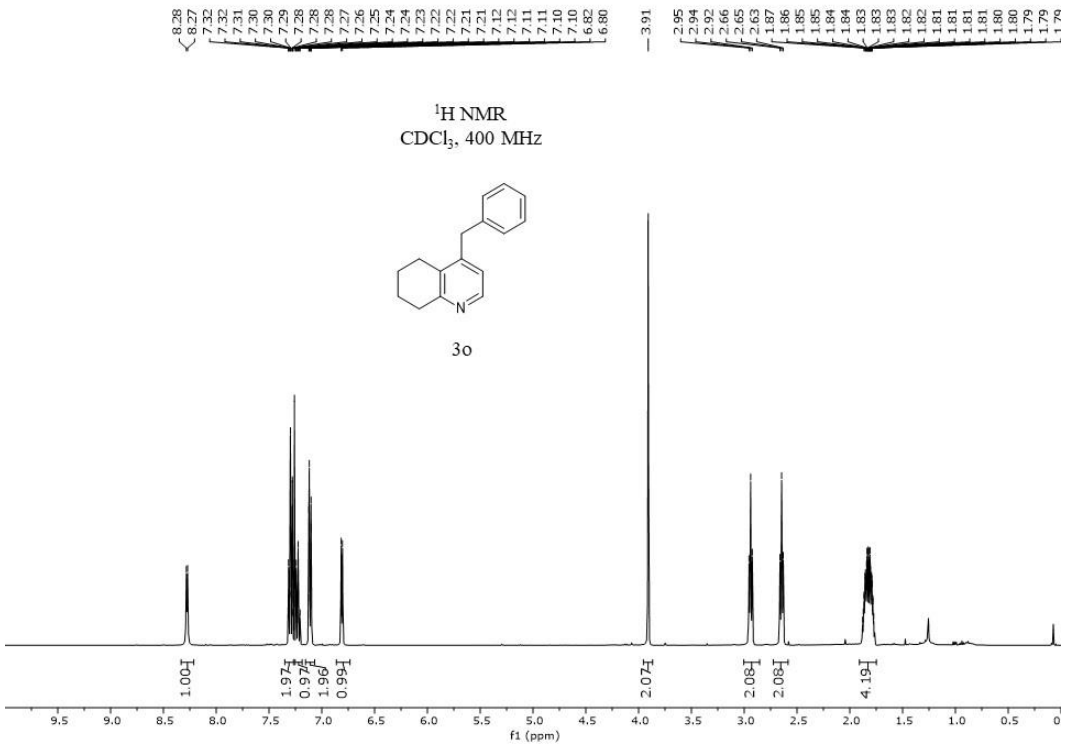

150.88
150.17
149.12
138.12
132.33
131.72
128.77
128.67
128.56
128.50
126.47
122.83
95.41
85.79
77.48
77.16
76.84
36.98
16.81
13C NMR
CDCl3, 100 MHz
Me
N
31
CDCl3
f1 (ppm)

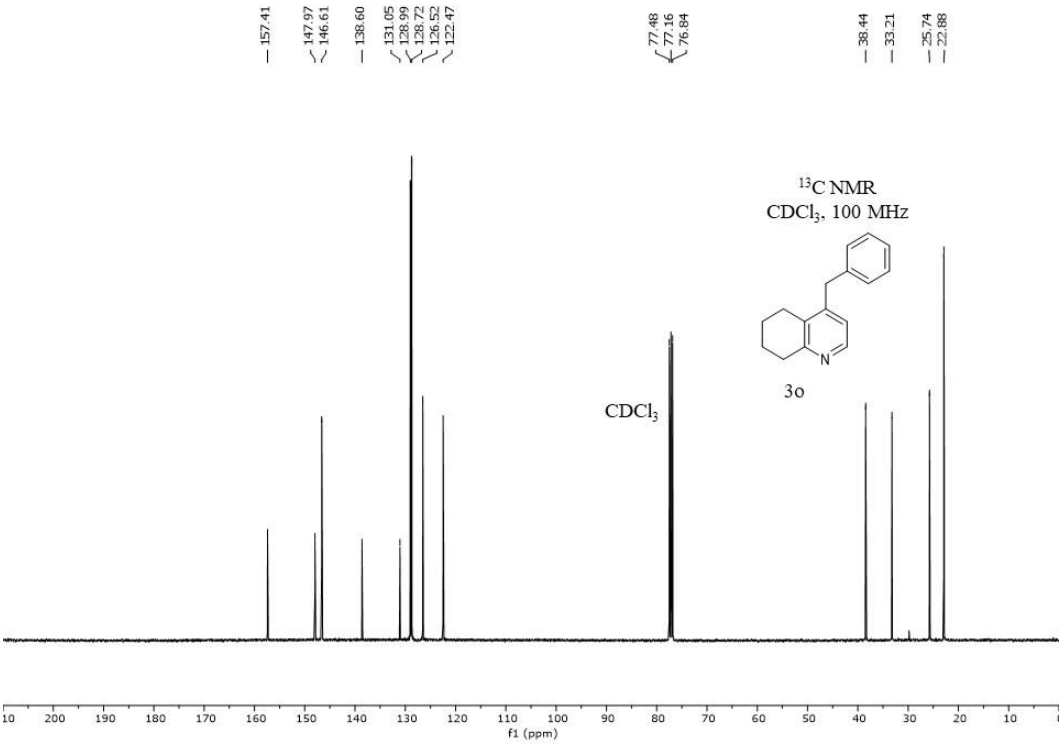

8.44
7.39
7.38
7.38
7.37
7.29
7.28
7.28
7.27
7.26
7.25
7.23
7.22
7.22
7.20
7.20
7.16
7.16
7.16
7.15
7.07
7.07
7.06
7.06
7.02
7.01
7.00
6.97
3.98
2.53
1H NMR
CDCl3, 400 MHz
2-Me-5-thiophenepyridine
S
N
Me
3m
1.00
1.15
2.53
2.15
1.06
2.07
1.04
2.17
3.19
f1 (ppm)

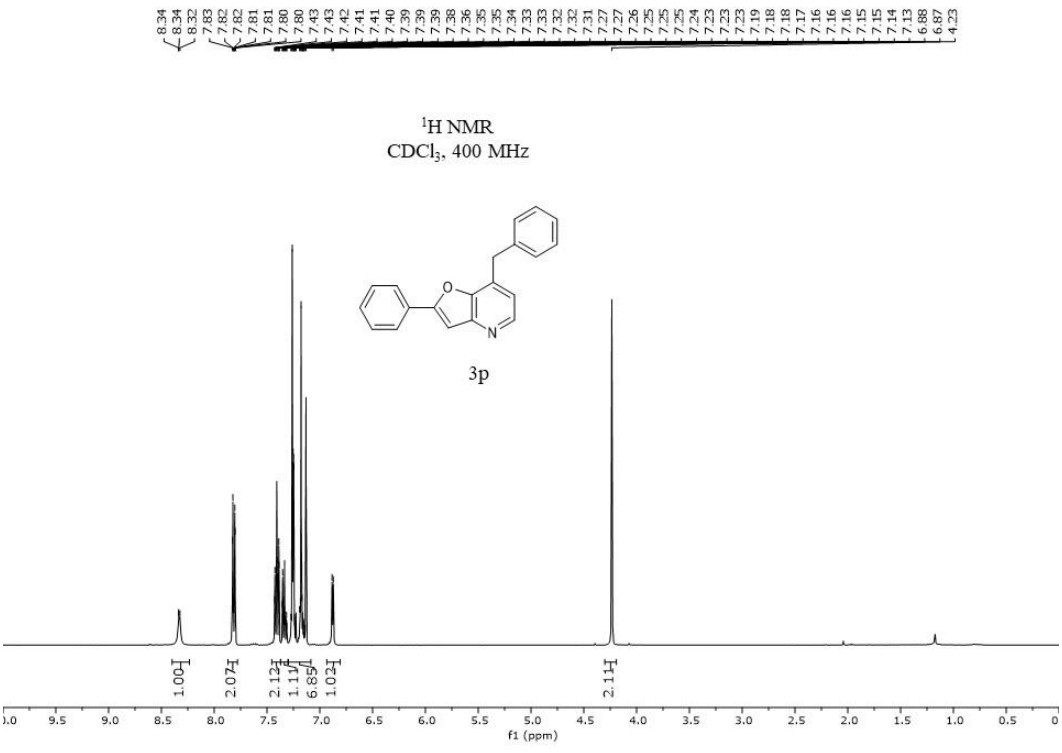

157.29
149.51
147.98
139.49
137.90
130.25
128.93
128.91
128.73
126.55
125.95
124.63
123.87
77.48
77.16
76.84
38.82
24.08
^{13}C NMR
$CDCl_3$, 100 MHz
S
N
Me
3m
$CDCl_3$
f1 (ppm)

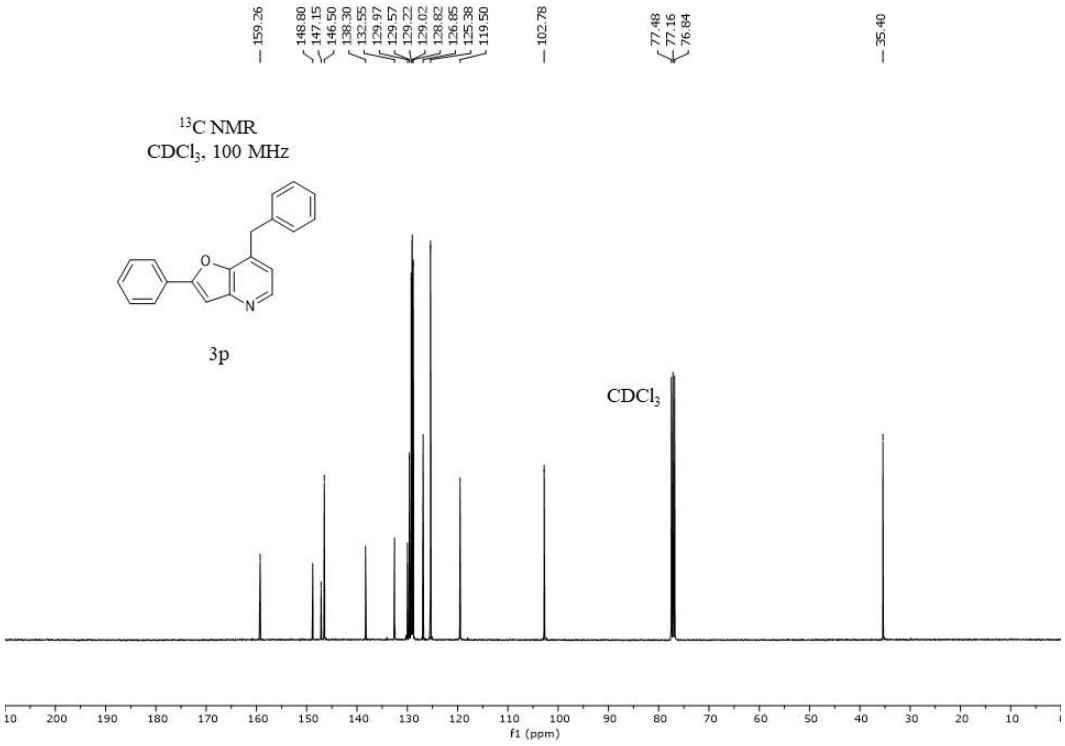

8.73
8.73
8.73
8.58
8.58
8.57
8.56
8.56
8.28
5.60
3.94
^{1}H NMR
CD_3CN, 400 MHz
Crude Reaction Mixture
3n
N
Me
Product
Triphenyl Methane
Product
Starting
Material
0.11
1.29
1.00
1.43
f1 (ppm)


^{1}H NMR
$CDCl_3$, 400 MHz
After column
chormatography
3n
Me
N
Product
Product
Product
Starting
Material
Starting
Material
f1 (ppm)


^{1}H NMR
$CDCl_3$, 400 MHz
3o
N
f1 (ppm)


157.41
147.97
146.61
138.60
131.05
128.99
128.72
126.52
122.47
77.48
77.16
76.84
38.44
33.21
25.74
22.88
13C NMR
CDCl3, 100 MHz
CDCl3
3o
f1 (ppm)


8.34
8.34
8.32
7.83
7.82
7.82
7.81
7.81
7.80
7.80
7.43
7.43
7.42
7.41
7.41
7.40
7.39
7.39
7.39
7.38
7.36
7.35
7.35
7.34
7.33
7.33
7.32
7.32
7.31
7.27
7.27
7.26
7.25
7.25
7.25
7.24
7.23
7.23
7.23
7.19
7.18
7.17
7.16
7.16
7.16
7.15
7.15
7.14
7.13
6.88
6.87
4.23
1H NMR
CDCl3, 400 MHz
3p
1.00
2.07
2.12
1.11
6.85
1.03
2.11
f1 (ppm)

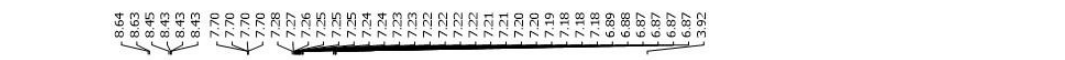


^{13}C NMR
$CDCl_3$, 100 MHz

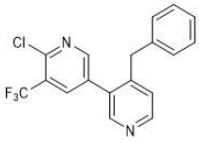
3p

$CDCl_3$

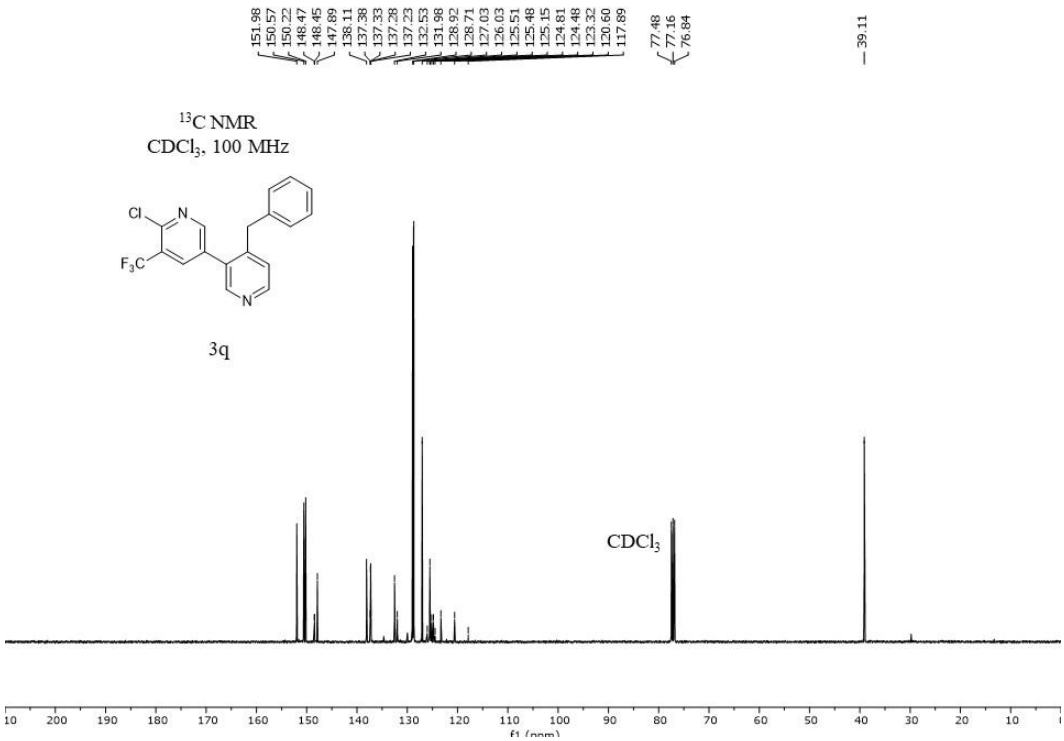
f1 (ppm)

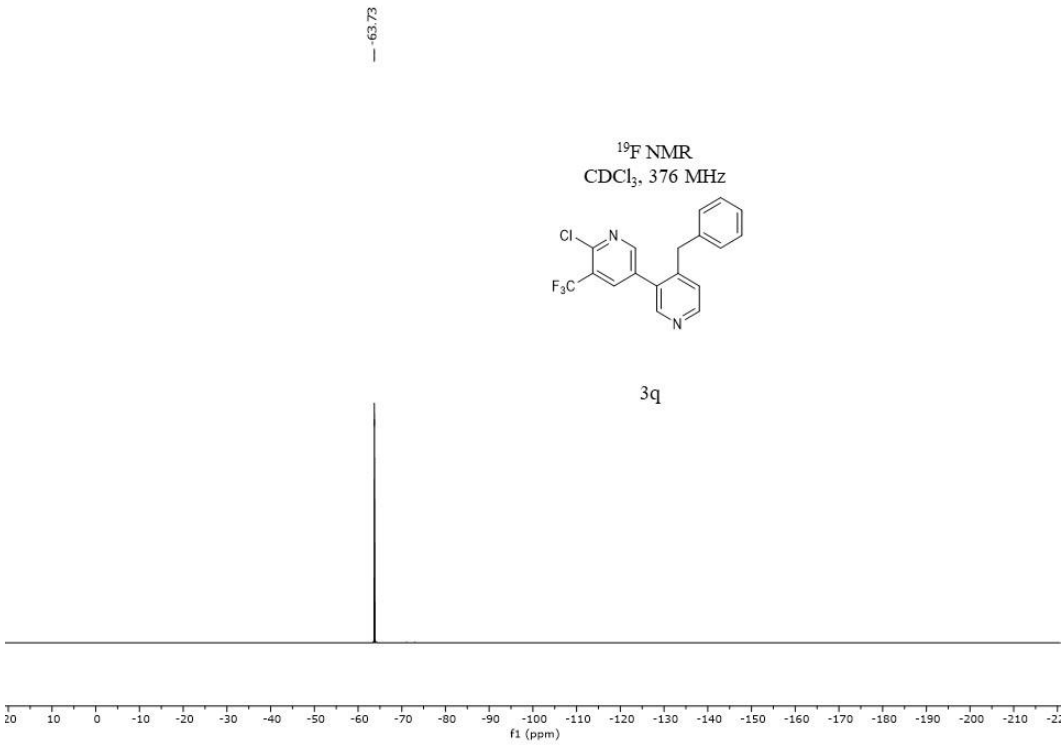


^{1}H NMR
$CDCl_3$, 400 MHz

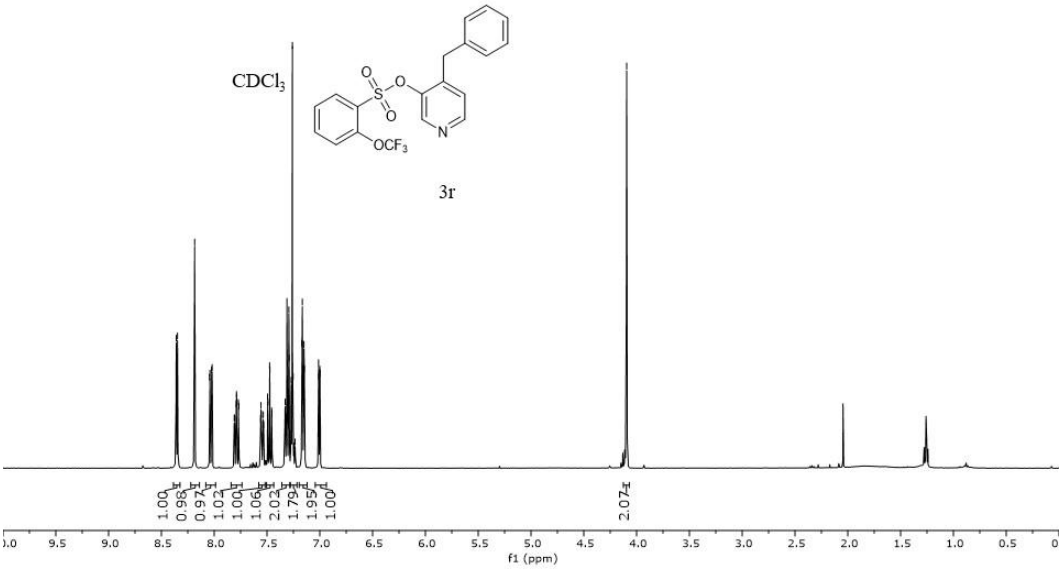


3q


151.98
150.57
150.22
148.47
148.45
147.89
138.11
137.38
137.33
137.28
137.23
132.53
131.98
128.92
128.71
127.03
126.03
125.51
125.48
125.15
124.81
124.48
123.32
120.60
117.89
77.48
77.16
76.84
39.11
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
N
F_3C
N
3q
$CDCl_3$
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

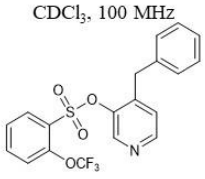

-63.73
^{19}F NMR
$CDCl_3$, 376 MHz
Cl
N
F_3C
N
3q
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

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

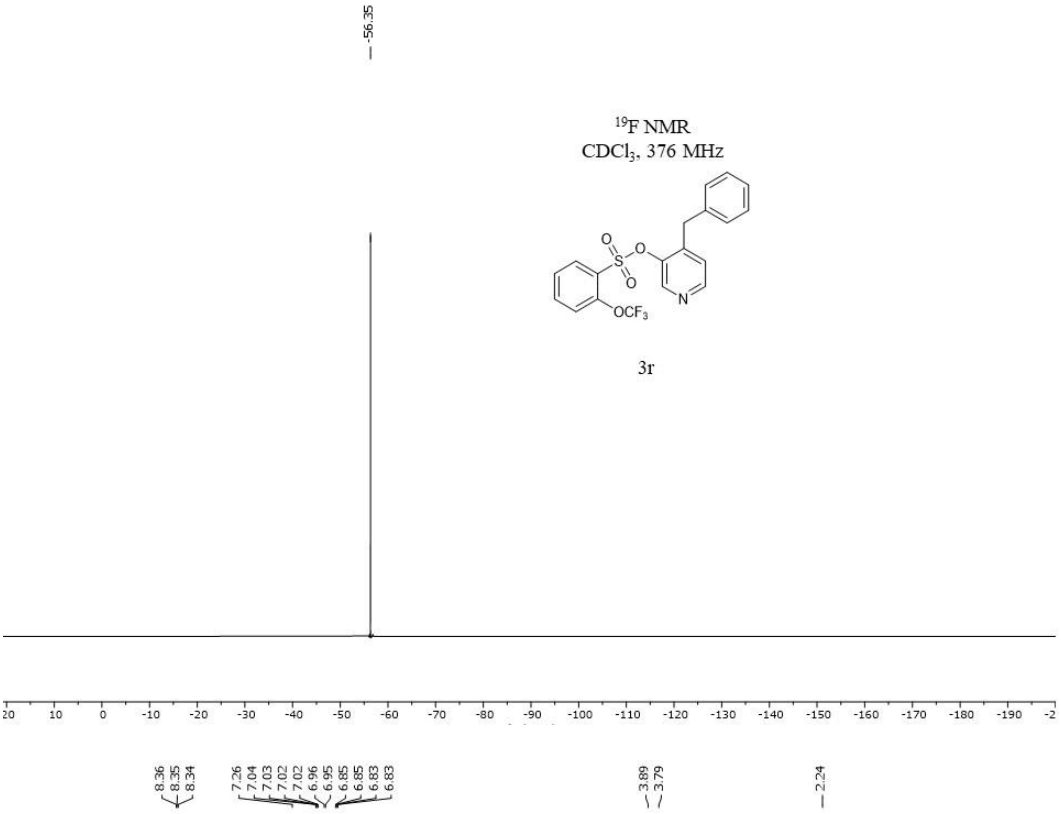


3r

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

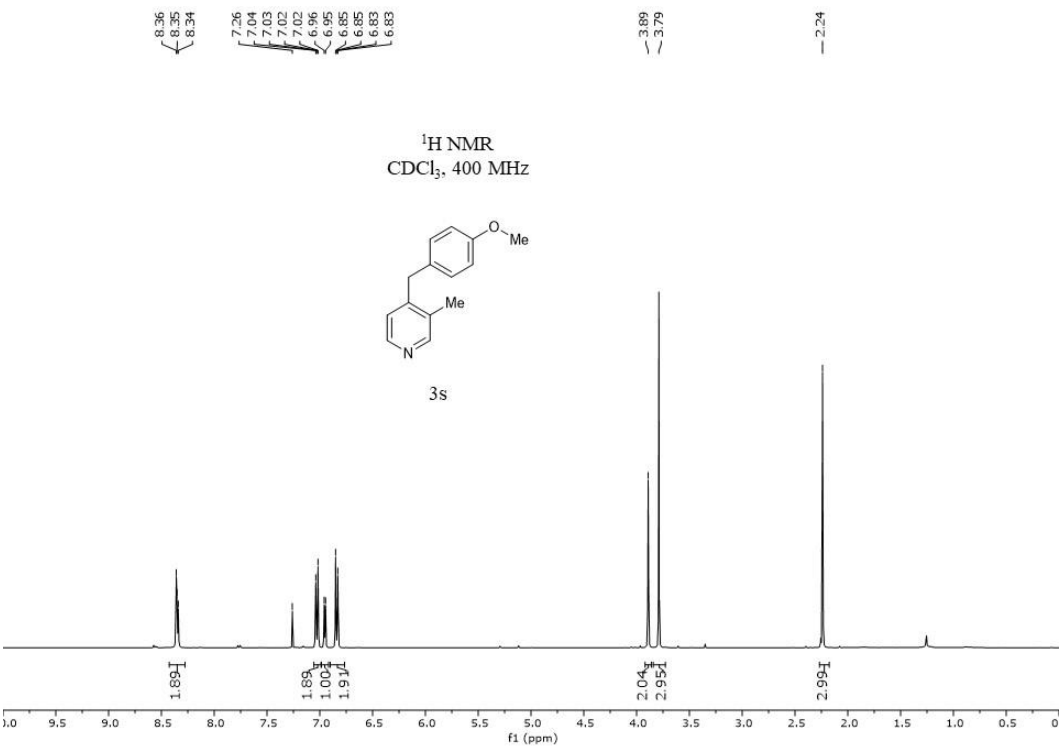


3r



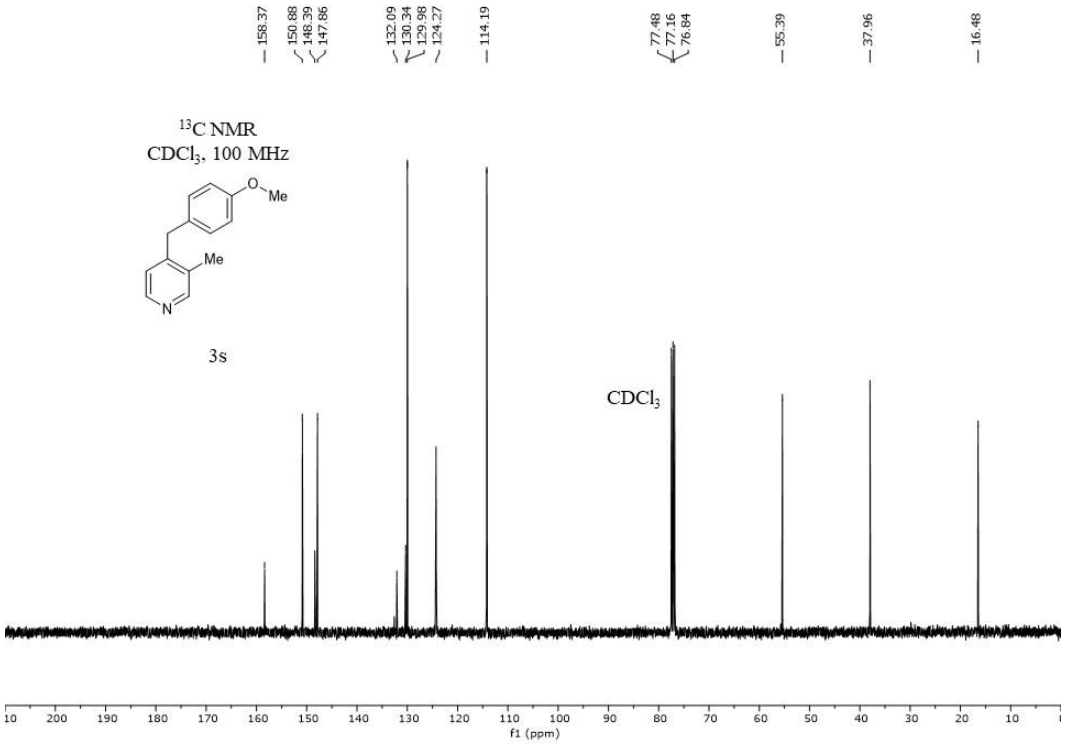
^{19}F NMR
$CDCl_3$, 376 MHz

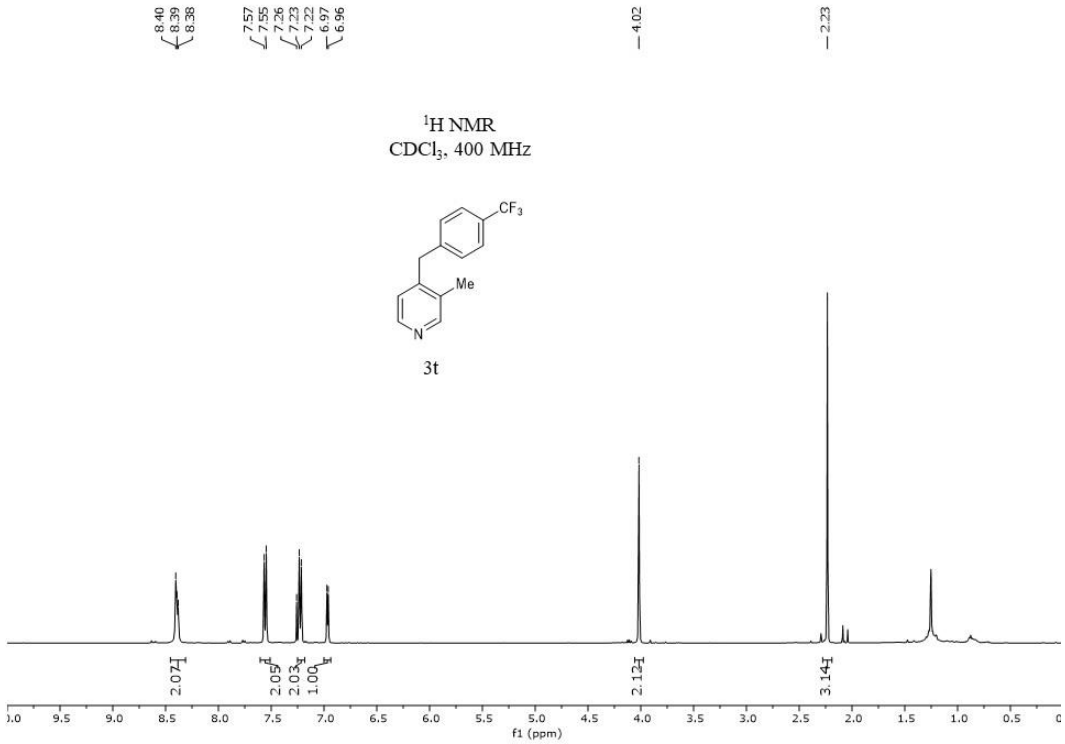
3r

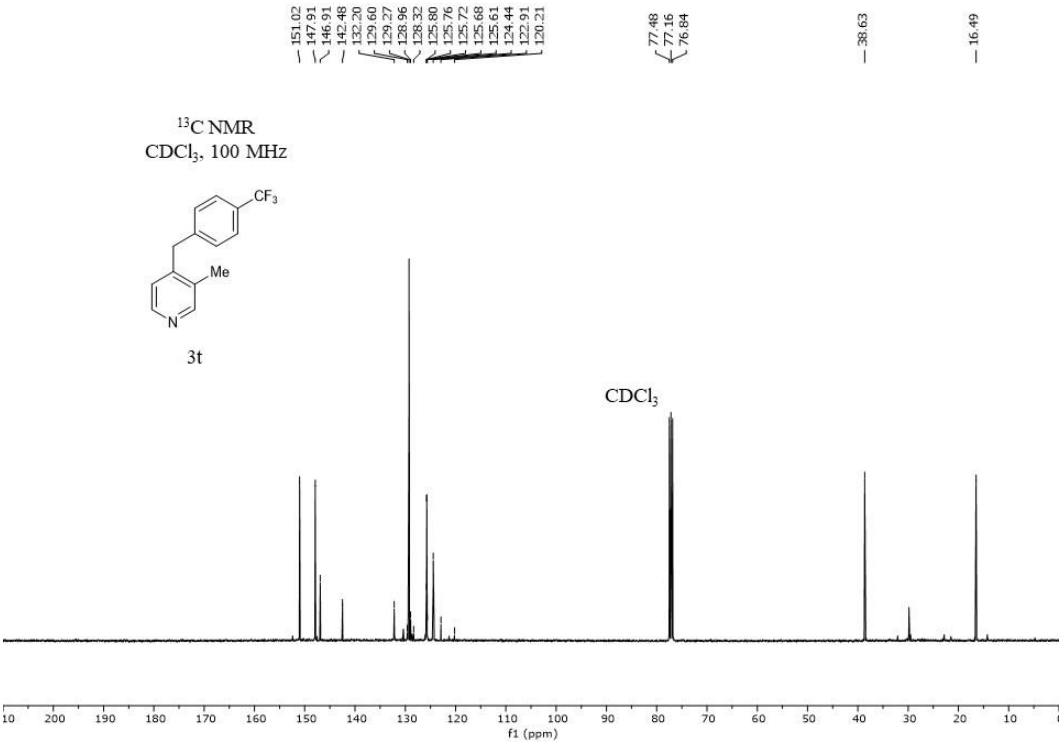


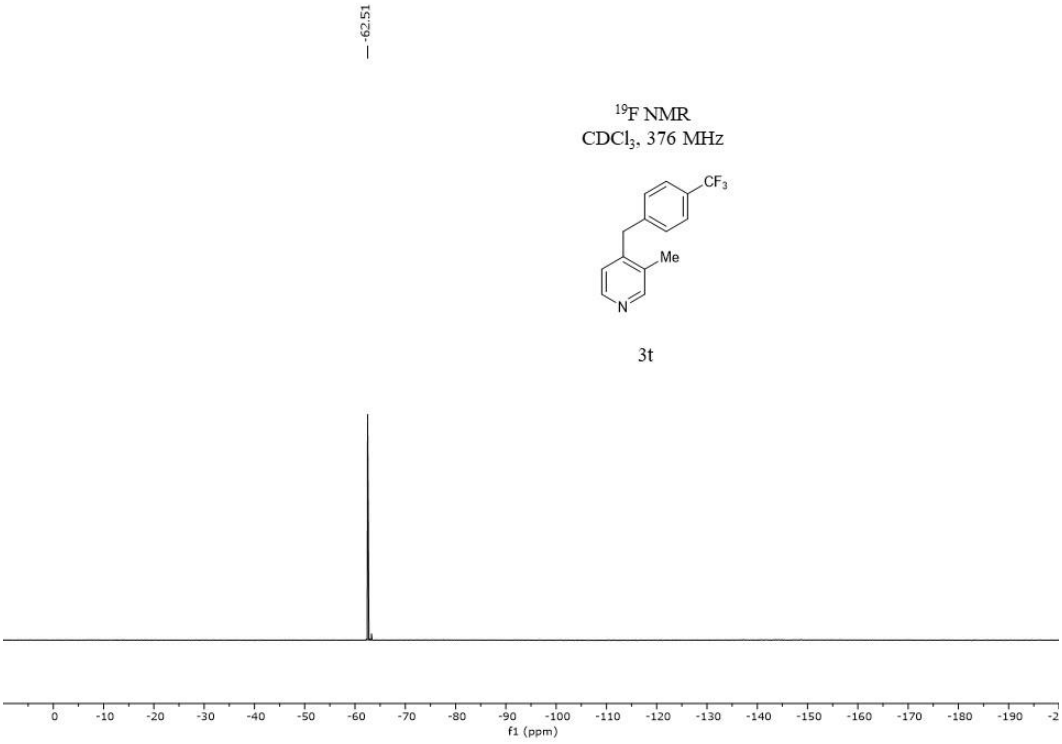
^{1}H NMR
$CDCl_3$, 400 MHz

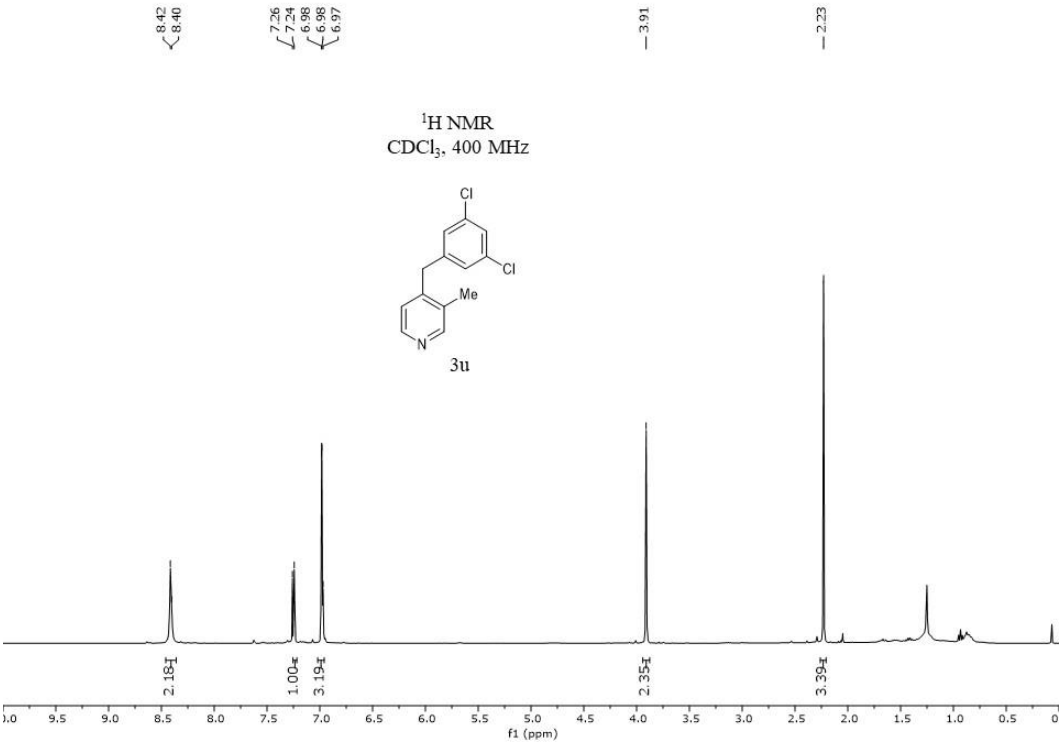
3s

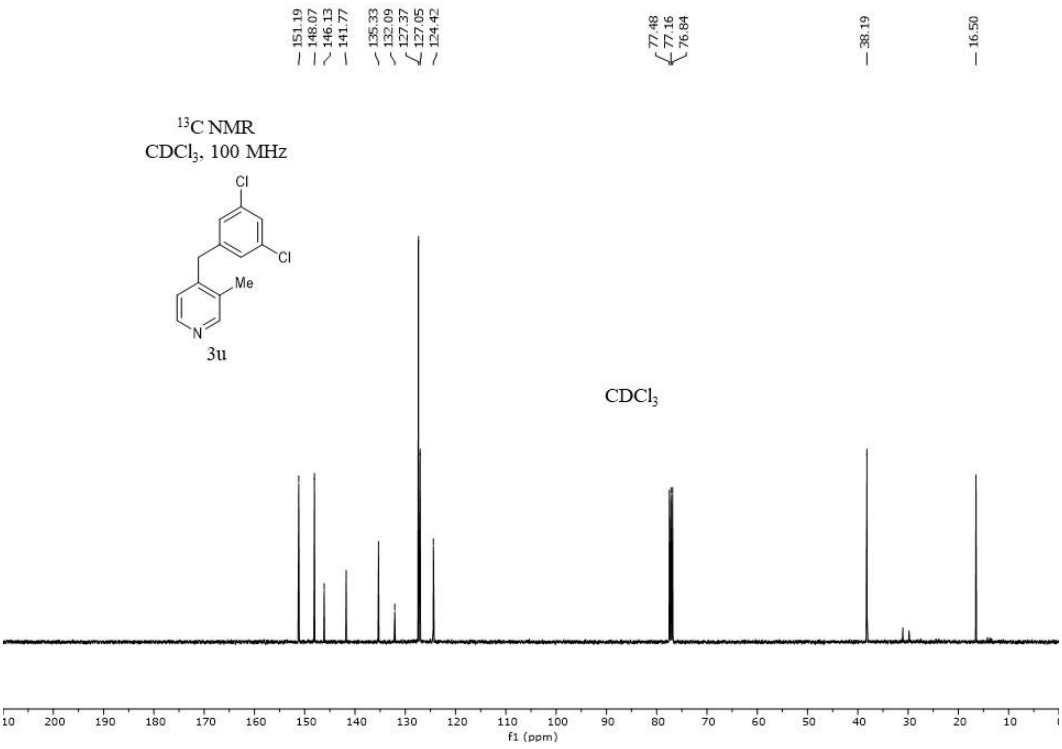

158.37
150.88
148.39
147.86
132.09
130.34
129.98
124.27
114.19
77.48
77.16
76.84
55.39
37.96
16.48
13C NMR
CDCl3, 100 MHz
O
Me
Me
N
3s
CDCl3
f1 (ppm)

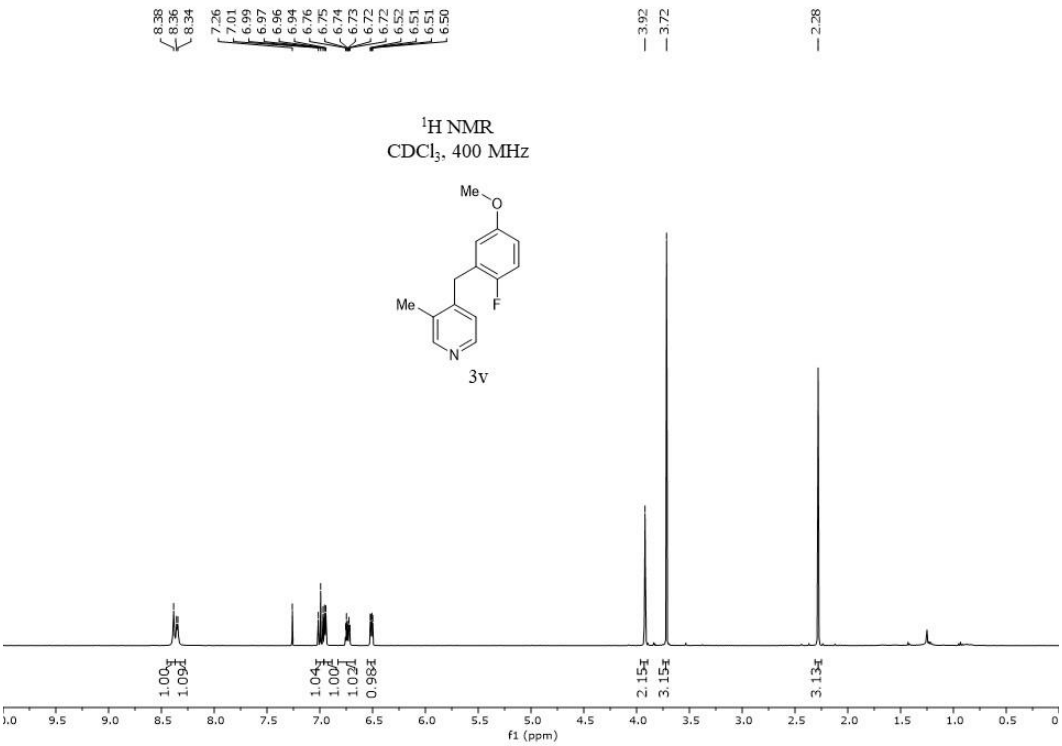

8.40
8.39
8.38
7.57
7.55
7.26
7.23
7.22
6.97
6.96
4.02
2.23
1H NMR
CDCl3, 400 MHz
CF3
Me
N
3t
2.07
2.05
2.03
1.00
2.12
3.14
f1 (ppm)

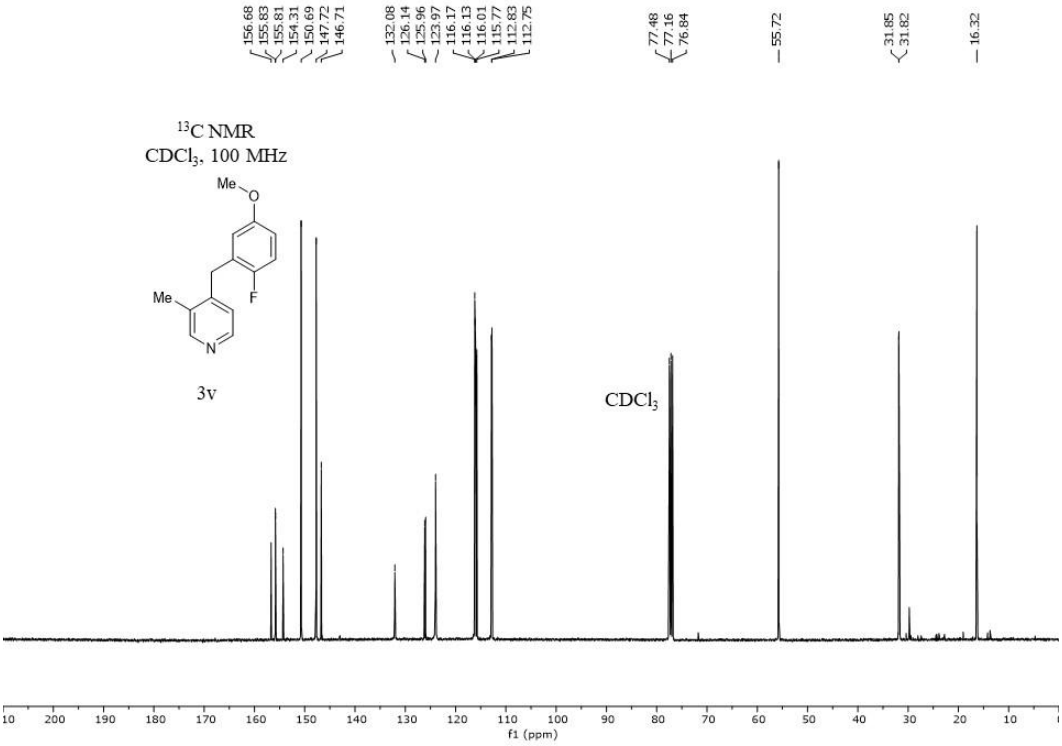

151.02
147.91
146.91
142.48
132.20
129.60
129.27
128.96
128.32
125.80
125.76
125.72
125.68
125.61
124.44
122.91
120.21
77.48
77.16
76.84
38.63
16.49
^{13}C NMR
$CDCl_3$, 100 MHz
CF_3
Me
N
3t
$CDCl_3$
f1 (ppm)

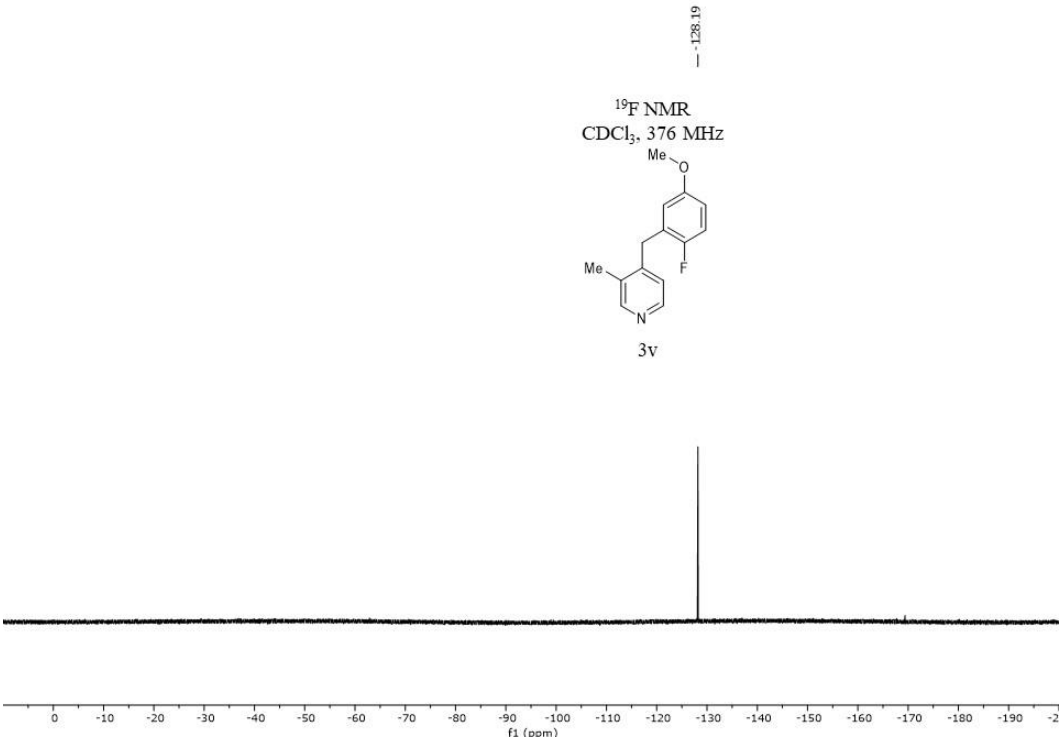

-62.51
^{19}F NMR
$CDCl_3$, 376 MHz
CF_3
Me
N
3t
f1 (ppm)


8.42
8.40
7.26
7.24
6.98
6.98
6.97
3.91
2.23
^{1}H NMR
$CDCl_3$, 400 MHz
Cl
Cl
Me
N
3u
2.18
1.00
3.19
2.35
3.39
f1 (ppm)


151.19
148.07
146.13
141.77
135.33
132.09
127.37
127.05
124.42
77.48
77.16
76.84
38.19
16.50
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
Cl
Me
N
3u
$CDCl_3$
f1 (ppm)

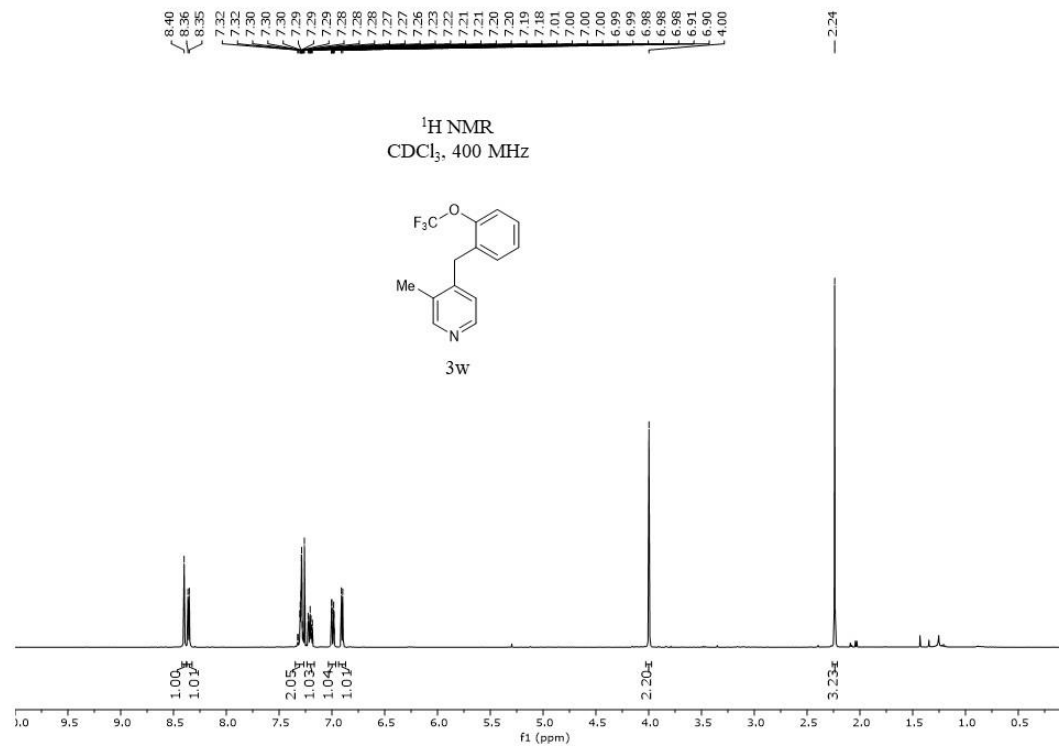

8.38
8.36
8.34
7.26
7.01
6.99
6.97
6.96
6.94
6.76
6.75
6.74
6.73
6.72
6.72
6.52
6.51
6.51
6.50
3.92
3.72
2.28
1H NMR
CDCl3, 400 MHz
Me
O
Me
F
N
3v
1.00
1.09
1.04
1.00
1.02
0.98
2.15
3.15
3.13
f1 (ppm)


156.68
155.83
155.81
154.31
150.69
147.72
146.71
132.08
126.14
125.96
123.97
116.17
116.13
116.01
115.77
112.83
112.75
77.48
77.16
76.84
55.72
31.85
31.82
16.32
13C NMR
CDCl3, 100 MHz
Me
O
Me
F
N
3v
CDCl3
f1 (ppm)



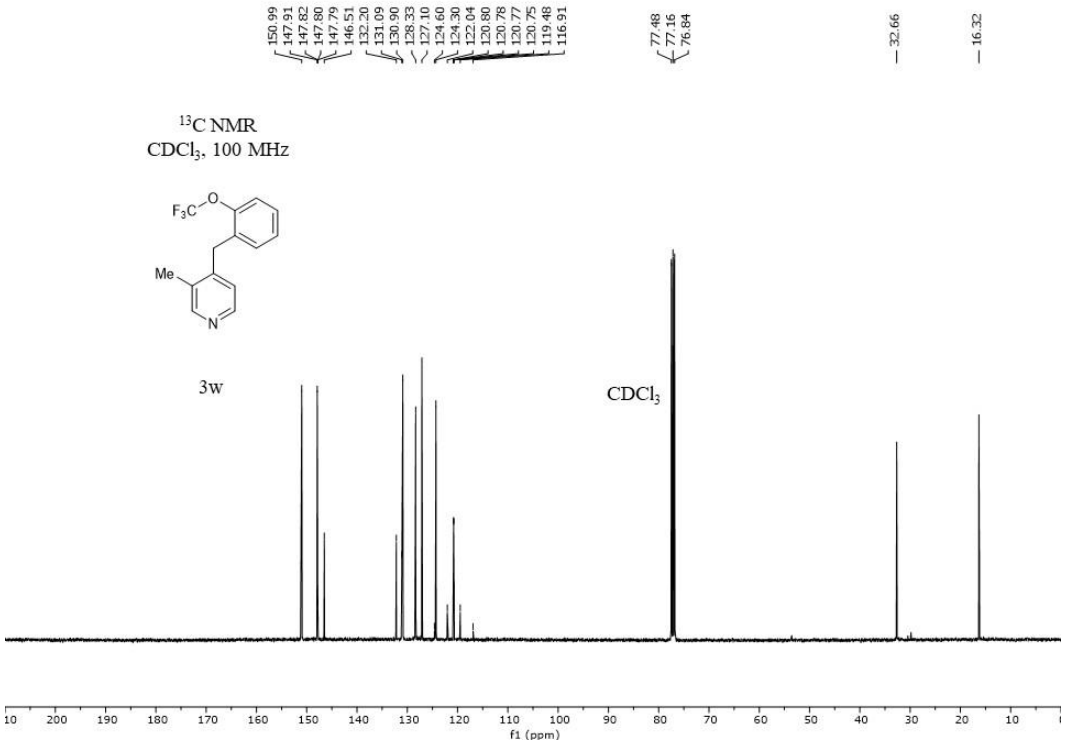
^{19}F NMR
$CDCl_3$, 376 MHz

3v



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

3w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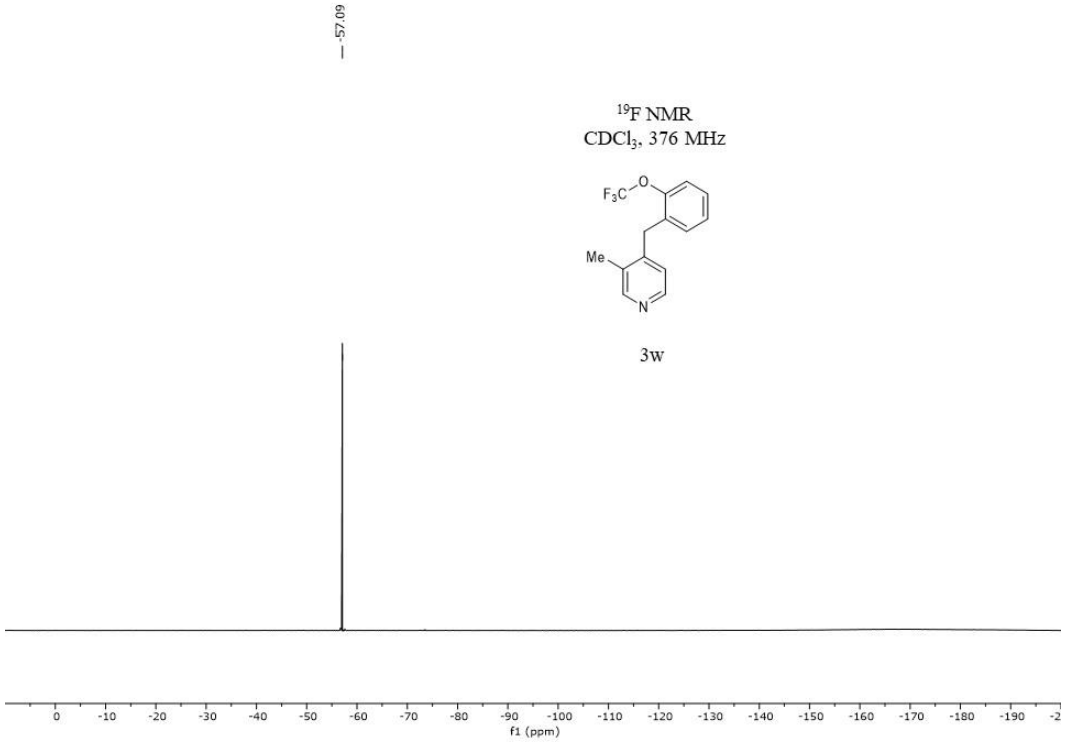
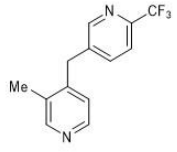
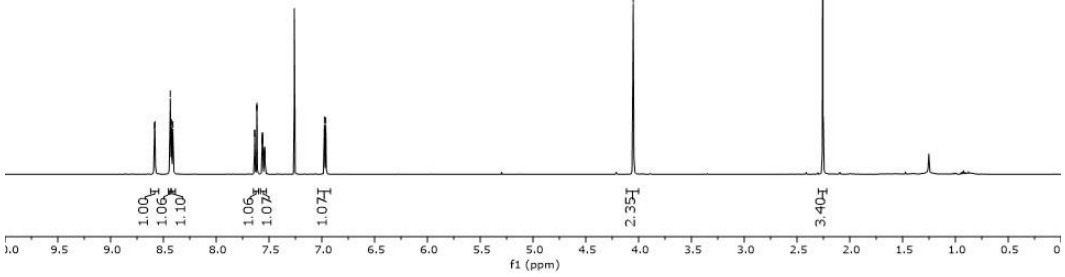
147.91
147.82
147.80
147.79
146.51
132.20
131.09
130.90
128.33
127.10
124.60
124.30
122.04
120.80
120.78
120.77
120.75
119.48
116.91
77.48
77.16
76.84
32.66
16.32
13C NMR
CDCl3, 100 MHz
F3C
O
Me
N
3w
CDCl3
f1 (ppm)


-57.09
19F NMR
CDCl3, 376 MHz
F3C
O
Me
N
3w
f1 (ppm)

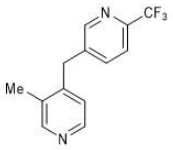
^{1}H NMR
$CDCl_3$, 400 MHz



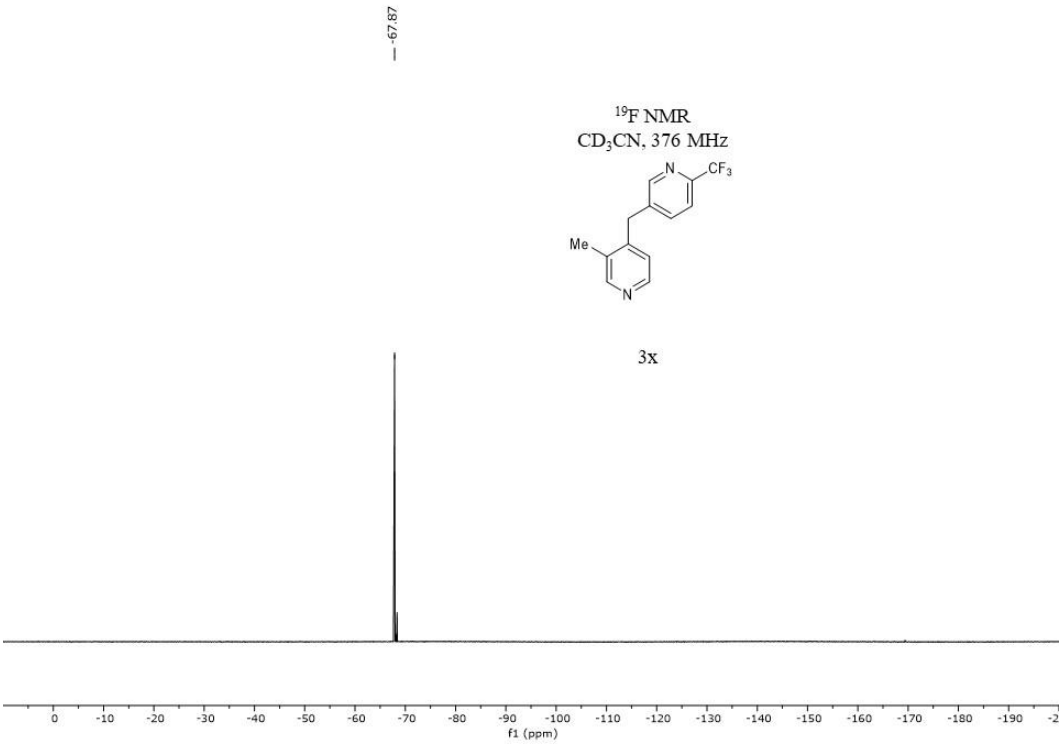
3x



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

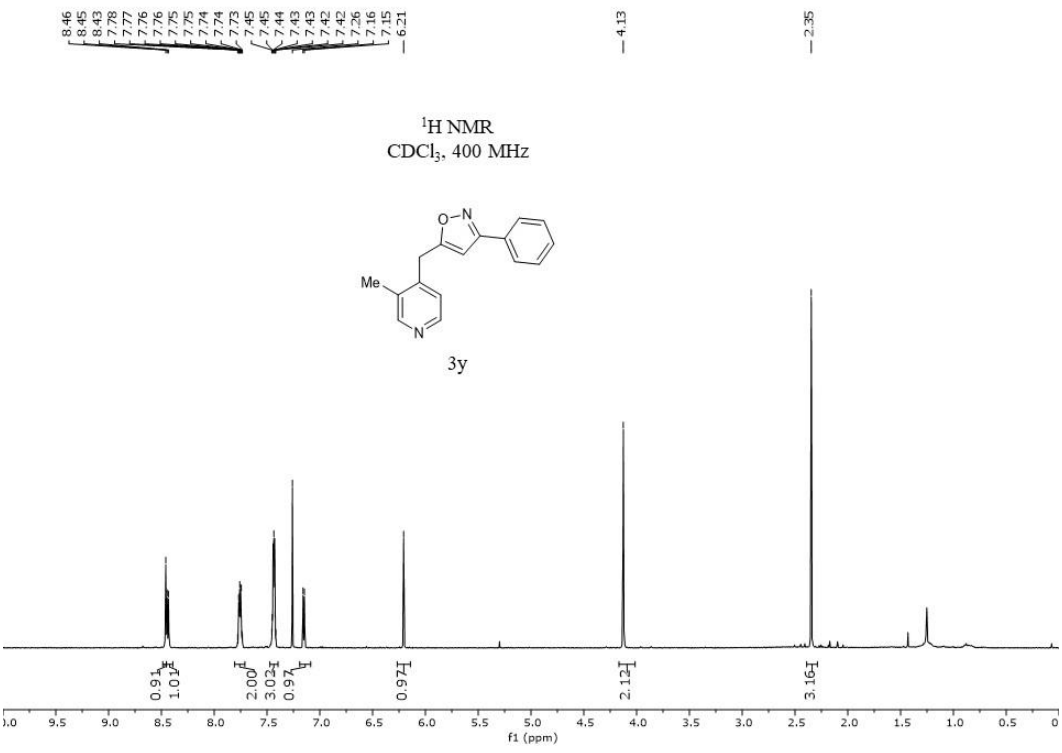


3x



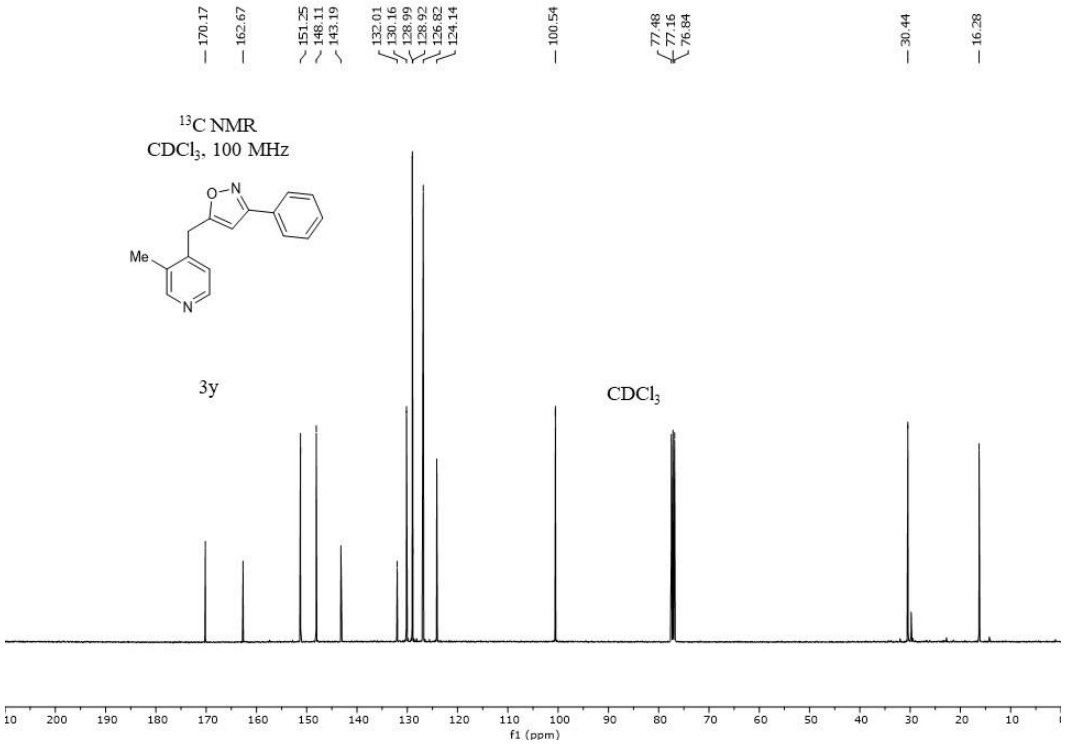
^{19}F NMR
CD_3CN, 376 MHz

3x



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

3y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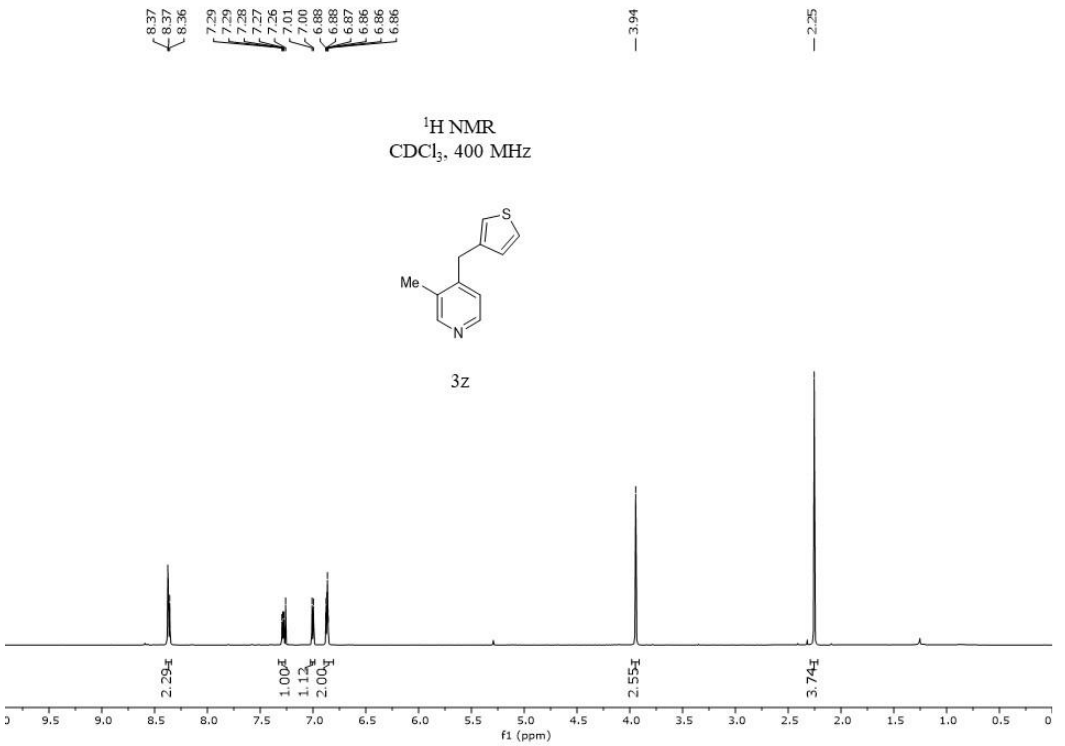
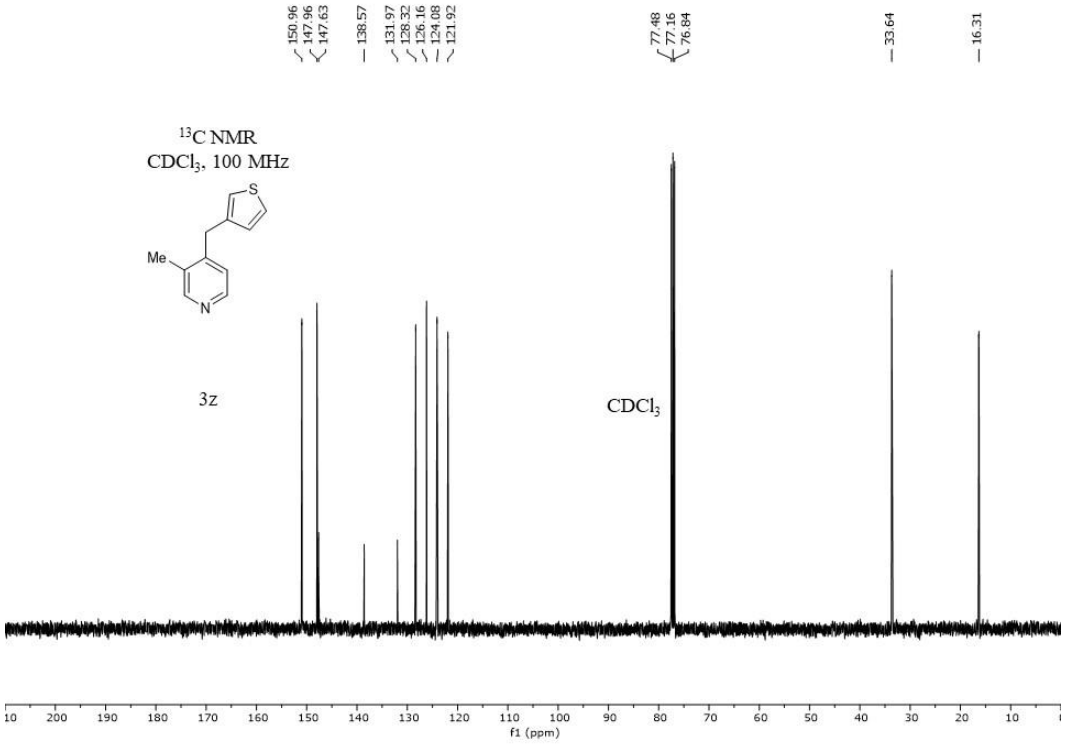
162.67
151.25
148.11
143.19
132.01
130.16
128.99
128.92
126.82
124.14
100.54
77.48
77.16
76.84
30.44
16.28
13C NMR
CDCl3, 100 MHz
Me
3y
CDCl3
f1 (ppm)


8.37
8.37
8.36
7.29
7.29
7.28
7.27
7.26
7.01
7.00
6.88
6.87
6.86
6.86
6.86
3.94
2.25
1H NMR
CDCl3, 400 MHz
Me
3z
2.29
1.00
1.12
2.00
2.55
3.74
f1 (ppm)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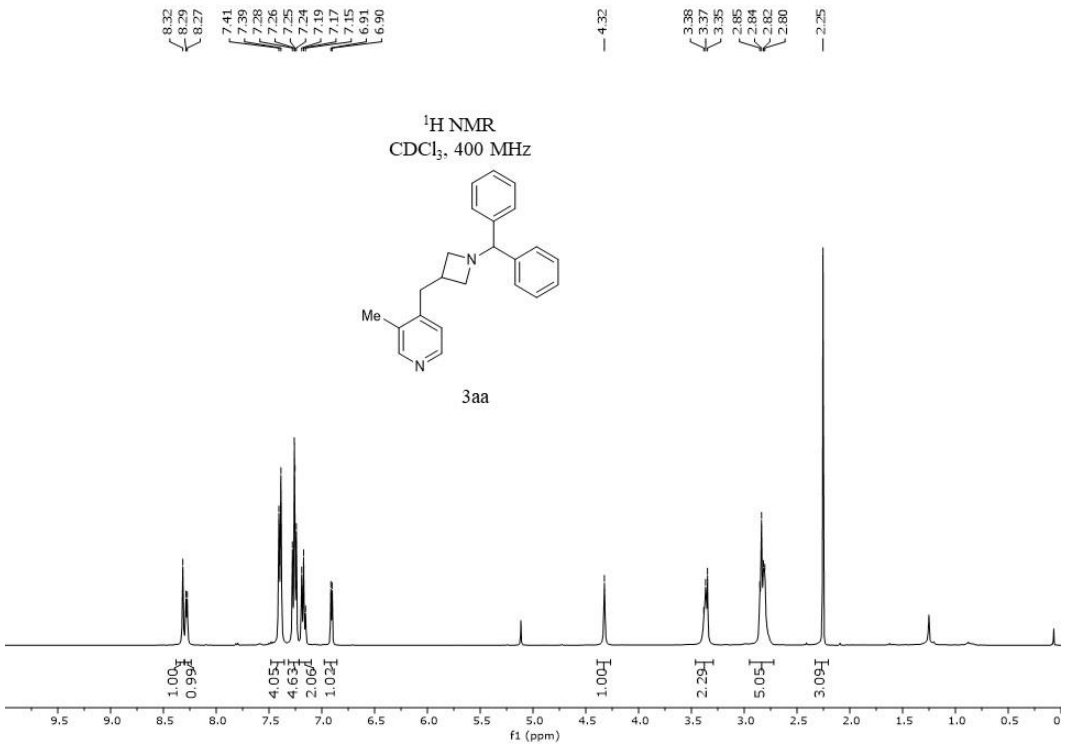
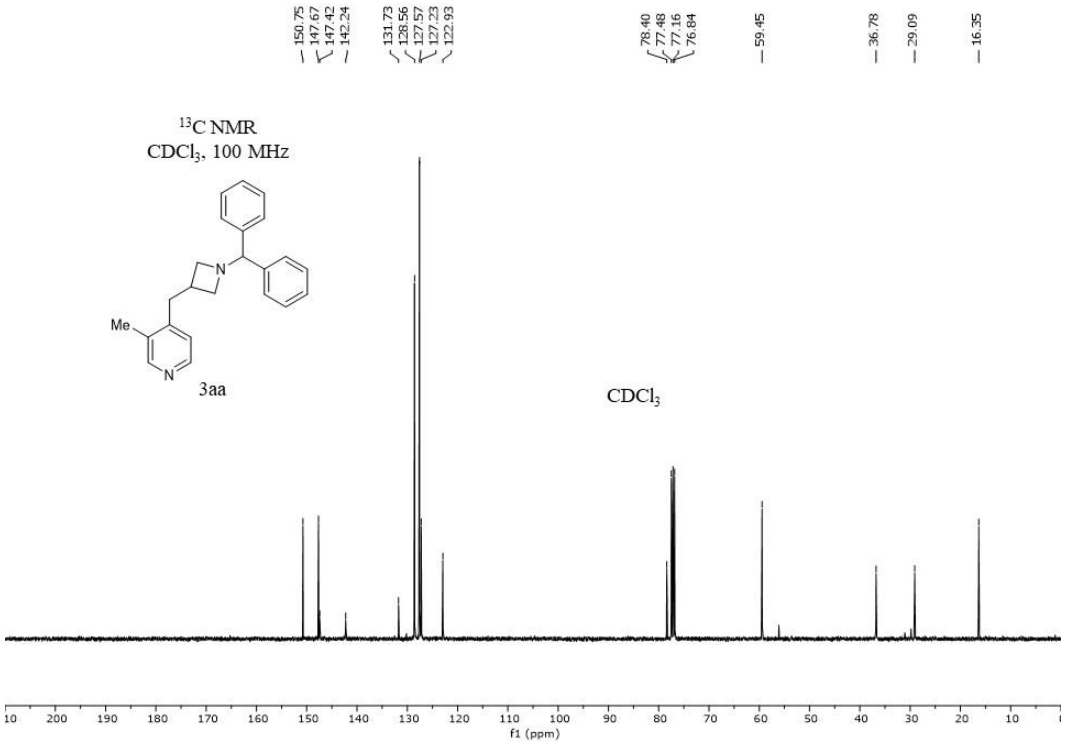
147.96
147.63
138.57
131.97
128.32
126.16
124.08
121.92
77.48
77.16
76.84
33.64
16.31
^{13}C NMR
$CDCl_3$, 100 MHz
S
Me
N
3z
$CDCl_3$
f1 (ppm)


8.32
8.29
8.27
7.41
7.39
7.28
7.26
7.25
7.24
7.19
7.17
7.15
6.91
6.90
4.32
3.38
3.37
3.35
2.85
2.84
2.82
2.80
2.25
^{1}H NMR
$CDCl_3$, 400 MHz
N
Me
N
3aa
1.00
0.99
4.05
4.63
2.06
1.02
1.00
2.29
5.05
3.09
f1 (ppm)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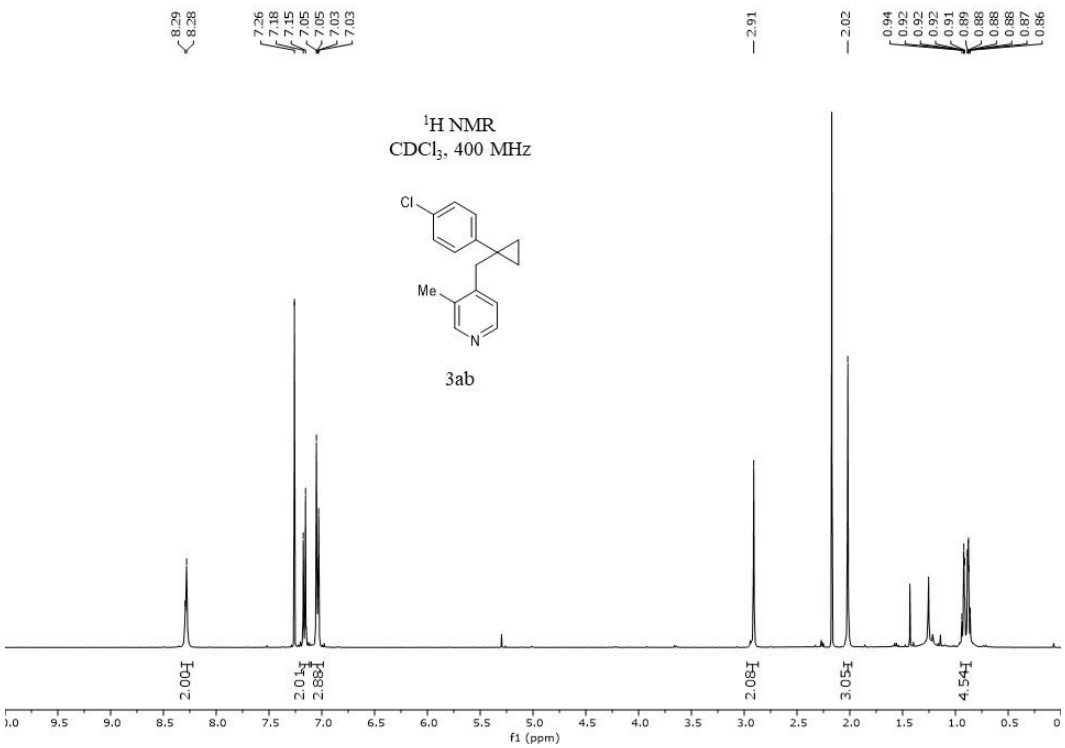
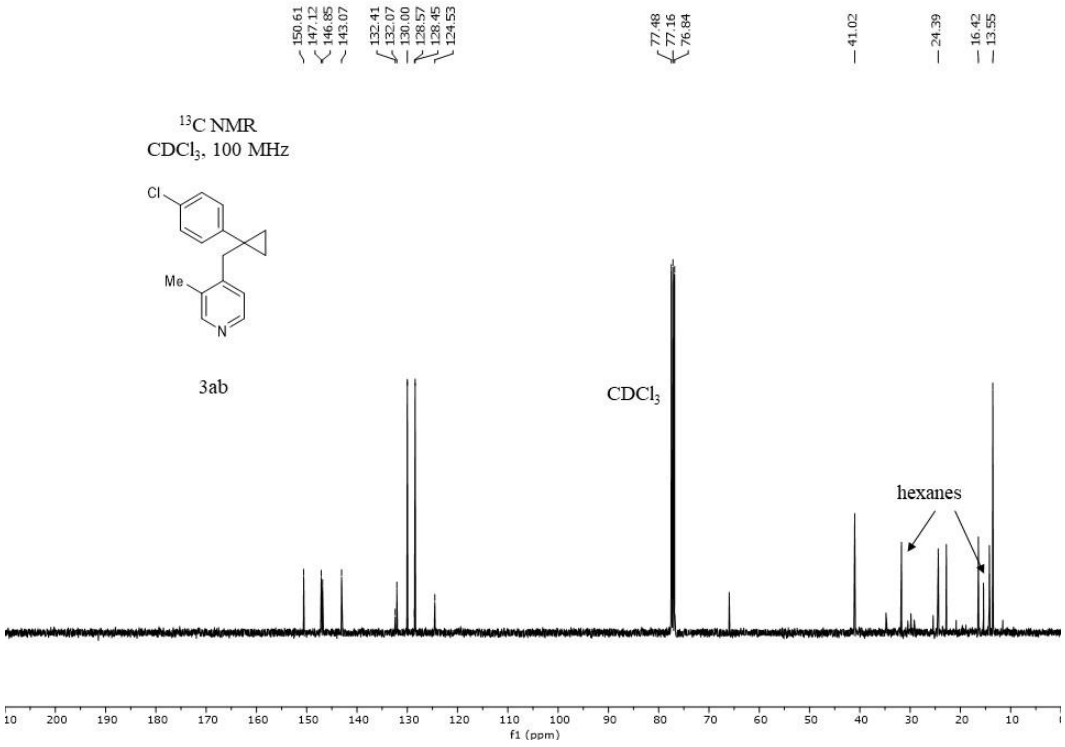
147.42
142.24
131.73
128.56
127.57
127.23
122.93
78.40
77.48
77.16
76.84
59.45
36.78
29.09
16.35
13C NMR
CDCl3, 100 MHz
Me
N
3aa
CDCl3
f1 (ppm)


8.29
8.28
7.26
7.18
7.15
7.05
7.05
7.03
7.03
2.91
2.02
0.94
0.92
0.92
0.92
0.91
0.89
0.88
0.88
0.88
0.87
0.86
1H NMR
CDCl3, 400 MHz
Cl
Me
N
3ab
2.00
2.01
2.88
2.08
3.05
4.54
f1 (ppm)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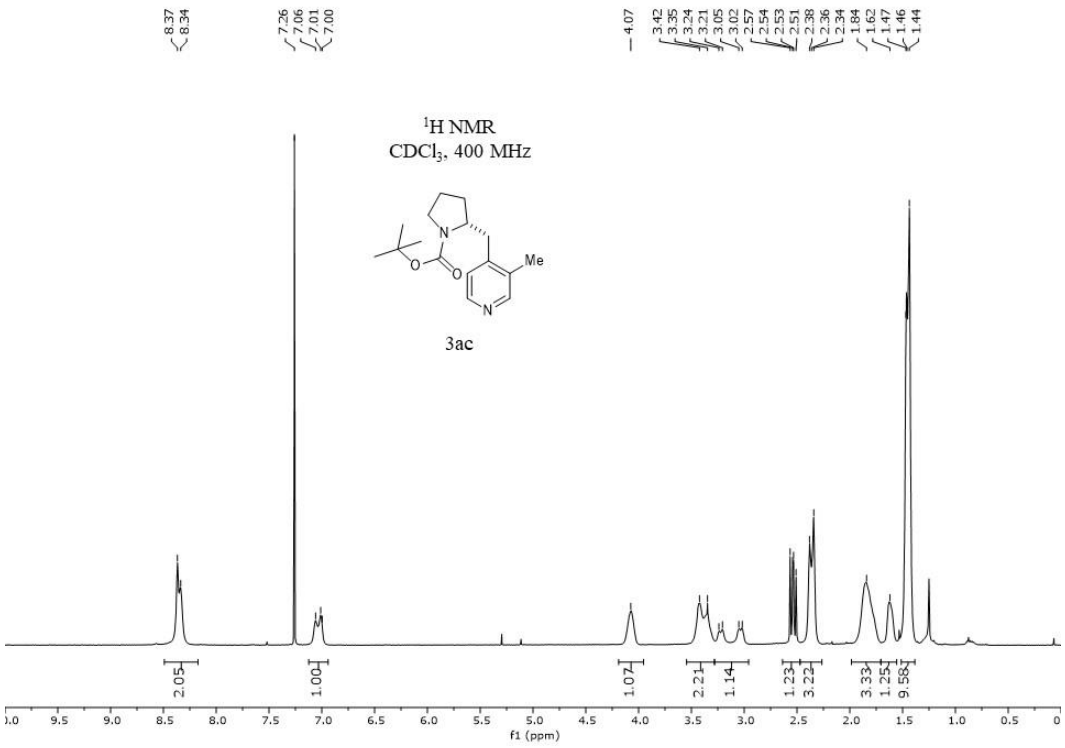
143.07
132.41
132.07
130.00
128.57
128.45
124.53
77.48
77.16
76.84
41.02
24.39
16.42
13.55
13C NMR
CDCl3, 100 MHz
Cl
Me
N
3ab
CDCl3
hexanes
f1 (ppm)


8.37
8.34
7.26
7.06
7.01
7.00
4.07
3.42
3.35
3.24
3.21
3.05
3.02
2.57
2.54
2.53
2.51
2.38
2.36
2.34
1.84
1.62
1.47
1.46
1.44
1H NMR
CDCl3, 400 MHz
N
O
O
Me
N
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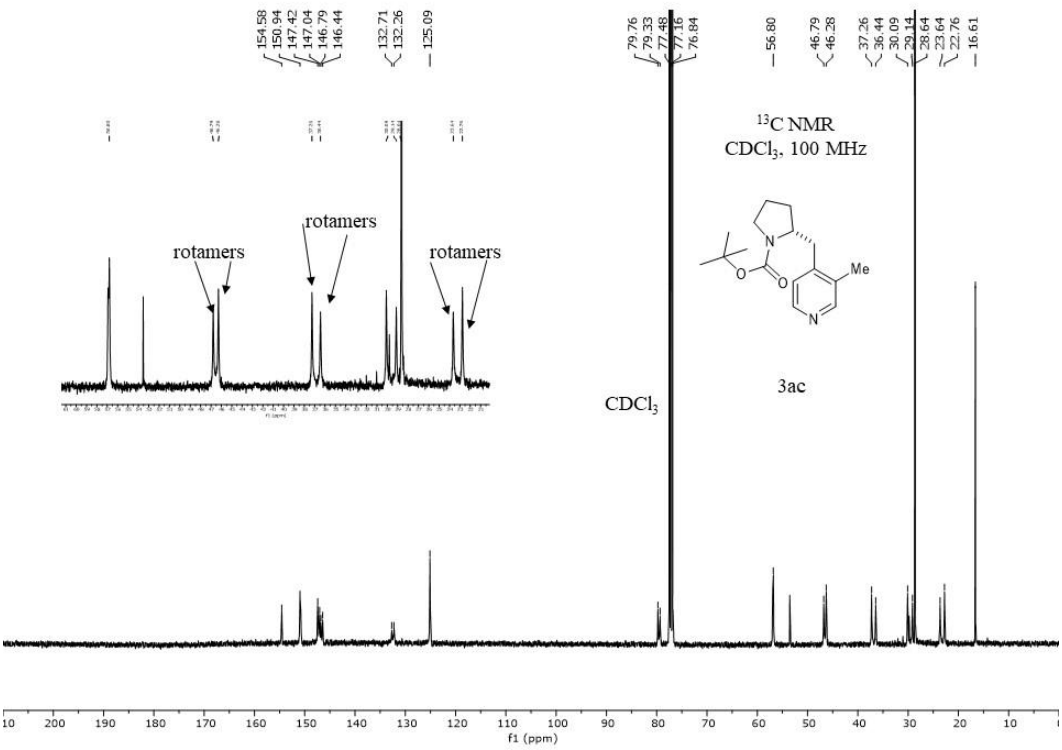
3.22
3.33
1.25
9.58
f1 (ppm)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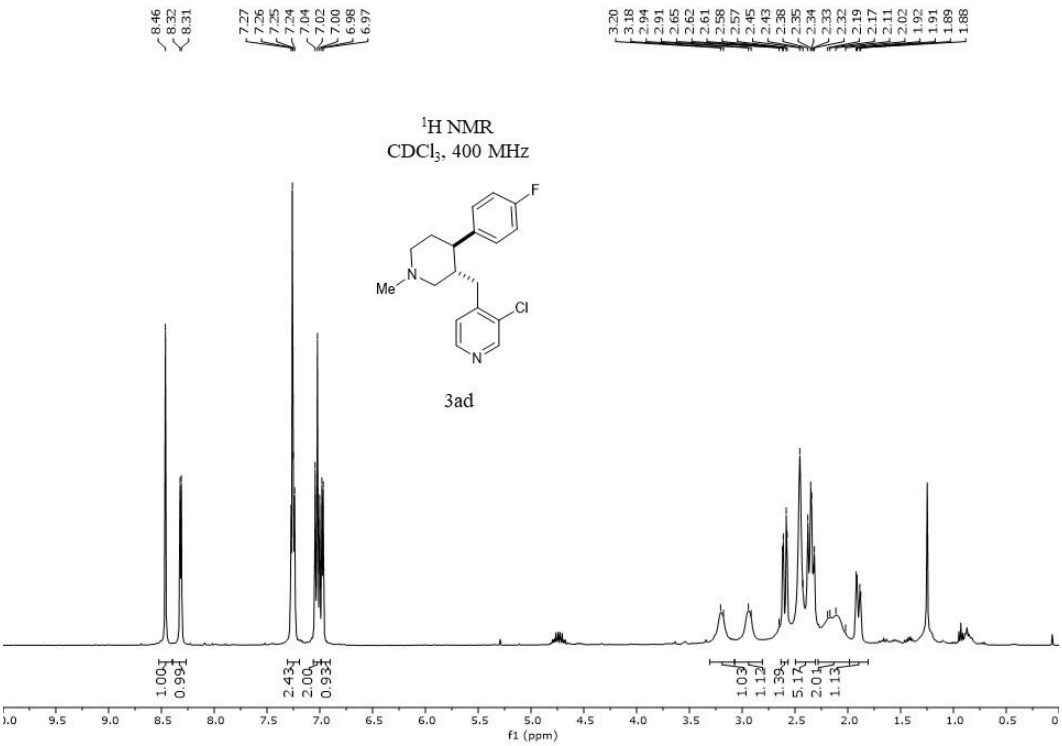
147.04
146.79
146.44
132.71
132.26
125.09
79.76
79.33
77.48
77.16
76.84
56.80
46.79
46.28
37.26
36.44
30.09
29.14
28.64
23.64
22.76
16.61
rotamers
rotamers
rotamers
^{13}C NMR
$CDCl_3$, 100 MHz
Me
3ac
$CDCl_3$
f1 (ppm)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8.32
8.31
7.27
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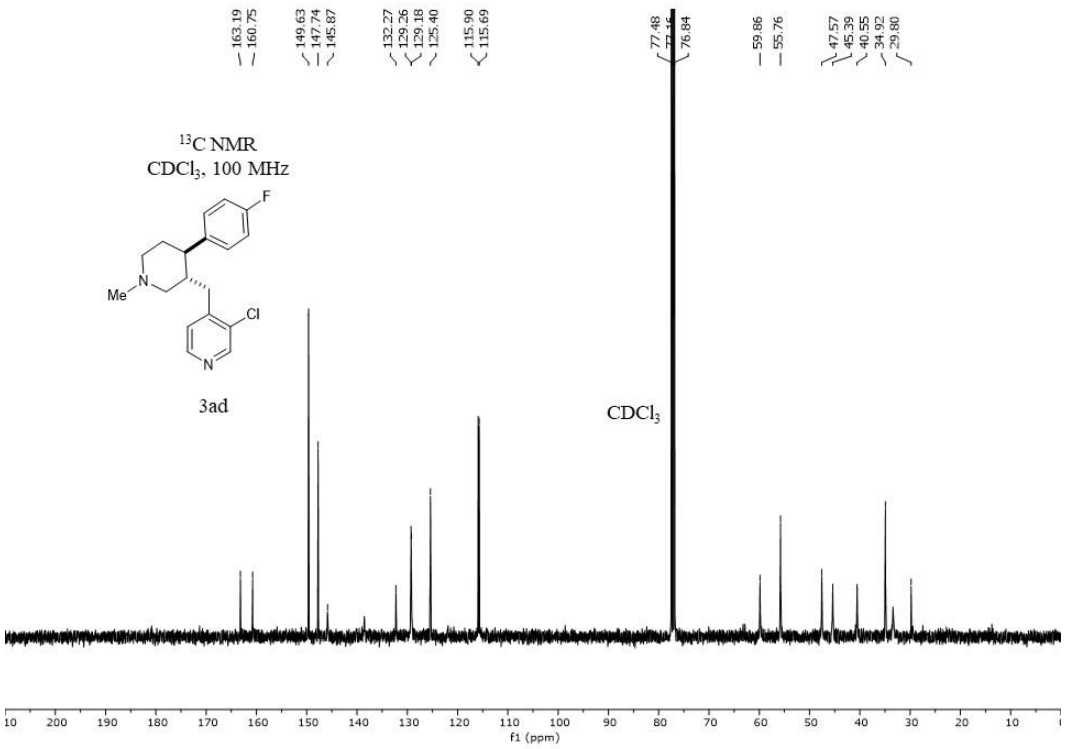
7.25
7.24
7.04
7.02
7.00
6.98
6.97
3.20
3.18
2.94
2.91
2.65
2.62
2.61
2.58
2.57
2.45
2.43
2.38
2.35
2.34
2.33
2.32
2.19
2.17
2.11
2.02
1.92
1.91
1.89
1.88
^{1}H NMR
$CDCl_3$, 400 MHz
F
Me
Cl
3ad
1.00
0.99
2.43
2.00
0.93
1.03
1.12
1.39
5.17
2.01
1.13
f1 (ppm)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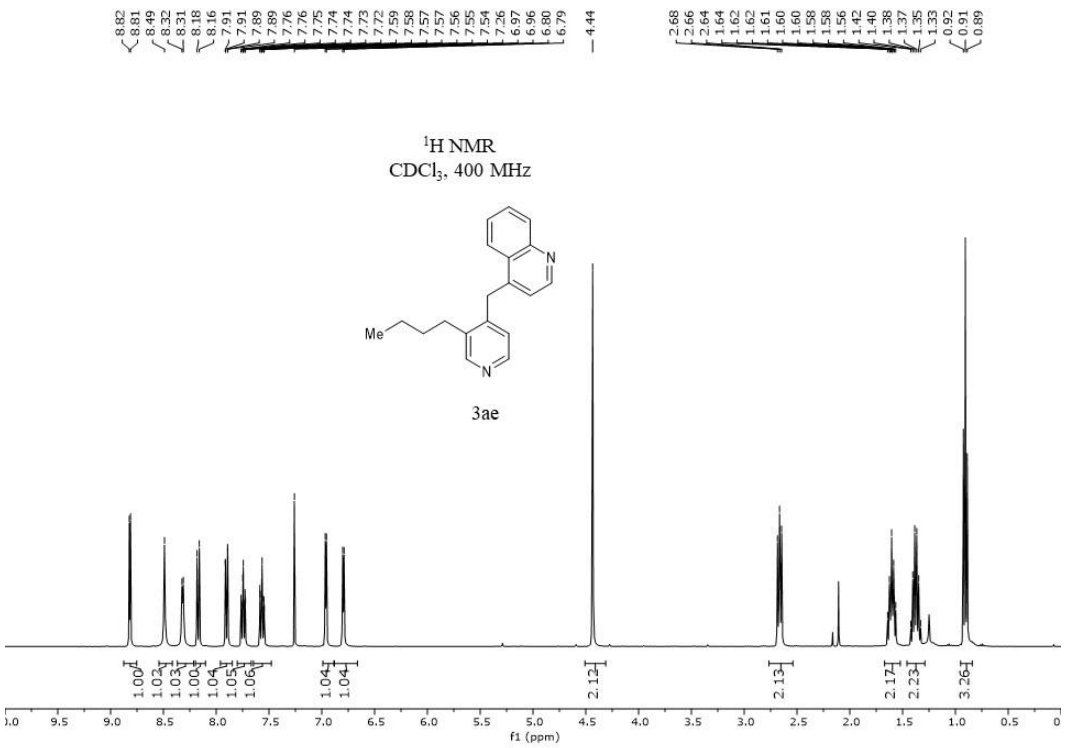
160.75
149.63
147.74
145.87
132.27
129.26
129.18
125.40
115.90
115.69
77.48
77.16
76.84
59.86
55.76
47.57
45.39
40.55
34.92
29.80
13C NMR
CDCl3, 100 MHz
F
Me
N
Cl
N
3ad
CDCl3
f1 (ppm)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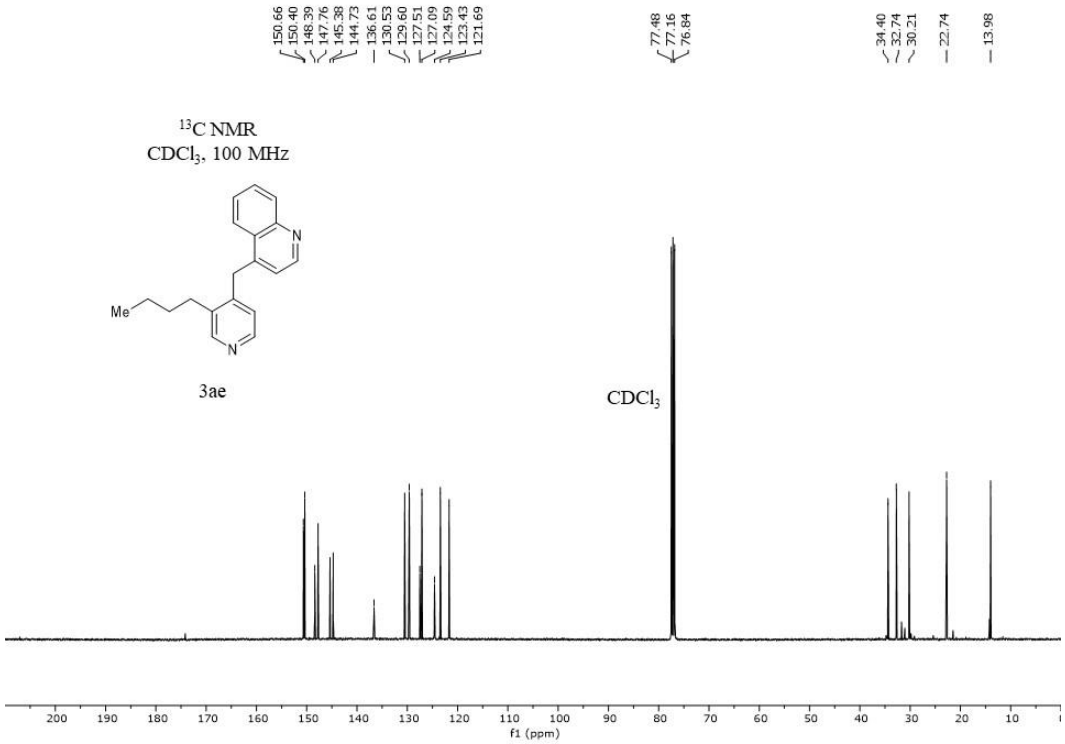
8.18
8.16
7.91
7.91
7.89
7.89
7.76
7.76
7.75
7.74
7.74
7.73
7.72
7.59
7.58
7.57
7.57
7.56
7.55
7.54
7.26
6.97
6.96
6.80
6.79
4.44
2.68
2.66
2.64
1.64
1.62
1.62
1.61
1.60
1.60
1.58
1.58
1.56
1.42
1.40
1.38
1.37
1.35
1.33
0.92
0.91
0.89
1H NMR
CDCl3, 400 MHz
N
Me
N
3ae
1.00
1.02
1.03
1.00
1.04
1.05
1.06
1.04
1.04
2.12
2.13
2.17
2.23
3.26
f1 (ppm)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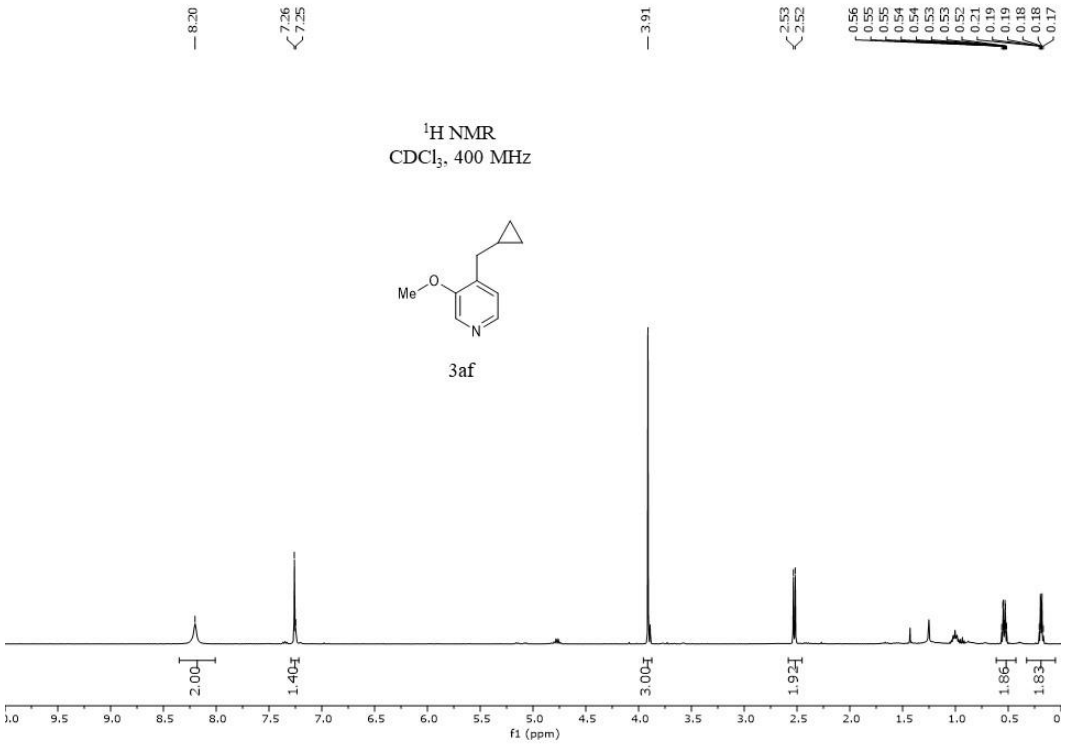
147.76
145.38
144.73
136.61
130.53
129.60
127.51
127.09
124.59
123.43
121.69
77.48
77.16
76.84
34.40
32.74
30.21
22.74
13.98
^{13}C NMR
$CDCl_3$, 100 MHz
Me
N
N
3ae
$CDCl_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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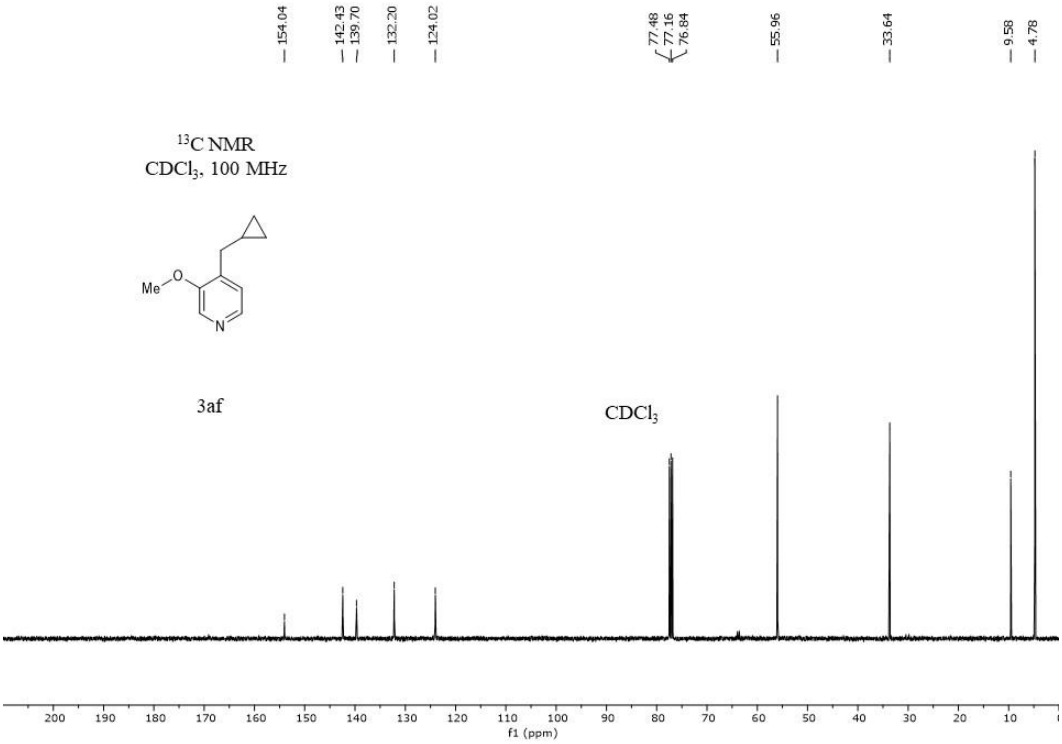
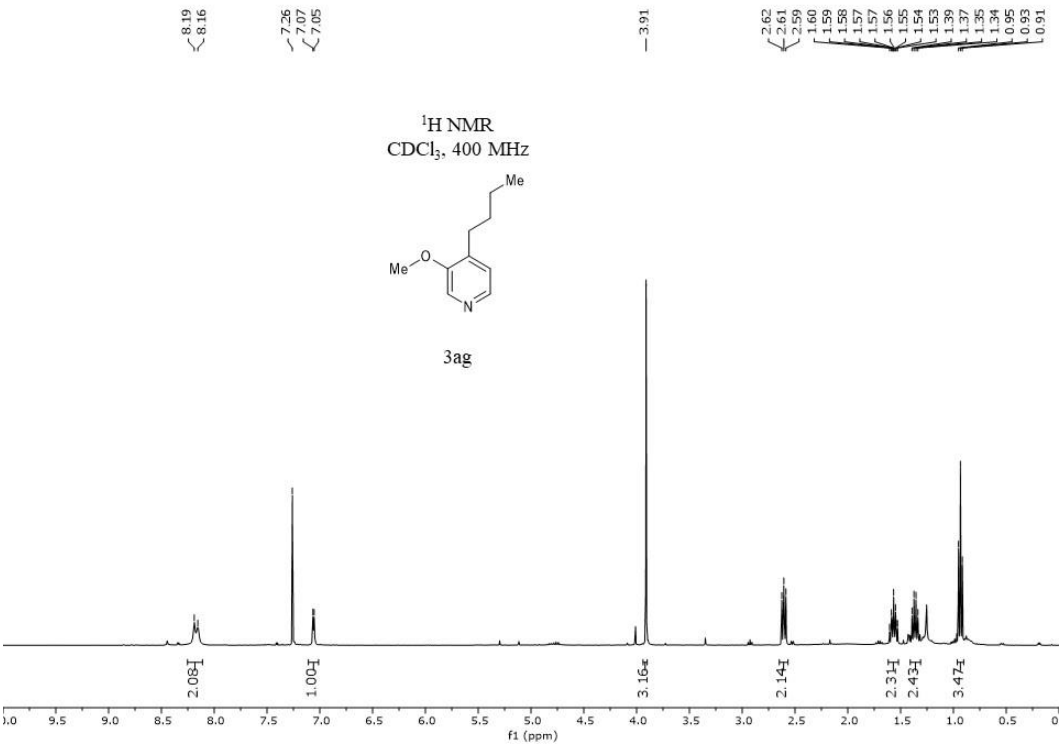
7.26
7.25
3.91
2.53
2.52
0.56
0.55
0.55
0.54
0.54
0.53
0.53
0.52
0.21
0.19
0.19
0.18
0.18
0.17
^{1}H NMR
$CDCl_3$, 400 MHz
Me
O
N
3af
2.00
1.40
3.00
1.92
1.86
1.83
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)


154.04
142.43
139.70
132.20
124.02
77.48
77.16
76.84
55.96
33.64
9.58
4.78
13C NMR
CDCl3, 100 MHz
Me
O
N
3af
CDCl3
f1 (ppm)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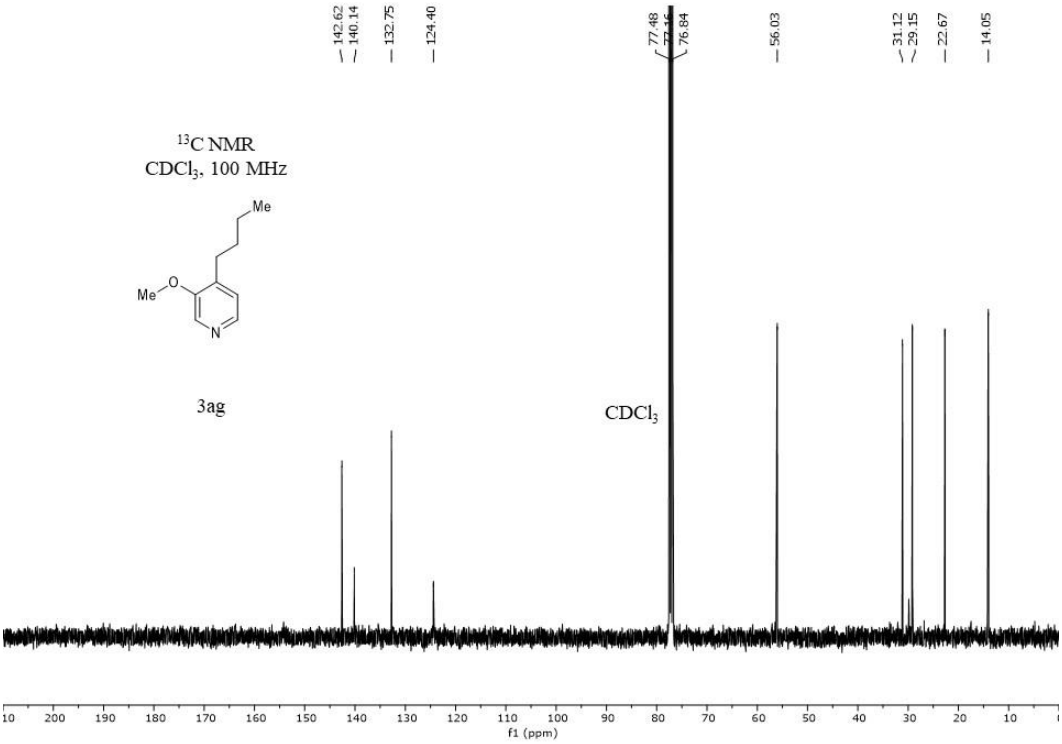
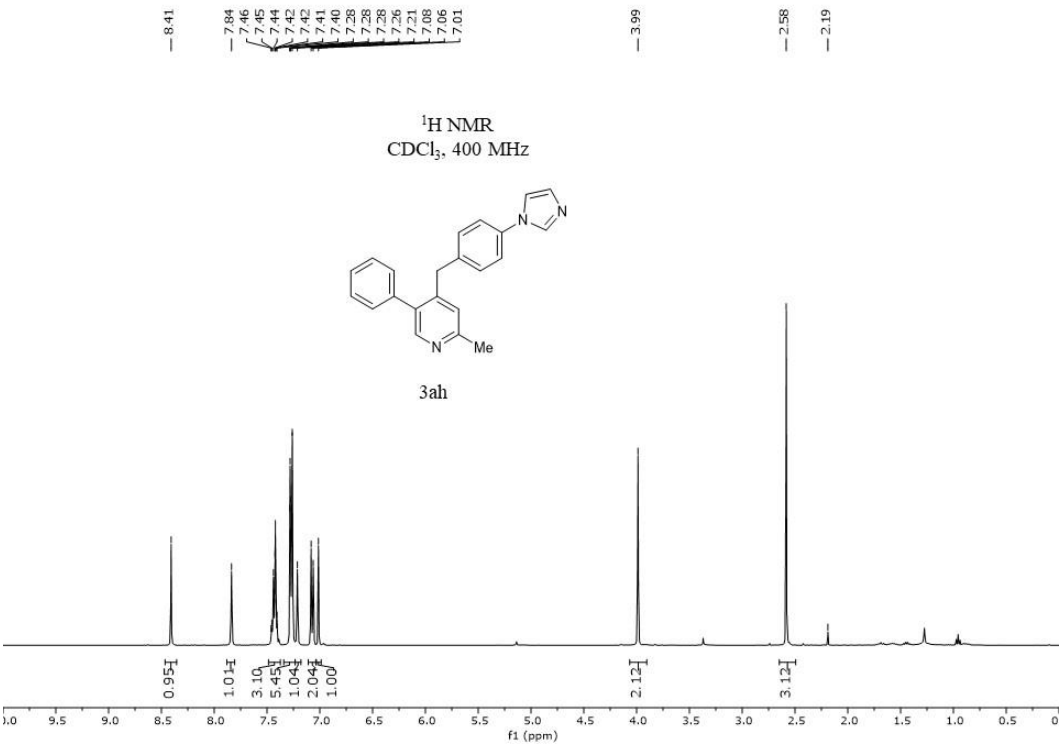
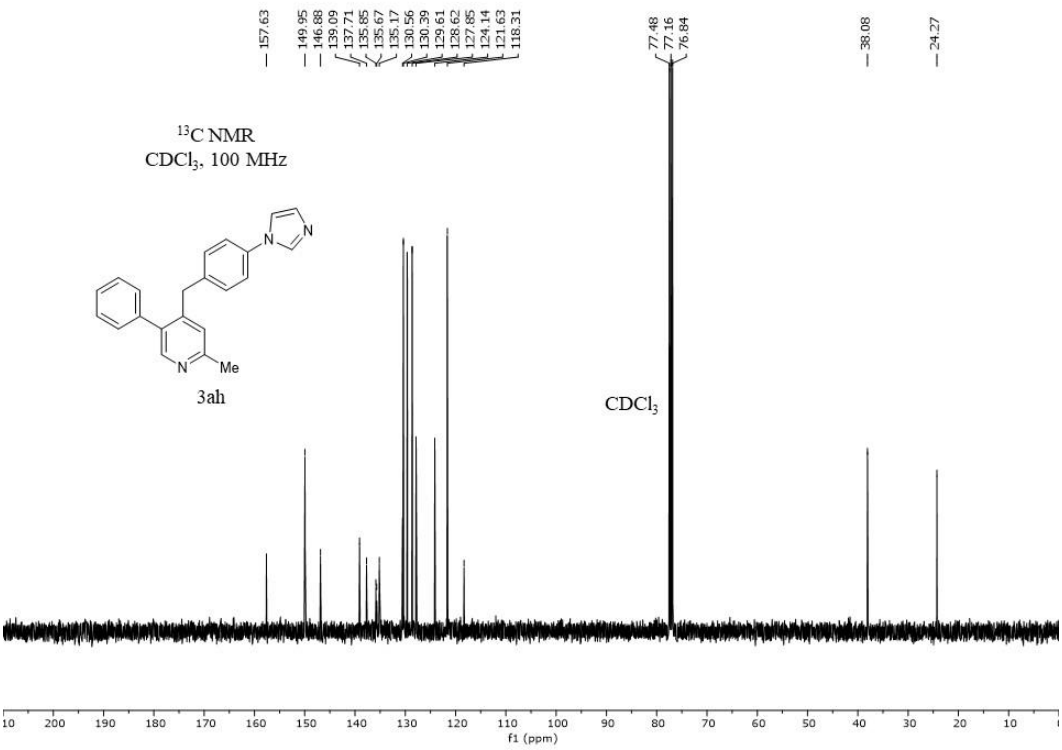
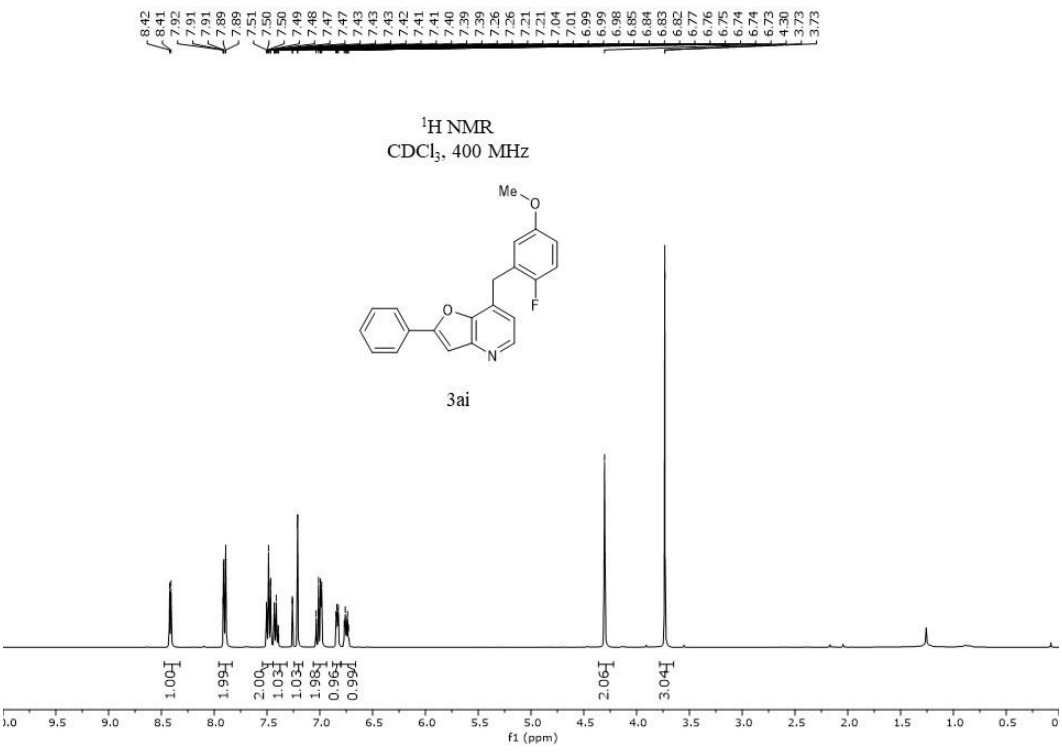
7.26
7.07
7.05
3.91
2.62
2.61
2.59
1.60
1.59
1.58
1.57
1.56
1.55
1.54
1.53
1.39
1.37
1.35
1.34
0.95
0.93
0.91
1H NMR
CDCl3, 400 MHz
Me
Me
O
N
3ag
2.08
1.00
3.16
2.14
2.31
2.43
3.47
f1 (ppm)


142.62
140.14
132.75
124.40
77.48
76.84
56.03
31.12
29.15
22.67
14.05
13C NMR
CDCl3, 100 MHz
Me
Me
O
N
3ag
CDCl3
f1 (ppm)


8.41
7.84
7.46
7.45
7.44
7.42
7.42
7.41
7.40
7.28
7.28
7.28
7.26
7.21
7.08
7.06
7.01
3.99
2.58
2.19
1H NMR
CDCl3, 400 MHz
N
N
N
Me
3ah
0.95
1.01
3.10
5.45
1.04
2.04
1.00
2.12
3.12
f1 (ppm)


157.63
149.95
146.88
139.09
137.71
135.85
135.67
135.17
130.56
130.39
129.61
128.62
127.85
124.14
121.63
118.31
77.48
77.16
76.84
38.08
24.27
13C NMR
CDCl3, 100 MHz
N
N
N
Me
3ah
CDCl3
f1 (ppm)


8.42
8.41
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7.91
7.91
7.89
7.89
7.51
7.50
7.50
7.49
7.48
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7.47
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7.21
7.21
7.04
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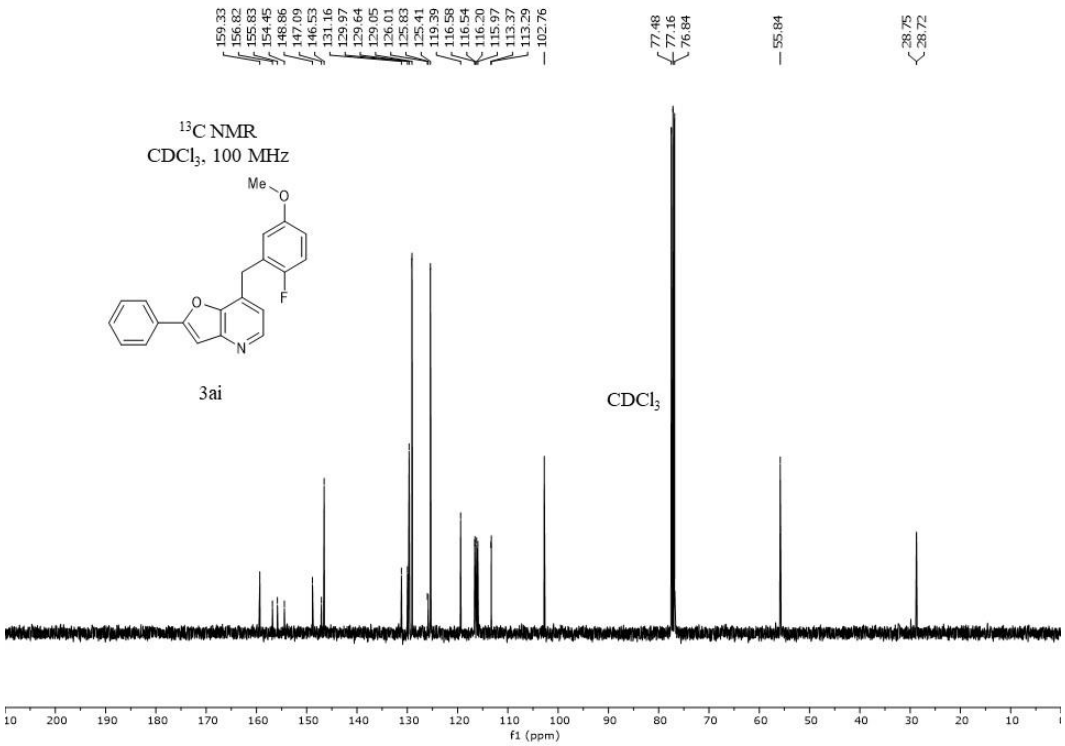
6.83
6.82
6.77
6.76
6.75
6.74
6.74
6.73
4.30
3.73
3.73
1H NMR
CDCl3, 400 MHz
Me
O
F
O
N
3ai
1.00
1.99
2.00
1.03
1.03
1.98
0.96
0.99
2.06
3.04
f1 (ppm)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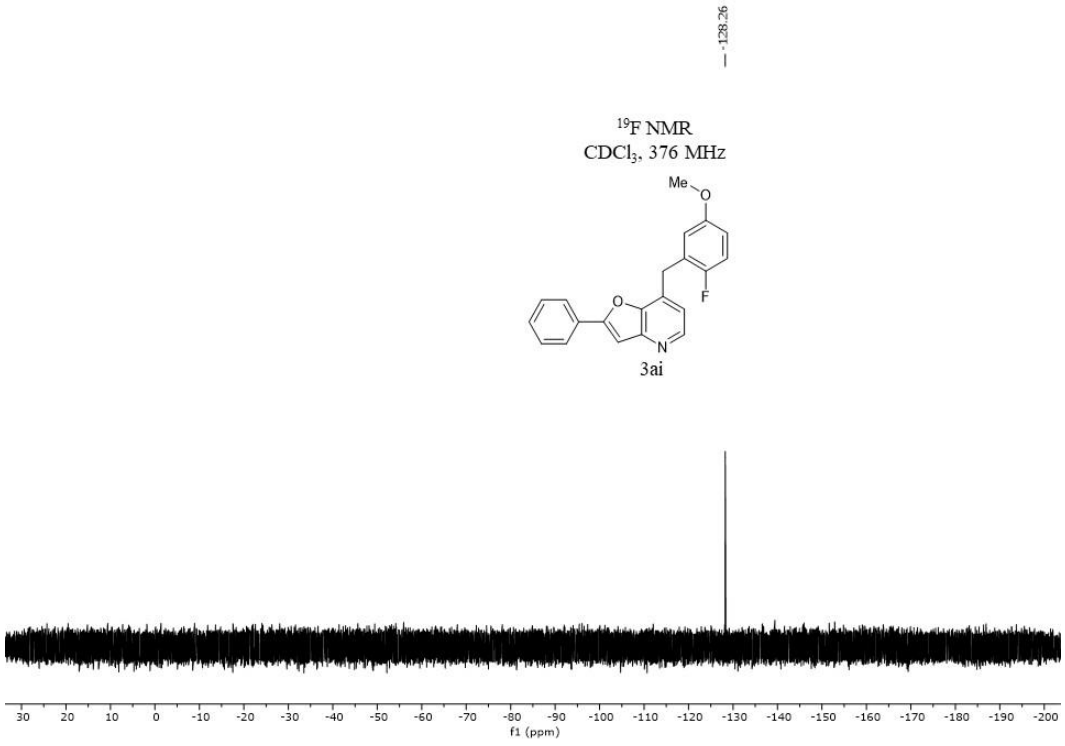
156.82
155.83
154.45
148.86
147.09
146.53
131.16
129.97
129.64
129.05
126.01
125.83
125.41
119.39
116.58
116.54
116.20
115.97
113.37
113.29
102.76
77.48
77.16
76.84
55.84
28.75
28.72
^{13}C NMR
$CDCl_3$, 100 MHz
Me
O
F
O
N
3ai
$CDCl_3$
f1 (ppm)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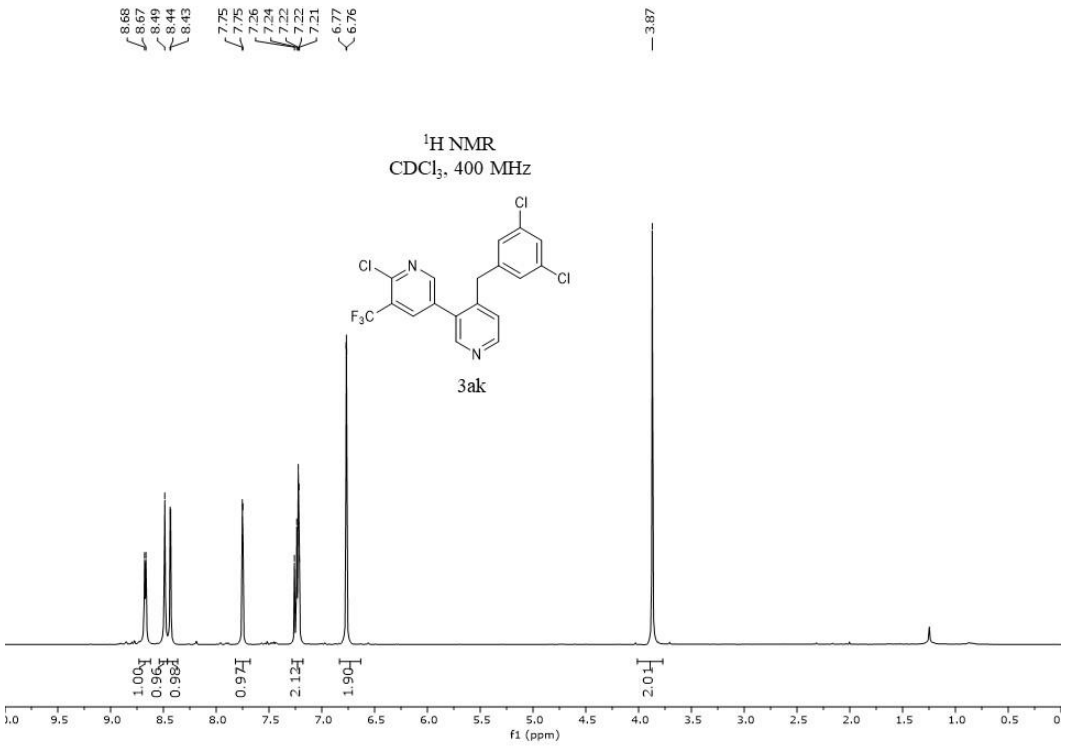
^{19}F NMR
$CDCl_3$, 376 MHz
Me
O
F
O
N
3ai
f1 (ppm)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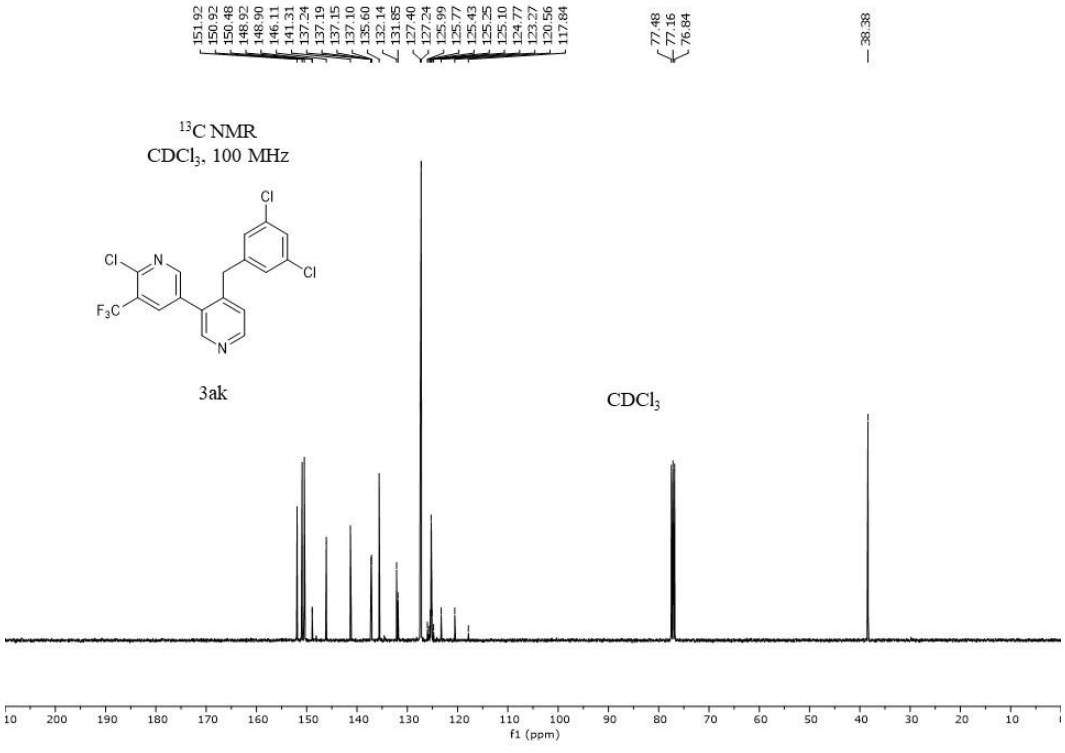
8.67
8.49
8.44
8.43
7.75
7.75
7.26
7.24
7.22
7.22
7.21
6.77
6.76
3.87
^{1}H NMR
$CDCl_3$, 400 MHz
Cl
N
Cl
F_3C
Cl
N
3ak
1.00
0.96
0.98
0.97
2.13
1.90
2.01
f1 (ppm)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146.11
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135.60
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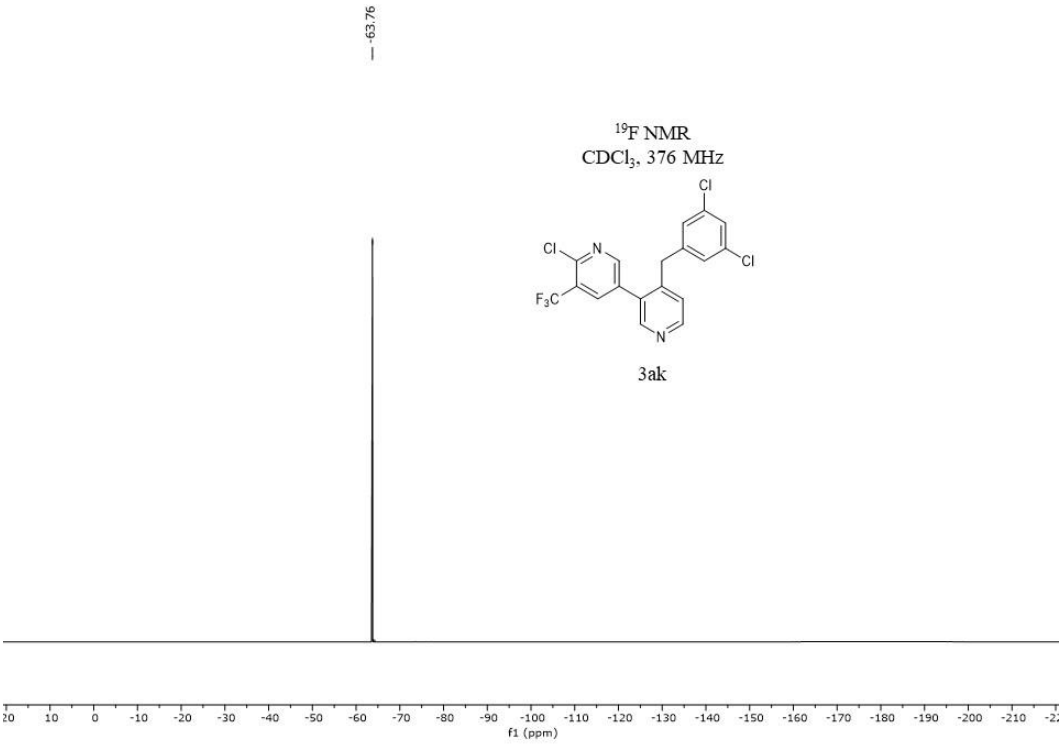
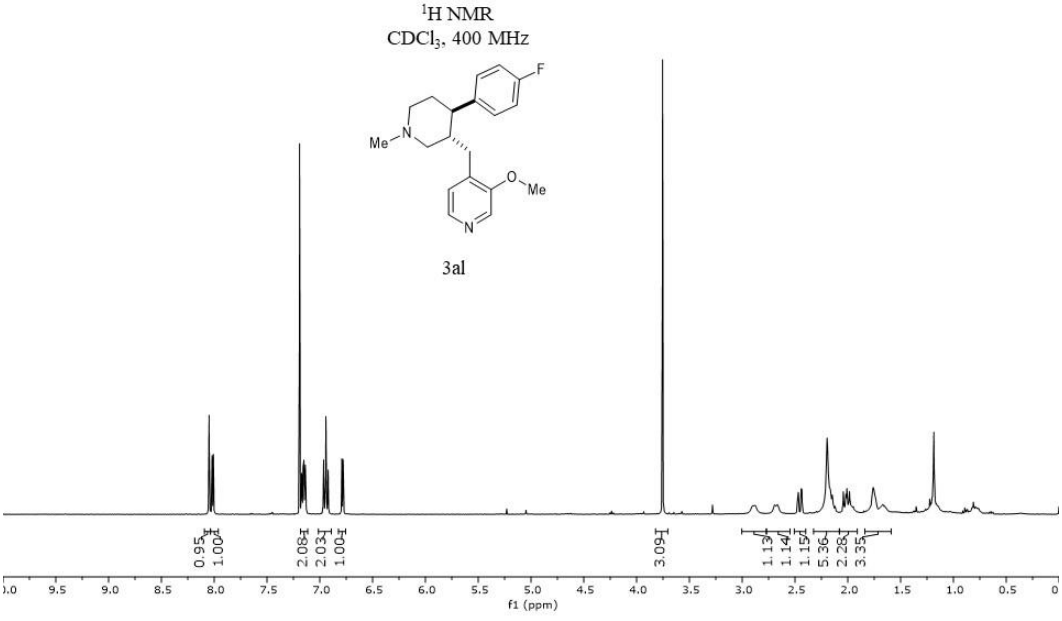
131.85
127.40
127.24
125.99
125.77
125.43
125.25
125.10
124.77
123.27
120.56
117.84
77.48
77.16
76.84
38.38
^{13}C NMR
$CDCl_3$, 100 MHz
Cl
N
Cl
F_3C
Cl
N
3ak
$CDCl_3$
f1 (ppm)



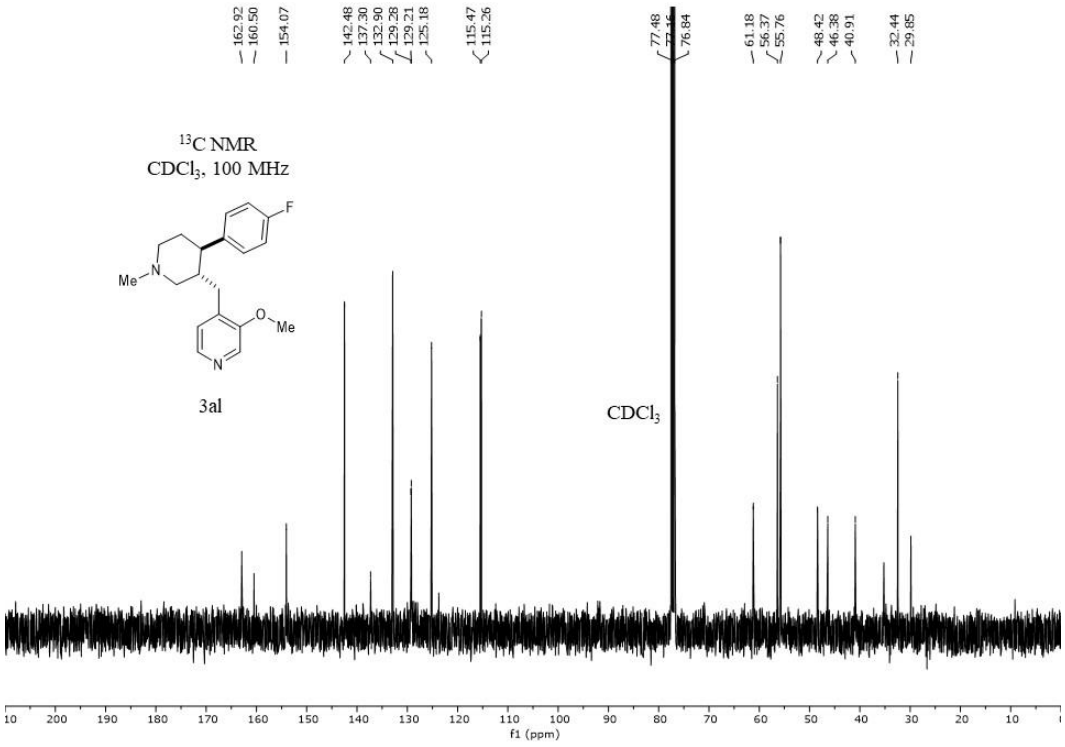
^{19}F NMR
$CDCl_3$, 376 MHz

3ak



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

3al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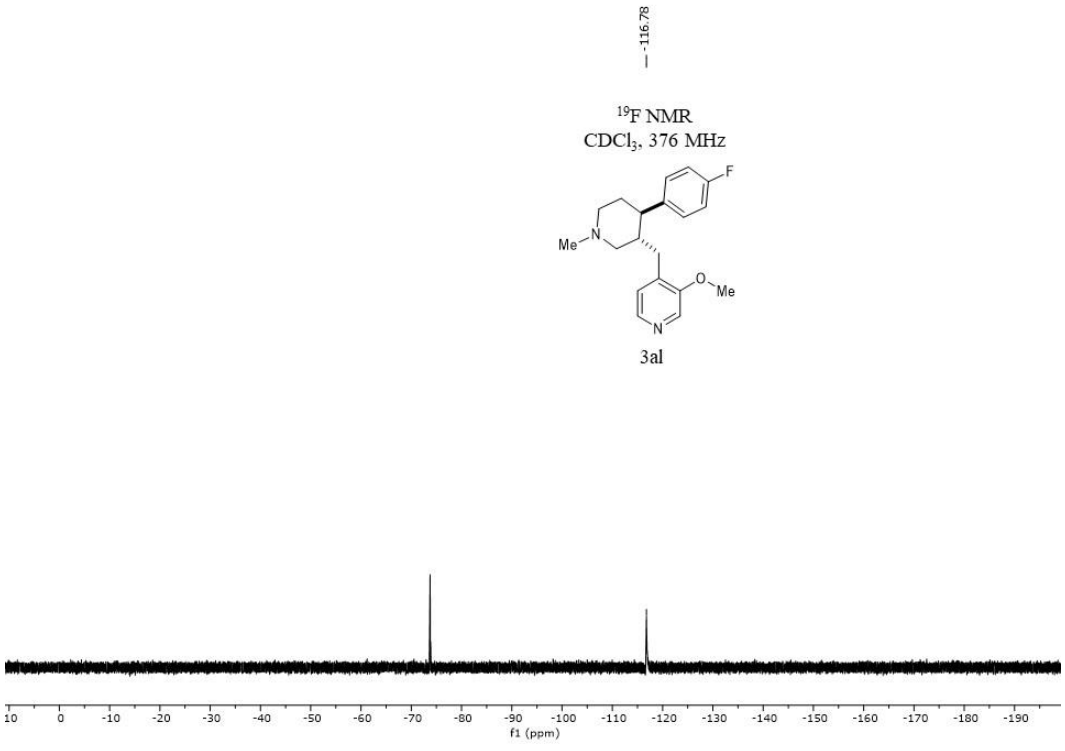
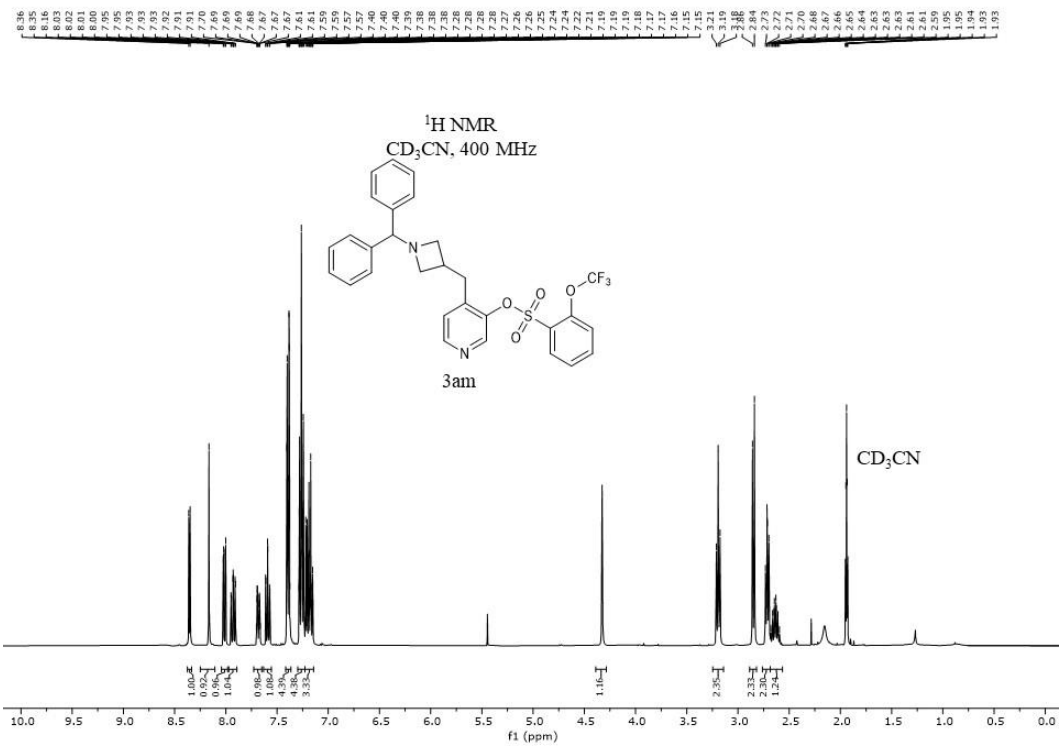
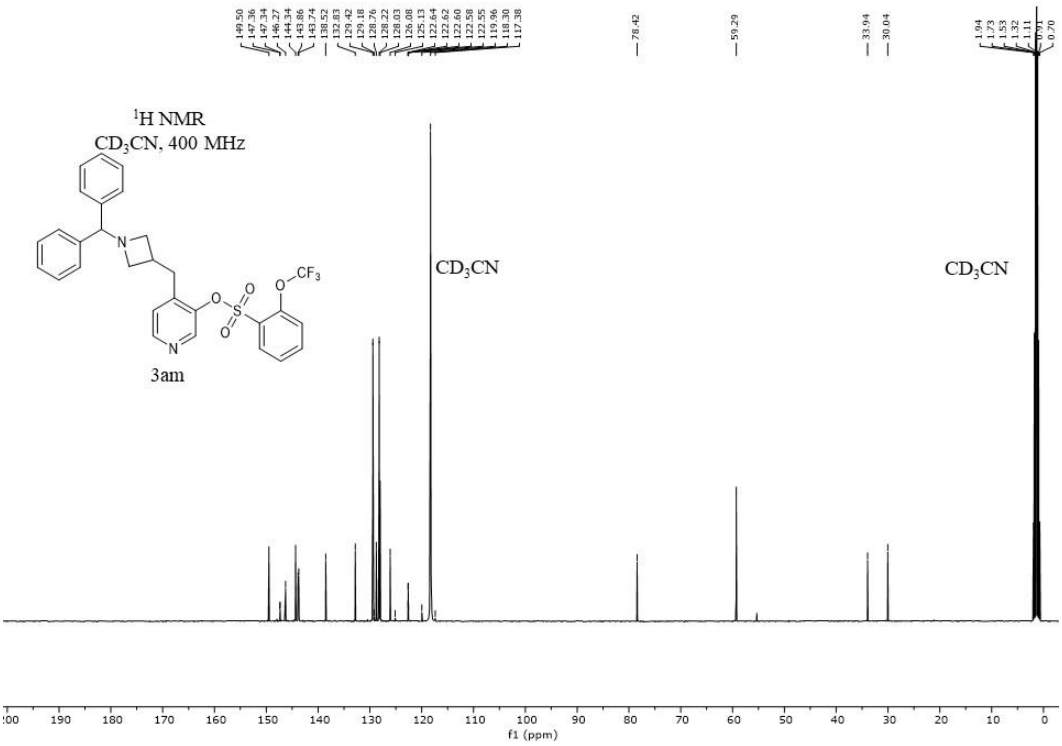
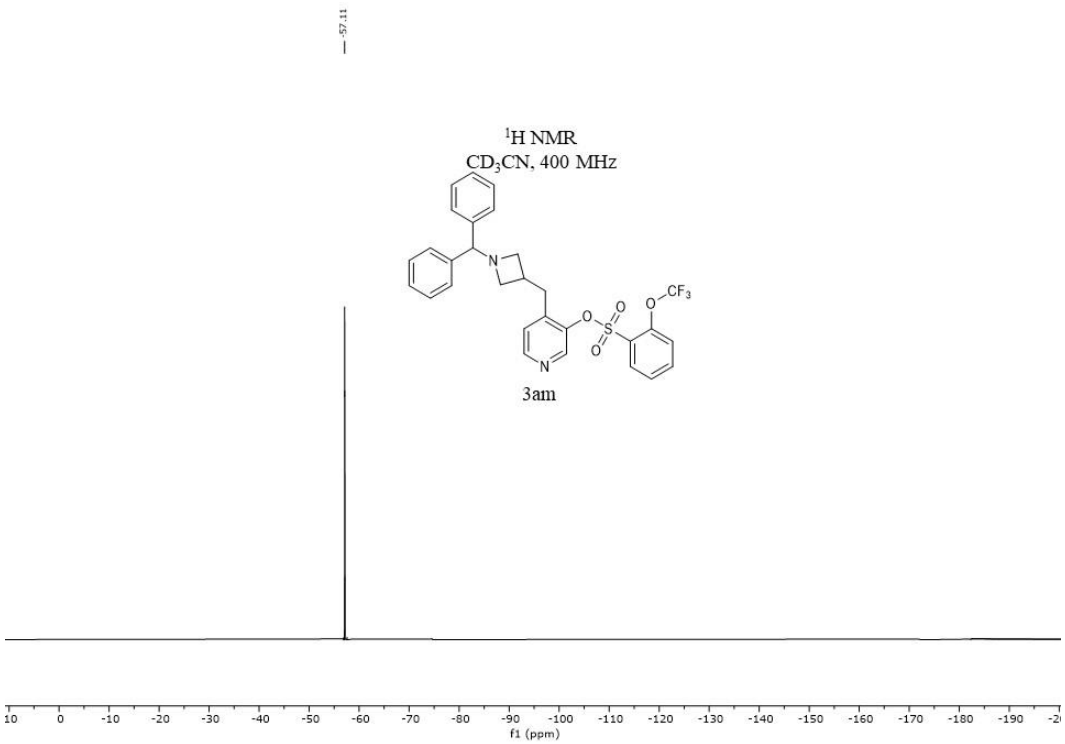
160.50
154.07
142.48
137.30
132.90
129.28
129.21
125.18
115.47
115.26
77.48
76.84
61.18
56.37
55.76
48.42
46.38
40.91
32.44
29.85
13C NMR
CDCl3, 100 MHz
F
Me
N
O
Me
N
3al
CDCl3
f1 (ppm)


-116.78
19F NMR
CDCl3, 376 MHz
F
Me
N
O
Me
N
3al
f1 (ppm)

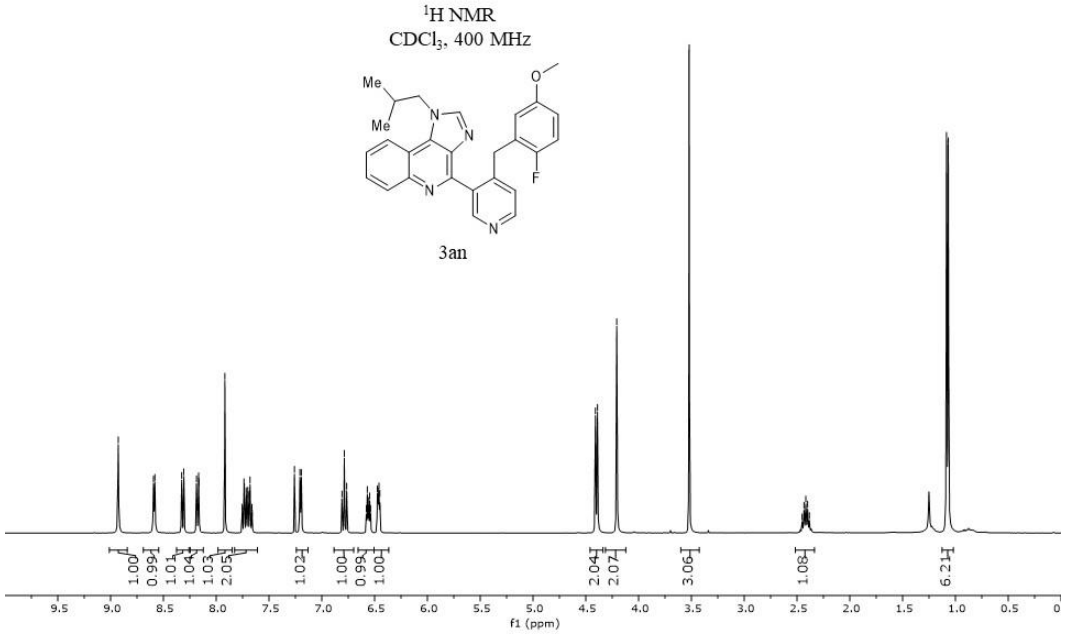

^{1}H NMR
CD_3CN, 400 MHz
3am
CD_3CN
f1 (ppm)


^{1}H NMR
CD_3CN, 400 MHz
3am
CD_3CN
CD_3CN
f1 (ppm)



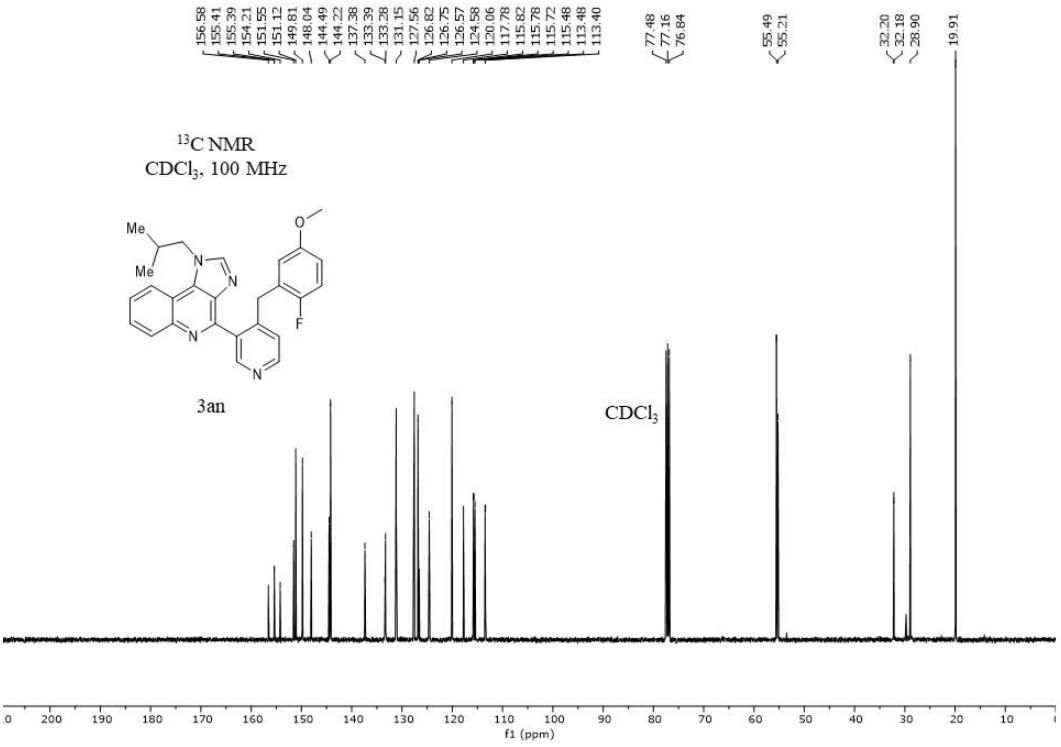
^{1}H NMR
CD_3CN, 400 MHz

3am



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

3an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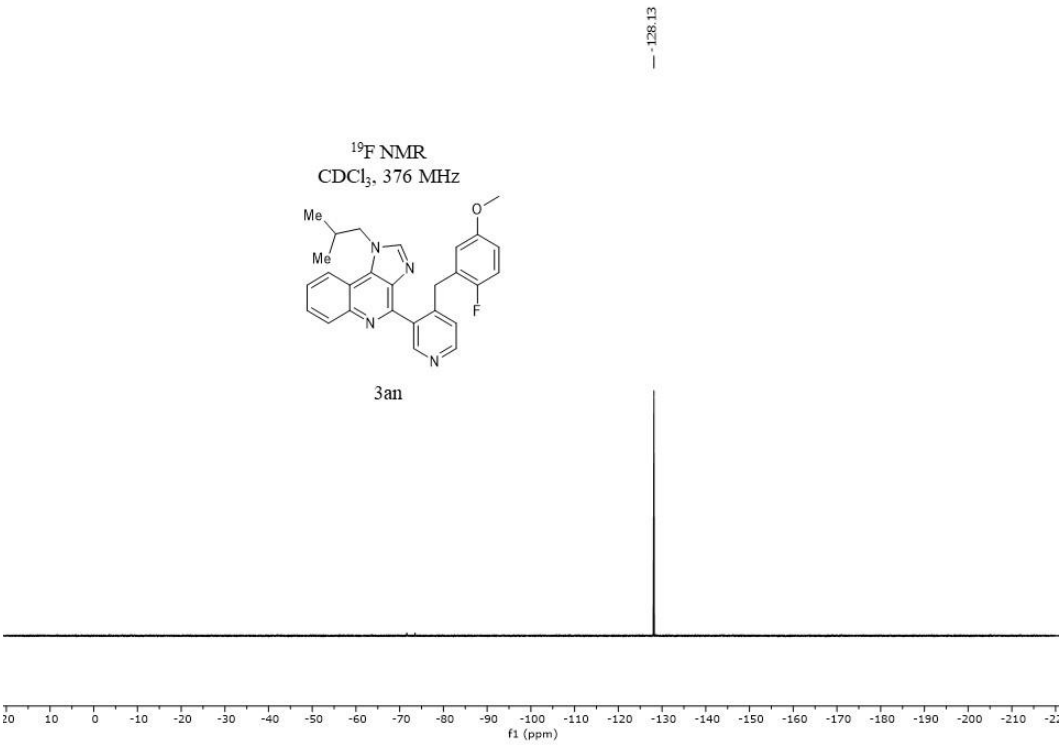
155.39
154.21
151.55
151.12
149.81
148.04
144.49
144.22
137.38
133.39
133.28
131.15
127.56
126.82
126.75
126.57
124.58
120.06
117.78
115.82
115.78
115.72
115.48
113.48
113.40
77.48
77.16
76.84
55.49
55.21
32.20
32.18
28.90
19.91
13C NMR
CDCl3, 100 MHz
Me
Me
N
N
N
O
F
N
3an
CDCl3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


-128.13
19F NMR
CDCl3, 376 MHz
Me
Me
N
N
N
O
F
N
3an
10
0
-10
-20
-30
-40
-50
-60
-70
-80
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-100
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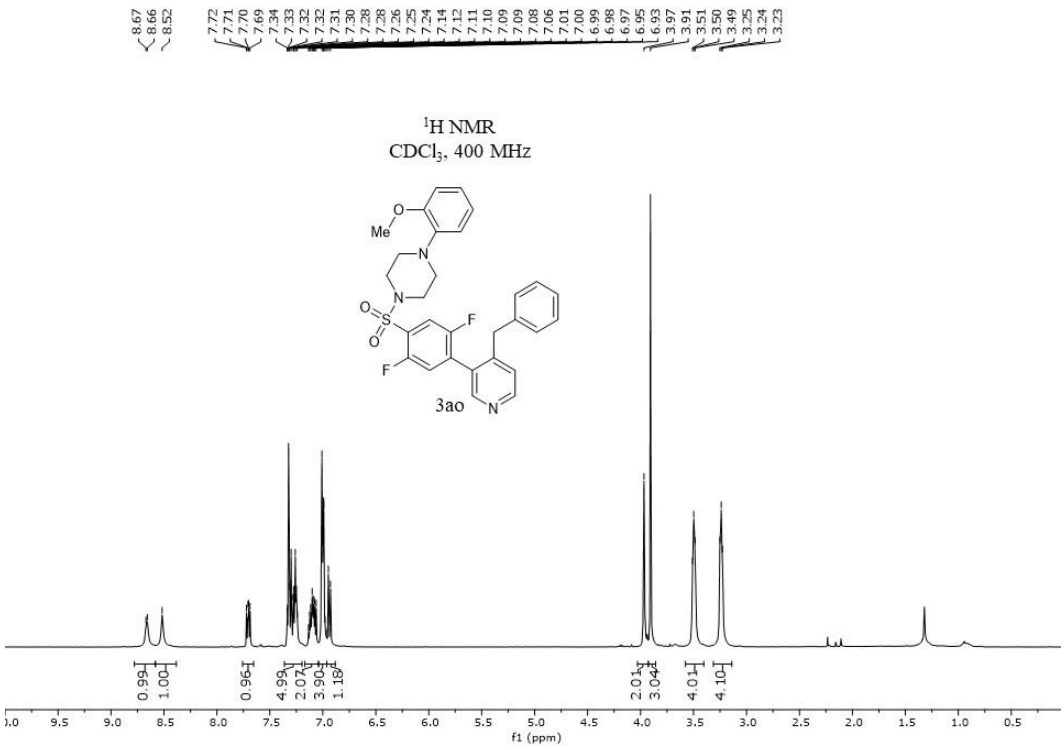
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)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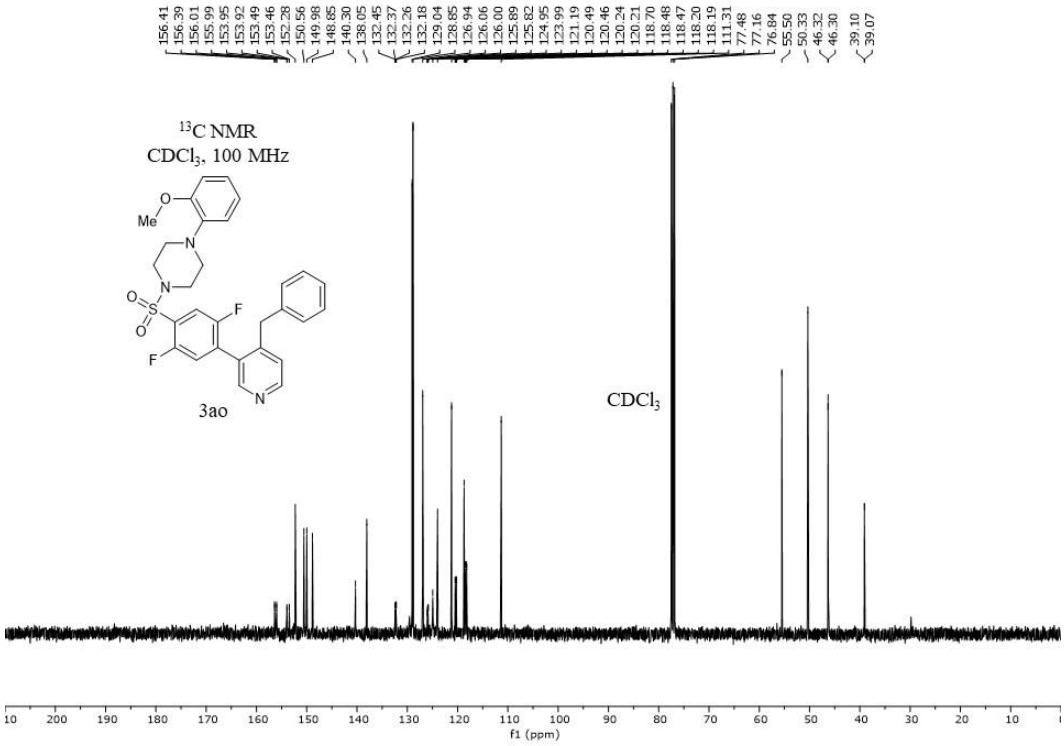
7.30
7.28
7.28
7.26
7.25
7.24
7.14
7.12
7.11
7.10
7.09
7.09
7.08
7.06
7.01
7.00
6.99
6.98
6.97
6.95
6.93
3.97
3.91
3.51
3.50
3.49
3.25
3.24
3.23
1H NMR
CDCl3, 400 MHz
Me
O
N
N
O
S
O
F
F
3ao
N
0.99
1.00
0.96
4.99
2.07
3.90
1.18
2.01
3.04
4.01
4.10
f1 (ppm)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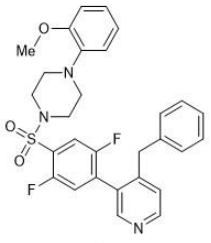
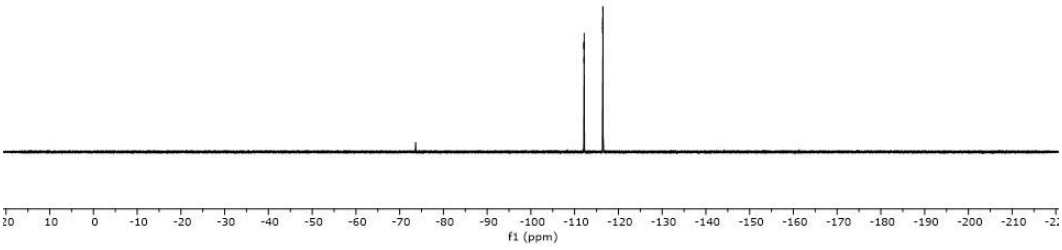
156.39
156.01
155.99
153.95
153.92
153.49
153.46
152.28
150.56
149.98
148.85
140.30
138.05
132.45
132.37
132.26
132.18
129.04
128.85
126.94
126.06
126.00
125.89
125.82
124.95
123.99
121.19
120.49
120.46
120.24
120.21
118.70
118.48
118.47
118.20
118.19
111.31
77.48
77.16
76.84
55.50
50.33
46.32
46.30
39.10
39.07
13C NMR
CDCl3, 100 MHz
Me
O
N
N
O
S
O
F
F
3ao
N
CDCl3
f1 (ppm)

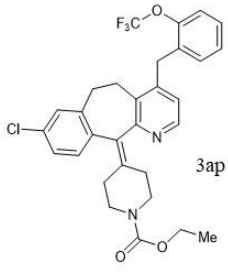
^{19}F NMR
$CDCl_3$, 376 MHz



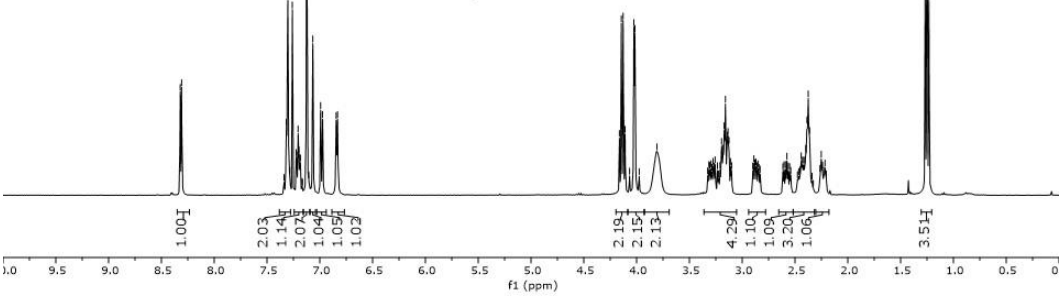
3ao

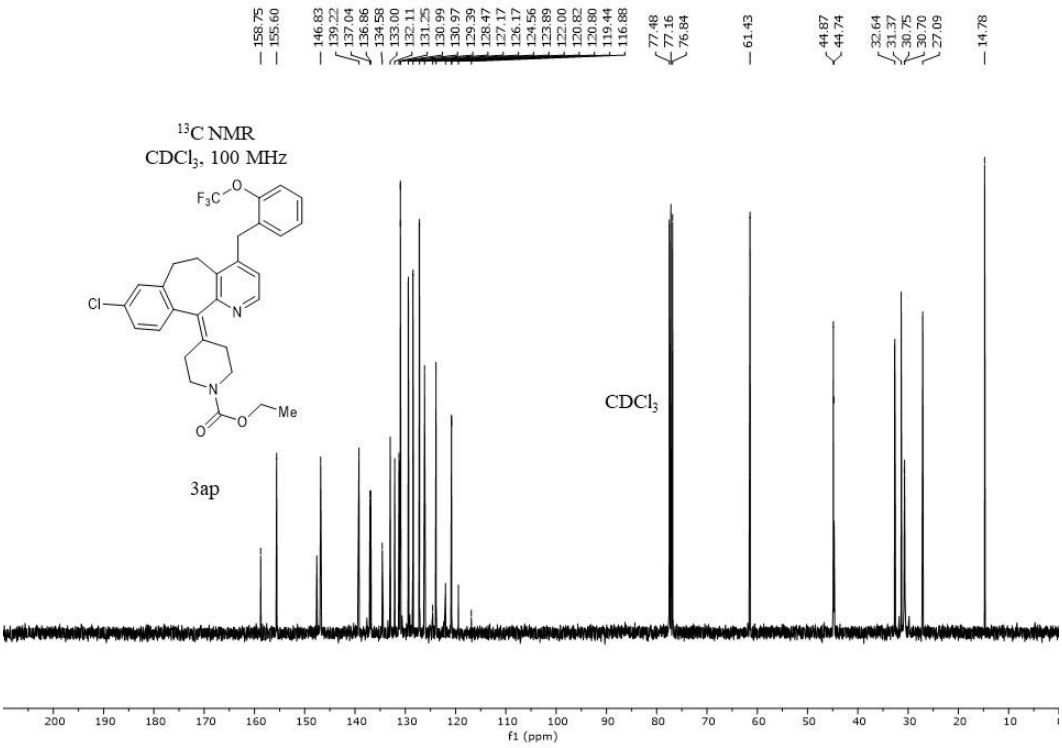


^{1}H NMR
$CDCl_3$, 400 MHz



3ap

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155.60
146.83
139.22
137.04
136.86
134.58
133.00
132.11
131.25
130.99
130.97
129.39
128.47
127.17
126.17
124.56
123.89
122.00
120.82
120.80
119.44
116.88
77.48
77.16
76.84
61.43
44.87
44.74
32.64
31.37
30.75
30.70
27.09
14.78
13C NMR
CDCl3, 100 MHz
F3C
O
Cl
N
N
O
O
Me
3ap
CDCl3
200
190
180
170
160
150
140
130
120
110
100
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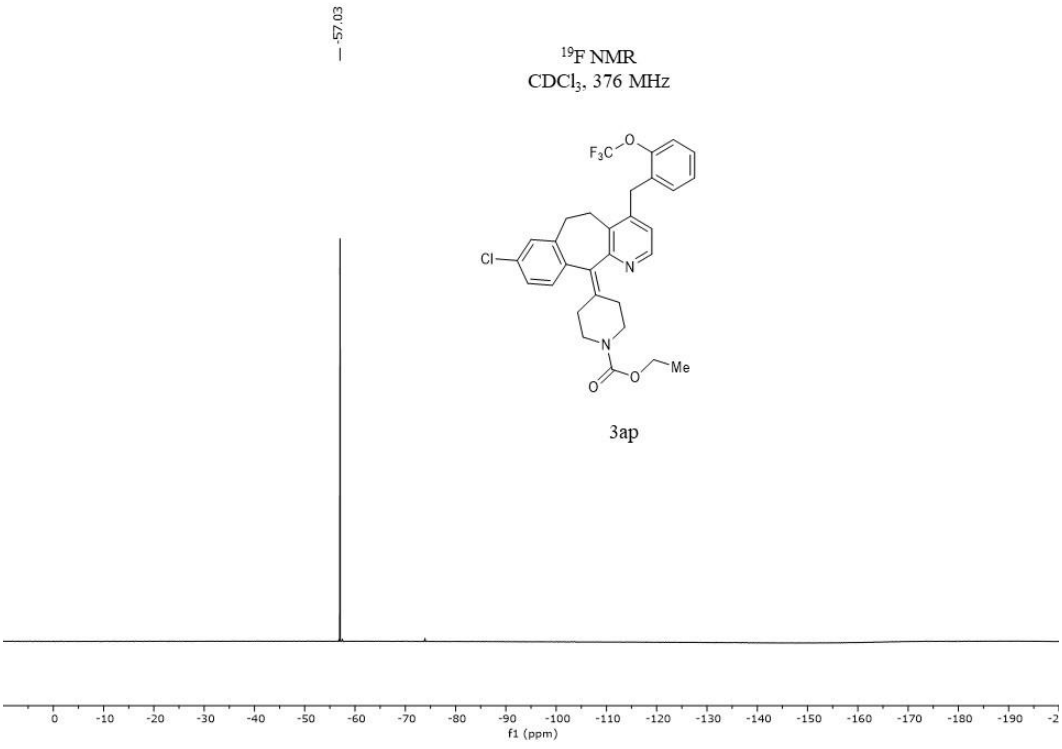
60
50
40
30
20
10
f1 (ppm)


-57.03
19F NMR
CDCl3, 376 MHz
F3C
O
Cl
N
N
O
O
Me
3ap
0
-10
-20
-30
-40
-50
-60
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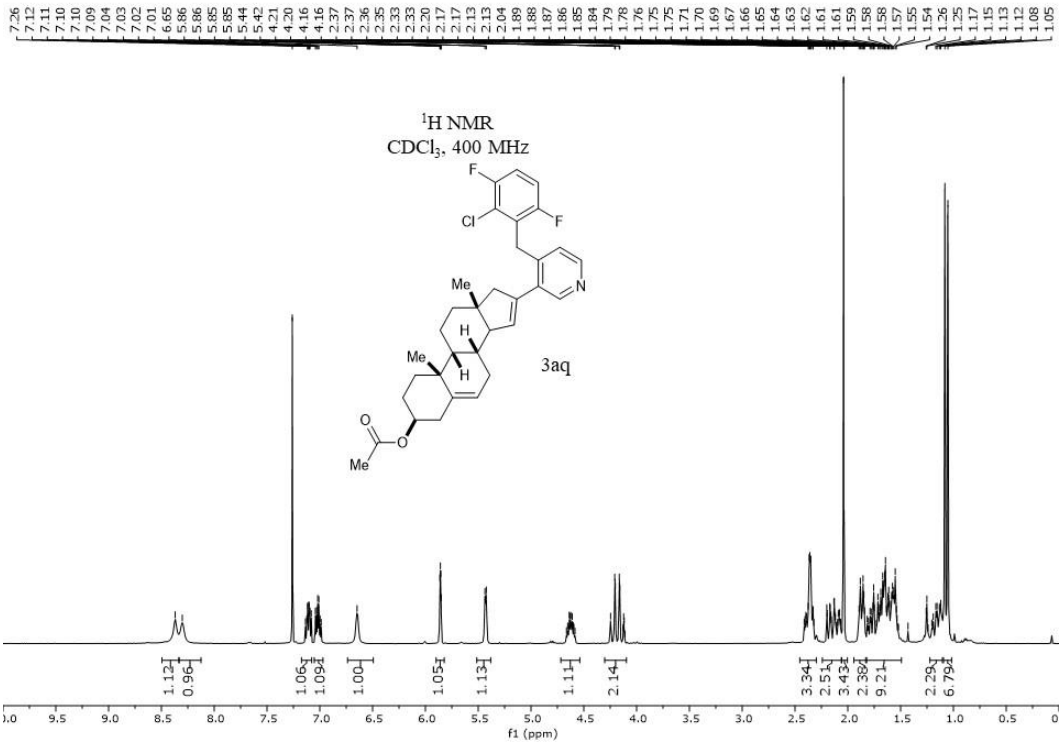
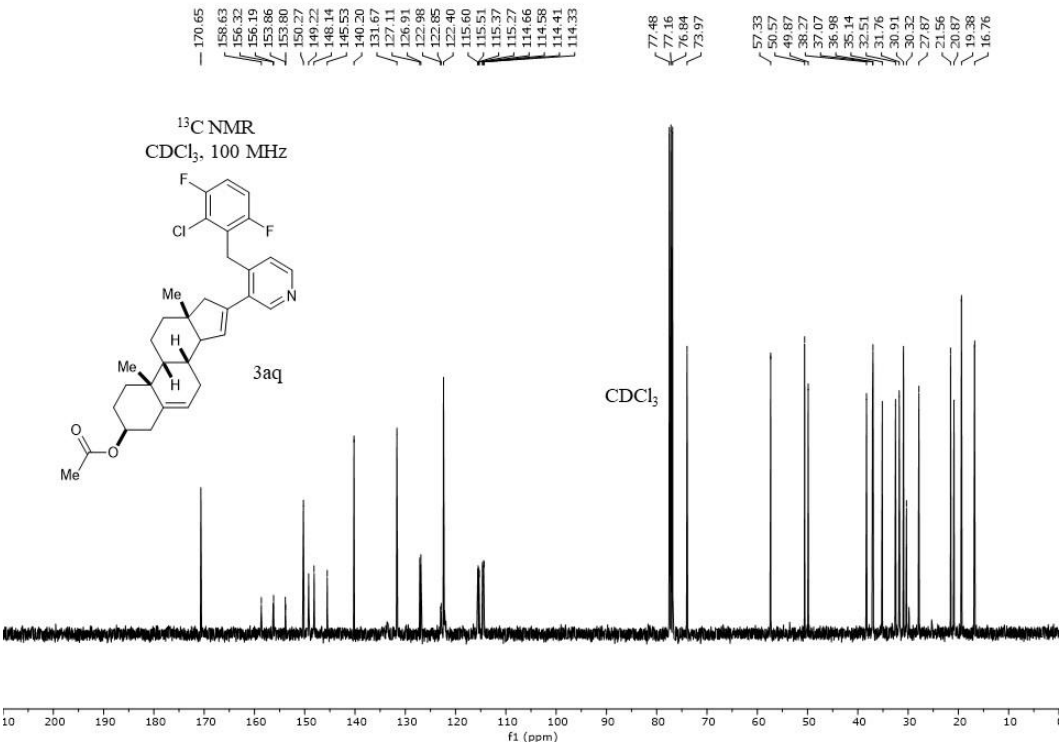
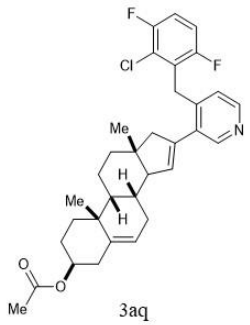
-160
-170
-180
-190
f1 (ppm)


^{1}H NMR
$CDCl_3$, 400 MHz
3aq

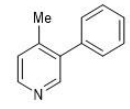

^{13}C NMR
$CDCl_3$, 100 MHz
3aq
$CDCl_3$

^{19}F NMR
$CDCl_3$, 376 MHz

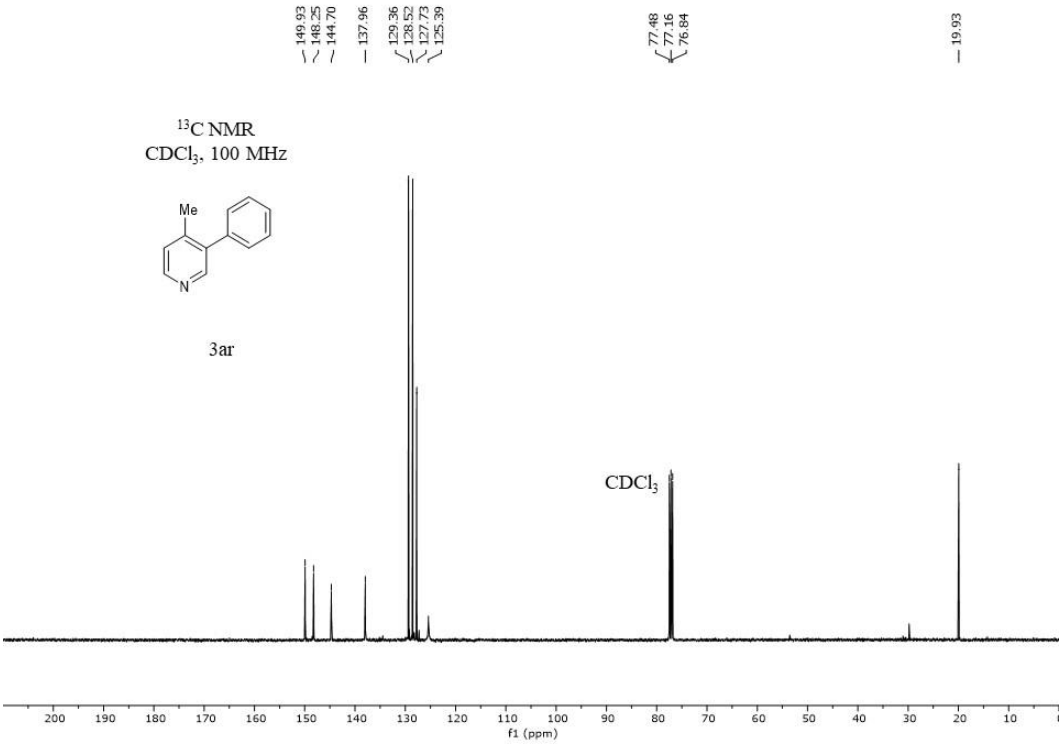


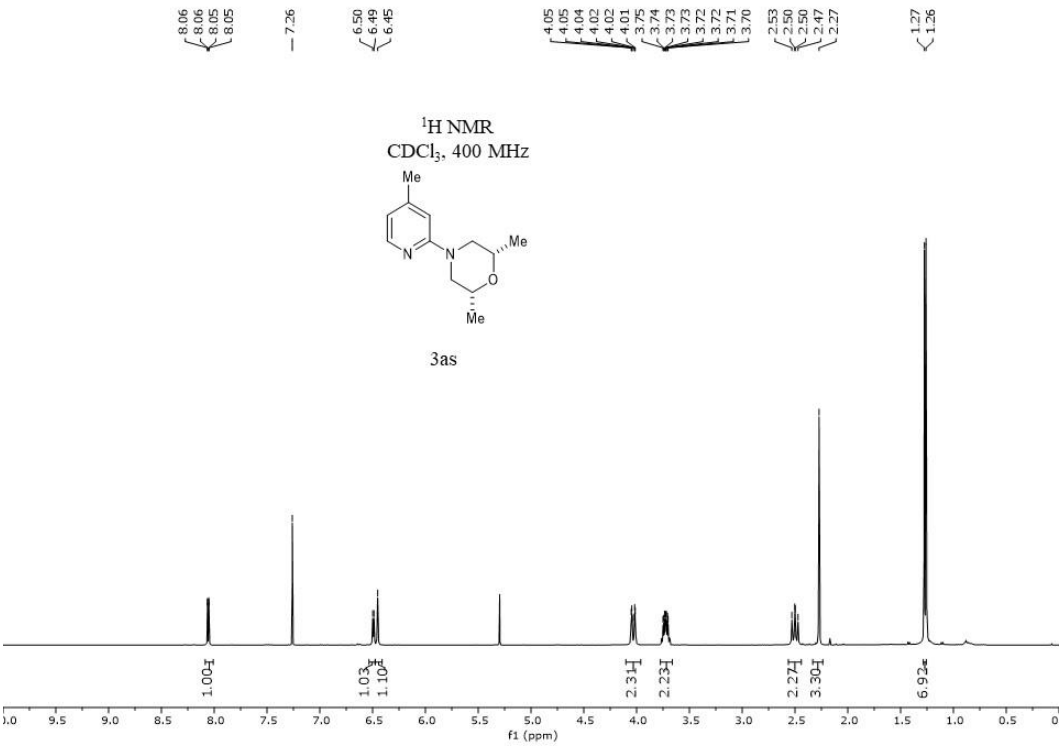
3aq

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



3ar


149.93
148.25
144.70
137.96
129.36
128.52
127.73
125.39
77.48
77.16
76.84
19.93
^{13}C NMR
$CDCl_3$, 100 MHz
Me
N
3ar
$CDCl_3$
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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8.06
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8.05
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6.50
6.49
6.45
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4.04
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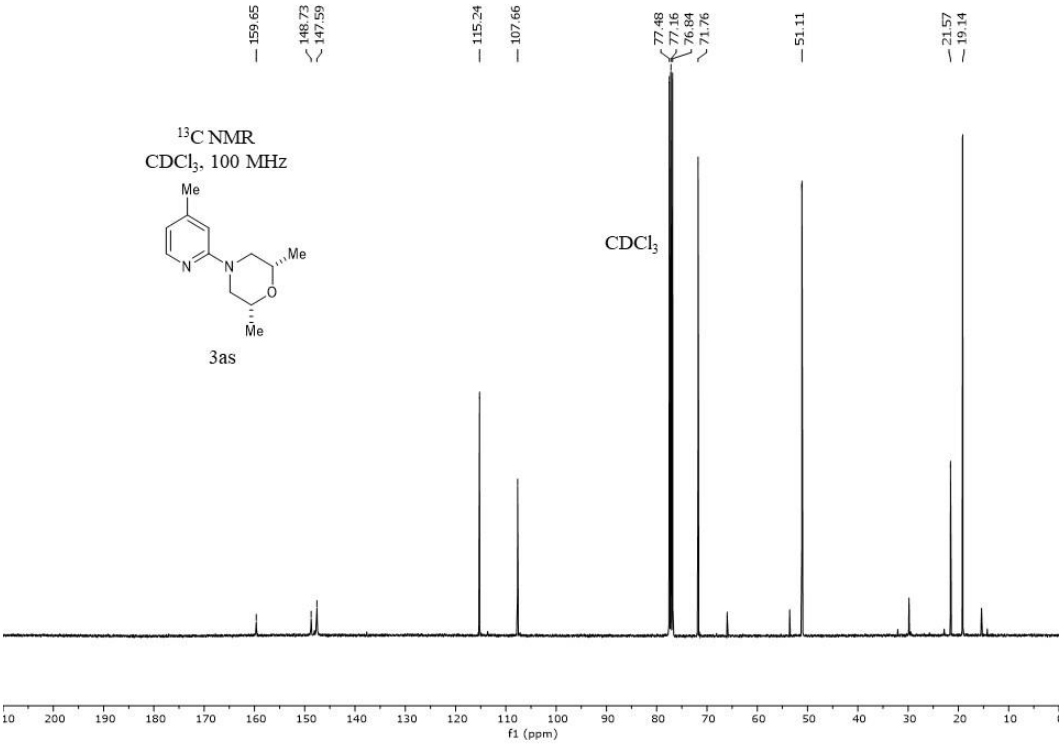
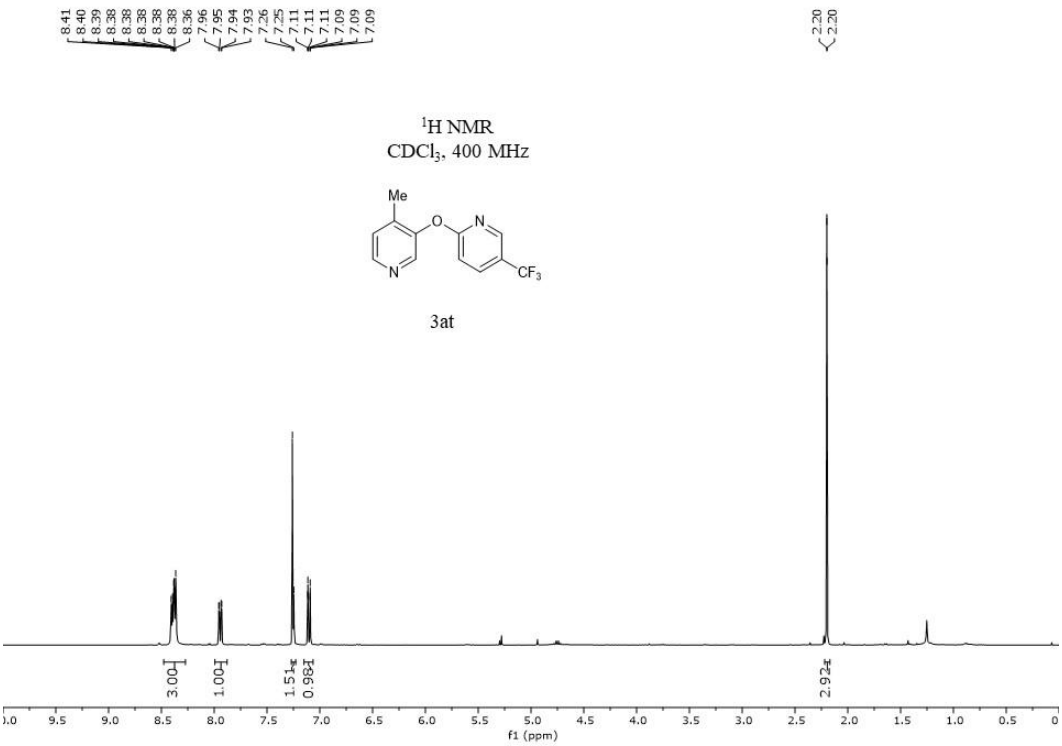
4.02
4.01
3.75
3.74
3.73
3.73
3.72
3.72
3.71
3.70
2.53
2.50
2.50
2.47
2.27
1.27
1.26
^{1}H NMR
$CDCl_3$, 400 MHz
Me
N
N
O
Me
Me
3as
1.00
1.03
1.10
2.31
2.23
2.27
3.30
6.92
f1 (ppm)


159.65
148.73
147.59
115.24
107.66
77.48
77.16
76.84
71.76
51.11
21.57
19.14
13C NMR
CDCl3, 100 MHz
Me
N
N
Me
O
Me
3as
CDCl3
f1 (ppm)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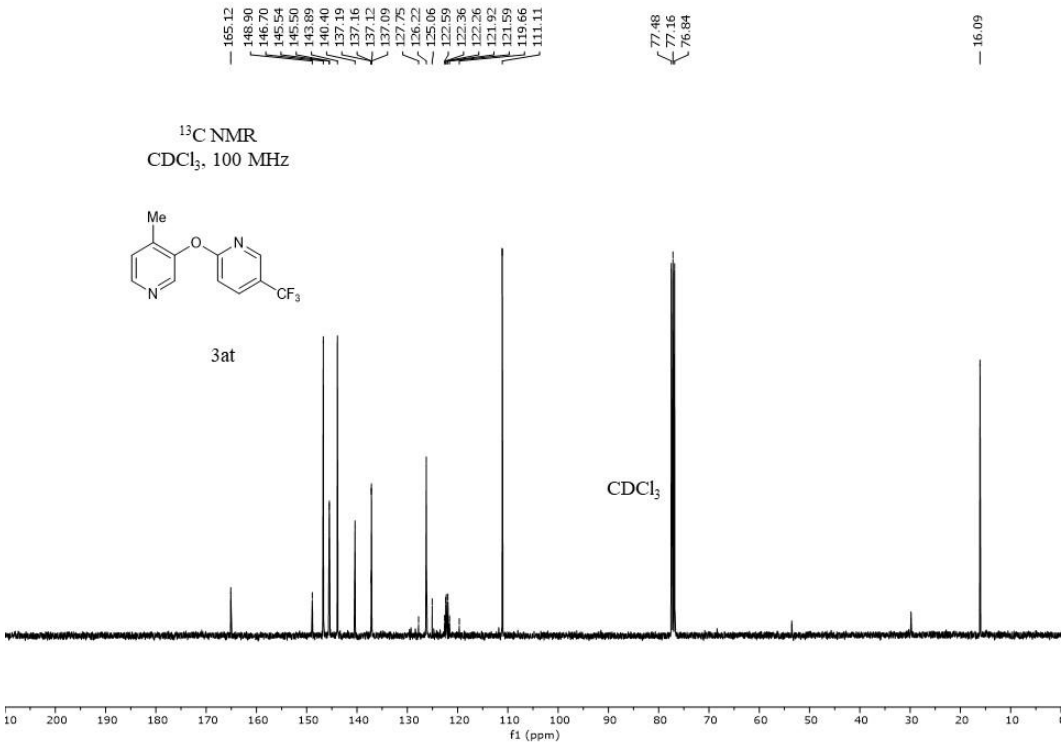
7.95
7.94
7.93
7.26
7.25
7.11
7.11
7.11
7.09
7.09
7.09
2.20
2.20
1H NMR
CDCl3, 400 MHz
Me
O
N
N
CF3
3at
3.00
1.00
1.51
0.98
2.92
f1 (ppm)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127.75
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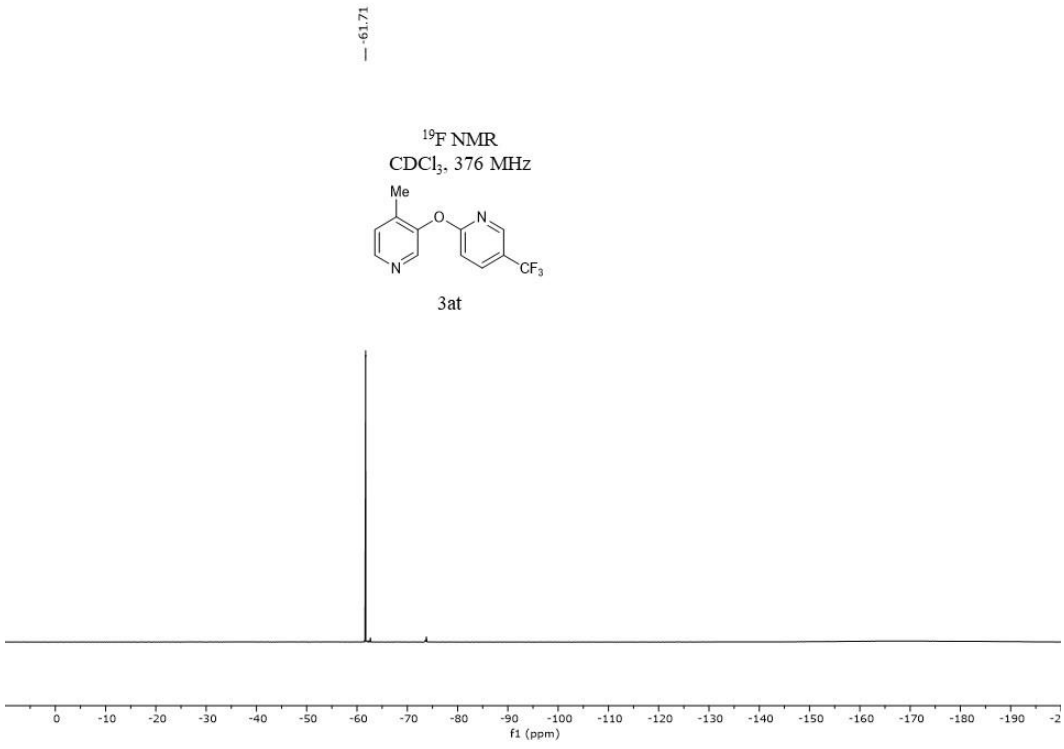
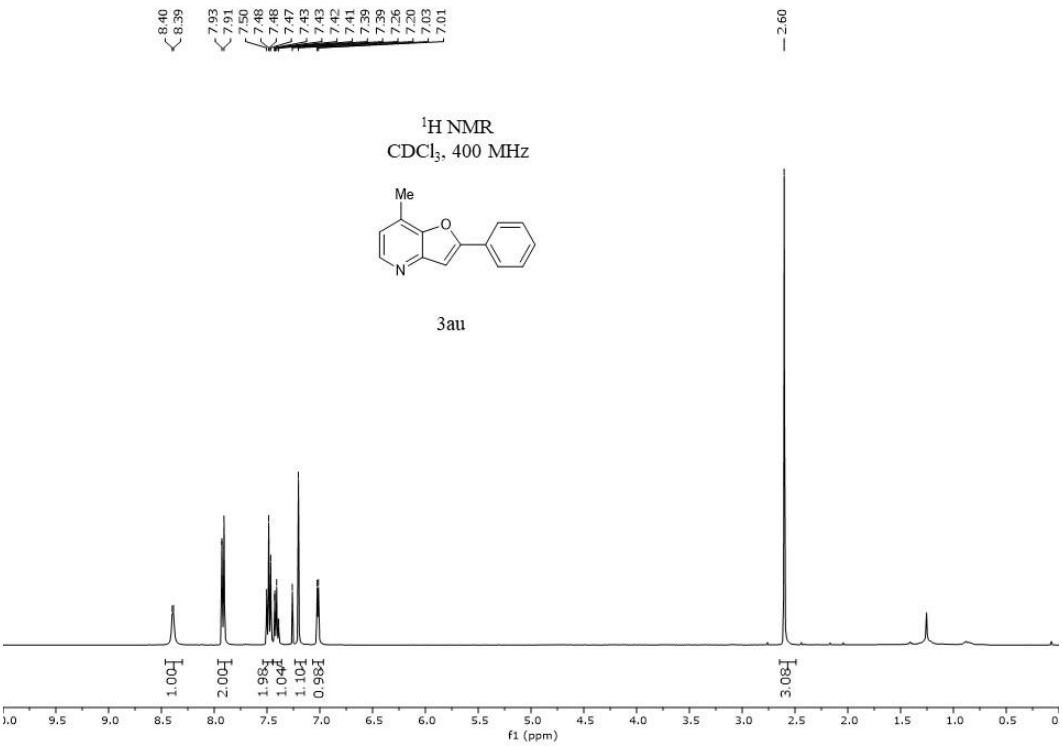
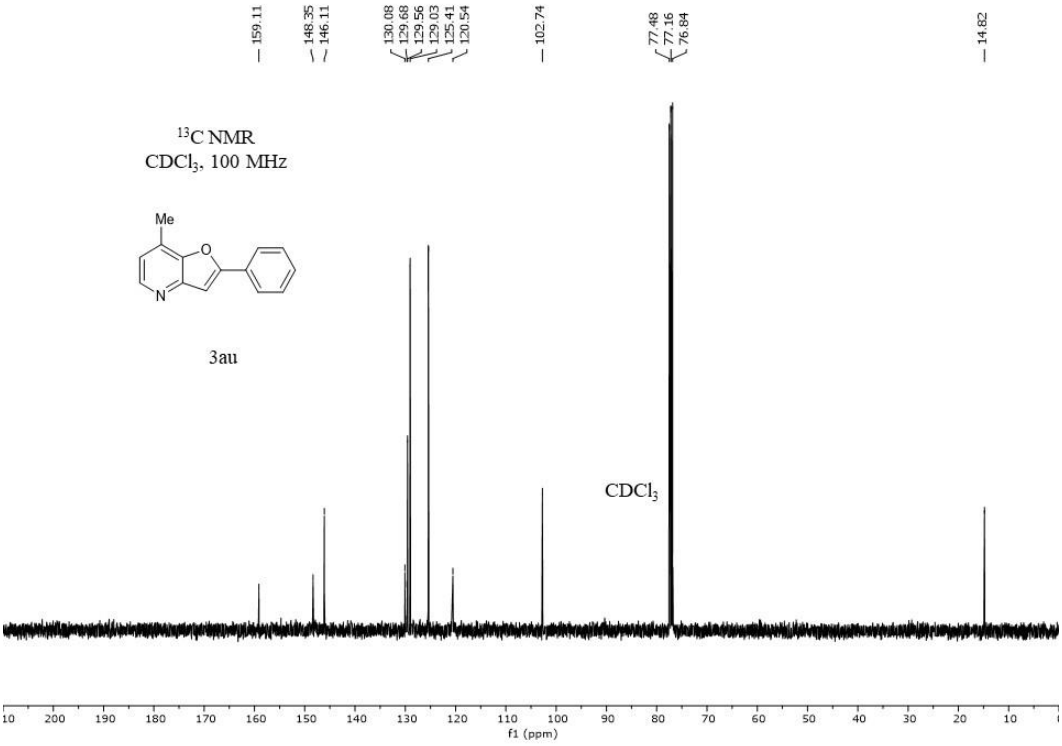
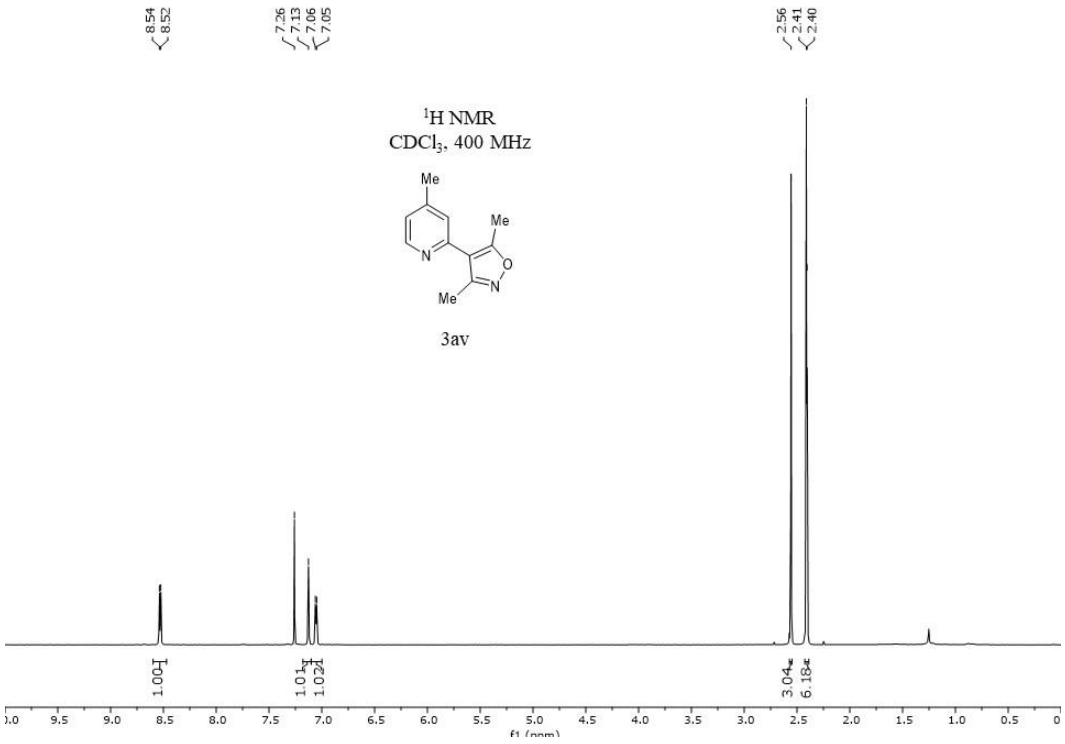
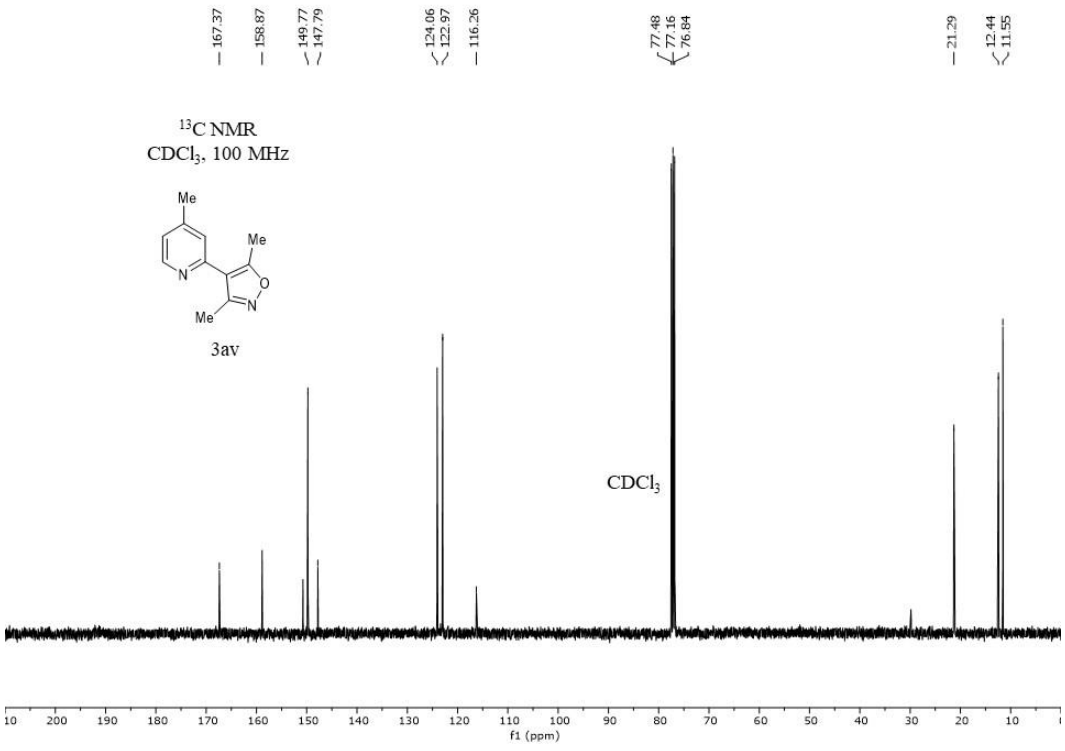
125.66
122.59
122.36
122.26
121.92
121.59
119.66
111.11
77.48
77.16
76.84
16.09
13C NMR
CDCl3, 100 MHz
Me
O
N
N
CF3
3at
CDCl3
f1 (ppm)

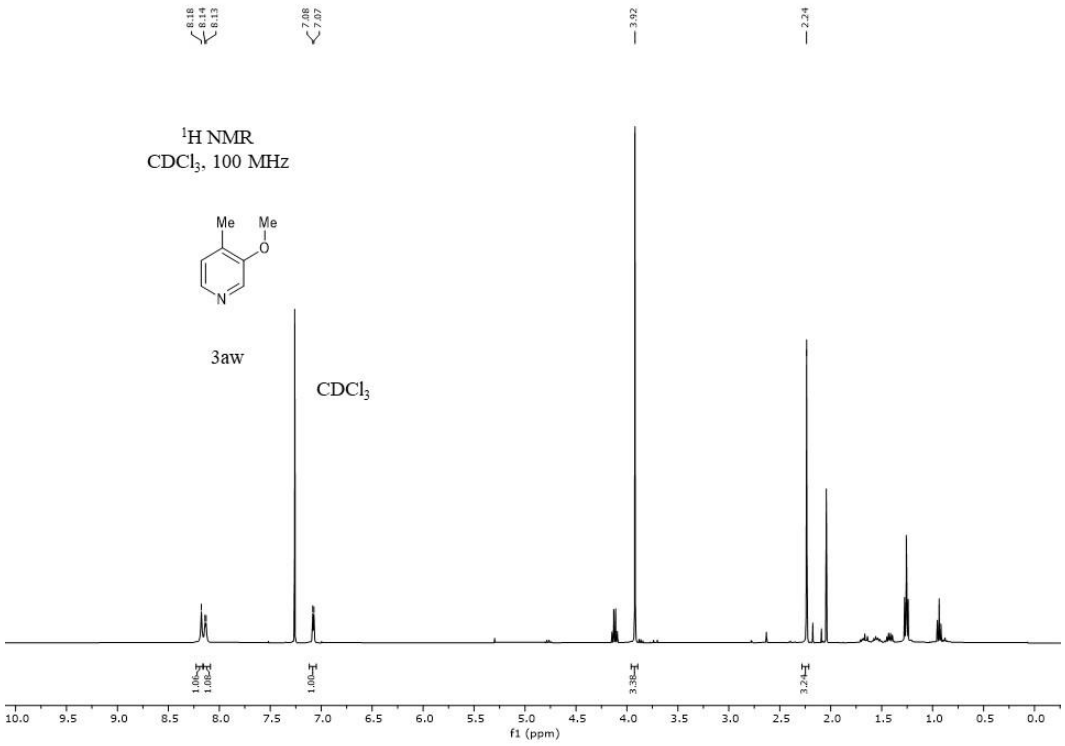

-61.71
19F NMR
CDCl3, 376 MHz
Me
O
N
N
CF3
3at
f1 (ppm)

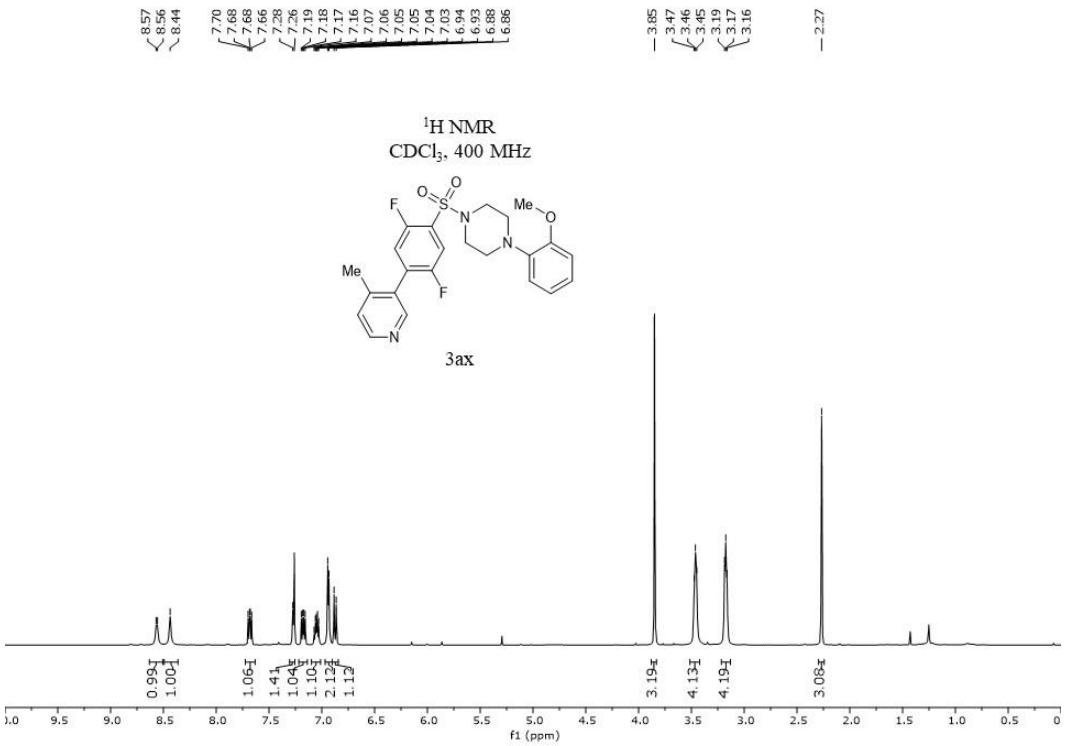

8.40
8.39
7.93
7.91
7.50
7.48
7.48
7.47
7.43
7.43
7.42
7.41
7.39
7.39
7.26
7.20
7.03
7.01
2.60
1H NMR
CDCl3, 400 MHz
Me
O
N
3au
1.00
2.00
1.98
1.04
1.10
0.98
3.08
f1 (ppm)


159.11
148.35
146.11
130.08
129.68
129.56
129.03
125.41
120.54
102.74
77.48
77.16
76.84
14.82
13C NMR
CDCl3, 100 MHz
Me
O
N
3au
CDCl3
f1 (ppm)

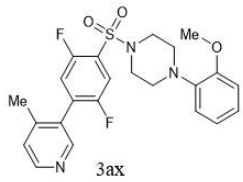

8.54
8.52
7.26
7.13
7.06
7.05
2.56
2.41
2.40
^{1}H NMR
$CDCl_3$, 400 MHz
Me
Me
Me
N
O
N
3av
1.00
1.01
1.02
3.04
6.18
f1 (ppm)


167.37
158.87
149.77
147.79
124.06
122.97
116.26
77.48
77.16
76.84
21.29
12.44
11.55
^{13}C NMR
$CDCl_3$, 100 MHz
Me
Me
Me
N
O
N
3av
$CDCl_3$
f1 (ppm)

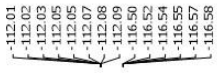

8.18
8.14
8.13
7.08
7.07
3.92
2.24
1H NMR
CDCl3, 100 MHz
Me
Me
O
N
3aw
CDCl3
1.06
1.00
1.00
3.38
3.24
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


8.57
8.56
8.44
7.70
7.68
7.68
7.66
7.28
7.26
7.19
7.18
7.17
7.16
7.07
7.06
7.05
7.05
7.04
7.03
6.94
6.93
6.88
6.86
3.85
3.47
3.46
3.45
3.19
3.17
3.16
2.27
1H NMR
CDCl3, 400 MHz
O
O
S
N
F
Me
O
N
Me
F
N
3ax
0.99
1.00
1.06
1.41
1.04
1.10
2.12
1.12
3.19
4.13
4.19
3.08
f1 (ppm)

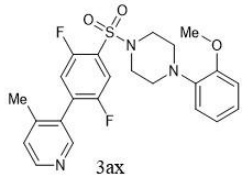
^{13}C NMR
$CDCl_3$, 100 MHz



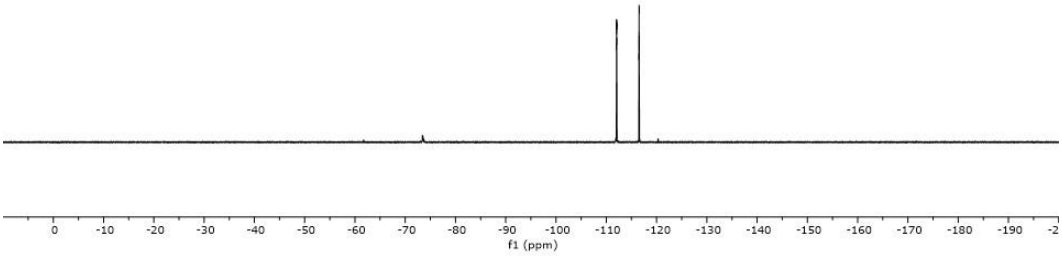
3ax

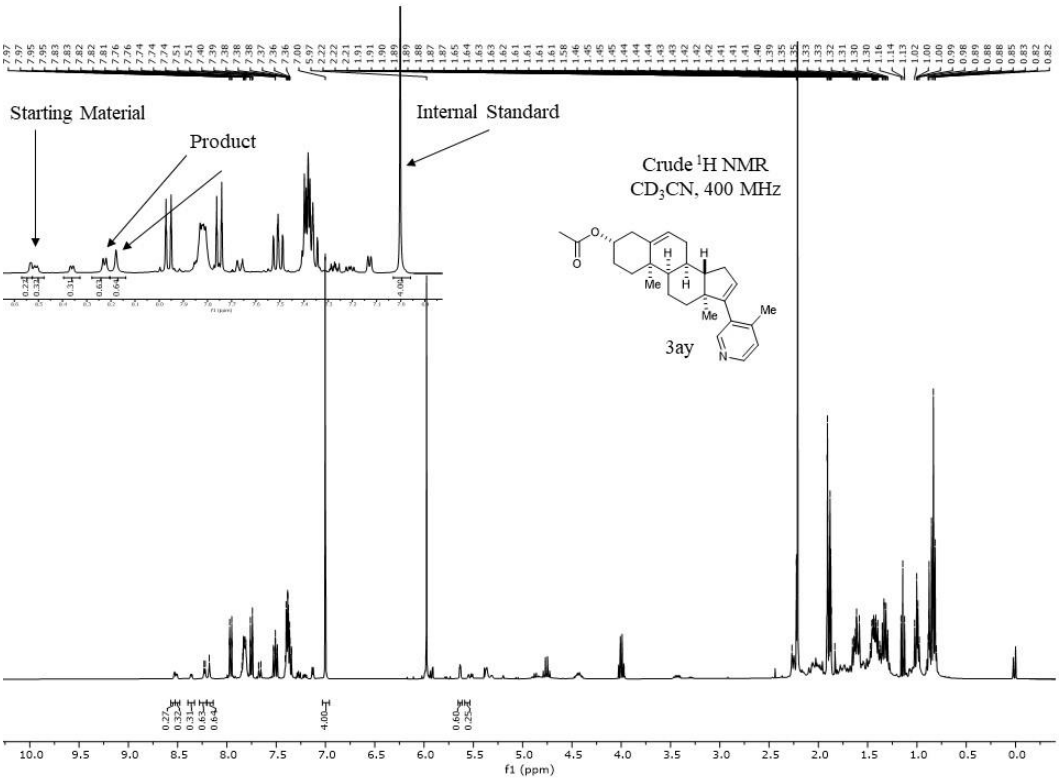


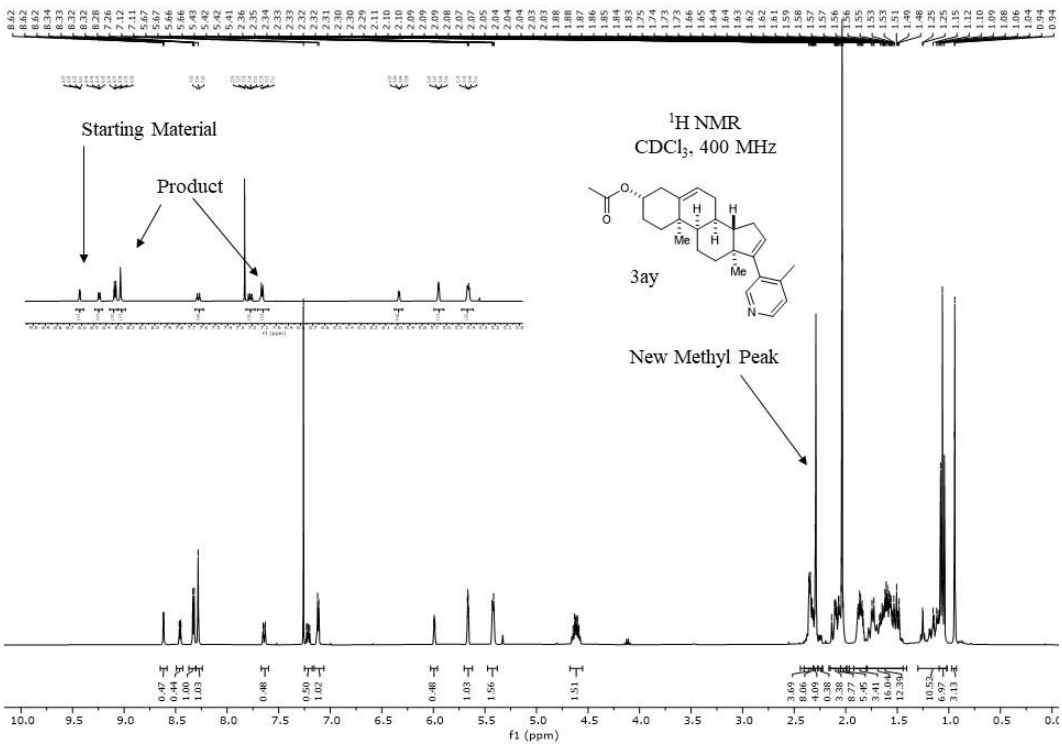
^{19}F NMR
$CDCl_3$, 376 MHz

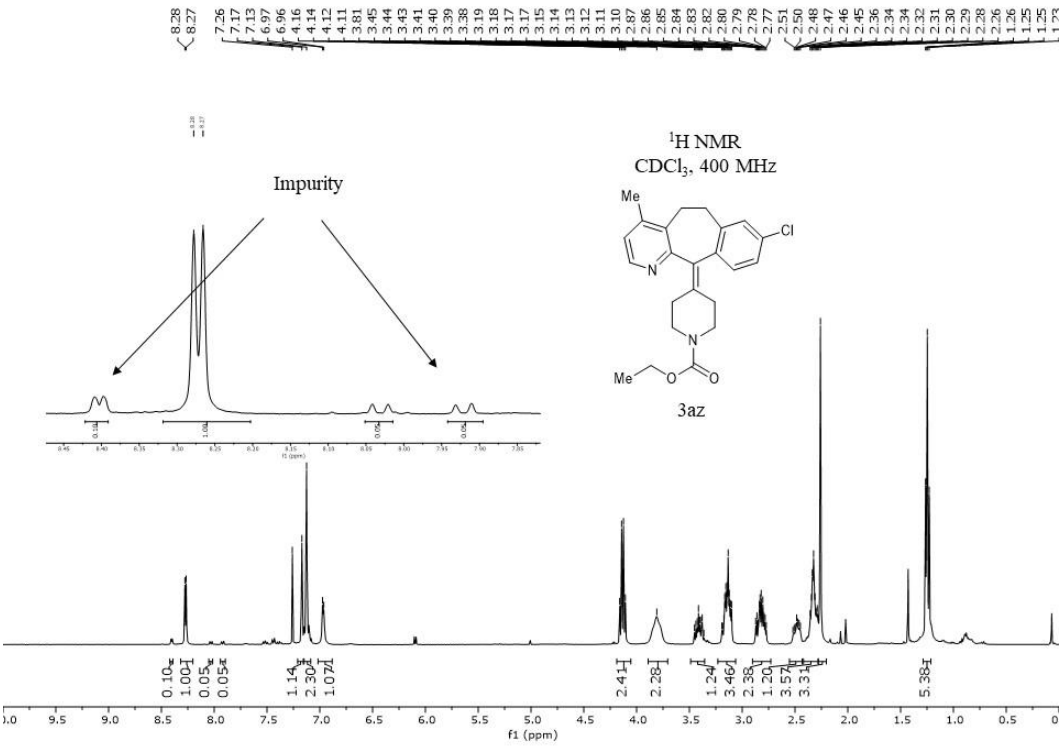


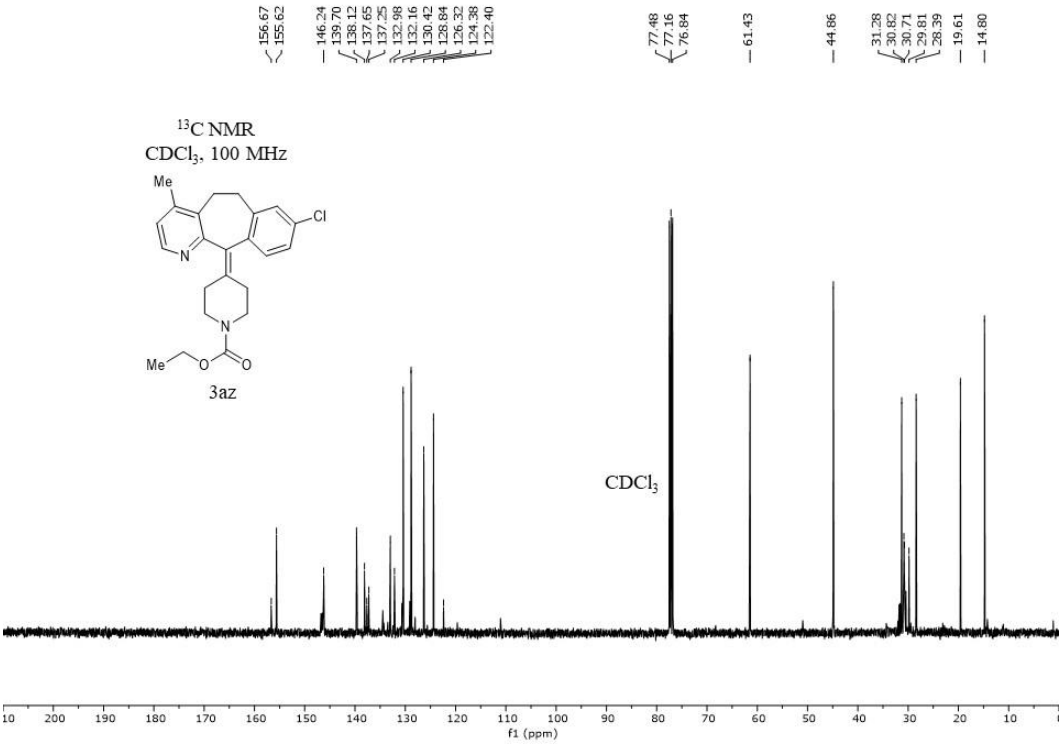
3ax

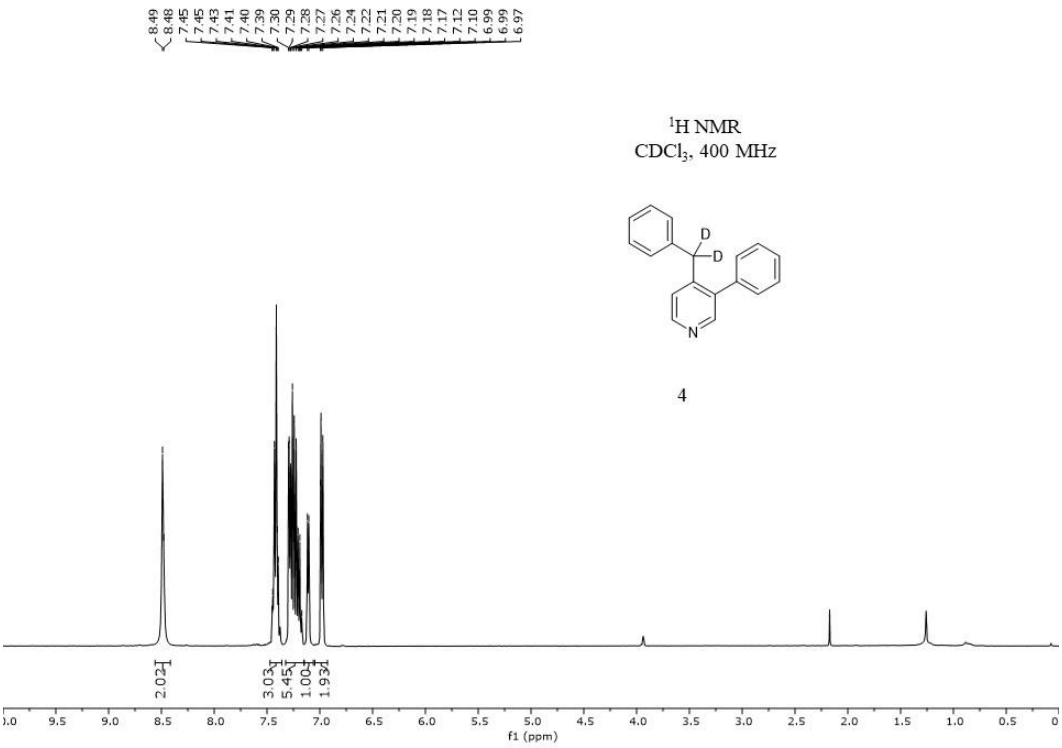


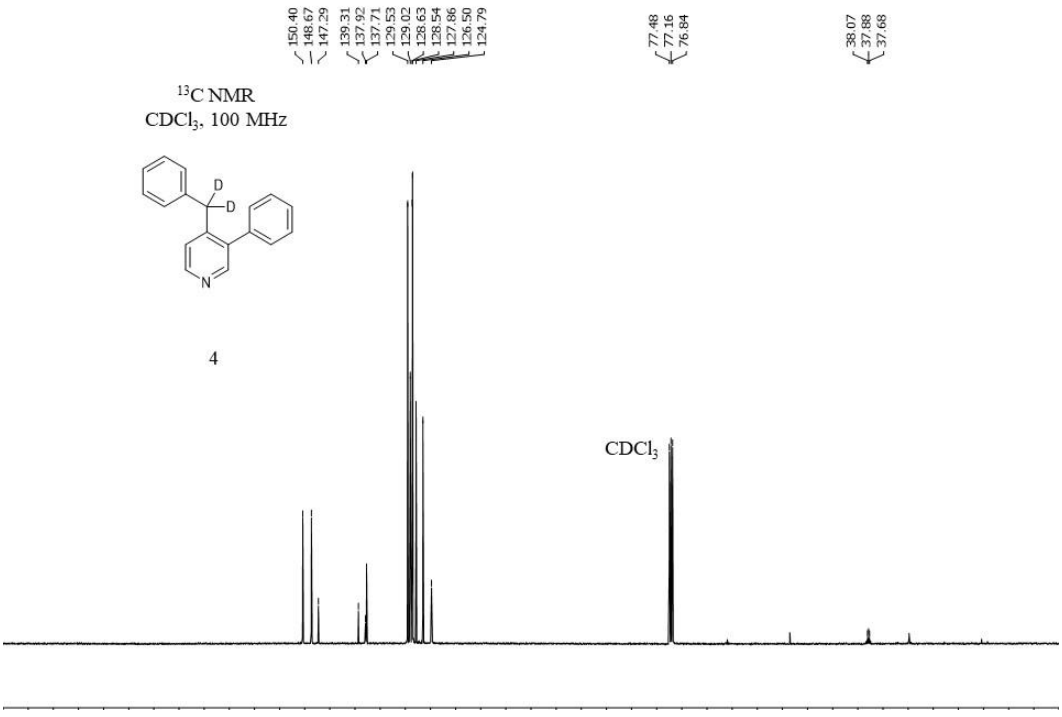

Starting Material
Product
Internal Standard
Crude ^{1}H NMR
CD_3CN, 400 MHz
3ay
f1 (ppm)

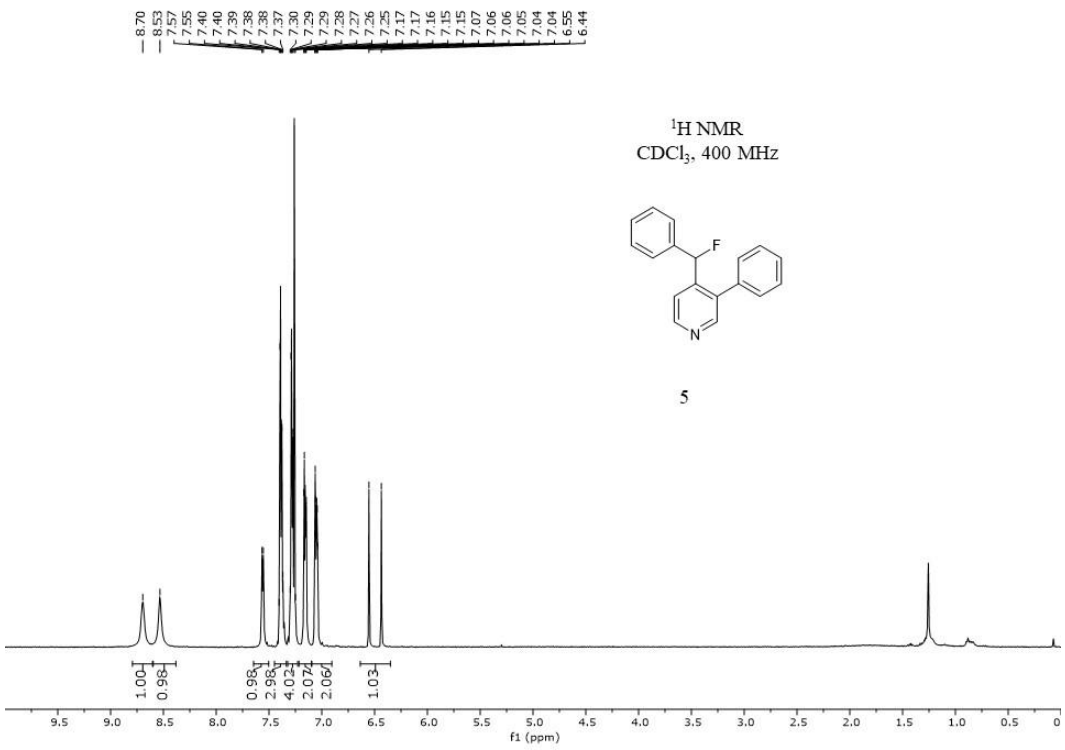

Starting Material
Product
^{1}H NMR
$CDCl_3$, 400 MHz
3ay
New Methyl Peak
f1 (ppm)

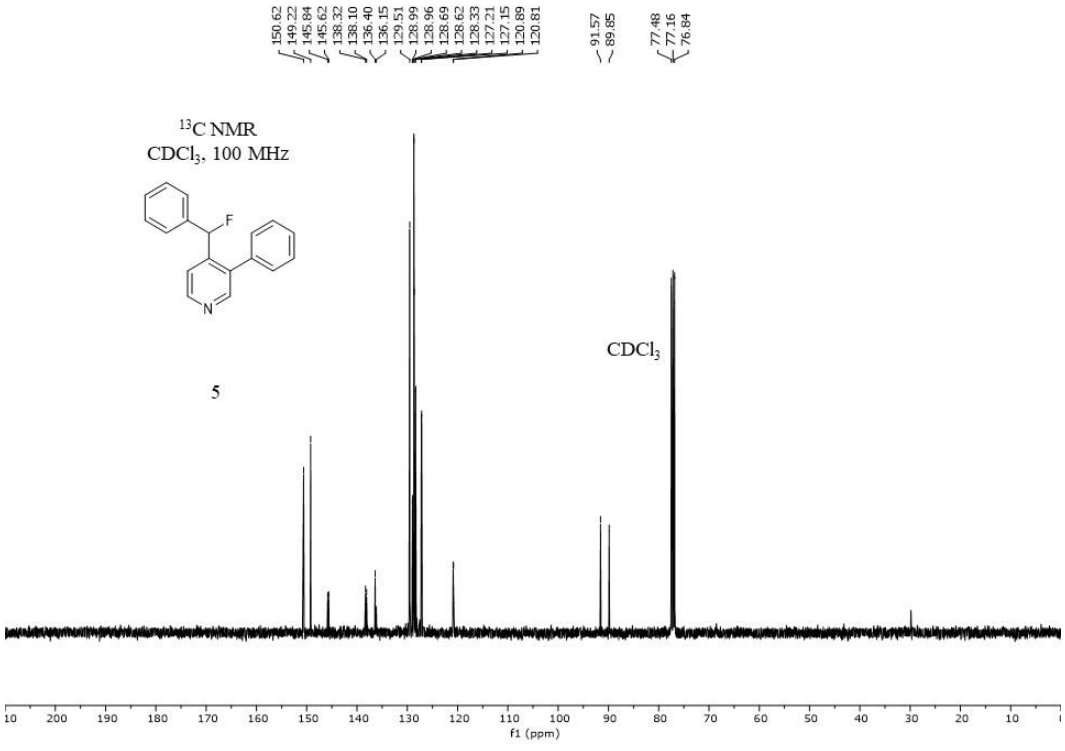

^{1}H NMR
$CDCl_3$, 400 MHz
Impurity
Me
Cl
N
N
Me
O
O
3az
f1 (ppm)

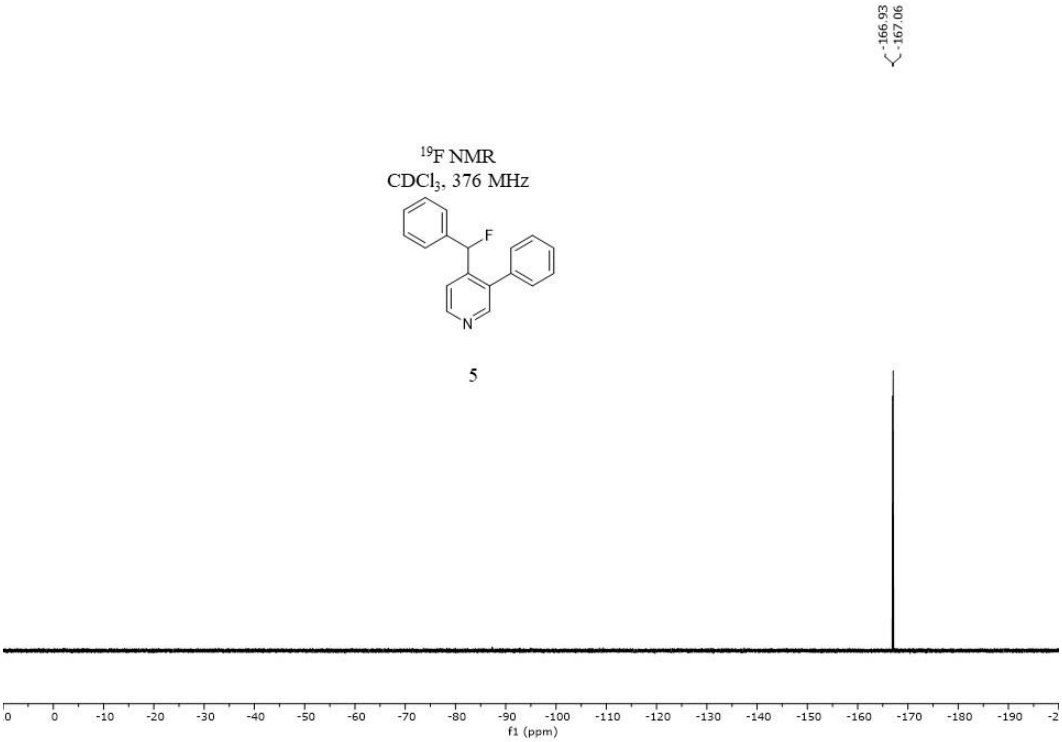

^{13}C NMR
$CDCl_3$, 100 MHz
Me
Cl
N
N
Me
O
O
3az
$CDCl_3$
f1 (ppm)


8.49
8.48
7.45
7.45
7.43
7.41
7.40
7.39
7.30
7.29
7.28
7.27
7.26
7.24
7.22
7.21
7.20
7.19
7.18
7.17
7.12
7.10
6.99
6.99
6.97
1H NMR
CDCl3, 400 MHz
D
D
N
4
2.02
3.03
5.45
1.00
1.93
f1 (ppm)


150.40
148.67
147.29
139.31
137.92
137.71
129.53
129.02
128.63
128.54
127.86
126.50
124.79
77.48
77.16
76.84
38.07
37.88
37.68
13C NMR
CDCl3, 100 MHz
D
D
N
4
CDCl3

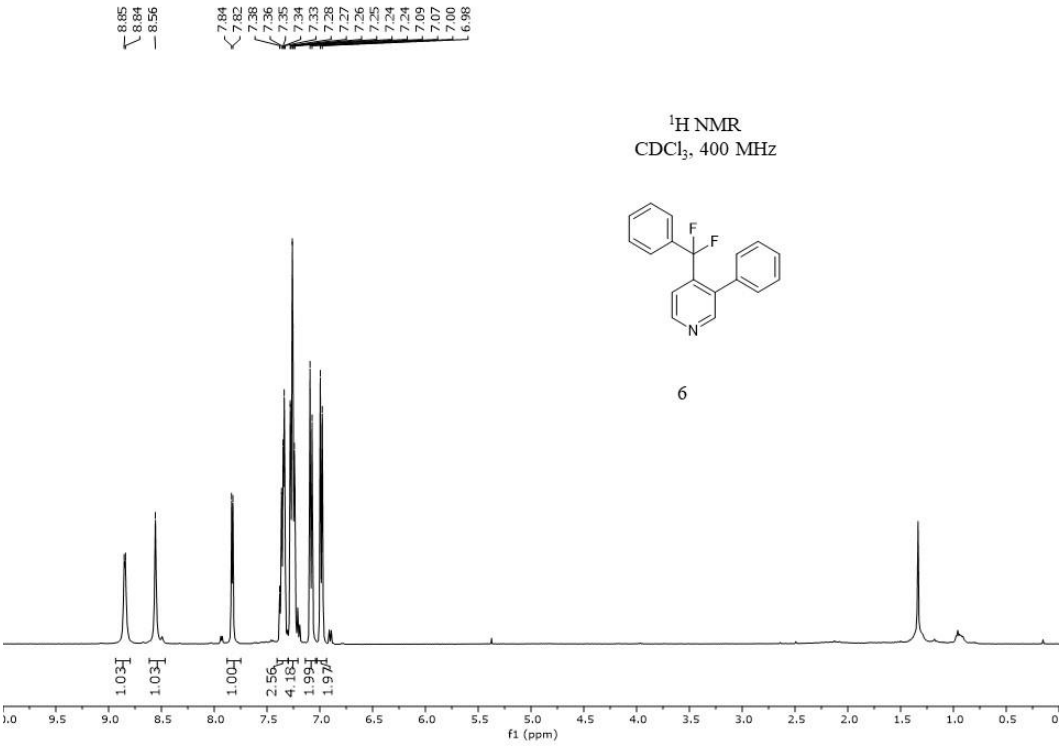

8.70
8.53
7.57
7.55
7.40
7.40
7.39
7.38
7.38
7.37
7.30
7.29
7.29
7.28
7.27
7.26
7.25
7.17
7.17
7.16
7.15
7.15
7.07
7.06
7.06
7.05
7.04
7.04
6.55
6.44
1H NMR
CDCl3, 400 MHz
F
N
5
1.00
0.98
0.98
2.98
4.03
2.07
2.06
1.03
f1 (ppm)


150.62
149.22
145.84
145.62
138.32
138.10
136.40
136.15
129.51
128.99
128.96
128.69
128.62
128.33
127.21
127.15
120.89
120.81
91.57
89.85
77.48
77.16
76.84
13C NMR
CDCl3, 100 MHz
F
N
5
CDCl3
f1 (ppm)



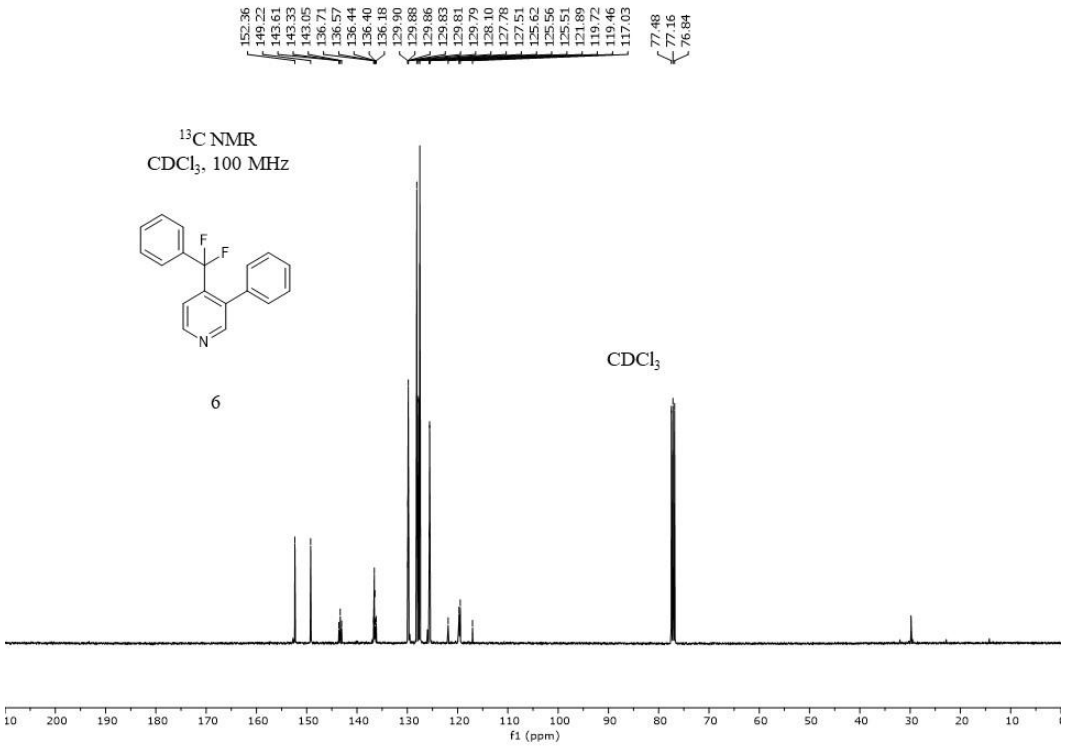
^{19}F NMR
$CDCl_3$, 376 MHz

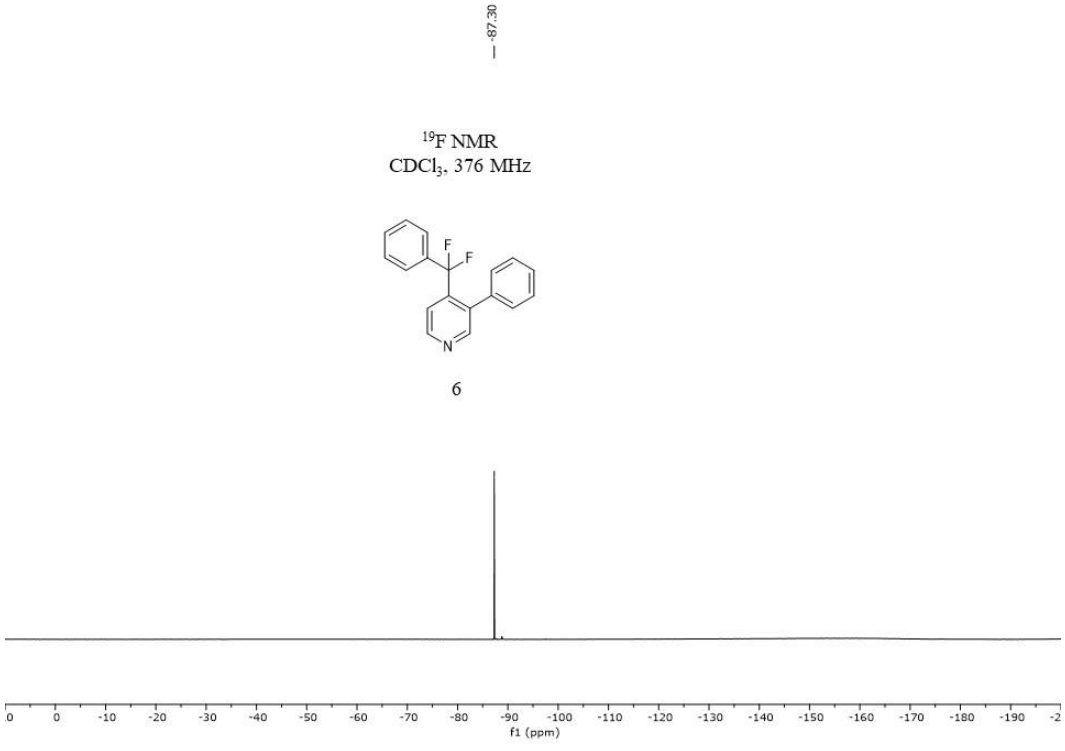
5



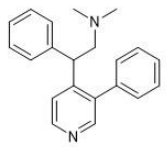
^{1}H NMR
$CDCl_3$, 400 MHz

6


152.36
149.22
143.61
143.33
143.05
136.71
136.57
136.44
136.40
136.18
129.90
129.88
129.86
129.83
129.81
129.79
128.10
127.78
127.51
125.62
125.56
125.51
121.89
119.72
119.46
117.03
77.48
77.16
76.84
13C NMR
CDCl3, 100 MHz
F
F
N
6
CDCl3
f1 (ppm)


-87.30
19F NMR
CDCl3, 376 MHz
F
F
N
6
f1 (ppm)

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



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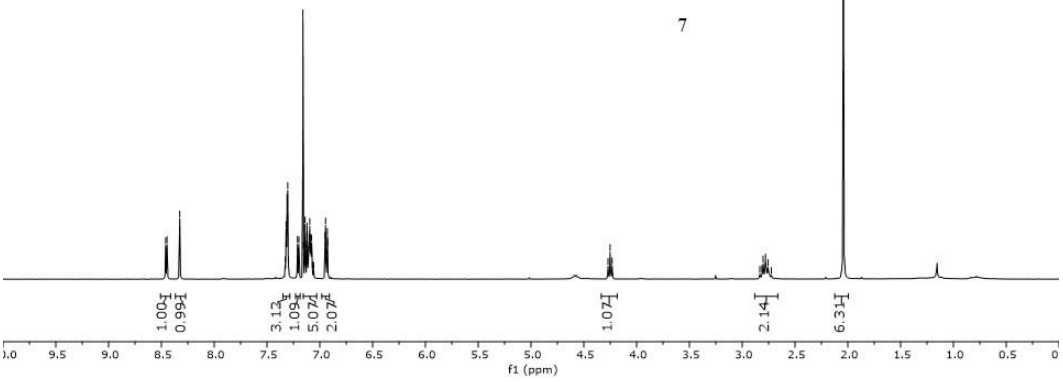
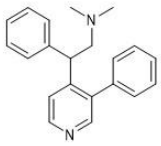


^{13}C NMR
$CDCl_3$, 100 MHz



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