DISSERTATION

SITE-SELECTIVE FUNCTIONALIZATION OF AZINES AND POLYAZINES VIA HETEROCYCLIC PHOSPHONIUM SALTS

Submitted by

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ABSTRACT

SITE-SELECTIVE FUNCTIONALIZATION OF AZINES AND POLYAZINES VIA HETEROCYCLIC PHOSPHONIUM SALTS

Pyridine and diazines are frequently found in FDA approved drugs, biologically active compounds, agrochemicals, and materials. Given the importance of these structural motifs, direct methods that selectively functionalize pyridine and diazine scaffolds have been developed. These methods and their associated challenges are discussed in chapter one.

In chapter two, a strategy to directly and selectively functionalize pyridines and diazines via heterocyclic phosphonium salts is presented. The process is broadly applicable for pyridines and diazines and the late-stage functionalization of pharmaceuticals. Four reaction manifolds are amenable to transforming heterocyclic phosphonium salts into valuable derivatives.

In chapter three, inherent factors that control site-selectivity in polyazine systems are described along with mechanistically driven approaches for site-selective switching, where the phosphonium ion can be predictably installed at other positions in a polyazine system.

The fourth chapter focuses on a new strategy to selectively alkylate pyridines via a traceless dearomatized phosphonium salt intermediate. Preliminary studies show this protocol is amenable to building-block pyridines, drug-like fragments and pharmaceuticals. A late-stage methylation strategy is also presented.

AKNOWLEDGMENTS

One of the most important things I've learned in graduate school is to not get discouraged when something doesn't work. Failure is an essential proponent of success.

I would like to thank Professor Andrew McNally for his guidance during my graduate career, for helping me develop as a chemist, and for providing direction when I needed help finding my footing. I would not be the chemist and person I am today without your help and support.

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CHAPTER ONE

INTRODUCTION TO PYRIDINE AND AZAARENE DIRECT FUNCTIONALIZATION

1.1 Importance of Pyridines and Azaarenes to Pharmaceuticals

Nitrogen-containing heterocycles (*N*-heterocycles) are among the most prevalent structural units found in FDA approved pharmaceuticals, naturally occurring bioactive compounds and agrochemicals.[1-3] In addition to bioactive compounds, *N*-heterocycles are common motifs in material sciences, and ligands for metal-catalysis.[4,5] In the context of small-molecule therapeutics, 59% of FDA approved pharmaceuticals in 2012 contained at least one *N*-heterocycle in their structure, with six-membered ring variants being the most common (**Figure 1.1**).[2] In this subclass, azaarenes such as pyridine were the second most frequently found in small-molecule therapeutics, while related azaarenes such as pyrimidines, pyrazines, and quinolines were also common.[2] In 2013, two of the five top-selling pharmaceuticals and six of the twenty-three small-molecule drugs approved by the FDA contained pyridines or related azaarenes.[2]

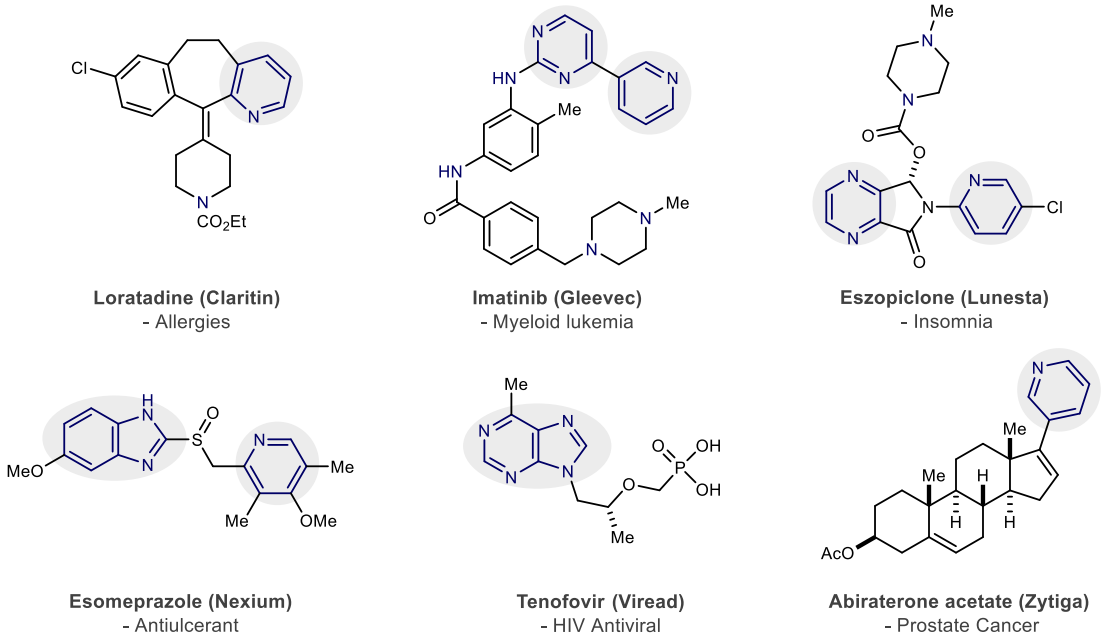

Figure 1.1. Examples of azaarenes in Pharmaceuticals.

The prevalence of azaarenes in pharmaceuticals and bioactive molecules is attributed to the effect these motifs have on the physical and chemical properties of the overall molecule.[2,6-8] Azaarenes, such as pyridine, are structurally similar to benzene with at least one carbon replaced with a nitrogen atom. This change results in several distinct properties relative to their benzenoid counterparts.[7,8] The nitrogen atom is sp^2-hybridized and has a lone pair perpendicular to the π-system of the ring. Since nitrogen is more electronegative than carbon, azaarenes are electron-deficient π-systems and are highly polarized with an induced dipole directed towards the nitrogen atom. These intrinsic characteristics result in azaarenes being soluble in aqueous media. Consequently, azaarenes are often implemented in drugs to enhance the aqueous solubility in order to improve bioavailability or uptake in the circulatory system.[9,10]

In addition to improving solubility, azaarenes can be implemented onto drug molecules to influence binding interactions with biological targets.[9,10] For instance, the nitrogen atom lone pair is a hydrogen bond acceptor and enhances binding affinity through hydrogen-bonding interactions between the drug and the target enzyme or receptor.[6] Examples of this key H-bonding interaction

include, the inhibition of Abl-kinase with the leukemia therapy-Bosutinib (**Figure 1.2**).[11,12] The nitrogen lone pair of electrons, on the quinoline ring of Bosutinib, forms a crucial hydrogen bond with the backbone amide of Met 318, preventing ATP from binding to the kinase and ultimately impeding the enzyme's function. On the other hand, the aromatic structure of azaarenes provide a rigid scaffold for the incorporation of functional groups that can participate in hydrogen-bonding with the target molecule.[13] For example, the lone pair of electrons on the nitrile group, attached to the quinoline scaffold, participates in hydrogen-bonding between a water molecule and an Asp 381 residue on the Abl-kinase (**Figure 1.2**).[12] Moreover, the ridged aromatic scaffold of azaarenes restricts bond rotation and therefore prevents undesired conformers which can be apparent in acyclic systems.[14]

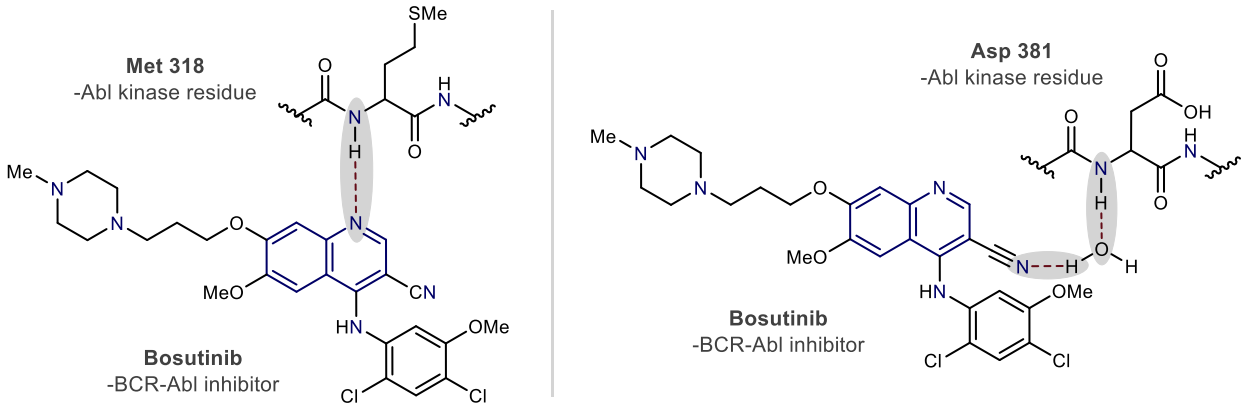

Figure 1.2. Hydrogen bonding interactions between Bosutinib and amino acid residues on Abl kinase.[11,12]

A major goal of drug design is to improve the efficacy, stability, membrane permeability, oral absorption, and adsorption, distribution, metabolism, and excretion (ADME) properties of the drug candidate.[15] A common approach to improve these properties is to replace a functional group in the drug candidate with its corresponding bioisostere, or functional group that display similar biological or physiochemical properties to the functional group that is being replaced.[16] For example, pyridines are often selected to replace certain arenes and heteroarenes with similar

physicochemical properties, such as isoxazoles, pyrazoles, nitrophenols, indanones, and even benzene.[16]

Drugs that pass through the liver are oxidatively metabolized by cytochrome P-450 (CYP-450) enzymes.[17,18] This class of enzymes oxidize weak C-H bonds found on electron-rich arenes into hydroxy groups. The increased polarity of the resulting metabolite consequently increases the water solubility, allowing the metabolized drug to be cleared from the body. While oxidation of electron-rich arenes by CYP-450 is a facile process, electron-deficient arenes, such as pyridines and diazines are less susceptible to oxidation by this class of enzymes.[17] Due to this key feature, azaarenes are often implemented into a drug candidate to tune its metabolic stability.[2,16-20]

1.2 Classical Methods for The Direct Functionalization of Pyridines and Diazines

Given the prevalence of azaarenes in pharmaceuticals, methods that selectively functionalize pyridine and diazine scaffolds are highly desirable. Strategies that can directly functionalize a C-H bond on pyridine are the most attractive, but present many challenges and limitations.[6,7] As previously mentioned, pyridines are electron-deficient and thus are poor π-nucleophiles. As a result, pyridines undergo electrophilic aromatic substitution reactions at much lower rates than benzene derivatives and often result in mixtures of regioisomers (**Figure 1.3**).[6] In addition, the Lewis-basic nitrogen lone pair can undergoe undesired ligation with metal complexes in metal-catalyzed reactions, and is susceptible to oxidation under oxidative conditions.[6,7] Despite these challenges, there have been several contributions and advancements for the direct functionalization of pyridines and diazines.

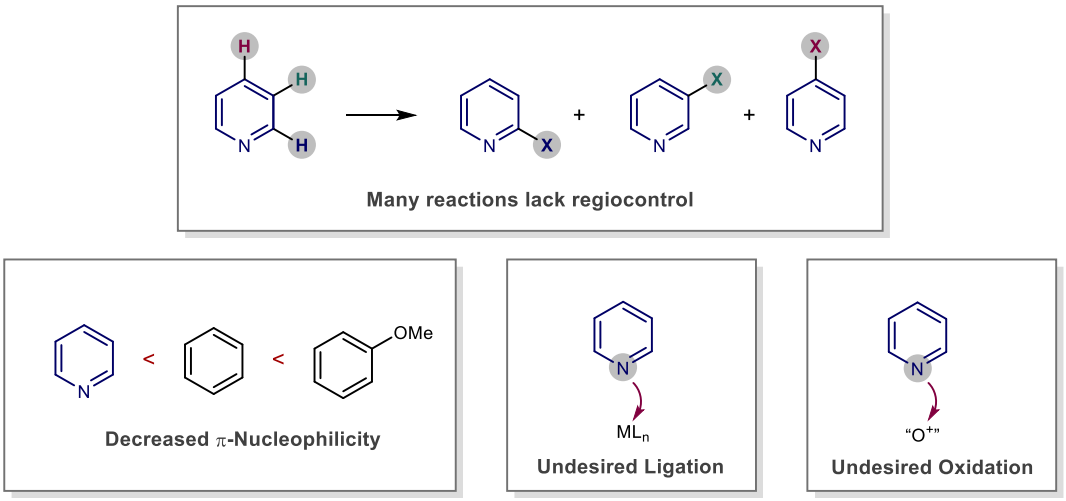

Figure 1.3. Challenges associated with direct functionalization of pyridine.

Electrophilic aromatic substitution (EAS) reactions, such as halogenation, represents a classical method to directly functionalize aromatics.[6,7] In an EAS process, a carbon-halogen bond is formed by reaction of the aromatic π-system with an electrophilic halogen source. The resulting carbon-halogen bond is a versatile synthetic handle for many processes including, cross-coupling reactions and radical processes, and can serve as a precursor for anion formation. While the halogenation of electron-rich arenes via EAS can be conducted at room temperature, the halogenation of pyridine is more challenging due to its poor π-nucleophilicity and therefore requires harsher conditions. For example, the bromination of pyridine requires heating in sulfuric acid in the presence of elemental bromine. While the bromination of pyridine is typically selective for the 3-position, polyhalogenation can also occur (**Figure 1.4**).[6,7] Given the severity of these conditions, functional group tolerance is very limited.

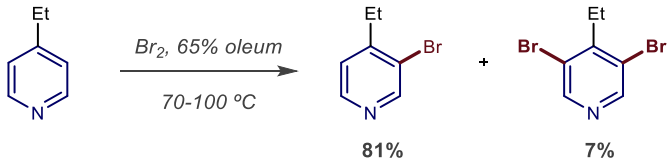

Figure 1.4. Bromination of pyridine via EAS.

Outside of EAS reactions, other methods for direct pyridine functionalization have also been developed. The Chichibabin reaction is a method to selectively install an amine at the 2-position of pyridines.[21,22] This method proceeds through an addition-elimination mechanism, where sodium amide first attacks pyridine at the 2-position forming a Meisenheimer σ-adduct intermediate (**1**), followed by the displacement of a hydride to regain aromaticity. A major drawback of this method, however, is the use of strongly basic $NaNH_2$, which limits the functional group tolerance of this reaction (**Figure 1.5**).[21]

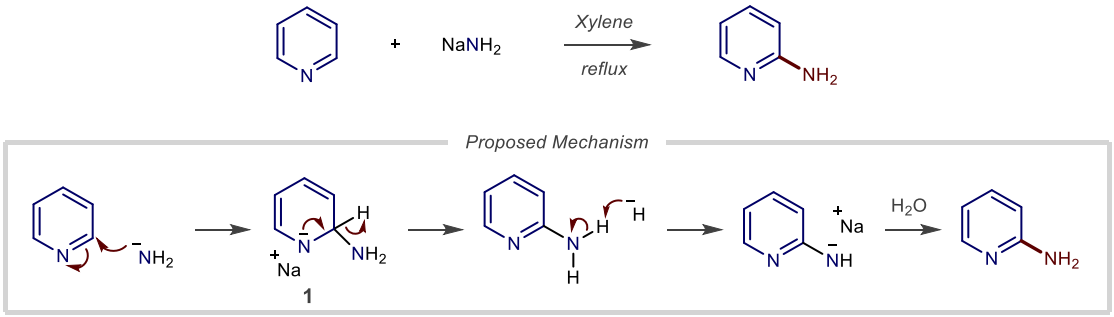

Figure 1.5. Chichibabin 2-amination reaction. A proposed mechanism is shown.

Direct metalation trapping reactions are one of the most traditional methods to directly functionalize pyridines.[23] Here, a lithium or magnesium base is used to deprotonate the pyridine ring to form a metalated species, followed by a reaction with an electrophile. On substituted pyridines, regioselectivity is typically controlled by using directing groups on the pyridine ring. The directing group coordinates to the metal ion, bringing the C-H bond in proximity to the metal to facilitate a selective deprotonation.[23,24] An alternative approach was reported by Knochel, where regioselective C-H activation of azaarenes is controlled by coordinating the nitrogen lone pair on the pyridine to a Lewis acid that prohibits reactions at the 2- and 3-positions via steric shielding (**Figure 1.6**).[24] Initial coordination of 3-fluoropyridine (**2**) with BF_3OEt_2 generates the pyridine-BF_3 Lewis pair (**3**), which is followed by selective deprotonation at the 4-position by tmpMgCl LiCl. Subsequent Negishi cross-coupling of the resulting 4-metalated pyridine (**4**) with an aryl

iodide (**5**) furnishes the 2-arylpyridine product (**6**). In the absence of this coordination with boron trifluoride (BF_3), Lewis pair tmpMgLi LiCl and BF_3, selectively deprotonates 3-fluoropyridine at the 2-position (**7**). The resulting 2-metalated pyridine (**8**) is then subjected to the Negishi-cross coupling conditions, to generate 4-arylated pyridine (**9**).

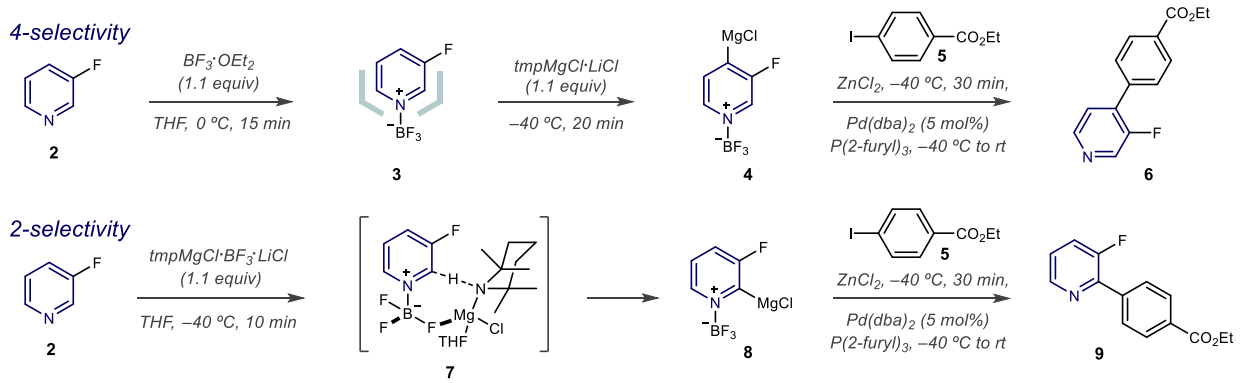

Figure 1.6. Regioselective metallation-trapping reactions on 3-fluoropyridine. Proposed mechanistic origin of selectivity is shown.[24]

Azaarenes can also be directly functionalized via radical pathways, such as the Minisci reaction, which directly installs carbon-fragments onto pyridines and diazines.[25-29] Aryl- and alkyl-radicals can be generated from the oxidative decarboxylation of a carboxylic acid using a catalytic amount silver nitrate ($AgNO_3$) and potassium persulfate ($K_2S_2O_8$). The resulting aryl radical **10** directly adds to a protonated azaarene **11** at elevated temperatures forming radical cation **12**, **Figure 1.7**).[27] Abstraction of the adjacent hydrogen atom generates the arylated pyridine (**13**). While this reaction often lacks regiocontrol between the 2-, 3-, and 4-positions, using acid has been shown to bias the selectivity towards the 2- and 4-positions. As there are a variety of carbon-centered radicals available, the Minisci reaction has been widely adopted by medicinal chemists to functionalize azaarene-containing intermediates.[25]

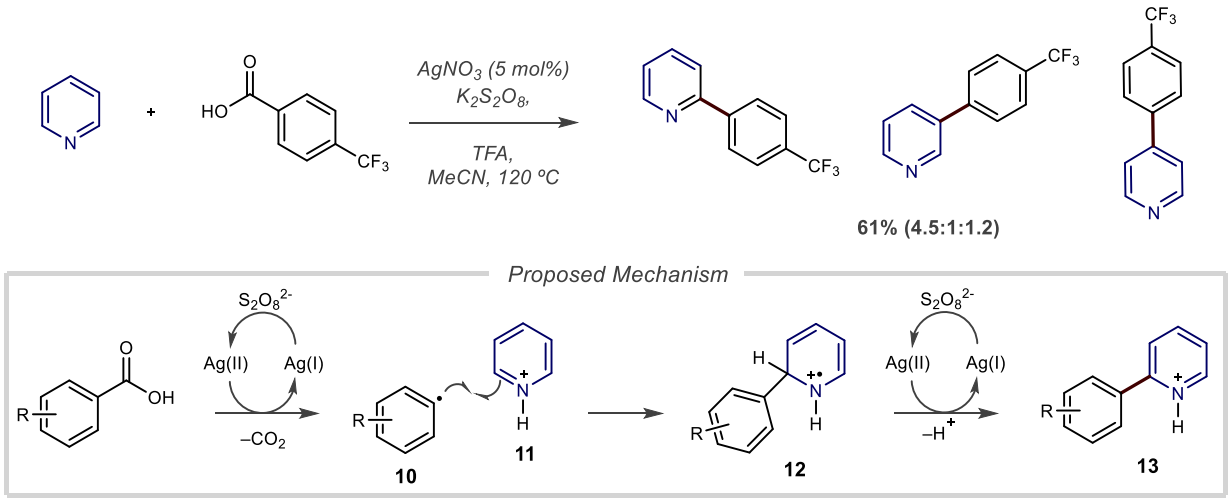

Figure 1.7. Example of the Minisci reaction and a proposed mechanism.[27]

1.3 Recent Advancements for The Direct Functionalization of Pyridines and Diazines

Using photoredox processes, different variations of Minisci-type reactions have emerged in recent years that rely on this mild and efficient method to generate radicals.[29] In 2014, DiRocco disclosed a method where methyl radicals, generated from *tert*-butylperacetate (*t*BPA) and visible-light photoredox catalysis, add to protonated azaarenes (**Figure 1.8**).[30] Following the excitation of Ir^{III} to Ir^{III*} using 450 nm light, *t*PBA is decomposed into *tert*-butyl radical (**I**) via a proton coupled electron transfer (PCET) event with Ir^{III*}. β-scission of the *tert*-butoxy radical (**I**), forms a methyl radical (**II**) which adds to the protonated azaarene. Oxidation of the resulting amino-radical cation (**III**) by Ir^{IV}, and subsequent deprotonation, generates the desired product (**IV**) and the active catalyst species. The direct methylation of Eszopiclone and Diflufenican are shown as representative examples using this method, where mixtures of regioisomers are formed. Additional photoredox-mediated Minisci-type reactions have been also developed by the groups of MacMillan, Stephenson, Baran, and Molander.[29,31-36]

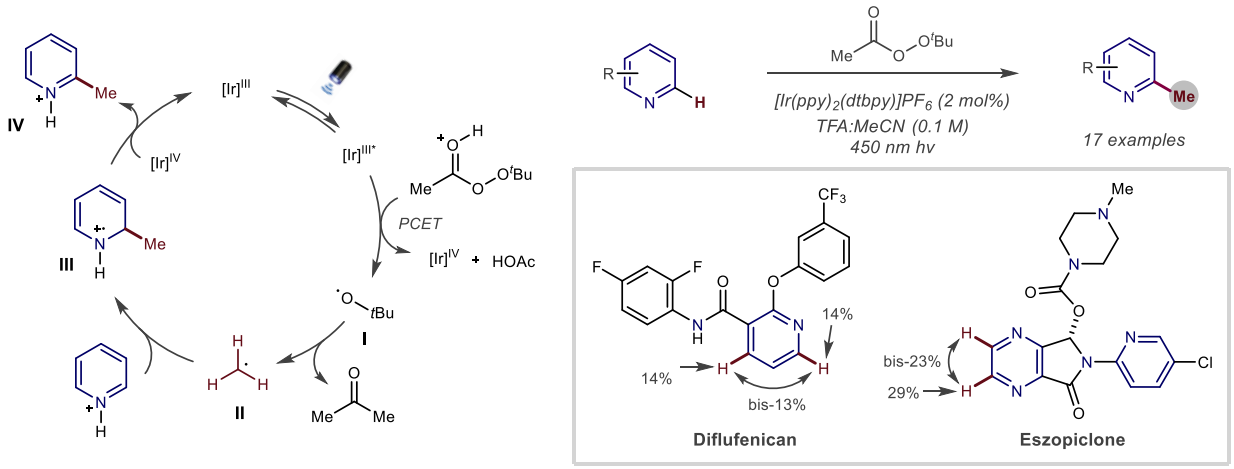

Figure 1.8. Late-stage alkylation of biologically active compounds via photoredox-mediated Minisci reaction. Proposed mechanism and examples are shown.[30]

Inspired by the Chichibabin reaction, Hartwig developed a strategy to directly fluorinate pyridines and diazines selectively at the 2-position, using commercially available silver(II) fluoride (AgF_2).[37,38] A proposed mechanism involves the initial coordination of AgF_2 with pyridine, followed by addition of the [Ag]-F bond across the N-C π-bond to form an amido-silver(II)-fluoride intermediate (**8**, **Figure 1.9**). Successive hydrogen atom abstraction via a second AgF_2 equivalent forms the fluorinated pyridine. The resulting 2-fluoropyridines can undergo subsequent S_NAr reactions with a variety of nucleophiles to generate a range of functionalized pyridines.[38] The selective fluorination and subsequent amination of (Me)-Roflumilast is shown as a representative example.

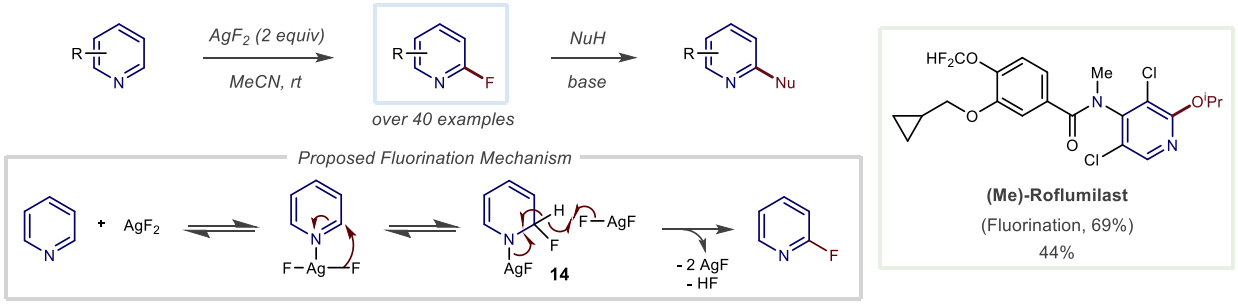

Figure 1.9. Hartwig's selective silver-mediated 2-fluorination of pyridines and subsequent S_NAr reaction. A proposed mechanism and representative example are shown.[37,38]

A recent method developed by Fier allows the direct nucleophilic functionalization of pyridines via a bifunctional aldoxime reagent.[39] After activation via α-chloro *O*-methanesulfonyl aloxime (**15**), the pyridinium salt (**16**) is subject to nucleophilic attack. In the presence of base, the activating reagent acts as a two-electron oxidant to rearomatize intermediate (**17**, **Figure 1.10**). This method was demonstrated to selectively cyanate a range of pyridines using a combination of silver triflate (NaOTf), sodium cyanide (NaCN), sodium carbonate (Na_2CO_3), and the activating reagent. The cyanation of a mixed progesterone agonist/antagonist is shown as a representative example. Preliminary results with other nucleophiles, such as alkoxides, malonates, Grignard and organozinc reagents have also been shown to selectively functionalize pyridines.[39]

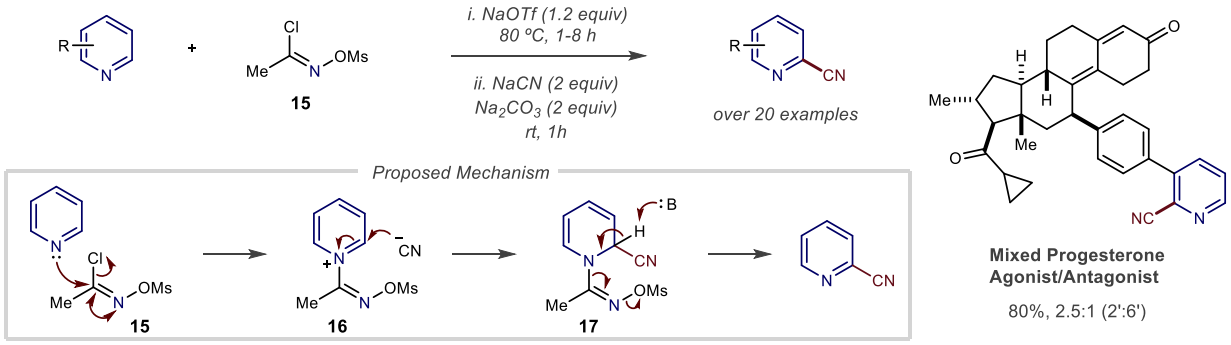

Figure 1.10. Fier's direct and selective functionalization of pyridines via a bifunctional reagent. A proposed mechanism and representative example are shown.[39]

Other modern methods to functionalize pyridines typically rely on transition metal catalyzed C-H activation approaches and are typically 2- or 3-selective. Common transition metals used in this strategy include, palladium, ruthenium, rhodium, iridium, nickel, and rare earth metal.[40-49] One of the most significant challenges in this approach is overcoming the strong coordination of the pyridine nitrogen atom with the transition metal catalyst. This coordination can lead to catalyst positioning or C-H functionalization at an undesired position on the pyridine ring.[49] In a recent study, Yu reported a Pd(II)-catalyzed 3-selective arylation of pyridines using 1,10-phenathroline (phen) as the ligand. Since 1,10-phenathroline is a stronger sigma donor than

pyridine, the coordination of the Pd catalyst with the pyridyl nitrogen atom is weakened by the *trans*-effect (**Figure 1.11**).[48] This in turn promotes the activation of the pyridyl C-H bonds over the coordination of the pyridine nitrogen atom with the Pd catalyst (**VI→VII**). C-H activation of pyridine at the 3-position is achieved after coordination of the Pd with the pi-system of the azaarene (**VII→IX**). Subsequent C-H activation of the arene partner is followed by reductive elimination (**IX→X**) to afford the 3-aryl pyridine **(XI)**.

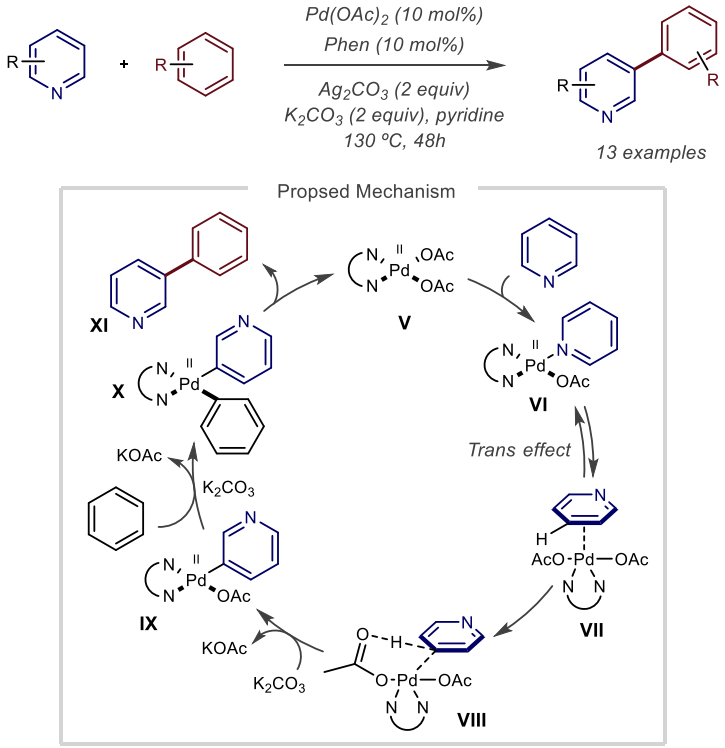

Figure 1.11. Yu's direct and selective arylation of pyridine. Proposed mechanism is shown.[48]

The iridium-catalyzed C-H borylation is an attractive method for the formation of aryl- and heteroaryl boronate esters. The resulting C-B bond is often used as a cross coupling partner in Suzuki reactions to form C-C bonds.[42] Hartwig reported a selective C-H borylation of pyridines using bis(pinacolato)-diboron (B_2pin_2) in combination with an iridium catalyst and bipyridine ligand (**Figure 1.12**).[50] C-H activation occurs at the 3-position of pyridine (**XIII**) followed by reductive elimination to afford the borylated pyridine (**XIV**). The reaction is generally 3-selective

but, can give mixtures of 2-, 3-, and 4-position isomers depending on the pyridine substitution pattern.

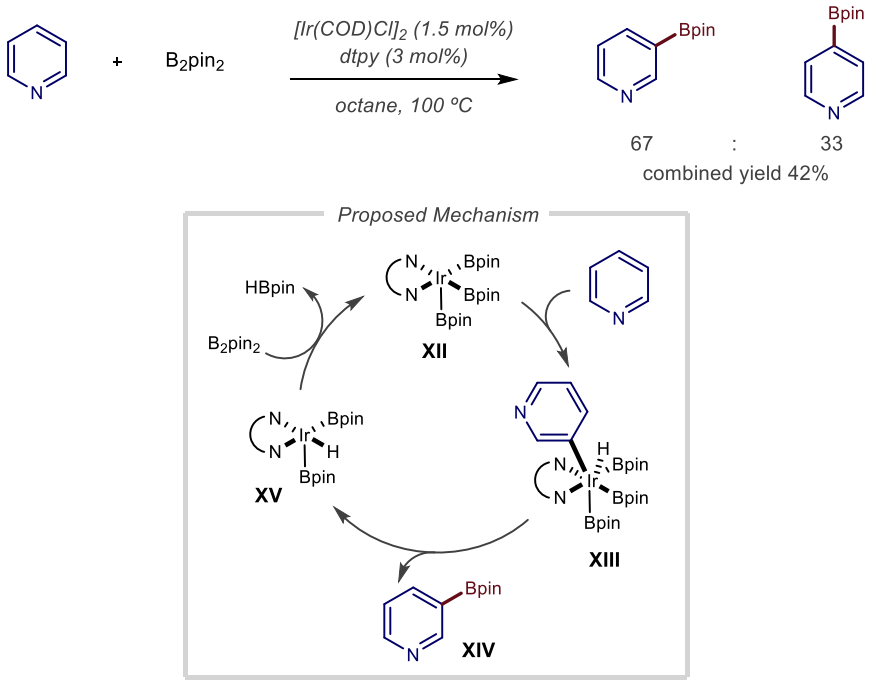

Figure 1.12. Iridium catalyzed-borylation of pyridine. Proposed mechanism is shown.[42,50]

1.4 Direct 4-Selective Methods for The Functionalization of Pyridines and Diazines

Compared with 2- and 3-selective methods, 4-selective pyridine functionalization methods are rare.[51-59] A common approach to selectively functionalize pyridines at the 4-position, involves reacting the pyridine nitrogen with an electrophile to form a pyridinium salt which makes the ring more electrophilic. This step is followed by a nucleophilic attack and subsequent oxidation to obtain the rearomatized product.[51,53] Comins has used this approach to selectively functionalize (*S*)-nicotine (**18**) at the 4-position using organocuprate reagents (**Figure 1.13**).[51] Nicotine is first reacted with pivaloyl chloride to form an *N*-acyl pyridinium salt (**19**). An organocuprate, formed from a reaction between a Grignard reagent and copper(I) bromide (CuBr), selectively adds to the 4-position of the pyridinium salt. The resulting dihydropyridine (**20**) is rearomatized with elemental sulfur to afford the functionalized nicotine product (**Figure 1.13**).

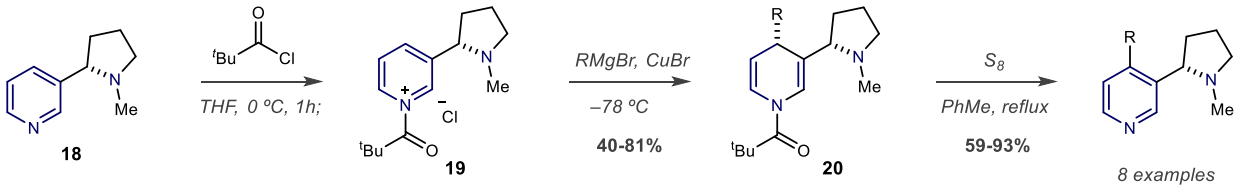

Figure 1.13. Comins' 4-selective functionalization of (*S*)-Nicotine.[51]

Direct, 4-selective pyridine alkylation and alkenylation has been achieved by the Nakao group, using synergistic Nickel/Lewis acid catalysis.[54,55] This process involves coordinating a bulky Lewis acid, methylaluminum bis (2,6-di-*tert*-butyl-4-methylphenoxide) (MAD, **21**), to the pyridine nitrogen which prohibits reactions at the 2- and 3-positions via steric shielding (**Figure 1.14**). C-H activation occurs at the 4-position of the pyridine using a nickel catalyst bound to an *N*-heterocyclic carbene (NHC) ligand, IPr. Subsequent migratory insertion across an alkene and reductive elimination affords the alkylated product as a mixture of branched and linear isomers. This method was also used to alkenylated pyridines with alkynes but results in mixtures of regioisomers on the pyridine ring.

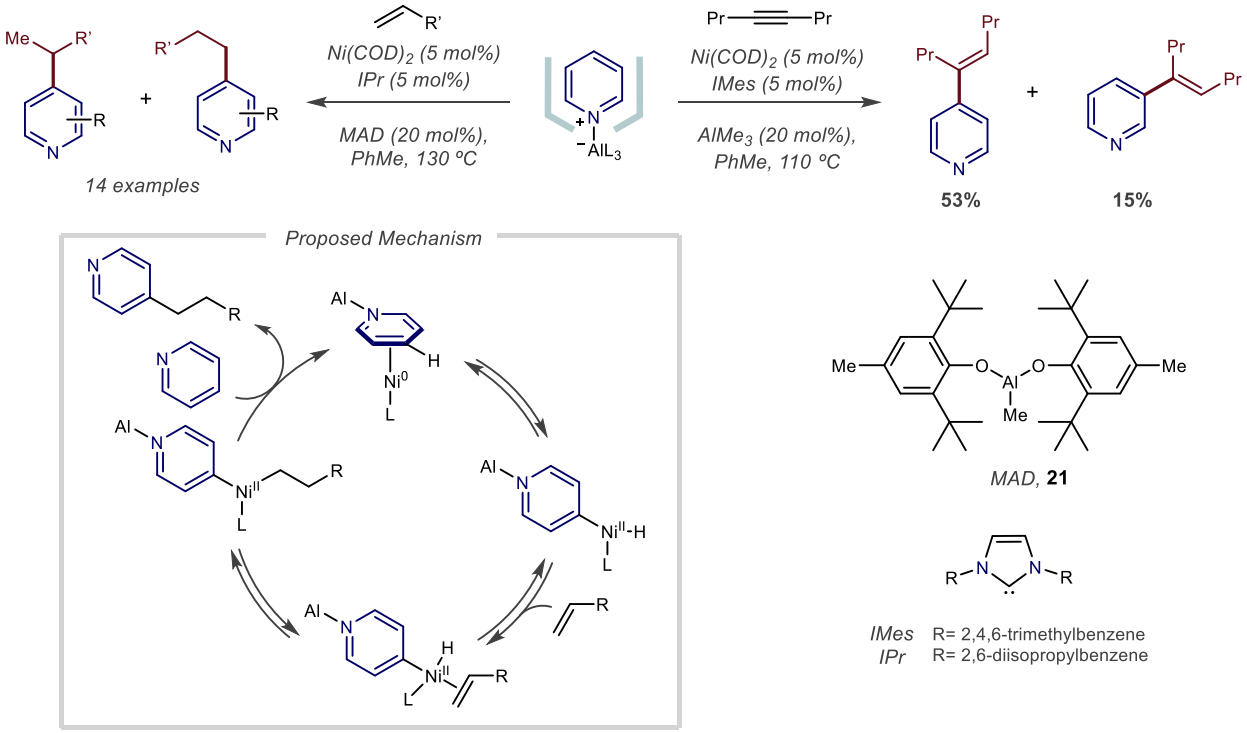

Figure 1.14. Nakao's alkylation and alkenylation via synergistic Ni/LA catalysis. A proposed mechanism, and structures of MAD catalyst and NHC ligands are shown.[54]

Kanai reported a 4-selective alkylation of pyridines using a catalytic nucleophilic addition-rearomatization sequence (**Figure 1.15**).[56] Cobalt-hydride [Co-H] catalyst (**XVI**) is generated by a reaction between cobalt(II) bromide ($CoBr_2$) and lithium triethylborohydride ($LiBEt_3H$). This step is followed by hydrometalation of a substituted alkene (**XVII**) to form a reactive alkyl-cobalt species (**XVIII**). Subsequent nucleophilic addition to pyridine, followed by rearomatization generates the 4-alkylpyridine (**XIX**). Although highly selective for the 4-position, the reaction is limited to mono-substituted pyridines and in most cases the products are generated as mixtures of branched and linear products.

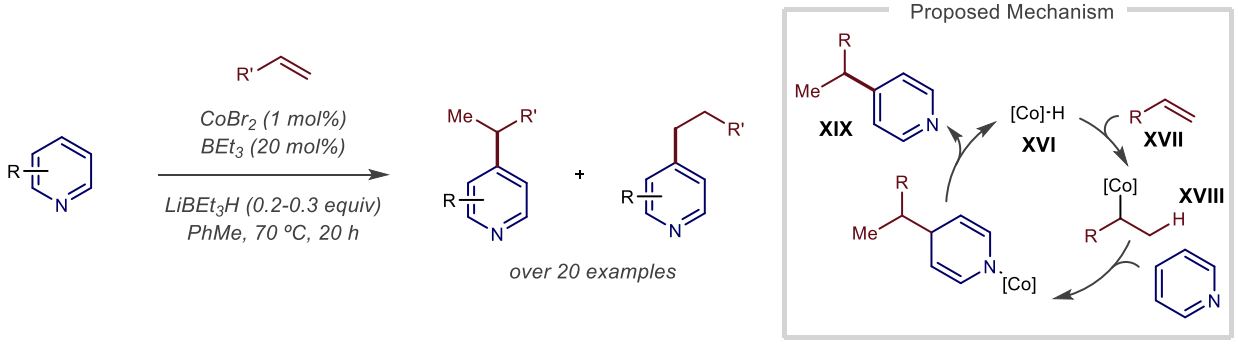

Figure 1.15. Kanai's 4-selective alkylation of pyridine via Co-H. Proposed mechanism is shown.[56]

Kanai also reported a 4-selective C-H perfluoroalkylation of pyridines and related six-membered heteroaromatics (**Figure 1.16**).[59] Similarly to the synergistic Ni/Lewis acid catalytic system, initial activation of the pyridine via a bulky borane Lewis acid, $B(C_6F_4\text{-}CF_3)_3$, sterically shields the 2- and 3-positions of the azaarene (**22**). A reaction between tetrabutylammonium difluorotriphenylsilicate (TBAT) and trimethyl(trifluoromethyl)silane (Me_3SiCF_3) generates a trifluormethyl anion that selectively attacks the 4-position of pyridine. The resulting dihydropyrdine intermediate (**23**) is subsequently oxidized via bis(trifluoroacetoxy)iodobenzene ($PhI(O_2CCF_3)_2$) affording the 4-trifluormethylated pyridine (**24**). The reaction requires an additional oxidation step to form the 4-trifluoromethylated pyridine product and, in most cases, a mixture of regioisomers at the 2- and 6-positions is produced, albeit in low yield.

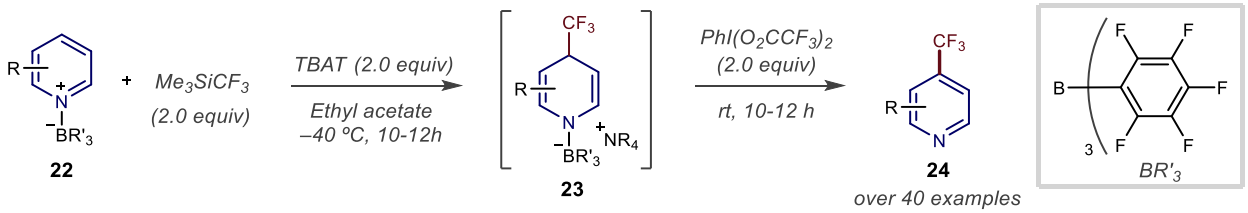

Figure 1.16. Kanai's 4-selective trifluoromethylation reaction.[59]

Recently, Martin developed a method that selectively installs a silyl-group onto the 4-position of azaarenes via silylboranes (**Figure 1.17**).[60] Initial complexation of pyridine with a solvated potassium ion occurs via the activation of silylborane, $Et_3SiBpin$ with potassium hexamethyldisilizane (KHMDS) in DME. Subsequent nucleophilic attack of the resultant boronate

species (**25**), selectively adds the silyl group at 4-position of pyridine and the silylated product is generated in an aqueous workup. When dioxane is used as the solvent the silyl group is selectively added to the 2-position of pyridine (**26**, **Figure 1.17**).

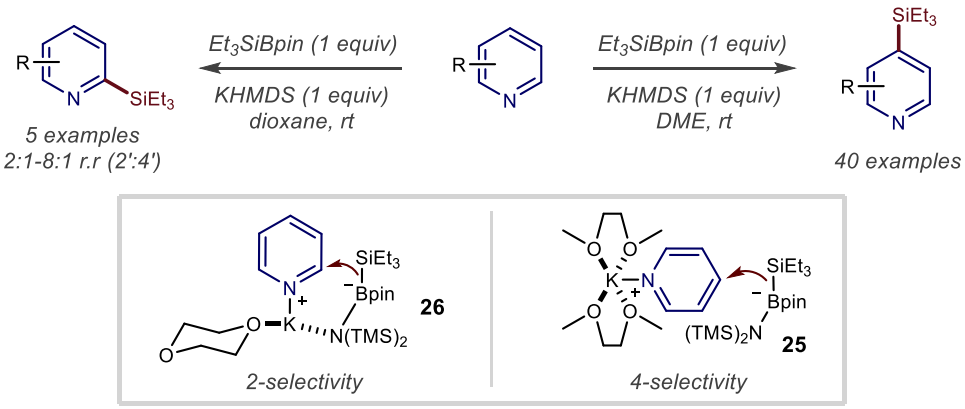

Figure 1.17. Martin's selective silylation of pyridines. Mechanistic origin of selectivity is shown.[60]

1.5 Conclusion

This chapter serves to highlight the importance of pyridines and diazines in pharmaceuticals and demonstrate the current methods and challenges in functionalizing these azaarenes. Classical methods, as well as recently developed strategies to directly functionalize pyridines are discussed. While many of these methods are 2- or 3-selective for pyridine, 4-selective processes are rare and limited to C-C and C-Si bond constructions.

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CHAPTER TWO

SELECTIVE FUNCTIONALIZATION OF PYRIDINES AND DIAZINES VIA PHOSPHONIUM SALTS

2.1 Introduction to Heterocyclic Phosphonium Salt Formation

As discussed in the previous chapter, there have been several advancements for the direct functionalization of azaarenes. While most of these methods are 2- and 3-selective processes (section **1.2** and **1.3**), reactions that selectively target the 4-position on pyridines are relatively scarce (section **1.4**).[3-13] Many of the existing methods are also limited to C-C bond forming processes such as Nakao's and Kanai's methods to install alkyl and perfluoroalkyl groups, respectfully.[7-9,12] While C-C bonds are important, they inherently result in a limited set of pyridine derivatives. An alternative strategy to make functionalized pyridines and diazines is to install a versatile synthetic handle that facilitates multiple subsequent bond-forming reactions (**Figure 2.1**).

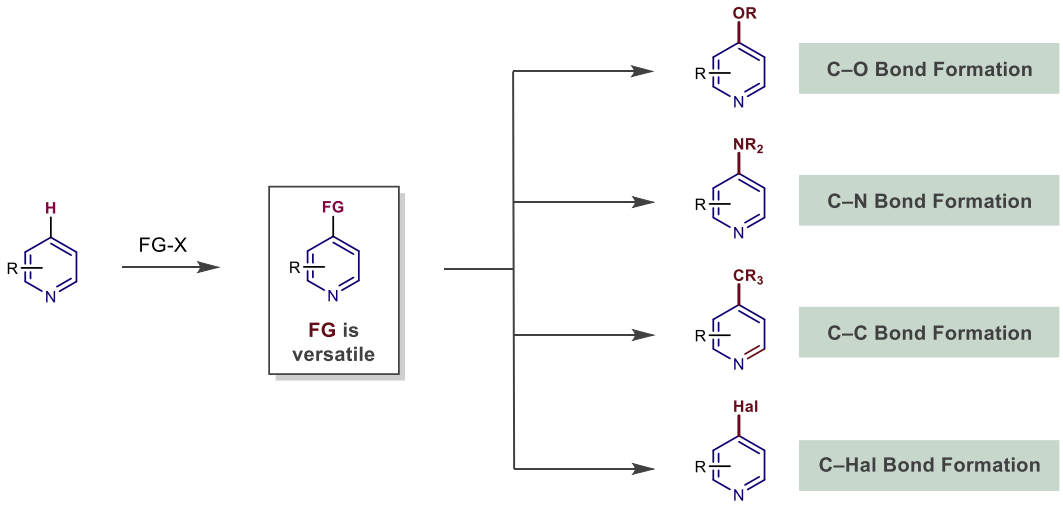


Figure 2.1. Design plan for the direct functionalization of pyridines.

The longstanding challenges associated with selective pyridine and diazine functionalization prompted us to develop an alternative strategy where a versatile functional group is directly and selectively installed at the 4-position of pyridines (**Figure 2.1**).[6,14,15] This strategy should employ simple, commercially available reagents, and be easily performed with high reproducibility. To be adopted by medicinal chemists, this protocol must be applicable to a broad range of substrates. Most pyridine functionalization reactions target building block molecules, which are relatively simple pyridines, and are used as starting materials at the beginning of a drug development process (**Figure 2.2**). A more useful method would allow the direct functionalization of more complex molecules found at the later stages of the drug discovery process, which include drug fragments and pharmaceutical compounds. However, as these molecules contain many polar functional groups such as amides and amines, selective functionalization is very challenging.

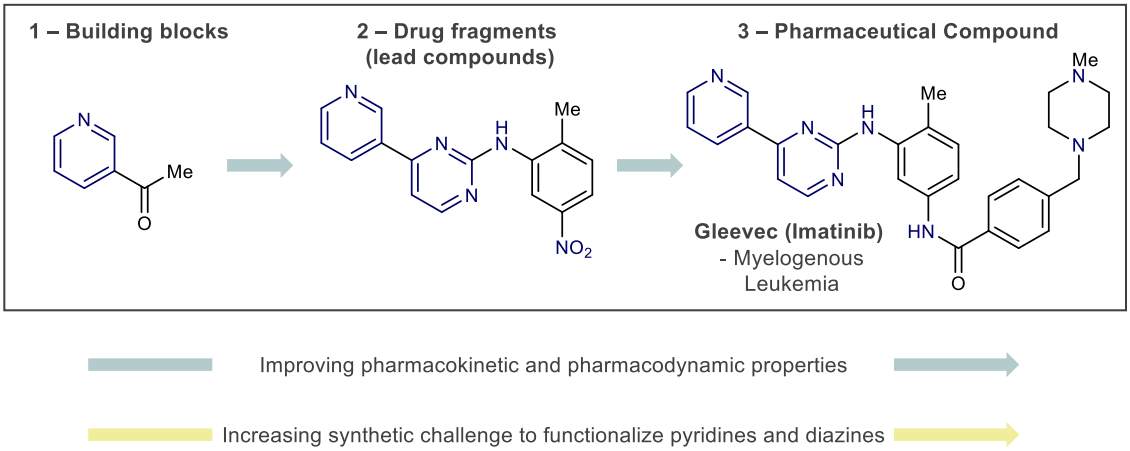


Figure 2.2. Development process of a drug molecule.

With the goal of creating a broad and practical method in mind, our strategy for pyridine functionalization centered on selectively adding a nucleophile to an activated pyridinium salt followed by rearomatization.[15] Through careful choice of the nucleophile, we hypothesized this strategy could result in addition of a versatile functional handle directly from the pyridine C-H bond. It is well known that pyridines (**I**) will react with reagents such as Tf_2O to form pyridinium

triflates (**II**, **Figure 2.3**). These intermediates are very electrophilic and are susceptible to attack by a range of nucleophiles, such as phosphines, to form a dearomatized intermediate (**III**).[15] Finally, a base-mediated elimination should rearomatize the intermediate, affording a heteroarylphosphonium salt (**IV**). During our own investigations, we became aware of a report from Anders in which pyridine could be transformed into a heterocyclic phosphonium salt by sequential addition of Tf_2O (trifluoromethanesulfonic anhydride), PPh_3 (triphenylphosphine) and NEt_3 (triethylamine) at low temperature with exclusive 4-selectivity.[16-22] While this process validates our mechanistic approach, the number of pyridine derivatives tested was limited. As such, we sought to develop a method that selectively installs a phosphonium ion onto a range of azaarenes of varying complexity and use the resulting heteroarylphosphonium salt to facilitate a variety of bond-forming transformations.

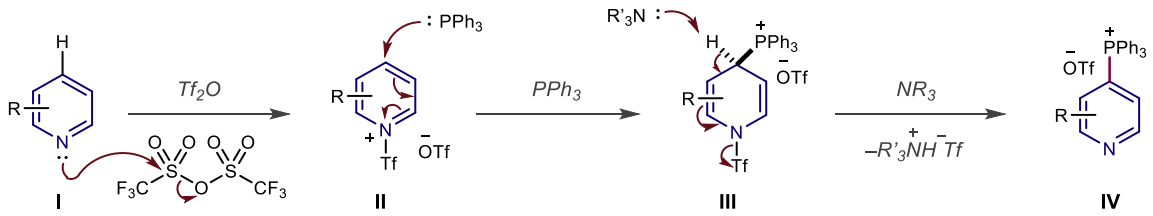


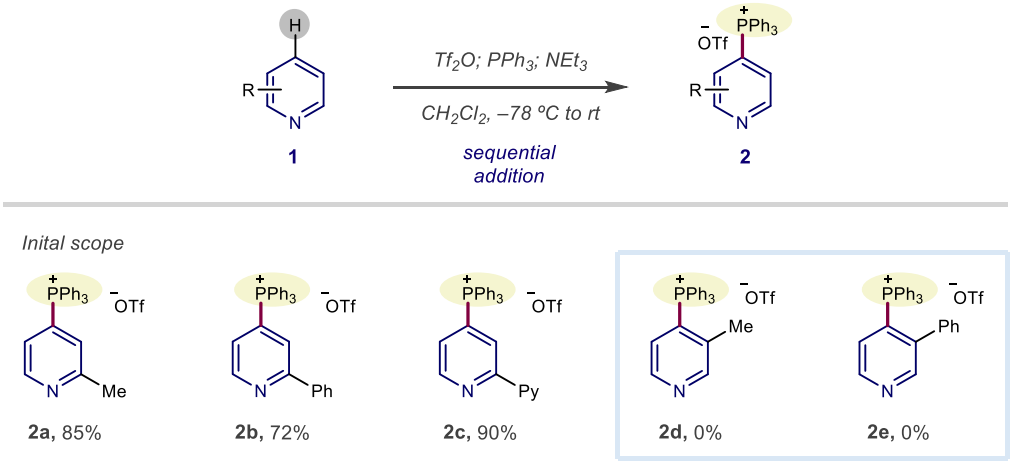
Figure 2.3. Proposed mechanism for phosphonium salt formation.

2.2 Optimization of Heterocyclic Phosphonium Salt Formation Protocol

To examine the scope of heteroarylphosphonium salt formation, we initially investigated simple mono-substituted pyridines (**Table 2.1**). While 2-substituted pyridines worked well under Anders' reported reaction conditions (**2a-2c**), 3-substituted alkyl or arylpyridines failed to form the corresponding phosphonium salt (**2d & 2e**).[16-22] We reasoned that triphenylphosphine was insufficient as a nucleophile to attack the *N*-triflyl pyridinium salt or the nucleophilic approach of the phosphine was sterically blocked by the 3-substituent on the pyridine. To address this issue, 3-methylpyridine (**1d**) was used as a representative substrate to screen a variety of phosphine

nucleophiles. Unfortunately, trialkylphosphines, triheteroarylphosphines, and phosphites proved unsuccessful in generating the desired product (not shown).

Table 2.1. Initial pyridine scope for phosphonium salt formation.



Yields determined from ^{1}H NMR are shown. 1,3,5-trimethoxybenzene is used as internal standard.

To further evaluate the reaction, ^{1}H NMR and mass spectrometry were used to observe intermediates in the reaction (**Figure 2.4**). Upon adding PPh_3 to the *N*-triflyl pyridinium salt **V**, the expected dearomatized species **VI** was not observed at room temperature via ^{1}H NMR analysis. However, when using PBu_3 (tributylphosphine) instead of PPh_3 as the phosphine source, dearomatized species **VII** was observed at the same temperature in near quantitative conversion from the *N*-triflyl pyridinium salt. It was later found that dearomatized intermediate **VI** can be observed at –80 °C via variable temperature (VT) NMR but decomposes into pyridine and PPh_3 upon warming to room temperature. As this information was unknown at the time of this study, we decided to procced with the optimization of this reaction using PBu_3 as a representative phosphine source since the reaction was easier to assay at room temperature.

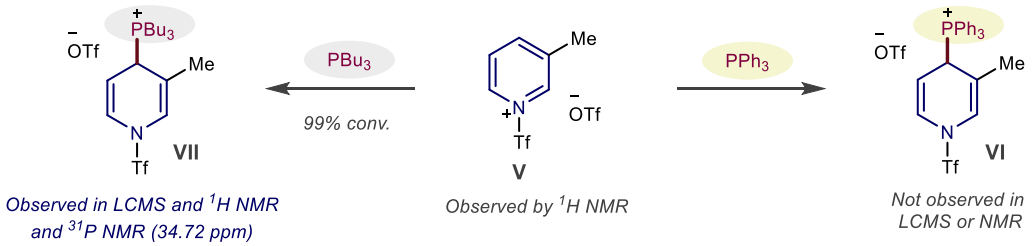
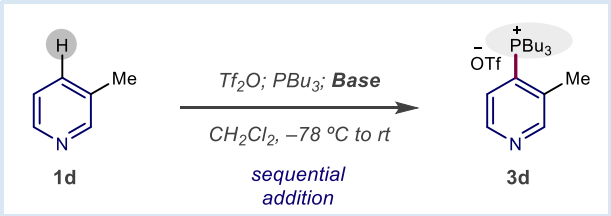


Figure 2.4. Effect of triphenyl vs trialkylphoshine in the formation of dearomatized intermediates. ^{1}H NMR experiments were run at room temperature, using 1,3,5-trimethoxybenzene as an internal standard.

We next investigated the effect of the base using PBu_3 (**Table 2.2**). After forming the dearomatized species **VII**, CH_2Cl_2 was evaporated and replaced with THF. Subsequent addition of sodium hydride (NaH) afforded the phosphonium salt (**3d**) in 90% yield via ^{1}H NMR analysis (entry 2). We next examined organic bases that would make solvent exchange 1.unnecessary. A range of organic bases were effective in forming the target product. Specifically, TMG (1,1,3,3-tetramethylguanidine), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), and TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) (**entries 3-5**) all gave phosphonium salt in reasonable yields. These experiments highlight that the selection of base has an important role in generating phosphonium salts.

Table 2.2. Optimization of base for tributylphosphonium salt.

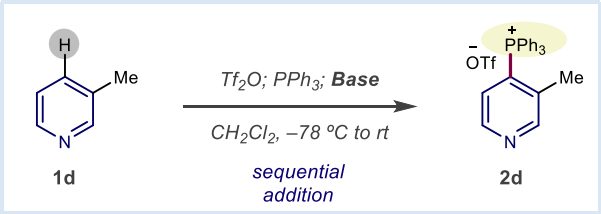


Entry	Base	% Yield
1	NEt_3	**0**
2	NaH/THF	**90**
3	DBU	**57**
4	TMG	**68**
5	TBD	**56**

Yields determined from ^{1}H NMR are shown. All NMR experiments were run at room temperature. 1,3,5-trimethoxybenzene is used as internal standard.

PBu_3 is routinely kept in a glovebox since it is readily oxidized to its corresponding phosphine oxide in the presence of oxygen, making handling and running reactions with PBu_3 challenging. To avoid this, we questioned whether the observed base effect with PBu_3 would also promote reactions with air stable PPh_3. A range of bases were evaluated using PPh_3 as the phosphine (**Table 2.3**). Stronger organic bases resulted in the desired phosphonium salt (**2d**) in high yield with complete 4-selectivity, while the NaH/THF system was unsuccessful for phosphonium ion formation. It was determined after further experimentation that DBU was the most consistent base across a broad substrate scope and was selected for reaction development. Using DBU as the base allowed us to significantly expand our substrate scope, as well as, improve the yields of substrates that previously had low product conversion when NEt_3 was used as the base (section **2.3**).

Table 2.3. Optimization of base for triphenylphosphonium salt.



Entry	Base	% Yield
1	NEt_3	**0**
2	NaH/THF	**0**
3	DBU	**78**
4	TMG	**74**
5	TBD	**70**

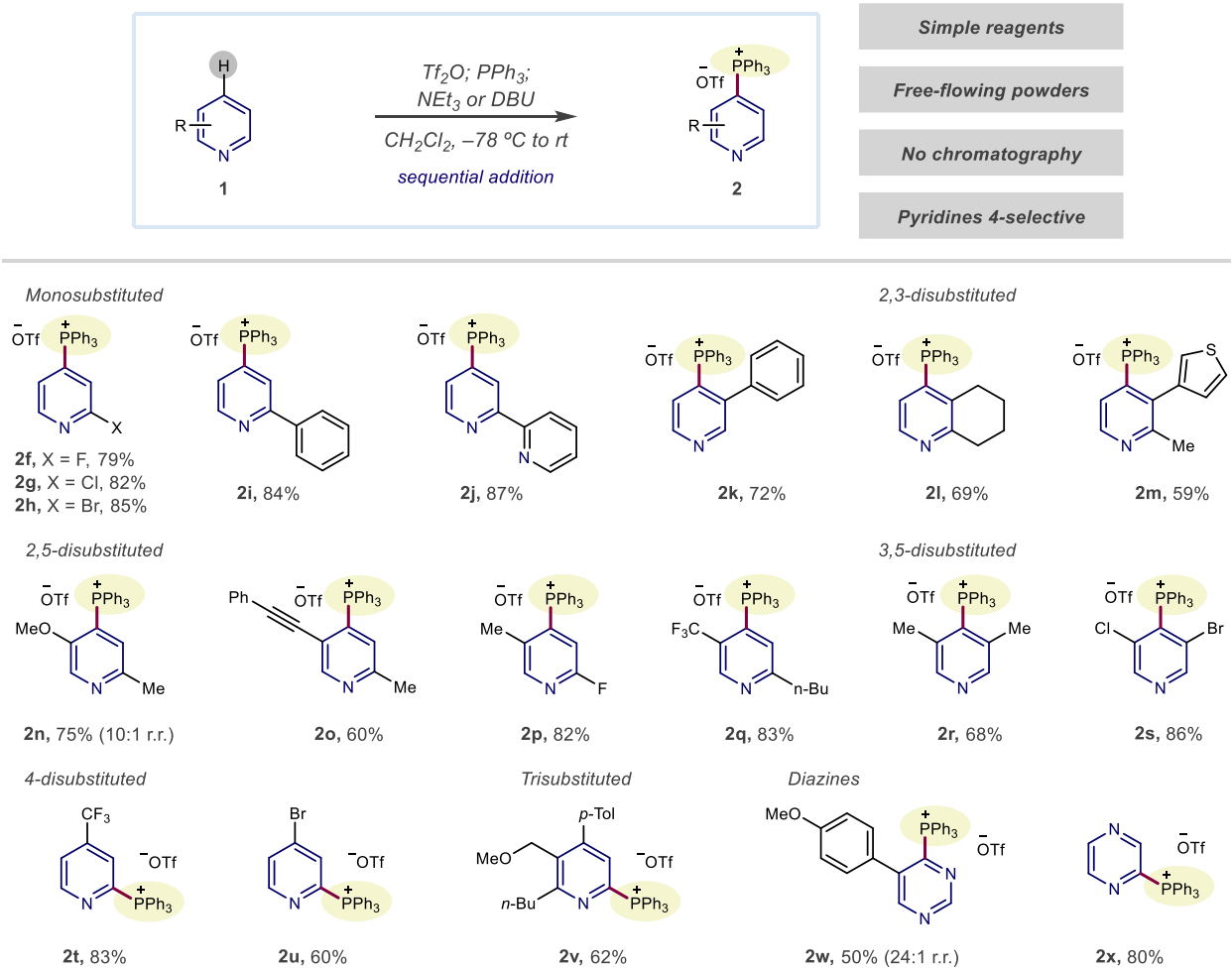
Yields determined from ^{1}H NMR are shown. 1,3,5-trimethoxybenzene is used as internal standard.

2.3 Heterocyclic Phosphonium Salt Formation Substrate Scope

Our optimized conditions for C-P bond formation includes, activation of pyridine with Tf_2O in CH_2Cl_2 at –78 °C, followed by sequential addition of PPh_3, and addition of DBU or NEt_3, to afford the heteroarylphosphonium salt (**Table 2.4**). The phosphonium salts are isolated as free-flowing powders via precipitation in cold diethyl ether, thus avoiding the need for column chromatography. Furthermore, in most cases, the salts are isolated exclusively as the 4-substituted product. We found monosubstituted pyridines to be excellent substrates for phosphonium ion formation (**2f-2k**). Notably, 2-halosubstituted pyridines are amenable under the reaction conditions, where no halogen displacement via competitive nucleophilic aromatic substitution (S_NAr) reactions was observed (**2f-2h**). A range of substitution patterns are applicable for phosphonium ion formation, including 2,3- (**2l & 2m**) and 2,5-disubstituted pyridines (**2n-2q**), with different electron-donating and electron-withdrawing groups occupying various positions on the rings. Interestingly, 3,5-disubstituted rings are amenable under the reaction conditions (**2r & 2s**). Despite the steric encumbrance created by the 3,5-substituents, the phosphine still prefers to

add at the 4-position over the 2-position. When the 4-position is substituted, as in 4-substituted **2t**, **2u**, and trisubstituted **2v**, the phosphonium ion is formed at the 2-position. Additionally, we found that diazines, such as pyrimidine (**2w**) and pyrazine (**2x**), are competent heterocycles under the phosphonium salt protocol.

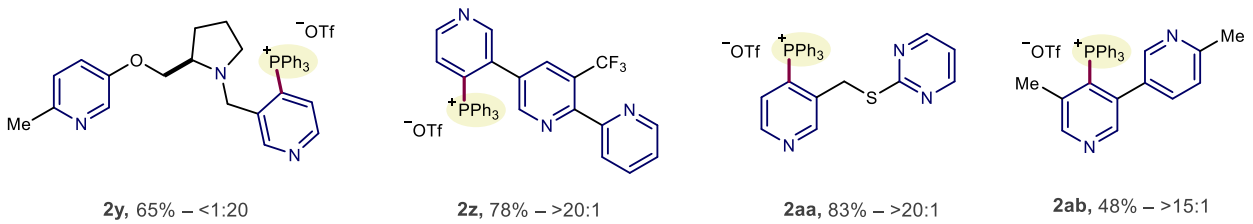
Table 2.4. Heterocyclic Phosphonium Salt Scope[a,b,c]



[a]Typical reaction stoichiometry: azaarene (1.0 equiv), Tf_2O (1.0 equiv), PPh_3 (1.1 equiv), organic base (1.0 equiv). [b]Isolated yields of single regioisomers (unless stated) are shown. [c]r.r. = regiomeric ratio. For 2n and 2w, the minor product is the 2-phosphonium salt isomer and the crude ^1H NMR ratios are 10:1 and 20:1, respectively.

With the optimized conditions established on a set of building block compounds, we next designed a set of more complex molecules representing drug-like fragments seen in medicinal chemistry. We found that the phosphonium ion can be selectively installed in the presence of

amines and other pyridines and/or diazines (**2y-2ab**, **Figure 2.5**). As such it was found that in addition to being regioselective, the phosphonium ion formation is also site-selective, with the phosphonium salt preferentially forming on one pyridine in these polyazine systems. The origin of the observed site-selectivity within these molecules is discussed in-depth in Chapter 3.



2y, 65% – <1:20 **2z**, 78% – >20:1 **2aa**, 83% – >20:1 **2ab**, 48% – >15:1

Figure 2.5. Examples of drug-like fragments. Isolated yields are shown. Ratios represent site-selectivity of phosphonium salt formation.

Furthermore, we investigated the viability of the phosphonium salt formation protocol for the late-stage functionalization of biologically active compounds and pharmaceuticals (**Figure 2.6**). Nicotine (**4**), despite containing a tertiary amine, affords the corresponding phosphonium salt in good yield. Pharmaceuticals such as Loratadine (**5**) and Abiraterone acetate (**9**), are effective substrates for salt formation. Initially, Cinchonidine (**6**) failed to form the phosphonium salt. It was hypothesized that the secondary hydroxyl group, rather than the pyridine, was reacting with Tf_2O. By protecting the hydroxy on Cinchonidine with a benzyl group, the phosphonium salt is installed with a yield of 52% (**6**). Similarly, Chlorphenamine (**7**) and Varenicline (**8**) did not produce phosphonium salts during our initial attempt. It was reasoned that the amines present in these molecules were reacting with Tf_2O, thus preventing phosphonium salt formation. Adding an equivalent of HOTf to Chlorphenamine to protonate the tertiary amine and protecting the secondary amine in Varenicline with a benzyl group, provided the corresponding phosphonium salts in reasonable yield (**7 & 8**). Interestingly, Imatinib (**11**), despite containing multiple basic nitrogen atoms and a pyrimidine ring, affords the phosphonium salt product in high regio and site-selectivity.

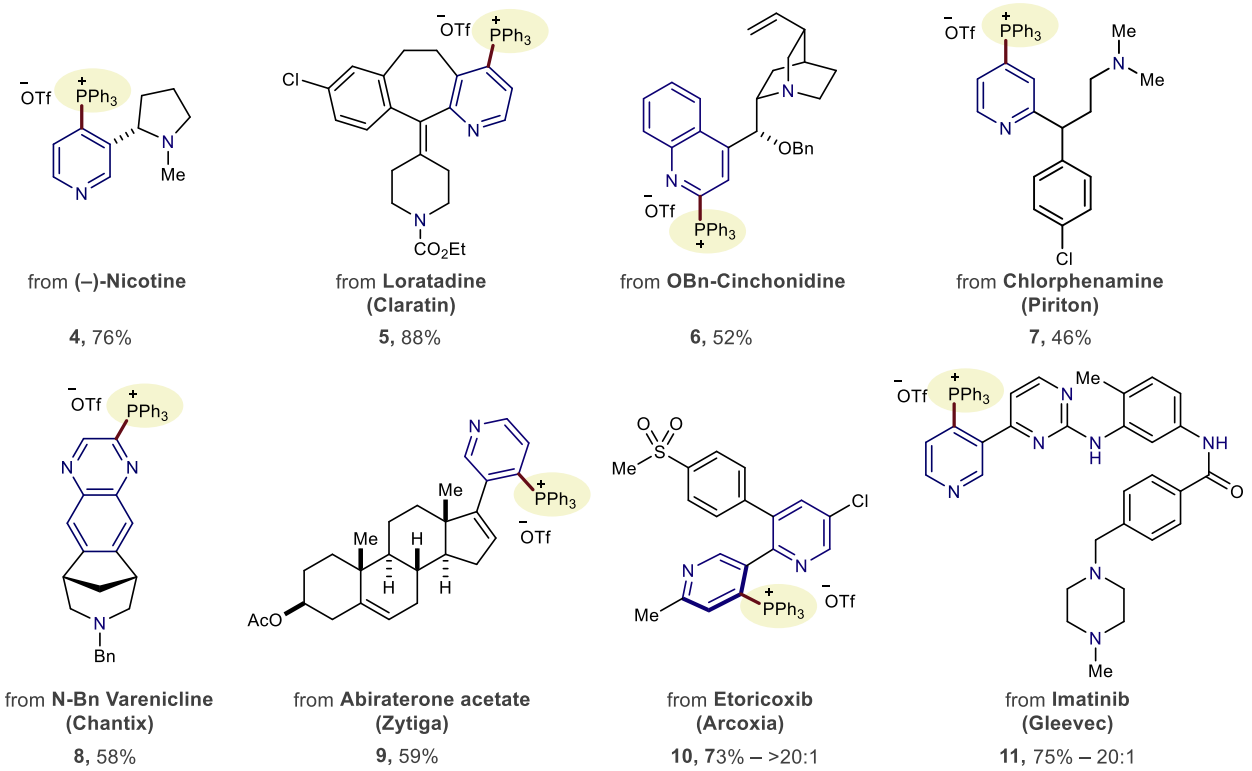


Figure 2.6. Examples of the late-stage functionalization of biologically active compounds and pharmaceuticals. Isolated yields are shown. Ratios represent site-selectivity of phosphonium salt formation.

Current limitations for phosphonium salt formation include substrates which contain functional groups that react with Tf_2O including, primary and secondary amines, hydroxyl groups, and alkyl amides (**Figure 2.7**). In such cases (**6-8**), the hydroxyl group or amine was protected, and the salt was formed in reasonable yields (**Figure 2.6**). In addition, 2,6-disubstituted pyridines form phosphonium salts in only trace amounts. We hypothesized that this outcome can be attributed to steric encumbrance at the nitrogen that prevents reaction of the pyridine with Tf_2O. Additionally, when substrates contain multiple electron-withdrawing groups, the nucleophilicity of the azaarene is decreased and prevents reaction with Tf_2O.

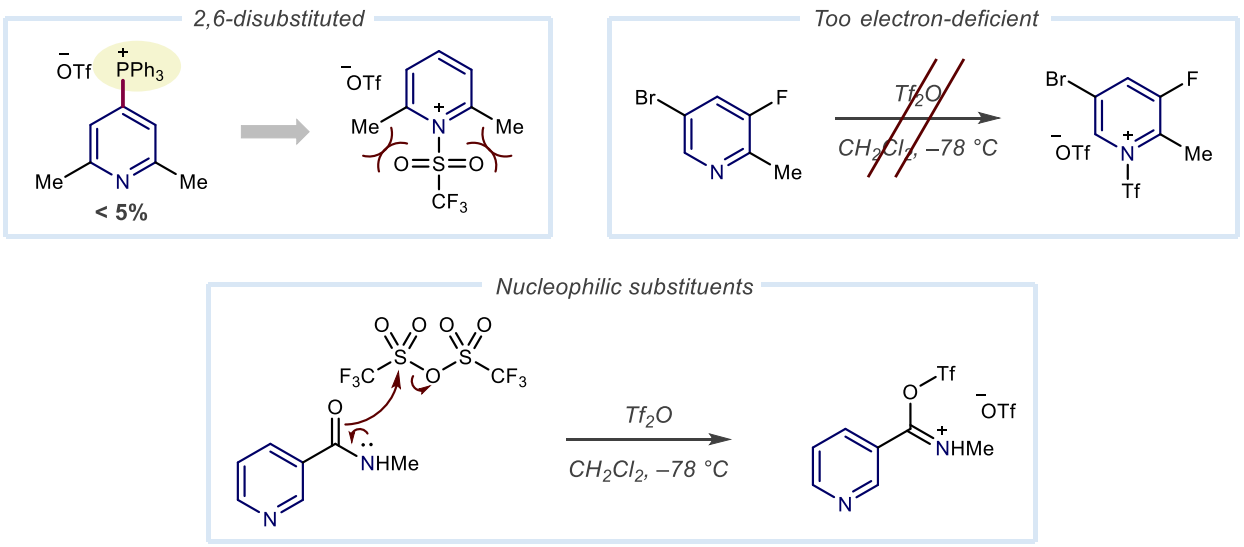


Figure 2.7. Limitations of phosphonium salt formation.

2.4 Heterocyclic Phosphonium Salt Formation Computation Study

After demonstrating a range of complex azaarenes are amenable under the phosphonium salt formation conditions, the origin of the observed 4-selectivity was next investigated computationally through a collaboration with the Paton group. The Gibbs free energy of activation ($\Delta G^{\ddagger}$) of the PPh_3 attacking the 4- and 2-position of the *N*-triflyl pyridinium salt, as well as, at the sulfur atom within the *N*-triflyl group was calculated using the dispersion-corrected density functional theory (DFT) functional ωB97X-D with the 6-31+G(d) basis set and the correlated wavefunction theory (WFT) DLPNO-CCSD(T)/cc-pV(DT)Z (**Figure 2.8**). It was found that the attack of PPh_3 at the 4-position is significantly more energetically favorable with a $\Delta G^{\ddagger} = 6$ kcal/mol. Upon further investigation, it was found that the DFT calculated transition state of the phosphine attacking the para-position shows a favorable π-stacking interaction between one of the phenyl rings on the phosphine and the *N*-triflyl pyridinium ring. A similar interaction is seen in the DFT calculated transition state for the 2-position attack, however, an additional steric interaction was observed between one of the phenyl rings on the phosphine and the *N*-triflyl group. The steric repulsion between the PPh_3 and the *N*-triflyl group is hypothesized to destabilize the

resulting dearomatized intermediate, which explains the preferred attack at the 4-position over the 2-position.

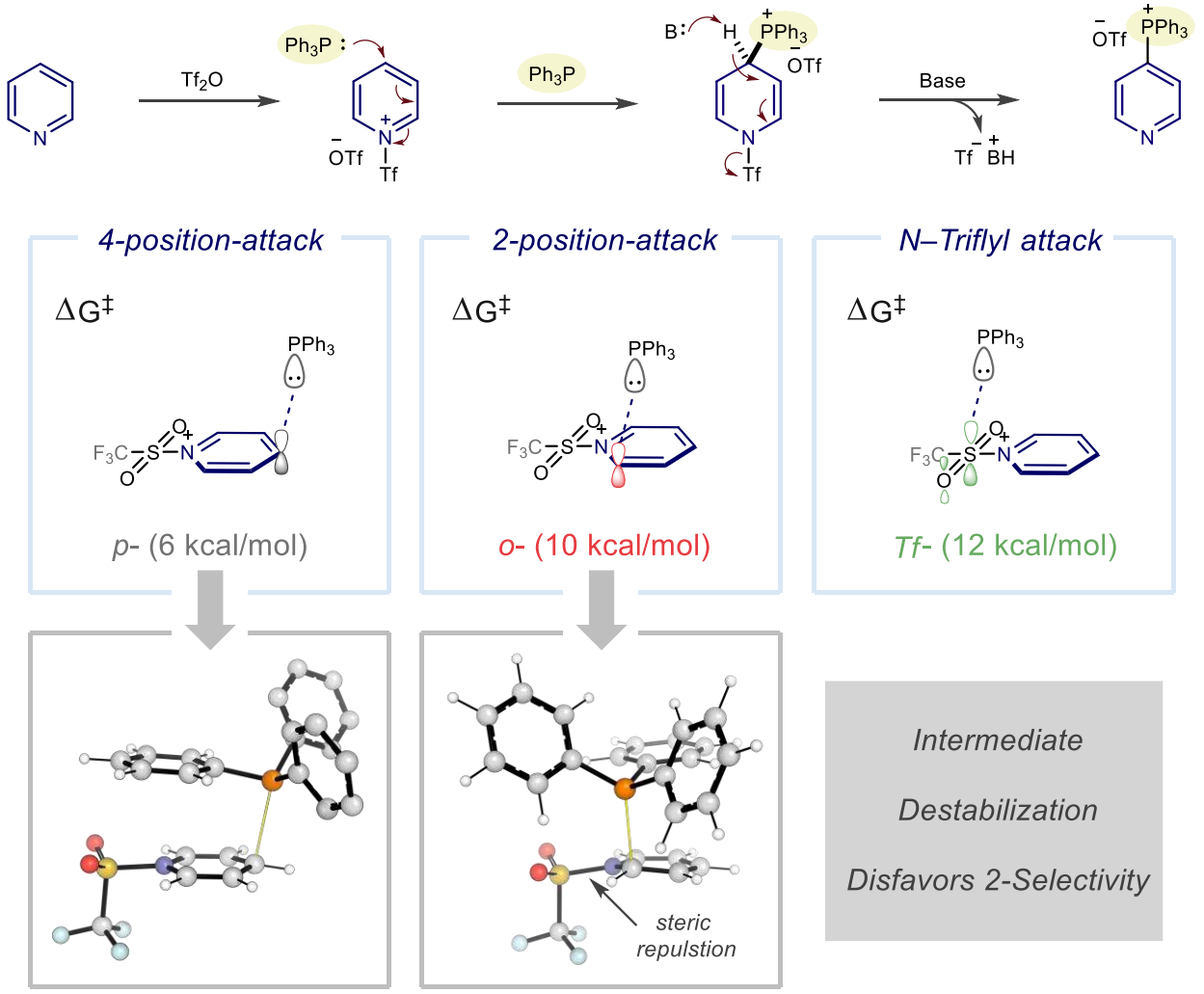


Figure 2.8. Density functional theory (DFT) calculated transition state energies and structures for phosphine attack at 4-position, 2-position, and triflyl group on *N*-triflyl pyridiniums. DFT computed Gibbs energies were obtained for transition state structures at the DLPNO-CCSD(T)/cc-pV(DT)Z//ωB97X-D/6-31+G(d) level of theory (SMD = CH_2Cl_2, –78 °C).

2.5 Reactions of Heterocyclic Phosphonium Salts

Our group has developed four reaction manifolds for transforming heterocyclic phosphonium salts into azaarene derivatives (**Figure 2.9**).[24-31] The phosphonium salts can act as electrophilic partners with certain heteroatom-nucleophiles in S_NAr-types pathways, expelling phosphine as the leaving group.[24-28] Ligand-coupling pathways have also been developed, where

a range of nucleophiles are added to azaarenes via a pentacoordinate P(V) intermediate.[24-28] In addition, phosphonium salts can be used as electrophilic partners in metal-catalyzed cross-coupling reactions.[29,30] Lastly, a fragmentation reaction has been developed which forms a 4-pyridyl anion equivalent *in situ*, followed by subsequent reaction with electrophiles.[31] My research focused on developing the phosphonium salt protocol, as well as establishing the ground work for the nucleophilic additions, alongside Michael Hilton.[24]

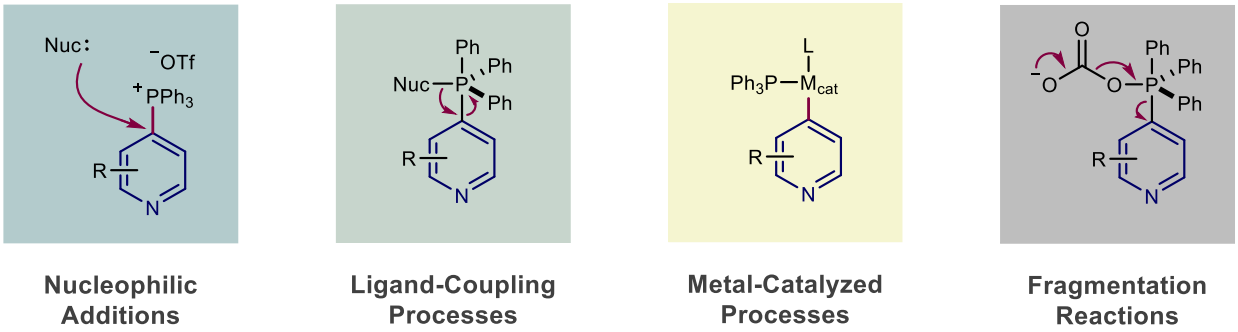
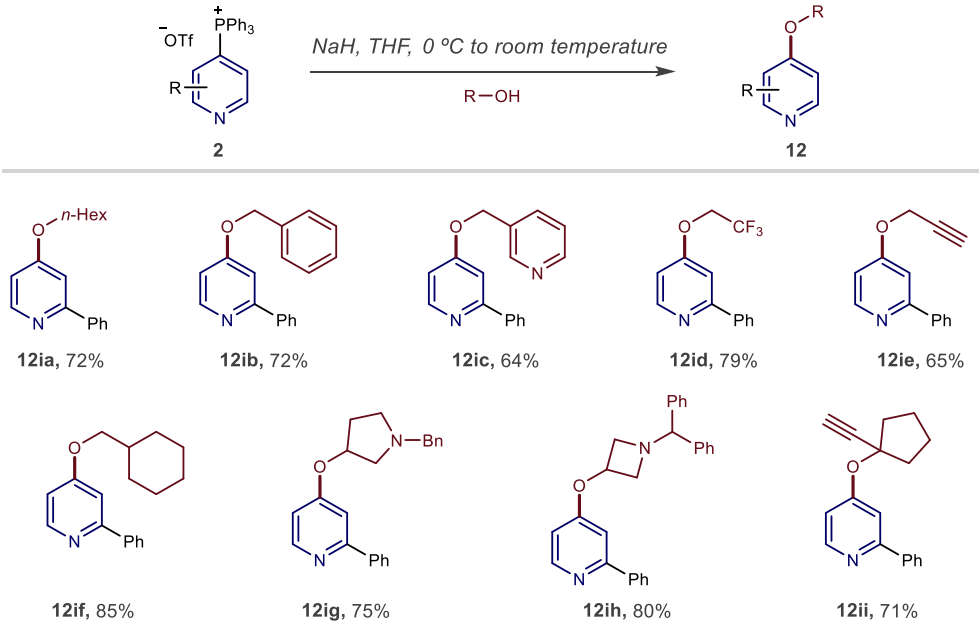


Figure 2.9. Heterocyclic phosphonium salt reaction platforms.[24-31]

Initially, we hypothesized that heterocyclic phosphonium salts could either participate in S_NAr-type reactions or a ligand-coupling process to form useful derivatives. In our first report, we described a method where C–O bonds are formed via a reaction between heterocyclic phosphonium salts and alkoxides.[24] Most methods to form heteroaryl ethers rely on halogenated substrates to participate in metal-catalyzed cross-coupling reactions or S_NAr reactions.[32-36] We found heteroaryl ethers can be selectively formed via deprotonation of an alcohol at 0 ºC in THF, followed by addition of the phosphonium salt, and subsequent stirring at room temperature (**Table 2.5**). It was found that primary alkoxides (**12ia**), including benzyl (**12ib**), pyridyl (**12ic**), trifluoromethyl (**12id**), and alkynyl (**12ie**) substituents are competent nucleophiles. In addition, secondary (**12ig**) and tertiary alcohols (**12ih & 12ii**) form heteroaryl ethers in good yields.

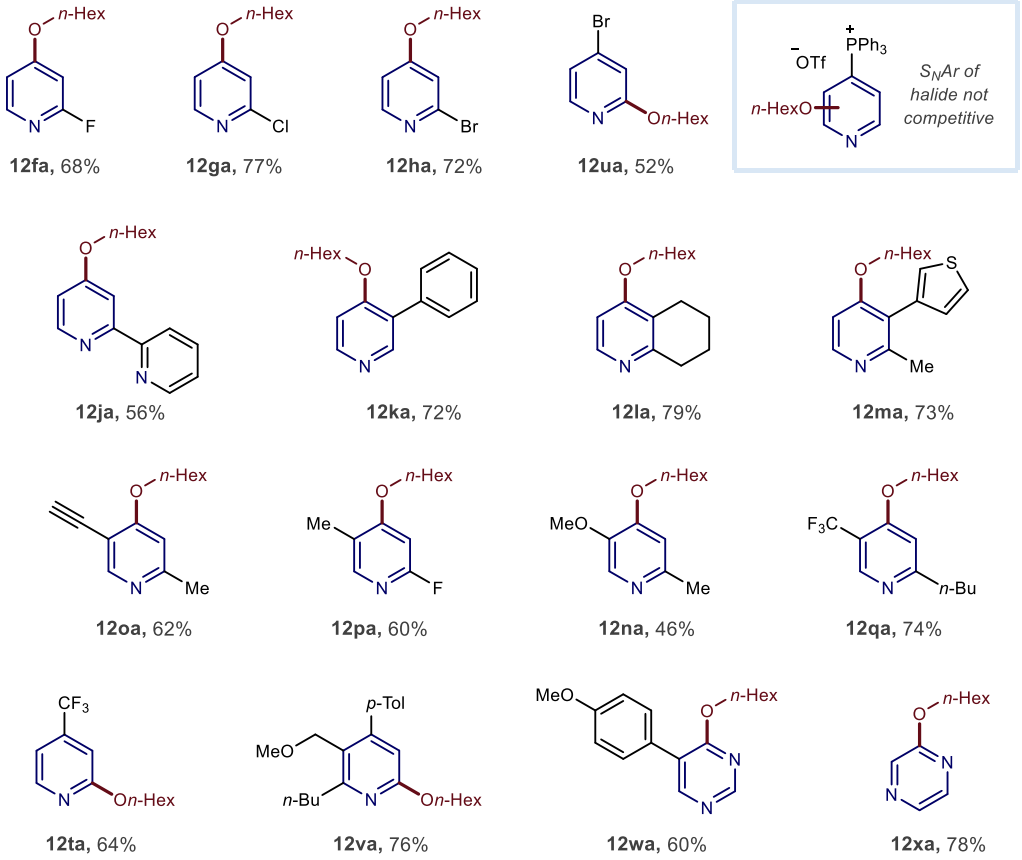
Table 2.5. Alcohol scope for C-O bond formation.



Isolated yields are shown.[24]

We next examined a selection of phosphonium salts derived from building block pyridines to test the heteroaryl ether bond forming conditions (**Table 2.6**). We found that 2-halo substituted salts undergo the reaction without displacement of the halide via a competitive S_NAr reaction (**12fa-12ha, 12ua**). Mono-substituted (**12ja & 12jk & 12ta**), di- (**12la-12qa**), and tri-substituted phosphonium salts (**12va**) were shown to form the heteroaryl ether in good yield. Diazine phosphonium salts also performed well making the diazinyl heteroaryl ether products under the standard reaction conditions (**12wa & 12xa**).

Table 2.6. Phosphonium salt scope of C-O bond formation.



12fa, 68% **12ga**, 77% **12ha**, 72% **12ua**, 52%

12ja, 56% **12ka**, 72% **12la**, 79% **12ma**, 73%

12oa, 62% **12pa**, 60% **12na**, 46% **12qa**, 74%

12ta, 64% **12va**, 76% **12wa**, 60% **12xa**, 78%

Isolated yields are shown.[24]

Furthermore, we showed that a range of pharmaceuticals were amenable for late-stage functionalization (**Figure 2.10**).[24,37] Loratadine (**14**) and Chlorphenamine (**15**) form heteroaryl ether products in modest yields. In addition, it was found that a 4-methoxy-nicotine analogue (**13**) can be synthesized in two steps using this method compared to the previously reported shortest literature synthesis of five-steps.[38] Finally, protected versions of Varenicline (**16**), Abiraterone (**17**), and Chinchonidine (**18**) are also amenable to heteroaryl ether formation in reasonable levels of efficiency. The phosphonium salt formation protocol and subsequent C-O bond formation reaction led to a publication in the Journal of the American Chemical Society.[24]

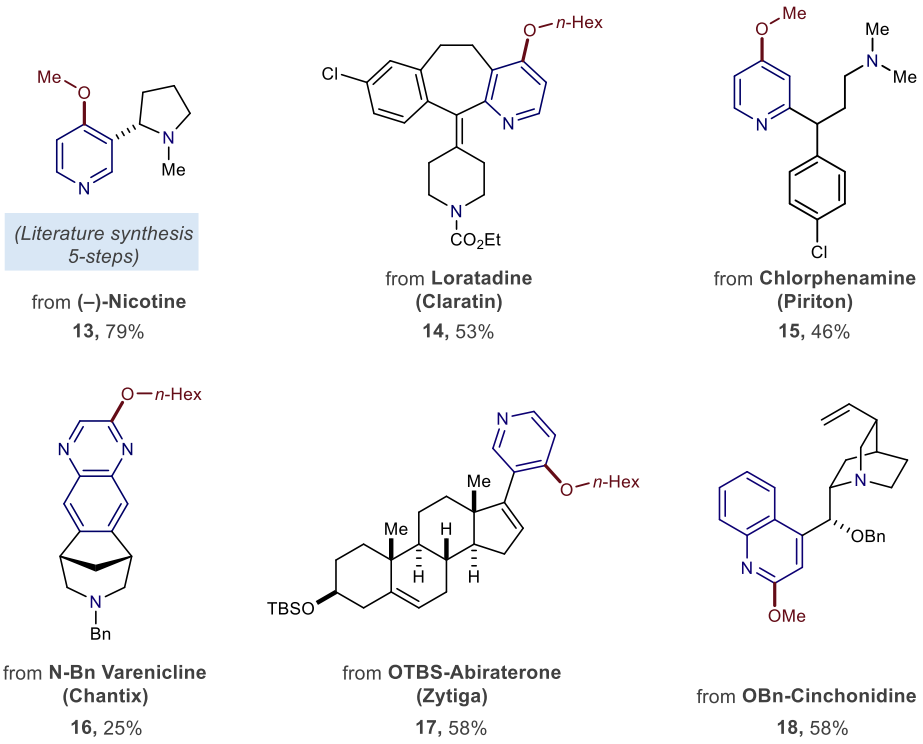


Figure 2.10. Late-stage functionalization of biologically active compounds and pharmaceuticals. Isolated yields are shown.[24]

As stated earlier in this section, heteroaryl ether bond formation was hypothesized to go through one of two potential mechanistic pathways (**Figure 2.11**). Path A is an S_NAr reaction where the alkoxide adds to the *ipso*-carbon of the pyridyl ring, resulting in a Meisenhiemer intermediate (**VIII**), followed by displacement of PPh_3. An alternative mechanism involves initial addition of an alkoxide to the phosphorous atom to form a P(V) alkoxyphosphorane intermediate (**IX**), followed by ligand-coupling to form the C-O bond.[39-44]

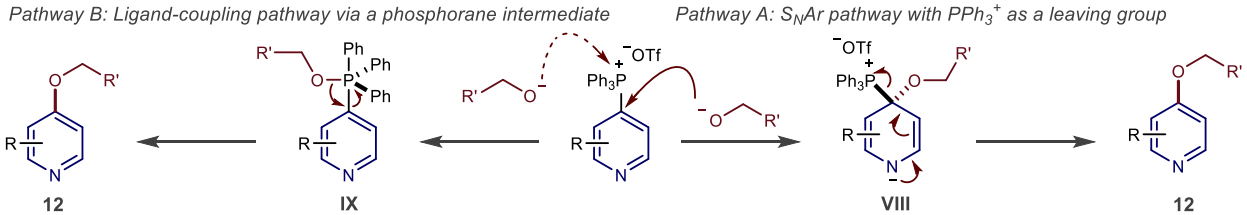


Figure 2.11. Possible mechanistic pathways for C-O bond formation.

2.6 Experimental and Computational Study of the C-O Bond Forming Mechanism

As phosphorus ligand-coupling processes are less explored than S_NAr reactions, we attempted to provide experimentally evidence of a P(V) alkoxyphosphorane intermediate, which would support a ligand-coupling pathway. In deuterated THF, *n*-hexanol was deprotonated by NaH at 0 ºC for 30 minutes before being cooled to –80 ºC. 2-phenylpyridine phosphonium salt **2i** was added to the alkoxide solution and the resulting mixture was immediately transferred to an NMR tube and observed via VT NMR. At –80 ºC, only the phosphonium salt peak at 25.25 ppm and minor amounts of phosphine oxide at 28.09 ppm were observed via ^{31}P NMR. The presence of phosphine oxide is hypothesized to arise from oxidation of the PPh_3 during the transfer of the reaction solution to the NMR tube. After approximately 30 minutes, and upon warming to –30 ºC, a new phosphorus peak was observed at –70.64 ppm. This chemical shift is consistent with those reported for other alkoxyphosphorane species as seen **Figure 2.12**.[45] The presence of the alkoxyphosphorane species provides experimental evidence that the C-O bond forming reaction using heterocyclic phosphonium salts could be proceeding through a ligand-coupling process, rather than an S_NAr pathway.

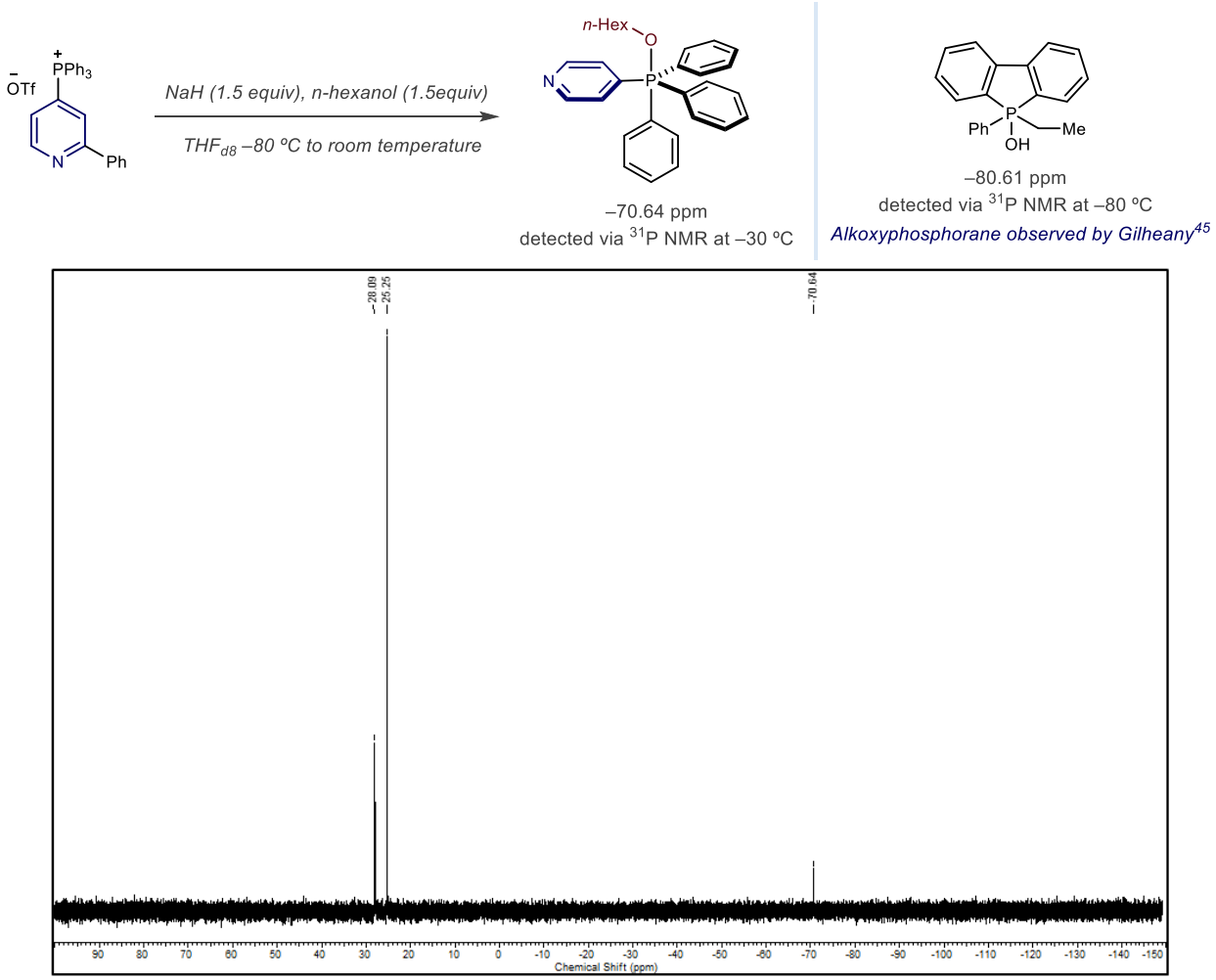


Figure 2.12. Detection of P(V) alkoxyphosphorane intermediate via VT ^{31}P NMR at –30 ºC in THF_{d8}. A literature reported P(V) alkoxyphosphorane species is shown.[45]

To provide further evidence that the C-O bond forming reaction could be proceeding through a ligand-coupling pathway, a computational study was conducted by the Paton group. All Gibbs free energies along the C-O forming reaction pathway were calculated via DFT at the DLPNO-CCSD(T)/cc-pV(DT)Z//ωB97X-D/6-31+G(d) level. After formation of the P(V) phosphorane intermediate, the C-O bond is formed via a three-center-four electron bonding transition state, where the alkoxide oxygen is bridged between the phosphorous atom and the *ipso*-carbon of the pyridine (**Figure 2.13**). DFT calculations indicate the activation energy for this transition state is relatively low at $\Delta G^{\ddagger}$ = 22.9 kcal/mol. Although phenyl, rather than, heteroaryl

migration is possible, it was found that a 7.4 kcal/mol preference for *O*-heteroaryl over *O*-phenyl coupling exists (not shown). Migration of the alkoxide results in a Meisenhiemer-type intermediate (**X**) with a ΔG = –21.1 kcal/mol, followed by elimination of phosphine to afford the heteroaryl ether. The computational and experimental evidence support an asynchronous ligand-coupling process over an S_NAr pathway.

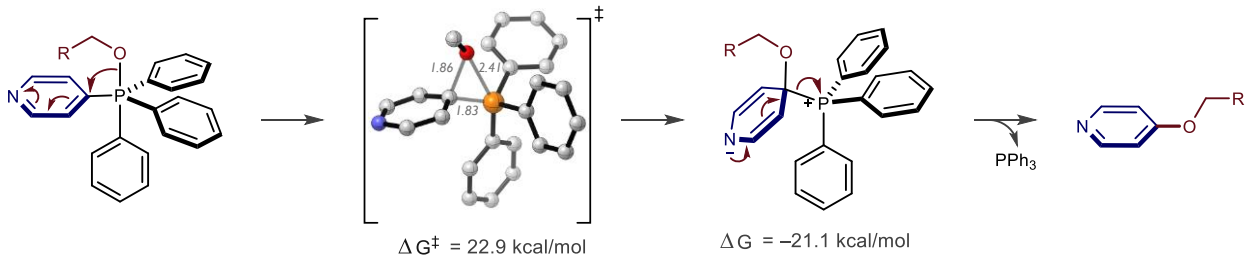


Figure 2.13. Proposed ligand-coupling mechanism for C-O bond formation. DFT computed Gibbs energies were obtained for transition state structures and intermediates at the DLPNO-CCSD(T)/cc-pV(DT)Z//ωB97X-D/6-31+G(d) level of theory.

2.7 Heteroaryl Phosphonium Salt Reaction Development by Other Group Members

Since our original report, other members in our lab have been able to expand the types of reaction platforms amenable to heterocyclic phosphonium salts (**Figure 2.14**). An extension of the C-O bond forming methodology was accomplished by Anderson and Jett, where phosphonium salts can be convert into C-S, C-O, and C-N bonds, using thiolates, phenolates, and nitrogen-containing nucleophiles, respectfully.[24,26,27] Patel and Mohnike found that sodium azide forms iminophosphoranes via a Staudinger-type reaction with heteroaryl phosphonium salts, which can then be transformed into a range of C-N bond-containing derivatives.[28] The ligand coupling pathway has also been exploited by Hilton, Zhang, and Boyle as a unique way to make complex heterobiaryls via formation of bis-heteroaryl phosphonium salts.[25] Xuan Zhang was able to use phosphonium salts as inputs into nickel- and cobalt-catalyzed cross-coupling reactions to form 4-arylated and 4-alkylated pyridines, respectfully.[29,30] Lastly, through a collaborative project between Luke Koniarczyk and Merck, a fragmentation-trapping sequence using a carbonate base

was developed to deuterate and tritiate pharmaceuticals.[31] Collectively, this chemistry represents the utility of the heterocyclic phosphonium salt methodology as a general means to selectively functionalize pyridines at the 4-position.

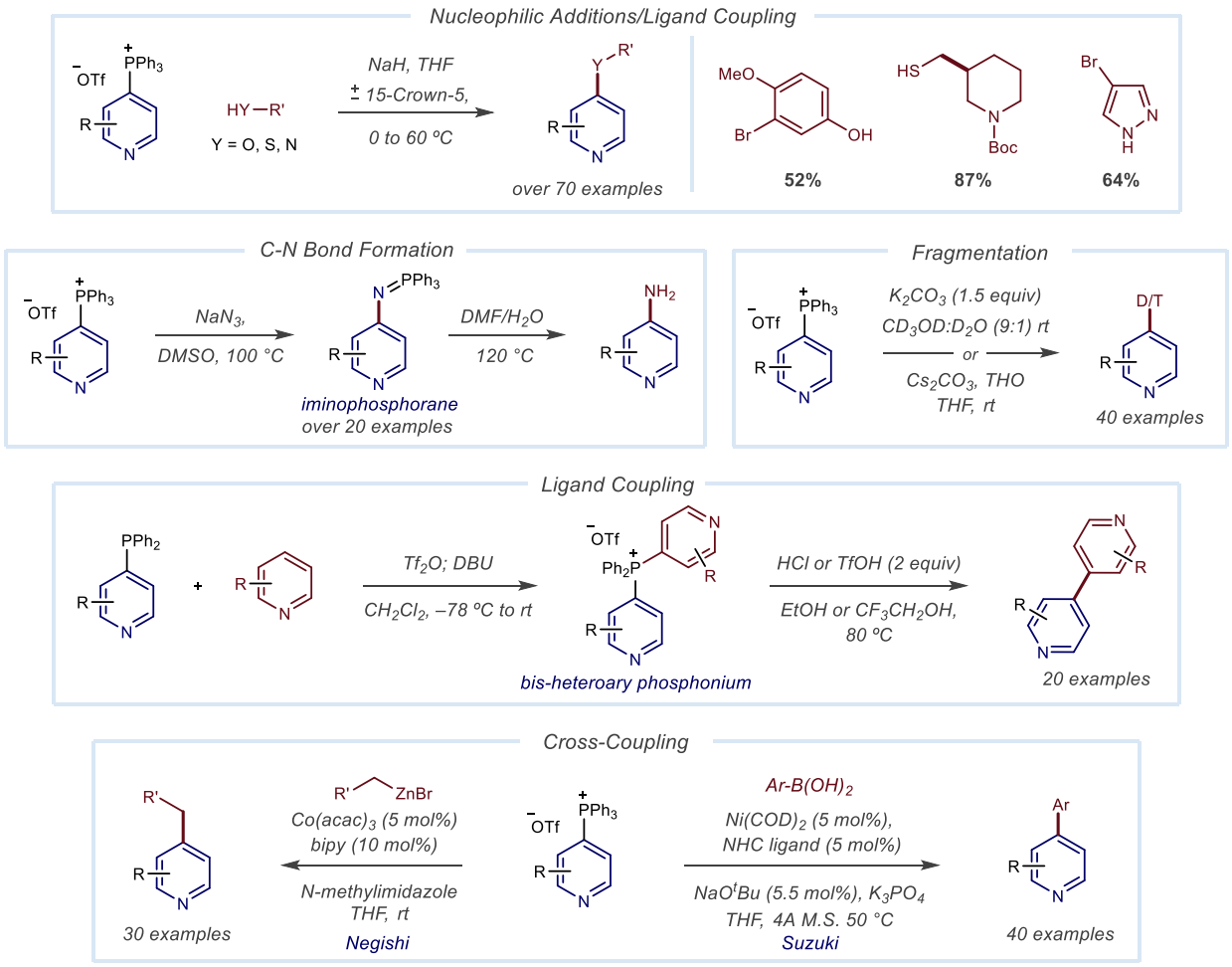


Figure 2.14. Additional reactions of heteroaryl phosphonium salts developed by other group members.[24-31]

2.8 Conclusion

A new strategy to directly and selectively functionalize pyridines and azaarenes via heteroaryl phosphonium salts is discussed. A range of azaarenes are amenable under the phosphonium salt conditions, including simple building-block pyridines, drug-like fragments, and biologically active compounds. In most cases the phosphonium ion is installed selectively at the 4-position of pyridines. Computational analysis regarding the origin of the observed selectivity

was also described. Several reaction platforms, developed by the McNally group, highlight the utility of heteroaryl phosphonium in subsequent bond-forming transformations.

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CHAPTER THREE

SITE-SELECTIVE FUNCTIONALIZATION OF POLYAZINES

3.1 Introduction to Site-Selective Functionalization

Site-selective functionalizations differentiate reactivity among the same kind of functional groups which have different chemical environments.[1,2] Site-selectivity is often challenging to achieve, since the same kind of functional groups have almost identical chemical properties and tend to undergo the same transformation under a given set of conditions. Methods that selectively and predictably target specific functional groups in the presence of similar functional groups offer an efficient strategy of accessing valuable derivatives and can significantly expedite drug discovery timelines.[3,4] Furthermore, this approach offers a favorable alternative to traditional de novo syntheses. Despite these advantages, reaction development in this regime is challenging as reactivity differences between sites are often dependent on subtle steric and electronic factors that must be recognized by the chemical entities involved in the process.

Several advancements have been in the site-selective differentiation of various poly-functionalized molecules. Polyhydroxylated compounds a are ubiquitous class of molecules found in carbohydrates, nucleic acids, and antibiotics.[5,6] Given their importance to human health, several advancements have been made to site-selectively functionalize different alcohols in polyhydroxylated molecules.[5-11] The ability to selectively functionalize different hydroxyl groups in these molecules could reveal aspects of structure-activity relationships (SAR), help our understanding of their biological function, and potentially lead to new therapies.[3,4] Scott Miller has developed several peptide-based catalysts capable of selectively modifying polyhydroxylated

molecules, such as Erythromycin A, Vancomycin, and Teicoplanin.[6,8-9] As an example, Teicoplanin, a glycopeptide antibiotic, contains three different sugar moieties located remotely from one another, each with a primary hydroxyl group.[9] Catalysts containing peptide chains that have specific hydrogen bonding interactions with Teicoplanin were designed to differentiate between the different primary hydroxyl groups. Each peptide-based catalyst contains a terminal nucleophilic π-methylhistidine, capable of reacting with diphenyl phosphoryl chloride (DPCP). The resulting phosphorylated peptide-catalyst can then be delivered near each primary hydroxyl by specific hydrogen bonding interactions with Teicoplanin (**Figure 3.1**). Using excess DPCP, 1,2,2,6,6-dimethyl piperidine (PEMP), and peptide catalyst **1** (10 mol%), the primary hydroxyl group of the *N*-decanoylglucosamine (red) was phosphorylated as a single isomer at 42% yield. Conversely, under similar reaction conditions, using 20 mol% of peptide-catalyst **2** and 30 mol% of **3** led to the site-selective phosphorylation of the mannose (blue) and *N*-acetylglucosamine (green) primary hydroxyl groups, respectively.

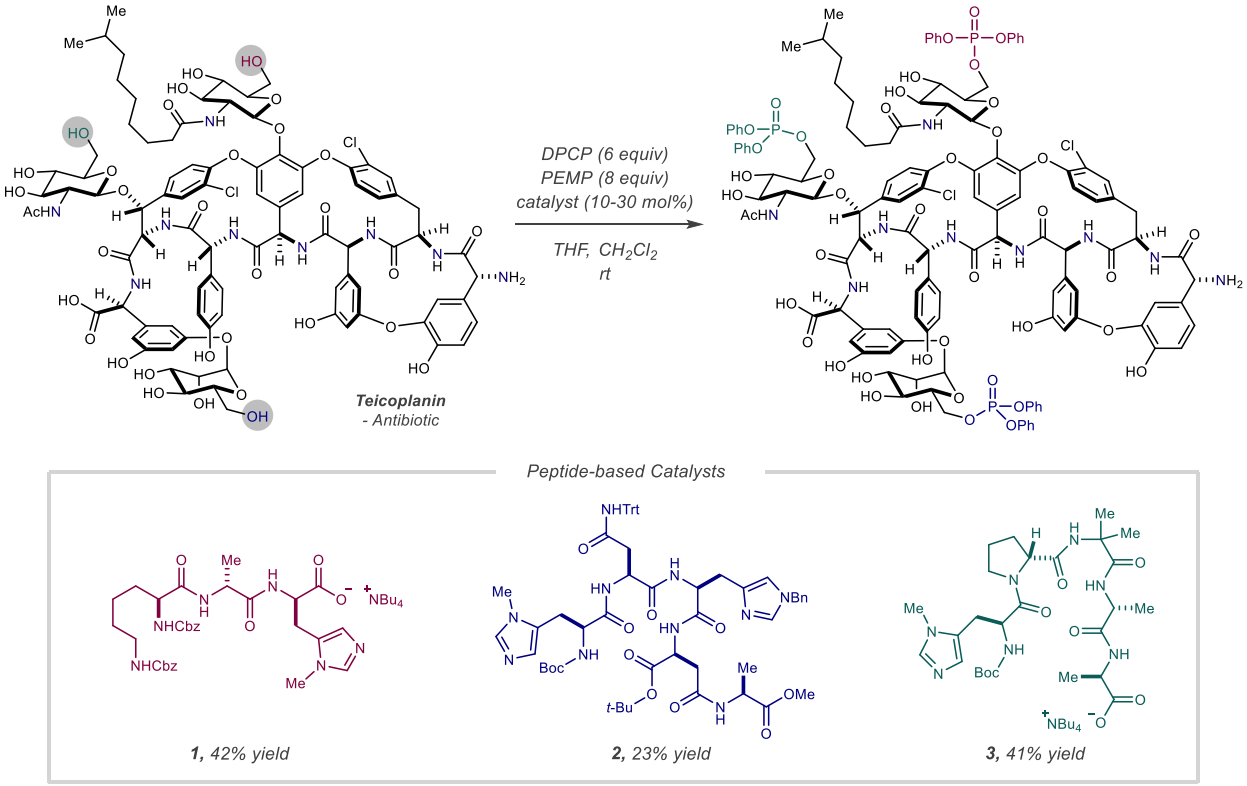


Figure 3.1. Site-selective phosphorylation of three primary hydroxy groups within Teicoplanin via peptide-based catalysts.[9] Yields for each separate phosphorylation is shown below the respected peptide catalyst.

Polyphenols are a ubiquitous class of molecules found largely in fruits, vegetables, coffee, and legumes. As antioxidants, polyphenols offer protection against cancer, cardiovascular diseases, diabetes, and neurodegenerative diseases.[12] As they are important to human health, several strategies have been developed to site-selectively functionalize individual C-H bonds on different arenes in polyphenols.[13,14] In 2011, Snyder developed a method to selectively brominate two of four, electronically identical aromatic positions on the core of flavonoid, ampelopsin F (H_A-H_D, **Figure 3.2**).[13] A variety of bromine sources were able to selectively brominate position H_A, with *N*-bromosuccinimide (NBS) providing **4** in 95% yield. As many brominating reagents of varying reactivity were effective, this selectivity outcome was proposed to reflect substrate control or inherent selectivity. Under reagent control, it was found that their recently developed bromine

source, BDSB (bromodiethylsulphide bromopentachloroantimonate) was able to afford **5** in 78% as a single isomer. The exact basis for this selectivity has yet to be disclosed.

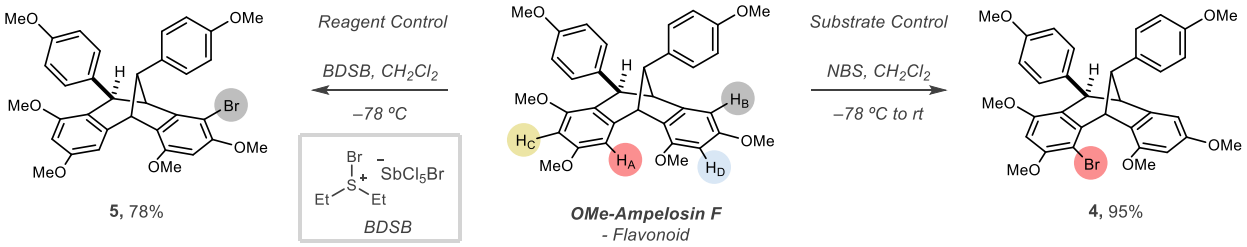


Figure 3.2. Site-selective bromination of electron-rich positions (highlighted positions) within OMe-protected Ampelosin F.[14]

The site-selective functionalization of similar reactive olefins in polyene containing molecules has been observed primarily though the study of enzymes.[15] Over the last few years, small-molecule catalysts have been used to enable selective oxidation of terminal olefins of polyenes, allylic olefin epoxidation, and selective oxidation of conjugated systems.[16-21] An approach by the Miller group, demonstrates a site- and enantio-selective epoxidation of two distinct olefins within the polyene, farnesol, using different peptide-based catalysts (**Figure 3.3**).[22] Each peptide catalyst contains a terminal aspartic acid capable of oxidizing an olefin after activation with DIC and hydrogen peroxide. Catalyst turnover is facilitated by nucleophilic co-catalyst 1-hydroxybenzotriazole (HOBt) and *N,N*-dimethylaminopyridine (DMAP). The basis for the selectivity hinges on specific hydrogen bonding interactions between the peptide catalyst and farnesol that selectively delivers a peroxyacid close to the target olefin. Using peptide-catalyst **6**, the selective epoxidation of the allylic alcohol within farnesol is selectively achieved in 86% e.e. Alternatively, selective epoxidation of the internal olefin is attained in slight enantiomeric excess with peptide catalyst **7**.

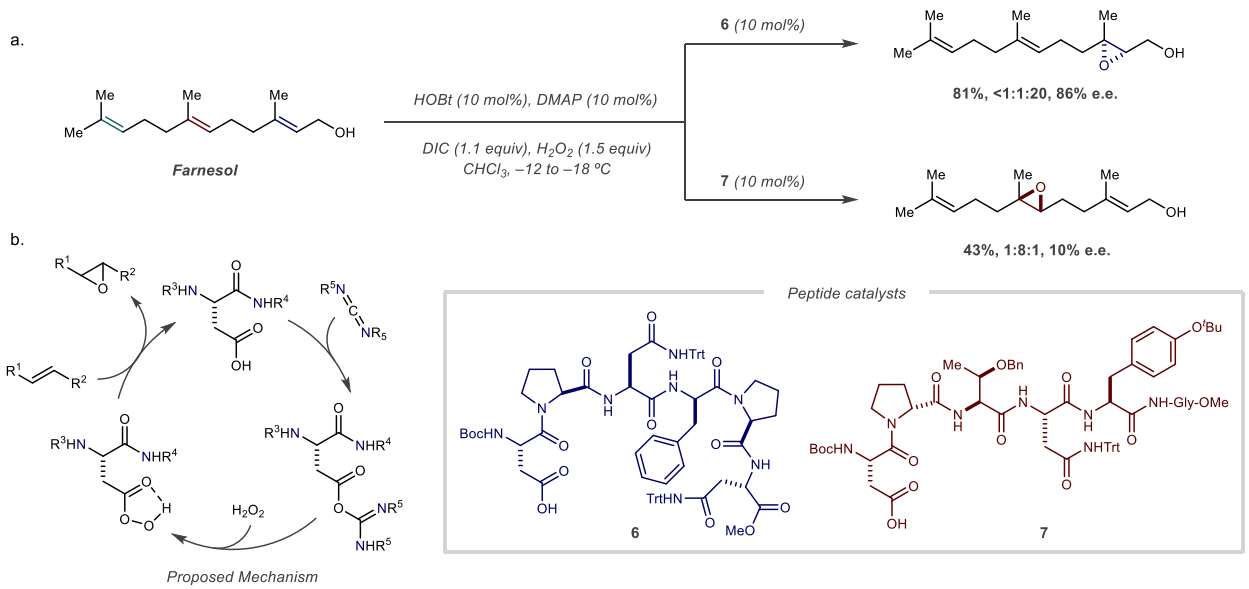


Figure 3.3. Site-selective and enantioselective epoxidation of farnesol via peptide-based catalysts.[22] a) Selective epoxidation of allylic (blue) and internal (red) olefins via peptide-catalysts. b) Proposed catalytic cycle of aspartic acid-mediated epoxidation.

Numerous methods have been developed for the site-selective functionalization of different sp^3 C-H bonds on highly saturated molecules.[23,24] Recently, Van Humbeck disclosed a strategy to site-selectively oxidize methylene C-H bonds adjacent to azaarenes over benzylic positions adjacent to electron-rich arenes (**Figure 3.4**).[25] Pyridines containing multiple benzylic positions were subjected to a catalytic amount of an iron tetrafluoroborate ($Fe(BF_4)_2$) Lewis acid, which can coordinate to the pyridine nitrogen. The heterobenzylic position on the resulting pyridinium is prone to hydrogen atom abstraction by *N*-hydroxyphthalimide (NHPI). The resulting radical is then converted into the carbonyl product via an autooxidation mechanism. Alternatively, using a catalytic amount of cobalt(II) acetate tetrahydrate ($Co(OAc)_2 \cdot 4\ H_2O$) and NHPI in acetic acid, the methylene adjacent to benzene is converted to carbonyl product as a single isomer.

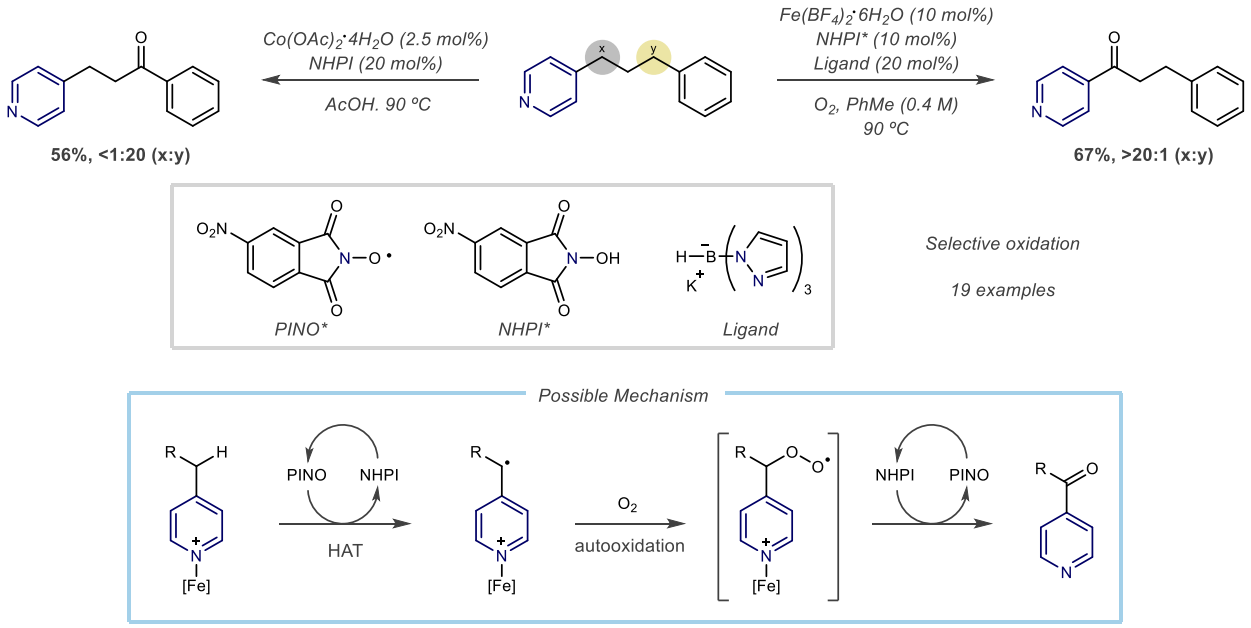


Figure 3.4. Synergistic LA/HAT for site-selective oxidation of positions adjacent to azaarenes.[25]

3.2 Introduction to Site-Selective Phosphonium Ion Formation of Polyazines

Although several advancements have been made in the site-selective functionalization of polyenes, polyphenols, and polyhydroxylated molecules, there is not a general approach to distinguish between different pyridines and diazines in polyazine-containing molecules.[26-28] Polyazines are often found in compound libraries containing drug-like molecules and are also found in a range of pharmaceuticals (**Figure 3.5**).[29,30] Some pharmaceuticals that contain polyazines include leukemia therapy, Imatinib, which contains a pyridine and a pyrimidine ring in its structure, as well as investigational insomnia therapy, MK-1064, which contains four pyridine rings (**Figure 3.5**). Given their significance in pharmaceuticals, methods that can distinguish and selectively functionalize different azaarenes in polyazine-containing compounds are highly desirable.[31,32] A strategy to achieve site-selectivity in polyazines was proposed using heterocyclic phosphonium ion formation.[33-37]

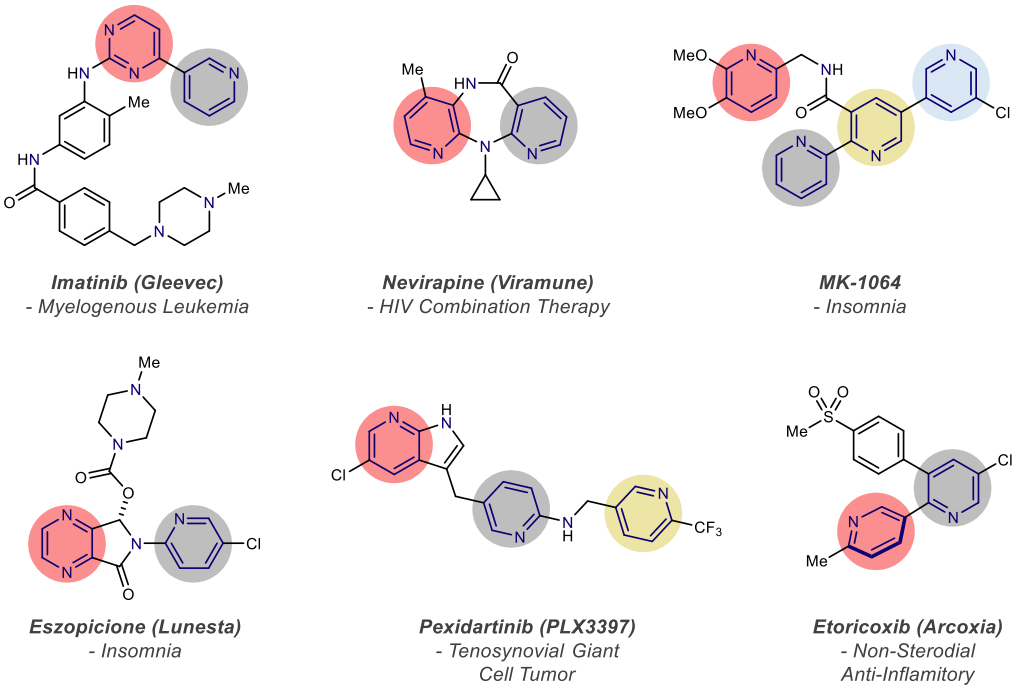


Figure 3.5. Examples of polyazine-containing pharmaceuticals. Different pyridines and diazines within each structure are highlighted in colored circles.

As mentioned in section **2.3**, site-selective phosphonium formation is possible on polyazines, although the precise reasons for the observed selectivity were not entirely understood.[34,38-44] This led us to systematically evaluate how substitution patterns and steric and electronic effects determine the inherent site of C–P bond formation and devise methods to predictably switch site-selectivity to other azaarenes/sites in polyazines.[45] Our hypothesis was that all three stages of the mechanism for C–P bond-formation influence site-selectivity (**Figure 3.6**): first, nucleophilic attack by the heterocyclic nitrogen with Tf_2O; second, phosphine addition to the activated *N*-triflyl pyridinium salt; and third, base-mediated elimination to reform the aromatic system. Furthermore, reaction parameters, such as the order the reagents are added, were also proposed to affect site-selectivity. The work presented in this chapter led to a publication in the Journal of the American Chemical Society.[45]

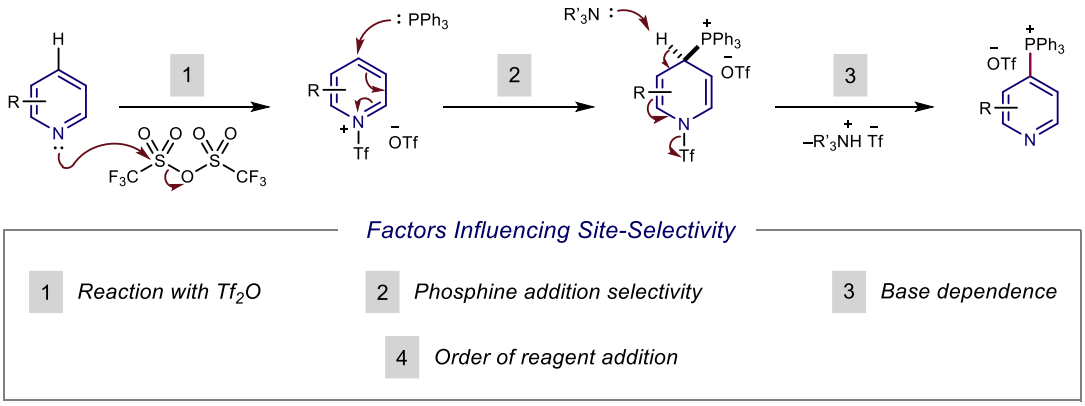


Figure 3.6. Mechanistic stages of phosphonium ion formation.

3.3 Acylation-Blocking Strategy

Beginning with the first step of phosphonium salt formation, it was reasoned that the nucleophilic attack of azaarene with Tf_2O would be heavily influenced by steric and electronic properties of the azaarene nucleophile. As *N*-triflyl salt formation is directly correlated with phosphonium salt formation, a site-selective bias would occur when one azaarene in a polyazine (**8**) is inherently more nucleophilic toward Tf_2O. Selective phosphine addition would then only occur on the azaarene that was selectively activated by Tf_2O in the polyazine system (**9**, **Figure 3.7**).[45] Based on the different nucleophilicities of the azaarenes, a blocking strategy was proposed where the most nucleophilic azaarene is first converted into an *N*-acylpyridinium salt. This would allow the remaining unactivated azaarene to react with Tf_2O, forming bis-pyridinium salt, **10**. As a result, PPh_3 should add into the more electrophilic *N*-triflylpyridinium salt over the *N*-acylpyridinium salt, allowing a selectivity switch between different azaarenes/sites in a polyazine system.

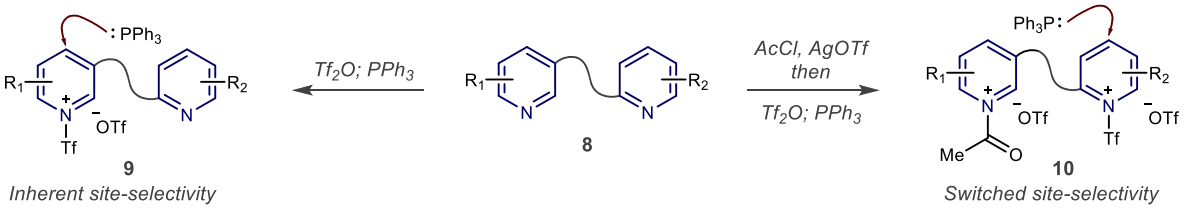


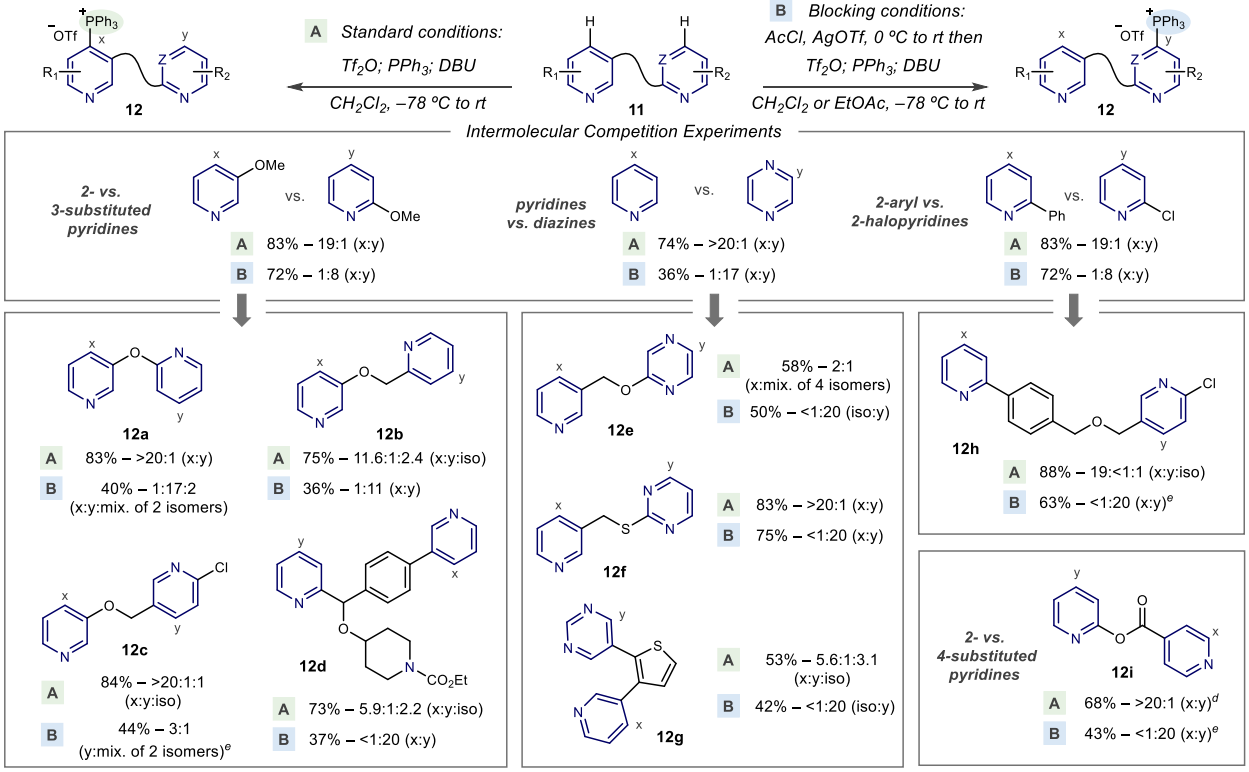
Figure 3.7. Acylation-blocking strategy for site-selective switching.[45]

To understand the factors that control inherent site-selectivity and to test the acylation blocking strategy, intermolecular competition reactions were performed between two azaarenes with distinct steric and/or electronic properties. To run the intermolecular competition reaction, a 1:1 solution of the two different azaarenes in CH_2Cl_2 at –78 ºC were subjected to the standard phosphonium salt conditions (A) using one equivalent of each Tf_2O, PPh_3, and DBU (**Table 3.1**).[45] The site-selectivity of the reaction was then determined by the ratio of the heterocyclic phosphonium salts produced via ^1H NMR. We first attempted to distinguish reactivity between pyridines with 2- vs 3-substitution patterns. An intermolecular competition reaction between 2- and 3-methoxypyridine was shown to form the phosphonium salt preferentially on the 3-methoxypyridine in a 19:1 ratio over the 2-methoxypyridine (**Table 3.1**). It was hypothesized that phosphonium salt formation occurs on the 3-methoxypyridine due to the absence of steric crowding at the pyridine nitrogen. This in turn makes the 3-substituted pyridine more nucleophilic towards Tf_2O and thus more susceptible to phosphonium formation. To test the acylation blocking strategy (B), the same pair of pyridines were first subjected to an equivalent of acetyl chloride (AcCl) and silver triflate (AgOTf) at 0 ºC in CH_2Cl_2, and then stirred at room temperature for 1h (**Table 3.1**). The reaction mixture was cooled to –78 ºC, and the phosphonium salt formation protocol was ran as normal. The combined yields of the phosphonium salts are shown in **Table 3.1** with a significant switch in selectivity toward the 2-methoxypyridine.

After validating the inherent selectivity and acylation-blocking strategy on the intermolecular systems, we next investigated whether this switchable selectivity would translate to polyazines containing 2- and 3-substituted pyridines (**Table 3.1**).[45] To test this, 2-(pyridine-3-yloxy)pyridine, **11a** was synthesized and subjected to the phosphonium salt forming protocols. Under the standard conditions, the phosphonium ion is formed exclusively on the 3-substituted

pyridyl ring in bis-pyridyl ether **12a**, which agrees with the analogous intermolecular competition system between 2- and 3-methoxypyridine. Phosphonium formation is then formed on the 2-substituted ring in good selectivity by employing the acylation blocking protocol. Similarly, 2-((pyridin-3-yloxy)methyl)pyridine **11b** shows a site-selectivity bias towards the 3-substituted pyridine under the standard conditions with a 2-position isomer tentatively assigned as the next significant phosphonium species. The phosphonium ion formation can then be switched and formed on the 2-subsitituted pyridine in a 11:1 ratio when the acylation blocking conditions are employed (**12b**). 2-Chloro substituents deter reactivity in the presence of 3-oxypyridine as shown in **12c**, but selectivity can be switched to a moderate level to the chloro-substituted ring using the acylation blocking conditions. Lastly, a derivative of the antihistamine bepotastine, **12d** was also tested as a representative drug fragment, where site-selectivity would be challenging.[46] Inherent C-P bond formation selectivity is modestly biased towards the 3-substituted ring, while the selectivity can be switched completely over to the 2-substituted ring, albeit in lower yield, under the acylation blocking conditions.

Table 3.1. Site-Selective Switching via an Acylation-Blocking Strategy.[a,b,c,d,e]



[a]Isolated yields of salt mixtures are reported.[45] [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.

In addition to steric effects, electronics were evaluated as factors in controlling the selectivity of C-P bond formation in polyazines. In an intermolecular competition reaction between pyridine and pyrazine, phosphonium ion formation was exclusively found on the pyridine ring under the standard conditions, reflecting the significant difference in nucleophilicities between these azaarenes (**Table 3.1**).[45] Selectivity can be switched to the less nucleophilic pyrazine ring under the acylation-blocking protocol (17:1 site selectivity). Next, polyazine systems containing a pyridine and diazine ring were used to test the switchable selectivity strategy. When subjected to the standard conditions, pyridine-pyrazine system **12e** resulted in an unbiased mixture of phosphonium salts, which disagrees with the results from the intermolecular competition reaction between pyridine and pyrazine. However, C-P bond formation can be formed on the pyrazine as a

single isomer when the acylation-blocking strategy is employed (20:1 site-selectivity). It was found that 2-((pyridin-3-ylmethyl)thio)pyrimidine **11f** forms the phosphonium ion on the pyridine under the standard conditions in a 20:1 ratio, and then on the pyrimidine ring as single isomer when using acylation-blocking conditions (**12f**). A 2,3-thiophene-linked pyridine-pyrimidine system **12g** was moderately selective towards the pyridine ring under the standard conditions with a 2-position isomer as the next significant phosphonium species. Selectivity can be switched to the pyrimidine ring in good yield when using the acylation blocking protocol (**12g**). It should be noted that the remaining mass balance for these reactions is unreacted starting material.

Polyazine systems that contain different 2-substituted pyridines are challenging substrates for C-P bond formation due to comparable steric crowding at the pyridyl nitrogen atoms. By altering the electronics of theses substituents, inherent phosphonium formation can selectively occur on the more nucleophilic ring. For example, in a competition reaction between 2-phenylpyridine and 2-chloropyridine, there is a clear selectivity bias for C-P bond formation on the pyridine containing the phenyl group over the chloro group (**Table 3.1**).[45] As the chloro substituent is more electron-withdrawing than the phenyl group, the 2-chloropyridine is less nucleophilic towards Tf_2O. To investigate this further, a pyridine-pyridine system, containing a 2-aryl and 2-chloro motif was shown to form the phosphonium ion selectively on the 2-aryl pyridine under the standard conditions (**12h**). Under the acylation blocking conditions, phosphonium salt formation occurs on the 2-chloro substituted pyridine in a 20:1 ratio. While investigating this system, PPh_3 was found to give low yields when used as the phosphine source, thus the more nucleophilic P(*p*-OMePh)$_3$ was used instead.

Lastly, we demonstrated a 2,4-substituted polyazine can be selectively functionalized on the 4-substituted pyridine under the standard C-P bond forming conditions in good yield (**12i**).

Phosphonium ion formation occurs on the 2-substituted pyridine using the blocking strategy (**Table 3.1**).[45] As in **12h**, P(*p*-OMePh)$_3$ was found to be the optimal phosphine for this transformation.

3.4 Base-Mediated Switching

Site-selectivity can be controlled by tuning the nature of the organic base during stage 3 of phosphonium ion formation in polyazines systems where there are minimal steric and electronic differences between the heterocycles. DBU and NEt$_3$ are typically used in the reaction protocol, with DBU generally providing higher yield (section **2.3**). An unexpected observation using 3-carbon-bearing substituted pyridines suggests that the choice of organic base can control site-selectivity (**Figure 3.8**). Using DBU as a base, 3-methyl and 3-phenylpyridine are both effective substrates for phosphonium salt formation, however, when the base is changed to NEt$_3$, no products are formed and starting materials are recovered. Conversely, 3-methoxypyridine and unsubstituted pyridine performed well with both DBU and NEt$_3$ as a base. Our current hypothesis is that when a carbon-bearing group is present at the 3-position, the pKa of 4-position C-H bond in dearomatized intermediate **I** is higher than the pKa of protonated NEt$_3$, thus preventing deprotonation. This could also explain why DBU is needed as base for these types of substrates (section **2.3**). Another possibility is that there is a steric repulsion between the carbon-bearing substituent on **I** and the incoming NEt$_3$ that prevents deprotonation and elimination of the triflyl anion. Alternatively, with 3-heteroatom substituted and unsubstituted pyridines, the pKa of the 4-position C-H bond in dearomatized **II** is low enough for deprotonation to occur by NEt$_3$, or there is no steric repulsion present between the substituent and the base.

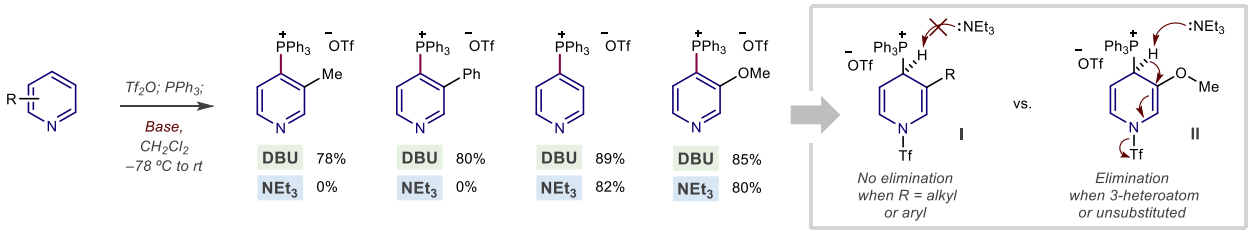


Figure 3.8. Effect of base on reactivity and site-selectivity. Yields calculated by ^{1}H NMR spectroscopy of the crude reaction mixture.[45]

To further investigate the observed base effect, we next considered 3,3'-substituted polyazine system **11j**, where an unselective outcome is observed under the standard phosphonium conditions (**Figure 3.9**).[45] We hypothesize the unselective bias is due to the similar nucleophilicities of each pyridine nitrogen with Tf_2O. As there is a lack of steric and electronic bias between the two pyridines, the acylation blocking-strategy would be ineffective in this system, thus a new approach was conceived using base dependent selectivity. We hypothesized that a doubly dearomatized species **III** could be generated *in-situ* by subjecting **11j** to the standard phosphonium conditions using 2 equivalents each of Tf_2O and PPh_3. A sequential addition of NEt_3 should then only deprotonate the dearomatized ring that contains the 3-oxy substituent, providing the phosphonium salt as a single isomer. By employing these base-mediated switching condition, **11j** forms the phosphonium salt on the 3-oxy substituted pyridine in a 20:1 ratio. The 3-carbon bearing substituted pyridine reforms after an aqueous workup. To provide experimental evidence of the doubly dearomatized intermediate **III**, we attempted to observe its formation. To a solution of **11j** in deuterated CH_2Cl_2 at –80 ºC, 2 equivalents of Tf_2O was added and stirred for 30 minutes. After a sequential addition of 2 equivalents of PPh_3, the reaction mixture was transferred to an NMR tube and observed via VT NMR. At –80 ºC, two major resonances at 21.93 and 19.53 ppm in a 1:1 ratio are visible via ^{31}P NMR suggesting the formation of intermediate **III** (**Figure 3.9**).

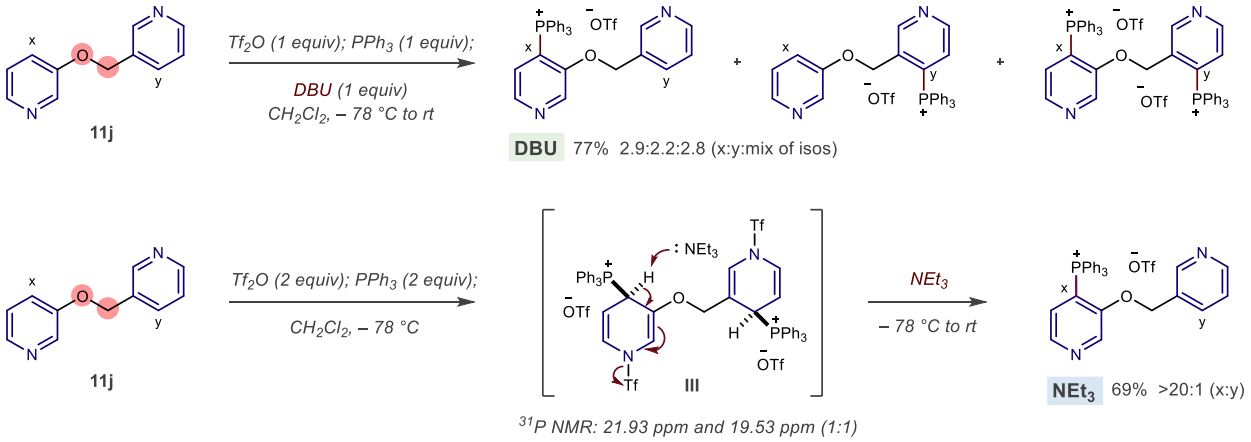


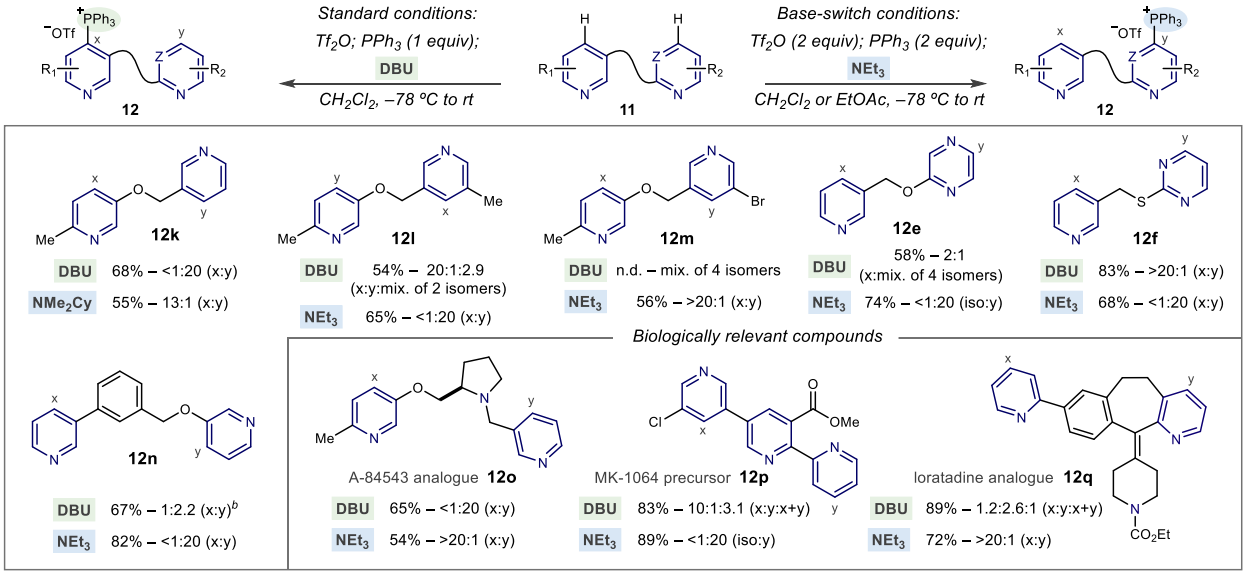
Figure 3.9. Base-controlled selectivity via double-dearomatized intermediates.[45] Yields and ratios reported as in **Table 3.1**.

To test the generality of the base-mediated switching protocol, we explored a series of oxymethyl-linked polyazine systems (**Table 3.2**).[45] Under the standard phosphonium conditions, the 3-substituted pyridine is preferred over the 2,5-disubstituted pyridyl ring in **12k**. Although using NEt_3 under the base-mediated switch conditions forms the phosphonium ion on the 2,5-disubstituted pyridine ring, it was found that using cyclohexyldimethylamine (NMe_2Cy) provided a higher yield. Under the standard phosphonium conditions, the 3,5-disubstituted pyridyl ring is preferred in **12l**, with a small mixture of 2-position isomers as the next significant phosphonium species. Alternatively, phosphonium formation occurs on the 3-oxy-substituted pyridyl ring in good selectivity when using the base-mediated switch protocol (**12l**). It was found that 5-((5-bromopyridin-3-yl)methoxy)-2-methylpyridine **12m** resulted in a complex mixture of four phosphonium isomers under the standard conditions. However, the phosphonium ion can be installed on 2-methyl-5-oxysubstituted ring in a 20:1 ratio under the base-mediated switch conditions. It was found that pyridine-diazine polyazine systems were also amenable to the base-mediated switch protocol. As described in **Table 3.1**, the standard phosphonium conditions are less effective for pyridine-pyrazine polyazine **12e** which resulted in a mixture of phosphonium isomers. However, using the base-mediated switching strategy, phosphonium formation occurs on

the pyrazine ring with a site-selectivity of 20:1. Similarly, pyridine-pyrimidine system **12f** forms the phosphonium ion on the pyrimidine ring in excellent selectivity when the base-mediated switching protocol is employed. Under the standard phosphonium conditions, 3-aryl polyazine **12n** forms the phosphonium salt on the 3-oxy-substituted pyridine in 2.2:1 ratio. However, using the base-mediated switch protocol, the selectivity for the 3-oxy-subsituted pyridine increase to 20:1 (**12n**).

To test the base-switching strategy further, a set of biologically active complex polyazines were selected for functionalization. An analogue of A-84543, a nicotinic acetylcholine receptor agonist,[47] **12o**, selectively forms the phosphonium ion on the 3-substituted pyridyl ring under the standard phosphonium conditions (**Table 3.2**).[45] Alternatively, using the base-mediated switching protocol, phosphonium formation occurs on the 2-methyl-5-oxy-substituted ring in excellent selectivity. A precursor to MK-1064, an investigational therapy for insomnia **12p**, is a challenging substrate for site-selective functionalization as it contains three distinct pyridine rings. Under the standard conditions, phosphonium ion formation occurs predominately on the 3,5-disubtituted ring, along with the 2-pyridyl isomer and a bis-phosphonium isomer and in a 10:1:3.1 ratio. As one of the substituents on the 3,5-disubstituted ring is carbon-bearing, the base-mediated switching protocol can be used to form the phosphonium ion on the 2-substituted pyridyl ring in very good selectivity and yield. It should be noted that phosphonium formation on the trisubstituted ring was noted detected. We hypothesize that the electron-withdrawing groups present on this pyridine decreases nucleophilicity of this ring towards Tf_2O (section **2.3**). Lastly, under the normal conditions, loratadine analogue **12q** resulted in a mixture of isomers. However, since there is a 2,3-fused carbocycle present, the base-mediated switching protocol can be used to form the phosphonium ion on the 2-substituted pyridyl ring in very good selectivity and yield.

Table 3.2. Base-Dependent Protocol for Site-Selective Switching[a,b,c]



[a]Yields and ratios reported as in **Table 3.1**. [b]Yield calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]x + y represents a bis-phosphonium salt.[45]

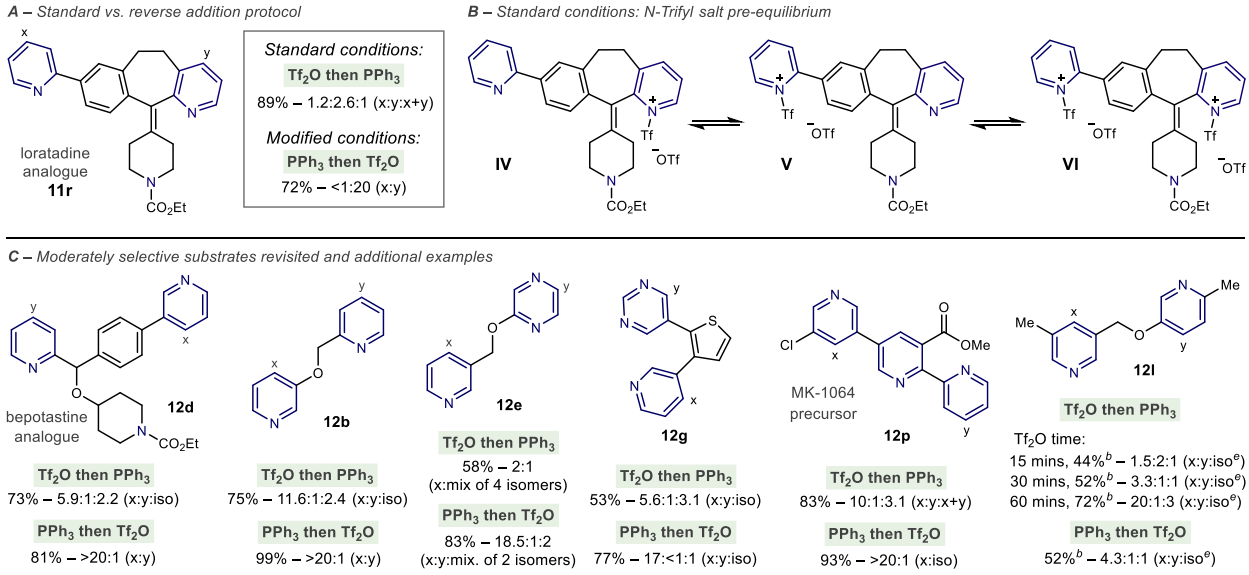
3.5 Order of Reagent Addition

Several polyazine examples in **Table 1** and **2** gave moderate site-selectivity (<5:1) under the standard phosphonium salt conditions. We hypothesized that the order the reagents are added in during the phosphonium protocol could influence the site-selectivity outcome in these systems. As mentioned in section **2.3**, under the standard phosphonium protocol, Tf_2O is stirred with the polyazine solution for 30 min at –78 ºC before adding PPh_3. This order of addition is chosen to minimize an unwanted reaction between Tf_2O and PPh_3 that leads to the formation of phosphine oxide. We decided to revisit phosphonium formation on loratadine analogue **11r**, where poor selectivity was observed under the standard phosphonium conditions (**Table 3.3**).[45] It was hypothesized that under the standard phosphonium conditions, an equilibrium mixture of *N*-triflyl pyridinium salt isomers **IV**, **V** and **VI** are formed in populations that relate to the observed selectivity profile of the reaction. To provide experimental evidence of an equilibrium mixture or isomers, a solution of **11r** in deuterated CH_2Cl_2 at –80 ºC was subjected to Tf_2O for 30 minutes

and observed via VT NMR. At –80 ºC, each pyridine proton peak was shifted downfield and broadened, compared to the ^{1}H NMR spectrum of **11r** without Tf_2O (section **A2.3**). It was hypothesized that the broadening of the peaks and downfield shifts indicate a rapidly interconverting mixture of triflyl-salt isomers. When the order of reagents is reversed, and PPh_3 is added before Tf_2O, a significant increase in site-selectivity was observed with minor amounts of phosphine oxide formed, as seen in **Table 3.3**. We propose that when PPh_3 is added before Tf_2O, *N*-triflyl pyridinium salt **IV** is the kinetically preferred isomer and is immediately reacted with PPh_3, preventing an equilibrium mixture of isomers.

Other polyazine systems that had moderate inherent selectivity were also tested using this order of reagent reversal strategy. Phosphonium ion formation on bepotastine analogue **12d**, previously shown as a mixture of isomers, is significantly increased in both yield and selectivity when reversing the order of reagent addition (**Table 3.3**).[45] Similarly, the efficiency and site-selectivity in different pyridine-pyridine and pyridine-diazine systems **12b**, **12e**, and **12g** are also improved under these conditions. Under the normal phosphonium conditions, MK-1064 produces a mixture of mono- and bis-phosphonium salts, whereas a single phosphonium isomer on the 3,5-disubstituted pyridine forms when reversing the order of reagent addition (**12p**). It was found that reversing the order of Tf_2O and PPh_3 was detrimental to certain polyazines like pyridine-pyridine system **12l**. Increasing the stirring time of Tf_2O before adding PPh_3 was necessary to increase the selectivity bias towards the 3,5-disubstituted pyridine. This indicates more time is required to establish a biased *N*-triflyl pyridinium salt equilibrium in certain systems like **12l**.

Table 3.3. Impact of Reagent Order on Site-Selectivity[a,b,c,d,e]

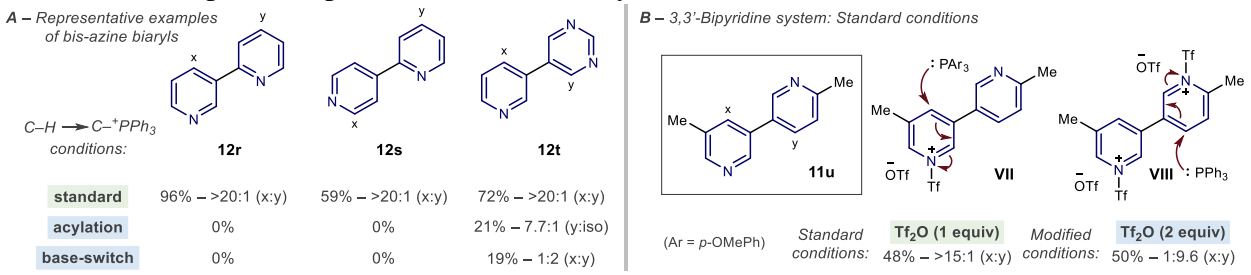


[a]Yields and ratios reported as in **Table 3.1**.[45] [b]Yield calculated by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]x + y represents a bis-phosphonium salt. [d]Iso refers to an unidentified phosphonium salt isomer. [e]Mixture of two unidentified isomers.

3.6 Initial Investigations of [*m,n*]-Bipyridines and Pyridine-Diazines

Heterobiaryls comprised of pyridine and diazines are key components of numerous biologically active compounds.[48] As seen in **Table 3.4**, under the standard phosphonium conditions, high levels of selectivity can be achieved in pyridine-pyridine and pyridine-diazine systems (**12r-12t**).[45] Conversely, no phosphonium salt formation was observed when either the acylation-blocking or base-mediated switching strategies were applied to these polyazine systems. We proposed that an increase of electrophilicity of the adjacent pyridinium in these systems deviates reactivity of PPh_3 to the sulfur on the *N*-triflyl pyridinium salt, thus generating phosphine oxide as the major product. Despite this, Pyridine-diazine (**12t**) shows that the switching strategies can be used to install the phosphonium ion on the pyrimidine ring, albeit in low yield.

Table 3.4. Phosphine-Dependent Site-Selectivity[a,b]



[a]Yields and ratios reported as in **Table 3.1**.[45] [b]Yields calculated by ^{1}H NMR spectroscopy of the crude reaction mixture.

Preliminary studies suggest that an alternative switching strategy, based on the phosphine addition step, stage 2, in the phosphonium salt protocol, is possible for substrates like **11u**.[45] As seen in **Table 3.4**, under the standard phosphonium conditions, P(*p*-OMePh)$_3$ adds selectively to the 3,5-disubstituted ring via Tf-salt **VII**. Attempts to switch the site-selectivity using the acylation-blocking strategy provided no formation of the target phosphonium salt. Instead, a steric-influenced switching strategy was devised based on the selective addition of phosphine to a bis-pyridinium salt **VIII**. It was proposed that the less hindered 2,5-disubstituted ring would be the preferred site of attack over the sterically hindered 3,5-system. It was shown that upon adding 1.75 equivalents of PPh_3 to a prestirred mixture of bipyridine **11u** and 2 equivalents of Tf_2O, a reversal of selectivity to the 2,5-system was achieved with good yield.

3.7 Derivatization Reactions of Polyazines

With site-selective phosphonium ion formation conditions in hand, transformations developed in our lab were used to generate a variety of analogue compounds (**Figure 3.10**).[38-42,45] Pyridine-diazine **11f** is used as an example where both phosphonium isomers are generated in high selectivity and reasonable yield using the standard and acylation-blocking conditions. Using bond forming transformations developed in the McNally group, as discussed in sections **2.5** and **2.7**, carbon-heteroatom bonds, including C–O (**14 & 18**) and C–S (**15 &19**) bonds are formed on both rings using alcohol **13** and benzyl thiolate, respectively. Heating with sodium azide, followed by

hydrolysis of the iminophosphorane products (not shown), results in heteroaryl aniline isomer **16** and **20**. In addition, deuterium can be selectively installed on both rings using K_2CO_3 in the presence of a mixture of CD_3OD and D_2O (**17 & 21**).

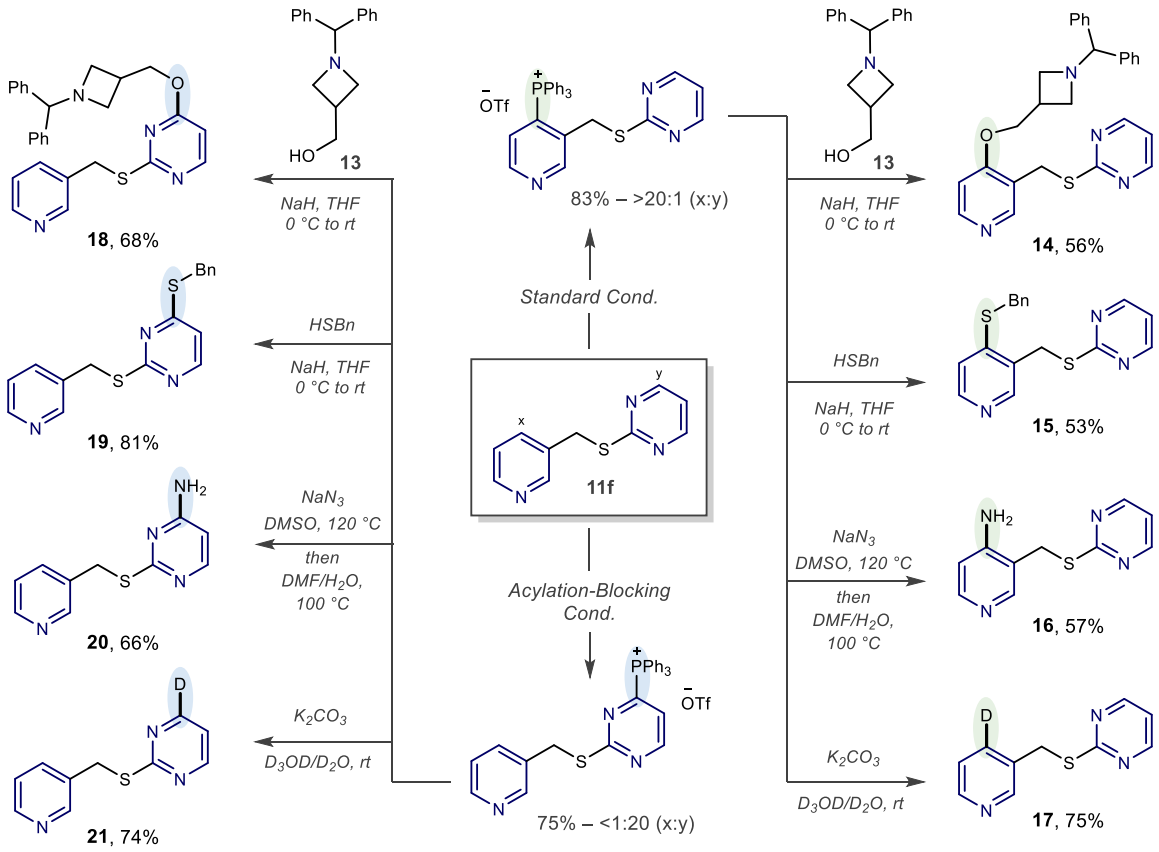


Figure 3.11. Derivatizations of Phosphonium Salt Isomers. Isolated yields are shown, and ratios are reported as in **Table 3.1**.[45]

To further show the utility of the site-selectivity protocol, a sequence of reactions was used to create drug-like scaffold **24** (**Figure 3.12**).[45] Under the base-switching protocol, phosphonium ion formation occurs exclusively on the pyrimidine ring of polyazine **22**. Subjecting this salt to a Nickel-catalyzed Suzuki reaction selectively installs a thiophene group on the pyrimidine ring (**23**). A second phosphonium ion is selectively formed on the 3-substituted pyridine, followed by C-O bond formation with azetidine-containing alcohol **13** to form drug-like fragment **24**.

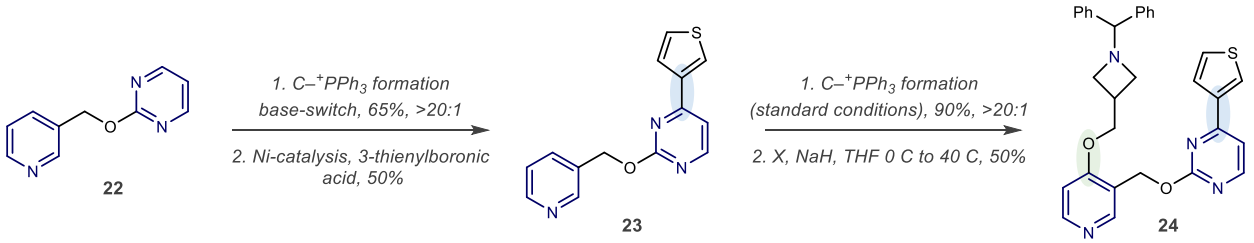


Figure 3.12. Sequential C-P and C-C bond-forming reactions. Isolated yields are shown, and ratios are reported as in **Table 3.1**.[45]

3.8 Conclusion

In this chapter, factors that control site-selective phosphonium formation in polyazine systems is presented. Steric and electronic factors in pyridines and diazines dictate the inherent site of C−P bond formation, which is predictable for complex polyazine systems. Examining the reaction mechanism for C−P bond formation allowed us to develop strategies for site-selective switching where phosphonium ion formation can be directed to other positions in a polyazine scaffold. Acylation-blocking, base-dependent selectivity, and selective phosphine addition enable control of selectivity in polyazines with distinct substitution patterns and electronic properties. The order that reagents are added was also found to have a significant impact on site-selectivity in polyazine systems. Furthermore, site-selective phosphonium ion formation was shown to be useful for generating a range of analogue compounds from a single polyazine. Collectively, site-selective phosphonium ion formation and subsequent bond transformation represent a means to deliver functional molecules that would be difficult to access otherwise.

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CHAPTER FOUR

DIRECT AND SELECTIVE ALKYLATION OF PYRIDINES VIA TRACELESS DEAROMATIZED PHOSPHONIUM INTERMEDIATES

4.1 Introduction into Alkylation of Pyridines

Alkylated pyridines are ubiquitous in biologically active compounds and pharmaceuticals and are commonly found in ligands and materials.[1-5] Examples of alkylated pyridines in drug molecules, such as Nevirapine and Pioglitazone, are shown in **Figure 4.1**. In this context, the alkyl group can impact the molecule's properties in several ways. The alkyl group can influence the binding properties of the Lewis basic pyridyl nitrogen, aid in occupying hydrophobic pockets, protect from oxidative metabolism, and tether additional groups to the drug molecule.[1,2] Additionally, the range of impact by the alkyl group makes alkylation of pyridines a common SAR strategy for medicinal chemists.[6] Given their importance to pharmaceuticals, strategies that install alkyl groups selectively and directly onto pyridine scaffolds are highly desirable.

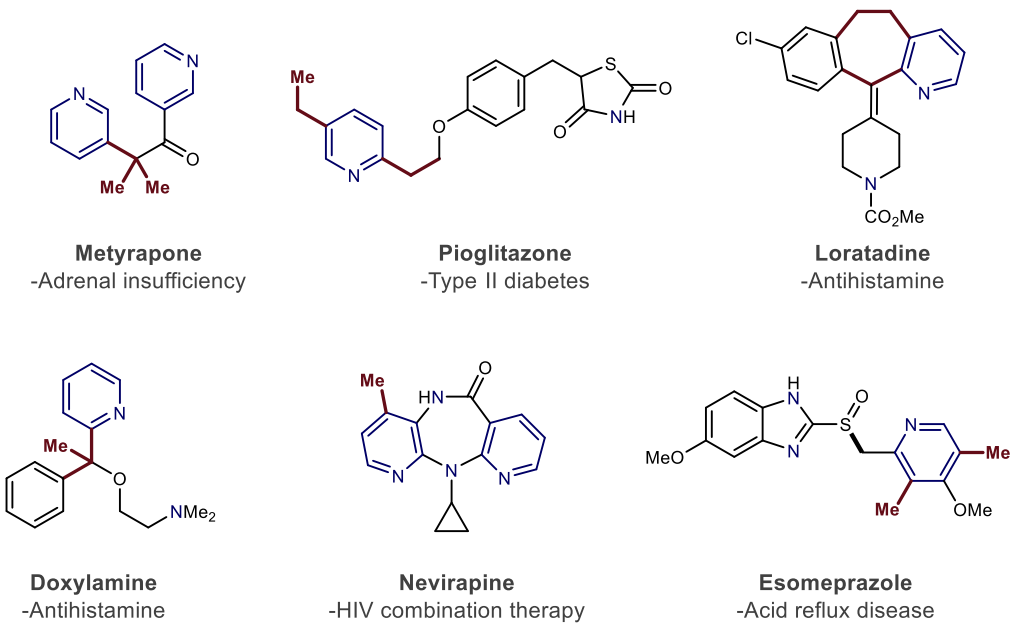


Figure 4.1. Examples of alkylated pyridines in pharmaceuticals.

As discussed in section **1.4**, several methods exist to directly install alkyl groups onto pyridines, including C-H functionalization via Minisci-type reactions, metal-catalyzed coupling processes with alkenes, and activation-addition reactions.[7-27] Despite significant progress, significant challenges remain. For example, controlling regioselectivity between the 2- and 4-positions on pyridines is difficult using Minisci-type reactions, as seen in DiRocco's late-stage alkylation strategy (section **1.4**). In addition, Nakao's and Kanai's alkylation methods are collectively limited to mono-substituted pyridines and three di-substituted pyridine examples (section **1.4**).

A recent advancement by Buchwald addresses some of these issues via a direct enantioselective 4-alkylation of azaarenes using a Cu-catalyzed styrene addition/rearomatization strategy (**Figure 4.2**).[28] Formation of an organocopper nucleophile (**I**) via enantioselective hydrometallation of styrene, followed by selective addition into an activated *N*-cuprated pyridine complex (**II**), generates an 1,4-*N*-cuprated dihydropyridine intermediate (**III**). A sigma-bond metathesis with dimethoxy(methyl)silane (DMMS) generates 1,4-*N*-silyl dihydropyridine (**IV**)

and the Cu-H catalyst (**V**). Aerobic oxidation forms the enantioenriched 4-alkylated pyridine. The bulky copper Lewis acid is proposed to sterically block reactivity at the 2- and 3- positions when coordinated to the pyridine nitrogen. The reaction is typically 4-selective and is currently limited to unsubstituted and 3-substituted pyridines and 2-substituted pyridazines.

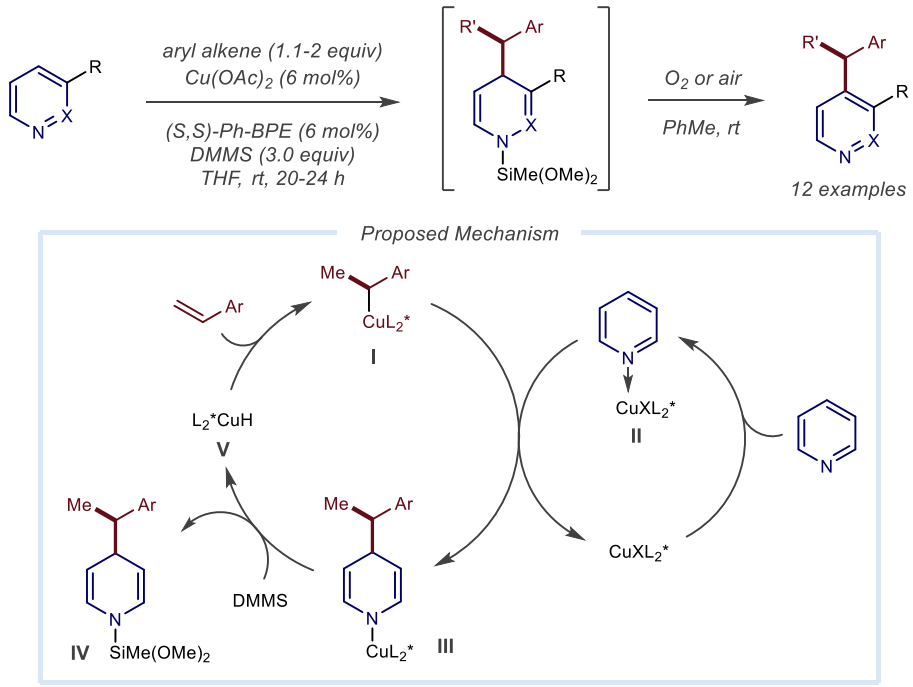


Figure 4.2. Buchwald's enantioselective 4-alkylation of azaarenes. Proposed mechanism is shown.[28]

4.2 Selective Alkylation of Pyridines via Traceless Phosphonium Dearomatized Intermediate

We hypothesized that an alternative strategy to directly alkylate pyridines at the 4-position could be achieved by intercepting the dearomatized phosphonium intermediate that is formed during the heterocyclic phosphonium salt reaction. As mentioned in section **2.3**, under the standard phosphonium salt forming conditions, dearomatized intermediate **VI** is converted into the aromatized phosphonium salt **VII** via elimination of the triflyl group using an organic base (**Figure 4.3**).[29] An alternative reaction was proposed in which the dearomatized intermediate **VI** is directly functionalized at the 4-position and aromatization occurs via a phosphorus-containing leaving group (**VIII**). One possible strategy involves formation of a phosphorous ylide (**X**) via the

deprotonation of dearomatized phosphonium intermediate **IX**. A Wittig reaction between the ylide and an aldehyde, followed by subsequent oxidation of the resulting pyridine anhydrobase (**XI**), should form the 4-alkylated pyridine (**XI→XII**). As the triflyl group in **VI** is eliminated in the presence of base, a different activating group that is resistant towards elimination is necessary for this alkylation strategy to work (**IX**, **Figure 4.3**).

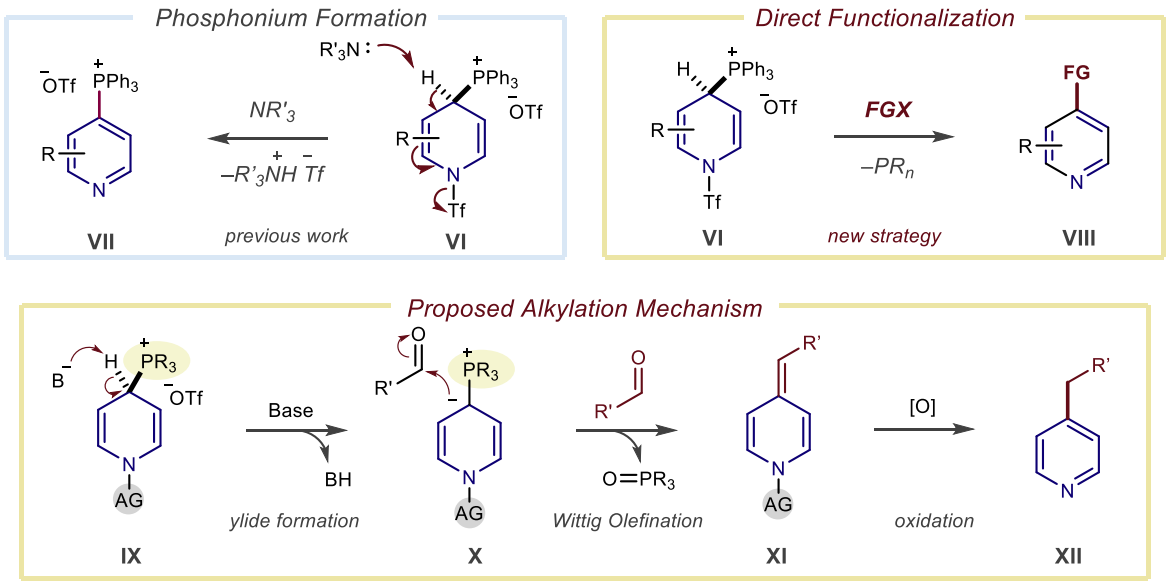


Figure 4.3. Phosphonium salt formation and a new strategy to directly functionalize dearomatized intermediate. Proposed alkylation mechanism is shown.

Alongside our own investigation into different activating groups, we became aware of a report by Lee and Park, where pyridine is first reacted with ethyl chloroformate to form an *N*-ethoxycarbonyl pyridinium salt which is then subjected to a mixture of triisopropylphosphite (PO^iPr_3) and sodium iodide (NaI) (**Figure 4.4**).[30-32] The PO^iPr_3 adds selectively to the 4-position of the pyridinium salt, where NaI dealkylates the generated phosphonium salt via the Michaelis-Arbuzov reaction (not shown). The resulting dearomatized intermediate, **XIII**, is then deprotonated by lithium diisopropylamine (LDA) to form a phosphonate-stabilized-carbanion (not shown) in a separate step which reacts with an aldehyde to form a betaine intermediate (**XIV**) via a Horner-Wadsworth-Emmons (HWE) olefination reaction. Lastly, potassium *tert*-butoxide

(KO^{t}Bu) is added to aromatize **XIV** and provide the 4-alkylpyridine **XV**. While this reaction validates our mechanistic hypothesis, the process requires 3 separate steps and is limited to unsubstituted pyridine. Given our experience with phosphines, we pursued to develop a one-pot strategy that alkylates pyridines via a traceless phosphonium dearomatized intermediate (**X**). We anticipated this process to hinge on the choice of activating group and phosphine source.

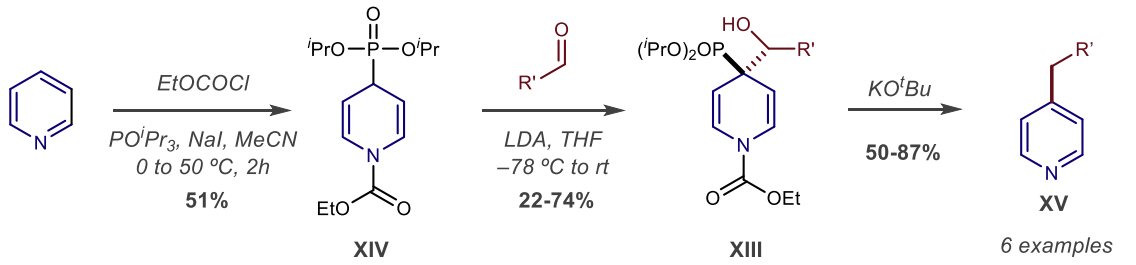
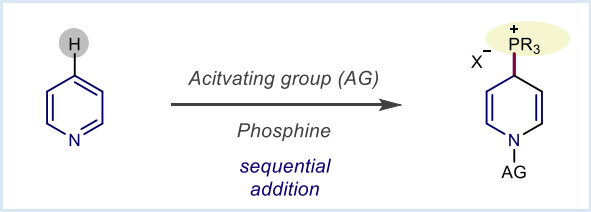


Figure 4.4. Lee and Park's alkylation of pyridine via a dearomatized pyridine phosphonate ester.[30-32]

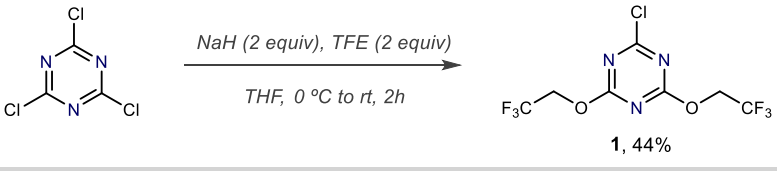
Since the stability of the dearomatized intermediate was critical to the reaction development, we first investigated the formation of the phosphonium dearomatized intermediate by screening combinations of different activating groups with PPh_3 and PBu_3 (**Table 4.1**). To a solution of 3-butyl pyridine in THF at 0 °C, an activating group from **Table 4.1** was added and the reaction was immediately warmed to room temperature. After stirring for 30 minutes, PPh_3 or PBu_3 was added to the reaction mixture and stirred for 30 minutes. The formation of the resulting dearomatized intermediate was observed via NMR analysis. We found that PPh_3 was not the ideal phosphine source as no product was observed when used in combination with any of the activating groups (**entries 1,3,5,7**). Although no dearomatized intermediate was observed with AcCl and tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) (**entries 2 & 8**), PBu_3 was found to be more reactive than PPh_3. Subjecting pyridine to a sequential addition of ethylchloroformate (EtOCOCl), silver triflate (AgOTf), and PBu_3 forms the corresponding dearomatized intermediate in 61% yield, however, an 8:1 mixture of 4- and 2-position isomers is present (**entry 2**). Using a combination of

trimethylsilyl trifluoromethanesulfonate (TMSOTf) and PBu_3 formed the dearomatized intermediate in only trace amounts (**entry 6**). We proposed that the lack of product is due to desilylation of the *N*-trimethylsilyl pyridinium intermediate by PBu_3 which deactivates the pyridine. We found that subjecting pyridine to a sequential addition of triazinyl chloride **1**, potassium hexafluorophosphate (KPF_6), and PBu_3 forms the dearomatized intermediate in near quantitative yield and as a single regioisomer (**entry 10**).[33,34] To form triazinyl chloride 1, a solution of cyanuric chloride and NaH in THF is cooled to 0 ºC, followed by the dropwise addition of 2 equivalents of trifluoroethanol (TFE) over 30 minutes. The reaction is warmed to room temperature and stirred for 2 hours to obtain 44% of the triazine.

Table 4.1. Activating group and phosphine optimization.



Entry	Activating group	Phosphine	% Yield	2':4' ratio
1	*EtOCOCl/AgOTf*	PPh_3	0	NA
2	*EtOCOCl/AgOTf*	PBu_3	61	1:8
3	*AcCl/AgOTf*	PPh_3	0	NA
4	*AcCl/AgOTf*	PBu_3	0	NA
5	*TMSOTf/AgOTf*	PPh_3	0	NA
6	*TMSOTf/AgOTf*	PBu_3	trace	NA
7	$B(C_6F_5)_3$	PPh_3	0	NA
8	$B(C_6F_5)_3$	PBu_3	0	NA
9	*triazinyl chloride*	PPh_3	0	NA
10	***triazinyl chloride,* 1**	PBu_3	**96**	**<1:20**

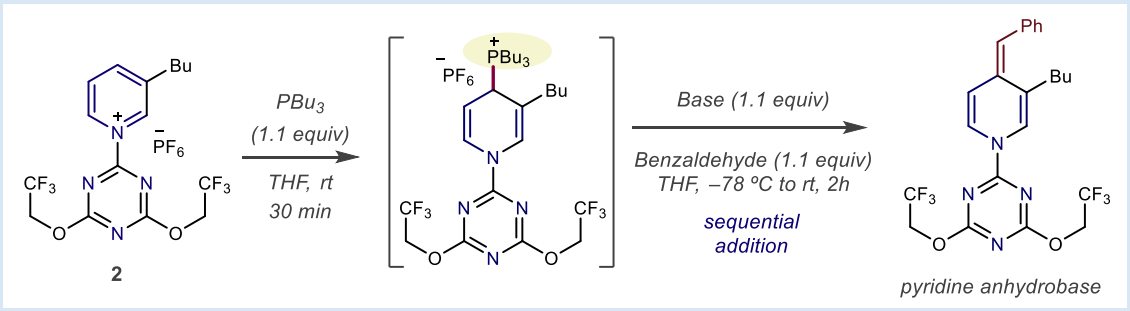


Yields and ratios determined from ^{1}H NMR are shown. 1,3,5-trimethoxybenzene is used as internal standard. Generation of triazinyl chloride, **1**, is shown.[33,34]

With the dearomatized intermediate in hand, we next investigated a series of bases to test the Wittig olefination between benzaldehyde and *N*-triazinyl-3-butylpyridinium salt (**2**, **Table 4.2**). To a solution of **2** in THF at room temperature, PBu_3 was added and stirred for 30 minutes. The reaction mixture was cooled to 0 ºC or –78 ºC, followed by the sequential addition of a base. After stirring for 15 minutes at the designated temperature, benzaldehyde was added, and the reaction was warmed to room temperature. LDA, potassium hexamethyldisilizane (KHMDS), and Massamune Roush conditions using DBU and LiCl were all effective in generating the pyridine

anhydrobase, however, attempts to improve the yields using these bases were unsuccessful (**entries 1-3**). Subjecting dearomatized intermediate to sequential addition of NaH and then benzaldehyde did not produce the pyridine anhydrobase (**entry 4**). Similarly, it was found that using KO^{t}Bu as the base produced the pyridine anhydrobase in only 10% yield (**entry 5**). It was later found that the ylide generated under these conditions, is unstable at temperatures higher than –30 ºC and decomposes into 3-butyl pyridine and phosphine oxide. As entries **4 & 5** are conducted at 0 ºC, the minor amount or lack of product is not surprising. In contrast, organolithium bases were found to form the pyridine anhydrobase in high yields, with MeLi performing the best (**entries 6-8**).

Table 4.2. Optimization of base in the formation of pyridine anhydrobase.[a,b]



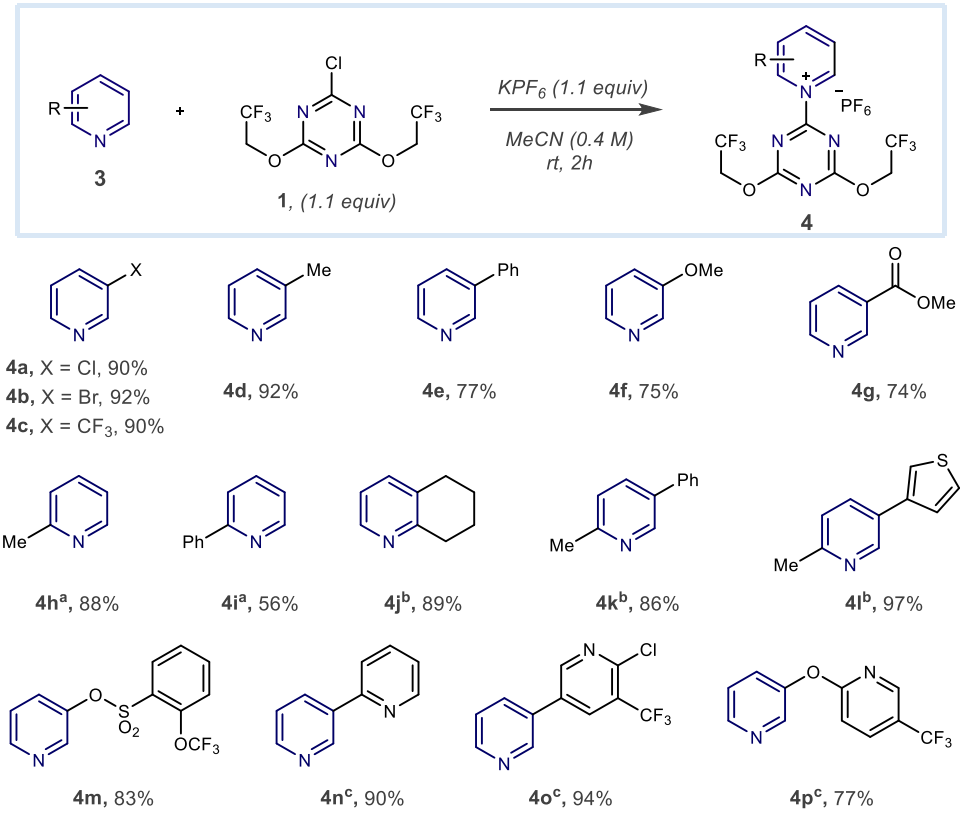
Entry	Base	% Yield	Entry	Base	% Yield
1	*LDA*	**43**	5[b]	*KOtBu*	**10**
2	*KHMDS*	**65**	6	*PhLi*	**77**
3[a]	*DBU/LiCl*	**35**	7	*n-BuLi*	**77**
4[b]	*NaH*	**0**	**8**	***MeLi***	**89**

Yields and ratios determined from ^{1}H NMR are shown. 1,3,5-trimethoxybenzene is used as internal standard. [a]reaction ran in MeCN at 0 ºC. [b]reaction ran at 0 ºC.

Although the goal of this study is to develop a one-pot method to alkylate pyridines, we first decided to generate a set of *N*-triazinyl pyridinium salts (**4**) to examine the Wittig olefination reaction (**Table 4.3**). Pyridines were subjected to 1.1 equivalents of triazinyl chloride, **1**, and KPF_6 in MeCN and stirred at either room temperature or at 50 ºC to 100 ºC for 2 hours to afford the

pyridinium salt. We found that a range of 3-substituted pyridines work well under the reaction conditions, including those with halo (**4a & 4b**), trifluoromethyl (**4c**), carbon-bearing (**4d & 4e**), and methoxy groups (**4f**) and esters (**4g**). While 2-methylpyridine (**4h**) works well in this process, other 2-substiuted pyridines such as 2-phenylpyridine (**4i**) were less effective in forming the pyridinium salt. Pyridines with other substitution patterns, including 2,3- (**4j**) and a 2,5-disubstituted pyridine (**4k & 4l**) were found to form the pyridinium in good yield. In addition, more complex drug-like fragments, such as pyridin-3-yl 2-benzenesulfonate **4m**, formed the pyridinium in good yield. Furthermore, polyazines (**4n-4p**) are amenable under the reaction conditions and form the pyridinium with excellent site-selectivity.

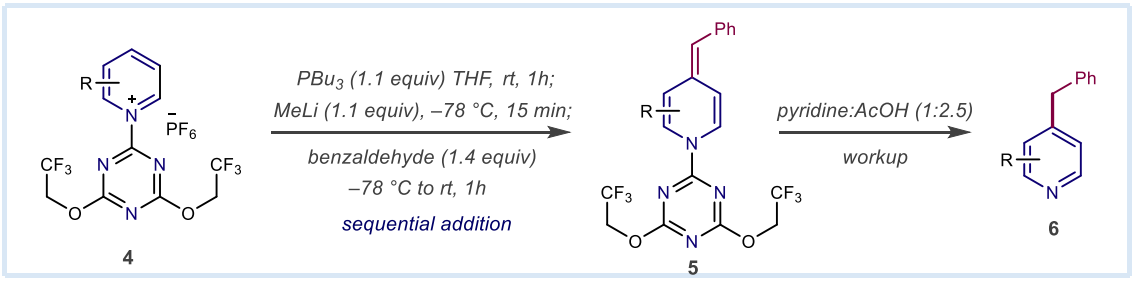
Table 4.3. *N*-triazinylpyridinium salt scope.[a,b]

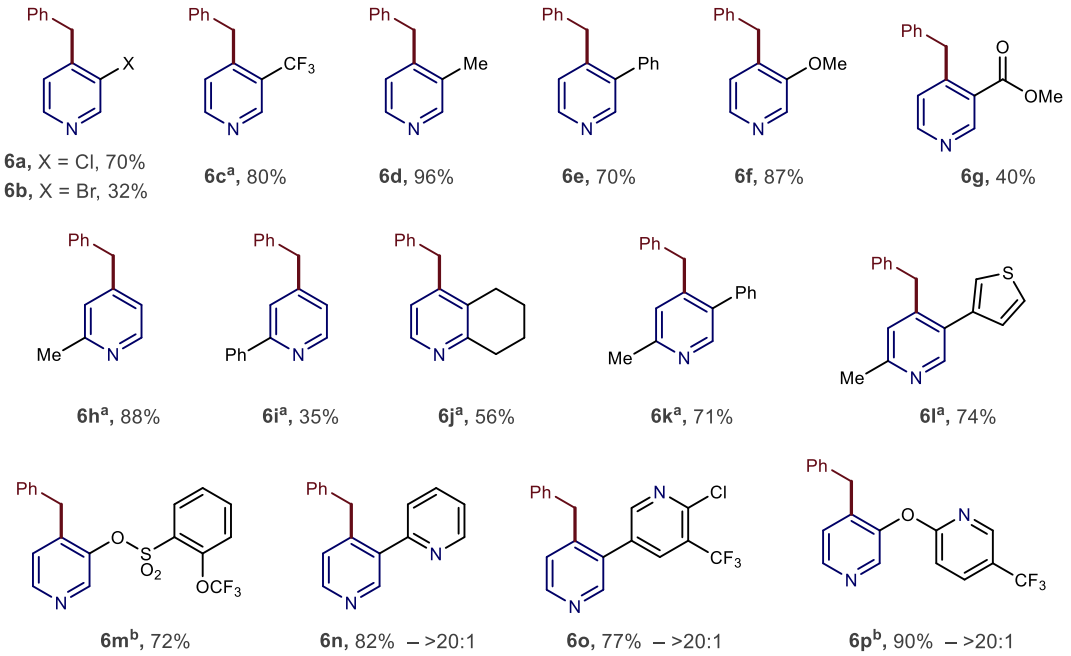


Isolated yields are shown. [a]Reaction ran at 100 ºC. [b]Reaction ran at 50 ºC. [c]*N*-triazinyl pyridinium formation occurs on the highlighted pyridine.

With a set of *N*-triazinyl pyridinium salts in hand, we next investigated the scope of the Wittig olefination (**Table 4.4**). To a solution of pyridinium salt **4** in THF at room temperature, PBu_3 was added and stirred for 1 hour. The reaction mixture was cooled to –78 ºC, followed by the sequential addition of MeLi at –78 ºC. After 15 minutes, benzaldehyde was added, and the reaction mixture was immediately warmed to room temperature and stirred for 1 hour to generate pyridine anhydrobase **5**. Under an acidic workup consisting of a 2.5:1 mixture of acetic acid and pyridine, **5** is rearomatized and deprotected to afford the 4-alkylated pyridine **6**. It was found that 3-subsituted pyridiniums work well under the reaction conditions (**6a-6g**). While alkylation works well for 2-methylpyridinium (**6h**), 2-phenylpyridinium (**6i**) is less effective. We hypothesized that a steric interaction between the phenyl ring and the *N*-triazinyl group destabilizes the dearomatized intermediate resulting in a lower yield of pyridine anhydrobase. It was found that 2,3- (**6j**) and 2-5- disubstituted pyridiniums (**6k & 6l**) form the 4-alkylated pyridine in good yields. Additionally, 4-benzylpyridines are generated with excellent site-selectivity, in polyazine examples **6n**, **6o**, and **6p**.

Table 4.4. Wittig Olefination of *N*-triazinyl pyridinium salts.[a,b]

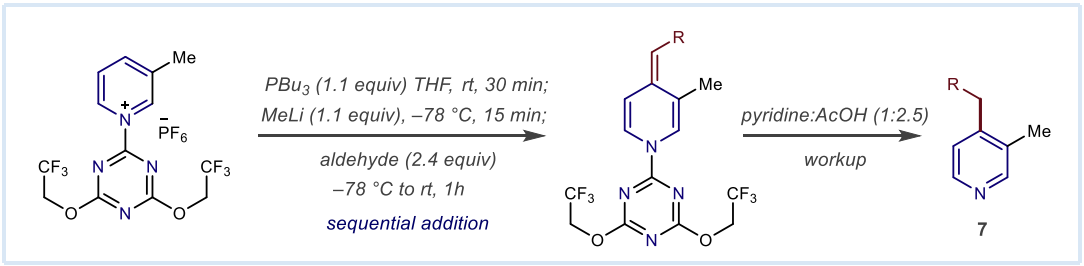


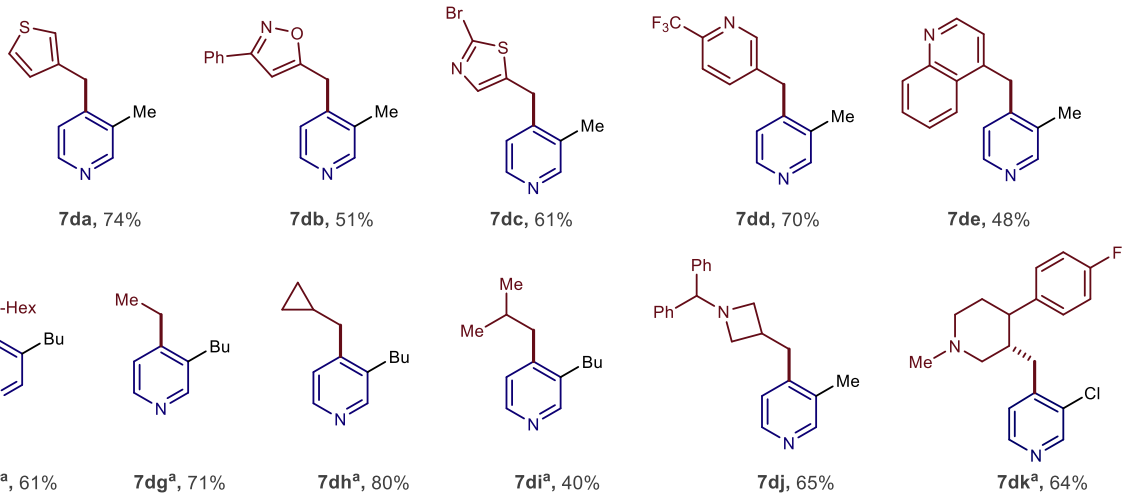


Yields and ratios determined from ^{1}H NMR are shown. 1,3,5-trimethoxybenzene is used as internal standard. [a]LiHMDS (1.1 equiv) and TMEDA (1.1 equiv) were used instead of MeLi. [b]rearomatization was conducted at 60 ºC instead of at rt.

The scope of aldehydes was next examined using *N*-triazinyl-3-methylpyridinium salt, **4d**, as a representative substrate (**Table 4.5**). We found that several aldehydes are amenable under the Wittig olefination procedure, including aryl aldehydes containing thiophene (**7da**), isoxazole (**7db**), thiazole (**7dc**), pyridine (**7dd**) and quinoline (**7de**). Additionally, several alkyl aldehydes work well to form alkylated pyridines containing hexyl (**7df**) and ethyl (**7dg**) chains, as well as, branched cyclopropyl (**7dh**) and sec-butyl groups (**7di**). Furthermore, complex aldehydes containing an azetidine ring (**7dj**) and a β-amino chiral center (**7dk**) form the alkylated pyridine in good yield.

Table 4.5. Aldehyde scope for Wittig olefination.[a]





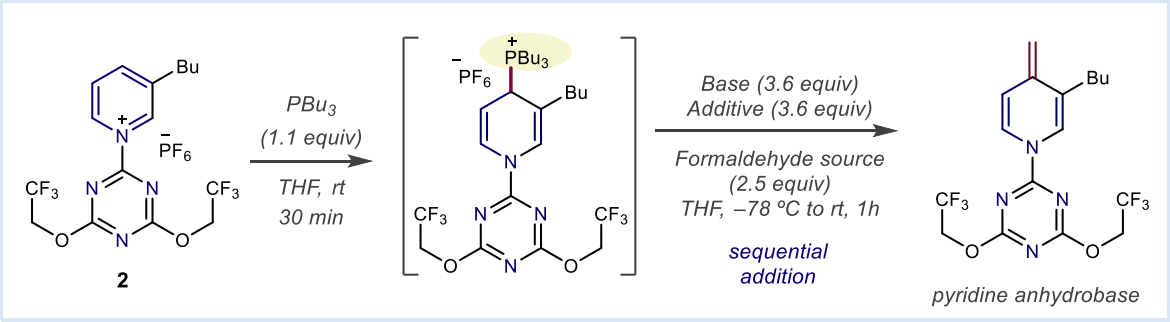
Yields and ratios determined from ^{1}H NMR are shown. 1,3,5-trimethoxybenzene is used as internal standard. [a]*N*-triazinyl-3-butylpyridinium salt used instead of *N*-triazinyl-3-methylpyridinium salt.

4.3 Selective Methylation of Pyridine

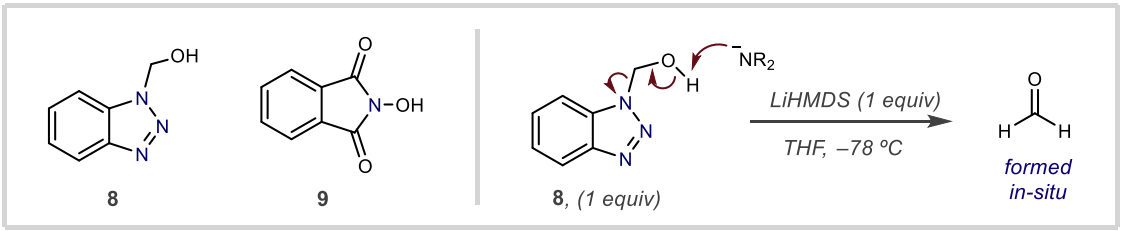
The methyl group is a ubiquitous motif found in many biologically active compounds, with more than 67% of the top 200 small-molecule drugs in 2011 containing at least one methyl group bound to a carbon atom.[35-38] Methyl groups are often installed to improve the biological activity and physical properties of a drug candidate. Methylation has been used to optimize a drug candidate's solubility and potency, as well as improve the selectivity against unwanted biological targets and block positions on the molecule that are prone to enzyme metabolism.[35-37] Given the potential benefits the methyl group brings to pharmaceuticals, methods that directly install the methyl group are highly desirable. We next investigated whether the methylation of pyridines would be possible under our developed alkylation reaction conditions.

To test the methylation protocol, a solution of *N*-triazinyl-3-butylpyridinium salt (**2**) in THF was first subjected to PBu_3 at room temperature for 30 minutes. The reaction mixture was cooled to –78 ºC, followed by the addition of base. After stirring for 15 minutes, a formaldehyde source was added, and the reaction was warmed to room temperature for 1 hour (**Table 4.6**). As seen in entry **1**, when paraformaldehyde was used as the formaldehyde source, only small amounts of the pyridine anhydrobase were formed under the alkylation conditions used in **Table 4.4**. As the generation of formaldehyde from either the oxidation of methanol or depolymerization of paraformaldehyde produces self-reacting toxic gas, we explored alternative methods to produce the formadehyde.[39.40] In 2007, the Bischoff group reported a method where formaldehyde is formed *in-situ* via a reaction between 1-(hydroxymethyl)benzotriazole, **8**, and LiHMDS at –78 ºC in THF.[41] Using Bischoff's method, a solution of LiHMDS in THF was cooled to –78 ºC, followed by the dropwise addition of a solution of 8 in THF (0.1 M) over 20 minutes. The resulting mixture was added to a solution of phosphonium ylide which was generating using MeLi under the optimized alkylation conditions. As seen in entry **2**, this strategy led to a 54% yield of the pyridine anhydrobase. Using LiHMDS instead of MeLi slightly increased the yield to 61% (**entry 3**). Using *N*-hydroxymethyl phthalimide (**9**) as a formaldehyde surrogate instead of **8**, decreased the yield of pyridine anhydrobase to 11% (**entry 4**). A screen of additives including hexamethylphosphoramide (HMPA), *N,N*-dimethylpropyleneurea (DMPU), *N,N'*-dimethylethylenediamine (DMEDA), TMEDA (*N,N,N',N'*-tetramethylethylenediamine) were shown to increase the efficiency of the reaction with TMEDA forming the pyridine anhydrobase in 84% yield (**entries 5-8**). We hypothesized that the TMDEA and the other additives break up any lithium aggregation that occurs under the reaction conditions.[42]

Table 4.6. Methylation optimization.



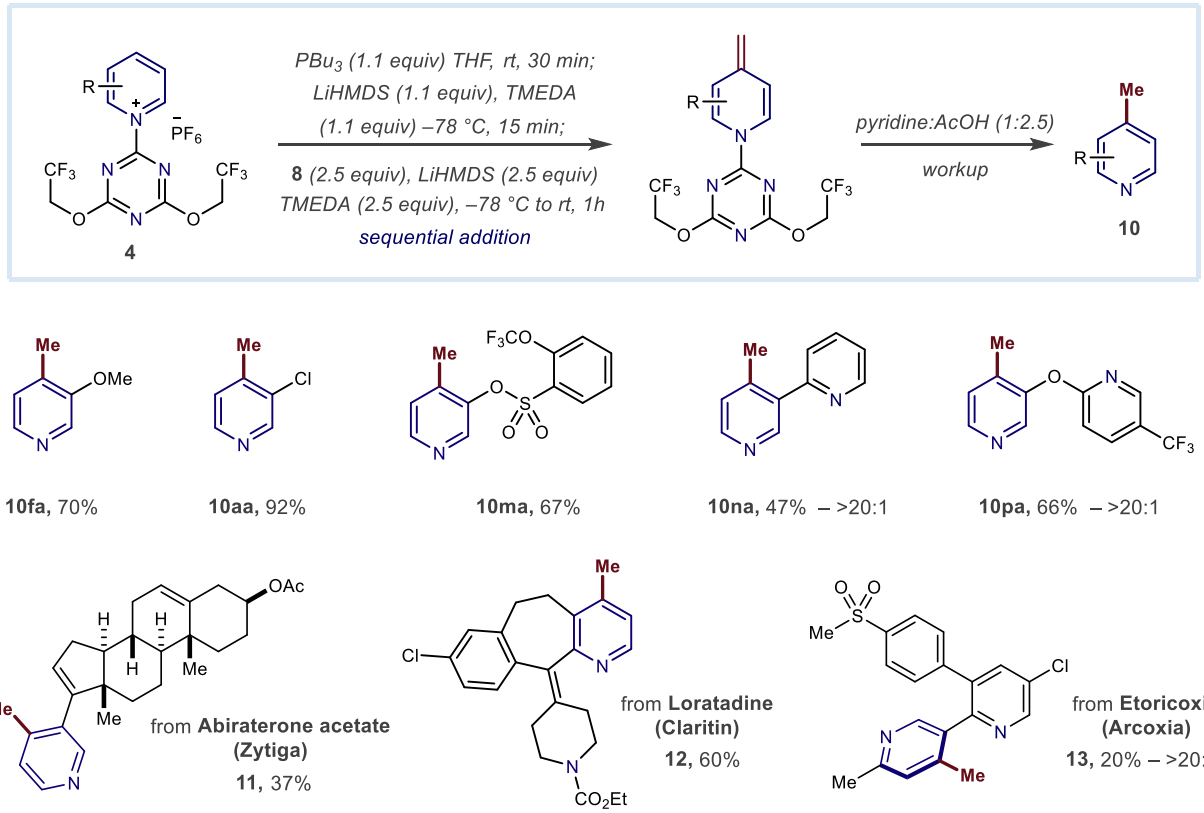
Entry	Formaldehyde Source	Base	Additive	% Yield
1	*paraformaldehyde*	*MeLi*	-	**11**
2	**8**, *LiHMDS*	*MeLi*	-	**54**
3	**8**, *LiHMDS*	*LiHMDS*	-	**61**
4	**9**, *LiHMDS*	*LiHMDS*	-	**11**
5	**8**, *LiHMDS*	*LiHMDS*	*HMPA*	**73**
6	**8**, *LiHMDS*	*LiHMDS*	*DMPU*	**68**
7	**8**, *LiHMDS*	*LiHMDS*	*DMEDA*	**0**
8	**8, *LiHMDS***	***LiHMDS***	***TMEDA***	**84**



Yields and ratios determined from ^{1}H NMR are shown. 1,3,5-trimethoxybenzene is used as internal standard. Reaction between **8** and LiHMDS forming formaldehyde *in-situ* is shown.[41]

We next applied the optimized methylation procedure to set of *N*-triazinyl pyridinium salts (**4**). Preliminary results show that 3-substituted pyridines, containing chloro (**10fa**), methoxy (**10aa**), and sulfonate groups (**10ma**) work well under the reaction conditions (**Table 4.7**). Additionally, 4-methylpyridines are generated site-selectively, in polyazine examples **10na** and **10pa**. Furthermore, we found that this methylation protocol is amenable to the late-stage functionalization of pharmaceuticals, including Zytiga (**11**), Loratadine (**12**), and Etoricoxib (**13**).

Table 4.7. Methylation of *N*-triazinylpyridinium salts.



Yields and ratios determined from ^{1}H NMR are shown. 1,3,5-trimethoxybenzene is used as internal standard.

During our investigations, we observed that in the absence of an acidic workup, pyridine anhydrobase **5** is particularly stable and can serve as a versatile intermediate for further derivatization (**Figure 4.5**).[43] After subjecting *N*-triazinyl-3-butyl pyridine to the alkylation conditions described in **Table 4.4**, the resulting 3-butylpyridine-derived-anhydrobase **14** was immediately subjected to different bond-forming reaction conditions instead of the acidic workup. Preliminary studies show that crude **14** can be successfully reduced to the 3,4-tetrahydropyridine **15** or hydrogenated to the piperidine analog (**16**), using an acidic sodium borohydride mixture or Pd/C under H_2 (1 atm), respectfully.[28] Additionally, using 1 or 4 equivalents of Selectfluor in the presence of sodium acetate converts **14** into the mono- or di-fluorinated alkylpyridine, respectfully

(**17,18**).[44] Subjecting **14** to a mixture of deuterated acetic acid and pyridine selectively deuterates the benzylic positions of the alkylated pyridine (**19**).

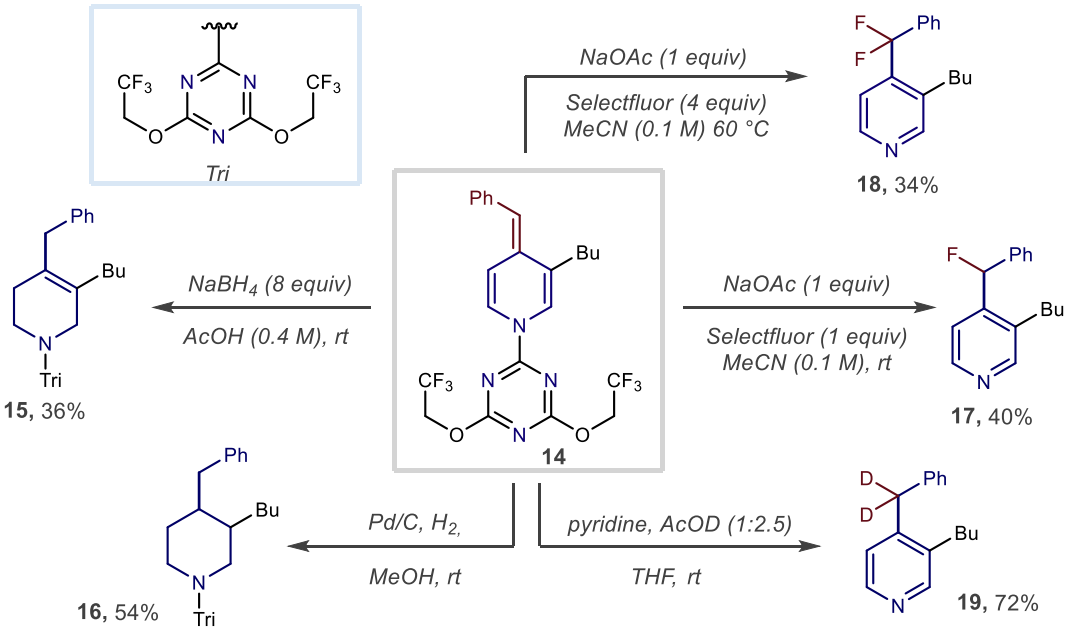


Figure 4.5. Post Wittig Transformations. Yields and ratios determined from ^{1}H NMR are shown. 1,3,5-trimethoxybenzene is used as internal standard.

4.4 Conclusion

A new strategy to selectively alkylated pyridines via a traceless dearomatize phosphonium salt is discussed. A range of pyridines are converted to pyridinium salts using a triazinyl chloride as an activating group. Subsequent addition of PBu_3, followed by a Wittig olefination between an aldehyde generates a range of alkylated pyridines. An adaption of the alkylation protocol led to strategy where building-blocking pyridines and pharmaceuticals can be selectively methylated at the 4-position. Post-Wittig transformations of the pyridine anhydrobase further highlights the utility of this reaction to form valuable pyridine derivatives. Collectively, this method provides a meaningful step forward in pyridine functionalization that medicinal chemists will find practical, convenient, and valuable for selective incorporation of alkyl groups into pyridine-containing molecules. A manuscript discussing the work in this chapter is currently in preparation.

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CHAPTER FIVE

CONCLUSION AND CLOSING REMARKS

5.1 Impact of Phosphonium Ion Formation on Azines and Polyazines

Within the context of electron-deficient heteroaromatics, nitrogen-containing six-membered ring variants represent the most prevalent structural units found in small molecule therapeutics.[1] Pyridine and diazines are frequently found in FDA approved drugs, agrochemicals, material sciences and ligands for metal catalysis.[2-5] Given the importance of these structural motifs, direct methods that selectively functionalize pyridine and diazine scaffolds are highly desirable.

As discussed in sections **1.2**, **1.3**, and **1.4**, there are many methods to directly functionalize pyridine and diazines. These methods are often 2- and 3-selective, whereas methods that directly functionalize pyridine at the 4-position are rare and have many limitations.[6-16] As discussed in section **1.4**, Nakao's and Kanai's methods to alkylated pyridines selectively at the 4-position are currently limited to mono-substituted pyridines and in most cases the products are generated as mixtures of branched and linear products.[11-13] Kanai's trifluoromethylation reaction is currently limited to mono-substituted pyridines and often results in mixtures of regioisomers at the 2- and 4-positions when the 3-posisiton is substituted.[15] Although Martin's strategy to install silyl groups at the 4-position of pyridines achieves excellent selectivity, the silylated products are limited by the types of subsequent bond forming transformations that can be done with the silyl group.[16] Given these limitations, methods that can selectively functionalize pyridines at the 4-position on a range of substrates of varying complexity, including building block molecules, drug-like fragments, and pharmaceuticals, are necessary to advance the field.

As discussed in section **2.3**, our method to selectively install phosphonium ions at the 4-position of pyridines addresses many of the problems and challenges associated with the existing methods to selectively functionalize pyridines at the 4-position.[17-22] Phosphonium salts can be installed on a range of building block pyridines including 2,3- 2,5- 3,5-disubstituted pyridines, trisubstituted pyridines, and several diazines, such as pyrazines and pyrimidines. The C-P bond forming method is also applicable to drug-like fragments and pharmaceuticals that contain multiple polar functional groups and different pyridines and diazines. The reaction is completely selective for the 4-position and is also site-selective for polyazine-containing molecules.[17,18]

As discussed in section **2.5**, four reaction manifolds are amenable to transforming heterocyclic phosphonium salts into valuable derivatives.[23-29] Adding nucleophiles such as alkoxides, thiolates and azides form C–O, C–S and C–N bonds via S_NAr or phosphorus ligand coupling pathways. The ligand coupling pathway has also been exploited as a unique way to make complex heterobiaryls. Phosphonium salts can be used as inputs into nickel- and cobalt-catalyzed cross-coupling reactions. Fragmentation-trapping sequences can be used to deuterate and tritiate pharmaceuticals. My research focused on developing the phosphonium salt protocol, as well as nucleophilic additions to phosphonium salts, both of which have been expanded by co-workers and led to several publications. The ability to functionalize pyridines of varying complexity, containing several substitution patterns with complete selectivity at the 4-position, could lead to the discovery of new molecules with biological activity which contain substituents at the 4-position, which until now was too challenging to synthesize.

5.2 Impact of 4-Alkylation of Pyridines Method

Since alkylated pyridines are ubiquitous in pharmaceuticals, strategies that install alkyl groups directly into pyridine scaffolds are highly desirable and offer advantages in terms of step

economy, as well as versatility.[30-36] As discussed in section **1.4**, several methods exist to directly install alkyl groups onto pyridines via C-H functionalization reactions including Minisci-type reactions and metal-catalyzed coupling reactions with alkenes. Despite significant progress, controlling regioselectivity and tolerating a broad range of pyridines can be problematic under these reaction platforms.

As discussed in section **4.2**, our method to alkylate pyridines is completely selective for the 4-position and can also be used for the selective incorporation of methyl groups and other alkyl groups selectively at the 4-position of pharmaceutical molecules.[10-12,37-48] This work represents a significant advancement in the field of 4-alkylation of pyridines, where a range of pyridines and polyazines are amenable under the reaction conditions. In addition, pyridine anhydrobases are a well-known synthetic handle that undergo a range of subsequent bond-forming transformations to form several alkylated derivatives, making our method more valuable. Collectively, this method provides a meaningful step forward in pyridine functionalization that medicinal chemists will find practical, convenient, and valuable for selective incorporation of alkyl groups directly from the C-H precursor.

5.3 Future Direction

In addition to coupling the nucleophiles discussed in section **2.5**, we hypothesize that trifluormethyl groups, alkenes, alkynes, nitriles, and other electron-withdrawing groups may be possible via the ligand-coupling pathway using phosphonium salts. Given the versatility of the pyridine anhydrobase in our alkylation reaction, we hypothesize that several additional bond-forming transformations are amenable, including Heck-cross couplings, Diels-Adler cycloaddition reactions and subsequent alkylation. Although the alkylation method is currently a 2-step procedure, work in our lab is being done to condense this method to a one-pot alkylation.

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APPENDIX ONE

SELECTIVE FUNCTIONALIZATION OF PYRIDINES AND DIAZINES VIA PHOSPHONIUM SALTS: EXPERIMENTAL

A. 1.1 General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (400 MHz) or an Agilent Inova 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), $(CD_3)_2SO$ (2.50 ppm), CD_3OD (3.31 ppm) or CD_3CN (1.94 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants, proton assignment). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (100 MHz) or an Agilent Inova 400 (100 MHz) spectrometer.[*] Chemical shift (δ) was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in $CDCl_3$ (77.00 ppm), C_6D_6 (128.06 ppm), $(CD_3)_2SO$ (39.51 ppm), CD_3OD (49.00 ppm) or

[*] Artifact from instrument with chemical shift of 194 ppm is observed in several ^{13}C NMR spectra (see *S56* for an example).

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}).

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

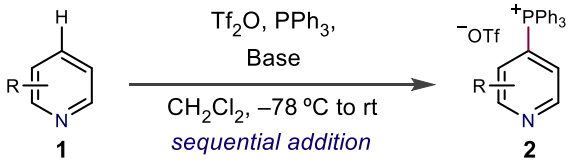
Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] 1,2-Dichloroethane (DCE), 1,4-dioxane, chloroform, chlorobenzene and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest 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 a Agilent 5977A fitted with a 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.

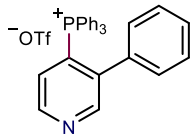
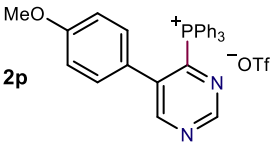
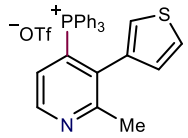
PPh_3 (99%) was purchased from Oakwood Chemical and is most effective when crushed to a powder before use. Tf_2O (99%) was purchased from Oakwood Chemical and used without further purification but was routinely stored in a –20 ºC fridge. NEt_3 and DBU were distilled before use. NaH (60% in mineral oil) was purchased from Sigma Aldrich and was typically distributed into vials and stored in a desiccator.

A. 1.2 Base and Temperature Effects During Heterocyclic Phosphonium Salt Formation

The choice of base can have a large effect on the yield of heterocyclic phosphonium salt for certain types of substrates. Shown below are representative examples of this effect. In general, either NEt_3 or DBU give optimal results.

Table S1. Effect of Base on Heterocyclic Phosphonium Salt Formation

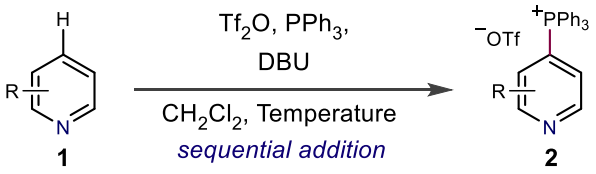


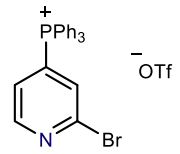
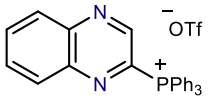
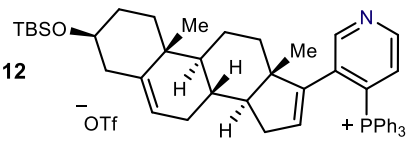
Substrates	Base Dependent Yields*			
	NEt_3	DBU	TMG	TBD
2f 	0%	82%	74%	71%
2p 	18%	63%	59%	50%
2h 	0%	65%	30%	31%

*^{1}H NMR yields shown using 1,3,5-trimethoxybenzene as an internal standard.

For the majority of examples –78 °C during the Tf_2O, PPh_3 and base stages of the reaction is optimal. Table S2 shows that yields can decrease if the temperature deviates from –78 °C. However, for a small number of substrates we found that optimal yields were obtained at different temperatures during the PPh_3 or base addition stages. These examples (**2b**, **10** and **12**) are also shown in Table S2 and are explicitly described in the Section 4.

Table S2. Effect of Temperature on Heterocyclic Phosphonium Salt Formation

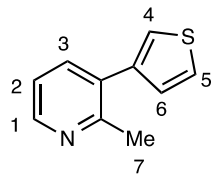


Substrates	Temperature Dependent Yields*		
2b 	–78 °C (Tf_2O) –78 °C (PPh_3) –78 °C (DBU) 85%	–78 °C (Tf_2O) –50 °C (PPh_3) –50 °C (DBU) 67%	–78 °C (Tf_2O) 0 °C (PPh_3) 0 °C (DBU) 17%
 (Model substrate for N-Bn Varenicline, **10**)	–78 °C (Tf_2O) –78 °C (PPh_3) –78 °C (DBU) 22%	–78 °C (Tf_2O) –30 °C (PPh_3) –30 °C (DBU) 37%	–78 °C (Tf_2O) 40 °C (PPh_3) 40 °C (DBU) 65%
12 	–78 °C (Tf_2O) –78 °C (PPh_3) –78 °C (DBU) 26%	–78 °C (Tf_2O) –50 °C (PPh_3) –50 °C (DBU) 59%	

*^{1}H NMR yields shown using 1,3,5-trimethoxybenzene as an internal standard.

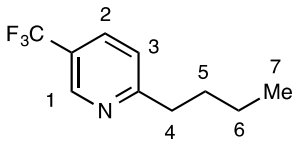
A. 1.3 Preparation of Heterocyclic Phosphonium Salt Precursors

2-Methyl-3-(thiophen-3-yl)pyridine



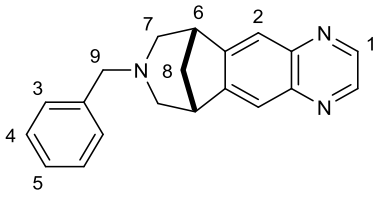
An oven dried 250 mL round bottom flask was charged with 2-methyl-3-pyridyltrifluoromethanesulfonate (1.45 g, 6.00 mmol), 3-thienylboronic acid (1.54 g, 12.00 mmol), $Pd(PPh_3)_4$ (693 mg, 0.60 mmol), and K_3PO_4 (2.55 g, 12.00 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill before addition of 1,4-dioxane (144 mL). The mixture was heated at 85 °C for 12 hours, cooled to room temperature and diluted with Et_2O. The suspension was washed with a saturated aqueous solution of K_2CO_3. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a purple/brown oil (893 mg, 5.10 mmol, 85% yield). IR ν_{max}/cm^{-1} (film): 3100, 3044, 2988, 2961, 1567, 1431, 863, 776, 734, 653; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.46 (1H, dd, J = 4.9, 1.8 Hz, H_1), 7.56 (1H, dd, J = 7.7, 1.8 Hz, H_3), 7.18-7.10 (2H, m, H_2 and H_5), 7.39 (1H, dd, J = 4.9, 3.1 Hz, H_6), 7.28-7.21 (1H, m, H_4), 2.56 (3H, s, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.93, 147.73, 139.99, 136.97, 131.77, 128.35, 125.60, 132.28, 120.93, 23.57 ; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 176.0, $C_{10}H_{10}NS^+$ requires 176.0.

2-Butyl-5-(trifluoromethyl)pyridine



An oven-dried 100 mL round bottomed flask was charged with $ZnCl_2$ (1.36 g, 10.00 mmol) and anhydrous THF (20 mL). The colorless solution was cooled to 0 °C, *n*-BuLi (2.5 M in hexanes, 4.00 mL, 10.00 mmol) was added dropwise, and the reaction mixture was stirred for 1 hour. The resulting *n*-butylzinc chloride solution (10.00 mmol) was added dropwise to a 50 mL round bottomed flask charged with 2-bromo-5-(trifluoromethyl)pyridine (1.13 g, 5.00 mmol), $Pd(PPh_3)_4$ (58 mg, 0.025 mmol), and 5 mL of anhydrous THF. After 3 hours of stirring the reaction mixture was quenched with H_2O (20 mL), organic layer separated, and aqueous layer extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 30% CH_2Cl_2 in hexanes) to provide the title compound as a colorless oil (864 mg, 4.26 mmol, 85% yield). IR n_{max}/cm^{-1} (film): 2960, 1609, 1325, 1161, 1124, 1080, 1016; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.77 (1H, s, H_1), 7.79 (1H, dd, J = 8.2, 1.8 Hz, H_2), 7.29-7.21 (1H, m, H_3), 2.84 (2H, t, J = 7.5 Hz, H_4), 1.71 (2H, qn, J = 7.5 Hz, H_5), 1.37 (2H, sext, J = 7.5 Hz, H_6), 0.92 (3H, t, J = 7.6 Hz, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.60, 146.12 (q, J = 4.1 Hz), 133.23 (q, J = 3.5 Hz), 123.99 (q, J = 32.8 Hz), 123.77 (q, J = 271.2 Hz), 122.36, 38.08, 31.70, 22.37, 12.82; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -62.32; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 204.1, $C_{10}H_{13}F_3N^+$ requires 204.1.

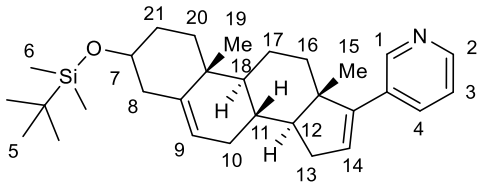
8-benzyl-7,8,9,10-tetrahydro-6H-6,10-methanoazepino[4,5-g]quinoxaline



An oven dried 8 mL vial was charged with Varenicline (7,8,9,10-tetrahydro-6H-6,10-methanoazepino[4,5-g]quinoxaline) (211 mg, 1.00 mmol), benzaldehyde (112 μL, 1.10 mmol), and 1,2-dichloroethane (3.5 mL). Sodium triacetoxyborohydride (318 mg, 1.50 mmol) was then added in one portion. The flask was subjected to three cycles of vacuum/nitrogen backfill. The mixture was stirred at room temperature for 12 hours.[†] The reaction mixture was diluted with CH_2Cl_2 and washed with a saturated solution of brine. 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 material was purified by flash chromatography (silica gel: 75% EtOAc in hexanes) to provide the title compound as a yellow oil (278 mg, 0.92 mmol, 92% yield). IR ν_{max}/cm^{-1} (film): 3057, 3027, 2944, 2787, 2750, 1472, 1453, 1358, 1186, 1025, 921, 885, 735, 697; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.77 (2H, s, H_1), 7.79 (2H, s, H_2), 7.16-7.06 (3H, m, H_4 and H_5), 6.89-6.79 (2H, m, H_3), 3.48 (2H, s, H_9), 3.41-3.30 (2H, m, H_6), 3.06-2.94 (2H, m, H_7), 2.57 (2H, d, J = 10.2 Hz, H_7), 2.39-2.28 (1H, m, H_8), 1.86 (1H, d, J = 10.8 Hz, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.86, 143.31, 143.25, 138.08, 128.23, 127.93, 126.59, 120.38, 61.45, 57.32, 43.08, 41.20; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 302.02, $C_{20}H_{20}N_3^+$ requires 302.2.

[†] An additional 0.75 equivalence of sodium triacetoxyborohydride (159 mg, 0.75 mmol) was added to the reaction mixture after 6 hours.

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

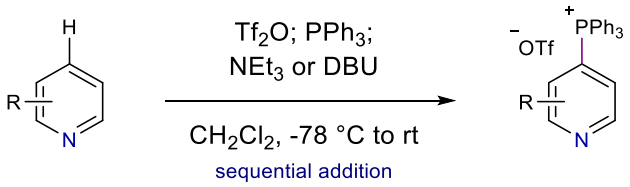


An oven dried 8 mL vial was charged with Abiraterone acetate (methyl (8*R*,9*S*,10*R*,13*S*,14*S*)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[a]phenanthrene-3-carboxylate) (391 mg, 1.00 mmol), methanol (5.00 mL), and THF (1.25 mL). Potassium hydroxide (56 mg, 1.00 mmol) was added in one portion and the vial was subjected to three cycles of vacuum/nitrogen backfill and was heated at 30 ºC for 1 hour. The reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate (10 mL), washed with water (10 mL) and a saturated solution of brine (10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting oil was transferred to an oven dried 8 mL vial that was charged with imidazole (102 mg, 1.50 mmol), *tert*-butyldimethylsilyl chloride (188 mg, 1.25 mmol), and dimethylformamide (9.00 mL). The reaction mixture was stirred at room temperature for 10 hours before additional amounts of imidazole (51 mg, 0.75 mmol), *tert*-butyldimethylsilyl chloride (94 mg, 0.62 mmol), and dimethylformamide (1.00 mL) were added. The reaction was stirred for a further 5 hours at room temperature before being quenched with water (10 mL) and diluted with ethyl acetate (10 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 10 mL), the combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 50% EtOAc in hexanes) to provide the title compound as a white solid (419 mg, 0.90 mmol, 90% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80-8.23 (2H, m), 7.63 (1H, d, *J*

= 7.8 Hz), 7.29-7.13 (1H, m), 5.97 (1H, br s), 5.33 (1H, d, *J* = 4.0 Hz), 3.46 (1H, m), 2.33-2.11 (3H, m), 2.10-1.93 (3H, m), 1.85-1.37 (9H, m), 1.11-0.94 (8H, m), 0.86 (9H, s), 0.03 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.61, 147.63, 141.88, 133.80, 129.37, 122.90, 120.77, 72.52, 57.57, 50.40, 47.32, 42.81, 37.27, 36.76, 35.23, 32.03, 31.80, 31.53, 30.42, 25.92, 20.83, 19.35, 16.55, -4.60. The spectroscopic data is in agreement with a reported synthesis.[2] *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 464.4, $C_{30}H_{46}NOSi^+$ requires 464.3.

A. 1.4. Preparation of Heterocyclic Phosphonium Salts

General Procedure A



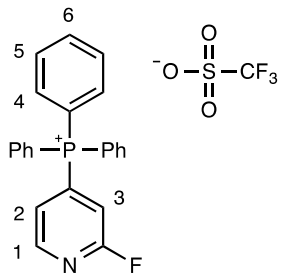
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv) was added dropwise 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.

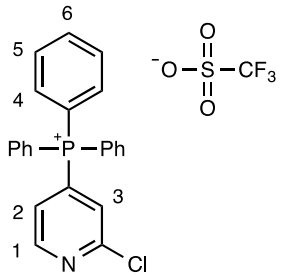
(2-Fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2f)



Prepared according to general procedure A using 2-fluoropyridine (859 μL, 10.00 mmol), Tf_2O (1.69 mL, 10.00 mmol), PPh_3 (2.89 g, 11.00 mmol), DBU (1.52 mL, 10.00 mmol) and CH_2Cl_2 (100 mL). After the purification procedure, the title compound was isolated as a white solid (3.96 g, 7.80 mmol, 79% yield). mp 192-196 ºC; IR ν_{max}/cm^{-1} (film): 3087, 3064, 1586, 1437, 1388, 1262, 1227, 1142, 1108, 1031, 726, 718, 687, 634; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.67 (1H, app

t, J = 5.3 Hz, H_1), 7.99-7.88 (3H, m, H_6), 7.87-7.75 (6H, m, H_5), 7.74-7.60 (7H, m, H_2 and H_4), 7.10 (1H, d, J = 13.4 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.28 (dd, J = 245.4, 16.9 Hz), 150.63 (dd, J = 13.7, 12.7 Hz), 136.09 (d, J = 3.2 Hz), 134. 21 (d, J = 10.7 Hz), 133.95 (dd, J = 84.4, 6.6 Hz), 130.81 (d, J = 13.8 Hz), 125.18 (dd, J = 8.2, 5.1 Hz), 122.44 (q, J = 321.6 Hz), 114.81 (d, J = 90.1 Hz), 114.19 (dd, J = 40.3, 10.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -61.56 (d, J = 10.3 Hz), -78.20; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.15, (d, J = 9.9 Hz); *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 358.1, $C_{23}H_{18}FNP^+$ requires 358.1.

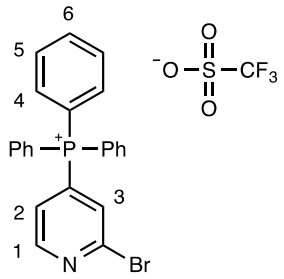
(2-Chloropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2g)



Prepared according to general procedure A using 2-chloropyridine (473 μL, 5.00 mmol), Tf_2O (845 μL, 5.00 mmol), PPh_3 (1.44 g, 5.50 mmol), NEt_3 (697 μL, 5.00 mmol) and CH_2Cl_2 (50 mL). After the purification procedure, the title compound was isolated as a white solid (2.14 g, 4.08 mmol, 82% yield). mp 158-160 ºC; IR ν_{max}/cm^{-1} (film): 3087, 3061, 3028, 1459, 1264, 1137, 1110, 1031, 749, 726, 634; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (1H, app t, J = 5.1 Hz, H_1), 7.98-7.89 (3H, m, H_6), 7.86-7.77 (6H, m, H_5), 7.75-7.62 (7H, m, H_2 and H_4), 7.40 (1H, d, J = 13.2 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.38 (d, J = 15.1 Hz), 152.31 (d, J = 11.3 Hz), 136.41 (d, J = 3.0 Hz), 134.49 (d, J = 10.4 Hz), 132.01 (d, J = 83.2 Hz), 131.11 (d, J = 13.0 Hz), 127.41 (d, J = 9.5 Hz), 126.28 (d, J = 8.4 Hz), 120.72 (q, J = 320.4 Hz), 115.02 (d, J = 90.0 Hz); ^{19}F NMR (365

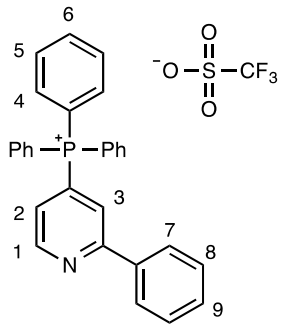
MHz, $CDCl_3$) δ: -78.19; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.27; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 374.1, $C_{23}H_{18}ClNP^+$ requires 374.1.

(2-Bromopyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2h)



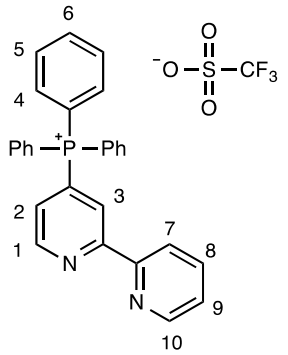
Prepared according to general procedure A using 2-bromopyridine (954 μL, 10.00 mmol), Tf_2O (1.69 mL, 10.00 mmol), PPh_3 (2.89 g, 11.00 mmol), DBU (1.52 mL, 10.00 mmol) and CH_2Cl_2 (100 mL). After the purification procedure, the title compound was isolated as a white solid (4.84 g, 8.52 mmol, 85% yield). mp 129-136 ºC; IR ν_{max}/cm^{-1} (film): 3099, 3059, 3027, 2996, 1264, 1136, 1109, 1030, 634; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.81 (1H, app t, J = 5.1 Hz, H_1), 7.99-7.89 (3H, m, H_6), 7.87-7.73 (7H, m, H_2 and H_5), 7.72-7.60 (6H, m, H_4), 7.54 (1H, d, J = 12.9 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.63 (d, J = 10.8 Hz), 143.77 (d, J = 14.0 Hz), 136.15 (d, J = 3.1 Hz), 134.47 (d, J = 10.6 Hz), 131.67 (d, J = 82.9 Hz), 131.11 (d, J = 13.2 Hz), 130.81 (d, J = 9.2 Hz), 126.58 (d, J = 8.3 Hz), 120.71 (d, J = 320.9 Hz), 115.01 (d, J = 89.7 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.19; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.00; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 418.1, $C_{23}H_{18}BrNP^+$ requires 418.0.

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



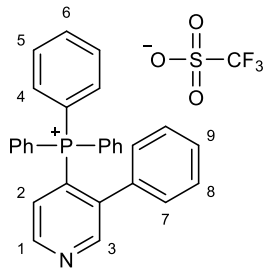
Prepared according to general procedure A using 2-phenylpyridine (2.57 mL, 18.00 mmol), Tf_2O (3.04 mL, 18.00 mmol), PPh_3 (5.19 g, 19.8 mmol), NEt_3 (2.51 mL, 18.00 mmol) and CH_2Cl_2 (180 mL). After the purification procedure, the title compound was isolated as a white solid (8.53 g, 15.08 mmol, 84% yield). mp 169–171 ºC; IR ν_{max}/cm^{-1} (film): 3087, 3066, 3011, 1584, 1570, 1471, 1439, 1374, 1079, 997, 751; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.01 (1H, app t, J = 5.1 Hz, H_1), 7.93–7.54 (18H, m, H_3, H_4, H_5, H_6, and H_7), 7.50 (1H, ddd, J = 17.8, 5.1, 1.1 Hz, H_2), 7.42–7.36 (3H, m, H_8 and H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.09 (d, J = 9.9 Hz), 151.63 (d, J = 10.7 Hz), 136.74 (d, J = 1.5 Hz), 136.14 (d, J = 3.2 Hz), 134.30 (d, J = 9.8 Hz), 130.91 (d, J = 13.0 Hz), 130.35, 129.23 (d, J = 84.1 Hz), 128.98, 127.00, 125.25 (d, J = 7.8 Hz), 123.08, (d, J = 8.4 Hz), 120.68 (q, J = 321.1 Hz), 115.49 (d, J = 89.1 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.7; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 416.2, $C_{29}H_{23}NP^+$ requires 416.2.

[2,2'-Bipyridin]-4-yltriphenylphosphonium trifluoromethanesulfonate (2j)



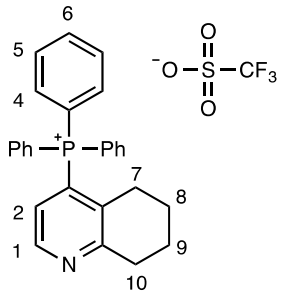
Prepared according to general procedure A using 2,2'-bipyridine (929 mg, 5.95 mmol), Tf_2O (1.00 mL, 5.95 mmol), PPh_3 (1.73 g, 6.55 mmol), NEt_3 (830 μL, 5.99 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a white solid (2.92 g, 5.15 mmol, 87% yield). mp 179-182 ºC; IR ν_{max}/cm^{-1} (film): 3060, 3014, 1576, 1438, 1261, 1142, 1106, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.06 (1H, app t, J = 5.1 Hz, H_1), 8.65 (1H, d, J = 13.8 Hz, H_3), 8.55 (1H, d, J = 4.4 Hz, H_{10}), 8.46 (1H, d, J = 7.9 Hz, H_7), 7.96-7.88 (3H, m, H_6), 7.87-7.74 (7H, m, H_5 and H_8), 7.72-7.55 (7H, m, H_2 and H_4), 7.35 (1H, dd, J = 7.7, 4.5 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.80 (d, J = 9.9 Hz), 153.36 (d, J = 2.3 Hz), 151.37 (d, J = 10.7 Hz), 149.34, 137.34, 136.17 (d, J = 3.1 Hz), 134.42 (d, J = 9.9 Hz), 130.97 (d, J = 13.0 Hz), 129.29 (d, J = 83.9 Hz), 126.91 (d, J = 8.4 Hz), 125.08, 123.89 (d, J = 9.2 Hz), 121.65, 120.80 (q, J = 321.2 Hz), 115.75 (d, J = 89.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.10; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.64; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 417.2, $C_{28}H_{22}N_2P^+$ requires 417.2.

Triphenyl(3-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (2k)



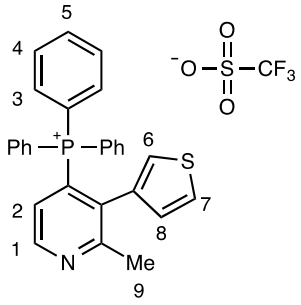
Prepared according to general procedure A (except that the stirring time after addition of PPh_3 was 1 hour instead of 30 minutes) using 3-phenylpyridine (400 mg, 2.58 mmol), Tf_2O (435 μL, 2.58 mmol), PPh_3 (744 mg, 2.84 mmol), DBU (285 μL, 2.58 mmol) and CH_2Cl_2 (26 mL). After the purification procedure, the title compound was isolated as a white solid (1.05 g, 1.86 mmol, 72% yield). mp 185-188 ºC; IR ν_{max}/cm^{-1} (film): 3032, 2980, 2948, 1518, 1407, 1292, 1249, 1186, 825; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.95 (1H, app t, J = 4.7 Hz, H_1), 8.74 (1H, d, J = 6.8 Hz, H_3), 7.85-7.73 (3H, m, H_6), 7.73-7.40 (13H, m, H_2, H_4, and H_5), 7.11 (1H, t, J = 7.6 Hz, H_9), 6.91 (2H, app t, J = 7.6 Hz, H_8), 6.71 (2H, d, J = 7.5 Hz, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.63 (d, J = 8.0 Hz), 149.97 (d, J = 10.4 Hz), 141.68 (d, J = 7.3 Hz), 135.43 (d, J = 3.0 Hz), 134.41 (d, J = 4.5 Hz), 134.18 (d, J = 10.3 Hz), 130.59 (d, J = 13.0 Hz), 129.21, 128.89, 128.30, 128.20, 126.35 (d, J = 83.4 Hz), 120.82 (q, J = 321.2 Hz), 116.89 (d, J = 89.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –77.68; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.73; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 416.2, $C_{29}H_{23}NP^+$ requires 416.2.

Triphenyl(5,6,7,8-tetrahydroquinolin-4-yl)phosphonium trifluoromethanesulfonate (2gl



Prepared according to general procedure A (except the product suspension was placed in a –20 ºC refrigerator for approximately 12 hours instead of 1 hour) using 5,6,7,8-tetrahydroquinoline (773 µL, 5.95 mmol), Tf_2O (1.00 mL, 5.95 mmol), PPh_3 (1.73 g, 6.55 mmol), DBU (890 µL, 5.95 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a pale tan solid (2.24 g, 4.13 mmol, 69% yield). mp 248-251 ºC; IR ν_{max}/cm^{-1} (film): 3019, 2954, 1442, 1259, 1144, 1029; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.74 (1H, app t, J = 5.1 Hz, H_1), 8.07-7.93 (3H, m, H_6), 7.92-7.71 (12H, m, H_4 and H_5), 6.94 (1H, dd, J = 15.3, 5.1 Hz, H_2), 3.12-2.97 (2H, m, H_{10}), 2.21-2.04 (2H, m, H_7), 1.84-1.71(2H, m, H_9), 1.60-1.44 (2H, m, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.25 (d, J = 8.4 Hz), 148.20 (d, J = 11.4 Hz), 135.48 (d, J = 7.6 Hz), 135.27 (d, J = 3.1 Hz), 134.06 (d, J = 10.7 Hz), 130.50 (d, J = 13.0 Hz), 126.18 (d, J = 9.9 Hz), 125.51 (d, J = 82.4 Hz), 120.40 (q, J = 322.0 Hz), 116.34 (d, J = 87.7 Hz), 32.01 (d, J = 2.3 Hz), 29.66 (d, J = 5.3 Hz), 21.03, 20.54; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -77.75; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.85; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 394.2, $C_{27}H_{25}NP^+$ requires 394.2.

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

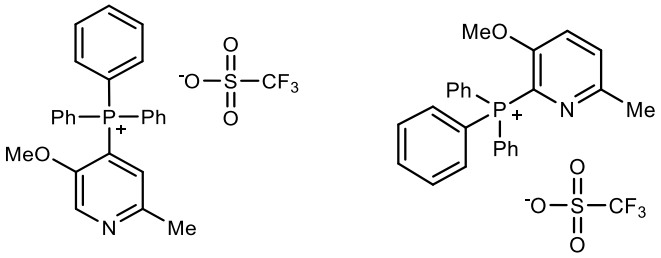


Prepared according to general procedure A (except that the stirring time after addition of PPh_3 was 1 hour instead of 30 minutes and an additional hour of stirring at room temperature after addition of DBU) using 2-methyl-3-(thiophen-3-yl)pyridine (518 mg, 3.00 mmol), Tf_2O (500 μL, 3.00 mmol), PPh_3 (775 mg, 3.30 mmol), DBU (448 μL, 3.00 mmol) and CH_2Cl_2 (30 mL). After the purification procedure,[‡] the title compound was isolated as a tan solid (1.04 g, 1.78 mmol, 59% yield). mp 182-185 ºC; IR ν_{max}/cm^{-1} (film): 3112, 3072, 2976, 1272, 1262, 1168, 1153, 1027, 632; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.82 (1H, app t, J = 5.0 Hz, H_1), 7.86-7.77 (3H, m, H_5), 7.75-7.65 (6H, m, H_4), 7.63-7.52 (6H, m, H_3), 7.28-7.18 (1H, m, H_2), 6.85 (1H, dd, J = 5.1, 2.9 Hz, H_8), 6.58 (1H, dd, J = 2.9, 1.1 Hz, H_6), 6.20 (1H, dd, J = 5.1, 1.2 Hz, H_7), 2.31 (3H, s, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.95 (d, J = 8.1 Hz), 149.44 (d, J = 10.8 Hz), 135.84 (d, J = 7.6 Hz), 135.21 (d, J = 3.0 Hz), 134.56 (d, J = 5.3 Hz), 133.80 (d, J = 9.9 Hz), 130.49 (d, J = 12.9 Hz), 128.05, 127.68 (d, J = 84.8 Hz), 126.48, 125.97, 125.86 (d, J = 9.6 Hz), 120.69 (q, J = 320.9 Hz), 117.16 (d, J =

[‡] The concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of chilled Et_2O (0 °C) instead of the order of addition in General Procedure A. The mixture was then placed in a -20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled Et_2O (0 °C). The solid was redissolved in approximately 10 mL of CH_2Cl_2 and was precipitated a second time via dropwise addition to an excess of chilled Et_2O (0 °C). The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt.

89.6 Hz), 23.54 (d, J = 2.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.03; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.38; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 436.1, $C_{28}H_{23}NPS^+$ requires 436.1.

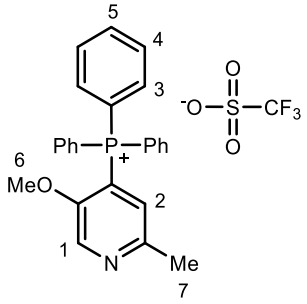
(5-Methoxy-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2n) and (3-methoxy-6-methylpyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (2n')



10:1 Mixture of Regioisomers

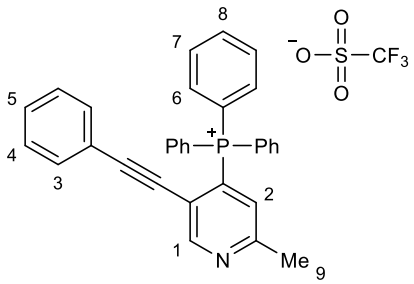
Prepared according to general procedure A using 5-methoxy-2-methylpyridine (397 mg, 3.23 mmol), Tf_2O (542 μL, 3.23 mmol), PPh_3 (931 mg, 3.35 mmol), DBU (482 μL, 3.23 mmol) and CH_2Cl_2 (32 mL). After the purification procedure, the title compounds (10:1 mixture of regioisomers) were isolated as a white solid (1.29 g, 2.43 mmol, 75% combined yield). An analytically pure sample of the major regioisomer was obtained by recrystallization from CH_2Cl_2 and Et_2O.

(5-Methoxy-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2n)



mp 211-212 ºC; IR ν_{max}/cm^{-1} (film): 3069, 2952, 1486, 1438, 1261, 1224, 1108, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (1H, d, *J* = 6.9 Hz, H_1), 7.95-7.40 (15H, m, H_3, H_4, and H_5), 6.79 (1H, d, *J* = 15.0 Hz, H_2), 3.62 (3H, s, H_6), 2.46 (3H, s, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.72, 153.05 (d, *J* = 10.7 Hz), 135.62 (d, *J* = 4.6 Hz), 135.46 (d, *J* = 3.1 Hz), 133.71 (d, *J* = 10.7 Hz), 130.51 (d, *J* = 13.0 Hz), 127.12 (d, *J* = 6.9 Hz), 120.72 (q, *J* = 321.21 Hz), 116.46 (d, *J* = 91.6 Hz), 115.62 (d, *J* = 87.0 Hz), 57.01, 23.55; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.13; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.36; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 384.2, $C_{25}H_{23}NOP^+$ requires 384.2.

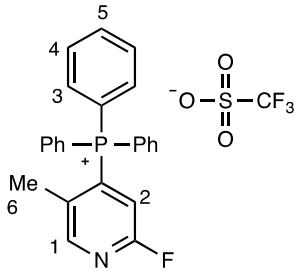
(2-Methyl-5-(phenylethynyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2o)



Prepared according to general procedure A using 2-methyl-5-(phenylethynyl)pyridine (860 mg, 4.45 mmol), Tf_2O (749 μL, 4.45 mmol), PPh_3 (1.29 g, 4.90 mmol), DBU (619 mL, 4.45 mmol) and CH_2Cl_2 (40 mL). After the purification procedure, the title compound was isolated as an off-

white solid (1.60 g, 2.65 mmol, 60% yield). mp 188–190 ºC; IR ν_{max}/cm^{-1} (film): 3098, 2214, 1584, 1462, 1260, 1028, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96 (1H, d, J = 2.8 Hz, H_1), 7.86 (3H, m, H_8), 7.80–7.68 (13H, m, H_7, H_6, and H_5), 7.17 (2H, app t, J = 7.7 Hz, H_4), 7.09 (1H, d, J = 15.1 Hz, H_2), 6.66 (2H, d, J = 7.4 Hz, H_3), 2.66 (3H, s, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.40 (d, J = 10.4 Hz), 154.04 (d, J = 7.1 Hz), 135.72 (d, J = 3.0 Hz), 134.22 (d, J = 10.5 Hz), 130.83, 130.67 (d, J = 13.2 Hz), 129.87, 128.65 (d, J = 85.9 Hz), 128.32, 128.11 (d, J = 8.8 Hz), 120.75 (q, J = 321.2 Hz), 120.37 (d, J = 4.5 Hz), 119.90, 115.82 (d, J = 90.3 Hz), 103.30, 83.97 (d, J = 6.1 Hz), 24.83; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.8; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 454.2, $C_{32}H_{25}NP^+$ requires 454.2.

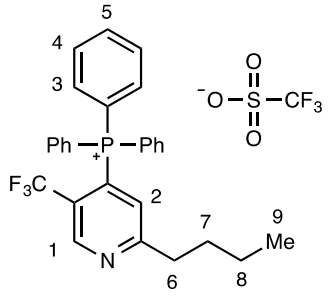
(2-Fluoro-5-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2p)



Prepared according to general procedure A using 2-fluoro-5-methylpyridine (620 μL, 5.98 mmol), Tf_2O (1.00 mL, 5.95 mmol), PPh_3 (1.73 g, 6.55 mmol), DBU (890 μL, 5.95 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a white solid (2.54 g, 4.87 mmol, 82% yield). mp 160-161 ºC; IR ν_{max}/cm^{-1} (film): 3066, 1438, 1261, 1142, 1032, 720; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.43 (1H, d, J = 6.8 Hz, H_1), 7.96-7.88 (3H, m, H_5), 7.87-7.79 (6H, m, H_4), 7.75-7.67 (6H, m, H_3), 6.72 (1H, dd, 15.6, 2.8 Hz, H_2), 2.00 (3H, s, H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.44 (dd, J = 244.1, 17.6 Hz), 152.46 (dd, J = 13.7, 10.7 Hz), 136.14 (d,

J = 3.1 Hz), 134.41 (app t, J = 6.4 Hz), 134.11 (d, J = 10.7 Hz), 131.74 (dd, J = 83.1, 6.9 Hz), 131.20 (d, J = 13.0 Hz), 120.71 (q, J = 320.4 Hz), 115.43 (dd, J = 40.4, 11.4 Hz), 115.26 (d, J = 89.27 Hz), 18.97 (d, J = 3.8 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -66.58 (d, J = 9.4 Hz), -78.17; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.40 (d, J = 9.4 Hz); *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 372.2, $C_{24}H_{20}FNP^+$ requires 372.1.

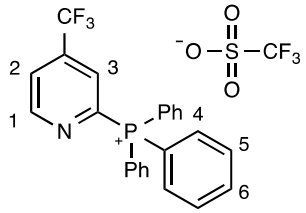
(2-Butyl-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (2q)



Prepared according to general procedure A using 2-butyl-5-(trifluoromethyl)pyridine (1.02 g, 5.00 mmol), Tf_2O (845 μL, 5.00 mmol), PPh_3 (1.44 g, 5.50 mmol), DBU (758 μL, 5.00 mmol) and CH_2Cl_2 (50 mL). After the purification procedure, the title compound was isolated as a white solid (2.55 g, 4.16 mmol, 83% yield). mp 152-154 ºC; IR ν_{max}/cm^{-1} (film): 3057, 2931, 1717, 1437, 1414, 1260, 1222, 1147, 1105, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.16 (1H, d, J = 6.8 Hz, H_1), 7.92–7.87 (3H, m, H_5), 7.80–7.76 (6H, m, H_4), 7.73–7.67 (6H, m, H_3), 7.18 (1H, d, J = 17.2 Hz, H_2), 2.93 (2H, t, J = 7.6 Hz, H_6), 1.69–1.62 (2H, m, H_7), 1.37–1.27 (2H, m, H_8), 0.88 (3H, t, J = 7.2 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.99 (d, J = 9.7 Hz), 150.06 (m), 135.96 (d, J = 3.1 Hz), 134.41 (d, J = 10.4 Hz), 130.74 (d, J = 13.0 Hz), 129.77 (d, J = 8.5 Hz), 125.90 (d, J = 80.1,

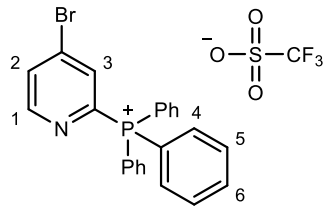
1.0 Hz), 124.42 (qd, J = 33.1, 4.0 Hz), 122.49 (qd, J = 275.1, 2.9 Hz), 120.76 (q, J = 321.2 Hz), 116.40 (d, J = 90.4 Hz), 37.93, 30.35, 22.11, 13.63; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.27, -53.55; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 27.4 (d, J = 2.3 Hz); *m/z* LRMS found $[M]^+$ 305.2, $C_{28}H_{26}F_3NP^+$ requires 305.2.

Triphenyl(4-(trifluoromethyl)pyridin-2-yl)phosphonium trifluoromethanesulfonate (2t)



Prepared according to general procedure A using 4-(trifluoromethyl)pyridine (926 μL, 8.00 mmol), Tf_2O (1.35 mL, 8.00 mmol), PPh_3 (2.31 g, 8.80 mmol), DBU (1.20 mL, 8.00 mmol) and CH_2Cl_2 (80 mL). After the purification procedure, the title compound was isolated as an off-white solid (3.69 g, 6.62 mmol, 83% yield). mp 110–112 ºC; IR ν_{max}/cm^{-1} (film): 3071, 1588, 1485, 1390, 1223, 1180, 998, 572, 535; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.33 (1H, d, J = 2.8 Hz, H_1), 8.02 (1H, m, H_2), 7.92 (3H, m, H_6), 7.82–7.69 (13H, m, H_3, H_4, and H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.20 (d, J = 19.9 Hz), 147.00 (d, J = 121.0 Hz), 139.92 (qd, J = 35.8 Hz, 11.3 Hz), 136.02 (d, J = 2.9 Hz), 134.55 (d, J = 10.2 Hz), 130.70 (d, J = 13.1 Hz), 126.05 (dq, J = 25.9, 3.6 Hz), 124.36 (m), 121.47 (qd, J = 274.1, 3.0 Hz), 120.70 (q, J = 320.5 Hz), 115.93 (d, J = 90.0 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –64.7, –78.2 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.2; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 408.1, $C_{24}H_{18}F_3NP^+$ requires 408.1.

(4-bromopyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (2u)

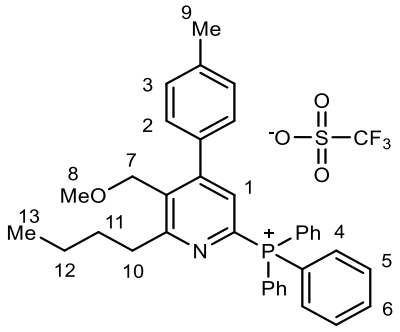


Prepared according to general procedure A[§] using 4-bromopyridine (198 μL, 2.00 mmol), Tf_2O (338 μL, 2.00 mmol), PPh_3 (577 mg, 2.20 mmol), DBU (303 μL, 2.00 mmol) and CH_2Cl_2 (40 mL). After the purification procedure,[**] the title compound was isolated as a tan solid (677 mg, 1.20 mmol, 60% yield). mp 147-149 ºC; IR ν_{max}/cm^{-1} (film): 3087, 3061, 1553, 1436, 1258, 1137, 1110, 1028, 635; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.88 (1H, d, J = 5.1 Hz, H_1), 8.03-7.84 (4H, m, H_3 and H_6), 7.84-7.59 (13H, m, H_2, H_4, and H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.28 (d, J = 20.6 Hz), 146.37 (d, J = 119.1 Hz), 135.97 (d, J = 3.1 Hz), 135.16 (d, J = 14.4 Hz), 134.55 (d, J = 10.8 Hz), 134.00 (d, J = 25.2 Hz), 131.88 (d, J = 3.1 Hz), 130.69 (d, J = 13.6 Hz), 120.80 (q, J = 321.0 Hz), 116.21 (d, J = 89.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.1 ; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 15.6; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 418.1, $C_{23}H_{18}BrNP^+$ requires 418.0.

[§] A solution of 4-bromopyridine in CH_2Cl_2 (20 mL) was added to a solution of Tf_2O in CH_2Cl_2 (20 mL) at –78 ºC over 10 minutes instead of the order of addition in General Procedure A.

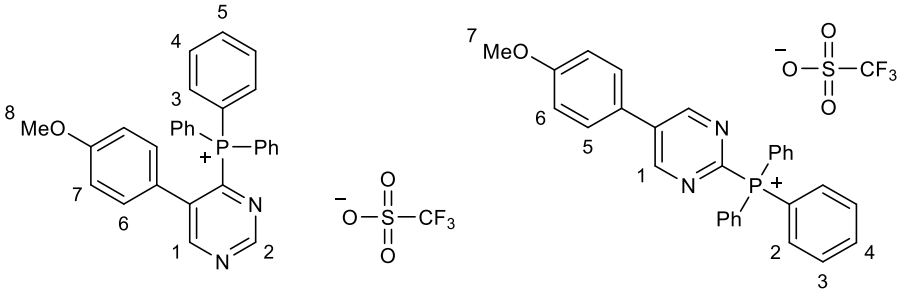
[**] Once the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*, the title compound was isolated by recrystallization from CH_2Cl_2 and Et_2O, instead of precipitated according to General Procedure A.

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



Prepared according to general procedure A using 2-butyl-3-(methoxymethyl)-4-(*p*-tolyl)pyridine (483 mg, 1.79 mmol), Tf_2O (300 μL, 1.79 mmol), PPh_3 (517 mg, 1.97 mmol), DBU (268 μL, 1.79 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a white solid (909 mg, 1.34 mmol, 75% yield). mp 149-150 ºC; IR ν_{max}/cm^{-1} (film): 3059, 2956, 2869, 1568, 1438, 1261, 1151, 1031 ; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.91-7.82 (3H, m, H_6), 7.78-7.62 (12H, m, H_5 and H_4), 7.35 (1H, d, J = 6.4 Hz, H_1), 7.26-7.23 (4H, m, H_3 and H_2), 4.35 (2H, s, H_7), 3.38 (3H, s, H_8), 3.06 (2H, t, J = 7.7 Hz, H_{10}), 2.35 (3H, s, H_9), 1.71 (2H, qn, J = 7.7 Hz, H_{11}), 1.33 (2H, sext, J = 7.6 Hz, H_{12}), 0.87 (3H, t, J = 7.5 Hz, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.00 (d, J = 19.1 Hz), 152.58 (d, J = 11.4 Hz), 143.18, 141.99, 139.39, 135.63 (d, J = 3.1 Hz), 134.47 (d, J = 10.7 Hz), 133.60 (d, J = 1.5 Hz), 133.19 (d, J = 3.8 Hz), 130.42 (d, J = 13.0 Hz), 129.91 (d, J = 25.2 Hz), 129.04 (d, J = 84.7 Hz), 120.83 (q, J = 321.2 Hz), 117.07 (d, J = 89.27 Hz), 67.93, 58.68, 34.27, 30.58, 22.31, 21.08, 13.83; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.07; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 14.49; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 530.3, $C_{36}H_{37}NOP^+$ requires 530.3.

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



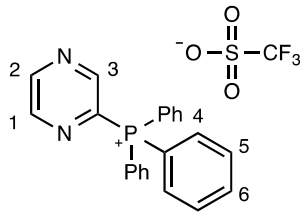
24:1 Mixture of Regioisomers

Prepared according to general procedure A (except that the stirring time after addition of PPh_3 was 1 hour instead of 30 minutes) using 5-(4-methoxyphenyl)pyrimidine (450 mg, 2.42 mmol), Tf_2O (409 μL, 2.42 mmol), PPh_3 (698 mg, 2.66 mmol), DBU (367 μL, 2.42 mmol) and CH_2Cl_2 (24 mL). After the purification procedure,[††] the title compound was isolated as a tan solid (724 mg, 1.21 mmol, 50% combined yield). Both isomers, IR ν_{max}/cm^{-1} (film): 3063, 2936, 1396, 1258, 1222, 1146, 1105, 1028, 634; Major isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.44 (1H, s, H_2), 8.98 (1H, d, J = 9.0 Hz, H_1), 7.80-7.70 (3H, m, H_5), 7.67-7.56 (12H, m, H_3 and H_4), 6.91 (2H, d, J = 8.7 Hz, H_6), 6.55 (2H, d, J = 8.7 Hz, H_7), 3.72 (3H, s, H_8); Minor isomer, ^1H NMR (400 MHz, $CDCl_3$) δ: 9.23 (2H, s, H_1), 7.80-7.70 (3H, m, H_4), 7.70 (2H, d, J = 8.7 Hz, H_5), 7.67-7.56 (12H, m, H_2 and

[††] The concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of chilled Et_2O (0 °C) instead of the order of addition in General Procedure A. The mixture was then placed in a -20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled Et_2O (0 °C). The solid was redissolved in approximately 10 mL of CH_2Cl_2 and was precipitated a second time via dropwise addition to an excess of chilled Et_2O (0 °C). The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt.

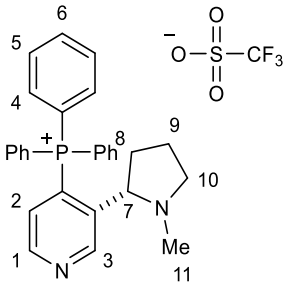
H_3), 7.09 (2H, d, J = 8.6 Hz, H_6), 3.88 (3H, s, H_7); Major isomer, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.84 (d, J = 5.3 Hz), 160.53, 156.97 (d, J = 16.8 Hz), 149.74 (d, J = 114.5 Hz), 142.72 (d, J = 19.2 Hz), 135.22 (d, J = 3.1 Hz), 134.67 (d, J = 10.2 Hz), 130.60, 130.25 (d, J = 13.1 Hz), 123.61, 120.82 (q, J = 321.3 Hz), 117.10 (d, J = 88.6 Hz), 114.37, 55.42; Both isomers, ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.01; Major isomer, ^{31}P NMR (162 MHz, $CDCl_3$) δ: 17.84; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 447.2, $C_{29}H_{24}N_2OP^+$ requires 447.2.

Triphenyl(pyrazin-2-yl)phosphonium trifluoromethanesulfonate (2x)



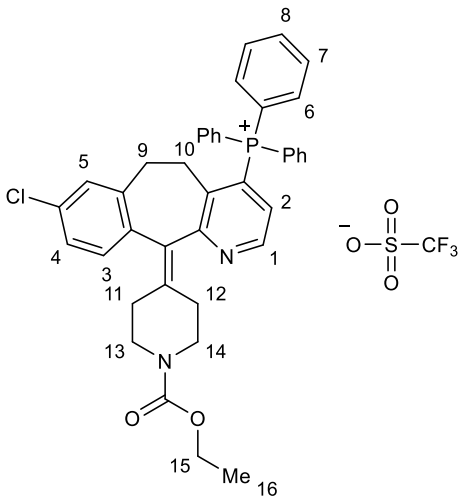
Prepared according to general procedure A using pyrazine (120 mg, 1.50 mmol), Tf_2O (252 μL, 1.50 mmol), PPh_3 (432 mg, 1.65 mmol), DBU (224 μL, 1.50 mmol) and CH_2Cl_2 (13.0 mL). After the purification procedure, the title compound was isolated as an off-white solid (525 mg, 1.07 mmol, 80% yield). mp 185–188 ºC; IR ν_{max}/cm^{-1} (film): 3066, 1587, 1484, 1395, 1186, 617, 571; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.09 (1H, br s), 9.06 (1H, br s), 8.86 (1H, br s), 7.91 (3H, m), 7.82–7.71 (12H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.72 (d, J = 24.0 Hz), 149.51 (d, J = 3.4 Hz), 147.25 (d, J = 14.7 Hz), 141.37 (d, J = 115.4 Hz), 136.02 (d, J = 3.1 Hz), 134.54 (d, J = 10.4 Hz), 130.71 (d, J = 13.1 Hz), 120.69 (q, J = 321.1 Hz), 115.71 (d, J = 89.3 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 13.9; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 341.1, $C_{22}H_{18}N_2P^+$ requires 341.1.

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



Prepared according to general procedure A using (-)-nicotine (803 μL, 5.00 mmol), Tf_2O (845 μL, 5.00 mmol), PPh_3 (1.44 g, 5.50 mmol), DBU (748 μL, 5.00 mmol) and CH_2Cl_2 (50 mL). After the purification procedure, the title compound was isolated as a tan solid (2.19 g, 3.82 mmol, 76% yield). mp 178-181 ºC; IR ν_{max}/cm^{-1} (film): 3066, 2971, 2758, 1338, 1264, 1223, 1142, 1108, 1102, 1031, 719, 636; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.37 (1H, d, J = 6.9 Hz, H_3), 8.79 (1H, app t, J = 4.6 Hz, H_1), 7.96-7.62 (15H, m, H_4, H_5, and H_6), 7.12 (1H, dd, J = 15.5, 5.1 Hz, H_2), 3.10-2.93 (2H, m, H_7 and H_{10}), 1.99 (1H, app q, J = 8.5 Hz, H_{10}), 1.87-1.67 (4H, m, H_9 and H_{11}), 1.49-1.23 (2H, m, H_8 and H_9), 1.01-0.83 (1H, m, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.01 (d, J = 8.1 Hz), 149.96 (d, J = 10.6 Hz), 144.24 (d, J = 6.7 Hz), 135.99 (d, J = 3.0 Hz), 134.39 (d, J = 10.2 Hz), 131.05 (d, J = 13.0 Hz), 127.53 (d, J = 9.9 Hz), 126.24 (d, J = 81.6 Hz), 120.83 (q, J = 321.3 Hz), 116.74 (d, J = 88.5 Hz), 66.03 (d, J = 4.9 Hz), 55.97, 39.39, 35.43, 22.93; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -77.01; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.69; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 423.2, $C_{28}H_{28}N_2P^+$ requires 423.2.

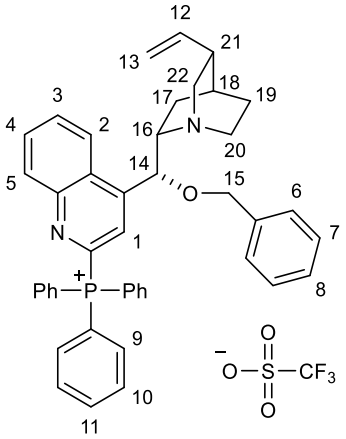
(8-Chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (5)



Prepared according to general procedure A using Loratadine (ethyl-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-b]pyridine-11-ylidene)-1-piperidinecarboxylate) (750 mg, 1.96 mmol), Tf_2O (329 μL, 1.96 mmol), PPh_3 (565 mg, 2.15 mmol), DBU (300 μL, 1.96 mmol) and CH_2Cl_2 (20 mL). After the purification procedure, the title compound was isolated as a white solid (1.37 g, 1.72 mmol, 88% yield). mp 129-136 ºC; IR ν_{max}/cm^{-1} (film): 3061, 2978, 2908, 2868, 1437, 1261, 1221, 1147, 1106, 1029, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (1H, app t, J = 5.0 Hz, H_1), 7.97-7.87 (3H, m, H_8), 7.86-7.74 (6H, m, H_7), 7.73-7.60 (6H, m, H_6), 7.16-7.01 (3H, m, H_2, H_3, and H_4), 6.71 (1H, s, H_5), 4.14 (2H, q, J = 7.0 Hz, H_{15}), 3.84-3.61 (2H, m, H_{13} or H_{14}), 3.45-3.20 (3H, m, H_{10} and H_{13} or H_{14}), 2.75 (1H, dt, J = 17.4, 4.7 Hz, H_9), 2.58 (1H, dt, J = 14.9, 4.7 Hz, H_{10}), 2.53-2.30 (3H, m, H_{11} or H_{12}), 2.26-2.09 (1H, m, H_{11} or H_{12}), 1.60-1.43 (1H, m, H_9), 1.25 (3H, t, J = 7.2 Hz, H_{16}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.64 (d, J = 8.3 Hz), 155.37, 149.08 (d, J = 11.4 Hz), 139.23, 136.84, 136.66 (d, J = 6.8 Hz), 136.06 (d, J = 3.1 Hz), 134.21 (d, J = 10.7 Hz), 133.95, 133.57, 132.37, 131.58, 131.13 (d, J = 13.0 Hz), 129.85, 127.22 (d, J = 10.0 Hz),

127.01 (d, J = 82.2 Hz), 126.43, 120.78 (q, J = 321.3 Hz), 116.42 (d, J = 88.5 Hz), 61.39, 44.65, 44.41, 30.74, 30.46, 30.39, 29.39, 14.59; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.16; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.17; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 643.2, $C_{40}H_{37}ClN_2O_2P^+$ requires 643.2.

(4-((*R*)-(Benzyloxy)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (6)

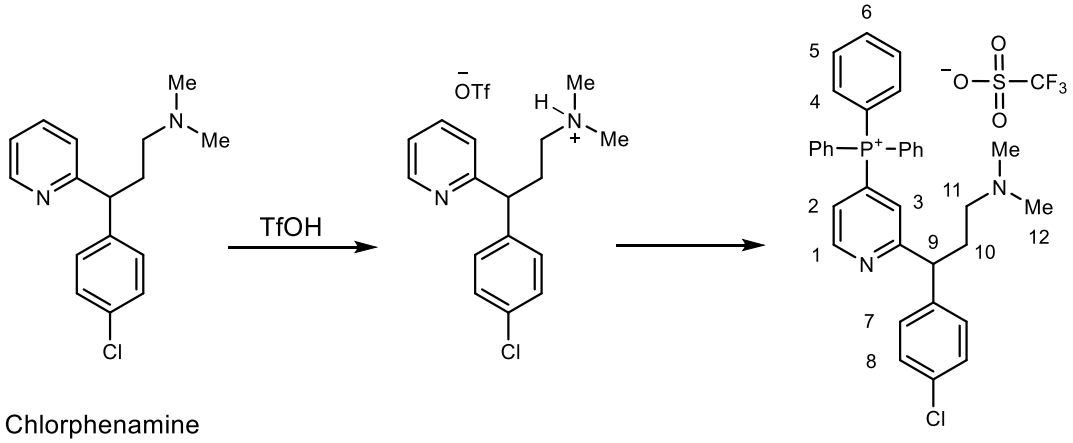


Prepared according to general procedure A (except that the stirring time after addition of PPh_3 was 1 hour instead of 30 minutes) using (1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(benzyloxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (472 mg, 1.23 mmol), Tf_2O (207 μL, 1.23 mmol), PPh_3 (354 mg, 1.35 mmol), NEt_3 (171 μL, 1.23 mmol) and CH_2Cl_2 (12 mL). After the purification procedure,[‡‡] the title compound was isolated as a yellow solid (507 mg, 0.638 mmol, 52% yield). mp 92-98 ºC; IR

[‡‡] The concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of chilled hexanes (0 °C) instead of the order of addition in General Procedure A. The mixture was then placed in a -20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled hexanes (0 °C). The solid was redissolved in approximately 10 mL of CH_2Cl_2 and was precipitated a second time via dropwise addition to an excess of chilled hexanes (0 °C). The resulting suspension was filtered on a frit, the solid washed with chilled hexanes (0 °C) and dried *in vacuo* to provide the pure phosphonium salt.

ν_{max}/cm^{-1} (film): 3062, 3031, 2940, 2866, 1144, 1108, 1029, 635; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, J = 8.1 Hz, H_5), 8.26 (1H, d, J = 8.6 Hz, H_2), 7.94 (1H, t, J = 7.2 Hz, H_3), 7.91-7.60 (17H, m, H_1, H_4, H_9, H_{10}, and H_{11}), 7.29-7.02 (3H, m, H_7 and H_8), 7.14-7.02 (2H, m, H_6), 5.83-5.45 (2H, m, H_{12} and H_{14}), 5.07-4.89 (2H, m, H_{13}), 4.60 (1H, d, J = 11.4 Hz, H_{15}), 4.33 (1H, d, J = 11.4 Hz, H_{15}), 3.52-3.06 (3H, m, H_{16}, H_{20}, and H_{22}), 2.84-2.62 (2H, m, H_{20} and H_{22}), 2.49-2.33 (1H, br s, H_{21}), 2.06-1.47 (5H, m, H_{17}, H_{18}, H_{19}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.20 (d, J = 22.1 Hz), 148.45, 145.10, 143.93, 139.54, 136.58, 135.68 (d, J = 3.0 Hz), 134.53 (d, J = 10.0 Hz), 131.99-131.79 (3C, m), 131.23, 130.44 (d, J = 13.2 Hz), 128.40, 127.89, 127.22, 126.71 (d, J = 3.1 Hz), 126.08, 123.78, 120.64 (q, J = 320.3 Hz), 116.99 (d, J = 87.7 Hz), 115.55, 71.81, 60.71, 55.61, 43.04, 38.32, 26.89, 25.83; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.15; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 14.92; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 645.3, $C_{44}H_{42}N_2OP^+$ requires 645.3.

(2-(1-(4-Chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (7)

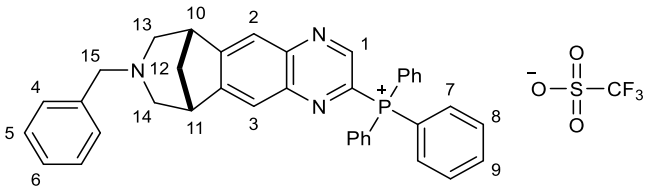


Chlorphenamine

Chlorphenamine (1.64 g, 5.95 mmol) was dissolved in Et_2O (10 mL) and cooled to 0 ºC. Trifluoromethanesulfonic acid (527 μL, 5.95 mmol) was added dropwise, the ice bath was

removed and the solution was stirred for 10 minutes at room temperature. The solution was concentrated *in vacuo* and the resulting acid salt was subjected to general procedure A (expect that the product was precipitated a second time using the same protocol and the product suspension was placed in a -20 °C refrigerator for 12 hours instead of 1) using Tf_2O (1.0 mL, 5.95 mmol), PPh_3 (1.73 g, 6.55 mmol), DBU (1.78 mL, 11.90 mmol) and CH_2Cl_2 (60 mL). After the purification procedure, the title compound was isolated as a yellow solid (1.63 g, 2.38 mmol, 40% yield). mp 52-58 ºC; IR ν_{max}/cm^{-1} (film): 3062, 2941, 2818, 2770, 1438, 1260, 1108, 1029; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.97 (1H, app t, J = 5.1 Hz, H_1), 7.93-7.86 (3H, m, H_6), 7.80-7.70 (6H, m, H_5), 7.61-7.50 (6H, m, H_4), 7.39 (1H, ddd, J = 12.8, 5.1, 1.5 Hz, H_2), 7.25-7.16 (5H, m, H_3, H_7, and H_8), 4.28 (1H, app t, J = 6.8 Hz, H_9), 2.56-2.43 (1H, m, H_{10}), 2.32-2.11 (9H, m, H_{10}, H_{11}, and H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.55 (d, J = 9.9 Hz), 150.97 (d, J = 9.9 Hz), 140.26, 135.82 (d, J = 3.1 Hz), 134.02 (d, J = 10.7 Hz), 132.25, 130.61 (d, J = 13.0 Hz), 128.92 (d, J = 85.5 Hz), 128.75, 127.92, 126.26 (d, J = 8.4 Hz), 124.42 (d, J = 7.6 Hz), 120.46 (q, J = 321.2 Hz), 115.31 (d, J = 89.3 Hz), 56.73, 49.77, 44.88, 31.99; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.14; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.38; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 535.2, $C_{34}H_{33}ClN_2P+$ requires 535.2.

((*rac*)-8-benzyl-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-g]quinoxalin-2-yl)triphenylphosphonium trifluoromethanesulfonate (8)

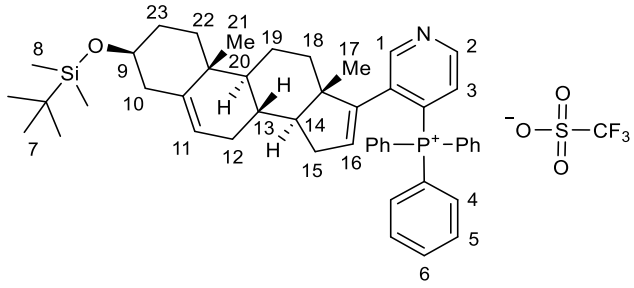


Prepared according to general procedure A (except that after the addition of PPh_3 the reaction mixture was heated to 40 °C for 1 hour, followed by addition of DBU at 40 °C instead of –78 °C) using 8-benzyl-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-g]quinoxaline (115 mg, 0.38 mmol), Tf_2O (64 μL, 0.38 mmol), PPh_3 (110 mg, 0.42 mmol), DBU (57 μL, 0.38 mmol) and CH_2Cl_2 (3.8 mL). After the purification procedure,[§§] the title compound was isolated as a tan solid (158 mg, 0.22 mmol, 58% yield). mp 101-106 ºC; IR ν_{max}/cm^{-1} (film): 3061, 2949, 2900,2797, 1439, 1262, 1148, 1109, 1029, 636; ^1H NMR (400 MHz, DMSO-d_6) δ: 9.09 (1H, s, H_1), 8.10-7.72 (17H, m, H_2, H_3, H_7, H_8, and H_9), 7.20-7.05 (3H, m, H_5 and H_6), 6.92-6.80 (2H, m, H_4), 3.55-3.27 (4H, m, H_{15}, H_{10}, and H_{11}), 3.03-2.87 (2H, m, H_{13} or H_{14}), 2.66-2.42 (2H, m, H_{13} or H_{14}), 2.29-2.15 (1H, m, H_{12}), 1.87 (1H, d, J = 10.8 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$)[***] δ: 144.90 (d, J = 23.5 Hz), 144.21, 143.45 (d, J = 16.9 Hz), 137.51 (br s), 136.00 (d, J = 2.9 Hz), 134.55 (d, J = 10.9 Hz), 130.72 (d, J = 13.0 Hz), 129.20-126.21 (3C, m), 120.69 (br s), 120.67 (q, J = 321.5 Hz), 116.42 (d, J = 88.3 Hz), 61.29, 57.90-56.06 (2C, m), 43.14-40.43 (3C, m); ^{19}F NMR (365 MHz, DMSO-d_6) δ: –77.80; ^{31}P NMR (162 MHz, DMSO-d_6) δ: 13.81; *m/z* LRMS found $[M+H]^+$ 562.2, $C_{38}H_{33}N_3P^+$ requires 562.2.

[§§] The concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of chilled Et_2O (0 °C) instead of the order of addition in General Procedure A. The mixture was then placed in a -20 °C refrigerator for approximately 1 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled Et_2O (0 °C). The solid was redissolved in approximately 10 mL of CH_2Cl_2 and was precipitated a second time via dropwise addition to an excess of chilled Et_2O (0 °C). The resulting suspension was filtered on a frit, the solid washed with chilled Et_2O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt.

[***] Please note that the ^{13}C NMR contains a number of broad peaks that account for the lower than expected number of carbon resonances. ^{13}C NMR does not improve with an increase in number of scans or by varying concentration.

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

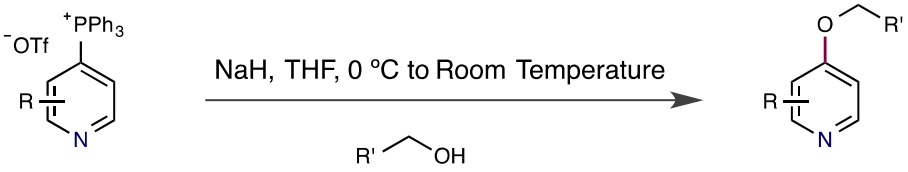


Prepared according to general procedure A (except that the reaction was warmed to -50 ºC before the addition of PPh_3, was stirred at -50 °C for 1 hour, and DBU was added at -50 °C instead of -78 °C. During the purification stage the product suspension was placed in a -20 ºC refrigerator for approximately 12 hours instead of 1) using 3-((8*R*,9S,10*R*,13S,14*S*)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)pyridine (295 mg, 0.64 mmol), Tf_2O (107 μL, 0.64 mmol), PPh_3 (184 mg, 0.70 mmol), DBU (95 μL, 0.64 mmol) and CH_2Cl_2 (6.5 mL). After the purification procedure, the title compound was isolated as a white solid (412 mg, 0.47 mmol, 74% yield). mp 158-163 ºC; IR ν_{max}/cm^{-1} (film): 3062, 2929, 1442, 1259, 1096, 1030, 909, 725; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.02 (1H, d, J = 7.2 Hz), 8.75 (1H, t, J = 4.6 Hz), 7.92-7.83 (3H, m), 7.83-7.73 (6H, m), 7.72-7.61 (6H, m), 7.33-7.24 (1H, m), 5.57 (1H, br s), 5.24 (1H, d, J = 4.4 Hz), 3.49 (1H, m), 2.30-2.10 (2H, m), 1.89-1.66 (6H, m), 1.62-0.71 (22H, m), 0.65-0.51 (1H, dt, J = 11.7 Hz, 4.92 Hz), 0.06 (6H, s), -0.12-(-0.23) (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.77 (d, J = 7.6 Hz), 149.14 (d, J = 3.8 Hz), 148.73 (d, J = 10.7 Hz), 141.78, 139.29, 137.51 (d, J = 6.1 Hz), 135.66 (d, J = 3.1 Hz) 134.31 (d, J = 9.9 Hz), 130.93 (d, J = 13.0 Hz), 129.99 (d, J = 10.7 Hz), 125.29 (d,

J = 83.9 Hz), 120.84 (q, J = 328.8 Hz), 120.18, 118.03 (d, J = 90.0 Hz), 72.31, 55.45, 49.91, 48.91, 42.68, 37.24, 36.58, 33.70, 32.64, 31.92, 31.17, 29.97, 25.92, 20.42, 19.20, 18.79, 18.24, -4.58; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -78.11; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.78; *m/z* LRMS found $[M+H]^+$ 724.4, $C_{48}H_{59}NOPSi^+$ requires 724.4.

A. 1.5 Preparation of Heteroaryl Ethers

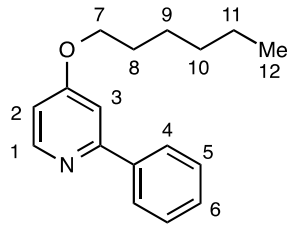
General procedure B



An oven dried 8 mL vial with a septa cap was charged with sodium hydride (60% dispersion in mineral oil, 1.5 equiv) and placed under a nitrogen atmosphere. THF (0.5 M) was added, the suspension was cooled to 0 ºC and the alcohol (1.5 equiv) was added dropwise over 5 minutes (if the alcohol was a solid or viscous liquid, it was added as a 1.0 M solution in THF to an equivalent volume 1.0 M solution of NaH in THF). The reaction was stirred for 30 minutes before the septa cap was briefly removed and the phosphonium salt (1.0 equiv) 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, the aqueous layer was separated and extracted with Et_2O (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 heteroaryl ether product.

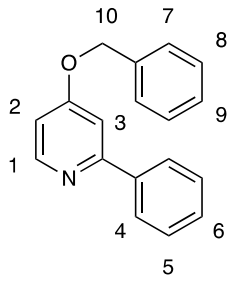
[†††] Vacuum was applied very briefly (less than a second) using a Schlenk manifold so that negligible solvent loss occurs.

4-(Hexyloxy)-2-phenylpyridine (12ia)



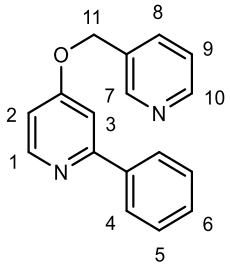
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white amorphous solid (92 mg, 0.36 mmol, 72% yield). mp 36-37 ºC; IR ν_{max}/cm^{-1} (film):3068, 2942, 1563, 1467, 1323, 1219, 1021; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (1H, d, *J* = 5.5 Hz, H_1), 7.97 (2H, d, *J* = 7.4 Hz, H_4), 7.46 (2H, t, *J* = 7.4 Hz, H_5), 7.40 (1H, t, *J* = 7.4 Hz, H_6), 7.22 (1H, d, *J* = 2.4 Hz, H_3), 6.74 (1H, dd, *J* = 5.7, 2.2 Hz, H_2), 4.05 (2H, t, *J* = 6.5 Hz, H_7) 1.82 (2H, qn, *J* = 6.5 Hz, H_8), 1.48 (2H, qn, *J* = 6.7 Hz, H_9), 1.40-1.31 (4H, m, H_{10} and H_{11}), 0.92 (3H, t, *J* = 7.0 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.83, 159.08, 150.79, 139.49 128.84, 128.57, 126.87, 108.45, 107.25, 67.92, 31.45, 28.86, 25.57, 22.52, 13.95; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 256.2, $C_{17}H_{22}NO^+$ requires 256.2.

4-(benzyloxy)-2-phenylpyridine 2-phenylpyridin-4-ol (12ib)



Prepared according to general procedure B (except that CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), benzyl alcohol (78 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (282 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 5% to 15% EtOAc in hexanes) to afford the title compound as a faintly purple amorphous solid (94 mg, 0.36 mmol, 72% yield). mp 71–73 ºC; IR ν_{max}/cm^{-1} (film): 3030, 2937, 2871, 1961, 1495, 1421, 1250, 1121, 1079, 1029, 646, 548; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.53 (1H, d, J = 5.7 Hz, H_1), 7.95 (2H, d, J = 7.6 Hz, H_4), 7.50–7.35 (8H, m, H_5, H_6, H_7, H_8, H_9), 7.32 (1H, d, J = 1.7 Hz, H_3), 6.85 (1H, dd, J = 5.4, 2.2 Hz, H_2), 5.18 (2H, s, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.44, 159.16, 150.87, 139. .29, 135.66, 128.93, 128.67, 128.59, 128.30, 1 27.46, 126.86, 108.70, 107.57, 69.78. The spectroscopic data is in agreement with a reported synthesis.[3] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 262.1, $C_{18}H_{16}NO^+$ requires 262.1.

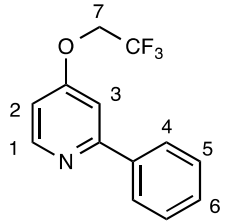
2-Phenyl-4-(pyridin-3-ylmethoxy)pyridine (12ic)



Prepared according to general procedure B (except that CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), pyridin-3-ylmethanol (73 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283mg, 0.50 mmol) and THF (1.0 mL). Prior to flash chromatography

the crude reaction product was dissolved in methanol (5.0 mL) and a methanolic solution of hydrochloric acid (5.0 mL of 4.2 M solution) was added dropwise. The resulting mixture was concentrated *in vacuo* and dry loaded onto a silica gel column (elution: 2.5% MeOH in CH_2Cl_2, then 30 mL of NEt_3, then EtOAc) afforded the title compound as a pink amorphous solid (84 mg, 0.32 mmol, 64% yield). mp 90-91 ºC; IR ν_{max}/cm^{-1} (film): 3027, 2984, 1561, 1207, 1013, 695; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.70 (1H, s, H_7), 8.61 (1H, d, J = 4.6 Hz, H_{10}), 8.52 (1H, d, J = 5.7 Hz, H_1), 7.94 (2H, d, J = 7.5 Hz, H_4), 7.76 (1H, d, J = 7.7 Hz, H_8), 7.48-7.36 (3H, m, H_5 and H_6), 7.33 (1H, dd, J = 7.7, 4.7 Hz, H_9), 7.29 (1H, d, J = 2.3 Hz, H_3), 6.81 (1H, dd, J = 5.7, 2.3 Hz, H_2), 5.15 (2H, s, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.07, 159.28, 150.95, 149.78, 148.93, 139.07, 135.23, 131.26, 129.05, 128.62, 126.84, 123.53, 108.52, 107.36, 67.27; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 263.2, $C_{17}H_{15}N_2O^+$ requires 263.1.

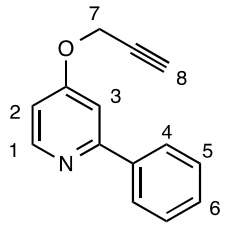
2-Phenyl-4-(2,2,2-trifluoroethoxy)pyridine (12id)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 2,2,2-trifluoroethan-1-ol (57 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 15% EtOAc in hexanes) afforded the title compound as an off white amorphous solid (100 mg, 0.40 mmol, 79% yield). mp 50-51 ºC; IR ν_{max}/cm^{-1} (film): 3095, 2975, 1568, 1271, 1164, 978, 776; ^1H NMR (400 MHz,

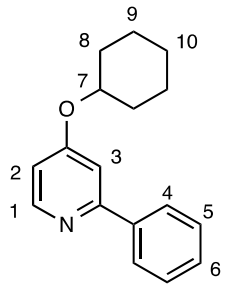
$CDCl_3$) δ: 8.56 (1H, d, J = 5.6 Hz, H_1), 7.96 (2H, d, J = 7.4 Hz, H_4), 7.49-7.40 (3H, m, H_5 and H_6), 7.26 (1H, d, J = 2.4 Hz, H_3), 6.77 (1H, dd, J = 5.6, 2.4 Hz, H_2), 4.43 (2H, q, J = 7.9 Hz, H_7); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.99, 159.68, 151.21, 138.79, 129.31, 128.71, 126.90, 122.9 (q, J = 227.7 Hz), 108.07, 107.15, 64.9 (q, J = 35.9 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: -73.70. The spectroscopic data is in agreement with a reported synthesis.[4] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 254.1, $C_{13}H_{11}F_3NO^+$ requires 254.1.

2-Phenyl-4-(prop-2-yn-1-yloxy)pyridine (12ie)



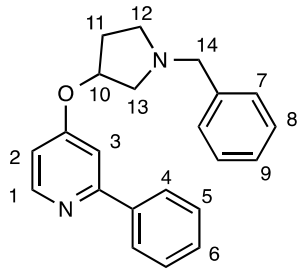
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), prop-2-yn-1-ol (43 μL, 0.75 mmol), triphenyl-(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the title compound as a yellow oil (68 mg, 0.33 mmol, 65% yield). IR ν_{max}/cm^{-1} (film): 3296, 3055, 2923, 1589, 1474, 1196, 1019; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.54 (1H, d, J = 5.6 Hz, H_1), 7.96 (2H, d, J = 7.4 Hz, H_4), 7.50-7.38 (3H, m, H_5 and H_6), 7.31 (1H, d, J = 2.4 Hz, H_3), 6.84 (1H, dd, J = 5.6, 2.4 Hz, H_2), 4.78 (2H, d, J = 2.3 Hz, H_7), 2.60 (1H, t, J = 2.3 Hz, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.29, 159.27, 150.88, 139.21, 129.03, 128.65, 126.91, 108.69, 107.45, 77.27, 76.62, 55.49. The spectroscopic data is in agreement with a reported synthesis.[5] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 210.1, $C_{14}H_{12}NO^+$ requires 210.1.

4-(Cyclohexyloxy)-2-phenylpyridine (12if)



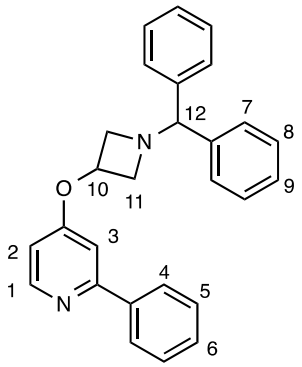
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), cyclohexanol (78 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (282 mg, 0.50 mmol) and THF (1.0 mL). The reaction was stirred for 13 hours after the addition of the phosphonium salt. Flash column chromatography (basic alumina: 6% EtOAc in hexanes) afforded the title compound as an amorphous white solid (107 mg, 0.42 mmol, 85% yield). mp 49-50 ºC; IR ν_{max}/cm^{-1} (film): 3032, 2939, 1559, 1476, 1211, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (1H, d, *J* = 5.7 Hz, H_1), 7.95 (2H, d, *J* = 7.5 Hz, H_4), 7.49-7.37 (3H, m, H_5 and H_6), 7.21 (1H, d, *J* = 2.2 Hz, H_3), 6.74 (1H, dd, *J* = 5.7, 2.2 Hz, H_2), 4.42 (1H, m, H_7), 2.07-1.96 (2H, m, H_8), 1.89-1.77 (2H, m, H_9), 1.67-1.53 (3H, m, H_8 and H_{10}), 1.48-1.30 (3H, m, H_9 and H_{10}) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.70, 159.17, 150.80, 139.56, 128.80, 128.56, 126.88, 109.18, 108.30, 75.16, 31.40, 25.38, 23.51; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 254.2, $C_{17}H_{20}NO^+$ requires 254.2.

4-((1-Benzylpyrrolidin-3-yl)oxy)-2-phenylpyridine (12ig)



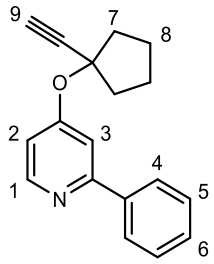
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 1-benzylpyrrolidin-3-ol (124 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (basic alumina, gradient elution: 10% EtOAc in hexanes to 30% EtOAc in hexanes) afforded the title compound as a yellow oil (125 mg, 0.38 mmol, 75% yield). IR ν_{max}/cm^{-1} (film): 3029, 2920, 2792, 1559,1207, 694; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (1H, d, J = 5.7 Hz, H_1), 7.96 (2H, d, J = 7.5 Hz, H_4), 7.52-7.23 (8H, m, H_5, H_6, H_7, H_8, and H_9), 7.19 (1H, d, J = 2.1 Hz, H_3), 6.68 (1H, dd, J = 5.7, 2.1 Hz, H_2), 4.98-4.86 (1H, m, H_{10}), 3.72 (1H, d, J = 12.7 Hz, H_{14}), 3.66 (1H, d, J = 12.7 Hz, H_{14}), 2.99 (1H, dd, J = 10.6, 6.1 Hz, H_{13}), 2.88-2.73 (2H, m, H_{12} and H_{13}), 2.59 (1H, app q, J = 7.6 Hz, H_{12}), 2.42-2.29 (1H, m, H_{11}), 2.09-1.96 (1H, m, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.53, 159.07, 150.78, 139.34, 138.31, 128.87, 128.71, 128.56, 128.23, 127.04, 126.82, 108.99, 108.02, 76.78, 60.06, 59.77, 52.56, 32.05; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 331.2, $C_{22}H_{23}N_2O^+$ requires 331.2.

4-((1-Benzhydrylazetidin-3-yl)oxy)-2-phenylpyridine (12ih)



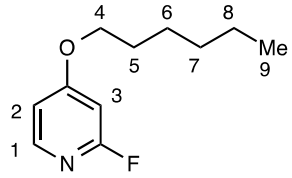
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 1-benzhydrylazetidin-3-ol (180 mg, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 30% EtOAc in hexanes) afforded the title compound as a yellow oil (158 mg, 0.40 mmol, 80% yield). IR ν_{max}/cm^{-1} (film): 3027, 2954, 2838, 1592, 1211, 906, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.47 (1H, d, J = 5.5 Hz, H_1), 7.92 (2H, d, J = 7.4 Hz, H_4), 7.48-7.38 (7H, m, H_5, H_6, and H_7), 7.30 (4H, app t, J = 7.4 Hz, H_8), 7.21 (2H, t, J = 7.4 Hz, H_9), 7.10 (1H, d, J = 2.3 Hz, H_3), 6.61 (1H, dd, J = 5.5, 2.3 Hz, H_2), 4.93 (1H, app qn, J = 5.6 Hz, H_{10}), 4.45 (1H, s, H_{12}), 3.76 (2H, app t, J = 5.6 Hz, H_{11}), 3.18 (2H, app t, J = 5.6 Hz, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.96, 159.39, 150.98, 141.67, 139.26, 129.05, 128.68, 128.55, 127.39, 127.34, 126.90, 108.68, 107.31, 78.28, 66.32, 60.16; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 393.2, $C_{27}H_{25}N_2O^+$ requires 393.2.

4-((1-Ethynylcyclopentyl)oxy)-2-phenylpyridine (12ii)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), 1-ethynylcyclopentan-1-ol (85 μL, 0.75 mmol), triphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a yellow oil (93 mg, 0.35 mmol, 71% yield). IR ν_{max}/cm^{-1} (film): 3292, 3032, 2960, 1590, 1472, 1189, 992; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, d, J = 5.6 Hz, H_1), 7.96 (2H, d, J = 7.8 Hz, H_4), 7.55-7.35 (4H, m, H_3, H_5 and H_6), 7.05 (1H, dd, J = 5.6, 2.4 Hz, H_2), 2.73 (1H, s, H_9), 2.43-2.33 (2H, m, H_7), 2.25-2.15 (2H, m, H_7), 1.86-1.78 (4H, m, H_8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.79, 158.76, 150.34, 139.51, 128.80,128.58, 126.85, 111.58, 110.10, 84.05, 80.99, 75.58, 40.73, 23.79; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 264.2, $C_{18}H_{18}NO^+$ requires 264.1.

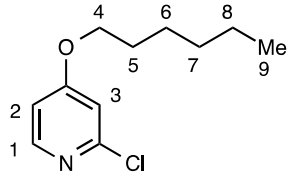
2-Fluoro-4-(hexyloxy)pyridine (12fa)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-fluoropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (254 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography

(silica gel, gradient elution: 2.5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a yellow oil (67 mg, 0.34 mmol, 68% yield). IR ν_{max}/cm^{-1} (film): 2955, 1609, 1467, 1417, 1159; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (1H, d, J = 5.6 Hz, H_1) 6.68 (1H, dd, J = 5.7, 2.1 Hz, H_2) 6.35 (1H, d, J = 2.1 Hz, H_3) 3.99 (2H, t, J = 6.5 Hz, H_4) 1.79 (2H, qn, J = 6.7 Hz, H_5), 1.44 (2H, qn, J = 6.7 Hz, H_6) 1.38-1.28 (4H, m, H_7 and H_8), 0.90 (3H, t, J = 6.7 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.00 (d, J = 12.0 Hz), 165.31 (d, J = 235.0 Hz), 147.90 (d, J = 19.1 Hz), 109.38 (d, J = 3.8 Hz), 94.43 (d, J = 41.6 Hz), 68.69, 31.41, 28.69, 25.50, 22.51, 13.95; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -67.03; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 198.2, $C_{11}H_{17}FNO^+$ requires 198.1.

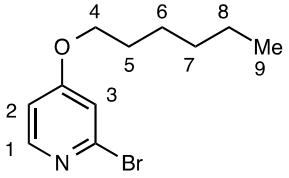
2-Chloro-4-(hexyloxy)pyridine (12ga)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-chloropyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (262 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 4% EtOAc in hexanes to 8% EtOAc in hexanes) afforded the title compound as a yellow oil (82 mg, 0.34 mmol, 77% yield). IR ν_{max}/cm^{-1} (film): 2930, 1584, 1460, 1304, 1070, 835; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (1H, d, J = 5.7 Hz, H_1), 6.80 (1H, d, J = 2.2 Hz, H_3), 6.71 (1H, dd, J = 5.7, 2.2 Hz, H_2), 3.98 (2H, t, J = 6.7 Hz, H_4), 1.77 (2H, qn, J = 6.9 Hz, H_5), 1.43 (2H, qn, J = 6.9 Hz, H_6), 1.37-1.27 (4H, m, H_7 and H_8), 0.89 (3H, t, J = 6.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.76, 152.52, 150.13, 110.03, 109.78, 68.53, 31.37, 28.66, 25.46,

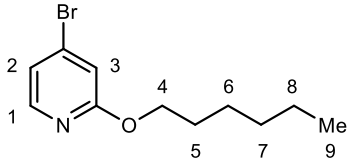
22.48, 13.92. The spectroscopic data is in agreement with a reported synthesis.[6] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 214.1, $C_{11}H_{17}ClNO^+$ requires 214.1.

2-Bromo-4-(hexyloxy)pyridine (12ha)



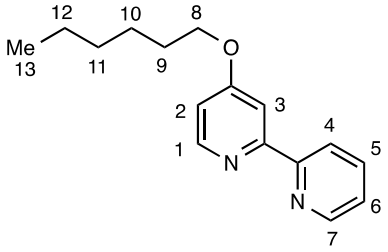
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-bromopyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (284 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 2.5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a pale orange oil (103 mg, 0.40 mmol, 80% yield). IR ν_{max}/cm^{-1} (film): 2929, 1580, 1302, 1062, 834; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.13 (1H, d, J = 5.7 Hz, H_1) 6.96 (1H, d, J = 2.2 Hz, H_3) 6.74 (1H, dd, J = 5.7, 2.2 Hz, H_2), 3.97 (2H, t, J = 6.6 Hz, H_4), 1.77 (2H, qn, J = 6.8 Hz, H_5), 1.43 (2H, qn, J = 6.8 Hz, H_6), 1.37-1.28 (4H, m, H_7 and H_8), 0.89 (3H, t, J = 6.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.32, 150.51, 142.92, 113.59, 110.46, 68.52, 31.37, 28.66, 25.46, 22.49, 13.94. The spectroscopic data is in agreement with a reported synthesis.[7] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 258.0, $C_{11}H_{17}BrNO^+$ requires 258.0.

4-bromo-2-(hexyloxy)pyridine (12ua)



Prepared according to general procedure B (except that the reaction was allowed to stir for 14 hours after the addition of the phosphonium salt and CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 11 mg, 0.28 mmol), hexanol (35 μL, 0.28 mmol), (4-bromopyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (142 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel, gradient elution: 10% toluene in hexanes to 20% toluene in hexanes) to afford the title compound as a clear oil (33 mg, 0.13 mmol, 52% yield). IR ν_{max}/cm^{-1} (film): 2927, 1577, 1553, 1466, 1410, 1351, 1308, 1221, 1016, 982; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.96 (1H, d, J = 5.7 Hz, H_1), 6.99 (1H, dd, J = 5.7, 1.5 Hz, H_2), 6.93 (1H, d, J = 1.5 Hz, H_3), 4.26 (2H, t, J = 6.7 Hz, H_4), 1.75 (2H, qn, J = 7.3 Hz, H_5), 1.49-1.28 (6H, m, H_6, H_7, and H_8), 0.90 (3H, m, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) 164.69, 147.44, 133.69, 119.97, 114.26, 66.61, 31.54, 28.91, 25.67, 22.58, 14.01; m/z LRMS (ESI + APCI) found $[M+H]^+$ 258.1, $C_{11}H_{17}BrNO^+$ requires 258.0.

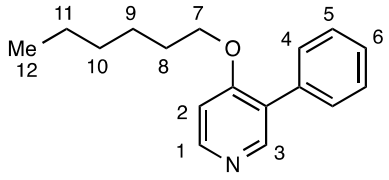
4-(Hexyloxy)-2,2'-bipyridine (12ja)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), [2,2'-bipyridin]-4-yltriphenylphosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (basic alumina, gradient elution: 5% EtOAc in hexanes to 20% EtOAc in hexanes) afforded the title compound as a pink oil (72 mg, 0.28 mmol, 56% yield). IR ν_{max}/cm^{-1} (film): 3058, 2929, 1582,

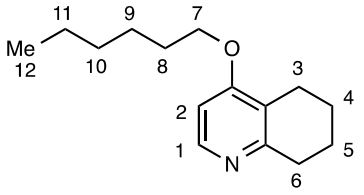
1458, 1302, 1209, 793; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (1H, d, J = 4.7 Hz, H_7), 8.43 (1H, d, J = 5.7 Hz, H_1), 8.36 (1H, d, J = 7.7 Hz, H_4), 7.92 (1H, d, J = 2.4 Hz, H_3), 7.76 (1H, t, J = 7.7 Hz, H_5), 7.25 (1H, dd, J = 7.7, 4.7 Hz, H_6), 6.78 (1H, dd, J = 5.7, 2.4 Hz, H_2), 4.08 (2H, t, J = 6.6 Hz, H_8), 1.78 (2H, qn, J = 6.8 Hz, H_9), 1.48-1.25 (6H, m, H_{10}, H_{11}, and H_{12}), 0.87 (3H, t, J = 6.5 Hz, H_{13}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.17, 157.86, 156.03, 150.18, 148.97, 136.79, 123.69, 121.18, 111.09, 106.56, 68.01, 31.44, 28.88, 25.56, 22.52, 13.95; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 257.2, $C_{16}H_{20}N_2O^+$ requires 257.2.

4-(Hexyloxy)-3-phenylpyridine (12ka)



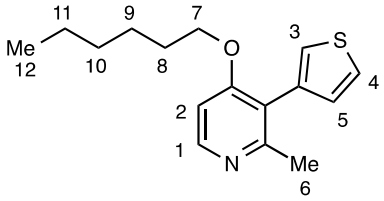
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), triphenyl(3-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a yellow oil (92 mg, 0.36 mmol, 72% yield). IR ν_{max}/cm^{-1} (film): 3055, 2930, 1584, 1280, 1007, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50-8.38 (2H, m, H_1 and H_3), 7.53 (2H, d, J = 7.5 Hz, H_4), 7.42 (2H, t, J = 7.5 Hz, H_5), 7.35 (1H, t, J = 7.5 Hz, H_6), 6.86 (1H, d, J = 5.5 Hz, H_2), 4.03 (2H, t, J = 6.5 Hz, H_7), 1.75 (2H, qn, J = 6.5 Hz, H_8), 1.41 (2H, qn, J = 6.7 Hz, H_9), 1.35-1.24 (4H, m, H_{10} and H_{11}), 0.88 (3H, t, J = 6.7, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.89, 150.82, 150.28, 134.91, 129.42, 128.04, 127.42, 126.38, 107.07, 68.09, 31.27, 28.61, 25.52, 22.44, 13.86; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 256.2, $C_{17}H_{22}NO^+$ requires 256.2.

4-(Hexyloxy)-5,6,7,8-tetrahydroquinoline (12la)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), triphenyl(5,6,7,8-tetrahydroquinolin-4-yl)phosphonium trifluoromethanesulfonate (272 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (neutralized silica gel: 20% EtOAc in hexanes) afforded the title compound as a yellow oil (93 mg, 0.40 mmol, 79% yield). IR ν_{max}/cm^{-1} (film): 2929, 2870, 1574, 1463, 1289, 1105; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (1H, d, J = 5.5 Hz, H_1), 6.51 (1H, d, J = 5.5 Hz, H_2), 3.94 (2H, t, J = 6.4 Hz, H_7), 2.83 (2H, t, J = 6.1 Hz, H_6), 2.60 (2H, t, J = 6.1 Hz, H_3), 1.88-1.67 (6H, m, H_4, H_5, and H_8), 1.43 (2H, qn, J = 6.7 Hz, H_9), 1.37-1.24 (4H, m, H_{10} and H_{11}), 0.88 (3H, t, J = 6.7 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.82, 157.70, 147.66, 121.04, 103.70, 67.68, 32.45, 31.40, 28.86, 25.61, 22.73, 22.49, 22.17, 22.14, 13.90; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 234.2, $C_{15}H_{24}NO^+$ requires 234.2.

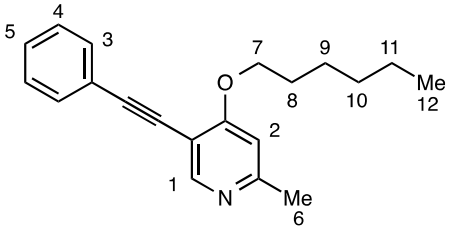
4-(Hexyloxy)-2-methyl-3-(thiophen-3-yl)pyridine (12ma)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-methyl-3-(thiophen-3-yl)pyridin-4-

yl)triphenylphosphonium trifluoromethanesulfonate (293 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (basic alumina, gradient elution: 15% EtOAc in hexanes to 25% EtOAc in hexanes) afforded the title compound as a yellow oil (100 mg, 0.36 mmol, 73% yield). IR ν_{max}/cm^{-1} (film): 2928, 1571, 1462, 1292, 1075, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (1H, d, J = 5.7 Hz, H_1), 7.33 (1H, dd, J = 5.0, 2.7 Hz, H_4), 7.15 (1H, d, J = 2.7 Hz, H_3), 7.02 (1H, d, J = 5.0 Hz, H_5), 6.68 (1H, d, J = 5.7 Hz, H_2), 3.92 (2H, t, J = 6.4 Hz, H_7), 2.38 (3H, s, H_6), 1.64 (2H, qn, J = 6.5 Hz, H_8), 1.34-1.17 (6H, m, H_9, $H_{10,}$ and H_{11}), 0.84 (3H, t, J = 6.7 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.79, 157.75, 149.13, 134.76, 129.34, 124.26, 123.95, 120.93, 104.79, 68.03, 31.17, 28.53, 25.35, 23.36, 22.40, 13.85; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 276.2, $C_{16}H_{22}NOS^+$ requires 276.1.

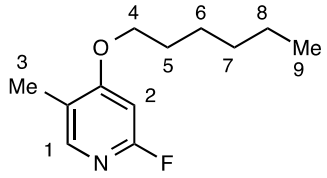
4-(Hexyloxy)-2-methyl-5-(phenylethynyl)pyridine (12oa)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-methyl-5-(phenylethynyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (302 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 15% EtOAc in hexanes) afforded the title compound as a white solid (91 mg, 0.31 mmol, 62% yield). mp 66–68 ºC; IR ν_{max}/cm^{-1} (film): 3055, 3035, 3019, 2954, 2930, 2871, 2855, 2731, 2594, 2224, 2161, 2050, 1979, 1966, 1947, 1893, 1822, 1802, 1667, 1544, 1426, 1325, 1237, 1147, 1126, 1068, 911, 768, 723, 678; ^{1}H NMR (400 MHz, $CDCl_3$) δ:

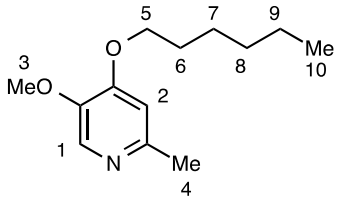
8.48 (1H, s, H_1), 7.53 (2H, dd, J = 4.1, 7.0 Hz, H_4), 7.38–7.31 (3H, m, H_3 and H_5), 6.66 (1H, s, H_2), 4.08 (2H, t, J = 6.4 Hz, H_7), 2.55 (3H, s, H_6), 1.88 (2H, qn, 7.0 Hz, H_8), 1.54 (2H, qn, 7.0 Hz, H_9), 1.44–1.31 (4H, m, H_{10} and H_{11}), 0.90 (3H, t, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.25, 159.73, 152.67, 131.48, 128.24, 128.20, 123.31, 107.58, 106.12, 95.08, 82.79, 68.38, 31.43, 28.76, 25.54, 24.91, 22.54, 13.94; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 294.2, $C_{20}H_{24}NO^+$ requires 294.2.

2-Fluoro-4-(hexyloxy)-5-methylpyridine (12pa)



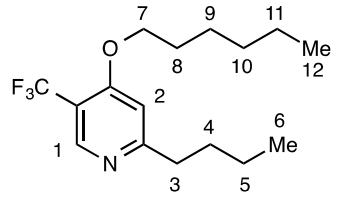
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 20 mg, 0.50 mmol), *n*-hexanol (63 μL, 0.50 mmol), (2-fluoro-5-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (261 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 2.5% EtOAc in hexanes) afforded the title compound as a white amorphous solid (64 mg, 0.30 mmol, 60% yield). mp 30-32 ºC; IR ν_{max}/cm^{-1} (film): 3073, 2944, 1610, 1493, 1332, 1160, 1026, 846; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (1H, s, H_1), 6.27 (1H, s, H_2), 3.98 (2H, t, J = 6.5 Hz, H_4), 2.10 (3H, s, H_3), 1.81 (2H, qn, J = 6.5 Hz, H_5), 1.54-1.27 (6H, m, H_6, H_7, and H_8), 0.90 (3H, t, J = 6.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.82 (d, J = 10.7 Hz), 163.77 (d, J = 233.5 Hz), 146.46 (d, J = 17.6 Hz), 120.38 (d, J = 4.6 Hz), 91.45 (d, J = 42.7 Hz), 68.47, 31.40, 28.66, 25.57, 22.51, 13.93, 12.59; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -69.11; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 212.2, $C_{12}H_{19}FNO^+$ requires 212.1.

4-(Hexyloxy)-5-methoxy-2-methylpyridine (12na)



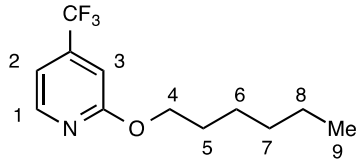
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), a 7:1 mixture of (5-methoxy-2-methylpyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate and (3-methoxy-6-methylpyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (267 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then gradient elution: 40% EtOAc in hexanes to 50% EtOAc in hexanes) afforded the title compound as a tan amorphous solid (51 mg, 0.23 mmol, 46% yield). mp 41-42 ºC; IR ν_{max}/cm^{-1} (film): 3068, 3004, 2938, 1590, 1511, 1231, 1026; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.96 (1H, s, H_1), 6.61 (1H, s, H_2), 4.00 (2H, t, J = 7.2 Hz, H_5), 3.86 (3H, s, H_3), 2.43 (3H, s, H_4), 1.82 (2H, qn, J = 7.2 Hz, H_6), 1.43 (2H, qn, J = 7.1 Hz, H_7), 1.35-1.26 (4H, m, H_8 and H_9), 0.87 (3H, t, J = 7.0 Hz, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.99, 152.62 143.98, 133.25, 106.80, 68.47, 56.85, 31.42, 28.70, 25.48, 24.10, 22.47, 13.92; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 224.2, $C_{13}H_{22}NO_2^+$ requires 224.2.

2-Butyl-4-(hexyloxy)-5-(trifluoromethyl)pyridine (12qa)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (2-butyl-5-(trifluoromethyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (307 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: CH_2Cl_2) afforded the title compound as a yellow oil (112 mg, 0.37 mmol, 74% yield). IR ν_{max}/cm^{-1} (film): 2957, 2861, 1603, 1325, 1129, 1043; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.52 (1H, s, H_1), 6.71 (1H, s, H_2), 4.07 (2H, t, J = 6.5 Hz, H_7), 2.76 (2H, t, J = 7.6 Hz, H_3), 1.81 (2H, qn, J = 6.5 Hz, H_8), 1.69 (2H, qn, J = 7.7 Hz, H_4), 1.50-1.25 (8H, m, H_5, H_9, H_{10}, and H_{11}), 0.95-0.85 (6H, m, H_6 and H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.62, 163.29, 147.39 (q, J = 5.8 Hz), 123.42 (q, J = 272.4 Hz), 113.06 (q, J = 31.3 Hz), 106.25, 68.64, 38.59, 31.74, 31.28, 28.57, 25.33, 22.46, 22.44, 13.86, 13.83; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -62.29; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 304.2, $C_{16}H_{25}F_3NO^+$ requires 304.2.

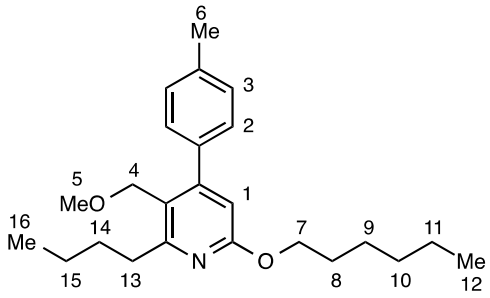
2-(Hexyloxy)-4-(trifluoromethyl)pyridine (12ta)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), triphenyl(4-(trifluoromethyl)pyridin-2-yl)phosphonium trifluoromethanesulfonate (279 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 2.5% EtOAc in hexanes) afforded the title compound as a yellow oil (79 mg, 0.32 mmol, 64% yield). IR ν_{max}/cm^{-1} (film): 2932, 1571, 1423, 1375, 1335, 1171, 1138; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.28 (1H, d, J = 5.3 Hz, H_1), 7.02 (1H, d, J = 5.3 Hz, H_2), 6.94

(1H, s, H_3), 4.32 (2H, t, J = 6.6 Hz, H_4), 1.77 (2H, qn, J = 6.7 Hz, H_5), 1.44 (2H, qn, J = 6.7 Hz, H_6), 1.38-1.28 (4H, m, H_7 and H_8), 0.90 (3H, t, J = 6.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.48, 148.26, 140.76 (q, J = 33.6 Hz), 122.72 (q, J = 273.1 Hz), 111.88 (q, J = 3.1 Hz), 107.76 (q, J = 4.0 Hz), 66.77, 31.57, 28.88, 25.70, 22.60, 13.98; ^{19}F NMR (365 MHz, $CDCl_3$) δ: -65.16; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 248.1, $C_{12}H_{17}F_3NO^+$ requires 248.1.

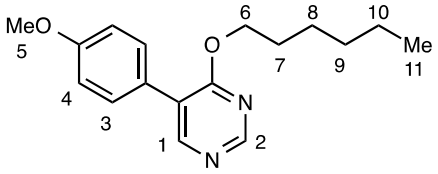
2-Butyl-6-(hexyloxy)-3-(methoxymethyl)-4-(*p*-tolyl)pyridine (12va)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), *n*-hexanol (47 μL, 0.38 mmol), (6-butyl-5-(methoxymethyl)-4-(*p*-tolyl)pyridin-2-yl)triphenylphosphonium trifluoromethanesulfonate (170 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel, gradient elution: 20% hexanes in CH_2Cl_2 to CH_2Cl_2) afforded the title compound as a yellow oil (69 mg, 0.19 mmol, 76 % yield). IR ν_{max}/cm^{-1} (film): 2927, 1594, 1342 1185, 1089, 821; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (2H, d, J = 7.7 Hz, H_2), 7.23 (2H, d, J = 7.7 Hz, H_3), 6.47 (1H, s, H_1), 4.31 (2H, t, J = 6.7 Hz, H_7), 4.20 (2H, s, H_4), 3.32 (3H, s, H_5), 2.85 (2H, t, J = 7.8 Hz, H_{13}), 2.41 (3H, s, H_6), 1.84-1.72 (4H, m, H_{14} and H_8), 1.52-1.41 (4H, m, H_{15} and H_9), 1.40-1.29 (4H, m, H_{10} and H_{11}), 0.99 (3H, t, J = 7.4 Hz, H_{16}), 0.91 (3H, t, J = 7.0 Hz, H_{12}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.64, 161.30, 154.16, 137.59,

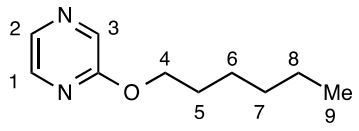
136.74, 128.80, 128.71, 121.05, 107.82, 68.36, 65.95, 57.86, 34.45, 31.67, 31.64, 29.12, 25.76, 22.87, 22.61, 21.17, 14.09, 14.02; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 370.3, $C_{24}H_{36}NO_2^+$ requires 370.3.

4-(Hexyloxy)-5-(4-methoxyphenyl)pyrimidine (12wa)



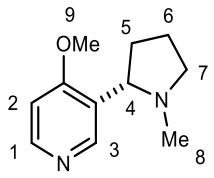
Prepared according to general procedure B (except that the reaction was allowed to stir for 30 hours after the addition of the phosphonium salt) using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), (5-(4-methoxyphenyl)pyrimidin-4-yl)triphenylphosphonium trifluoromethanesulfonate (298 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 20% EtOAc in hexanes) afforded the title compound as a yellow oil (85 mg, 0.30 mmol, 60% yield). IR ν_{max}/cm^{-1} (film): 3038, 2930, 1554, 1448, 1306, 1249, 995, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (1H, s, H_2), 8.45 (1H, br s, H_1), 7.52-7.47 (2H, m, H_3), 6.99-6.93 (2H, m, H_4), 4.41 (2H, t, J = 6.7 Hz, H_6), 3.84 (3H, s, H_5), 1.77 (2H, qn, J = 6.8 Hz, H_7), 1.41 (2H, qn, J = 6.8 Hz, H_8), 1.36-1.27 (4H, m, H_9 and H_{10}), 0.87 (3H, t, J = 6.9 Hz, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.87, 159.57, 156.36, 155.36, 130.06, 125.29, 121.84, 113.87, 66.87, 55.22, 31.35, 28.53, 25.59, 22.46, 13.90; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 287.2, $C_{17}H_{23}N_2O_2^+$ requires 287.2.

2-(Hexyloxy)pyrazine (12xa)



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), *n*-hexanol (94 μL, 0.75 mmol), triphenyl(pyrazin-2-yl)phosphonium trifluoromethanesulfonate (245 mg, 0.5 mmol) and THF (1.0 mL). Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a yellow oil (70 mg, 0.39 mmol, 78% yield). IR ν_{max}/cm^{-1} (film): 3060, 2923, 1532, 1414, 1284, 1005; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (1H, br s, H_1), 8.10-7.97 (2H, br s, H_2 and H_3), 4.28 (2H, t, J = 6.7 Hz, H_4), 1.76 (2H, qn, J = 6.8 Hz, H_5), 1.42 (2H, qn, J = 6.8 Hz, H_6), 1.37-1.25 (4H, m, H_7 and H_8), 0.88 (3H, t, J = 6.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.46, 140.49, 136.18, 136.02, 66.40, 31.49, 28.74, 25.60, 22.54, 13.97. The spectroscopic data is in agreement with a reported synthesis.[8] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 181.2, $C_{10}H_{17}N_2O^+$ requires 181.1.

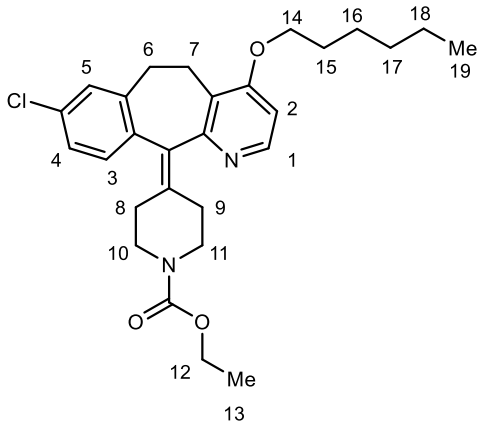
(*S*)-4-methoxy-3-(1-methylpyrrolidin-2-yl)pyridine (13)



Prepared according to general procedure B (except that CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 30 mg, 0.75 mmol), methanol (30 μL, 0.75 mmol), (*S*)-(3-(1-methylpyrrolidin-2-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (286 mg, 0.50 mmol) and THF (1.0 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then

gradient elution: 1% MeOH in CH_2Cl_2 to 10% MeOH in CH_2Cl_2) followed by a second flash column (basic alumina: 2% MeOH in CH_2Cl_2) afforded the title compound as a tan amorphous solid (76 mg, 0.40 mmol, 79% yield). mp 73-75 ºC; IR ν_{max}/cm^{-1} (film): 3031, 2969, 2780, 1589, 1455, 1274, 1023, 805; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.51 (1H, br s, H_3), 8.34 (1H, br s, H_1), 6.70 (1H, d, J = 5.7 Hz, H_2), 3.81 (3H, s, H_9), 3.44 (1H, app t, J = 8.3 Hz, H_4), 3.19 (1H, app t, J = 8.5 Hz, H_7), 2.30-2.14 (5H, m, H_5, H_7, and H_8), 1.93-1.80 (1H, m, H_6), 1.80-1.69 (1H, m, H_6), 1.64-1.52 (1H, m, H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.51, 149.64, 148.92, 126.87, 105.58, 62.64, 56.96, 55.14, 40.73, 33.02, 22.66. The spectroscopic data is in agreement with a reported synthesis.[9] *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 193.1, $C_{11}H_{17}N_2O^+$ requires 193.1.

Ethyl 4-(8-chloro-4-(hexyloxy)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (14)

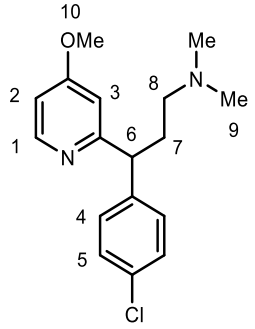


Prepared according to general procedure B (except that the reaction was allowed to stir for 15 hours after the addition of the phosphonium salt and CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), *n*-hexanol (47 μL, 0.38 mmol), (8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-4-yl)triphenylphosphonium

trifluoromethanesulfonate (198 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then: 1% NEt_3, 50% CH_2Cl_2 in hexanes) followed by a second flash column (basic alumina, gradient elution: 30% EtOAc in hexanes to 50% EtOAc in hexanes)[‡‡‡] afforded the title compound as a yellow oil (64 mg, 0.13 mmol, 53% yield). IR ν_{max}/cm^{-1} (film): 3010, 2929, 1688, 1567, 1435, 1230, 748 ^1H NMR (400 MHz, $CDCl_3$) δ: 8.27 (1H, d, J = 5.6 Hz, H_1), 7.18 (1H, s, H_5), 7.14-7.07 (2H, m, H_3 and H_4), 6.61 (1H, d, J = 5.6 Hz, H_2), 4.12 (2H, q, J = 7.1 Hz, H_{12}), 4.01-3.69 (4H, m, H_{10} or H_{11} and H_{12}), 3.40-3.28 (1H, m, H_6), 3.17-2.98 (3H, m, H_7 and H_{10} or H_{11}), 2.92-2.71 (2H, m, H_6 and H_7), 2.58-2.45 (1H, m, H_8 or H_9), 2.43-2.18 (3H, m, H_8 or H_9), 1.77 (2H, qn, J = 6.9 Hz, H_{15}), 1.50-1.28 (6H, m, H_{16}, H_{17}, and H_{18}), 1.27-1.17 (3H, m, H_{12}), 0.89 (3H, t, J = 6.9 Hz, H_{19}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.41, 156.51, 155.43, 147.69, 140.30, 138.79, 137.37, 133.98, 132.73, 129.73, 128.28, 126.05, 122.03, 104.98, 68.08, 61.22, 44.78, 44.70, 31.40, 30.70, 30.56, 29.64, 28.86, 25.67, 25.33, 22.49, 14.63, 13.94; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 483.3, $C_{28}H_{36}ClN_2O_3^+$ requires 483.2.

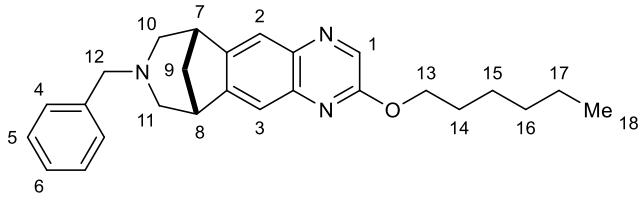
‡‡‡ To remove an impurity the product was dissolved in Et_2O (10 mL) and trifluoroacetic acid (0.5 mL) was added dropwise at 0 ºC and then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with a saturated aqueous solution of sodium bicarbonate (10 mL). The organic layer was washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*.

3-(4-Chlorophenyl)-3-(4-methoxypyridin-2-yl)-*N*,*N*-dimethylpropan-1-amine (15)



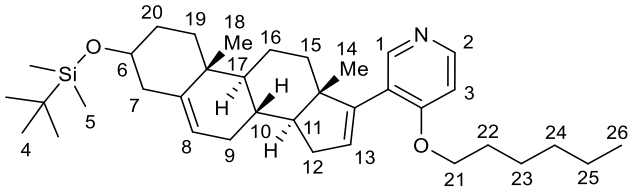
Prepared according to general procedure B (except that the reaction was allowed to stir for 18 hours after the addition of the phosphonium salt and CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), methanol (15 μL, 0.38 mmol), (2-(1-(4-chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (171 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then: 1% MeOH, 1% NEt_3 in CH_2Cl_2) followed by a second flash column (basic alumina: 2% MeOH in CH_2Cl_2) afforded the title compound as a tan oil (35 mg, 0.12 mmol, 46% yield). IR ν_{max}/cm^{-1} (film): 3011, 2940, 2768, 1593, 1567, 1488, 1304, 1037, 749; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.35 (1H, d, J = 5.6 Hz, H_1), 7.28-7.18 (4H, m, H_4 and H_5), 6.64 (1H, d, J = 2.4 Hz, H_3), 6.60 (1H, dd, J = 5.6, 2.4 Hz, H_2), 4.05-4.00 (1H, m, H_6), 3.75 (3H, s, H_{10}), 2.44-2.30 (1H, m, H_7), 2.21-2.06 (9H, m, H_7, H_8, and H_9); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.01, 164.65, 150.60, 142.03, 132.15, 129.33, 128.54, 108.86, 107.51, 57.59, 54.98, 50.60, 45.36, 32.69; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 305.2, $C_{17}H_{22}ClN_2O^+$ requires 305.1.

(*rac*)-2-(Hexyloxy)-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxaline (16)



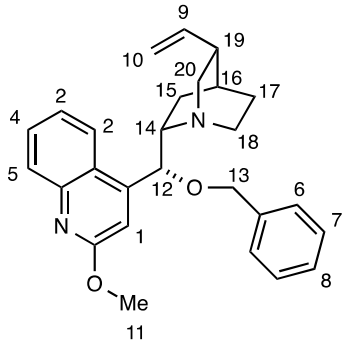
Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 11 mg, 0.28 mmol), *n*-hexanol (35 μL, 0.28 mmol), triphenyl((*rac*)-7,8,9,10-tetrahydro-6*H*-6,10-methanoazepino[4,5-*g*]quinoxalin-2-yl)phosphonium trifluoromethanesulfonate (130 mg, 0.18 mmol) and THF (0.4 mL). Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a tan oil (18 mg, 0.045 mmol, 25% yield).; IR ν_{max}/cm^{-1} (film): 3026, 2950, 1570, 1473, 1345, 1300, 1204; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (1H, s, H_1), 7.69 (1H, s, H_2) 7.56 (1H,s, H_3), 7.15-7.09 (3H, m, H_5 and H_6), 6.90-6.82 (2H, m, H_4), 4.47 (2H, t, J = 6.8 Hz, H_{13}), 3.48 (2H, s, H_{12}) 3.32-3.25 (2H, br s, H_7 and H_8), 2.95 (2H, m, H_{10} or H_{11}), 2.53 (2H, m, H_{10} or H_{11}), 2.37-2.27 (1H, m, H_9), 1.91-1.78 (3H, m, H_9 and H_{14}), 1.57-1.45 (2H, m, H_{15}), 1.44-1.32 (4H, m, H_{16} and H_{17}), 0.93 (3H, t, J = 7.0 Hz, H_{18}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.19, 150.56, 146.56, 140.35, 138.59, 138.38, 137.42, 128.34, 127.99, 126.58, 120.32, 118.83, 66.29, 61.59, 57.31, 57.12, 43.51, 41.38, 40.98, 31.58, 28.83, 25.75, 22.61, 14.06; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 402.2, $C_{26}H_{32}N_3O^+$ requires 402.3.

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



Prepared according to general procedure B using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), *n*-hexanol (47 μL, 0.38 mmol), (3-((8*R*,9*S*,10*R*,13*S*,14*S*)-3-((*tert*-butyldimethylsilyl)oxy)-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[a]phenanthren-17-yl)pyridin-4-yl)triphenylphosphonium trifluoromethanesulfonate (219 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel, gradient elution: 30% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a white solid (82 mg, 0.15 mmol, 60% yield). mp 59-64 ºC; IR ν_{max}/cm^{-1} (film): 2928, 1577, 1496, 1382, 1279, 1250, 1077, 1022, 888; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40-8.15 (2H, m), 6.76 (1H, d, J = 5.6 Hz), 5.89-5.84 (1H, dd, J = 3.0, 1.5 Hz), 5.38-5.32 (1H, m), 3.98 (2H, t, J = 6.6 Hz), 3.49 (1H, m), 2.34-2.14 (3H, m), 2.12-1.99 (2H, m), 1.85-1.27 (18H, m), 1.12-0.81 (20H, m), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.00, 150.04, 149.49, 148.60, 141.88, 130.91, 123.01, 120.90, 106.78, 72.57, 68.01, 57.21, 50.59, 48.61, 42.83, 37.29, 36.79, 34.99, 32.14, 32.05, 31.63, 31.38, 30.71, 28.74, 25.92, 25.66, 22.56, 20.84, 19.35, 18.24, 16.12, 13.98, -4.60; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 564.4, $C_{36}H_{58}NO_2Si^+$ requires 564.4.

(1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(Benzyloxy)(2-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine (18)



Prepared according to general procedure B (except that the reaction was allowed to stir for 11 hours after the addition of the phosphonium salt and CH_2Cl_2 was used instead of Et_2O for the extraction stage of the workup) using sodium hydride (60% dispersion in mineral oil, 15 mg, 0.38 mmol), methanol (15 μL, 0.38 mmol), (4-((*R*)-(benzyloxy)((1*S*,2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)quinolin-2-yl)triphenylphosphonium trifluoromethanesulfonate (199 mg, 0.25 mmol) and THF (0.5 mL). Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then: 1% NEt_3, 50% CH_2Cl_2 in hexanes) afforded the title compound as a pale yellow oil (60 mg, 0.14 mmol, 58% yield). IR ν_{max}/cm^{-1} (film): 3065, 2938, 1609, 1382, 1338, 1236, 1045, 754; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.00 (1H, d, J = 8.0 Hz, H_2), 7.91 (1H, d, J = 8.2 Hz, H_5), 7.64 (1H, t, J = 7.5 Hz, H_4), 7.45-7.27 (6H, m , H_6, H_7, H_8 and H_3), 7.06 (1H s, H_1), 5.83-5.64 (1H, m, H_9), 5.31-5.15 (1H, br s, H_{12}), 5.00-4.85 (2H, m, H_{10}), 4.50 (1H, d, J = 11.3 Hz, H_{13}), 4.40 (1H, d, J = 11.3 Hz, H_{13}), 4.07 (3H, s, H_{11}), 3.45-3.31 (1H, m , H_{18}), 3.18-3.03 (2H, m, H_{20} and H_{14}), 2.72-2.55 (2H, m, H_{18} and H_{20}), 2.30-2.18 (1H, m, H_{19}), 1.89-1.40 (5H, m, H_{15}, H_{16}, and H_{17}); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.30, 148.70, 147.35, 141.69, 137.83, 129.26, 128.38, 128.17, 127.65, 127.61, 124.10, 123.38, 123.23, 114.29, 110.34, 80.78, 71.23, 60.30, 56.94, 53.24, 43.17, 39.89, 27.89, 27.55, 22.07; *m/z* LRMS (ESI + APCI) found $[M+H]^+$ 415.3, $C_{27}H_{31}N_2O_2^+$ requires 415.2.

A. 1.6 Comparative Literature Syntheses of Heteroaryl Ethers

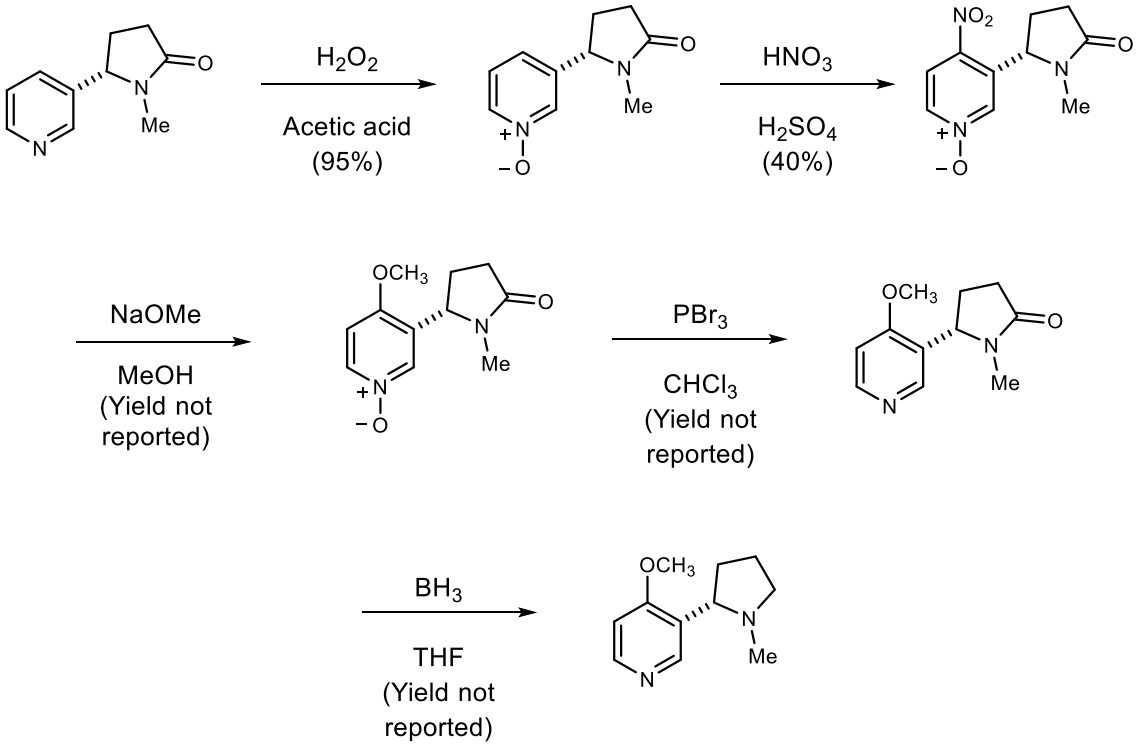


Figure S1. Literature Synthesis of Nicotine derivative **13**.[9,11,12]

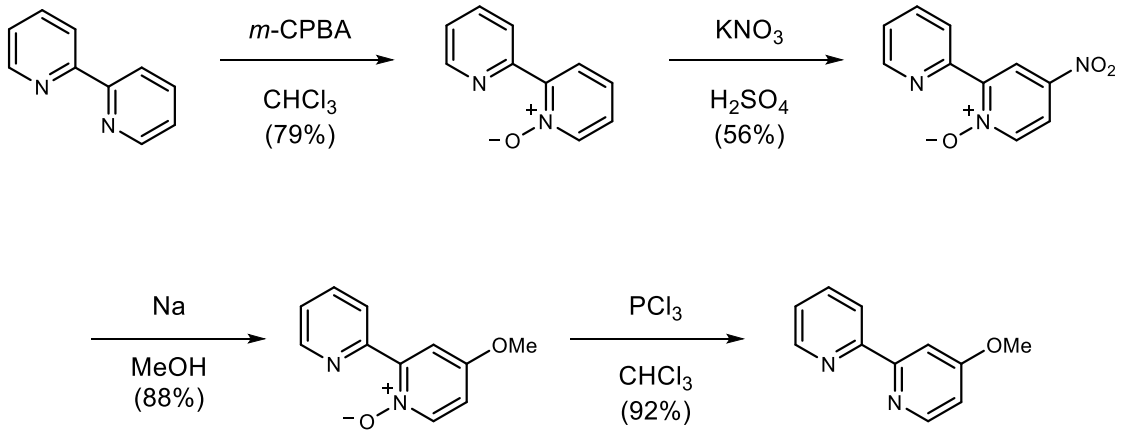
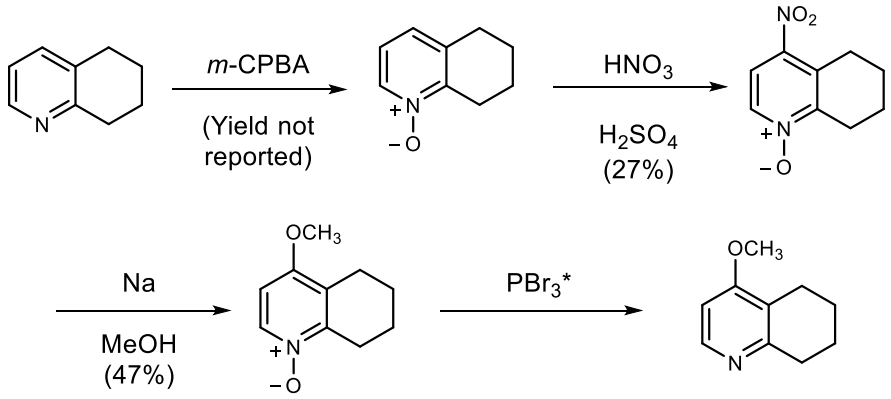


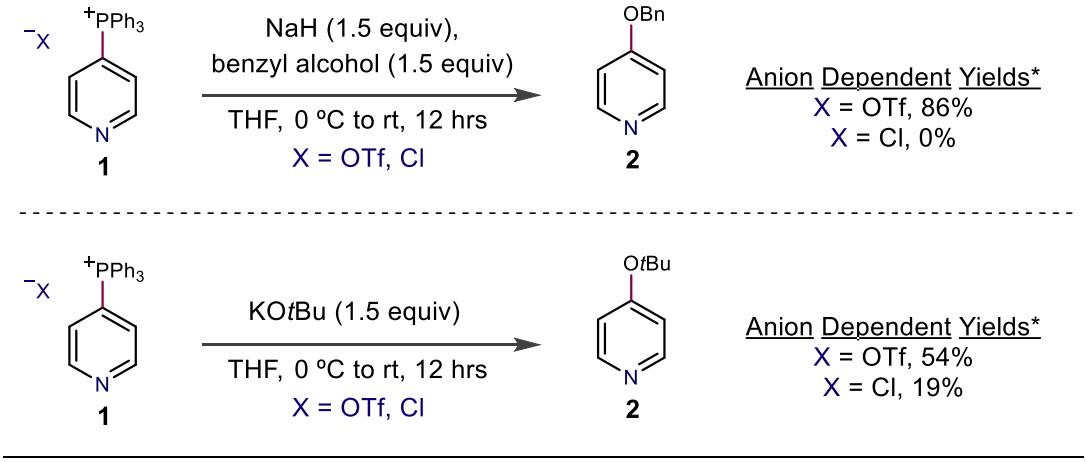
Figure S2. Literature Synthesis of Structure **12ja** analog.[13]



*Reduction step not reported in this manuscript but related analogs were reduced using PBr_3

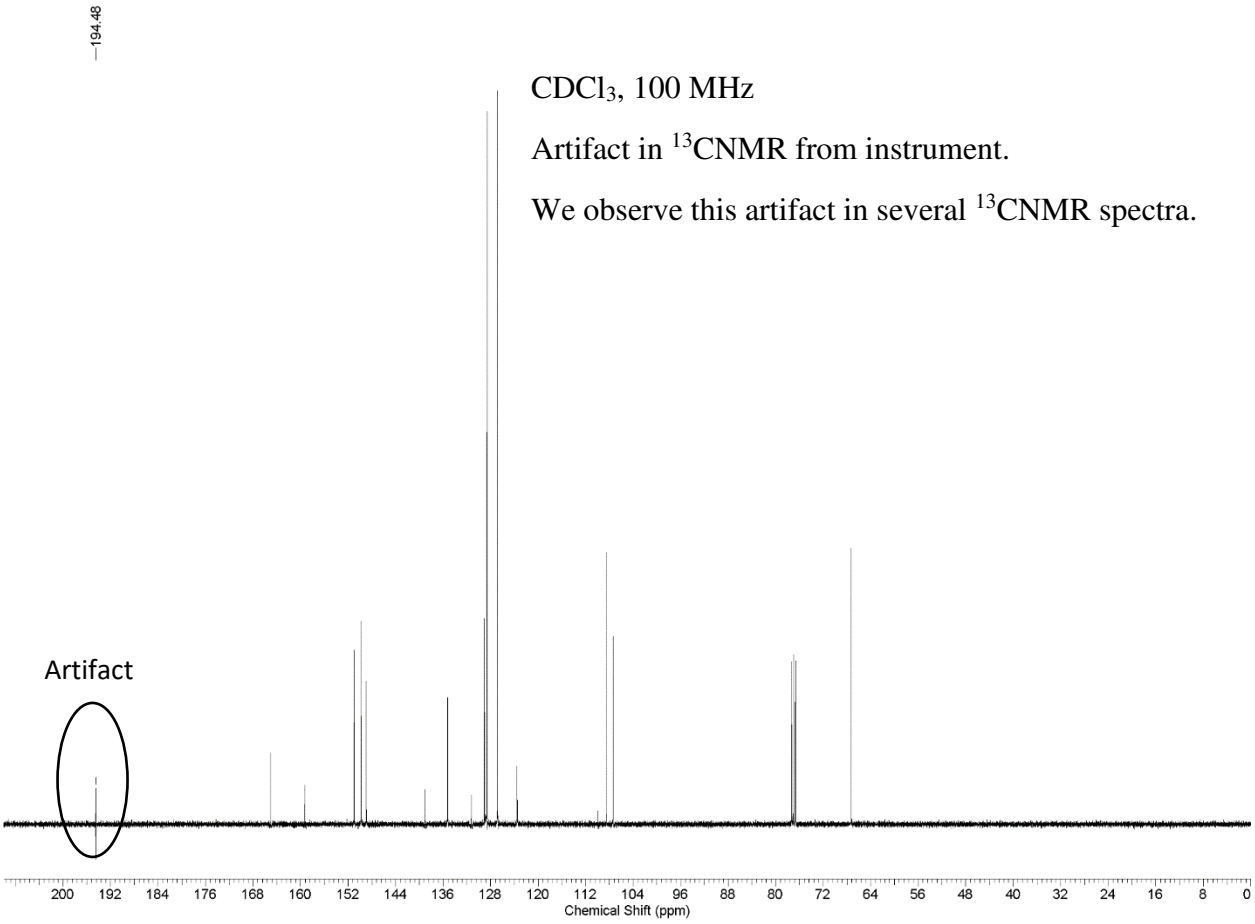
Figure S3. Literature Synthesis of Substrate **12la** analog.[14]

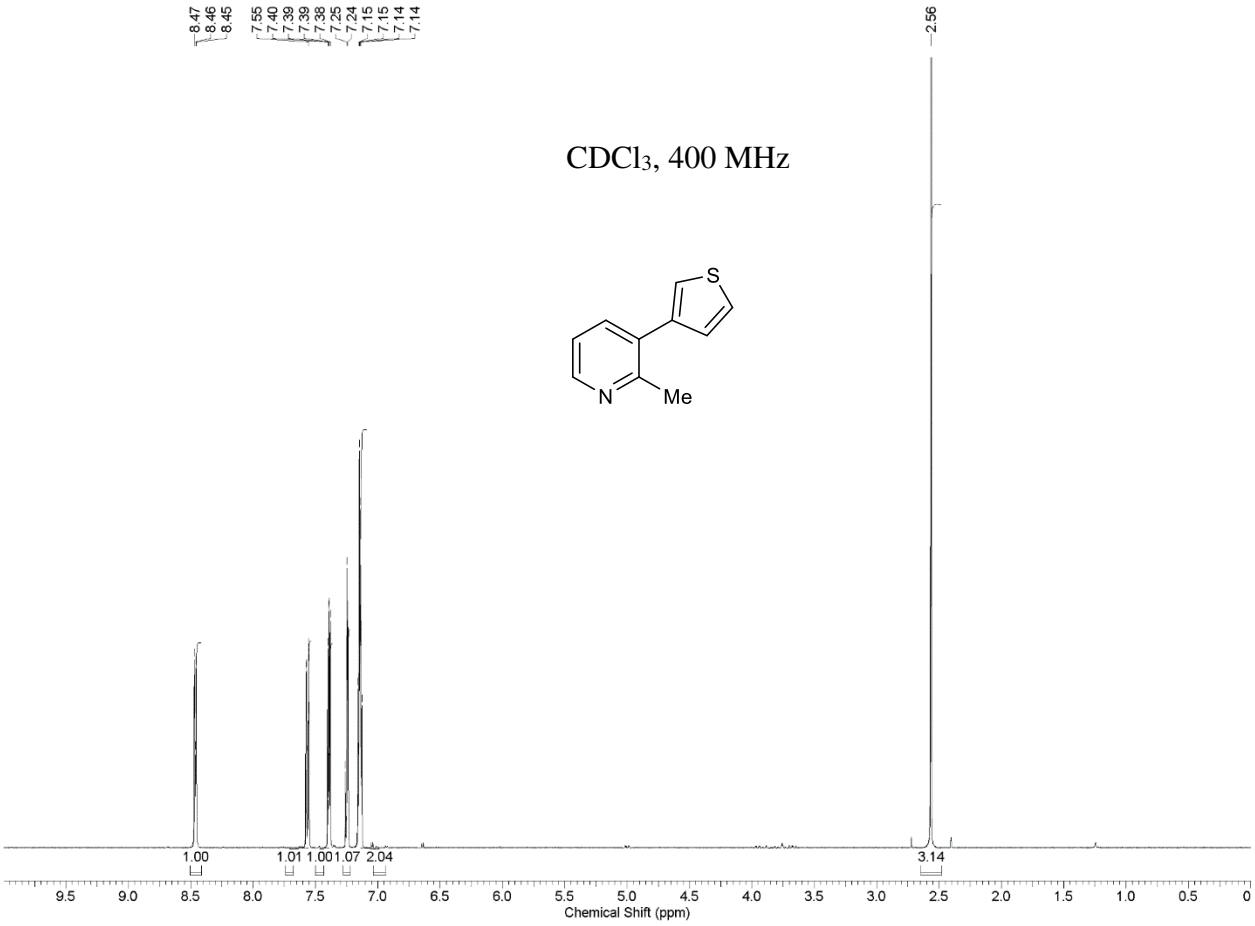
A. 1.7 Counterion Study

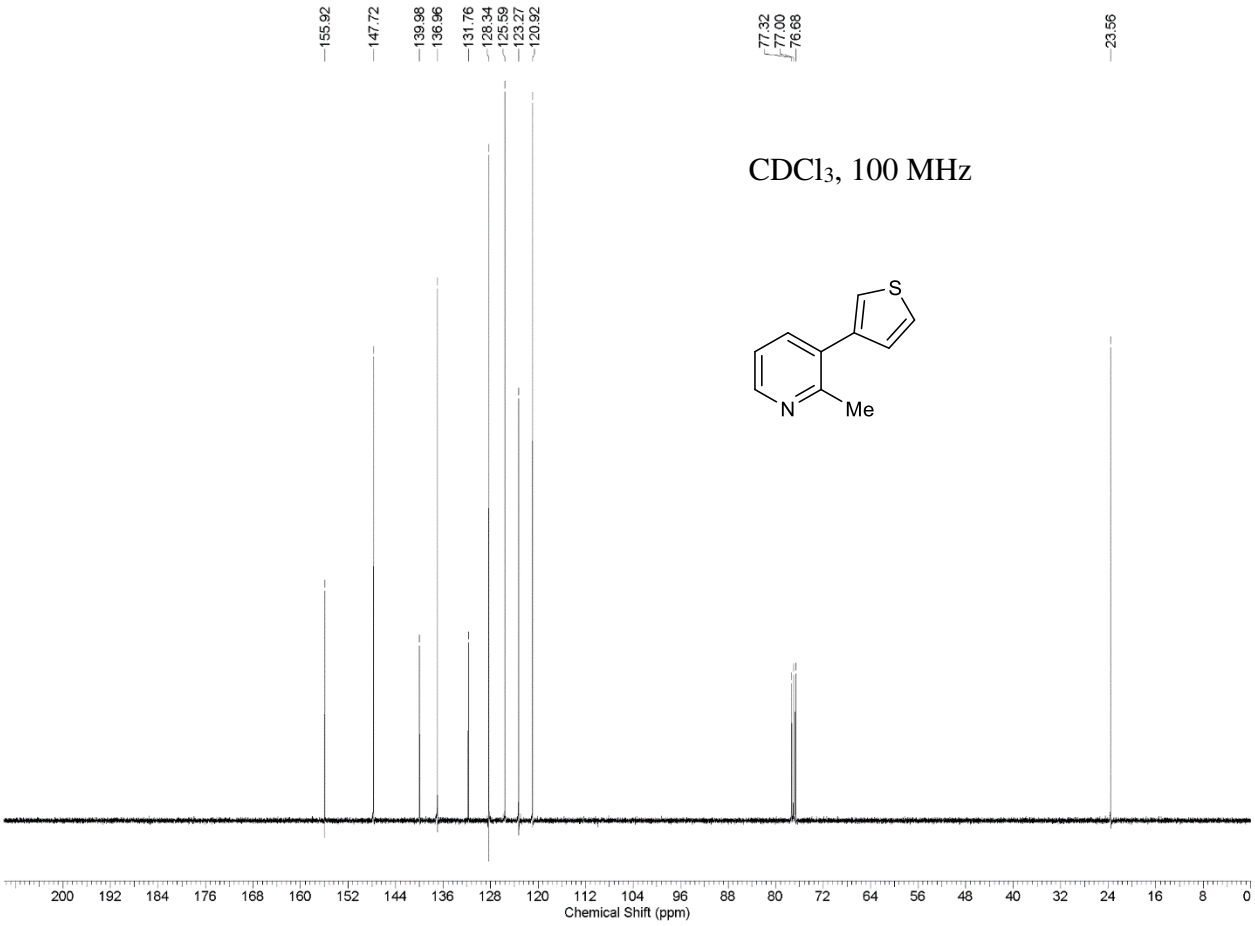


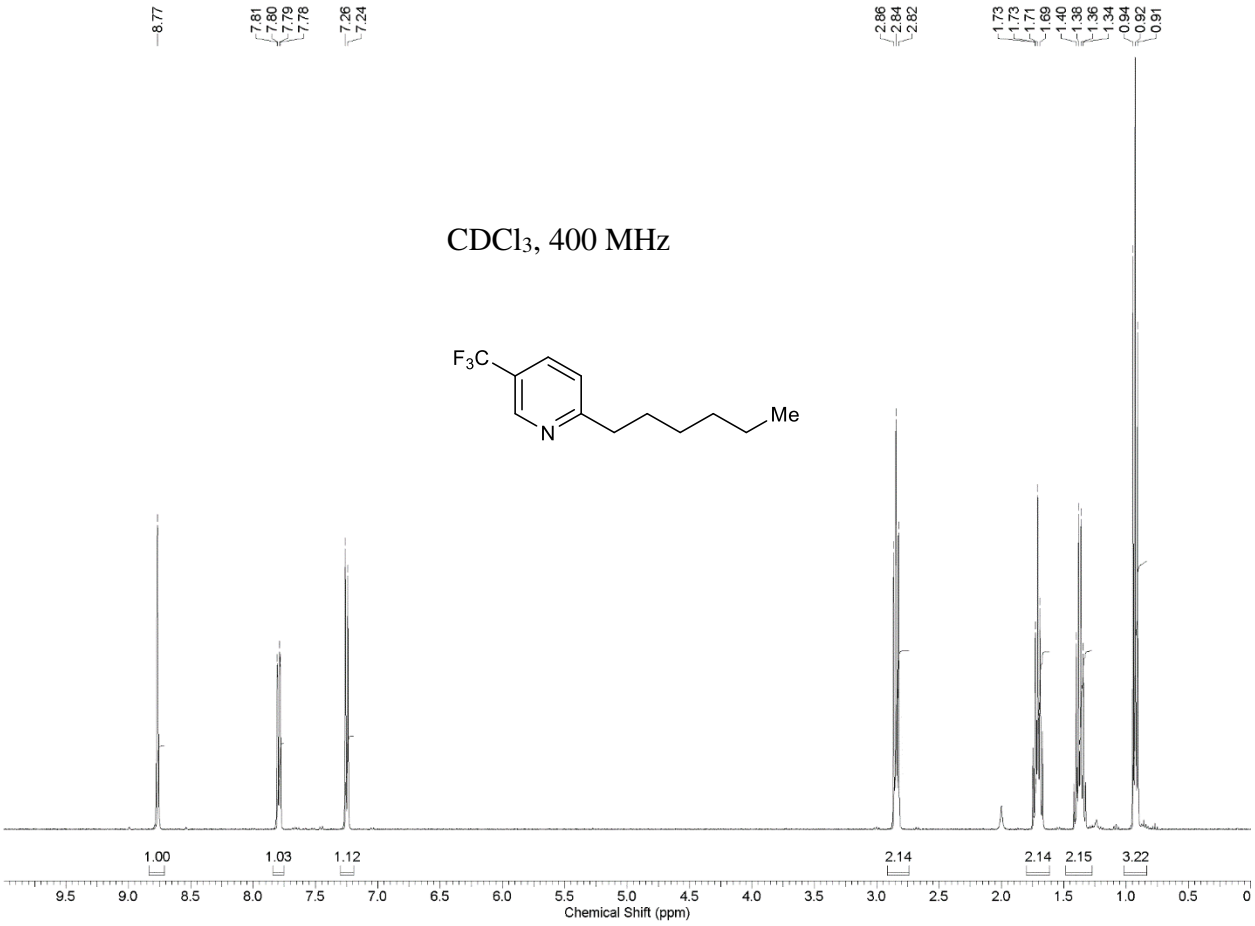
*^{1}H NMR yields shown using 1,3,5-trimethoxybenzene as an internal standard.

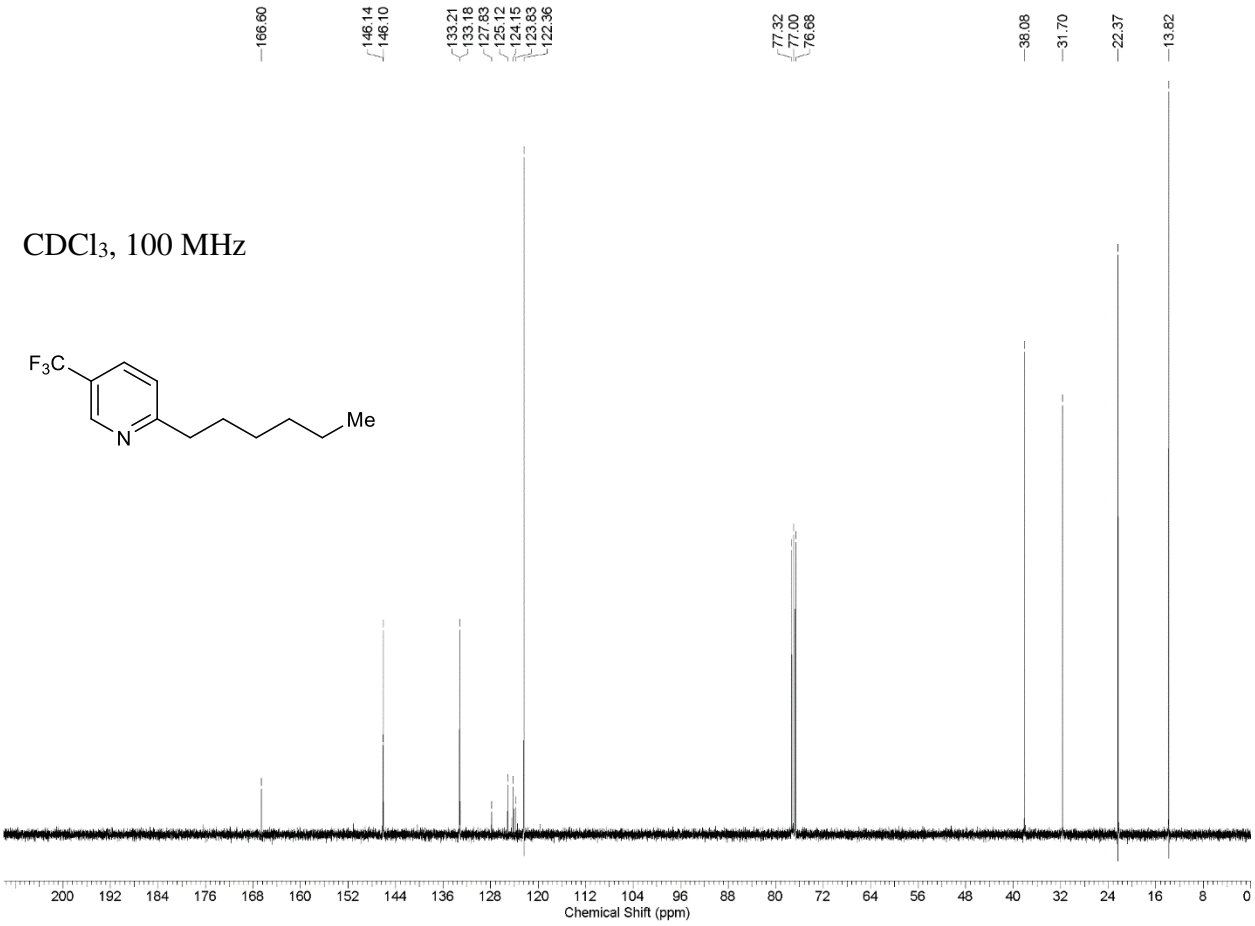
A. 1.8 ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR Spectra

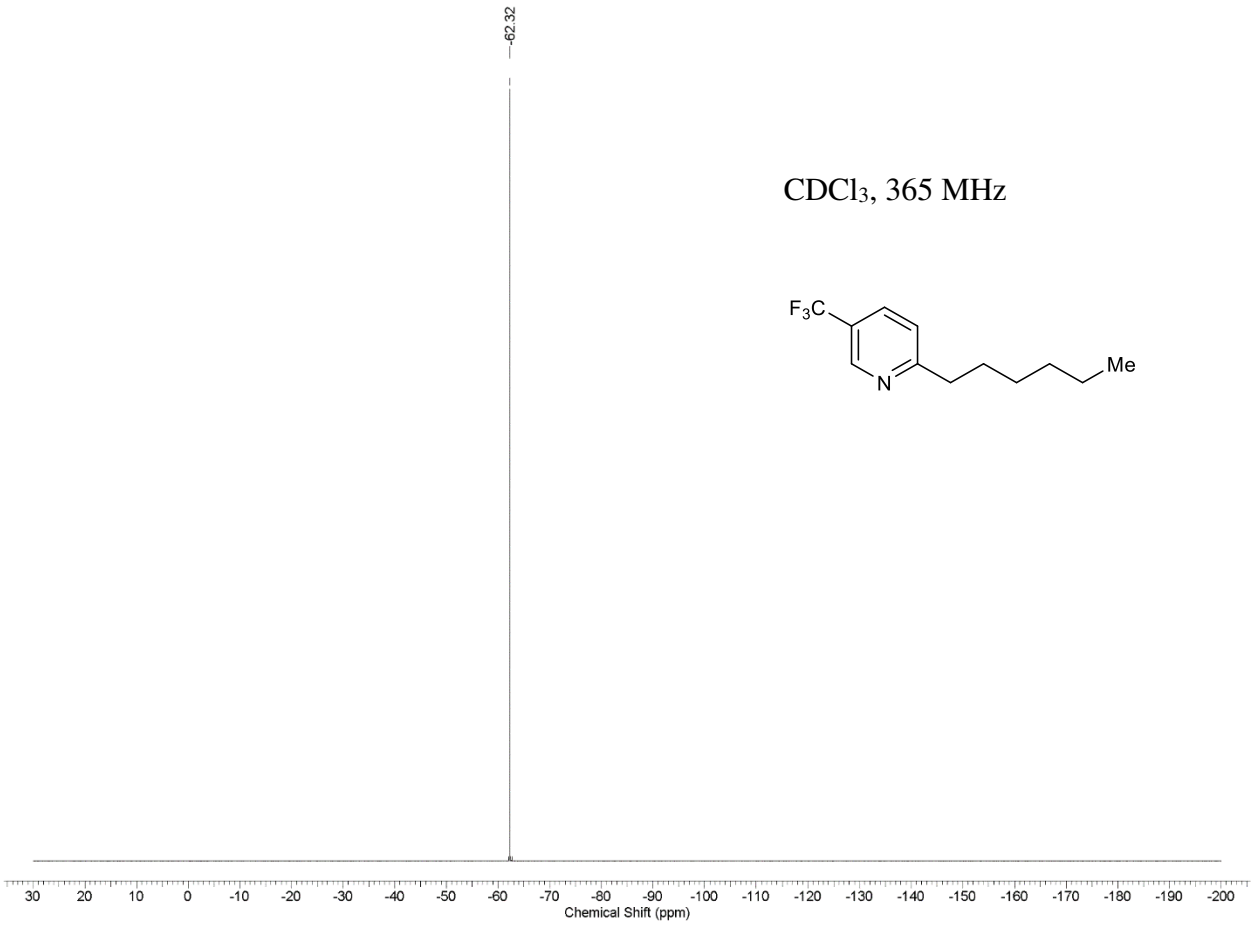


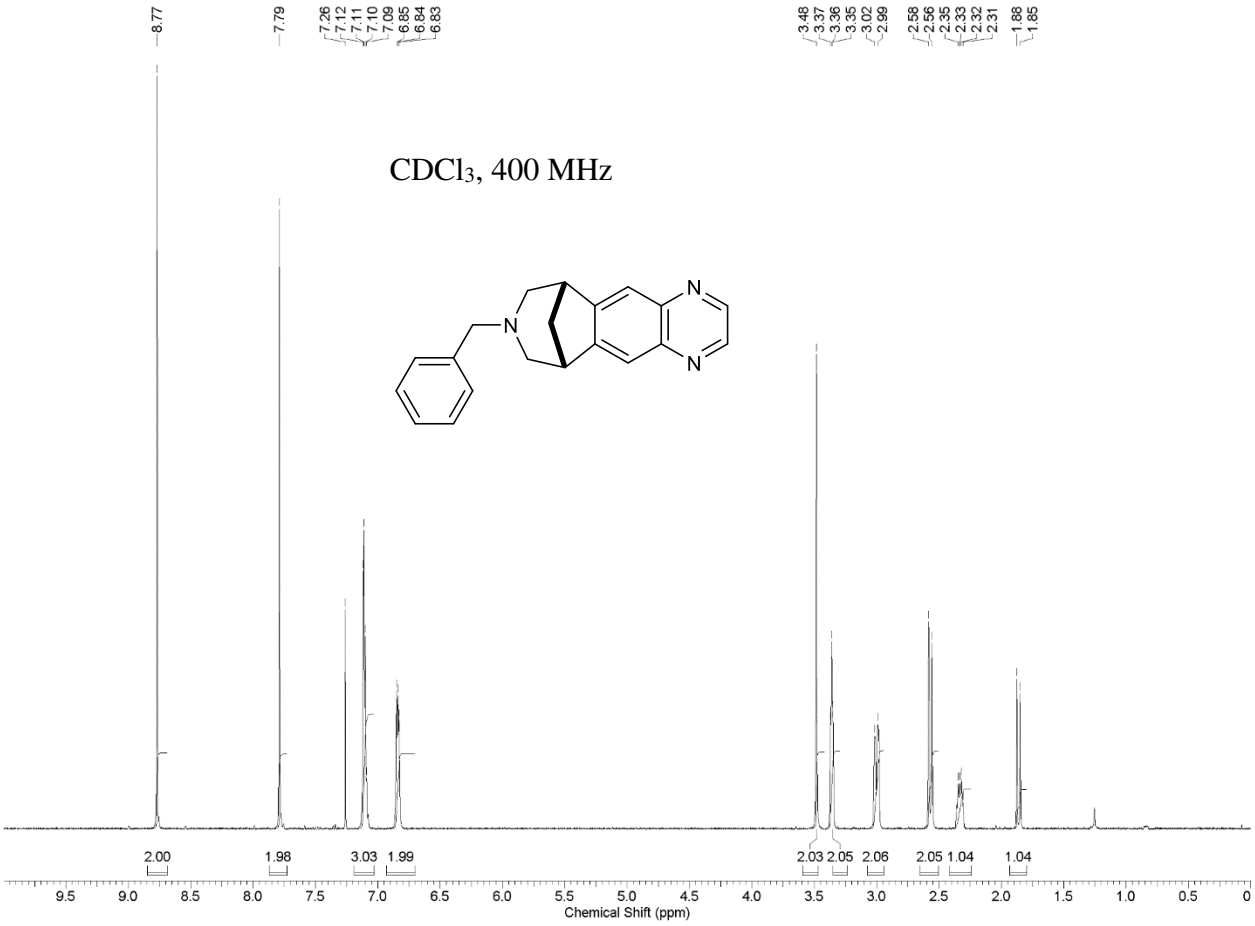

8.47
8.46
8.45
7.55
7.40
7.39
7.39
7.38
7.25
7.24
7.15
7.15
7.14
7.14
2.56
CDCl3, 400 MHz
S
N
Me
1.00
1.01
1.00
1.07
2.04
3.14
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


155.92
147.72
139.98
136.96
131.76
128.34
125.59
123.27
120.92
77.32
77.00
76.68
23.56
CDCl3, 100 MHz
S
N
Me
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

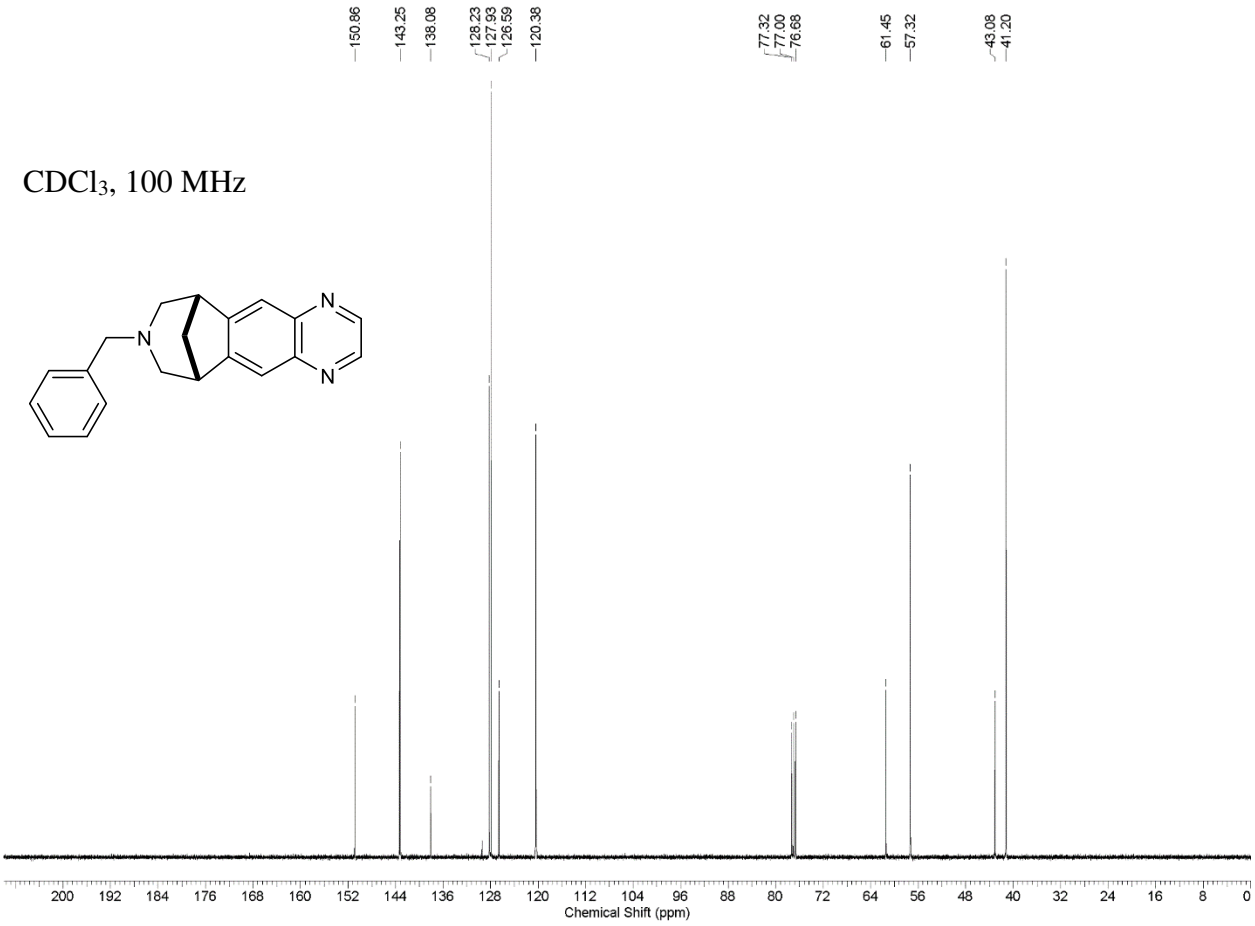

8.77
7.81
7.80
7.79
7.78
7.26
7.24
2.86
2.84
2.82
1.73
1.73
1.71
1.69
1.40
1.38
1.36
1.34
0.94
0.92
0.91
CDCl3, 400 MHz
F3C
N
Me
1.00
1.03
1.12
2.14
2.14
2.15
3.22
Chemical Shift (ppm)

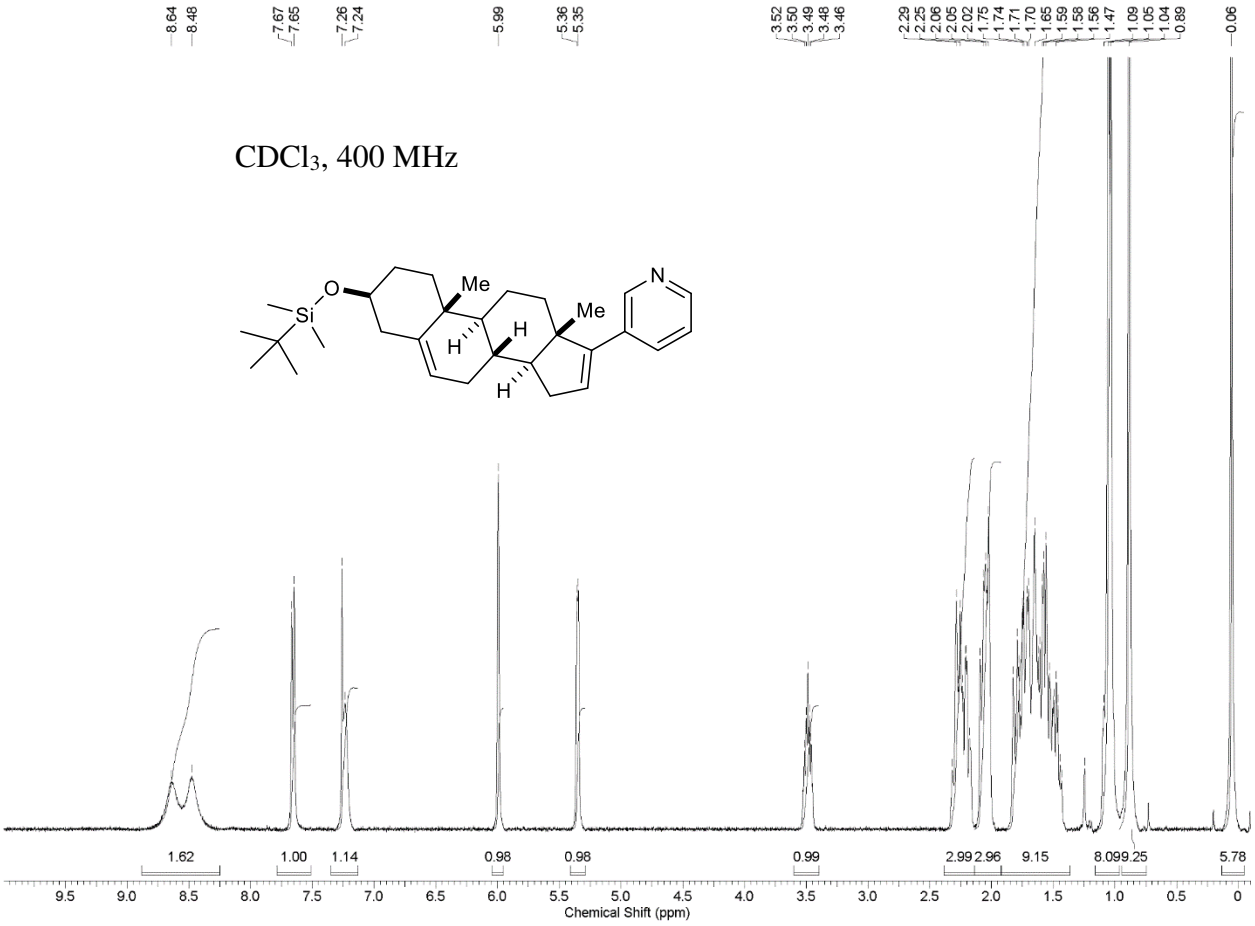

166.60
146.14
146.10
133.21
133.18
127.83
125.12
124.15
123.83
122.36
77.32
77.00
76.68
38.08
31.70
22.37
13.82
CDCl3, 100 MHz
F3C
N
Me
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

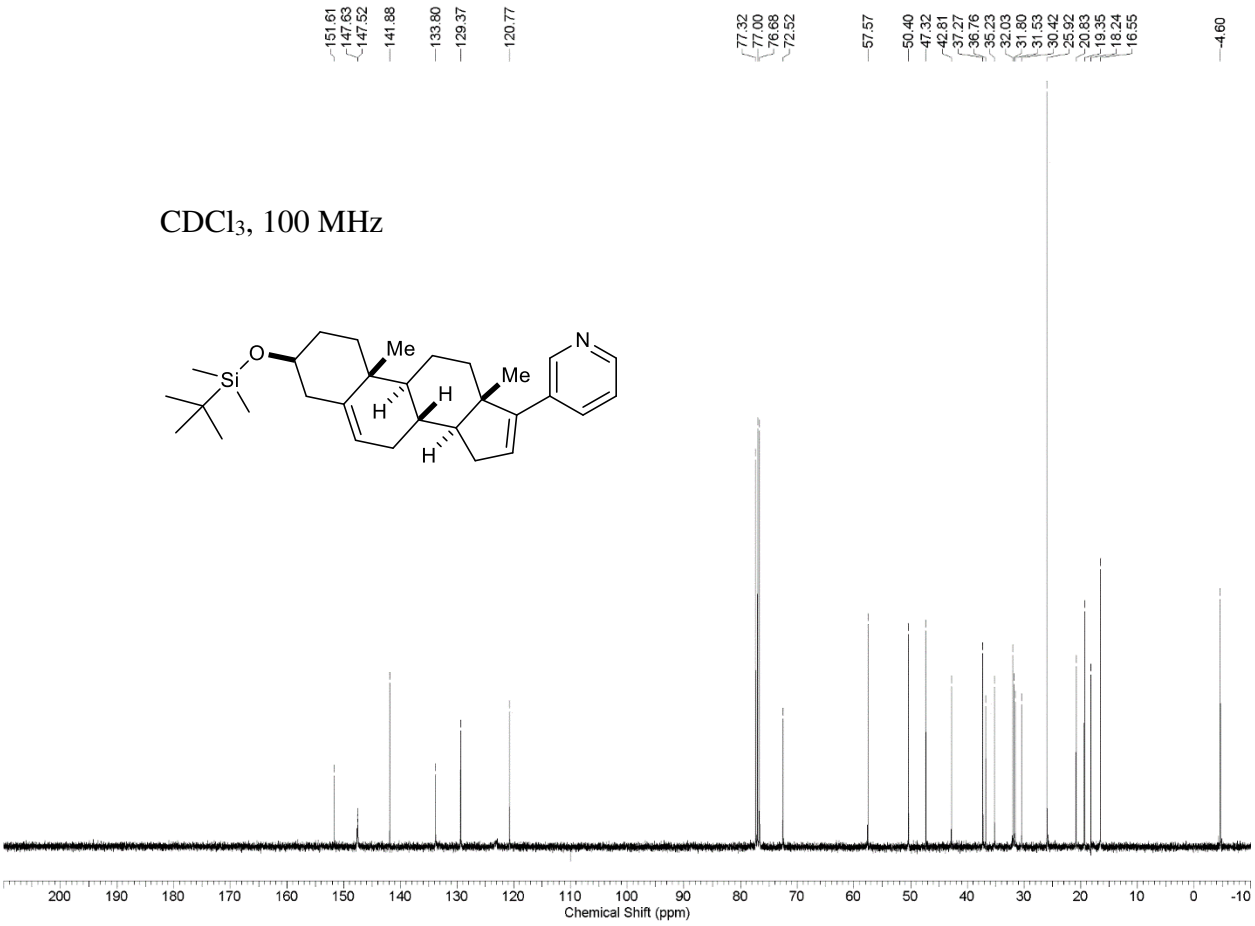

-62.32
CDCl3, 365 MHz
F3C
N
Me
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
Chemical Shift (ppm)

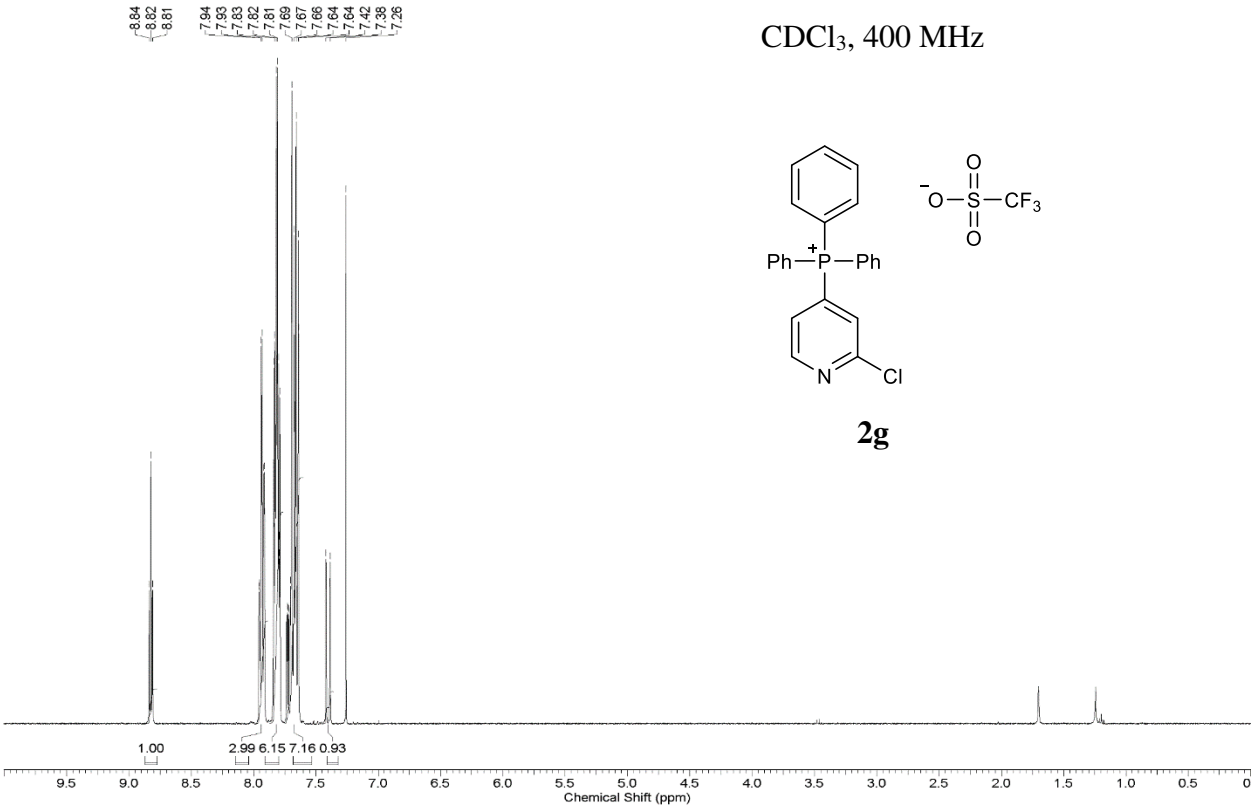

8.77
7.79
7.26
7.12
7.11
7.10
7.09
6.85
6.84
6.83
3.48
3.37
3.36
3.35
3.02
2.99
2.58
2.56
2.35
2.33
2.32
2.31
1.88
1.85
CDCl3, 400 MHz
N
N
N
2.00
1.98
3.03
1.99
2.03
2.05
2.06
2.05
1.04
1.04
Chemical Shift (ppm)

$CDCl_3$, 100 MHz



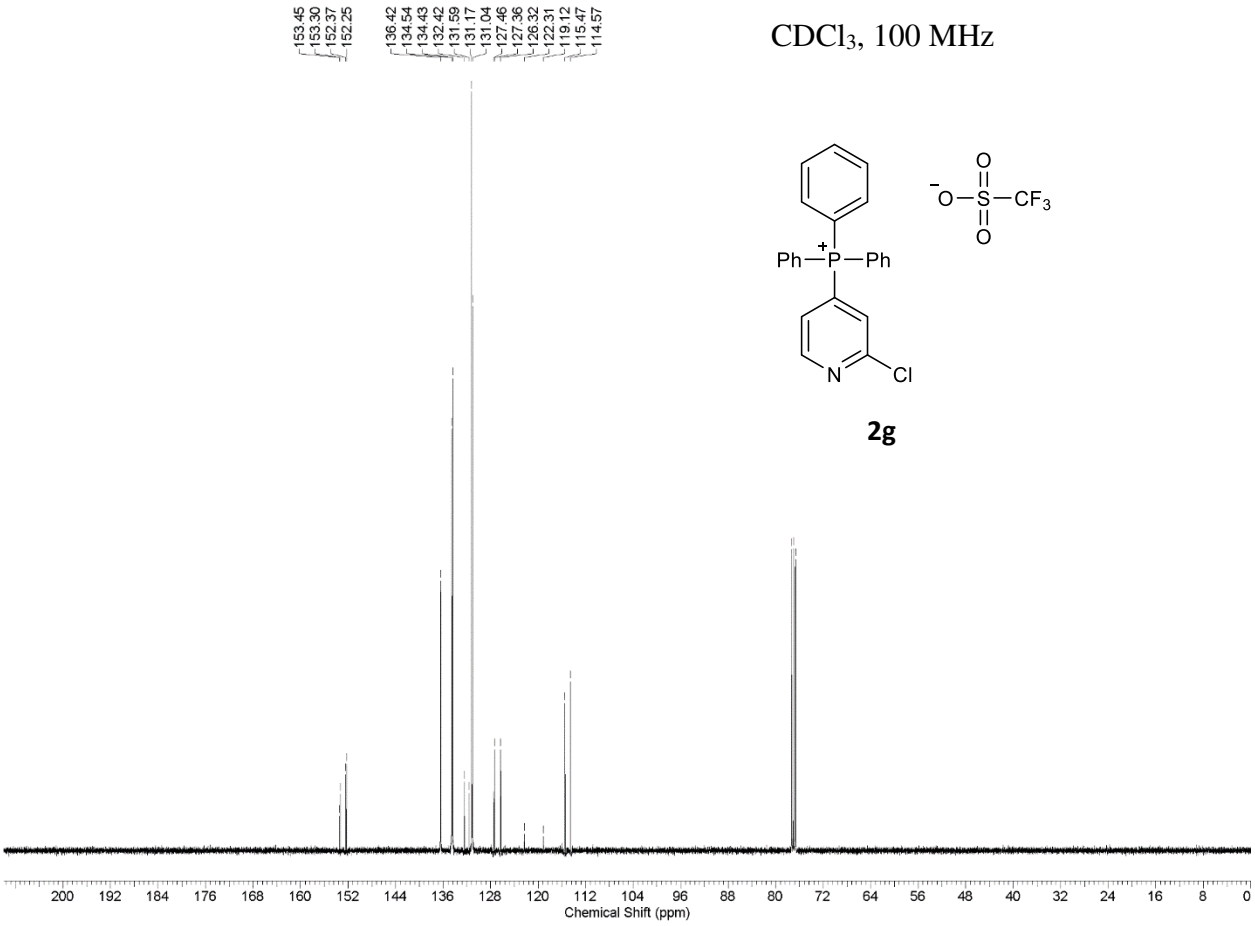

8.64
8.48
7.67
7.65
7.26
7.24
5.99
5.36
5.35
3.52
3.50
3.49
3.48
3.46
2.29
2.25
2.06
2.05
2.02
1.75
1.74
1.71
1.70
1.65
1.59
1.58
1.56
1.47
1.09
1.05
1.04
0.89
0.06
CDCl3, 400 MHz
O
Si
Me
Me
H
H
H
N
1.62
1.00
1.14
0.98
0.98
0.99
2.99
2.96
9.15
8.09
9.25
5.78
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


151.61
147.63
147.52
141.88
133.80
129.37
120.77
77.32
77.00
76.68
72.52
57.57
50.40
47.32
42.81
37.27
36.76
35.23
32.03
31.80
31.53
30.42
25.92
20.83
19.35
18.24
16.55
-4.60
CDCl3, 100 MHz
Si
O
Me
H
H
H
Me
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



$CDCl_3$, 400 MHz

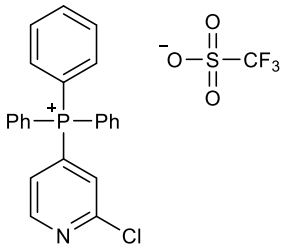
2g



$CDCl_3$, 100 MHz

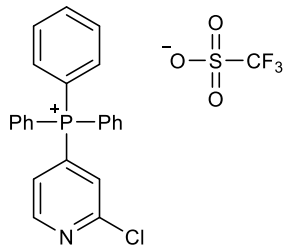
2g

$CDCl_3$, 365 MHz



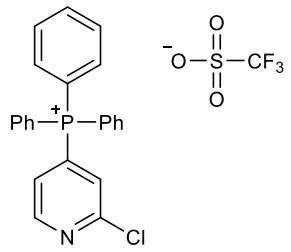
2g

$CDCl_3$, 162 MHz

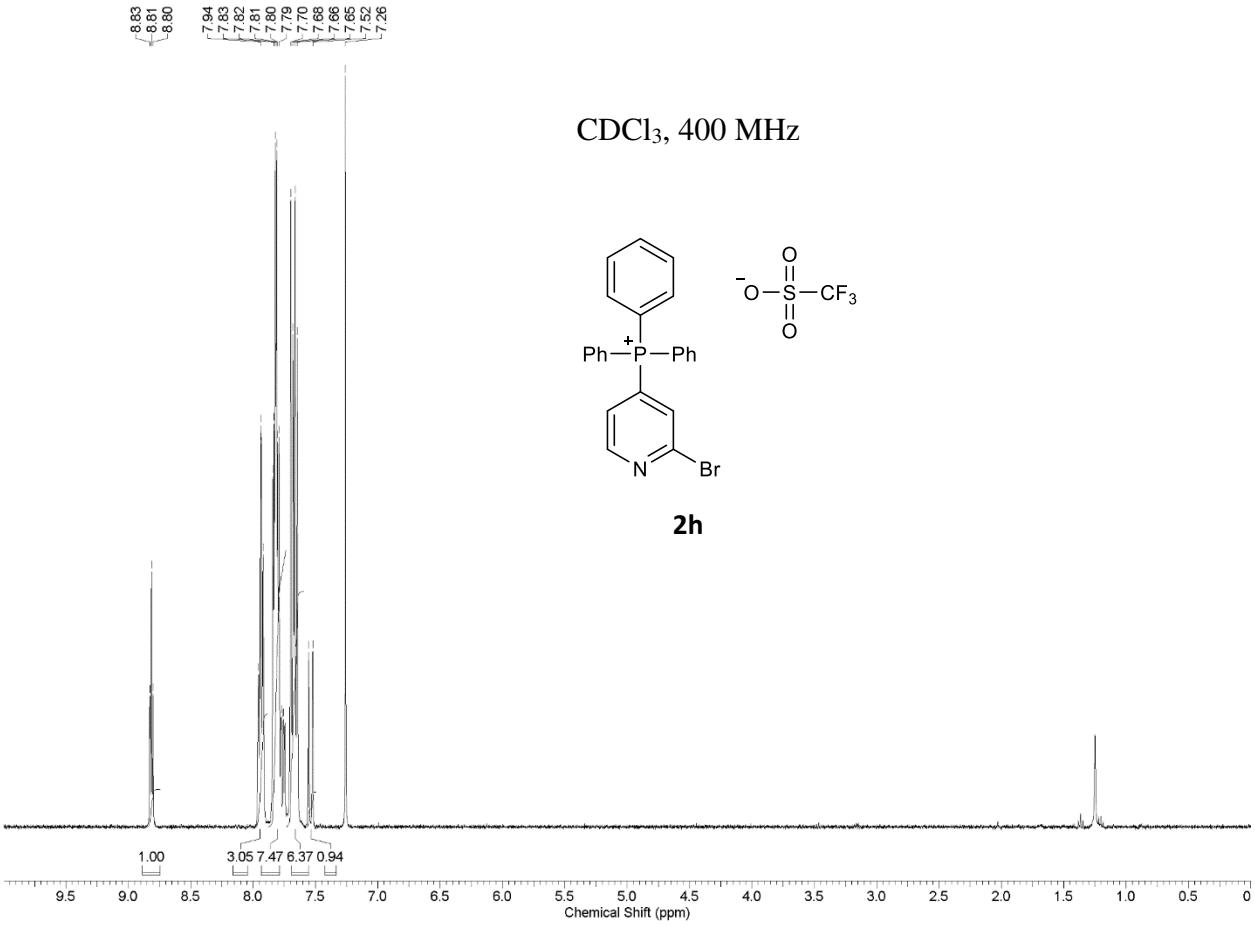


2g

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

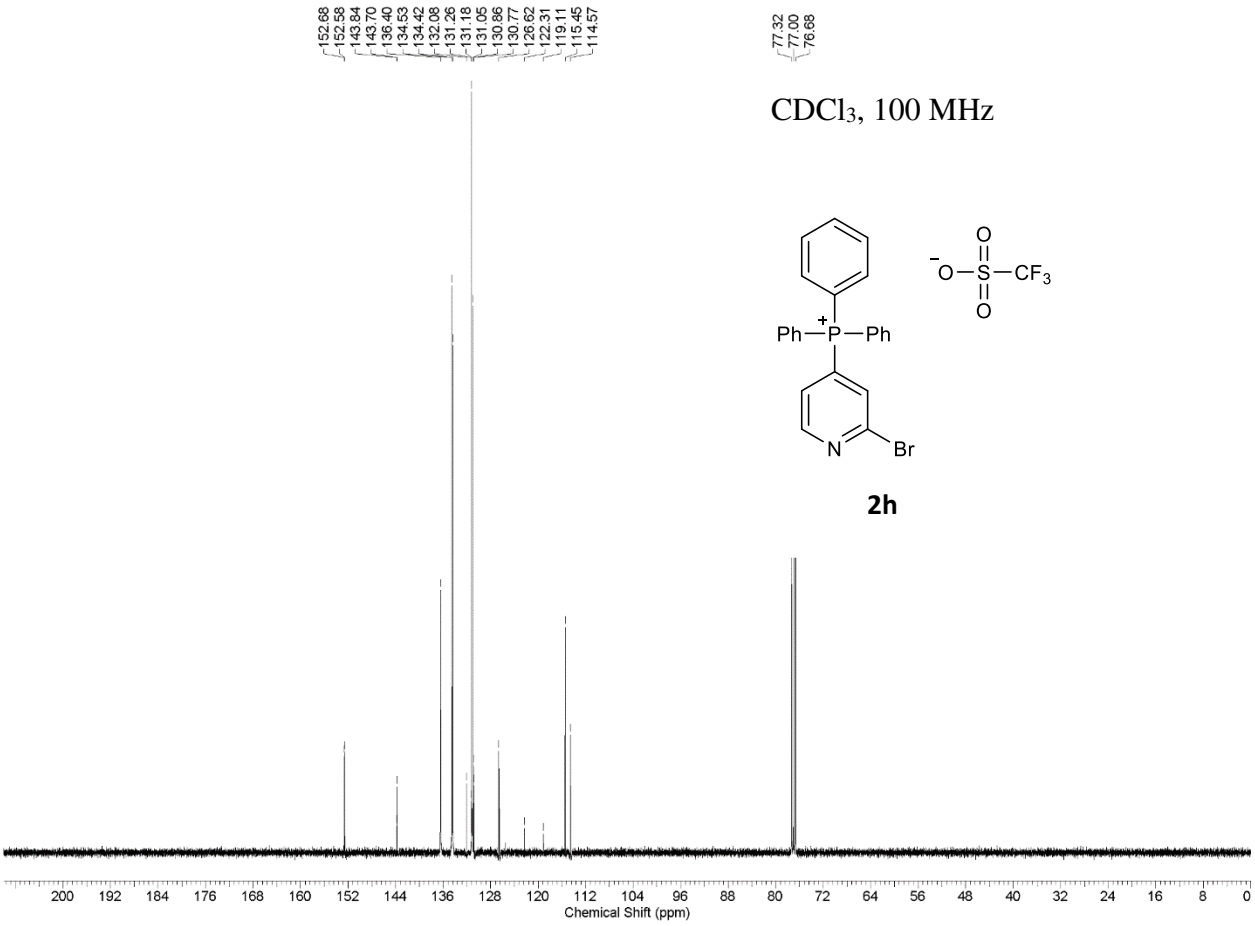


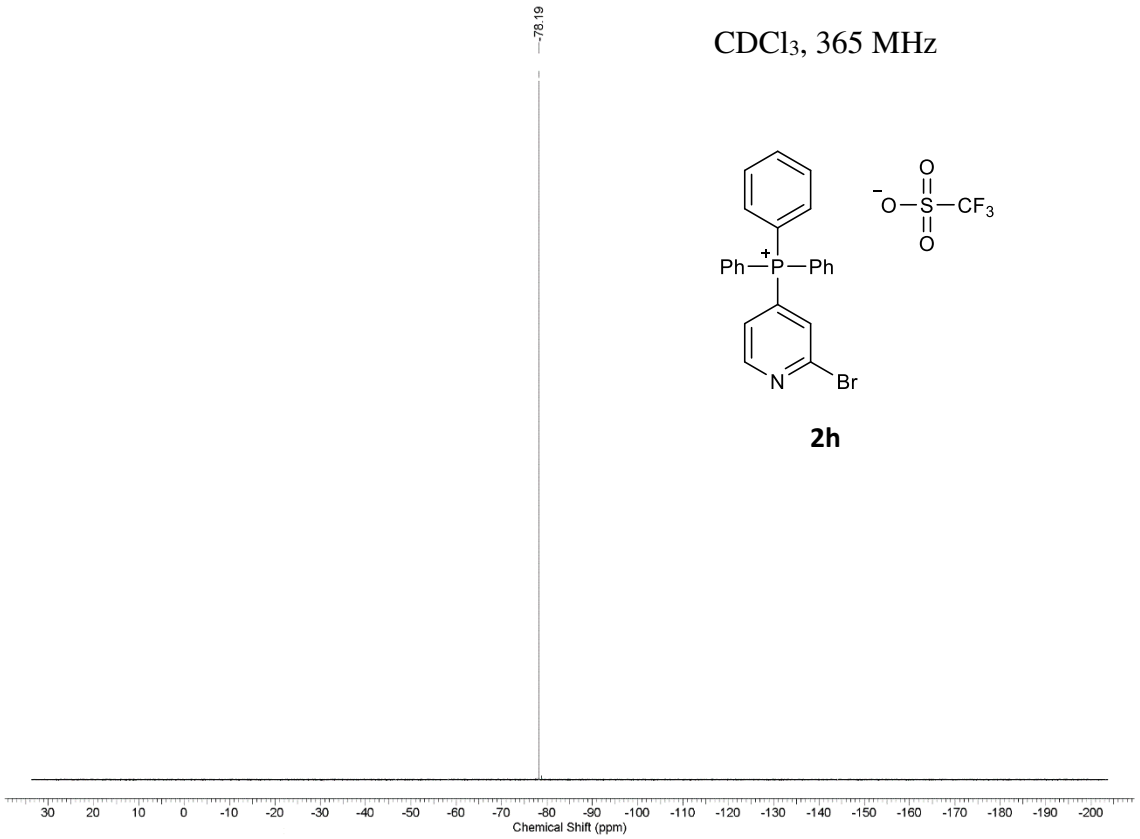
2g



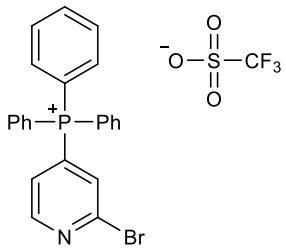
$CDCl_3$, 400 MHz

2h


152.68
152.58
143.84
143.70
136.40
134.53
134.42
132.06
131.26
131.18
131.05
130.86
130.77
126.62
122.31
119.11
115.45
114.57
77.32
77.00
76.68
CDCl3, 100 MHz
Ph
P
Ph
N
Br
O
S
CF3
2h
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

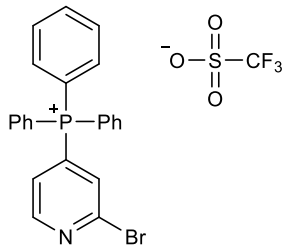

-78.19
CDCl3, 365 MHz
Ph
P
Ph
N
Br
O
S
CF3
2h
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
Chemical Shift (ppm)

$CDCl_3$, 162 MHz

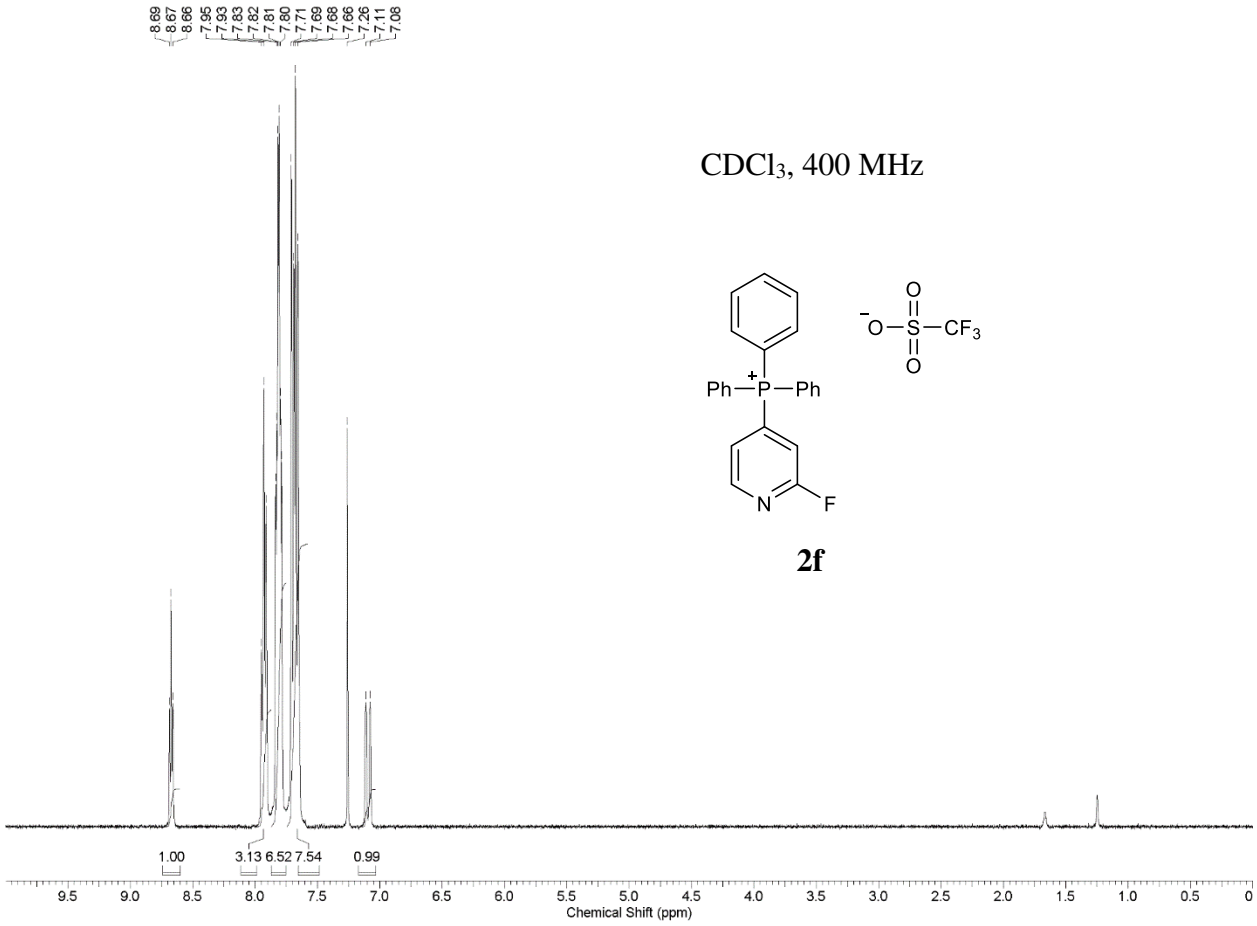


2h

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

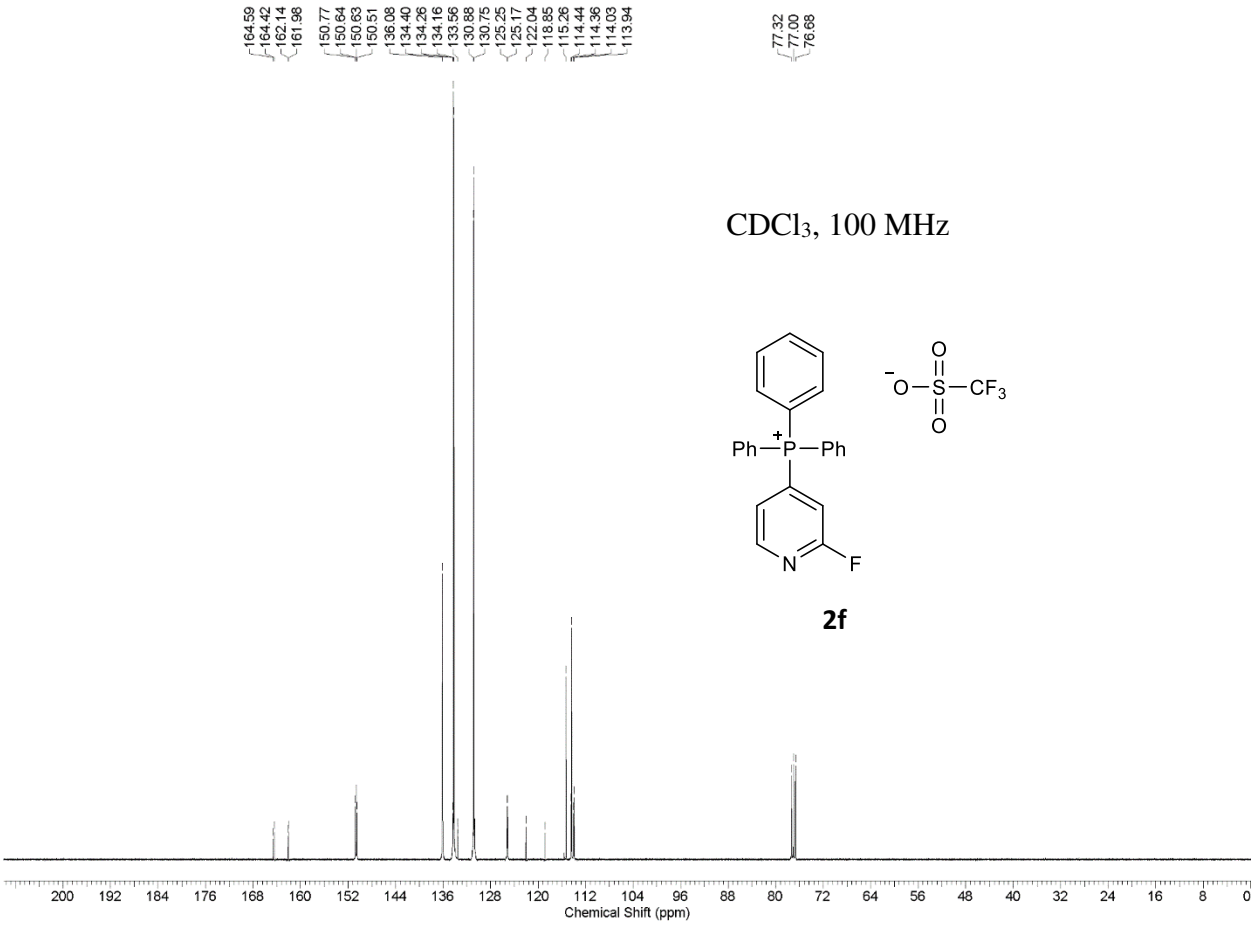


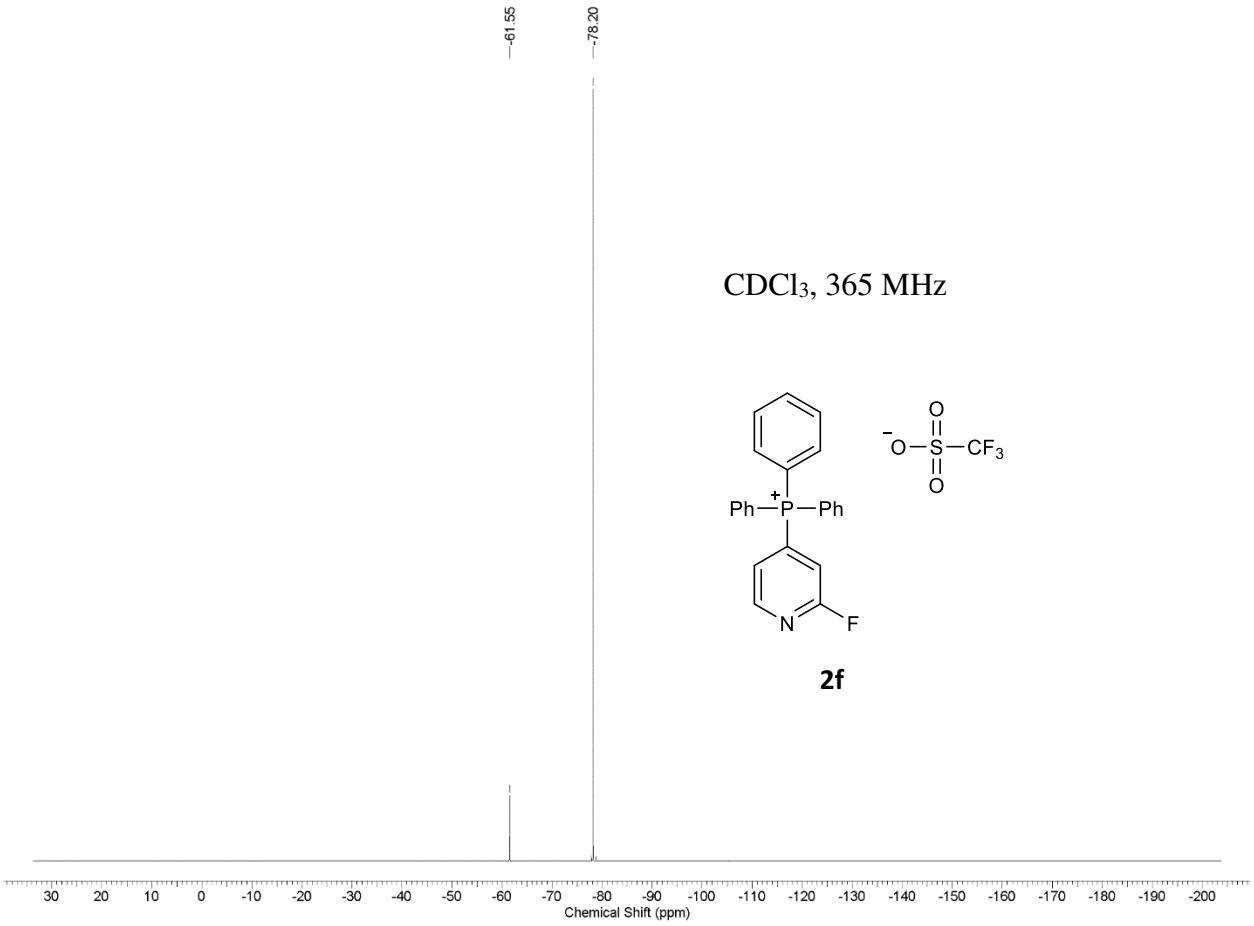
2h



$CDCl_3$, 400 MHz

2f

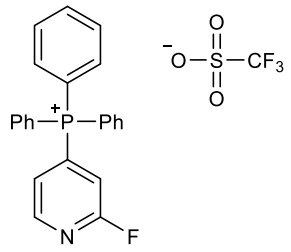

164.59
164.42
162.14
161.98
150.77
150.64
150.63
150.51
136.08
134.40
134.26
134.16
133.56
130.88
130.75
125.25
125.17
122.04
118.85
115.26
114.44
114.36
114.03
113.94
77.32
77.00
76.68
CDCl3, 100 MHz
Ph—P—Ph
N
F
O—S—CF3
2f
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



$CDCl_3$, 365 MHz

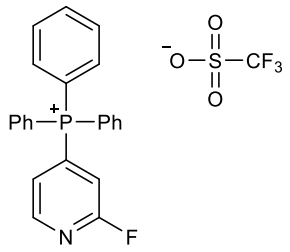
2f

$CDCl_3$, 162 MHz

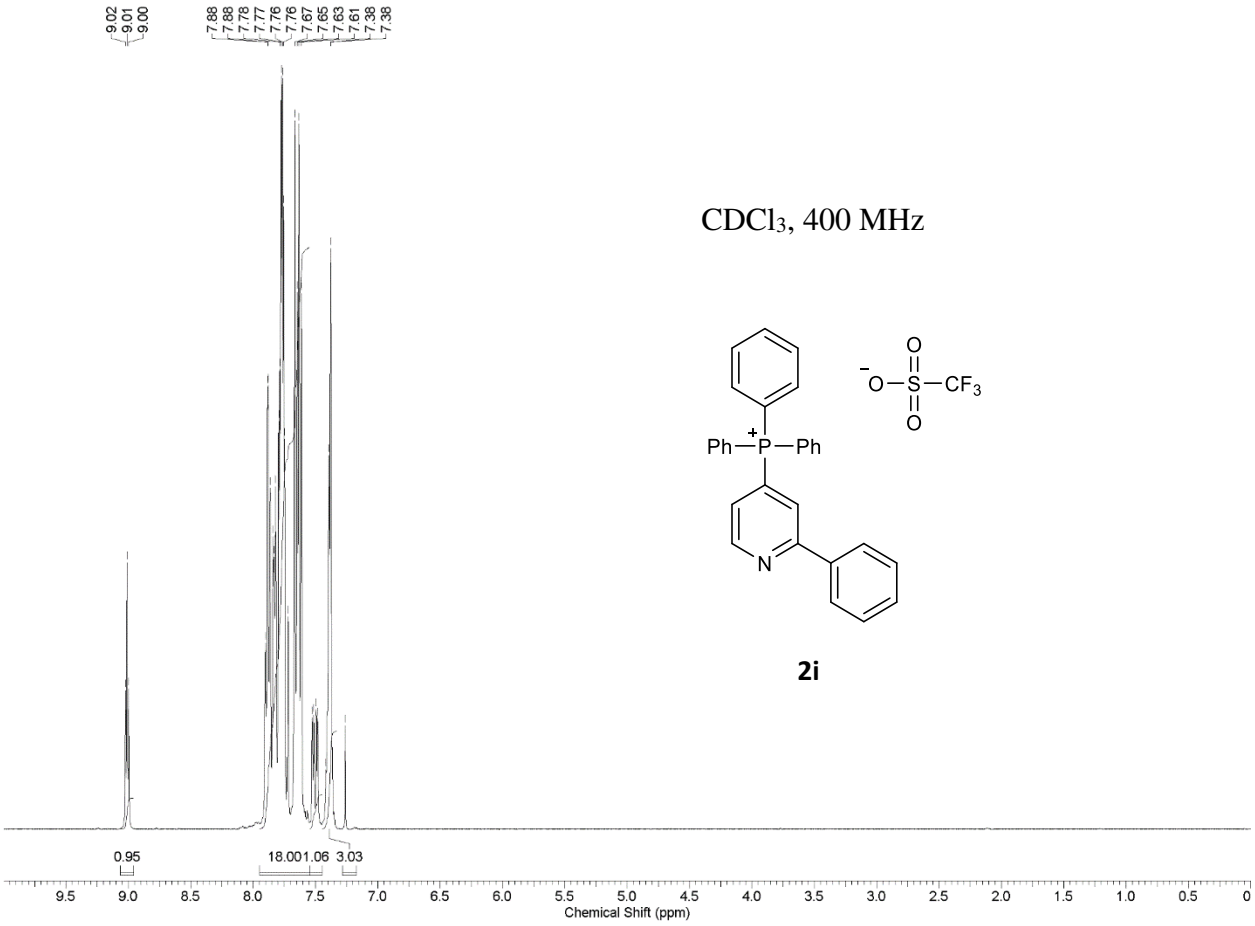


2f

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

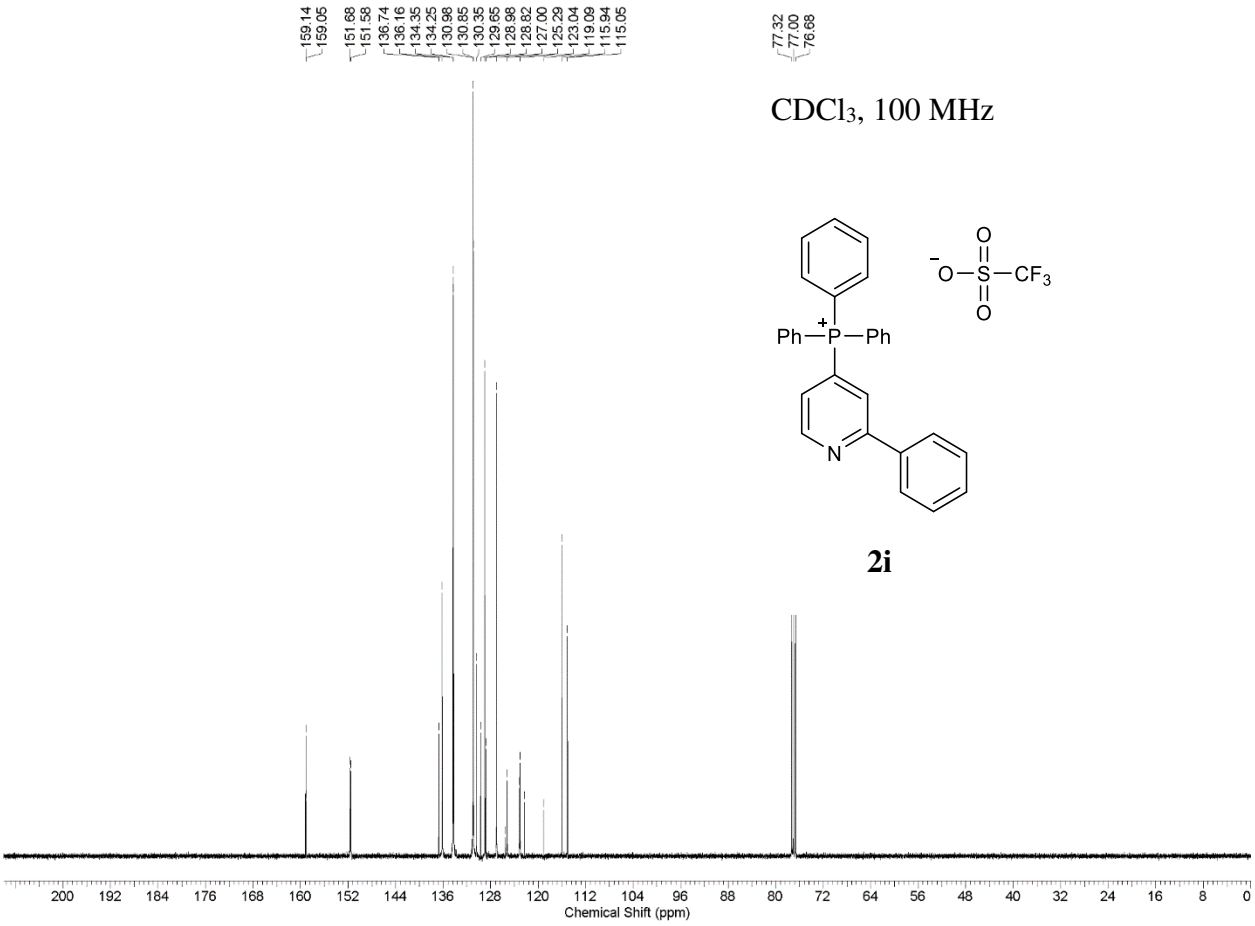


2f



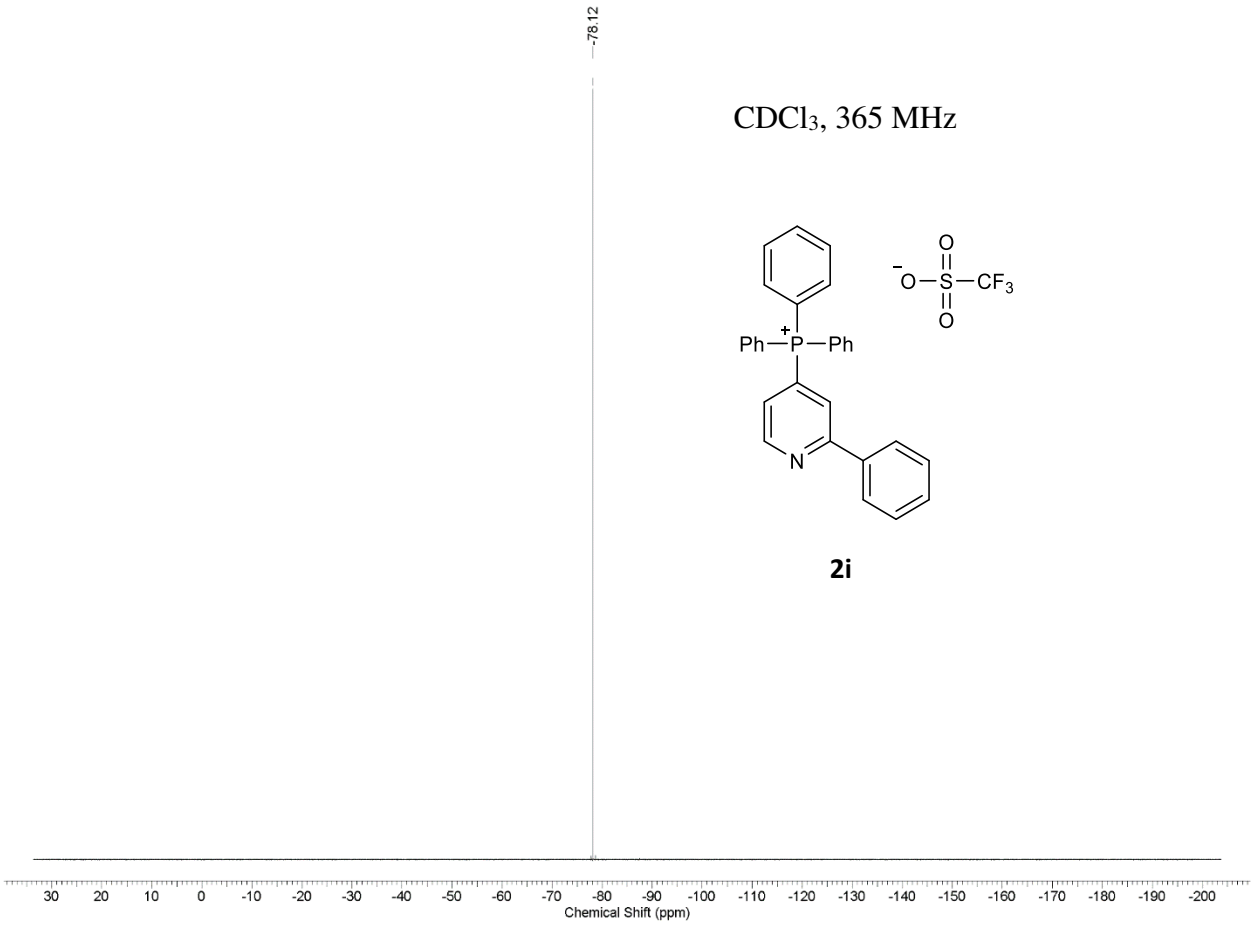
$CDCl_3$, 400 MHz

2i



$CDCl_3$, 100 MHz

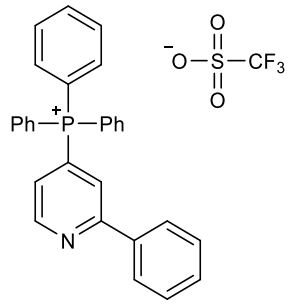
2i



$CDCl_3$, 365 MHz

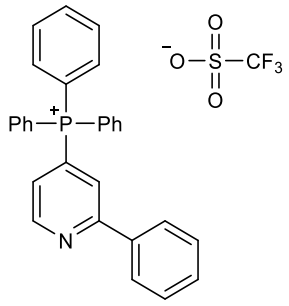
2i

$CDCl_3$, 162 MHz

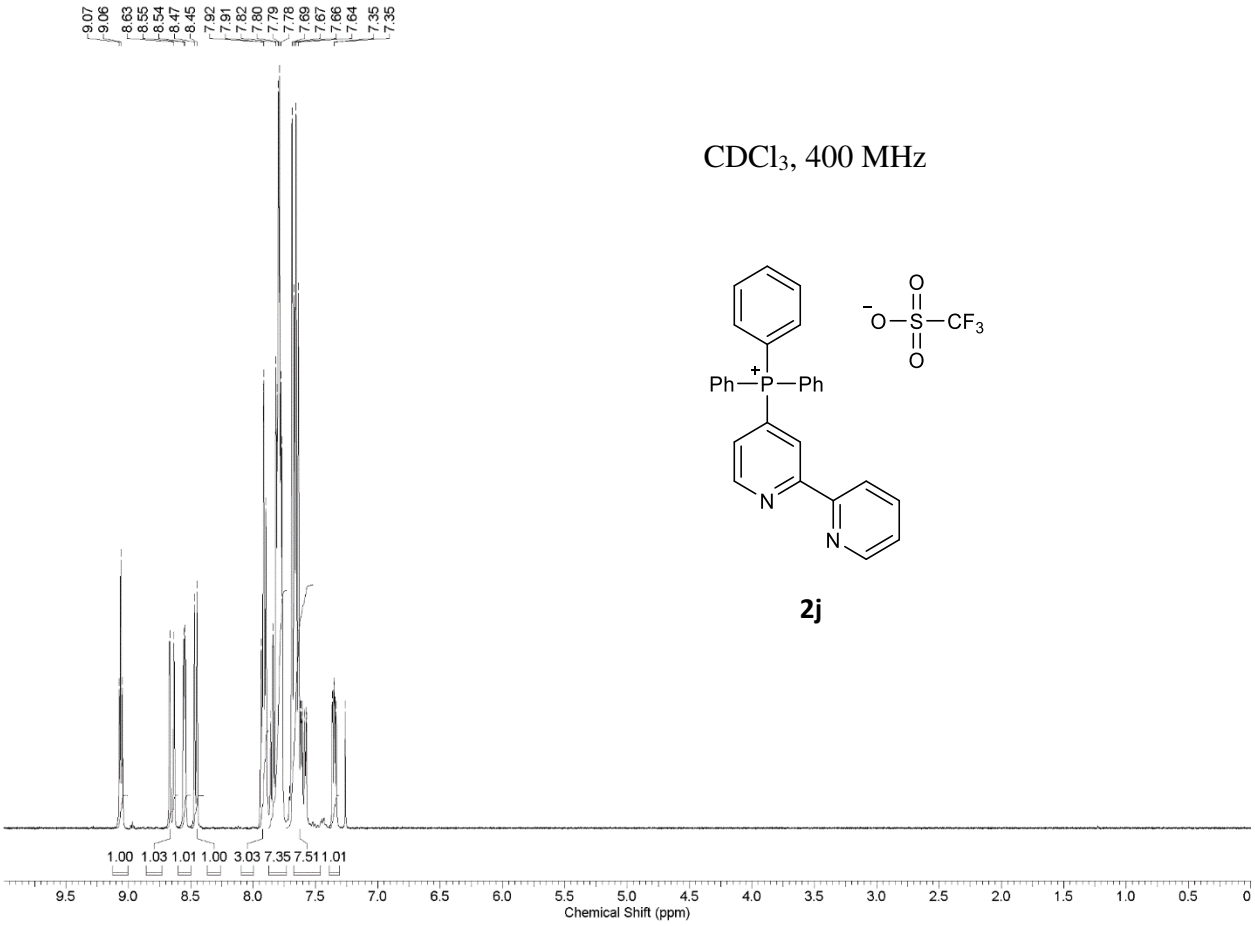


2i

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

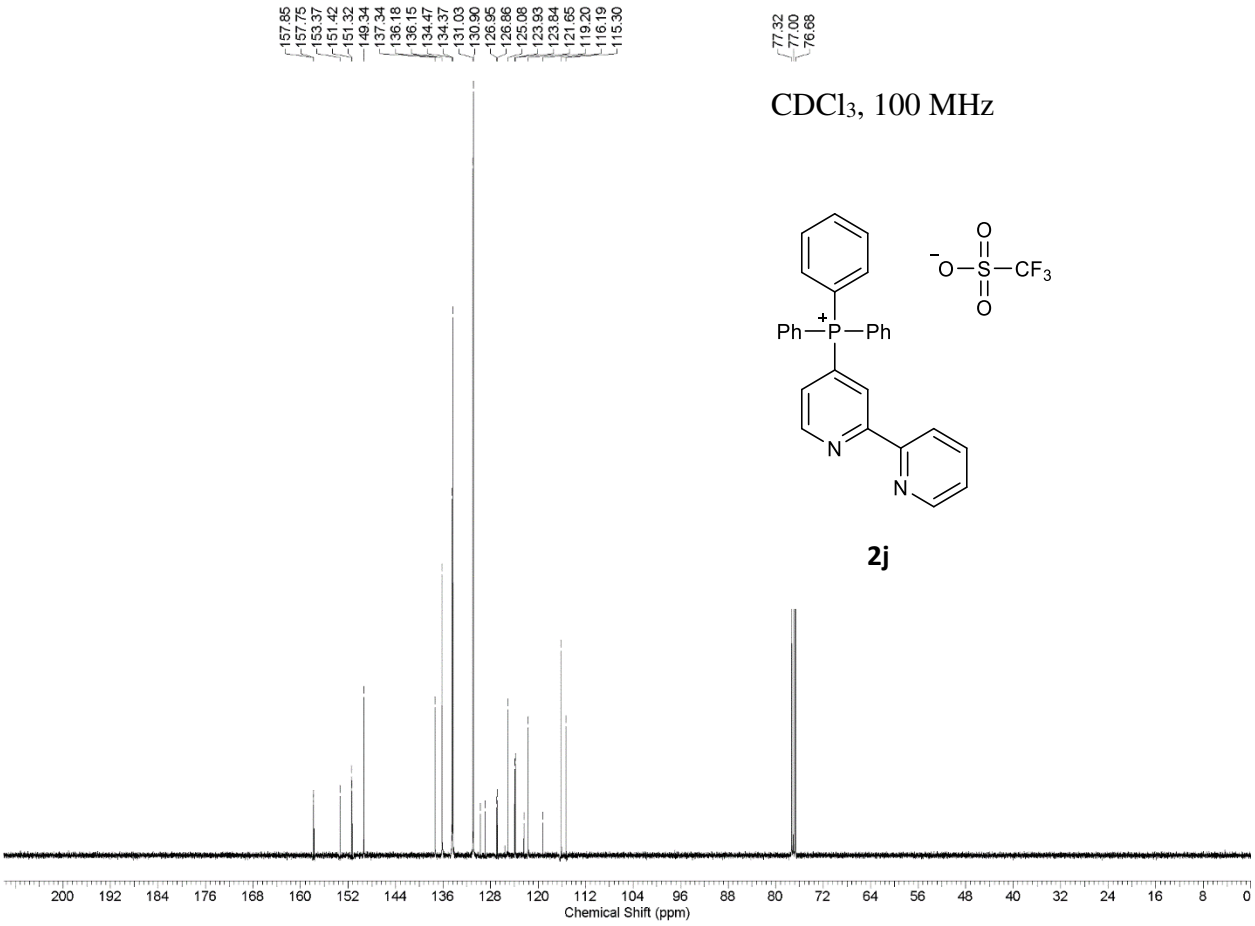


2i



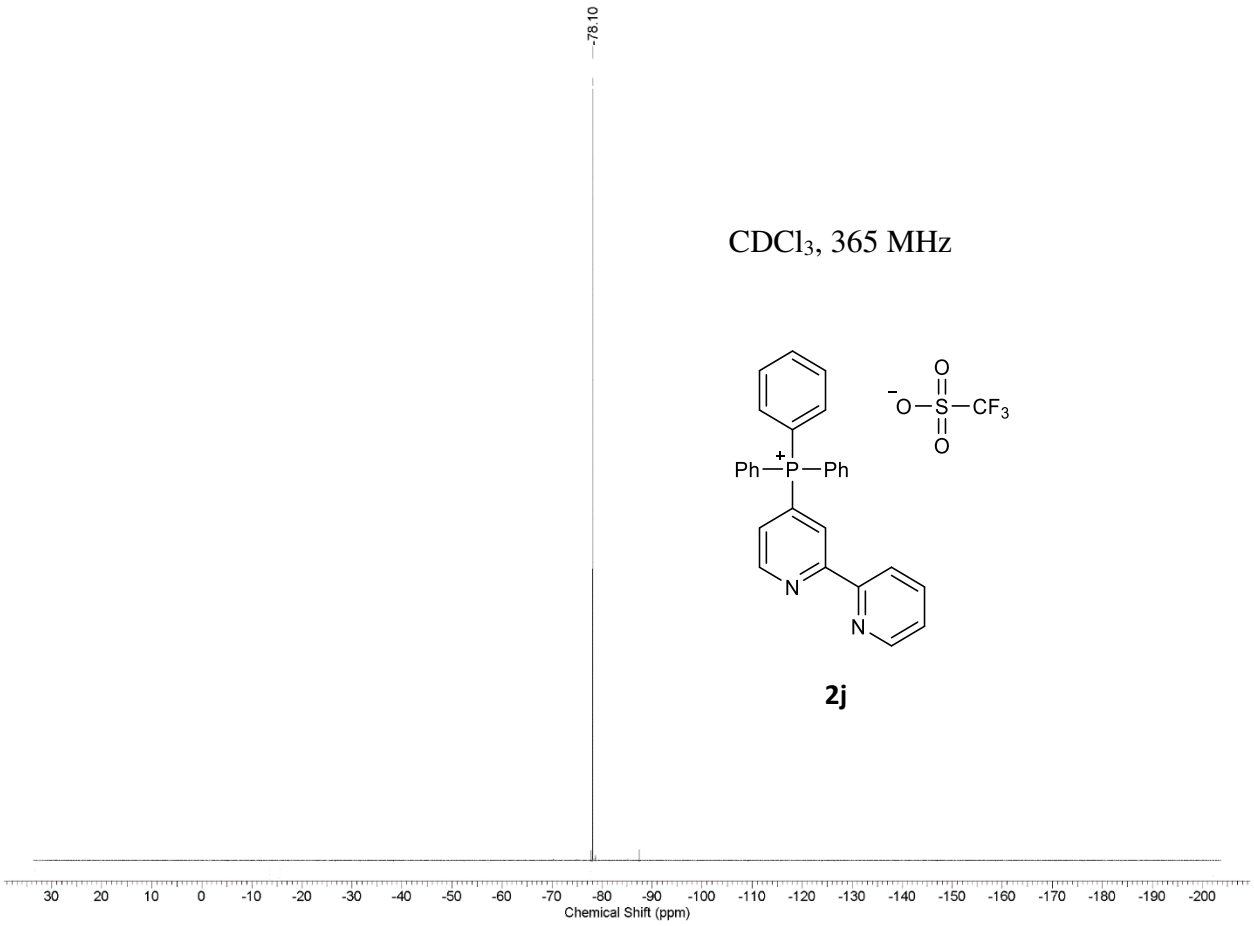
$CDCl_3$, 400 MHz

2j



$CDCl_3$, 100 MHz

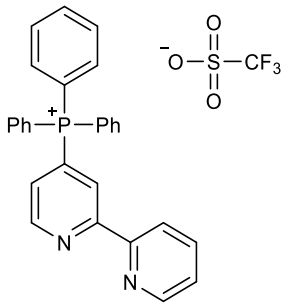
2j



$CDCl_3$, 365 MHz

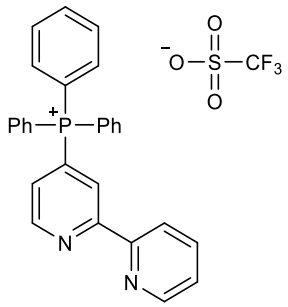
2j

$CDCl_3$, 162 MHz

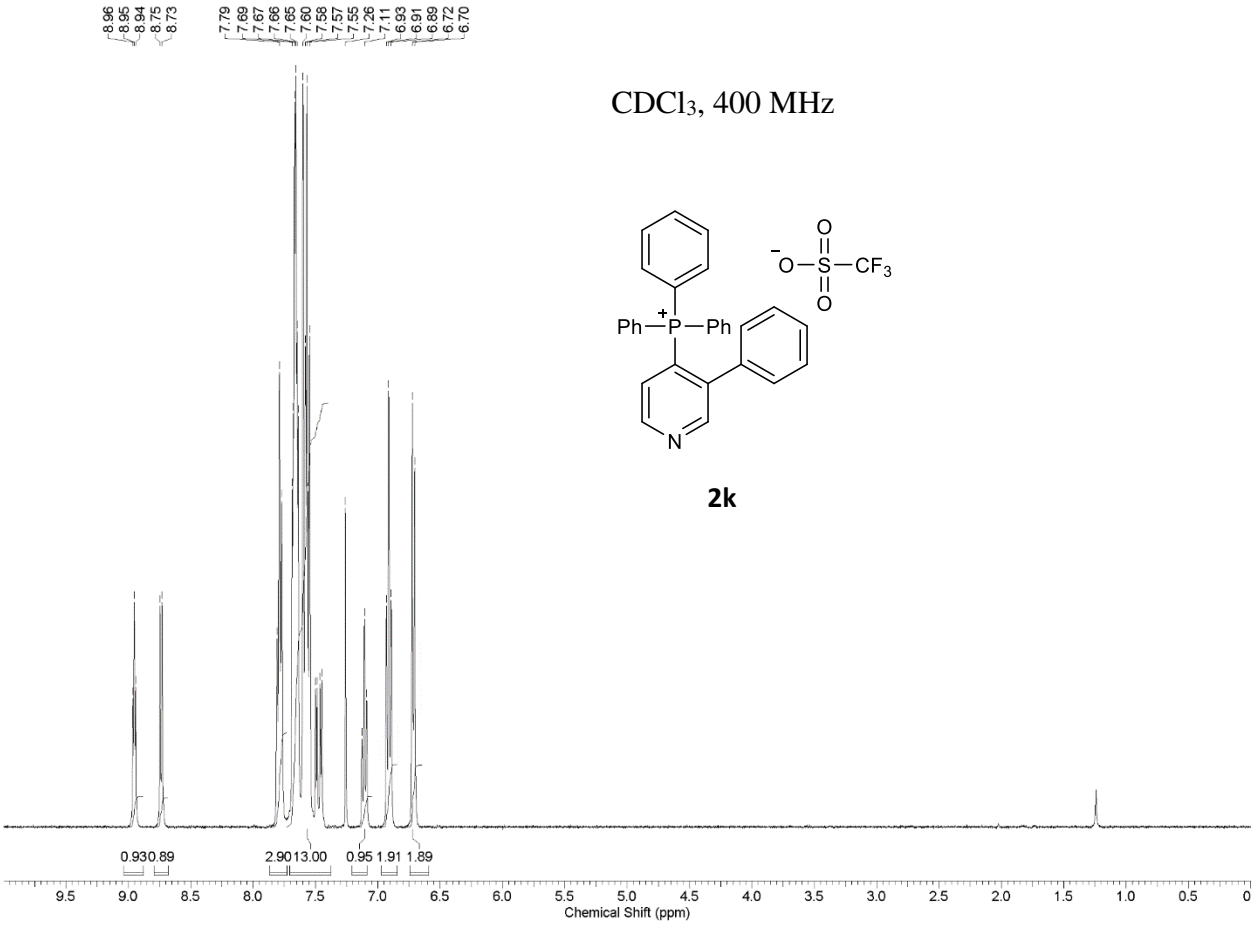


2j

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

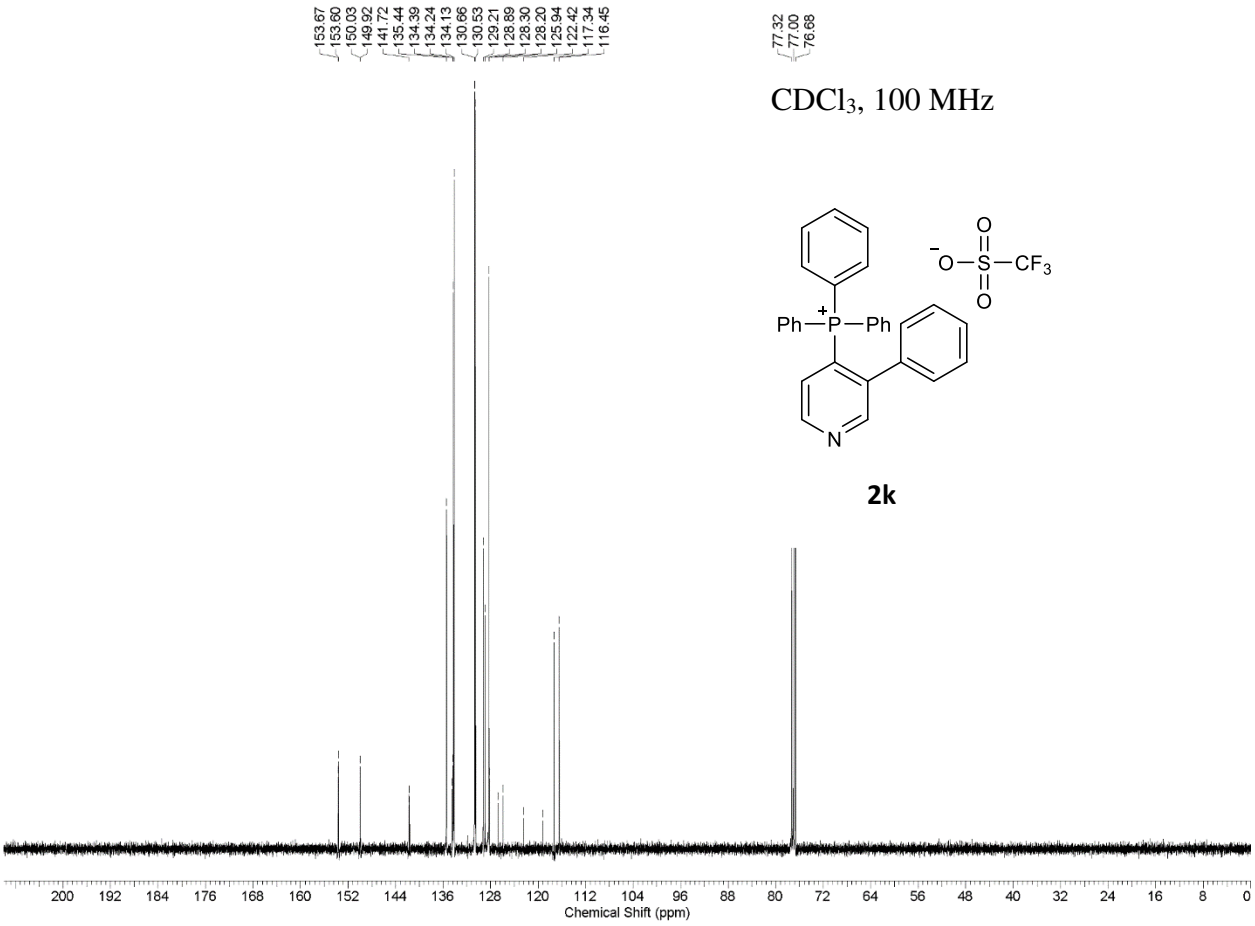


2j



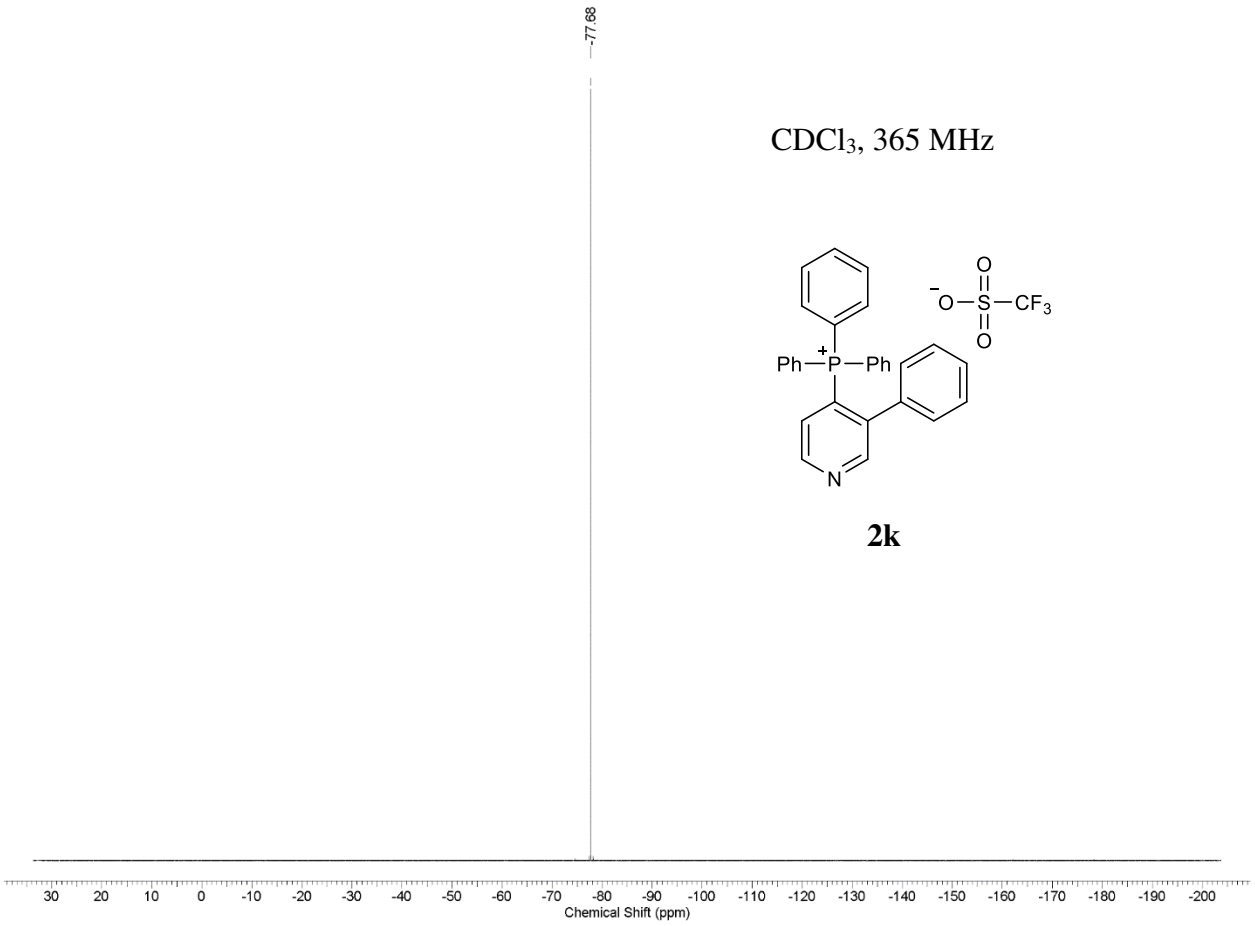
$CDCl_3$, 400 MHz

2k



$CDCl_3$, 100 MHz

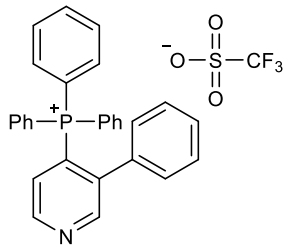
2k



$CDCl_3$, 365 MHz

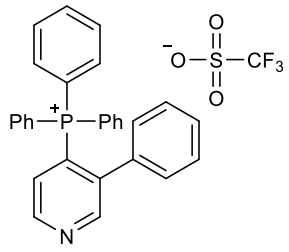
2k

$CDCl_3$, 162 MHz

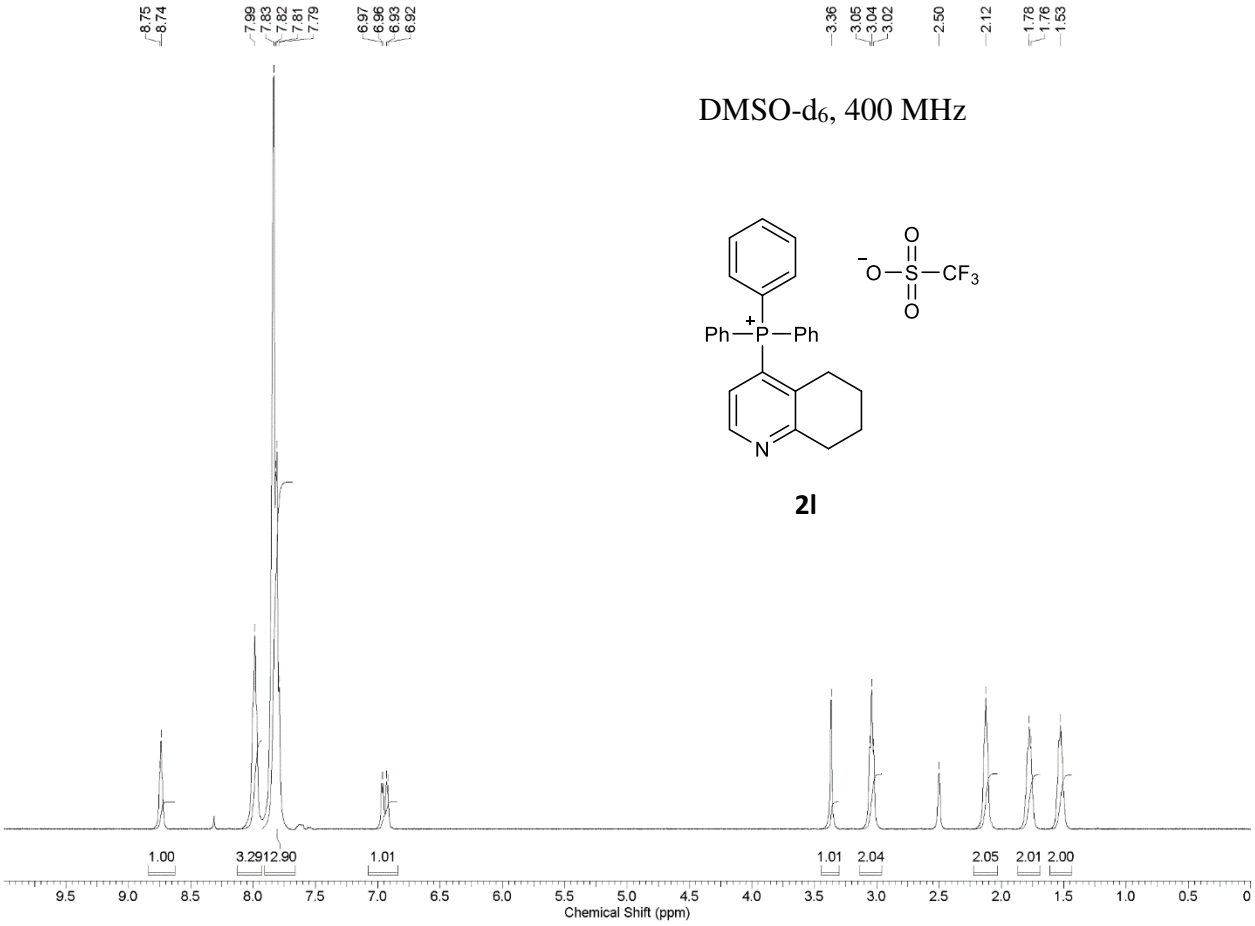


2k

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



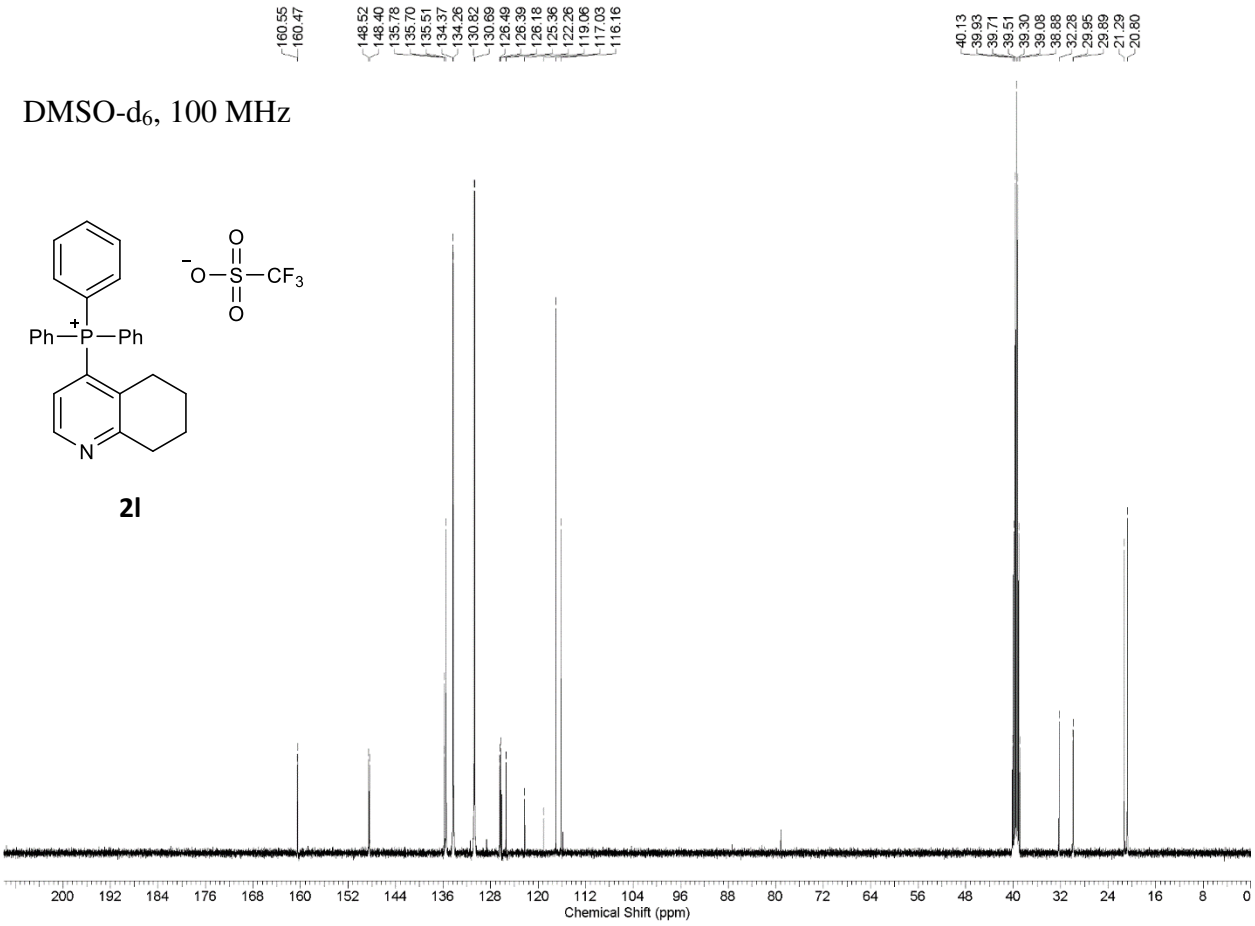
2k



DMSO-d_6, 400 MHz

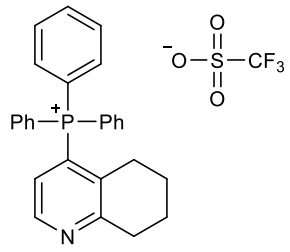
2l

DMSO-d_6, 100 MHz



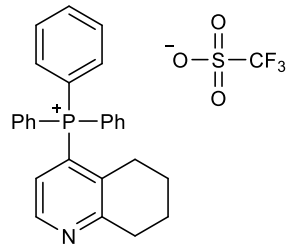
2l

DMSO-d_6, 365 MHz



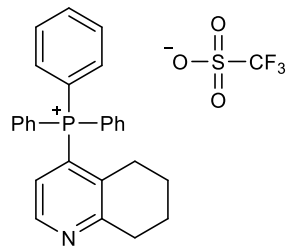
2l

DMSO-d_6, 162 MHz

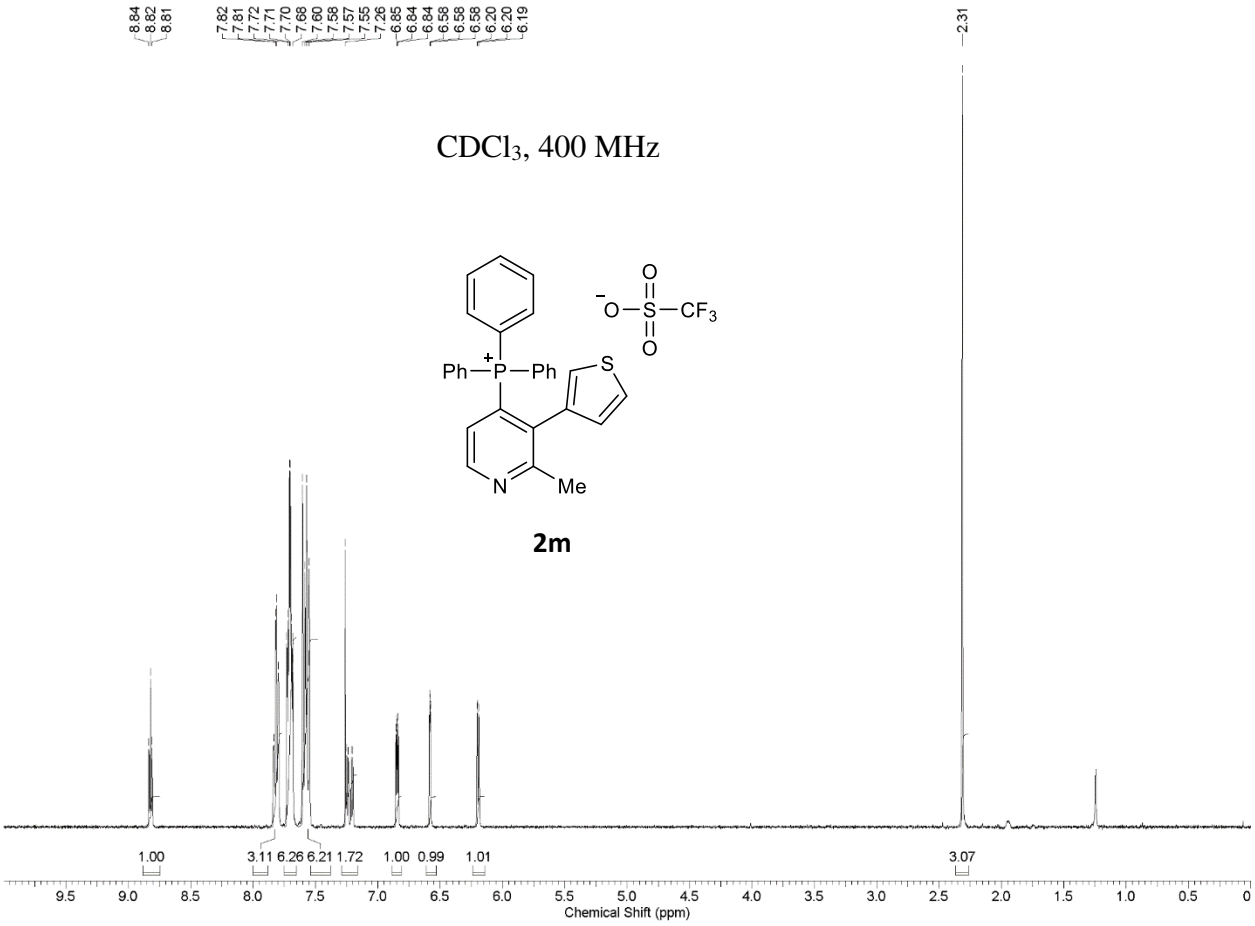


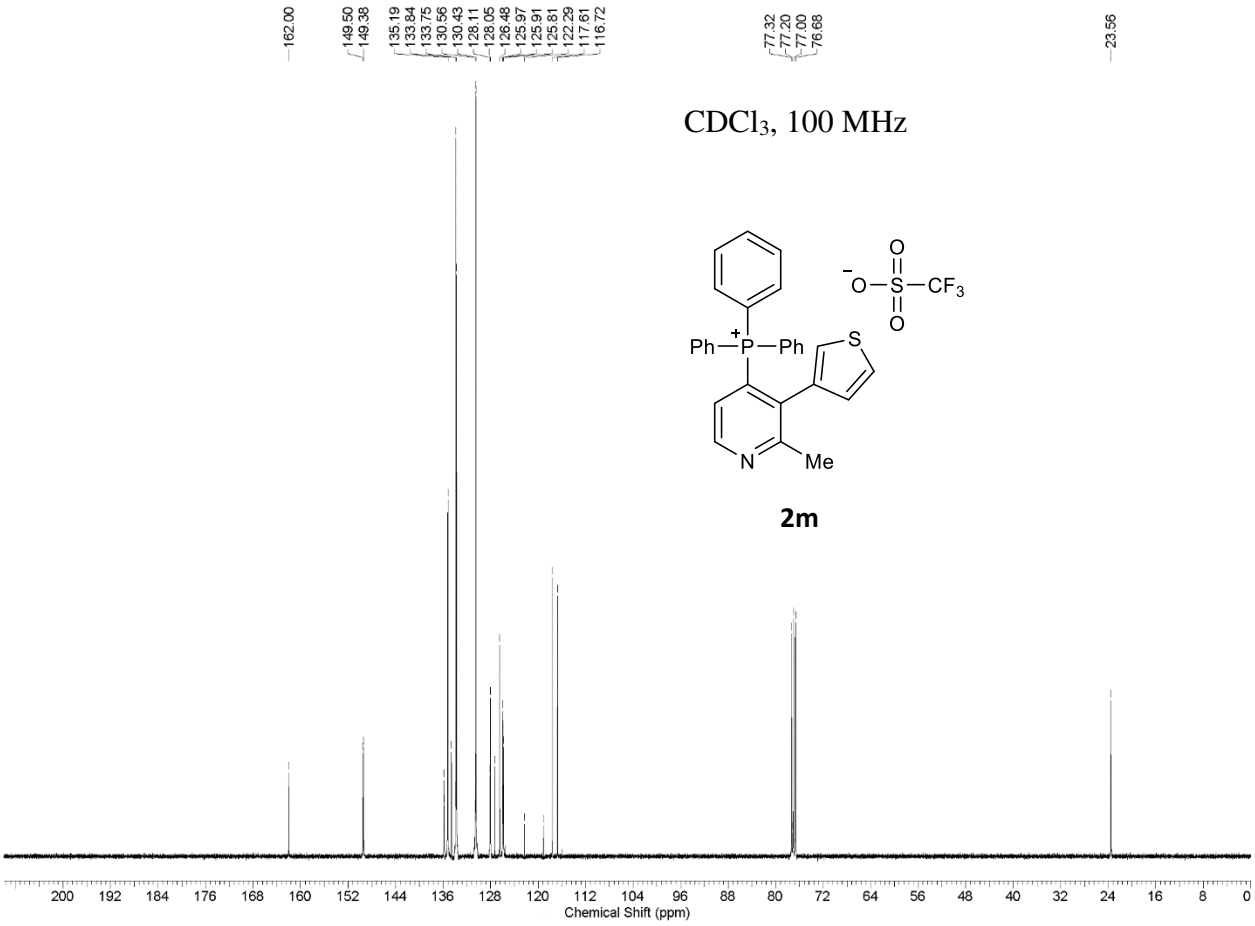
2l

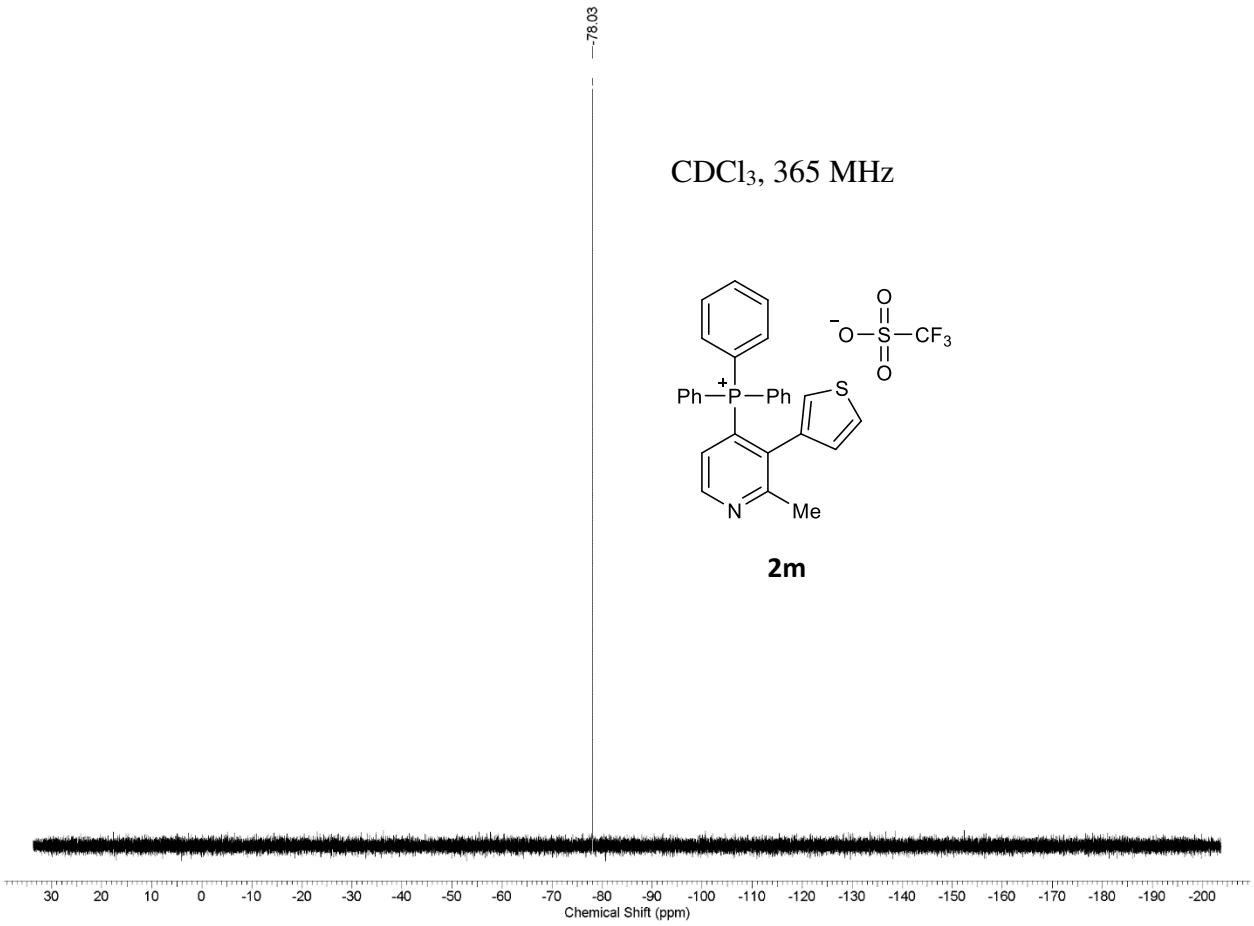
DMSO-d_6, 162 MHz (crude ^{31}P NMR)



2l


8.84
8.82
8.81
7.82
7.81
7.72
7.71
7.70
7.68
7.60
7.58
7.57
7.55
7.26
6.85
6.84
6.84
6.58
6.58
6.58
6.20
6.20
6.19
2.31
CDCl3, 400 MHz
Ph
P
Ph
S
O
S
CF3
N
Me
2m
1.00
3.11
6.26
6.21
1.72
1.00
0.99
1.01
3.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

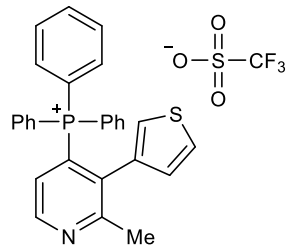

162.00
149.50
149.38
135.19
133.84
133.75
130.56
130.43
128.11
128.05
126.48
125.97
125.91
125.81
122.29
117.61
116.72
77.32
77.20
77.00
76.68
23.56
CDCl3, 100 MHz
Ph
P
Ph
S
N
Me
O
O
S
CF3
O
2m
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



$CDCl_3$, 365 MHz

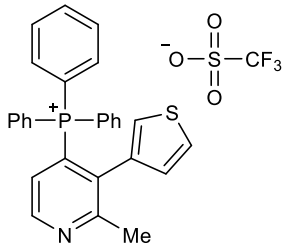
2m

$CDCl_3$, 162 MHz

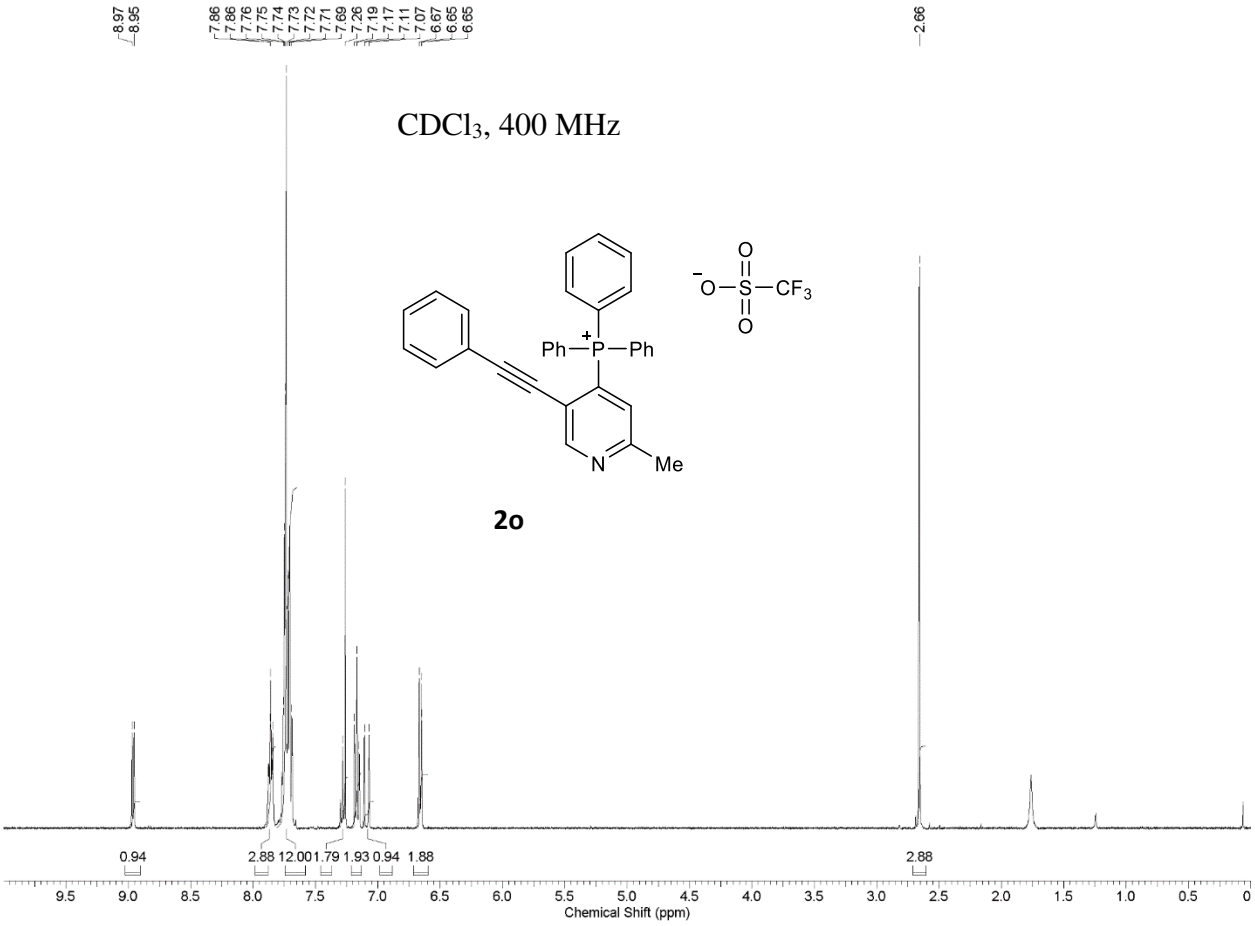


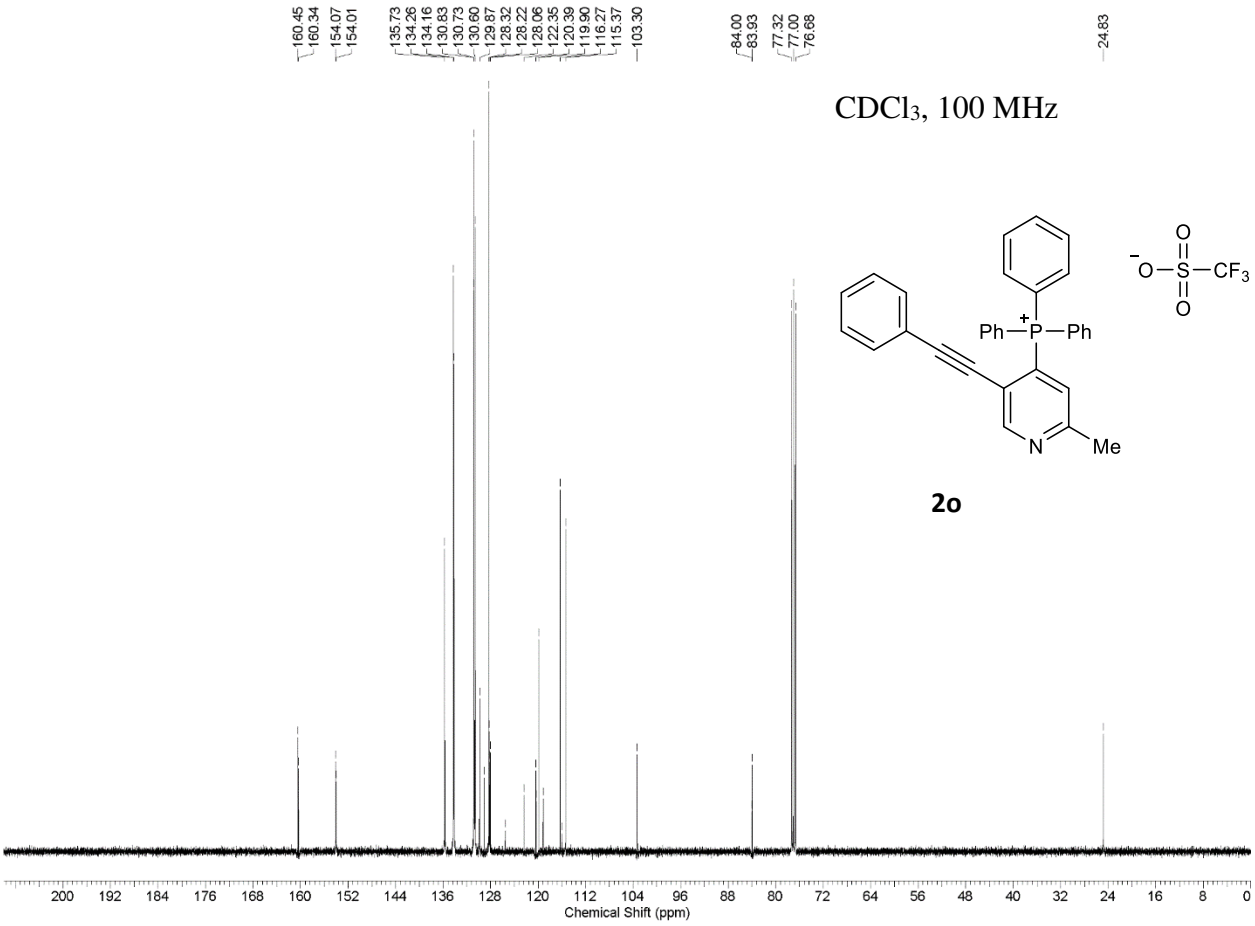
2m

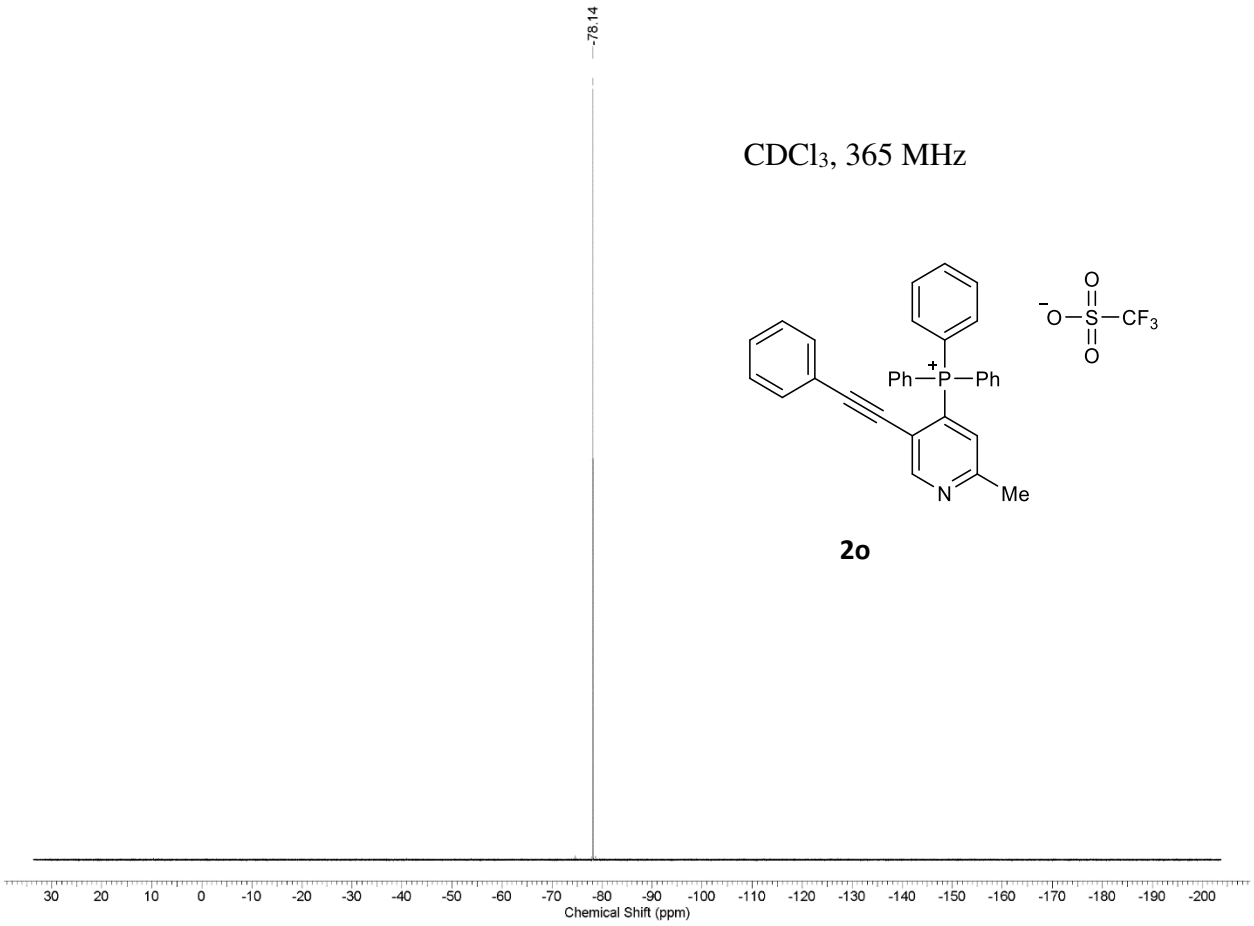
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



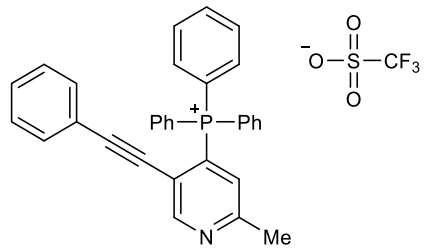
2m


8.97
8.95
7.86
7.86
7.76
7.75
7.74
7.73
7.72
7.71
7.69
7.26
7.19
7.17
7.11
7.07
6.67
6.65
6.65
2.66
CDCl3, 400 MHz
Ph
P
Ph
O
S
CF3
N
Me
2o
0.94
2.88
12.00
1.79
1.93
0.94
1.88
2.88
Chemical Shift (ppm)


160.45
160.34
154.07
154.01
135.73
134.26
134.16
130.83
130.73
130.60
129.87
128.32
128.22
128.06
122.35
120.39
119.90
116.27
115.37
103.30
84.00
83.93
77.32
77.00
76.68
24.83
CDCl3, 100 MHz
Ph
P
Ph
N
Me
O
S
CF3
2o
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

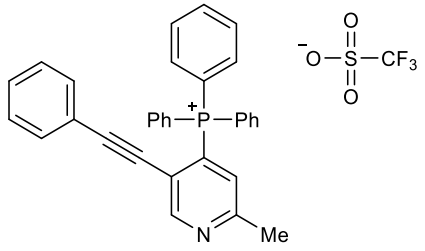

-78.14
CDCl3, 365 MHz
Ph
P
Ph
O
S
CF3
N
Me
2o
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
Chemical Shift (ppm)

$CDCl_3$, 162 MHz

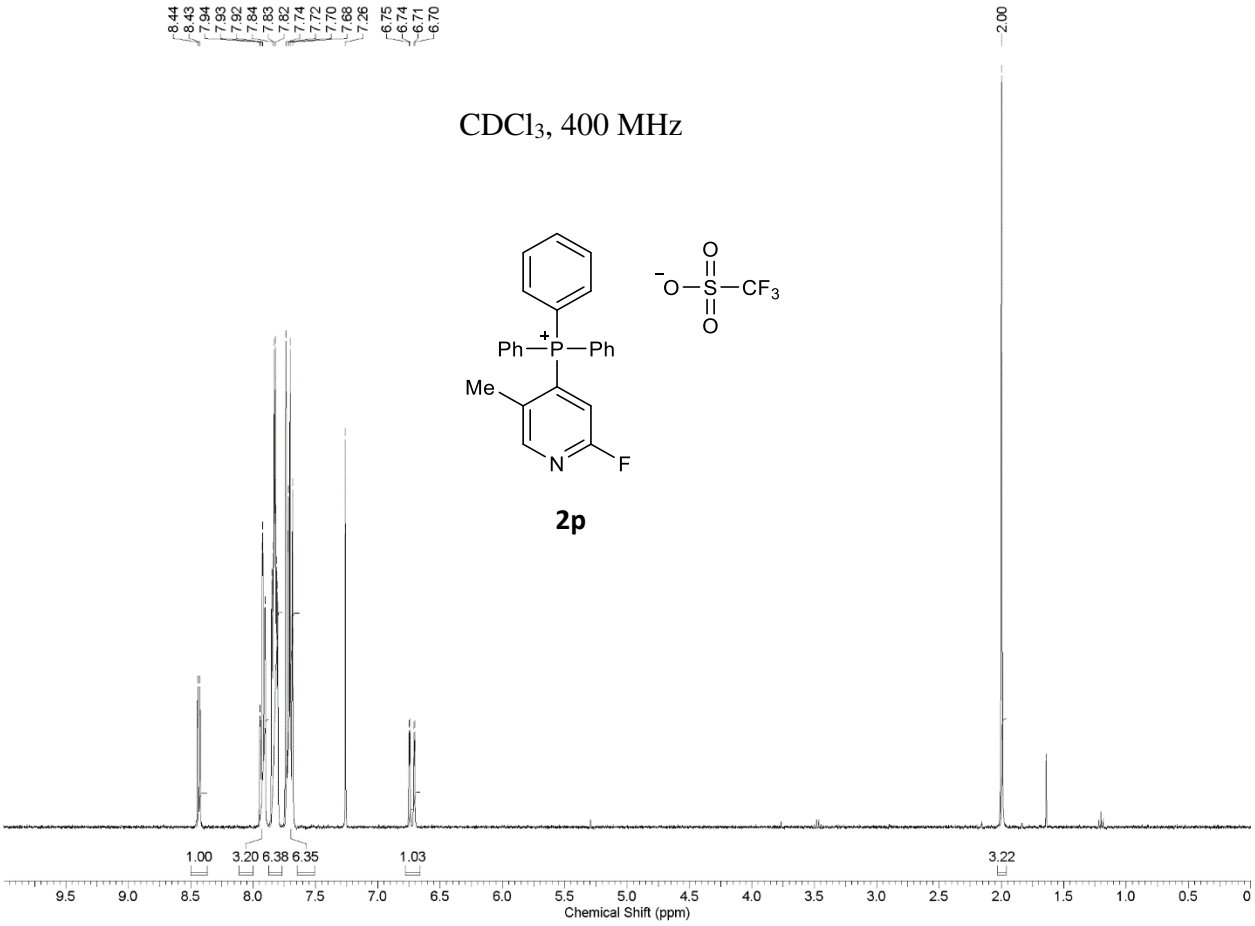


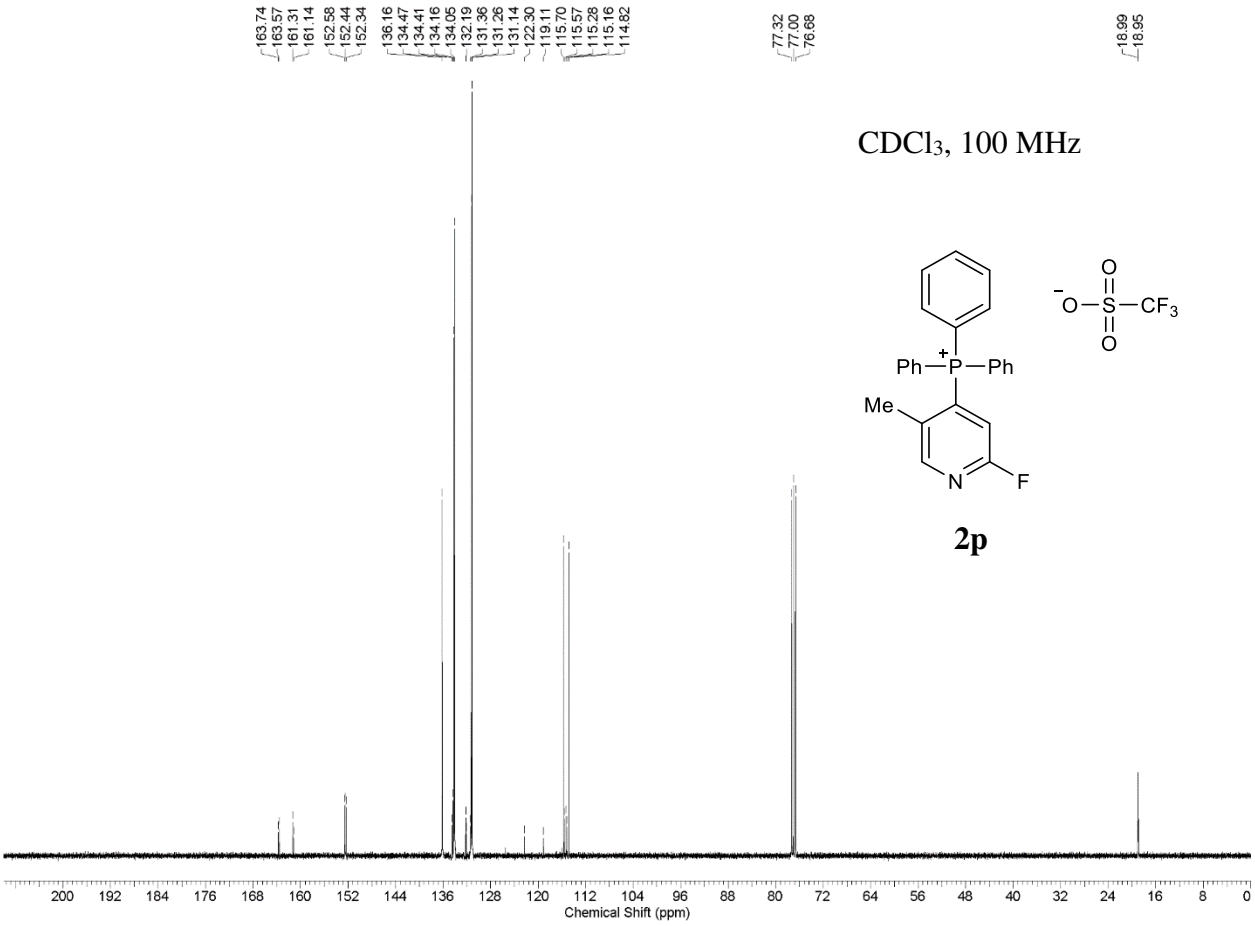
2o

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

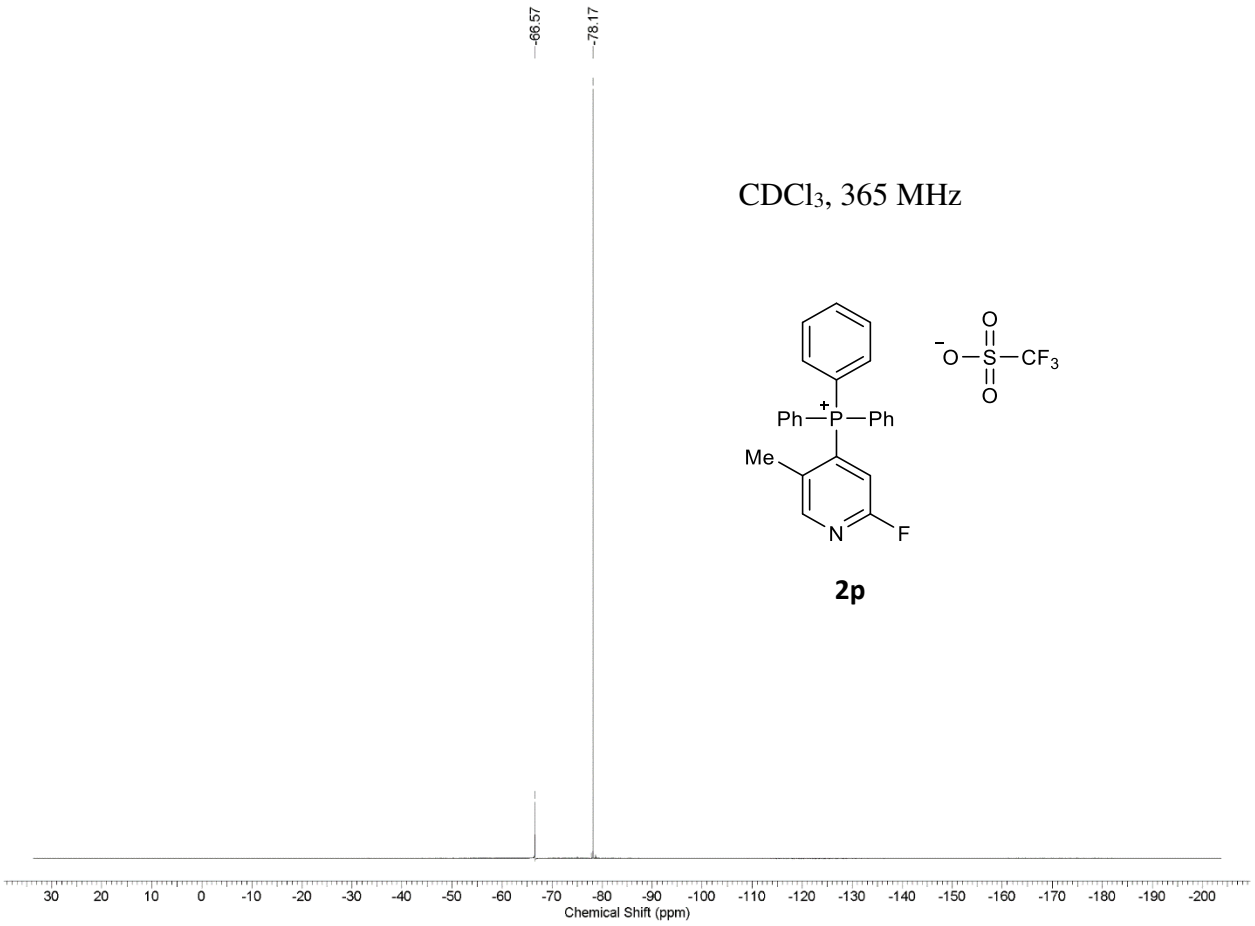


2o

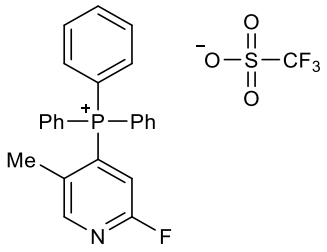

8.44
8.43
7.94
7.93
7.92
7.84
7.83
7.82
7.74
7.72
7.70
7.68
7.26
6.75
6.74
6.71
6.70
2.00
CDCl3, 400 MHz
Ph
P
Ph
Me
N
F
O
O
S
O
CF3
2p
1.00
3.20
6.38
6.35
1.03
3.22
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


163.74
163.57
161.31
161.14
152.58
152.44
152.34
136.16
134.47
134.41
134.16
134.05
132.19
131.36
131.26
131.14
122.30
119.11
115.70
115.57
115.28
115.16
114.82
77.32
77.00
76.68
18.99
18.95
CDCl3, 100 MHz
Ph
P
Ph
Me
N
F
O
S
CF3
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

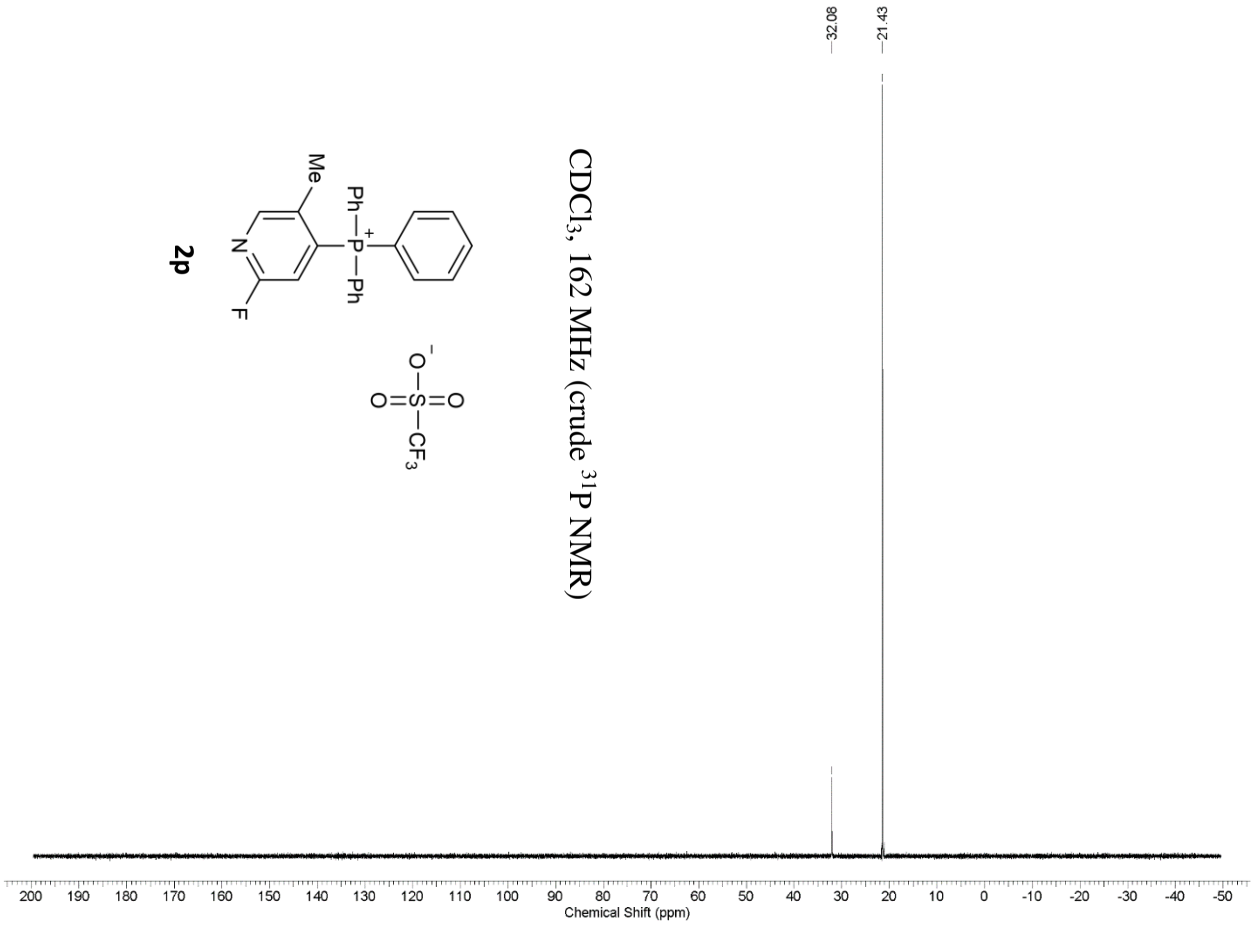
2p


-66.57
-78.17
CDCl3, 365 MHz
Ph
P
Ph
Me
N
F
O
S
CF3
2p
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
Chemical Shift (ppm)

$CDCl_3$, 162 MHz



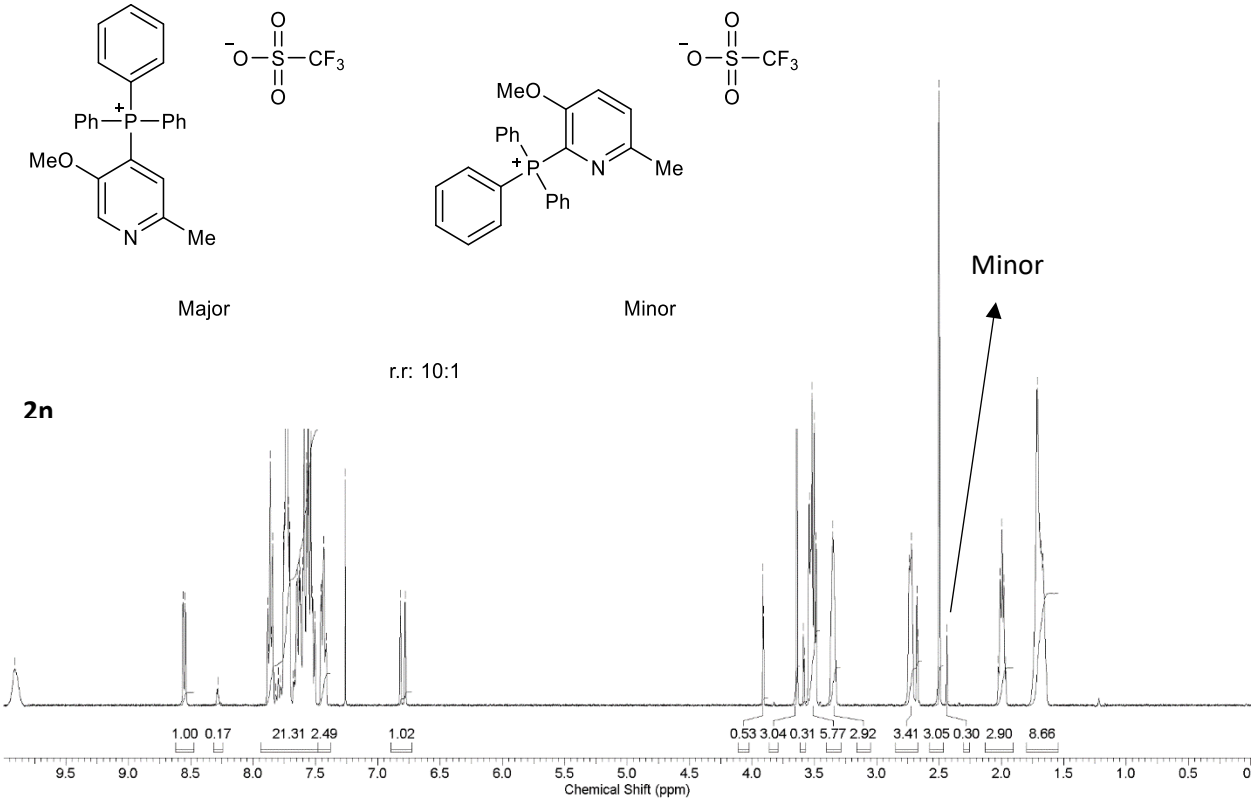
2p



2p

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

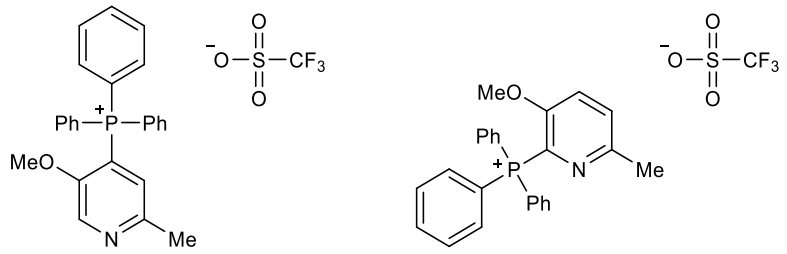
$CDCl_3$, 400 MHz (crude ^1H NMR)



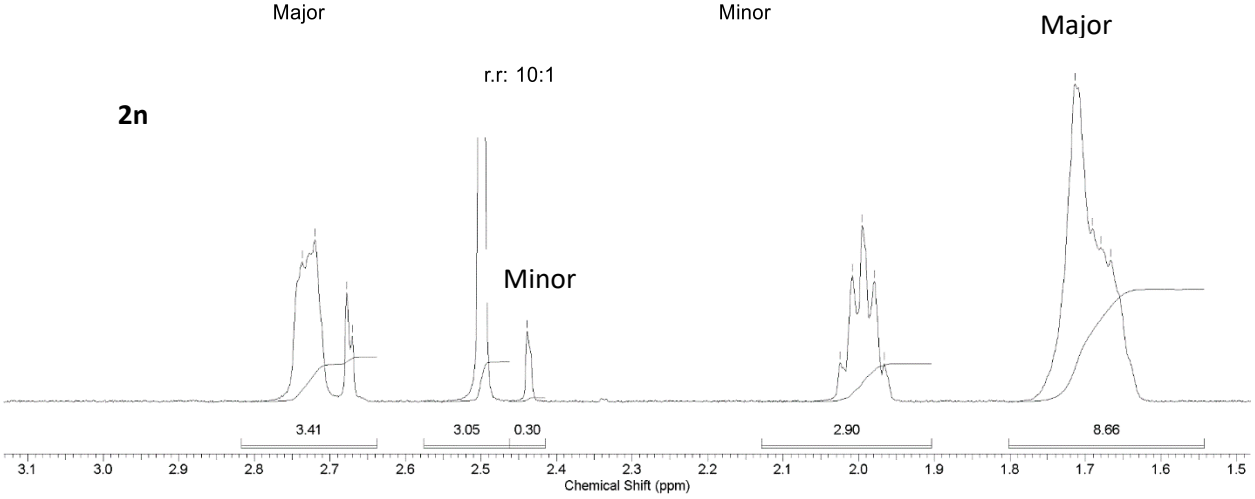
Major

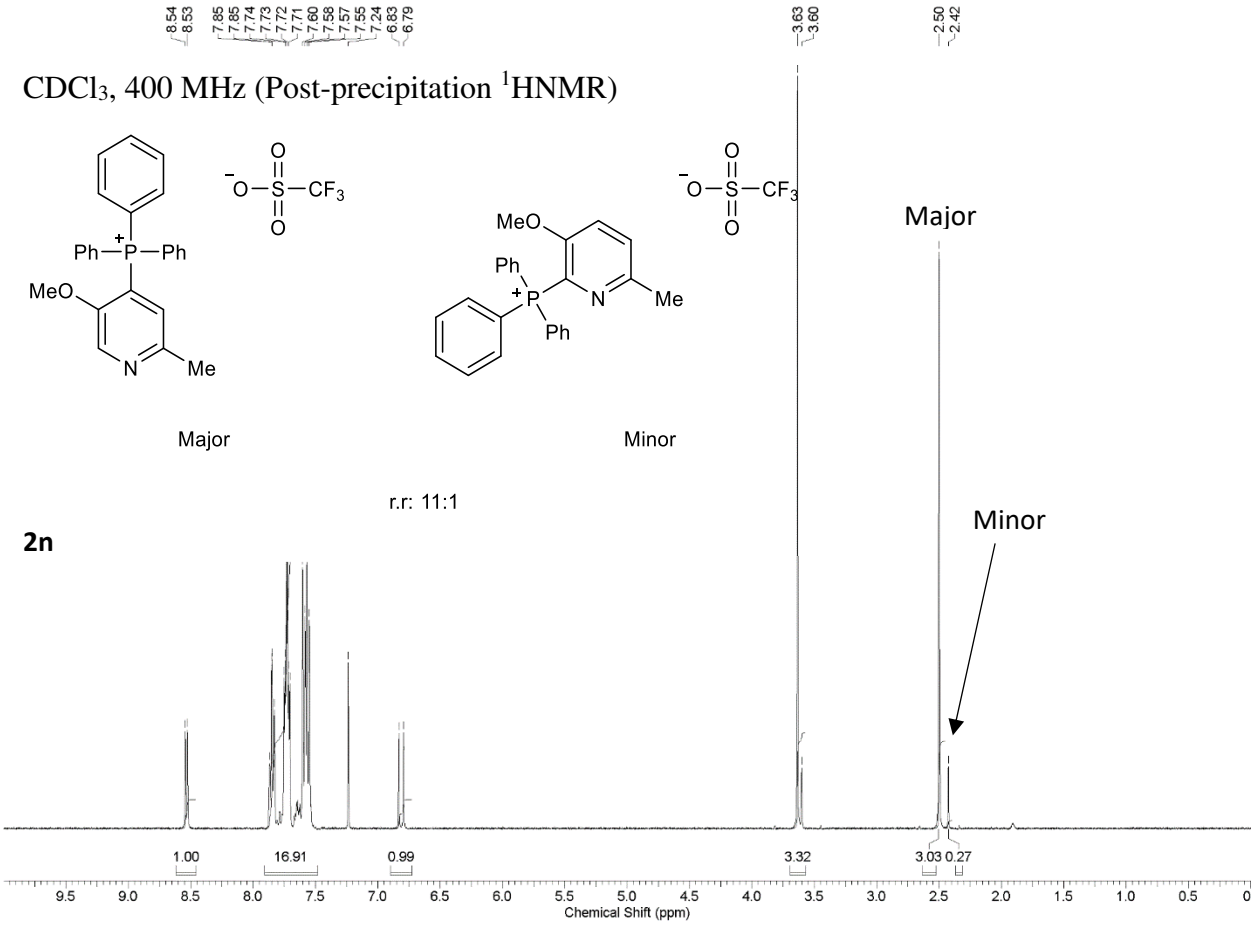
2.74 2.72 2.68 2.67 2.50 2.44 2.03 2.01 2.00 1.98 1.97 1.71 1.69 1.68 1.67

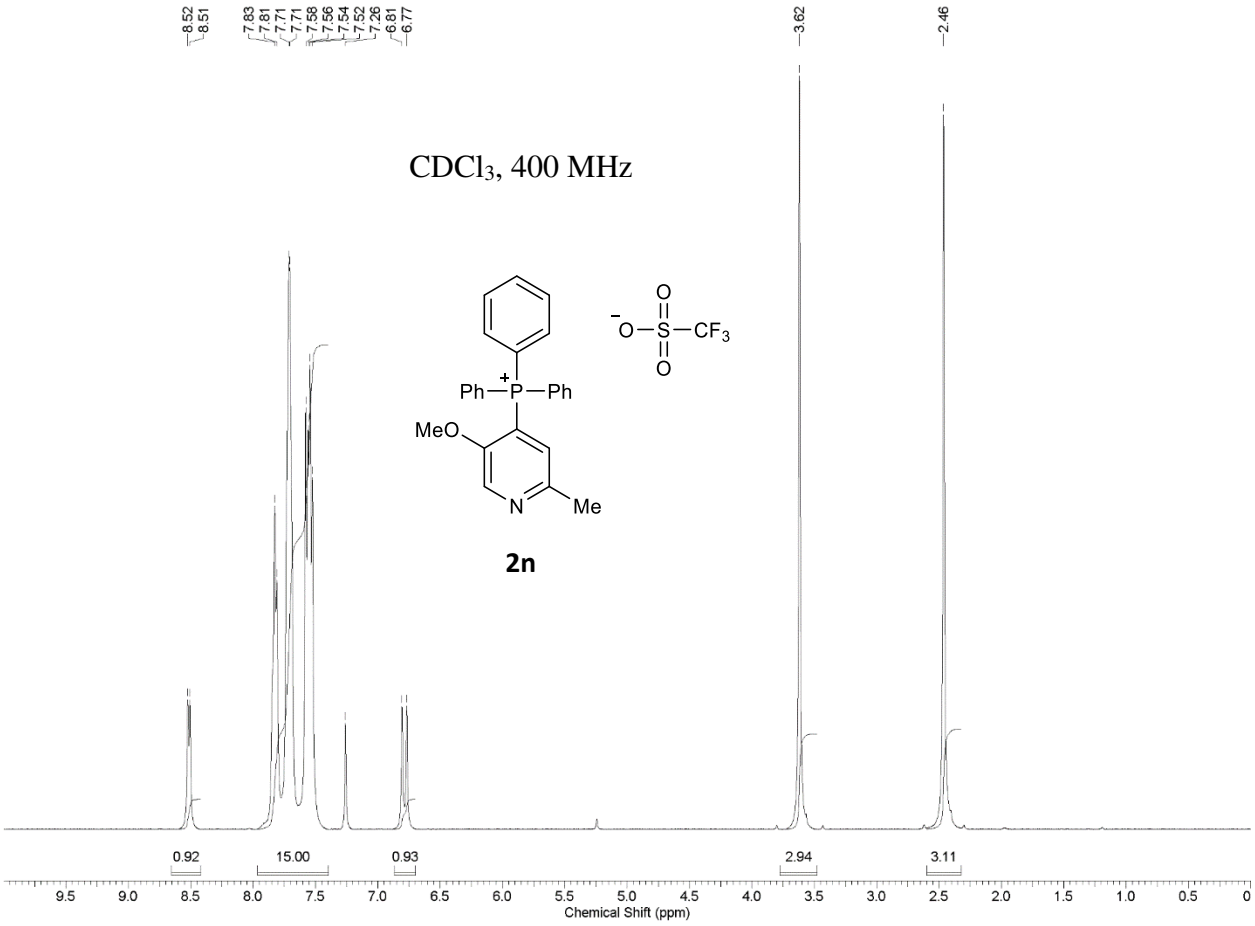
$CDCl_3$, 400 MHz (crude ^1H NMR)

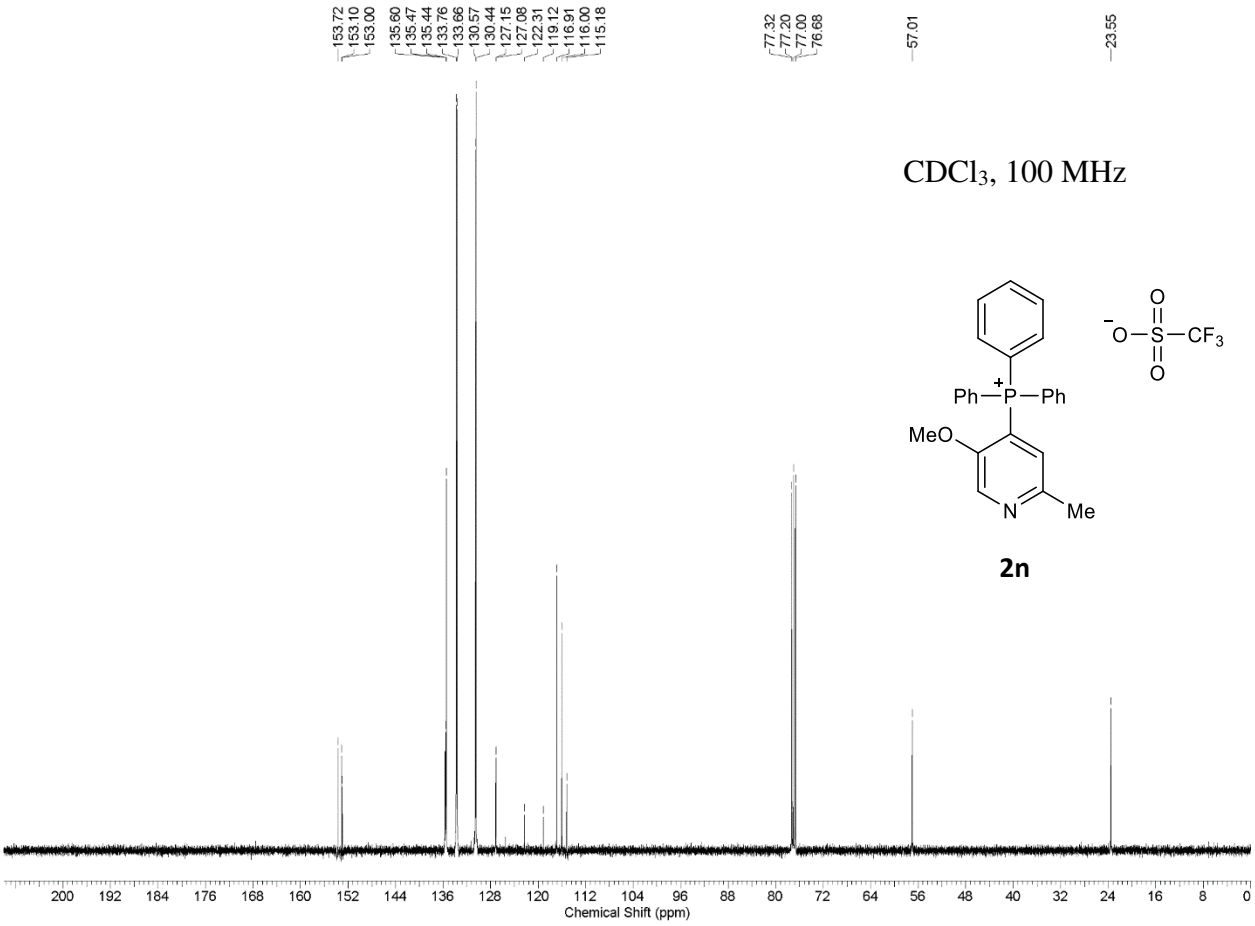


Major Minor



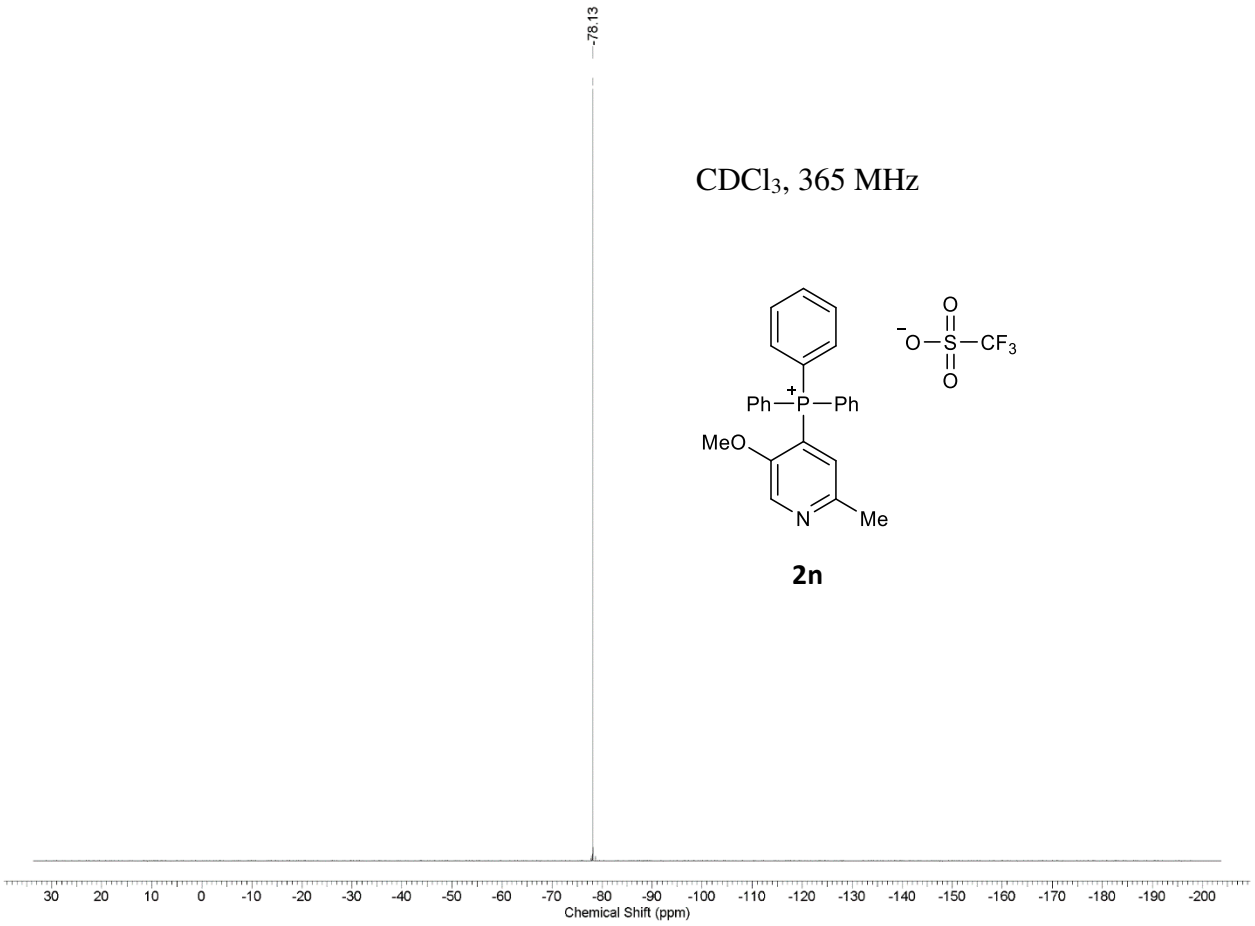

8.54
8.53
7.85
7.85
7.74
7.73
7.72
7.71
7.60
7.58
7.57
7.55
7.24
6.83
6.79
3.63
3.60
2.50
2.42
CDCl3, 400 MHz (Post-precipitation 1HNMR)
Major
Minor
r.r: 11:1
2n
Major
Minor
1.00
16.91
0.99
3.32
3.03
0.27
Chemical Shift (ppm)


8.52
8.51
7.83
7.81
7.71
7.71
7.58
7.56
7.54
7.52
7.26
6.81
6.77
3.62
2.46
CDCl3, 400 MHz
Ph
P
Ph
MeO
N
Me
O
S
CF3
2n
0.92
15.00
0.93
2.94
3.11
Chemical Shift (ppm)



$CDCl_3$, 100 MHz

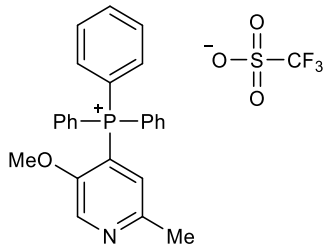
2n



$CDCl_3$, 365 MHz

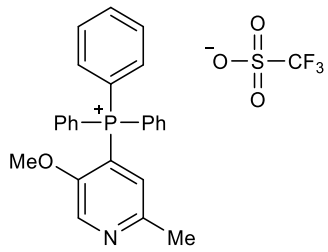
2n

$CDCl_3$, 162 MHz

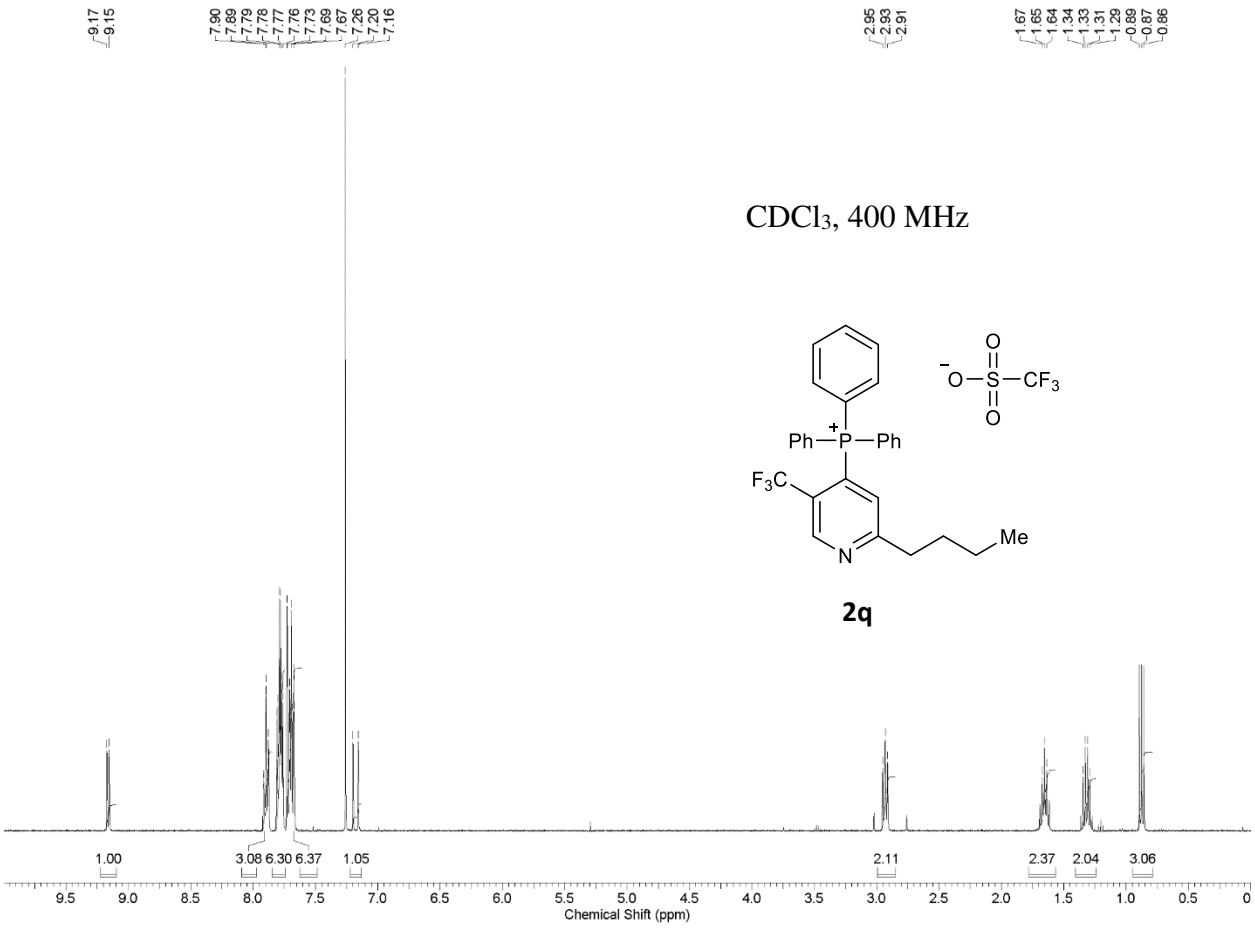


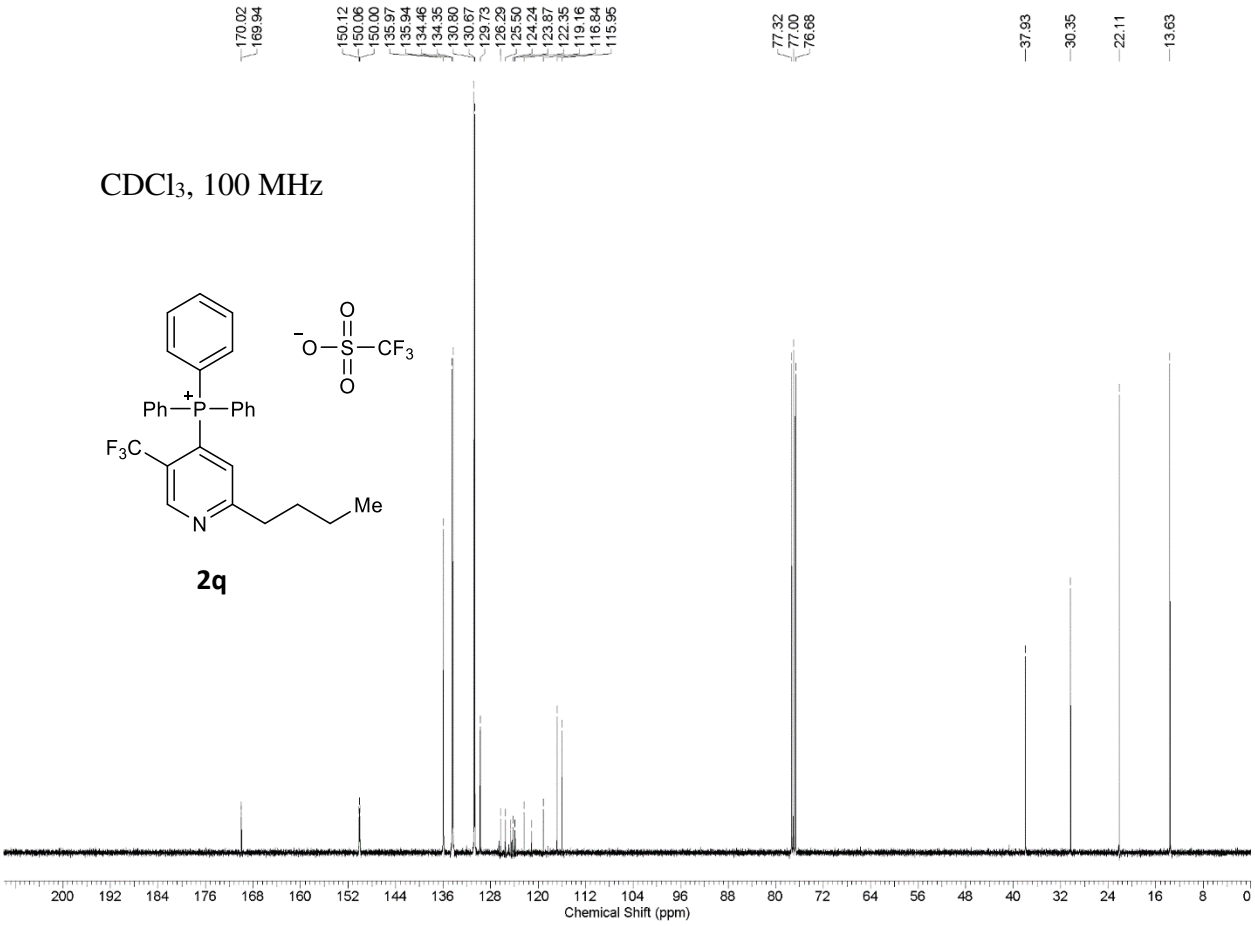
2n

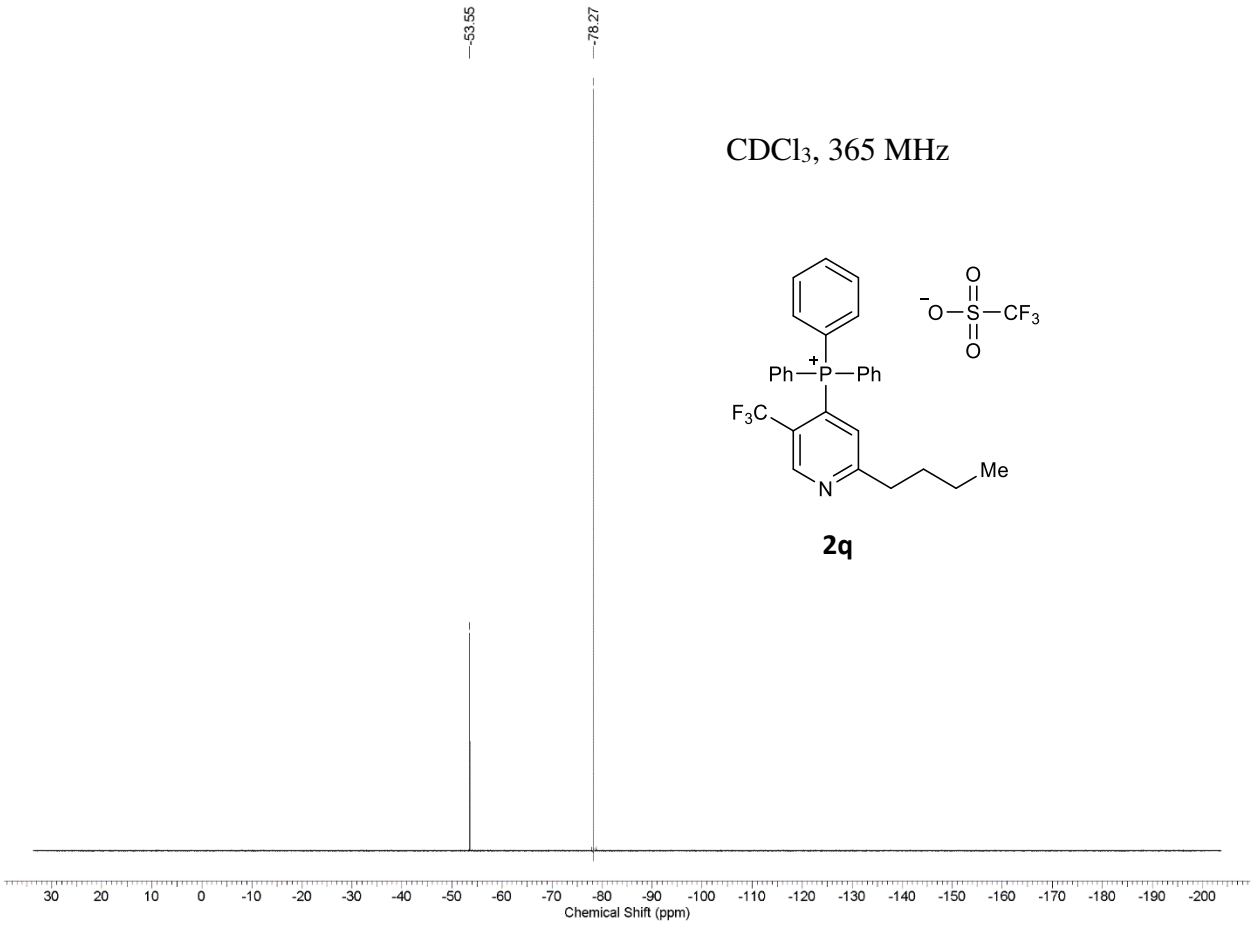
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



2n


9.17
9.15
7.90
7.89
7.79
7.78
7.77
7.76
7.73
7.69
7.67
7.26
7.20
7.16
2.95
2.93
2.91
1.67
1.65
1.64
1.34
1.33
1.31
1.29
0.89
0.87
0.86
CDCl3, 400 MHz
Ph—P—Ph
F3C
Me
N
O—S—CF3
2q
1.00
3.08
6.30
6.37
1.05
2.11
2.37
2.04
3.06
Chemical Shift (ppm)

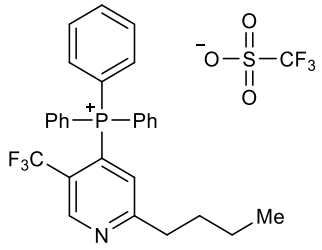

170.02
169.94
150.12
150.06
150.00
135.97
135.94
134.46
134.35
130.80
130.67
129.73
126.29
125.50
124.24
123.87
122.35
119.16
116.84
115.95
77.32
77.00
76.68
37.93
30.35
22.11
13.63
CDCl3, 100 MHz
Ph—P—Ph
F3C
Me
N
O—S—CF3
2q
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



$CDCl_3$, 365 MHz

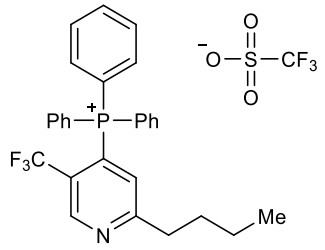
2q

$CDCl_3$, 162 MHz

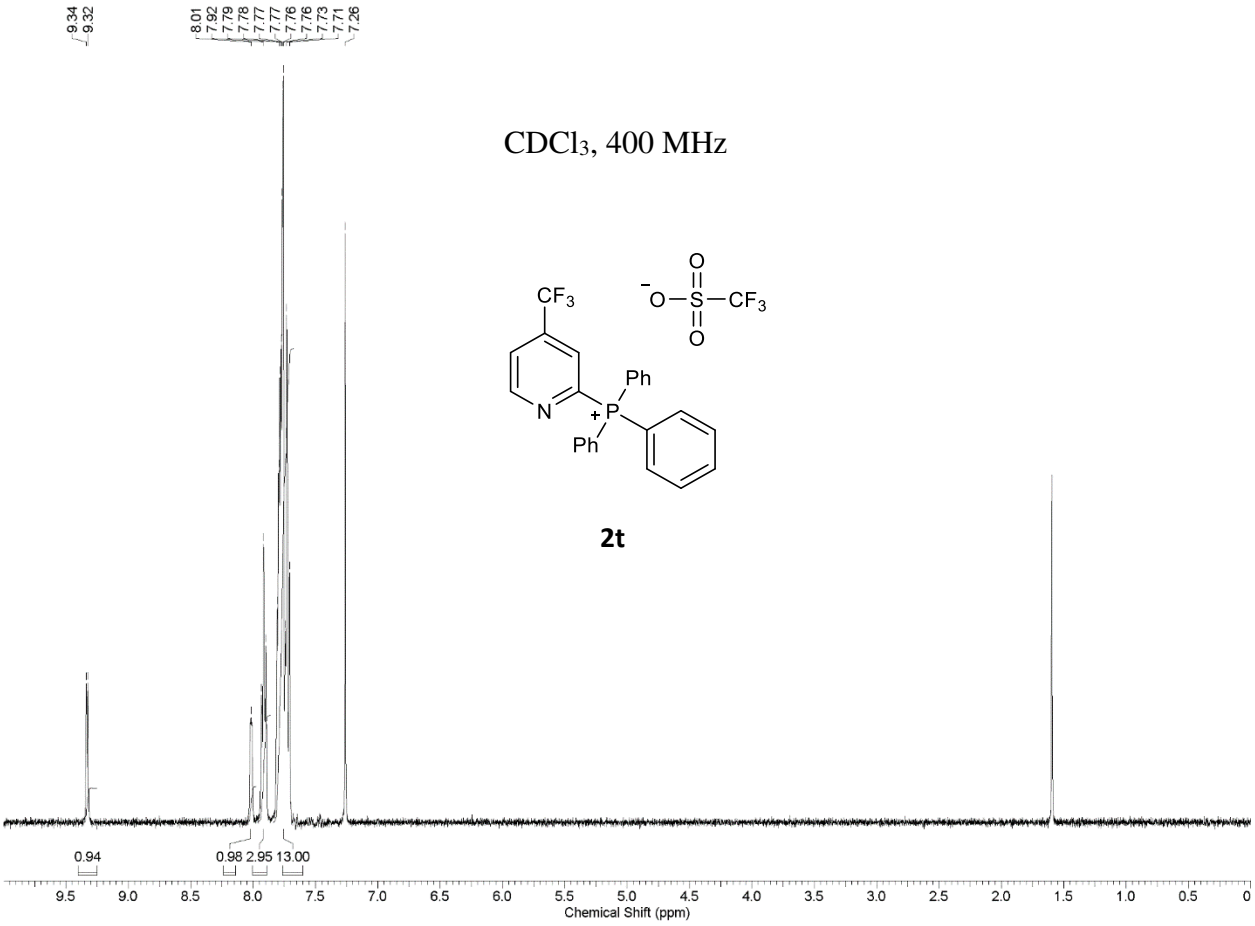


2q

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

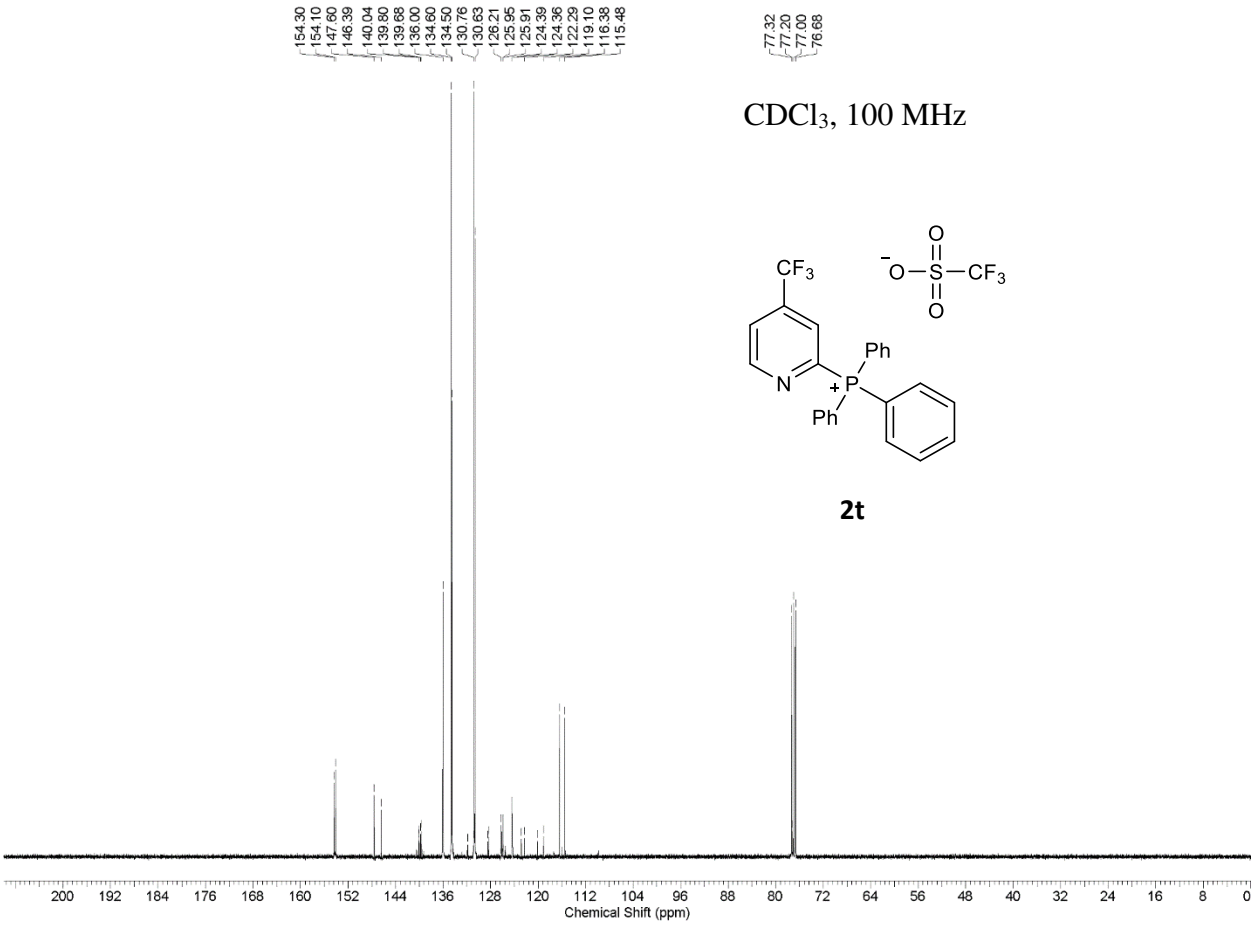


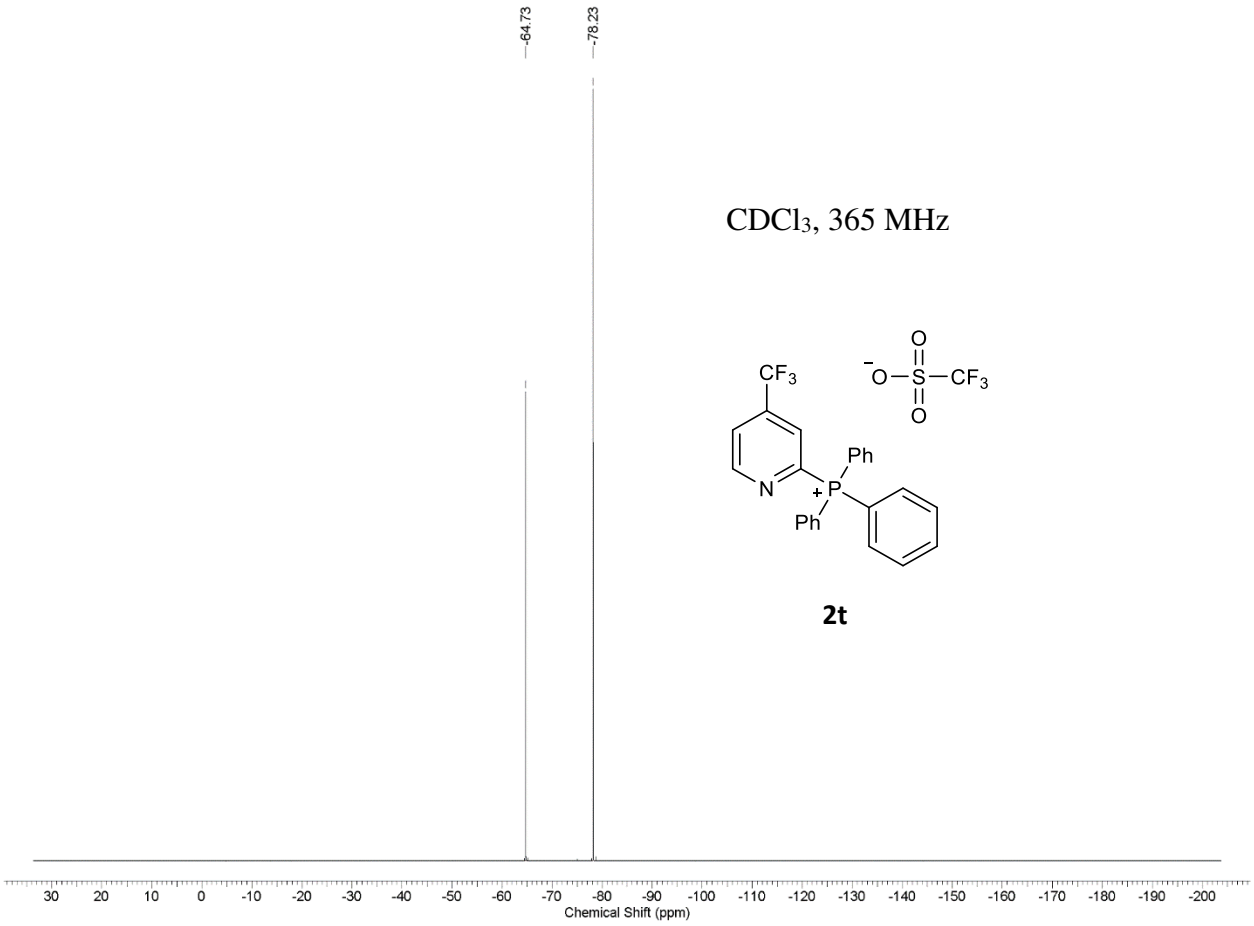
2q



$CDCl_3$, 400 MHz

2t

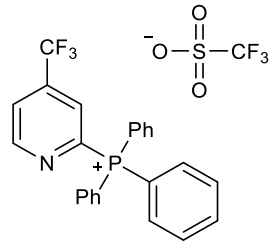

154.30
154.10
147.60
146.39
140.04
139.80
139.68
136.00
134.60
134.50
130.76
130.63
126.21
125.95
125.91
124.39
124.36
122.29
119.10
116.38
115.48
77.32
77.20
77.00
76.68
CDCl3, 100 MHz
CF3
O
O
S
CF3
O
O
N
P
Ph
Ph
2t
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



$CDCl_3$, 365 MHz

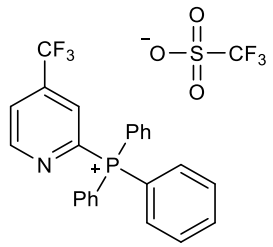
2t

$CDCl_3$, 162 MHz

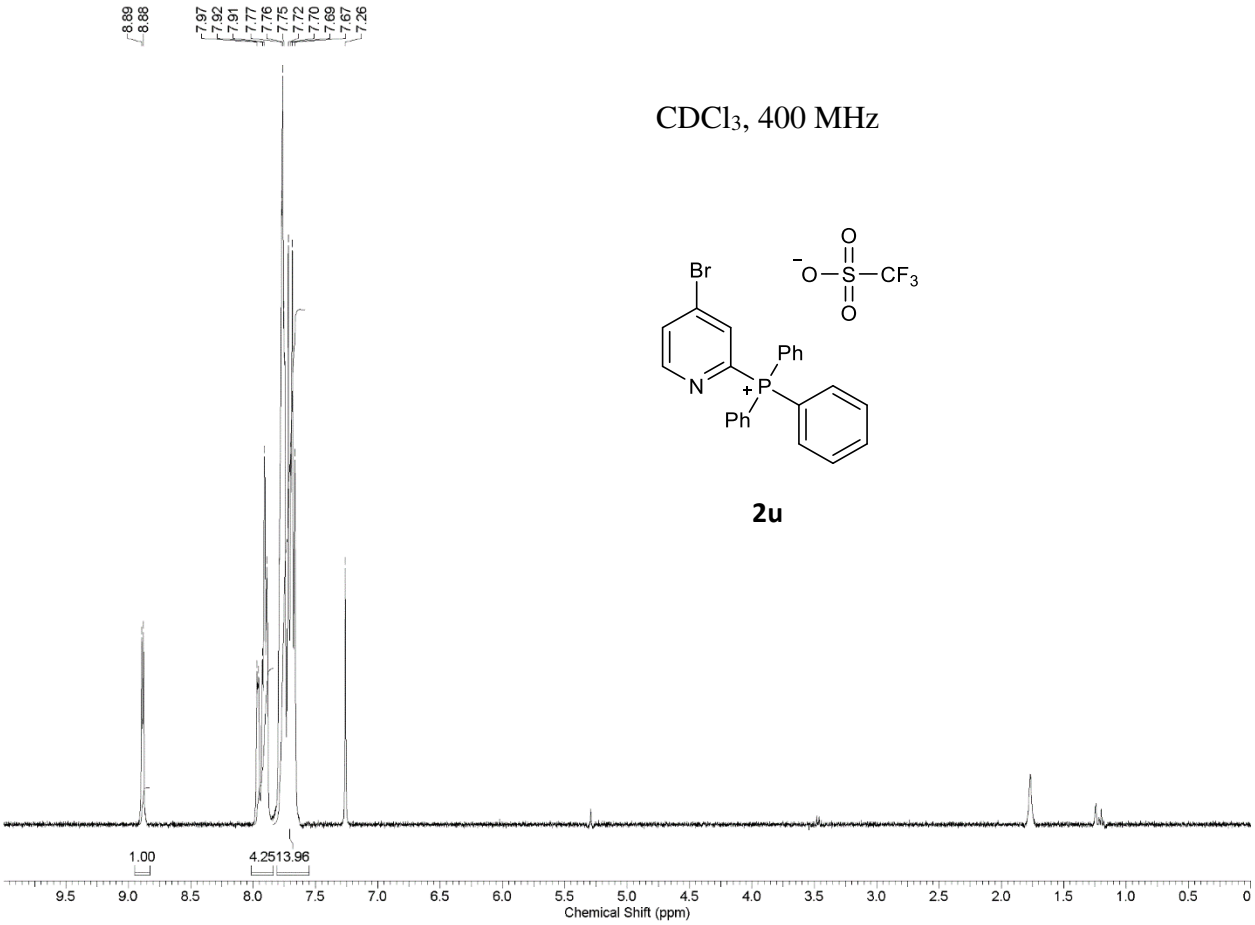


2t

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

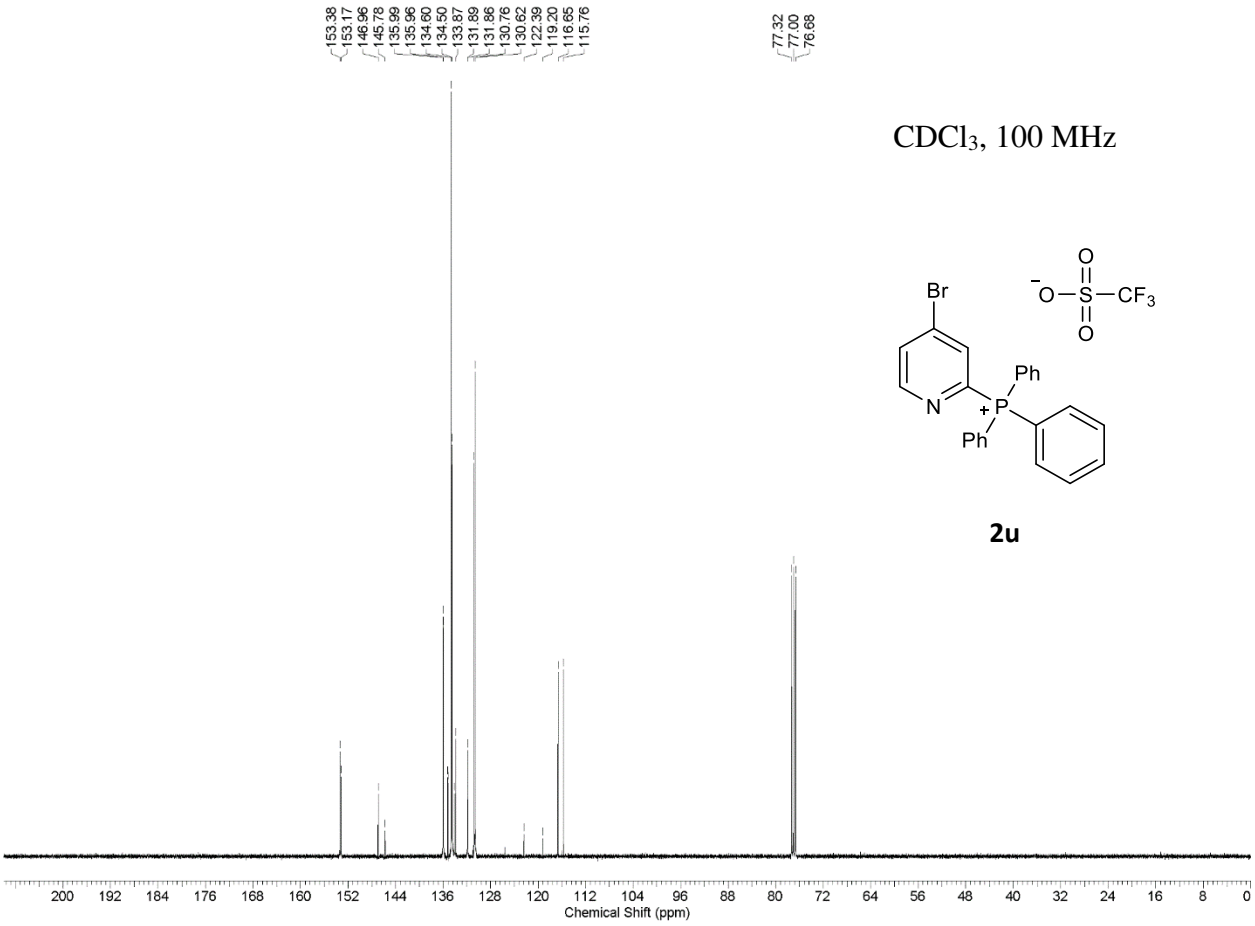


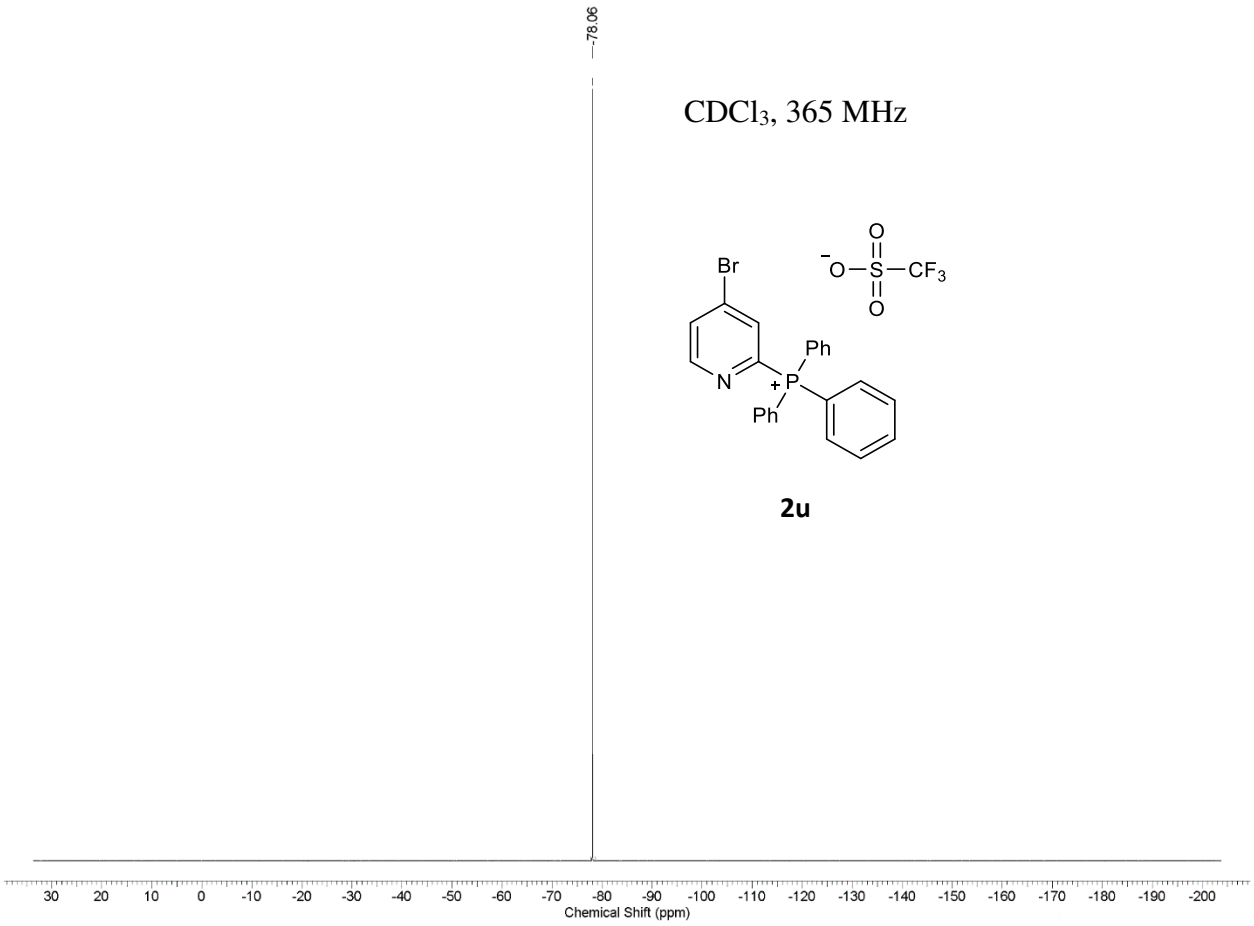
2t



$CDCl_3$, 400 MHz

2u

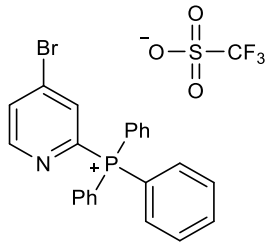

153.38
153.17
146.96
145.78
135.99
135.96
134.60
134.50
133.87
131.89
131.86
130.76
130.62
122.39
119.20
116.65
115.76
77.32
77.00
76.68
CDCl3, 100 MHz
Br
O
O
S
CF3
N
P
Ph
Ph
2u
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



$CDCl_3$, 365 MHz

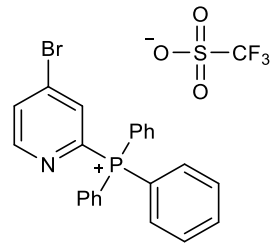
2u

$CDCl_3$, 162 MHz

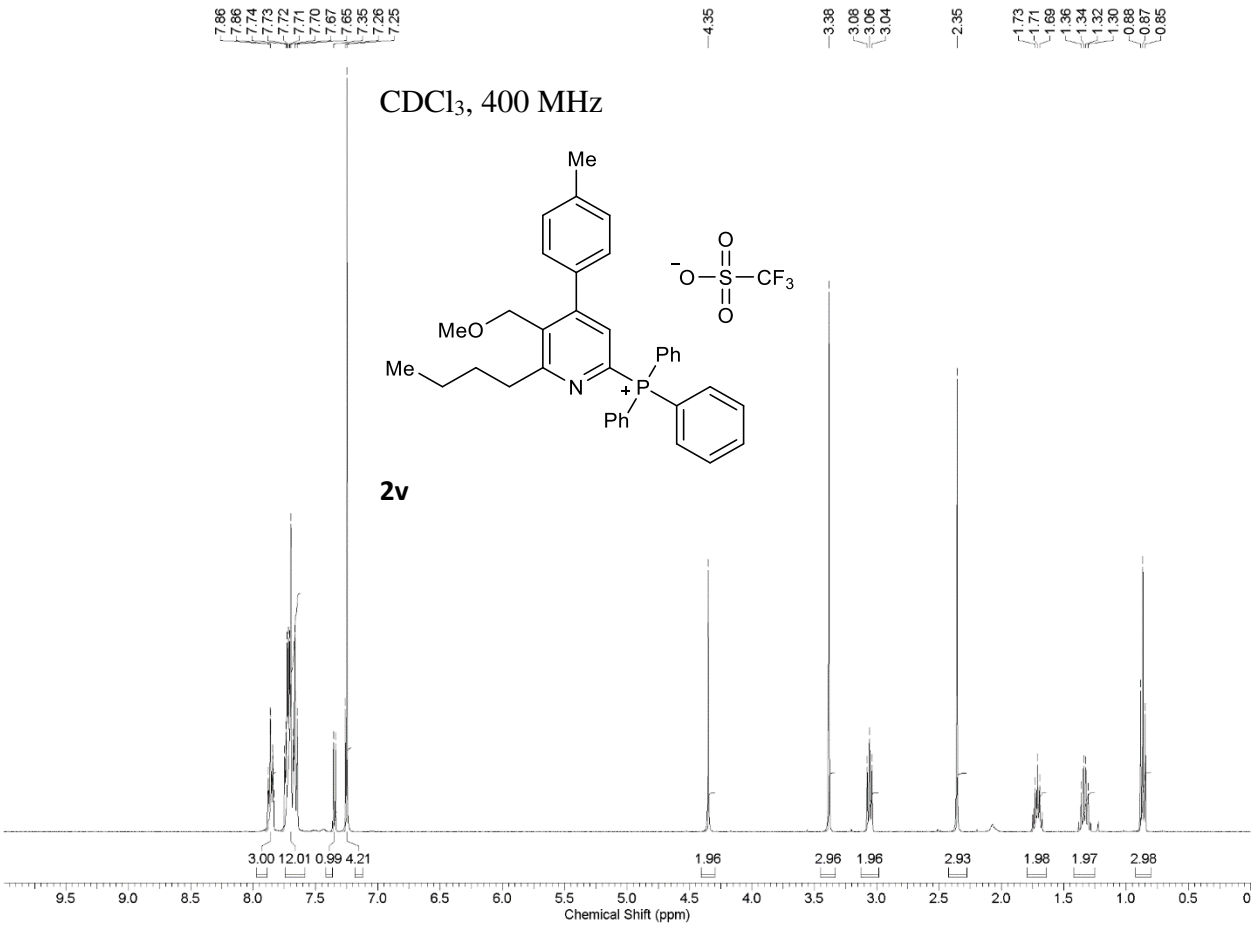


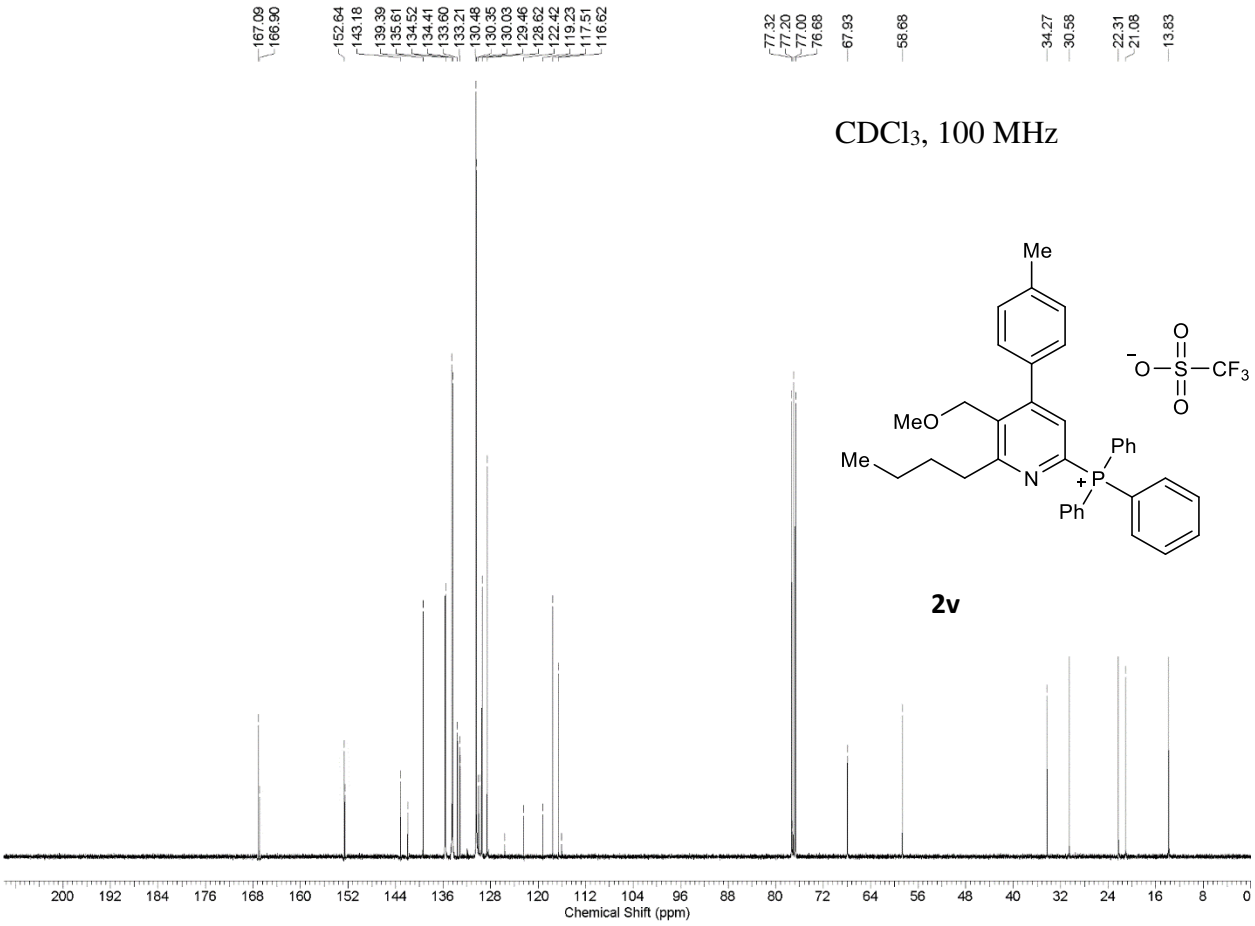
2u

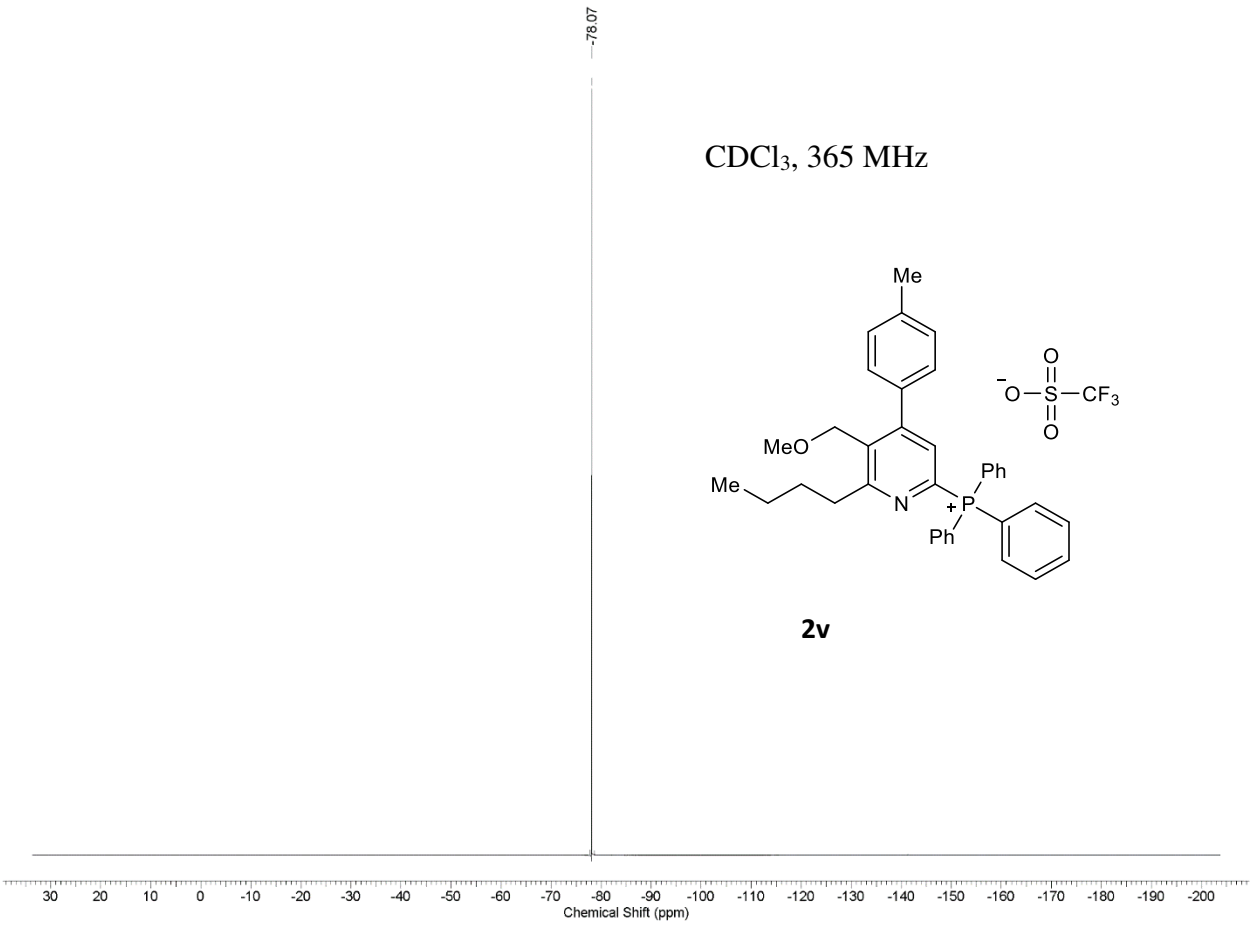
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



2u


7.86
7.86
7.74
7.73
7.72
7.71
7.70
7.67
7.65
7.35
7.26
7.25
4.35
3.38
3.08
3.06
3.04
2.35
1.73
1.71
1.69
1.36
1.34
1.32
1.30
0.88
0.87
0.85
CDCl3, 400 MHz
Me
MeO
Me
N
+P
Ph
Ph
O
O
S
O
CF3
2v
3.00 12.01 0.99 4.21
1.96
2.96 1.96
2.93
1.98 1.97 2.98
Chemical Shift (ppm)

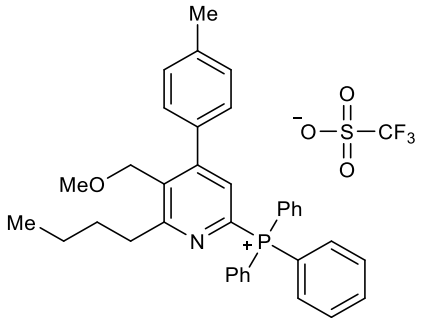

167.09
166.90
152.64
143.18
139.39
135.61
134.52
134.41
133.60
133.21
130.48
130.35
130.03
129.46
128.62
122.42
119.23
117.51
116.62
77.32
77.20
77.00
76.68
67.93
58.68
34.27
30.58
22.31
21.08
13.83
CDCl3, 100 MHz
Me
MeO
Me
N
Ph
P
Ph
O
O
S
CF3
2v
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



$CDCl_3$, 365 MHz

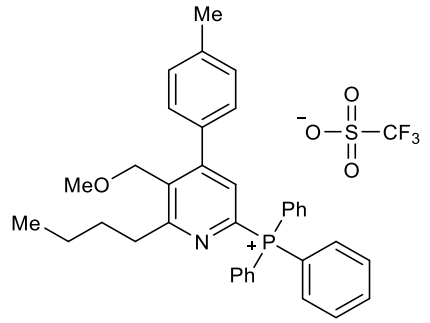
2v

$CDCl_3$, 162 MHz



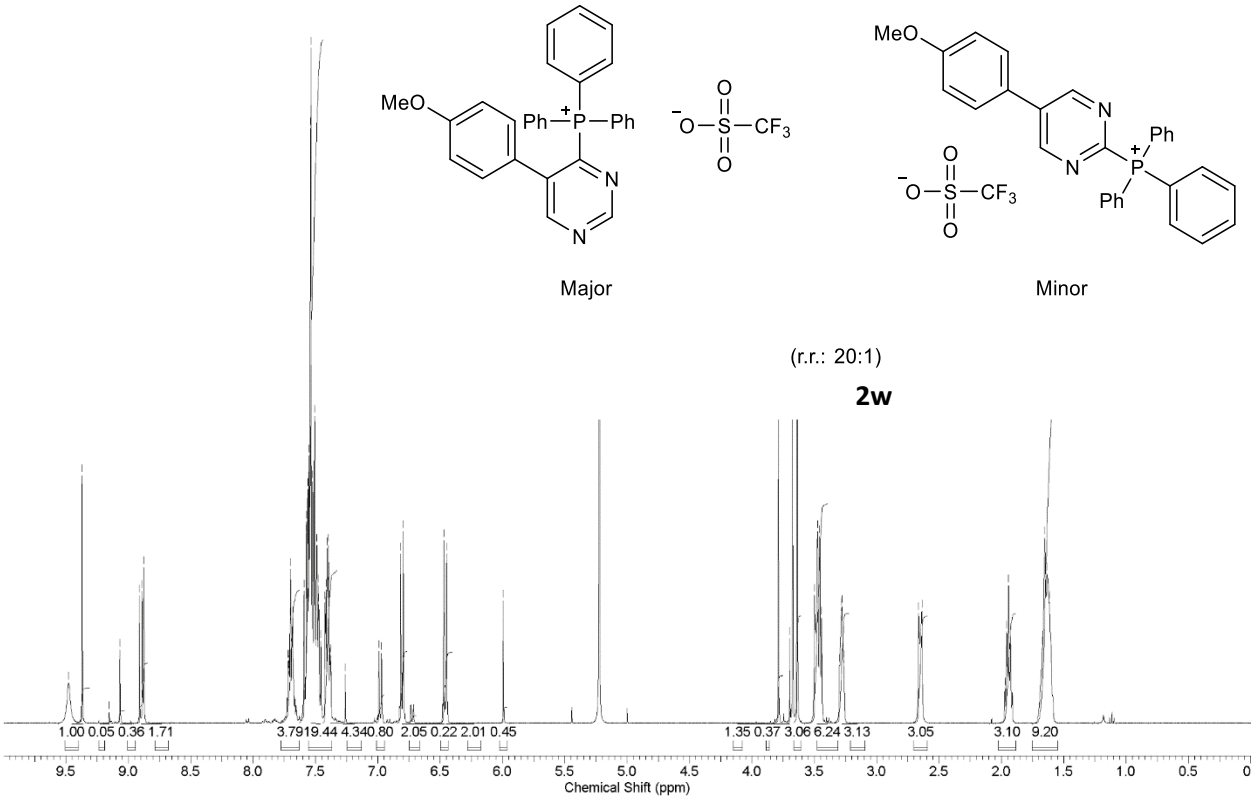
2v

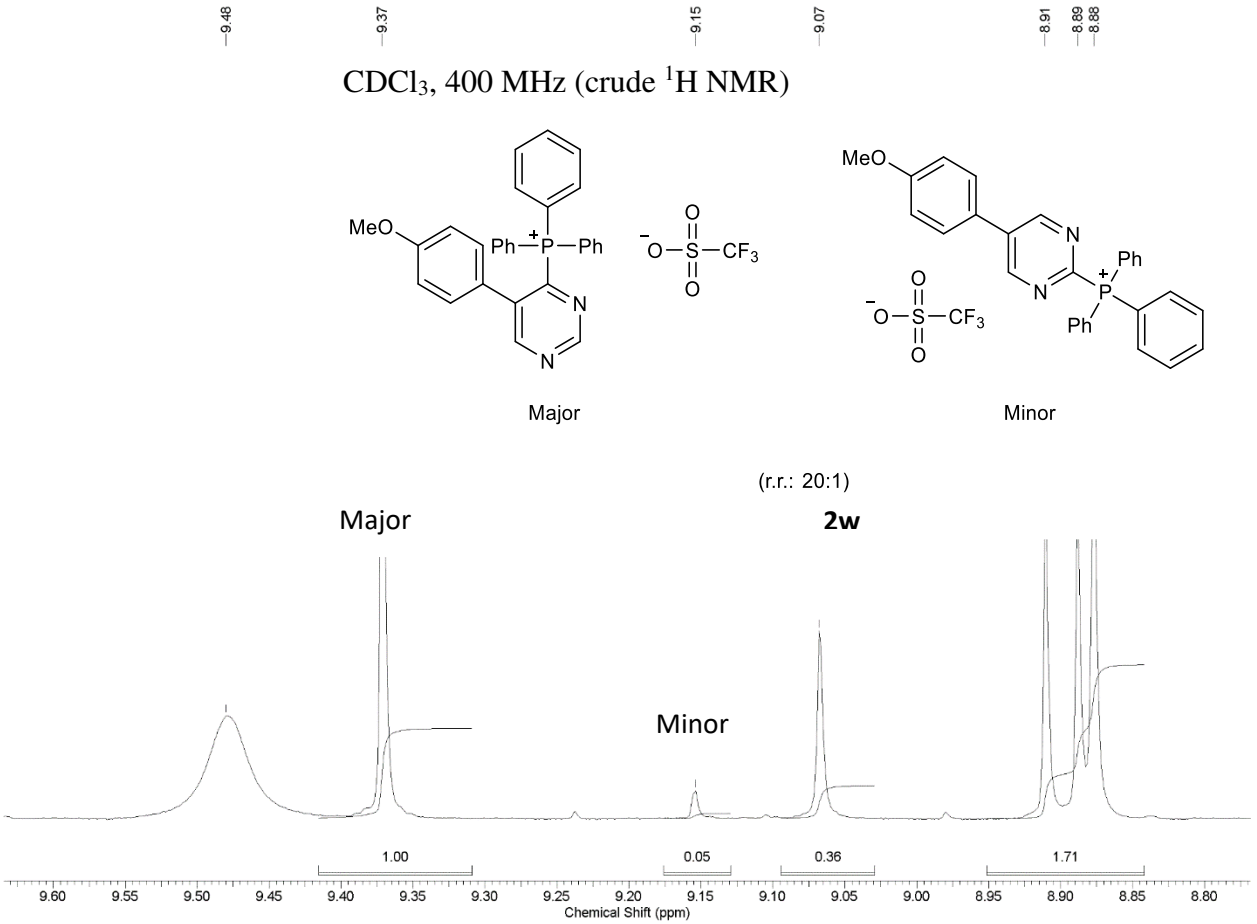
$CDCl_3$, 162 MHz (crude ^{31}P NMR)

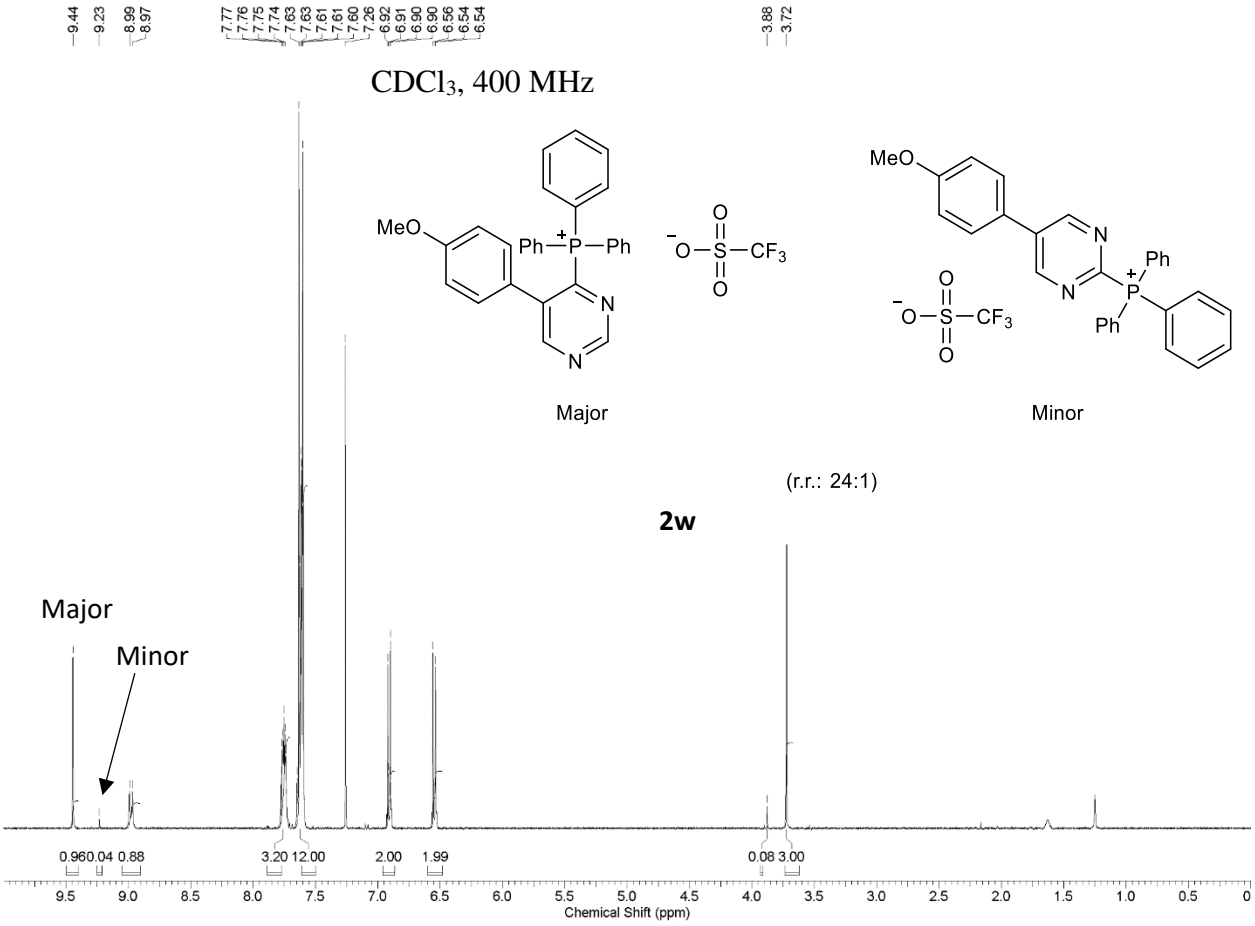


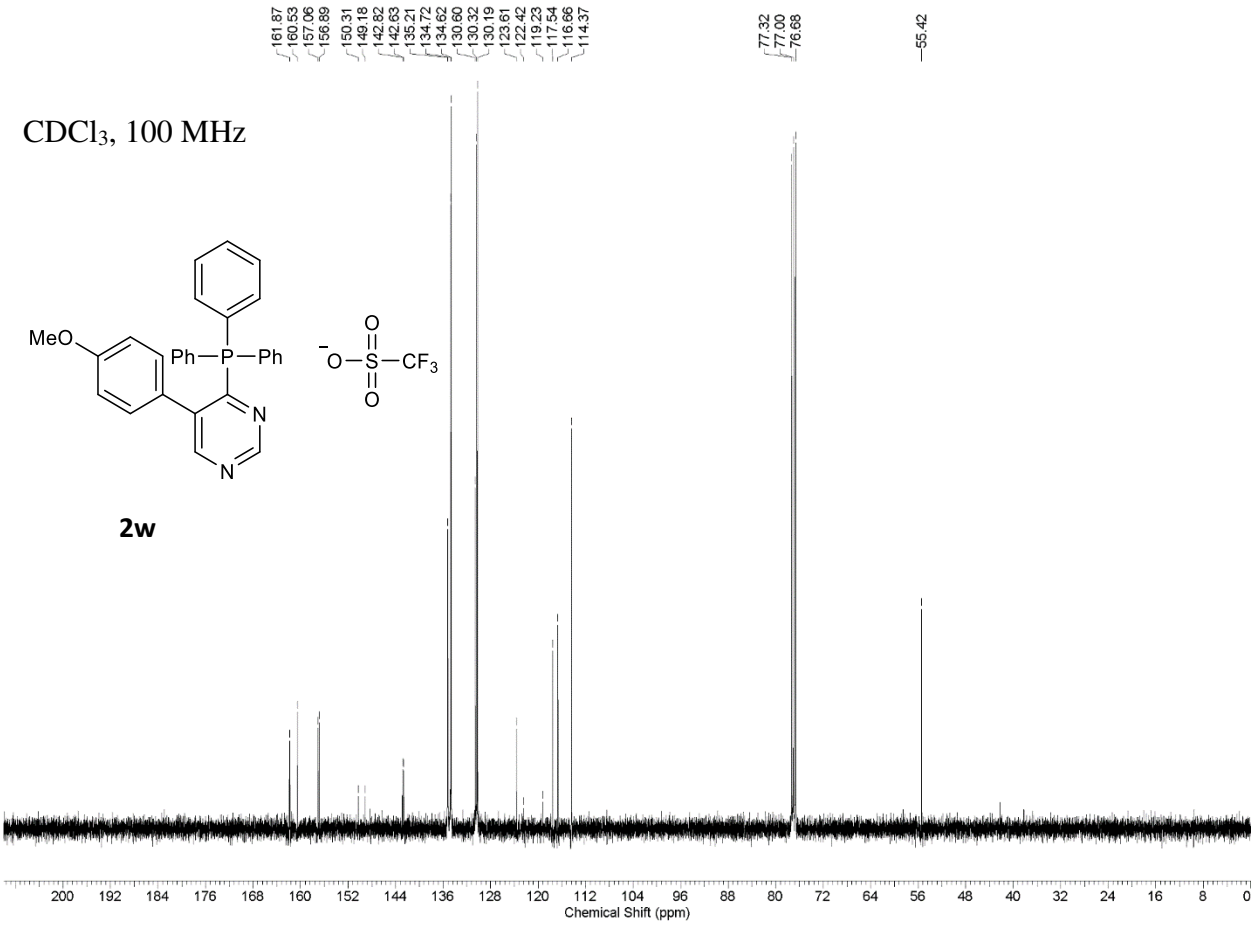
2v

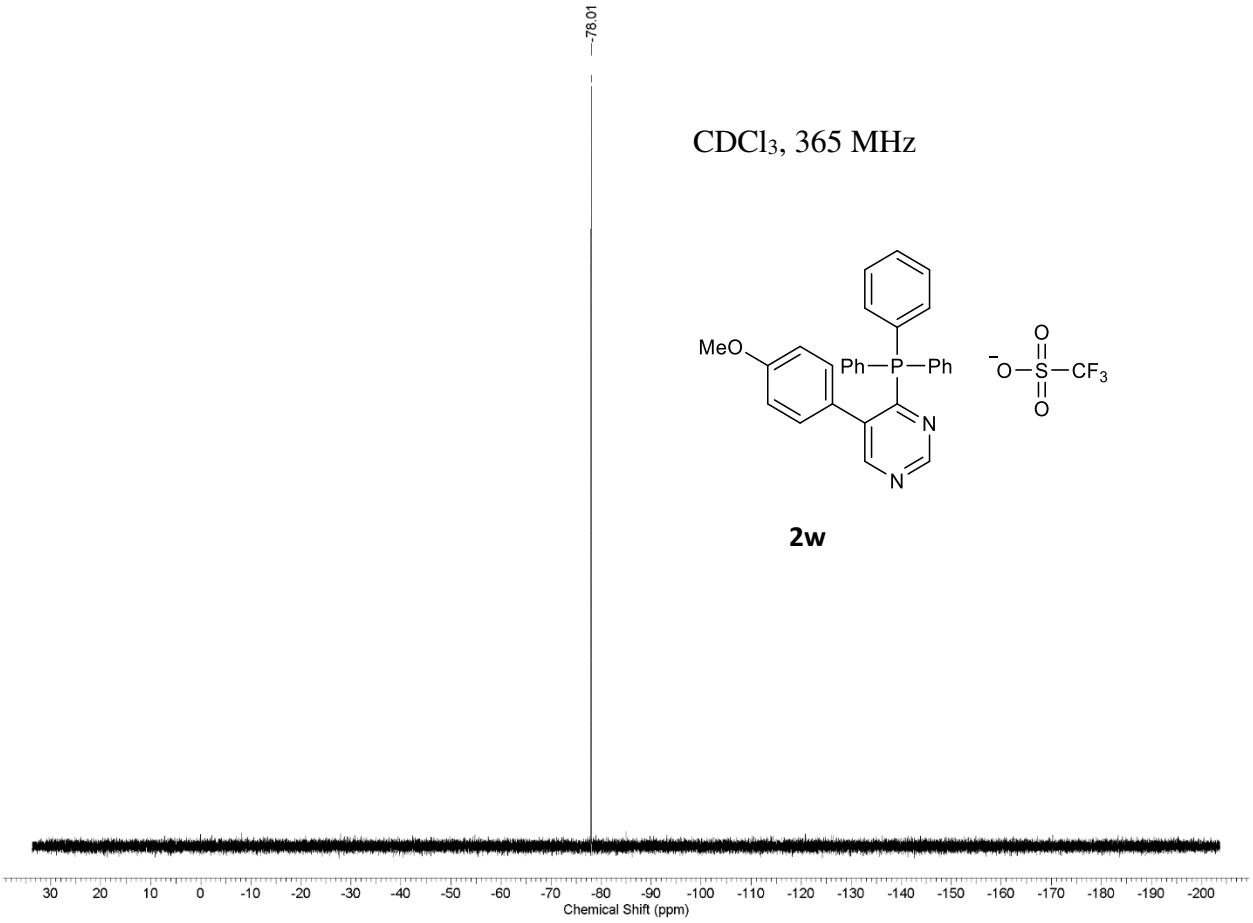
$CDCl_3$, 400 MHz (crude ^1H NMR)



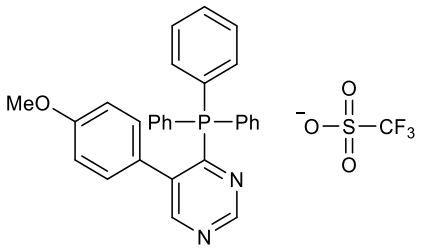

9.48
9.37
9.15
9.07
8.91
8.89
8.88
CDCl3, 400 MHz (crude 1H NMR)
MeO
Ph
P
Ph
N
N
O
S
CF3
Major
MeO
N
N
Ph
P
Ph
Minor
(r.r.: 20:1)
Major
2w
Minor
1.00
0.05
0.36
1.71
9.60
9.55
9.50
9.45
9.40
9.35
9.30
9.25
9.20
9.15
9.10
9.05
9.00
8.95
8.90
8.85
8.80
Chemical Shift (ppm)


9.44
9.23
8.99
8.97
7.77
7.76
7.75
7.74
7.63
7.61
7.61
7.60
7.26
6.92
6.91
6.90
6.90
6.56
6.54
6.54
3.88
3.72
CDCl3, 400 MHz
MeO
Ph
P
Ph
N
N
O
S
CF3
Major
MeO
N
N
Ph
P
Ph
O
S
CF3
Minor
(r.r.: 24:1)
2w
Major
Minor
0.96
0.04
0.88
3.20
12.00
2.00
1.99
0.08
3.00
Chemical Shift (ppm)


161.87
160.53
157.06
156.89
150.31
149.18
142.82
142.63
135.21
134.72
134.62
130.60
130.32
130.19
123.61
122.42
119.23
117.54
116.66
114.37
77.32
77.00
76.68
55.42
CDCl3, 100 MHz
MeO
Ph—P—Ph
N
N
O
O—S—CF3
O
2w
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

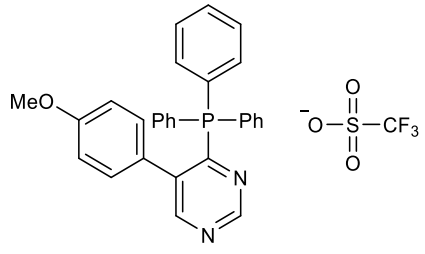

-78.01
CDCl3, 365 MHz
MeO
Ph—P—Ph
O
O—S—CF3
O
N
N
2w
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
Chemical Shift (ppm)

$CDCl_3$, 162 MHz

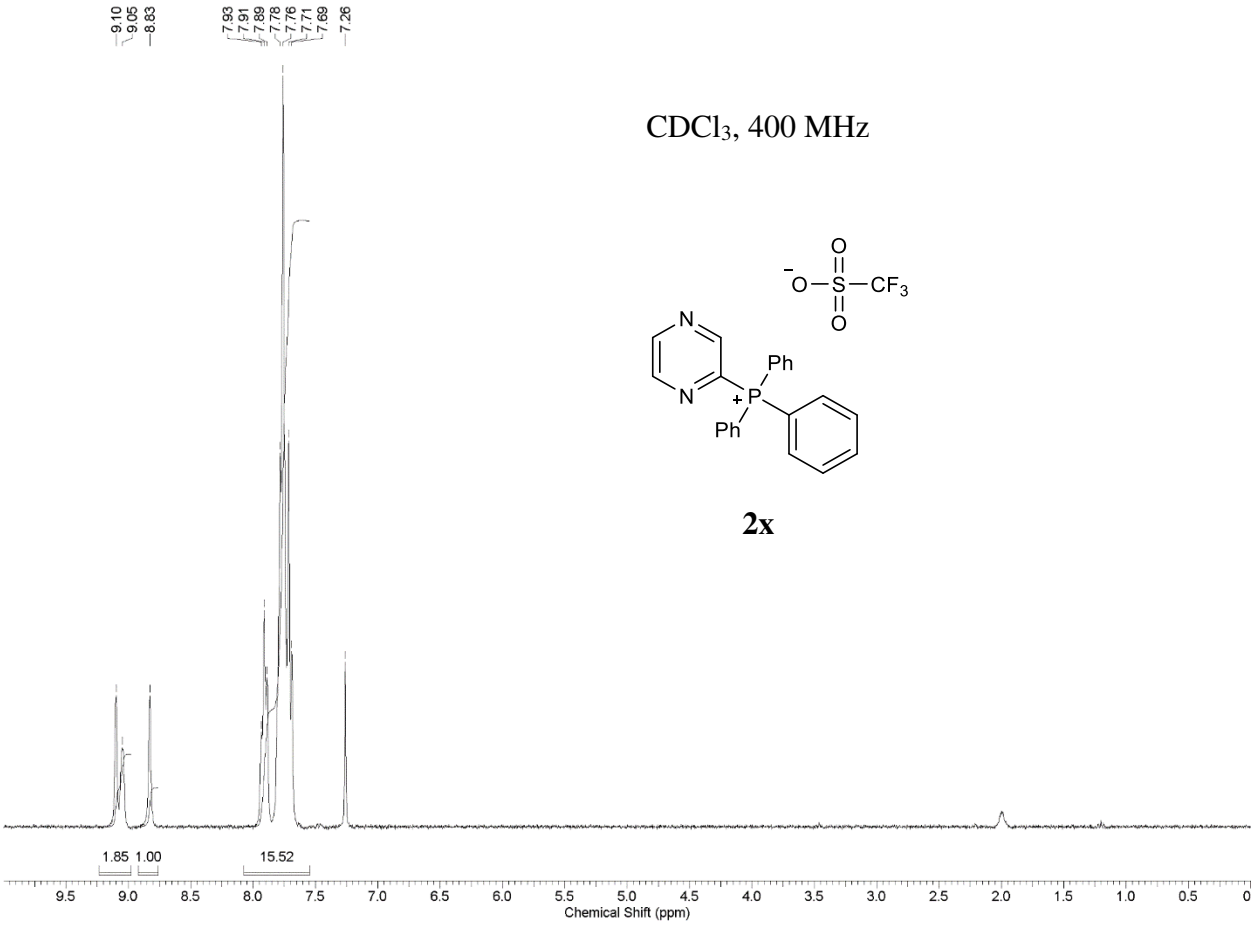


2w

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

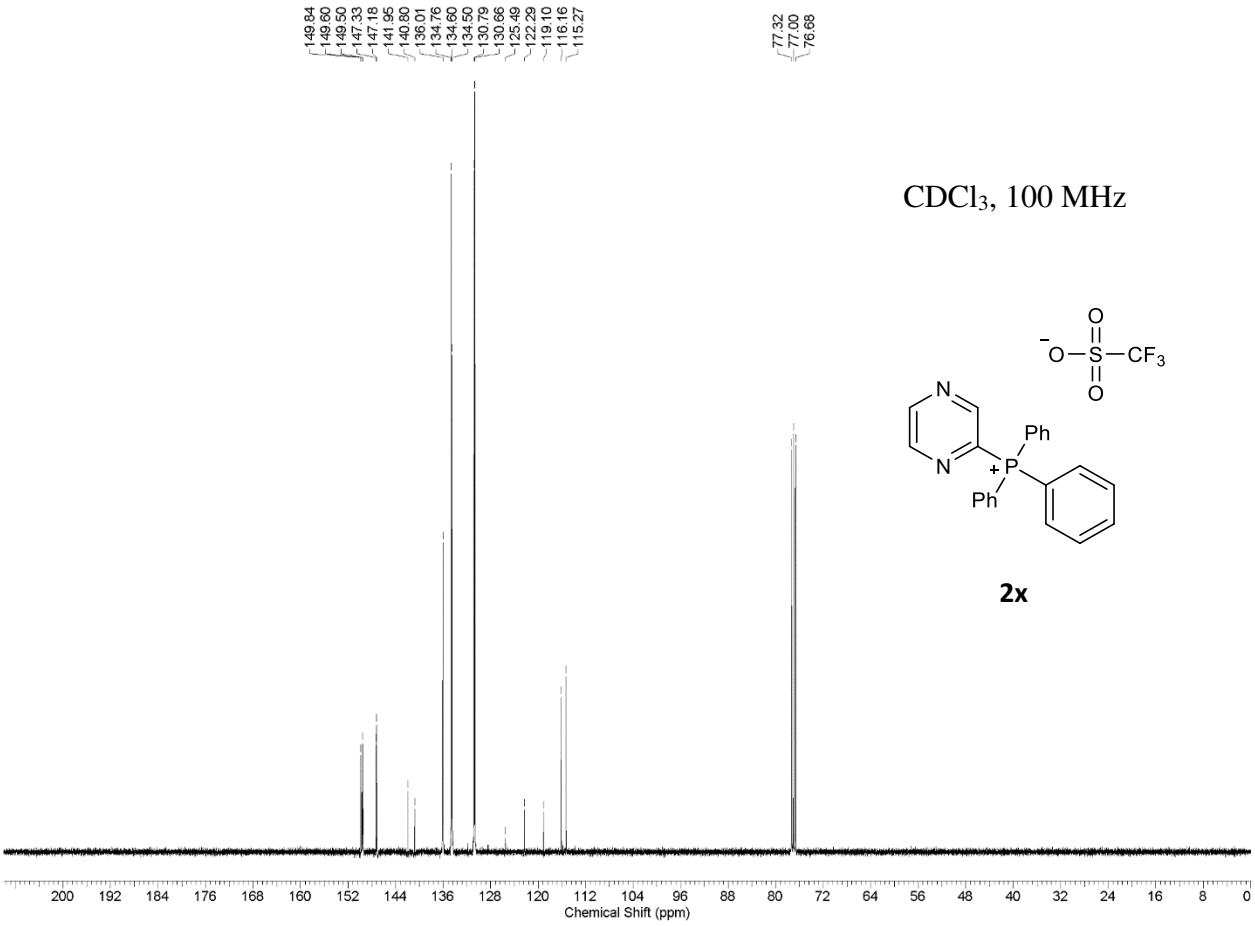


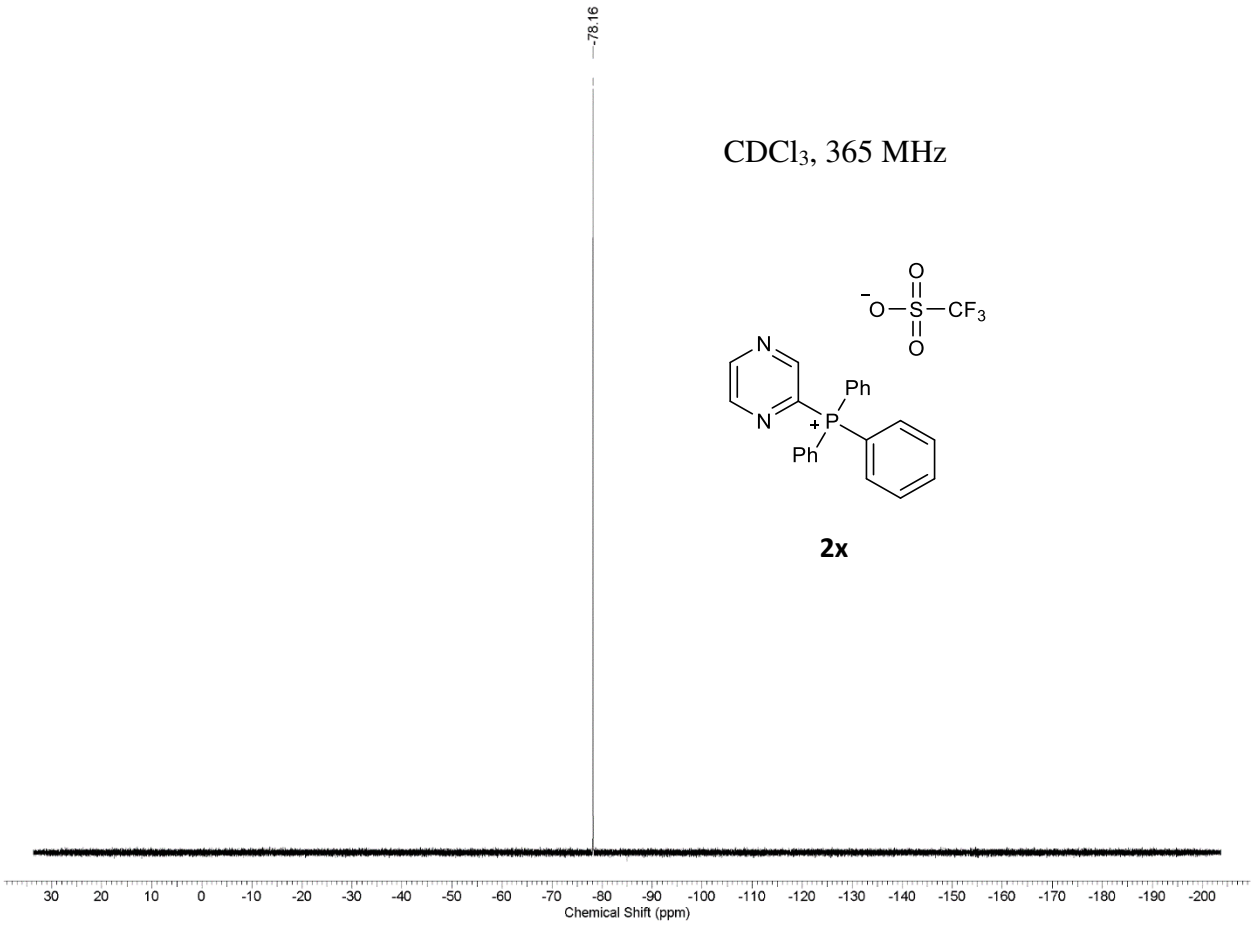
2w



$CDCl_3$, 400 MHz

2x

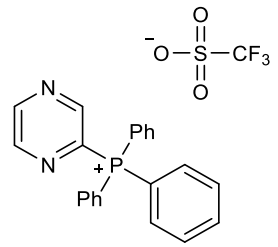

149.84
149.60
149.50
147.33
147.18
141.95
140.80
136.01
134.76
134.60
134.50
130.79
130.66
125.49
122.29
119.10
116.16
115.27
77.32
77.00
76.68
CDCl3, 100 MHz
Ph
Ph
2x
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



$CDCl_3$, 365 MHz

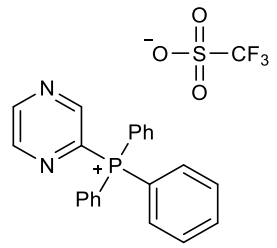
2x

$CDCl_3$, 162 MHz

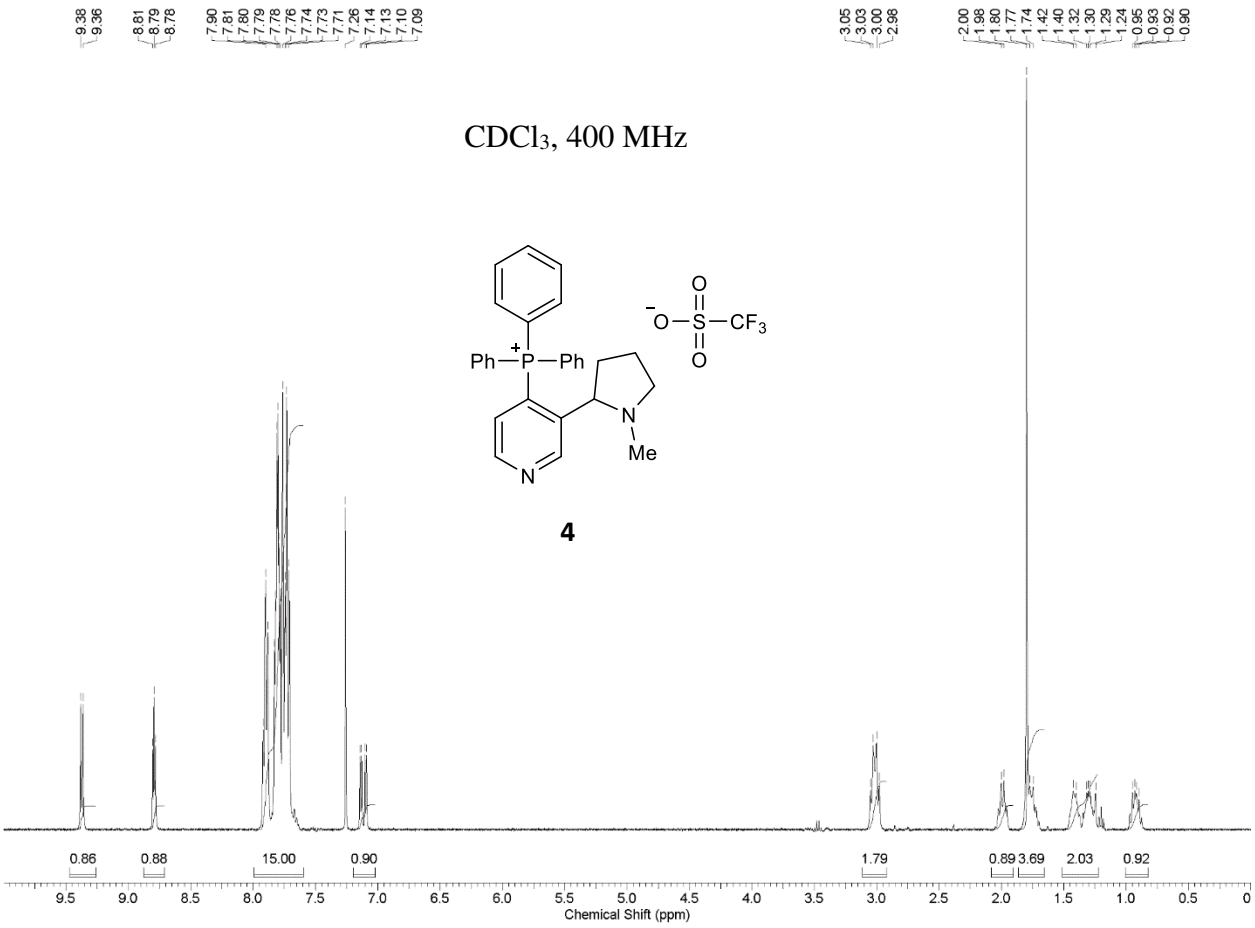


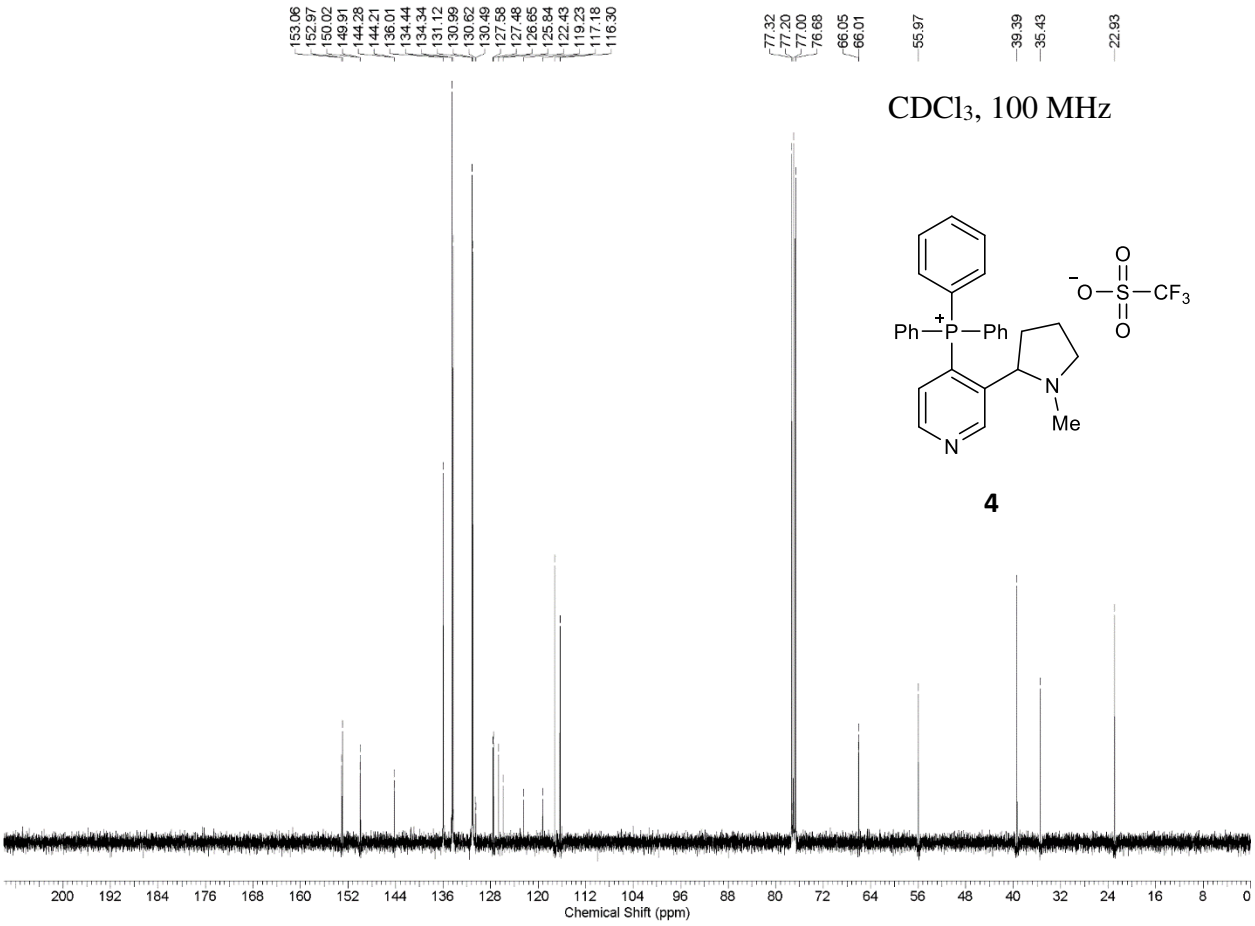
2x

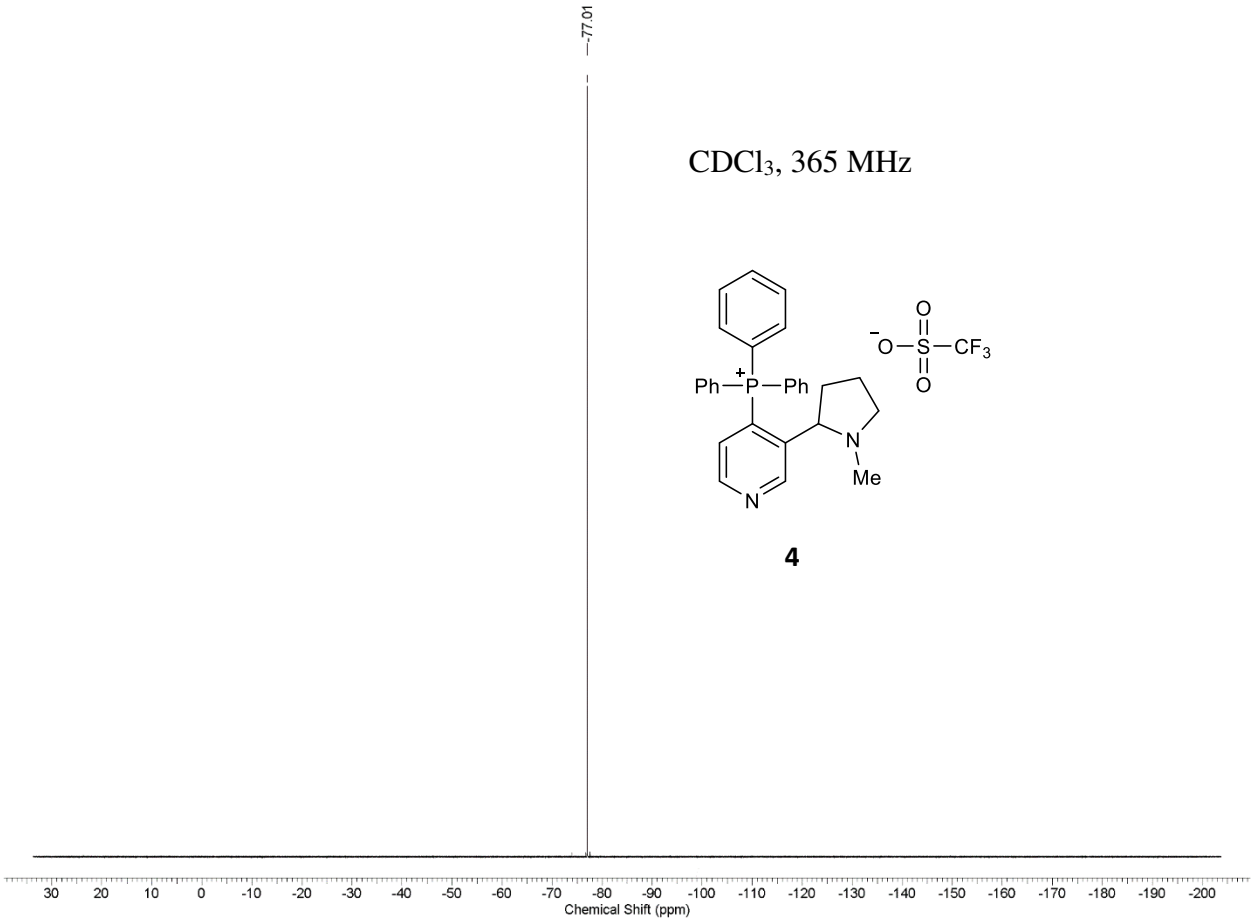
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



2x


9.38
9.36
8.81
8.79
8.78
7.90
7.81
7.80
7.79
7.78
7.76
7.74
7.73
7.71
7.26
7.14
7.13
7.10
7.09
3.05
3.03
3.00
2.98
2.00
1.98
1.80
1.77
1.74
1.42
1.40
1.32
1.30
1.29
1.24
0.95
0.93
0.92
0.90
CDCl3, 400 MHz
Ph
P
Ph
O
O
S
CF3
O
O
N
Me
N
4
0.86
0.88
15.00
0.90
1.79
0.89
3.69
2.03
0.92
Chemical Shift (ppm)

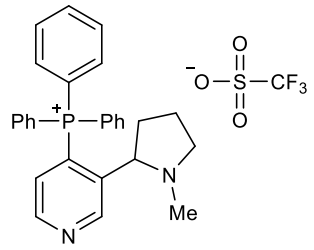

153.06
152.97
150.02
149.91
144.28
144.21
136.01
134.44
134.34
131.12
130.98
130.62
130.49
127.58
127.48
126.65
125.84
122.43
119.23
117.18
116.30
77.32
77.20
77.00
76.68
66.05
66.01
55.97
39.39
35.43
22.93
CDCl3, 100 MHz
Ph
P
Ph
O
S
CF3
N
Me
N
4
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



$CDCl_3$, 365 MHz

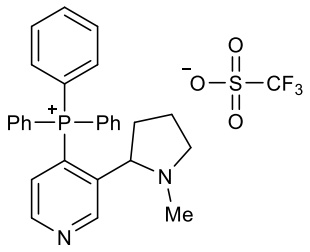
4

$CDCl_3$, 162 MHz

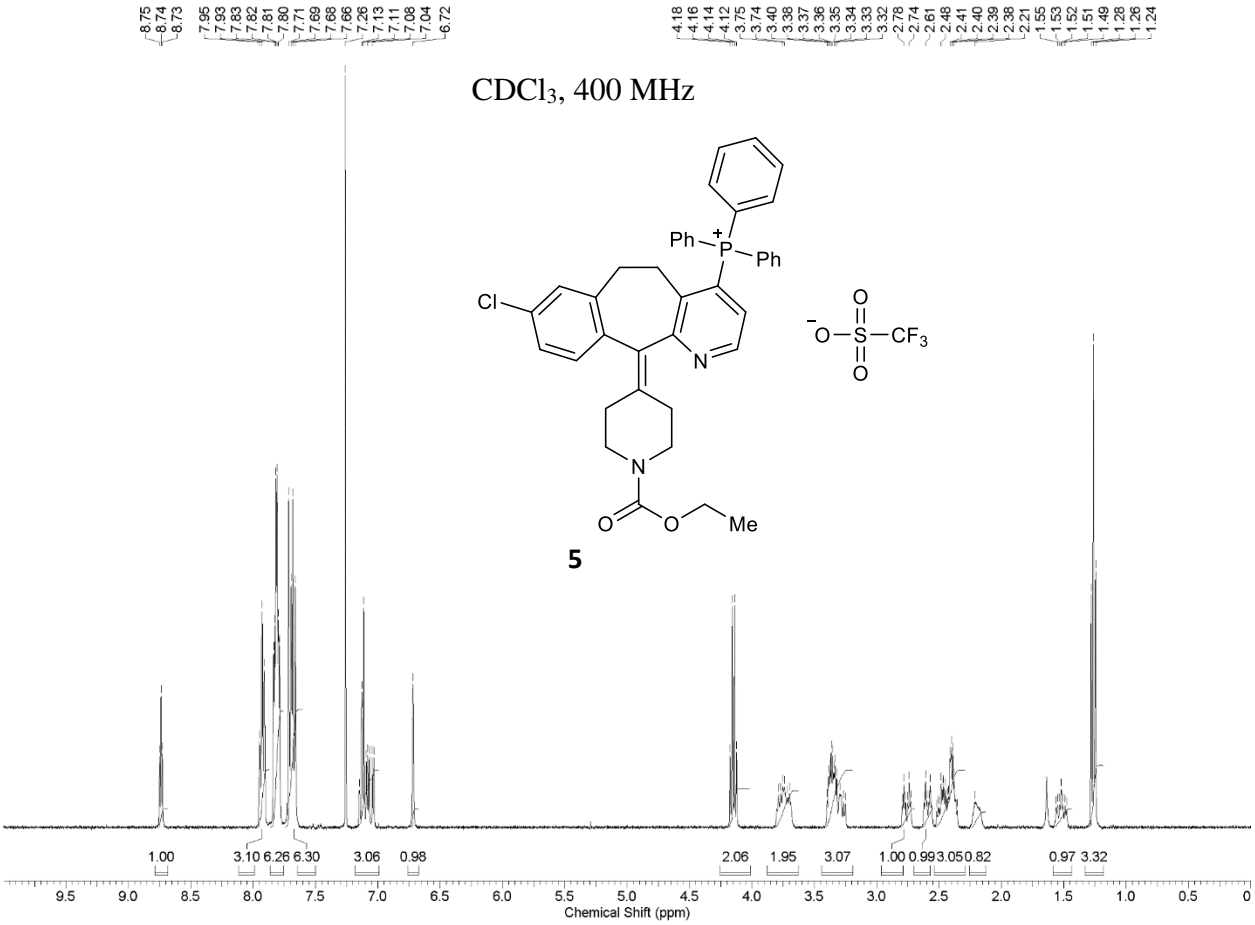


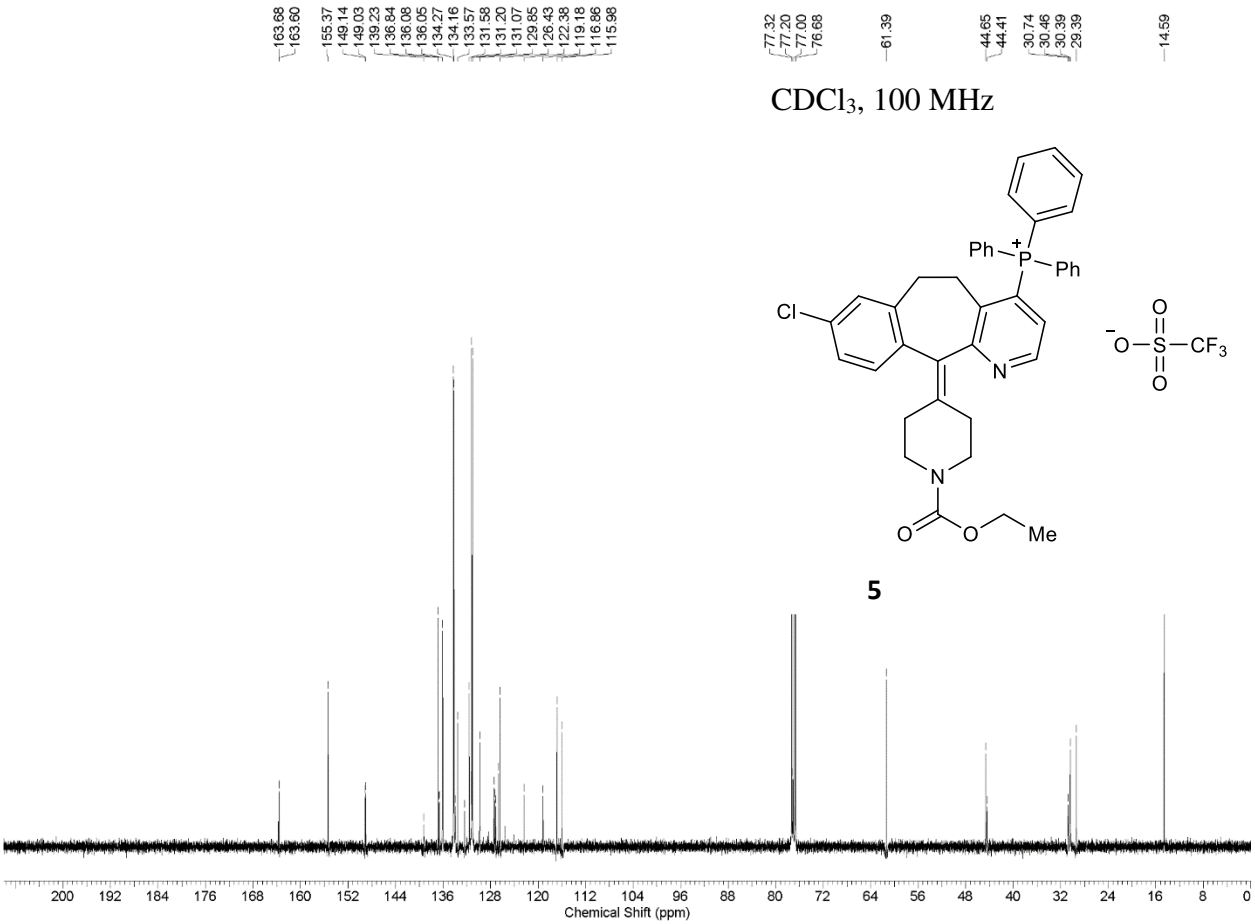
4

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

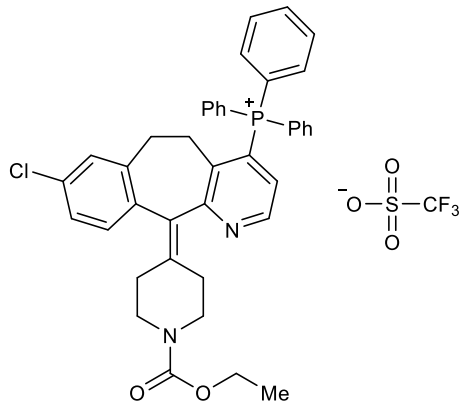


4


8.75
8.74
8.73
7.95
7.93
7.83
7.82
7.81
7.80
7.71
7.69
7.68
7.66
7.26
7.13
7.11
7.08
7.04
6.72
4.18
4.16
4.14
4.12
3.75
3.74
3.40
3.38
3.37
3.36
3.35
3.34
3.33
3.32
2.78
2.74
2.61
2.46
2.41
2.40
2.39
2.38
2.21
1.55
1.53
1.52
1.51
1.49
1.28
1.26
1.24
CDCl3, 400 MHz
Ph
P
Ph
Cl
N
O
S
CF3
N
O
O
Me
5
1.00
3.10
6.26
6.30
3.06
0.98
2.06
1.95
3.07
1.00
0.99
3.05
0.82
0.97
3.32
Chemical Shift (ppm)

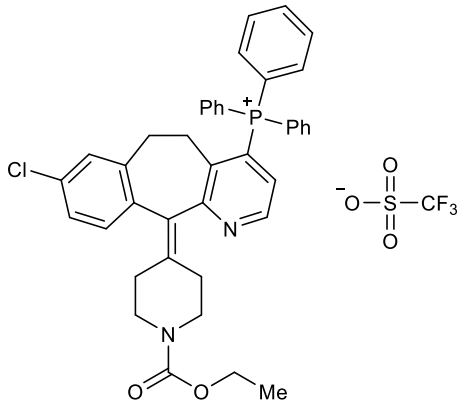

163.68
163.60
155.37
149.14
149.03
139.23
136.84
136.08
136.05
134.27
134.16
133.57
131.58
131.20
131.07
129.85
126.43
122.38
119.18
116.86
115.98
77.32
77.20
77.00
76.68
61.39
44.65
44.41
30.74
30.46
30.39
29.39
14.59
CDCl3, 100 MHz
Ph
P
Ph
Cl
N
O
S
CF3
N
O
O
Me
5
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

$CDCl_3$, 365 MHz



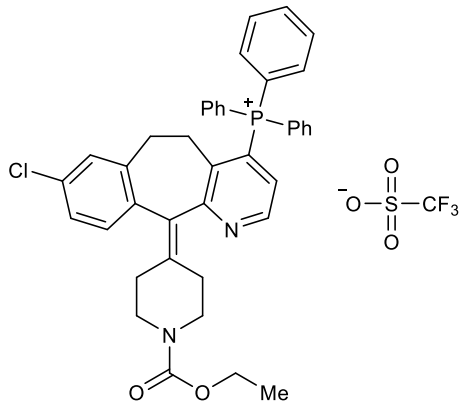
5

$CDCl_3$, 162 MHz

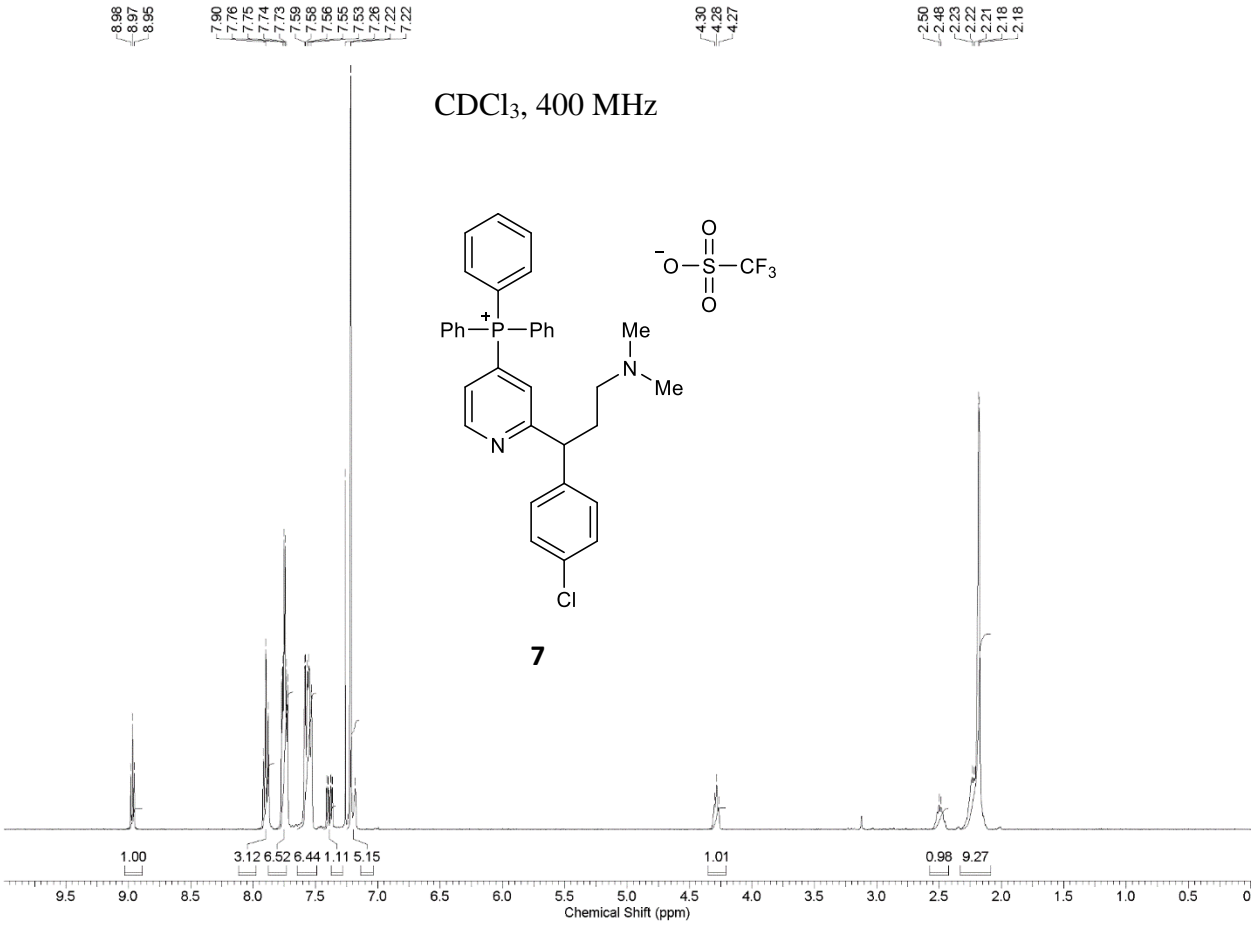


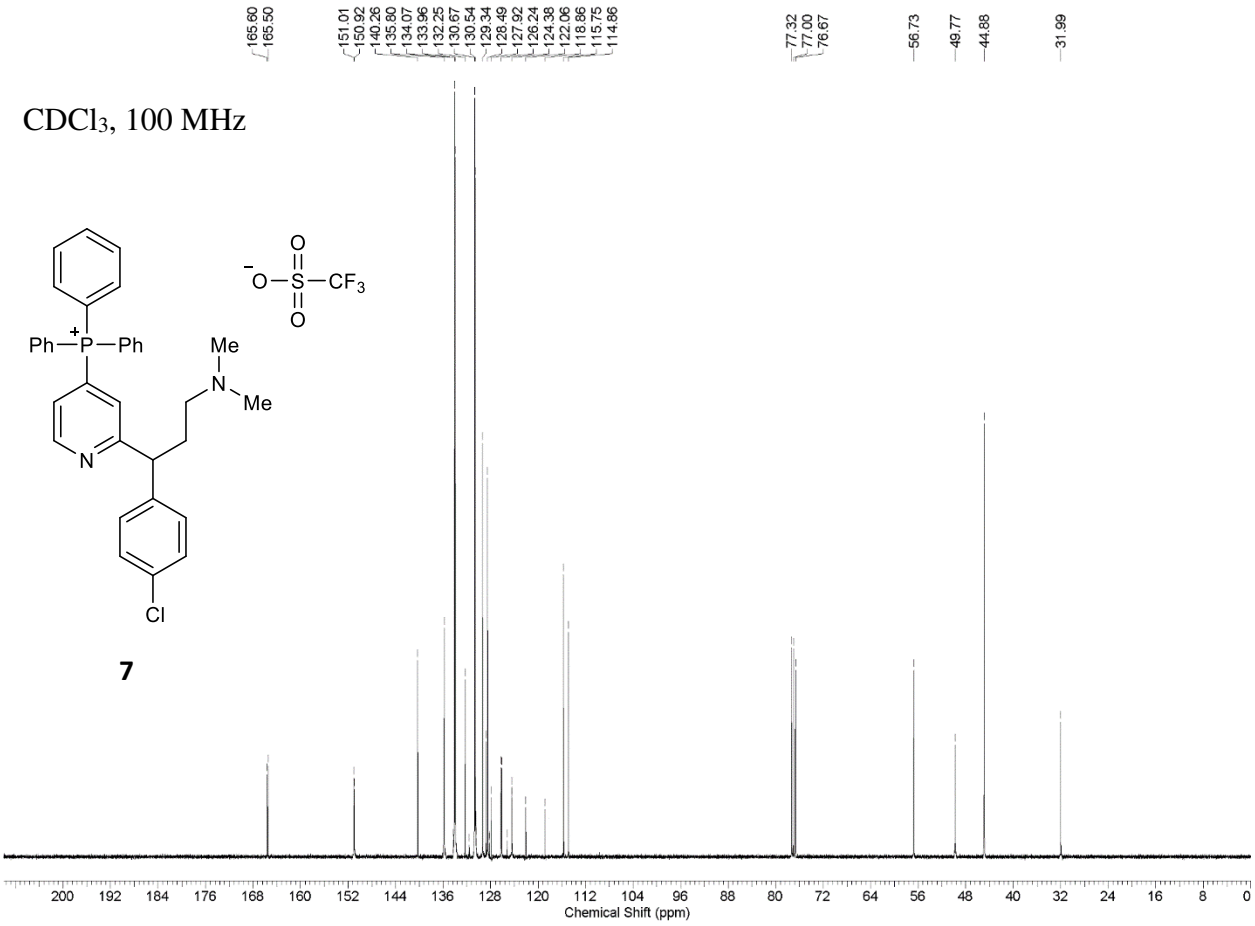
5

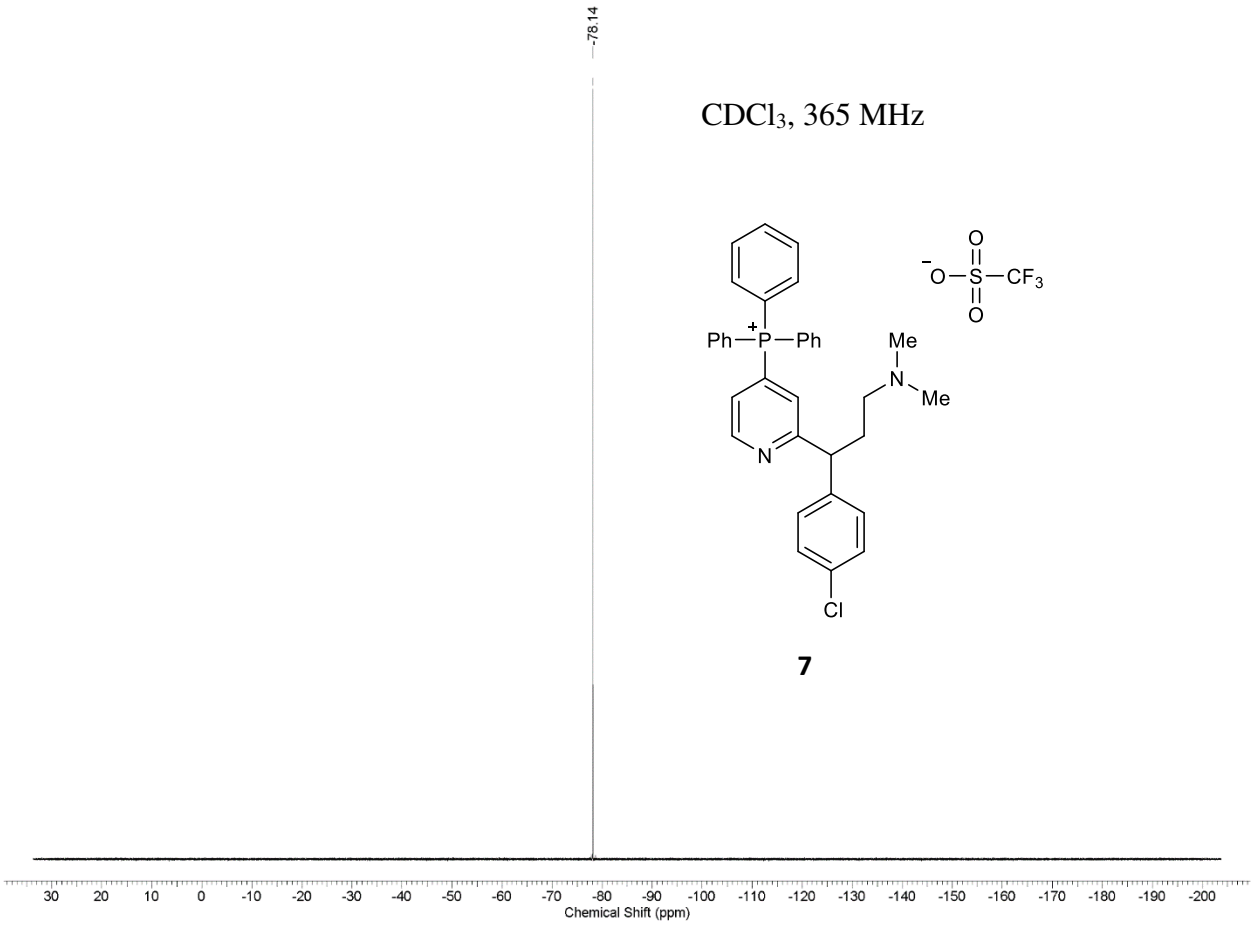
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



5


8.98
8.97
8.95
7.90
7.76
7.75
7.74
7.73
7.59
7.58
7.56
7.55
7.53
7.26
7.22
7.22
4.30
4.28
4.27
2.50
2.48
2.23
2.22
2.21
2.18
2.18
CDCl3, 400 MHz
Ph
P
Ph
Me
N
Me
N
O
S
CF3
O
O
Cl
7
1.00
3.12
6.52
6.44
1.11
5.15
1.01
0.98
9.27
Chemical Shift (ppm)

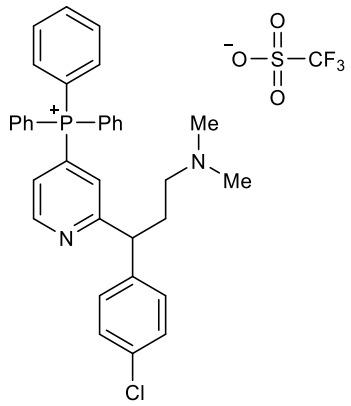

165.60
165.50
151.01
150.92
140.26
135.80
134.07
133.96
132.25
130.67
130.54
129.34
128.49
127.92
126.24
124.38
122.06
118.86
115.75
114.86
77.32
77.00
76.67
56.73
49.77
44.88
31.99
CDCl3, 100 MHz
Ph
P
Ph
Me
N
Me
N
Cl
O
O
S
CF3
O
7
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



$CDCl_3$, 365 MHz

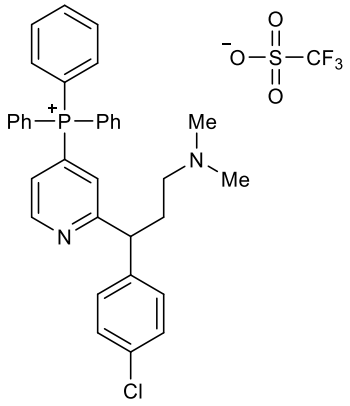
7

$CDCl_3$, 162 MHz

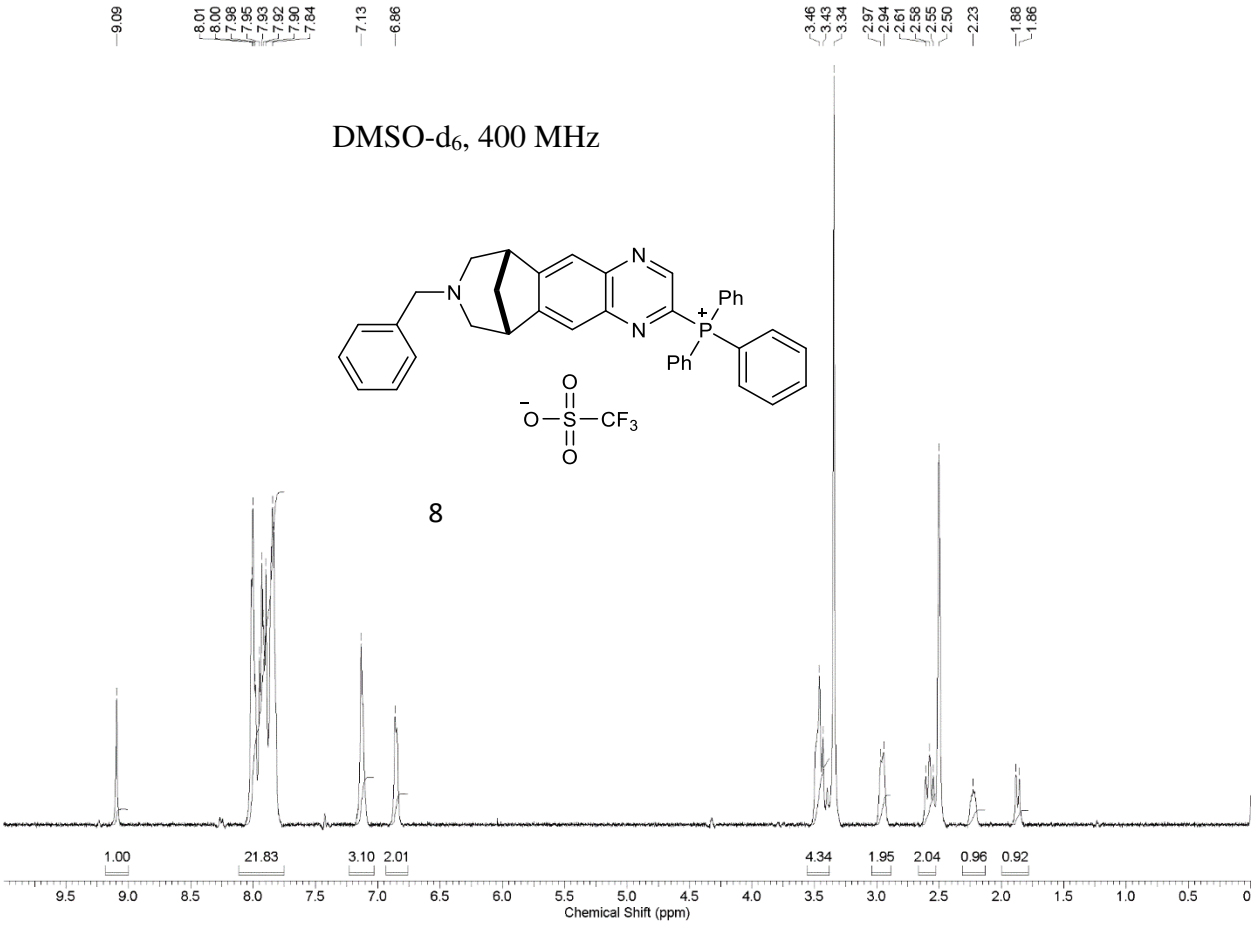


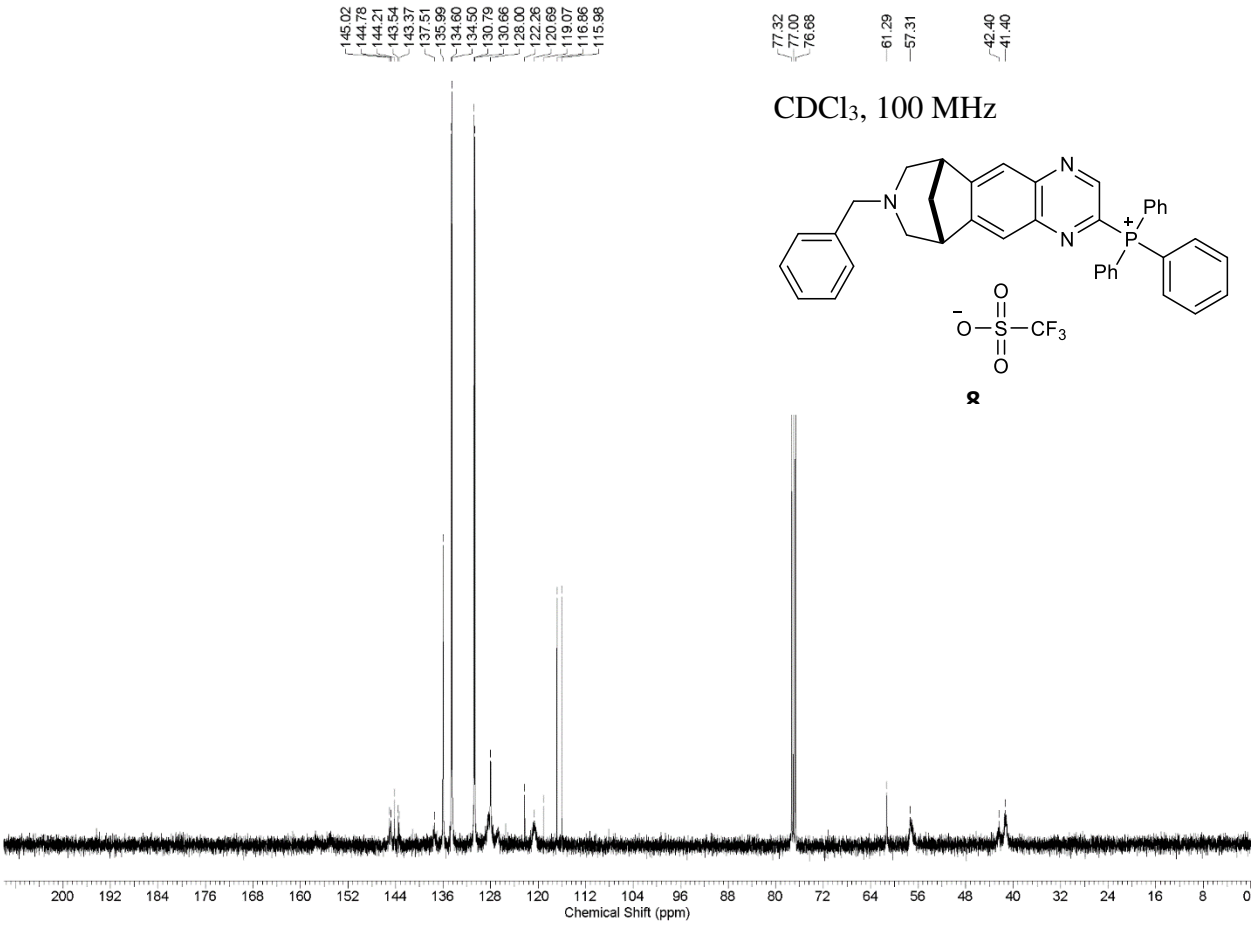
7

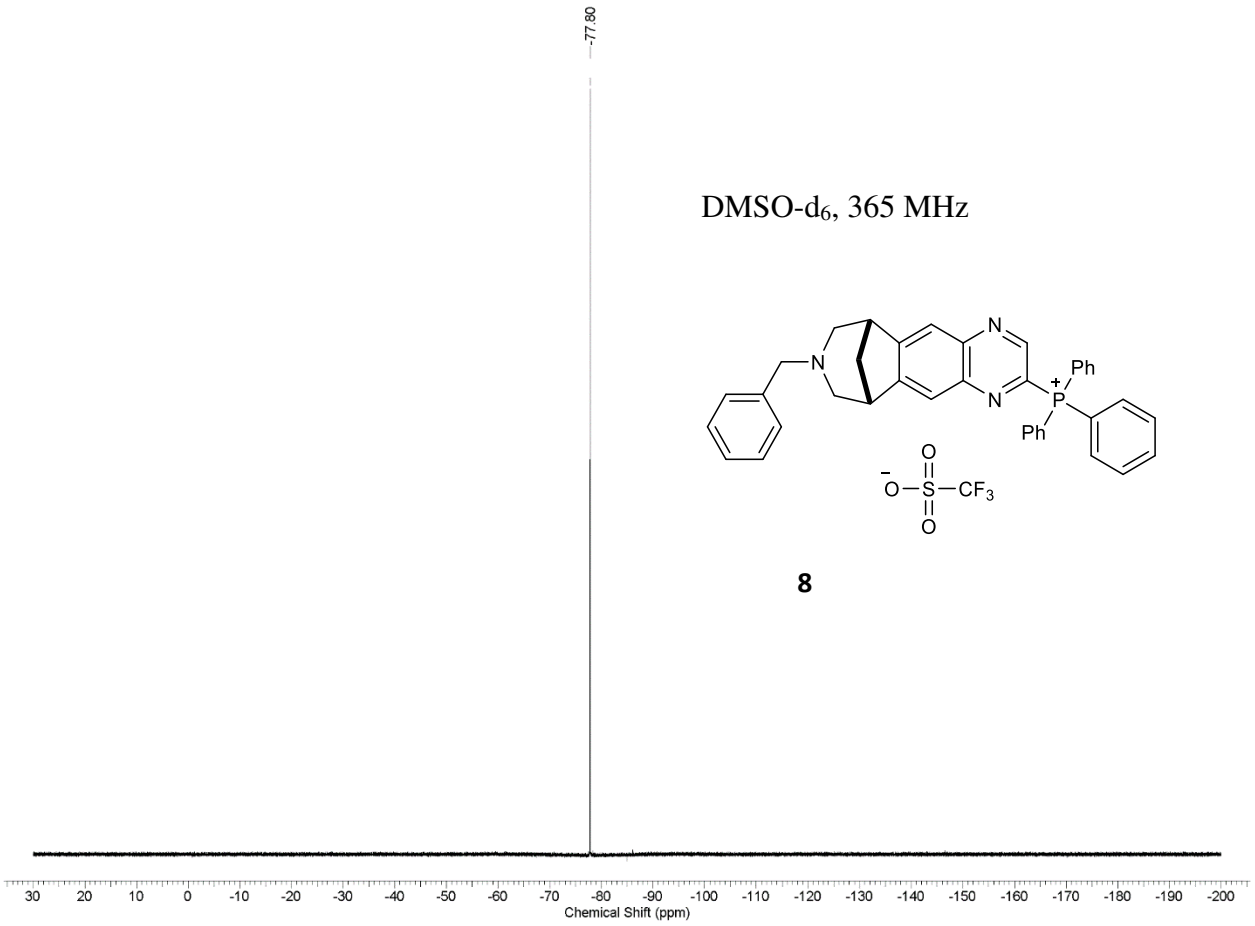
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



7


9.09
8.01
8.00
7.98
7.95
7.93
7.92
7.90
7.84
7.13
6.86
3.46
3.43
3.34
2.97
2.94
2.61
2.58
2.55
2.50
2.23
1.88
1.86
DMSO-d6, 400 MHz
N
N
N
Ph
P
Ph
O
O
S
CF3
O
8
1.00
21.83
3.10
2.01
4.34
1.95
2.04
0.96
0.92
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
Chemical Shift (ppm)

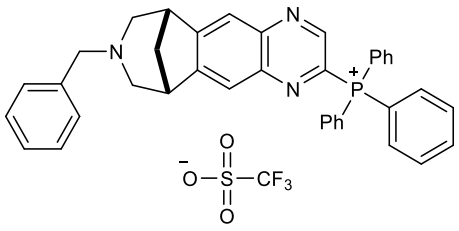

145.02
144.78
144.21
143.54
143.37
137.51
135.99
134.60
134.50
130.79
130.66
128.00
122.26
120.69
119.07
116.86
115.98
77.32
77.00
76.68
61.29
57.31
42.40
41.40
CDCl3, 100 MHz
N
N
N
P
Ph
Ph
Ph
O
O
S
CF3
8
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)



DMSO-d_6, 365 MHz

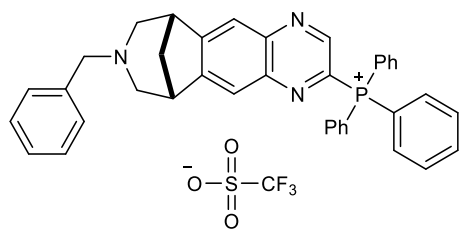
8

DMSO-d_6, 162 MHz

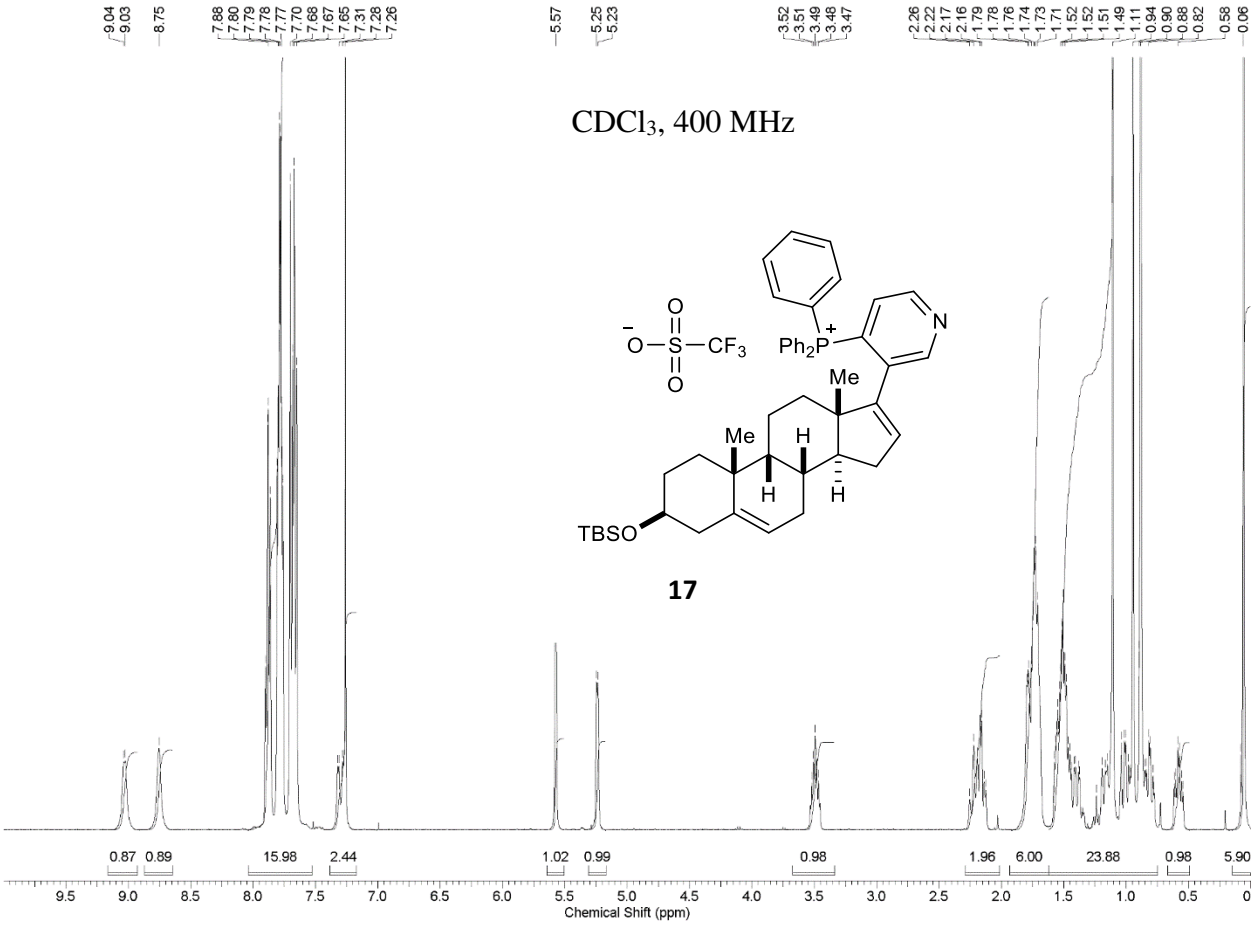


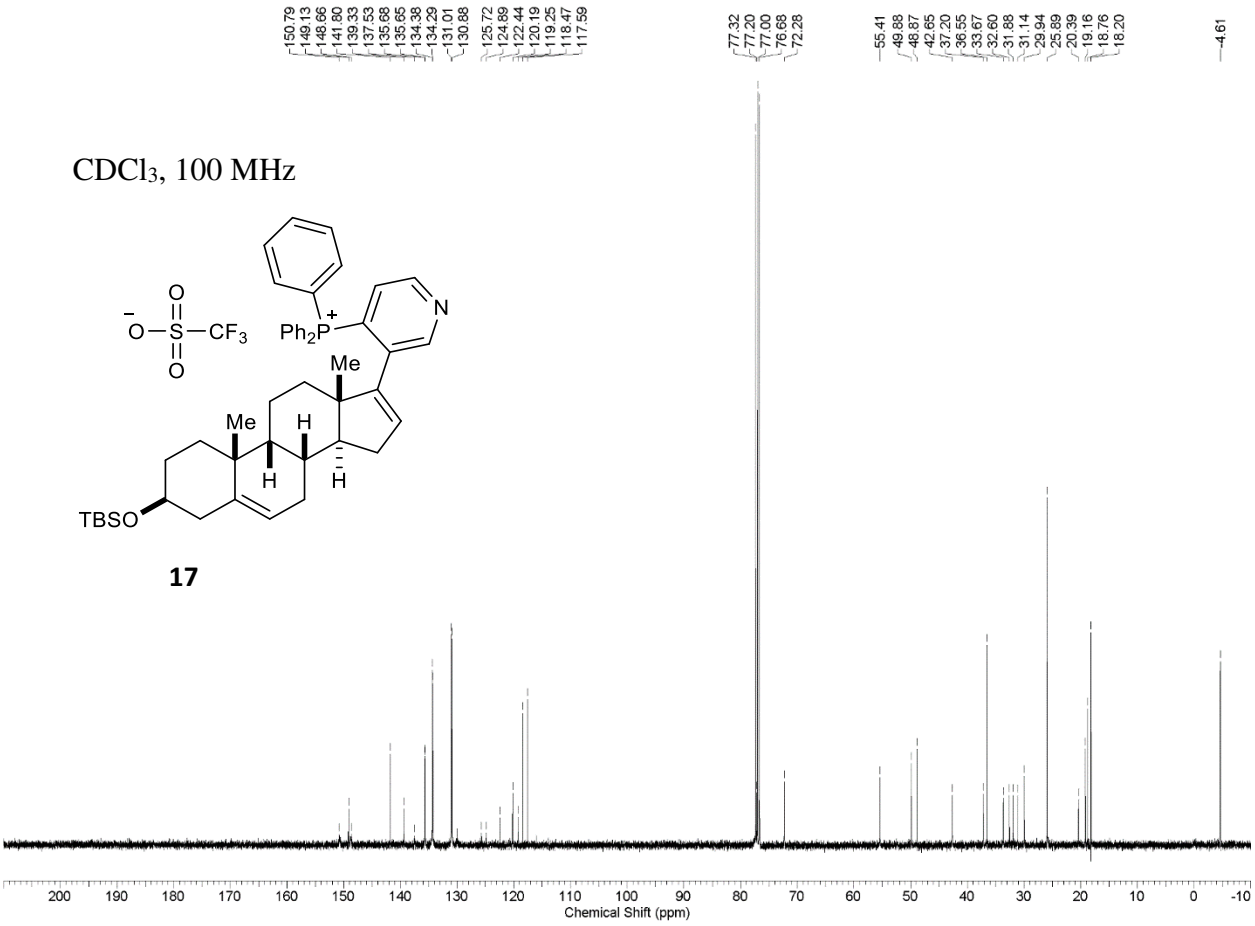
8

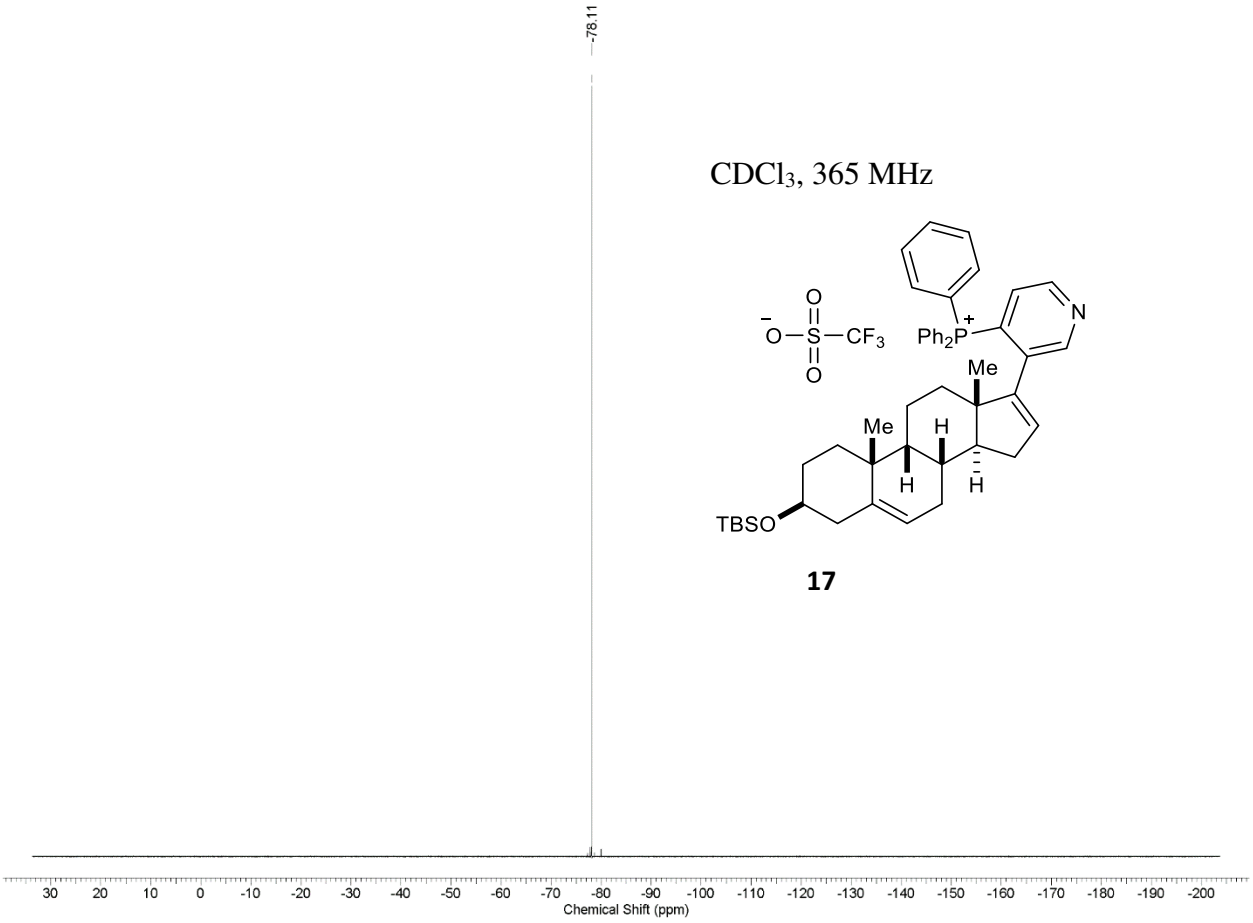
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



8


9.04
9.03
8.75
7.88
7.80
7.79
7.78
7.77
7.70
7.68
7.67
7.65
7.31
7.28
7.26
5.57
5.25
5.23
3.52
3.51
3.49
3.48
3.47
2.26
2.22
2.17
2.16
1.79
1.78
1.76
1.74
1.73
1.71
1.52
1.52
1.51
1.49
1.11
0.94
0.90
0.88
0.82
0.58
0.06
CDCl3, 400 MHz
O
O
O
S
CF3
Ph2P
N
Me
Me
H
H
H
TBSO
17
0.87
0.89
15.98
2.44
1.02
0.99
0.98
1.96
6.00
23.88
0.98
5.90
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
Chemical Shift (ppm)

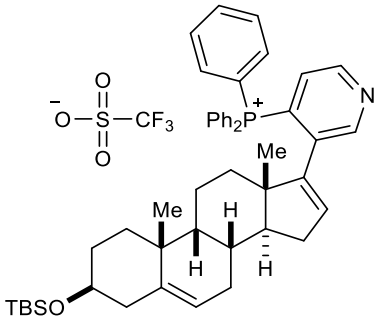

150.79
149.13
148.66
141.80
139.33
137.53
135.68
135.65
134.38
134.29
131.01
130.88
125.72
124.89
122.44
120.19
119.25
118.47
117.59
77.32
77.20
77.00
76.68
72.28
55.41
49.88
48.87
42.65
37.20
36.55
33.67
32.60
31.88
31.14
29.94
25.89
20.39
19.16
18.76
18.20
-4.61
CDCl3, 100 MHz
O
O
S
CF3
Ph2P
N
Me
Me
H
H
H
TBSO
17
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
Chemical Shift (ppm)



$CDCl_3$, 365 MHz

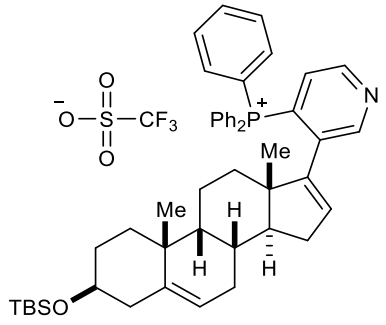
17

$CDCl_3$, 162 MHz

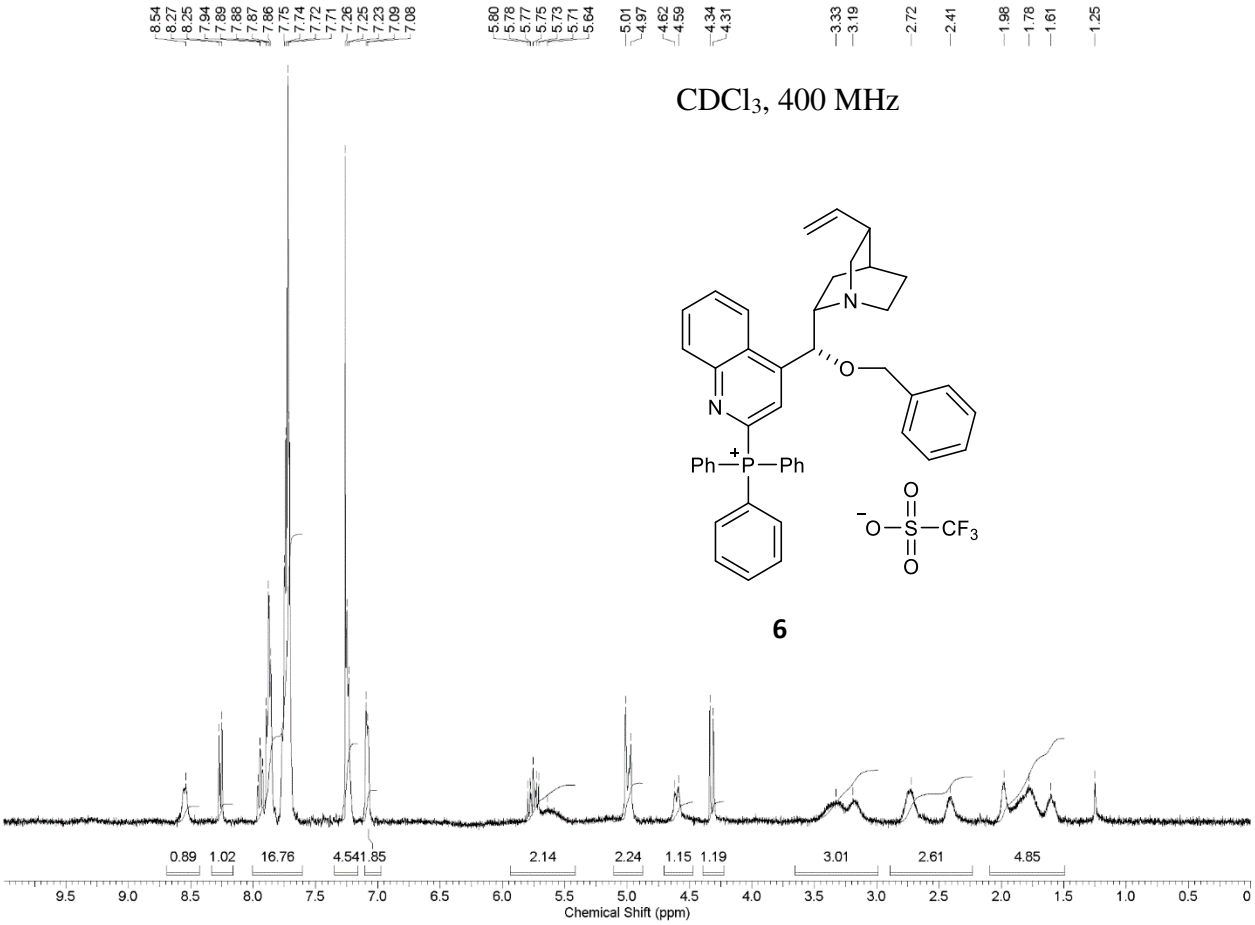


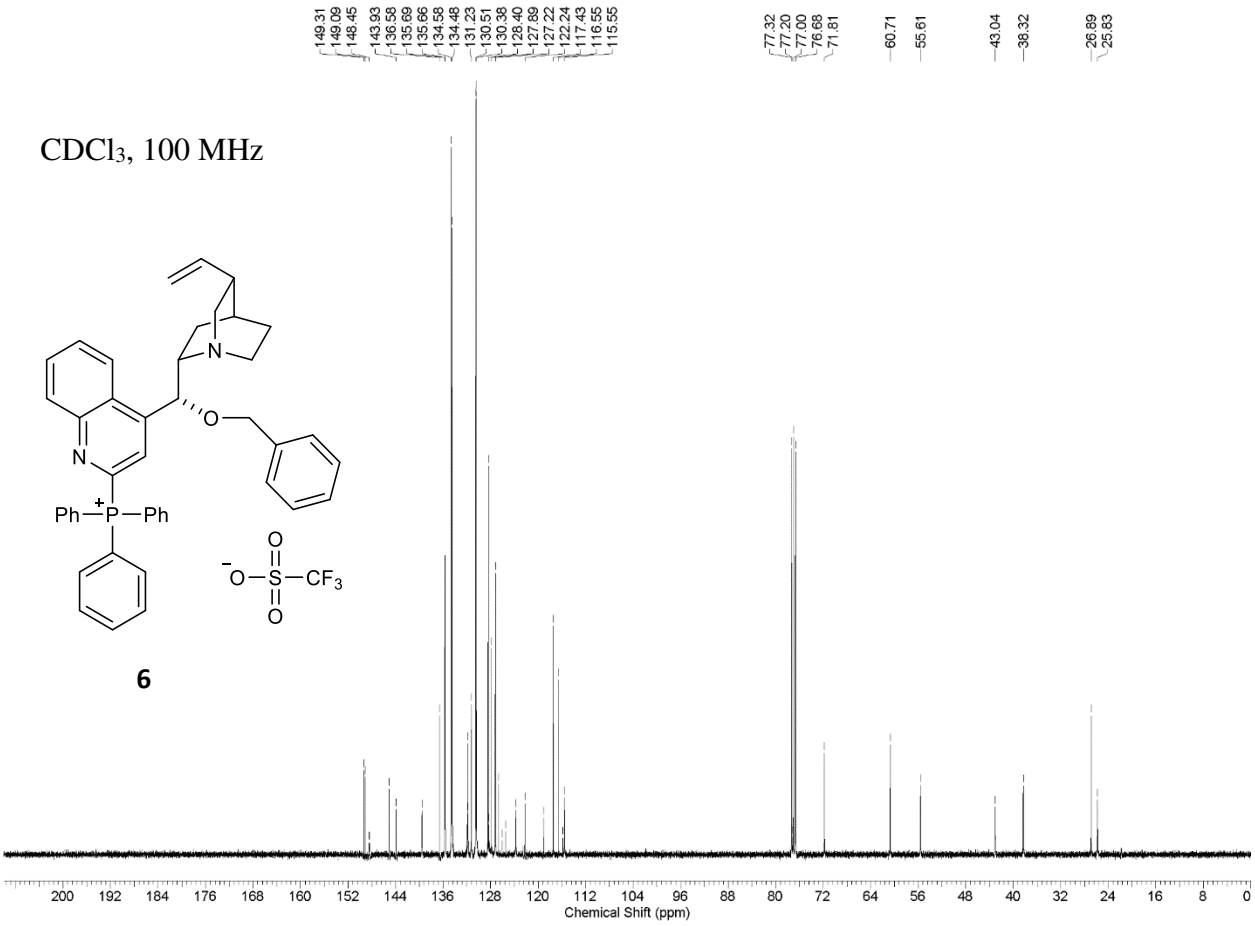
17

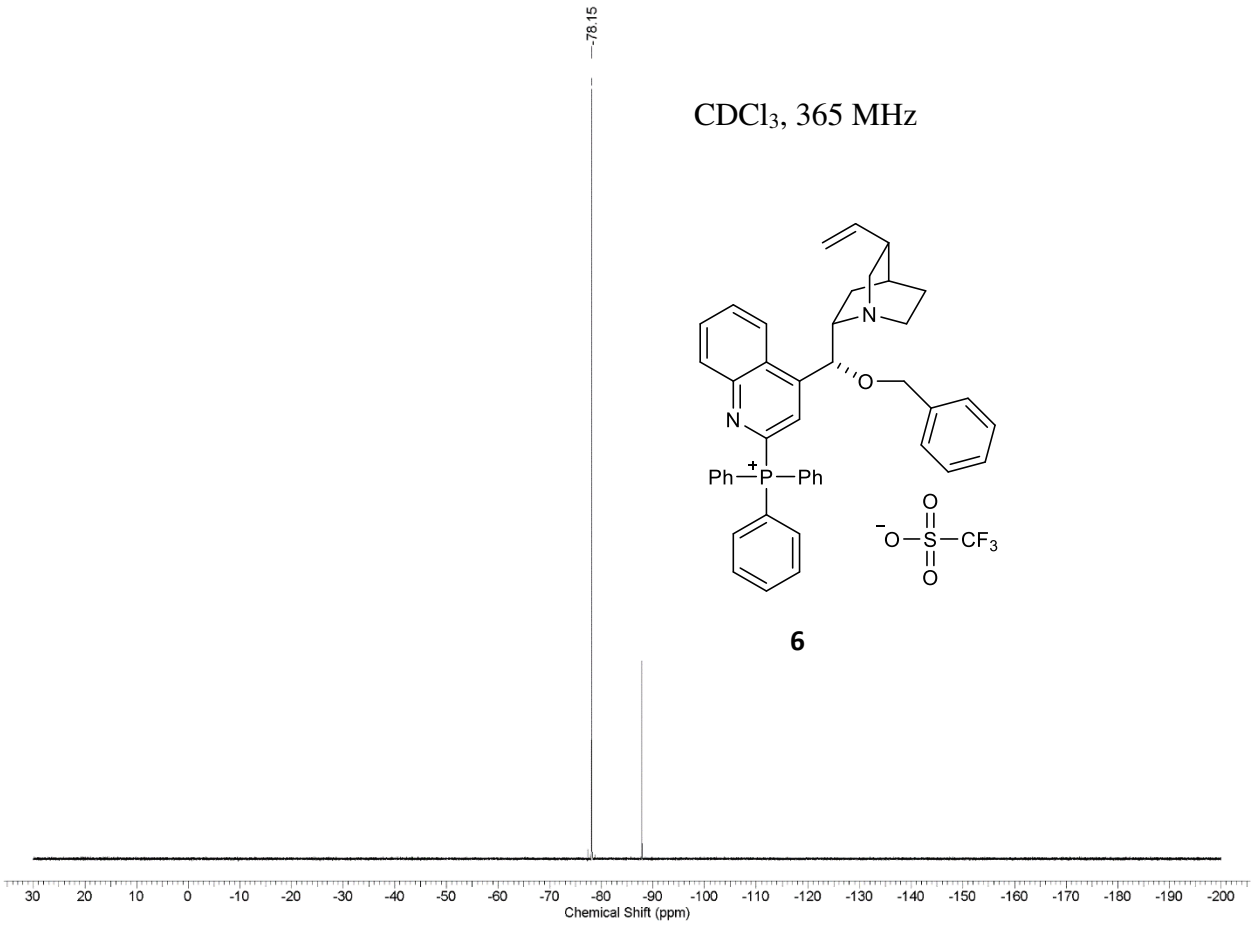
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



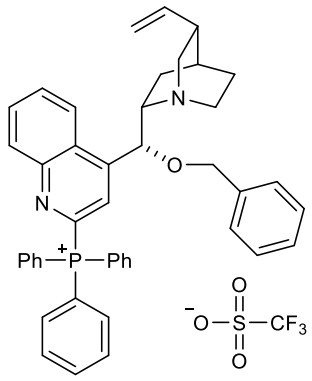
17


8.54
8.27
8.25
7.94
7.89
7.88
7.87
7.86
7.75
7.74
7.72
7.71
7.26
7.25
7.23
7.09
7.08
5.80
5.78
5.77
5.75
5.73
5.71
5.64
5.01
4.97
4.62
4.59
4.34
4.31
3.33
3.19
2.72
2.41
1.98
1.78
1.61
1.25
CDCl3, 400 MHz
Ph
P
Ph
O
S
CF3
6
0.89
1.02
16.76
4.54
1.85
2.14
2.24
1.15
1.19
3.01
2.61
4.85
Chemical Shift (ppm)


149.31
149.09
148.45
143.93
136.58
135.69
135.66
134.58
134.48
131.23
130.51
130.38
128.40
127.89
127.22
122.24
117.43
116.55
115.55
77.32
77.20
77.00
76.68
71.81
60.71
55.61
43.04
38.32
26.89
25.83
CDCl3, 100 MHz
N
O
N
Ph
P
Ph
O
O
S
CF3
O
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 0
Chemical Shift (ppm)

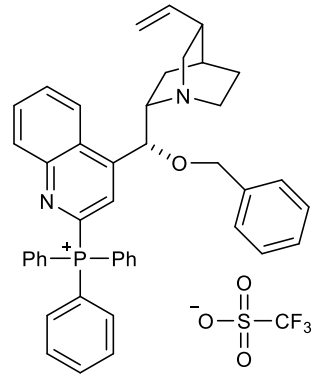

-78.15
CDCl3, 365 MHz
N
O
N
Ph
P
Ph
O
O
S
CF3
O
6
30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
Chemical Shift (ppm)

$CDCl_3$, 162 MHz

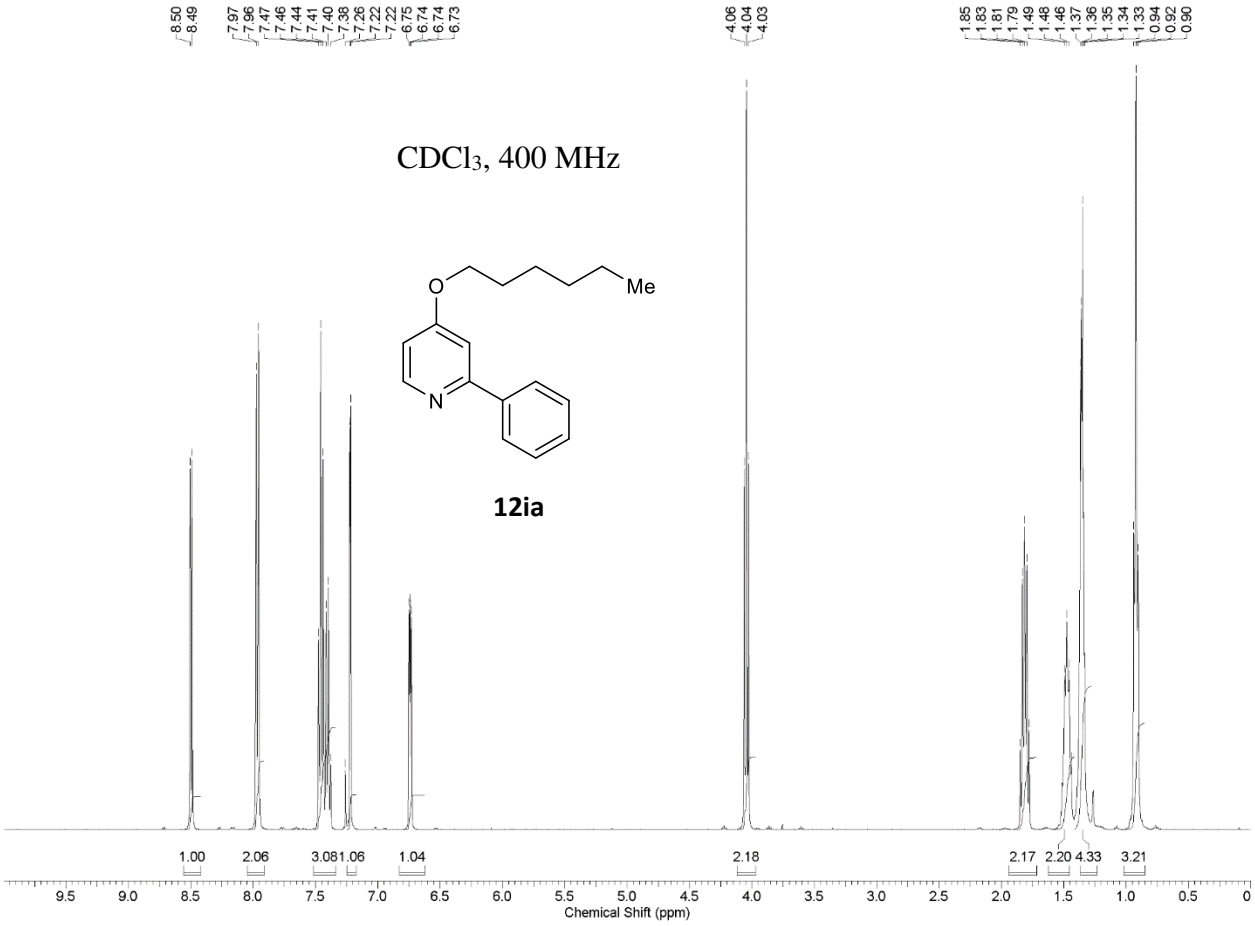


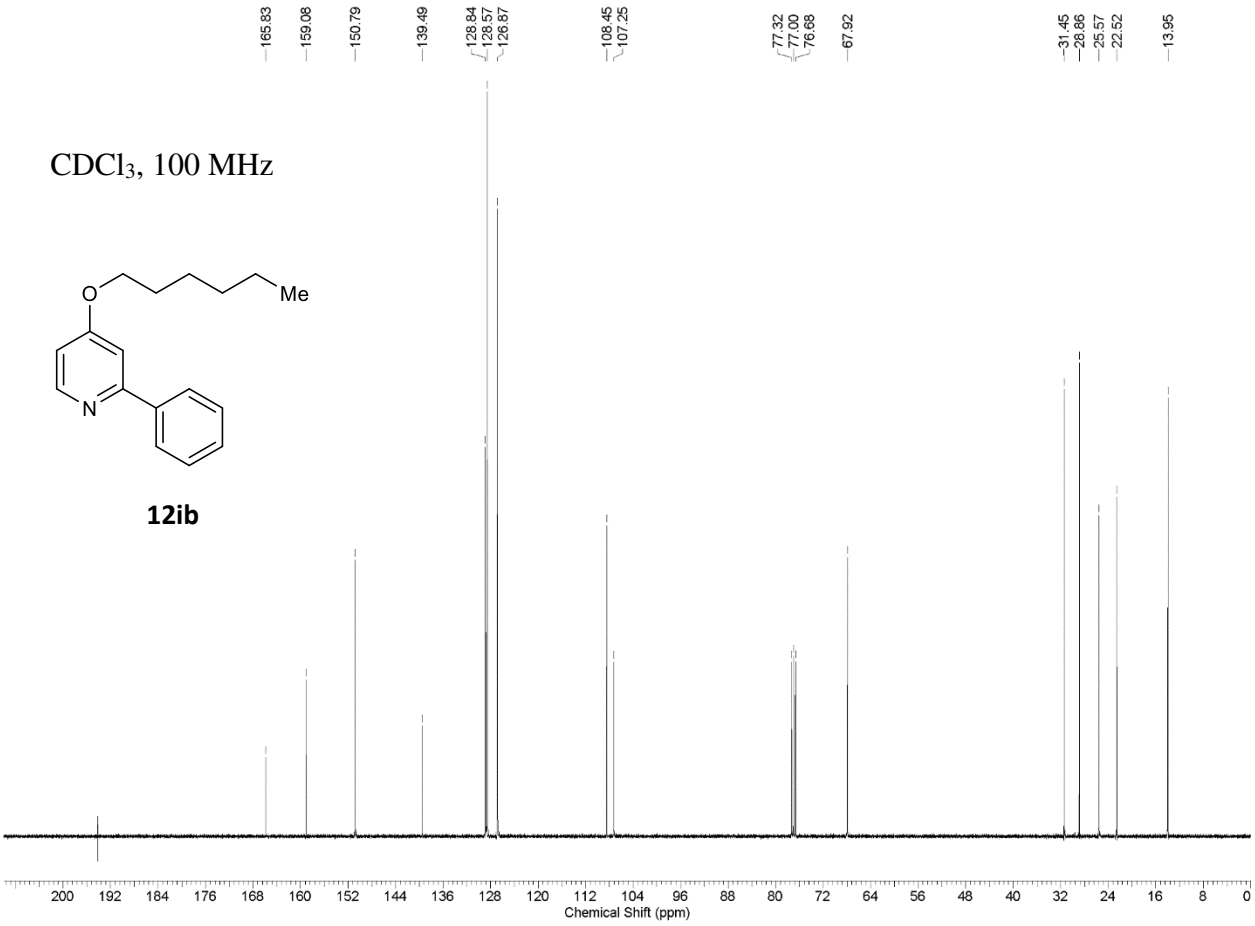
6

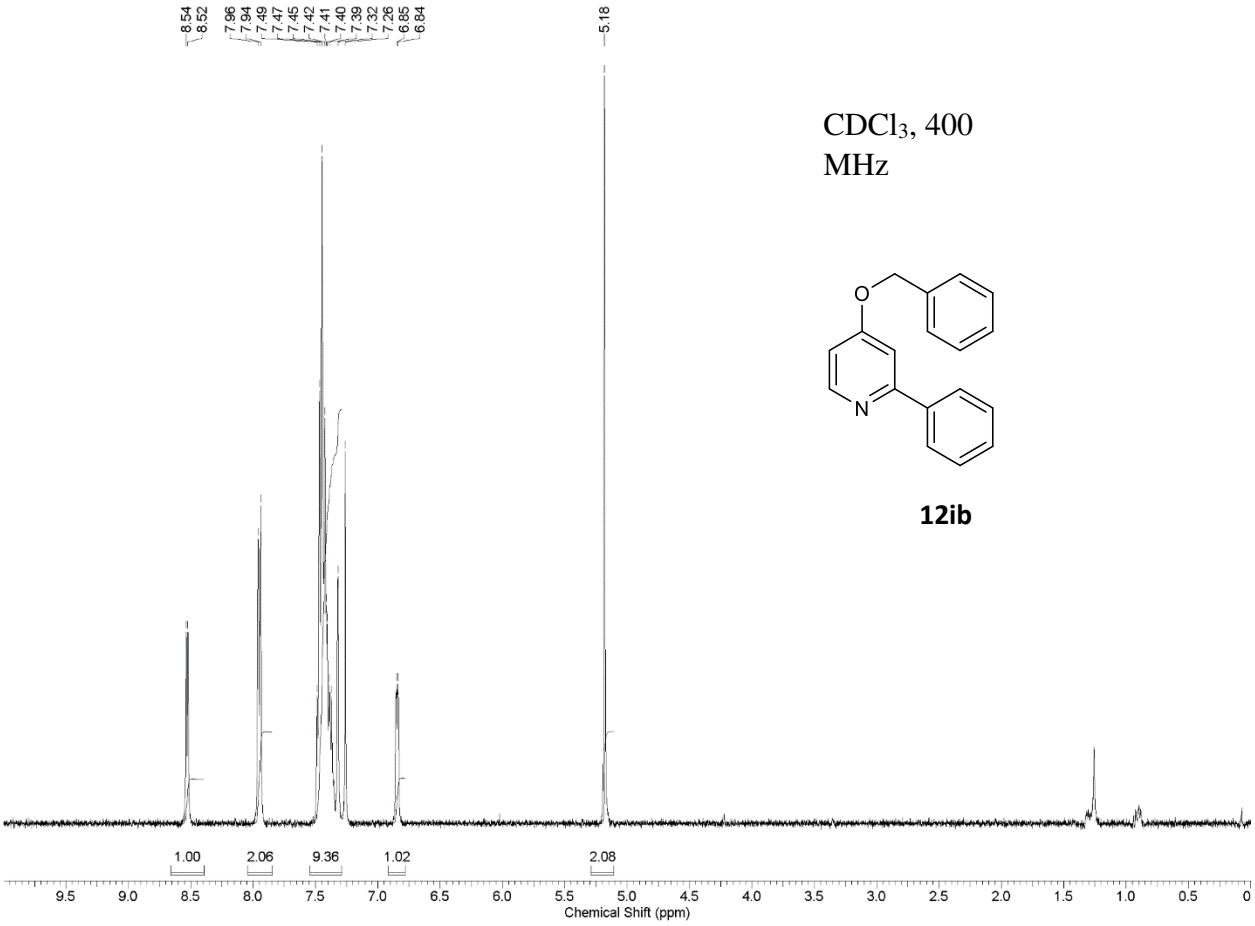
$CDCl_3$, 162 MHz (crude ^{31}P NMR)



6

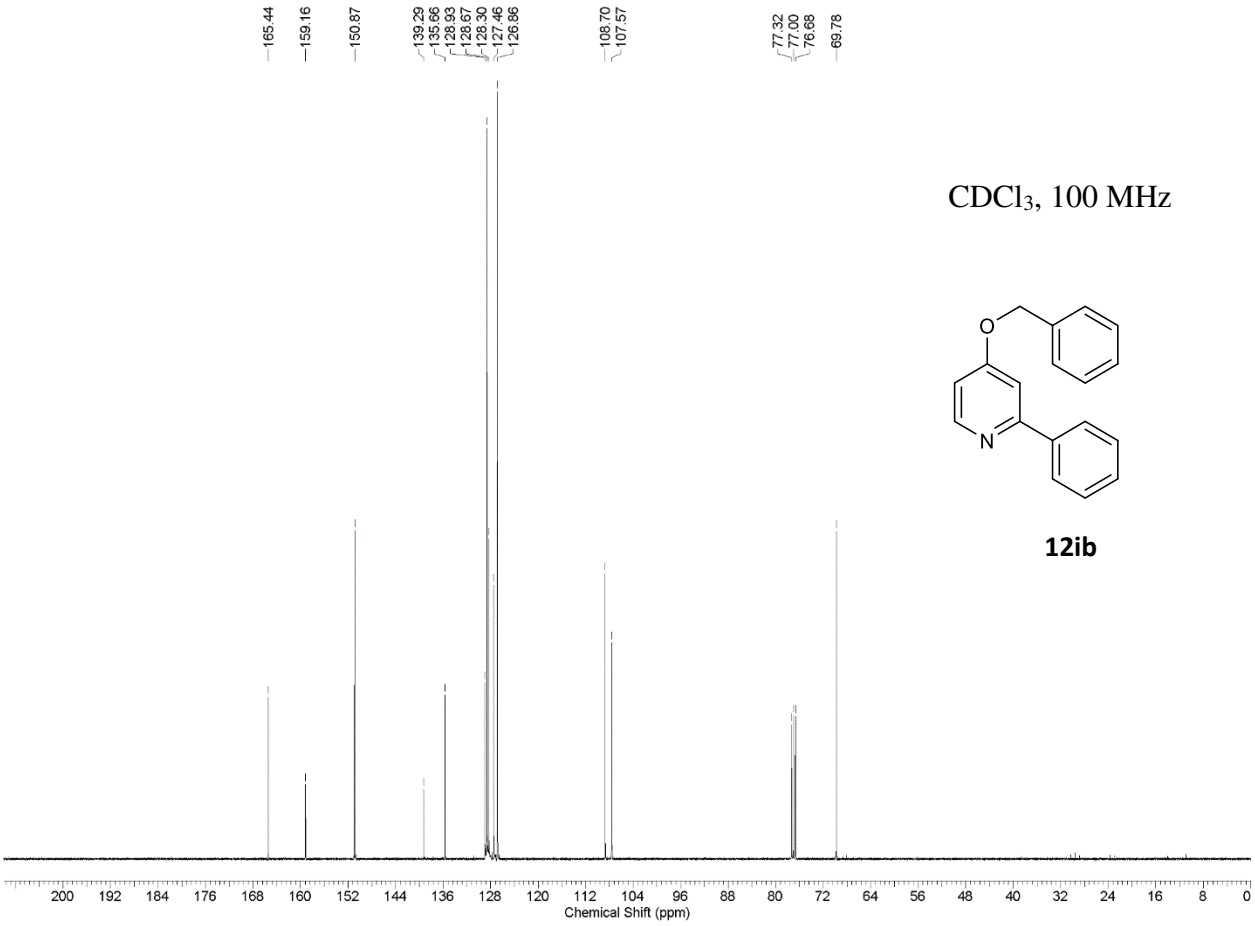

8.50
8.49
7.97
7.96
7.47
7.46
7.44
7.41
7.40
7.38
7.26
7.22
7.22
6.75
6.74
6.74
6.73
4.06
4.04
4.03
1.85
1.83
1.81
1.79
1.49
1.48
1.46
1.37
1.36
1.35
1.34
1.33
0.94
0.92
0.90
CDCl3, 400 MHz
O
Me
N
12ia
1.00
2.06
3.08
1.06
1.04
2.18
2.17
2.20
4.33
3.21
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


165.83
159.08
150.79
139.49
128.84
128.57
126.87
108.45
107.25
77.32
77.00
76.68
67.92
31.45
28.86
25.57
22.52
13.95
CDCl3, 100 MHz
O
Me
N
12ib
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)



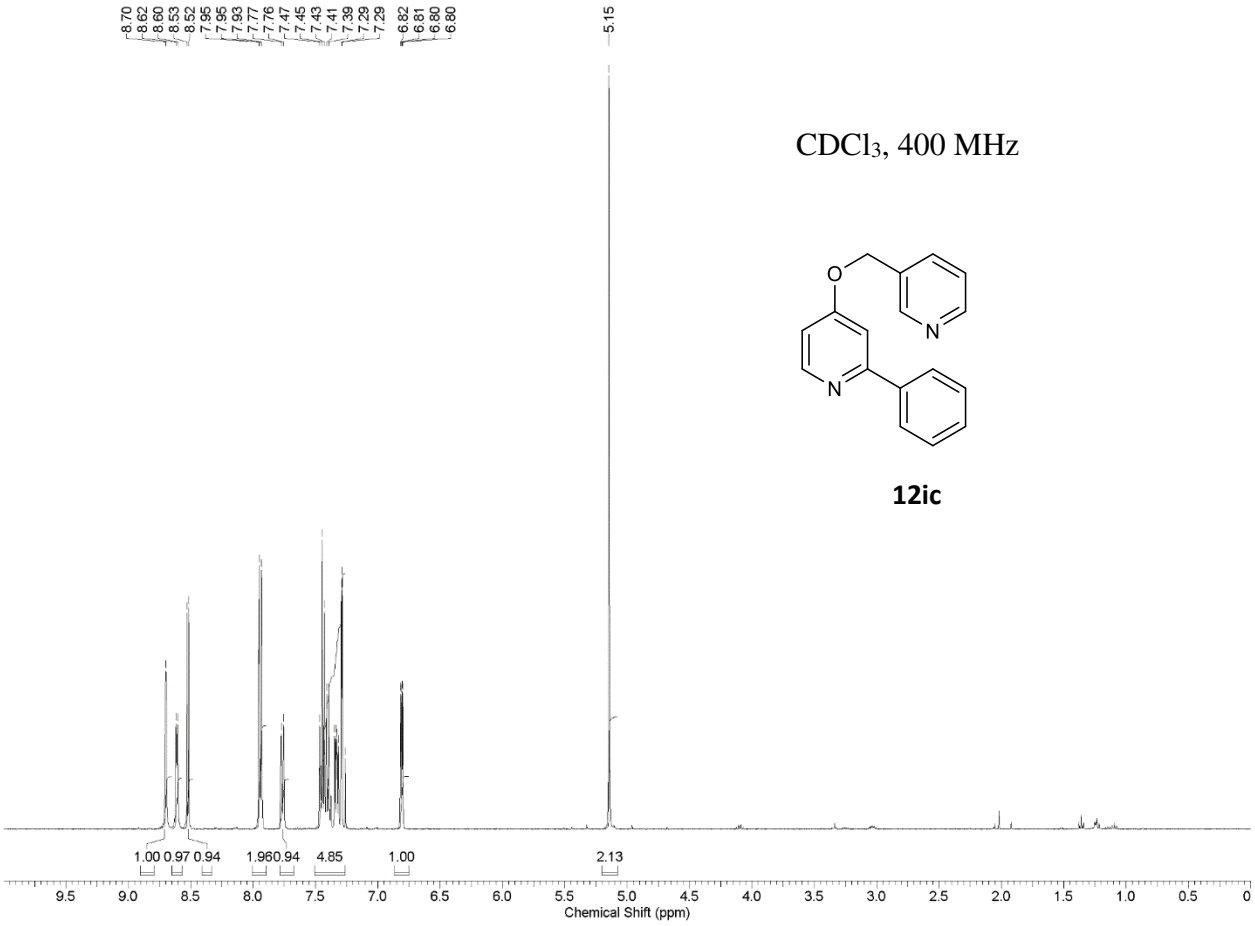
$CDCl_3$, 400 MHz

12ib



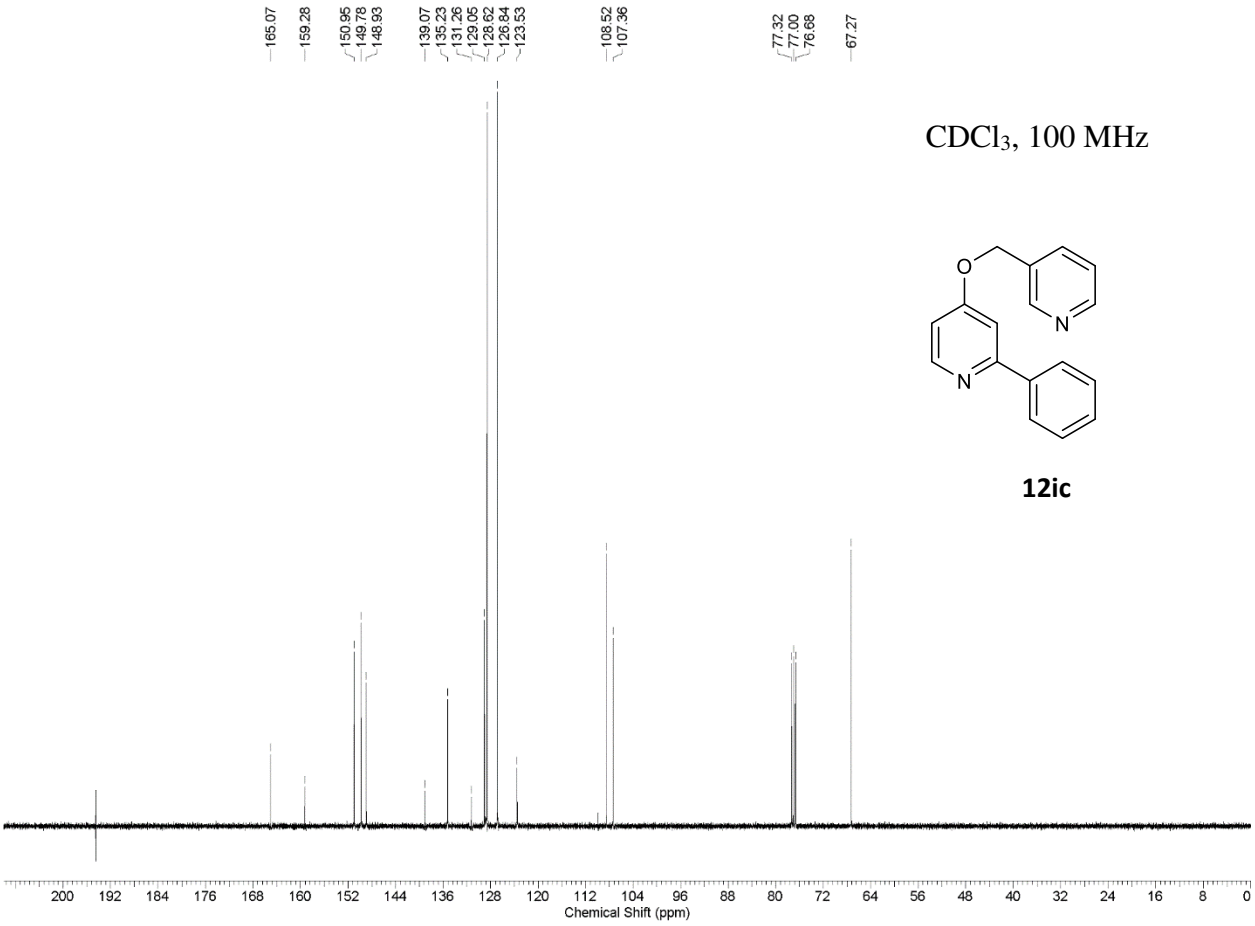
$CDCl_3$, 100 MHz

12ib



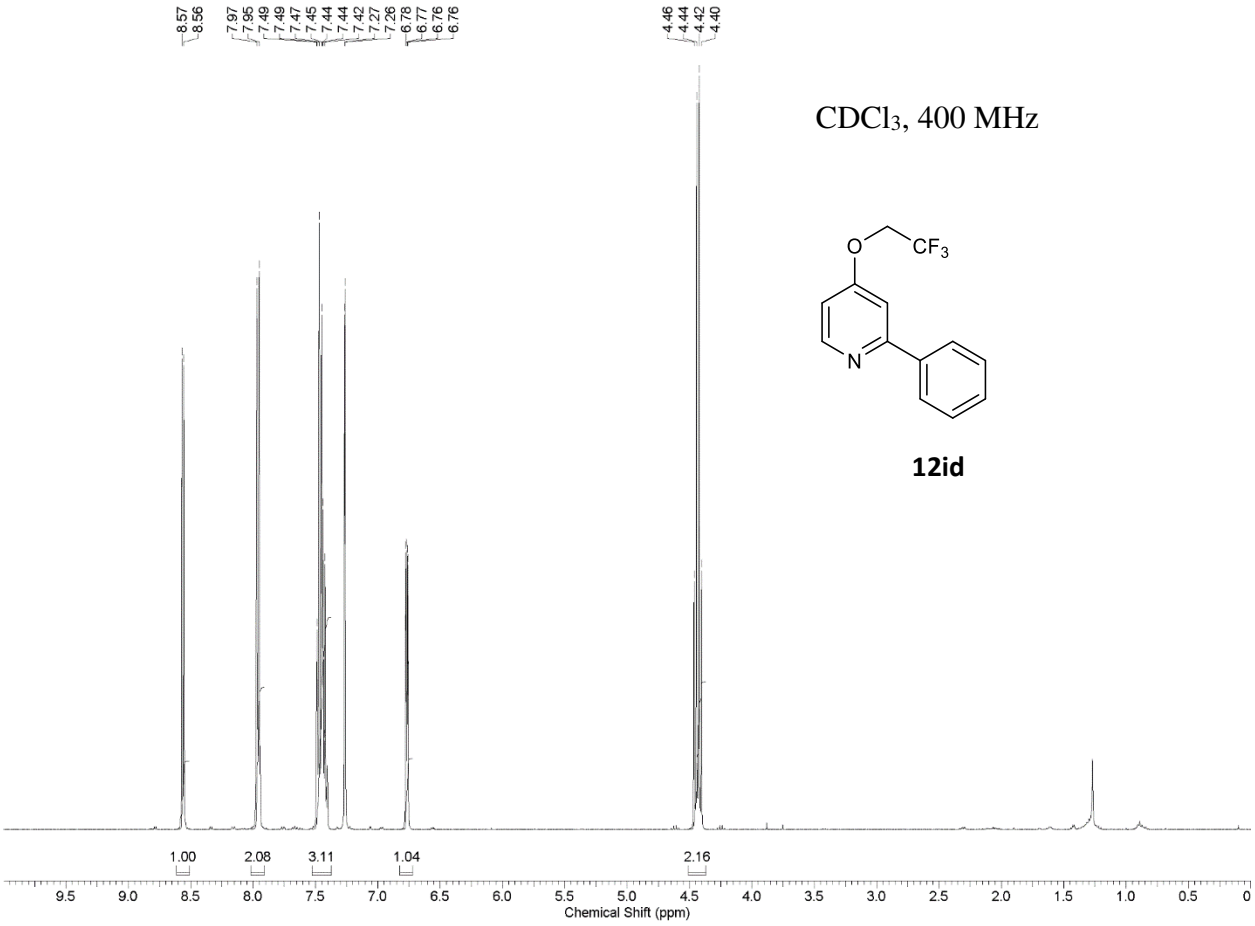
$CDCl_3$, 400 MHz

12ic



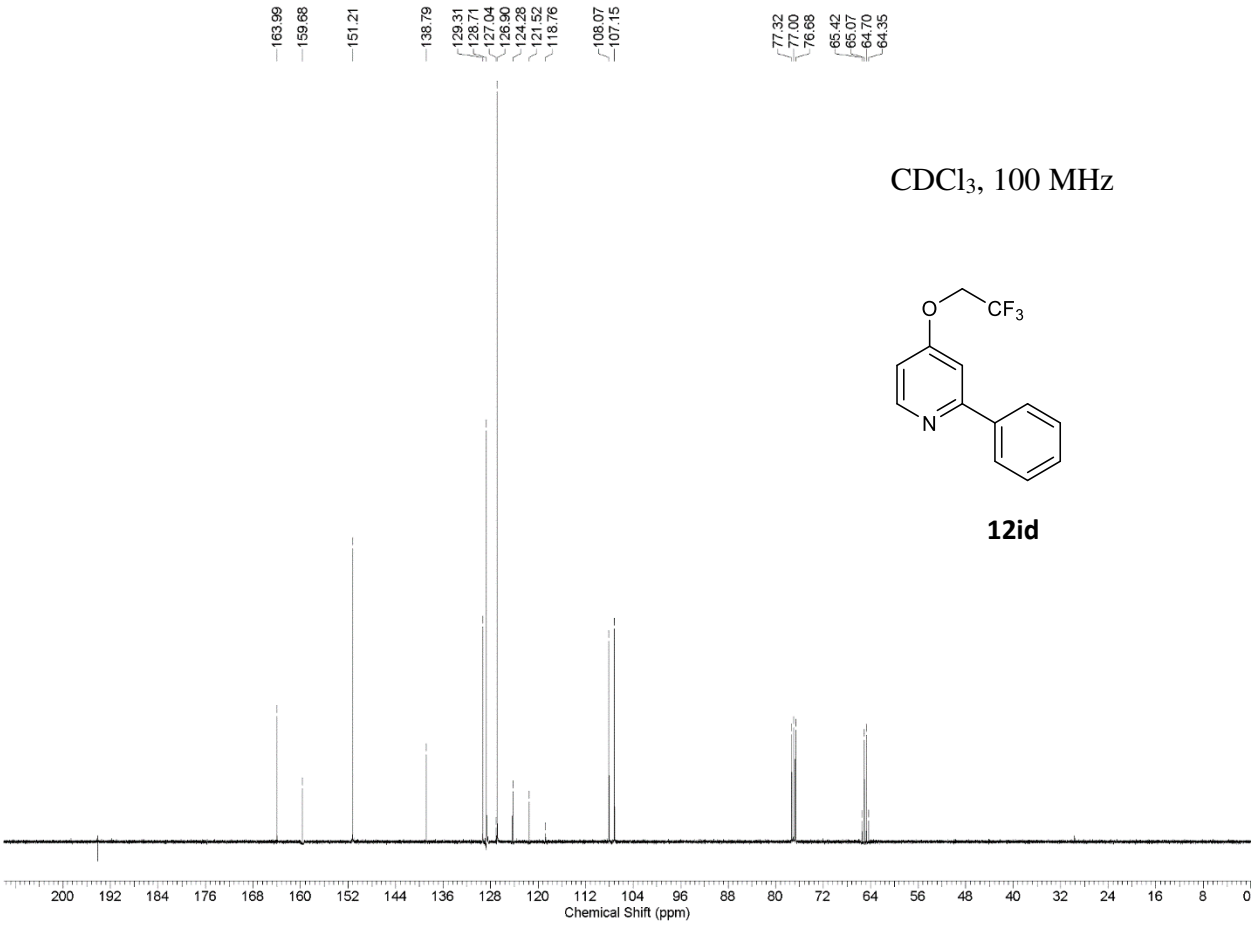
$CDCl_3$, 100 MHz

12ic



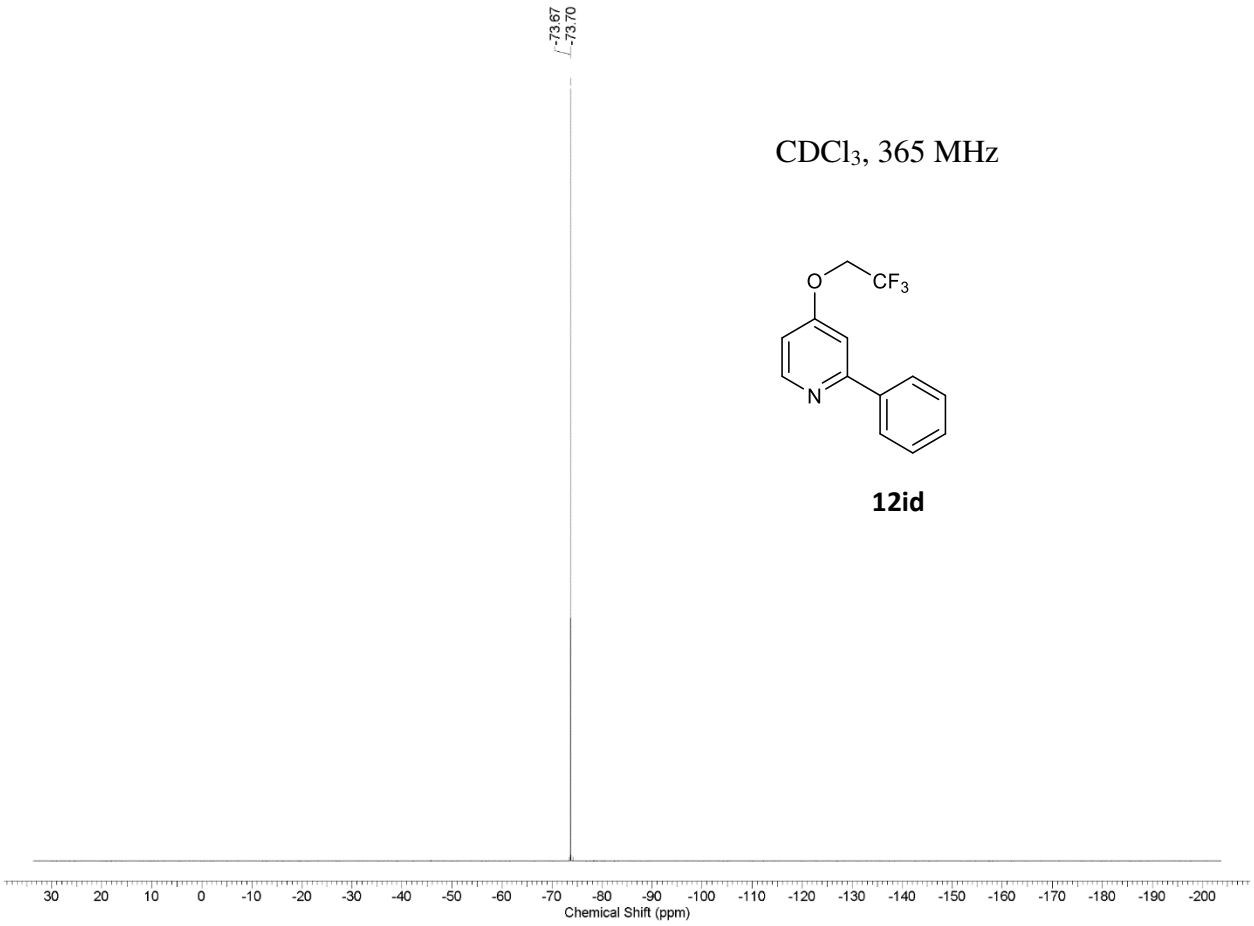
$CDCl_3$, 400 MHz

12id



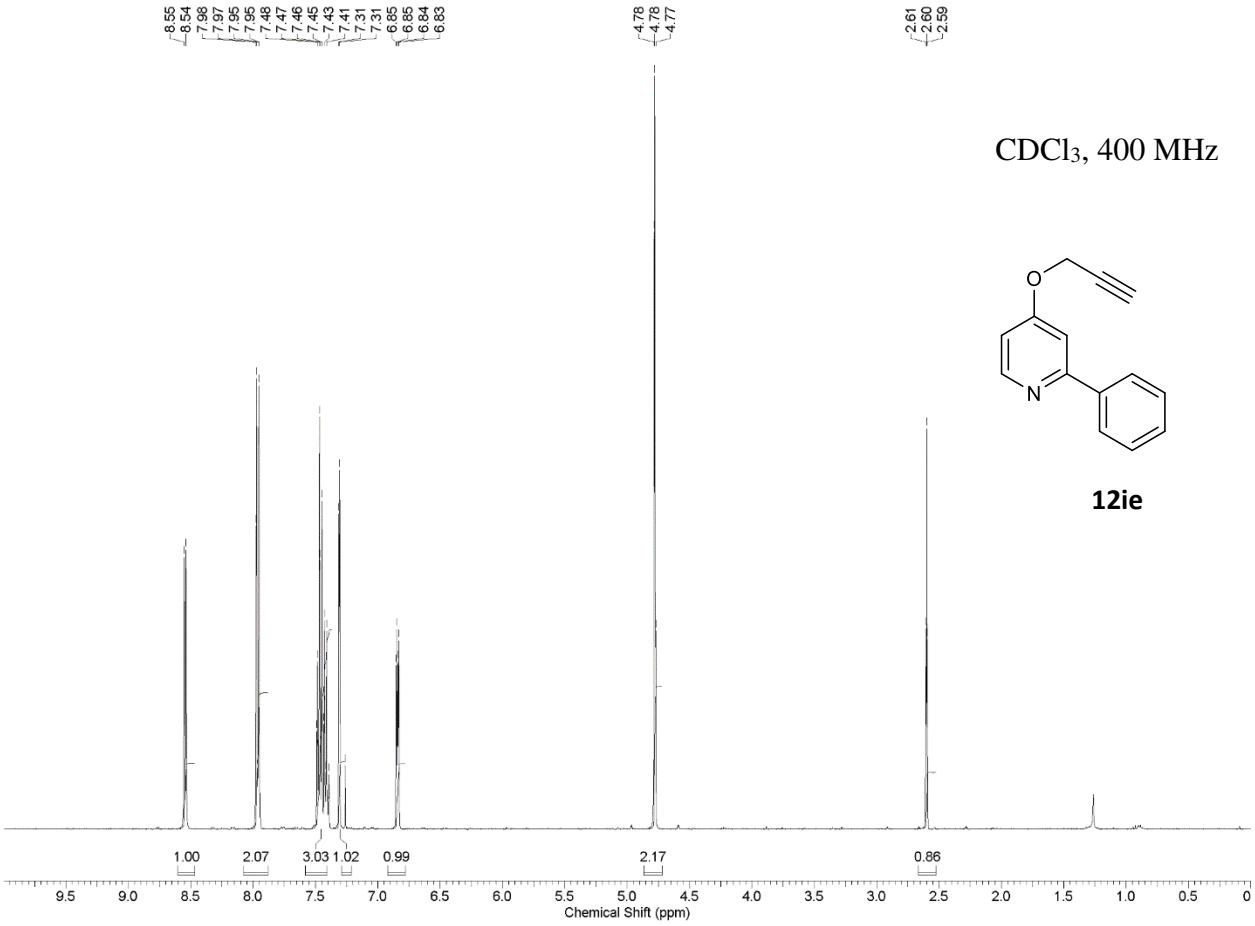
$CDCl_3$, 100 MHz

12id



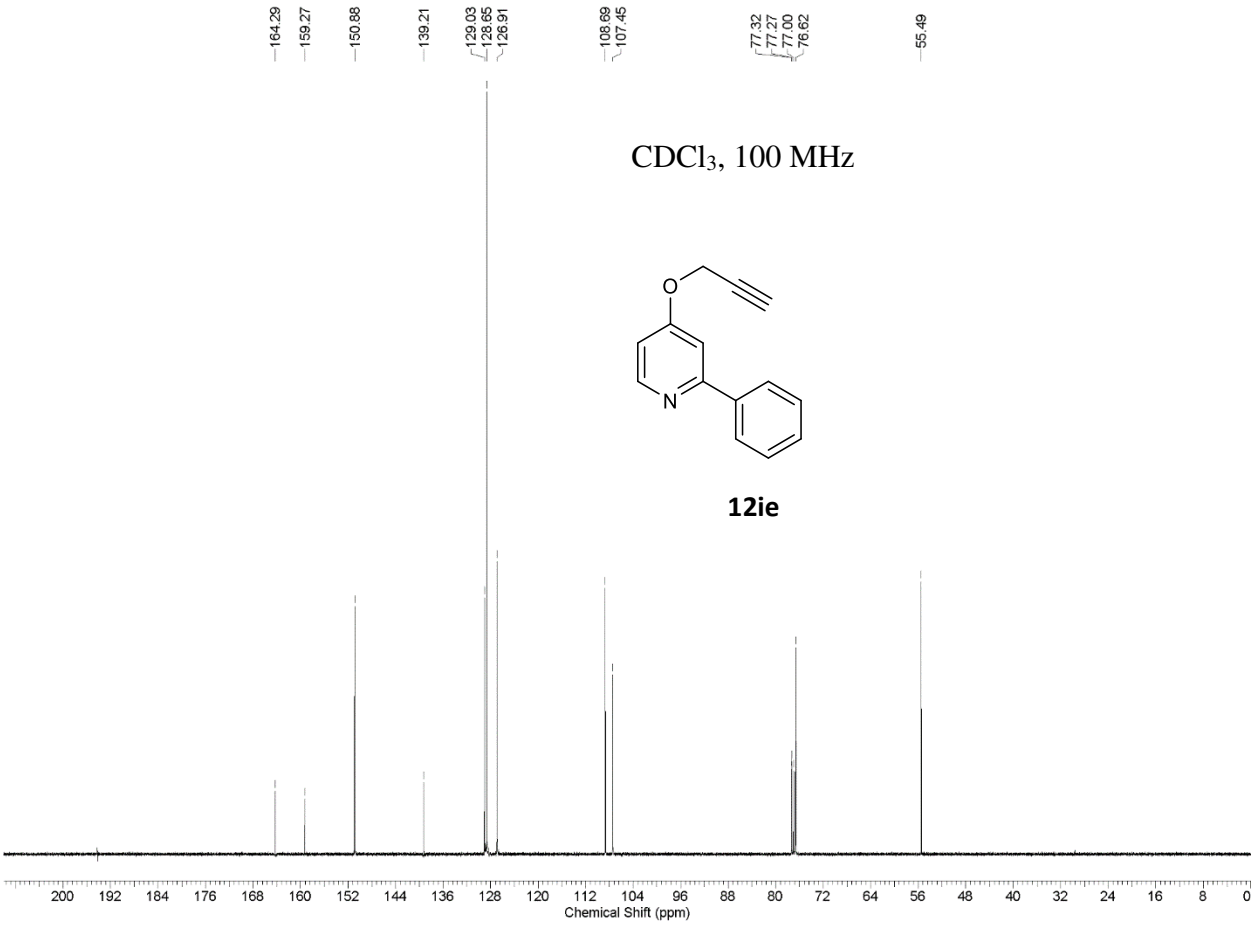
$CDCl_3$, 365 MHz

12id



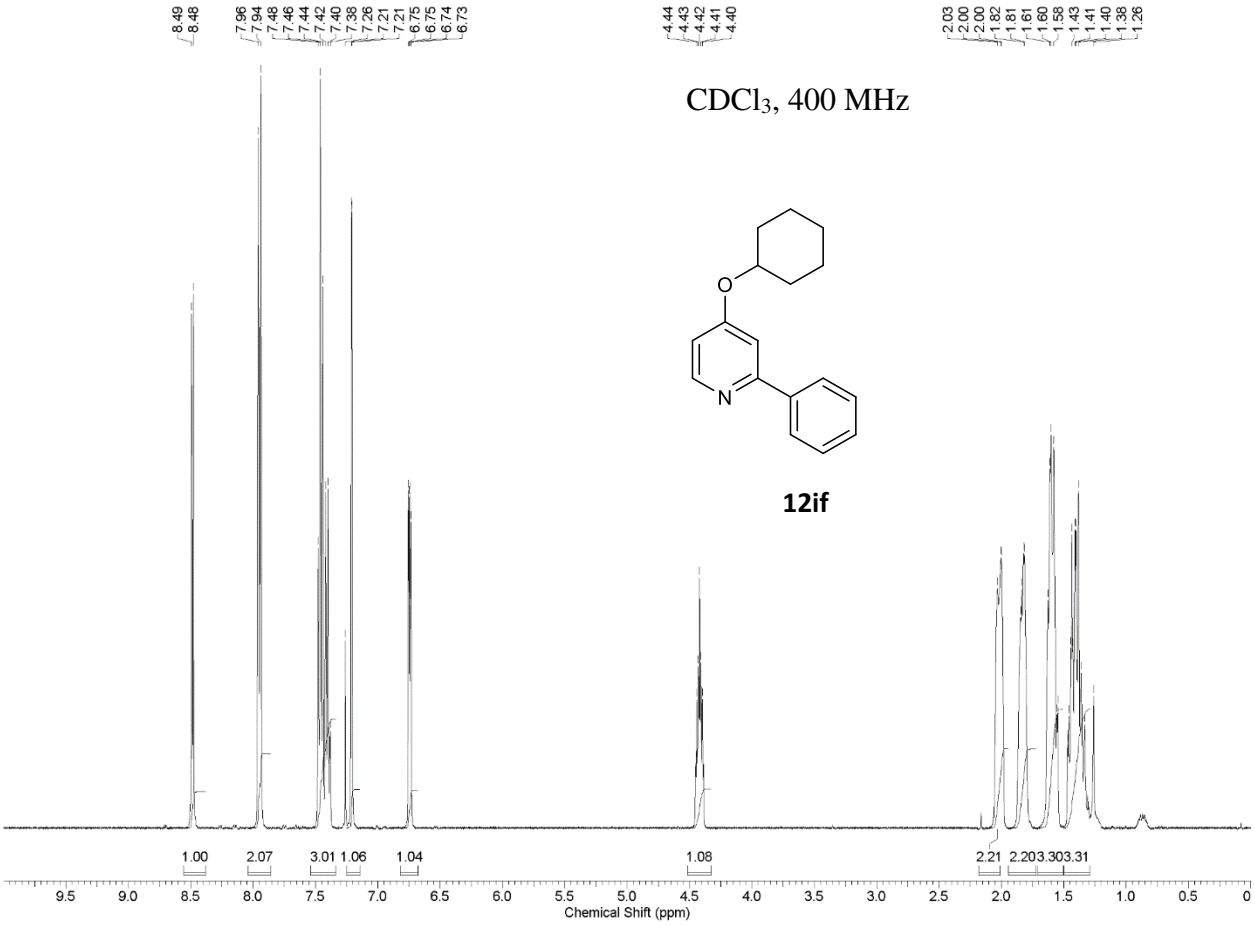
$CDCl_3$, 400 MHz

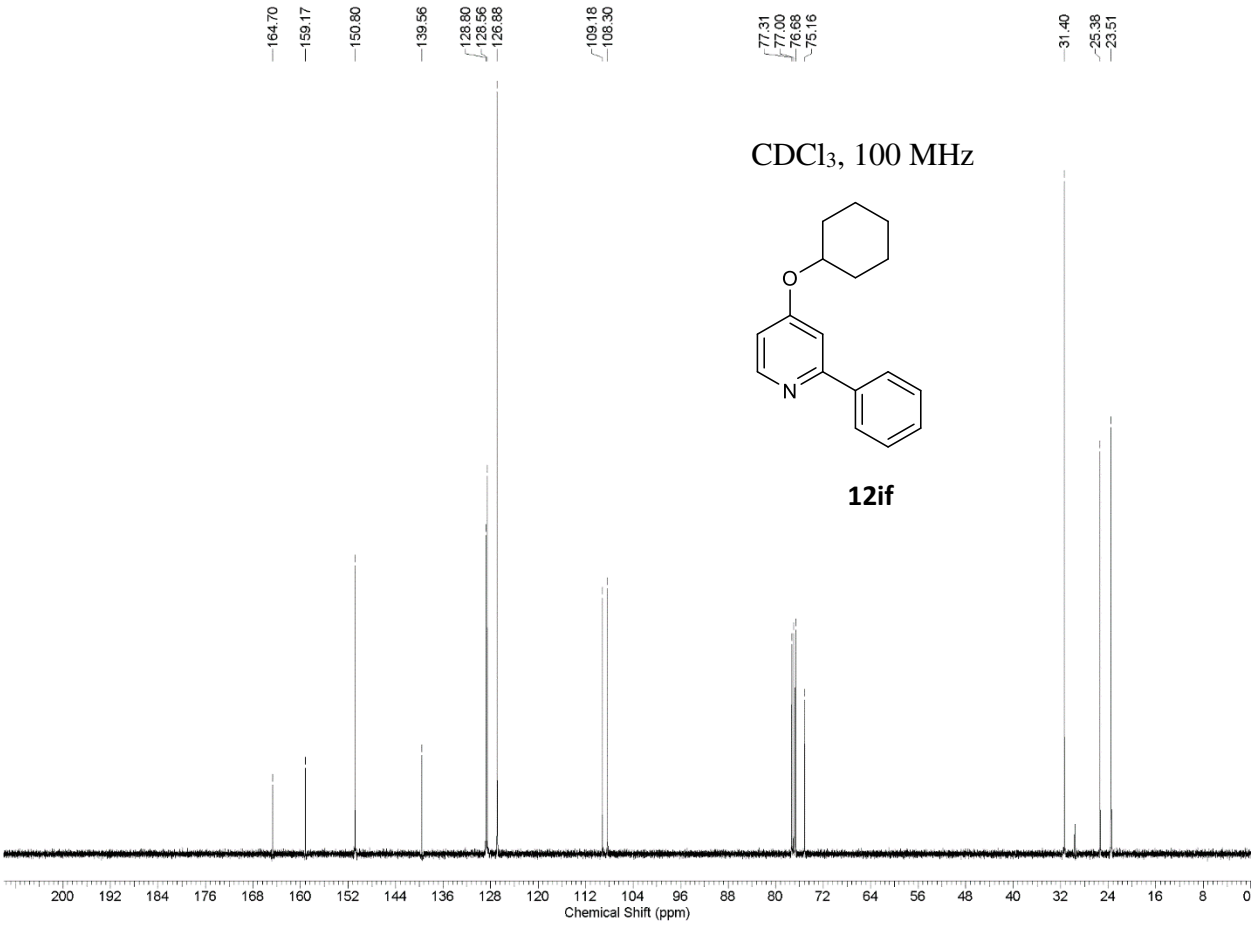
12ie

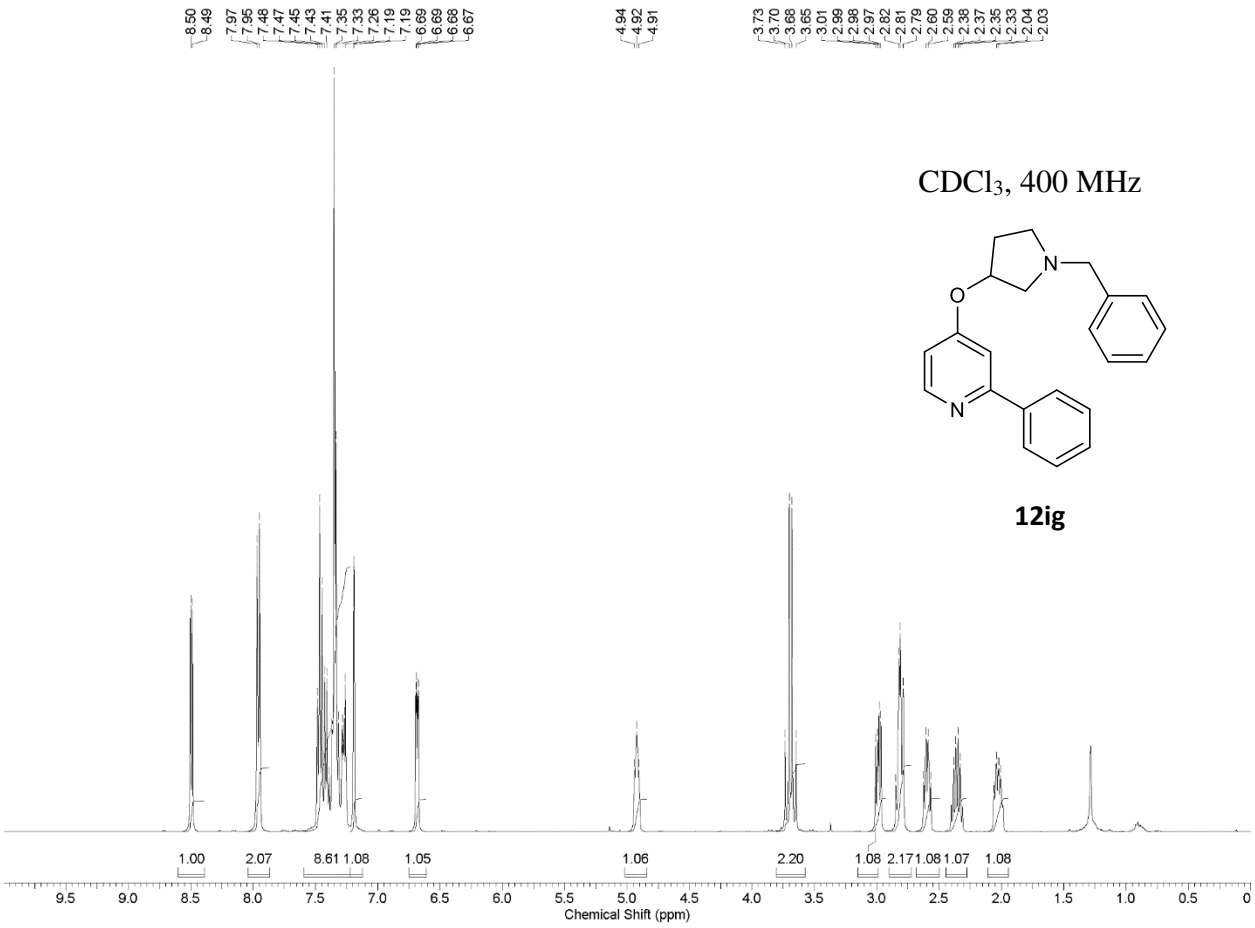


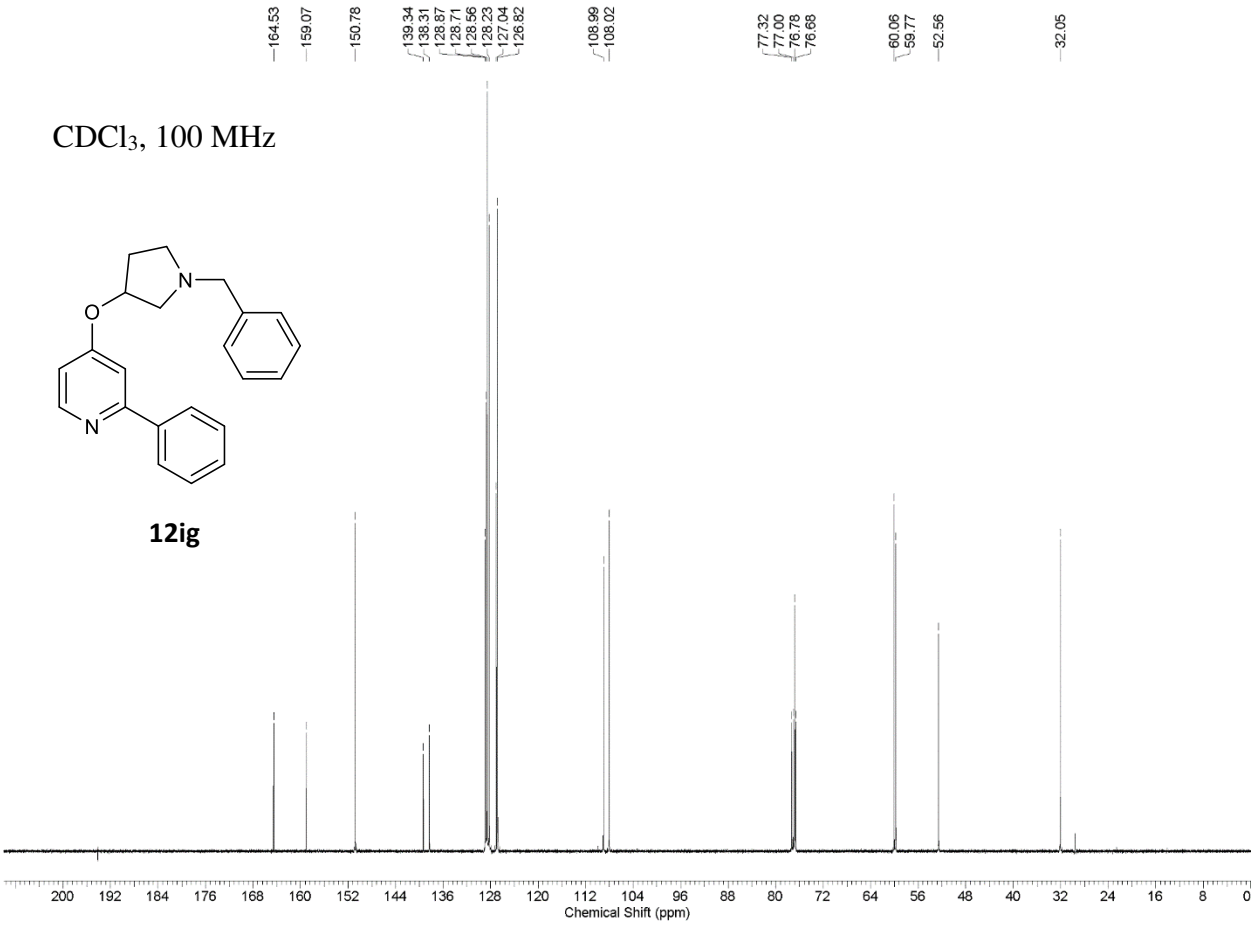
$CDCl_3$, 100 MHz

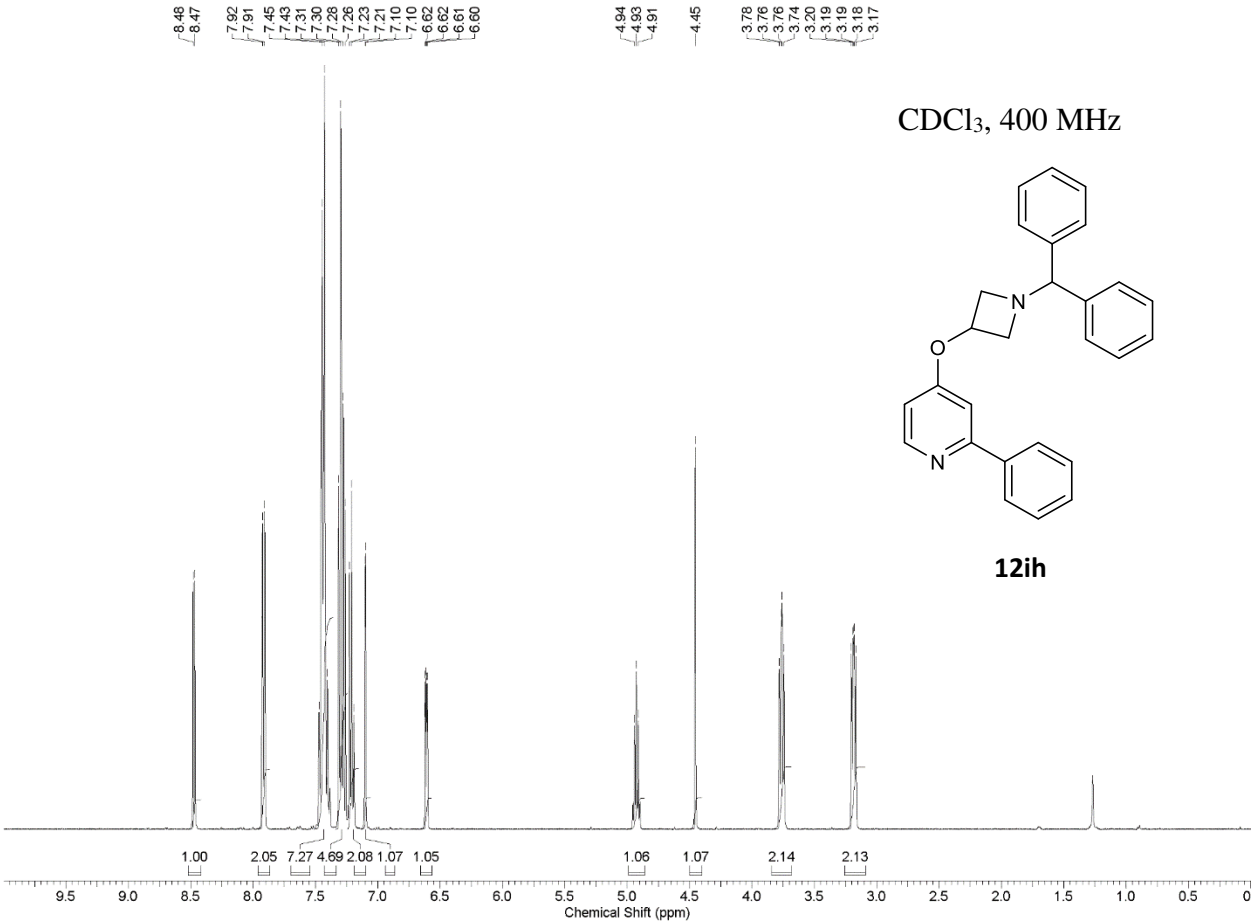
12ie


8.49
8.48
7.96
7.94
7.48
7.46
7.44
7.42
7.40
7.38
7.26
7.21
7.21
6.75
6.74
6.73
4.44
4.43
4.42
4.41
4.40
2.03
2.00
2.00
1.82
1.81
1.61
1.60
1.58
1.43
1.41
1.40
1.38
1.26
CDCl3, 400 MHz
O
N
12if
1.00
2.07
3.01
1.06
1.04
1.08
2.21
2.20
3.30
3.31
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
Chemical Shift (ppm)


164.70
159.17
150.80
139.56
128.80
128.56
126.88
109.18
108.30
77.31
77.00
76.68
75.16
31.40
25.38
23.51
CDCl3, 100 MHz
O
N
12if
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

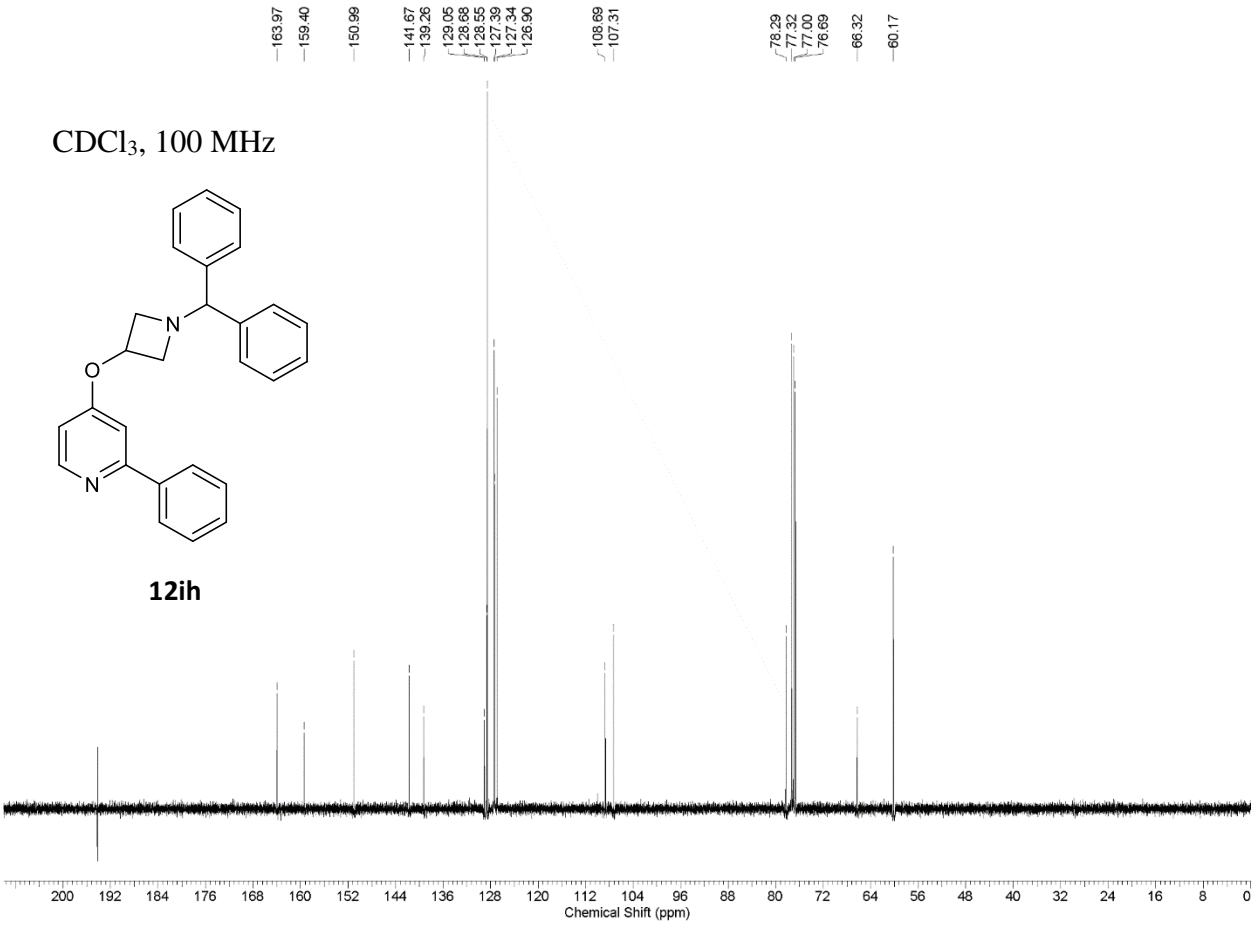

8.50
8.49
7.97
7.95
7.48
7.47
7.45
7.43
7.41
7.35
7.33
7.26
7.19
6.69
6.69
6.68
6.67
4.94
4.92
4.91
3.73
3.70
3.68
3.65
3.01
2.99
2.98
2.97
2.82
2.81
2.79
2.60
2.59
2.38
2.37
2.35
2.33
2.04
2.03
CDCl3, 400 MHz
N
O
N
12ig
1.00
2.07
8.61
1.08
1.05
1.06
2.20
1.08
2.17
1.08
1.07
1.08
9.5
9.0
8.5
8.0
7.5
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
Chemical Shift (ppm)

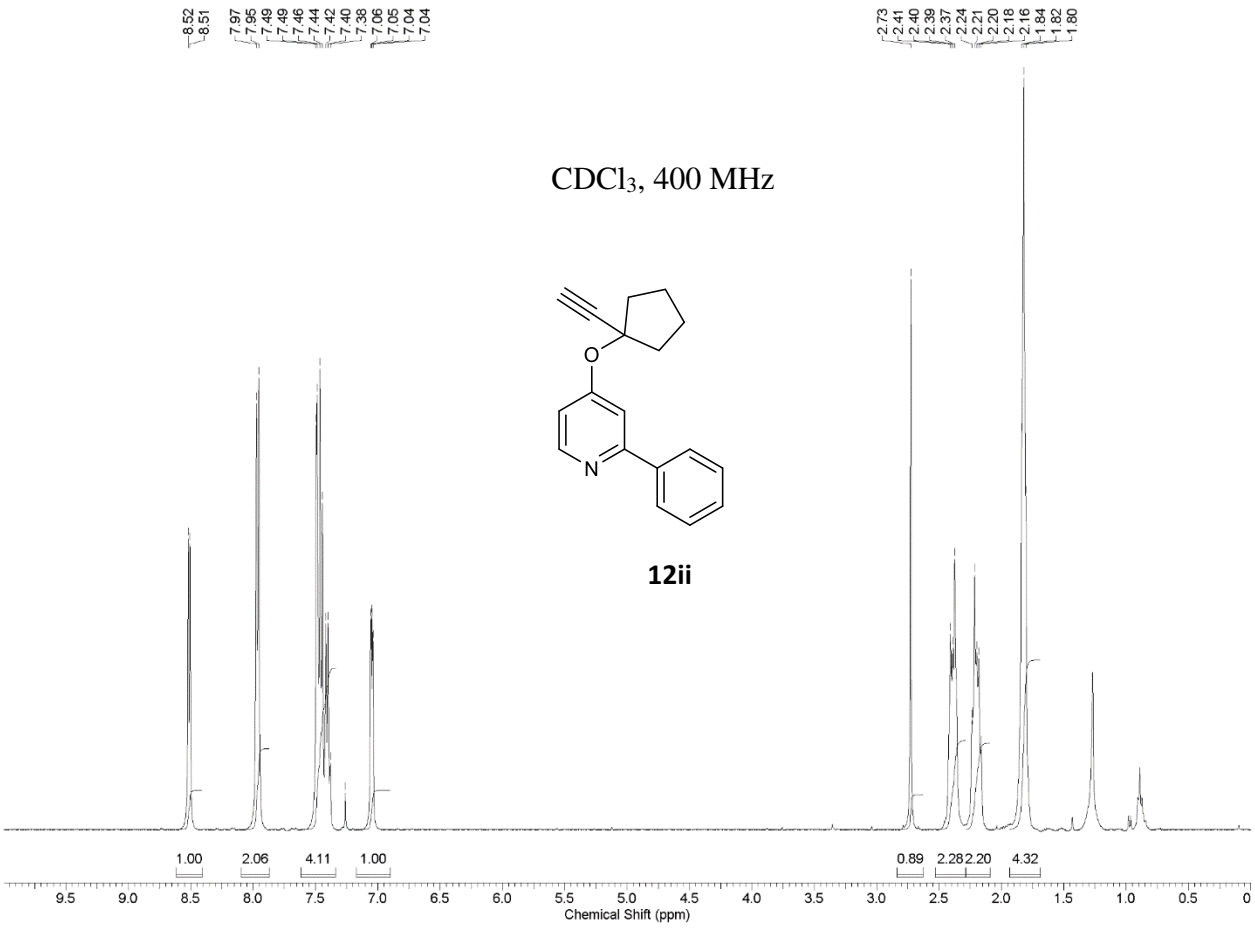

164.53
159.07
150.78
139.34
138.31
128.87
128.71
128.56
128.23
127.04
126.82
108.99
108.02
77.32
77.00
76.78
76.68
60.06
59.77
52.56
32.05
CDCl3, 100 MHz
O
N
N
12ig
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

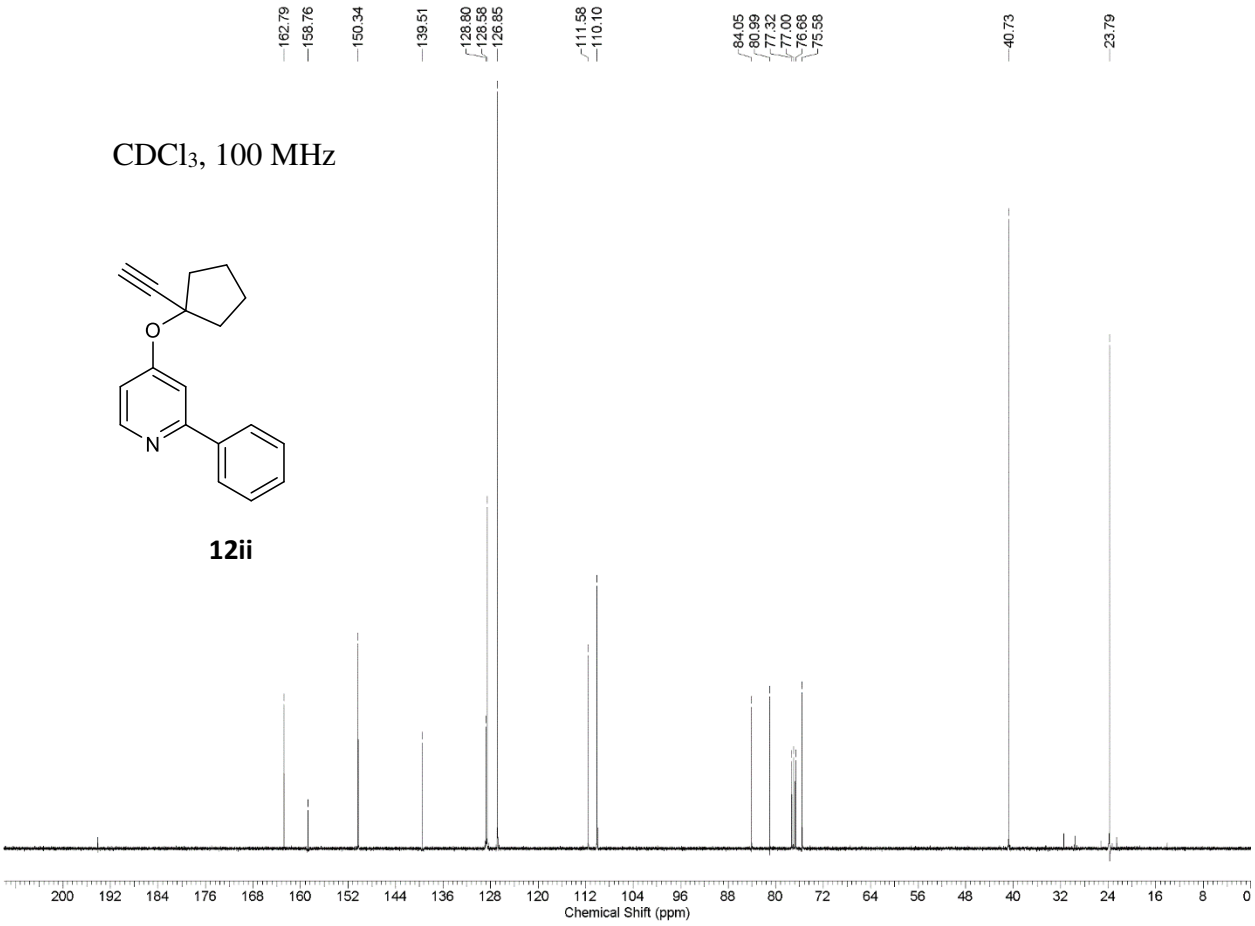


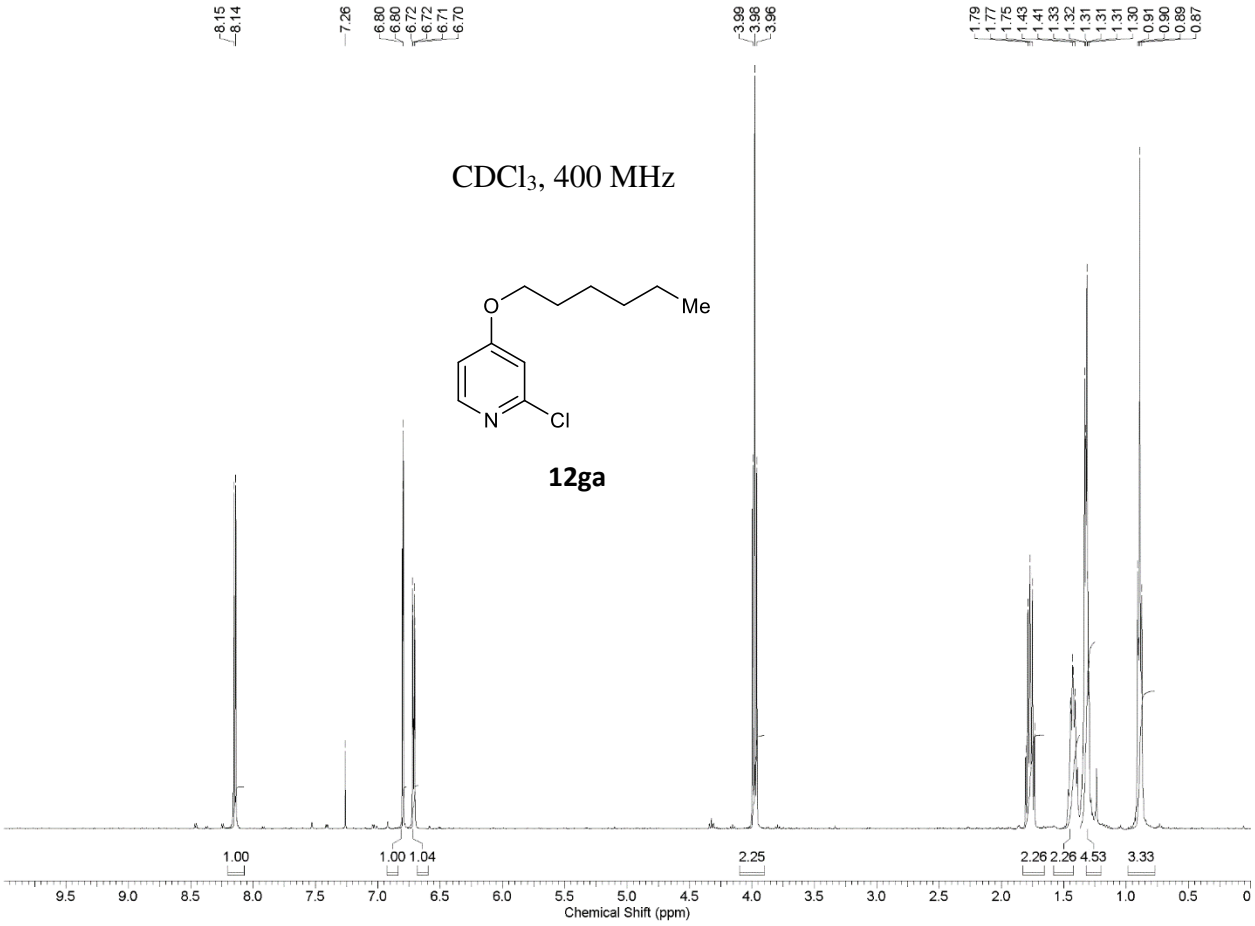
$CDCl_3$, 400 MHz

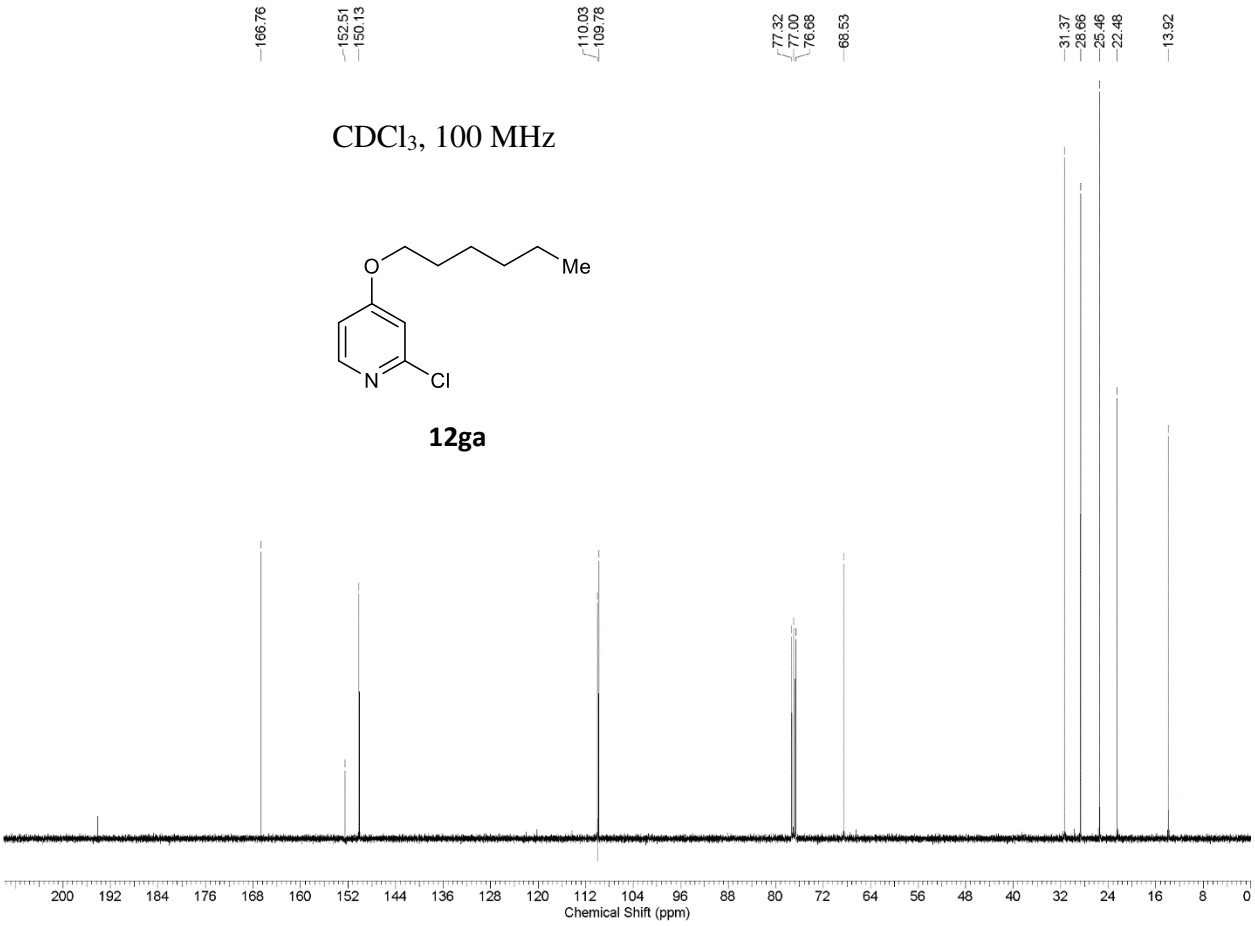
12ih

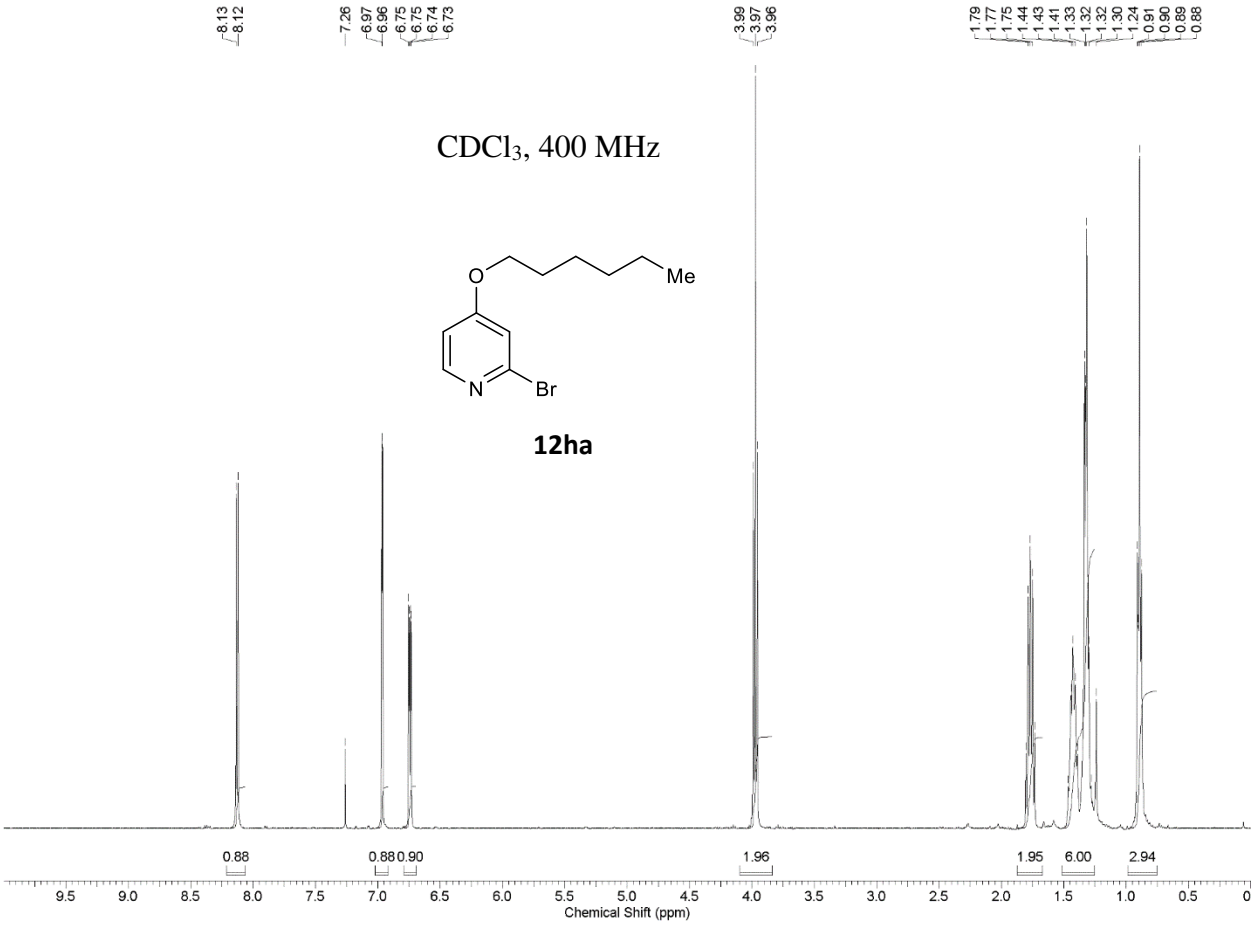

163.97
159.40
150.99
141.67
139.26
129.05
128.68
128.55
127.39
127.34
126.90
108.69
107.31
78.29
77.32
77.00
76.69
66.32
60.17
CDCl3, 100 MHz
N
O
N
12ih
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

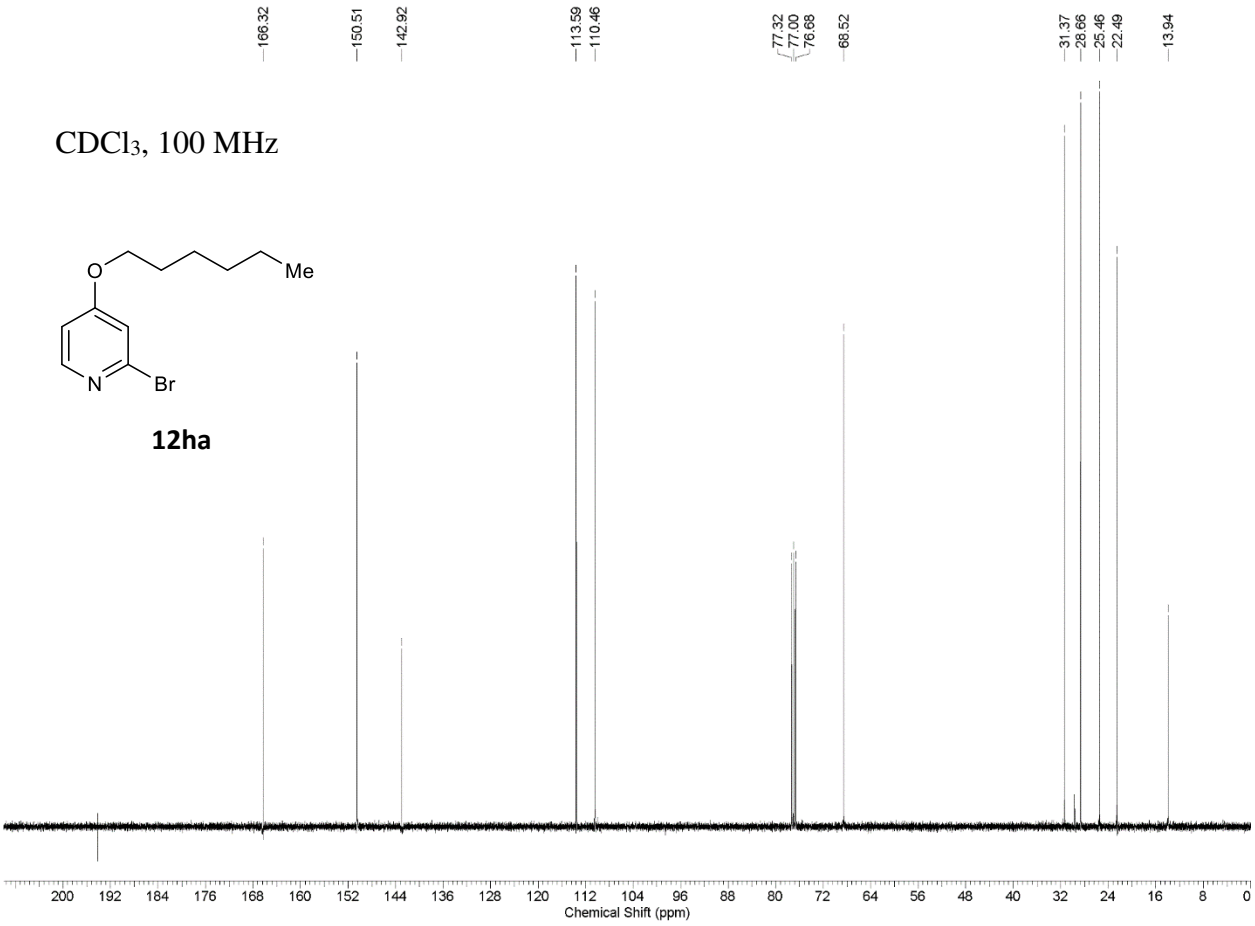

8.52
8.51
7.97
7.95
7.49
7.49
7.46
7.44
7.42
7.40
7.38
7.06
7.05
7.04
7.04
2.73
2.41
2.40
2.39
2.37
2.24
2.21
2.20
2.18
2.16
1.84
1.82
1.80
CDCl3, 400 MHz
O
N
12ii
1.00
2.06
4.11
1.00
0.89
2.28
2.20
4.32
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


162.79
158.76
150.34
139.51
128.80
128.58
126.85
111.58
110.10
84.05
80.99
77.32
77.00
76.68
75.58
40.73
23.79
CDCl3, 100 MHz
O
N
12ii
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

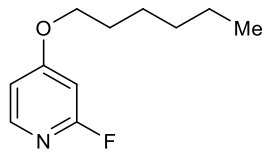

8.15
8.14
7.26
6.80
6.80
6.72
6.72
6.71
6.70
3.99
3.98
3.96
1.79
1.77
1.75
1.43
1.41
1.33
1.32
1.31
1.31
1.31
1.30
0.91
0.90
0.89
0.87
CDCl3, 400 MHz
O
Me
N
Cl
12ga
1.00
1.00
1.04
2.25
2.26
2.26
4.53
3.33
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


166.76
152.51
150.13
110.03
109.78
77.32
77.00
76.68
68.53
31.37
28.66
25.46
22.48
13.92
CDCl3, 100 MHz
O
Me
N
Cl
12ga
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

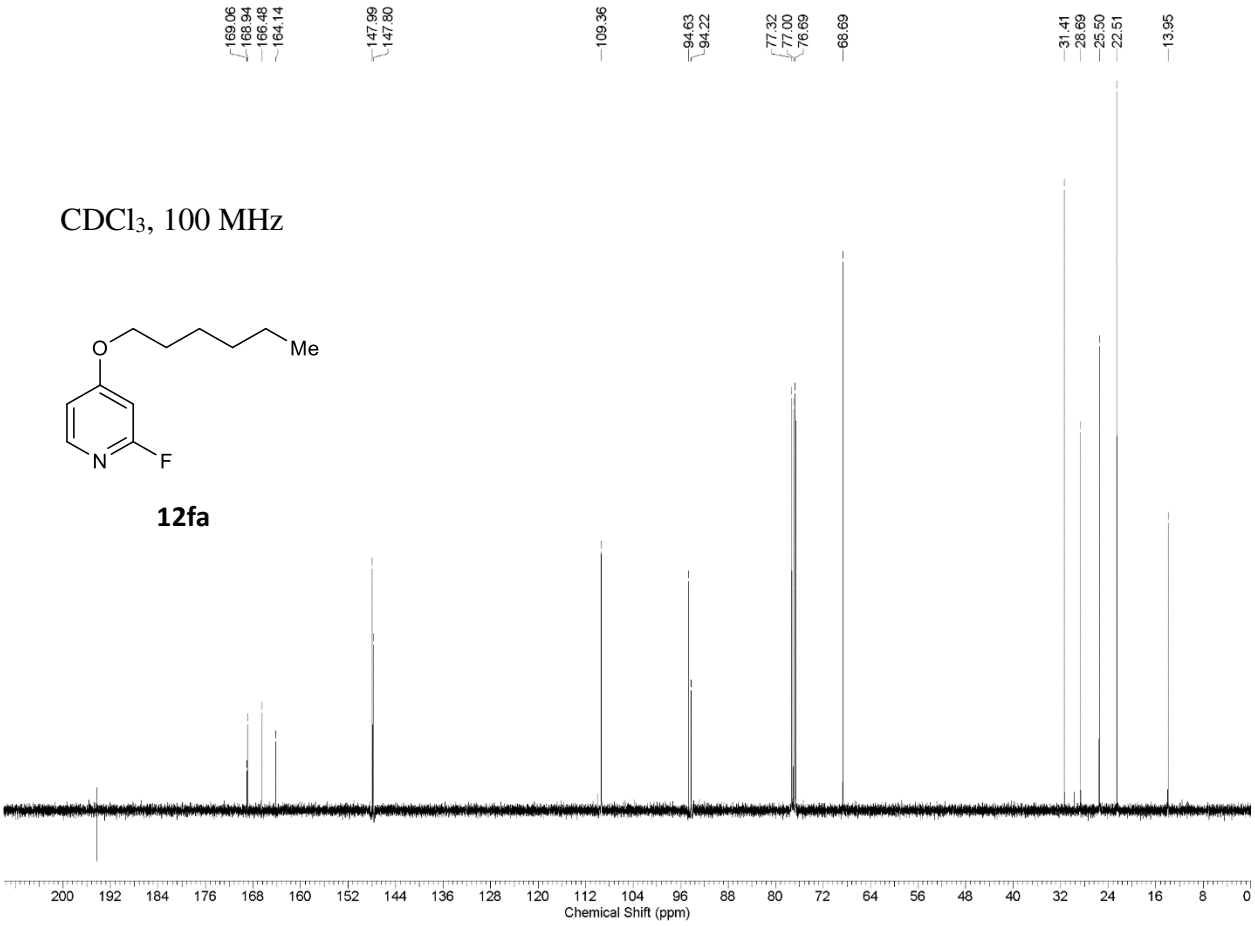

8.13
8.12
7.26
6.97
6.96
6.75
6.75
6.74
6.73
3.99
3.97
3.96
1.79
1.77
1.75
1.44
1.43
1.41
1.33
1.32
1.32
1.30
1.24
0.91
0.90
0.89
0.88
CDCl3, 400 MHz
O
Me
N
Br
12ha
0.88
0.88
0.90
1.96
1.95
6.00
2.94
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

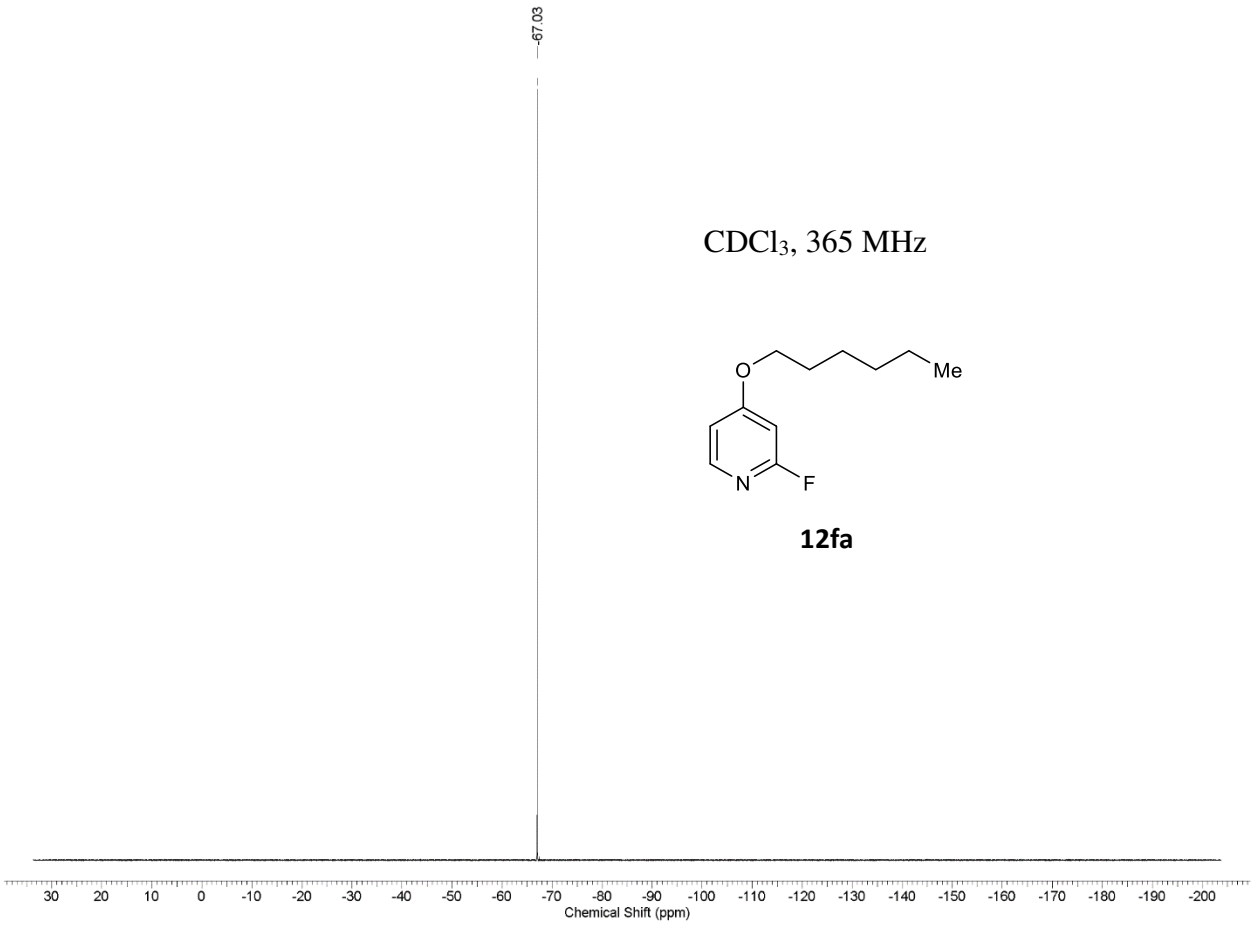

166.32
150.51
142.92
113.59
110.46
77.32
77.00
76.68
68.52
31.37
28.66
25.46
22.49
13.94
CDCl3, 100 MHz
O
Me
N
Br
12ha
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

$CDCl_3$, 400 MHz



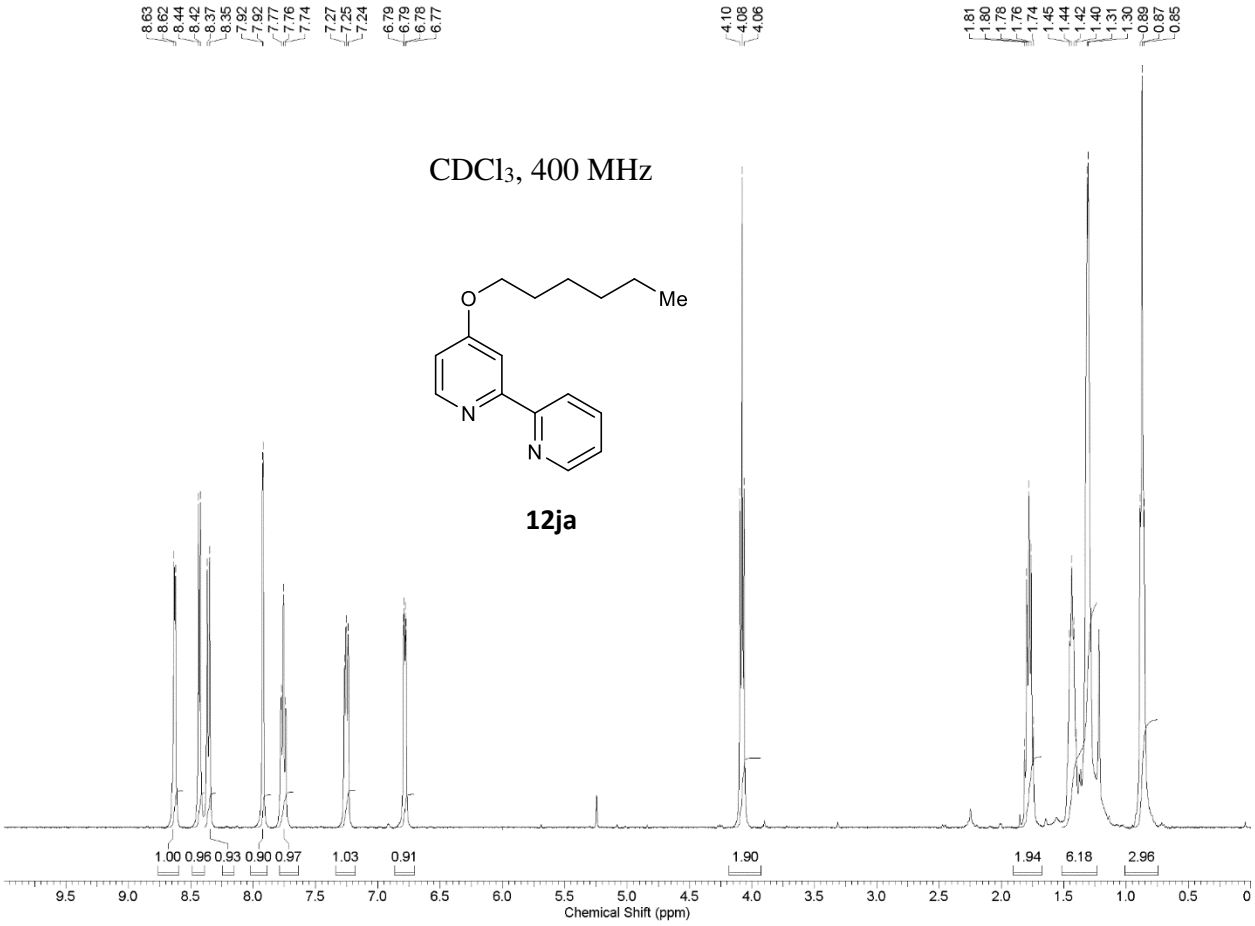
12fa

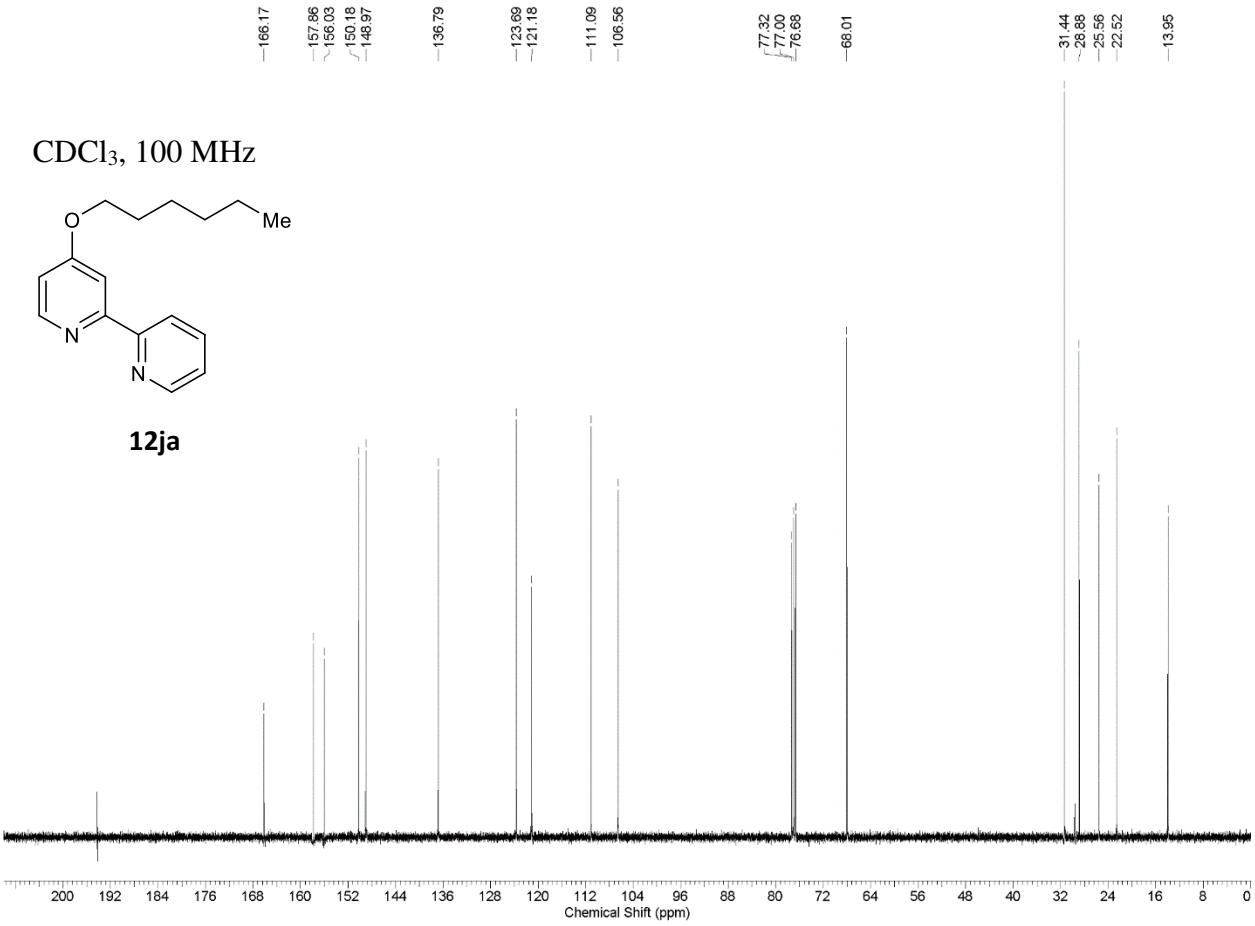

169.06
168.94
166.48
164.14
147.99
147.80
109.36
94.63
94.22
77.32
77.00
76.69
68.69
31.41
28.69
25.50
22.51
13.95
CDCl3, 100 MHz
O
Me
N
F
12fa
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

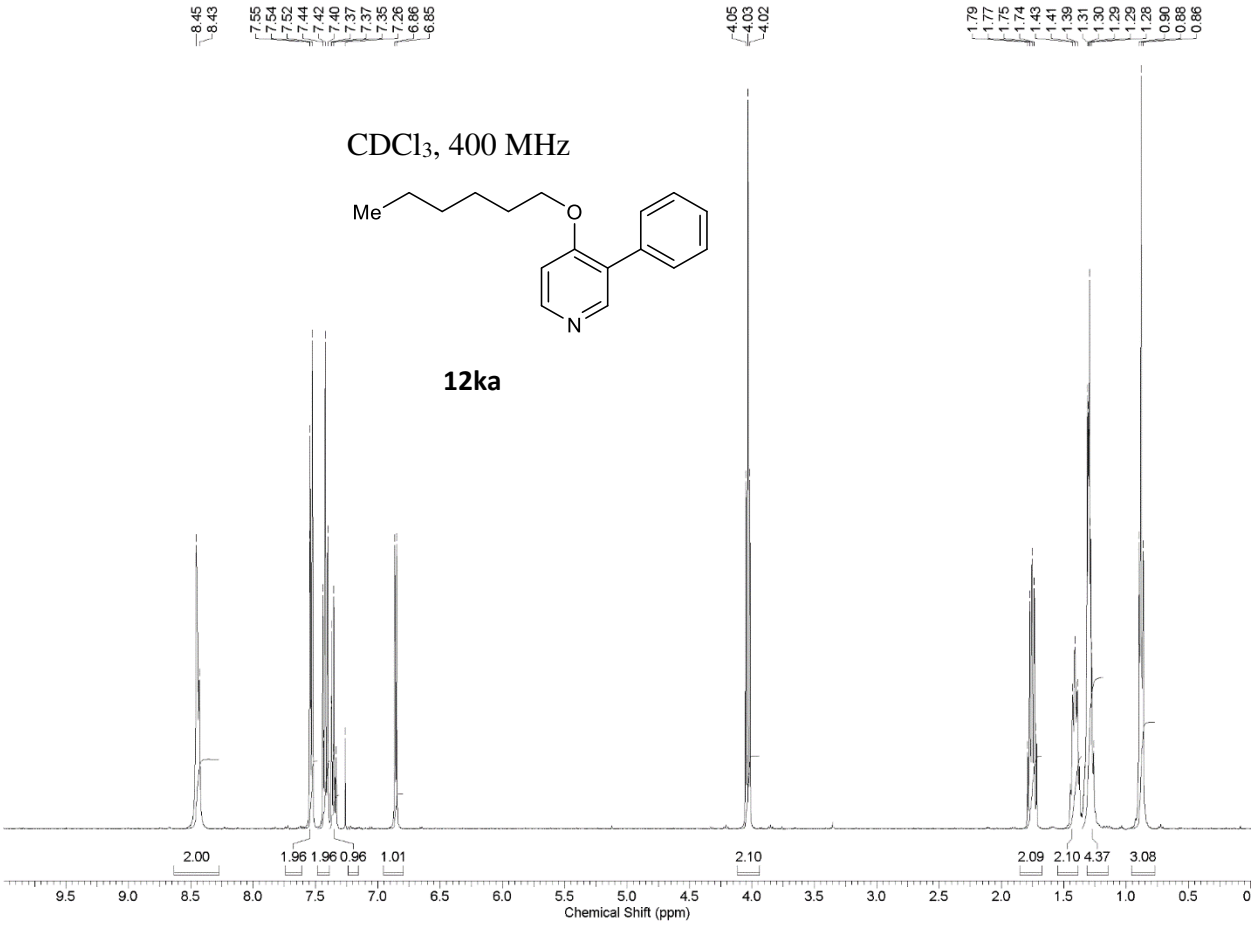


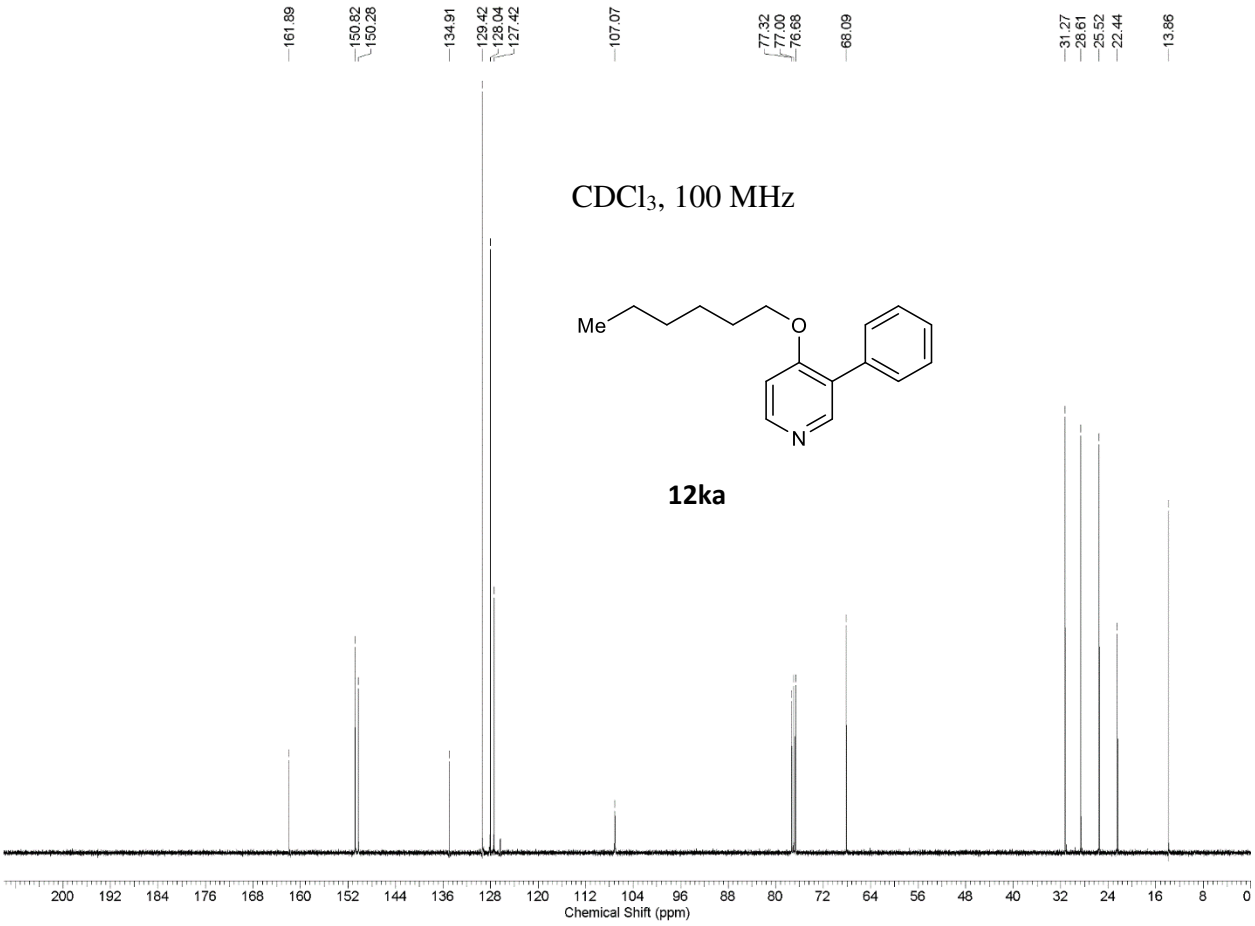
$CDCl_3$, 365 MHz

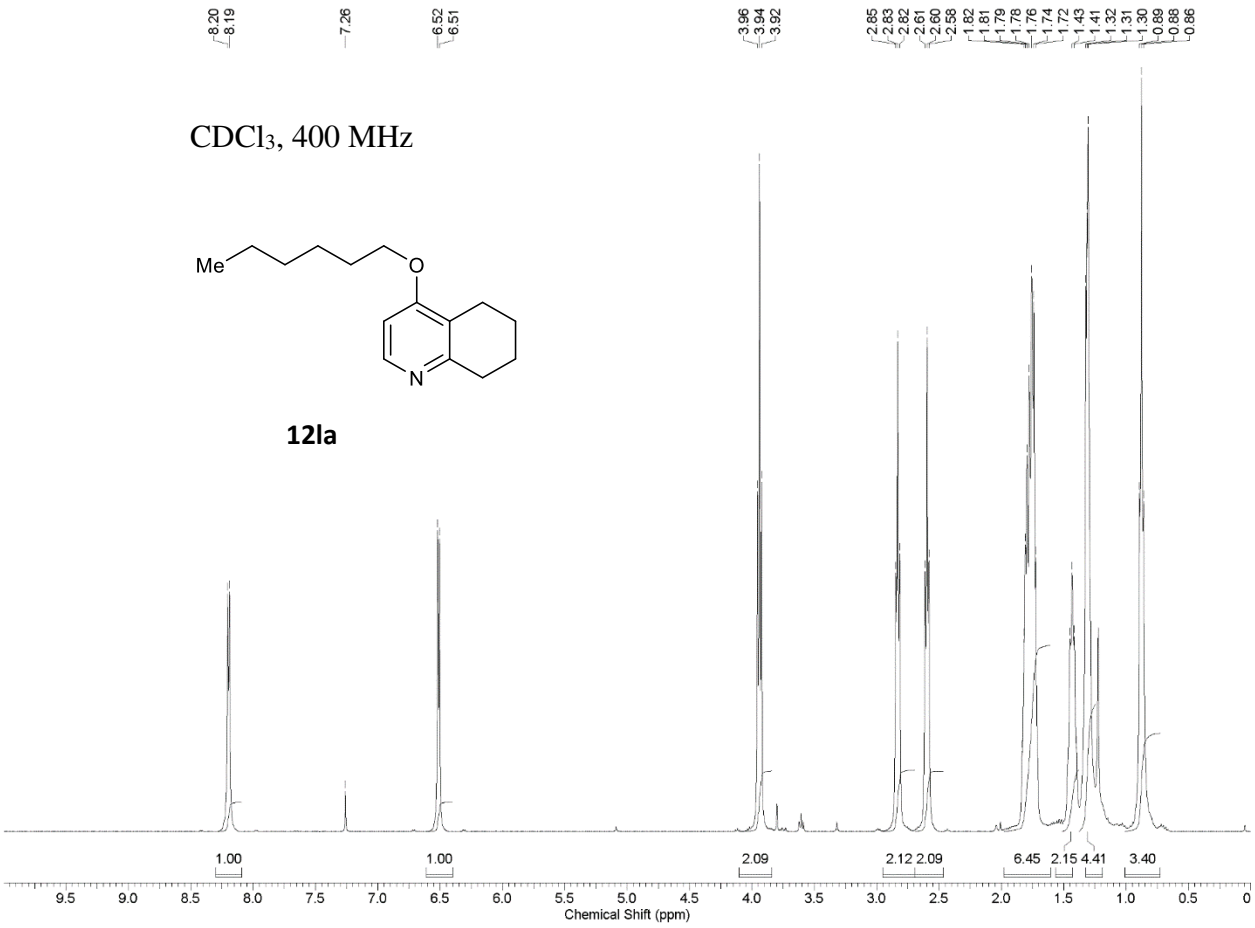
12fa

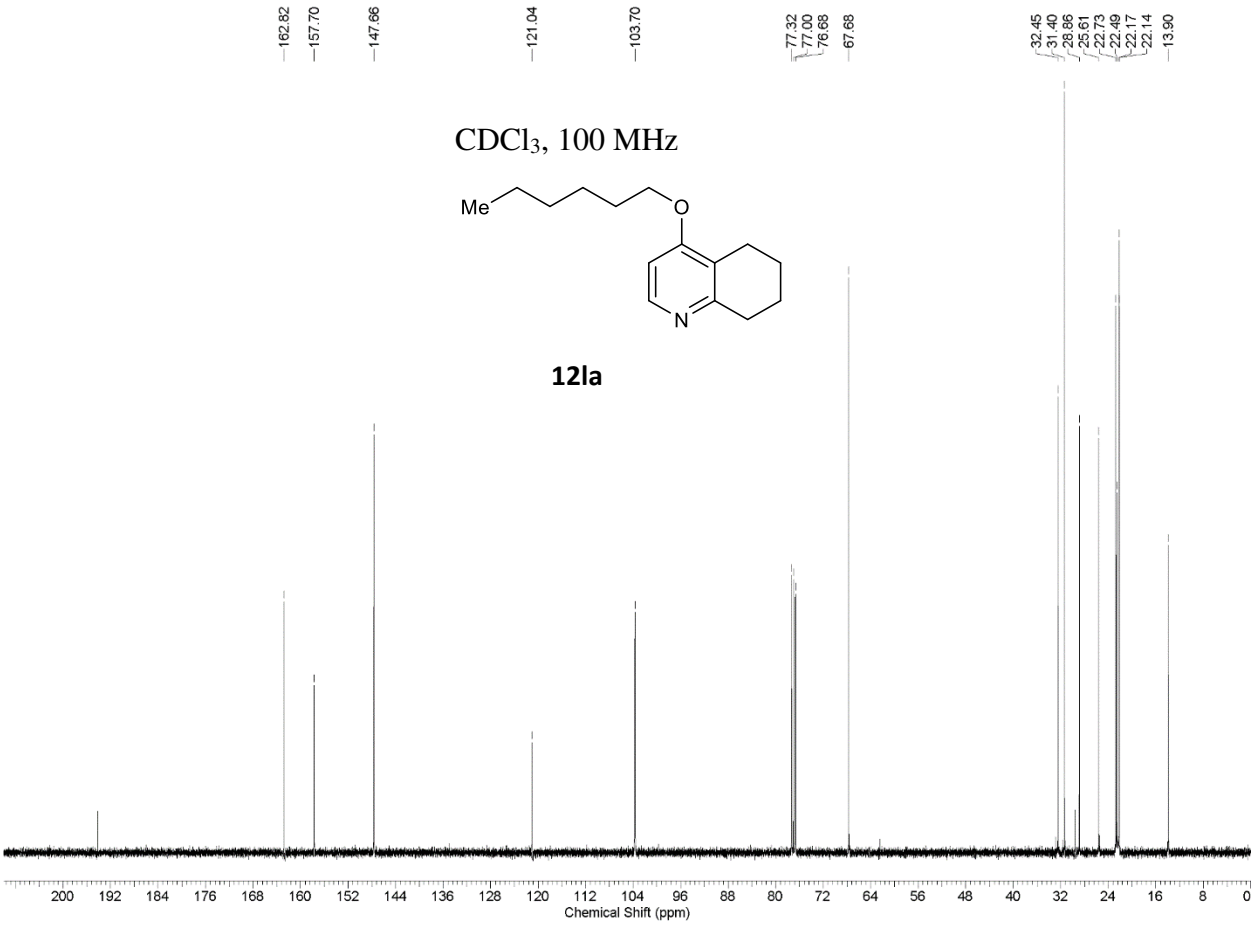

8.63
8.62
8.44
8.42
8.37
8.35
7.92
7.92
7.77
7.76
7.74
7.27
7.25
7.24
6.79
6.79
6.78
6.77
4.10
4.08
4.06
1.81
1.80
1.78
1.76
1.74
1.45
1.44
1.42
1.40
1.31
1.30
0.89
0.87
0.85
CDCl3, 400 MHz
O
Me
N
N
12ja
1.00 0.96 0.93 0.90 0.97 1.03 0.91 1.90 1.94 6.18 2.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

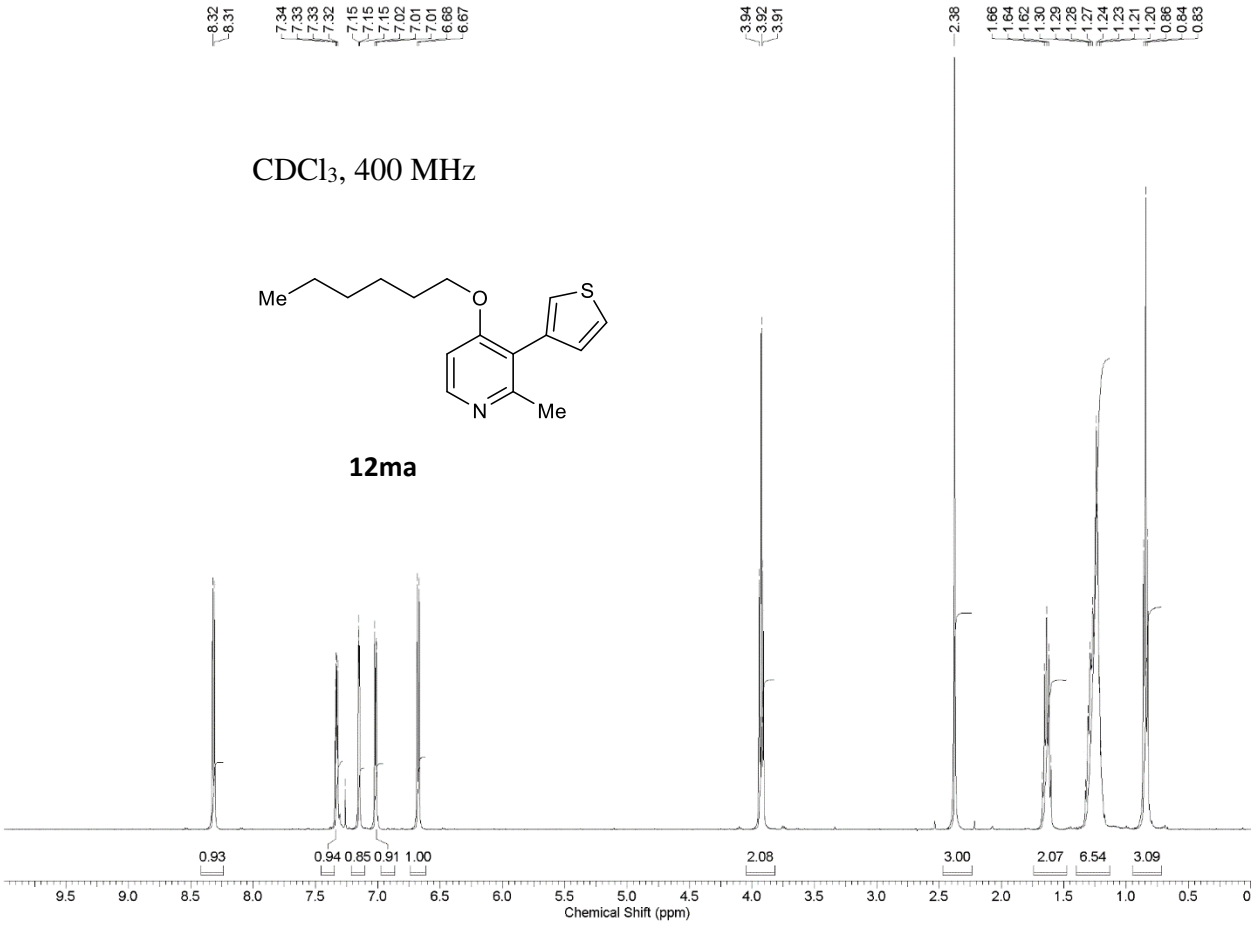

166.17
157.86
156.03
150.18
148.97
136.79
123.69
121.18
111.09
106.56
77.32
77.00
76.68
68.01
31.44
28.88
25.56
22.52
13.95
CDCl3, 100 MHz
O
Me
N
N
12ja
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

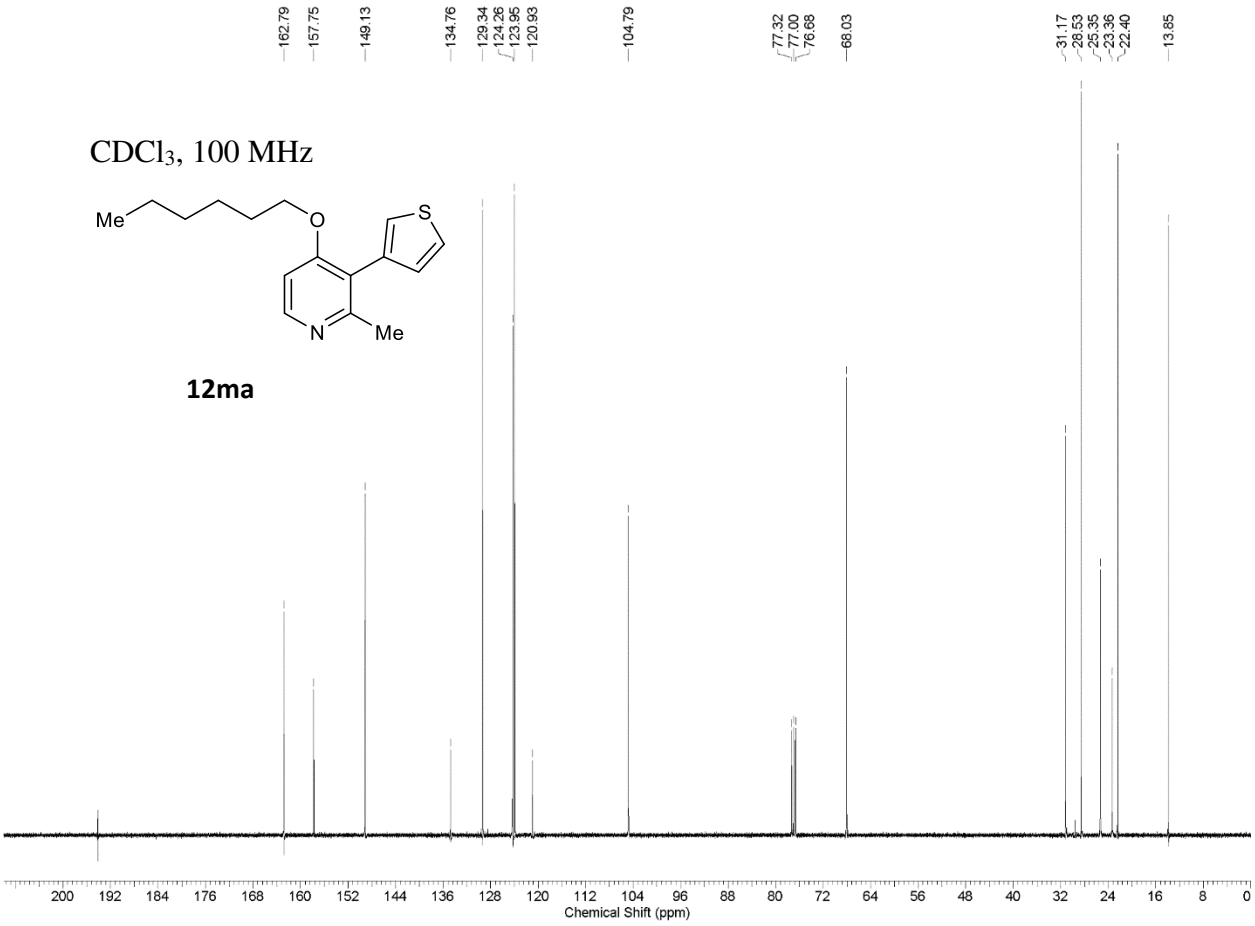

8.45
8.43
7.55
7.54
7.52
7.44
7.42
7.40
7.37
7.37
7.35
7.26
6.86
6.85
4.05
4.03
4.02
1.79
1.77
1.75
1.74
1.43
1.41
1.39
1.31
1.30
1.29
1.29
1.28
0.90
0.88
0.86
CDCl3, 400 MHz
Me
O
N
12ka
2.00
1.96
1.96
0.96
1.01
2.10
2.09
2.10
4.37
3.08
Chemical Shift (ppm)

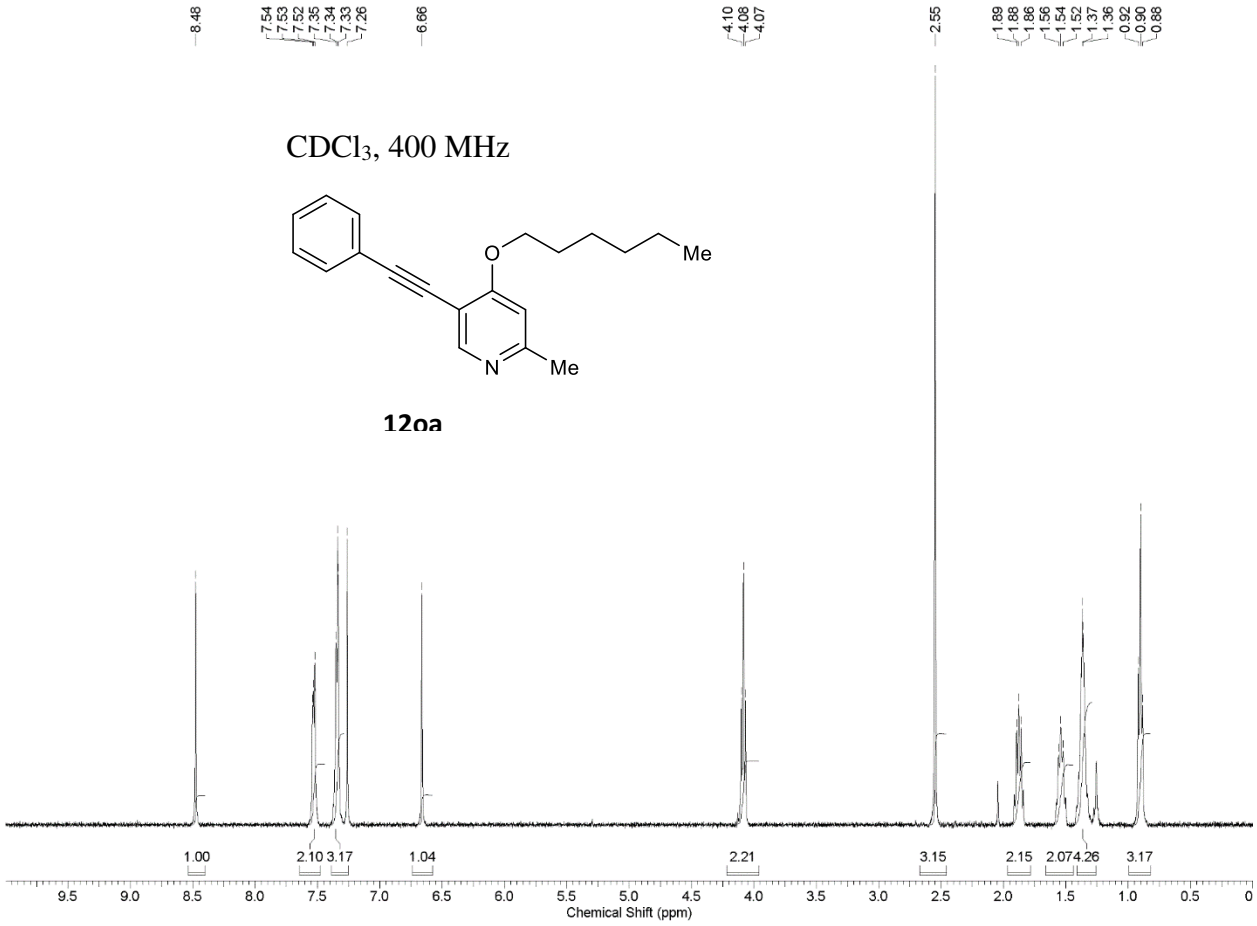

161.89
150.82
150.28
134.91
129.42
128.04
127.42
107.07
77.32
77.00
76.68
68.09
31.27
28.61
25.52
22.44
13.86
CDCl3, 100 MHz
Me
O
N
12ka
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

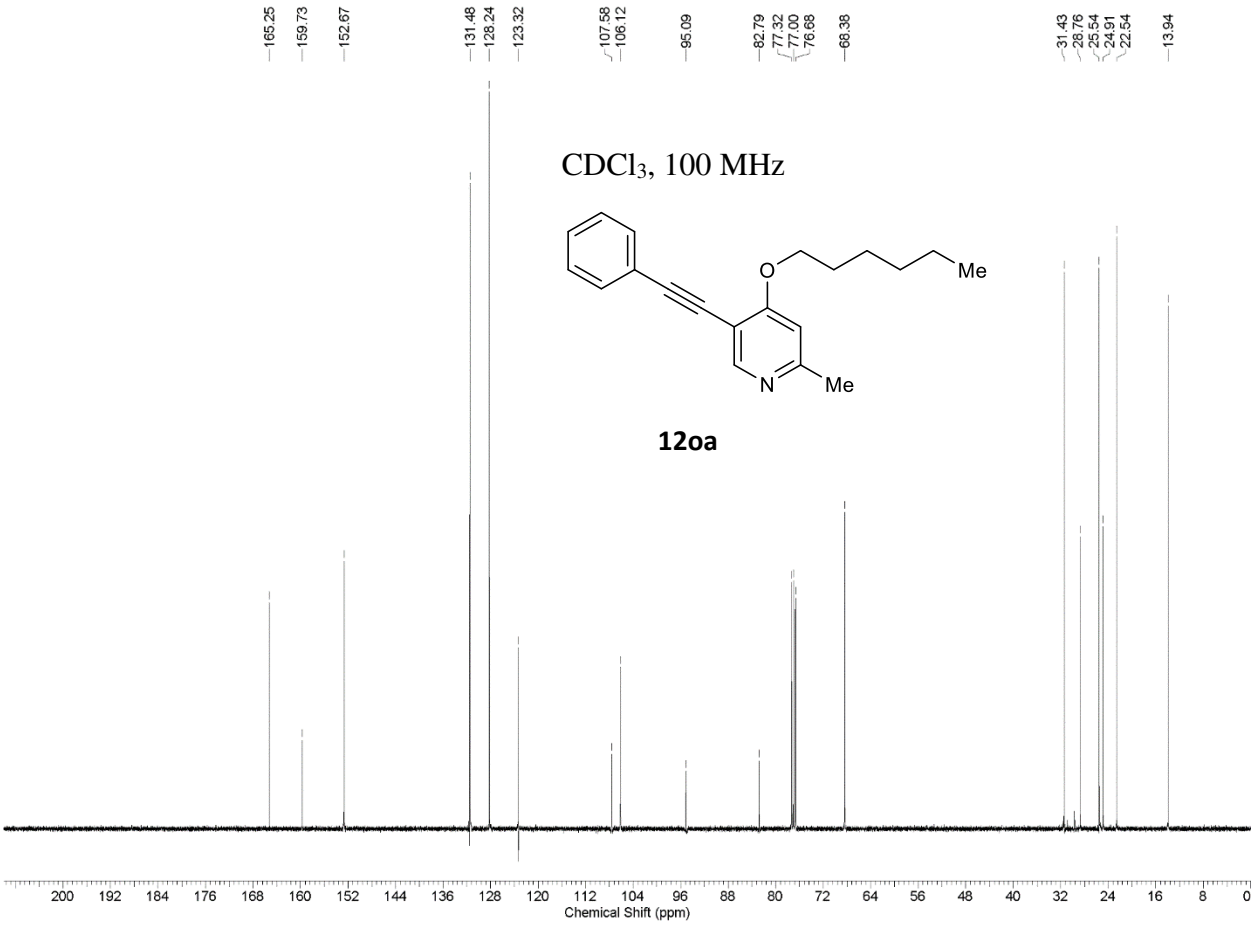

8.20
8.19
7.26
6.52
6.51
3.96
3.94
3.92
2.85
2.83
2.82
2.61
2.60
2.58
1.82
1.81
1.79
1.78
1.76
1.74
1.72
1.43
1.41
1.32
1.31
1.30
0.89
0.88
0.86
CDCl3, 400 MHz
Me
O
N
12la
1.00
1.00
2.09
2.12
2.09
6.45
2.15
4.41
3.40
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


162.82
157.70
147.66
121.04
103.70
77.32
77.00
76.68
67.68
32.45
31.40
28.86
25.61
22.73
22.49
22.17
22.14
13.90
CDCl3, 100 MHz
Me
O
N
12la
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

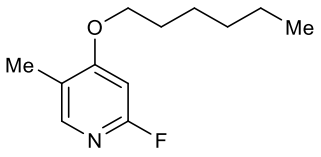

8.32
8.31
7.34
7.33
7.33
7.32
7.15
7.15
7.15
7.02
7.01
7.01
6.68
6.67
3.94
3.92
3.91
2.38
1.66
1.64
1.62
1.30
1.29
1.28
1.27
1.24
1.23
1.21
1.20
0.86
0.84
0.83
CDCl3, 400 MHz
Me
O
S
N
Me
12ma
0.93
0.94
0.85
0.91
1.00
2.08
3.00
2.07
6.54
3.09
Chemical Shift (ppm)


162.79
157.75
149.13
134.76
129.34
124.26
123.95
120.93
104.79
77.32
77.00
76.68
68.03
31.17
28.53
25.35
23.36
22.40
13.85
CDCl3, 100 MHz
Me
O
S
N
Me
12ma
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

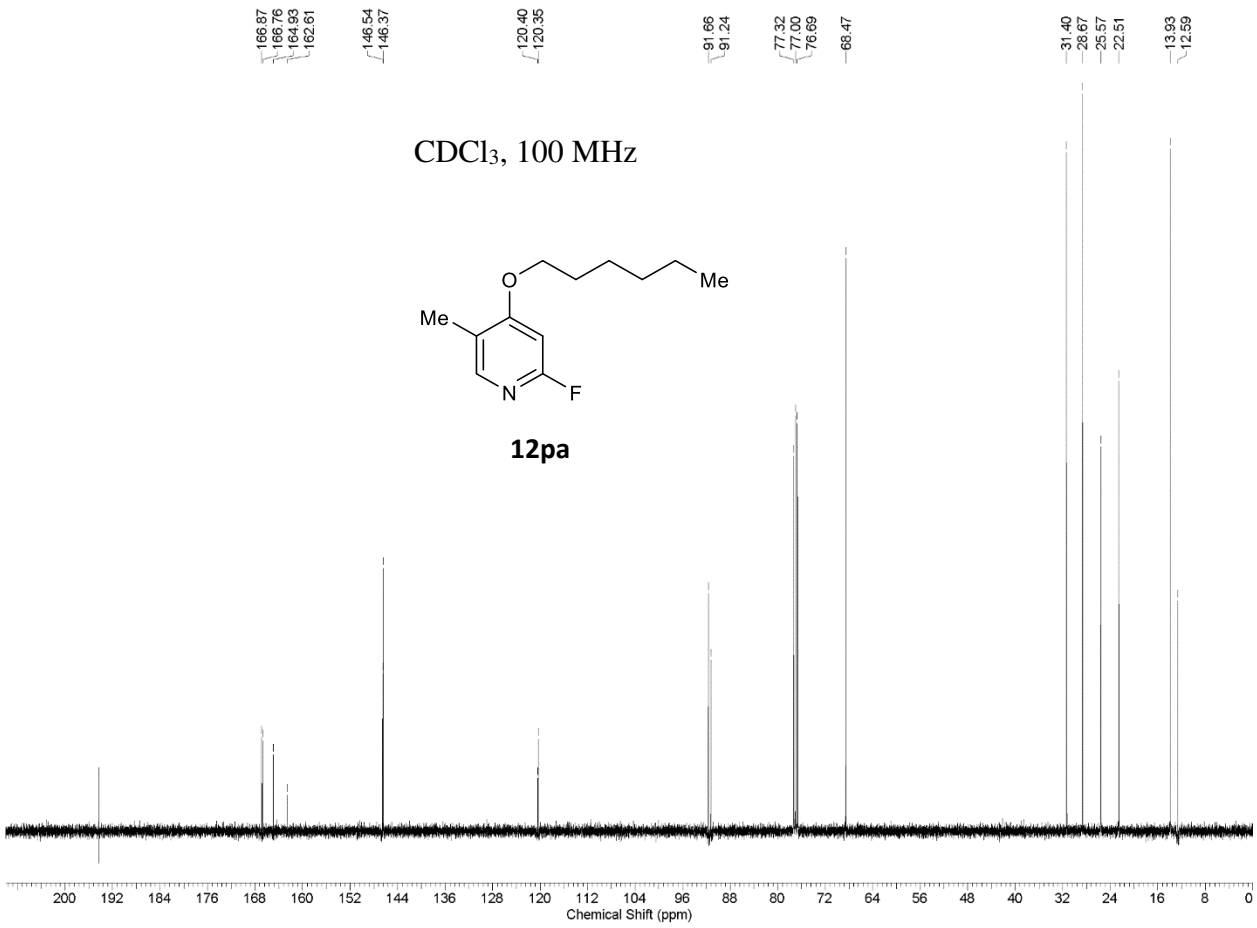

8.48
7.54
7.53
7.52
7.35
7.34
7.33
7.26
6.66
4.10
4.08
4.07
2.55
1.89
1.88
1.86
1.56
1.54
1.52
1.37
1.36
0.92
0.90
0.88
CDCl3, 400 MHz
O
Me
N
Me
12oa
1.00
2.10
3.17
1.04
2.21
3.15
2.15
2.07
4.26
3.17
Chemical Shift (ppm)

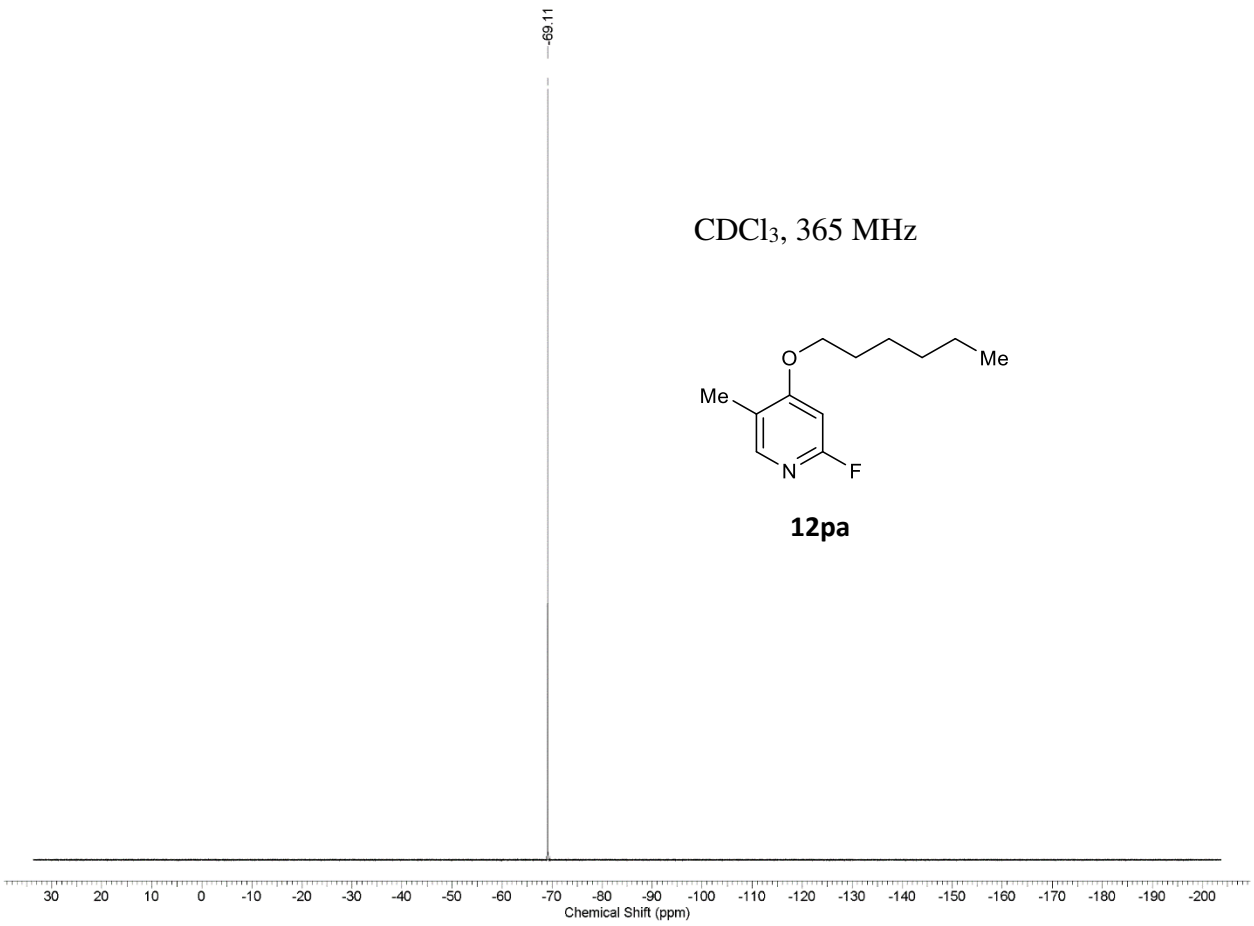

165.25
159.73
152.67
131.48
128.24
123.32
107.58
106.12
95.09
82.79
77.32
77.00
76.68
68.38
31.43
28.76
25.54
24.91
22.54
13.94
CDCl3, 100 MHz
O
Me
N
Me
12oa
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

$CDCl_3$, 400 MHz



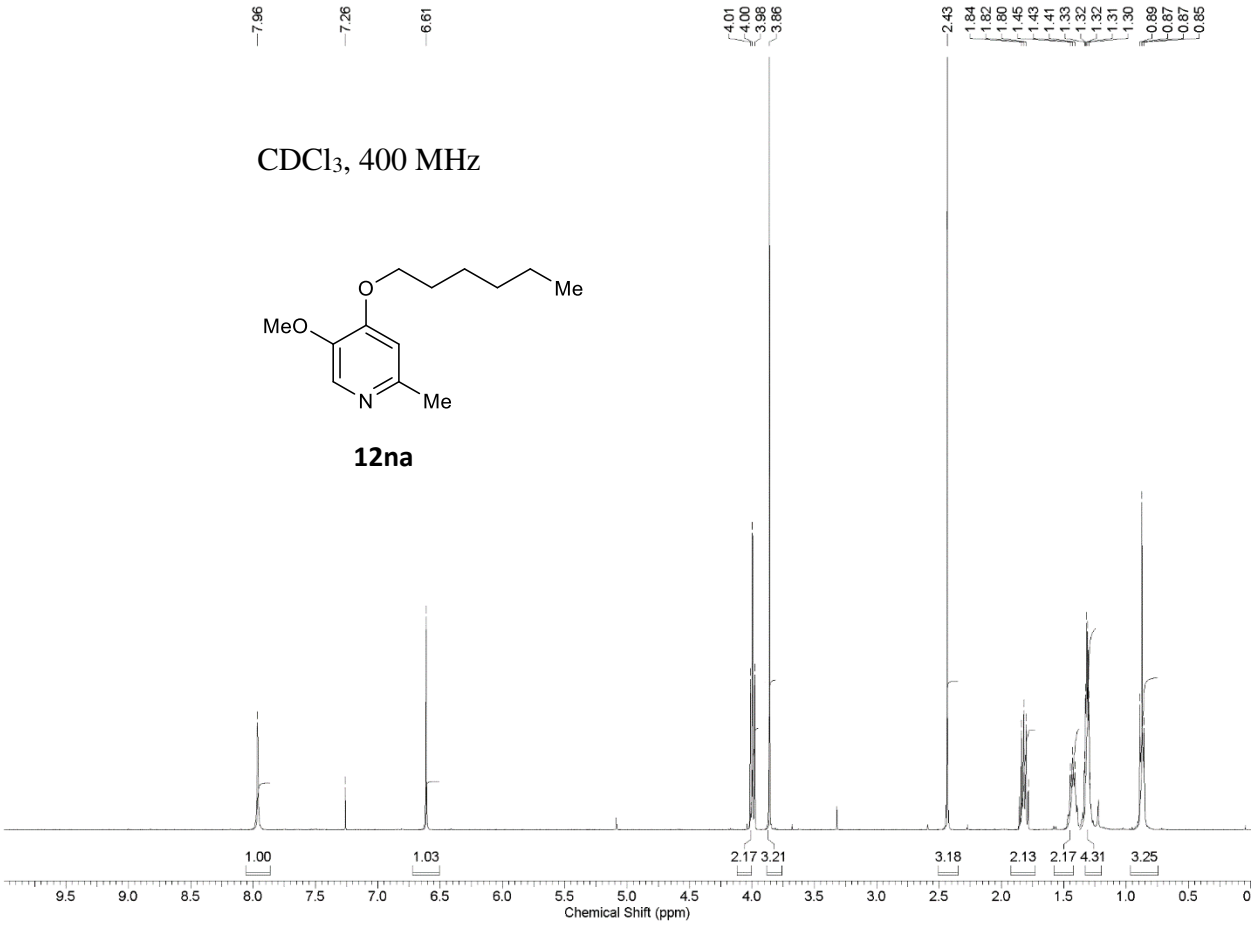
12pa

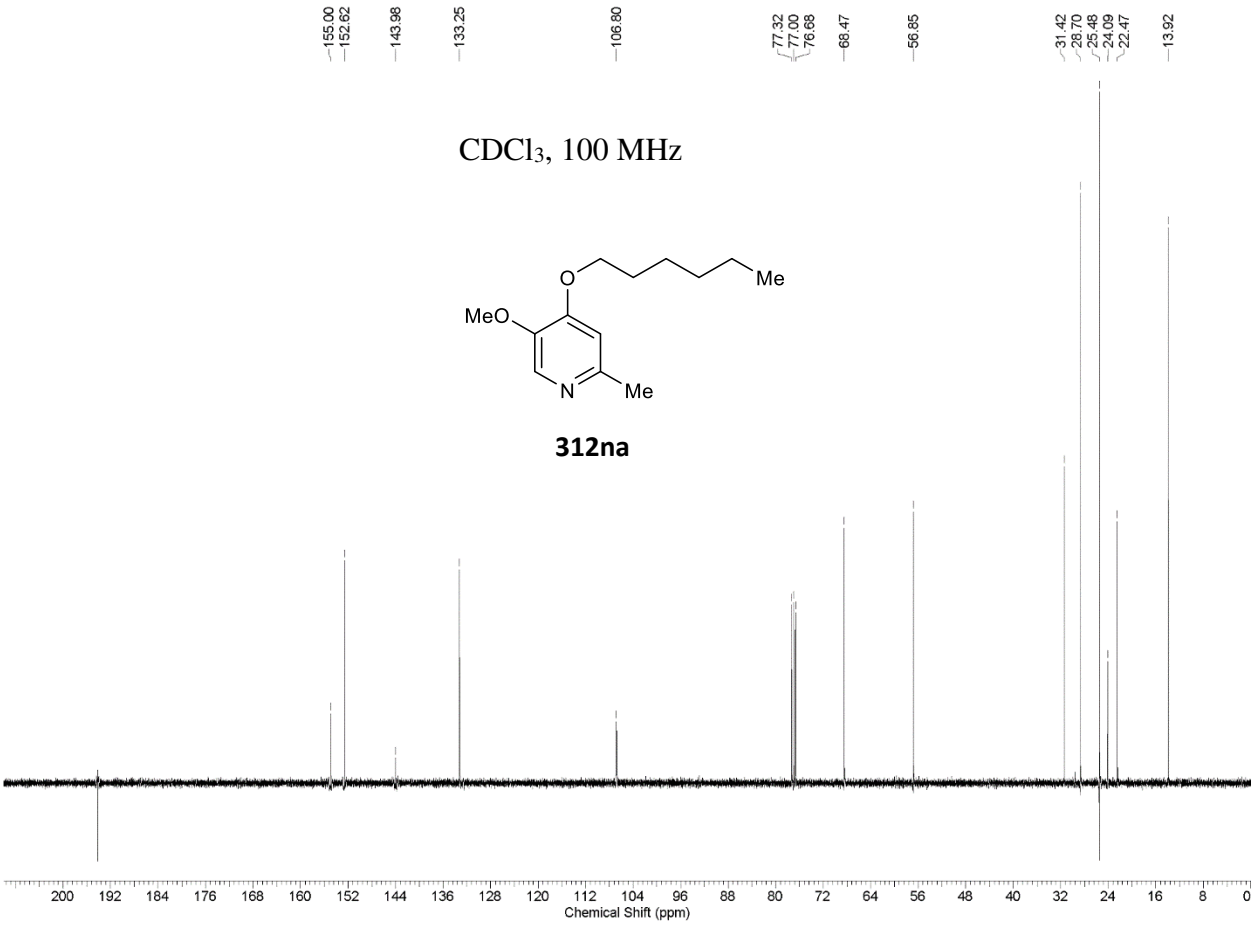

166.87
166.76
164.93
162.61
146.54
146.37
120.40
120.35
91.66
91.24
77.32
77.00
76.69
68.47
31.40
28.67
25.57
22.51
13.93
12.59
CDCl3, 100 MHz
O
Me
Me
N
F
12pa
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

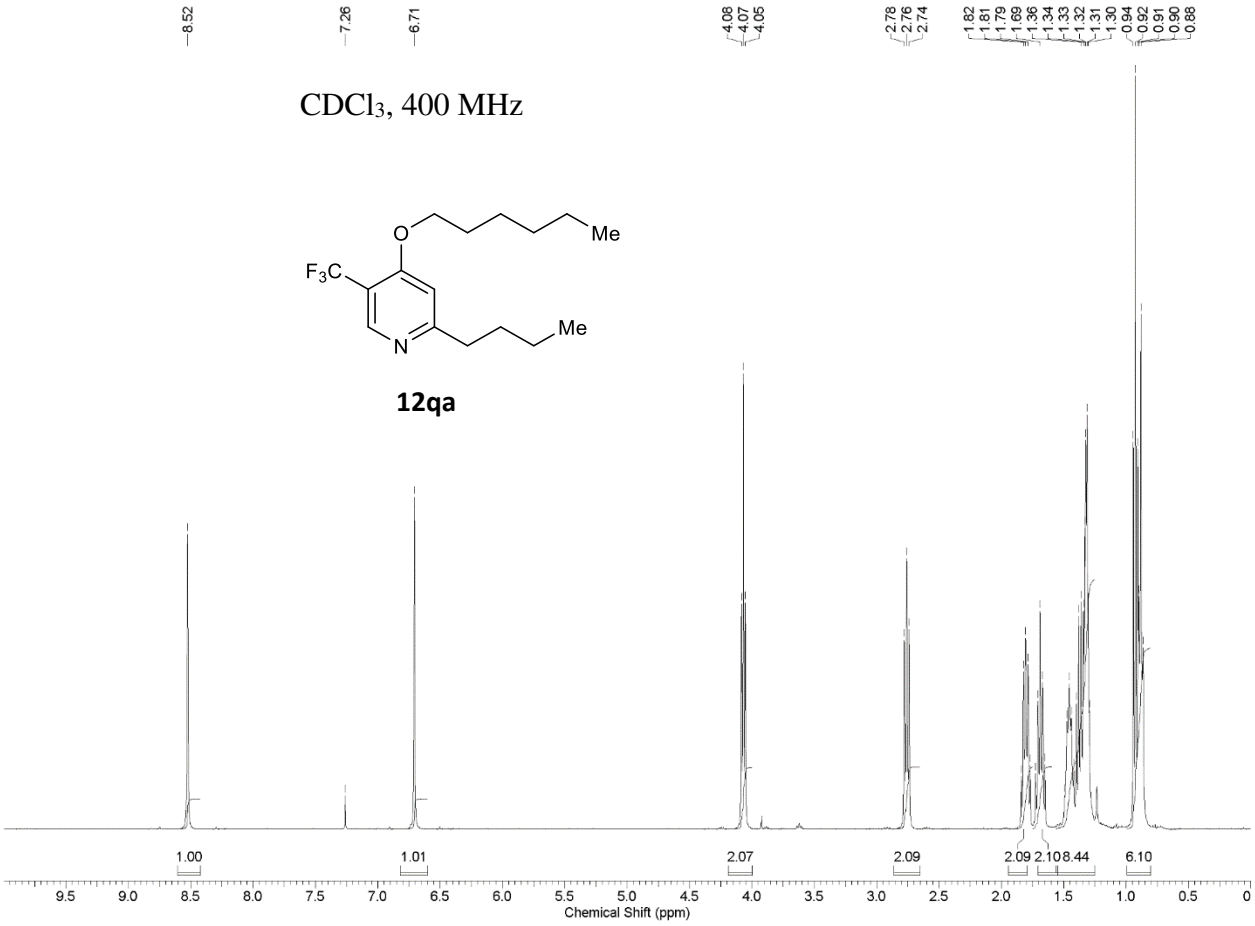


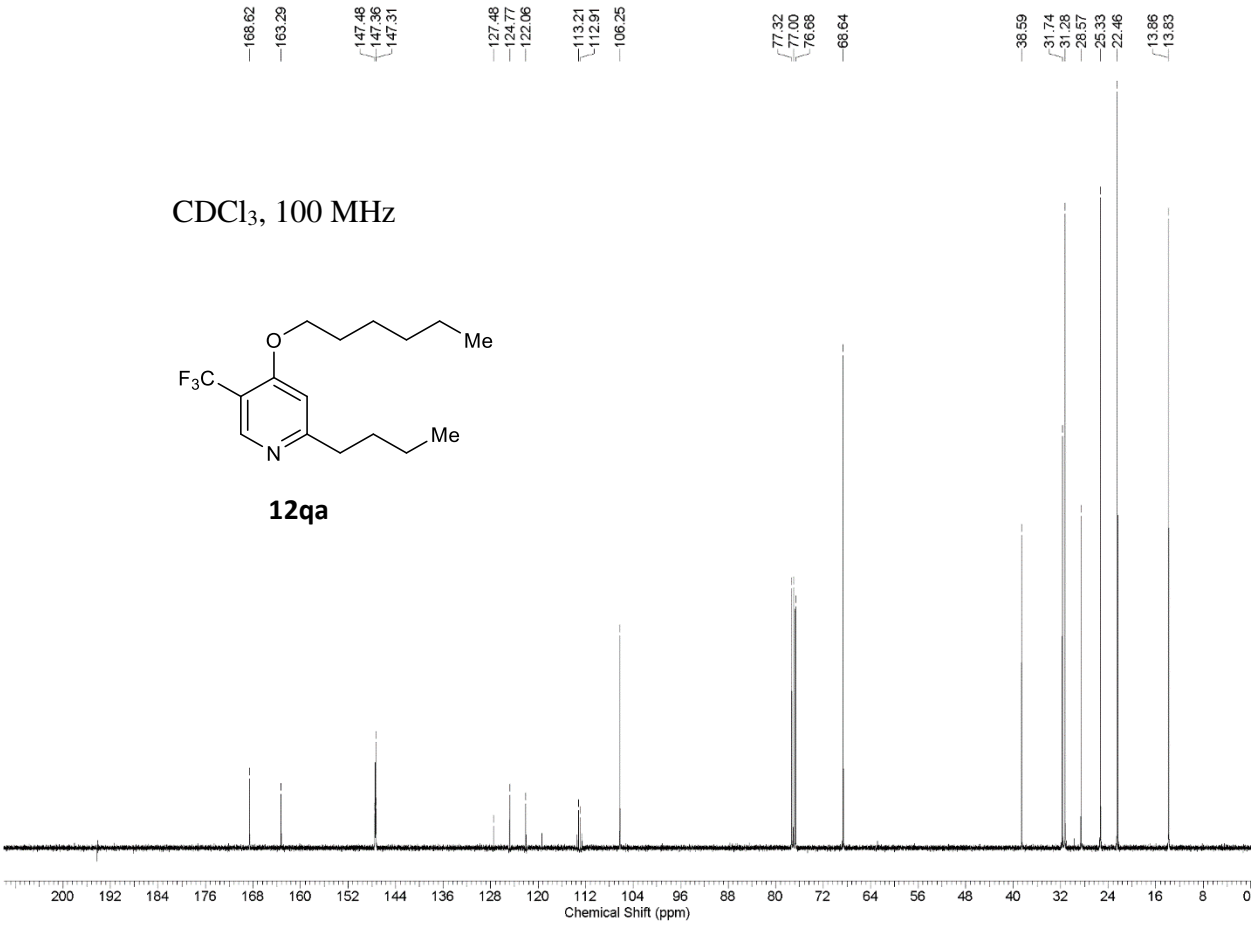
$CDCl_3$, 365 MHz

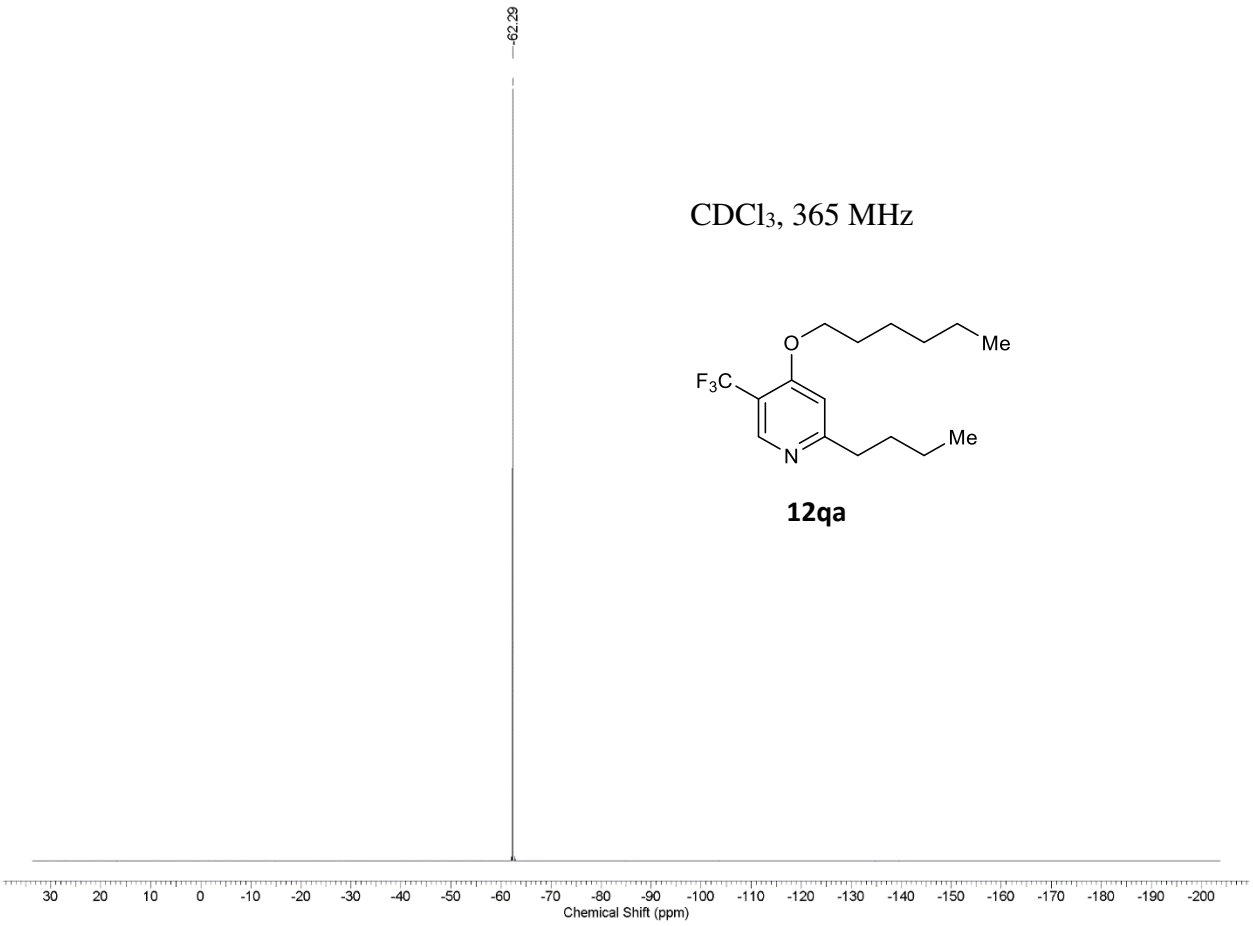
12pa


7.96
7.26
6.61
4.01
4.00
3.98
3.86
2.43
1.84
1.82
1.80
1.45
1.43
1.41
1.33
1.32
1.32
1.31
1.30
0.89
0.87
0.87
0.85
CDCl3, 400 MHz
O
Me
MeO
N
Me
12na
1.00
1.03
2.17
3.21
3.18
2.13
2.17
4.31
3.25
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
0
Chemical Shift (ppm)


155.00
152.62
143.98
133.25
106.80
77.32
77.00
76.68
68.47
56.85
31.42
28.70
25.48
24.09
22.47
13.92
CDCl3, 100 MHz
O
Me
MeO
N
Me
312na
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

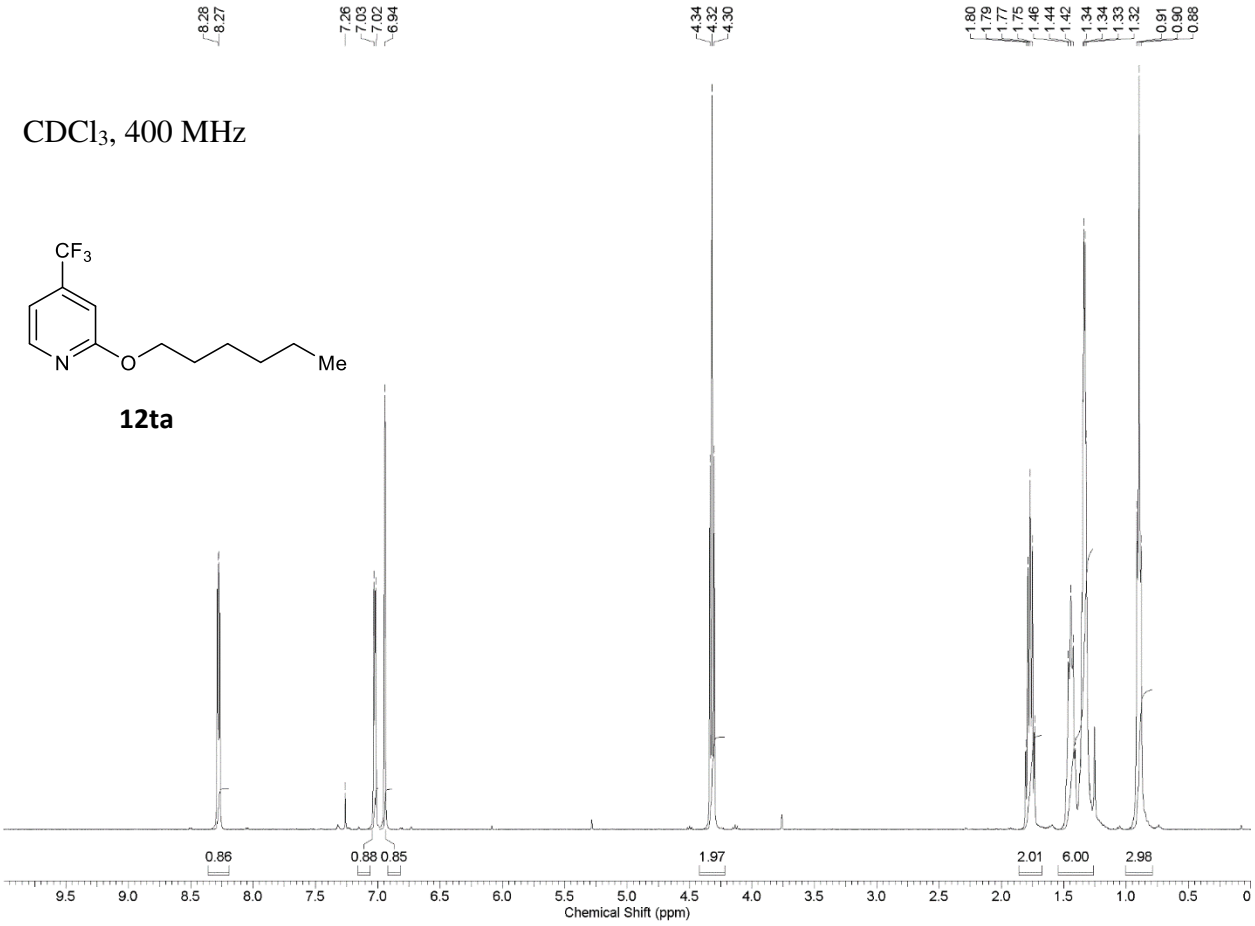

8.52
7.26
6.71
4.08
4.07
4.05
2.78
2.76
2.74
1.82
1.81
1.79
1.69
1.36
1.34
1.33
1.32
1.31
1.30
0.94
0.92
0.91
0.90
0.88
CDCl3, 400 MHz
O
Me
F3C
N
Me
12qa
1.00
1.01
2.07
2.09
2.09
2.10
8.44
6.10
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

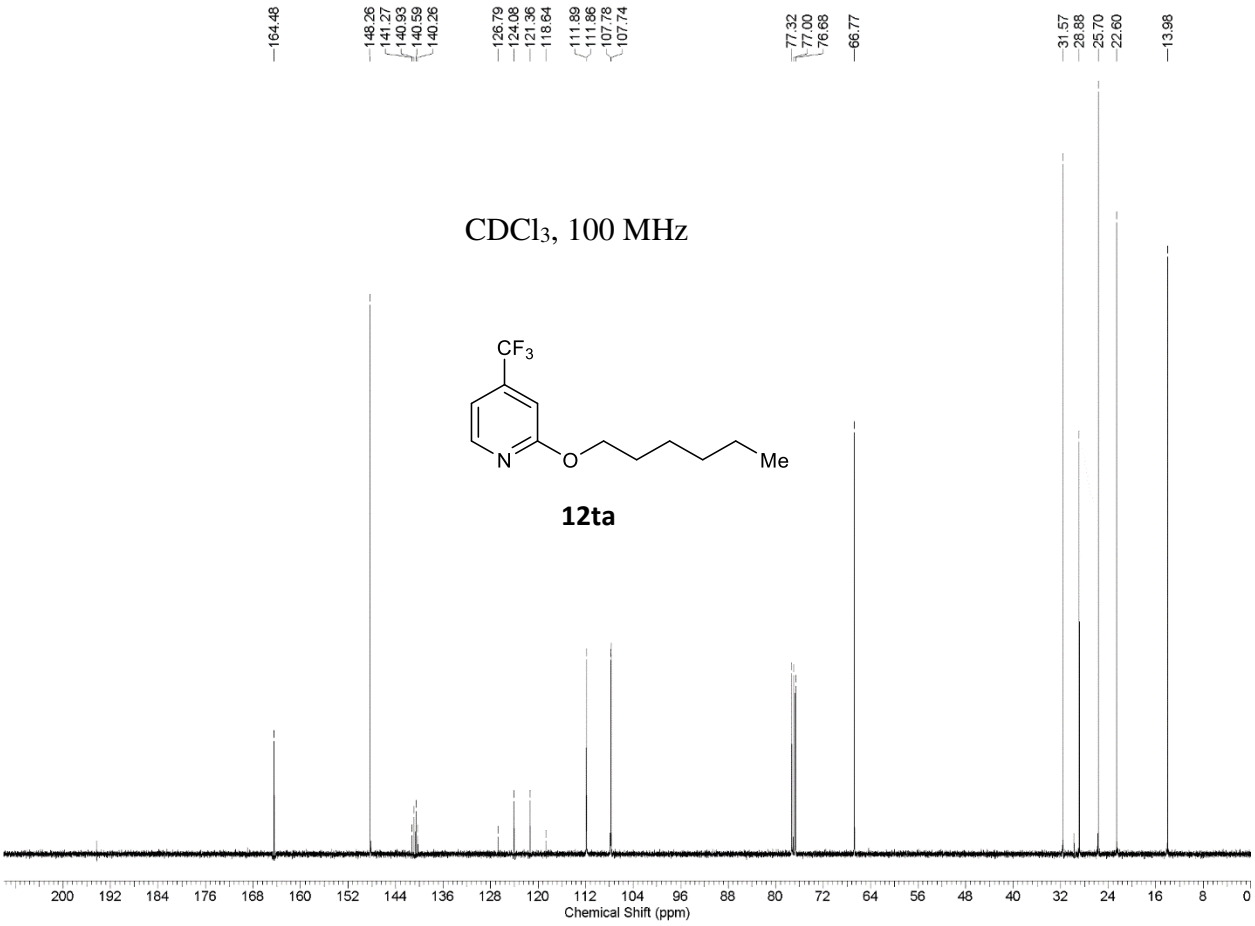

168.62
163.29
147.48
147.36
147.31
127.48
124.77
122.06
113.21
112.91
106.25
77.32
77.00
76.68
68.64
38.59
31.74
31.28
28.57
25.33
22.46
13.86
13.83
CDCl3, 100 MHz
O
Me
F3C
Me
N
12qa
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

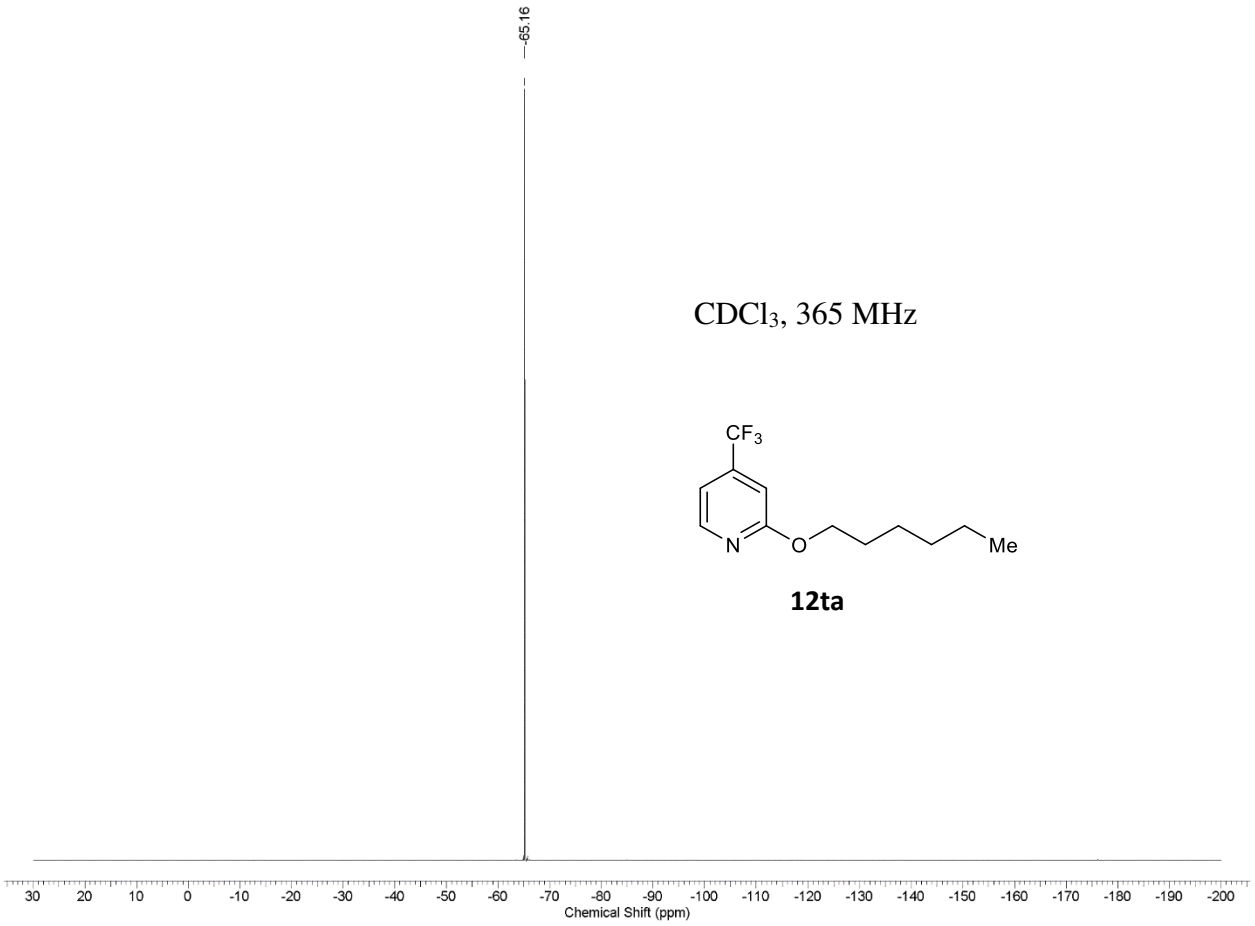


$CDCl_3$, 365 MHz

12qa

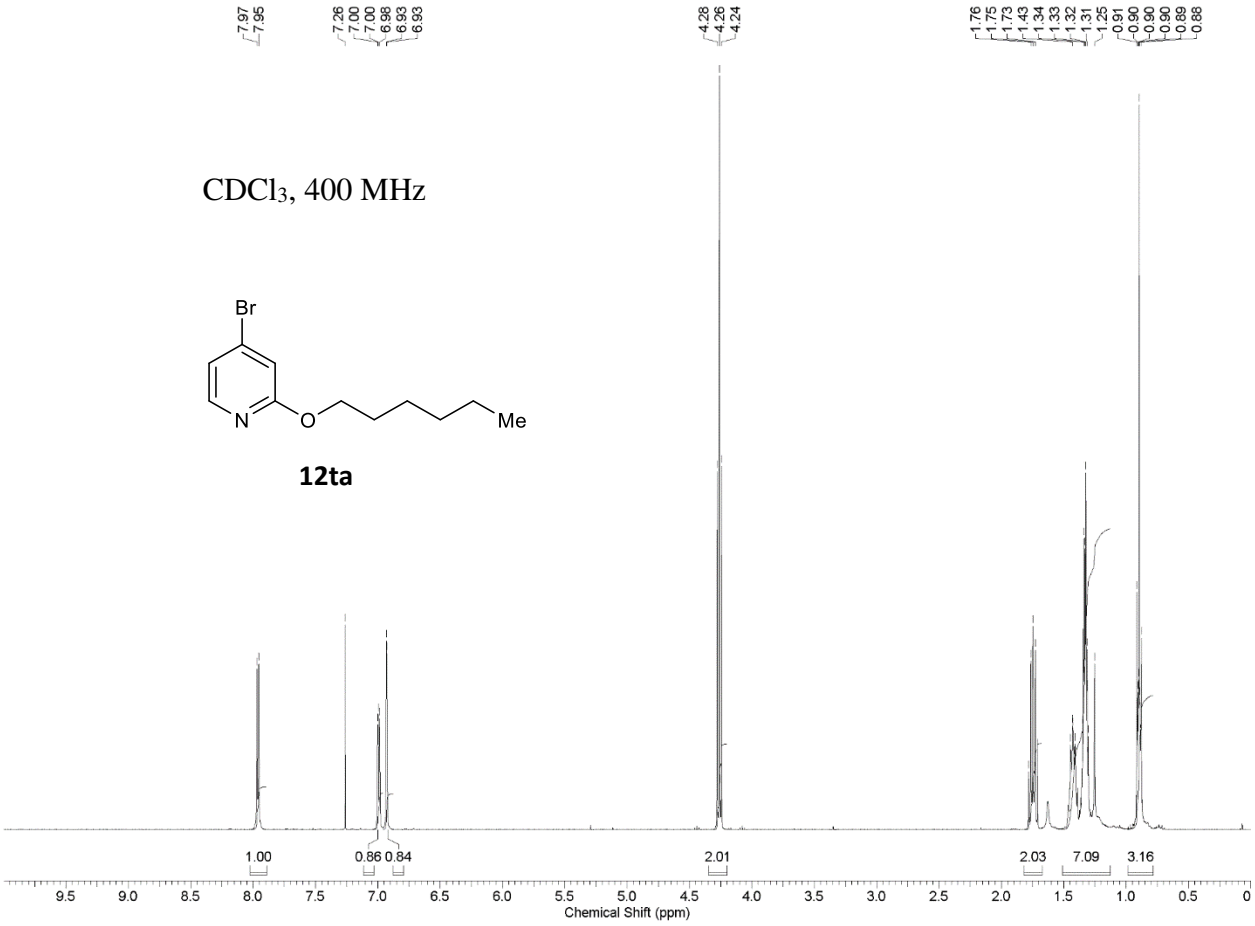

8.28
8.27
7.26
7.03
7.02
6.94
4.34
4.32
4.30
1.80
1.79
1.77
1.75
1.46
1.44
1.42
1.34
1.34
1.33
1.32
0.91
0.90
0.88
CDCl3, 400 MHz
CF3
N
O
Me
12ta
0.86
0.88
0.85
1.97
2.01
6.00
2.98
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


164.48
148.26
141.27
140.93
140.59
140.26
126.79
124.08
121.36
118.64
111.89
111.86
107.78
107.74
77.32
77.00
76.68
66.77
31.57
28.88
25.70
22.60
13.98
CDCl3, 100 MHz
CF3
N
O
Me
12ta
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

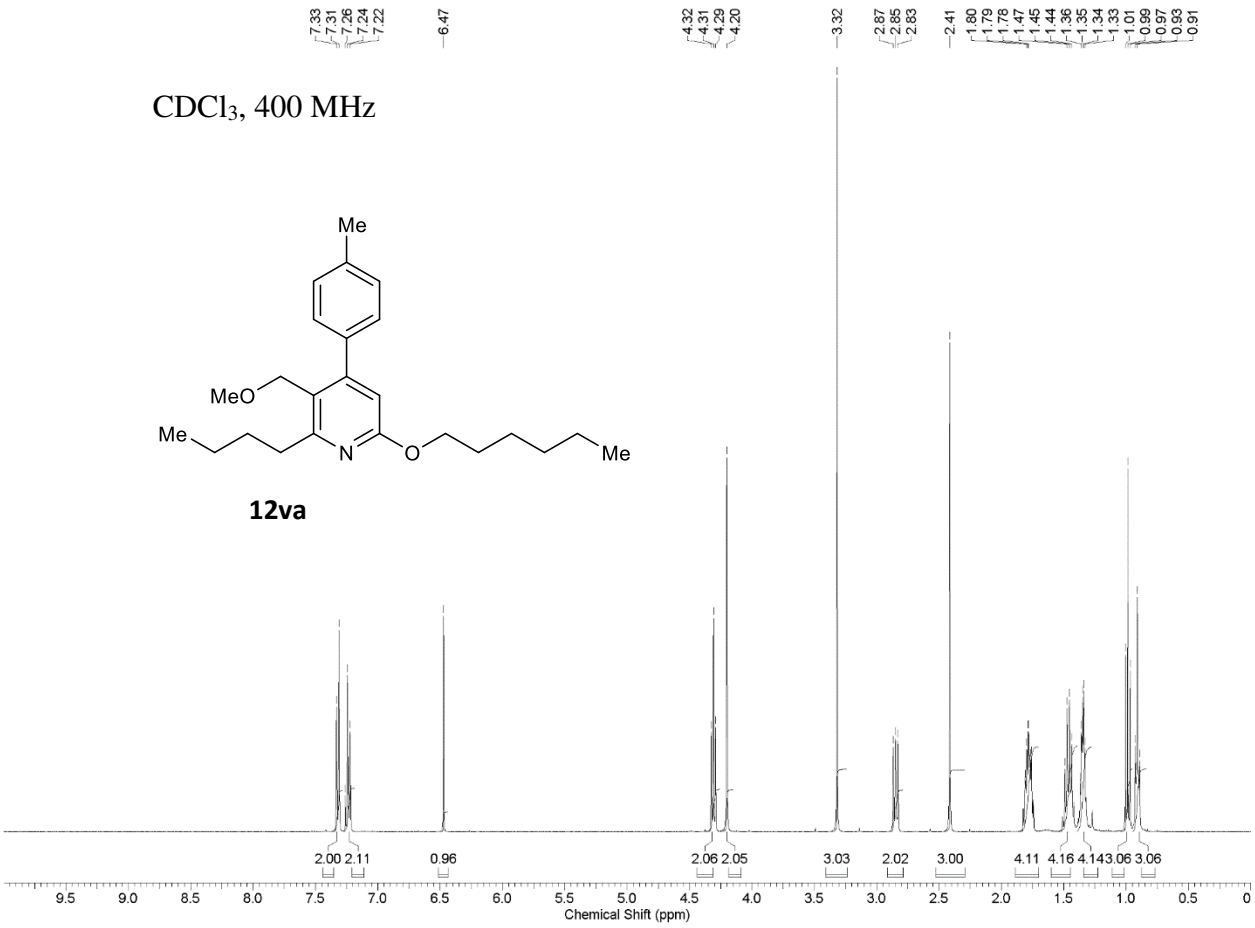


$CDCl_3$, 365 MHz

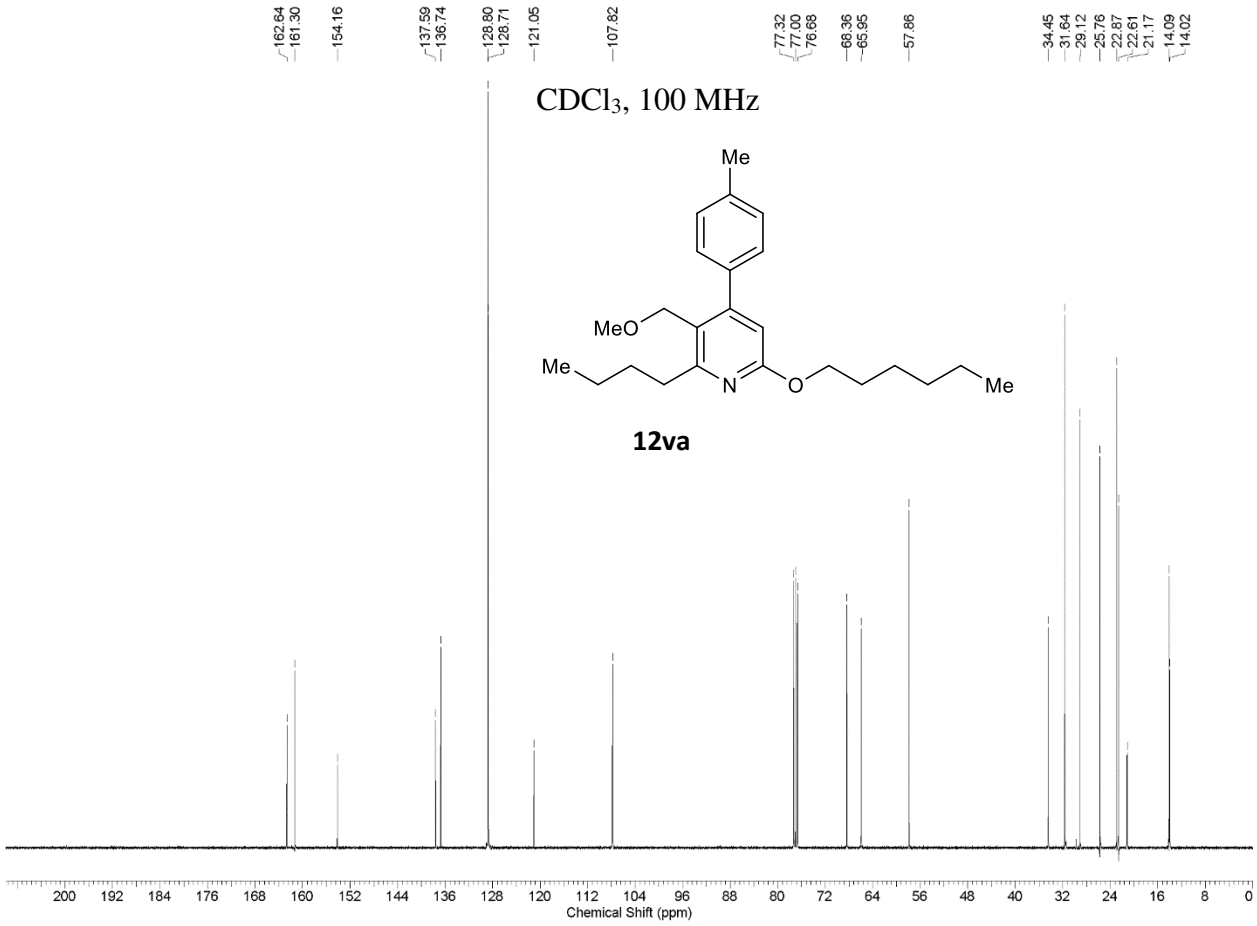
12ta

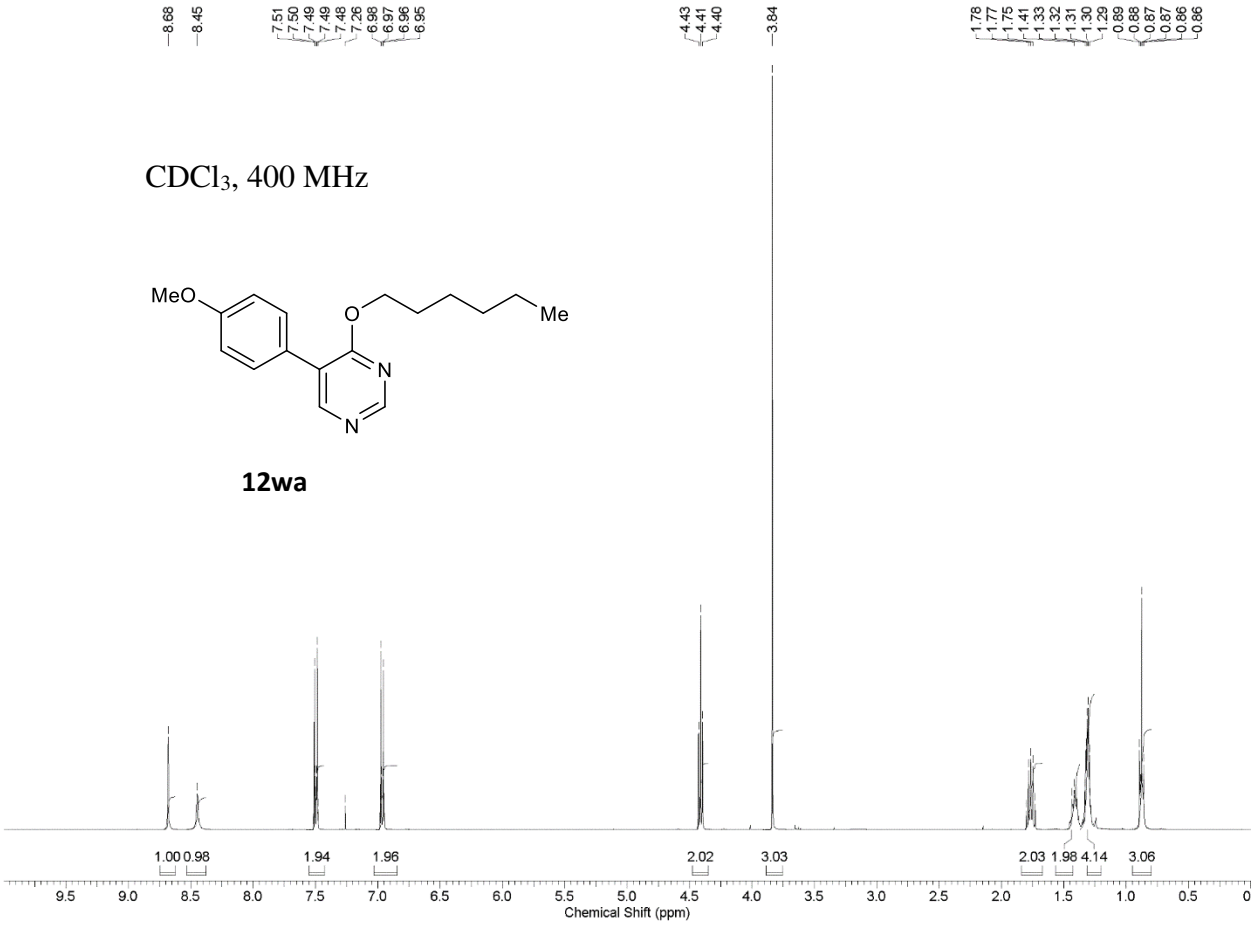

7.97
7.95
7.26
7.00
7.00
6.98
6.93
6.93
4.28
4.26
4.24
1.76
1.75
1.73
1.43
1.34
1.33
1.32
1.31
1.25
0.91
0.90
0.90
0.90
0.89
0.88
CDCl3, 400 MHz
Br
N
O
Me
12ta
1.00
0.86
0.84
2.01
2.03
7.09
3.16
Chemical Shift (ppm)

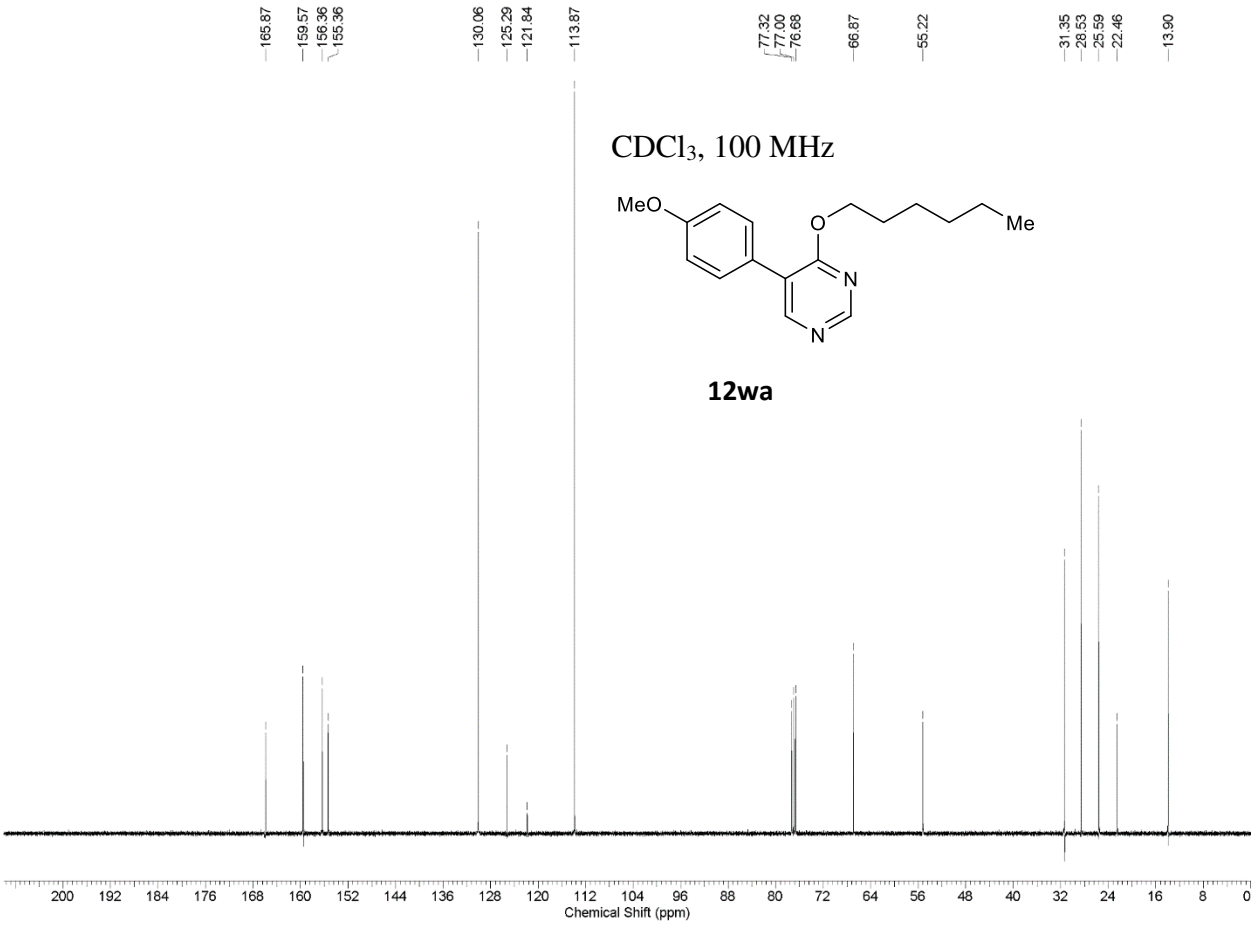
$CDCl_3$, 400 MHz

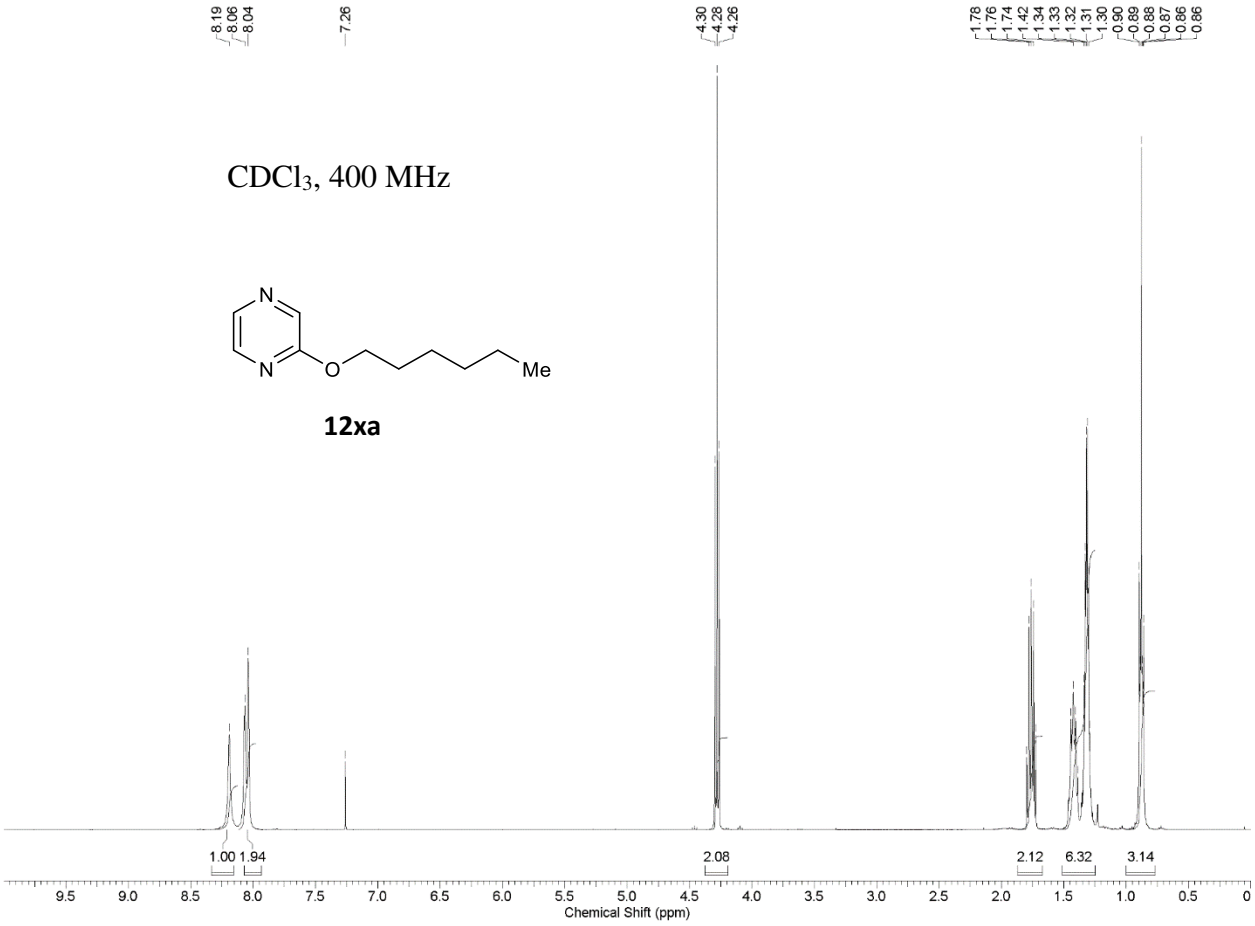


12va

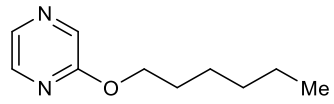

162.64
161.30
154.16
137.59
136.74
128.80
128.71
121.05
107.82
77.32
77.00
76.68
68.36
65.95
57.86
34.45
31.64
29.12
25.76
22.87
22.61
21.17
14.09
14.02
CDCl3, 100 MHz
Me
MeO
Me
N
O
Me
12va
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)


8.68
8.45
7.51
7.50
7.49
7.49
7.48
7.26
6.98
6.97
6.96
6.95
4.43
4.41
4.40
3.84
1.78
1.77
1.75
1.41
1.33
1.32
1.31
1.30
1.29
0.89
0.88
0.87
0.87
0.86
0.86
CDCl3, 400 MHz
MeO
O
Me
N
N
12wa
1.00 0.98
1.94
1.96
2.02
3.03
2.03 1.98 4.14
3.06
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
Chemical Shift (ppm)


165.87
159.57
156.36
155.36
130.06
125.29
121.84
113.87
77.32
77.00
76.68
66.87
55.22
31.35
28.53
25.59
22.46
13.90
CDCl3, 100 MHz
MeO
O
Me
N
N
12wa
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

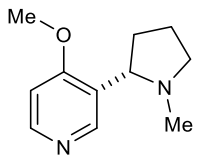

8.19
8.06
8.04
7.26
4.30
4.28
4.26
1.78
1.76
1.74
1.42
1.34
1.33
1.32
1.31
1.30
0.90
0.89
0.88
0.87
0.86
0.86
CDCl3, 400 MHz
N
N
O
Me
12xa
1.00
1.94
2.08
2.12
6.32
3.14
Chemical Shift (ppm)

$CDCl_3$, 100 MHz

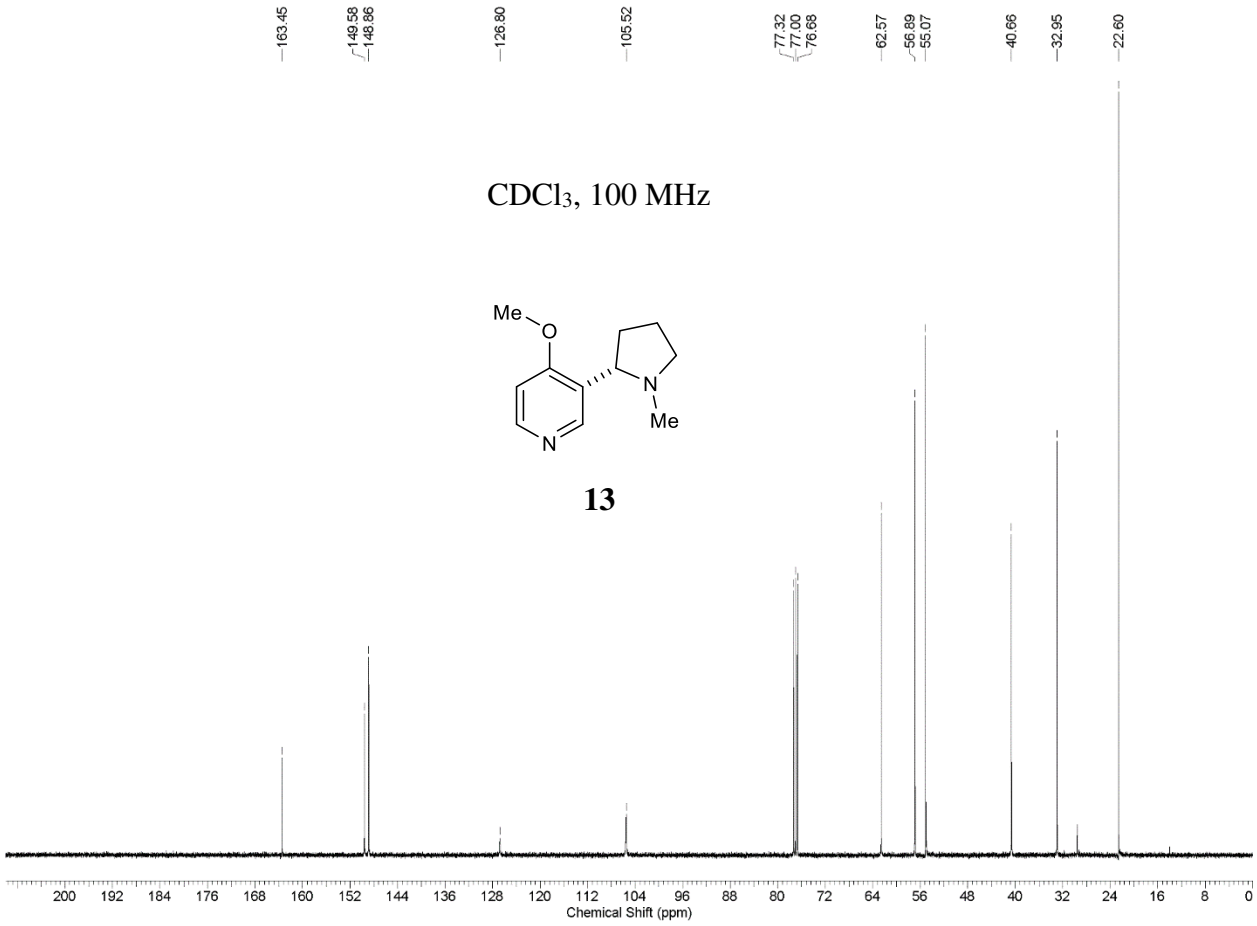


12xa

$CDCl_3$, 400 MHz

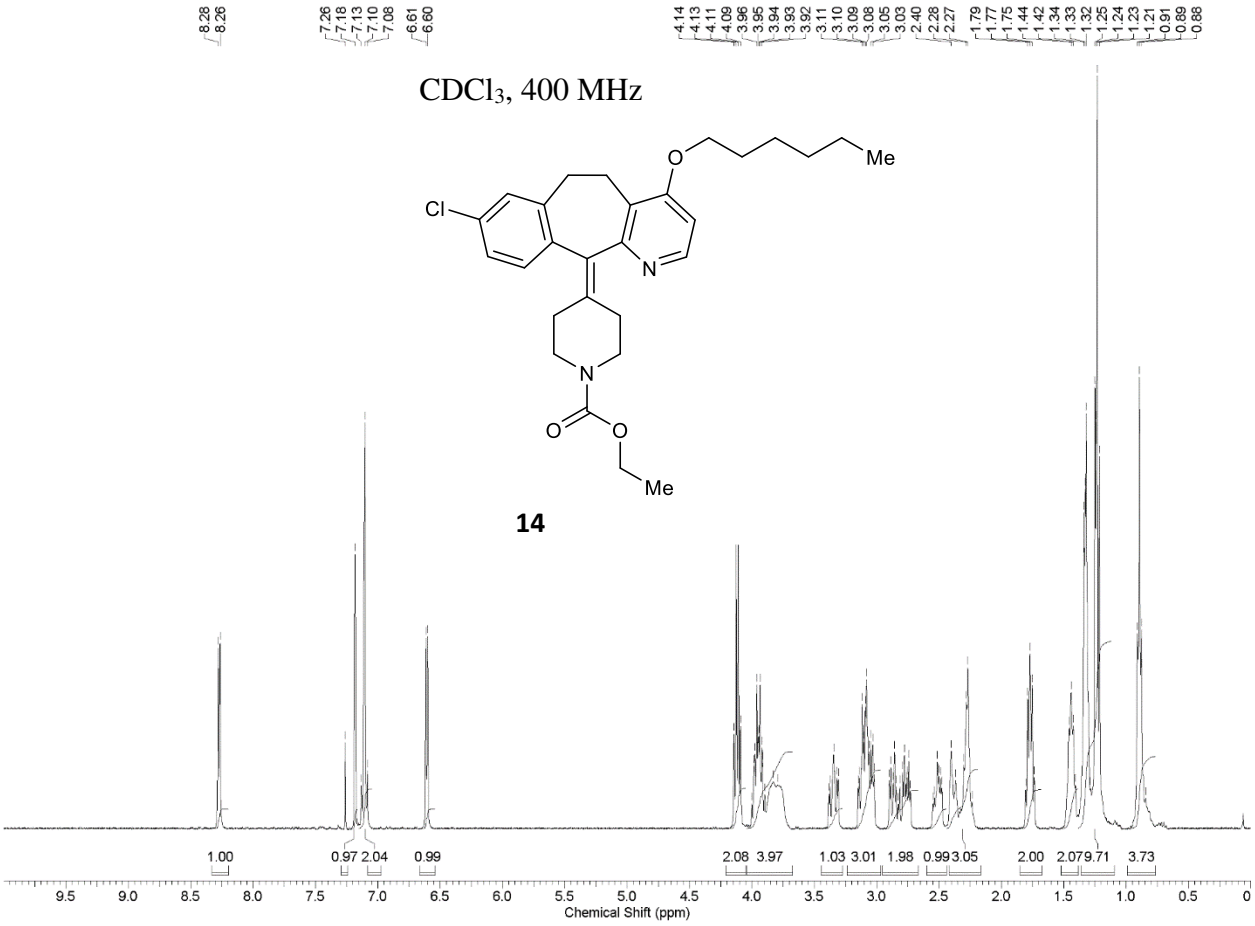


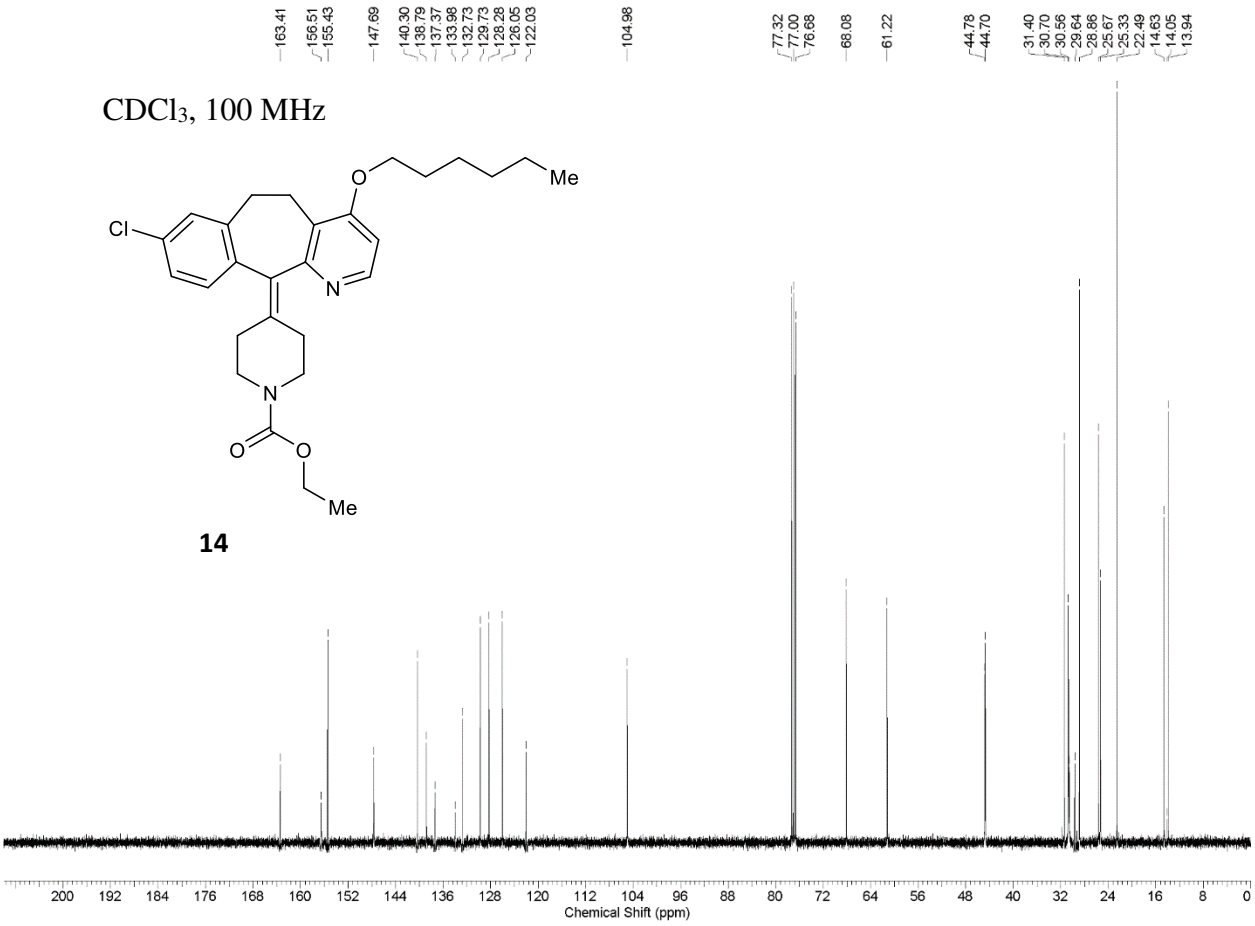
13

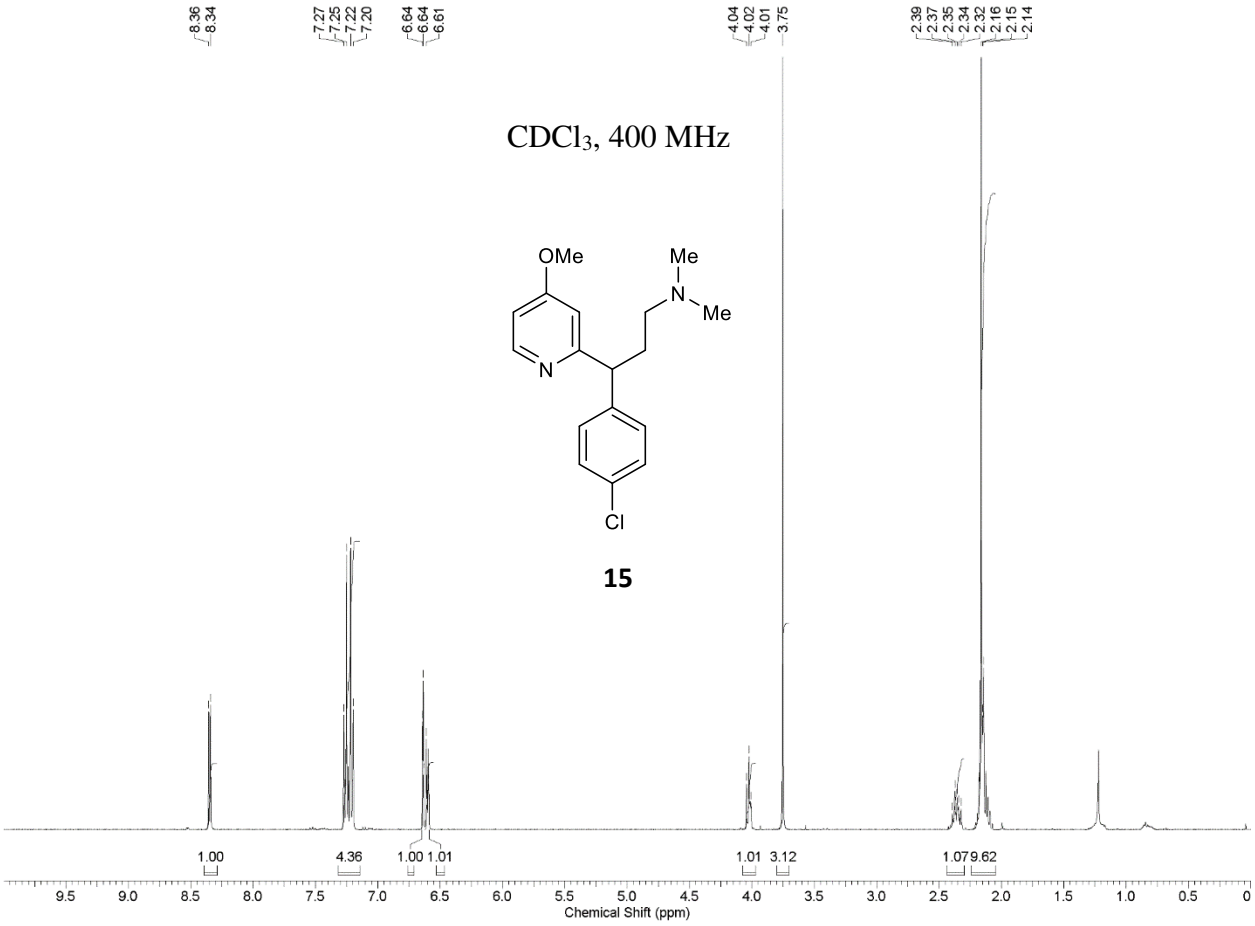


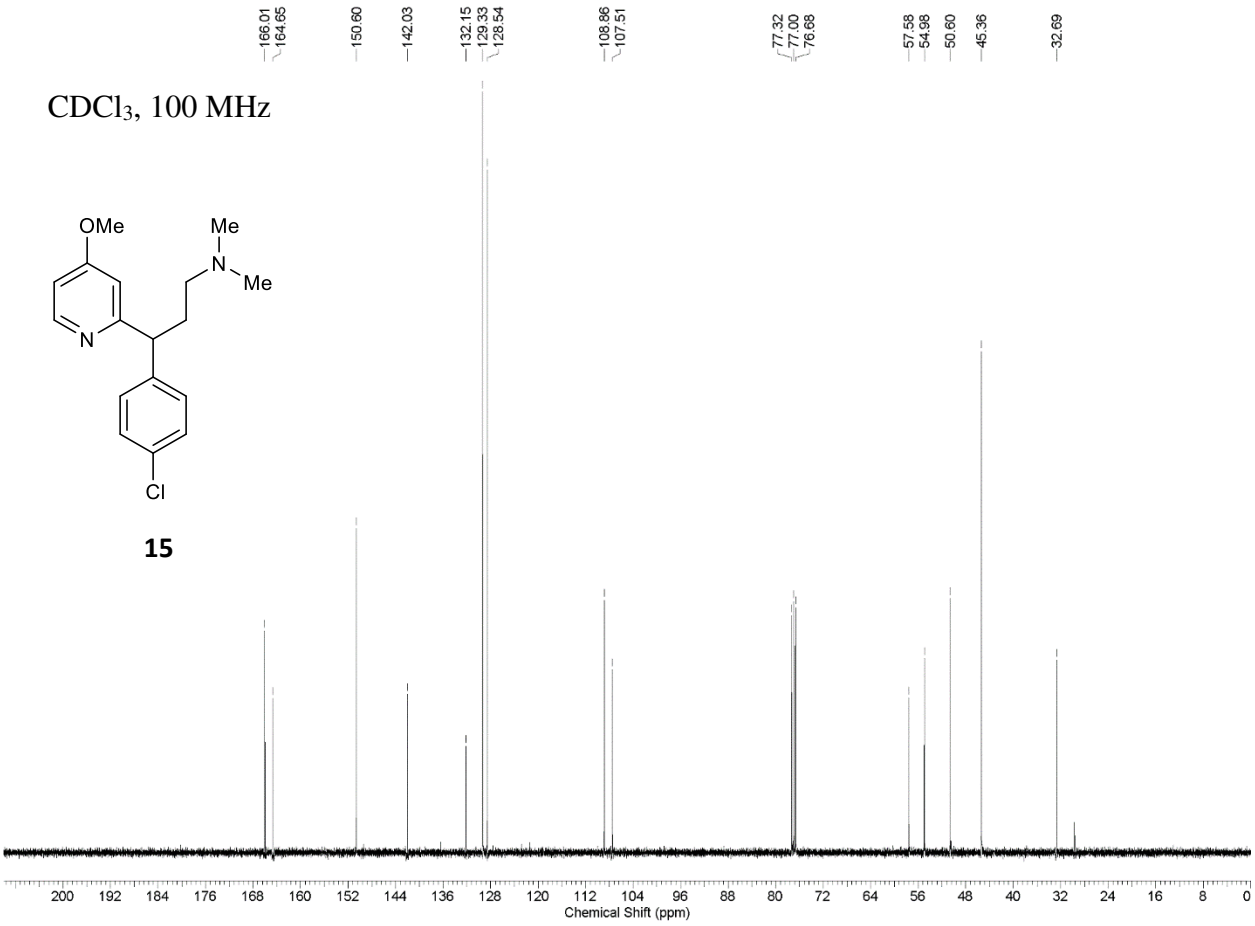
$CDCl_3$, 100 MHz

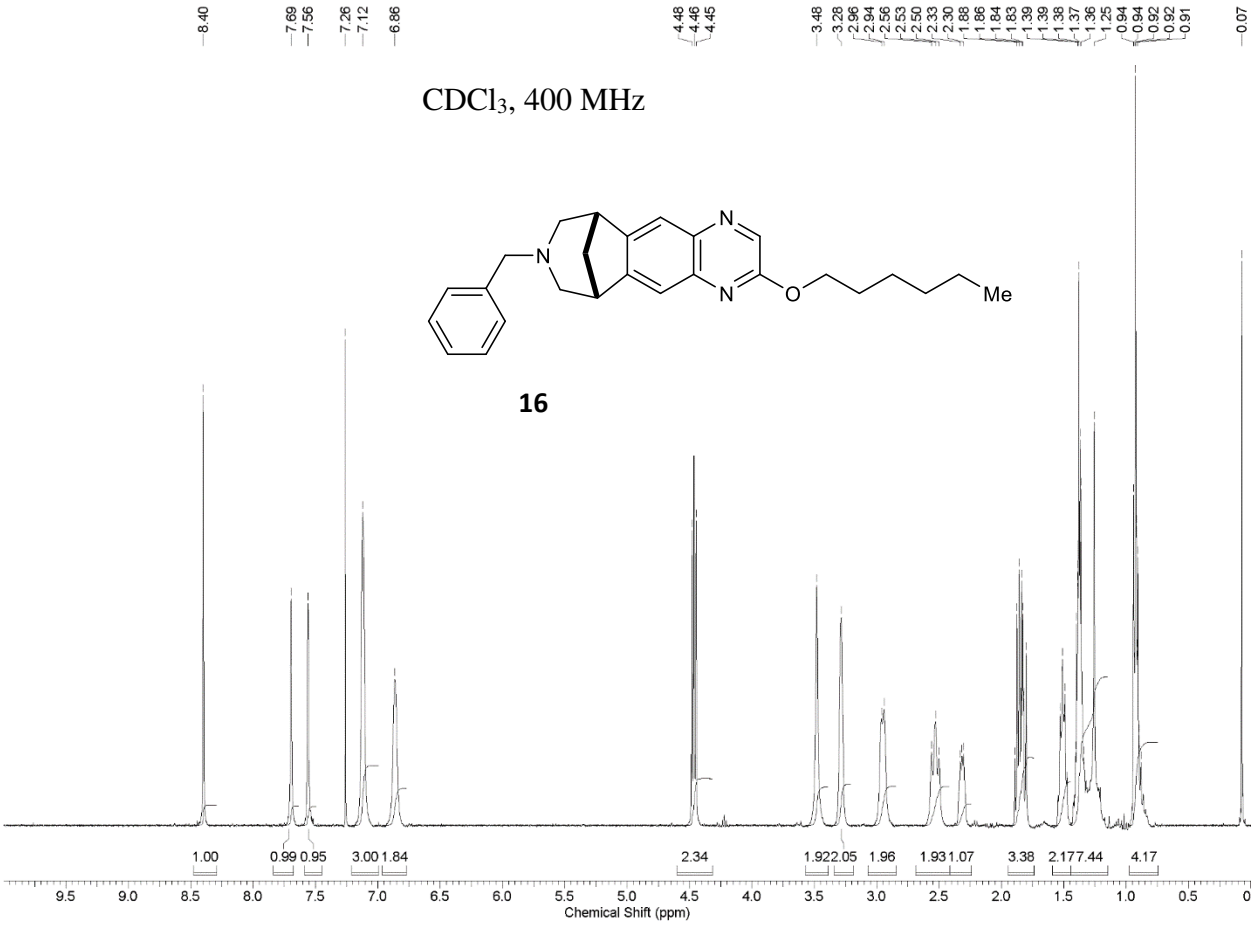
13

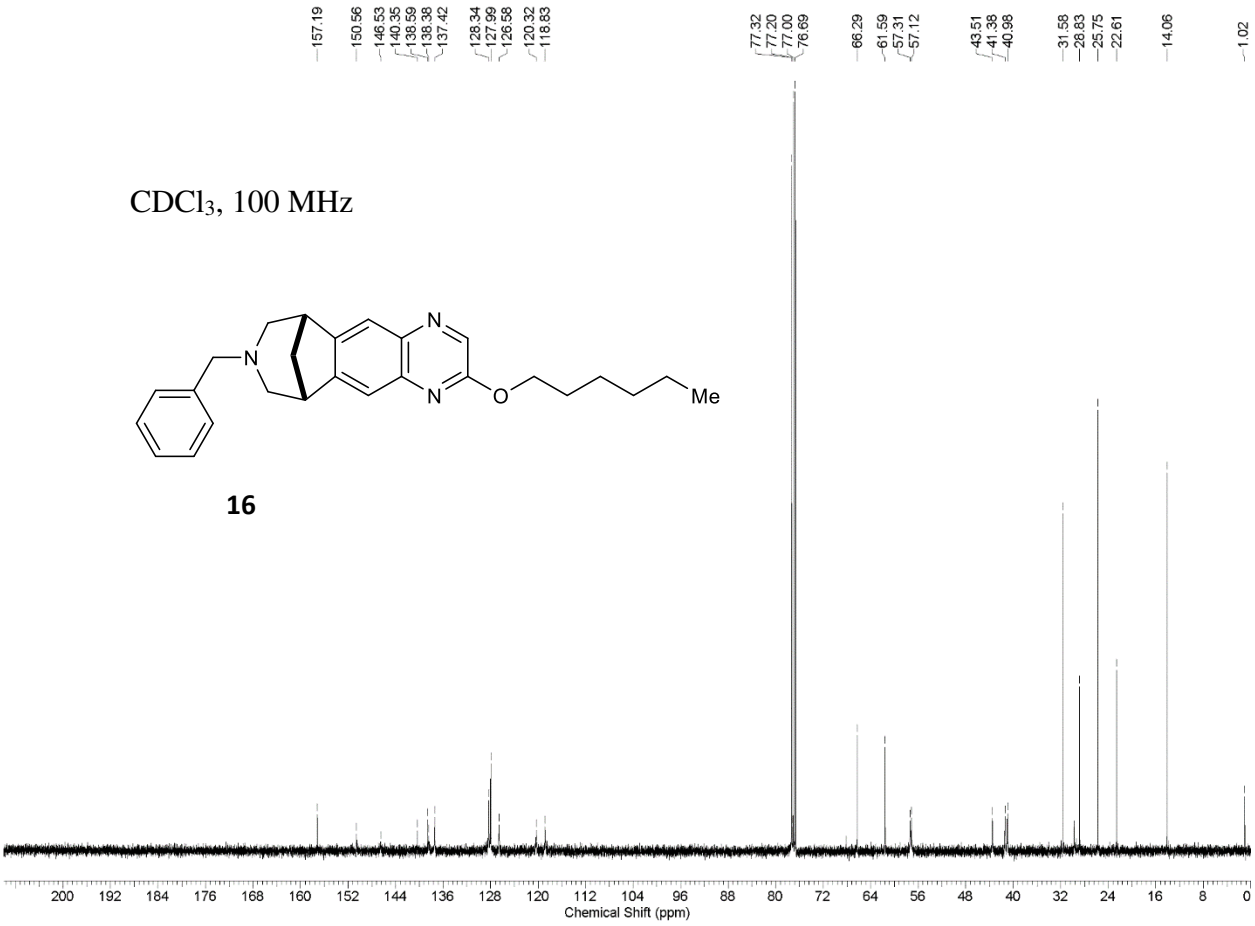

8.28
8.26
7.26
7.18
7.13
7.10
7.08
6.61
6.60
4.14
4.13
4.11
4.09
3.96
3.95
3.94
3.93
3.92
3.11
3.10
3.09
3.08
3.05
3.03
2.40
2.28
2.27
1.79
1.77
1.75
1.44
1.42
1.34
1.33
1.32
1.25
1.24
1.23
1.21
0.91
0.89
0.88
CDCl3, 400 MHz
O
Me
Cl
N
N
O
O
Me
14
1.00
0.97
2.04
0.99
2.08
3.97
1.03
3.01
1.98
0.99
3.05
2.00
2.07
9.71
3.73
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
0
Chemical Shift (ppm)

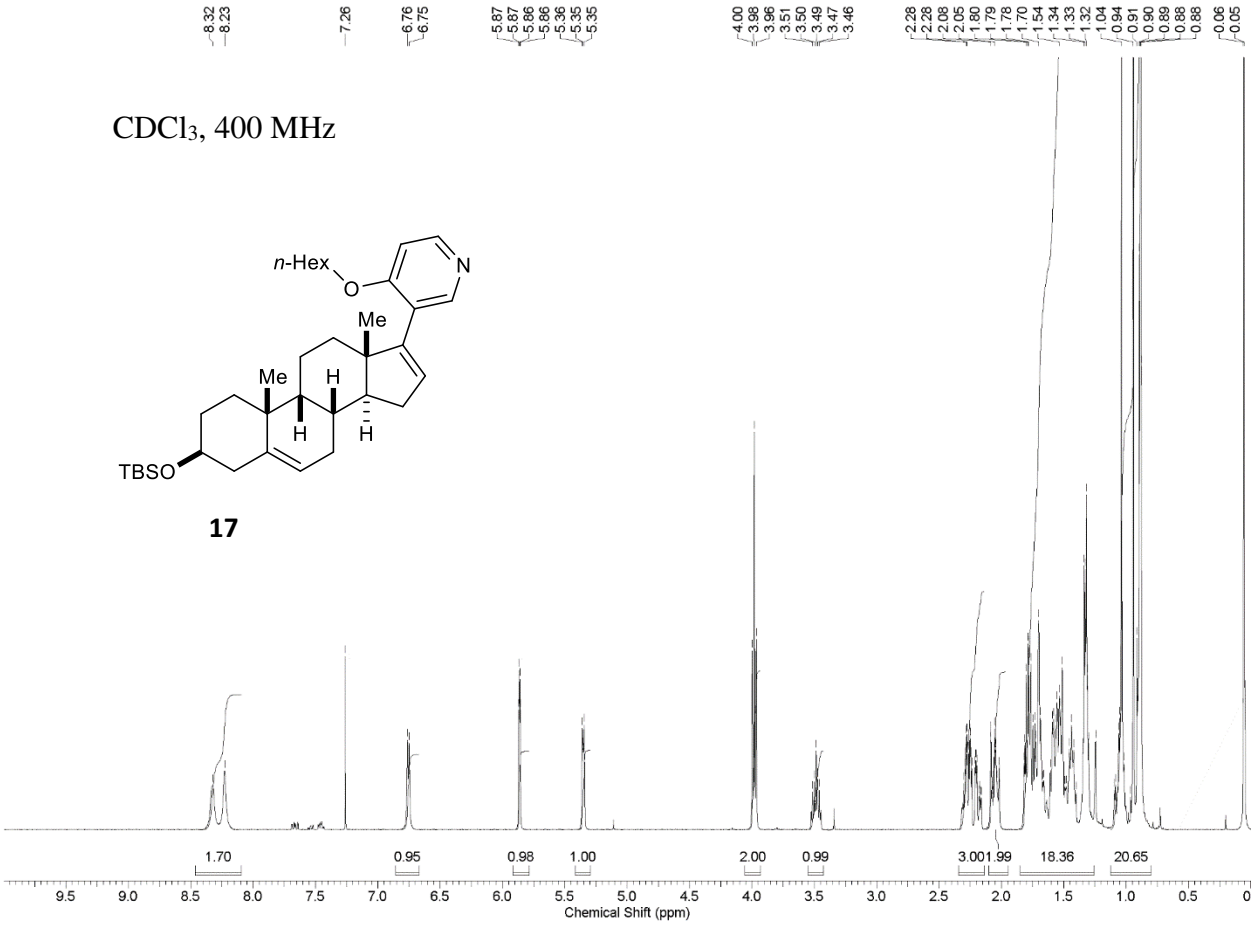

163.41
156.51
155.43
147.69
140.30
138.79
137.37
133.98
132.73
129.73
128.28
126.05
122.03
104.98
77.32
77.00
76.68
68.08
61.22
44.78
44.70
31.40
30.70
30.56
29.64
28.86
25.67
25.33
22.49
14.63
14.05
13.94
CDCl3, 100 MHz
O
Me
Cl
N
N
O
O
Me
14
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

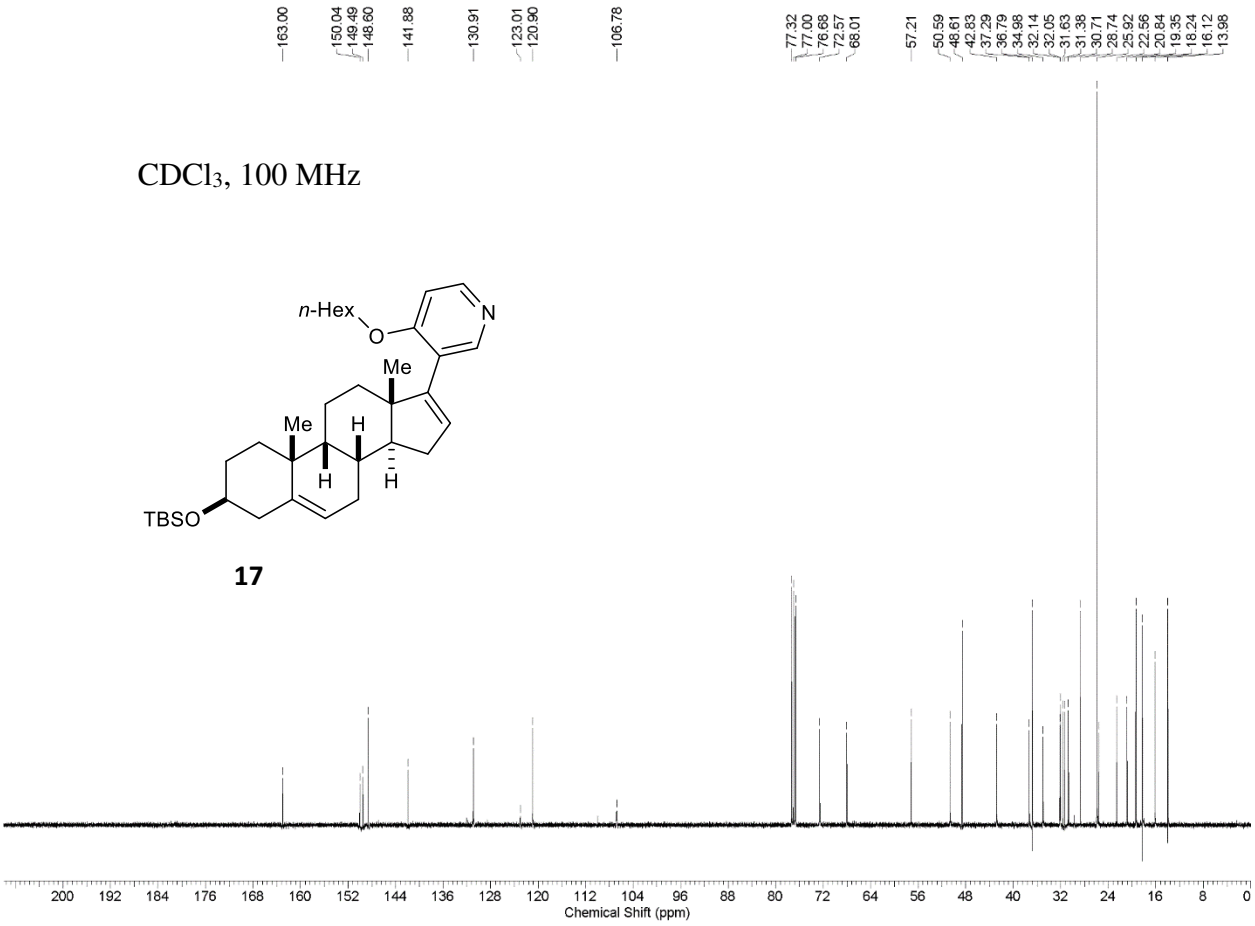

8.36
8.34
7.27
7.25
7.22
7.20
6.64
6.64
6.61
4.04
4.02
4.01
3.75
2.39
2.37
2.35
2.34
2.32
2.16
2.15
2.14
CDCl3, 400 MHz
OMe
Me
N
Me
N
Cl
15
1.00
4.36
1.00
1.01
1.01
3.12
1.07
9.62
Chemical Shift (ppm)

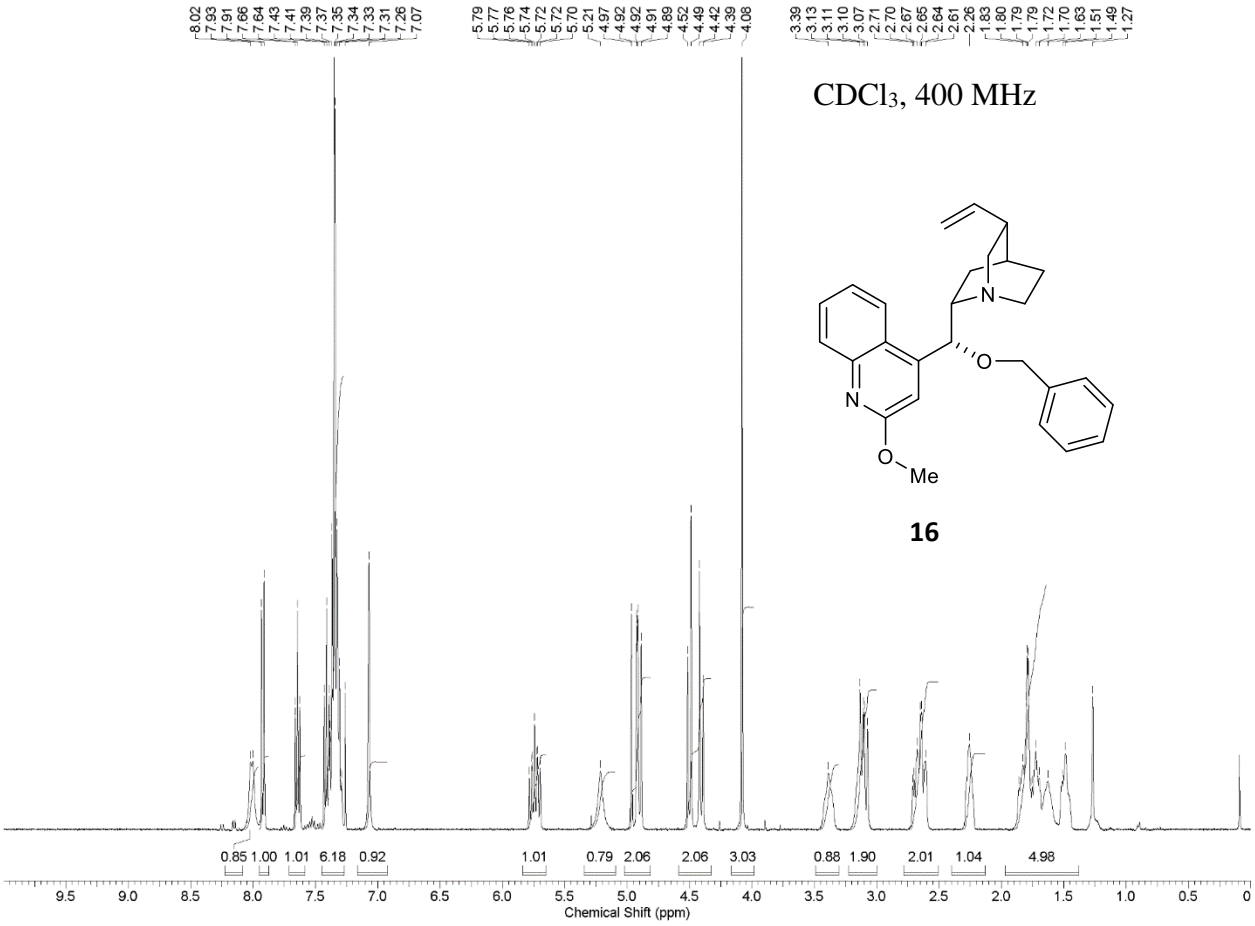

166.01
164.65
150.60
142.03
132.15
129.33
128.54
108.86
107.51
77.32
77.00
76.68
57.58
54.98
50.60
45.36
32.69
CDCl3, 100 MHz
OMe
Me
N
Me
N
Cl
15
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

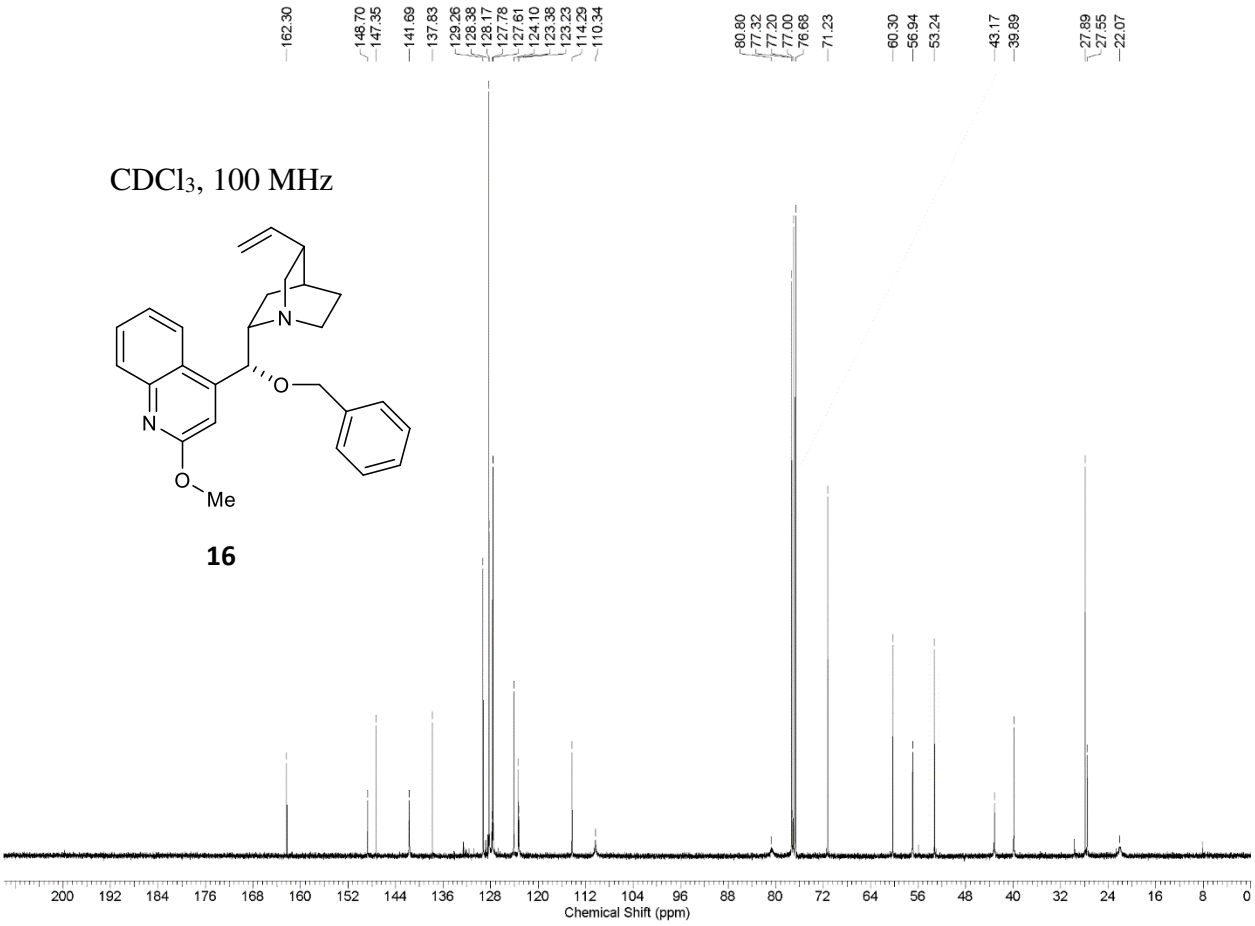

8.40
7.69
7.56
7.26
7.12
6.86
4.48
4.46
4.45
3.48
3.28
2.96
2.94
2.56
2.53
2.50
2.33
2.30
1.88
1.86
1.84
1.83
1.39
1.38
1.37
1.36
1.25
0.94
0.94
0.92
0.92
0.91
0.07
CDCl3, 400 MHz
N
N
N
O
Me
16
1.00
0.99
0.95
3.00
1.84
2.34
1.92
2.05
1.96
1.93
1.07
3.38
2.17
7.44
4.17
Chemical Shift (ppm)


157.19
150.56
146.53
140.35
138.59
138.38
137.42
128.34
127.99
126.58
120.32
118.83
77.32
77.20
77.00
76.69
66.29
61.59
57.31
57.12
43.51
41.38
40.98
31.58
28.83
25.75
22.61
14.06
1.02
CDCl3, 100 MHz
N
N
N
O
Me
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 0
Chemical Shift (ppm)

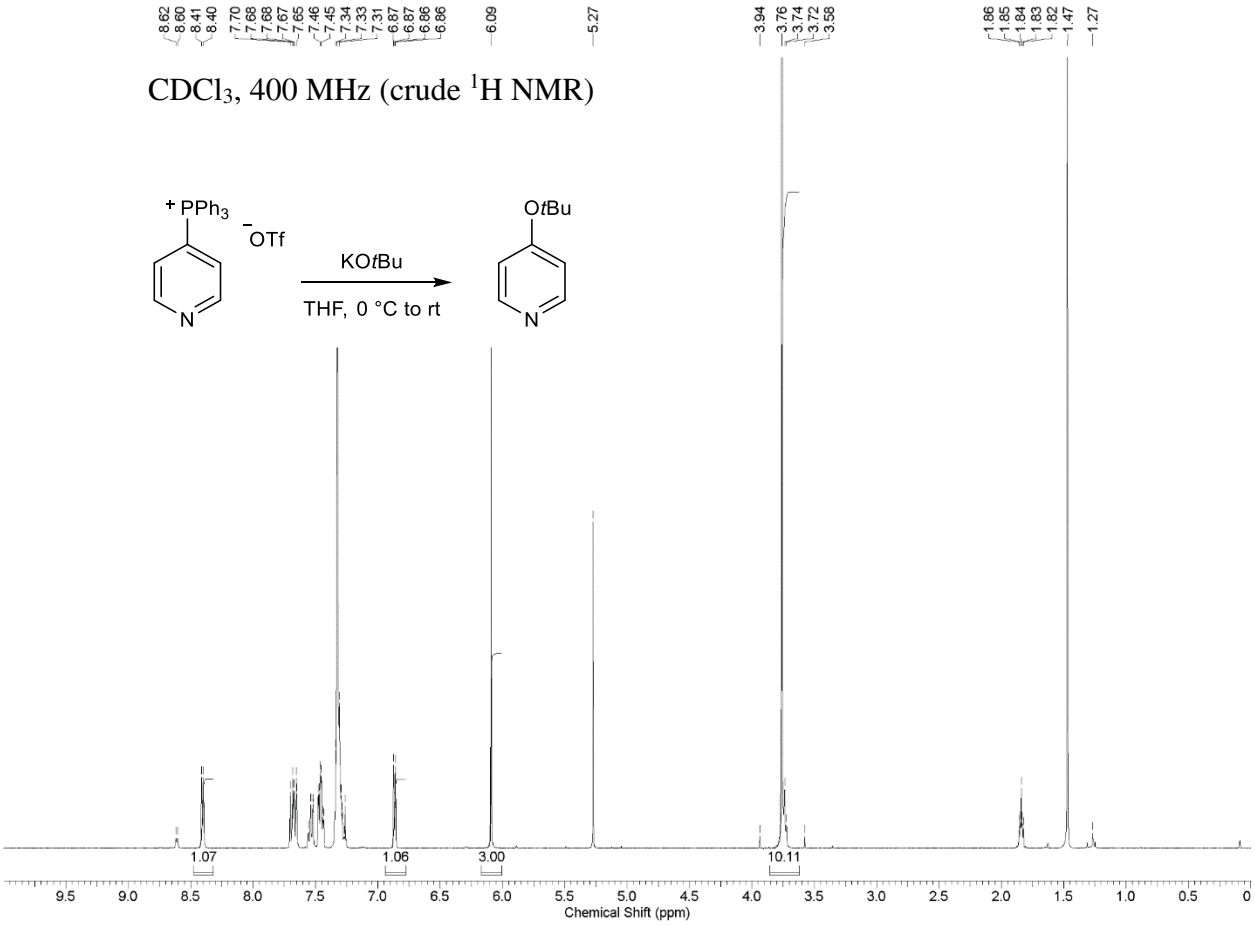

8.32
8.23
7.26
6.76
6.75
5.87
5.87
5.86
5.86
5.36
5.35
5.35
4.00
3.98
3.96
3.51
3.50
3.49
3.47
3.46
2.28
2.26
2.08
2.05
1.80
1.79
1.78
1.70
1.54
1.34
1.33
1.32
1.04
0.94
0.91
0.90
0.89
0.88
0.88
0.06
0.05
CDCl3, 400 MHz
n-Hex
O
N
Me
Me
H
H
H
TBSO
17
1.70
0.95
0.98
1.00
2.00
0.99
3.00
1.99
18.36
20.65
Chemical Shift (ppm)

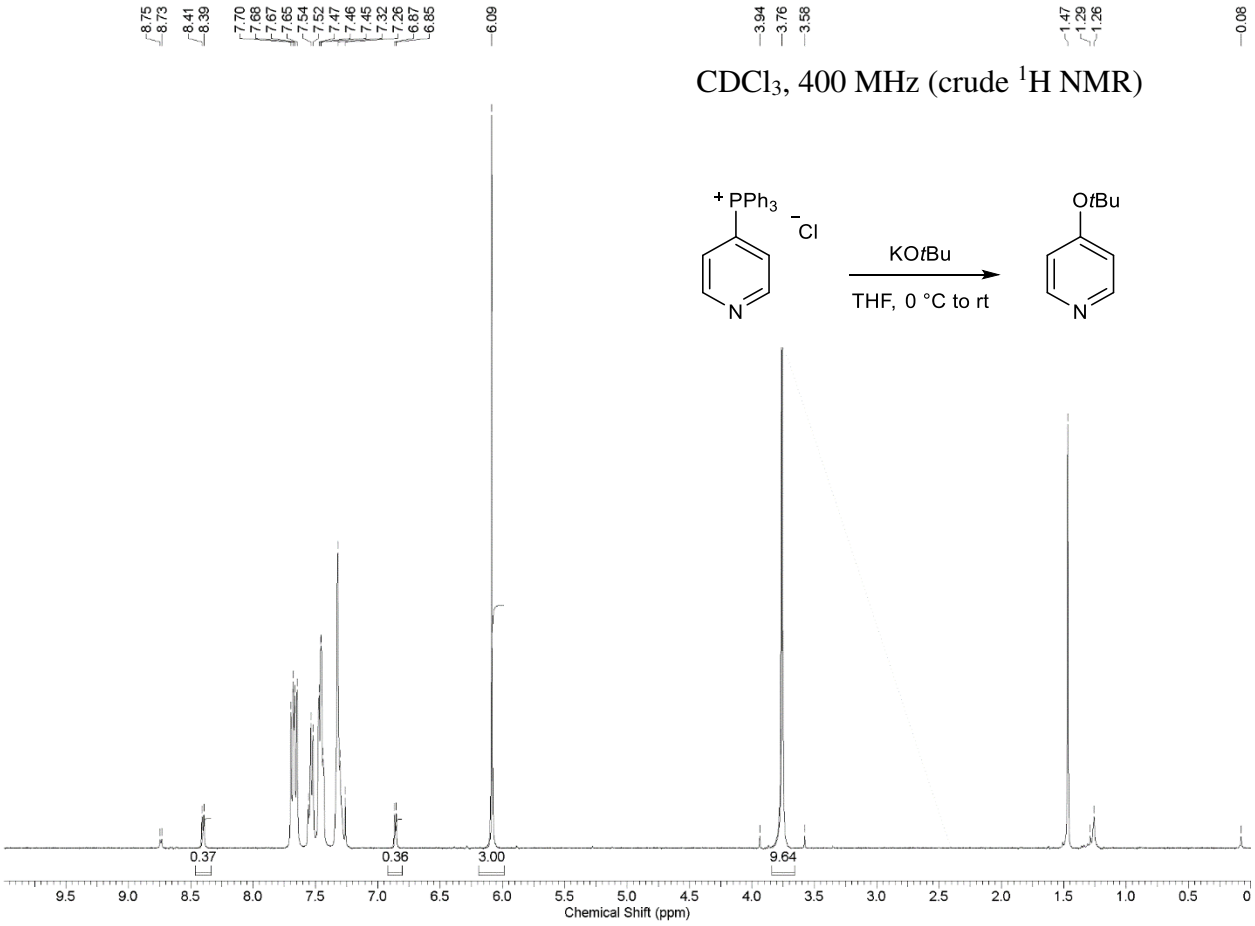

163.00
150.04
149.49
148.60
141.88
130.91
123.01
120.90
106.78
77.32
77.00
76.68
72.57
68.01
57.21
50.59
48.61
42.83
37.29
36.79
34.98
32.14
32.05
31.63
31.38
30.71
28.74
25.92
22.56
20.84
19.35
18.24
16.12
13.98
CDCl3, 100 MHz
n-Hex
O
N
Me
Me
H
H
H
TBSO
17
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

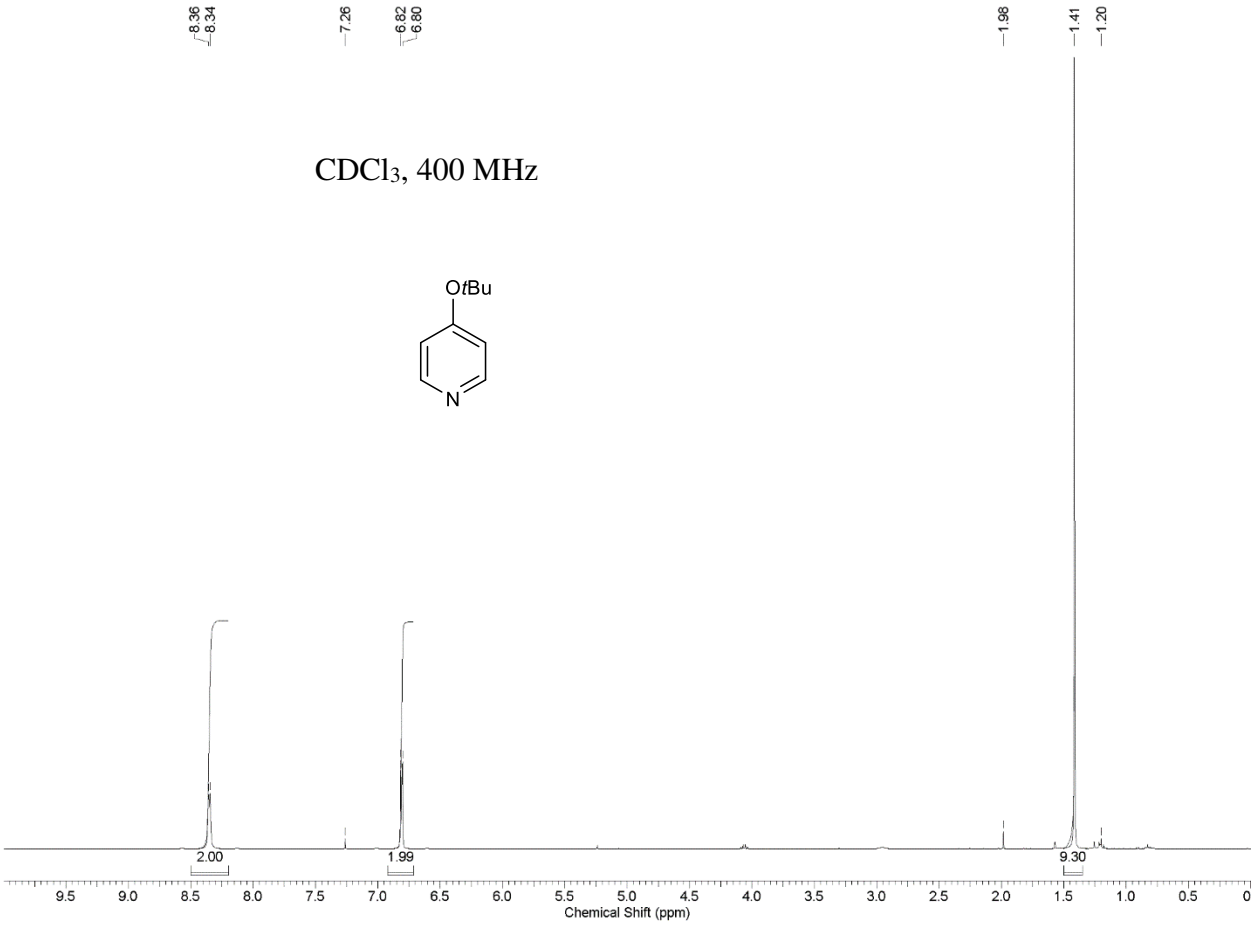

8.02
7.93
7.91
7.66
7.64
7.43
7.41
7.39
7.37
7.35
7.34
7.33
7.31
7.26
7.07
5.79
5.77
5.76
5.74
5.72
5.72
5.70
5.21
4.97
4.92
4.92
4.91
4.89
4.52
4.49
4.42
4.39
4.08
3.39
3.13
3.11
3.10
3.07
2.71
2.70
2.67
2.65
2.64
2.61
2.26
1.83
1.80
1.79
1.79
1.72
1.70
1.63
1.51
1.49
1.27
CDCl3, 400 MHz
N
O
N
O
Me
16
0.85 1.00 1.01 6.18 0.92
1.01
0.79 2.06
2.06
3.03
0.88 1.90
2.01
1.04
4.98
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 0
Chemical Shift (ppm)

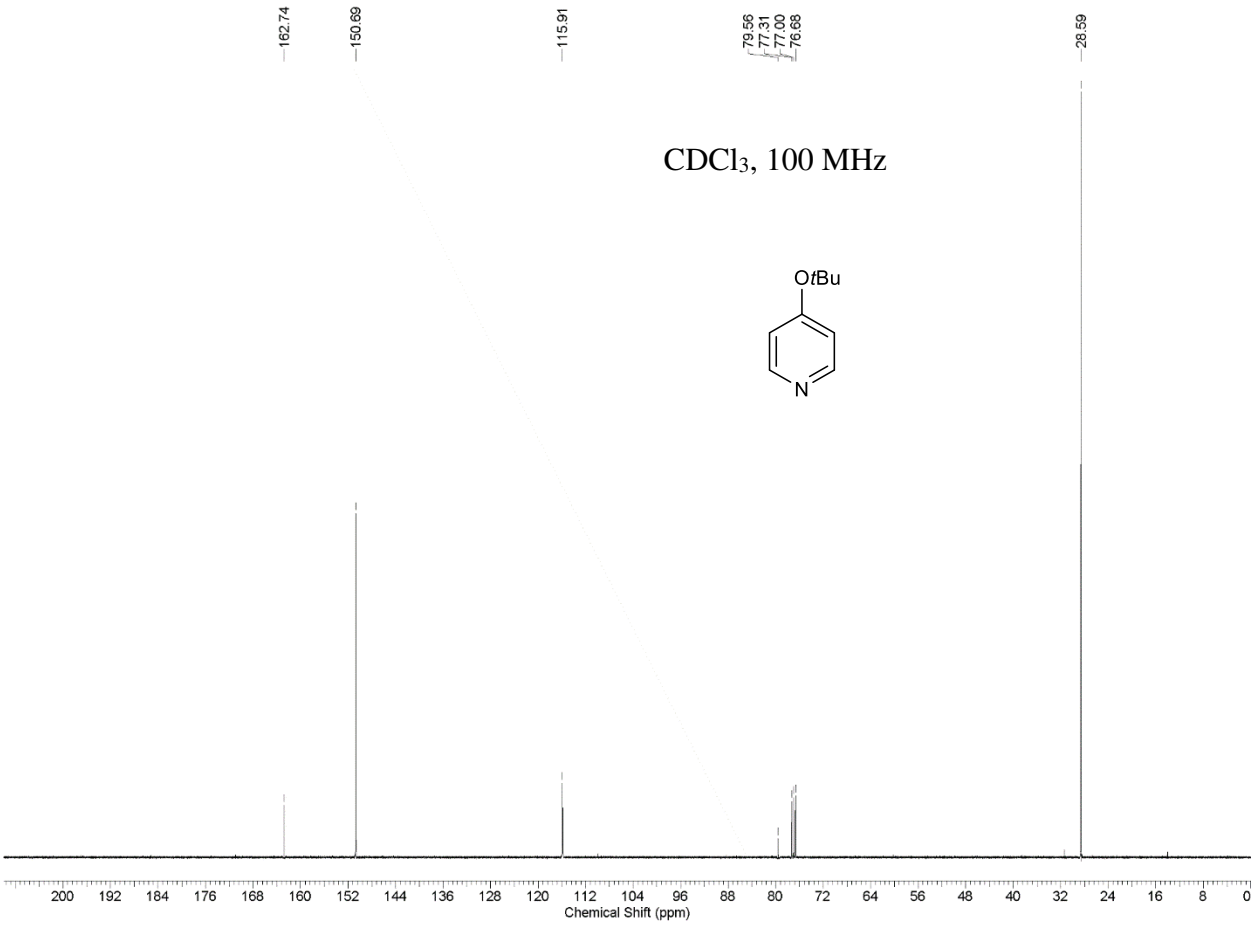

162.30
148.70
147.35
141.69
137.83
129.26
128.38
128.17
127.78
127.61
124.10
123.38
123.23
114.29
110.34
80.80
77.32
77.20
77.00
76.68
71.23
60.30
56.94
53.24
43.17
39.89
27.89
27.55
22.07
CDCl3, 100 MHz
N
O
N
O
Me
16
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

$CDCl_3$, 400 MHz (crude ^1H NMR)




8.75
8.73
8.41
8.39
7.70
7.68
7.67
7.65
7.54
7.52
7.47
7.46
7.45
7.32
7.26
6.87
6.85
6.09
3.94
3.76
3.58
1.47
1.29
1.26
0.00
CDCl3, 400 MHz (crude 1H NMR)
+ PPh3
Cl
KOtBu
THF, 0 °C to rt
OtBu
N
N
0.37
0.36
3.00
9.64
Chemical Shift (ppm)


8.36
8.34
7.26
6.82
6.80
1.98
1.41
1.20
CDCl3, 400 MHz
OtBu
N
2.00
1.99
9.30
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 0
Chemical Shift (ppm)


162.74
150.69
115.91
79.56
77.31
77.00
76.68
28.59
CDCl3, 100 MHz
OtBu
N
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

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APPENDIX TWO

SITE-SELECTIVE FUNCTIONALIZATION OF POLYAZINES: EXPERIMENTAL

A 2.1 General Information

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR (400 MHz) spectrometer or an Agilent Inova 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.01 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), C_6D_6 (7.16 ppm), $(CD_3)_2SO$ (2.50 ppm), CD_3OD (3.31 ppm) or CD_3CN (1.94 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (number of protons, multiplicity, coupling constants). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on either a Bruker Ultrashield–400 (400 MHz) spectrometer, a Varian 400 MR spectrometer (100 MHz) or an Agilent Inova 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.1 ppm relative to the residual solvent peaks in $CDCl_3$ (77.0 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.

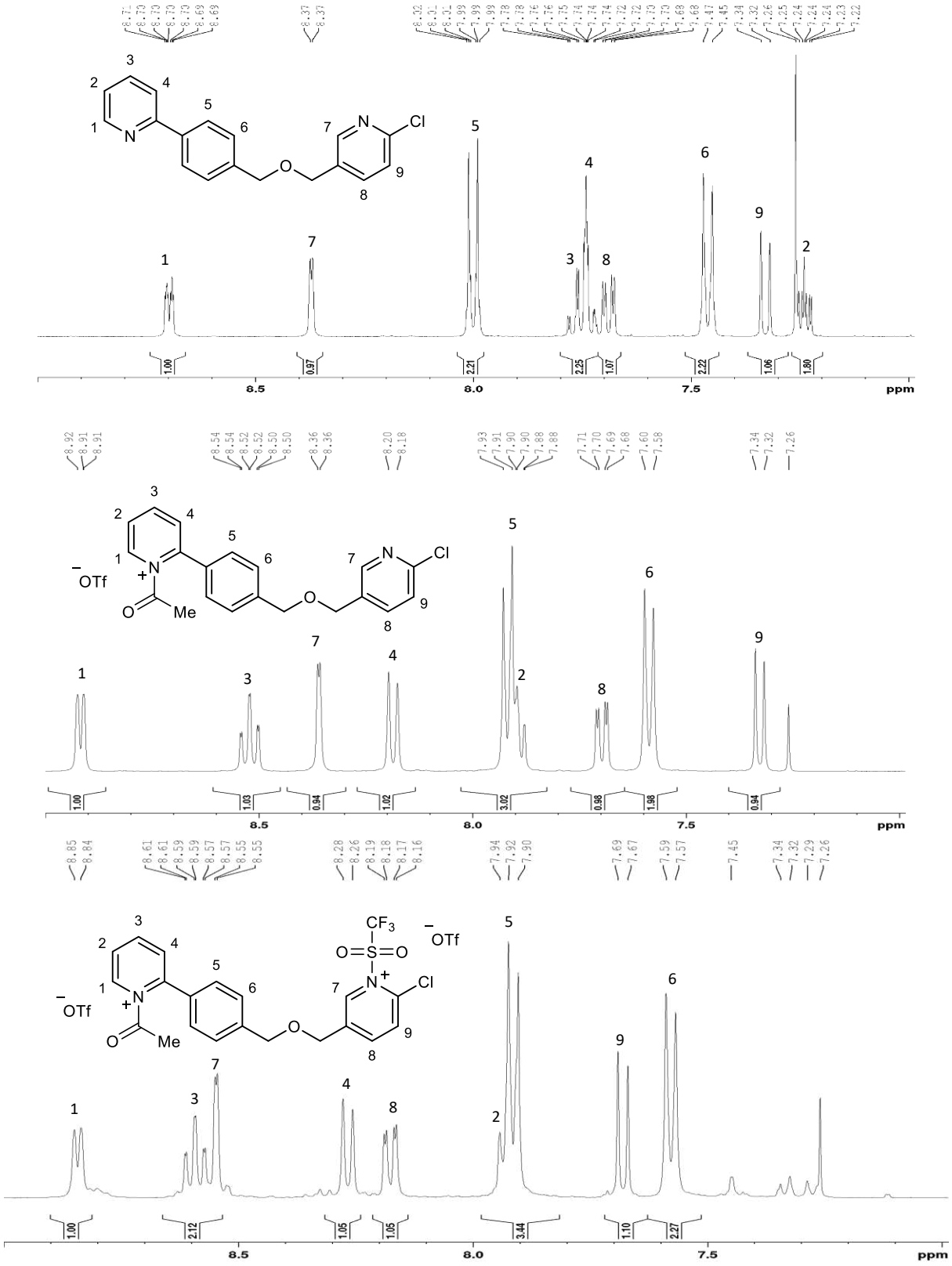
Analytical thin layer chromatography (TLC) was performed using pre–coated Merck glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Fluka or Material Harvest silica gel (230–400 mesh) under a positive pressure of air. Visualization was achieved using ultraviolet 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

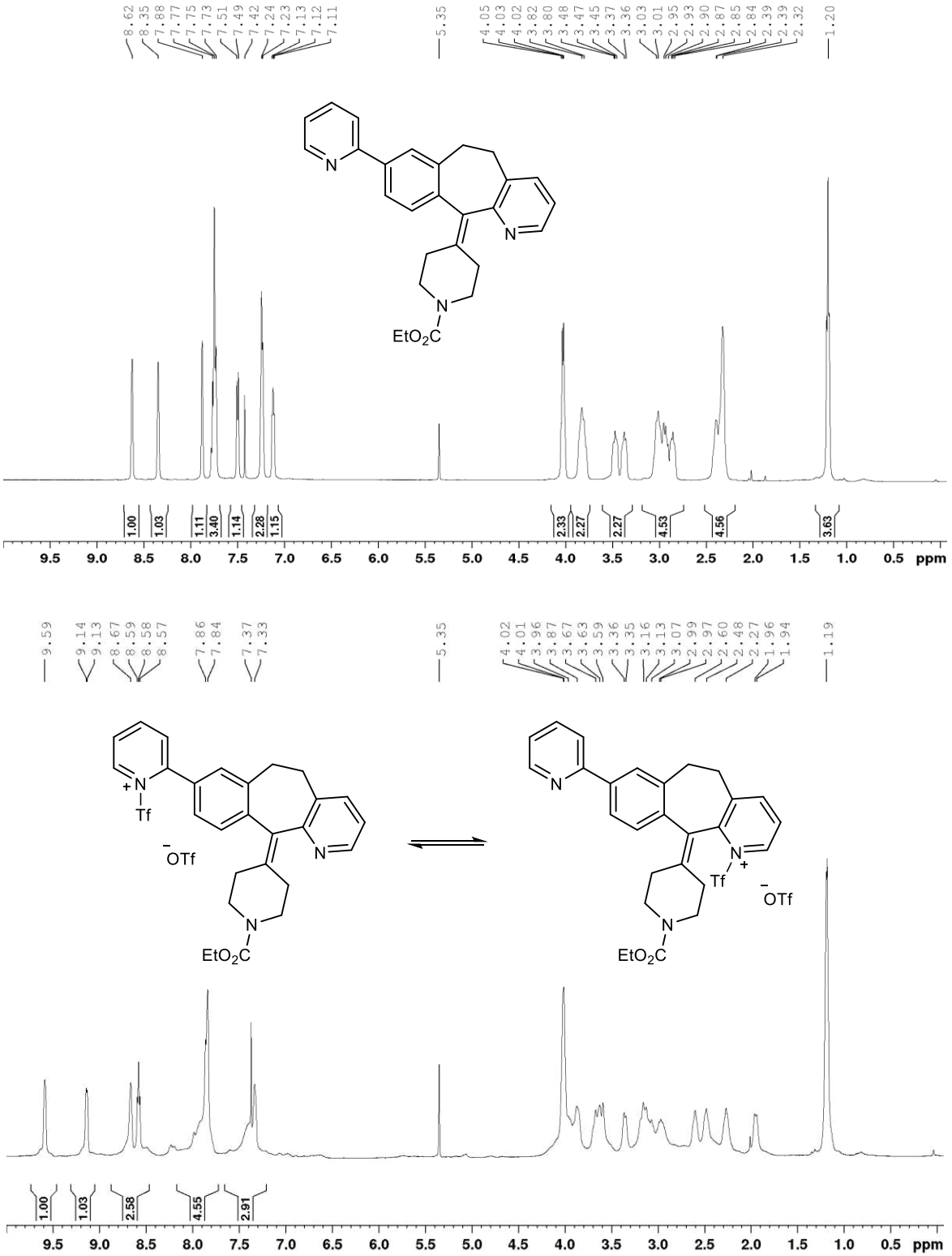
Quadrupole Mass Spectrometer. Melting points (mp) were recorded using a Büchi B–450 melting point apparatus and are reported uncorrected.

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 Acetyl and Triflyl Pyridinium Formation of 12h

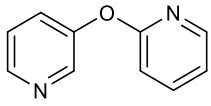


A. 2.3 Rapid Interconversion of 12q Tf salt isomers



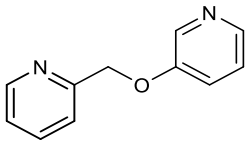
A. 2.4 Preparation of Heterocyclic Phosphonium Salt Precursors

2–(pyridin–3–yloxy)pyridine



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]

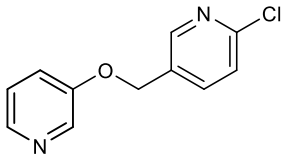
2–((pyridin–3–yloxy)methyl)pyridine



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; ^{1}H 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.

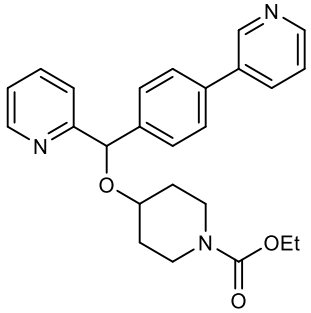
2–chloro–5–((pyridin–3–yloxy)methyl)pyridine



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

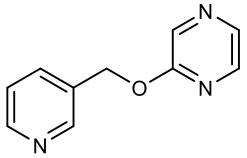
3–hydroxypyridine (1.90 g, 20.00 mmol) in THF (20 mL) was added dropwise over 5 minutes. The reaction mixture was warmed to room temperature and stirred for 1 hour before being cooled to 0 °C. A solution of 2–chloro–5–(chloromethyl)pyridine (3.40 g, 21.00 mmol) in DMF (20 mL) was then added dropwise 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



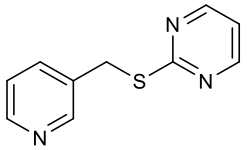
An oven dried 50 mL Schlenk flask was charged with ethyl 4–((4–chlorophenyl)(pyridin–2–yl)methoxy)piperidine–1–carboxylate (1.46 g, 3.50 mmol), 3–pyridylboronic acid (473 mg, 3.85 mmol), $Pd_2(dba)_3$ (64 mg, 0.07 mmol), and tricyclohexylphosphine (47 mg, 0.17 mmol). The flask was subjected to five cycles 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; ^1H 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



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; ^1H 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.

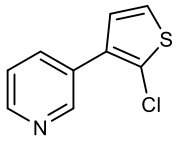
2–((pyridin–3–ylmethyl)thio)pyrimidine



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; ^1H 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.

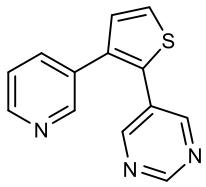
3–(2–chlorothiophen–3–yl)pyridine



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; ^1H 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.

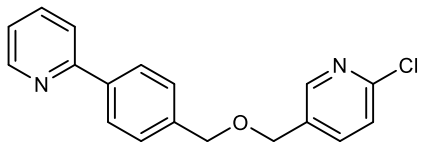
5–(3–(pyridin–3–yl)thiophen–2–yl)pyrimidine



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.

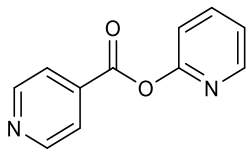
2–chloro–5–(((4–(pyridin–2–yl)benzyl)oxy)methyl)pyridine



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.

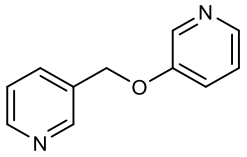
Pyridin–2–yl isonicotinate



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.

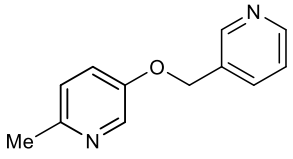
3–(pyridin–3–ylmethoxy)pyridine



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; ^1H 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.

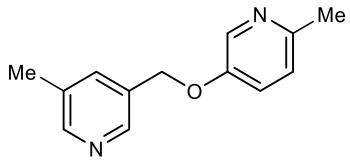
2–methyl–5–(pyridin–3–ylmethoxy)pyridine



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; ^{1}H 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.

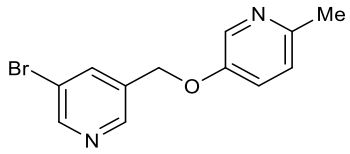
2–methyl–5–((5–methypyridin–3–yl)methoxy)pyridine



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.

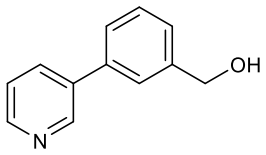
5–((5–bromopyridin–3–ly)methoxy)–2–methylpyridine



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; ^1H 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.

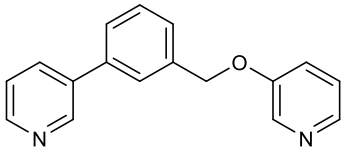
(3–(pyridin–3–yl)phenyl)methanol



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; ^1H 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

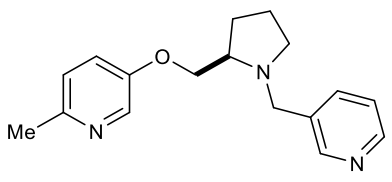


An oven dried 50 mL round bottom flask was charged with 4–dimethylaminopyridine (99 mg, 0.81 mmol) and (3–(pyridin–3–yl)phenyl)methanol (1.50 g, 8.11 mmol) and subjected to three cycles of vacuum/nitrogen backfill, before CH_2Cl_2 (13 mL) was added. The mixture was cooled to 0 °C and 4–toluenesulfonyl 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; ^{1}H 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.

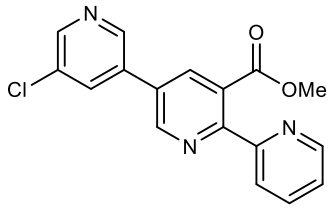
(R)–2–methyl–5–((1–(pyridin–3–ylmethyl)pyrrolidin–2–yl)methoxy)pyridine



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; ^1H 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, $CHCl_3$).

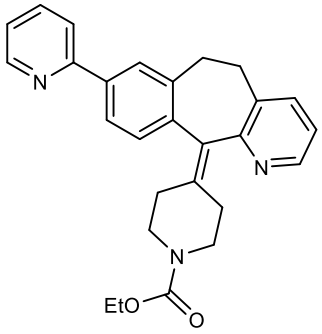
3–(2–chlorothiophen–3–yl)pyridine



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]

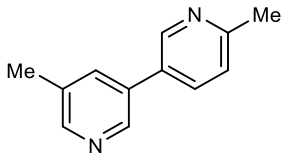
Ethyl 4–(8–(pyridin–2–yl)–5,6–dihydro–11H–benzo[5,6]cyclohepta[1,2–b]pyridin–11–ylidene)piperidine–1–carboxylate



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.

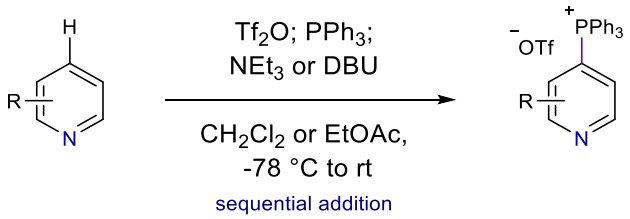
5,6'–dimethyl–3,3'–bipyridine



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.

2.5 Preparation of Heterocyclic Phosphonium Salts

General Procedure A



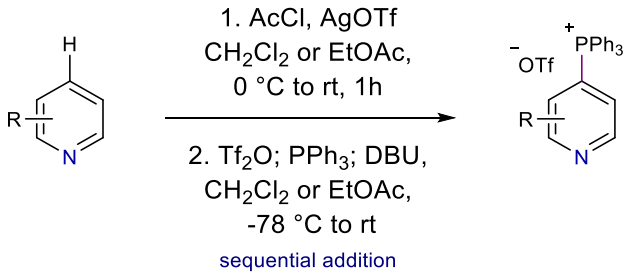
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 ºC and Tf_2O (1.0 equiv)

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 ^{1}H 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

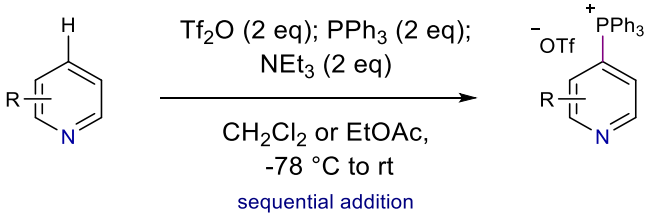
* Uniformed stirring is important for the reaction; the reaction vessel was placed directly on the middle of the stir plate and the mixture stirred at 1400–2000 rpms for the duration of the reaction.

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.
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 ^1H 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

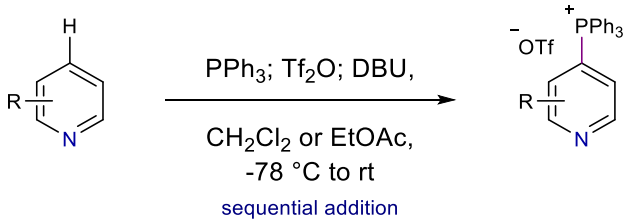
[†] Uniformed stirring is important for the reaction; the reaction vessel was placed directly on the middle of the stir plate and the mixture stirred at 1400–2000 rpms for the duration of the reaction.

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 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.

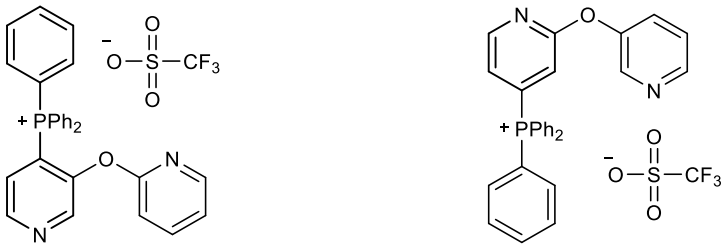
Notes.

1) PPh_3 was crushed into a powder prior to use.

[‡] 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.

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

Triphenyl(3–(pyridin–2–yloxy)pyridin–4–yl)phosphonium trifluoromethanesulfonate (12a)



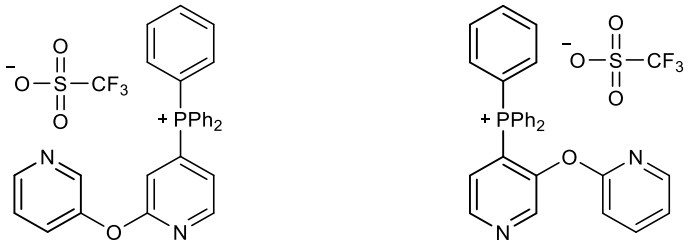
Major Minor

>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 (12a)

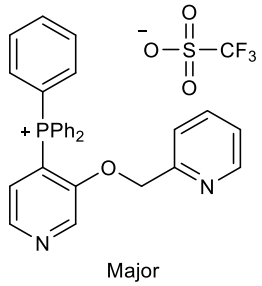


17:1:1:1 (Major:Minor:Undefined phosphonium isomers) Mixture of Isomers

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 (12b)



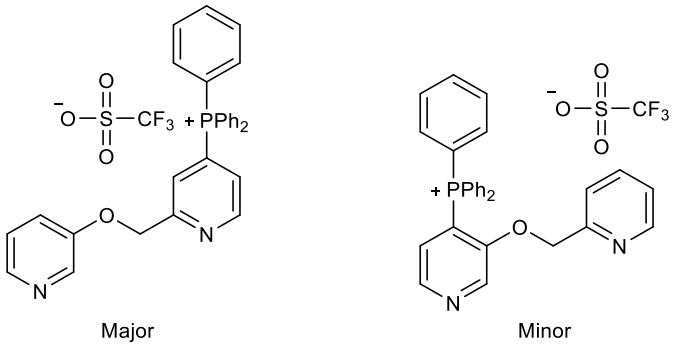
Major

>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, ^{1}H 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 (12b)

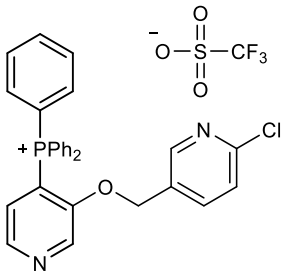


11:1 (Major:Minor) Mixture of Isomers

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, ^{1}H 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 (12c)



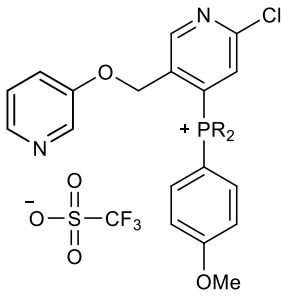
Major

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 (2c)



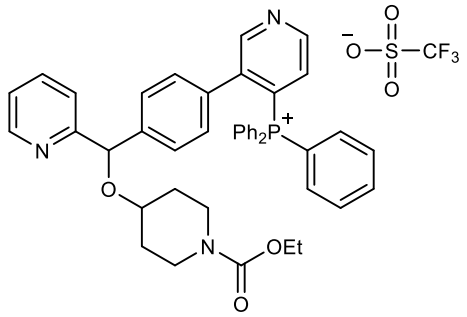
Major

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, ^1H 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 (12d)

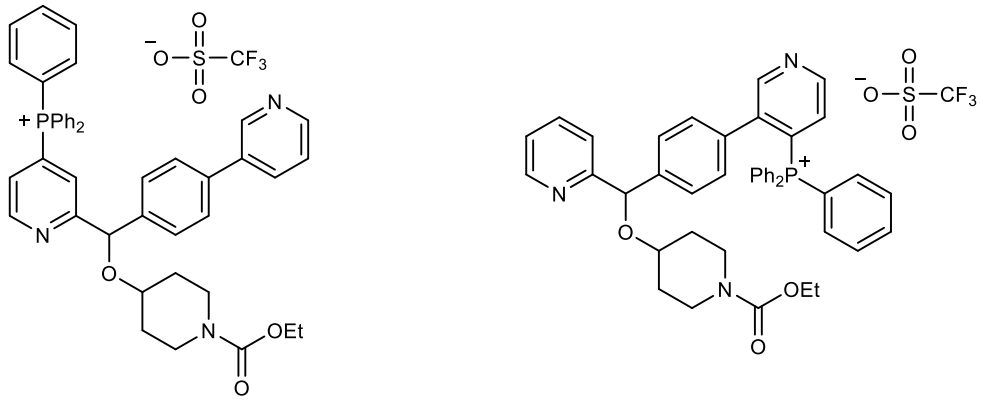


Major

5.9:2.2:1 (Major: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 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 ^1H NMR yield: 73%). Major isomer, ^1H 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 (12d)



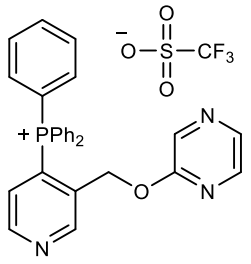
Major Minor

>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, ^1H 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 (12e)

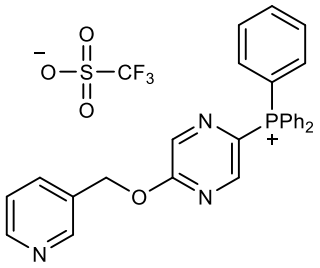


Major

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 (12e)

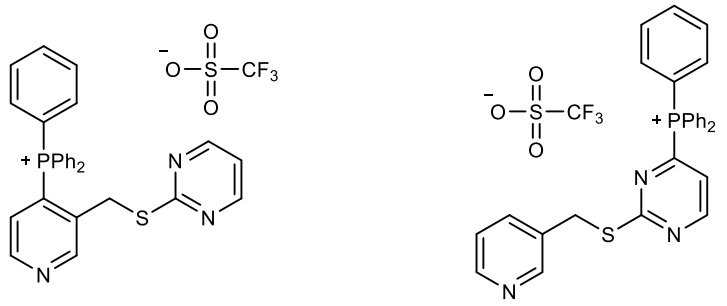


Major

>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 (12f)

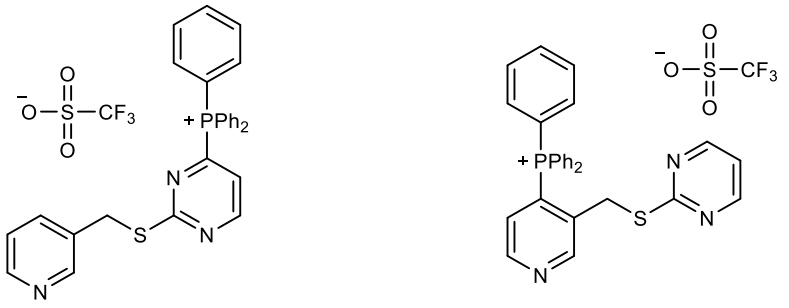


Major Minor

>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, ^{1}H 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 (12f)

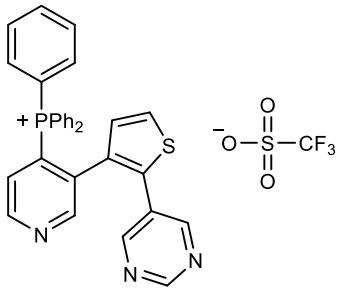


Major Minor

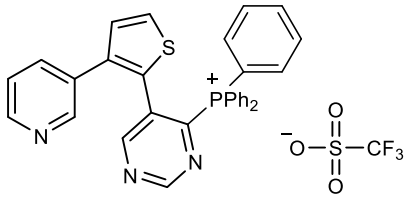
>20:1 (Major:Minor) Mixture of Isomers

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 (12g)



Major

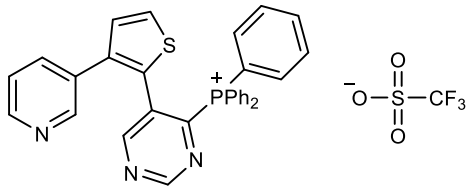


Minor

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 (12g)

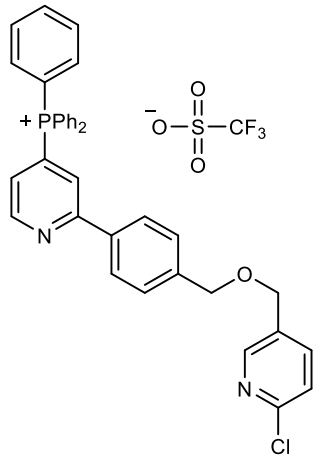


Major

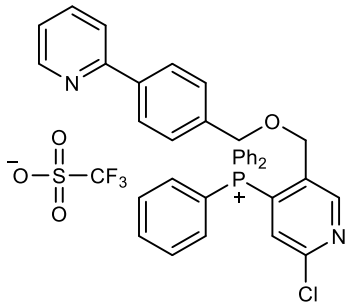
>20:1 (Major:2–position phosphonium isomer) Mixture of Isomers

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 (12h)



Major



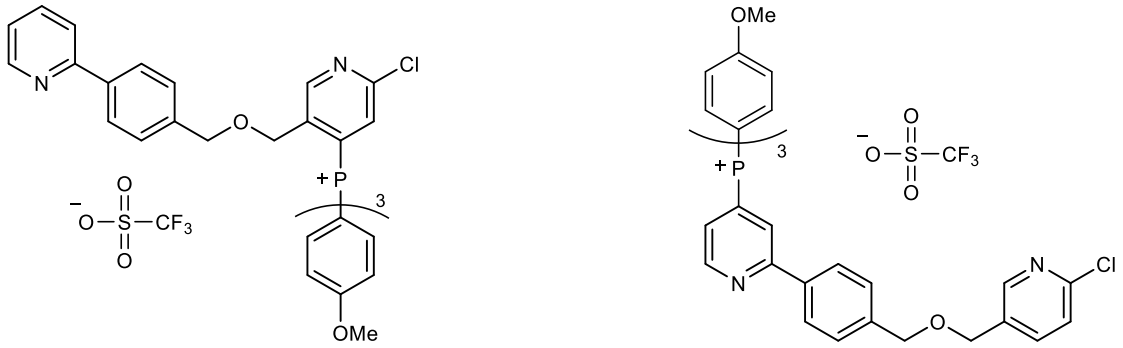
Minor

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, ^1H 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 (12h)

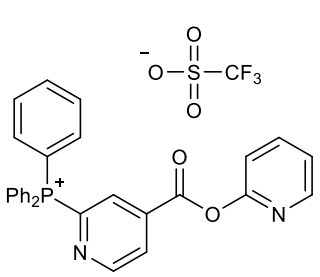


>20:1 (Major:Minor) Mixture of Isomers

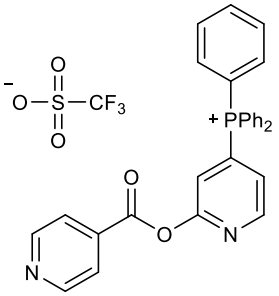
Prepared according to general procedure B (except that the phosphine was added as a solution in CH_2Cl_2 (4.5 mL) dropwise over 30 minutes) using acetyl chloride (43 μL, 0.60 mmol), silver trifluoromethanesulfonate (154 mg, 0.60 mmol), 2–chloro–5–(((4–(pyridin–2–yl)benzyl)oxy)methyl)pyridine (186 mg, 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 (12i)



Major



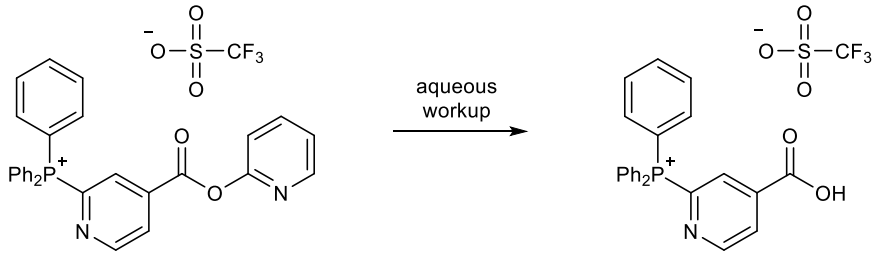
Minor

>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.

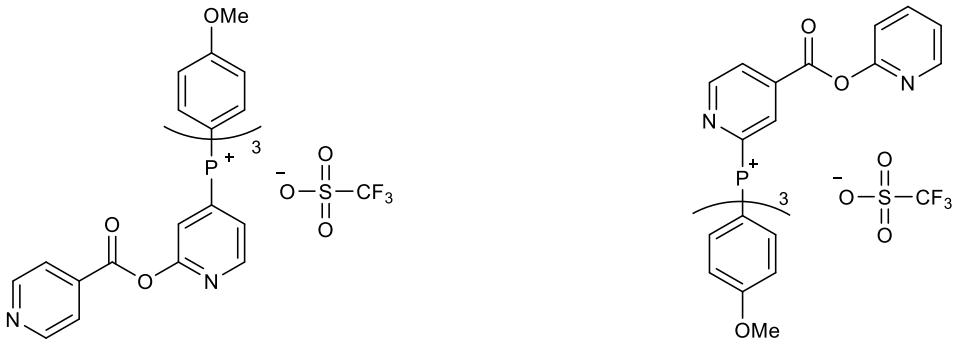
mmol), triphenylphosphine (75 mg, 0.28 mmol), DBU (39 μL, 0.26 mmol), 1,3,5-trimethoxybenzene as an internal standard (44 mg, 0.26 mmol), and CH_2Cl_2 (2.6 mL) to afford the title compound (combined ^{1}H NMR yield: 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.23 (1H, d *J* = 4.8 Hz), 8.50-8.44 (1H, m), 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 (12i)

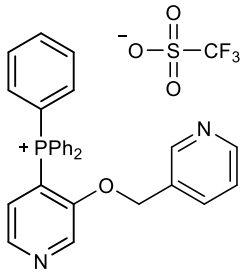


Major Minor

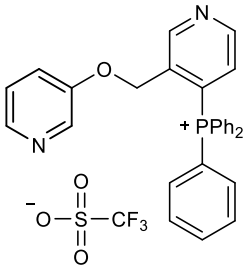
>20:1 (Major:Minor) Mixture of Isomers

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 (12j)



Major

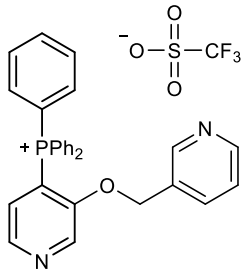


Minor

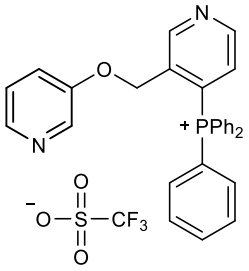
2.9:2.2:2.8 (Major:Minor:mix of 2 phosphonium isomers) Mixture of Isomers

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 (12j)



Major

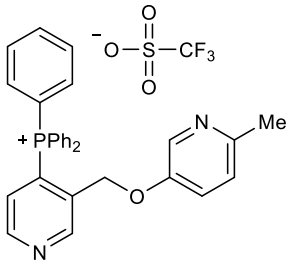


Minor

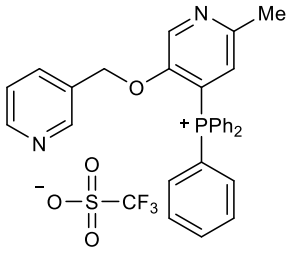
>20:1 (Major:Minor) Mixture of Isomers

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 (12k)



Major

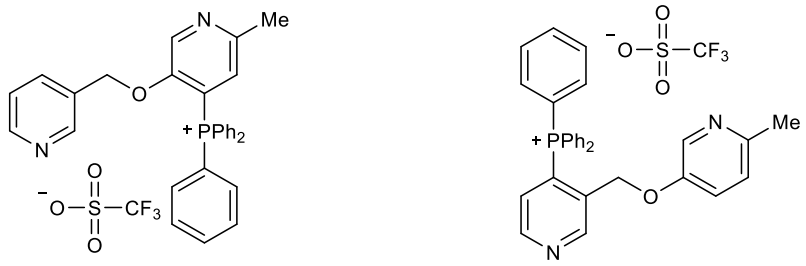


Minor

>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 (12k)

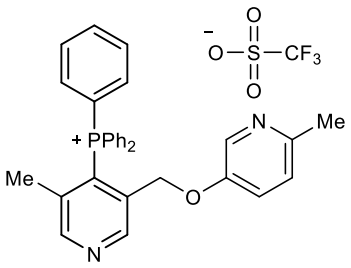


Major Minor

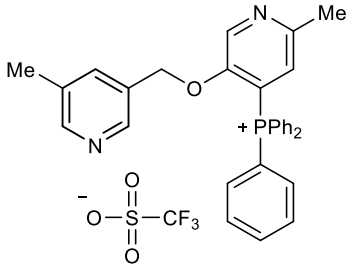
13:1 (Major:Minor) Mixture of Isomers

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 (12l)



Major

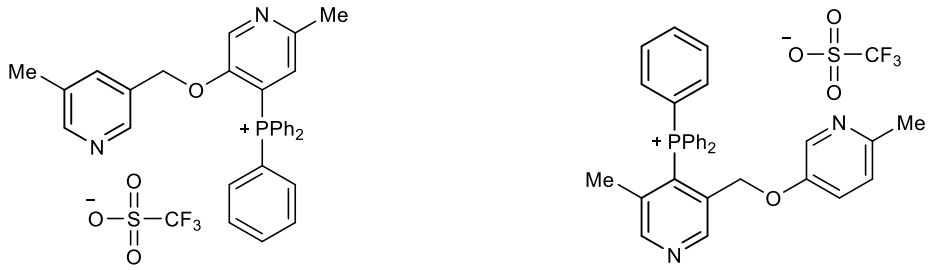


Minor

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.

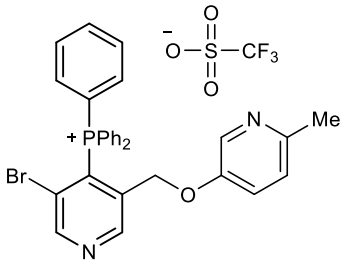
(2–methyl–5–((5–methylpyridin–3–yl)methoxy)pyridin–4–yl)triphenylphosphonium trifluoromethanesulfonate (12l)



>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, ^1H 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 (12m)

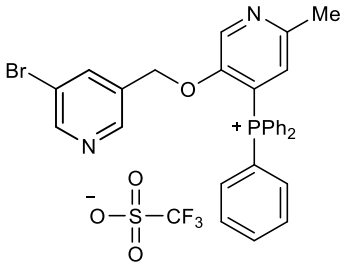


Major

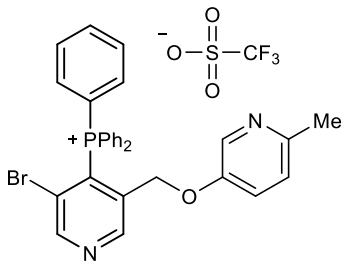
Mixture of Isomers

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 (12m)



Major

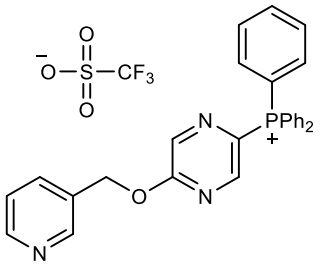


MInor

>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 (12e)

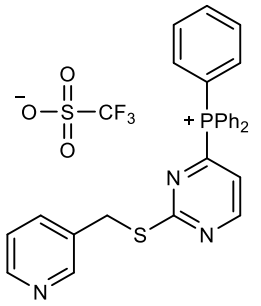


Major

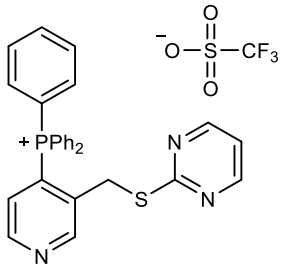
>20:1 (Major:2–position phosphonium isomer) Mixture of Isomers

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 (12f)



Major



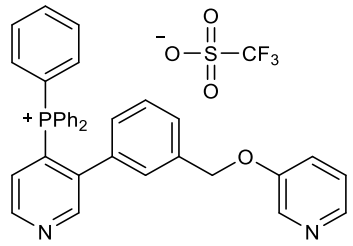
Minor

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

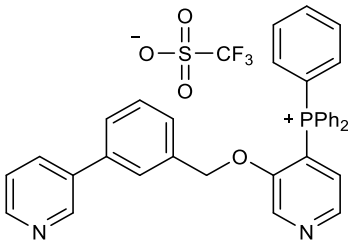
Prepared according to general procedure C using 2–((pyridin–3–ylmethyl)thio)pyrimidine (102 mg, 0.50 mmol), Tf_2O (169 μL, 1.00 mmol), PPh_3 (262 mg, 1.00 mmol), NEt_3 (139 μL, 1.00 mmol) and CH_2Cl_2 (5.0 mL). After the purification procedure, the title compound was isolated as a white solid (210 mg, 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 (1

2n)



Major

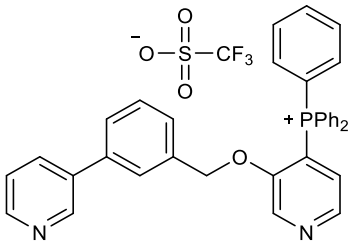


Minor

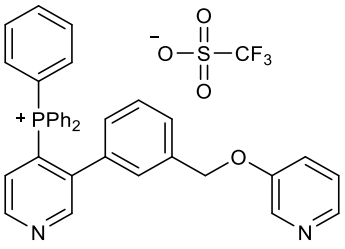
2.2:1 (Major:Minor) Mixture of Isomers

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 (12n)



Major

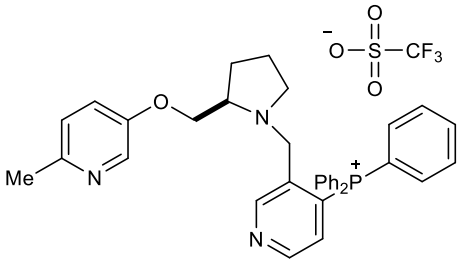


Minor

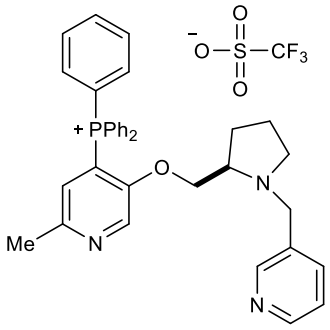
>20:1 (Major:Minor) Mixture of Isomers

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 (12o)



Major



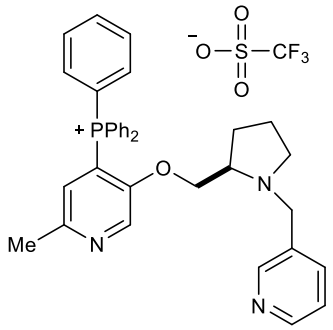
Minor

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

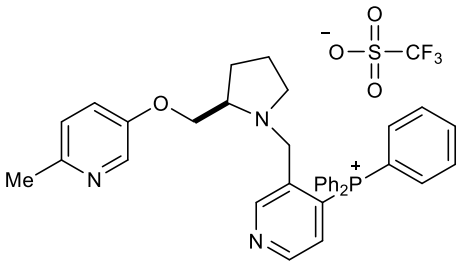
Prepared according to general procedure A using 2–methyl–5–((1–(pyridin–3–ylmethyl)pyrrolidin–2–yl)methoxy)pyridine (150 mg, 0.53 mmol), Tf_2O (89 μL, 0.53 mmol), PPh_3 (153 mg, 0.58 mmol), DBU (80 μL, 0.53 mmol) and CH_2Cl_2 (5.3 mL). After the purification procedure, the title compound was isolated 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 (12o)



Major



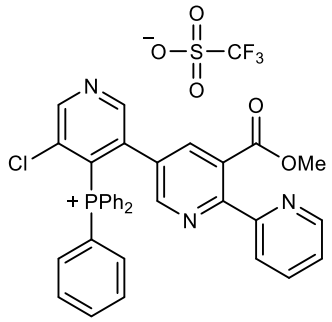
Minor

>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, $CHCl_3$).

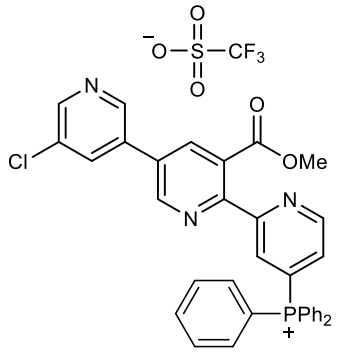
(5''–chloro–3'–(methoxycarbonyl)–[2,2':5',3''–terpyridin]–4''–yl)triphenylphosphonium trifluoromethanesulfonate (12p)



Major

10:3.1:1 (Major:Bis-phosphonium isomer: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 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 ^{1}H NMR yield: 83%). Major isomer ^{1}H 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 (12p)



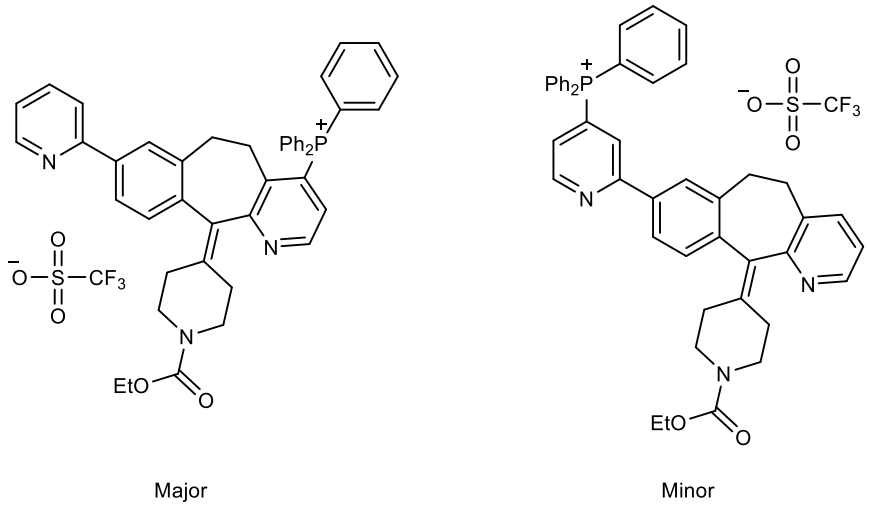
Major

>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, ^{1}H 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 (12q)

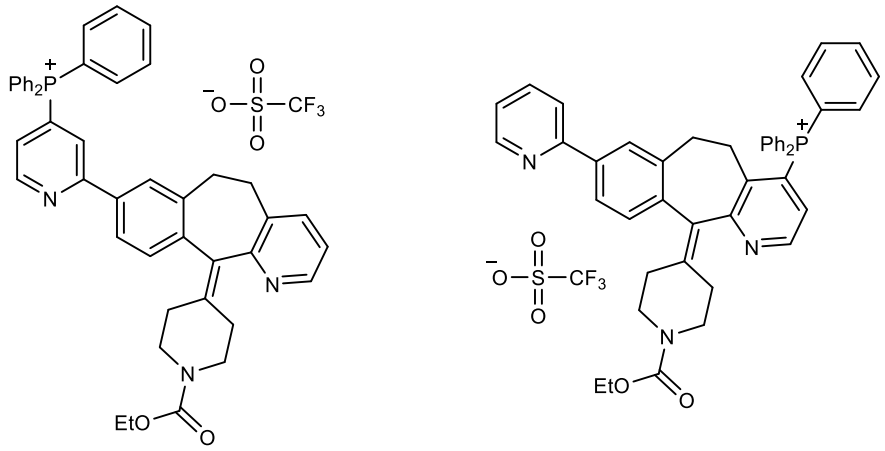


10:3.1:1 (Major:Bis-phosphonium isomer:Minor) Mixture of Isomers

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 (12q)

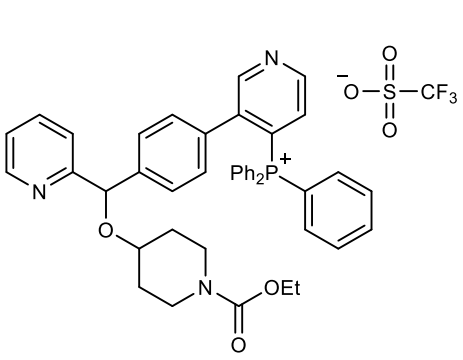


>20:1 (Major:Minor) Mixture of Isomers

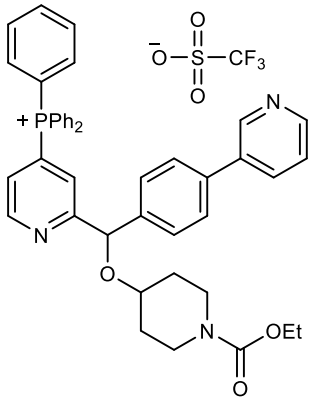
Prepared according to general procedure C using ethyl 4–(8–(pyridin–2–yl)–5,6–dihydro–11H–benzo[5,6]cyclohepta[1,2–b]pyridin–11–ylidene)piperidine–1–carboxylate (213 mg, 0.50 mmol), Tf_2O (169 μL, 1.00 mmol), PPh_3 (262 mg, 1.00 mmol), NEt_3 (139 μL, 1.00 mmol) and CH_2Cl_2 (5.0 mL). After the purification 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 (12d)



Major



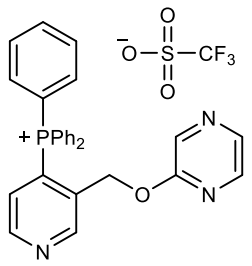
Minor

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

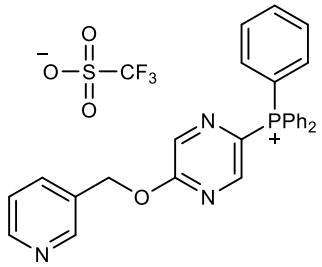
Prepared according to general procedure D (except that Tf_2O was added at –50 ºC and stirred for 1 hour instead of at –78 ºC for 1 hour) using ethyl 4–(pyridin–2–yl(4–(pyridin–3–yl)phenyl)methoxy)piperidine–1–carboxylate (104 mg, 0.25 mmol), Tf_2O (42 μL, 0.25 mmol), PPh_3 (66 mg, 0.25 mmol), DBU (37 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 (12e)



Major

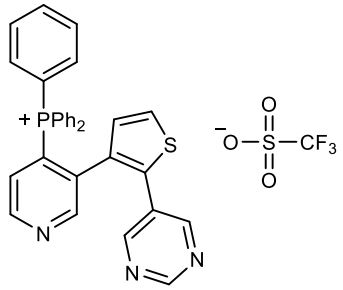


Minor

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 (12g)

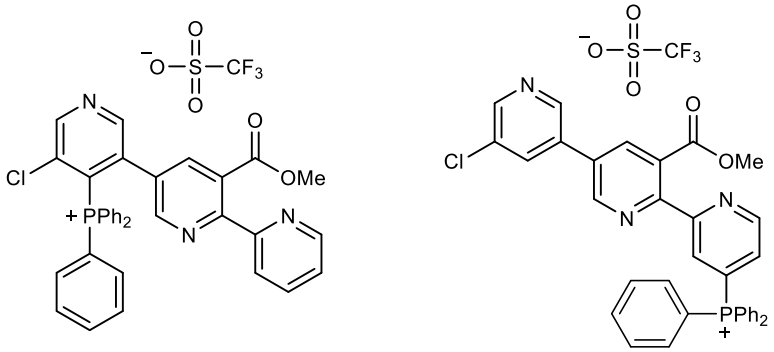


Major

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 (12p)

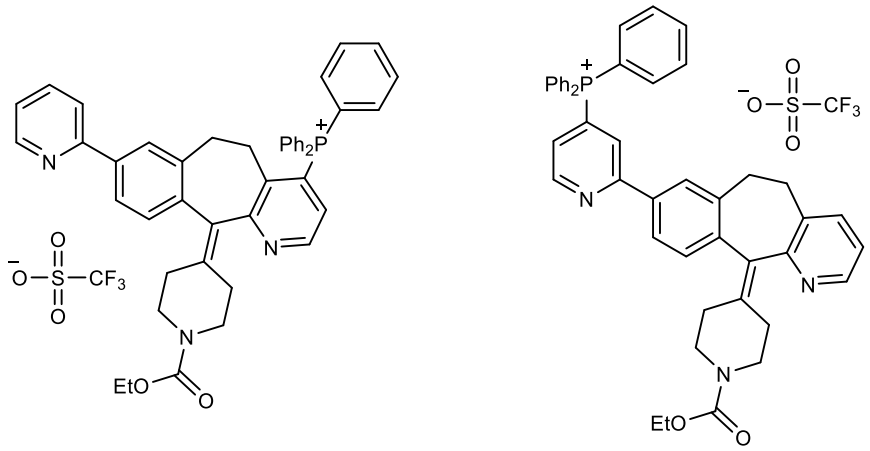


Major Minor

>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 (12q)

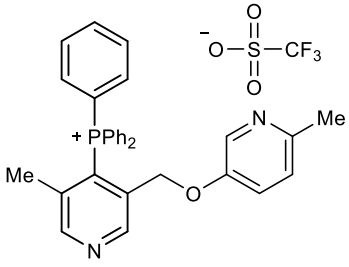


>20:1 (Major:Minor) Mixture of Isomers

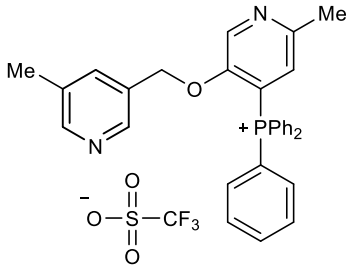
Prepared according to general procedure D using ethyl 4–(8–(pyridin–2–yl)–5,6–dihydro–11H–benzo[5,6]cyclohepta[1,2–b]pyridin–11–ylidene)piperidine–1–carboxylate (86 mg, 0.20 mmol), Tf_2O (34 μL, 0.20 mmol), PPh_3 (59 mg, 0.20 mmol), DBU (30 μL, 0.20 mmol) and CH_2Cl_2 (2.0 mL). After the purification 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 (12l)



Major

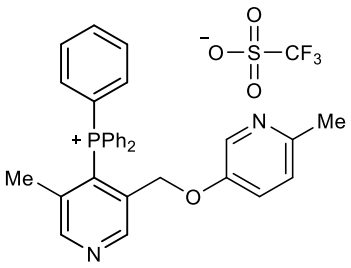


Minor

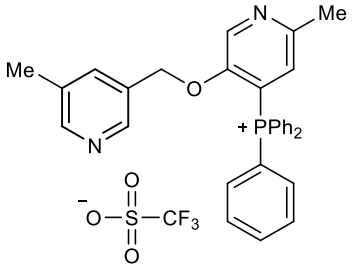
1:1.5:2 (Mixure of 2 phosphonium isomers:Major:Minor) Mixture of Isomers

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 (12l)



Major

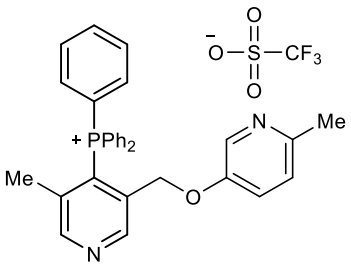


Minor

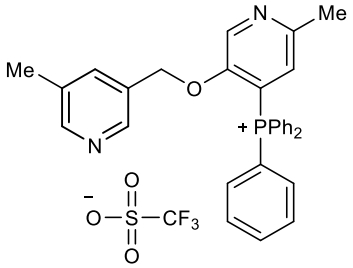
3.3:1:1 (Major:Minor:Mixture of 2 phosphonium isomers) Mixture of Isomers

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 (12l)



Major

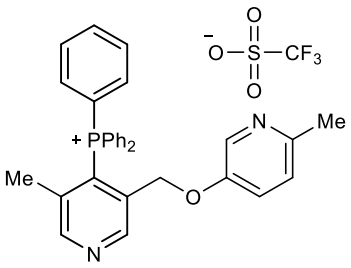


Minor

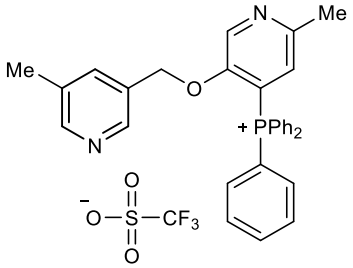
20:1:2.9 (Major:Minor:Mixture of 2 phosphonium isomers) Mixture of Isomers

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 (12l)



Major

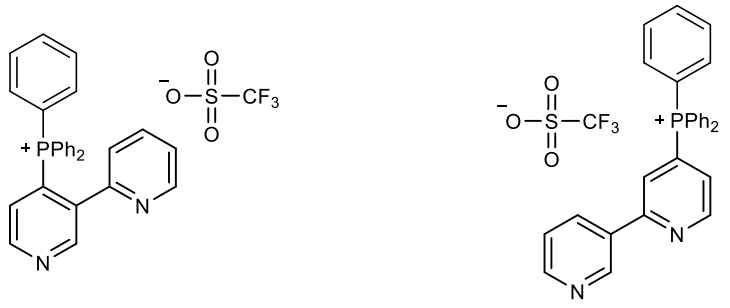


Minor

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.

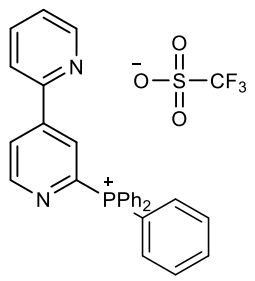
[2,3'–bipyridin]–4'–yltriphenylphosphonium trifluoromethanesulfonate (12r)



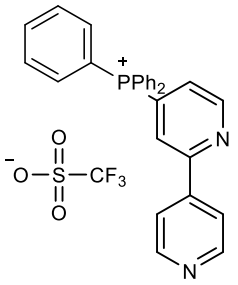
>20:1 (Major:Minor) Mixture of Isomers

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 (12s)



Major

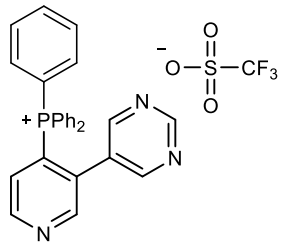


Minor

>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 (12t)

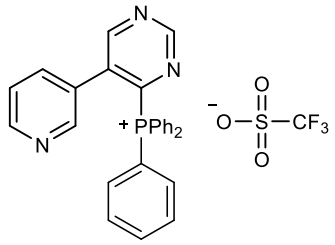


Major

>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 (12t)

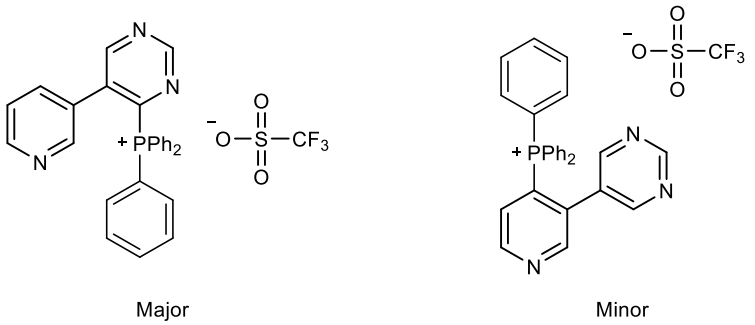


Major

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, ^{1}H 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 (12t)

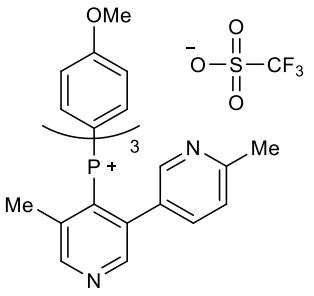


Major Minor

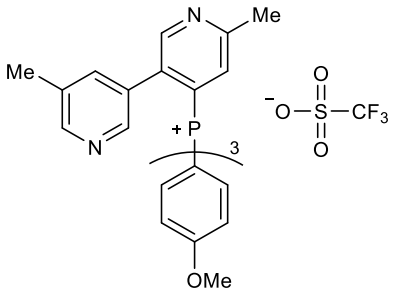
2:1 (Major:Minor) Mixture of Isomers

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 (12u)



Major

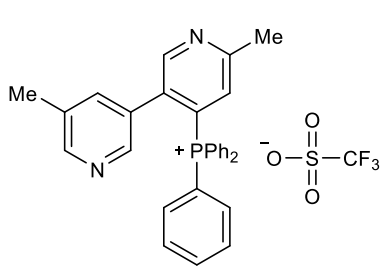


Minor

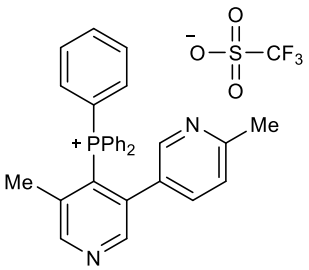
14:1 (Major:Minor) Mixture of Isomers

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 (12u)



Major



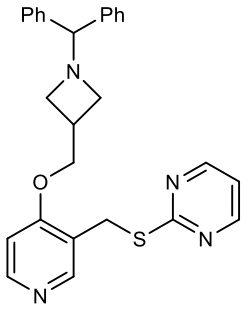
Minor

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 (14)

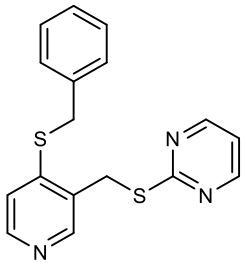


An oven dried 8 mL vial with a stir bar and septa cap was charged with sodium hydride (60% dispersion in mineral oil, 15 mg, 1.5 equiv) and placed under a nitrogen atmosphere. THF (250 μL) was added, the suspension was cooled to 0 ºC and a solution of (1–benzhydrylazetidin–3–yl)methanol (95 mg, 0.38 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 (15)

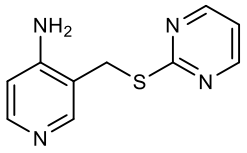


An oven dried 8 mL vial with a stir bar and septa cap was charged with sodium hydride (60% dispersion in mineral oil, 15 mg, 1.5 equiv) and placed under a nitrogen atmosphere. THF (1.0 mL) was added, the suspension was cooled to 0 ºC and benzyl mercaptan (32 μL, 0.38 mmol) was added dropwise over 5 minutes. 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.

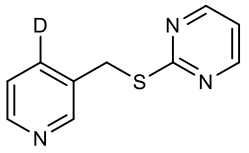
3–((pyrimidin–2–ylthio)methyl)pyridin–4–amine (16)



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.

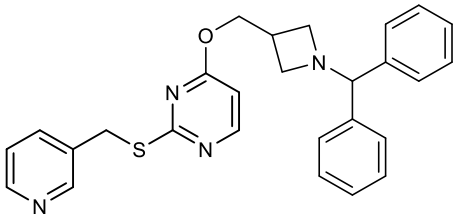
2–(((pyridin–3–yl–4–d)methyl)thio)pyrimidine (17)



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 (18)

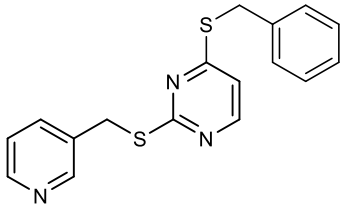


An oven dried 8 mL vial with a stir bar and septa cap was charged with sodium hydride (60% dispersion in mineral oil, 1.5 equiv) and placed under a nitrogen atmosphere. THF (250 μL) was added, the suspension was cooled to 0 ºC and a solution of (1–benzhydrylazetidin–3–yl)methanol (95 mg, 0.38 mmol) in 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 (1)

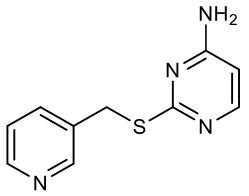


An oven dried 8 mL vial with a stir bar and septa cap was charged with sodium hydride (60% dispersion in mineral oil, 1.1 eq) and placed under a nitrogen atmosphere. THF (1.0 mL) was added, the suspension was cooled to 0 ºC and benzyl mercaptan (32 μL, 0.28 mmol) was added dropwise over 5 minutes. The 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.

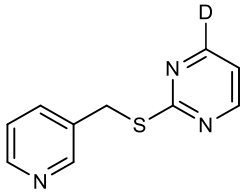
4–((1–benzhydrylazetidin–3–yl)methoxy)–2–((pyridin–3–ylmethyl)thio)pyrimidine (20)



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.

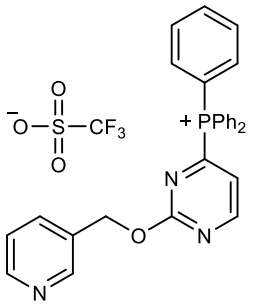
2–((pyridin–3–ylmethyl)thio)pyrimidine–4–d (21)



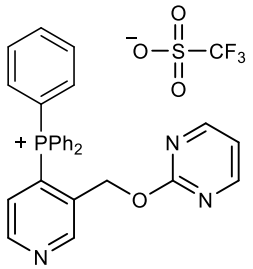
An oven dried 8 mL vial was charged with K_2CO_3 (52 mg, 0.38 mmol) and triphenyl(2–((pyridin–3–ylmethyl)thio)pyrimidin–4–yl)phosphonium trifluoromethanesulfonate (153 mg, 0.25 mmol) and subjected to three rapid vacuum/nitrogen backfills. CD_3OD:D_2O 9:1 (750 μL) was added at room temperature and the 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.

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



Major

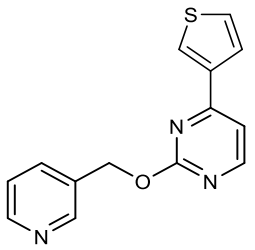


Minor

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

Prepared according to general procedure C using 2–(pyridin–3–ylmethoxy)pyrimidine (190 mg, 1.01 mmol), Tf_2O (342 μL, 2.02 mmol), PPh_3 (531 mg, 2.02 mmol), Et_3N (282 μL, 2.02 mmol) and CH_2Cl_2 (10.1 mL). After the purification procedure, the title compound was isolated as a red amorphous solid (388 mg, 0.65 mmol, 64% yield); IR ν_{max}/cm^{-1} (film): 3063, 1559, 1545, 1437, 1420, 1356, 1259, 1149, 1029, 726, 634; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.05 (1H, dd, *J* = 7.8, 5.0 Hz), 8.60–8.59 (2H, m), 7.91–7.67 (17H, m), 7.31 (1H, dd, *J* = 7.8, 4.7 Hz), 5.45 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.7 (d, *J* = 19.5 Hz), 163.5 (d, *J* = 8.5 Hz), 156.5, 155.4, 149.2, 136.2, 136.1 (d, *J* = 3.0 Hz), 134.7 (d, *J* = 10.4 Hz), 130.7 (d, *J* = 13.1 Hz), 123.6, 122.0 (d, *J* = 20.5 Hz), 120.7 (q, *J* = 321.1 Hz), 115.1 (d, *J* = 89.1 Hz), 67.8; ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.21; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 16.31; *m/z* LRMS (ESI + APCI) found $[M – OTf]^+$ 448.2, $C_{28}H_{23}N_3OP^+$ requires 448.2.

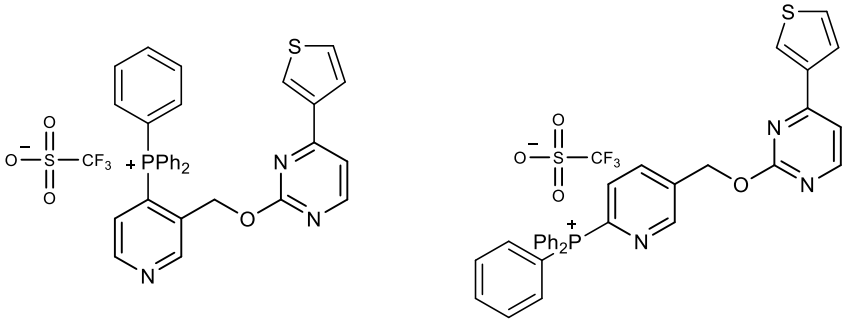
2–(pyridin–3–ylmethoxy)–4–(thiophen–3–yl)pyrimidine (23)



An oven dried 8 mL vial was charged with triphenyl(2–((pyridin–3–ylmethyl)thio)pyrimidin–4–yl)phosphonium trifluoromethanesulfonate (152.0 mg, 0.25 mmol) and 3–thienylboronic acid (65.1 mg, 0.508 mmol) and added to a glovebox. Bis(1,5–cyclooctadiene)nickel(0) (7.0 mg, 0.025 mmol), SiPRHCl (11.0 mg, 0.025 mmol), sodium tertbutoxide (2.5 mg, 0.025 mmol), potassium phosphate tribasic (107.8 mg, 0.508 mmol) and 4A molecular sieves (170.5 mg) were added to the vial and sealed. The sealed vial was taken out of the glove box and THF (2.5 mL) was added. The solution stirred at room temperature for 20 min before being heated to 70°C for 24 hours. The solution was cooled to room temperature and quench with water. The organic layer was separated from the aqueous and the aqueous was extracted three times with CH_2Cl_2. The organic layers were combined, washed with brine once, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 100% EtOAc) followed by flash chromatography (silica gel: 90% EtOAc in Hexanes with 1% AcOH) to provide title compound as a yellow oil (33.6 mg, 0.12 mmol, 50% yield); IR ν_{max}/cm^{-1} (film): 3090, 2954, 2923, 1574, 1448, 1429, 1409, 1347, 1314, 1262, 1021, 786, 711; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.78 (1H, s), 8.57 (1H, d, *J* = 4.8 Hz), 8.51 (1H, d, *J* = 5.2 Hz), 8.13 (1H, dd, *J* = 2.3, 1.2 Hz), 7.89 (1H, d, *J* = 7.8 Hz), 7.67 (1H, dd, *J* = 5.1, 1.1 Hz), 7.41–7.40 (1H, m), 7.32 (1H, dd, *J* = 7.8, 4.9 Hz), 7.22–7.21

(1H, m), 5.52 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.9, 162.1, 159.8, 149.7, 149.4, 139.5, 136.0, 132.3, 127.4, 126.9, 126.0, 123.4, 111.0, 66.4; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 270.1, $C_{14}H_{12}N_3OS$ requires 270.1.

triphenyl(3–(((4–(thiophen–3–yl)pyrimidin–2–yl)oxy)methyl)pyridin–4–yl)phosphonium trifluoromethanesulfonate

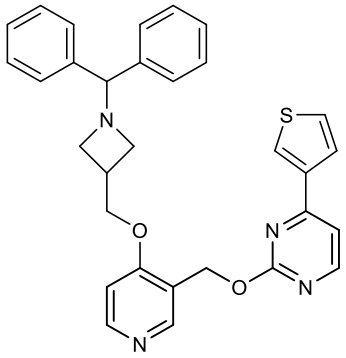


20:1 (Major:Minor) Mixture of Isomers

Prepared according to general procedure D (except that the reaction was stirred at –50 °C) using 2–(pyridine–3–ylmethoxy)–4–(thiophen–3–yl)pyrimidine (195.7 mg, 0.73 mmol), Tf_2O (123 μL, 0.73 mmol), PPh_3 (209.6 mg, 0.80 mmol), DBU (109 μL, 0.73 mmol) and CH_2Cl_2 (7.3 mL). After the purification procedure, the title compound was isolated as white solid (445 mg, 0.66 mmol, 90% yield); IR ν_{max}/cm^{-1} (film): 3090, 3061, 1576, 1558, 1438, 1417, 1260, 1222, 1149, 1105, 1029, 721, 636; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.14 (1H, app d, *J* = 6.6 Hz), 8.91 (1H, app t, *J* = 4.6 Hz), 8.23 (1H, d, *J* = 5.2 Hz), 7.86 (1H, d, *J* = 1.5 Hz), 7.81–7.64 (15H, m), 7.40–7.35 (2H, m), 7.28 (1H, dd, *J* = 15.5, 5.0 Hz), 7.19 (1H, d, *J* = 5.2 Hz), 5.02 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.0, 161.6, 159.4, 152.9 (d, *J* = 7.7 Hz), 151.6 (d, *J* = 10.5 Hz), 138.7, 135.7 (d, *J* = 3.0 Hz), 134.7 (d, *J* = 5.6 Hz), 134.2 (d, *J* = 10.5 Hz), 130.6 (d, *J* = 13.1 Hz), 128.7 (d, *J* = 9.3 Hz), 127.6, 126.9, 126.5 (d, *J* = 81.4 Hz), 125.7, 120.7 (q, *J* = 321.2 Hz), 116.1 (d, *J* = 89.2 Hz),

111.6, 64.6 (d, J = 4.2 Hz); ^{19}F NMR (365 MHz, $CDCl_3$) δ: –78.04; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.73; *m/z* LRMS (ESI + APCI) found $[M - OTf]^+$ 530.2, $C_{27}H_{25}NP^+$ requires 530.1.

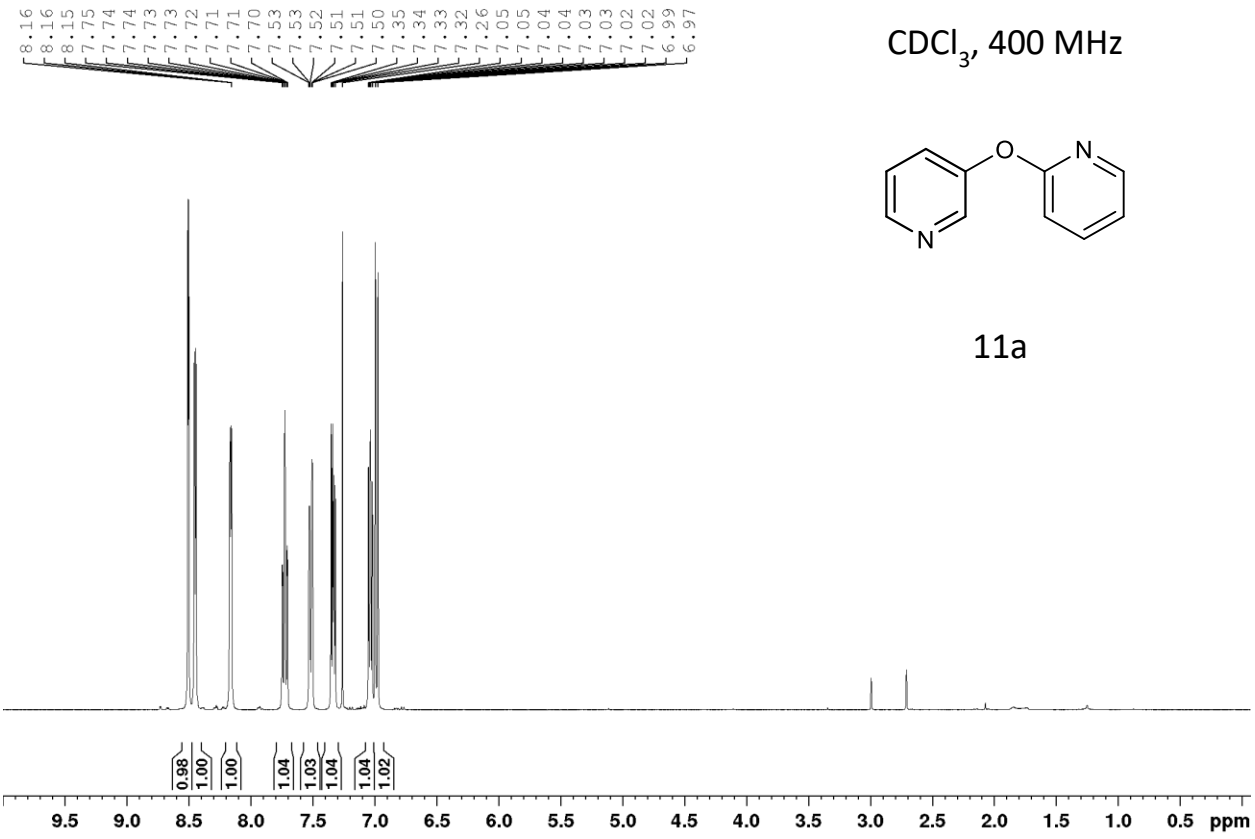
2–((4–((1–benzhydrylazetidin–3–yl)methoxy)pyridin–3–yl)methoxy)–4–(thiophen–3–yl)pyrimidine (24)



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 eq.) and placed under a nitrogen atmosphere. THF (375 μL) was added, the suspension was cooled to 0 ºC and a solution of (1–benzhydrylazetidin–3–yl)methanol (57 mg, 0.255 mmol) in THF (375 μL) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before the septa cap was briefly removed and triphenyl(3–(((4–(thiophen–3–yl)pyrimidin–2–yl)oxy)methyl)pyridin–4–yl)phosphonium trifluoromethanesulfonate (102 mg, 0.15 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 at 40ºC. The reaction was quenched with H_2O (2.0 mL), the aqueous layer was separated and extracted with Et_2O (10 mL x 3). 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 (silica gel: 90% EtOAc in Hexanes) to provide the title

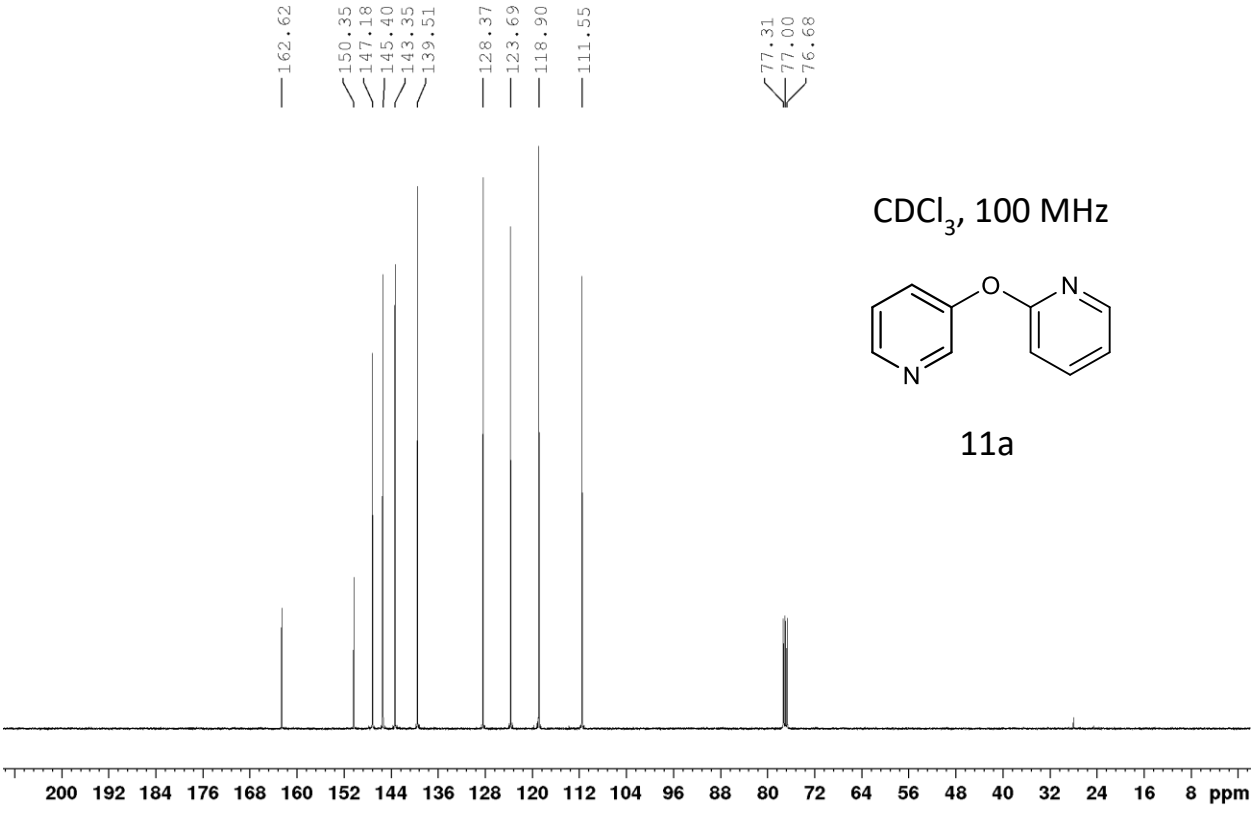
[***] Vacuum was applied very briefly (less than a second) using a Schlenk manifold so that negligible solvent loss occurs.

compound as a white solid (39 mg, 0.08 mmol, 50% yield); IR ν_{max}/cm^{-1} (film): 3027, 2952, 2839, 1594, 1576, 1412, 1341, 1269, 906, 727, 704; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.61 (1H, s), 8.47–8.46 (2H, m), 8.12 (1H, dd, *J* = 2.9, 1.2 Hz), 7.67 (1H, dd, *J* = 5.1, 1.2 Hz), 7.39–7.32 (5 H, m), 7.23–7.12 (7H, m), 6.81 (1H, d, *J* = 5.7 Hz), 5.55 (2H, s), 4.28 (1H, s), 4.18 (2H, d, *J* = 6.0 Hz), 3.26 (2H, t, *J* = 7.8 Hz), 3.05 (2H, t, *J* = 7.8 Hz), 2.88 (1H, m);^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.2, 163.2, 162.0, 159.6, 151.6, 151.1, 141.9, 139.6, 128.3, 127.4, 127.3, 127.0, 126.7, 126.0, 120.8, 110.8, 106.6, 77.9, 69.3, 62.4, 55.5, 29.0; *m/z* LRMS (ESI + APCI) found $[M + H]^+$ 521.3, $C_{31}H_{29}N_4O_2S^+$ requires 520.2.



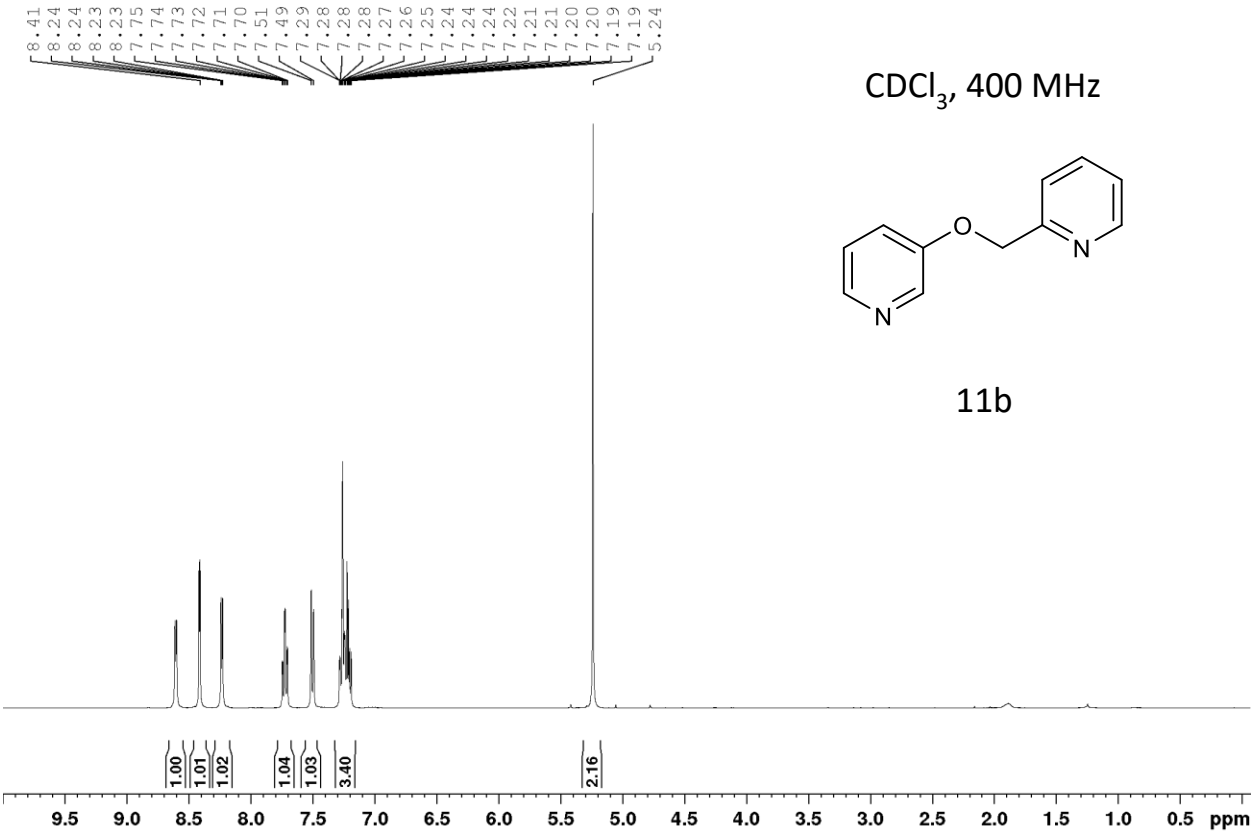
$CDCl_3$, 400 MHz

11a



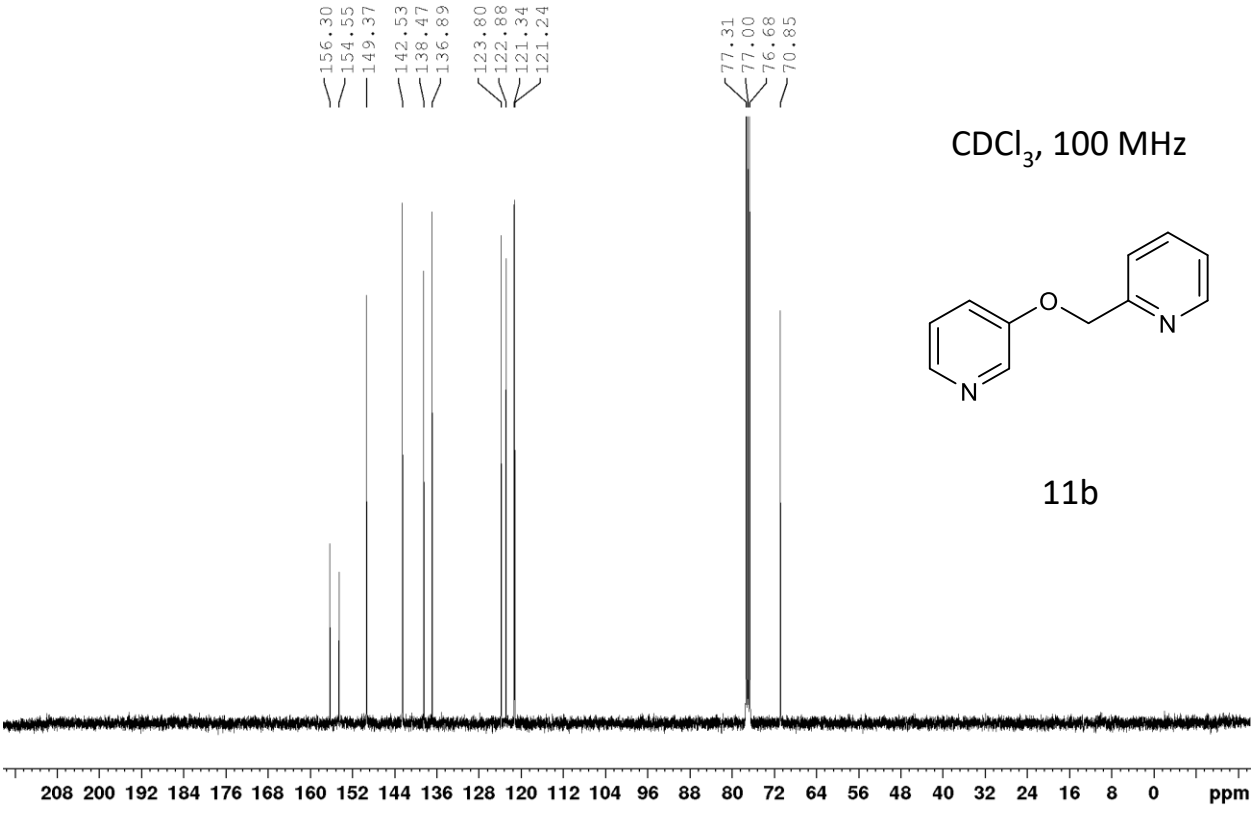
$CDCl_3$, 100 MHz

11a



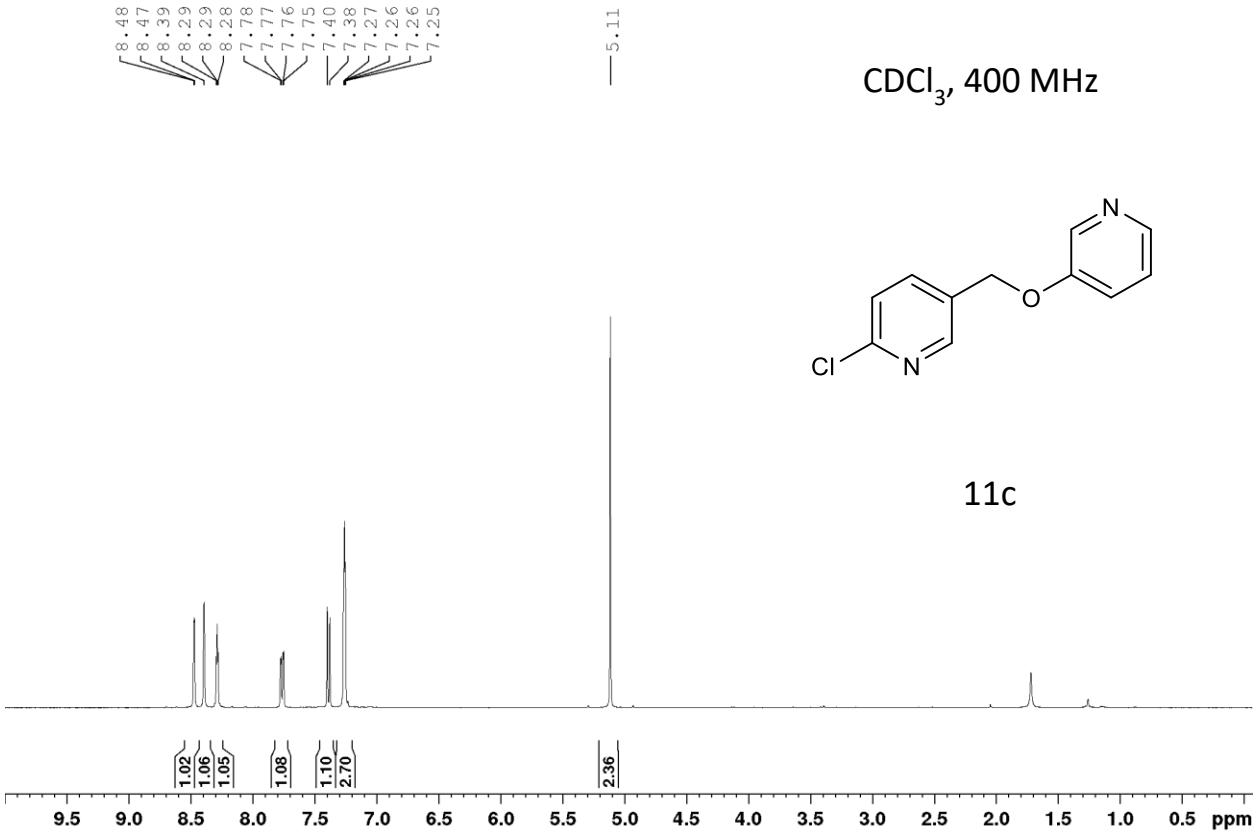
$CDCl_3$, 400 MHz

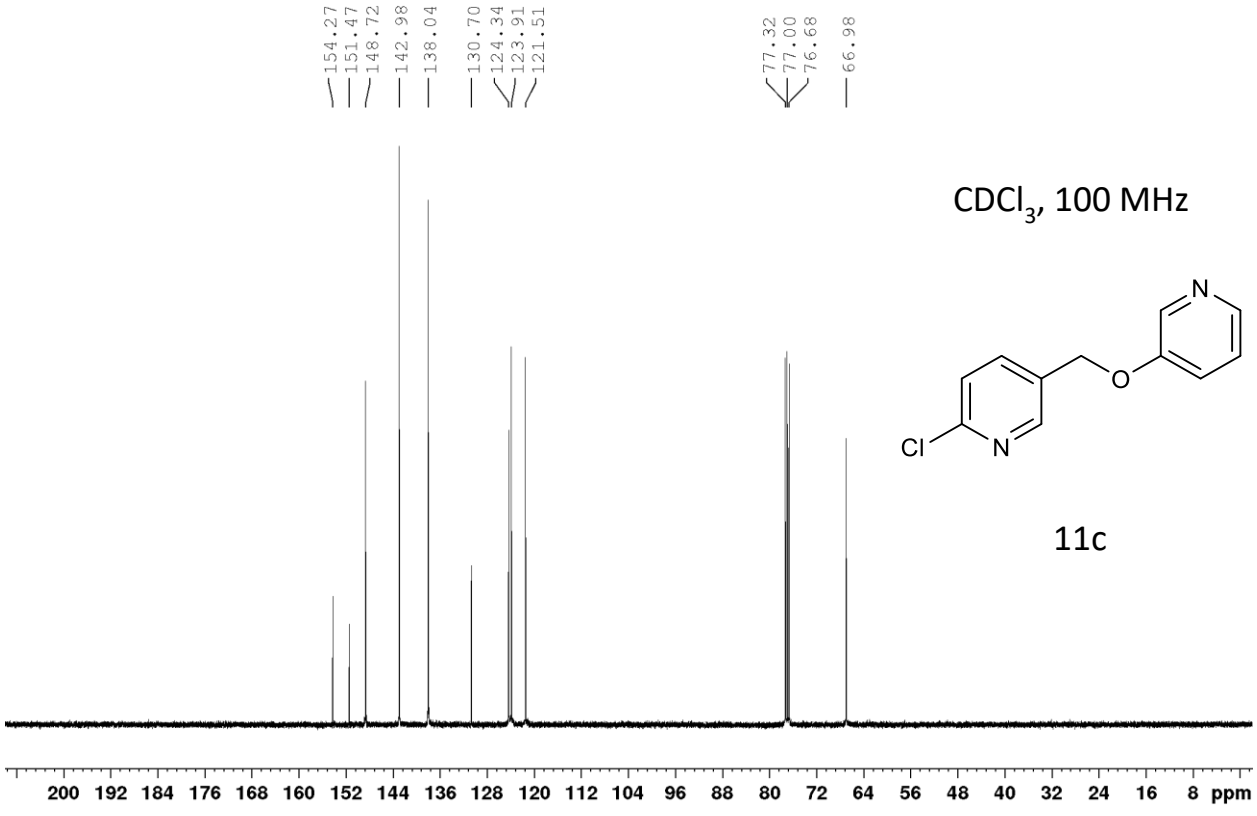
11b

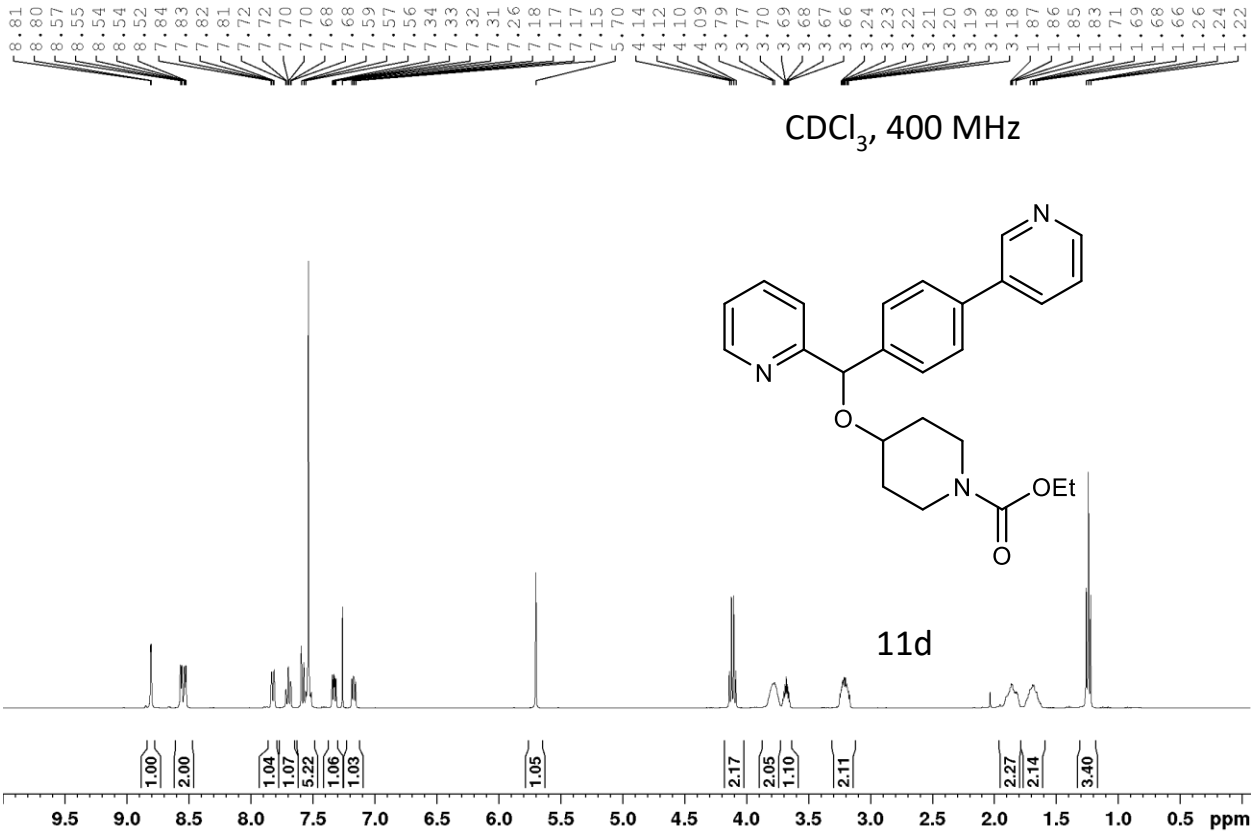


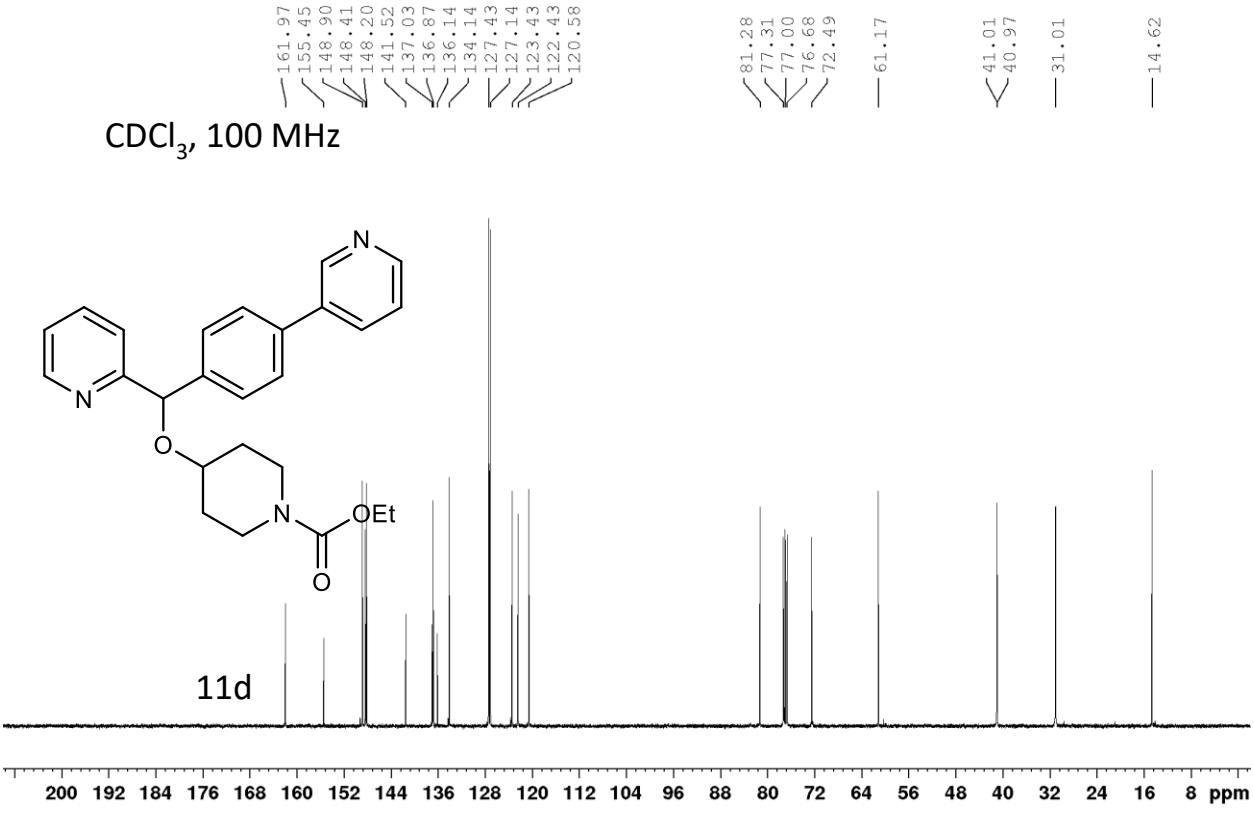
$CDCl_3$, 100 MHz

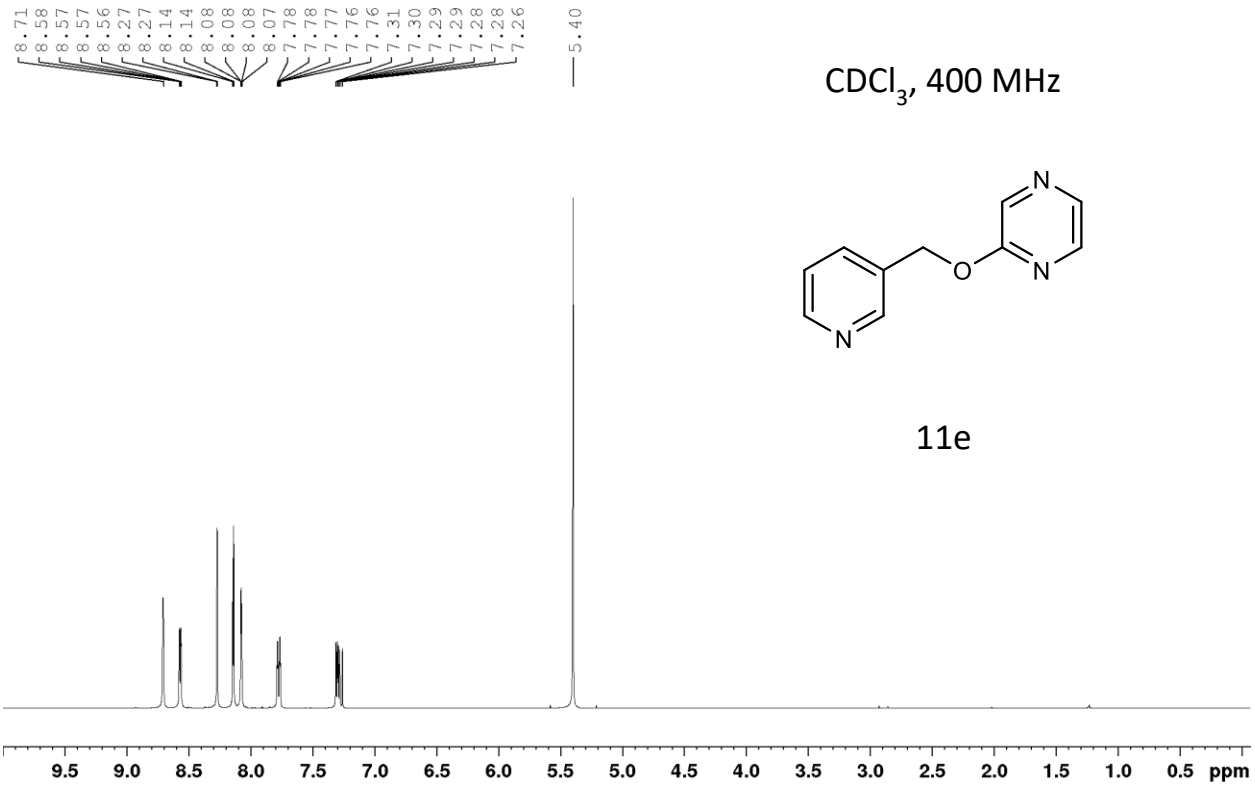
11b

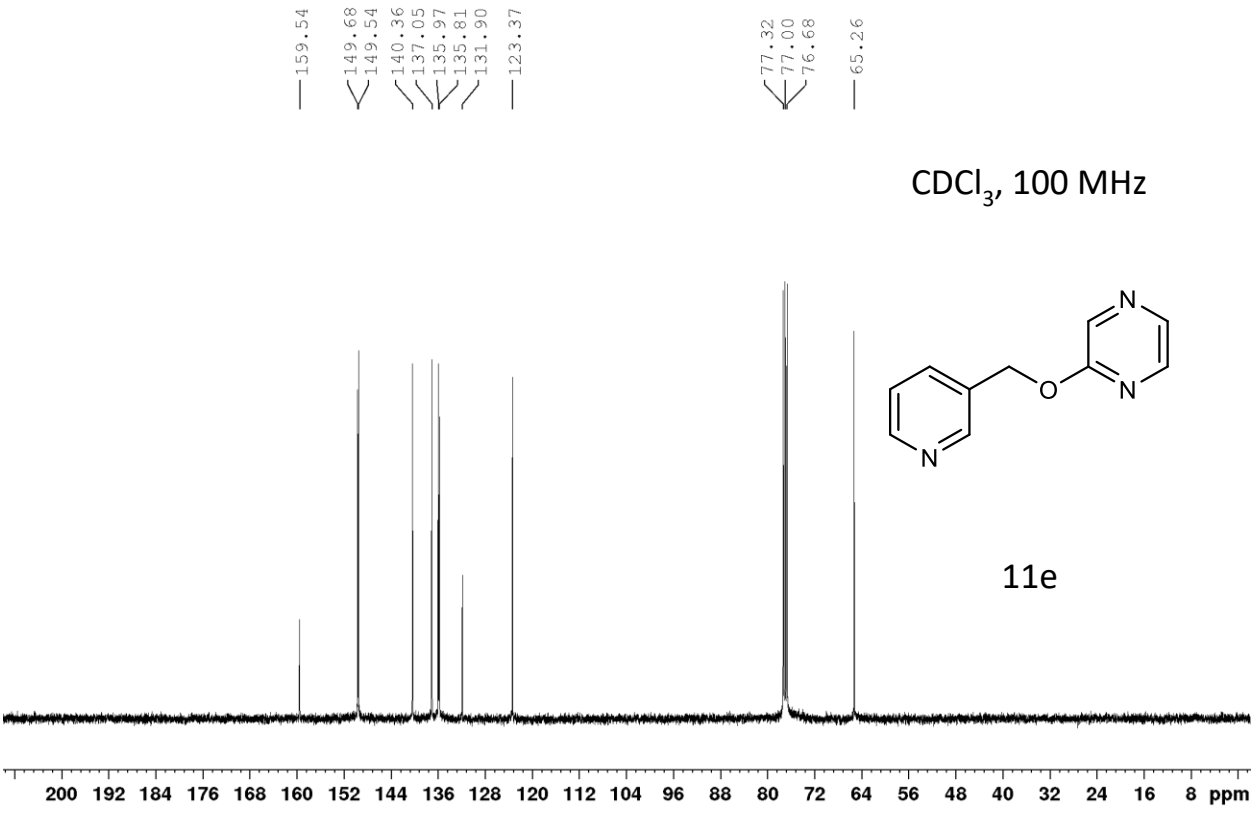

8.48
8.47
8.39
8.29
8.29
8.28
7.78
7.77
7.76
7.75
7.40
7.38
7.27
7.26
7.26
7.25
5.11
CDCl3, 400 MHz
N
O
Cl
N
11c
1.02
1.06
1.05
1.08
1.10
2.70
2.36
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

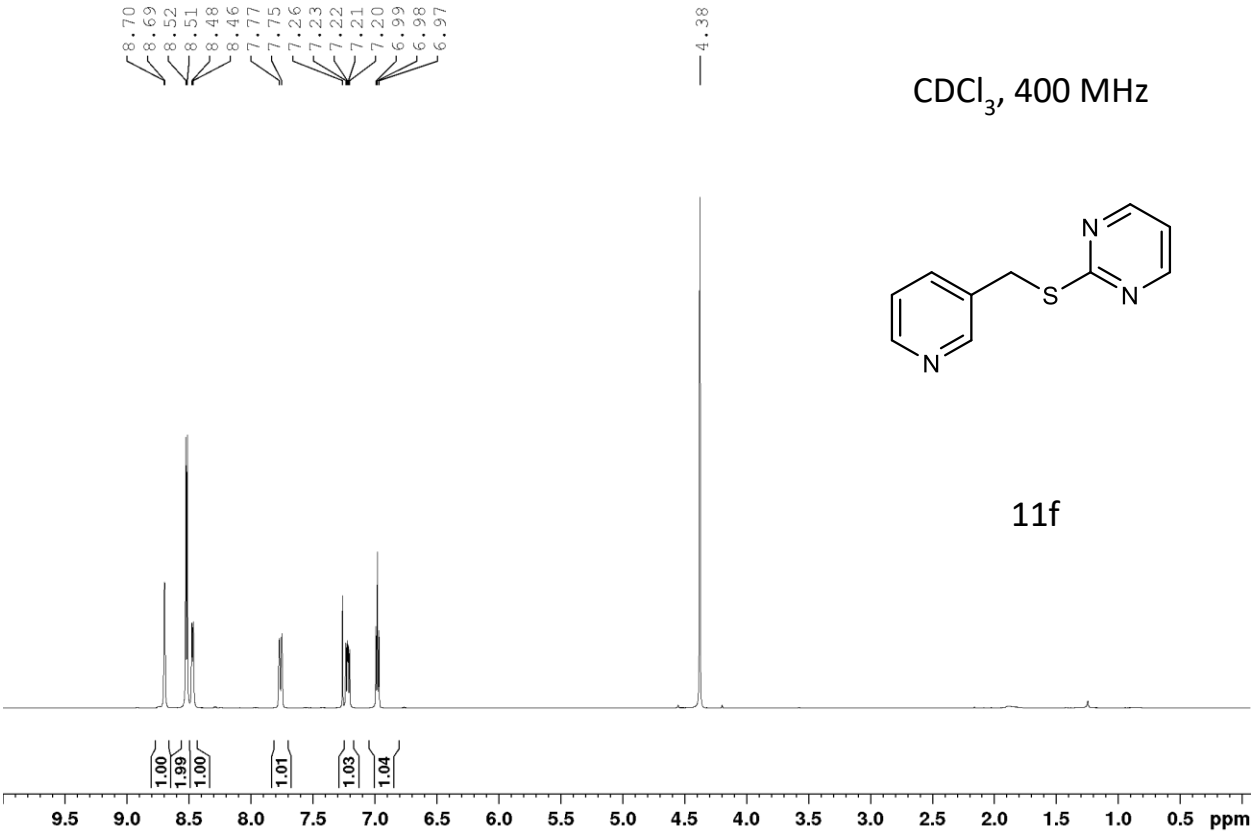

154.27
151.47
148.72
142.98
138.04
130.70
124.34
123.91
121.51
77.32
77.00
76.68
66.98
CDCl3, 100 MHz
N
O
Cl
N
11c
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

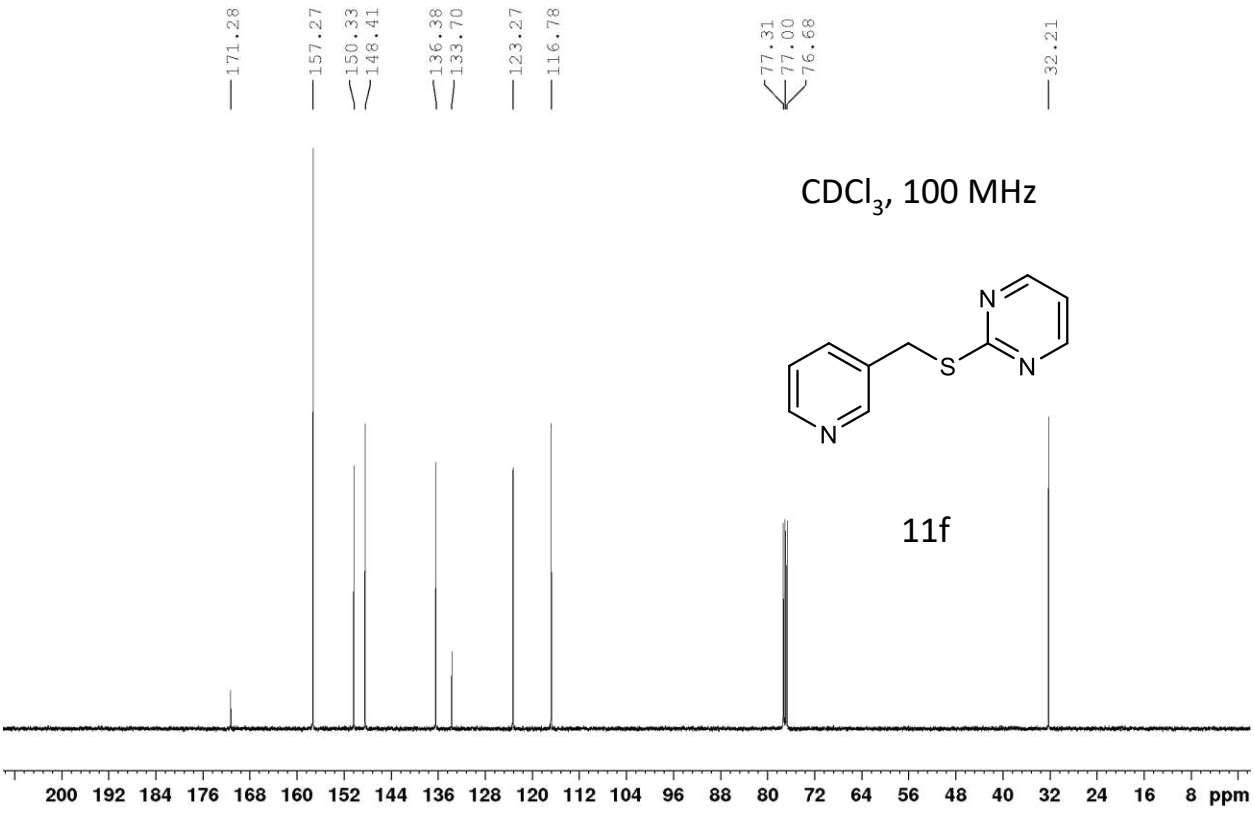

8.81
8.80
8.57
8.55
8.54
8.54
8.52
7.84
7.83
7.82
7.81
7.72
7.72
7.70
7.70
7.68
7.68
7.59
7.57
7.56
7.34
7.33
7.32
7.31
7.26
7.18
7.17
7.17
7.15
5.70
4.14
4.12
4.10
4.09
3.79
3.77
3.70
3.69
3.68
3.67
3.66
3.24
3.23
3.22
3.21
3.20
3.19
3.18
3.18
1.87
1.86
1.85
1.83
1.71
1.69
1.68
1.66
1.26
1.24
1.22
CDCl3, 400 MHz
N
N
O
N
OEt
O
11d
1.00
2.00
1.04
1.07
5.22
1.06
1.03
1.05
2.17
2.05
1.10
2.11
2.27
2.14
3.40
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

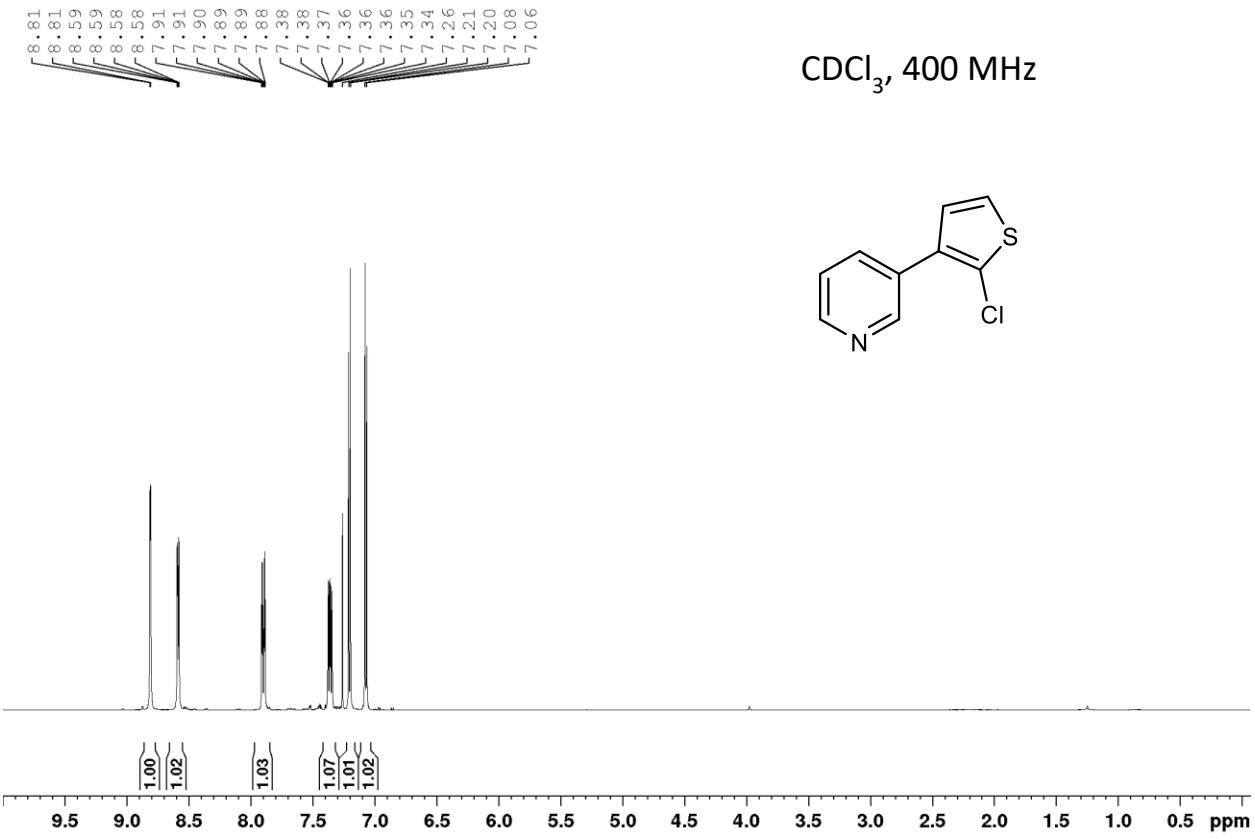

161.97
155.45
148.90
148.41
148.20
141.52
137.03
136.87
136.14
134.14
127.43
127.14
123.43
122.43
120.58
81.28
77.31
77.00
76.68
72.49
61.17
41.01
40.97
31.01
14.62
CDCl3, 100 MHz
N
N
O
N
OEt
O
11d
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

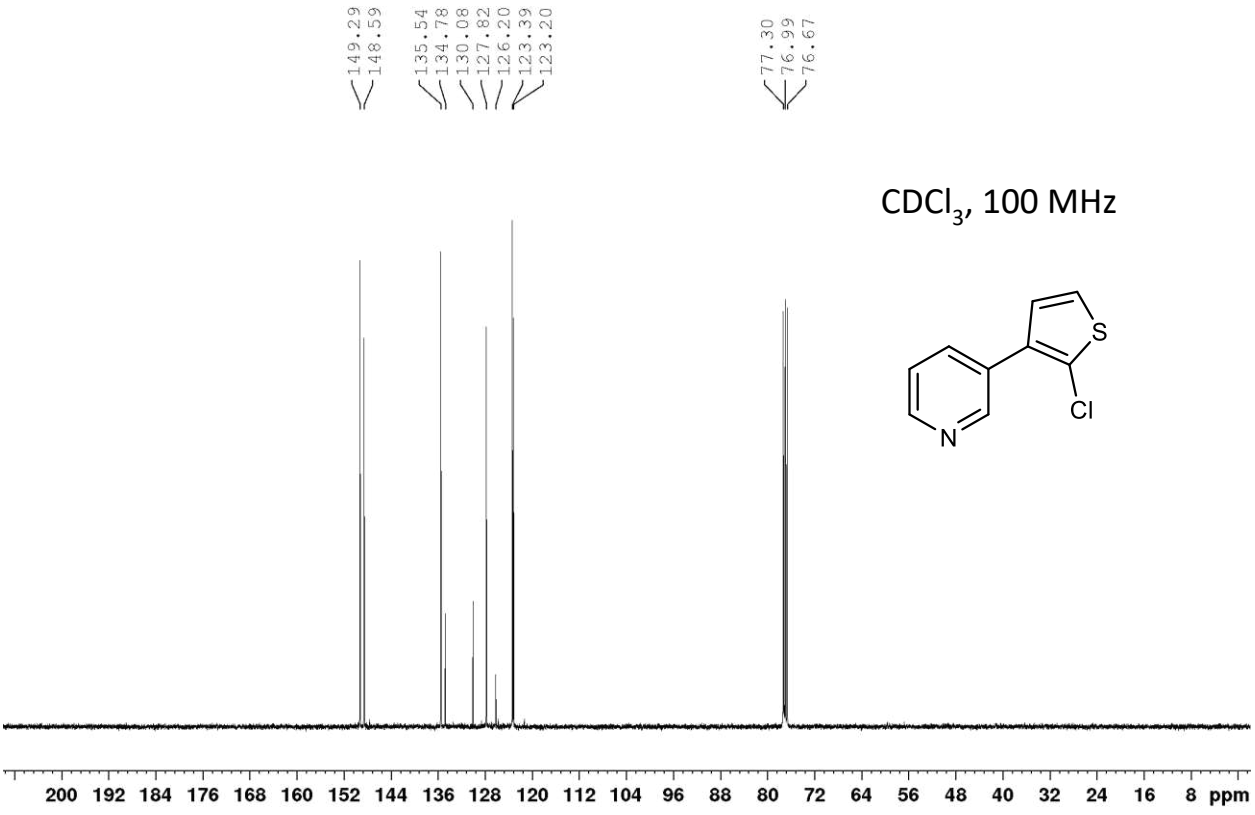

8.71
8.58
8.57
8.57
8.56
8.27
8.27
8.14
8.14
8.08
8.08
8.08
8.07
7.78
7.78
7.77
7.76
7.76
7.31
7.30
7.29
7.29
7.28
7.28
7.26
5.40
CDCl3, 400 MHz
N
O
N
N
11e
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

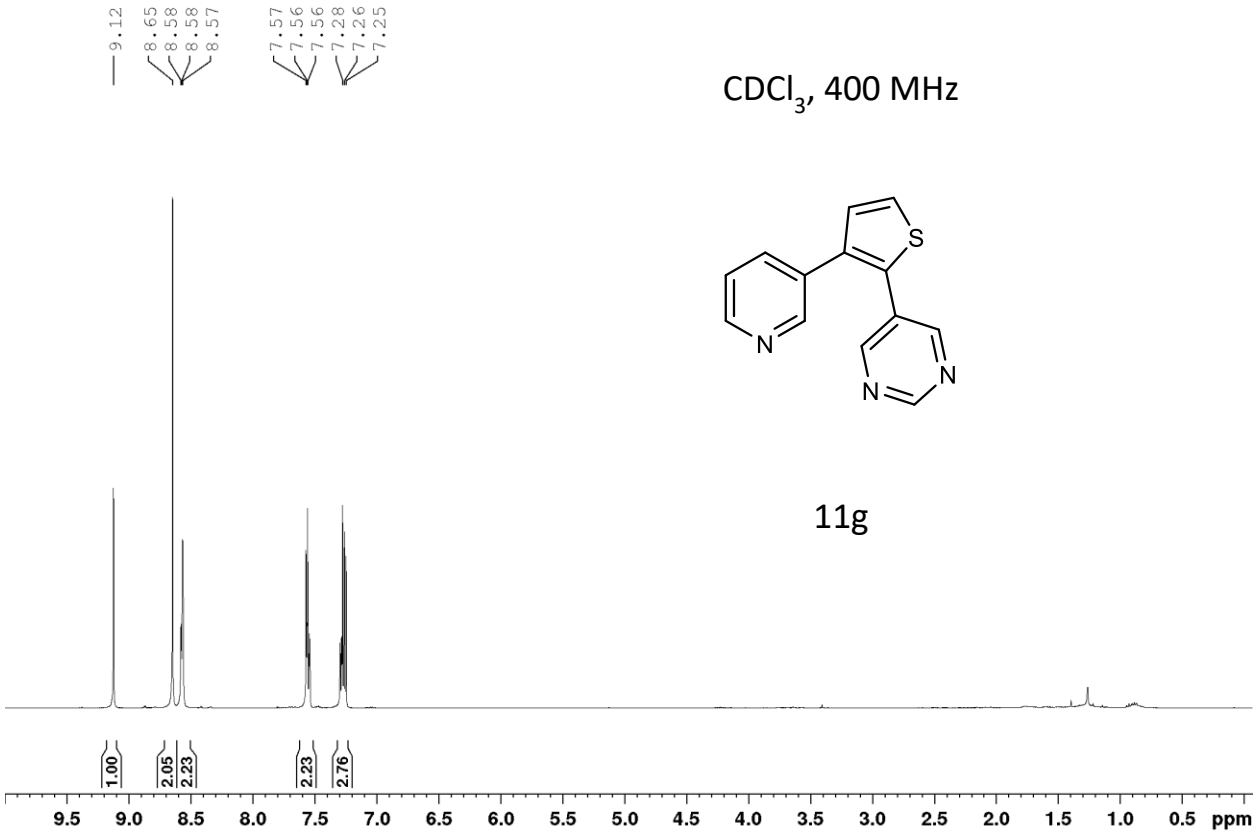

159.54
149.68
149.54
140.36
137.05
135.97
135.81
131.90
123.37
77.32
77.00
76.68
65.26
CDCl3, 100 MHz
N
O
N
N
11e
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm


8.70
8.69
8.52
8.51
8.48
8.46
7.77
7.75
7.26
7.23
7.22
7.21
7.20
6.99
6.98
6.97
4.38
CDCl3, 400 MHz
11f
1.00
1.99
1.00
1.01
1.03
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


171.28
157.27
150.33
148.41
136.38
133.70
123.27
116.78
77.31
77.00
76.68
32.21
CDCl3, 100 MHz
11f
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

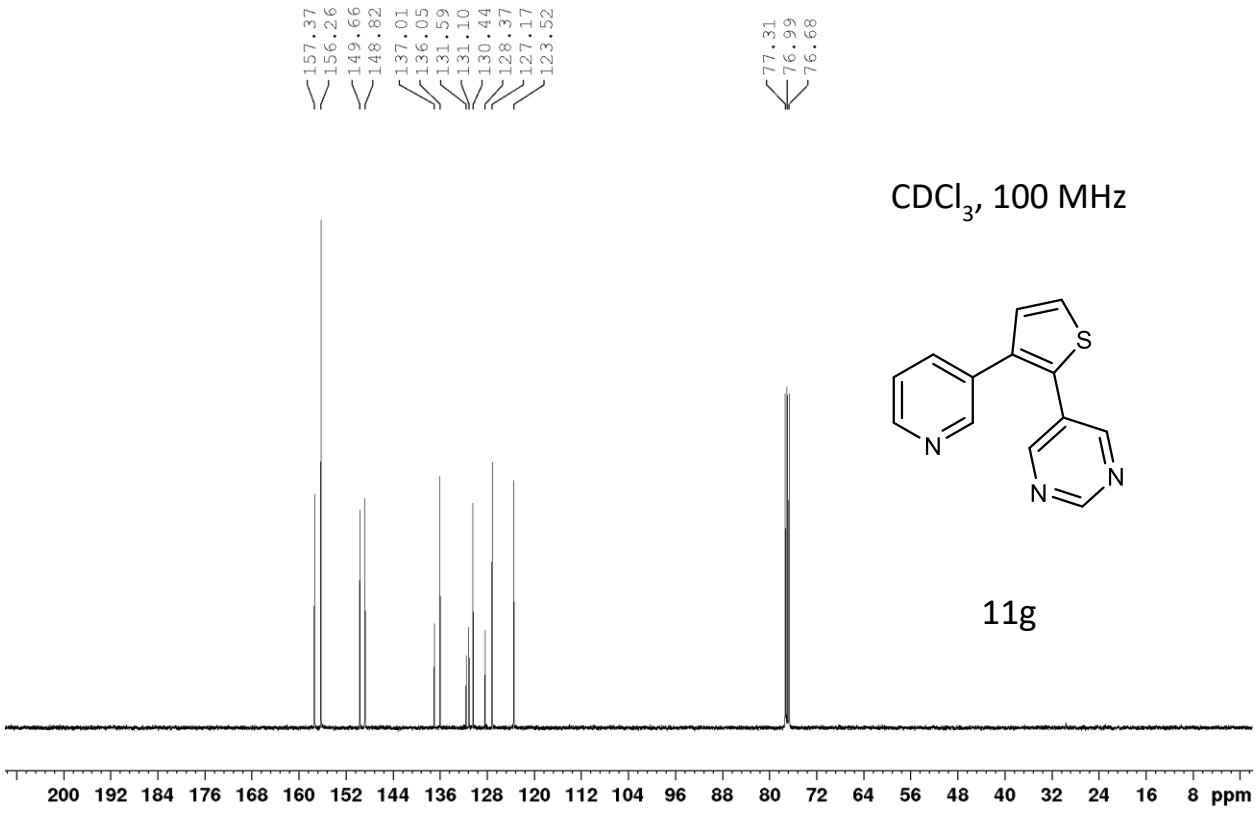

8.81
8.81
8.59
8.59
8.58
8.58
7.91
7.91
7.90
7.89
7.89
7.88
7.38
7.38
7.37
7.36
7.36
7.36
7.35
7.34
7.26
7.21
7.20
7.08
7.06
CDCl3, 400 MHz
S
Cl
N
1.00
1.02
1.03
1.07
1.01
1.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


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



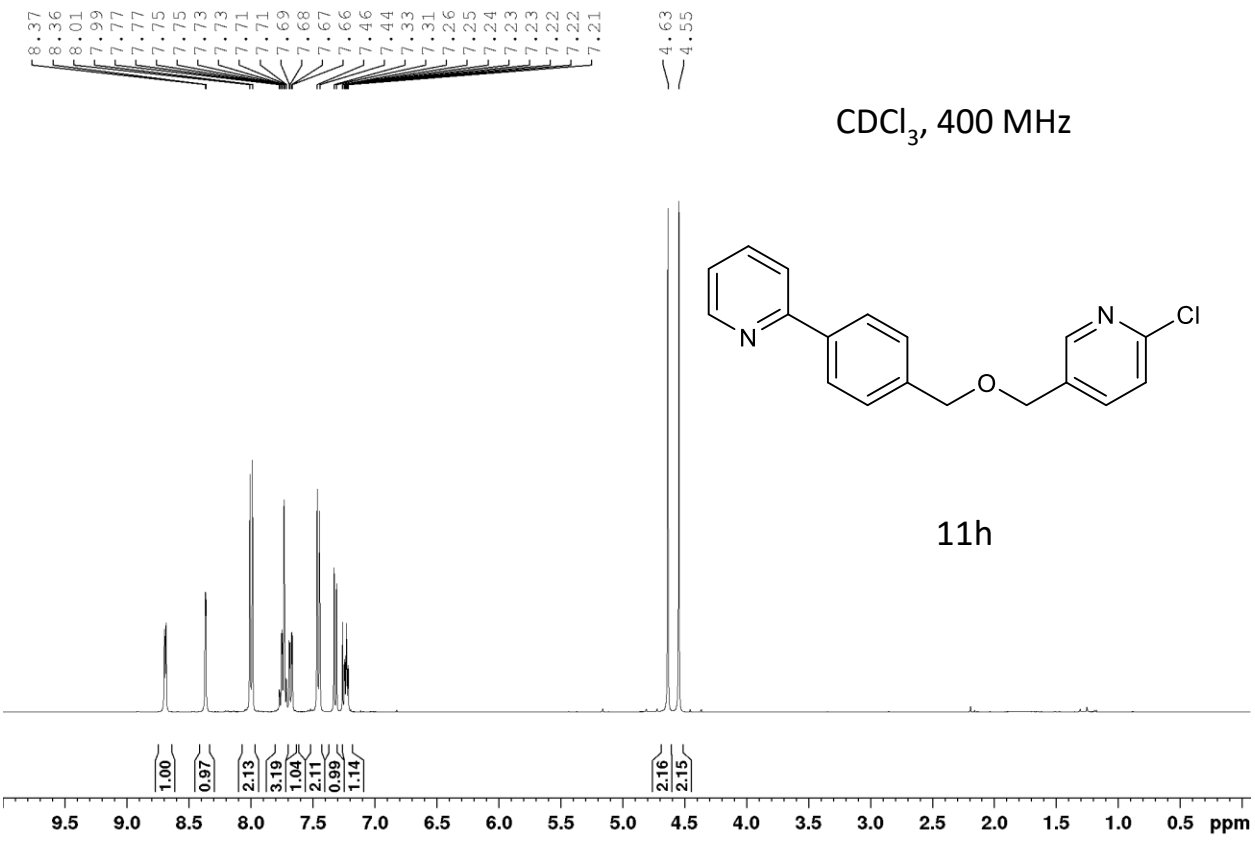
$CDCl_3$, 400 MHz

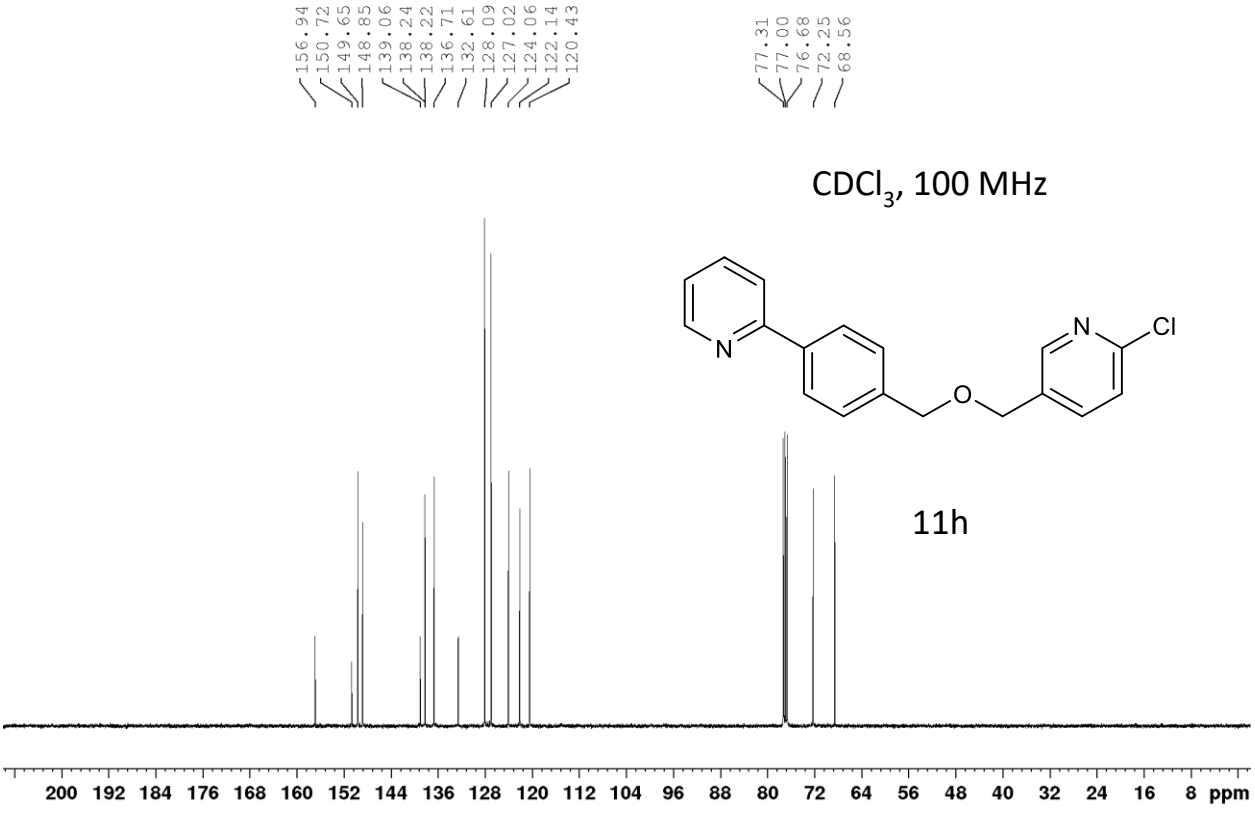
11g

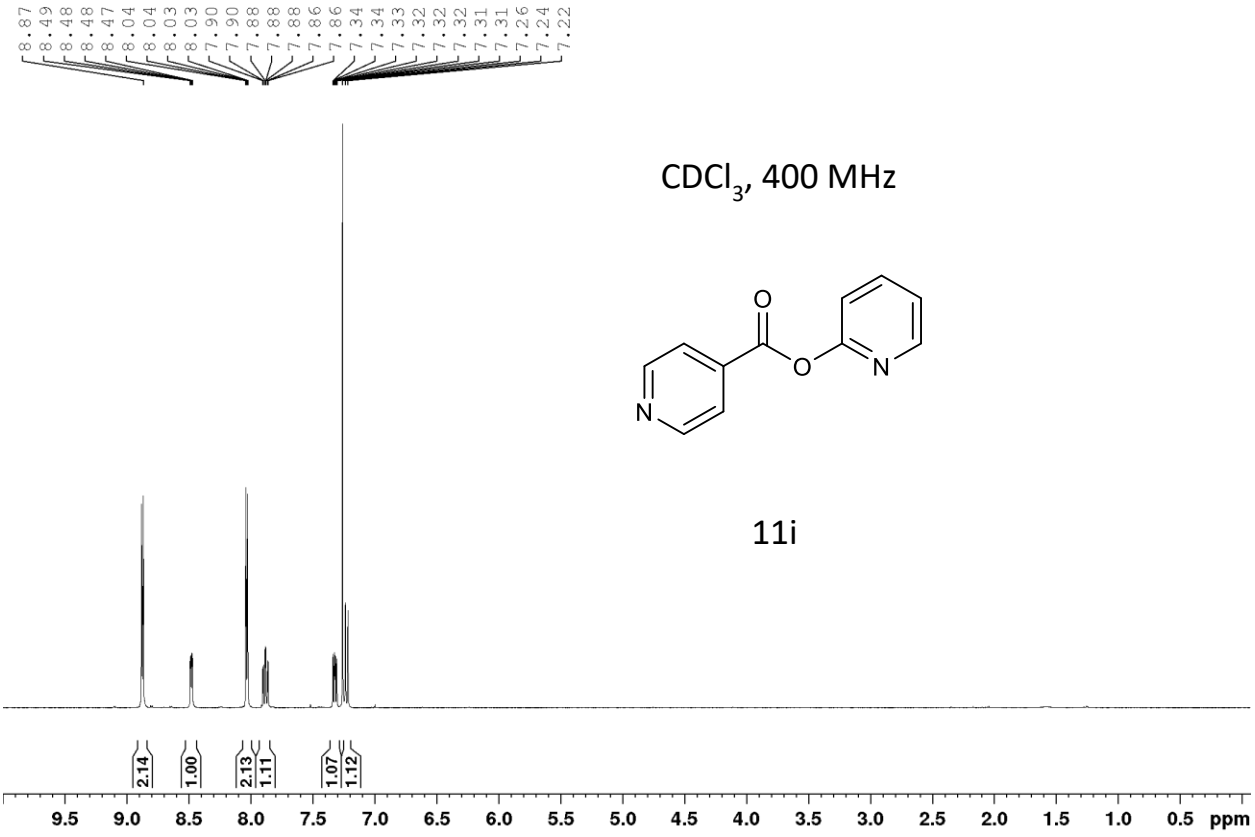


$CDCl_3$, 100 MHz

11g


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
N
Cl
O
11h
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


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
N
Cl
O
11h
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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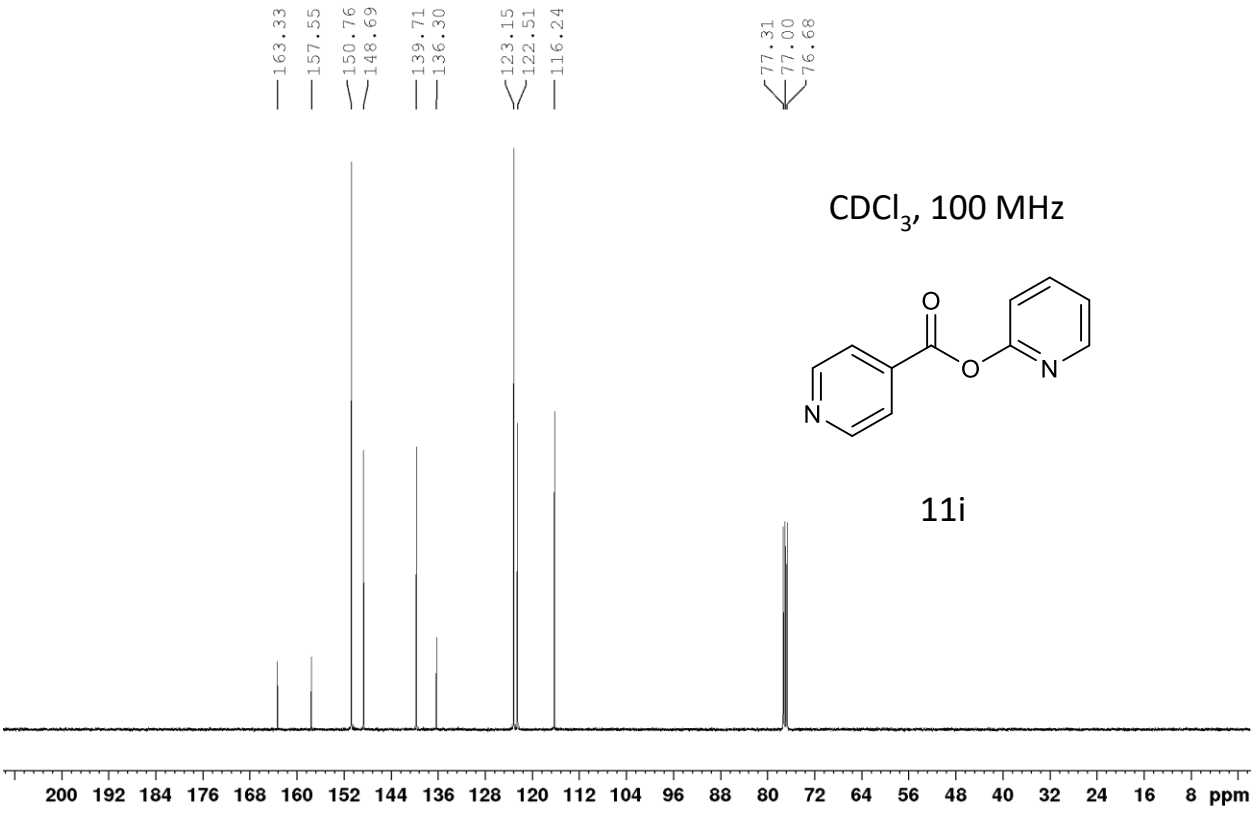
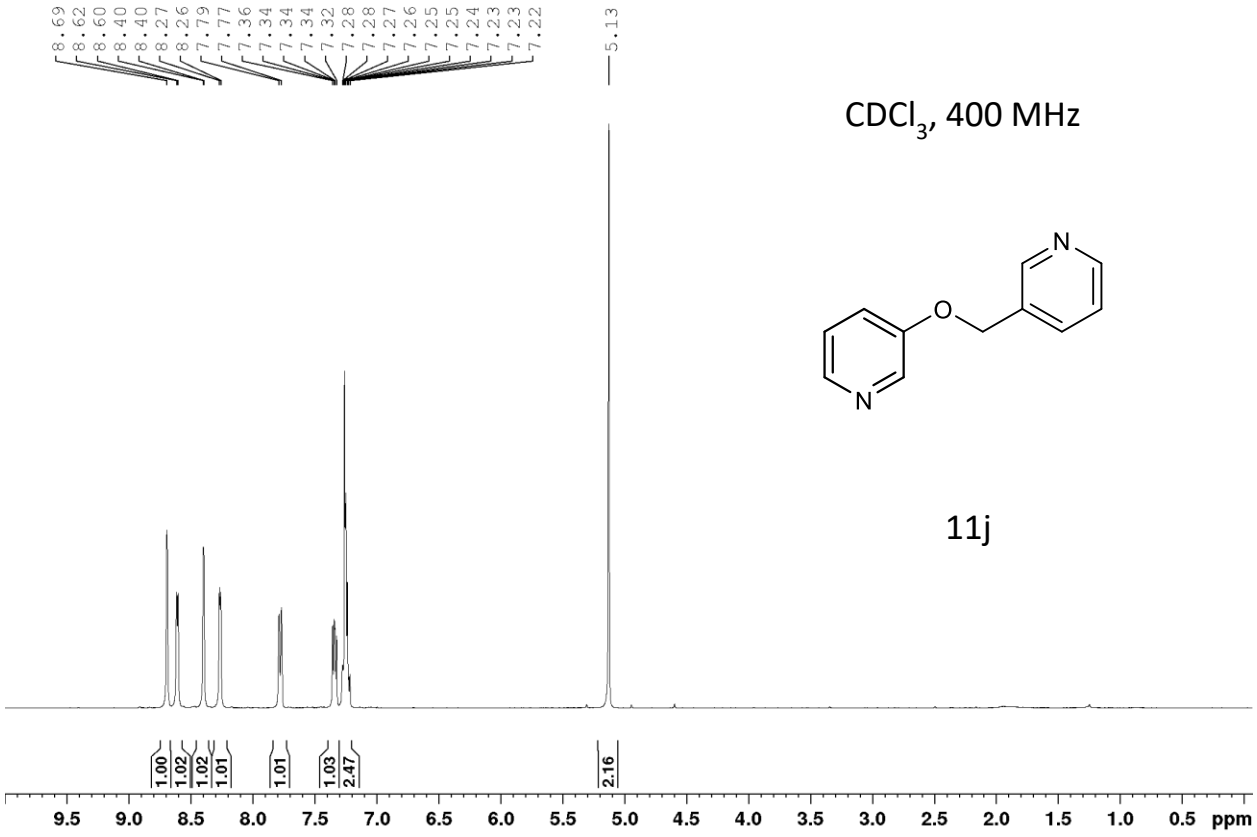
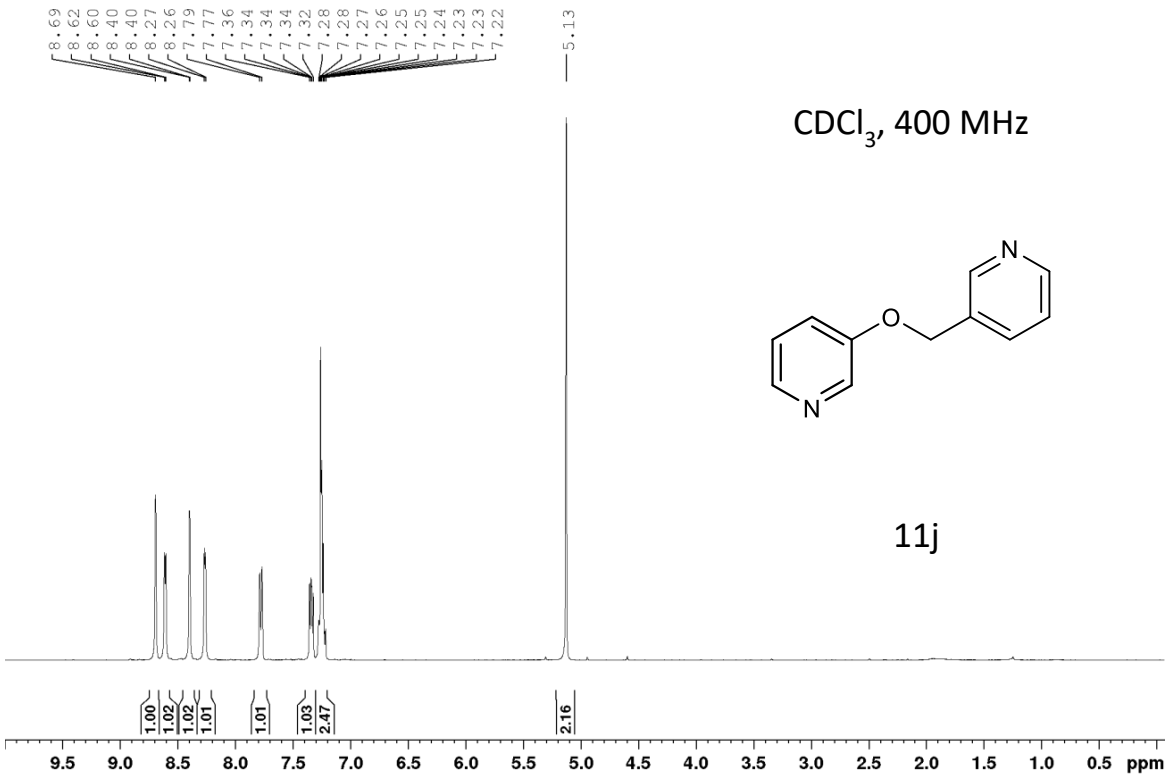
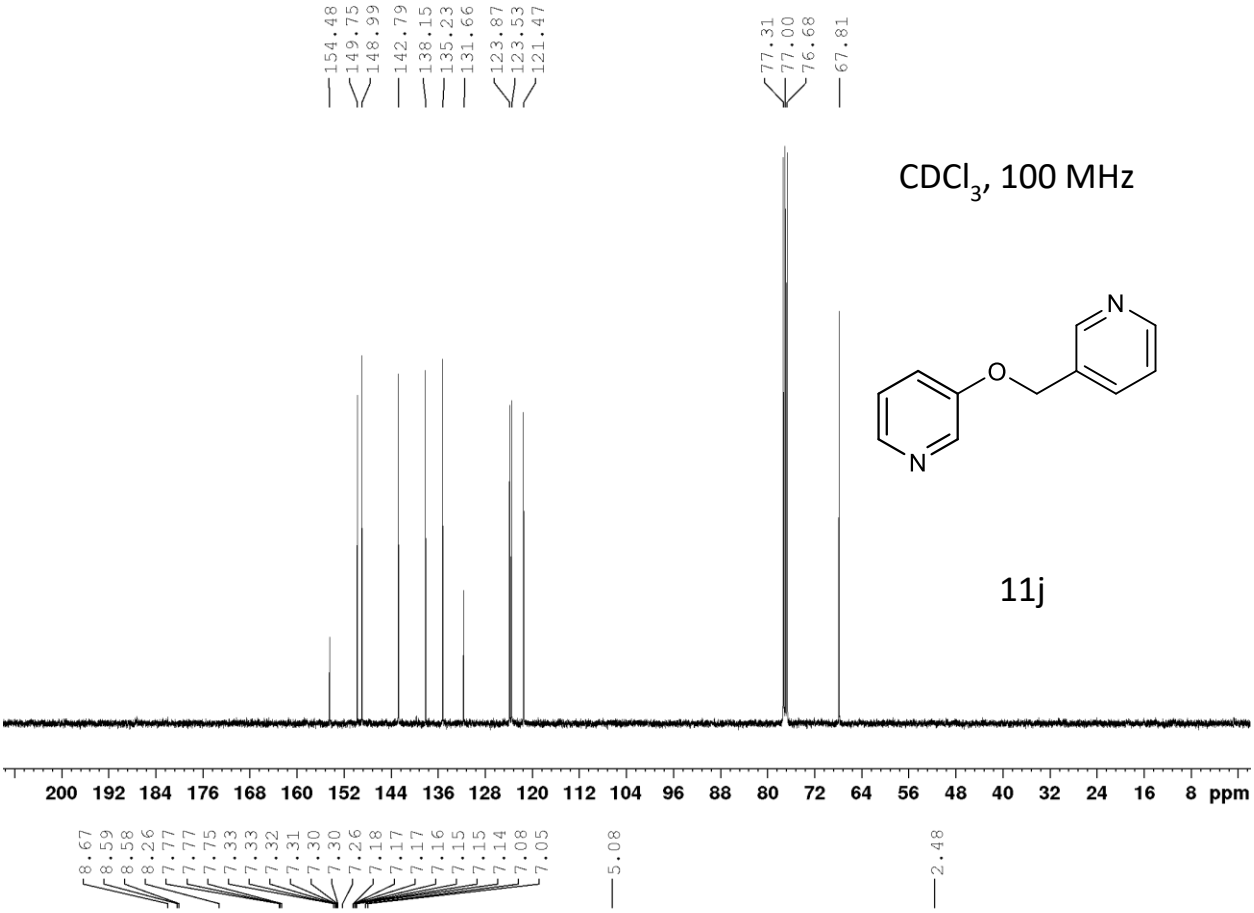
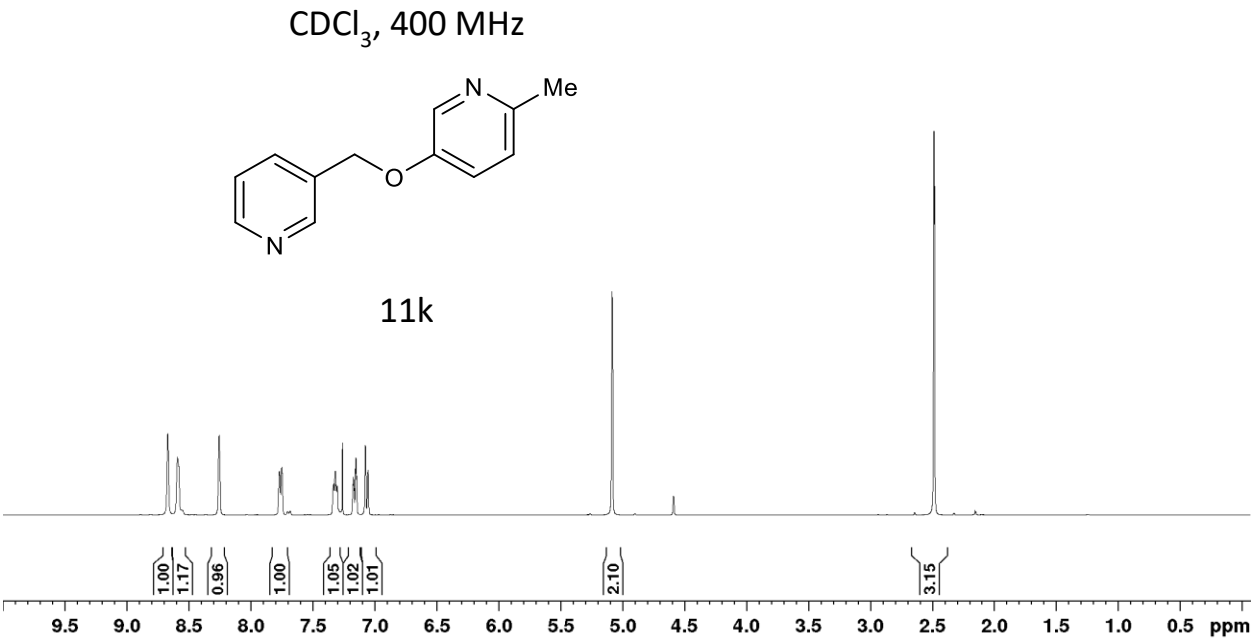
8.49
8.48
8.48
8.47
8.04
8.04
8.03
8.03
7.90
7.90
7.88
7.88
7.88
7.86
7.86
7.34
7.34
7.33
7.32
7.32
7.32
7.31
7.31
7.26
7.24
7.22
CDCl3, 400 MHz
O
O
N
N
11i
2.14
1.00
2.13
1.11
1.07
1.12
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

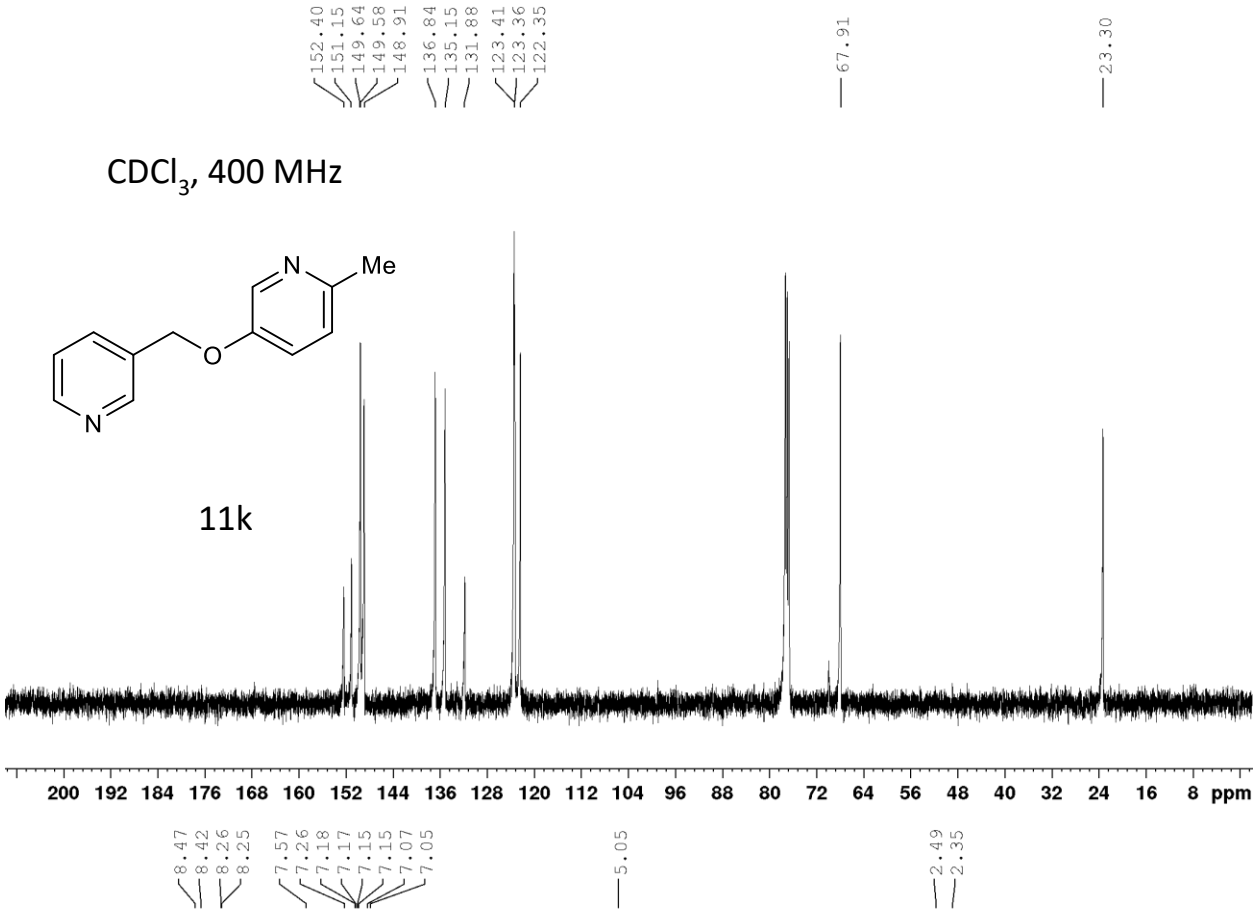

163.33
157.55
150.76
148.69
139.71
136.30
123.15
122.51
116.24
77.31
77.00
76.68
CDCl3, 100 MHz
O
O
N
N
11i
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

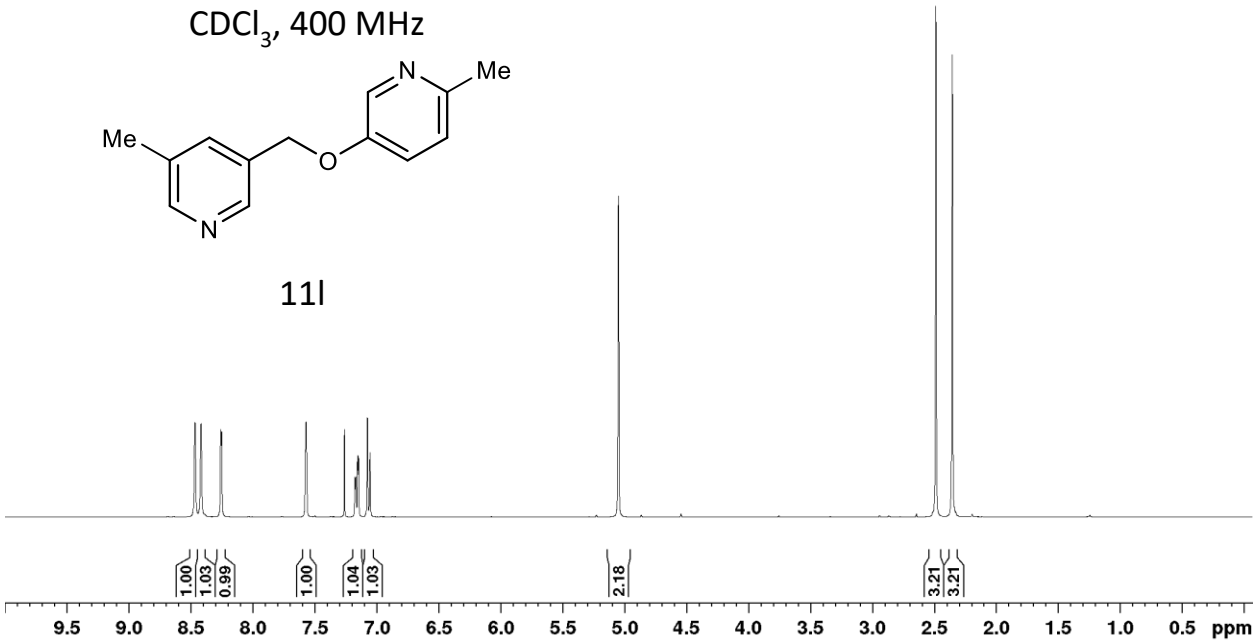

8.69
8.62
8.60
8.40
8.40
8.27
8.26
7.79
7.77
7.36
7.34
7.34
7.34
7.32
7.28
7.28
7.27
7.26
7.25
7.25
7.24
7.23
7.23
7.22
5.13
CDCl3, 400 MHz
N
O
N
11j
1.00
1.02
1.02
1.01
1.01
1.03
2.47
2.16
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

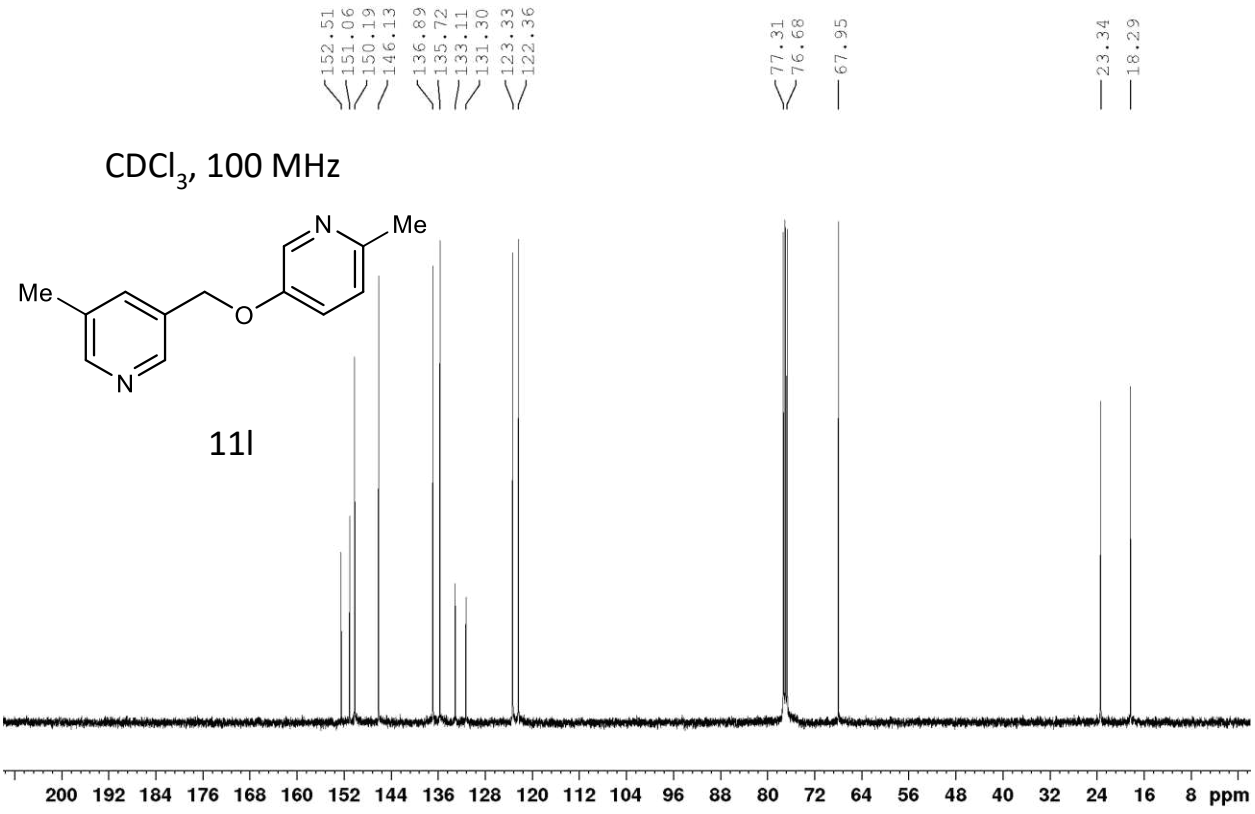

8.69
8.62
8.60
8.40
8.40
8.27
8.26
7.79
7.77
7.36
7.34
7.34
7.34
7.32
7.28
7.28
7.27
7.26
7.25
7.25
7.24
7.23
7.23
7.22
5.13
CDCl3, 400 MHz
N
O
N
11j
1.00
1.02
1.02
1.01
1.01
1.03
2.47
2.16
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

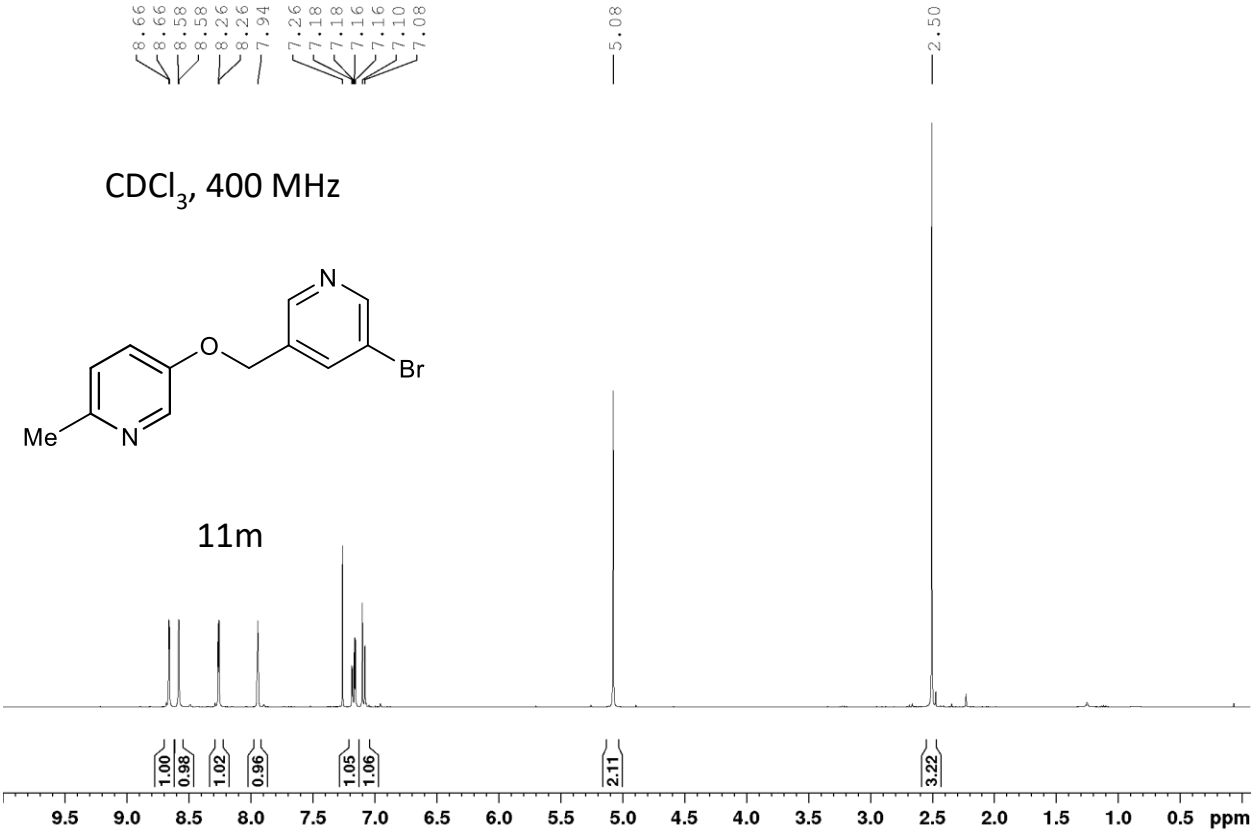

154.48
149.75
148.99
142.79
138.15
135.23
131.66
123.87
123.53
121.47
77.31
77.00
76.68
67.81
CDCl3, 100 MHz
N
O
N
11j
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm
8.67
8.59
8.58
8.26
7.77
7.77
7.75
7.33
7.33
7.32
7.31
7.30
7.30
7.26
7.18
7.17
7.17
7.16
7.15
7.15
7.14
7.08
7.05
5.08
2.48

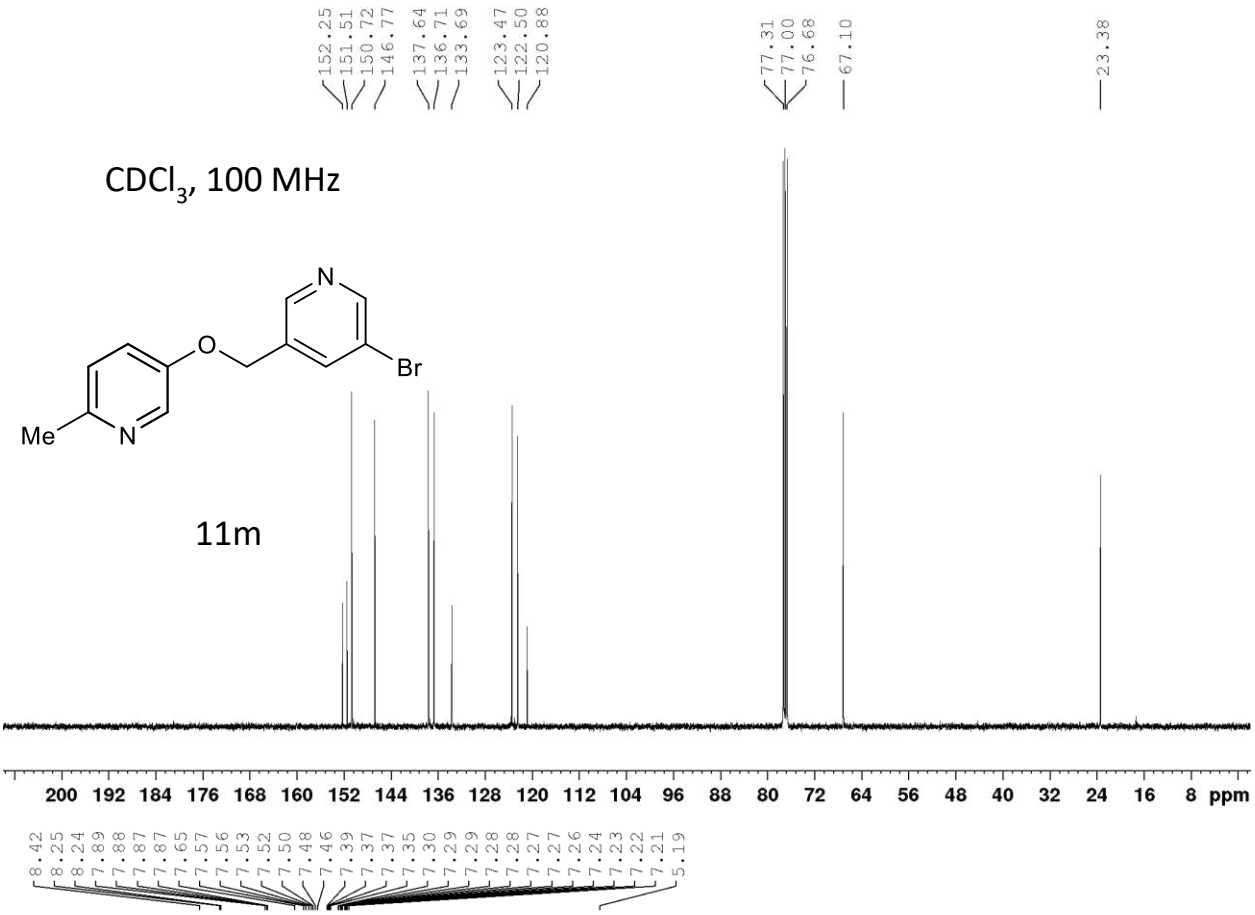

CDCl3, 400 MHz
N
Me
O
N
11k
1.00
1.17
0.96
1.00
1.05
1.02
1.01
2.10
3.15
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


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
N
Me
O
N
11k
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

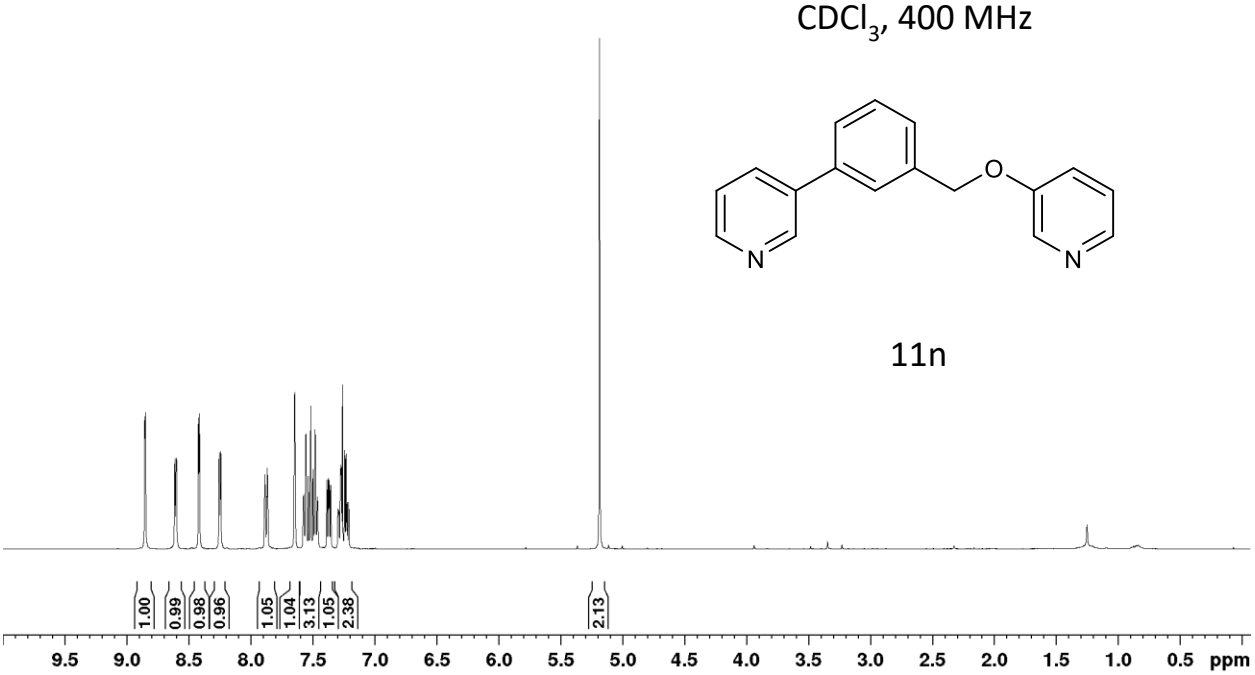

CDCl3, 400 MHz
N
Me
Me
O
N
11l
1.00
1.03
0.99
1.00
1.04
1.03
2.18
3.21
3.21
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


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
N
Me
Me
O
N
11l
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

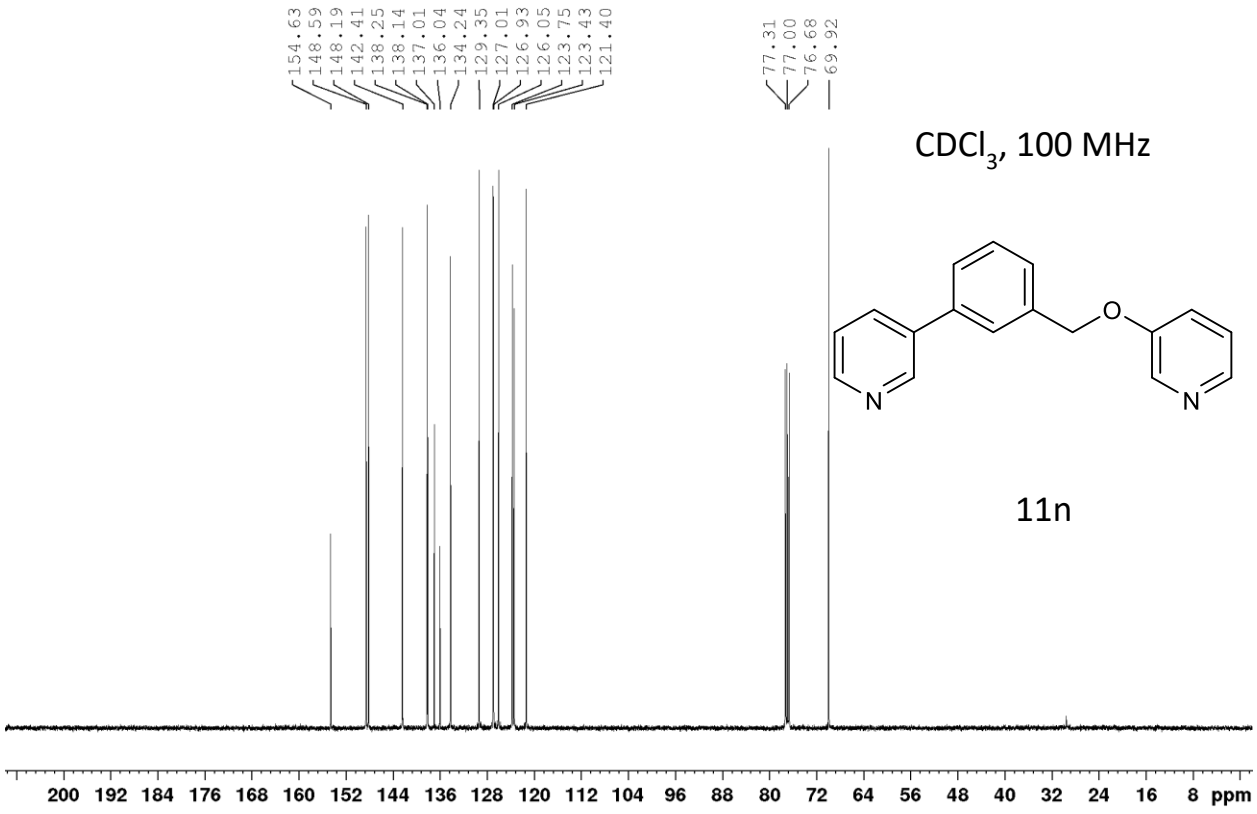

8.66
8.66
8.58
8.58
8.26
8.26
7.94
7.26
7.18
7.18
7.16
7.16
7.10
7.08
5.08
2.50
CDCl3, 400 MHz
N
O
Br
Me
N
11m
1.00
0.98
1.02
0.96
1.05
1.06
2.11
3.22
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

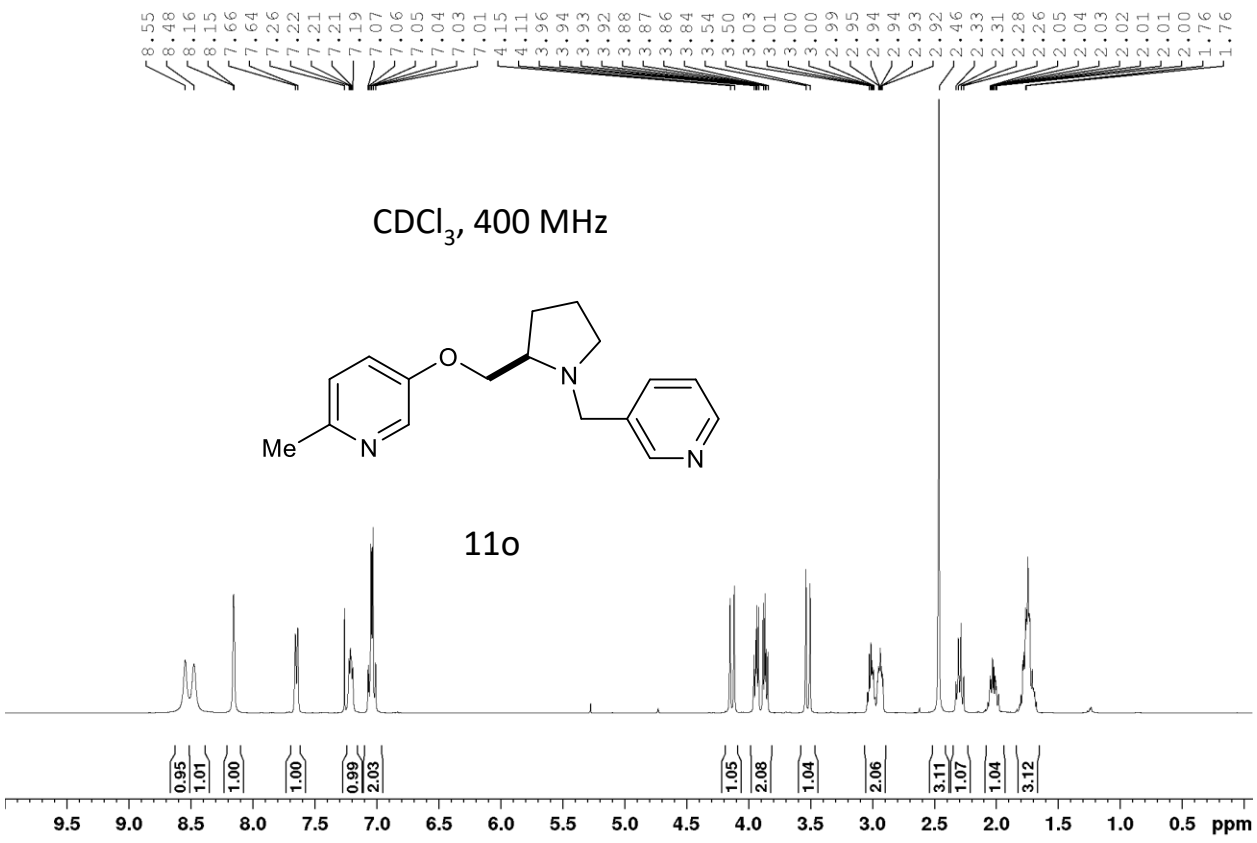

152.25
151.51
150.72
146.77
137.64
136.71
133.69
123.47
122.50
120.88
77.31
77.00
76.68
67.10
23.38
CDCl3, 100 MHz
N
O
Br
Me
N
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm
8.42
8.25
8.24
7.89
7.88
7.87
7.87
7.65
7.57
7.56
7.53
7.52
7.50
7.48
7.46
7.39
7.37
7.37
7.35
7.30
7.29
7.29
7.28
7.28
7.27
7.27
7.26
7.24
7.23
7.22
7.21
5.19

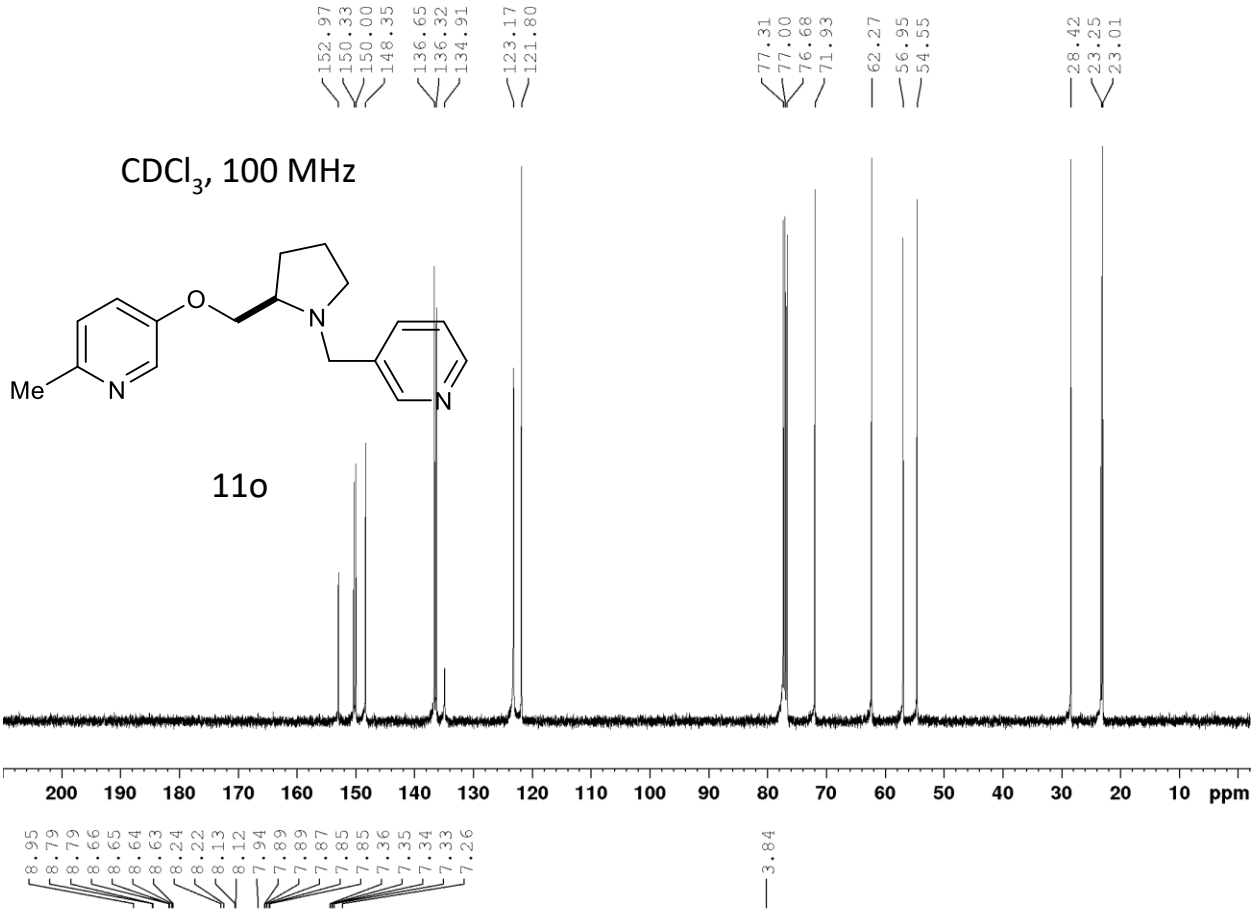
11m

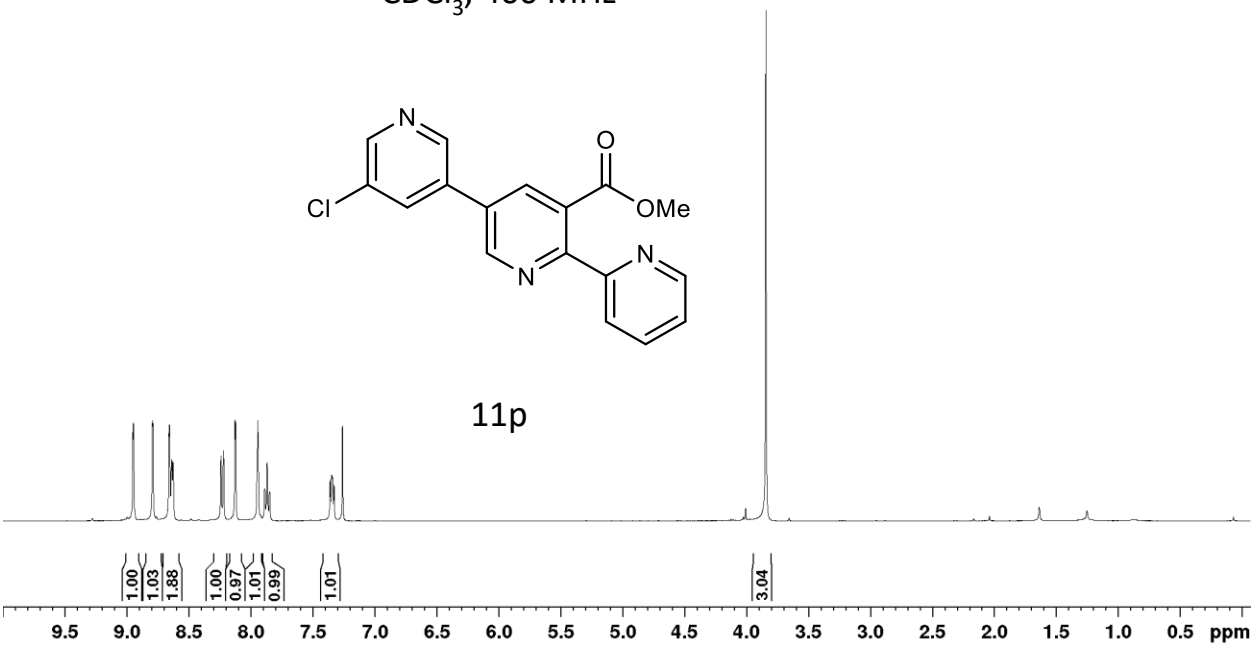

CDCl3, 400 MHz
O
N
N
1.00
0.99
0.98
0.96
1.05
1.04
3.13
1.05
2.38
2.13
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

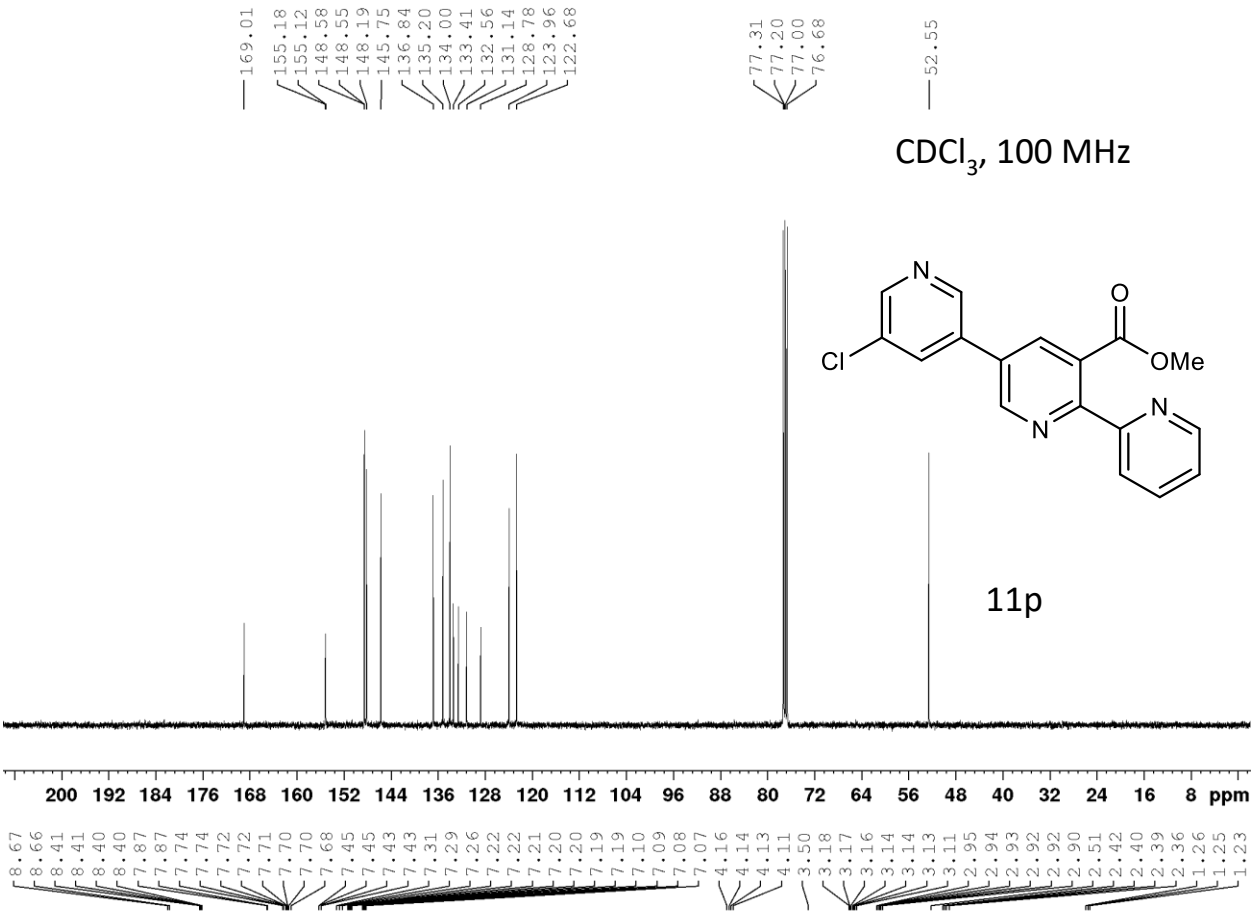
11n

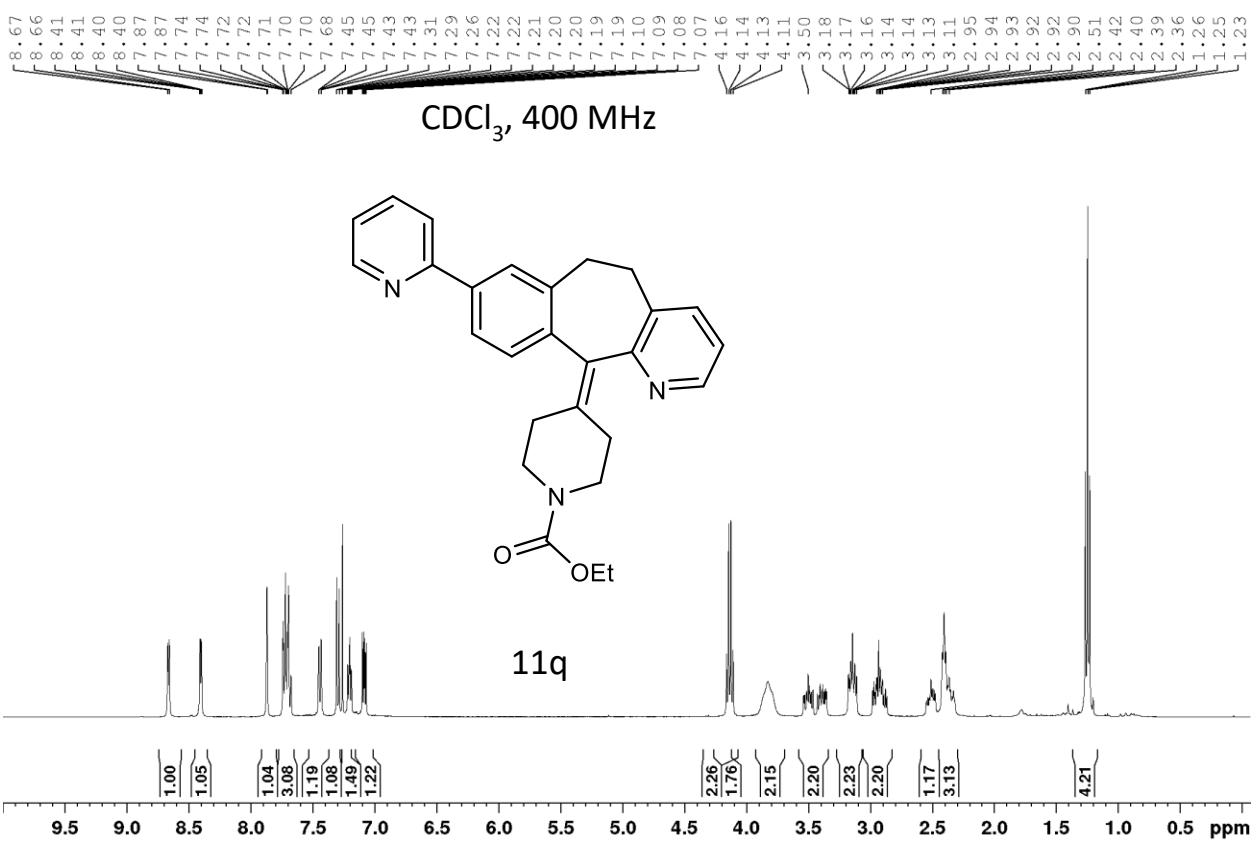

154.63
148.59
148.19
142.41
138.25
138.14
137.01
136.04
134.24
129.35
127.01
126.93
126.05
123.75
123.43
121.40
77.31
77.00
76.68
69.92
CDCl3, 100 MHz
O
N
N
11n
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

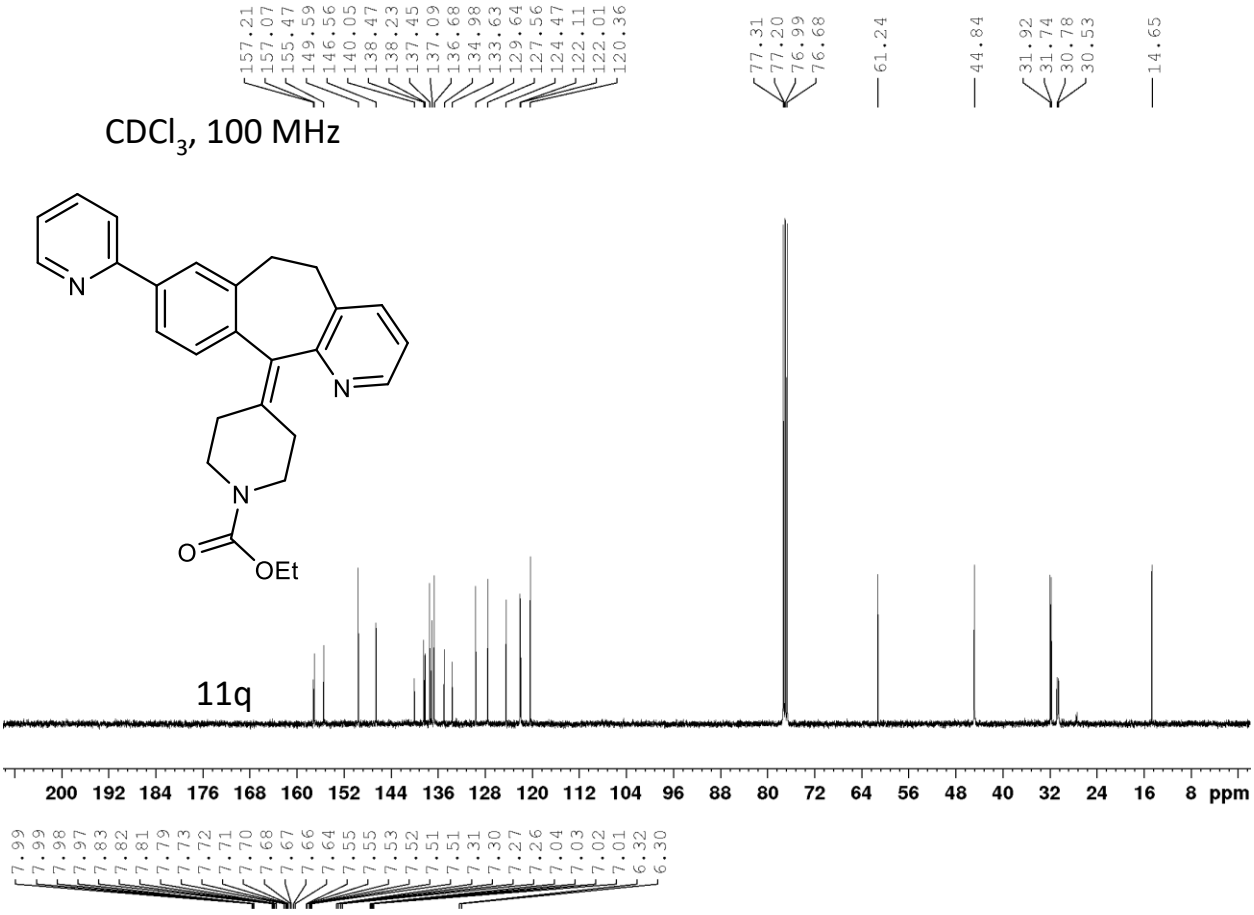

8.55
8.48
8.16
8.15
7.66
7.64
7.26
7.22
7.21
7.21
7.19
7.07
7.06
7.05
7.04
7.03
7.01
4.15
4.11
3.96
3.94
3.93
3.92
3.88
3.87
3.86
3.84
3.54
3.50
3.03
3.01
3.00
3.00
2.99
2.95
2.94
2.94
2.93
2.92
2.46
2.33
2.31
2.28
2.26
2.05
2.04
2.03
2.02
2.01
2.00
1.76
1.76
CDCl3, 400 MHz
O
N
N
Me
N
11o
0.95
1.01
1.00
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

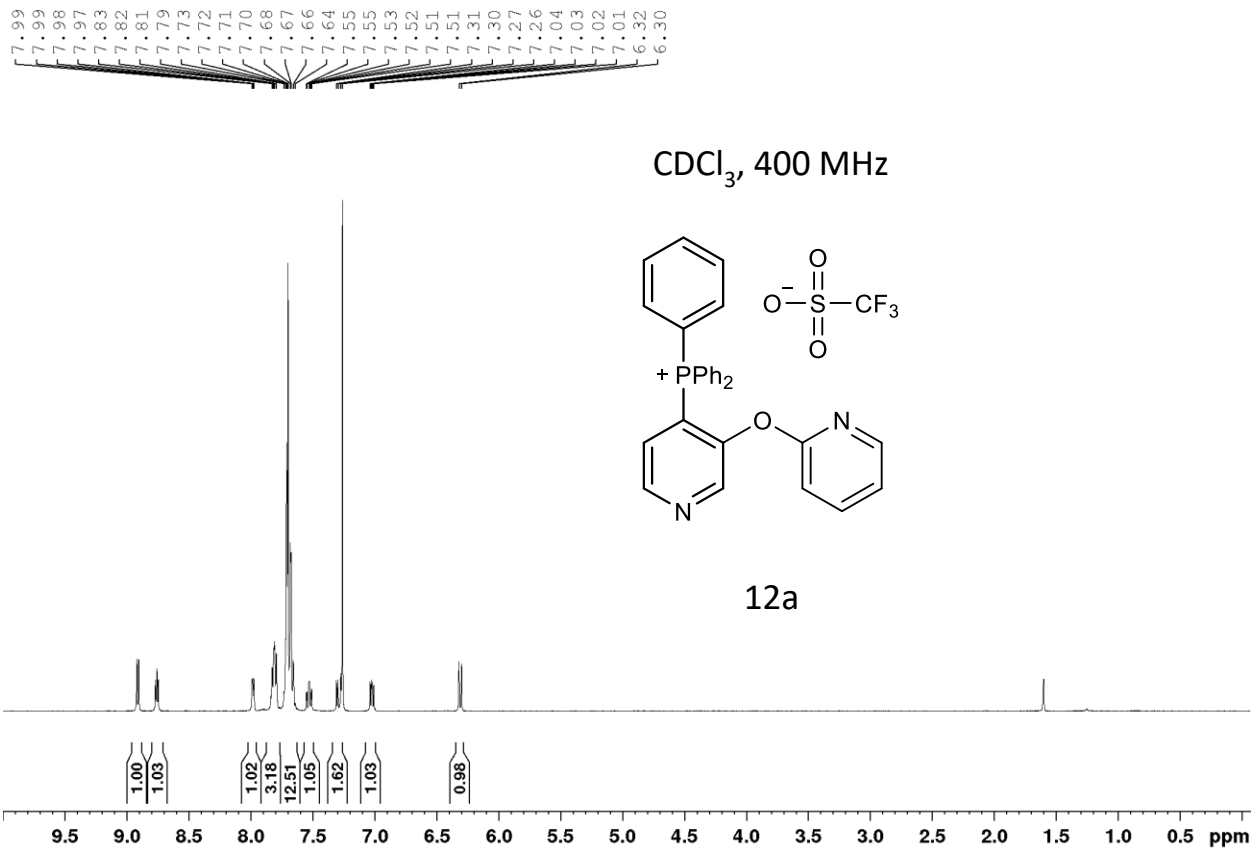

152.97
150.33
150.00
148.35
136.65
136.32
134.91
123.17
121.80
77.31
77.00
76.68
71.93
62.27
56.95
54.55
28.42
23.25
23.01
CDCl3, 100 MHz
O
N
Me
N
N
11o
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
8.95
8.79
8.79
8.66
8.65
8.64
8.63
8.24
8.22
8.13
8.12
7.94
7.89
7.89
7.87
7.85
7.85
7.36
7.35
7.34
7.33
7.26
3.84

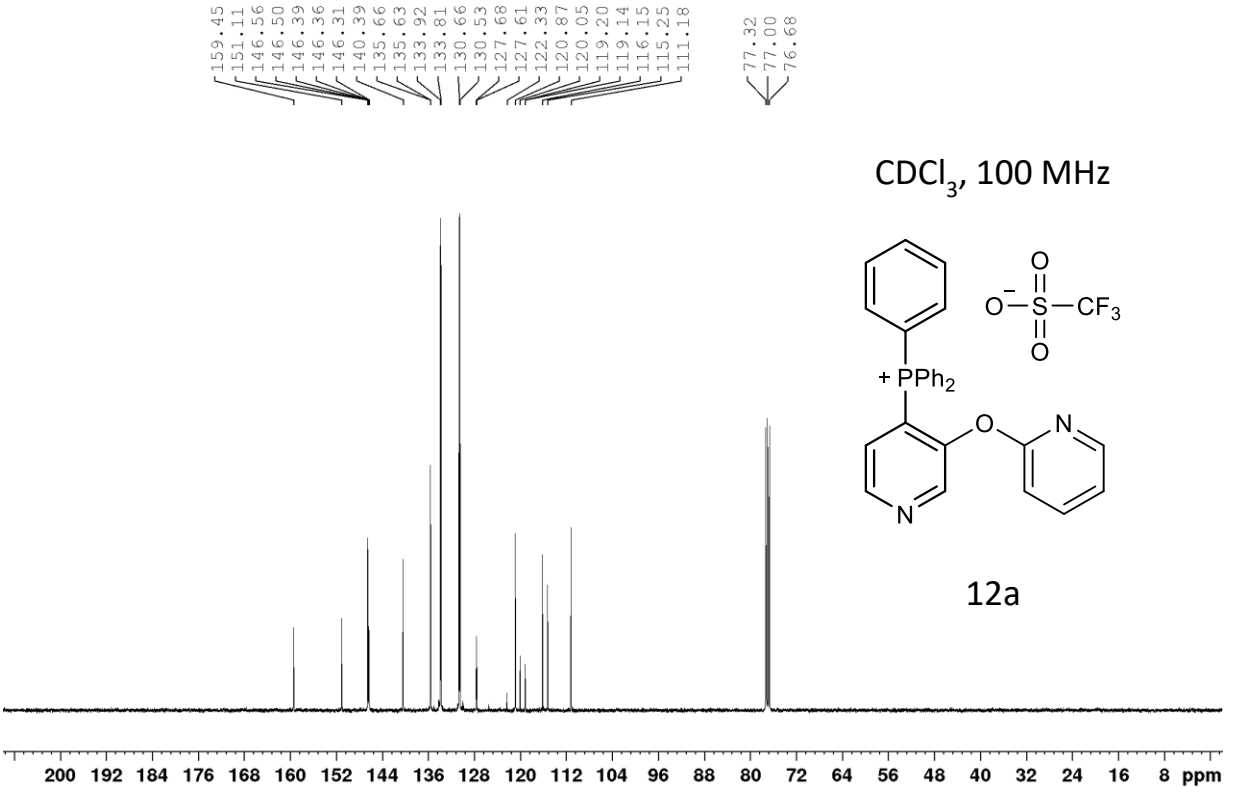

CDCl3, 400 MHz
N
Cl
O
OMe
N
N
11p
1.00
1.03
1.88
1.00
0.97
1.01
0.99
1.01
3.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


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
N
O
Cl
OMe
N
N
11p
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

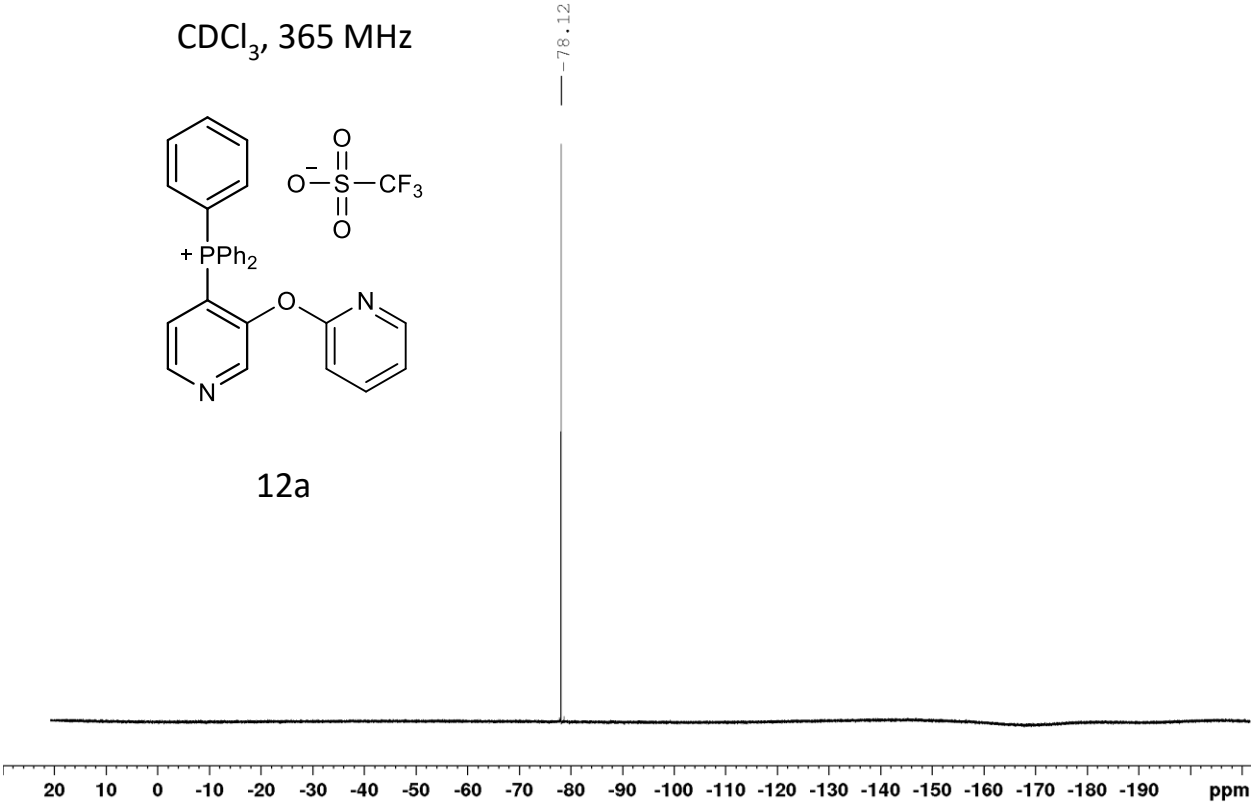

8.67
8.66
8.41
8.41
8.40
8.40
7.87
7.87
7.74
7.74
7.72
7.72
7.71
7.70
7.70
7.68
7.45
7.45
7.43
7.43
7.31
7.29
7.26
7.22
7.22
7.21
7.20
7.20
7.19
7.19
7.10
7.09
7.08
7.07
4.16
4.14
4.13
4.11
3.50
3.18
3.17
3.16
3.14
3.14
3.13
3.11
2.95
2.94
2.93
2.92
2.92
2.90
2.51
2.42
2.40
2.39
2.36
1.26
1.25
1.23
CDCl3, 400 MHz
N
N
N
O
OEt
11q
1.00
1.05
1.04
3.08
1.19
1.08
1.49
1.22
2.26
1.76
2.15
2.20
2.23
2.20
1.17
3.13
4.21
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


157.21
157.07
155.47
149.59
146.56
140.05
138.47
138.23
137.45
137.09
136.68
134.98
133.63
129.64
127.56
124.47
122.11
120.36
77.31
77.20
76.99
76.68
61.24
44.84
31.92
31.74
30.78
30.53
14.65
CDCl3, 100 MHz
N
N
N
O
OEt
11q
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


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
O
O
S
CF3
+ PPh2
O
N
N
12a
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

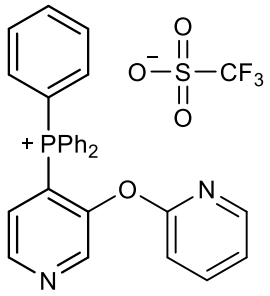

159.45
151.11
146.56
146.50
146.39
146.36
146.31
140.39
135.66
135.63
133.92
133.81
130.66
130.53
127.68
127.61
122.33
120.87
120.05
119.20
119.14
116.15
115.25
111.18
77.32
77.00
76.68
CDCl3, 100 MHz
+ PPh2
O
N
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

12a


CDCl3, 365 MHz
-78.12
+ PPh2
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

12a

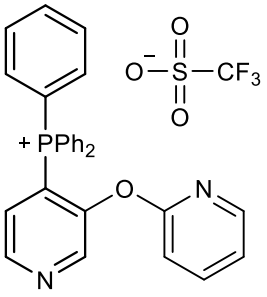
$CDCl_3$, 162 MHz



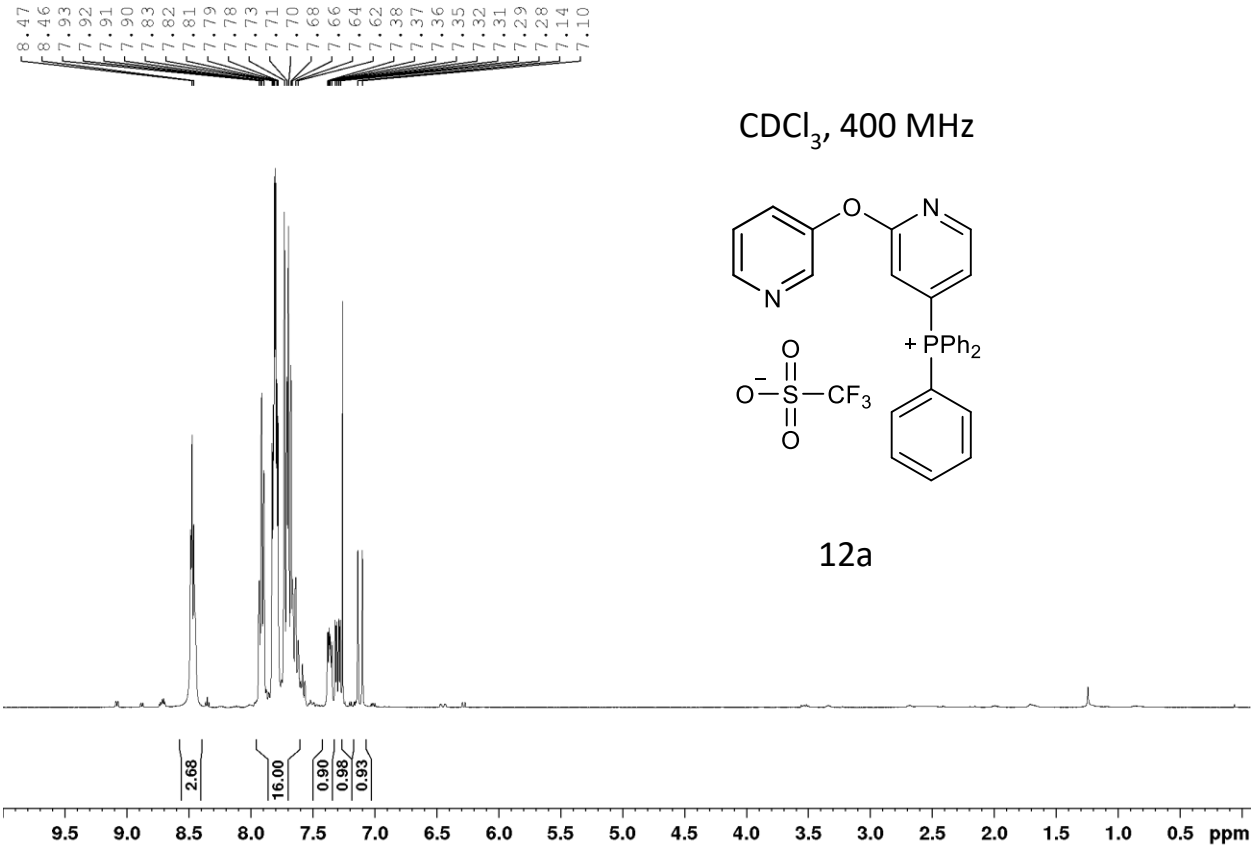
12a

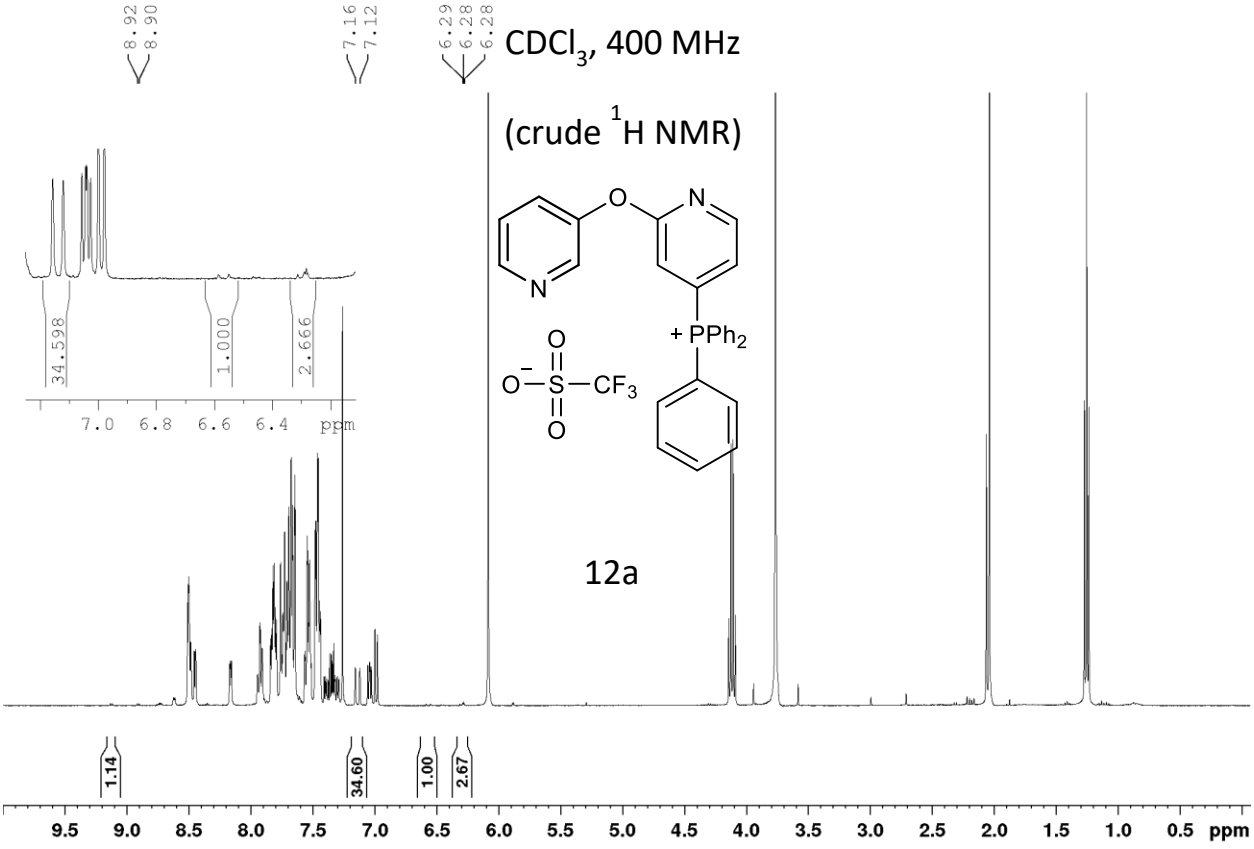
$CDCl_3$, 162 MHz

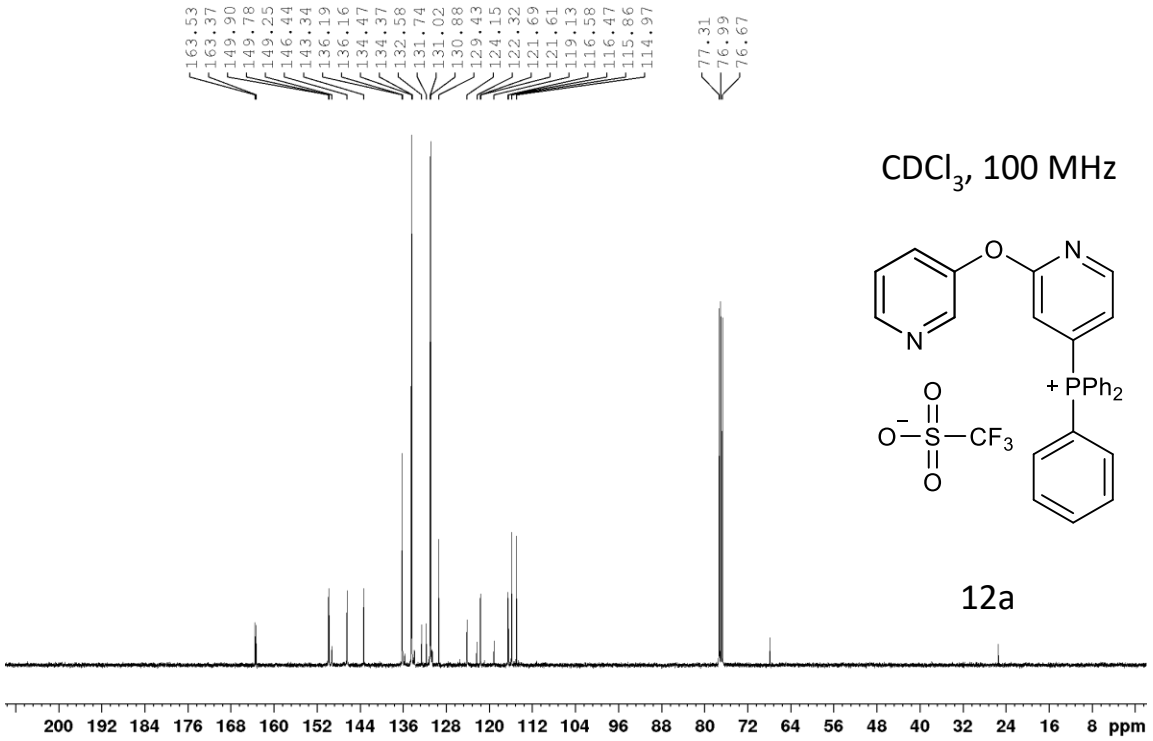
(crude ^{31}P NMR)

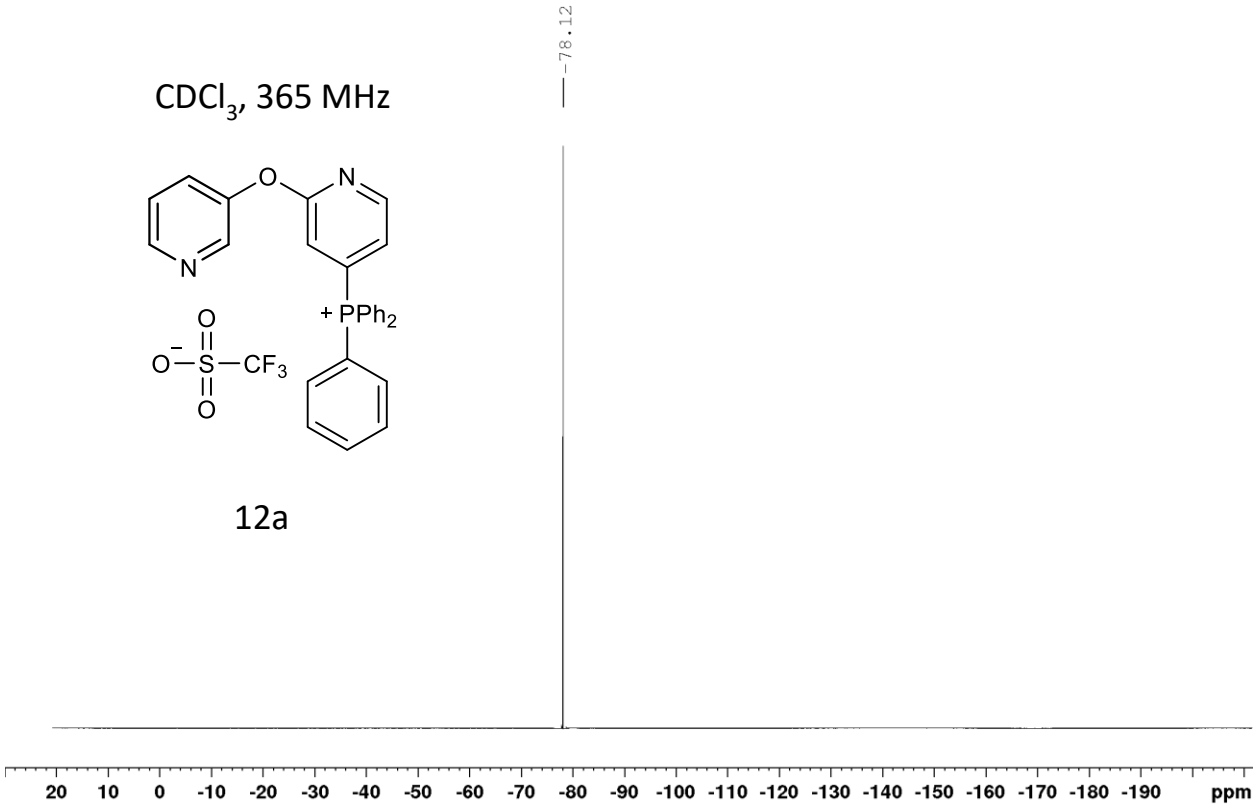


12a

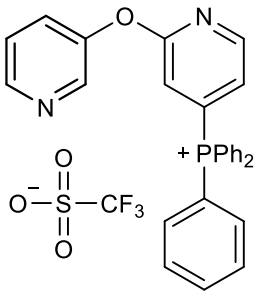

8.47
8.46
7.93
7.92
7.91
7.90
7.83
7.82
7.81
7.79
7.78
7.73
7.71
7.70
7.68
7.66
7.64
7.62
7.38
7.37
7.36
7.35
7.32
7.31
7.29
7.28
7.14
7.10
CDCl3, 400 MHz
12a
2.68
16.00
0.90
0.98
0.93
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


8.92
8.90
7.16
7.12
6.29
6.28
6.28
CDCl3, 400 MHz
(crude 1H NMR)
12a
34.598
1.000
2.666
7.0 6.8 6.6 6.4 ppm
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

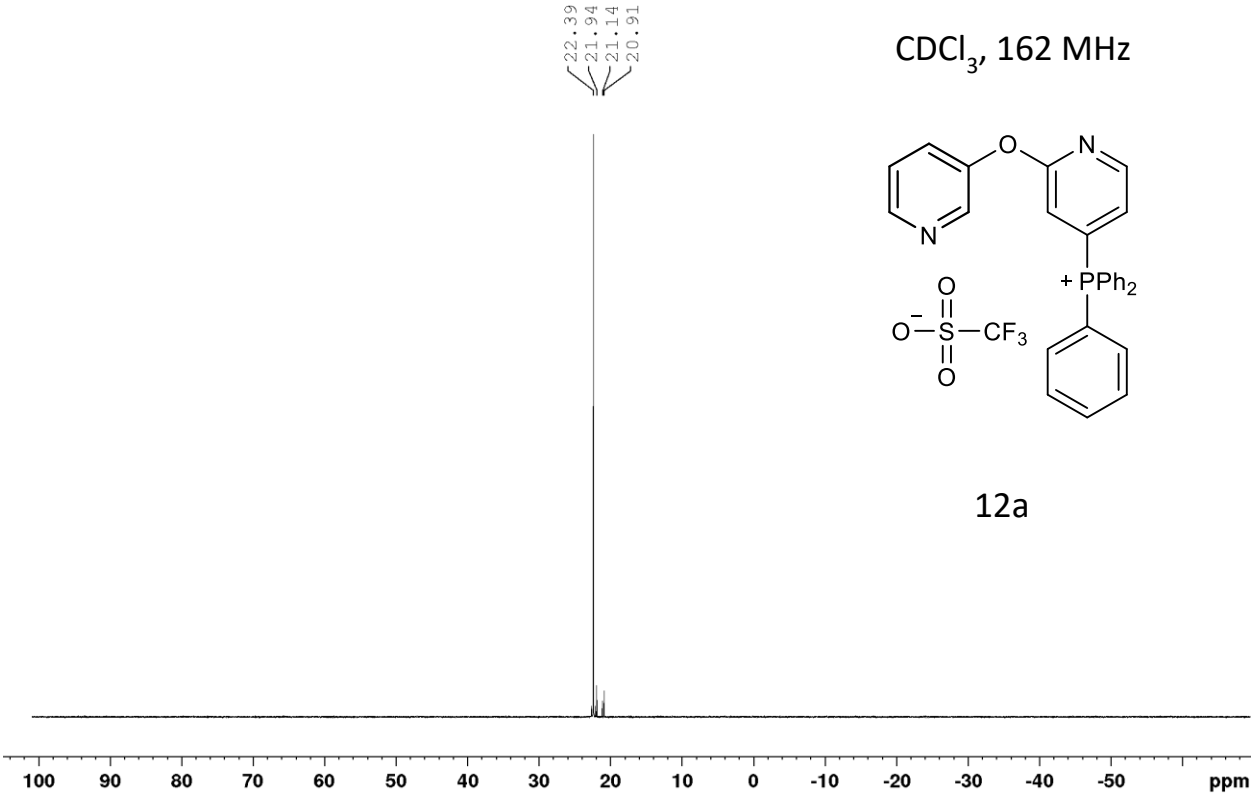

163.53
163.37
149.90
149.78
149.25
146.44
143.34
136.19
136.16
134.47
134.37
132.58
131.74
131.02
130.88
129.43
124.15
122.32
121.69
121.61
119.13
116.58
116.47
115.86
114.97
77.31
76.99
76.67
CDCl3, 100 MHz
12a
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm


-78.12
CDCl3, 365 MHz
12a
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



12a

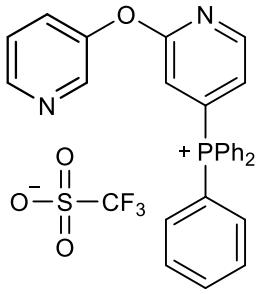


$CDCl_3$, 162 MHz

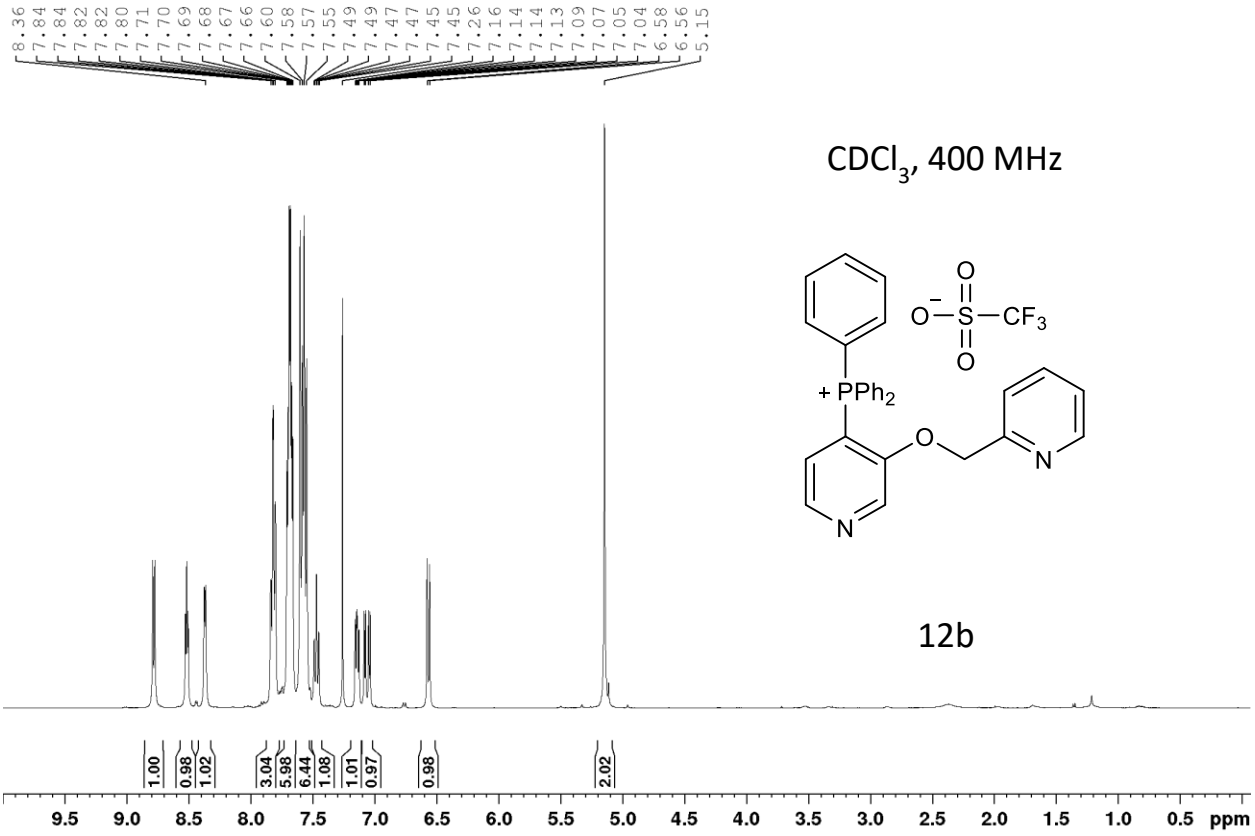
12a

$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

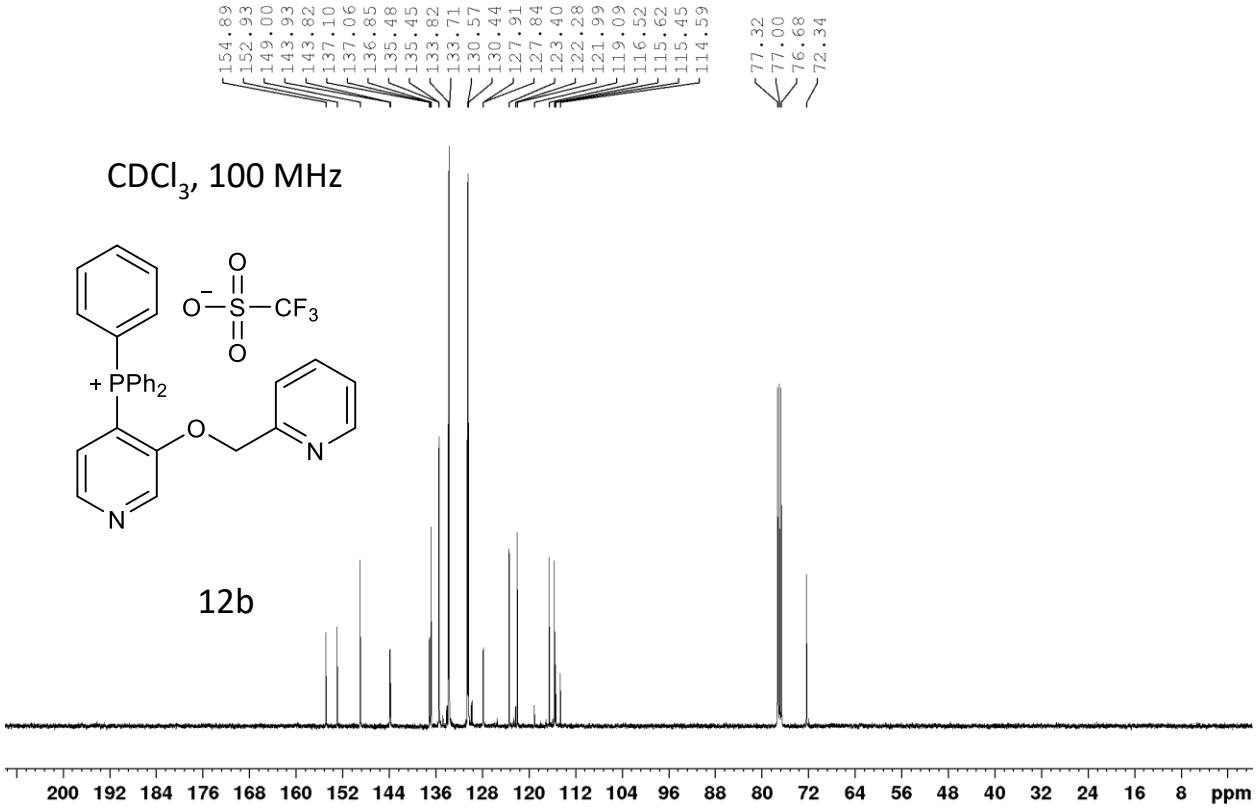


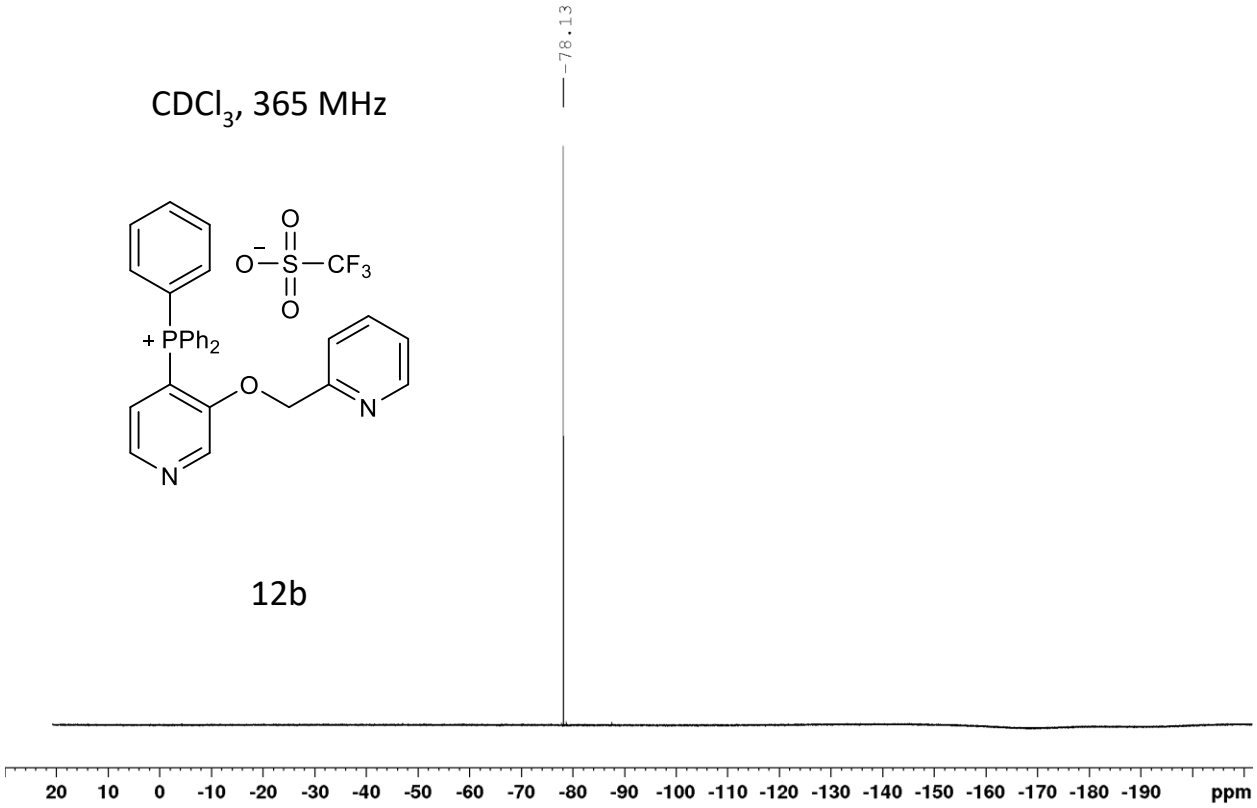
12a

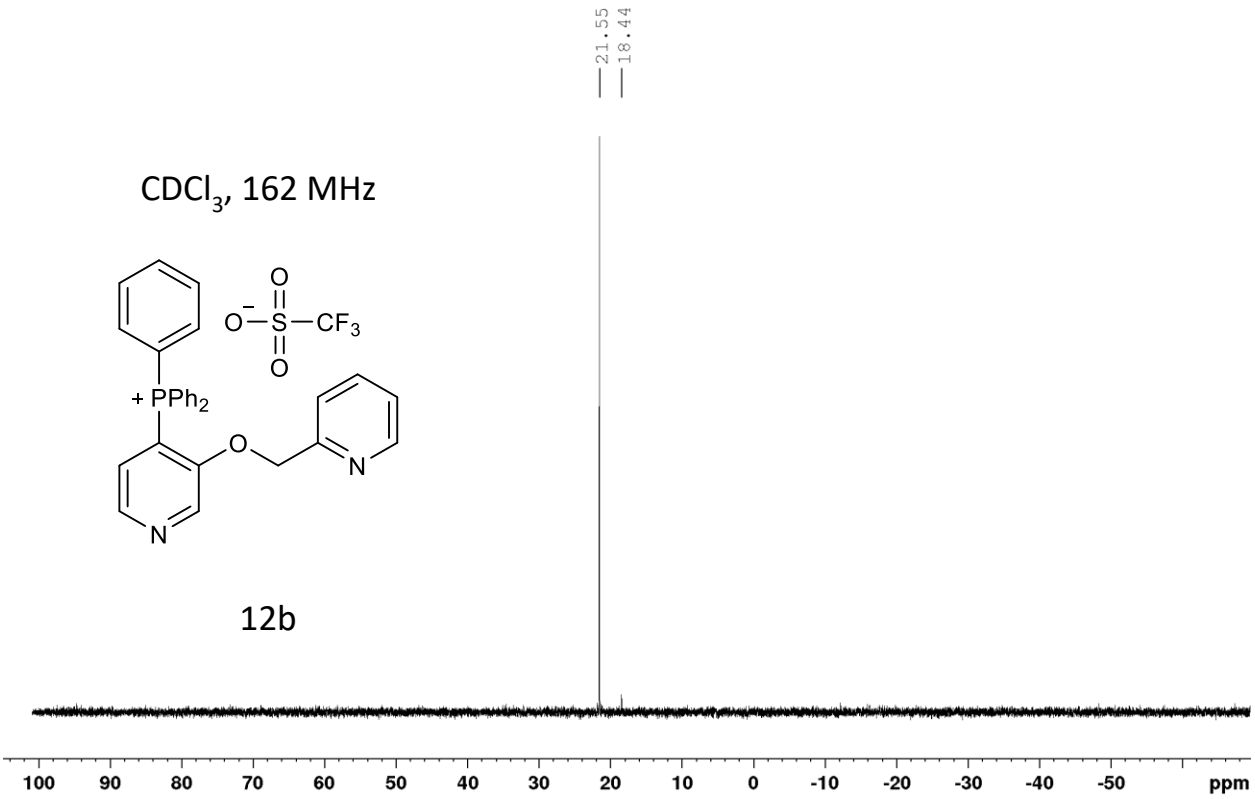


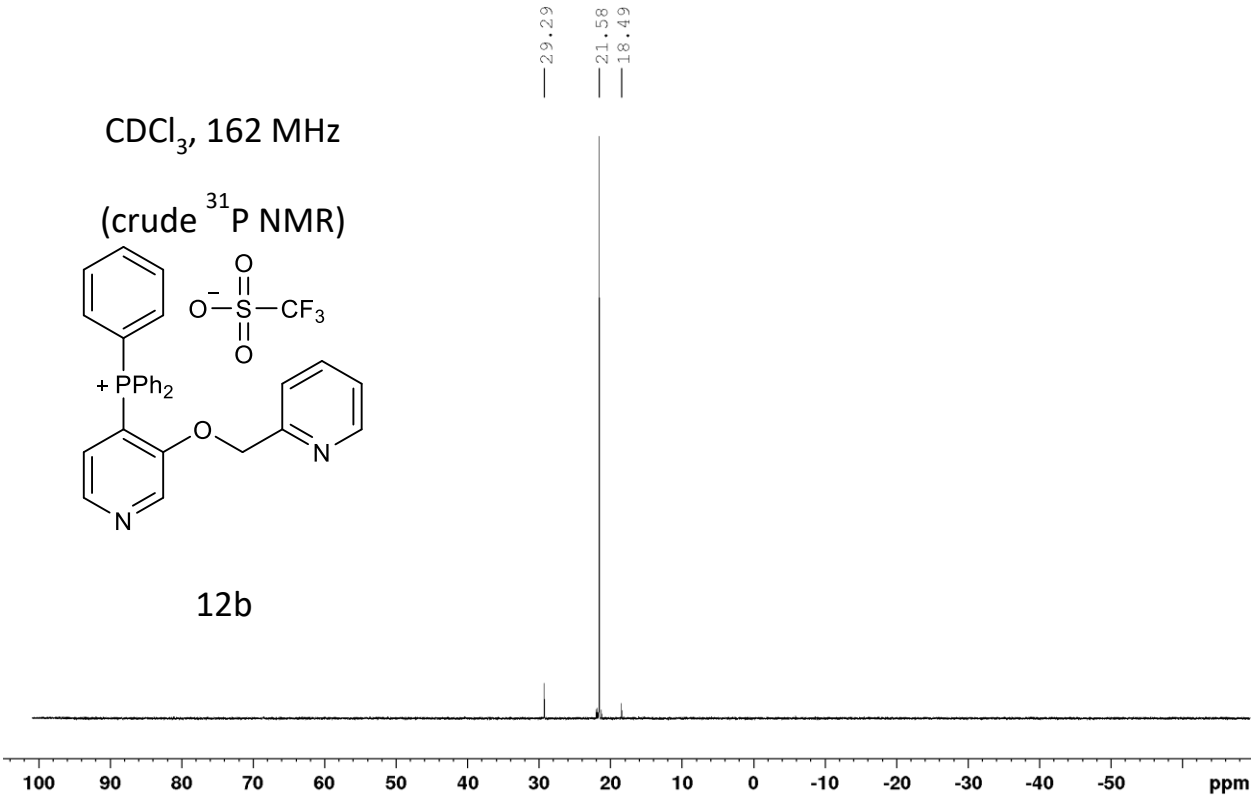
$CDCl_3$, 400 MHz

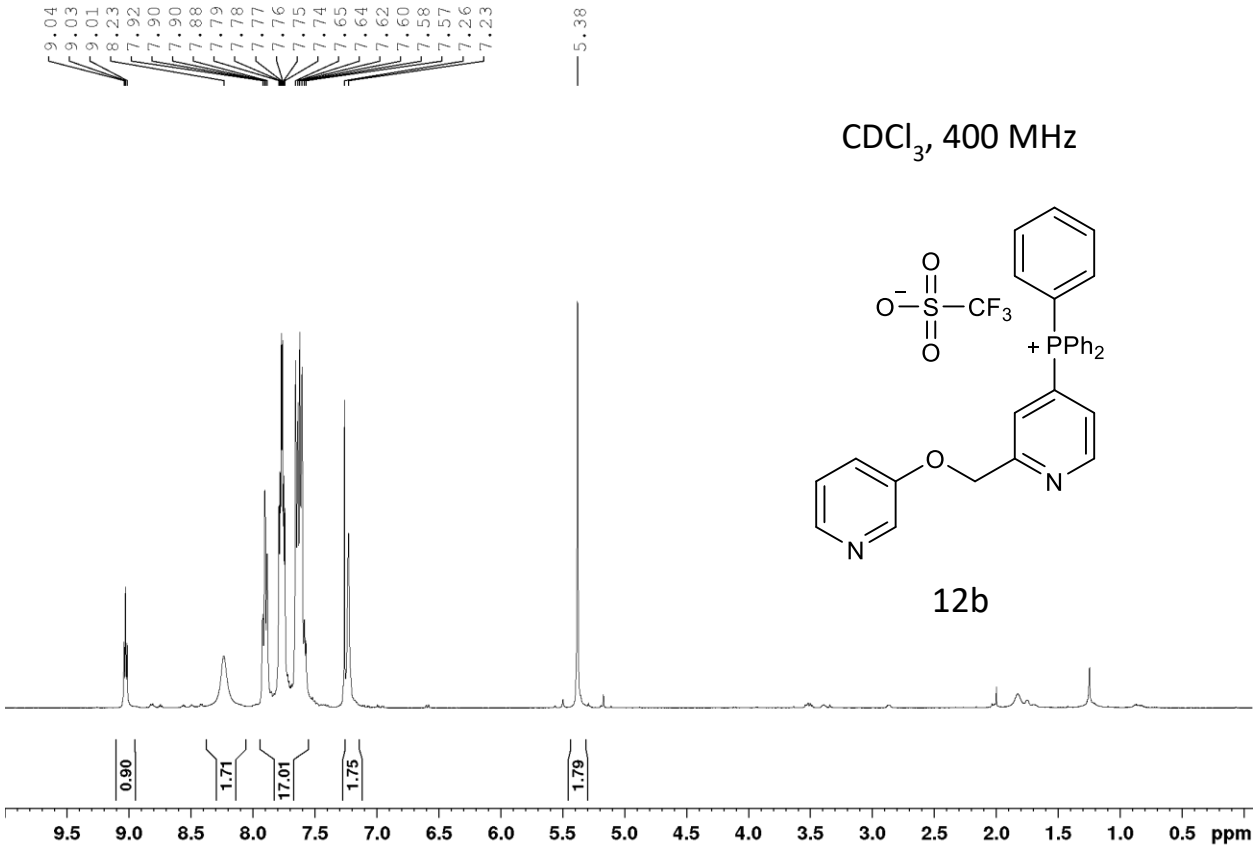
12b

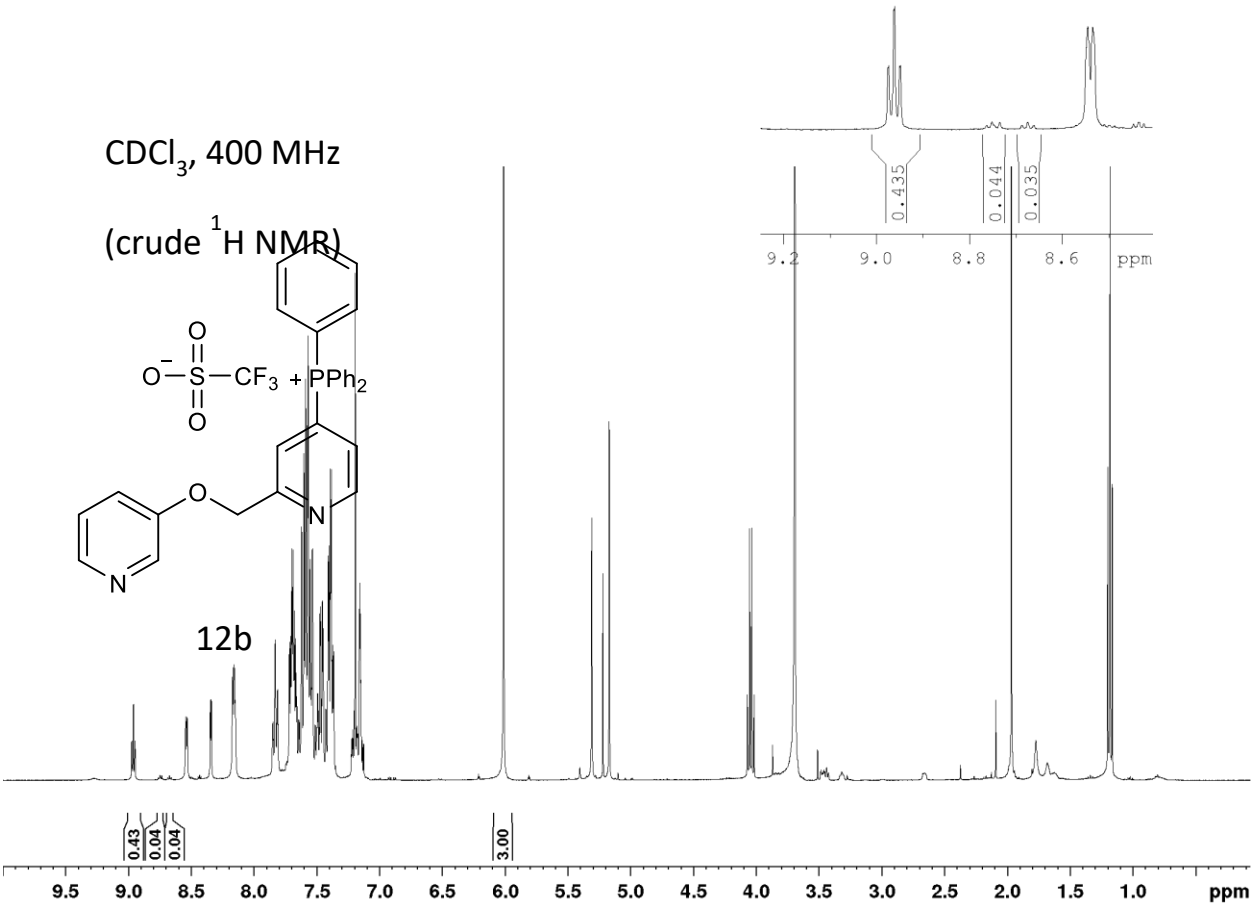

154.89
152.93
149.00
143.93
143.82
137.10
137.06
136.85
135.48
135.45
133.82
133.71
130.57
130.44
127.91
127.84
123.40
122.28
121.99
119.09
116.52
115.62
115.45
114.59
77.32
77.00
76.68
72.34
CDCl3, 100 MHz
+ PPh2
O
S
CF3
N
12b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

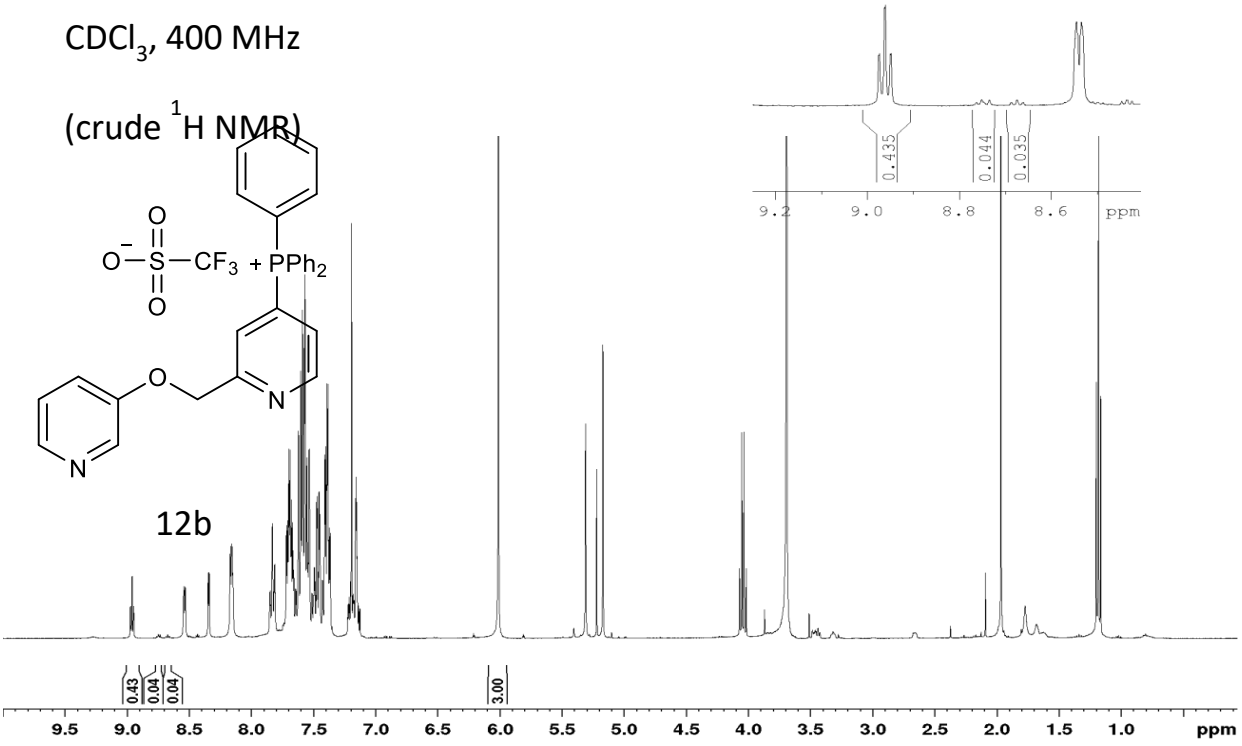

-78.13
CDCl3, 365 MHz
+ PPh2
O
S
CF3
N
12b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

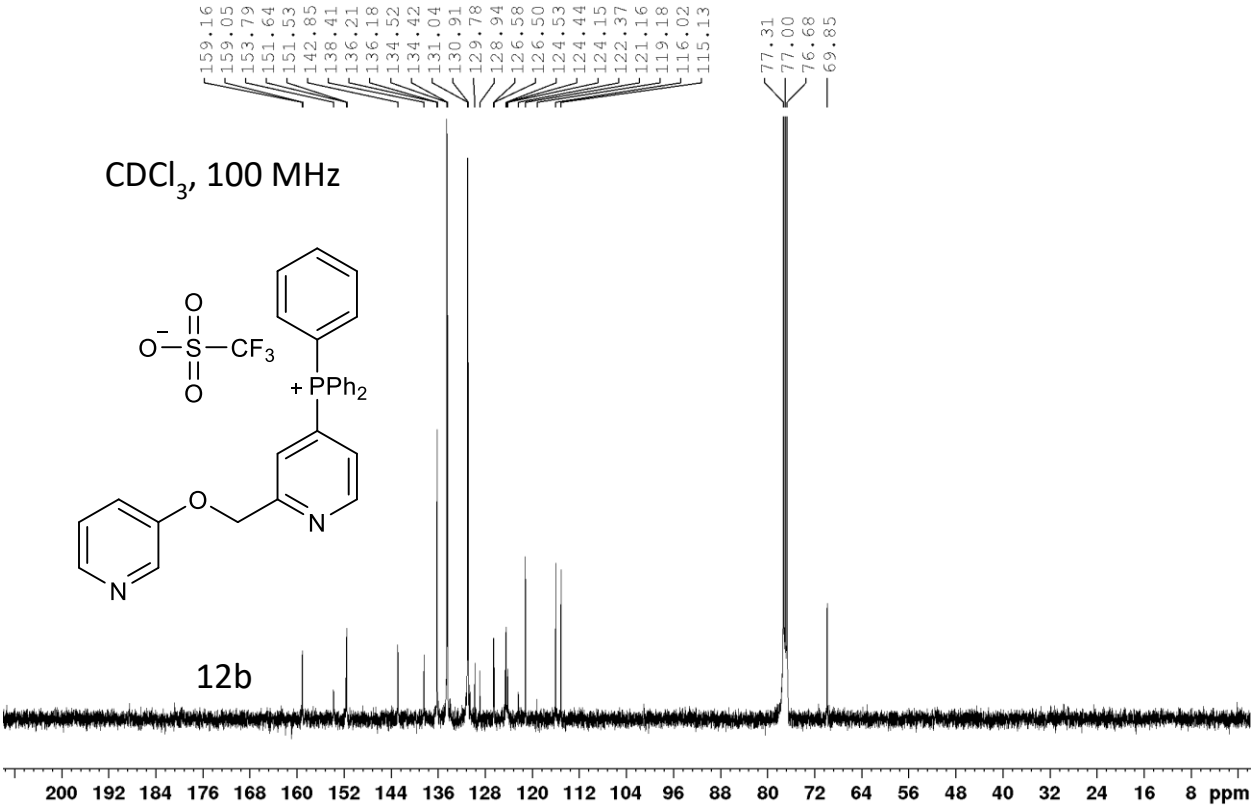

21.55
18.44
CDCl3, 162 MHz
+ PPh2
O
S
CF3
N
12b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

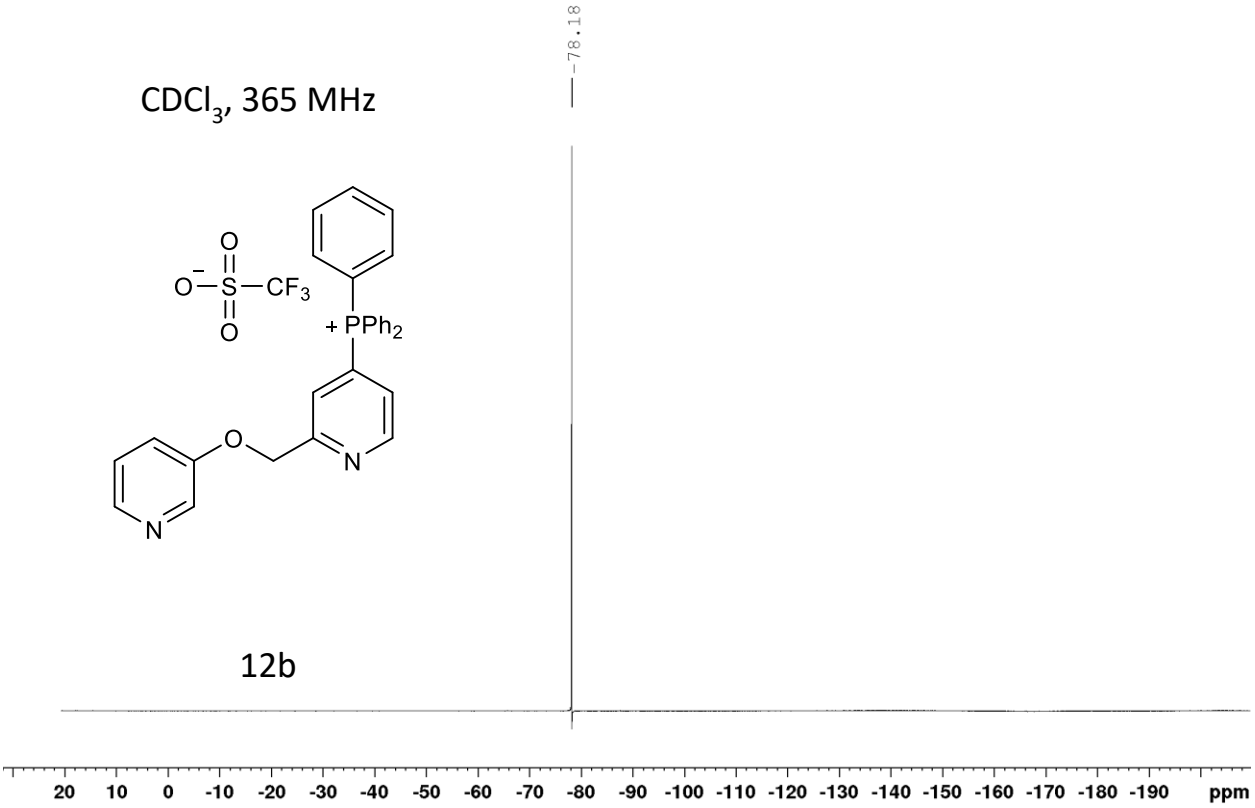

29.29
21.58
18.49
CDCl3, 162 MHz
(crude 31P NMR)
+ PPh2
O
S
CF3
N
12b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

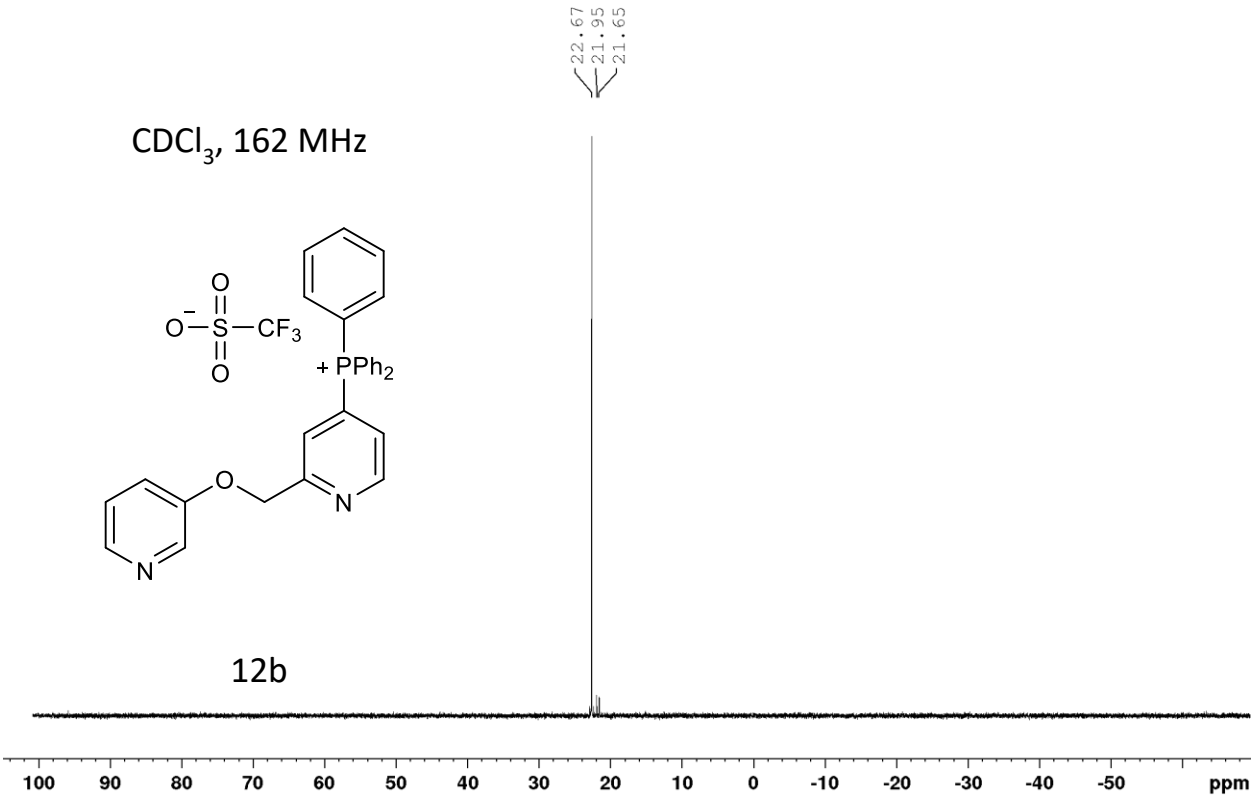

9.04
9.03
9.01
8.23
7.92
7.90
7.90
7.88
7.79
7.78
7.77
7.76
7.75
7.74
7.65
7.64
7.62
7.60
7.58
7.57
7.26
7.23
5.38
CDCl3, 400 MHz
O
O
O
S
CF3
+ PPh2
N
O
N
12b
0.90
1.71
17.01
1.75
1.79
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

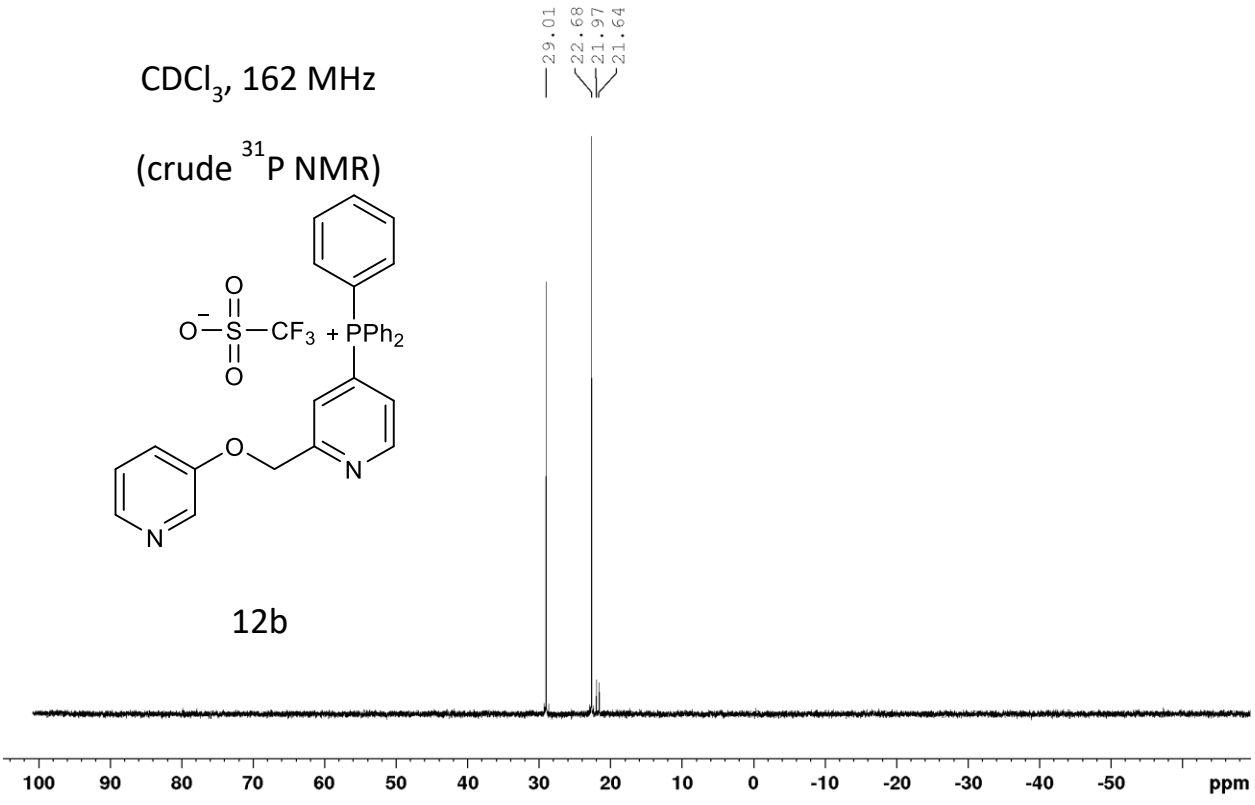

CDCl3, 400 MHz
(crude 1H NMR)
12b
0.435
0.044
0.035
9.2
9.0
8.8
8.6
ppm
0.43
0.04
0.04
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

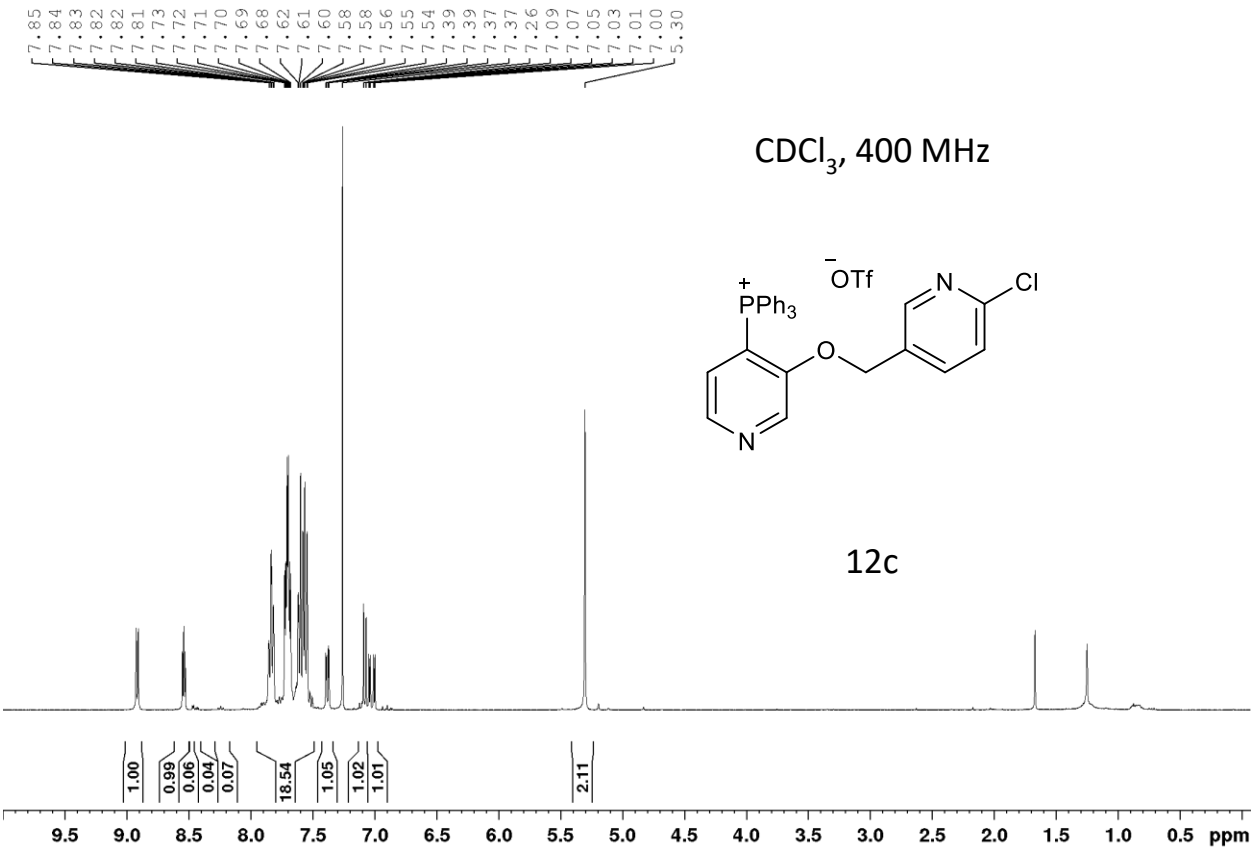

CDCl3, 400 MHz
(crude 1H NMR)
12b
0.435
0.044
0.035
9.2
9.0
8.8
8.6
ppm
0.43
0.04
0.04
3.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

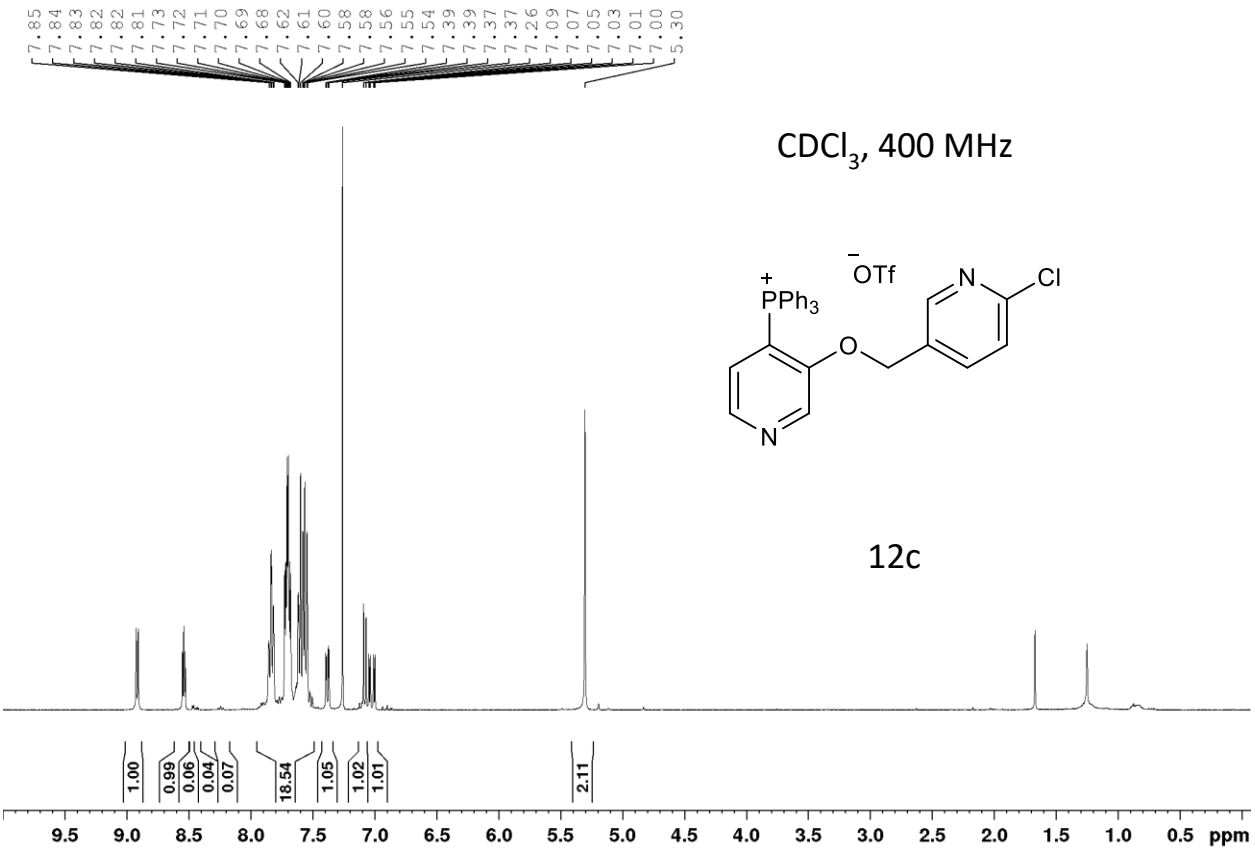

159.16
159.05
153.79
151.64
151.53
142.85
138.41
136.21
136.18
134.52
134.42
131.04
130.91
129.78
128.94
126.58
126.50
124.53
124.44
124.15
122.37
121.16
119.18
116.02
115.13
77.31
77.00
76.68
69.85
CDCl3, 100 MHz
12b
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

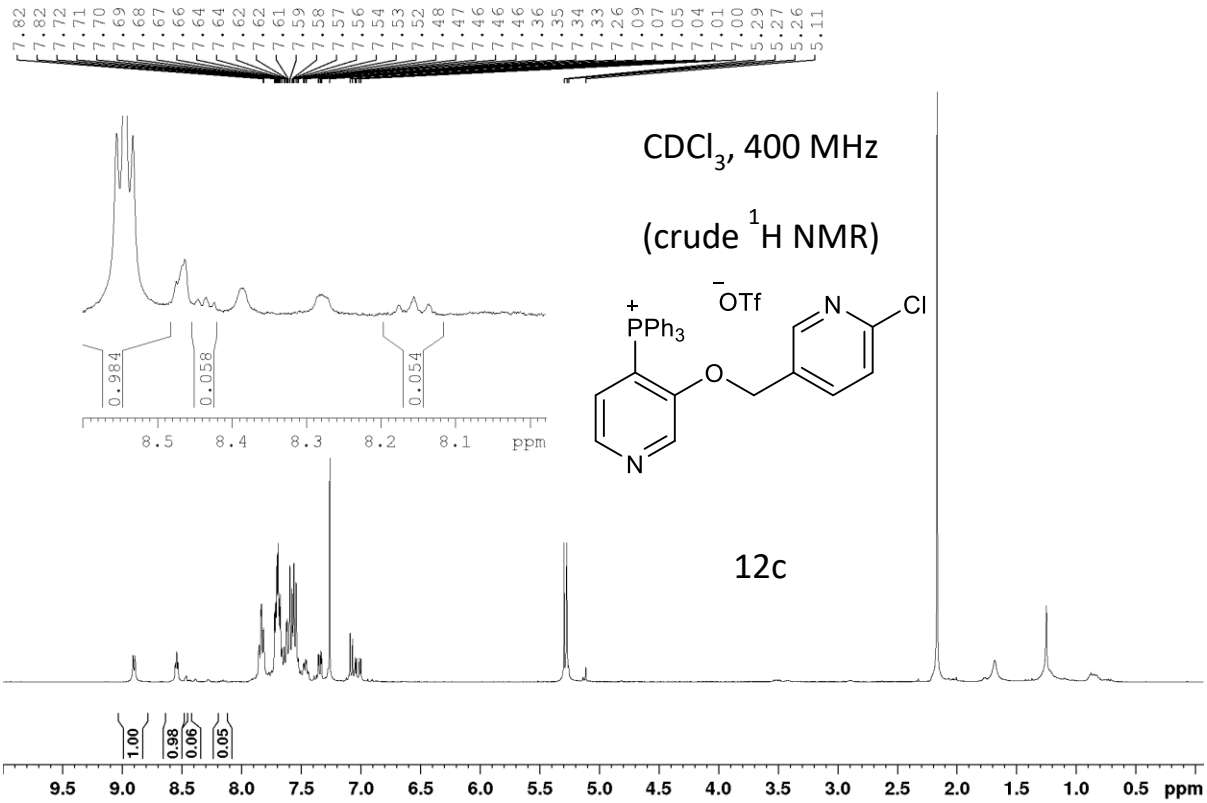

-78.18
CDCl3, 365 MHz
12b
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

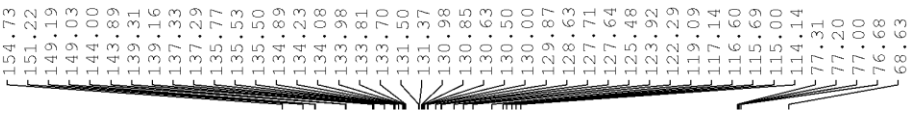

22.67
21.95
21.65
CDCl3, 162 MHz
12b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm


29.01
22.68
21.97
21.64
CDCl3, 162 MHz
(crude 31P NMR)
12b
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

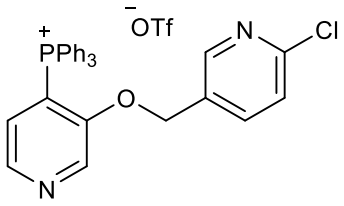

7.85
7.84
7.83
7.82
7.82
7.81
7.73
7.72
7.71
7.70
7.69
7.68
7.62
7.61
7.60
7.58
7.58
7.56
7.55
7.54
7.39
7.39
7.37
7.37
7.26
7.09
7.07
7.05
7.03
7.01
7.00
5.30
CDCl3, 400 MHz
OTf
PPh3
N
Cl
O
N
12c
1.00
0.99
0.06
0.04
0.07
18.54
1.05
1.02
1.01
2.11
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


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
12c
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


7.82
7.82
7.72
7.71
7.70
7.69
7.68
7.67
7.66
7.64
7.64
7.62
7.62
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
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
12c
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

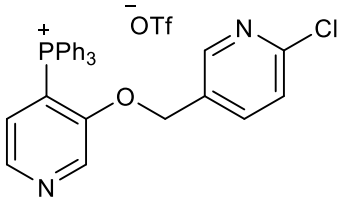


$CDCl_3$, 100 MHz

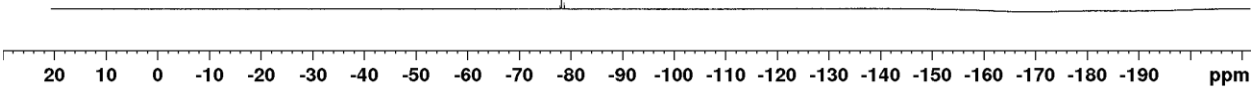


12c

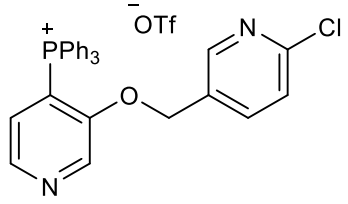
$CDCl_3$, 365 MHz



12c

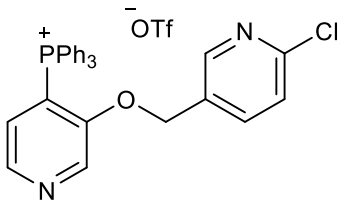


$CDCl_3$, 365 MHz

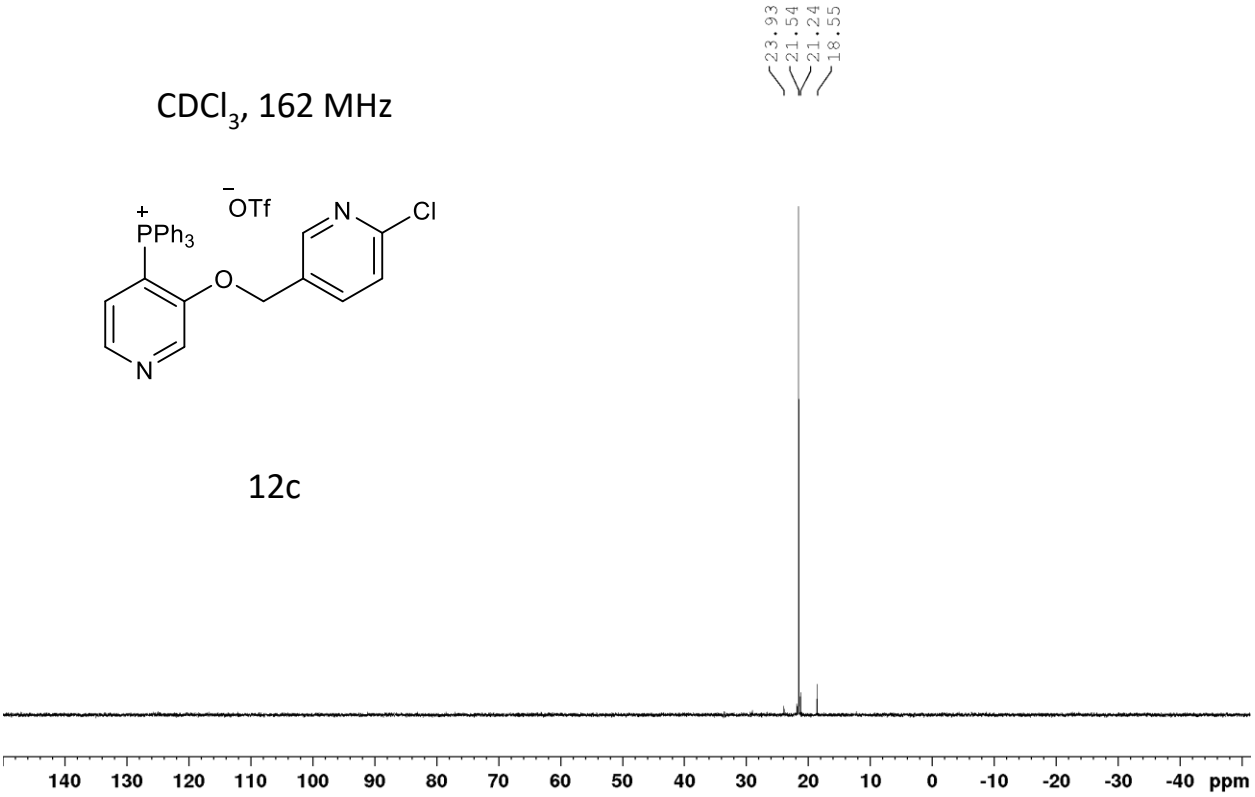


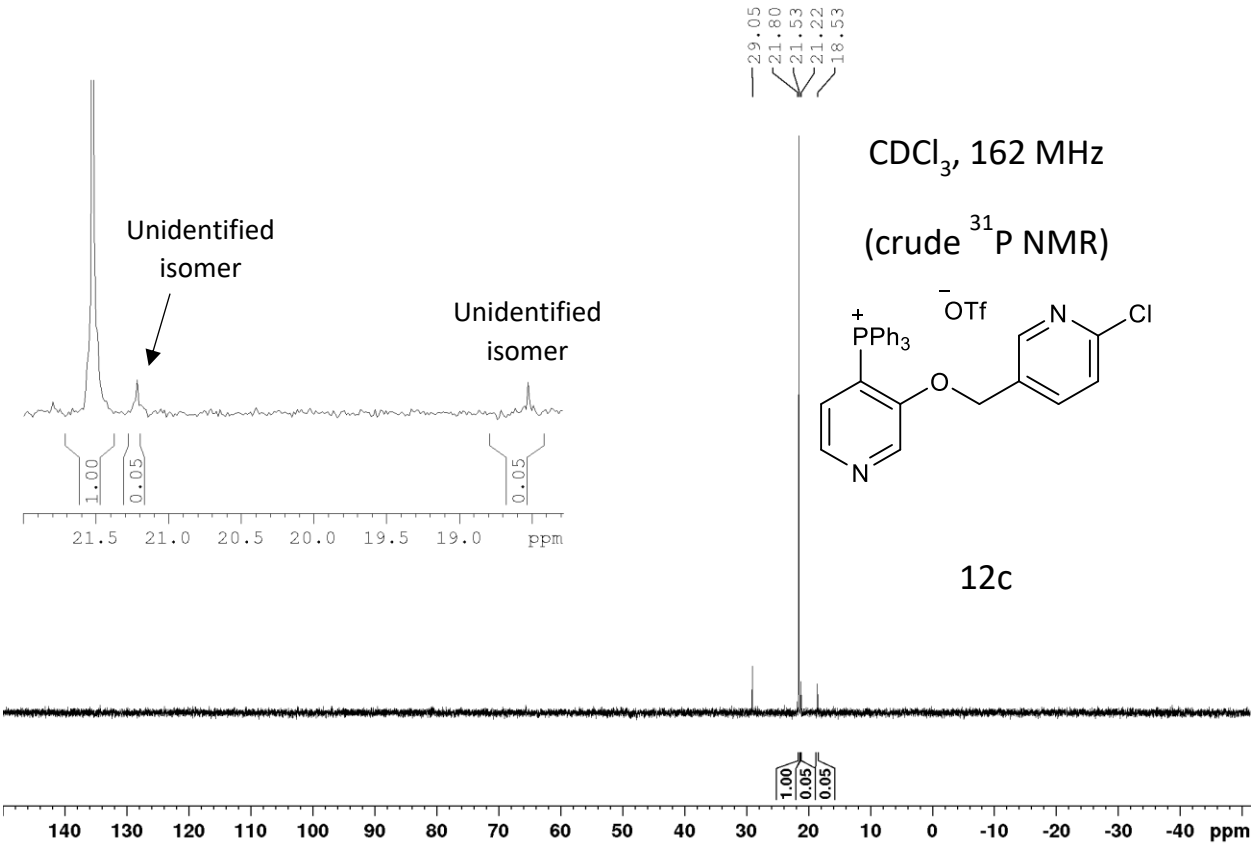
12c

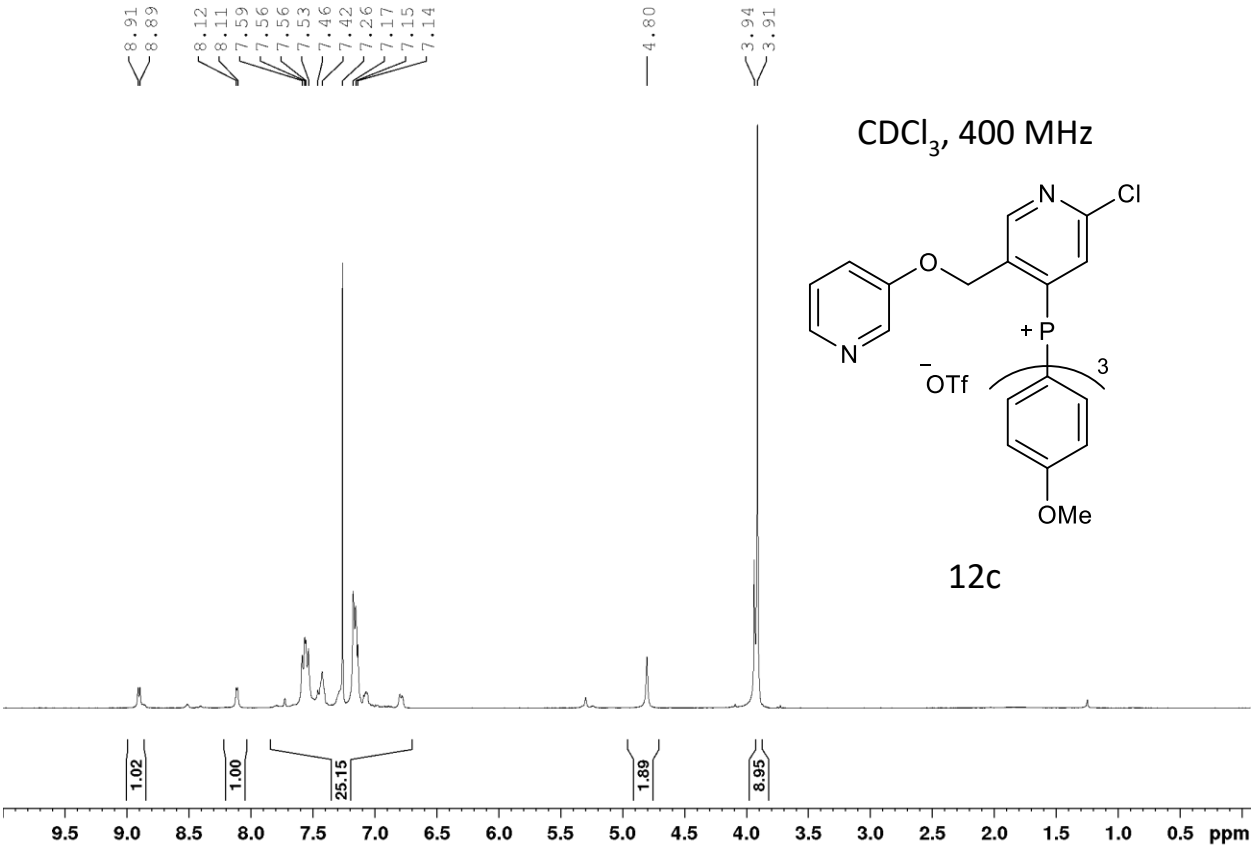
$CDCl_3$, 365 MHz

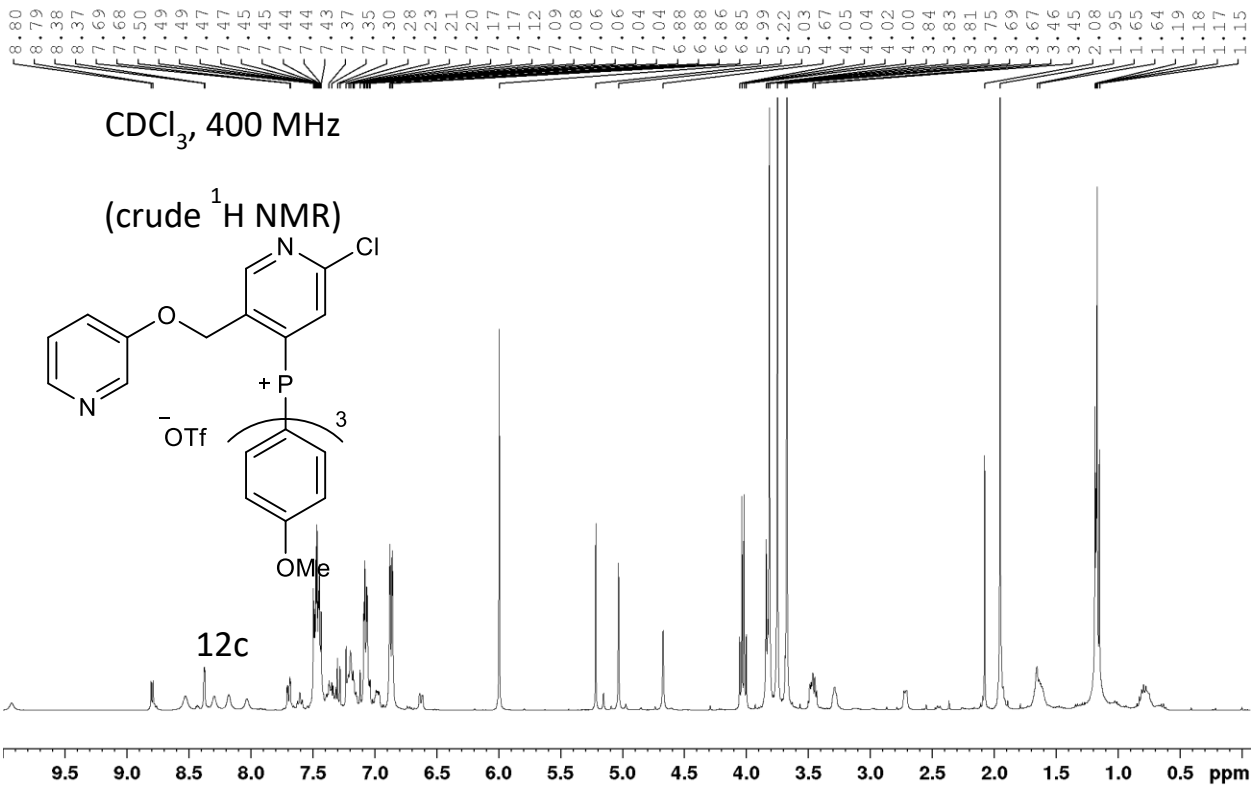


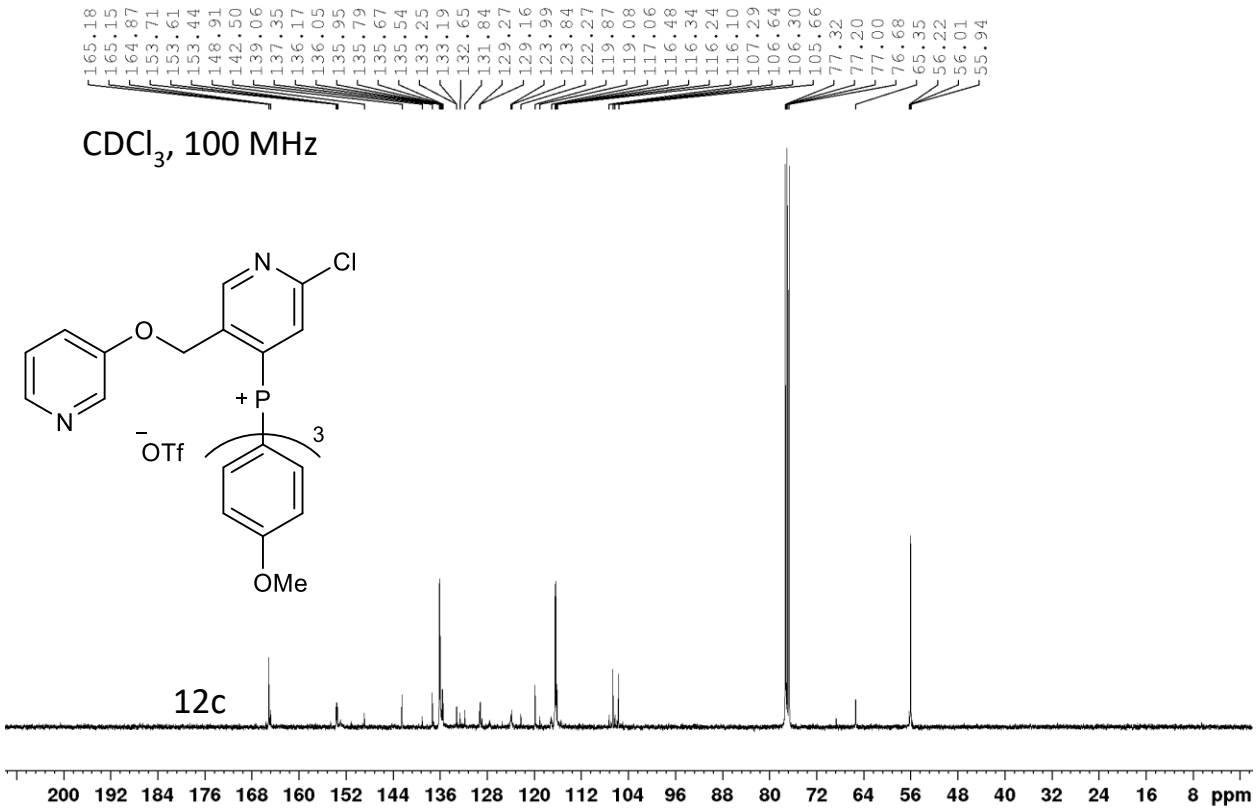
12c

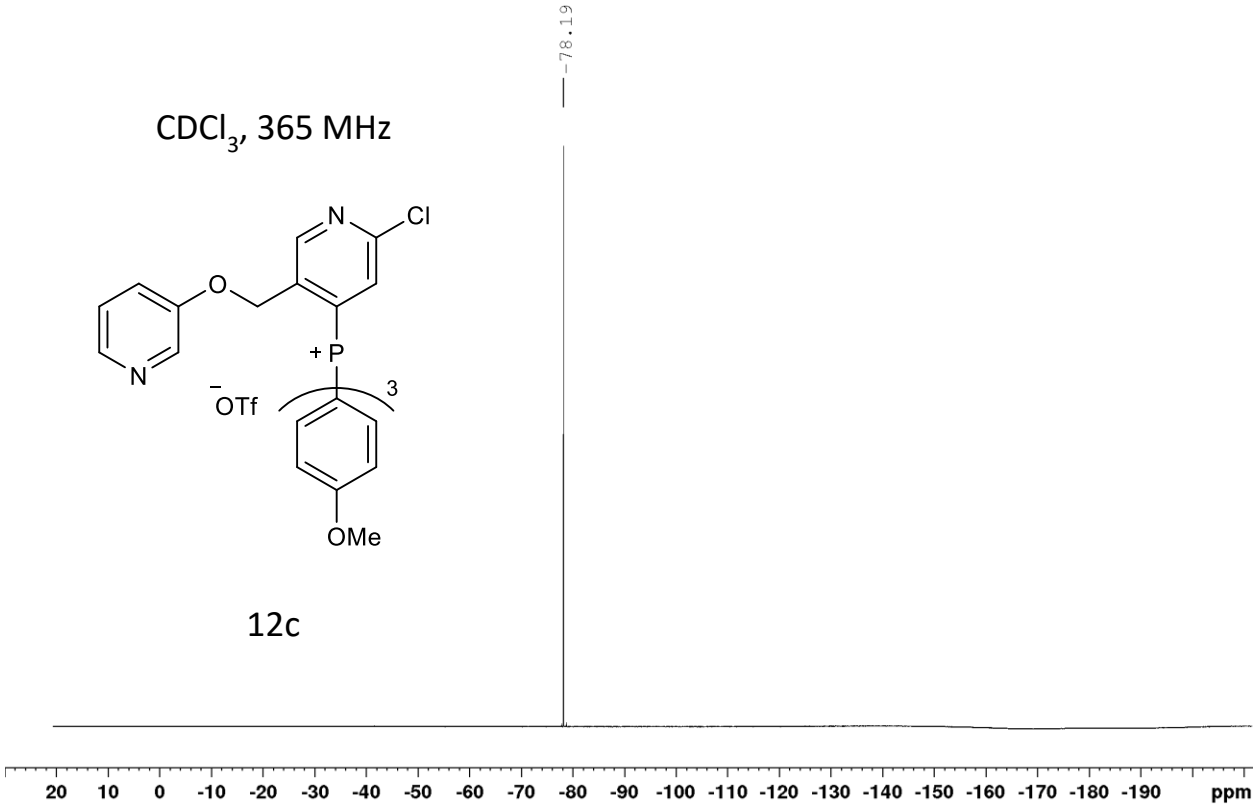

23.93
21.54
21.24
18.55
CDCl3, 162 MHz
+
PPh3
OTf
N
Cl
O
N
12c
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


29.05
21.80
21.53
21.22
18.53
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
12c
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

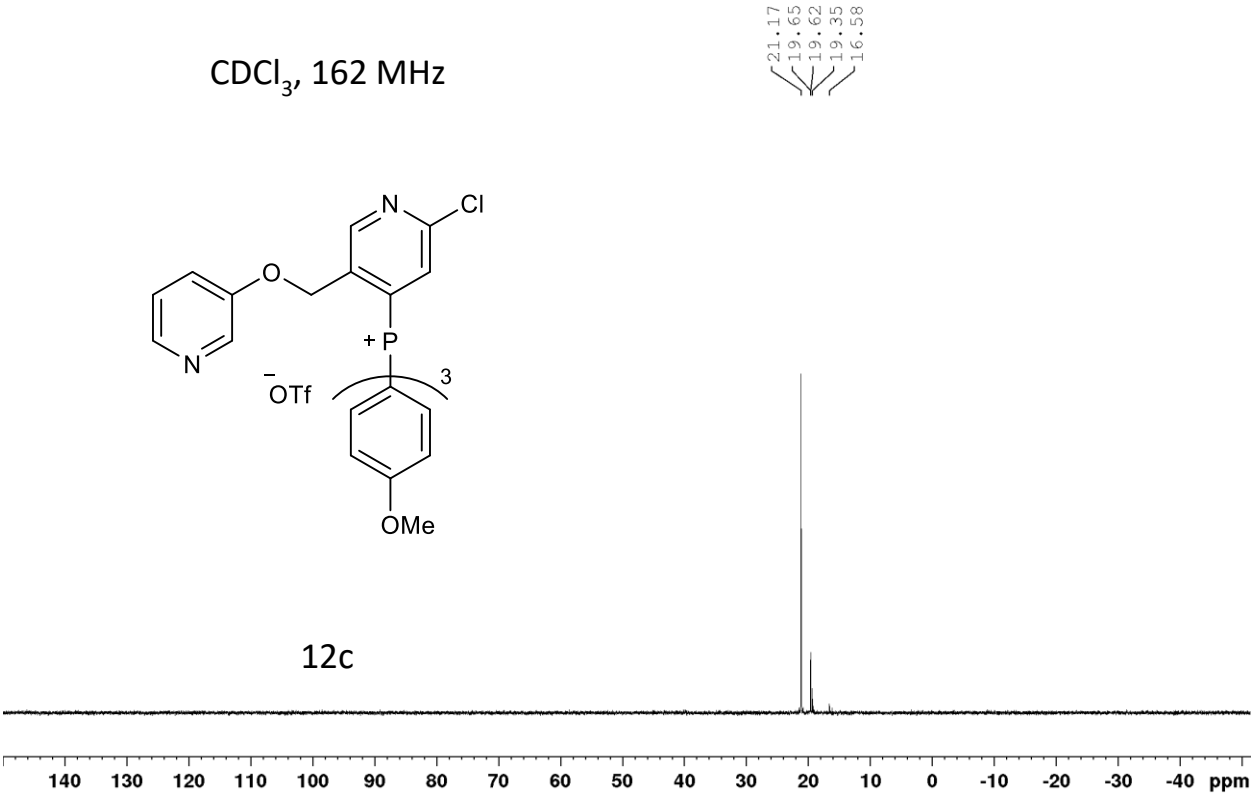

8.91
8.89
8.12
8.11
7.59
7.56
7.56
7.53
7.46
7.42
7.26
7.17
7.15
7.14
4.80
3.94
3.91
CDCl3, 400 MHz
N
Cl
O
N
+ P
OTf
3
OMe
12c
1.02
1.00
25.15
1.89
8.95
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


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
12c
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

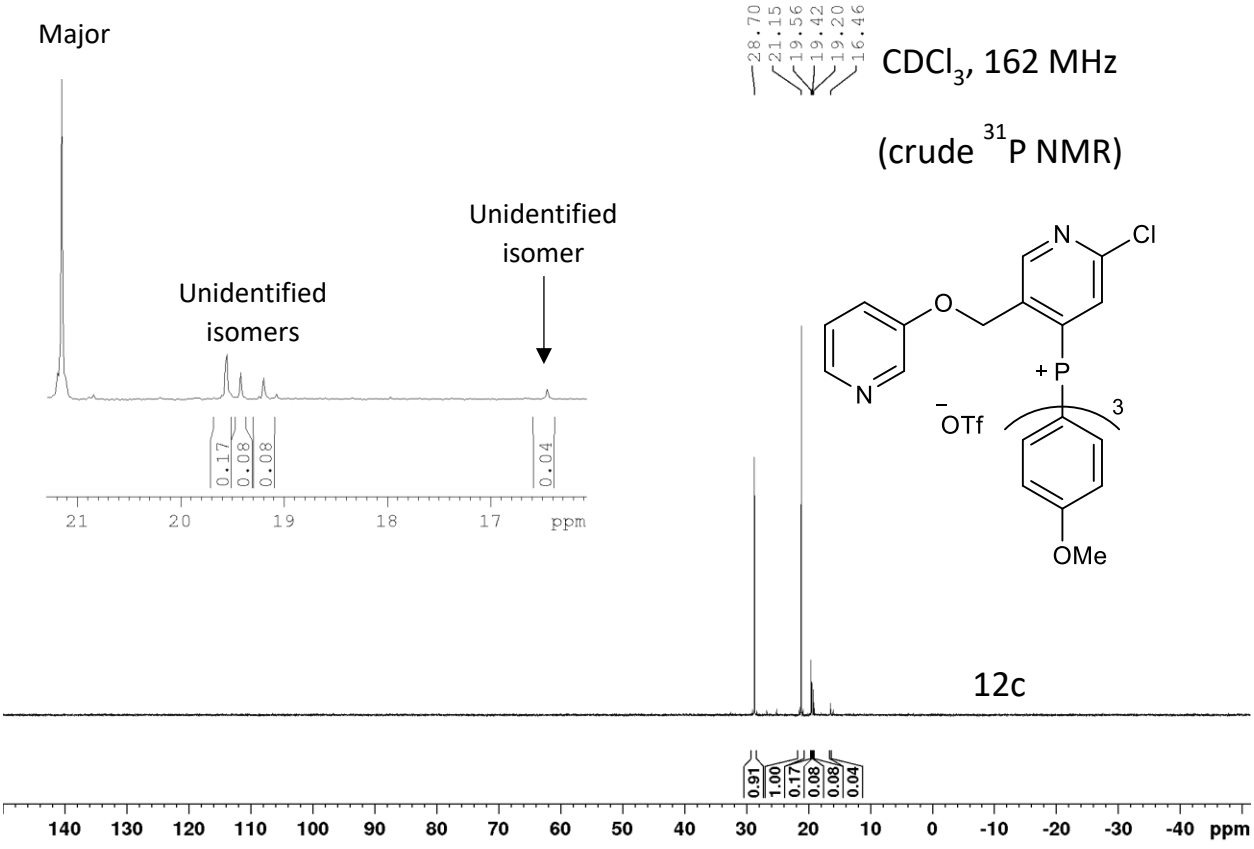

165.18
165.15
164.87
153.71
153.61
153.44
148.91
142.50
139.06
137.35
136.17
136.05
135.95
135.79
135.67
135.54
133.25
133.19
132.65
131.84
129.27
129.16
123.99
123.84
122.27
119.87
119.08
117.06
116.48
116.34
116.24
116.10
107.29
106.64
106.30
105.66
77.32
77.20
77.00
76.68
65.35
56.22
56.01
55.94
CDCl3, 100 MHz
N
Cl
O
N
+ P
3
OTf
OMe
12c
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

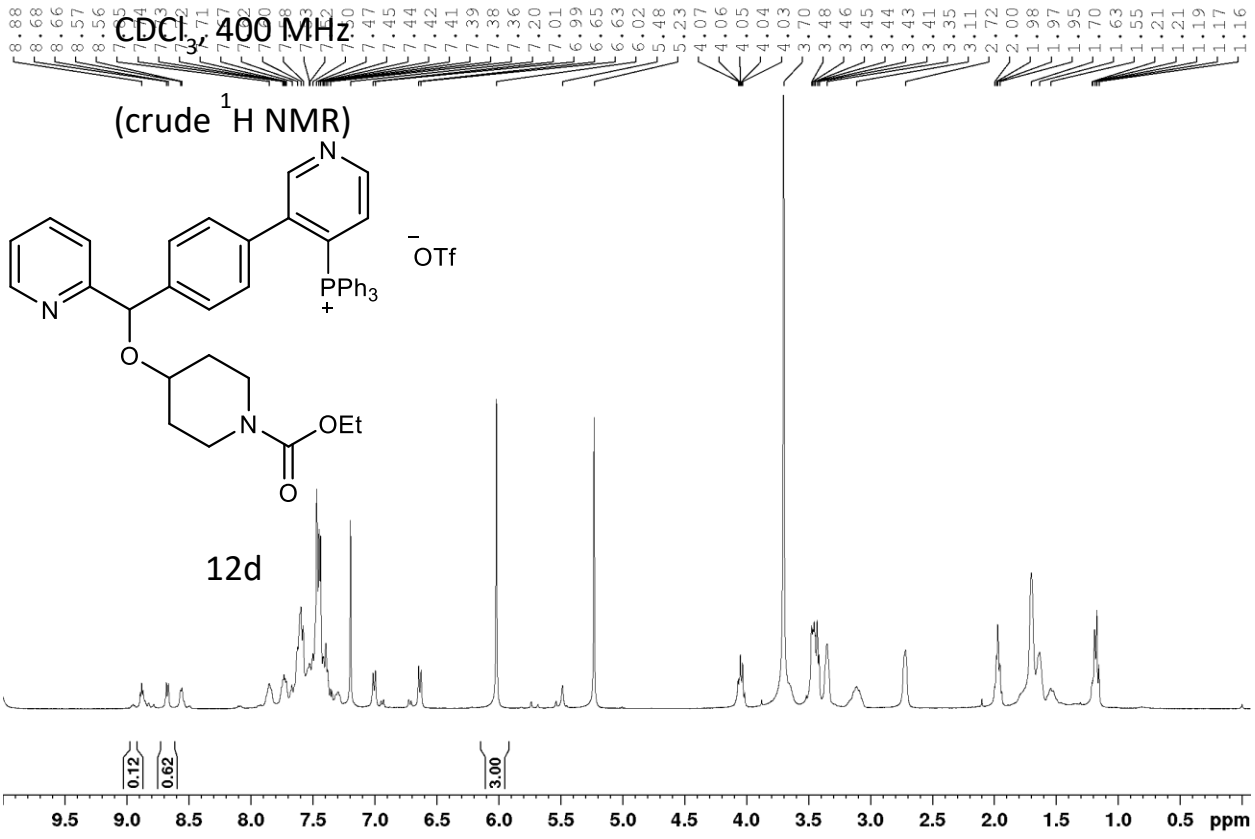

-78.19
CDCl3, 365 MHz
N
Cl
O
N
+ P
3
OTf
OMe
12c
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

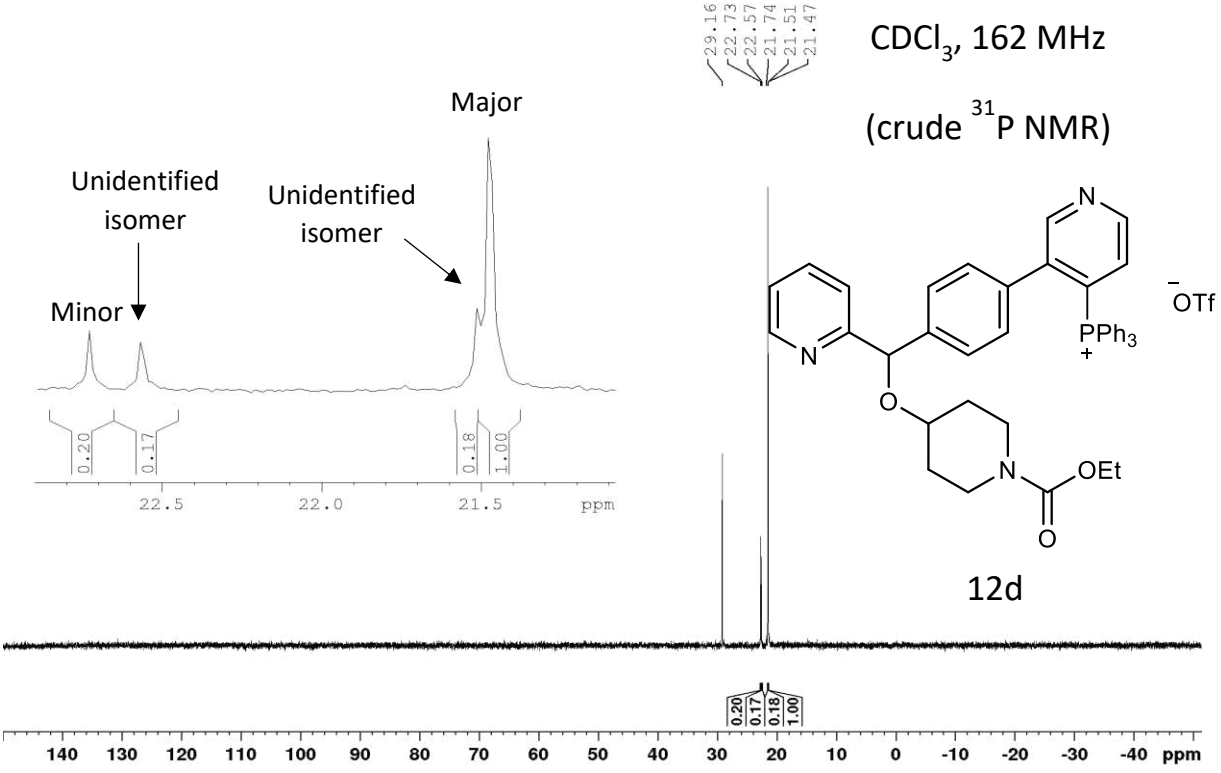
$CDCl_3$, 162 MHz

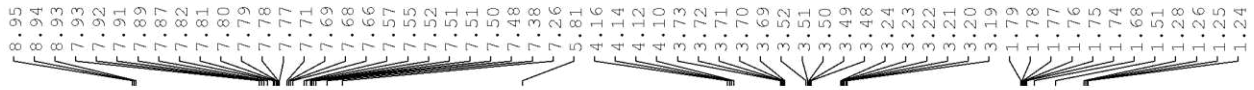


Major

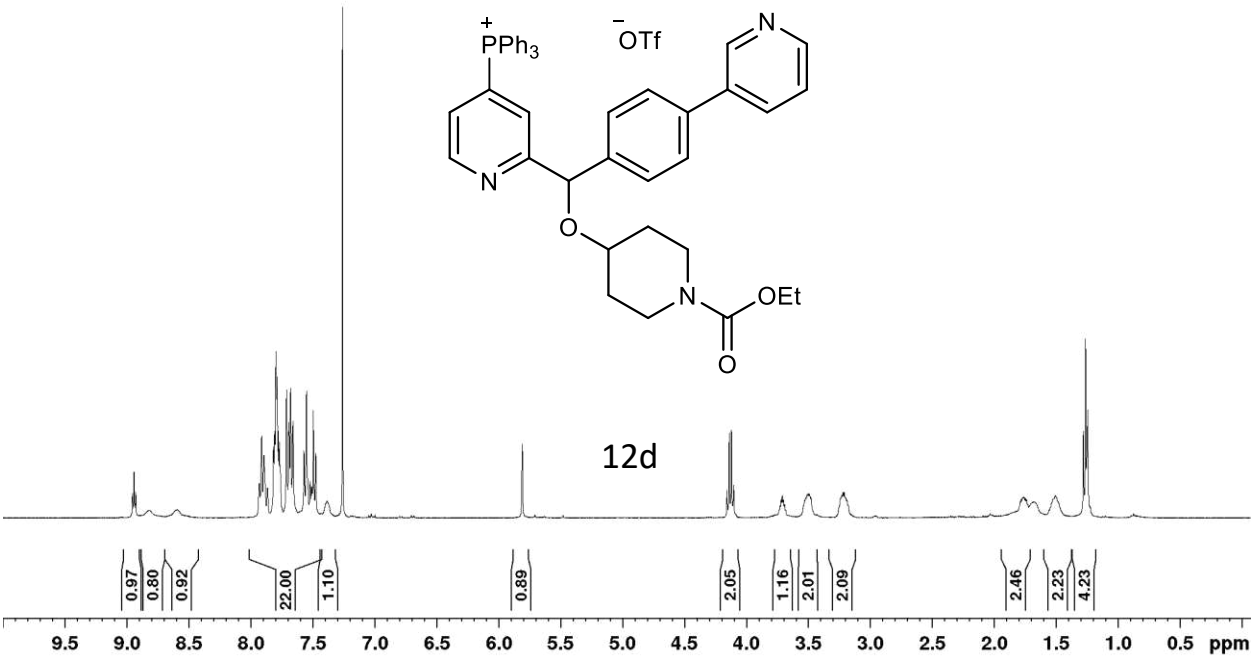


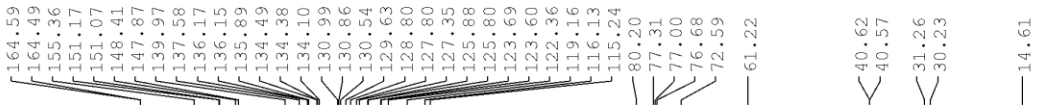

CDCl3, 400 MHz
(crude 1H NMR)
OTf
PPh3
OEt
12d
0.12
0.62
3.00
ppm


CDCl3, 162 MHz
(crude 31P NMR)
Major
Unidentified isomer
Unidentified isomer
Minor
OTf
PPh3
OEt
12d
0.20
0.17
0.18
1.00
ppm

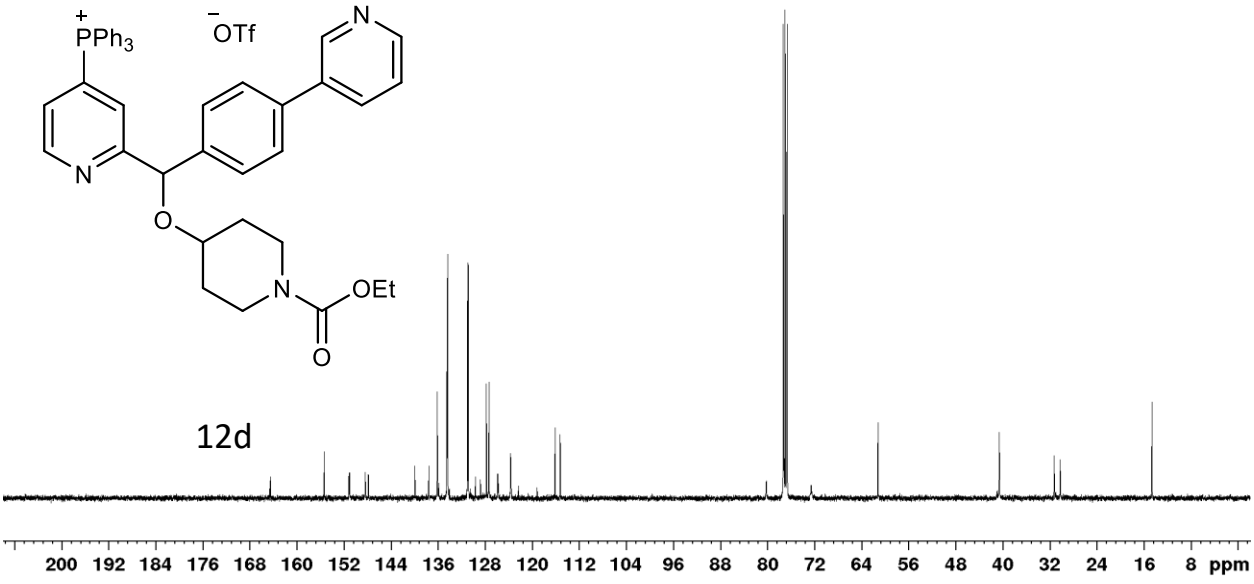


$CDCl_3$, 400 MHz

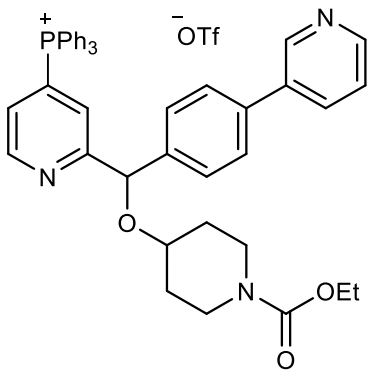




$CDCl_3$, 100 MHz

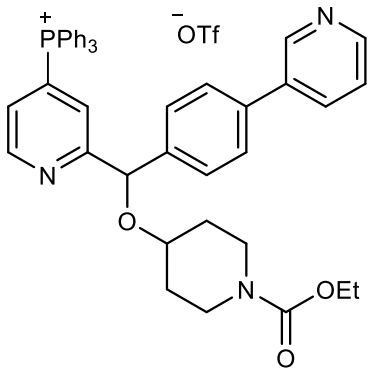


$CDCl_3$, 365 MHz



12d

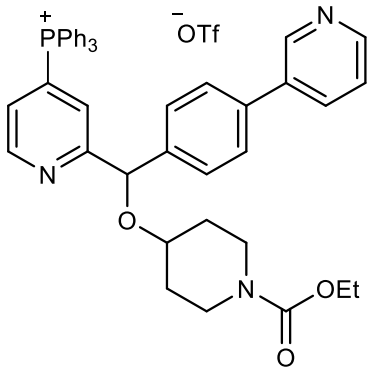
$CDCl_3$, 162 MHz



12d

$CDCl_3$, 162 MHz

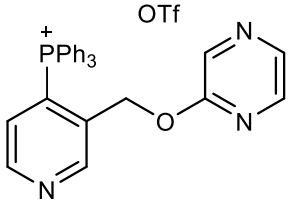
(crude ^{31}P NMR)



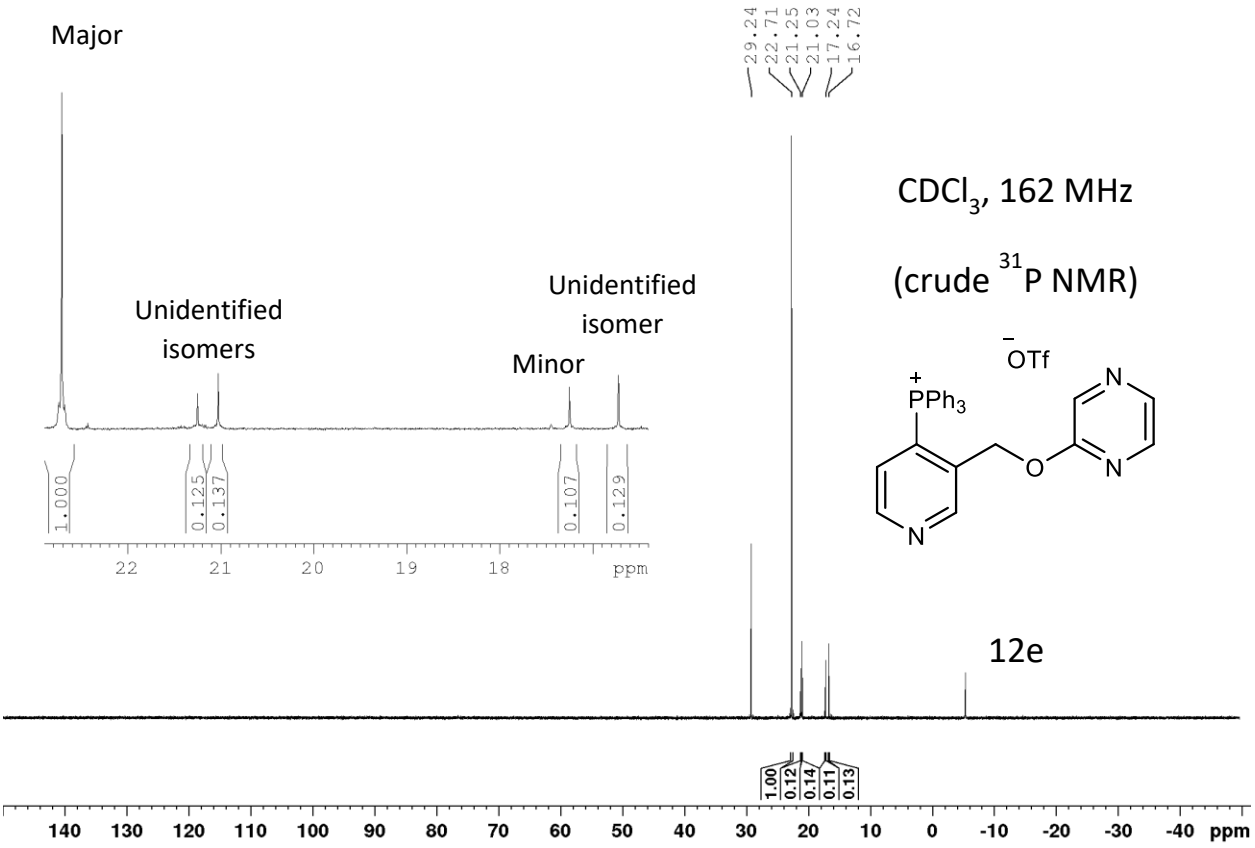
12d

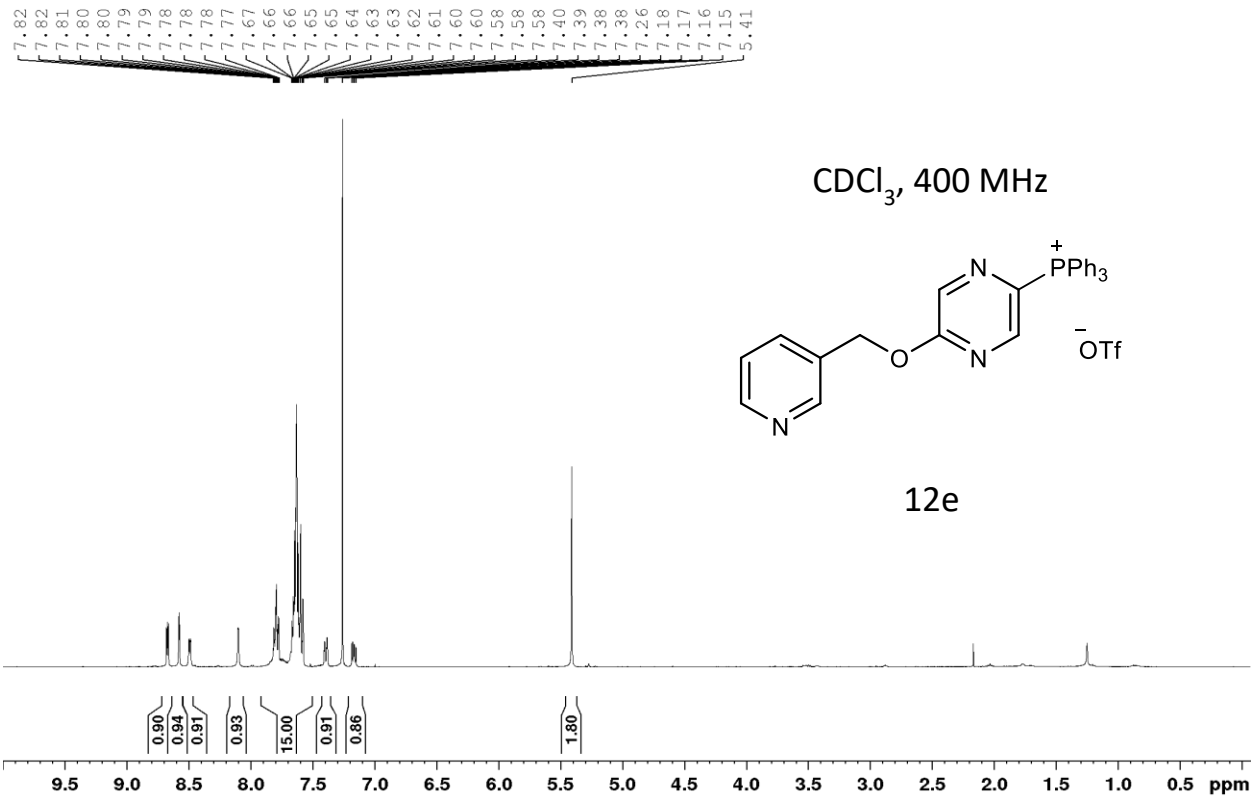
$CDCl_3$, 400 MHz

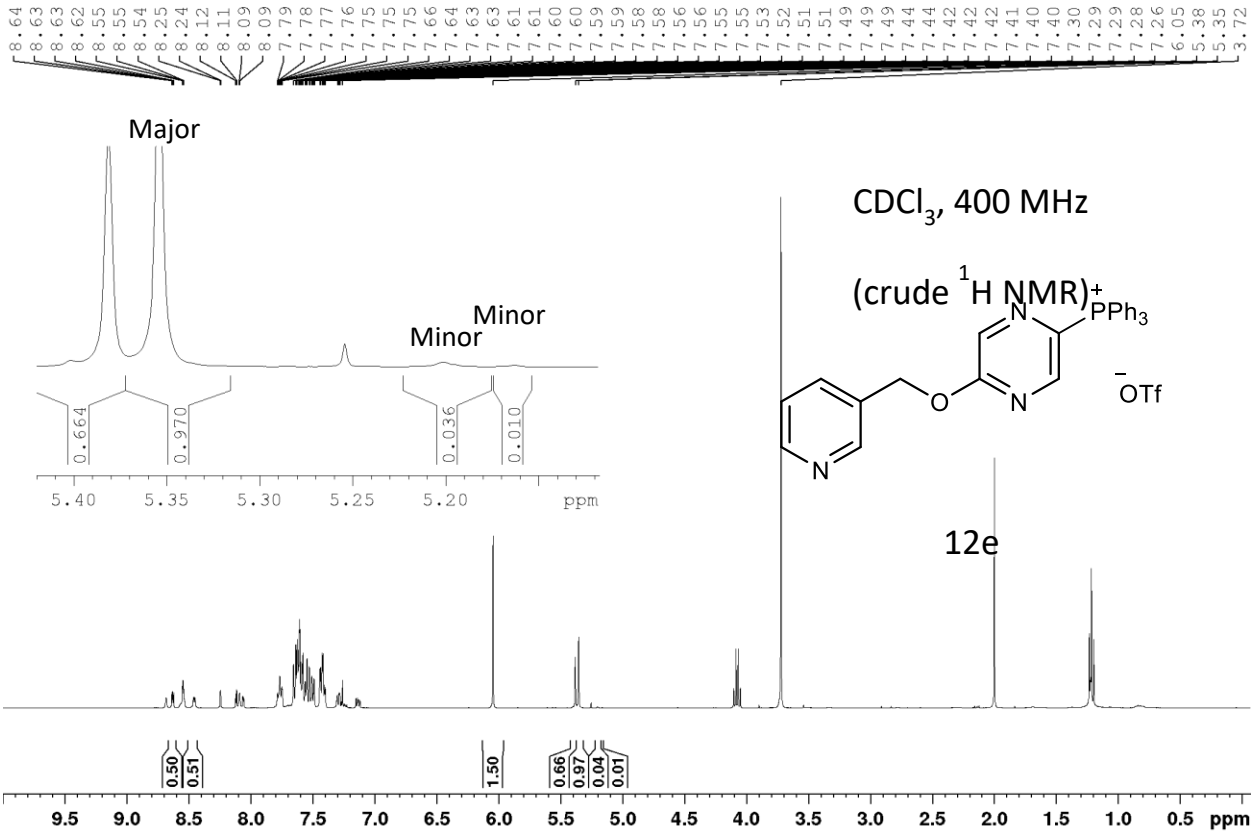
(crude ^{1}H NMR)

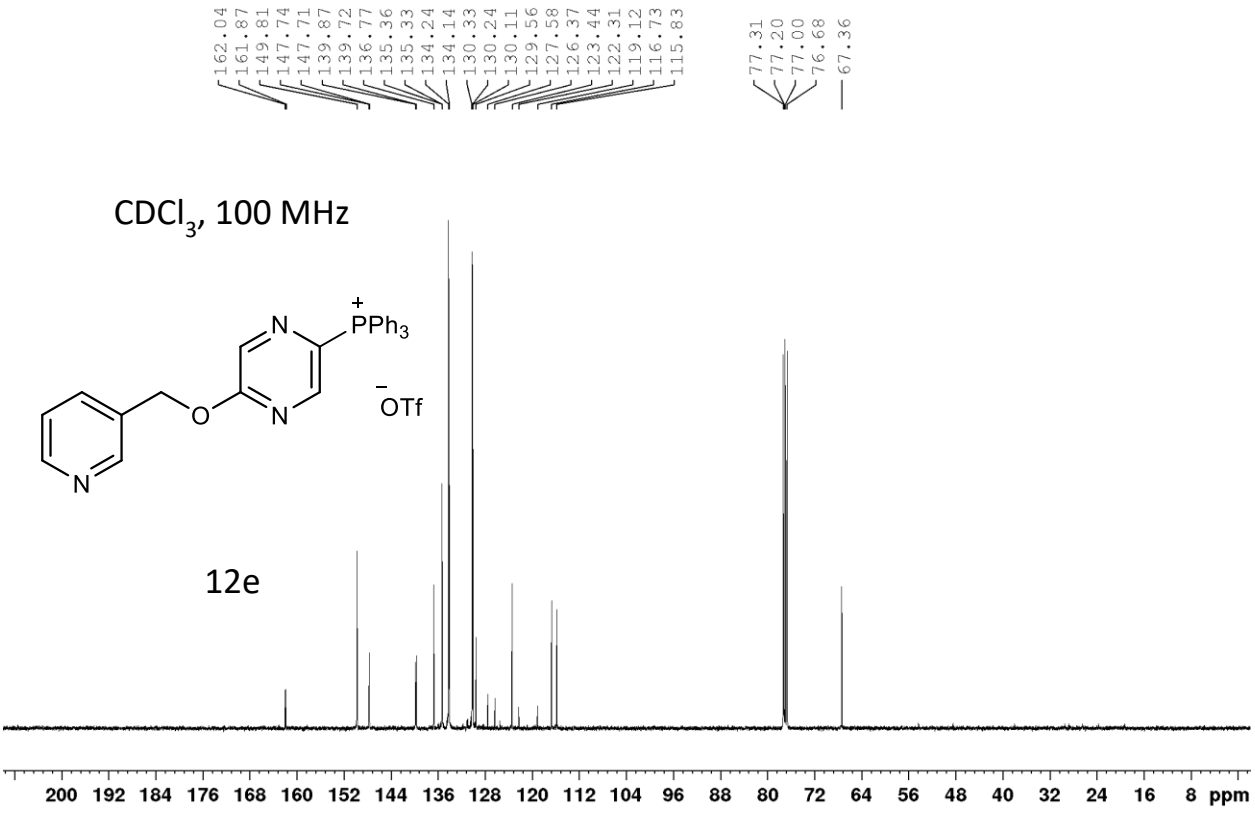


12e

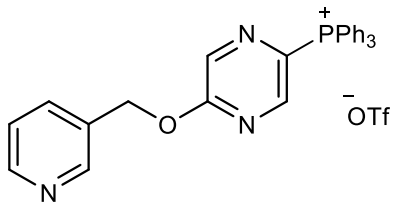

Major
29.24
22.71
21.25
21.03
17.24
16.72
CDCl3, 162 MHz
(crude 31P NMR)
Unidentified isomers
Unidentified isomer
Minor
OTf
PPh3
12e
1.000
0.125
0.137
0.107
0.129
1.00
0.12
0.14
0.11
0.13
ppm


CDCl3, 400 MHz
PPh3
OTf
12e
0.90
0.94
0.91
0.93
15.00
0.91
0.86
1.80
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
12e
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

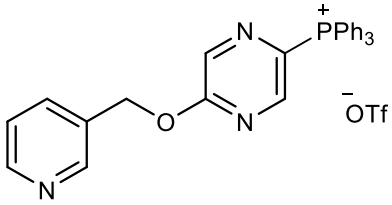

CDCl3, 100 MHz
PPh3
OTf
12e
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
ppm

$CDCl_3$, 365 MHz



12e

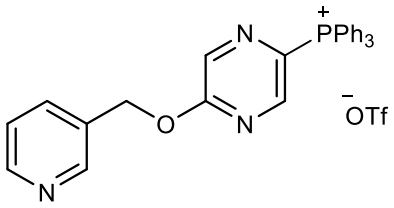
$CDCl_3$, 162 MHz



12e

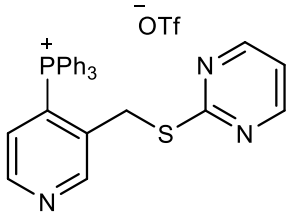
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

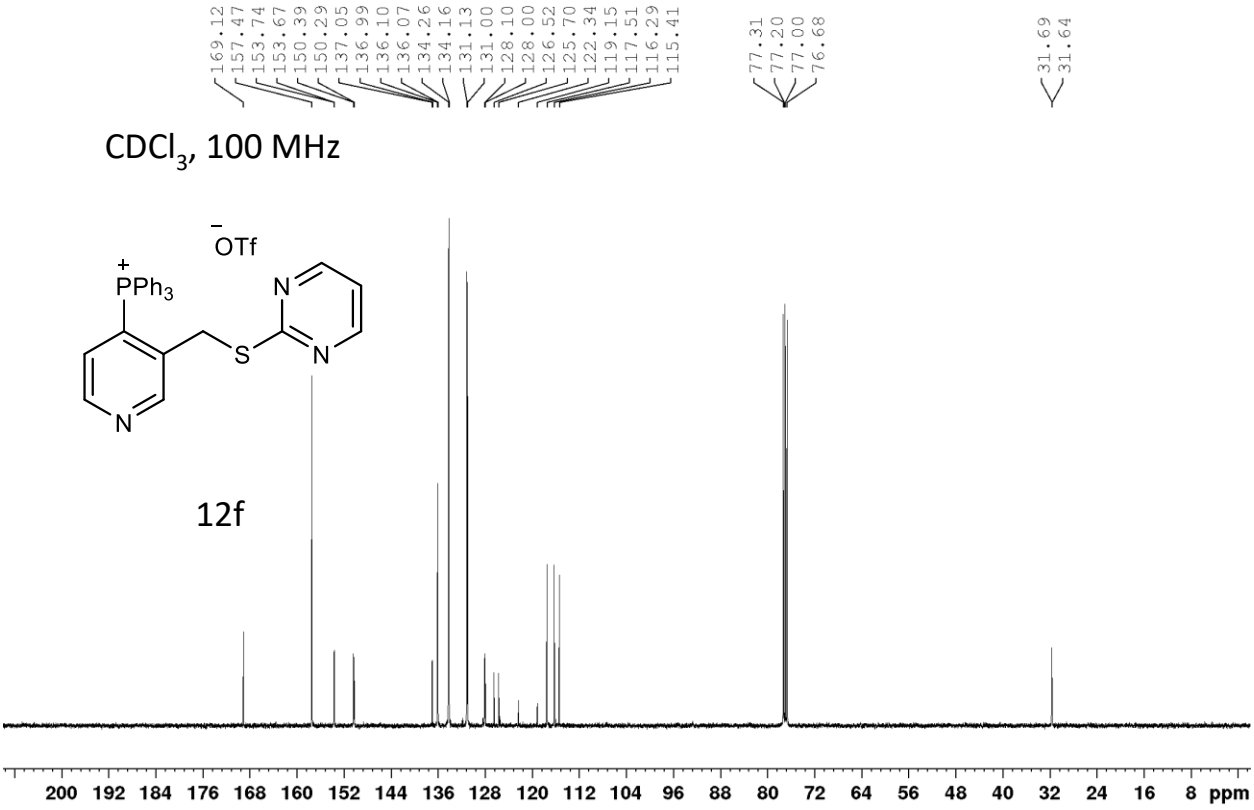


12e

$CDCl_3$, 400 MHz

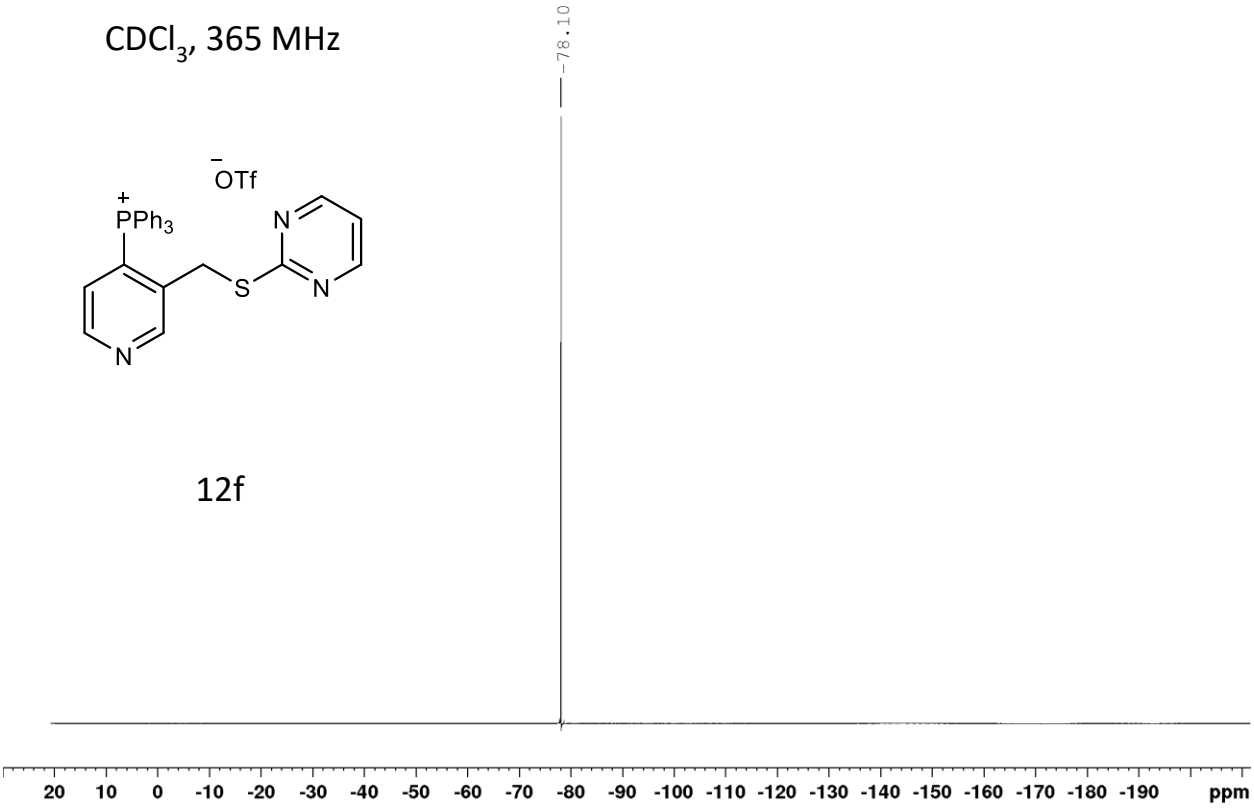


12f



$CDCl_3$, 100 MHz

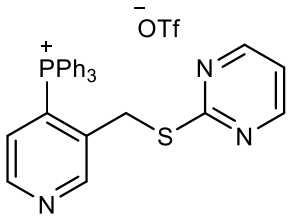
12f



$CDCl_3$, 365 MHz

12f

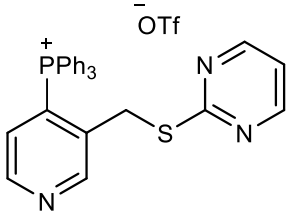
$CDCl_3$, 162 MHz



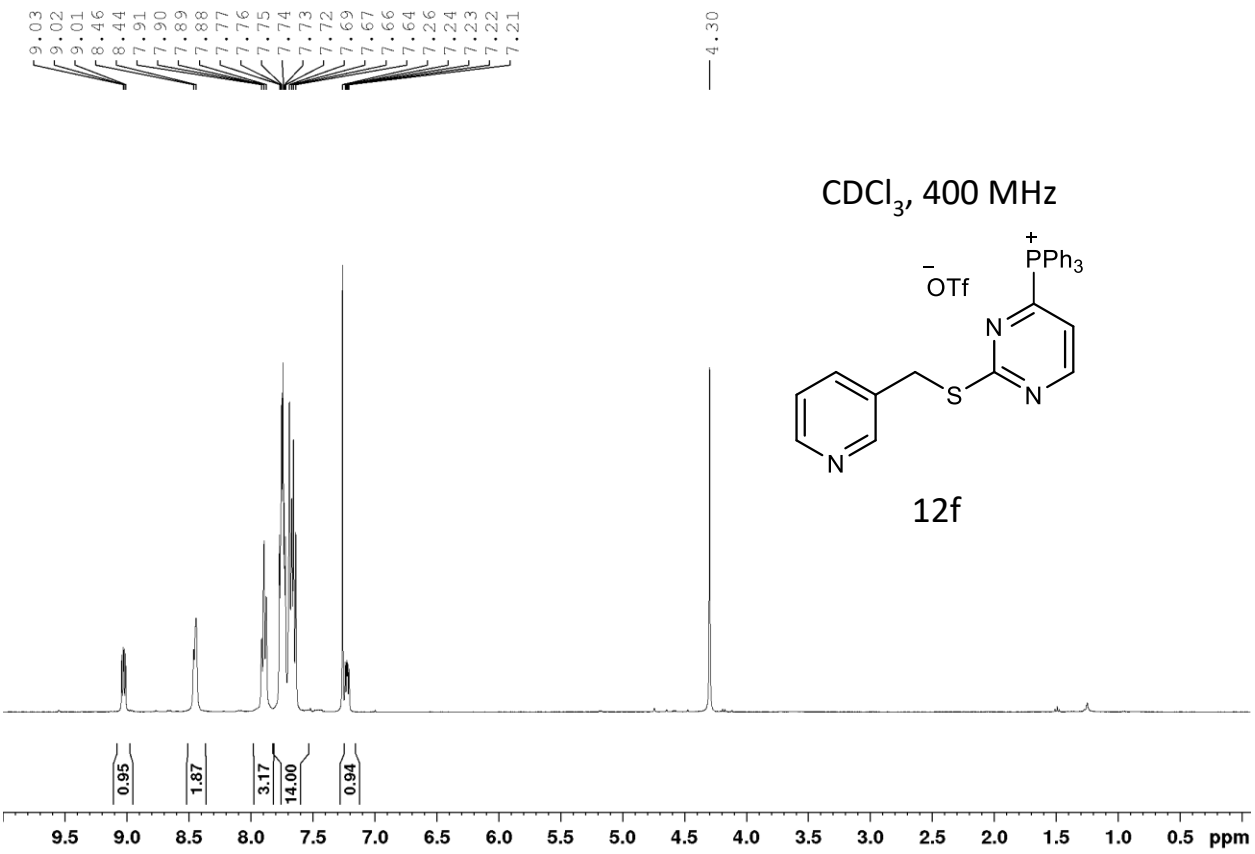
12f

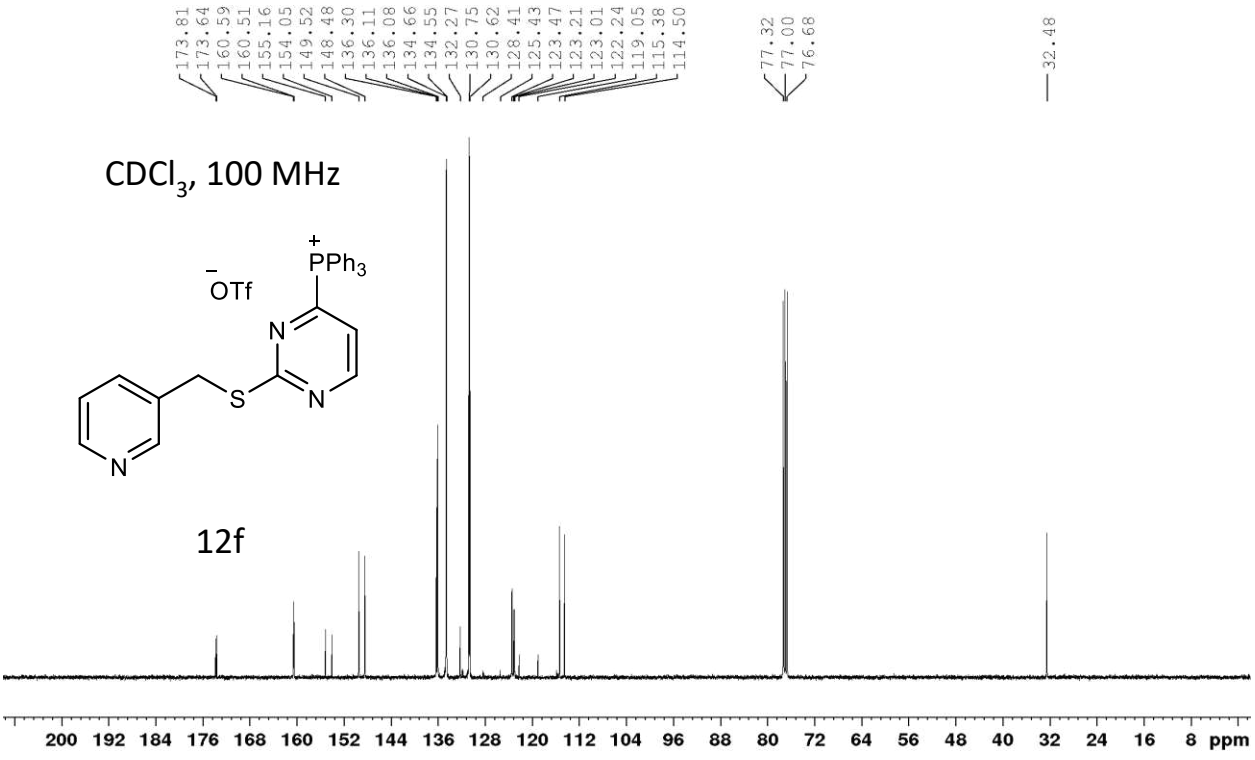
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

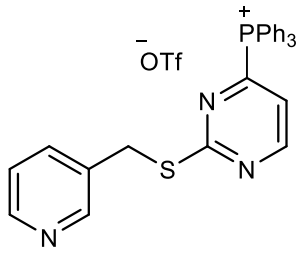


12f


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
PPh3
OTf
N
S
N
N
12f
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

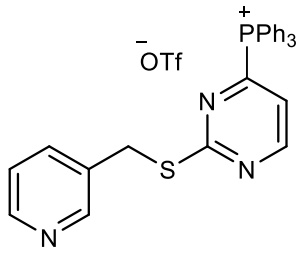

173.81
173.64
160.59
160.51
155.16
154.05
149.52
148.48
136.30
136.11
136.08
134.66
134.55
132.27
130.75
130.62
128.41
125.43
123.47
123.21
123.01
122.24
119.05
115.38
114.50
77.32
77.00
76.68
32.48
CDCl3, 100 MHz
PPh3
OTf
N
S
N
N
12f
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz



12f

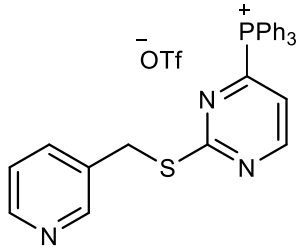
$CDCl_3$, 162 MHz



12f

$CDCl_3$, 162 MHz

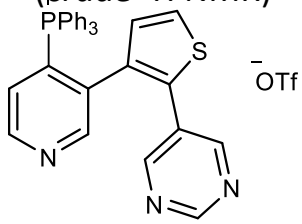
(crude ^{31}P NMR)



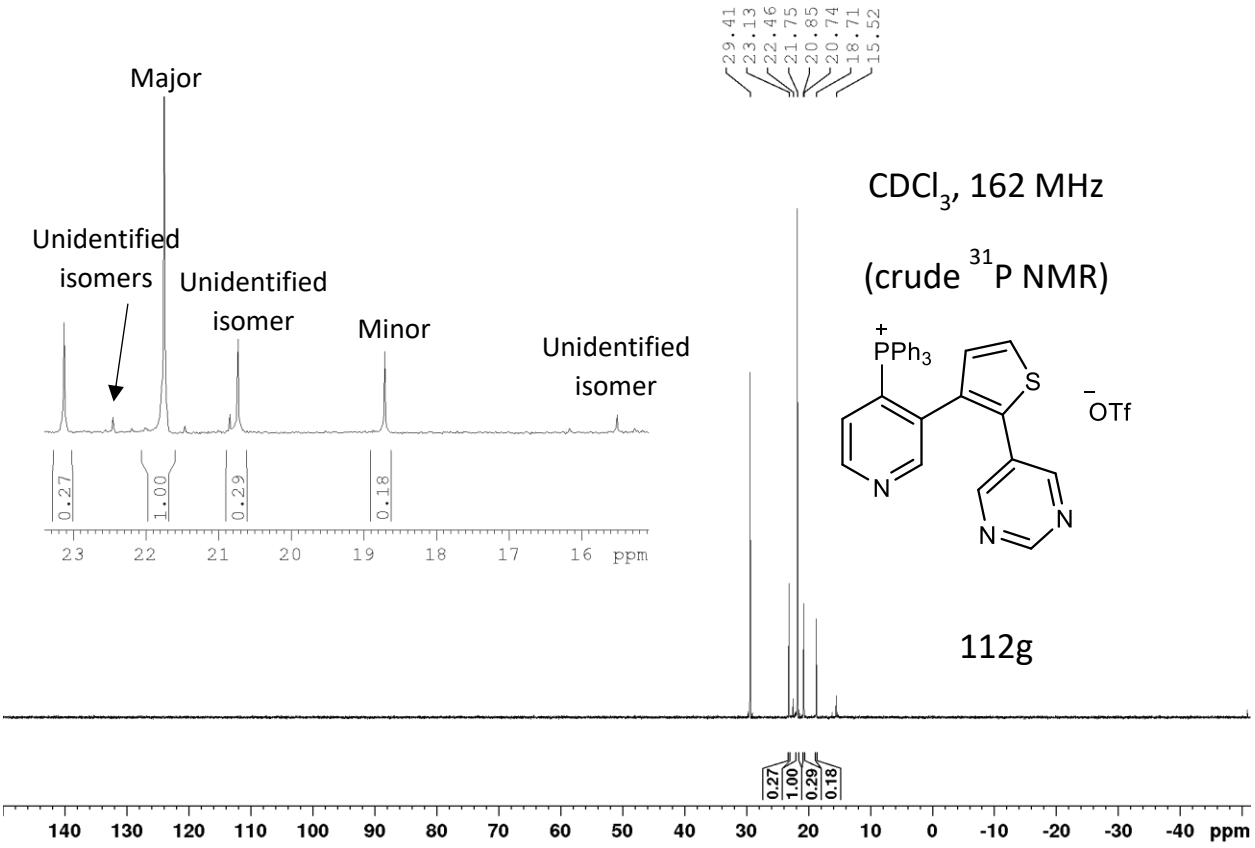
12f

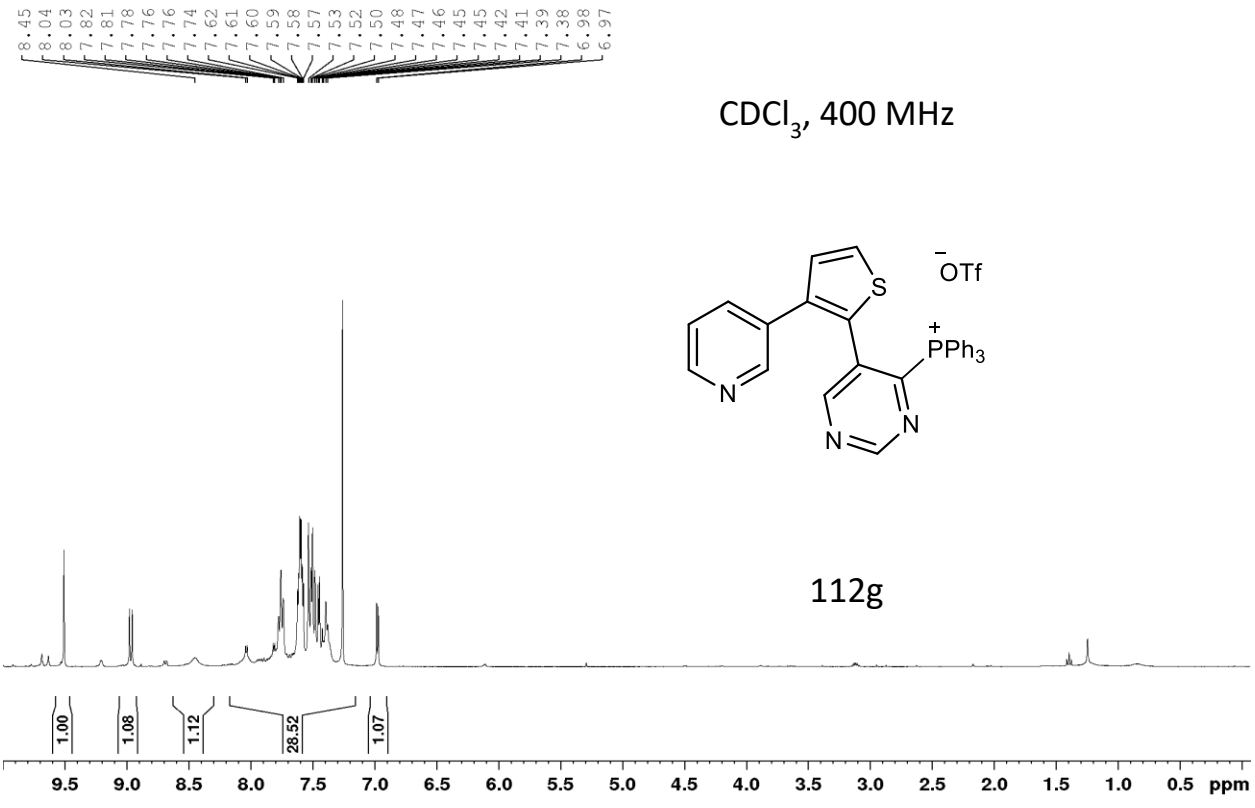
$CDCl_3$, 400 MHz

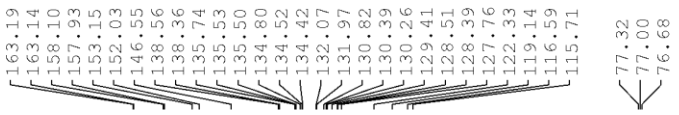
(crude ^{1}H NMR)



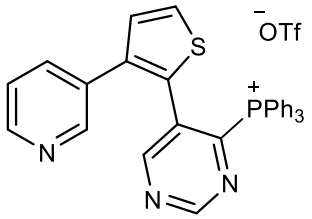
112g


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
112g
0.27
1.00
0.29
0.18
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
112g
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

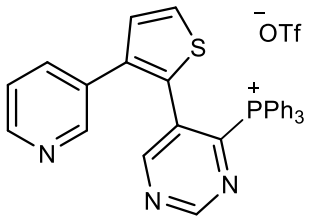


$CDCl_3$, 100 MHz



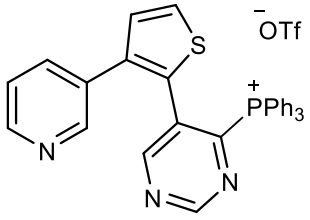
12g

$CDCl_3$, 365 MHz



12g

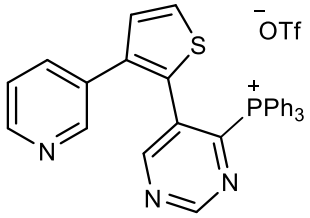
$CDCl_3$, 162 MHz



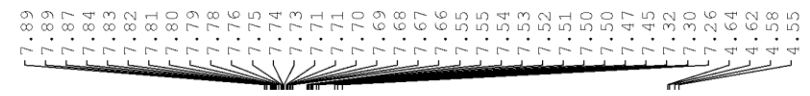
12g

$CDCl_3$, 162 MHz

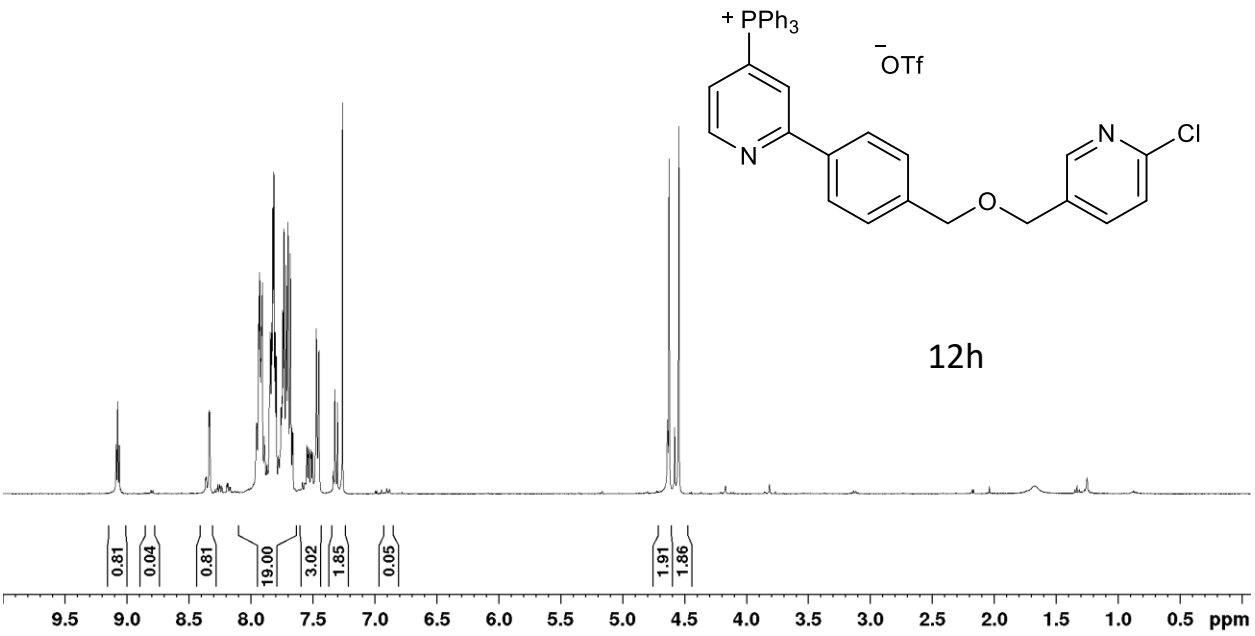
(crude ^{31}P NMR)

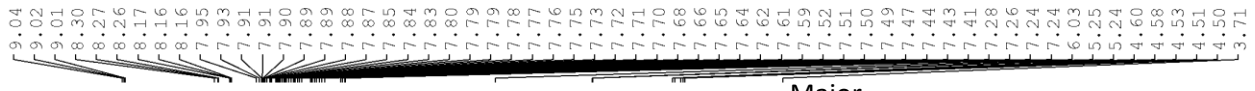


12g



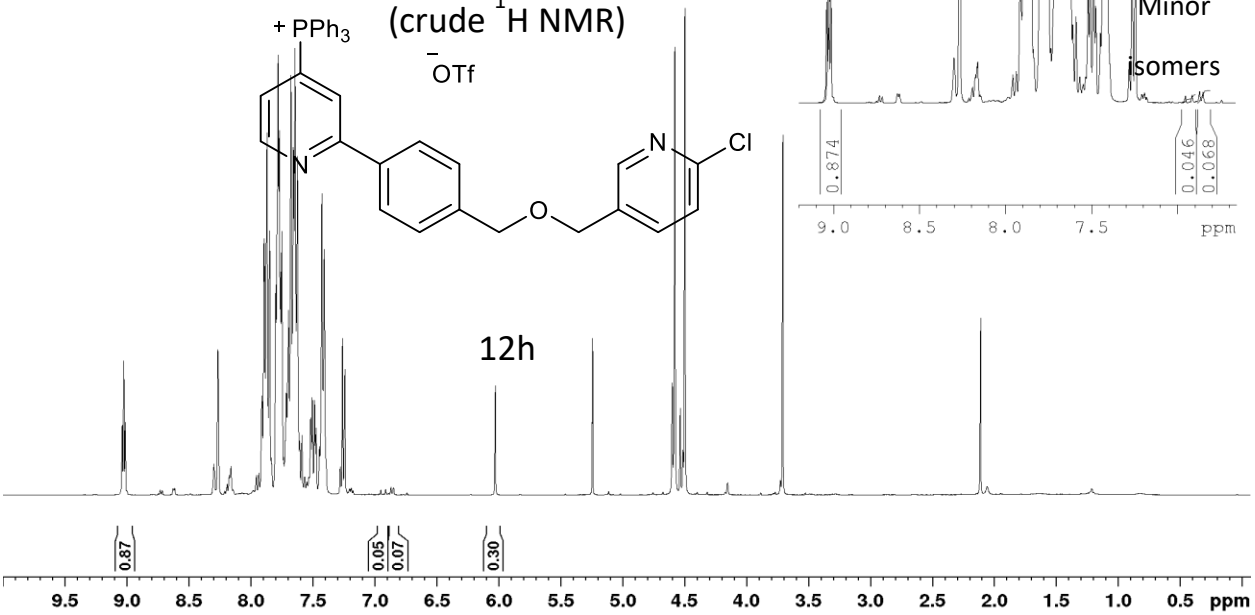
$CDCl_3$, 400 MHz

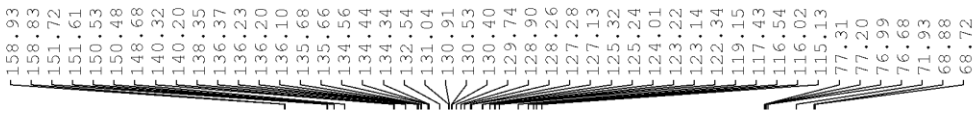




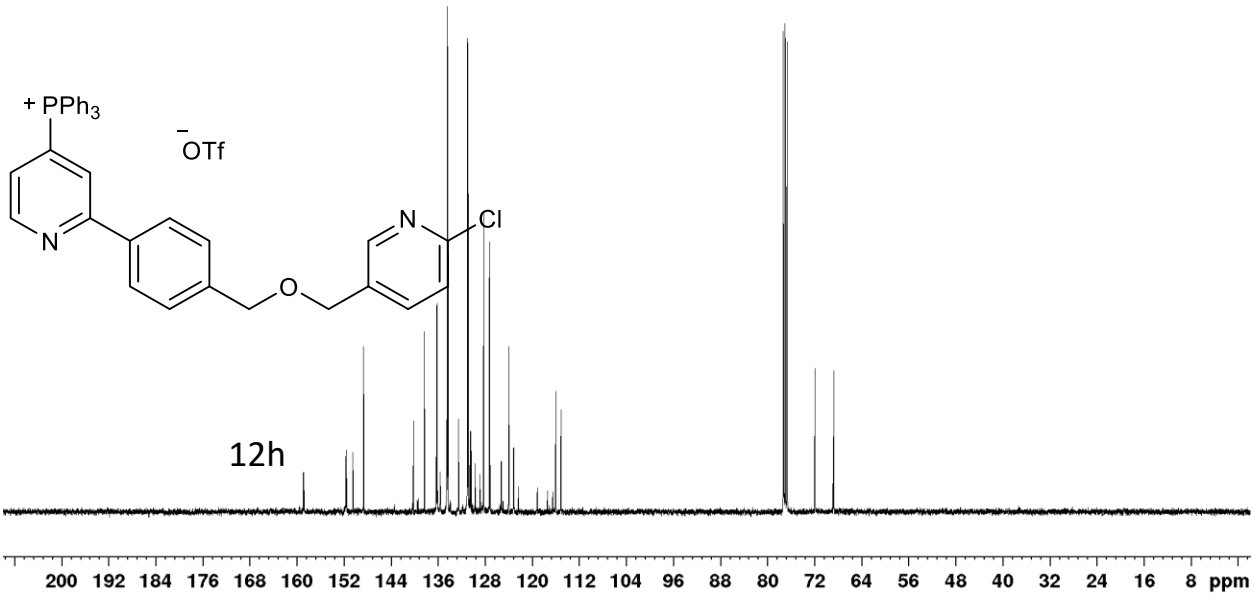
$CDCl_3$, 400 MHz

(crude ^{1}H NMR)

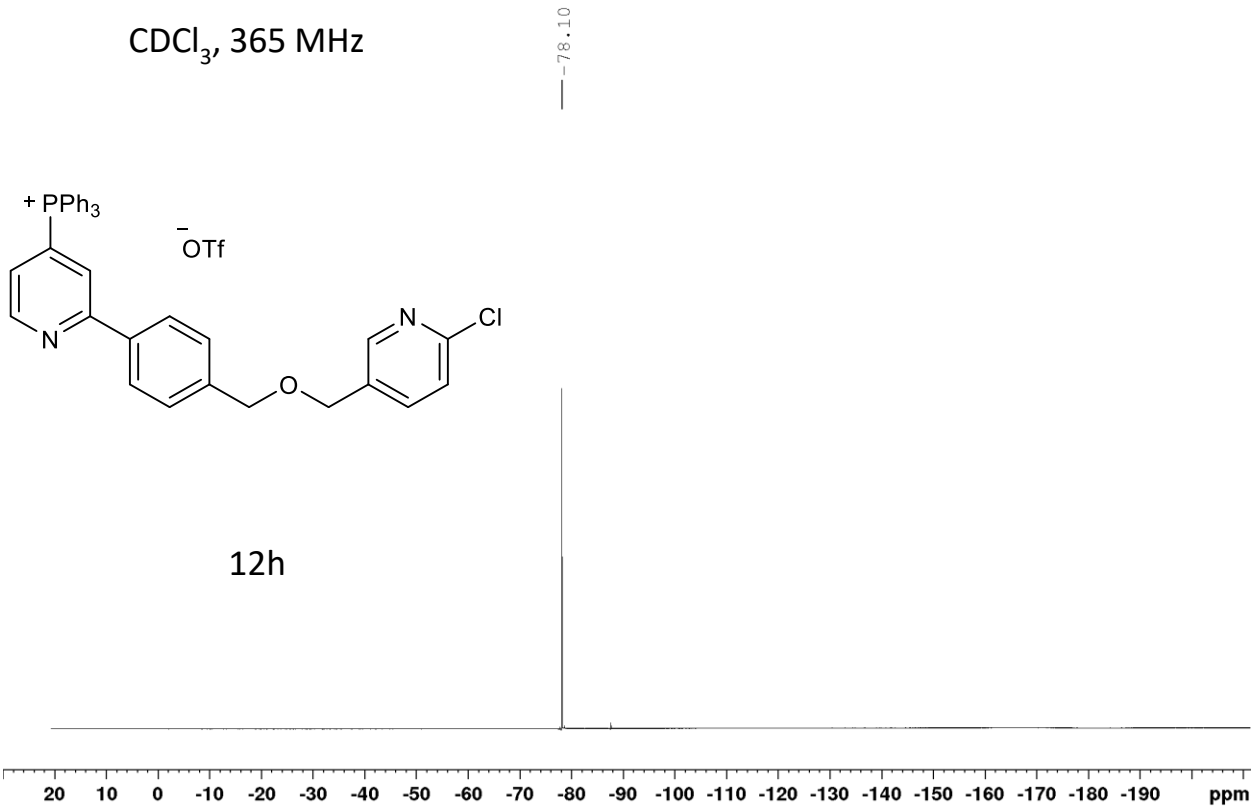




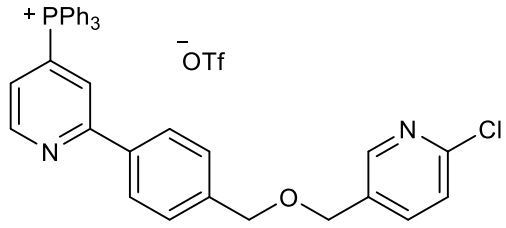
$CDCl_3$, 100 MHz



$CDCl_3$, 365 MHz

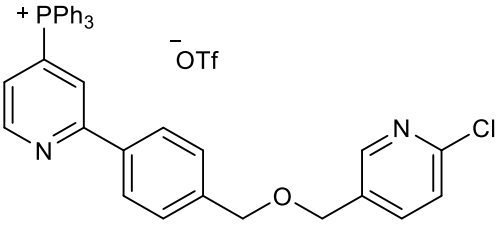


$CDCl_3$, 162 MHz

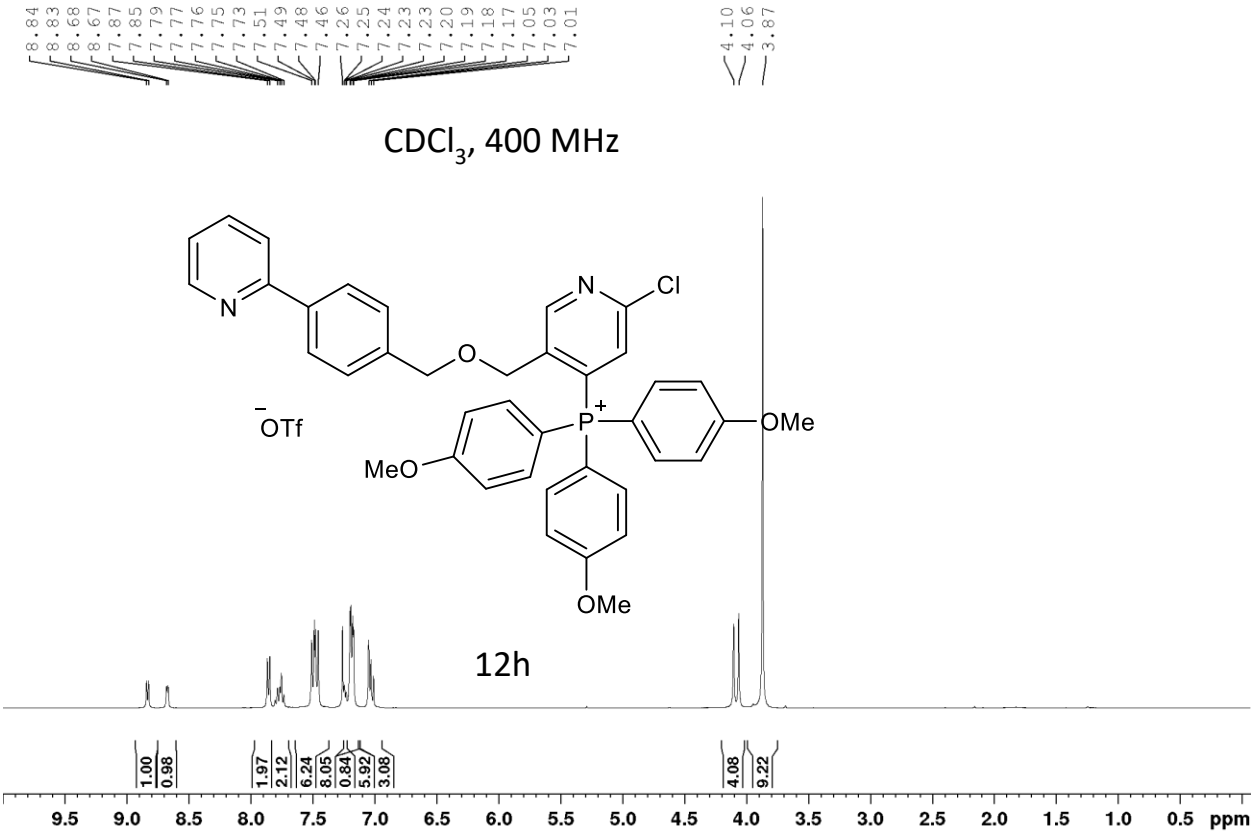


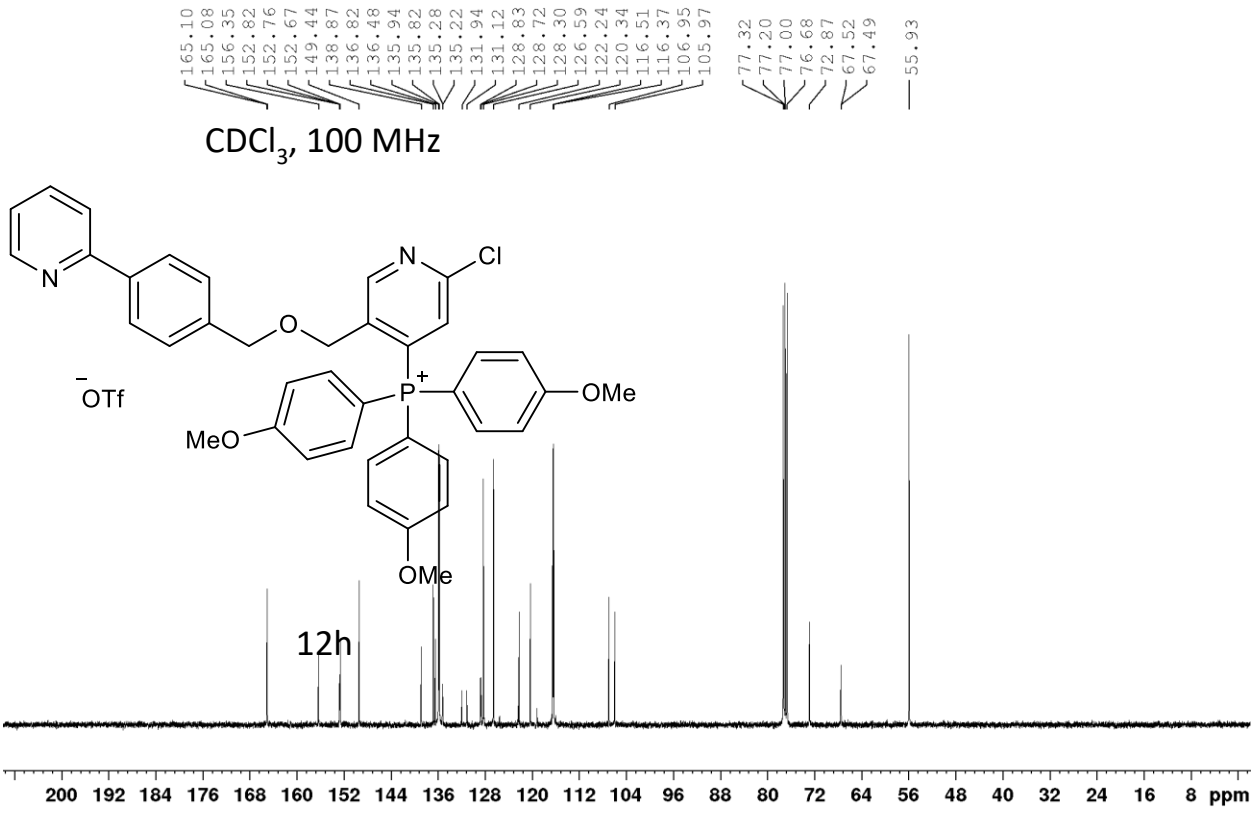
12h

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

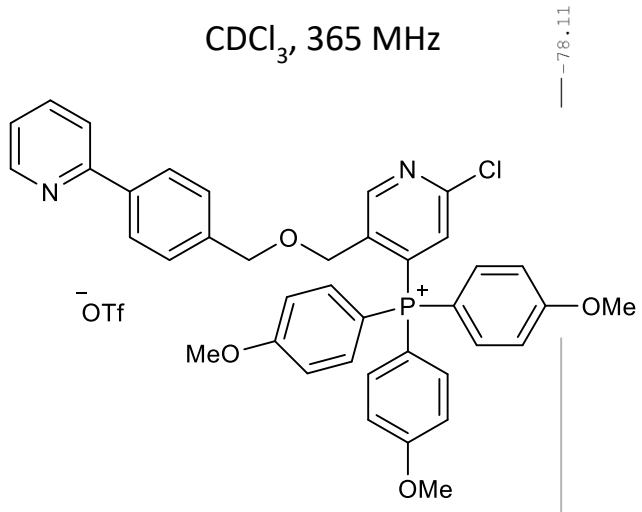


12h

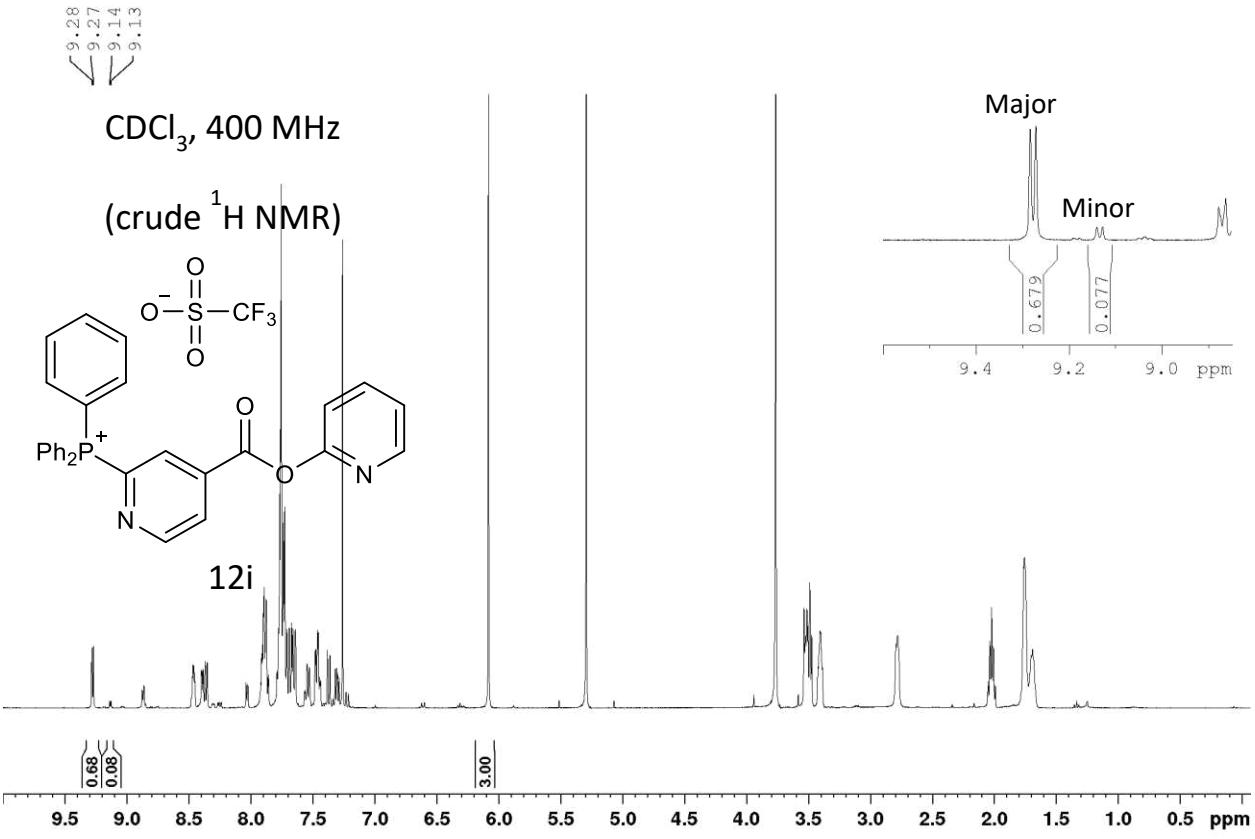

8.84
8.83
8.68
8.67
7.87
7.85
7.79
7.77
7.76
7.75
7.73
7.51
7.49
7.48
7.46
7.26
7.25
7.24
7.23
7.23
7.20
7.19
7.18
7.17
7.05
7.03
7.01
4.10
4.06
3.87
CDCl3, 400 MHz
N
Cl
O
OTf
P+
OMe
MeO
OMe
12h
1.00
0.98
1.97
2.12
6.24
8.05
0.84
5.92
3.08
4.08
9.22
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


165.10
165.08
156.35
152.82
152.76
152.67
149.44
138.87
136.82
136.48
135.94
135.82
135.28
135.22
131.94
131.12
128.83
128.72
128.30
126.59
122.24
120.34
116.51
116.37
106.95
105.97
77.32
77.20
77.00
76.68
72.87
67.52
67.49
55.93
CDCl3, 100 MHz
N
Cl
O
OTf
P+
OMe
MeO
OMe
12h
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

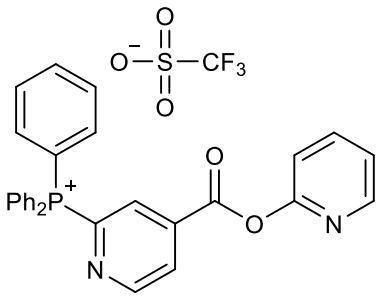


12h

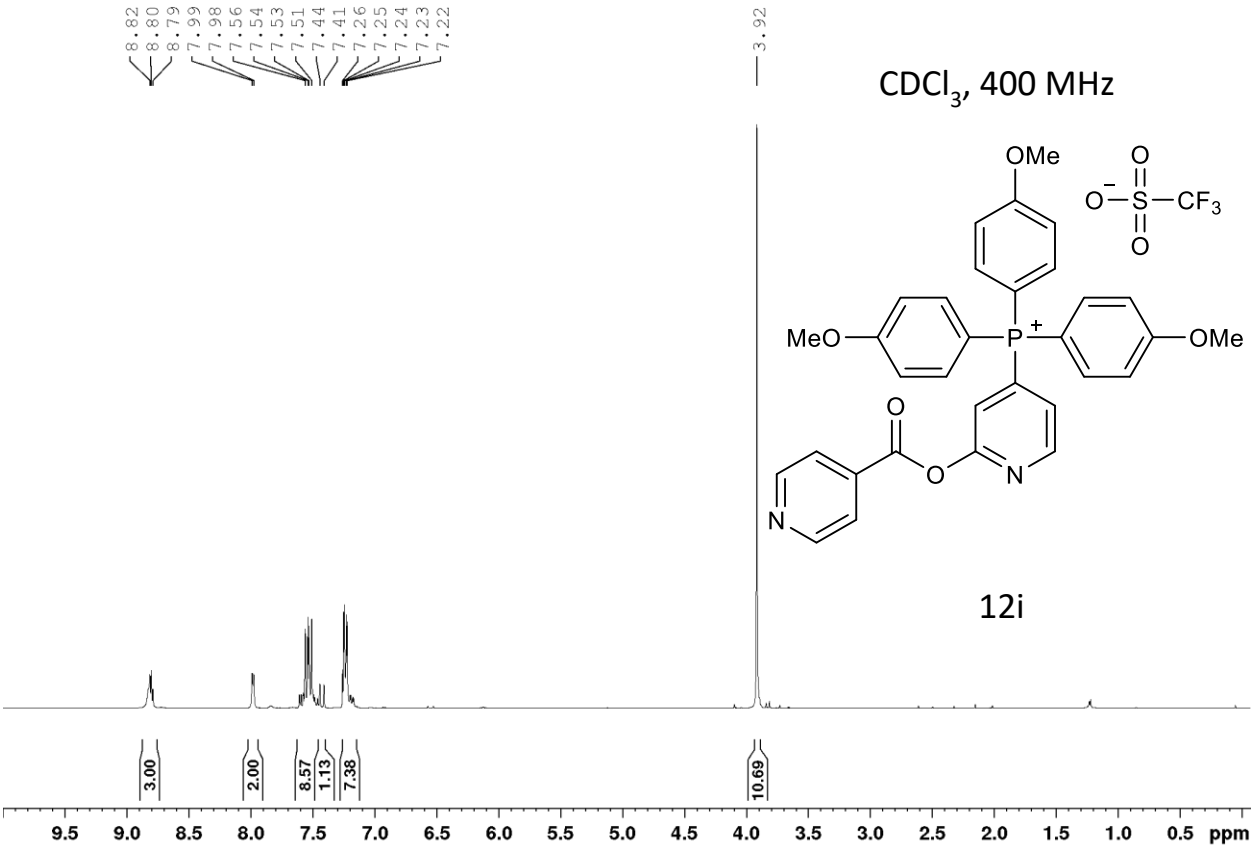


$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

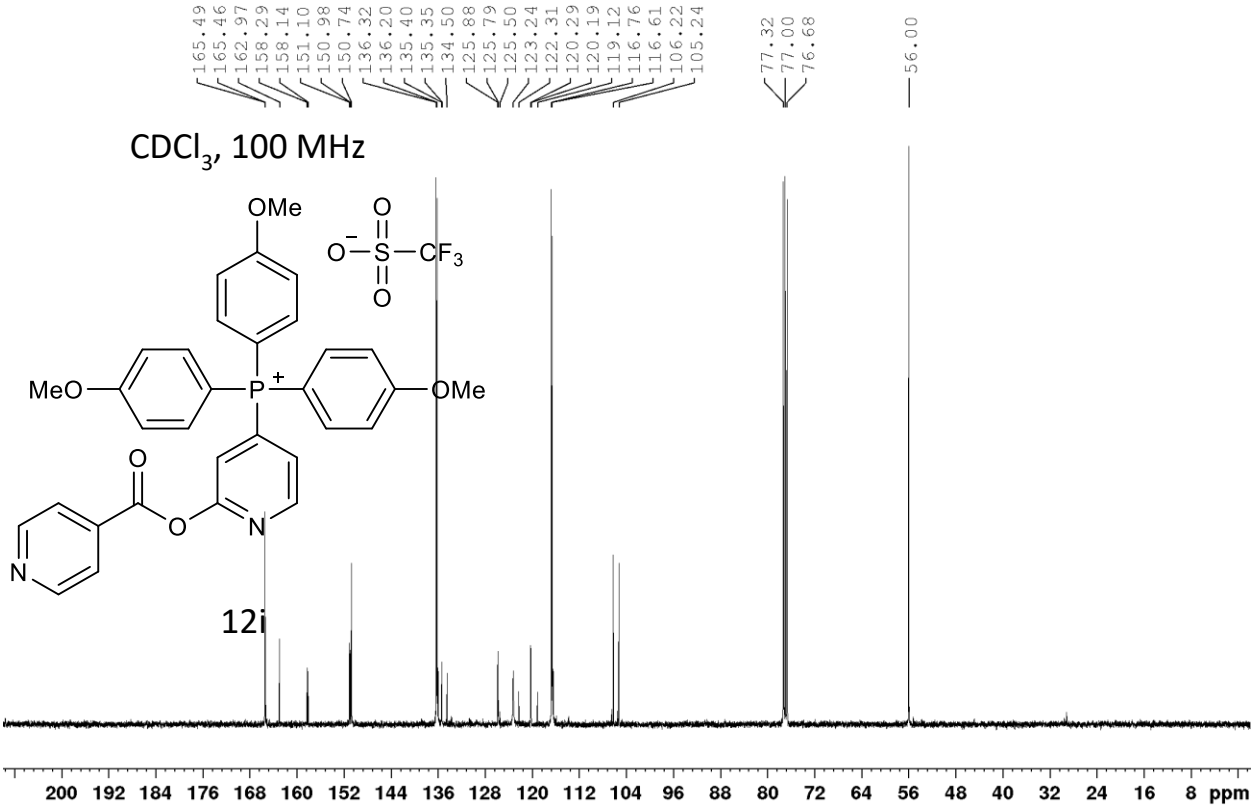


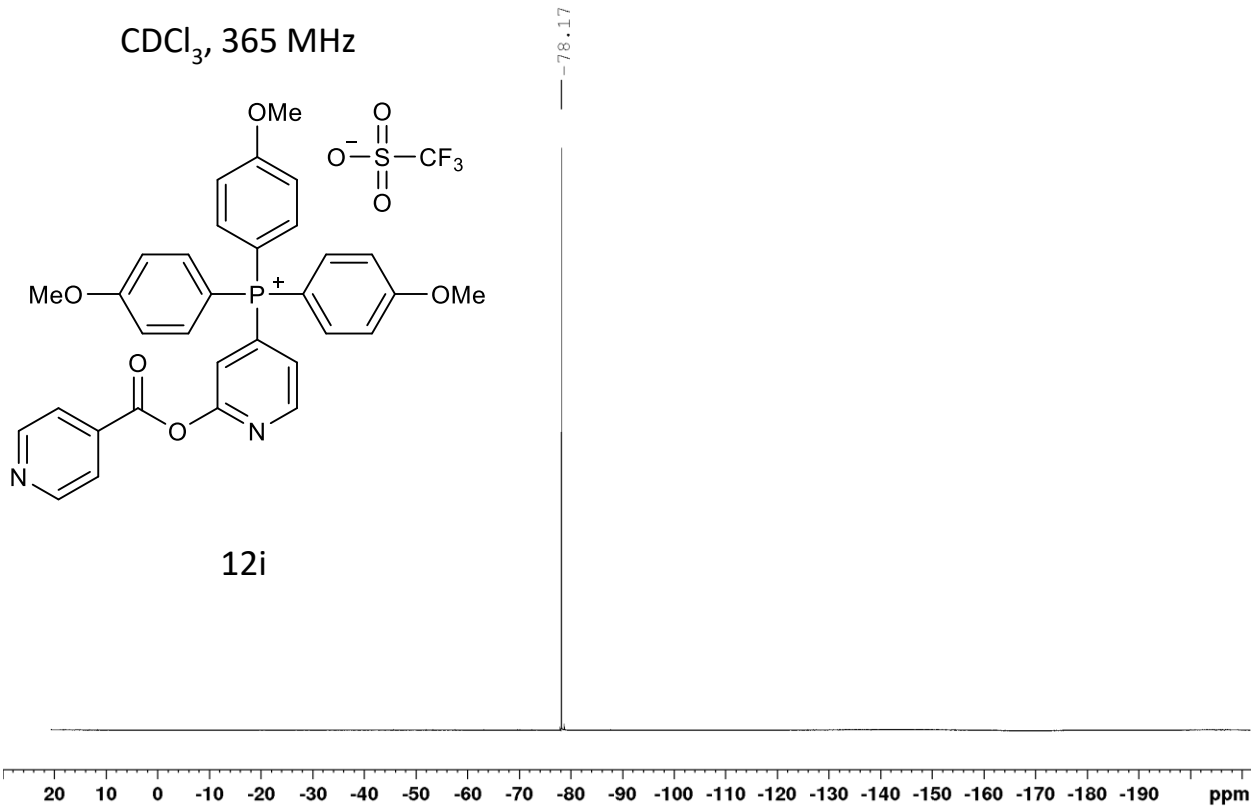
12i



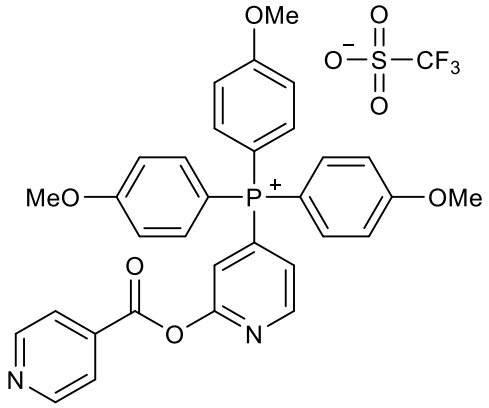
$CDCl_3$, 400 MHz

12i


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
O
O−S−CF3
O
MeO
P+
OMe
O
O
N
N
12i
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
O
O−S−CF3
O
MeO
P+
OMe
O
O
N
N
12i
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

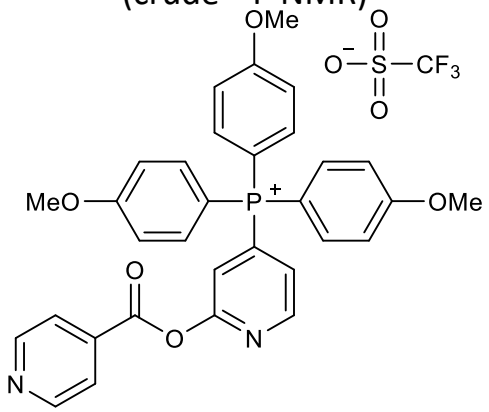
$CDCl_3$, 162 MHz



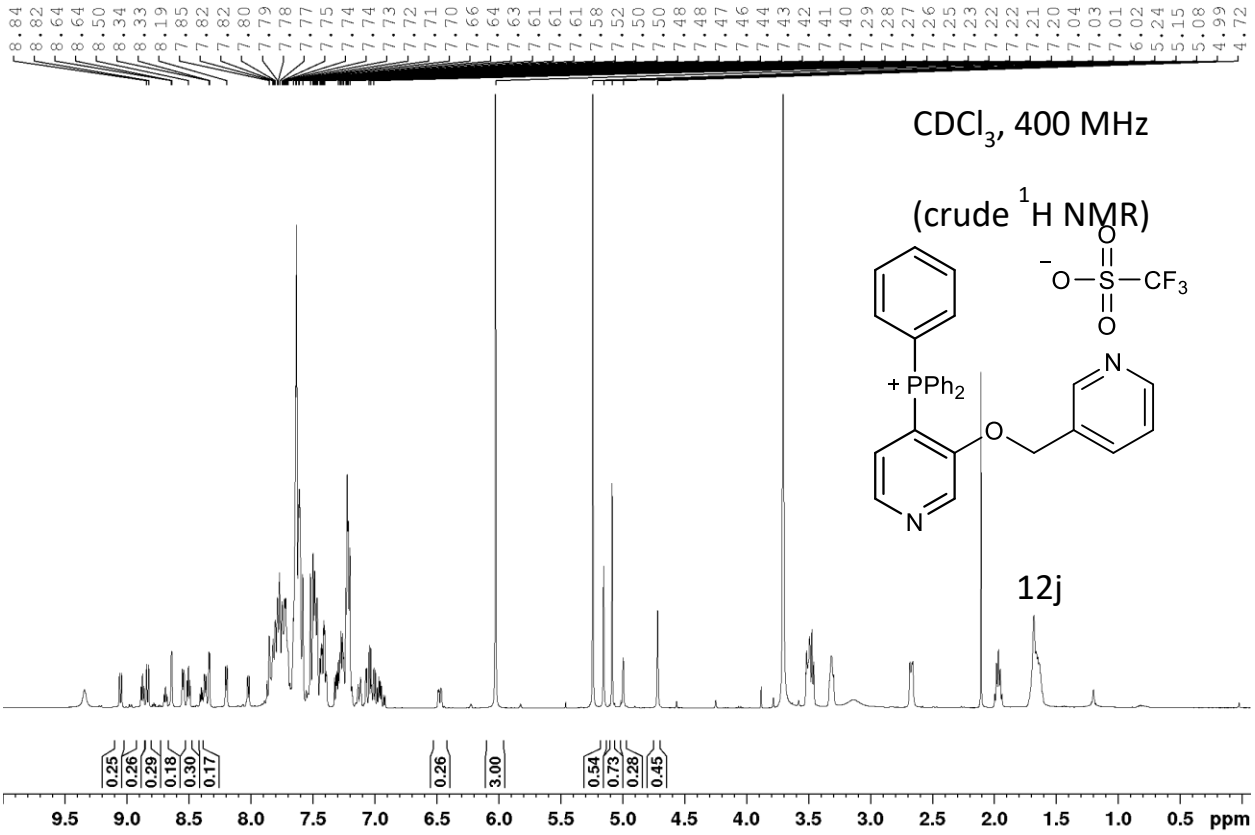
12i

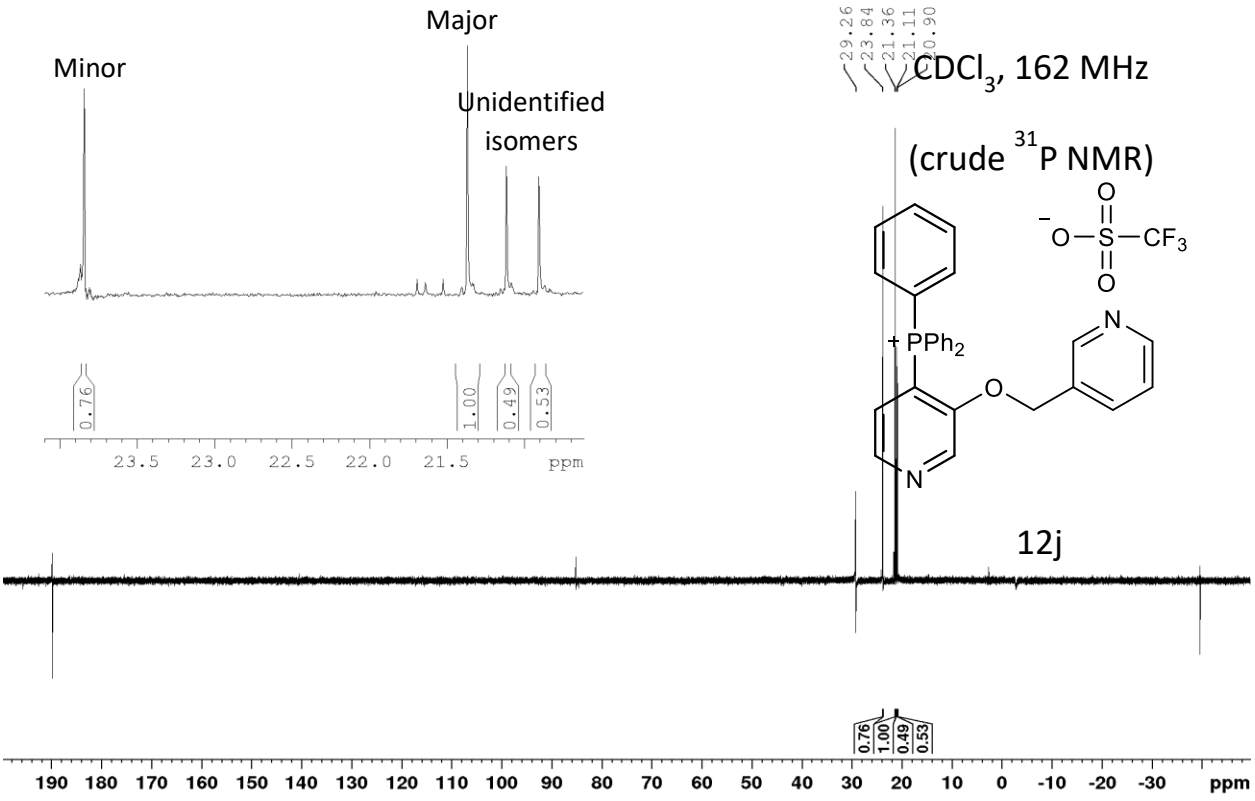
$CDCl_3$, 162 MHz

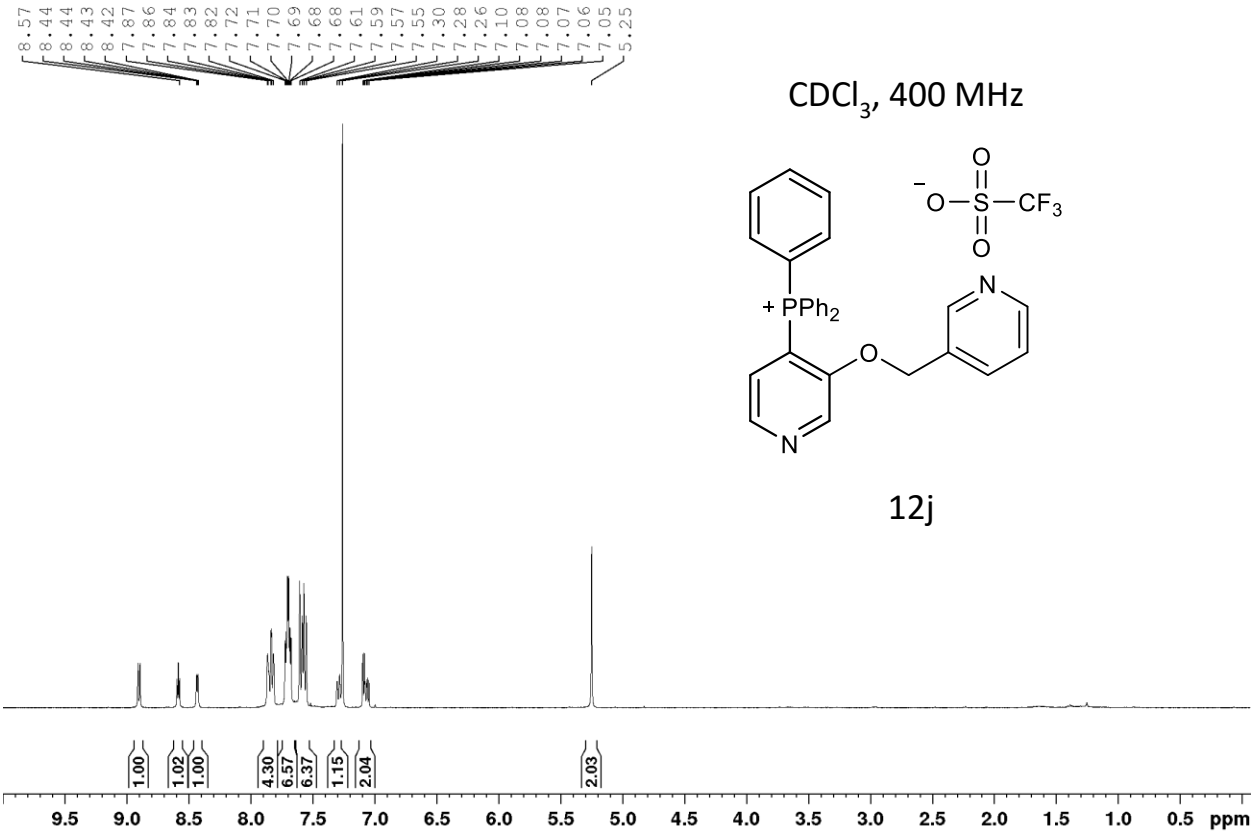
(crude ^{31}P NMR)

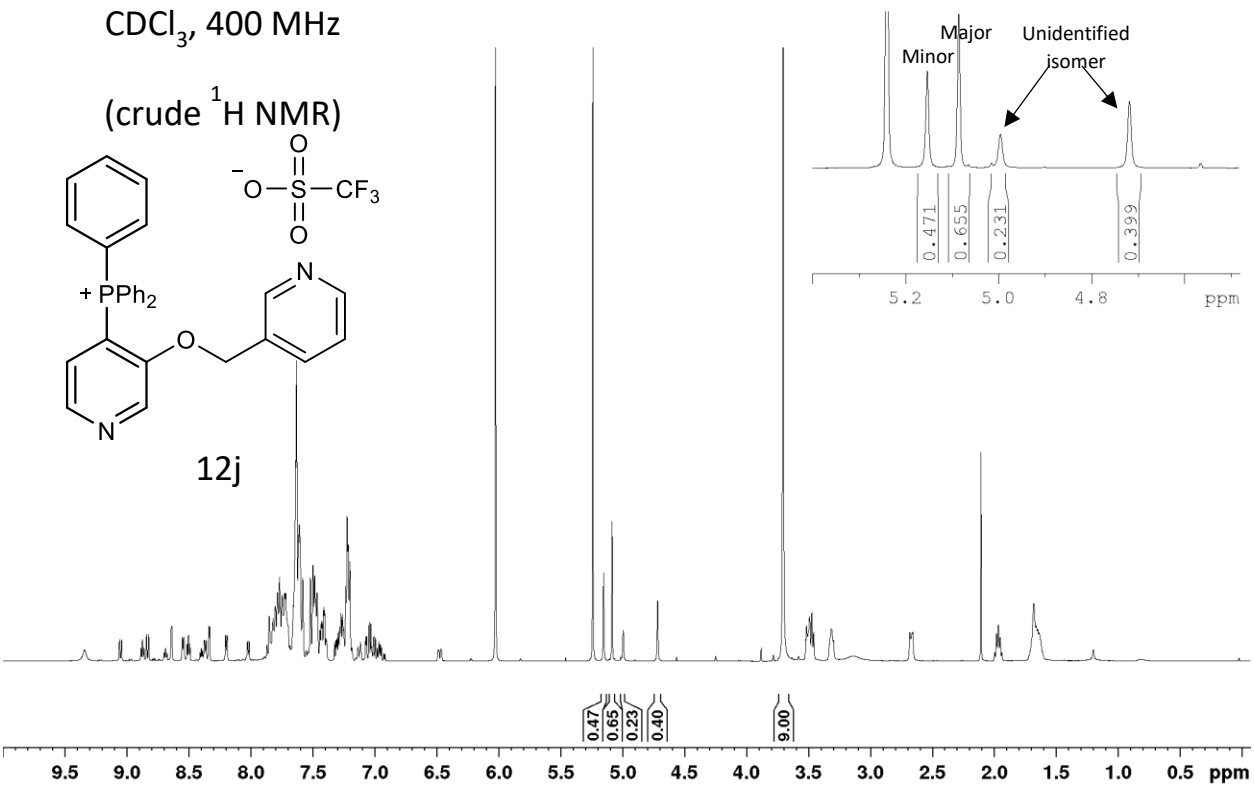


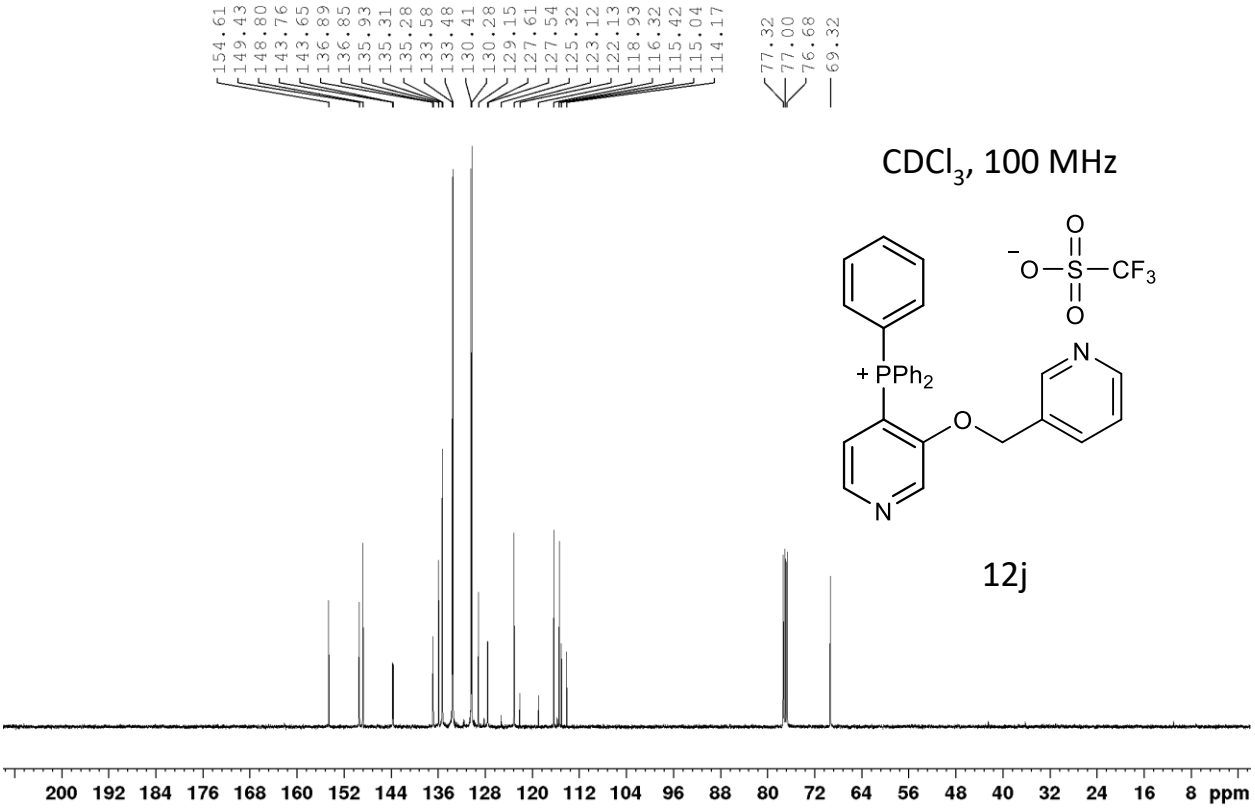
12i

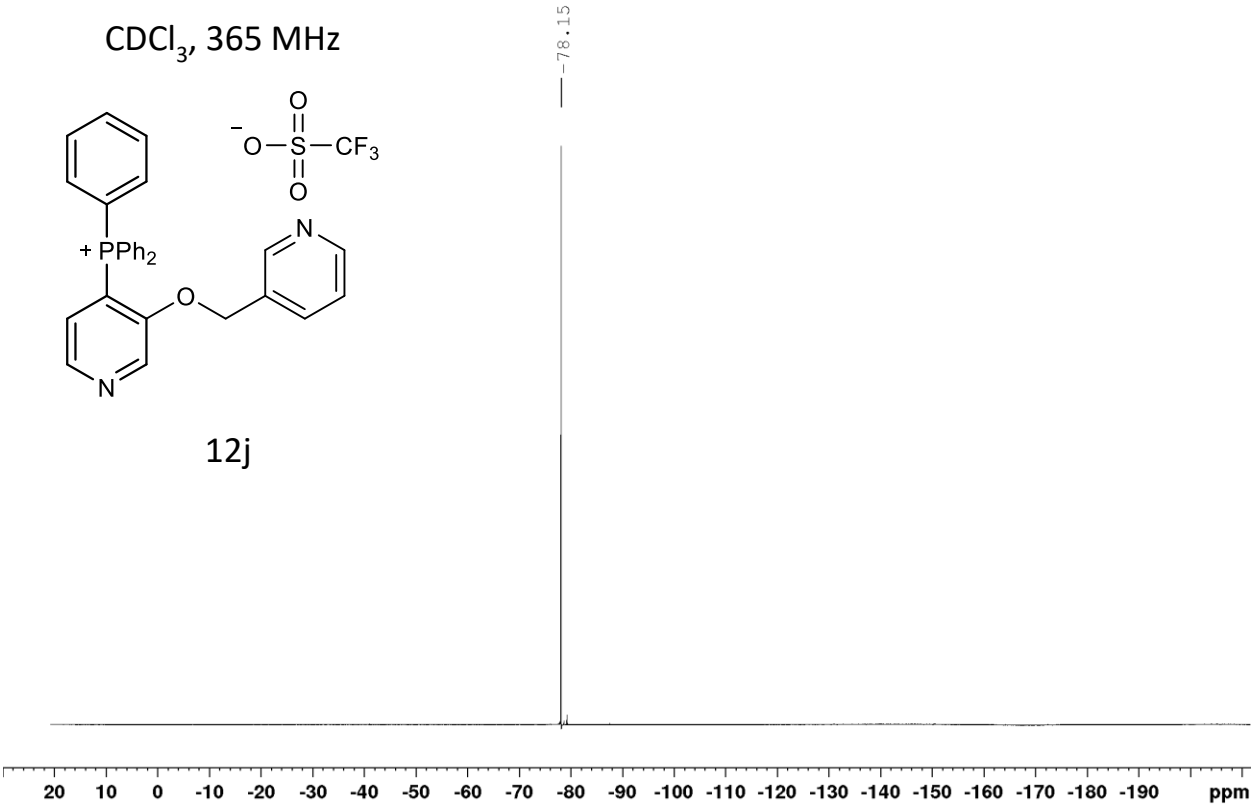

CDCl3, 400 MHz
(crude 1H NMR)
12j
ppm


Major
Minor
Unidentified
isomers
CDCl3, 162 MHz
(crude 31P NMR)
12j
ppm

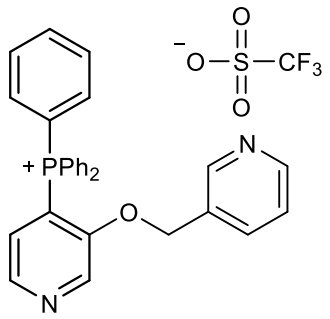

8.57
8.44
8.44
8.43
8.42
7.87
7.86
7.84
7.83
7.82
7.72
7.71
7.70
7.69
7.68
7.68
7.61
7.59
7.57
7.55
7.30
7.28
7.26
7.10
7.08
7.08
7.07
7.06
7.05
5.25
CDCl3, 400 MHz
+ PPh2
O
N
12j
1.00
1.02
1.00
4.30
6.57
6.37
1.15
2.04
2.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


CDCl3, 400 MHz
(crude 1H NMR)
+ PPh2
O
N
12j
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
12j
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
-78.15
12j
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

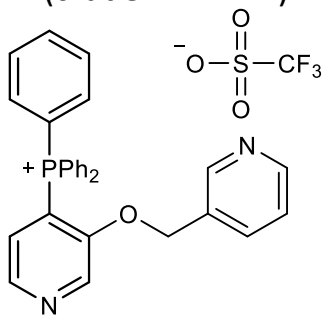
$CDCl_3$, 162 MHz



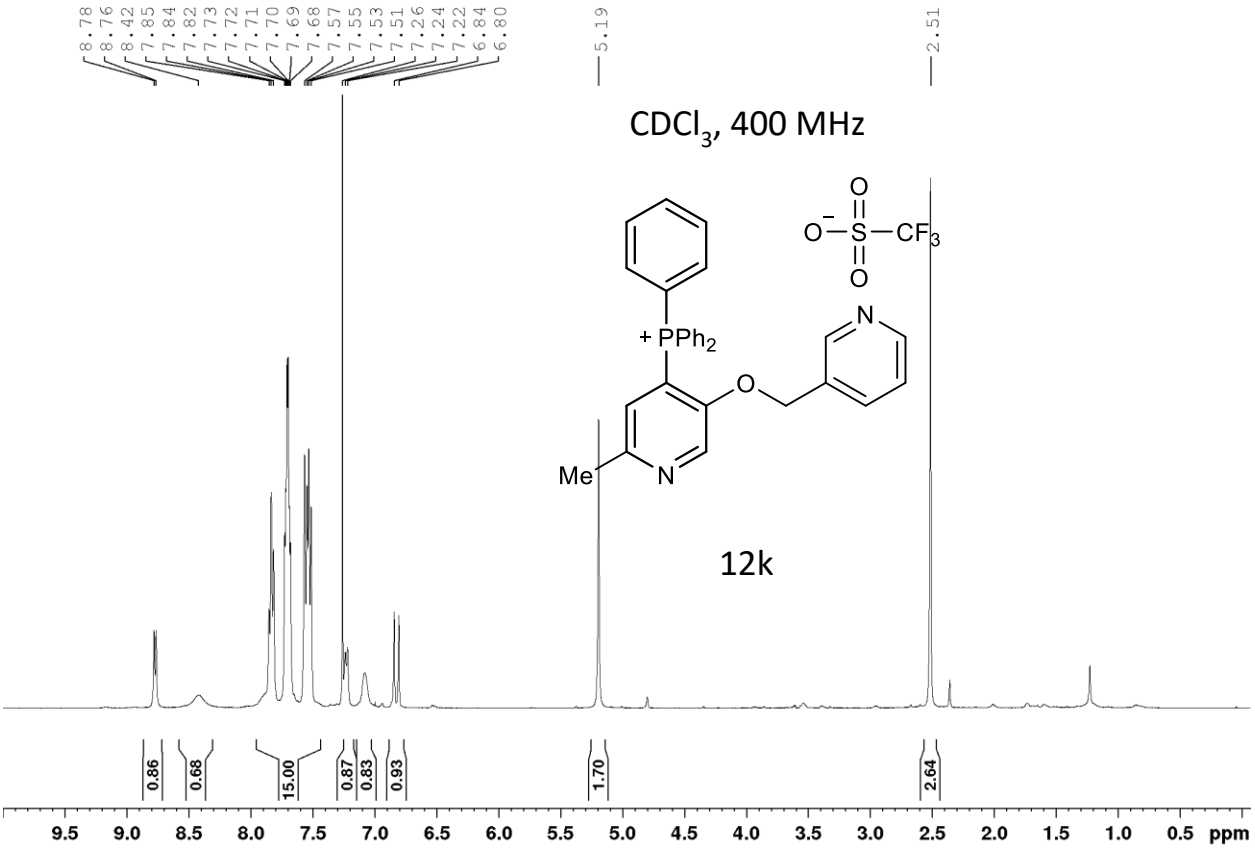
12j

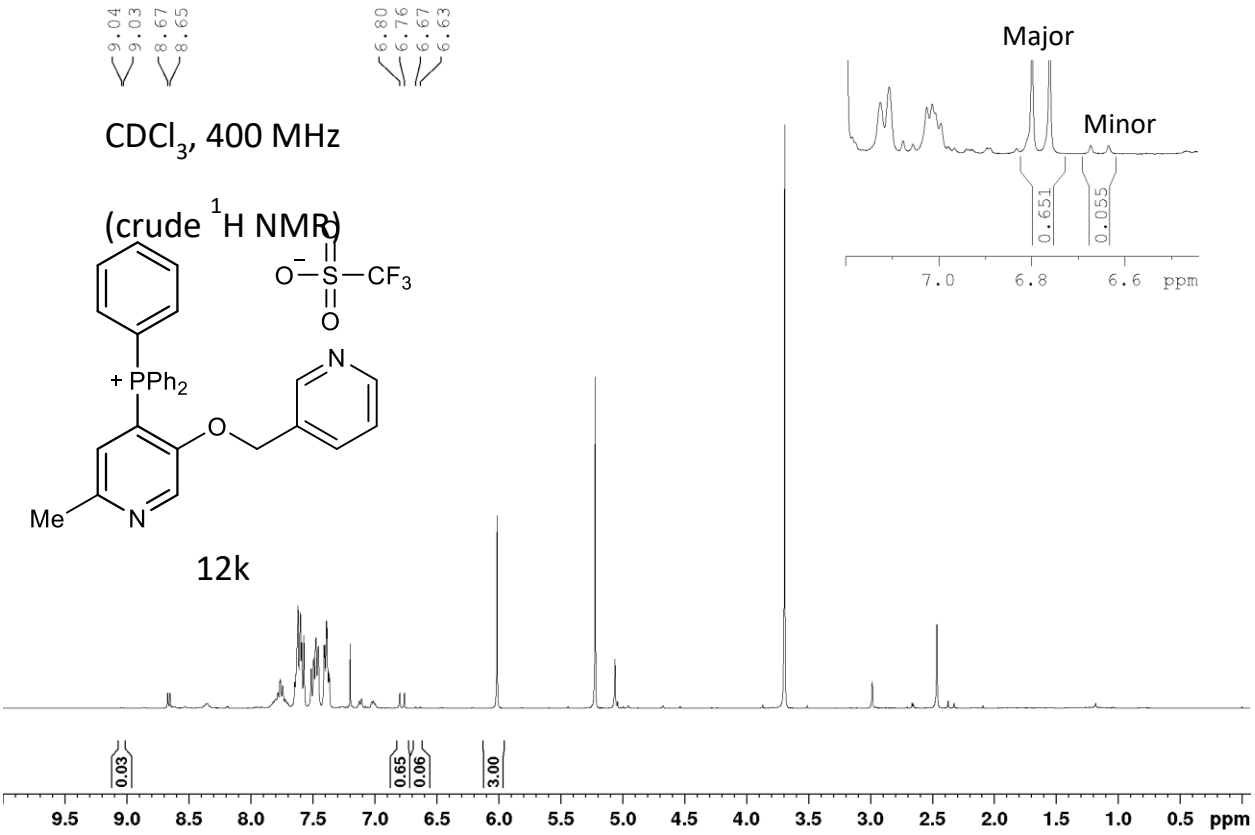
$CDCl_3$, 162 MHz

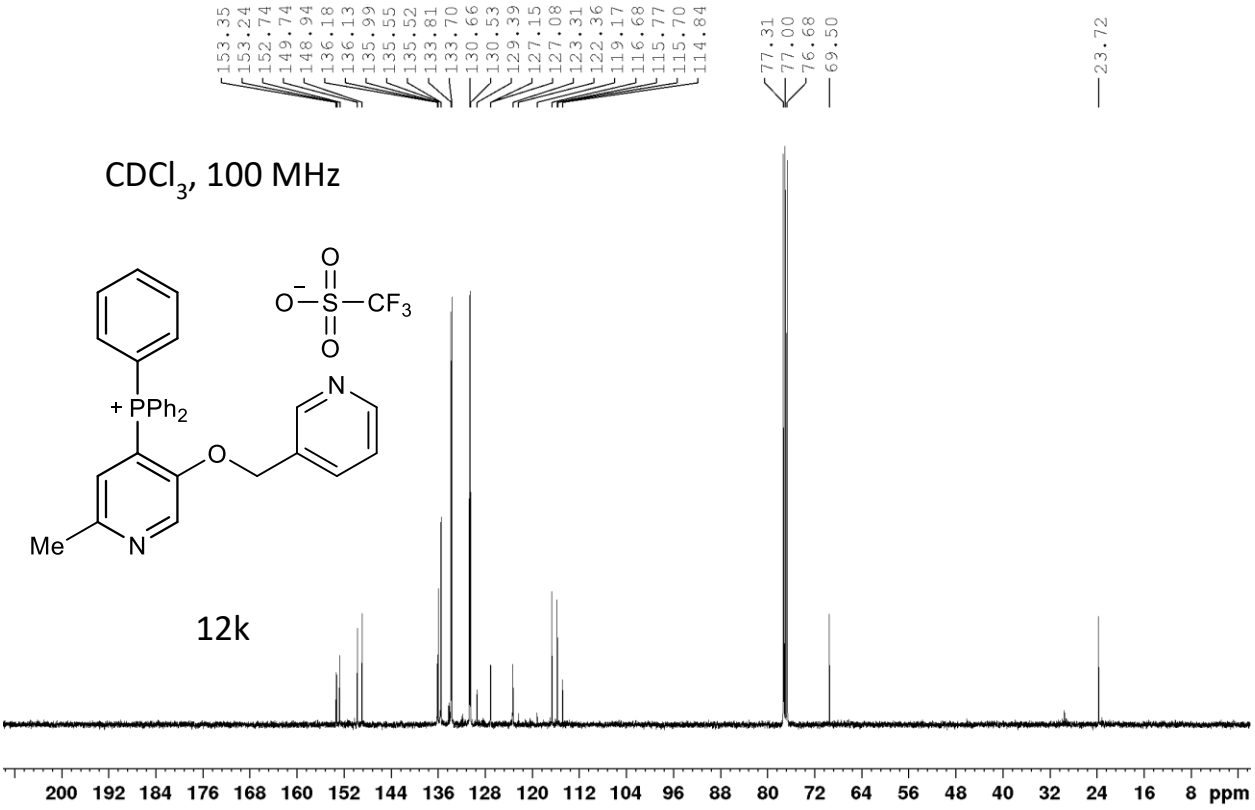
(crude ^{31}P NMR)

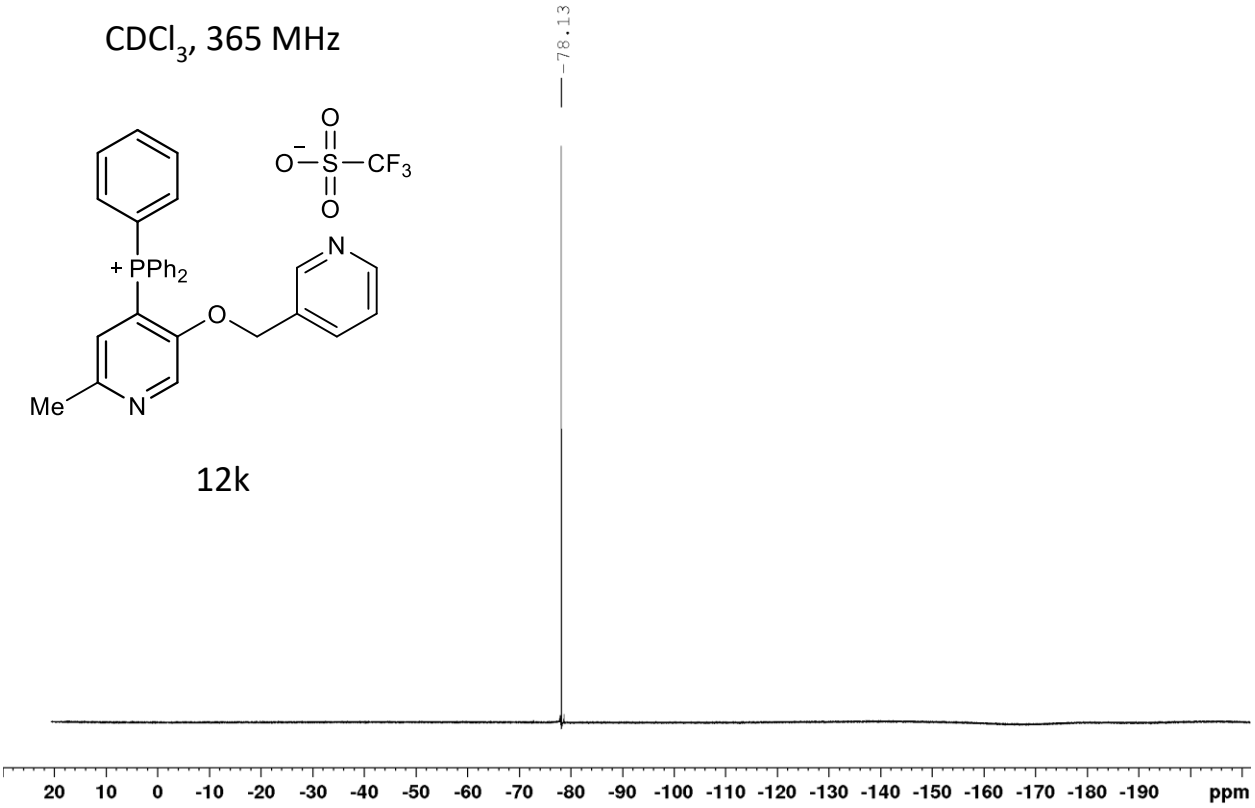


12j

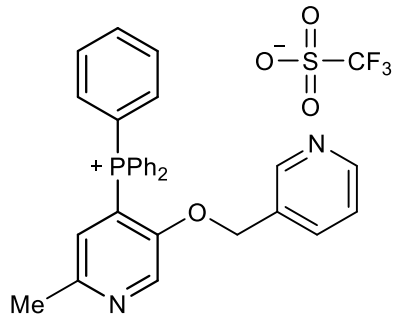

8.78
8.76
8.42
7.85
7.84
7.82
7.73
7.72
7.71
7.70
7.69
7.68
7.57
7.55
7.53
7.51
7.26
7.24
7.22
6.84
6.80
5.19
2.51
CDCl3, 400 MHz
+PPh2
O
N
Me
O
O
S
CF3
O
12k
0.86
0.68
15.00
0.87
0.83
0.93
1.70
2.64
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


9.04
9.03
8.67
8.65
6.80
6.76
6.67
6.63
CDCl3, 400 MHz
(crude 1H NMR)
+PPh2
O
N
Me
O
O
S
CF3
O
12k
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
12k
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
12k
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

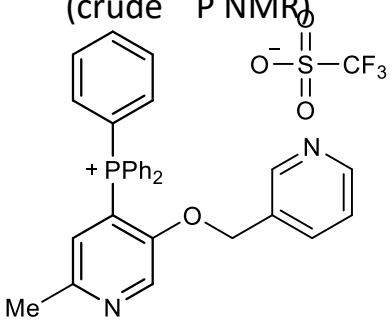
$CDCl_3$, 162 MHz



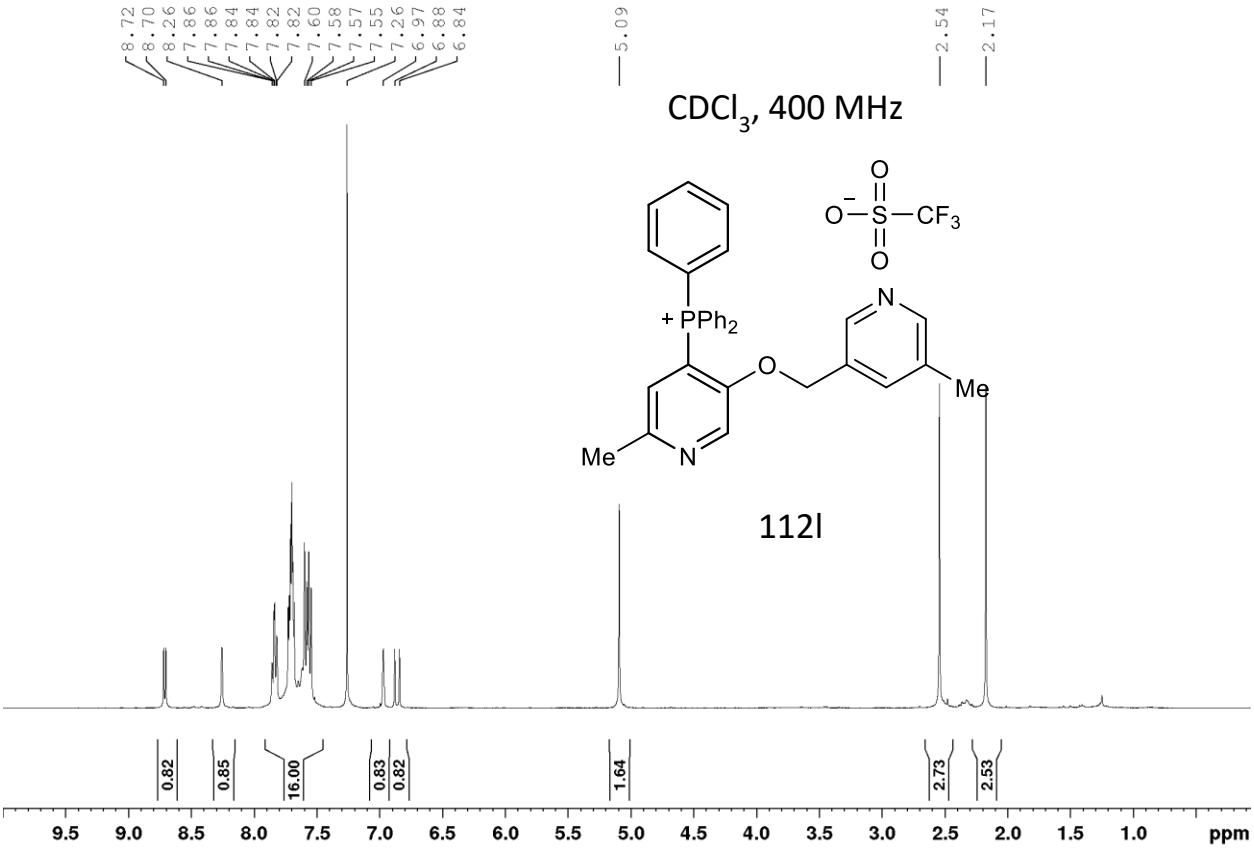
12k

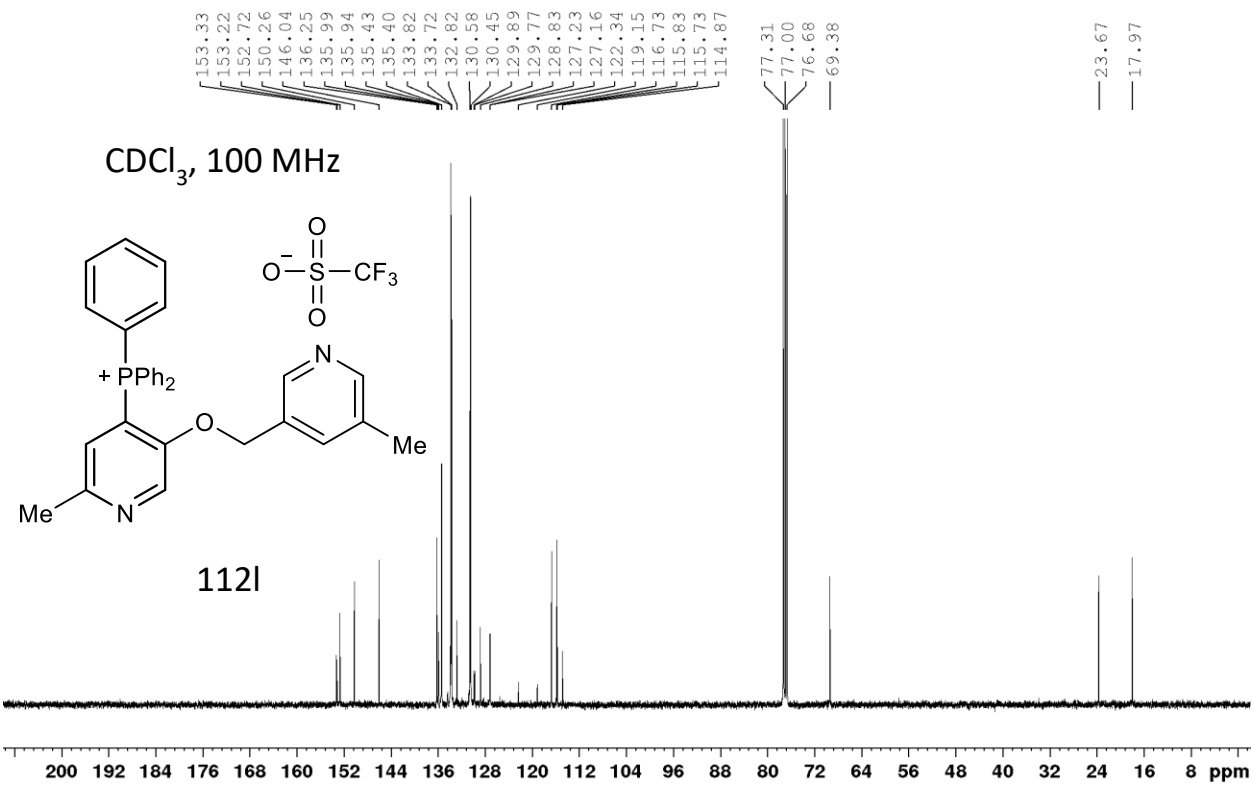
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

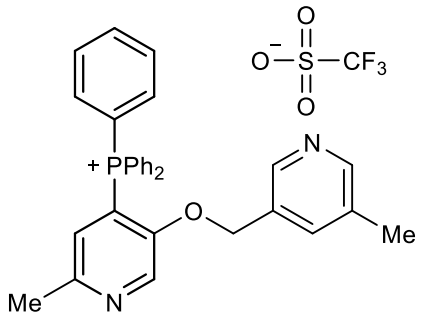


12k


8.72
8.70
8.26
7.86
7.86
7.84
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
+ PPh2
O
O
S
CF3
N
Me
Me
N
112l
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

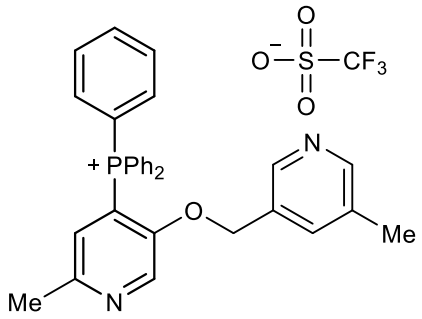

153.33
153.22
152.72
150.26
146.04
136.25
135.99
135.94
135.43
135.40
133.82
133.72
132.82
130.58
130.45
129.89
129.77
128.83
127.23
127.16
122.34
119.15
116.73
115.83
115.73
114.87
77.31
77.00
76.68
69.38
23.67
17.97
CDCl3, 100 MHz
+ PPh2
O
O
S
CF3
N
Me
Me
N
112l
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz



112l

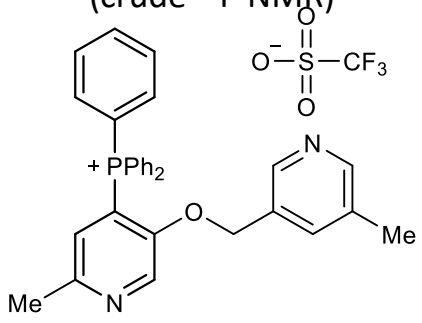
$CDCl_3$, 162 MHz



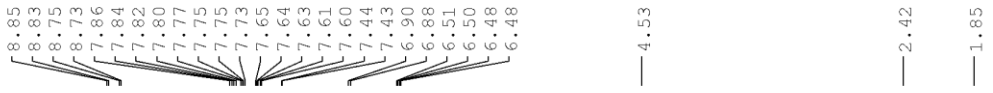
112l

$CDCl_3$, 162 MHz

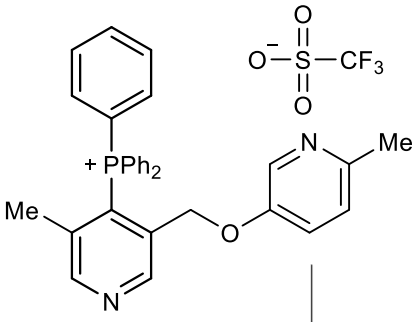
(crude ^{31}P NMR)



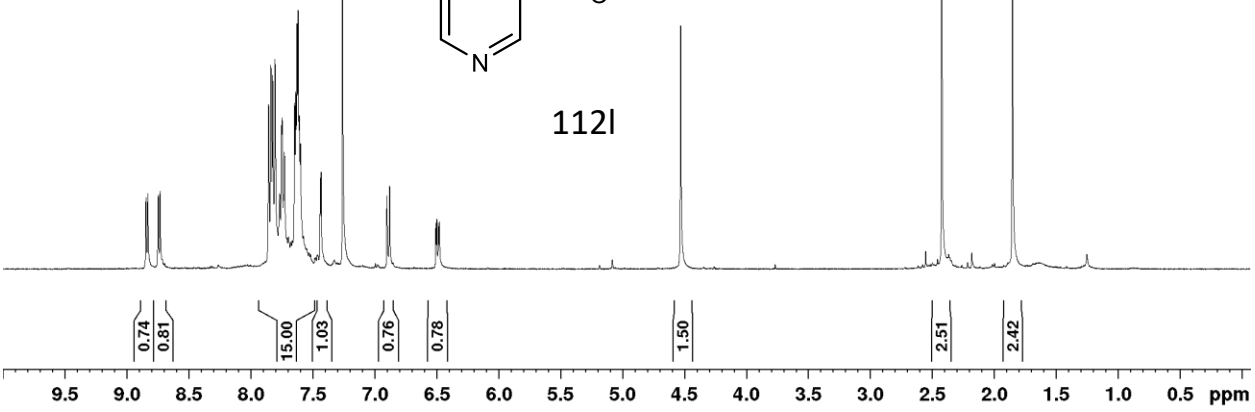
112l

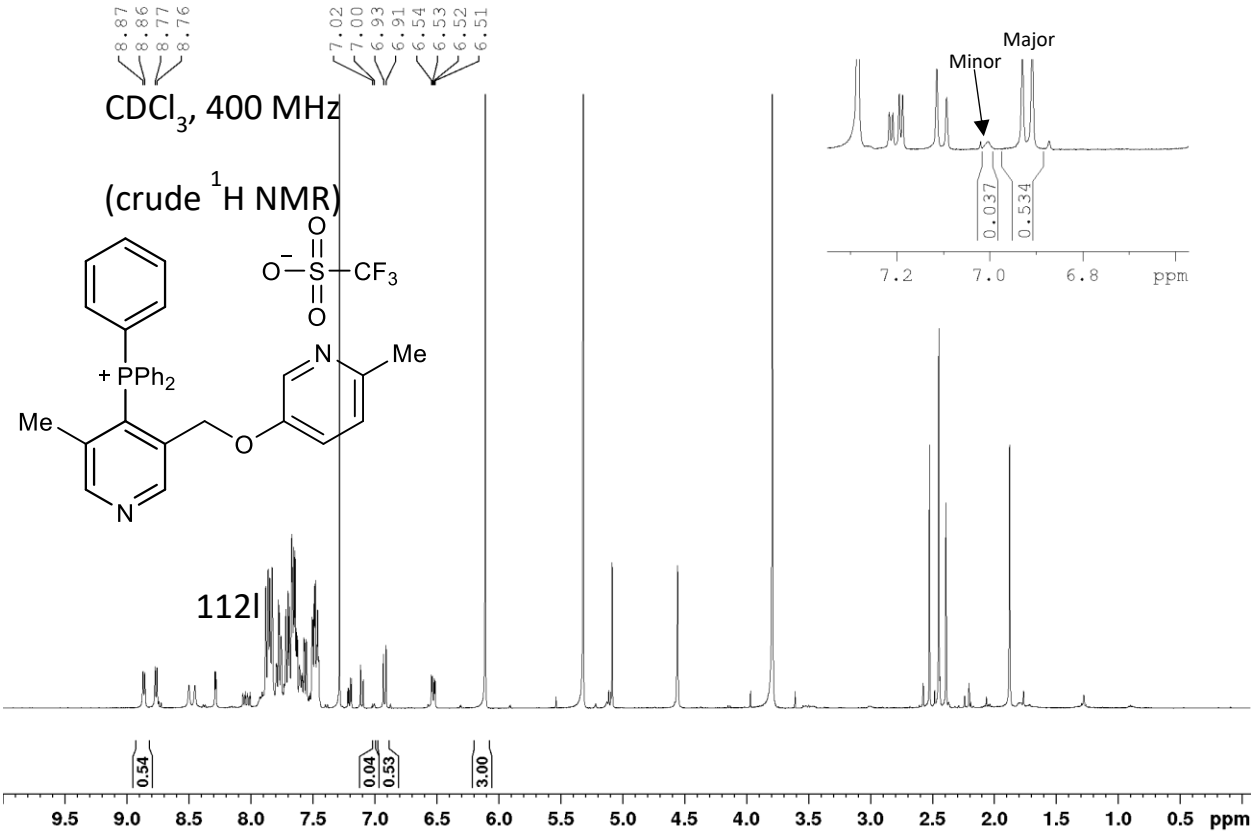


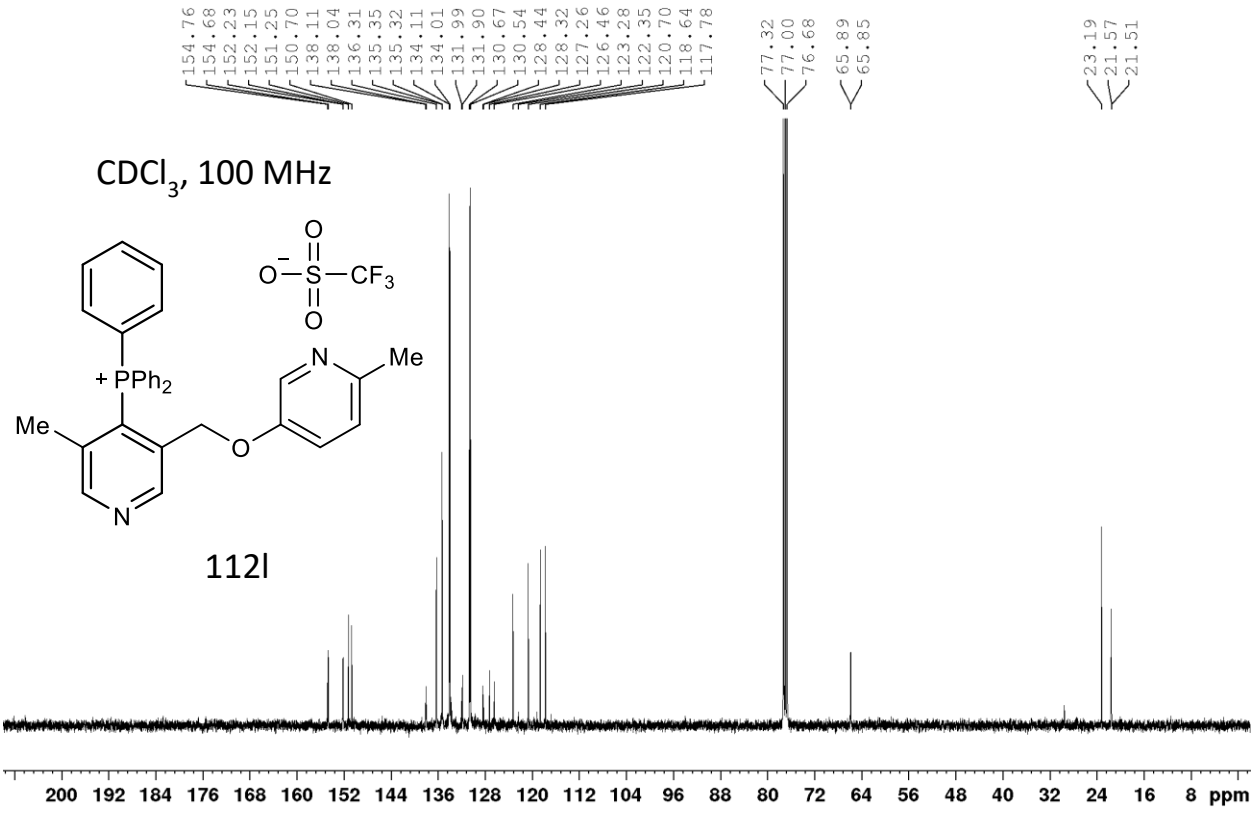
$CDCl_3$, 400 MHz



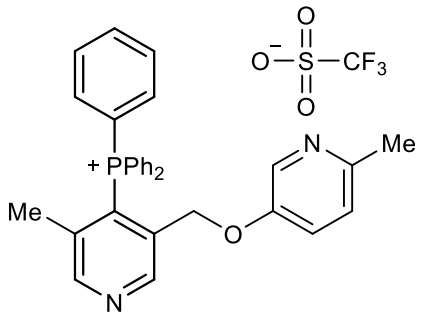
112l




8.87
8.86
8.77
8.76
7.02
7.00
6.93
6.91
6.54
6.53
6.52
6.51
CDCl3, 400 MHz
(crude 1H NMR)
Major
Minor
0.037
0.534
7.2
7.0
6.8
ppm
112l
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

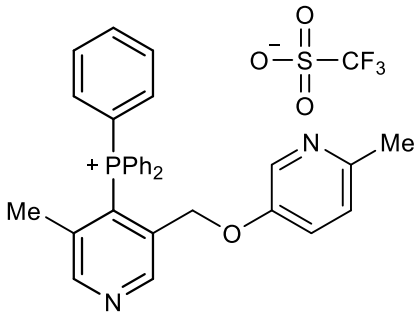

154.76
154.68
152.23
152.15
151.25
150.70
138.11
138.04
136.31
135.35
135.32
134.11
134.01
131.99
131.90
130.67
130.54
128.44
128.32
127.26
126.46
123.28
122.35
120.70
118.64
117.78
77.32
77.00
76.68
65.89
65.85
23.19
21.57
21.51
CDCl3, 100 MHz
112l
200 192 184 176 168 160 152 144 136 128 120 112 104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

$CDCl_3$, 365 MHz

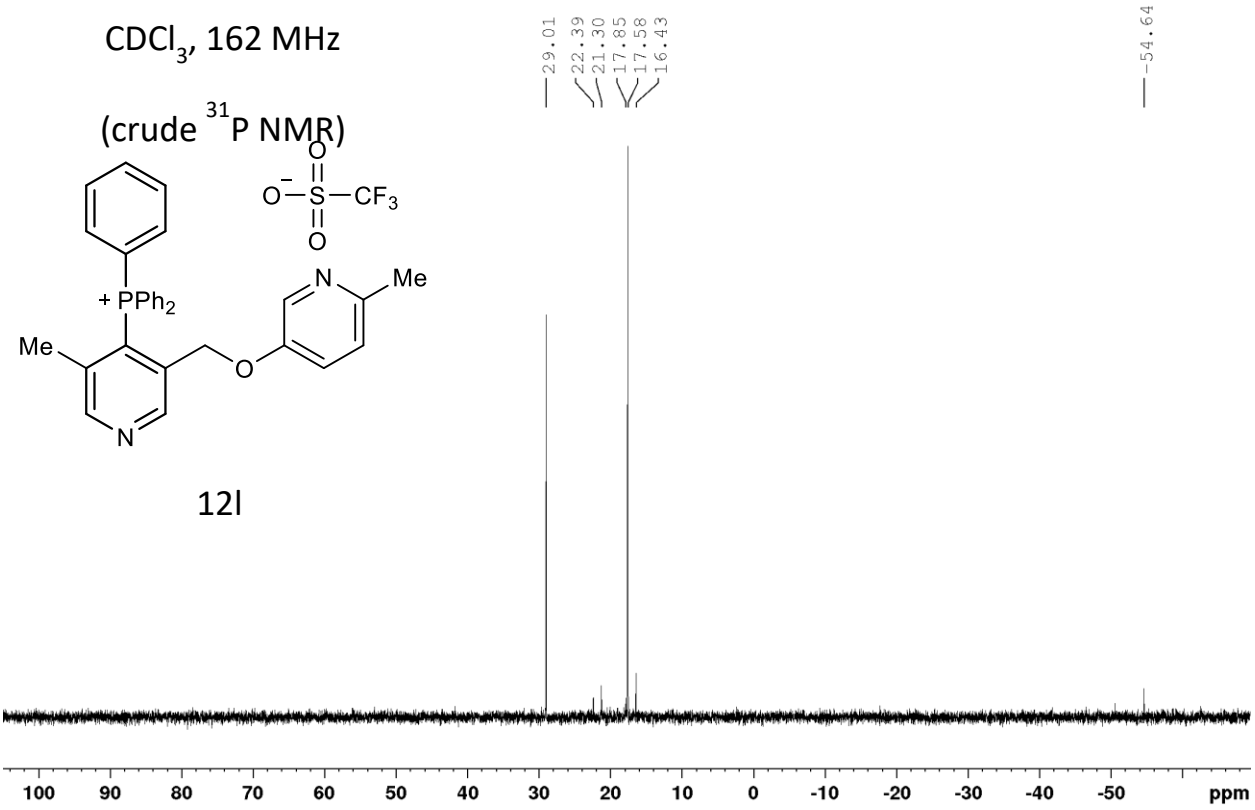


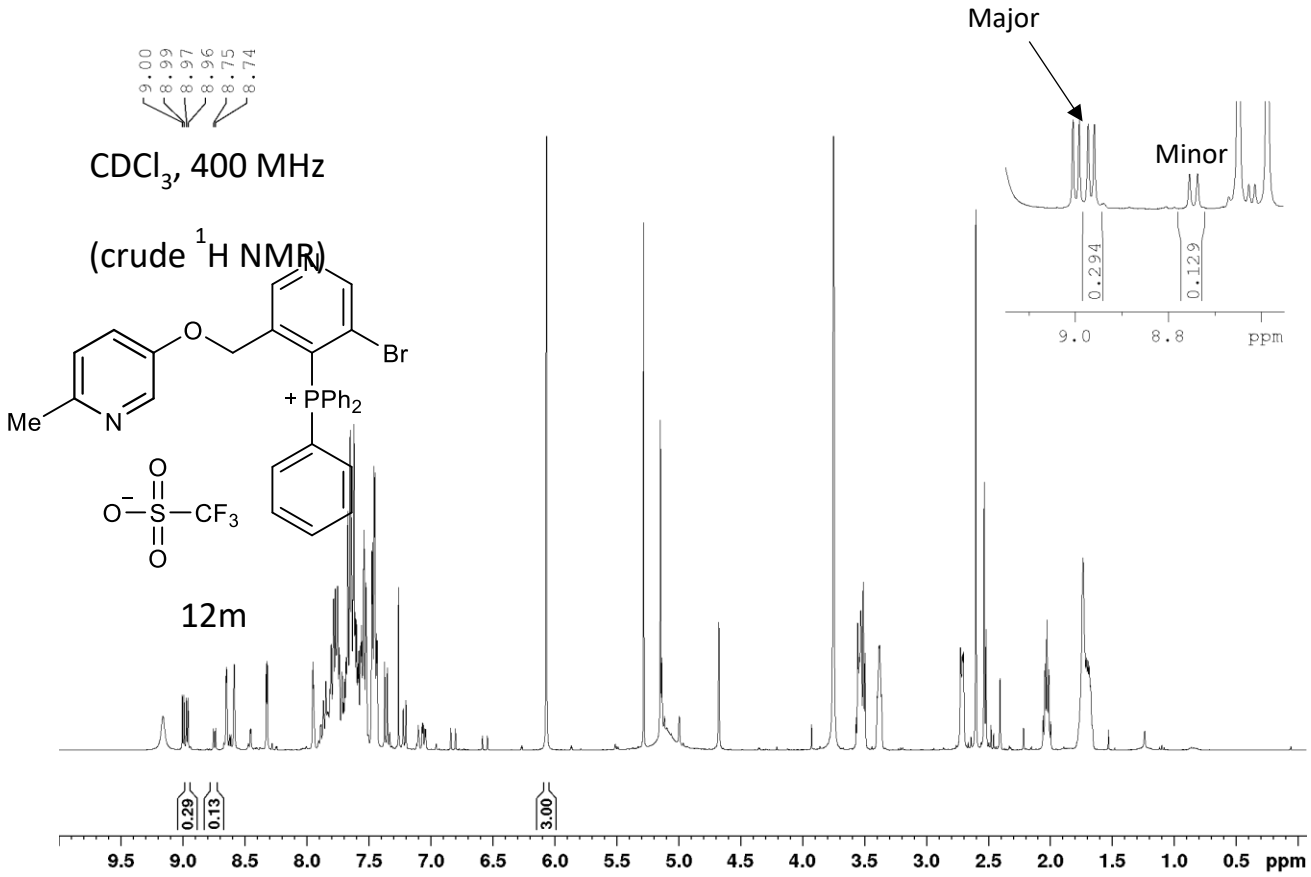
112l

$CDCl_3$, 162 MHz



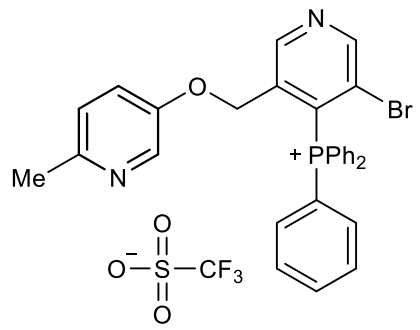
12l


CDCl3, 162 MHz
(crude 31P NMR)
12l
29.01
22.39
21.30
17.85
17.58
16.43
-54.64
ppm


CDCl3, 400 MHz
(crude 1H NMR)
12m
Major
Minor
0.294
0.129
0.29
0.13
3.00
ppm

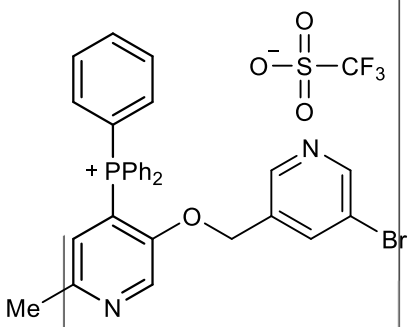
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

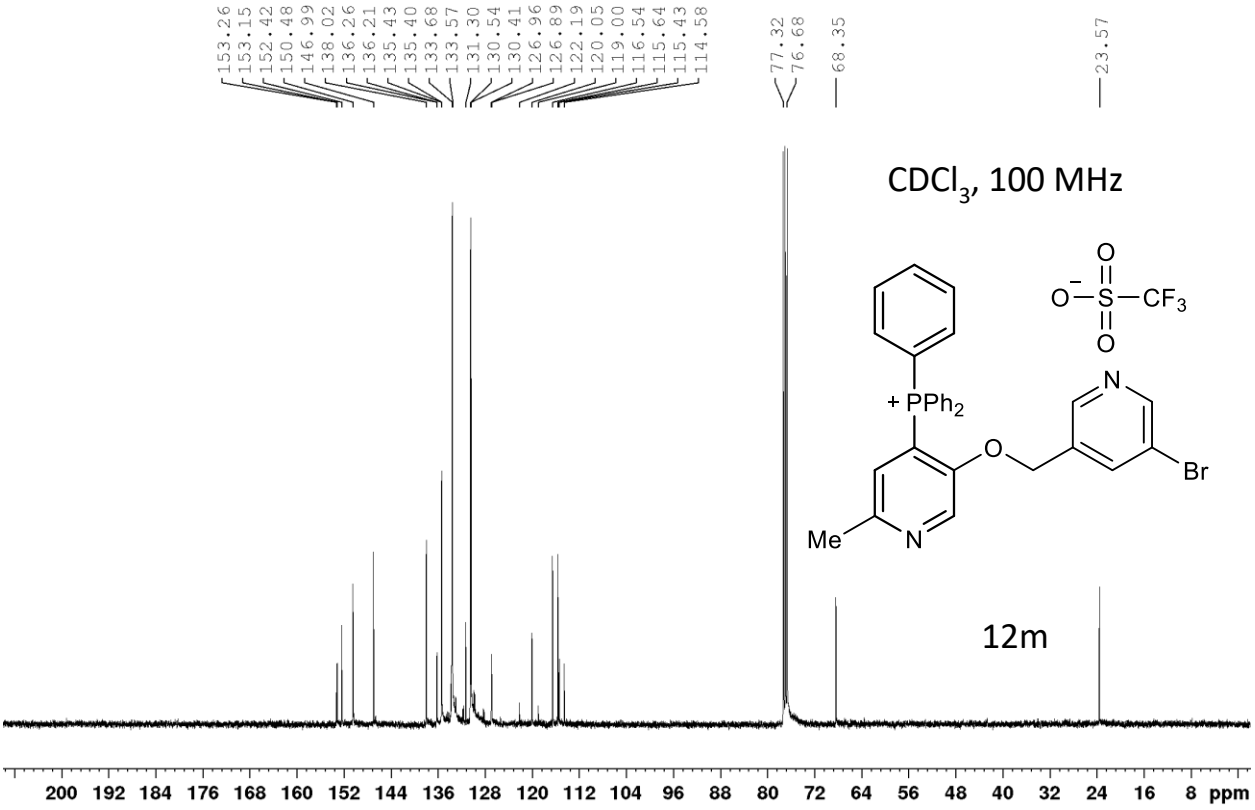


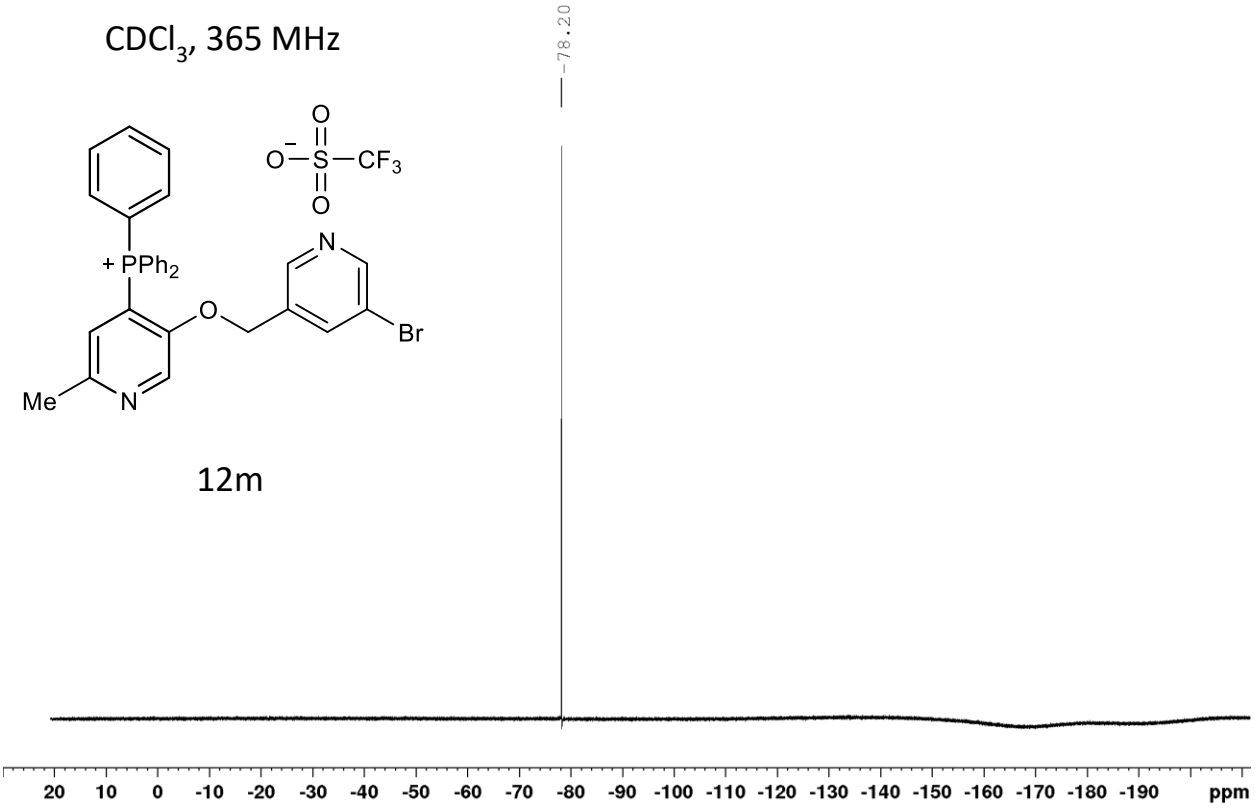
12m

$CDCl_3$, 400 MHz

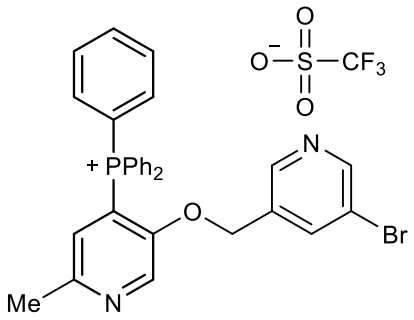


12m


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
12m
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
-78.20
12m
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

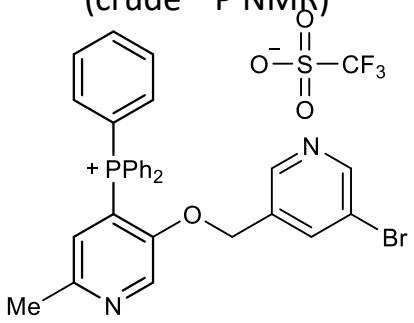
$CDCl_3$, 162 MHz



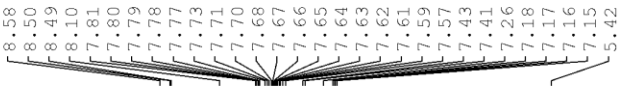
12m

$CDCl_3$, 162 MHz

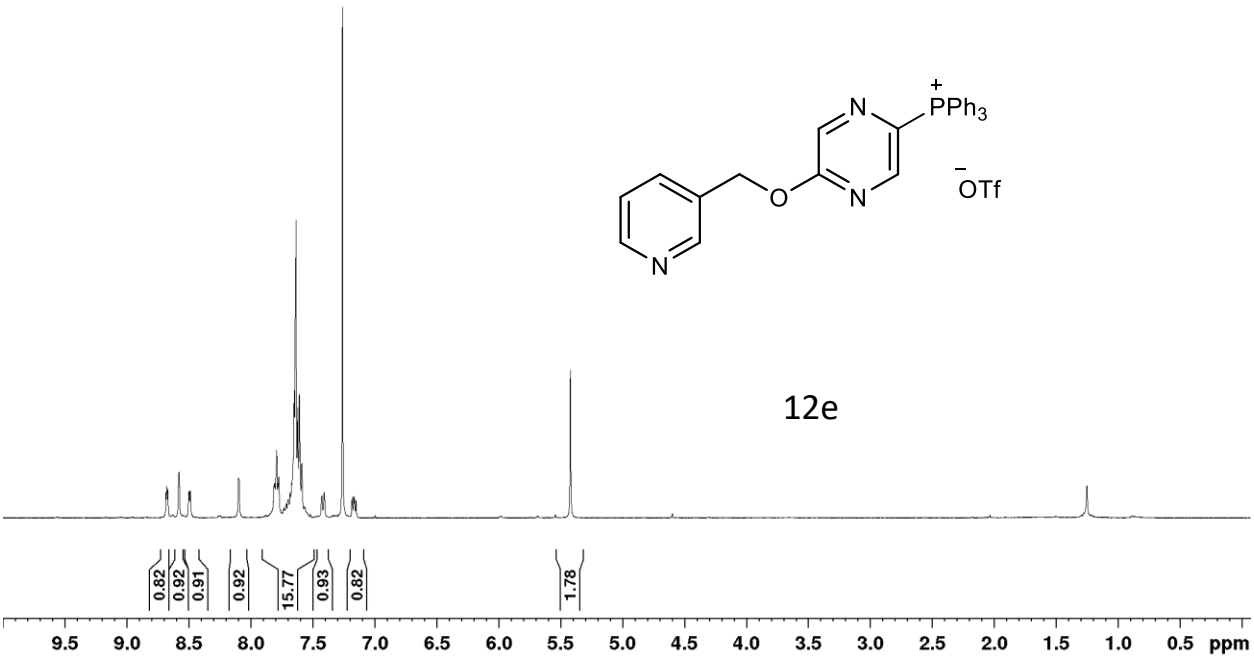
(crude ^{31}P NMR)



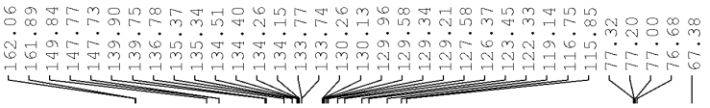
12m



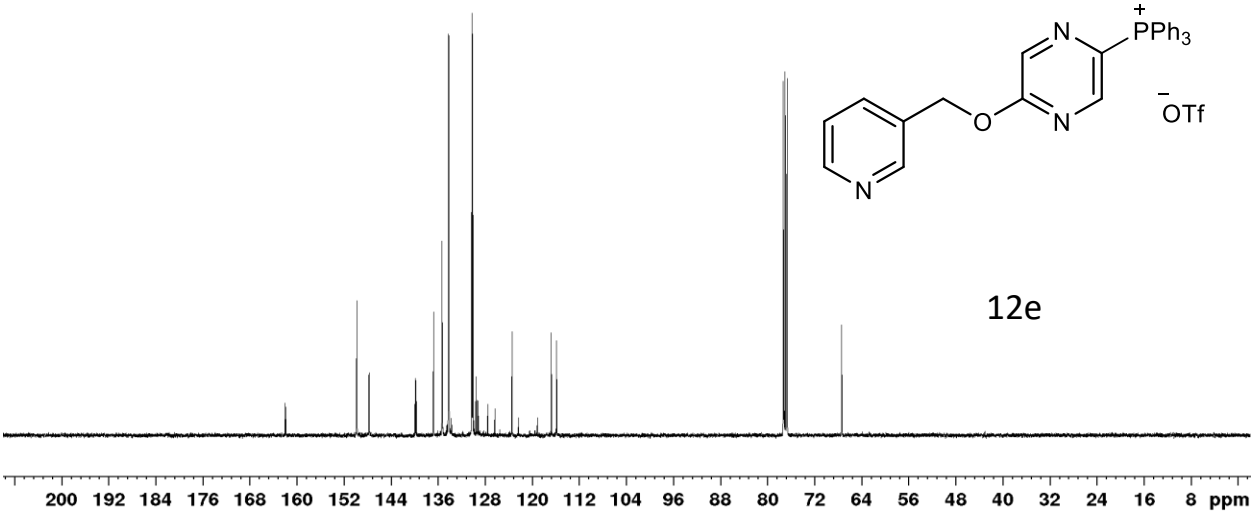
$CDCl_3$, 400 MHz



12e

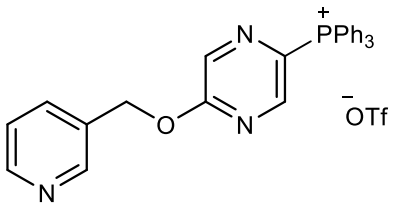


$CDCl_3$, 100 MHz



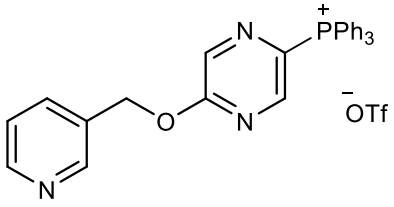
12e

$CDCl_3$, 365 MHz

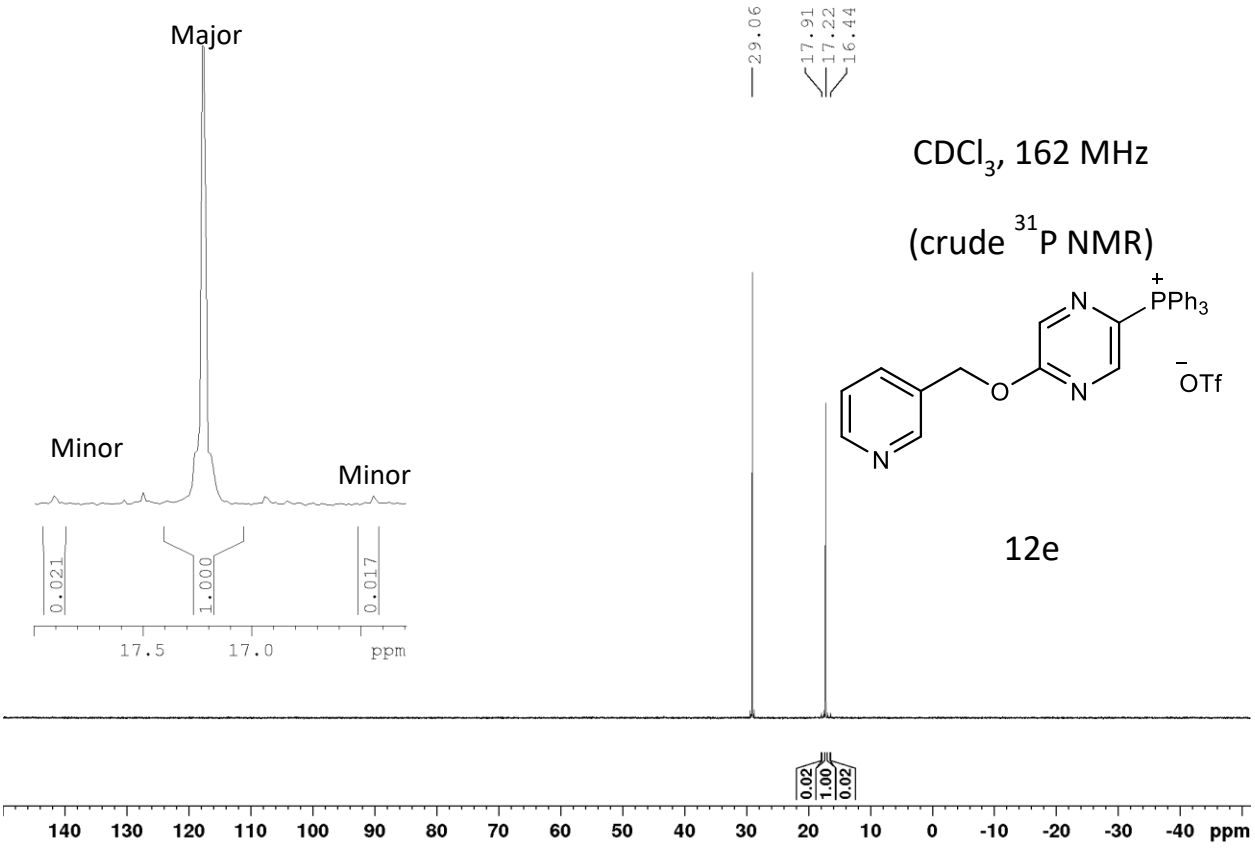


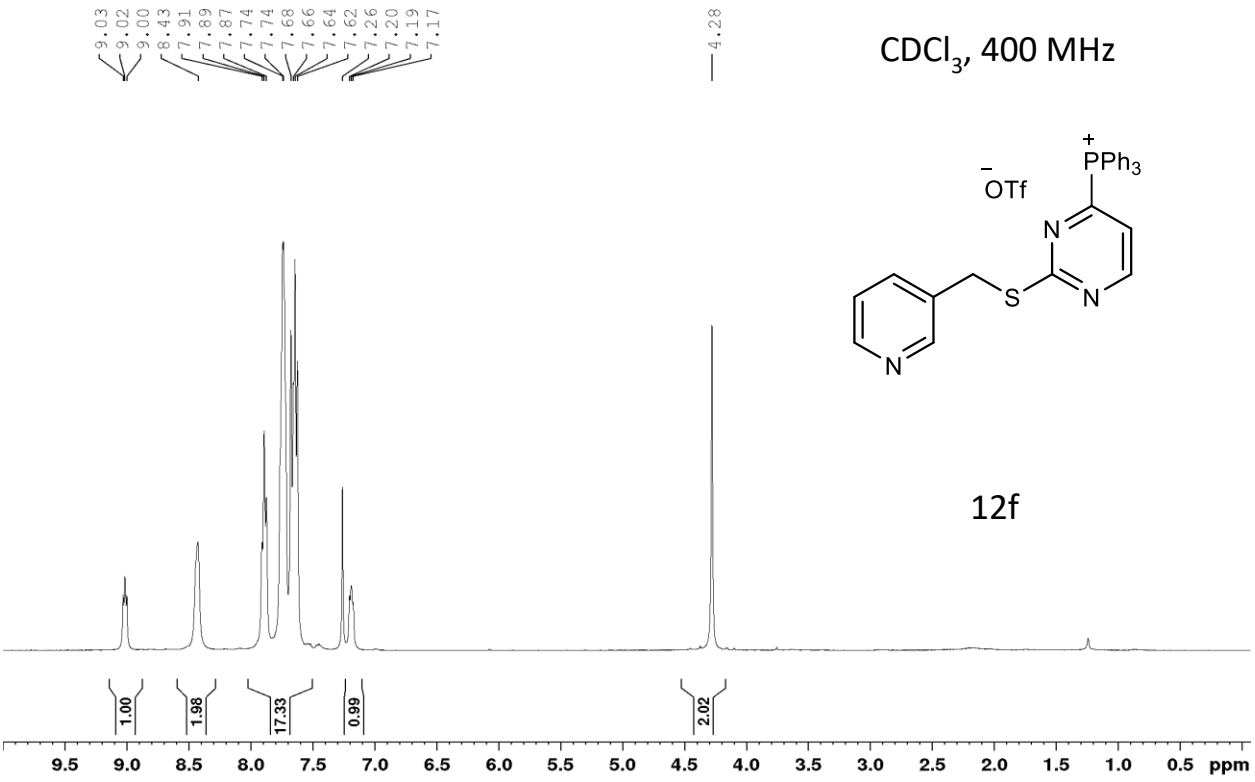
12e

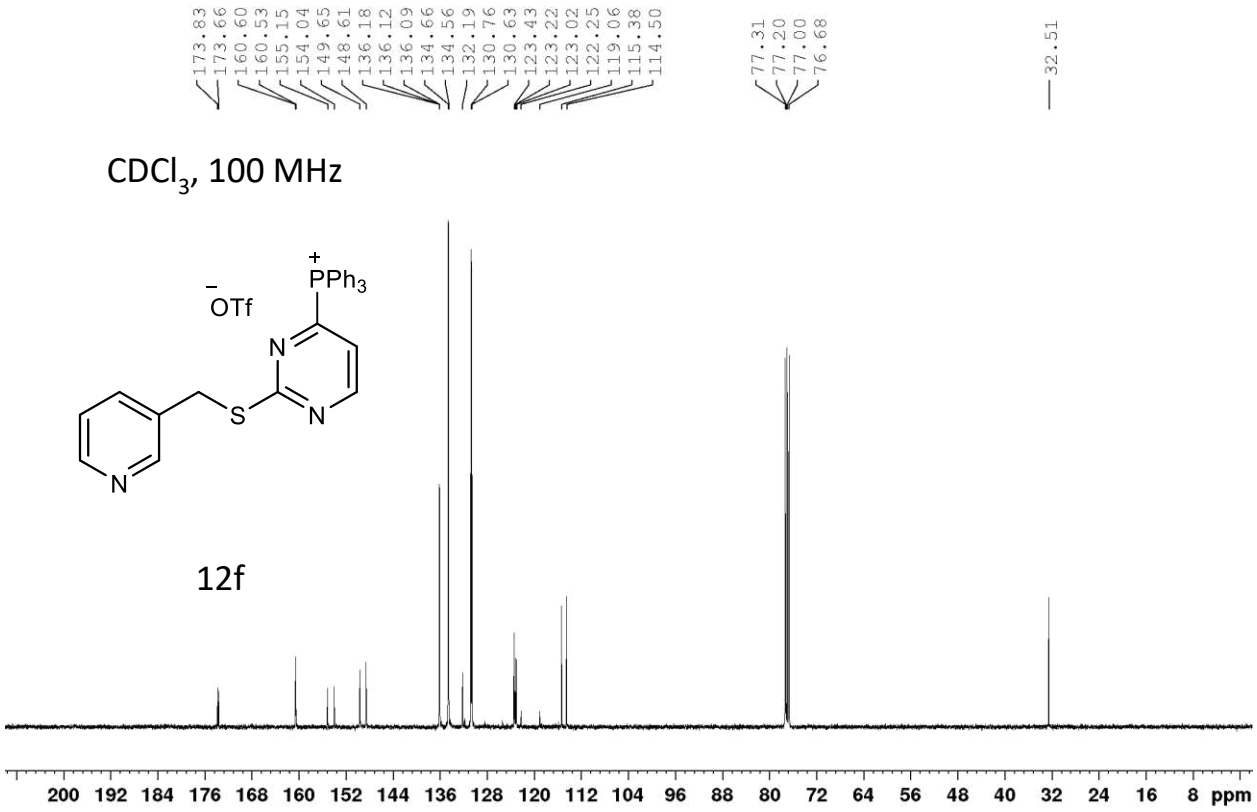
$CDCl_3$, 162 MHz

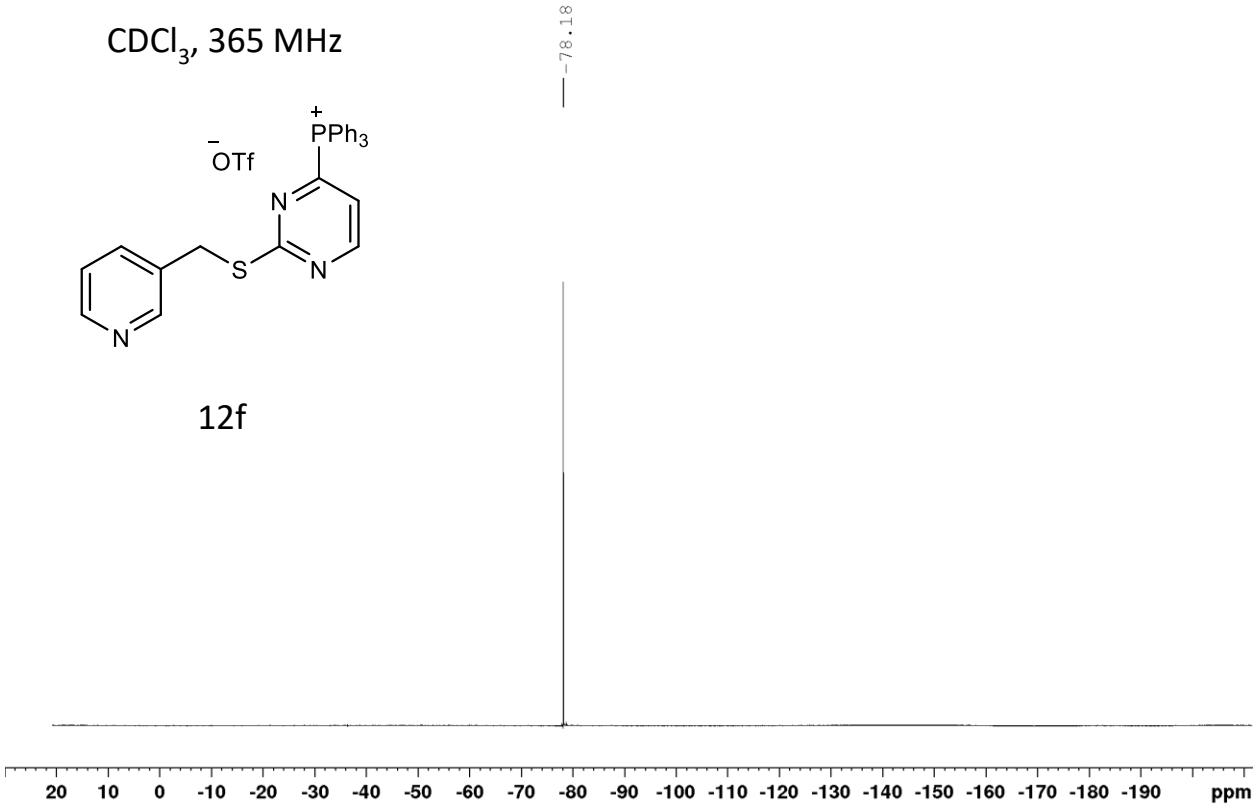


12e

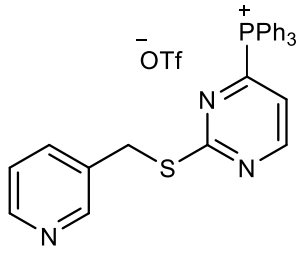

Major
Minor
Minor
29.06
17.91
17.22
16.44
0.021
1.000
0.017
17.5
17.0
ppm
CDCl3, 162 MHz
(crude 31P NMR)
PPh3
OTf
12e
0.02
1.00
0.02
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


9.03
9.02
9.00
8.43
7.91
7.89
7.87
7.74
7.74
7.68
7.66
7.64
7.62
7.26
7.20
7.19
7.17
4.28
CDCl3, 400 MHz
PPh3
OTf
12f
1.00
1.98
17.33
0.99
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

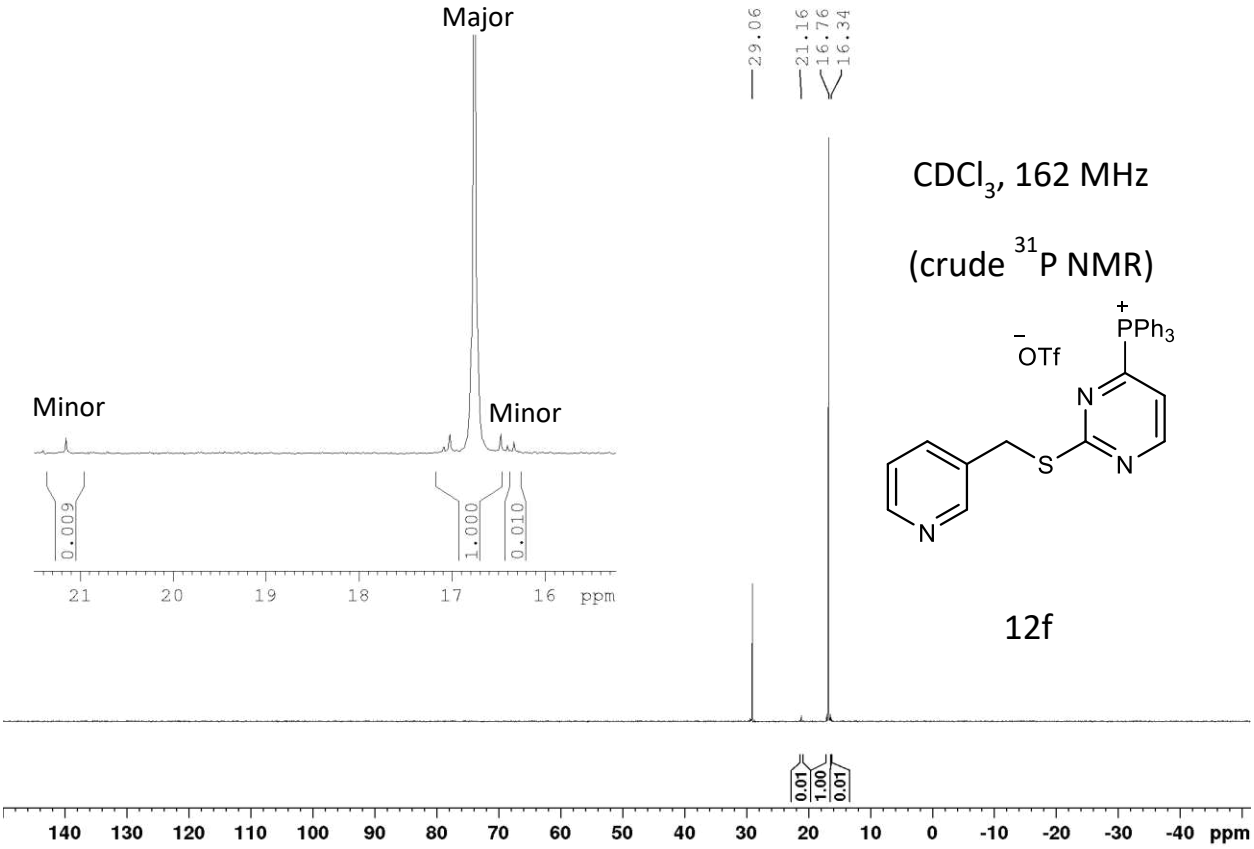

173.83
173.66
160.60
160.53
155.15
154.04
149.65
148.61
136.18
136.12
136.09
134.66
134.56
132.19
130.76
130.63
123.43
123.22
123.02
122.25
119.06
115.38
114.50
77.31
77.20
77.00
76.68
32.51
CDCl3, 100 MHz
PPh3
OTf
N
S
N
N
12f
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm


-78.18
CDCl3, 365 MHz
PPh3
OTf
N
S
N
N
12f
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



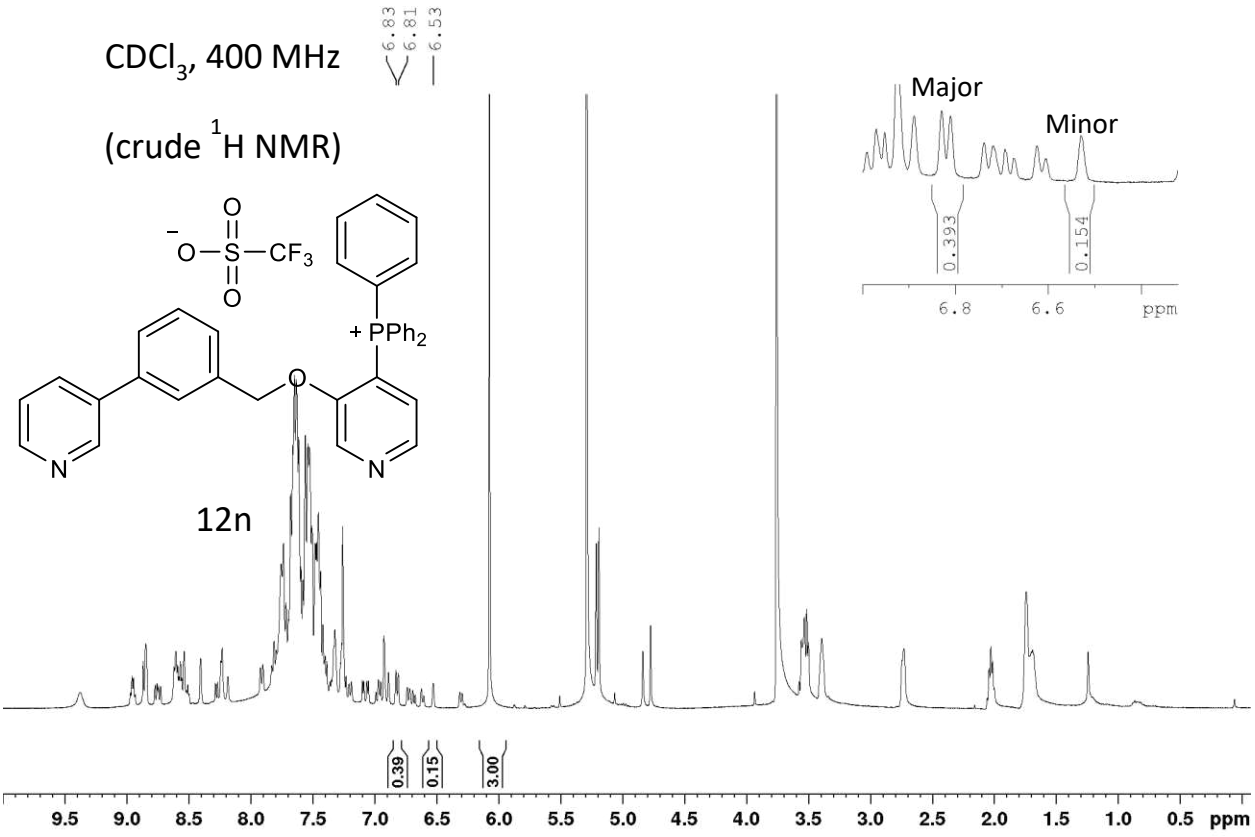
12f

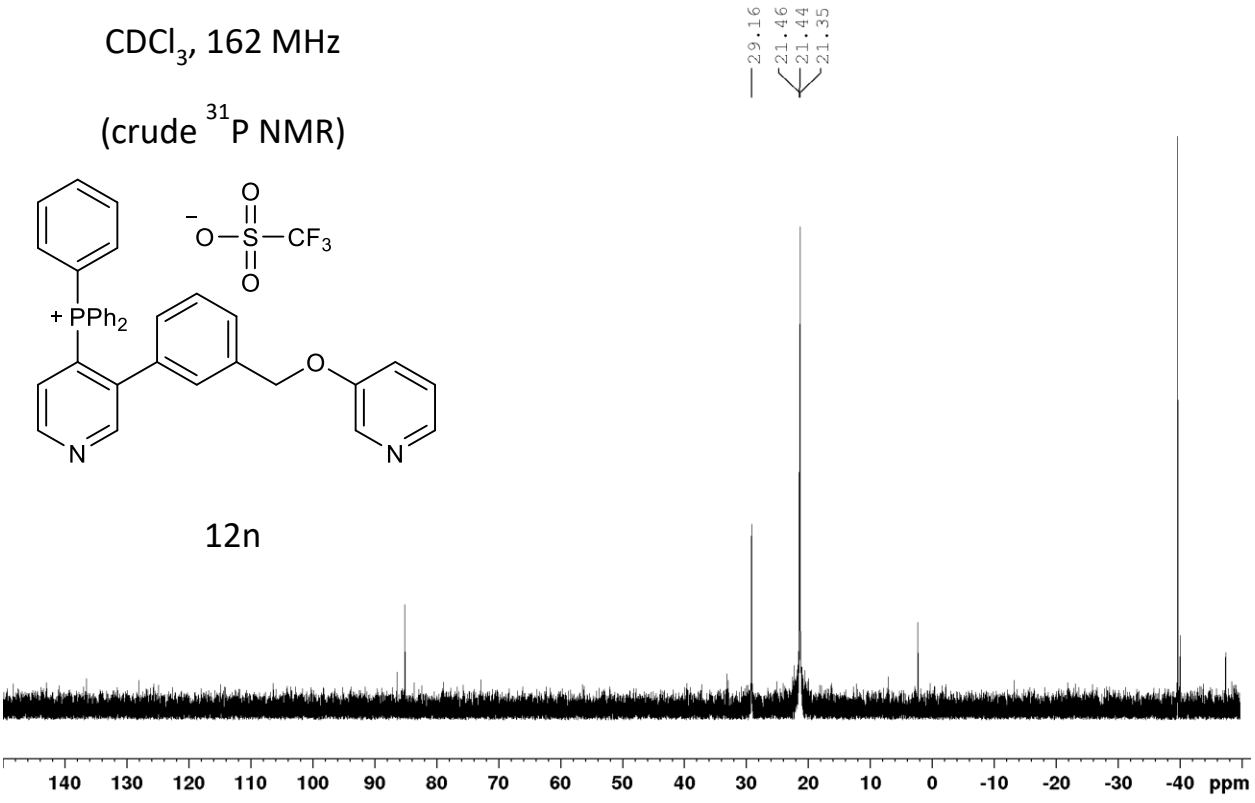


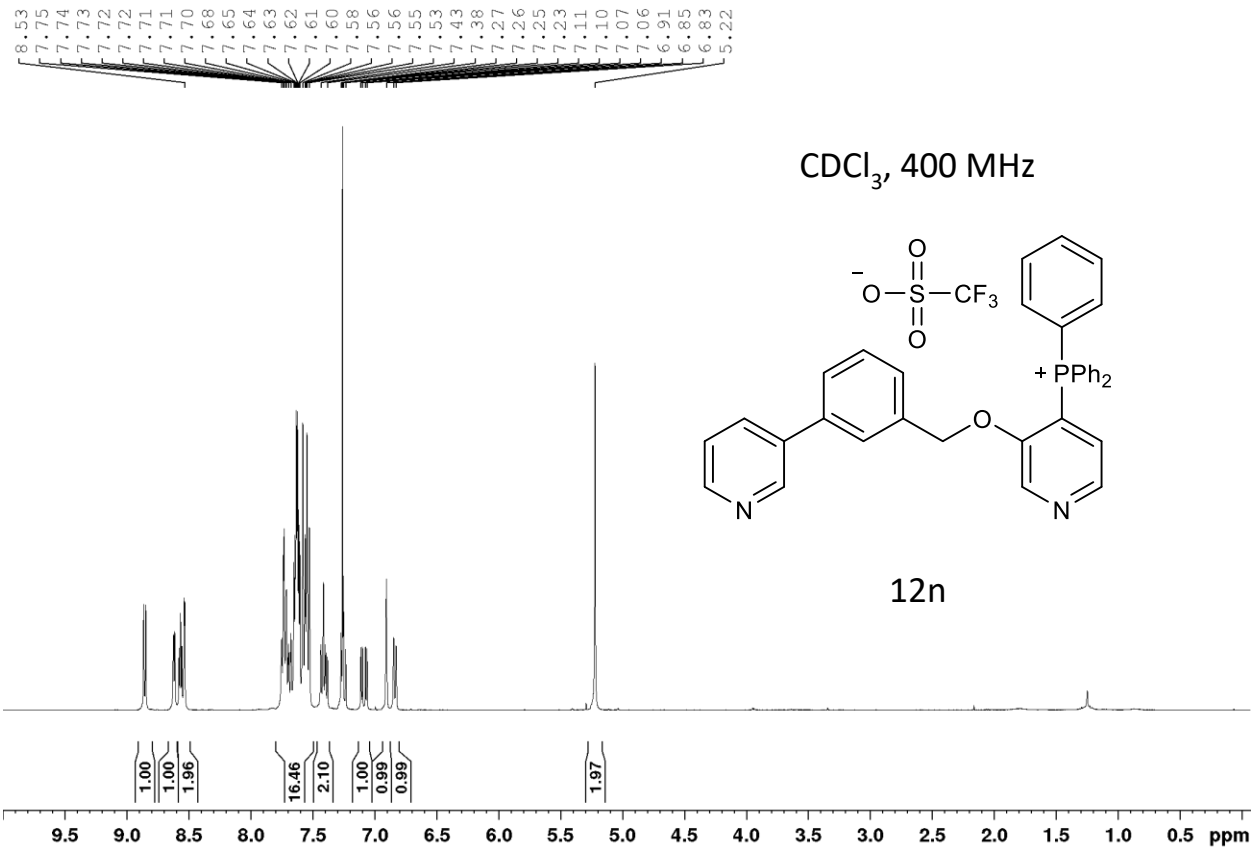
$CDCl_3$, 162 MHz

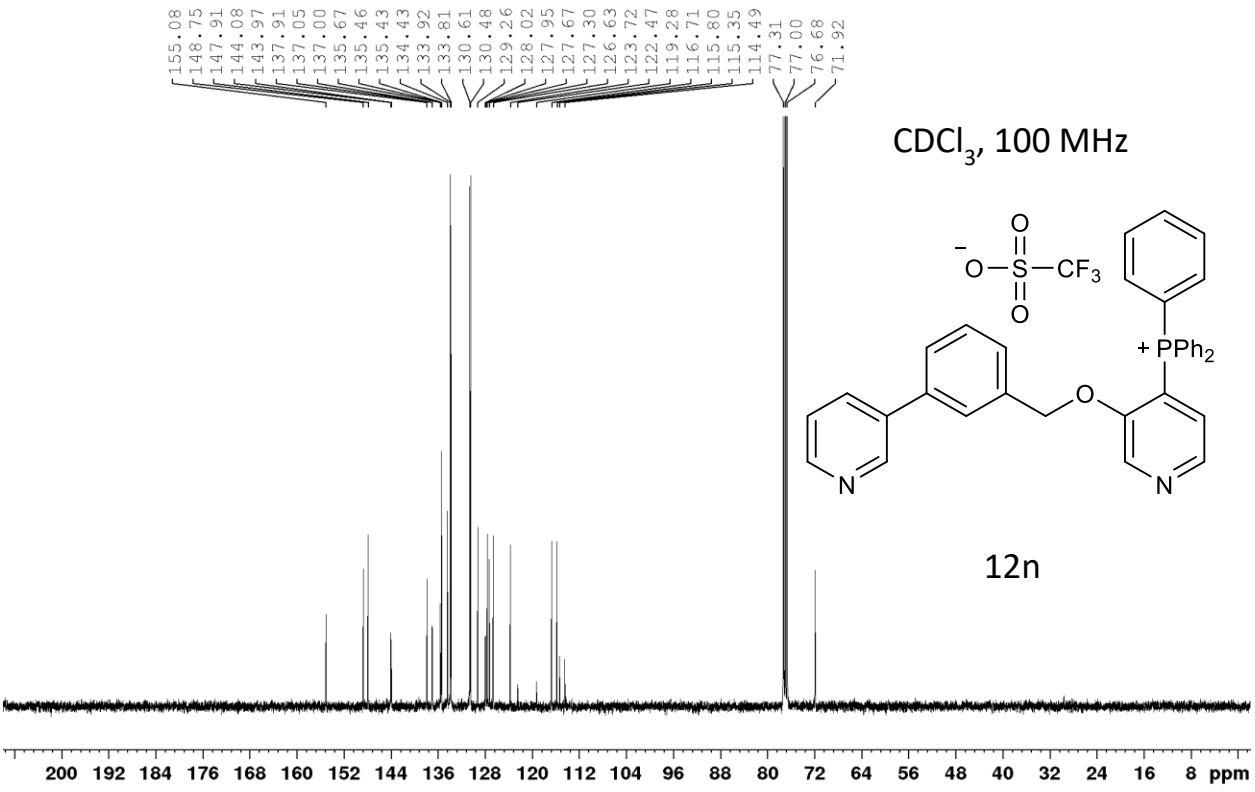
(crude ^{31}P NMR)

12f

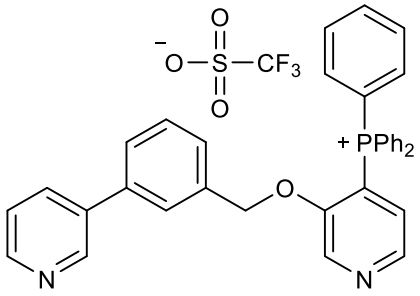

CDCl3, 400 MHz
(crude 1H NMR)
6.83
6.81
6.53
Major
Minor
0.393
0.154
6.8
6.6
ppm
+ PPh2
O
N
12n
0.39
0.15
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


CDCl3, 162 MHz
(crude 31P NMR)
29.16
21.46
21.44
21.35
+ PPh2
O
N
12n
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
+ PPh2
12n
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

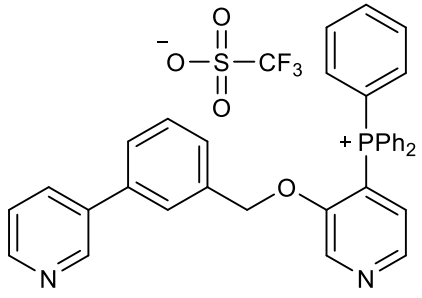

155.08
148.75
147.91
144.08
143.97
137.91
137.05
137.00
135.67
135.46
135.43
134.43
133.92
133.81
130.61
130.48
129.26
128.02
127.95
127.67
127.30
126.63
123.72
122.47
119.28
116.71
115.80
115.35
114.49
77.31
77.00
76.68
71.92
CDCl3, 100 MHz
+ PPh2
12n
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz



12n

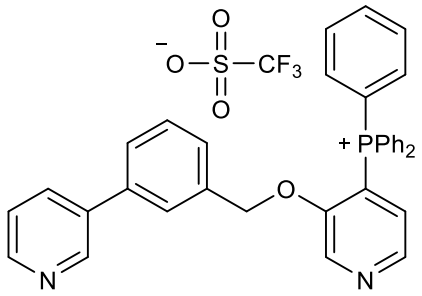
$CDCl_3$, 162 MHz



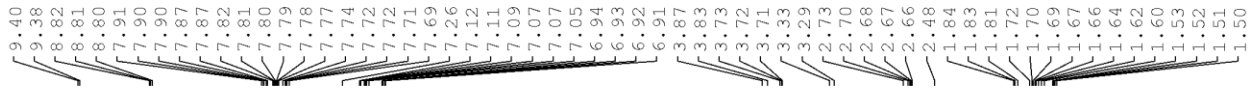
12n

$CDCl_3$, 162 MHz

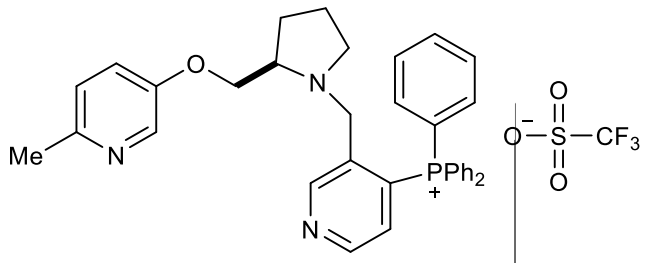
(crude ^{31}P NMR)



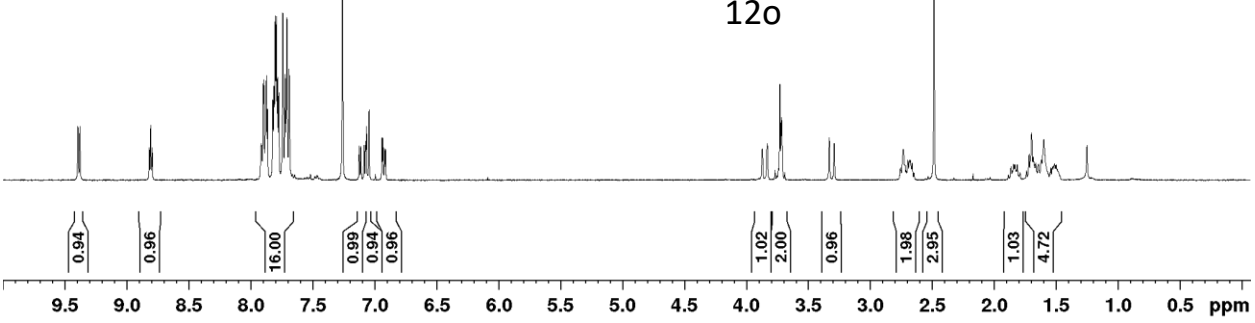
12n

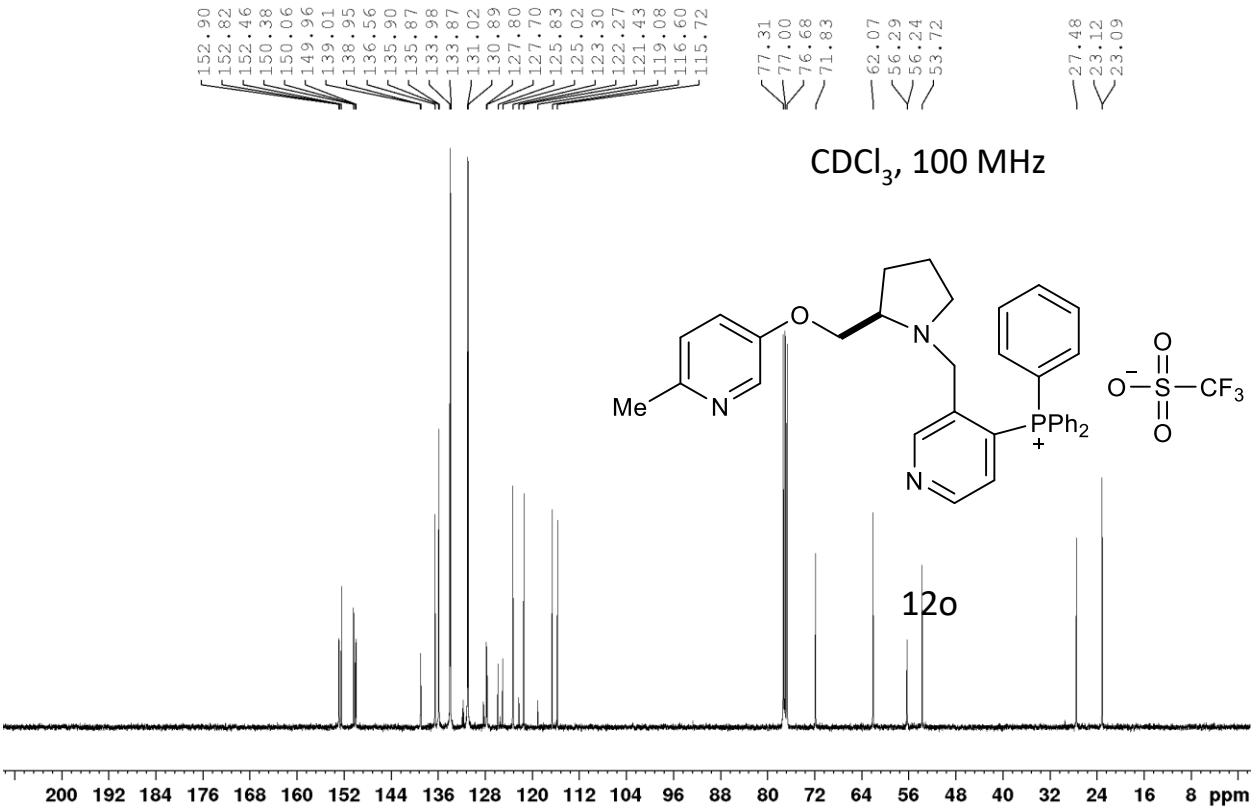


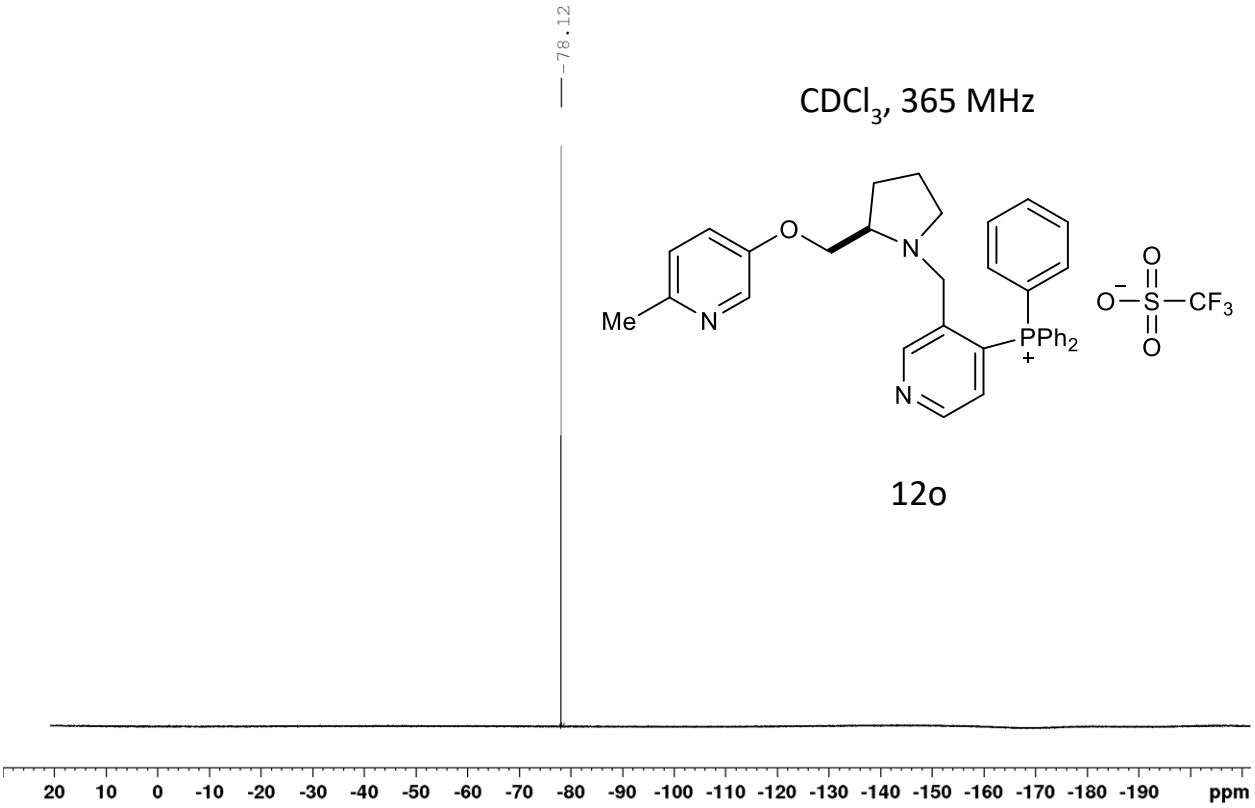
$CDCl_3$, 400 MHz

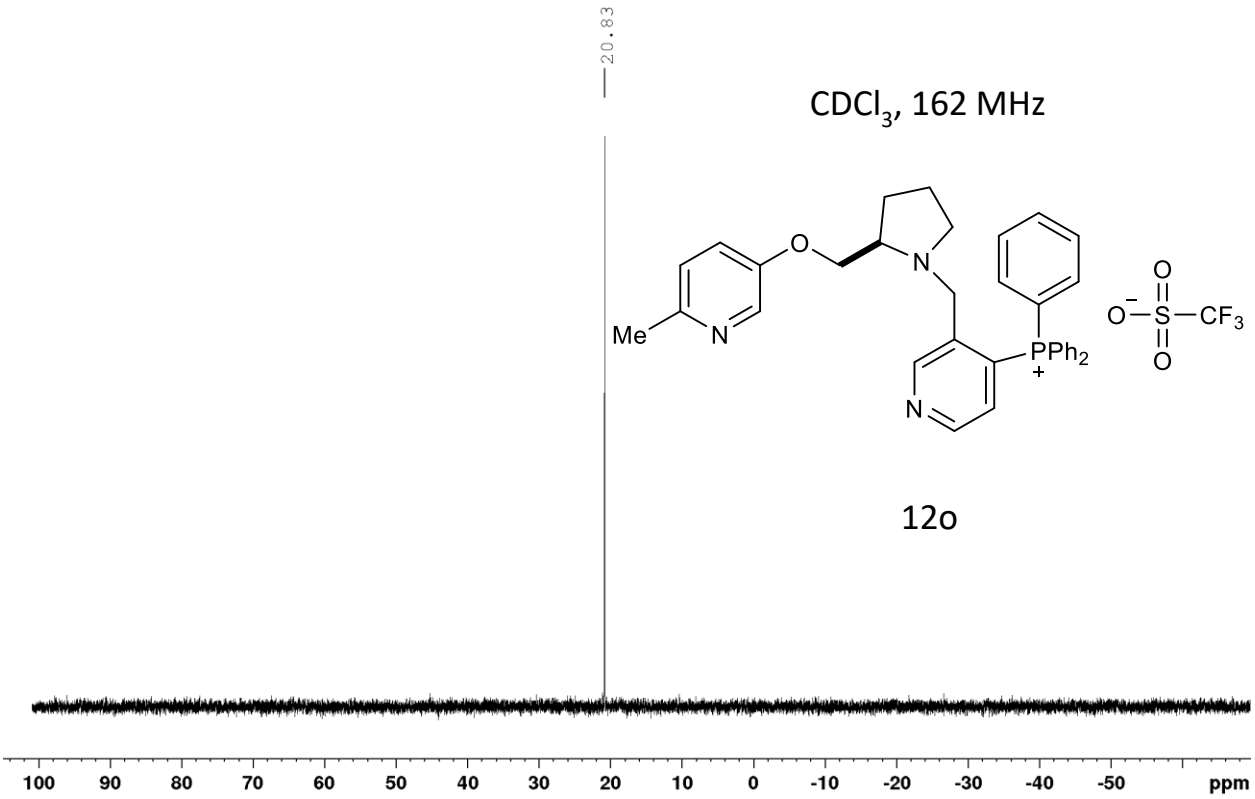


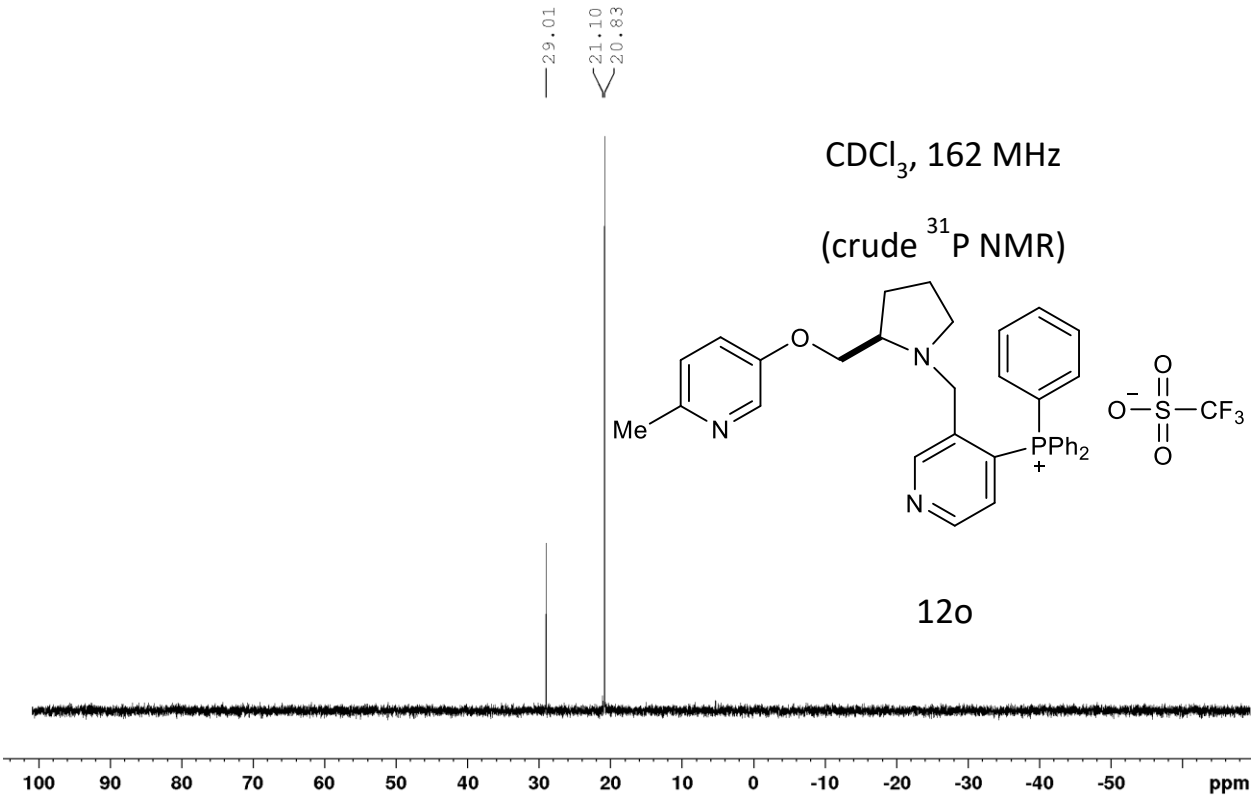
12o

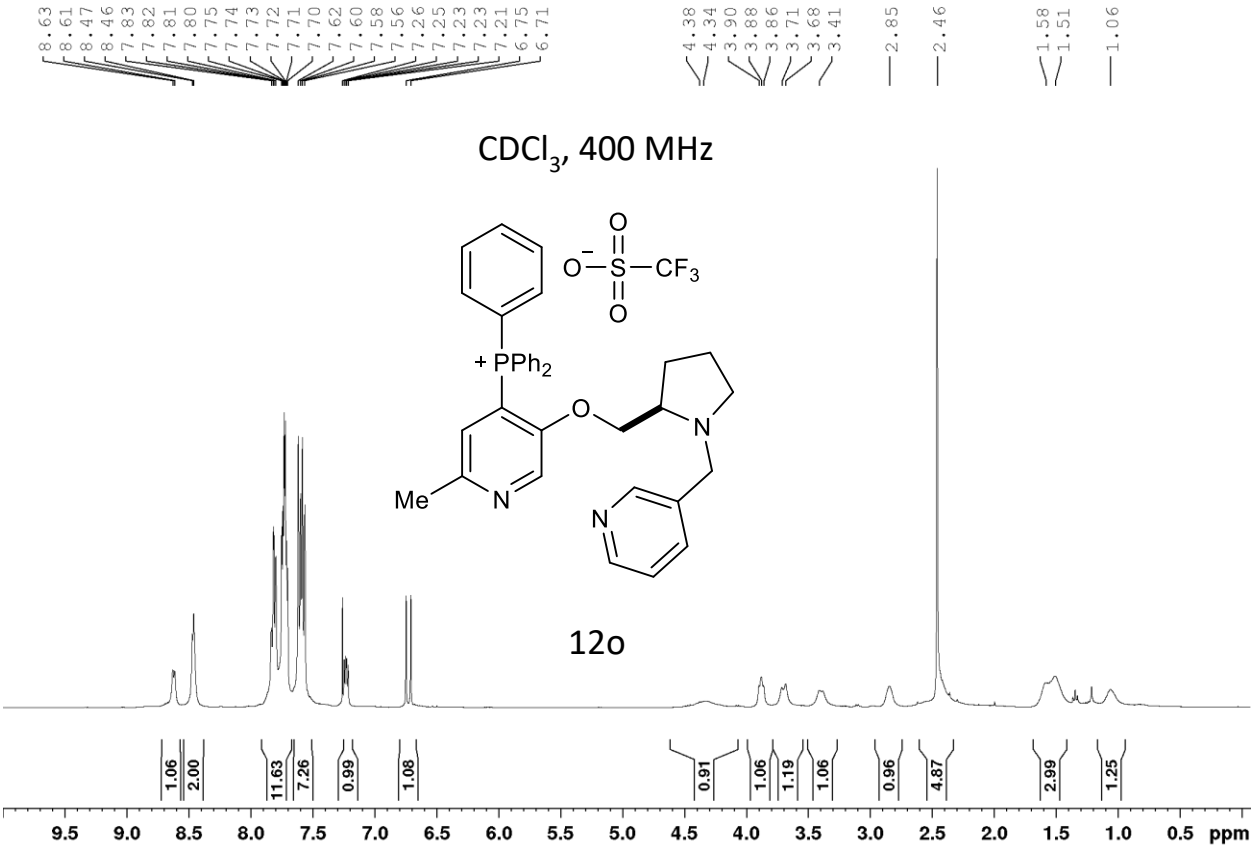


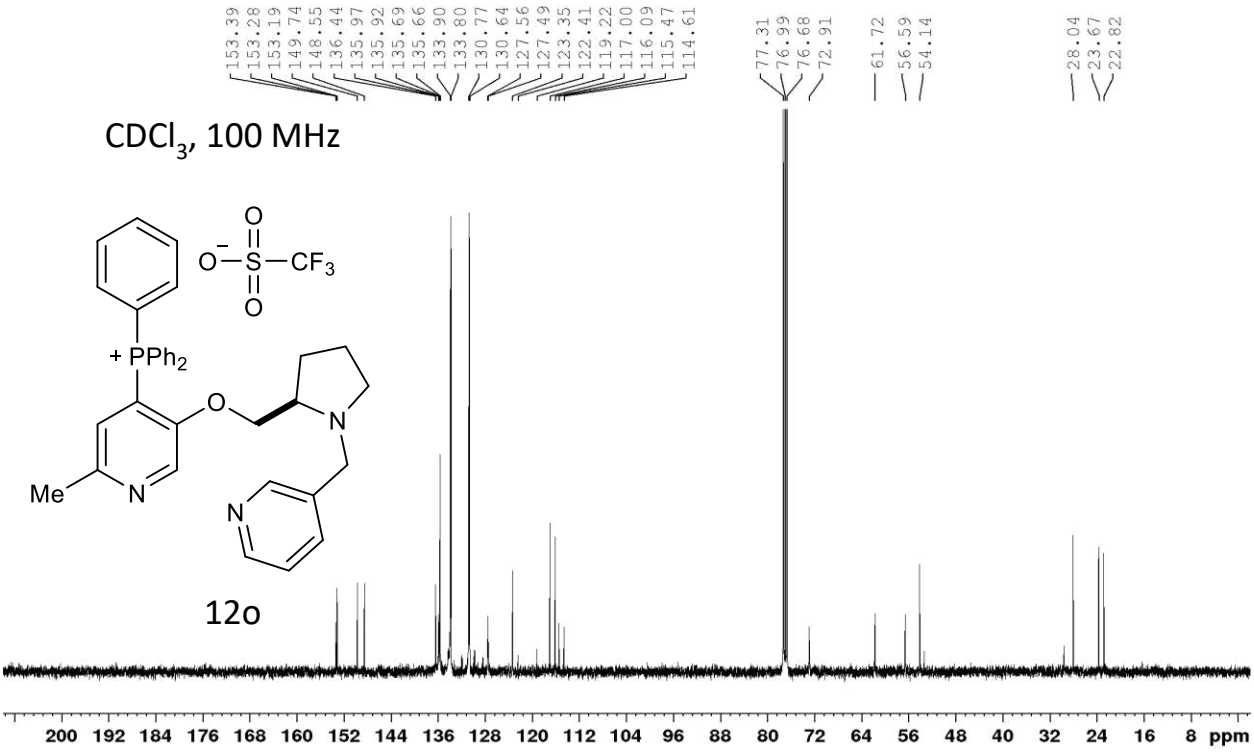

152.90
152.82
152.46
150.38
150.06
149.96
139.01
138.95
136.56
135.90
135.87
133.98
133.87
131.02
130.89
127.80
127.70
125.83
125.02
123.30
122.27
121.43
119.08
116.60
115.72
77.31
77.00
76.68
71.83
62.07
56.29
56.24
53.72
27.48
23.12
23.09
CDCl3, 100 MHz
Me
N
O
N
PPh2
+
N
O
O
S
CF3
O
O
12o
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

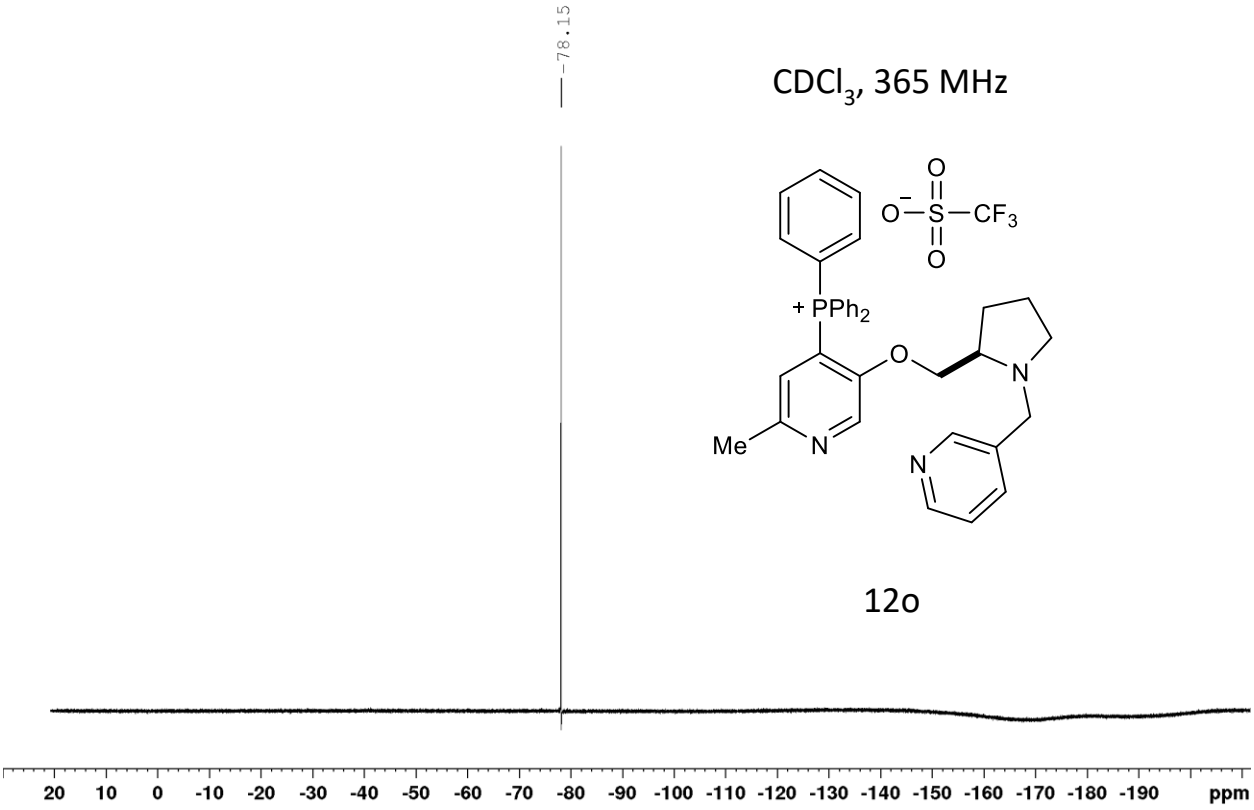

-78.12
CDCl3, 365 MHz
Me
N
O
N
PPh2
+
N
O
O
S
CF3
O
O
12o
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

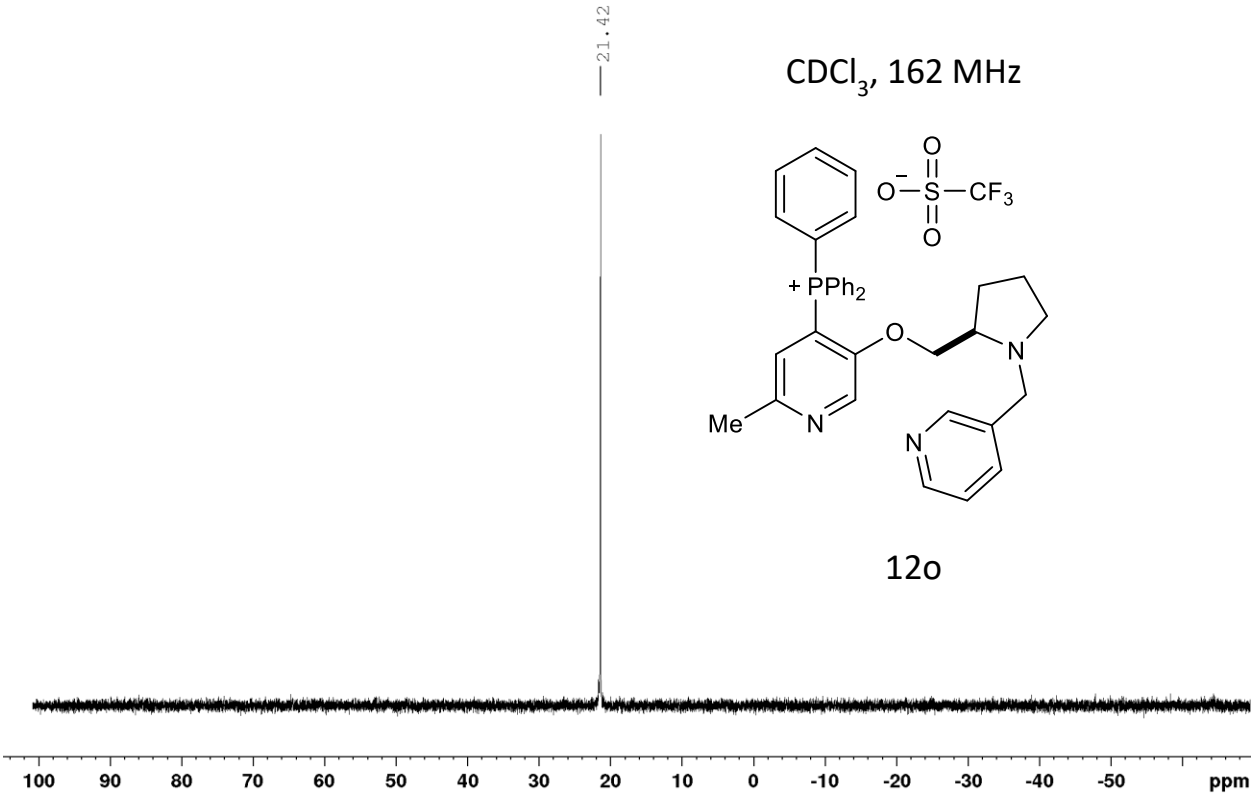

20.83
CDCl3, 162 MHz
Me
N
O
N
PPh2
+
N
O
O
S
CF3
O
O
12o
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

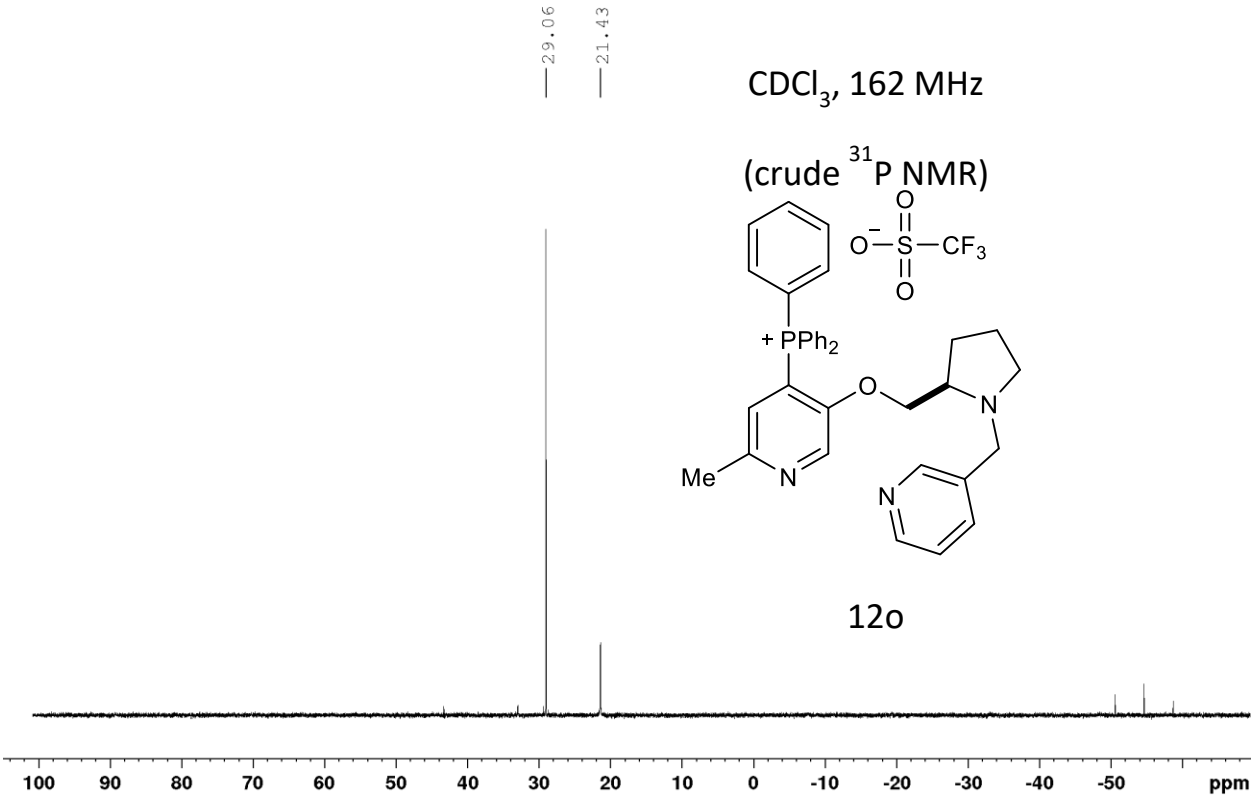

29.01
21.10
20.83
CDCl3, 162 MHz
(crude 31P NMR)
Me
N
O
N
PPh2
+
N
O
O
S
CF3
O
O
12o
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

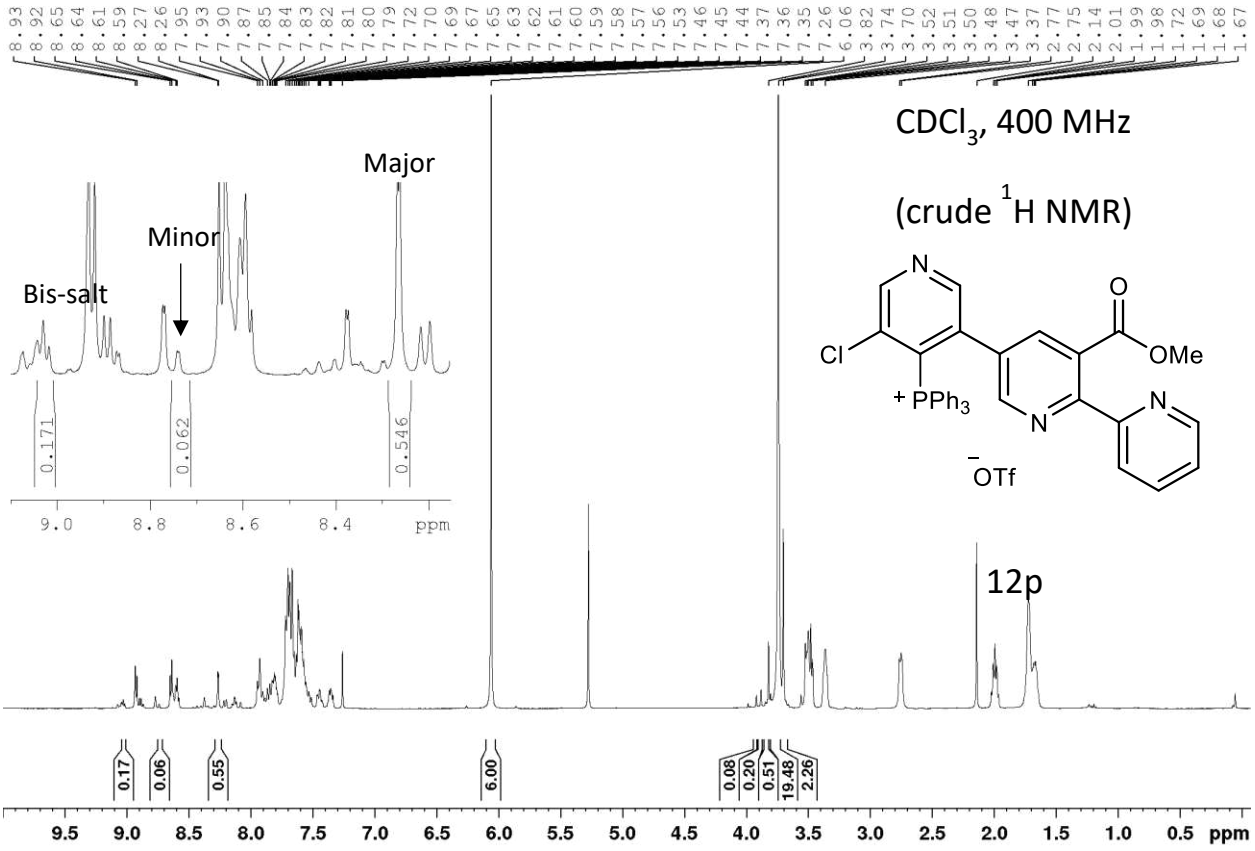

8.63
8.61
8.47
8.46
7.83
7.82
7.81
7.80
7.75
7.74
7.73
7.72
7.71
7.70
7.62
7.60
7.58
7.56
7.26
7.25
7.23
7.23
7.21
6.75
6.71
4.38
4.34
3.90
3.88
3.86
3.71
3.68
3.41
2.85
2.46
1.58
1.51
1.06
CDCl3, 400 MHz
O
O
O−S−CF3
O
+ PPh2
O
N
Me
N
N
12o
1.06
2.00
11.63
7.26
0.99
1.08
0.91
1.06
1.19
1.06
0.96
4.87
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

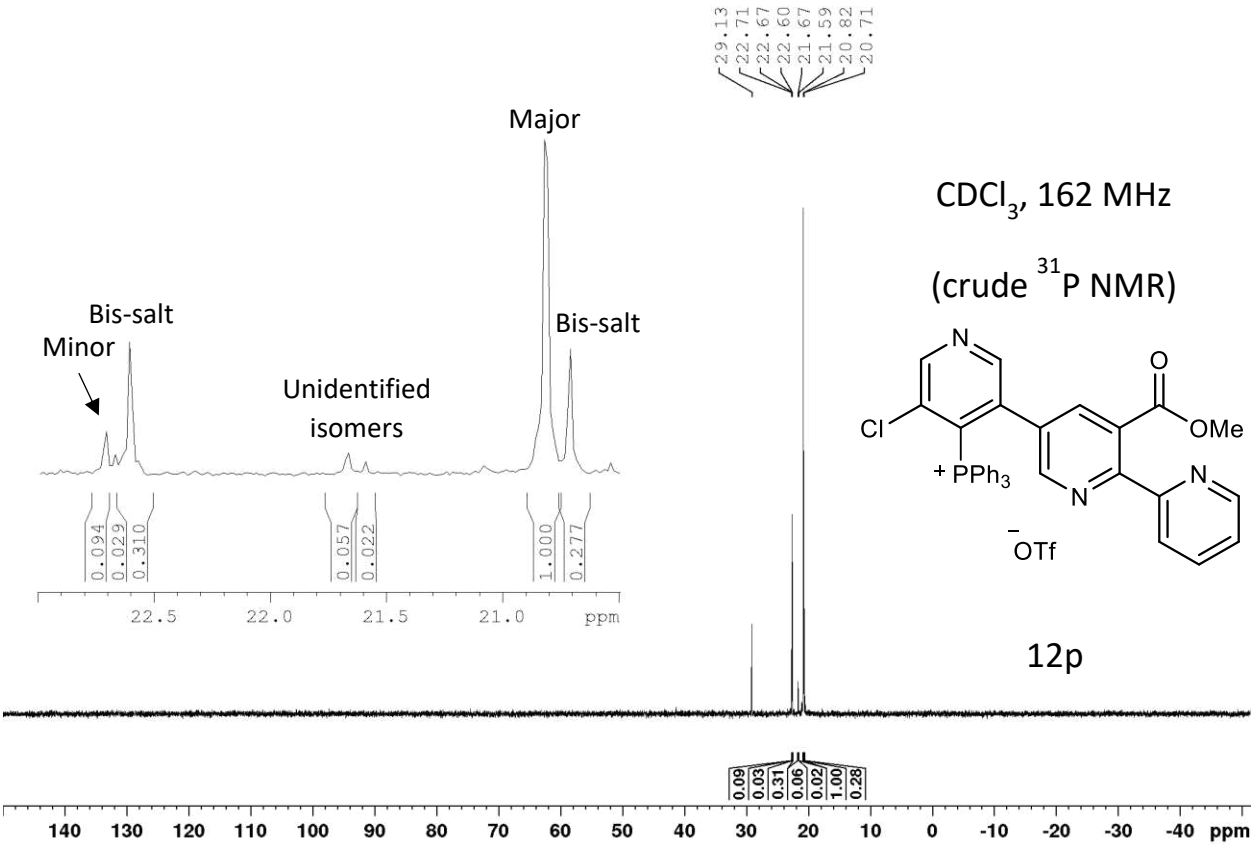

153.39
153.28
153.19
149.74
148.55
136.44
135.97
135.92
135.69
135.66
133.90
133.80
130.77
130.64
127.56
127.49
123.35
122.41
119.22
117.00
116.09
115.47
114.61
77.31
76.99
76.68
72.91
61.72
56.59
54.14
28.04
23.67
22.82
CDCl3, 100 MHz
O
O
O−S−CF3
O
+ PPh2
O
N
Me
N
N
12o
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

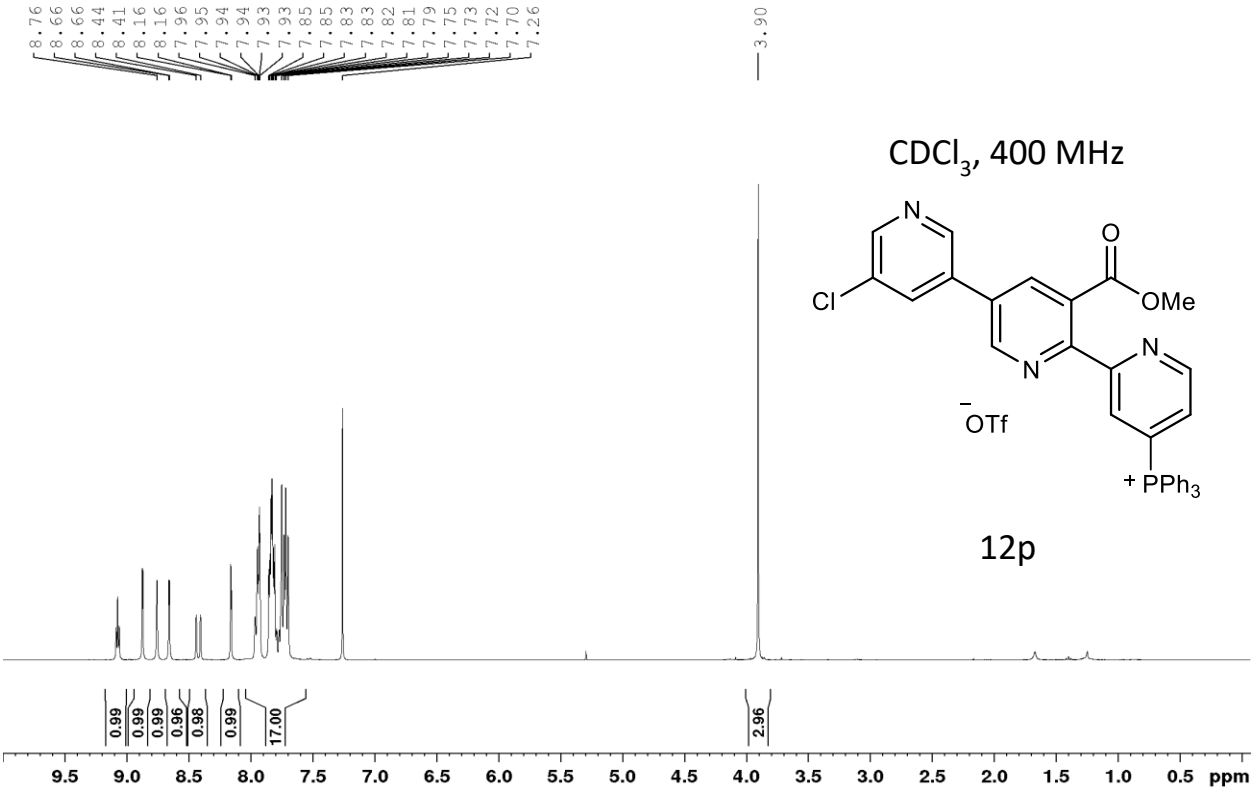

-78.15
CDCl3, 365 MHz
+PPh2
Me
N
O
S
CF3
12o
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

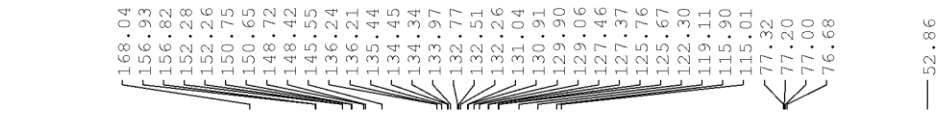

21.42
CDCl3, 162 MHz
+PPh2
Me
N
O
S
CF3
12o
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm


29.06
21.43
CDCl3, 162 MHz
(crude 31P NMR)
O
O−S−CF3
O
+ PPh2
O
N
Me
N
N
12o
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

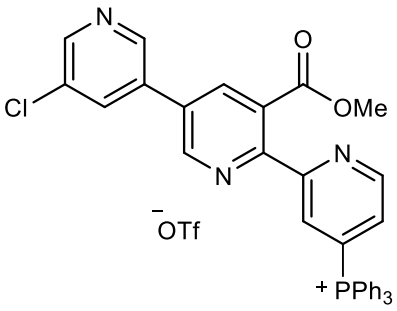

CDCl3, 400 MHz
(crude 1H NMR)
Major
Minor
Bis-salt
0.171
0.062
0.546
9.0 8.8 8.6 8.4 ppm
N
O
Cl
OMe
+ PPh3
N
N
OTf
12p
0.17
0.06
0.55
6.00
0.08
0.20
0.51
19.48
2.26
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


29.13
22.71
22.67
22.60
21.67
21.59
20.82
20.71
Major
Bis-salt
Minor
Unidentified
isomers
Bis-salt
0.094
0.029
0.310
0.057
0.022
1.000
0.277
22.5
22.0
21.5
21.0
ppm
CDCl3, 162 MHz
(crude 31P NMR)
Cl
N
O
OMe
+ PPh3
N
N
OTf
12p
0.09
0.03
0.31
0.06
0.02
1.00
0.28
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

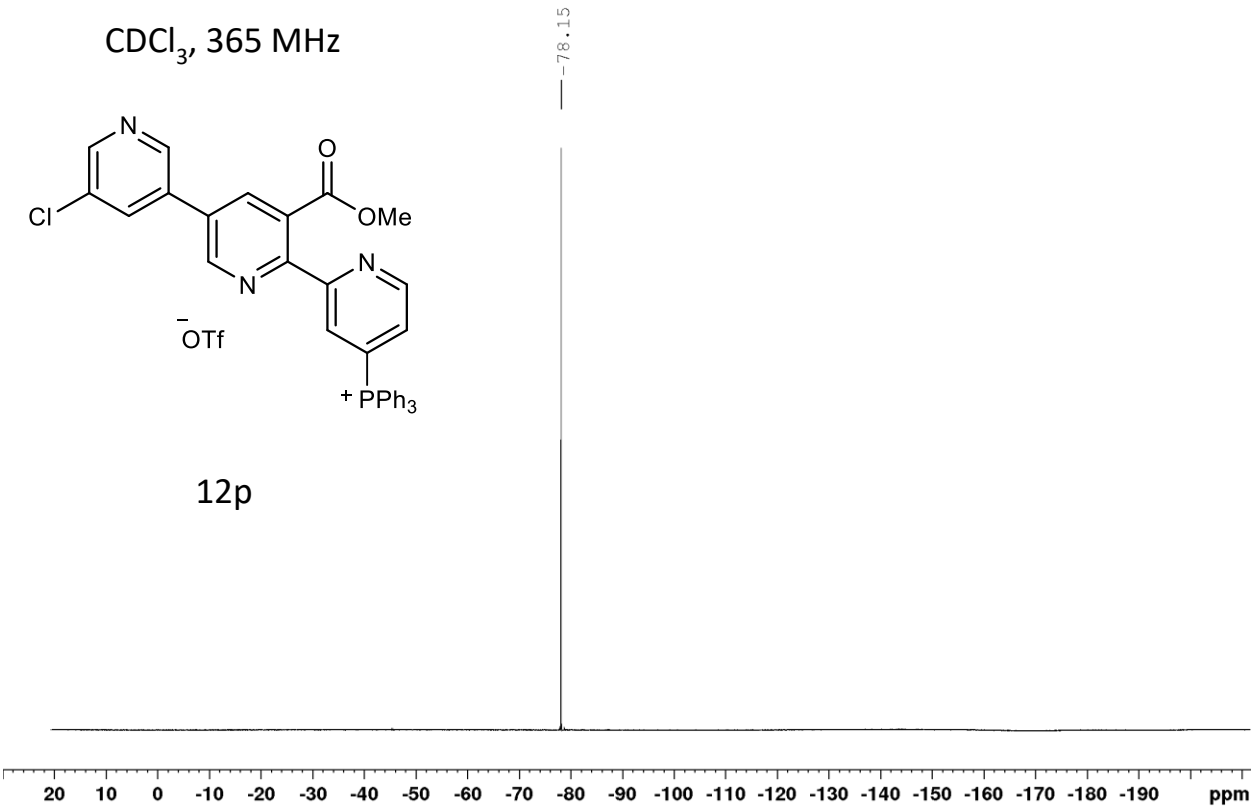

8.76
8.66
8.66
8.44
8.41
8.16
8.16
7.96
7.95
7.94
7.94
7.93
7.93
7.85
7.85
7.83
7.83
7.82
7.81
7.79
7.75
7.73
7.72
7.70
7.26
3.90
CDCl3, 400 MHz
Cl
N
O
OMe
N
N
OTf
+ PPh3
12p
0.99
0.99
0.99
0.96
0.98
0.99
17.00
2.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm



$CDCl_3$, 100 MHz



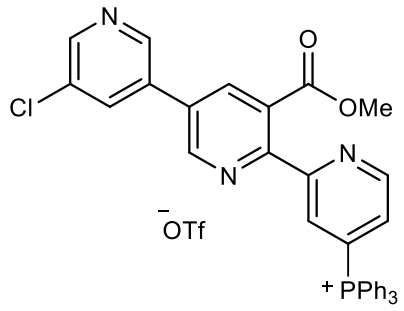
12p



$CDCl_3$, 365 MHz

12p

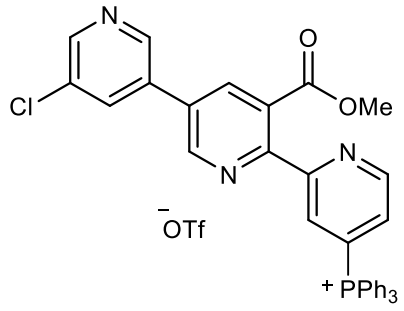
$CDCl_3$, 162 MHz



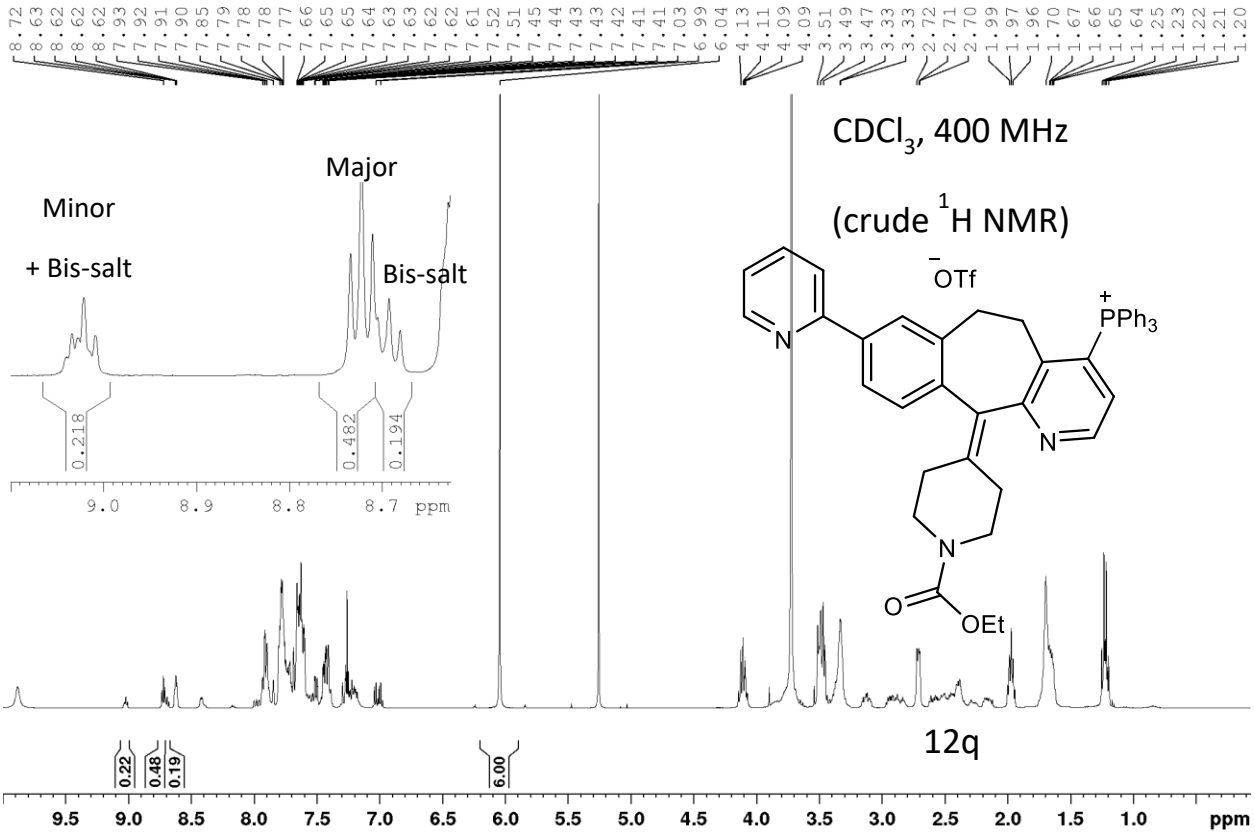
12p

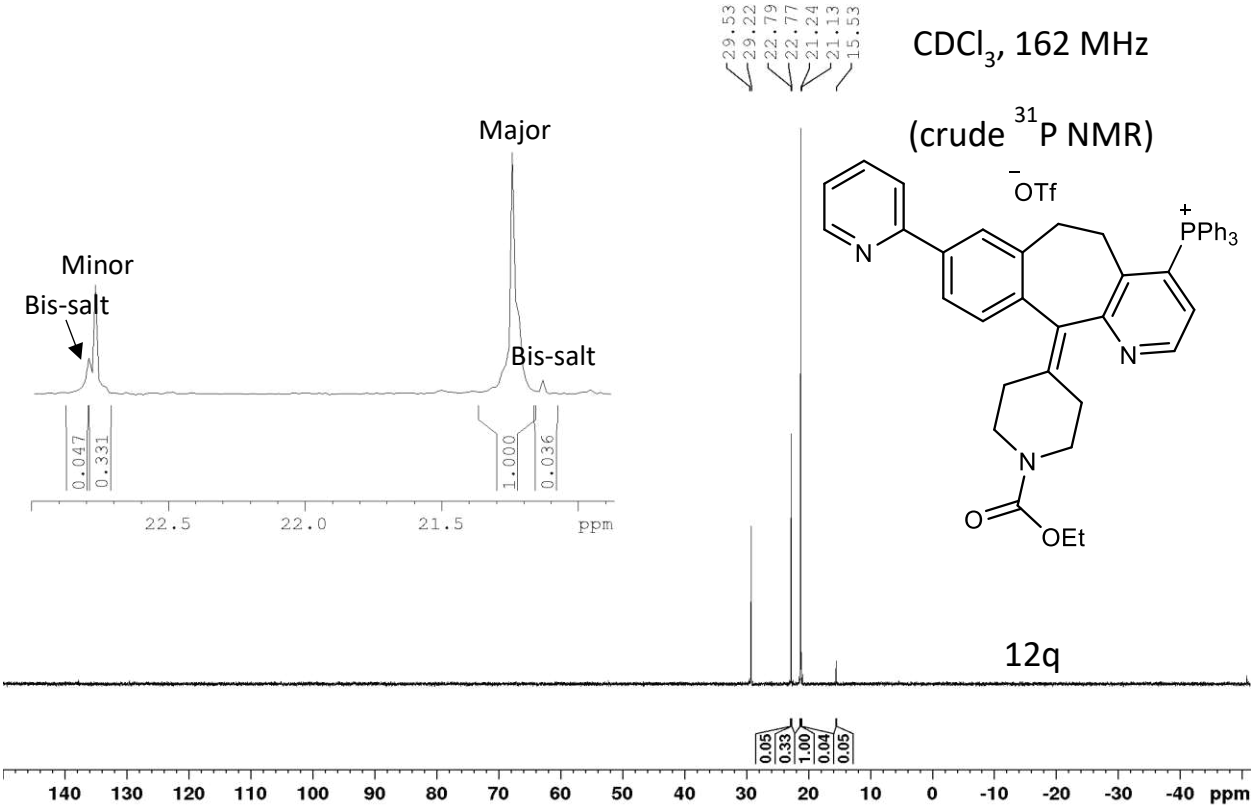
$CDCl_3$, 162 MHz

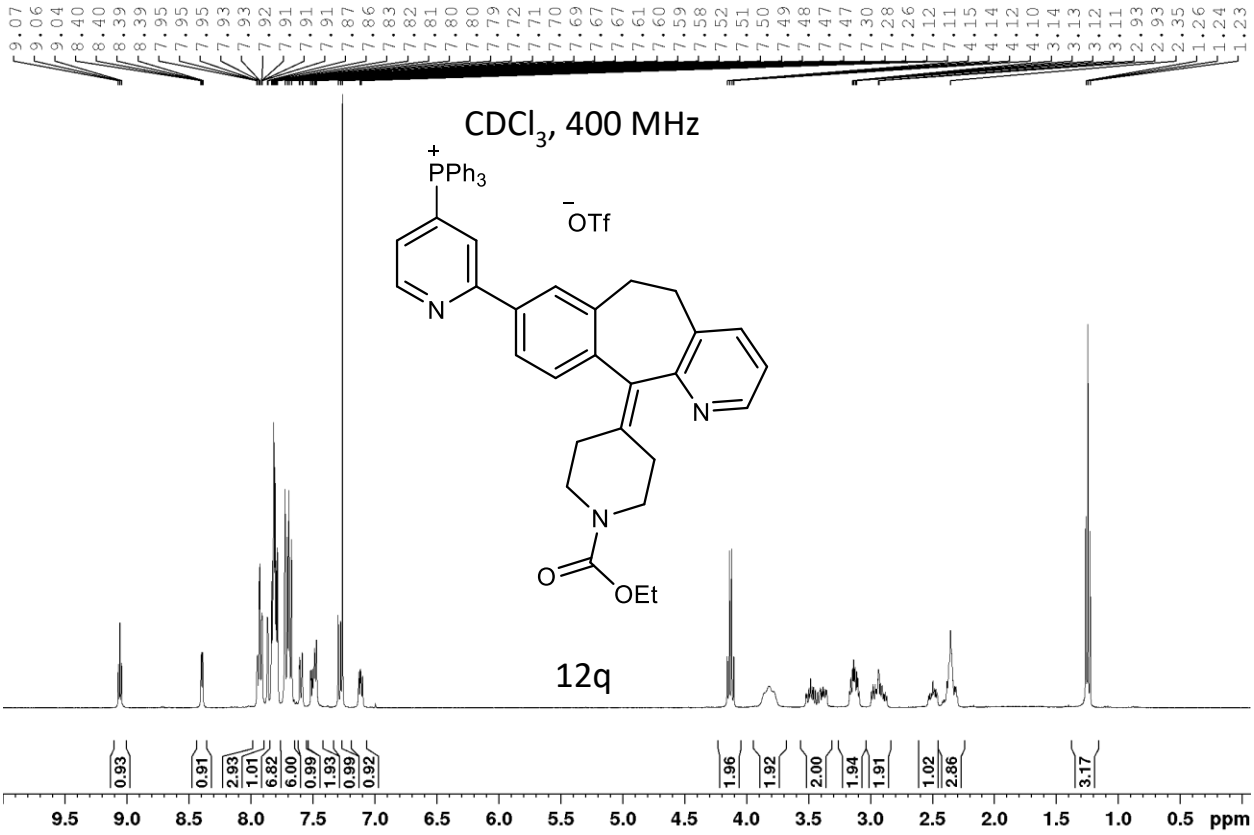
(crude ^{31}P NMR)

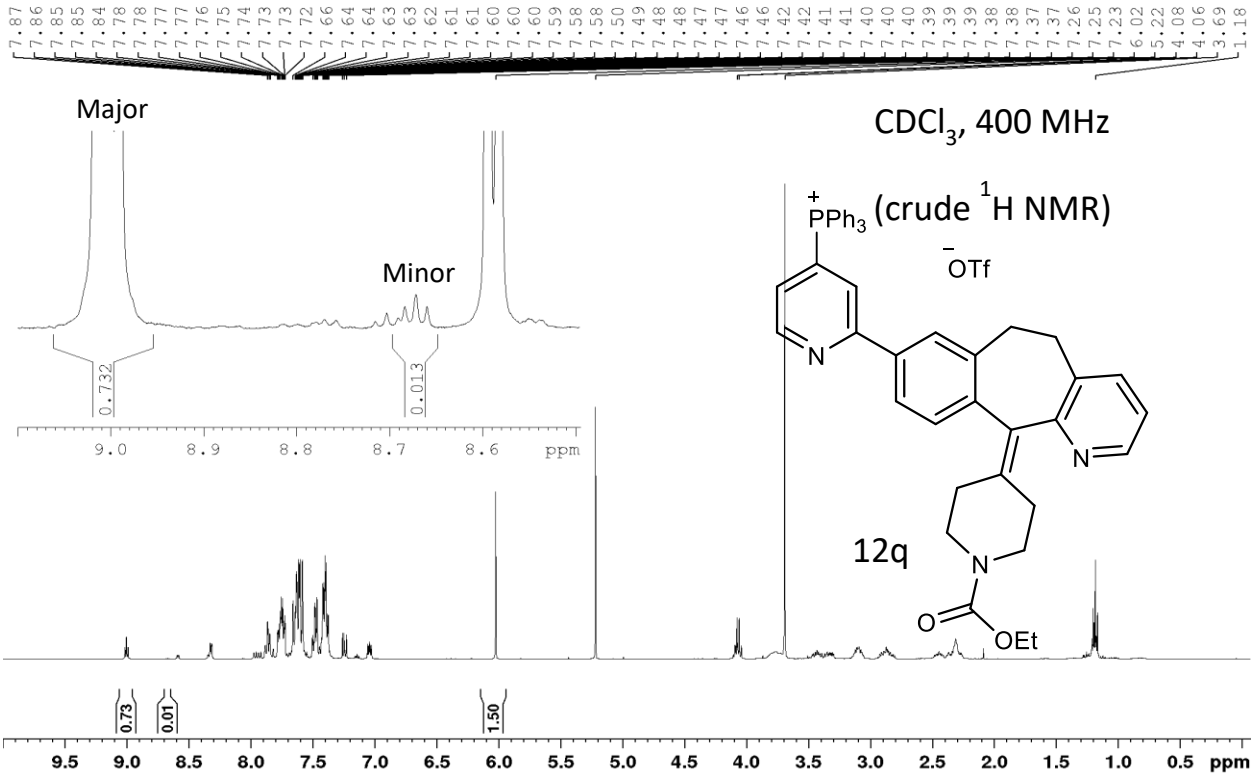


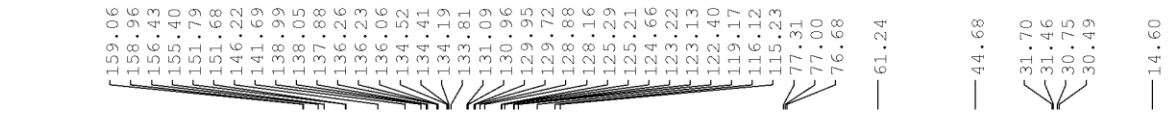
12p


CDCl3, 400 MHz
(crude 1H NMR)
Major
Minor
+ Bis-salt
Bis-salt
OTf
PPh3
N
O
OEt
12q
ppm

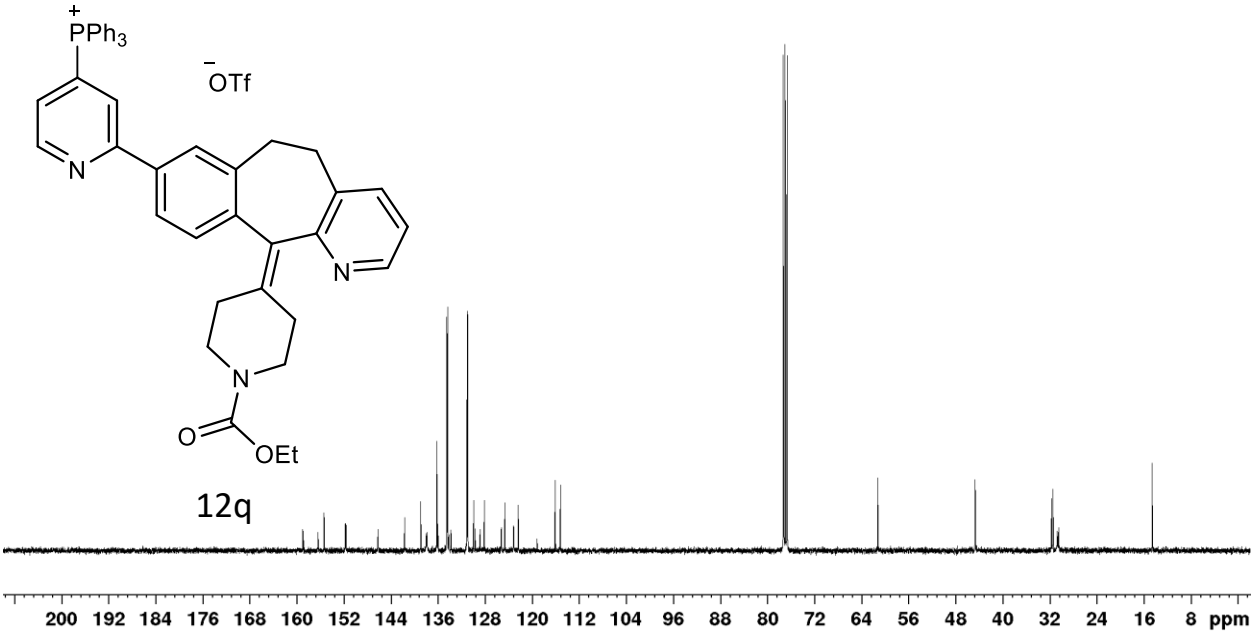

CDCl3, 162 MHz
(crude 31P NMR)
Major
Minor
Bis-salt
Bis-salt
OTf
PPh3
N
O
OEt
12q
ppm


CDCl3, 400 MHz
PPh3
OTf
N
N
N
O
OEt
12q
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
PPh3 (crude 1H NMR)
OTf
N
N
N
O
OEt
12q
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

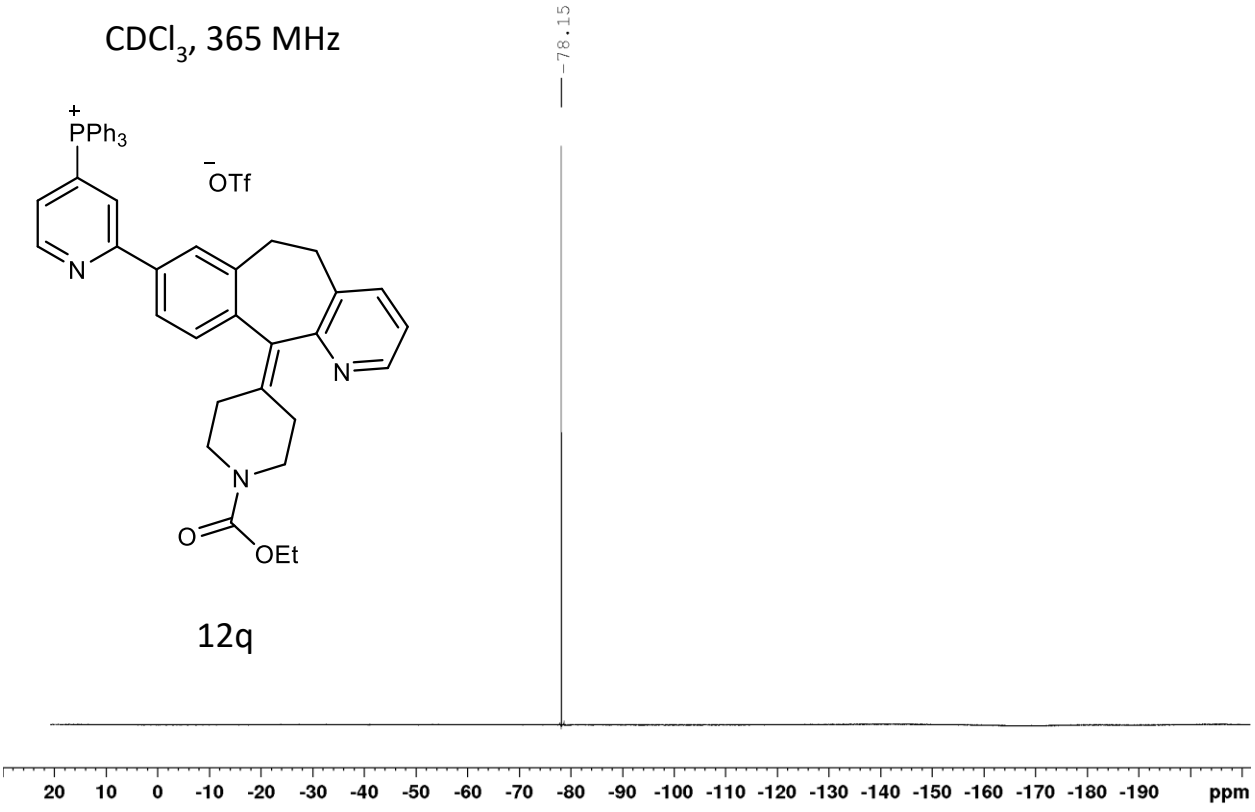


$CDCl_3$, 100 MHz



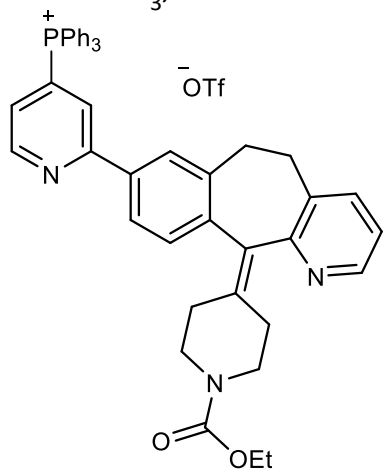
12q

$CDCl_3$, 365 MHz



12q

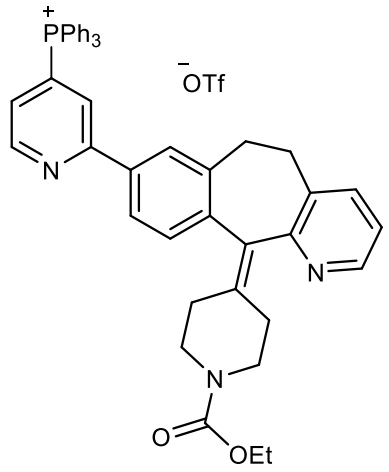
$CDCl_3$, 162 MHz



12q

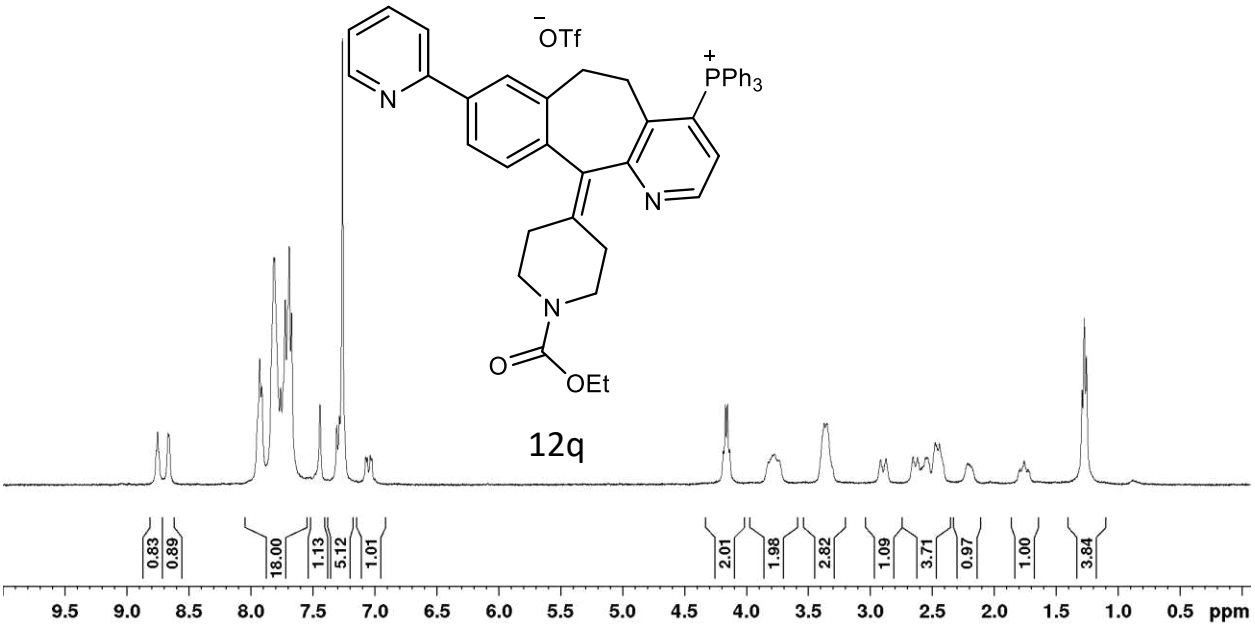
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)



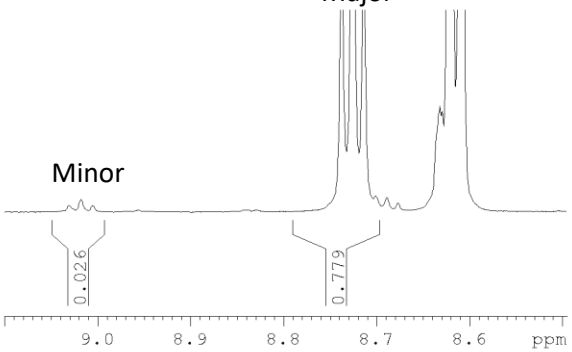
12q

$CDCl_3$, 400 MHz



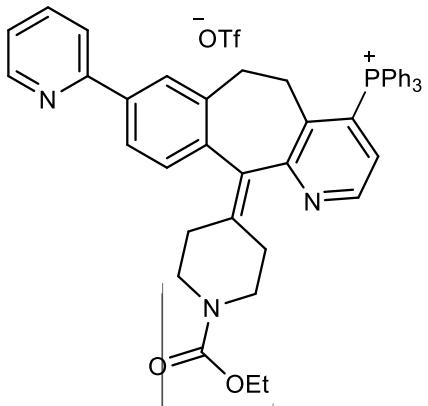
Major

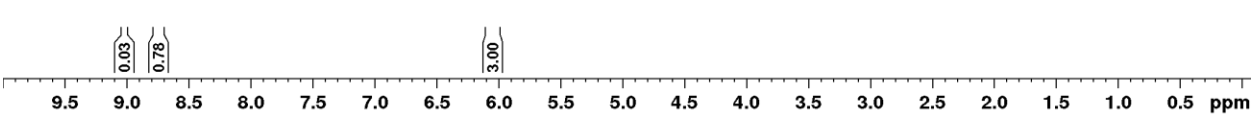
Minor

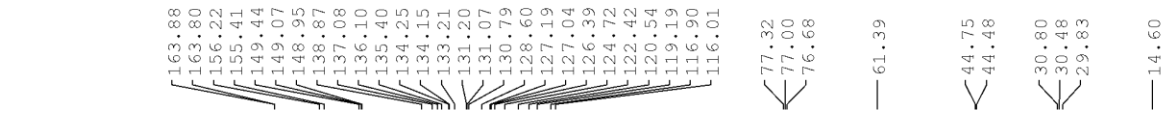


$CDCl_3$, 400 MHz

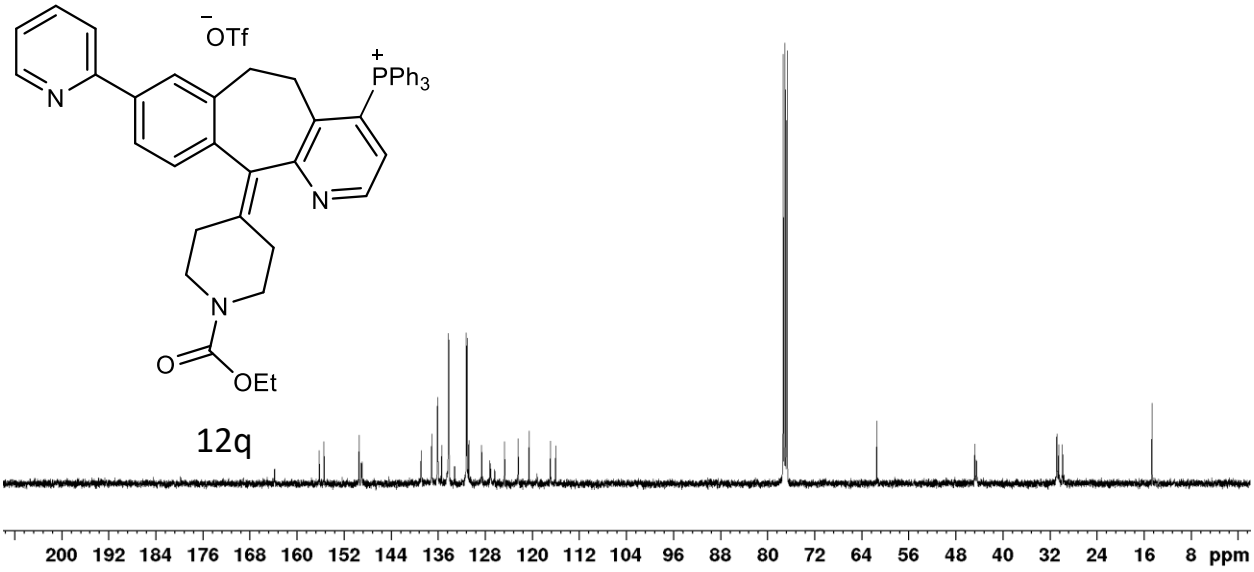
(crude ^{1}H NMR)



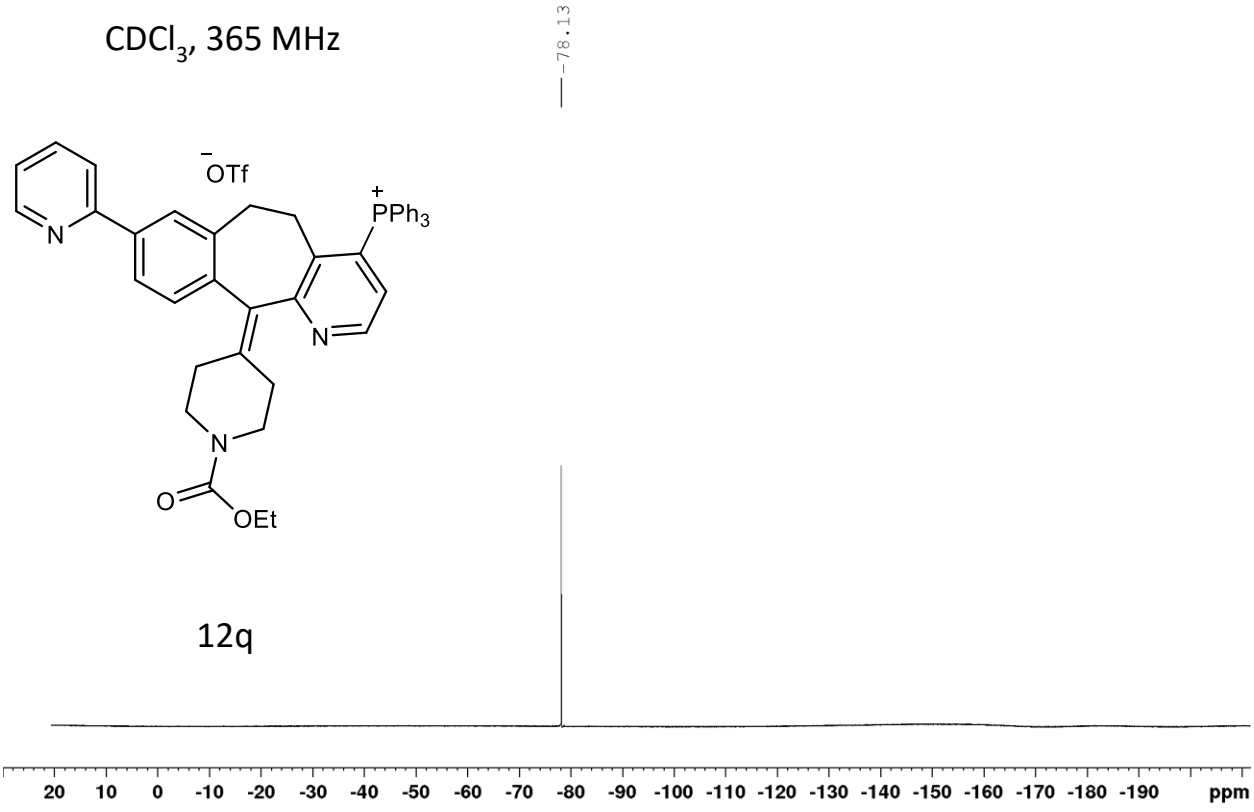




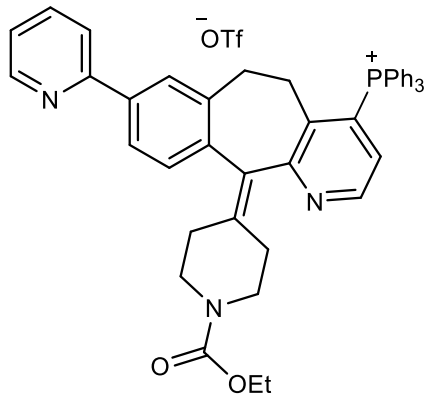
$CDCl_3$, 100 MHz



$CDCl_3$, 365 MHz



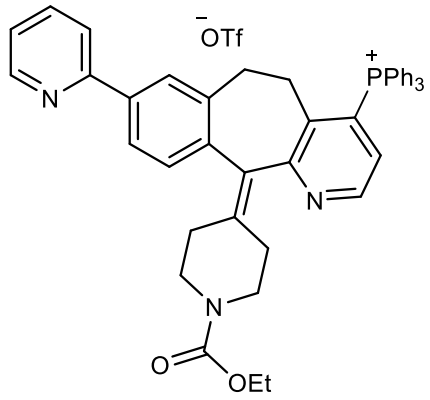
$CDCl_3$, 162 MHz



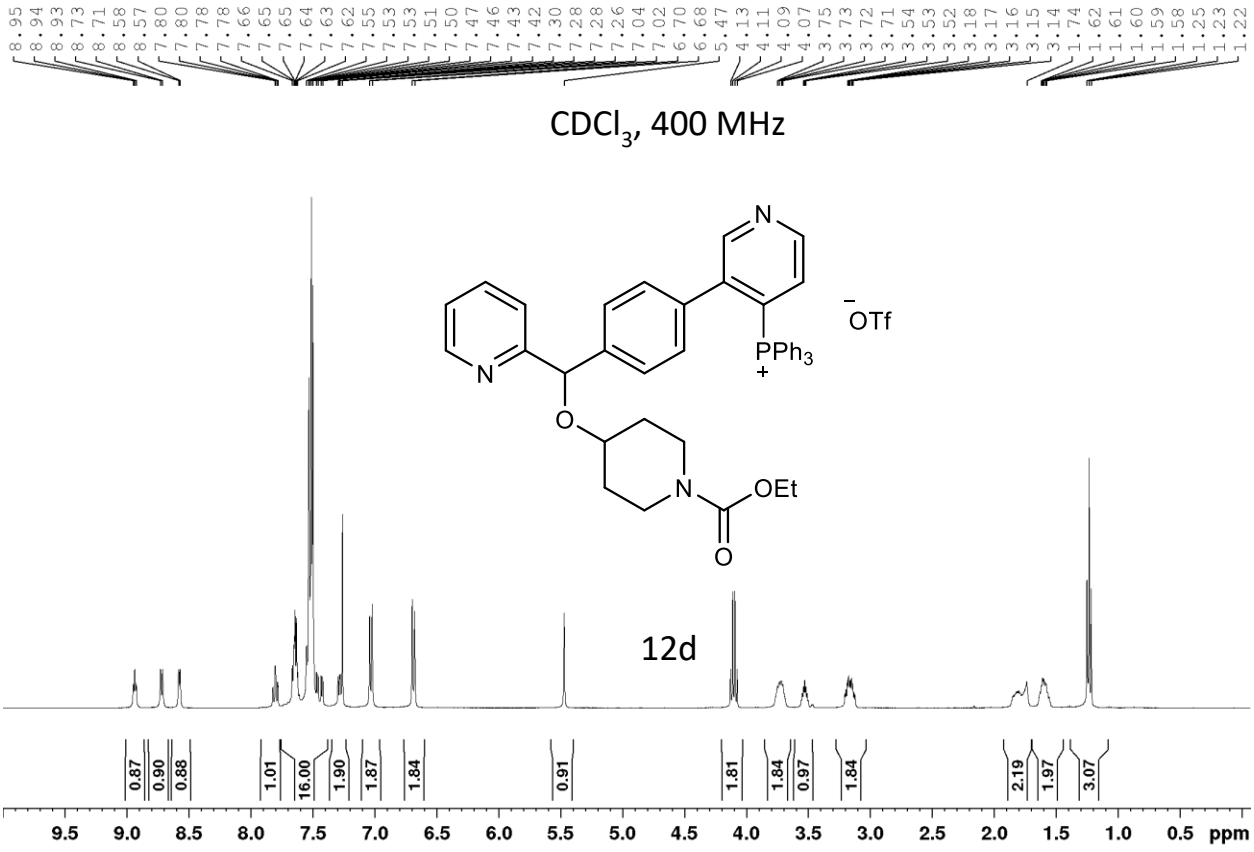
12q

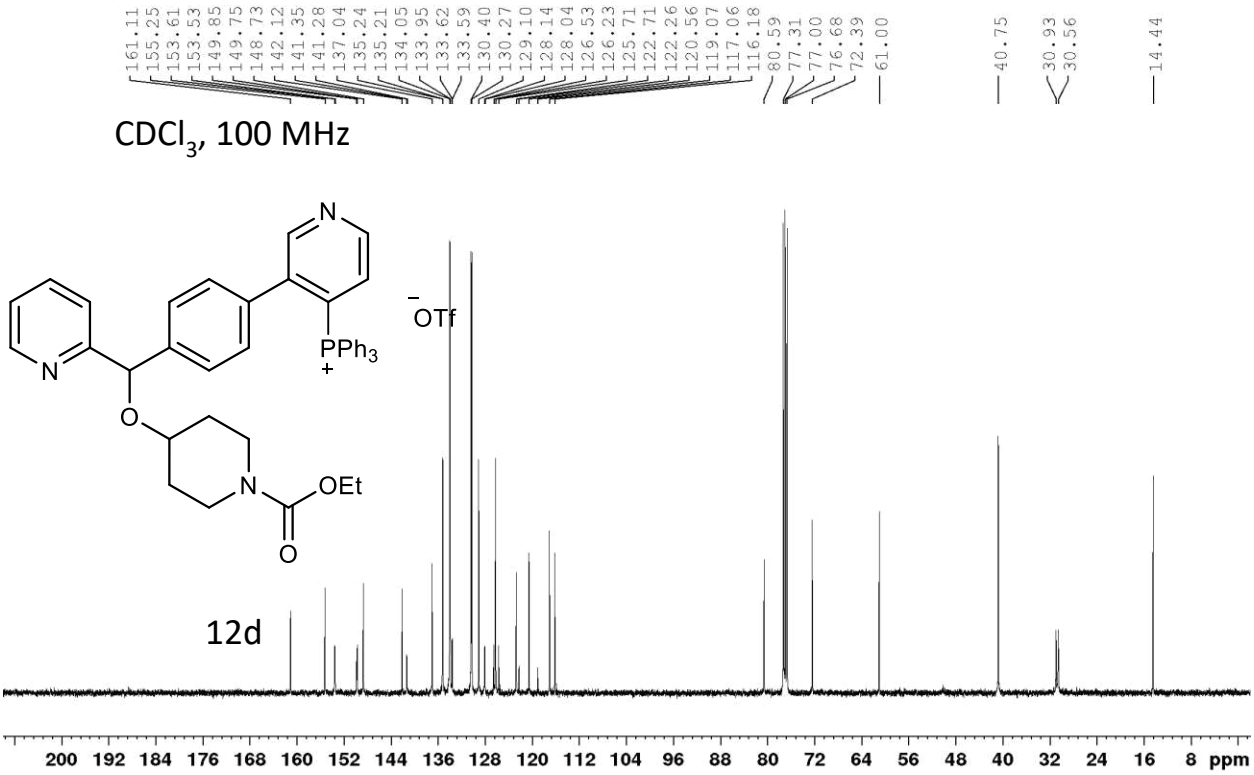
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

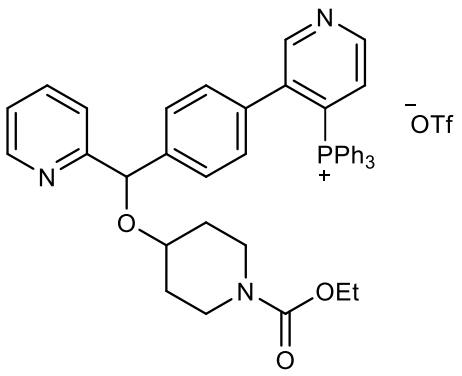


12q


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
N
OTf
PPh3
+
N
O
N
OEt
O
12d
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

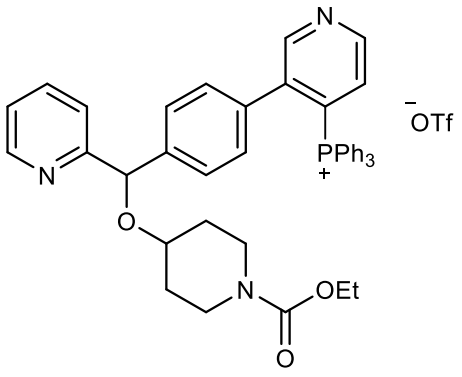

161.11 155.25 153.61 153.53 149.85 149.75 148.73 142.12 141.35 141.28 137.04 135.24 135.21 134.05 133.95 133.62 133.59 130.40 130.27 129.10 128.14 128.04 126.53 126.23 125.71 122.71 122.26 120.56 119.07 117.06 116.18 80.59 77.31 77.00 76.68 72.39 61.00 40.75 30.93 30.56 14.44
CDCl3, 100 MHz
N
OTf
PPh3
+
N
O
N
OEt
O
12d
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



12d

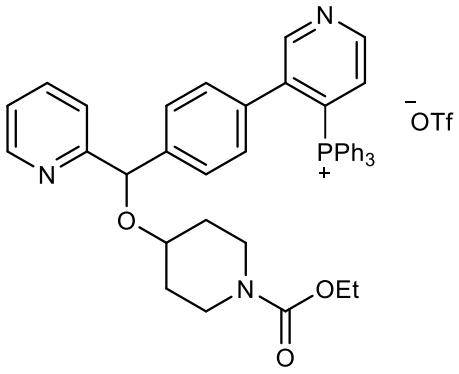
$CDCl_3$, 162 MHz



12d

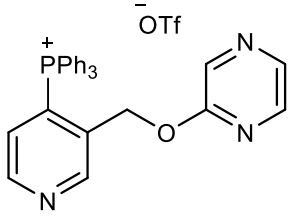
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

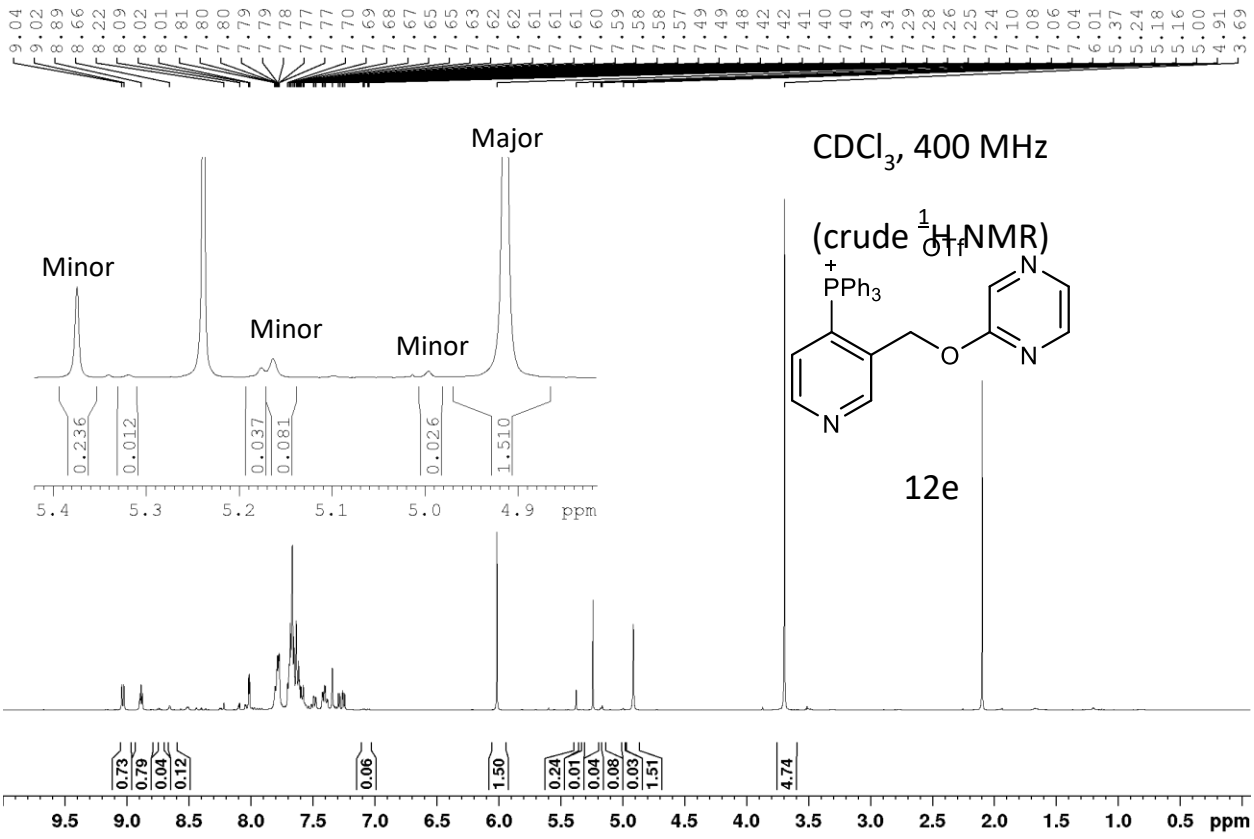


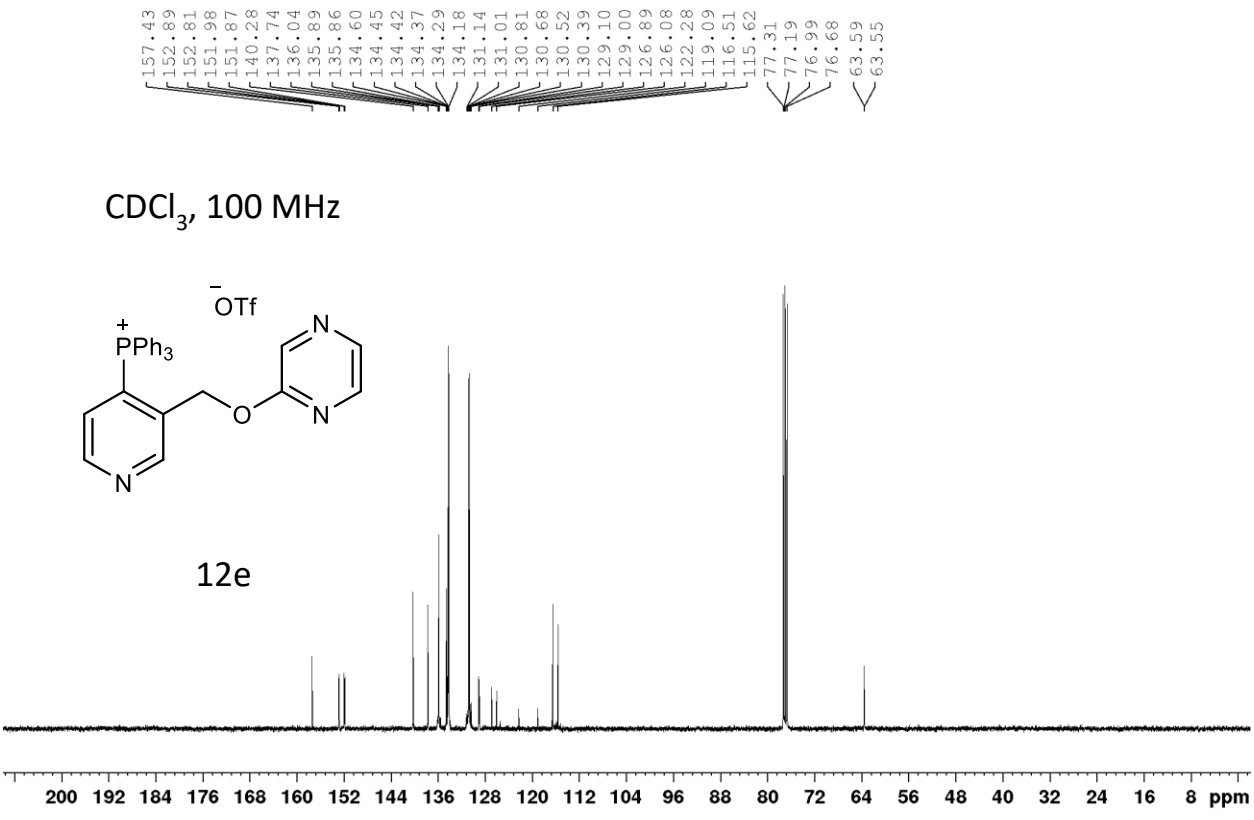
12d

$CDCl_3$, 400 MHz

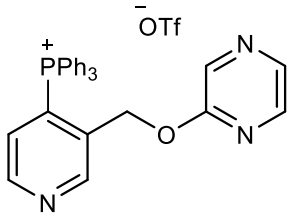


12e


Major
Minor
Minor
Minor
CDCl3, 400 MHz
(crude 1H-NMR)
OTf
PPh3
N
O
N
N
12e
0.236
0.012
0.037
0.081
0.026
1.510
5.4
5.3
5.2
5.1
5.0
4.9
ppm
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
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

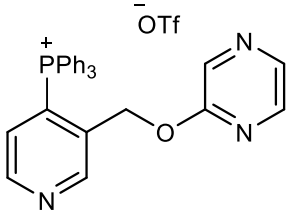

CDCl3, 100 MHz
OTf
PPh3
N
O
N
N
12e
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
ppm

$CDCl_3$, 162 MHz



12e

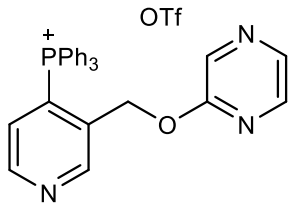
$CDCl_3$, 365 MHz



12e

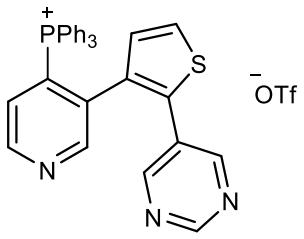
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

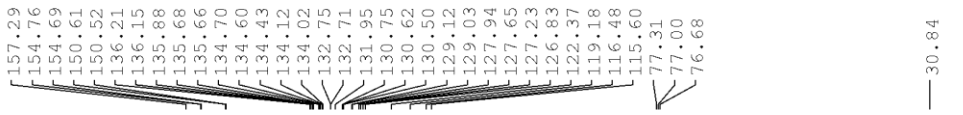


12e

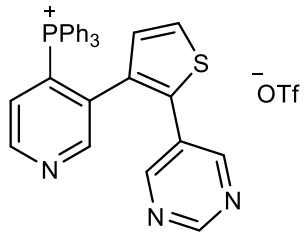
$CDCl_3$, 400 MHz



12g

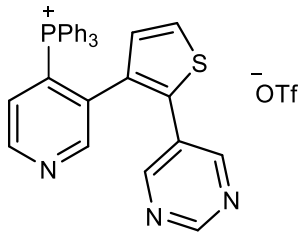


$CDCl_3$, 100 MHz



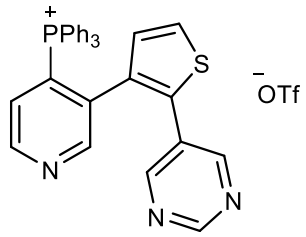
12g

$CDCl_3$, 365 MHz



12g

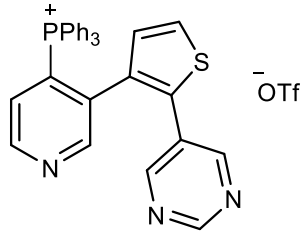
$CDCl_3$, 162 MHz



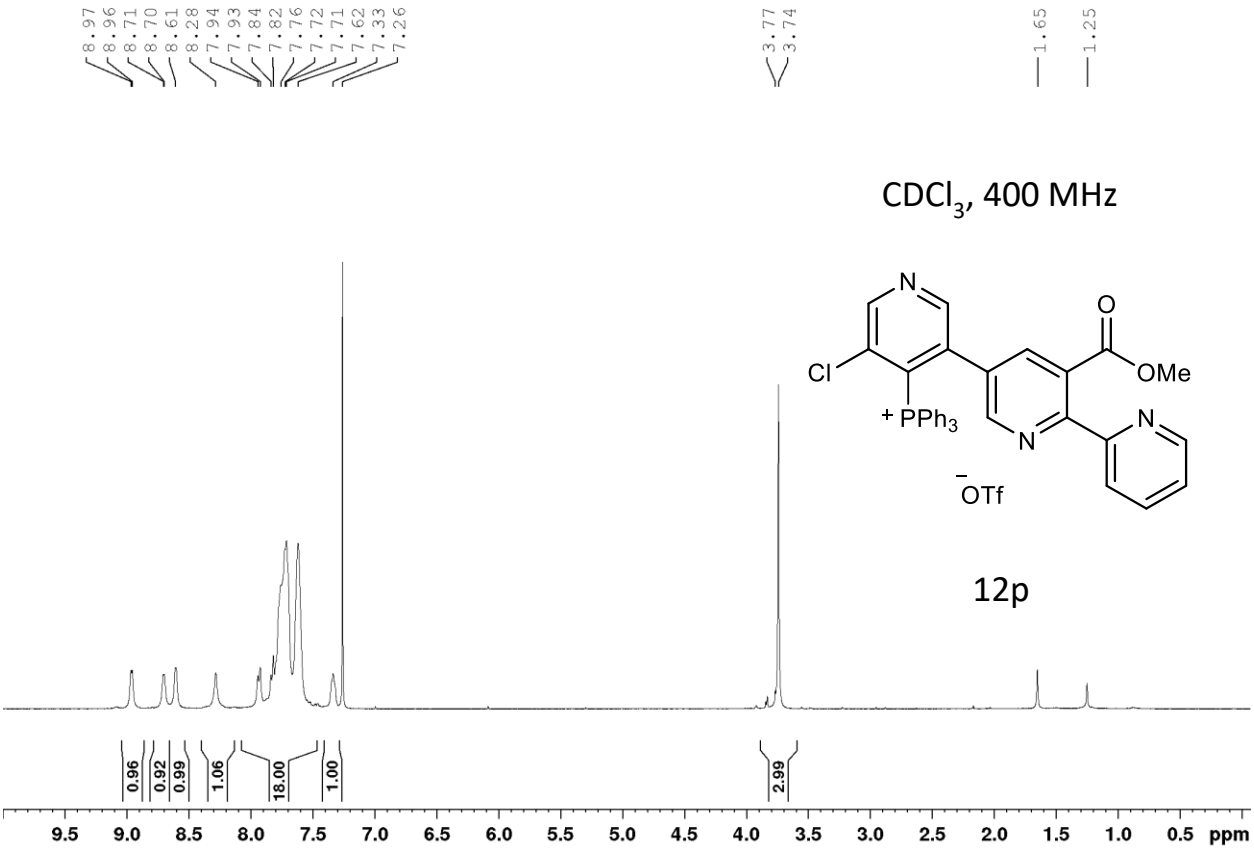
12g

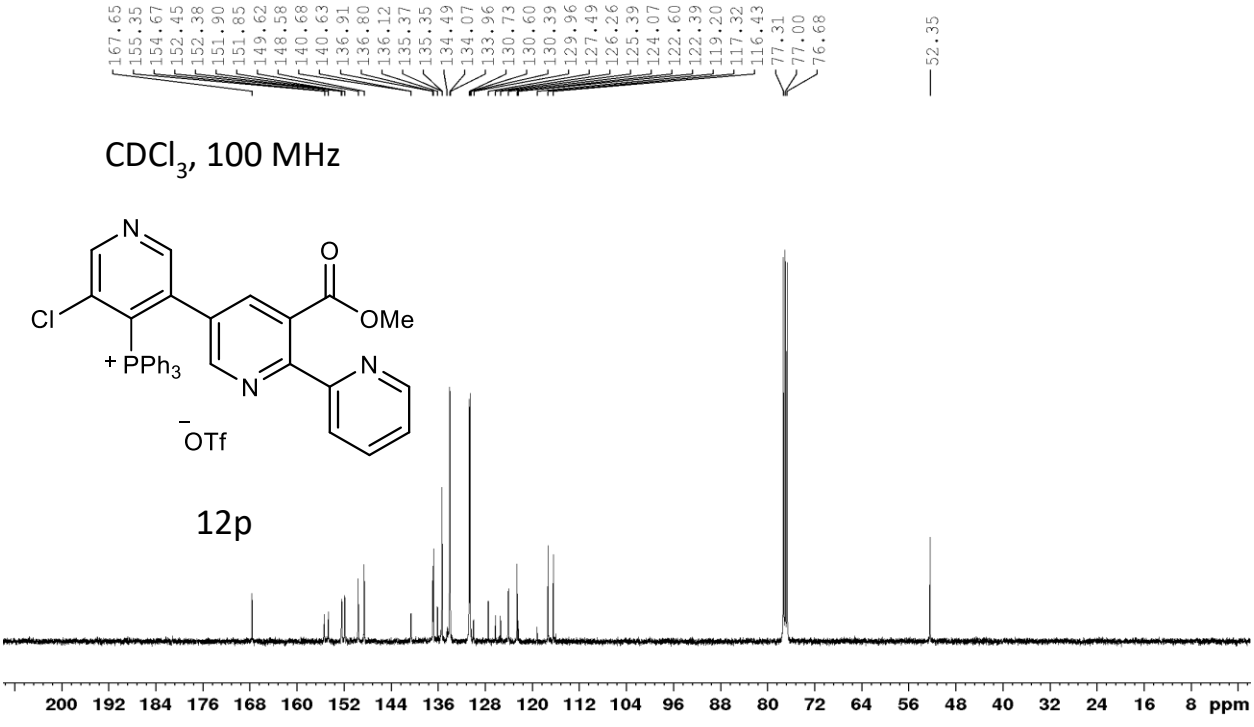
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

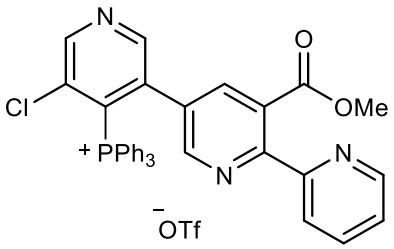


12g


8.97
8.96
8.71
8.70
8.61
8.28
7.94
7.93
7.84
7.82
7.76
7.72
7.71
7.62
7.33
7.26
3.77
3.74
1.65
1.25
CDCl3, 400 MHz
N
O
Cl
OMe
+ PPh3
N
N
OTf
12p
0.96
0.92
0.99
1.06
18.00
1.00
2.99
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

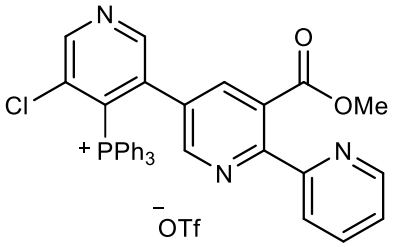

167.65
155.35
154.67
152.45
152.38
151.90
151.85
149.62
148.58
140.68
140.63
136.91
136.80
136.12
135.37
135.35
134.49
134.07
133.96
130.73
130.60
130.39
129.96
127.49
126.26
125.39
124.07
122.60
122.39
119.20
117.32
116.43
77.31
77.00
76.68
52.35
CDCl3, 100 MHz
N
O
Cl
OMe
+ PPh3
N
N
OTf
12p
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz



12p

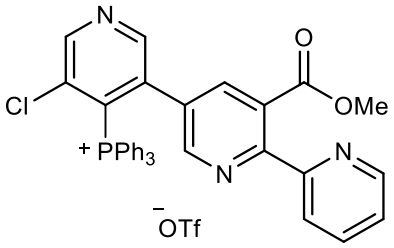
$CDCl_3$, 162 MHz



12p

$CDCl_3$, 162 MHz

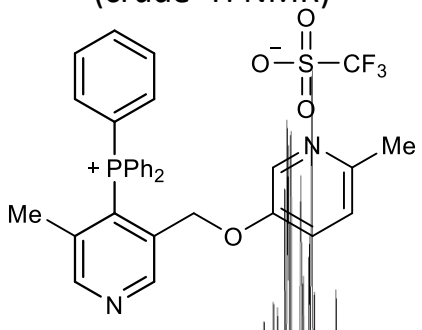
(crude ^{31}P NMR)



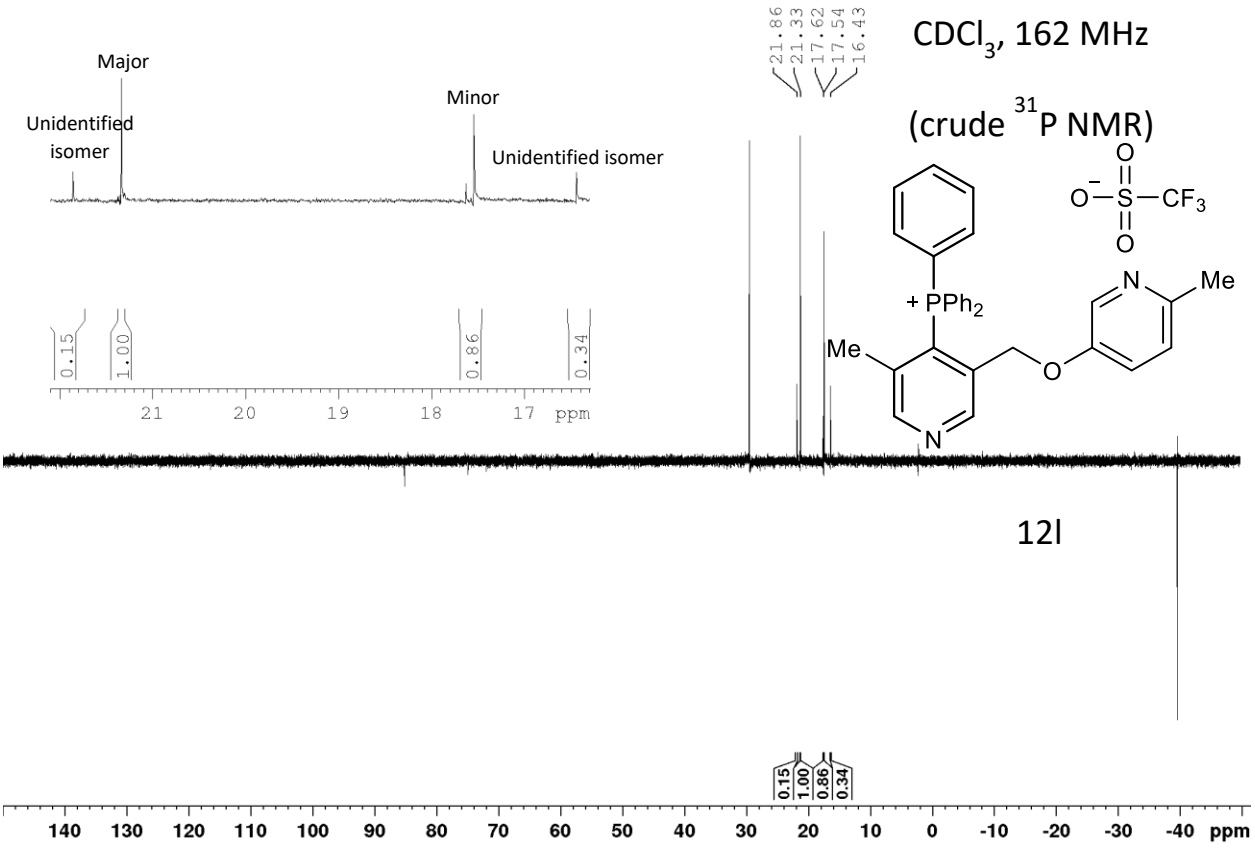
12p

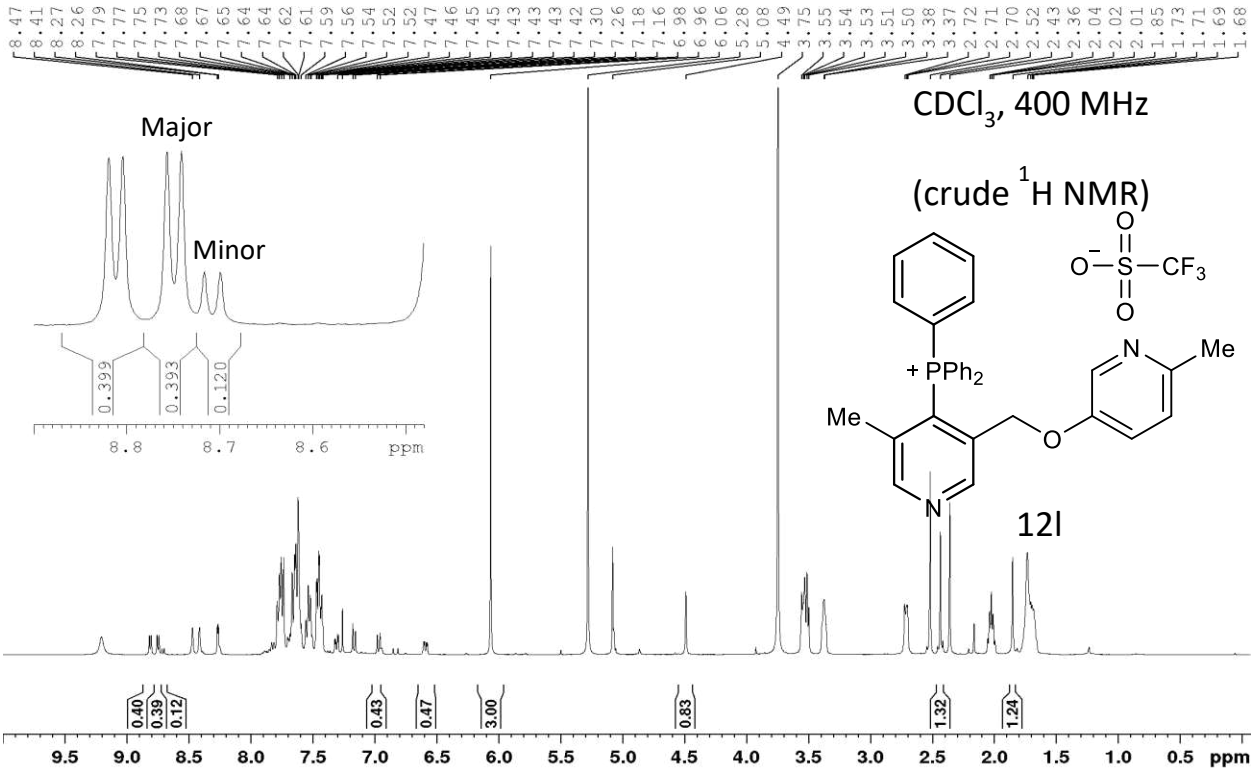
$CDCl_3$, 400 MHz

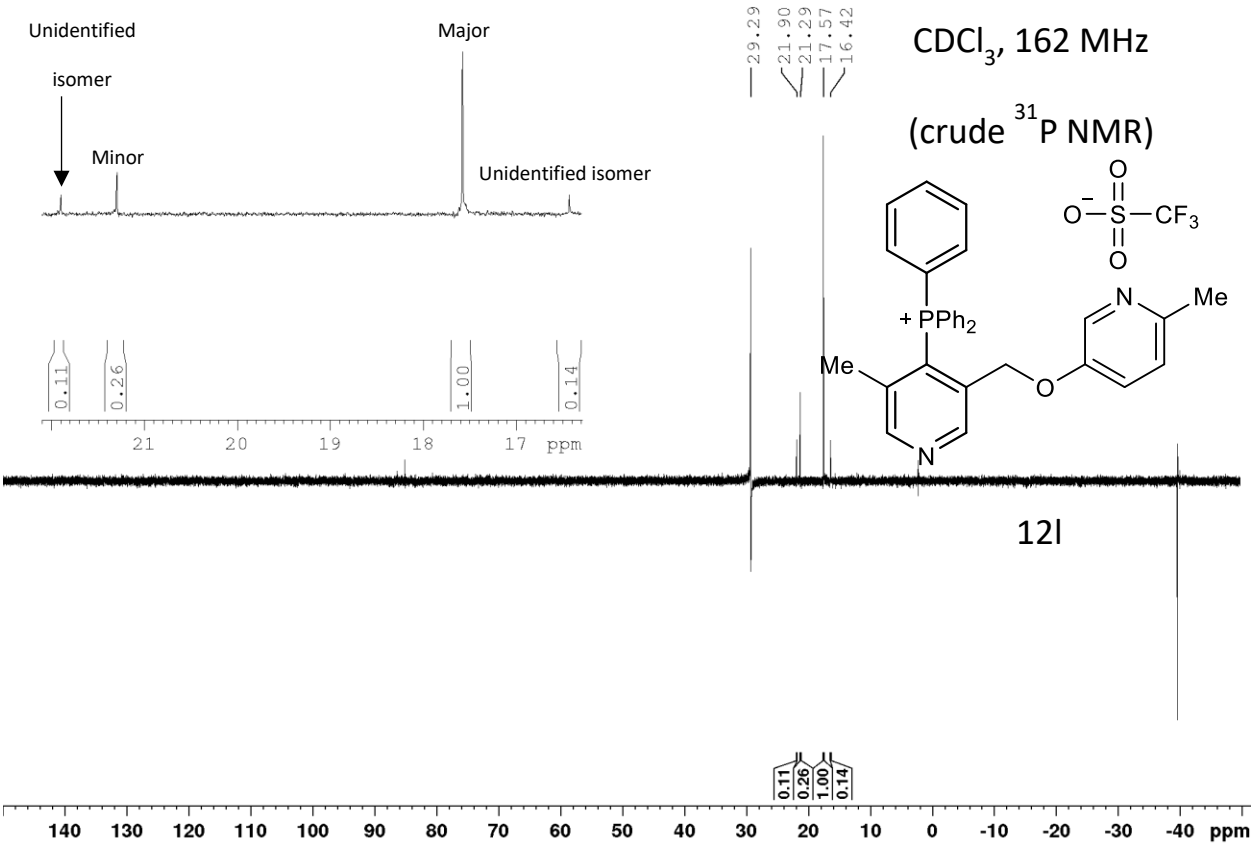
(crude ^{1}H NMR)

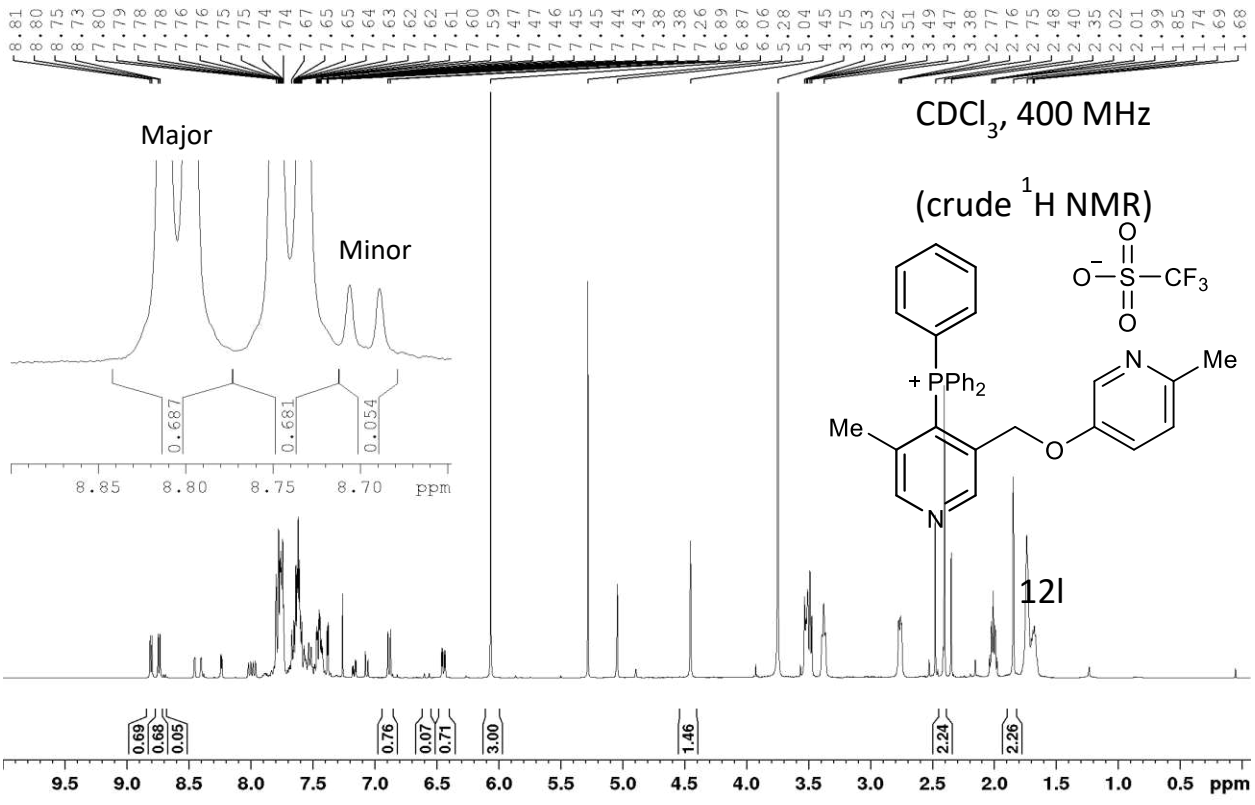


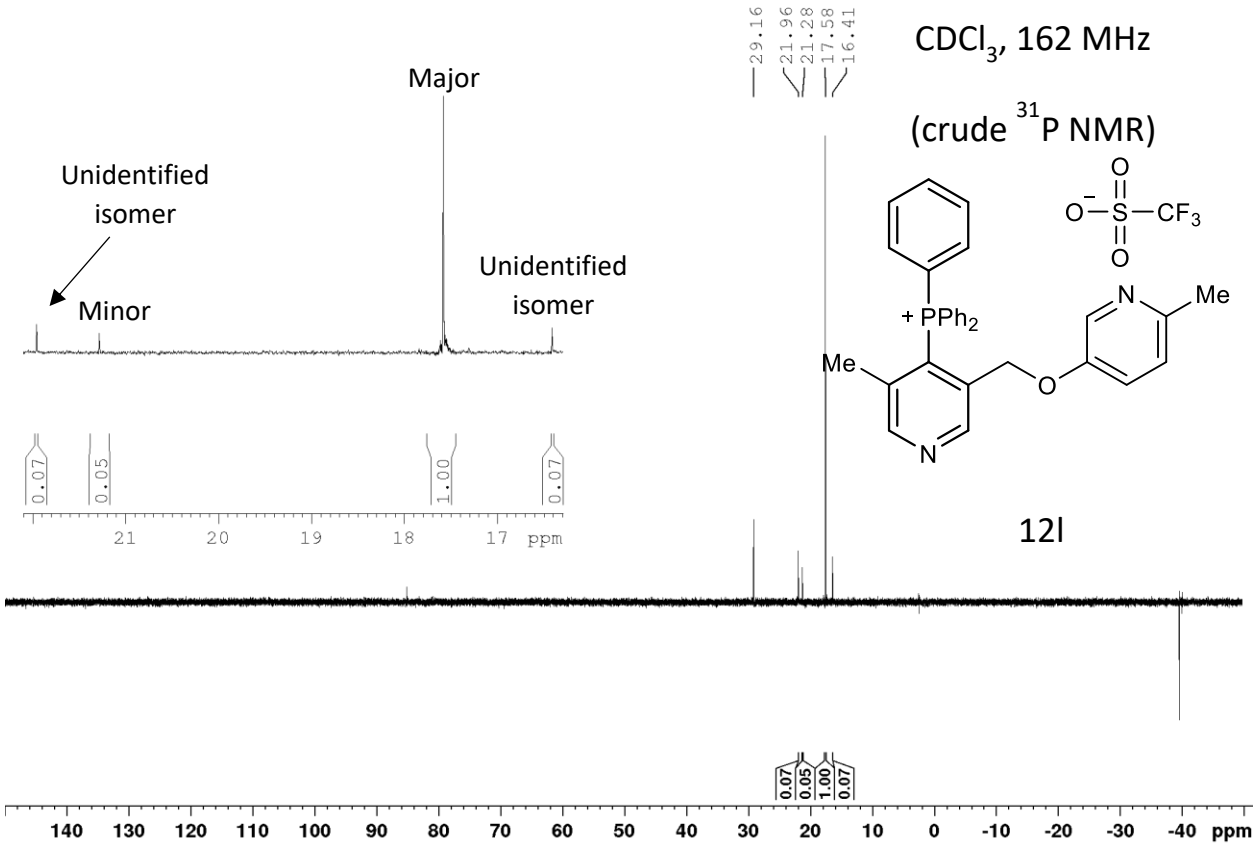
12l

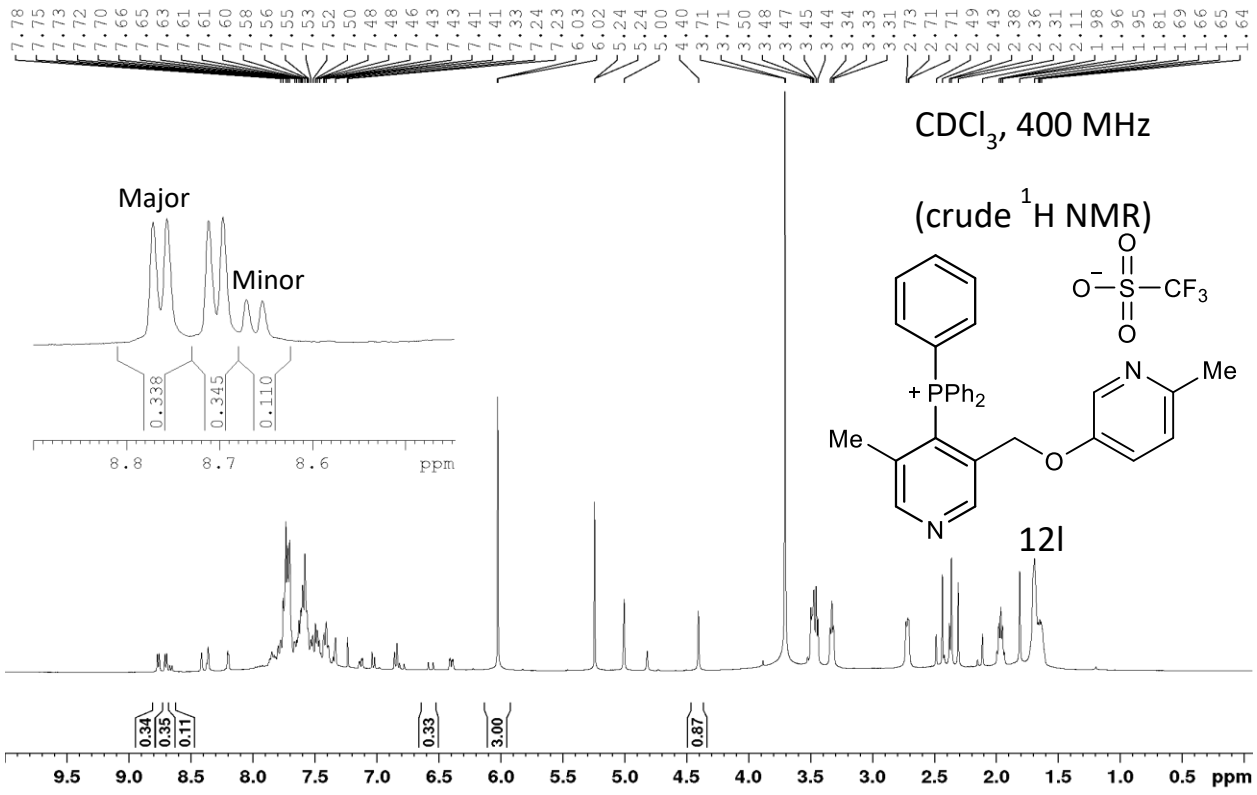

Major
Minor
Unidentified isomer
Unidentified isomer
21.86
21.33
17.62
17.54
16.43
0.15
1.00
0.86
0.34
21 20 19 18 17 ppm
CDCl3, 162 MHz
(crude 31P NMR)
12l
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm

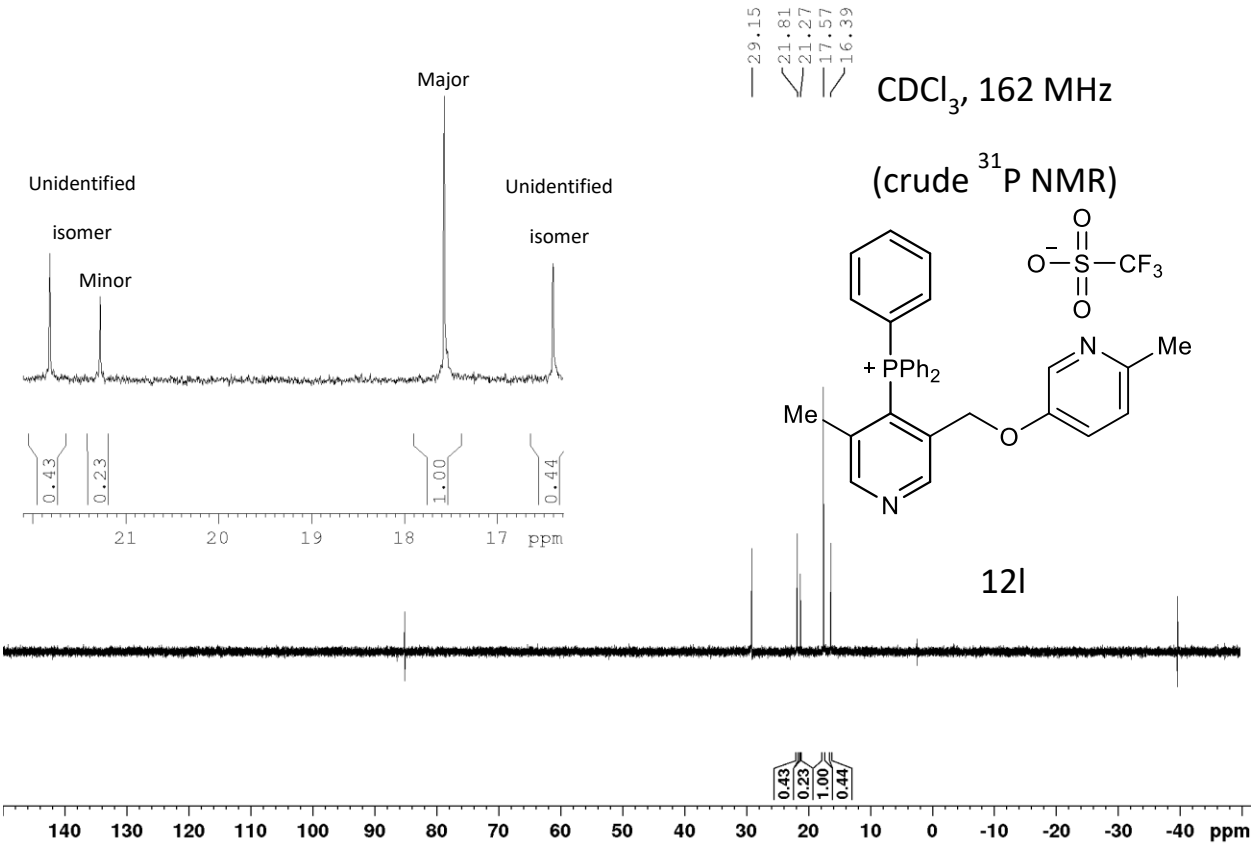

Major
Minor
0.399
0.393
0.120
8.8 8.7 8.6 ppm
CDCl3, 400 MHz
(crude 1H NMR)
12l
0.40
0.39
0.12
0.43
0.47
3.00
0.83
1.32
1.24
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

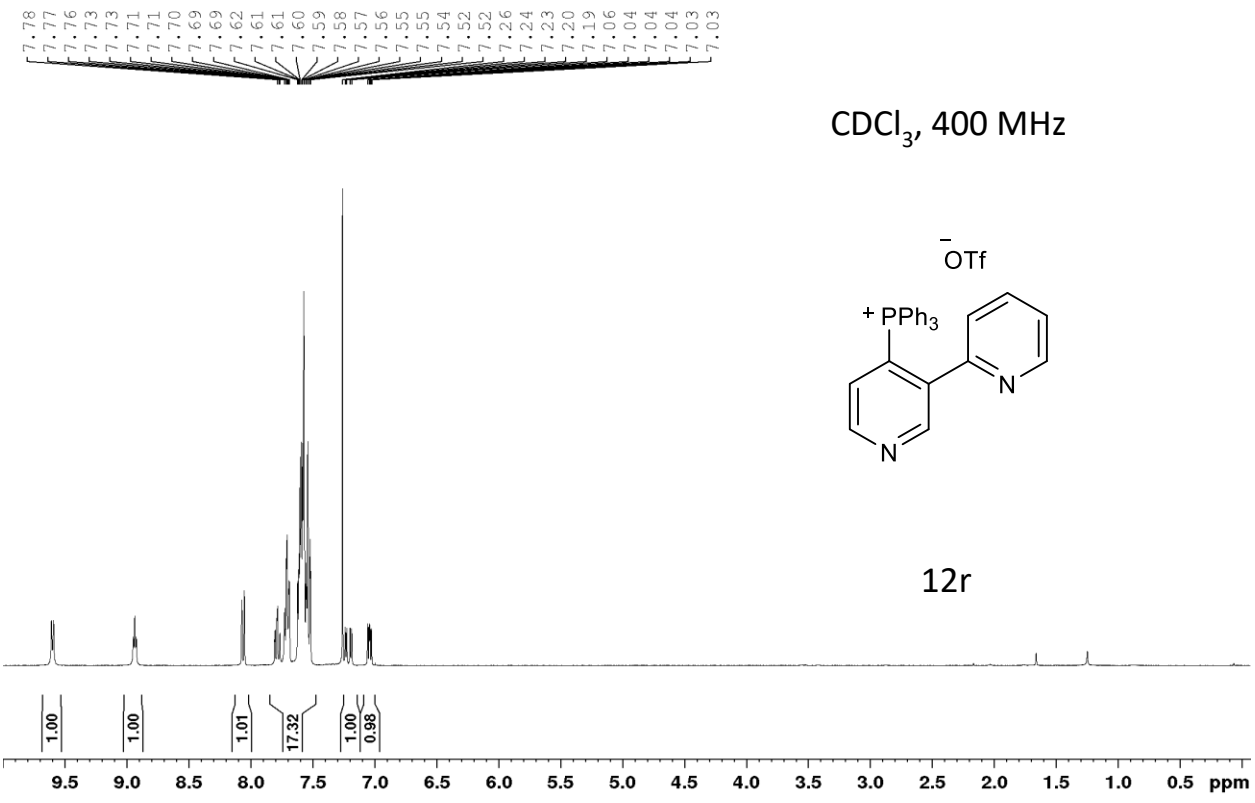

Unidentified
isomer
Minor
Major
Unidentified isomer
29.29
21.90
21.29
17.57
16.42
CDCl3, 162 MHz
(crude 31P NMR)
12l

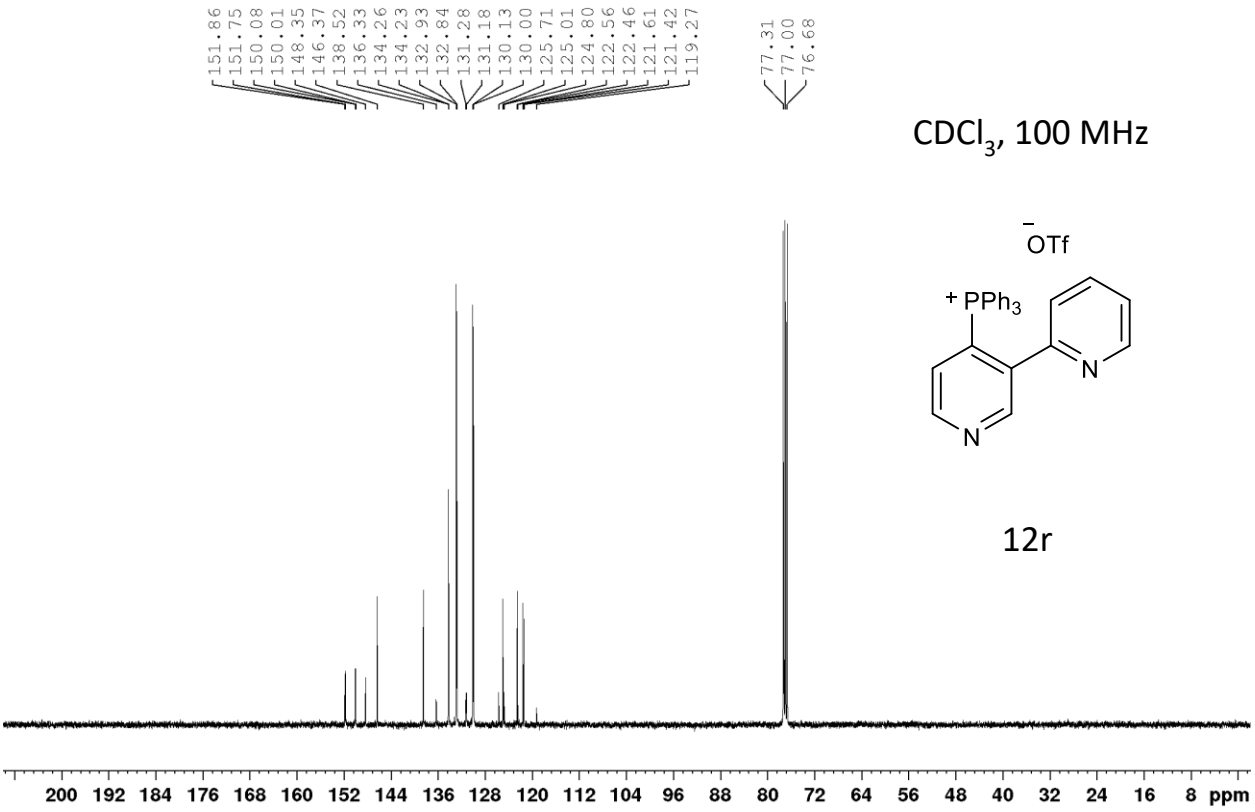

Major
Minor
CDCl3, 400 MHz
(crude 1H NMR)
12l

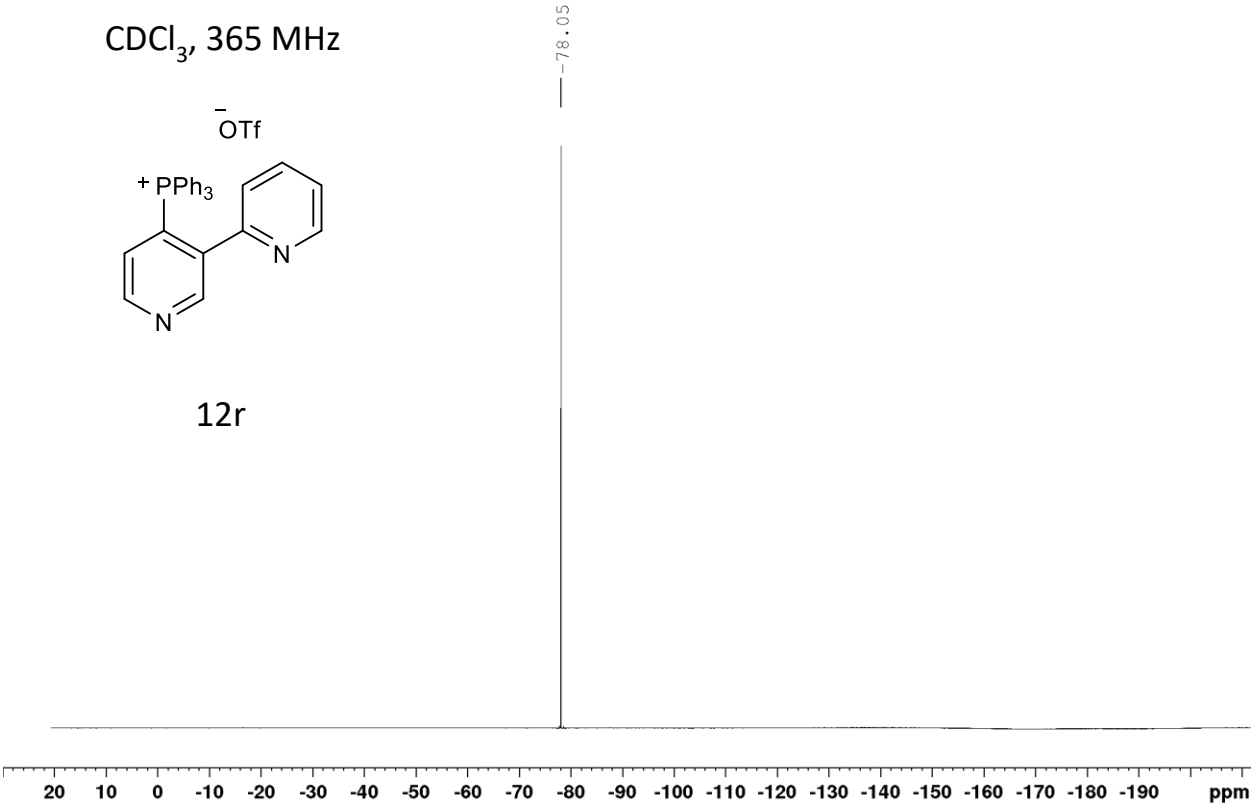

CDCl3, 162 MHz
(crude 31P NMR)
Major
Unidentified isomer
Minor
Unidentified isomer
29.16
21.96
21.28
17.58
16.41
+ PPh2
Me
N
Me
O
O
O
O
S
CF3
12l
ppm


CDCl3, 400 MHz
(crude 1H NMR)
Major
Minor
+ PPh2
Me
N
Me
O
O
O
O
S
CF3
12l
ppm

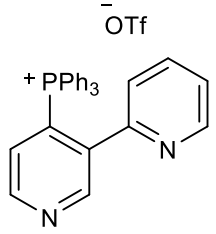

29.15
21.81
21.27
17.57
16.39
Major
Unidentified
isomer
Minor
Unidentified
isomer
0.43
0.23
1.00
0.44
21 20 19 18 17 ppm
CDCl3, 162 MHz
(crude 31P NMR)
+ PPh2
Me
N
Me
O
O
O
O
S
CF3
12l
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


7.78
7.77
7.76
7.73
7.73
7.71
7.71
7.70
7.69
7.69
7.62
7.61
7.61
7.60
7.59
7.58
7.57
7.56
7.55
7.55
7.54
7.52
7.52
7.26
7.24
7.23
7.20
7.19
7.06
7.04
7.04
7.04
7.03
7.03
CDCl3, 400 MHz
OTf
+ PPh3
N
N
12r
1.00
1.00
1.01
17.32
1.00
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


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
12r
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
OTf
+ PPh3
N
N
12r
-78.05
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

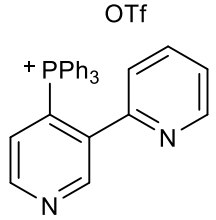
$CDCl_3$, 162 MHz



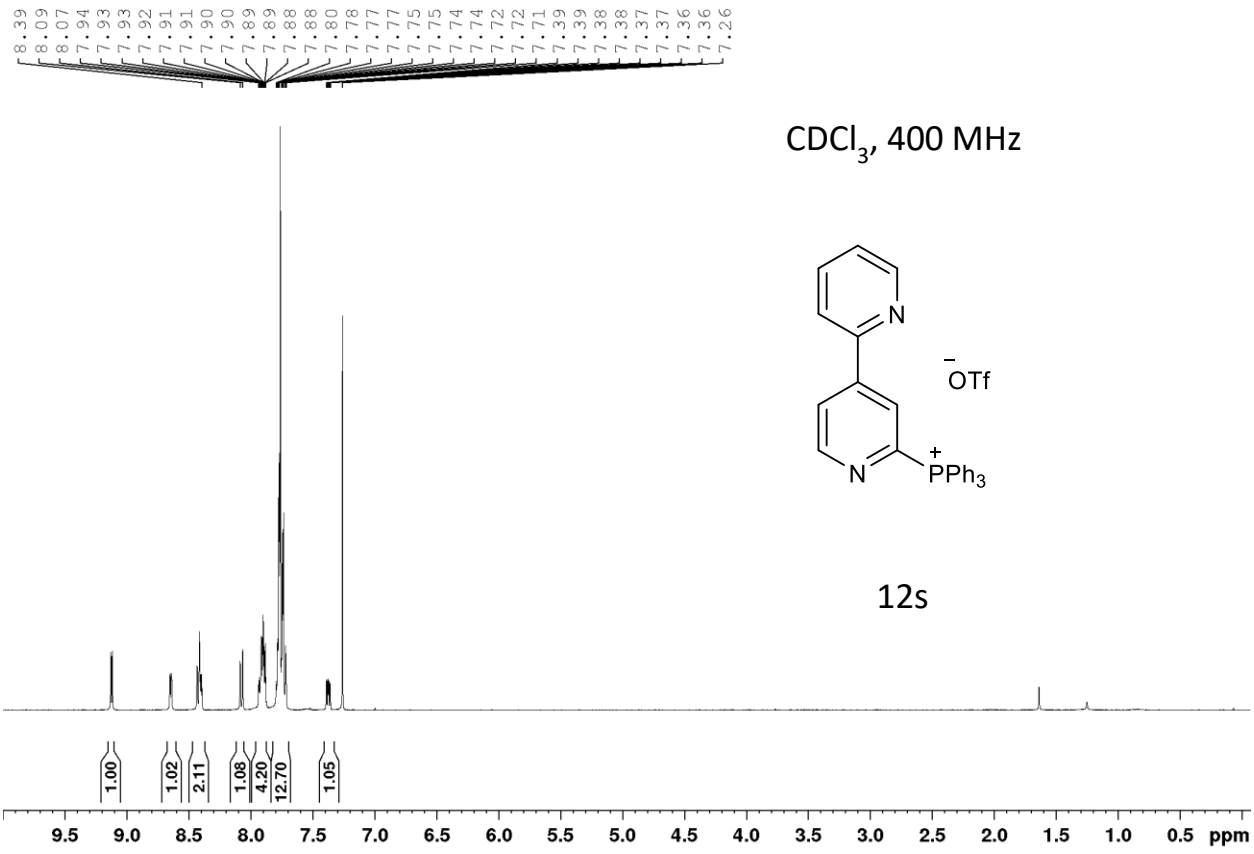
12r

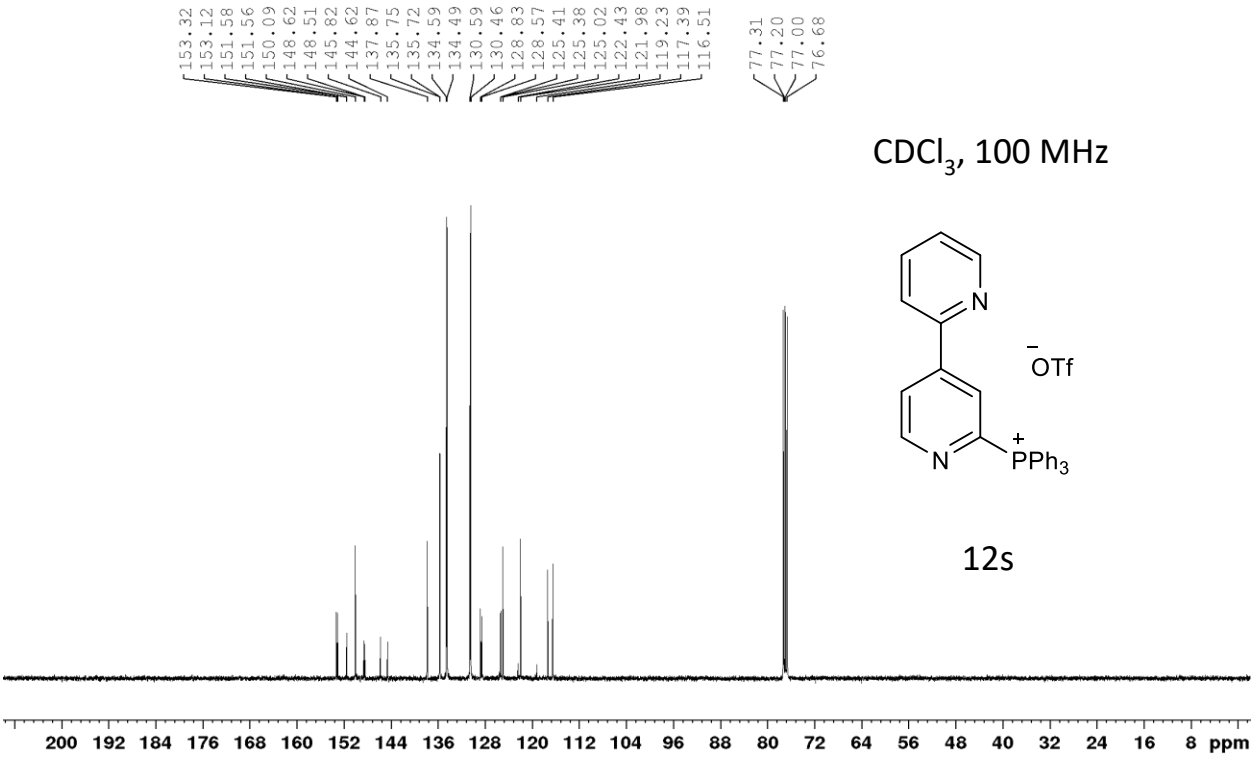
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

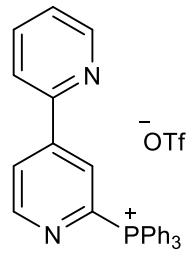


12r


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
7.37
7.37
7.36
7.36
7.26
CDCl3, 400 MHz
N
OTf
N
PPh3
12s
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

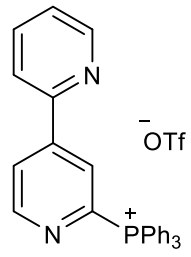

153.32
153.12
151.58
151.56
150.09
148.62
148.51
145.82
144.62
137.87
135.75
135.72
134.59
134.49
130.59
130.46
128.83
128.57
125.41
125.38
125.02
122.43
121.98
119.23
117.39
116.51
77.31
77.20
77.00
76.68
CDCl3, 100 MHz
N
OTf
N
PPh3
12s
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz



12s

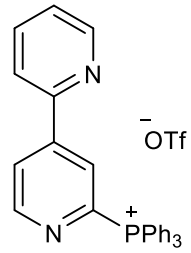
$CDCl_3$, 162 MHz



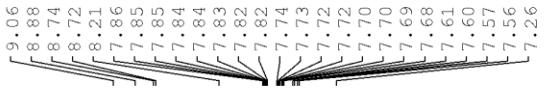
12s

$CDCl_3$, 162 MHz

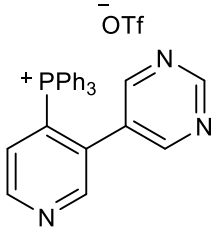
(crude ^{31}P NMR)



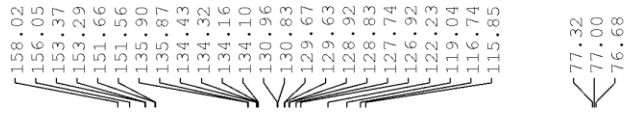
12s



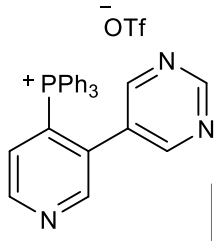
$CDCl_3$, 400 MHz



12t

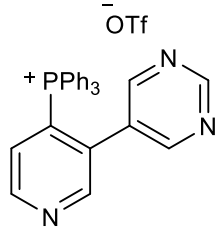


$CDCl_3$, 100 MHz



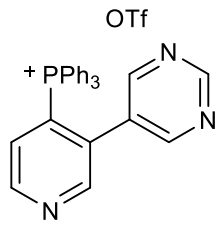
12t

$CDCl_3$, 365 MHz



12t

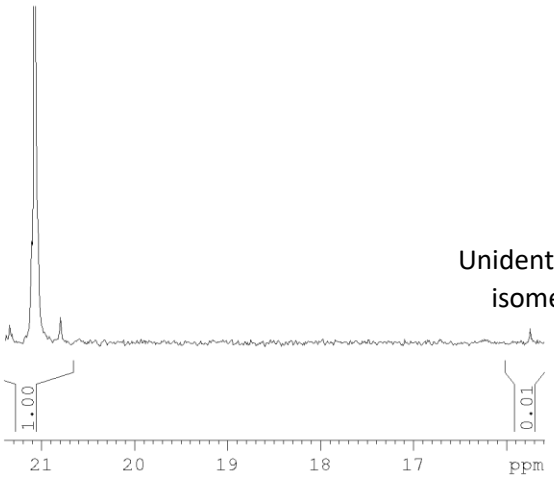
$CDCl_3$, 162 MHz



12t

Major

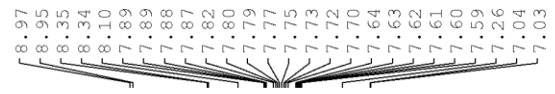
Unidentified isomer



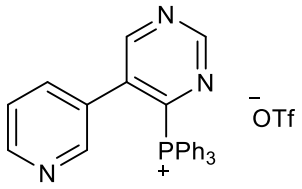
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

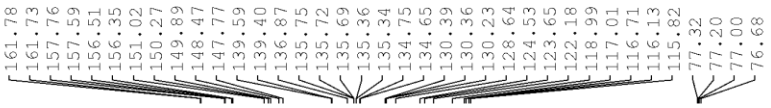
12t



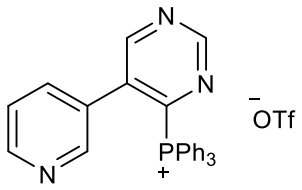
$CDCl_3$, 400 MHz



12t

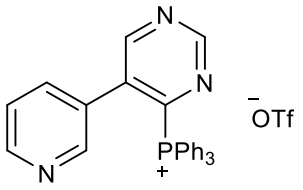


$CDCl_3$, 100 MHz



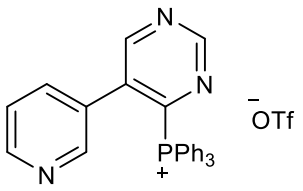
12t

$CDCl_3$, 365 MHz

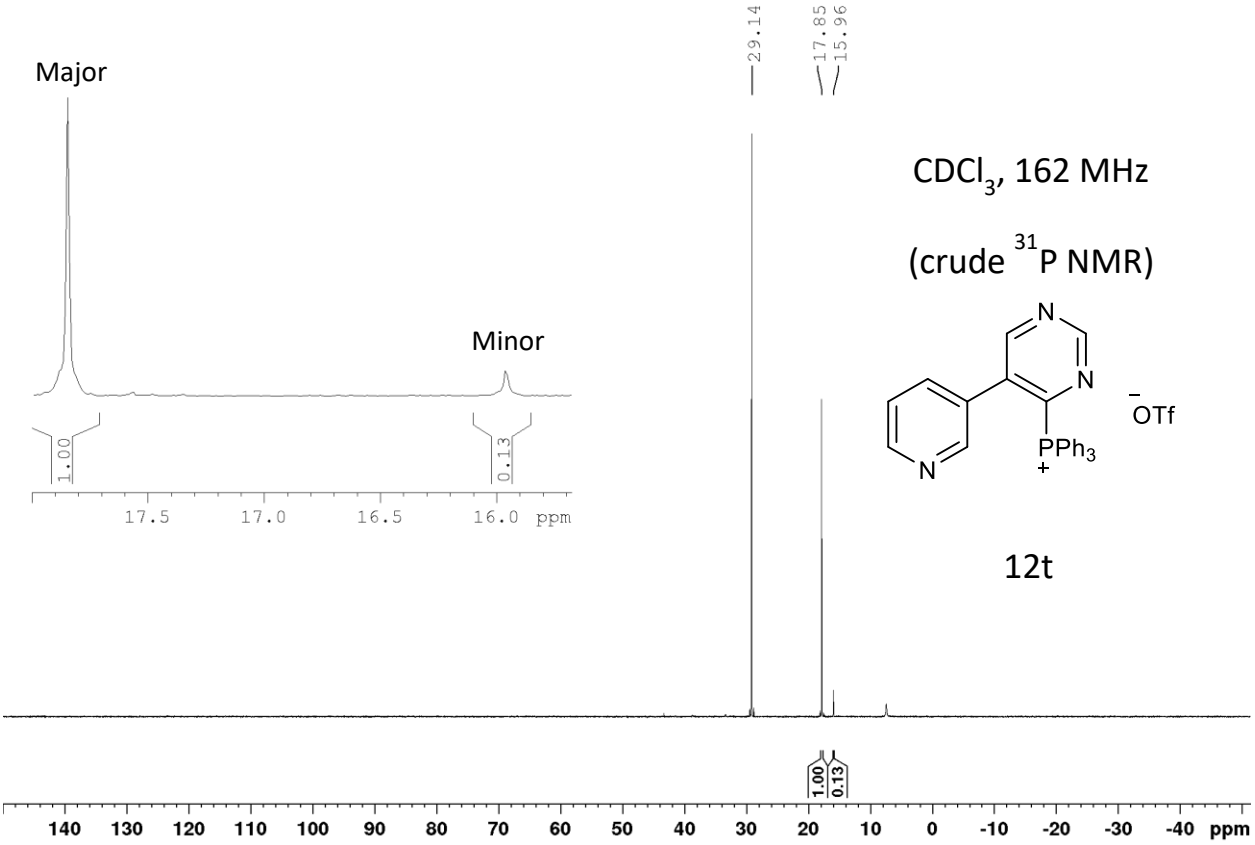


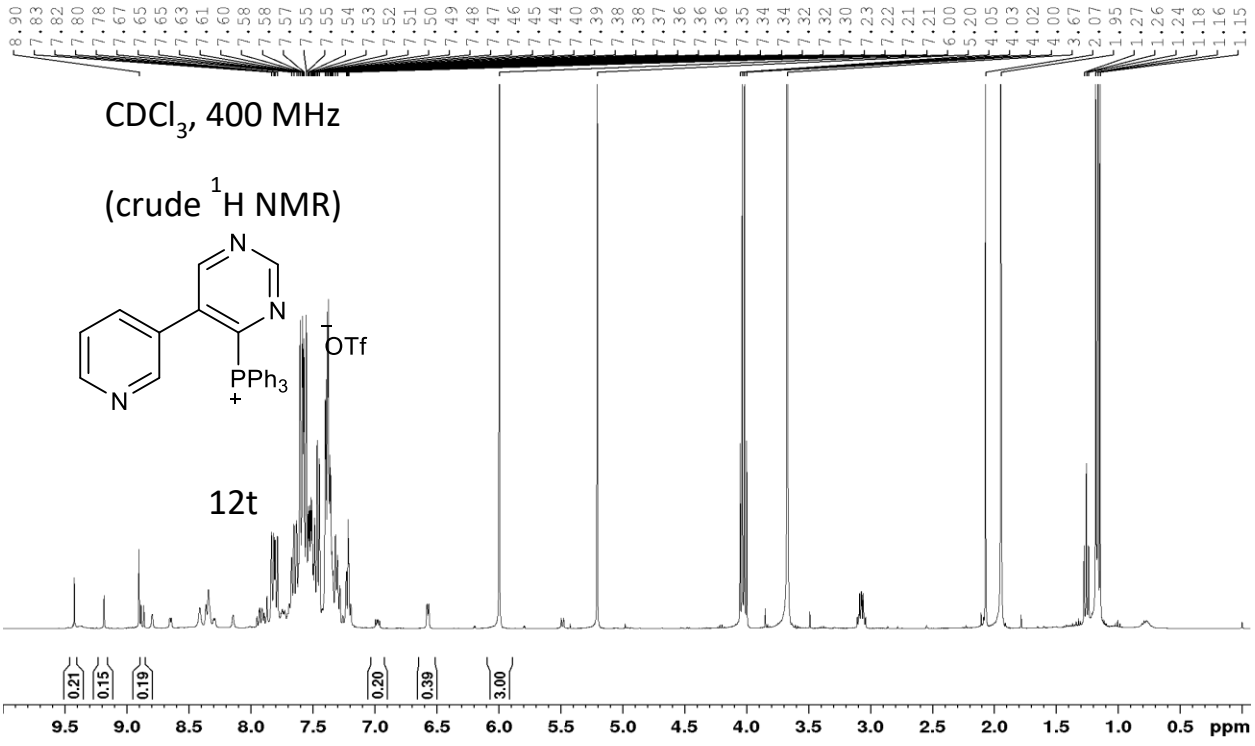
12t

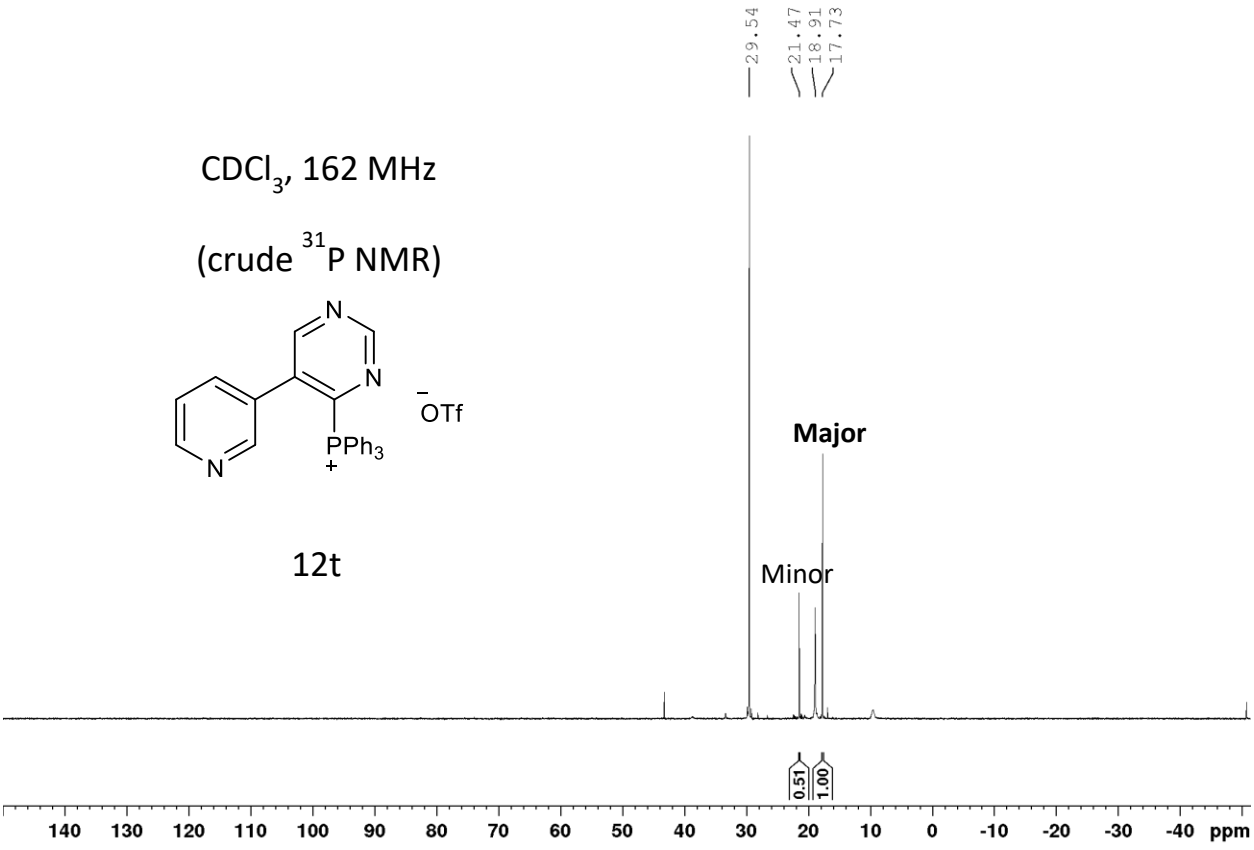
$CDCl_3$, 162 MHz

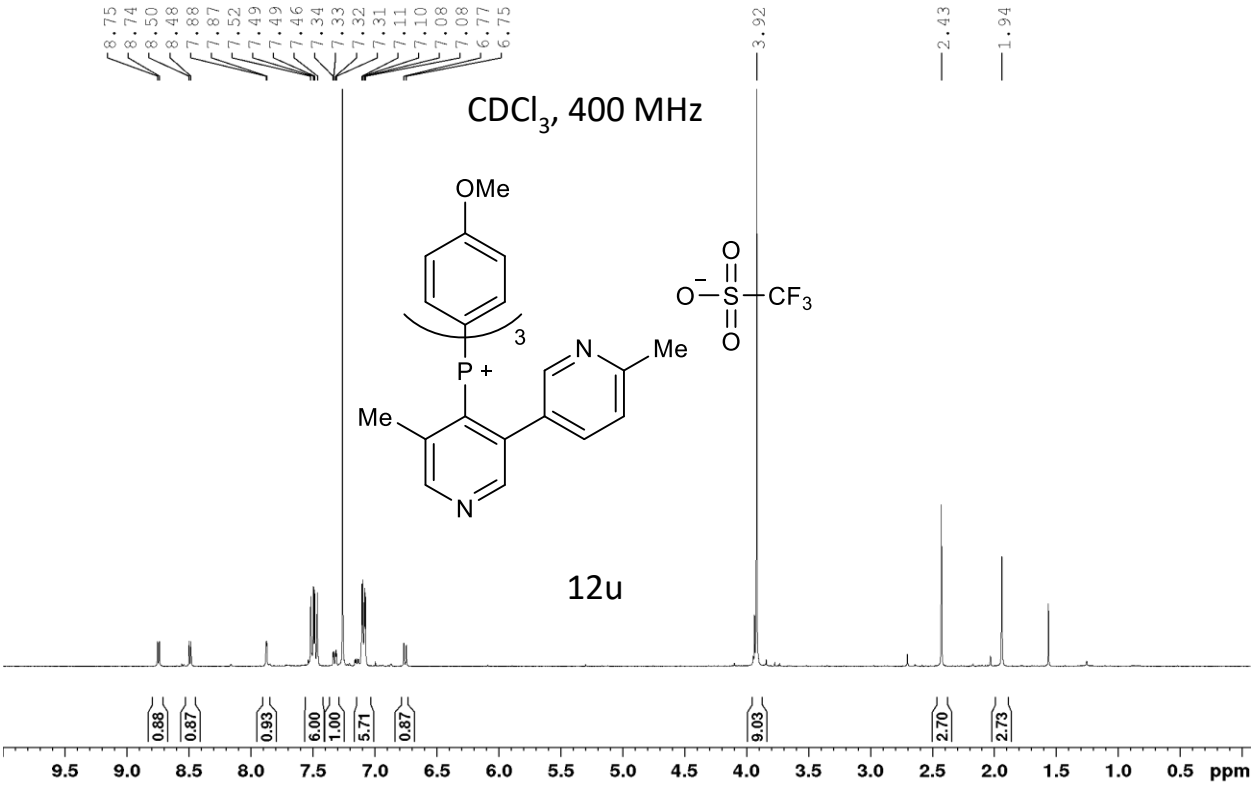


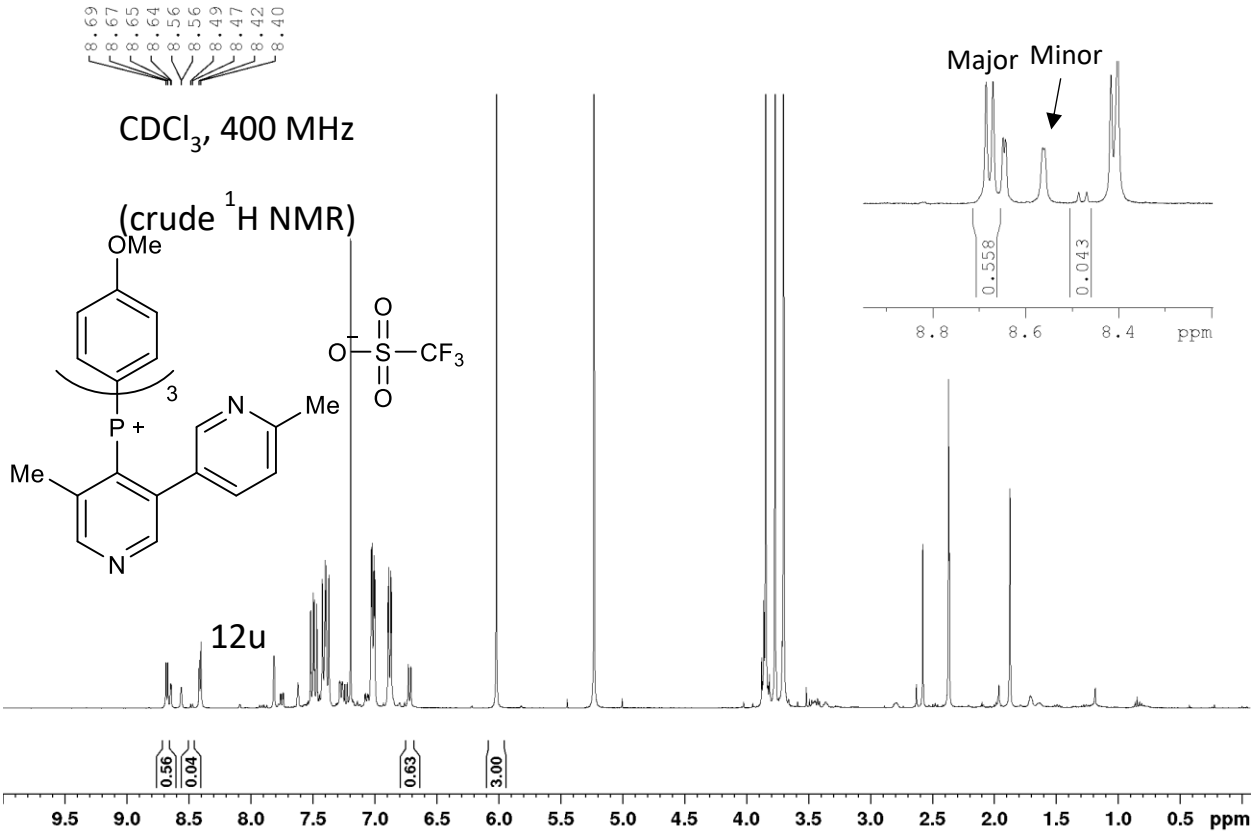
12t

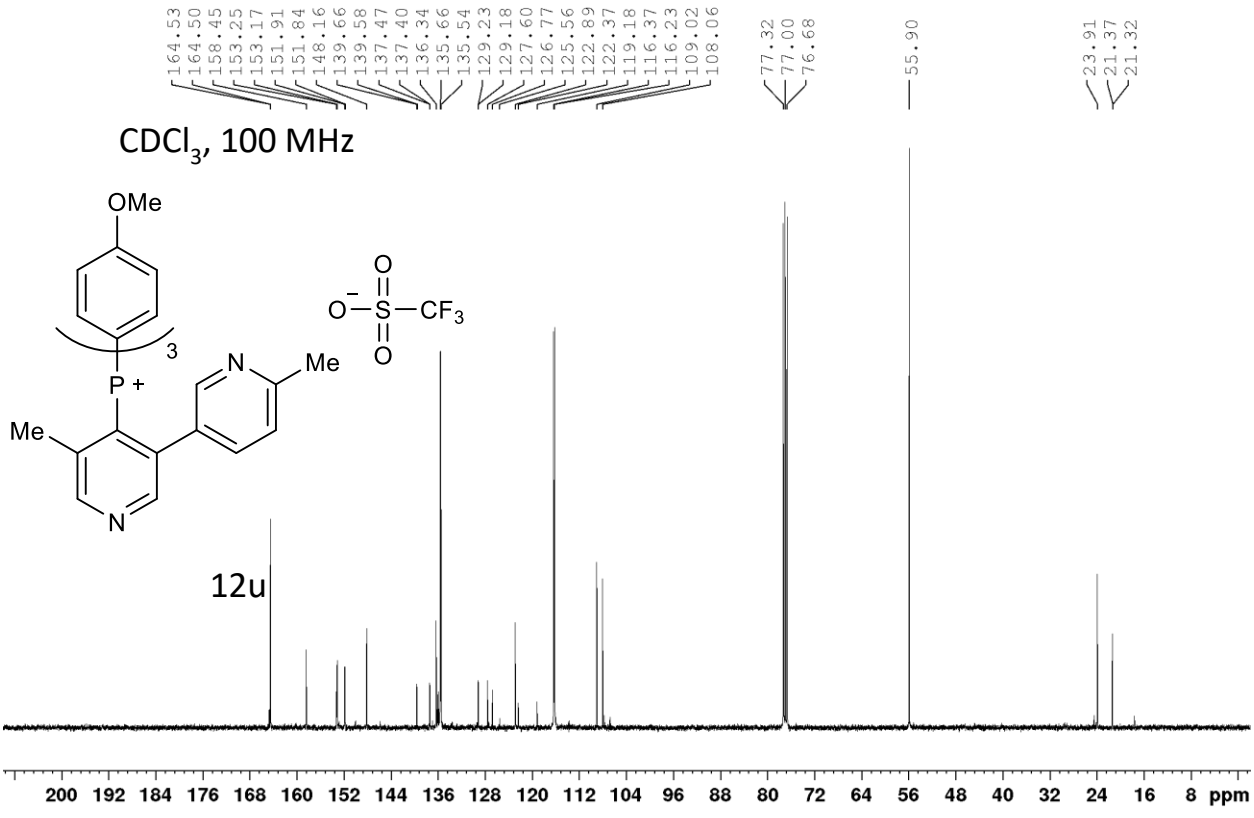

Major
Minor
29.14
17.85
15.96
1.00
0.13
17.5
17.0
16.5
16.0 ppm
CDCl3, 162 MHz
(crude 31P NMR)
N
N
N
PPh3
+
OTf
12t
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


CDCl3, 400 MHz
(crude 1H NMR)
N
N
N
PPh3
+
OTf
12t
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

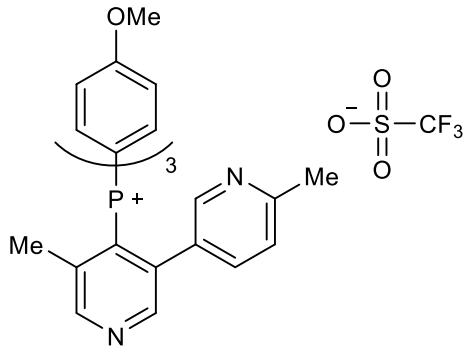

29.54
21.47
18.91
17.73
CDCl3, 162 MHz
(crude 31P NMR)
OTf
PPh3
Major
Minor
12t
0.51
1.00
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 ppm


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
CF3
Me
Me
12u
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)
Major
Minor
0.558
0.043
8.8
8.6
8.4
ppm
OMe
3
P +
N
Me
Me
N
O
S
CF3
12u
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

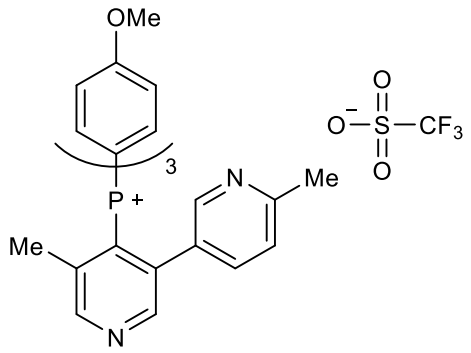

164.53
164.50
158.45
153.25
153.17
151.91
151.84
148.16
139.66
139.58
137.47
137.40
136.34
135.66
135.54
129.23
129.18
127.60
126.77
125.56
122.89
122.37
119.18
116.37
116.23
109.02
108.06
77.32
77.00
76.68
55.90
23.91
21.37
21.32
CDCl3, 100 MHz
OMe
3
P +
N
Me
Me
N
O
S
CF3
12u
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz



12u

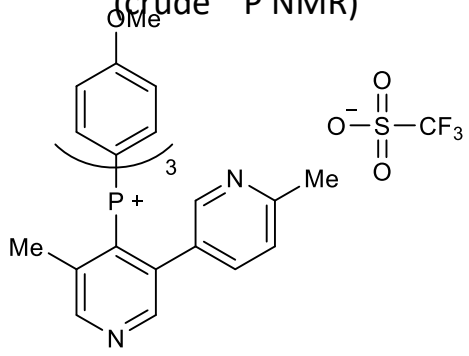
$CDCl_3$, 162 MHz



12u

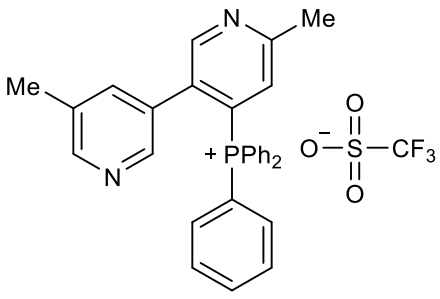
$CDCl_3$, 162 MHz

(crude ^{31}P NMR)

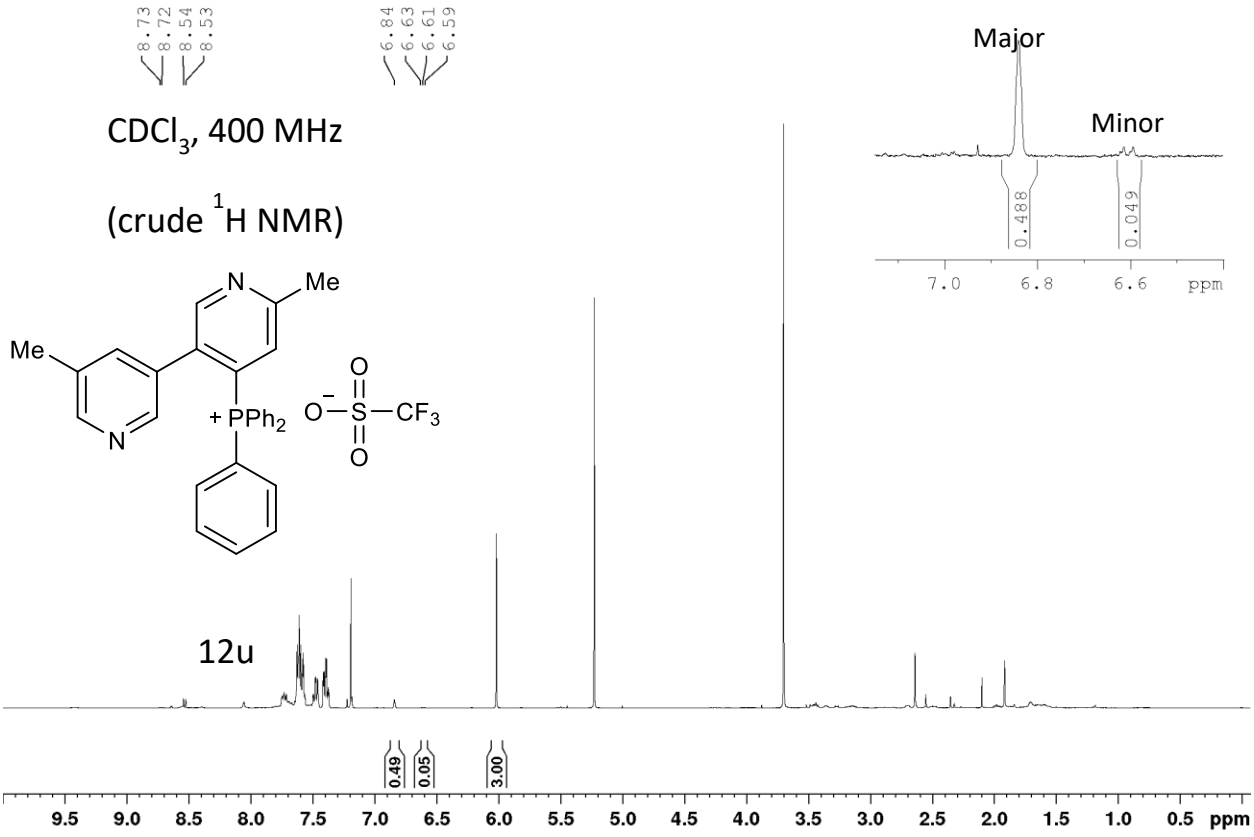


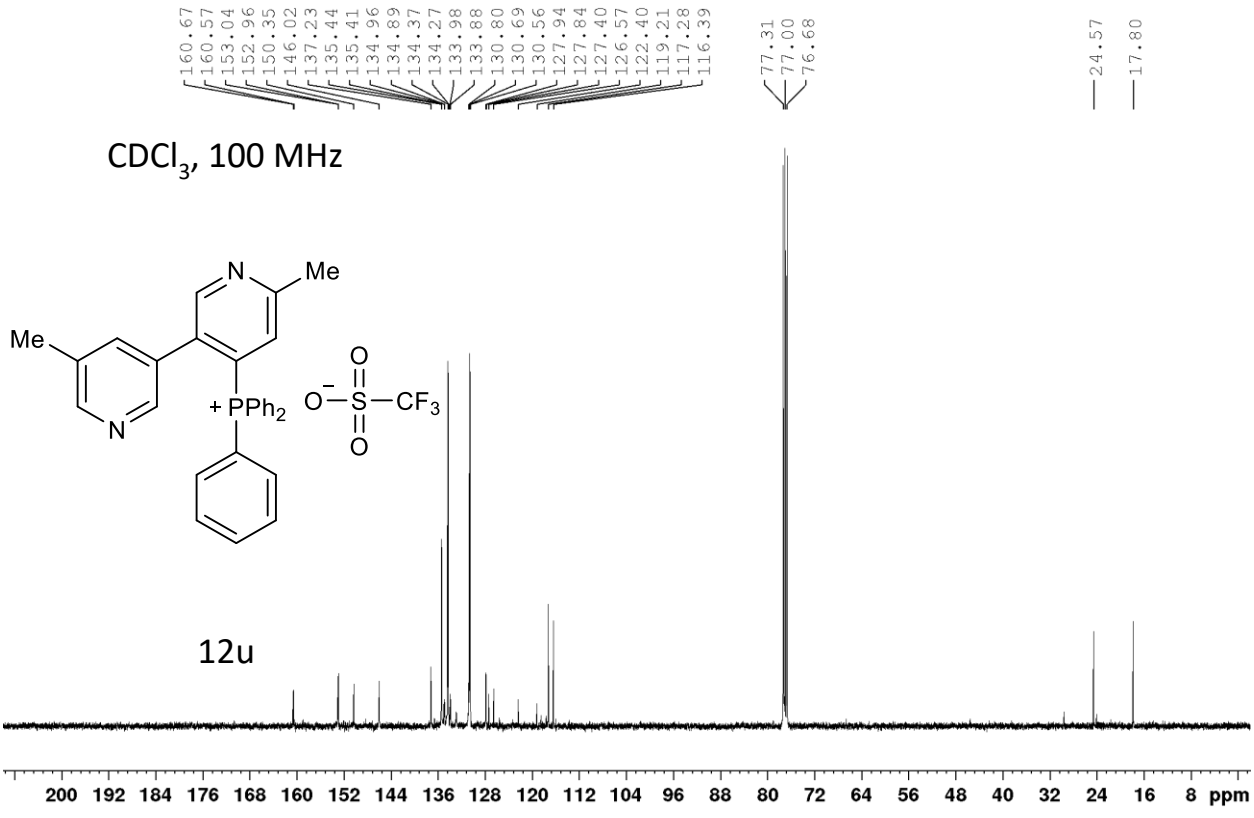
12u

$CDCl_3$, 400 MHz

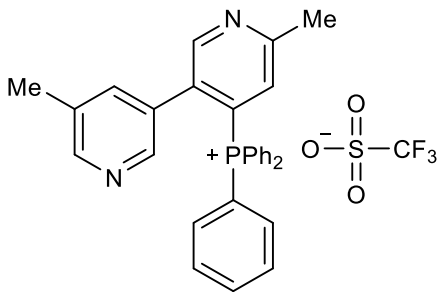


12u


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
12u
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

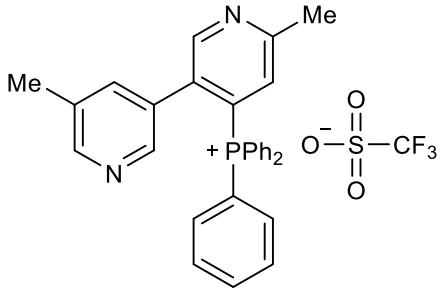

160.67
160.57
153.04
152.96
150.35
146.02
137.23
135.44
135.41
134.96
134.89
134.37
134.27
133.98
133.88
130.80
130.69
130.56
127.94
127.84
127.40
126.57
122.40
119.21
117.28
116.39
77.31
77.00
76.68
24.57
17.80
CDCl3, 100 MHz
Me
N
Me
+PPh2
O
S
CF3
12u
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

$CDCl_3$, 365 MHz

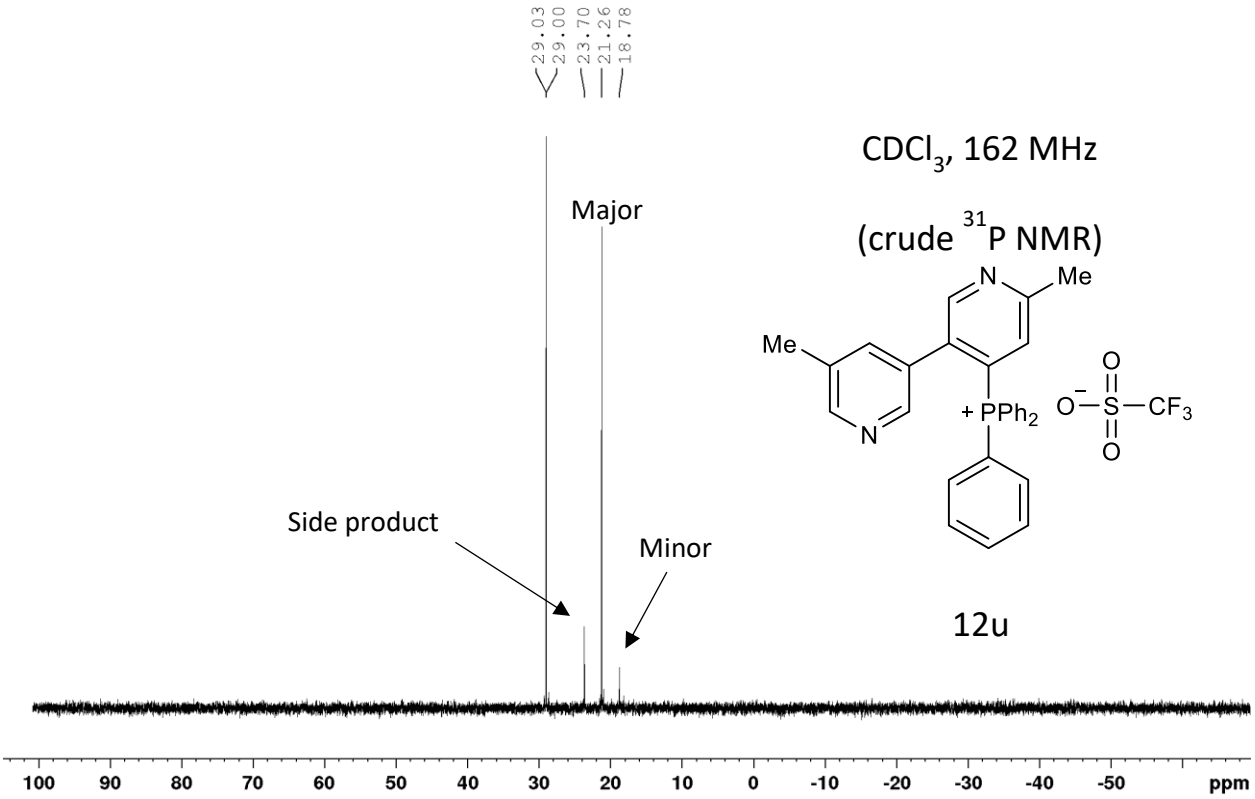


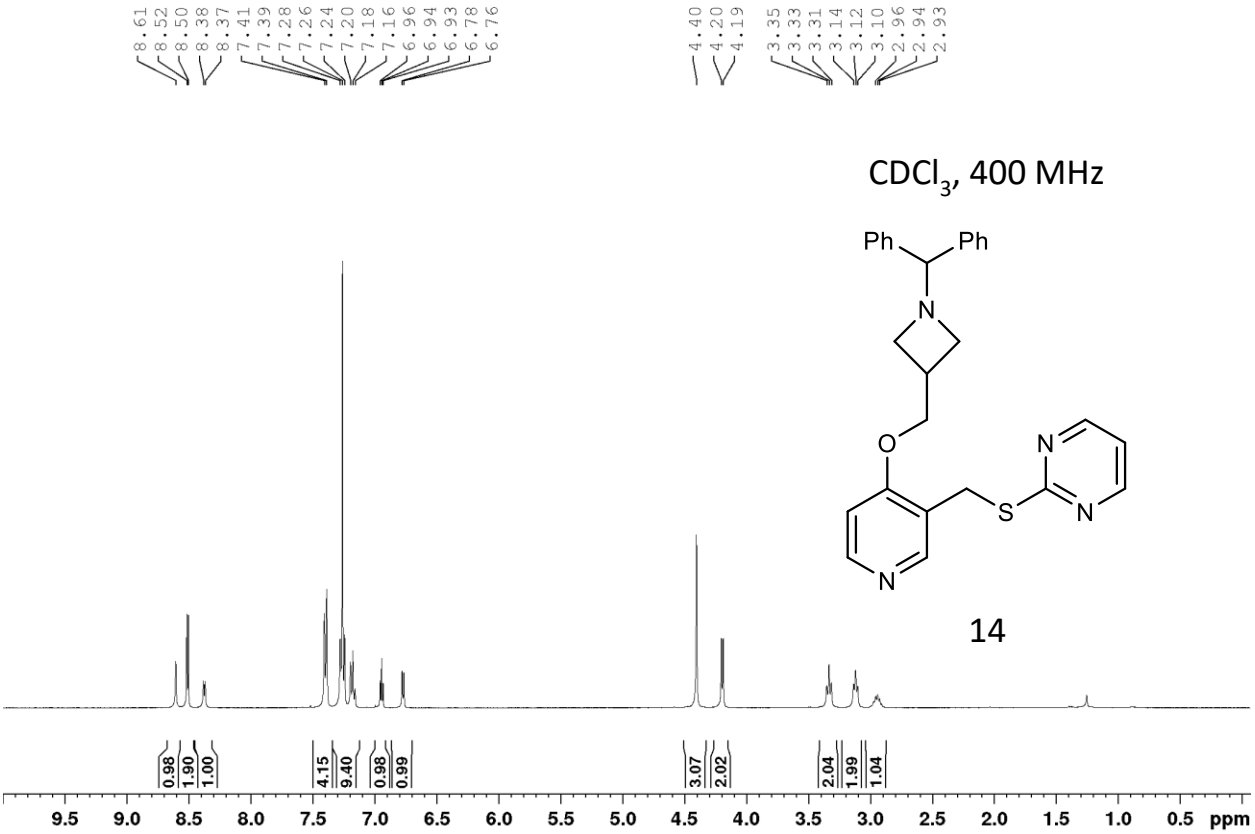
12u

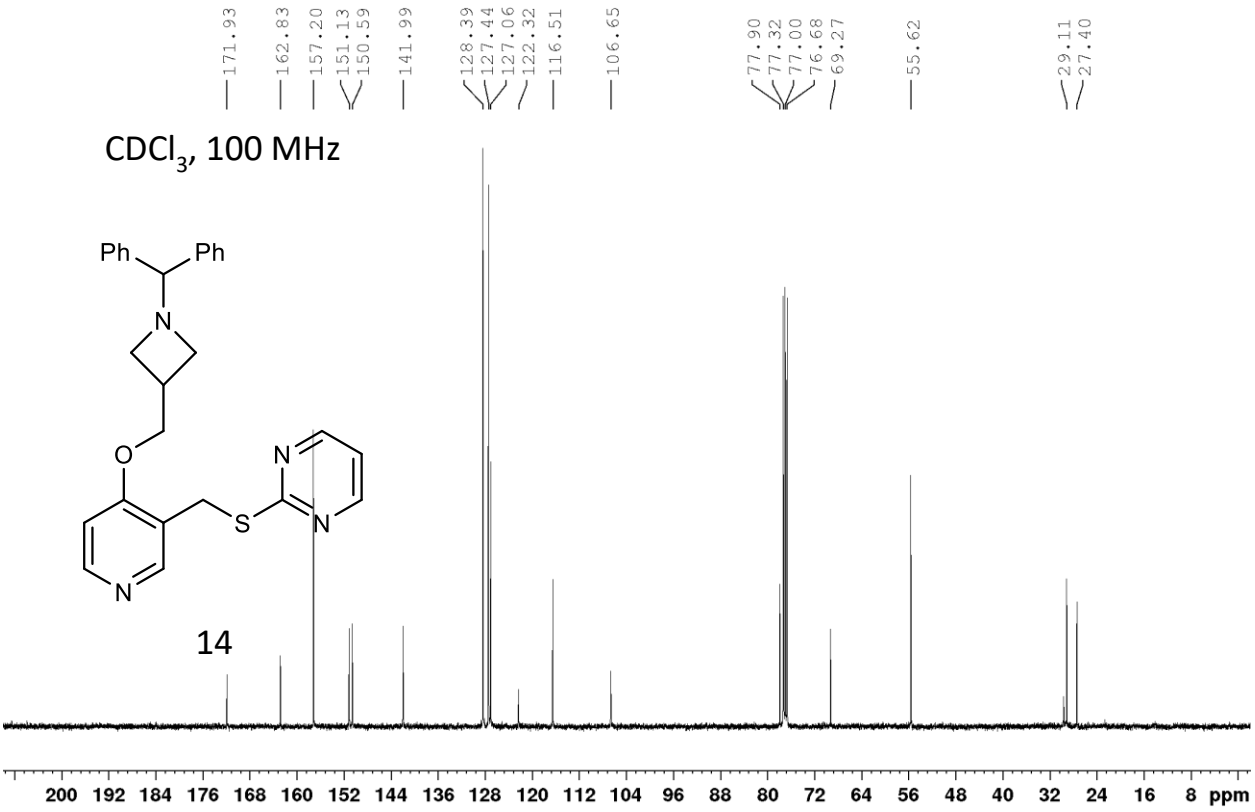
$CDCl_3$, 162 MHz

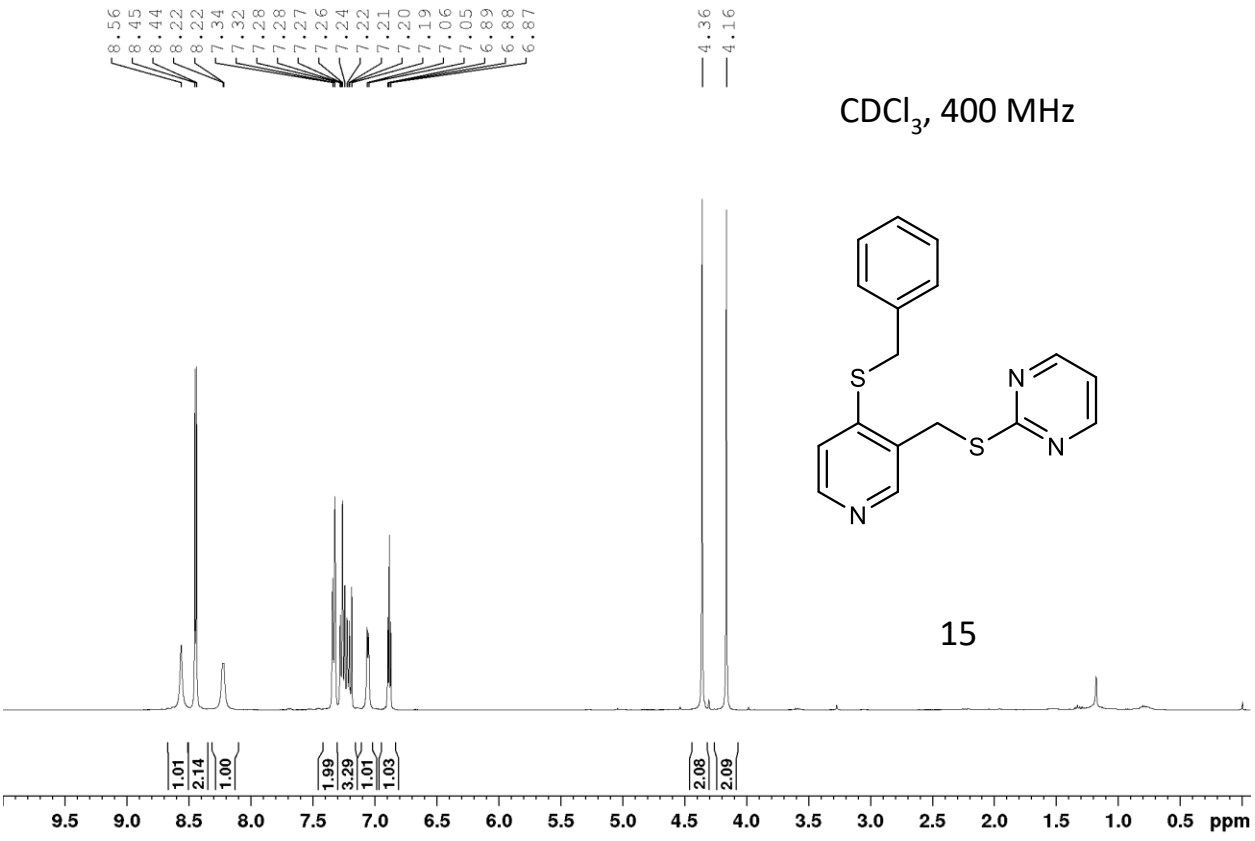


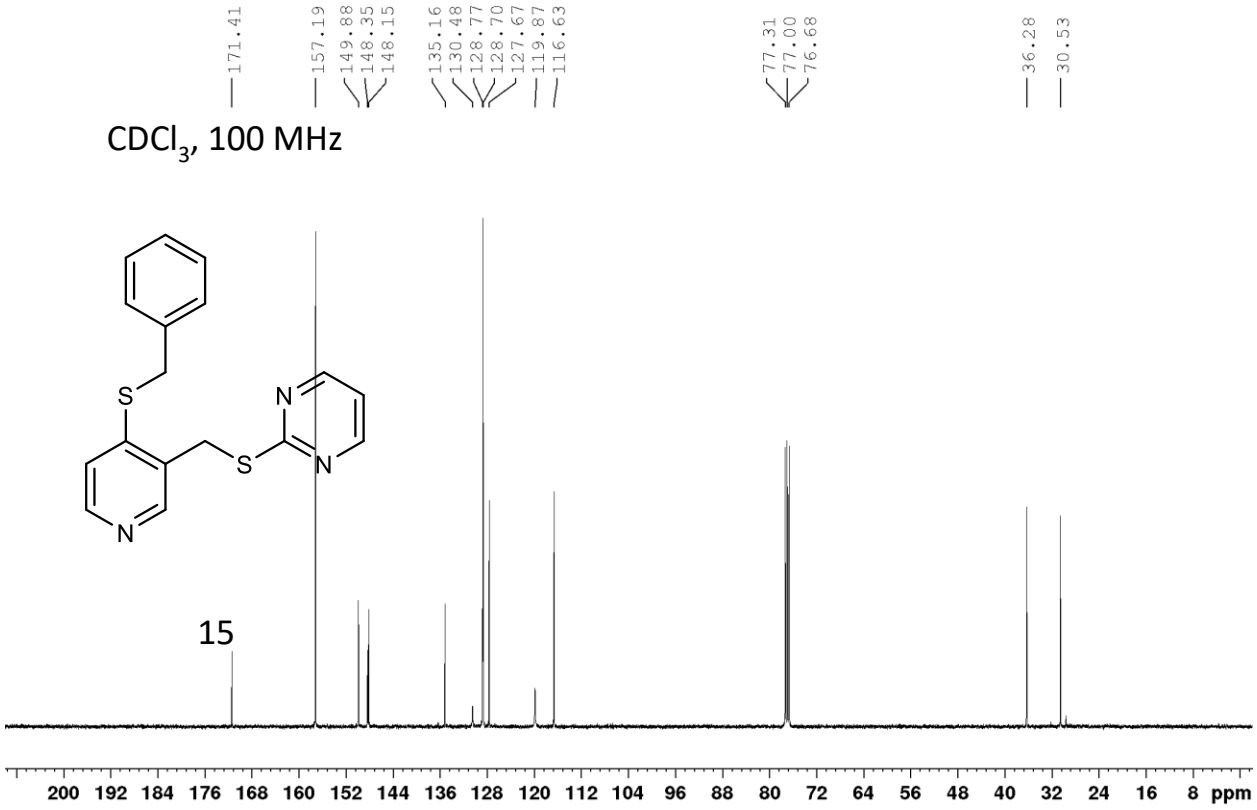
12u

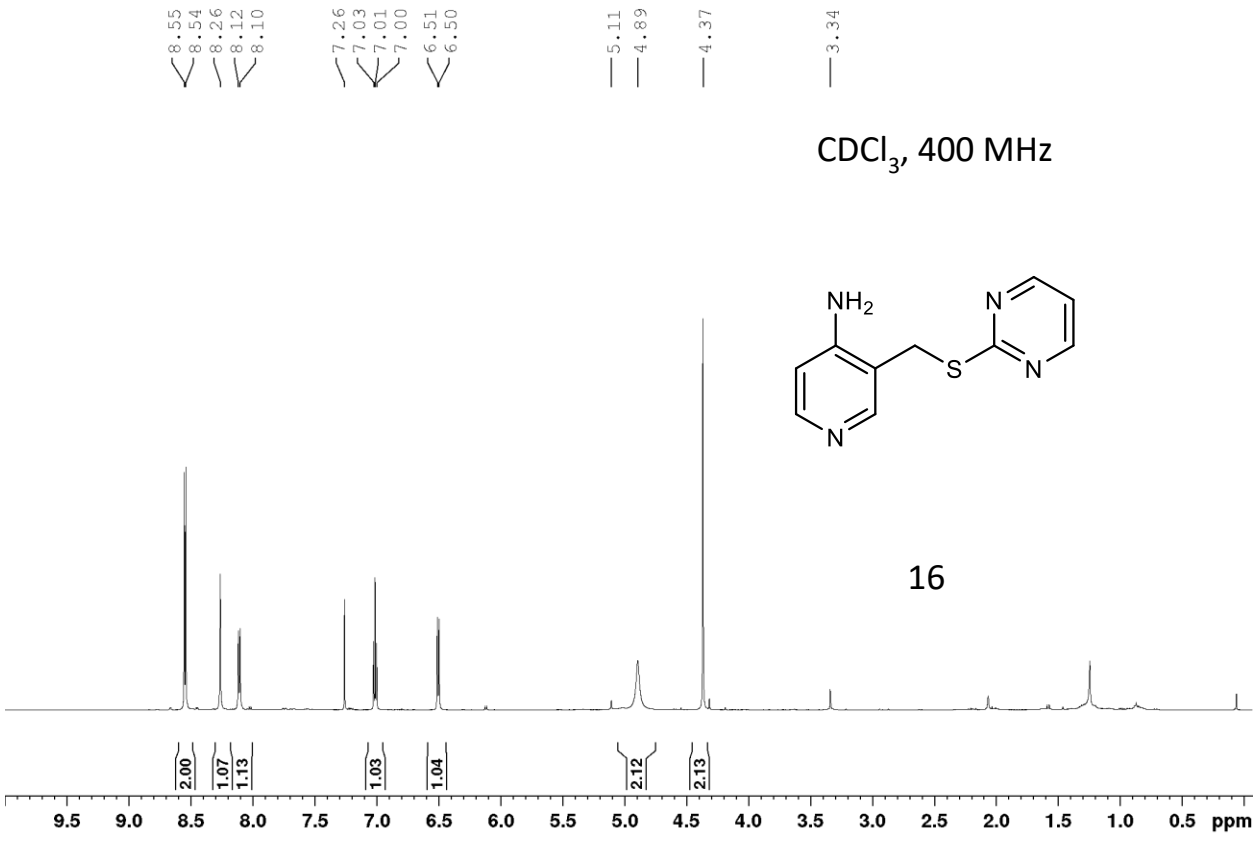

29.03
29.00
23.70
21.26
18.78
CDCl3, 162 MHz
(crude 31P NMR)
Major
Side product
Minor
12u
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm

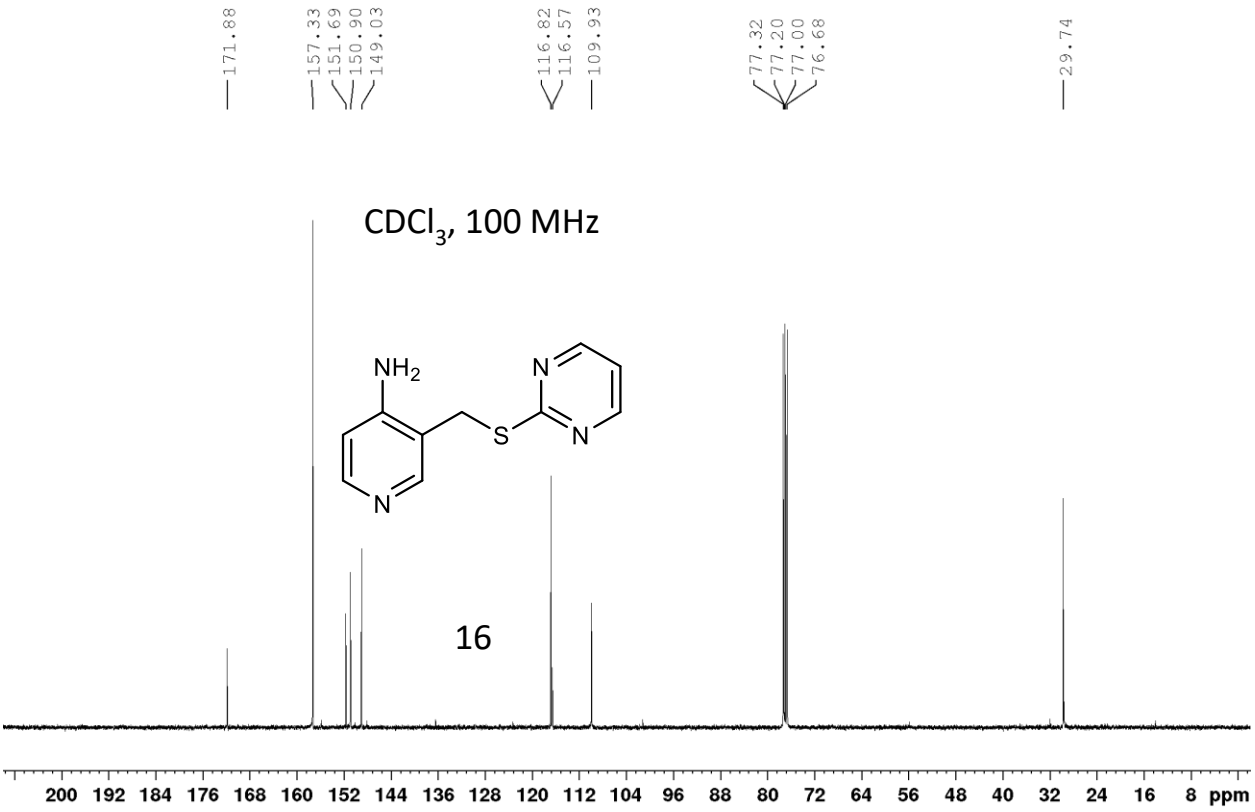

8.61
8.52
8.50
8.38
8.37
7.41
7.39
7.28
7.26
7.24
7.20
7.18
7.16
6.96
6.94
6.93
6.78
6.76
4.40
4.20
4.19
3.35
3.33
3.31
3.14
3.12
3.10
2.96
2.94
2.93
CDCl3, 400 MHz
14
0.98
1.90
1.00
4.15
9.40
0.98
0.99
3.07
2.02
2.04
1.99
1.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

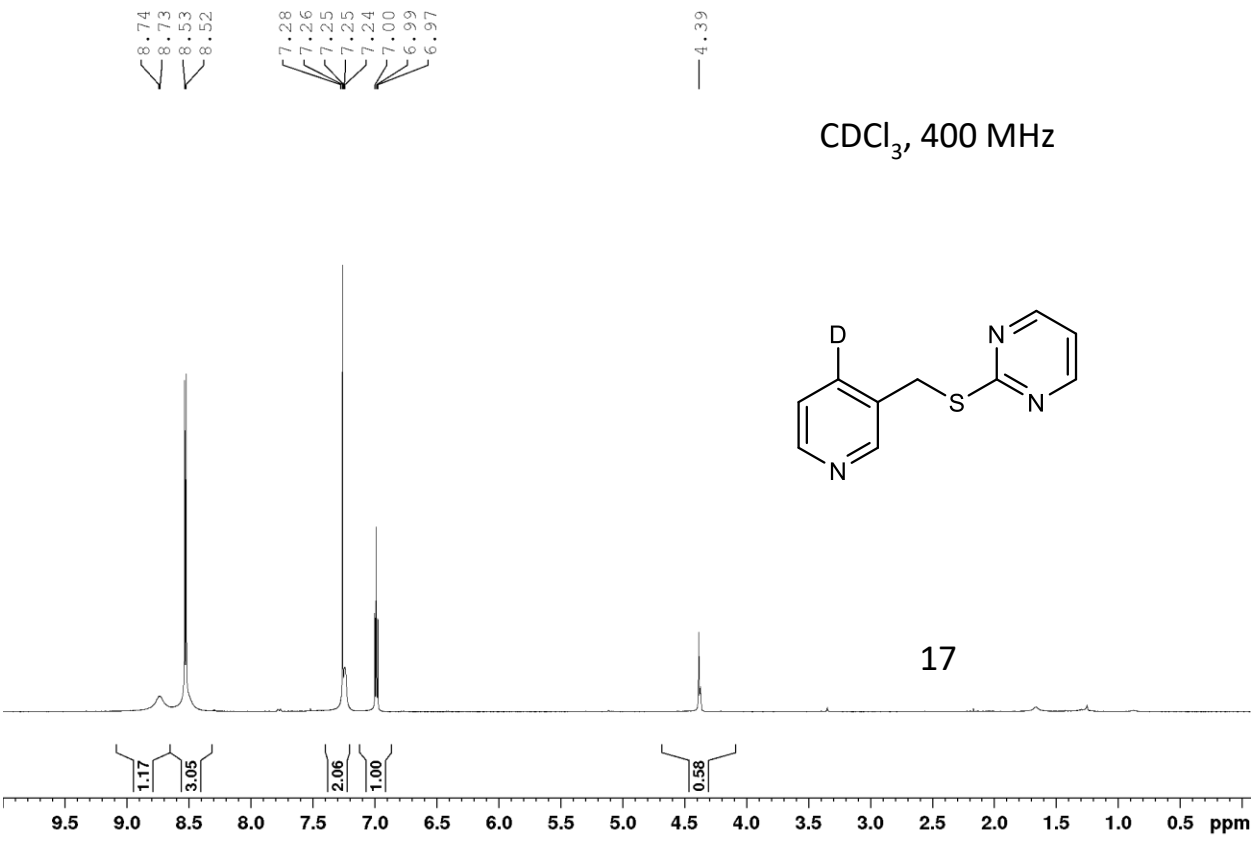

171.93
162.83
157.20
151.13
150.59
141.99
128.39
127.44
127.06
122.32
116.51
106.65
77.90
77.32
77.00
76.68
69.27
55.62
29.11
27.40
CDCl3, 100 MHz
Ph
Ph
N
O
N
S
N
N
14
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

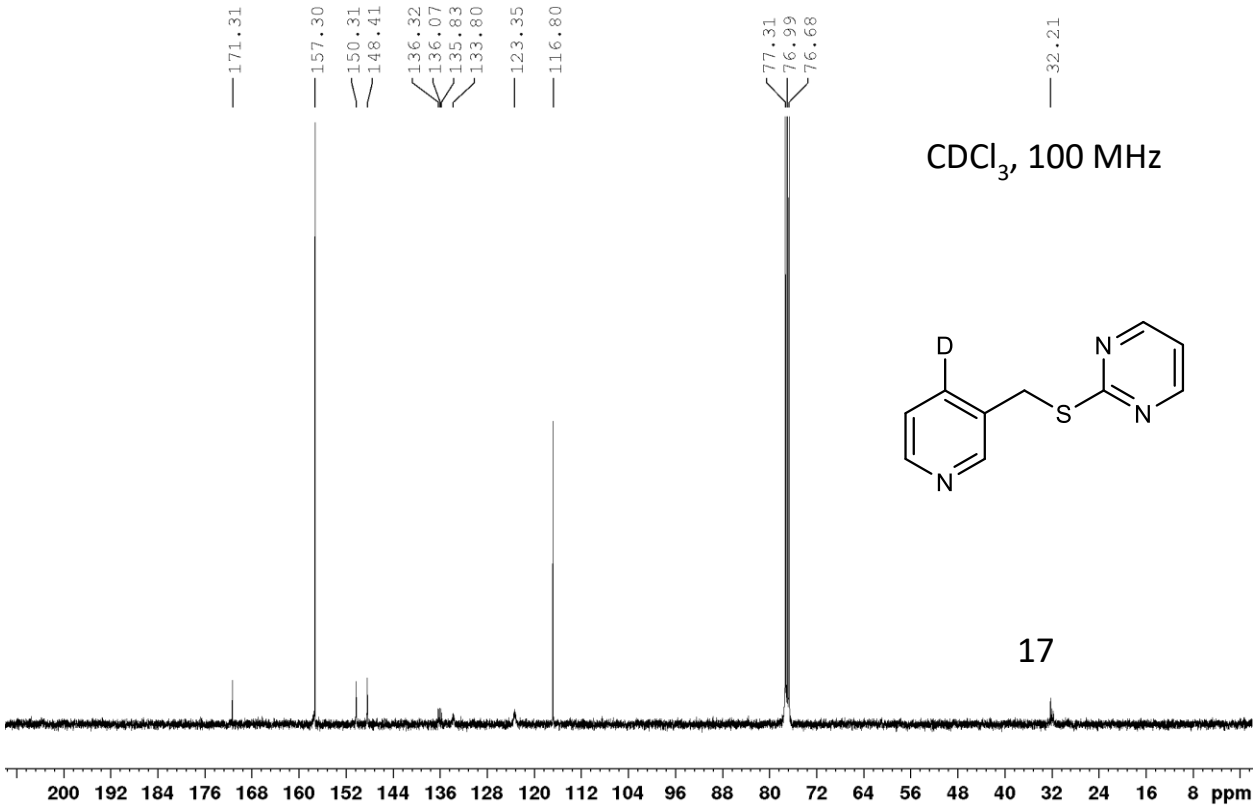

8.56
8.45
8.44
8.22
8.22
7.34
7.32
7.28
7.28
7.27
7.26
7.24
7.22
7.21
7.20
7.19
7.06
7.05
6.89
6.88
6.87
4.36
4.16
CDCl3, 400 MHz
S
N
S
N
N
15
1.01
2.14
1.00
1.99
3.29
1.01
1.03
2.08
2.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

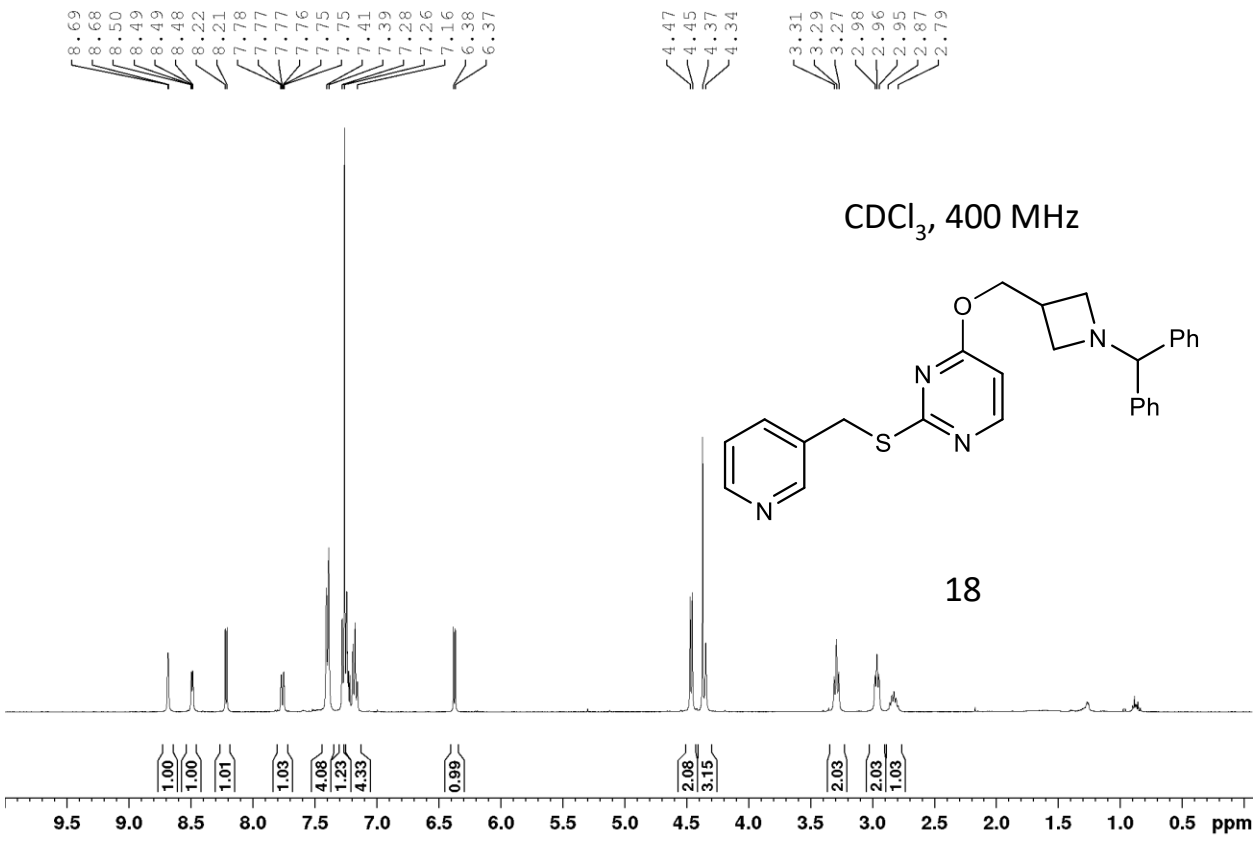

171.41
157.19
149.88
148.35
148.15
135.16
130.48
128.77
128.70
127.67
119.87
116.63
77.31
77.00
76.68
36.28
30.53
CDCl3, 100 MHz
S
N
S
N
N
15
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

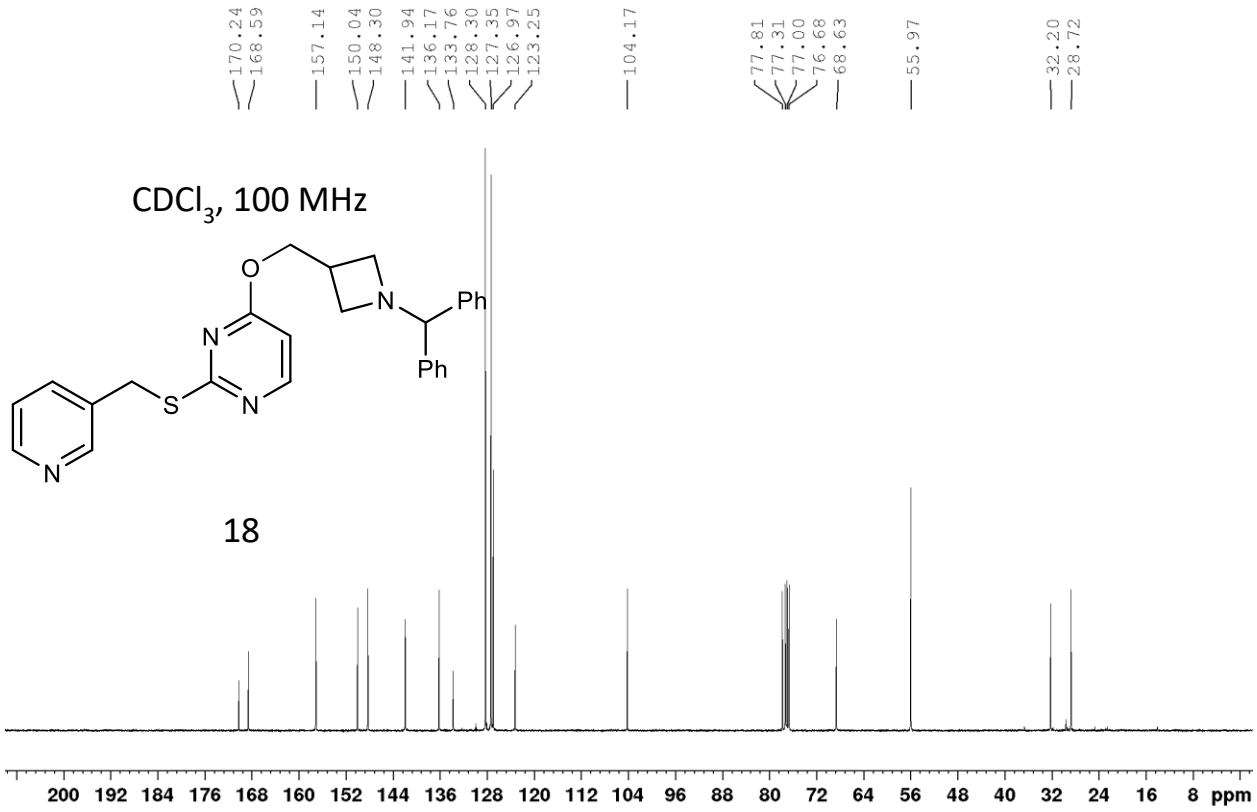

8.55
8.54
8.26
8.12
8.10
7.26
7.03
7.01
7.00
6.51
6.50
5.11
4.89
4.37
3.34
CDCl3, 400 MHz
NH2
N
S
N
N
16
2.00
1.07
1.13
1.03
1.04
2.12
2.13
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

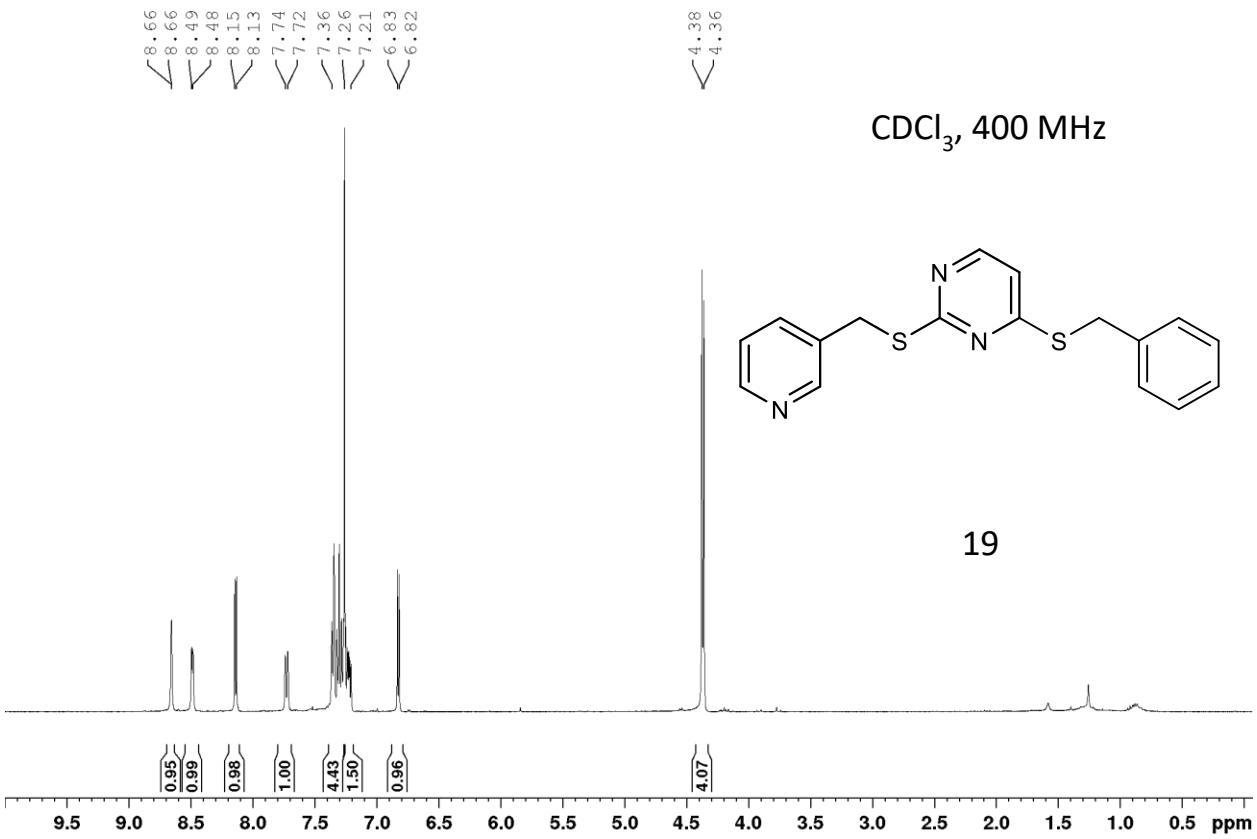

171.88
157.33
151.69
150.90
149.03
116.82
116.57
109.93
77.32
77.20
77.00
76.68
29.74
CDCl3, 100 MHz
NH2
N
S
N
N
16
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

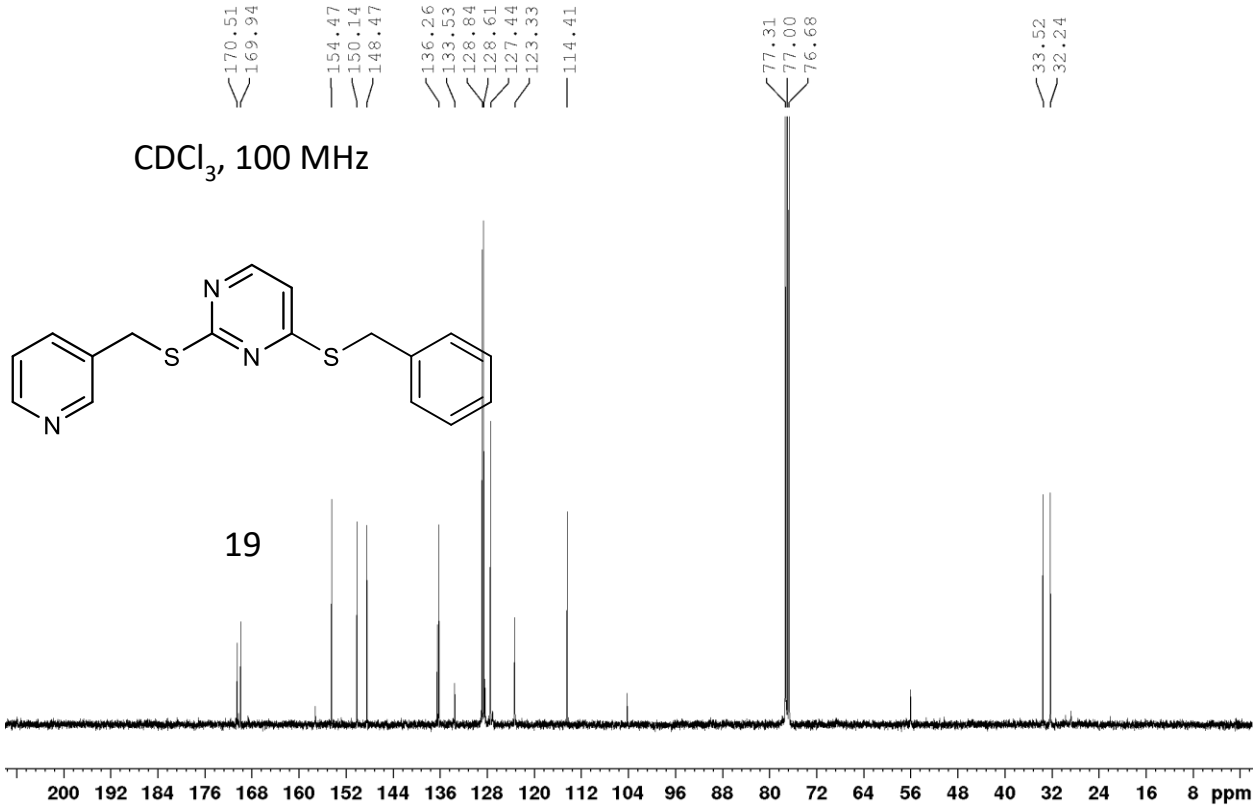

8.74
8.73
8.53
8.52
7.28
7.26
7.25
7.25
7.24
7.00
6.99
6.97
4.39
CDCl3, 400 MHz
D
N
S
N
N
17
1.17
3.05
2.06
1.00
0.58
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

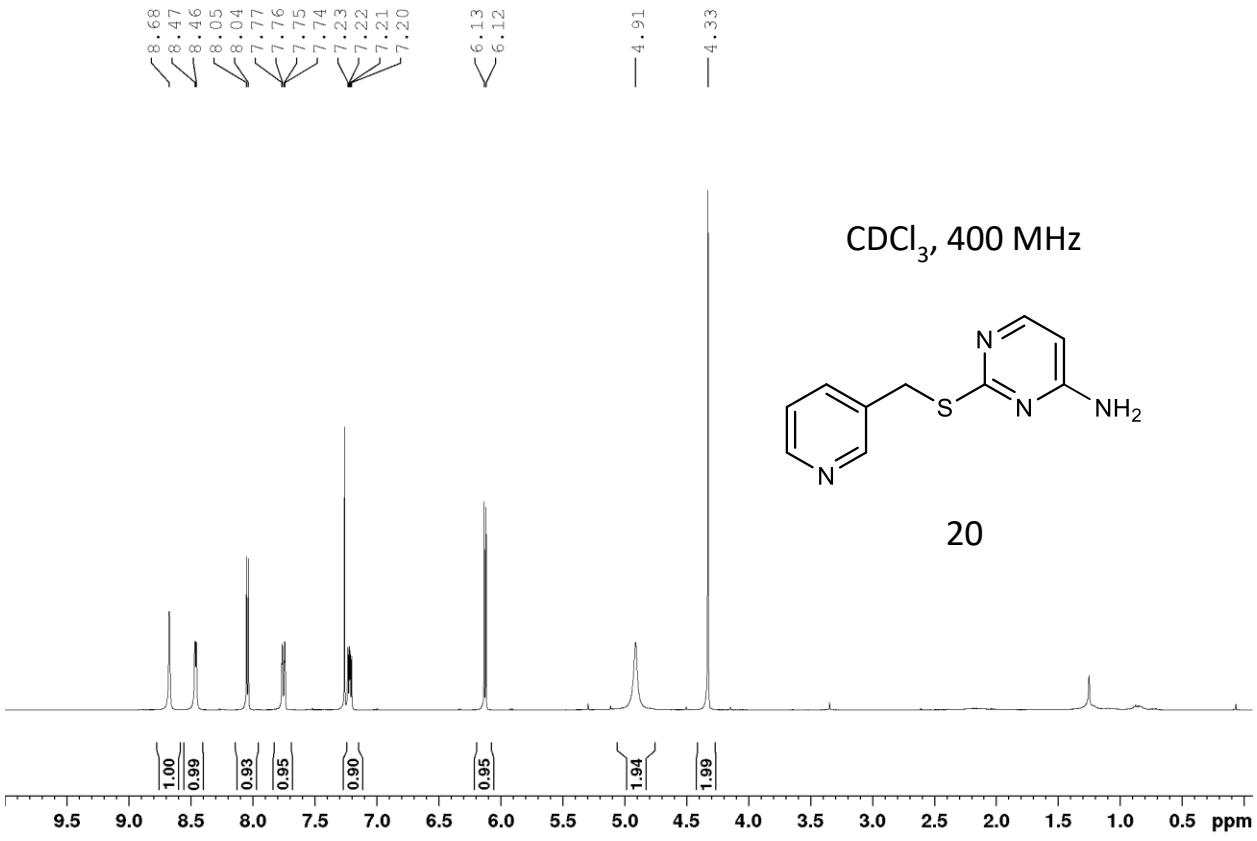

171.31
157.30
150.31
148.41
136.32
136.07
135.83
133.80
123.35
116.80
77.31
76.99
76.68
32.21
CDCl3, 100 MHz
D
N
S
N
N
17
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

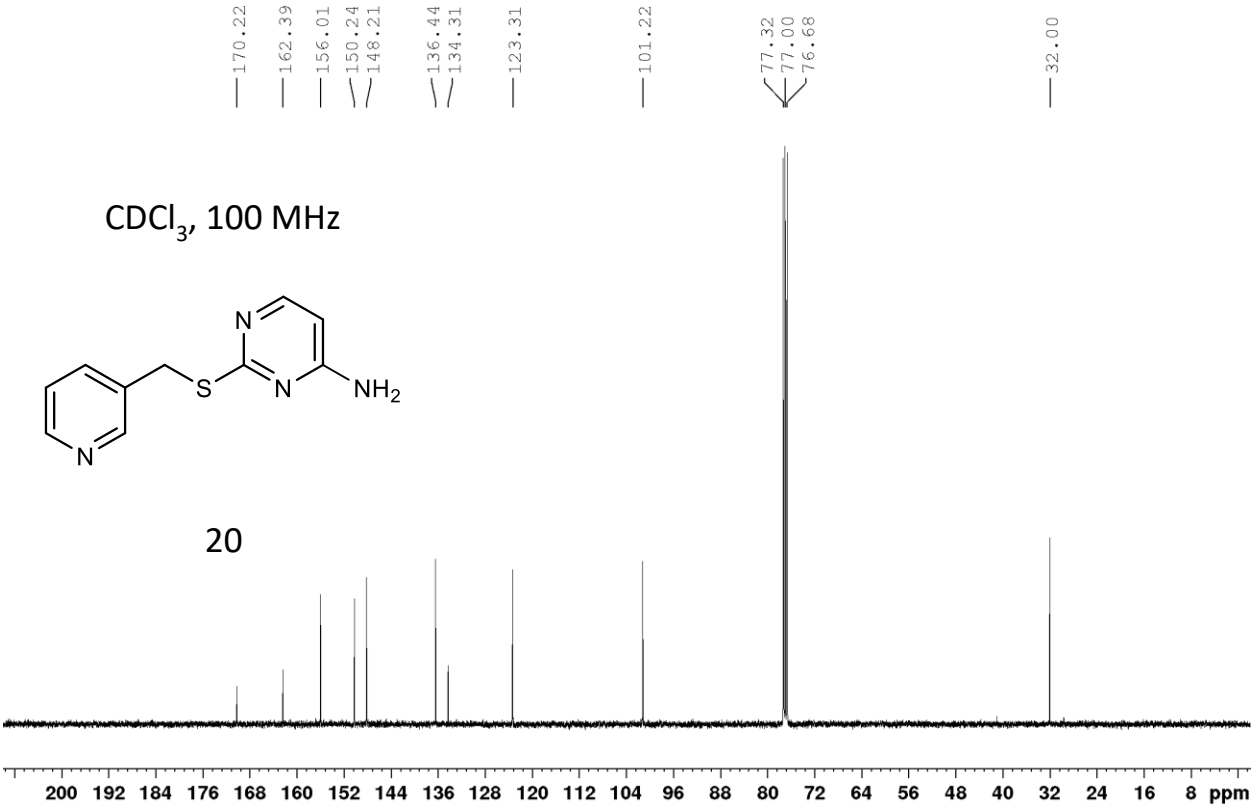

8.69
8.68
8.50
8.49
8.49
8.48
8.22
8.21
7.78
7.77
7.77
7.76
7.75
7.75
7.41
7.39
7.28
7.26
7.16
6.38
6.37
4.47
4.45
4.37
4.34
3.31
3.29
3.27
2.98
2.96
2.95
2.87
2.79
CDCl3, 400 MHz
O
N
Ph
Ph
N
S
N
N
18
1.00
1.00
1.01
1.03
4.08
1.23
4.33
0.99
2.08
3.15
2.03
2.03
1.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

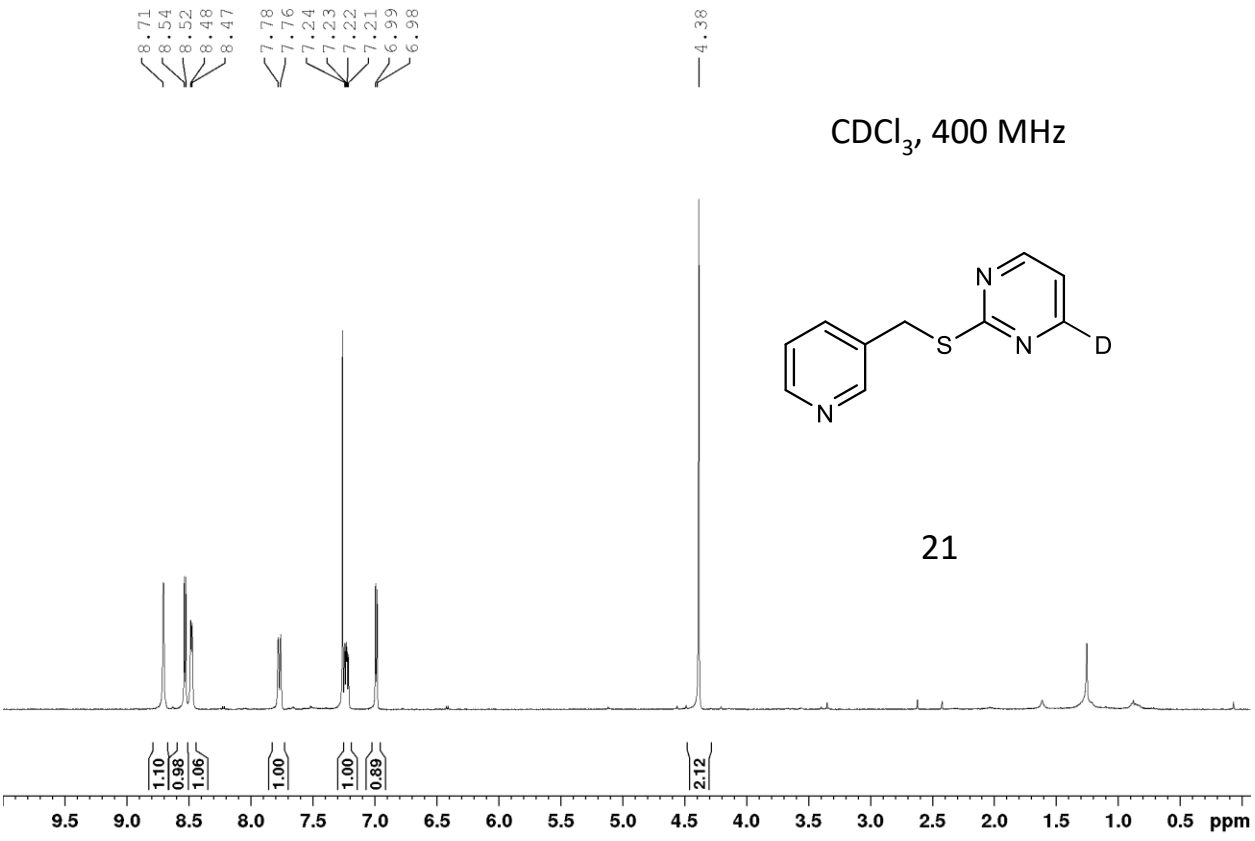

170.24
168.59
157.14
150.04
148.30
141.94
136.17
133.76
128.30
127.35
126.97
123.25
104.17
77.81
77.31
77.00
76.68
68.63
55.97
32.20
28.72
CDCl3, 100 MHz
O
N
Ph
Ph
N
S
N
N
18
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

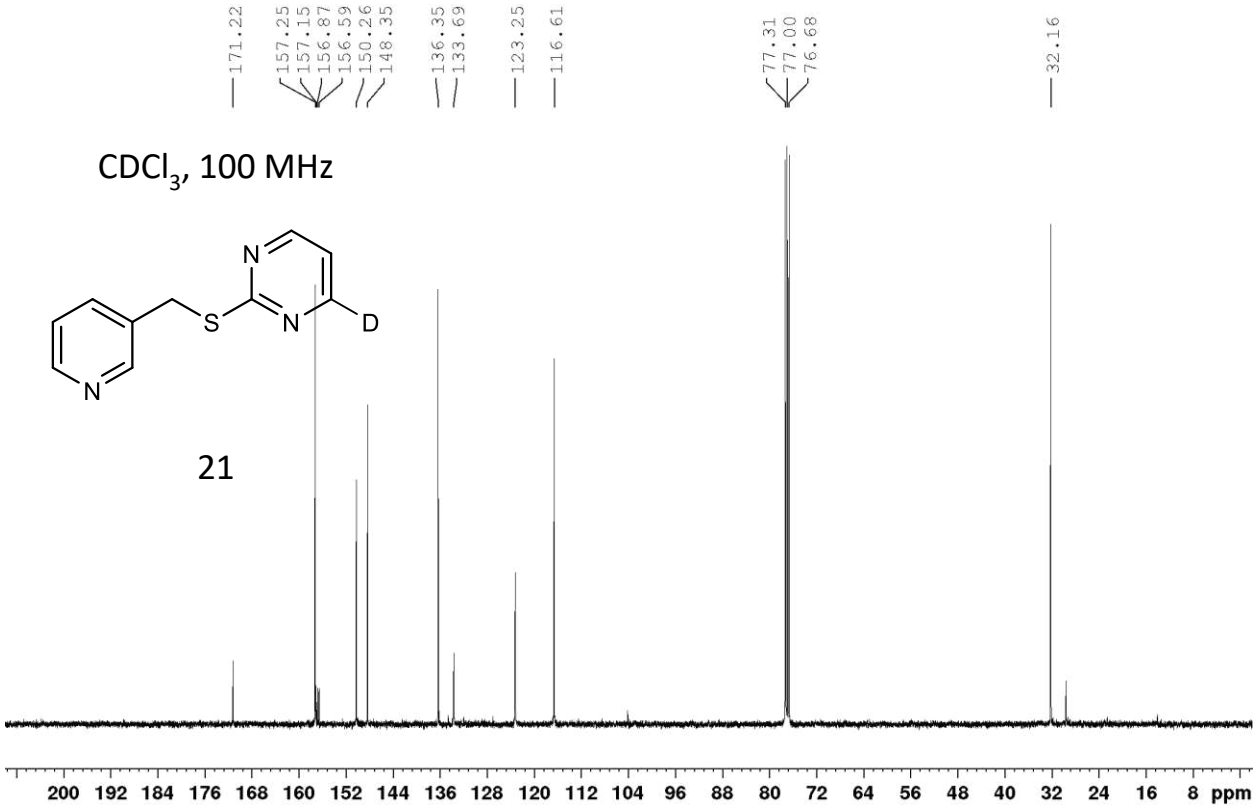

8.66
8.66
8.49
8.48
8.15
8.13
7.74
7.72
7.36
7.26
7.21
6.83
6.82
4.38
4.36
CDCl3, 400 MHz
N
S
N
S
N
19
0.95
0.99
0.98
1.00
4.43
1.50
0.96
4.07
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


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
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

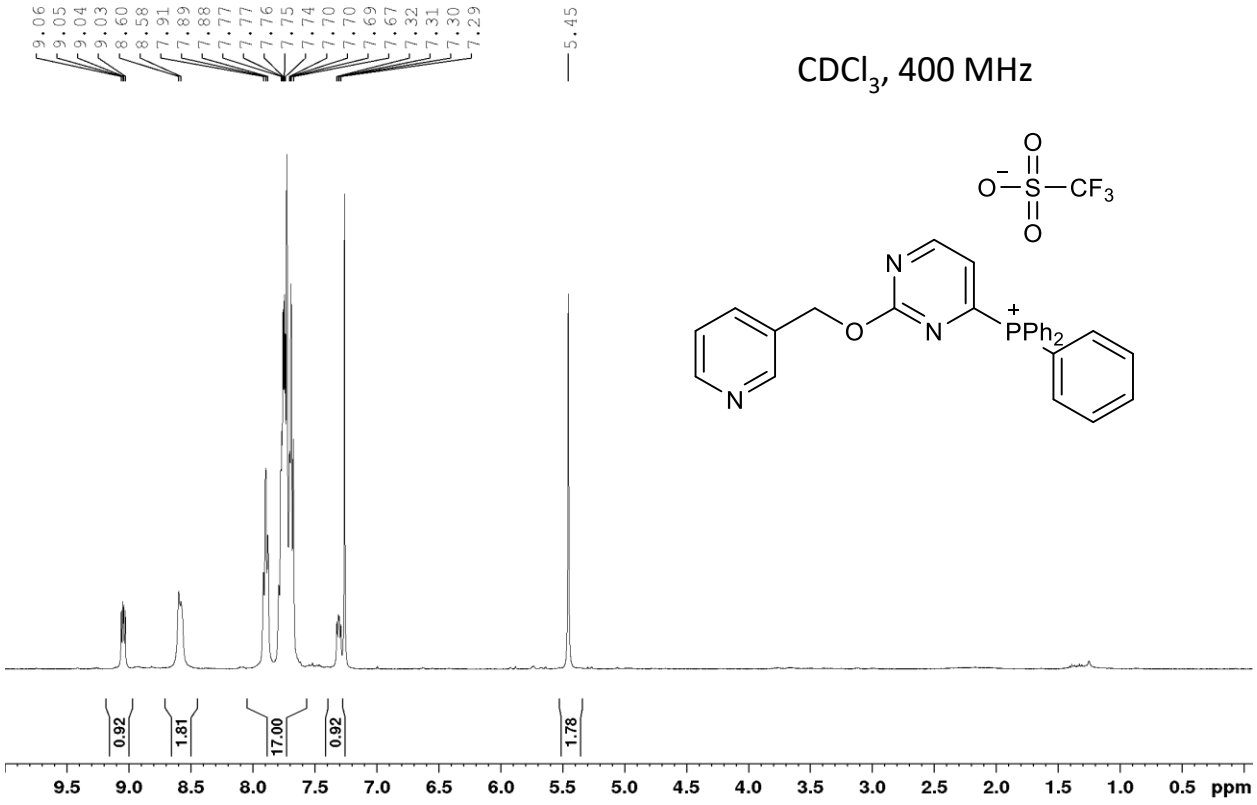

8.68
8.47
8.46
8.05
8.04
7.77
7.76
7.75
7.74
7.23
7.22
7.21
7.20
6.13
6.12
4.91
4.33
CDCl3, 400 MHz
N
S
N
NH2
N
20
1.00
0.99
0.93
0.95
0.90
0.95
1.94
1.99
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

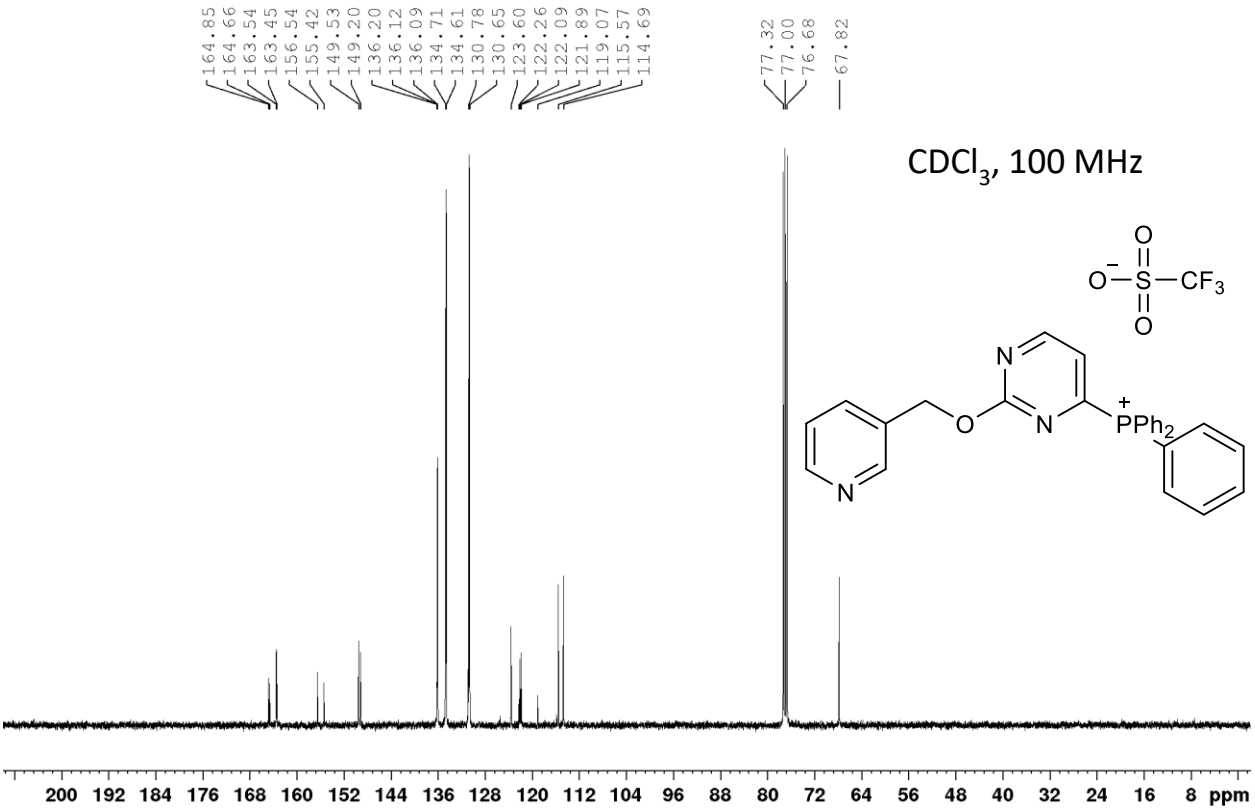

170.22
162.39
156.01
150.24
148.21
136.44
134.31
123.31
101.22
77.32
77.00
76.68
32.00
CDCl3, 100 MHz
N
S
N
NH2
N
20
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

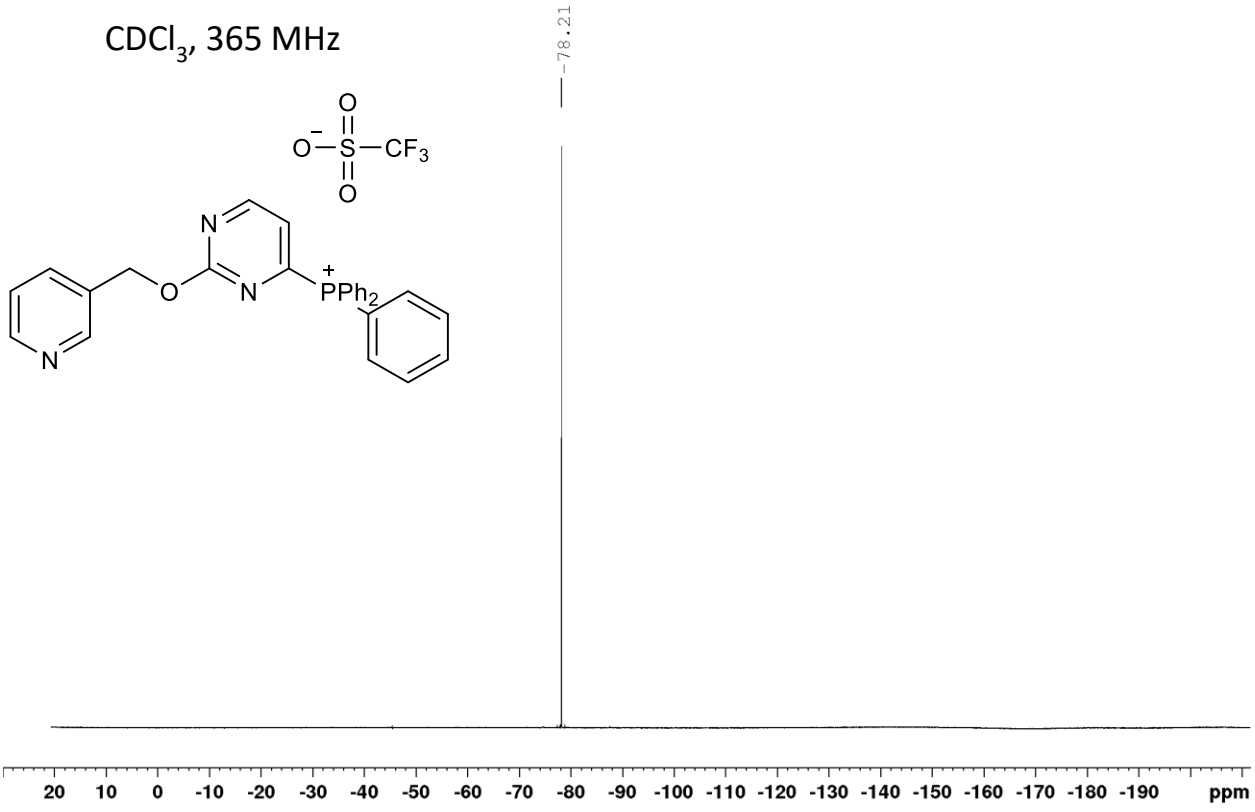

8.71
8.54
8.52
8.48
8.47
7.78
7.76
7.24
7.23
7.22
7.21
6.99
6.98
4.38
CDCl3, 400 MHz
N
S
N
D
N
21
1.10
0.98
1.06
1.00
1.00
0.89
2.12
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


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

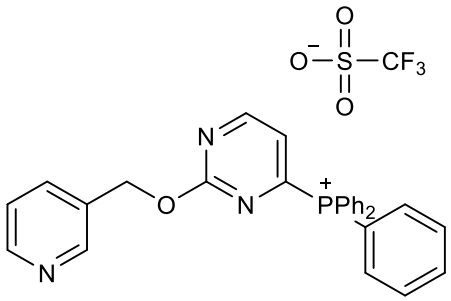
21


9.06
9.05
9.04
9.03
8.60
8.58
7.91
7.89
7.88
7.77
7.77
7.76
7.75
7.74
7.70
7.70
7.69
7.67
7.32
7.31
7.30
7.29
5.45
CDCl3, 400 MHz
O
O
S
CF3
O
N
O
N
PPh2
N
0.92
1.81
17.00
0.92
1.78
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


164.85
164.66
163.54
163.45
156.54
155.42
149.53
149.20
136.20
136.12
136.09
134.71
134.61
130.78
130.65
123.60
122.26
122.09
121.89
119.07
115.57
114.69
77.32
77.00
76.68
67.82
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

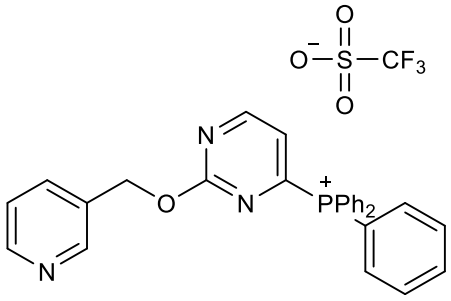

CDCl3, 365 MHz
-78.21
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm

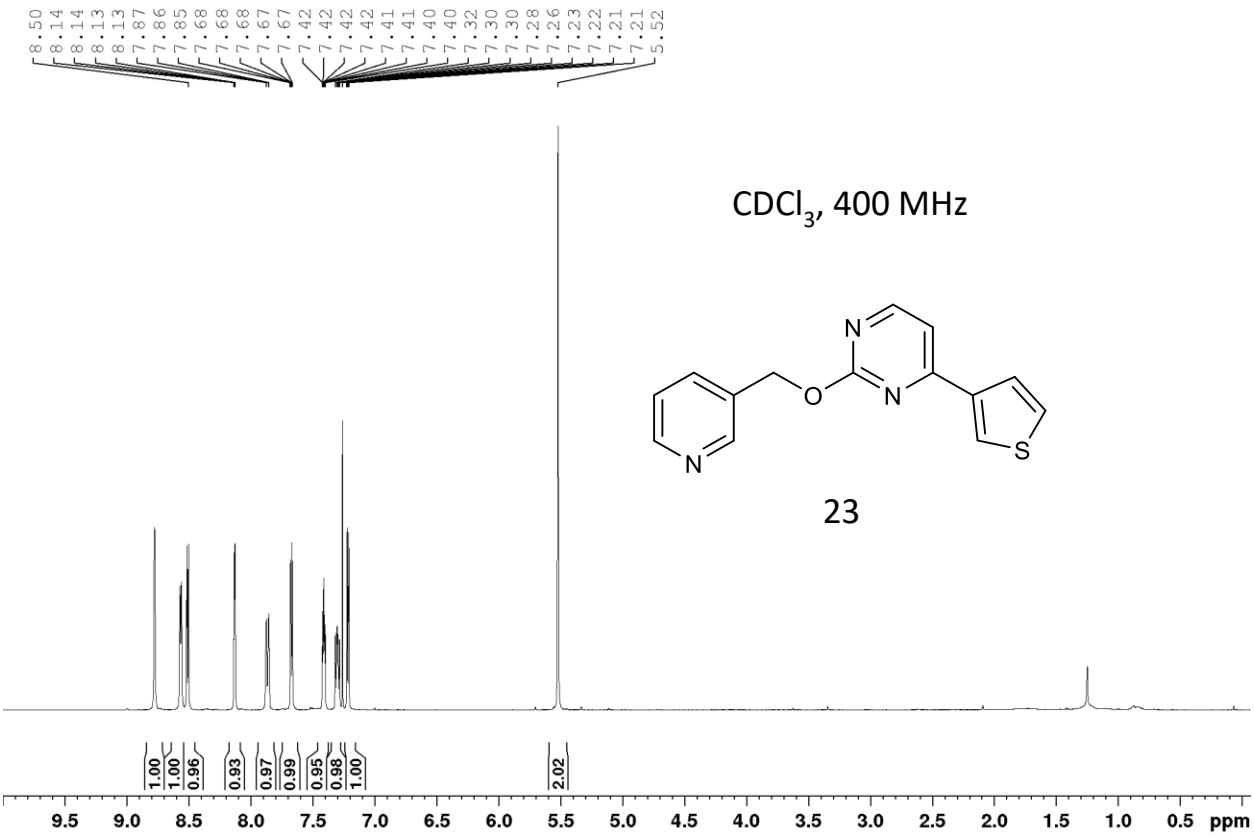
$CDCl_3$, 162 MHz

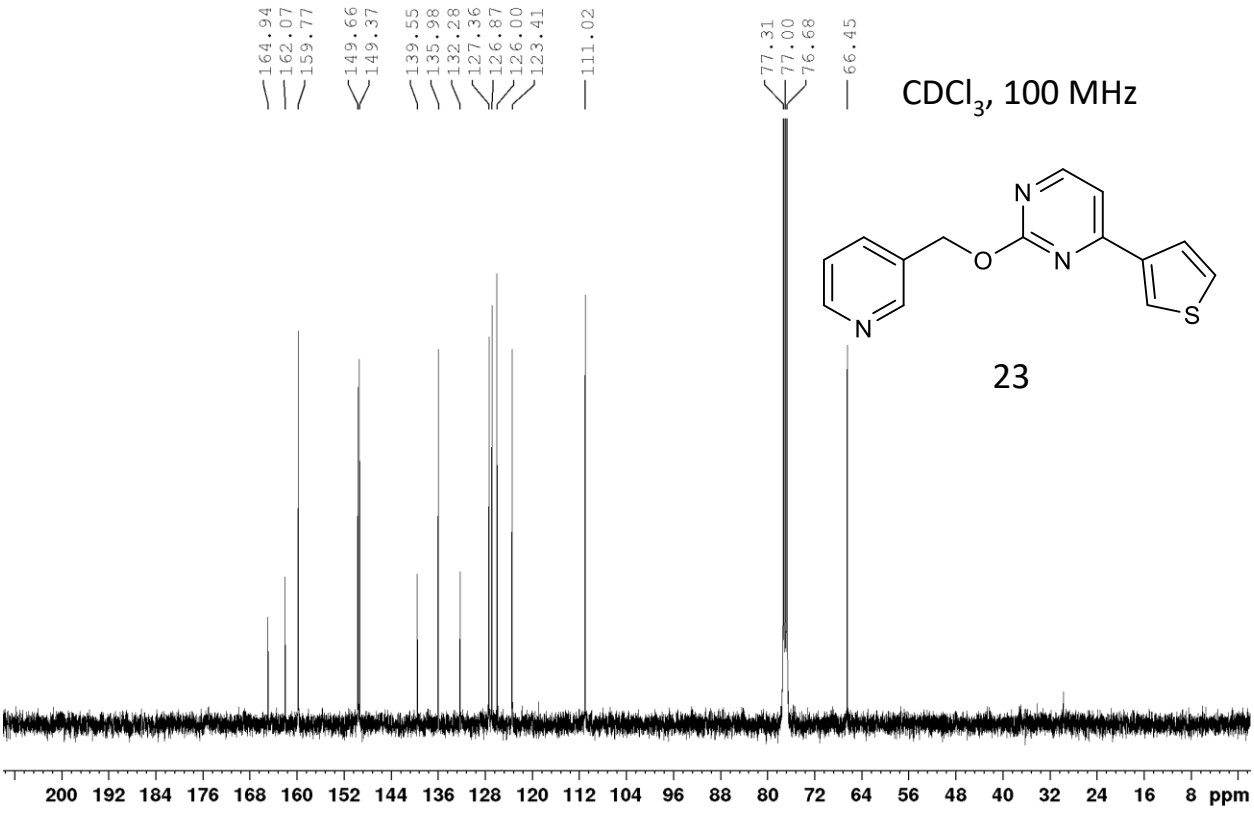


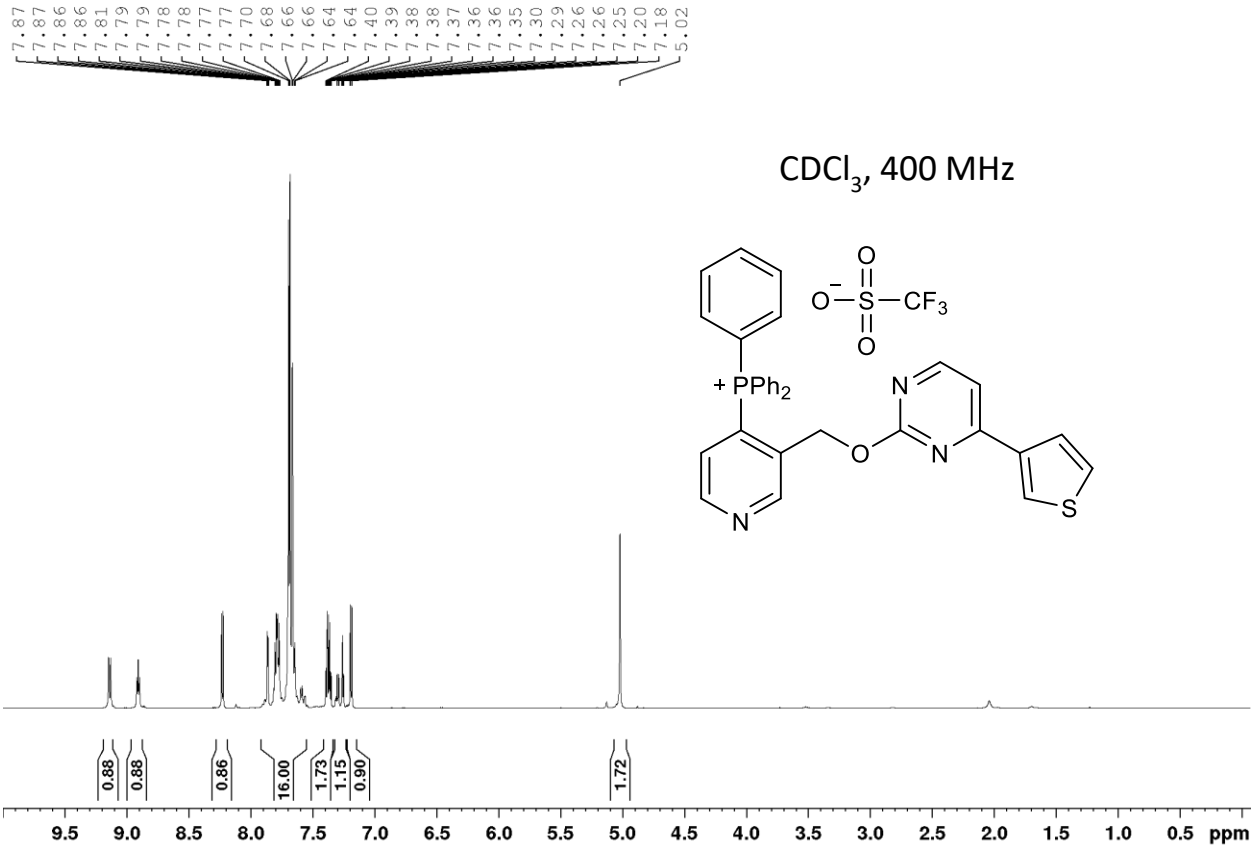
$CDCl_3$, 162 MHz

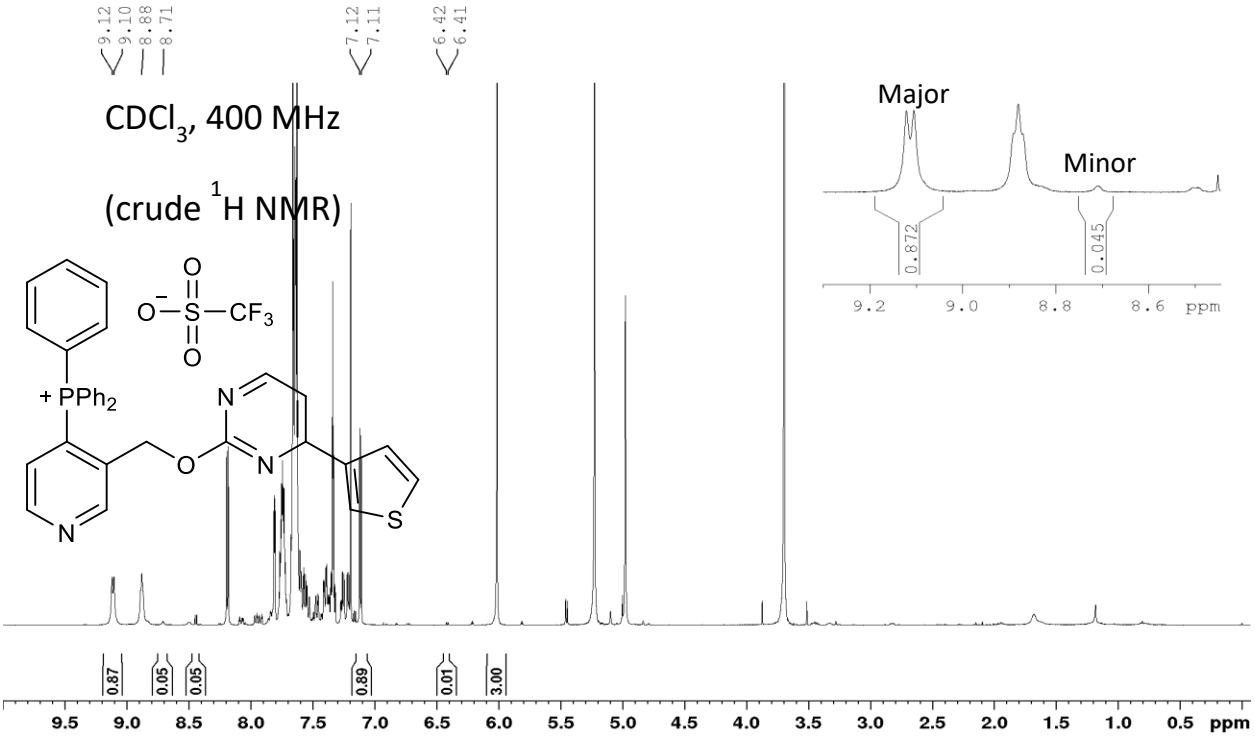
(crude ^{31}P NMR)

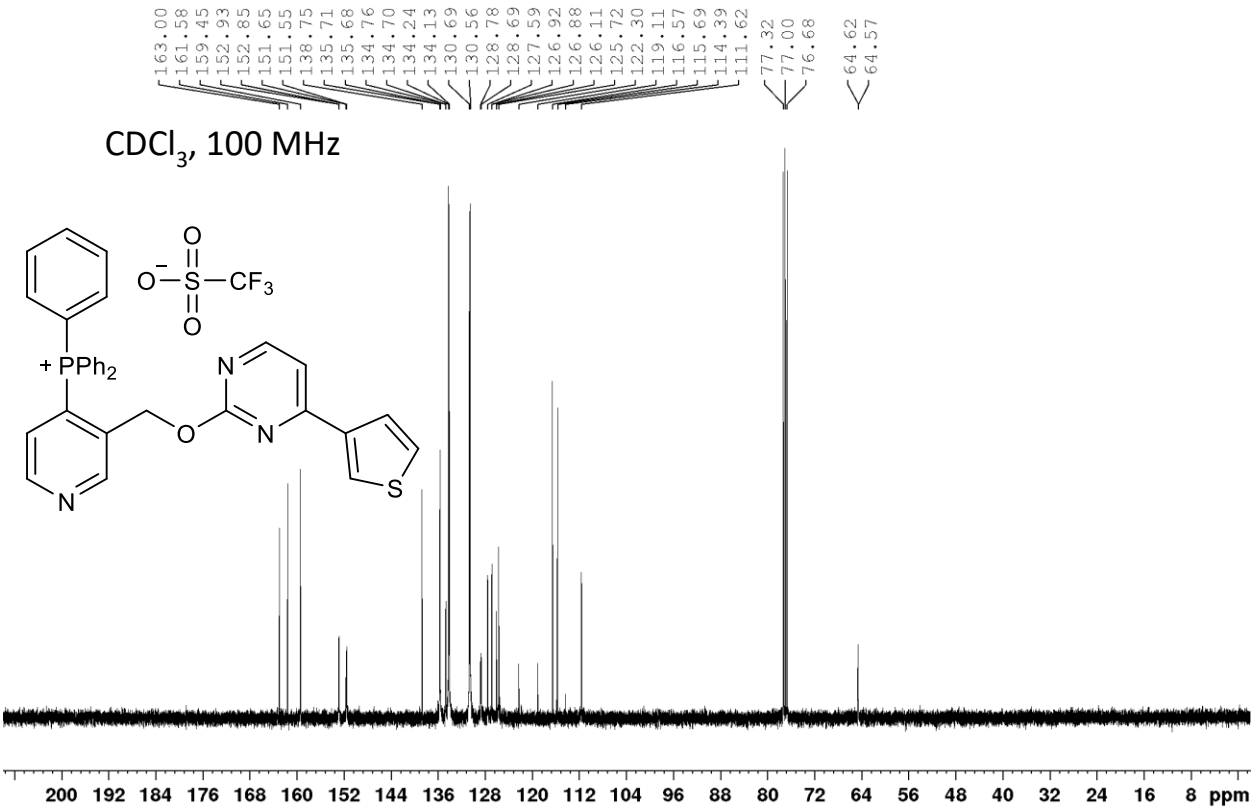


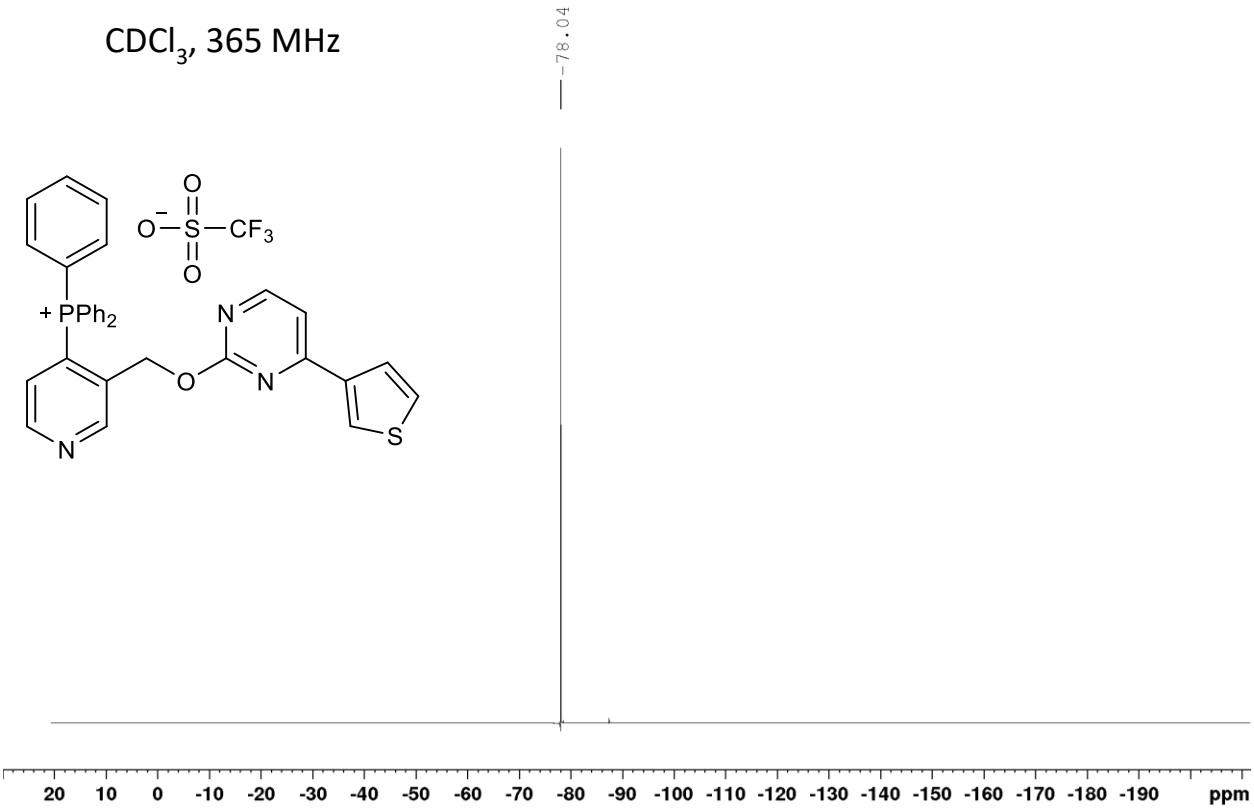

8.50
8.14
8.14
8.13
8.13
7.87
7.86
7.85
7.68
7.68
7.68
7.67
7.67
7.42
7.42
7.42
7.42
7.41
7.41
7.40
7.40
7.32
7.30
7.28
7.26
7.23
7.22
7.21
7.21
5.52
CDCl3, 400 MHz
N
O
N
N
S
23
1.00
1.00
0.96
0.93
0.97
0.99
0.95
0.98
1.00
2.02
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

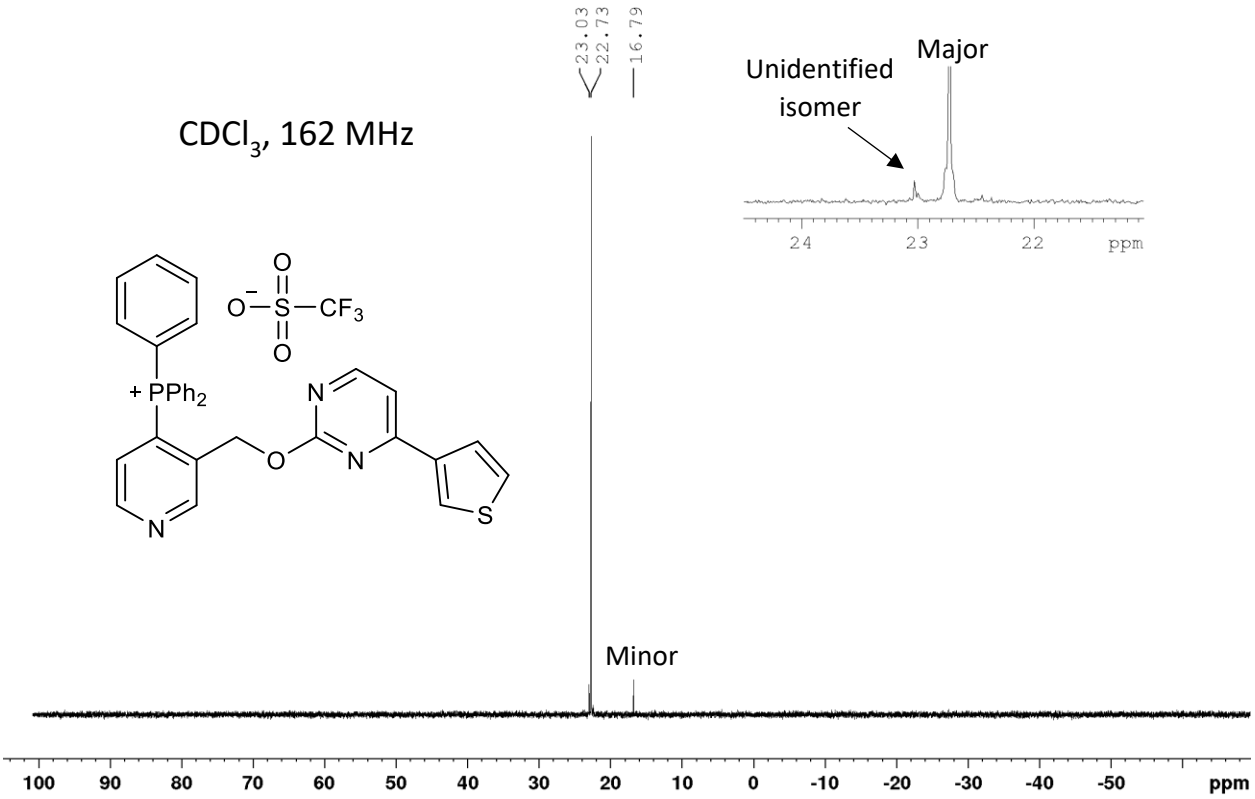

164.94
162.07
159.77
149.66
149.37
139.55
135.98
132.28
127.36
126.87
126.00
123.41
111.02
77.31
77.00
76.68
66.45
CDCl3, 100 MHz
N
O
N
N
S
23
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm

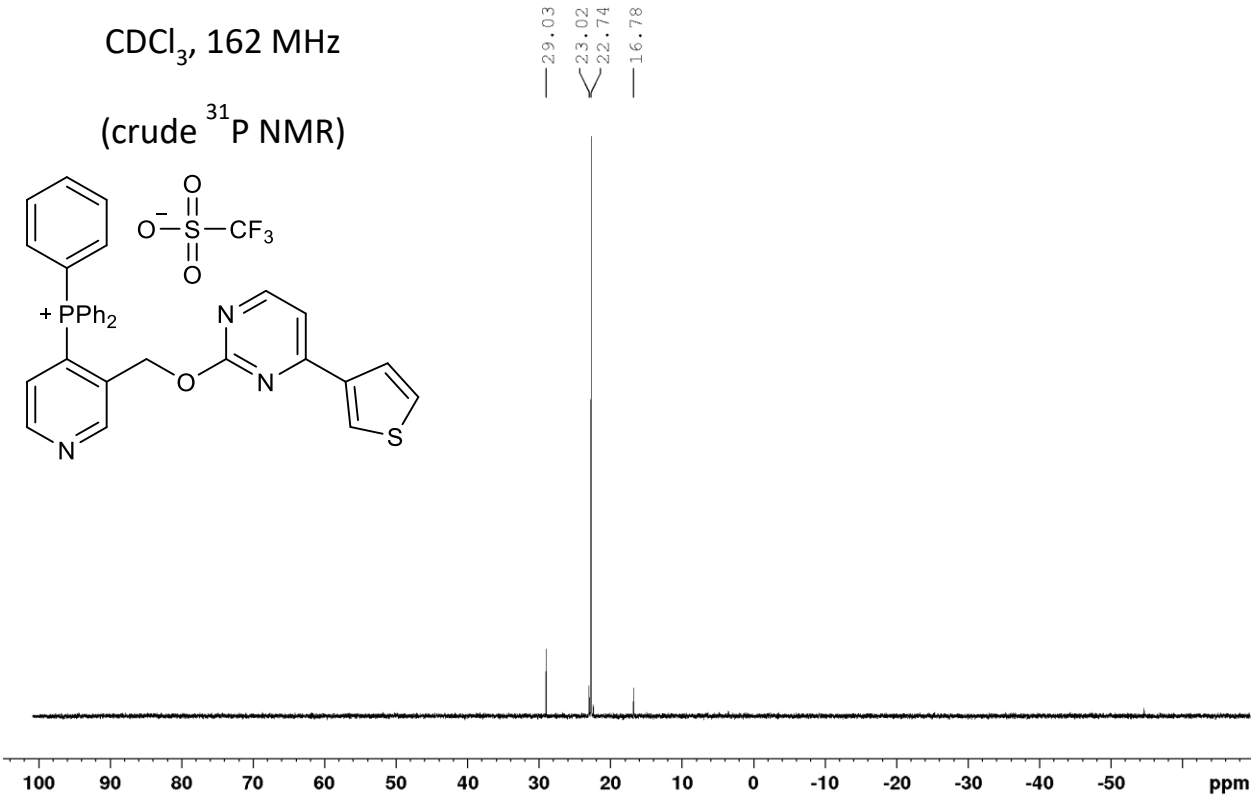

7.87
7.87
7.86
7.86
7.81
7.79
7.79
7.78
7.78
7.77
7.77
7.70
7.68
7.66
7.66
7.64
7.64
7.40
7.39
7.38
7.38
7.37
7.36
7.36
7.35
7.30
7.29
7.26
7.26
7.25
7.20
7.18
5.02
CDCl3, 400 MHz
0.88
0.88
0.86
16.00
1.73
1.15
0.90
1.72
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

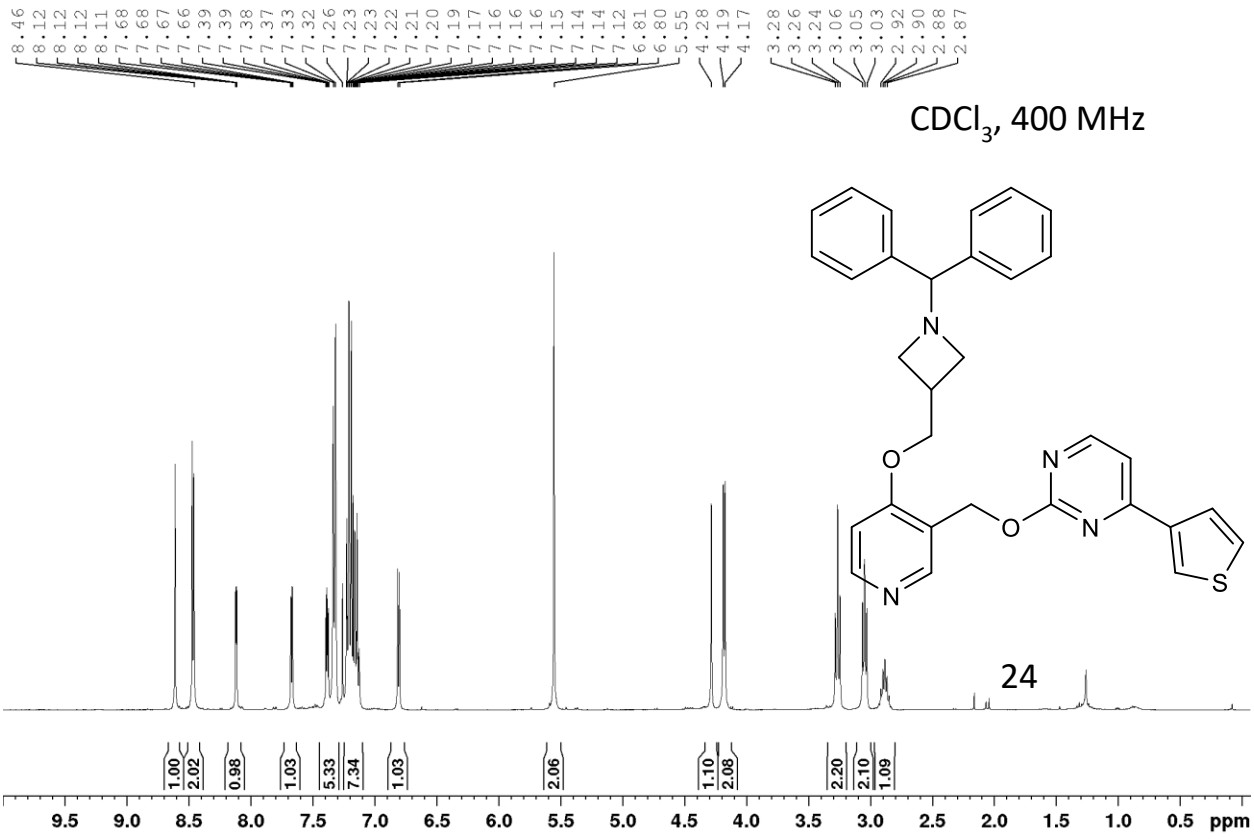

9.12
9.10
8.88
8.71
7.12
7.11
6.42
6.41
CDCl3, 400 MHz
(crude 1H NMR)
Major
Minor
0.872
0.045
9.2 9.0 8.8 8.6 ppm
0.87
0.05
0.05
0.89
0.01
3.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

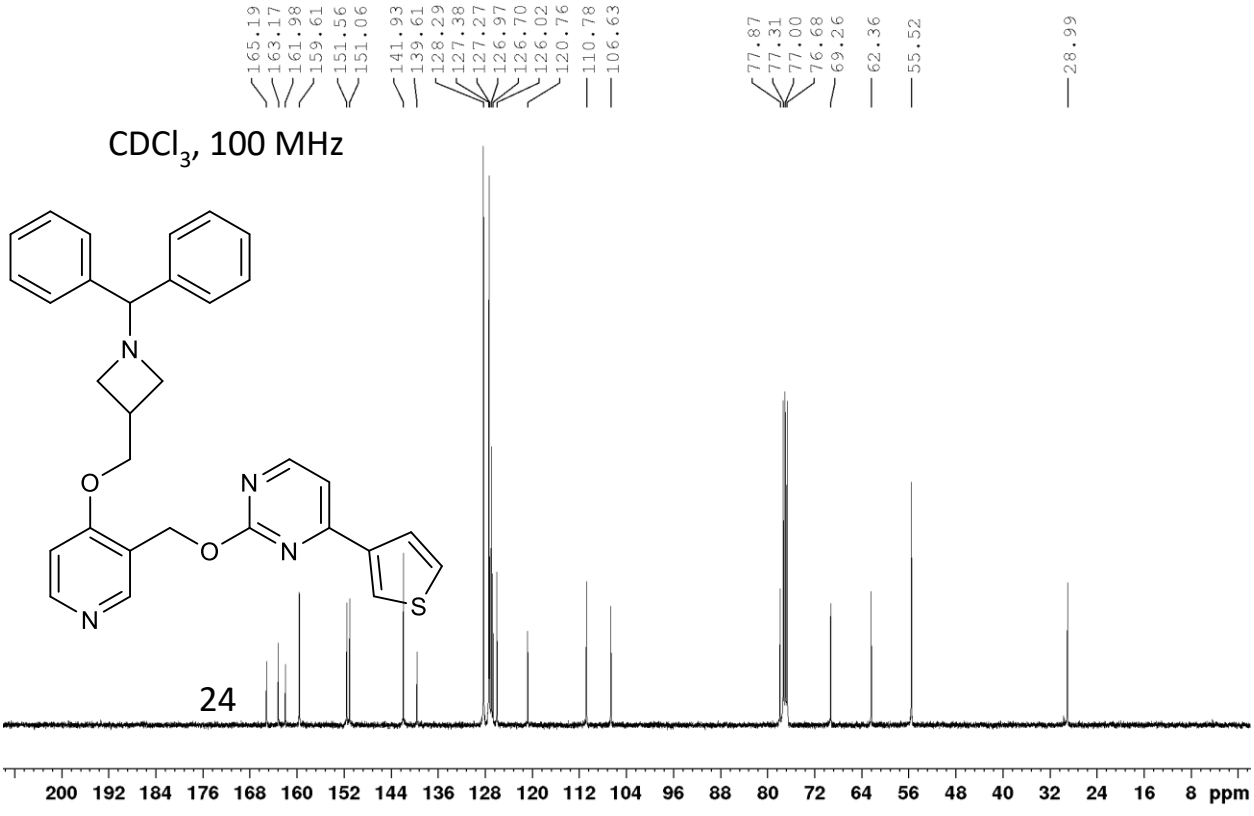

163.00
161.58
159.45
152.93
152.85
151.65
151.55
138.75
135.71
135.68
134.76
134.70
134.24
134.13
130.69
130.56
128.78
128.69
127.59
126.92
126.88
126.11
125.72
122.30
119.11
116.57
115.69
114.39
111.62
77.32
77.00
76.68
64.62
64.57
CDCl3, 100 MHz
+ PPh2
O
O
S
CF3
N
O
N
S
N
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 ppm


-78.04
CDCl3, 365 MHz
+ PPh2
O
O
S
CF3
N
O
N
S
N
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 ppm


CDCl3, 162 MHz
23.03
22.73
16.79
Unidentified isomer
Major
24
23
22
ppm
Minor
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm


CDCl3, 162 MHz
(crude 31P NMR)
29.03
23.02
22.74
16.78
100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 ppm


8.46
8.12
8.12
8.12
8.11
7.68
7.68
7.67
7.66
7.39
7.39
7.38
7.37
7.33
7.32
7.26
7.23
7.23
7.22
7.21
7.20
7.19
7.17
7.16
7.16
7.16
7.15
7.14
7.14
7.12
6.81
6.80
5.55
4.28
4.19
4.17
3.28
3.26
3.24
3.06
3.05
3.03
2.92
2.90
2.88
2.87
CDCl3, 400 MHz
N
O
N
O
N
N
S
24
1.00
2.02
0.98
1.03
5.33
7.34
1.03
2.06
1.10
2.08
2.20
2.10
1.09
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


165.19
163.17
161.98
159.61
151.56
151.06
141.93
139.61
128.29
127.38
127.27
126.97
126.70
126.02
120.76
110.78
106.63
77.87
77.31
77.00
76.68
69.26
62.36
55.52
28.99
CDCl3, 100 MHz
N
O
N
O
N
N
S
24
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

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