

DISSERTATION

REGIOSELECTIVE FUNCTIONALIZATION OF
PYRIDINES AND OTHER AZINES

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ABSTRACT

REGIOSELECTIVE FUNCTIONALIZATION OF PYRIDINES AND OTHER AZINES

Pyridines and diazines serve as cores in pharmaceuticals and are common motifs in organomaterials and ligands. Selective functionalization of these motifs is of importance for discovery and optimization of new bioactive molecules. Pyridine functionalization is of interest for synthetic chemists, and despite modern advances in derivatization challenges and limitations remain.

Chapter one focuses on the impact of pyridines and diazines in the pharmaceutical industry. Classical and modern methods for C-H functionalization are discussed. Chapter two describes work on phosphorus ligand-coupling for bisazine synthesis using a three-stage protocol. This method provides an alternative to traditional metal-catalysis for bisazine synthesis and can be applied to drug-like fragments. This work is expanded on in chapter three by using a tandem S_NAr -ligand-coupling strategy for bisazine synthesis, in particular 2,2'-bipyridines.

Chapter four describes a facile S_NAr reaction by phosphines on iodopyridines. A bis-salt *N*-phosphonium pyridinium is the key intermediate and provides a broad scope of reactivity. Chapter five shifts towards functionalization of the 3-position of pyridine through a Zincke-type intermediate. By exploiting a ring-opening-functionalization-rearomatization strategy a selective halogenation of pyridines was achieved. The Zincke imine intermediate is also viable for other functionalizations and provides products directly from the C-H bond on the initial pyridine.

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Chapter One

Importance of Azines in Pharmaceuticals and Methods for Their Direct Functionalization

1.1 Relevance of Electron-deficient Azines in Pharmaceuticals

Nitrogen heterocycles (*N*-heterocycles) are ubiquitous in naturally occurring bioactive molecules, pharmaceuticals, and agrochemicals. Electron-deficient aromatic *N*-heterocycles (azines), such as pyridines and diazines, are common and a survey conducted in 2014 of FDA-approved drugs found that azines are contained in 101 out of 1035 examples.¹ Several top-selling drugs like Claritin, Lunesta, and Nexium all contain an azine (**Figure 1.1**; left). Azines have applications in ligands for metal-catalysis, organic materials, and batteries.²⁻⁴

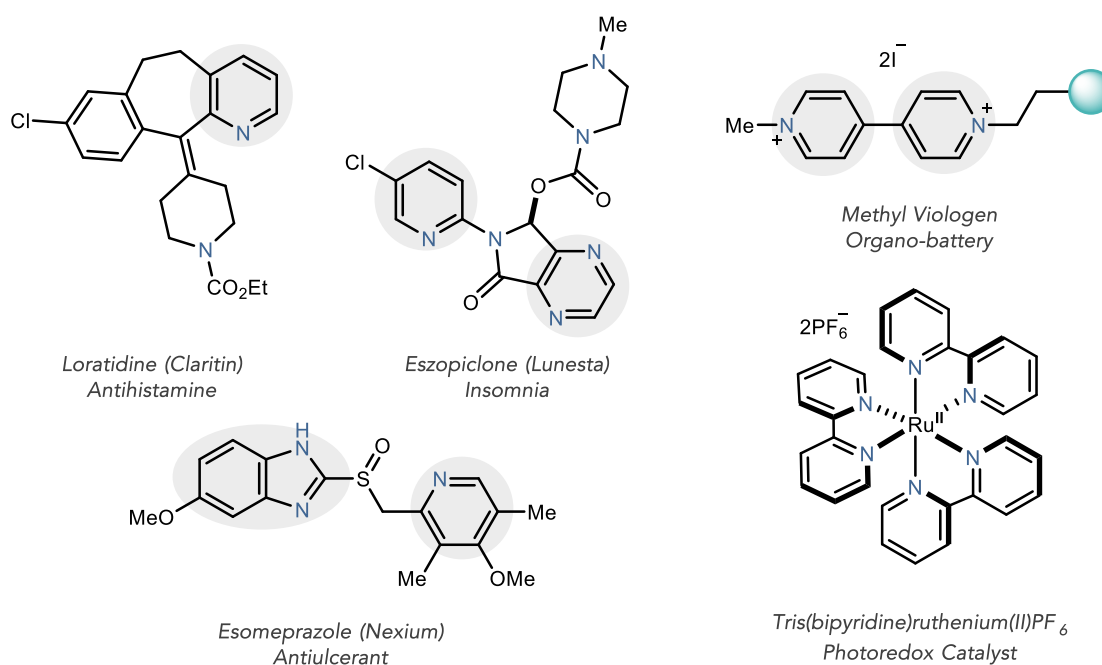


Figure 1.1. Examples of Azines in Pharmaceuticals, Materials, and Ligands

1.2 Properties of Pyridine and Other Azines

Azines have different physical properties than their all-carbon counterparts due to the nitrogen atom.⁵ Nitrogen is more electronegative than carbon and pyridine has a net dipole

moment. This net dipole plays a role in pyridine's physical properties like aqueous solubility. Since the nitrogen atom is sp^2 -hybridized, its lone pair is perpendicular to the π -system and is unable to donate electron-density to the ring itself (**Figure 1.2**). Reactivity is also influenced by the nitrogen atom. Electrophiles react with pyridines at relative rates analogous to nitrobenzene (10^{-7}) (**Figure 1.2**).⁵ Pyridines are electrophilic at the 2- and 4-positions through nucleophilic aromatic substitution (S_NAr) reactivity with halogen leaving groups or by a vicarious mechanism (*vide infra*).⁵

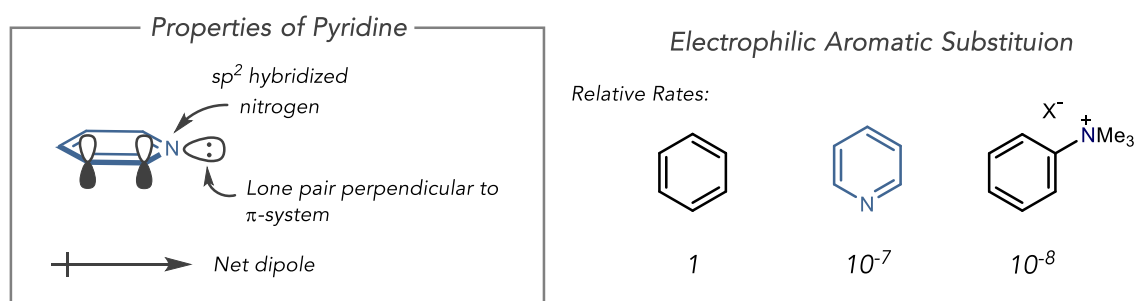


Figure 1.2. Properties and Reactivity of Pyridine

1.3 Azines in Drug Design

Pyridines and other azines have three fundamental properties; 1. increased polarity; 2. hydrogen bond acceptor; 3. resistance to oxidative metabolism.^{6,7} These properties influence the pharmacodynamic and pharmacokinetic properties of the drug. Aqueous solubility is an important medicinal chemistry property and impacts a drug's pharmacokinetics.⁶ Azines are incorporated into drugs to increase aqueous solubility as part of the drug discovery process.

Azines play a role in a bioactive molecule's target binding. The lone pair on the nitrogen atom is a hydrogen bond acceptor and used to increase binding affinity. **Figure 1.3** shows this with the leukemia treatment drug Imatinib.⁸ Imatinib binds to tyrosine kinase ABL and, as a key part of this interaction, the pyridine nitrogen hydrogen bonds to a specific methionine residue (Met318).⁸ The rigid azine scaffold leads to fewer potential conformations for the drug in the body.⁹ Bosutinib,

where a 3-cyanoquinoline directs hydrogen bonding between a water molecule and the target Asp381 residue (**Figure 1.3**, right).¹¹

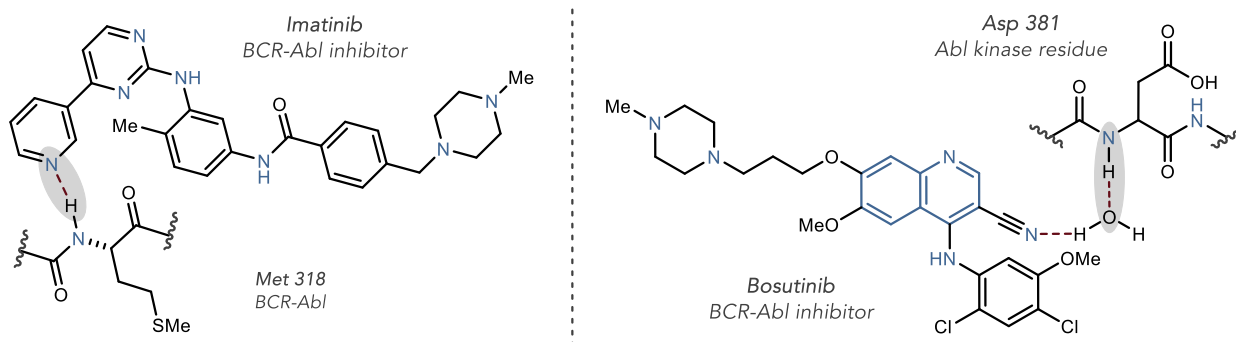


Figure 1.3. Hydrogen Bonding Facilitates Drug-Target Interactions

Azines are also incorporated into drugs to increase resistance to oxidative metabolism.⁷ The cytochrome P450 enzyme metabolizes drugs in the liver, targeting electron-rich aromatic C-H bonds and transforming them into hydroxyl groups.⁷ The metabolite is then rapidly excreted from the body. As part of absorption, distribution, metabolism, and excretion (ADME) studies, electron-rich aromatics will often be replaced with azines, like pyridines, to mitigate this metabolic pathway.¹²

1.4 Direct Functionalization of Pyridines and Diazines

1.4.1 Classical Methods for C-H Functionalization of Pyridines

Methods that directly functionalize azines from their C-H bonds are highly sought. This strategy is challenging and current examples are limited.^{5,13} Aromatic rings react directly with electrophiles through electrophilic aromatic substitution (S_EAr) reactions.^{5,14} In an S_EAr halogenation reaction, the π -system of the aromatic ring acts as a nucleophile to attack an electrophilic halogen source.¹⁵ Due to their decreased π -nucleophilicity, the bromination of pyridine uses refluxing sulfuric acid and elemental bromine, leading to a complex mixture of

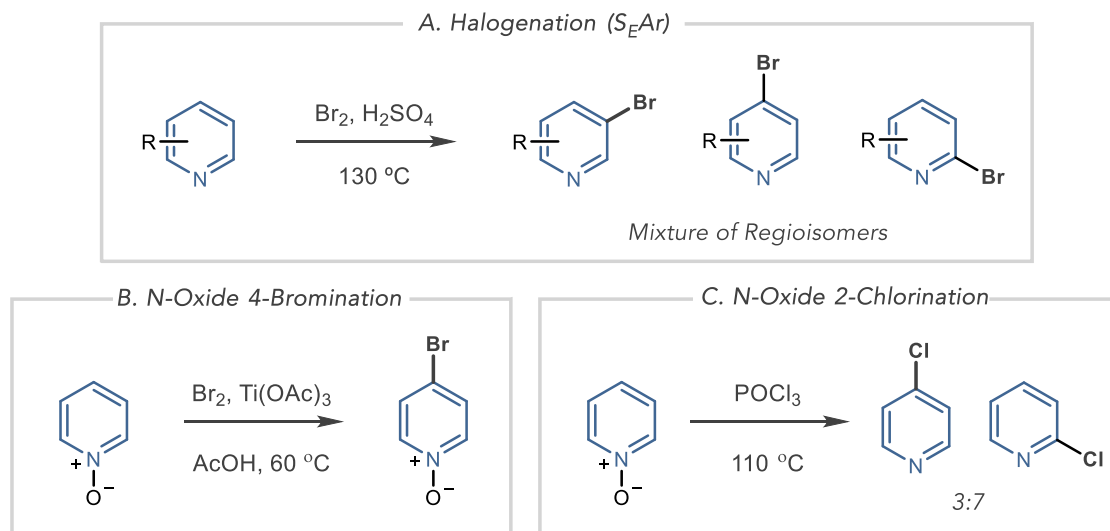


Figure 1.4. Pyridine Halogenation Methods

bromopyridines and bis-halogenation (**Figure 1.4, A**).¹⁶ The conditions used limits S_EAr halogenation of pyridines. The lack of π -nucleophilicity is partially addressed through use of pyridine *N*-oxides, which are formed through reaction with hydrogen peroxide or *meta*-chloroperoxybenzoic acid (*m*CPBA) and pyridine.¹⁷ The presence of the exocyclic oxygen leads to higher reactivity and is used to halogenate pyridines at the 4-position or 2-position under milder conditions (**Figure 1.4, B, C**).¹⁸ The additional steps required to form and remove the *N*-oxide limit the application of these methods.

Beyond S_EAr reactivity, direct metalation using a strong base is a classical method for pyridine functionalization.¹⁹ This strategy uses a strong lithium or magnesium base to deprotonate the pyridine ring and subsequently trap it with an electrophile *in situ* (**Figure 1.5, A**). For unsubstituted pyridine, selectivity is achieved through use of kinetic and thermodynamic deprotonation conditions targeting the 2- and 4-positions respectively.¹⁹ Recently, the Knochel group has extended this chemistry using Lewis acid coordination to BF_3OEt and a bulky tmp-magnesium (tmp = tetramethylpiperidine) species to selectively deprotonate the 4-position. The 2-

position is deprotonated when no Lewis acid is used (**Figure 1.5, B, C**).²⁰ More commonly, a directing group on the pyridine ring coordinates to the base and controls regioselectivity.²¹

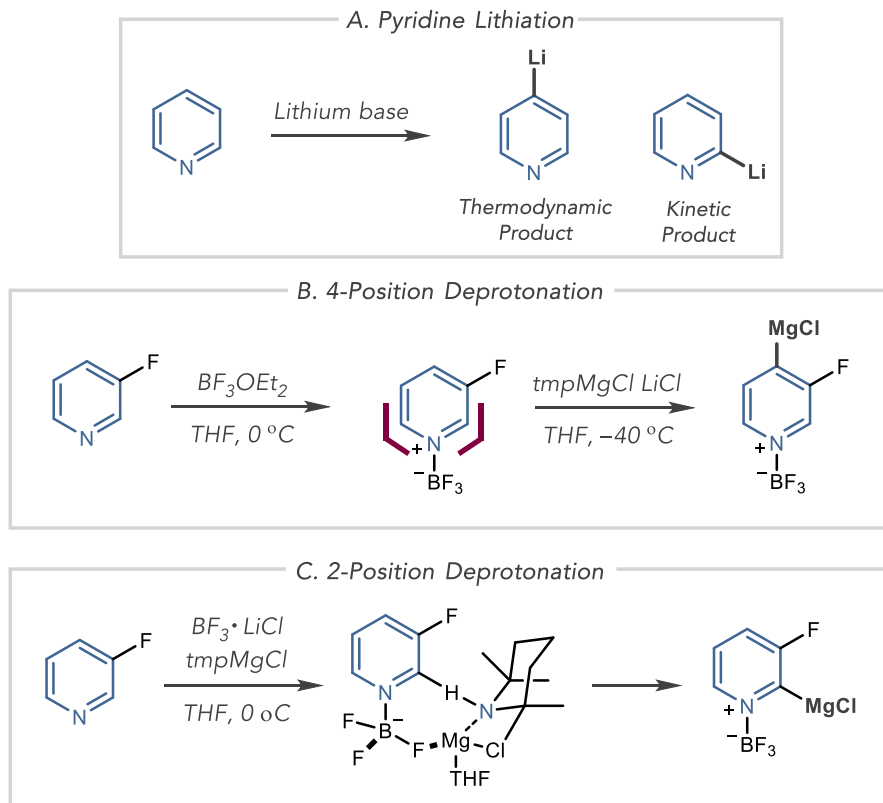


Figure 1.5. Deprotonation of Pyridines.

Two electron nucleophiles are used to directly react with azines, typically through an activation-addition-elimination sequence. The Chichibabin reaction is a classical example for this reactivity for 2-position amination of pyridines using sodium amide (**Figure 1.6, A**).²² The requirement of sodium amide limits the functional group tolerance and utility of this method. Merck and Fier have recently addressed this limitation through a bifunctional chloropyrazine that delivers H₂N-Boc to the 2-position on pyridine through addition-elimination (**Figure 1.6, B**).²³ While this method shows improved functional group tolerance, the substitution pattern is limited to 3- and 4-substituted pyridines.

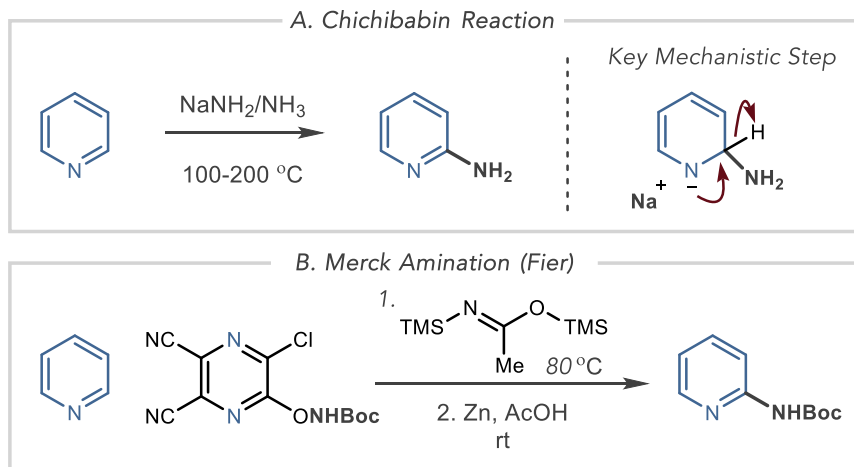


Figure 1.6. Addition-Elimination Strategies for CH Functionalization of Pyridine.

The Minisci reaction is a method for pyridine and diazine functionalization through addition of nucleophilic carbon-centered radicals (**Figure 1.7**).²⁴ The radical is generated through decarboxylation of a carboxylic acid using a catalytic silver salt (AgNO_3), stoichiometric potassium persulfate ($\text{K}_2\text{S}_2\text{O}_8$), and elevated temperature. While the initially developed conditions showed limited selectivity between the 2-, 3-, and 4-positions, further development demonstrated that using acid to protonate the pyridine results in excellent selectivity towards the 2-position.^{25,26} The Minisci reaction is widely applicable in medicinal chemistry as a method to couple alkyl groups and pyridines together.²⁵

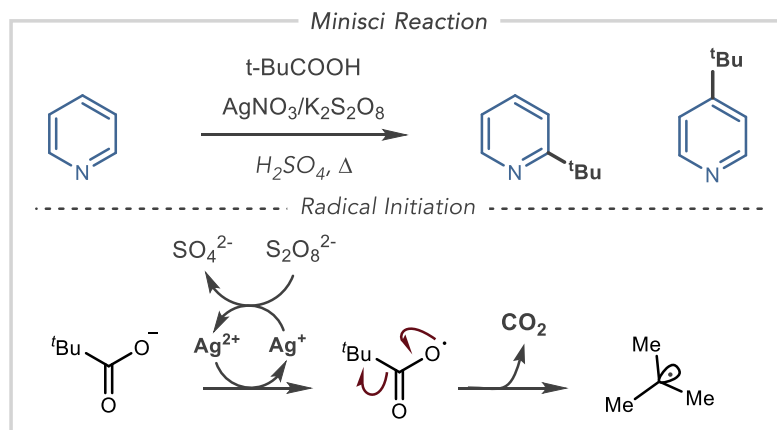


Figure 1.7. Minisci Reaction for Pyridine Alkylation and Arylation.

1.4.2 Modern Advancements in Direct Azine Functionalization

Direct azine functionalization has seen modern advances. Hartwig developed a 2-position selective fluorination by using AgF_2 (**Figure 1.8, A**),²⁷ and derivatized the fluorinated products through $\text{S}_{\text{N}}\text{Ar}$ reactions.²⁸ 4-Selective trifluoromethylation through a boron activation, addition, and oxidation strategy is showcased by the Kanai lab, leading to fluoroalkylated pyridines and a rare example of a 4-selective functionalization (**Figure 1.8, B**).²⁹ The Dixon lab and others cyanated of pyridines, with reasonable selectivities between the 2- and 4-positions, by activation with trifluoromethanesulfonic (triflic) anhydride, addition with TMSCN , and rearomatization with a base (**Figure 1.8, C**).³⁰ A similar strategy was utilized by Merck and Fier for cyano addition.³¹ Recently, Martin used an activation-addition method to silylate a range of pyridines with solvent controlled selectivity at the 2- and 4-positions (**Figure 1.8, D**).³²

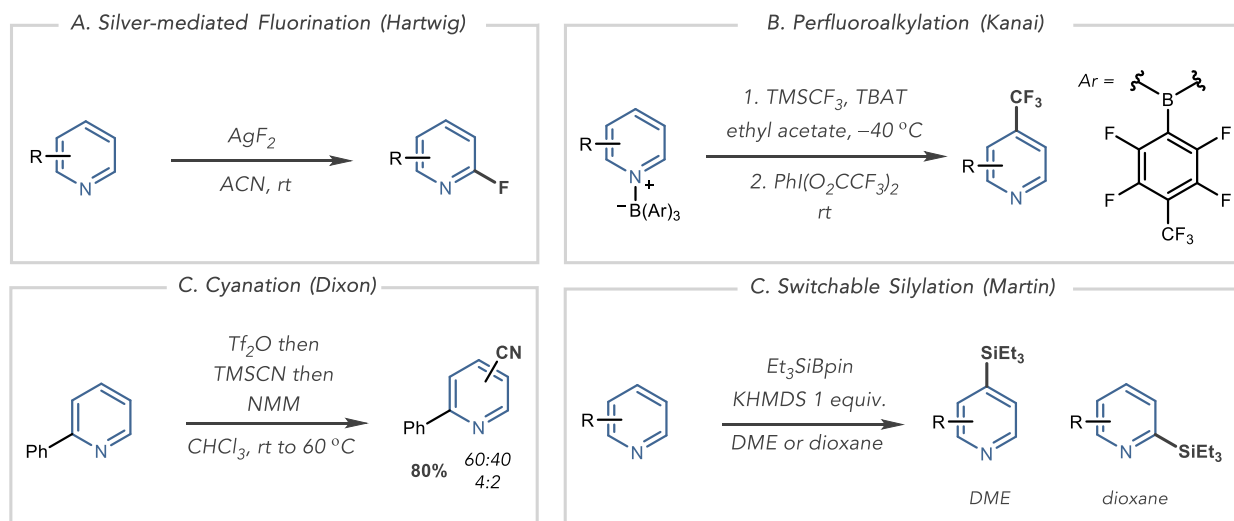


Figure 1.8. Modern Advances in Nucleophilic Additions to Pyridine.

Photoredox catalysis provides methods for radical generation. Seminal work by MacMillan showed trifluoromethylation of pyridines through photoredox (**Figure 1.9, A**).³³ Merck/DiRocco used photoredox to methylate pyridines under a mild set of reaction conditions using an iridium photocatalyst and *tert*-butylperacetate as the methyl source (**Figure 1.9, B**).³⁴ These reactions were

applied to complex molecules. The Molander, Baran, and Stephenson groups have also contributed key advancements in Minisci reactivity.³⁵⁻³⁹

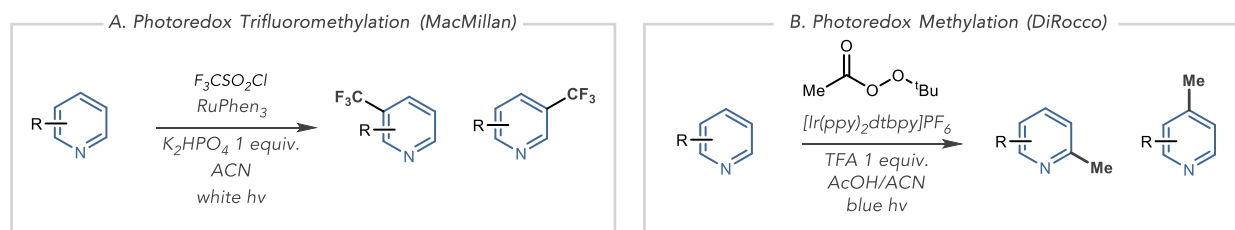


Figure 1.9. Photoredox Minisci Examples.

Pyridine C-H activation using transition metal-catalysis have been developed. Iridium-catalyzed C-H borylation installs a pinacol boronic ester (Bpin) at the 3-position of pyridines (**Figure 1.10, A**).⁴⁰⁻⁴³ The selectivity for this reaction is governed by sterics, targeting the more accessible C-H bond between the 3- and 5-positions on pyridine. 3-Position C-H functionalization is achieved using a palladium catalyst with conditions pioneered by the Yu lab (**Figure 1.10, B**).⁴³⁻⁴⁵ C-H activation accesses the 4-position using conditions developed by Nakao, for alkylation and alkenylation,⁴⁶ and Kanai, for alkylation using a cobalt catalyst.⁴⁷ Nakao exploits using a bulky Lewis acid and Kanai uses an organocobalt intermediate to achieve selectivity. New methods for azine functionalization remain in demand.

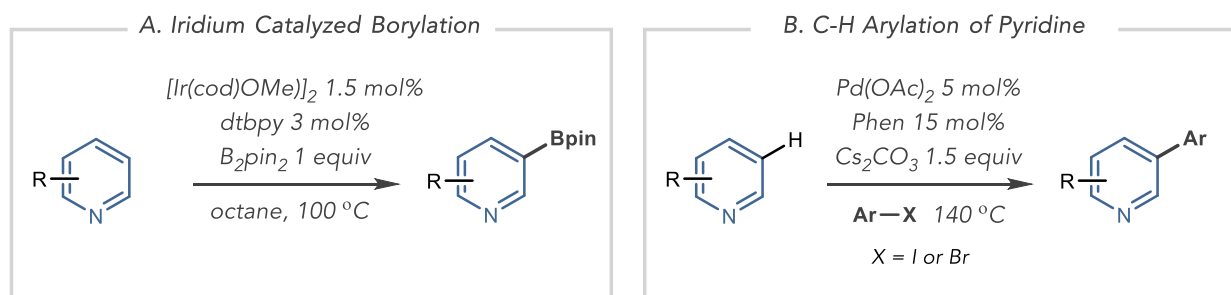


Figure 1.10. Examples of Transition Metal-Catalyzed C-H Activation of Pyridine

1.4.3 Pyridylphosphonium Salts for Pyridine Functionalization

Methods to selectively target the 4-position remain scarce with limited examples from Martin, Nakao, and Kanai.^{29,32,46,47} The McNally group set out to develop a versatile strategy to derivatize the 4-position with high selectivity. Our initial approach was to selectively install a versatile functional group directly from the C-H bond of the pyridine that could enable a range of valuable transformations (**Figure 1.11, top**).⁴⁸ Beyond simply installing this functional handle, we wanted the strategy to be amenable to each stage of the drug discovery process.⁴⁹ An example of this process can be seen with imatinib (**Figure 1.11, bottom**). The process begins with a building block pyridine that can be functionalized into a lead compound (drug fragment). The lead compound contains important functionality, such as amines, and often has desirable bioactive characteristics.⁴⁹ The pharmacokinetic and pharmacodynamic properties are then tuned resulting in the final pharmaceutical. Methods that are applicable to each stage of this process are valuable.

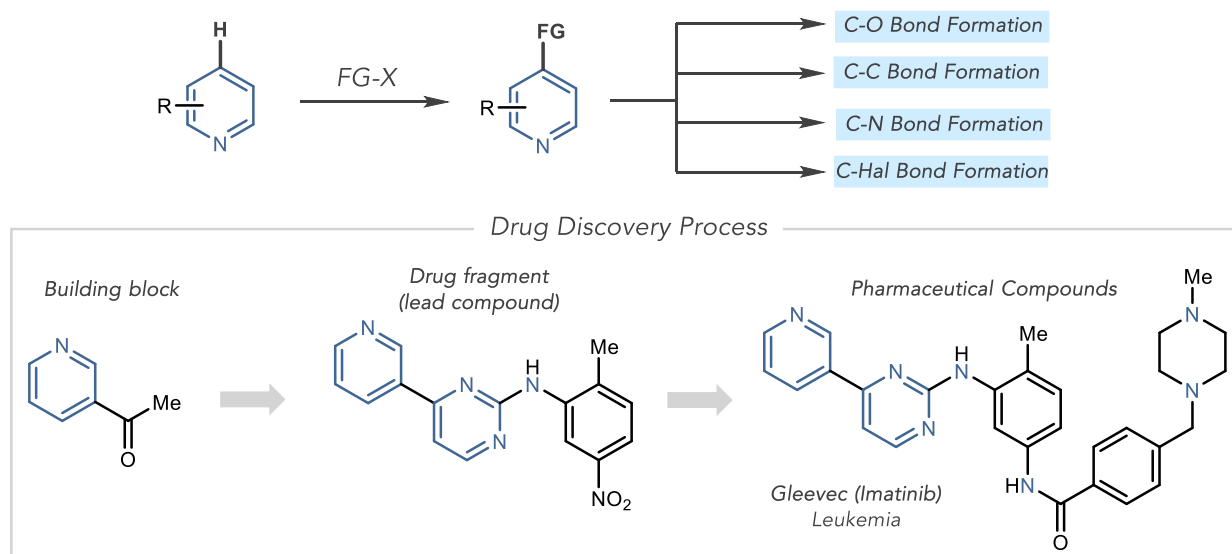


Figure 1.11. Proposed Strategy for Pyridine Functionalization using Versatile Functional Handle (top), Abbreviated Drug-Discovery Process (bottom).

While investigating triflic anhydride activation of pyridines, phosphines added selectively to the 4-position of pyridine and, after rearomatization with an amine base, a 4-position pyridylphosphonium salt could be formed. The proposed mechanism for this transformation is shown in **Figure 1.12**. Initially, the pyridine attacks triflic anhydride to form triflyl pyridinium triflate **1**, which is attacked selectively at the 4-position by triphenylphosphine (PPh_3) generating dearomatized phosphonium intermediate **2**. Subsequent addition of triethyl amine (Et_3N) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) rearomatizes the pyridine and results in a 4-position pyridyl phosphonium salt (**3**). This strategy had been reported by Anders in the late 1980's, however limited examples were presented and subsequent transformations were not pursued past initial results.⁵⁰⁻⁵²

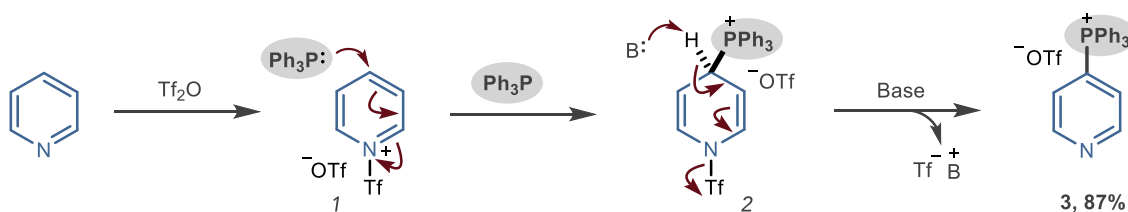


Figure 1.12. Formation of 4-Pyridyl Phosphonium Salts through Activation-Addition-Elimination

After the initial reaction optimization, the group's attention turned towards the scope of pyridines that could be transformed into phosphonium salts (**Figure 1.13**). Building block pyridines were found to be particularly effective under the optimized reaction conditions, with a range of substitution patterns amenable (**4-8**). If the 4-position is blocked phosphonium formation occurs at the 2-position (**9**). Other azines such as quinolines and diazines are effective (**Figure 1.13, 10-13**). The reaction remained 4-position selective with perfect regioselectivity obtained in most examples.^{53,54} More complex structures comparable to lead compounds are effective and 4-selective under the reaction conditions (**Figure 1.13, 14-15**). Pharmaceuticals, such as imatinib,

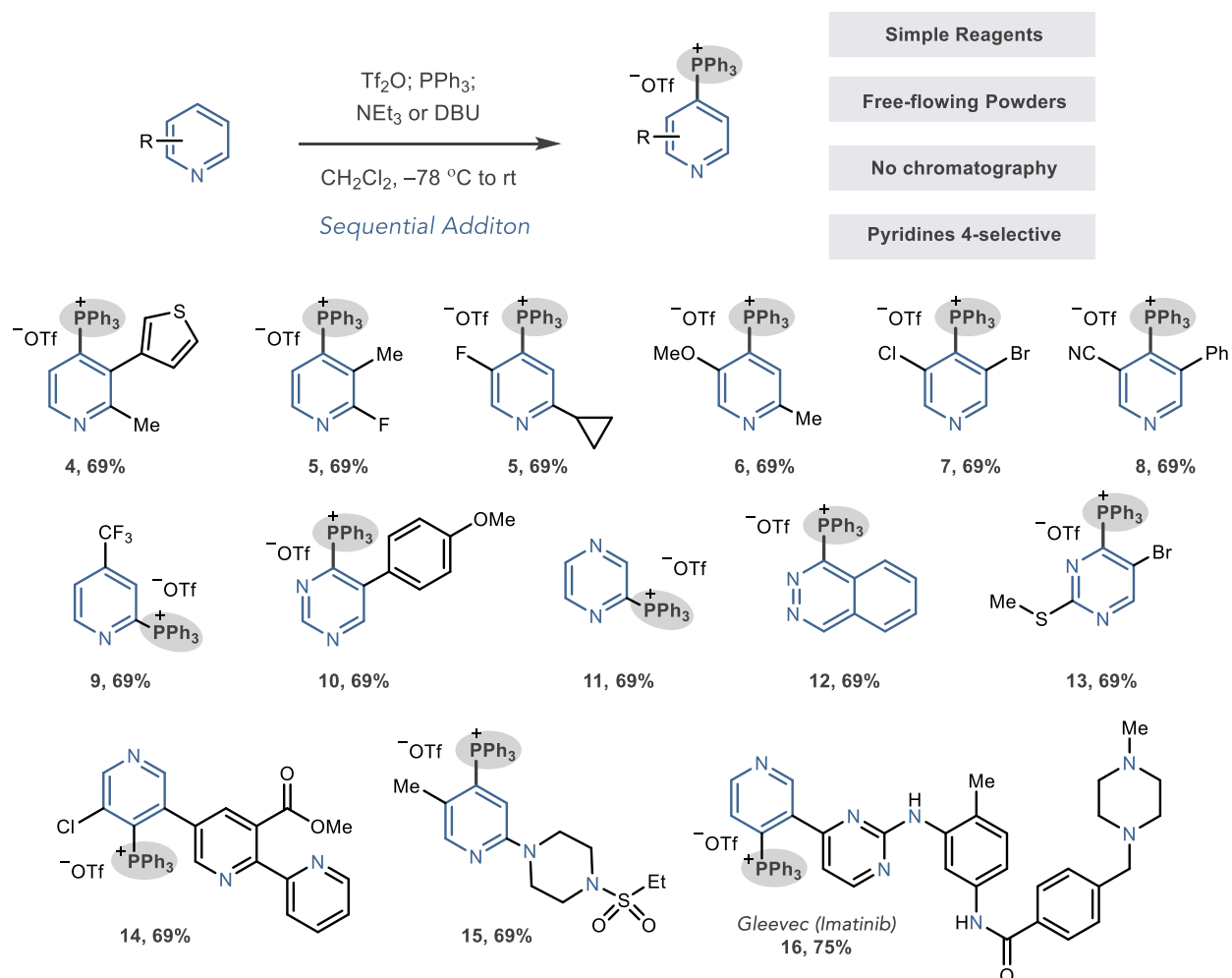


Figure 1.13. Examples of 4-Pyridyl Phosphonium Salts from the McNally Group.

etoricoxib, and loratadine, are transformed into phosphonium salts (**Figure 1.13, 16**). All phosphonium salts are isolated through precipitation by adding the crude reaction mixtures to diethyl ether (Et_2O).

Attention next turned to developing reactions exploiting the phosphonium salt as a functional handle. Five distinct reaction manifolds were developed: nucleophilic additions, fragmentation pathways, metal-catalyzed cross-couplings, one-electron pathways, and ligand-coupling processes (**Figure 1.14**). Initial investigations centered around addition of nucleophiles, such as alkoxides, thiolates, (thio)phenolates, azides, and halides.^{53,55-58} Fragmentation of

phosphoniums salt using carbonates achieves deuteration and tritiation of pyridines.⁵⁹ Pyridylphosphonium salts were also found to serve as electrophilic coupling partners for nickel and cobalt-catalyzed arylation and alkylation reactions.^{60,61} Radical pathways of phosphoniums were developed: synthesizing 2,4'-bipyridines through a boryl-stabilized radical coupling and as alternatives to cyanopyridines for photoredox radical-anion couplings with trifluoroborate potassium salts.^{62,63} Finally, phosphorus ligand-coupling pathways via P(V) phosphorane intermediates enables bipyridine formation and fluoroalkylation of pyridines.⁶⁴⁻⁶⁶ The development, optimization, and mechanism of phosphorus ligand-coupling for bipyridine synthesis will be discussed in detail later in this dissertation.

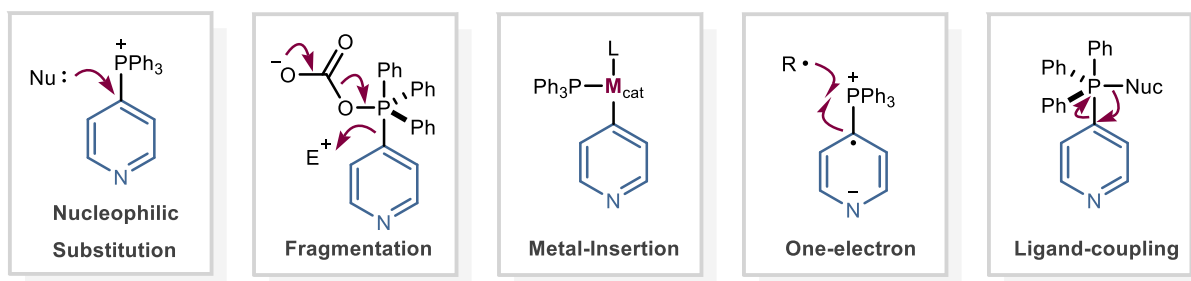


Figure 1.14. Reaction Manifolds for Phosphonium Salt Derivatization.

1.5 Conclusion

This section serves to provide background into the importance of pyridines and diazines across chemical fields, such as pharmaceuticals, materials, and ligands. Classical methods and modern advances to pyridine C-H functionalization and challenges towards pyridine derivatization were discussed. It also highlights advances in the 4-position functionalization of pyridines through pyridyl phosphonium salts developed by the McNally lab.

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Chapter Two

Phosphorus Ligand-Coupling for Bisazine Synthesis

2.1 Overview

This chapter describes a new method for bisazine formation through phosphorus ligand-coupling. Bisazines, which are molecules containing two azines covalently bound to each other, are common in pharmaceuticals, ligands, and materials.¹⁻³ Challenges remain in synthesizing this motif through conventional methods. Through a three-step sequence, two azines are coupled together by transforming one into an azinyl phosphine, formation of a bisazine phosphonium salt, then triggering ligand-coupling via a P(V) phosphorane intermediate. This method enables direct coupling from pyridine and diazine C-H bonds with excellent regioselectivity and demonstrates one of the first synthetically useful transformations using phosphorus ligand-coupling. Michael Hilton developed the fragmentable phosphine for azinyl phosphine synthesis and together with Xuan Zhang contributed towards synthesis of the bisazines. Professor Rob Paton (CSU) and Dr. Juan Alegre-Requena carried out the computational studies. The work presented in this chapter culminated in a publication in the journal *Science*.⁴

2.2 Background

2.2.1 Importance of Bisazines

Bisazines consist of two azines, such as pyridine, quinoline, or diazines, directly connected through a carbon-carbon bond. This scaffold is present in pharmaceuticals, with examples of imatinib, an oral treatment to Leukemia,⁵ which contains a pyridine-pyrimidine core, etoricoxib, a 2,3'-bipyridine anti-inflammatory,⁶ and MK-1064, a terpyridine in clinical trials for insomnia

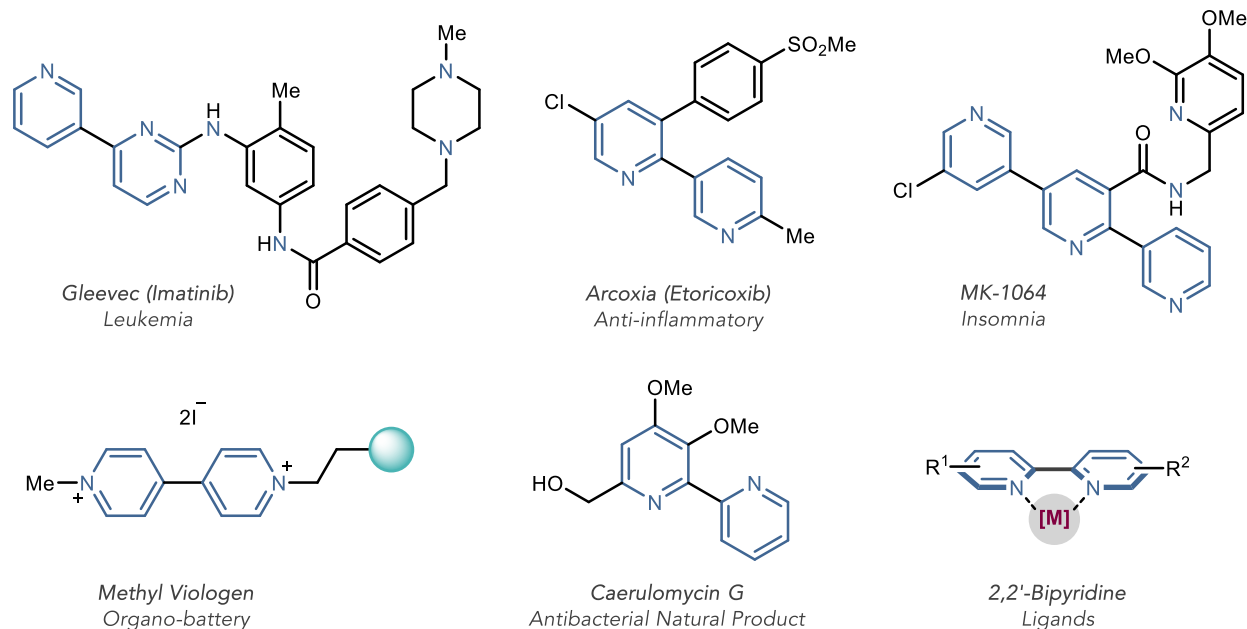


Figure 2.1. Bipyridines are a Common Motif Across Chemical Industries treatment (**Figure 2.1**).⁷ Bisazines are also present in natural products such as Caerulomycin G,⁸ organic materials such as viologen based batteries, and ligands for transition metal-catalysis.⁹

2.2.2 Synthetic Strategies to Bisazines through Metal-Catalysis

Biaryl scaffolds are commonly synthesized using transition metal-catalysis through a disconnection of the aryl-aryl bond.^{10,11} This disconnection leads to two aryl starting materials, referred to as the nucleophilic, such as boronic acid, organozinc, or organostannane, and electrophilic, containing a halide or pseudohalide, coupling partners (**Figure 2.2**).¹² Bisazine synthesis through metal-catalysis follows this disconnection. This section will discuss strategies for bisazine synthesis through transition metal-catalysis and challenges associated with this strategy.

For biaryl synthesis, the Suzuki-Miyaura reaction represents one of the most popular reactions in medicinal chemistry and benefits from two readily available and stable coupling partners being employed in the reaction, in aryl boronic acids and aryl halides, typically iodide or

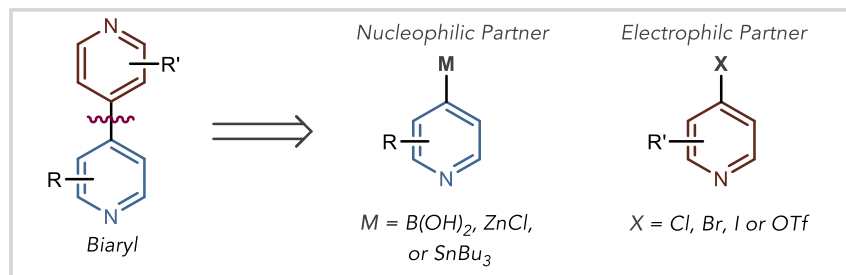


Figure 2.2. Metal-Catalyzed Cross-Coupling Disconnection for Biaryls.

bromide.^{13,14} Numerous groups have employed the Suzuki reaction for bisazine synthesis, and an example for its use from the Fu group is shown in **Figure 2.3**.¹⁵ The Suzuki reaction has numerous modifications depending on the scaffold that is being assembled, with various ligand, palladium catalyst/pre-catalyst, base, and solvent combinations employed.¹⁶ Limitations remain in the Suzuki reaction. Polar functionalities, such as amines, can coordinate to the metal center, interfering with the catalytic cycle.¹⁷ Couplings involving complex drug-like fragments, which often contain multiple basic and polar functionalities, can be low-yielding or unreactive. Aryl halides and aryl boronic acids are often only abundantly available at the building block stage of drug discovery.¹⁸ *De novo* installation of the halogen is required when applying cross-couplings to complex pyridines and diazines (**Section 1.4.1**).¹⁹ The nucleophilic coupling partner shares this limitation and limited pyridyl and diazinyl boronic acids and derivatives are commercially available. Pyridyl boronic acids are also unstable under the reaction conditions required for coupling, in particular 2-pyridyl boronic acids.^{20,21}

Suzuki-Miyaura Coupling: Fu (2006)

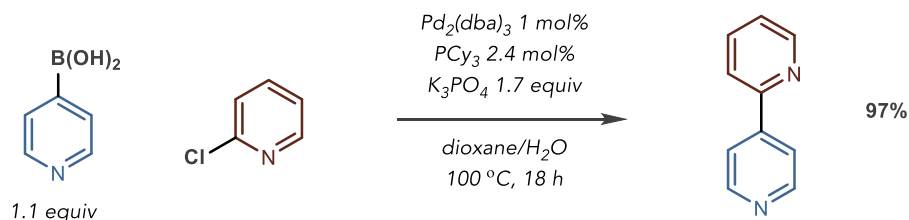


Figure 2.3. Example of the Suzuki-Miyaura Reaction for Bipyridine Formation (Fu 2006).

The Stille and Negishi reactions are used to synthesize bisazines, employing an aryl organostanne or aryl organozinc respectively as the nucleophilic coupling partner that reacts with an aryl (pseudo)halide. The Stille reaction employs an organostannane, which are commonly synthesized from the corresponding halide.²² Azinyl organostannanes have improved stability when compared to their boronic acid counterparts. The reaction suffers due to the toxic nature of both the initial organostannane and the reaction byproduct, a tributylstannane derivative.²³ An example of the Stille reaction for bisazine synthesis from the Schubert group is shown in **Figure 2.4**, where a 2-pyridyl organostannane and 2-bromo-4-methylpyridine are coupled together in reasonable yield.²⁴ The aryl organozinc species used in the Negishi reaction are commonly prepared from a halide precursor.²⁵⁻²⁷ This is done through halogen-metal exchange either directly through zinc metal or through generating an organolithium or Grignard and trapping with a zinc halide.²⁸ Organozinc species have limited stability and are typically prepared immediately prior to drug-like fragments.^{17,18} The Negishi reaction is robust, and an example of its use in forming

Stille Coupling: Schubert (2000)

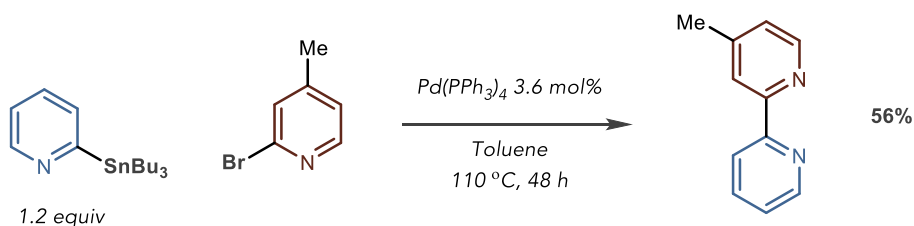


Figure 2.4. Example of the Stille Coupling for Bipyridine Formation (Schubert 2000).

bisazines from Merck Process is shown in **Figure 2.5**.²⁹ Significant challenges remain particularly in bisazine synthesis and in applying the chemistry to complex structures.

Negishi Coupling: Merck Process (2010)

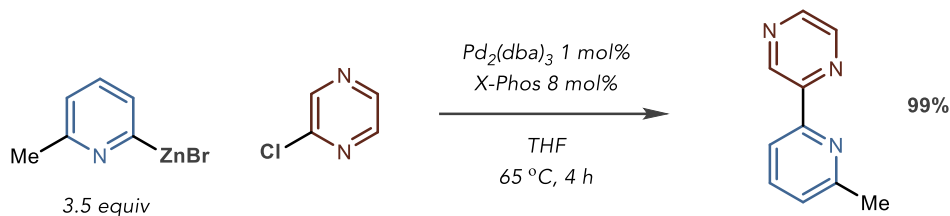


Figure 2.5. Example of the Negishi Coupling for Bisazine Formation (Merck Process 2010).

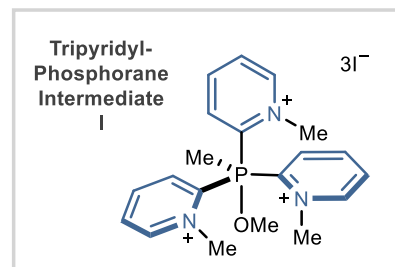
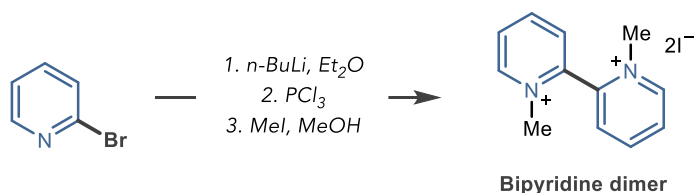
2.2.3 Bipyridine Synthesis through Phosphorus Ligand-Coupling

An underrepresented strategy to synthesis bisazines is phosphorus ligand-coupling, where two groups on a high valent phosphorus species couple together similar to transition metal-catalyzed reductive elimination.³⁰ 2,2'-bipyridine synthesis through phosphorus ligand-coupling has been reported by the Oae, Uchida, Newkome, and Mann groups.³¹⁻³⁴ Phosphorus ligand-coupling requires the azinyl groups to be pre-installed on the phosphorus atom. The precursors for phosphorus ligand-coupling can be phosphine oxides or phosphonium salts, often with two or three pyridyl ligands. A nucleophile attacks the phosphorus atom resulting in a P(V) phosphorane species. Two ligands on the phosphorane then break their bonds with phosphorus and couple together.³⁵ The overall process provides a bisazine product and a new P(III) byproduct through the course of the reaction. An in-depth mechanism and description will be presented later in this chapter (**Section 2.4**).

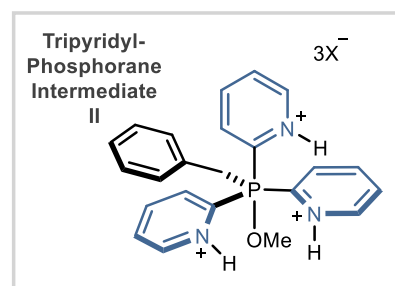
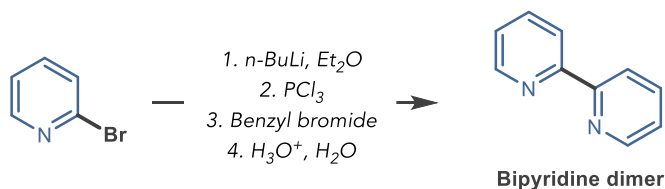
Phosphorus ligand-coupling for bipyridine synthesis was first reported by Mann in 1948 through a phosphonium intermediate.³¹ To install the pyridyl groups on the phosphorus atom, Mann reacted 2-lithio pyridine with phosphorus trichloride, resulting in a tris-2-pyridylphosphine (**Figure 2.6, A**). The pyridylphosphine was then heated with methyl iodide in methanol providing

bis-*N*-methyl-2,2'-bipyridinium. This reaction presumably occurs through alkylation of the phosphorus atom to form a phosphonium, which is then attacked by methanol at the phosphorus center, resulting in phosphorane intermediate **I**. Uchida and Oae reported a similar strategy for bipyridine formation through a phosphonium intermediate in 1989, where benzyl bromide and acid was used in place of methyl iodide (**Figure 2.6, B**).³² Aqueous hydrochloric acid protonates the

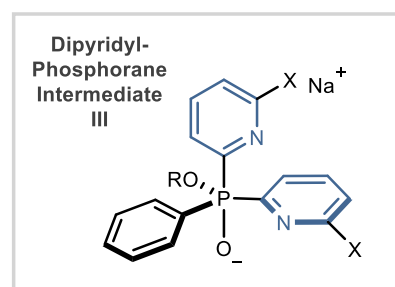
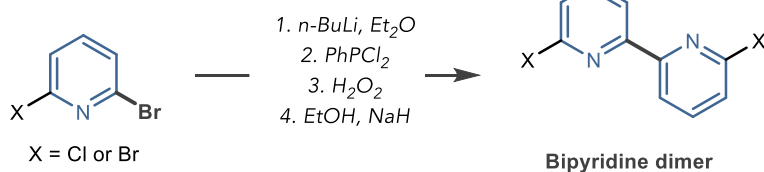
A. Mann:1948



B. Uchida and Oae: 1989



C. Newkome: 1978



D. Uchida and Oae: 1990

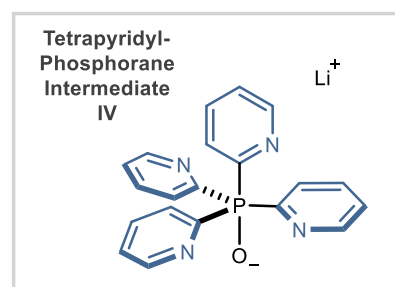
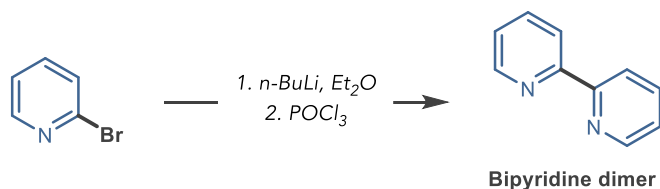


Figure 2.6. Seminal Examples of Bipyridine Formation through Phosphorus Ligand-Coupling

pyridines and attack of water at the phosphorus atom forms phosphorane **II**. This strategy selectively couples two pyridyl ligands, with no benzylation of pyridine reported. These reports from Mann, Uchida, and Oae showcase the ability to synthesize bipyridines through phosphorus ligand-coupling using a phosphonium intermediate containing pyridines activated by alkylation or protonation.

An alternative strategy for phosphorus ligand-coupling was reported by Newkome in 1978 using a phosphine oxide as the initial phosphorus species (**Figure 2.6, C**).³³ A dipyridylphenylphosphine oxide is generated through addition of lithiated pyridines to dichlorophenylphosphine and oxidation using hydrogen peroxide. Ligand coupling is then triggered through addition of an alkoxide and alkoxy-phosphorane intermediate **III**. Bipyridine is reported as the sole ligand-coupling related product with no phenyl-pyridine coupling observed. Uchida and Oae reported using pyridyl phosphine oxides (**Figure 2.6, D**), synthesized using phosphoranyl chloride, as the phosphorus starting materials.³⁴ The tris-pyridyl phosphine oxide is attacked *in situ* by 2-lithyl pyridine (**IV**), triggering ligand-coupling and providing 2,2'-bipyridine. The seminal reports from Mann, Uchida, Oae, and Newkome demonstrate the potential of phosphorus ligand-coupling for bisazine synthesis. These methods required highly reactive lithiated species, derived from halogenated pyridine starting materials, and were only shown to form dimer products. Our group believed phosphorus ligand-coupling could be transformed into a practical alternative to metal-catalysis for bipyridine formation by directly installing C-P bonds selectively on pyridines.

2.3 Result and Discussion

2.3.1 Initial Formation of Bis-azinyl Phosphonium Salt and Ligand-Coupling

The McNally group has previously showed that phosphonium salts could be installed selectively on pyridines and diazines directly from C-H bonds (**Section 1.4.3**).^{36,37} We envisioned the limitations of installing the azinyl groups on the phosphorus could be overcome by using our previously developed phosphonium salt chemistry. To test this hypothesis, we synthesized bis-azinyl phosphonium salt (**1**) by sequentially reacting 2-phenylpyridine with triflic anhydride (Tf₂O), phosphine **Phos**, and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) to 2-phenylpyridine in CH₂Cl₂ (**Figure 2.7**).

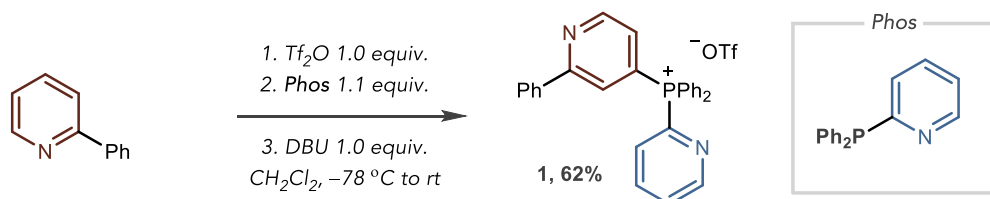
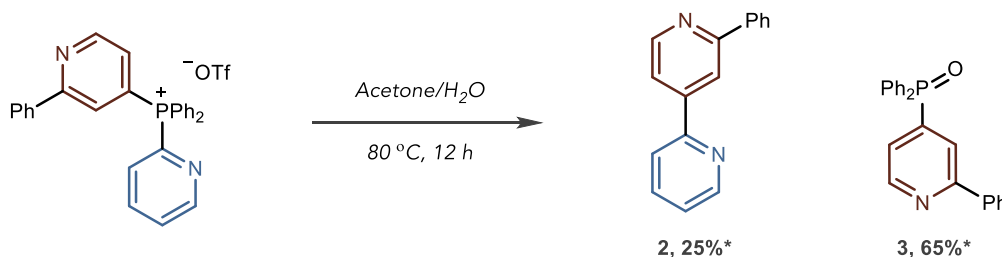


Figure 2.7. Initial Results for Bisazinyl Phosphonium Salt Formation.

We next set to determine if we could trigger ligand-coupling. Our initial system tested triggering coupling from salt **1** using a 1:1 mixture of acetone/water at 80 °C for 12 hours (**Figure 2.8**). These conditions were effective triggering ligand-coupling forming the desired 2'-phenyl-2,4'-bipyridine (**2**) in 25% yield and undesired pyridylphosphine oxide (**3**) in 63% through a ligand-exchange pathway.^{30,38}



*Determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard

Figure 2.8. Initial Result for Ligand-Coupling.

2.3.2 Optimization of Ligand-Coupling Conditions

Our initial experiments showed that we could synthesize bis-azinyl phosphonium salts through a similar set of conditions to what had been developed by our lab,^{36,37} and ligand-coupling was viable to achieve bipyridines from the bis-azinyl phosphonium salts. We next optimized the ligand-coupling conditions by modifying the nucleophile used and activation employed. When methanol was used as the solvent, no reaction was observed at 80 °C and phosphonium salt starting material remained (**Table 2.1, entry 1**). When 2 equivalents of anhydrous HCl were added and the reaction was heated to 80 °C in methanol, full conversion of the phosphonium salt was observed and 76% of the desired bipyridine (**2**) obtained (**entry 2**). A series of alcohols were investigated with isopropanol, tertbutanol, trifluoroethanol, and hexafluoroisopropanol proving effective albeit in lower yields ranging from 51-68% (**entries 3-6**). Two equivalents of acid proved critical to achieve full conversion, with 0.5 and 1.0 equivalents resulting in 48% and 62% product respectively (**entries 7, 8**). Anhydrous HCl and triflic acid (TfOH) gave comparable yields, while weaker acids, such as trifluoroacetic acid, provided limited conversion. Lowering the temperature below 80 °C resulted in slower conversion and no reaction was observed at room temperature (**entries 9-11**). Substituting methanol for ethanol provided comparable product at 70% and was preferable due to its higher boiling point (**entry 12**). Increasing the concentration from 0.2M to 0.4M resulting in an increase to 80% yield, however further concentration changes were found to not improve the yield (**entry 13**). This optimization gave final conditions of 2 equivalents of acid (anhydrous HCl or TfOH) in ethanol (0.4M) at 80 °C for 12 hours.

Table 2.1. Optimization of Bipyridine Formation through Phosphorus Ligand-Coupling

**Determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard*

Entry	Solvent	HCl (equiv)	Temperature ($^{\circ}\text{C}$)	Concentration (M)	% Product
1	MeOH	-	80	0.2	0
2	MeOH	2.0	80	0.2	76
3	IPA	2.0	80	0.2	57
4	TBA	2.0	80	0.2	51
5	TFE	2.0	80	0.2	59
6	HFIPA	2.0	80	0.2	68
7	MeOH	1.0	80	0.2	62
8	MeOH	0.5	80	0.2	48
9	MeOH	2.0	60	0.2	44
10	MeOH	2.0	40	0.2	12
11	EtOH	2.0	80	0.2	70
12	EtOH	2.0	80	0.4	80
13	EtOH	2.0	80	1.0	80

2.3.3 Development of the Fragmentable Phosphine

We sought to develop a strategy to synthesize a range of pyridylphosphines that were not commercially available. Pyridyl phosphines can be prepared through lithiation of a pyridine followed by reaction with diphenylchlorophosphine, through the direct reaction of triphenylphosphine and halopyridines in the presence of lithium or sodium metal,³⁹ or through metal-catalyzed processes.⁴⁰ These methods require pre-functionalized pyridine starting materials and in the case of lithiation strategies, strongly basic conditions. We sought to develop a strategy

to install the phosphine directly from the C-H bond on the azine to avoid these limitations. We envisioned this could be achieved by formation of a pyridyl phosphonium salt that could fragment under basic conditions to generate the desired pyridyl phosphine and an alkene.⁴¹

The key to our proposed strategy was designing a phosphine with the appropriate alkyl ligand that could eliminate under mild base conditions after the phosphonium salt had been formed. A report from Alonso showed that alkyldiphenylphosphines could be synthesized under a simple set of conditions by reacting diphenylphosphine with Michael acceptors, such as methyl acrylate (**Figure 2.9**).⁴² We believed this “fragmentable” phosphine would provide an effective route to synthesize a variety of azinyl phosphines and synthesized methyl acrylate derived fragmentable phosphine (**FragPhos**).

Alonso (2012)

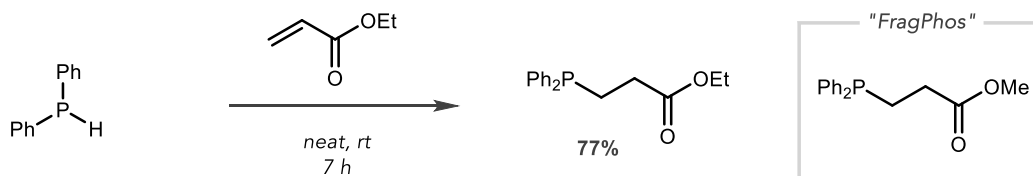


Figure 2.9. Addition of Diphenylphosphine to Acrylates and Proposed Fragmentable Phosphine

Employing a modified set of phosphonium salt formation conditions, we could synthesize heteroaryl phosphines with excellent regioselectivity. Substituting triphenylphosphine for methyl 3-(diphenylphosphanyl)propanoate (**FragPhos**), increasing the equivalents of base (DBU) from 1 to 3, and prolonging the reaction time from 30 minutes to 2 hours synthesized pyridyl phosphine **4** in good yield (**Figure 2.10**). DBU plays two roles in the reaction: rearomatization of the pyridine (**Int V**) and fragmentation of methyl acrylate from the resulting phosphonium (**Int VI**) via an E₁CB mechanism.

2.3.4 Scope of Bisazine Synthesis through Phosphorus Ligand-Coupling

Our couple strategy for two azines from their C-H bonds is shown in **Figure 2.10**. In the first step (**A**), the azinyl phosphine (**4**) is synthesized through sequential addition of Tf_2O , **FragPhos**, and DBU to the desired pyridine or diazine. The second C-P bond (**B**) is formed using a different azine and sequential addition of Tf_2O , azinyl phosphine **4**, and DBU generating bis-azinylphosphonium salt **5**. Ligand-coupling is triggered through addition of 2 equivalents of HCl in ethanol at 80 °C and forms the desired bipyridine product **6** with exclusive coupling selectivity (**C**).

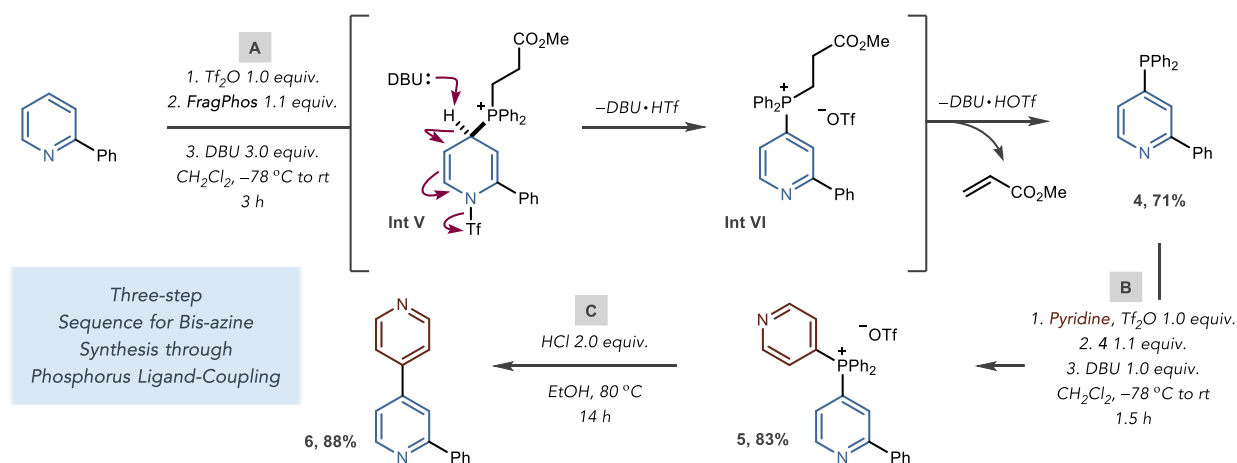


Figure 2.10. Phosphorus Installation and Coupling Sequence for Bisazine Synthesis

We examined the scope of bisazines formed using this protocol (**Figure 2.11**). Our initial result demonstrated the ability to synthesize 2,4'-bipyridines and we next investigated formation of 4,4'-bisazines and 2,2'-bisazines. The reaction proved effective at synthesizing a range of bisazines. Electron- withdrawing and electron-donating groups located directly off the azine ring are tolerated, and traditional cross-coupling handles like halogens are stable under the reaction conditions (**7-11**, **14**). The 4-position must be blocked to access coupling at the 2-position (**13**), and we found that both quinolines (**12-16**) and pyridines (**13**) were adept at coupling at this position. Diazines, such as pyrimidine (**15**) and pyrazine (**16**), can also be coupled together,

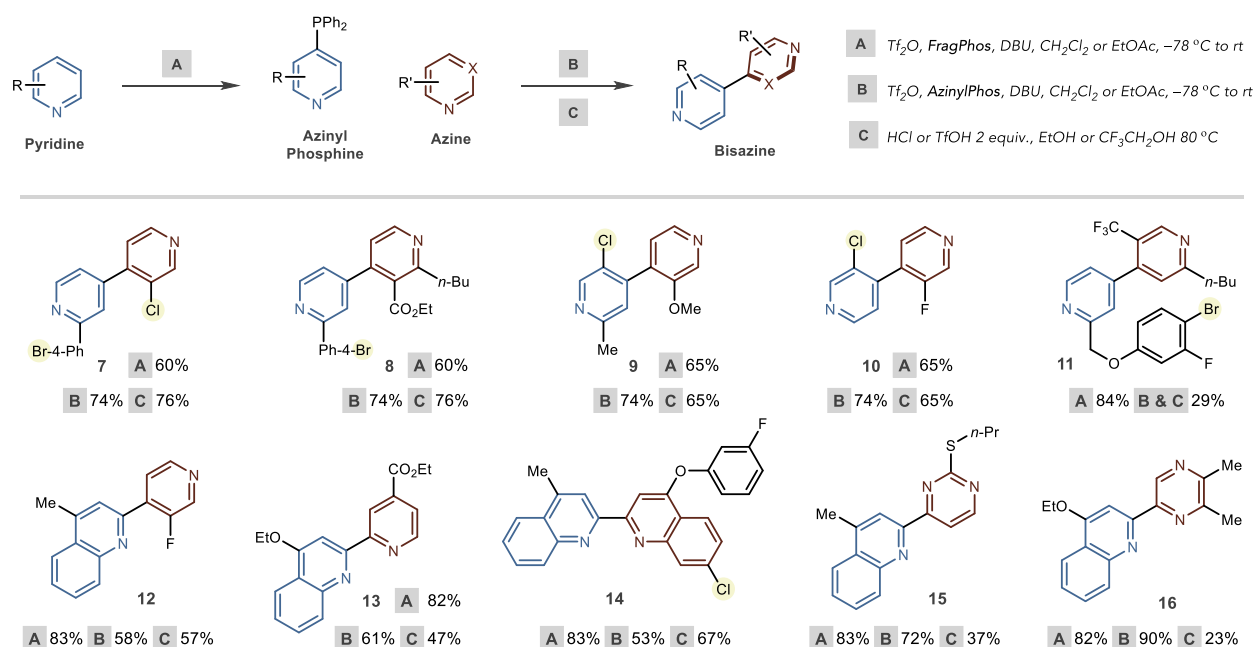


Figure 2.11. Scope of Phosphorus Ligand-Coupling for Building Block Bisazines.

although ligand-coupling yields were typically lower than examples on pyridine and quinoline. Fluorinated building blocks proceed well even when present directly off the azine ring (**10-12**).

After investigating the scope of building block pyridines, we synthesized four complex drug-like fragments (**17-20**) and sought to employ the coupling strategy to these complex systems where traditional metal-catalysis would be challenging. The fragments were designed to mimic functionalities that a medicinal chemist might encounter in a drug discovery campaign. In addition to containing polar functionalities that are problematic in traditional metal-catalysis, installing the required coupling handles, halides or boronic acids, would be challenging and likely result in poor yields and mixtures of isomers. Our sequential C-P bond formations proceeded with perfect regioselectivity for each example. Triggering ligand-coupling under the standard set of conditions couples each fragment together (**Figure 2.12**).

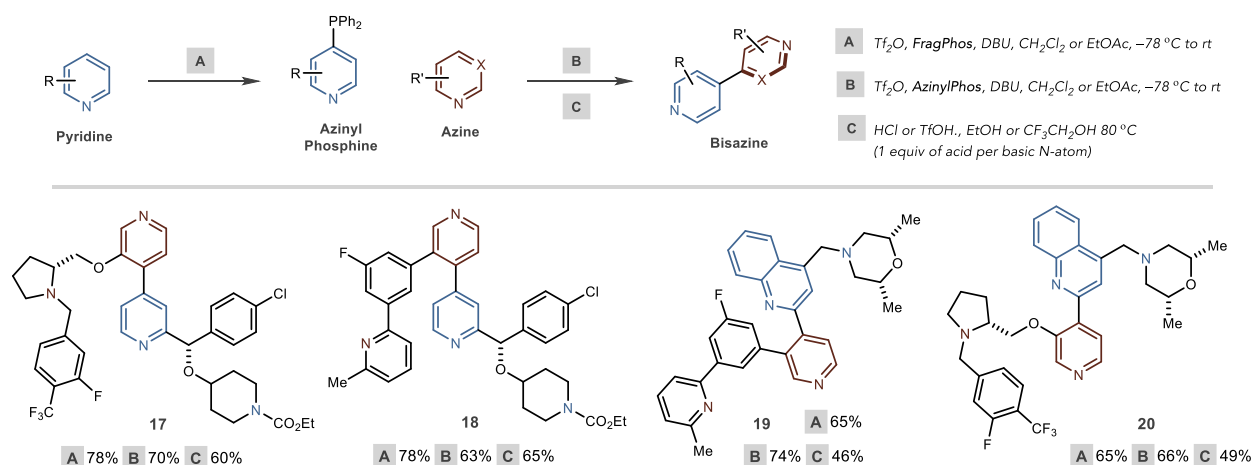


Figure 2.12. Scope of Phosphorus Ligand-Coupling for Convergent Drug-Fragment Couplings.

We next applied the three-step process to pharmaceuticals and drug candidates (**Figure 2.13**). While installing an azine on an existing drug is a dramatic change for late-stage functionalization,^{43,44} performing the chemistry on these bioactive molecules demonstrates tolerance of functionalities that are common in drug discovery. Risk of metal contamination is a concern in performing transition metal-catalyzed couplings at the later stages in development routes. For example, palladium can be challenging to remove and can impact the toxicity and potency of a drug.⁴⁵ Consequently, developing and employing metal-free reactions is of interest to medicinal chemists.

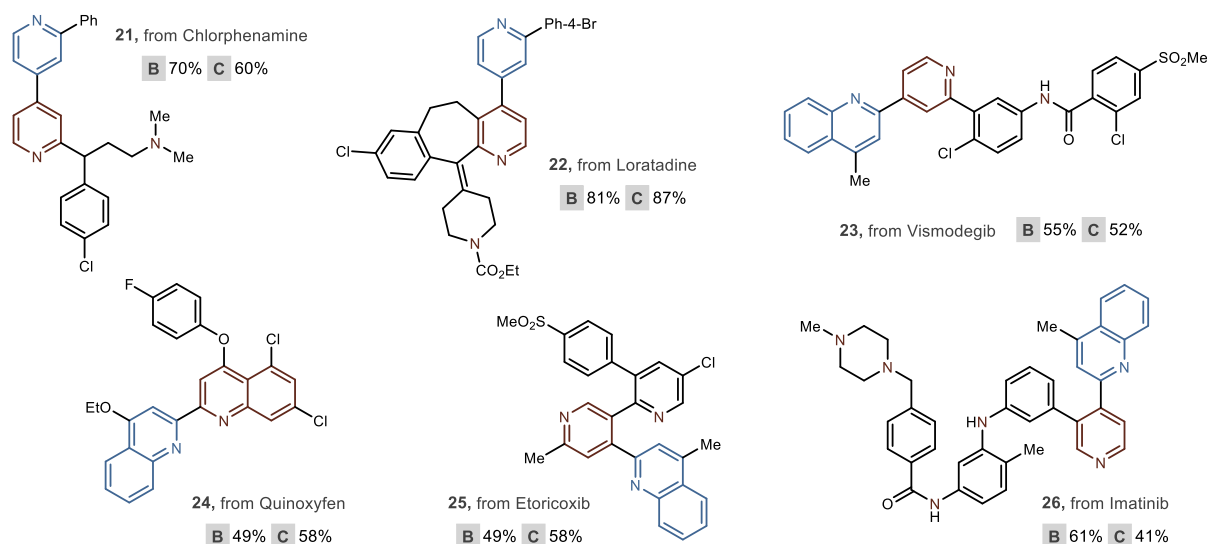
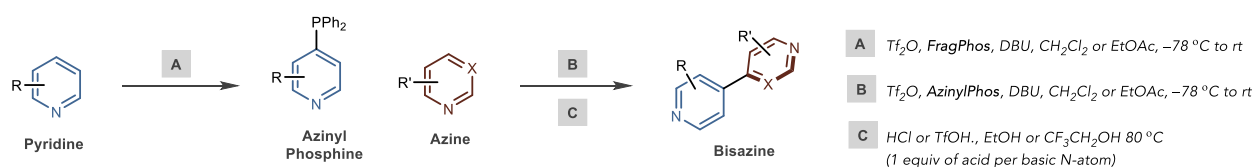


Figure 2.13. Scope of Phosphorus Ligand-Coupling for Pharmaceuticals and Drug Candidates.

2.3.5 Considerations for Performing Ligand-Coupling

While employing the phosphorus ligand-coupling conditions, there are two main considerations: what order to install each azine onto the phosphorus atom; and the choice of acid and equivalents. The order of addition onto the phosphorus atom plays a critical role to avoid undesired side pathways in the salt forming reaction. For example, the reaction between 2-aryl pyridyl phosphine **27** and 3-chloropyridine successfully forms the phosphonium **28** in 82% yield (**Figure 2.14**). However, when the order is swapped and 3-chloro pyridyl phosphine **29** is reacted

with 2-arylpyridine, no desired phosphonium salt is formed. This is due to activating group exchange between the 2-substituted pyridine and the 3-substituted pyridine. For steric reasons, the triflyl group will equilibrate onto the less hindered 3-substituted pyridine, which is then attacked by another equivalent of the azinyl phosphine, generating pseudodimer product **30**. It is required to make the more sterically hindered azine into the phosphine and then employ this in the phosphonium salt reaction.

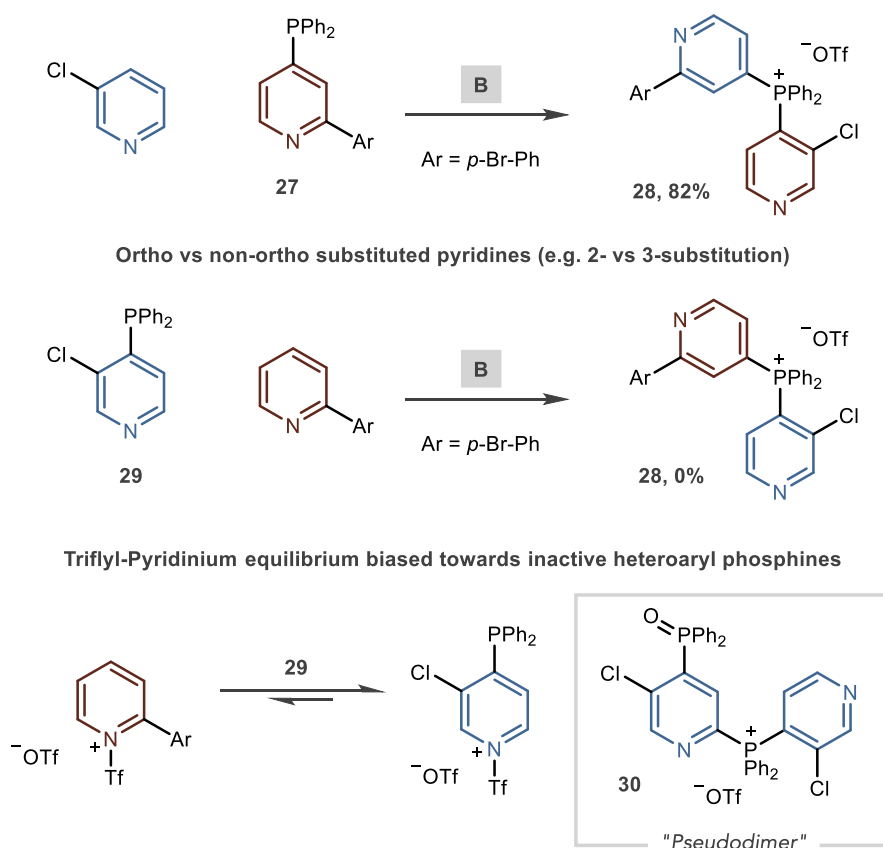


Figure 2.14. Considerations for Order of Installation onto the Phosphorus Atom

The choice of HCl vs TfOH and how many equivalents play key roles in achieving the desired reactivity. The equivalents of acid must match the number of basic nitrogens in the molecule. If too little acid is employed, the reaction rate will be significantly slower due to

insufficient activation in the phosphorane intermediate. While HCl and TfOH gave comparable yields in most cases, there were cases where TfOH significantly outperformed HCl (*vide infra*).

The choice of acid is critical when a bulky was present at the 3-position on one of the two pyridines or one partner was too electron-deficient (containing two or more electron withdrawing groups). An example of the undesired reaction is shown in **Figure 2.15** (top), where under the standard conditions using HCl, chlorination of Loratidine was observed along with the desired coupling product. After protonation of the two pyridine rings, we believe that the chloride counterion can add into the azine, displacing an azinyl phosphine forming the chlorinated product. This reactivity was investigated further by Jeff Levy, a coworker in the McNally group, and culminated in a publication in the *Journal of the American Chemical Society*.⁴⁶ When a 3-trifluoromethyl group was present on the phosphonium, we observe ethanol addition into the pyridine (**Figure 2.15, bottom**). This likely proceeds through initial chlorination and subsequent S_NAr solvolysis. These two products could be avoided by using TfOH in place of HCl in the reaction. The non-

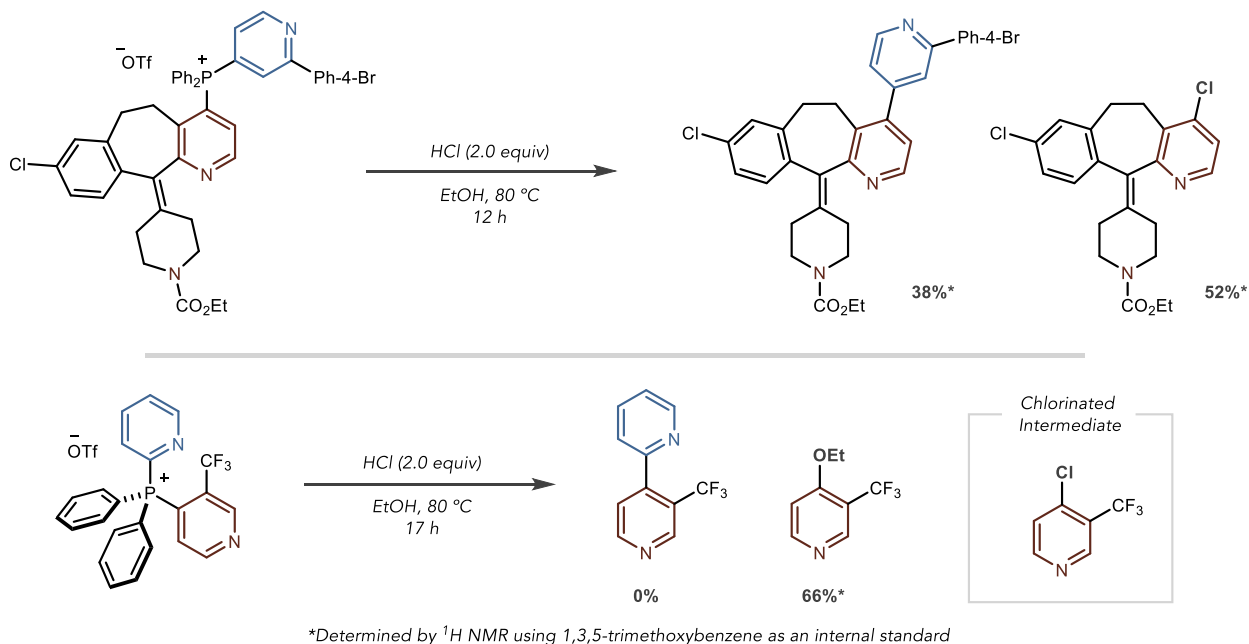


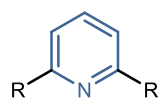
Figure 2.15. Undesired Chlorination Observed under Ligand-Coupling Conditions

nucleophilic triflate counterion is unable to perform the S_NAr reaction and the desired ligand-coupling product forms.

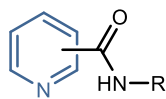
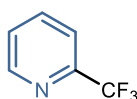
2.3.6 Limitations of Phosphorus Ligand-Coupling Bisazine Synthesis

Limitations were observed both in installing the C-P bond and with the ligand-coupling step itself (**Figure 2.16**). When synthesizing the phosphine and phosphonium, 2,6-disubstituted pyridines, pyridines with an excess of electron withdrawing groups (three or more directly off the ring), and 2-trifluoromethyl pyridines are ineffective. This is likely due to insufficient activation with Tf_2O , leading to undesired attack on the triflyl group by the phosphine nucleophile. Pyridine with alkyl or aryl substituents at the 4-position do not form the C-P bond in high yields (<25%), although the exact reason is not well understood.⁴⁷ Functionality that can react with Tf_2O , like alkyl amides and alcohols, also shuts down the reactivity.⁴⁸

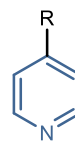
Difficult Motifs for Steps A and B



R $\neq$ H

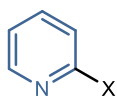


R = alkyl

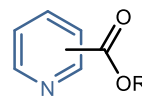
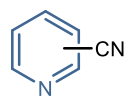
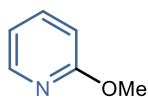


R = alkyl or aryl

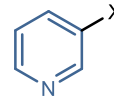
Difficult Motifs for Step C



X = F, Cl, Br



R $\neq$ Et



X = Br, I

Figure 2.16. Challenges and Limitations for Phosphine/Phosphonium Formation and Ligand-Coupling.

Limitations in the ligand-coupling step are related to the nucleophilicity of both the solvent and the chloride counterion when using HCl. Pyridines with halogens at the 2-positions are not effective due to a competing S_NAr reaction with ethanol. Dealkylation of 2-methoxypyridines and hydrolysis of cyano groups directly off the pyridine ring limit the scope. When TfOH and trifluoroethanol (TFE) were used instead, reaction rates were slow with low conversion after

multiple days. Ethyl esters are amenable to the reaction, however other esters will undergo transesterification with the solvent. Halogens at the 3-positions can be tolerated if the halogen is chlorine or fluorine, however dehalogenation was observed when 3-bromo or 3-iodopyridine was used.

2.4 Mechanism and Selectivity of Phosphorus Ligand-Coupling

2.4.1 Mechanism

The mechanism for phosphorus ligand-coupling was probed experimentally and through computational studies (performed by Professor Rob Paton and Dr. Juan Alegre-Requena). Using a 4,4'-bipyridine coupling as our model system, this study sought to understand the role of acid in the reaction, identify the rate determining step, and gain insight into the origin of selectivity for the coupling itself. We began with investigating the role of acid in the reaction and found that both pyridines on the phosphonium salt are protonated. This is observed through a ^{31}P NMR study

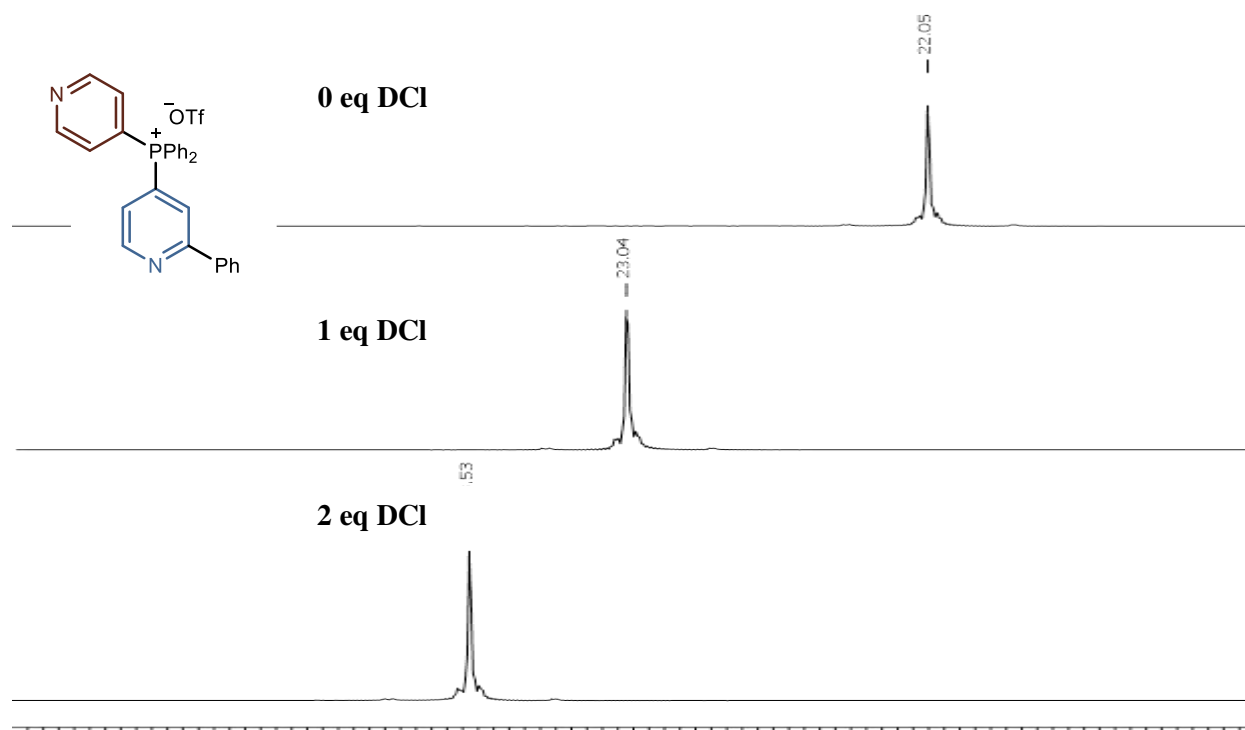


Figure 2.17. Effect of Protonation on ^{31}P NMR Shift for Bisazinyl Phosphonium Salt.

(**Figure 2.17**). Each equivalent of acid increases the electrophilicity of the phosphorus atom and shifts the phosphonium peak further downfield in the ^{31}P NMR. Protonation plays a role in the attack on the phosphorus atom by the alcohol nucleophile and explains the observation that no reaction occurs when no acid is present.

We hypothesized that alcohol addition to the phosphorus was the rate determining step for the reaction. This idea was supported by an *in situ* ^1H and ^{31}P NMR experiment on the reaction, where no intermediate phosphorane was observed despite formation of the bipyridine product. To test our hypothesis, we synthesized bisazine phosphonium salts with different substituents at the para-position of the aryl rings, from electron-rich (-OMe), neutral (-H and -Me), and electron-deficient (-Cl) (**Figure 2.18, top**). Relative initial rates support our hypothesis. The electron-rich *p*-OMe phosphonium resulting in a K_{Rel} of 0.16 and electron-deficient *p*-Cl increasing the rate with a K_{Rel} of 1.89. Building on this result, we used a stronger alkoxide nucleophile to trigger ligand-coupling at room temperature and found the reaction produced the desired bipyridine product

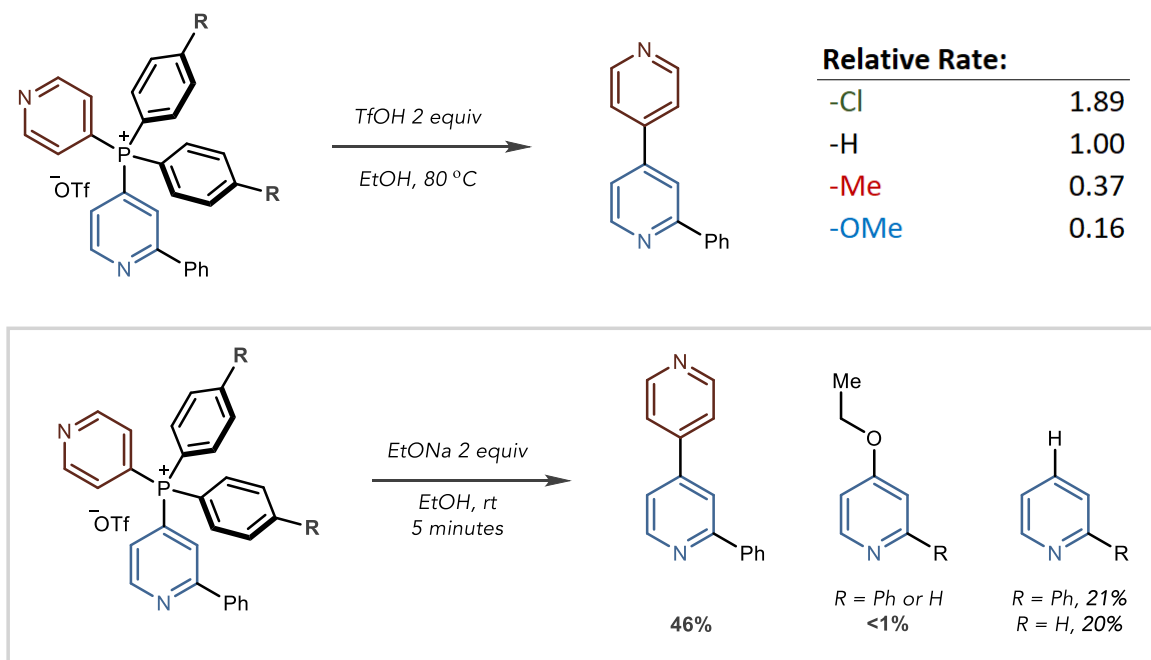


Figure 2.18. Relative Rate Differences Due to Electron Variation on Aryl Rings.

within 5 minutes at room temperature (**Figure 2.18, bottom**), in contrast to the acidic conditions that required 40 °C for coupling to be observed and 80 °C for a synthetically useful rate.

Our attention next turned towards the mechanism of the ligand-coupling step itself, and we collaborated with the Paton lab to probe this computationally. Their study indicates that after the phosphorane intermediate (**Int VII**) is formed, the bond between the phosphorus atom and the apical pyridine group is weakened due to the trans effect.⁴⁹ This results in a buildup of negative charge on the 4-position of the apical pyridine. The weakening is seen in the computed bond lengths for the phosphorane intermediate where the apical pyridine C-P bond is elongated

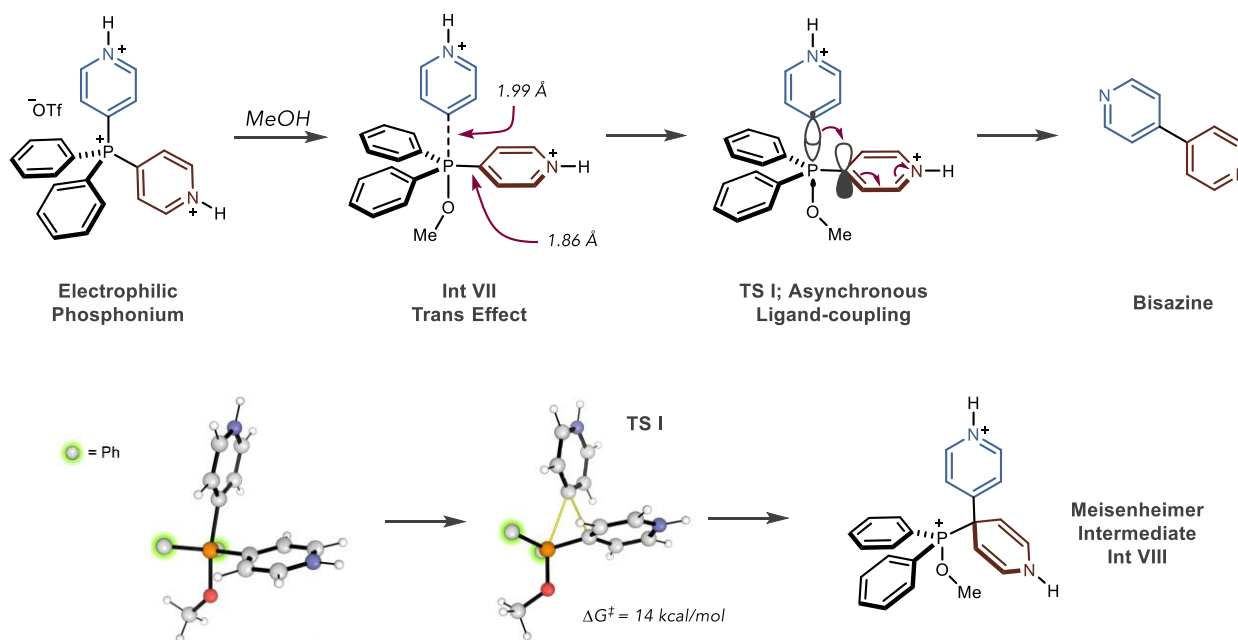


Figure 2.19. Key Intermediates and DFT Calculated Transition State for Phosphorus Ligand-Coupling compared to the equatorial pyridine C-P bond (1.99 Å vs 1.86 Å) (**Figure 2.19**). The charge buildup causes the apical pyridine to migrate onto the π^* of the equatorial pyridine, going through a 3-center 4 e^- transition state (**TS I**). The computed barrier for this process is 14 kcal/mol, and the observed rate at room temperature with alkoxide supports this. After migration, a dearomatized

Meisenheimer-like intermediate forms (**Int VIII**), which rapidly rearomatizes by kicking off methyl diphenylphosphinite resulting in the desired bisazine.

2.4.2 Selectivity in Phosphorus Ligand-Coupling

The computational investigation provided insight into the observed exclusive selectivity for azine-azine coupling. From the phosphorane intermediate (**Int VII**), phenyl or alkoxy migration could occur and C-O bond formation through a similar intermediate has been shown by our group.³⁶ Once the phosphorane has been formed, each phosphorane isomer can be obtained through a Berry pseudorotation.⁵⁰ The most stable phosphorane isomer places the methoxy group and one of the two azines at the apical positions, which follows the rules of apicophilicity (**Figure 2.20**).^{51,52} The ability to couple is dictated the apical groups stabilization of the negative charge buildup from the trans effect. A protonated pyridine is more suitable than a phenyl group at stabilizing charge build-up. The apical pyridine can potentially migrate onto a protonated pyridine or a phenyl ring. A protonated pyridine is a better electrophile than a phenyl ring and migration occurs onto the pyridine because of this. Stabilization of negative charge buildup through the reaction provides selectivity for azine-azine coupling over the options of phenyl-phenyl or phenyl-pyridine couplings.

The experimental selectivity is supported by DFT calculations performed by the Paton lab (**Figure 2.20**). The barrier for migration is 14 kcal/mol in bisazine formation. An increase in $\Delta G^\ddagger$ is observed when no acid is used (30 kcal/mol) reflecting the role protonation has in stabilizing the negative charge buildup. Phenyl coupling was calculated to be 11 kcal/mol and alkoxy migration is 4 kcal/mol higher in energy compared to the desired coupling. These values agree with the experimental results of exclusive coupling for the desired bisazine.

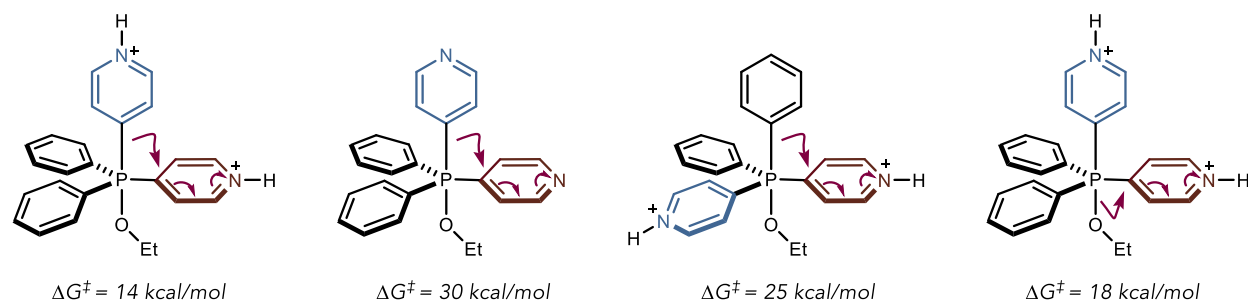


Figure 2.20. DFT Calculated $\Delta G^\ddagger$ for Potential Ligand-Couplings

2.5 Conclusion

Phosphorus ligand-coupling was developed as an alternative strategy to transition metal-catalysis for bisazine synthesis. Challenges in coupling partner availability and functional group tolerance are addressed through this method and late-stage convergent couplings are effective. Couplings are accessed directly from the C-H bonds on the precursor pyridines. The mechanism for bisazine synthesis was probed through computational and experimental studies. Alcohol addition to the phosphonium salt is rate determining and selectivity is determined by the ability to stabilize negative charge over the course of the reaction. The overall mechanism proceeds through phosphorane formation, trans-effect induced migration, and rearomatization to form the desired bisazine.

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Chapter Three

Bisazine Synthesis from Chloroazines

3.1 Overview

This chapter discusses the development of an alternative approach to bisazines from chloroazine precursors. A sequential S_NAr ligand-coupling strategy using diphenylphosphine and chloroazines yields a bisazine product. An improved set of conditions were used to trigger ligand-coupling and a distinct set of azines are amenable. 2,2'-bipyridines, a common motif in pharmaceuticals and ligands are accessed through this method and overcome the limitations of our previously developed ligand-coupling. The described method is an important advance in bisazine formation and uses commercially available chloroazines. Michael Hilton contributed to the discovery and synthesis of bisazine products. This work culminated in a publication in the *Journal of the American Chemical Society* in 2019.¹

3.2 Background

3.2.1 Importance of 2,2'-Bipyridines

Bisazines are a common motif in several chemical fields (*vide supra*) and 2,2'-bipyridines are particularly common in pharmaceuticals, materials, and ligands (**Figure 3.1**). MK-1064, a bioactive molecule currently being investigated as an insomnia treatment, has a 2,2'-bipyridine

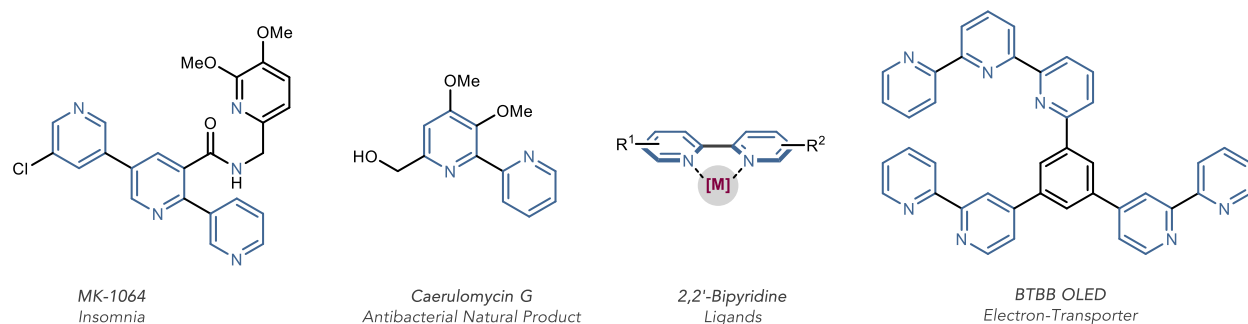


Figure 3.1. Examples of 2,2'-Bipyridines in Bioactive Molecules, Ligands, and Materials.

core as part of its terpyridine scaffold.² 2,2'-bipyridines have application in transition metal-catalysis as ligands, with examples in traditional and photoredox catalysts.³⁻⁵ Bipyridines are in organomaterials such as OLEDs and organobatteries.⁶⁻⁸

3.3.2 Modern Approaches to 2,2'-Bipyridines

Most strategies for 2,2'-bipyridines use transition metal-catalyzed cross-couplings to form the biaryl bond.⁹ The reliance on metal-catalysis is problematic when synthesizing 2,2'-bipyridines due to challenges related to the nucleophilic coupling partner. The Suzuki-Miyaura reaction is the most popular strategy for biaryl formation, however 2-pyridyl boronic acids are unstable and prone to protodeborylation.¹⁰ Lloyd-Jones has shown that 2-pyridyl boronic acids rapidly decompose under Suzuki reaction conditions via a zwitterionic intermediate.^{11,12} The lack of reliability in the coupling partner for the Suzuki reaction is a challenge in the pharmaceutical industry, and a recent study of Pfizer electronic notebooks found there was a <8% success rate (yield >20% was set as successful) for reactions involving 2-pyridyl boronic acids.¹³

Figure 3.2 shows alternatives to boronic acids for 2,2'-bipyridine synthesis.¹⁴ Burke and Molander have both developed boronic acid derivatives that display increased stability.¹⁵⁻¹⁷ Burke synthesized *N*-methyliminodiacetic acid (MIDA) boronates, which slowly release the boronic acid *in situ*. The MIDA boronate is synthesized from the corresponding halide through a halogen-metal exchange, triisopropyl borate trapping, and ligand exchange with MIDA. Burke achieved a number of 2,2'-bipyridine and other bisazine couplings using MIDA boronates.¹⁷ A related strategy using potassium trifluoroborate salts has been pioneered by the Molander lab. While the initial report did not demonstrate their efficacy in 2,2'-bipyridine synthesis, the Wu group in 2012 showed their viability in synthesizing this motif.¹⁸ The scope appears limited to 6-substituted 2-pyridyl trifluoroborate salts and this substitution provides increased stability for 2-pyridyl boronic

acids and derivatives.¹⁹ A recent advance in 2-pyridyl boronic acid alternatives has been developed by the Willis lab using pyridyl sulfinate salts and allyl sulfones (**Figure 3.2**).^{13,20} These can be synthesized from 2-mercapto or 2-halopyridine starting materials and are benchtop stable. Willis demonstrated these sulfur-based reagents are an alternative to boronic acids and derivatives. 2,2'-bipyridine synthesis remains challenging and new methods are of value.

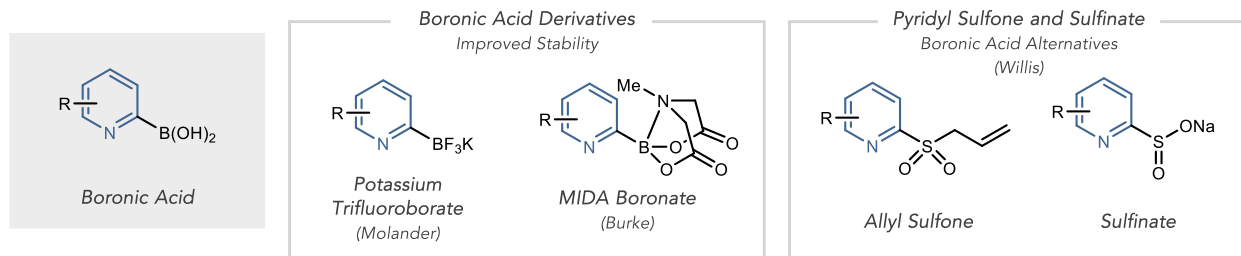


Figure 3.2. Alternatives for 2-Pyridyl Boronic Acids in Suzuki-Miyaura Cross-Couplings.

3.2.3 Pyridyl Phosphonium Salts through S_NAr

Heteroaryl phosphonium salts can be prepared through nucleophilic aromatic substitution (S_NAr) between a heteroaryl halide and triphenylphosphine. Toma reported 2-halo pyridines react neat with triphenylphosphine at elevated temperatures (120-180 °C) resulting in a 2-pyridyl triphenylphosphonium salt (**Figure 3.3**).²¹ Inorganic salts such as $LiPF_6$ and $LiBr$ improve the yield of the reaction on the 2-position, although their role under the reaction conditions is not understood. While 2-iodo, 2-bromo, and 2-chloropyridines are effective, no reaction was observed with 2-fluoropyridine. This is noteworthy since it follows counter to the established trends in S_NAr reactivity.²²

Toma (2017)

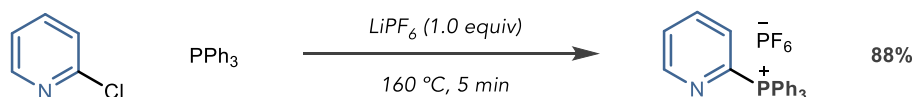
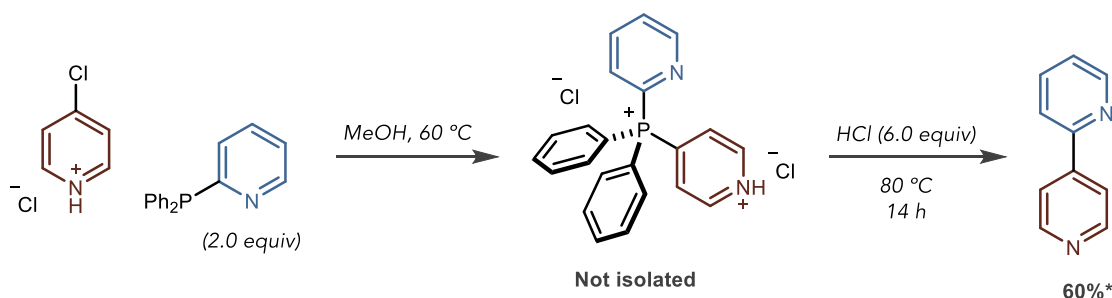


Figure 3.3. Synthesis of Triphenylphosphonium Salt through S_NAr on 2-Chloropyridine.

3.3 Results and Discussion

3.3.1 Development of a One-pot Tandem S_NAr -Ligand-Coupling

We sought to expand the scope ligand-coupling to pyridines and diazines that could not be functionalized directly from their C-H bonds through our previous strategy. The new strategy centers around S_NAr reactivity to install the desired C-P bonds followed by ligand-coupling to form the desired bisazine. Our initial system used 4-chloropyridine hydrochloride with 2 equivalents of 2-pyridyldiphenylphosphine in ethanol at 60 °C (**Figure 3.4**). After observing clean conversion to the desired bisazine phosphonium salt, addition of an equivalent of anhydrous HCl and heating the reaction to 80 °C led to 60% of the desired 2,4'-bipyridine.



*Determined using 1H NMR with 1,3,5-trimethoxybenzene as an internal standard.

Figure 3.4. Initial Result for Tandem S_NAr -Ligand-Coupling for Bisazine Synthesis.

3.3.2 Optimization of S_NAr and Ligand-Coupling Conditions for 2,4'- and 4,4'-Bipyridines

The conditions for phosphonium salt formation on pyridines was optimized further. The phosphine was changed to the limiting reagent to improve atom economy and ethanol was substituted for dioxane in the first stage. While the reaction now required higher temperatures (120 °C) and the use of sodium triflate as an additive, the conditions apply pyridines of different electronics and sterics. Dioxane was chosen as the solvent due to being higher boiling and removes an undesired S_NAr solvolysis reaction when alcoholic solvents are employed. Sodium triflate

increases conversion to the desired phosphonium salt, likely through halogen trapping via precipitation of sodium chloride. Ligand-coupling was then triggered by cooling the reaction to 80 °C and addition of anhydrous HCl, 10 equivalents of water, and dilution with 2,2,2-trifluoroethanol (TFE). Triflic acid (TfOH) provided similar yields to HCl under the reaction conditions. The optimized conditions synthesized a range of 2,4'- and 4,4'-bipyridines that are inaccessible via the previously developed strategy (**Figure 3.5**). This method accesses the 2-position without requiring the 4-position to be blocked and groups that previously reacted with Tf₂O, such as alkyl amides are also tolerated (**5**). Fluoro and bromopyridines could be used in place of chloropyridines with a

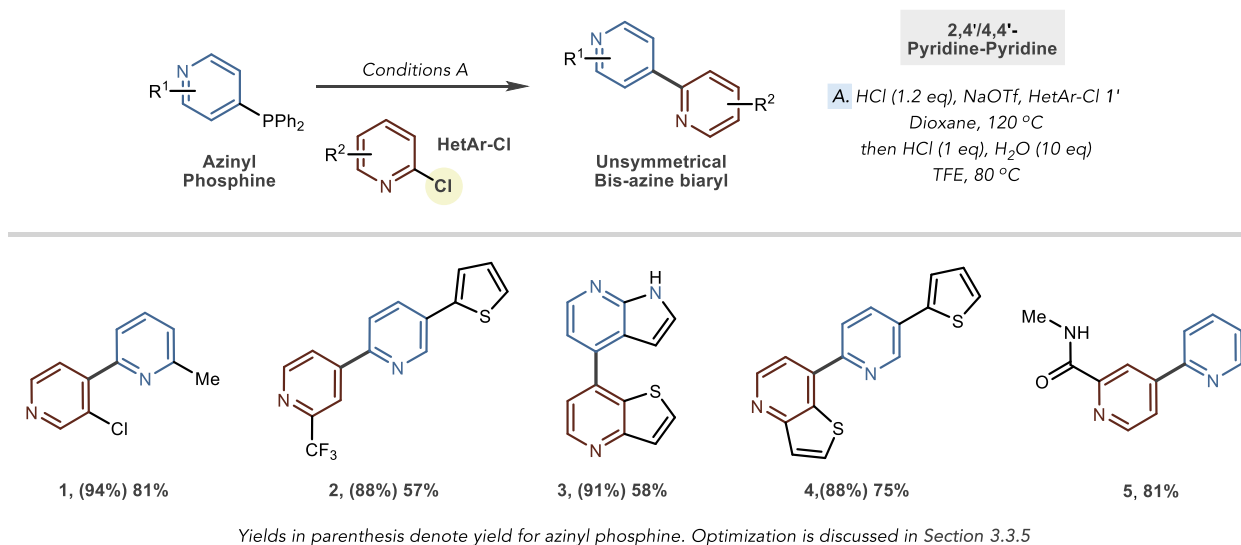


Figure 3.5. Initial Result for Tandem S_NAr-Ligand-Coupling for Bisazine Synthesis.

decrease in yield.

3.3.3 Optimization of S_NAr and Ligand-Coupling Conditions for Quinolines and Diazines

The optimized set of conditions using dioxane, HCl, and sodium triflate failed to produce any product when applied to quinoline or diazine examples. The initial phosphonium salt forming conditions were not providing the desired phosphonium salt and only starting materials were observed. This was an unexpected result as quinolines and diazines are significantly more S_NAr active than their pyridine counterparts.²² The formation of the phosphonium salt lies on an

equilibrium with the chloroazine starting material (**Figure 3.6**). On the more S_NAr active substrates, the equilibrium favored the chlorinated starting material. This unexpected result led to

Nucleophilic Counterion Leads to Reversible S_NAr Reactivity

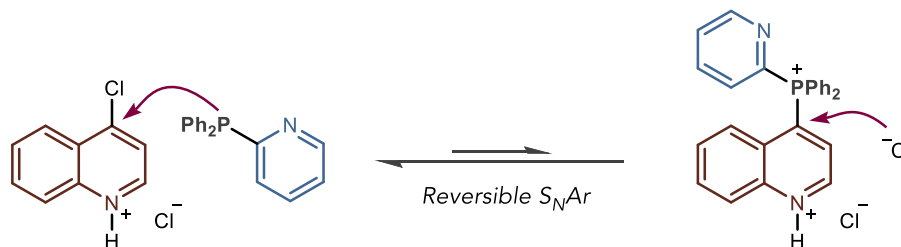


Figure 3.6. Reversible S_NAr on Quinolines due to Nucleophilic Counterion

further optimization for chloroquinoline and chlorodiazine systems.

Michael Hilton, a coworker in the McNally lab, proposed trapping of the phosphonium *in situ* to push the equilibrium forward by having the nucleophilic trigger for ligand-coupling in from the beginning of the reaction. The nucleophile reacts with the phosphonium salt prior to the reverse reaction occurring. By using 1.2 equivalents of HCl, 10 equivalents of H₂O, 2.2 equivalents of sodium triflate in TFE at 80 °C, the phosphonium is trapped and the desired bisazine product was obtained (**Figure 3.7**). By using the trapping conditions, unprotected phenols and benzyl alcohols are tolerated under the reaction conditions (**9**, **14**). Pyridine-quinoline and quinoline-quinoline couplings are effective under the reaction conditions, and diazine-diazine products are also obtained. Certain diazines, such as pyrazines and pyridazines, gave low yields of the desired product or decomposition under the reaction conditions.

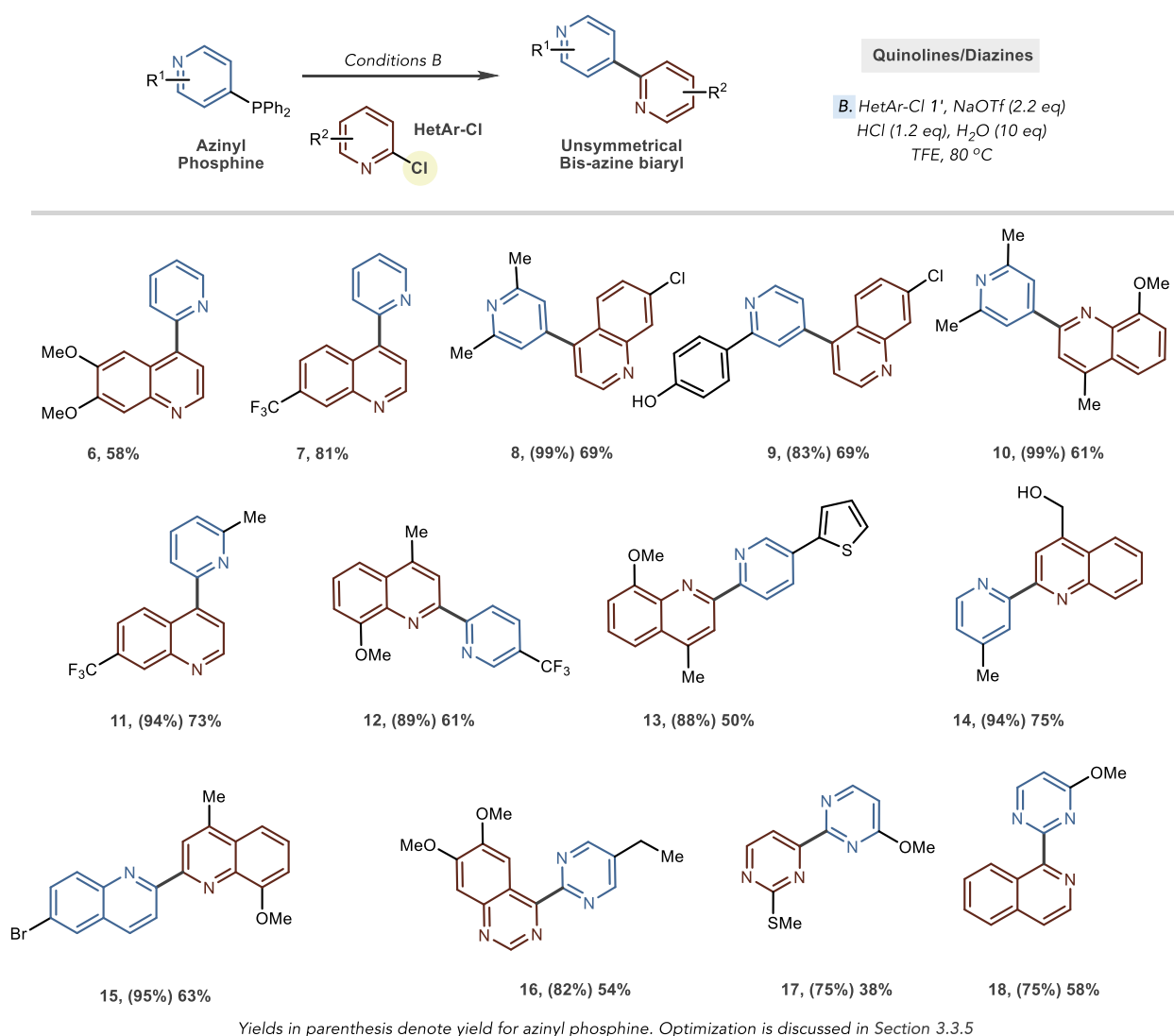
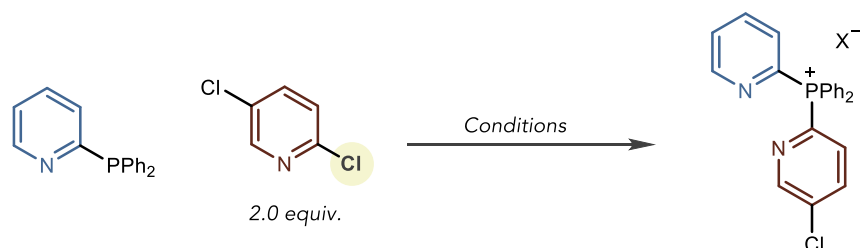


Figure 3.7. Selected Scope of Ligand-Coupling with Quinolines and Diazines.

3.3.4 Development of 2,2'-Bipyridine S_NAr and Ligand-Coupling Conditions

The optimized conditions were not effective on 2-chloropyridines. Starting material remaining indicated slow conversion to the desired bisazinyl phosphonium. The 2-position of pyridine is less S_NAr active than the 4-position and required modified conditions. 2-Pyridyldiphenylphosphine and 2,5-dichloropyridine were used as the model system for the optimization of 2,2'-bipyridines. A series of optimization results are present in **Table 3.1**. We found that replacing dioxane with less polar solvents such as toluene (tol) and

Table 3.1. Optimization of 2,2'-Bipyridine Phosphonium Salt Formation via S_NAr . * 1H NMR yields shown using triphenylmethane as an internal standard. †Undesired phosphonium salt observed. ‡1.5 equivalents of KPF_6 was used instead of 1.0 equivalents.



Entry	Solvent	Additive	Temp. °C	Conc. (M)	Acid	Yield (%)*
1	dioxane/tol. (1:1)	NaOTf	120	2	HCl	43
2	dioxane/tol. (1:1)	KPF_6	120	2	HCl	49
3	dioxane/tol. (1:1)	NaOTf	120	2	TfOH	42
4	dioxane/tol. (1:1)	none	120	2	TfOH	57
5	dioxane	none	120	2	TfOH	46
6	tol.	none	120	2	TfOH	60
7	tol.	KPF_6	120	2	TfOH	66
8	tol.	none	130	2	TfOH	70
9	PhCl	none	120	2	TfOH	51
10	PhCl	none	130	2	TfOH	67
11	PhCl	none	140	2	TfOH	69†
12	PhCl	KPF_6	130	2	TfOH	81
13	PhCl	KPF_6 ‡	130	2	TfOH	73
14	PhCl	$NaPF_6$	130	2	TfOH	79
15	PhCl	$LiPF_6$	130	2	TfOH	78

chlorobenzene (PhCl) provided an increase in yield (**entries 1-9**). Swapping HCl for TfOH and use of KPF₆ as the reaction additive also increased the yield of the phosphonium salt. Further optimization by increasing the reaction temperature to 130 °C proved to give the final set of conditions (**entry 12**). Higher temperatures give undesired phosphonium products, likely from a chloride addition and phosphine scrambling reaction (**entry 13**).

The 2,2'-pyridylphosphonium salts undergo ligand-coupling with 10 equivalents of H₂O in TFE at 80 °C conditions. 2,2'-bipyridines could be synthesized through our ligand-coupling protocol (**Figure 3.8**). Medicinally relevant motifs, such as SF₅ (**20**), CF₃ (**21**, **22**), and OCF₃ (**23**) groups were well tolerated under the reaction conditions.²³ Other functionalities, such as amines, amides, and halogens are also amenable to the coupling (**19**, **22**, **24**). In general, the yields obtained

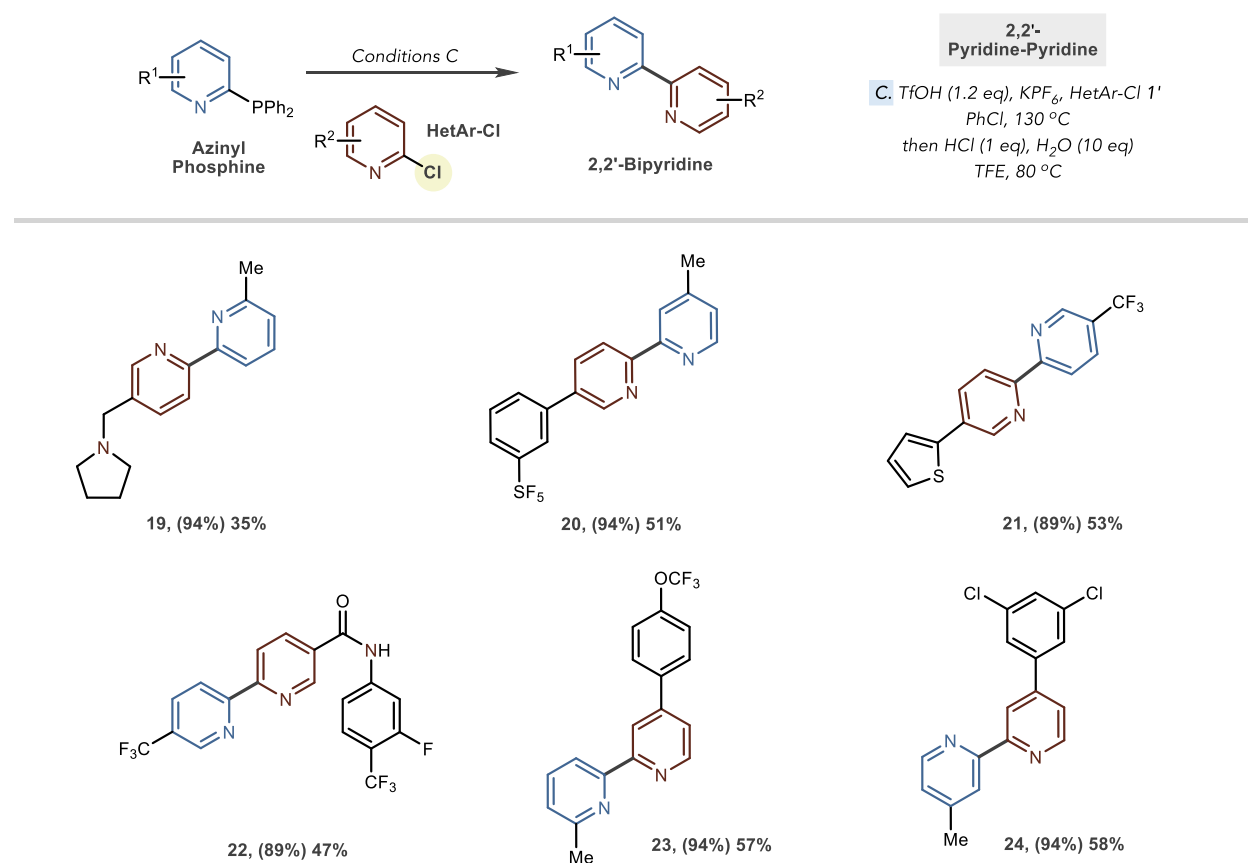
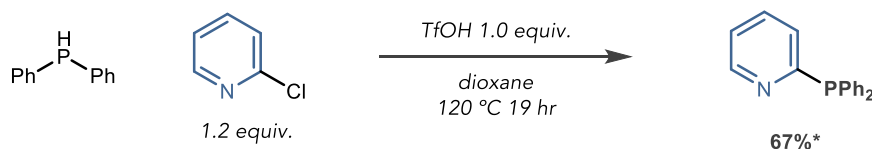


Figure 3.8. Scope of Ligand-Coupling for 2,2'-Bipyridine Synthesis.

for 2,2'-bipyridine couplings are lower than those observed for the other couplings and an investigation into this observation is currently underway in a collaboration between the McNally and Paton groups.

3.3.5 Azinyl Phosphine Synthesis through S_NAr on Chloroazines

Azinyl phosphines can be synthesized through an acidic S_NAr strategy. When diphenylphosphine was heated with 1.2 equivalents of 2-chloropyridine and 1.0 equivalent of TfOH in dioxane at 120 °C overnight, the desired 2-pyridyldiphenylphosphine was obtained in 67% yield (**Figure 3.9**). Use of acid in the reaction conditions helped increase the reactivity of the 2-chloropyridine and is hypothesized to help prevent undesired phosphonium salt formation by protonation of the resulting triarylphosphine.



* ^{31}P NMR Yield using tributylphosphine oxide used as an internal standard

Figure 3.9. Initial Result for Azinyl Phosphine Synthesis via Acidic S_NAr .

Phosphine synthesis was further optimized. The chloropyridine was made the limiting reagent to address a challenging separation between starting material and pyridylphosphine product and chlorobenzene used as the solvent to accommodate the higher temperatures (130 °C) required for reactivity at the 2-position of pyridine. The full optimized conditions and scope associated with pyridylphosphine synthesis can be seen in **Figure 3.10**. The resulting phosphines are stable on the benchtop with trace oxidation observed, however, a -20 °C fridge was used for long-term storage.

No desired phosphine was observed and only diphenylphosphine oxide and quinoline were present via ^1H and ^{31}P NMR when employing the optimized conditions to 4-chloroquinoline. This undesired pathway was due to the conditions used, and by lowering the temperature to 80 °C, removing the acid, and using TFE as the reaction solvent, 4-quinolinylphosphines are obtained in high yields (**Figure 3.10**). The conditions are effective on 2-chloroquinolines, isoquinolines,

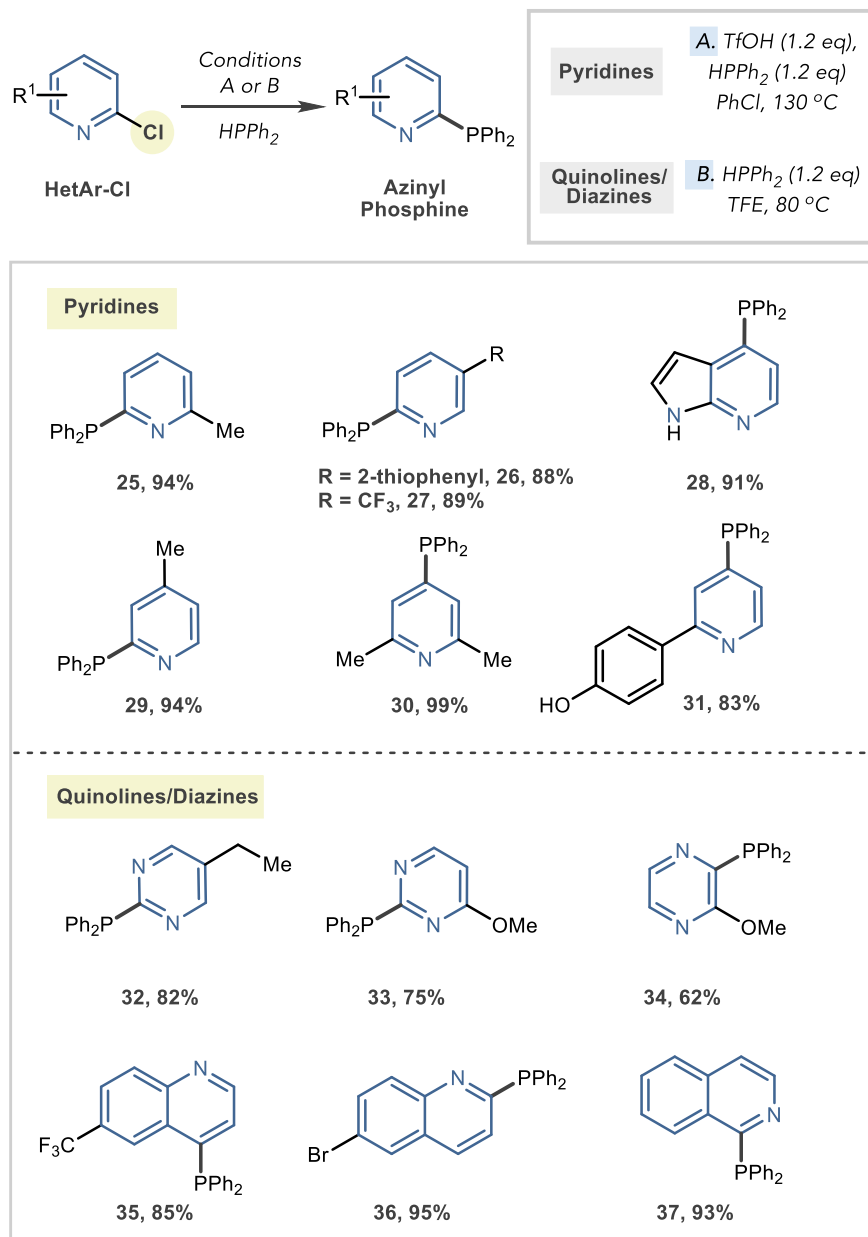


Figure 3.10. Select Scope of Azinyl Phosphines through Acidic $\text{S}_{\text{N}}\text{Ar}$ with Diphenylphosphine.

pyrimidines, and pyrazines. Other diazines, such as pyridazines, decompose under the reaction conditions, however, shortening the reaction time to <30 minutes improve their yield.

3.3.5 One-pot Coupling of Chloroazines

We envisioned that a 3-step one-pot process could synthesize bisazines (**Figure 3.11**). Chloroazines were transformed into azinyl phosphines under the standard set of phosphine formation conditions. Phosphonium salt formation and ligand-coupling reactions proceed smoothly. This strategy is a formal cross-electrophile coupling and the modified strategy applied to 2,4'-, 4,4', and 2,2'-bisazines.

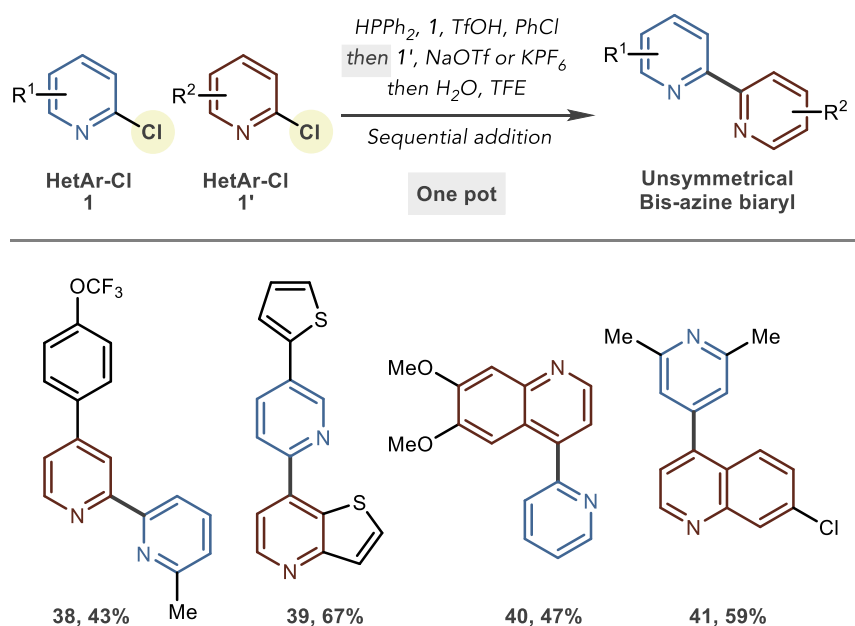


Figure 3.11. One-Pot Couplings of Chloroazines through $\text{S}_{\text{N}}\text{Ar}$ -Ligand-Coupling Strategy.

3.3.6 Guidelines and Limitations of $\text{S}_{\text{N}}\text{Ar}$ Ligand-Coupling Strategy

There are considerations for the order of phosphine synthesis. One should make the less $\text{S}_{\text{N}}\text{Ar}$ active coupling partner into the phosphine. This avoids undesired side-reactivity and prevents decomposition and the possibility of dimerization. As a rule, the reactivity can be classed by 2-chloropyridines < 4-chloropyridines < 2-chloroquinolines < 4-chloroquinolines = chlorodiazines

(**Figure 3.12, A**). As an example, if one is synthesizing a 2,4'-bipyridine, the 2-chloropyridine should be converted into the phosphine and then reacted with the 4-chloropyridine.

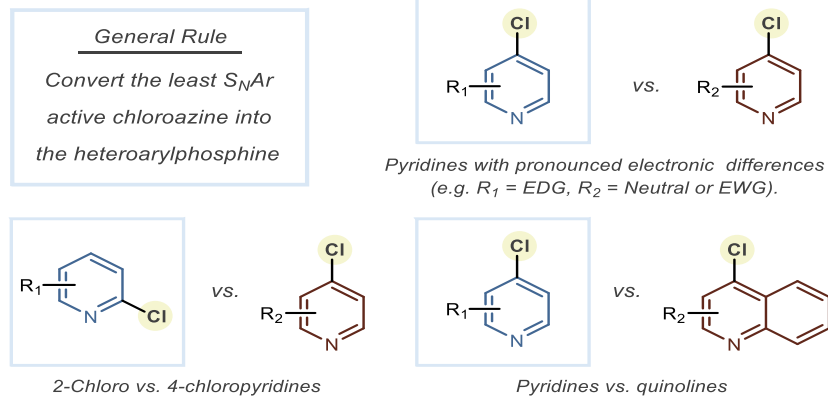
The main undesired pathway during phosphonium formation is a chloride salt metathesis reaction, that results in phosphine-chloride scrambling (**Figure 3.12, B**). This process occurs when the phosphonium salt is initially formed, but the liberated chloride counterion performs the reverse reaction. This process leads to an azinyl phosphine and chloroazine, and if the chlorination is unselective results in a mixture of coupling products after ligand-coupling is performed. This can be partially addressed by swapping the chloroazine that is being transformed into the phosphine, although the exact reasoning behind this is unknown.

The reactivity and limitations of coupling are tied to inherent S_NAr reactivity. A consequence is 3-chloropyridines are unreactive, while 2- and 4-chloropyridines are viable substrates. Pyridines with electron-donating groups are low yielding due to the lower S_NAr reactivity (**Figure 3.12, C**). When multiple S_NAr active halogens are present, poor selectivity is obtained and a complicated mixture of phosphine isomers and phosphonium salts result. Fluorinated 2-chloropyridines are poor electrophiles and result in decomposition and oxidation of the phosphine when applied in the reaction. Like our initial report, 3-iodo and 3-bromo pyridines dehalogenate under the reaction conditions and alkoxy groups were avoided due to a dealkylation pathway (**Section 2.3.6**).

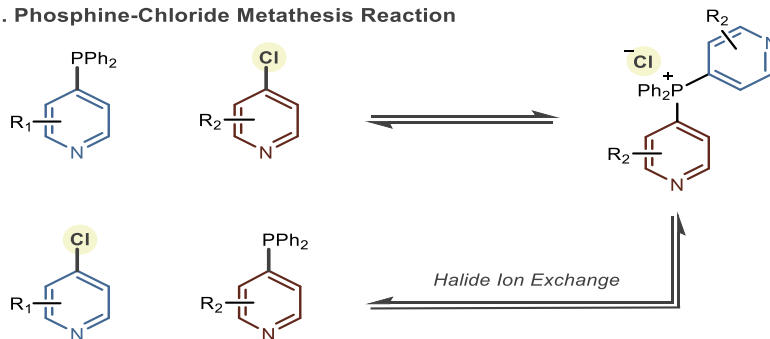
Certain substrates were unreactive during the ligand-coupling step, despite salt formation proceeding smoothly. 4,4'-biquinoline couplings remain as the phosphonium salt and more forcing coupling conditions led to undesired phosphine oxide or reversion to starting materials. When performing a 2,2'-bipyridine coupling, electron-donating amino groups directly off the pyridine

ring resulted in no desired reactivity. Similar to the case of 4,4'-biquinolines no desired product was observed and the phosphonium salt was not consumed.

A. Guidelines for Heteroarylphosphine Synthesis



B. Phosphine-Chloride Metathesis Reaction



C. Problematic Substrates for Phosphine Formation and Ligand-Coupling

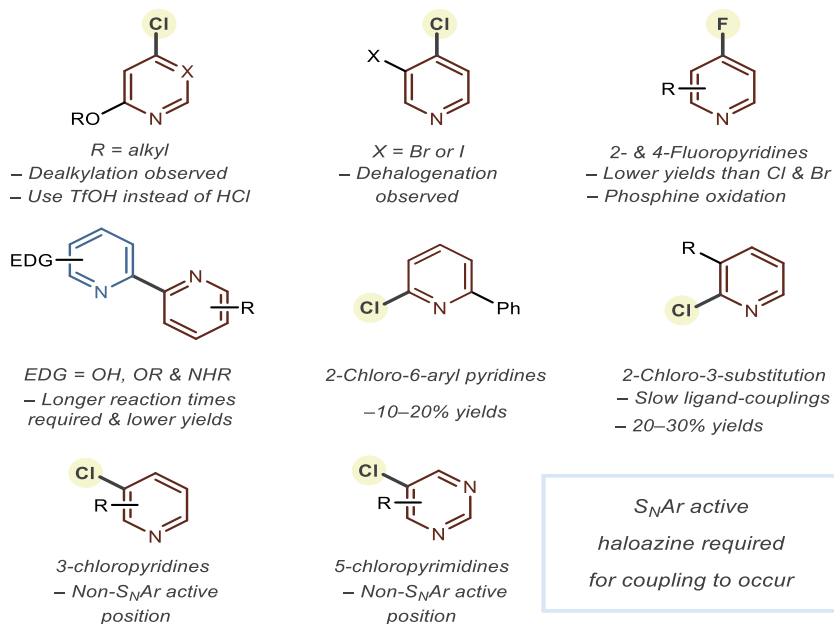


Figure 3.12. Challenges and Limitations of Tandem S_NAr -Ligand-Coupling.

3.4 Comparison to Alternative Cross-Coupling Methods

3.4.1 Comparison to Transition Metal-Catalysis

We next performed a series of comparisons to transition metal-catalyzed methods for bisazine synthesis. The S_NAr -ligand-coupling is tied to installing the C-P bonds via S_NAr and provides selectivity in poly-halogenated substrates. Using 4,7-dibromoquinoline as a model substrate, the S_NAr -ligand-coupling is completely selective for the 4-position coupling, while established Negishi and Stille coupling conditions give mixtures of coupling products (**Figure 3.13**).^{24,25}

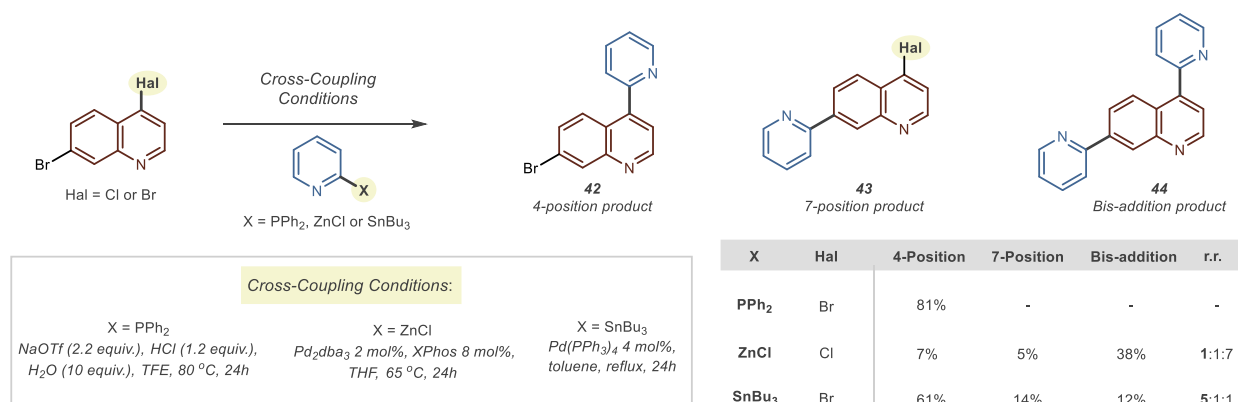


Figure 3.13. Selectivity Comparison to Transition Metal-Catalyzed Cross-Couplings.

We sought to show that the ligand-coupling strategy was equivalent or superior to previously developed reactions for 2,2'-bipyridine synthesis. We compared the ligand-coupling to Suzuki coupling conditions using 2-pyridyl potassium trifluoroborate or 2-pyridyl MIDA boronate as the nucleophilic coupling partner (**Figure 3.14**).^{17,18} Using both 2-chloro and 2-bromopyridine as coupling partners, the ligand-coupling method outperforms the Suzuki coupling reactions demonstrating the potential of this method to synthesize this motif. The azinyl phosphines tolerate Suzuki coupling conditions, using coupling conditions established by Fu.²⁶

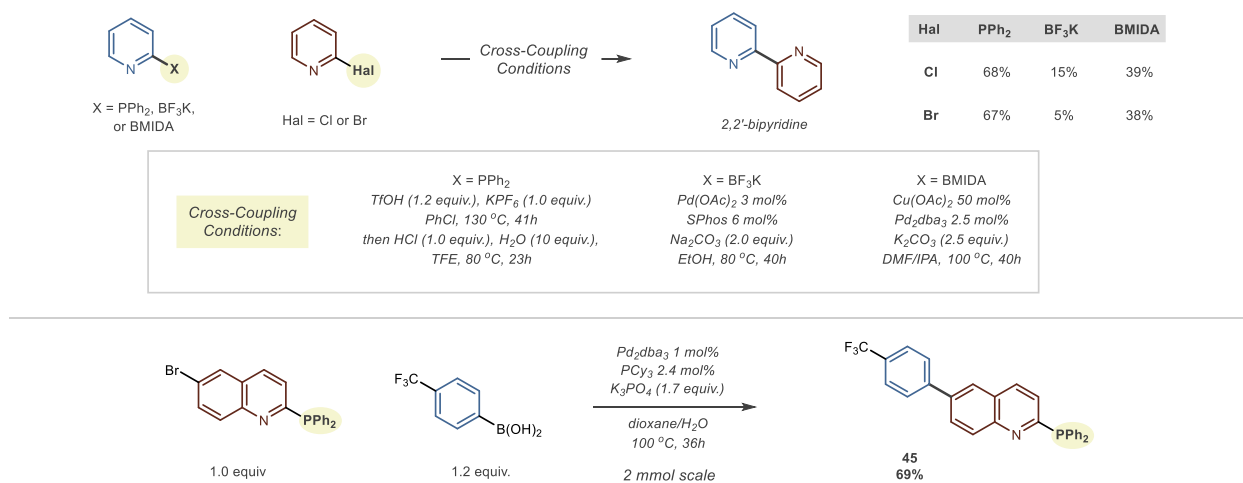


Figure 3.14. Comparison for 2,2'-Bipyridine Synthesis and Compatibility Under Suzuki Conditions.

3.4.2 Improvements to Previously Developed Phosphorus Ligand-Coupling

The tandem reaction provides improvements to our initial phosphorus ligand-coupling report.²⁷ The inherent selectivity of the triflyl activation strategy limits the ability to access valuable couplings such as 2,2'-bipyridine formation. By using the C-Cl bond, 2,2'- and 2,4'-bipyridines are easily synthesized that would not be accessible through the previously developed method. Triflic anhydride (Tf₂O) has shown a remarkable scope for pyridine activation.^{28,29} Certain functionalities such as alkyl amides, hydroxyl, and phenolic groups react with Tf₂O, but proceed through the S_NAr ligand-coupling conditions (**Figure 3.15**).³⁰ Additional substitution patterns are effective, such as 2,6-disubstituted and 2-trifluoromethyl pyridines.

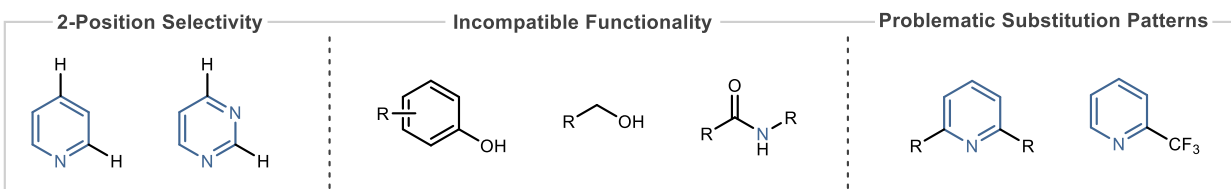


Figure 3.15. Limitations with Previous Ligand-Coupling Approach Addressed through S_NAr Strategy

3.5 Conclusion

Building on our initial report of phosphorus ligand-coupling for bisazine synthesis, a tandem S_NAr -ligand-coupling strategy was developed. This method enables an expanded scope of coupling partners and substitution patterns for bisazine formation and increases the functionalities that are tolerated. In particular, 2,2'-bipyridine synthesis was achieved through this method and provides a valuable alternative to metal catalysis for this important motif. The reaction is operationally simple and exploits abundantly commercially available chloroazines as coupling partners.

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Chapter Four

Facile S_NAr on Iodopyridines through *N*-Phosphonium Pyridinium Intermediates

4.1 Overview

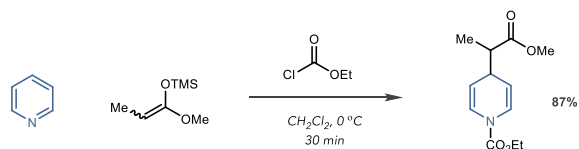
This chapter describes investigation into a S_NAr on iodopyridines using triarylphosphines. The reaction was serendipitously discovered and optimized as an alternative to triflic anhydride activation for C-P bond formation with a wide functional group tolerance. Investigation into the reactivity led to a proposed *N*-phosphonium-pyridinium generated *in situ* as the key intermediate. Trace amounts of iodine lead to an iodo-triarylphosphonium, which is attacked by the pyridine nitrogen, and the bis-cationic species is highly activated for S_NAr by another equivalent of phosphine. Evidence of the role of iodine is presented through addition of catalytic iodine turning on reactivity for bromo and chloropyridines that are unreactive. This reaction demonstrates the first example of *N*-phosphonium-pyridiniums in a synthetic method. Luke Koniarczyk ran the initial reaction and identified the formation of a pyridylphosphonium salt. This work culminated with publication in *SynLett* as part of the Modern Heterocycle Synthesis and Functionalization Cluster.¹

4.2 S_NAr Reactions of Pyridines

Pyridine activation is a strategy to increase the reactivity of the π -system for nucleophilic addition. An activating group, such as ethylchloroformate, followed by addition and elimination has been exploited for C-H functionalization of pyridines for a range of bond formations (**Figure 4.1, A**).^{2,3} Acid is often used to activate a pyridine for S_NAr reactions and similarly Lewis acids provide a route to facilitate additions (**Figure 4.1, B**).⁴ S_NAr on pyridines still often require strong

nucleophiles, such as alkoxides or organometallics, and high temperatures (>100 °C).^{4,5} The conditions required for phosphine addition to pyridines is discussed in **Chapter 3**.⁶ New strategies for pyridine activation for additions that demonstrate improved scope or reactivity are of value.

A. Pyridine Activation for Nucleophilic Addition: Akiba (1983)



B. Lewis Acid Catalyzed Activation of Pyridines: Williams (2015)

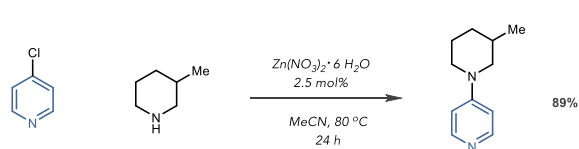


Figure 4.1. Select Examples of Activation of Pyridines for Nucleophilic Addition.

4.3 Results and Discussion

4.3.1 Optimization of Initial Phosphonium Formation

While investigating a strategy to synthesize pyridyl phosphonium salts reaction using 4-iodopyridine and triphenylphosphine, Luke Koniarczyk, a coworker in the McNally group, discovered 4-pyridyl phosphonium salt (**1**) could be obtained at room temperature when 2 equivalents of triphenylphosphine were stirred with 4-iodopyridine in CH_2Cl_2 (**Figure 4.2**). While the yield of the reaction and conversion were poor, the unusual reactivity for C-P bond formation led to the reaction being further investigated.

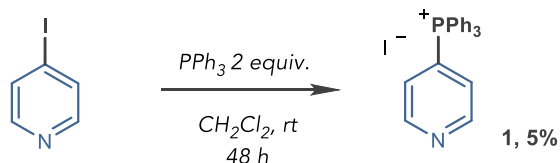


Figure 4.2. Initial Reaction for Phosphonium Formation via $\text{S}_{\text{N}}\text{Ar}$.

Following the initial result, a range of phosphines were tested (**Table 4.1**). More nucleophilic triethylphosphine (PEt_3) and tributylphosphine (PBu_3) provide limited yield increase (**entry 2,3**), while substituting two ethyl groups for a phenyl ring increase the yield to 79% (**entry 4**). Diethylphenylphosphine provided 86% of the 4-pyridyl phosphonium product (**entry 5**). While the increase in yield was promising, the requirement for storage under inert atmosphere makes

diethylphenylphosphine unattractive for the optimized reaction. Based on these results, we believed that an aryl ring was required for reasonable

Table 4.1. Optimization of Phosphonium Formation. *¹H NMR yield using triphenylmethane as internal standard. ‡One equivalent of phosphine used.

of	Entry	Phosphine	Solvent	Iodopyridine (%)*	Yield (%)*
	1	PPh ₃	CH ₂ Cl ₂	71	5
	2	P <i>n</i> Bu ₃	CH ₂ Cl ₂	82	5
	3	PEt ₃	CH ₂ Cl ₂	64	8
	4	PPh ₂ Et	CH ₂ Cl ₂	10	79
	5	PPhEt ₂	CH ₂ Cl ₂	4	86
	6	P(<i>p</i> -tol) ₃	CH ₂ Cl ₂	15	78
	7	P(<i>p</i> -anisole) ₃	CH ₂ Cl ₂	3	89
	8	P(<i>p</i> -anisole) ₃	CHCl ₃	1	85
	9	P(<i>p</i>-anisole)₃‡	CHCl₃	3	97

conversion and a more electron-rich phosphine would perform better. Tris-*para*-tolylphosphine give a reasonable yield at 78% (**entry 6**). Tris-*para*-anisolephosphine (*p*-OMePh₃P) provides excellent conversion to the desired product and chloroform (CHCl₃) as the reaction solvent allows lowering of the phosphine equivalents to one (**entries 7-9**).

4.3.2 Expansion of Iodopyridine Scope

We set out to determine the limitations of C-P bond formation (**Figure 4.3**). Starting with 3-substituted iodopyridines, electron-deficient and electron-rich pyridines are effective (**2-5**). 3,5-Dimethyl-4-iodopyridine (**6**) is also a competent substrate despite the additional sterics, although higher temperature (80 °C) is required. 2-Substituted pyridines are also competent, with functionality like 2-hydroxy (**7**) and 2-amino groups (**8**) tolerated in addition to phenyl derivatives (**9**). The ability to tolerate electron-donating groups at the 2- and 3-positions under a mild set of conditions demonstrates the unusual reactivity in this reaction. 2,3-Disubstituted pyridines are also effective (**10, 11**). S_NAr active chlorides are tolerated under the reaction conditions, with perfect regioselectivity for displacing the C-I bond (**11, 12**). Diazines are not effective under the reaction

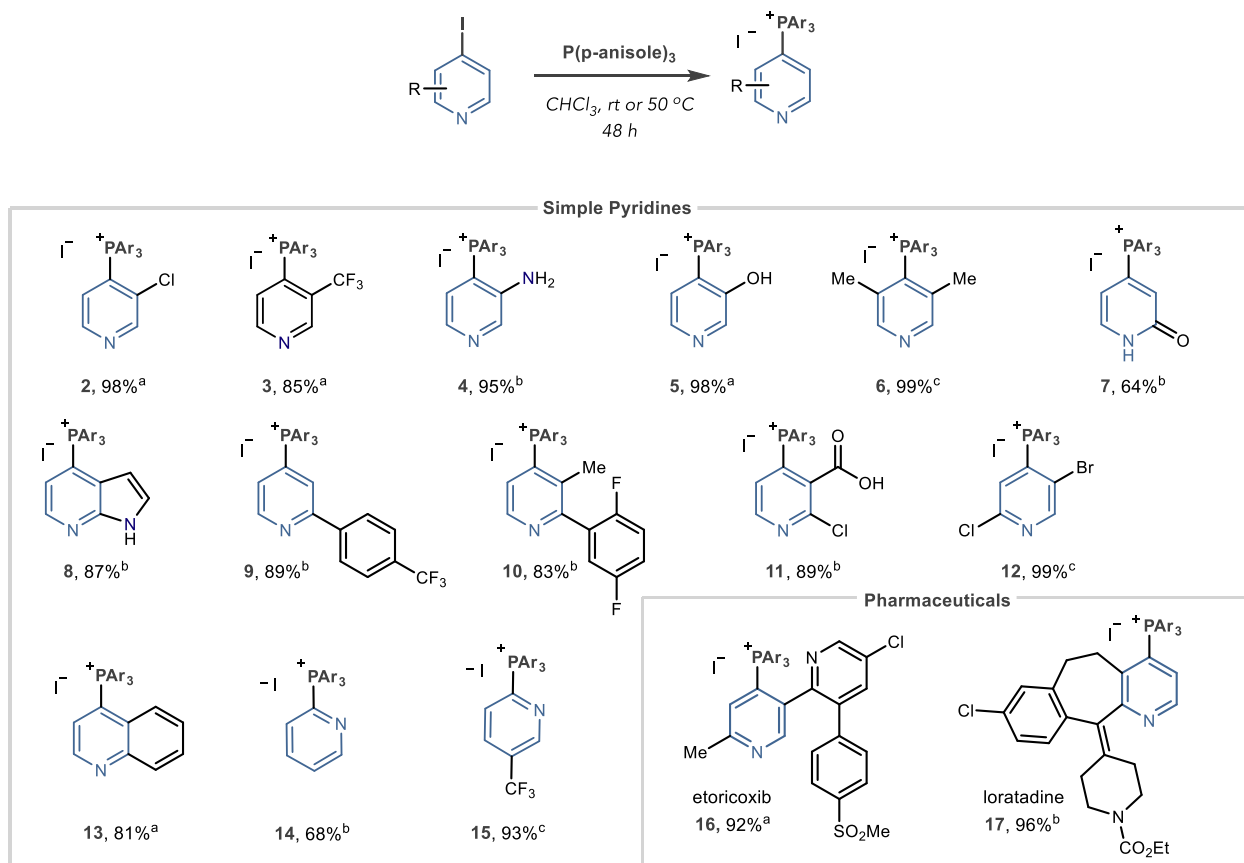


Figure 4.3. Scope of Iodopyridines for Phosphonium Formation. ^aReaction ran at room temperature. ^bReaction ran at 50 °C. ^cReaction ran at 80 °C.

conditions, despite being more S_NAr active.⁷ 4-Iodoquinoline reacts cleanly and 2-iodopyridines transformed to the corresponding phosphonium salt at 80 °C (**13-15**). Iodinated pharmaceutical compounds, loratadine and etoricoxib underwent C-P bond formation in high yields (**16, 17**).

4.3.3 Limitations of Iodopyridine to Phosphonium Salt Reaction

There were limitations for the desired reactivity (**Figure 4.4**). Pyridines with a bulky 2-substituent or 2,6'-disubstituted are ineffective. 2-Iodopyridines have a limited scope and required higher temperatures for the bond formation. An example of a 2-fluoropyridine gave a difluorophosphorane biproduct and defluorination of the starting material with no phosphonium salt observed. Diazines, such as pyrazine and pyrimidine, provided limited product and decomposition of the iododiazine, and a similar outcome was observed with 2-methoxypyridine. 2,4-Diiodopyridine gave a mixture of 2- and 4-position isomers when ran at room temperature. When 2-iodo-3-hydroxypyridine was employed in the reaction, 25% of the desired phosphonium salt was observed along with 53% of an aryloxyphosphonium salt.

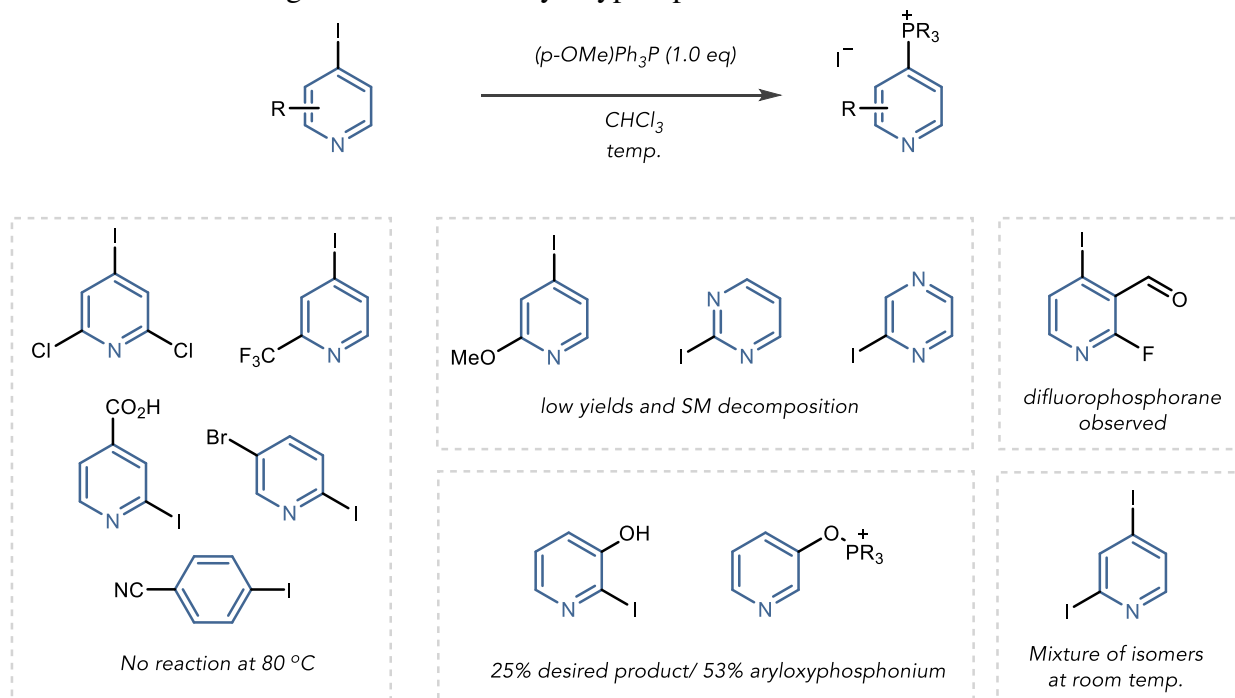
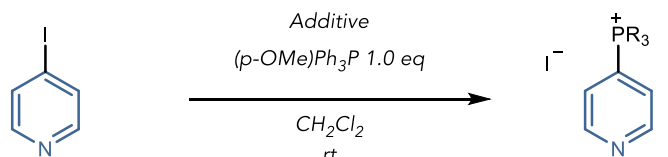


Figure 4.4. Limitations of Iodopyridine to Phosphonium Reaction.

4.4 Mechanism for Facile S_NAr on Iodopyridines

We next turned to investigating the mechanism and activation mode. Additives were spiked in the reaction to gain insight into the reactivity (**Table 4.2**). The reaction was unaffected by addition of water while the presence of cesium carbonate or running the reaction in methanol completely shut down the reaction (**entries 1-3**). Since iodoarenes are known to be light sensitive, the reaction was ran with rigorous exclusion of light, however the yield was unaffected (**entry 4**). Interestingly, when 4-iodopyridine was freshly sublimed prior to the reaction, a slower rate was observed indicating that there was a potential contaminate speeding up the reaction (**entry 5**).

Table 4.2. Additive Study for Phosphonium Formation. * 1H NMR yields shown using triphenylmethane an internal standard. $\dagger$ Products were not detected by LCMS or 1H NMR. $\ddagger$ MeOH was used as the solvent instead of CH_2Cl_2 .

		
Entry	Conditions/Additive	Yield (%)*
1	H ₂ O (10 eq)	83
2	Cs ₂ CO ₃	n.d. $\dagger$
3	MeOH $\ddagger$	n.d. $\dagger$
4	Light excluded	83
5	Sublimed Iodopyridine	66
6	Standard	87

When other 4-halopyridines were employed in the reaction, such as 4-chloro and 4-bromopyridine, no desired product was observed (**Figure 4.5, A**). This goes counter to the established trends for S_NAr halogen rates, where fluoro and chloro are the fastest followed by bromo, with few examples of iodopyridines being used.⁷ This reactivity led us to suspect a potential radical mechanism. When known radical initiator azobisisobutyronitrile (AIBN) was spiked into the reaction (**Figure 4.5, B**), no rate increase was observed when compared to the standard conditions. When radical trap 4-iodo-3-allyloxypyridine was subjected to the reaction, no

cyclization onto the pendent alkene was observed indicating the reaction does not proceed through a radical intermediate (**Figure 4.5, C**).⁸

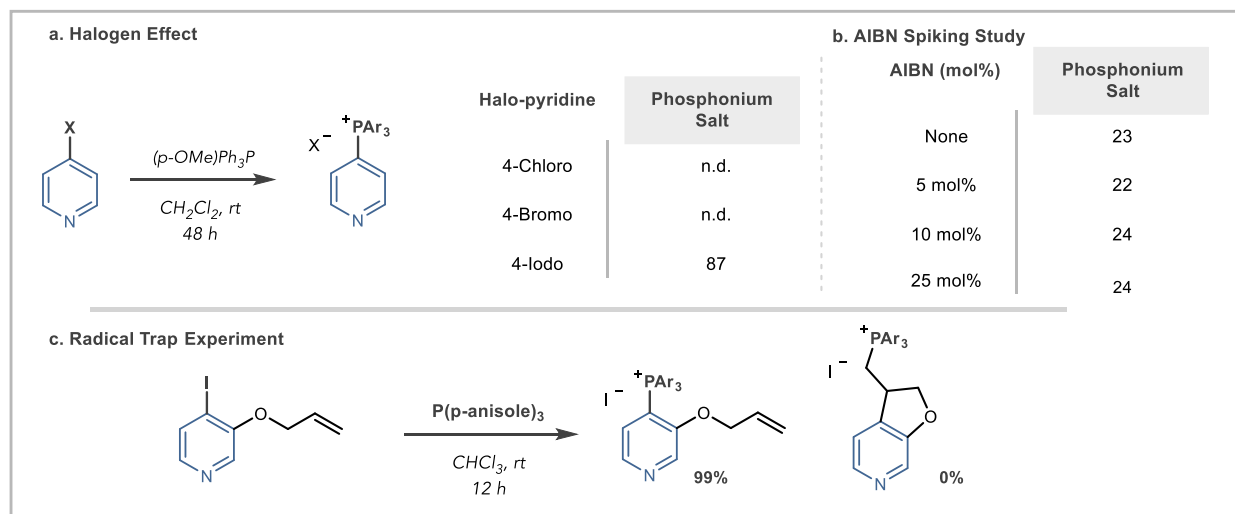


Figure 4.5. Halogen Effect on Phosphonium Formation and Radical Mechanism Probes.

The lack of radical pathway led us to consider an activated pyridine as the key intermediate under the reaction conditions. We were interested in the effect sublimation of the 4-iodopyridine had on the reaction (*vide supra*). We hypothesized that iodopyridines could contain a trace amount of iodine (I_2), which reacts with the phosphine to form an iodophosphonium salt.⁹ The resulting iodophosphonium can then be attacked by the pyridine nitrogen, resulting in an *N*-phosphonium-pyridinium species that would be extremely electrophilic (**Int I**). Once the activation occurs, another equivalent of the phosphine can undergo addition to the pyridine ring through an S_NAr pathway resulting in a tris-cationic intermediate (**II**). The activating group is then cleaved through addition of the iodine counterion or by a 4-iodopyridine. The proposed mechanism for the reaction is presented in **Figure 4.6**.

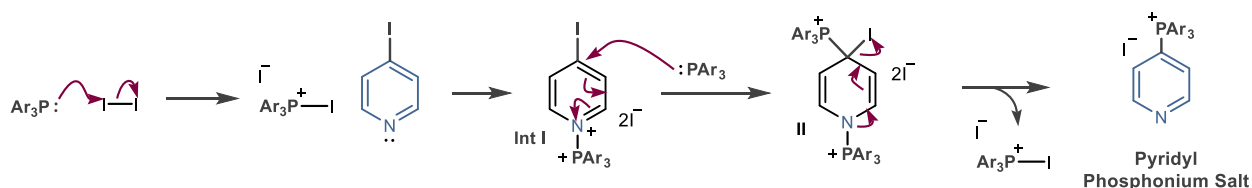


Figure 4.6. Proposed Mechanism for Phosphonium Formation from Iodopyridines.

Our proposed *N*-phosphonium-pyridinium species have been reported previously in the literature. Dutton and Weigand have both reported synthesis of a 4-dimethylaminopyridine (DMAP) derived *N*-phosphonium-pyridinium using triphenylphosphine and trimethylphosphine respectively (**Figure 4.7, A**).¹⁰⁻¹³ The amino group serves to stabilize the positive charge and these bis-cationic salts can be isolated, however neither group pursued any synthetic application of these species. To provide support to our proposed mechanism, we performed spiking studies with iodine with 4-chloro, 4-bromo, and 4-iodopyridines. When iodine was excluded from the reaction, 4-chloro and 4-bromo pyridine were unreactive. Addition of 10 mol% of iodine into the reaction resulted in comparable yields between each of the halogens tested in the study (**Figure 4.7, B**). This study provides support for the proposed mechanism, and further ¹H NMR studies support the formation of an *N*-phosphonium pyridinium species over an *N*-iodopyridinium.

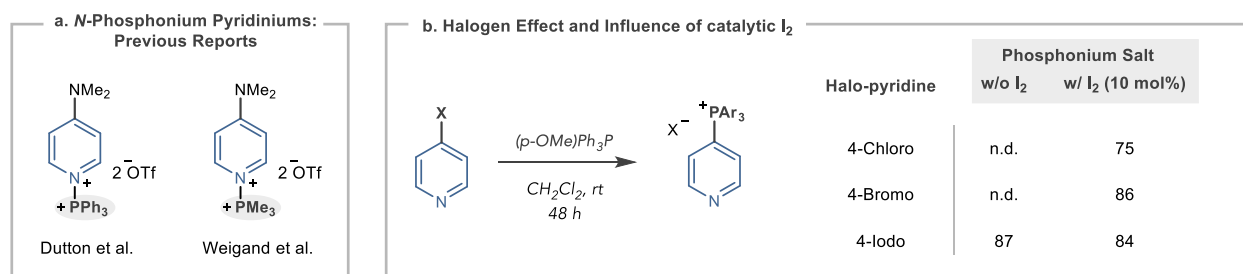


Figure 4.7. Previous Examples of *N*-Phosphonium Pyridiniums and Iodine Spiking Study.

4.5 Conclusion

This chapter describe the development of an *S_NAr* reaction on iodopyridines using phosphine nucleophiles. The reaction shows a broad scope and tolerates electron-rich pyridines that are problematic under traditional *S_NAr* conditions. An investigation into the mechanism for the reaction provided support for an *N*-phosphonium-pyridinium bis-cation as the key intermediate. This represents the first example of phosphonium activation of pyridines being used in a synthetic strategy and further development of this strategy is ongoing in the McNally group.

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Chapter Five

Selective Functionalization of Pyridines via Zincke Imine Intermediates

5.1 Overview

This chapter describes a ring-opening-functionalization-ring-closing sequence for pyridine derivatization. As shown in **Section 1.4**, the lack of π -nucleophilicity of pyridine limits the ability to perform classical aromatic functionalizations reactions, such as electrophilic aromatic substitution (S_EAr). Our strategy overcomes this challenge by performing a ring-opening reaction on pyridine using a Zincke-type reaction, transforming the π -system from electron-deficient to electron-rich. The Zincke imine intermediate enables mild halogenation of pyridines with complete regioselectivity and a broad scope. Other functionalizations, such as C-C bond formations and radical reactions, are also effective. Jeff Levy, a coworker in the McNally lab, developed the halogenation conditions and performed the halogenations on the building block examples. Hillary Nguyen and Ben Uhlenbruck, McNally lab coworkers, performed reaction development for pyridine-pyridine couplings and radical reactions, respectively. Louis de Lescure, a joint student between the McNally and Paton labs, has performed computational studies into the selectivity and ring-opening. Work presented in this chapter is currently ongoing in the McNally group.

5.2 Installation of Functional Handles at the 3-Position of Pyridine

Selective functionalization of pyridine C-H bonds is of interest to synthetic chemists. While C-H activation strategies have been developed to functionalize pyridine,^{1,2} each different bond formation requires a new set of conditions to be developed and optimized. An alternative strategy

for functionalization is to install a versatile functional handle at the desired position on pyridine and use the versatility to achieve a range of bond formations. The McNally group has addressed the challenge for functionalizing the 4-position on pyridine through pyridylphosphonium salts.³⁻¹⁶ (**Figure 5.1, left**). Our attention turned next to addressing the challenges of C-H functionalization of the 3-position on pyridine (**Figure 5.1, right**).

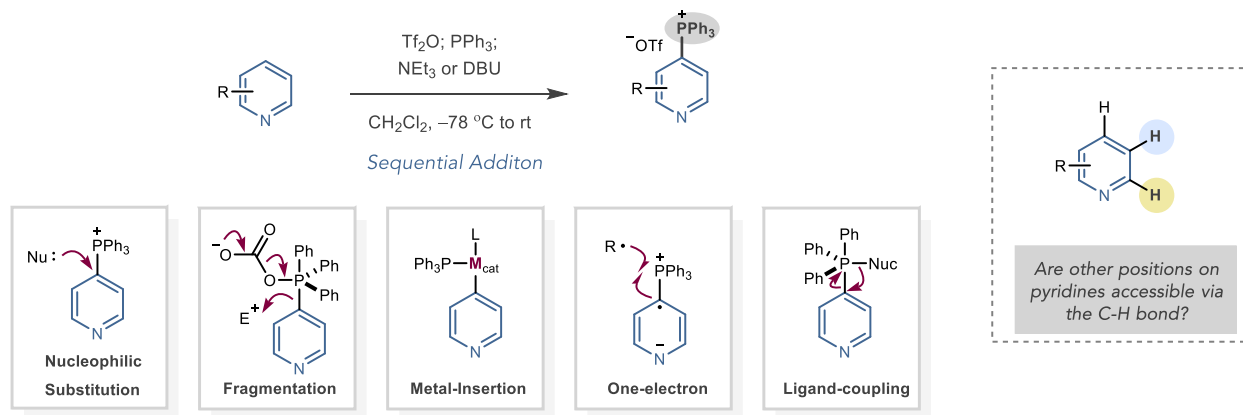


Figure 5.1. Phosphonium Salts for 4-Position Functionalization and Goal to Extend to 3-Position.

Halogens bonded to aromatic rings are one of the most versatile functional handles in organic synthesis and undergo a number of bond formations through transition metal-catalysis, metallaphotoredox approaches, and halogen-metal exchanges.¹⁷⁻²⁰ Accessing 3-halogenated pyridines is limited to relatively simple building block-type pyridines due to the conditions required to install the halogen (**Figure 5.2, A**).²¹ Elemental bromine and fuming sulfuric acid are required on non-activated pyridines due to the π -nucleophilicity (**Section 1.2**).²¹ Modern methodologies have been developed to address 3-position derivatization of pyridines. One of these methods is iridium-catalyzed borylation, developed by Ishiyama, Miyaura, and Hartwig (**Figure 5.2, B**).²²⁻²⁴ In this method, an Ir(I) complex reacts with B_2pin_2 and a bipyridine ligand to generate an active Ir(III) catalyst. C-H activation proceeds at the 3-position with reasonable selectivity (2:1 3- vs 4-pos on unsubstituted pyridine).²⁴ On pyridines with a 2-substituent, regioselectivity is governed by sterics resulting in C-B bond formation at the 5-position over the 3-position, however

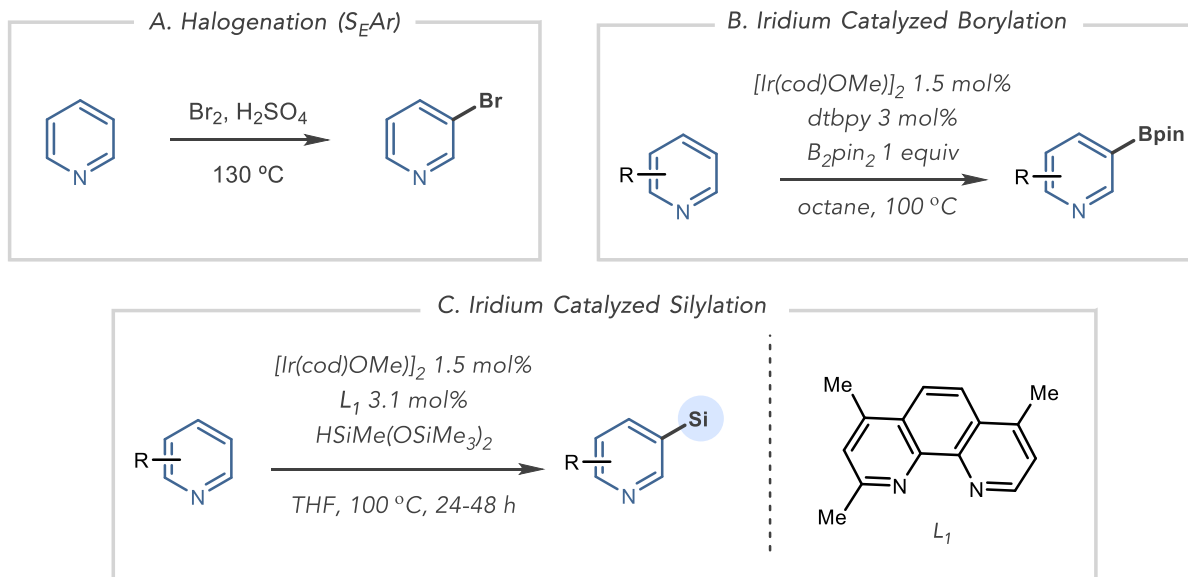


Figure 5.2. Strategies for Versatile Functional Group Installation at the 3-Position of Pyridines.

still results in a mixture of 4-pos and 5-pos isomers (1:1).^{22,24} The Bpin group can be derivatized through metal-catalyzed cross-couplings, such as the Suzuki reaction. A related method for 3-selective pyridine functionalization is iridium-catalyzed silylation, pioneered by Li, Shi, and Hartwig (**Figure 5.2, C**). Like iridium-catalyzed borylation, this functionalizes the 3- or 5-position on pyridines, however regioselectivity is a potential challenge.^{25,26} The silyl group can be derivatized through cross-couplings or transformed into a halogen.²⁷ Borylation and silylation of pyridines through C-H activation are the current “state-of-the-art” for installing a functional handle at the 3-position of pyridines.

5.3 Pyridine Functionalization through Ring-Opening-Functionalization-Ring-Closure

Strategy

5.3.1 Proposed Strategy for Polarity-Inversion of Pyridine π -System

We envisioned a facile halogenation of pyridines through disruption of the aromatic ring. An outline of the proposed strategy is shown in **Figure 5.3**. Through an activation strategy and nucleophile, a ring-opening of the pyridine occurs (**Int I**). The ring-opened intermediate results in

a series of polarized alkenes and can be reacted with an electrophile forming **1**. After the desired bond formation, ring-closure provides the 3-substituted pyridine product (**2**). The overall strategy provides a route to polarity-inversion of the pyridine π -system, equating the reactivity to an enamine or electron-rich aromatic and expanding the possible pyridine functionalization strategies to a range of established reactions.

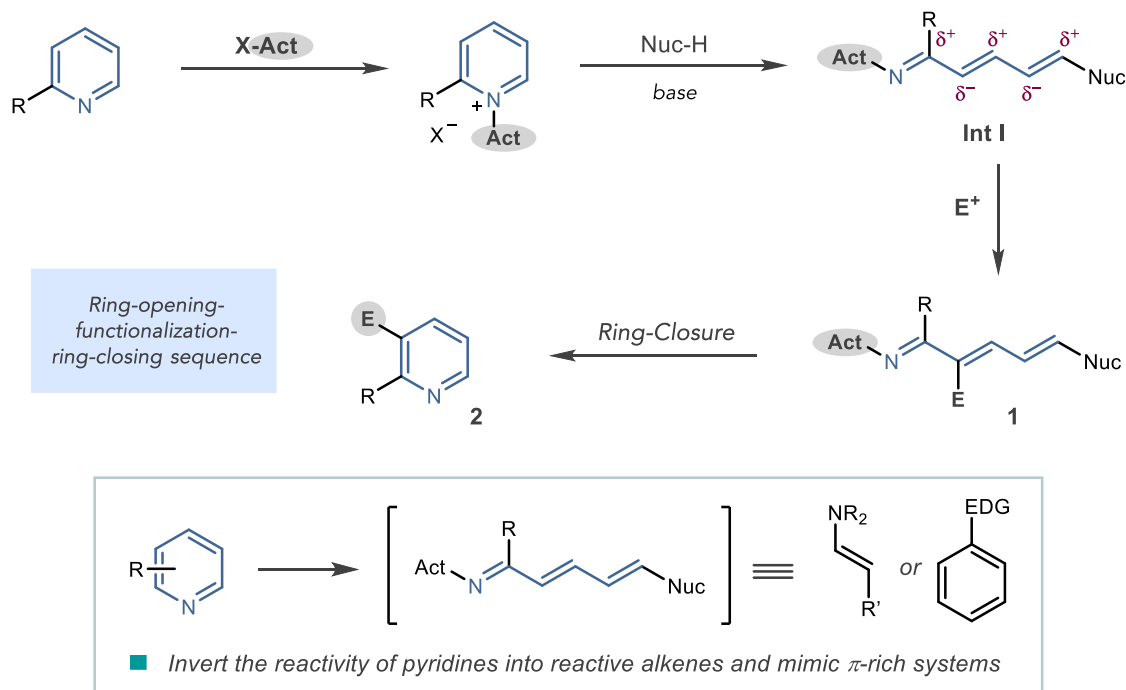


Figure 5.3. Proposed Strategy for Pyridine Reactivity Inversion.

5.3.2 Zincke Reaction for Pyridine Functionalization

Our proposed strategy for ring-opening was inspired by reactivity established in the Zincke reaction, a reaction commonly employed to produce *N*-aryl or *N*-alkyl pyridiniums (**Figure 5.4**)²⁸⁻

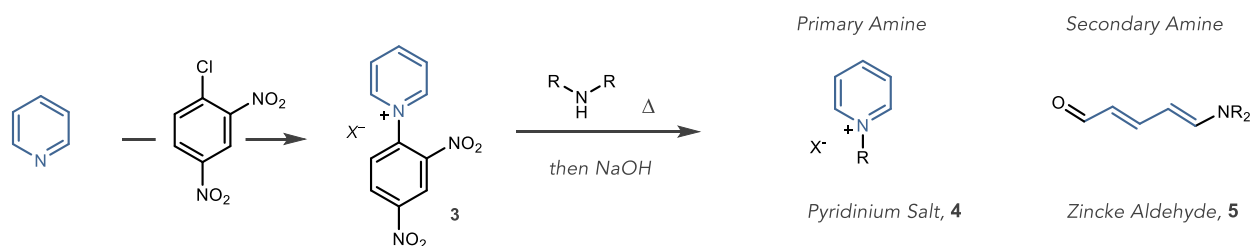


Figure 5.4. The Zincke Reaction for Pyridinium Metathesis or Ring-opening of Pyridines.

³⁰ Originally reported in 1904 by Zincke, a pyridine is activated with 1-chloro-2,4-dinitrobenzene through an S_NAr reaction to generate *N*-arylpyridinium **3**, which then reacts with a primary amine forming an *N*-substituted pyridinium (**4**).³¹⁻³³ Alternatively, reaction of the *N*-arylpyridinium with a secondary amine produces a Zincke aldehyde (**5**).³⁰ Similar activation strategies, using cyanogen bromide and sulfur trioxide as the activating groups, for pyridine ring opening have been reported.³⁴⁻³⁶ The Zincke reaction has also been employed for natural product synthesis, notably by the Vanderwal group in their synthesis of strychnine.^{29,37} Using Zincke aldehydes as intermediates in natural products is their primary application in organic synthesis outside of pyridinium formations.

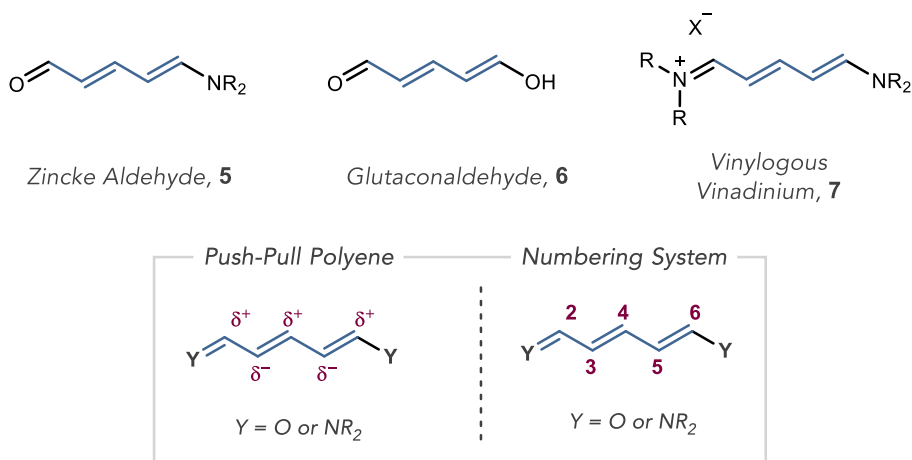


Figure 5.5. Zincke Aldehydes and Related Scaffolds.

Zincke aldehydes (**5**) glutaconaldehydes (**6**), and vinylogous vinadiniums (**7**) (Zincke iminiums) have seen use as routes to functionalized pyridines. The donor-acceptor nature of the polyene scaffold makes these structures attractive intermediates in synthetic routes (**Figure 5.5**). Carbons at the 3 and 5 positions of the structure have nucleophilic (δ^-) character while the 2, 4, and 6 positions can be viewed as electrophilic (δ^+). The lone pair of the heteroatom has resonance throughout the π -system and the delocalization of the electrons results in a brightly colored species.³⁸ Recently Zincke aldehydes have been exploited as precursors for cyanine dyes due to

their visible light absorbance.³⁹ This section will focus on the functionalization of the carbon backbone of Zincke aldehydes and related systems.

The nucleophilic nature of the Zincke aldehyde backbone is observed in the reactivity of related glutaconaldehydes. Bis-deuteration of **6** is achieved by heating in D₂O and reaction with bromine results in mono or bis-bromination of the 3- and 5-positions (**Figure 5.6, A, B**).^{40,41} While two nucleophilic sites are present in the molecule, a single halogenated product at the 3-position is observed when a slight excess of Br₂ is employed. Reaction with a Vilsmeier reagent results in formylation of the Zincke iminium **7** (**Figure 5.6, C**).⁴² These systems are symmetrical and fail to give an indication of the regioselectivity for the bond formation itself. An unpublished result from the Vanderwal group indicates that when unsymmetrical systems are used, initial arylation with diphenyliodonium tetrafluoroborate occurs selectively at the 3-position (**Figure 5.6, D**).⁴³ Despite this results, the regioselectivity for functionalization of Zincke-type systems with electrophiles has not been extensively studied.

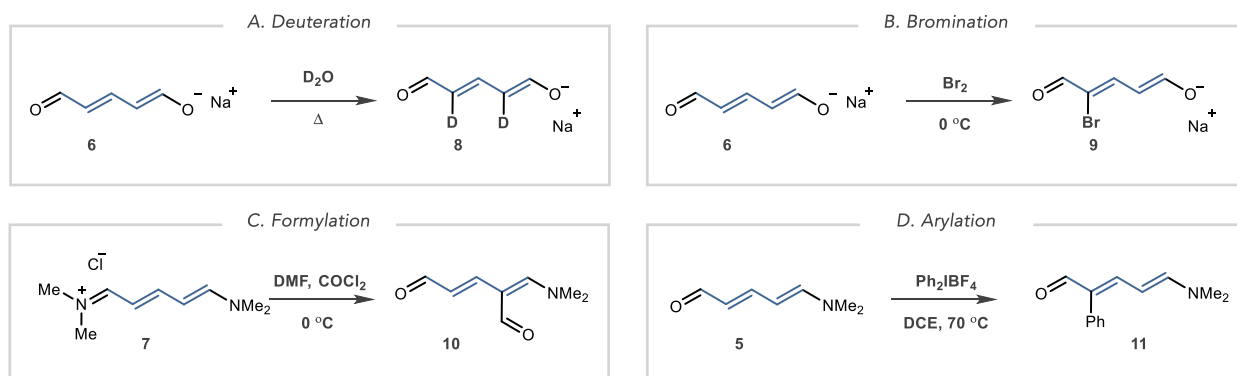


Figure 5.6. Examples of Electrophilic Functionalization of Zincke Aldehydes and Related Systems.

Zincke-type aldehydes and iminiums can be readily converted back to the parent pyridine. When a Zincke aldehyde is reacted with a primary amine and heated, an *N*-alkyl pyridinium is formed (**Figure 5.7, A**). A similar reaction with anilines requires higher temperatures. Importantly for our proposed strategy, reaction of ammonium acetate (NH₄OAc) with a Zincke aldehyde or

glutaconaldehyde results in conversion back to pyridine and this approach can incorporate ^{15}N labels into pyridines (**Figure 5.7, B**).³⁶

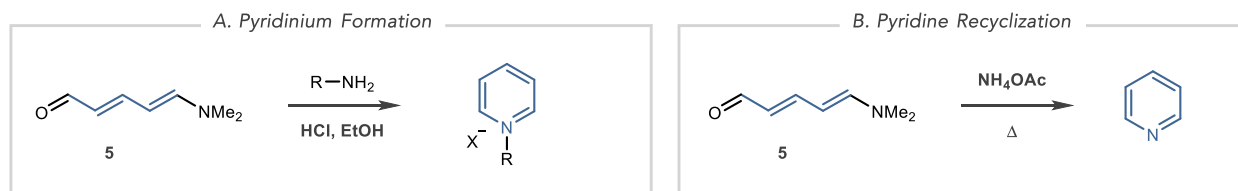


Figure 5.7. Recycling of Zincke Aldehydes Using Amines or Ammonium Salts.

5.3.3 Limitations of the Zincke Reaction for Pyridine Ring-opening

The Zincke reaction is a convenient route to *N*-alkyl and *N*-aryl pyridiniums and can be exploited in natural product synthesis.²⁹ Limitations to the ring-opening, however, hold back the application of this chemistry as a synthetic method. 1-Chloro-2,4-dinitrobenzene activation fails when applied to 2-substituted pyridines (**Figure 5.8**).⁴³ While this can be worked around for natural product synthesis, any methodology based on the established strategy would be severely limited in positional group tolerance on the pyridine ring. Typically, high temperatures are required for high conversion in the Zincke reaction and the Zincke aldehyde uses alkali conditions (NaOH) which are problematic for base sensitive functionalities.

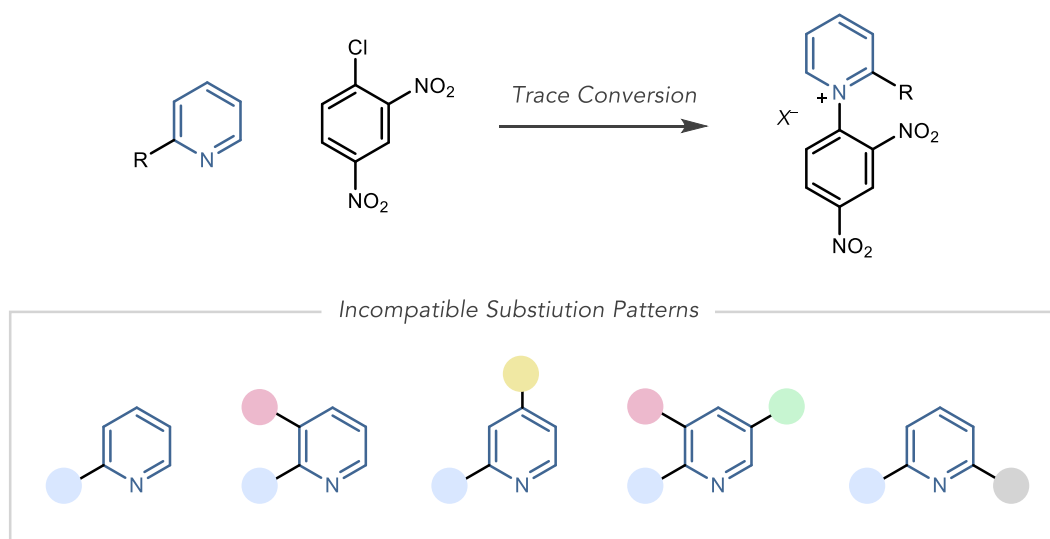


Figure 5.8. Limitation of the Zincke Ring-Opening of Pyridines.

5.4 Results and Discussion

5.4.1 Triflic Anhydride Activation for Zincke-type Ring-openings on Pyridine

A goal in our lab has been to expand the scope of pyridines that can undergo the Zincke reaction to access ring-opened derivatives. We have previously found that triflic anhydride ($\text{ Tf}_2\text{O}$) activates a range of pyridines and diazines, including complex drug-like fragments and pharmaceuticals (**Section 1.4.3**). While attempting to use triflyl activation for pyridine amination with piperidine, we observed Zincke-type ring opening under the reaction conditions (**Figure 5.9, top**). Conversion to a mixture of Zincke imine (**12**) and iminium (**13**) was obtained on pyridine using 3 equivalents of piperidine. After our initial result, we found Toscano previously reported $\text{ Tf}_2\text{O}$ activation for Zincke-type reactivity using diethyl amine in excess resulting in Zincke iminium (**14**) (**Figure 5.9, bottom**).⁴⁴ We turned to optimizing the ring-opening and sought to exclusively obtain *N*-triflyl Zincke imines.

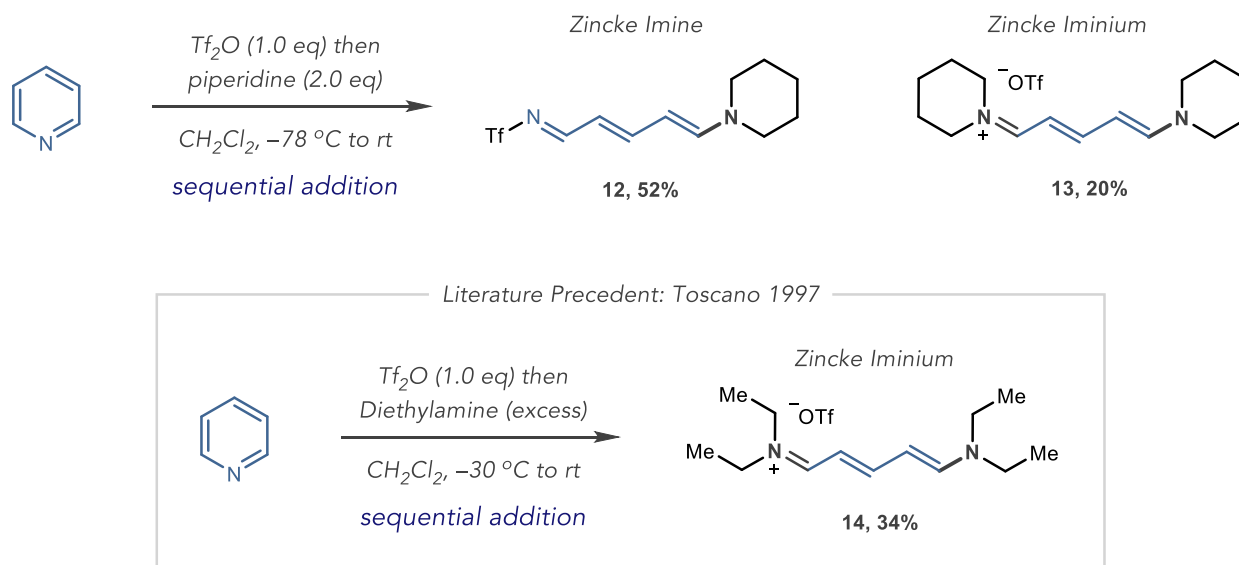
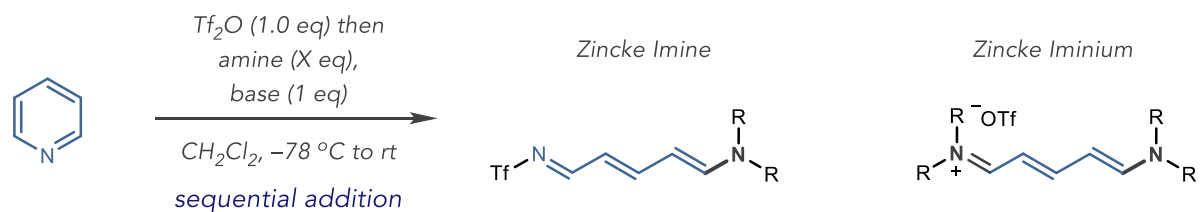


Figure 5.9. Initial Reaction for *N*-Triflyl Zincke Imines and Literature Precedent.

A series of optimization results can be seen in **Table 5.1**. Using pyridine as our model substrate, we first explored lowering the equivalents of piperidine in the reaction and incorporating

Table 5.1. Optimization of *N*-Tf Zincke Imine Formation. *Yield determined by ¹H NMR using triphenylmethane as an internal standard.



Entry	Amine (eq)	Base (eq)	Zincke Imine (%)*	Zincke Iminium (%)*
1	piperidine (2)	none	52	20
2	piperidine (1)	Et ₃ N (2)	51	15
3	piperidine (1)	lutidine (1)	75	6
4	piperidine (3)	none	-	78
5	pyrrolidine (2)	none	28	57
6	<i>N</i> -benzylmethyl amine (2)	none	52	6
7	dibenzylamine (2)	none	88	-
8	dibenzylamine (3)	None	98	-
9	dibenzylamine (1.2)	collidine (1)	97	-

the use of amine bases (**entries 2,3**). The results showed improvement in selectivity between Zincke imine and iminium. Use of 3 equivalents of piperidine led to complete conversion to the Zincke iminium product (**entry 4**). Our attention turned next to exploring other secondary amines (**entries 5-7**). More nucleophilic pyrrolidine resulted in higher conversion to the undesired Zincke iminium while *N*-methylbenzyl amine showed reasonable selectivity for *N*-triflyl imine formation. When dibenzylamine was employed, complete selectivity for the desired imine product was observed and increasing to 3 equivalents of amine proved to not impact selectivity (**entry 8**). Further optimization showed that the amine equivalents can be lowered to 1.2 when 1 equivalent

of collidine is used as a base in the reaction (**entry 9**). While CH₂Cl₂ proved effective for pyridine as a substrate, ethyl acetate (EtOAc) is more general for all substrates.

Following optimization, our attention turned to the scope of the Zincke ring-opening on pyridines (**Figure 5.10**). Our experience with Tf₂O gave us an understanding of the potential scope for activation and we began investigating substitution patterns on the pyridine ring itself. Pyridines with substituents at the 3-position ring-open under the optimized conditions, with reasonable

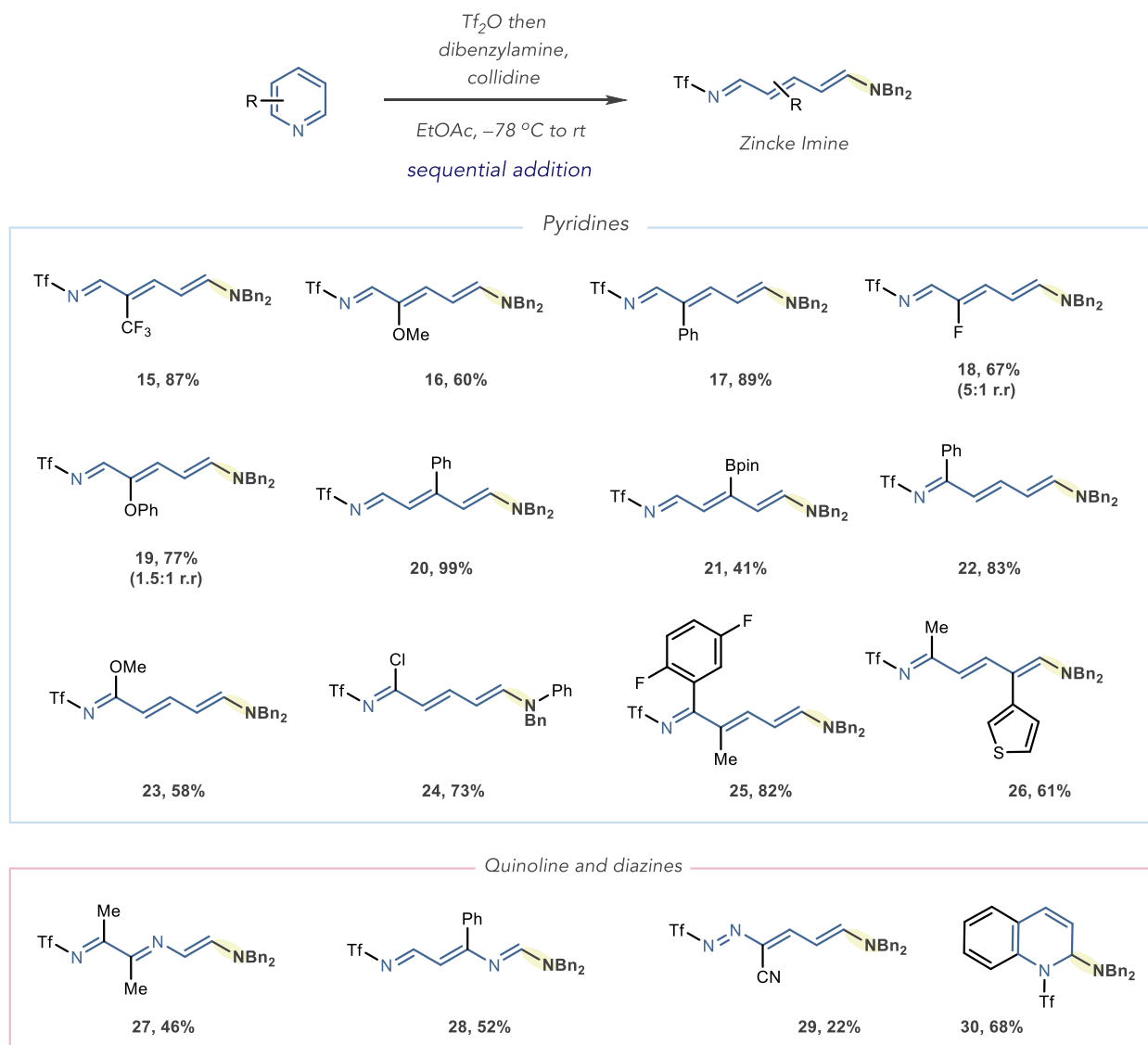


Figure 5.10. Selected Scope for *N*-Tf Zincke Imine Formation. Yields determined by ¹H NMR using triphenylmethane as an internal standard.

yields obtained with electron-withdrawing, electron-donating, and neutral groups (**15-19**). Addition of dibenzylamine occurs selectively *para* to the existing 3-substituent in most cases, with 3-phenoxy and 3-fluoro pyridines providing mixtures of both attack at the 2- and 6-positions (**18,19**). While 4-aryl and 4-alkyl substituents are not viable substrates in our previously developed phosphonium formation, they ring-open under the reaction conditions (**20**). Electron-withdrawing trifluoromethyl and cyano groups are also tolerated at the 4-position and 4-Bpin-pyridine provides reasonable yield of product (**21**). Pyridines with substituents at the 2-position are effective substrates, with examples of 2-phenyl, 2-methyl, 2-methoxy, and 2-amino pyridines (**22,23**). 2-Halo pyridines do not provide the desired product when dibenzylamine is used, but by switching the nucleophile to *N*-benzylaniline reasonable yields can be obtained (**24**). These 2-substituted examples are not viable for the traditional Zincke reaction giving limited amounts of product due to the dinitrobenzene activating group.⁴³ Disubstituted pyridines can also be ring-opened (**25, 26**) along with diazines, such as pyrazines (**27**), pyridazines (**28**), and pyrimidines (**29**), although these are more susceptible to iminium formation. Quinoline and isoquinolines do not ring-open under the reaction conditions, however a dearomatized *N*-Tf adduct forms instead (**30**). While the resulting Zincke imines are stable to silica gel flash column chromatography, pure products are achieved as brightly colored solids through precipitation from excess hexanes.

We turned to applying the ring-opening to more complex substrates (**Figure 5.11, top**). Bipyridines ring-open selectively and follow the established rules regarding triflic anhydride activation of pyridines (**31**).⁸ Functionalized pyridines containing esters (**32**), amines (**33**), and

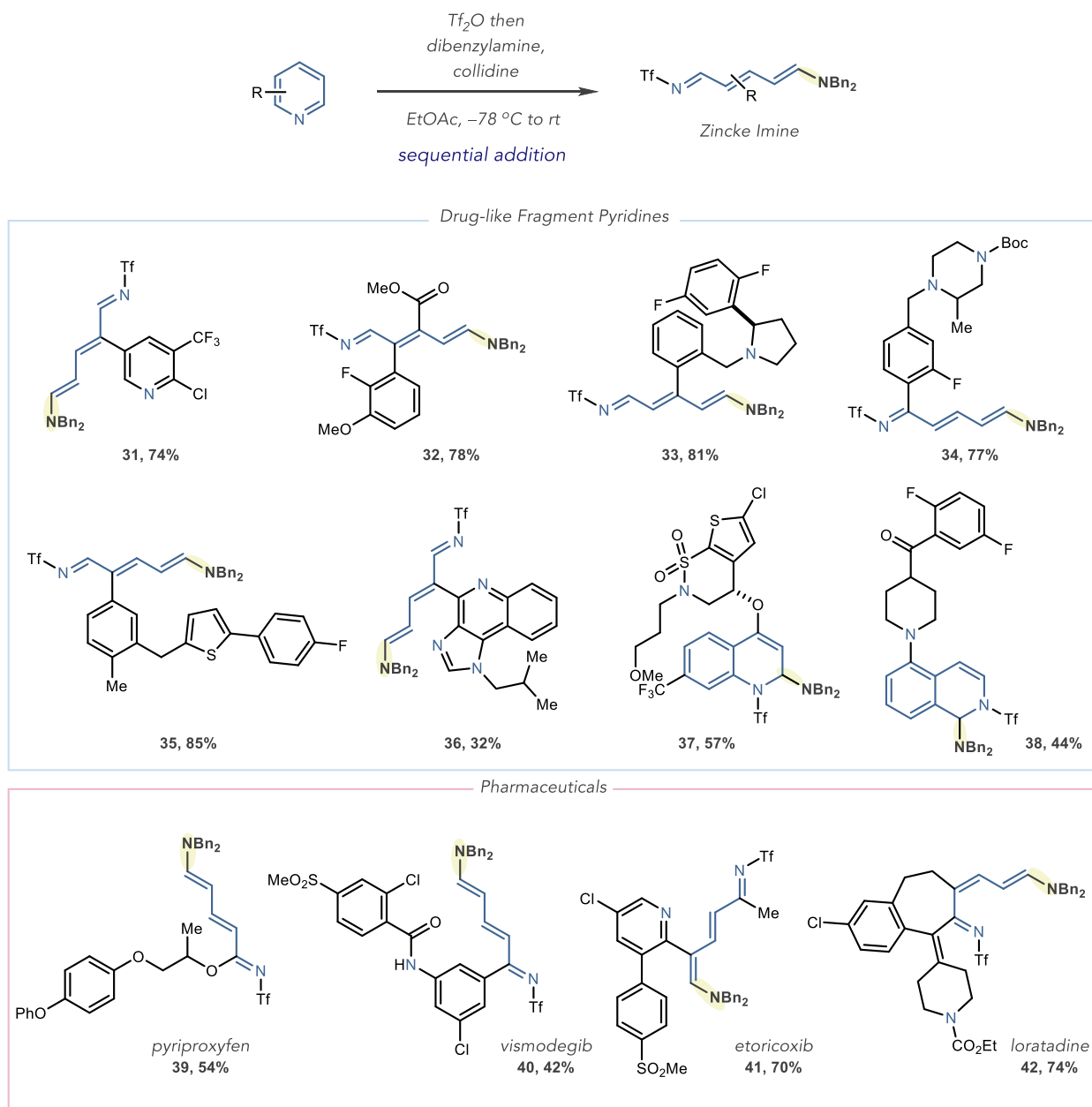


Figure 5.11. Selected Scope for *N*-Tf Zincke Imine Formation on Complex Pyridines. Yields determined by ^1H NMR using triphenylmethane as an internal standard.

aromatic rings (**34-36**) form Zincke imines. Quinoline and isoquinoline fragments form a ring-closed adduct under the reaction conditions (**37, 38**). Pharmaceuticals and bioactive molecules were also applied in the ring-opening (**Figure 5.11, bottom**). Despite the added complexity, ring-opening proceeds on these bioactive examples and demonstrates the potential of this method for pyridine functionalization.

We next tested rearomatization of Zincke imines. Based on literature precedent, we examined ammonia sources to rearomatize Zincke imines (**Figure 5.12, top**). Ammonium salts, NH_4OAc and NH_4Cl , proved effective for rearomatization at 50 °C after 16h and increasing temperature to 60 °C gave >90% conversion to the desired pyridine product after 2h. Ammonium hydroxide also can be used for rearomatization with the reaction proceeding at room temperature. Using trifluoroacetic acid (TFA) can also recyclize 2-substituted Zincke imines at 50 °C while triflic acid (TfOH) was ineffective in most cases. When a 3-substituted Zincke imine is used, TFA rapidly converts the imine back to the pyridine (**Figure 5.12, bottom**). Based on these results, rearomatization of 2- and 4-substituted Zincke imines is performed with 10 equivalents of NH_4OAc in EtOH at 60 °C and 3-substituted are recyclized with 2 equivalents of TFA at room temperature.

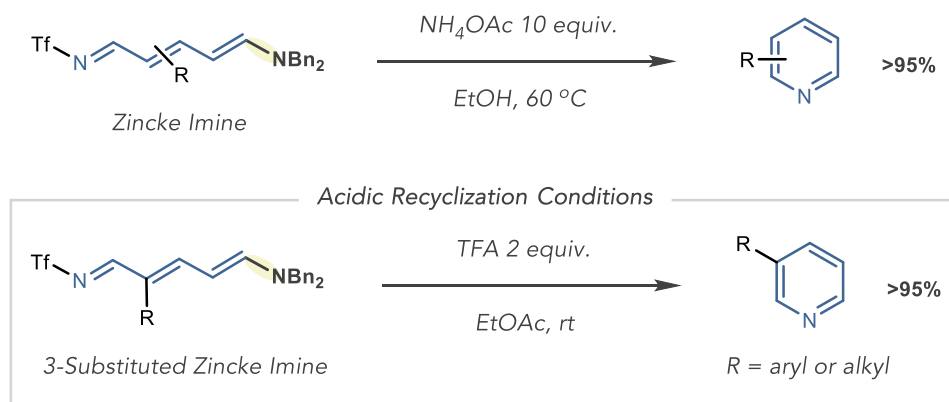


Figure 5.12. Ammonium and Acidic Recyclization Conditions for *N*-Tf Zincke Imines. Yields determined by ^1H NMR using triphenylmethane as an internal standard.

5.4.2 Optimization of Halogenation of Zincke Imine and Iminium

Following successful formation of the Zincke imines through Tf_2O activation, we turned to developing a mild halogenation protocol. Our interest in halogenation was spurred by the harsh conditions required for halogen installation on pyridines and the versatility of halopyridines for derivatization.¹⁷⁻²⁰ Jeff Levy, a coworker in the McNally group, performed optimization for

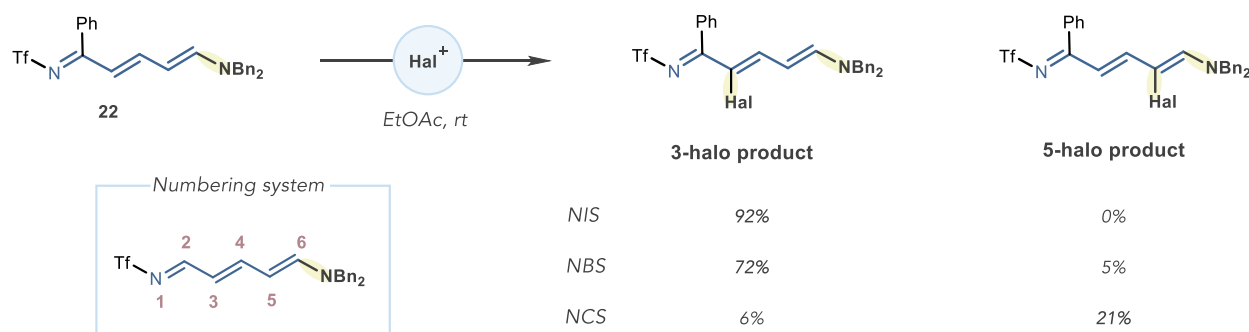


Figure 5.13. Halogenation Conditions for 2-Substituted *N*-Tf Zincke Imines. Yields determined by ^1H NMR using triphenylmethane as an internal standard.

halogenation on Zincke imines. We were interested in the regioselectivity of the halogenation. Our initial investigation used 2-phenylpyridine derived Zincke imine (**22**) and succinimide-based halogenation reagents (NCS/NBS/NIS) (**Figure 5.13**). These halogenating reagents have previously been employed for enamine functionalization.⁴⁵ When NIS (1.0 equiv.) is reacted with **22**, iodination proceeds quickly (<5 min) and in high yield with perfect regioselectivity for the 3-position. Similar regioselectivity is observed when NBS is used in place of NIS, with a 40:1 selectivity when the reaction is performed in CH_2Cl_2 and 12:1 in EtOAc. NCS favors 5-position chlorination (1:3) and gives comparably low yields of the desired product. A collaboration between the McNally lab and Paton lab is currently investigating the origin of selectivity in the halogenation of Zincke imines. Iodinated 2-substituted Zincke imines rearomatize using the established NH_4OAc conditions at 60 $^\circ\text{C}$, however the NIS is first quenched using 1,3,5-trimethoxybenzene to avoid undesired byproducts.

With optimized conditions for 2-substituted Zincke imines in hand, we attempted to apply the halogenation to 3-butyl Zincke imine (**43**) (**Figure 5.14**). When the standard NIS conditions are used, no desired halogenation is observed. Based on differences in the ^1H NMR, we propose

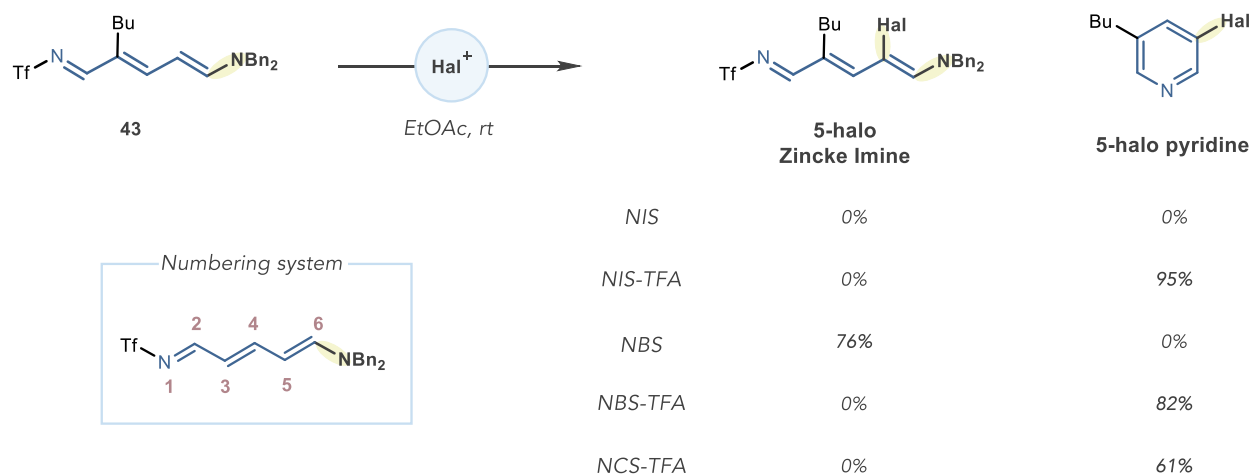


Figure 5.14. Halogenation Conditions for 3-Substituted *N*-Tf Zincke Imines. Yields determined by ^1H NMR using triphenylmethane as an internal standard.

that an *N*-iodo Zincke imine is initially formed and is unreactive under the reaction conditions. An alternative set of conditions, using NIS (1.0 equiv.) and TFA (1.0 equiv.), provide 95% of 3-butyl-5-iodopyridine. TFA serves to facilitate the halogenation, via blocking the imine lone pair and activating the NIS, and rearomatizes the Zincke imine to the pyridine.⁴⁶ NBS and NCS provide the corresponding 5-halopyridines when the TFA conditions are employed.

Halogenation optimization next turned towards developing a set of conditions to “switch” selectivity on 2-substituted Zincke imines from the 3-position to the 5-position. This investigation was started based on the ability to achieve 5-position halogenation using NIS/TFA conditions on 3-substituted pyridines. When NXS/TFA conditions were used on **22**, halogenation favors the 5-position product while the yields and selectivity are relatively modest (**Figure 5.15, top**). This served as a proof-of-concept for changing the selectivity for halogenation. We next tried pyrrolidine 2-phenyl Zincke iminium **44**, readily synthesized through addition of pyrrolidine to **22**, in the halogenation to probe selectivity (**Figure 5.15, bottom**). Halogenation occurs with exclusive selectivity for the 5-position, providing a simple strategy for synthesizing 3- and 5-iodopyridines.

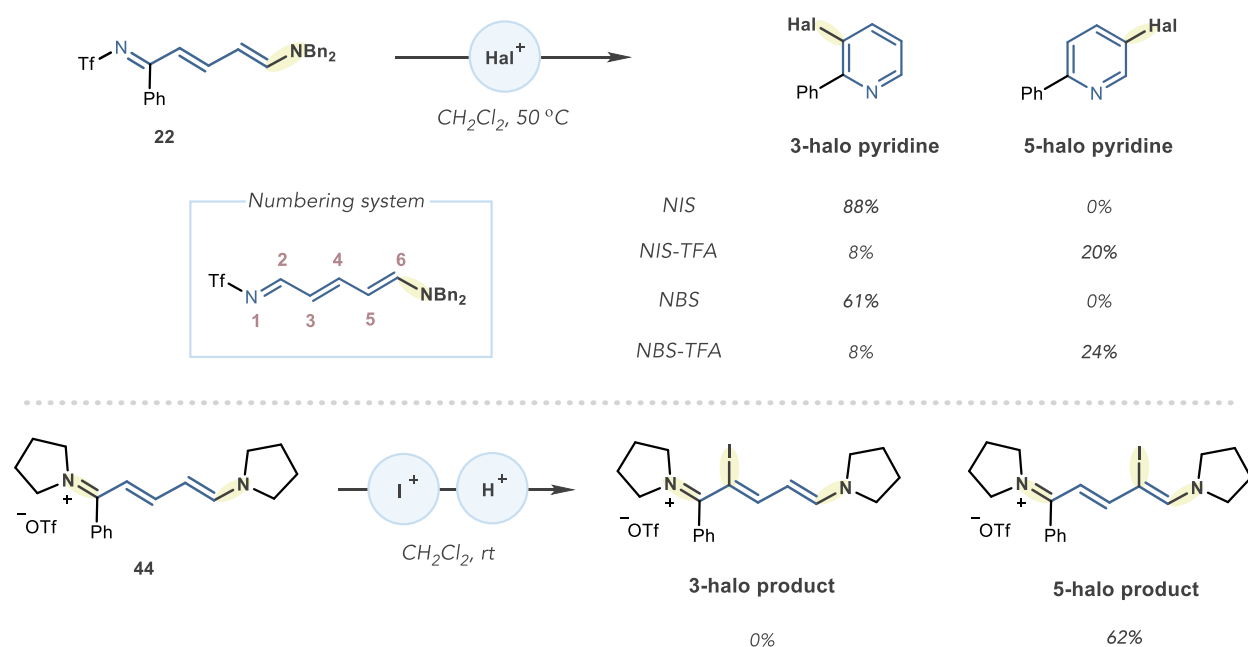


Figure 5.15. Regioselective Halogenation “Switch” using Zincke Iminium. Yields determined by ^1H NMR using triphenylmethane as an internal standard.

5.4.3 Halogenation Scope on *N*-Triflyl Zincke Imines

The proposed strategy for pyridine functionalization through polarity inversion of the π -system centers around the ability to perform a series of ring-manipulation steps; ring-opening, functionalization, and ring-closure. Performing all three stages in a single reaction was the goal for the process. We first attempted to halogenate 2-phenylpyridine and through sequential ring-opening, halogenation, and ring-closure achieved 3-iodo-2-phenylpyridine **45** in 68% yield (**Figure 5.16**). Successful one-pot halogenation was also ran using NIS/TFA halogenation conditions on 3-butylpyridine.

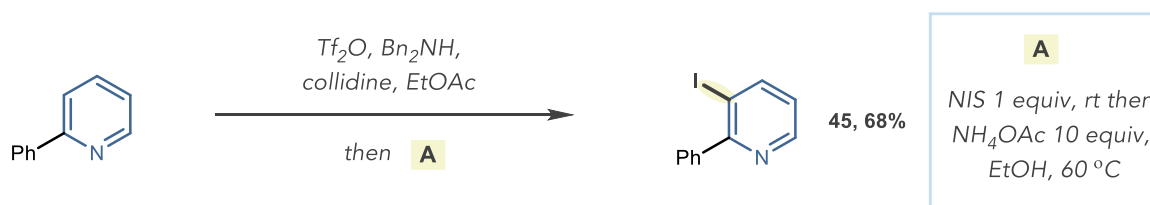


Figure 5.16. One-Pot Iodination of 2-Phenyl Pyridine Via Zincke Imine Intermediate. Yield determined by ^1H NMR using triphenylmethane as an internal standard.

We began exploring the scope of building block pyridines that can be iodinated (**Figure 5.17**). 3-Position halogenation proceeds on 2-aryl and 2-alkyl pyridines with perfect regioselectivity (**46-49**). Similarly, 3-substituted pyridines are iodinated in the one-pot protocol even when 3-CF₃ pyridine is used as the starting material (**50-53**). 4-Substituted pyridines are also halogenated through the polarity inversion strategy with no bis-halogenation observed (**54, 55**). Disubstituted pyridines can be halogenated, with 2,4-disubstituted pyridines retaining perfect regioselectivity for the 3-position (**56-62**). The reaction tolerates S_NAr active chloropyridines

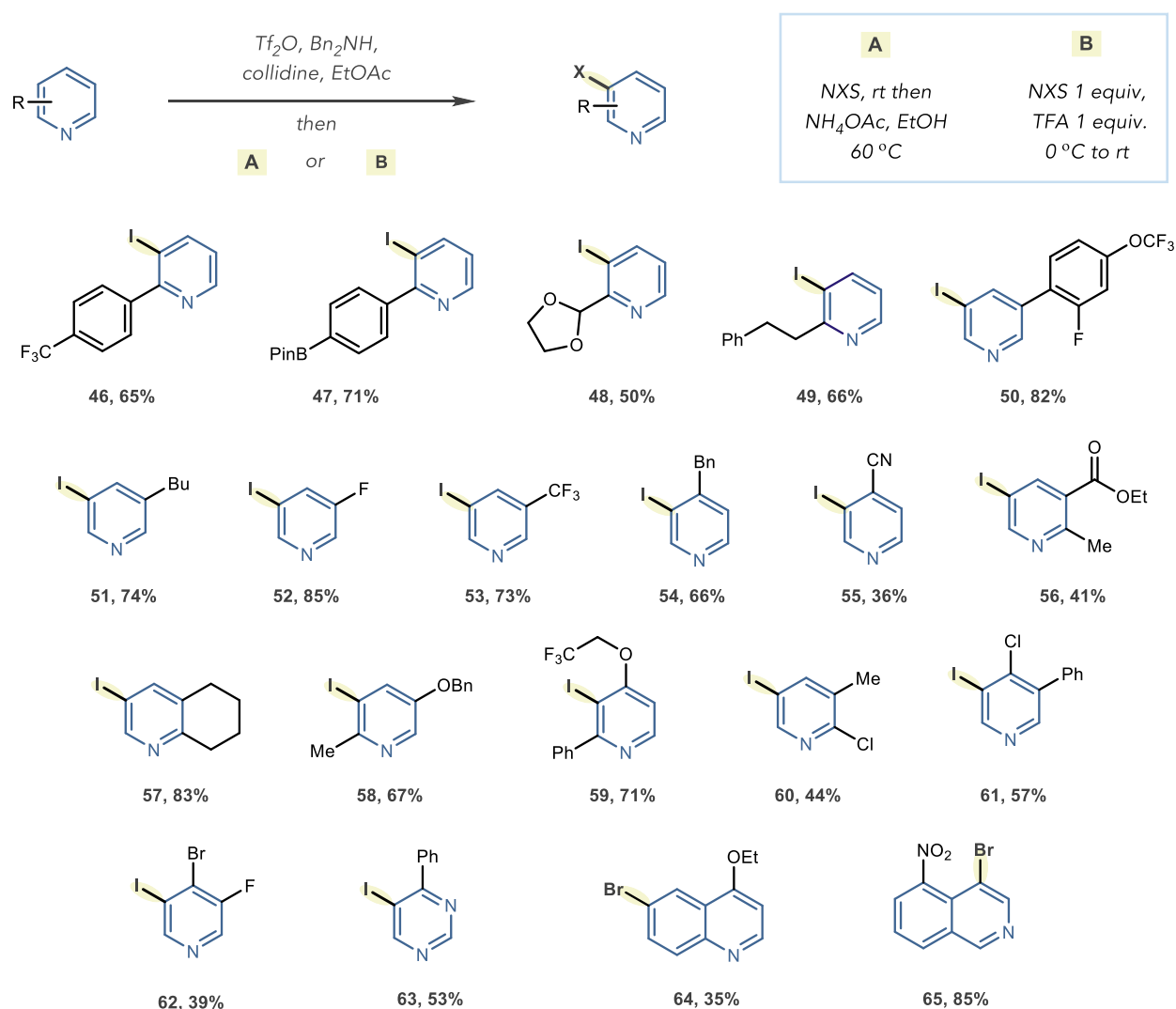


Figure 5.17. Scope of One-Pot Halogenation of Building Block Pyridines Via Zincke Imine Intermediate. Yields determined by ¹H NMR using triphenylmethane as an internal standard.

leading to polyhalogenated pyridines (**60**, **61**). 4-Phenylpyrimidine showcases the iodination on a diazine (**63**) and (iso)quinolines can also be halogenated, though NBS is better than NIS for halogenation due to the ring-closed intermediate (**64**, **65**).

We were interested in determining how nucleophilic the Zincke imine π -system is. A robustness study was performed on 2-phenyl Zincke imine **22** by spiking in one equivalent of electron-rich π -systems. While aniline and indole outcompeted the Zincke system for halogenation, the Zincke imine provided excellent yields in most cases (**Figure 5.18, top**). The

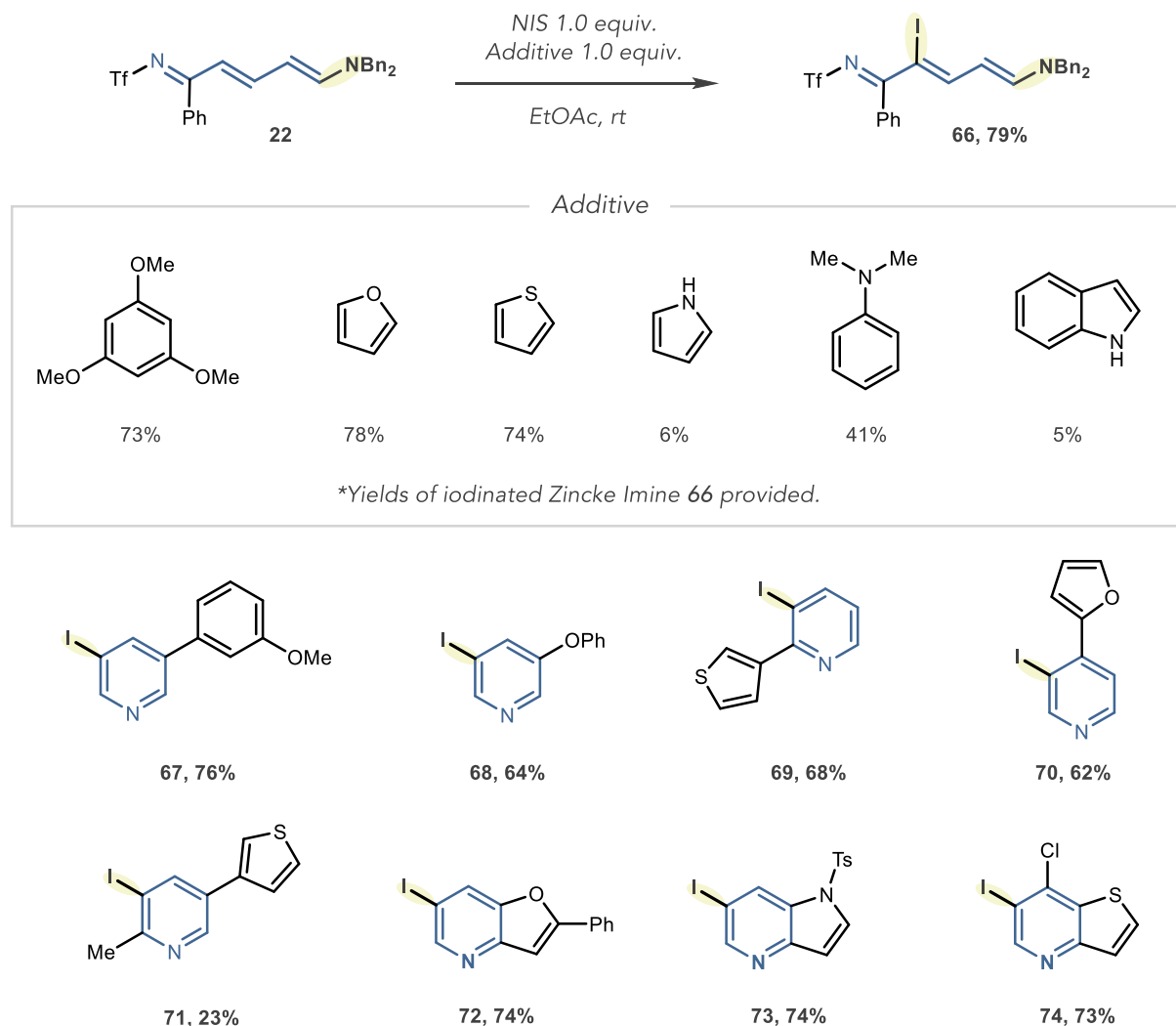


Figure 5.18. Robustness Screen of Zincke Imine Halogenation and One-Pot Selective Halogenation of Pyridines. Yields determined by ^1H NMR using triphenylmethane as an internal standard.

site-selectivity is extended to intramolecular competitions, with the desired pyridine halogenation occurring with exclusive selectivity in each example (**Figure 5.18, bottom**).

Following the success at applying the one-pot halogenation to building block pyridines, our attention turned to halogenation of drug-like fragments and pharmaceutical molecules (**Figure**

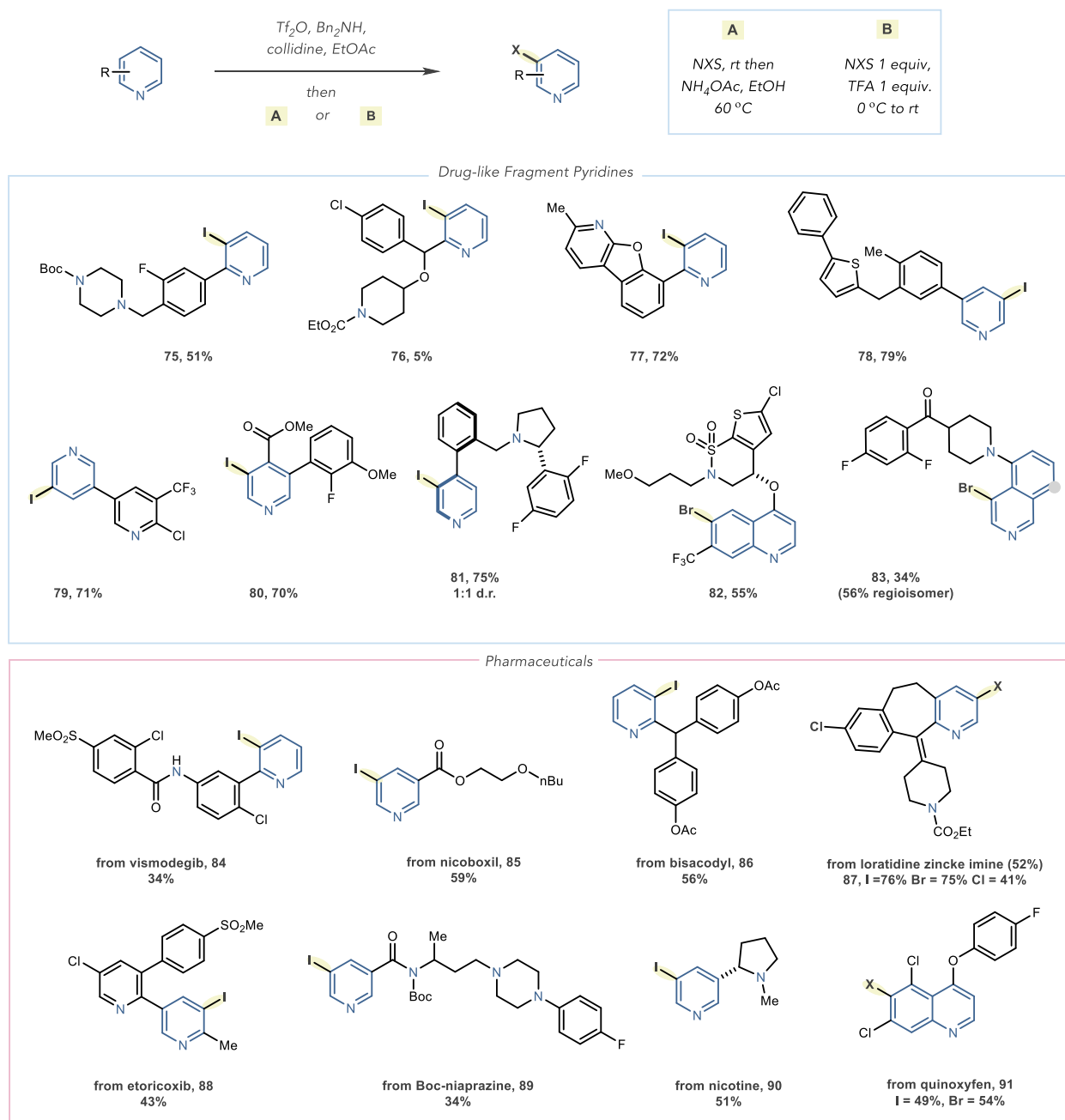


Figure 5.19. Halogenation of Complex Azines and Pharmaceuticals Via Zincke Imine Intermediate. Yields determined by ¹H NMR using triphenylmethane as an internal standard.

After investigating the scope for mono-halogenation of pyridines, we developed conditions for bis-halogenation (**Figure 5.20**). Under our optimized reaction conditions, 3-position iodination or bromination is achieved and the 3-halogenated Zincke imine is isolated through precipitation from the reaction solvent. From these intermediates, a variety of halogenations using NXS/TFA can be performed giving bis-halogenated pyridines with excellent regioselectivity directly from their C-H bonds. The protocol extends to vismodegib, a skin cancer treatment, in a tandem iodination-chlorination sequence. The versatility of the iodination Zincke imine extends beyond bis-halogenation and a Suzuki-Miyaura cross-coupling followed by rearomatization shows formal 3-position arylation of 2-phenylpyridine (**Figure 5.21**).

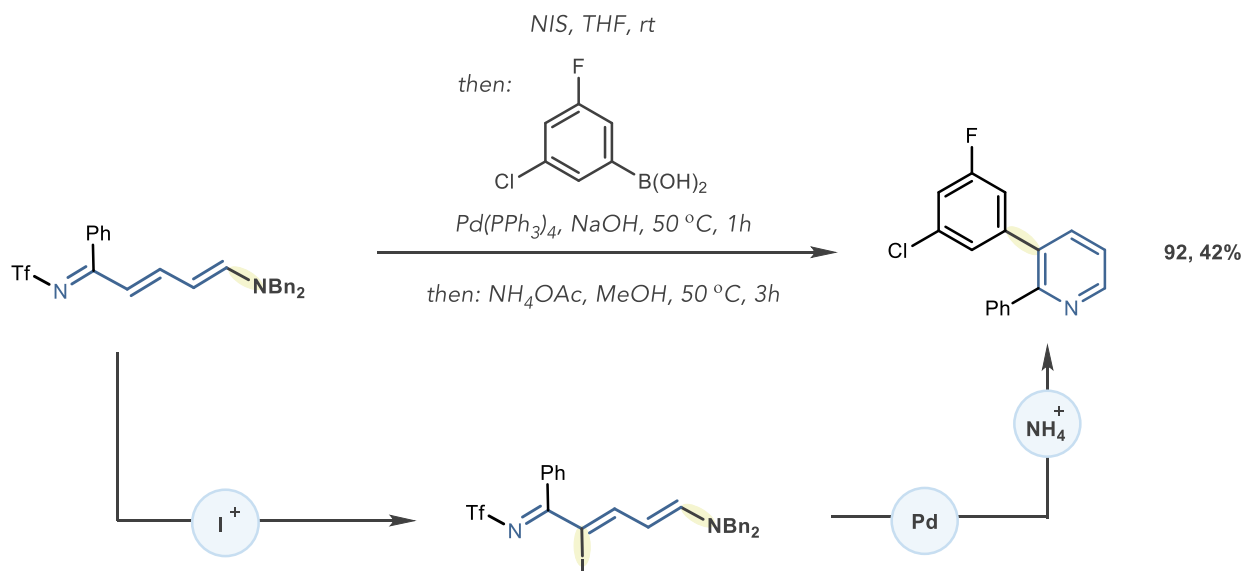


Figure 5.21. Tandem Halogenation-Arylation-Recyclization of 2-Phenyl Zincke Imine. Yields determined by ^1H NMR using triphenylmethane as an internal standard.

5.5 Other Functionalizations through *N*-Triflyl Zincke Imines

We next began exploring other bond forming reactions with *N*-Triflyl Zincke imines. This area started with reaction of *N*-triflyl Zincke imines with activated two-electron electrophiles. Heterocycles and azines are prominent in pharmaceuticals (*vide supra*),^{48,49} and our interest turned to *N*-triflyl-pyridinium salts. Electron-rich aromatics react with triflyl-activated pyridines and

Toscano showed that reaction of Zincke imines with *N*-triflyl-pyridiniums is possible, although low yielding.^{44,50} Our investigation found the reaction of these activated pyridines with Zincke imines proceeds at low temperatures using collidine as a base in ethyl acetate (**Figure 5.22**). Hillary Nguyen, a coworker in the McNally lab, worked on further optimization for the reaction greatly expanded the scope of viable coupling partners. Selective coupling occurs at the 3-position of the Zincke imine and rearomatization gives 3-substituted pyridines (**Figure 5.22**). The resulting

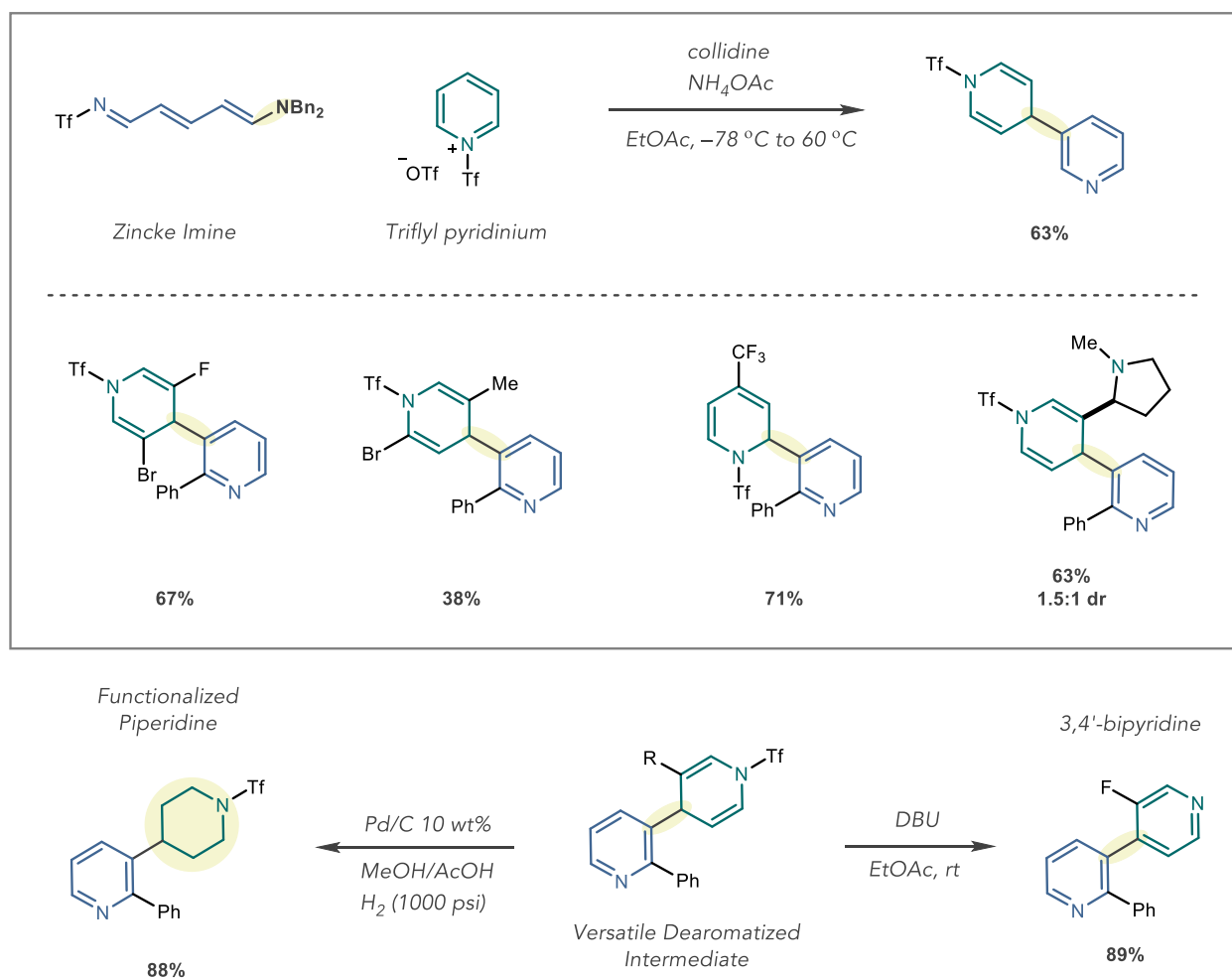


Figure 5.22. Reaction of Zincke Imine with *N*-Tf Pyridiniums and Intermediate Derivatization. Yields determined by ^1H NMR using triphenylmethane as an internal standard.

dearomatized products are of interest due to their versatility and Hillary has demonstrated that several valuable heterocycle products can be obtained through this strategy (**Figure 5.22**).

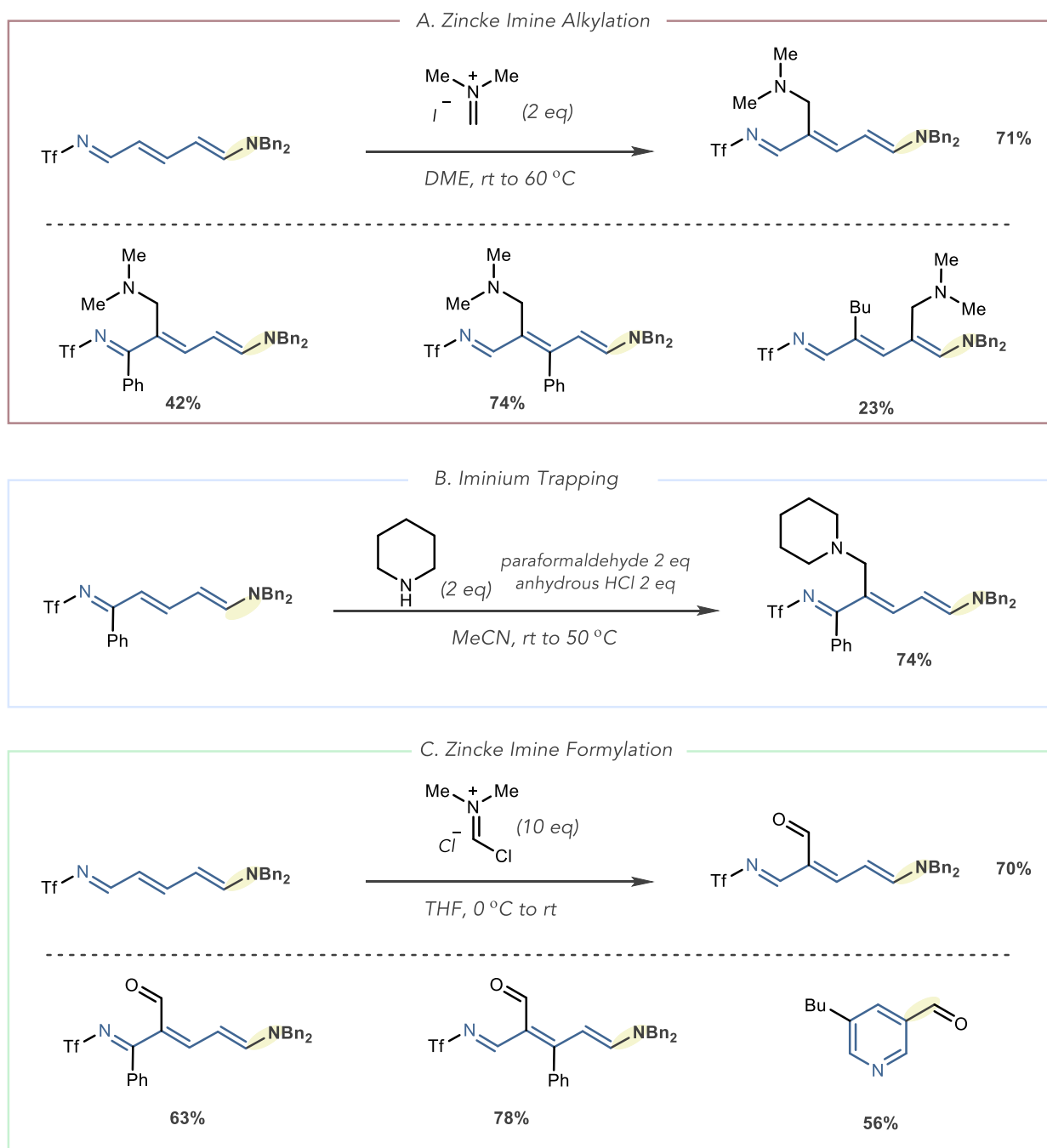


Figure 5.23. Reaction of Zincke Imine with Iminium Electrophiles. Yields determined by ^1H NMR using triphenylmethane as an internal standard.

Building on our success with electrophiles, we turned to developing methods to achieve C-C bond formations through iminium trapping. Starting with commercially available Eschenmoser salt, dimethylbenzylamine products can be formed and selectivity remains exclusive for the 3-position unless this site is blocked (**Figure 5.23, A**). Iminium trapping can be extended to formation of iminiums *in situ* by reaction with paraformaldehyde and unoptimized results indicate a practical strategy for amine-pyridine couplings through this strategy (**Figure 5.23, B**). Besides the value of benzyl amines in pharmaceuticals,^{51,52} this method provides a potential route for methylation by exploiting a gramine fragmentation pathway.⁵³⁻⁵⁵ Using the Vilsmeier reagent, generated *in situ* by reaction of POCl₃ and dimethylformamide, formylation occurs and the

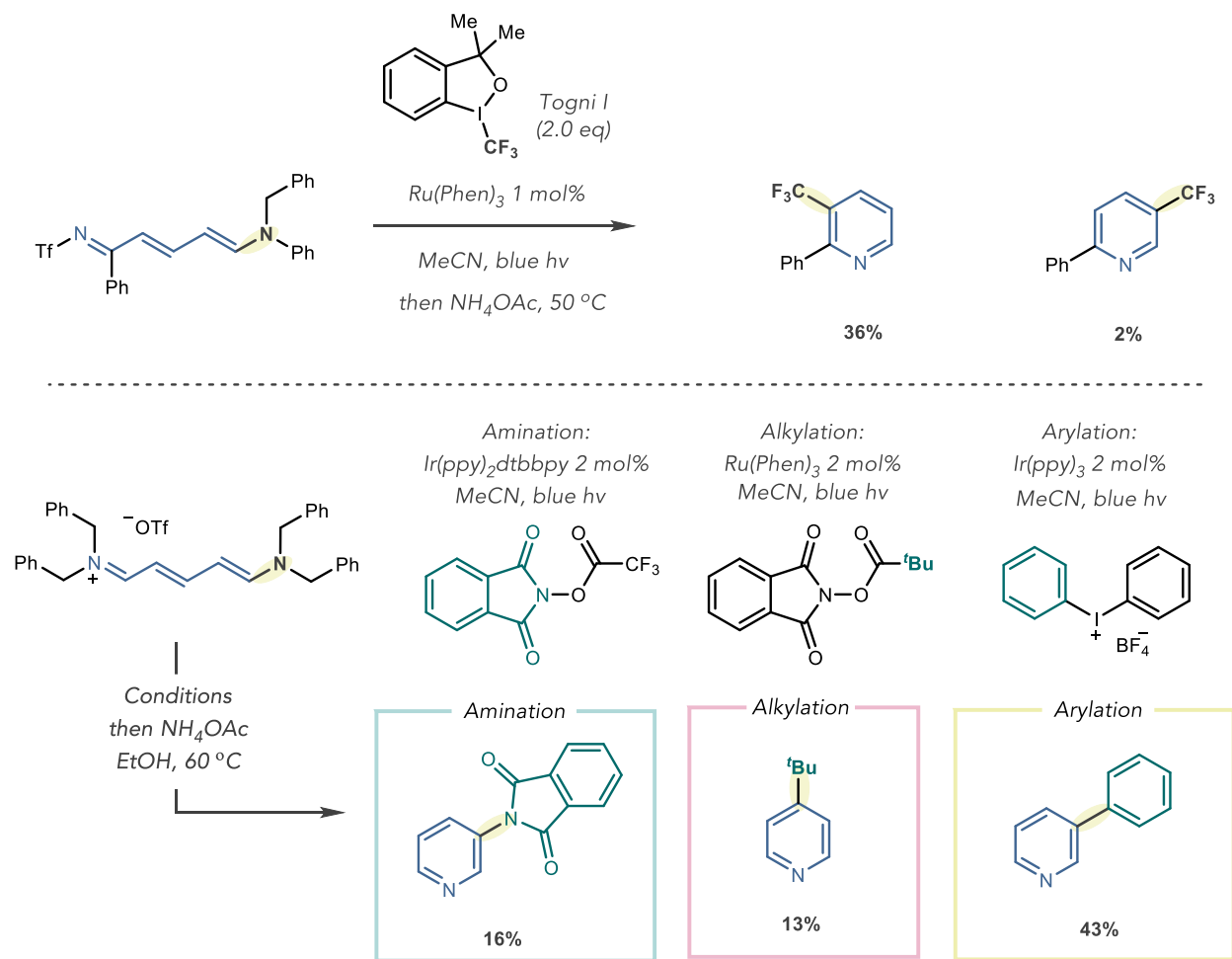


Figure 5.24. Radical Derivatization of Zincke Imine and Iminiums. Yields determined by ¹H NMR using triphenylmethane as an internal standard.

resulting aldehyde can be functionalized through established methods such as reductive amination (**Figure 5.23, C**).

Radical methods for functionalization have seen a resurgence in recent years with the advent of electrochemical and photoredox methods.⁵⁶⁻⁵⁸ We envisioned the extended enamine-type π -system could be amenable for radical additions. While limitations remain in the strategies developed, initial reactions show the potential of this method (**Figure 5.24**). Through photoredox methods, trifluoromethylation, alkylation, arylation, and amination have been demonstrated. While regioselectivity is still being investigated, the mild conditions and range of products available through radical processes makes these attractive methods for pyridine functionalization. Ben Uhlenbruck is currently investigating and optimizing radical reactivity of *N*-triflyl Zincke imines.

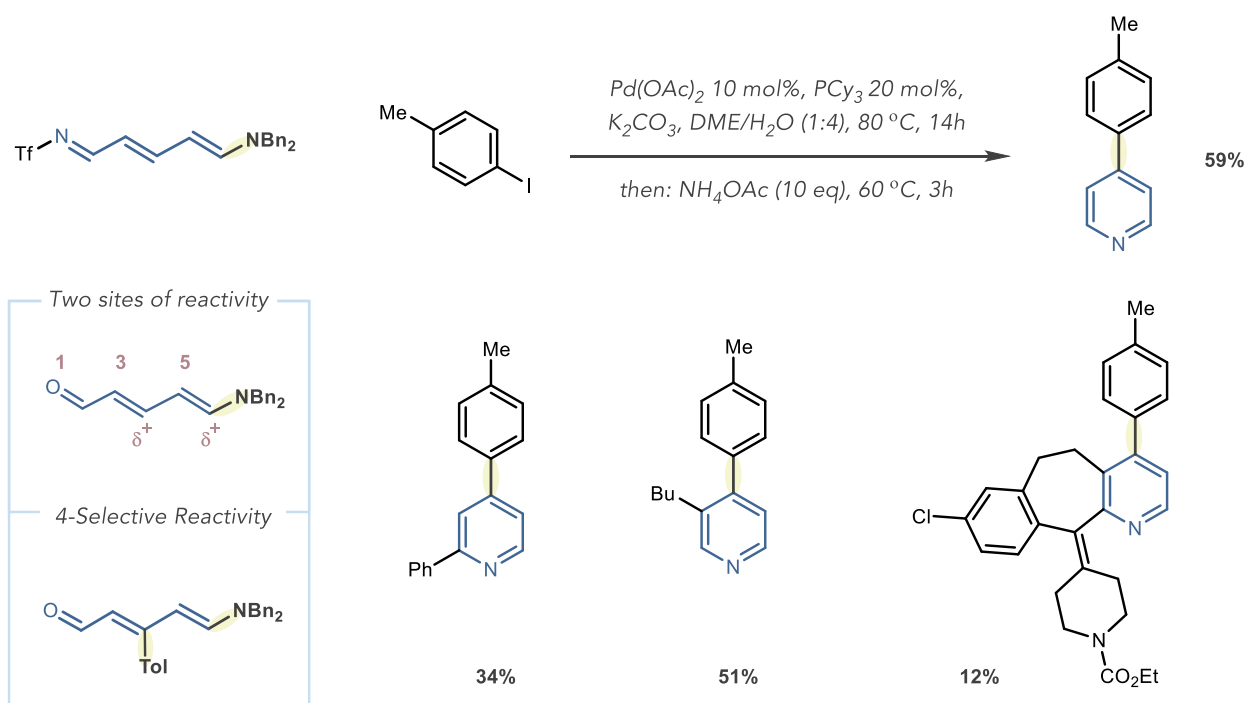


Figure 5.25. Heck Arylation of Zincke Imines. Yields determined by ¹H NMR using triphenylmethane as an internal standard.

While most of our attention has focused on exploiting the nucleophilic nature of Zincke imines, the push-pull π -system results in δ^+ positions at the 2-, 4-, and 6- positions. The Heck reaction is a method for arylation of alkenes through palladium catalysis.⁵⁹⁻⁶¹ Using tricyclohexylphosphine and palladium(II) acetate as the catalytic system and *para*-iodotoluene as the coupling partner, the Zincke imine arylated with exclusive selectivity for the 4-position (**Figure 5.25**).⁴³ Hydrolysis of the *N*-Tf imine occurs *in situ* and H₂O is critical to achieve the desired reactivity. While optimization is ongoing, a one-pot arylation and rearomatization on a range of Zincke imines demonstrates this reaction as a C-H arylation. Future work will extend reactivity to other couplings such as alkenylation and alkylation.

5.6 Conclusion

By exploiting a polarity inversion of the pyridine π -system, a set of functionalizations at the 3-position of pyridine have been developed. A ring-opening-functionalization-ring-closure sequence provides conditions for halogenation and C-C bond formations on pyridine. Reactivity extends to radical reactions and transition metal-catalyzed couplings and further reaction development is ongoing. Most reactions proceed with exclusive regioselectivity and the origin of selectivity is currently under experimental and computational investigation.

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Appendix One

Phosphorus Ligand-Coupling for Bisazine Synthesis: Experimental

A 1.1 General Methods and Materials

Tf₂O (99%) was purchased from Oakwood Chemical and used without further purification but was routinely stored in a –20 °C fridge. DBU was distilled before use. (2,2,2)-Trifluoroethanol (TFE) was purchased from Oakwood Chemicals and used without further purification. 200 proof ethanol was purchased from PHARMCO-AAPER and used without further purification. HCl (4.0 M in dioxanes) and trifluoromethanesulfonic acid (98%) were purchased from Sigma Aldrich chemical company and used without further purification but were routinely stored in a –20 °C fridge. All reactions were run under a nitrogen atmosphere unless otherwise noted.

A 1.2 Instrumentation

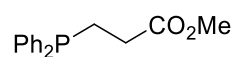
¹H NMR spectra were recorded using a Varian 400 MR spectrometer, an Agilent Inova 400 spectrometer, an Agilent Inova 500 spectrometer, or a Bruker AV-111 400 spectrometer. The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: CDCl₃ (7.26 ppm), (CD₃)₂SO (2.50 ppm), or CD₃OD (3.31 ppm). Coupling constants (J) were reported in Hertz (Hz) and the multiplicity was reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. ¹³C NMR spectra were recorded using a Bruker Ultrashield-400, a Varian 400 MR or an Agilent Inova 400 spectrometer. The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: CDCl₃ (77.00 ppm), (CD₃)₂SO (39.51 ppm), or CD₃OD (49.00 ppm). Low-resolution mass spectra were recorded on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared spectra were recorded

on a Bruker Tensor 27 FT-IR spectrometer with absorptions reported in wavenumbers (cm^{-1}). Melting points were recorded using a Büchi B-450 melting point apparatus.

A. 1.3 General Procedures

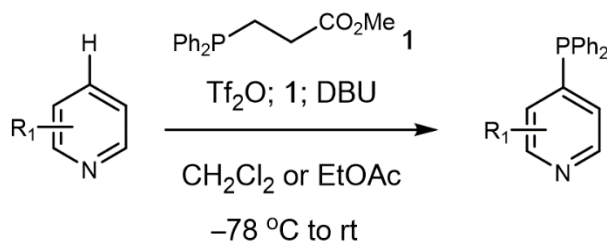
A. 1.3.1 Synthesis of the Fragmentable Phosphine

Methyl 3-(diphenylphosphaneyl)propanoate (FragPhos)



An oven-dried round bottomed flask was charged with diphenylphosphane (17.4 mL, 100 mmol) under a nitrogen atmosphere. Methyl acrylate (9.0 mL, 100 mmol), previously degassed via N_2 sparging, was added dropwise at room temperature over 15 minutes. The reaction was stirred for 16 hours at room temperature before concentrating *in vacuo*. The crude material was purified by flash chromatography (silica gel: 9% EtOAc in hexanes) afforded the title compound as a colorless oil (24.26 g, 89.10 mmol, 89% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3053, 2949, 1735, 1481, 1433, 1353, 1221, 1164, 736, 695; ^1H NMR (400 MHz, CDCl_3) δ : 7.47-7.39 (4H, m), 7.38-7.30 (6H, m), 3.65 (3H, s), 2.46-2.31 (4H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 173.05 (d, $J = 15.3$ Hz), 137.52 (d, $J = 13.0$ Hz), 132.39 (d, $J = 19.2$ Hz), 128.47, 128.22 (d, $J = 6.6$ Hz), 51.33, 30.21 (d, $J = 19.8$ Hz), 22.69 (d, $J = 12.2$ Hz); ^{31}P (162 MHz, CDCl_3) δ : -15.76; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 273.1057, $\text{C}_{16}\text{H}_{18}\text{O}_2\text{P}^+$ requires 273.1039.

A. 1.3.2 General Procedure A (Preparation of Heteroaryl Phosphines)

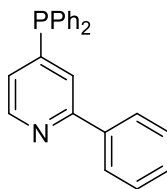


An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH₂Cl₂ (0.1 M) was added, the reaction vessel cooled to -78 °C and Tf₂O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before the mixture was warmed to -50 °C and then methyl 3-(diphenylphosphaneyl)propanoate (1.1 equiv) was added dropwise as a solution (2.0 M in CH₂Cl₂). The reaction was subjected to three rapid cycles of vacuum / nitrogen backfill and was stirred for a further 30 minutes at -50 °C. The reaction was cooled to -78 °C and DBU (3.0 equiv) was added dropwise via syringe, the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring for approximately 2 hours. The reaction was diluted with H₂O and then extracted with CH₂Cl₂ (3x). The combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl phosphine product.

Notes.

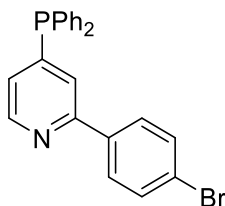
- 1) To maximize the yield vigorous stirring is required.
- 2) For long term storage (>2 weeks) it is best to keep the heteroaryl phosphine product in a -20 °C fridge.

4-(Diphenylphosphaneyl)-2-phenylpyridine (4)



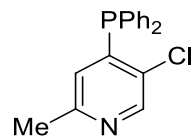
Prepared according to general procedure A using 2-phenylpyridine (2.13 mL, 14.90 mmol), Tf_2O (2.50 mL, 14.90 mmol), methyl 3-(diphenylphosphaneyl)propanoate (4.44 g, 16.30 mmol), DBU (6.67 mL, 44.70 mmol) and CH_2Cl_2 (149 mL). Crude (to determine the inherent regioselectivity a separate reaction was ran with 1eq DBU instead of 3eq resulting in a pre-fragmented phosphonium salt. See crude ^{31}P NMR for structure) regiomeric ratio 13.3:1.0 (4-position:2-position). Flash column chromatography (silica gel, gradient elution: 1% Et_2O in toluene to 2.5% Et_2O in toluene) afforded the title compound as a white solid (3.59 g, 10.57 mmol, 71% yield). mp 73-74 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3053, 1570, 1434, 1373, 1026, 907, 837, 733, 693; ^1H NMR (400 MHz, CDCl_3) δ : 8.63 (1H, dd, $J = 5.1, 2.4$ Hz), 7.92 (2H, d, $J = 7.5$ Hz), 7.65 (1H, d, $J = 7.5$ Hz) 7.50-7.35 (13H, m), 7.06 (1H, dd, $J = 6.2, 5.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 156.79 (d, $J = 5.1$ Hz), 149.48 (d, $J = 17.5$ Hz), 149.12 (d, $J = 4.2$ Hz), 139.04, 134.93 (d, $J = 10.1$ Hz), 134.09 (d, $J = 20.4$ Hz), 129.44, 128.94, 128.76 (d, $J = 7.5$ Hz), 128.62, 126.86, 125.48 (d, $J = 13.5$ Hz), 124.13 (d, $J = 18.0$ Hz); ^{31}P (162 MHz, CDCl_3) δ : -6.38; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 340.1271, $\text{C}_{23}\text{H}_{19}\text{NP}^+$ requires 340.1250.

2-(4-Bromophenyl)-4-(diphenylphosphaneyl)pyridine (7a)



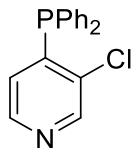
Prepared according to general procedure A using 2-(4-bromophenyl)pyridine (2.20 g, 9.40 mmol), TiF_4 (1.58 mL, 9.40 mmol), methyl 3-(diphenylphosphaneyl)propanoate (2.82 g, 10.34 mmol), DBU (4.21 mL, 28.20 mmol) and CH_2Cl_2 (94 mL). Crude (to determine the inherent regioselectivity a separate reaction was run with 1eq DBU instead of 3eq resulting in a pre-fragmented phosphonium salt. See crude ^{31}P NMR for structure.) regiomeric ratio 13.9:1.0 (4-position:2-position). Flash column chromatography (silica gel: 1% ether in toluene) afforded the title compound as a white solid (2.40 g, 5.75 mmol, 61% yield). mp 120-123 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3056, 1580, 1462, 1431, 1403, 1366, 1070, 826, 741, 694; ^1H NMR (400 MHz, CDCl_3) δ : 8.61 (1H, dd, $J = 5.0, 2.4$ Hz), 7.79 (2H, d, $J = 8.6$ Hz), 7.61 (1H, d, $J = 7.3$ Hz), 7.55 (2H, d, $J = 8.6$ Hz), 7.48-7.36 (10H, m), 7.06 (1H, t, $J = 5.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 155.52 (d, $J = 5.3$ Hz), 149.85 (d, $J = 18.3$ Hz), 149.12 (d, $J = 4.1$ Hz), 137.81, 134.77 (d, $J = 9.9$ Hz), 134.07 (d, $J = 20.6$ Hz), 131.70, 129.49, 128.78 (d, $J = 7.6$ Hz), 128.37, 125.73 (d, $J = 13.0$ Hz), 123.77 (d, $J = 18.4$ Hz), 123.45; ^{31}P (162 MHz, CDCl_3) δ : -6.35; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 418.1046, $\text{C}_{23}\text{H}_{18}\text{BrNP}^+$ requires 418.1036.

5-Chloro-4-(diphenylphosphino)-2-methylpyridine (9a)



Prepared according to general procedure A using 5-chloro-2-methylpyridine (333 mg, 2.60 mmol), TiF_4 (437 μL , 2.60 mmol), methyl 3-(diphenylphosphino)propanoate (779 mg, 2.86 mmol), DBU (1.17 mL, 7.80 mmol) and CH_2Cl_2 (26 mL). Flash chromatography (silica gel: 9% EtOAc in hexanes to 16% EtOAc in hexanes) afforded the title compound as a white amorphous powder (524 mg, 1.69 mmol, 65% yield). mp 112–114 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3052, 2990, 2921, 1563, 1477, 1441, 1434, 1323, 1127, 749, 744; ^1H NMR (400 MHz, CDCl_3) δ : 8.42 (1H, d, $J = 4.5$ Hz), 7.44–7.37 (6H, m), 7.32–7.28 (4H, m), 6.48 (1H, d, $J = 3.0$ Hz), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 156.39, 148.01, 147.45 (d, $J = 19.8$ Hz), 134.15 (d, $J = 20.7$ Hz), 133.52 (d, $J = 8.9$ Hz), 133.28 (d, $J = 22.2$ Hz), 129.58, 128.87 (d, $J = 7.6$ Hz), 126.91, 23.93; ^{31}P NMR (162 MHz, CDCl_3) δ : –11.81; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 312.0710, $\text{C}_{18}\text{H}_{16}\text{ClNP}^+$ requires 312.0709.

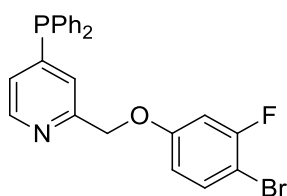
3-Chloro-4-(diphenylphosphino)pyridine (10a)



Prepared according to general procedure A using 3-chloropyridine (380 μL , 4.00 mmol), TiF_4 (672 μL , 4.00 mmol), methyl 3-(diphenylphosphino)propanoate (1.20 g, 4.40 mmol), DBU (1.80 mL, 12.00 mmol) and CH_2Cl_2 (40 mL). Flash chromatography (silica gel: CH_2Cl_2 to 5% EtOAc in CH_2Cl_2) afforded the title compound as a white powder (1.08 g, 3.64 mmol, 91% yield).

mp 66-68 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3047, 1568, 1478, 1447, 1433, 1392, 1265, 1181, 1119, 1095, 1077, 1029, 836, 744; ^1H NMR (400 MHz, CDCl_3) δ : 8.54 (1H, d, $J = 4.4$ Hz), 8.32 (1H, dd, $J = 4.9, 0.8$ Hz), 7.46–7.36 (6H, m), 7.34–7.27 (4H, m), 6.64 (1H, ddd, $J = 5.0, 2.8, 0.5$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 148.85, 147.70 (d, $J = 20.5$ Hz), 147.34, 136.20 (d, $J = 22.2$ Hz), 134.14 (d, $J = 20.9$ Hz), 133.29 (d, $J = 9.1$ Hz), 129.66, 128.91 (d, $J = 7.8$ Hz), 127.35; ^{31}P NMR (162 MHz, CDCl_3) δ : -11.94; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 298.1, $\text{C}_{17}\text{H}_{14}\text{ClNP}^+$ requires 298.1.

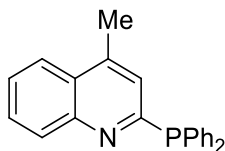
2-((4-Bromo-3-fluorophenoxy)methyl)-4-(diphenylphosphino)pyridine (11a)



Prepared according to general procedure A using 2-((4-bromo-3-fluorophenoxy)methyl)pyridine (1.41 g, 5.00 mmol), Tf_2O (840 μL , 5.00 mmol), methyl 3-(diphenylphosphino)propanoate (1.50 g, 5.50 mmol), DBU (2.25 mL, 15.00 mmol) and CH_2Cl_2 (50 mL). Flash chromatography (silica gel: 16% EtOAc in hexanes) afforded the title compound as a white amorphous powder (1.96 g, 4.20 mmol, 84% yield). mp 125–127 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3091, 3068, 2915, 1603, 1580, 1540, 1490, 1476, 1470, 1447, 1435, 1431, 1375, 1294, 1242, 1168, 1149, 1094, 1062, 1027, 991, 949, 887, 853, 831, 804, 747, 731; ^1H NMR (400 MHz, CDCl_3) δ : 8.50–8.48 (1H, m), 7.42–7.27 (11H, m), 7.22–7.20 (1H, m), 7.05–7.02 (1H, m), 6.64 (1H, dd, $J = 10.2, 2.8$ Hz), 6.56 (1H, ddd, $J = 8.9, 2.8, 1.0$ Hz), 5.13 (2H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 159.36 (d, $J = 245.5$ Hz), 158.60 (d, $J = 9.7$ Hz), 155.60 (d, $J = 4.2$ Hz), 150.34 (d, $J = 18.4$ Hz), 148.87 (d, $J = 4.3$ Hz), 134.60 (d, $J = 9.8$ Hz), 134.12 (d, $J = 20.4$ Hz), 133.32 (d, $J = 1.9$ Hz), 129.58, 128.83 (d, $J = 7.5$ Hz), 126.30 (d, $J = 14.9$ Hz), 124.69 (d, $J = 15.9$ Hz), 112.01 (d, $J = 3.2$ Hz), 104.02 (d, $J = 25.4$ Hz), 99.87 (d, $J = 21.2$ Hz), 70.83; ^{19}F NMR (365 MHz, CDCl_3) δ : -

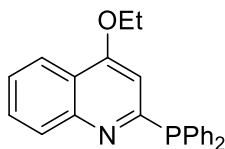
105.03 (t, $J = 8.2$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ : -6.50 ; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 466.0399, $\text{C}_{24}\text{H}_{19}\text{BrFNOP}^+$ requires 466.0372.

2-(Diphenylphosphino)-4-methylquinoline (12a)



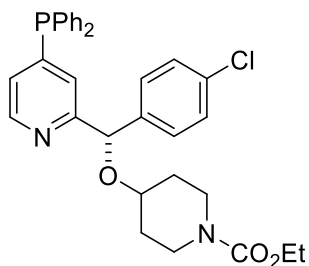
Prepared according to general procedure A using 4-methylquinoline (793 μL , 6.00 mmol), Tf_2O (1.01 mL, 6.00 mmol), methyl 3-(diphenylphosphino)propanoate (1.80 g, 6.60 mmol), DBU (2.70 mL, 18.00 mmol) and CH_2Cl_2 (60 mL). Flash chromatography (silica gel: 16% EtOAc in hexanes) afforded the title compound as a white amorphous powder (1.63 g, 4.98 mmol, 83% yield). mp 99–102 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3058, 2953, 2926, 2858, 1727, 1576, 1541, 1497, 1479, 1444, 1435, 1431, 761, 751, 739; ^1H NMR (400 MHz, CDCl_3) δ : 8.17 (1H, d, $J = 8.4$ Hz), 7.96 (1H, d, $J = 8.3$ Hz), 7.72–7.68 (1H, m), 7.58–7.54 (1H, m), 7.50–7.46 (4H, m), 7.40–7.37 (6H, m), 7.06 (1H, s), 2.58 (3H, d, $J = 0.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.19 (d, $J = 3.8$ Hz), 148.32 (d, $J = 15.3$ Hz), 143.42 (d, $J = 2.8$ Hz), 136.40 (d, $J = 11.4$ Hz), 134.11 (d, $J = 19.4$ Hz), 130.24, 129.17, 128.86, 128.48 (d, $J = 7.0$ Hz), 126.88, 126.53, 124.88 (d, $J = 14.6$ Hz), 123.60, 18.71; ^{31}P NMR (162 MHz, CDCl_3) δ : -2.45 ; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 328.1254, $\text{C}_{22}\text{H}_{19}\text{NP}^+$ requires 328.1255.

2-(Diphenylphosphaneyl)-4-ethoxyquinoline (13a)



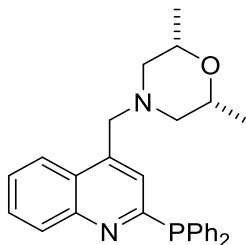
Prepared according to general procedure A, using 4-ethoxyquinoline (500 mg, 3.00 mmol), TiF_2O (500 μL , 3.00 mmol), methyl-3-(diphenylphosphaneyl)propanoate (900 mg, 3.30 mmol), DBU (1.35 mL, 9.00 mmol), and CH_2Cl_2 (60 mL). The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a white crystalline solid (880 mg, 2.46 mmol, 82% yield). mp 114-118 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3058, 2975, 1482, 1231, 1115, 1018, 696; ^1H NMR (400 MHz, CDCl_3) δ : 8.18 (1H, dd, $J = 8.8, 1.2$ Hz), 8.05 (1H, d, $J = 8.2$ Hz), 7.70-7.64 (1H, m), 7.51-7.39 (5H, m); 7.38-7.31 (6H, m), 6.49 (1H, d, $J = 0.6$ Hz), 3.94 (2H, q, $J = 7.0$ Hz), 1.41 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.60 (d, $J = 4.7$ Hz), 160.96 (d, $J = 3.5$ Hz), 149.60 (d, $J = 16.9$ Hz), 136.56 (d, $J = 11.9$ Hz), 134.10 (d, $J = 19.4$ Hz), 129.73, 129.15, 128.92, 128.49 (d, $J = 7.0$ Hz), 125.72, 121.72, 120.23, 104.02, 63.69, 14.22 ^{31}P NMR (162 MHz, CDCl_3) δ : -1.06; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 358.1349 $\text{C}_{23}\text{H}_{21}\text{N}_2\text{OP}^+$ requires 358.1355.

Ethyl (S)-4-((4-chlorophenyl)(4-(diphenylphosphaneyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate (17a)



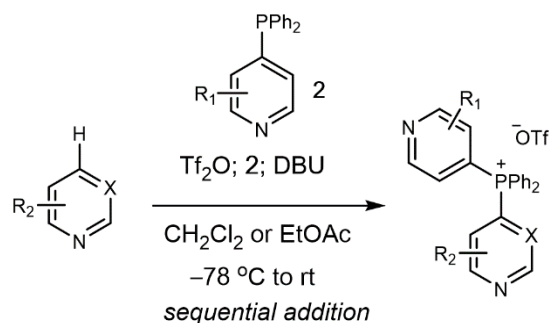
Prepared according to general procedure A using ethyl (S)-4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (1.026 g, 2.74 mmol), TiCl_4 (0.46 mL, 2.74 mmol), methyl 3-(diphenylphosphaneyl)propanoate (820 mg, 3.01 mmol), DBU (1.22 mL, 8.21 mmol) and CH_2Cl_2 (27.5 mL). Flash column chromatography (silica gel, gradient elution: 45% EtOAc in hexanes to 50% EtOAc in hexanes) afforded the title compound as a tan oil (1.19 g, 2.13 mmol, 78% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3052, 2981, 2928, 1692, 1577, 1489, 1434, 1381, 1272, 1227, 1087, 742; ^1H NMR (400 MHz, CDCl_3) δ : 8.37 (1H, ddd, $J = 5.1, 2.3, 0.8$ Hz), 7.41-7.19 (15H, m), 6.95 (1H, m), 5.52 (1H, s), 4.10 (2H, q, $J = 7.2$ Hz), 3.61-3.45 (3H, m), 3.25-3.06 (2H, m), 1.80-1.67 (1H, m), 1.63-1.38 (3H, m), 1.23 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 161.03 (d, $J = 4.2$ Hz), 155.36, 150.31 (d, $J = 18.2$ Hz), 148.31 (d, $J = 4.2$ Hz), 139.82, 134.79 (d, $J = 10.1$ Hz), 134.76 (d, $J = 10.1$ Hz), 134.12 (d, $J = 20.7$ Hz), 134.01 (d, $J = 20.7$ Hz), 133.31, 129.51 (d, $J = 2.8$ Hz), 128.72 (d, $J = 7.6$ Hz), 128.45, 128.14, 125.75 (d, $J = 15.0$ Hz), 123.83 (d, $J = 15.6$ Hz), 80.72, 72.23, 61.13, 40.69, 30.80, 30.66, 14.64; ^{31}P NMR (162 MHz, CDCl_3) δ : -6.35; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 559.1947, $\text{C}_{32}\text{H}_{33}\text{ClN}_2\text{O}_3\text{P}^+$ requires 559.1917.

(2*R*, 6*S*)-4-((2-(Diphenylphosphaneyl)quinolin-4-yl)methyl)-2,6-dimethylmorpholine (19a)



Prepared according to general procedure A, using (2*R*, 6*S*)-2,6-dimethyl-4-(quinolin-4-ylmethyl)morpholine (1.28 g, 5.00 mmol), Tf₂O (840 μL, 5.00 mmol), methyl-3-(diphenylphosphaneyl)propanoate (1.50 g, 5.50 mmol), DBU (2.25 mL, 15.00 mmol), and CH₂Cl₂ (50 mL). Crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a white amorphous solid (1.42 g, 3.25 mmol, 65% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3054, 2971, 2932, 2868, 2811, 2236, 570, 566, 542, 537, 529; ¹H NMR (400 MHz, CDCl₃) δ : 7.95 (1H, d, J = 8.5 Hz), 7.88 (1H, d, J = 8.0 Hz), 7.48 (1H, m), 7.33 (1H, m), 7.30-7.24 (4H, m), 7.20-7.12 (6H, m), 7.07 (1H, s), 3.59 (2H, s), 3.35-3.24 (2H, m), 2.37 (2H, d, J = 10.4 Hz), 1.57 (2H, t, J = 10.7 Hz), 0.90 (6H, d, J = 6.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 164.39 (d, J = 3.7 Hz), 148.59 (d, J = 15.1 Hz), 142.58 (d, J = 2.7 Hz), 136.39 (d, J = 11.3 Hz), 134.05 (d, J = 19.5 Hz) 130.26, 129.12, 128.90, 128.45 (d, J = 6.9 Hz), 126.5, 125.96, 123.94 (d, J = 14.5 Hz), 123.45, 71.46, 59.42, 58.82, 18.94; ³¹P NMR (162 MHz, CDCl₃) δ : -2.22; m/z HRMS (DART) found [M+H]⁺ 441.2065, C₂₈H₃₀N₂OP⁺ requires 441.2090.

A. 1.3.3 General Procedure B (Preparation of Heteroaryl Phosphonium Salts)

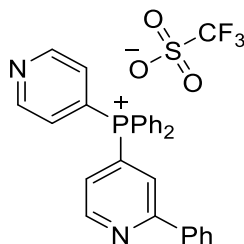


An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to -78°C and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before the mixture was warmed to -50°C and then the heteroaryl phosphine (1.1 equiv) was added in one portion as a solid or dropwise as a solution (2.0 M in CH_2Cl_2). The reaction was subjected to three rapid cycles of vacuum / nitrogen backfill and was stirred for a further 30 minutes at -50°C . The reaction was cooled to -78°C and DBU (1.0 equiv) was added dropwise via syringe, the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (approximately 15-30 minutes). The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O (3x). The organic layer was dried (MgSO_4), filtered and concentrated *in vacuo* to approximately 2-10 mL (depending on the scale of the reaction). The concentrated reaction mixture was added dropwise to an excess of chilled Et_2O (0°C) that was then placed in a -20°C refrigerator for approximately 2-12 hours. The 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.

Notes.

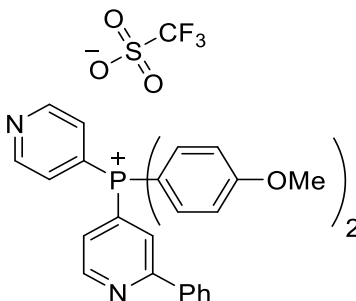
- 1) In a small number of cases, residual CH_2Cl_2 can become trapped in the phosphonium salt products. In these cases, heating the salts under vacuum (50-100 °C) removed the solvent.
- 2) To maximize the yield vigorous stirring is required.
- 3) Filtration can be done as soon as the precipitate settles.
- 4) In cases where an oil forms instead of a solid it is recommended to decant using Et_2O (0 °C) instead of washing on a frit.
- 5) In general, CH_2Cl_2 results in the best yields for pyridine salt formation and EtOAc should be used for diazine salt formation for best results.
- 6) Et_2O typically works best for crashing out the phosphonium salt, however crashing out with 50:50 Et_2O :hexanes or hexanes have been seen to improve isolation of the phosphonium salt.
- 7) At lower temperatures (−78 °C) on select substrates pseudodimer formation was observed, raising the temperature (−50 °C or −30 °C) generally eliminated this undesired side reaction.

Diphenyl(2-phenylpyridin-4-yl)(pyridin-4-yl)phosphonium trifluoromethanesulfonate (5)



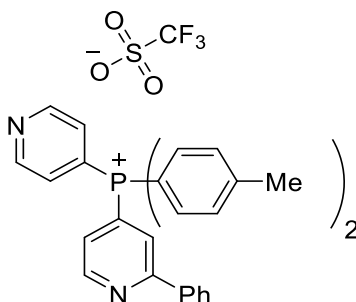
Prepared according to general procedure B using pyridine (119 μ L, 1.50 mmol), Ti_2O (250 μ L, 1.50 mmol), 4-(diphenylphosphaneyl)-2-phenylpyridine (560 mg, 1.65 mmol), DBU (224 μ L, 1.50 mmol) and CH_2Cl_2 (15 mL). After the purification procedure (solid was dissolved in approximately 2-10 mL of CH_2Cl_2 and the solution was again added dropwise to an excess of chilled Et_2O (0 $^\circ\text{C}$). The mixture was then placed in -20 $^\circ\text{C}$ refrigerator for 5 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled Et_2O (0 $^\circ\text{C}$) and dried *in vacuo* to provide the pure phosphonium salt), the title compound was isolated as a white solid (702 mg, 1.24 mmol, 83% yield). mp 73 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3059, 1573, 1440, 1262, 1223, 1150, 1109, 1030; ^1H NMR (400 MHz, CDCl_3) δ : 9.09 (1H, app t, $J = 5.1$ Hz), 9.03 (2H, app t, $J = 5.1$ Hz), 7.99-7.87 (4H, m) 7.87-7.78 (5H, m), 7.77-7.63 (6H, m), 7.57 (1H, dd, $J = 13.1, 5.1$ Hz), 7.48-7.41 (3H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.99 (d, $J = 10.4$ Hz), 151.60 (d, $J = 11.8$ Hz), 151.49 (d, $J = 10.3$ Hz), 136.49 (d, $J = 1.6$ Hz), 136.35 (d, $J = 3.0$ Hz), 134.29 (d, $J = 10.7$ Hz), 130.93 (d, $J = 13.3$ Hz), 130.14, 128.75, 127.40 (d, $J = 84.4$ Hz), 126.98 (d, $J = 8.2$ Hz), 126.89, 126.39 (d, $J = 84.3$ Hz), 125.18 (d, $J = 8.3$ Hz), 122.96 (d, $J = 8.9$ Hz), 120.38 (q, $J = 321.4$ Hz), 113.59 (d, $J = 89.4$ Hz); ^{19}F NMR (365 MHz, CDCl_3) δ : -78.14 ; ^{31}P NMR (162 MHz, CDCl_3) δ : 21.76; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 417.1537, $\text{C}_{28}\text{H}_{22}\text{N}_2\text{P}^+$ requires 417.1521.

Bis(4-methoxyphenyl)(2-phenylpyridin-4-yl)(pyridin-4-yl)phosphonium trifluoromethanesulfonate (5')



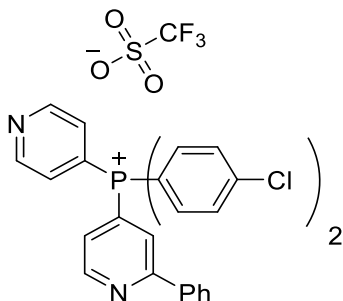
Prepared according to general procedure B using pyridine (24 μ L, 0.30 mmol), TiF_2O (50 μ L, 0.30 mmol), 4-(bis(4-methoxyphenyl)phosphaneyl)-2-phenylpyridine (135 mg, 0.33 mmol), DBU (46 μ L, 0.30 mmol) and CH_2Cl_2 (3 mL). After the purification procedure (solid was dissolved in approximately 2-10 mL of CH_2Cl_2 and the solution was again added dropwise to an excess of chilled Et_2O (0 $^\circ\text{C}$). The mixture was then placed in -20 $^\circ\text{C}$ refrigerator for 5 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled Et_2O (0 $^\circ\text{C}$) and dried *in vacuo* to provide the pure phosphonium salt), the title compound was isolated as a white crystalline solid (136 mg, 0.22 mmol, 72% yield). mp 73-74 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3046, 2934, 1592, 1573, 1536, 754, 563, 556; ^1H NMR (400 MHz, CDCl_3) δ : 9.10-8.93 (3H, m), 7.95-7.86 (2H, m), 7.79 (1H, d, $J = 14.1$ Hz), 7.66-7.55 (6H, m), 7.53-7.42 (4H, m), 7.34-7.27 (4H, m), 3.95 (6H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 166.00 (d, $J = 3.0$ Hz), 159.39 (d, $J = 10.4$), 151.78 (d, $J = 10.7$ Hz), 151.74 (d, $J = 10.0$ Hz), 136.88 (d, $J = 1.7$ Hz), 136.65 (d, $J = 12.4$ Hz), 130.56, 129.27 (d, $J = 85.2$ Hz), 129.15, 128.39 (d, $J = 85.4$ Hz), 127.22, 127.06 (d, $J = 7.7$ Hz), 125.16 (d, $J = 8.3$ Hz), 123.09 (d, $J = 8.7$ Hz), 120.76 (q, $J = 321.2$ Hz), 117.14 (d, $J = 14.5$ Hz), 103.51 (d, $J = 98.2$ Hz), 56.19; ^{19}F NMR (365 MHz, CDCl_3) δ : -78.20; ^{31}P NMR (162 MHz, CDCl_3) δ : 20.74; m/z LRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 477.2, $\text{C}_{30}\text{H}_{26}\text{N}_2\text{O}_2\text{P}^+$ requires 477.2.

(2-phenylpyridin-4-yl)(pyridin-4-yl)di-p-tolylphosphonium trifluoromethanesulfonate (5'')



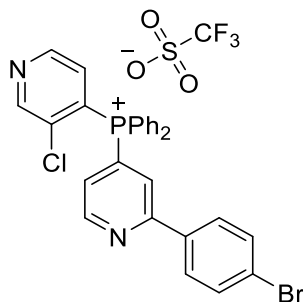
Prepared according to general procedure B using pyridine (60 μ L, 0.75 mmol), $\text{ Tf}_2\text{O}$ (126 μ L, 0.75 mmol), 4-(di-*p*-tolylphosphaneyl)-2-phenylpyridine (312 mg, 0.83 mmol), DBU (112 μ L, 0.75 mmol) and CH_2Cl_2 (7.5 mL). After the purification procedure (solid was dissolved in approximately 2-10 mL of CH_2Cl_2 and the solution was again added dropwise to an excess of chilled Et_2O (0 $^\circ\text{C}$). The mixture was then placed in -20 $^\circ\text{C}$ refrigerator for 5 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled Et_2O (0 $^\circ\text{C}$) and dried *in vacuo* to provide the pure phosphonium salt), the title compound was isolated as a brown crystalline solid (375 mg, 0.63 mmol, 84% yield). mp 70-71 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2936, 2861, 1574, 1444, 547, 543, 538, 528; ^1H NMR (400 MHz, CDCl_3) δ : 9.15-8.93 (3H, m), 7.97-7.87 (2H, m), 7.82 (1H, d, $J = 14.4$ Hz), 7.72-7.44 (14H, m), 2.55 (6H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 159.34 (d, $J = 10.3$ Hz), 151.83 (d, $J = 10.8$), 151.63 (d, $J = 9.9$ Hz), 148.52 (d, $J = 3.3$ Hz), 136.79, 134.46 (d, $J = 11.2$ Hz), 131.96 (d, $J = 13.6$ Hz), 130.52, 129.10, 128.31 (d, $J = 84.5$ Hz), 127.67 (d, $J = 75.5$ Hz), 127.30, 127.20, 125.33 (d, $J = 8.4$ Hz), 123.17 (d, $J = 8.7$), 120.64 (q, $J = 321.0$ Hz), 110.34 (d, $J = 92.3$ Hz), 21.92; ^{19}F NMR (365 MHz, CDCl_3) δ : -78.29 ; ^{31}P NMR (162 MHz, CDCl_3) δ : 21.61; m/z LRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 445.2, $\text{C}_{30}\text{H}_{26}\text{N}_2\text{P}^+$ requires 445.2.

Bis(4-chlorophenyl)(2-phenylpyridin-4-yl)(pyridin-4-yl)phosphonium trifluoromethanesulfonate (5''')



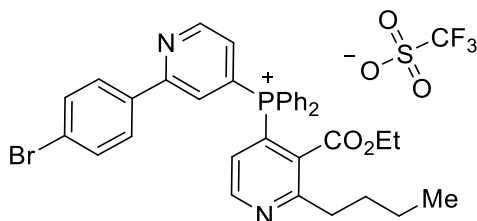
Prepared according to general procedure B using pyridine (84 μ L, 1.00 mmol), Tf₂O (168 μ L, 1.00 mmol), 4-(bis(4-chlorophenyl)phosphaneyl)-2-phenylpyridine (449 mg, 1.10 mmol), NEt₃ (140 μ L, 1.10 mmol) and CH₂Cl₂ (10 mL). After the purification procedure (solid was dissolved in approximately 2-10 mL of CH₂Cl₂ and the solution was again added dropwise to an excess of chilled Et₂O (0 °C). The mixture was then placed in –20 °C refrigerator for 5 hour. The resulting suspension was filtered on a frit and the solid was washed with chilled Et₂O (0 °C) and dried *in vacuo* to provide the pure phosphonium salt), the title compound was isolated as a yellow crystalline solid (366 mg, 0.57 mmol, 57% yield). mp 88-90 °C; IR ν_{max} /cm^{–1} (film): 3046, 2974, 2844, 1592, 1536, 727, 560, 555; ¹H NMR (400 MHz, CDCl₃) δ : 9.21-8.97 (3H, m), 8.00-7.91 (2H, m), 7.87 (1H, d, *J* = 14.3 Hz), 7.84-7.61 (10H, m), 7.57-7.43 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 159.71 (d, *J* = 10.4 Hz), 152.04 (d, *J* = 11.0), 152.00 (d, *J* = 10.2 Hz), 144.30 (d, *J* = 3.9 Hz), 136.67 (d, *J* = 1.8 Hz), 136.09 (d, *J* = 11.9 Hz), 132.01 (d, *J* = 12.4 Hz), 131.79 (d, *J* = 14.3 Hz), 130.74, 129.43 (d, *J* = 13.5 Hz), 129.20, 127.09 (d, *J* = 85.0 Hz), 127.04 (d, *J* = 83.2), 125.78, 125.26 (d, *J* = 8.7 Hz), 123.27 (d, *J* = 9.0), 120.58 (q, *J* = 321.0 Hz), 112.22 (d, *J* = 92.7 Hz); ¹⁹F NMR (365 MHz, CDCl₃) δ : –78.40; ³¹P NMR (162 MHz, CDCl₃) δ : 21.96; *m/z* LRMS (ESI + APCI) found [M-OTf]⁺ 485.1, C₂₈H₂₀Cl₂N₂P⁺ requires 485.1.

(2-(4-Bromophenyl)pyridin-4-yl)(3-chloropyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (7b)



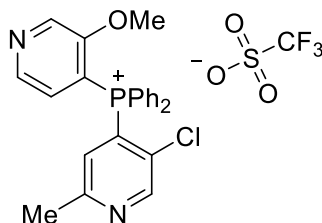
Prepared according to general procedure B using 3-chloropyridine (95 μL , 1.00 mmol), TF_2O (168 μL , 1.00 mmol), 2-(4-Bromophenyl)-4-(diphenylphosphaneyl)pyridine (460 mg, 1.10 mmol), DBU (149 μL , 1.00 mmol) and CH_2Cl_2 (10 mL). After the purification procedure, the title compound was isolated as a white solid (556 mg, 0.82 mmol, 82% yield). mp 94-96 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3062, 1579, 1439, 1258, 1223, 1149, 1107, 1029, 724; ^1H NMR (400 MHz, CDCl_3) δ : 9.04 (1H, app t, $J = 5.4$ Hz), 8.97-8.82 (2H, m), 8.02 (1H, d, $J = 14.5$ Hz), 7.96-7.85 (4H, m), 7.84-7.72 (8H, m), 7.64-7.52 (3H, m), 7.41 (1H, dd, $J = 15.1, 5.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.30 (d, $J = 10.8$ Hz), 151.78 (d, $J = 11.1$ Hz), 151.59 (d, $J = 5.1$ Hz), 150.33 (d, $J = 10.1$ Hz), 136.46 (d, $J = 3.0$ Hz), 135.67 (d, $J = 1.7$ Hz), 134.51, 134.27, 132.14, 131.17 (d, $J = 13.6$ Hz), 130.91 (d, $J = 8.4$ Hz), 128.93, 127.66 (d, $J = 85.7$ Hz), 125.57 (d, $J = 88.3$ Hz), 125.33 (d, $J = 8.5$ Hz), 125.13, 123.02 (d, $J = 9.1$ Hz), 120.57 (q, $J = 321.2$ Hz), 113.39 (d, $J = 90.4$ Hz); ^{19}F NMR (365 MHz, CDCl_3) δ : -78.18; ^{31}P (162 MHz, CDCl_3) δ : 22.17; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 529.0239, $\text{C}_{28}\text{H}_{20}\text{BrClN}_2\text{P}^+$ requires 529.0236.

(2-(4-Bromophenyl)pyridin-4-yl)(2-butyl-3-(ethoxycarbonyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (8b)



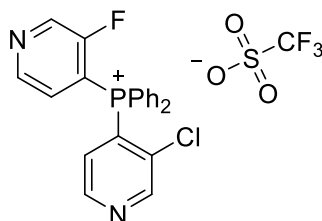
Prepared according to general procedure B (except that after 2-(4-bromophenyl)-4-(diphenylphosphino)pyridine was added, the reaction mixture was stirred for 30 min at -30 °C) using ethyl 2-butylnicotinate (300.4 mg, 1.45 mmol), Tf₂O (244 μL, 1.45 mmol), 2-(4-bromophenyl)-4-(diphenylphosphino)pyridine (667 mg, 1.60 mmol), DBU (218 μL, 1.45 mmol) and CH₂Cl₂ (14.5 mL). After the purification procedure, the title compound was isolated as a white amorphous powder (831 mg, 1.07 mmol, 74% yield). mp 212-214 °C; IR ν_{max} /cm⁻¹ (film): 3045, 2950, 2927, 2870, 1706, 1787, 1578, 1547, 1538, 1463, 1440, 1435, 1404, 1369, 1291, 1275, 1258, 1223, 1177, 1152, 1136, 1105, 1069, 1030, 1013, 1004, 816, 751, 727, 721, 697, 685; ¹H NMR (400 MHz, CDCl₃) δ : 9.04-9.00 (2H, m), 7.94-7.84 (5H, m), 7.80-7.69 (8H, m), 7.60-7.54 (3H, m), 7.33 (1H, dd, J = 15.7, 5.0 Hz), 3.51 (2H, q, J = 7.2 Hz), 3.07 (2H, t, J = 7.8 Hz), 1.82-1.74 (2H, m), 1.41 (2H, sext, J = 7.4 Hz), 0.99-0.93 (6H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 166.34 (d, J = 3.7 Hz), 164.12 (d, J = 6.3 Hz), 157.79 (d, J = 10.6 Hz), 153.20 (d, J = 11.6 Hz), 151.37 (d, J = 11.0 Hz), 135.91 (d, J = 2.9 Hz), 135.84 (d, J = 1.7 Hz), 134.53 (d, J = 10.5 Hz), 132.17, 130.65 (d, J = 13.3 Hz), 129.71 (d, J = 86.4 Hz), 128.79, 128.50 (d, J = 4.9 Hz), 127.95 (d, J = 9.5 Hz), 126.79 (d, J = 83.3 Hz), 125.40 (d, J = 8.1 Hz), 125.07, 123.09 (d, J = 8.8 Hz), 120.66 (q, J = 319.6 Hz), 115.84 (d, J = 90.5 Hz), 63.18, 37.27 (d, J = 1.5 Hz), 31.87, 22.62, 13.75, 13.26; ¹⁹F NMR (365 MHz, CDCl₃) δ : -78.19; ³¹P NMR (162 MHz, CDCl₃) δ : 27.28; m/z HRMS (ESI + APCI) found [M-OTf]⁺ 623.1460, C₃₅H₃₃BrN₂O₂P⁺ requires 623.1463.

(5-Chloro-2-methylpyridin-4-yl)(3-methoxypyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (9b)



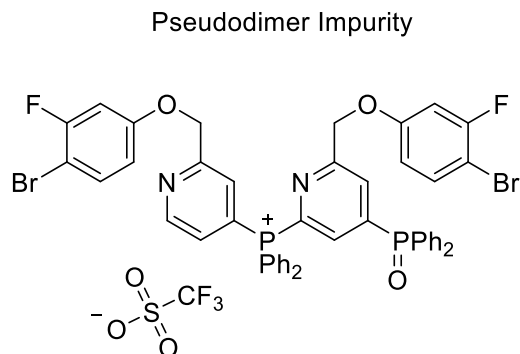
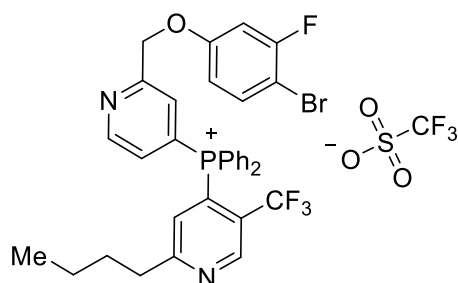
Prepared according to general procedure B (except that after 5-chloro-4-(diphenylphosphino)-2-methylpyridine was added, the reaction mixture was stirred for 30 min at $-30\text{ }^{\circ}\text{C}$) using 3-methoxypyridine (202 μL , 2.00 mmol), Tf₂O (336 μL , 2.00 mmol), 5-chloro-4-(diphenylphosphino)-2-methylpyridine (686 mg, 2.20 mmol), DBU (300 μL , 2.00 mmol) and CH₂Cl₂ (20 mL). After the purification procedure, the title compound was isolated as an amorphous white powder (842 mg, 1.48 mmol, 74% yield). mp 182-186 $^{\circ}\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3060, 2951, 1570, 1544, 1483, 1460, 1439, 1411, 1380, 1326, 1300, 1258, 1222, 1140, 1103, 1087, 1072, 1043, 1029, 998, 914, 823, 808, 753, 722, 688, 646; ¹H NMR (400 MHz, CDCl₃) δ : 8.74 (1H, d, $J = 6.6\text{ Hz}$), 8.70 (1H, d, $J = 6.7\text{ Hz}$), 8.62 (1H, t, $J = 4.6\text{ Hz}$), 7.91-7.87 (2H, m), 7.81-7.76 (4H, m), 7.72-7.67 (4H, m), 7.39 (1H, dd, $J = 15.2, 5.0\text{ Hz}$), 7.26 (1H, d, $J = 15.6\text{ Hz}$), 3.72 (3H, s), 2.65 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 160.05 (d, $J = 10.2\text{ Hz}$), 155.60, 150.83 (d, $J = 5.7\text{ Hz}$), 144.17 (d, $J = 11.3\text{ Hz}$), 136.64 (d, $J = 4.5\text{ Hz}$), 135.91 (d, $J = 3.1\text{ Hz}$), 134.11 (d, $J = 11.2\text{ Hz}$), 130.81 (d, $J = 13.7\text{ Hz}$), 130.79 (d, $J = 2.2\text{ Hz}$), 129.12 (d, $J = 8.1\text{ Hz}$), 127.68 (d, $J = 6.8\text{ Hz}$), 126.35 (d, $J = 90.1\text{ Hz}$), 120.68 (q, $J = 319.6\text{ Hz}$), 114.06 (d, $J = 92.0\text{ Hz}$), 113.45 (d, $J = 88.4\text{ Hz}$), 57.39 (dd, $J = 4.6, 5.9\text{ Hz}$), 24.19; ¹⁹F NMR (365 MHz, CDCl₃) δ : -78.26 ; ³¹P NMR (162 MHz, CDCl₃) δ : 21.15; m/z HRMS (ESI + APCI) found [M-OTf]⁺ 419.1099, C₂₄H₂₁ClN₂OP⁺ requires 419.1080.

(3-Chloro-pyridin-4-yl)(3-fluoropyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (10b)



Prepared according to general procedure B (except that after the initial extraction the aqueous layer was extracted an additional 3 times with CH_2Cl_2 and then the combined organic was washed once with water prior to concentration) using 3-fluoropyridine (43 μL , 0.50 mmol), Tf_2O (84 μL , 0.50 mmol), 3-chloro-4-(diphenylphosphino)pyridine (164 mg, 0.55 mmol), DBU (75 μL , 0.50 mmol) and CH_2Cl_2 (5.0 mL). After the purification procedure (concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of 50% Et_2O in hexanes instead of Et_2O), the title compound was isolated as a pale yellow solid (148 mg, 0.27 mmol, 54% yield). mp 59-62 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3085, 3024, 1586, 1546, 1472, 1440, 1403, 1282, 1247, 1225, 1201, 1184, 1154, 1132, 1106, 1030, 996, 749; ^1H NMR (400 MHz, CDCl_3) δ : 8.99-8.71 (4H, m), 8.02-7.68 (2H, m), 7.83-7.57 (9H, m), 7.45 (1H, dd, $J = 15.4, 4.8$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ : 160.39 (d, $J = 264.3$ Hz), 153.28 (d, $J = 5.2$ Hz), 151.07 (d, $J = 10.4$ Hz), 149.09 (dd, $J = 10.7, 5.3$ Hz), 141.83 (dd, $J = 24.0, 4.1$ Hz), 137.73 (d, $J = 3.2$ Hz), 136.19 (d, $J = 2.0$ Hz), 135.86 (d, $J = 11.7$ Hz), 132.22 (d, $J = 14.1$ Hz), 131.34 (d, $J = 8.7$ Hz), 129.60 (d, $J = 3.8$ Hz), 127.07 (d, $J = 91.3$ Hz), 121.73 (d, $J = 319.0$ Hz), 116.20 (dd, $J = 87.5, 13.3$ Hz), 115.76 (d, $J = 13.3$ Hz); ^{19}F NMR (365 MHz, CD_3OD) δ : -79.79, -111.00; ^{31}P NMR (162 MHz, CDCl_3) δ : 19.61 (d, $J = 4.0$ Hz); m/z LRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 393.1, $\text{C}_{22}\text{H}_{16}\text{ClFN}_2\text{OP}^+$ requires 393.1.

(2-((4-Bromo-3-fluorophenoxy)methyl)pyridin-4-yl)(2-butyl-5-(trifluoromethyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate and (6-((4-bromo-3-fluorophenoxy)methyl)-4-(diphenylphosphoryl)pyridin-2-yl)(2-((4-bromo-3-fluorophenoxy)methyl)pyridin-4-yl)diphenylphosphonium (11b)

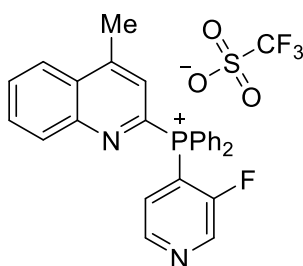


5.6:1

Prepared according to general procedure B using 2-butyl-5-(trifluoromethyl)pyridine (93 mg, 0.46 mmol), Ti_2O (77 μL , 0.46 mmol), 2-((4-bromo-3-fluorophenoxy)methyl)-4-(diphenylphosphino)pyridine (234 mg, 0.50 mmol), DBU (68 μL , 0.46 mmol) and CH_2Cl_2 (4.6 mL). After the purification procedure, the title compounds were isolated as a mixture (crude: 3.7:1; pure: 5.6:1) as a white amorphous powder (204 mg). The mixture was carried forward through the ligand coupling step. IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3063, 2959, 2932, 2872, 1603, 1578, 1532, 1486, 1439, 1384, 1320, 1259, 1223, 1143, 1120, 1106, 1029, 997, 968, 945, 909, 848, 834, 727; Major, ^1H NMR (400 MHz, CDCl_3) δ : 9.16 (1H, d, $J = 7.3$ Hz), 9.03 (1H, t, $J = 5.2$ Hz), 7.93-7.90 (2H, m), 7.80-7.62 (10H, m), 7.36 (1H, t, $J = 8.4$ Hz), 7.21 (1H, d, $J = 17.4$ Hz), 6.63 (1H, dd, $J = 10.0$, 2.7 Hz), 6.58 (1H, dd, $J = 8.7$, 2.4 Hz), 5.33 (2H, s), 2.94 (2H, t, $J = 7.7$ Hz), 1.66 (2H, qn, $J = 7.6$ Hz), 1.31 (2H, sext, $J = 7.5$ Hz), 0.87 (3H, t, $J = 7.3$ Hz); Major, ^{13}C NMR (100 MHz, CDCl_3) δ : 170.37 (d, $J = 9.8$ Hz), 159.21 (d, $J = 245.9$ Hz), 158.88 (d, $J = 10.3$ Hz), 157.97 (d, $J = 9.8$ Hz), 151.53 (d, $J = 10.7$ Hz), 150.06 (m), 136.40 (d, $J = 3.0$ Hz), 134.56 (d, $J = 7.7$ Hz), 133.52, 130.93 (d, $J = 13.4$ Hz), 130.24 (d, $J = 8.5$ Hz), 128.43 (d, $J = 84.9$ Hz), 126.52 (d, $J = 8.5$ Hz), 124.46 (d, $J = 8.8$ Hz), 124.17 (d, $J = 4.1$ Hz), 123.82 (d, $J = 79.6$ Hz), 122.48 (qd, $J = 273.8$, 2.3 Hz), 120.56

(q, $J = 319.5$ Hz), 114.65 (d, $J = 89.3$ Hz), 111.81 (d, $J = 3.0$ Hz), 103.90 (d, $J = 25.5$ Hz), 100.22 (d, $J = 21.1$ Hz), 70.00 (d, $J = 1.5$ Hz), 37.94, 30.25, 22.14, 13.63; Major, ^{19}F NMR (365 MHz, CDCl_3) δ : -53.41 (d, $J = 1.7$ Hz), -78.35, -104.68 (t, $J = 8.4$ Hz); Major, ^{31}P NMR (162 MHz, CDCl_3) δ : 26.97 (d, $J = 2.4$ Hz); m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 667.1166, $\text{C}_{34}\text{H}_{29}\text{BrF}_4\text{N}_2\text{OP}^+$ requires 667.1137.

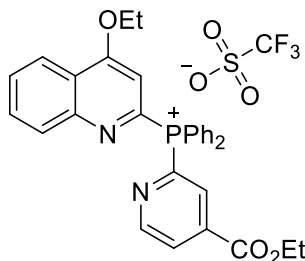
(3-Fluoropyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (12b)



Prepared according to general procedure B, using 3-fluoropyridine (171 μL , 2.00 mmol), Tf_2O (336 μL , 2.00 mmol), 2-(diphenylphosphaneyl)-4-methylquinoline (720 mg, 2.20 mmol), DBU (300 μL , 2.00 mmol), and CH_2Cl_2 (20 mL). After purification procedure, the title compound was provided as a light brown crystalline solid (660 mg, 1.16 mmol, 58% yield). mp 65-66 $^\circ\text{C}$ IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3064, 1545, 1505, 997, 857, 688; ^1H NMR (400 MHz, CDCl_3) δ : 8.88-8.83 (2H, m), 8.19 (1H, d, $J = 8.2$ Hz), 8.14 (1H, d, $J = 8.2$ Hz), 7.95-7.78 (13H, m), 7.41 (1H, dt, $J = 14.2$, 5.1 Hz), 2.88 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.98 (d, $J = 265.8$ Hz), 149.37 (d, $J = 11.4$ Hz), 148.49 (d, $J = 23.9$ Hz), 148.15 (dd, $J = 9.9$, 6.4 Hz), 142.67 (d, $J = 120.2$ Hz), 139.85 (dd, $J = 22.9$, 3.8 Hz), 136.27 (d, $J = 31.1$ Hz), 134.67 (d, $J = 10.6$ Hz), 131.68, 130.92 (d, $J = 13.4$ Hz), 130.65 (d, $J = 1.2$ Hz), 130.54, 129.45 (d, $J = 3.1$ Hz), 128.86 (dd, $J = 7.0$, 1.7 Hz), 125.22 (d, $J = 27.1$ Hz), 124.61 (d, $J = 1.4$ Hz), 120.79 (q, $J = 321.1$ Hz), 116.43 (dd, $J = 84.7$, 13.9 Hz), 114.84 (d, $J = 88.9$ Hz), 19.19 (d, $J = 1.6$ Hz); ^{19}F NMR (365 MHz, CDCl_3) δ : -78.25, -109.74

(d, $J = 6.6$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ : 11.79; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 423.1454, $\text{C}_{27}\text{H}_{21}\text{FN}_2\text{P}^+$ requires 423.1426.

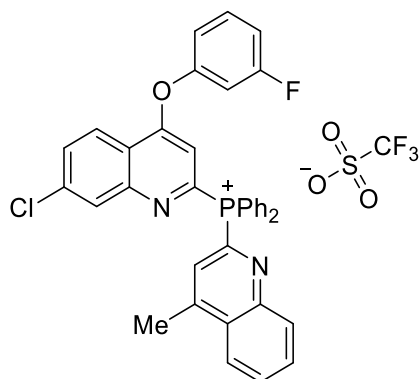
(4-(Ethoxycarbonyl)pyridin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (13b)



Prepared according to general procedure B, using 4- picolyl acid ethyl ester (150 μL , 1.00 mmol), Tf_2O (168 μL , 1.00 mmol), 2-(diphenylphosphaneyl)-4-ethoxyquinoline (392 mg, 1.10 mmol), DBU (150 μL , 1.00 mmol), and CH_2Cl_2 (10 mL). After purification procedure, (concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of 50% Et_2O in hexanes instead of Et_2O) the title compound was provided as a light brown amorphous solid (400 mg, 0.61 mmol, 61% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3064, 2986, 1729, 1476, 942, 851, 557, 537; ^1H NMR (400 MHz, CDCl_3) δ : 9.19 (1H, d, $J = 4.8$ Hz), 8.48 (1H, d, $J = 5.8$ Hz), 8.35 (1H, d, $J = 8.3$ Hz), 8.31-8.25 (1H, m), 8.05 (1H, d, $J = 8.5$ Hz), 7.93-7.66 (12H, m), 7.18 (1H, d, $J = 6.2$ Hz), 4.40 (2H, q, $J = 7.1$ Hz), 4.22 (2H, q, $J = 7.0$ Hz), 1.51 (3H, t, $J = 7.0$ Hz), 1.35 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.46 (d, $J = 14.2$ Hz), 163.15 (d, $J = 2.7$ Hz), 153.32 (d, $J = 20.0$ Hz), 149.59 (d, $J = 25.9$ Hz), 145.87 (d, $J = 120.4$ Hz), 145.13 (d, $J = 119.0$ Hz), 139.52 (d, $J = 10.4$ Hz), 135.75 (d, $J = 3.1$ Hz), 134.91 (d, $J = 9.9$ Hz), 131.83, 131.26 (d, $J = 24.2$ Hz), 130.45 (d, $J = 13.0$ Hz), 129.31 (d, $J = 18.0$ Hz), 127.48 (d, $J = 3.5$ Hz), 122.66, 121.93 (d, $J = 2.5$ Hz), 120.78 (q, $J = 321.0$ Hz), 116.87 (d, $J = 87.9$ Hz), 106.06, 105.78, 65.83, 62.74, 14.04, 13.92;

^{19}F NMR (365 MHz, CDCl_3) δ : -78.25 ; ^{31}P NMR (162 MHz, CDCl_3) δ : 9.58 ; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 507.1919 , $\text{C}_{31}\text{H}_{28}\text{N}_2\text{O}_3\text{P}^+$ requires 507.1832 .

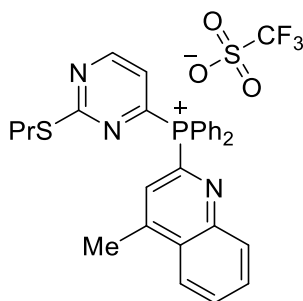
(7-Chloro-4-(3-fluorophenoxy)quinolin-2-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (14b)



Prepared according to general procedure B, using 7-chloro-4-(3-fluorophenoxy)quinoline (244 mg, 0.89 mmol), Tf_2O (151 μL , 0.89 mmol), 2-(diphenylphosphaneyl)-4-methylquinoline (320 mg, 0.99 mmol), DBU (133 μL , 0.89 mmol), and CH_2Cl_2 (9 mL). After purification procedure, the title compound was provided as a brown amorphous solid (330 mg, 0.47 mmol, 53% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3067, 1607, 666, 605, 579, 544, 532; ^1H NMR (400 MHz, CDCl_3) δ : 8.41 (1H, d, $J = 9.0$ Hz), 8.16-8.14 (2H, m), 7.92-7.67 (15H, m), 7.54 (1H, d, $J = 4.6$ Hz), 7.31 (1H, q, $J = 5.8$ Hz), 7.10 (1H, d, $J = 5.6$ Hz), 6.98 (1H, dd, $J = 8.2, 1.8$ Hz), 6.92-6.84 (2H, m), 2.78 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.16 (d, $J = 249.9$ Hz), 162.90 (d, $J = 13.9$ Hz), 153.49 (d, $J = 10.4$ Hz), 150.56 (d, $J = 25.7$ Hz), 148.76 (d, $J = 10.6$ Hz), 148.15 (d, $J = 8.6$ Hz), 147.67 (d, $J = 132.3$ Hz), 143.40 (d, $J = 114.9$ Hz), 138.65, 135.63 (d, $J = 3.1$ Hz), 134.76 (d, $J = 9.8$ Hz), 131.75 (d, $J = 9.4$ Hz), 131.56, 130.77, 130.66, 130.35 (d, $J = 12.9$ Hz), 128.87 (d, $J = 3.0$ Hz), 128.57 (d, $J = 1.0$ Hz), 128.56, 126.04 (d, $J = 25.7$ Hz), 124.47 (d, $J = 1.3$ Hz), 123.78, 120.77 (q, $J = 321.2$ Hz), 119.87 (d, $J = 2.5$ Hz), 116.91 (d, $J = 87.7$ Hz), 117.03 (d, $J = 3.5$ Hz),

113.69 (d, $J = 20.9$ Hz), 109.23 (d, $J = 27.4$ Hz), 108.87 (d, $J = 24.2$ Hz), 19.14 (d, $J = 1.5$ Hz) ; ^{19}F NMR (365 MHz, CDCl_3) δ : -78.19, -108.64 (q, $J = 8.3$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ : 8.06; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 599.1450, $\text{C}_{38}\text{H}_{27}\text{ClFN}_2\text{OP}^+$ requires 599.1467.

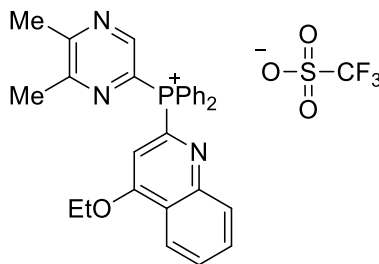
(4-Methylquinolin-2-yl)diphenyl(2-(propylthio)pyrimidin-4-yl)phosphonium trifluoromethanesulfonate (15b)



Prepared according to general procedure B (except the stirring time after the addition of the heteroaryl phosphine was 45 minutes instead of 30 minutes) using 2-(propylthio)pyrimidine (154 mg, 1.00 mmol), Tf_2O (168 μL , 1.00 mmol), 2-(diphenylphosphaneyl)-4-methylquinoline (360 mg, 1.10 mmol), DBU (149, 1.00 mmol) and EtOAc (5 mL). After the purification procedure, the title compound was isolated as a brown solid (433 mg, 0.72 mmol, 72% yield). mp 52-54 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3064, 2963, 1576, 1544, 1526, 1439, 1259, 1143, 1029, 727; ^1H NMR (400 MHz, CDCl_3) δ : 8.91 (1H, dd, $J = 7.6, 4.8$ Hz), 8.21-8.12 (2H, m), 7.95-7.87 (3H, m), 7.87-7.80 (5H, m), 7.80-7.73 (4H, m), 7.70 (1H, dd, $J = 6.0, 4.8$ Hz), 7.65 (1H, d, $J = 4.8$ Hz), 2.93 (2H, t, $J = 7.3$ Hz), 2.83 (3H, s), 1.53 (2H, sext, $J = 7.3$ Hz), 0.84 (3H, t, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 174.98 (d, $J = 18.0$ Hz), 159.91 (d, $J = 7.3$ Hz), 154.41 (d, $J = 111.9$ Hz), 148.87 (d, $J = 10.7$

Hz), 148.51 (d, $J = 23.4$ Hz), 142.36 (d, $J = 117.1$ Hz), 136.04 (d, $J = 3.0$ Hz), 134.99 (d, $J = 9.9$ Hz), 131.72, 130.77-130.43 (3C, m), 129.12 (d, $J = 3.0$ Hz), 125.98 (d, $J = 26.5$ Hz), 124.51 (d, $J = 1.2$ Hz), 123.11 (d, $J = 19.6$ Hz), 120.74 (q, $J = 321.1$ Hz), 115.21 (d, $J = 87.3$ Hz), 33.05, 22.02, 19.18 (d, $J = 1.5$ Hz), 13.23; ^{19}F NMR (365 MHz, CDCl_3) δ : -78.21; ^{31}P (162 MHz, CDCl_3) δ : 9.49; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 480.1673, $\text{C}_{29}\text{H}_{27}\text{N}_3\text{PS}^+$ requires 480.1663.

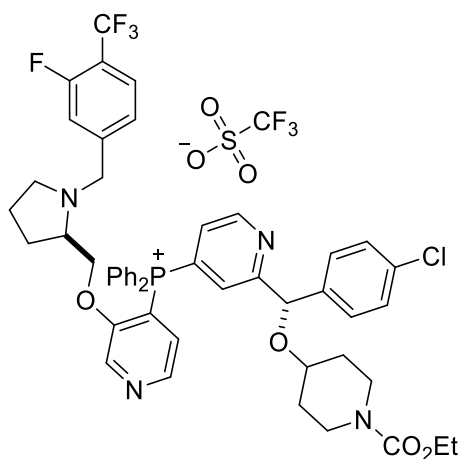
(5,6-Dimethylpyrazin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (16b)



Prepared according to general procedure B using 2,3-dimethylpyrazine (128 μL , 1.20 mmol), Tf_2O (336 μL , 1.20 mmol), 2-(diphenylphosphino)-4-ethoxyquinoline (472 mg, 1.32 mmol), DBU (180 μL , 1.20 mmol) and CH_2Cl_2 (12 mL). After the purification procedure (concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of hexanes instead of Et_2O and placed at room temperature overnight), the title compound was isolated as a light brown amorphous powder (663 mg, 1.08 mmol, 90% yield). mp 145-148 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3066, 2989, 1571, 1551, 1507, 1438, 1410, 1385, 1354, 1316, 1260, 1222, 1192, 1145, 1108, 1029, 997, 771, 751, 728, 707; ^1H NMR (400 MHz, CDCl_3) δ : 8.67 (1H, s), 8.35 (1H, d, $J = 8.4$ Hz), 8.04 (1H, d, $J = 8.5$ Hz), 7.90-7.81 (7H, m), 7.77-7.70 (5H, m), 7.26 (1H, d, $J = 6.1$ Hz), 4.25 (2H, q, $J = 7.0$ Hz), 2.73 (3H, s), 2.69 (3H, s), 1.52 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.27 (d, $J = 14.0$ Hz), 159.36 (d, $J = 3.4$ Hz), 156.13 (d, $J = 15.5$ Hz), 149.50 (d, $J = 25.9$ Hz), 147.83 (d, $J = 23.3$ Hz), 144.83 (d, $J = 118.6$ Hz), 136.09 (d, $J = 83.7$ Hz), 135.67 (d, $J = 3.0$ Hz), 134.74 (d, $J =$

9.9 Hz), 131.76, 130.37 (d, $J = 12.9$ Hz), 129.38, 129.16, 122.50, 121.80 (d, $J = 2.4$ Hz), 120.73 (q, $J = 319.6$ Hz), 116.49 (d, $J = 87.7$ Hz), 105.64 (d, $J = 29.0$ Hz), 65.66, 22.76, 22.42, 14.01; ^{19}F NMR (365 MHz, CDCl_3) δ : -78.26; ^{31}P NMR (162 MHz, CDCl_3) δ : 7.50; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 464.1931, $\text{C}_{29}\text{H}_{27}\text{N}_3\text{OP}^+$ requires 464.1892.

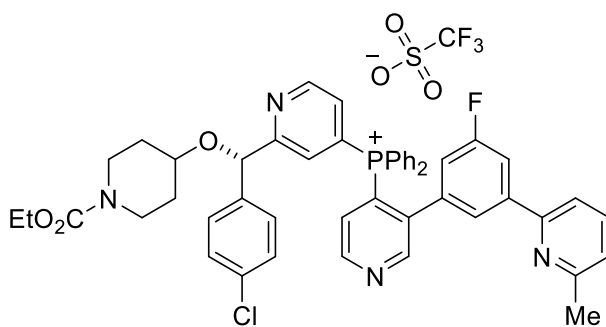
(2-((*S*)-(4-Chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)(3-(((*R*)-1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (17b)



Prepared according to general procedure B, using (*R*)-3-((1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridine (177 mg, 0.50 mmol), TF_2O (85 μL , 0.50 mmol), ethyl (*S*)-4-((4-chlorophenyl)(4-(diphenylphosphaneyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate (307 mg, 0.55 mmol), DBU (75 μL , 0.89 mmol), and CH_2Cl_2 (5 mL). After the purification procedure (concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of 50% Et_2O in hexanes instead of Et_2O), the title compound was provided as a brown amorphous solid (370 mg, 0.35 mmol, 70% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3061, 2950, 2873, 825, 560, 557, 535, 528; ^1H NMR (500 MHz, CDCl_3) δ : 8.90 (1H, t, $J = 5.1$ Hz), 8.74 (1H, d, $J = 6.4$ Hz), 8.57 (1H, t, $J = 4.4$ Hz), 7.92-7.45 (13H, m), 7.36-7.27 (4H, m), 7.14-6.96 (3H, m),

5.72 (1H, s), 4.21-4.04 (3H, m), 3.89-3.78 (1H, m), 3.69-3.44 (4H, m), 3.32-3.05 (3H, m), 2.85-2.65 (1H, m), 2.24-1.94 (2H, br), 1.83-1.63 (3H, m), 1.48-1.35 (4H, m), 1.34-1.16 (4H, m); ^{13}C NMR (125 MHz, CDCl_3) δ : 164.41 (d, $J = 9.9$ Hz), 159.67 (dq, $J = 256.0, 2.4$ Hz), 155.43, 155.18, 151.30 (d, $J = 10.5$ Hz), 144.50 (d, $J = 11.4$ Hz), 138.69, 136.28-136.10 (m), 134.25-134.02 (m, 2C), 132.57, 131.94 (dd, $J = 14.6, 4.6$ Hz), 131.03 (dd, $J = 13.4, 7.7$ Hz), 128.89, 128.86 (d, $J = 15.3$ Hz), 128.69 (d, $J = 4.8$ Hz), 128.59 (d, $J = 85.2$ Hz), 128.52 (d, $J = 70.8$ Hz), 128.32, 127.31-127.08 (m), 125.56 (d, $J = 8.6$ Hz), 123.15 (d, $J = 9.4$ Hz), 122.51 (dq, $J = 271.8, 1.9$ Hz), 120.63 (q, $J = 320.7$ Hz), 114.79 (dd, $J = 81.0, 28.2$ Hz), 113.05 (d, $J = 88.0$ Hz), 72.56, 61.37, 57.85, 54.02, 53.99, 40.82, 40.76, 31.46, 30.43, 29.67, 27.89, 22.63, 14.66; ^{19}F NMR (365 MHz, CDCl_3) δ : -61.18 (d, $J = 13.2$ Hz), -78.25, -113.33-115.80 (m); ^{31}P NMR (162 MHz, CDCl_3) δ : 21.01; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+ 911.3094$, $\text{C}_{50}\text{H}_{49}\text{ClF}_4\text{N}_4\text{O}_4\text{P}^+$ requires 911.3116.

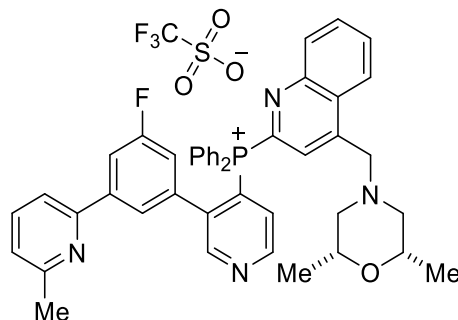
(S)-2-((4-Chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)(3-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (18b)



Prepared according to general procedure B using 2-(3-fluoro-5-(pyridin-3-yl)phenyl)-6-methylpyridine (132 mg, 0.50 mmol), TF_2O (84 μL , 0.50 mmol), ethyl (S)-4-((4-chlorophenyl)(4-(diphenylphosphaneyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate (308 mg, 0.55 mmol),

DBU (75 μ L, 0.50 mmol) and CH_2Cl_2 (5 mL). After the purification procedure, the title compound was isolated as a white solid (305 mg, 0.31 mmol, 63% yield). mp 103-109 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3063, 2928, 1687, 1438, 1261, 1224, 1149, 1030, 796; ^1H NMR (400 MHz, CDCl_3) δ : 9.00 (1H, app t, $J = 4.7$ Hz), 8.82 (1H, d, $J = 7.0$ Hz), 8.74 (1H, app t, $J = 5.3$ Hz), 7.81-7.72 (2H, m), 7.71-7.60 (9H, m), 7.58-7.47 (3H, m), 7.44 (1H, d, $J = 9.8$ Hz), 7.28 (1H, s), 7.29-7.19 (6H, m), 7.07 (1H, d, $J = 7.6$ Hz), 7.02 (1H, d, $J = 7.7$ Hz), 6.46 (1H, d, $J = 8.3$ Hz) 5.62 (1H, s), 4.09 (2H, q, $J = 7.2$ Hz), 3.62-3.44 (3H, m), 3.17-3.02 (2H, m), 2.44 (3H, s), 1.73-1.59 (2H, m), 1.48-1.33 (2H, m), 1.23 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.84 (d, $J = 9.9$ Hz), 162.21 (d, $J = 249.4$ Hz), 158.45, 155.36, 153.28 (d, $J = 7.8$ Hz), 152.76 (d, $J = 2.2$ Hz), 150.98-150.64 (2C, m), 141.63 (d, $J = 7.8$ Hz), 140.06 (d, $J = 7.2$ Hz), 138.47, 137.34, 136.68-136.51 (m), 136.01-135.82 (m), 134.63-134.36 (m), 133.90, 130.80 (d, $J = 13.3$ Hz), 128.74 (d, $J = 83.4$ Hz), 128.72, 128.62 (d, $J = 9.0$ Hz), 128.43, 125.91 (d, $J = 8.1$ Hz), 124.96 (d, $J = 83.9$ Hz), 124.06, 123.52 (d, $J = 9.0$ Hz), 122.95, 120.73 (q, $J = 321.2$ Hz), 117.38, 116.4 (d, $J = 23.3$ Hz), 115.36 (d, $J = 88.8$ Hz), 115.12 (d, $J = 88.8$ Hz), 114.44 (d, $J = 22.2$ Hz), 79.76, 72.91, 61.24, 40.78, 40.70, 31.32, 30.27, 24.50, 14.63; ^{19}F NMR (365 MHz, CDCl_3) δ : -110.66 (t, $J = 9.4$ Hz), -78.16; ^{31}P (162 MHz, CDCl_3) δ : 20.63; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 821.2852, $\text{C}_{49}\text{H}_{44}\text{ClFN}_4\text{O}_3\text{P}^+$ requires 821.2824.

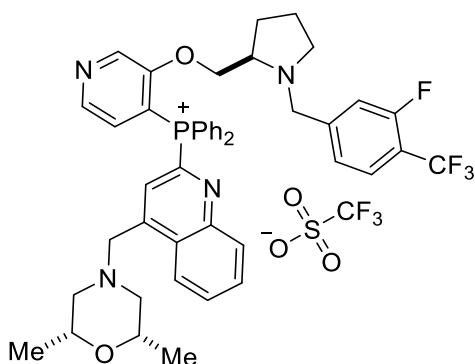
(4-(((2*R*, 6*S*)-2,6-Dimethylmorpholino)methyl)quinolin-2-yl)(3-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (19b)



Prepared according to general procedure B using 2-(3-fluoro-5-(pyridin-3-yl)phenyl)-6-methylpyridine (132 mg, 0.50 mmol), Tf₂O (84 μ L, 0.50 mmol), (2*R*, 6*S*)-4-((2-(diphenylphosphaneyl)quinolin-4-yl)methyl)-2,6-dimethylmorpholine (242 mg, 0.55 mmol), DBU (75 μ L, 0.50 mmol) and CH₂Cl₂ (5 mL). After the purification procedure, the title compound was isolated as an off white solid (317 mg, 0.37 mmol, 74% yield). mp 106-111 °C; IR ν_{max} /cm⁻¹ (film): 3063, 2971, 2930, 2856, 1575, 1439, 1263, 1223, 1143, 1030, 728; ¹H NMR (400 MHz, CDCl₃) δ : 9.03 (1H, app t, *J* = 4.7 Hz), 8.75 (1H, d, *J* = 6.8 Hz), 8.12 (1H, d, *J* = 8.4 Hz), 8.02-7.89 (6H, m), 7.88-7.75 (6H, m), 7.59 (1H, t, *J* = 7.7 Hz), 7.55-7.36 (4H, m), 7.05 (1H, d, *J* = 7.7 Hz), 6.93 (1H, s), 6.64 (1H, d, *J* = 7.8 Hz), 6.31 (1H, d, *J* = 8.2 Hz), 3.75 (2H, s), 3.43-3.21 (2H, m), 2.52-2.38 (5H, m), 1.83 (2H, t, *J* = 10.2 Hz), 1.07 (6H, d, *J* = 6.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 162.04 (d, *J* = 249.4 Hz), 158.29, 152.53 (d, *J* = 7.4 Hz), 152.27 (d, *J* = 2.5 Hz), 150.80 (d, *J* = 10.5 Hz), 148.33 (d, *J* = 23.0), 147.71 (br), 144.34 (d, *J* = 118.4 Hz), 141.49 (d, *J* = 8.0 Hz), 139.73 (d, *J* = 7.3 Hz), 137.38-137.20 (m), 137.12, 136.08 (d, *J* = 3.1 Hz), 135.06 (d, *J* = 9.8 Hz), 131.61, 130.76 (d, *J* = 12.9 Hz), 130.22 (2C, m), 128.95 (d, *J* = 9.7 Hz), 128.39 (d, *J* = 85.0 Hz), 127.11 (d, *J* = 3.4 Hz), 123.26, 123.04 (d, *J* = 2.5 Hz), 122.91, 122.44 (d, *J* = 28.4 Hz), 120.85

(q, $J = 321.3$ Hz), 116.58 (d, $J = 86.4$ Hz), 116.55, 116.00 (d, $J = 23.4$ Hz), 113.76 (d, $J = 22.6$ Hz), 71.62, 59.29, 57.36, 24.58, 18.86; ^{19}F NMR (365 MHz, CDCl_3) δ : -78.07, -111.47 (t, $J = 10.2$ Hz); ^{31}P (162 MHz, CDCl_3) δ : 11.94; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 703.2979, $\text{C}_{45}\text{H}_{41}\text{FN}_4\text{OP}^+$ requires 703.3002.

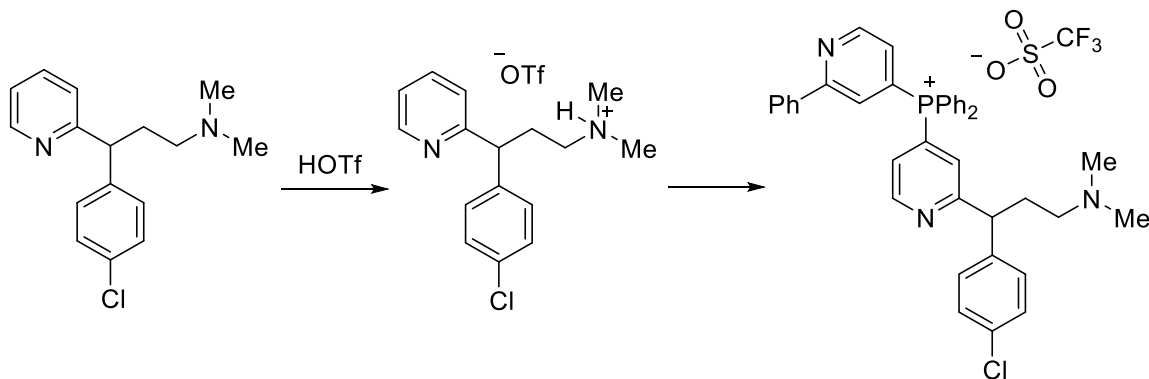
(4-(((2*S*, 6*R*)-2,6-Dimethylmorpholino)methyl)quinolin-2-yl)(3-(((*R*)-1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (20b)



Prepared according to general procedure B, using (*R*)-3-(((1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridine (177 mg, 0.50 mmol), TF_2O (85 μL , 0.50 mmol), (2*R*, 6*S*)-4-((2-(diphenylphosphaneyl)quinolin-4-yl)methyl)-2,6-dimethylmorpholine (242 mg, 0.55 mmol), DBU (75 μL , 0.89 mmol), and CH_2Cl_2 (5 mL). After the purification procedure (concentrated CH_2Cl_2 solution of crude product was added dropwise to an excess of 50% Et_2O in hexanes instead of Et_2O), the title compound was provided as a brown amorphous solid (310 mg, 0.33 mmol, 66% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3061, 3012, 2974, 2935, 2875, 2818, 1630, 1440, 909, 689, 665, 636, 603; ^1H NMR (400 MHz, CDCl_3) δ : 8.75 (1H, d, $J = 6.6$ Hz), 8.65-8.60 (1H, m), 8.23 (1H, dd, $J = 7.9, 0.7$ Hz), 8.15 (1H, d, $J = 8.4$ Hz), 7.98-7.69 (13H, m), 7.34 (1H, t, $J = 7.7$ Hz), 7.12 (1H, dd, $J = 19.6, 9.8$ Hz), 6.85-6.69 (2H, m), 4.10-3.91 (4H, m), 3.53-3.40 (2H, m), 3.34 (1H, d, $J = 14.2$ Hz), 2.80 (1H, d, $J = 13.8$ Hz), 2.65-2.51 (3H, m), 2.07-

1.87 (3H, m), 1.87-1.74 (1H, m), 1.69-1.54 (1H, m), 1.47-1.25 (3H, m), 1.11 (6H, app t, $J = 5.9$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 159.46 (dq, $J = 257.36$ 257.4, 2.3 Hz), 155.69, 148.76 (d, $J = 23.1$ Hz), 148.24, (d, $J = 11.2$ Hz), 144.40 (d, $J = 10.2$ Hz), 143.96 (d, $J = 120.6$ Hz), 136.87 (m), 135.79 (m), 134.55-134.19 (m), 131.76, 130.66 (d, $J = 13.2$ Hz), 130.63, 129.17, 128.57, 128.27 (d, $J = 73.9$ Hz), 127.00-126.76 (m, 2C), 124.03, 123.86, 123.63 (d, $J = 3.6$ Hz), 122.37, 122.50 (dq, $J = 273.6$ Hz), 120.76 (q, $J = 318.4$ Hz), 116.78 (dd, $J = 89.6, 3.1$ Hz), 116.11 (dd, $J = 91.4, 1.4$ Hz), 114.57 (d, $J = 86.2$ Hz), 73.54, 71.64, 62.21, 59.64, 59.39 (d, $J = 4.7$ Hz), 58.10, 54.07, 27.83, 22.56, 19.96 (d, $J = 3.2$ Hz); ^{19}F NMR (365 MHz, CDCl_3) δ : -61.13 (d, $J = 13.74$ 13.7 Hz), -78.14, -114.39-(-)115.04 (m); ^{31}P NMR (162 MHz, CDCl_3) δ : 12.52; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 793.3407, $\text{C}_{46}\text{H}_{46}\text{F}_4\text{N}_4\text{O}_2\text{P}^+$ requires 793.3295.

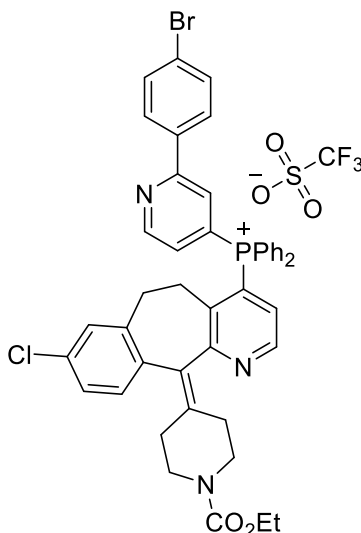
(2-(1-(4-Chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)diphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (21b)



Chlorphenamine (412.2 mg, 1.50 mmol) was dissolved in Et_2O (3 mL) and cooled to 0 °C. Trifluoromethanesulfonic acid (134 μL , 1.50 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 B (except that after 4-(diphenylphosphino)-2-phenylpyridine was added, the reaction mixture was stirred for 30 min at -78 °C) using Tf_2O (252 μL , 1.50 mmol), 4-(diphenylphosphino)-2-phenylpyridine (560

mg, 1.65 mmol), DBU (450 μ L, 3.00 mmol) and CH_2Cl_2 (15 mL). After the purification procedure, the title compound was isolated as a white amorphous powder (714 mg, 0.95 mmol, 63% yield). mp 130-133 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3060, 1574, 1489, 1468, 1440, 1378, 1259, 1223, 1150, 1124, 1109, 1028, 729, 636; ^1H NMR (400 MHz, CDCl_3) δ : 9.05 (1H, d, $J = 5.2$ Hz), 9.00 (1H, t, $J = 5.2$ Hz), 7.95-7.87 (4H, m), 7.80-7.77 (5H, m), 7.70-7.65 (4H, m), 7.52-7.45 (5H, m), 7.39 (1H, dd, $J = 13.0, 4.8$ Hz), 7.27 (2H, d, $J = 8.3$ Hz), 7.17 (2H, d, $J = 8.3$ Hz), 4.46 (1H, t, $J = 7.4$ Hz), 3.07-2.93 (2H, m), 2.83-2.76 (1H, m), 2.69 (6H, s), 2.44-2.35 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.22 (d, $J = 9.6$ Hz), 159.31 (d, $J = 10.3$ Hz), 151.77 (d, $J = 10.9$ Hz), 151.36 (d, $J = 10.5$ Hz), 139.50, 136.68 (d, $J = 1.6$ Hz), 136.48 (d, $J = 2.5$ Hz), 134.56 (d, $J = 10.6$ Hz), 133.05, 131.13, 130.99, 130.53, 129.42, 129.06, 128.98, 127.58 (d, $J = 83.9$ Hz), 127.27 (d, $J = 83.6$ Hz), 127.13, 125.31 (d, $J = 8.3$ Hz), 125.09 (d, $J = 8.2$ Hz), 123.20 (d, $J = 8.8$ Hz), 120.40 (q, $J = 318.7$ Hz), 114.01 (d, $J = 88.9$ Hz), 56.27, 49.15, 43.36, 29.65; ^{19}F NMR (365 MHz, CDCl_3) δ : -78.30; ^{31}P NMR (162 MHz, CDCl_3) δ : 22.06; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 612.2328, $\text{C}_{39}\text{H}_{36}\text{ClN}_3\text{P}^+$ requires 612.2335.

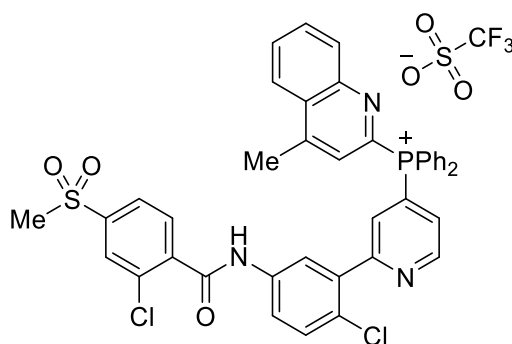
(2-(4-Bromophenyl)pyridin-4-yl)(8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (22b)



Prepared according to general procedure B using loratadine (383 mg, 1.00 mmol), TiF_2O (168 μL , 1.00 mmol), 2-(4-Bromophenyl)-4-(diphenylphosphaneyl)pyridine (460 mg, 1.10 mmol), DBU (149 μL , 1.00 mmol) and CH_2Cl_2 (10 mL). After the purification procedure, the title compound was isolated as an off white solid (770 mg, 0.81 mmol, 81% yield). mp 159-164 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3055, 2981, 1687, 1438, 1262, 1223, 1109, 1030, 730; ^1H NMR (400 MHz, CDCl_3) δ : 9.01 (1H, app t, $J = 5.1$ Hz), 8.73 (1H, app t, $J = 4.7$ Hz), 8.05-7.62 (13H, m), 7.60-7.40 (3H, m) 7.16 (1H, dd, $J = 7.7, 5.1$ Hz), 7.06 (2H, s), 6.63 (1H, s), 4.06 (2H, q, $J = 6.8$ Hz), 3.80-3.57 (2H, m), 3.40-3.16 (3H, m) 2.74 (1H, d, $J = 17.4$ Hz), 2.63-2.09 (5H, m), 1.60-1.39 (1H, m), 1.20 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.34 (d, $J = 8.5$ Hz), 158.14 (d, $J = 10.5$ Hz), 155.15, 151.83 (d, $J = 10.9$ Hz), 149.26 (d, $J = 11.6$ Hz), 139.30, 136.53, 136.46-136.12 (2C, m), 135.45 (d, $J = 1.4$ Hz), 134.26 (d, $J = 10.6$ Hz), 133.83, 133.37, 132.17-131.89 (2C, m), 131.41, 131.20 (d, $J = 13.2$ Hz), 129.64, 128.71, 128.64 (d, $J = 83.6$ Hz), 127.54 (d, $J = 10.3$ Hz),

126.28, 125.35 (d, $J = 8.3$ Hz), 125.14 (d, $J = 82.3$ Hz), 122.94 (d, $J = 8.9$ Hz), 120.48 (q, $J = 321.4$ Hz), 114.84 (d, $J = 88.2$ Hz), 114.39 (d, $J = 88.1$ Hz), 61.17, 44.48, 44.34, 30.52, 30.43-30.10 (2C, m), 29.30, 14.45; ^{19}F NMR (365 MHz, CDCl_3) δ : -78.15; ^{31}P (162 MHz, CDCl_3) δ : 20.87; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 798.1693, $\text{C}_{45}\text{H}_{39}\text{BrClN}_3\text{O}_2\text{P}^+$ requires 798.1652.

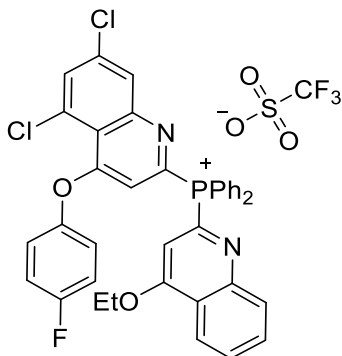
(2-(2-Chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (23b)



Prepared according to general procedure B (except the stirring time after the addition of Tf_2O was 2 hours instead of 30 minutes, the stirring time after the addition of the phosphine was 1.5 hours instead of 30 minutes, and after the addition of DBU the reaction was allowed to slowly warm from -78°C to 0°C over 3 hours instead of warming from -78°C to room temperature over approximately 15-30 minutes) using vismodegib (506 mg, 1.20 mmol), Tf_2O (200 μL , 1.20 mmol), 2-(diphenylphosphaneyl)-4-methylquinoline (432 mg, 1.32 mmol), DBU (180 μL , 1.20 mmol) and CH_2Cl_2 (30 mL). After the purification procedure (concentrated CH_2Cl_2 solution was added dropwise to an excess of Et_2O at room temperature. The resulting suspension was immediately filtered on a frit and the solid was washed with room temperature Et_2O . The solid was dissolved

in approximately 5 mL CH₂Cl₂ and this process was repeated (4x) before the solid was dried *in vacuo* to provide the pure phosphonium salt), the title compound was isolated as a pale yellow solid (592 mg, 0.66 mmol, 55% yield). mp 119-125 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3255, 3062, 1681, 1575, 1539, 1439, 1364, 1315, 1274, 1246, 1152, 1029, 726; ¹H NMR (400 MHz, CDCl₃) δ : 9.90 (1H, s), 8.98 (1H, app t, J = 5.1 Hz), 8.24-8.09 (3H, m), 8.01-7.59 (18H, m), 7.56 (1H, d, J = 4.8 Hz), 7.31-7.23 (1H, m), 2.93 (3H, s), 2.77 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 164.27, 157.96 (d, J = 10.9 Hz), 150.87 (d, J = 10.6 Hz), 148.76 (d, J = 10.9 Hz), 148.46 (d, J = 23.0 Hz), 142.65 (d, J = 118.3), 142.04, 140.23, 137.66, 136.79 (d, J = 1.6 Hz), 136.05 (d, J = 2.7 Hz), 134.58 (d, J = 10.3 Hz), 132.23, 131.83, 130.92-130.42 (2C, m), 130.29, 129.85, 128.77 (d, J = 3.1 Hz), 128.46 (d, J = 83.7 Hz), 128.59-128.24 (3C, m), 126.35, 125.82 (d, J = 7.6 Hz), 125.59, 125.10 (d, J = 27.0 Hz), 124.31, 123.07, 122.38, 120.24 (d, J = 320.9 Hz), 115.31 (d, J = 87.8 Hz), 44.14, 19.05 (d, J = 1.4 Hz); ¹⁹F NMR (365 MHz, CDCl₃) δ : -78.30; ³¹P (162 MHz, CDCl₃) δ : 13.30; m/z HRMS (ESI + APCI) found [M-OTf]⁺ 746.1185, C₄₁H₃₁Cl₂N₃O₃PS⁺ requires 746.1201.

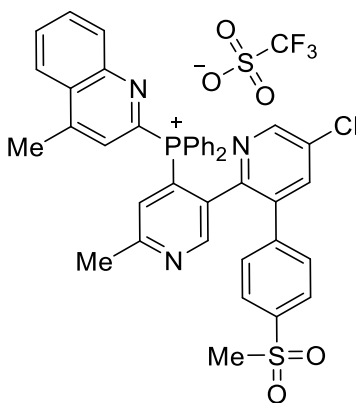
(5,7-Dichloro-4-(4-fluorophenoxy)quinolin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (24b)



Prepared according to general procedure B, using 5,7-dichloro-4-(4-fluorophenoxy)quinoline (308 mg, 1.00 mmol), Tf₂O (168 μ L, 1.00 mmol), 2-(diphenylphosphaneyl)-4-ethoxyquinoline (392 mg, 1.10 mmol), DBU (150 μ L, 1.00 mmol), and EtOAc (10 mL). After the purification procedure (concentrated CH₂Cl₂ solution of crude product was added dropwise to an excess of 50% Et₂O in hexanes instead of Et₂O), the title compound was provided as a brown amorphous solid (400 mg, 0.49 mmol, 49% yield). IR ν_{max} /cm⁻¹ (film): 3070, 2989, 2248, 855, 834, 646, 594, 572; ¹H NMR (400 MHz, CDCl₃) δ : 8.31 (1H, d, J = 8.1 Hz), 8.02 (1H, d, J = 2.1 Hz), 7.87-7.64 (14H, m), 7.16-7.04 (3H, m), 7.00 (1H, d, J = 6.4 Hz), 6.96-6.88 (2H, m), 4.14 (2H, q, J = 7.0 Hz), 1.47 (3H, t, J = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 164.34 (d, J = 12.9 Hz), 153.30 (d, J = 14.0 Hz), 160.27 (d, J = 246.1 Hz), 151.68 (d, J = 25.5 Hz), 149.24 (d, J = 25.4 Hz), 148.30 (d, J = 117.4 Hz), 148.14 (d, J = 2.8 Hz), 144.56 (d, J = 116.9 Hz), 136.97, 135.54 (d, J = 2.9 Hz), 134.68 (d, J = 10.0 Hz), 132.24, 131.67, 131.09 (d, J = 1.2 Hz), 130.27 (d, J = 13.0 Hz), 129.13, 127.99, 122.77 (d, J = 8.6 Hz), 122.45, 121.56 (d, J = 2.3 Hz), 120.64 (q, J = 321.3 Hz), 118.17 (d, J = 2.3 Hz), 117.21, 116.96, 116.51 (d, J = 87.5 Hz), 110.93 (d, J = 26.9 Hz), 105.92 (d, J = 29.0 Hz), 65.51, 13.93; ¹⁹F NMR (365 MHz, CDCl₃) δ : -78.19, -114.90- (-)115.01 (m);

^{31}P NMR (162 MHz, CDCl_3) δ : 8.41; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 663.1166, $\text{C}_{38}\text{H}_{27}\text{Cl}_2\text{FN}_2\text{O}_2\text{P}^+$ requires 663.1199.

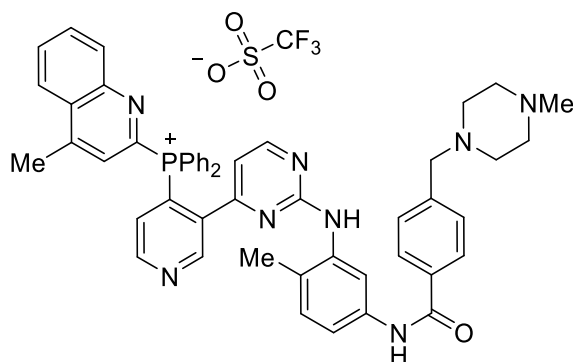
(5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (25b)



Prepared according to general procedure B except with NaOAc added with phosphine, using 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (538 mg, 1.50 mmol), Tf_2O (255 μL , 1.50 mmol), 2-(diphenylphosphaneyl)-4-methylquinoline (540 mg, 1.65 mmol), DBU (225 μL , 1.50 mmol), NaOAc (123 mg, 1.50 mmol) and CH_2Cl_2 (15 mL). After the purification procedure (concentrated CH_2Cl_2 solution was added dropwise to an excess of Et_2O at room temperature. The resulting suspension was immediately filtered on a frit and the solid was washed with room temperature Et_2O . The solid was dissolved in approximately 5 mL CH_2Cl_2 and this process was repeated (3x) before the solid was dried *in vacuo* to provide the pure phosphonium salt), the title compound was provided as a yellow crystalline solid (840 mg, 1.04 mmol, 69% yield). mp 165-170 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3060, 1576, 1312, 770, 721, 547; ^1H NMR (400 MHz, CDCl_3) δ : 8.24 (1H, d, $J = 7.0$ Hz), 8.12-7.93 (8H, m), 7.87-7.67 (9H, m), 7.62-7.55 (3H, m), 7.30-7.23 (2H, m), 3.17 (3H, s), 2.74 (3H, s), 2.60 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 160.87 (d, $J = 11.1$ Hz), 152.08 (d, $J = 7.2$ Hz), 148.24 (d, $J = 11.1$ Hz), 147.98 (d, $J = 2.1$ Hz), 147.32 (d, J

= 24.0 Hz), 147.15 (d, J = 125.9 Hz), 146.15, 141.55, 141.15, 138.54, 135.30, 135.29, 135.13 (d, J = 3.0 Hz), 134.85 (d, J = 9.4 Hz), 133.39 (d, J = 3.2 Hz), 131.95, 131.71, 130.71 (d, J = 10.1 Hz), 130.23, 130.07 (d, J = 6.3 Hz), 129.74 (d, J = 1.3 Hz), 128.92 (d, J = 87.0 Hz), 128.36, 128.12 (d, J = 3.1 Hz), 124.45, 123.53 (d, J = 26.9 Hz), 120.83 (q, J = 321.2 Hz), 119.37 (d, J = 88.5 Hz), 44.14, 24.62, 18.84 (d, J = 1.6 Hz); ^{19}F NMR (365 MHz, CDCl_3) δ : -78.15; ^{31}P NMR (162 MHz, CDCl_3) δ : 16.31; m/z HRMS (ESI + APCI) found $[\text{M-OTf}]^+$ 684.1666 $\text{C}_{40}\text{H}_{32}\text{ClN}_3\text{O}_2\text{PS}^+$ requires 684.1641.

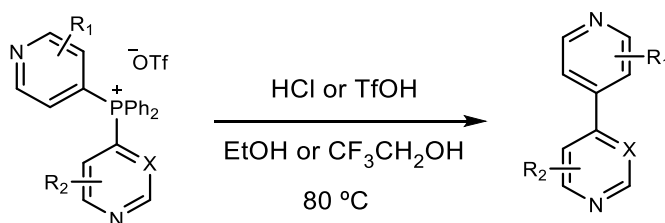
(3-(2-((2-Methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (26b)



Prepared according to general procedure B (except that the stirring time after addition of Tf_2O was 2 hours instead of 30 minutes, the stirring time after addition of 2-(diphenylphosphino)-4-methylquinoline was 1.5 hours instead of 30 minutes, and after the addition of DBU the reaction was allowed to slowly warm from -78°C to 0°C over 3 hours instead of warming from -78°C to room temperature over approximately 15-30 minutes) using (1*S*,2*S*,4*S*,5*R*)-2-((*R*)-(benzyloxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (592 mg, 1.20 mmol), Tf_2O (200 μL , 1.20 mmol), 2-(diphenylphosphino)-4-methylquinoline (432 mg, 1.32 mmol), DBU (180 μL , 1.20 mmol) and CH_2Cl_2 (30 mL). After the purification procedure (concentrated CH_2Cl_2 solution was added dropwise to an excess of Et_2O at room temperature. The resulting suspension was

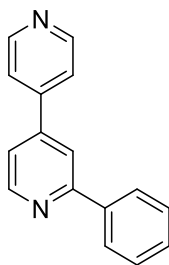
immediately filtered on a frit and the solid was washed with room temperature Et₂O. The solid was dissolved in approximately 5 mL CH₂Cl₂ and this process was repeated (3x) before the solid was dried *in vacuo* to provide the pure phosphonium salt), the title compound was isolated as a yellow amorphous powder (710 mg, 0.73 mmol, 61% yield). mp 155-158 °C; IR ν_{max} /cm⁻¹ (film): 3316, 3056, 2795, 1662, 1568, 1527, 1505, 1474, 1450, 1406, 1254, 1222, 1149, 1104, 1028, 857, 815, 752, 726, 689; ¹H NMR (400 MHz, CDCl₃) δ : 9.52 (1H, d, *J* = 6.4 Hz), 9.04 (1H, dd, *J* = 4.8, 4.4 Hz), 8.53 (1H, s), 8.23 (1H, d, *J* = 5.1 Hz), 8.01–7.99 (1H, m), 7.87-7.59 (15H, m), 7.52 (1H, d, *J* = 4.8 Hz), 7.45 (1H, dd, *J* = 4.3, 2.0 Hz), 7.39 (2H, d, *J* = 8.2 Hz), 7.28 (1H, dd, *J* = 15.7, 5.1 Hz), 7.22 (1H, d, *J* = 5.2 Hz), 7.06 (1H, d, *J* = 1.9 Hz), 6.92 (1H, d, *J* = 8.5 Hz), 5.51 (1H, s), 3.54 (2H, s), 2.77-2.51 (14H, m), 1.50 (3H, s); ¹³C NMR (100 MHz, CD₃CN) δ : 166.21, 161.17, 159.55 (d, *J* = 1.1 Hz), 159.01, 154.33 (d, *J* = 1.1 Hz), 152.10 (d, *J* = 6.3 Hz), 149.77 (d, *J* = 11.3 Hz), 149.43, 148.63, 148.38, 148.10, 142.66, 137.94, 136.82, 136.06 (d, *J* = 2.1 Hz), 135.71 (d, *J* = 9.3 Hz), 135.33 (d, *J* = 85.6 Hz), 132.86 (d, *J* = 9.8 Hz), 132.23, 131.02 (d, *J* = 12.7 Hz), 130.44 (d, *J* = 4.4 Hz), 129.85, 129.45 (d, *J* = 3.0 Hz), 128.45, 126.72, 126.06 (d, *J* = 84.5 Hz), 125.56 (d, *J* = 1.0 Hz), 123.30, 123.04, 122.31 (d, *J* = 90.6 Hz), 122.01 (q, *J* = 319.1 Hz), 117.99, 115.59, 110.10, 62.06, 55.02, 51.51, 44.62, 18.95 (d, *J* = 1.6 Hz), 17.29; ¹⁹F NMR (365 MHz, CDCl₃) δ : -78.13; ³¹P NMR (162 MHz, CDCl₃) δ : 18.51; *m/z* HRMS (ESI + APCI) found [M-OTf]⁺ 819.3695, C₅₁H₄₈N₈OP⁺ requires 819.3689.

A. 1.3.4 General Procedure C (Ligand-coupling Reactions to Make Heterobiaryls)



An oven dried 8 mL vial with a septa cap was charged with the phosphonium salt (1.0 equiv) and EtOH or TFE (0.4 M). The vial was subjected to three rapid cycles of vacuum / nitrogen backfill and then HCl or TfOH (2.0 equiv) was added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 80 °C for the stated time. The reaction was quenched with a saturated aqueous solution of Na₂CO₃ and the aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl.

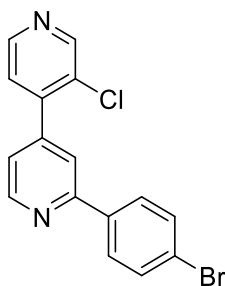
2-Phenyl-4,4'-bipyridine (6c)



Prepared according to general procedure C using diphenyl(2-phenylpyridin-4-yl)(pyridin-4-yl)phosphonium trifluoromethanesulfonate (283 mg, 0.50 mmol), 4.0 M HCl in dioxanes (250 μL, 1.00 mmol), and EtOH (1.25 mL). The reaction was heated to 80 °C for 14 hours. Flash column

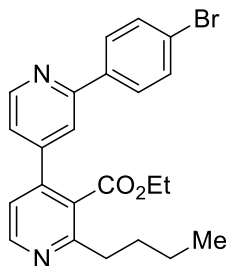
chromatography (silica gel, gradient elution: 40% EtOAc in hexanes to 50% EtOAc in hexanes) afforded the title compound as an off white solid (102 mg, 0.44 mmol, 88% yield). mp 64-65 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3029, 1590, 1532, 1472, 1444, 1389, 1225, 808, 770, 731, 687; ^1H NMR (400 MHz, CDCl_3) δ : 8.87-8.59 (3H, m), 8.02 (2H, d, $J = 7.2$ Hz), 7.88 (1H, s), 7.62-7.32 (6H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.34, 150.51, 150.34, 146.25, 145.67, 138.78, 129.21, 128.71, 126.86, 121.34, 119.70, 118.16; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 233.1092, $\text{C}_{16}\text{H}_{13}\text{N}_2^+$ requires 233.1073.

2-(4-Bromophenyl)-3'-chloro-4,4'-bipyridine (7c)



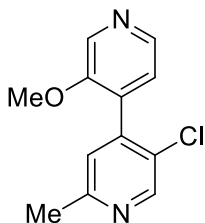
Prepared according to general procedure C using (2-(4-bromophenyl)pyridin-4-yl)(3-chloropyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (340 mg, 0.50 mmol), 4.0 M HCl in dioxanes (250 μL , 1.00 mmol), and EtOH (1.25 mL). The reaction was heated to 80 °C for 17 hrs. Flash column chromatography (silica gel: 25% EtOAc in hexanes) afforded the title compound as a white solid (111 mg, 0.32 mmol, 64% yield). mp 153-154 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3053, 1603, 1579, 1552, 1461, 1412, 1376, 1111, 1006, 831, 741; ^1H NMR (400 MHz, CDCl_3) δ : 8.79 (1H, d, $J = 5.0$ Hz), 8.74 (1H, s), 8.60 (1H, d, $J = 4.9$ Hz), 7.91 (2H, d, $J = 8.5$ Hz), 7.77 (1H, s), 7.61 (2H, d, $J = 8.5$ Hz), 7.37-7.28 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 156.61, 150.35, 149.96, 148.15, 145.03, 144.91, 137.56, 131.92, 129.72, 128.46, 124.53, 123.87, 122.03, 120.01; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 344.9812, $\text{C}_{16}\text{H}_{11}\text{BrN}_2^+$ requires 344.9789.

Ethyl 2'-(4-bromophenyl)-2-butyl-[4,4'-bipyridine]-3-carboxylate (8c)



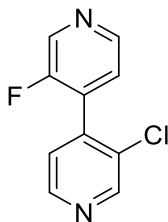
Prepared according to general procedure C using (2-(4-bromophenyl)pyridin-4-yl)(2-butyl-3-(ethoxycarbonyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (155 mg, 0.20 mmol), trifluoromethanesulfonic acid (36 μ L, 0.40 mmol) and EtOH (0.5 mL) at 80 °C for 14 hours. Flash column chromatography (silica gel: 16% EtOAc in hexanes to 33% EtOAc in hexanes) afforded the title compound as a colorless oil (67 mg, 0.15 mmol, 76% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3051, 2956, 2929, 2870, 1722, 1601, 1589, 1575, 1537, 1491, 1475, 1455, 1405, 1379, 1258, 1138, 1099, 1071, 1045, 1008, 825; ^1H NMR (400 MHz, CDCl_3) δ : 8.73 (1H, d, $J = 5.0$ Hz), 8.68 (1H, d, $J = 5.0$ Hz), 7.90 (2H, d, $J = 8.3$ Hz), 7.71 (1H, s), 7.60 (2H, d, $J = 8.3$ Hz), 7.26 (1H, d, $J = 5.8$ Hz), 7.18 (1H, d, $J = 5.0$ Hz), 4.11 (2H, q, $J = 7.2$ Hz), 2.89 (2H, t, $J = 7.8$ Hz), 1.76 (2H, qn, $J = 7.6$ Hz), 1.42 (2H, sext, $J = 7.4$ Hz), 1.00 (3H, t, $J = 7.2$ Hz), 0.94 (3H, t, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 167.97, 160.08, 156.52, 150.14, 149.95, 147.22, 145.26, 137.49, 131.99, 128.40, 127.85, 123.92, 121.29, 120.68, 119.21, 61.69, 36.02, 31.93, 22.66, 13.86, 13.60; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 439.1029, $\text{C}_{23}\text{H}_{23}\text{BrN}_2\text{O}_2^+$ requires 439.1021.

5-Chloro-3'-methoxy-2-methyl-4,4'-bipyridine (9c)



Prepared according to general procedure C using (5-chloro-2-methylpyridin-4-yl)(3-methoxypyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (285 mg, 0.50 mmol), trifluoromethanesulfonic acid (89 μ L, 1.00 mmol) and EtOH (1.25 mL) at 80 °C for 14 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a colorless crystalline solid (77 mg, 0.33 mmol, 65% yield). mp 105-108 °C; IR ν_{max} /cm⁻¹ (film): 3029, 2968, 2938, 2842, 1582, 1556, 1506, 1492, 1469, 1441, 1379, 1360, 1312, 1306, 1291, 1269, 1256, 1239, 1213, 1195, 1101, 1017, 846, 833; ¹H NMR (400 MHz, CDCl₃) δ : 8.52 (1H, s), 8.39 (1H, s), 8.33 (1H, d, *J* = 4.7 Hz), 7.09 (1H, d, *J* = 4.7 Hz), 7.05 (1H, s), 3.88 (3H, s), 2.54 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 156.62, 152.18, 148.70, 142.83, 142.52, 134.21, 133.11, 128.01, 124.66, 124.11, 56.18, 23.74; *m/z* HRMS (DART) found [M+H]⁺ 235.0664, C₁₂H₁₂ClN₂O⁺ requires 235.0638.

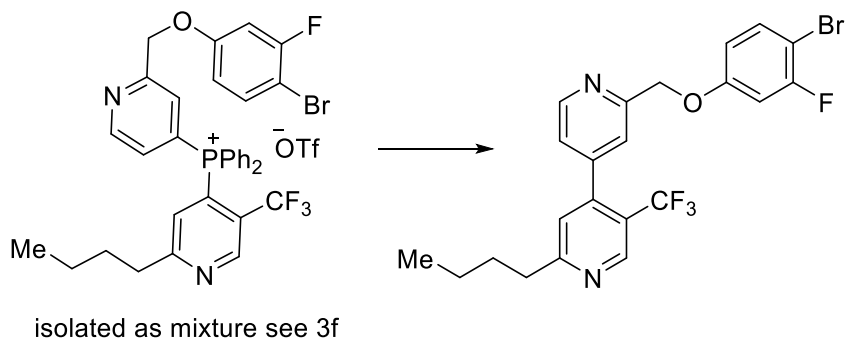
3-Chloro-3'-fluoro-4,4'-bipyridine (10c)



Prepared according to general procedure C using (3-chloro-pyridin-4-yl)(3-fluoropyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (136 mg, 0.25 mmol), 4.0M HCl in dioxane (125 μ L, 0.50 mmol) and EtOH (0.625 mL) at 80 °C for 23 hours. Flash column chromatography

(silica gel: 40% EtOAc in hexanes to 50% EtOAc in hexanes) followed by flash column chromatography (neutral alumina: 20% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a white crystalline solid (34 mg, 0.16 mmol, 65% yield). mp 92-94 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3021, 1578, 1470, 1413, 1398, 1268, 1217, 1202, 1176, 1110, 1027, 830, 752; ^1H NMR (400 MHz, CDCl_3) δ : 8.69 (1H, s), 8.60-8.44 (3H, m), 7.29-7.17 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 155.86 (d, $J = 259.5$ Hz), 150.15, 147.84, 145.81 (d, $J = 5.4$ Hz), 139.81, 139.05 (d, $J = 24.1$ Hz), 131.57 (d, $J = 13.0$ Hz), 130.70, 124.97, 124.63; ^{19}F NMR (365 MHz, CDCl_3) δ : -128.06 (d, $J = 5.5$ Hz); m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 209.0, $\text{C}_{10}\text{H}_7\text{ClFN}_2^+$ requires 209.0.

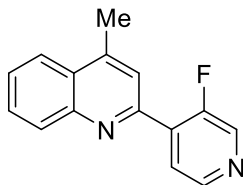
2'-((4-Bromo-3-fluorophenoxy)methyl)-2-butyl-5-(trifluoromethyl)-4,4'-bipyridine (11c)



Prepared according to general procedure C using (2'-((4-bromo-3-fluorophenoxy)methyl)pyridin-4-yl)(2-butyl-5-(trifluoromethyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (204 mg, isolated as a mixture see 3f), Trifluoromethanesulfonic acid (45 μL , 0.50 mmol) and EtOH (0.625 mL) at 80 °C for 12 hours. Flash column chromatography (silica gel: 2% EtOAc in CH_2Cl_2 to 5% EtOAc in CH_2Cl_2) afforded the title compound as a white amorphous powder (63 mg, 0.13 mmol, 29% yield over two steps). mp 79-81 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3027, 2958, 2924, 2875, 2860, 1597, 1589, 1564, 1539, 1492, 1467, 1452, 1426, 1415, 1380, 1323, 1292, 1268, 1249, 1189, 1177, 1153, 1130, 1101, 1089, 1057,

1032, 974, 942, 902, 855, 843, 820; ^1H NMR (400 MHz, CDCl_3) δ : 8.88 (1H, s), 8.68 (1H, d, J = 5.0 Hz), 7.44-7.38 (2H, m), 7.22 (1H, d, J = 4.8 Hz), 7.08 (1H, s), 6.78 (1H, dd, J = 10.2, 2.8 Hz), 6.69 (1H, dd, J = 8.9, 2.8 Hz), 5.22 (2H, s), 2.88 (2H, t, J = 7.7 Hz), 1.74 (2H, qn, J = 7.3 Hz), 1.40 (2H, sext, J = 7.5 Hz), 0.94 (3H, t, J = 7.3 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 166.90, 159.44 (d, J = 245.7 Hz), 158.68 (d, J = 9.7 Hz), 156.50, 149.21, 147.06 (q, J = 5.5 Hz), 146.29, 146.23 (q, J = 1.8 Hz), 133.47 (d, J = 1.7 Hz), 123.90, 123.50 (q, J = 272.3 Hz), 122.27 (d, J = 1.1 Hz), 121.38 (q, J = 30.6 Hz), 120.59, 111.98 (d, J = 3.2 Hz), 103.98 (d, J = 25.6 Hz), 100.11 (d, J = 21.2 Hz), 70.86, 37.99, 31.58, 22.44, 13.83; ^{19}F NMR (365 MHz, CDCl_3) δ : -56.55, -104.87 (t, J = 8.4 Hz); m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 483.0690, $\text{C}_{22}\text{H}_{20}\text{BrF}_4\text{N}_2\text{O}^+$ requires 483.0695.

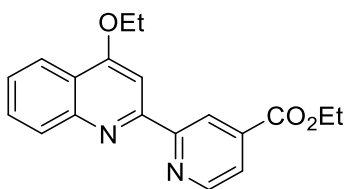
2-(3-Fluoropyridin-4-yl)-4-methylquinoline (12c)



Prepared according to general procedure C, using (3-fluoropyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (286 mg, 0.50 mmol), 4.0M HCl in dioxane (250 μL , 1.00 mmol), and EtOH (1.25 mL) at 80 $^\circ\text{C}$ for 12 hours. The crude material was purified by flash chromatography (silica gel gradient elution: 25% EtOAc in hexanes to 50% EtOAc in hexanes) to provide the title compound as a white crystalline solid (68 mg, 0.31 mmol, 57% yield). mp 94-95 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3038, 2968, 1464, 1350, 1277, 1235, 746; ^1H NMR (400 MHz, CDCl_3) δ : 8.62 (1H, d, J = 2.8 Hz), 8.59 (1H, dd, J = 4.9, 0.9 Hz), 8.19 (1H, dd, J = 8.4, 0.5 Hz), 8.10 (1H, dd, J = 7.3, 5.0 Hz), 8.05 (1H, dd, J = 8.4, 0.9 Hz), 7.80-7.75 (2H, m), 7.66-7.62 (1H, m), 2.80 (3H, d, J = 0.8 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 157.28 (d, J = 258.8 Hz); 158.84 (d,

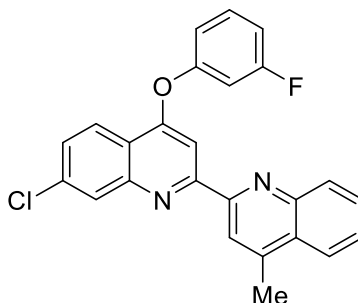
$J = 2.0$ Hz), 148.09, 146.25 (d, $J = 5.1$ Hz), 145.16, 139.33 (d, $J = 26.1$ Hz), 134.60 (d, $J = 9.5$ Hz), 130.50, 129.74, 127.79, 127.20, 124.58, 123.74, 122.69 (d, $J = 8.2$ Hz), 19.00; ^{19}F NMR (365 MHz, CDCl_3) δ : -131.61 (d, $J = 7.5$ Hz); m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 239.0973, $\text{C}_{15}\text{H}_{12}\text{FN}_2^+$ requires 239.0979.

Ethyl 2-(4-ethoxyquinolin-2-yl)isonicotinate (13c)



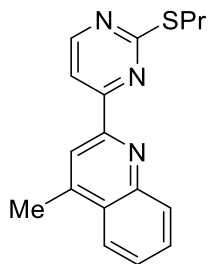
Prepared according to general procedure C, using (4-(ethoxycarbonyl)pyridin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (164 mg, 0.25 mmol), trifluoromethanesulfonic acid (42 μL , 0.50 mmol), and EtOH (0.63 mL) at 80 $^{\circ}\text{C}$ for 12 hours. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes to 25% EtOAc in hexanes) to provide the title compound as a white crystalline solid (38 mg, 0.12 mmol, 47% yield). mp 102-104 $^{\circ}\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3038, 2968, 1464, 1350, 1277, 1235, 746; ^1H NMR (400 MHz, CDCl_3) δ : 9.18 (1H, s), 8.84 (1H, d, $J = 5.0$ Hz), 8.26 (1H, dd, $J = 3.16$ 3.2, 1.2 Hz), 8.15 (1H, d, $J = 8.4$ Hz), 7.97 (1H, s), 7.97 (1H, dd, $J = 5.0, 1.6$ Hz), 7.71-7.70 (1H, m), 7.56-7.49 (1H, m), 4.55-4.38 (4H, m), 1.62 (3H, t, $J = 7.0$ Hz), 1.47 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.36, 162.43, 157.71, 156.56, 149.59, 148.98, 138.80, 129.89, 129.35, 125.93, 123.05, 121.94, 121.54, 121.16, 98.12, 64.34, 61.83, 14.55, 14.29; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 323.1386, $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_3^+$ requires 323.1390.

7-Chloro-4-(3-fluorophenoxy)-4'-methyl-2,2'-biquinoline (14c)



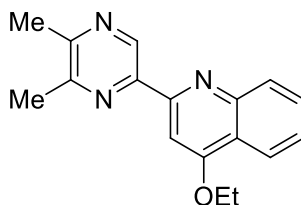
Prepared according to general procedure C, using (7-chloro-4-(3-fluorophenoxy)quinolin-2-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (187 mg, 0.25 mmol), trifluoromethanesulfonic acid (42 μ L, 0.50 mmol), and (2,2,2)-Trifluoroethanol (0.63 mL) at 80°C for 12 hours. The crude material was purified by flash chromatography (silica gel, 10% EtOAc in hexanes) to provide the title compound as a white crystalline solid (70 mg, 0.17 mmol, 67% yield). mp 208-210 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3068, 1615, 1094, 947, 831, 755, 526; ^1H NMR (400 MHz, CDCl_3) δ : 8.60 (1H, d, J = 0.8 Hz), 8.28 (1H, d, J = 8.9 Hz), 8.25 (1H, d, J = 1.8 Hz), 8.13 (1H, s), 8.07 (1H, dd, J = 8.4, 0.7 Hz), 8.03 (1H, dd, J = 8.3, 0.9 Hz), 7.69 (1H, m), 7.60-7.53 (2H, m), 7.47 (1H, td, J = 12.2, 7.5 Hz), 7.10-6.99 (3H, m), 2.83 (3H, d, J = 0.9 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.60 (d, J = 248.4 Hz), 161.43, 158.99, 155.76 (d, J = 10.6 Hz), 154.93, 150.04, 147.57, 145.07, 136.33, 131.10, (d, J = 9.6 Hz), 130.50, 129.22, 128.57, 128.54, 127.50, 126.90, 123.75, 123.26, 120.13, 119.70, 116.32 (d, J = 3.4 Hz), 112.44 (d, J = 21.1 Hz), 108.65 (d, J = 24.2 Hz), 108.65 (d, J = 24.2 Hz), 103.43, 18.95; ^{19}F NMR (365 MHz, CDCl_3) δ : -109.72-(-)109.79 (m); m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 415.1024, $\text{C}_{25}\text{H}_{17}\text{ClFN}_2\text{O}^+$ requires 415.1008.

4-Methyl-2-(2-(propylthio)pyrimidin-4-yl)quinoline (15c)



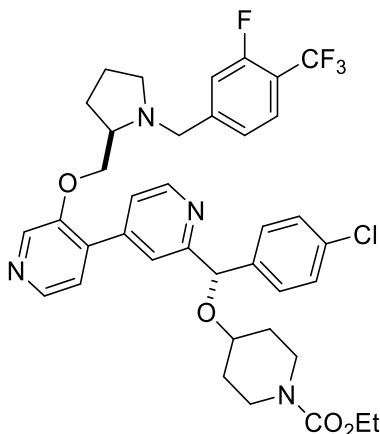
Prepared according to general procedure C using (4-Methylquinolin-2-yl)diphenyl(2-(propylthio)pyrimidin-4-yl)phosphonium trifluoromethanesulfonate (149 mg, 0.25 mmol), trifluoromethanesulfonic acid (44 μ L, 0.50 mmol), and EtOH (0.63 mL). The reaction was heated to 80 $^{\circ}$ C for 5.5 hours. Flash column chromatography (silica gel: 5% EtOAc in hexanes) followed by a second flash column (silica gel, gradient elution: 3% EtOAc in hexanes to 5% EtOAc in hexanes) afforded the title compound as a white solid (27 mg, 0.091 mmol, 37% yield). mp 57-58 $^{\circ}$ C; IR ν_{max} /cm $^{-1}$ (film): 2925, 1557, 1539, 1505, 1417, 1352, 1317, 1194, 1160, 782; ^1H NMR (400 MHz, CDCl_3) δ : 8.67 (1H, d, $J = 4.7$ Hz), 8.40 (1H, s), 8.23 (1H, d, $J = 4.7$ Hz), 8.17 (1H, d, $J = 8.1$ Hz), 8.03 (1H, d, $J = 8.1$ Hz), 7.75 (1H, t, $J = 7.0$ Hz), 7.61 (1H, t, $J = 7.0$ Hz), 3.26 (2H, t, $J = 7.1$ Hz), 2.80 (3H, s), 1.88 (2H, sext, $J = 7.1$ Hz), 1.13 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 172.21, 163.22, 158.12, 153.22, 147.70, 145.37, 130.61, 129.53, 128.96, 127.37, 123.80, 119.29, 112.97, 33.04, 22.72, 19.02, 13.62; m/z LRMS (ESI + APCI) found $[\text{M} + \text{H}]^+$ 296.2, $\text{C}_{17}\text{H}_{18}\text{N}_3\text{S}^+$ requires 296.1.

2-(5,6-Dimethylpyrazin-2-yl)-4-ethoxyquinoline (16c)



Prepared according to general procedure C using (5,6-dimethylpyrazin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (154 mg, 0.25 mmol), trifluoromethanesulfonic acid (67 μ L, 0.75 mmol) and EtOH (625 μ L) at 100 $^{\circ}$ C for 14 hours. Flash column chromatography (silica gel: 33% EtOAc in hexanes) afforded the title compound as a gray amorphous powder (16 mg, 0.06 mmol, 23% yield). mp 189-191 $^{\circ}$ C; IR ν_{max} /cm $^{-1}$ (film): 3080, 2999, 2977, 2919, 1615, 1586, 1500, 1472, 1460, 1445, 1420, 1402, 1376, 1359, 1347, 1273, 1249, 1232, 1185, 1156, 1114, 1105, 1089, 1027, 993, 953, 919, 861, 837, 818, 784, 777, 767; ^1H NMR (400 MHz, CDCl_3) δ : 9.52 (1H, s), 8.24 (1H, d, J = 8.2 Hz), 8.10 (1H, d, J = 8.4 Hz), 7.86 (1H, s), 7.71 (1H, dd, J = 7.2, 7.1 Hz), 7.50 (1H, dd, J = 7.8, 7.3 Hz), 4.42 (2H, q, J = 7.0 Hz), 2.64 (3H, s), 2.62 (3H, s), 1.61 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 162.28, 156.03, 152.39, 150.85, 149.00, 148.17, 140.21, 129.87, 129.28, 125.77, 121.89, 121.37, 97.86, 64.26, 22.23, 22.02, 14.55; m/z LRMS (DART) found $[\text{M}+\text{H}]^+$ 280.2, $\text{C}_{17}\text{H}_{18}\text{N}_3\text{O}^+$ requires 280.1.

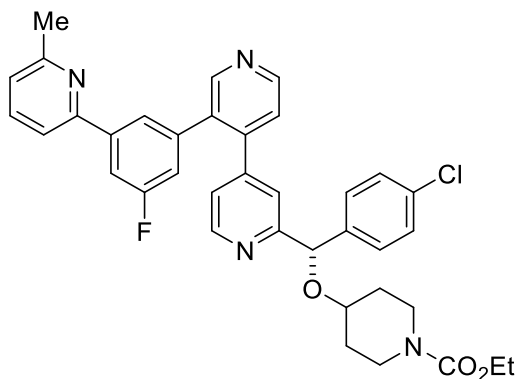
Ethyl 4-((*S*)-(4-chlorophenyl)(3'-(((*R*)-1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)-[4,4'-bipyridin]-2-yl)methoxy)piperidine-1-carboxylate (17c)



Prepared according to general procedure C, using (2-((*S*)-(4-chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)(3-(((*R*)-1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (106 mg, 0.10 mmol), trifluoromethanesulfonic acid (25 μ L, 0.30 mmol), and EtOH (0.25 mL) at 80 $^{\circ}$ C for 72 hours. The crude material was purified by flash chromatography (silica gel: 2% MeOH in CH_2Cl_2) followed by a second flash chromatography column (silica gel: 2% MeOH in CH_2Cl_2) to provide the title compound as a faint brown oil (43 mg, 0.06 mmol, 60% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3055, 2928, 2872, 1689, 1629, 1604, 1586, 1564, 1502, 964, 766, 645, 619, 534; ^1H NMR (400 MHz, CDCl_3) δ : 8.40 (1H, d, $J = 5.5$ Hz), 8.35-8.25 (2H, m), 7.62 (1H, s), 7.40-7.34 (1H, s), 7.40-7.34 (3H, m), 7.24 (1H, t, $J = 1.7$ Hz), 7.22 (2H, m), 6.93-6.85 (2H, m), 5.60 (1H, s), 4.05 (2H, q, $J = 7.1$ Hz), 3.95 (2H, d, $J = 5.4$ Hz), 3.79-3.62 (3H, m), 3.57 (1H, m), 3.17-3.04 (3H, m), 2.86-2.72 (2H, m), 2.10 (1H, q, $J = 8.4$ Hz), 1.96-1.47 (5H, m), 1.25-1.12 (6H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 161.94, 159.72 (dq, $J = 255.5, 2.3$ Hz), 155.47, 151.76 (m), 148.82, 147.49 (d, $J = 7.2$ Hz), 144.64, 143.16, 140.14, 135.40, 134.77, 133.47, 128.65, 128.08, 126.75 (2C, m), 122.64 (dq, $J = 270.5, 1.1$ Hz), 123.86 (m), 123.22 (d, J

= 3.4 Hz), 122.58, 116.09 (d, J = 20.7 Hz), 72.80, 62.61, 61.28, 58.75, 54.74, 41.07, 40.99, 31.16, 31.01, 29.67, 28.59, 23.26, 14.66; ^{19}F NMR δ : -61.13 (d, J = 12.8 Hz), -114.89-(-)115.21 (m); m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 727.2688, $\text{C}_{38}\text{H}_{40}\text{ClF}_4\text{N}_4\text{O}_4^+$ requires 727.2669.

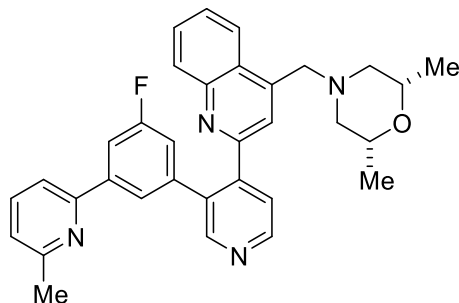
Ethyl (*S*)-4-((4-chlorophenyl)(3'-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)-[4,4'-bipyridin]-2-yl)methoxy)piperidine-1-carboxylate (18c)



Prepared according to general procedure C using (*S*)-(2-((4-chlorophenyl)((1-(ethoxycarbonyl)piperidin-4-yl)oxy)methyl)pyridin-4-yl)(3-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (97 mg, 0.10 mmol), trifluoromethanesulfonic acid (26.5 μL , 0.30 mmol), and EtOH (0.25 mL). The reaction was heated to 80 $^{\circ}\text{C}$ for 26 hours. Flash column chromatography (the crude reaction mixture was dissolved in 5 mL of CH_2Cl_2 and then 1 mL of trifluoroacetic acid was added, the mixture was loaded onto a silica column and then gradient elution: CH_2Cl_2 to 3% MeOH in CH_2Cl_2) followed by a second flash column (the crude reaction mixture was dissolved in 5 mL of CH_2Cl_2 and then 1 mL of trifluoroacetic acid was added, the mixture was loaded onto a silica column and then gradient elution: CH_2Cl_2 to 2% MeOH in CH_2Cl_2) followed by preparatory thin layer chromatography (silica gel: 3% MeOH in CH_2Cl_2) afforded the title compound as a colorless oil.

(41 mg, 0.07 mmol, 65% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3060, 2953, 2925, 1690, 1585, 1576, 1432, 1384, 1228, 1087, 751; ^1H NMR (400 MHz, CDCl_3) δ : 8.74 (2H, br s), 8.54 (1H, d, $J = 5.0$ Hz), 7.69 (1H, d, $J = 9.9$ Hz), 7.60-7.50 (2H, m), 7.35 (1H, d, $J = 4.2$ Hz), 7.24-7.15 (3H, m), 7.13-7.04 (5H, m), 6.84 (1H, d, $J = 8.7$ Hz), 5.47 (1H, s), 4.09 (2H, q, $J = 7.2$ Hz), 3.63-3.49 (2H, m), 3.49-3.38 (1H, m), 3.16-3.03 (2H, m), 2.58 (3H, s), 1.72-1.55 (2H, m), 1.54-1.36 (2H, m), 1.23 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 162.95 (d, $J = 246.7$ Hz), 161.95, 158.64, 155.38, 154.23 (d, $J = 2.9$ Hz), 151.02, 149.66-149.29 (2C, m), 147.16, 145.05, 142.20 (d, $J = 7.8$ Hz), 139.54, 138.93 (d, $J = 8.3$ Hz), 136.94, 134.56, 133.30, 128.52, 127.81, 124.11-123.81 (2C, m), 122.47, 122.44, 120.99, 117.20, 116.54 (d, $J = 22.6$ Hz), 113.28 (d, $J = 22.7$ Hz), 80.38, 72.19, 61.19, 40.78, 40.72, 30.88, 30.68, 24.62, 14.66; ^{19}F NMR (365 MHz, CDCl_3) δ : -112.23; m/z HRMS (ESI) found $[\text{M}+\text{H}]^+$ 637.2391, $\text{C}_{37}\text{H}_{35}\text{ClFN}_4\text{O}_3^+$ requires 637.2376.

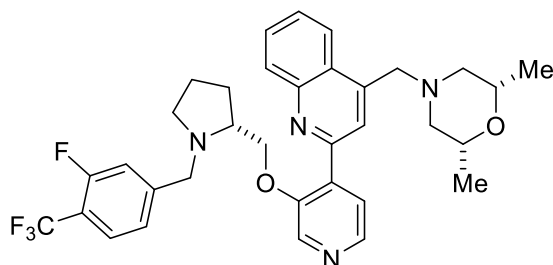
(2*R*, 6*S*)-4-((2-(3-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)pyridin-4-yl)quinolin-4-yl)methyl)-2,6-dimethylmorpholine (19c)



Prepared according to general procedure C (except an additional 18 μ L, 0.20 mmol of trifluoromethanesulfonic acid was added after 40.5 hours) using (4-(((2*R*, 6*S*)-2,6-dimethylmorpholino)methyl)quinolin-2-yl)(3-(3-fluoro-5-(6-methylpyridin-2-yl)phenyl)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (85 mg, 0.10 mmol), trifluoromethanesulfonic acid (35 μ L, 0.40 mmol), and EtOH (0.25 mL). The reaction was heated to 80 $^{\circ}$ C for 58.5 hours. Flash column chromatography (silica gel: 60% EtOAc in hexanes) followed by a second flash column (silica gel, gradient elution: 1% MeOH in CH_2Cl_2 to 2.5% MeOH in CH_2Cl_2) afforded the title compound as a colorless oil (23.7 mg, 0.046 mmol, 46%). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3063, 2972, 2928, 1586, 1455, 1430, 1344, 1083, 757; ^1H NMR (400 MHz, CDCl_3) δ : 8.81 (2H, br s), 8.27-8.15 (2H, m), 7.85-7.73 (3H, m), 7.68 (1H, d, J = 9.9 Hz), 7.58 (1H, t, J = 7.6 Hz), 7.51 (1H, t, J = 7.7 Hz), 7.23 (1H, d, J = 7.7 Hz), 7.15-7.03 (2H, m), 6.92 (1H, d, J = 9.0 Hz), 3.63 (2H, s), 3.54-3.38 (2H, m), 2.50 (3H, s), 2.40 (2H, d, J = 11.5 Hz), 1.63 (2H, t, J = 10.5 Hz), 1.00 (6H, d, J = 6.3 Hz) ^{13}C NMR (100 MHz, CDCl_3) δ : 162.86 (d, J = 246.4), 158.62, 156.36, 154.36 (d, J = 2.7 Hz), 150.76, 149.56, 148.57, 146.77, 143.77, 142.18 (d, J = 8.6 Hz), 139.74 (d, J = 8.2 Hz), 136.94, 134.58, 130.19, 129.63, 126.87, 126.64, 124.68, 124.24, 123.95 (d, J = 2.7 Hz), 122.63, 122.40, 117.22, 116.79 (d, J = 22.5 Hz), 113.16 (d, J = 22.7 Hz),

71.51, 59.81, 59.38, 24.51, 18.83; ^{19}F NMR (365 MHz, CDCl_3) δ : -112.28 (t, $J = 9.3$ Hz); m/z HRMS (ESI) found $[\text{M}+\text{H}]^+$ 519.2572, $\text{C}_{33}\text{H}_{32}\text{FN}_4\text{O}^+$ requires 519.2555.

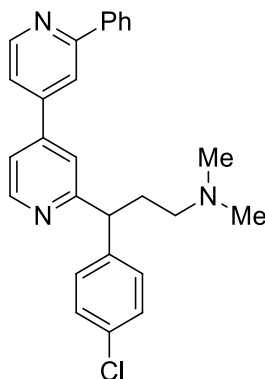
(2*S*, 6*R*)-4-((2-(3-(((*R*)-1-(3-Fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)quinolin-4-yl)methyl)-2,6-dimethylmorpholine (20c)



Prepared according to general procedure C, using (4-(((2*S*, 6*R*)-2,6-dimethylmorpholino)methyl)quinolin-2-yl)(3-(((*R*)-1-(3-fluoro-4-(trifluoromethyl)benzyl)pyrrolidin-2-yl)methoxy)pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (94 mg, 0.10 mmol), 4.0M HCl in dioxane (100 μL , 0.40 mmol), and EtOH (0.25 mL) at 80 $^{\circ}\text{C}$ for 72 hours. The crude material was purified by flash chromatography (silica gel: 2% MeOH in CH_2Cl_2) to provide the title compound as a brown amorphous solid (30 mg, 0.05 mmol, 49% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3063, 2971, 2930, 2871, 2813, 1629, 1587, 1545, 693, 653, 602, 550, 531, 526; ^1H NMR (400 MHz, CDCl_3) δ : 8.50-8.39 (2H, m), 8.23 (1H, d, $J = 8.3$ Hz), 8.11 (1H, d, $J = 8.4$ Hz), 7.85 (1H, s), 7.75 (1H, d, $J = 4.8$ Hz), 7.71 (1H, m), 7.56 (1H, m), 7.29 (1H, t, $J = 7.7$ Hz), 6.97-6.87 (2H, m), 4.21-4.06 (2H, m), 4.01 (1H, d, $J = 14.16$ 14.2 Hz), 3.80 (2H, d, $J = 1.8$ Hz), 3.73-3.61 (2H, m), 3.30 (1H, d, $J = 14.2$ Hz), 3.08-2.97 (1H, m), 2.91-2.80 (1H, m), 2.79 (2H, d, $J = 11.5$ Hz), 2.15 (1H, q, $J = 6.2$ Hz), 2.06-1.94 (1H, m), 1.86 (2H, q, $J = 10.6$ Hz), 1.78-1.65 (3H, m), 1.14 (6H, d, $J = 6.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 159.57 (dq, $J = 253.8$, 2.1 Hz), 154.01, 152.42, 148.39, 147.22 (d, $J = 5.5$ Hz), 143.38, 143.23, 136.59, 135.72, 130.16, 129.47, 126.94-126.32 (m, 4C), 124.75, 124.17, 123.30 (d, $J = 3.3$ Hz),

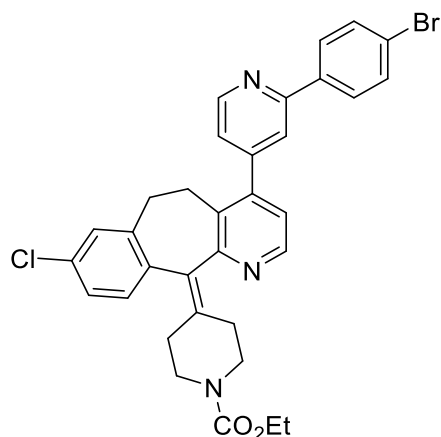
122.97, 122.62 (dq, $J = 273.1, 1.0$ Hz), 116.89 (d, $J = 20.6$ Hz), 73.11, 71.67 (d, $J = 2.2$ Hz), 62.43, 60.13, 59.69 (d, $J = 8.4$ Hz), 58.86, 54.66, 28.60, 23.29, 19.88 (d, $J = 1.1$ Hz); ^{19}F NMR δ : -61.10 (d, $J = 12.9$ Hz), -114.67- (-)115.23 (m); m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 609.2839, $\text{C}_{34}\text{H}_{37}\text{F}_4\text{N}_4\text{O}_2^+$ requires 609.2847.

3-(4-Chlorophenyl)-N,N-dimethyl-3-(2'-phenyl-[4,4'-bipyridin]-2-yl)propan-1-amine (21c)



Prepared according to general procedure C using (2-(1-(4-chlorophenyl)-3-(dimethylamino)propyl)pyridin-4-yl)diphenyl(2-phenylpyridin-4-yl)phosphonium trifluoromethanesulfonate (381 mg, 0.50 mmol), trifluoromethanesulfonic acid (134 μL , 1.50 mmol) and EtOH (1.25 mL) at 80 $^{\circ}\text{C}$ for 12 hours. Flash column chromatography (silica gel: 9% MeOH in CH_2Cl_2) afforded the title compound as a light yellow oil (179 mg, 0.42 mmol, 84% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3410, 3027, 2940, 2856, 2815, 2766, 2430, 2203, 1590, 1533, 1488, 1467, 1445, 1379, 1261, 1089, 1025, 1014, 907, 829, 775, 756, 727, 694; ^1H NMR (400 MHz, CDCl_3) δ : 8.74 (1H, d, $J = 4.9$ Hz), 8.68 (1H, d, $J = 4.9$ Hz), 8.01 (2H, d, $J = 7.4$ Hz), 7.87 (1H, s), 7.49–7.33 (8H, m), 7.25 (2H, d, $J = 8.6$ Hz), 4.29 (1H, t, $J = 7.4$ Hz), 2.70–2.34 (10H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.01, 158.27, 150.26, 150.06, 146.48, 146.27, 141.11, 138.76, 132.47, 129.21, 129.15, 128.66, 126.88, 120.96, 119.79, 119.49, 118.23, 56.90, 49.98, 44.25, 31.30; m/z HRMS (DART) found $[\text{M}+\text{H}]^+$ 428.1921, $\text{C}_{27}\text{H}_{27}\text{ClN}_3^+$ requires 428.1894.

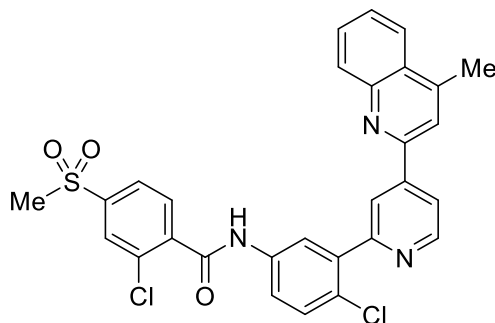
Ethyl 4-(4-(2-(4-bromophenyl)pyridin-4-yl)-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (22c)



Prepared according to general procedure C using (2-(4-bromophenyl)pyridin-4-yl)(8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)diphenylphosphonium trifluoromethanesulfonate (237 mg, 0.25 mmol), trifluoromethanesulfonic acid (44 μ L, 0.50 mmol), and EtOH (625 μ L). The reaction was heated to 80 $^{\circ}$ C for 30 hrs. Flash column chromatography (basic alumina, gradient elution: 20% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a white solid (133 mg, 0.22 mmol, 87% yield). mp 95-98 $^{\circ}$ C; IR ν_{max} /cm $^{-1}$ (film): 3050, 2972, 2922, 1690, 1578, 1473, 1428, 1222, 1008, 826, 729; ^1H NMR (400 MHz, CDCl_3) δ : 8.77 (1H, d, J = 5.0 Hz), 8.49 (1H, d, J = 5.0 Hz), 7.91 (2H, d, J = 8.6 Hz), 7.66-7.58 (3H, m), 7.21-7.14 (3H, m), 7.12 (1H, s), 7.06 (1H, d, J = 5.0 Hz), 4.14 (2H, q, J = 7.2 Hz), 3.82 (2H, br s), 3.41-3.29 (1H, m), 3.27-3.12 (3H, m), 2.88-2.72 (2H, m), 2.56-2.35 (3H, m), 2.34-2.20 (1H, m), 1.26 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 159.73, 156.58, 155.34, 149.87, 147.81, 147.09, 146.77, 138.50, 137.53, 137.34, 135.89, 134.11, 133.01, 131.90, 131.21, 130.30, 129.60, 128.41, 126.07, 123.84,

122.53, 121.87, 119.70, 61.24, 44.69, 44.57, 32.12, 30.60, 30.51, 27.48, 14.48; m/z HRMS (DART) found $[M+H]^+$ 614.1235, $C_{33}H_{30}BrClN_3O_2^+$ requires 614.1204.

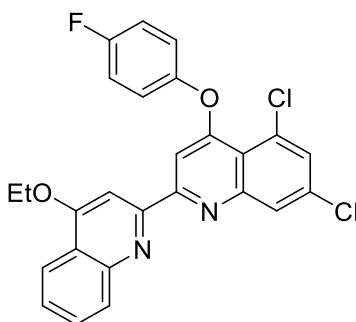
2-Chloro-N-(4-chloro-3-(4-(4-methylquinolin-2-yl)pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (23c)



Prepared according to general procedure C using (2-(2-chloro-5-(2-chloro-4-(methylsulfonyl)benzamido)phenyl)pyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (224 mg, 0.25 mmol), 4.0 M HCl in dioxanes (125 μ L, 0.50 mmol), and (2,2,2)-Trifluoroethanol (625 μ L). The reaction was heated to 80 $^{\circ}$ C for 37 hours. Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt_3 then gradient elution: CH_2Cl_2 to 1.5% MeOH in CH_2Cl_2) followed by a second flash column (basic alumina, gradient elution: CH_2Cl_2 to 2% MeOH in CH_2Cl_2) and the resulting solid was washed on a frit with 200 mL of Et_2O and then 25 mL of chilled CH_2Cl_2 (0 $^{\circ}$ C). The title compound was isolated as a white solid (73 mg, 0.13 mmol, 52% yield). decomp. 270-275 $^{\circ}$ C; IR ν_{max}/cm^{-1} (film): 3318, 3018, 2992, 2914, 1689, 1539, 1299, 1152, 1030, 816, 751; 1H NMR (400 MHz, $CDCl_3$) δ : 10.99, (1H, s), 8.89 (1H, d, J = 5.2 Hz), 8.28 (1H, d, J = 5.2 Hz), 8.21 (1H, s), 8.18-8.07 (4H, m), 8.02 (1H, dd, J = 8.0, 1.5 Hz), 7.94 (1H, d, J = 8.0 Hz), 7.87-7.76 (2H, m), 7.72-7.59 (2H, m), 3.36 (3H, s), 2.79 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 163.87, 156.84, 152.95, 150.28, 147.31, 146.12,

146.03, 143.13, 140.84, 139.31, 137.65, 130.97, 130.44, 130.08-129.82 (3C, m), 128.10, 127.60, 127.16, 125.99, 125.91, 124.21, 122.35, 121.81, 125.99, 125.91, 124.21, 122.35, 121.81, 121.07, 120.42, 119.31, 43.09, 18.39; m/z HRMS (ESI + APCI) found $[M+H]^+$ 562.0766, $C_{29}H_{22}Cl_2N_3O_3S^+$ requires 562.0753.

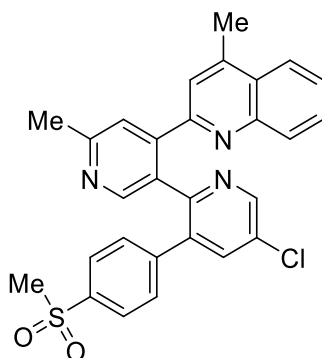
5,7-Dichloro-4'-ethoxy-4-(4-fluorophenoxy)-2,2'-biquinoline (24c)



Prepared according to general procedure C, using (5,7-dichloro-4-(4-fluorophenoxy)quinolin-2-yl)(4-ethoxyquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (203 mg, 0.25 mmol), trifluoromethanesulfonic acid (42 μ L, 0.50 mmol), and (2,2,2)-Trifluoroethanol (625 μ L) at 80 $^{\circ}$ C for 36 hours. The crude material was suspended in a 5mL CH_2Cl_2 and filtered over a frit with cold CH_2Cl_2 to provide the title compound as a white crystalline solid (69 mg, 0.15 mmol, 58% yield). mp 235-238 $^{\circ}$ C; IR ν_{max}/cm^{-1} (film): 3065, 2978, 1430, 1296, 1214, 1117, 733; 1H NMR (400 MHz, $CDCl_3$) δ : 8.24 (1H, d, J = 8.2 Hz), 8.19-8.12 (2H, m), 8.10 (1H, s), 7.97 (1H, d, J = 8.4 Hz), 7.67 (1H, t, J = 7.3 Hz), 7.60 (1H, d, J = 1.8 Hz), 7.51 (1H, t, J = 15.0 Hz), 7.24 (4H, m), 4.47 (2H, q, J = 7.0 Hz), 1.64 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 162.60, 162.32, 159.93 (d, J = 243.8 Hz), 158.99, 155.89, 151.37, 150.39 (d, J = 2.7 Hz), 148.69, 134.94, 130.24, 129.86, 129.67, 129.42, 128.18, 126.26, 122.87 (d, J = 8.5 Hz), 121.94, 121.77, 118.42, 116.98 (d, J = 23.6 Hz), 105.31, 98.17, 64.38, 14.55; ^{19}F

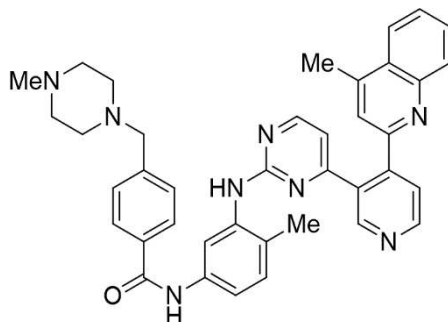
NMR δ : -117.56 (m); m/z HRMS (DART) found $[M+H]^+$ 479.0709, $C_{26}H_{18}Cl_2FN_2O_2^+$ requires 479.0724.

2-(5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)-4-methylquinoline (25c)



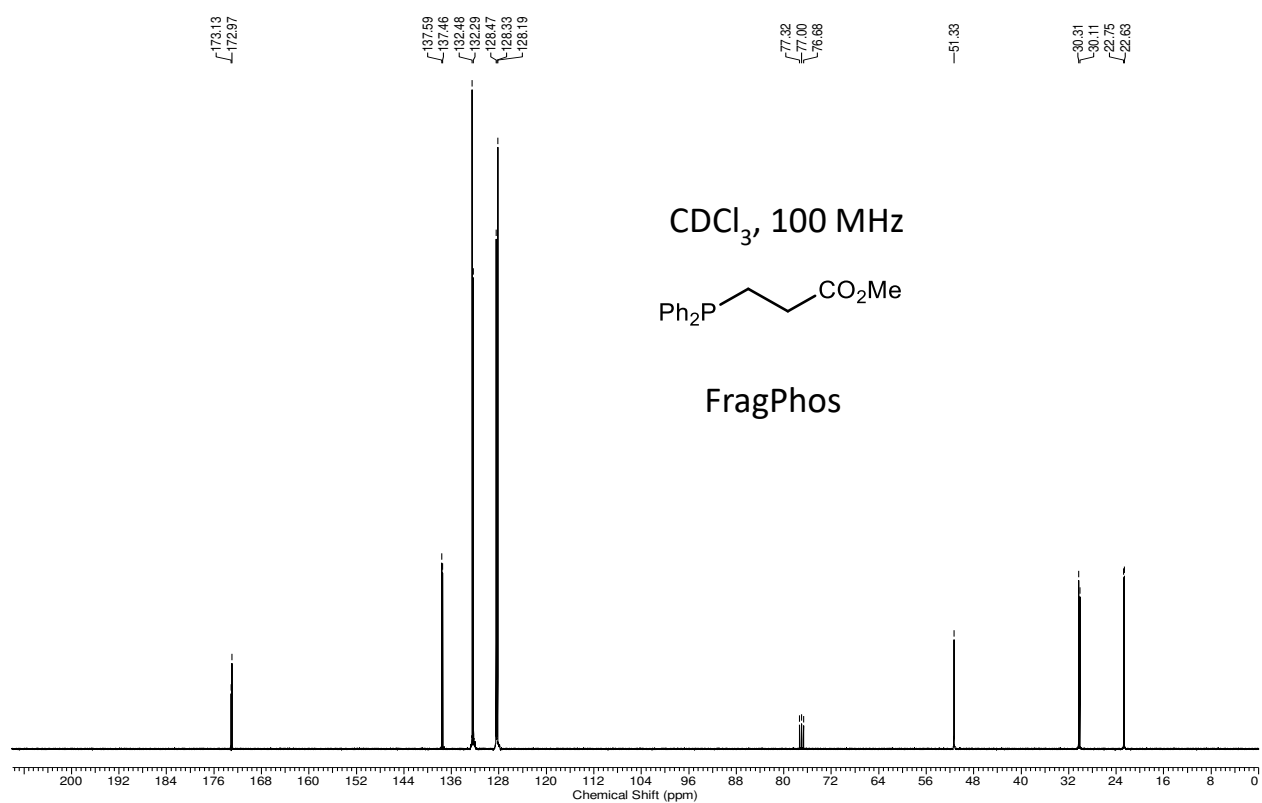
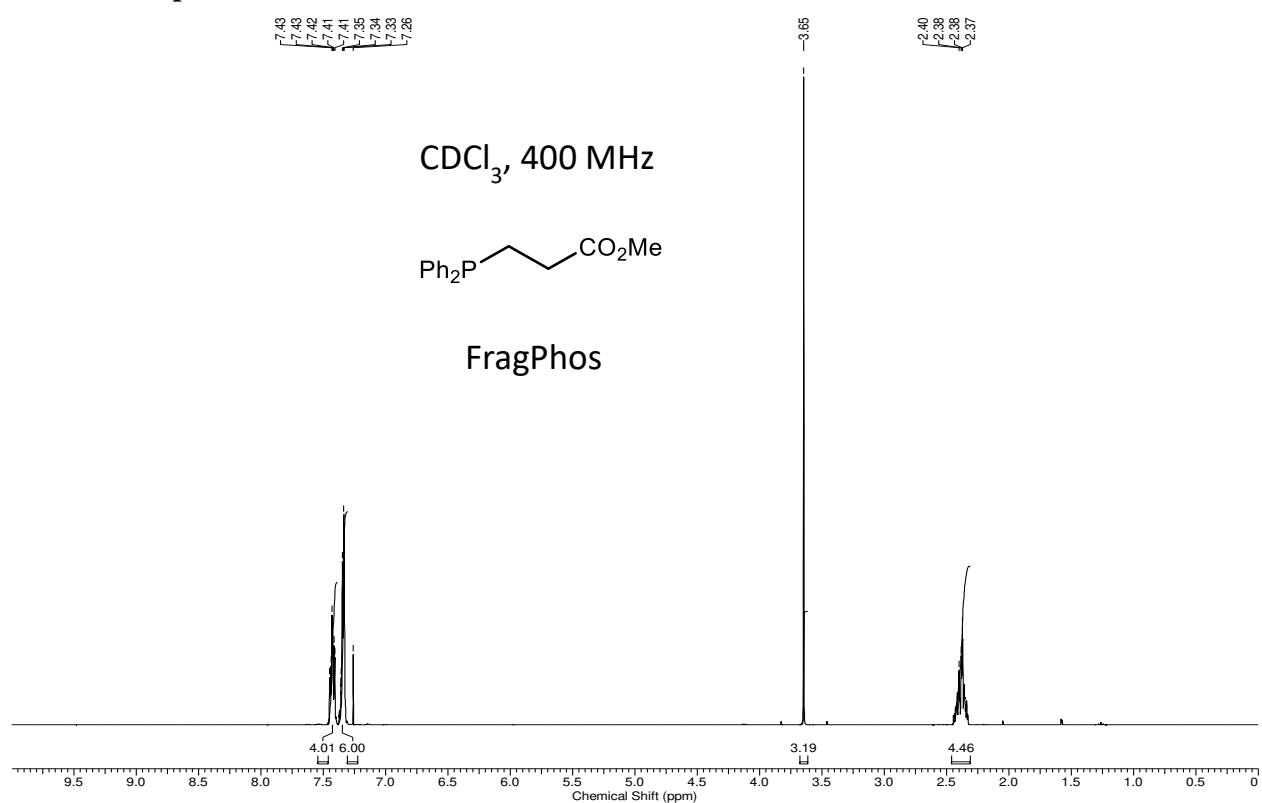
Prepared according to general procedure C, using (5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (83 mg, 0.10 mmol), trifluoromethanesulfonic acid (26 μ L, 0.30 mmol), and EtOH (0.25 mL) at 80 $^{\circ}$ C for 22 hours. The crude material was purified by flash chromatography (silica gel gradient elution: 3% MeOH in CH_2Cl_2 to 4% MeOH in CH_2Cl_2) to provide the title compound as a white crystalline solid (40 mg, 0.08 mmol, 80% yield). mp 286-290 $^{\circ}$ C; IR ν_{max}/cm^{-1} (film): 3034, 2926, 1506, 1264, 1034, 873, 863; 1H NMR (400 MHz, $CDCl_3$) δ : 8.69-8.59 (2H, m), 7.96 (1H, d, J = 8.0 Hz), 7.68-7.43 (6H, m), 7.35 (1H, s), 6.94-6.81 (3H, m), 3.00 (3H, s), 2.67 (3H, s), 2.61 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 159.16, 154.96, 154.07, 151.54, 147.94, 147.32, 147.11, 145.21, 143.07, 139.47, 136.47, 136.03, 130.77, 130.59, 130.02, 129.61, 129.56, 127.08, 126.92, 126.75, 123.57, 122.81, 120.92, 44.39, 24.42, 18.78; m/z HRMS (DART) found $[M+H]^+$ 500.1175, $C_{28}H_{23}ClN_3O_2S^+$ requires 500.1194.

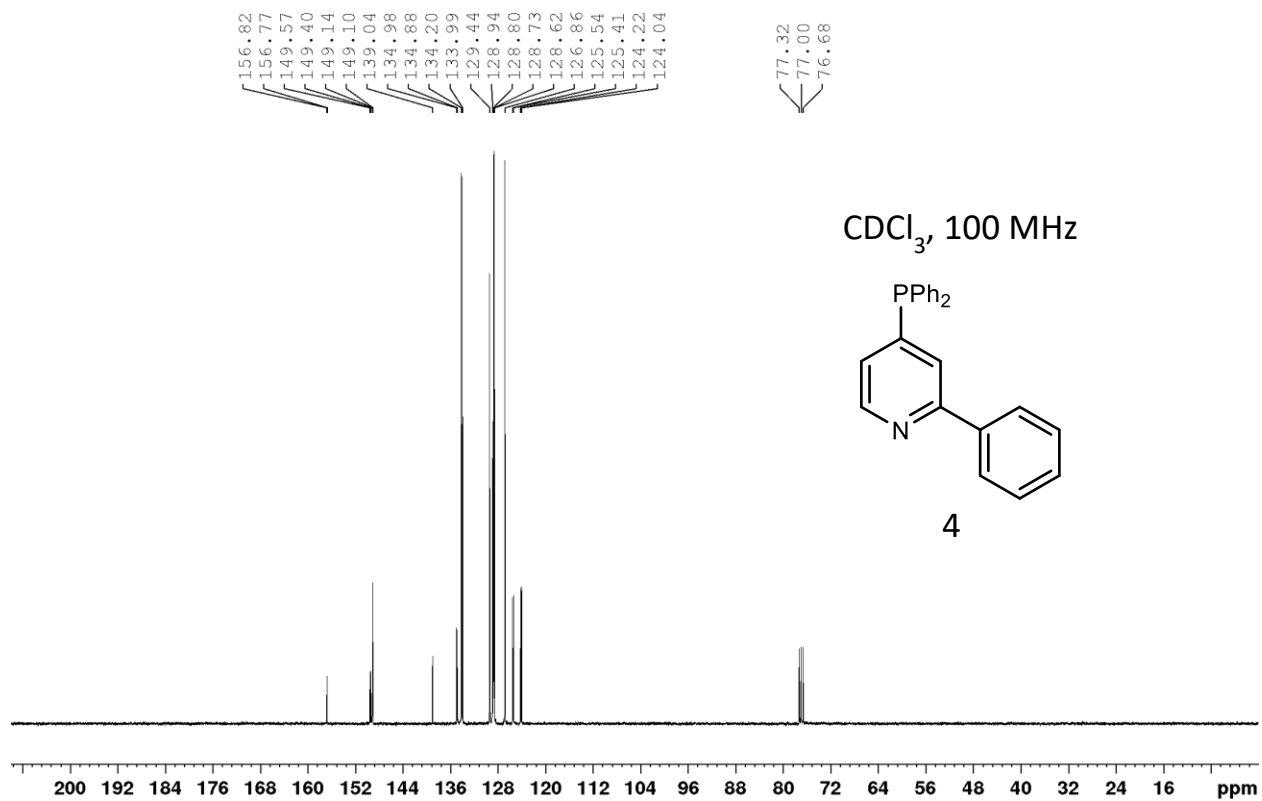
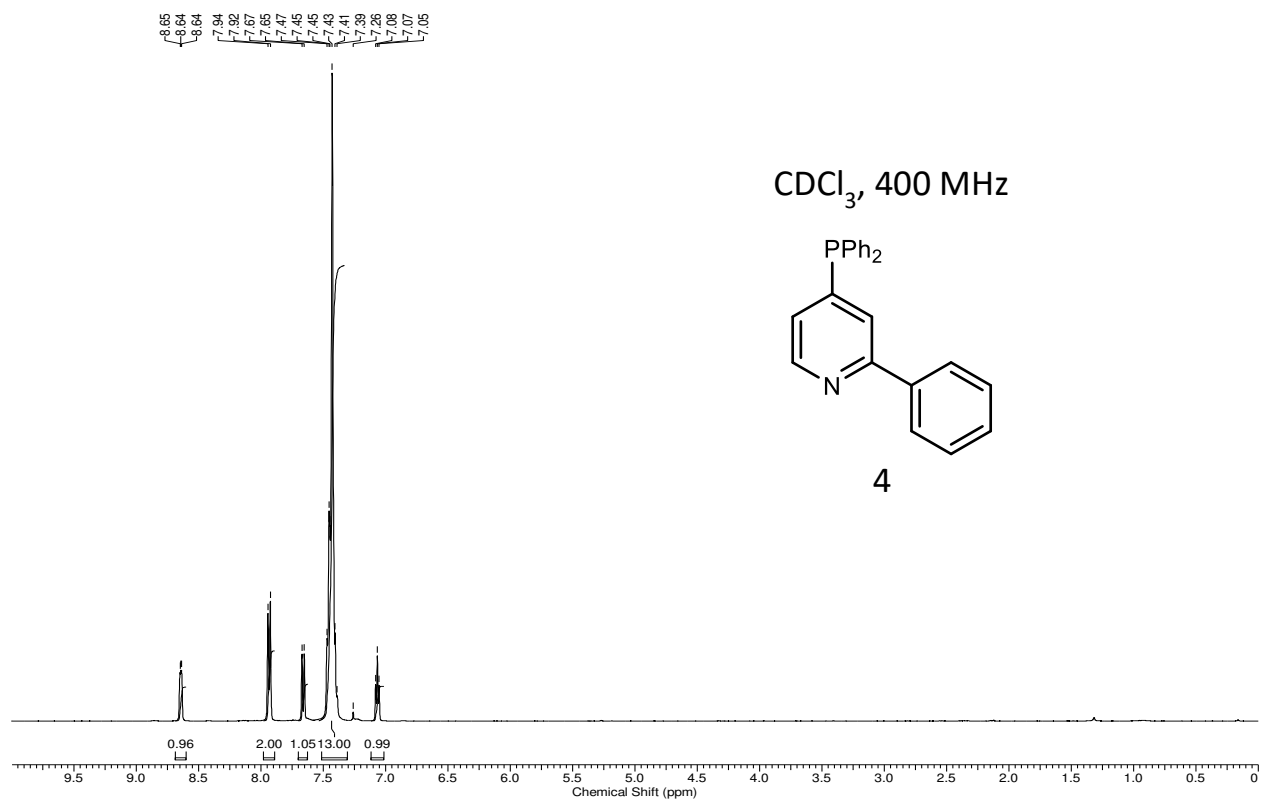
***N*-(4-Methyl-3-((4-(4-(4-methylquinolin-2-yl)pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (26c)**

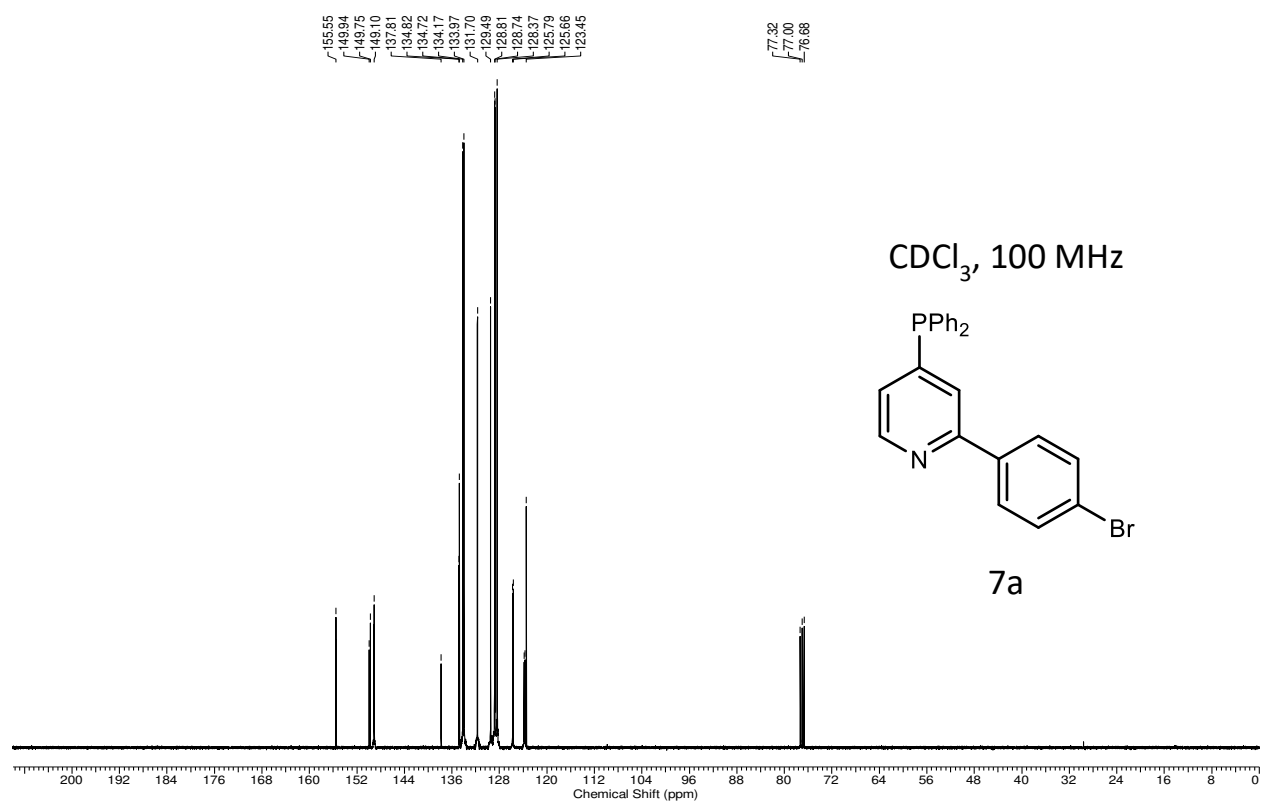
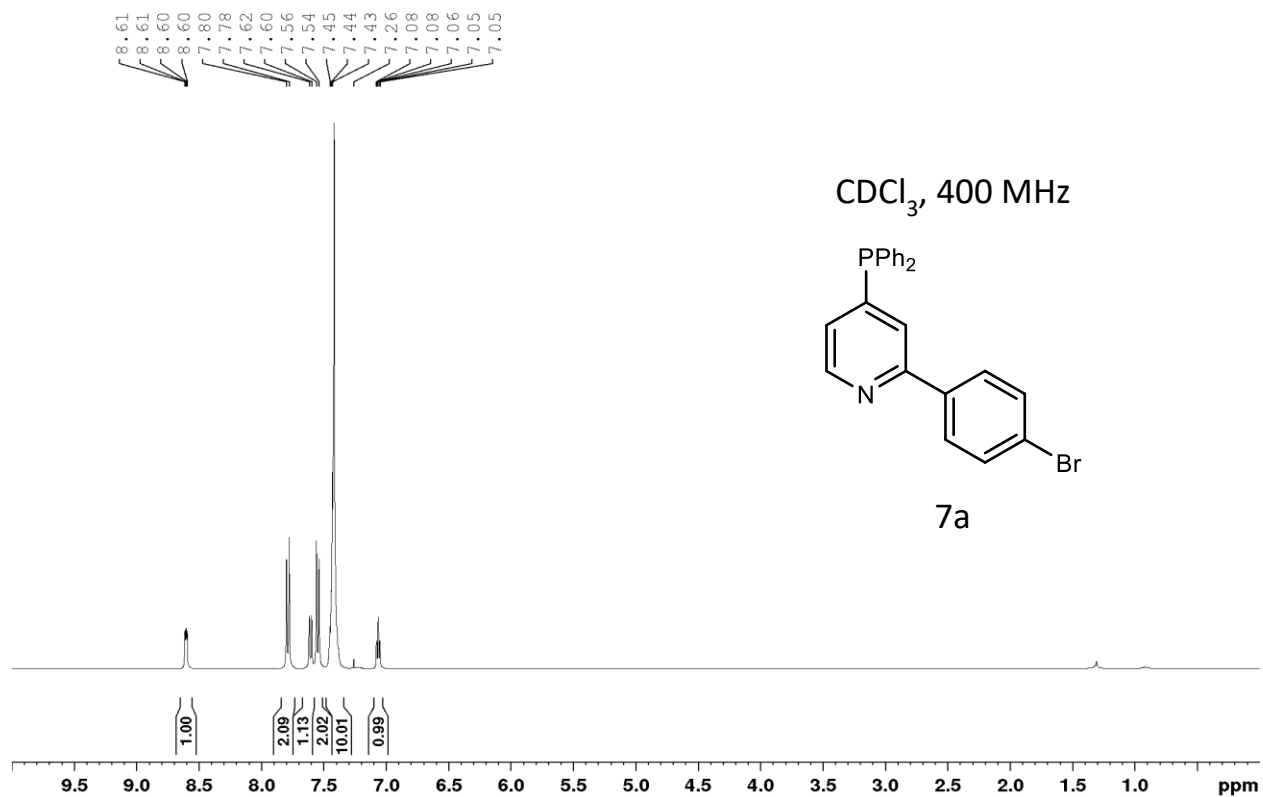


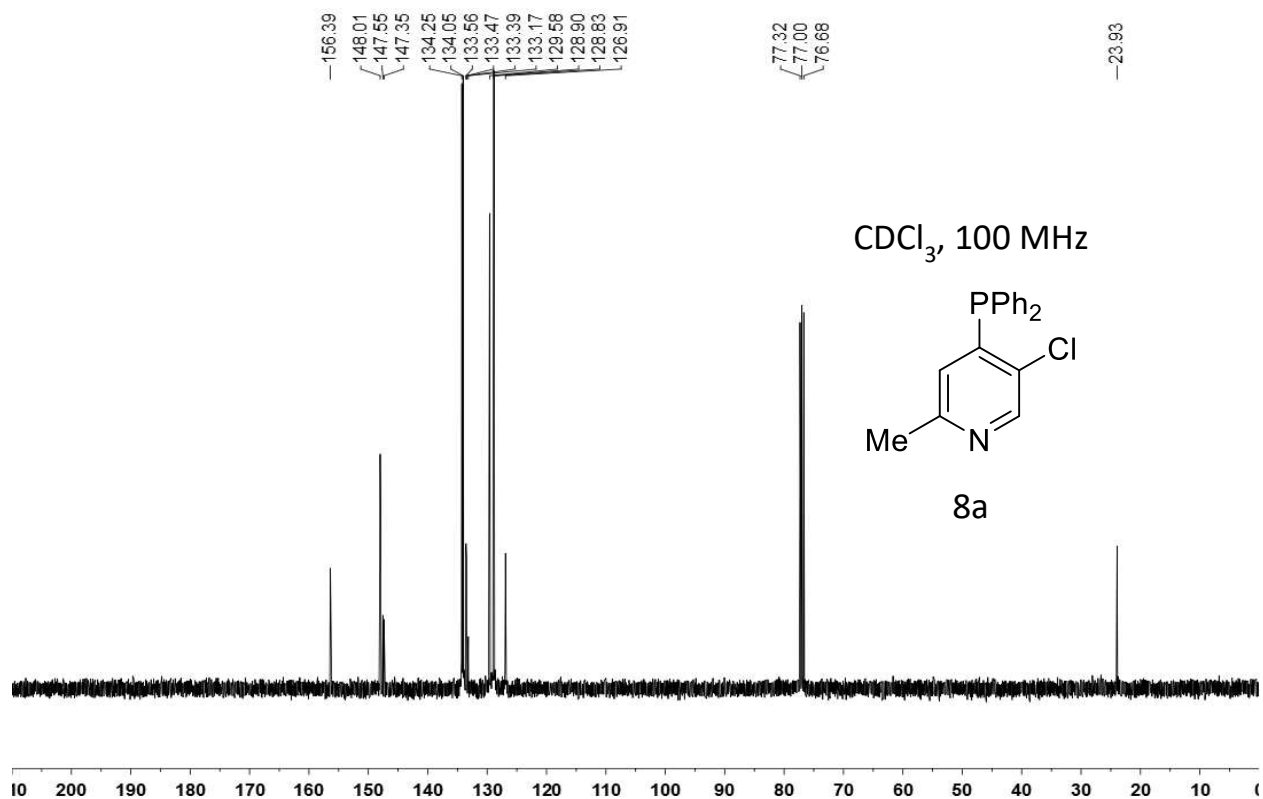
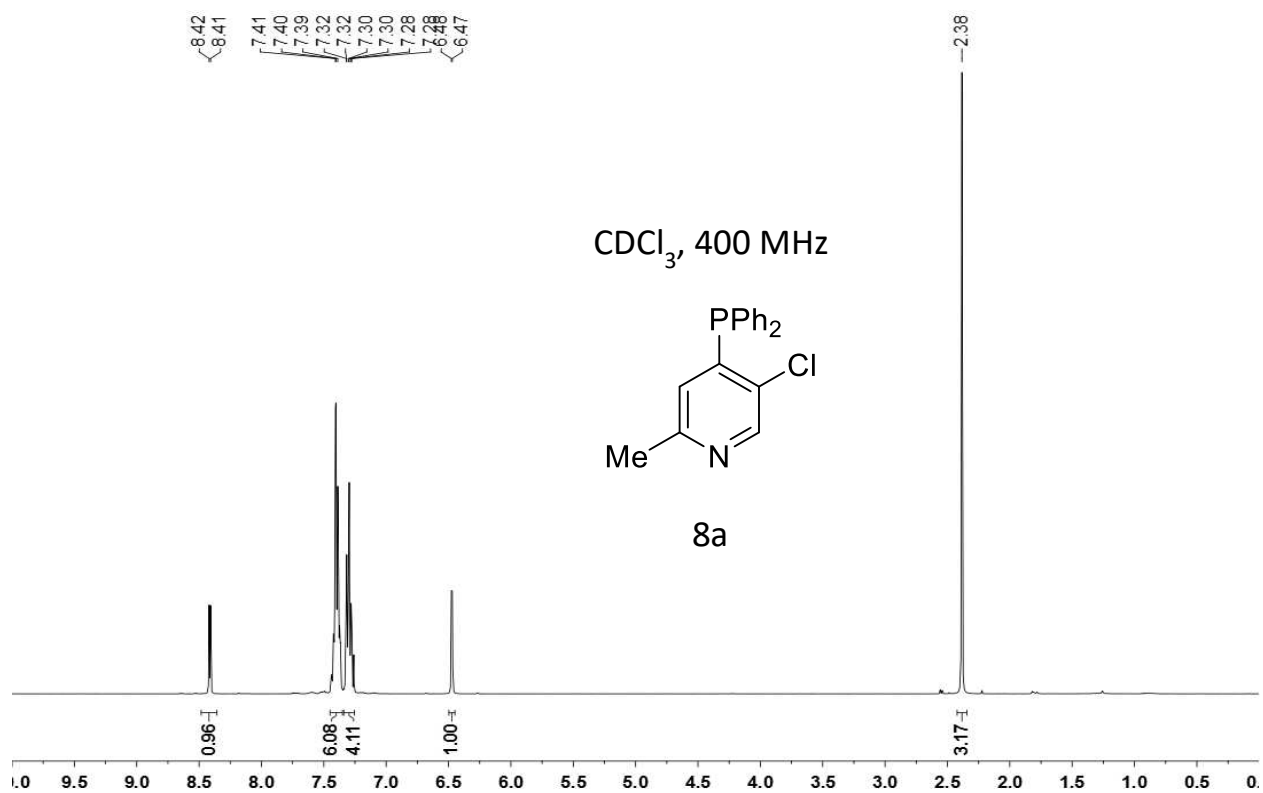
Prepared according to general procedure C using (3-(2-((2-methyl-5-(4-((4-methylpiperazin-1-yl)methyl)benzamido)phenyl)amino)pyrimidin-4-yl)pyridin-4-yl)(4-methylquinolin-2-yl)diphenylphosphonium trifluoromethanesulfonate (97 mg, 0.10 mmol), trifluoromethanesulfonic acid (36 μ L, 0.40 mmol) and EtOH (0.25 mL) at 80 $^{\circ}$ C for 48 hours. Flash column chromatography by three times (silica gel: 30% toluene, 3% MeOH and 1% Et₃N in CH₂Cl₂) afforded the title compound as a colorless oil (26 mg, 0.04 mmol, 41% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3249, 3036, 2933, 2796, 1663, 1572, 1553, 1525, 1505, 1446, 1406, 1349, 1287, 1204, 1162, 1138, 1010, 906, 816, 758, 730; ¹H NMR (400 MHz, CDCl₃) δ : 9.02 (1H, s), 8.83 (1H, d, J = 5.0 Hz), 8.26 (1H, d, J = 5.1 Hz), 8.09 (1H, s), 7.96–7.87 (5H, m), 7.72 (1H, d, J = 5.0 Hz), 7.66 (1H, t, J = 7.5 Hz), 7.55 (1H, t, J = 7.4 Hz), 7.48–7.44 (3H, m), 7.09–7.06 (2H, m), 6.83 (1H, s), 6.62 (1H, d, J = 5.1 Hz), 3.56 (2H, s), 2.57–2.29 (14H, m), 2.13 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 165.33, 164.51, 160.07, 157.95, 156.20, 150.85, 150.62, 147.78, 147.57, 144.55, 142.50, 137.36, 136.47, 133.86, 132.78, 130.60, 129.99, 129.67, 129.24, 127.14, 127.12, 126.91, 124.53, 123.66, 123.51, 122.41, 115.13, 112.72, 112.53, 62.52, 55.08, 53.12, 45.99, 18.74, 17.32; m/z HRMS (ESI + APCI) found $[M+H]^+$ 635.3221, C₃₉H₃₉N₈O⁺ requires 635.3247.

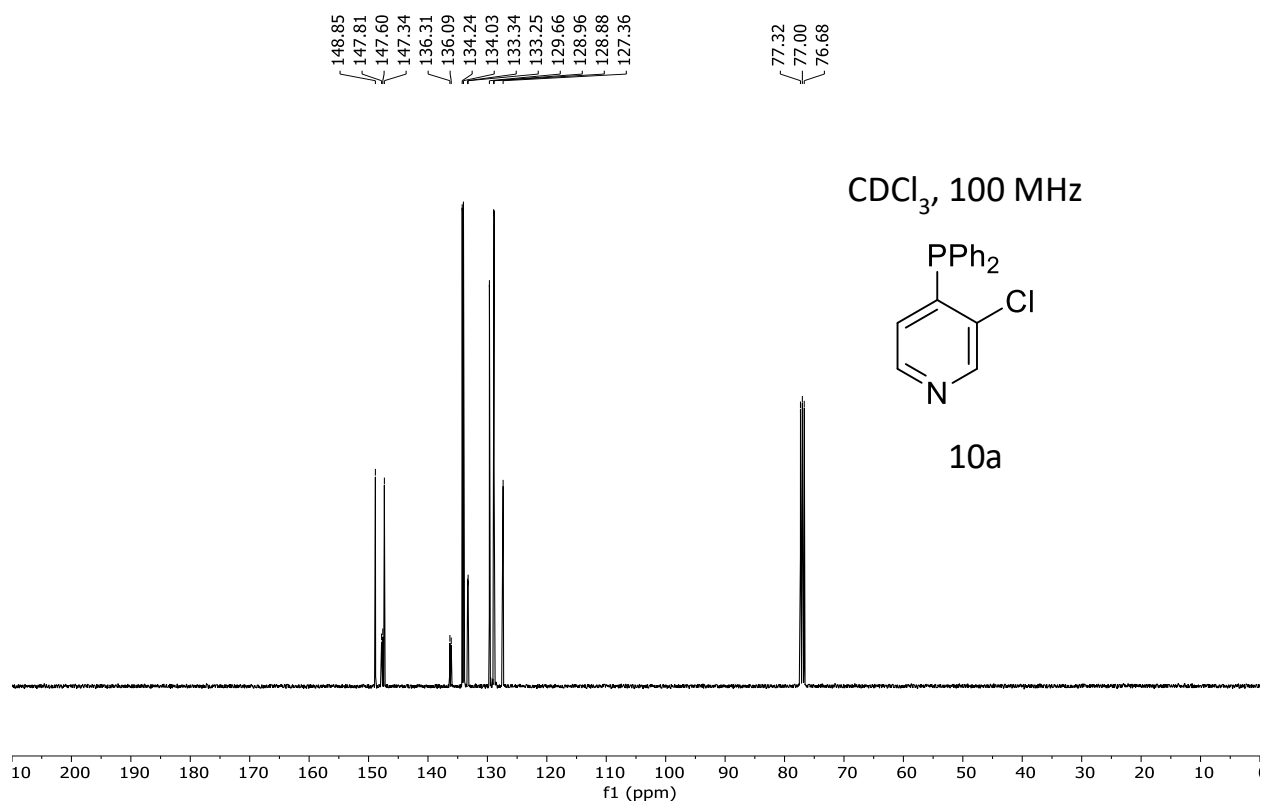
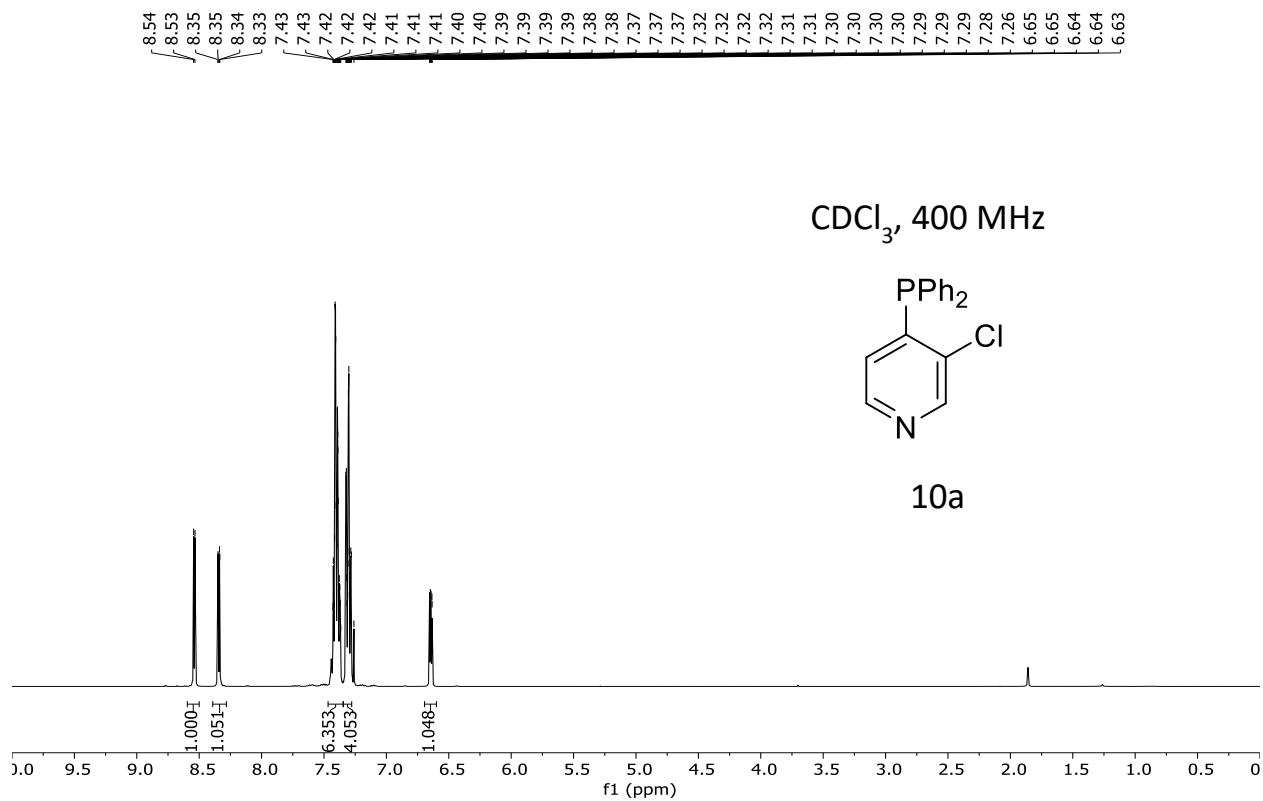
A 1.4 Spectra

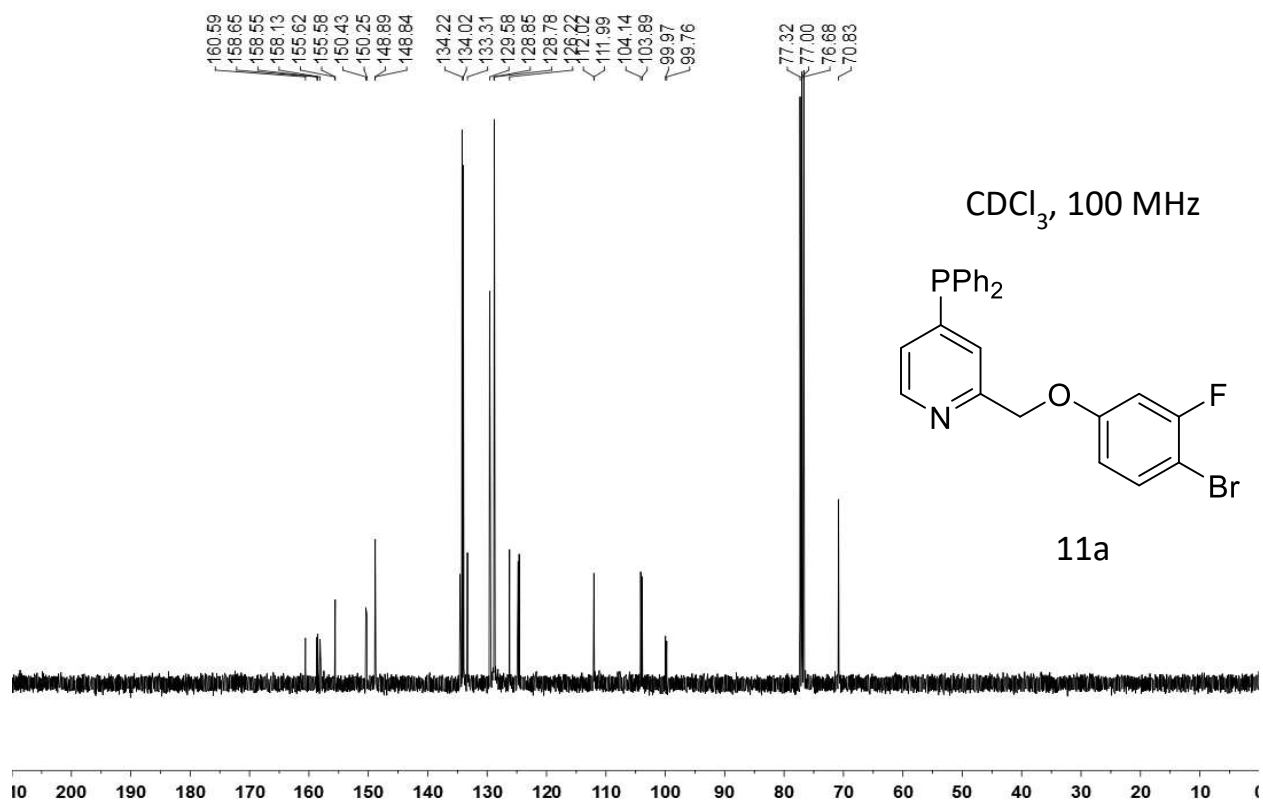
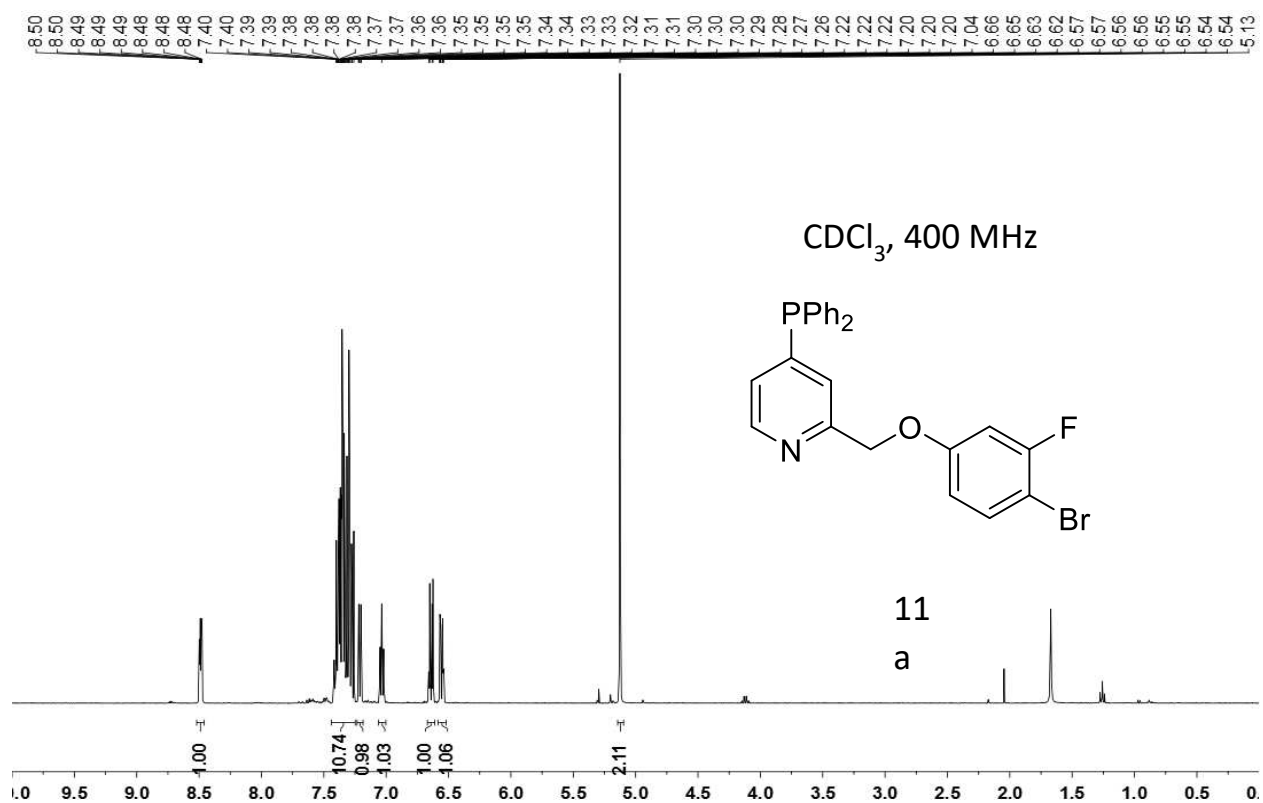


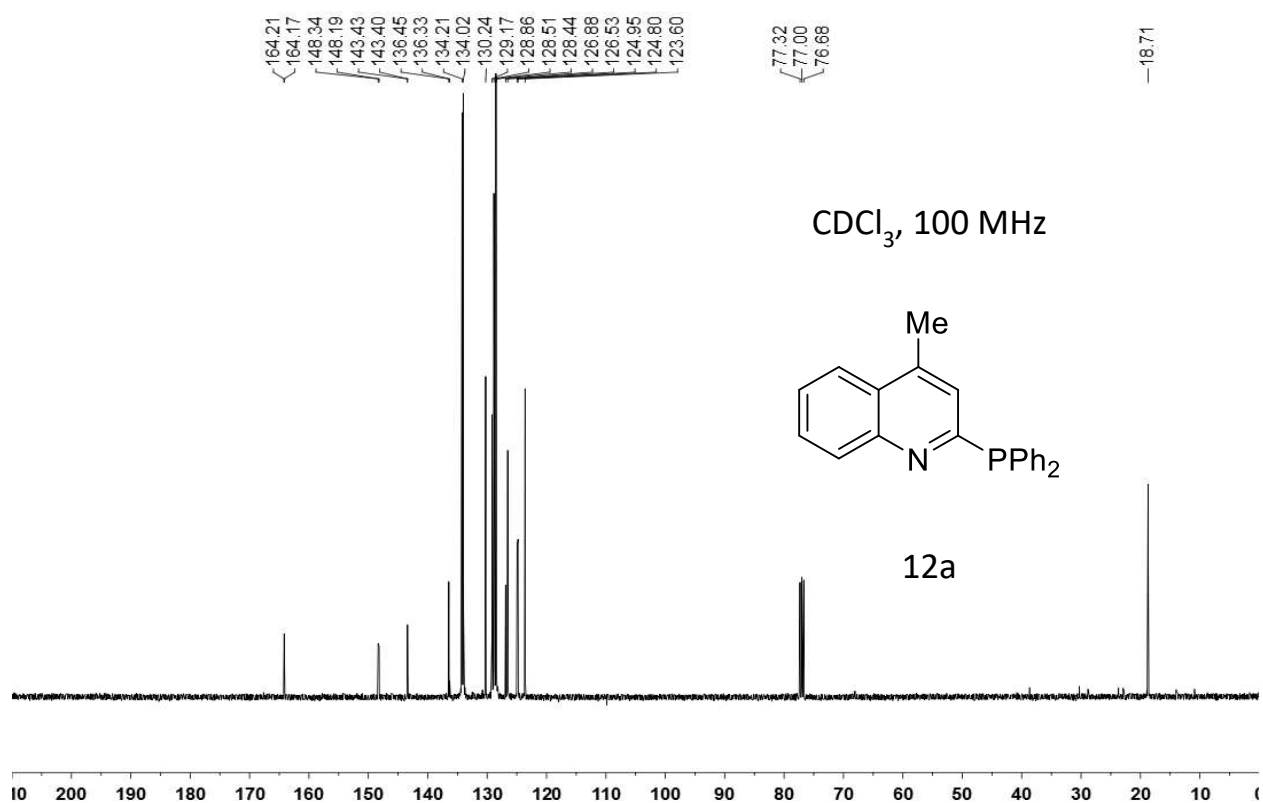
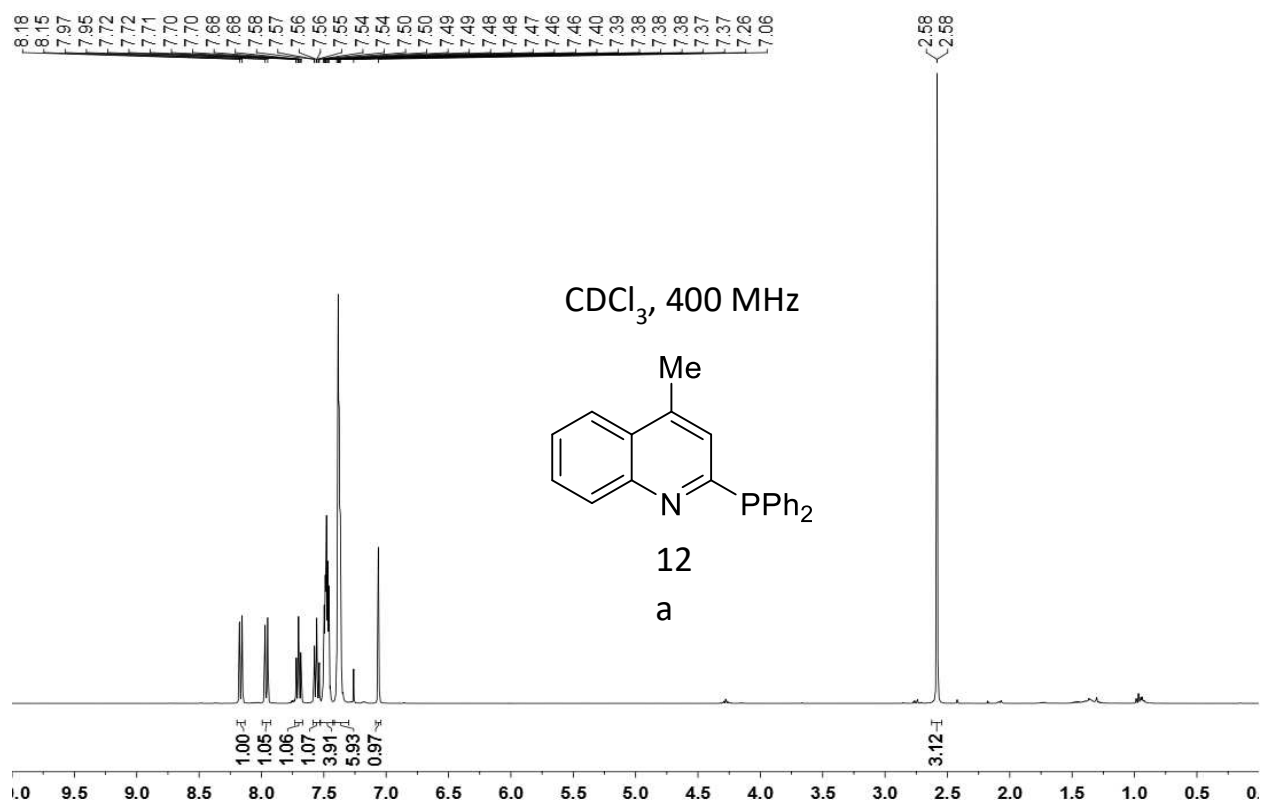


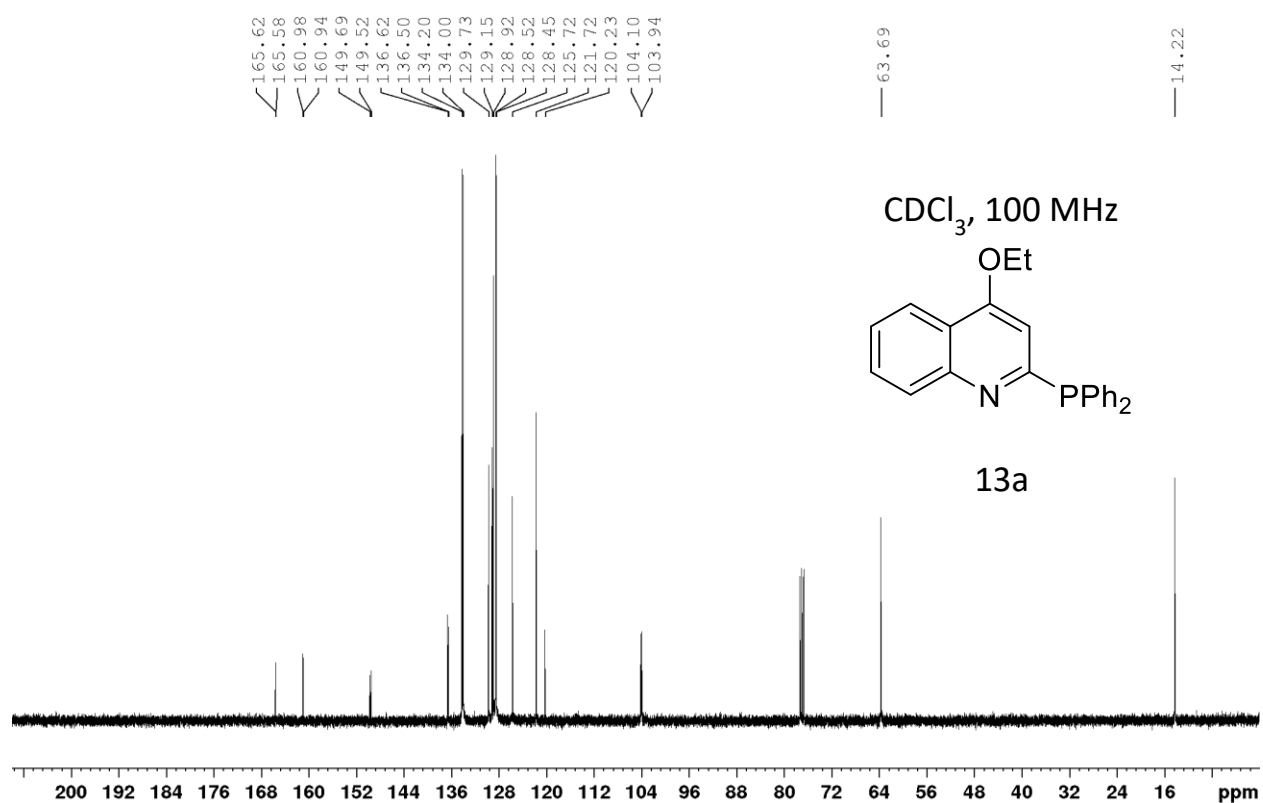
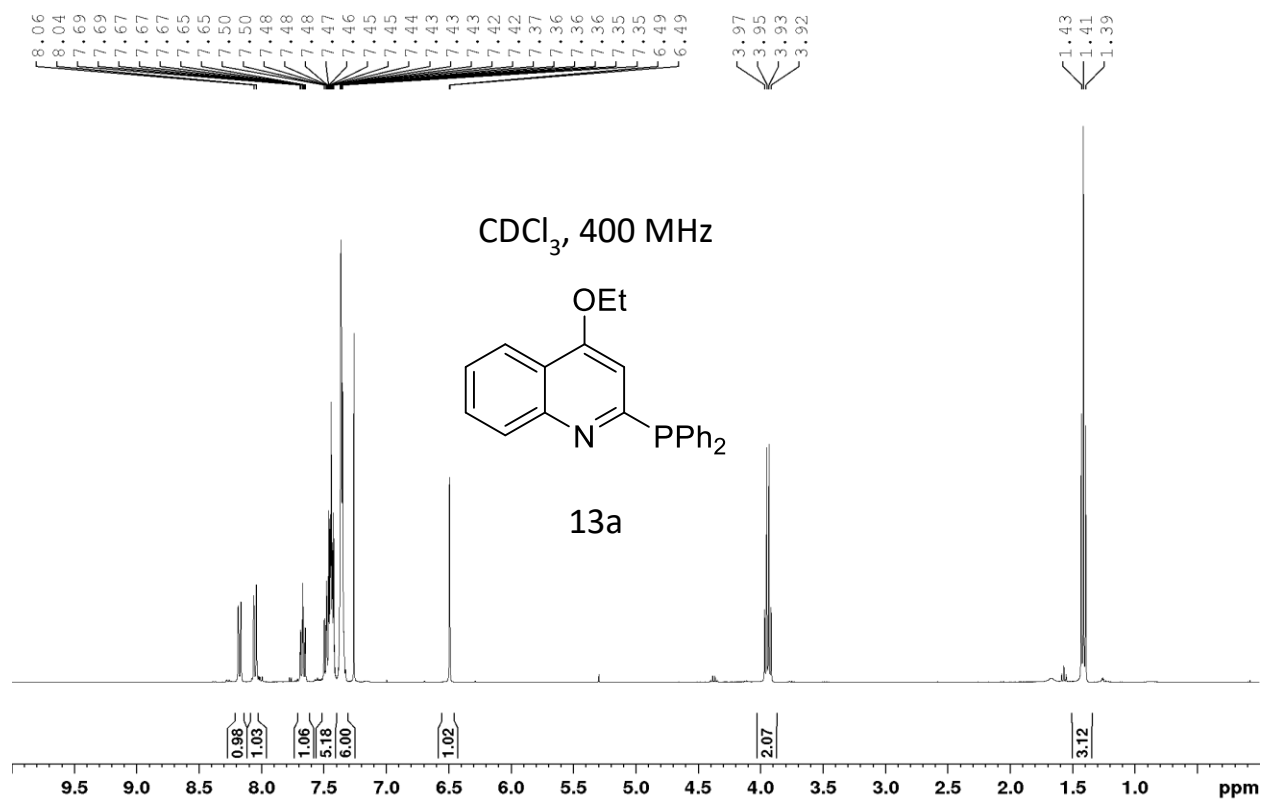


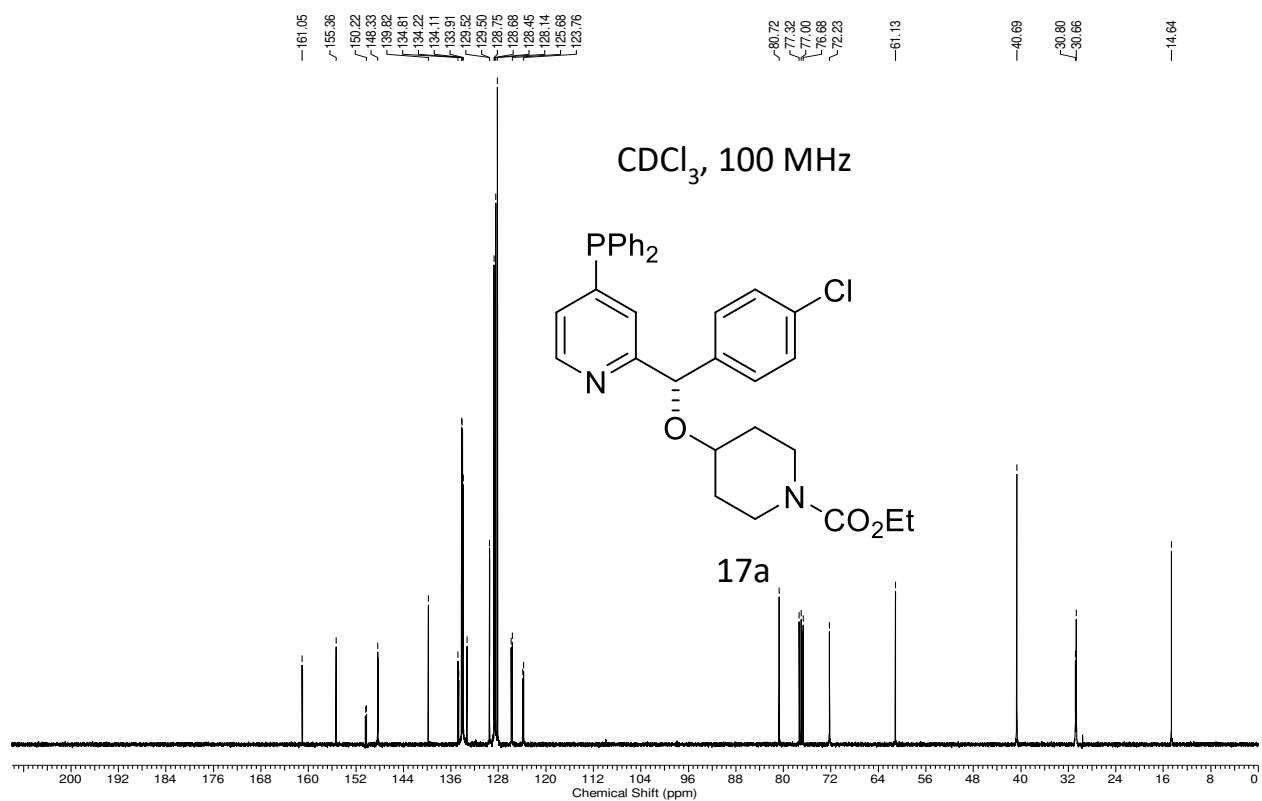
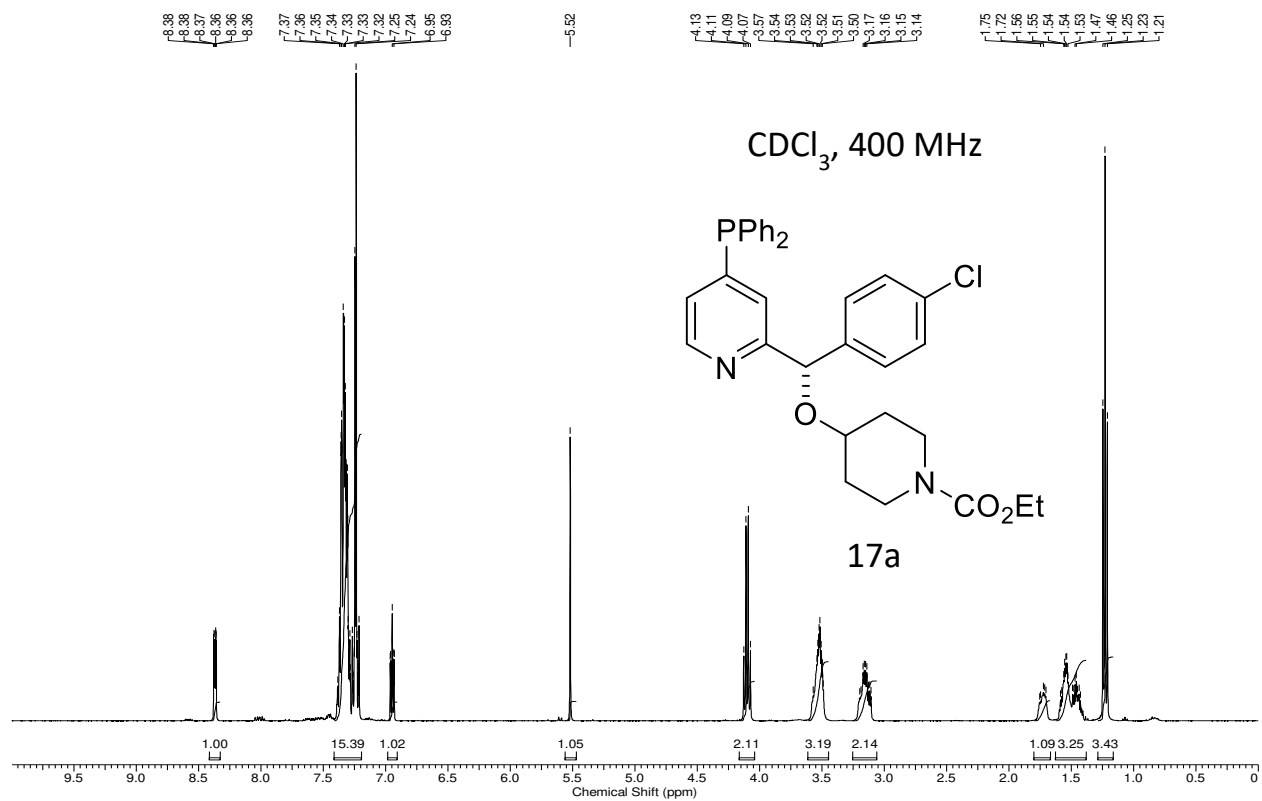


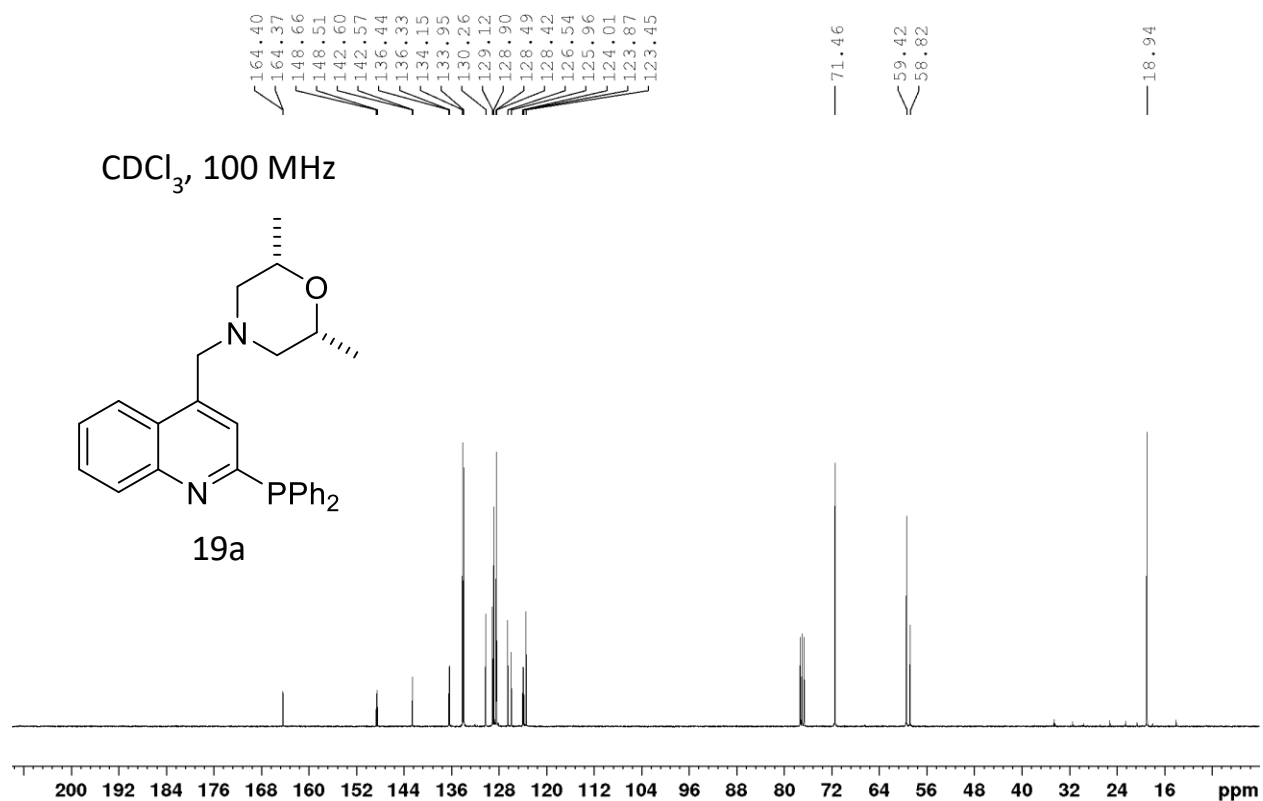
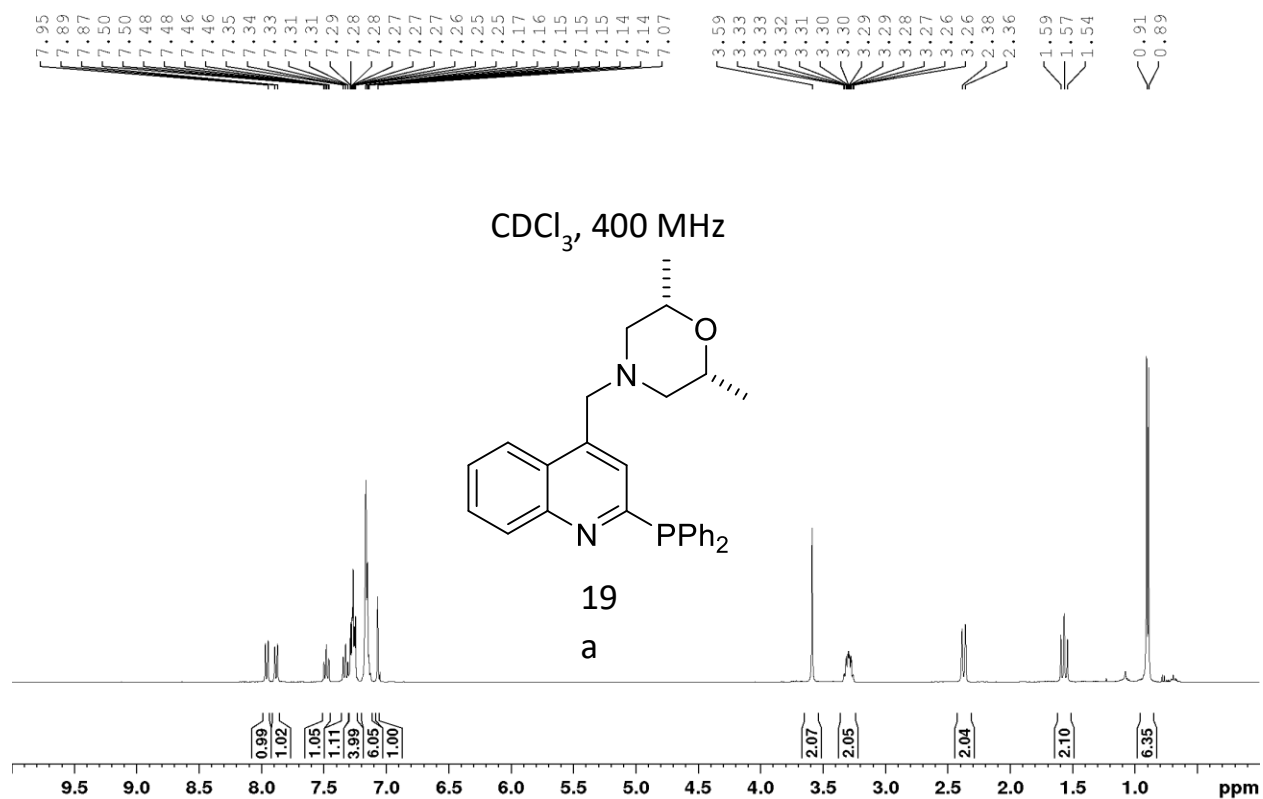


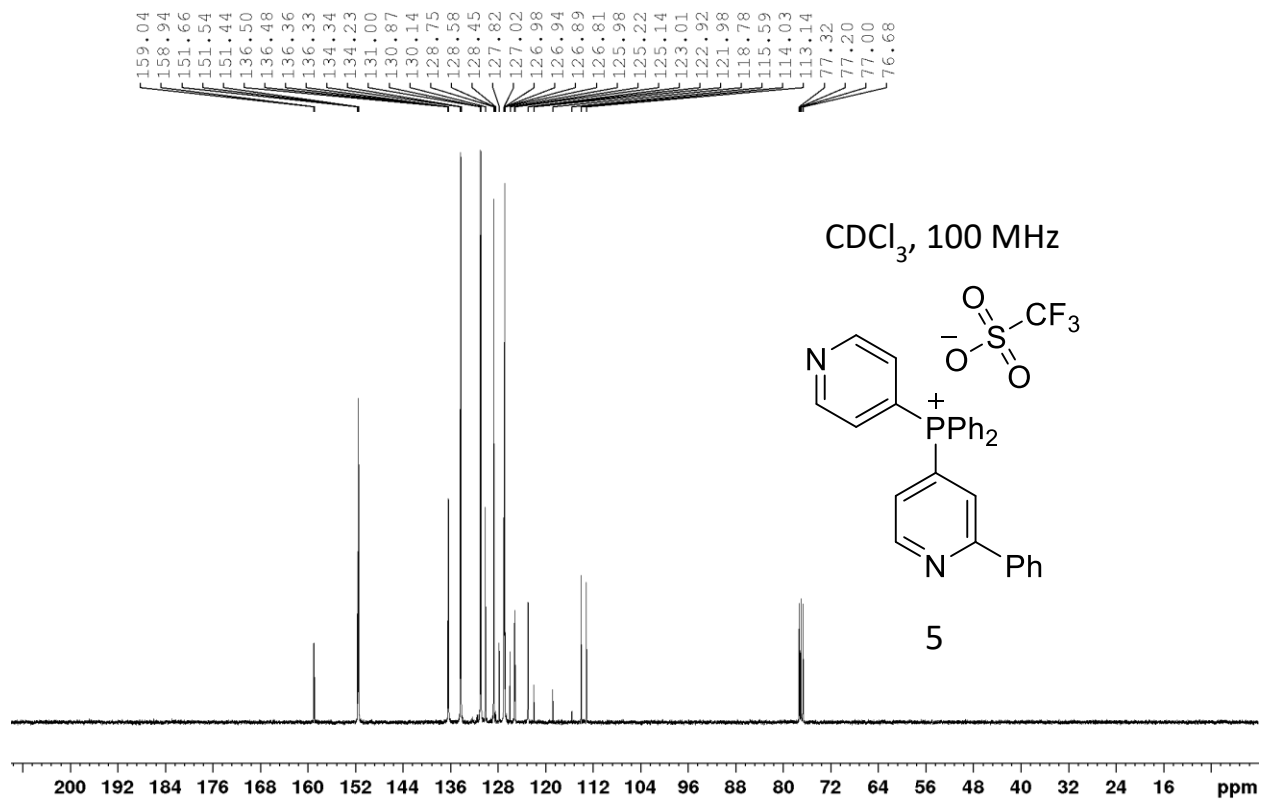
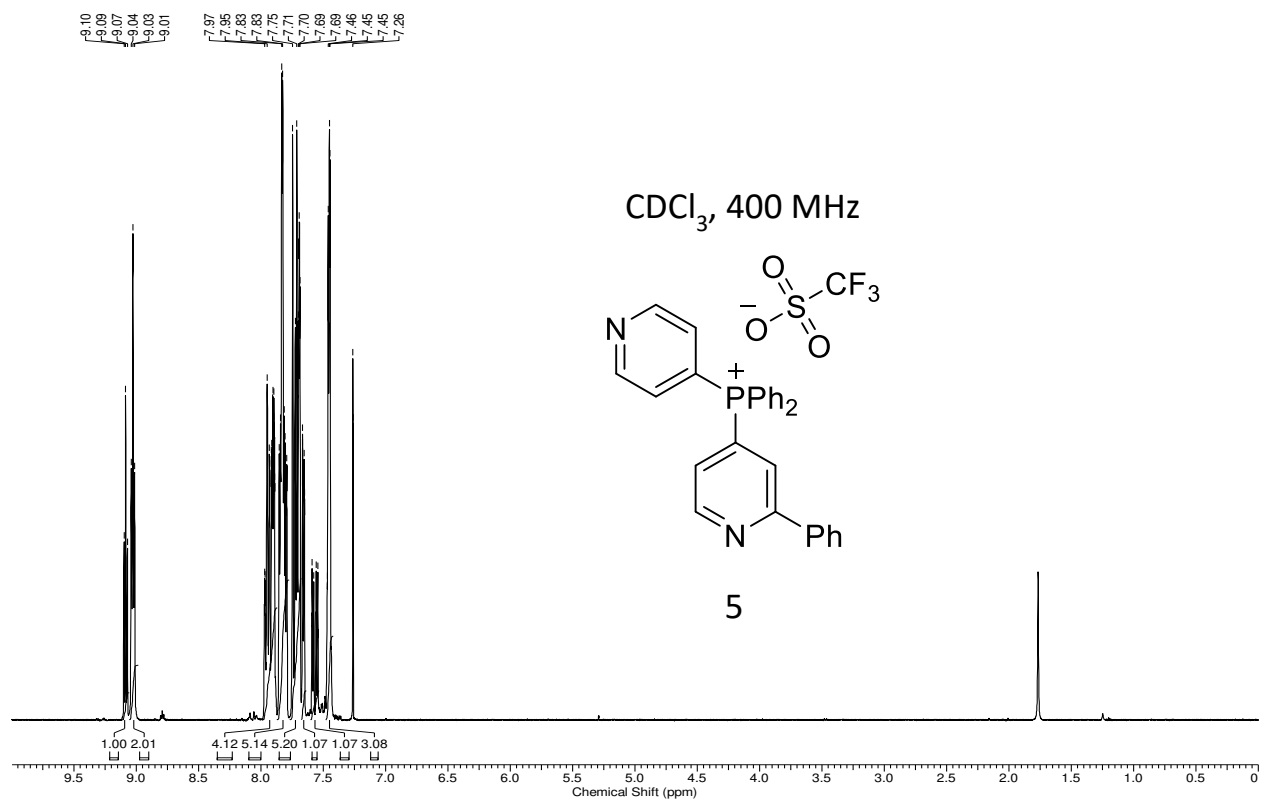


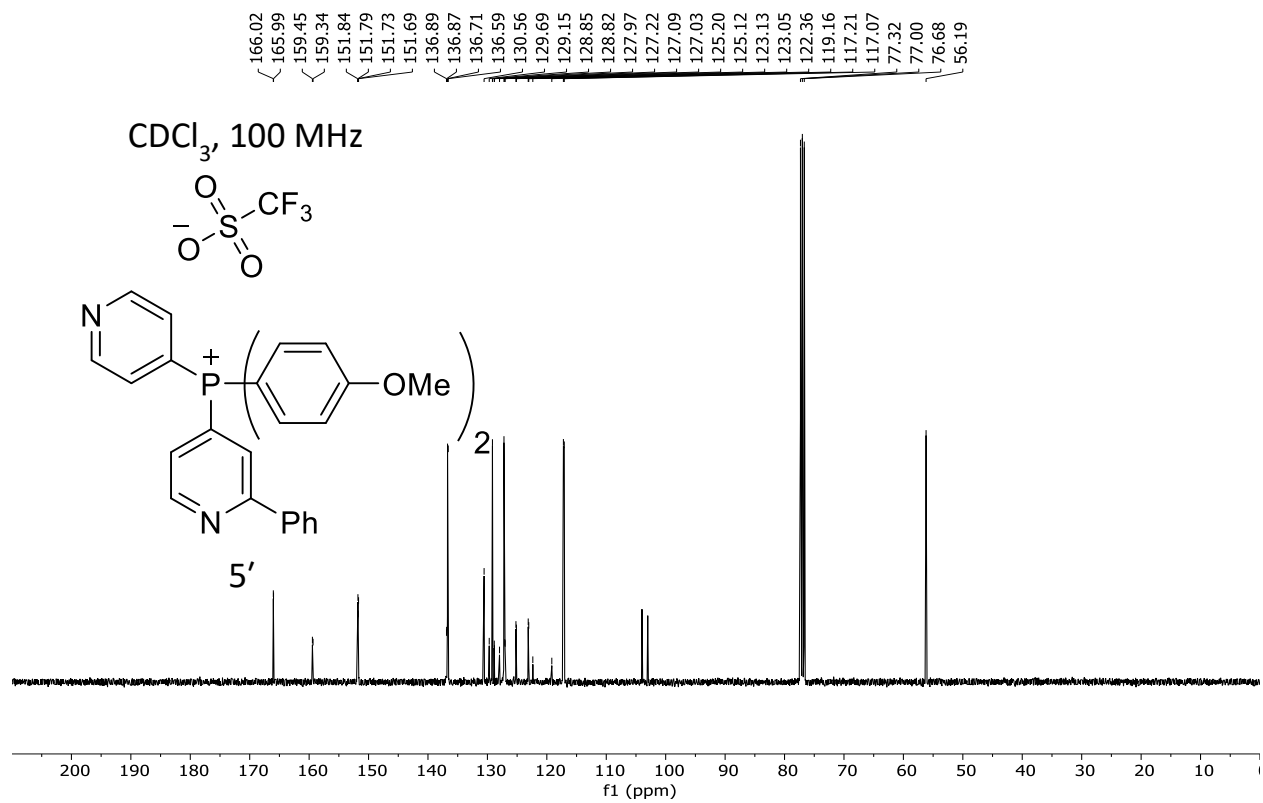
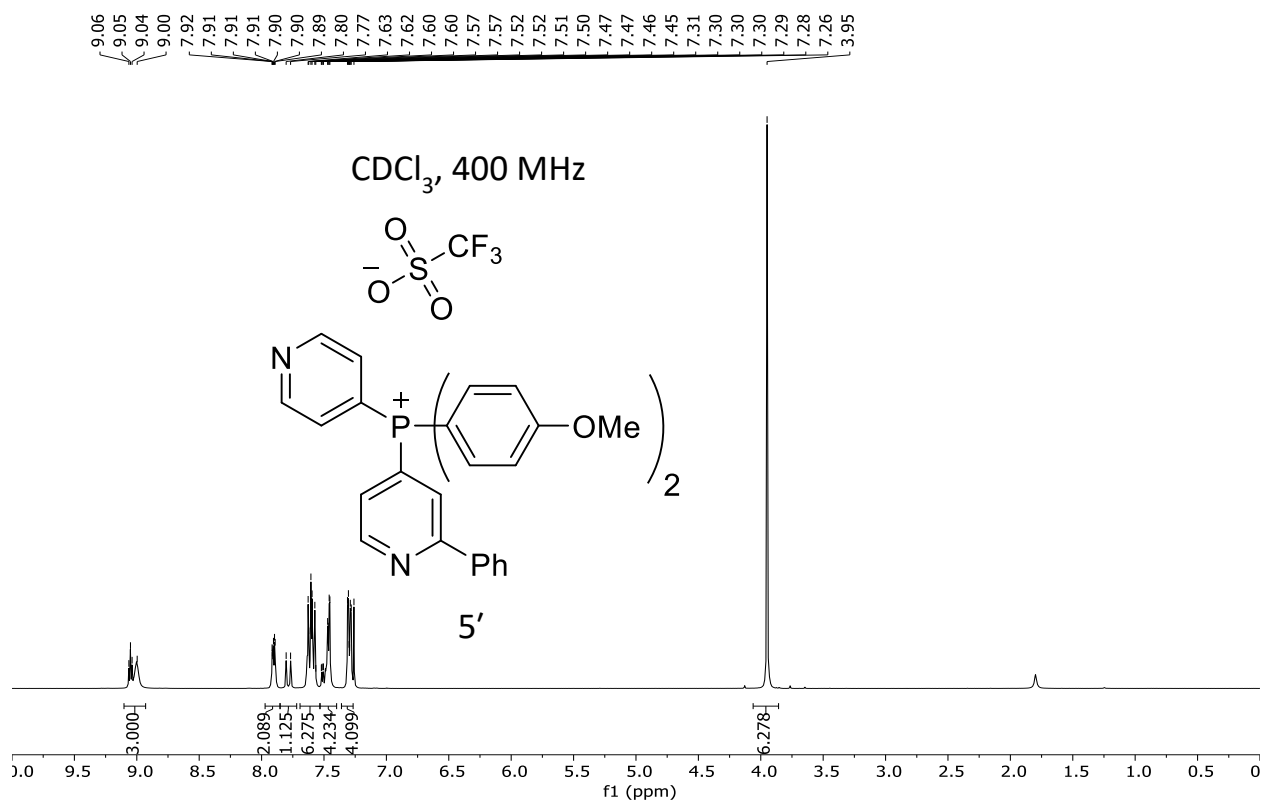


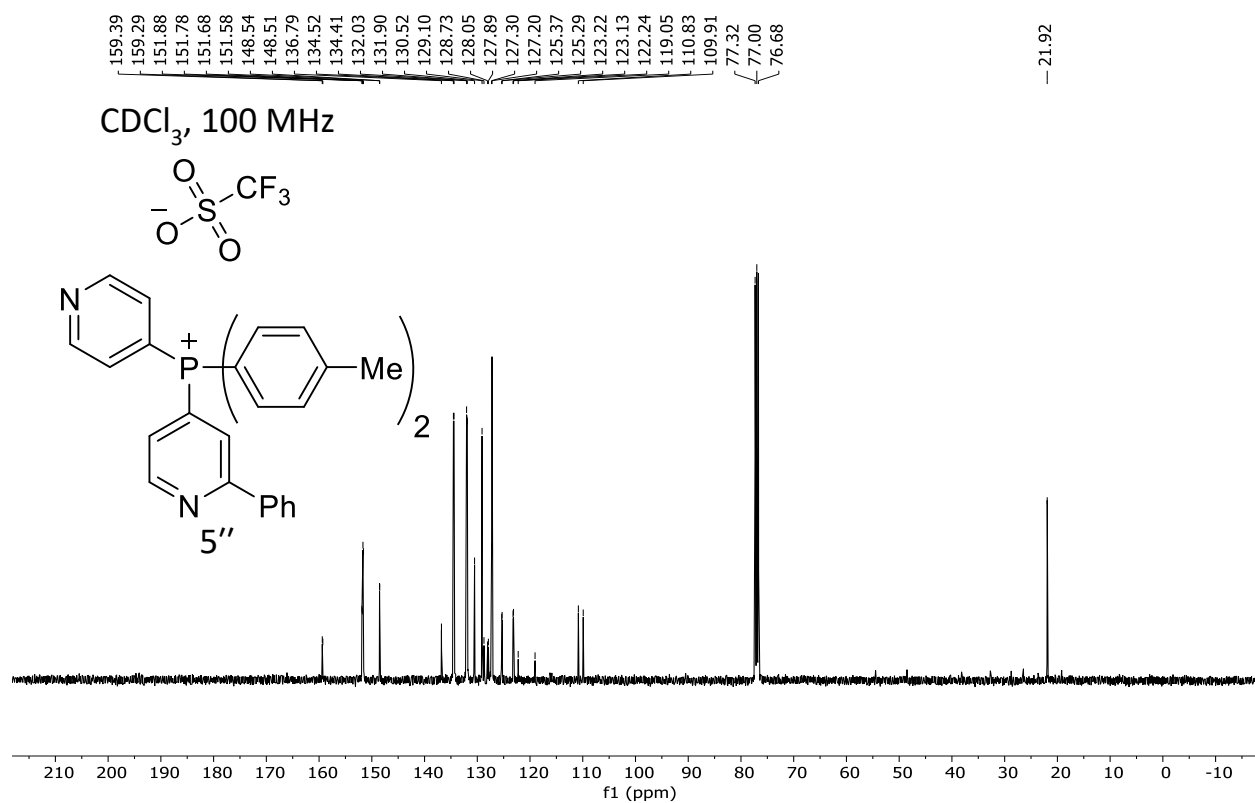
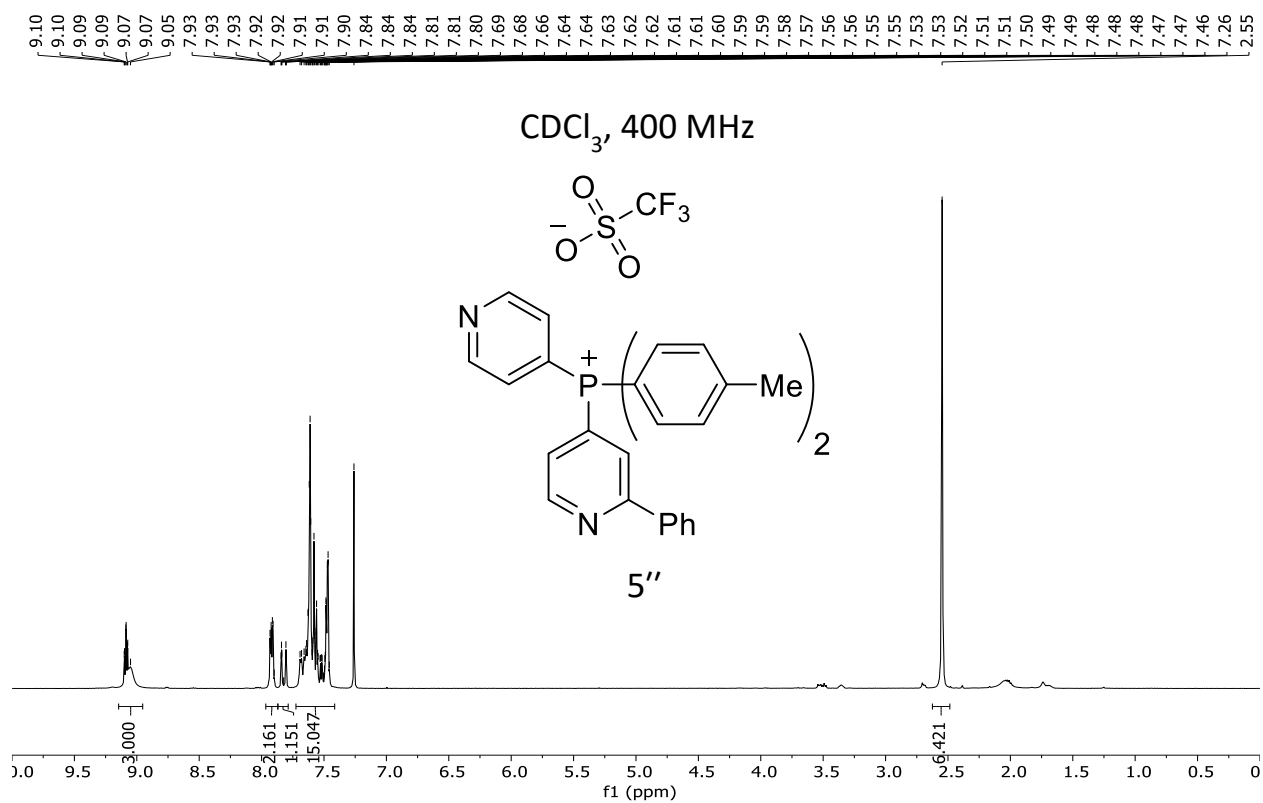


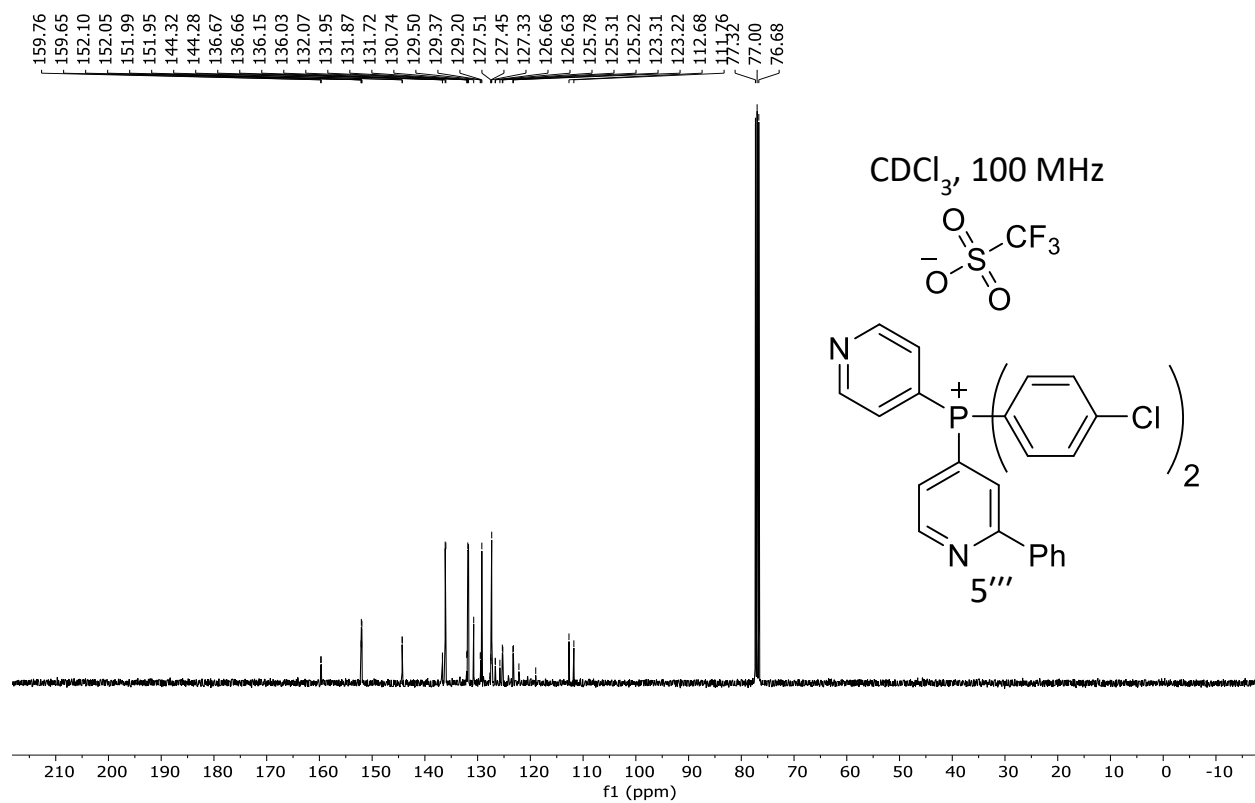
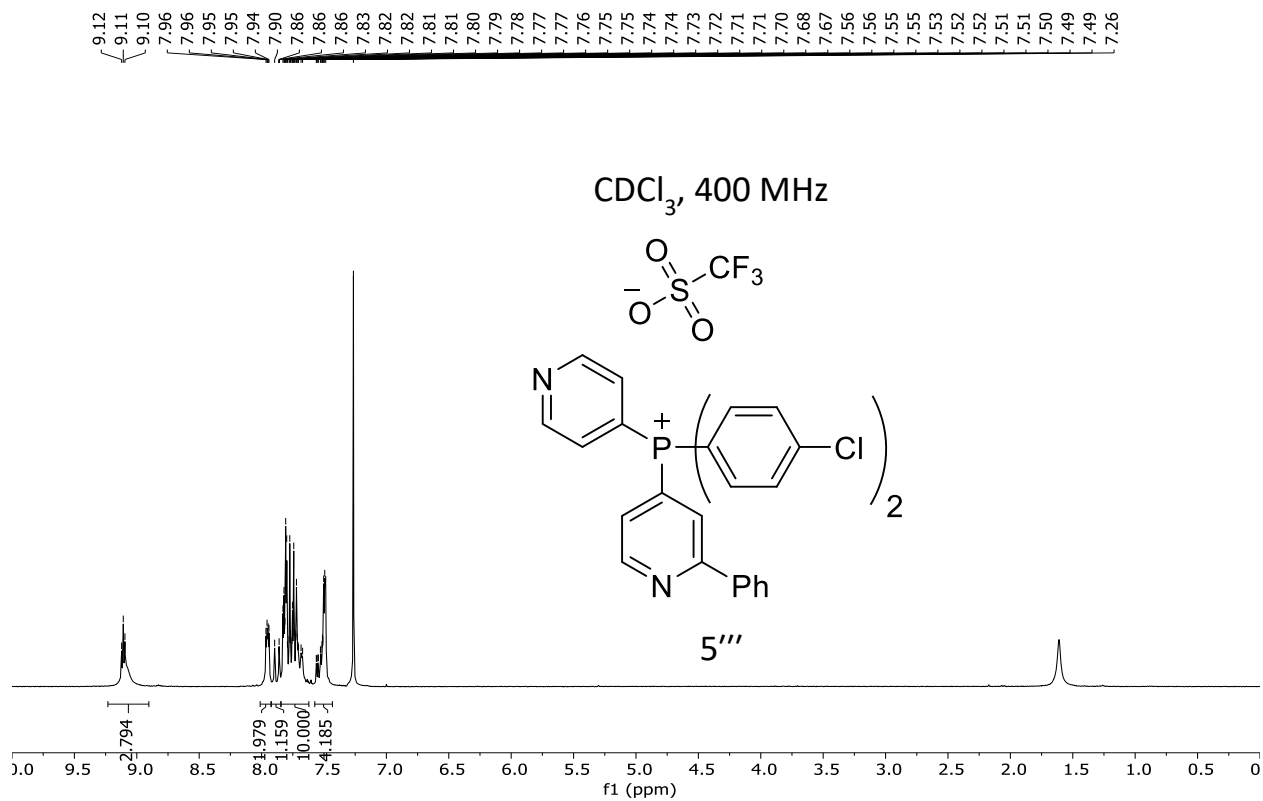


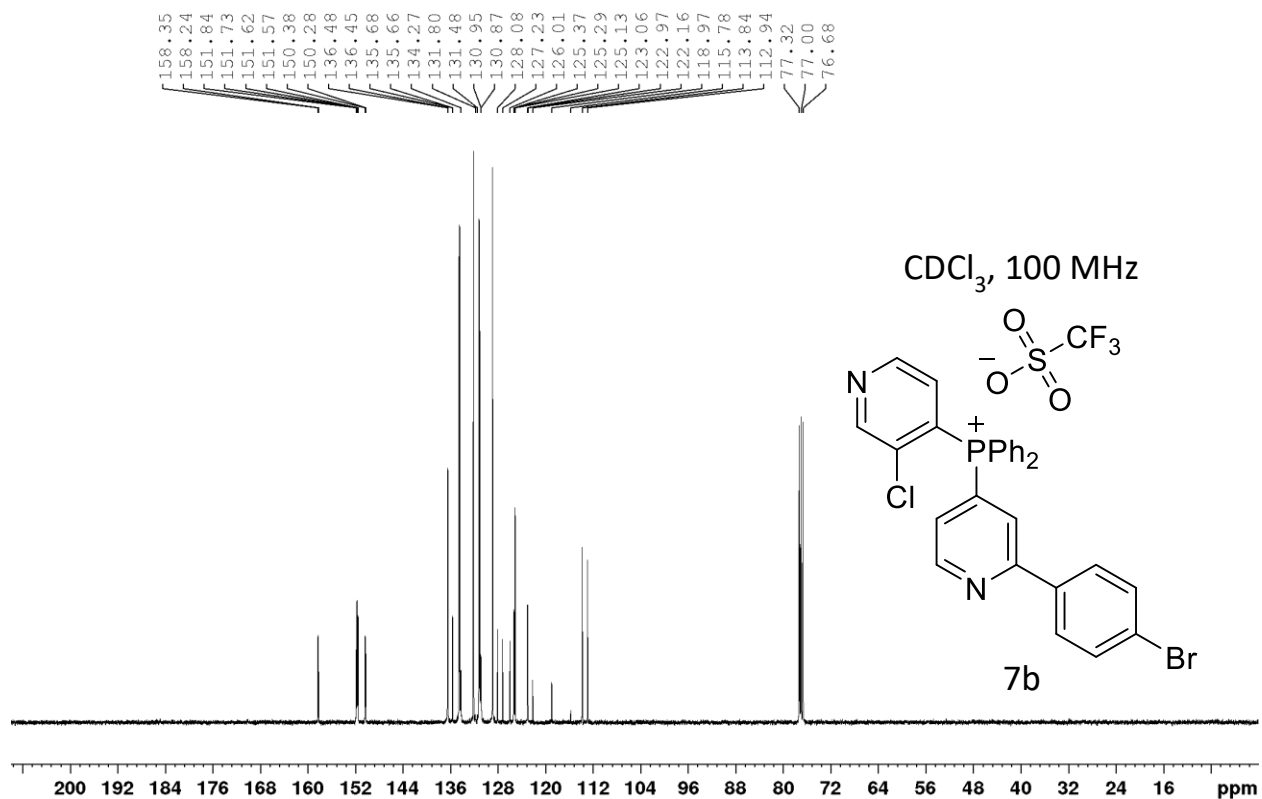
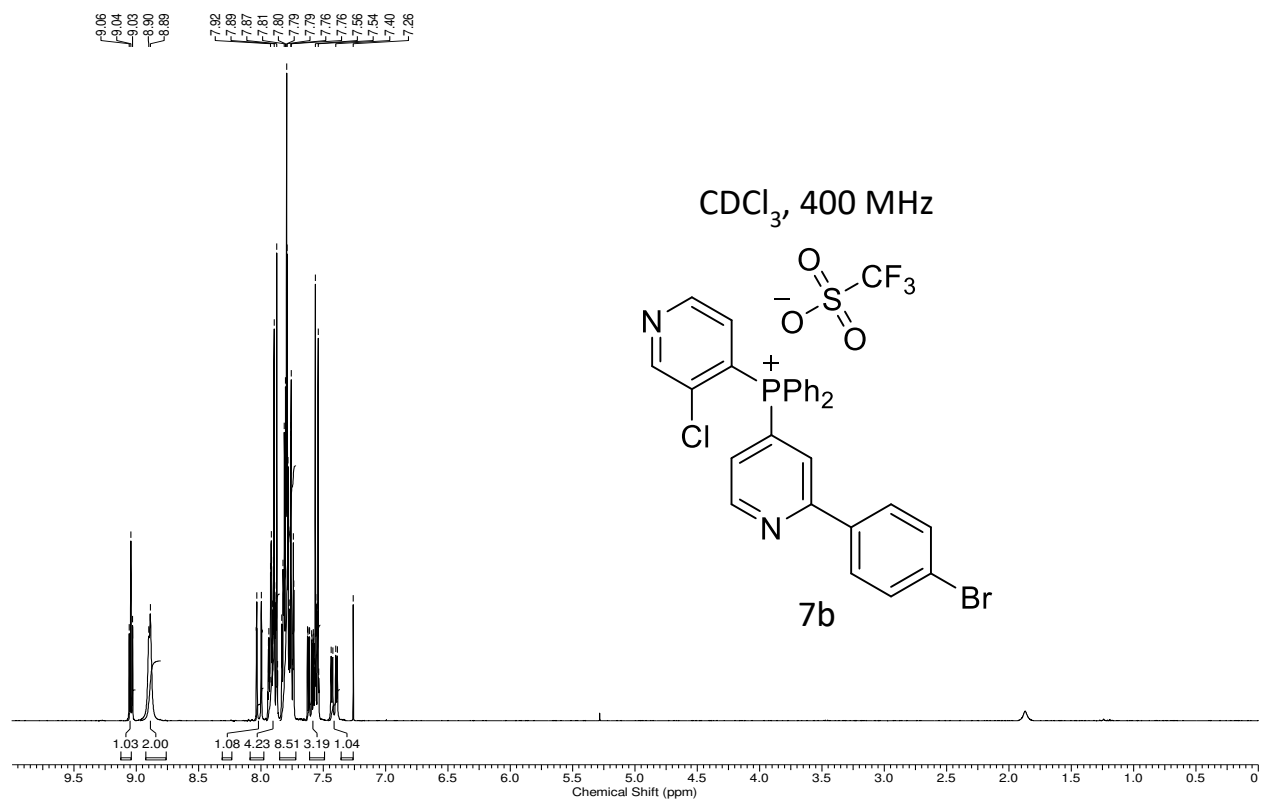


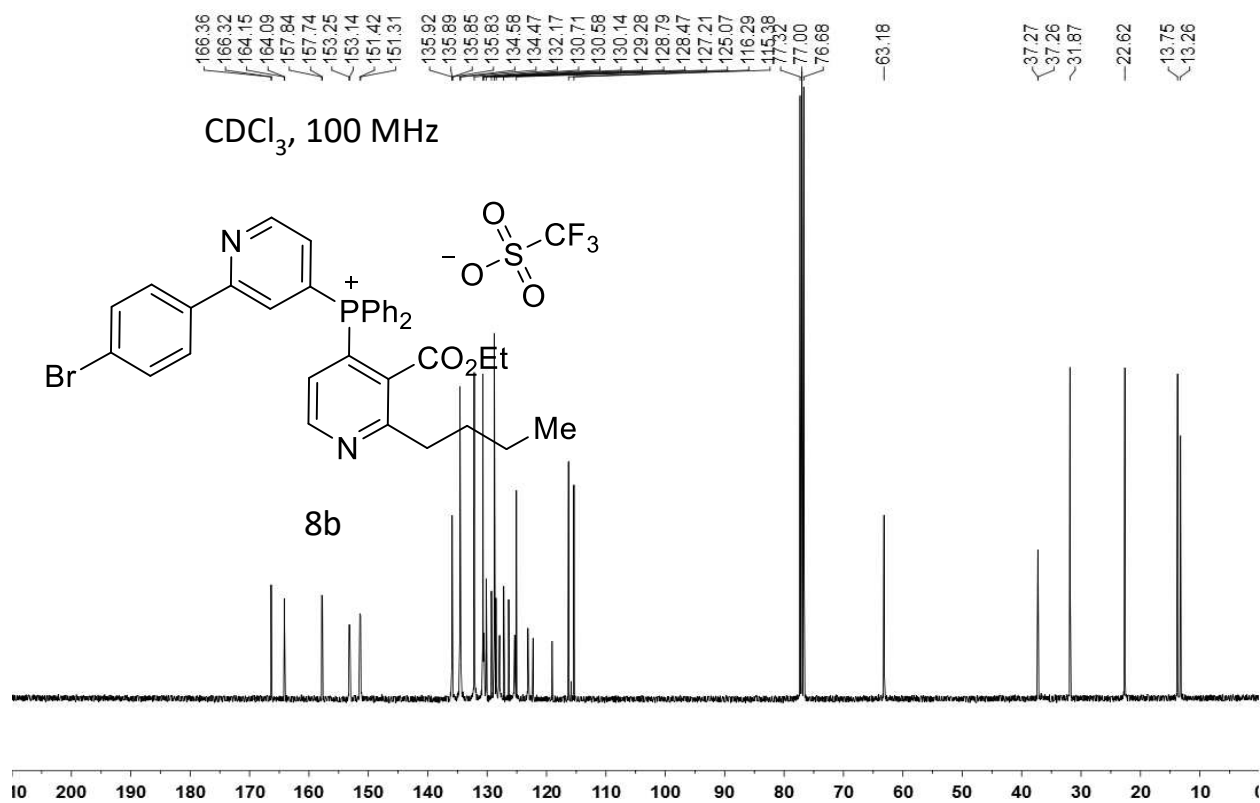
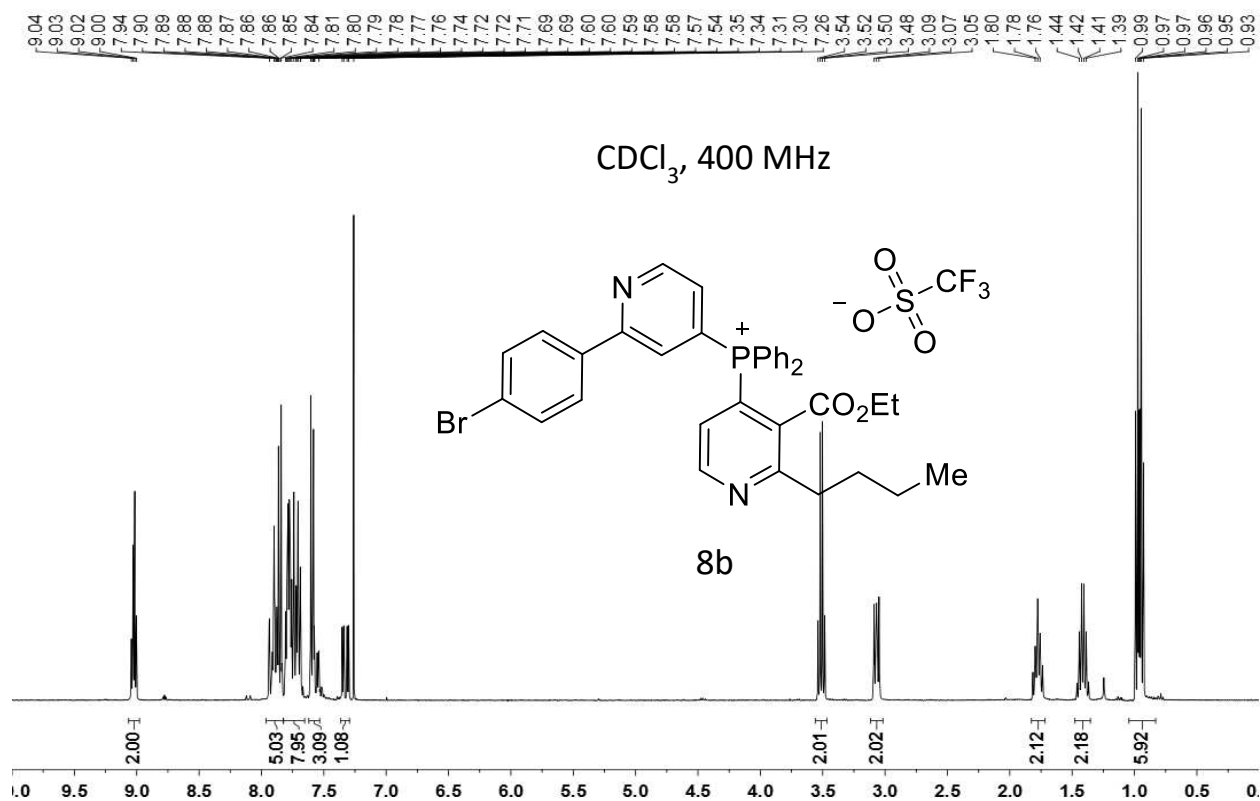


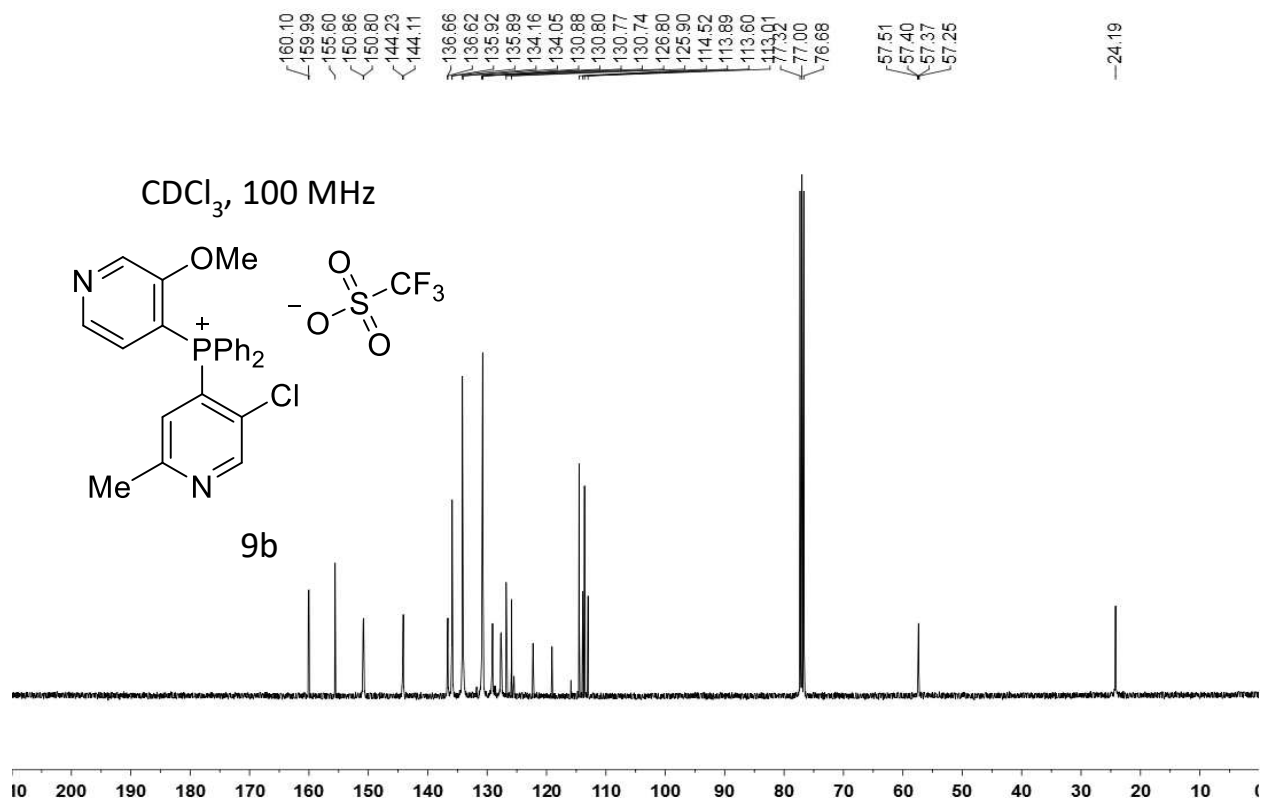
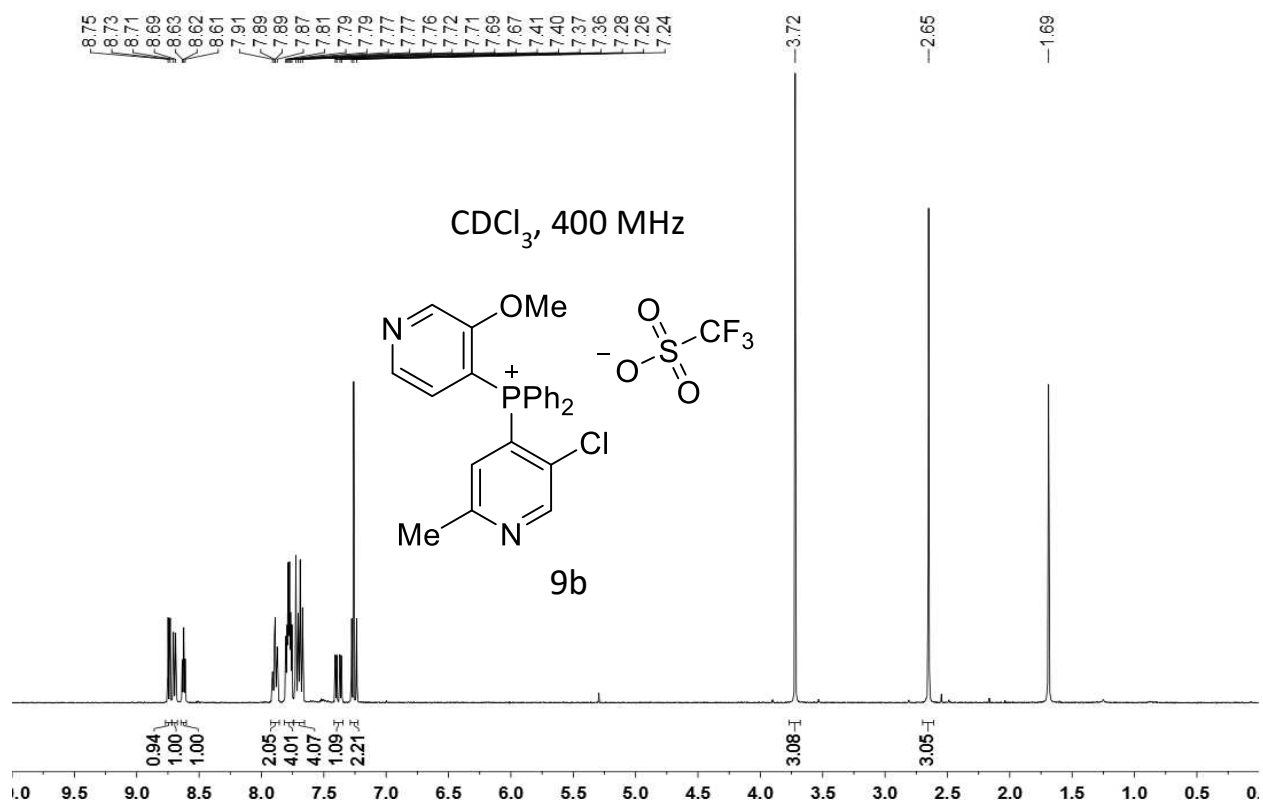


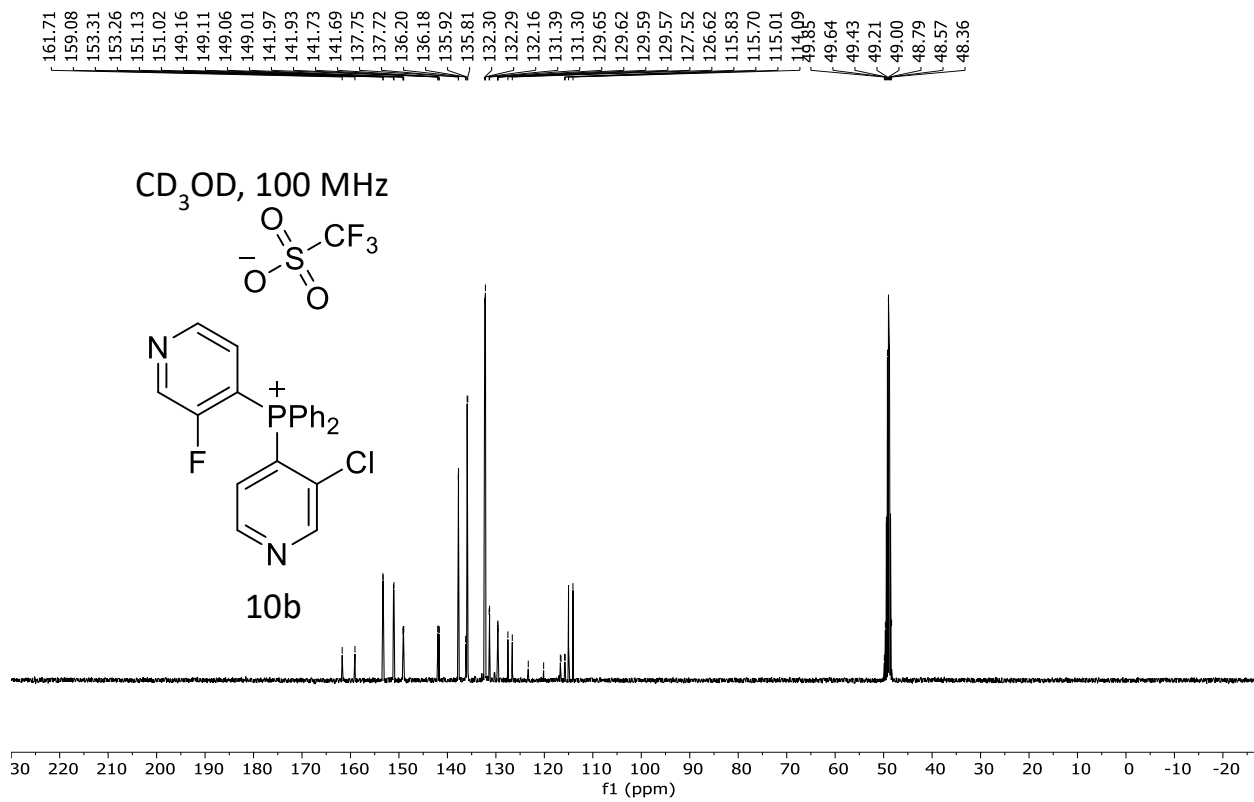
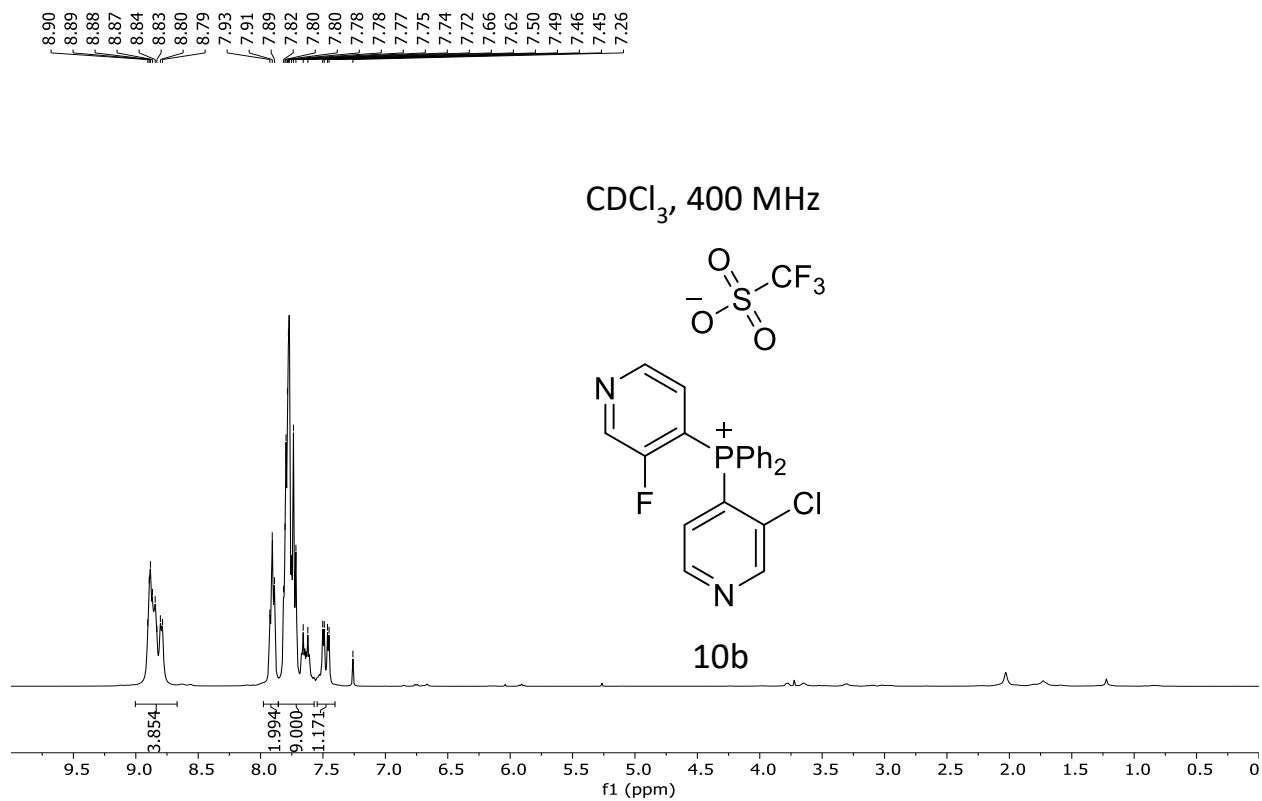


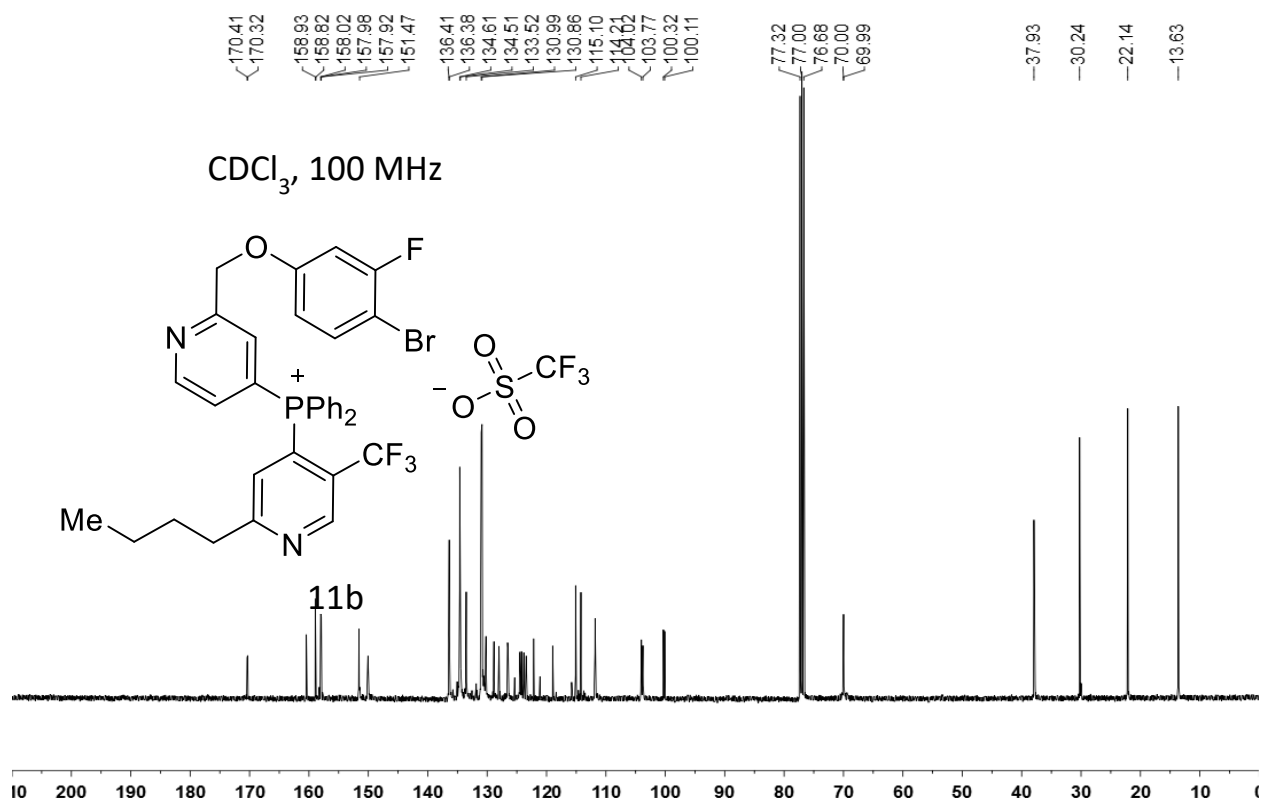
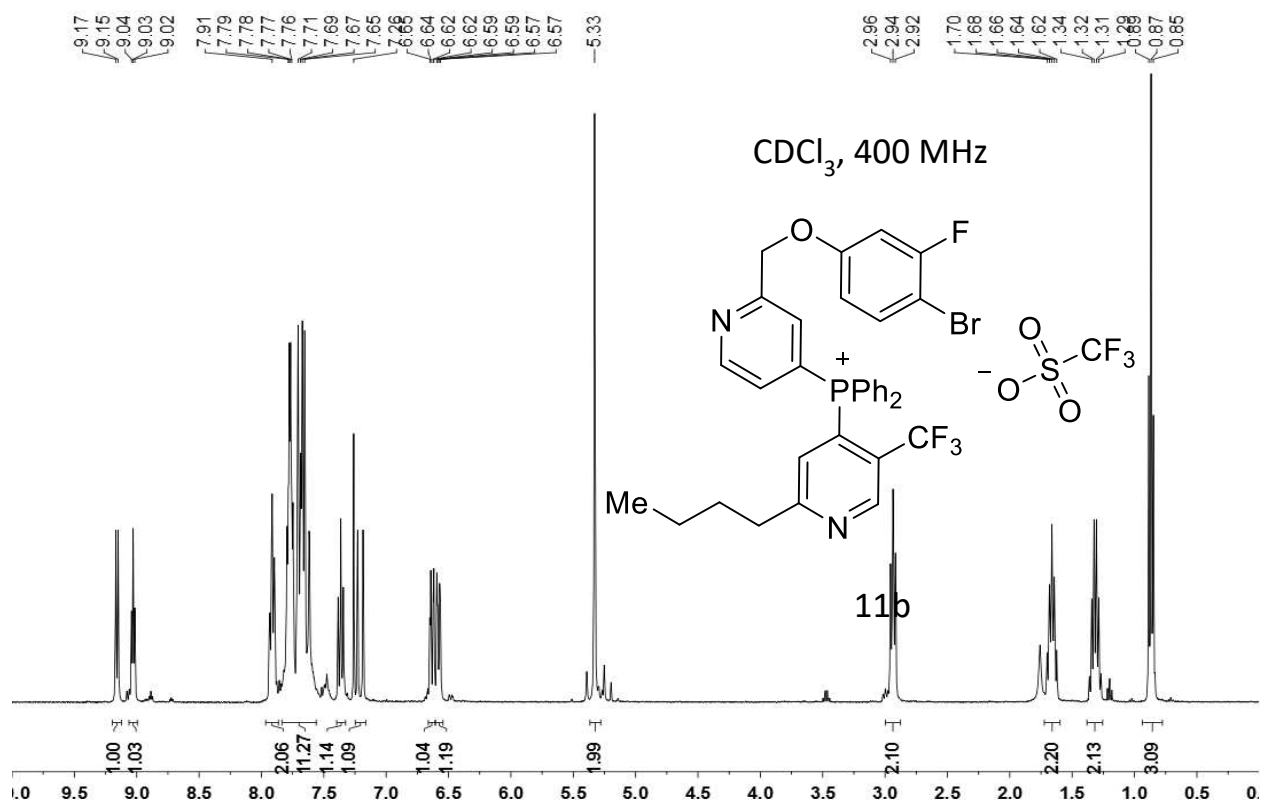


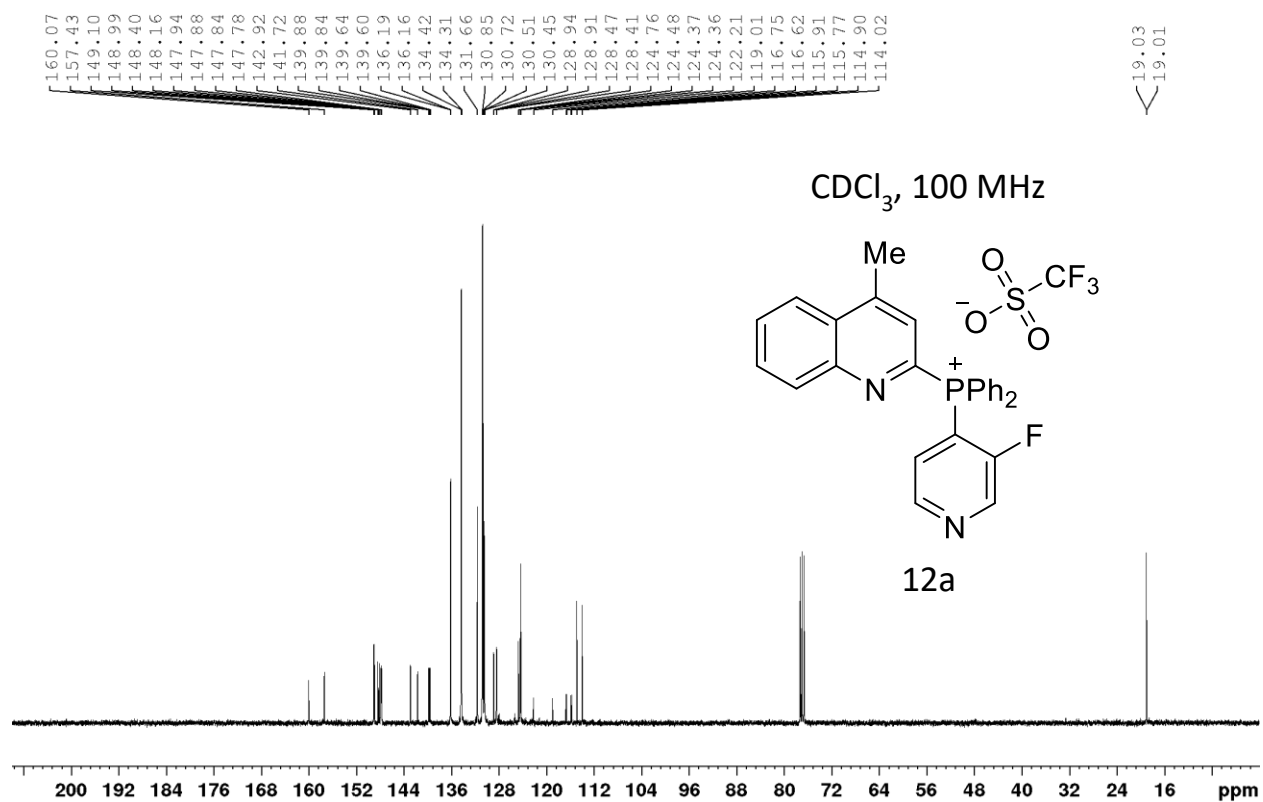
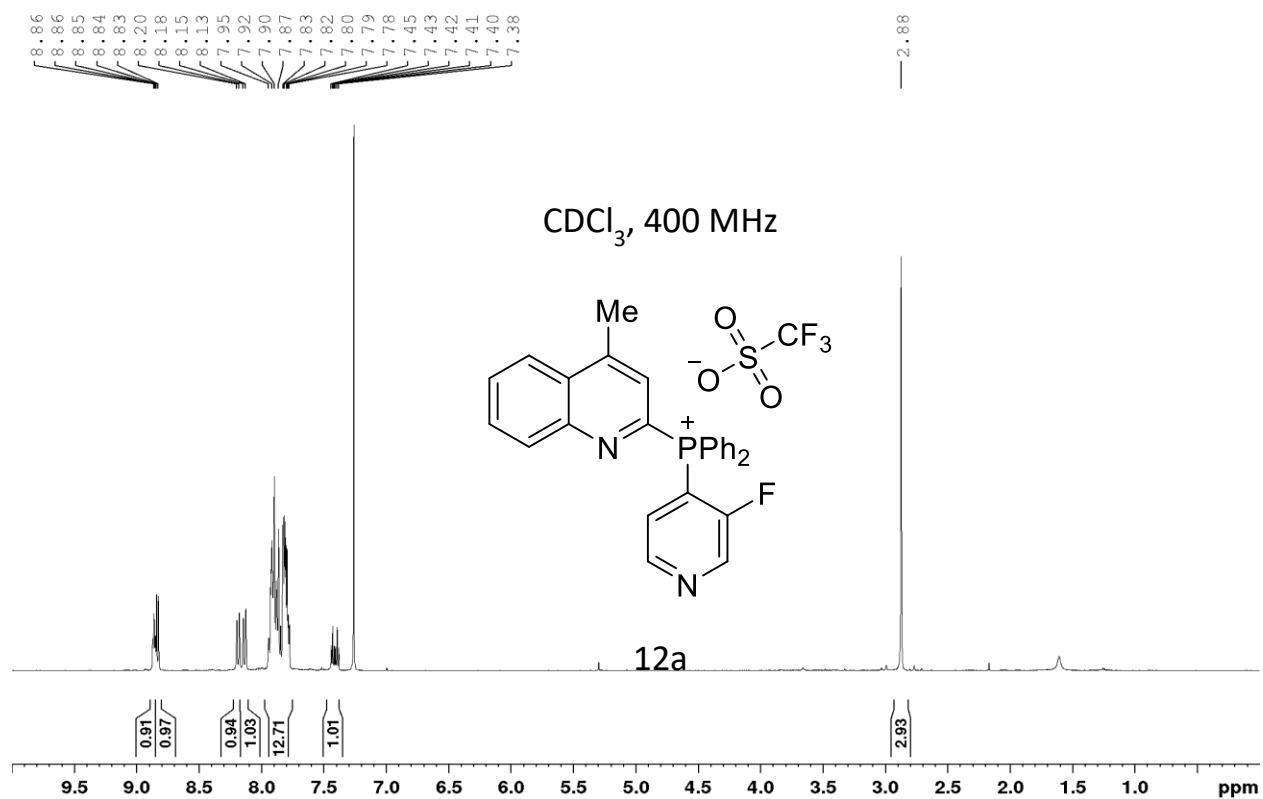


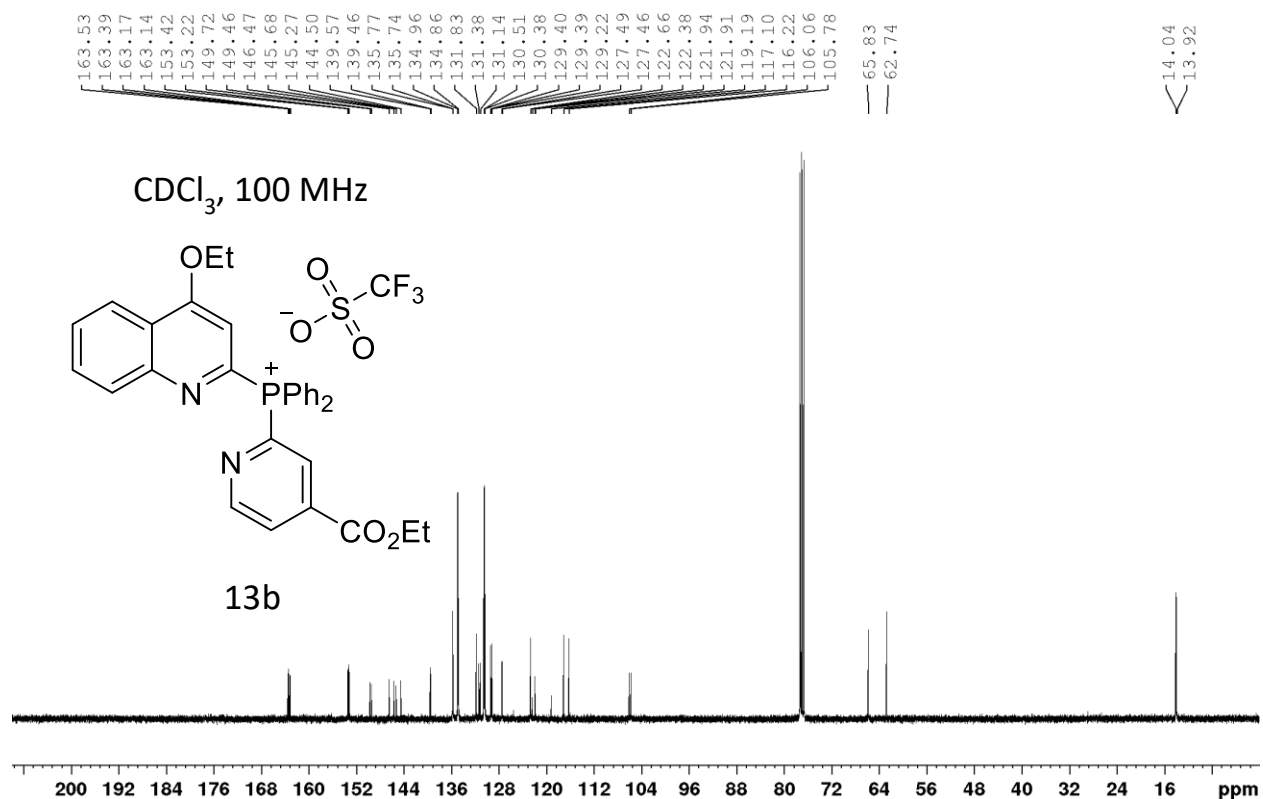
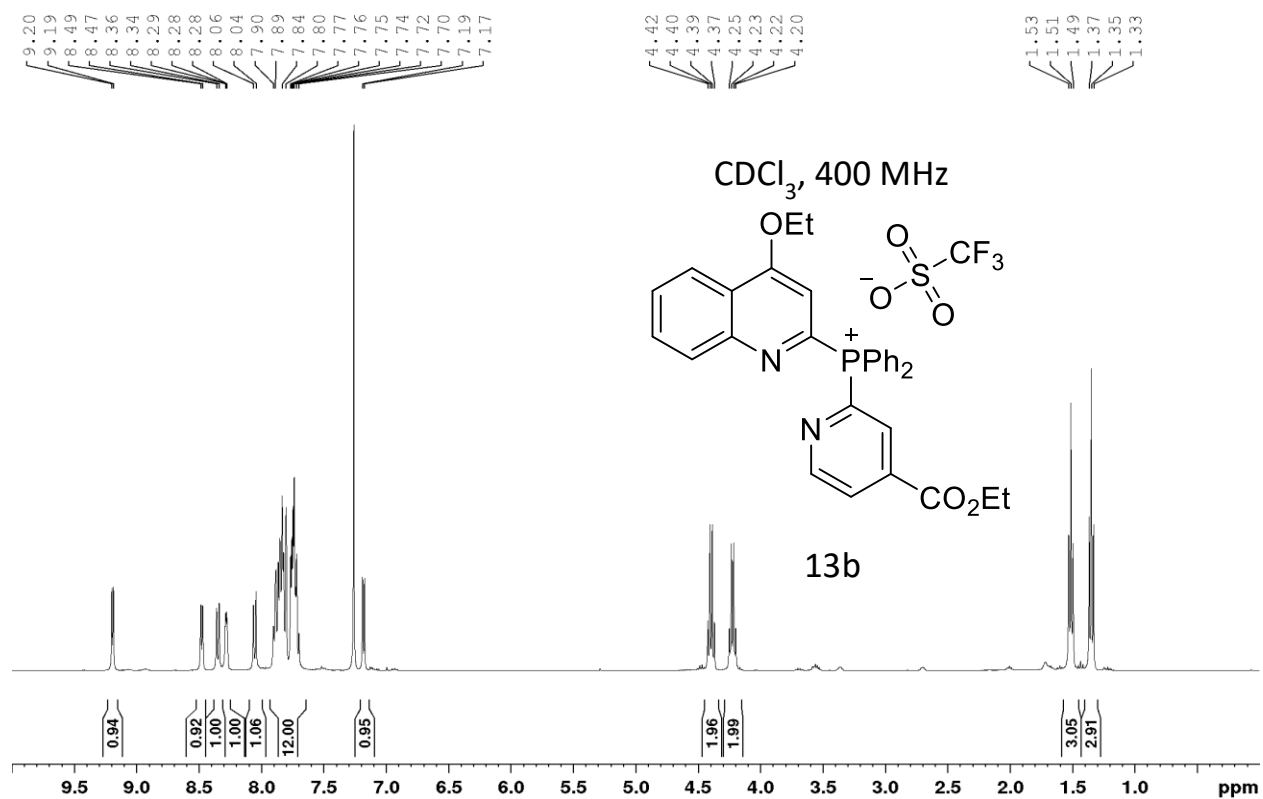


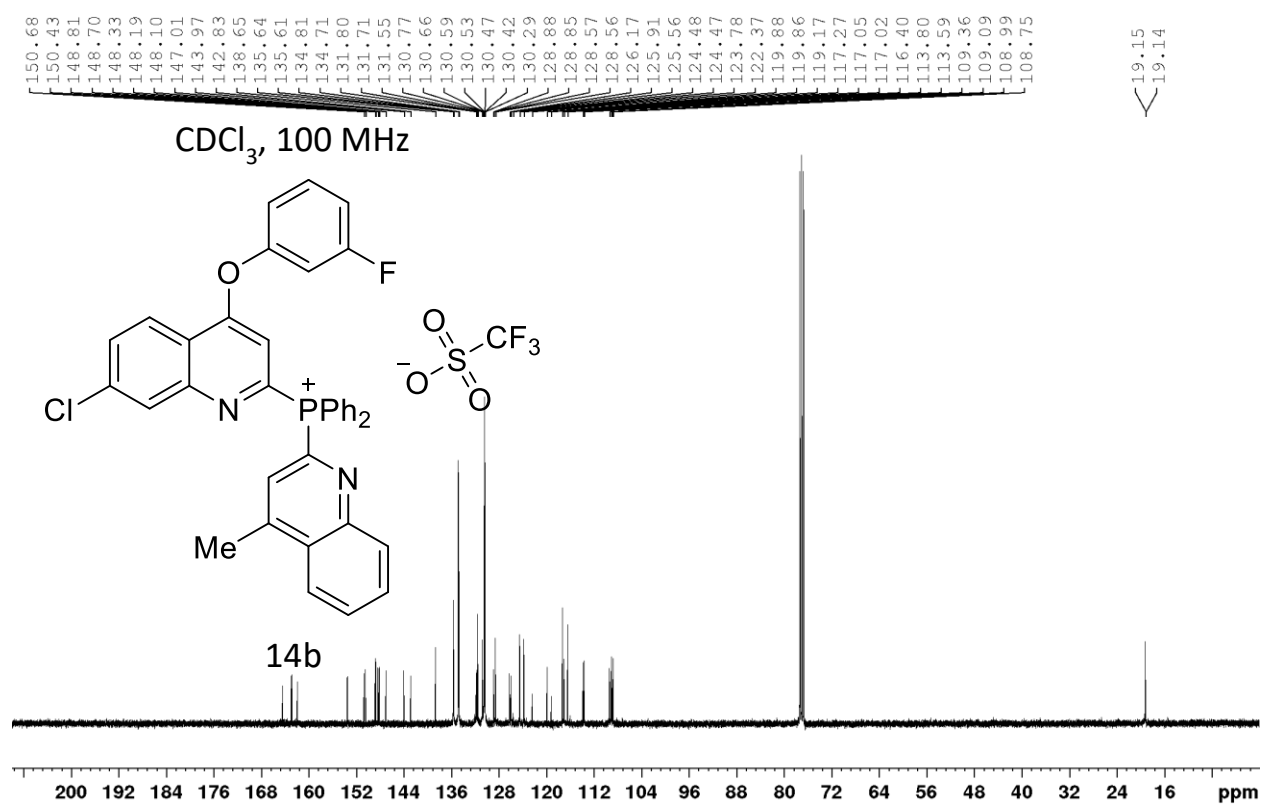
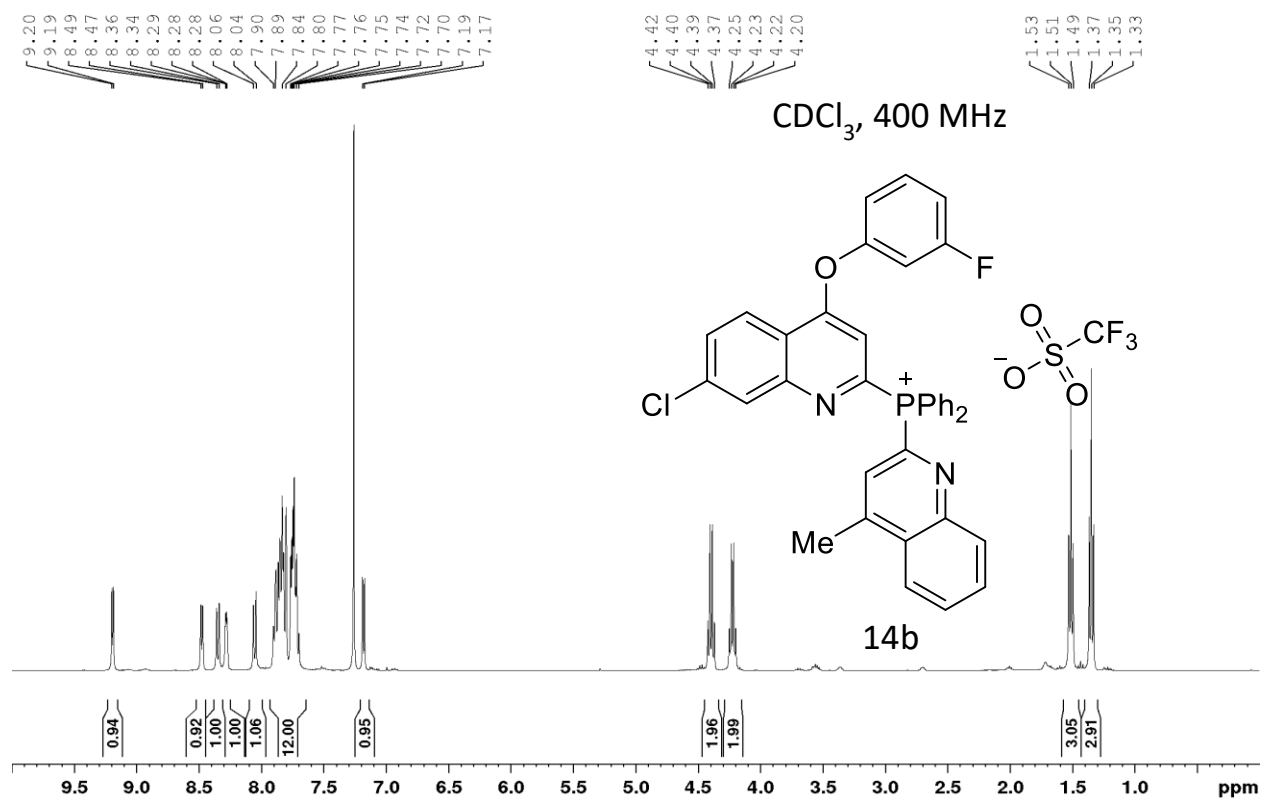


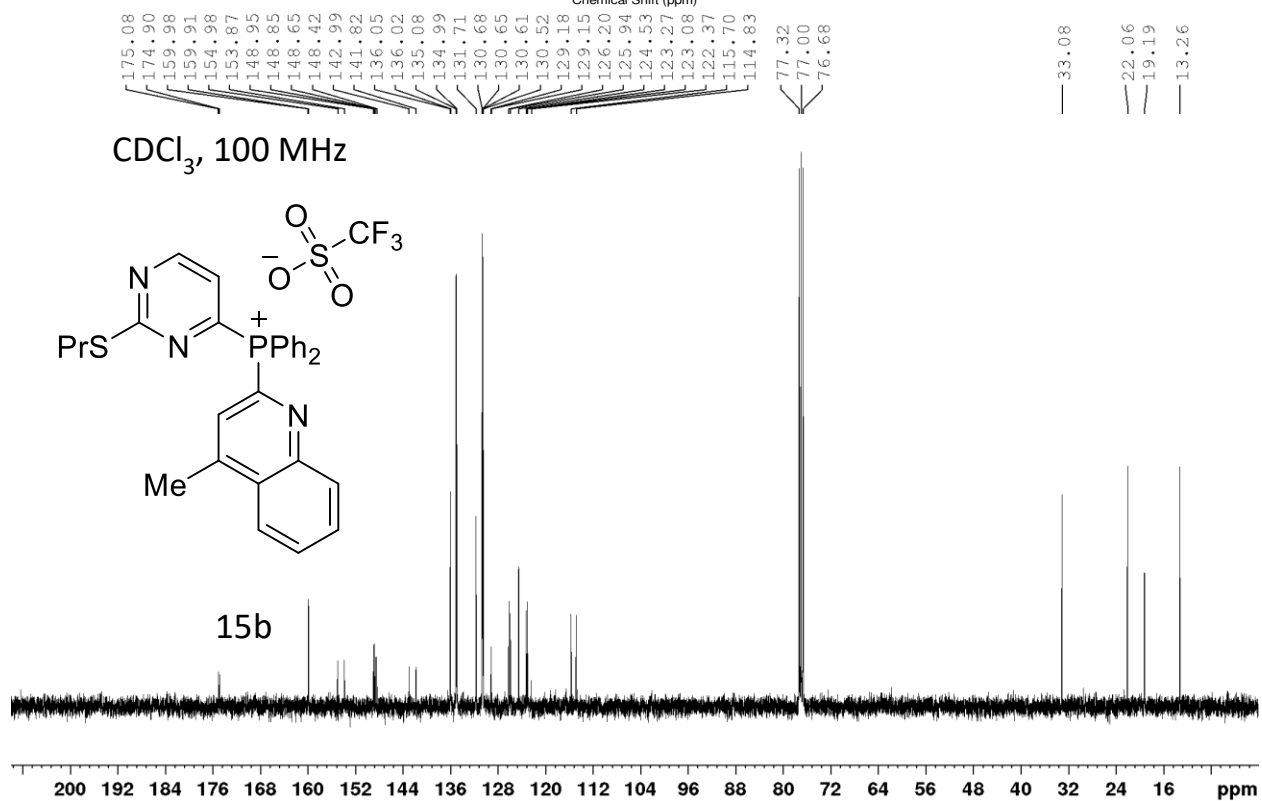
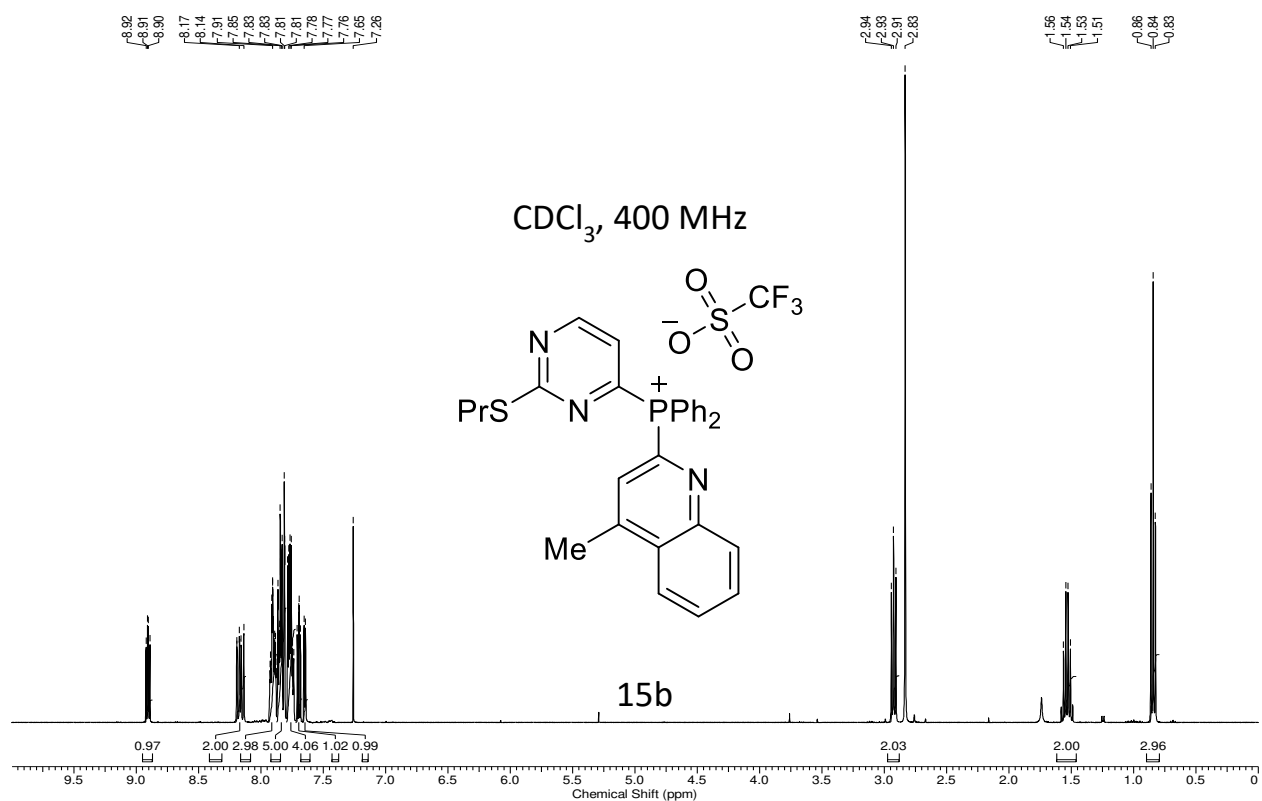


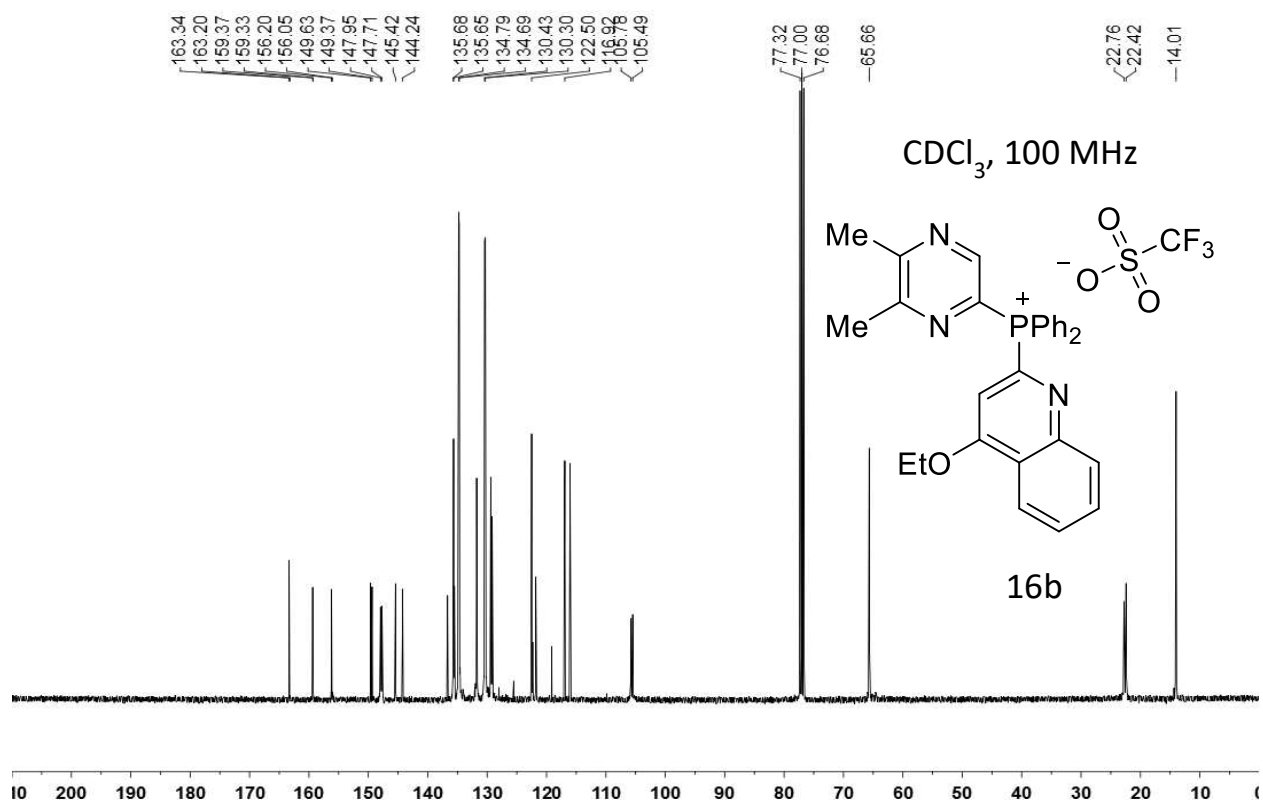
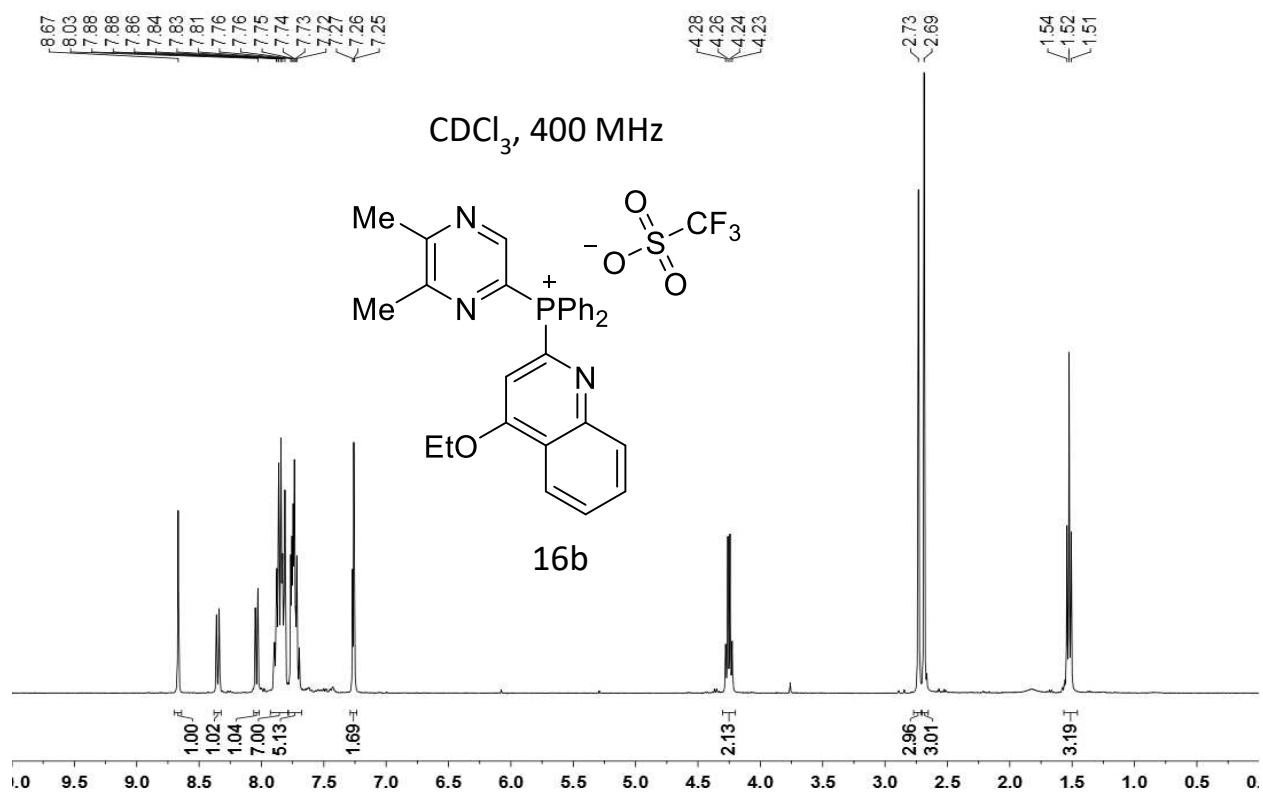


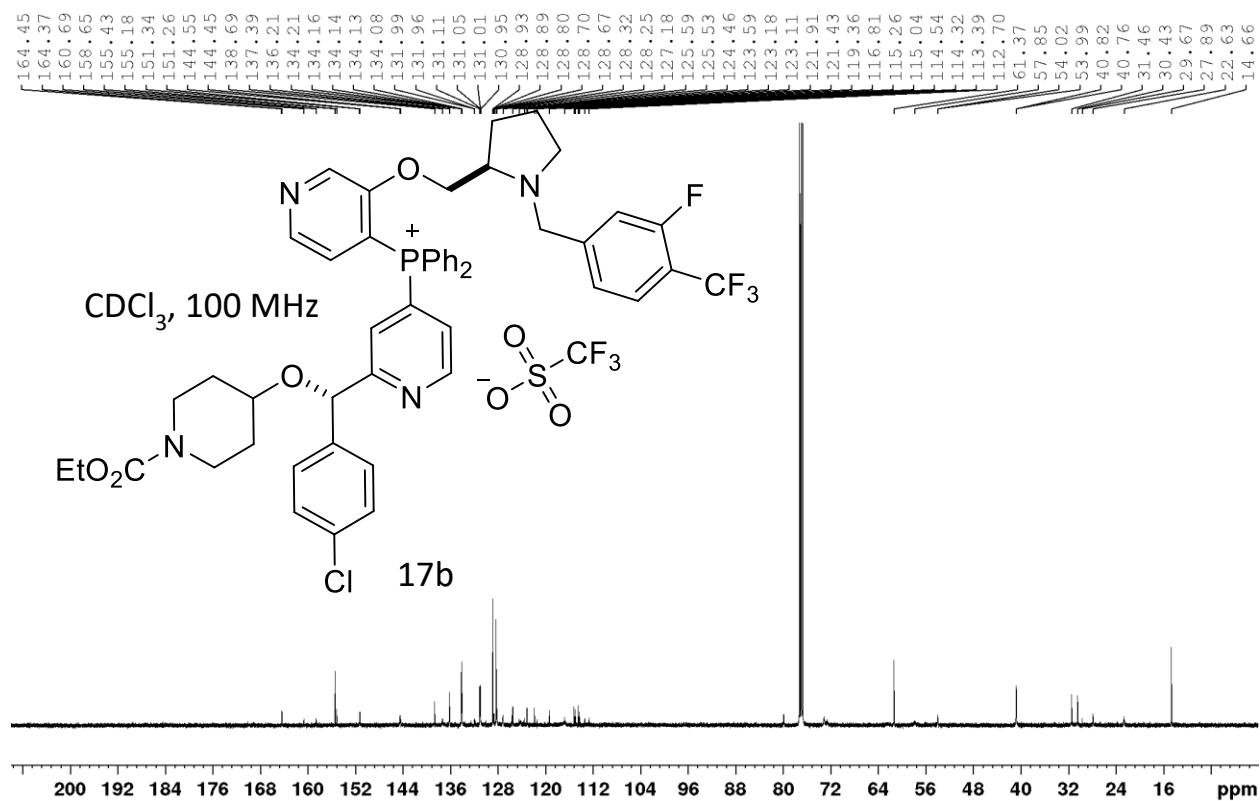
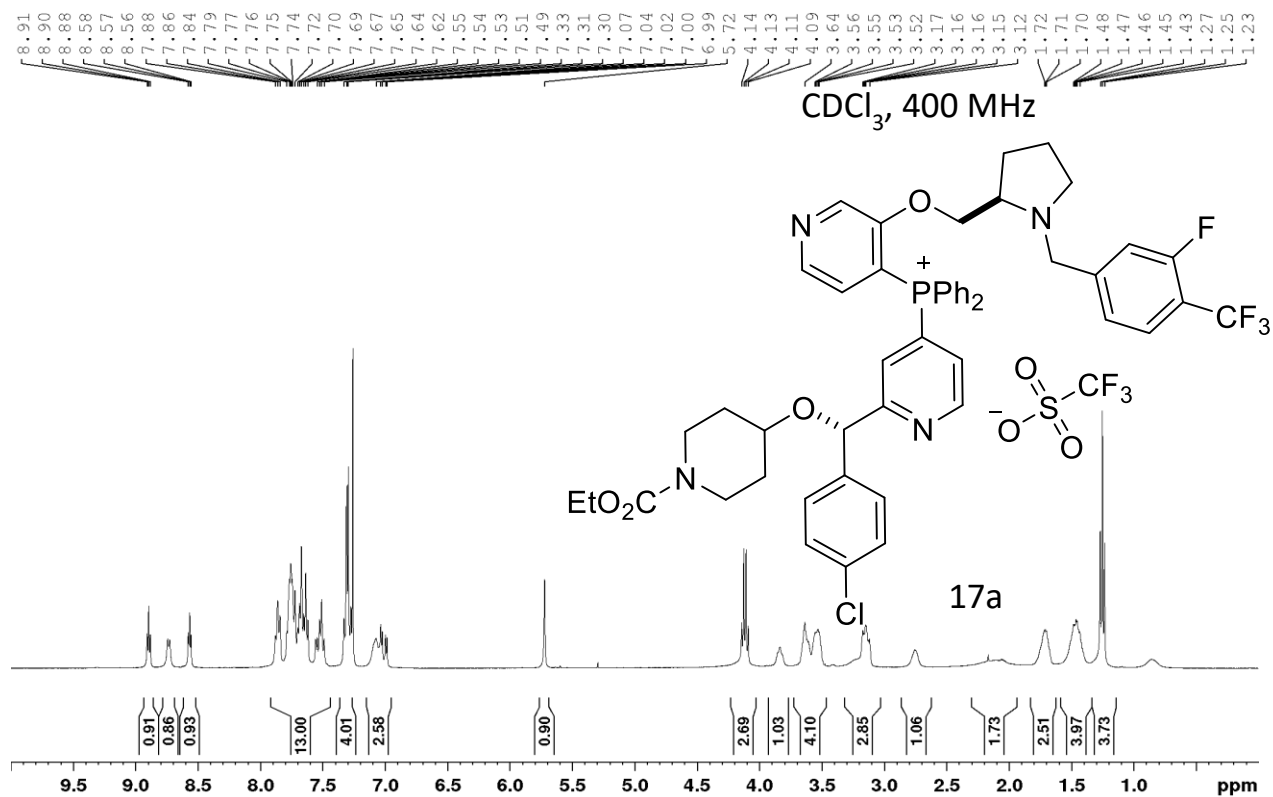


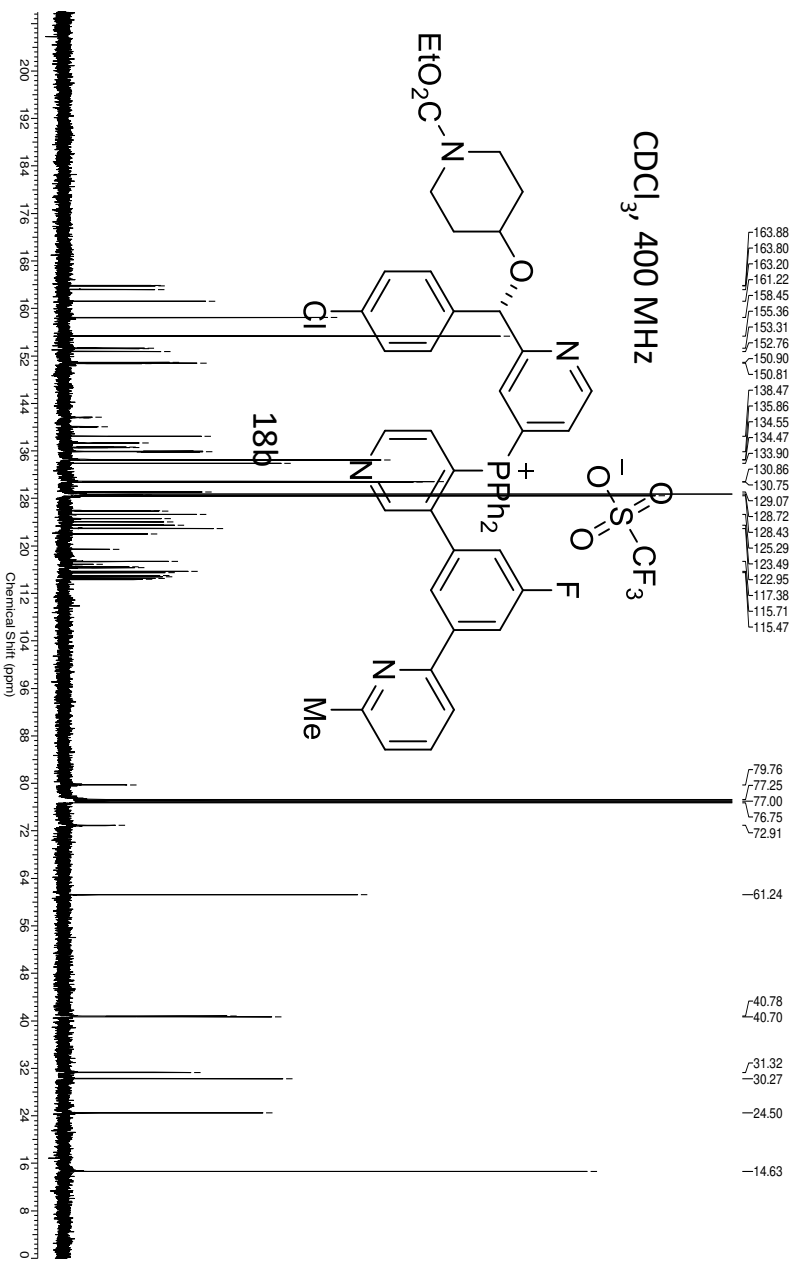
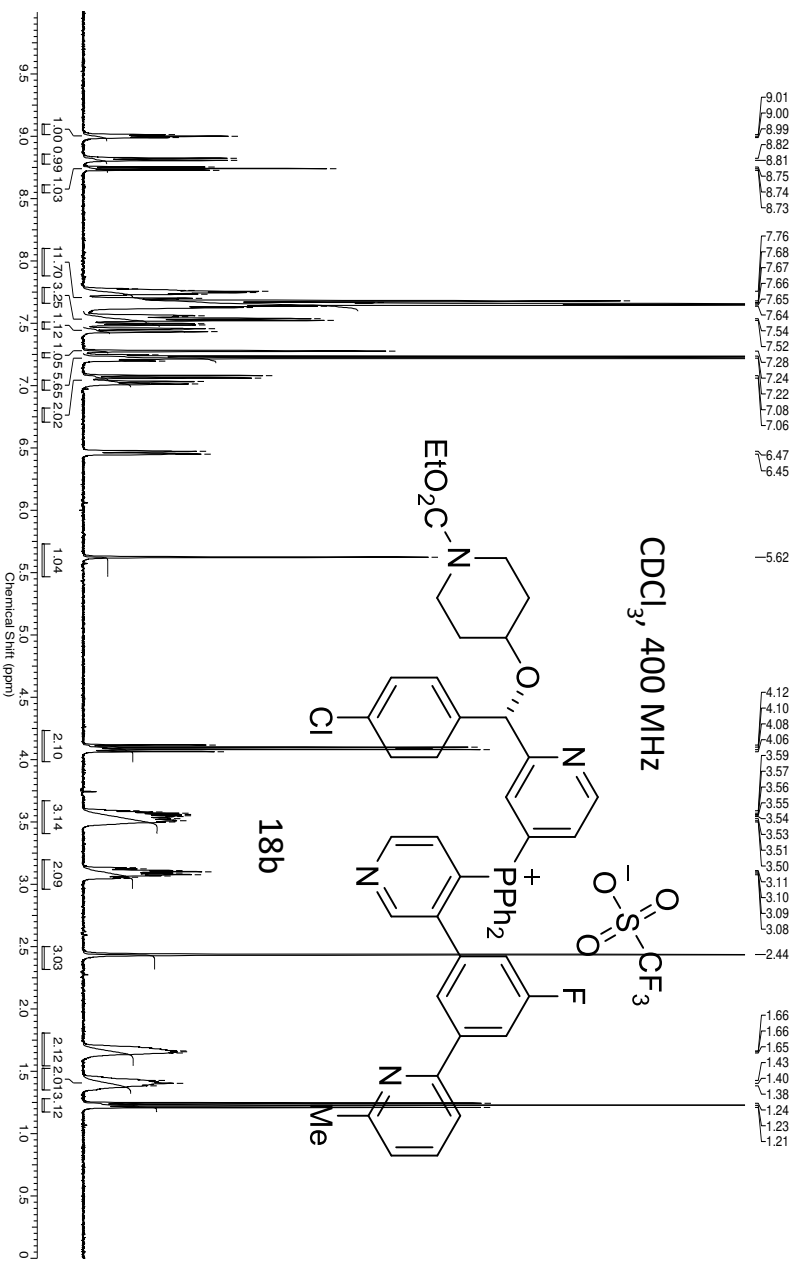


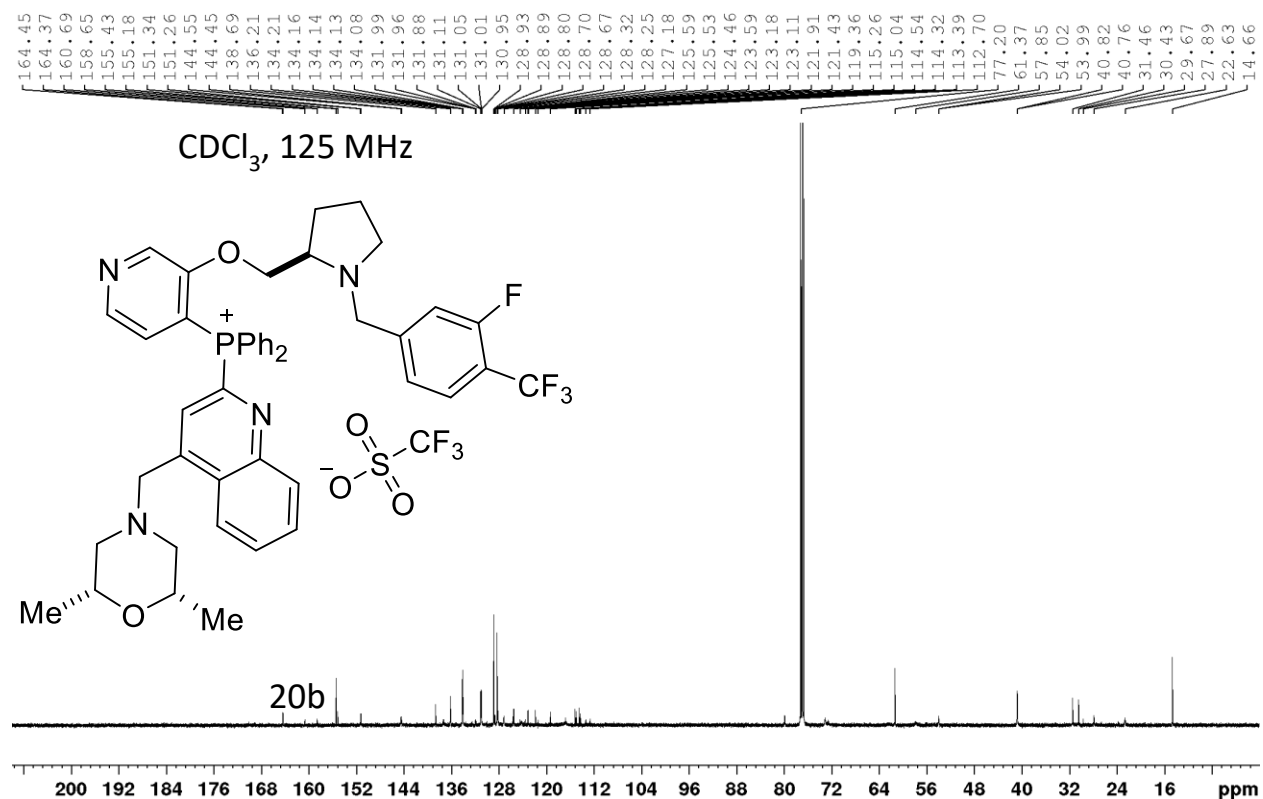
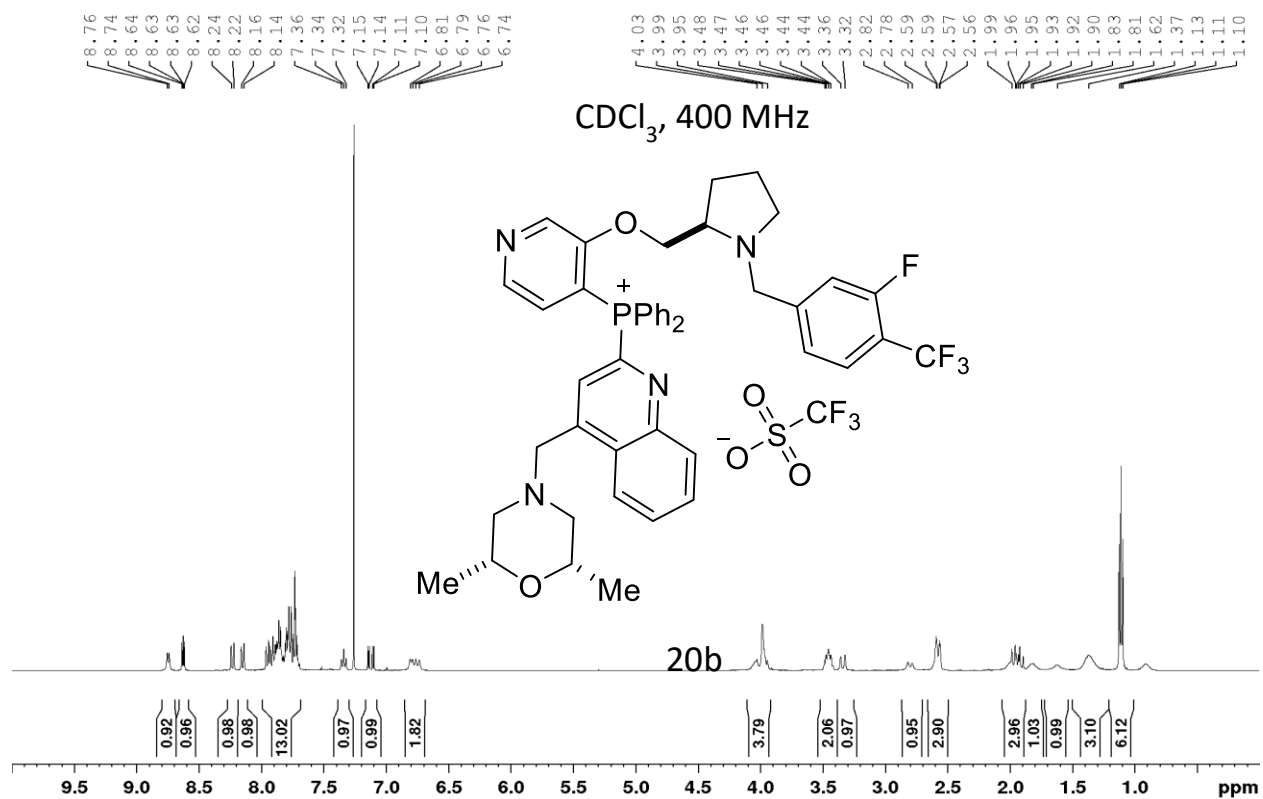


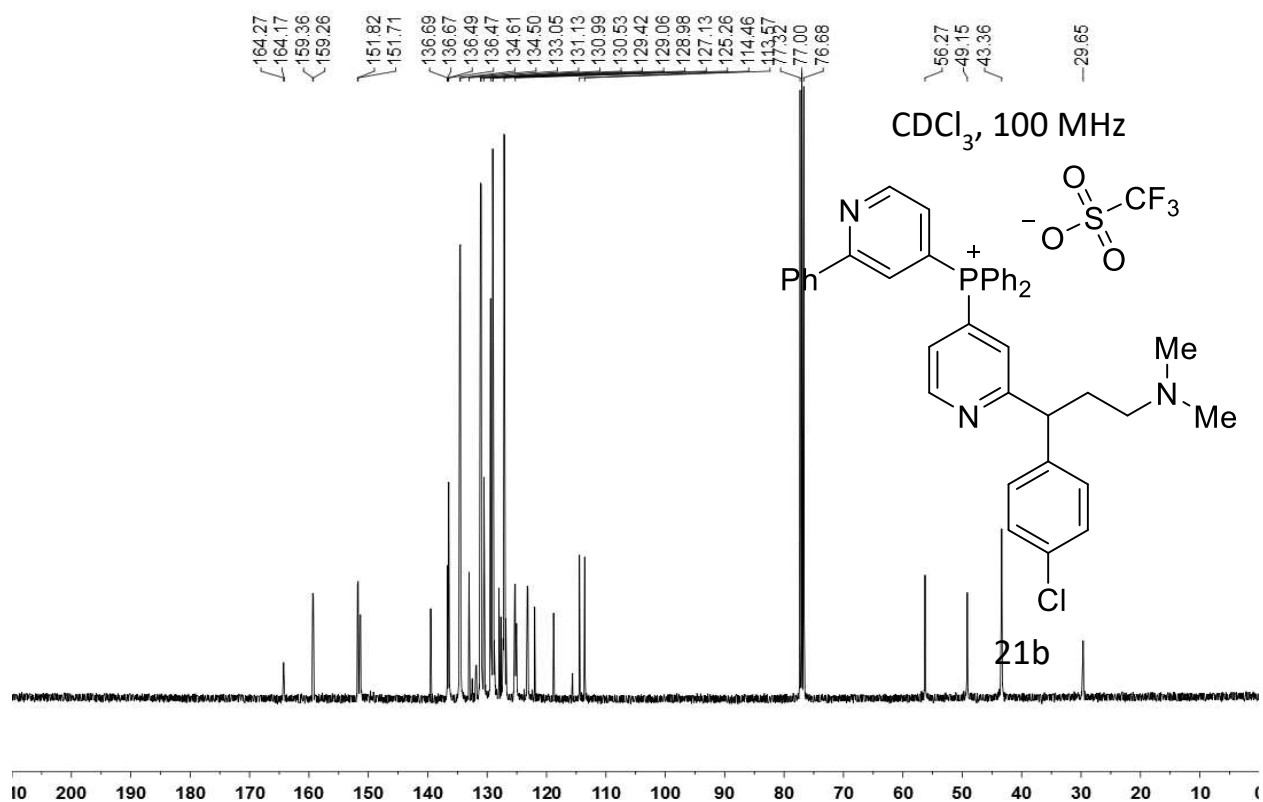
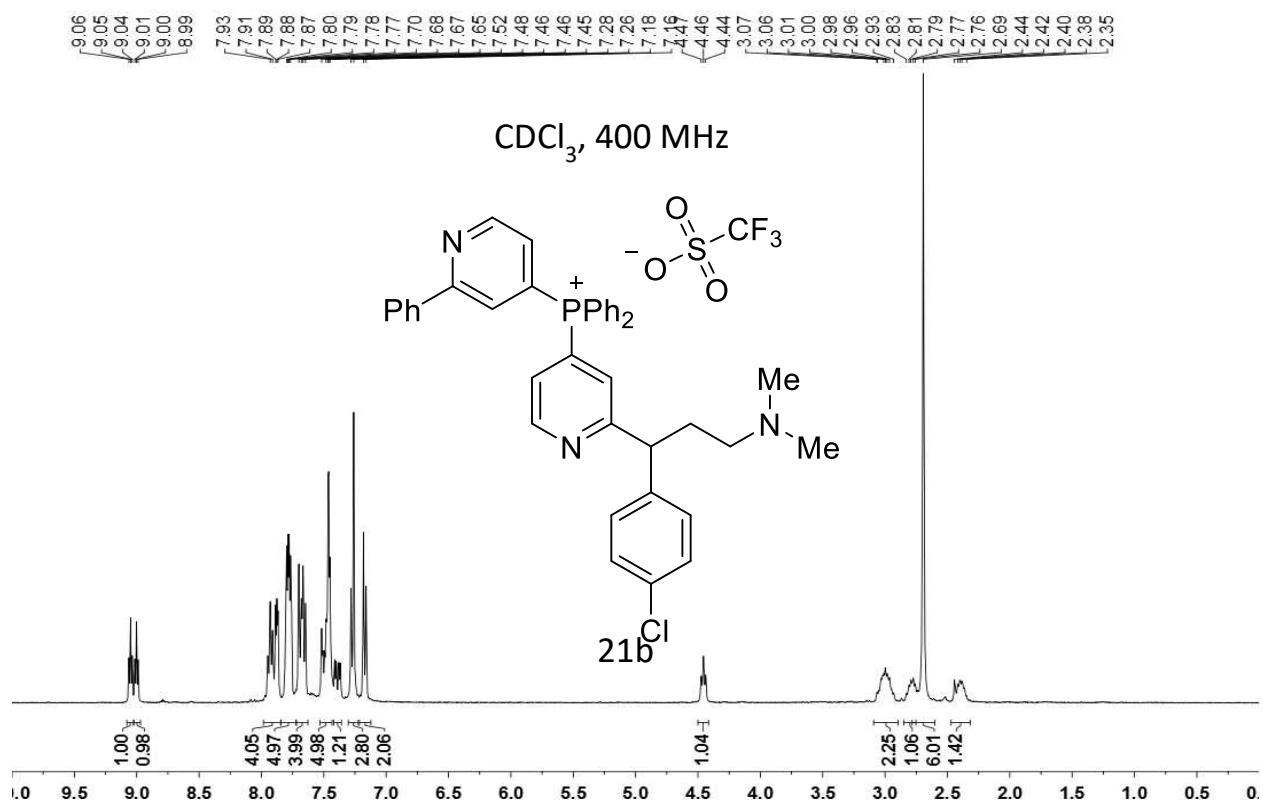


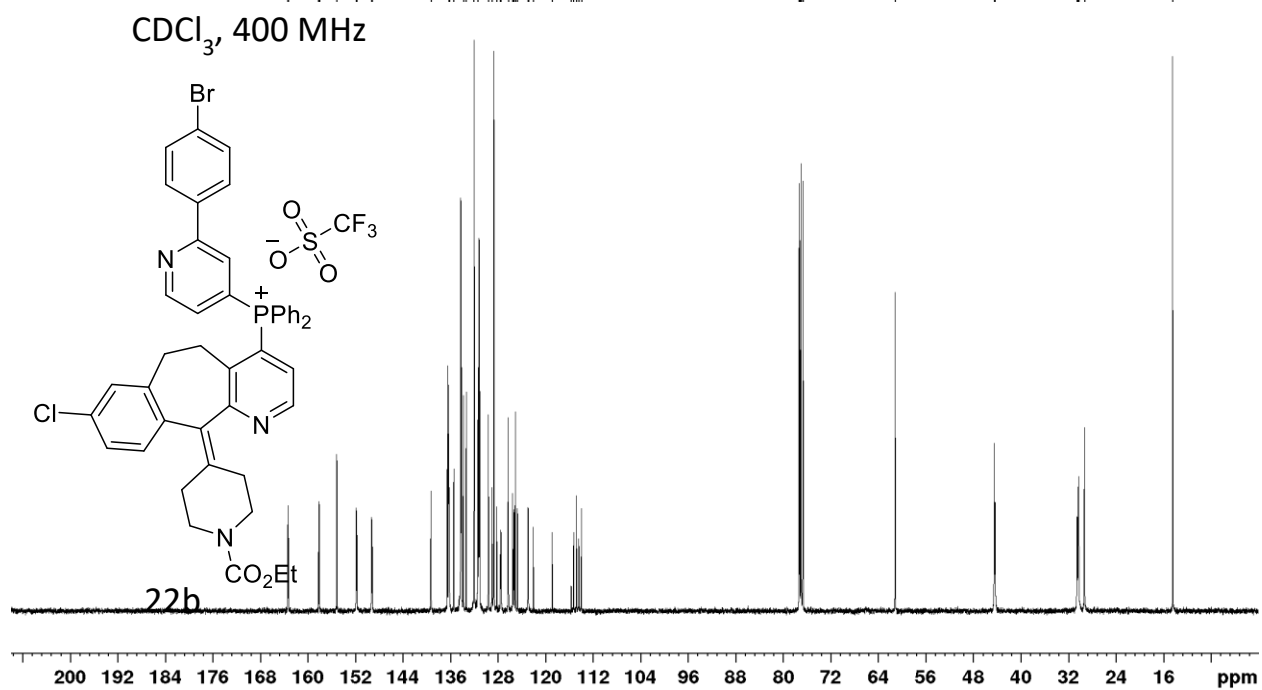
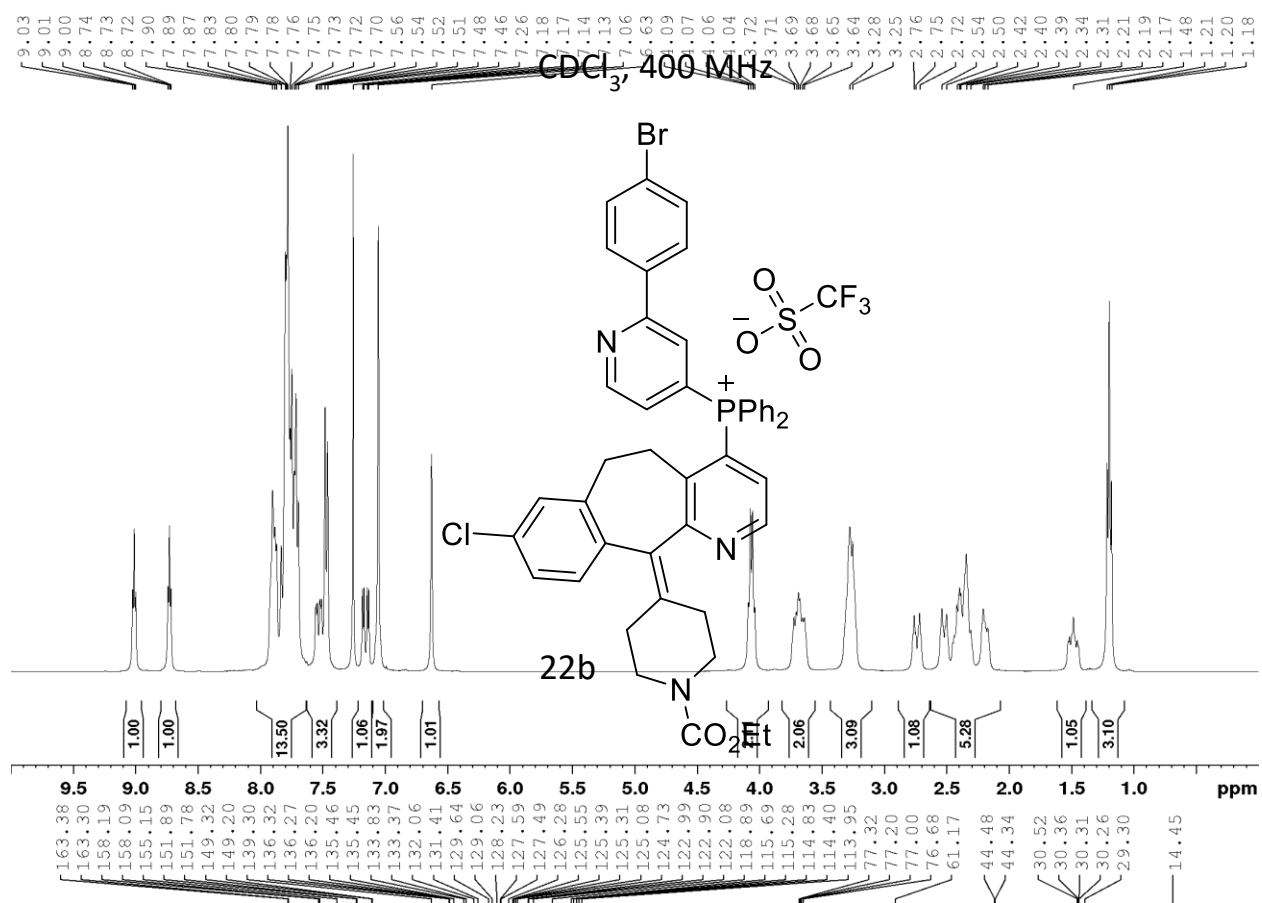


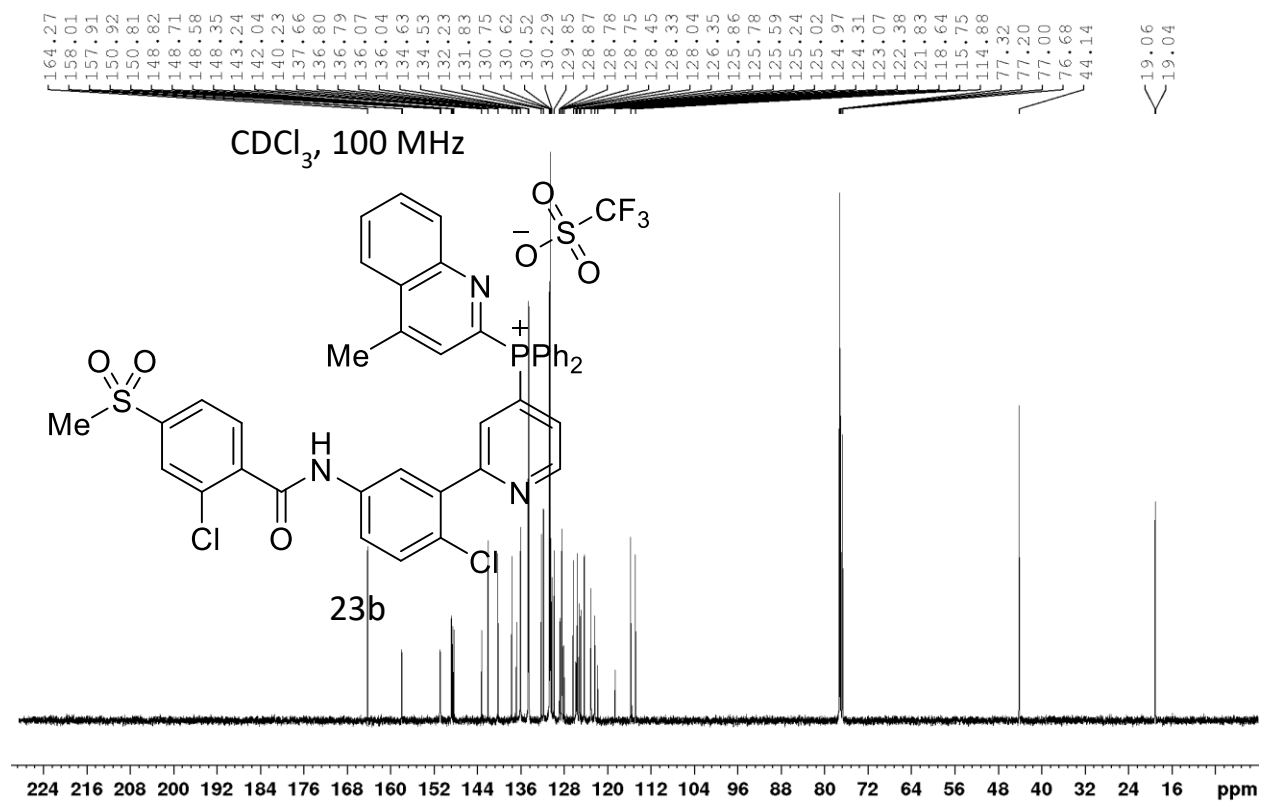
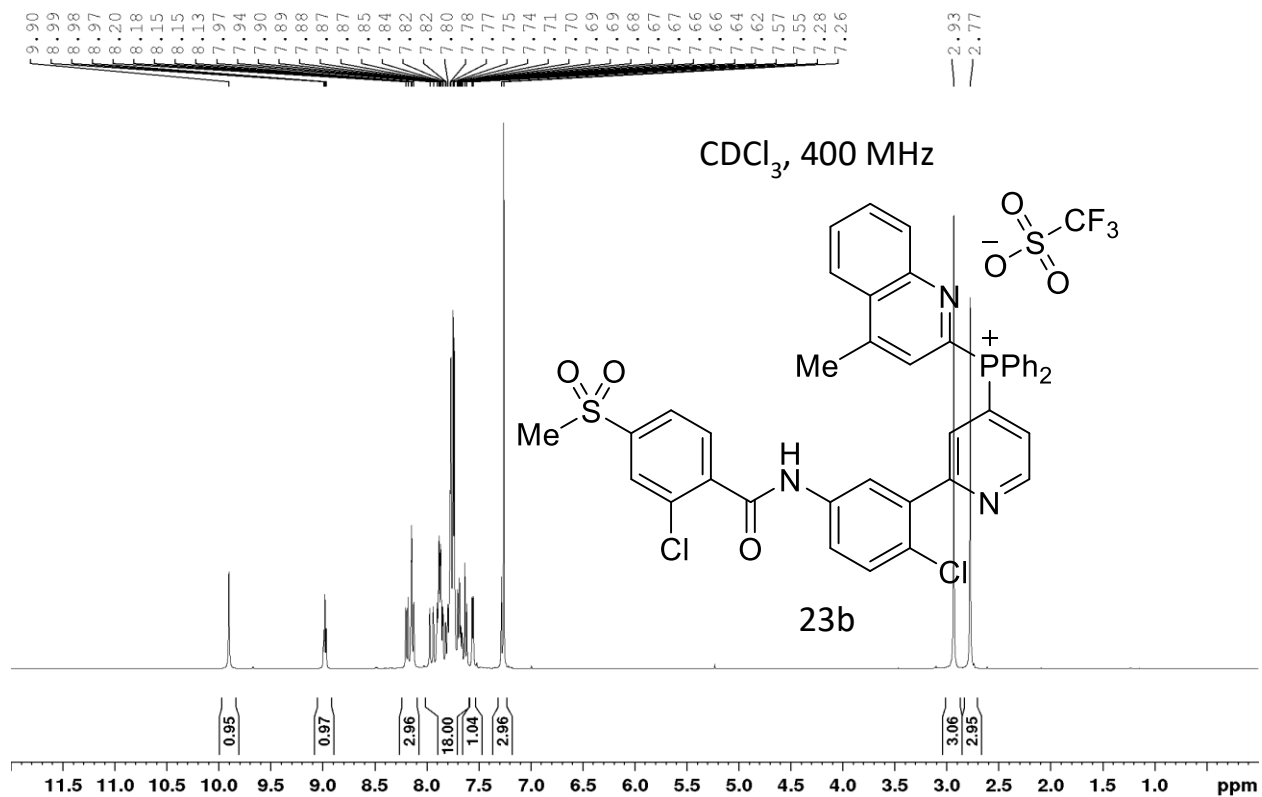


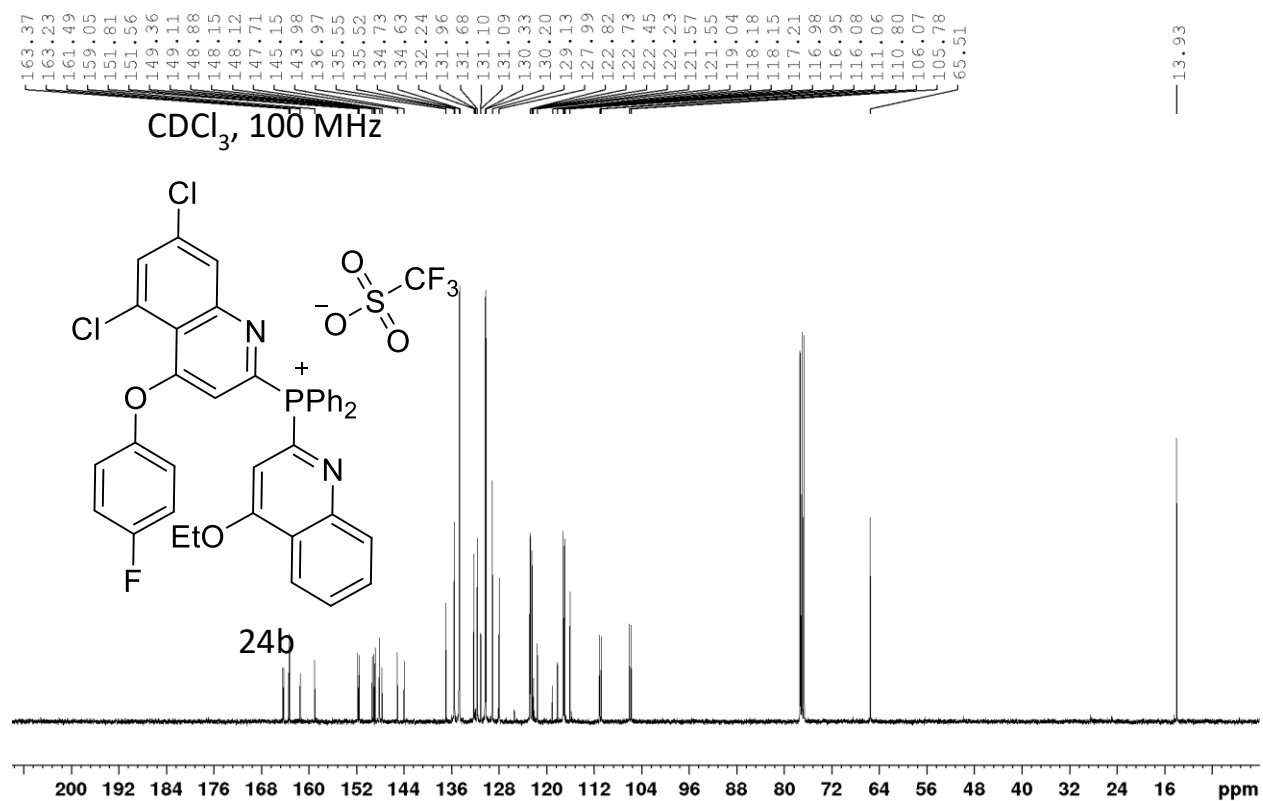
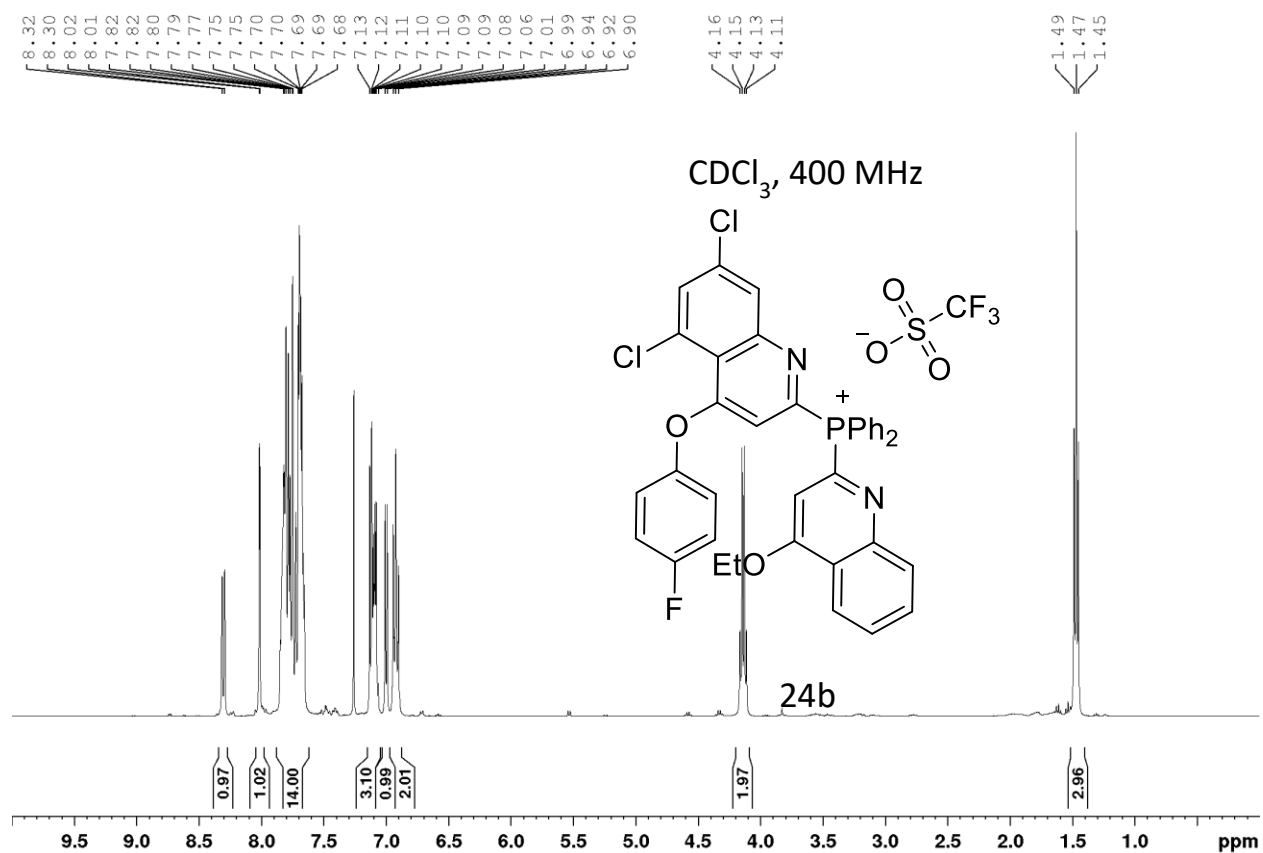


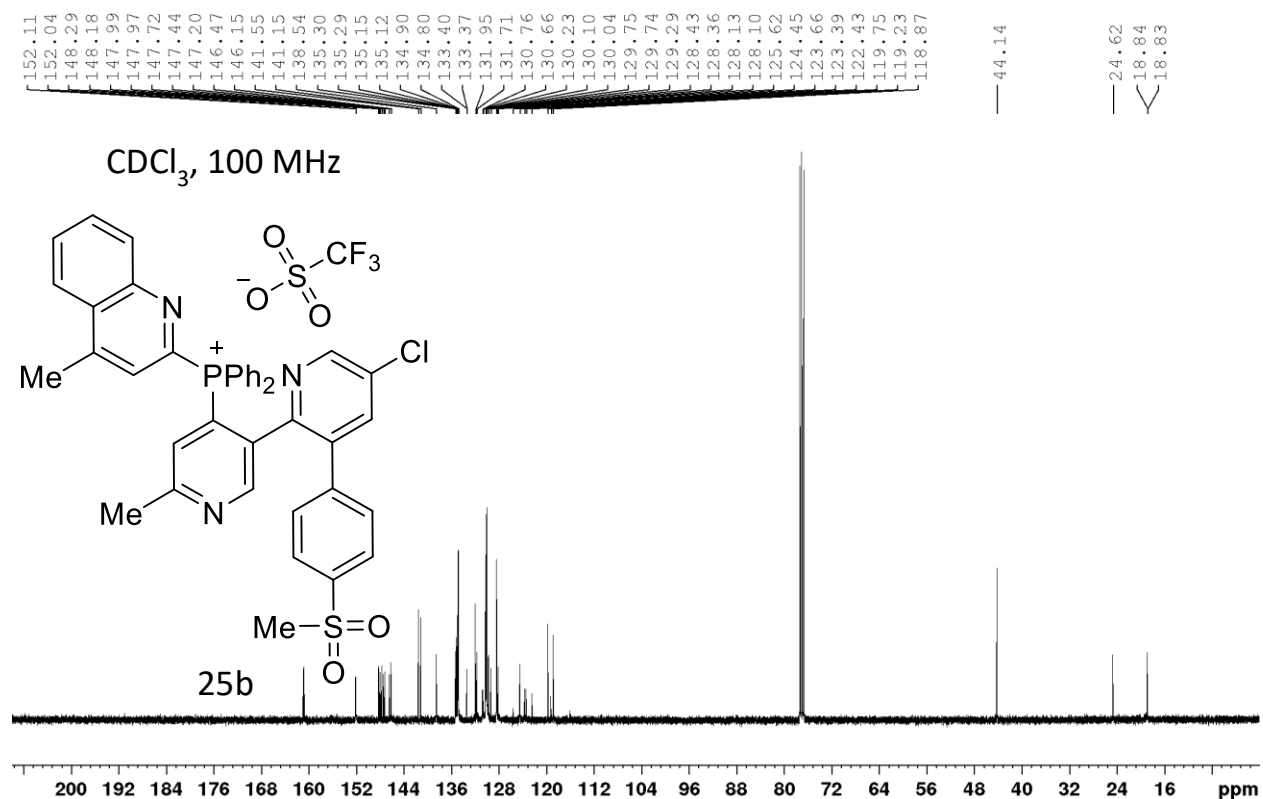
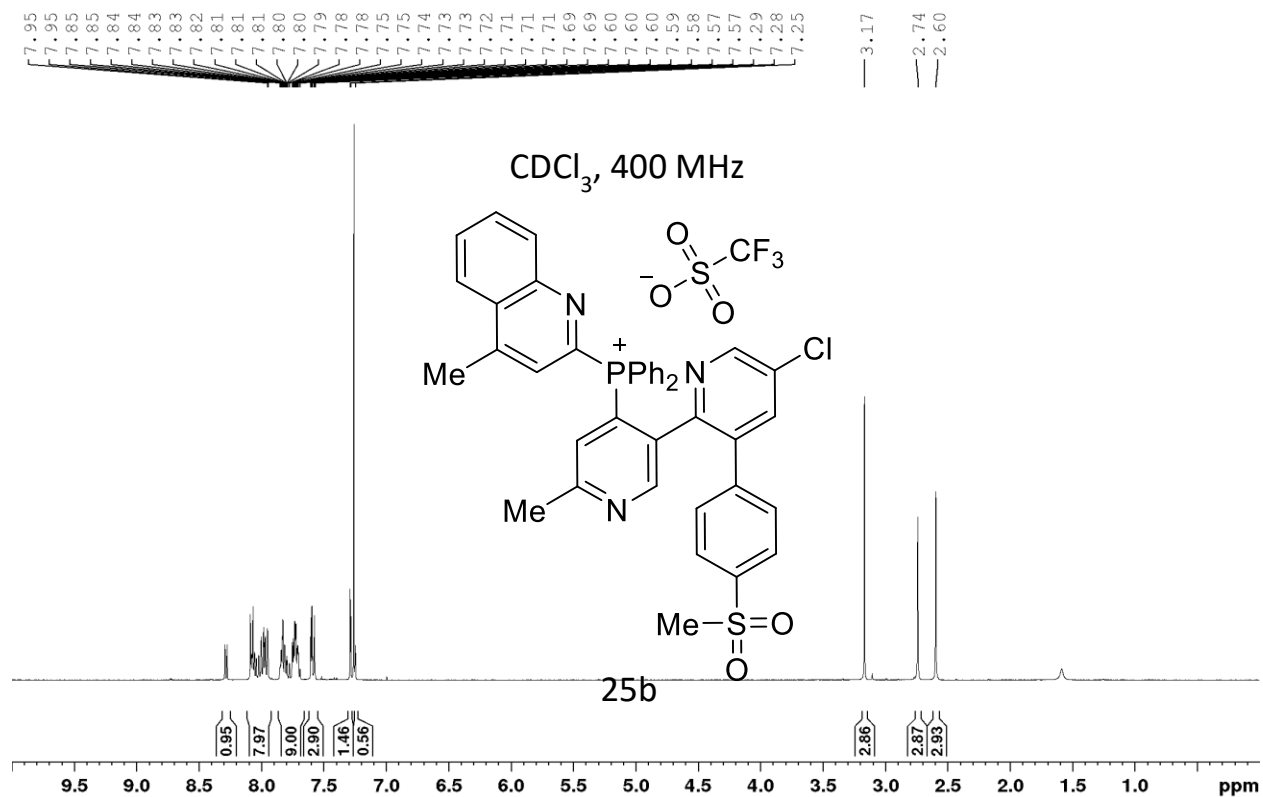


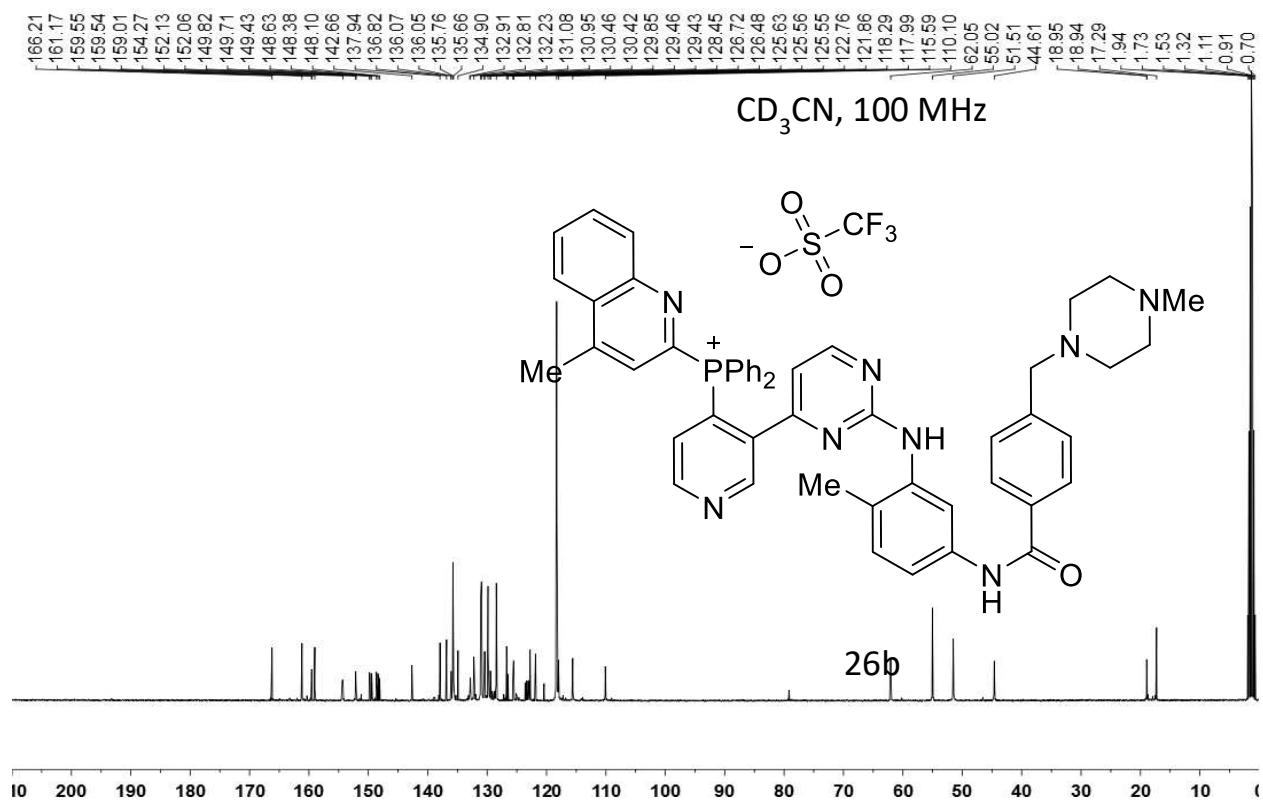
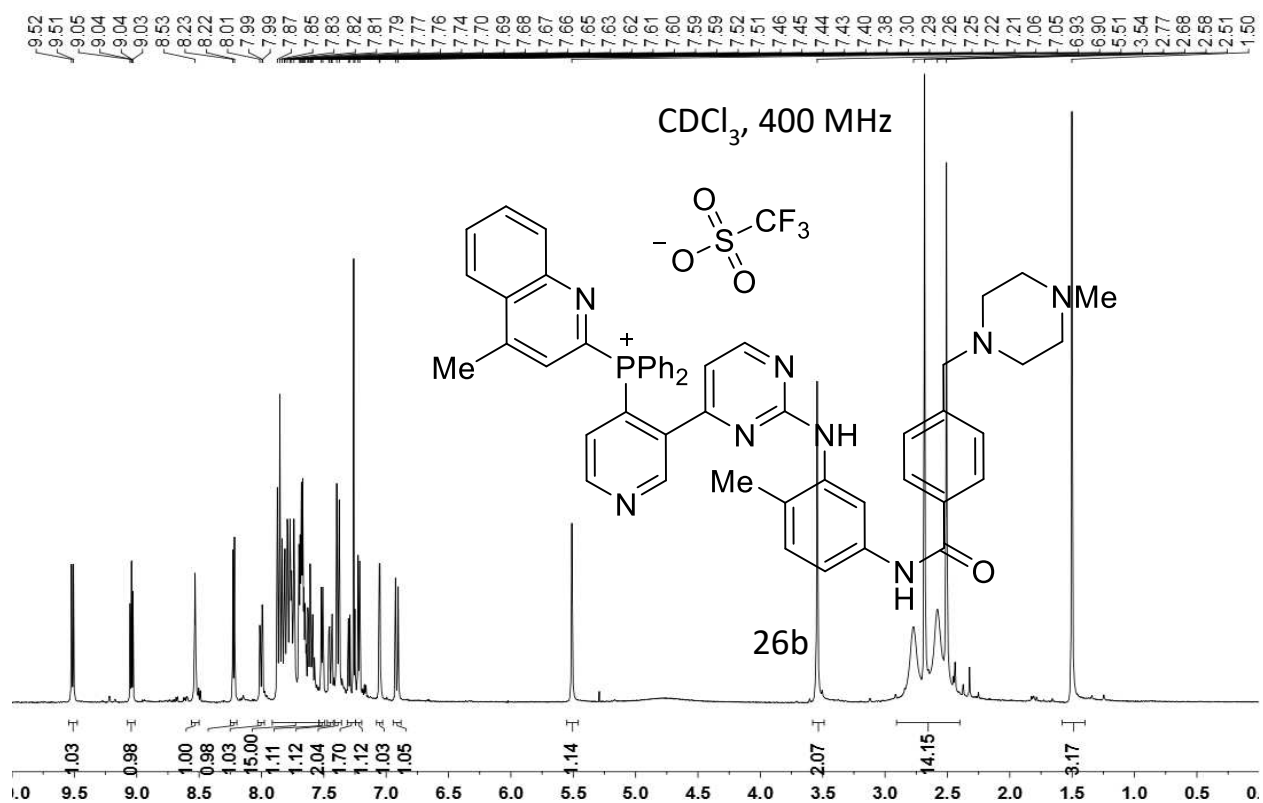


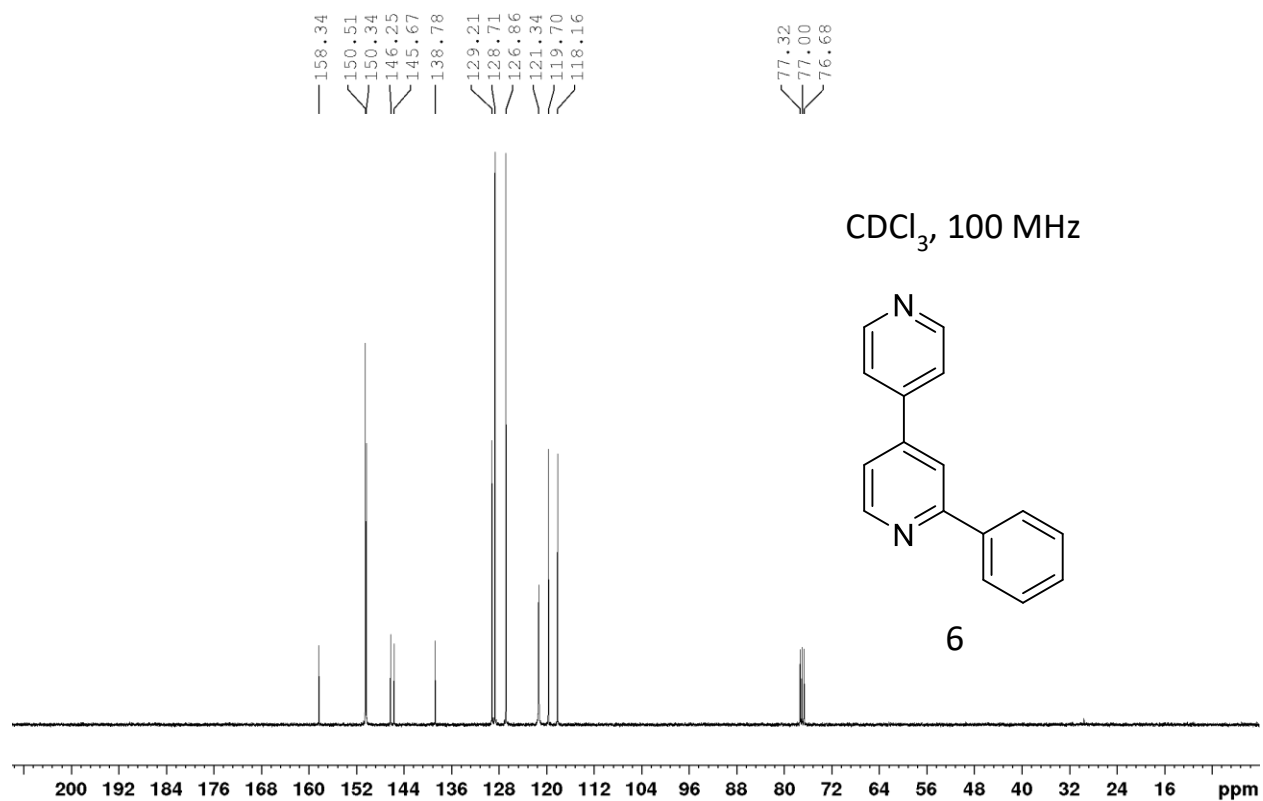
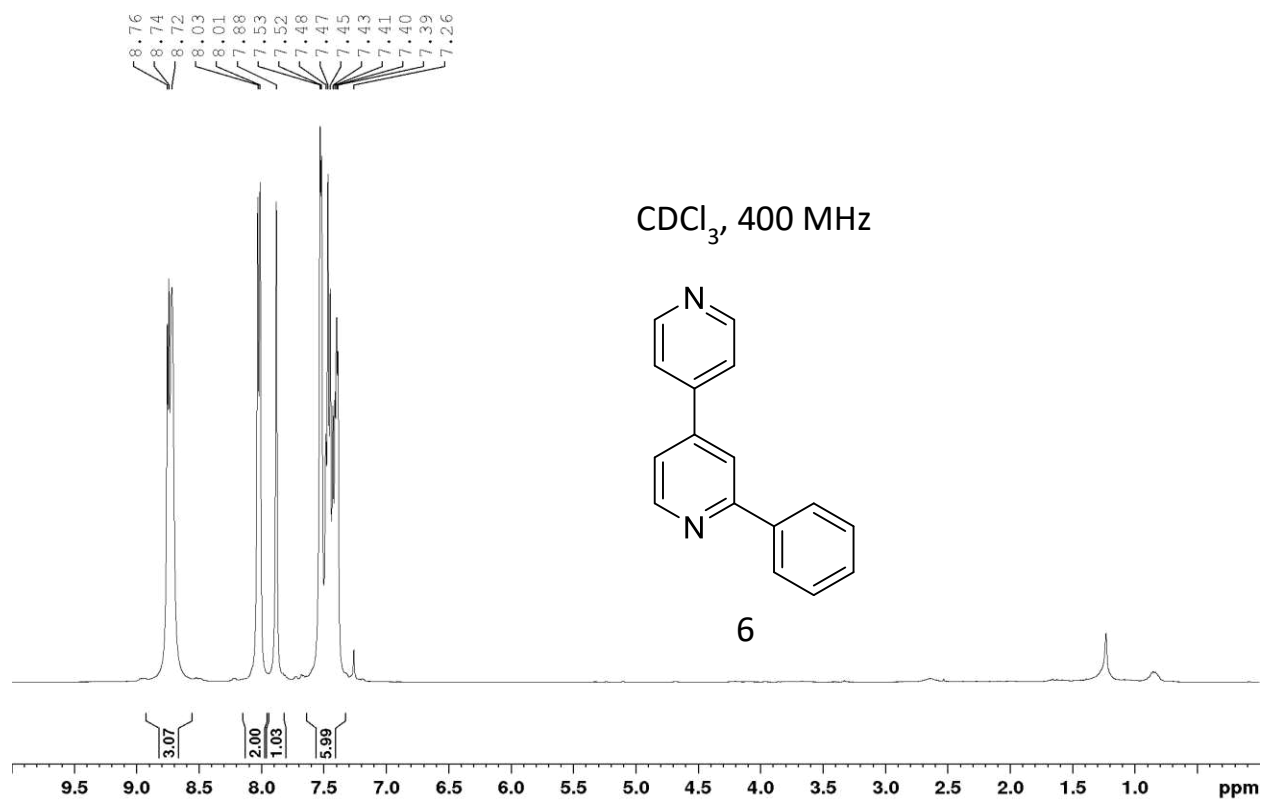


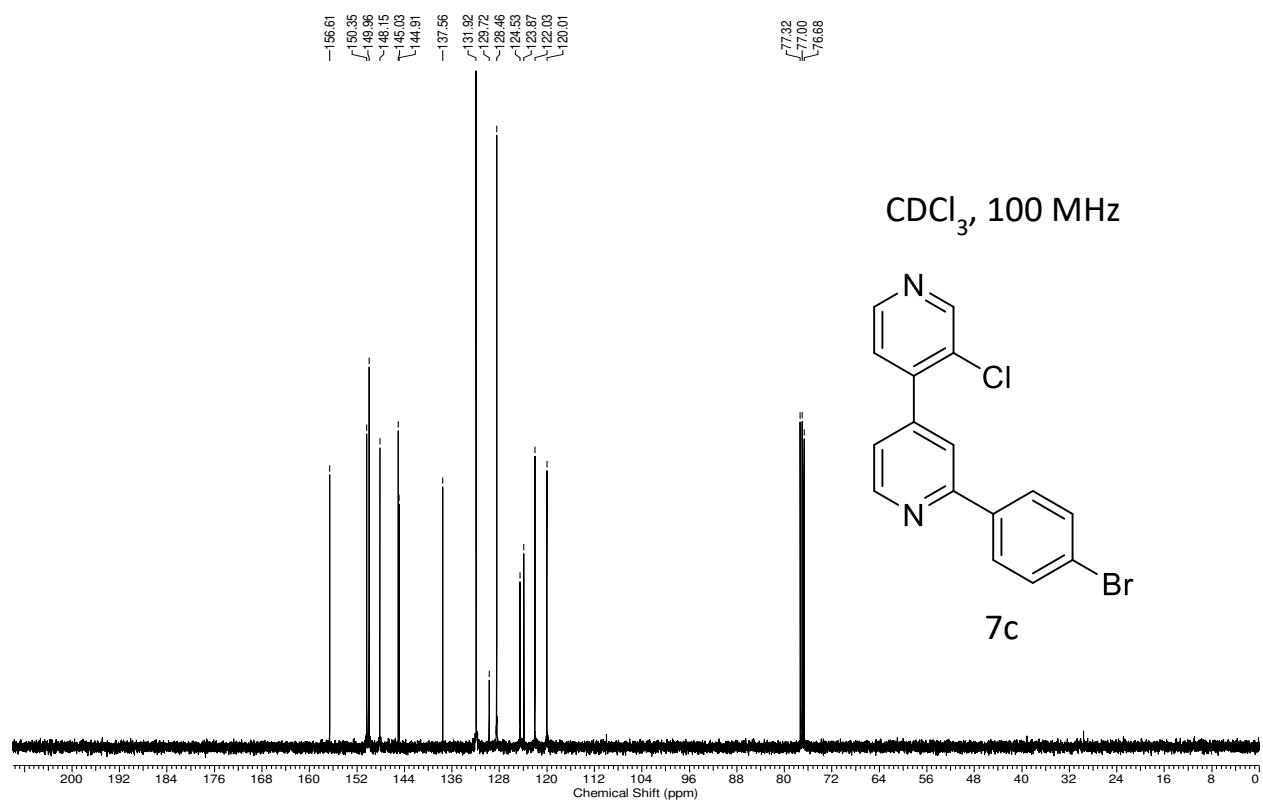
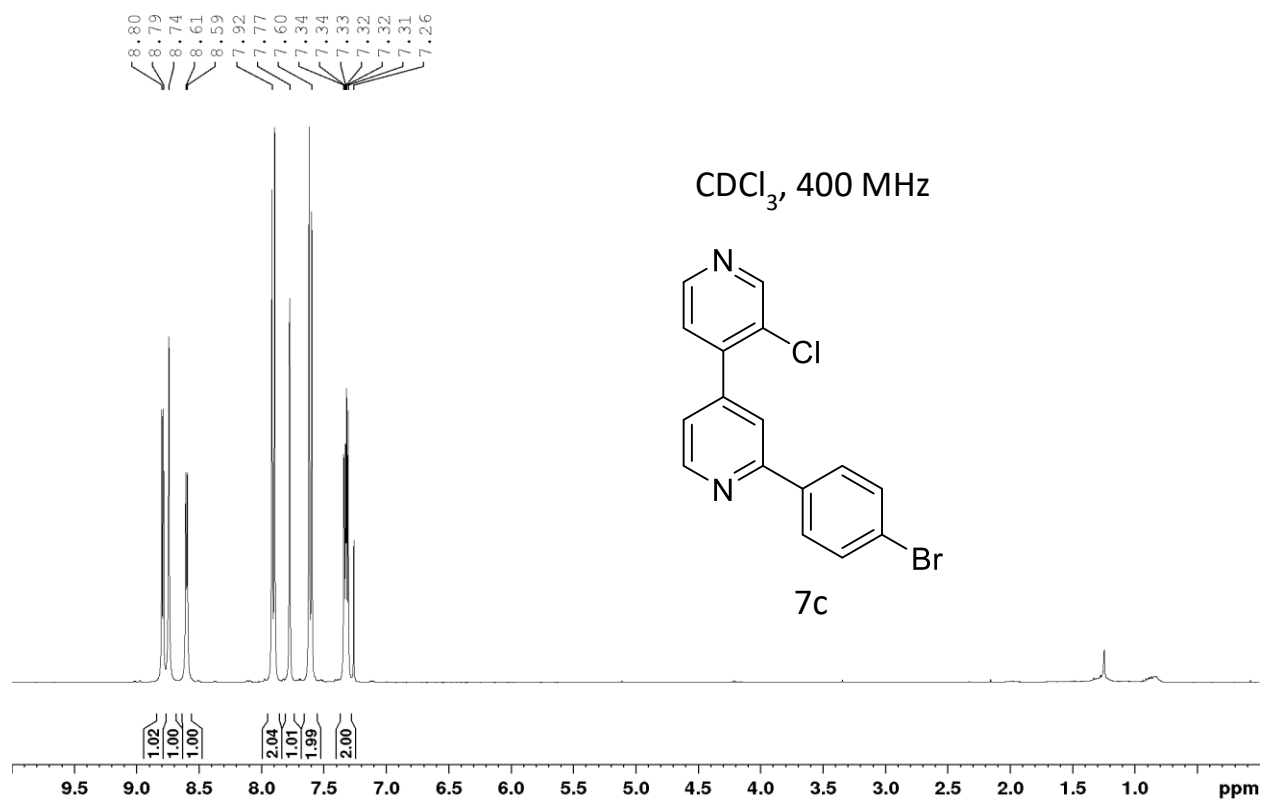


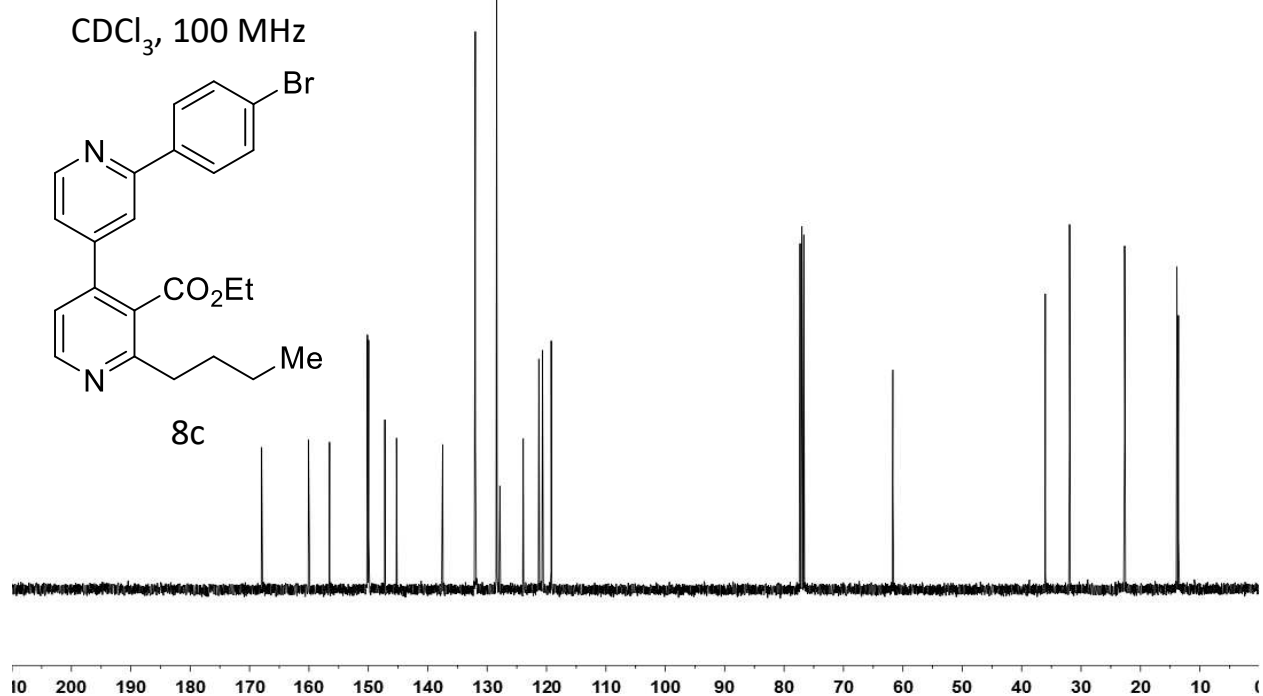
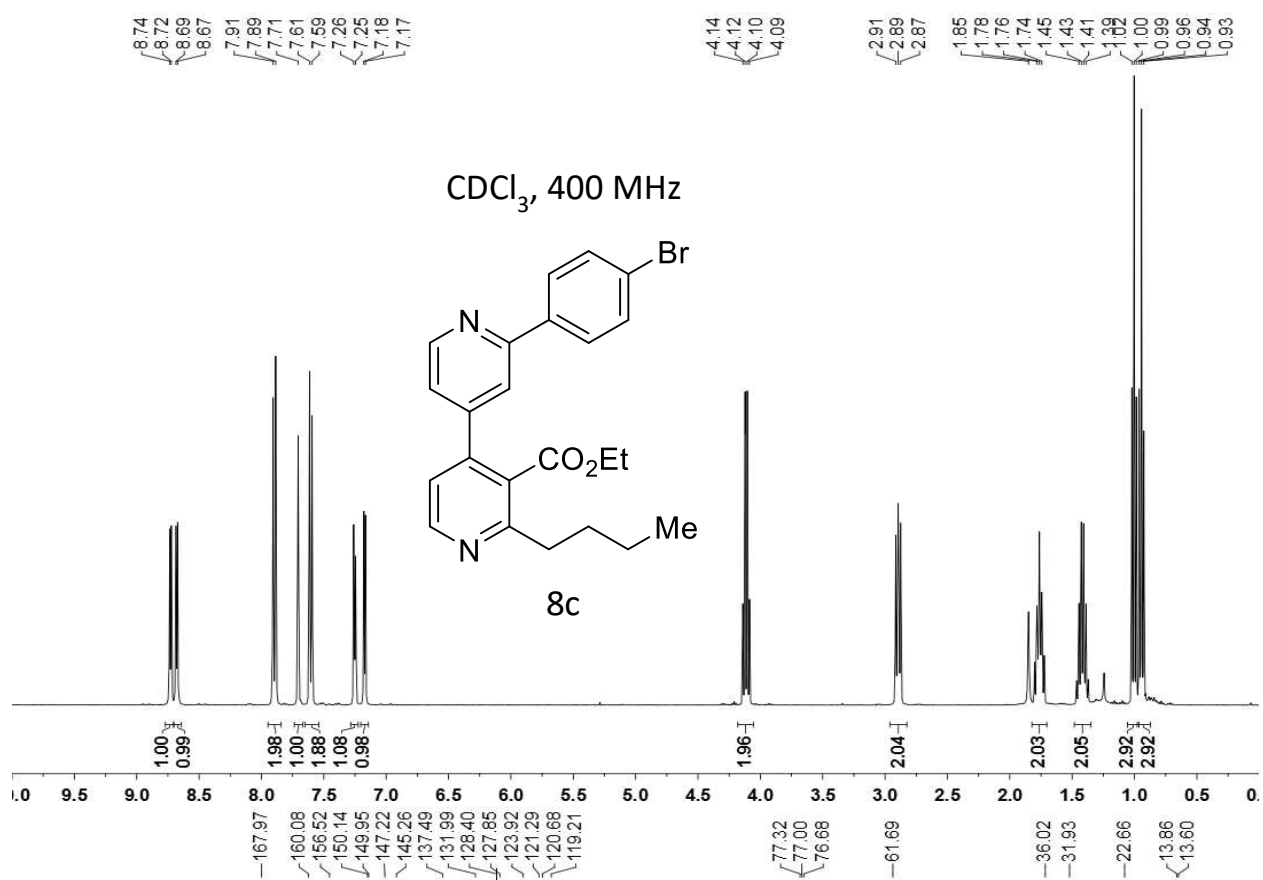


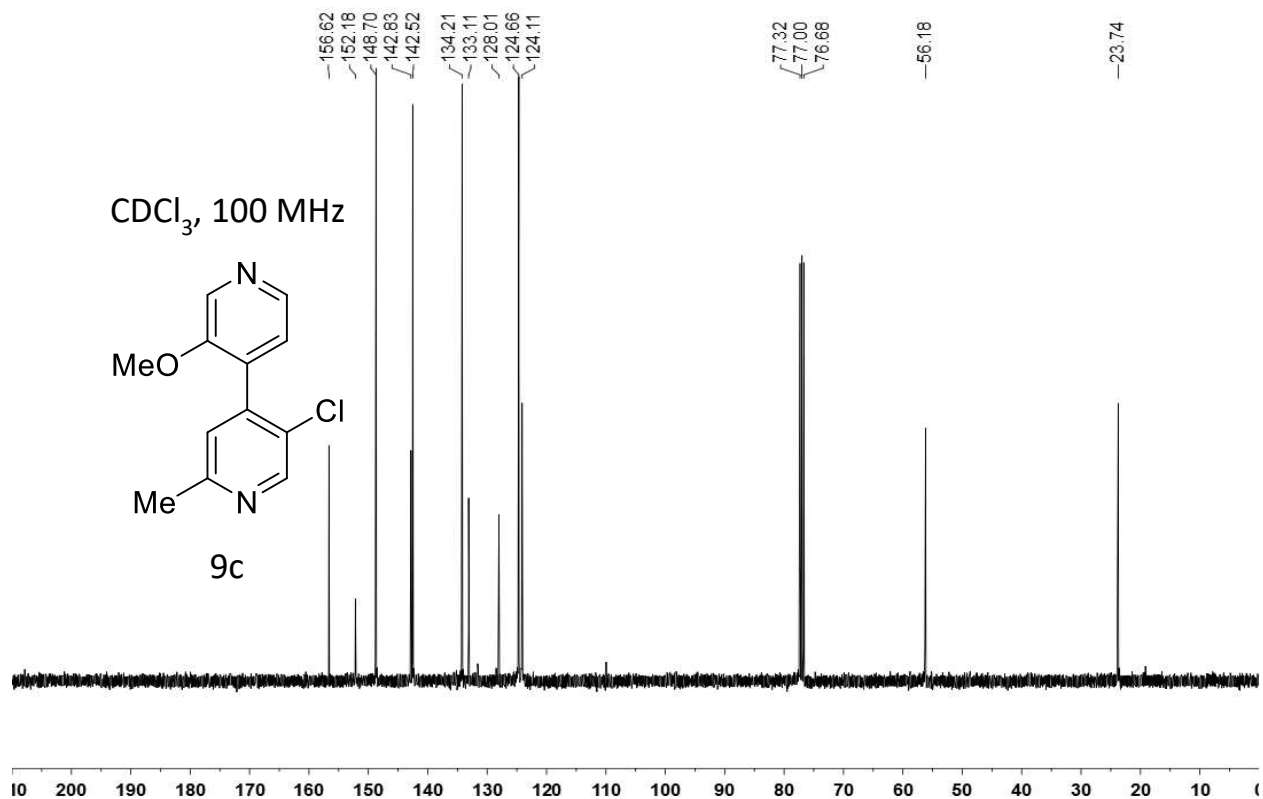
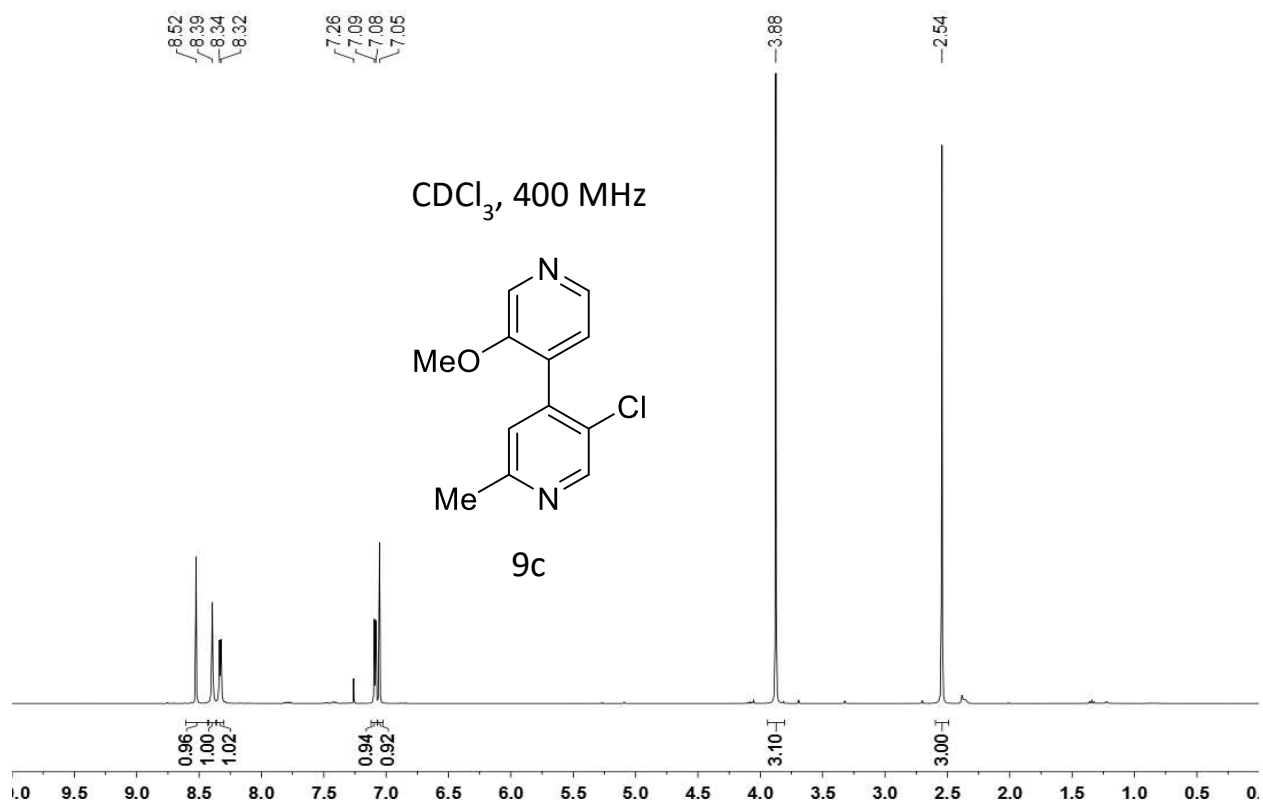


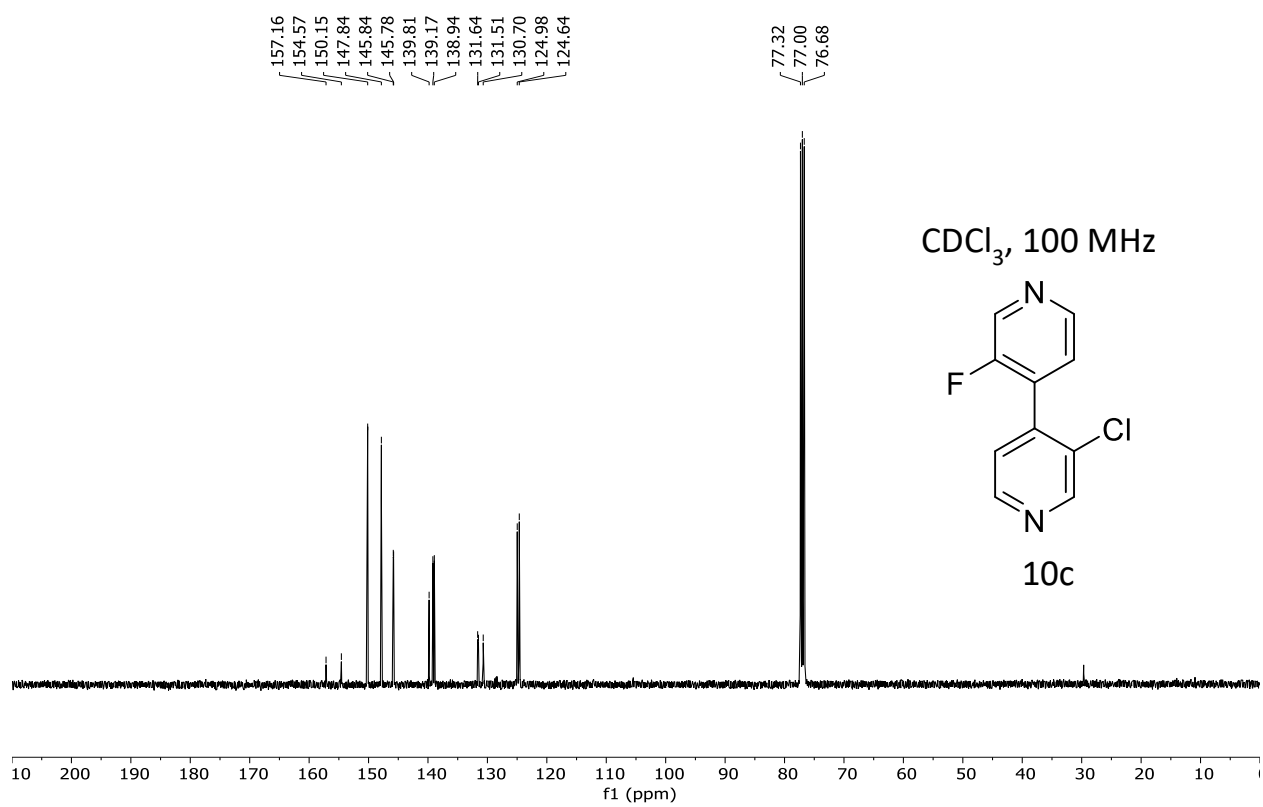
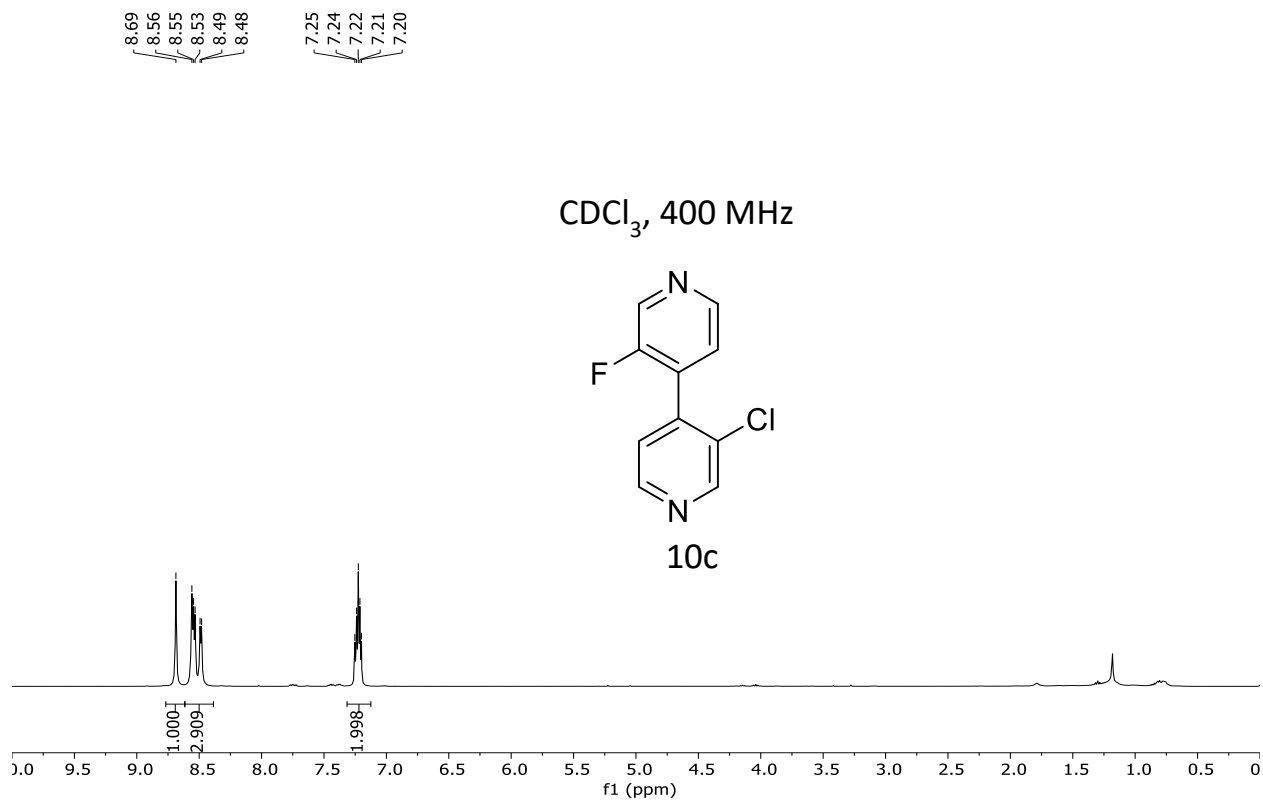


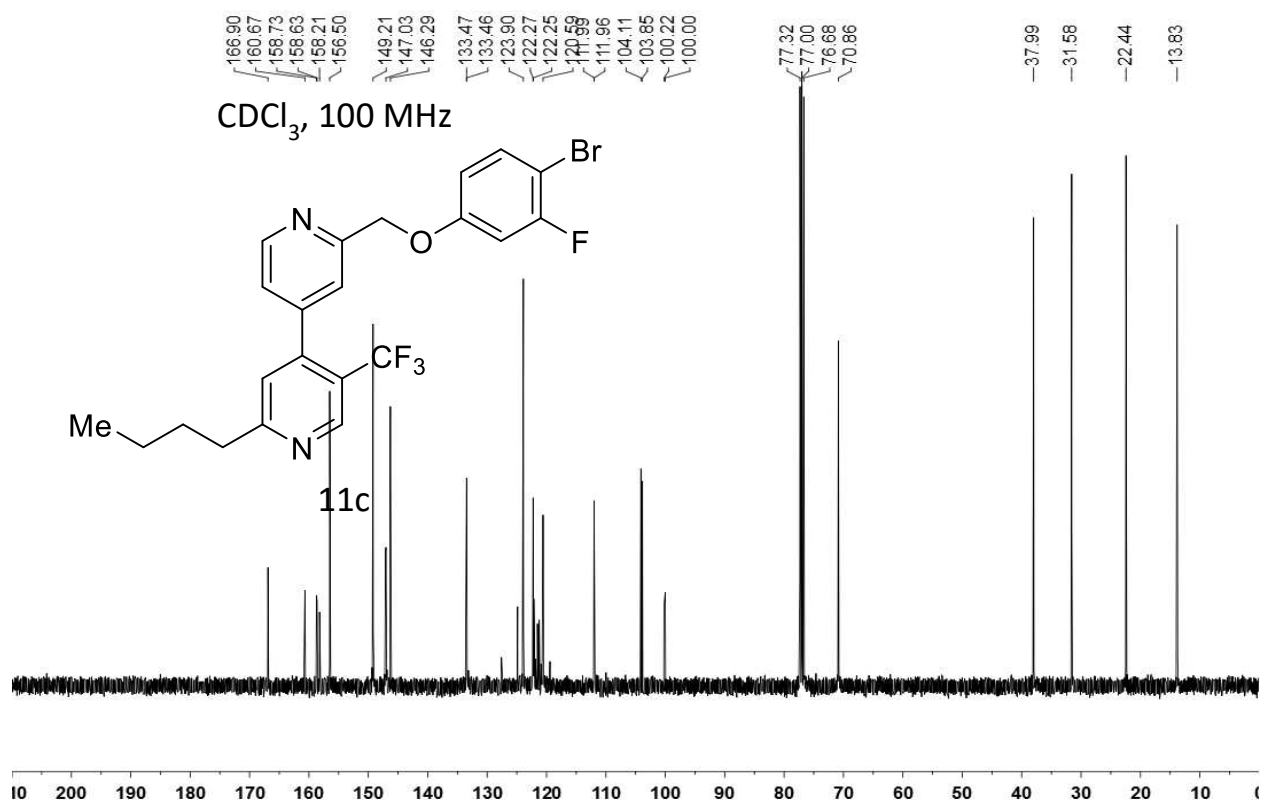
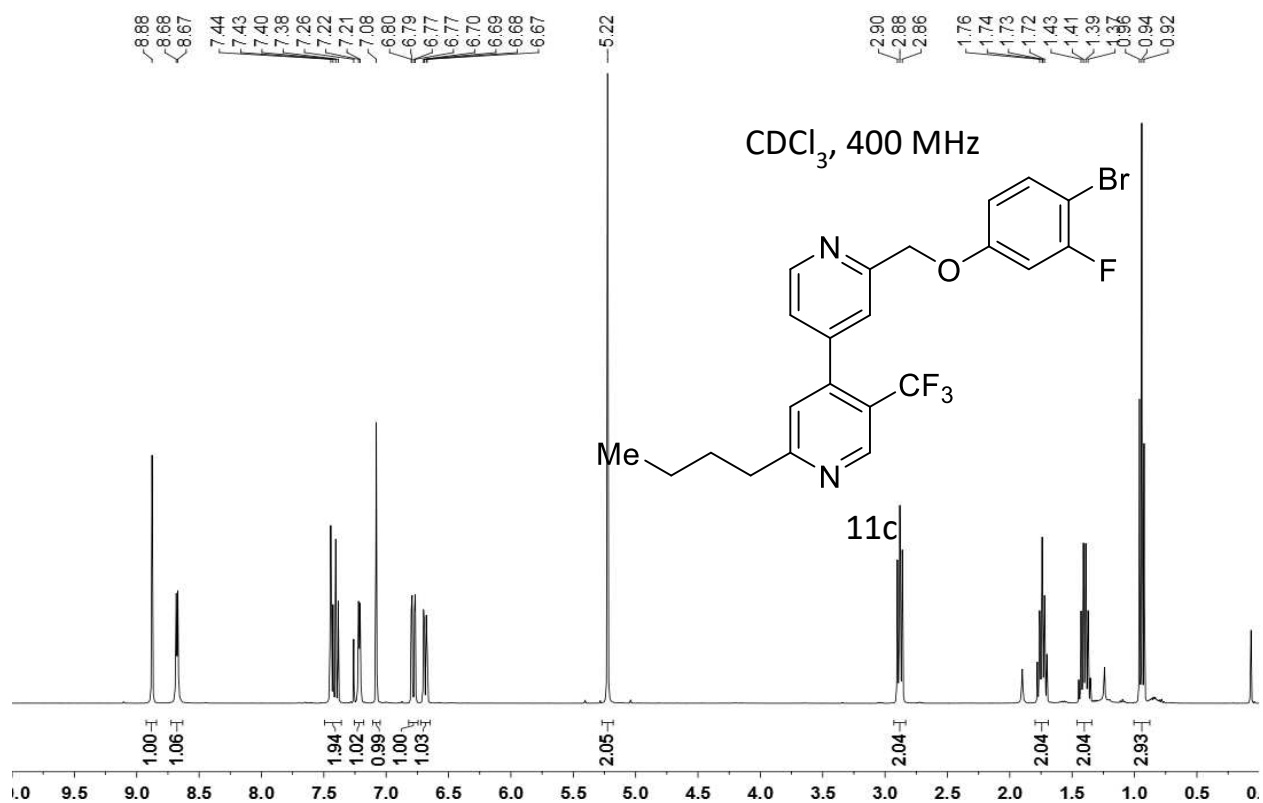


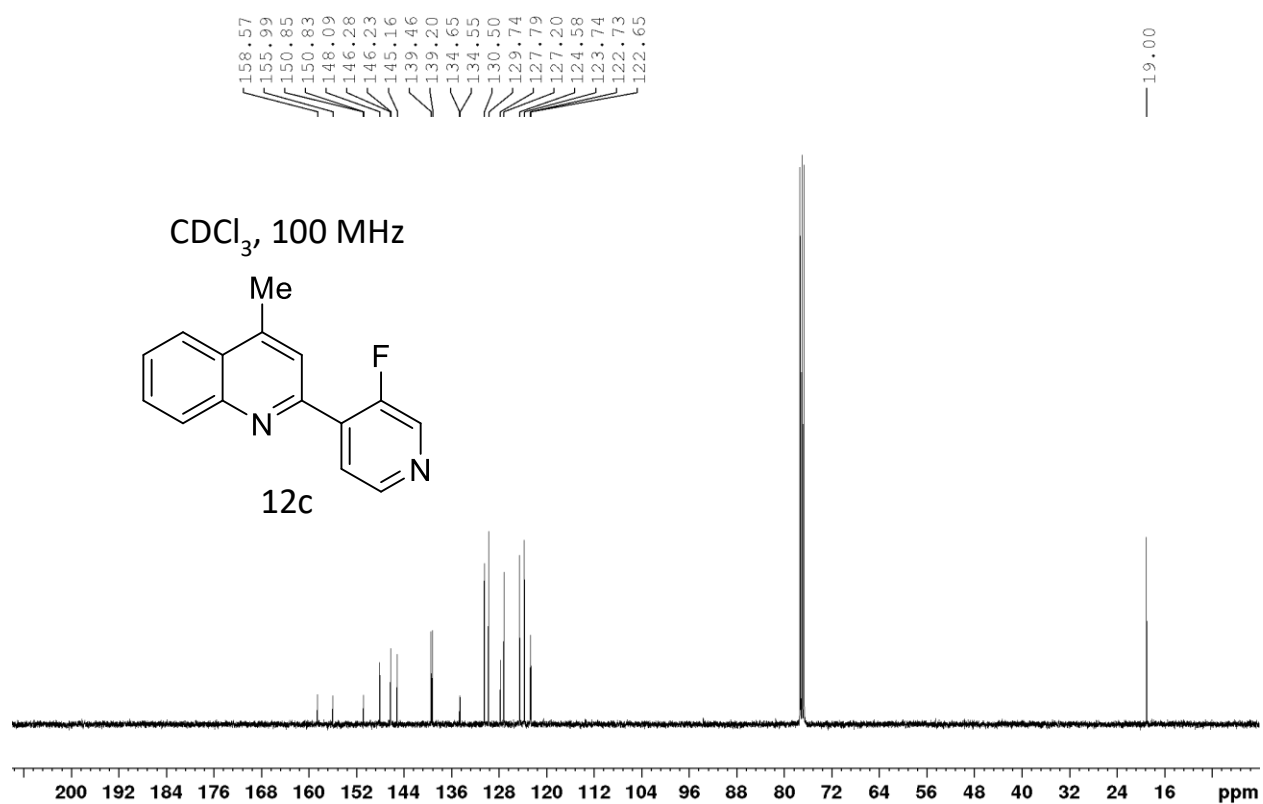
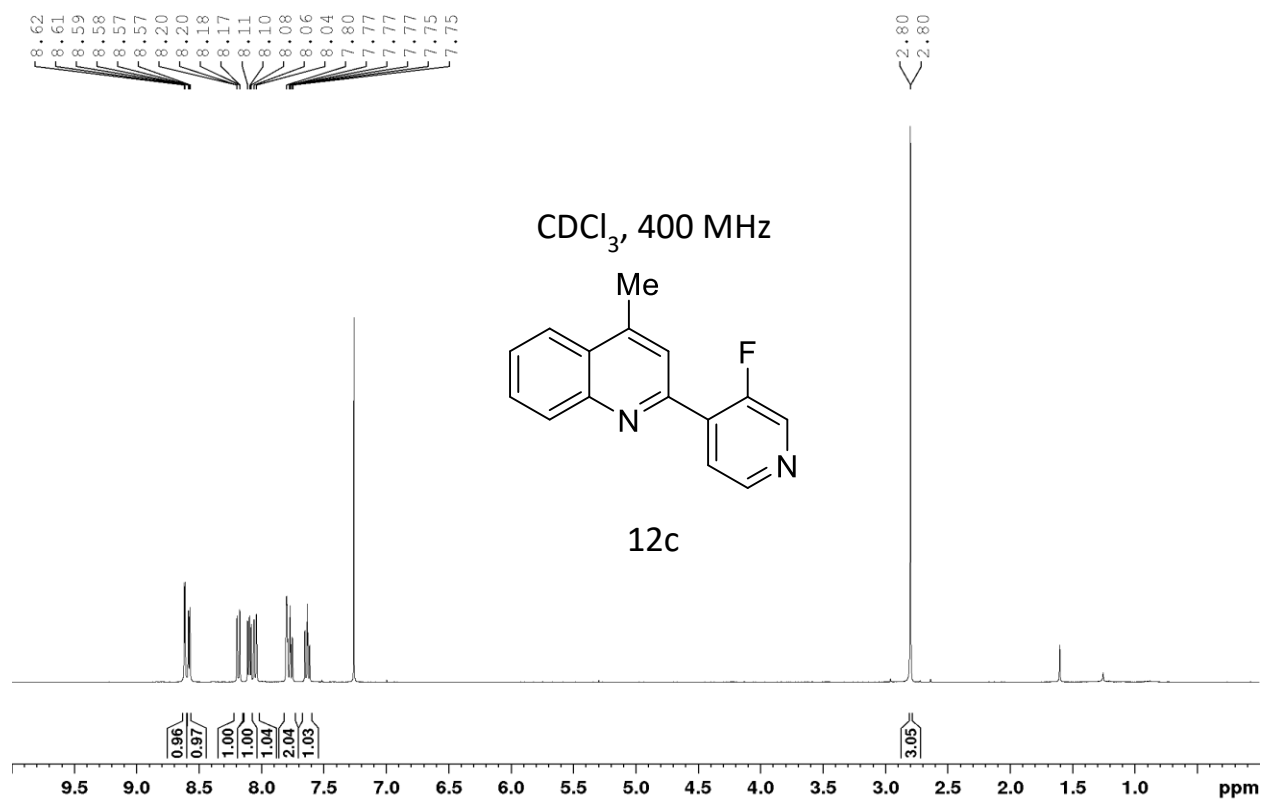


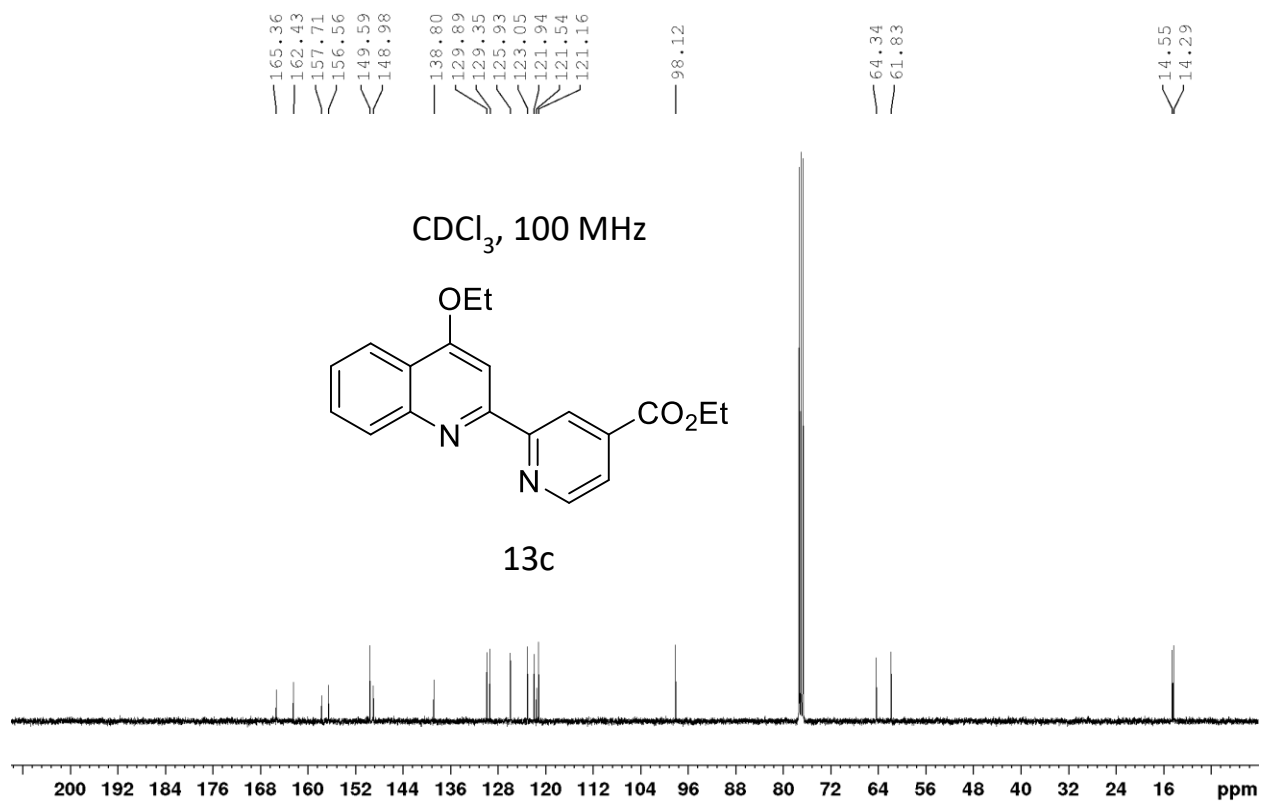
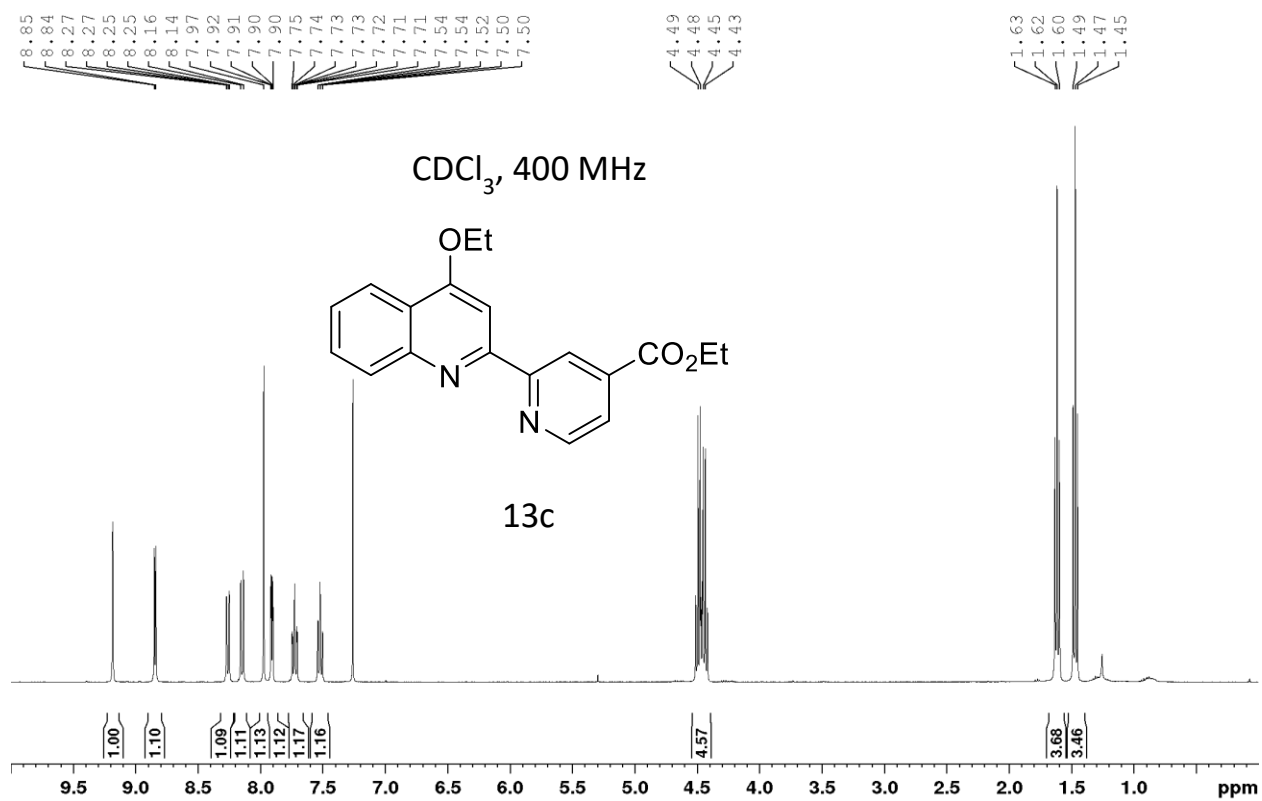


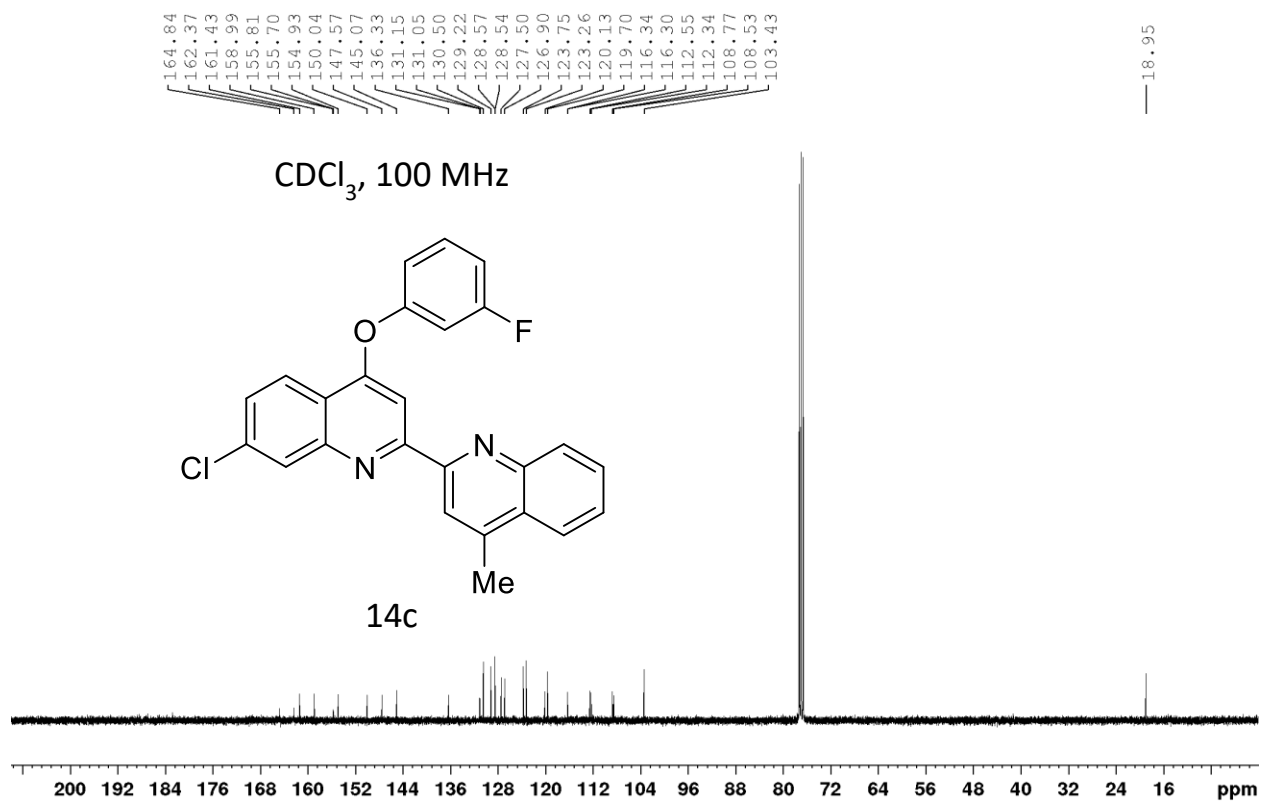
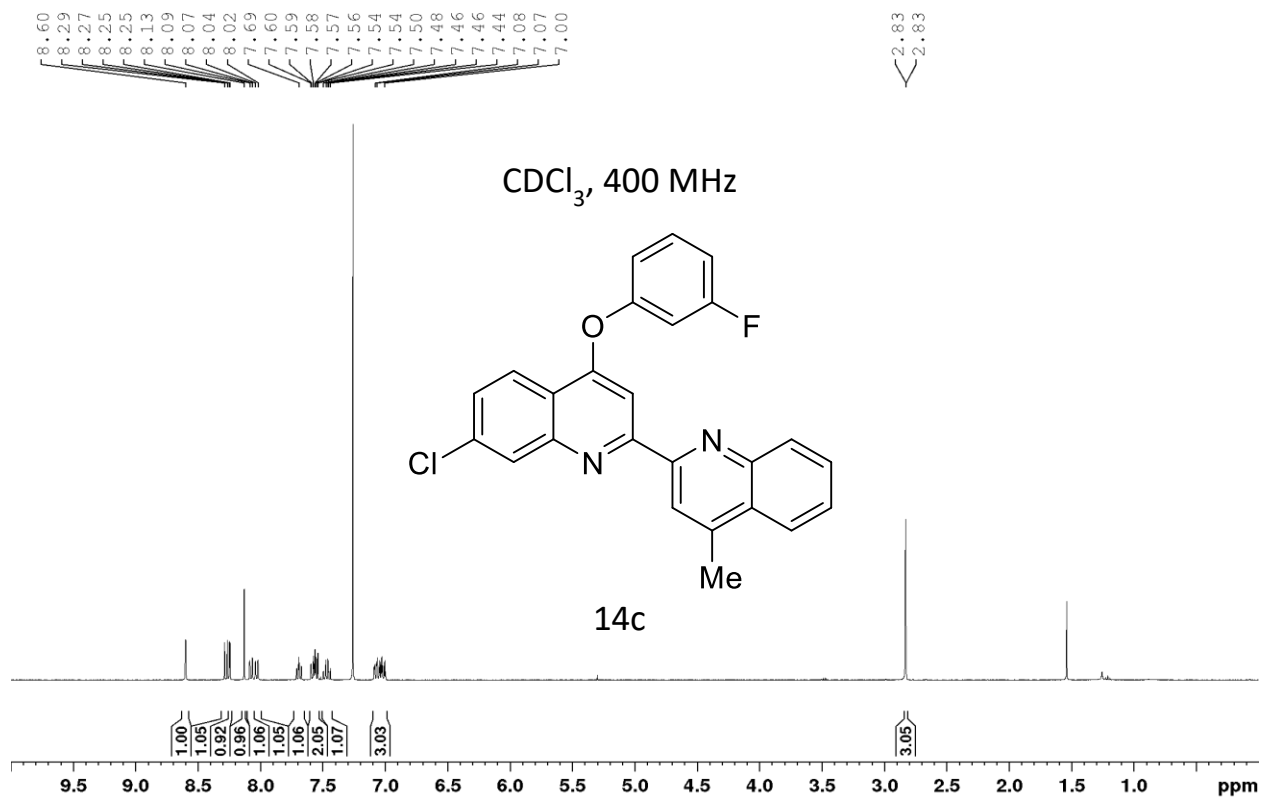


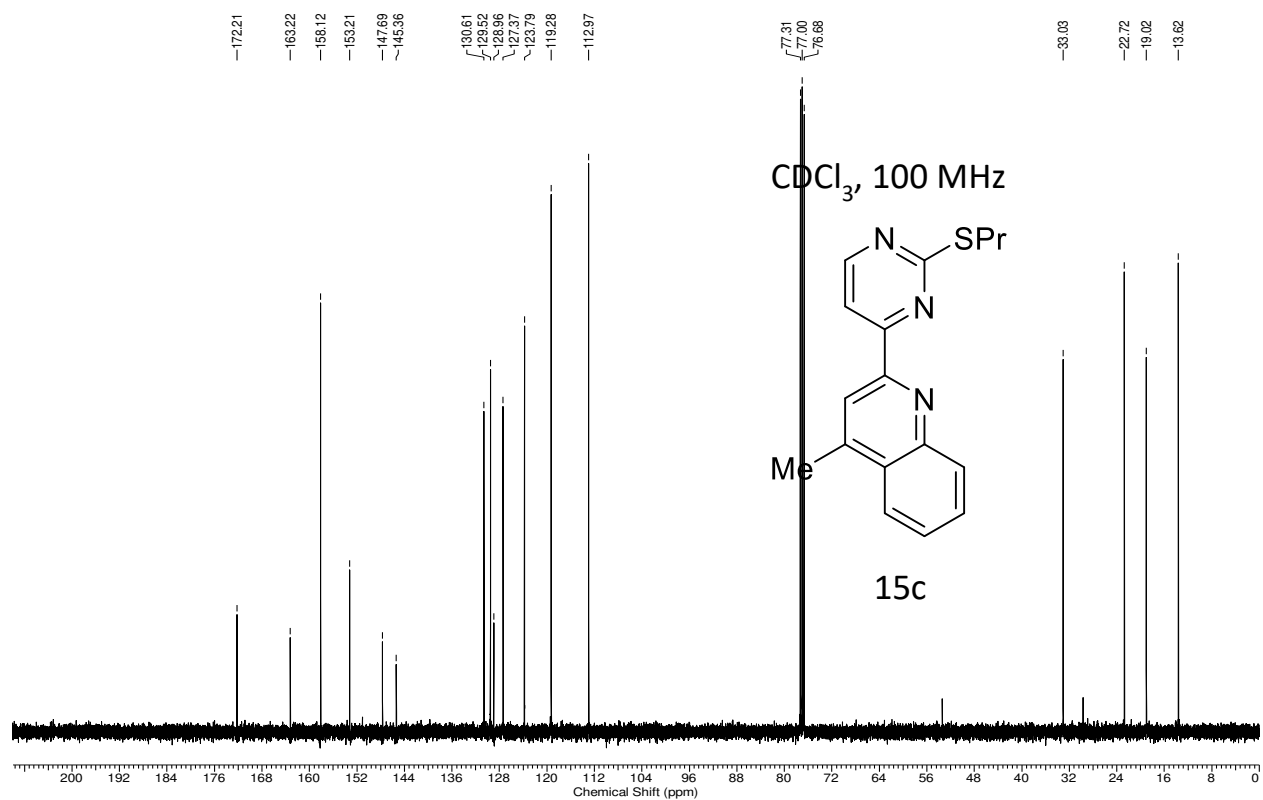
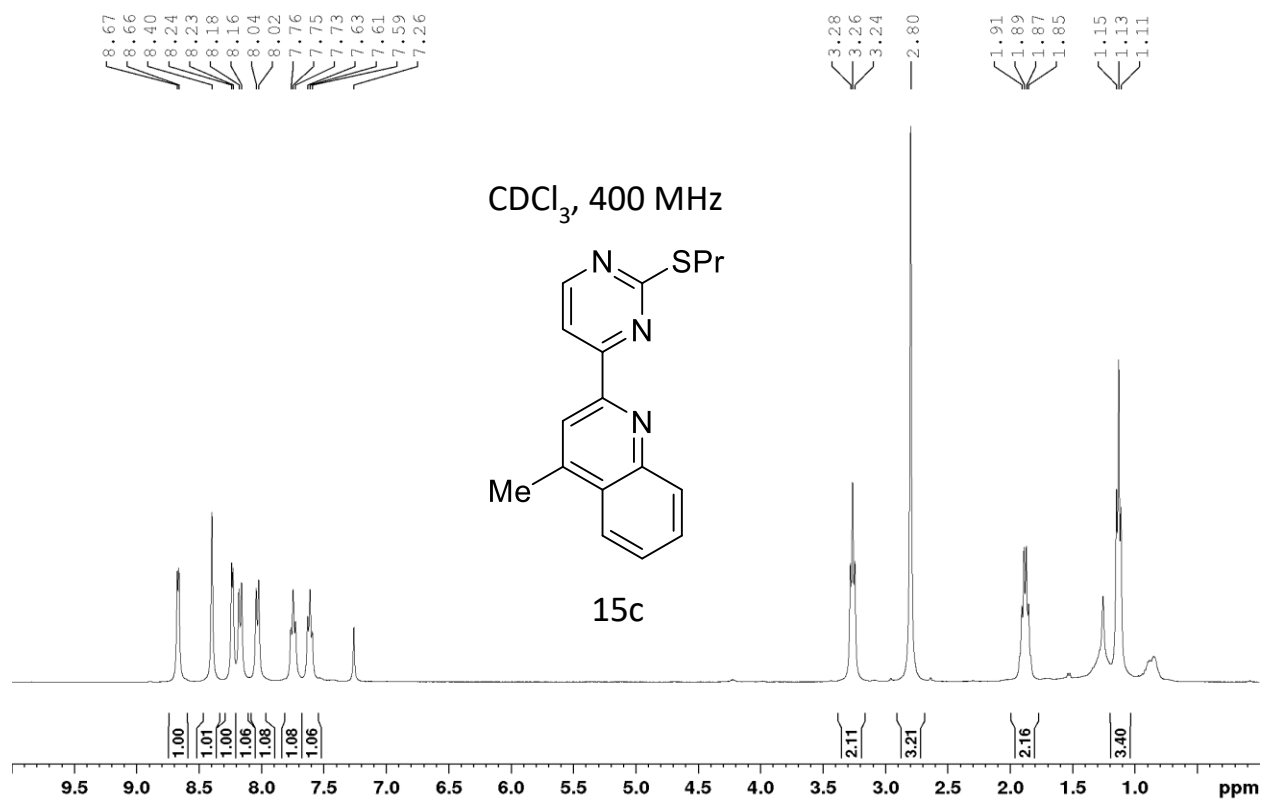


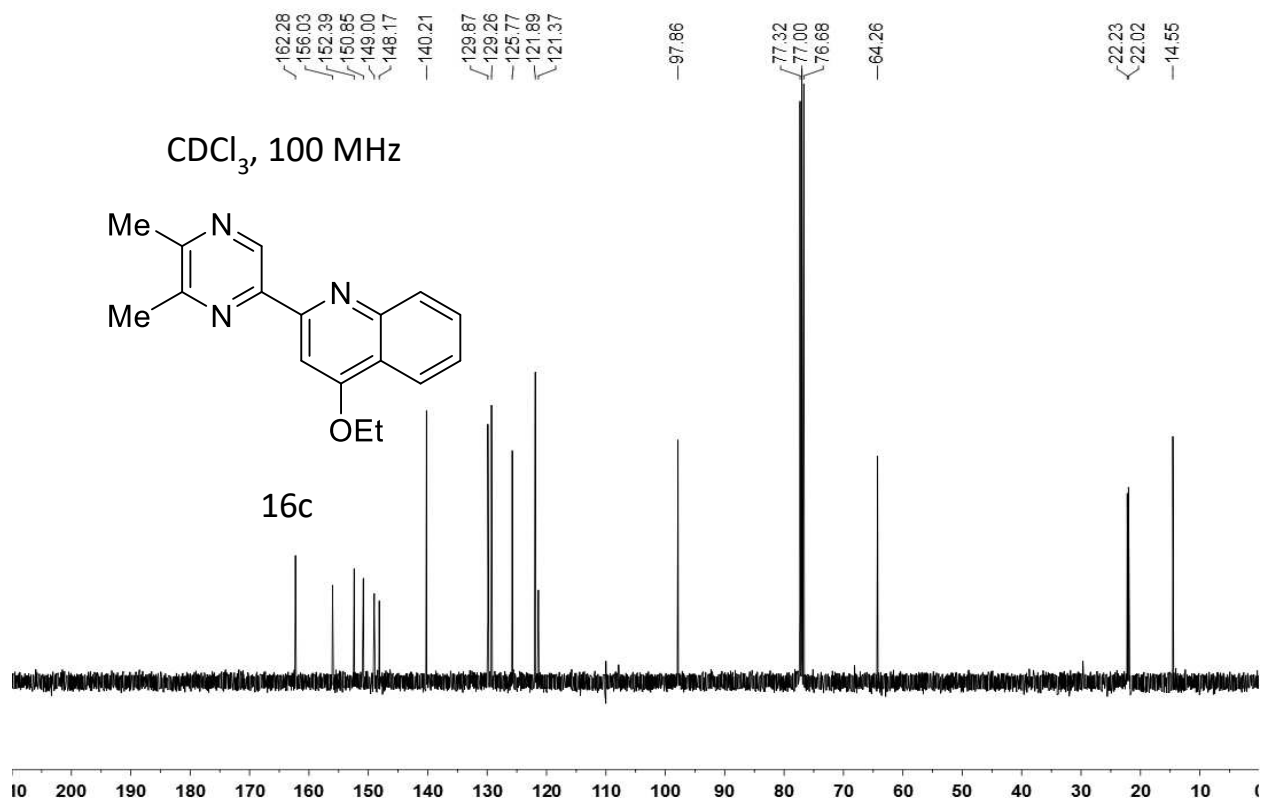
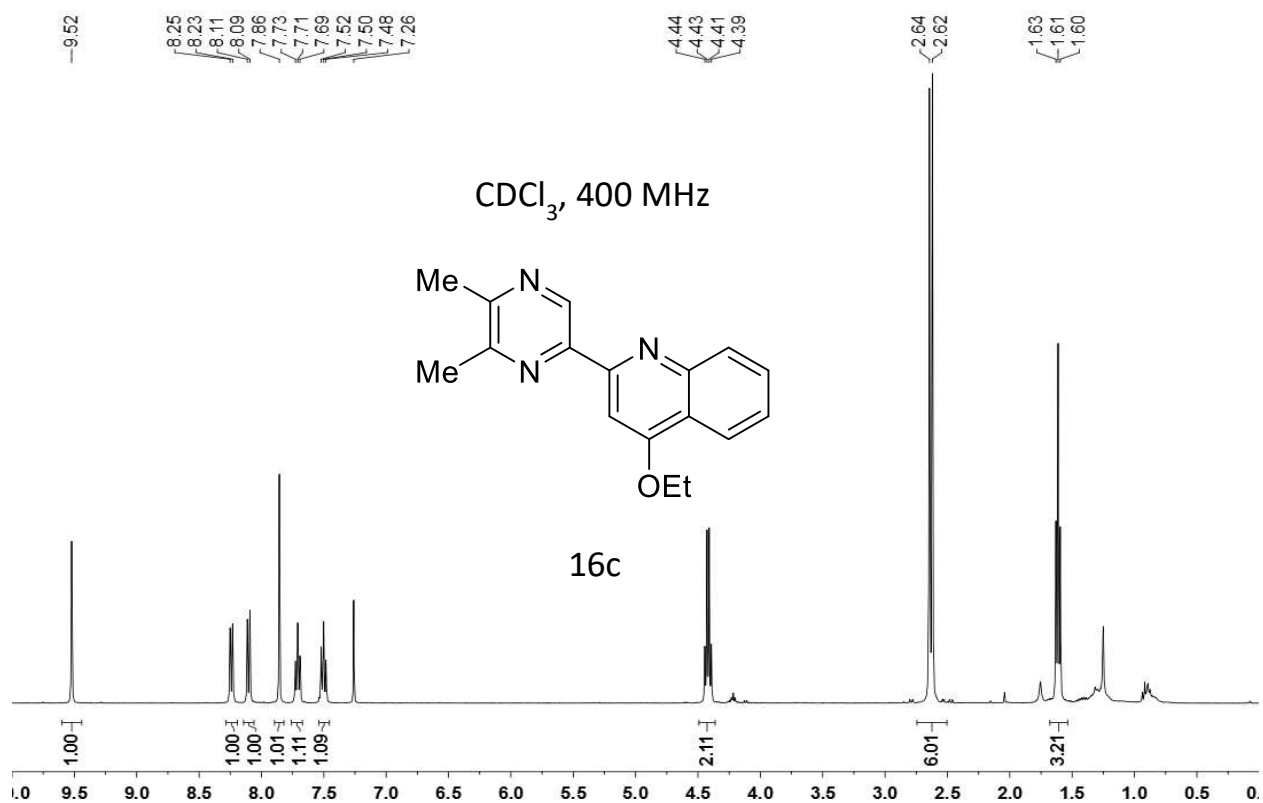


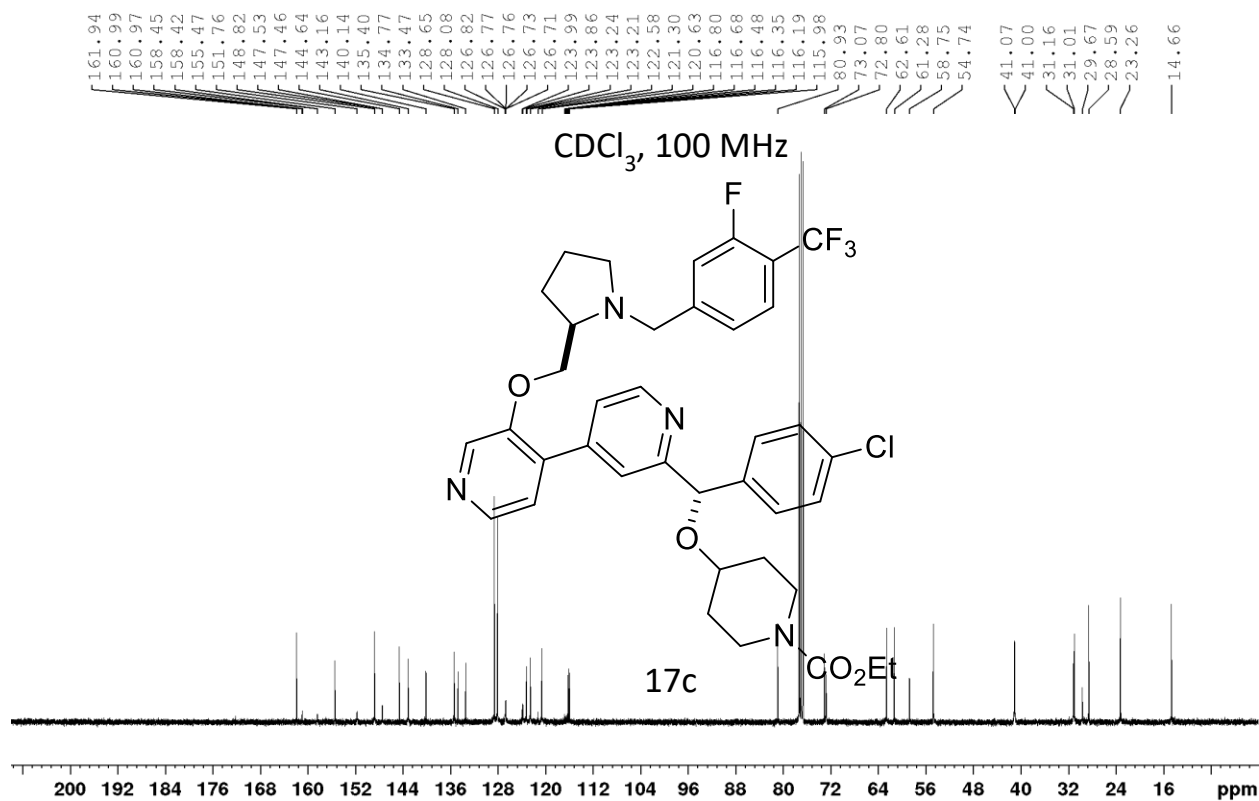
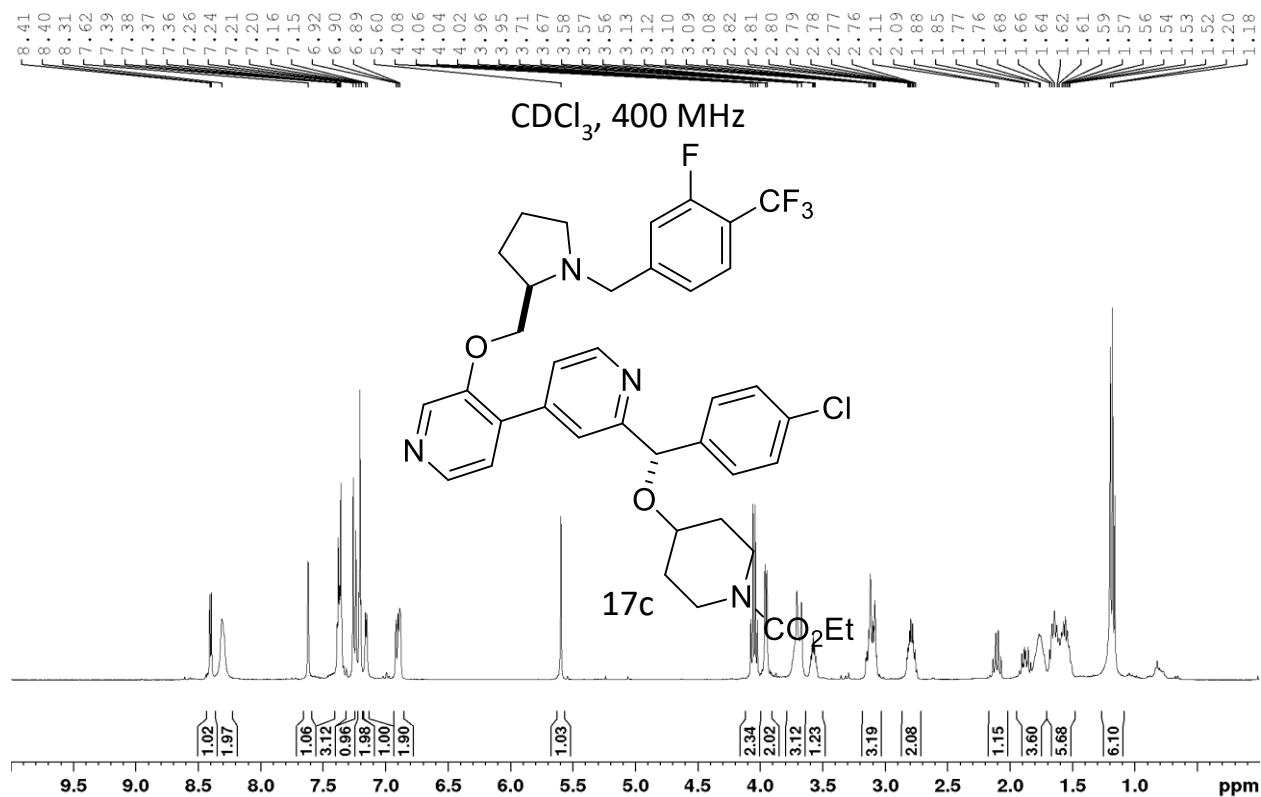


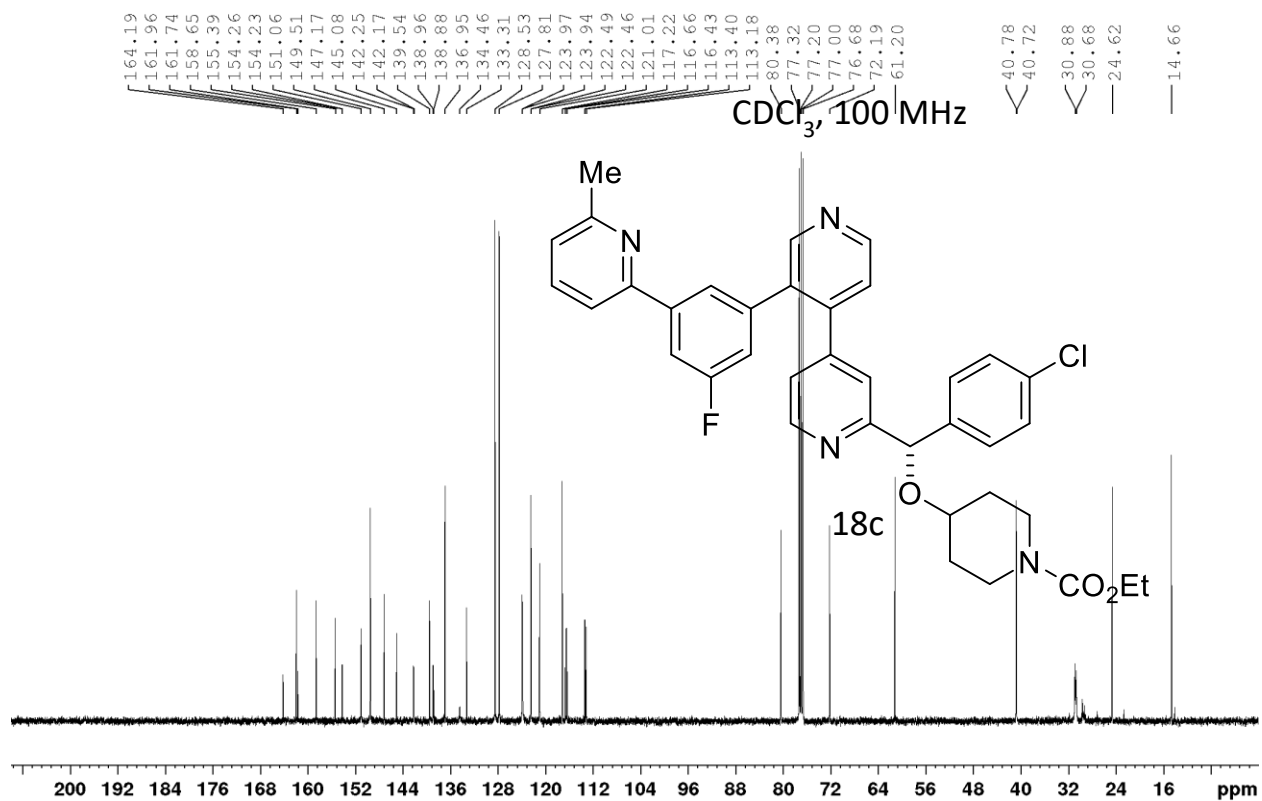
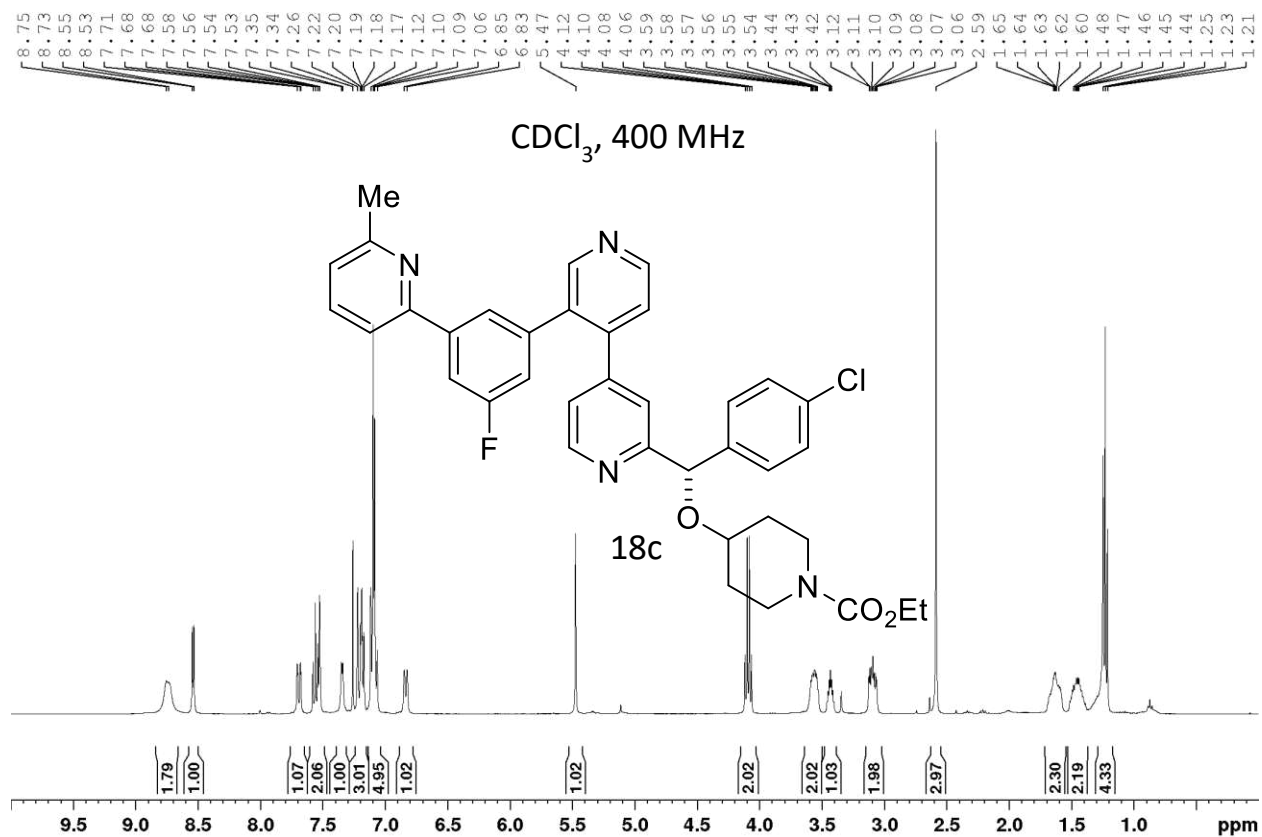


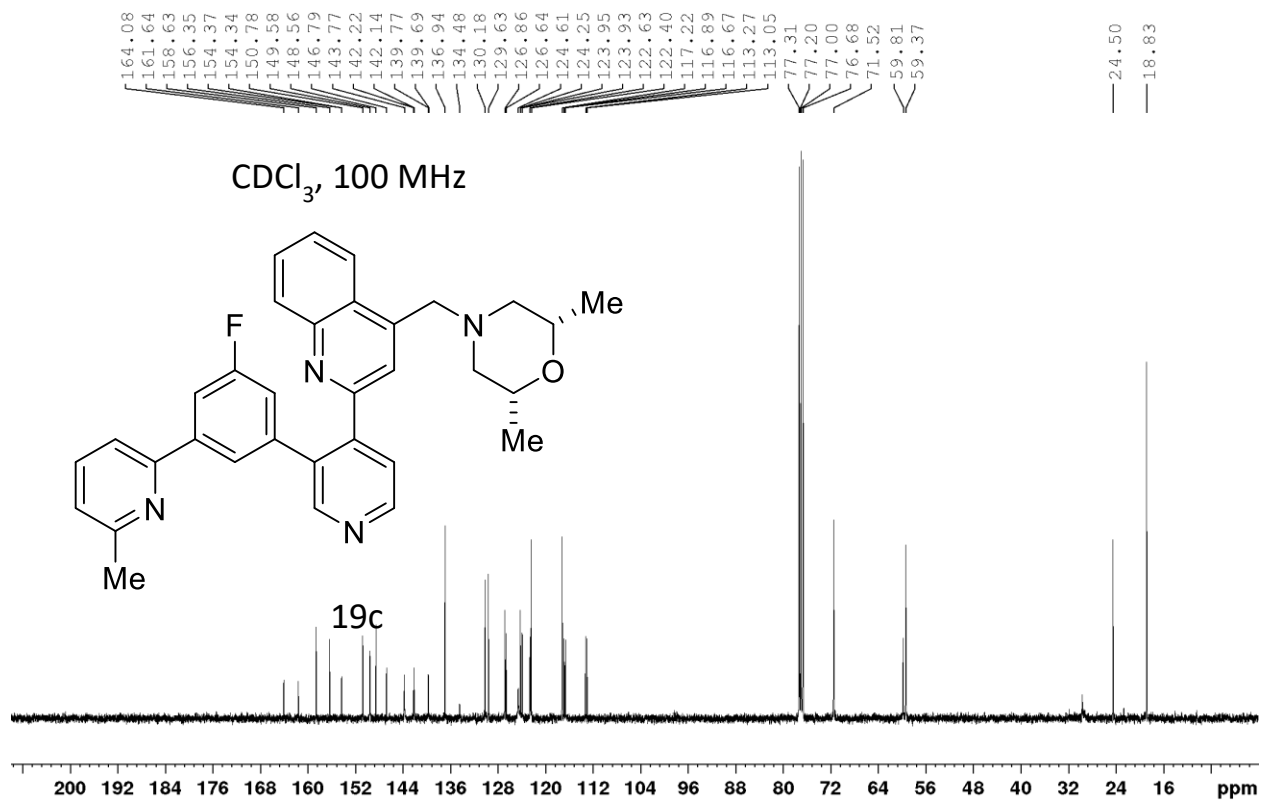
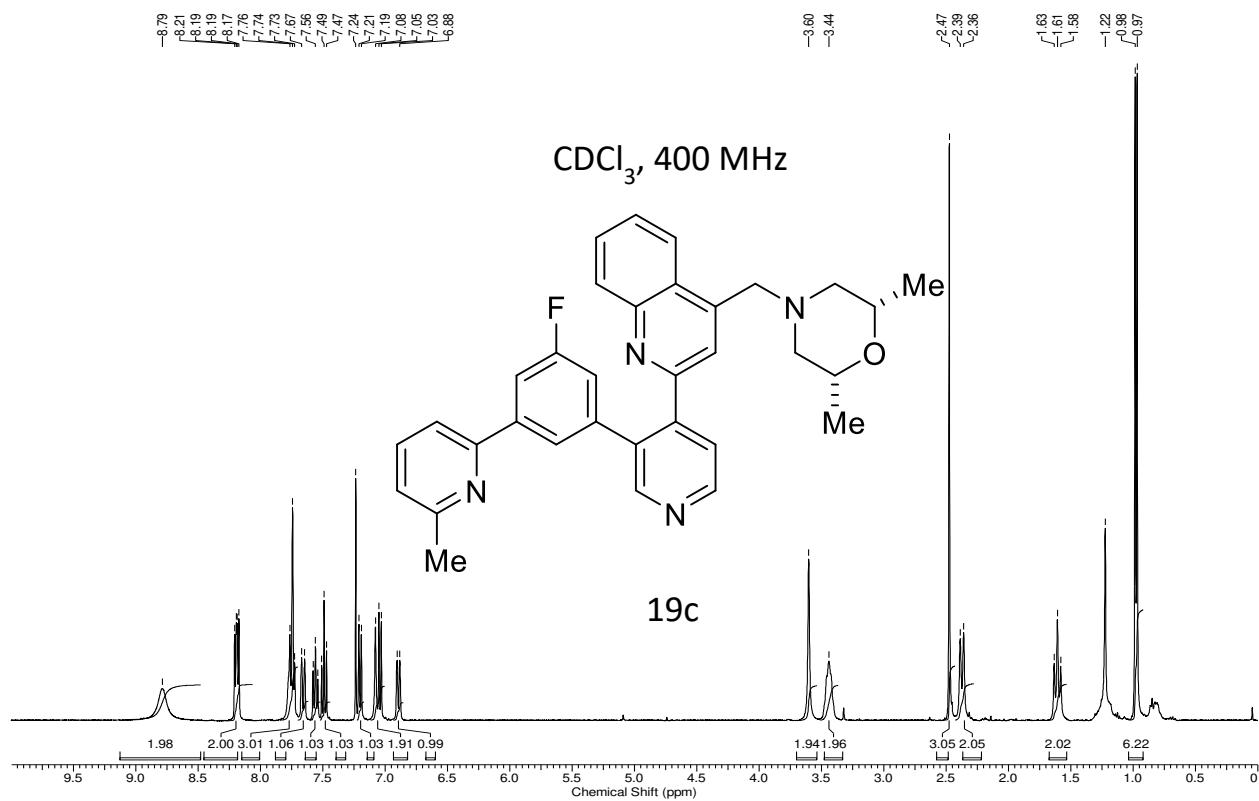


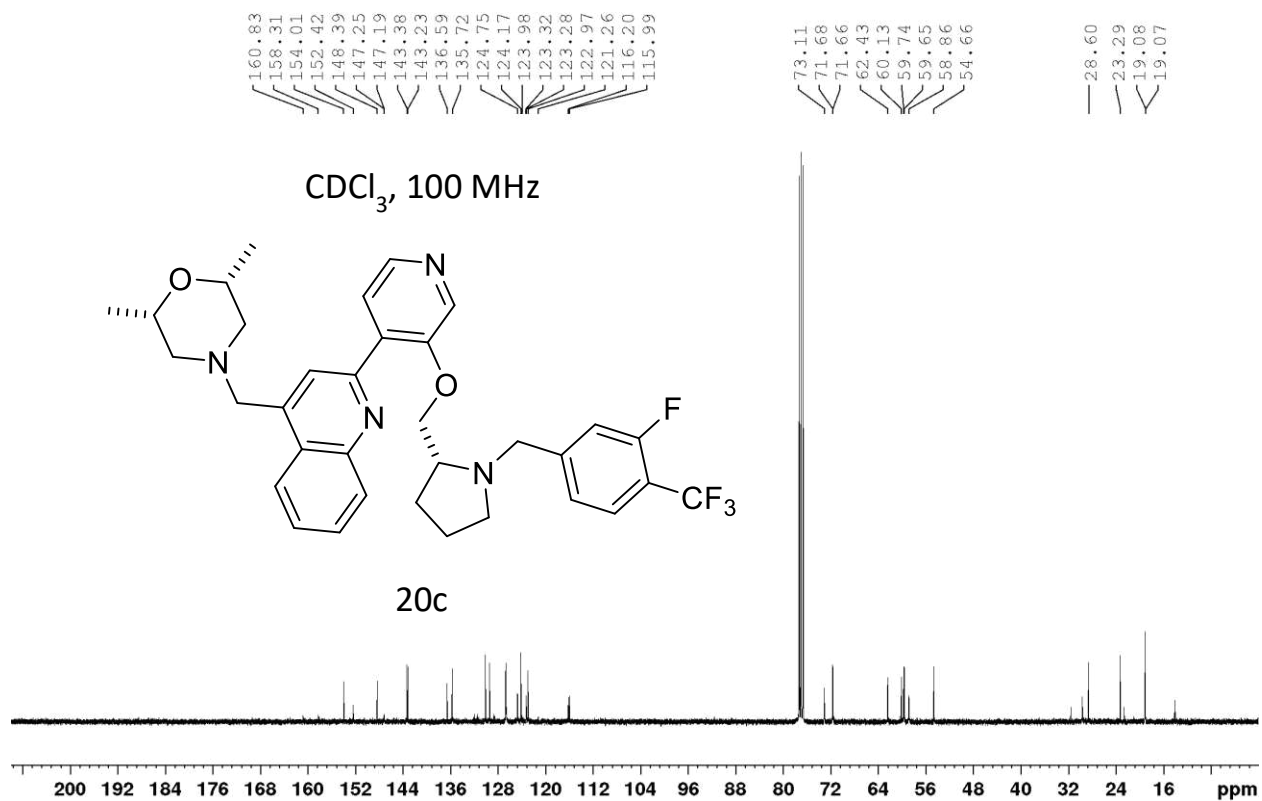
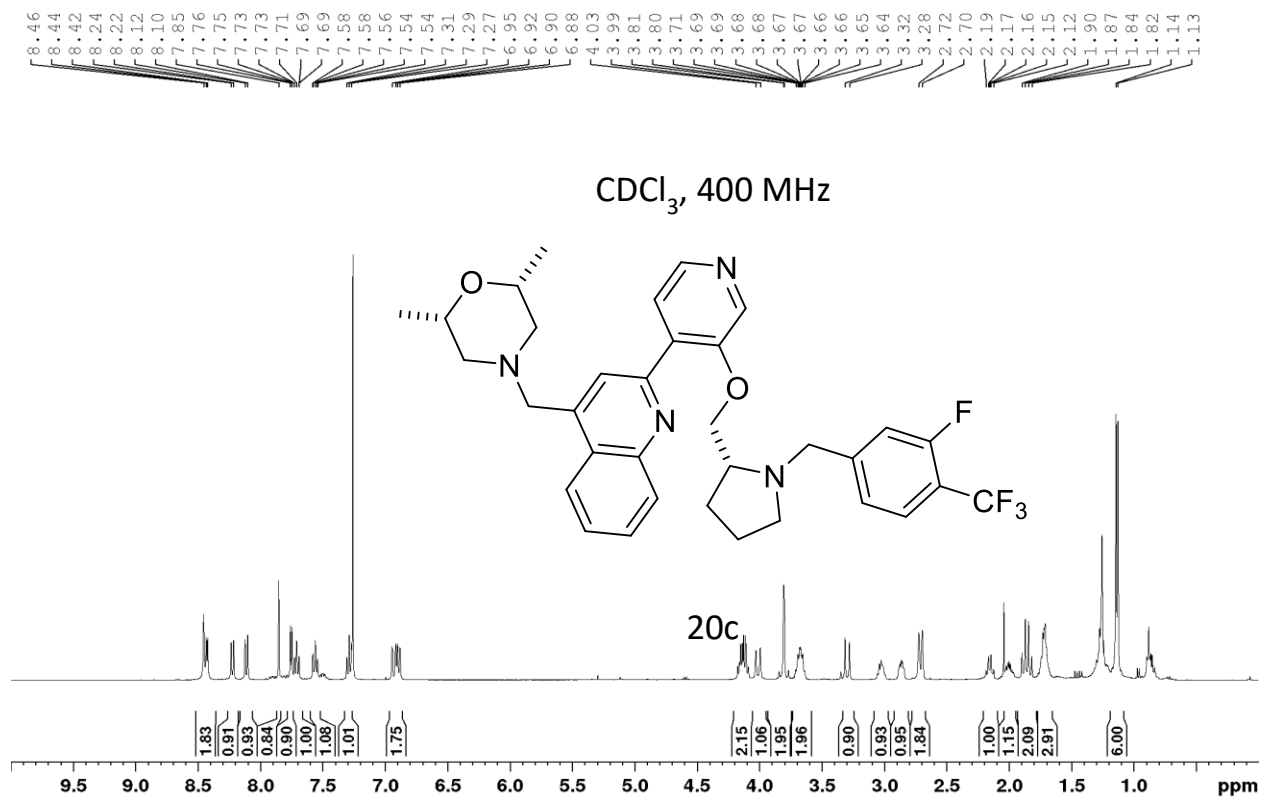


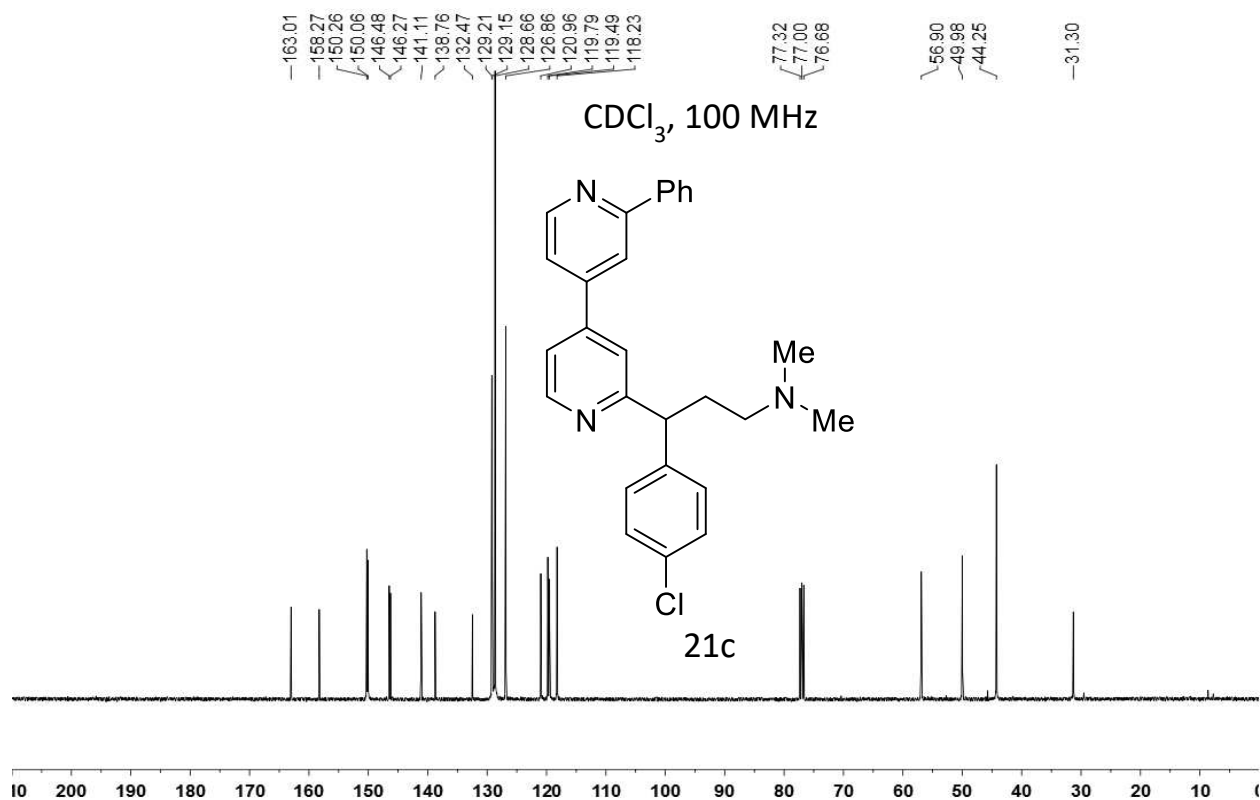
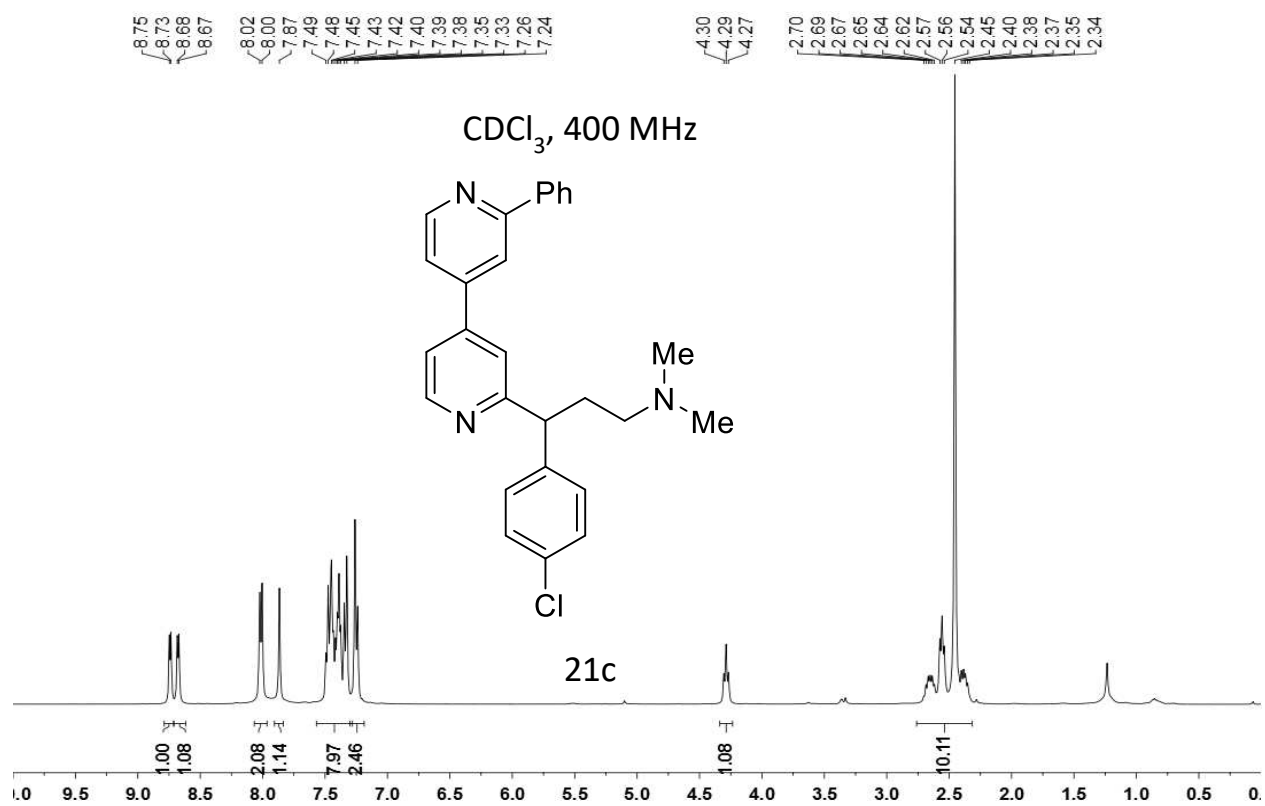


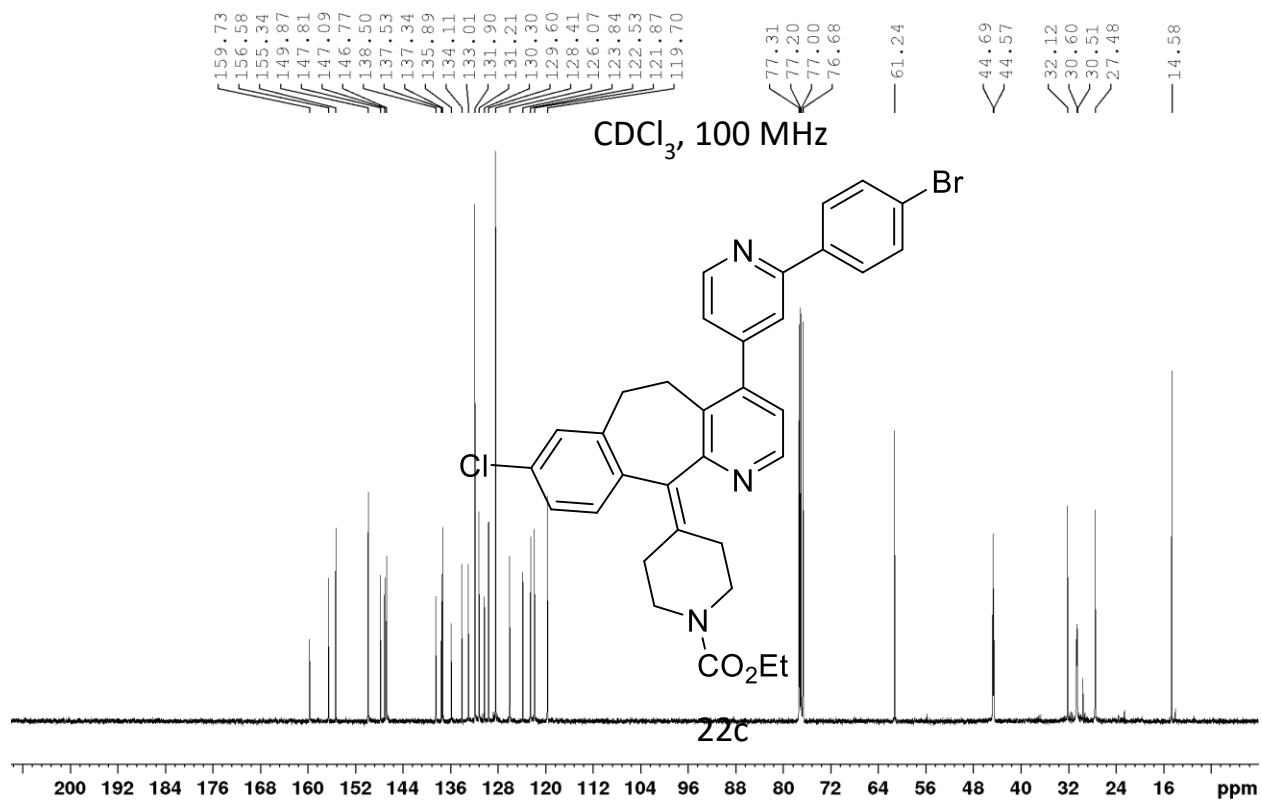
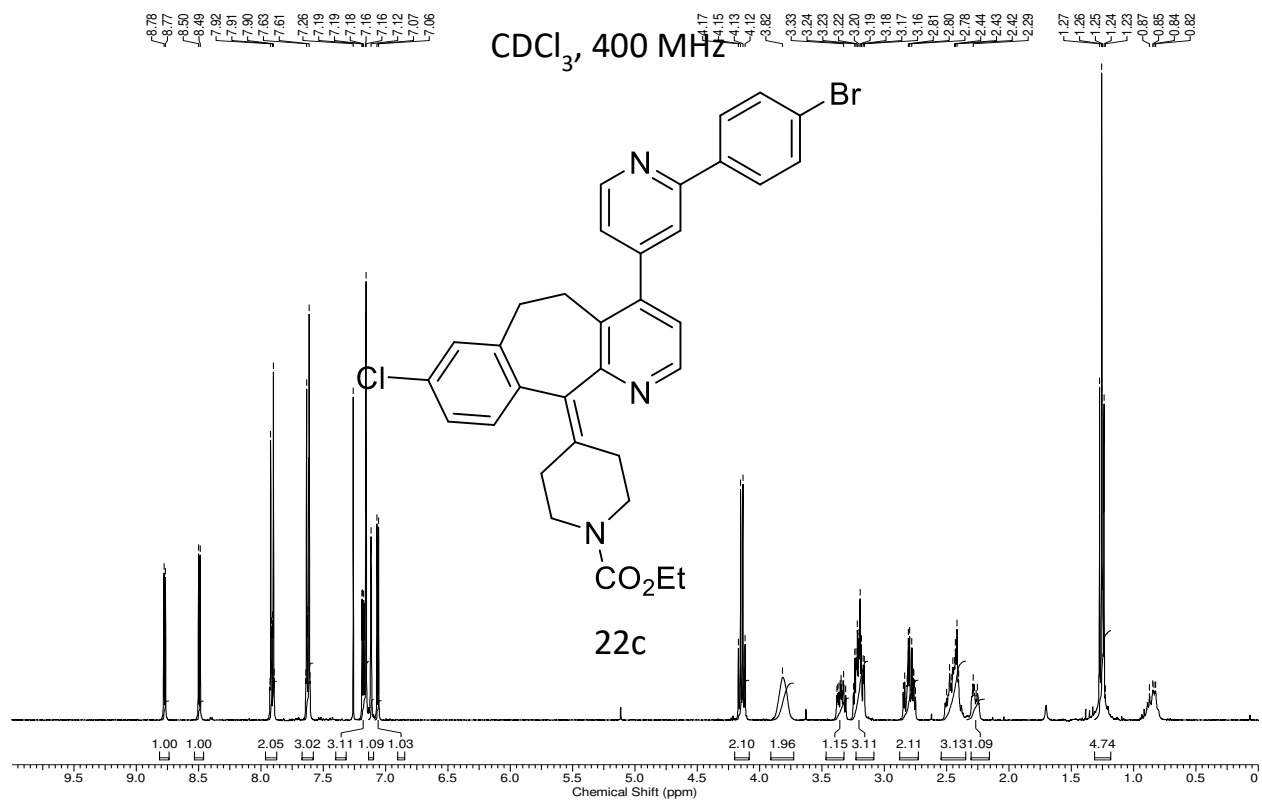


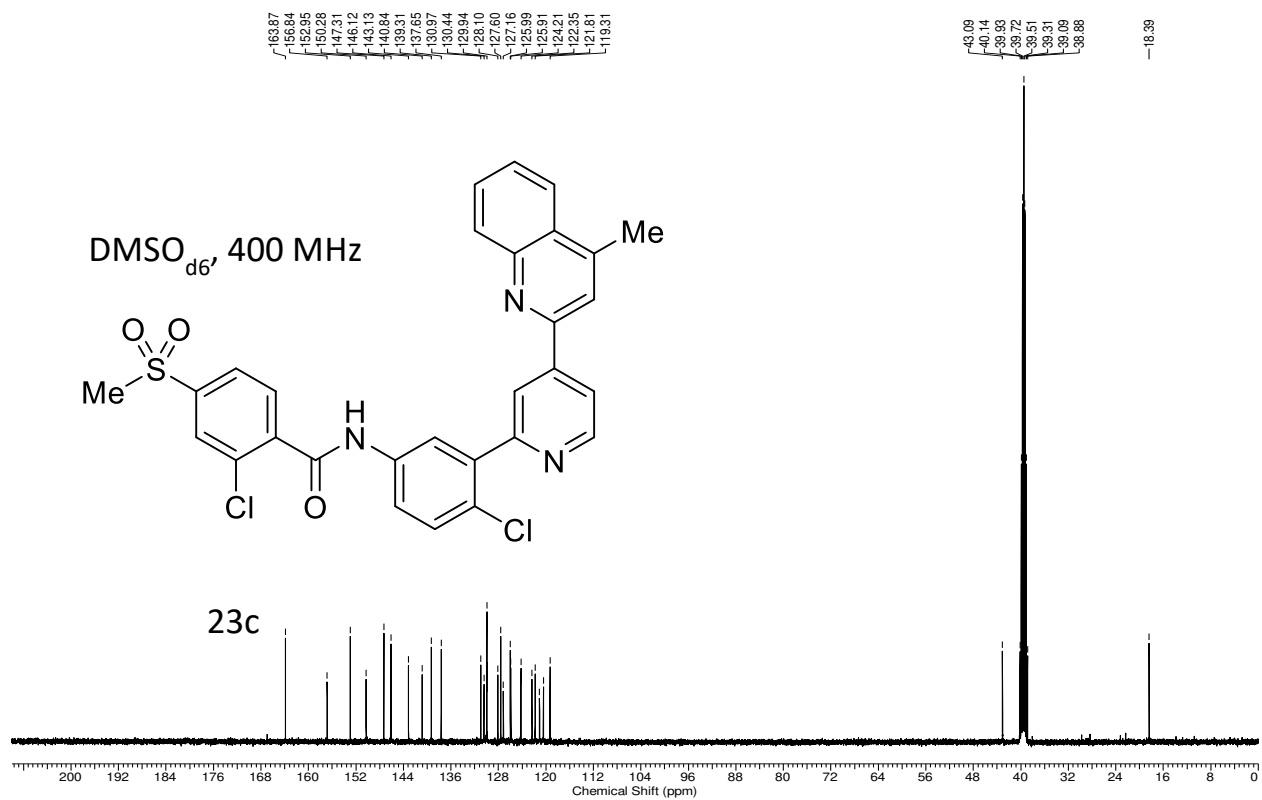
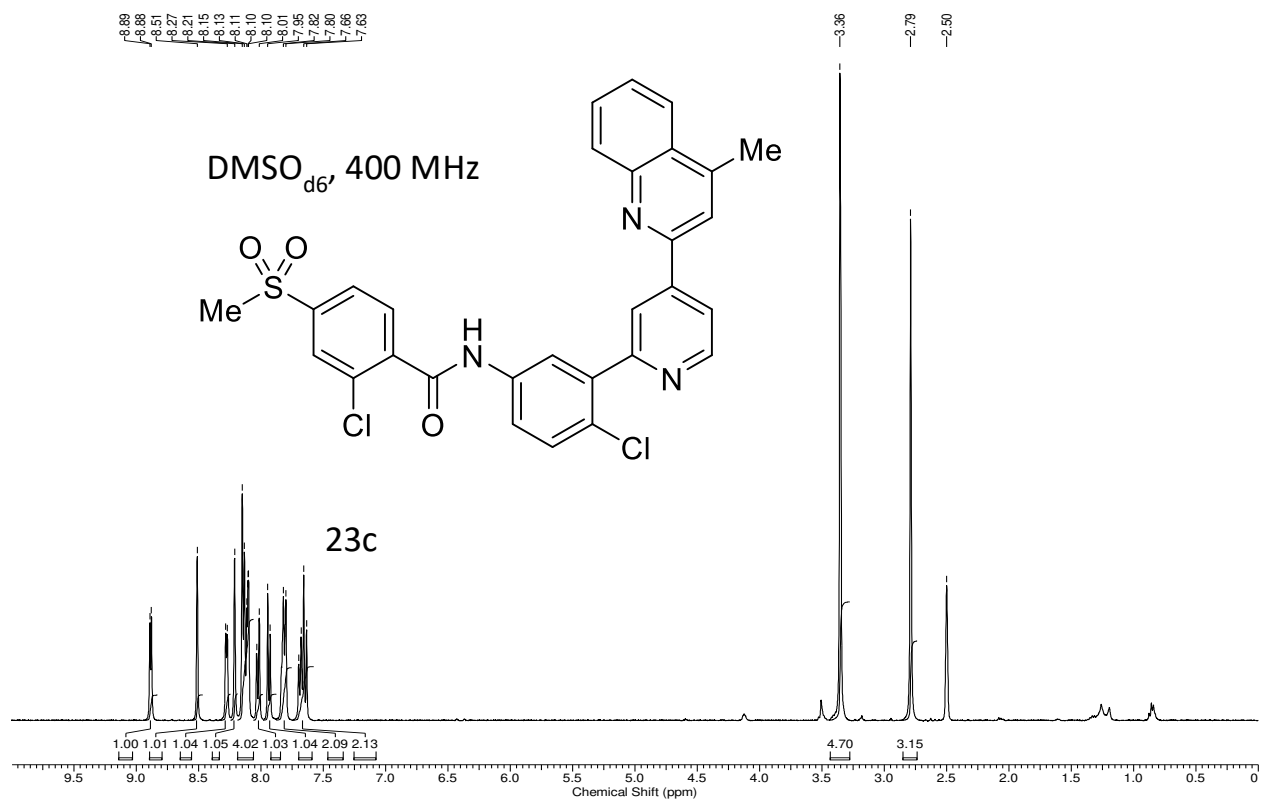


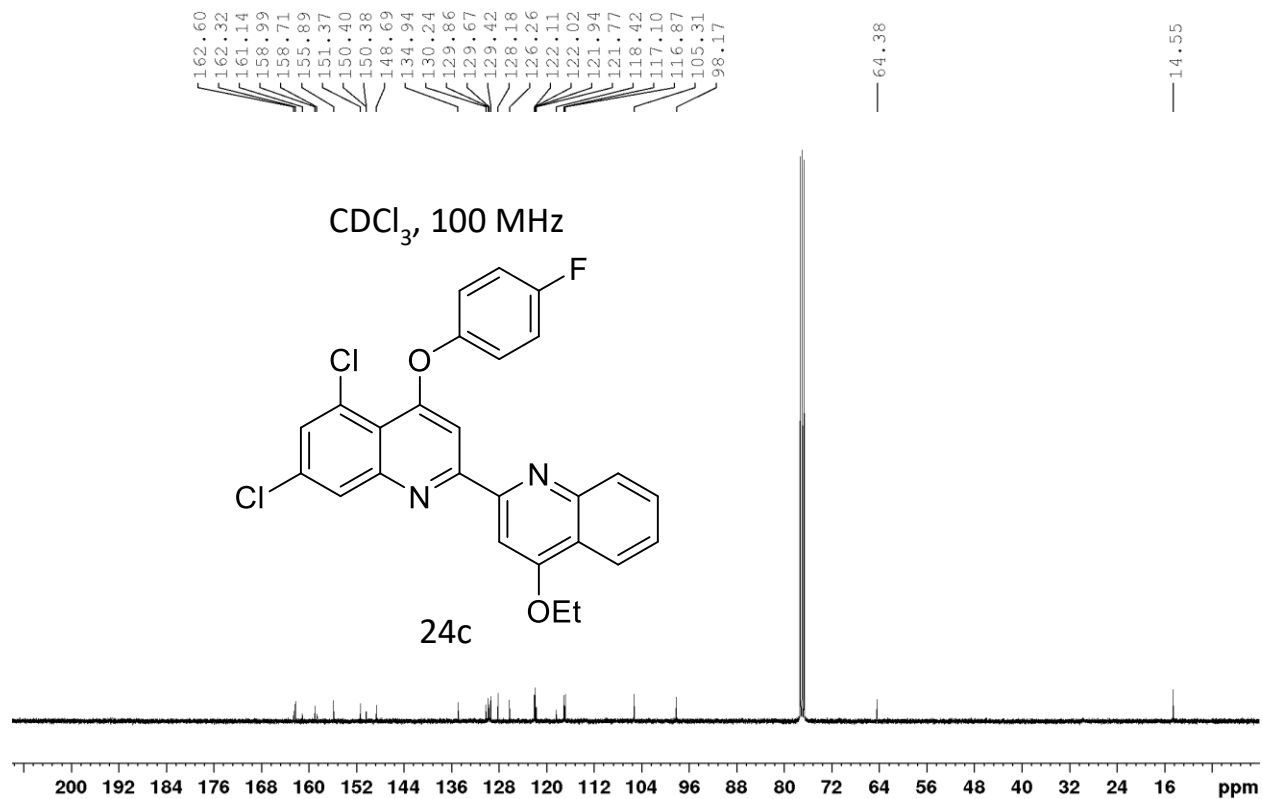
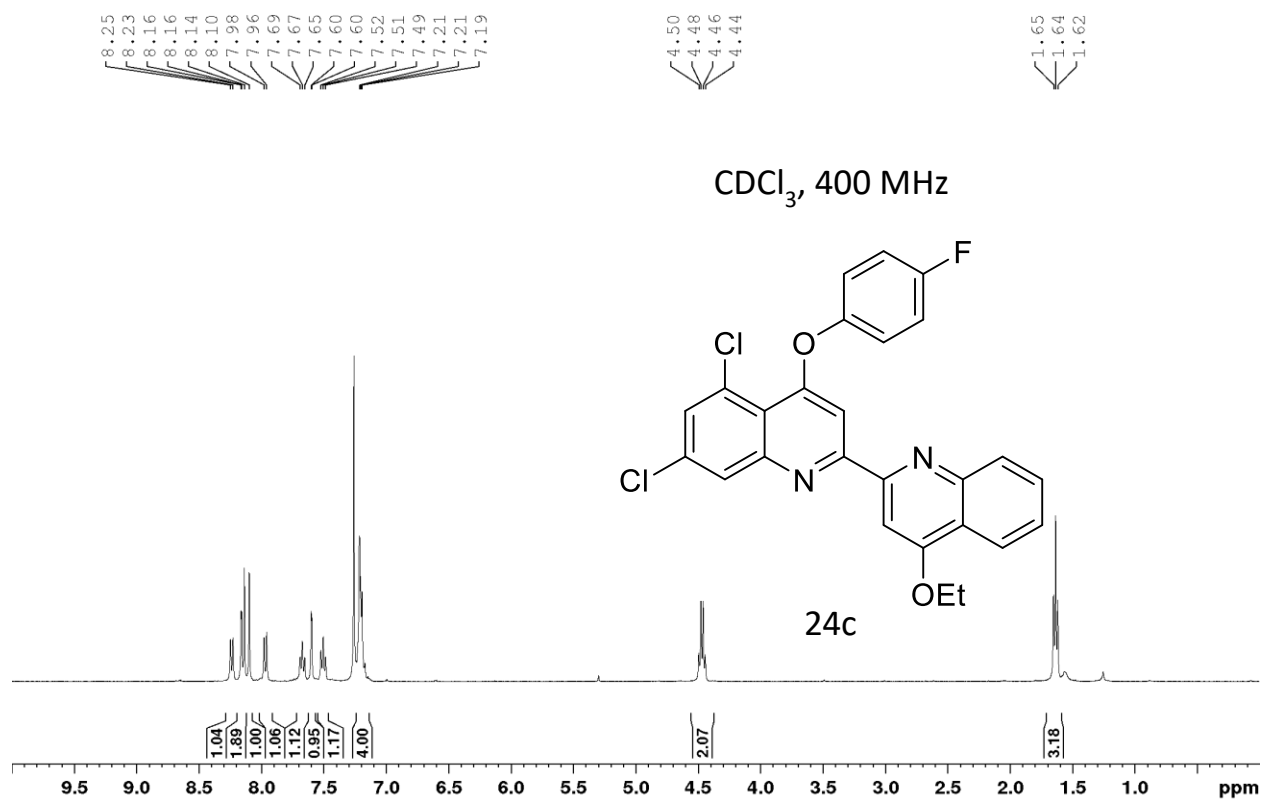


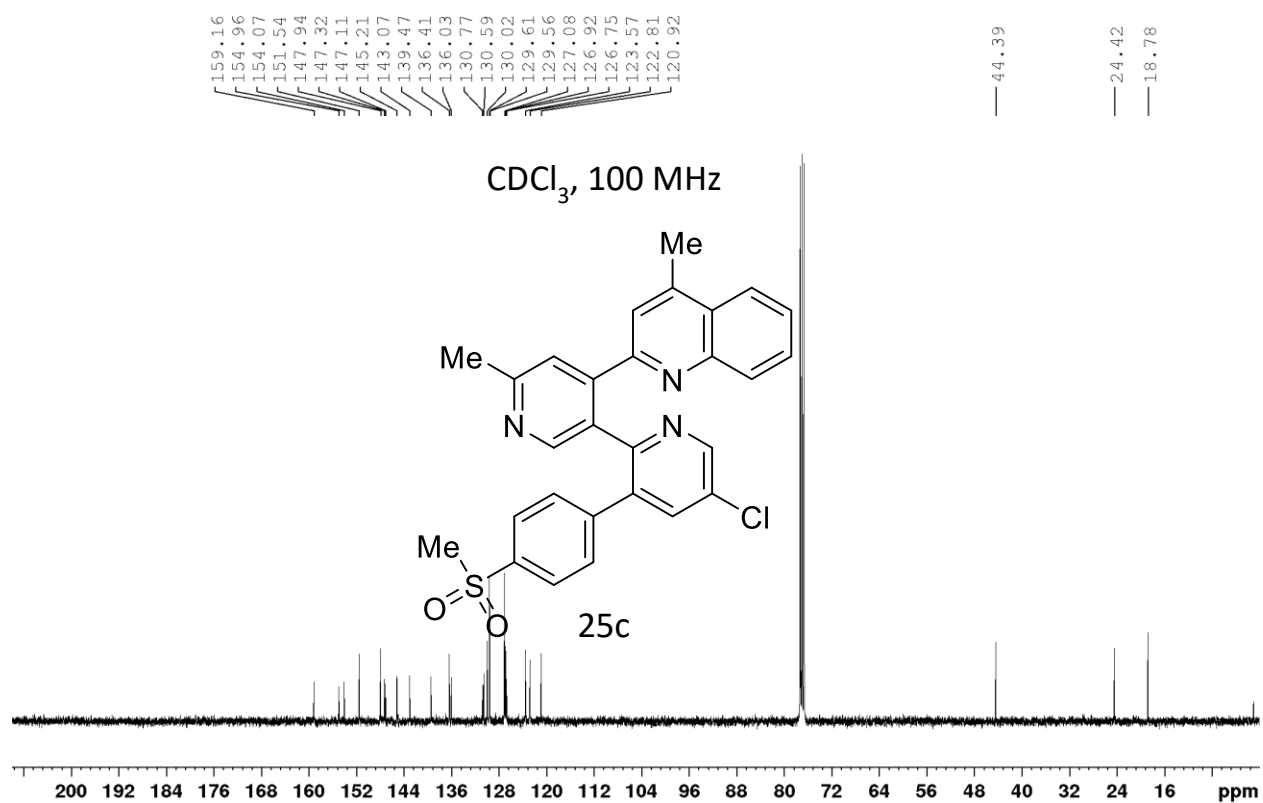
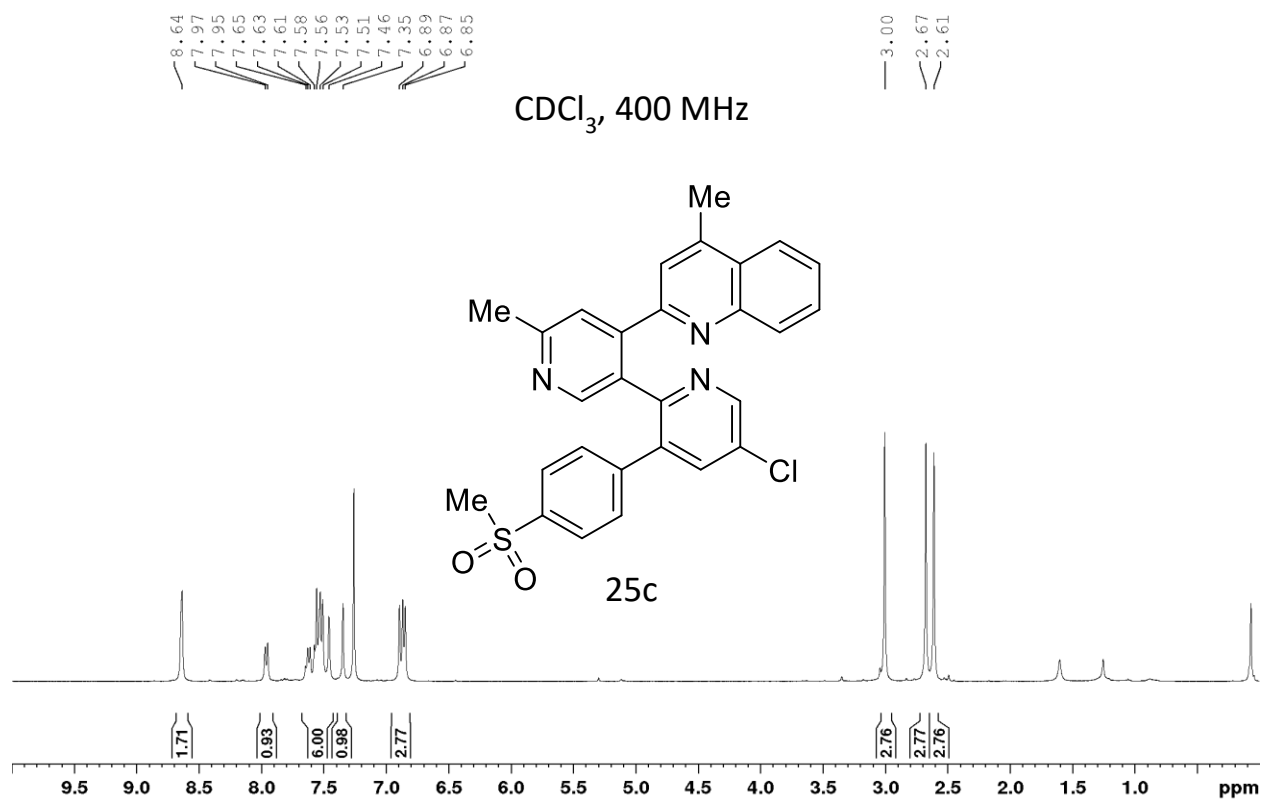


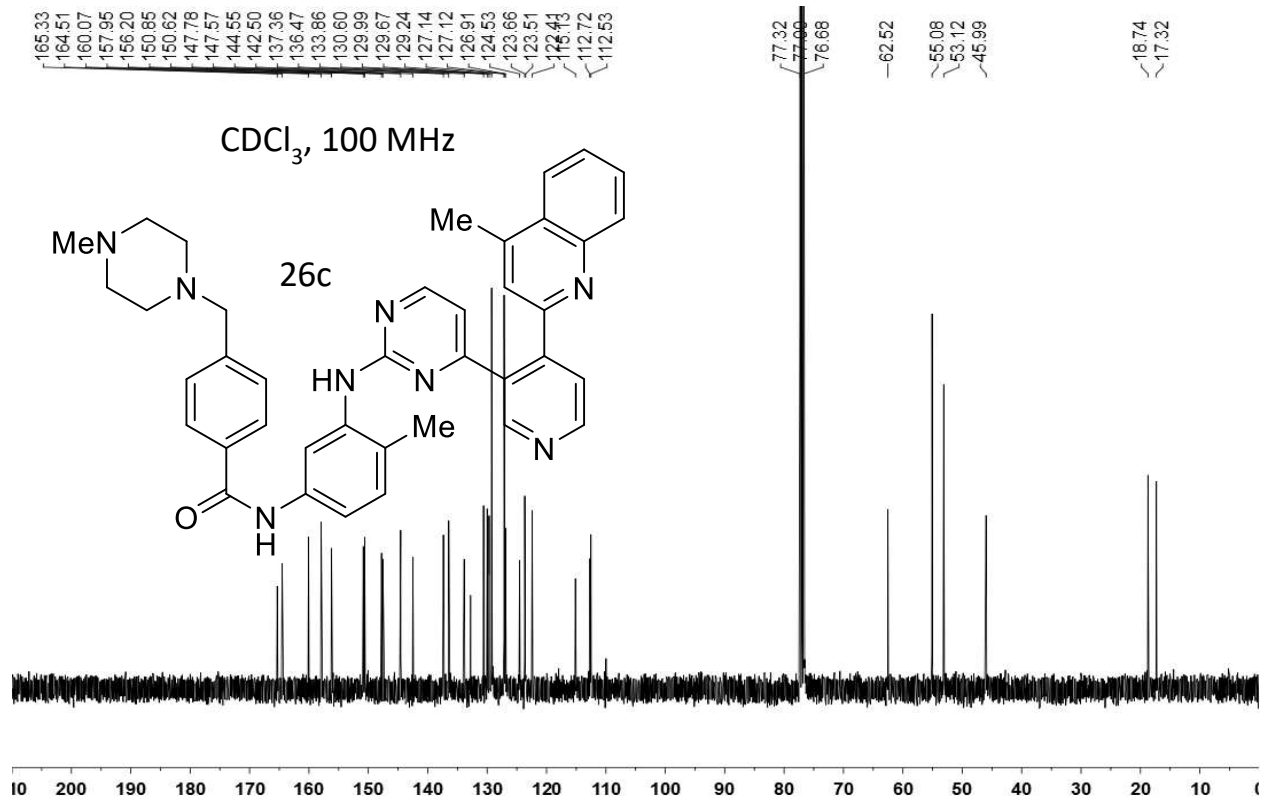
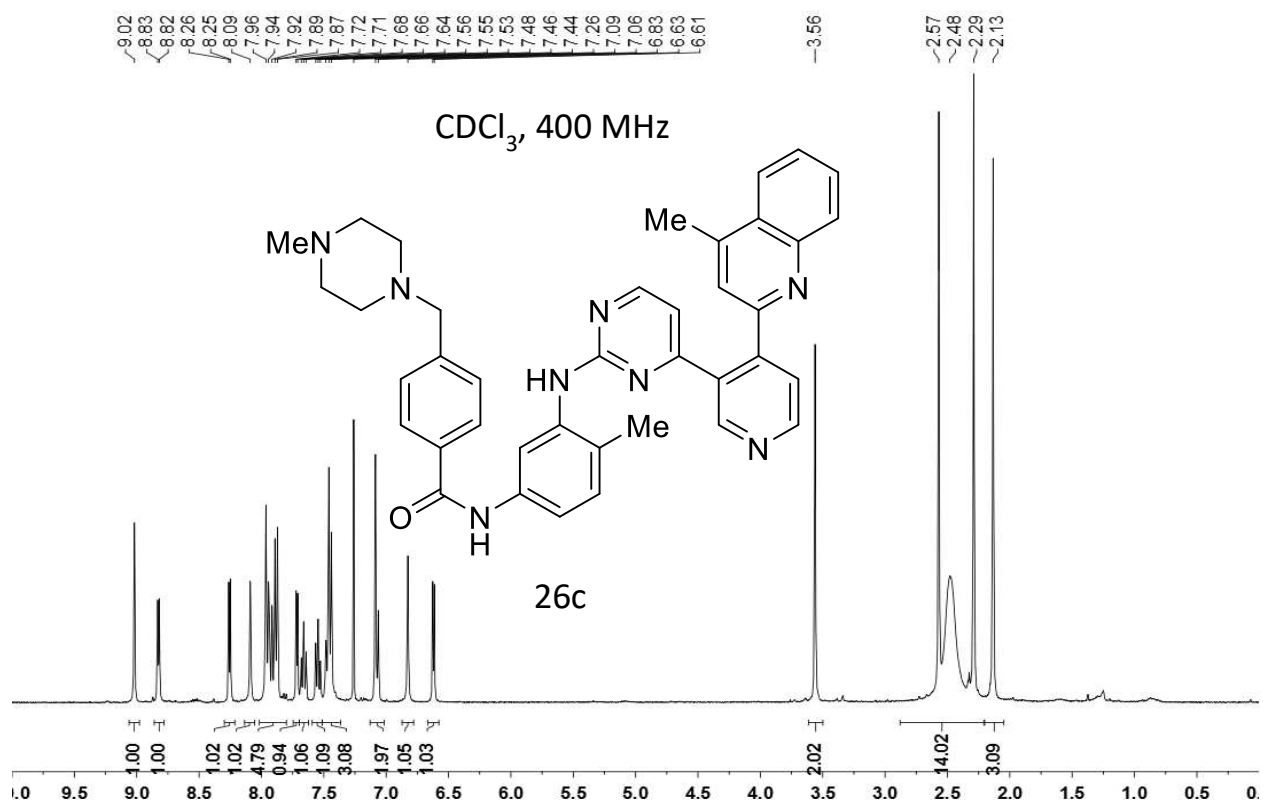












Appendix Two

Bisazine Synthesis from Chloroazines: Experimental

A 2.1 General Methods and Materials

HPPH2 (99%) was purchased from Oakwood Chemicals and stored in a glovebox. (2,2,2)-Trifluoroethanol (TFE) was purchased from Oakwood Chemicals and used without further purification. Anhydrous chlorobenzene (>99.8%) was purchased from Sigma Aldrich chemical company and used without further purification. HCl (4.0 M in dioxanes) and trifluoromethanesulfonic acid (98%) were purchased from Sigma Aldrich chemical company and used without further purification but were routinely stored in a -20 °C fridge. KPF6 (>99%) was purchased from Sigma Aldrich chemical company and used without further purification but was routinely stored in a desiccator. NaOTf was purchased from Oakwood Chemicals and used without further purification but was routinely stored in a desiccator. All reactions were run under a nitrogen atmosphere unless otherwise noted.

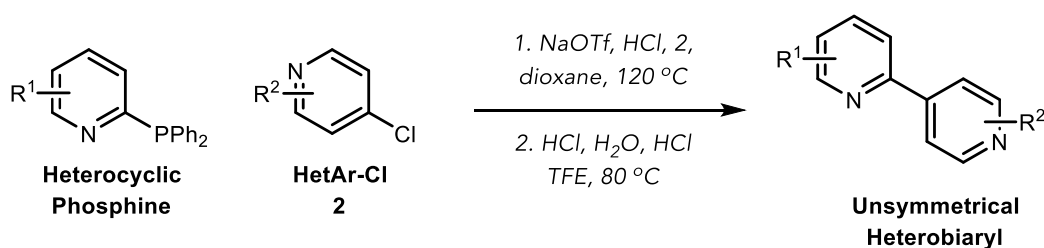
A 2.2 Instrumentation

¹H NMR spectra were recorded using a Varian 400 MR spectrometer, an Agilent Inova 400 spectrometer, an Agilent Inova 500 spectrometer, or a Bruker AV-111 400 spectrometer. The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: CDCl₃ (7.26 ppm), (CD₃)₂SO (2.50 ppm), or CD₃OD (3.31 ppm). Coupling constants (J) were reported in Hertz (Hz) and the multiplicity was reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. ¹³C NMR spectra were recorded using a Bruker Ultrashield-400, a Varian 400 MR or an Agilent Inova 400 spectrometer.

The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: CDCl_3 (77.00 ppm), $(\text{CD}_3)_2\text{SO}$ (39.51 ppm), or CD_3OD (49.00 ppm). Low-resolution mass spectra were recorded on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer with absorptions reported in wavenumbers (cm^{-1}). Melting points were recorded using a Büchi B-450 melting point apparatus.

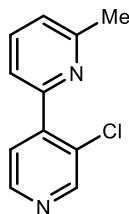
A. 2.3 General Procedures

A. 2.3.1 General Procedure A' (2,4'- or 4,4'-bipyridine synthesis)



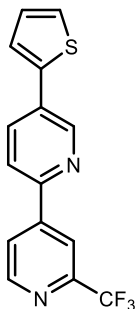
An oven dried 8 mL vial with a septa cap was charged with the heterocyclic phosphine (1.0 equiv), sodium trifluoromethanesulfonate (3.2 equiv) and heteroaryl chloride **2** (1.2 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill and then dioxane (2.0M) and 4.0M HCl in dioxane (1.0 equiv) were added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 120 °C and allowed to stir for the stated time. The reaction was allowed to cool to room temperature before the septa cap was removed and 4.0M HCl in dioxanes (1.0 equiv), H_2O (10 equiv), and TFE (dilute to 0.4M) were quickly added. The reaction vial was heated to 80 °C and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were 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 heterobiaryl.

3'-Chloro-6-methyl-2,4'-bipyridine (1)



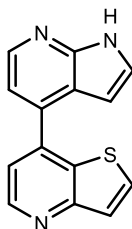
Prepared according to general procedure A' using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 3,4-dichloropyridine (44 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and dioxanes (0.13 mL) at 120 °C for 17 hours; then H₂O (45 μ L, 2.5 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 22 hours. Flash column chromatography (silica gel: 45% EtOAc in hexanes) afforded the title compound as a white crystalline solid (41 mg, 0.20 mmol, 81% yield). mp 59-60 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3063, 3035, 3014, 3002, 2958, 1371, 1248, 980, 750, 742, 613; ¹H NMR (400 MHz, CDCl₃) δ : 8.68 (1H, s), 8.57 (1H, d, J = 5.0 Hz), 7.70 (1H, t, J = 7.8 Hz), 7.57 (1H, d, J = 4.9 Hz), 7.52 (1H, d, J = 7.7 Hz), 7.23 (1H, d, J = 7.7 Hz), 2.64 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 159.1, 153.6, 150.4, 148.2, 146.3, 136.6, 129.9, 125.5, 123.3, 121.7, 24.8; m/z LRMS (ESI + APCI) found [M+H]⁺ 205.1, C₁₁H₁₀ClN₂⁺ requires 205.1.

5-(Thiophen-2-yl)-2'-(trifluoromethyl)-2,4'-bipyridine (2)



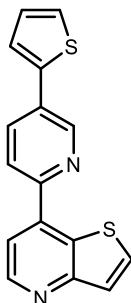
Prepared according to general procedure A' using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 4-chloro-2-(trifluoromethyl)pyridine (31 μ L, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and dioxanes (0.13 mL) at 120 $^{\circ}$ C for 24 hours; then H₂O (45 μ L, 2.5 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and TFE (0.50 mL) at 80 $^{\circ}$ C for 22 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a faint yellow crystalline solid (44 mg, 0.14 mmol, 57% yield). mp 93-94 $^{\circ}$ C; IR ν_{max} /cm⁻¹ (film): 3071, 3046, 2954, 2922, 2851, 1606, 1572, 1471, 958, 856, 749; ¹H NMR (400 MHz, CDCl₃) δ : 9.03 (1H, dd, J = 2.4, 0.9 Hz), 8.84 (1H, d, J = 5.1 Hz), 8.37 (1H, dd, J = 1.7, 0.8 Hz), 8.12 (1H, dd, J = 5.1, 1.7 Hz), 8.03 (1H, dd, J = 8.3, 2.4 Hz), 7.88 (1H, dd, J = 8.3, 0.9 Hz), 7.51-7.41 (2H, m), 7.18 (1H, dd, J = 5.1, 3.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 151.7, 150.9, 149.4 (d, J = 34.54 Hz), 147.8, 147.5, 139.7, 134.1, 131.5, 128.8, 127.2, 125.2, 123.4, 123.3, 121.9 (q, J = 274.34 Hz), 117.9 (d, J = 2.57 Hz); ¹⁹F NMR (365 MHz, CDCl₃) δ : -67.99; m/z LRMS (ESI + APCI) found [M+H]⁺ 307.1, C₁₅H₁₀F₃N₂S⁺ requires 307.1.

7-(1H-pyrrolo[2,3-b]pyridin-4-yl)thieno[3,2-b]pyridine (3)



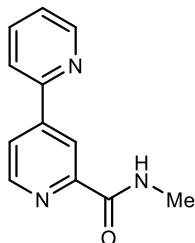
Prepared according to general procedure A' using 4-(diphenylphosphaneyl)-1H-pyrrolo[2,3-b]pyridine (76 mg, 0.25 mmol), 7-chlorothieno[3,2-b]pyridine (51 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and dioxanes (0.13 mL) at 120 $^{\circ}$ C for 18.5 hours; then H₂O (45 μ L, 2.5 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and TFE (0.50 mL) at 80 $^{\circ}$ C for 24 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a white crystalline solid (37 mg, 0.15 mmol, 58% yield). mp 250-251 $^{\circ}$ C; IR ν_{max} /cm⁻¹ (film): 3122, 2996, 2924, 2860, 2762, 2710, 2215, 2041, 1557, 1541, 1325; ¹H NMR (400 MHz, CDCl₃) δ : 9.79 (1H, s), 8.85 (1H, d, *J* = 4.8 Hz), 8.50 (1H, d, *J* = 5.0 Hz), 7.81 (1H, d, *J* = 5.6 Hz), 7.68 (1H, d, *J* = 5.6 Hz), 7.52 (1H, d, *J* = 4.7 Hz), 7.50-7.42 (2H, m), 6.55 (1H, dd, *J* = 3.6, 2.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 157.4, 149.5, 147.8, 143.4, 141.8, 138.5, 132.3, 131.3, 126.0, 125.7, 118.8, 118.3, 115.2, 100.7; *m/z* LRMS (ESI + APCI) found [M+H]⁺ 252.1, C₁₄H₁₀N₃S⁺ requires 252.1.

7-(5-(Thiophen-2-yl)pyridin-2-yl)thieno[3,2-b]pyridine (4)



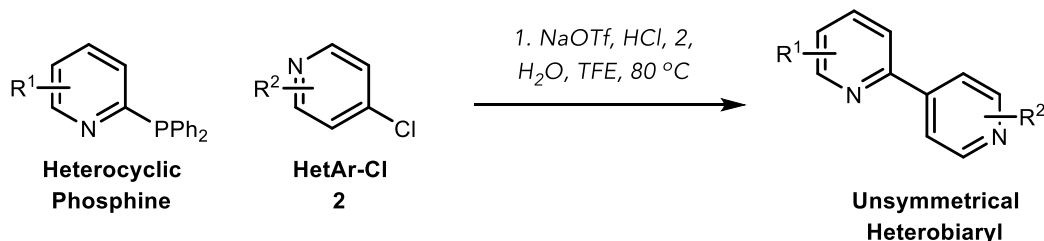
Prepared according to general procedure A' using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 7-chlorothieno[3,2-b]pyridine (51 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and dioxanes (0.13 mL) at 120 $^{\circ}$ C for 12 hours; then H₂O (45 μ L, 2.5 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and TFE (0.50 mL) at 80 $^{\circ}$ C for 22 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a bright yellow crystalline solid (55 mg, 0.19 mmol, 75% yield). mp 129-130 $^{\circ}$ C; IR ν_{max} /cm⁻¹ (film): 3089, 3063, 3041, 3004, 2975, 2923, 2852, 2520, 2157, 1555, 1389, 1139, 1026, 832, 674; ¹H NMR (400 MHz, CDCl₃) δ : 9.15 (1H, dd, J = 2.1, 1.1 Hz), 8.83 (1H, d, J = 4.9 Hz), 8.12-8.02 (2H, m), 7.90 (1H, d, J = 5.7 Hz), 7.76 (1H, d, J = 4.9 Hz), 7.64 (1H, d, J = 5.7 Hz), 7.50 (1H, dd, J = 3.6, 1.1 Hz), 7.43 (1H, dd, J = 5.0 Hz), 7.18 (1H, dd, J = 5.1, 3.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 158.4, 152.5, 147.5, 146.0, 140.0, 139.9, 134.6, 133.7, 130.5, 129.8, 128.7, 126.8, 124.9, 124.8, 121.2, 115.0; m/z LRMS (ESI + APCI) found [M+H]⁺ 295.1, C₁₆H₁₁N₂S₂⁺ requires 295.0.

N-methyl-[2,4'-bipyridine]-2'-carboxamide (5)



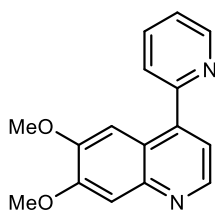
Prepared according to general procedure A' except with additional 4.0M HCl in dioxanes (1.2 equiv.) using 2-(diphenylphosphaneyl)pyridine (66 mg, 0.25 mmol), 4-chloro-N-methylpicolinamide (51 mg, 0.30 mmol), sodium trifluoromethanesulfonate (138 mg, 0.80 mmol), 4.0M HCl in dioxanes (75 μ L, 0.3 mmol), and dioxanes (0.13 mL) at 120 $^{\circ}$ C for 22 hours; then H₂O (45 μ L, 2.5 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and TFE (0.50 mL) at 80 $^{\circ}$ C for 25.5 hours. Flash column chromatography (silica gel: 70% EtOAc in hexanes) afforded the title compound as a colorless oil (42 mg, 0.20 mmol, 79% yield). IR ν_{max} /cm⁻¹ (film): 3404, 3053, 2926, 1670, 1603, 1587, 1533, 1461, 1433, 1412, 1265, 735; ¹H NMR (400 MHz, CDCl₃) δ : 8.73 (1H, d, *J* = 4.9 Hz), 8.69 (1H, d, *J* = 1.8 Hz), 8.63 (1H, d, *J* = 5.1 Hz), 8.16 (1H, dd, *J* = 5.1, 1.9 Hz), 8.08 (1H, br s), 7.91 (1H, d, *J* = 7.9 Hz), 7.86–7.77 (1H, m), 7.34 (1H, ddd, *J* = 7.5, 4.8, 1.1 Hz), 3.05 (3H, d, *J* = 5.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 164.9, 153.9, 150.6, 150.1, 148.8, 147.9, 137.1, 124.1, 123.5, 121.1, 119.2, 26.1; *m/z* LRMS (ESI + APCI) found [M+H]⁺ 214.1, C₁₂H₁₂N₃O⁺ requires 214.1.

A. 2.3.2 General Procedure B' (Couplings involving quinolines/diazines)



An oven dried 8 mL vial with a septa cap was charged with the heterocyclic phosphine (1.0 equiv), sodium trifluoromethanesulfonate (2.2 equiv) and heteroaryl chloride **2** (1.2 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill and then TFE (0.4M), H₂O (10 equiv), and HCl (1.2 equiv) were added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 80 °C and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na₂CO₃ and the aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl.

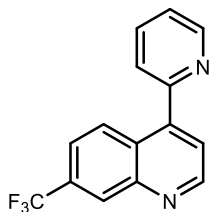
6,7-Dimethoxy-4-(pyridin-2-yl)quinoline (**6**)



Prepared according to general procedure B' using 2-(diphenylphosphaneyl)pyridine (66 mg, 0.25 mmol), 4-chloro-6,7-dimethoxyquinoline (67 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), and TFE (0.63 mL) at 80 °C for 18.5 hours; then H₂O (45 μL, 2.5 mmol) and 4.0M HCl (75 μL, 0.3 mmol) at 80 °C for 21 hours. Flash column chromatography (neutral

alumina, gradient elution: 50% EtOAc in hexanes to 80% EtOAc in hexanes) afforded the title compound as an off-white powder (39 mg, 0.14 mmol, 58% yield). mp 62-65 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3018, 2922, 2851, 1504, 1490, 1473, 1432, 1421, 1351, 1244, 1217, 1126, 1013, 847, 795; ^1H NMR (400 MHz, CDCl_3) δ : 8.81 (1H, d, J = 4.8 Hz), 8.78 (1H, d, J = 4.6 Hz), 7.87 (1H, td, J = 7.7, 1.8 Hz), 7.62 (1H, d, J = 7.8 Hz), 7.54-7.46 (2H, m), 7.39 (1H, ddd, J = 7.7, 4.9, 0.9 Hz), 7.34 (1H, d, J = 4.6 Hz), 4.04 (3H, s) 3.88 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 157.5, 152.4, 150.2, 149.8, 147.8, 146.4, 144.3, 137.0, 124.7, 123.1, 121.6, 120.0, 108.4, 103.4, 56.2, 56.0; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 267.1, $\text{C}_{16}\text{H}_{15}\text{N}_2\text{O}_2^+$ requires 267.1.

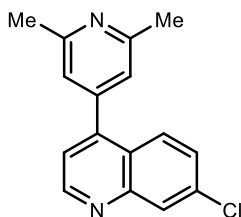
4-(Pyridin-2-yl)-7-(trifluoromethyl)quinoline (7)



Prepared according to general procedure B' using 2-(diphenylphosphaneyl)pyridine (63 mg, 0.25 mmol), 4-chloro-7-(trifluoromethyl)quinoline (69 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL , 0.30 mmol), H_2O (45 μL , 2.5 mmol), and TFE (0.63 mL) at 80 °C for 17 hours. Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a white crystalline solid (55 mg, 0.20 mmol, 81% yield). mp 77-79 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3053, 3024, 2957, 2925, 2852, 1183, 973, 646, 601, 547; ^1H NMR (400 MHz, CDCl_3) δ : 9.10 (1H, d, J = 4.4 Hz), 8.85 (1H, d, J = 4.5 Hz), 8.59 (1H, s), 8.32 (1H, d, J = 8.9), 7.92 (1H, td, J = 7.7, 1.8 Hz), 7.72 (1H, dd, J = 8.4, 1.9 Hz),

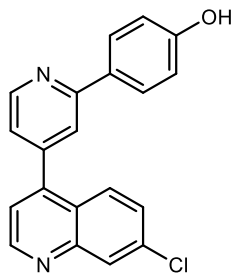
7.68-7.60 (2H, m), 7.50-7.55 (1H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 156.1, 151.5, 150.2, 148.2, 146.3, 131.3 (d, $J = 32.7$ Hz), 129.5 (q, $J = 274.6$ Hz), 128.0-127.7 (2C, m), 127.4, 125.4, 124.9, 123.6, 123.1, 122.9-122.6 (m); ^{19}F NMR (365 MHz, CDCl_3) δ : -62.83; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 275.1, $\text{C}_{15}\text{H}_{10}\text{F}_3\text{N}_2^+$ requires 275.1.

7-Chloro-4-(2,6-dimethylpyridin-4-yl)quinoline (8)



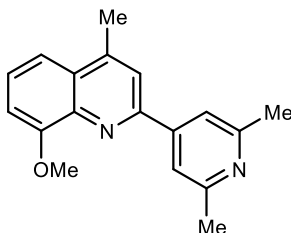
Prepared according to general procedure B' using 4-(diphenylphosphaneyl)-2,6-dimethylpyridine (73 mg, 0.25 mmol), 4,7-dichloroquinoline (60 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μL , 0.30 mmol), H_2O (45 μL , 2.5 mmol), and TFE (0.63 mL) at 80 $^\circ\text{C}$ for 14 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a white crystalline solid (46 mg, 0.17 mmol, 69% yield). mp 88-90 $^\circ\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3361, 3087, 3040, 3026, 2961, 2857, 1551, 1349, 822, 735, 656, 591; ^1H NMR (400 MHz, CDCl_3) δ : 8.96 (1H, s), 8.19 (1H, d, $J = 2.1$ Hz), 7.77 (1H, d, $J = 9.0$ Hz), 7.49 (1H, dd, $J = 9.0, 2.2$ Hz), 7.30 (1H, d, $J = 4.4$ Hz), 7.07 (2H, s), 2.64 (6H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 158.5, 151.1, 149.2, 146.5, 146.1, 135.8, 129.1, 128.2, 126.9, 124.6, 121.1, 120.8, 24.7; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 269.1, $\text{C}_{16}\text{H}_{14}\text{ClN}_2^+$ requires 269.1.

4-(4-(7-Chloroquinolin-4-yl)pyridin-2-yl)phenol (9)



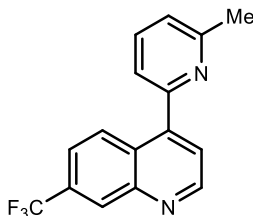
Prepared according to general procedure B' using 4-(4-(diphenylphosphaneyl)pyridin-2-yl)phenol (71 mg, 0.20 mmol), 4,7-dichloroquinoline (48 mg, 0.24 mmol), sodium trifluoromethanesulfonate (76 mg, 0.44 mmol), 4.0M HCl in dioxanes (60 μ L, 0.24 mmol), H₂O (36 μ L, 2.0 mmol), and TFE (0.5 mL) at 80 °C for 44.5 hours. Flash column chromatography (silica gel: 60% EtOAc in hexanes) afforded the title compound as an off-white powder (50 mg, 0.15 mmol, 75% yield). mp 258-260 °C; IR ν_{max} /cm⁻¹ (film): 3033, 2921, 2850, 1608, 1580, 1539, 1520, 1451, 1419, 1382, 1274, 1240, 1179, 878, 833, 822; ¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.78 (1H, s), 9.04 (1H, d, *J* = 4.4 Hz), 8.77 (1H, dd, *J* = 4.9, 0.8 Hz), 8.20 (1H, d, *J* = 2.2 Hz), 8.07–8.00 (2H, m), 7.98 (1H, s), 7.89 (1H, d, *J* = 9.0 Hz), 7.71–7.57 (2H, m), 7.42 (1H, dd, *J* = 4.9, 1.5 Hz), 6.87 (2H, d, *J* = 8.7 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 158.8, 156.8, 151.5, 149.7, 148.4, 145.5, 145.4, 134.4, 129.2, 128.3, 128.1, 128.0, 127.3, 124.0, 121.8, 119.4, 115.5; *m/z* LRMS (ESI + APCI) found [M+H]⁺ 333.1, C₂₀H₁₄ClN₂O⁺ requires 333.1.

2-(2,6-Dimethylpyridin-4-yl)-8-methoxy-4-methylquinoline (10)



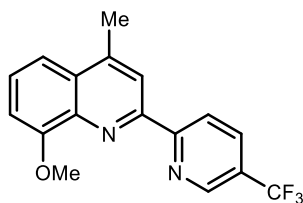
Prepared according to general procedure B' using 4-(diphenylphosphaneyl)-2,6-dimethylpyridine (73 mg, 0.25 mmol), 2-chloro-8-methoxy-4-methylquinoline (62 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μ L, 0.30 mmol), H₂O (45 μ L, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 25.5 hours. Flash column chromatography (silica gel: 20% EtOAc in hexanes) followed by a second flash column (silica gel, gradient elution: 1% MeOH and 1% acetic acid in CH₂Cl₂ to 5% MeOH and 1% acetic acid in CH₂Cl₂) and then dilution with a saturated aqueous solution of Na₂CO₃ and extraction with CH₂Cl₂ (3x) afforded the title compound as a tan powder (43 mg, 0.15 mmol, 61% yield). mp 148-150 °C; IR ν_{max} /cm⁻¹ (film): 3056, 2920, 2851, 1602, 1588, 1573, 1546, 1510, 1471, 1459, 1418, 1389, 1260, 1207, 1154, 1106, 852, 804; ¹H NMR (400 MHz, CDCl₃) δ : 7.77-7.70 (3H, m), 7.57 (1H, dd, *J* = 8.5, 1.1 Hz), 7.50 (1H, t, *J* = 7.7 Hz), 7.08 (1H, dd, *J* = 7.6, 0.8 Hz), 4.10 (3H, s), 2.75 (3H, d, 0.6 Hz), 2.63 (6H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 158.5, 156.1, 153.7, 147.5, 145.5, 140.1, 129.1, 127.1, 120.2, 118.5, 115.6, 108.0, 56.3, 24.7, 19.7; *m/z* LRMS (ESI + APCI) found [M+H]⁺ 279.2, C₁₈H₁₉N₂O⁺ requires 279.2.

4-(6-Methylpyridin-2-yl)-7-(trifluoromethyl)quinoline (11)



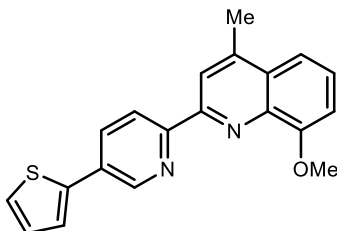
Prepared according to general procedure B' using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 4-chloro-7-(trifluoromethyl)quinoline (69 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μ L, 0.30 mmol), H₂O (45 μ L, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 15.5 hours. Flash column chromatography (silica gel: 25% EtOAc in hexanes) afforded the title compound as a white crystalline solid (53 mg, 0.19 mmol, 73% yield). mp 54-55 °C; IR ν_{max} /cm⁻¹ (film): 3053, 2954, 2856, 1655, 1637, 1623, 1574, 1555, 1368, 1080, 872, 662; ¹H NMR (400 MHz, CDCl₃) δ : 9.09 (1H, d, J = 4.4 Hz), 8.48 (1H, dd, J = 2.0, 1.0 Hz), 8.32-8.26 (1H, m), 7.80 (1H, t, J = 7.7 Hz), 7.71 (1H, dd, J = 8.9, 1.9 Hz), 7.62 (1H, d, J = 4.4 Hz), 7.42 (1H, d, J = 7.6 Hz), 7.31 (1H, d, J = 7.8 Hz), 2.70 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 159.2, 155.4, 151.5, 148.1, 146.7, 137.3, 131.3 (q, J = 32.85 Hz), 128.0-127.7 (2C, m), 127.5, 124.1 (q, J = 272.54 Hz), 123.2, 123.1, 122.7-122.5 (m), 121.9, 24.8; ¹⁹F NMR (365 MHz, CDCl₃) δ : -62.81; m/z LRMS (ESI + APCI) found [M+H]⁺ 289.2, C₁₆H₁₂F₃N₂⁺ requires 289.1.

8-Methoxy-4-methyl-2-(5-(trifluoromethyl)pyridin-2-yl)quinoline (12)



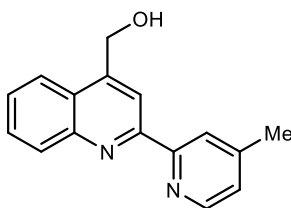
Prepared according to general procedure B' using 2-(diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (83 mg, 0.25 mmol), 2-chloro-8-methoxy-4-methylquinoline (62 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μ L, 0.30 mmol), H₂O (45 μ L, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 18 hours. Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a faint yellow solid (49 mg, 0.16 mmol, 61% yield). mp 105-108 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 2958, 2919, 2815, 2829, 1603, 1576, 1554, 1507, 1452, 1212, 980, 777, 694, 639; ¹H NMR (400 MHz, CDCl₃) δ : 8.96 (1H, dq, J = 2.4, 0.9 Hz), 8.84 (1H, dt, J = 8.3, 0.8 Hz), 8.47 (1H, q, J = 1.0 Hz), 8.07 (1H, ddd, J = 8.3, 2.4, 0.7 Hz), 7.61 (1H, dd, J = 8.5, 1.2 Hz), 7.53 (1H, dd, J = 8.5, 7.6 Hz), 7.10 (1H, dd, J = 7.7, 1.2 Hz), 4.13 (3H, s), 2.80 (3H, d, J = 0.9); ¹³C NMR (100 MHz, CDCl₃) δ : 159.8 (d, J = 1.7 Hz), 156.2, 153.1, 146.1 (q, J = 4.2 Hz), 145.7, 139.9, 134.1 (q, J = 3.5 Hz), 129.9, 127.5, 126.5 (q, J = 32.9 Hz), 123.9 (q, J = 272.2 Hz), 121.9, 120.3, 115.9, 108.1, 56.4, 19.7; ⁹F NMR (365 MHz, CDCl₃) δ : -62.27; m/z LRMS (ESI + APCI) found [M+H]⁺ 319.1, C₁₇H₁₄F₃N₂O⁺ requires 319.1.

8-Methoxy-4-methyl-2-(5-(thiophen-2-yl)pyridin-2-yl)quinoline (13)



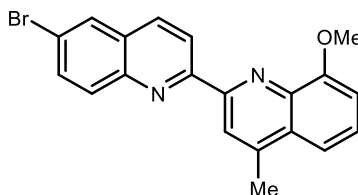
Prepared according to general procedure B' using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 2-chloro-8-methoxy-4-methylquinoline (62 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μ L, 0.30 mmol), H₂O (45 μ L, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 18 hours. Flash column chromatography (silica gel: 60% EtOAc in Et₂O) followed by a second flash column (silica gel neutralized with NEt₃: gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a yellow amorphous solid (42 mg, 0.13 mmol, 50% yield). IR ν_{max} /cm⁻¹ (film): 3070, 2956, 2934, 2832, 1600, 1567, 1546, 1126, 958, 814, 663, 647; ¹H NMR (400 MHz, CDCl₃) δ : 8.98 (1H, dd, J = 2.4, 0.8 Hz), 8.74 (1H, dd, J = 8.3, 0.8 Hz), 8.48 (1H, s), 8.04 (1H, dd, J = 8.3, 2.4 Hz), 7.61 (1H, dd, J = 8.5, 1.2 Hz), 7.55-7.44 (2H, m), 7.40 (1H, dd, J = 5.1, 1.1 Hz), 7.16 (1H, dd, J = 5.1, 3.6 Hz), 7.09 (1H, dd, J = 7.7, 1.2 Hz), 4.13 (3H, s), 2.80 (3H, d, J = 1.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 156.1, 155.3, 154.1, 146.1, 145.1, 145.2, 140.6, 139.9, 133.8, 130.6, 129.6, 128.5, 126.8, 126.3, 124.5, 122.2, 120.1, 115.9, 107.9, 56.4, 19.6; m/z LRMS (ESI + APCI) found [M+H]⁺ 333.2, C₂₀H₁₇N₂OS⁺ requires 333.1.

(2-(4-Methylpyridin-2-yl)quinolin-4-yl)methanol (14)



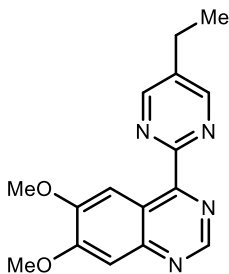
Prepared according to general procedure B' using 2-(diphenylphosphaneyl)-4-methylpyridine (69 mg, 0.25 mmol), (2-chloroquinolin-4-yl)methanol (58 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μ L, 0.30 mmol), H₂O (45 μ L, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 43 hours. Flash column chromatography (silica gel: 4% MeOH in CH₂Cl₂) followed by a second flash column (silica gel: 3% MeOH in CH₂Cl₂) afforded the title compound as an off-white powder (26 mg, 0.10 mmol, 42% yield). mp 154-157 °C; IR ν_{max} /cm⁻¹ (film): 3292, 2923, 2852, 1602, 1555, 1509, 1480, 1447, 1332, 1093, 1080, 826, 763; ¹H NMR (400 MHz, CDCl₃) δ : 8.59 (1H, s), 8.56 (1H, d, *J* = 5.0 Hz), 8.41 (1H, d, *J* = 1.7 Hz), 8.17 (1H, dd, *J* = 8.4, 1.3 Hz), 7.95 (1H, dd, *J* = 8.4, 1.4 Hz), 7.70 (1H, ddd, *J* = 8.4, 6.8, 1.4 Hz), 7.52 (1H, ddd, *J* = 8.2, 6.8, 1.3 Hz), 7.18 (1H, dd, *J* = 5.1, 1.7 Hz), 5.20 (2H, s), 3.14 (1H, br s), 2.48 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 156.2, 156.0, 148.9, 148.4, 147.9, 146.7, 130.4, 129.4, 126.9, 126.0, 125.2, 123.1, 122.7, 116.7, 62.4, 21.3; *m/z* LRMS (ESI + APCI) found [M+H]⁺ 251.1, C₁₆H₁₅N₂O⁺ requires 251.1.

6'-Bromo-8-methoxy-4-methyl-2,2'-biquinoline (15)



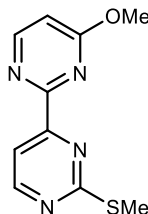
Prepared according to general procedure B' using 2-(diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (86 mg, 0.25 mmol), 2-chloro-8-methoxy-4-methylquinoline (62 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μ L, 0.30 mmol), H₂O (45 μ L, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 18 hours. Flash column chromatography (silica gel: 60% EtOAc in hexanes) followed by a second flash column (silica gel: gradient elution: CH₂Cl₂ to 2% MeOH in CH₂Cl₂) afforded the title compound as an orange crystalline solid (60 mg, 0.16 mmol, 63% yield). mp 173-174 °C; IR ν_{max} /cm⁻¹ (film): 3496, 3061, 3010, 2969, 2941, 2835, 1592, 1560, 1546, 1402, 1318, 1160, 884; ¹H NMR (400 MHz, CDCl₃) δ : 8.92 (1H, dd, J = 8.6, 1.9 Hz), 8.70 (1H, s), 8.22 (1H, dd, J = 8.7, 1.8 Hz), 8.10 (1H, d, J = 8.9 Hz), 8.04 (1H, d, J = 2.1 Hz), 7.81 (1H, dt, J = 9.1, 2.1 Hz), 7.63 (1H, d, J = 8.4 Hz), 7.54 (1H, dt, J = 8.0, 1.9 Hz), 7.12 (1H, d, J = 7.7 Hz), 4.15 (3H, d, J = 1.9 Hz), 2.84 (3H, d, J = 1.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 157.0, 156.2, 154.1, 146.6, 145.3, 139.9, 135.7, 133.0, 131.6, 129.9, 129.8, 129.6, 127.2, 120.8, 120.8, 120.4, 115.9, 108.0, 56.4, 19.6; m/z LRMS (ESI + APCI) found [M+H]⁺ 379.1, C₂₀H₁₆BrN₂O⁺ requires 379.0.

4-(5-Ethylpyrimidin-2-yl)-6,7-dimethoxyquinazoline (16)



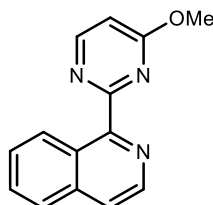
Prepared according to general procedure B' using 2-(diphenylphosphaneyl)-5-ethylpyrimidine (73 mg, 0.25 mmol), 4-chloro-6,7-dimethoxyquinazoline (67 mg, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μ L, 0.30 mmol), H₂O (45 μ L, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 12 hours. Flash column chromatography (silica gel: 4% MeOH in CH₂Cl₂) afforded the title compound as a yellow crystalline solid (40 mg, 0.14 mmol, 54% yield). mp 163-164 °C; IR ν_{max} /cm⁻¹ (film): 3090, 3043, 3009, 2928, 1557, 1341, 940, 827, 630, 599, 562; ¹H NMR (400 MHz, CDCl₃) δ : 9.34 (1H, s), 8.89 (2H, s), 8.21 (1H, s), 7.42 (1H, s), 4.09 (3H, s), 4.01 (3H, s), 2.82 (2H, q, J = 7.6 Hz), 1.40 (3H, t, J = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 162.2, 159.0, 157.1 (2C), 156.1, 153.7, 151.0, 151.0, 137.6, 119.1, 107.1, 104.4, 56.6, 56.3, 23.8, 14.9,; m/z LRMS (ESI + APCI) found [M+H]⁺ 297.2, C₁₆H₁₇N₄O₂⁺ requires 297.1.

4-Methoxy-2'-(methylthio)-2,4'-bipyrimidine (17)



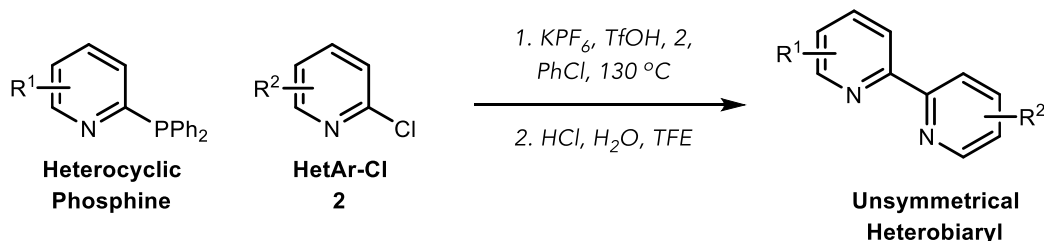
Prepared according to general procedure B' using 2-(diphenylphosphanyl)-4-methoxypyrimidine (74 mg, 0.25 mmol), 4-chloro-2-(methylthio)pyrimidine (35 μ L, 0.30 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), 4.0M HCl in dioxanes (75 μ L, 0.30 mmol), H₂O (45 μ L, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 13 hours. Flash column chromatography (silica gel, gradient elution: 20% EtOAc in hexanes to 40% EtOAc in hexanes) afforded the title compound as a white powder (23 mg, 0.10 mmol, 38% yield). mp 93-95 °C; IR ν_{max} /cm⁻¹ (film): 3068, 3035, 2993, 2952, 2923, 2852, 1567, 1553, 1536, 1469, 1370, 1337, 1286, 1207, 843, 788; ¹H NMR (400 MHz, CDCl₃) δ : 8.71 (1H, d, J = 5.1 Hz), 8.65 (1H, d, J = 5.7 Hz), 7.99 (1H, d, J = 5.1 Hz), 6.81 (1H, d, J = 5.8 Hz), 4.10 (3H, s), 2.66 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 173.8, 170.1, 162.0, 161.8, 158.5, 158.1, 114.9, 109.1, 54.0, 14.4; m/z LRMS (ESI + APCI) found [M+H]⁺ 235.1, C₁₀H₁₁N₄OS⁺ requires 235.1.

1-(4-Methoxypyrimidin-2-yl)isoquinoline (18)



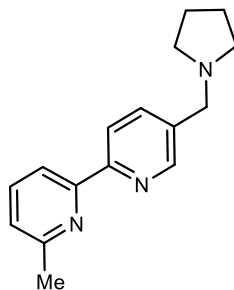
Prepared according to general procedure B' using 2-(diphenylphosphaneyl)-4-methoxypyrimidine (74 mg, 0.25 mmol), 1-chloroisoquinoline (49 mg, 0.30 mmol), sodium trifluoromethanesulfonate (43 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μ L, 0.30 mmol), H₂O (45 μ L, 2.5 mmol), and TFE (0.63 mL) at 80 °C for 17.5 hours. Flash column chromatography (silica gel: 3% MeOH in CH₂Cl₂) followed by a second flash column (silica gel: 2.5% MeOH in CH₂Cl₂) afforded the title compound as an off-white amorphous solid (34 mg, 0.14 mmol, 58% yield). mp 146-148 °C; IR ν_{max} /cm⁻¹ (film): 3053, 2954, 2856, 1655, 1637, 1623, 1574, 1080, 872, 528; ¹H NMR (400 MHz, CDCl₃) δ : 8.75 (2H, m), 8.48 (1H, dd, J = 8.6, 1.1 Hz), 7.89 (1H, dt, J = 8.3, 1.1 Hz), 7.76 (1H, dd, J = 5.6, 1.0 Hz), 7.70 (1H, ddd, J = 8.2, 6.8, 1.2 Hz), 7.59 (1H, ddd, J = 8.3, 6.8, 1.3 Hz), 6.84 (1H, d, J = 5.8 Hz), 4.07 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 169.8, 165.1, 157.7, 156.1, 142.3, 137.2, 130.2, 127.7, 127.2, 127.2, 126.7, 122.0, 107.6, 54.2; m/z LRMS (ESI + APCI) found [M+H]⁺ 238.1, C₁₄H₁₂N₃O⁺ requires 238.1.

A. 2.3.3 General Procedure C' (2,2'-bipyridines synthesis)



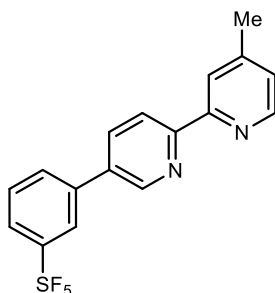
An oven dried 8 mL vial with a septa cap was charged with the heterocyclic phosphine (1.0 equiv), potassium hexafluorophosphate (1.0 equiv), and heteroaryl chloride 2 (2.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill and then chlorobenzene (2.0M) and trifluoromethanesulfonic acid (1.2 equiv) were added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 130 °C for the stated time. The reaction was then allowed to cool to room temperature. The septa cap was removed and 4.0M HCl in dioxanes (1.0 equiv), H₂O (10 equiv), and TFE (dilute to 0.4M) were quickly added. The reaction vial was then heated at 80 °C for the stated time. The reaction was quenched with a saturated aqueous solution of Na₂CO₃ and the aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl.

6'-Methyl-5-(pyrrolidin-1-ylmethyl)-2,2'-bipyridine (19)



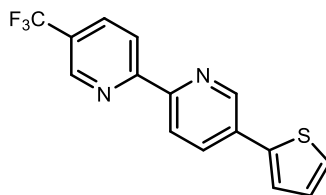
Prepared according to general procedure C' using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 2-chloro-5-(pyrrolidin-1-ylmethyl)pyridine (98 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (71 μ L, 0.80 mmol), and chlorobenzene (0.13 mL) at 130 $^{\circ}$ C for 39.5 hours; then H₂O (45 μ L, 2.5 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and TFE (0.50 mL) at 80 $^{\circ}$ C for 24 hours. Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt₃ then gradient elution: 30% EtOAc in hexanes to 70% EtOAc in hexanes) afforded the title compound as an orange oil (22 mg, 0.09 mmol, 35% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3057, 2960, 2786, 1593, 1573, 1560, 1454, 1410, 1347, 1080, 1025, 800, 759; ¹H NMR (400 MHz, CDCl₃) δ : 8.59 (1H, d, J = 1.7 Hz), 8.35 (1H, d, J = 8.1 Hz), 8.14 (1H, d, J = 7.8 Hz), 7.81 (1H, dd, J = 8.1, 2.1 Hz), 7.68 (1H, t, J = 7.7 Hz), 7.15 (1H, d, J = 7.6 Hz), 3.69 (2H, s), 2.62 (3H, s), 2.58-2.50 (4H, m), 1.83-1.77 (4H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 158.1, 155.7, 155.6, 149.7, 137.6, 137.2, 134.5, 123.2, 121.0, 118.2, 57.7, 54.2, 24.8, 23.6; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^{+}$ 254.2, C₁₆H₂₀N₃⁺ requires 254.2.

4-Methyl-5'-(3-(pentafluoro- λ^6 -sulfaneyl)phenyl)-2,2'-bipyridine (20)



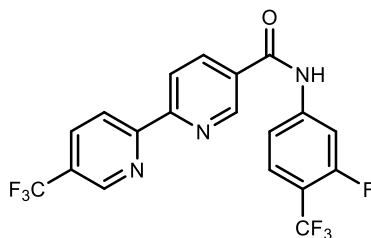
Prepared according to general procedure C' using 2-(diphenylphosphaneyl)-4-methylpyridine (69 mg, 0.25 mmol), 2-chloro-5-(3-(pentafluoro- λ^6 -sulfaneyl)phenyl)pyridine (158 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μ L, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 °C for 39 hours; then H₂O (45 μ L, 2.5 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 22 hours. Flash column chromatography (silica gel: 40% EtOAc in hexanes) afforded the title compound as a light tan powder (48 mg, 0.13 mmol, 51% yield). mp 129-131 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3022, 2923, 2852, 1606, 1595, 1465, 1435, 1368, 1115, 859, 825; ¹H NMR (400 MHz, CDCl₃) δ : 8.89 (1H, s), 8.66-8.44 (2H, m), 8.29 (1H, s), 8.11-7.93 (2H, m), 7.89-7.72 (2H, m), 7.60 (1H, t, J = 7.8 Hz), 7.17 (1H, d, J = 3.6 Hz), 2.46 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 156.2, 155.3, 154.9 (app t, J = 17.4 Hz), 149.2, 148.5, 147.7, 139.0, 135.6, 134.8, 130.3, 129.7, 125.6 (app qn, J = 4.5 Hz), 125.2, 124.8 (app qn, J = 4.5 Hz), 122.2, 121.4, 21.4; ¹⁹F NMR (365 MHz, CDCl₃) δ : 83.77 (qn, J = 151.8 Hz), 62.75 (d, J = 150.0 Hz); m/z LRMS (ESI + APCI) found $[M+H]^+$ 373.2, C₁₇H₁₄F₅N₂S⁺ requires 373.1.

5-(Thiophen-2-yl)-5'-(trifluoromethyl)-2,2'-bipyridine (21)



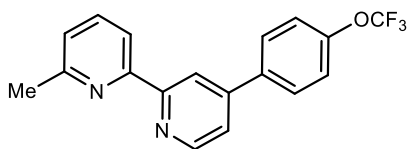
Prepared according to general procedure C' using 2-(diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (83 mg, 0.25 mmol), 2-chloro-5-(thiophen-2-yl)pyridine (98 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μ L, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 $^{\circ}$ C for 45 hours; then H₂O (45 μ L, 2.5 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and TFE (0.50 mL) at 80 $^{\circ}$ C for 19 hours. Flash column chromatography (silica gel: 2% EtOAc in hexanes) afforded the title compound as a white crystalline solid (41 mg, 0.13 mmol, 53% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3124, 3067, 2921, 1599, 1579, 1548, 1530, 1468, 1209, 782, 751, 644; ^1H NMR (400 MHz, CDCl₃) δ : 8.98 (1H, dd, J = 2.4, 0.8 Hz), 8.93 (1H, dt, J = 2.5, 0.9 Hz), 8.58 (1H, dt, J = 8.4, 0.8 Hz), 8.49 (1H, dd, J = 8.3, 0.8 Hz), 8.09-7.99 (2H, m), 7.47 (1H, dd, J = 3.6, 1.1 Hz), 7.42 (1H, dd, J = 5.1, 1.1 Hz), 7.17 (1H, dd, J = 5.1, 3.6 Hz); ^{13}C NMR (100 MHz, CDCl₃) δ : 158.9, 153.4, 146.6, 146.3 (q, J = 4.1 Hz), 140.2, 134.2, (q, J = 3.5 Hz), 134.0, 131.4, 128.6, 126.8, 126.4 (q, J = 33.00 Hz), 124.9, 123.9 (q, J = 272.1 Hz), 121.9, 120.7; ^{19}F NMR (365 MHz, CDCl₃) δ : -62.32; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 307.1, C₁₅H₁₀F₃N₂S⁺ requires 307.1.

N-(3-fluoro-4-(trifluoromethyl)phenyl)-5'-(trifluoromethyl)-[2,2'-bipyridine]-5-carboxamide (22)



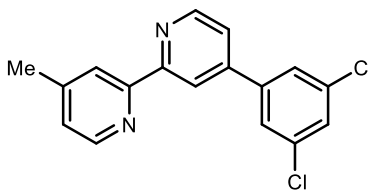
Prepared according to general procedure C' using 2-(diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (66 mg, 0.20 mmol), 6-chloro-N-(3-fluoro-4-(trifluoromethyl)phenyl)nicotinamide (128 mg, 0.40 mmol), potassium hexafluorophosphate (36 mg, 0.20 mmol), trifluoromethanesulfonic acid (21 μ L, 0.24 mmol), and chlorobenzene (0.13 mL) at 130 $^{\circ}$ C for 45 hours; then H₂O (45 μ L, 2.5 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and TFE (0.50 mL) at 80 $^{\circ}$ C for 19 hours. Preparatory thin layer chromatography (40% EtOAc in hexanes) followed by flash column chromatography (silica gel: 1% MeOH in CH₂Cl₂) afforded the title compound as a white amorphous solid (40 mg, 0.09 mmol, 47% yield). IR ν_{max} /cm⁻¹ (film): 3853, 3750, 2923, 2852, 2359, 2342, 1733, 1652, 1598, 1540, 1468, 1426, 1132, 1083, 820, 552, 532; ¹H NMR (400 MHz, DMSO-d₆) δ : 11.06 (1H, s), 9.27 (1H, d, *J* = 2.2 Hz), 9.15 (1H, s), 8.67 (1H, d, *J* = 8.4 Hz), 8.61 (1H, d, *J* = 8.3 Hz), 8.54 (1H, dd, *J* = 8.3, 2.2 Hz), 8.43 (1H, dd, *J* = 8.5, 2.4 Hz), 8.02 (1H, dd, *J* = 13.6, 1.9 Hz), 7.86-7.74 (2H, m); ¹³C NMR (100 MHz, DMSO-d₆) δ : 164.4, 160.3, 157.8, 156.2, 149.1, 146.4 (d, *J* = 4.1 Hz), 144.6 (d, *J* = 11.9 Hz), 137.3, 135.2 (d, *J* = 3.7 Hz), 130.7, 127.9 (2C, m), 125.7 (d, *J* = 32.5 Hz), 123.7 (q, *J* = 272.3 Hz), 122.8 (q, *J* = 270.59 Hz), 121.1 (d, *J* = 41.7 Hz), 115.8 (d, *J* = 3.0 Hz), 110.9 (d, *J* = 32.8 Hz), 107.7 (d, *J* = 25.4 Hz); ¹⁹F NMR (365 MHz, CDCl₃) δ : -59.19 (d, *J* = 12.0 Hz), -60.89, -114.19 (tt, *J* = 13.0, 6.7 Hz); *m/z* LRMS (ESI + APCI) found [M+H]⁺ 430.2, C₁₉H₁₁F₇N₃O⁺ requires 430.1.

6'-Methyl-4-(4-(trifluoromethoxy)phenyl)-2,2'-bipyridine (23)



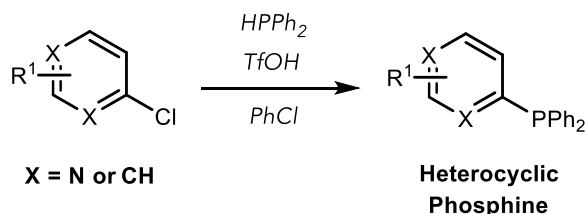
Prepared according to general procedure C' using 2-(diphenylphosphaneyl)-6-methylpyridine (69 mg, 0.25 mmol), 2-chloro-4-(4-(trifluoromethoxy)phenyl)pyridine (137 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μ L, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 °C for 39.5 hours; then H₂O (45 μ L, 2.5 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 27 hours. Flash column chromatography (silica gel was packed in hexanes and neutralized with NEt₃: 10% EtOAc in hexanes) afforded the title compound as colorless crystals (47 mg, 0.14 mmol, 57% yield). mp 46-48 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3055, 3012, 2920, 1587, 1511, 1459, 1271, 1208, 1150, 1106, 1086, 834, 803; ¹H NMR (400 MHz, CDCl₃) δ : 8.73 (1H, dd, J = 5.1, 0.8 Hz), 8.67-8.62 (1H, m), 8.23 (1H, d, J = 7.8 Hz), 7.84-7.75 (2H, m), 7.73 (1H, t, J = 7.7), 7.48 (1H, dd, J = 5.1, 1.9 Hz), 7.36 (2H, dq, J = 8.6, 1.0 Hz), 7.20 (1H, d, J = 7.6 Hz), 2.66 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 158.2, 157.4, 155.5, 150.0 (q, J = 1.9 Hz), 149.9, 148.0, 137.4, 137.3, 128.8, 124.5, 121.5, 121.4, 120.6 (q, J = 257.7 Hz), 119.2, 118.4, 24.8; ¹⁹F NMR (365 MHz, CDCl₃) δ : -57.76; m/z LRMS (ESI + APCI) found [M+H]⁺ 331.2, C₁₈H₁₄F₃N₂O⁺ requires 331.1.

4-(3,5-Dichlorophenyl)-4'-methyl-2,2'-bipyridine (24)



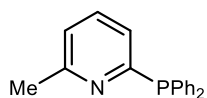
Prepared according to general procedure C' using 2-(diphenylphosphanyl)-4-methylpyridine (69 mg, 0.25 mmol), 2-chloro-4-(3,5-dichlorophenyl)pyridine (129 mg, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μ L, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 $^{\circ}$ C for 43 hours; then H₂O (45 μ L, 2.5 mmol), 4.0M HCl in dioxanes (63 μ L, 0.25 mmol), and TFE (0.50 mL) at 80 $^{\circ}$ C for 20 hours. Flash column chromatography (silica gel: 2% MeOH in Et₂O) followed by a second flash column (silica gel: 2% MeOH in CH₂Cl₂) afforded the title compound as a white amorphous solid (46 mg, 0.15 mmol, 58% yield). IR ν_{max} /cm⁻¹ (film): 3054, 3011, 2922, 2855, 1670, 1595, 1556, 1490, 1138, 849, 720, 650, 533; ¹H NMR (400 MHz, CDCl₃) δ : 8.73 (1H, dd, J = 5.0, 0.8 Hz), 8.53 (1H, dd, J = 4.9, 0.8 Hz), 8.44 (1H, dd, J = 1.7, 0.8 Hz), 8.28 (1H, dt, J = 1.6, 0.8 Hz), 7.52 (1H, dd, J = 1.8, 0.7 Hz), 7.42-7.32 (3H, m), 7.15 (1H, ddd, J = 5.0, 1.7, 0.8 Hz), 2.45 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ : 156.7, 155.7, 149.2, 149.1, 148.4, 147.2, 136.8, 135.2, 133.1, 131.9, 130.1, 127.6, 125.1, 124.2, 122.2, 121.8, 21.4; m/z LRMS (ESI + APCI) found [M+H]⁺ 315.1, C₁₇H₁₃Cl₂N₂⁺ requires 315.0.

A. 2.3.4 General Procedure A (pyridine heterocyclic phosphine)



An oven dried 8 mL vial equipped with a stir bar was charged with the heterocycle (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, chlorobenzene (2.0 M) was added, followed by diphenylphosphine (1.2 equiv), and trifluoromethanesulfonic acid (1.0 equiv). The reaction was heated to 130 °C and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were 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 phosphine product.

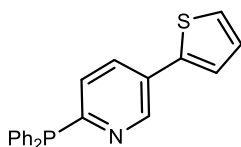
2-(Diphenylphosphaneyl)-6-methylpyridine (25)



Prepared according to general procedure A using 2-chloro-6-methylpyridine (0.22 mL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL , 2.00 mmol), and chlorobenzene (1.0 mL) at 130 °C for 21 hours. Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white powder (522 mg, 1.88 mmol, 94% yield). mp 80-82 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3048, 3001, 2961, 1576, 1555, 1443, 1433, 1094, 796, 754, 698; ^1H NMR (400 MHz, CDCl_3) δ : 7.44 (1H, td,

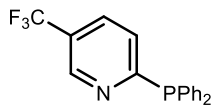
$J = 7.2, 1.2$ Hz), 7.40-7.29 (10H, m), 7.03 (1H, d, $J = 7.8$ Hz), 6.82 (1H, d, $J = 7.6$ Hz), 2.57 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.2 (d, $J = 7.3$ Hz), 159.1 (d, $J = 14.5$ Hz), 136.7 (d, $J = 11.2$ Hz), 136.0, 134.2 (d, $J = 19.5$ Hz), 129.0, 128.6 (d, $J = 7.1$ Hz), 125.0 (d, $J = 11.6$ Hz), 122.1, 24.8; ^{31}P NMR (162 MHz, CDCl_3) δ : -4.96 ; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 278.1, $\text{C}_{18}\text{H}_{17}\text{NP}^+$ requires 278.1.

2-(Diphenylphosphaneyl)-5-(thiophen-2-yl)pyridine (26)



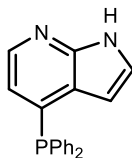
Prepared according to general procedure A using 2-chloro-5-(thiophen-2-yl)pyridine (391 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL , 2.00 mmol), and chlorobenzene (1.0 mL) at 130 $^{\circ}\text{C}$ for 21 hours. Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white powder (610 mg, 1.77 mmol, 88% yield). mp 89-91 $^{\circ}\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3053, 1544, 1478, 1458, 1432, 1378, 1267, 1206, 1095, 1025, 850, 828; ^1H NMR (400 MHz, CDCl_3) δ : 8.99(1H, d, $J = 2.0$ Hz), 7.74 (1H, dt, $J = 8.1, 2.0$ Hz), 7.47-7.32 (12H, m), 7.14-7.07 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) δ : 162.6 (d, $J = 3.1$ Hz), 147.4 (d, $J = 13.0$ Hz), 140.3, 136.2 (d, $J = 10.7$ Hz), 134.3 (d, $J = 19.8$ Hz), 132.5 (d, $J = 2.3$ Hz), 129.2, 128.9, 128.8 (d, $J = 6.9$ Hz), 128.4, 128.0 (d, $J = 16.8$ Hz), 126.3, 124.4; ^{31}P NMR (162 MHz, CDCl_3) δ : -4.05 ; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 346.1, $\text{C}_{21}\text{H}_{17}\text{NPS}^+$ requires 346.1.

2-(Diphenylphosphaneyl)-5-(trifluoromethyl)pyridine (27)



Prepared according to general procedure A using 2-chloro-5-trifluoromethylpyridine (363 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μ L, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 °C for 15.5 hours. Flash column chromatography (silica gel, gradient elution: 1% EtOAc in hexanes to 2% EtOAc in hexanes) afforded the title compound as a yellow oil (590 mg, 1.78 mmol, 89% yield). IR ν_{max} /cm⁻¹ (film): 3055, 3003, 2359, 1955, 1881, 1684, 1594, 1558, 1479, 1281, 938, 578; ¹H NMR (400 MHz, CDCl₃) δ : 8.95 (1H, s), 7.76 (1H, d, J = 8.1), 7.48-7.31 (10H, m), 7.19 (1H, d, J = 8.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 169.7 (d, J = 2.2 Hz), 146.8 (dd, J = 11.7, 4.0 Hz), 135.2 (d, J = 9.9), 134.5 (d, J = 20.3 Hz), 132.9-132.6 (m), 132.3 (d, J = 9.6 Hz), 129.7, 129.0 (d, J = 7.5 Hz), 127.3 (d, J = 16.1 Hz), 123.7 (q, J = 272.3 Hz); ¹⁹F NMR (365 MHz, CDCl₃) δ : -62.51; ³¹P NMR (162 MHz, CDCl₃) δ : -2.34; m/z LRMS (ESI + APCI) found [M+H]⁺ 332.1, C₁₈H₁₄F₃NP⁺ requires 332.1.

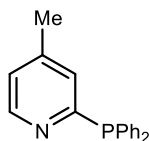
4-(Diphenylphosphaneyl)-1H-pyrrolo[2,3-b]pyridine (28)



Prepared according to general procedure A using 4-chloro-1H-pyrrolo[2,3-b]pyridine (305 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol, trifluoromethanesulfonic acid (177 μ L, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 °C for 20 hours. Flash column

chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a faint yellow crystalline solid (550 mg, 1.82 mmol, 91% yield). mp 146-148 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3119, 3069, 3054, 2902, 2802, 2763, 1592, 1182, 792, 611; ^1H NMR (400 MHz, CDCl_3) δ : 9.76 (1H, s), 8.20 (1H, d, $J = 4.9$ Hz), 7.46-7.31 (11H, m), 6.71-6.57 (1H, m), 6.28 (1H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 147.6 (d, $J = 6.9$ Hz), 142.2, 140.5 (d, $J = 17.2$ Hz), 135.2 (d, $J = 20.3$ Hz), 134.4 (d, $J = 20.3$ Hz), 129.4, 128.8 (d, $J = 7.7$ Hz), 125.4, 123.3, 119.2 (d, $J = 4.4$ Hz), 101.2 (d, $J = 6.9$ Hz); ^{31}P NMR (162 MHz, CDCl_3) δ : -12.55; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 303.1, $\text{C}_{19}\text{H}_{16}\text{N}_2\text{P}^+$ requires 303.1.

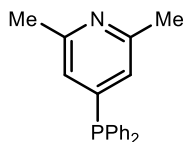
2-(Diphenylphosphaneyl)-4-methylpyridine (29)



Prepared according to general procedure A using 2-chloro-4-methylpyridine (0.22 mL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL , 2.00 mmol), and chlorobenzene (1.0 mL) at 130 °C for 14 hours. Flash column chromatography (silica gel, gradient elution: 10% EtOAc in hexanes to 15% EtOAc in hexanes) afforded the title compound as a white powder (523 mg, 1.89 mmol, 94% yield). mp 69-71 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3066, 3045, 2922, 1584, 1547, 1477, 1457, 1434, 1388, 1373, 1311, 1089, 1025, 999, 826, 752 ; ^1H NMR (400 MHz, CDCl_3) δ : 8.58 (1H, d, $J = 4.6$ Hz), 7.44-7.29 (10H, m), 7.00 (1H, d, $J = 4.1$ Hz), 6.93 (1H, s), 2.25 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 163.4 (d, $J = 4.6$ Hz), 150.2 (d, $J = 13.0$ Hz), 146.9 (d, $J = 2.6$ Hz), 136.4 (d, $J = 10.8$ Hz), 134.2 (d, $J = 19.8$ Hz), 129.1, 128.9 (d,

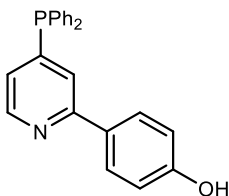
$J = 16.4$ Hz), 128.7 (d, $J = 6.9$ Hz), 123.4, 21.2; ^{31}P NMR (162 MHz, CDCl_3) δ : -4.06 ; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 278.2, $\text{C}_{18}\text{H}_{17}\text{NP}^+$ requires 278.1.

4-(Diphenylphosphaneyl)-2,6-dimethylpyridine (30)



Prepared according to general procedure A using 4-chloro-2,6-dimethylpyridine (283 mL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 μL , 2.00 mmol), and chlorobenzene (1.0 mL) at 130 $^{\circ}\text{C}$ for 20 hours. Flash column chromatography (silica gel: 25% EtOAc in hexanes) afforded the title compound as a white crystalline solid (582 mg, 2.00 mmol, 99% yield). mp 118-119 $^{\circ}\text{C}$; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3069, 3052, 3000, 2984, 2954, 2916, 2361, 1739, 1675, 1158, 831, 618, 542; ^1H NMR (400 MHz, CDCl_3) δ : 7.47-7.29 (10H, m), 6.79 (2H, d, $J = 7.2$ Hz), 2.46 (6H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 157.5 (d, $J = 5.1$ Hz), 149.0 (d, $J = 16.2$ Hz), 135.4 (d, $J = 10.0$ Hz), 134.3 (d, $J = 20.3$ Hz), 129.5, 128.9 (d, $J = 7.5$ Hz), 123.9 (d, $J = 15.9$ Hz), 24.6; ^{31}P NMR (162 MHz, CDCl_3) δ : -6.96 ; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 292.2, $\text{C}_{19}\text{H}_{19}\text{NP}^+$ requires 292.1.

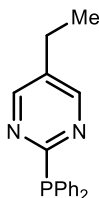
4-(4-(Diphenylphosphaneyl)pyridin-2-yl)phenol (31)



Prepared according to general procedure A using 4-(4-chloropyridin-2-yl)phenol (206 mg, 1.00 mmol), diphenylphosphane (0.21 mL, 1.20 mmol), trifluoromethanesulfonic acid (88 μL , 1.00

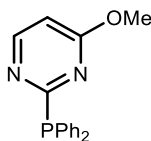
brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl phosphine product.

2-(Diphenylphosphaneyl)-5-ethylpyrimidine (32)



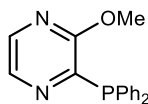
Prepared according to general procedure B using 2-chloro-5-ethylpyrimidine (243 μ L, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and TFE (5.0 mL) at 80 °C for 19 hours. Flash column chromatography (silica gel: 20% EtOAc in hexanes) afforded the title compound as a white crystalline solid (478 mg, 1.64 mmol, 82% yield). mp 78-80 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3070, 3045, 3006, 2929, 1962, 1536, 1208, 1100, 816; ¹H NMR (400 MHz, CDCl₃) δ : 8.57 (2H, s), 7.59-7.43 (4H, m), 7.42-7.30 (6H, m), 2.62 (2H, q, J = 7.63 Hz), 1.27 (3H, t, J = 7.63 Hz); ¹³C NMR (100 MHz, CDCl₃) δ : 173.8 (d, J = 12.4 Hz), 156.3 (d, J = 6.7 Hz), 135.9 (d, J = 20.1 Hz), 134.6 (d, J = 20.1 Hz), 134.1, 129.3, 128.6 (d, J = 7.6 Hz), 23.6, 14.9; ³¹P NMR (162 MHz, CDCl₃) δ : -0.70; m/z LRMS (ESI + APCI) found $[M+H]^+$ 293.2, C₁₈H₁₈N₂P⁺ requires 293.2.

2-(Diphenylphosphaneyl)-4-methoxypyrimidine (33)



Prepared according to general procedure B using 2-chloro-4-methoxypyrimidine (723 mg, 5.00 mmol), diphenylphosphane (1.04 mL, 6.00 mmol, and TFE (13.50 mL) at 80 °C for 19.5 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a clear oil (1.10 g, 3.75 mmol, 75% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3052, 3002, 2950, 2363, 2153, 1963, 1907, 1825, 1683, 1610, 782, 617, 578; ^1H NMR (400 MHz, CDCl_3) δ : 8.40 (1H, dd, $J = 5.8, 0.7$ Hz), 7.59-7.47 (4H, m), 7.40-7.30 (6H, m), 6.54 (1H, dd, $J = 5.8, 0.9$ Hz), 3.75 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 176.0 (d, $J = 12.4$ Hz), 168.2 (d, $J = 6.2$ Hz), 156.8 (d, $J = 7.6$ Hz), 135.7 (d, $J = 7.6$ Hz), 134.7 (d, $J = 19.8$ Hz), 129.1, 128.3 (d, $J = 7.6$ Hz), 106.1 (d, $J = 2.0$ Hz), 53.7; ^{31}P NMR (162 MHz, CDCl_3) δ : -1.62; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 295.1, $\text{C}_{17}\text{H}_{16}\text{N}_2\text{OP}^+$ requires 295.1.

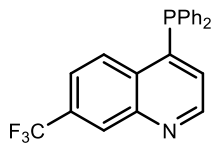
2-(Diphenylphosphaneyl)-3-methoxypyrazine (34)



Prepared according to general procedure B using 2-chloro-3-methoxypyrazine (434 mg, 3.00 mmol), diphenylphosphane (0.63 mL, 3.60 mmol, and TFE (7.5 mL) at 80 °C for 2 hours. Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes to 10% EtOAc in hexanes) afforded the title compound as a white powder (549 mg, 1.87 mmol, 62% yield). mp 104-105 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3052, 2943, 1515, 1479, 1454, 1434, 1368, 1353, 1297, 1220, 1179, 1157, 1099, 999, 866, 747; ^1H NMR (400 MHz, CDCl_3) δ : 8.19 (1H, d, $J = 2.7$ Hz), 8.01 (1H, d, $J = 2.8$ Hz), 7.44-7.29 (10H, m), 3.86 (3H, s); ^{13}C NMR (100 MHz, CDCl_3) δ : 161.7 (d, $J = 21.8$ Hz), 148.6 (d, $J = 13.4$ Hz), 139.6, 137.6, 134.6 (d, $J = 7.2$ Hz), 134.3 (d, $J = 20.2$ Hz), 129.0,

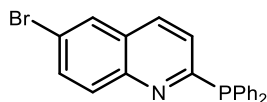
128.3 (d, $J = 7.6$ Hz), 53.7; ^{31}P NMR (162 MHz, CDCl_3) δ : -10.32 ; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 295.1, $\text{C}_{17}\text{H}_{16}\text{N}_2\text{OP}^+$ requires 295.1.

4-(diphenylphosphaneyl)-7-(trifluoromethyl)quinoline (35)



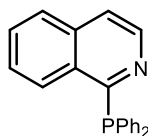
Prepared according to general procedure B using 4-chloro-7-(trifluoromethyl)quinoline (926 mg, 4.00 mmol), diphenylphosphane (0.84 mL, 4.80 mmol), and TFE (10.0 mL) at 80 °C for 16 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a faint yellow solid (1.30 g, 3.41 mmol, 85% yield). mp 86-89 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3074, 3052, 3016, 1569, 1505, 1478, 1433, 1206, 856, 600, 529; ^1H NMR (400 MHz, CDCl_3) δ : 8.84 (1H, dd, $J = 4.4, 1.2$ Hz), 8.44 (1H, s), 8.34 (1H, dd, $J = 8.8, 3.4$ Hz), 7.62 (1H, dd, $J = 8.8, 2.0$ Hz), 7.46-7.27 (10H, m), 6.93 (1H, t, $J = 4.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 151.1, 147.6 (d, $J = 22.5$ Hz), 146.8 (d, $J = 2.7$ Hz), 134.5 (d, $J = 20.5$ Hz), 133.9 (d, $J = 8.3$ Hz), 131.5 (d, $J = 3.5$ Hz), 131.4 (d, $J = 47.7$ Hz), 129.2, 129.2 (d, $J = 7.6$ Hz), 128.2-127.9 (m), 127.6 (d, $J = 22.0$ Hz), 127.1, 124.0 (q, $J = 272.5$ Hz), 122.6-122.2 (m); ^{19}F NMR (365 MHz, CDCl_3) δ : -62.75 ^{31}P NMR (162 MHz, CDCl_3) δ : -14.95 ; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 382.2, $\text{C}_{22}\text{H}_{16}\text{F}_3\text{NP}^+$ requires 382.1.

6-Bromo-2-(diphenylphosphaneyl)quinoline (36)



Prepared according to general procedure B using 2-chloro-6-bromoquinoline (485 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and TFE (5.0 mL) at 80 °C for 19 hours. Flash column chromatography (silica gel: 5% EtOAc in hexanes) afforded the title compound as an orange viscous oil (748 mg, 1.90 mmol, 95% yield). IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3047, 3006, 2967, 2929, 2872, 223, 1963, 1575, 1537, 1286, 999; ^1H NMR (400 MHz, CDCl_3) δ : 7.98 (1H, d, $J = 9.01$), 7.95-7.88 (2H, m), 7.76 (1H, dd, $J = 9.0, 2.2$ Hz), 7.52-7.30 (10H, m), 7.20 (1H, d, $J = 8.5$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.9 (d, $J = 1.54$ Hz), 147.2 (d, $J = 14.4$ Hz), 136.1 (d, $J = 11.1$ Hz), 134.4 (d, $J = 19.8$ Hz), 134.4 (d, $J = 2.6$ Hz), 133.3, 131.5, 129.8, 129.3, 128.8 (d, $J = 7.2$ Hz), 128.0, 125.2 (d, $J = 14.7$ Hz), 120.9; ^{31}P NMR (162 MHz, CDCl_3) δ : -1.83; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 392.1, $\text{C}_{21}\text{H}_{16}\text{BrNP}^+$ requires 392.0.

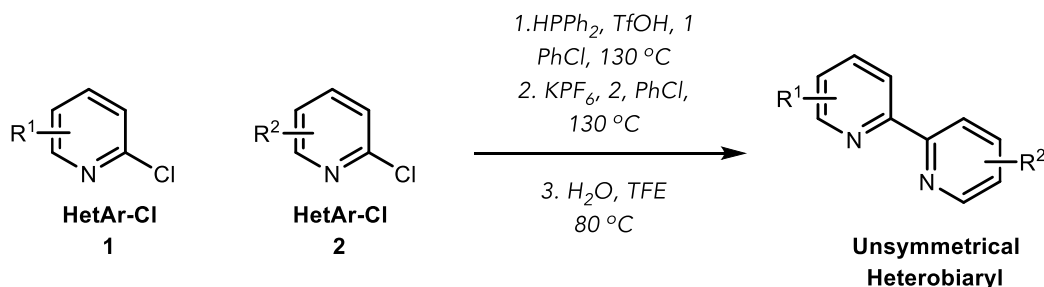
1-(diphenylphosphaneyl)isoquinoline (37)



Prepared according to general procedure B using 1-chloro-isoquinoline (328 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and TFE (5.0 mL) at 80 °C for 16.5 hours. Flash column chromatography (silica gel: 10% EtOAc in hexanes) afforded the title compound as a white crystalline solid (579 mg, 1.86 mmol, 93% yield). mp 143-145; °C IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3069, 3046, 3004, 2924, 2361, 2340, 1577, 1543, 1492, 1434, 1304, 828, 694, 672, 546, 539, 527; ^1H

NMR (400 MHz, CDCl₃) δ : 8.66-8.56 (2 H, m), 7.82 (1H, d, J = 8.2 Hz), 7.65 (1H, t, J = 7.5 Hz), 7.58 (1H, d, J = 5.6 Hz), 7.52 (1H, ddd, J = 8.3, 6.8, 1.3 Hz), 7.45-7.29 (10H, m); ¹³C NMR (100 MHz, CDCl₃) δ : 168.8 (d, J = 10.0 Hz), 143.4 (d, J = 4.1 Hz), 136.1 (d, J = 6.9 Hz), 135.5 (d, J = 4.0 Hz), 134.6 (d, J = 20.0 Hz), 132.2 (d, J = 29.0 Hz), 130.1 (d, J = 1.3 Hz), 129.0, 128.5 (d, J = 7.6 Hz), 127.5 (d, J = 2.0 Hz), 127.3 (d, J = 1.8 Hz), 127.1 (d, J = 23.0 Hz), 120.5; ³¹P NMR (162 MHz, CDCl₃) δ : -8.33; m/z LRMS (ESI + APCI) found [M+H]⁺ 314.2, C₂₁H₁₇NP⁺ requires 314.1.

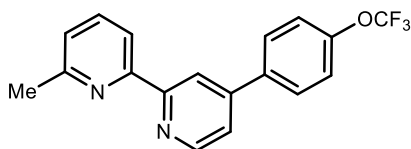
A. 2.3.6 General Procedure D (2,2'-bipyridines one-pot synthesis)



An oven dried 8 mL vial equipped with a stir bar was charged with heteroaryl chloride 1 (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, and chlorobenzene (2.0 M) was added, followed by diphenylphosphine (1.0 equiv) and trifluoromethanesulfonic acid (1.0 equiv). The reaction was heated to 130 °C and allowed to stir for the stated time. The reaction was then cooled to room temperature. The vial cap was removed and potassium hexafluorophosphate (2.0 equiv) and HetAr-Cl 2 (2.0 equiv) were quickly added. The vial was heated to 130 °C and allowed to stir for the stated time. The reaction was then cooled to room temperature and the vial cap was removed. H₂O (10 equiv) and TFE (dilute to 0.4M) were added to the reaction vial quickly. The vial heated to 80 °C and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na₂CO₃ and the aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic extracts were washed with a saturated

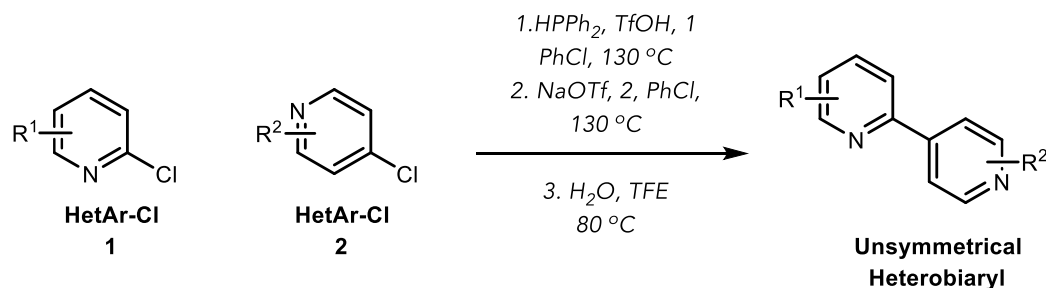
aqueous solution of brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl product.

6'-Methyl-4-(4-(trifluoromethoxy)phenyl)-2,2'-bipyridine (38)



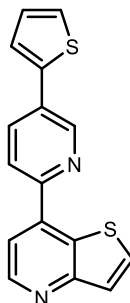
Prepared according to general procedure D using 2-chloro-6-methylpyridine (27 μ L, 0.25 mmol), diphenylphosphane (44 μ L, 0.25 mmol), trifluoromethanesulfonic acid (22 μ L, 0.25 mmol), and chlorobenzene (0.13 mL) at 130 $^{\circ}$ C for 16 hours; then 2-chloro-4-(4-(trifluoromethoxy)phenyl)pyridine (137 mg, 0.50 mmol), potassium hexafluorophosphate (92 mg, 0.50 mmol) at 130 $^{\circ}$ C for 41 hours; then H₂O (45 μ L, 2.5 mmol) and TFE (0.50 mL) at 80 $^{\circ}$ C for 23 hours. Flash column chromatography (silica gel: 30% EtOAc in hexanes) followed by a second flash column (silica gel neutralized with NEt₃: 10% EtOAc in hexanes) afforded the title compound as colorless crystals (36 mg, 0.11 mmol, 43% yield). Spectral data is consistent with compound **23**.

2.3.7 General Procedure D' (2,4' or 4,4'-bipyridines one-pot synthesis)



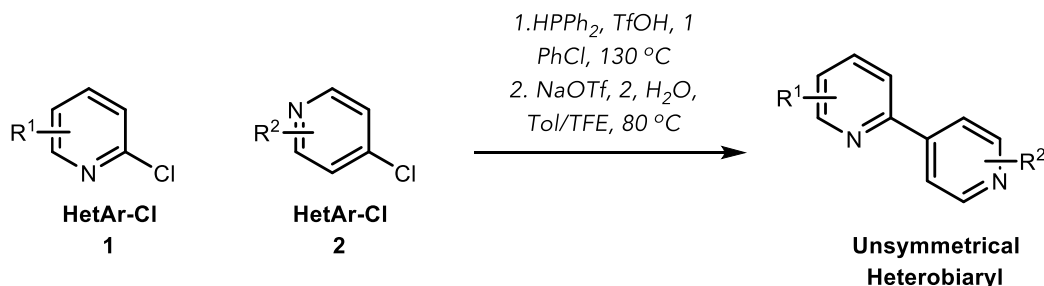
An oven dried 8 mL vial equipped with a stir bar was charged with heteroaryl chloride 1 (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, and chlorobenzene (2.0 M) was added, followed by diphenylphosphine (1.0 equiv) and trifluoromethanesulfonic acid (1.0 equiv). The reaction was heated to $130\text{ }^\circ\text{C}$ and allowed to stir for the stated time. The reaction was then cooled to room temperature. The vial cap was removed and sodium trifluoromethanesulfonate (2.0 equiv) and heteroaryl chloride 2 (1.2 equiv) were quickly added. The vial was then placed in a pre-heated oil bath at $130\text{ }^\circ\text{C}$ and allowed to stir for the stated time. The reaction was then cooled to room temperature and the vial cap was removed and H_2O (10 equiv) and TFE (dilute to 0.4M) were added to the reaction vial quickly. The vial heated to $80\text{ }^\circ\text{C}$ and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic extracts were 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 heterobiaryl product.

7-(5-(Thiophen-2-yl)pyridin-2-yl)thieno[3,2-b]pyridine (39)



Prepared according to general procedure D' using 2-chloro-5-(thiophen-2-yl)pyridine (49 mg, 0.25 mmol), diphenylphosphane (44 μ L, 0.25 mmol), trifluoromethanesulfonic acid (22 μ L, 0.25 mmol), and chlorobenzene (0.13 mL) at 130 °C for 16 hours; then 7-chlorothieno[3,2-b]pyridine (51 mg, 0.30 mmol), sodium trifluoromethanesulfonate (86 mg, 0.50 mmol) at 130 °C for 12 hours; then H₂O (45 μ L, 2.5 mmol) and TFE (0.50 mL) at 80 °C for 22 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) afforded the title compound as a bright yellow crystalline solid (49 mg, 0.17 mmol, 67% yield). Spectral data is consistent with compound **4**.

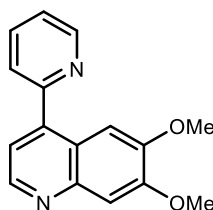
A. 2.3.7 General Procedure D'' (Couplings with quinolines/diazines one-pot synthesis)



An oven dried 8 mL vial equipped with a stir bar was charged with heteroaryl chloride **1** (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, and chlorobenzene (2.0 M) was added, followed by diphenylphosphine (1.0 equiv) and

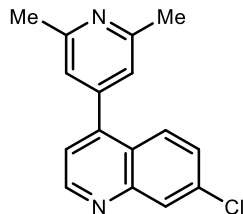
trifluoromethanesulfonic acid (1.0 equiv). The reaction was heated to 130 °C and allowed to stir for the stated time. The reaction was then cooled to room temperature. The vial cap was removed and sodium trifluoromethanesulfonate (2.0 equiv), H₂O (10 equiv), HetAr-Cl 2 (1.2 equiv), 50:50 toluene/TFE (dilute to 0.4M) were quickly added. The vial heated to 80 °C and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na₂CO₃ and the aqueous layer was extracted with CH₂Cl₂ (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (MgSO₄), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heterobiaryl product.

6,7-Dimethoxy-4-(pyridin-2-yl)quinoline (40)



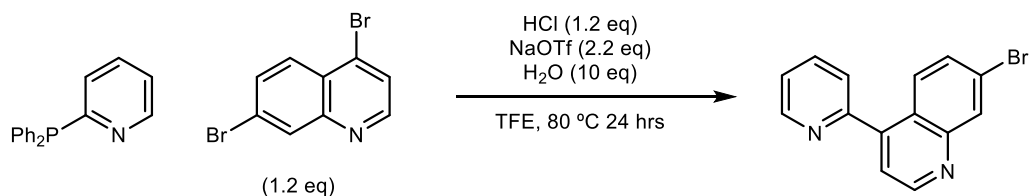
Prepared according to general procedure D'' using 2-chloropyridine (24 µL, 0.25 mmol), diphenylphosphane (44 µL, 0.25 mmol), trifluoromethanesulfonic acid (22 µL, 0.25 mmol), and chlorobenzene (0.13 mL) at 130 °C for 16 hours; then 4-chloro-6,7-dimethoxyquinoline (67 mg, 0.30 mmol), sodium trifluoromethanesulfonate (86 mg, 0.50 mmol), H₂O (45 µL, 2.5 mmol), TFE (0.25 mL), and toluene (0.25 mL) at 80 °C for 22 hours. Flash column chromatography (silica gel: 75% EtOAc in CH₂Cl₂) followed by a second flash column (neutral alumina: 75% EtOAc in hexanes) afforded the title compound as a tan crystalline solid (31 mg, 0.12 mmol, 47% yield). Spectral data is consistent with compound **6**.

7-Chloro-4-(2,6-dimethylpyridin-4-yl)quinoline (41)



Prepared according to general procedure D'' using 4-chloro-2,6-dimethylpyridine (31 μ L, 0.25 mmol), diphenylphosphane (44 μ L, 0.25 mmol), trifluoromethanesulfonic acid (22 μ L, 0.25 mmol), and chlorobenzene (0.13 mL) at 130 $^{\circ}$ C for 16 hours; then 4,7-dichloroquinoline (60 mg, 0.30 mmol), sodium trifluoromethanesulfonate (86 mg, 0.50 mmol), H₂O (45 μ L, 2.5 mmol), TFE (0.25 mL), and toluene (0.25 mL) at 80 $^{\circ}$ C for 22 hours. Flash column chromatography (silica gel: 50% EtOAc in hexanes) followed by a second flash column (silica gel: 100% Et₂O) afforded the title compound as a white crystalline solid (40 mg, 0.15 mmol, 59% yield). Spectral data is consistent with compound **8**.

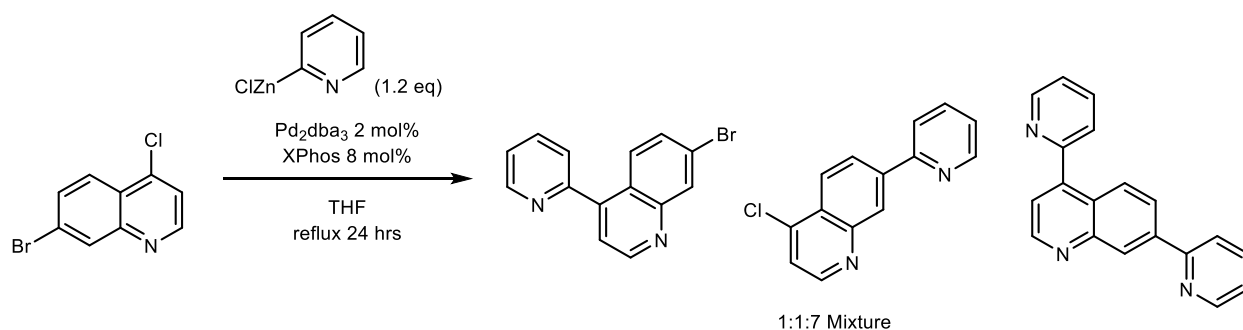
A. 3.3.9 Tandem S_NAr-Ligand-Coupling



Prepared according to general procedure B'. An oven dried 8 mL vial with a septa cap was charged with 2-(diphenylphosphane)pyridine (63 mg, 0.25 mmol), sodium trifluoromethanesulfonate (95 mg, 0.55 mmol), and 4,7-dibromoquinoline (86 mg, 0.30 mmol). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill and then TFE (0.63 mL),

H₂O (45 μ L, 2.5 mmol), and 4.0M HCl in dioxanes (75 μ L, 0.30 mmol) were added via a syringe. The septa cap was quickly replaced with an unpierced one and the reaction was heated to 80 °C and allowed to stir for 24 hours. The reaction was quenched with a saturated aqueous solution of Na₂CO₃ and the aqueous layer was extracted with CH₂Cl₂ (3x). 1,3,5-Trimethoxybenzene (42 mg, 0.25 mmol) was added as an internal standard and the ¹H NMR yield was determined to be 81%.

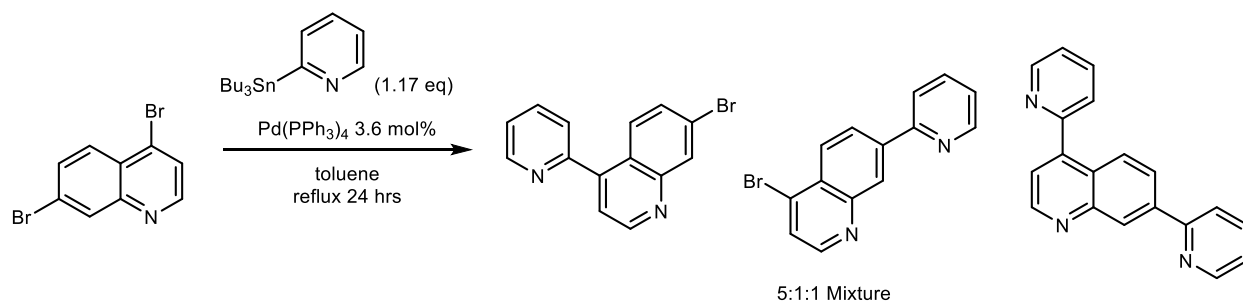
A. 3.3.10 Negishi Coupling:



Prepared according to established procedure.⁶ A 5 mL oven dried round-bottom flask equipped with a stir bar was purged with nitrogen and charged with 2.0M iPrMgCl in THF (550 μ L, 1.10 mmol) and 2-bromopyridine (97 μ L, 1.00 mmol) was added dropwise over 20 minutes at room temperature. Mixture was allowed to stir at room temperature for 4 hours prior to dropwise addition of ZnCl₂ in THF (164 mg, 1.20 mmol, 0.5M, 2.40 mL). A separate 10 mL two-necked flask fitted with a reflux condenser was charged with Pd₂dba₃ (4.6 mg, 0.01 mmol, 2.0 mol%), XPhos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 9.5 mg, 0.02 mmol, 8.0 mol%) and THF (630 μ L). Flask was then heated to 65 °C and stirred for 15 minutes prior to addition of 7-bromo-4-chloroquinoline (61 mg, 0.25 mmol). Mixture was allowed to stir for 20 minutes at 65 °C before addition of pyridin-2-ylzinc(II) chloride in THF (0.33M, 900 μ L, 1.20 mmol). Reaction was stirred at 65 °C for 24 hours prior to cooling to room temperature. After reaching room temperature, reaction was quenched with saturated aqueous solution of NaHCO₃ and the organic

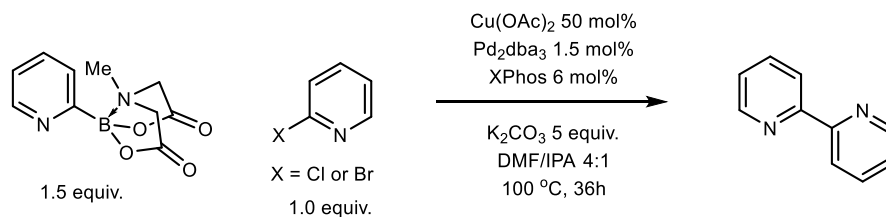
layer was separated. The aqueous layer was extracted 3x with EtOAc and the organic layers were combined and washed with H₂O. The organic layer was then dried with MgSO₄ and concentrated *in vacuo*. 1,3,5-trimethoxybenzene (42 mg, 0.25 mmol) was added as an internal standard and the ¹H NMR yield was determined to be 7%, 5%, and 38% respectively (1:1:7). Starting material remaining (25%) was observed by ¹H NMR.

A. 3.3.11 Stille Coupling



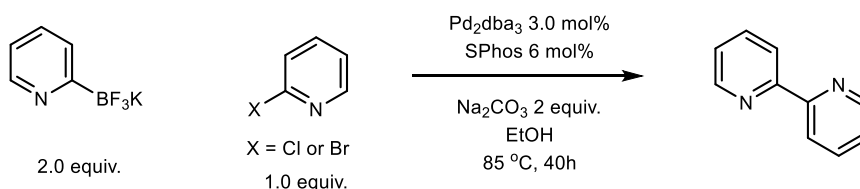
Prepared according to established procedure.⁷ An 8 mL oven dried vial equipped with a stir bar was charged with 4,7-dibromoquinoline (72 mg, 0.25 mmol), Pd(PPh₃)₄ (10 mg, 0.009 mmol), toluene (0.72 mL), and subjected to three cycles of vacuum/nitrogen backfill. 2-(tributylstannyl)pyridine (95 μ L, 0.29 mmol) was added via a syringe before the reaction was heated to reflux for 24 hours. After cooling to room temperature, 1,3,5-trimethoxybenzene (42 mg, 0.25 mmol) was added as an internal standard. ¹H NMR yield of 7-bromo-4-(pyridin-2-yl)quinoline, 4-bromo-7-(pyridin-2-yl)quinoline, and 4,7-di(pyridin-2-yl)quinoline was determined to be 61%, 14%, and 13% respectively (5:1:1). The crude material was purified by flash column chromatography (silica gel, gradient elution: 30% EtOAc in hexanes to 40% EtOAc in hexanes) followed by a second flash column (neutral alumina, gradient elution: 25% EtOAc in hexanes to 30% EtOAc in hexanes) to afford the title compounds.

A. 2.3.12 BMIDA Cross Coupling



Prepared according to established procedure.⁴ An 8 mL oven dried vial equipped with a stir bar was purged with nitrogen and charged with 6-methyl-2-(pyridin-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (70 mg, 0.30 mmol), 2-chloropyridine (19 mL, 0.20 mmol) or 2-bromopyridine (19 mL, 0.20 mmol), $\text{Cu}(\text{OAc})_2$ (18 mg, 0.10 mmol), K_2CO_3 (138 mg, 1.0 mmol), and isopropylalcohol (400 μL). In a separate 8 mL oven dried vial in a glove box, Pd_2dba_3 (2.7 mg, 0.003 mmol, 1.5 mol%), XPhos (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 5.7 mg, 0.01 mmol, 6.0 mol%), and DMF (1.6 mL) were stirred together at 100 °C for 10 minutes. This mixture was then transferred to the other 8 mL vial while mixture was soluble in DMF (around 40 °C for transfer). Reaction was then allowed to stir at 100 °C for 36 hours. Reaction was cooled to room temperature and quenched with 10% NaOH in H_2O and aqueous layer was extracted 3x with Et_2O . The combined organic layers were dried with MgSO_4 and concentrated *in vacuo*. 1,3,5-Trimethoxybenzene (34 mg, 0.20 mmol) was added as an internal standard and the ^1H NMR yield was determined to be 39% for 2-chloropyridine and 38% for 2-bromopyridine.

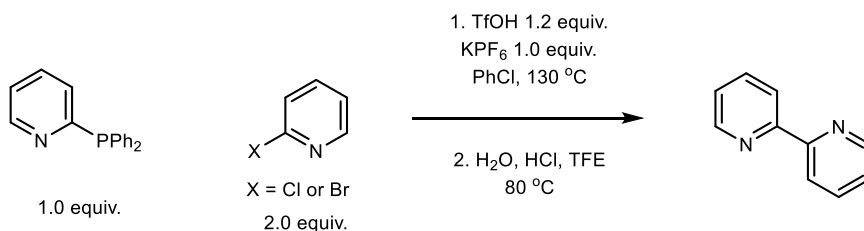
A. 2.3.13 BF_3K Cross Coupling



Prepared according to established procedure.⁵ An 8 mL oven dried vial equipped with a stir bar was purged with nitrogen and charged with 2-(trifluoro- I^4 -boraneyl)pyridine, potassium salt

(93 mg, 0.50 mmol), 2-chloropyridine (23 mL, 0.25 mmol) or 2-bromopyridine (24 mL, 0.25 mmol), Na₂CO₃ (53mg, 0.5 mmol), Pd(OAc)₂ (1.7 mg, 0.008 mmol, 3.0 mol%), and SPhos (2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 6.2 mg, 0.016 mmol, 6 mol%) and EtOH (2.0 mL). Reaction was then heated to 80 °C for 40 hours. Reaction was cooled to room temperature and filtered through a pad of silica gel eluting with EtOAc. The filtrate was concentrated *in vacuo*. 1,3,5-Trimethoxybenzene (42 mg, 0.25 mmol) was added as an internal standard and the ¹H NMR yield was determined to be 15% for 2-chloropyridine and 5% for 2-bromopyridine.

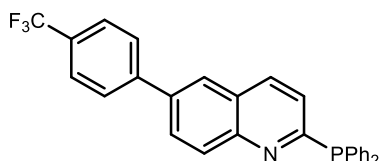
A. 2.3.14 Tandem S_NAr-Ligand-Coupling



Prepared according to general procedure C' using 2-(diphenylphosphanyl)-5-(trifluoromethyl)pyridine (66 mg, 0.25 mmol), 2-chloropyridine (47 μL, 0.50 mmol) or 2-bromopyridine (48 μL, 0.50 mmol), potassium hexafluorophosphate (46 mg, 0.25 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), and chlorobenzene (0.13 mL) at 130 °C for 41 hours; then H₂O (45 μL, 2.5 mmol), 4.0M HCl in dioxanes (63 mL, 0.25 mmol), and TFE (0.50 mL) at 80 °C for 23 hours. 1,3,5-Trimethoxybenzene (42 mg, 0.25 mmol) was added as an internal standard and the ¹H NMR yield was determined to be 68% for 2-chloropyridine and 67% for 2-bromopyridine.

A. 2.3.14 Phosphine Compatibility: Suzuki-Miyaura Reaction

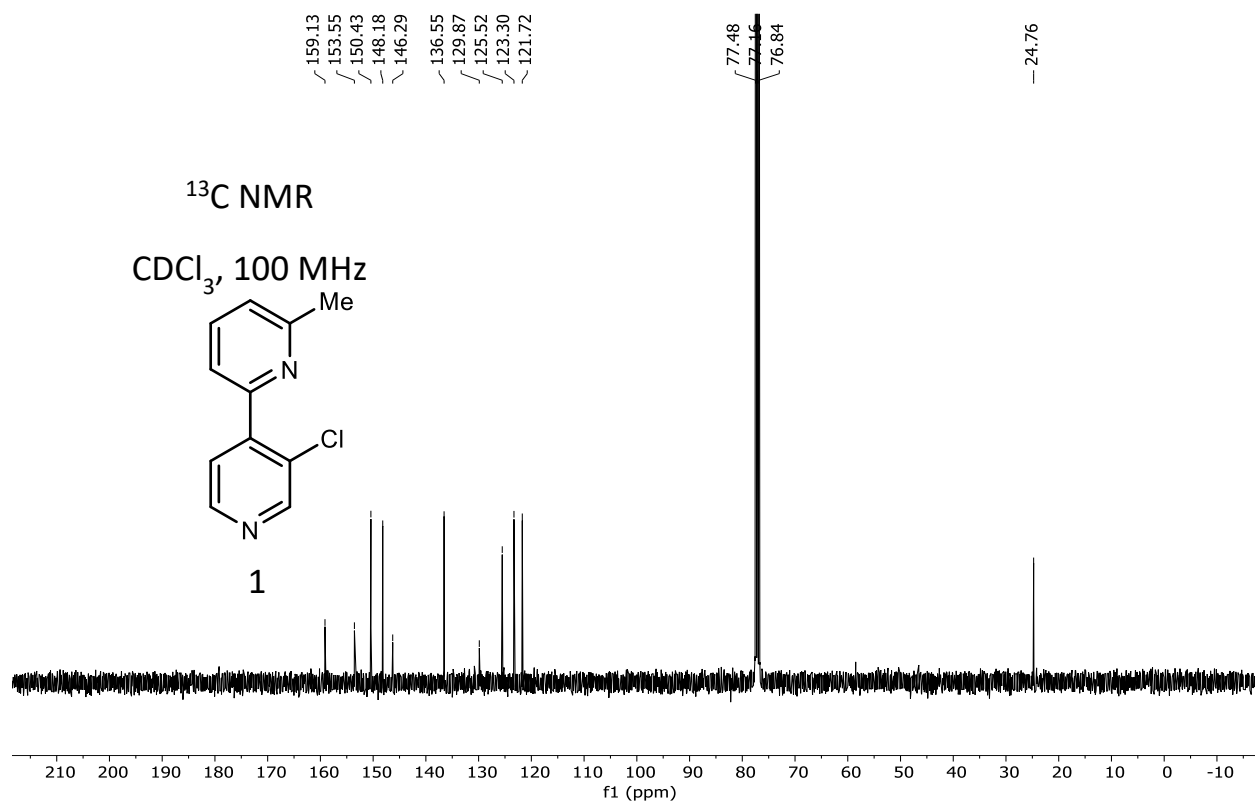
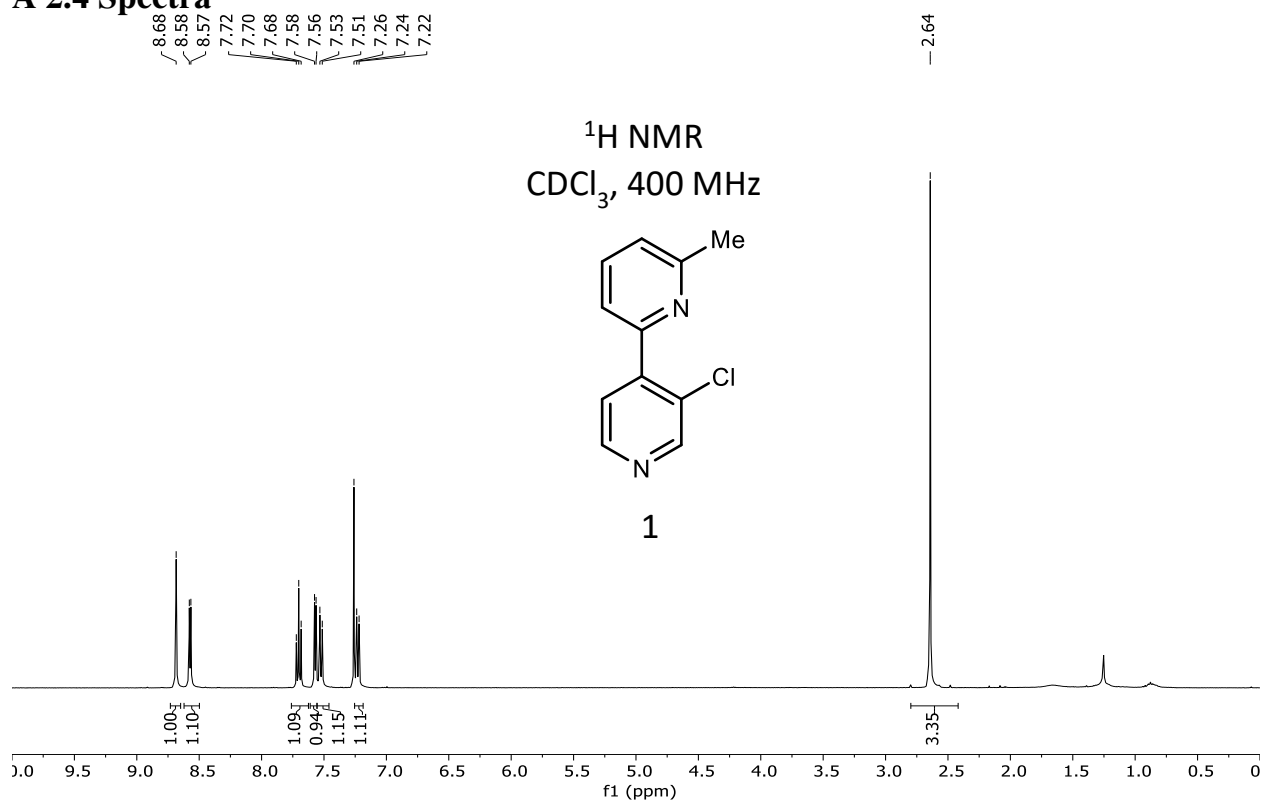
2-(Diphenylphosphaneyl)-6-(4-(trifluoromethyl)phenyl)quinoline (45)

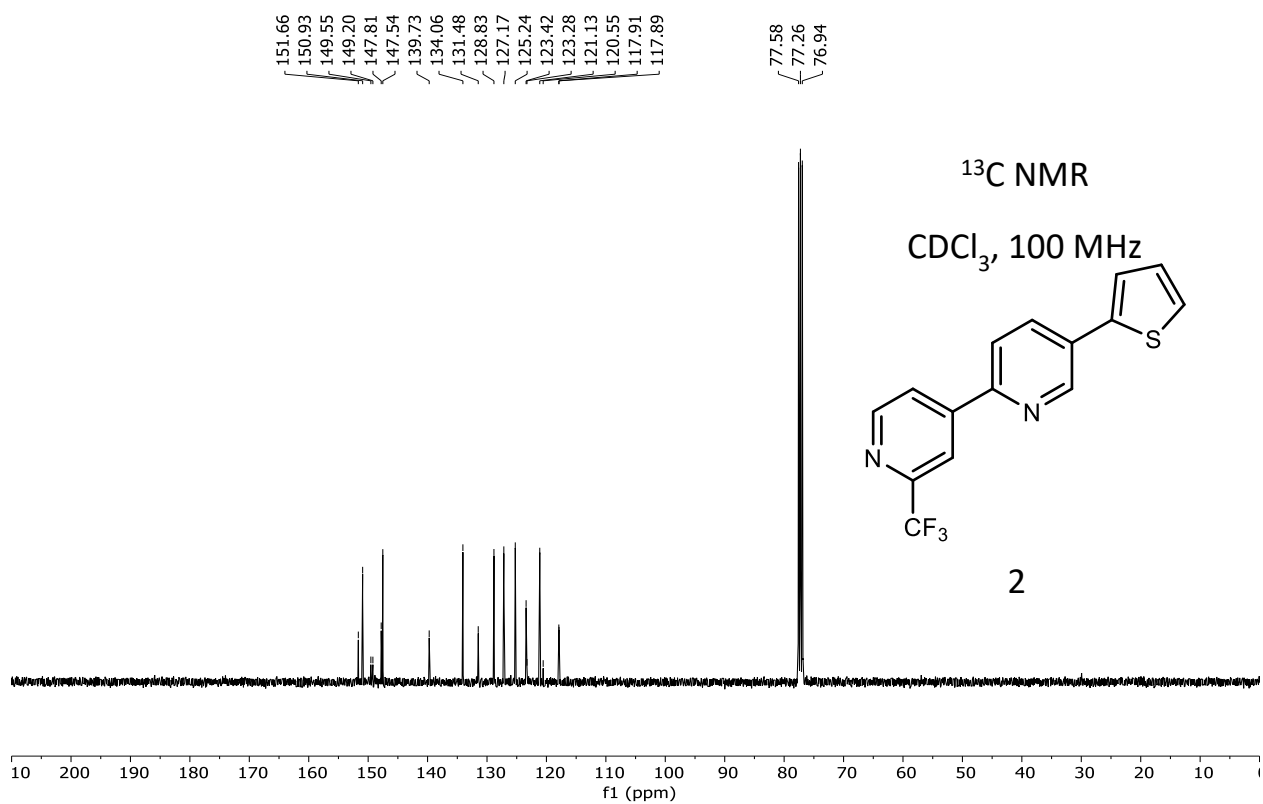
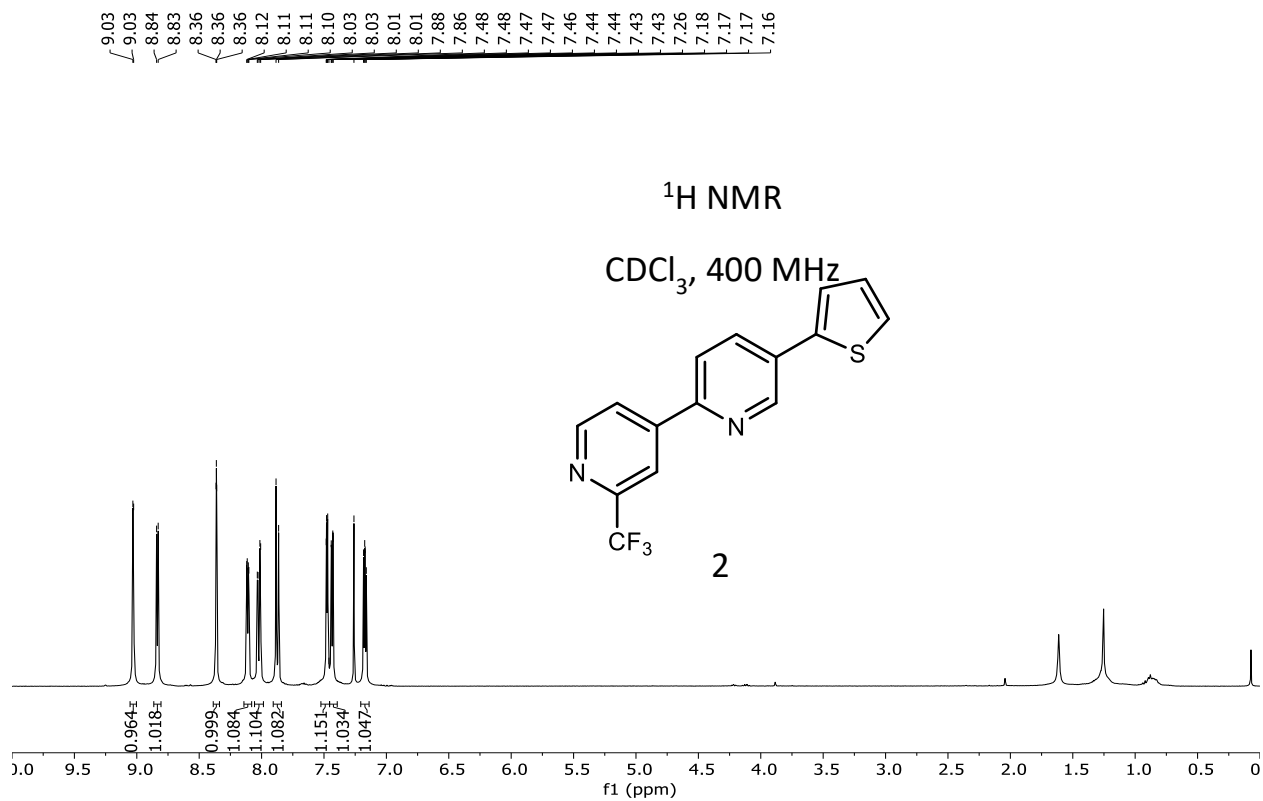


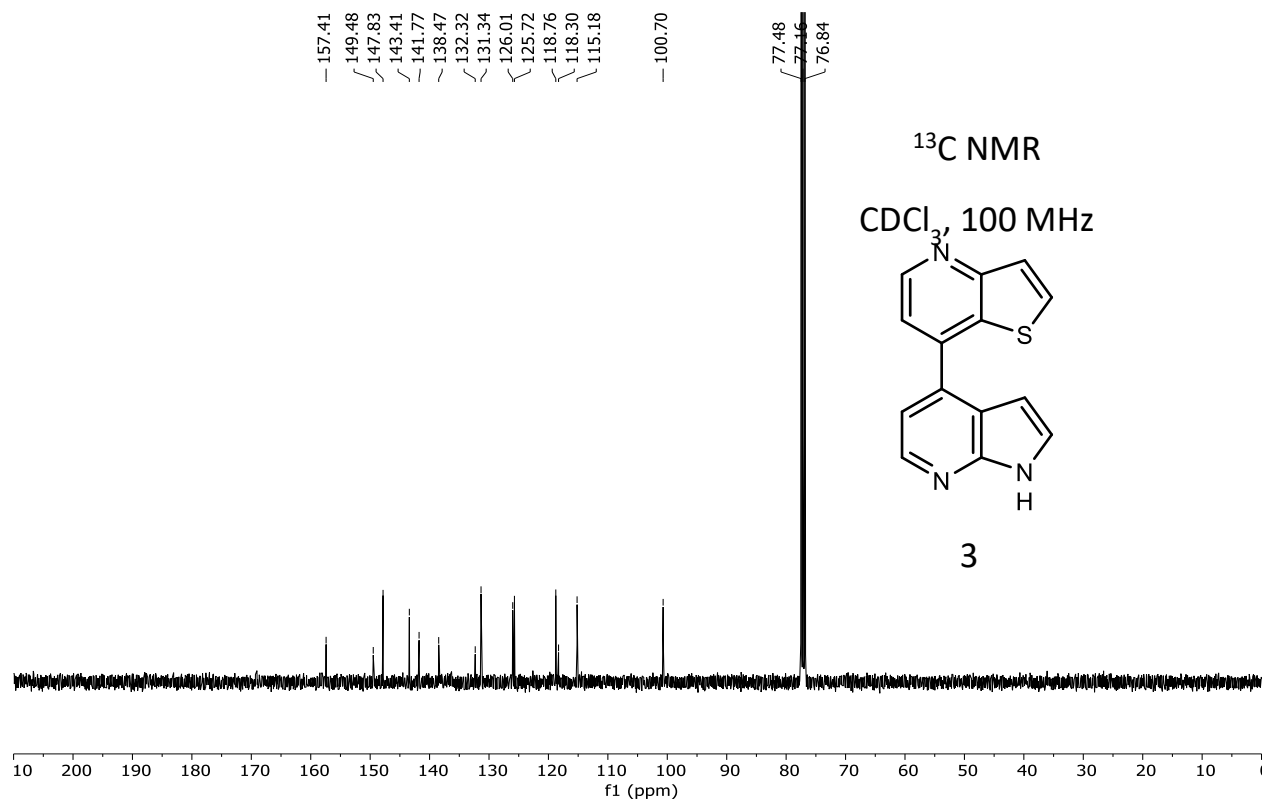
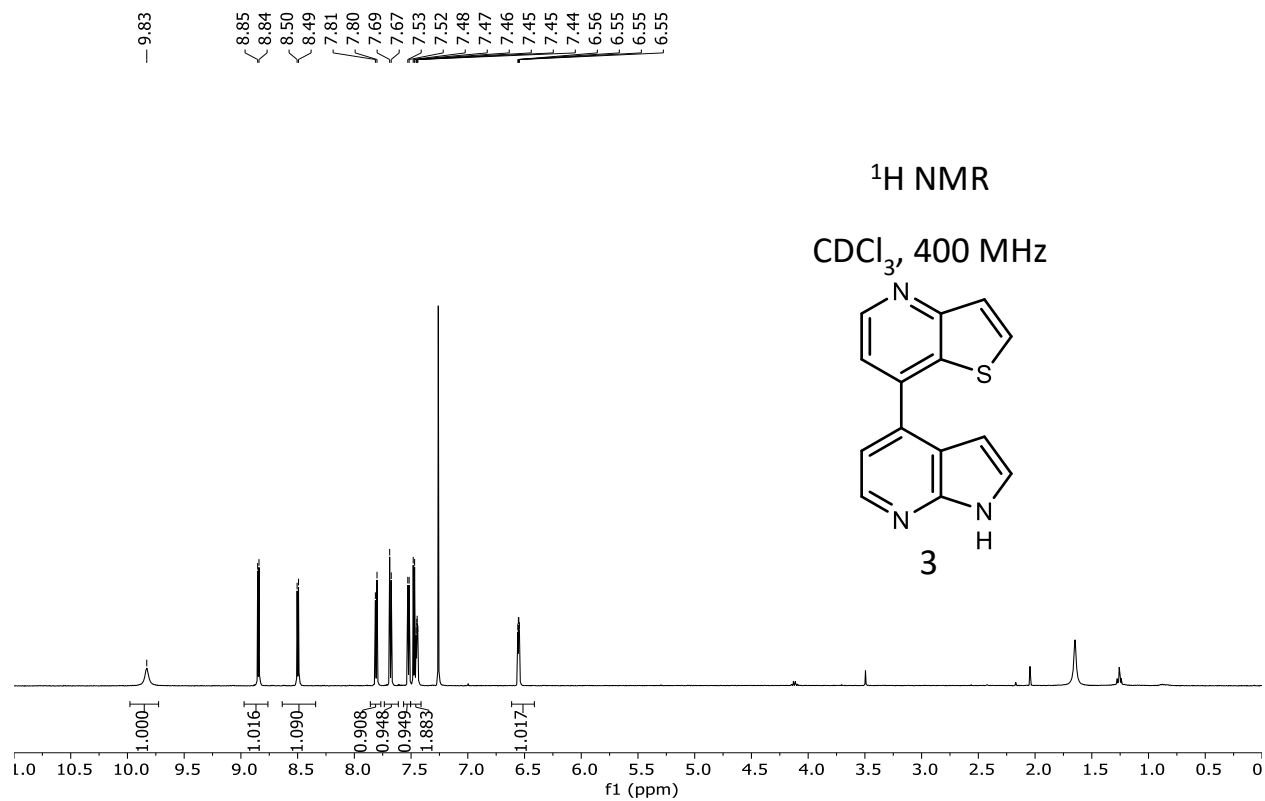
Prepared using 6-bromo-2-(diphenylphosphaneyl)quinoline (784 mg, 2.00 mmol), (4-(trifluoromethyl)phenyl)boronic acid (454 mg, 2.40 mmol), $\text{Pd}_2(\text{dba})_3$ (18 mg, 0.02 mmol), tricyclohexylphosphane (14 mg, 0.048 mmol), aqueous K_3PO_4 (1.25 M, 2.7 mL, 3.40 mmol), and dioxanes (5.3 mL). Flash column chromatography (silica gel, gradient elution: 5% EtOAc in hexanes) afforded the title compound as a faint yellow powder (631 mg, 1.38 mmol, 69% yield). mp 130-131 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3071, 3040, 1615, 1550, 1456, 1386, 1257, 895, 753, 546; ^1H NMR (400 MHz, CDCl_3) δ : 8.24 (1H, d, $J = 8.7$ Hz), 8.07 (1H, dd, $J = 8.6, 1.8$ Hz), 8.01-7.92 (2H, m), 7.81 (2H, d, $J = 8.2$ Hz), 7.75 (2H, d, $J = 8.3$ Hz), 7.55-7.35 (10H, m), 7.24 (1H, d, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.9 (d, $J = 2.1$ Hz), 148.3 (d, $J = 14.5$ Hz), 138.1, 136.2 (d, $J = 11.2$), 135.7 (d, $J = 2.8$ Hz), 134.4 (d, $J = 19.7$ Hz), 132.3 (d, $J = 9.4$ Hz), 130.5, 129.9 (q, $J = 32.5$ Hz), 129.3, 129.2, 128.8 (d, $J = 7.2$ Hz), 127.8, 127.0, 126.0, 125.96, 125.0 (d, $J = 14.3$ Hz), 124.3 (q, $J = 272.1$ Hz); ^{19}F NMR (365 MHz, CDCl_3) δ : -62.39; ^{31}P NMR (365 MHz, CDCl_3) δ : -1.80; m/z LRMS (ESI + APCI) found $[\text{M}+\text{H}]^+$ 458.2, $\text{C}_{28}\text{H}_{20}\text{F}_3\text{NP}^+$ requires 458.1.

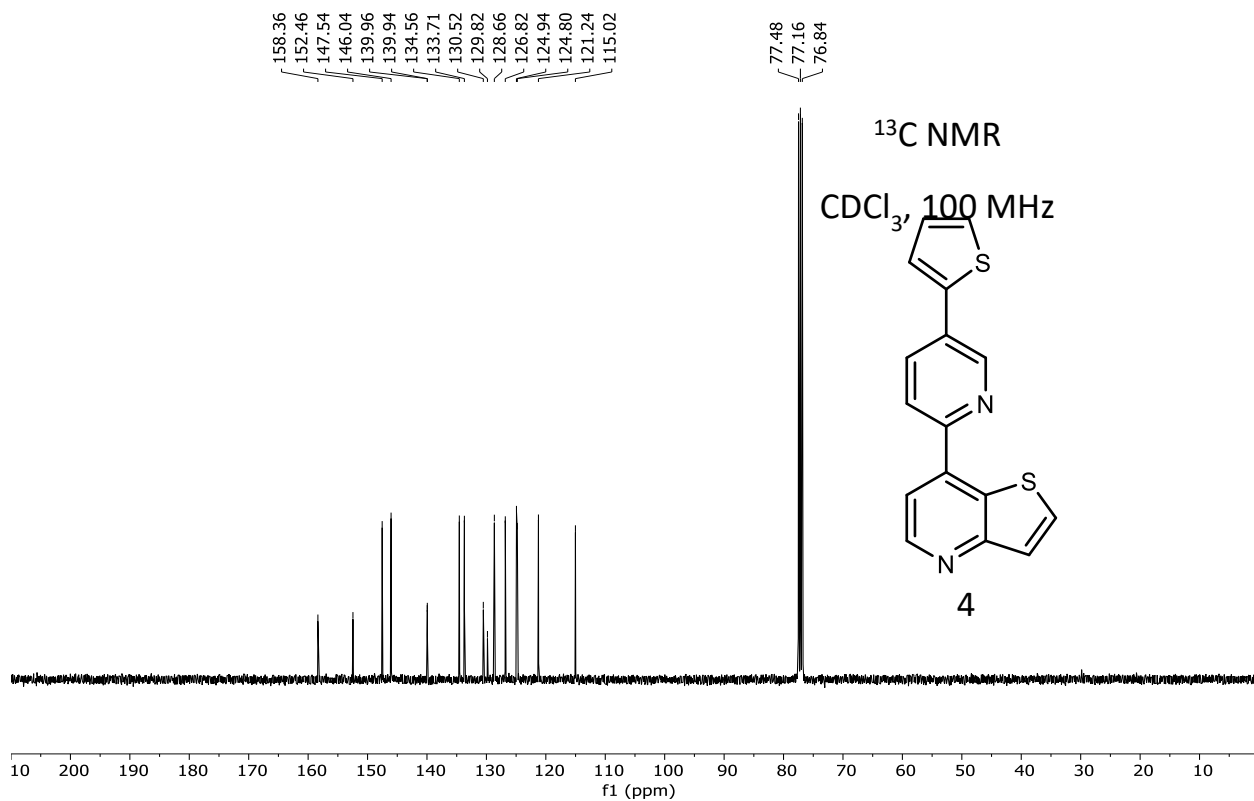
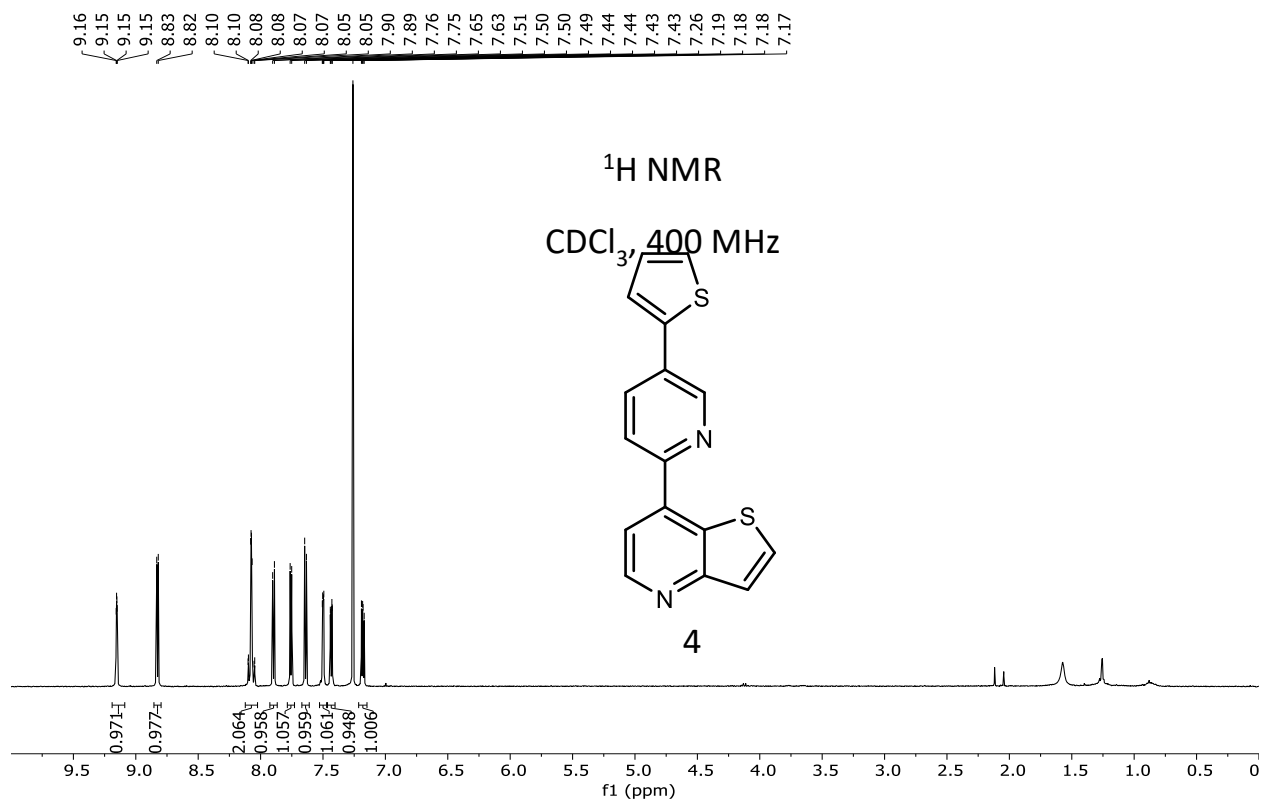
Note: Other reaction conditions for Suzuki-Miyaura reaction gave undesired oxidation of phosphine product. It is recommended to use this set of conditions and to vigorously degas all solvents prior to use in reaction.

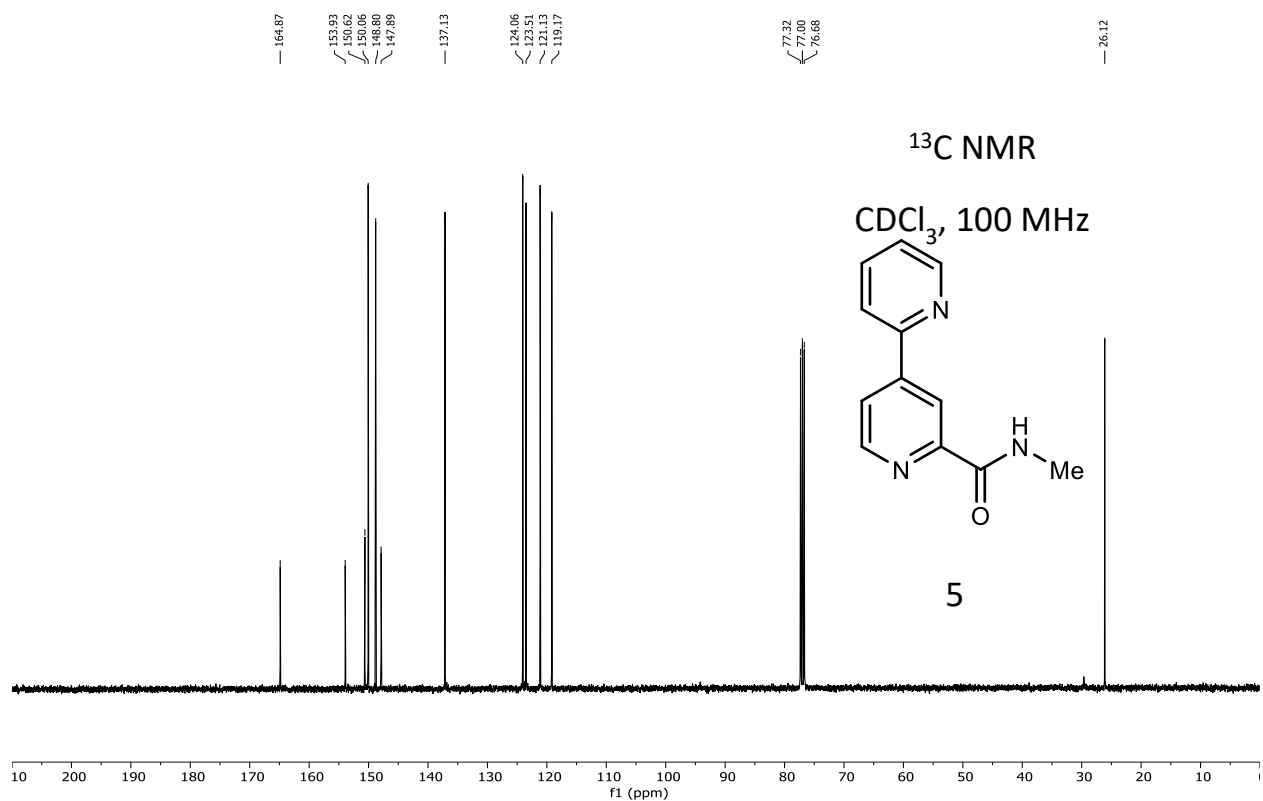
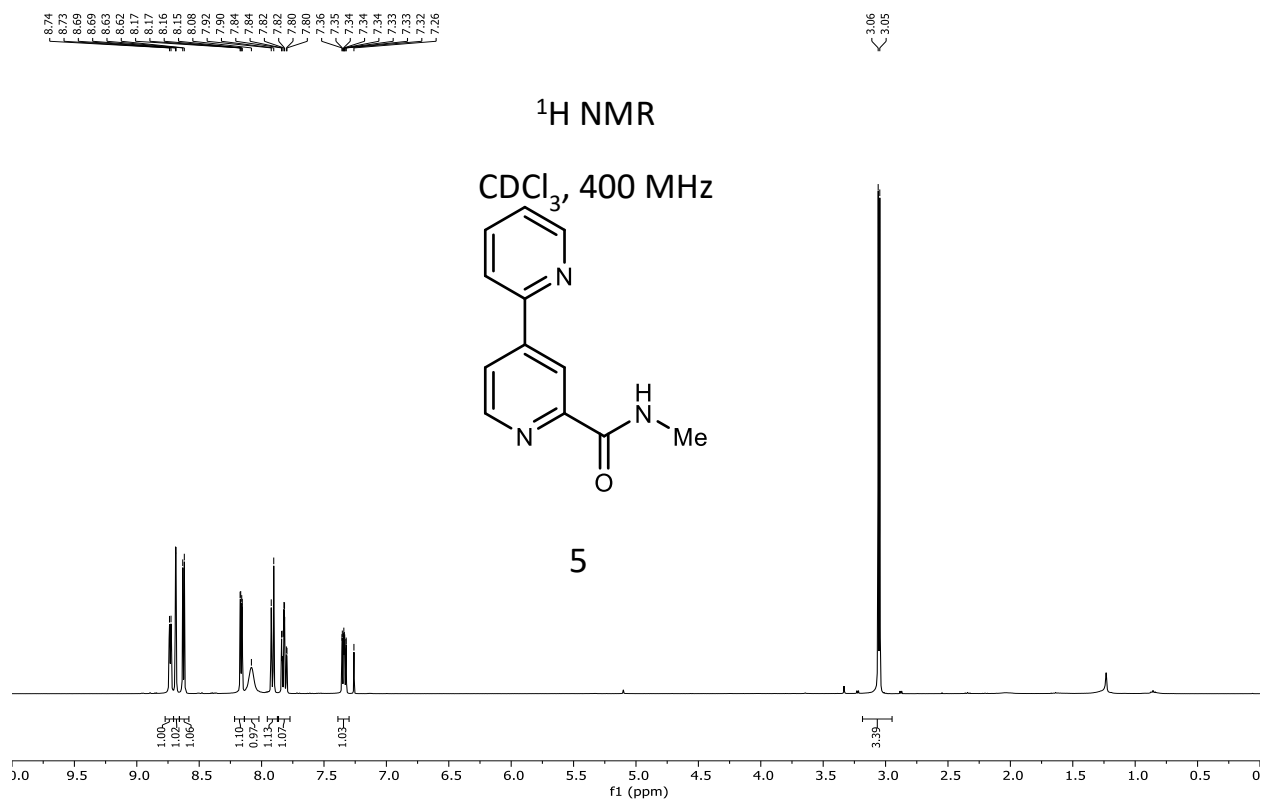
A 2.4 Spectra

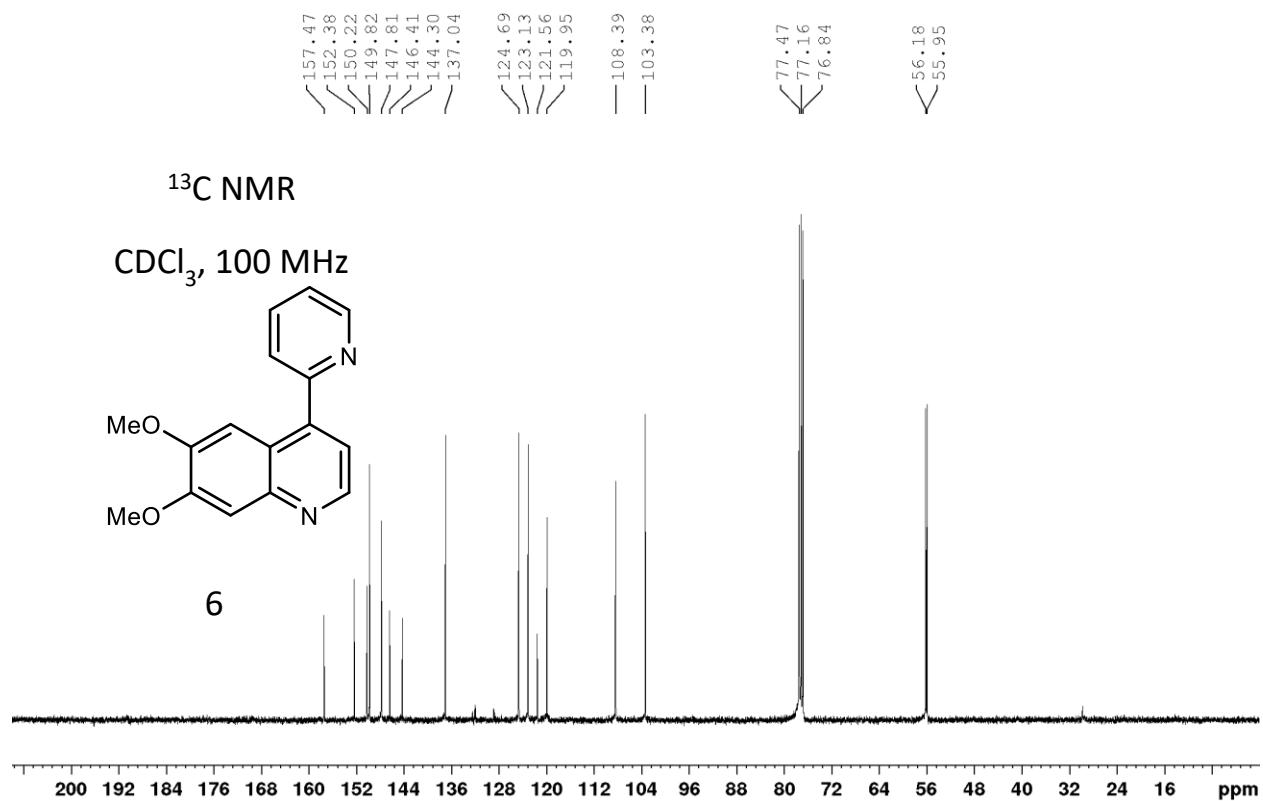
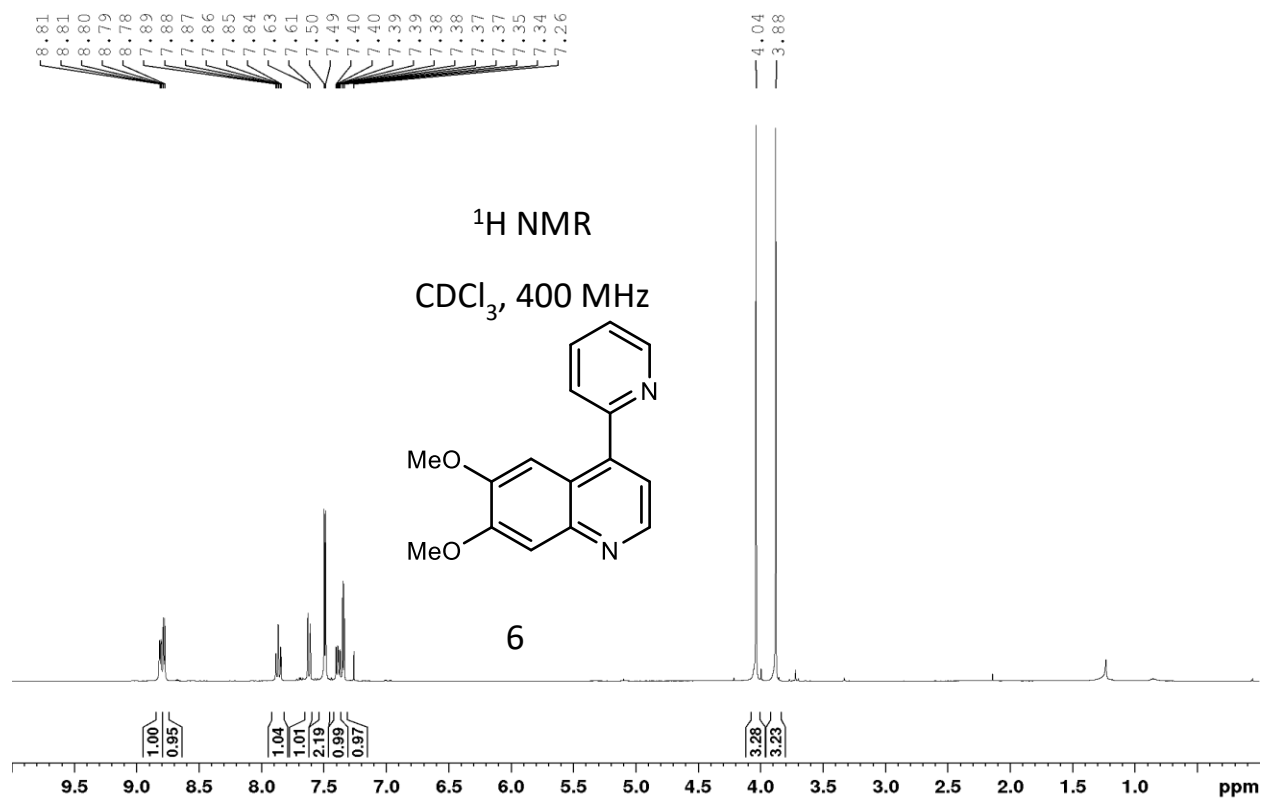


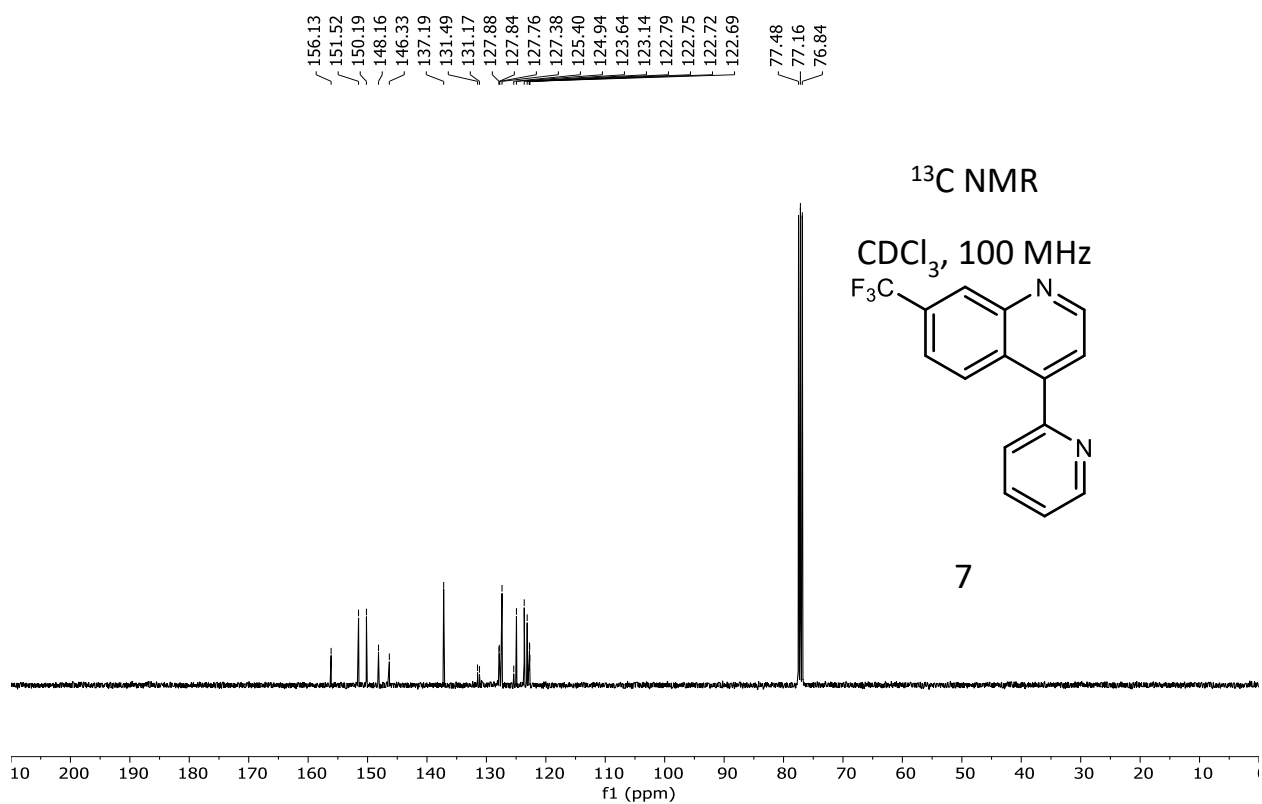
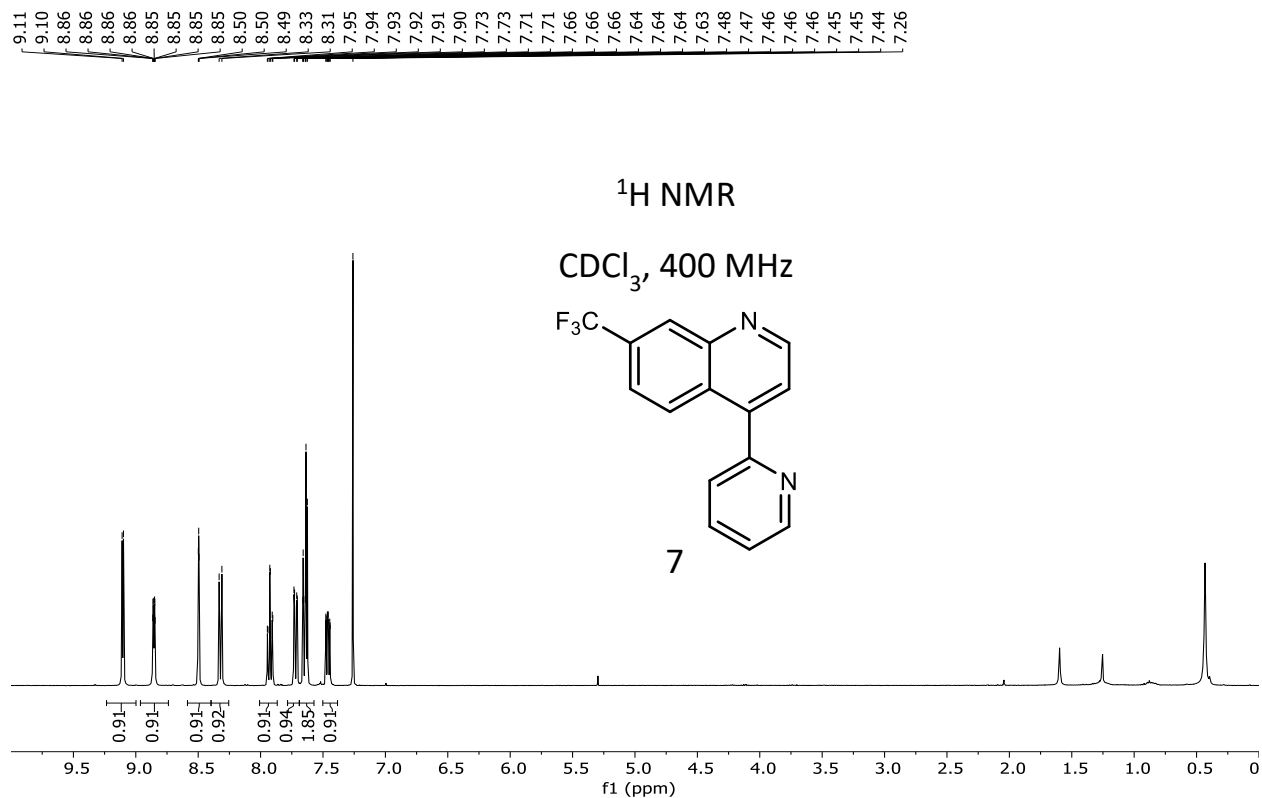


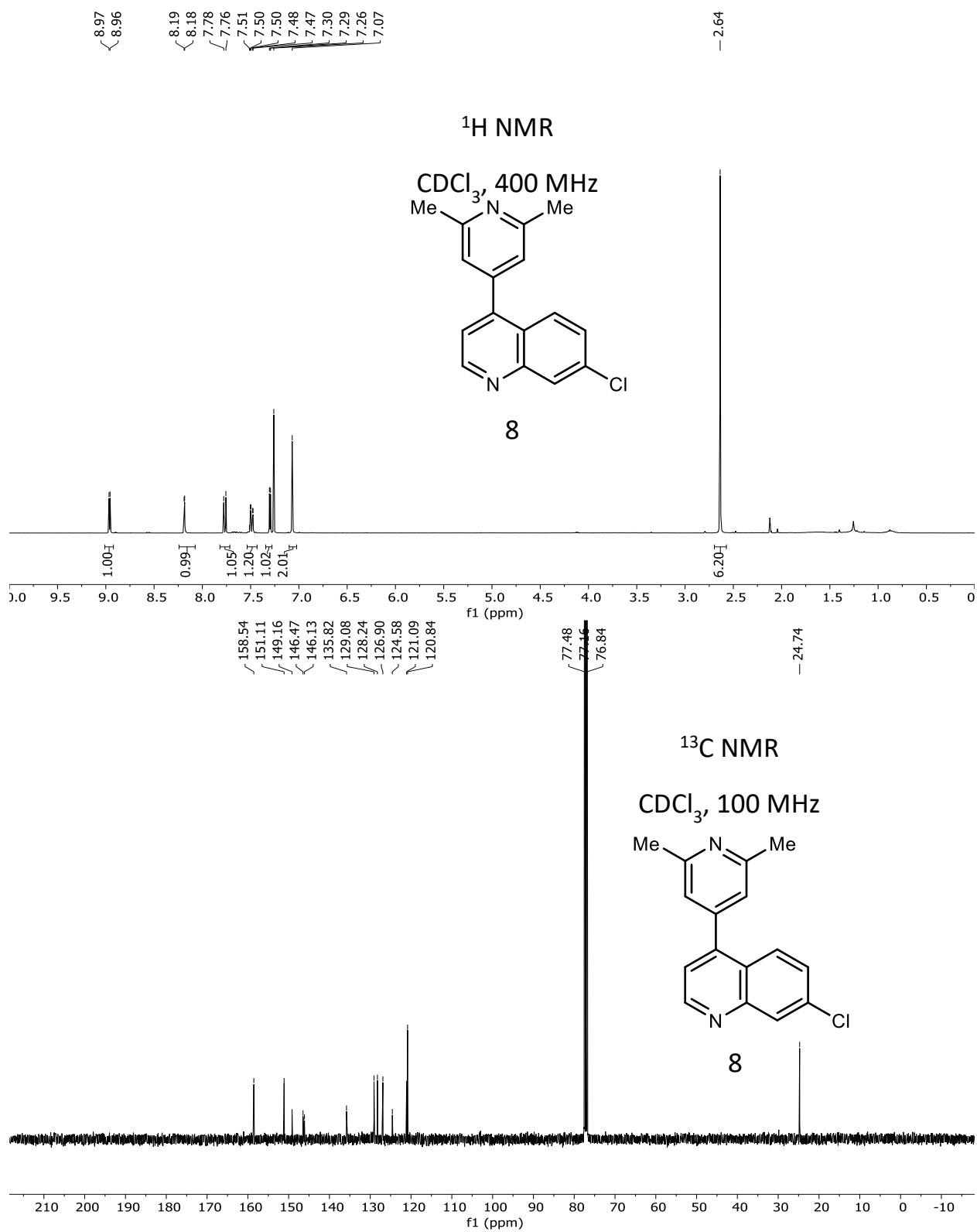


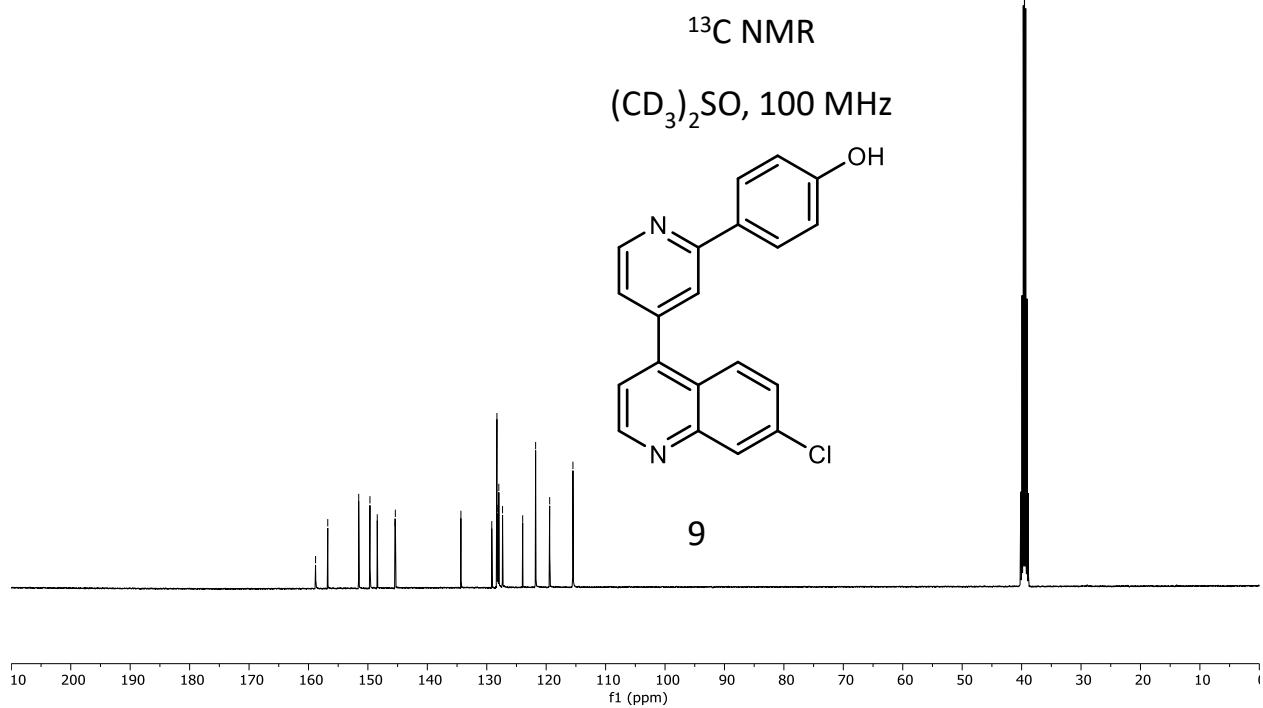
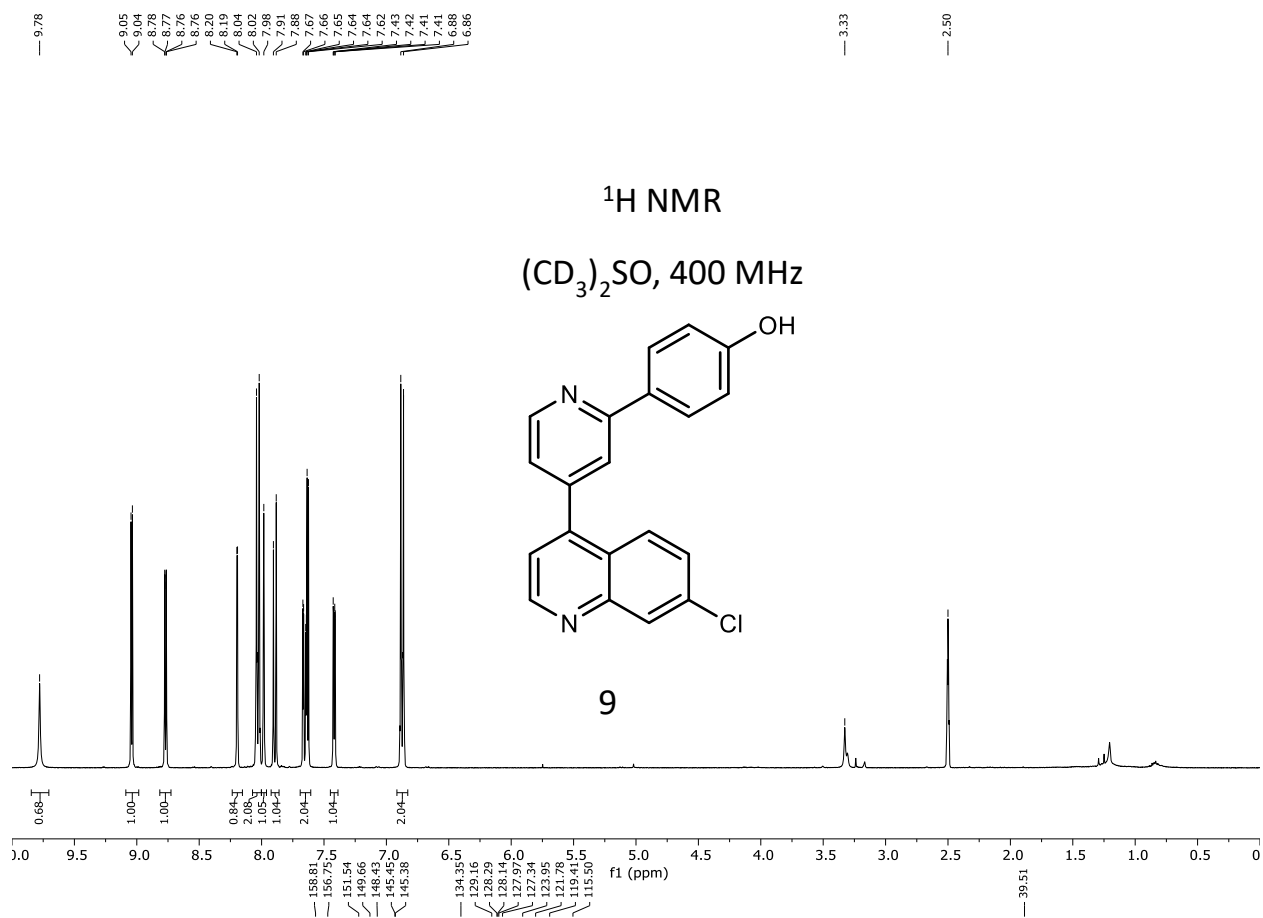


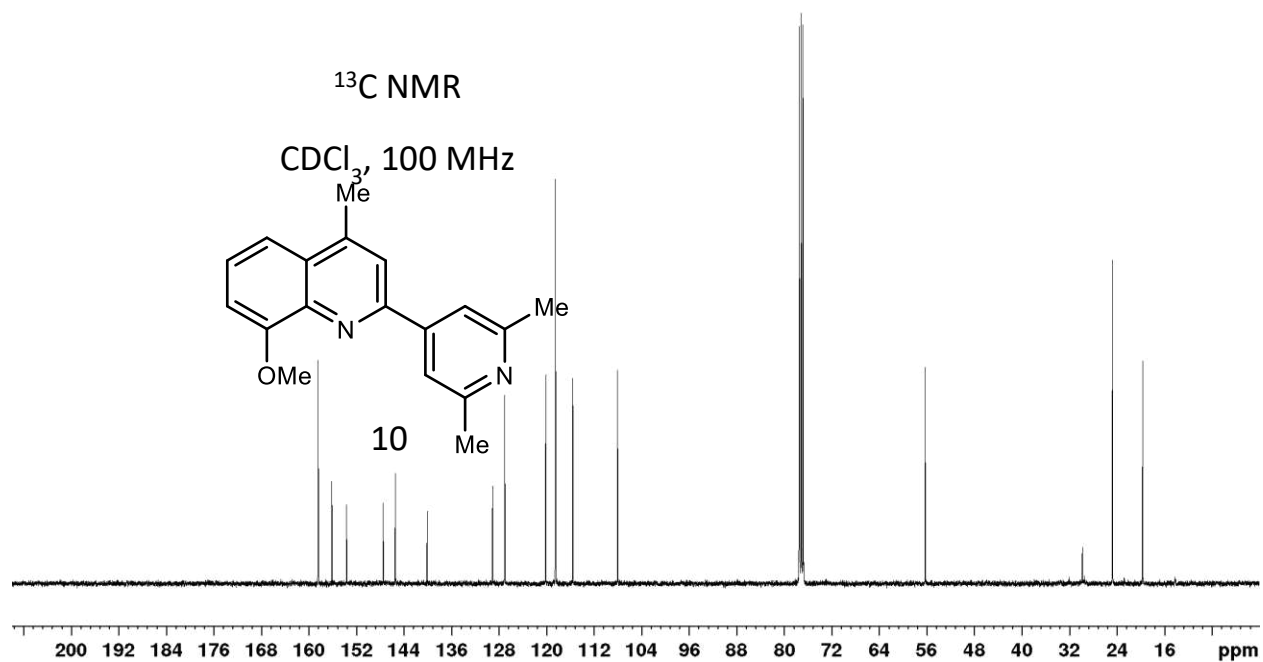
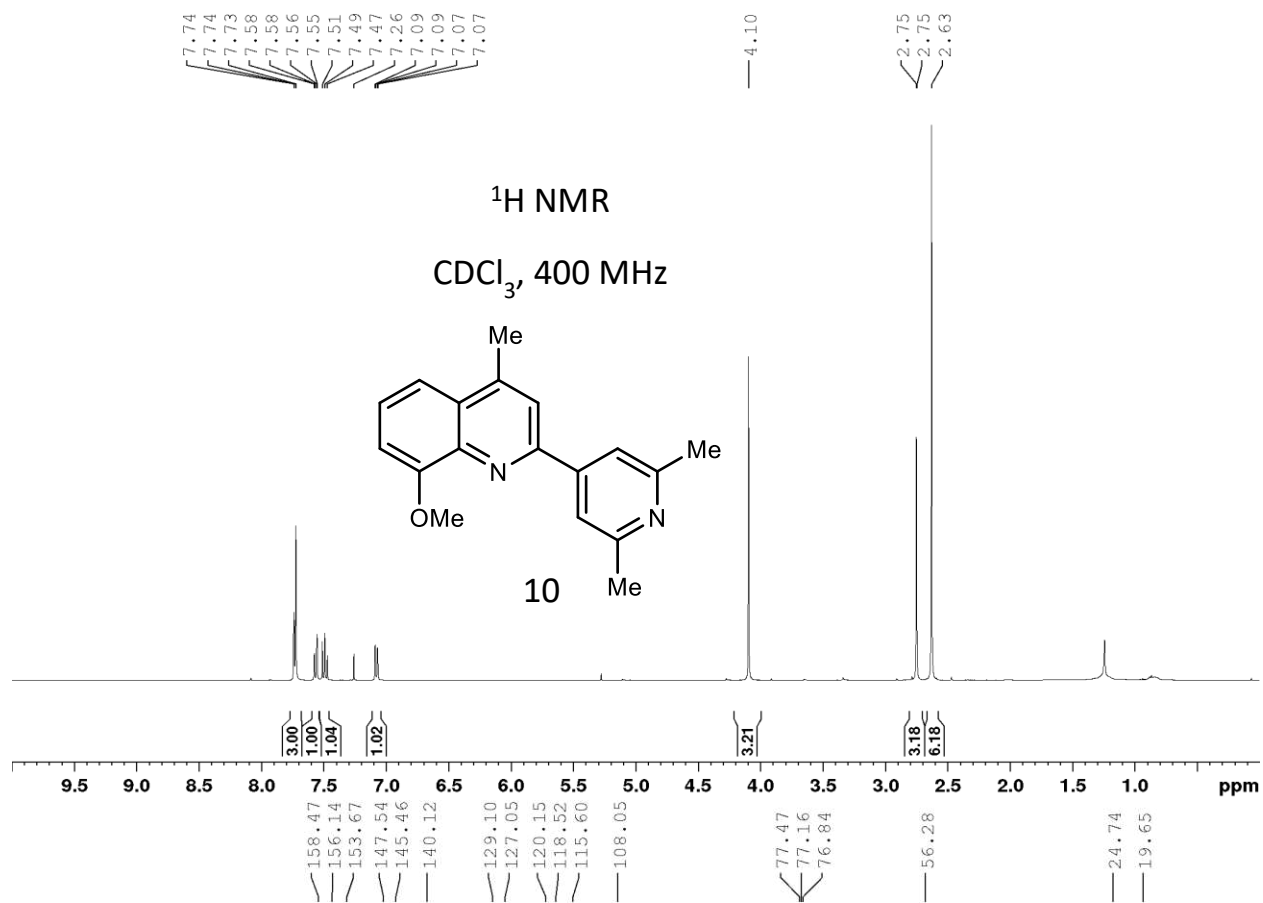


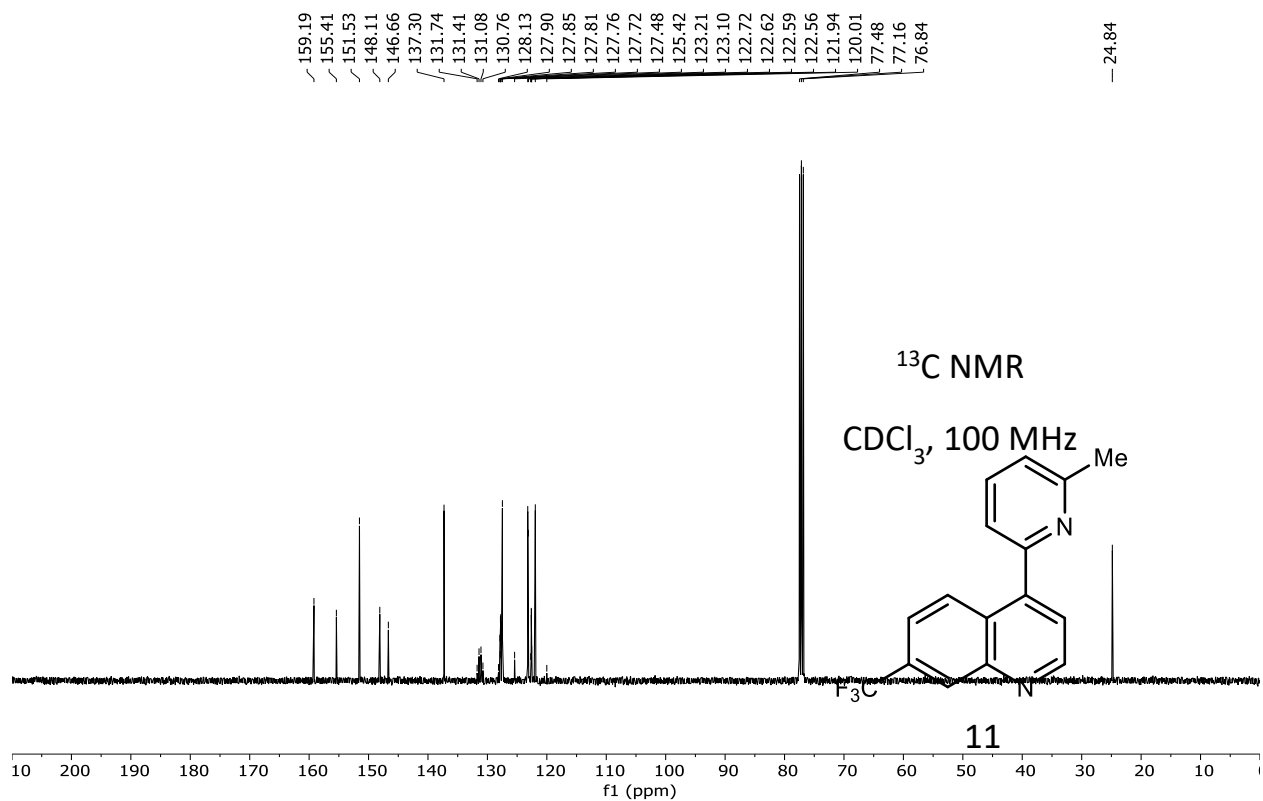
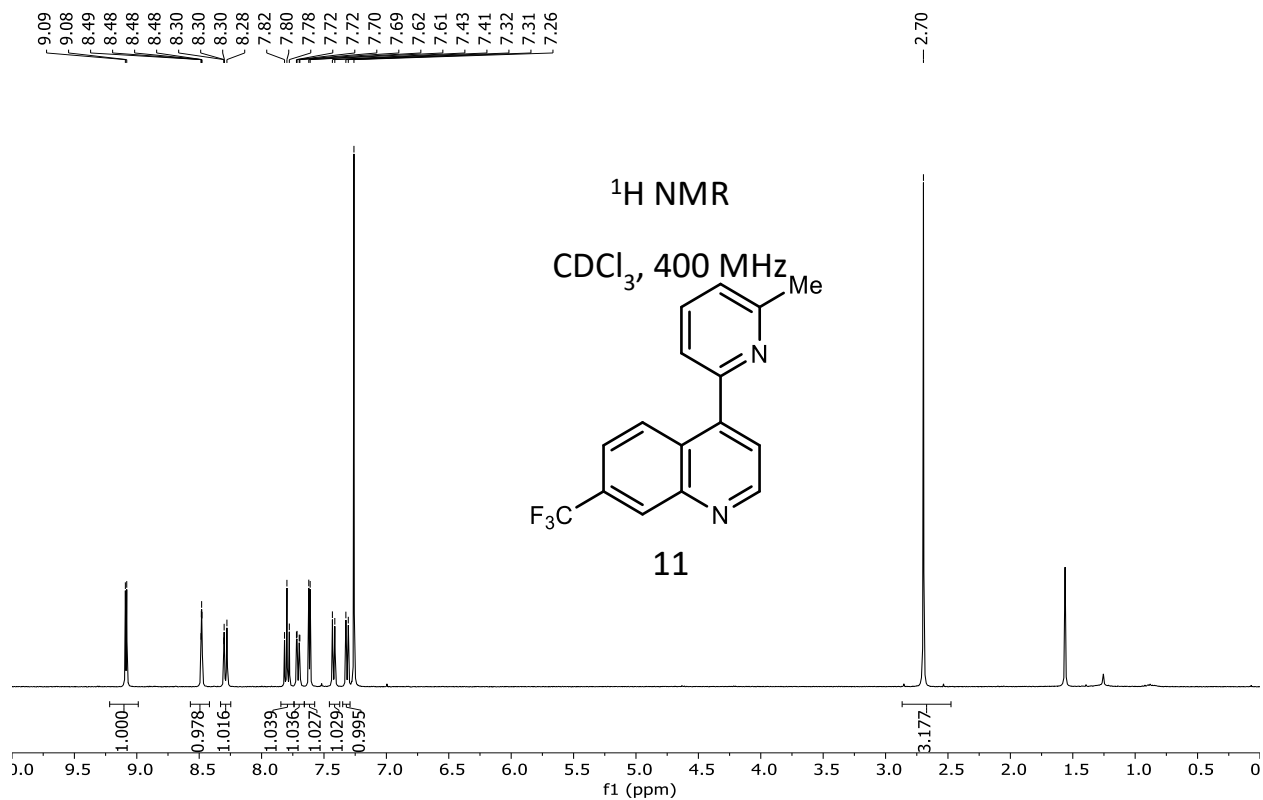


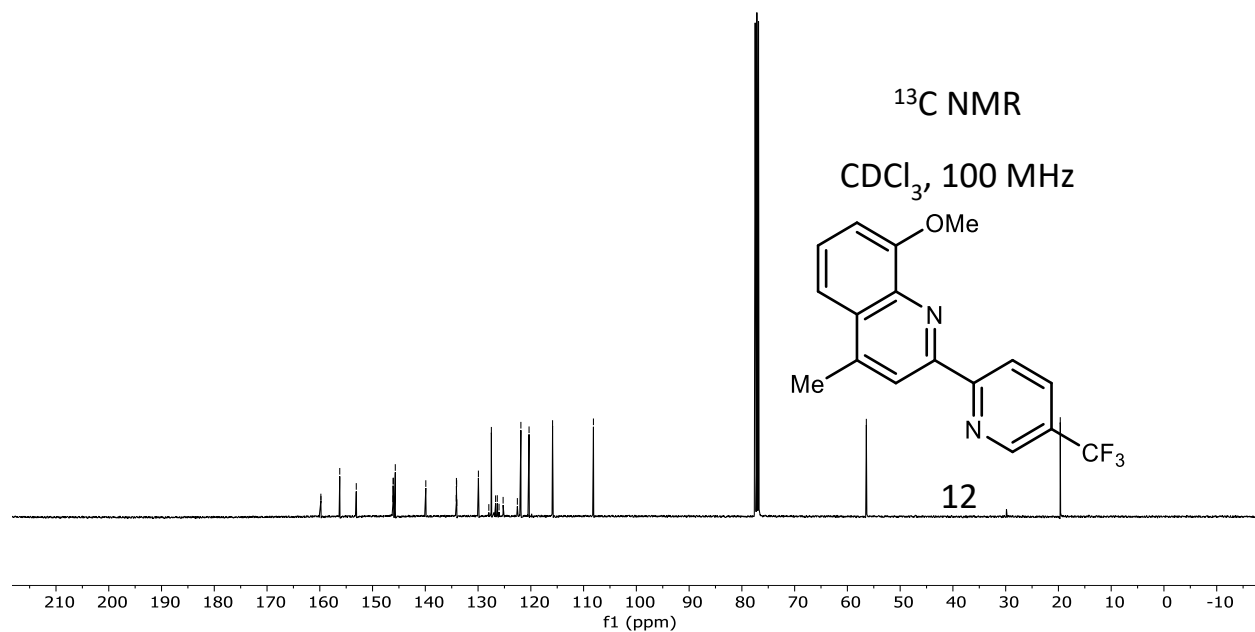
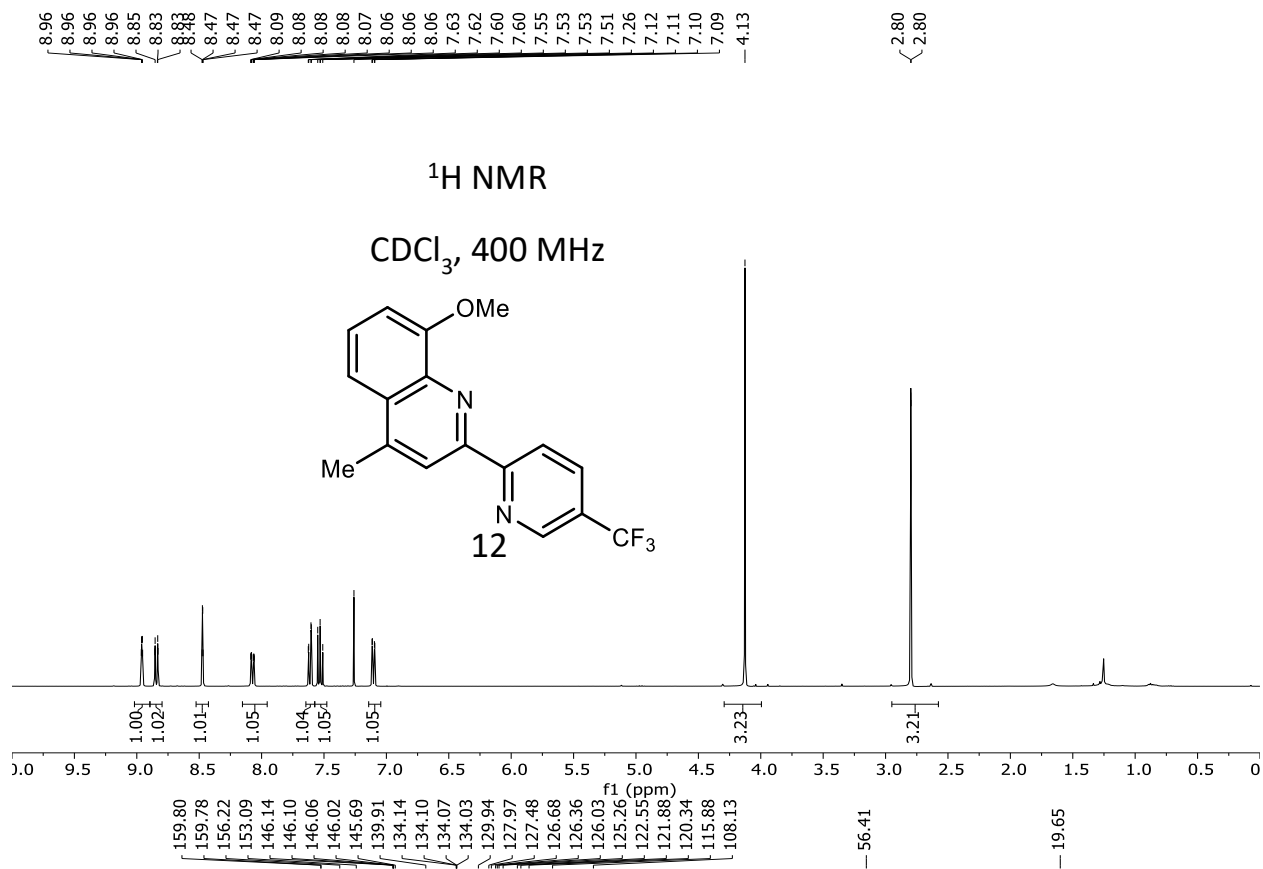


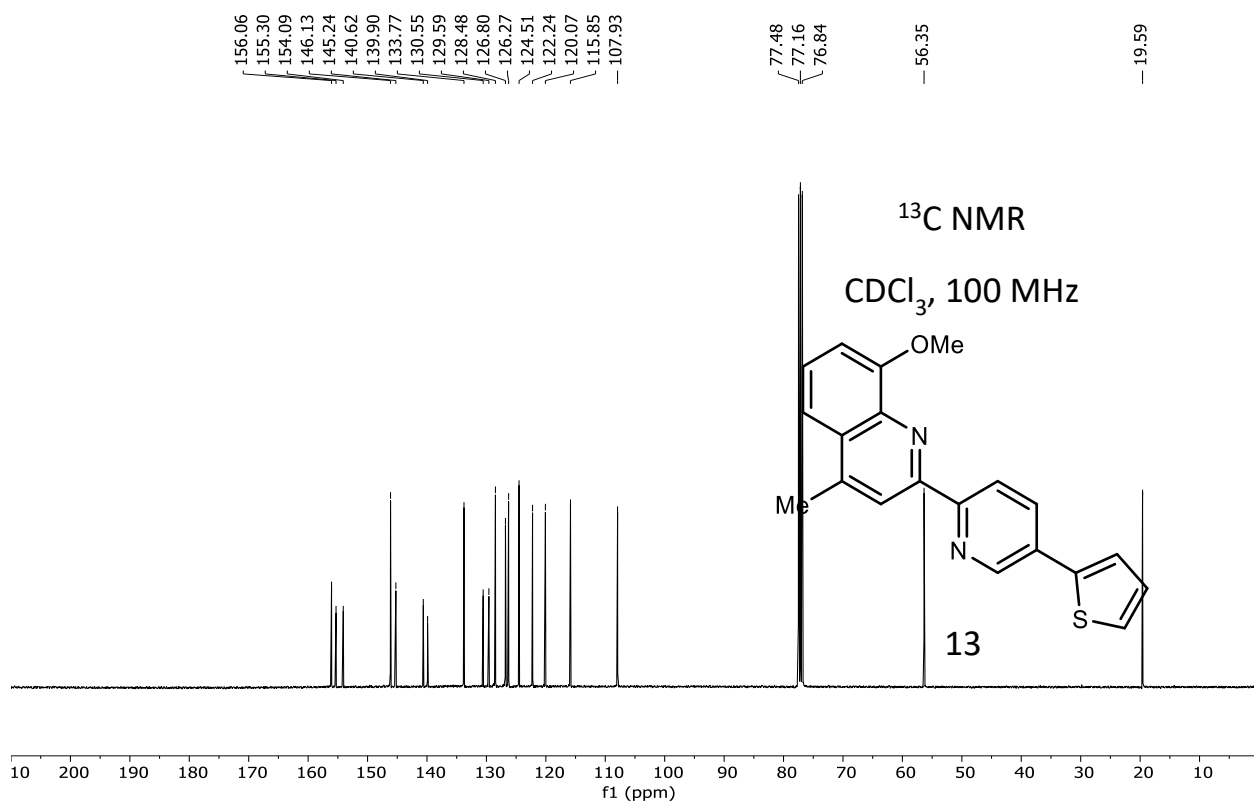
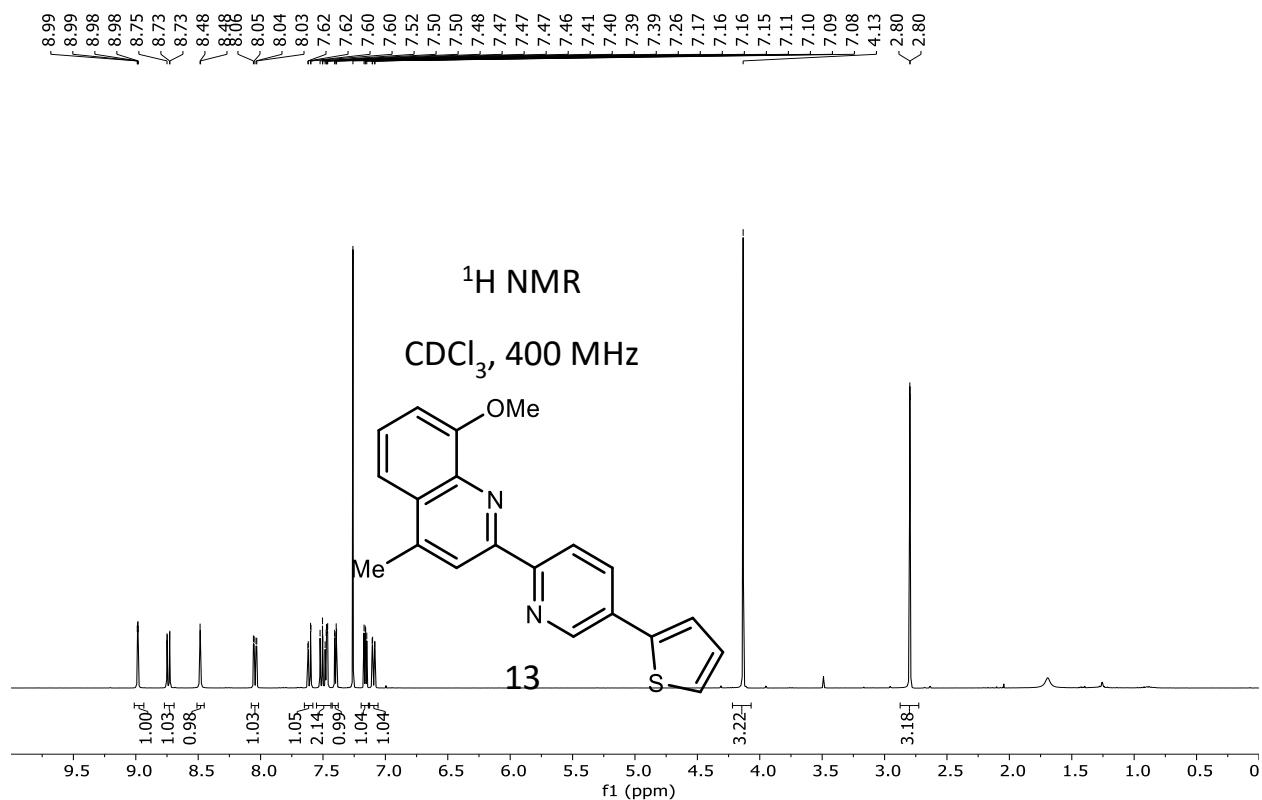


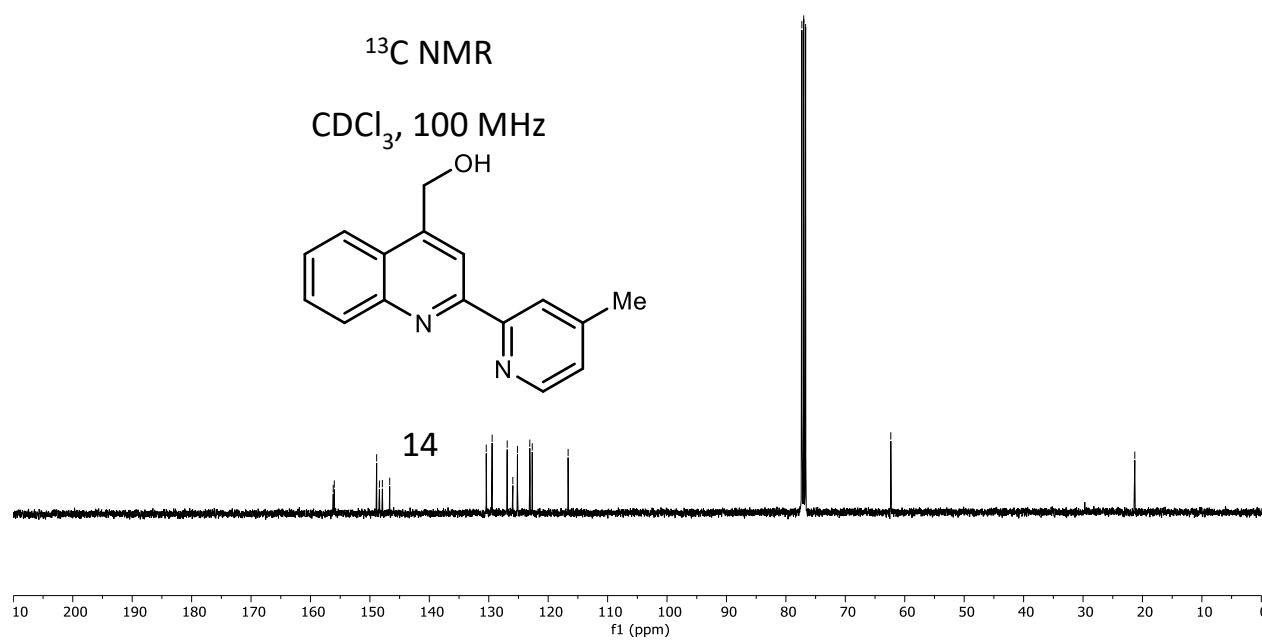
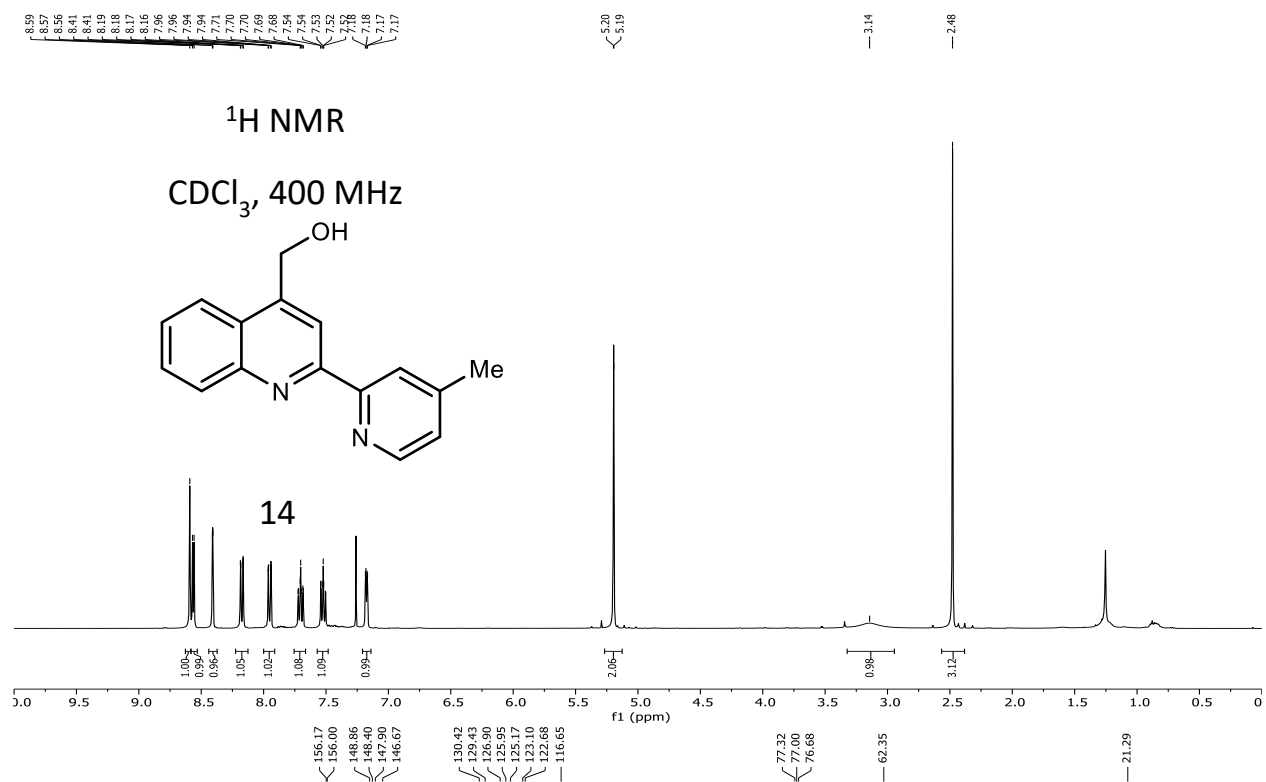


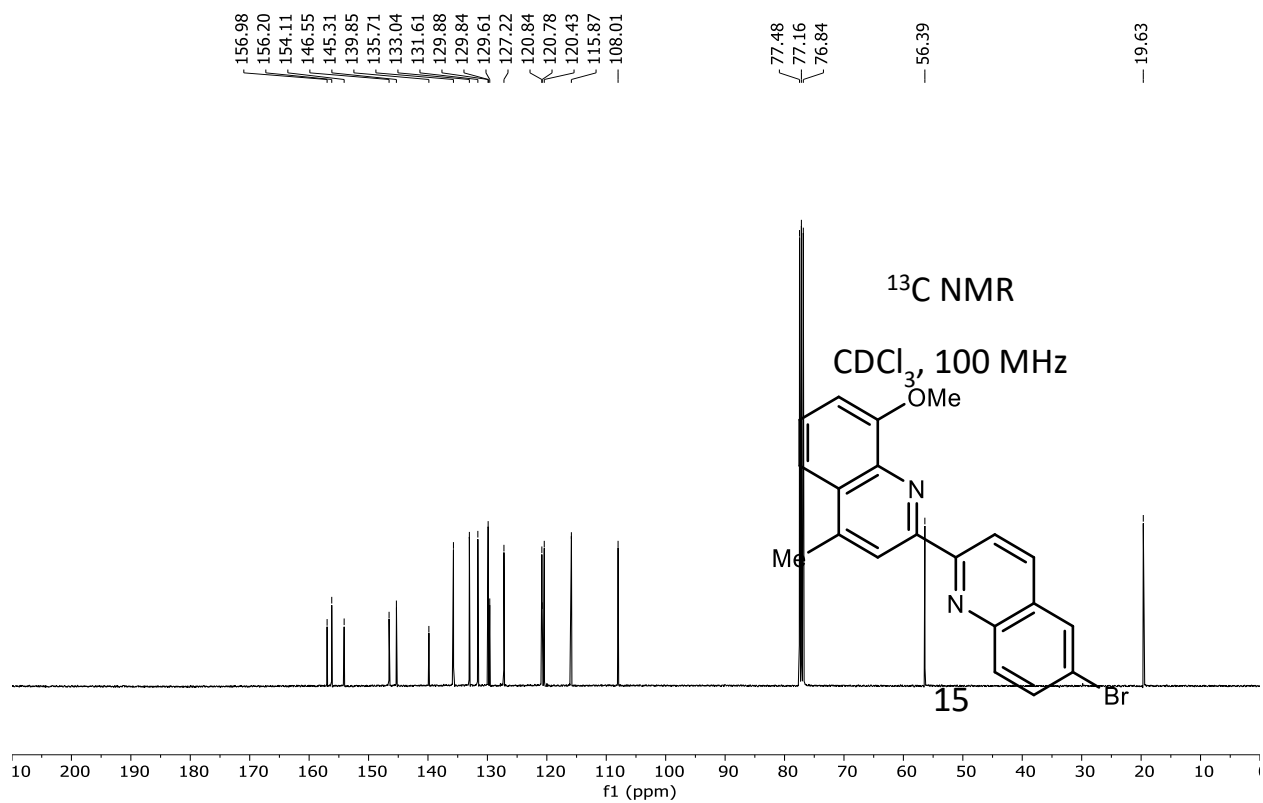
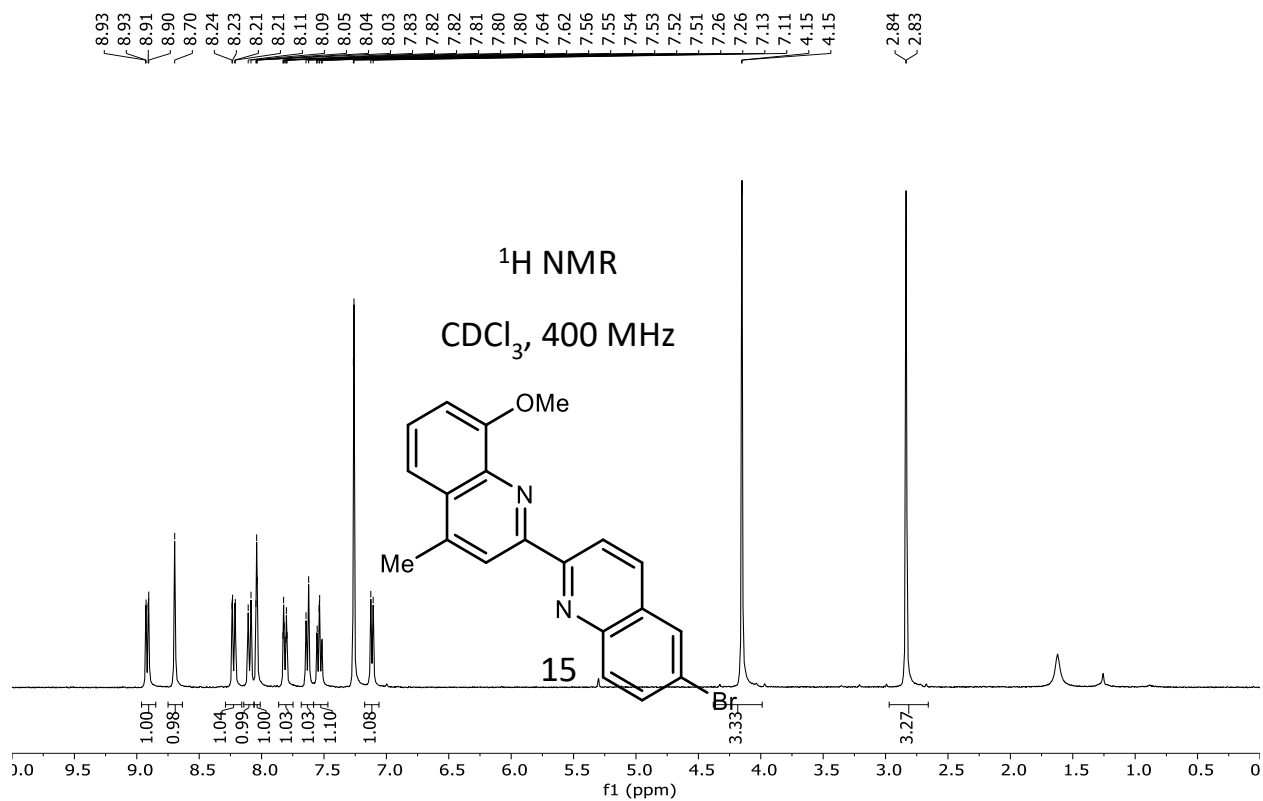


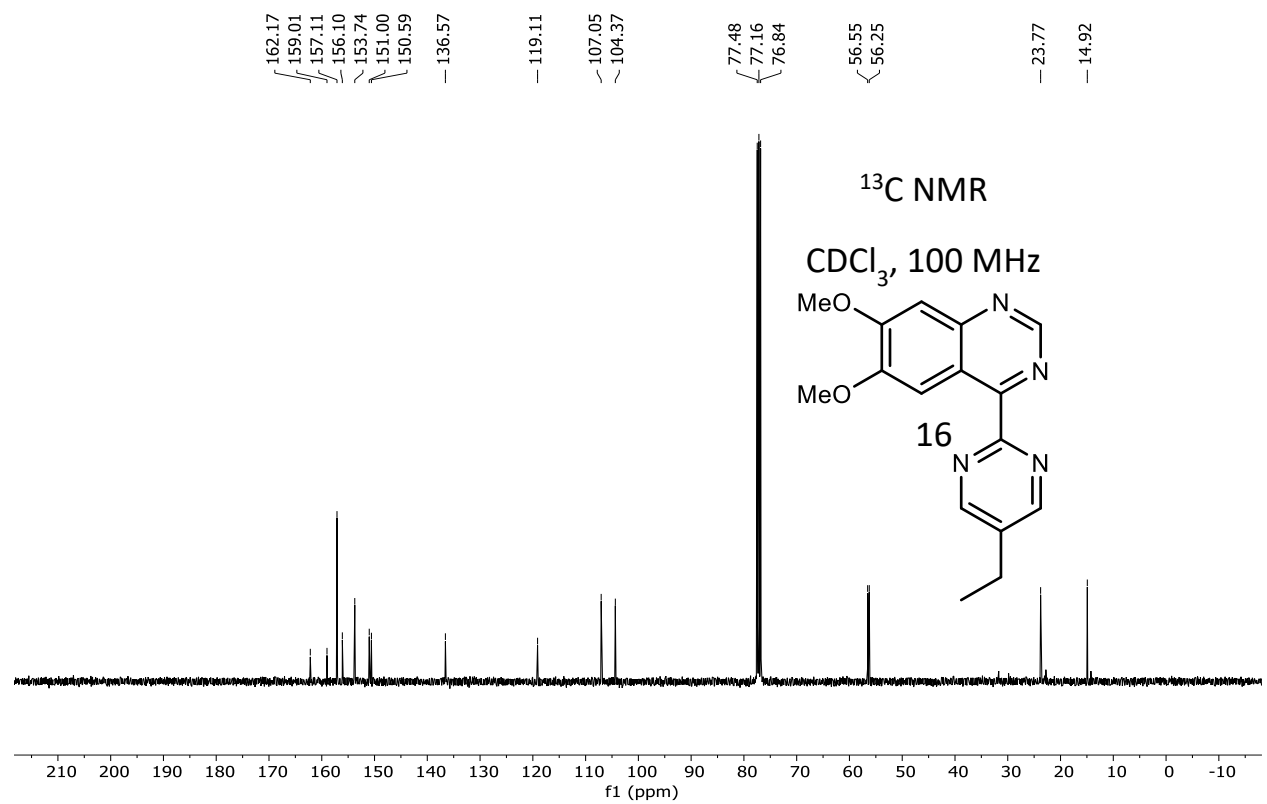
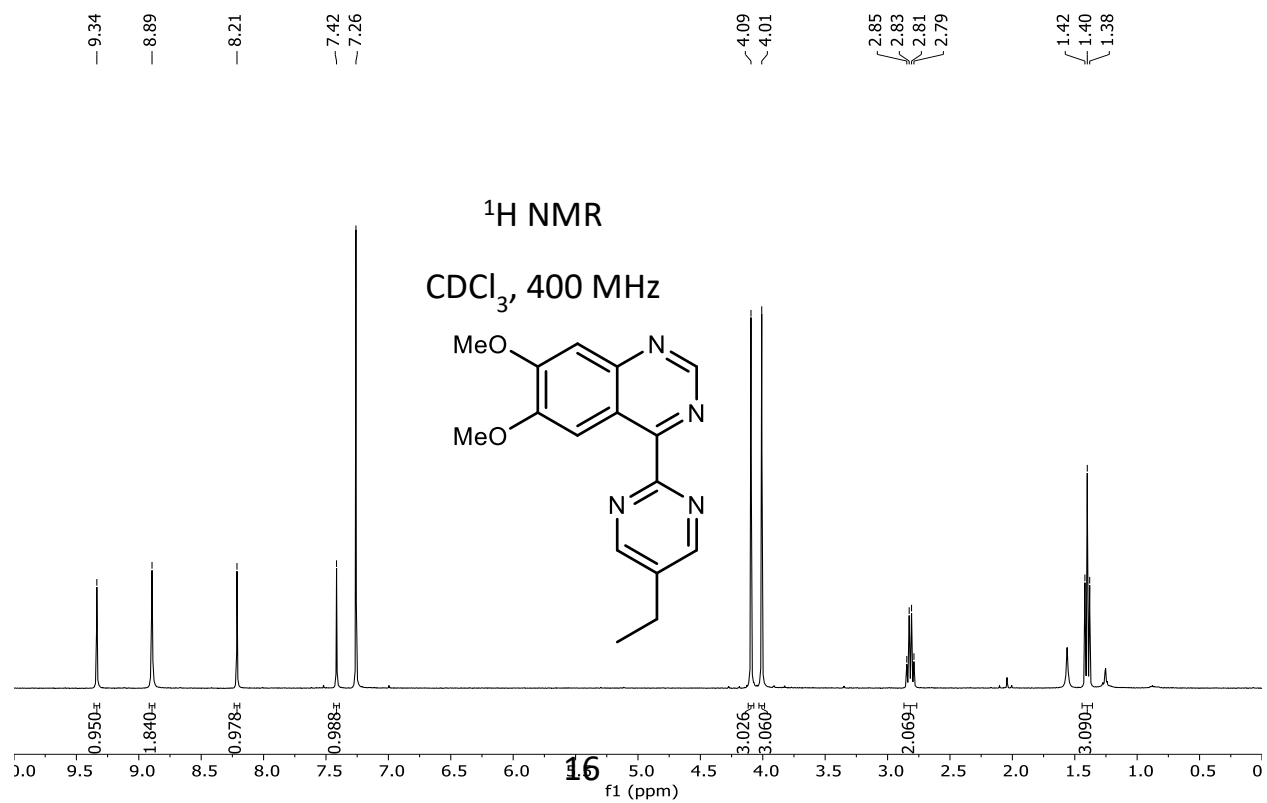


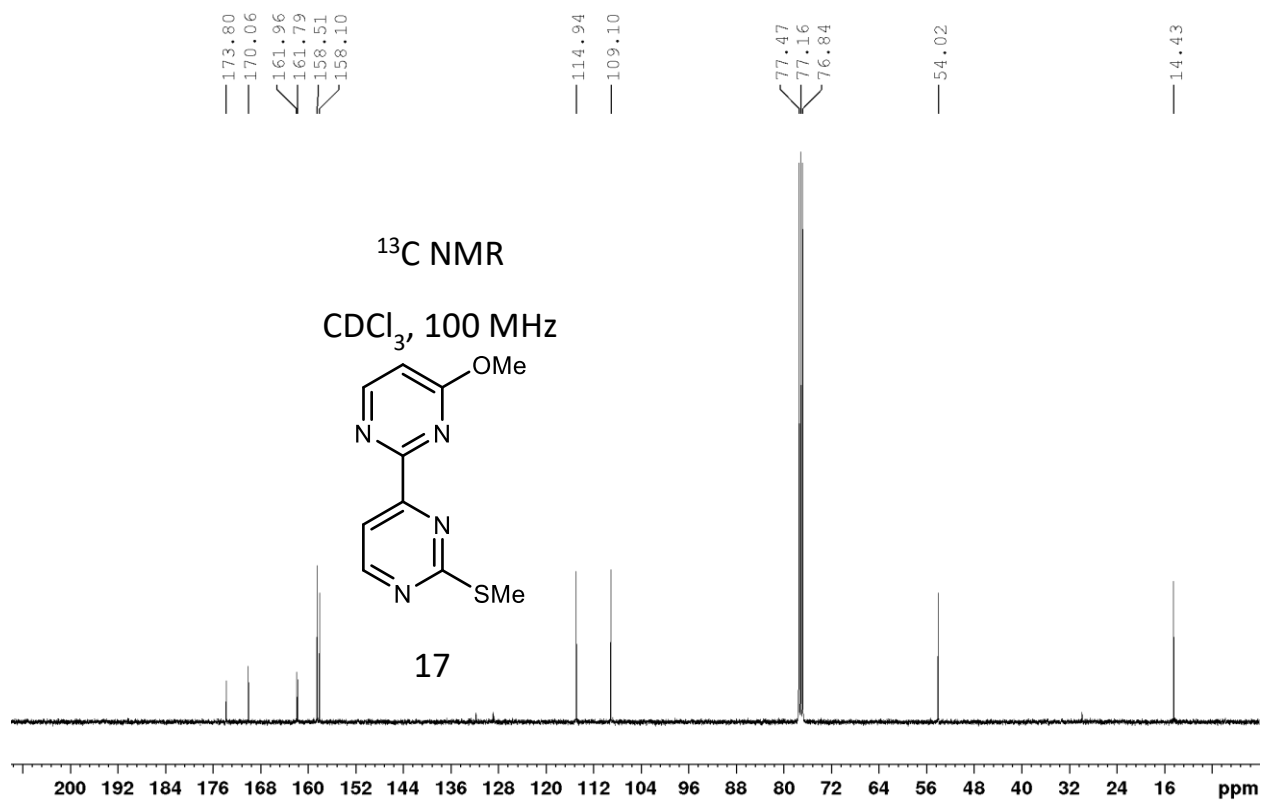
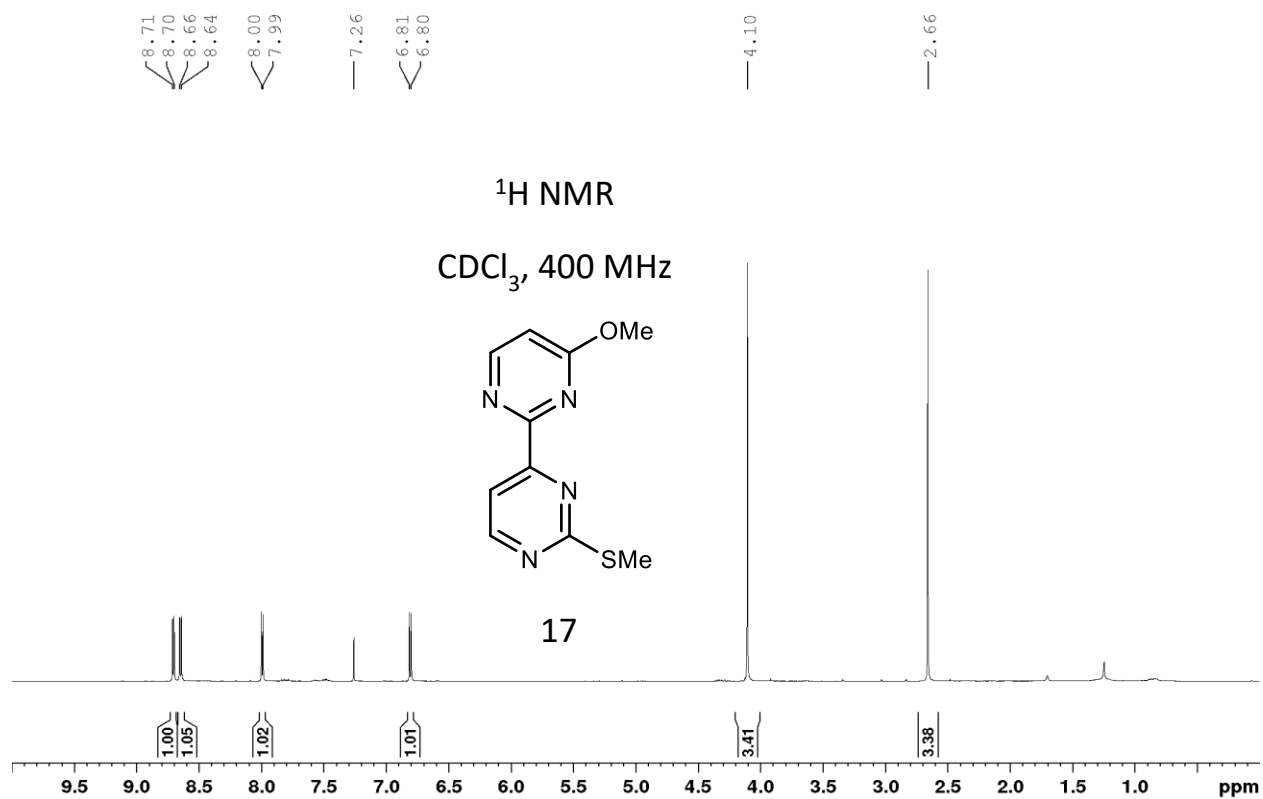


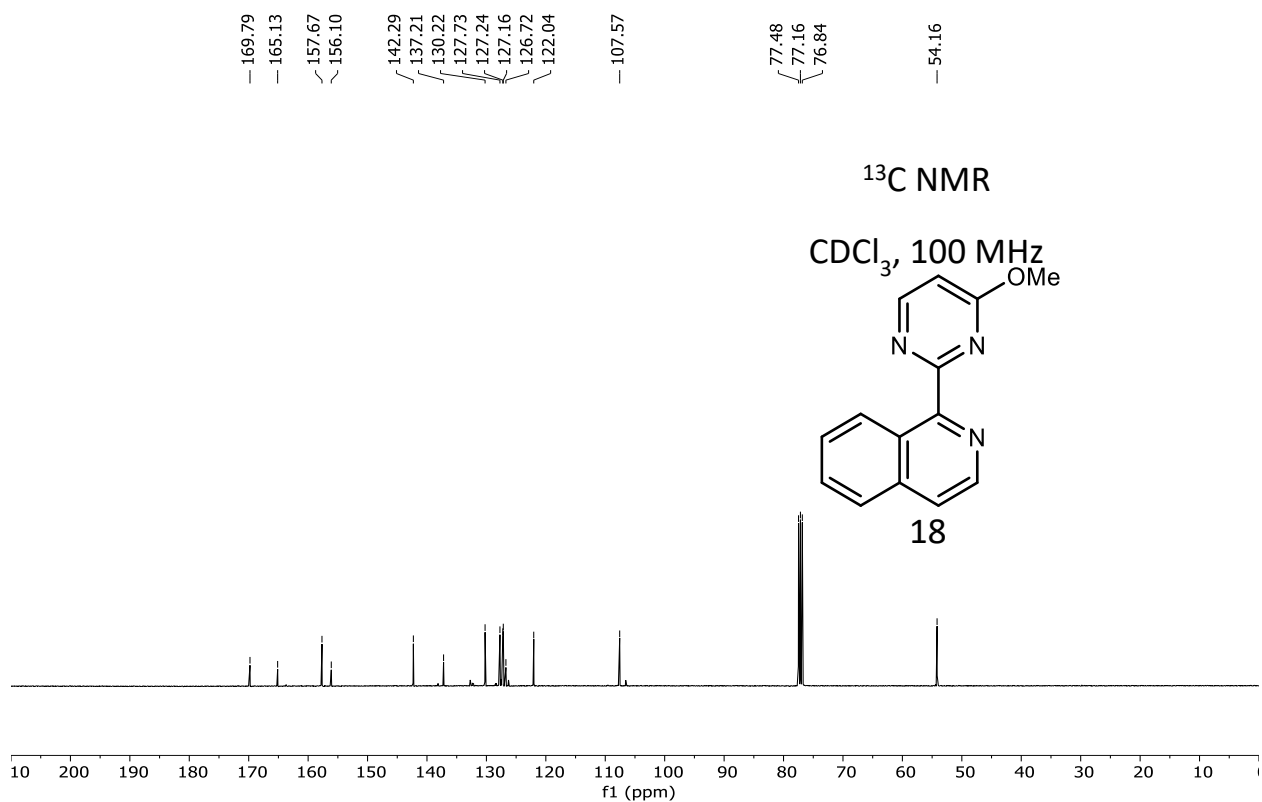
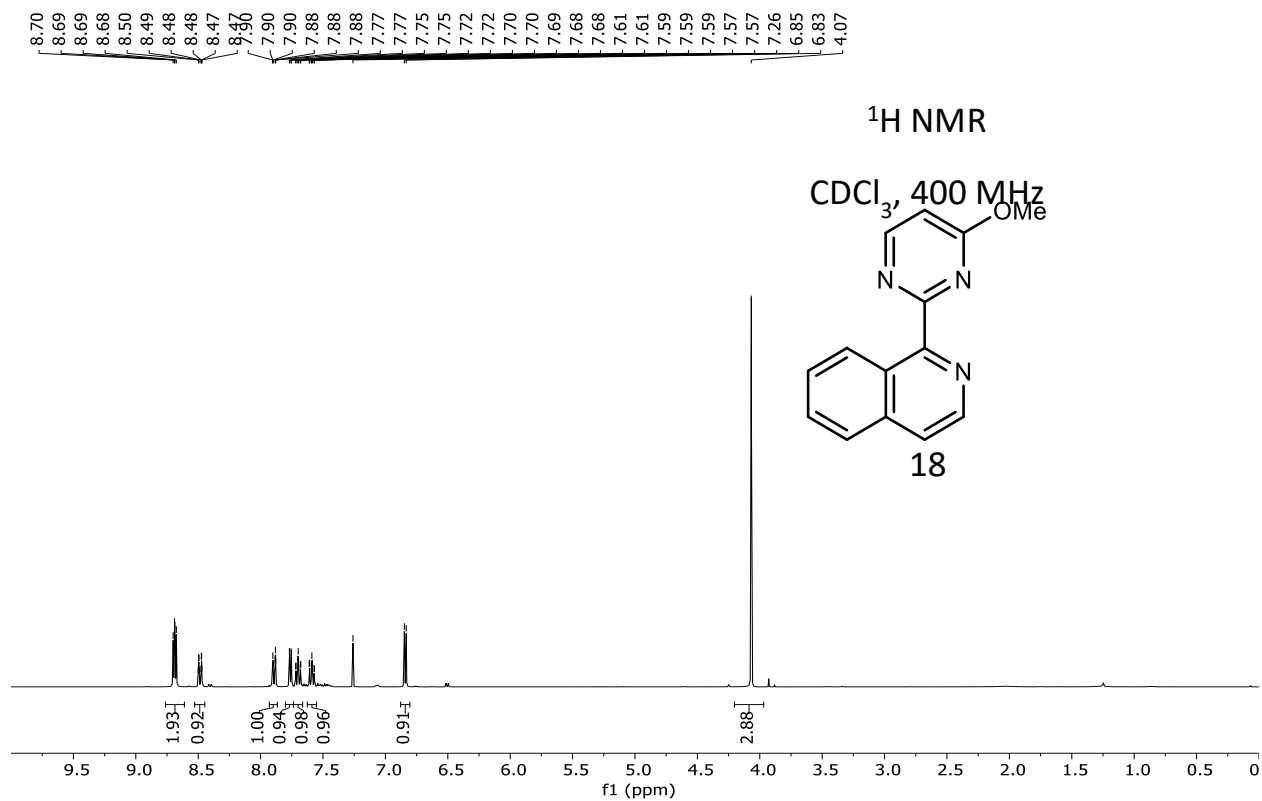


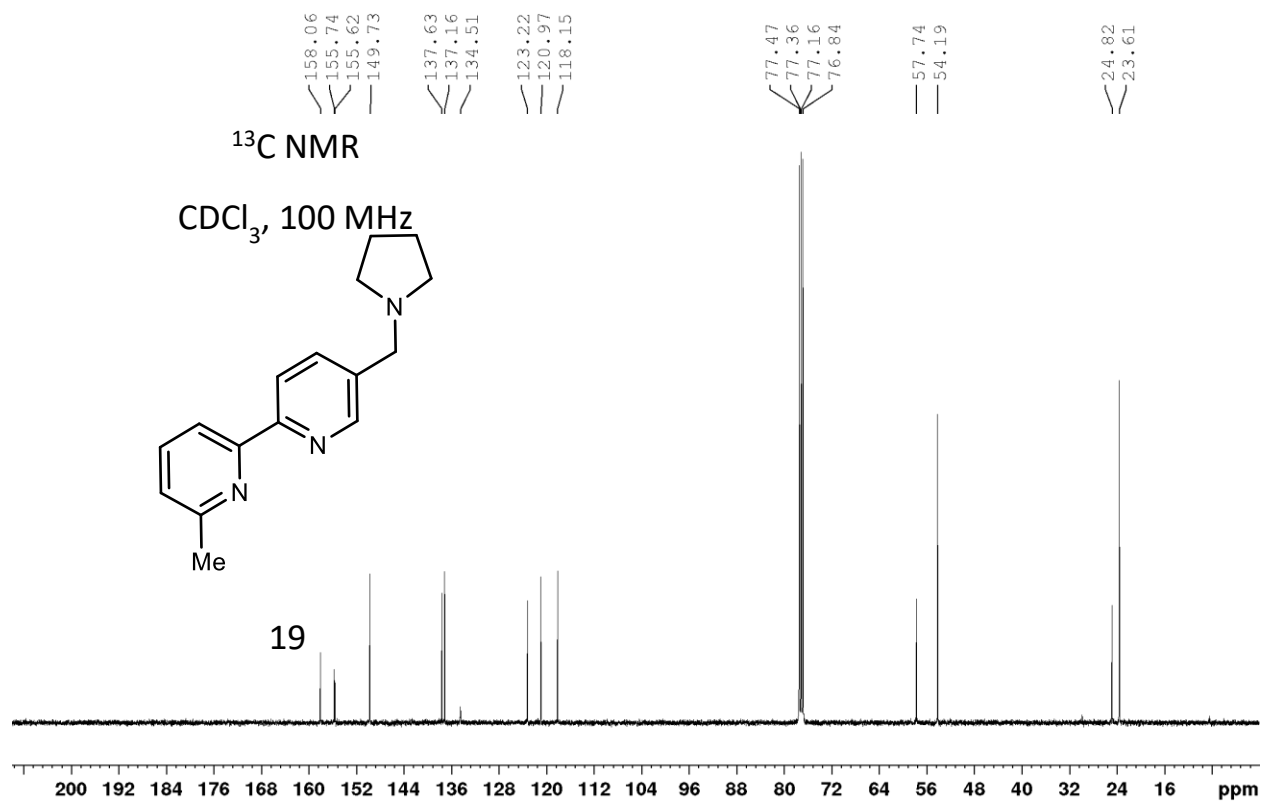
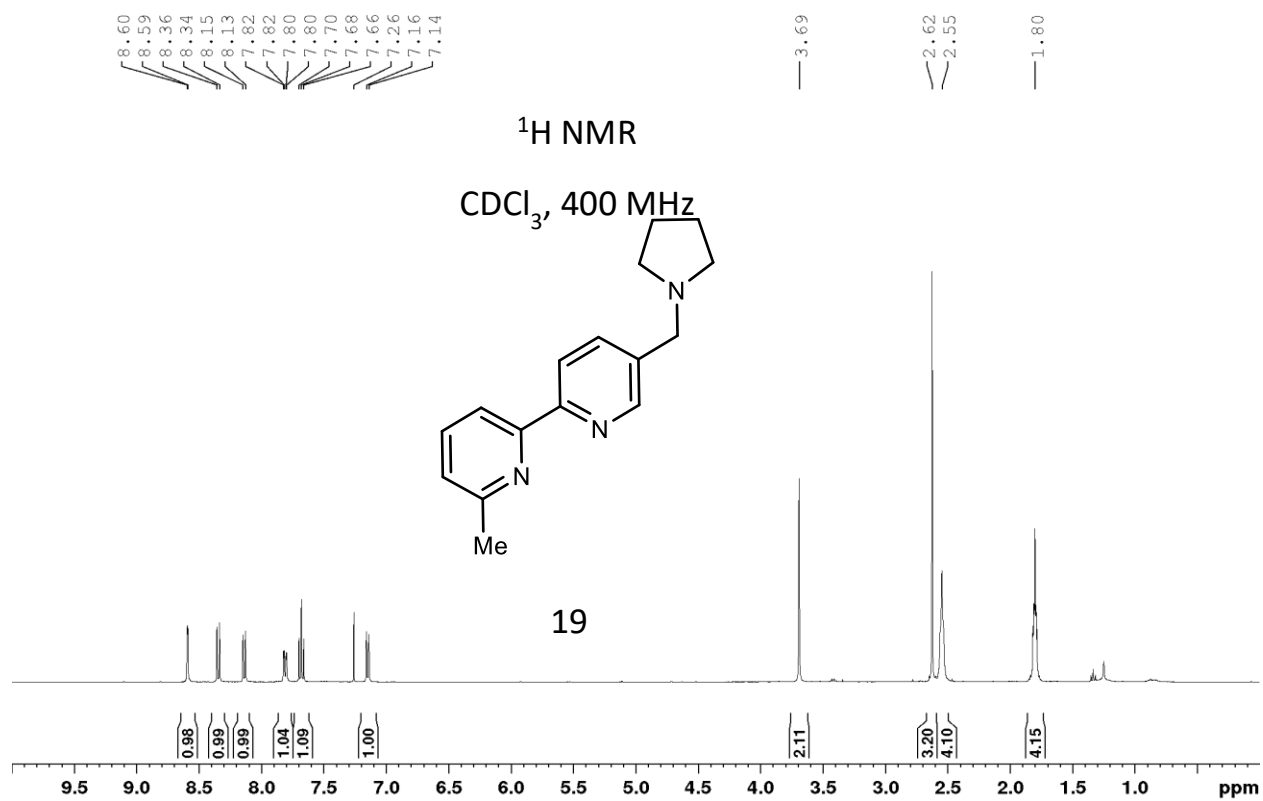


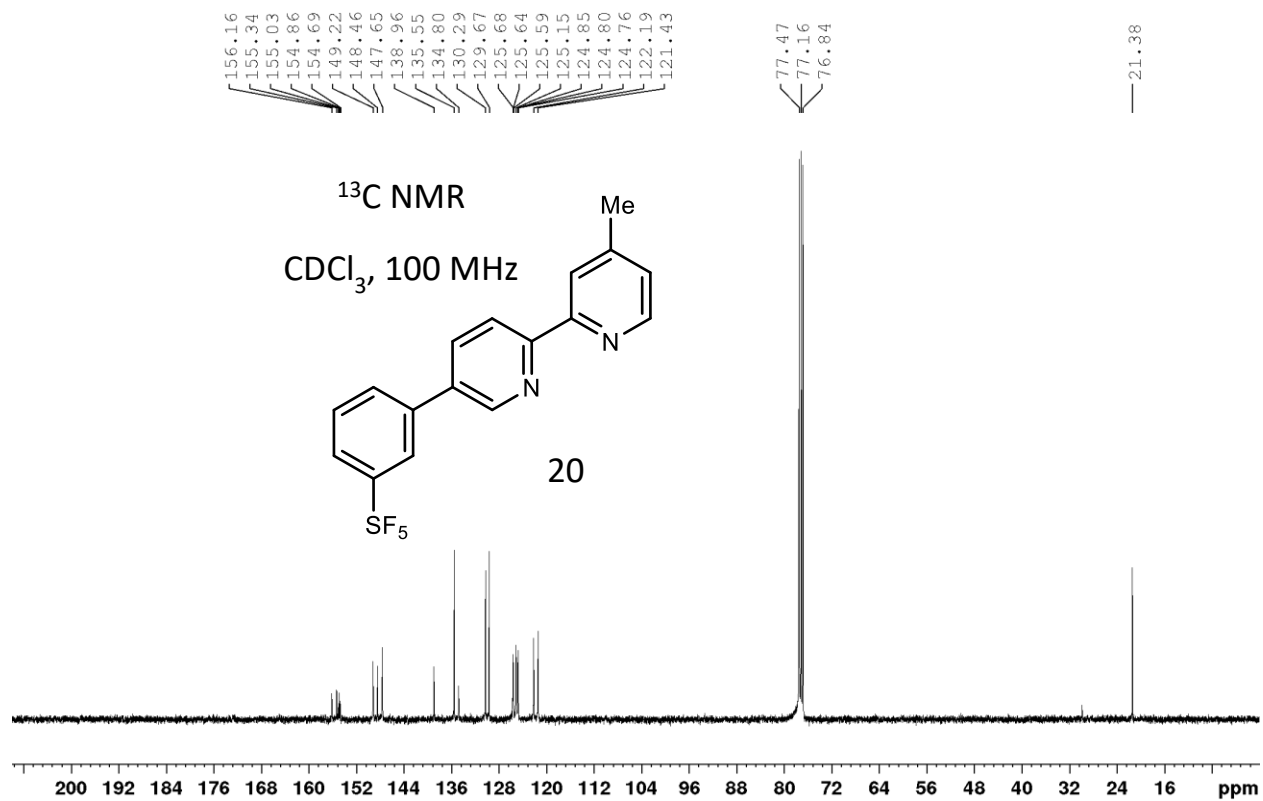
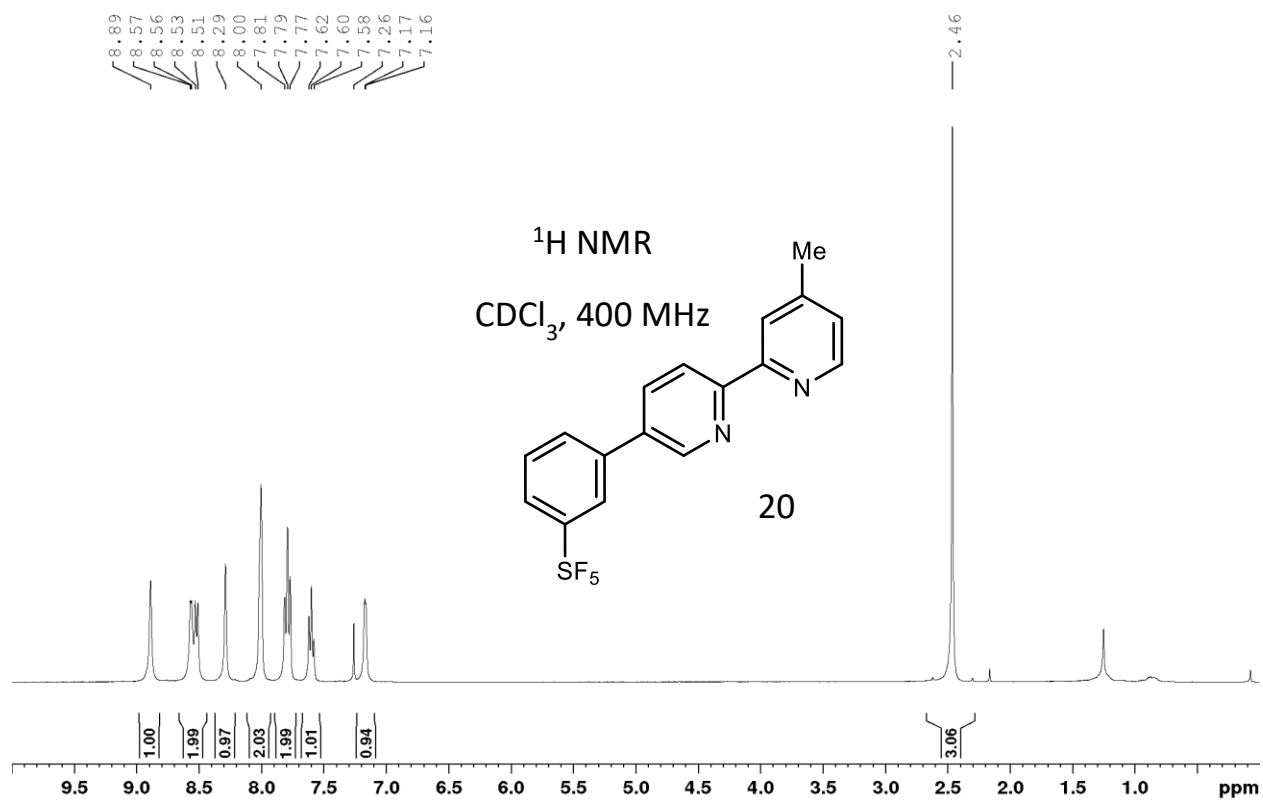


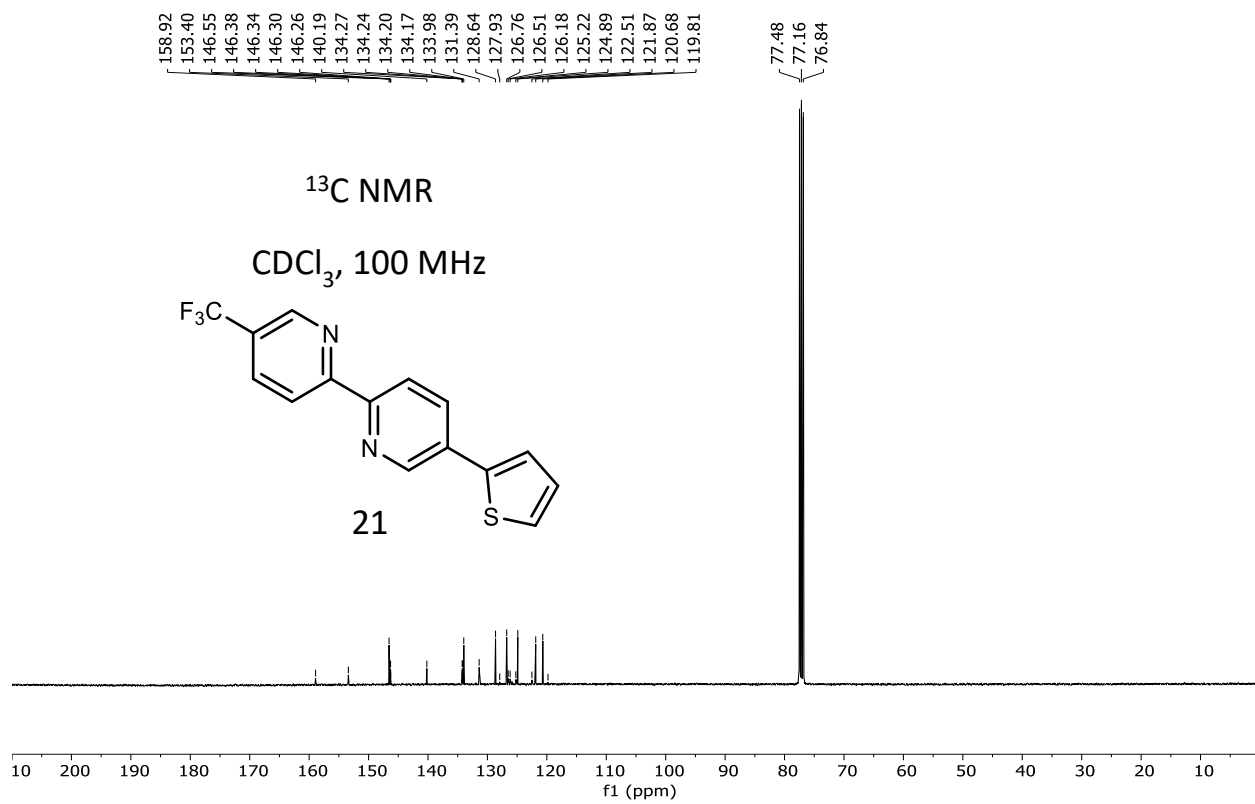
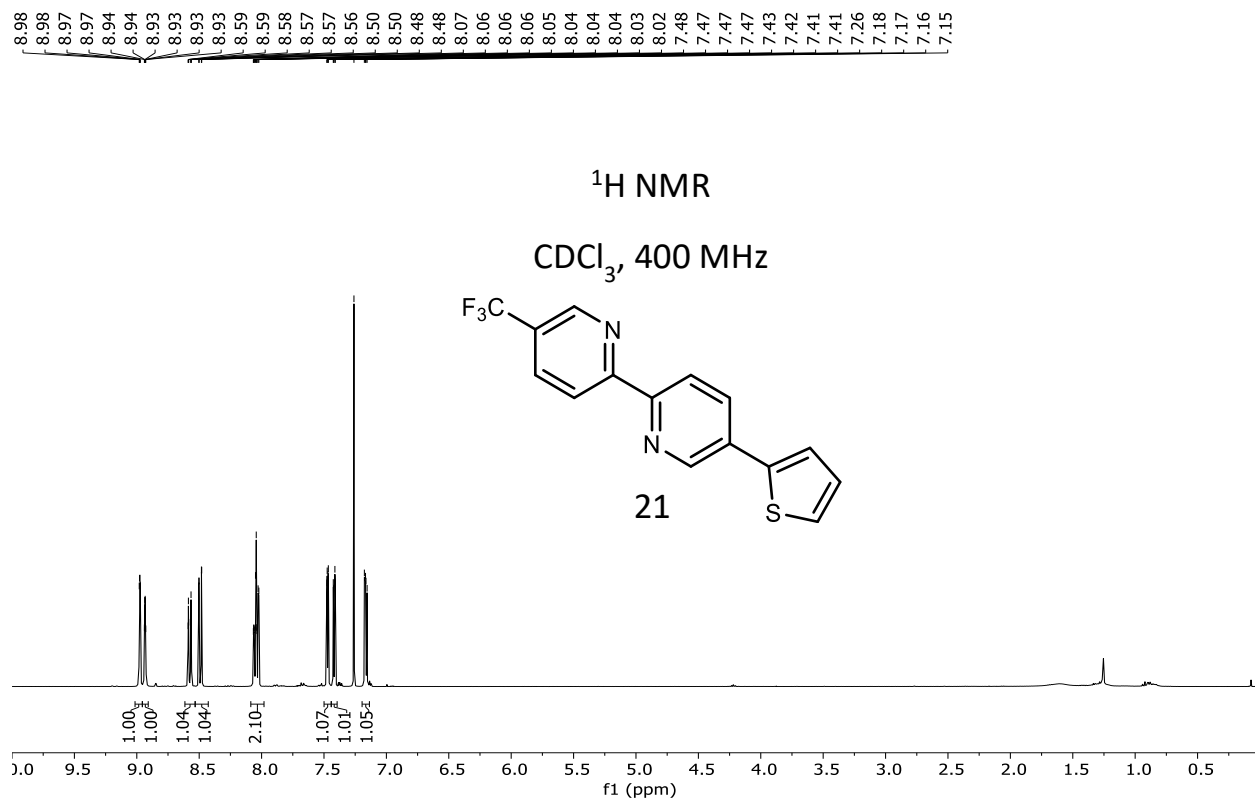


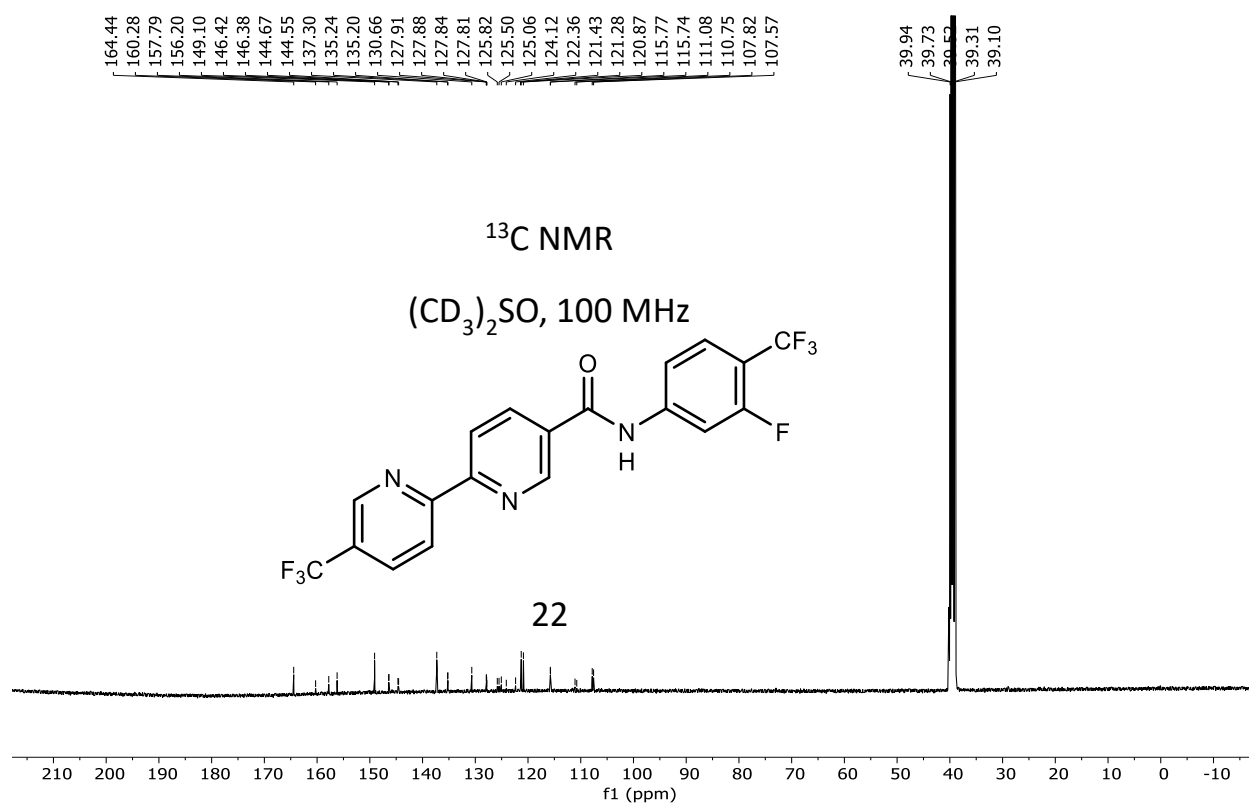
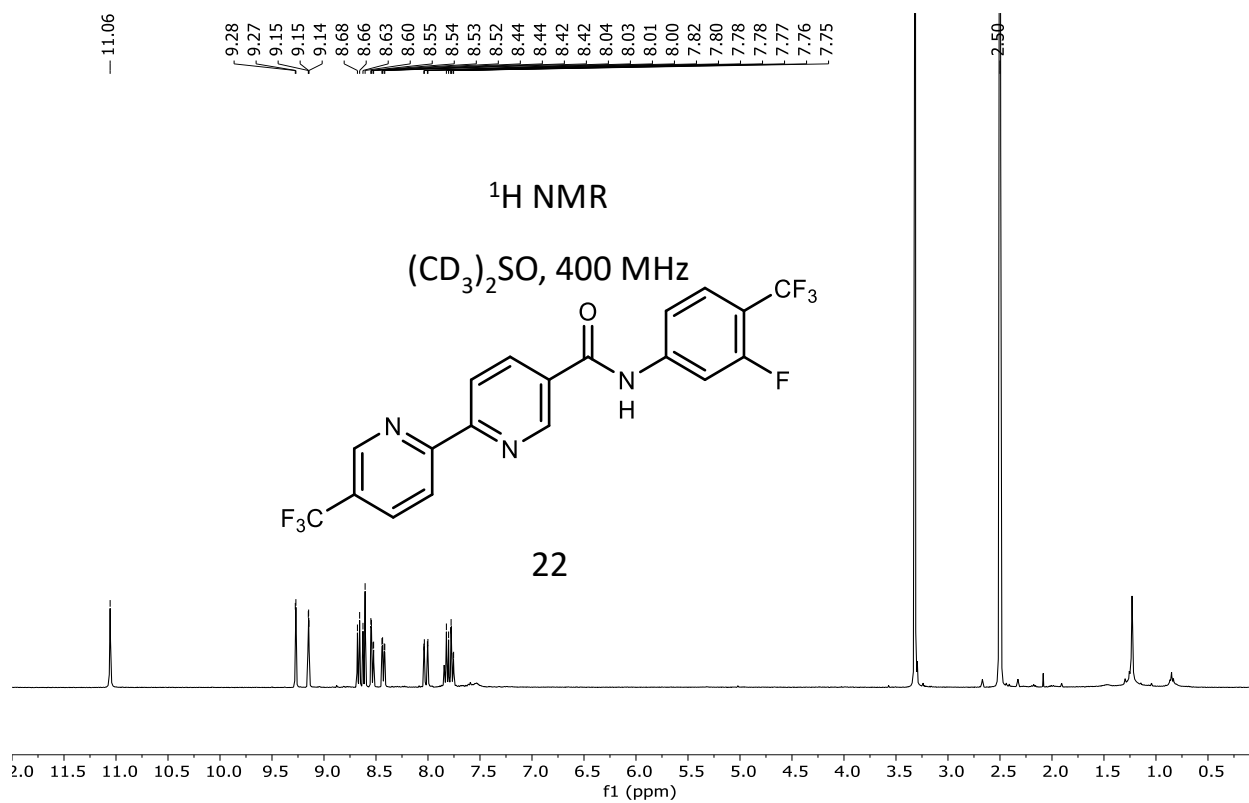


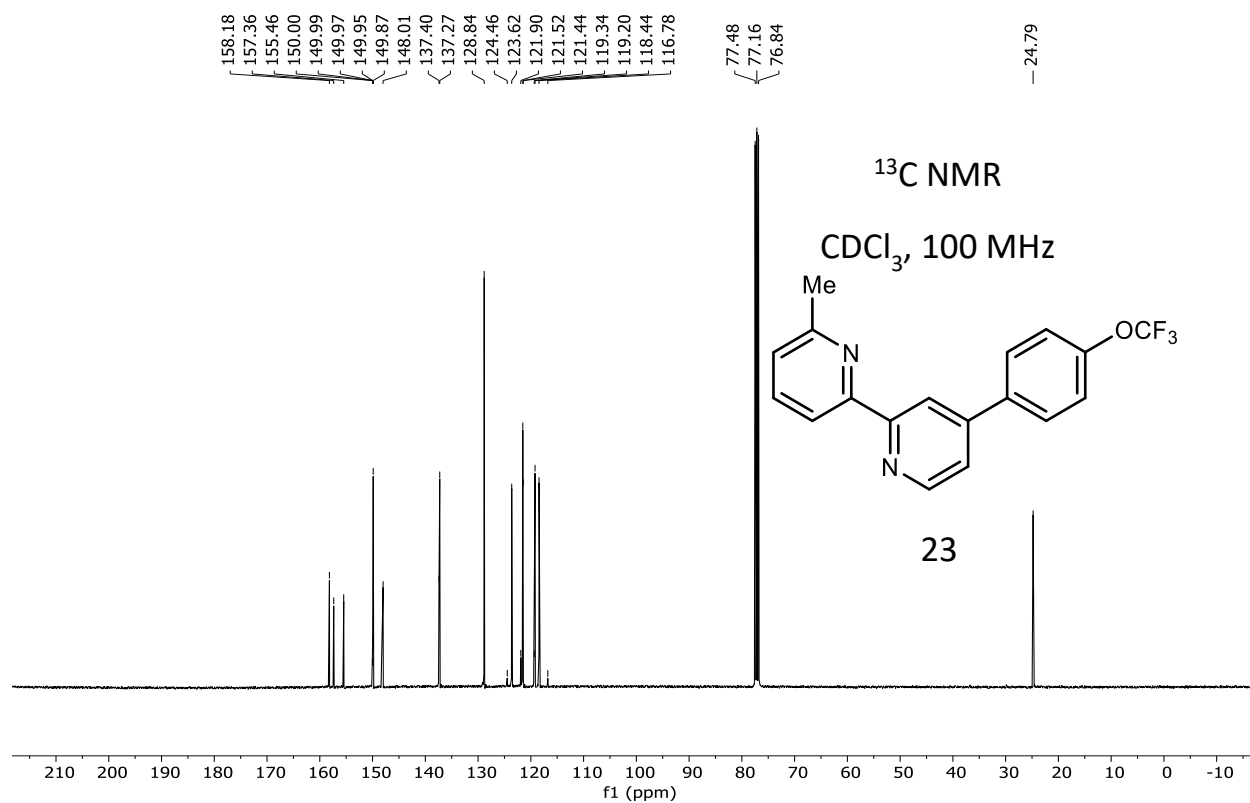
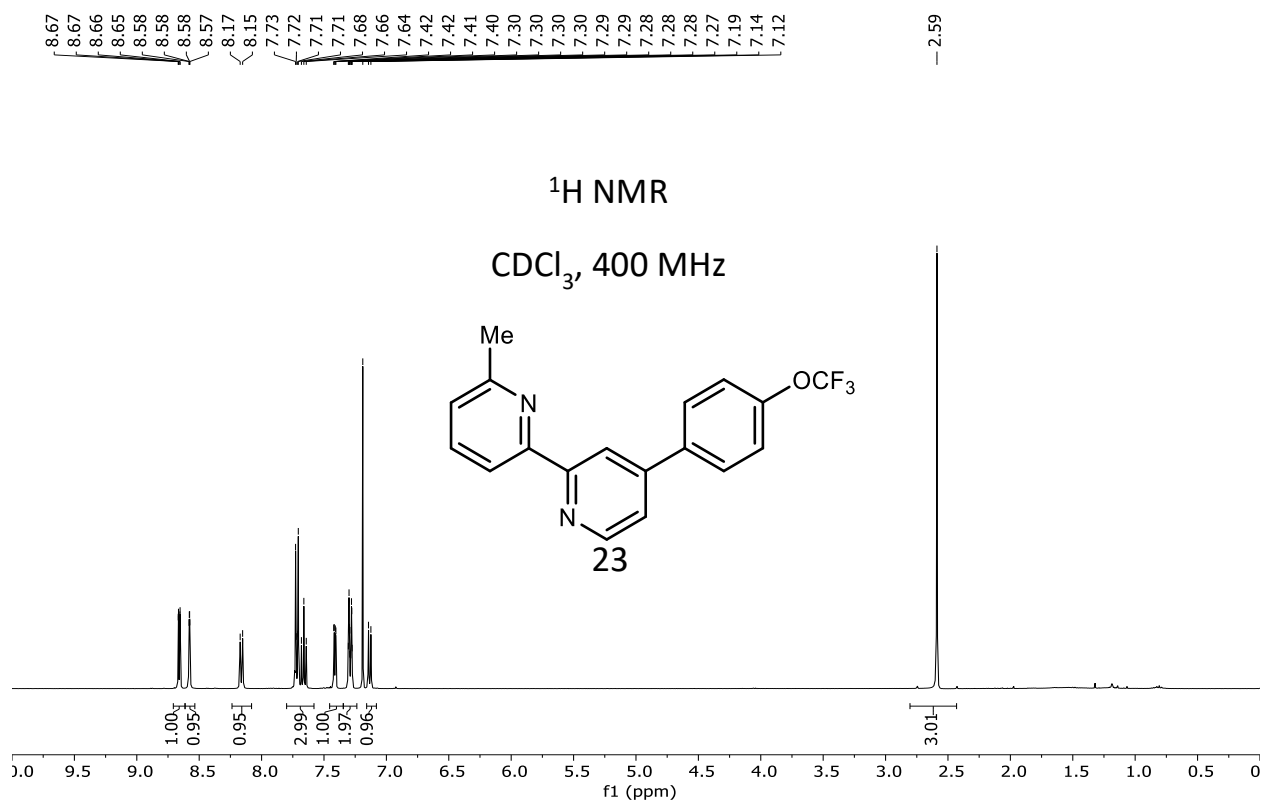


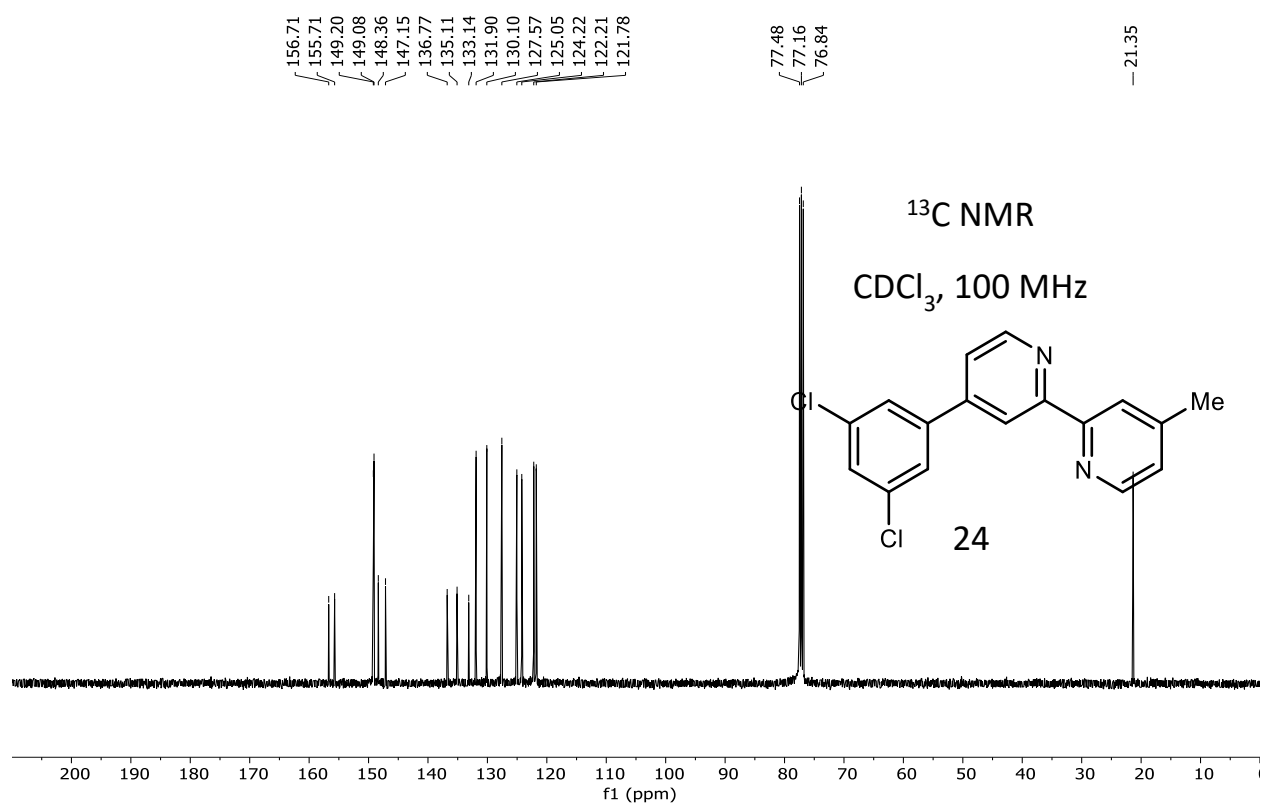
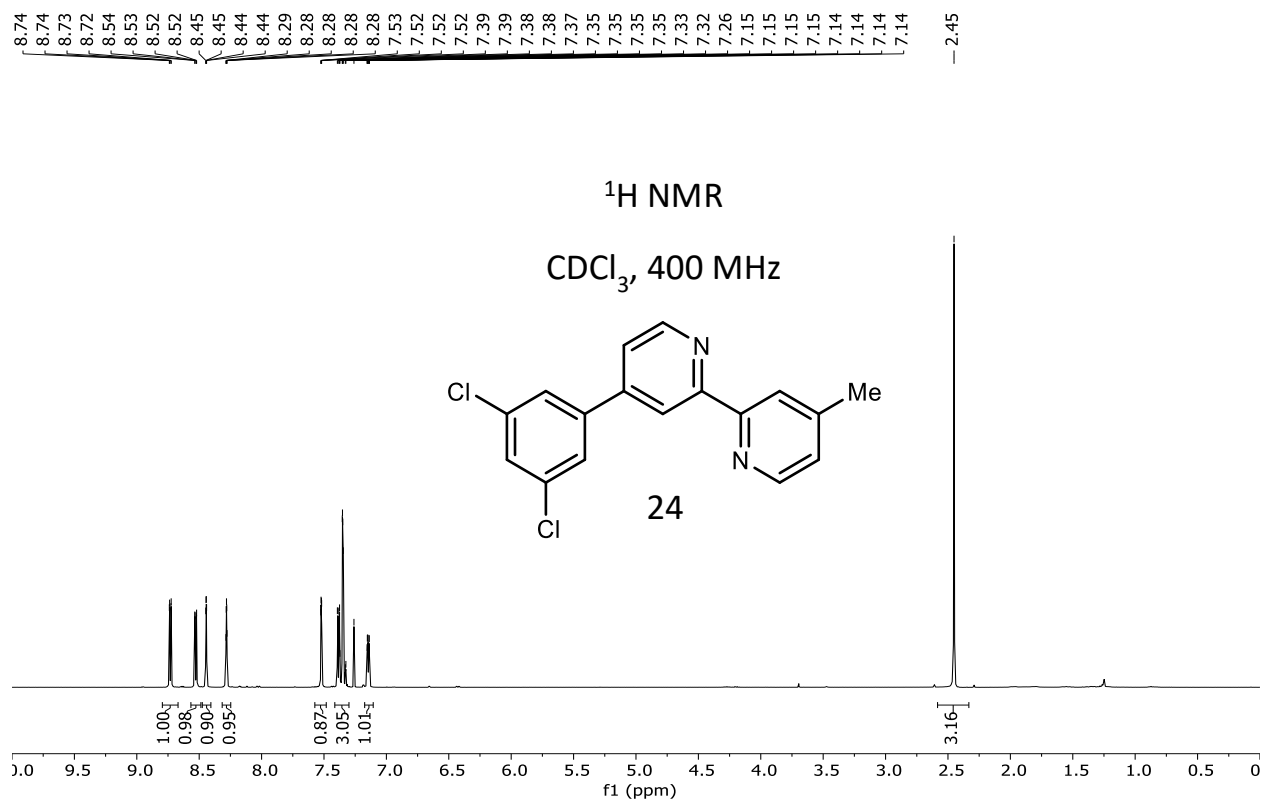


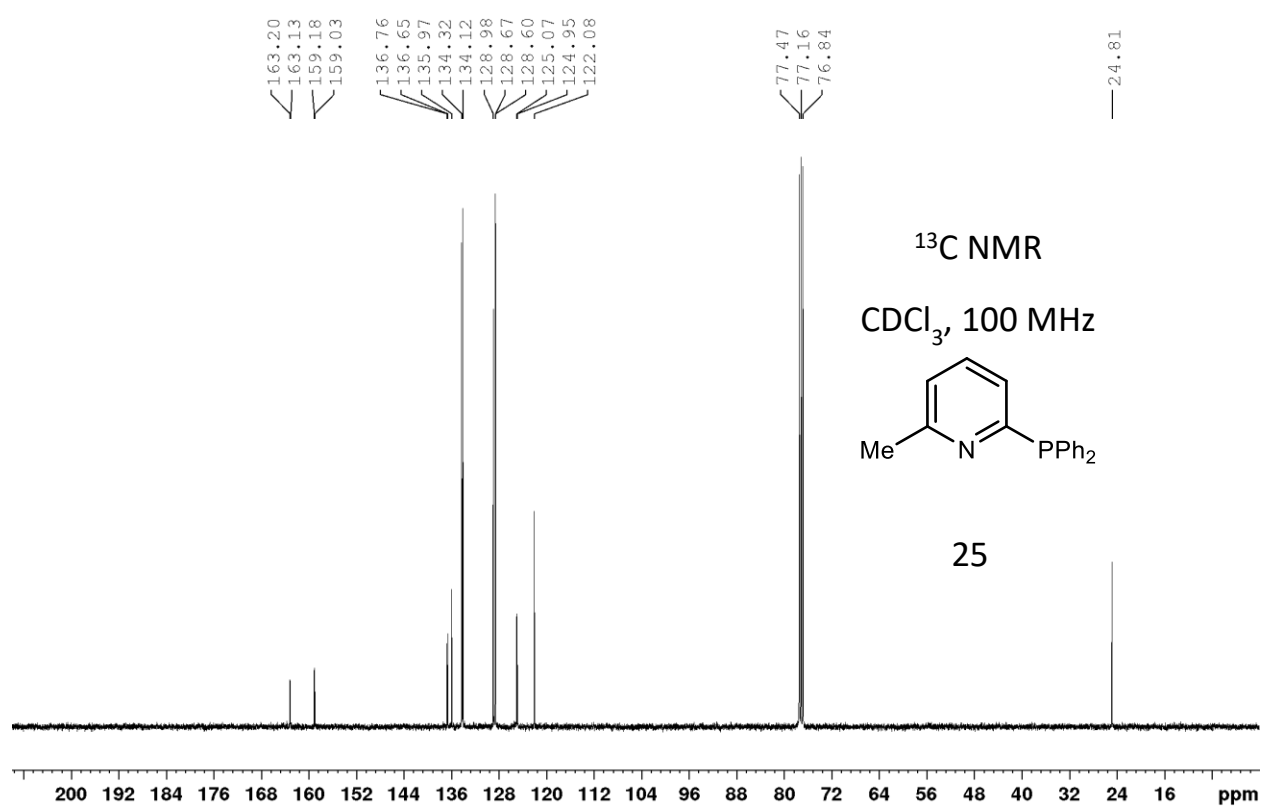
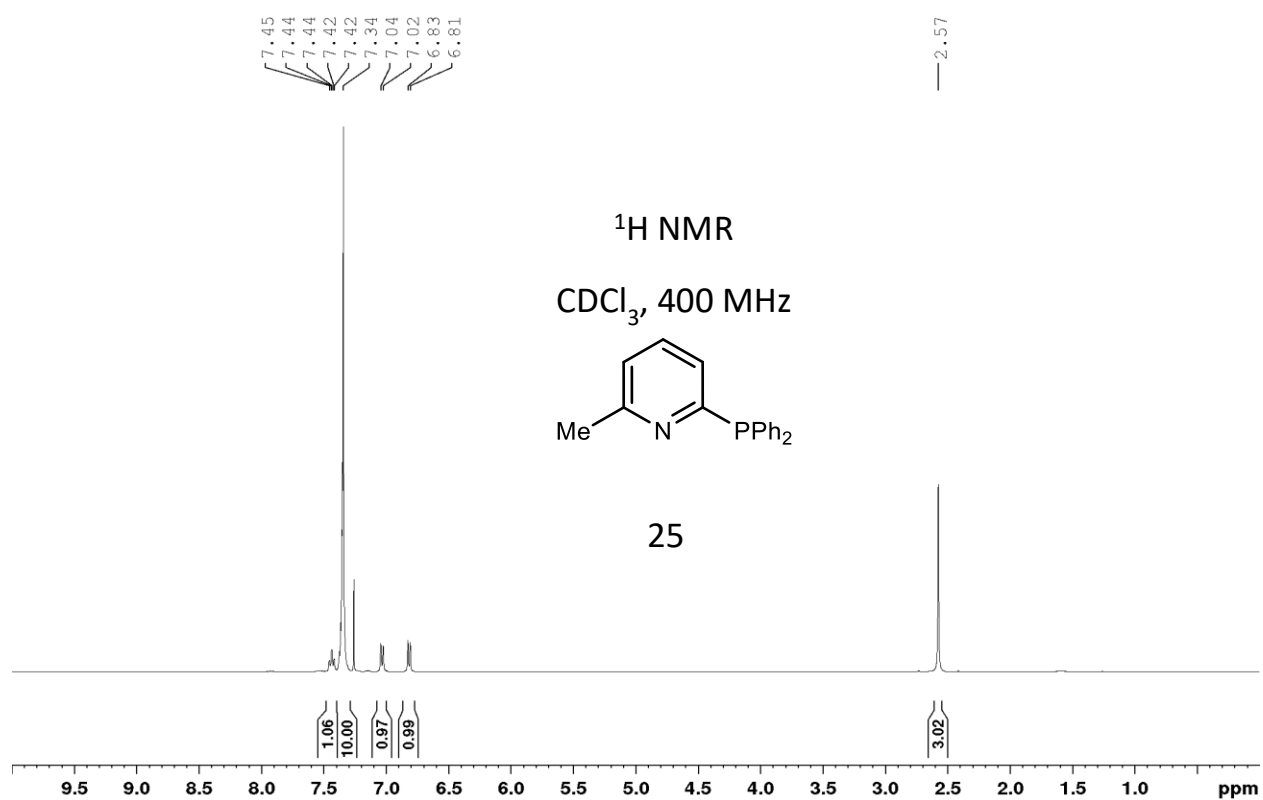


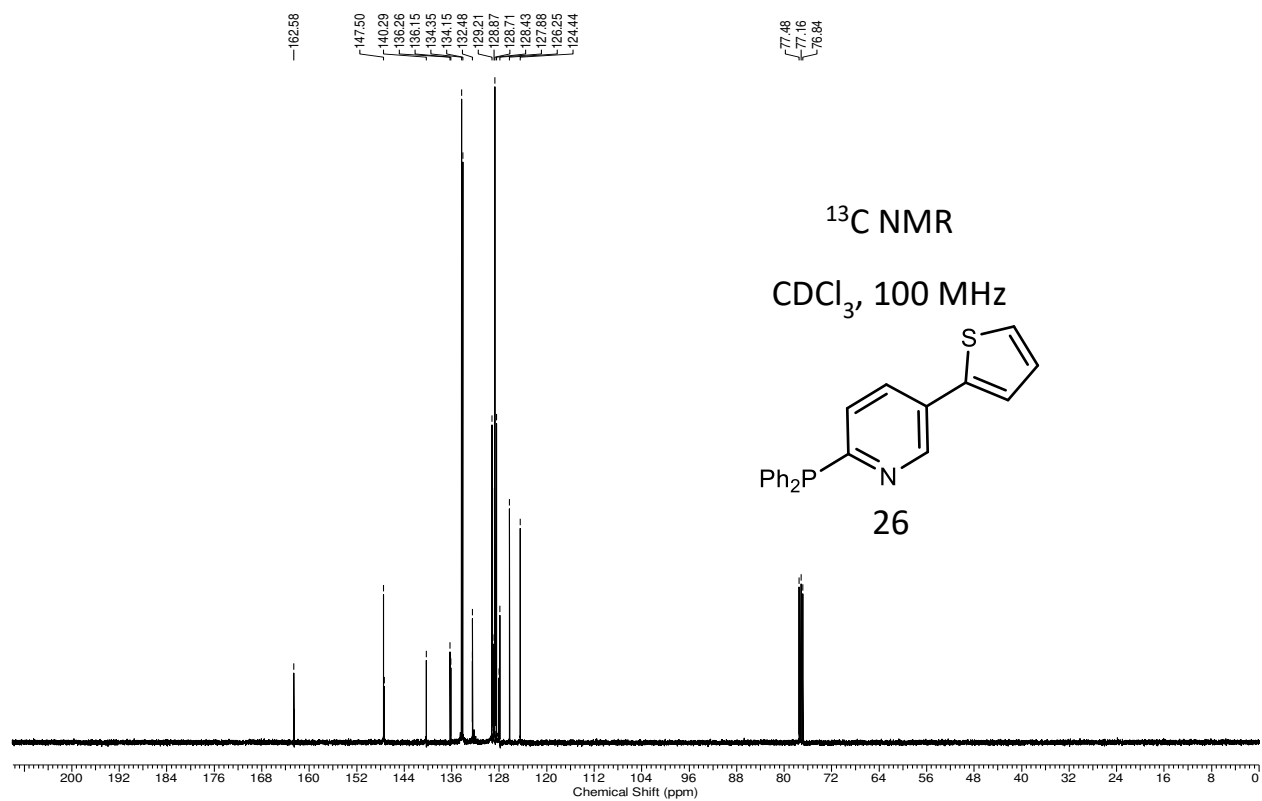
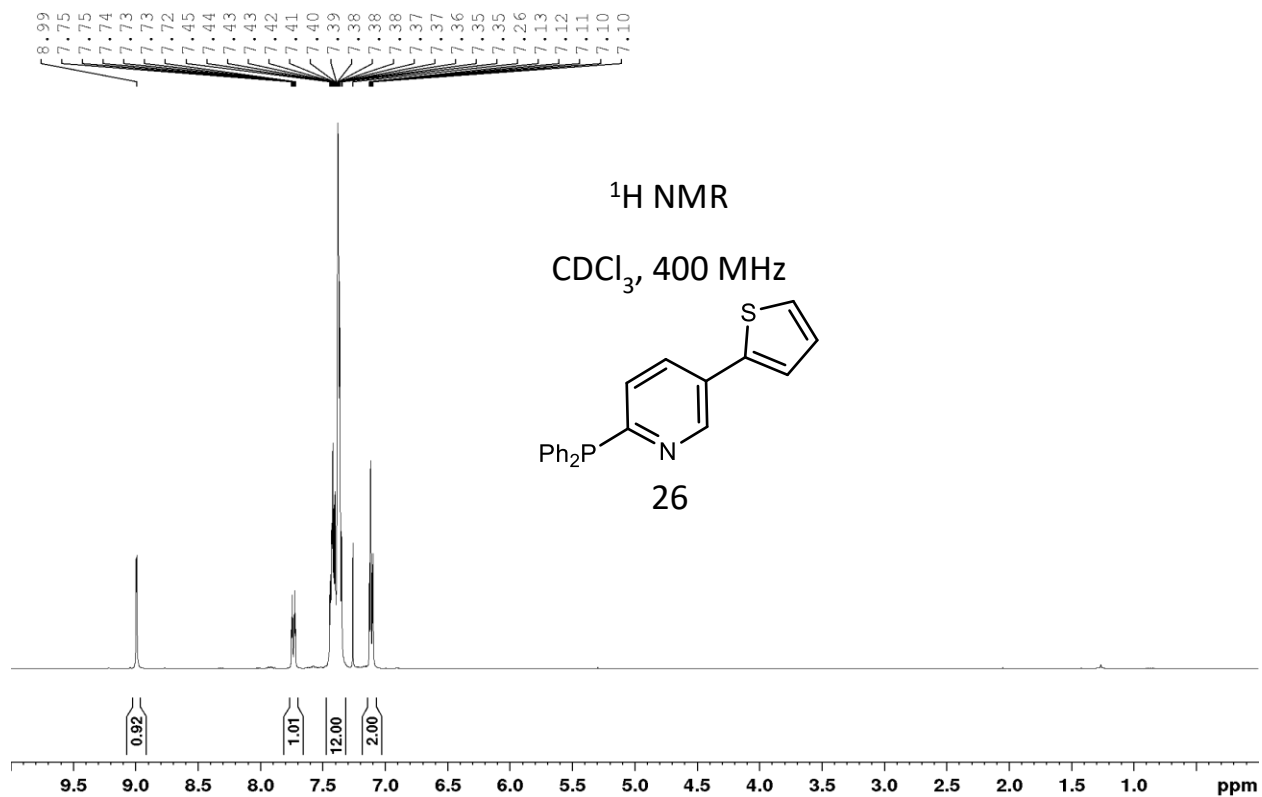


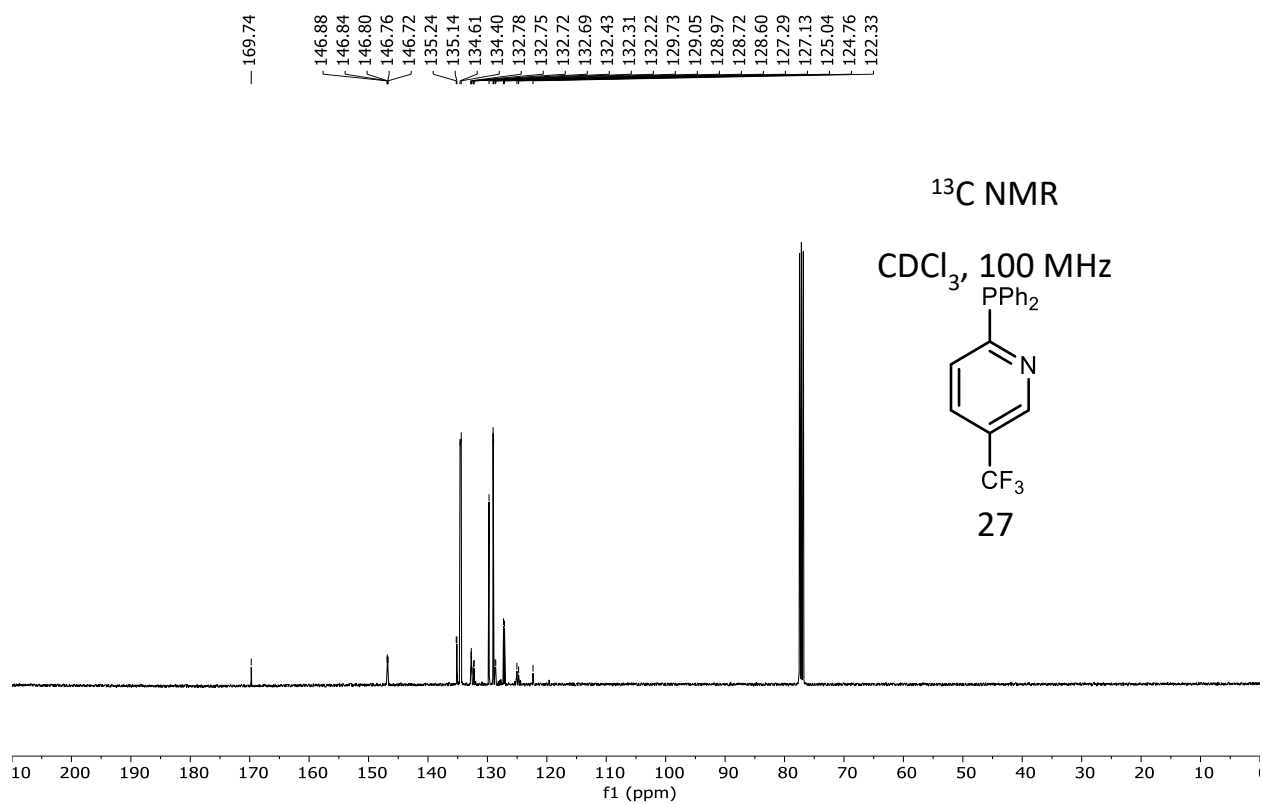
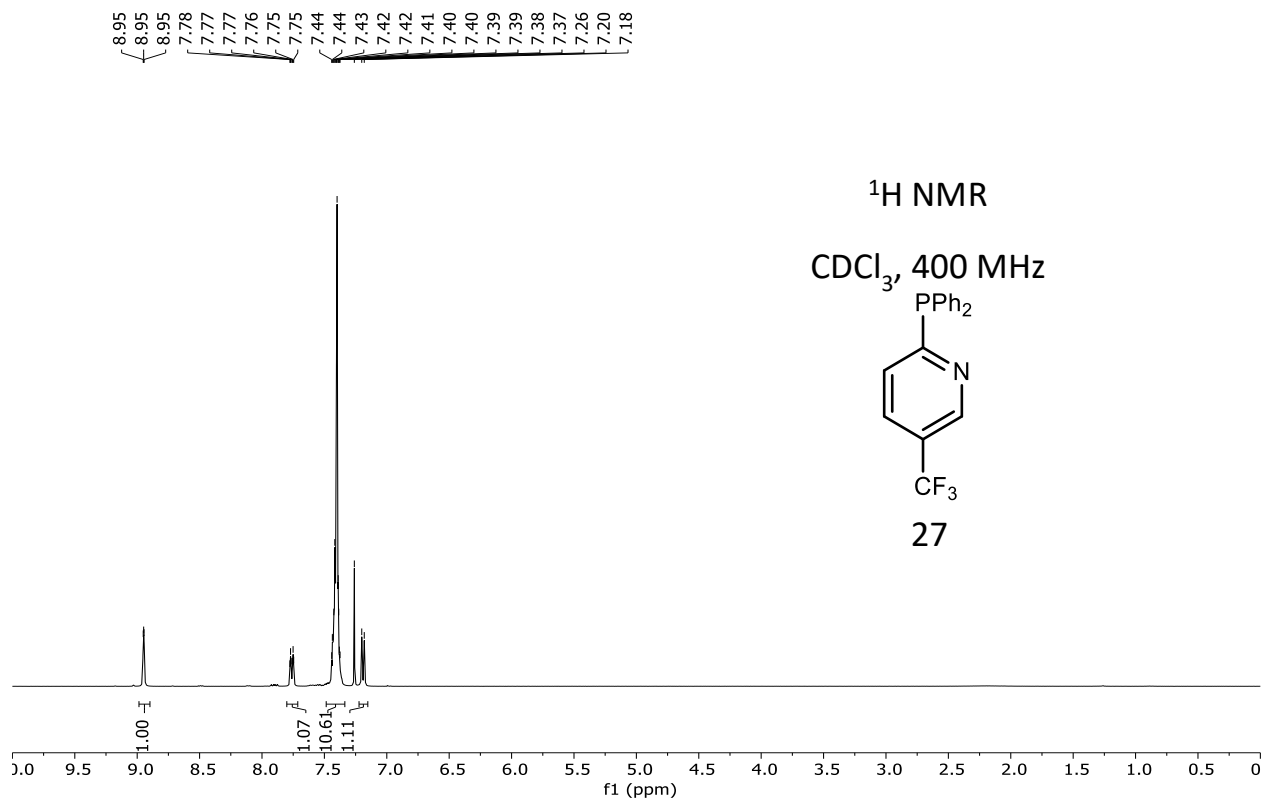


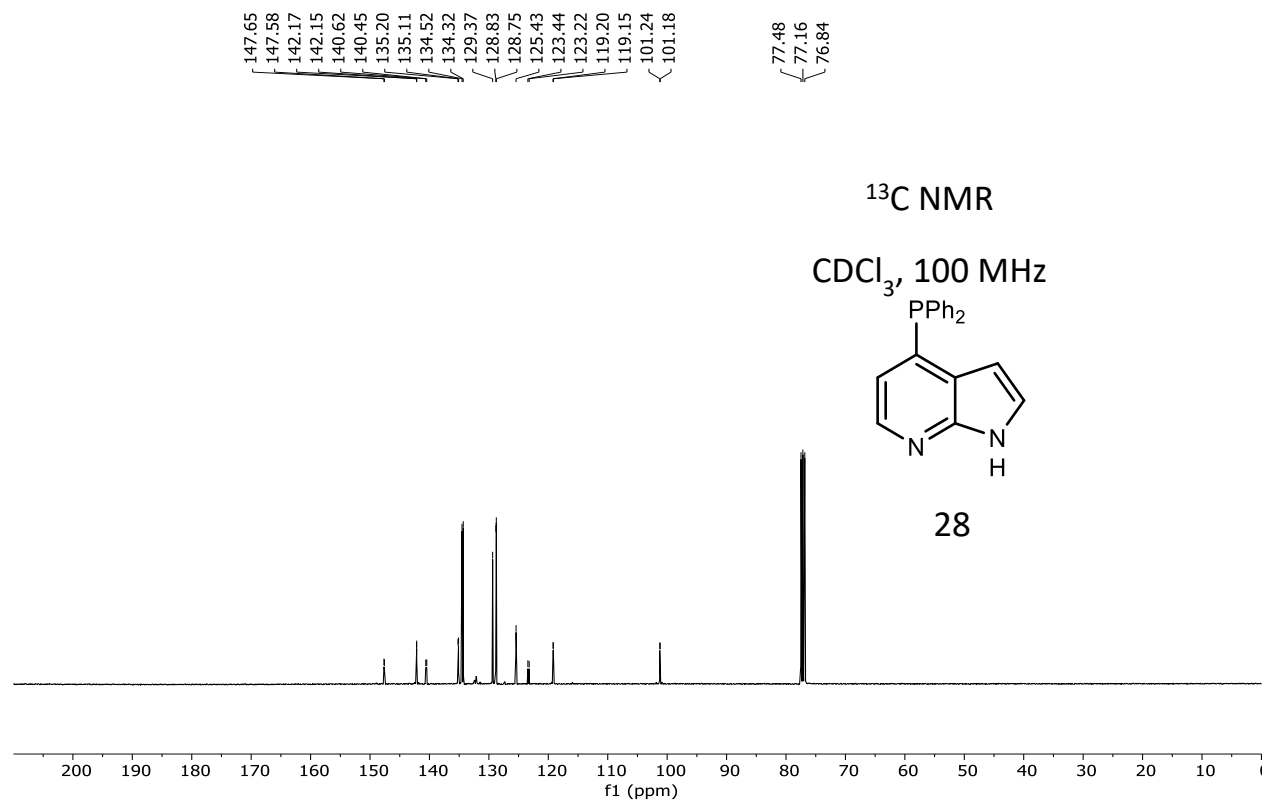
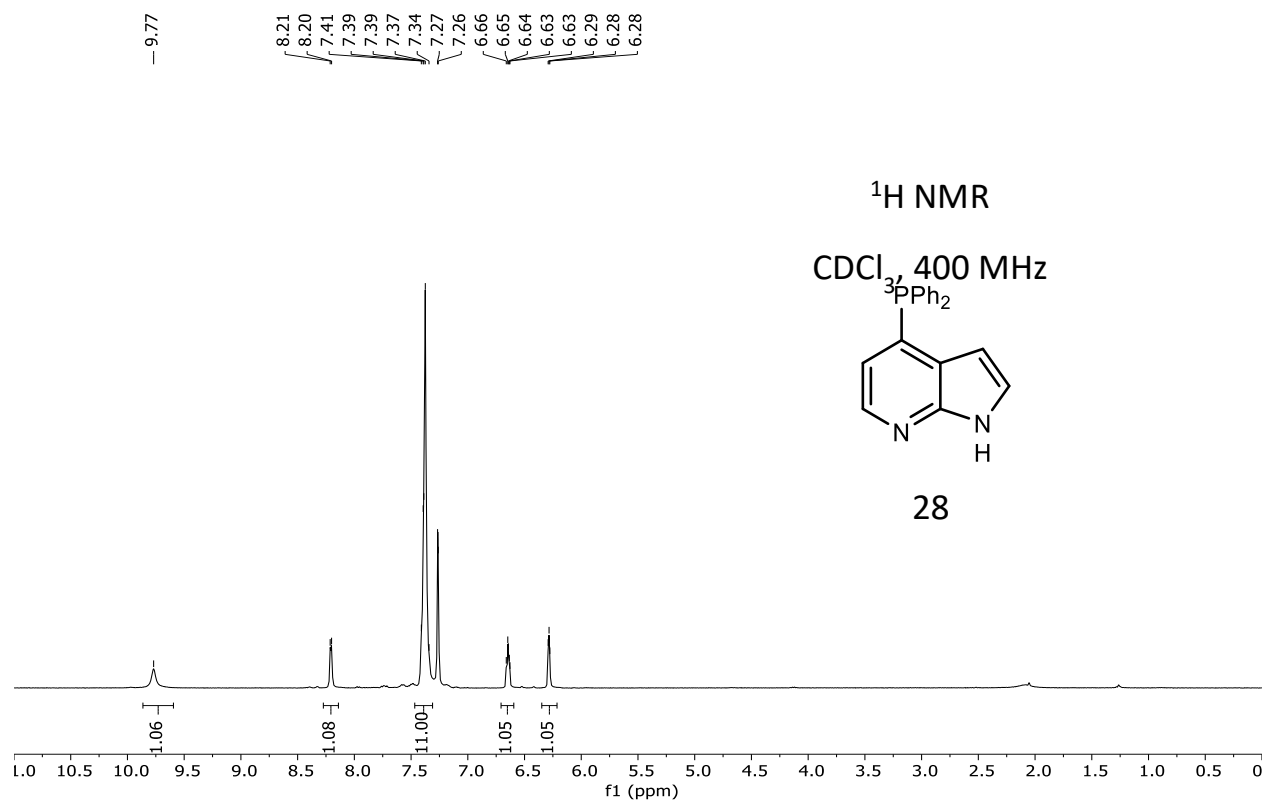


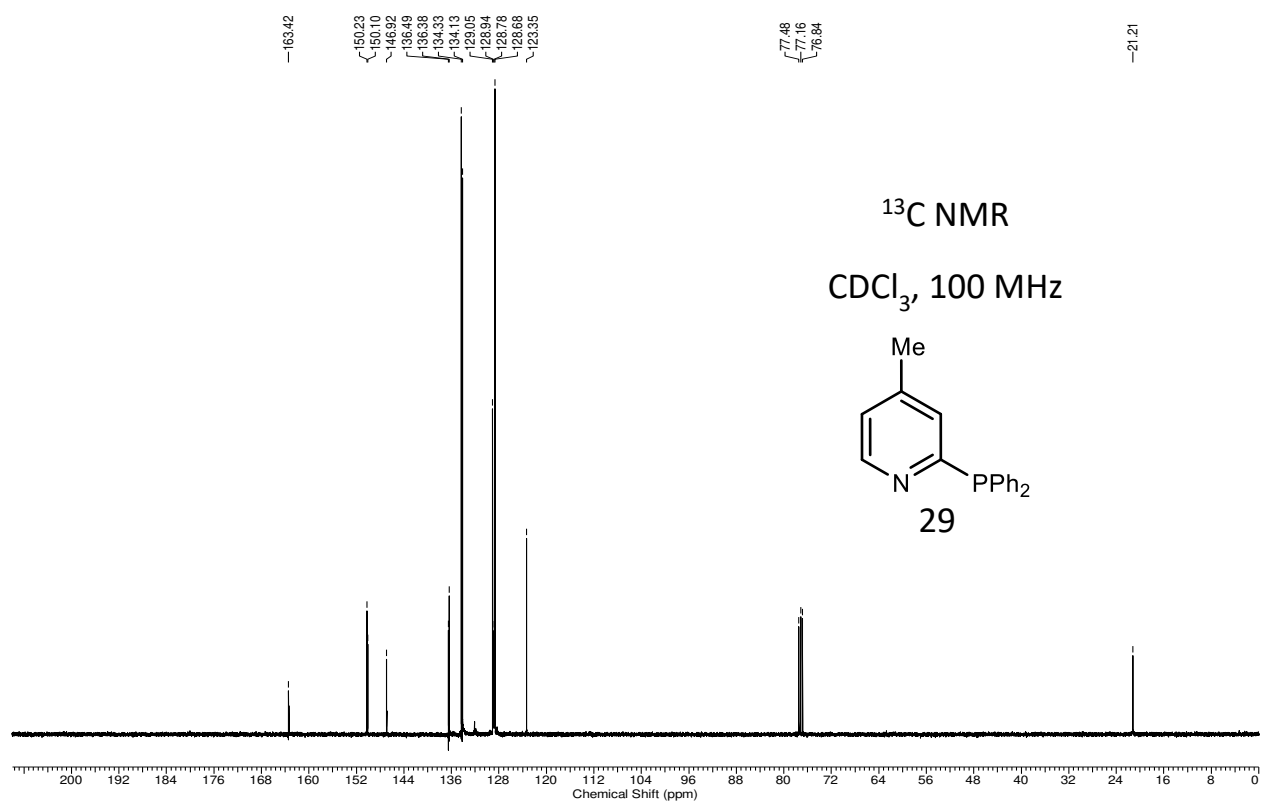
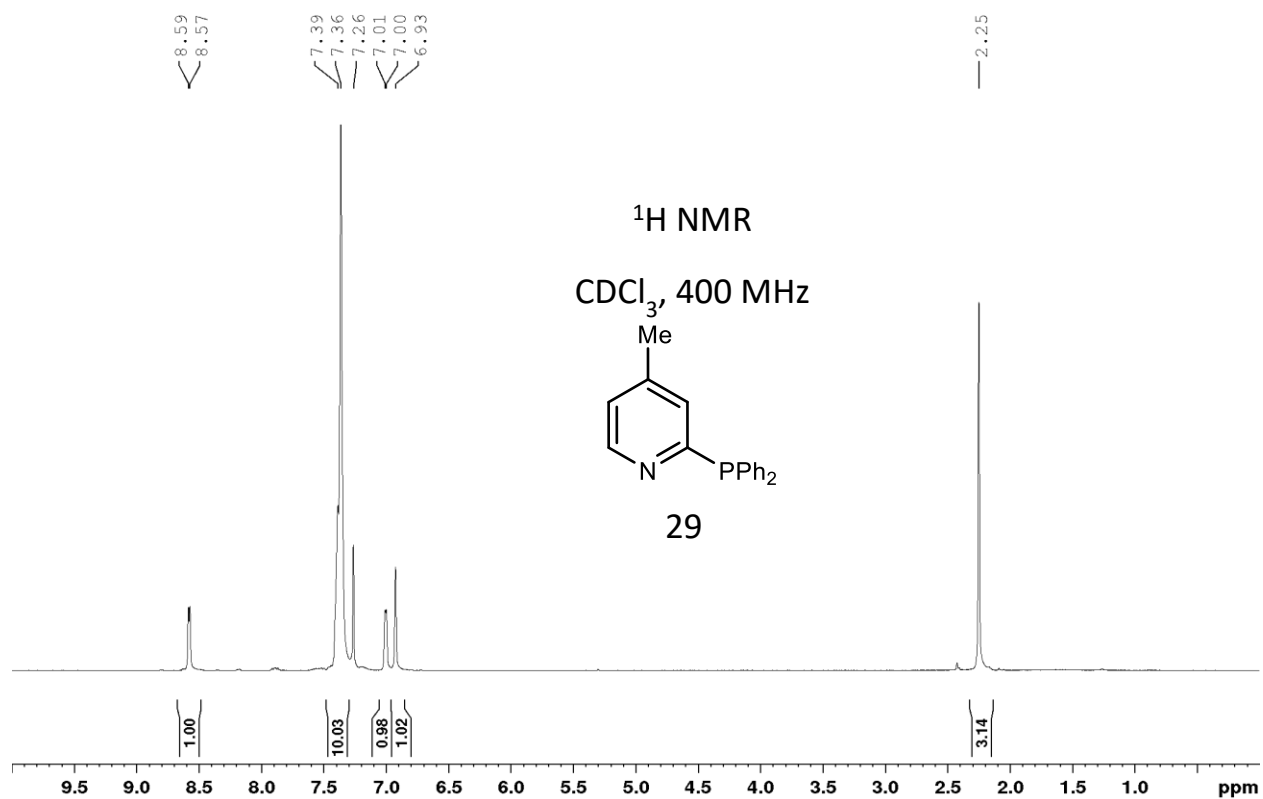


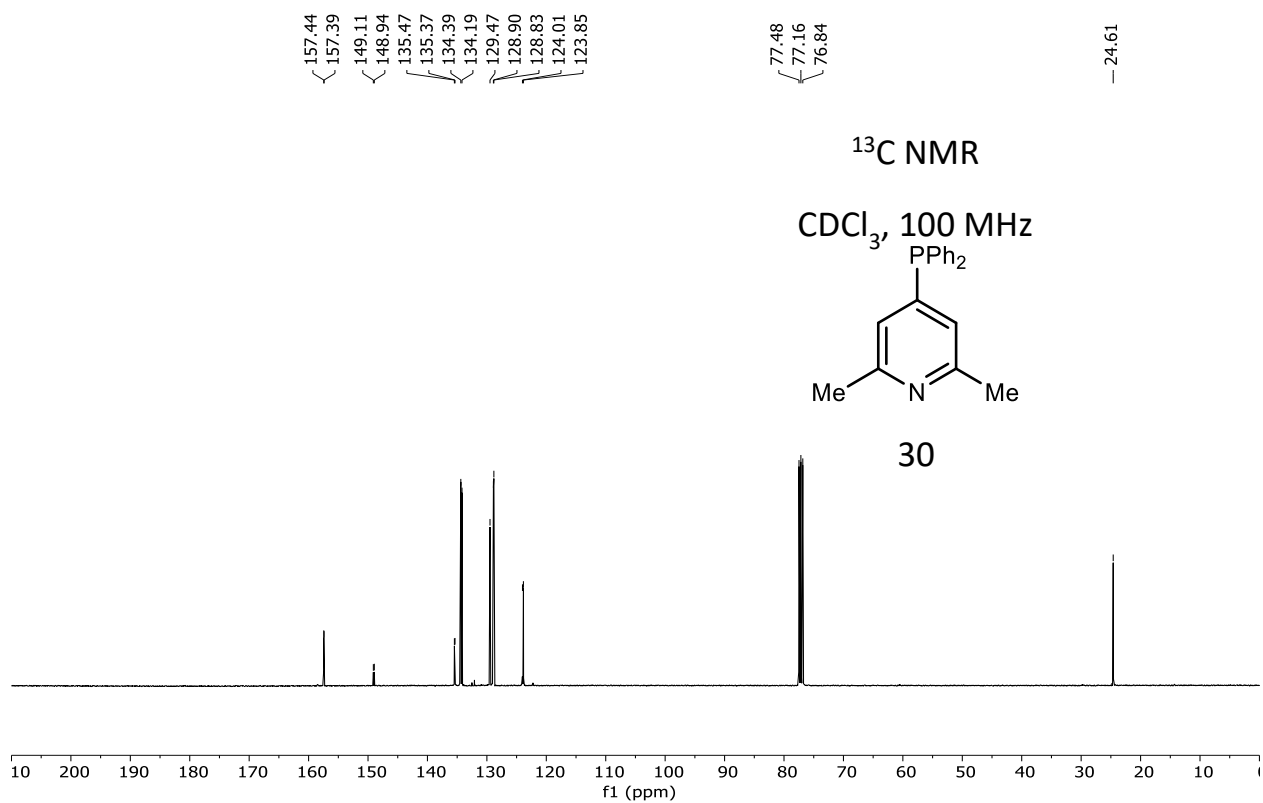
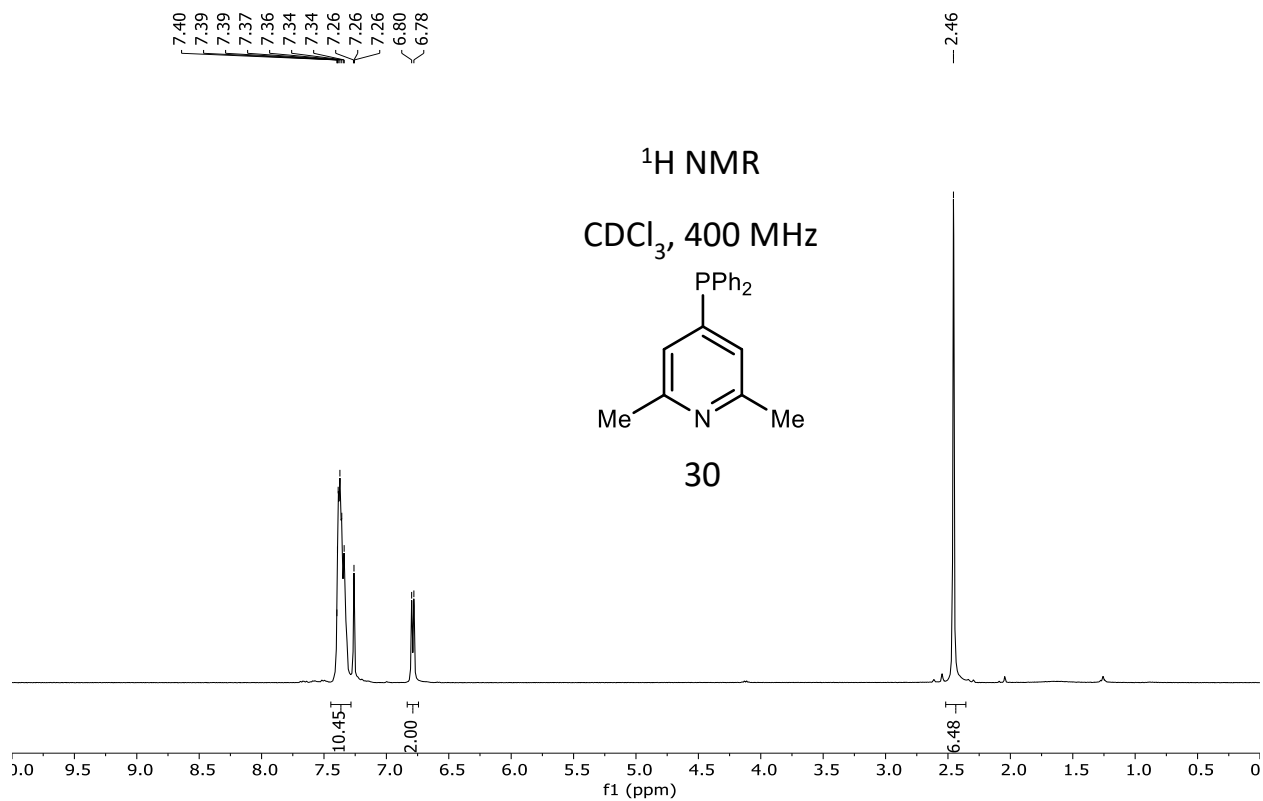


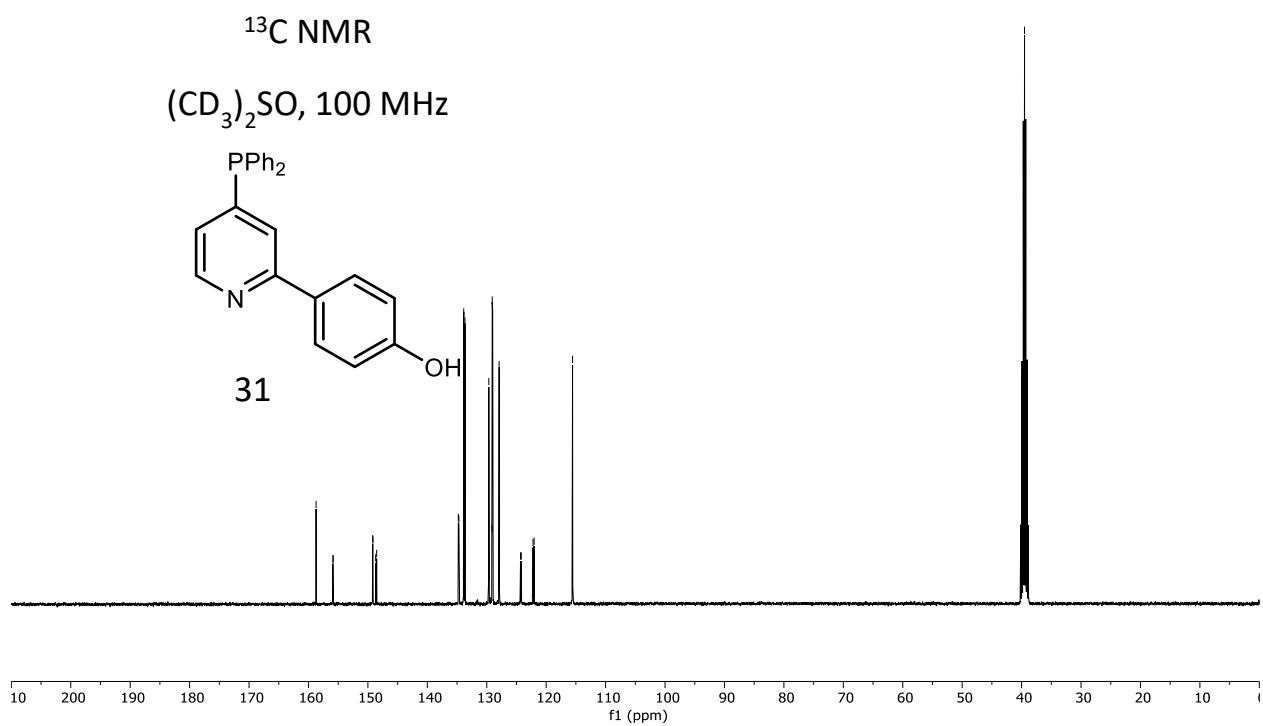
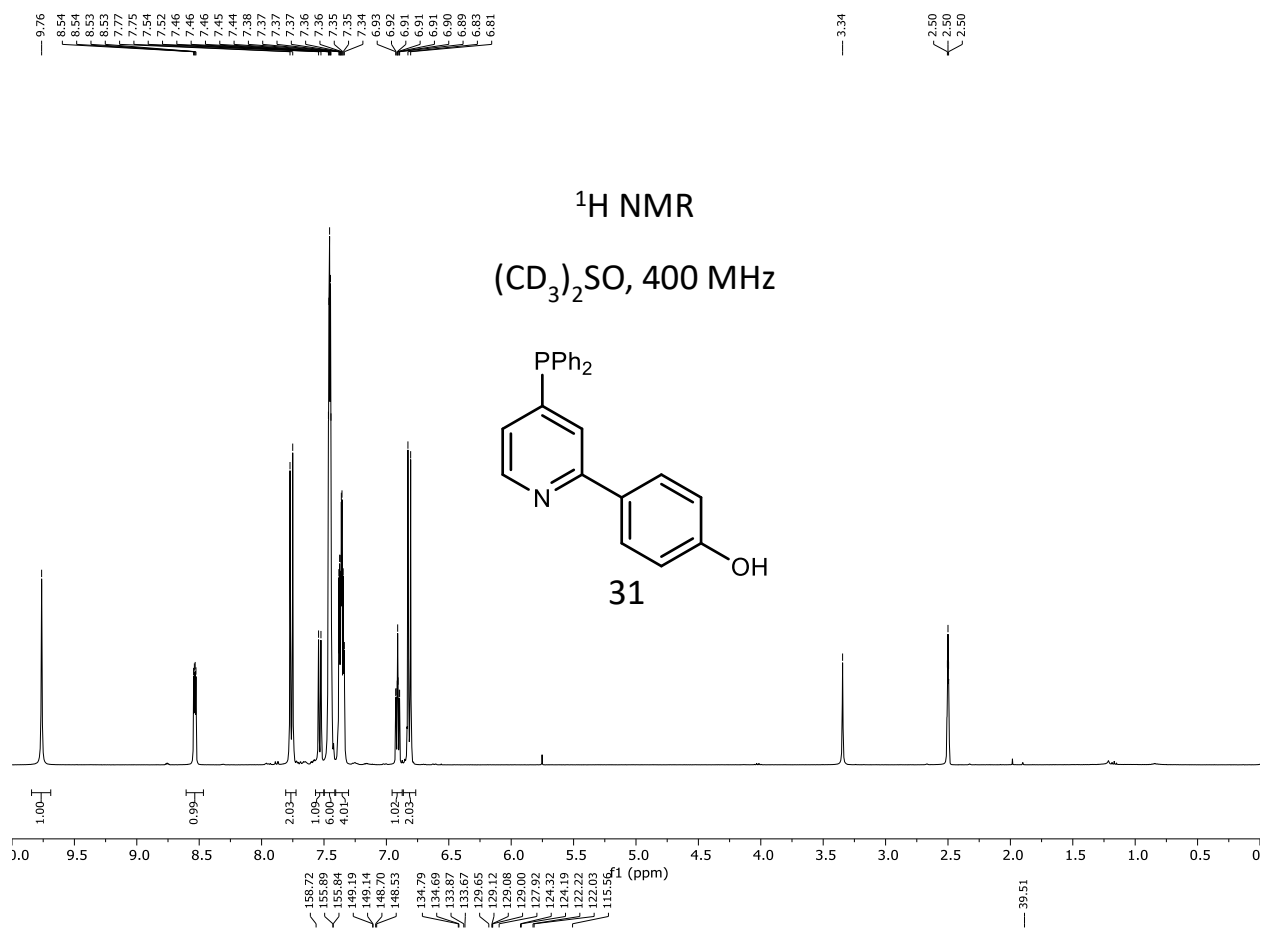


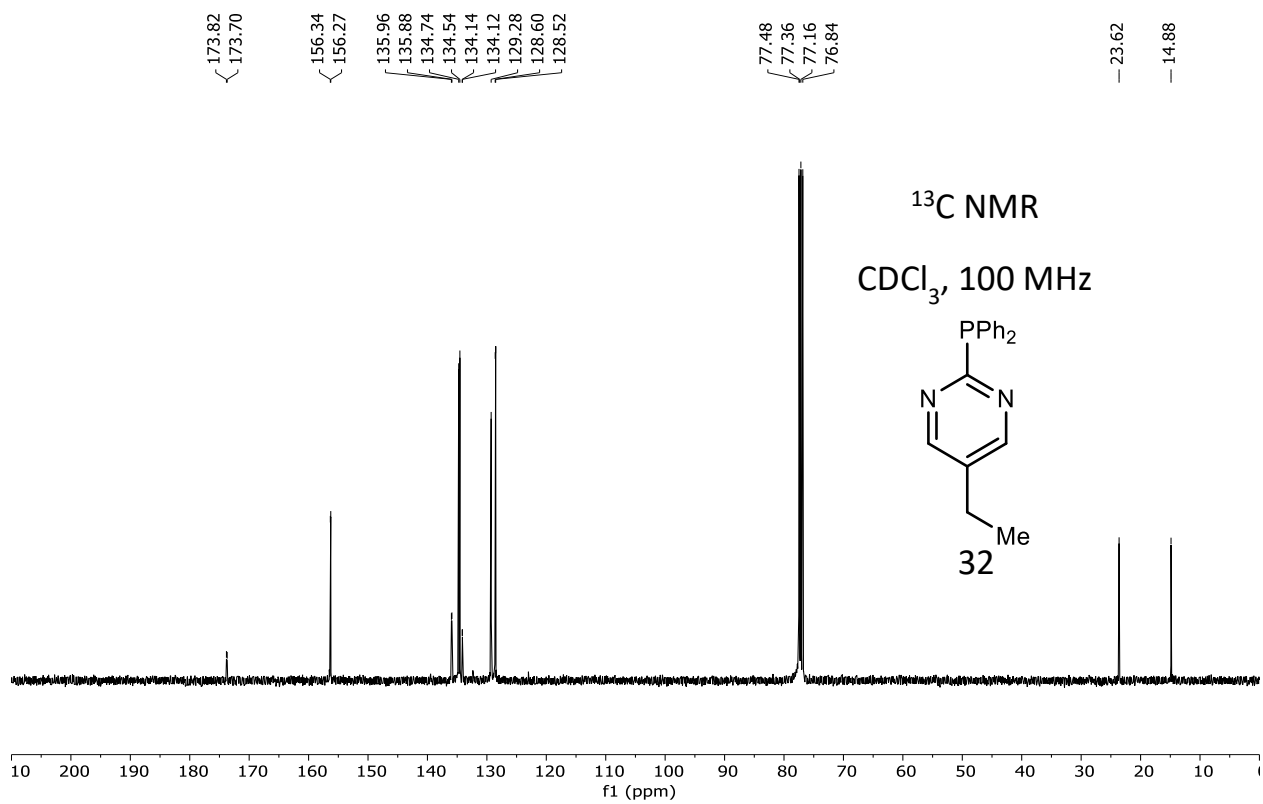
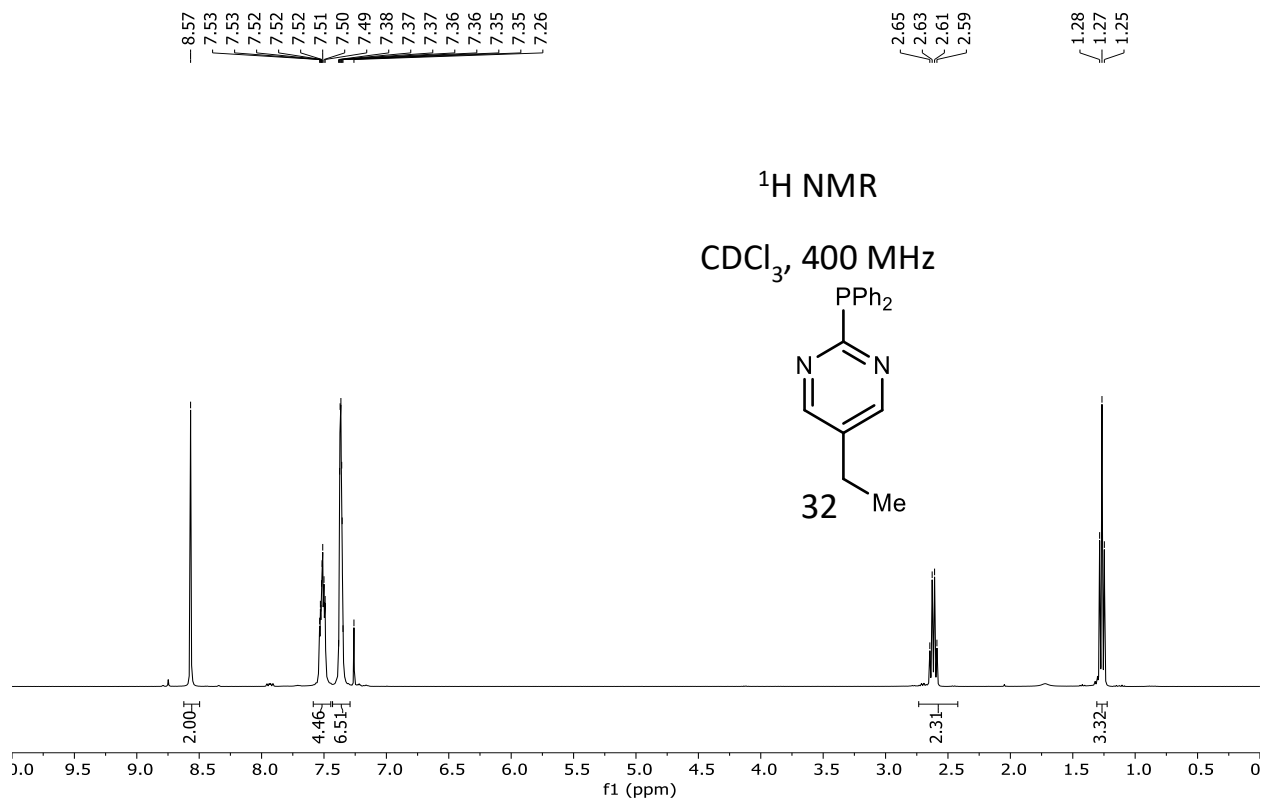


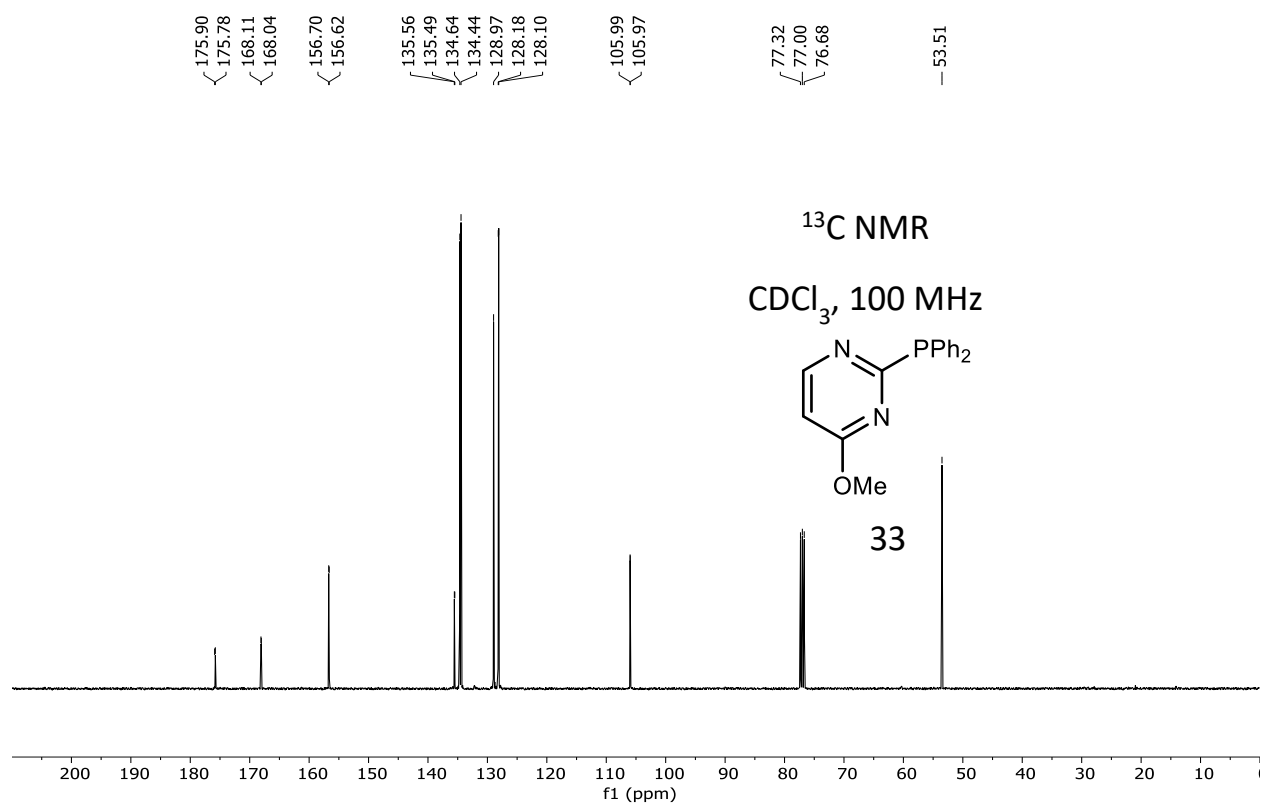
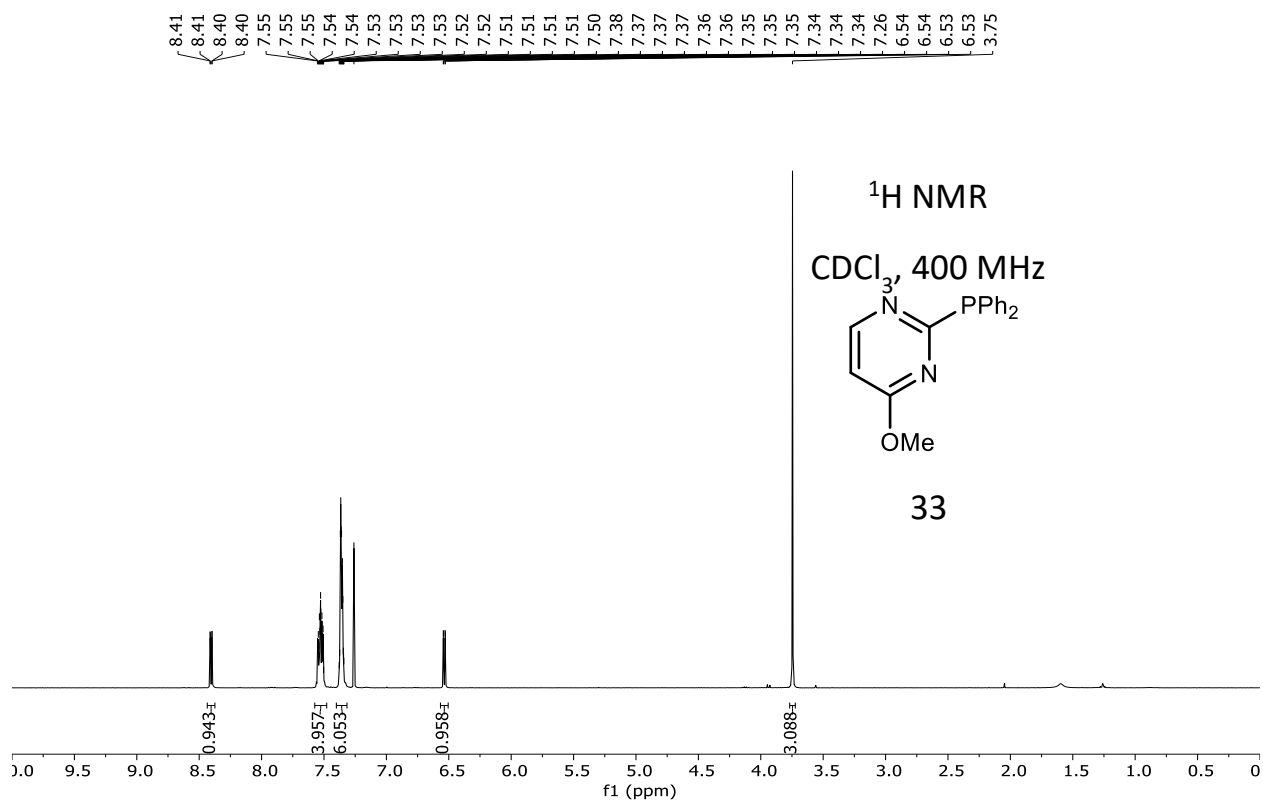


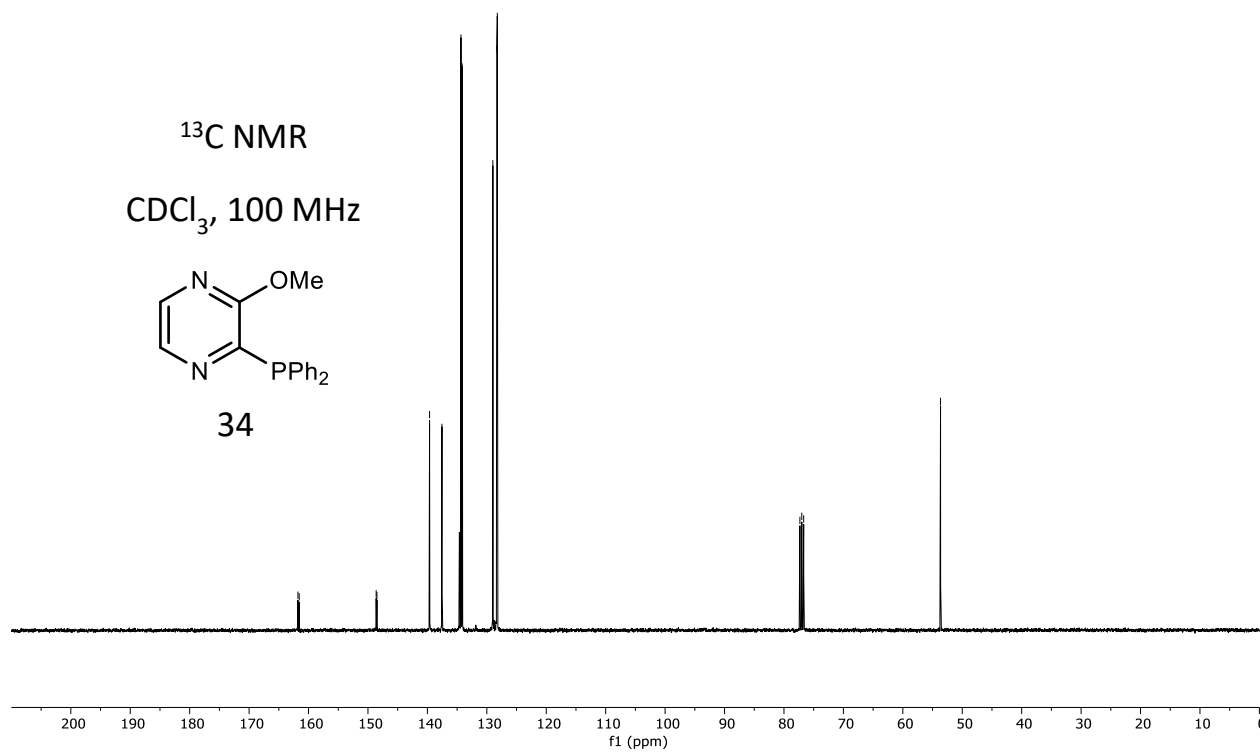
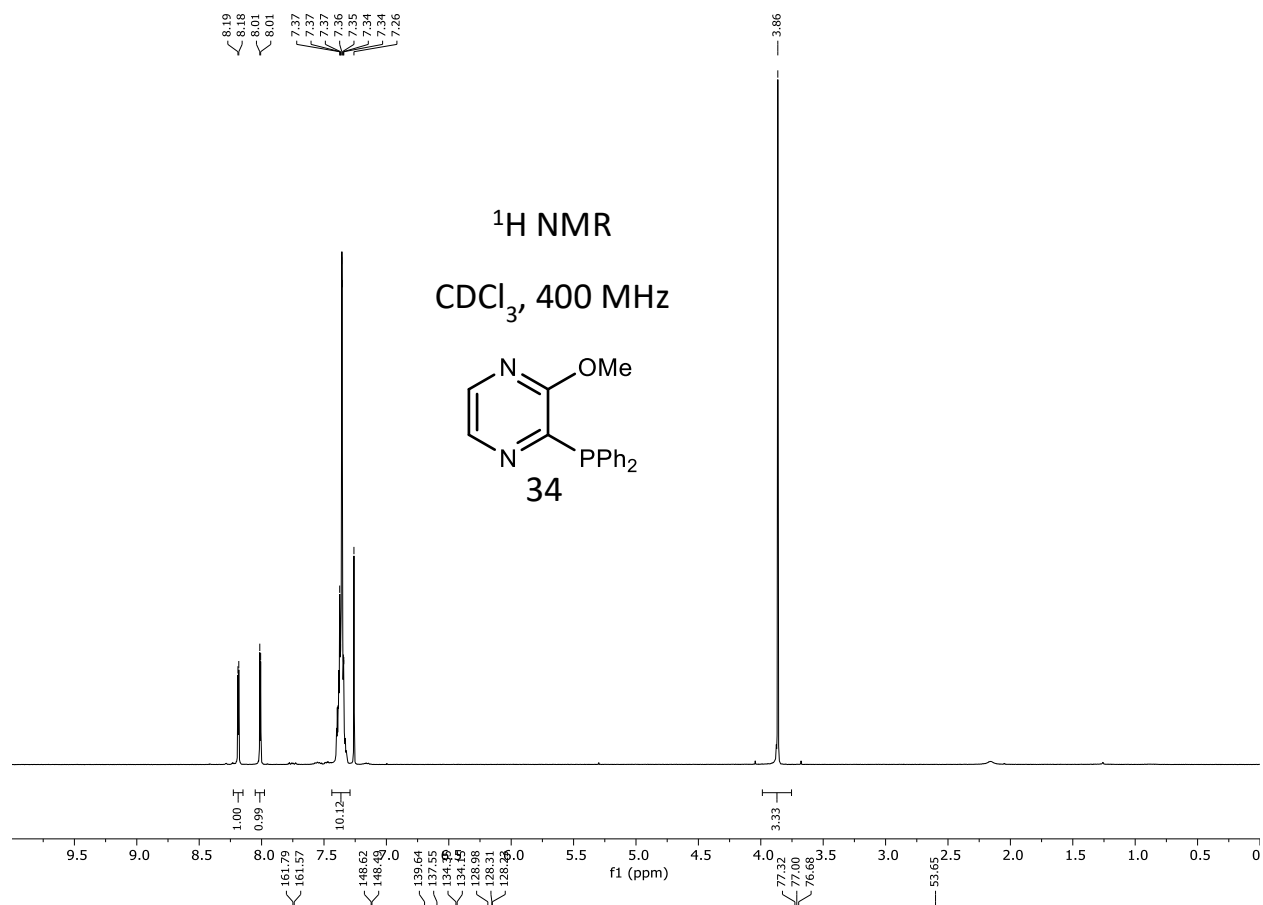


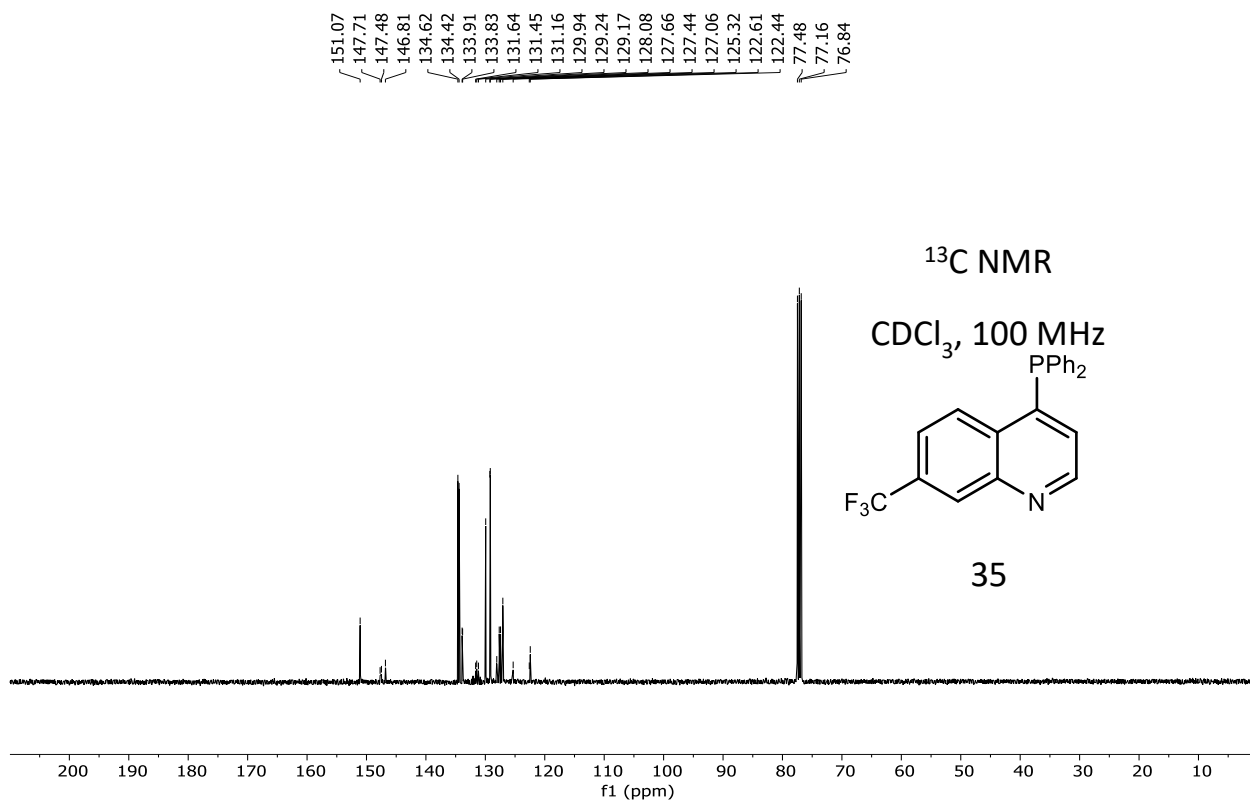
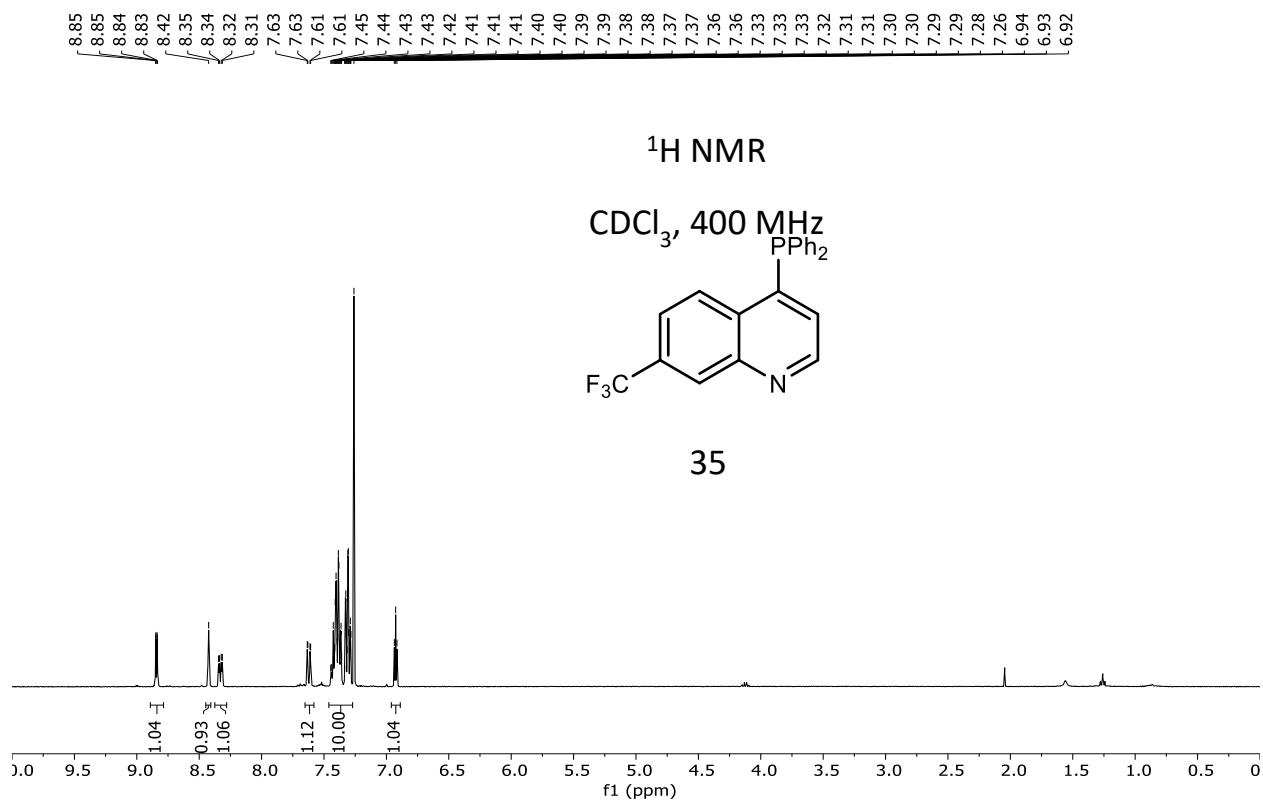


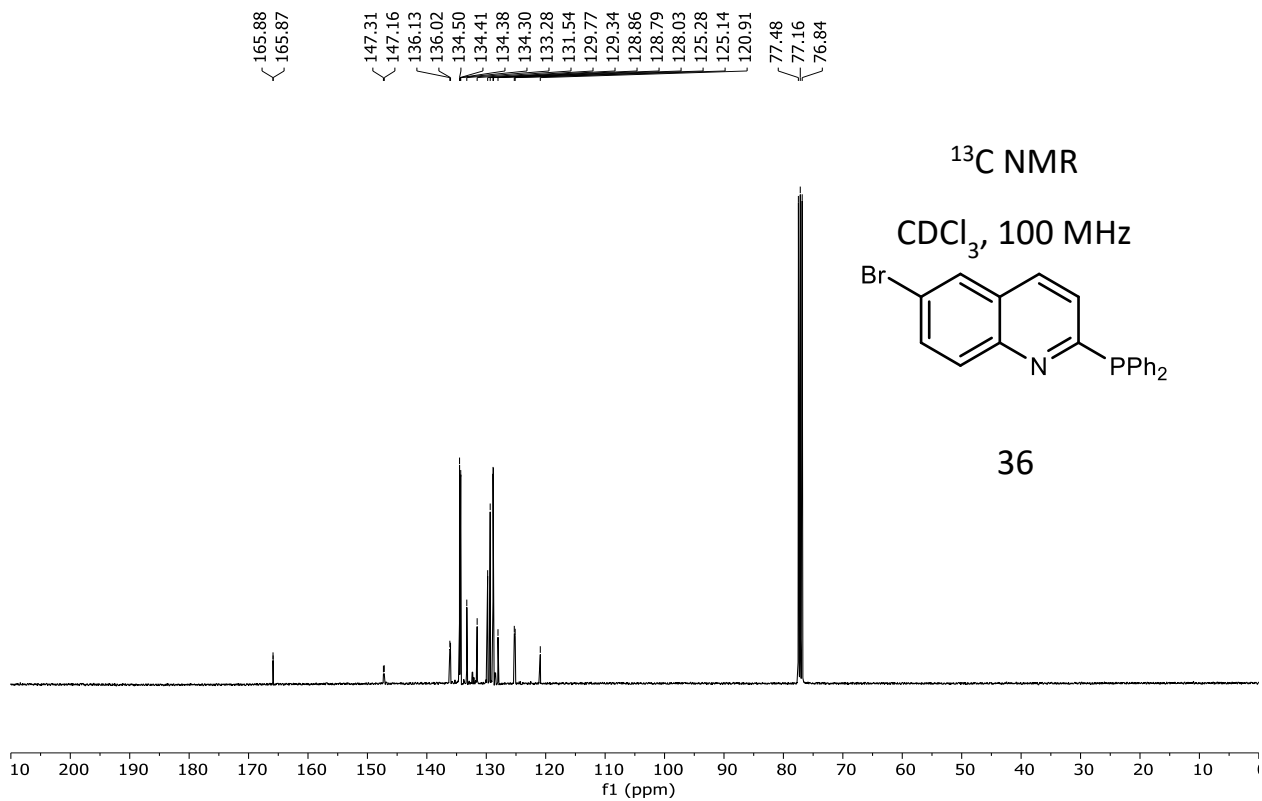
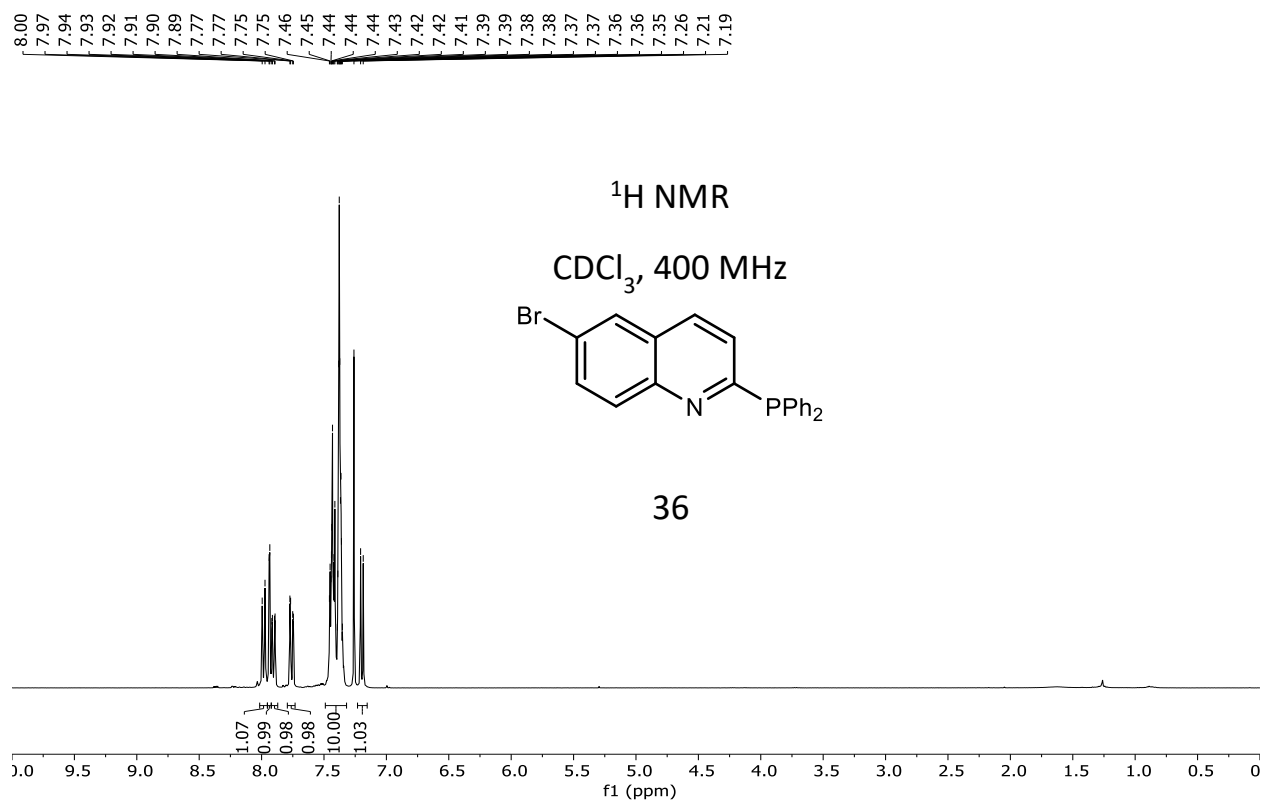


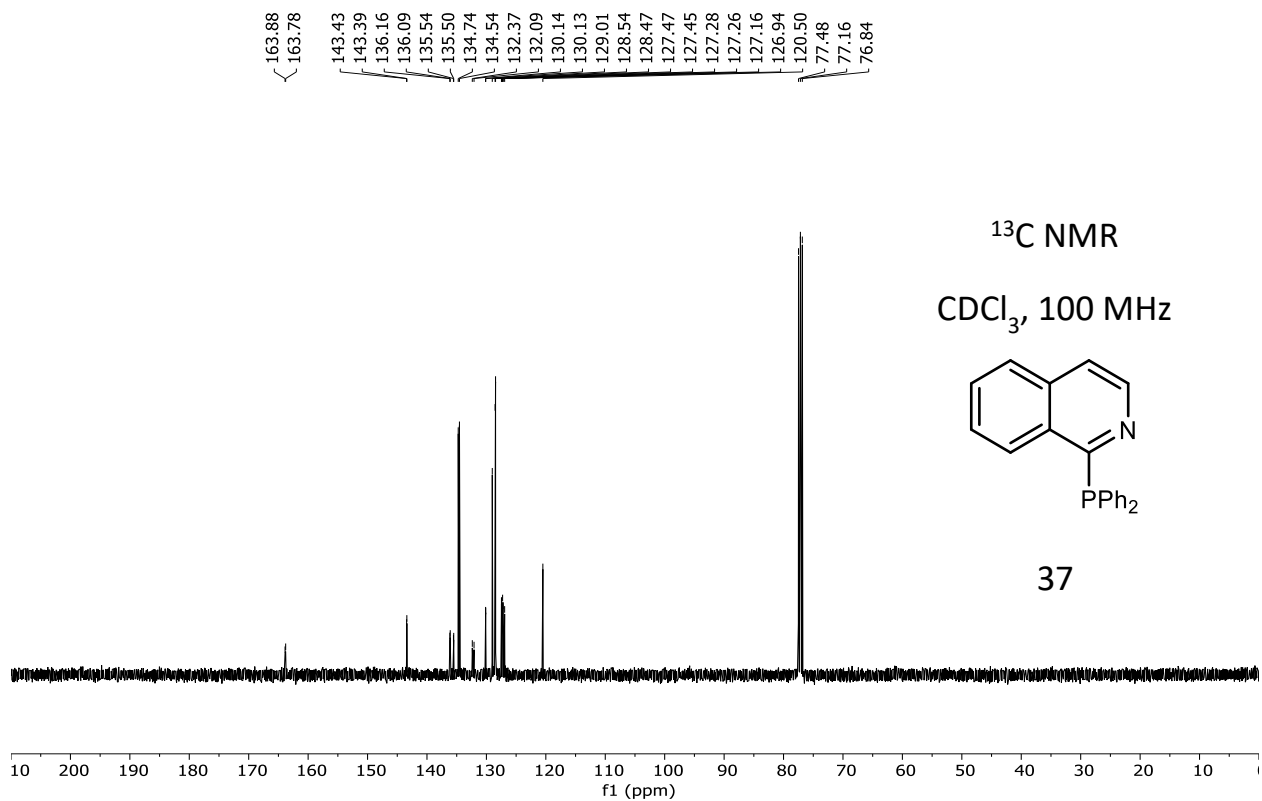
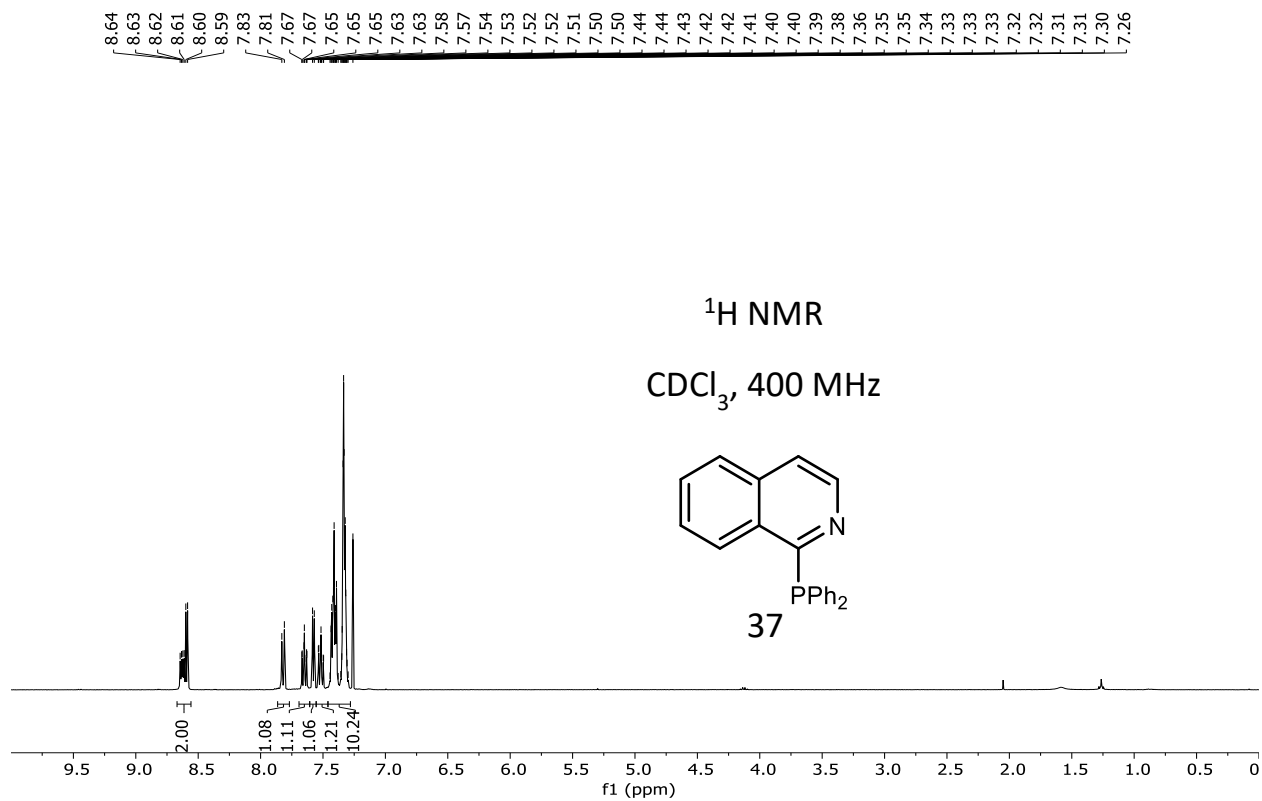


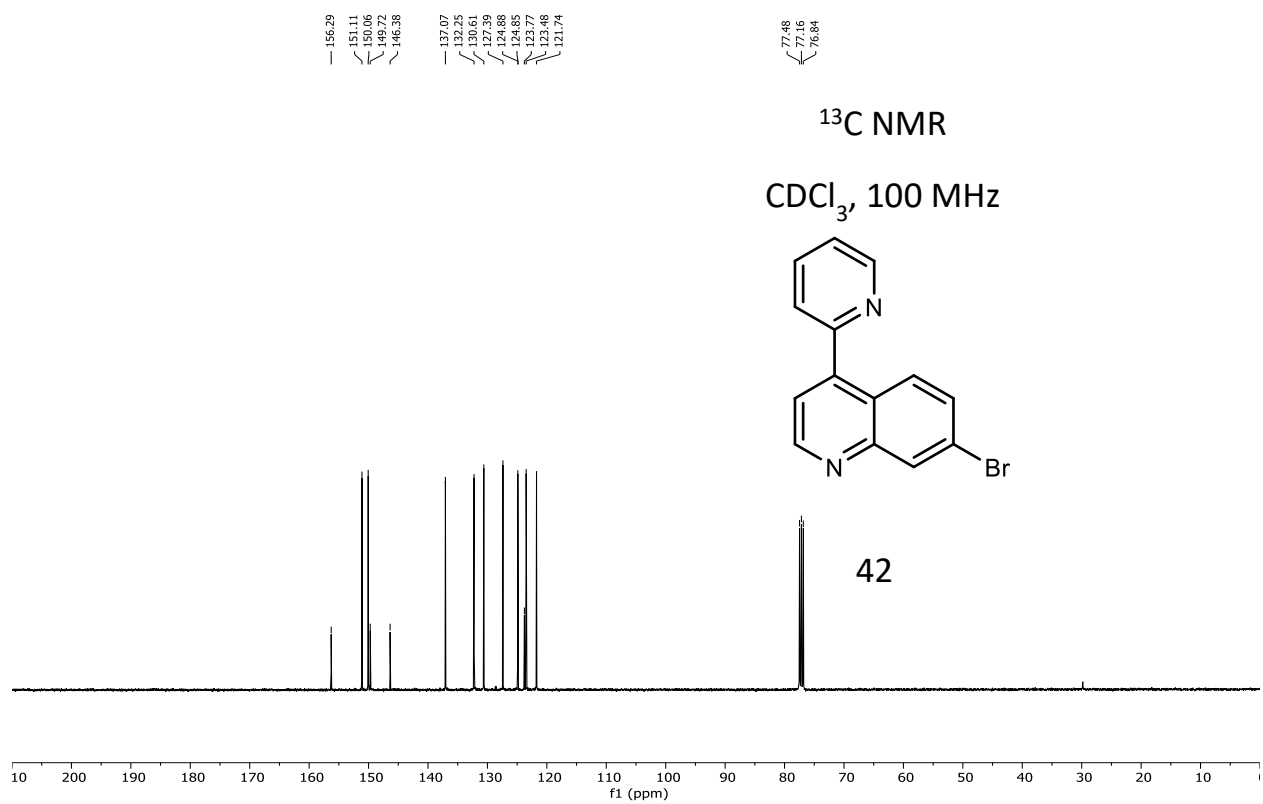
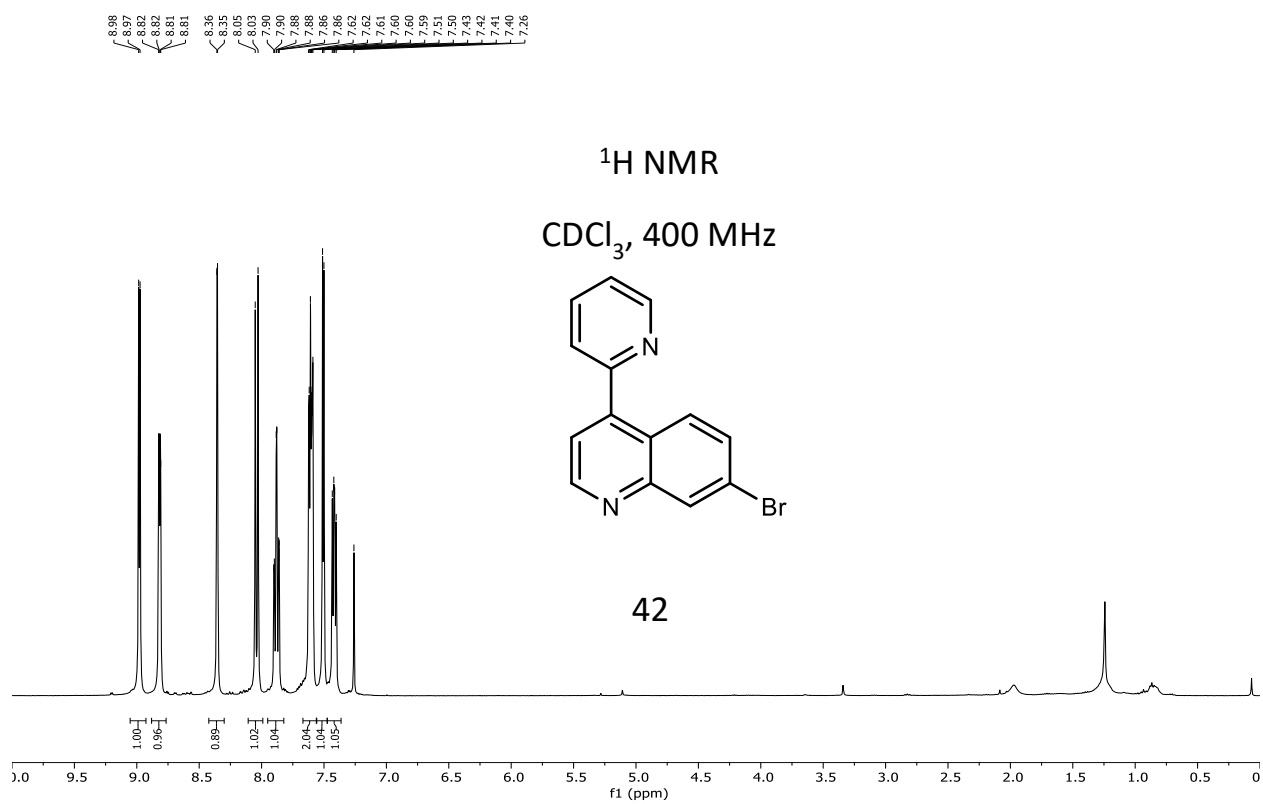


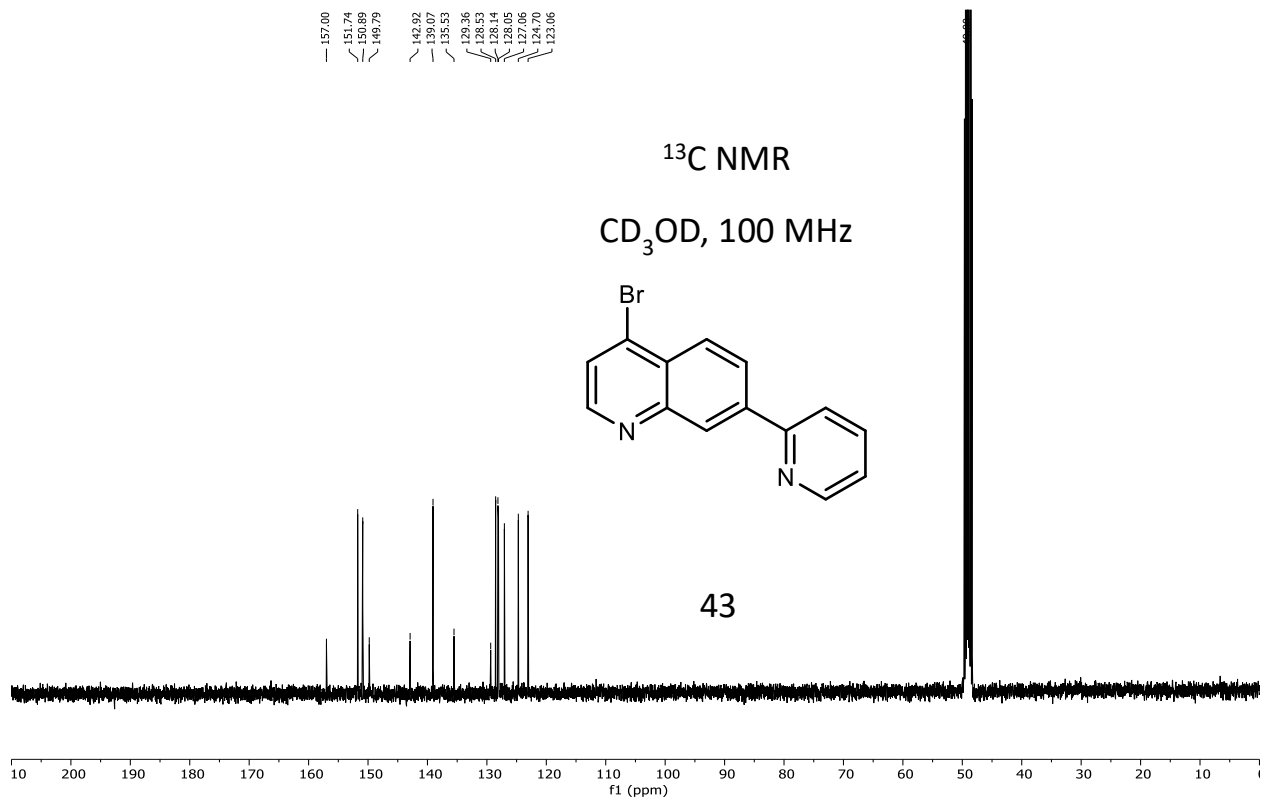
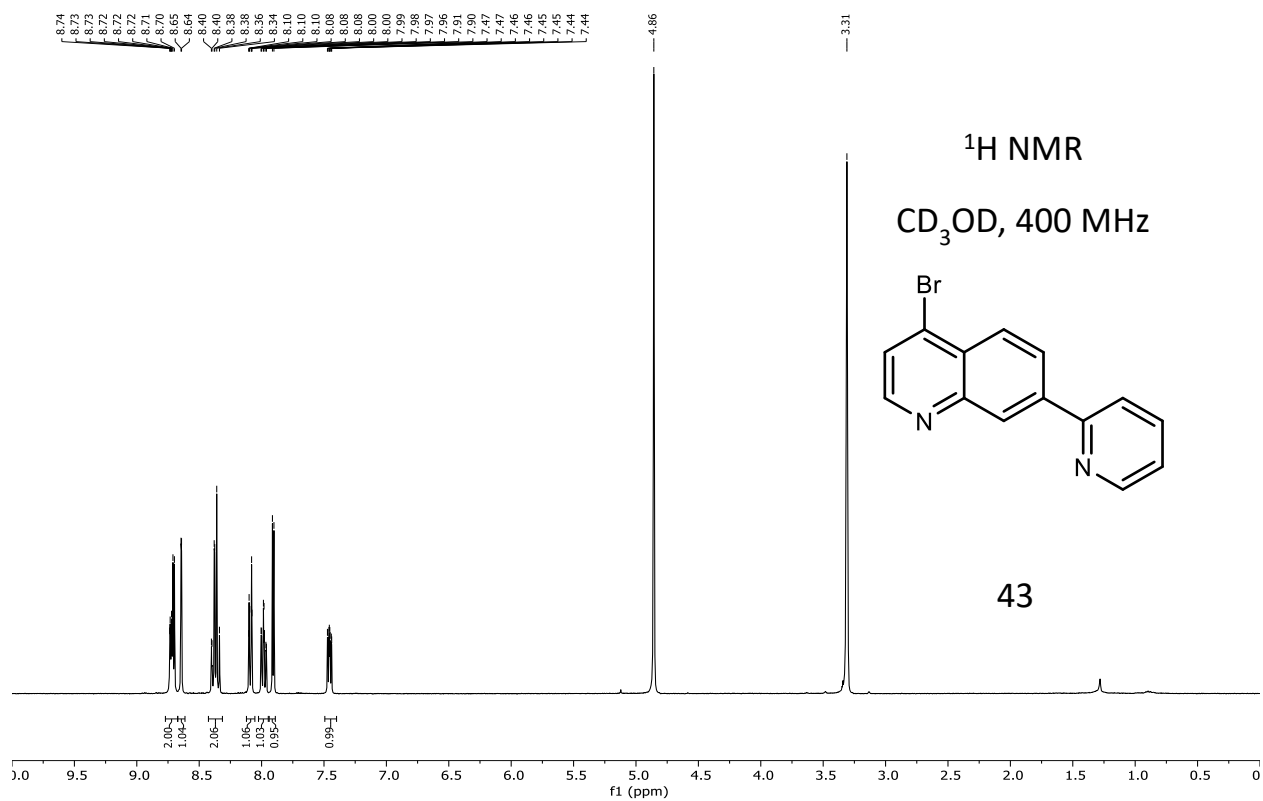


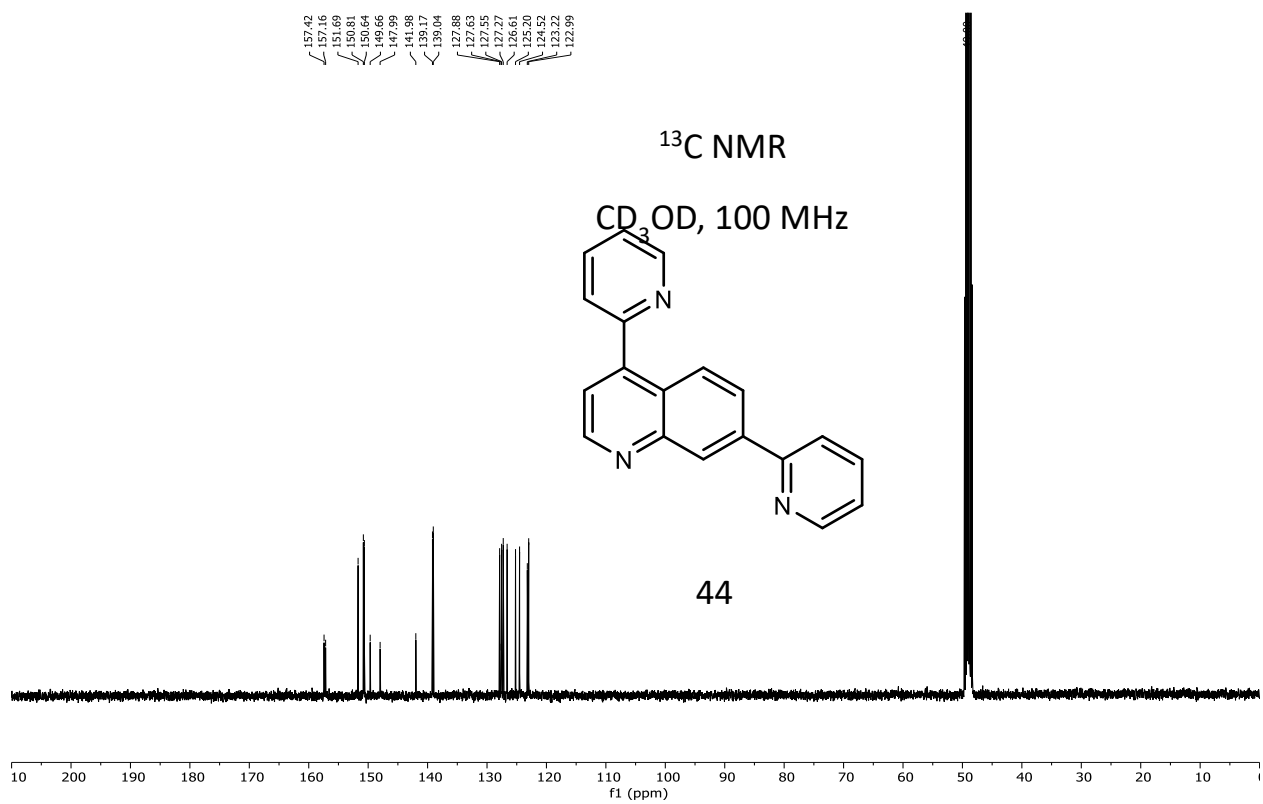
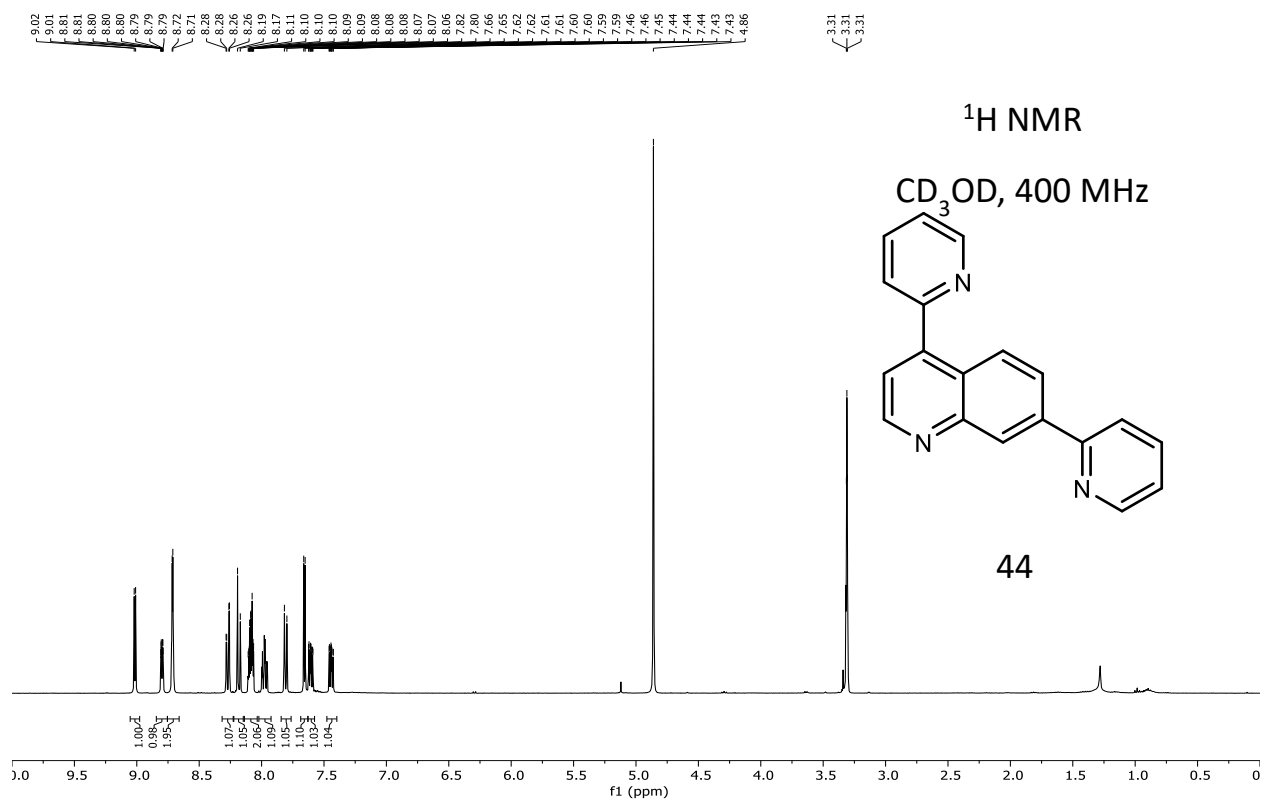


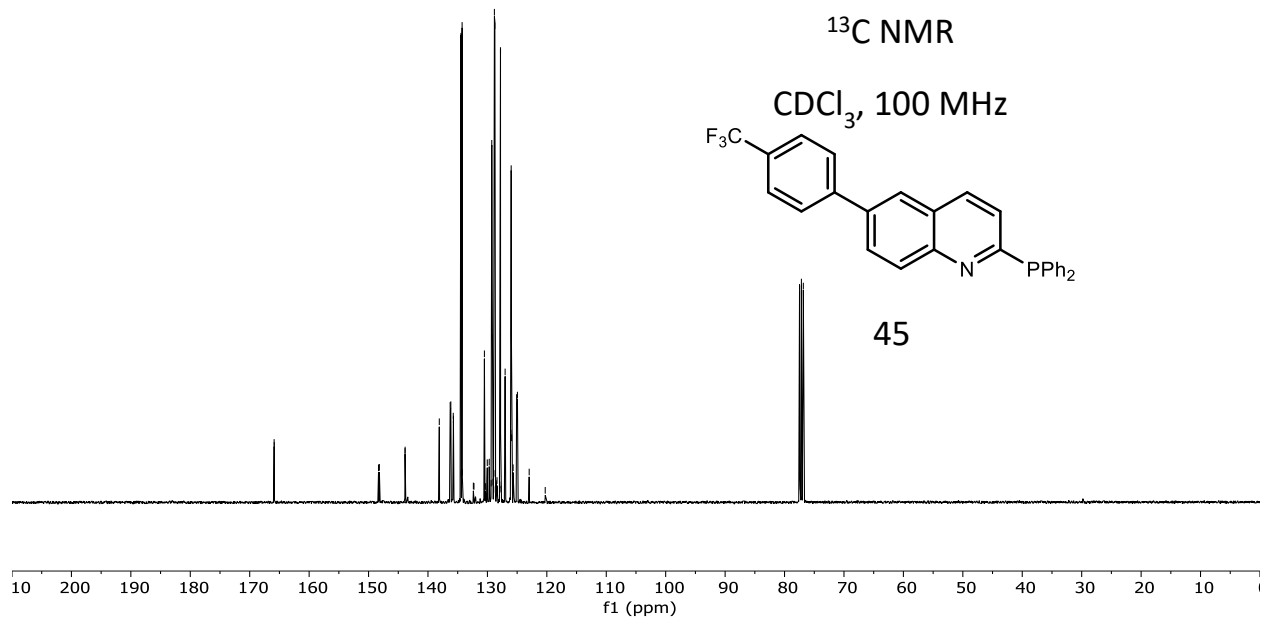
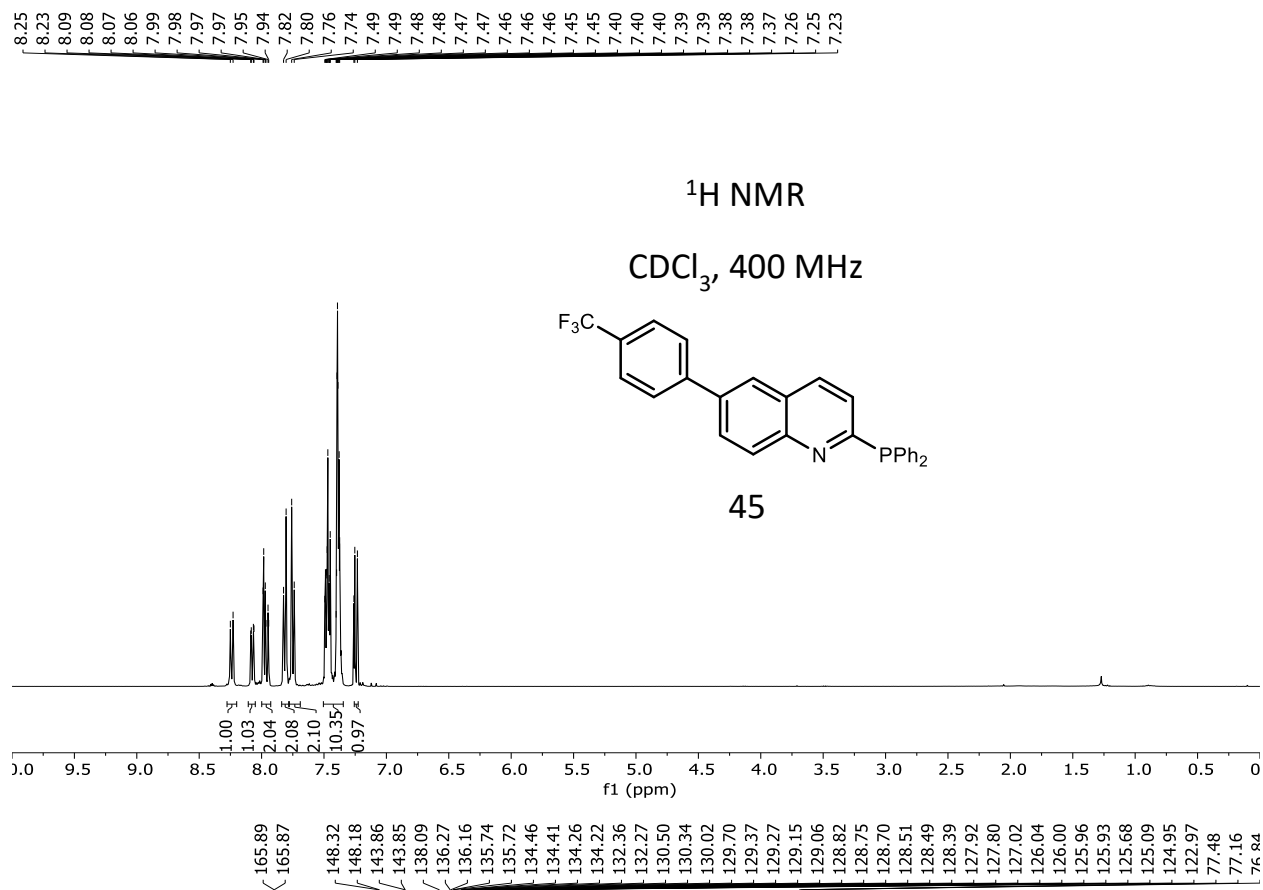












Appendix Three

Facile S_NAr on Iodopyridines through *N*-Phosphonium Pyridinium Intermediates: Experimental

A 3.1 General Methods and Materials

Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.¹ Chloroform (CHCl₃) was purchased anhydrous from Sigma Aldrich chemical company. Tri-*p*-anisole phosphine (99%) was purchased from Oakwood Chemicals and stored in a glovebox. Tri-*p*-anisole phosphine was commonly dispensed into vials for use in the reaction and stored under air on a benchtop prior to use. Anhydrous chloroform (0.05-0.1% EtOH as stabilizer) was purchased from Sigma Aldrich chemical company and used without further purification. All reagents were purchased at the highest commercial quality and used without further purification. Reactions were carried out under an atmosphere of air unless otherwise stated.

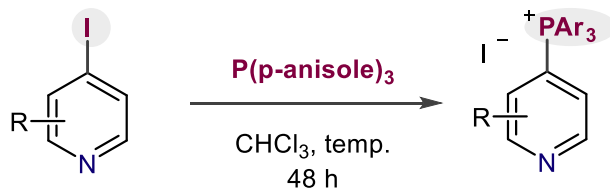
A 3.2 Instrumentation

¹H NMR spectra were recorded using a Varian 400 MR spectrometer, an Agilent Inova 400 spectrometer, an Agilent Inova 500 spectrometer, or a Bruker AV-111 400 spectrometer. The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: CDCl₃ (7.26 ppm), (CD₃)₂SO (2.50 ppm), or CD₃OD (3.31 ppm). Coupling constants (J) were reported in Hertz (Hz) and the multiplicity was reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. ¹³C NMR spectra were recorded using a Bruker Ultrashield-400, a Varian 400 MR or an Agilent Inova 400 spectrometer. The chemical shifts (δ) were reported in ppm and referenced to the corresponding NMR solvent: CDCl₃ (77.00 ppm), (CD₃)₂SO (39.51 ppm), or CD₃OD (49.00 ppm). Low-resolution mass spectra

were recorded on an Agilent 6310 Quadrupole Mass Spectrometer. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer with absorptions reported in wavenumbers (cm^{-1}). Melting points were recorded using a Büchi B-450 melting point apparatus.

A 3.3 General Procedures

A 3.3.1. Preparation of Heteroaryl Phosphonium Salts

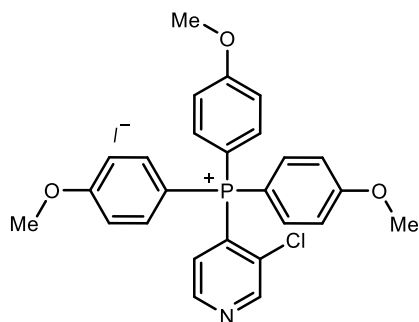


An oven dried 8 mL vial (< 1.0 mmol) or 16 mL vial (1.0-4.0 mmol) equipped with a stir bar was charged with the iodopyridine (1.0 equiv) and $(\text{p-anisole})_3\text{P}$ (1.0 equiv) and CHCl_3 (0.5 M). The reaction was then stirred at the temperature indicated (rt, 50°C or 80°C) for the stated time. The reaction was then purified by diluting the crude reaction with CHCl_3 and by crashing out in Et_2O (100 mL per 1.0 mmol) at room temperature.

Notes:

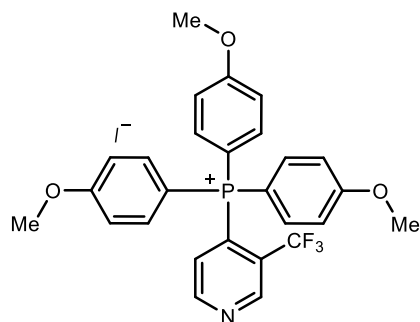
1. Reaction was ran under air and N_2 atmospheres and no notable differences in yields were observed.
2. Additional phosphine can be used to increase the reaction rate (1^{st} order in phosphine)
3. In general the reaction does not product by-products besides trace phosphine oxide.

(3-Chloropyridin-4-yl)tris(4-methoxyphenyl)phosphonium iodide (2)



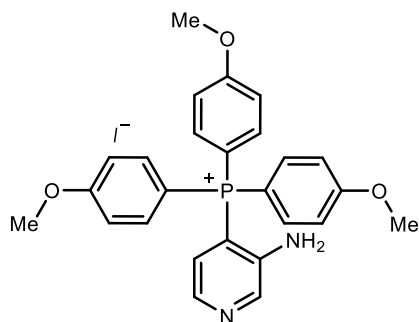
Prepared according to general procedure A using 3-chloro-4-iodopyridine (72 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at room temperature for 36 hours. After purification procedure, the title compound was isolated as a light brown solid (174 mg, 0.3 mmol, 98% yield). mp 91-93 °C; ¹H NMR (400 MHz, CDCl₃) δ: 9.12 – 8.59 (m, 2H), 7.58 (dd, *J*=12.7, 8.9, 6H), 7.48 – 7.10 (m, 7H), 3.95 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ: 165.40 (d, *J*=3.0), 151.98 (d, *J*=5.0), 150.11 (d, *J*=9.8), 136.35 (d, *J*=12.4), 134.75 (d, *J*=2.2), 130.32 (d, *J*=8.4), 129.29 (d, *J*=88.3), 117.02 (d, *J*=14.5), 105.78 (d, *J*=100.0), 56.51; ³¹P NMR (162 MHz, CDCl₃) δ: 21.08; *m/z* LRMS (ESI + APCI) found [M-I]⁺ 464.2, C₂₆H₂₄ClNO₃P⁺ requires 464.1.

Tris(4-methoxyphenyl)(3-(trifluoromethyl)pyridin-4-yl)phosphonium iodide (3)



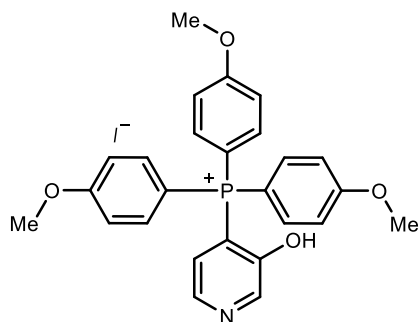
Prepared according to general procedure A using 4-iodo-3-(trifluoromethyl)pyridine (27 mg, 0.10 mmol), tris(4-methoxyphenyl)phosphane (35 mg, 0.10 mmol), and chloroform (0.2 mL) at room temperature for 37 hours. After purification procedure, the title compound was isolated as a yellow solid (53 mg, 0.09 mmol, 85% yield). mp 93-96 °C. ^1H NMR (400 MHz, CDCl_3) δ : 9.26 (m, 2H), 7.72 – 7.56 (m, 7H), 7.26 (m, 6H), 3.97 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.41 (d, $J=3.0$), 156.20 (d, $J=9.5$), 150.29, 150.21 (d, $J=5.2$), 136.67 (d, $J=12.3$), 131.24 (d, $J=8.9$), 122.51 (qd, $J=273.2$, 2.7), 116.80 (d, $J=14.6$), 106.96 (d, $J=99.9$), 56.4; ^{19}F NMR (365 MHz, CDCl_3) δ : -54.14 (d, $J=2.1$); ^{31}P NMR (162 MHz, CDCl_3) δ : 25.27; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+$ 498.2, $\text{C}_{27}\text{H}_{24}\text{F}_3\text{NO}_3\text{P}^+$ requires 498.1.

(3-Aminopyridin-4-yl)tris(4-methoxyphenyl)phosphonium iodide (4)



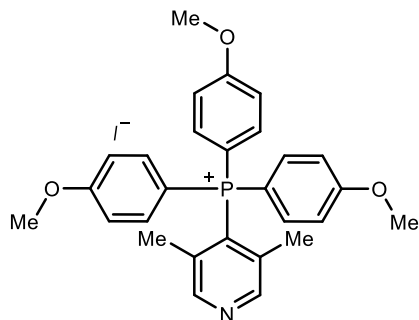
Prepared according to general procedure A using 4-iodopyridin-3-amine (66 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at 50 °C for 19 hours. After purification procedure, the title compound was isolated as a dark red crystalline solid (163 mg, 0.29 mmol, 95% yield). mp 148-151 °C; IR $\nu_{\text{max}}/\text{cm}^{-1}$ (film): 3048, 3001, 2961, 1576, 1555, 1443, 1433, 1094, 796, 754, 698; ^1H NMR (400 MHz, CD_3CN) δ : 8.46 (d, $J=7.3$, 1H), 7.99 (dd, $J=5.3$, 3.4, 1H), 7.74 – 7.48 (m, 6H), 7.24 (dd, $J=9.0$, 2.7, 6H), 6.76 (dd, $J=15.4$, 5.4, 1H), 4.85 (s, 2H), 3.92 (s, 9H); ^{13}C NMR (100 MHz, CD_3CN) δ : 166.18 (d, $J=2.9$), 147.39 (d, $J=3.5$), 141.32 (d, $J=5.9$), 138.31 (d, $J=10.8$), 137.39 (d, $J=12.4$), 134.47 (d, $J=11.1$), 128.00 (d, $J=8.6$), 117.20 (d, $J=14.2$), 107.65 (d, $J=98.0$), 56.8; ^{31}P NMR (162 MHz, CDCl_3) δ : 17.57; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+$ 445.3, $\text{C}_{26}\text{H}_{26}\text{N}_2\text{O}_3\text{P}^+$ requires 445.2.

(3-Hydroxypyridin-4-yl)tris(4-methoxyphenyl)phosphonium iodide (5)



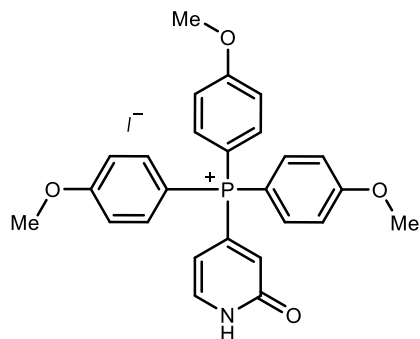
Prepared according to general procedure A using 4-iodopyridin-3-ol (66 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at 50 °C for 19 hours. After purification procedure, the title compound was isolated as a yellow solid (169 mg, 0.29 mmol, 99% yield). mp 123 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.79 (d, $J=6.5$, 1H), 8.09 (dd, $J=5.2$, 3.7, 1H), 7.50 (dd, $J=12.7$, 8.9, 6H), 7.15 (dd, $J=9.0$, 2.7, 6H), 6.90 (dd, $J=14.6$, 5.2, 1H), 3.91 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 164.81 (d, $J=2.9$), 159.17, 140.97, 136.05 (d, $J=12.4$), 133.87 (d, $J=11.8$), 127.72 (d, $J=8.0$), 116.24 (d, $J=14.5$), 114.31 (d, $J=13.5$), 108.13 (d, $J=100.0$), 56.2; ^{31}P NMR (162 MHz, CDCl_3) δ : 19.74; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+$ 446.2, $\text{C}_{26}\text{H}_{25}\text{NO}_4\text{P}^+$ requires 446.2

(3,5-Dimethylpyridin-4-yl)tris(4-methoxyphenyl)phosphonium iodide (6)



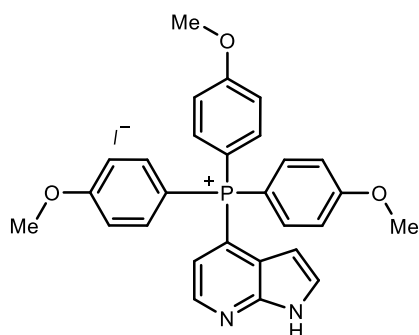
Prepared according to general procedure A using 4-iodo-3,5-dimethylpyridine (70 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at 80 °C for 19 hours. After purification procedure, the title compound was isolated as a red crystalline solid (175 mg, 0.3 mmol, 99% yield). mp 122-124 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.50 (d, $J=6.0$, 2H), 7.68 – 7.55 (m, 6H), 7.28 – 7.23 (m, 7H), 3.94 (s, 9H), 1.83 (d, $J=1.1$, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.16 (d, $J=3.0$), 152.49 (d, $J=8.5$), 137.55 (d, $J=7.6$), 136.14 (d, $J=12.2$), 126.41 (d, $J=81.8$), 117.09 (d, $J=14.2$), 109.34 (d, $J=95.7$), 56.51, 21.08 (d, $J=5.2$); ^{31}P NMR (162 MHz, CDCl_3) δ : 15.33; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+$ 458.3, $\text{C}_{28}\text{H}_{29}\text{NO}_3\text{P}^+$ requires 458.2.

Tris(4-methoxyphenyl)(2-oxo-1,2-dihydropyridin-4-yl)phosphonium iodide (7)



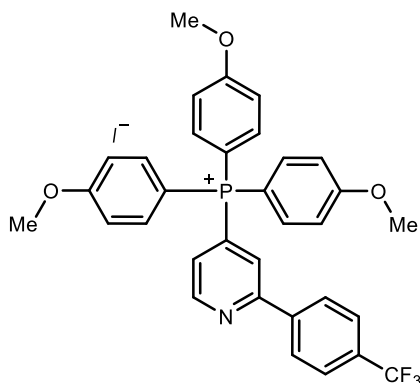
Prepared according to general procedure A using 4-iodopyridin-2-ol (66 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at 50 °C for 19 hours. After purification procedure, the title compound was isolated as a brown solid (160 mg, 0.29 mmol, 98% yield). mp 78-80 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.13 (s, 1H), 7.54 (dd, *J*=12.5, 8.5, 6H), 7.25 – 7.18 (m, 6H), 7.13 (d, *J*=6.7, 1H), 7.08 (d, *J*=1.6, 1H), 6.67 – 6.55 (m, 2H), 6.30 (s, 1H), 3.95 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ: 165.53 (d, *J*=2.9), 139.50 (d, *J*=14.1), 136.44 (d, *J*=12.0), 135.43 (d, *J*=79.6), 134.30, 129.62 (d, *J*=8.1), 116.87 (d, *J*=14.2), 105.81 (d, *J*=10.3), 105.80, 56.4; ³¹P NMR (162 MHz, CDCl₃) δ: 20.74; *m/z* LRMS (ESI + APCI) found [M-I]⁺ 446.2, C₂₆H₂₅NO₄P⁺ requires 446.2.

Tris(4-methoxyphenyl)(1H-pyrrolo[2,3-b]pyridin-4-yl)phosphonium iodide (8)



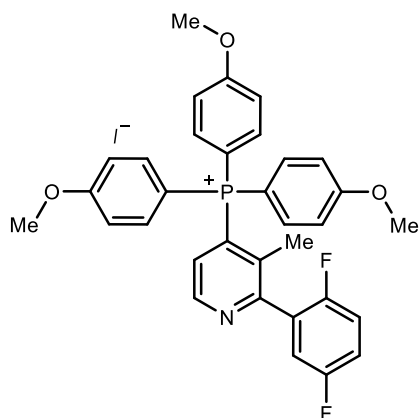
Prepared according to general procedure A using 4-iodo-1H-pyrrolo[2,3-b]pyridine (73 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at 50 °C for 19 hours. After purification procedure, the title compound was isolated as a yellow solid (156 mg, 0.26 mmol, 87% yield). mp 131 °C; ^1H NMR (400 MHz, CDCl_3) δ : 11.66 (s, 1H), 8.55 (t, $J=4.7$, 1H), 7.85 (t, $J=2.9$, 1H), 7.50 (dd, $J=12.5$, 8.9, 6H), 7.18 (dd, $J=9.0$, 2.7, 6H), 6.98 (dd, $J=14.8$, 4.9, 1H), 5.63 (d, $J=3.5$, 1H), 3.92 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.15 (d, $J=2.9$), 148.35 (d, $J=11.6$), 142.84 (d, $J=11.4$), 136.20 (d, $J=12.1$), 131.61, 121.71 (d, $J=8.8$), 120.82 (d, $J=9.1$), 118.42 (d, $J=88.1$), 116.60 (d, $J=14.2$), 107.66 (d, $J=98.1$), 100.09 (d, $J=3.0$), 56.37; ^{31}P NMR (162 MHz, CDCl_3) δ : 18.33; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+$ 469.3, $\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_3\text{P}^+$ requires 469.2.

Tris(4-methoxyphenyl)(2-(4-(trifluoromethyl)phenyl)pyridin-4-yl)phosphonium iodide (9)



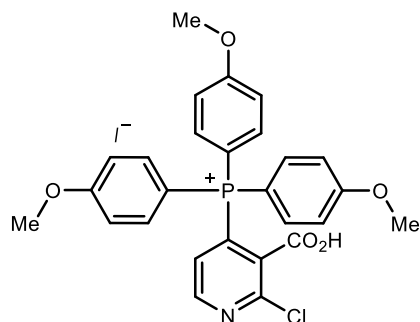
Prepared according to general procedure A using 4-iodo-2-(4-(trifluoromethyl)phenyl)pyridine (35 mg, 0.10 mmol), tris(4-methoxyphenyl)phosphane (35 mg, 0.10 mmol), and chloroform (0.2 mL) at 50 °C for 18 hours. After purification procedure, the title compound was isolated as a yellow amorphous solid (62 mg, 0.09 mmol, 89% yield). ^1H NMR (400 MHz, CDCl_3) δ : 9.08 (td, $J=5.0, 0.9$, 1H), 8.10 – 8.04 (m, 2H), 7.83 (ddd, $J=13.6, 1.6, 0.9$, 1H), 7.74 – 7.66 (m, 2H), 7.58 (dd, $J=12.4, 8.9$, 7H), 7.29 (dd, $J=9.0, 2.8$, 6H), 3.95 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.52 (d, $J=2.9$), 157.68 (d, $J=10.2$), 151.84 (d, $J=10.6$), 140.44, 136.50 (d, $J=12.1$), 132.10 (d, $J=85.2$), 131.95 (d, $J=32.7$), 127.86, 126.23 (d, $J=8.1$), 126.09 (q, $J=3.8$), 123.90 (q, $J=272.5$), 123.52 (d, $J=8.8$), 117.04 (d, $J=14.2$), 106.13 (d, $J=98.6$), 56.52; ^{19}F NMR (365 MHz, CDCl_3) δ : -62.76; ^{31}P NMR (162 MHz, CDCl_3) δ : 20.80; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+$ 574.3, $\text{C}_{33}\text{H}_{28}\text{F}_3\text{NO}_3\text{P}^+$ requires 574.2.

(2-(2,5-Difluorophenyl)-3-methylpyridin-4-yl)tris(4-methoxyphenyl)phosphonium iodide
(10)



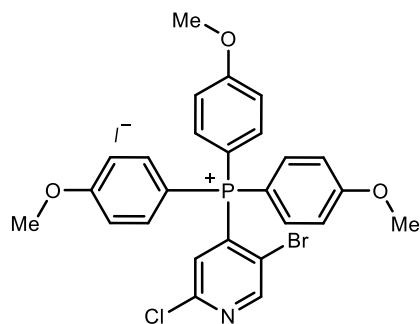
Prepared according to general procedure A using 2-(2,5-difluorophenyl)-4-iodo-3-methylpyridine (99 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at 50 °C for 21 hours. After purification procedure, the title compound was isolated as a white solid (171 mg, 0.25 mmol, 83% yield). mp 112 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.82 (t, *J*=4.5, 1H), 7.59 (dd, *J*=12.5, 8.9, 6H), 7.40 – 7.25 (m, 7H), 7.21 – 7.03 (m, 3H), 3.94 (s, 9H), 1.91 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 165.30 (d, *J*=3.0), 158.86 (dd, *J*=244.9, 2.2), 156.54 (d, *J*=2.4), 156.60 – 156.33 (m), 154.13 (d, *J*=2.6), 148.96 (d, *J*=11.6), 136.14 (d, *J*=12.1), 130.02 (d, *J*=84.0), 128.48 (d, *J*=10.5), 127.95 (ddd, *J*=18.4, 8.0, 2.4), 118.25 – 117.76 (m), 117.88 (d, *J*=24.1), 117.14 (d, *J*=14.2), 116.90 (d, *J*=8.6), 106.84 (d, *J*=97.9), 56.52, 19.93; ¹⁹F NMR (365 MHz, CDCl₃) δ: –116.86 – –117.90 (m), –120.61 – –122.10 (m); ³¹P NMR (162 MHz, CDCl₃) δ: 20.32; *m/z* LRMS (ESI + APCI) found [M-I]⁺ 556.3, C₃₃H₂₉F₂NO₃P⁺ requires 556.2.

(3-Carboxy-2-chloropyridin-4-yl)tris(4-methoxyphenyl)phosphonium iodide (11)



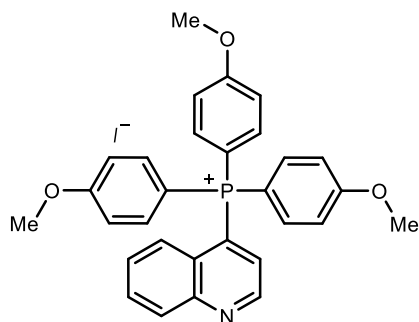
Prepared according to general procedure A using 2-chloro-4-iodonicotinic acid (85 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at 50 °C for 19 hours. After purification procedure, the title compound was isolated as a yellow solid (136 mg, 0.27 mmol, 89% yield). mp 95-98 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.61 – 8.57 (m, 1H), 7.58 (dd, $J=12.5, 9.0$, 6H), 7.25 – 7.21 (m, 1H), 7.15 (dd, $J=9.0, 2.9$, 6H), 3.91 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.05 (d, $J=3.7$), 164.88 (d, $J=3.0$), 162.59 (d, $J=2.8$), 151.07 (d, $J=12.5$), 149.73 (d, $J=11.9$), 136.88 (d, $J=12.1$), 130.92 (d, $J=86.4$), 126.90 (d, $J=9.9$), 116.08 (d, $J=14.5$), 108.06 (d, $J=100.0$), 56.21; ^{31}P NMR (162 MHz, CDCl_3) δ : 22.97; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+$ 508.2, $\text{C}_{27}\text{H}_{24}\text{ClNO}_5\text{P}^+$ requires 508.1.

(5-Bromo-2-chloropyridin-4-yl)tris(4-methoxyphenyl)phosphonium iodide (12)



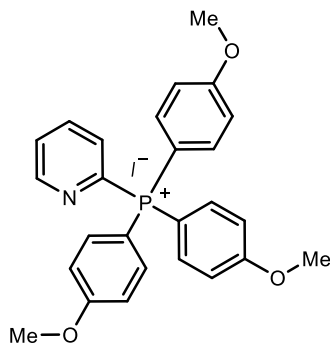
Prepared according to general procedure A using 5-bromo-2-chloro-4-iodopyridine (96 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at 80 °C for 19 hours. After purification procedure, the title compound was isolated as a golden yellow solid (201 mg, 0.3 mmol, 99% yield). mp 111-114 °C; ¹H NMR (400 MHz, CDCl₃) δ: 8.75 (d, *J*=5.7, 1H), 7.61 (dd, *J*=12.8, 8.9, 6H), 7.30 – 7.24 (m, 6H), 7.12 (d, *J*=14.1, 1H), 3.95 (s, 10H); ¹³C NMR (100 MHz, CDCl₃) δ: 165.56 (d, *J*=3.0), 154.76 (d, *J*=6.7), 152.76 (d, *J*=13.7), 136.61 (d, *J*=12.4), 134.49 (d, *J*=87.9), 131.87 (d, *J*=10.5), 123.00 (d, *J*=3.5), 117.16 (d, *J*=14.5), 105.14 (d, *J*=100.1), 56.5; ³¹P NMR (162 MHz, CDCl₃) δ: 23.14; *m/z* LRMS (ESI + APCI) found [M-I]⁺ 542.1, C₂₆H₂₃BrClINO₃P⁺ requires 542.0.

Tris(4-methoxyphenyl)(quinolin-4-yl)phosphonium iodide (13)



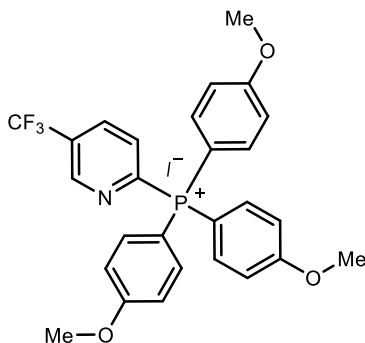
Prepared according to general procedure A using 4-iodoquinoline (78 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at room temperature for 39 hours. After purification procedure, the title compound was isolated as a yellow solid (147 mg, 0.24 mmol, 81% yield). mp 112-113 °C; ^1H NMR (400 MHz, CDCl_3) δ = 9.10 (t, J =4.1, 1H), 8.23 (d, J =8.2, 1H), 7.79 (t, J =7.7, 1H), 7.54 – 7.29 (m, 9H), 7.18 (dd, J =8.9, 2.6, 6H), 3.88 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ = 165.24 (d, J =3.0), 150.10 (d, J =12.2), 148.72 (d, J =6.9), 136.23 (d, J =12.3), 131.72 (d, J =2.3), 131.15, 130.11 (d, J =9.0), 129.31, 126.59 (d, J =74.2), 126.15 (d, J =2.7), 125.92 (d, J =6.4), 116.95 (d, J =14.3), 107.15 (d, J =98.0), 56.46; ^{31}P NMR (162 MHz, CDCl_3) δ : 19.60; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+$ 480.2, $\text{C}_{30}\text{H}_{27}\text{NO}_3\text{P}^+$ requires 480.2.

Tris(4-methoxyphenyl)(pyridin-2-yl)phosphonium iodide (14)



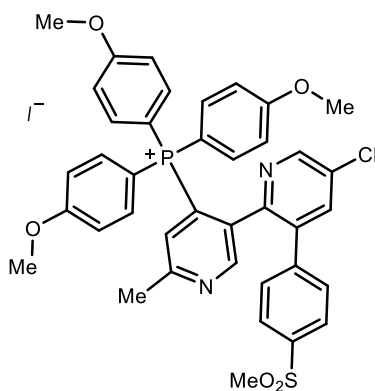
Prepared according to general procedure A using 2-iodopyridine (32 μ L, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at 50 $^{\circ}$ C for 19 hours. After purification procedure, the title compound was isolated as a yellow solid (114 mg, 0.20 mmol, 63% yield). mp 75-76 $^{\circ}$ C; ^1H NMR (400 MHz, CDCl_3) δ : 8.96 (dt, $J=4.7, 1.4$, 1H), 8.20 (tdd, $J=7.9, 5.0, 1.7$, 1H), 7.86 (ddt, $J=7.6, 6.4, 1.2$, 1H), 7.73 (dddd, $J=7.8, 4.7, 2.8, 1.1$, 1H), 7.58 (dd, $J=12.3, 8.9$, 6H), 7.21 (dd, $J=9.0, 2.7$, 6H), 3.95 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.21 (d, $J=2.9$), 152.29 (d, $J=19.4$), 147.10, 145.89, 138.90 (d, $J=10.4$), 136.70 (d, $J=11.8$), 131.73 (d, $J=24.5$), 128.13, 116.53 (d, $J=14.0$), 107.85 (d, $J=97.7$), 56.36; ^{31}P NMR (162 MHz, CDCl_3) δ : 13.80; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+$ 430.2, $\text{C}_{26}\text{H}_{25}\text{NO}_3\text{P}^+$ requires 430.2.

Tris(4-methoxyphenyl)(5-(trifluoromethyl)pyridin-2-yl)phosphonium iodide (15)



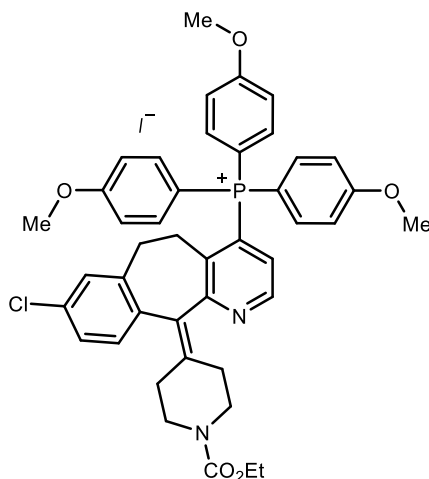
Prepared according to general procedure A using 2-iodo-5-(trifluoromethyl)pyridine (82 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at 80 °C for 19 hours. After purification procedure, the title compound was isolated as a golden solid (174 mg, 0.28 mmol, 93% yield). mp 87 °C; ^1H NMR (400 MHz, CDCl_3) δ : 9.11 (s, 1H), 8.65 – 8.41 (m, 1H), 8.31 (dd, $J=8.1, 5.9$, 2H), 7.58 (dd, $J=12.4, 8.9$, 6H), 7.21 (dd, $J=9.0, 2.8$, 6H), 3.92 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.37 (d, $J=3.0$), 150.84 (d, $J=118.7$), 148.36 (dd, $J=19.7, 3.8$), 136.74 (d, $J=12.0$), 136.33 (dd, $J=10.4, 3.6$), 131.98 (d, $J=24.6$), 129.81 (d, $J=31.0$), 122.44 (qd, $J=275.3, 1.7$), 116.67 (d, $J=14.2$), 106.65 (d, $J=98.3$), 56.34; ^{19}F NMR (365 MHz, CDCl_3) δ : –62.82; ^{31}P NMR (162 MHz, CDCl_3) δ : 15.08; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+$ 498.2, $\text{C}_{27}\text{H}_{24}\text{F}_3\text{NO}_3\text{P}^+$ requires 498.1.

(5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-[2,3'-bipyridin]-4'-yl)tris(4-methoxyphenyl)phosphonium iodide (16)



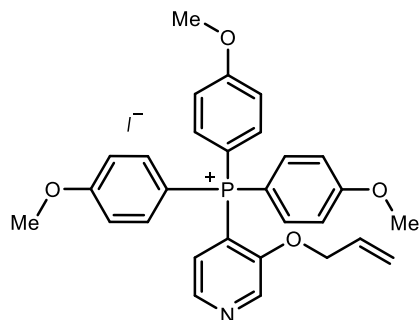
Prepared according to general procedure A using 5-chloro-4'-iodo-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (48 mg, 0.10 mmol), tris(4-methoxyphenyl)phosphane (35 mg, 0.10 mmol), and chloroform (0.2 mL) at room temperature for 34 hours. After purification procedure, the title compound was isolated as a yellow solid (76 mg, 0.09 mmol, 92% yield). mp 180 °C (decomposition); ¹H NMR (400 MHz, CDCl₃) δ: 8.23 (d, *J*=6.9, 1H), 8.10 (d, *J*=8.4, 2H), 7.82 (d, *J*=2.3, 1H), 7.63 (dd, *J*=12.3, 9.0, 6H), 7.51 (d, *J*=2.3, 1H), 7.44 (d, *J*=8.5, 2H), 7.22 (d, *J*=16.1, 1H), 7.14 (dd, *J*=9.0, 2.8, 6H), 3.89 (s, 9H), 3.12 (s, 3H), 2.55 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 164.54 (d, *J*=3.0), 160.57 (d, *J*=10.9), 152.82 (d, *J*=7.3), 148.29 (d, *J*=2.7), 146.71, 141.56, 140.92, 138.61, 135.82, 133.76 (d, *J*=4.0), 132.12, 130.65, 130.30, 130.01 (d, *J*=43.3), 128.90, 116.01 (d, *J*=14.3), 109.34 (d, *J*=100.2), 56.36, 44.39, 25.00; ³¹P NMR (162 MHz, CDCl₃) δ: 23.46; *m/z* LRMS (ESI + APCI) found [M-I]⁺ 709.3, C₃₉H₃₅ClN₂O₅PS⁺ requires 709.2.

(8-chloro-11-(1-(ethoxycarbonyl)piperidin-4-ylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-4-yl)tris(4-methoxyphenyl)phosphonium iodide (17)



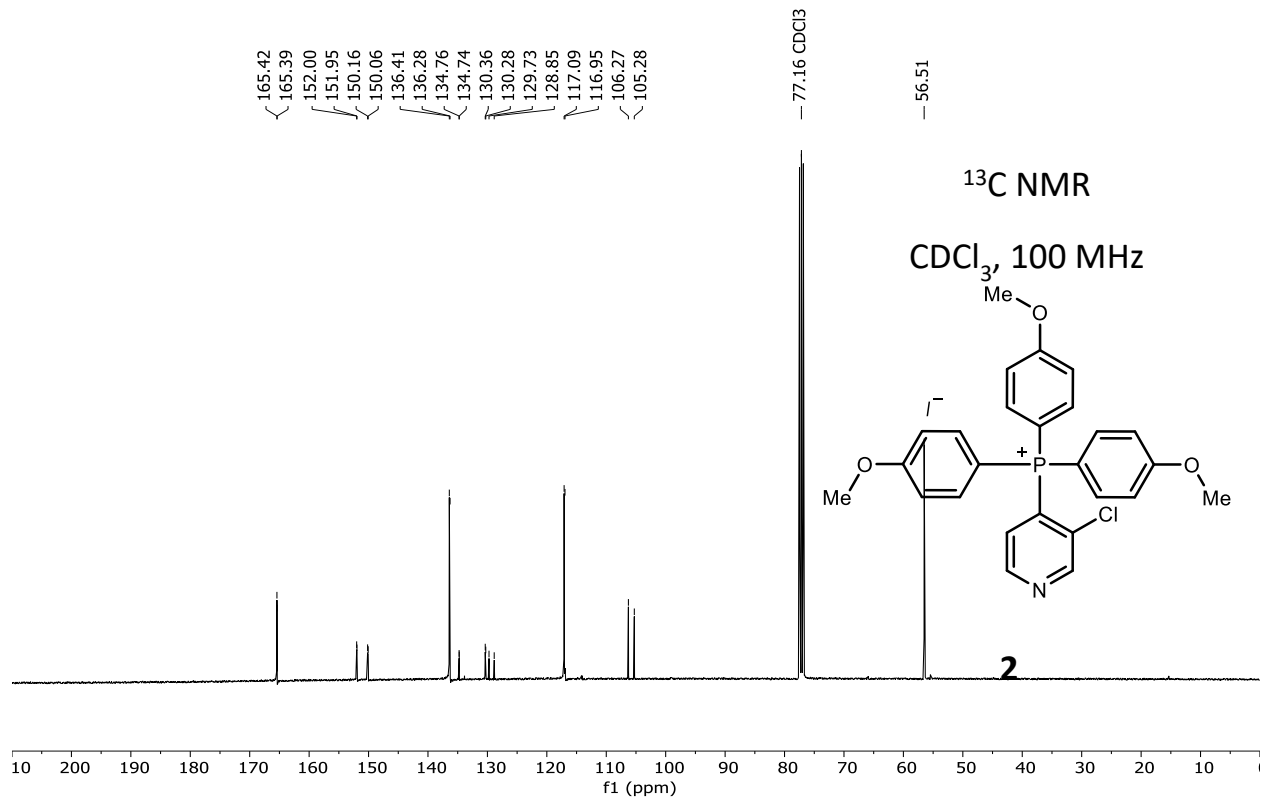
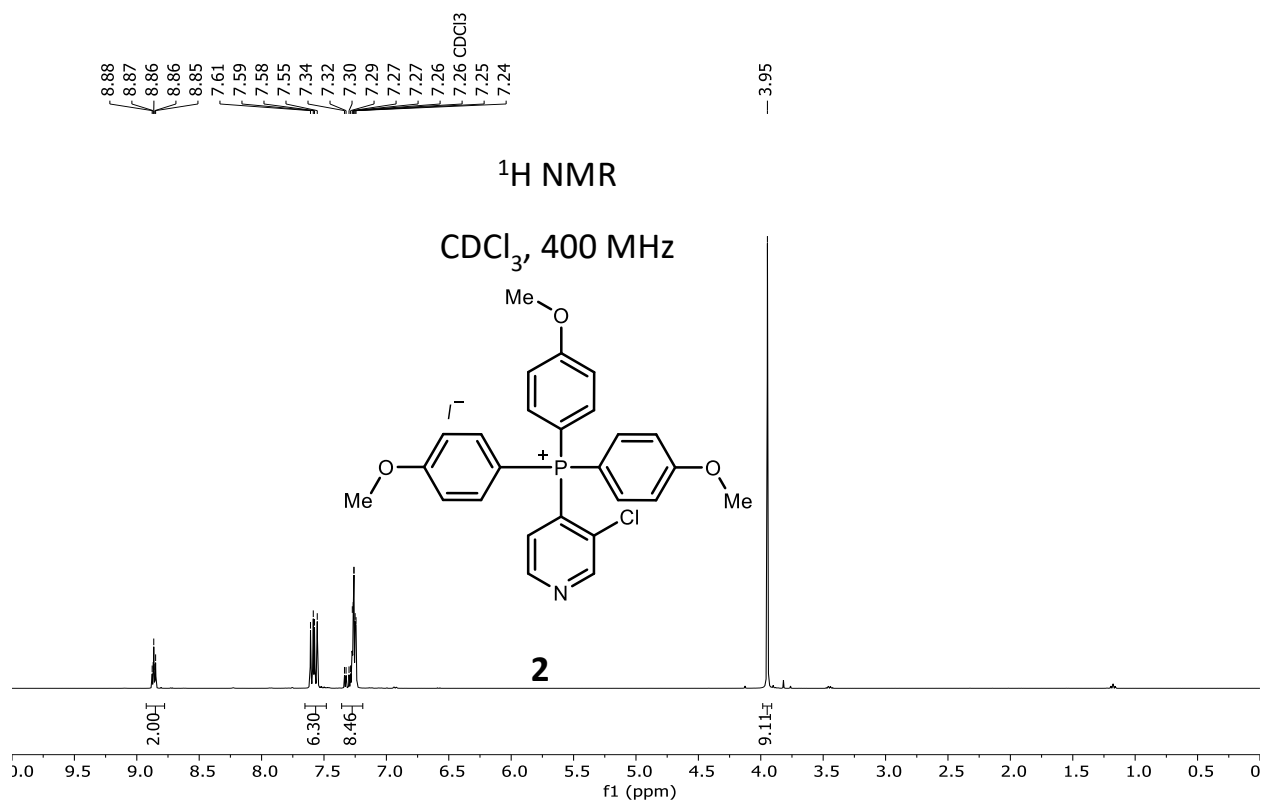
Prepared according to general procedure A using ethyl 4-(8-chloro-4-iodo-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (51 mg, 0.10 mmol), tris(4-methoxyphenyl)phosphane (35 mg, 0.10 mmol), and chloroform (0.2 mL) at 50 °C for 19 hours. After purification procedure, the title compound was isolated as a yellow solid (83 mg, 0.1 mmol, 96% yield). mp 153 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.69 (dd, $J=5.1, 4.2$, 1H), 7.56 (dd, $J=12.5, 8.9$, 6H), 7.28 (dd, $J=9.0, 2.8$, 6H), 7.22 – 7.06 (m, 2H), 7.00 (dd, $J=14.8, 5.1$, 1H), 6.78 (d, $J=2.0$, 1H), 4.13 (q, $J=7.1$, 2H), 3.97 (s, 9H), 3.73 (ddd, $J=22.4, 12.2, 5.8$, 2H), 3.37 (ddd, $J=12.7, 8.2, 4.1$, 2H), 3.28 (ddd, $J=14.8, 11.6, 5.7$, 1H), 2.83 (dt, $J=17.4, 5.2$, 1H), 2.63 (dt, $J=15.0, 4.8$, 1H), 2.53 – 2.32 (m, 2H), 2.21 (s, 1H), 1.72 (ddd, $J=17.2, 11.8, 5.3$, 2H), 1.25 (t, $J=7.1$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.34 (d, $J=3.0$), 163.60 (d, $J=8.2$), 155.55, 148.92 (d, $J=11.4$), 139.15, 137.23, 136.80 (d, $J=6.5$), 136.28 (d, $J=12.0$), 133.66, 132.73, 131.66, 130.01, 129.15 (d, $J=83.0$), 127.18 (d, $J=10.3$), 126.58, 117.12 (d, $J=14.2$), 107.04 (d, $J=97.8$), 61.57, 56.54, 44.82, 44.61, 31.01, 30.54, 29.88, 14.7; ^{31}P NMR (162 MHz, CDCl_3) δ : 19.39; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+ 733.3$, $\text{C}_{43}\text{H}_{43}\text{ClN}_2\text{O}_5\text{P}^+$ requires 733.3.

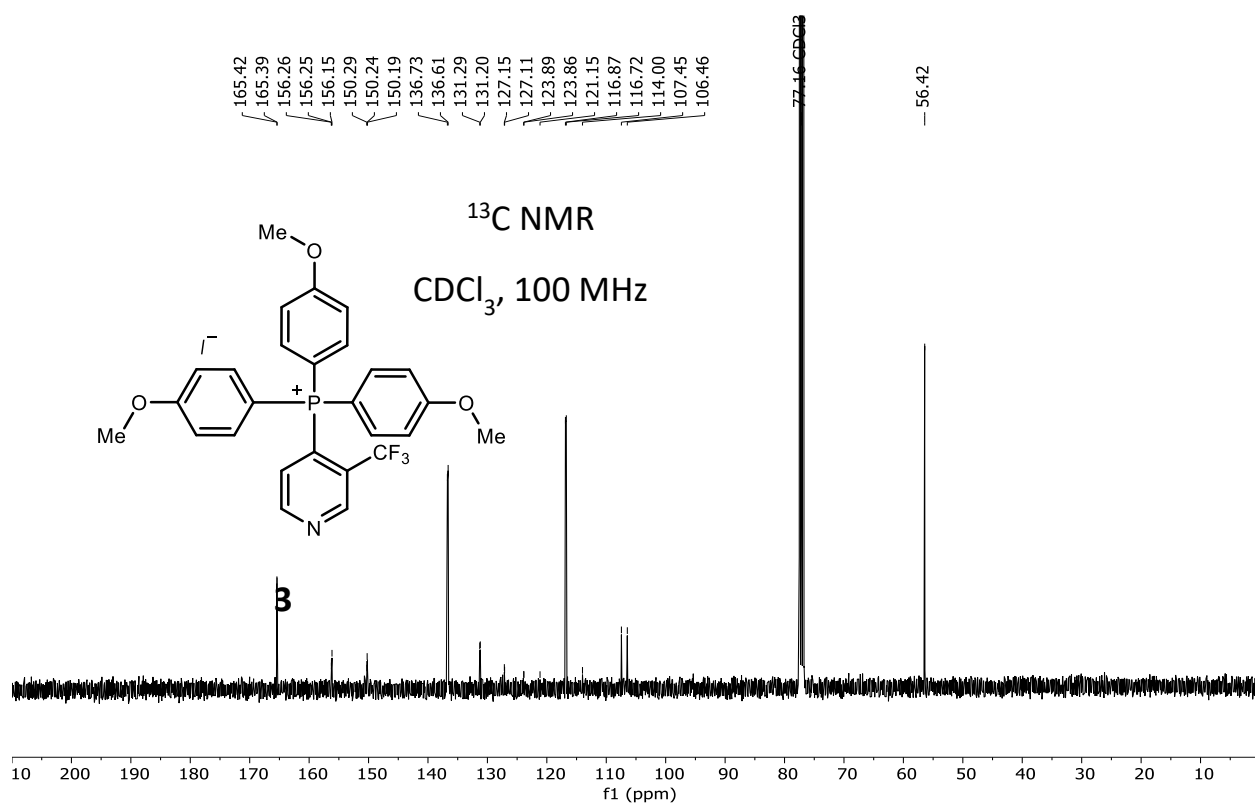
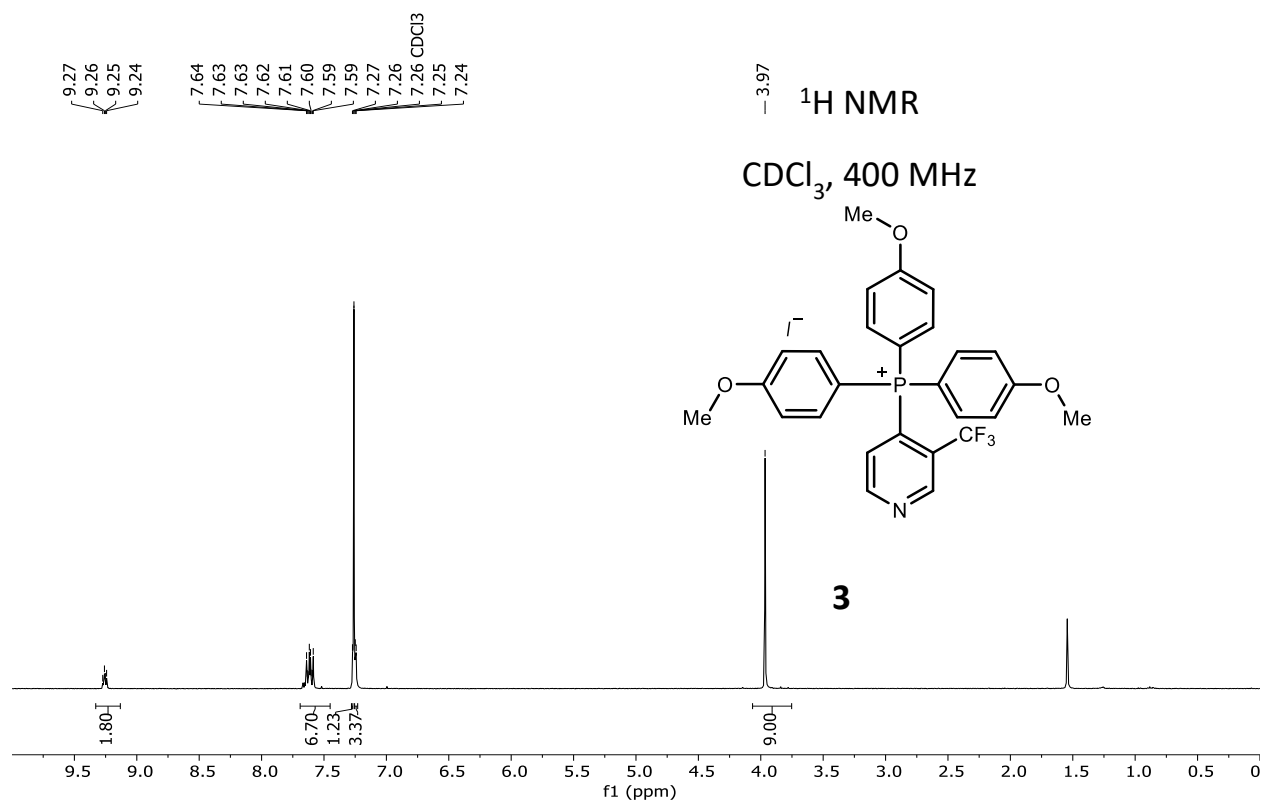
Tris(4-methoxyphenyl)(2-oxo-1,2-dihydropyridin-4-yl)phosphonium iodide

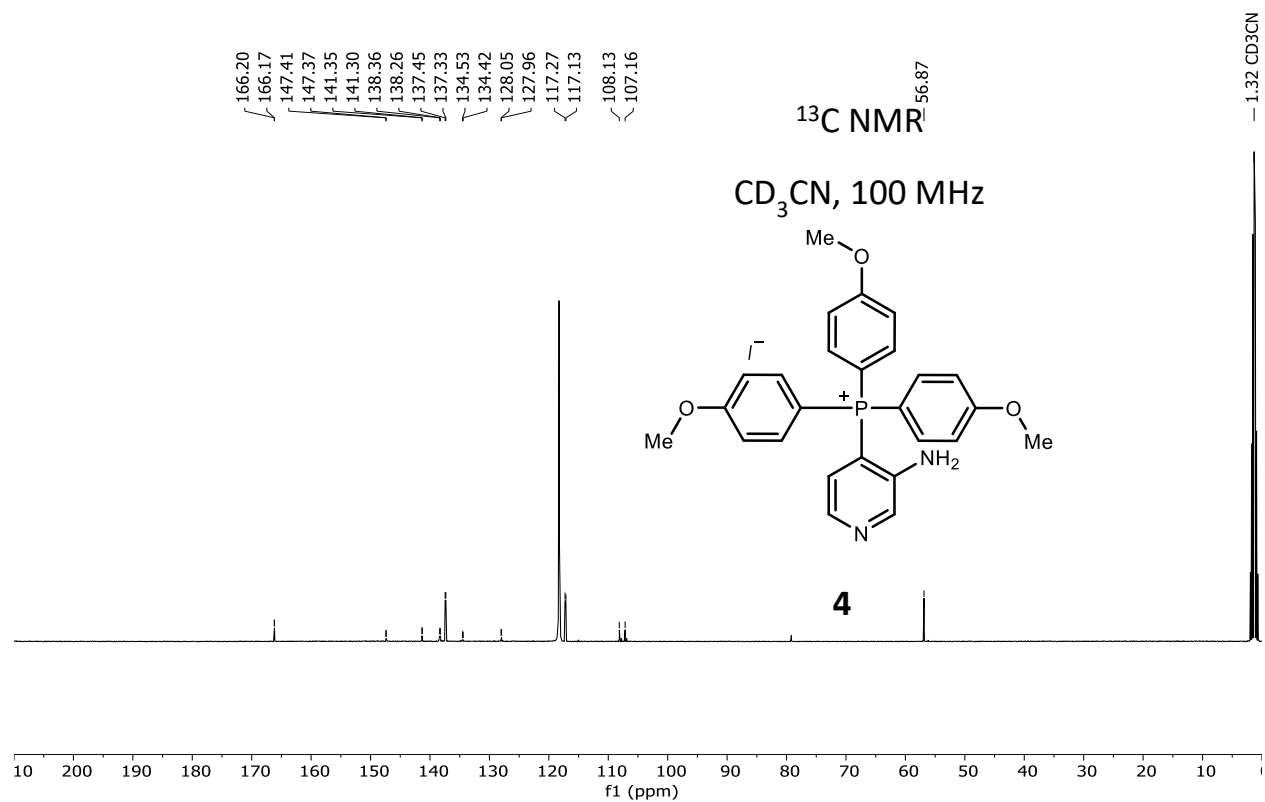
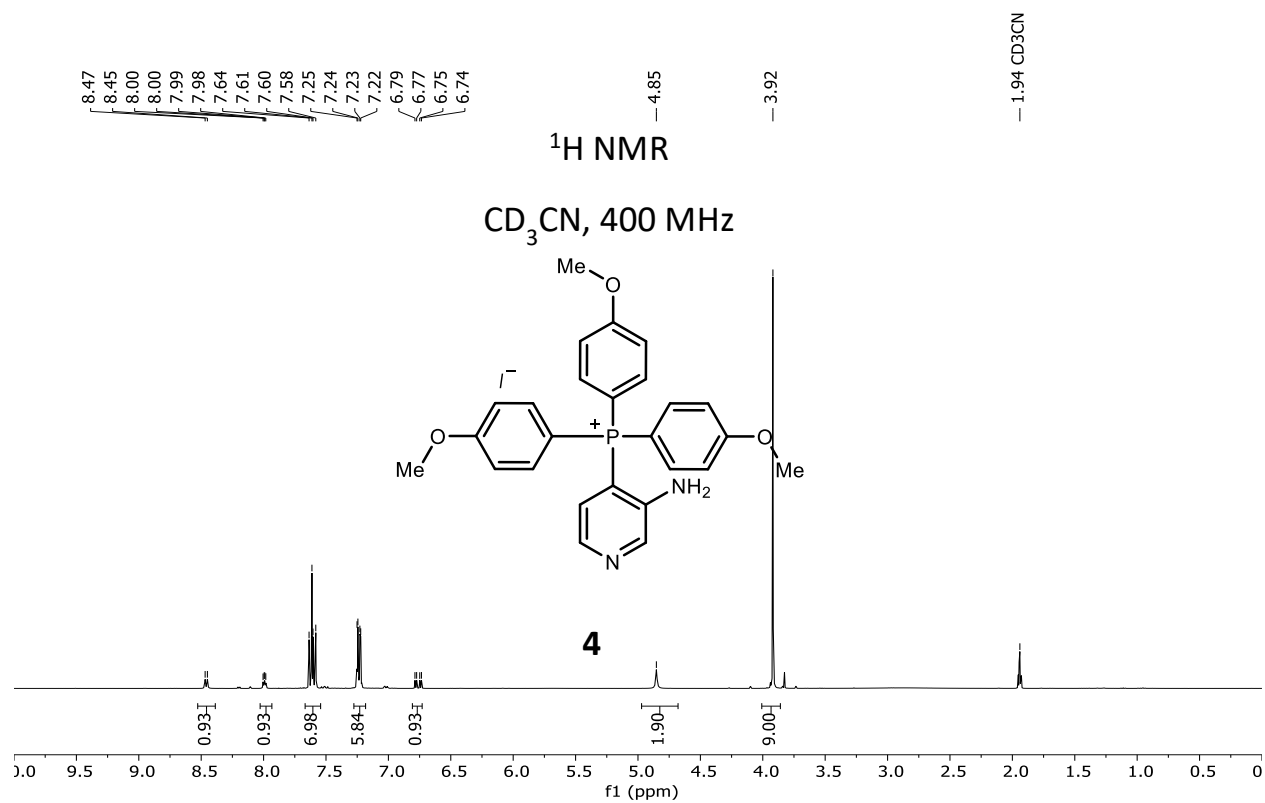


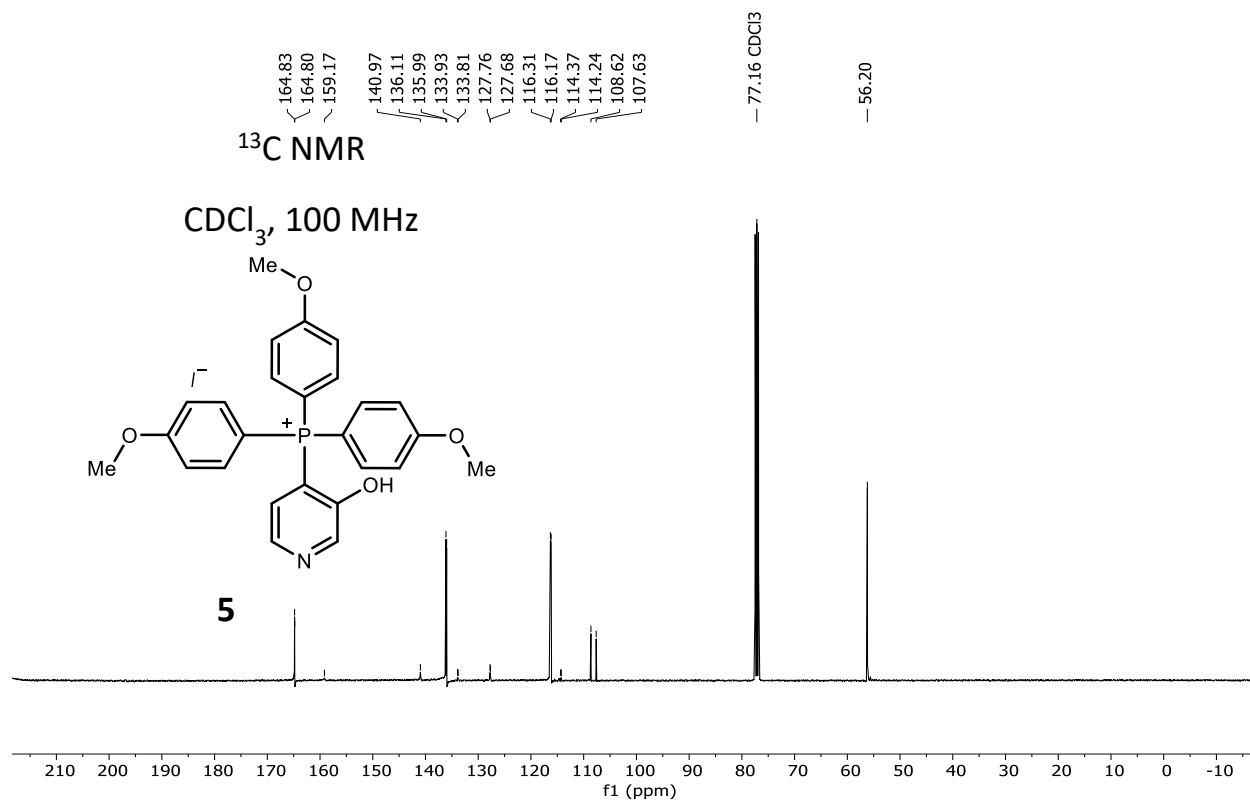
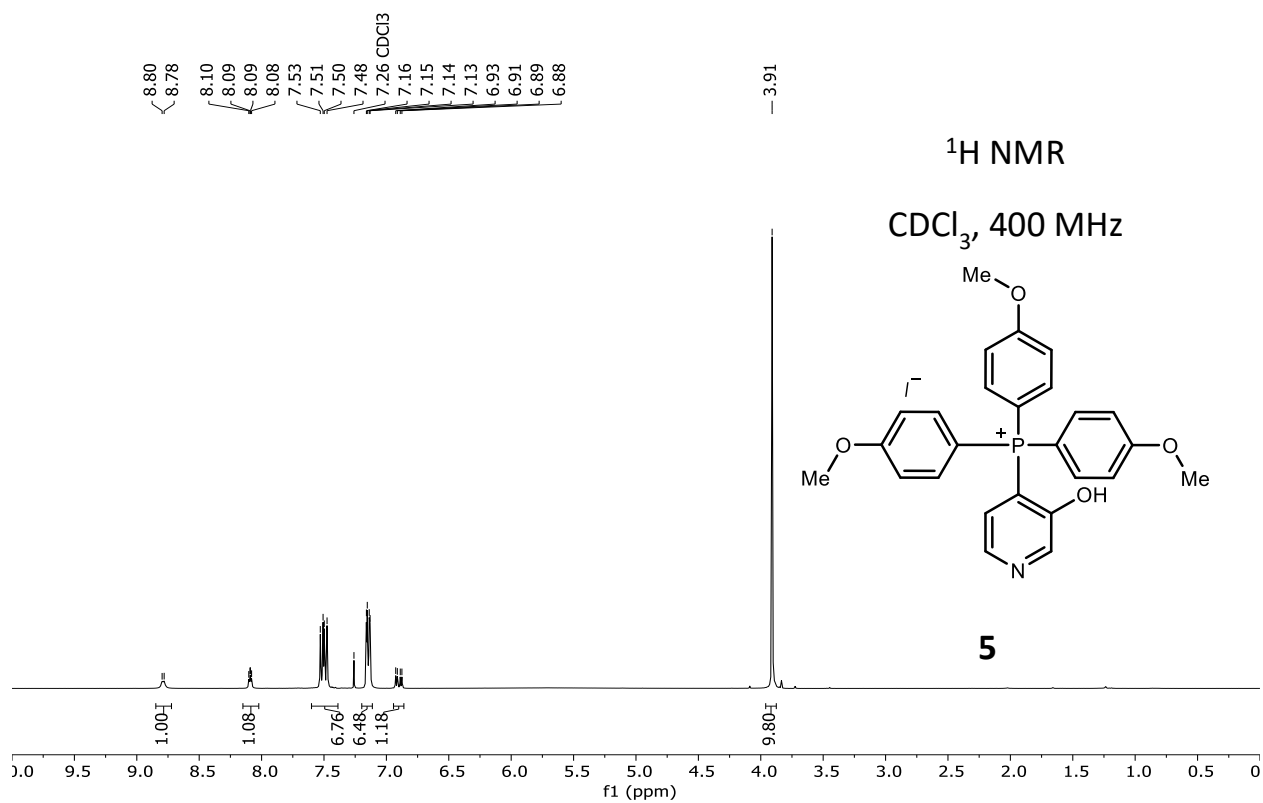
Prepared according to general procedure A using 3-(allyloxy)-4-iodopyridine (78 mg, 0.30 mmol), tris(4-methoxyphenyl)phosphane (106 mg, 0.30 mmol), and chloroform (0.6 mL) at room temperature for 36 hours. After purification procedure, the title compound was isolated as a yellow solid (160 mg, 0.30 mmol, 99% yield). mp 71 °C; ^1H NMR (400 MHz, CDCl_3) δ : 8.66 (d, $J=6.5$, 1H), 8.53 (dd, $J=4.9$, 3.6, 1H), 7.54 (dd, $J=12.8$, 8.9, 6H), 7.26 – 7.16 (m, 6H), 7.08 (dd, $J=14.8$, 4.9, 1H), 5.40 (ddd, $J=16.2$, 10.7, 5.4, 1H), 5.09 (dd, $J=10.5$, 1.2, 1H), 5.00 (dd, $J=17.2$, 1.4, 1H), 4.59 (d, $J=5.5$, 2H), 3.96 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ : 165.02 (d, $J=3.0$), 154.93, 143.88 (d, $J=11.0$), 137.18 (d, $J=4.5$), 135.95 (d, $J=12.5$), 130.09, 128.12 (d, $J=7.2$), 119.85, 117.55 (d, $J=87.3$), 116.54 (d, $J=14.5$), 107.11 (d, $J=100.3$), 70.98, 56.4; ^{31}P NMR (162 MHz, CDCl_3) δ : 19.64; m/z LRMS (ESI + APCI) found $[\text{M-I}]^+$ 486.3, $\text{C}_{29}\text{H}_{29}\text{NO}_4\text{P}^+$ requires 486.2.

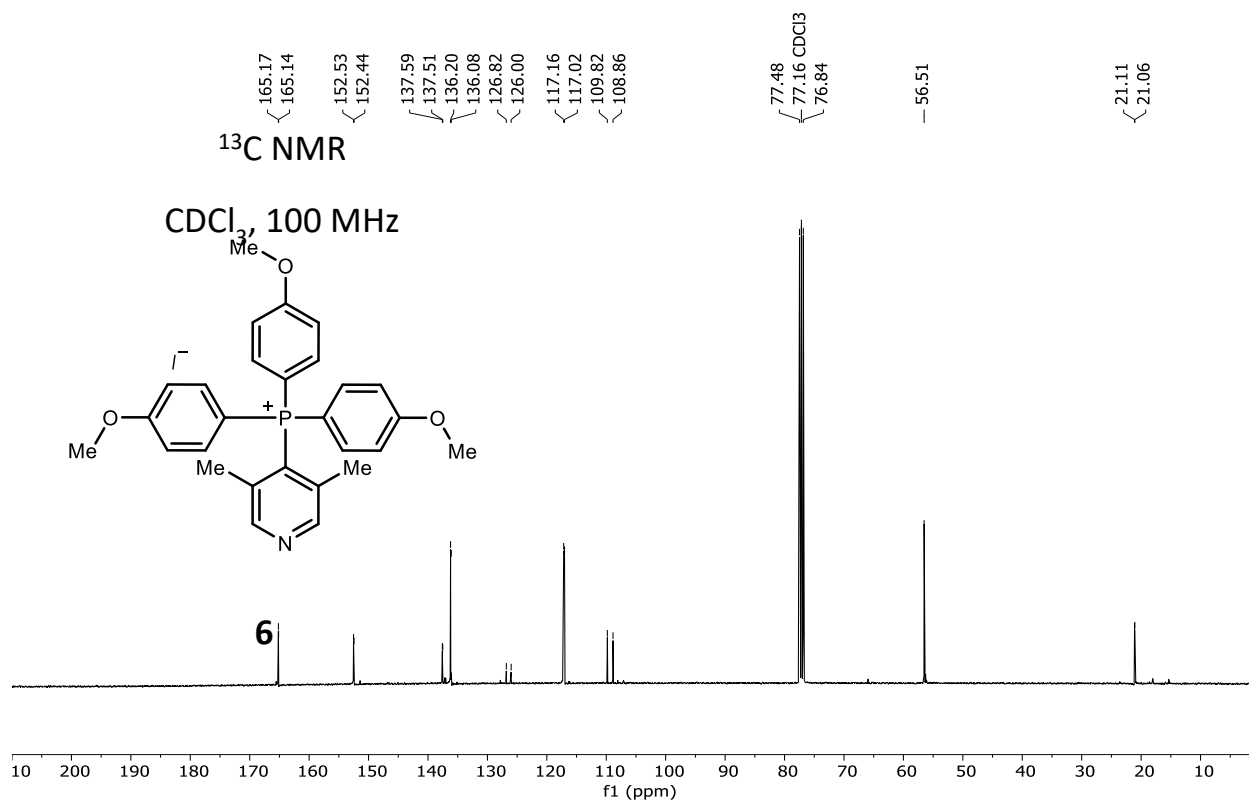
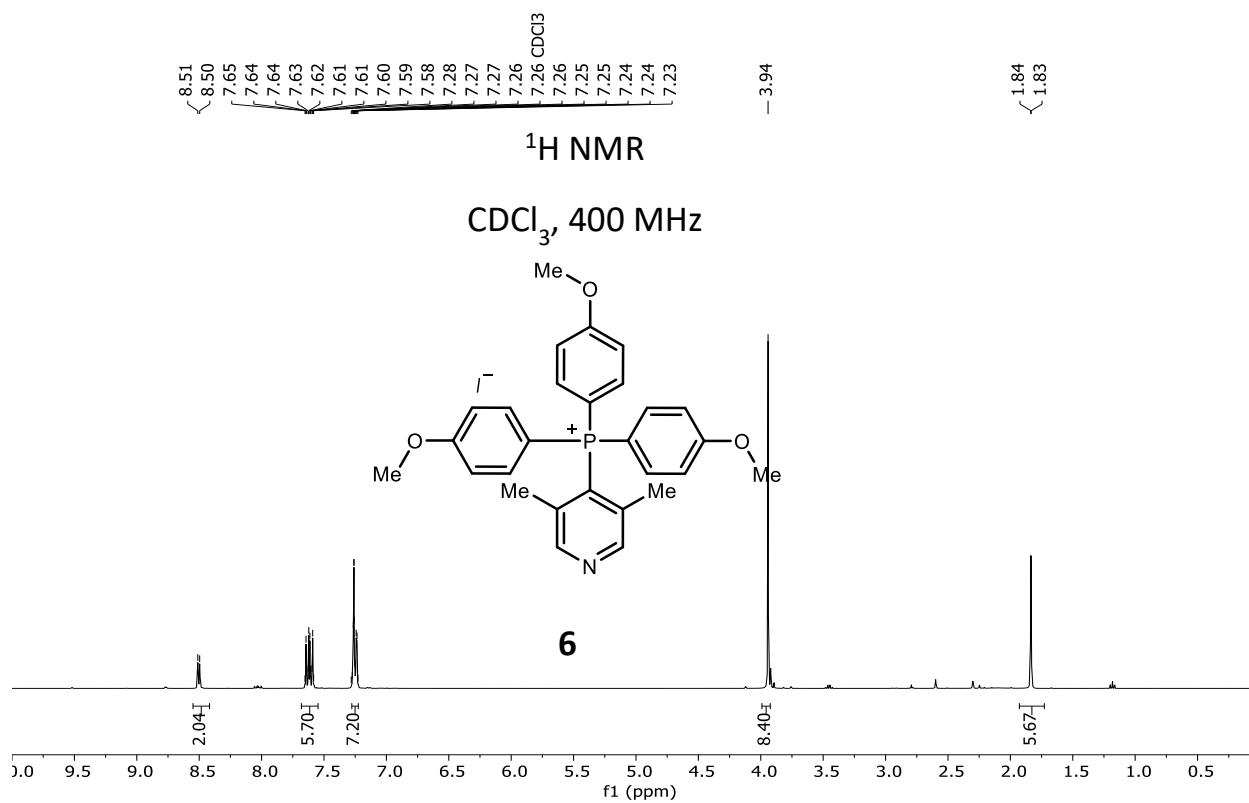
A 3.4 Spectra

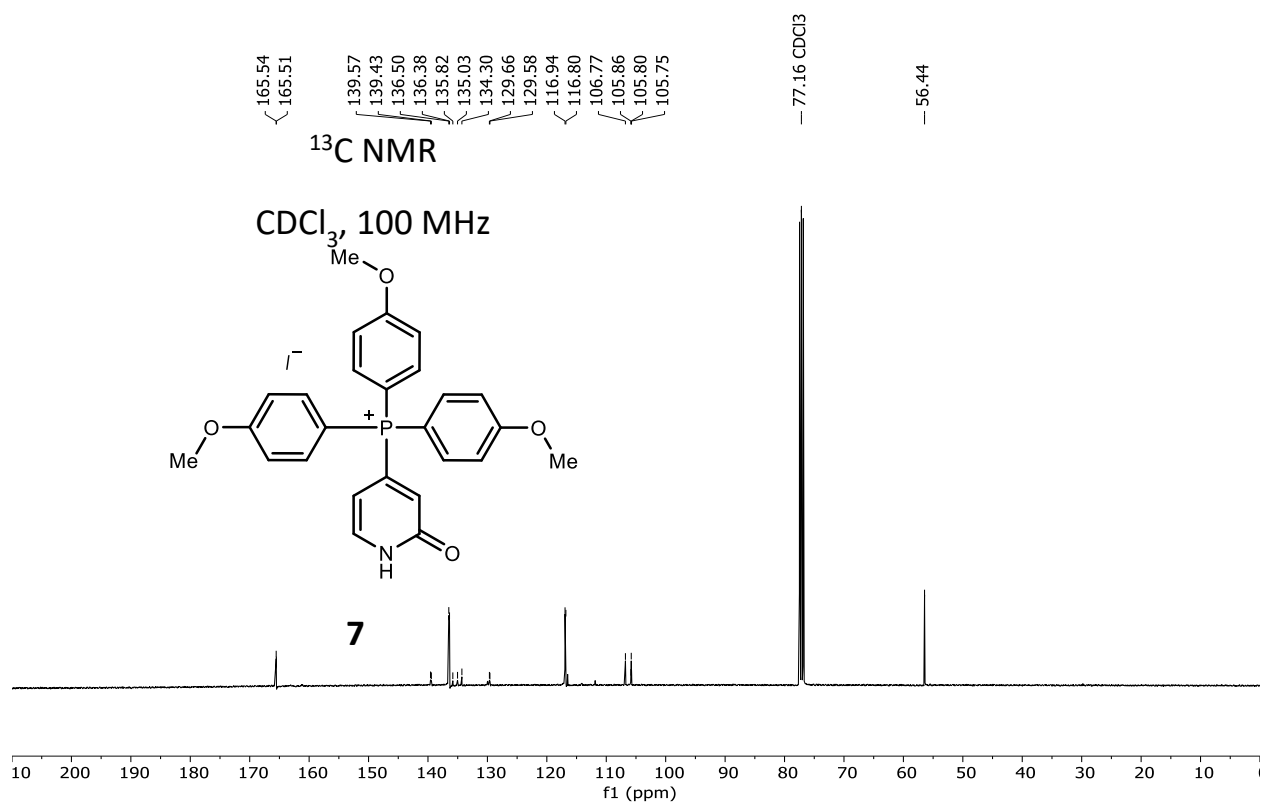
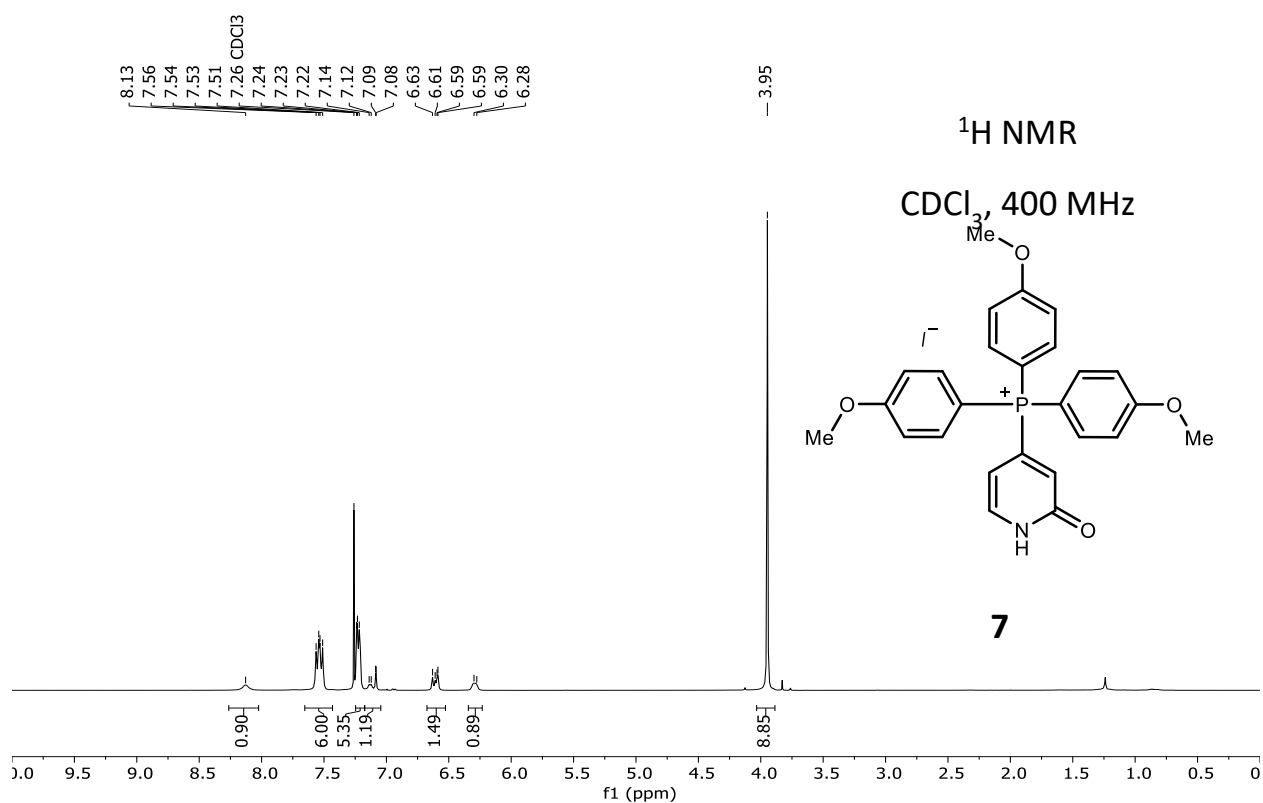


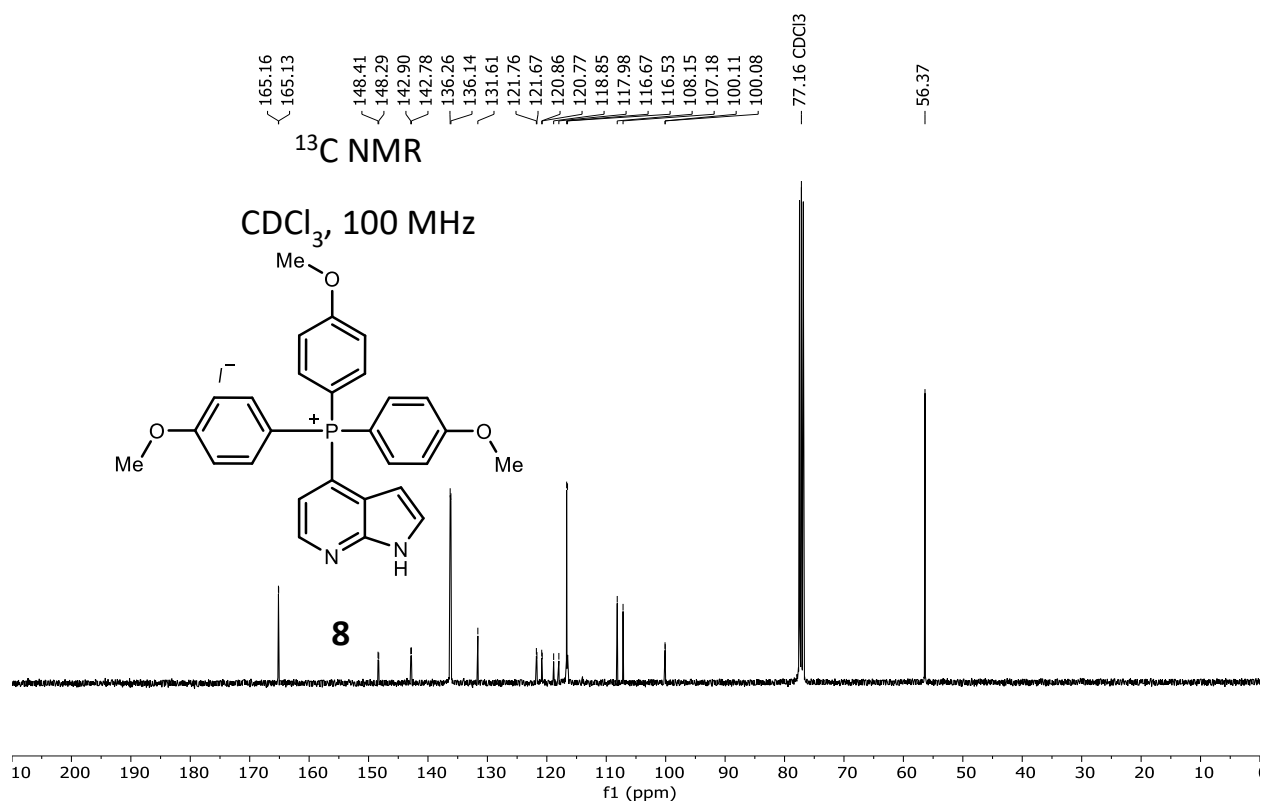
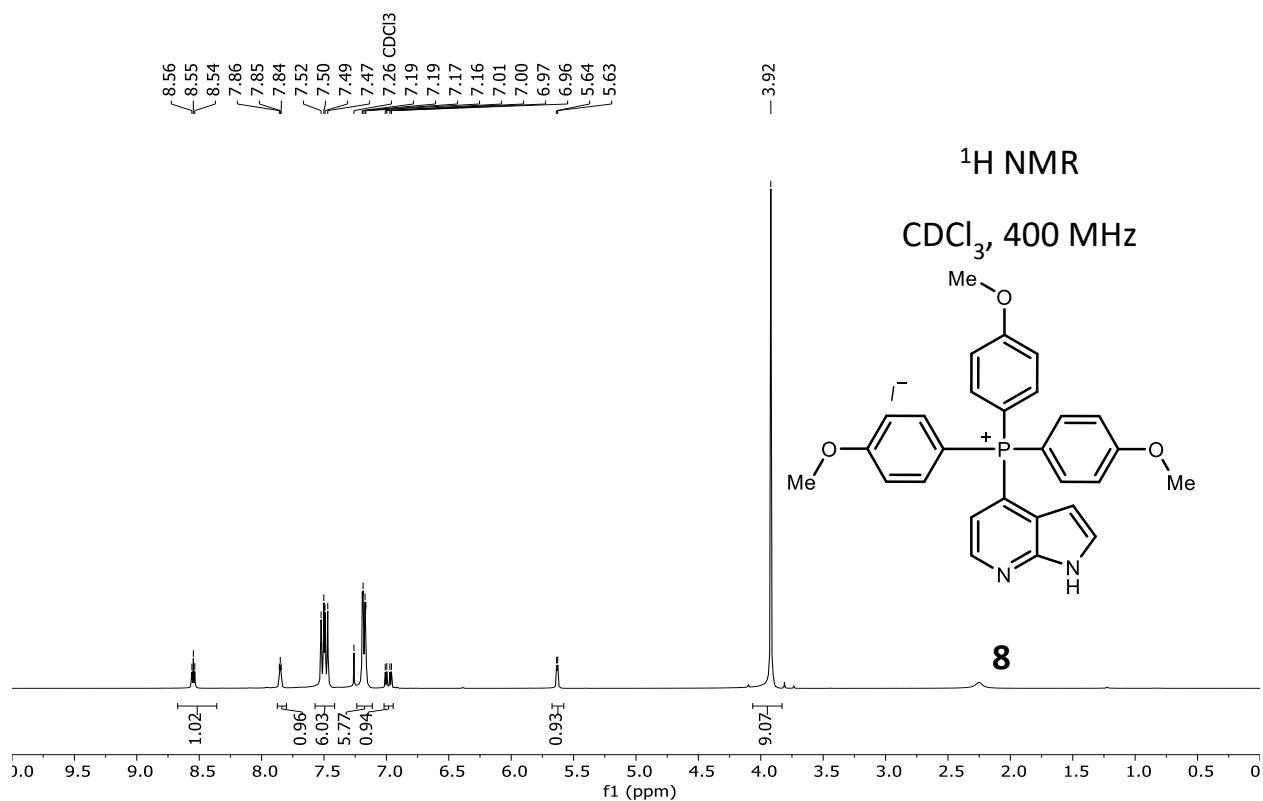


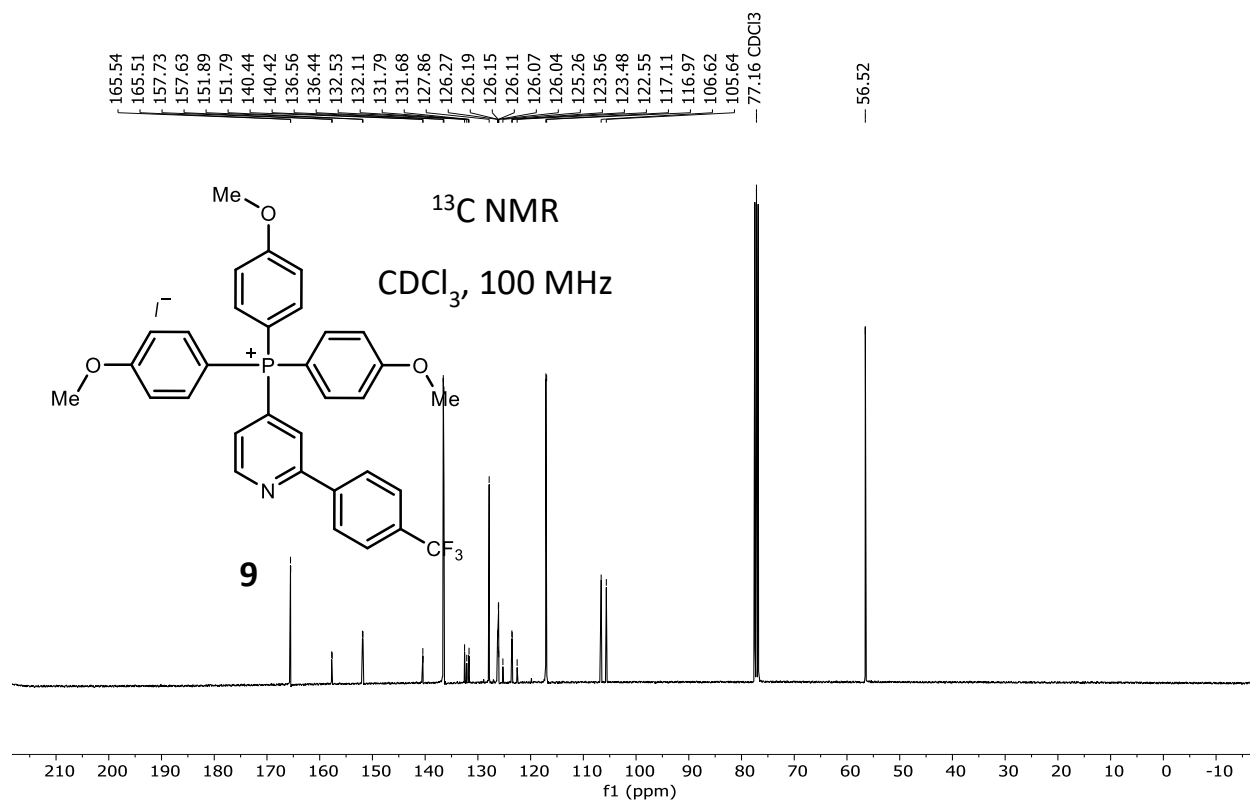
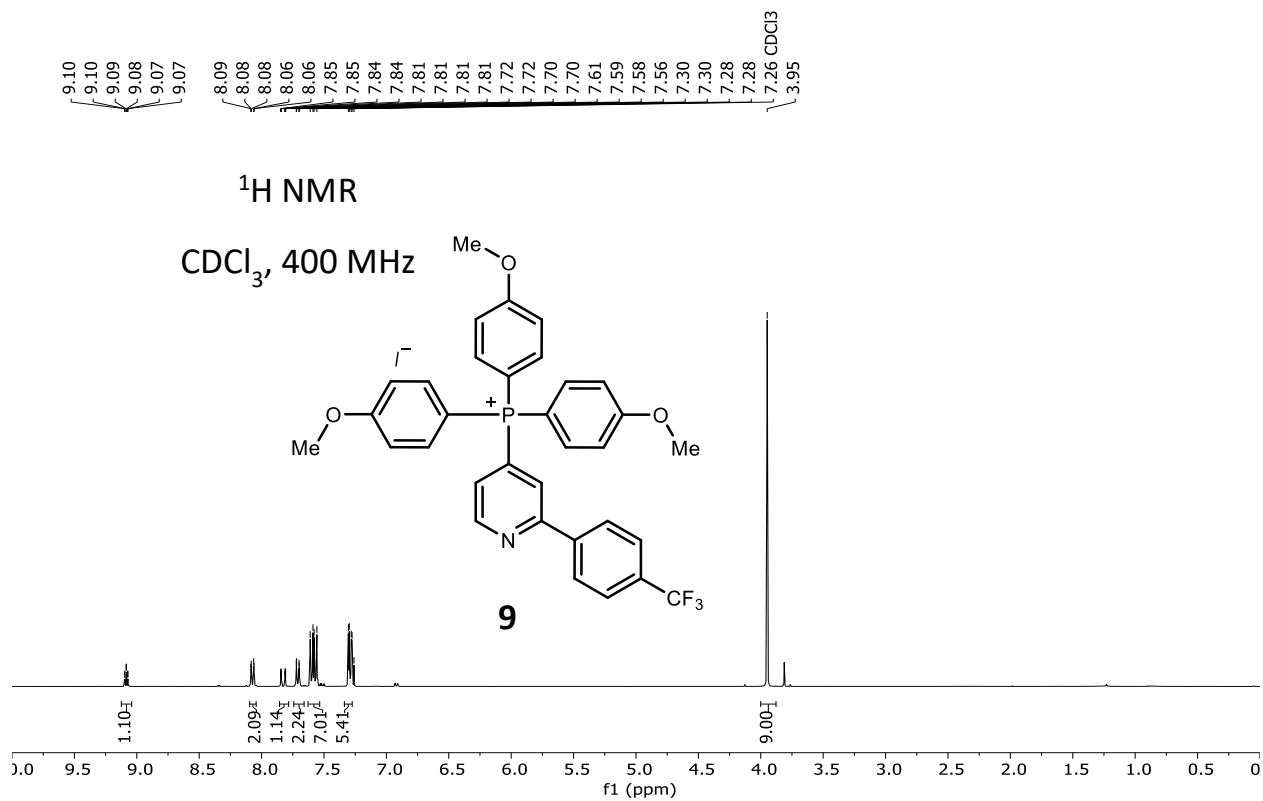


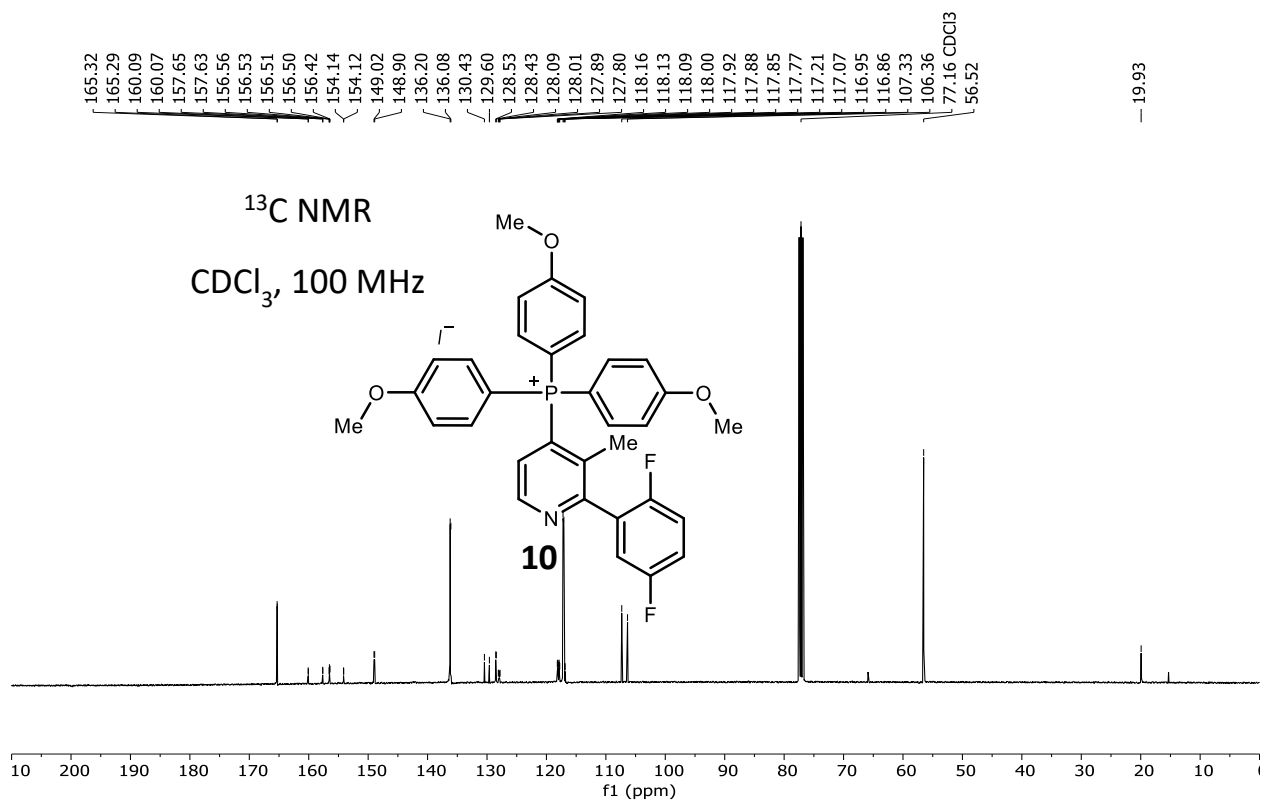
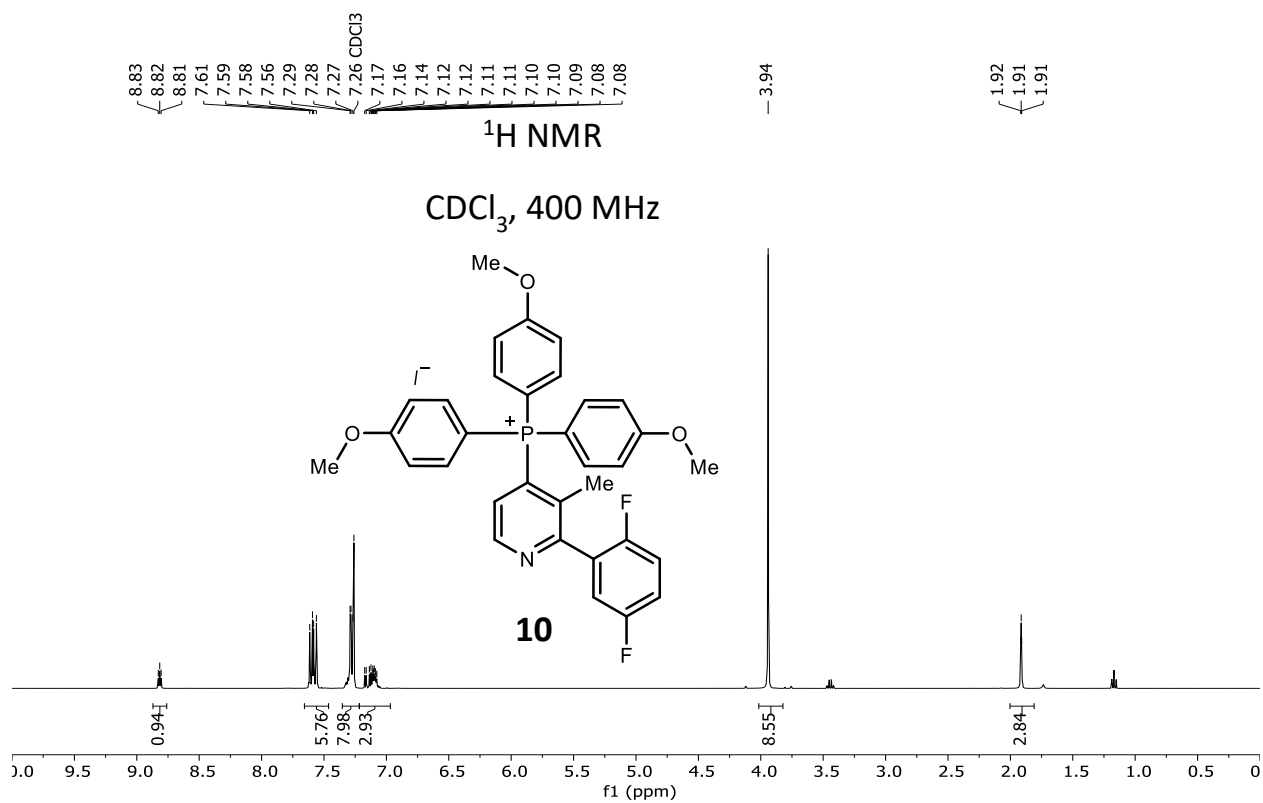


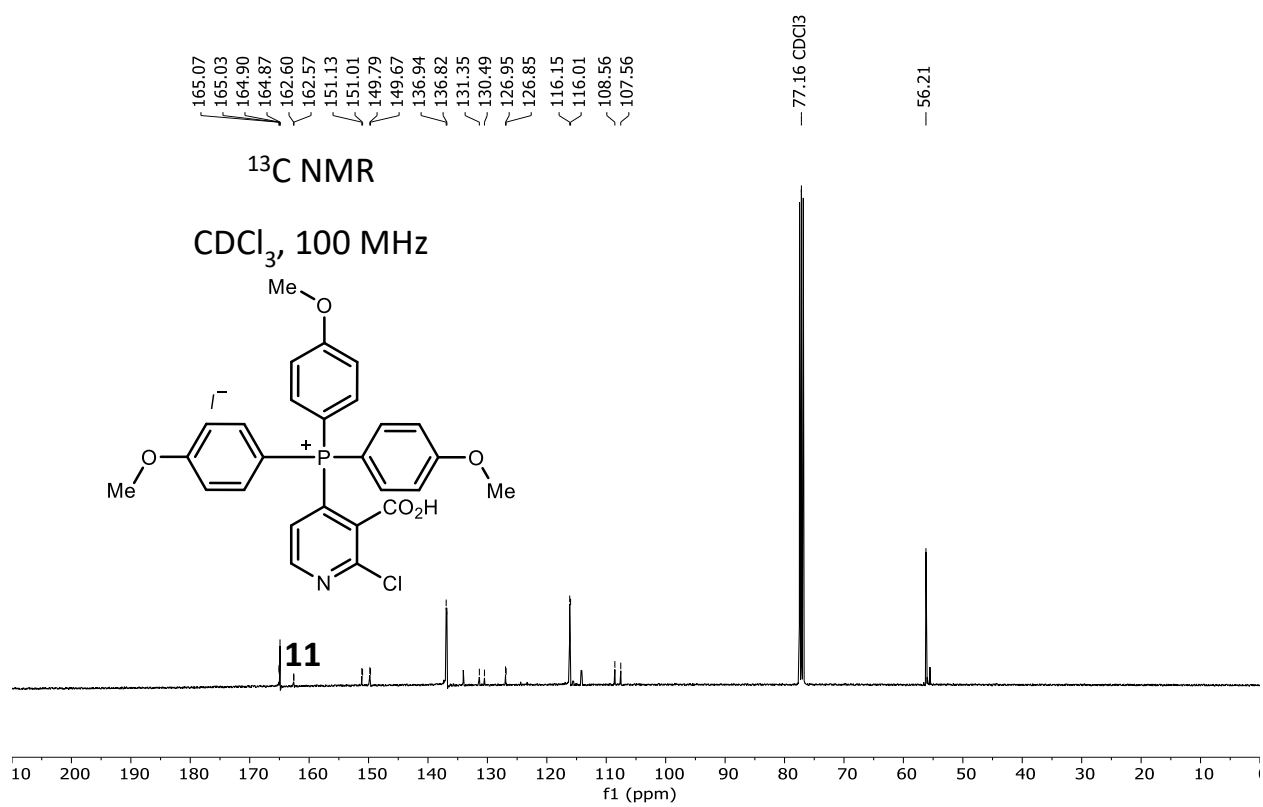
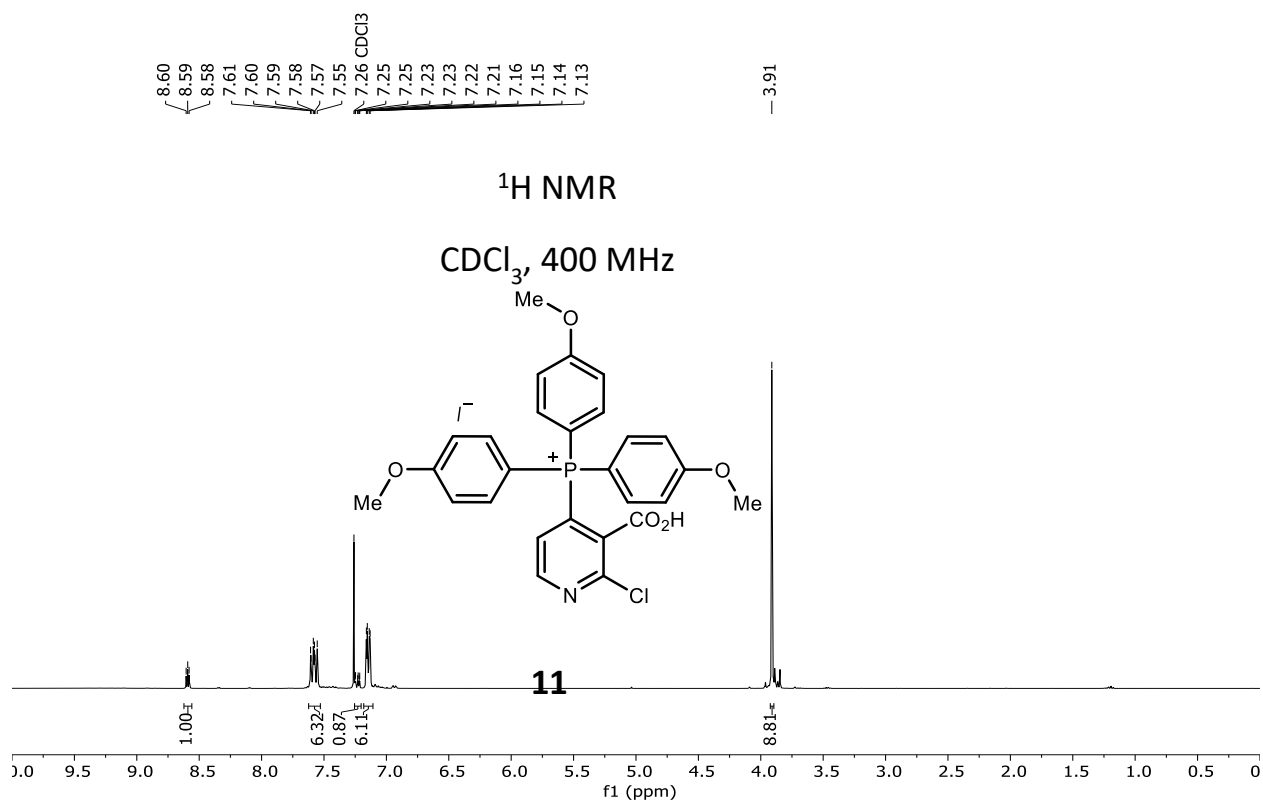


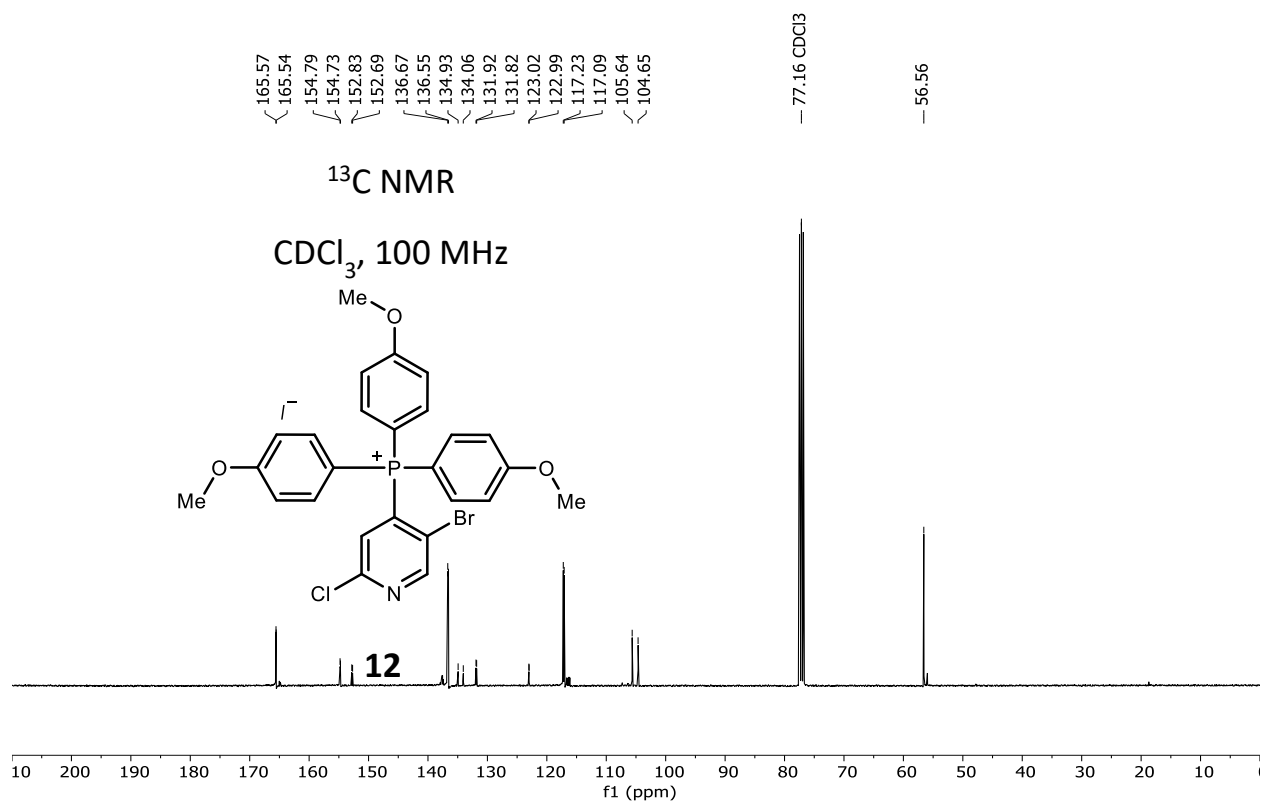
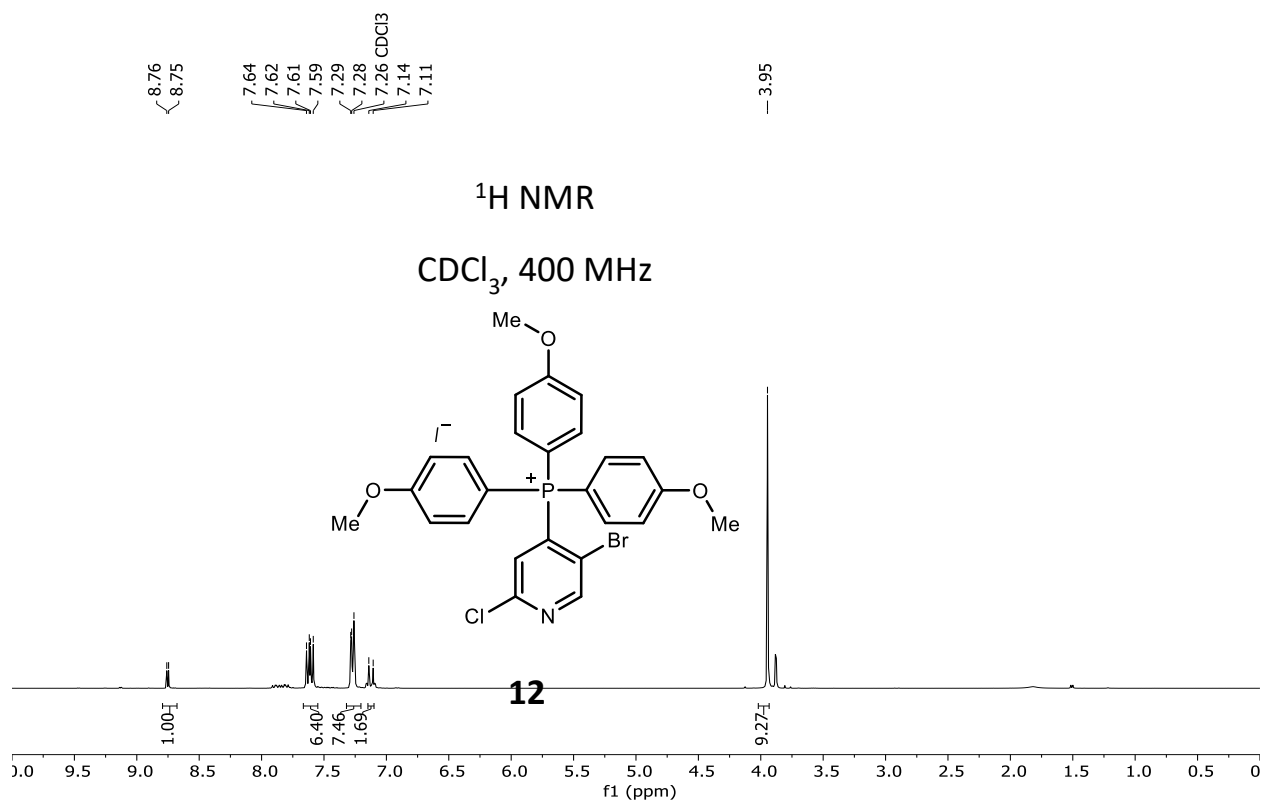


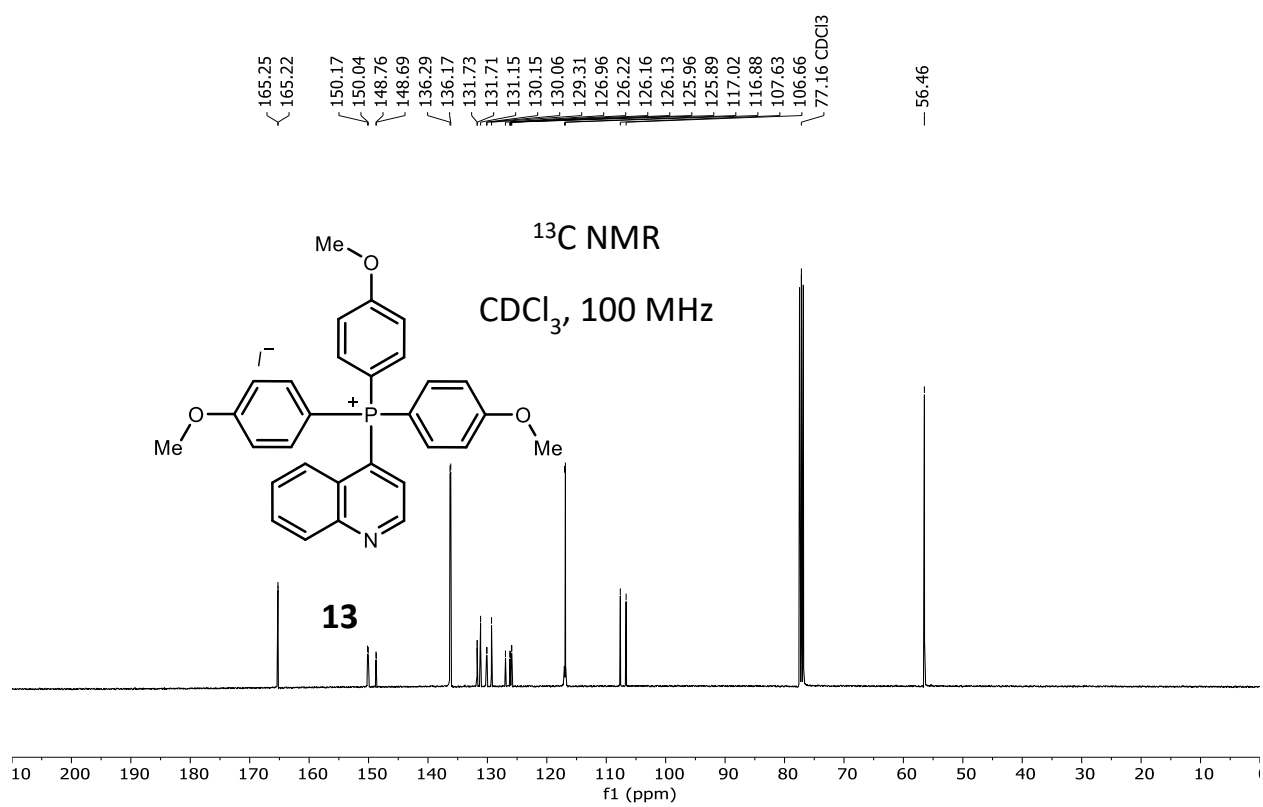
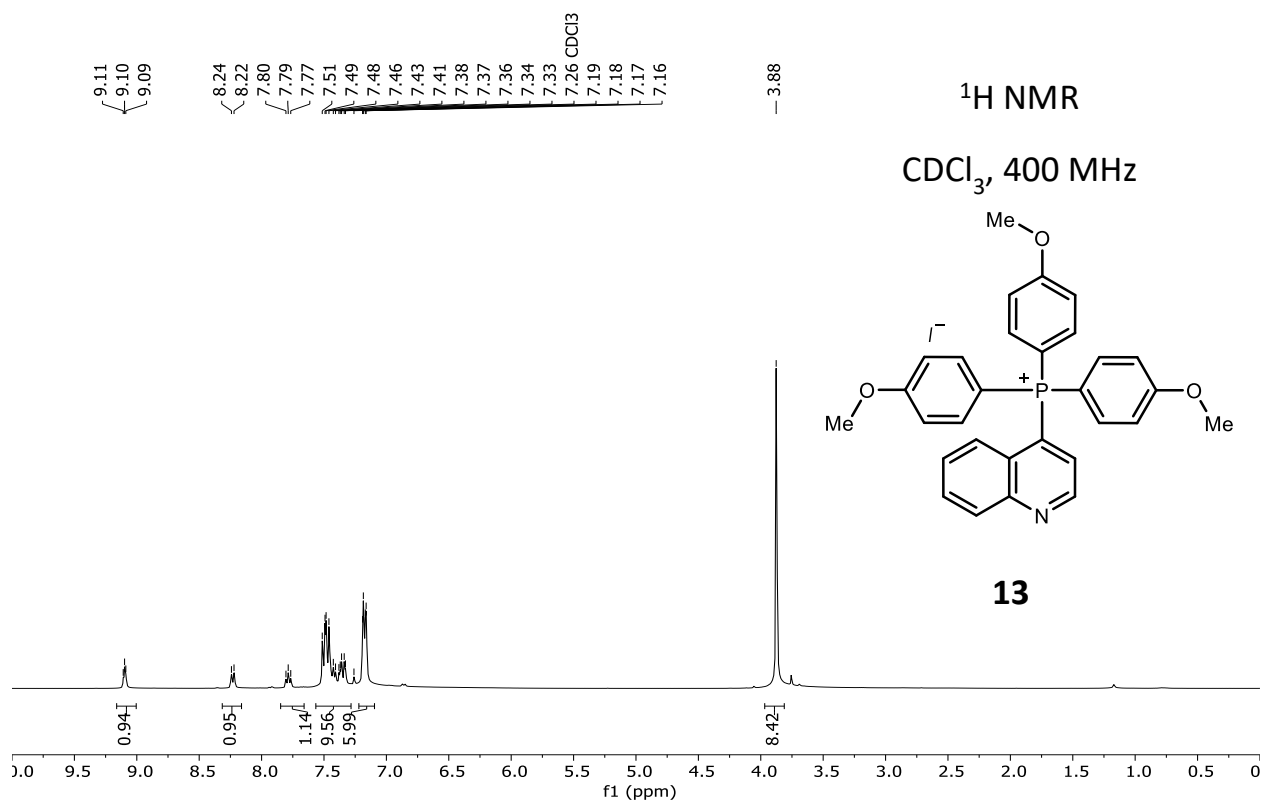


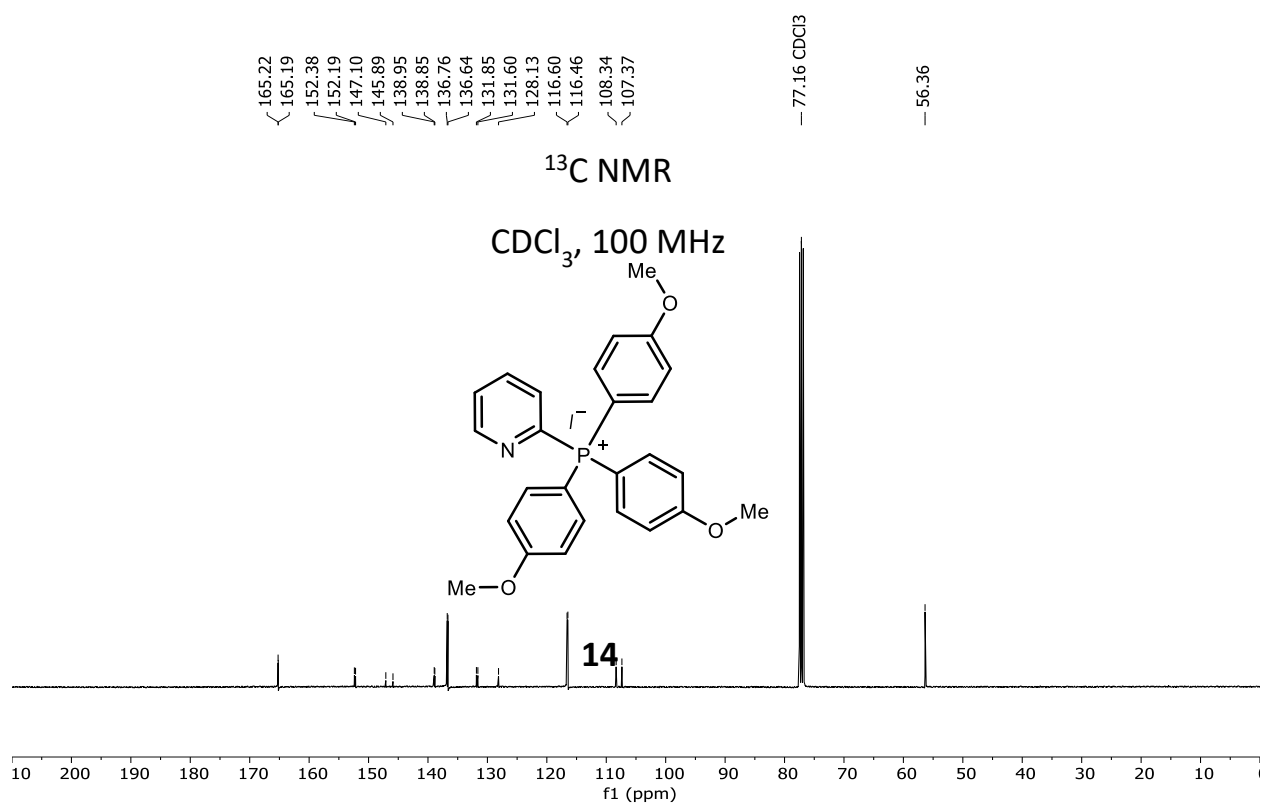
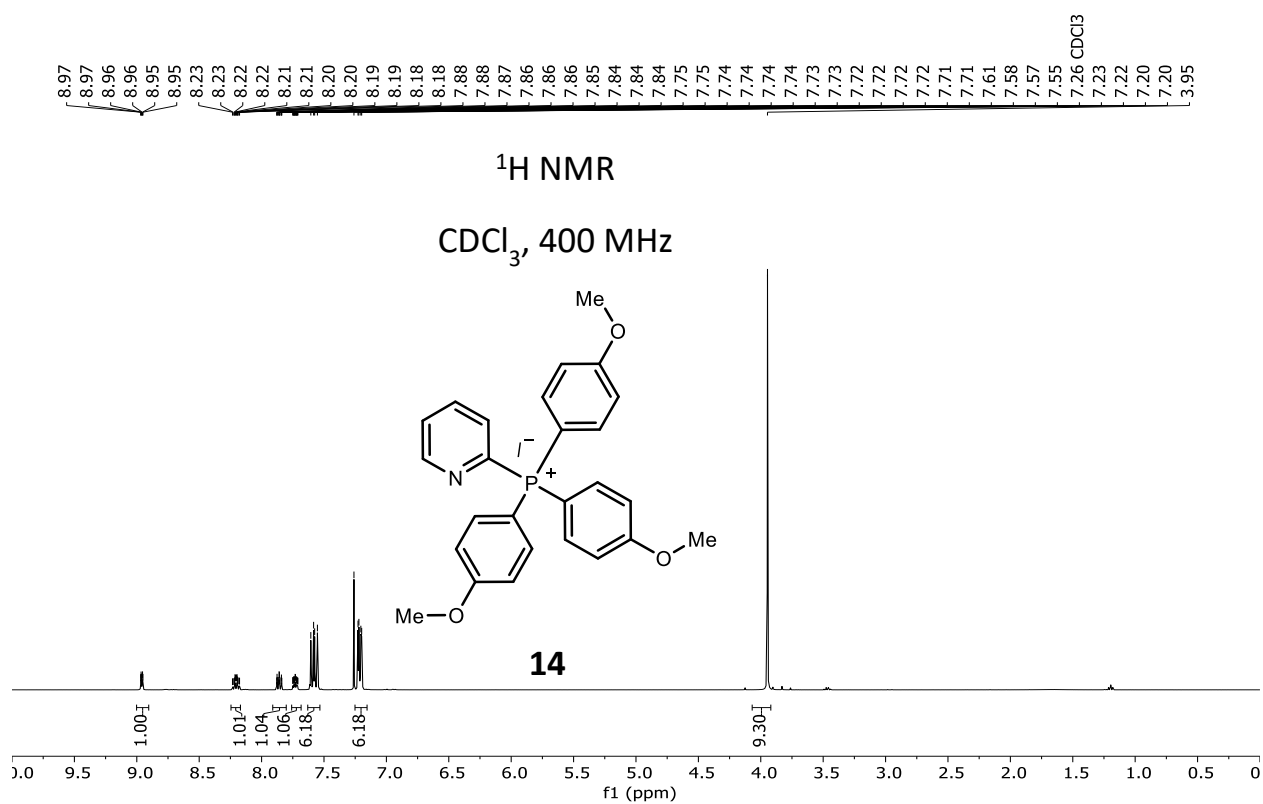


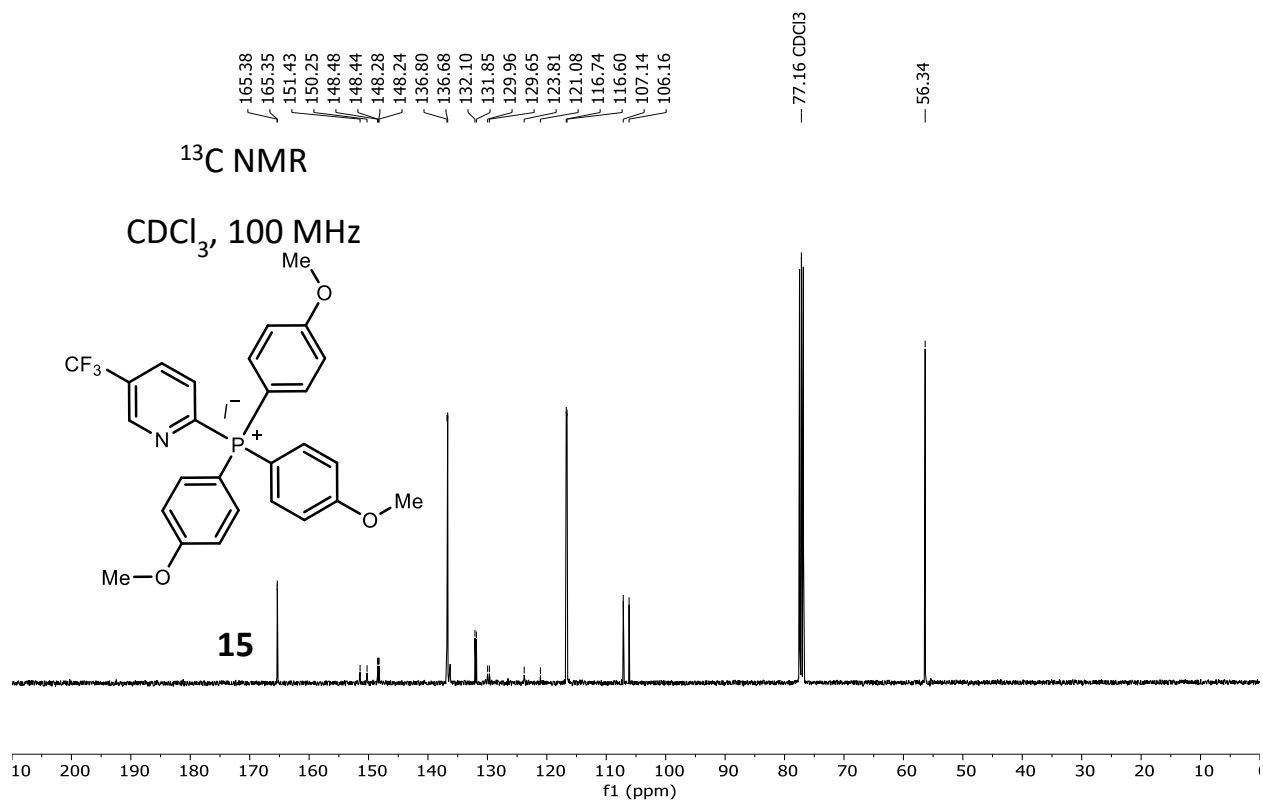
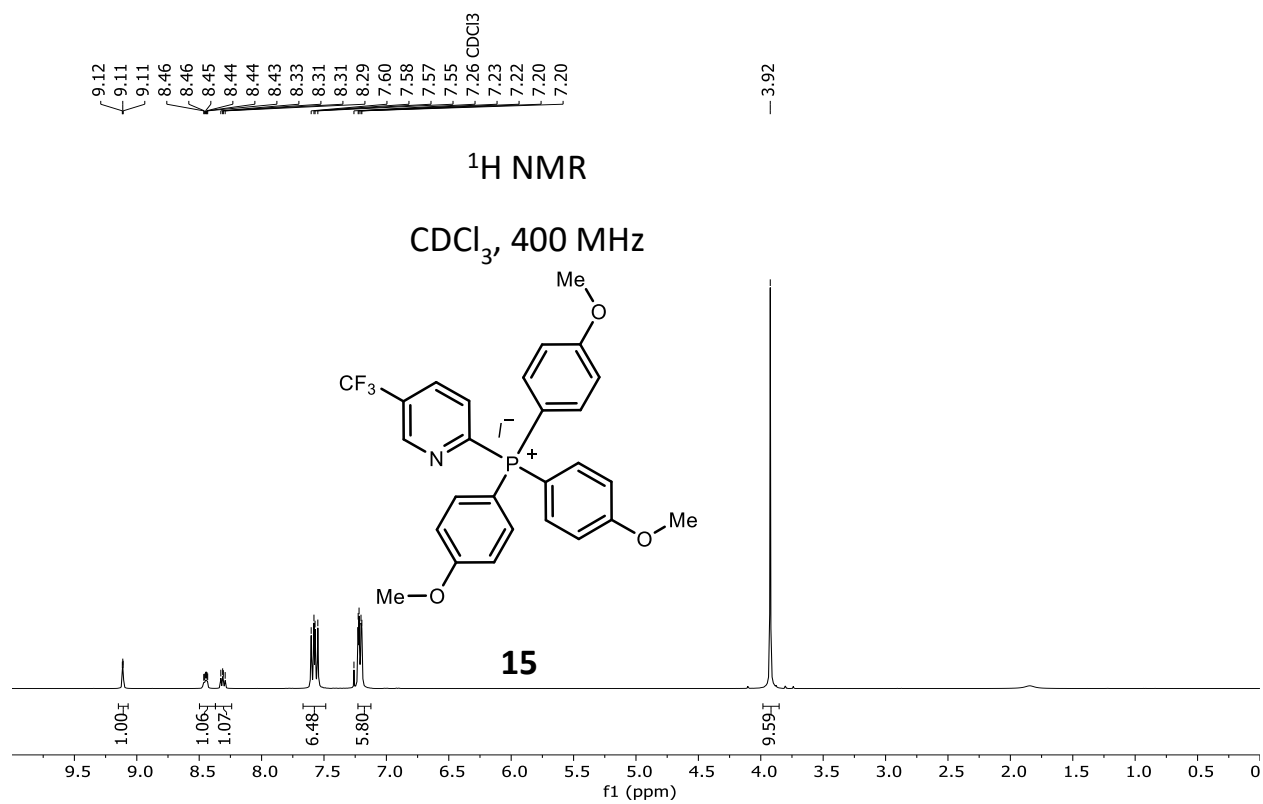


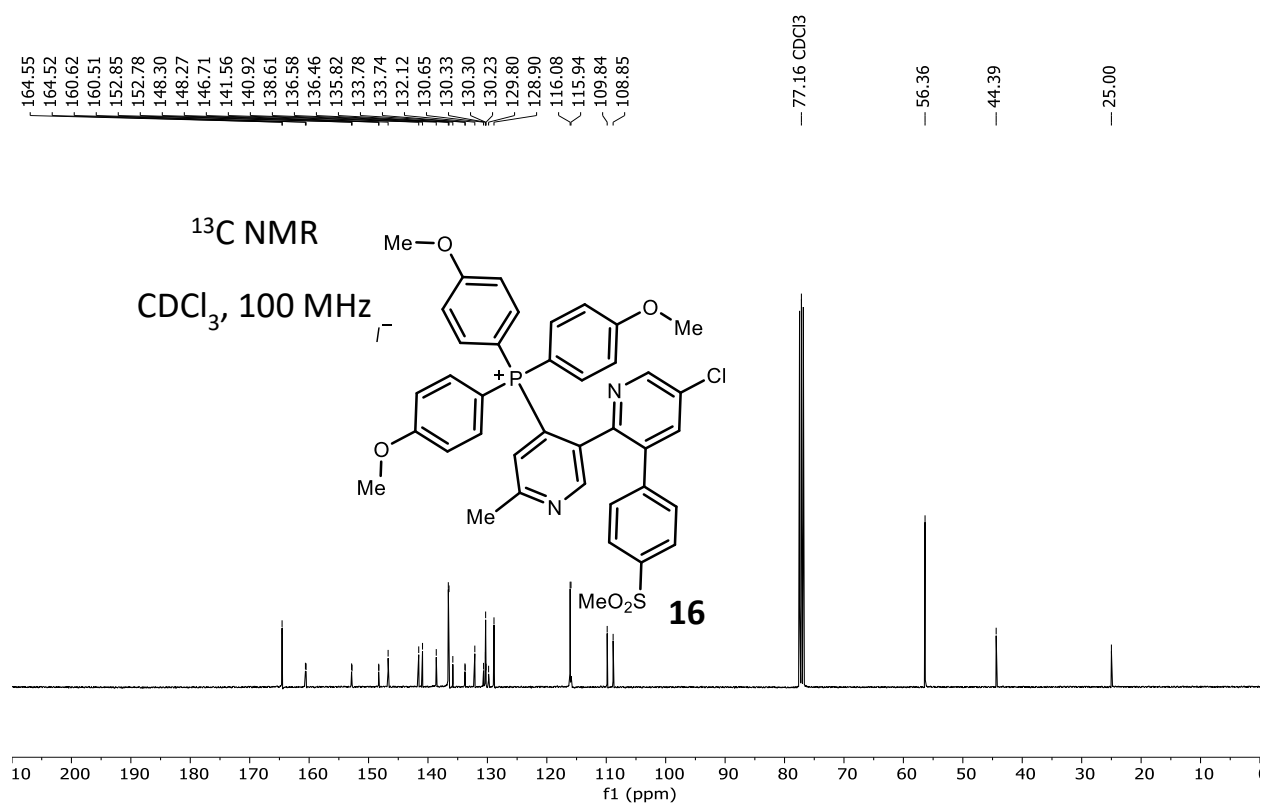
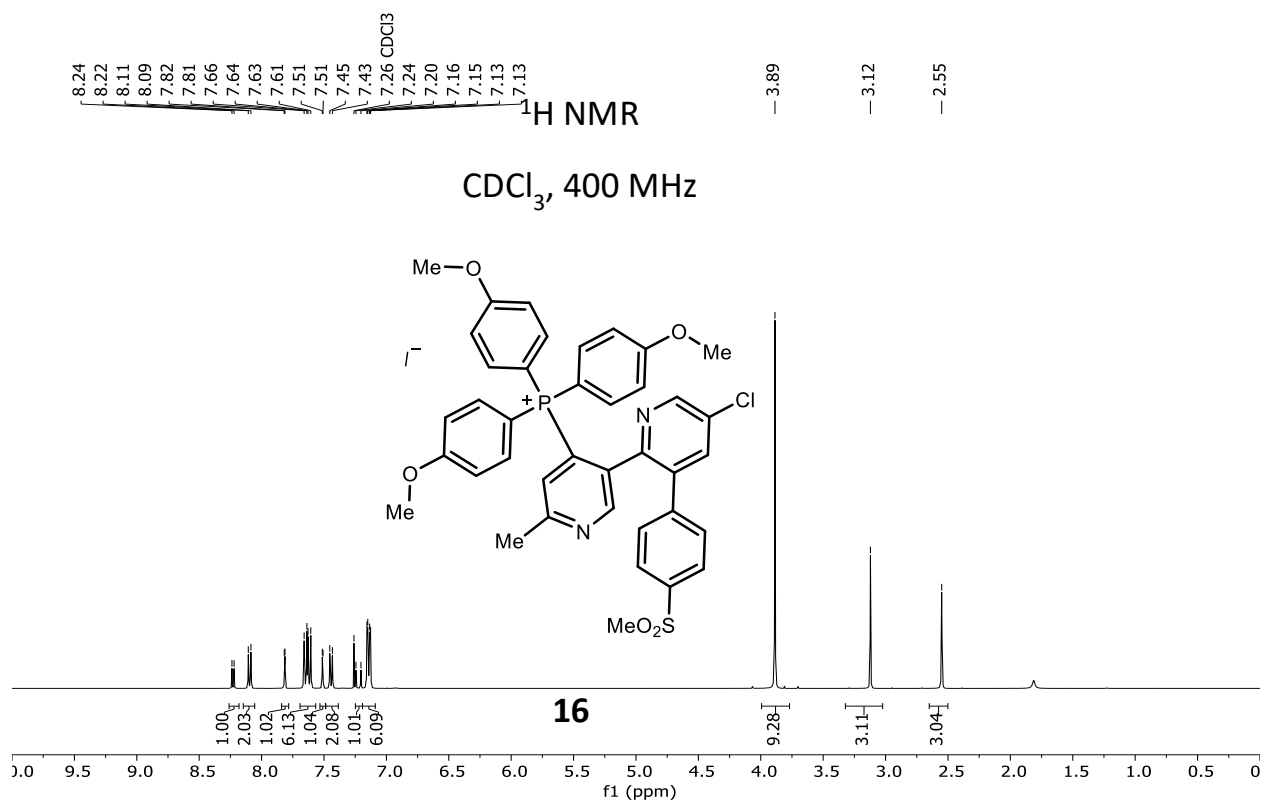


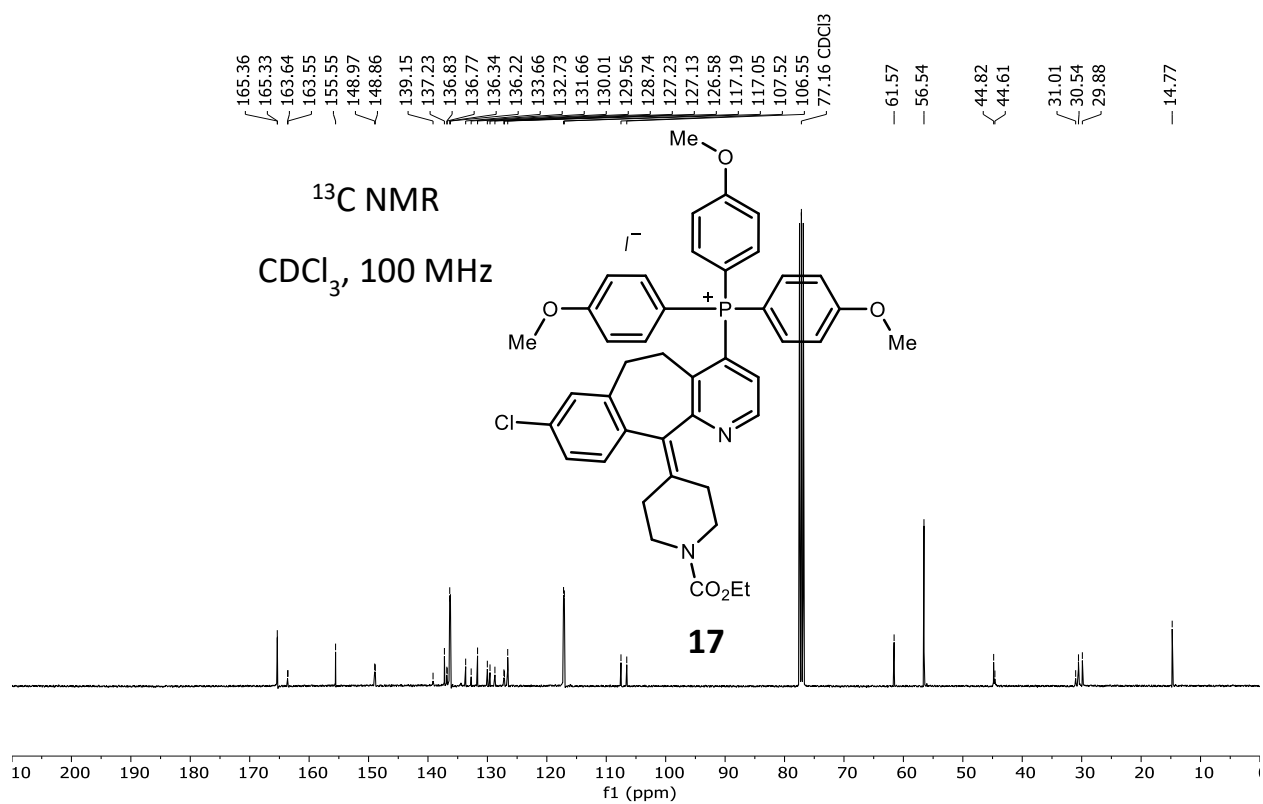
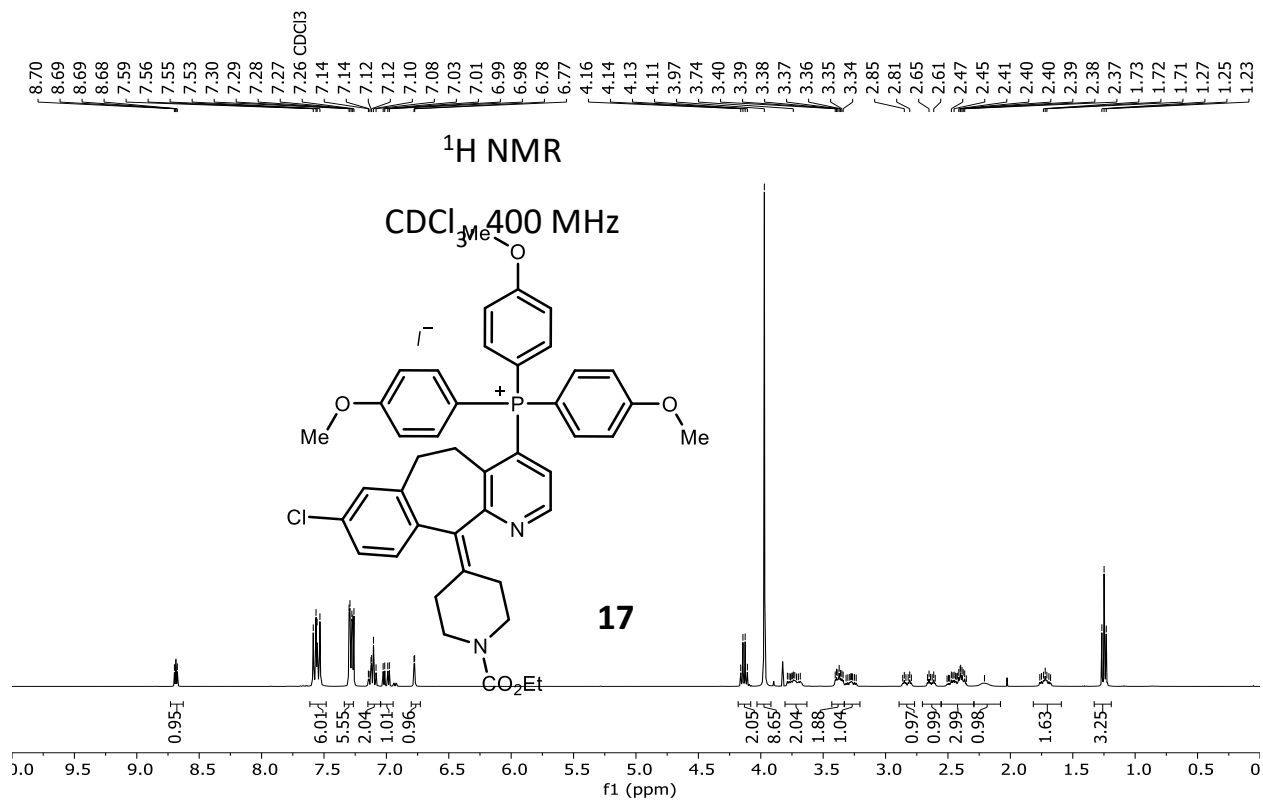


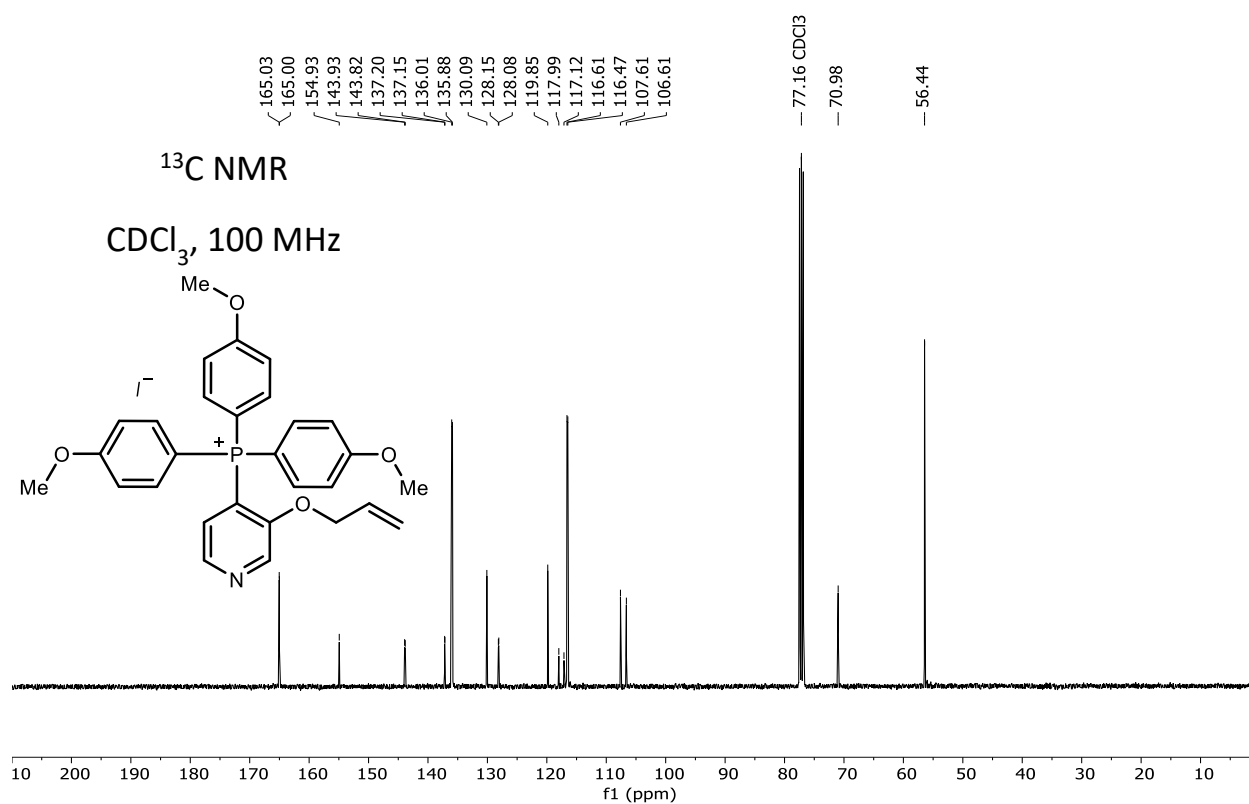
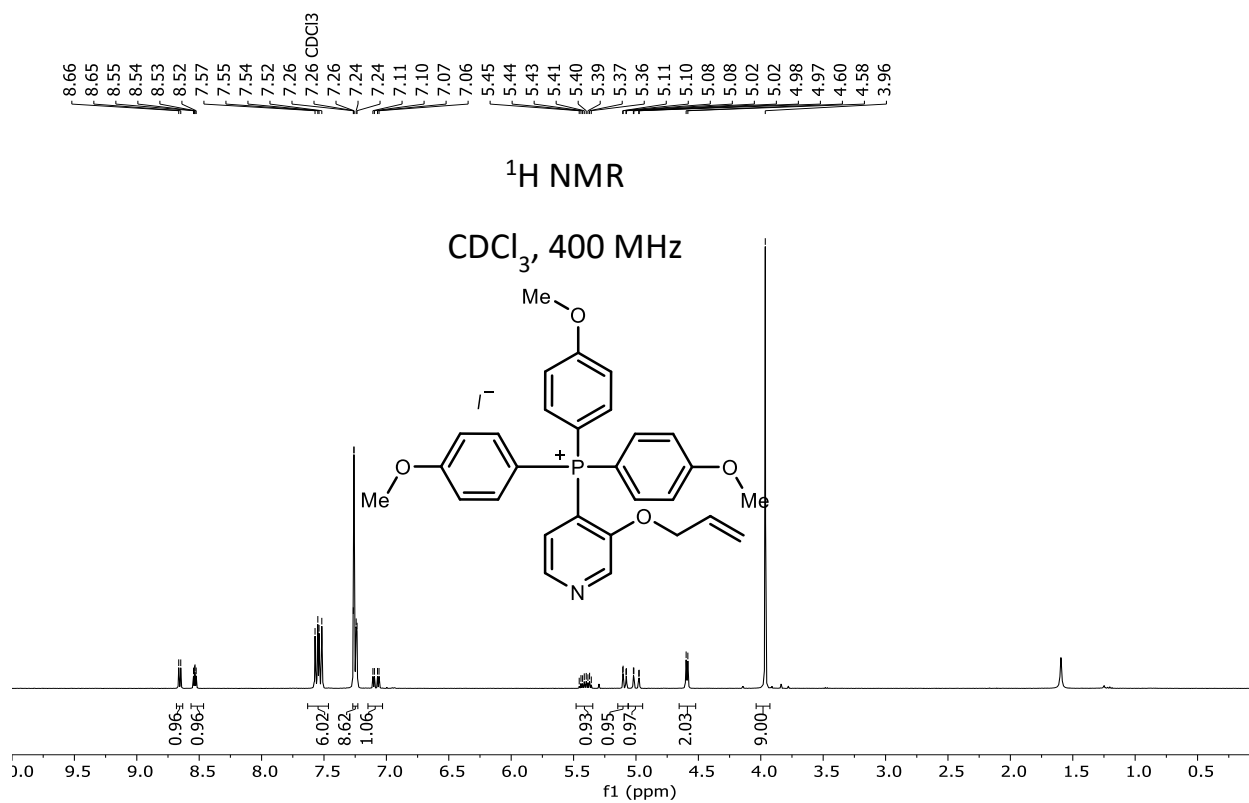












Appendix Four

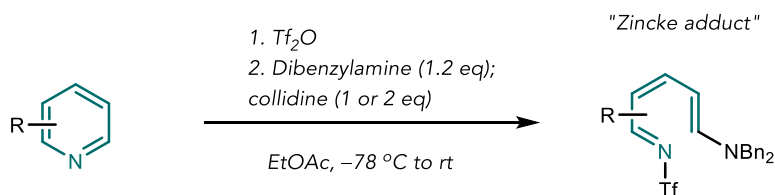
Selective Functionalization of Pyridines via Zincke Imine Intermediates: Experimental

A 4.1 General Methods and Materials

Tf₂O (99%) was purchased from Oakwood Chemical and used without further purification but was routinely stored in a –20 °C fridge. Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.¹ Ethyl acetate (EtOAc) was purchased anhydrous from Acros Chemicals. 2,4,6-Collidine and dibenzylamine were purchased from Tokyo Chemical Industry (TCI) and used without further purification. Halosuccinimides were purchased from Combi-blocks and a –20 °C fridge when not in use. Palladium acetate (Pd(OAc)₂) was purchased from Sigma Aldrich. Tricyclohexylphosphine (Cy₃P) was purchased from Combi-blocks and used stored in a glovebox. 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.

A 4.2 General Procedures

A 4.2.1 General Procedure A (Zincke Imine Formation)



An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.1 M) was added, the reaction vessel cooled to $-78\text{ }^\circ\text{C}$ and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before dibenzylamine (1.2 equiv) was added dropwise as a solution (1.0 M in EtOAc) followed by collidine (1.0 eq). The reaction was stirred for a further 30 minutes at $-78\text{ }^\circ\text{C}$. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. The reaction was diluted with EtOAc then washed with H_2O (3x). The organic extract was dried (MgSO_4) and filtered. After filtration, the organic extract was added dropwise to excess hexanes (approx. 100 mL per 1.0 mmol) and the resulting oil was allowed to settle overnight in a $-20\text{ }^\circ\text{C}$ fridge. After the oil has settled, the hexanes was decanted off and the residual oil was washed with hexanes and then dissolved in CH_2Cl_2 and concentrated *in vacuo* to provide the pure "Zincke imine" product.

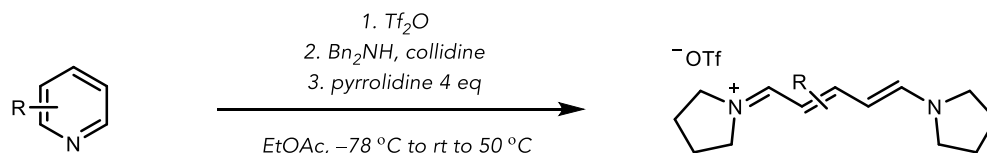
Reaction Notes:

- Reaction is sensitive to excess of Tf_2O added (use of 1.2 eq results in substantial yield loss).
- Majority of substrates comparably with 1.0 equiv. and 2.0 equiv. collidine, 1.0 equiv. can be used regardless of substrate (Yields in scope table below denote how many equivalents

were used for that specific yield, but were within 5% when repeated with the other collidine amount).

- Stirring is critical to achieve consistent yields; recommended stirring 500-750 rpm
- For larger scales, it is recommended to allow the reaction to warm fully to room temperature, the 30 minutes was based on initial smaller scale reactions.
- Substrates with a 4-substituent (and unsubstituted pyridine) are susceptible to “bis-adduct” formation and care should be taken prior to crash out. Vacing down prior to crash out results in significant (>20%) yield loss to bis-addition.
- If “bis-adduct” is observed, a short plug of silica (2-3 inches) and appropriate solvent eluent will remove it.
- Substrates with a 4-substituent (and unsubstituted pyridine) can be run with 1.0 eq Bn_2NH to minimize potential for bis-addition product formation.
- For substrates with a 2-R substituent, the organic extract can be concentrated *in vacuo* then redissolved in 2-10 mL CH_2Cl_2 prior to addition to the hexanes. This will provide higher yields.

A 4.2.2 General Procedure B (Zincke Iminium Formation)



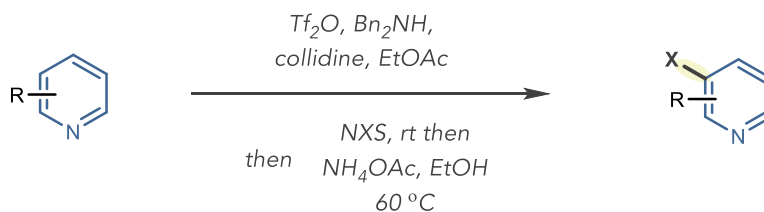
An oven dried 8 mL vial (≤ 0.5 mmol scale) or a round bottom flask (> 0.5 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and placed under a nitrogen atmosphere. EtOAc (0.1 M) was added, the reaction vessel cooled to $-78\text{ }^\circ\text{C}$ and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before dibenzylamine (1.0 equiv) was added dropwise as a solution (1.0 M in EtOAc) followed by collidine (1.0 eq). The reaction was stirred for a further 30 minutes at $-78\text{ }^\circ\text{C}$. The cooling bath was removed and the reaction was allowed to warm to room temperature while stirring for approximately 30 minutes. Pyrrolidine was then added to the reaction mixture at room temperature then heated to $50\text{ }^\circ\text{C}$ for 1 hour. The reaction was then cooled to room temperature, and an equal volume of saturated aqueous Na_2CO_3 was added and stirred for 30 minutes at room temperature. The organic layer was then extracted, dried (MgSO_4), and filtered. After filtration, the organic extract was added dropwise to excess Et_2O /hexanes (1:1 ratio, approx. 100 mL per 1.0 mmol) and the resulting solid/oil was allowed to settle overnight in a $-20\text{ }^\circ\text{C}$ fridge. After the oil has settled, the solution was decanted and the residual solid/oil was washed with hexanes, dissolved in CH_2Cl_2 , and concentrated *in vacuo* to provide the pure “Zincke iminium” product.

Reaction Notes:

- Reaction is sensitive to excess of Tf_2O added (use of 1.2 eq results in substantial yield loss).

- Stirring is critical to achieve consistent yields; recommended stirring 500-750 rpm
- While an extensive study has not been done, concentrating the organic extract *in vacuo* prior to precipitation likely slightly increases yield.
- 100% Et₂O can be used for the precipitation for certain substrates, however more iminium is lost to the mother liquor.
- Recommended not to wash the iminium with water due to loss of product to the water layer (73% to 44% after 2 washes).
- 3 equivalents of pyrrolidine was also found to be effective, however the additional equivalent helps the reaction be more consistent across all substrates.
- Other secondary amines are also effective in the iminium formation, with the notable exception of Bn₂NH on 2-substituted pyridines requiring 80 °C.

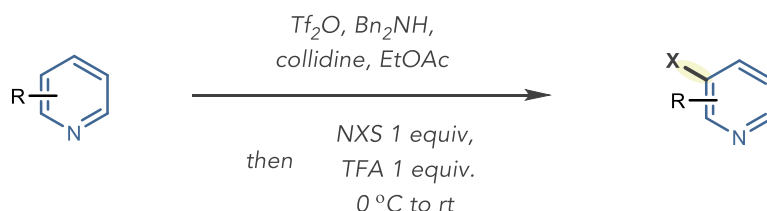
A 4.2.3 General Procedure C (One-Pot Halogenation of 2- or 4-substituted pyridines)



An 8 mL vial charged with EtOAc (0.1 M) and pyridine (1 equiv) was cooled to -78°C , and Tf₂O (1 equiv) was added dropwise. After stirring for 30 minutes at -78°C , Bn₂NH (1.2 equiv as a 1M solution in EtOAc) and collidine (1 equiv) were added sequentially. After stirring for 30 minutes at -78°C , the reaction was warmed to room temperature. After reaching room temperature NIS (1 equiv) was added as a solid. After 10 minutes, TMB (1 equiv) was added as a solid. Then, EtOH (2x the volume of EtOAc) and NH₄OAc (10 equiv) were added and the reaction was stirred

at 60 °C for 2 hours. The reaction is then cooled to room temperature, concentrated down, and purified on silica.

A 4.2.4 General Procedure D (One-Pot Halogenation of 3-substituted pyridines)



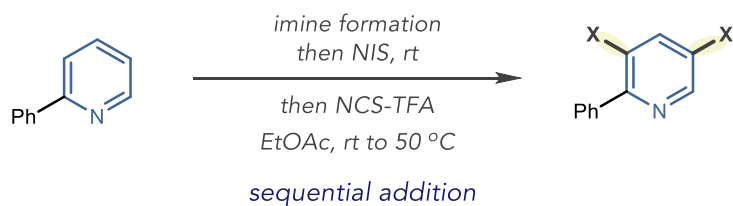
An 8 mL vial charged with EtOAc (0.1 M) and pyridine (1 equiv) was cooled to $-78\text{ }^\circ\text{C}$, and Tf_2O (1 equiv) was added dropwise. After stirring for 30 minutes at $-78\text{ }^\circ\text{C}$, Bn_2NH (1.2 equiv as a 1M solution in EtOAc) and collidine (1 equiv) were added sequentially. After stirring for 30 minutes at $-78\text{ }^\circ\text{C}$, the reaction was warmed to room temperature. After reaching room temperature, the reaction was then cooled to $0\text{ }^\circ\text{C}$. NIS (1 eq.) was added as a solid, and then TFA (1 eq.) was added immediately after. The reaction was allowed to warm to room temperature and stirred for 2 hours. The reaction was quenched with aqueous sodium bicarbonate and aqueous sodium thiosulfate, and the aqueous layer is extracted from with EtOAc three times. The organic extracts are dried with MgSO_4 , concentrated down, and purified on silica.

Notes:

- For substrates without a 2- or 6- substituent, 1.0 equiv of Bn_2NH is used to prevent formation of the Zincke iminium.
- In some cases, CH_2Cl_2 is sometimes used instead of EtOAc.
- In some cases, two equivalents of TFA and NIS are used instead of one.

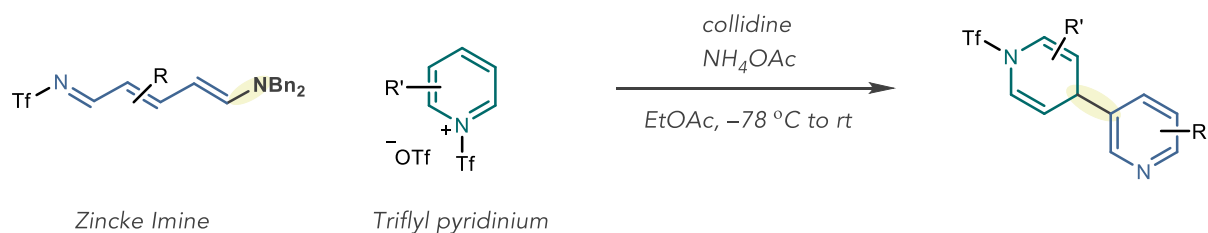
- In some cases, the TFA aromatization step takes longer than two hours, and the reaction is left to stir overnight.
- For pyridines with a chlorine at the 2-position, BnPhNH is used instead of Bn₂NH.

A 4.2.5 General Procedure E (Bis-Halogenation of pyridines)



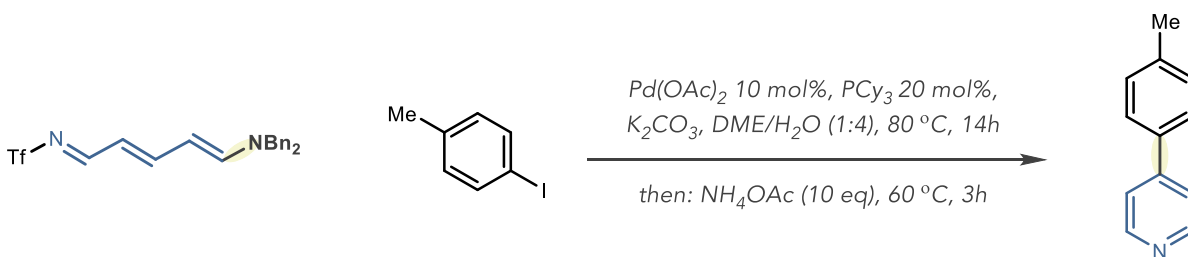
An 8 mL vial charged with EtOAc (0.1 M) and 2-phenylpyridine (1 equiv) was cooled to $-78\text{ }^\circ\text{C}$, and Tf₂O (1 equiv) was added dropwise. After stirring for 30 minutes at $-78\text{ }^\circ\text{C}$, Bn₂NH (1.2 equiv as a 1M solution in EtOAc) and collidine (1 equiv) were added sequentially. After stirring for 30 minutes at $-78\text{ }^\circ\text{C}$, the reaction was warmed to room temperature. After reaching room temperature NXS (1 equiv) was added as a solid. After 10 minutes, TMB (1 equiv) was added as a solid. The reaction mixture was then filtered and the solid collected. The solid was then dissolved in CH₂Cl₂ and cooled to $0\text{ }^\circ\text{C}$. NXS (1 eq.) was added as a solid, and then TFA (1 eq.) was added immediately after. The reaction was allowed to warm to room temperature and stirred for 2 hours. The reaction was quenched with aqueous sodium bicarbonate and aqueous sodium thiosulfate, and the aqueous layer is extracted from with EtOAc three times. The organic extracts are dried with MgSO₄, concentrated down, and purified on silica.

A 4.2.6 General Procedure F (*N*-Tf Pyridinium Addition with Zincke Imines)



An 8 mL vial charged with EtOAc (0.1 M) and pyridine (1 equiv) was cooled to -78°C , and Tf_2O (1 equiv) was added dropwise. After stirring for 30 minutes at -78°C , Zincke Imine (1.2 equiv) and collidine (1 equiv) were added sequentially. After stirring for 30 minutes at -78°C , the reaction was warmed to room temperature. After reaching room temperature the reaction is stirred for 4 hours. Then NH_4OAc (10 equiv) were added and the reaction was stirred at 60°C for 2 hours. The reaction is then cooled to room temperature, quenched with aqueous sodium bicarbonate, and the aqueous layer is extracted from with EtOAc three times. The organic extracts are dried with MgSO_4 , concentrated down, and purified on silica.

A 4.2.7 General Procedure F (*N*-Tf Pyridinium Addition with Zincke Imines)



An 8 mL vial charged with Zincke imine (1 equiv), $\text{Pd}(\text{OAc})_2$ (10 mol%), K_2CO_3 (3 equiv), and *p*-iodotoluene (2 equiv). The vial was then pumped into a glovebox and charged with PCy_3 (20 mol%) and DME/ H_2O (0.1 M 1:4). The reaction was then heated to 80°C overnight. After heating overnight, the reaction was cooled to room temperature and charged with NH_4OAc (10

equiv) were added and the reaction was stirred at 60 °C for 3 hours. The reaction is then cooled to room temperature and the aqueous layer is extracted from with EtOAc three times. The organic extracts are dried with MgSO₄, concentrated down, and purified on silica.