DISSERTATION

PHOSPHORUS LIGAND-COUPLING REACTIONS FOR THE FUNCTIONALIZATION OF PYRIDINE AND OTHER AZINES

Submitted by

Kyle G. Nottingham

Department of Chemistry

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Doctoral Committee:

Advisor: Andrew McNally

Robert Paton
Chuck Henry
Robert Cohen

ABSTRACT

PHOSPHORUS LIGAND-COUPLING REACTIONS FOR THE FUNCTIONALIZATION OF PYRIDINE AND OTHER AZINES

Pyridines and related azines are ubiquitous in pharmaceuticals, agrochemicals, and materials. The discovery and development of new purpose-built molecules is contingent on our ability to modify these motifs. Described herein are the development of methods that selectively functionalize pyridine and diazine scaffolds through phosphorus ligand-coupling. Novel phosphine reagents were designed and leveraged to construct C–C, C–O, and C–N bonds on azines from their C–H precursors.

Chapter one introduces the history of phosphorus ligand-coupling and defines the reactivity explored throughout this thesis. Both seminal and contemporary examples of phosphorus ligand-coupling reactions are also discussed to provide context for this work. Chapter two focuses on a method to incorporate fluoroalkyl groups onto azines and pharmaceuticals using phosphorus ligand-coupling. This method offers a complementary alternative to widely used radical addition approaches which often produce regiomeric product mixtures on azines.

Chapter three presents the investigation of a phosphorus-mediated alkenylation reaction on pyridines and quinolines. Examination of the reaction of pyridylphosphines with alkyne acceptors uncovered divergent reaction pathways from alkenylphosphonium salts. Mechanistic studies provide an explanation for the origin of selectivity obtained in these reactions. Lastly, chapter four expands upon one of these reaction pathways and describes the development of a method for the direct conversion of pyridines into pyridones and aminopyridines.

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CHAPTER ONE

PHOSPHORUS LIGAND-COUPLING AND ITS SYNTHETIC UTILITY

1.1 Introduction to Phosphorus Ligand-Coupling

Organophosphorus chemistry has a rich history in organic synthesis, and a wide array of reactions and their mechanisms have been explored for over more than a century. The significance of phosphorus compounds is reflected in their deployment as fertilizers, pesticides, flame retardants, ancillary ligands to metals, and medicines, as well as their crucial roles in biological systems.[1–7] Furthermore, organophosphorus compounds serve as necessary components or intermediates in general organic synthesis. Named reactions including the Wittig, Staudinger, Appel, Mitsunobu, and many others are routinely used for the preparation of purpose-built molecules. These methods highlight the ability of organophosphorus compounds to engage in a wide array of mechanistically distinct pathways. Among these, ligand-coupling remains a relatively unexploited mechanism for phosphorus-mediated reaction development.

The term "ligand-coupling" was first coined by Oae in 1986 to describe a distinct mode of reactivity for hypervalent sulfur and phosphorus species, though this reactivity was discovered prior and studied in various contexts for decades.[8,9] As described by Oae, there are three possible ways for hypervalent species to collapse to form stable products: self-decomposition, ligand exchange, and ligand-coupling (**Figure 1.1**). The Wittig reaction constitutes an example of self-decomposition. The hypervalent oxaphosphetane intermediate **1** collapses via the mechanism shown in **Figure 1.1a** to form triphenylphosphine oxide and an olefin. An example of ligand

exchange is phosphate hydrolysis, which proceeds with substitution at phosphorus via phosphorane (P^V) intermediate **2** (**Figure 1.1b**).

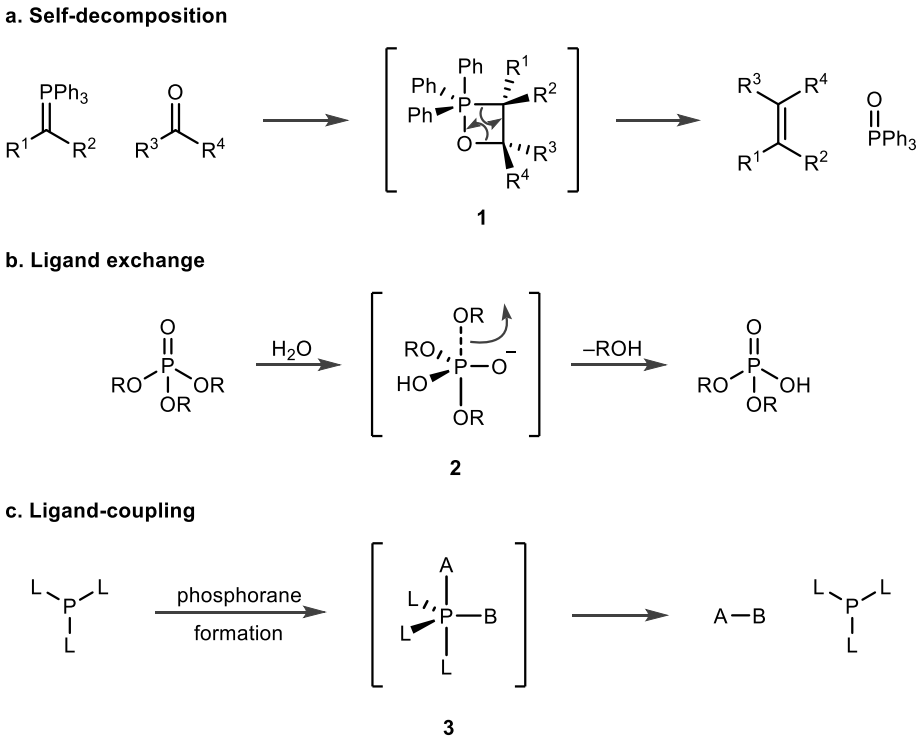

Figure 1.1 Phosphorane decomposition pathways.

Ligand-coupling, on the other hand, is a process in which two ligands, with a pair of electrons, are extruded from a central atom which returns to a more stable valency (**Figure 1.1c**). This definition, however, does not fully describe the classes of experimentally determined ligand-coupling reactions and their precise mechanisms; a more comprehensive categorization of ligand-coupling processes was consequently established by Finet (**Figure 1.2**).[10] Type A ligand-coupling reactions (denoted LC) involve ligands appended to the heteroatom by σ-bonds and contain two subclasses. Coupling between two of the same ligands or two ligands of similar polarity has been proposed to occur via a relatively synchronous process and is considered a homocoupling (denoted LC_H). Though limited studies have been conducted, the decomposition of tetraphenyltellurium

species has been proposed to occur through a symmetry-allowed concerted ligand coupling process (**Figure 1.2a**).[11]

When the two pairing ligands are of sufficiently different polarity, the coupling is closer to an internal nucleophilic substitution, which is typically asynchronous and involves a polar transition state. The example provided (**Figure 1.2b**) is one of the reactions discovered in Oae's studies of ligand-coupling from sulfoxide derivatives.[12] This subclass, denoted LC_N, encompasses each of the phosphorus-mediated reactions discussed in the chapters of this dissertation that follow. Type B ligand-coupling reactions occur between one σ-bonded ligand and one allylic atom. Denoted LC' (by analogy to S_N2 and S_N2' reactions), Type B reactions contain two subclasses (LC_N' and LC_E') determined by the philicity of the σ-bonded ligand for the allylic atom. These transformations are comparatively less common than Type A and are relevant to ligand-couplings from organolead, organobismuth, and organothallium compounds, as illustrated by the bismuth-mediated ortho-arylation of carbonyl compounds discovered by Barton (LC_N'), and the reaction of lead tetraacetate with phenols discovered by Wessely (LC_E') (**Figure 1.2c, d**).[13,14]

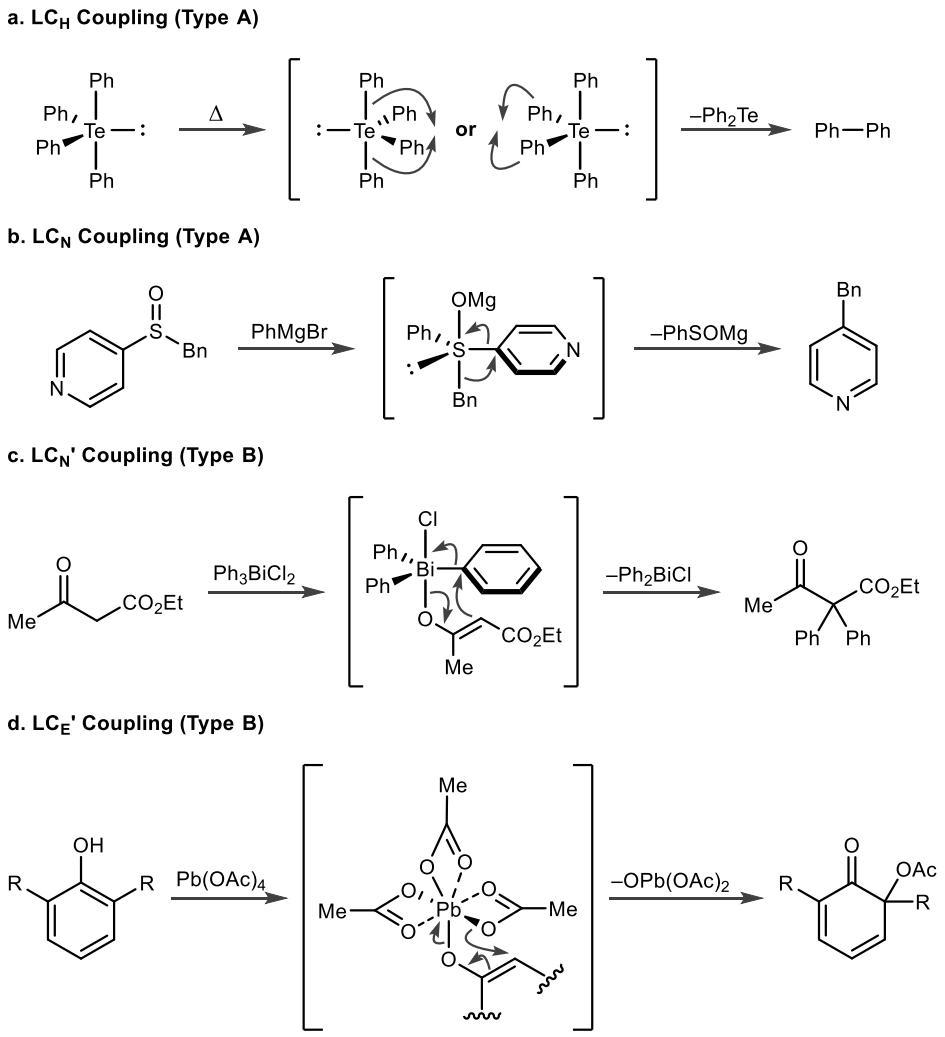

Figure 1.2 Ligand-coupling subclasses and representative examples.

1.2 Seminal Examples of Ligand Migration and Coupling from P^V Intermediates

1.2.1 Ligand Migration Examples

LC_N reactions operate by a characteristic mechanism from the phosphorane intermediate: first, an apical ligand undergoes 1,2-migration onto an equatorial acceptor, and second, elimination of a P^{III} species occurs to form the new product. In some cases, migration from the phosphorane takes place, but elimination of a P^{III} byproduct is disfavored or impossible. The most studied example of this reactivity is the Allen-Millar-Trippett rearrangement.[15–18] In the late 1960s Allen and Millar, and in related work, Trippett, reported that certain cyclic phosphonium salts

decompose by hydrolysis to ring-expanded products. After alkylation of 9-phosphafluorene **4** with methylene iodide and addition of water to phosphonium **5**, the apical phenyl ligand in trigonal bipyramidal phosphorane **6** undergoes a 1,2-migration onto the equatorial iodomethyl group with loss of hydrogen iodide (**Figure 1.3**). While this pathway is not a complete ligand coupling process as no elimination occurs, it highlights one of the conditions that must be met for LC_N reactions to take place. The apical ligand can only migrate onto an equatorial ligand which acts as an electrophilic acceptor, such as the alkyl iodide in **6**.

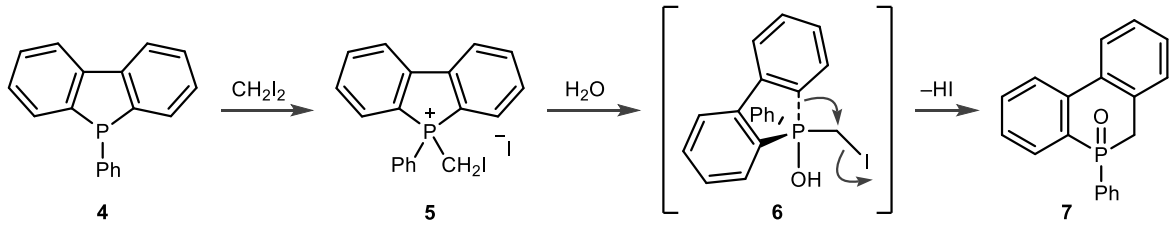

Figure 1.3 The Allen-Millar-Trippett rearrangement.

Richards and Tebby later found that a similar ring expansion occurred from phosphoranes generated by addition of phosphine **4** to methyl propiolate **8** under aqueous conditions.[19] Here, migration of the apical carbon group onto the equatorial acrylate substituent followed by protonation of the resulting enolate yields the dihydrophosphinine oxide (**Figure 1.4a**). Chapter 3 of this dissertation contains additional discussions of this type of system and the possible reaction pathways from vinylphosphoranes like **5**. The next extension of this ring expansion approach was reported by Mathey, who found that acylphosphonium salts (**12**) generated from phospholes (**11**) and acyl chlorides were hydrolyzed to the corresponding 2-hydroxy-1,2-dihydrophosphinines (**14**, **Figure 1.4b**).[20]

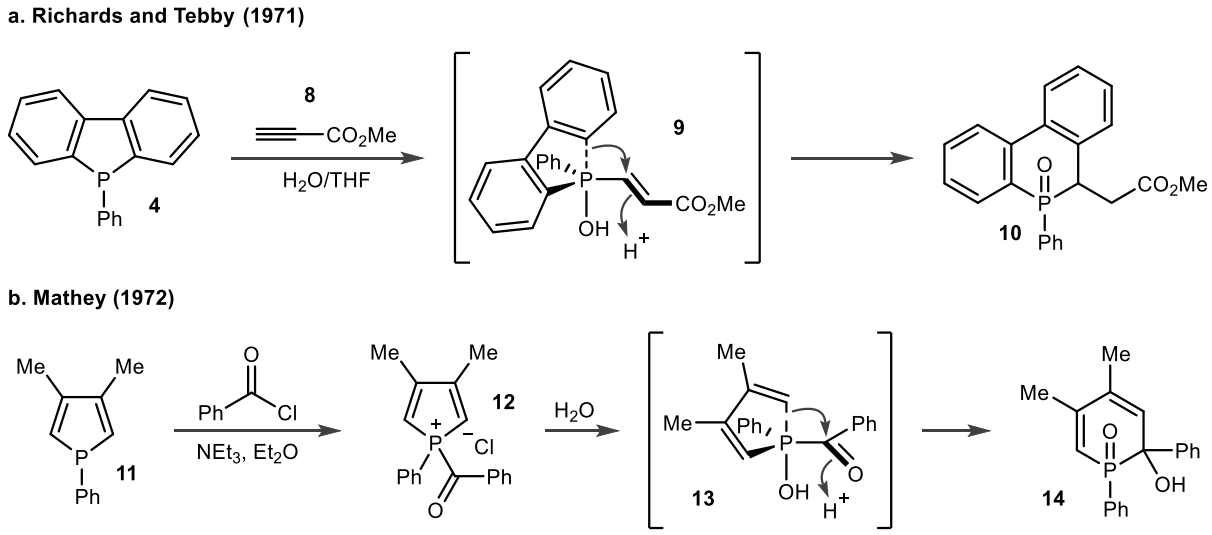

Figure 1.4 Additional acceptors for phosphorane ring-expansion.

Mathey also discovered that when the phosphole contained a P-*tert*-butyl substituent (**15**), ring expansion failed, and an alternative pathway in which the acyl group migrated onto the phosphole olefin was preferred (**16**, **Figure 1.5a**).[21] Smith found that related acylphosphoniums from 2,3-dihydrophospholes (**18**) disfavored ring expansion, instead preferring a ligand exchange pathway (**19**) to form 2,3-dihydrophosphole oxides (**20**) and the corresponding aldehydes (**21**, **Figure 1.5b**).[22] These results from Mathey and Smith underscore the ability of the same or very similar phosphoranes to decompose through multiple distinct pathways; consequently, obtaining selectivity for the desired pathway poses a challenge to reaction development.

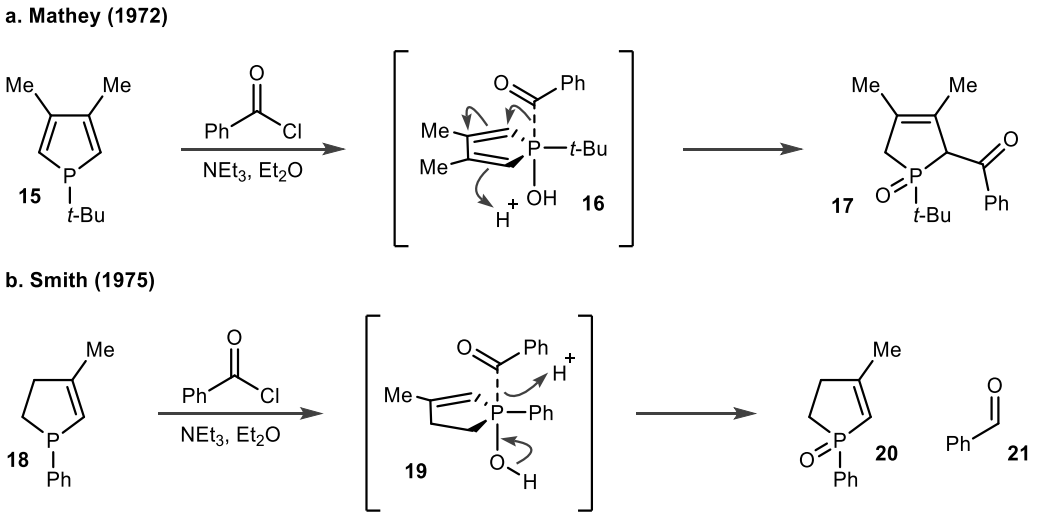

Figure 1.5 Alternative decomposition pathways from cyclic phosphorane intermediates.

1.2.2 Ligand-Coupling Examples

Studies on the pyrolysis of pentaphenylphosphorane by Wittig established early examples of phosphorus ligand-coupling reactions.[23] Heating Ph_5P to 130 °C forms triphenylphosphine and biphenyl in 22%, along with benzene and other byproducts (**Figure 1.6a**). Related studies of spirocyclic phosphoranes gave similar aryl-aryl coupling products (**Figure 1.6b**).[24]

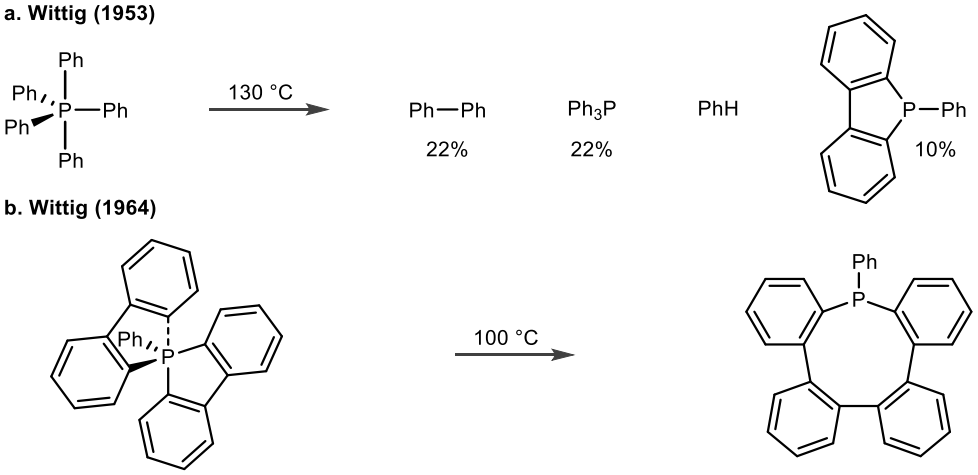

Figure 1.6 Early examples of P^V contractive coupling.

Alkoxy and aryloxyphosphoranes are prepared by heating Ph_5P (**22**) with the corresponding alcohol (**Figure 1.7**). Decomposition of these reagents under thermal conditions

yields a mixture of products depending on the nature of the oxygen substituent. Phenoxy groups yield mainly the corresponding phenol (**26**) and triphenylphosphine (**25**) via protonation of the phenoxy ligand; a minor amount of diphenyl ether (**24**), presumably from an LC_N pathway was observed (**Figure 1.7a**). Alkoxy groups favor the ligand-coupling pathway to yield mostly alkyl phenyl ether (**24**, R = Me), triphenylphosphine, and a minor amount of the corresponding alcohol (**26**).[25] Similar results were obtained from alkoxy methyltriphenylphosphoranes (**Figure 1.7b**).[26]

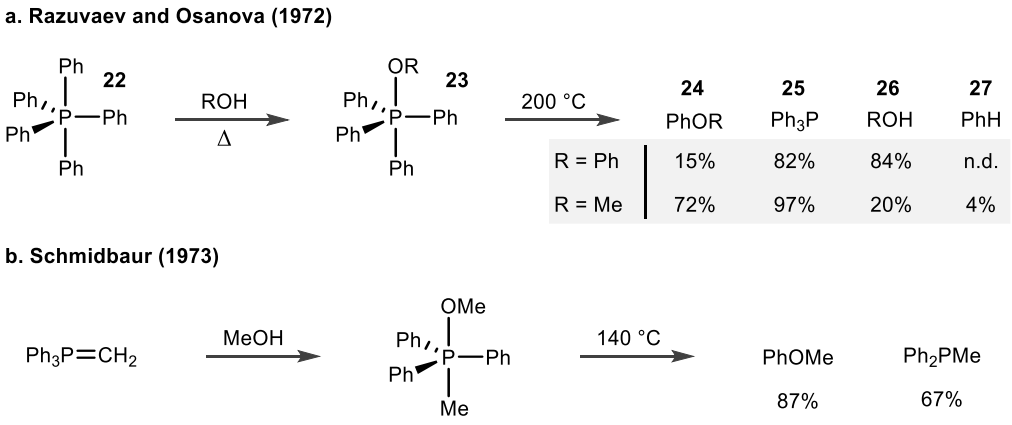

Figure 1.7. Examples of C–O bond formation from P^V species.

While the decomposition of stable phosphoranes served as early examples of ligand-coupling, the approach is inherently limited by the conditions needed to achieve coupling and by the number of phosphoranes which are stable enough for isolation. More often, it is common to generate a phosphorane *in situ* as part of a multistage process from accessible starting materials. Early examples of this strategy were still not synthetically useful but previewed the types of useful bond constructions which could be achieved through ligand-coupling.

An early approach to bipyridine synthesis via P^V coupling was reported by Mann in 1948.[27] Lithium-halogen exchange on 2-bromopyridine followed by addition to phosphorus trichloride forms a tripyridylphosphine. Alkylation of this phosphine and both pyridine nitrogen atoms by methyl iodide in methanol forms a bis-methylated bipyridininium (**Figure 1.8a**). Formation of an

alkoxyphosphorane via attack of methanol on the methyl phosphonium salt likely results in the ligand-coupled product. Later examples from Newkome, as well as Uchida and Oae, demonstrated that bipyridine synthesis could be achieved from multiple different phosphorus precursors (PCl_3, $PhPCl_2$, $OPCl_3$) and lithiated pyridines through similar phosphorane intermediates, but none were suitable for the practical synthesis of unsymmetrical bipyridines (**Figure 1.8b-d**).[28–30]

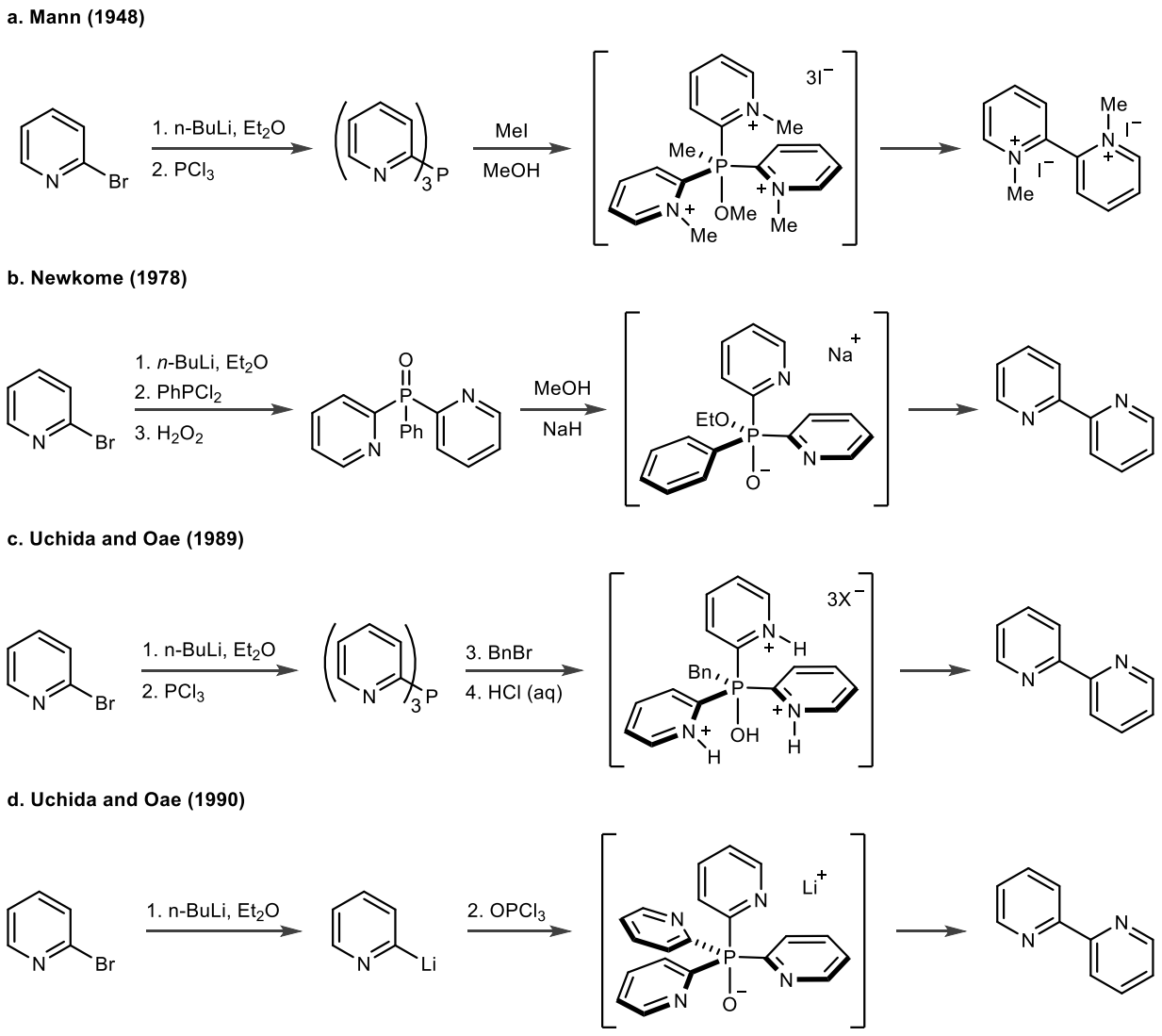

Figure 1.8 Examples of pyridine-pyridine coupling from phosphorane intermediates.

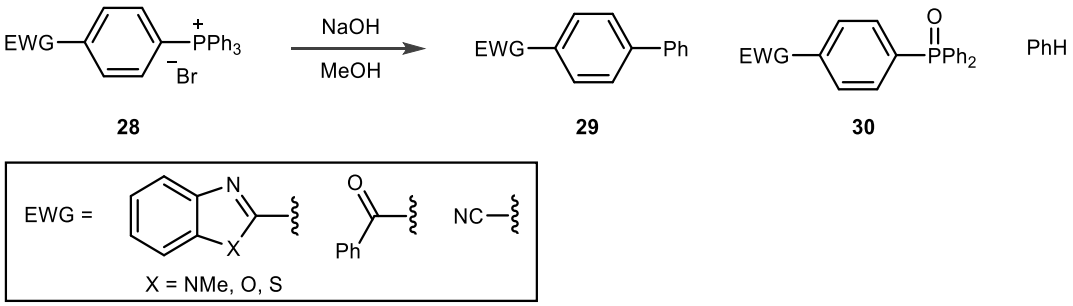

Figure 1.9 Aryl-aryl coupling via phosphorus ligand-coupling.

Aryl-aryl coupling from P^V intermediates is typically not a favored pathway but has been observed in instances where a sufficient electronic bias is present. Allen reported that *para*-substitution of an aryl ligand by an electron-withdrawing group allows the ring to act as a sufficient electron sink for coupling to proceed from tetraarylphosphonium salts (**28**, **Figure 1.9**).[31,32] However, a limited set of withdrawing groups were tested (benzimidazole, benzoxazole, benzothiazole, benzoyl and cyano) and yields of the coupled products were low (≤ 30%). The remainder of the reaction mass balance was made up by phosphine oxide **30** and benzene. Phosphonium salts containing *ortho*-substituted aryl ligands gave only phosphine oxide and benzene through ligand exchange.

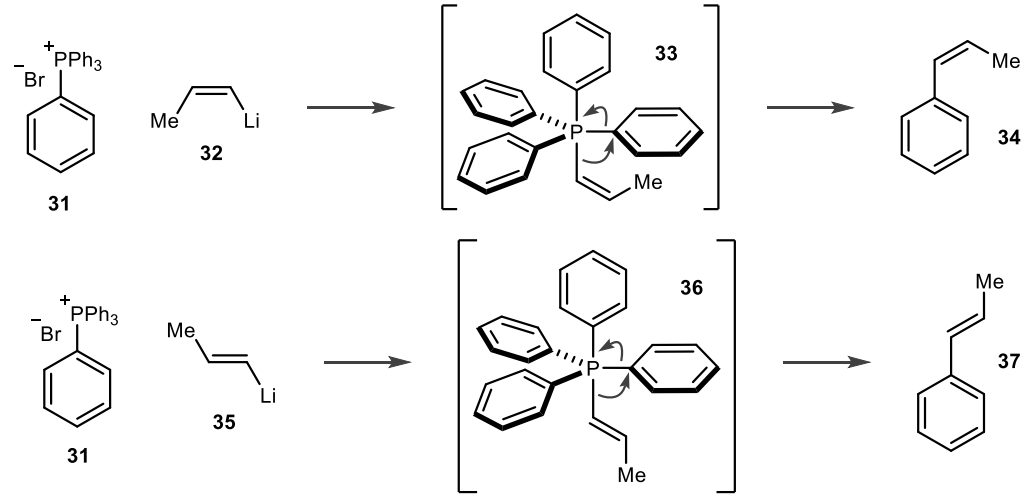

Figure 1.10 Vinyl-aryl coupling via a phosphorus LC_N process.

Addition of vinyllithium to tetraphenylphosphonium salts, in contrast to aryllithium or arylmagnesium reagents, forms a P^V intermediate which is not stable and readily decomposes to the styrene coupling product (**Figure 1.10**).[33] Furthermore, when starting from either *cis*- or *trans*-2-propenyllithium (**32** or **35**), complete retention of stereochemistry was observed in both styrene products (**34** and **37**). This indicates that migration of the apical vinyl group onto the equatorial phenyl ligand (**33** and **36**) is the operative coupling pathway, as the reverse scenario, in which the phenyl ligand migrates onto the vinyl group, would destroy the initial stereochemistry and likely provide a mixture of both isomers.

1.3 Contemporary Examples of Phosphorus Ligand-Coupling

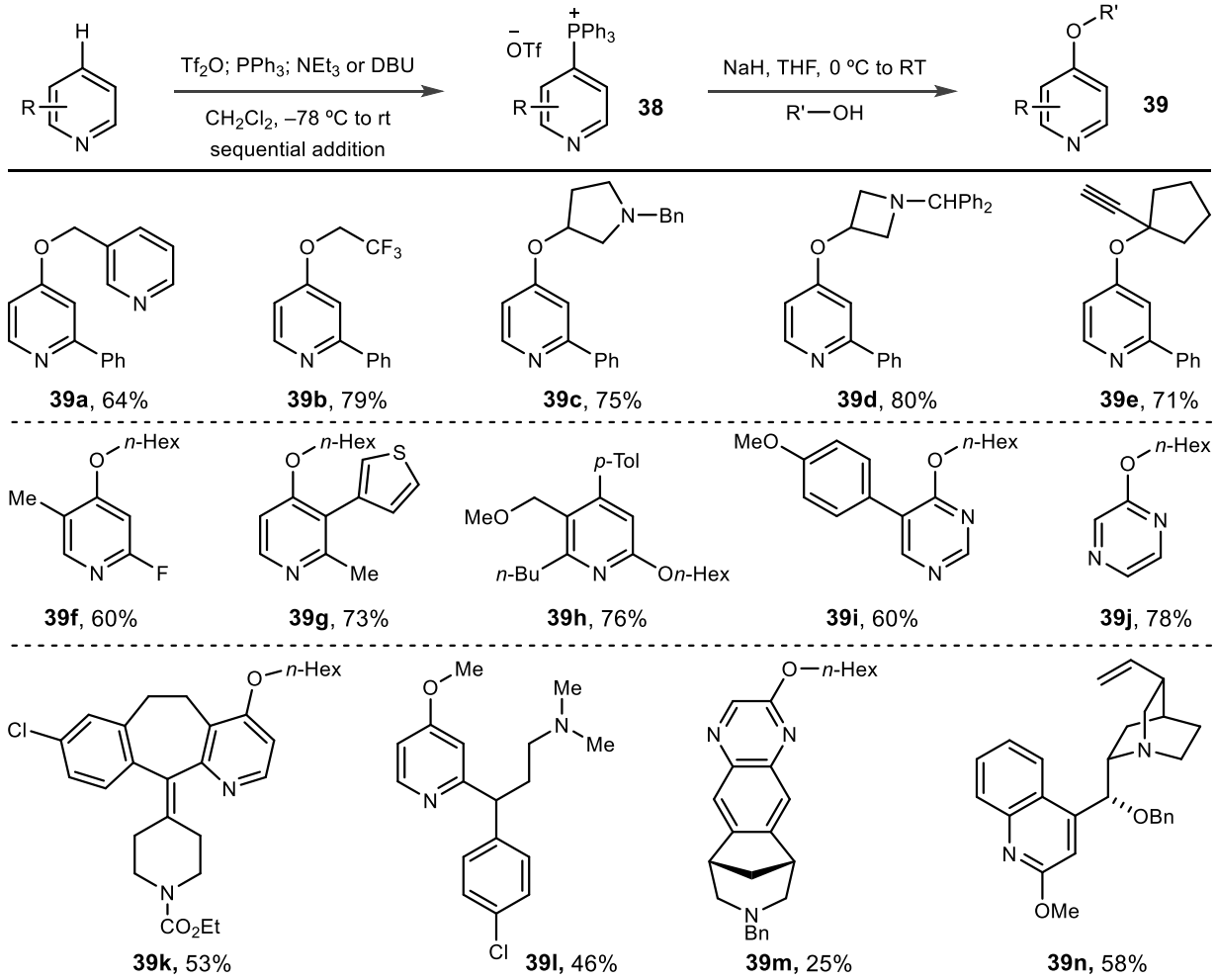

Figure 1.11 Pyridyl ether synthesis via heterocyclic phosphonium salts.

1.3.1 Heteroaryl Ether Synthesis

In 2016, coworkers in the McNally group first reported the preparation and application of heterocyclic phosphonium salts toward pyridyl ether synthesis.[34] Treating pyridyl phosphonium salts with sodium alkoxides in THF at 0 °C gave the desired ether in good yields on a scope of complex pyridines, pharmaceutical compounds, and other classes of heterocycles (**Figure 1.11**). Formation of the C–O coupled product is proposed to occur through a ligand-coupling process. Attack of the alkoxide at phosphorus results in an alkoxyphosphorane which is suited for an LC_N pathway which would produce the heteroaryl ether and triphenylphosphine. To determine if this pathway was operative, attempts to observe a phosphorane intermediate (**40**) were made via *in situ* variable temperature (VT) ^{31}P NMR. In the reaction between the phosphonium salt of 2-phenylpyridine and sodium hexan-1-olate in THF at –30 °C, a new phosphorus shift was observed at –70.64 ppm, which falls in the expected range for alkoxyphosphoranes.[35]

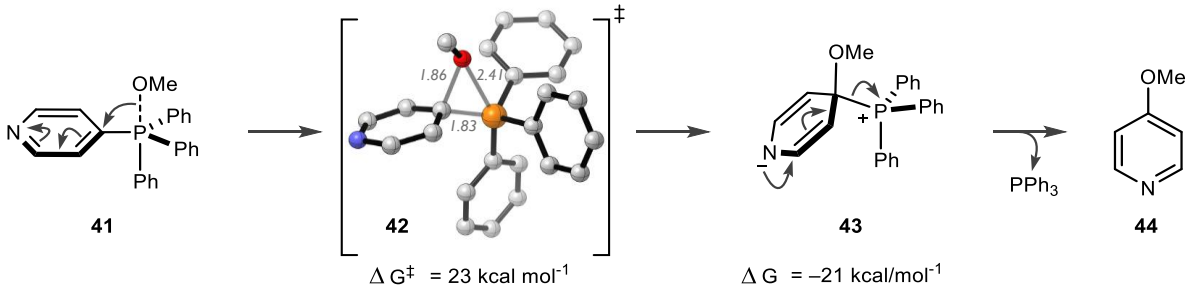

Figure 1.12 Proposed ligand-coupling mechanism for C–O bond formation.

Additional support in favor of an asynchronous ligand coupling pathway was provided through a computational study from the Paton group (**Figure 1.12**). Starting from phosphorane **41**, migration of the apical alkoxy group onto the equatorial pyridine is proposed to occur via a 3-center-4-electron bond between the phosphorus atom, pyridine *ipso* carbon, and the oxygen of the bridging alkoxy ligand, with an energy barrier of 22.9 kcal mol^{-1}. The resulting Meisenheimer-like intermediate **43** collapses to form the rearomatized ether product and triphenylphosphine. The

selectivity for alkoxy ligand migration over other possible ligand-couplings is noteworthy; the computed barrier for the unobserved phenyl migration from phosphorane **42** is 7.4 kcal mol^{-1} higher in energy. During the migration event, a build-up of negative charge occurs on the migrating atom; the ability of the alkoxy group to stabilize this negative charge build-up over the less electronegative phenyl is likely responsible for this energy difference.

1.3.2 Unsymmetrical Bipyridine Synthesis

Inspired by the seminal works in bipyridine synthesis described previously, coworkers in the McNally group developed a practical strategy for ligand-coupling between two azines (**Figure 1.13**). A phosphine with a fragmentable group (**50**) was designed that, upon phosphonium salt formation, could be cleaved via a base-mediated E1cB elimination to yield a heteroaryl phosphine (**46**).[36] This new heteroaryl phosphine could then be subjected to the salt formation conditions on another azine (**47**), allowing for the preparation of a range of bis-heterobiaryl phosphonium salts (**48**). The strategy allowed for the preparation of heteroaryl phosphines on a range of substrates in good to excellent yields. Treatment of the bis-heteroaryl phosphoniums with two equivalents of HCl in ethanol at 80 °C provided the bipyridine products (**49**), and the conditions were applied on a set of simple and complex phosphonium salts to afford valuable products that would otherwise be difficult to access.

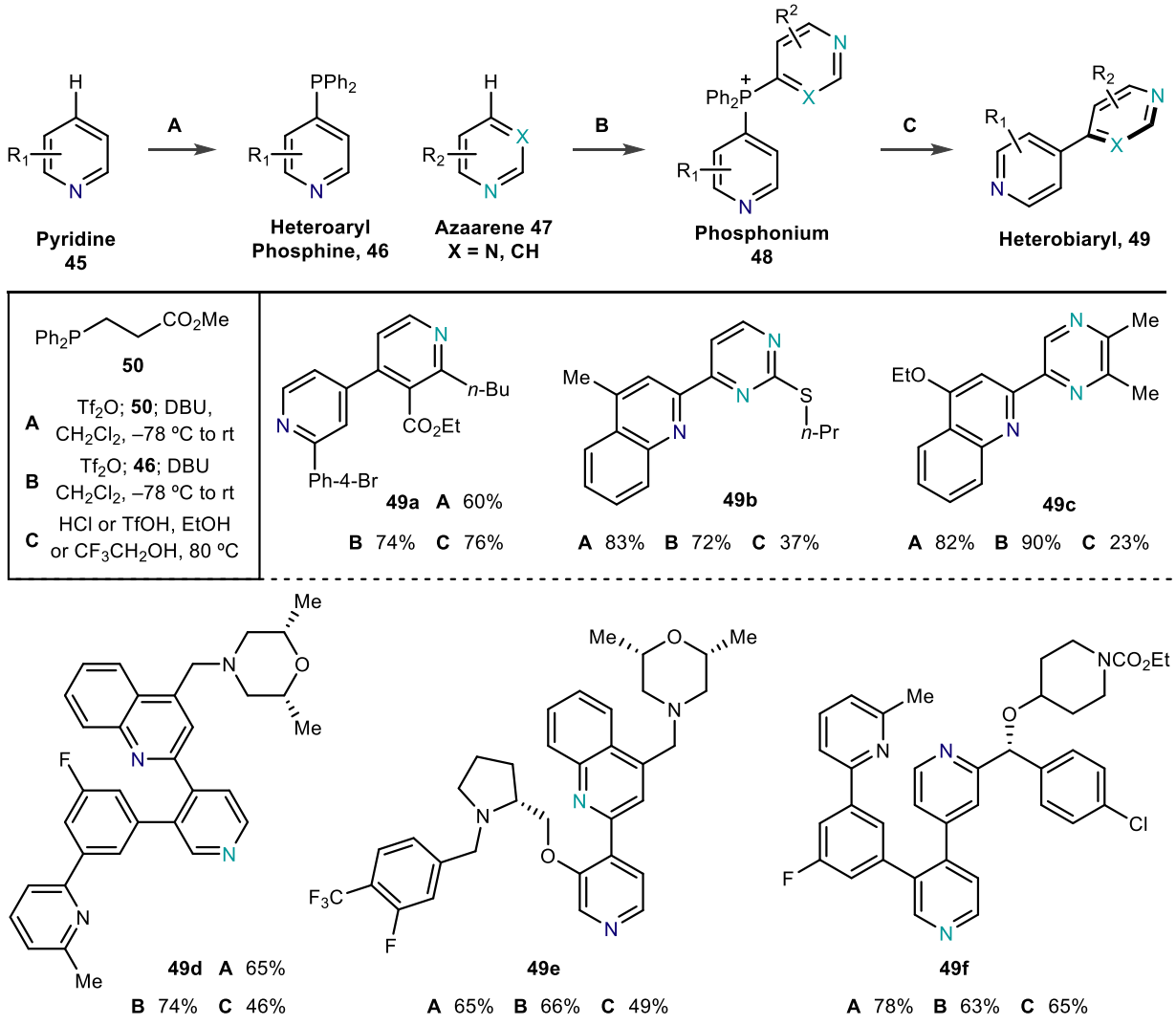

Figure 1.13 Bis-heterobiaryl synthesis via phosphorous ligand-coupling.

Based on the hypothesis that methanol attacks the phosphorus center and forms a P^V species, the Paton group investigated the conformers available to the bisheterobiaryl phosphorane. The most favored conformer was phosphorane **51** (**Figure 1.14**). σ-Withdrawing groups such as alkoxy and heteroaryl groups preferentially occupy the apical positions, while the phenyl rings and the remaining pyridine hold the three equatorial positions. The computed structure contains stronger, shorter bonds to equatorial ligands and weaker, longer bonds to those in the apical positions, indicating a dramatic *trans*-effect. The resulting weaker, more polar P–$C_{(py)}$ bond is

favored to perform a nucleophilic 1,2-migration onto the equatorial pyridine, which acts as the electrophilic acceptor (**52**, **Figure 1.14**). Successive *N*-protonation of the heterocycles decreases the activation barrier to this process significantly from 30 to 20 kcal mol^{-1} upon the first protonation, followed by a further decrease to 14 kcal mol^{-1} upon the second protonation. After migration of the P-$C_{(py)}$ bond to the *ipso* carbon of the acceptor, Meisenheimer-type intermediate **53** is formed. Intermediate **53** rapidly rearomatizes to form the desired heterobiaryl **54**, generating methyl diphenylphosphinite as a byproduct.

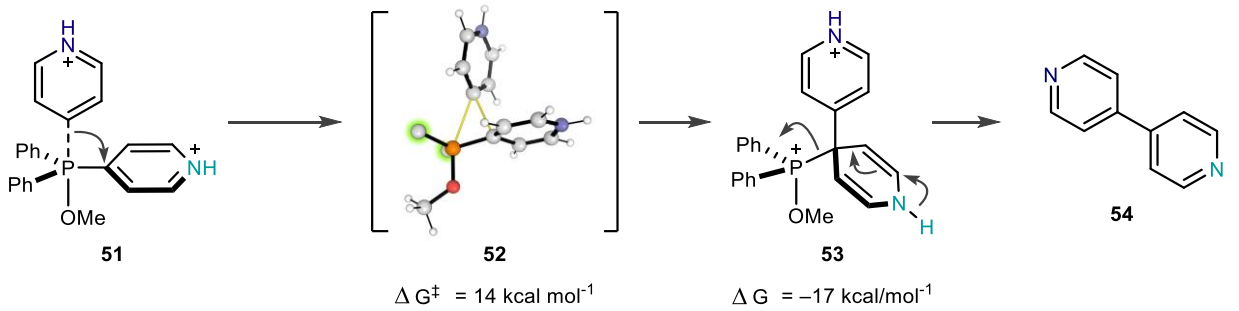

Figure 1.14. Mechanism of bis-heterobiaryl formation via phosphorus ligand-coupling.

Once again, selective coupling is achieved in this reaction. Phosphorane stereoisomers can interconvert through Berry pseudorotation, and the energy barrier to this process is typically quite low.[37,38] Coupling between the methoxy ligand and pyridine from phosphorane **51** is possible (**58**, **Figure 1.15**); however, calculations indicate that the barrier to C–O bond formation via alkoxy group migration is 4 kcal mol^{-1} higher in energy, giving exclusive selectivity for bipyridine formation experimentally. The barrier to phenyl migration is even higher in energy (**57**). The difference in ability of the pyridinium ligand to stabilize anionic charge build-up compared to the alkoxy or phenyl ligands during migration accounts for the selectivity obtained. The successful

development and mechanistic understanding of this overall strategy inspired the work discussed in Chapter 2 of this dissertation.

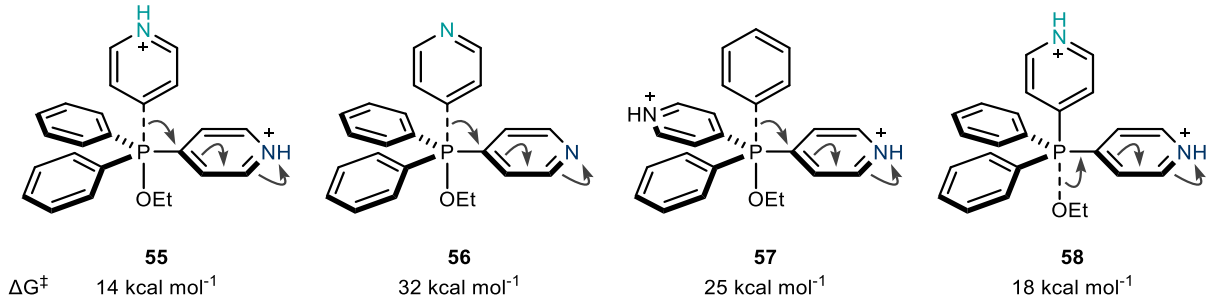

Figure 1.15 Comparison of computed barriers to ligand-coupling processes from bis-azine phosphoranes.

1.3.3. Acylfluorination of Alkynes

Tobisu and coworkers recently reported a phosphine-catalyzed acylfluorination of alkynes.[39] Treating an acid fluoride (**59**) and ynoate (**60**) with 20 mol% of tricyclohexylphosphine in toluene at 80 °C results in the formation of product **61** in 76% yield as a mixture of *E* and *Z* isomers. The authors invoke the ligand-coupling pathway proposed in **Figure 1.16**. After Michael addition to the alkyne acceptor **62**, the resulting anion is acylated by acyl fluoride **64**. Attack at phosphorus by the fluoride leaving group forms phosphorane **65**, which can undergo an LC_N by migration of the apical fluoride onto the equatorial olefin acceptor. The computed barrier to this process is quite low at only 6.9 kcal mol^{-1}. Finally, elimination of the phosphine catalyst forms the desired product and completes the cycle. The authors found that the product *E* isomer was favored in the initial stages of the reaction, but that the phosphine catalyst caused the product to isomerize closer to a 1:1 ratio of *E*:*Z* as the reaction continued to progress. While this scope of this transformation is somewhat limited and the 1,1-diacyl-2-fluoroalkene products are not highly sought after, this reaction represents the first example of a ligand-coupling process which is catalytic in phosphorus and underscores the utility of phosphorus-mediated coupling.

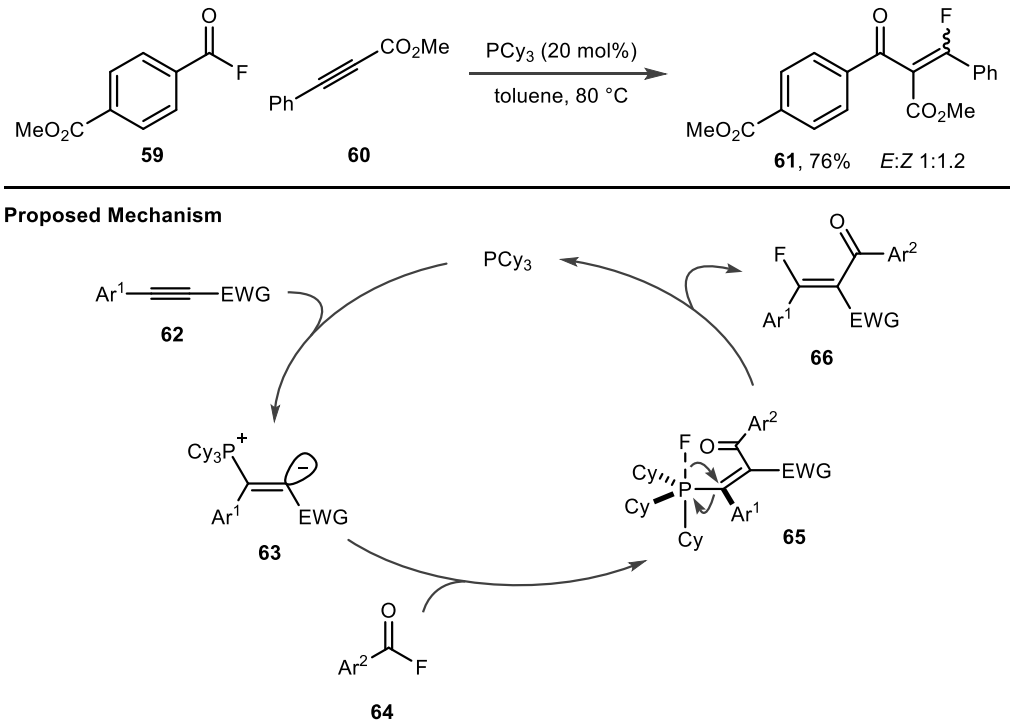

Figure 1.16 Carbofluorination via phosphorus catalysis.

1.4 Conclusion

Phosphorus ligand-coupling is a distinct reaction manifold that has practical synthetic utility but has been underdeveloped in comparison to other phosphorus-mediated chemistry. The work detailed in this chapter shows that important bond constructions including C–C, C–O, and C–F are possible through applications of this approach. Contemporary efforts to exploit phosphorus ligand-coupling in new reaction development are slowly increasing, as shown by the work in our lab as well as the Tobisu lab. The challenges to develop transformations via this strategy include accessing the desired phosphonium and phosphorane under relatively mild conditions, as well as determining systems which are suited toward both the migration and elimination steps of coupling.

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CHAPTER TWO

SELECTIVE C–H FLUOROALKYLATION OF AZINES THROUGH PHOSPHORUS LIGAND-COUPLING

2.1 Introduction to Fluoroalkylation

2.1.1 Importance of Fluoroalkyl Groups in Bioactive Compounds

The chemoselective incorporation of fluoroalkyl substituents is a powerful strategy in the design of pharmaceuticals, as these groups can have a profound influence on the metrics associated with a drug's pharmacokinetic and pharmacodynamic profiles.[1,2] Drug and agrochemical candidates increasingly contain trifluoromethyl (CF_3) and difluoromethyl (CF_2H) groups; strategic installation of these moieties can increase hydrophobic binding contacts, improve cell membrane permeability, and limit metabolic susceptibility.[3,4] In comparison to the widely applied incorporation of trifluoromethyl groups, the installation of difluoromethyl substituents has only recently begun to receive significant attention. In addition to the previous benefits, CF_2H groups also have specific roles as lipophilic hydrogen bond donors, acting as bioisosteres of hydroxyl, thiol, and amine derivatives.[5–9]

2.1.2 Importance of Pyridine Functionalization in Pharmaceutical Discovery

A recent report by Njardarson found that of all small-molecule therapeutics (MW <900 Daltons), nearly 59 % include a nitrogen-containing heterocycle (*N*-heterocycle) in their structure.[10] Pyridines are the second most prominent *N*-heterocycle, and quinolines, pyrimidines, and other diazines are also well represented. These motifs are found in a range of pharmaceuticals, including Nexium (esomeprazole), Arcoxia (etoricoxib), and Gleevec (imatinib) (**Figure 2.1**). Due

to the prevalence of azines in drugs, developing methods to selectively functionalize these molecules is of high importance.

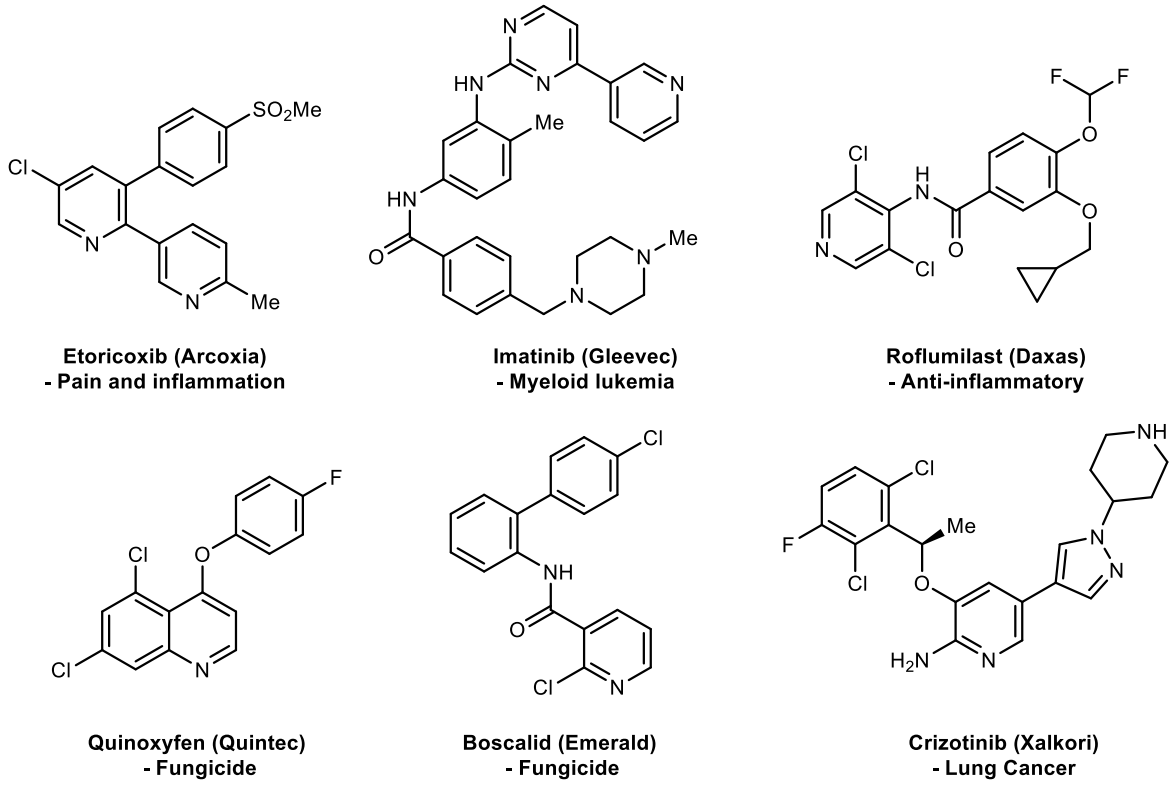


Figure 2.1 Electron-deficient azines in drugs and agrochemicals.

The popularity of the electron-deficient azines in small-molecule therapeutics is largely due to the physical and chemical properties that these motifs can introduce to a drug scaffold upon their incorporation.[11] A drug that is too hydrophobic will only accumulate at a low concentration in the bloodstream, which necessitates higher dosing. The presence of an induced dipole in the azine ring results in a polar aromatic system which is often more soluble in aqueous media. Azine incorporation thus enables a medicinal chemist to modulate the bioavailability or uptake of a drug in the circulatory system.[12,13] Drugs that pass through the liver are oxidatively metabolized by cytochrome P-450 (CYP450) enzymes. CYP450 enzymes target weak C–H bonds and form metabolic products which are easier to excrete from the body.[14] Azines are generally less

susceptible to this process in comparison to electron-rich arenes, and can be installed in a drug scaffold to tune its metabolic stability.[12,15,16]

Beyond pharmacokinetic advantages, azines can influence the performance of a drug through conformational effects. Due to the rigid structure that their sp^2 character imposes into a scaffold, azines are introduced to avoid unwanted conformers that might be present in acyclic systems. Incorporating an azine into a drug reduces its overall free-rotation, and thus the entropic cost of binding is lowered. Incorporating functional groups on the azine ring can also specifically complement binding sites of the therapeutic target.[17] Additionally, the Lewis basic nitrogen of azines is an excellent hydrogen bond acceptor that can assist in binding to the target, resulting in a more effective interaction.[11,18]

2.2 Chemical Methods for the Fluoroalkylation of Pyridine and Related Heterocycles

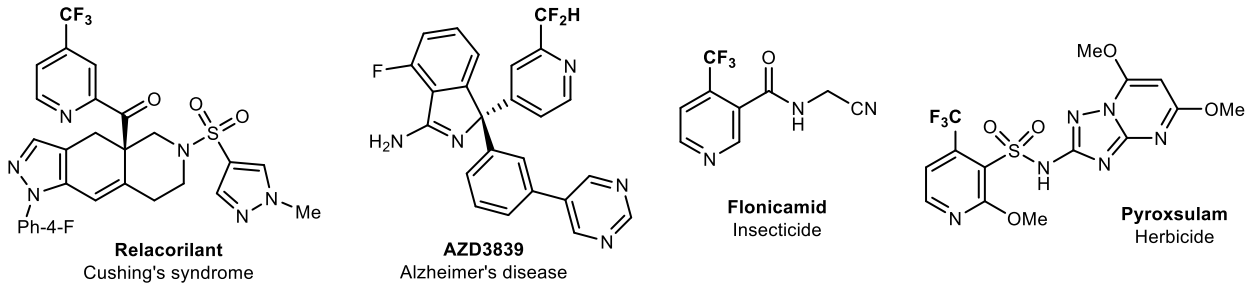


Figure 2.1 Fluoroalkyl-containing azines in pharmaceuticals and agrochemicals.

The effect of fluoroalkyl groups in structure-activity relationship (SAR) studies on azines has resulted in numerous candidates and marketed compounds (**Figure 2.2**). While incremental advances in pyridine functionalization of have been made in recent years, challenges remain, and specific methods to directly convert C–H bonds to C–CF_2X (X = F or H) on pyridine fail to meet the demand necessary for drug discovery. The electron-deficient nature and Lewis-basicity of the ring make relatively simple reactions on pyridine more difficult in comparison to other arenes. Synthesis of fluoroalkyl pyridines from acyclic precurors can provide simple building blocks, but

functionalization of existing pyridines is preferable in drug discovery. Indirect approaches require either synthesis from acyclic precursors, or preinstallation of reactive functional groups (halide, aldehyde, etc.) on the azine ring prior to the desired reaction. While this strategy may be possible on simple building-block compounds, it becomes increasingly more difficult on complex fragments and drug molecules. For instance, the classical electrophilic bromination of pyridine is an extremely harsh process, and requires refluxing pyridine in sulfuric acid in the presence of bromine.[19] Direct functionalization from the azine C–H bond is a much more appealing strategy, though regioselectivity for existing strategies is still a major challenge, leading to mixtures of regioisomers that can be difficult to separate.

2.2.1 Indirect Incorporation of Fluoroalkyl Groups on Pyridine

Several methods have been established to introduce fluoroalkyl groups onto pyridine rings via an indirect pathway from azines with preinstalled functional handles. Difluoromethylated pyridines have been prepared through the deoxofluorination of heteroaryl aldehydes with sulfur tetrafluoride, *N*,*N*-diethylaminosulfur trifluoride (DAST), and other related reagents (**Figure 2.3a**).[20–22] Treatment of (hetero)aryl carboxylic acids with SF_4 results in the trifluoromethylated product. A recent report from Mykhailiuk and coworkers demonstrated the application of this strategy on a variety of azine building blocks.[23] However, the toxicity of HF and SF_4, reagents that require special care and technical training, is a considerable downside and limits the practicality of this approach.[24]

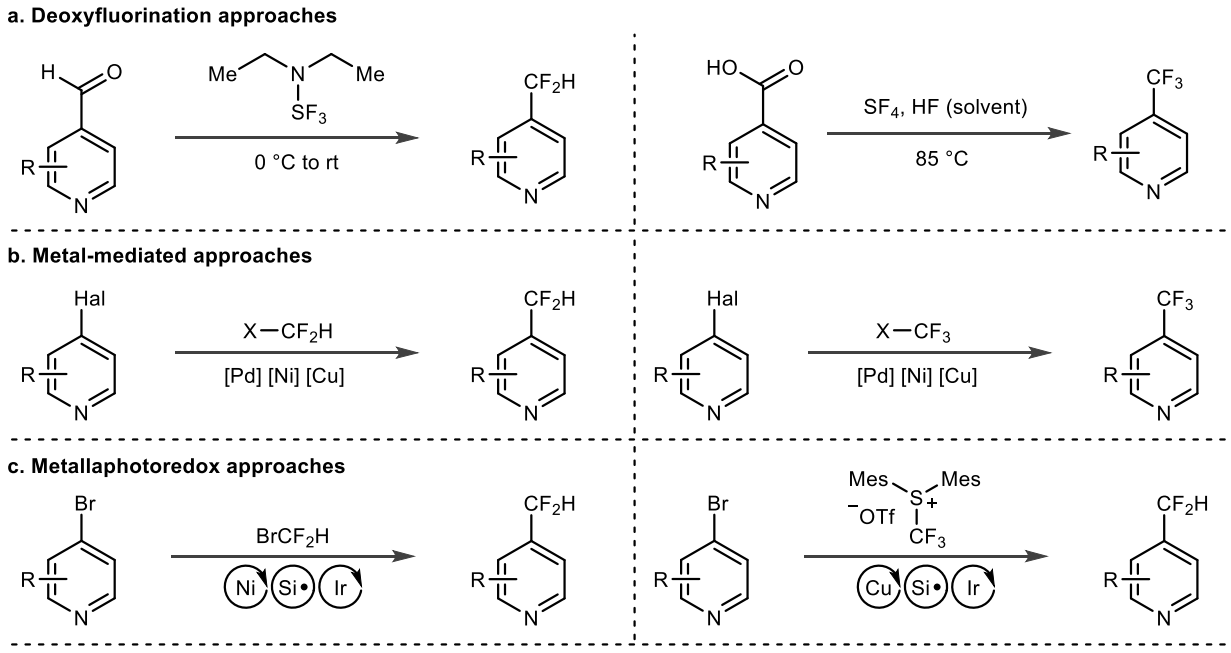


Figure 2.3. Strategies for indirect fluoroalkylation on pyridine.

A variety of di- and trifluoromethylation reactions on heteroarenes have been reported that utilize metal complexes (**Figure 2.3b**).[25,26] Olah and co-workers developed a copper-mediated difluoromethylation of (hetero)aryl iodides with tributyl(difluoromethyl)stannane.[27] Some other notable examples include using stoichiometric $CuCF_3$ reagents for nucleophilic trifluoromethylation of heteroaryl halides as demonstrated by the Grushin lab and the palladium- and nickel-catalyzed difluoromethylation of heteroaryl halides reported by the Shen and Zhang groups.[28–30] Two reports recently published by the MacMillan group established the current state of the art for di-and trifluoromethylation of heteroaryl bromides using metallaphotoredox catalysis (**Figure 2.3c**).[31,32] Both methods use mild conditions and were demonstrated on a variety of heteroaryl bromides.

2.2.2 Direct Incorporation of Fluoroalkyl Groups on Pyridine

Compared to indirect methods, direct methods for incorporation of fluoroalkyl groups on pyridine are rare. The current state of the art for direct C–H fluoroalkylation of pyridines in

complex drug-like scaffolds is Minisci-type radical addition (**Figure 2.4a**). While this approach has enabled medicinal chemists to access new chemical space with various heteroarene inputs, there exists a need for complementary approaches with distinct chemo- and regioselectivity. The Baran group published conditions for the electrophilic addition of CF_3 radical to pyridines and other heterocycles in 2011 (**Figure 2.4b**).[33] In the same year, MacMillan and co-workers developed a radical trifluoromethylation of (hetero)arenes via photoredox catalysis (**Figure 2.4c**).[34] In both cases, the regioselectivity of the reaction is a problem, and typically multiple product isomers are formed that can be a challenge to separate or identify (**Figure 2.4d, e**). Similar other works have been published by other groups that employ alternative trifluoromethyl radical precursors.[35,36]

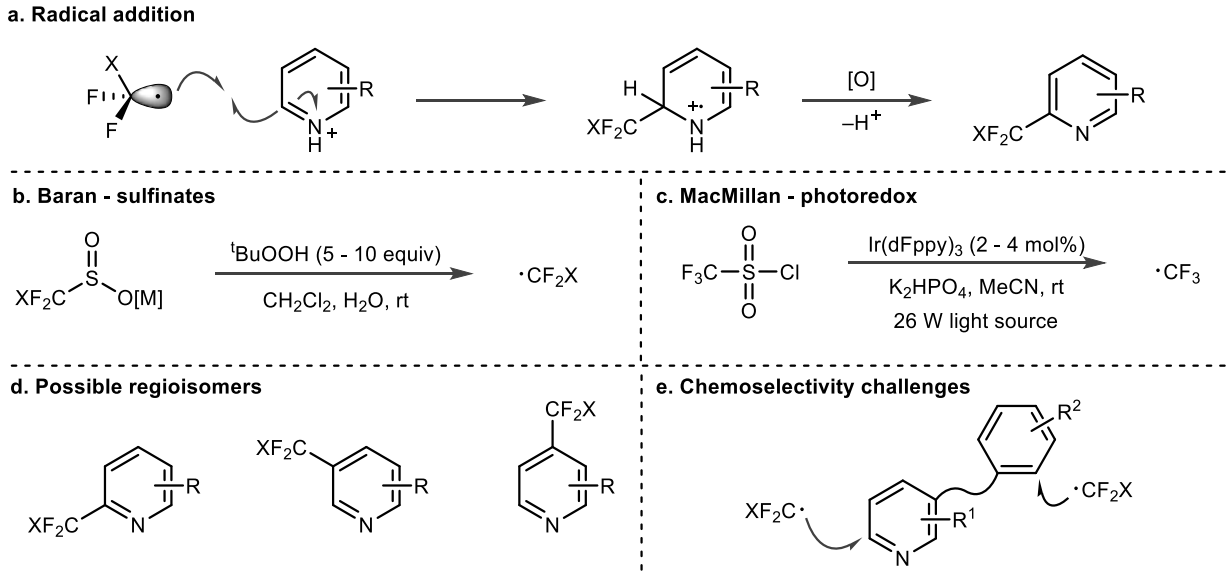


Figure 2.4 Radical addition for C–H fluoroalkylation of pyridines.

A 2016 report by Kanai and co-workers details a 4-selective process for perfluoroalkylation and perfluoroarylation through activation of azines with a strong Lewis acid. More recently, the group disclosed a 2-selective perfluoroalkylation of quinolines through a similar strategy (**Figure 2.5**).[37,38] However, the multistage protocol does not tolerate certain substitution patterns on

pyridine and requires an oxidation step after installation of the perfluoroalkyl or perfluoroaryl group. Limited evidence of the reaction's capacity to function on drug candidates reinforces the need for complementary strategies.

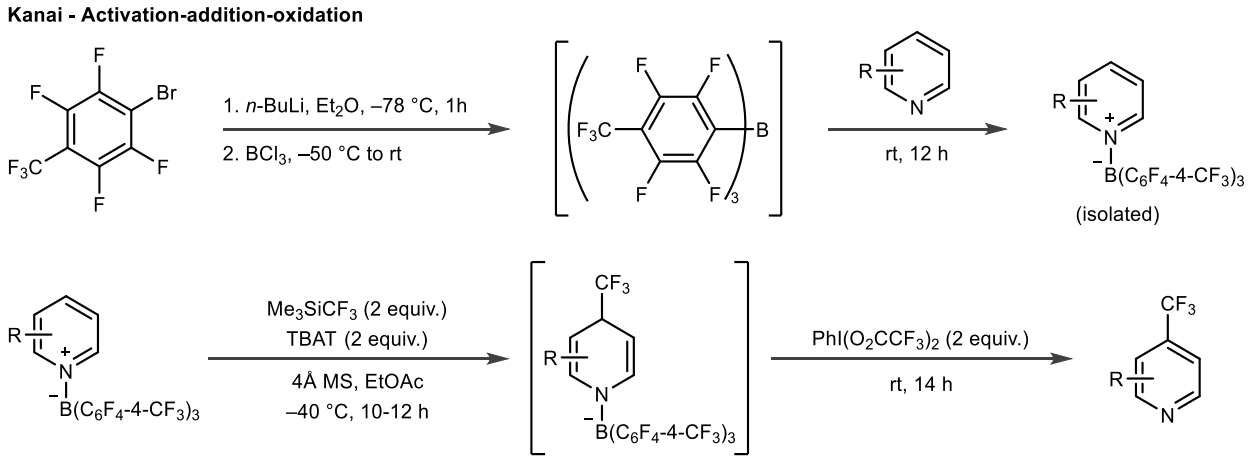


Figure 2.5 Kanai's strategy for azine fluoroalkylation.

Only a handful of reactions have been reported for the direct difluoromethylation of pyridines and other azines.[39–42] Most notable among these are the reports by the Baran and Nielsen groups which operate by generating a nucleophilic CF_2H radical which typically adds to the pyridine 2-position. While these methods allow access to highly desirable products, they also suffer from poor regiocontrol, and formation of 4-difluoromethylated pyridines is disfavored.

2.3 Phosphonium Salts as a General Functional Handle on Azines

Methods for selective functionalization at the 4-position on pyridine and other azines from C–H precursors are not just rare for organofluorine incorporation; a brief survey of the literature reveals that compared to the number of methods that install 2- and 3-position substitutents, few have been published for 4-selective installation.[43–48] The McNally group has focused on contributing to this area of the literature to provide medicinal chemists with methods that allow access to valuable 4-functionalized azine products. To ensure uptake in the medicinal chemistry

community, the reactions must be of high utility; they should be selective, operationally simple, and applicable on a broad scope of compounds.

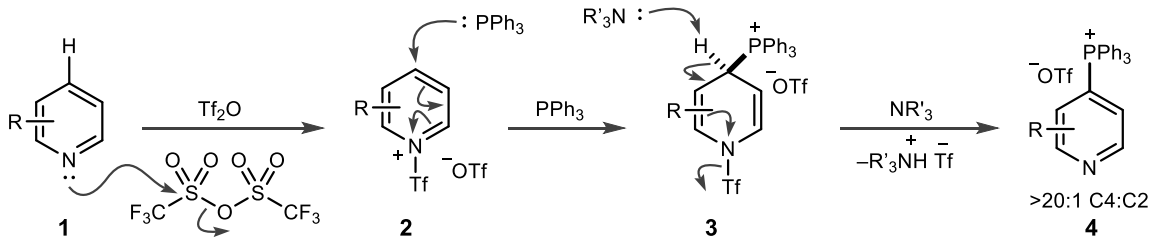


Figure 2.6 Installation of phosphonium salts on pyridine.

It was anticipated that installation of a reactive functional group from the pyridine 4-position C–H bond would enable further functionalization via a suite of reaction conditions. Coworkers in the McNally group succeeded in establishing this precedent; inspired by an initial report from Anders, it was found that phosphonium salts could be installed with precise regiocontrol on pyridines and other azines.[49–52] Sequential addition of triflic anhydride, triphenylphosphine, and an organic base (NEt_3 or DBU) at –78 °C forms the phosphonium salt by the mechanism proposed in **Figure 2.6**. In addition, it was found that not only could regiocontrol be achieved, but also switchable site-selectivity in systems containing multiple azines.[53] This methodology translated well to modification of complex drug fragments and actual drug molecules, enabling late-stage functionalization. After achieving a high level of control over installation, group efforts turned to discover applications of the phosphonium salts (**Figure 2.7**).

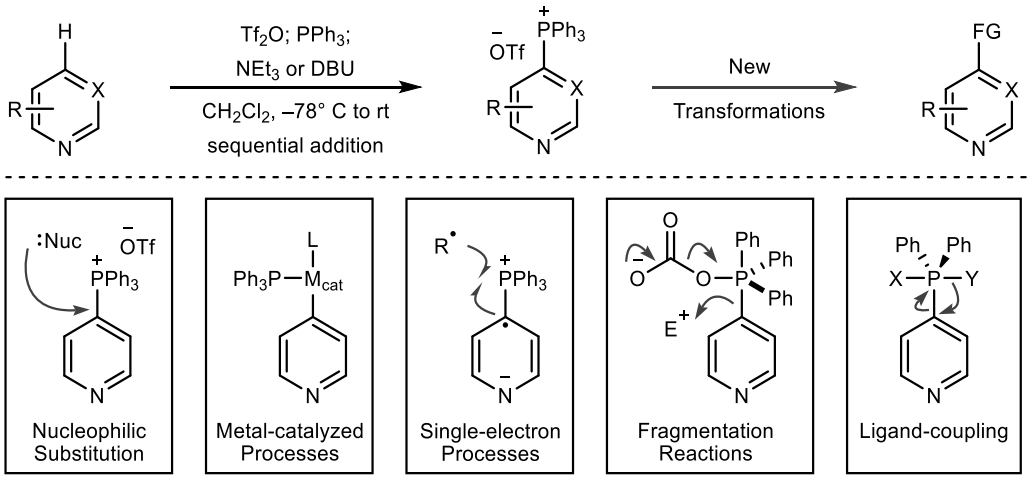


Figure 2.7 Application of heterocyclic phosphonium salts.

Heteroatom nucleophiles were tested and found to be quite effective at displacing the phosphonium handle, enabling construction of C–O, C–S, and C–N bonds at the 4-position on a broad range of substrates (**Figure 2.8a**).[54–56] The phosphonium can also serve as a pseudohalide to facilitate C–C bond formation via metal-catalyzed cross coupling reactions (**Figure 2.8b**).[57,58] Products of these reactions would be a challenge to make through conventional methods, notably because of difficulties in accessing the corresponding pyridyl halide precursor. To improve access to halopyridines an S_NAr strategy was developed that employs a designed phosphine with electron-deficient ligands. Chlorination, bromination, and iodination are achieved on both simple and complex phosphonium salts by heating to 80 °C with the lithium halide in dioxane (**Figure 2.8c**).[59] Single electron reduction of pyridyl phosphonium salts enables cross coupling with radical precursors (**Figure 2.8d**).[60–62]

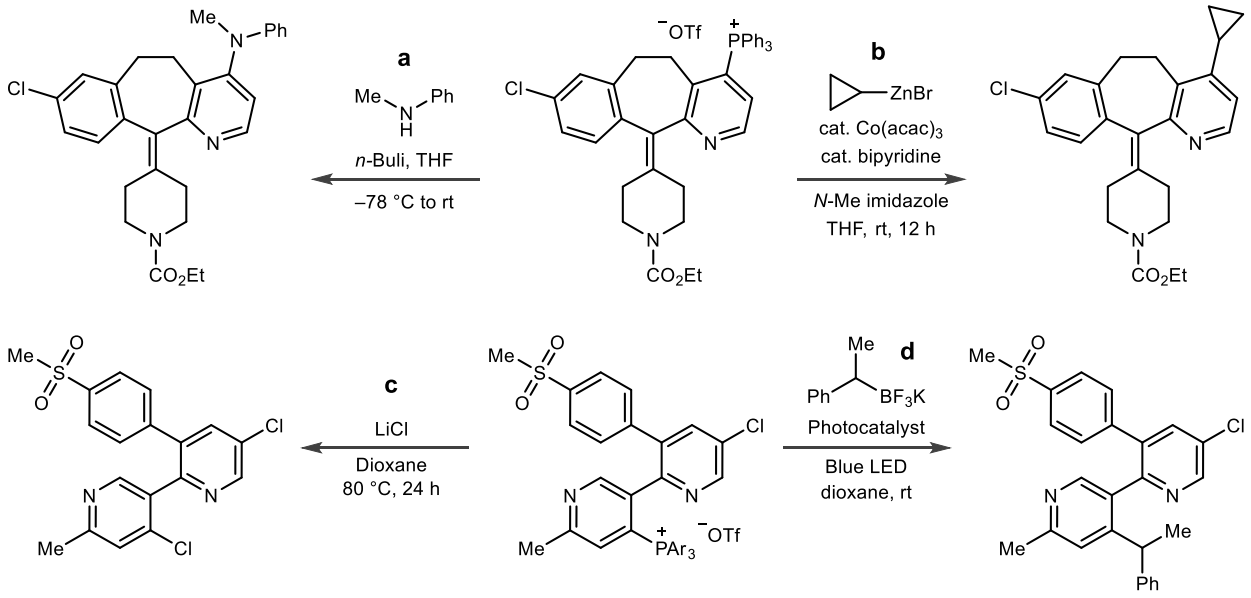


Figure 2.8 Examples of pyridine functionalization via phosphonium salts.

2.4 Design of a Phosphorous Ligand-Coupling Approach to Fluoroalkylation

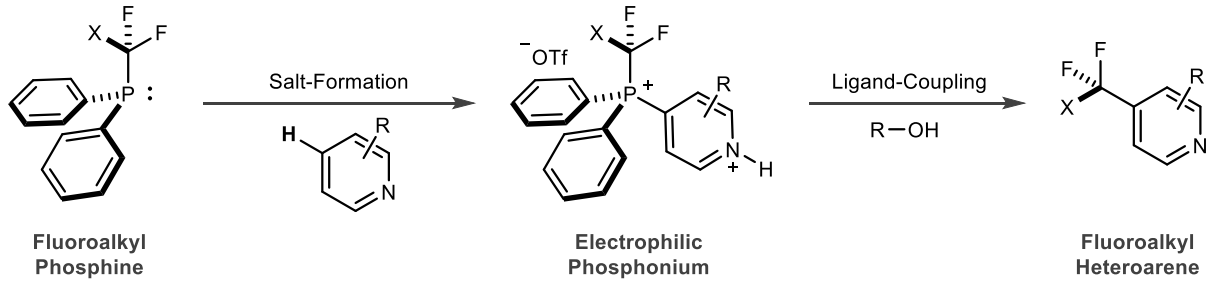


Figure 2.9 Design plan for pyridine fluoroalkylation via phosphorus ligand-coupling

We hypothesized that synthesizing fluoroalkylphosphonium salts on pyridine and triggering an LC_N process with oxygen nucleophiles would form the desired fluoroalkylated pyridine (**Figure 2.9**). While Csp^2–Csp^2 bond formation via ligand-coupling had been previously achieved using this strategy, Csp^2–Csp^3 coupling is virtually unknown. Uchida reported in 1989 that treatment of tris(2-pyridyl)phosphine oxides with benzyl Grignard reagents gave low yields of the 2-benzylpyridine amongst other ligand-coupled products.[63] However, both the lack of control over coupling selectivity and the limited accessibility of the starting materials make this approach impractical for pyridine alkylation. We reasoned that selective coupling was achievable

based on the mechanistic understanding developed for bipyridine synthesis described in **Section 1.3.2**.[64]

2.4.1 Initial Results

To determine if our hypothesized coupling reaction was feasible, phosphine **6** was synthesized using a known literature procedure.[65] Treatment of phenyl diphenylphosphinite **5** in diethyl ether with cesium fluoride and $TMSCF_3$ at room temperature gave 70% of the diphenyl trifluoromethylphosphine **6** (**Figure 2.10**). This phosphine was then applied in a modified version of our standard phosphonium formation protocol on 2-phenylpyridine (**7**). To a mixture of the phosphine and 2-phenylpyridine was added triflic anhydride at –78 °C and the mixture stirred for 1 hour. After addition of DBU at –78 °C, warming to room temperature, and an aqueous workup, none of the expected phosphonium salt (**8**) was observed. Instead, 6% of the ligand-coupled 2-phenyl-4-(trifluoromethyl)pyridine product **9** was observed by ^{1}H and ^{19}F NMR. Presumably the trifluoromethyl phosphine was not nucleophilic enough for productive phosphonium formation, and the small amount of phosphonium salt that formed was unstable to the aqueous workup conditions.

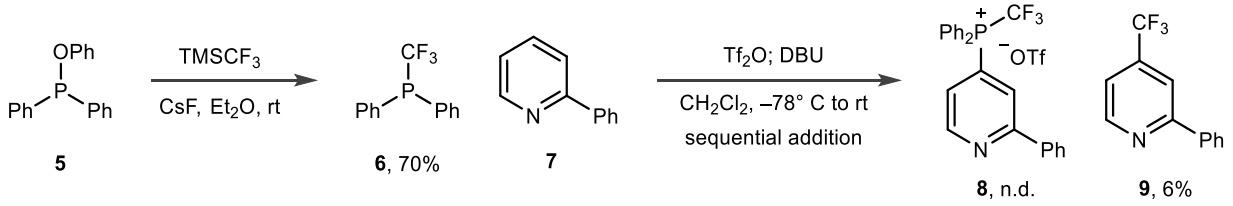


Figure 2.10 Initial attempt at fluoroalkylphosphonium salt synthesis. n.d. = not detected.

2.4.2 Optimization of Phosphonium Formation

Having validated our hypothesis, we then focused on optimizing phosphonium formation. To prepare the necessary phosphines for optimization, we employed several synthetic strategies (**Figure 2.11**). Diarylphosphine oxides **10** were prepared by addition of aryl Grignard reagents to diethyl phosphite. The first method employed for the synthesis trifluoromethyl phosphines **13-15** required reduction to the diarylphosphine **11** and careful exclusion of oxygen. Treatment of this phosphine with a modified Umemoto reagent **12** in DMF provided the desired product in good yields.[66] The difluoromethyl phosphines were initially prepared by reaction of the diarylphosphine oxides with $TMSCF_2Br$.[67] Formation of difluoromethylcarbene and addition to the diaryl oxide provided the difluoromethylphosphine oxides **16** for reduction to the desired phosphines **17**-**19**.

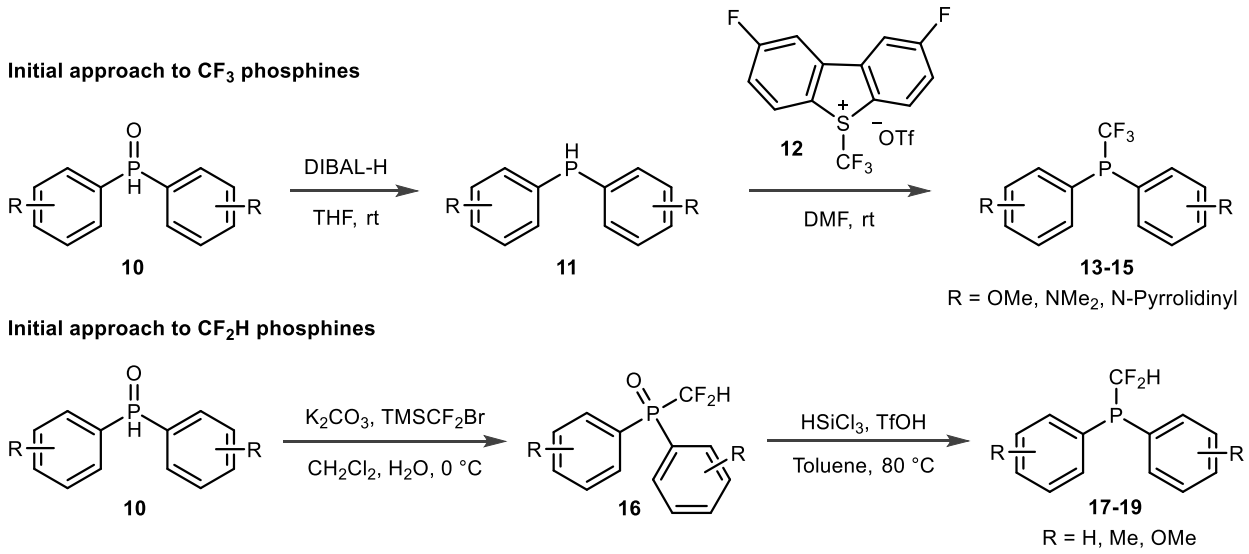


Figure 2.11 Initial strategies for fluoroalkylphosphine synthesis.

Though the initial synthetic routes to phosphines **13**-**19** were effective, we sought to address certain drawbacks. Diarylphosphine intermediate **11** is air sensitive, and isolation must be carried out in a nitrogen-filled glovebox. $TMSCF_2Br$, used to prepare **17**-**19**, is a relatively expensive difluoromethylation reagent. Fortunately, during our investigation of the

fluoroalkylation transformation, a method was published by Prakash which allows access to both trifluoromethyl and difluoromethyl phosphines from the diaryl oxide.[68] More importantly, the method uses inexpensive $TMSCF_3$ as both a CF_3 and CF_2H source, and no air sensitive intermediates need to be isolated during the synthetic sequence. The standard conditions for trifluoromethylphosphine synthesis proved unsuitable for the substrates of interest to us, yielding difluoromethylphosphine oxide as the main undesired byproduct. A brief optimization sequence led us to the conditions shown in **Figure 2.12** which provide the desired products in good to excellent yields. The standard conditions for difluoromethylphosphine oxide synthesis reported by Prakash were sufficient and no additional optimization was necessary.

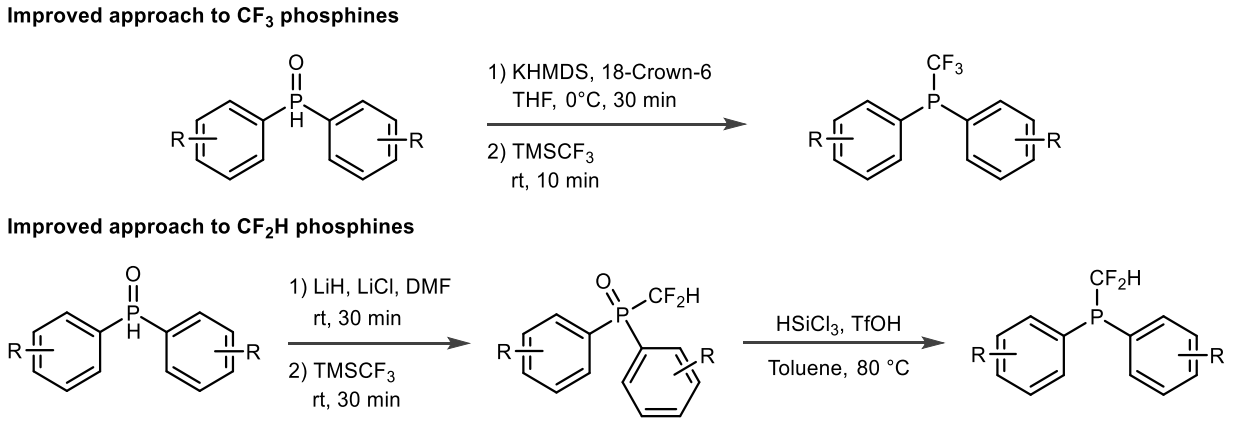
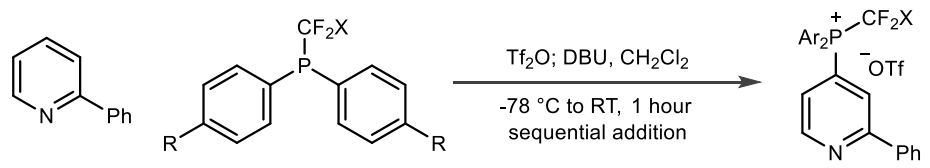


Figure 2.12 Improved synthesis of fluoroalkylphosphines.

Table 2.1 Initial optimization of fluoroalkylphosphonium formation on 2-phenylpyridine.

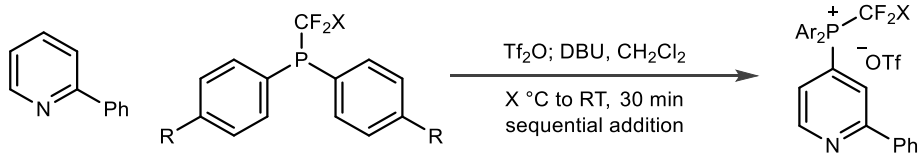


7 **13-19** X = F, **20**; X = H, **21**

Phosphine	R	X	Salt yield (%)
13	H	F	n.d.
14	OMe	F	54
15	NMe_2	F	81
16	**N-pyrrolidinyl**	**F**	**85**
17	H	H	65
18	Me	H	85
19	**OMe**	**H**	**90**

We tested a range of phosphines with *para*-substituted aryl ligands to determine the impact of electron-donating groups on phosphonium formation (**Table 2.1**). *Para*-alkylamino substituents proved optimal on 2-phenylpyridine; in a preliminary scope of substrates explored, the *p*-pyrrolidinyl (**16**) gave higher yields. A parallel study of difluoromethylphosphines **17**-**19** gave a similar trend, and due to the less electron-withdrawing nature of the CF_2H ligand, optimal yields were obtained with methoxy-substituted phosphine **19** (**Table 2.1**). An investigation into the temperature for triflic anhydride addition affirmed that our previously established phosphonium-forming reaction parameters (–78 °C for Tf_2O addition, DBU as the optimal organic base, etc.), were compatible with phosphines **16** and **19** (**Table 2.2**).

Table 2.2 Continued optimization of phosphonium formation.

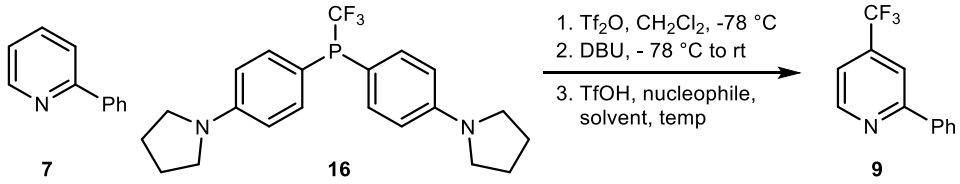


7 **13-19** X = F, **20** X = H, **21**

Phosphine	R	temp (°C)	base	Salt yield (%)
16	N-pyrrolidinyl	–30	DBU	76
16	N-pyrrolidinyl	–50	DBU	81
16	**N-pyrrolidinyl**	**–78**	**DBU**	**85**
18	Me	–78	NEt_3	79
18	Me	–78	TBD	51
18	Me	–78	MTBD	82
18	Me	–78	TMG	70
18	Me	–78	DBU	84
19	OMe	–50	DBU	68
19	**OMe**	**–78**	**DBU**	**90**

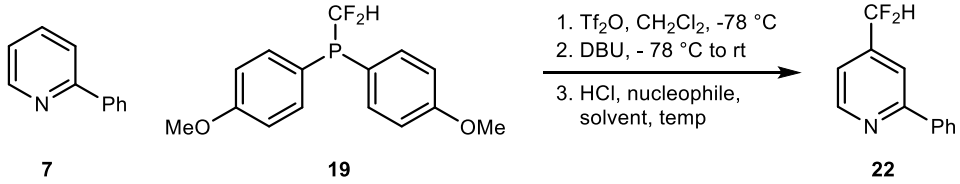
Efforts then turned to optimizing the ligand-coupling stage of the reaction. Our initial observation that coupling occurred after a simple aqueous wash of the reaction mixture indicated that these phosphonium salts were particularly prone to ligand-coupling. We rationalized that a one-pot coupling process was feasible, and that adding acid (to protonate the pyridine and enhance electrophilicity of the phosphonium) and water to the crude phosphonium reaction and stirring at room temperature would yield the desired product. **Tables 2.3** and **2.4** show the optimization of ligand-coupling for both trifluoromethylation and difluoromethylation. In both cases, addition of water, methanol/ethanol, and acid (1-1.5 equiv. of HCl or TfOH) to the crude phosphonium reaction mixture were sufficient to provide the coupled product in high yield and in 12-24 hours.

Table 2.3 Optimization of ligand-coupling for trifluoromethylation.



nucleophile	temp(°C)	solvent	time	X yield (%)
MeOH	40	MeOH	>48 h	-
H_2O	**RT**	**MeOH**	**12 h**	**84**
H_2O	RT	THF	12 h	79
H_2O	RT	EtOH	12 h	80
H_2O	RT	iPrOH	12 h	75
$NaHCO_3$	RT	THF	24 h	73
$NaHCO_3$	**RT**	**THF/H_2O**	**30 min**	**78**

Table 2.4 Optimization of ligand-coupling for difluoromethylation.



nucleophile	temp(°C)	solvent	time	X yield (%)
MeOH	40	MeOH	>48 h	-
H_2O	RT	MeOH	>48 h	-
H_2O	40	MeOH	36 h	79
H_2O	40	EtOH	24 h	81
H_2O	40	THF	24 h	79
H_2O	40	iPrOH	24 h	80
TBAF	40	THF	14 h	75
K_2CO_3	RT	H_2O/THF	15 min	64
$NaHCO_3$	RT	H_2O/THF	15 min	43

Using the optimized conditions, we directly obtained fluoroalkyl pyridine derivatives from their C–H precursors without isolation of the intermediate phosphonium salts. Our previous study of bipyridine synthesis found that the rate determining step in ligand coupling was addition of the nucleophile to the phosphonium salt, requiring temperatures of 80 °C to achieve coupling

overnight. The withdrawing effect of the fluoroalkyl groups presumably makes this addition more facile, enabling coupling at room temperature (–CF_3) or 40 °C (–CF_2H), reflecting the relative electrophilicities of phosphoniums **20** and **21**.

2.4.3 Fluoroalkylation Scope: Simple Examples

The scope of the trifluoromethylation protocol was then investigated on a range of building block azines (**Figure 2.13a**). In general, the coupling proceeds in 12 hours between room temperature and 40 °C on the substrates tested. The couplings on **23** and **24** provide the monotrifluoromethylated product with exclusive selectivity directly from the C–H precursors. 2-amino substituted pyridines **25** and **33** are less efficient in the coupling and provide low yields of product. 3-aryloxypyridine **26** formed in high yield, and the reaction also tolerates amide functionality, providing **27** in moderate yield despite the proclivity for amides to react with Tf_2O.[69] A series of 2,5-disubstituted pyridines gave good yields of coupled product, and underscore the reaction's tolerance for imides, esters, alkynes and halogens (**29-32**). Standard conditions lead to hydrolysis of ester **30**, but alternative coupling conditions discovered during optimization ($NaHCO_3$, H_2O in THF) avoid the undesired side reaction. We propose nucleophilic addition of bicarbonate to the phosphonium acts as the trigger for ligand-coupling in this instance without requiring protonation of the pyridine, as this pathway to phosphorane formation was previously

exploited by our group in a pyridine deuteration protocol.[60] A set of 2,3-disubstituted pyridines were successfully trifluoromethylated (**34** and **35**) as well as 3,5-disubstituted example **36**.

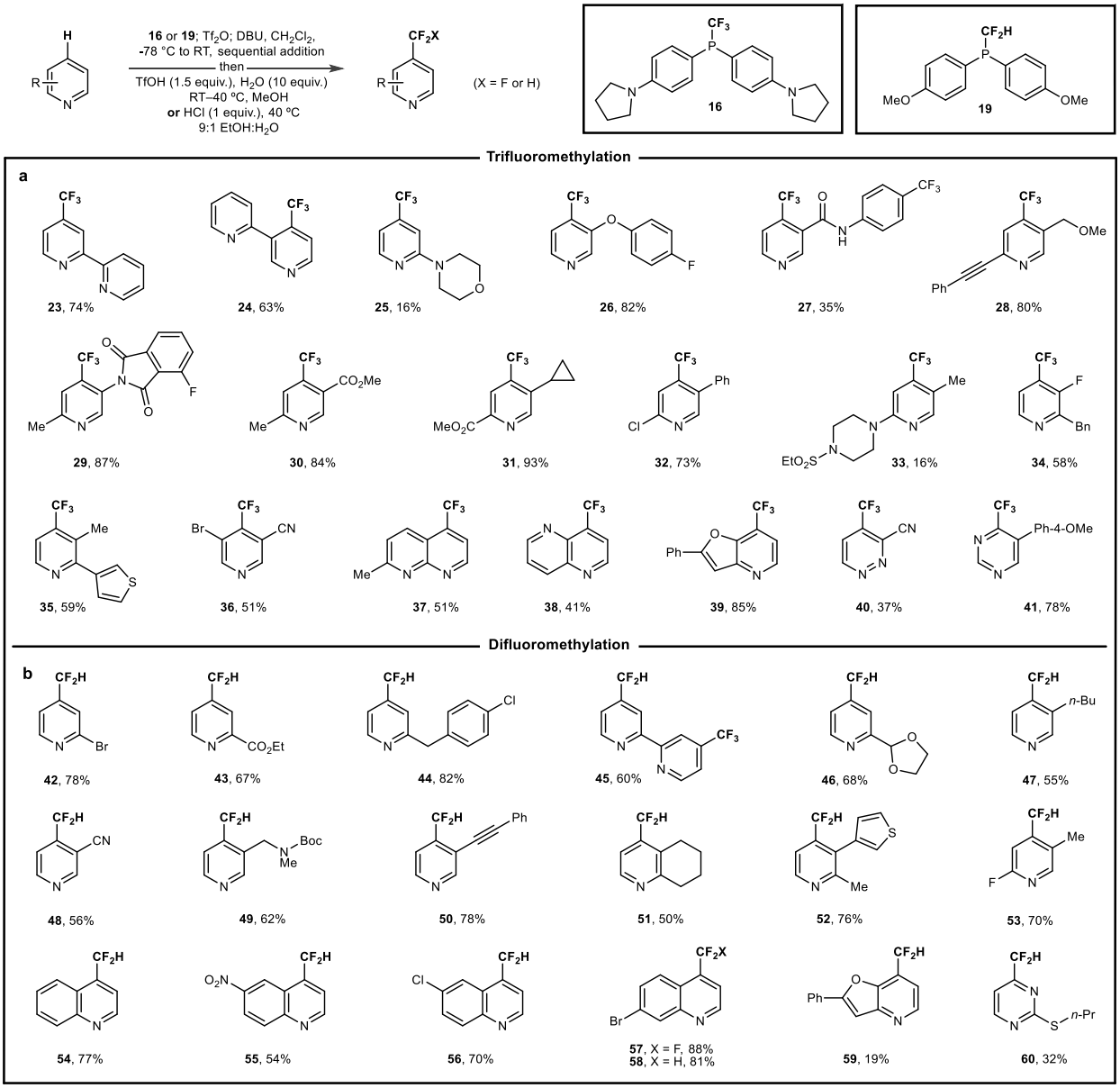


Figure 2.13. Building blocks tested for trifluoromethylation and difluoromethylation.

Fused heterocycles are also tolerated, including naphthyridines (**37** and **38**) and a furopyridine (**39**). Preliminary results for the coupling on diazines are promising, as both **40** and **41** give the desired product in moderate yields.

Current limitations for trifluoromethylation include substrates for which phosphonium formation is unsuitable, such as 2,6-disubstituted pyridines and 2-CF_3 pyridines, where activation of the pyridine nitrogen by triflic anhydride is disfavored. Additionally, functional groups which are not compatible with Tf_2O, including alcohols and *N*-alkyl amides, also fail to deliver the desired phosphonium. Despite giving good yields of the phosphonium, substrates with donating groups at the 3-position of the pyridine ring, such as amines and alkoxy groups, provide yields below 10% in the ligand coupling stage of the process.

Figure 2.13b shows that a similar set of building block azines to those explored for trifluoromethylation are amenable for ligand-coupling with CF_2H. A notable example is bipyridine **45** which was successively difluoromethylated from substrate **24**. 2-Halopyridines such as **42** gave a peculiar result upon attempted coupling under acidic conditions; the phosphonium persisted in the reaction mixture even upon heating to 80 °C, presumably because the withdrawing 2-substituent prevents sufficient activation of the pyridine nitrogen to achieve the necessary phosphonium electrophilicity for the addition of water. Coupling under basic conditions alleviates this issue and provides the desired product in high yield. The reaction operates on acid-sensitive functional groups including *tert*-butoxycarbonyl protected **49** and ester **43**. Acetal **46** was hydrolyzed under standard conditions, but replacement of water with TBAF in THF delivered the difluoromethylated product with the protecting group intact. In this case coupling may proceed by either a fluorophosphorane intermediate or from residual amounts of water in the reaction mixture.[59,70,71] As was the case for trifluoromethylation, 2,3- and 2,5-disubstituted examples (**51-53**) are amenable, in addition to quinolines, a furopyridine, and a pyrimidine (**54-59**).

The limits for difluoromethylation comprise those described previously for trifluoromethylation and some which are specific to CF_2H installation. Pyridines with halogen or

ester substituents at the 3-position and pyridines with substituents at both the 3- and 5-positions gave yields of less than 10%; protiodephosphination is the dominant reaction pathway in these cases and returns the pyridine starting material. This ligand exchange pathway seems to be favored over migration of the difluoromethyl group when certain electronic or steric constraints are imposed on the pyridine ring. Phosphonium formation occurs at the 2-position of pyridines when the 4-position is blocked but applying the difluoromethylation conditions results in protiodephosphination as the sole reaction pathway. This was also observed for trifluoromethylation although a notable exception is that ligand-coupling of the CF_3 group is viable at the 2-position of quinolines.

2.4.4 Fluoroalkylation Scope: Complex Azines, Pharmaceuticals, and Agrochemicals

We then focused on demonstrating that this approach to fluoroalkylation was applicable to fragments representing drug-like intermediates and lead compounds (**Figure 2.14a**). These substrates are structurally diverse and serve as representations of what practicing medicinal and agricultural chemists routinely encounter and seek to functionalize. They are particularly challenging to modify, as they generally lack pre-installed functional handles or biases towards selective reaction outcomes for radical-based fluoroalkylation chemistry. Notable examples include quinoline **64**, where trifluoromethylation occurs at the 2-position, and esters **70** and **71**, where solvolysis is avoided with the use of our modified TBAF conditions to deliver both fluoroalkylated products in good yield. Furthermore, polyazines are well-suited toward our method; site-selective fluoroalkylation in **65-68** results from selective *N*-Tf activation of the 3-subsituted pyridines over the tethered 2-substituted pyridines during the phosphonium formation stage.[53]

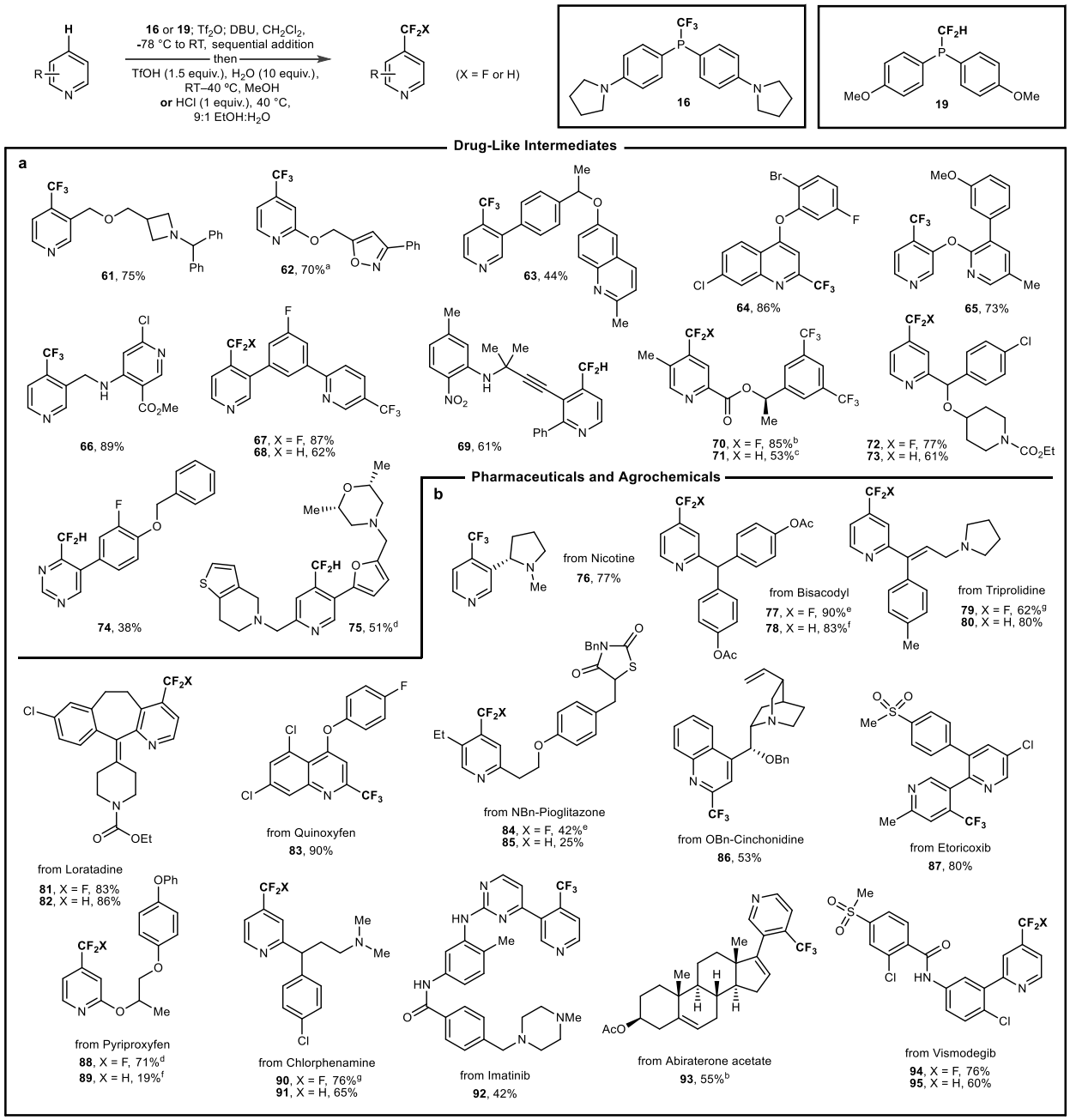


Figure 2.14 Direct fluoroalkylation of complex azine-containing molecules.

The introduction of new functionality on advanced drug and agrochemical candidates later in their synthesis, referred to as late-stage functionalization, is an ideal strategy to identify compounds with superior properties. This approach can save time and money by circumventing the need to design synthetic routes to new derivatives. Our fluoroalkylation strategy was used to

transform 11 different pharmaceuticals and two agrochemicals into their fluoroalkyl derivatives (**Figure 2.14b**). Once again, we obtained products as single regioisomers, demonstrating a scope and regioselectivity profile that is different from Minisci-type fluoroalkylation processes.

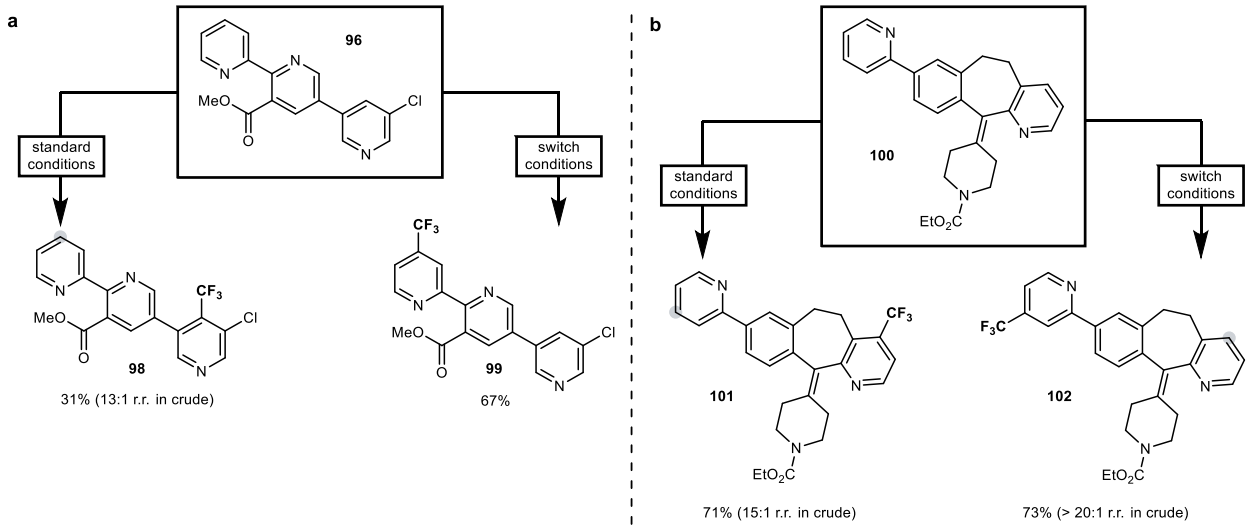


Figure 2.15 Application of site-selective switching strategy to trifluoromethylation of polyazines.

An advantage of radical addition approaches to fluoroalkylation is that on polyazines, multiple regioisomers form, and these can all be tested as viable drug analogues. To emphasize the ability of our trifluoromethylation approach to access multiple regioisomers with site-selectivity in polyazine systems, we applied our previously reported protocol for switching the selectivity of C–P bond formation on an MK-1064 precursor (**Figure 2.15a**) and a loratadine derivative (**Figure 2.15b**). Using our standard conditions, trifluoromethylation occurs with selectivity for the kinetically preferred 3-subtituted pyridine during reaction with Tf_2O (**98** and **101**). Applying the base-switch protocol, using NEt_3 as well as 2 equiv. of Tf_2O and **16** allowed us to prepare the regioisomeric products with excellent control of 4-position selectivity and site-selectivity (**99** and **102**). The switch in selectivity occurs due to an inability of NEt_3 to rearomatize

3-carbon-bearing *N*-Tf adducts, while the 2-subsituted equivalent is rearomatized to the phosphonium without issue.

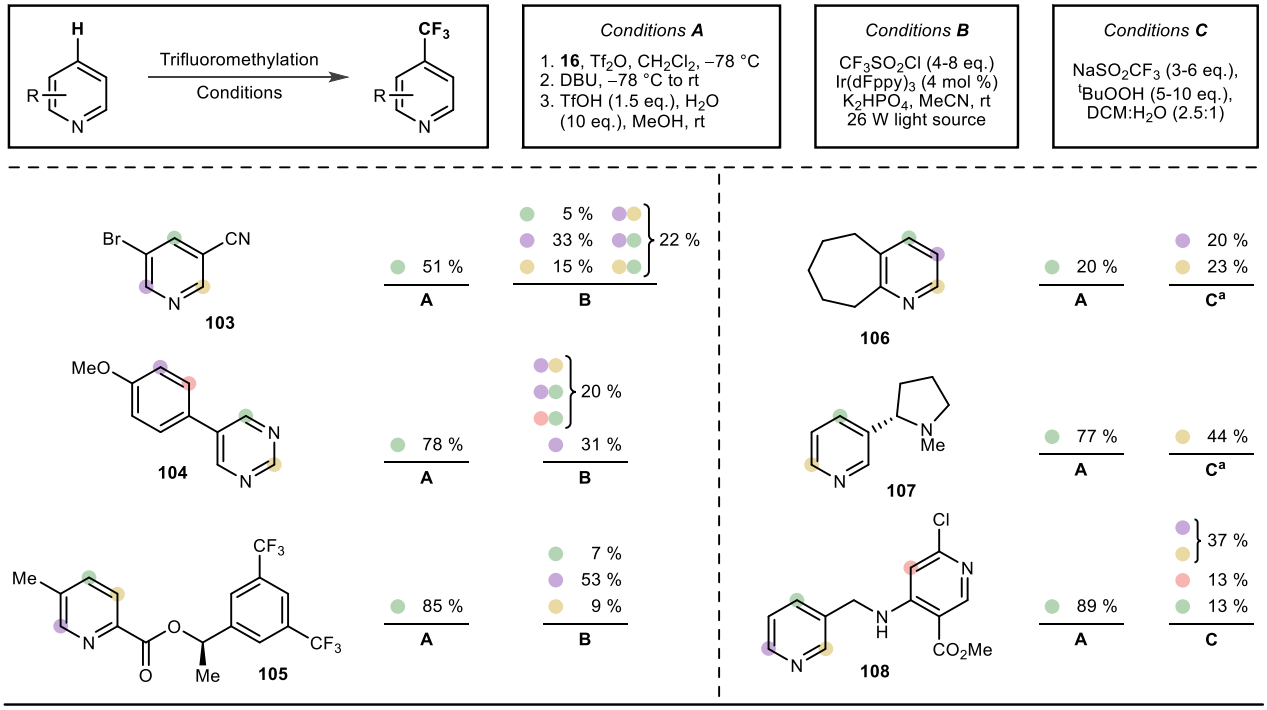


Figure 2.16 Comparison of regioselectivities for phosphorous mediated fluoroalkylation to radical-based approaches.

To provide evidence of distinct regioselectivity, direct comparisons were made between Baran's and MacMillan's approaches to our ligand-coupling approach on a set of substrates that are compatible with all three methods (**Figure 2.16**). MacMillan's approach provided complex mixtures of regioisomers as shown in substrates **103-105**. Notably, the 4-position regioisomer was often the minor isomer (**103 and 105**) or could not be obtained due to addition of the trifluoromethyl radical to both the pyridine tehtered arene ring (**105**). Baran's strategy also disfavored 4-position addition, often providing 2- or 3-substituted products instead (**106** and **107**). The 4-position isomer formed on **108**, but in low yield, and separation of the multiple isomers that formed was challenging.

2.4.5 Additional Polyfluorinated Coupling Partners

Based on the hypothesis that other polyfluorinated coupling partners should perform favorably during ligand-coupling, we designed and synthesized phosphines **109** and **110** (**Figure 2.17**). 4-(perfluoroethyl)-2-phenylpyridine **111** was prepared in excellent yield, validating this hypothesis. Similarly, perfluoroaryl phosphine delivered the coupled product **112** in 85% yield. Future efforts to develop these processes are ongoing in our laboratory.

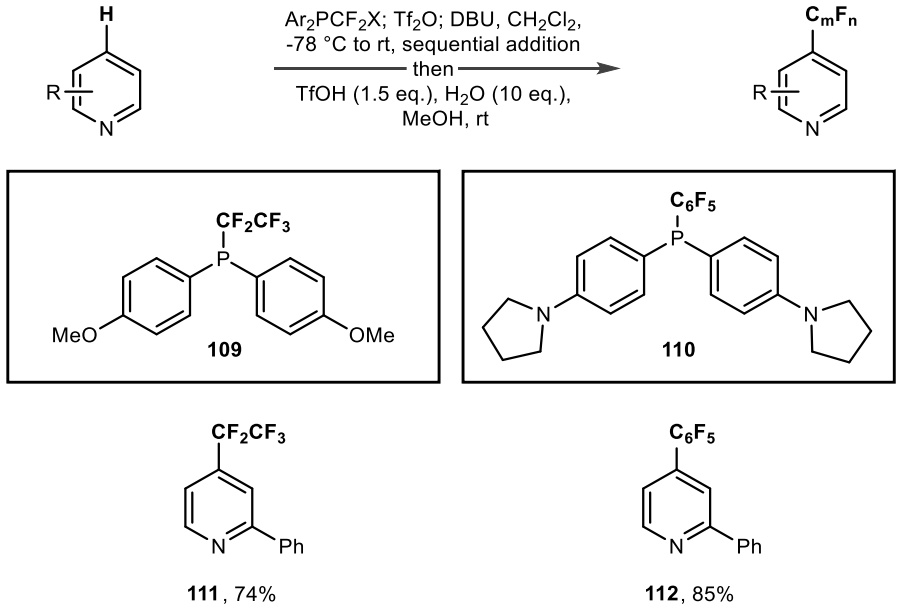


Figure 2.17 Preliminary results for other polyfluorinated coupling partners.

2.5 Mechanism

2.5.1. Computational Probe of the Reaction Mechanism

The Paton lab performed computational analysis of the trifluoromethylation reaction mechanism to help rationalize the reaction outcome (**Figure 1.18**). Their study indicates that upon formation of phosphorane **113** from the phosphonium, the C–P bond to the apical trifluoromethyl group weakens due to the trans-effect, which is indicated by a pronounced bond lengthening from 1.9 to 2.1 Å. Simultaneously, accumulation of negative charge on the CF_3 ligand (–0.16 to –0.43

e) occurs, preempting migration as electron density from the C–P σ-bond is donated into the π* molecular orbital of the equatorial pyridinium ring. In the ligand-coupling transition state, the trifluoromethyl group stretches to 2.8 Å and accumulates up to –0.50 e of charge in the 3-center, 4-electron bond between the phosphorus atom and *ipso* pyridine carbon (**114**). The barrier to this process is 19 kcal mol^{-1}, which is achievable at room temperature. For difluoromethylation the barrier to ligand migration is also 19 kcal mol^{-1} (**115**). The resulting intermediate **116** rearomatizes to provide trifluoromethylated pyridine and hydroxydiphenylphosphine, which rapidly tautomerizes to diphenylphosphine oxide.

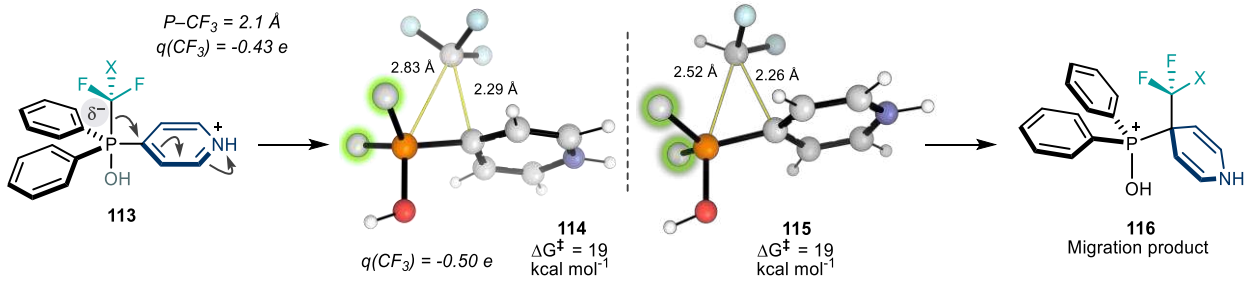
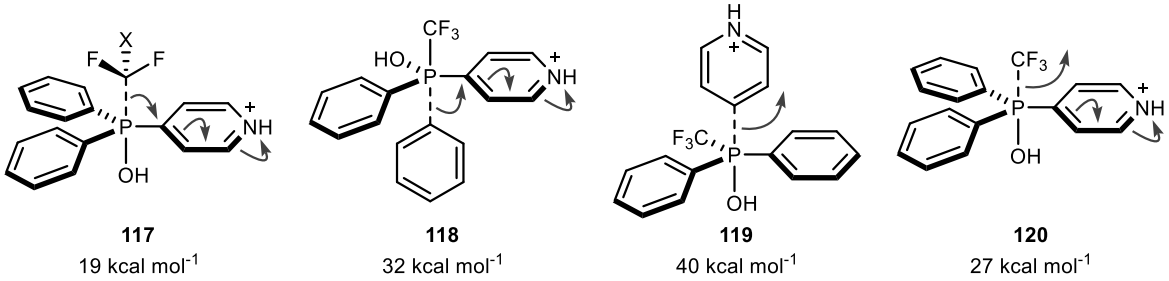


Figure 2.18 Computational study of the fluoroalkylation mechanism.

2.5.2 Rationalization of Ligand-Coupling Selectivity

Previous ligand-coupling reactions in the lab delivered excellent selectivity for the desired coupling over undesired pathways. For fluoroalkylation, the energy barriers for other potentially competitive mechanistic pathways were determined and are presented in **Figure 2.19**. Phenyl migration (**118**) is substantially less favorable compared to CF_3 migration ($\Delta G^{\ddagger}$ = 32 kcal mol^{-1}). We hypothesize that migration of fluoroalkyl groups is preferred due to the superior ability of these ligands to stabilize anionic charge build-up in the transition state.



117 19 kcal mol^{-1} **118** 32 kcal mol^{-1} **119** 40 kcal mol^{-1} **120** 27 kcal mol^{-1}

Figure 2.19 Comparison of CF_3 migration to other pathways from the phosphorane intermediate.

Ejection of apical ligands through ligand exchange processes were also considered, and these pathways were sometimes observed experimentally. Based on the computed barrier of 40 kcal mol^{-1}, protiodephosphination to form pyridine from **119** is non-competitive. We expect that withdrawing groups at the 3-position and sterically bulky substituents at the 3- and 5-positions lower this barrier considerably, as this outcome has been observed experimentally for difluoromethylation as part of the limitations discussed in **Section 2.4.3**. Protonation of the CF_3 group to deliver the pyridylphosphine oxide was also observed on some substrates (**120**). The computed barrier to this process (27 kcal mol^{-1}) is still much higher than the barrier to fluoroalkylation but may become viable in cases where the pyridine is a poor acceptor.

2.6 Conclusion

A new strategy for C–H pyridine fluoroalkylation based on phosphorus Csp^2–Csp^3 ligand-coupling was developed. New phosphines were designed which are used to prepare pyridylphosphonium salts, and adding an acidic aqueous solution forms the fluoroalkylpyridine products in a one-pot process. A computational investigation indicates that fluoroalkyl groups are suited toward facile LC_N reactions due to their capacity to stabilize negative charge buildup at the apical positions of phosphorane intermediates. This method offers a complementary approach to Minisci-type fluoroalkylation reactions and was applied not only on simple building block

pyridines, but also on advanced intermediates and toward the late-stage functionalization of several drugs and agrochemicals.

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CHAPTER THREE

INVESTIGATION OF MIGRATION SELECTIVITY FROM P^V SPECIES FOR THE ALKENYLATION OF PYRIDINES

3.1 Importance of Alkenylpyridines

Alkenylpyridines serve as important pharmaceutical cores, such as in triprolidine, vorapaxar, and axitinib, as well as strategic intermediates in the synthesis of natural products and drug molecules (**Figure 3.1**).[1–4] Additionally, simple vinylpyridines serve as monomers for polymer synthesis and can function as reagents for cysteine-selective bioconjugation and covalent inhibition.[5,6] Accordingly, the expedient synthesis of alkenyl pyridines from simple starting materials is of high priority to synthetic chemists.

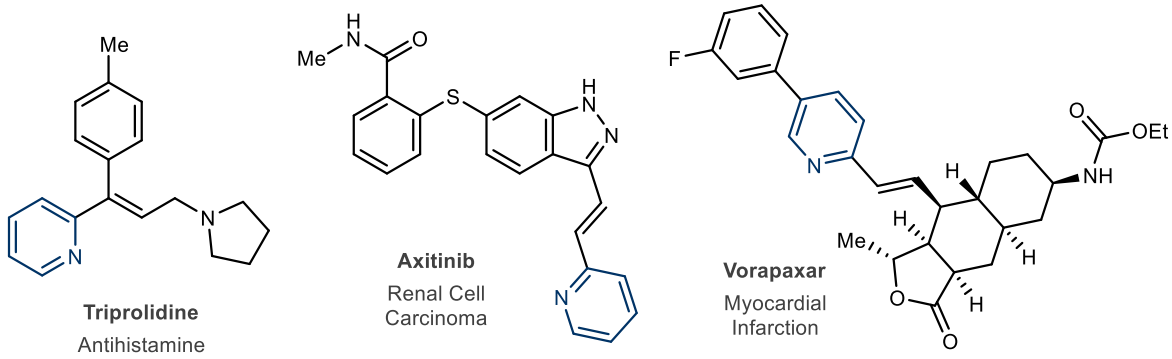


Figure 3.1 Alkenylpyridine pharmaceuticals.

3.2 Synthesis of Alkenylpyridines

3.2.1 Metal-Catalyzed Approaches to Alkenylation

The Heck reaction remains the premier strategy for the coupling of olefins with aryl halides.[7–10] However, as described in Chapter 2, pyridine halogenation is sometimes a bottleneck to the application of indirect functionalization strategies. Additionally, the pyridine nitrogen atom can ligate to the palladium catalyst, resulting in deleterious effects on the desired reactivity.

Nonetheless, advancements have been made which allow for the application of C–H activation approaches to coupling on pyridine. For pyridine, these methods rely on two strategies: The first requires the preparation of pyridine *N*-oxides and exploits the oxygen as a directing group to achieve 2-selective alkenylation. Chang and coworkers successfully executed this strategy as part of a Fujiwara-Moritani reaction on pyridine, which consists of C–H activation followed by an oxidative Heck coupling with an olefin (**Figure 3.2a**).[11] Nakao and Hiyama reported an alternative Nickel-catalyzed method which circumvents the need for oxidative coupling conditions by coupling with alkynes (**Figure 3.2b**).[12] While effective, the need for a strong oxidant to prepare pyridine *N*-oxides is a significant drawback to the functional group tolerance of these and related approaches, which were only demonstrated on very simple building blocks.

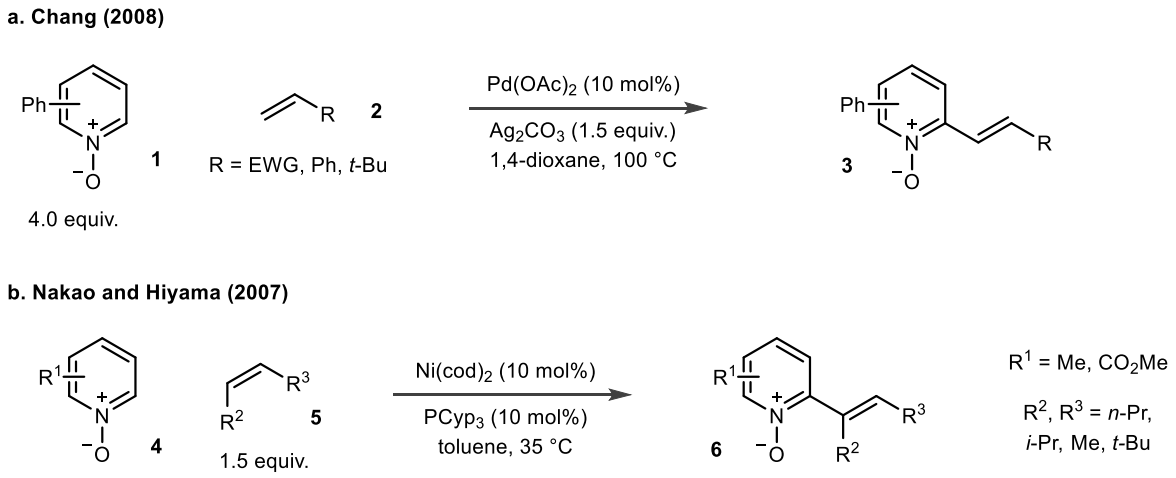


Figure 3.2 Selective alkenylation of pyridine *N*-oxides. Cod, cyclooctadiene; Cyp, cyclopropyl.

The second strategy relies on activation of the pyridine nitrogen by Lewis acids to bias the pyridine ring for C–H activation. Nakao and Hiyama improved on their previous nickel-catalyzed approach using diorganozincs or trimethylaluminum to facilitate mono- or bis-alkenylation, respectively, at the 2-position of pyridine (**Figure 3.3**).[13] The authors propose that activation of the pyridine nitrogen by the Lewis acid acidifies the 2-position C–H and provides a sufficient bias

for activation at that position over the 3- or 4-positions. The Yap group discovered that 4-selective alkenylation could be achieved using a $AlMe_3$-amino-NHC lewis acid (**13**, **Figure 3.3**).[14] The application of this bulky Lewis acid appears to disfavor activation at the 2-position, and metal-insertion occurs at the electronically activated 4-position C-H bond, with minor amounts of 3-position activation in some cases. A recent modification of this approach uses a cobalt catalyst and methylaluminium bis(4-substituted-2,6-di-tert-butyl-phen-oxide) (MAD) to achieve the desired coupling.[15] While these strategies are an improvement over the previous *N*-oxide approaches, there is still room for improvement. Oftentimes while the reaction provides a majority of the desired isomer, other isomers are still generated. Furthermore, the use of bulky Lewis acids precludes substrates that are too sterically hindered or electronically deactivated at the pyridine nitrogen, including most 2-substituted pyridines.

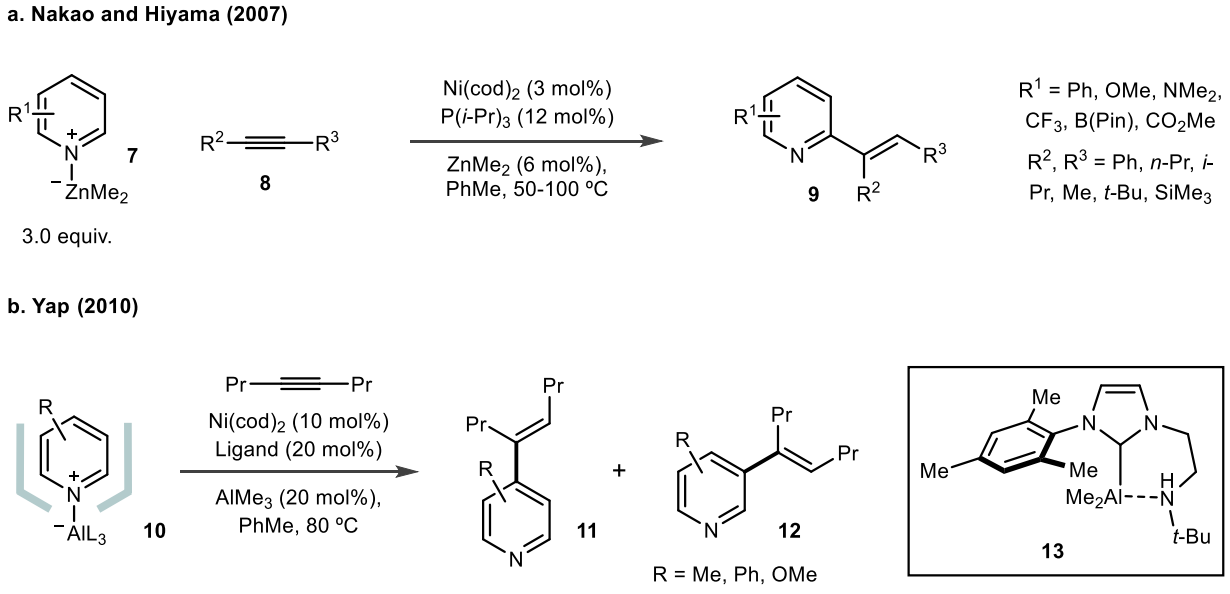


Figure 3.3 Selective alkenylation of pyridines via Lewis acid activation.

Yu and co-workers found that 1,10-phenanthroline provides a bias toward 3-selective C–H activation on pyridine under oxidative Fujiwara-Moritani-type conditions with palladium catalysis (**Figure 3.4**).[16] While the reaction gives a majority of 3-substituted product, 2- and 4-

position isomers form in most of the examples studied. Additionally, 16 equivalents of the pyridine starting material are required, reducing the practicality of the method.

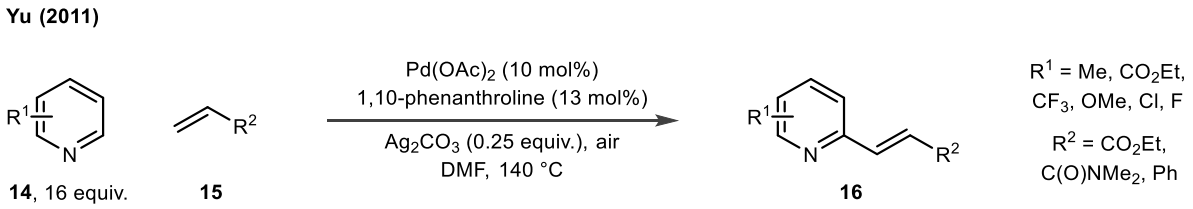


Figure 3.4 3-selective alkenylation of pyridines.

3.2.2 Radical Approach to Alkenylation

Radical-based processes offer a complementary alternative to metal catalysis for the functionalization of pyridines. In 2019, the Chu lab reported a photoredox-catalyzed method for the coupling of cyanopyridines with olefins.[17] Treating a mixture of pyridine and styrene with sodium methanesulfinate, DBU, and Iridium (Ir) photocatalyst under blue LEDs provides the α-vinylpyridine products in good yield with complete selectivity over addition to the styrene β-position. The authors propose the mechanism shown in **Figure 3.5** where after reduction of the cyanopyridine, Ir photocatalyst **22** undergoes reductive quenching by sodium methanesulfinate. The resulting sulfonyl radical adds to styrene, and the newly formed persistent benzylic radial **26** couples with pyridine radical anion **20**. Elimination of cyanide rearomatizes the pyridine ring, and E1 elimination of sulfinate from **27** provides the vinylpyridine. The scope for this transformation is relatively broad and provides a strategy to quickly access Triprolidine in a one-pot process. However, the need for cyanopyridine starting materials can limit applications of this strategy late in a synthetic sequence.

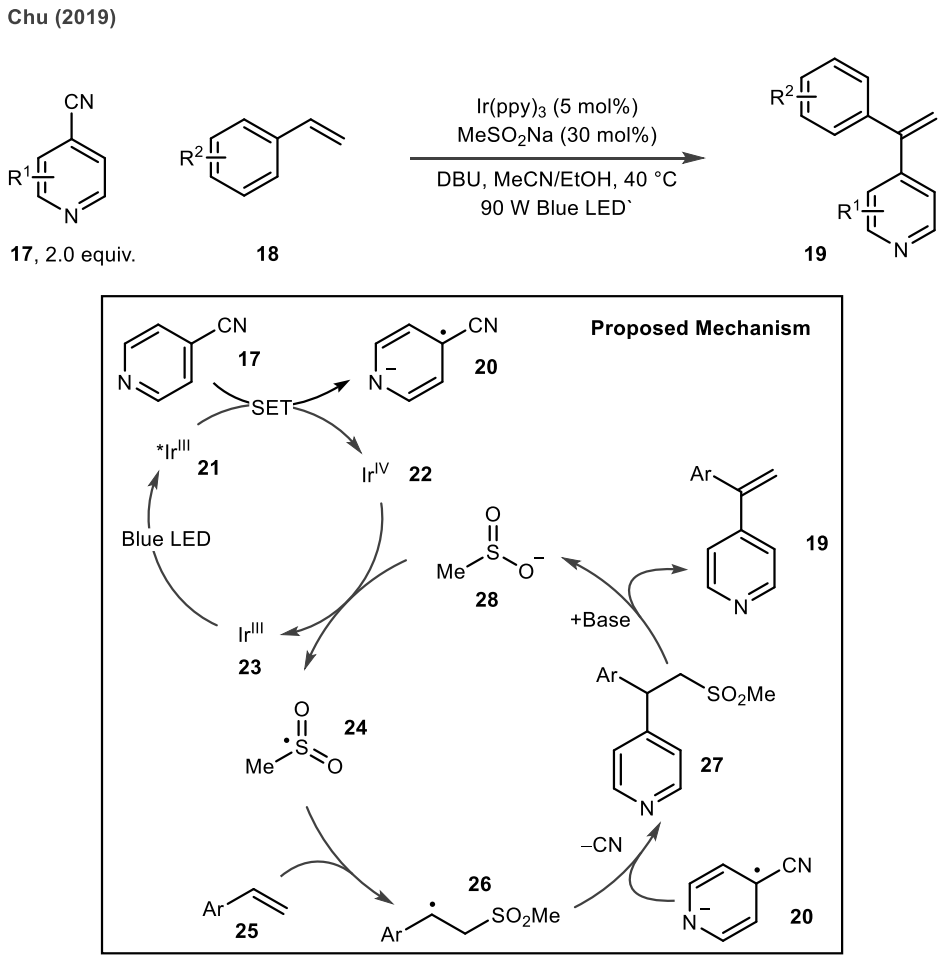


Figure 3.5 Photoredox approach to pyridine alkenylation.

3.3. Previous Studies of P^V Reactivity in Alkenylphosphonium Salts

A potential alternative to metal- or radical-based approaches to pyridine alkenylation is phosphorous ligand-coupling. Ligand-coupling from alkenylphosphonium salts is a very undeveloped research area with only a few previous studies. Aryl-vinyl coupling from all carbon-substituted P^V species was discussed in **Section 1.2.2** and constitutes the only example of alkenylation mediated by phosphorus ligand-coupling.[18] However, early reports of the alkaline hydrolysis of alkenylphosphonium salts offer insight into the decomposition of oxyphosphoranes containing both an aryl and alkenyl ligand.

In 1967 Allen and Tebby discovered that the reaction of triphenylphosphine and phenylacetylene in aqueous ethylene glycol at reflux produces phosphine oxide **32**, through the proposed migration pathway shown in **Figure 3.6a**.[19] The installation of *para*-withdrawing groups on the aryl acetylene favored coupling in shorter reaction times, while *para*-donating groups such as a methoxy substitutent extended the reaction time to 5 days and only produced ~25% product (**33**). Later reports explored the scope of the migrating arene onto the phenyl-substituted vinyl ligand and found that substitutents that moderately stabilize the corresponding aryl anion (**37**, **38**) were better suited toward coupling.[20] However, arenes capable of even greater anion stabilization (**39**, **40**) were prone toward protonation via the ligand exchange pathway **B** shown in **Figure 3.6b**.

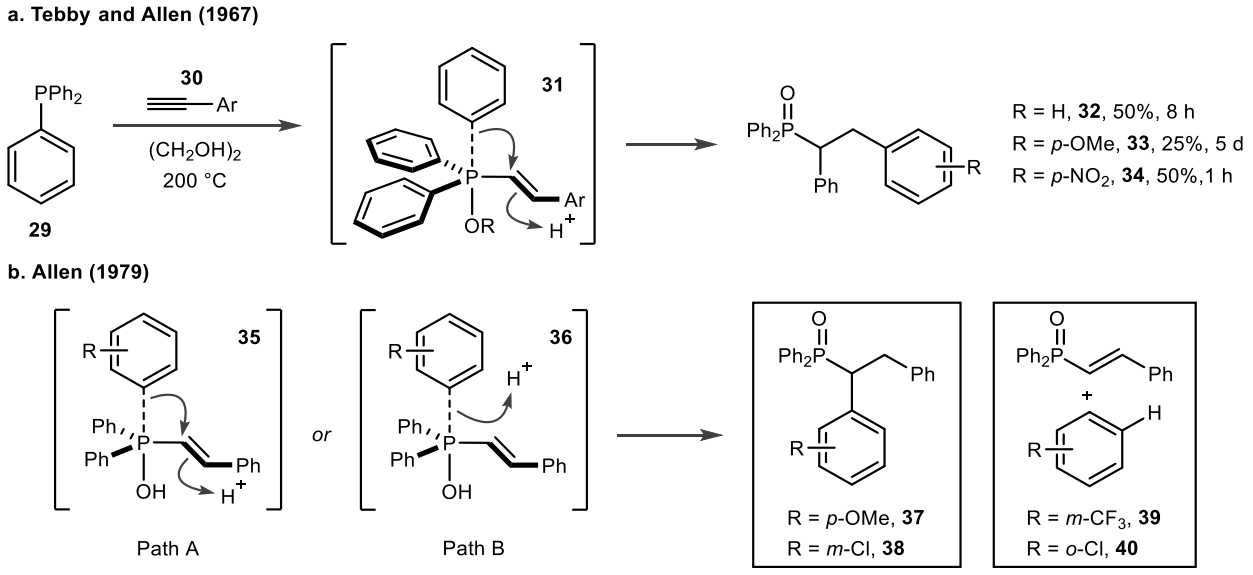


Figure 3.6 Studies of the hydrolysis of alkenylphosphonium salts derived from aryl acetylenes.

This aryl migration reaction translated to other alkyne acceptors, including ynoates, ynones, and sulfides, and encompasses the ring expansion reaction discussed earlier in **Section 1.2.1**. In contrast to the reactions with phenylacetylene, aryl migration onto ester-substituted alkenes was often quantitative and proceeded under more mild conditions (**Figure 3.7**).[21] Furthermore, arenes which previously had undergone ligand exchange (**39**, **40**) in the reactions

with phenylacetylene produced the migration product in these new systems instead (**43**), highlighting the influence of the alkene acceptor on the outcome of phosphorane decomposition. Additional studies of the substituent on the ynoate (R^2) found that methyl substitution still provided the migration product, though in substantially lower yield (10%), while phenyl substitution resulted in protonation of the vinyl group (**44**) and formation of the triarylphosphine oxide (**45**).

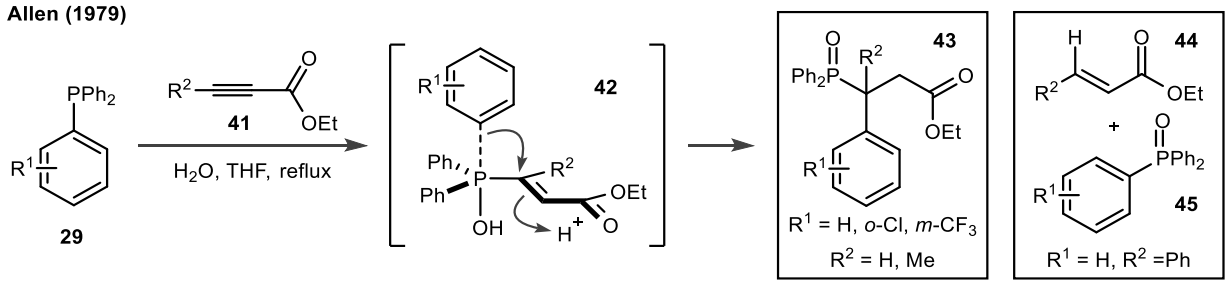


Figure 3.7 Studies of the hydrolysis of alkenylphosphonium salts derived from ynoates.

Interestingly, in the above studies, phosphines incorporating some heteroarenes (2-thienyl, 2-furyl, 1-methyl-pyrrol-2-yl) were investigated for their capacity to migrate, but pyridylphosphines were unexplored. In 2011, the Trofimov group reported that the reaction of triphenyl phosphine **29** and aryl ynone acceptors **49**-**52** in water at room temperature gave exclusive protonation of the alkene ligand (**Figure 3.8a**).[22] Following this report, the group showed that tris-2-pyridylphosphine **53** undergoes a similar process, though with a change in selectivity for protonation of the pyridine, resulting in alkenyl phosphine oxides **56**-**60** with excellent stereoselectivity.[23] Notably, this represents the only study of the alkaline hydrolysis of alkenylphosphonium salts containing a pyridine ligand. No cases of vinyl migration onto the pyridine were observed in the investigation of this reaction (**Figure 3.8b**).

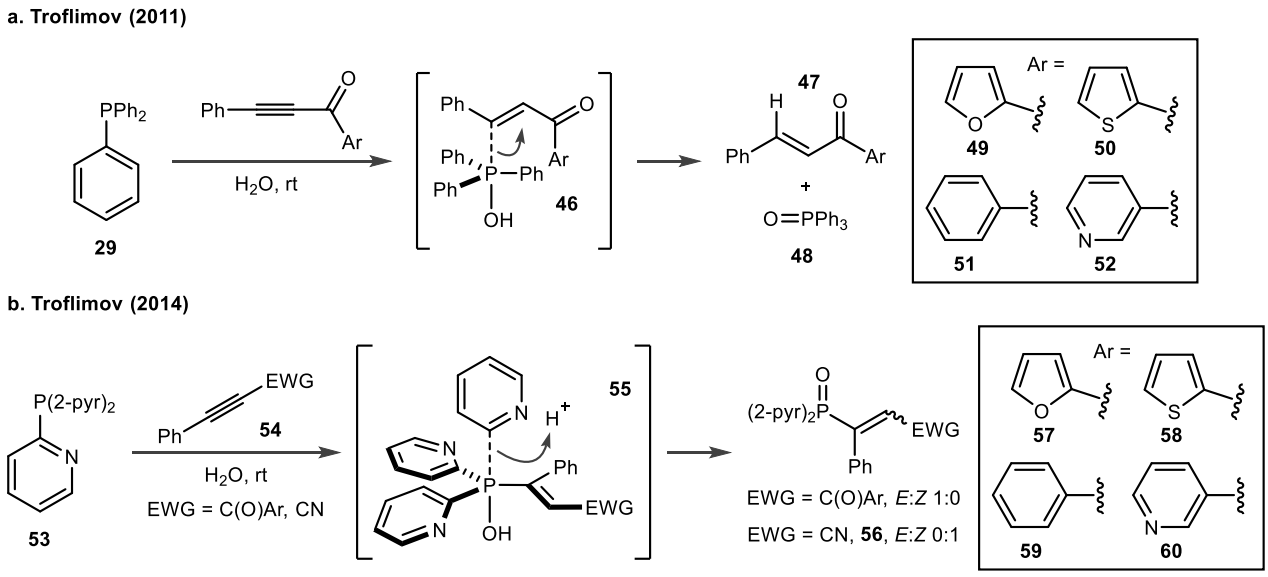


Figure 3.8 Examples of ligand-exchange from alkenylphosphonium salts.

3.4. Design of a Phosphorus Ligand-Coupling Approach to Pyridine Alkenylation

3.4.1 Synthesis of Pyridylphosphines

Following the successful development of a strategy for pyridine-pyridine coupling at phosphorus, we were interested in exploring other cross coupling reactions of pyridylphosphines. These reagents are bench stable and can be prepared through two approaches which were developed for bipyridine synthesis. The first approach is a modification of our phosphonium formation that uses fragmentable phosphine **62**.[24] After formation of the phosphonium, excess DBU facilitates elimination of methyl acrylate through an E1cB mechanism (**Figure 3.9**). This strategy provides 4-pyridylphosphines in good yields and with excellent 4-position selectivity directly from the pyridine C–H bond.

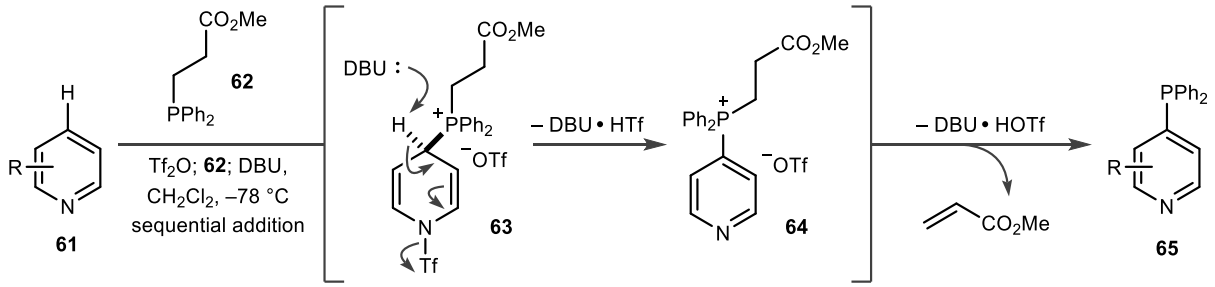


Figure 3.9 Pyridylphosphine synthesis using fragmentable phosphine **62**.

However, there are certain limitations to the phosphonium formation reaction. 2,6-disubstituted pyridines, as well as pyridines containing functionality that can react with Tf_2O (alcohols, primary and secondary amines, *N*-alkyl amides) are often unable to form the phosphonium salt. Additionally, because the phosphonium forming reaction is inherently selective for the 4-position, the synthesis of 2-pyridylphosphines requires a substituent blocking that site. A second approach to phosphine synthesis alleviates many of these issues and expands the scope of available pyridylphosphines (**Figure 3.10**).[25] Heating chloroazines with diphenylphosphine and one equivalent of triflic acid produces the desired phosphine in good yield and allows for phosphine synthesis at both the 2- and 4-positions based on the chloroazine starting material.

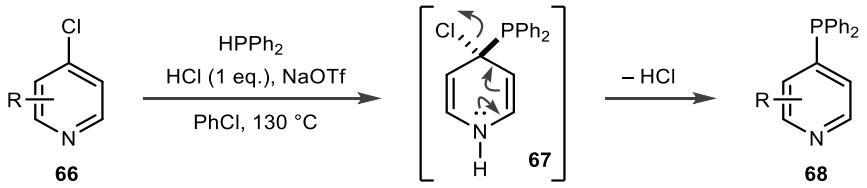


Figure 3.10 S_NAr approach to pyridylphosphine synthesis.

3.4.2. Initial Reaction Development

Inspired by previous studies in the hydrolysis of alkenylphosphonium salts we began to investigate the reactivity of pyridylphosphines with alkyne acceptors under reaction conditions that were developed for bipyridine coupling. Treating 2-pyridylphosphine **69** with ethyl propiolate in acidic ethanol at 80 °C produced a mixture of aryl migration products in low yield (**Figure**

3.11). Previous studies in ligand coupling indicated that the 2-pyridyl ligand is less adept at migration compared to its 4-position counterpart. When 4-pyridylphosphine **74** was subjected to the same conditions, exclusive pyridine migration was observed, and in substantially higher yield (**76**). The aryl migration product undergoes dephosphinylation under basic conditions to provide the alkylpyridine product.

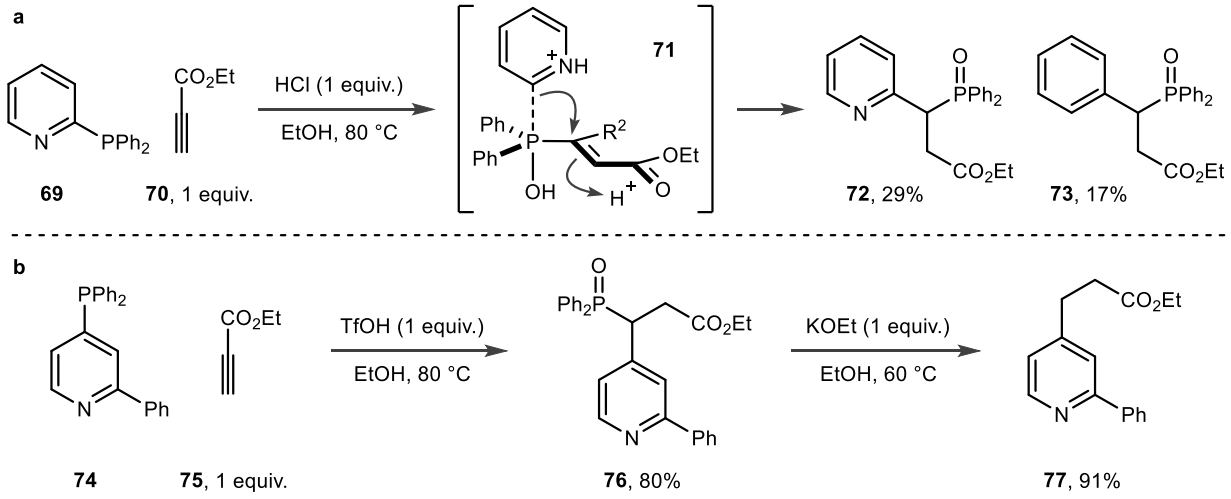


Figure 3.11 Initial studies of pyridine migration from vinylphosphonium salts.

While the aryl-migration pathway has some synthetic utility, we continued to focus on discovering a system capable of ligand-coupling. Examination of several different alkyne acceptors revealed that the acceptor identity has a large impact on the reaction outcome (**Figure 3.12**). Ester **79a**, sulfone **79b**, and ketone **79c**, all produced the migration product in varying yield, with ligand exchange as the main side-pathway (**Figure 3.12b**). Dephosphinylation of sulfone **79b** followed by elimination of sulfinate provides 4-vinyl-2-phenylpyridine **83** in 39% under unoptimized conditions (**Figure 3.12c**). Substitution of ynoate with methyl and phenyl groups (**80a** and **80b**) resulted in phosphonium formation but no further reaction, presumably due to lack of phosphorane formation on these intermediates (**Figure 3.12d**). A similar result was obtained with ynamide **80c** and 4-(phenylethynyl)pyridine **80d**. Aldehyde **84** produced an intriguing result as no

migration or alkenylation were observed, but instead 4-hydroxy-2-phenylpyridine formed in 33% yield (**Figure 3.12**, **e**). Similar results were obtained with trifluoromethyl ynone **85**; further discussion of these results is the subject of Chapter 4 of this dissertation.

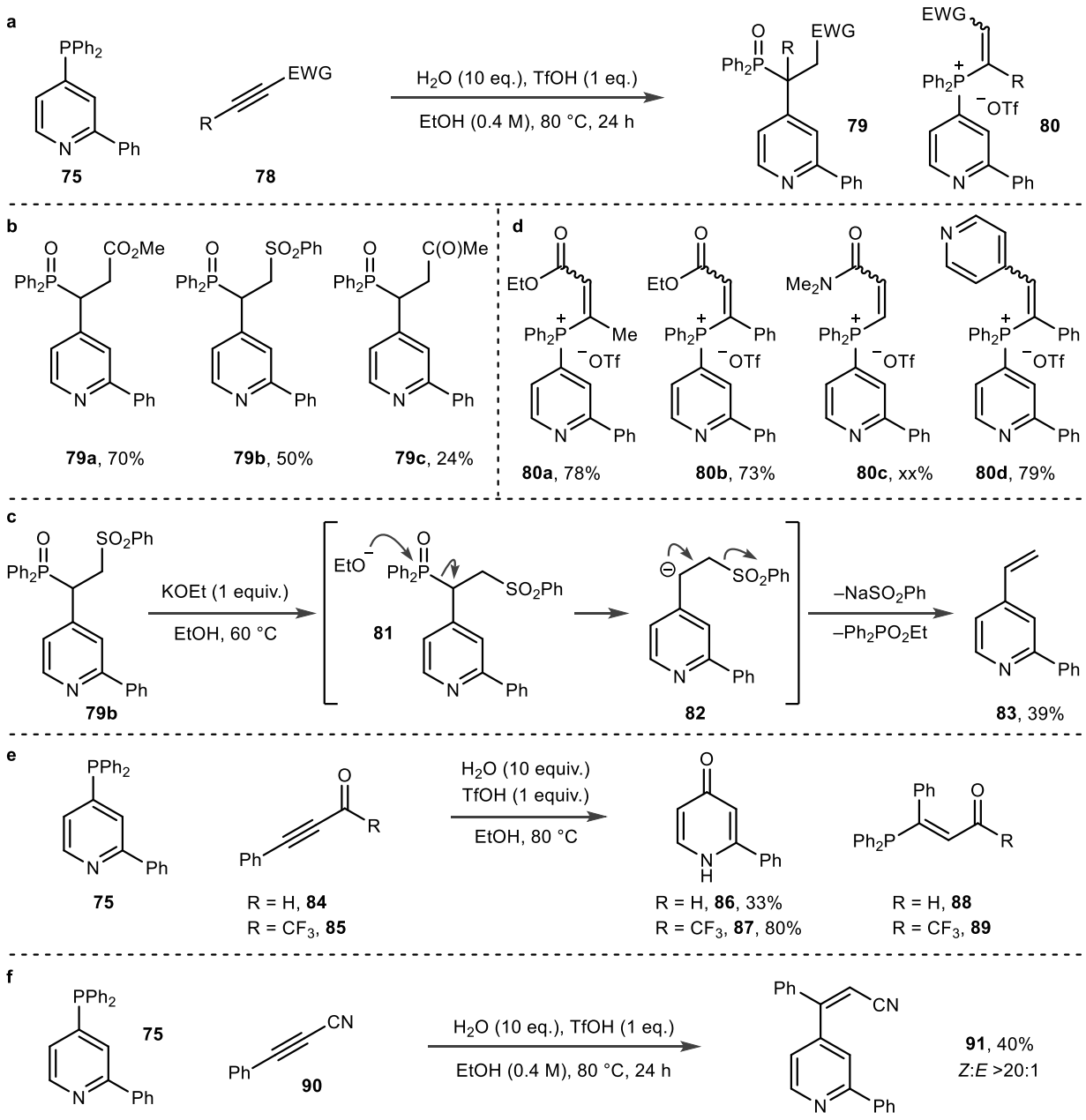
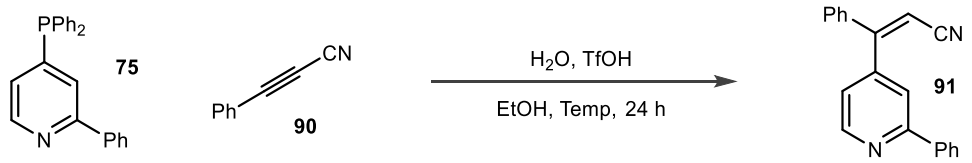


Figure 3.12 Exploration of alkyne acceptor scope.

Finally, a system was discovered that provided the desired 4-alkenylpyridine product with complete selectivity. The reaction of pyridylphosphine **75** with 3-phenylpropiolonitrile **90** in acidic

aqueous ethanol produced product **91** in 40% yield with ~20:1 selectivity for the *Z* isomer (**Figure 3.12**, **f**). Notably, none of the pyridine migration product is obtained, and to our knowledge, this is the first example of pyridine alkenylation through phosphorus ligand-coupling.

Table 3.1 Optimization of alkenylation on 2-phenylpyridine.



Entry	Concentration (M)	H_2O Equiv.	TfOH Equiv.	Temp °C	75 Equiv.	90 Equiv.	91 yield (%)
1	0.125	10	1.0	80	1.0	1.0	n.d.
2	0.25	10	1.0	80	1.0	1.0	31
3	0.4	10	1.0	80	1.0	1.0	42
4	1	10	1.0	80	1.0	1.0	42
5	0.4	0	1.0	80	1.0	1.0	n.d.
6	0.4	50	1.0	80	1.0	1.0	45
7	0.4	100	1.0	80	1.0	1.0	45
8	0.4	10	0	80	1.0	1.0	n.d.
9	0.4	10	0.5	80	1.0	1.0	n.d.
10	0.4	10	1.0	80	1.0	1.0	43
11	0.4	10	1.5	80	1.0	1.0	43
12	0.4	10	1.0	RT	1.0	1.0	4
13	0.4	10	1.0	40	1.0	1.0	19
14	0.4	10	1.0	60	1.0	1.0	30
15	0.4	10	1.0	80	1.5	1.0	51
16	0.4	10	1.0	80	2.0	1.0	50
17	0.4	10	1.0	80	1.0	1.5	75
18	0.4	10	1.0	80	1.0	2.0	71

Efforts then turned to optimizing the transformation on 2-phenylpyridine (**Table 3.1**). Concentration had a considerable influence on the reaction outcome; at lower concentrations (0.125 M), the reaction only produced phosphonium salt (entries 1-4). Increasing the amount of water in the reaction did not appear to influence the yield, though running the reaction without water produces none of the desired product, indicating that phosphorane formation likely occurs by attack of water on the phosphonium (entries 5-7). An acid equivalents screen revealed that at

least one equivalent was necessary to produce the desired product (entries 8-11). Temperature studies confirmed that our initial temperature of 80 °C was optimal (entries 12-14). Increasing the equivalents of phosphine relative to alkyne provided a modest increase in yield to 50% (entries 15 and 16). The largest yield increase was observed when altering the equivalents of cyanoalkyne. Adding an additional half-equivalent to the reaction produced the desired product in 75% yield with further equivalence increases producing similar yields (entries 17 and 18). We hypothesize that the reaction byproduct, diphenylphosphine oxide, is able add to the cyanoalkyne starting material, diminishing the amount available to react with pyridylphosphine.

3.5 Alkenylation Scope Studies

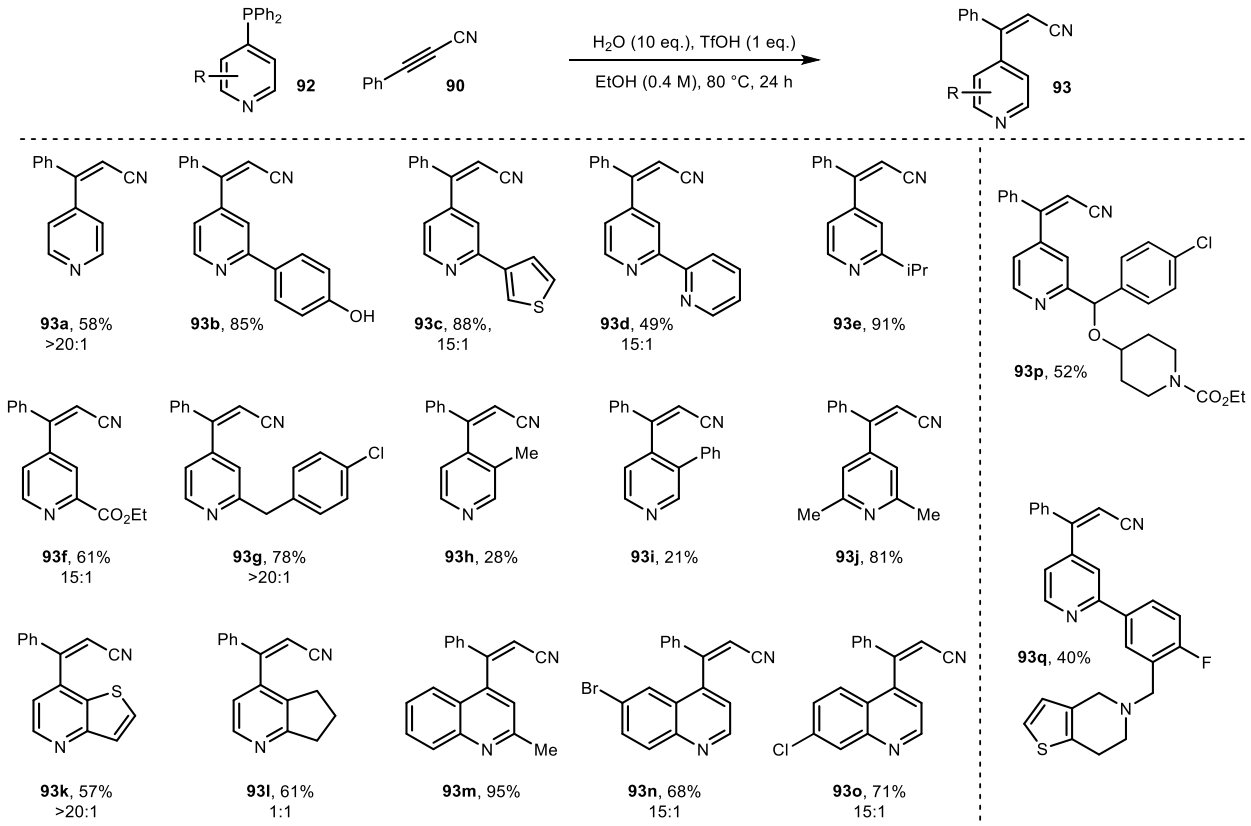


Figure 3.13 Pyridine scope for alkenylation reaction.

We then turned our attention to exploring the pyridyl phosphine and cyanoalkyne scopes of the ligand-coupling process (**Figure 3.13**). Notably, in all cases, none of the pyridine migration

product (**93**) was observed during the investigation. Pyridine-derived product **93a** was produced in good yield and with excellent diastereoselectivity. 2-heteroaryl pyridines **93c** and **93d** are alkenylated with good selectivity for the Z isomer in moderate yields. The reaction tolerates free hydroxyl substitutents, shown in example **93b**, as well as ester **93f**. As series of fused systems such as **93k** and quinolines **93m**-**93o** demonstrate the capacity of the reaction to function on heterocycles other than pyridine. 2,3-disubsituted pyridine **93l** is the only example in this series which produces a 1:1 ratio of alkene isomers; we hypothesize isomerization of the alkenylphosphonium prior to ligand-coupling is faster on this substrate due to the sterically demanding cyclopentane ring. Notably, 3-substituted pyridines, such as **93h** and **93i**, function in the reaction but provide substantially lower yields of the desired product. Other 3-substitutents tested (Cl, Br, CO_2Et, OMe) produced the unfunctionalized pyridine through undesired protiodephosphination. Finally, to highlight the reaction's utility for the modification of drug-like fragments, we functionalized **93p** and **93q**.

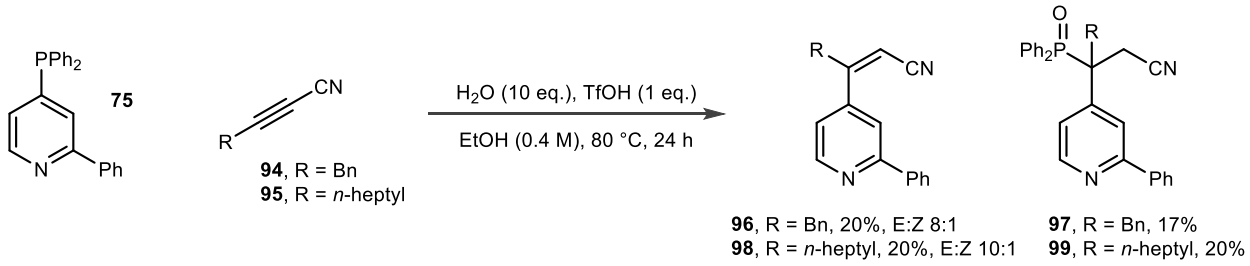


Figure 3.14 Examination of alkyl-substituted cyanoalkynes for phosphorus ligand-coupling.

Next the scope of cyanoalkynes was investigated. Investigation of the alkyne substituent revealed that with benzyl and alkyl substitution (**94** and **95**), the reaction produced a mixture of both pyridine-migration and vinylation products (**Figure 3.14**). Aryl substituents, however, produced the alkene-substituted product exclusively (**Figure 3.15**). The reaction tolerates *ortho* fluoro (**101a**) and methyl groups (**101b**), though with lower diastereoselectivity. Both electron

withdrawing groups (**101c**, **101g**, **101h**) and donating groups (**101e**, **101f**, **101i**, **101j**) are tolerated, with strongly withdrawing groups providing single isomers of the alkenyl product. Importantly, alkene-substituted **101l** functions in the reaction albeit in lower yield; none of the undesired aryl migration product was observed.

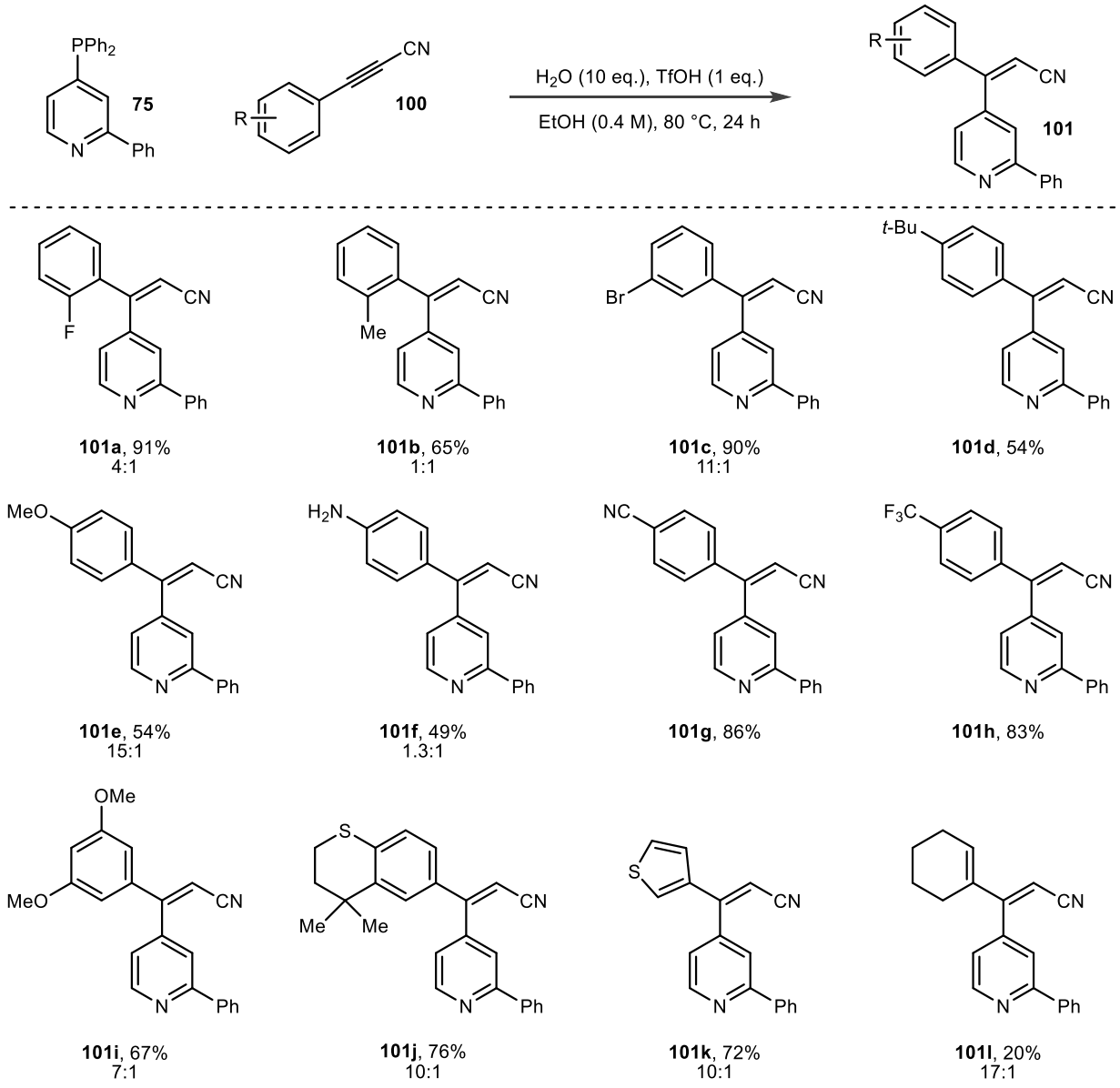


Figure 3.15 Cyanoalkyne scope for pyridine alkenylation.

3.6 Mechanism

3.6.1 Computational Probe of Aryl Migration Pathway

To rationalize the product selectivity obtained in the alkenylation reaction, a computational probe of the mechanism was initiated in collaboration with the Paton group. First, an effort was made to rationalize the selectivity for aryl migration in the reaction with ynoates (**Figure 3.16**). Attack of phosphonium **102** by water results in phosphorane isomer **103**, which can isomerize through Berry pseudorotation to isomer **104** in the equilibrium shown. Notably, **104** is nearly 6 kcal mol^{-1} higher in energy than isomer **103**, which is the most likely isomer to lead to the aryl migration product. Examination of the relative transition state energies (G_{rel}) for the migration pathways from these two phosphoranes reveals that pyridine migration onto the alkene acceptor is favored by nearly 8 kcal mol^{-1}, giving a clear indication that alkene migration to form **105** is not feasible in this system. Based on our experimental results, the resulting enolate **106** appears to favor the protonation pathway to form **108** over E1cB elimination of hydroxydiphenylphosphine to form **107**. Energy barriers to these processes could not be determined using DFT.

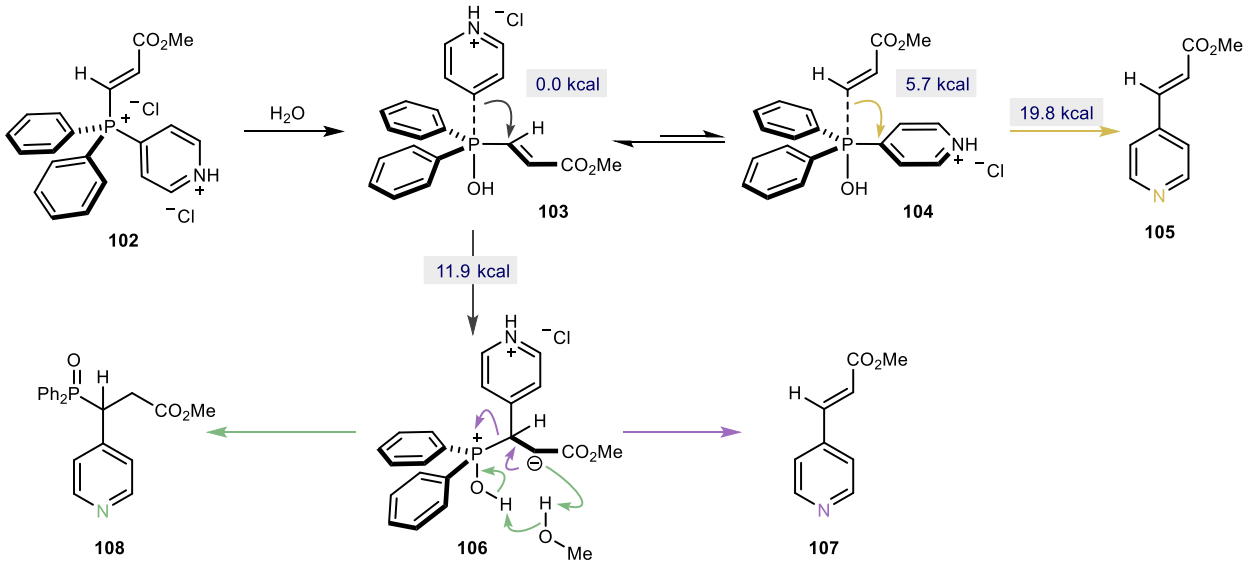


Figure 3.16 Reaction pathways for ynoate-derived phosphonium **102**. Relevant G_{rel} values are provided for both intermediates (next to structures) and transition states (on reaction arrows) and are reported in kcal mol^{-1}.

3.6.2 Computational Probe of Alkene Migration Pathway

The alkene migration reaction was then investigated to determine if any deviation existed in the transition state energies for the previously described reaction pathways. We hypothesized that the mechanism for this process proceeded by alkene migration with retention of olefin stereochemistry, and indeed, the calculations reported in **Figure 3.17** support this hypothesis. While the phosphorane **110** is slightly higher in energy than its isomer **109**, the transition state energy for apical alkene migration is roughly 4 kcal mol^{-1} lower than for aryl migration and thus this pathway should be favored. Additionally, the energies for other feasible reaction pathways were explored. Hydroxyl migration onto either the alkene or pyridine ring (**115** or **116**) were determined to be close in energy to pyridine migration, but still not favorable pathways in comparison to alkene migration.

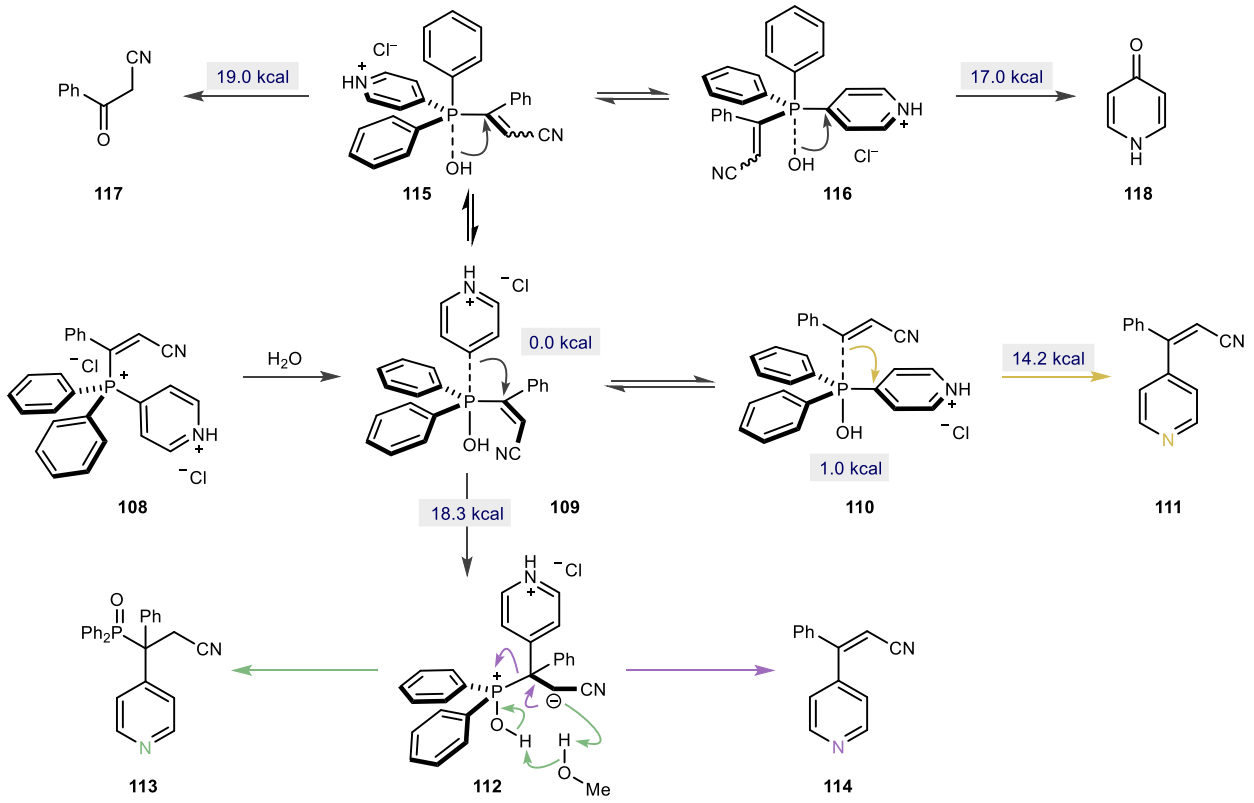
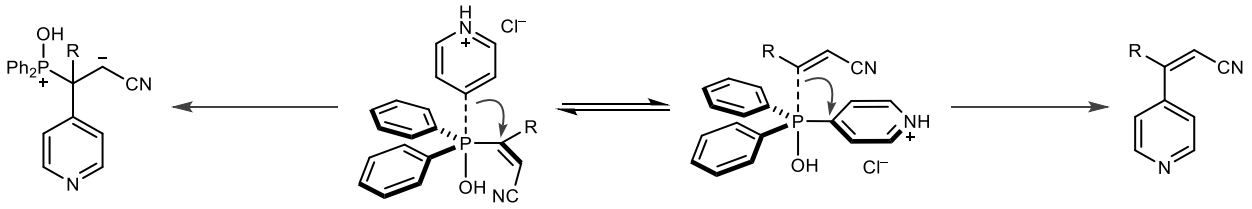


Figure 3.17 Computed energies for reaction pathways from phosphonium **108**. Relevant G_{rel} values are provided for both intermediates (next to structures) and transition states (on reaction arrows) and are reported in kcal mol^{-1}.

We next sought to determine the underlying reasons for the differences in transition state energies for ligand-coupling from both **102** and **108**. To establish the influence of the alkene substituent on the two competing pathways, the relative transition state energies of both processes were determined for H, Me, Ph, and *tert*-butyl substituted **115** and **116** (**Table 3.2**). The reaction outcome appears to be influenced heavily by the alkene substituent. More sterically demanding substituents appear to enhance elongation of the C–P bond during alkene migration, which should make that process more favorable. However, electronic stabilization of the anion formed during migration is also contributing factor in determining selectivity. *tert*-Butyl substituted **120** (entry 3) is predicted to cause substantial C–P bond elongation in the transition state for alkene migration, but pyridine migration is still favored energetically, presumably due to a lack of anion stabilization.

Notably the energy for pyridine migration is relatively high compared to entries 1 and 2; though energy values were not determined, hydroxyl migration onto either the pyridine or alkene ligands (see **Figure 3.17**, **115** and **116**) may start to compete in this system. Phenyl substituted **120** (entry 4) also experiences substantial C–P bond elongation in the transition state but is better at stabilizing anionic charge buildup through delocalization, and thus the barrier to alkene migration is lowered enough to favor that pathway. Unsubstituted substituted **120** (entry 1) and methyl substituted **120** (entry 2) are predicted to yield pyridine migration selectively due to both a lack of steric bulk and anionic charge stabilization.

Table 3.2 Examination of alkene substituent on transition state energies for ligand-coupling.



121 **119** **120** **122**

Entry	R	G_{rel} for **119** (kcal mol^{-1})	G_{rel} for **120** (kcal mol^{-1})	C–P bond distance in **120** (Å)
1	H	**12.3**	16.6	1.94
2	Me	**15.9**	17.7	1.95
3	*t*-Bu	**18.8**	20.1	1.98
4	Ph	18.3	**14.2**	2.00

Finally, efforts turned toward rationalizing the outcome observed in **Figure 3.14**. Methyl substituted **123** served as a proxy for the phosphonium generated from alkyl-substituted cyanoalkyne **95** described earlier, which gave a mixture of both migration and alkenylation products. Using a molecular dynamics simulation, yields of **127** and **129** shown in **Figure 3.18** were determined. The simulation predicts that products result from intermediate **128** which agrees with our model but is surprising given that from intermediate **106** in **Figure 3.16**, none of the

alkene-coupled product forms. Further investigation of the influence of withdrawing groups over these outcomes is ongoing.

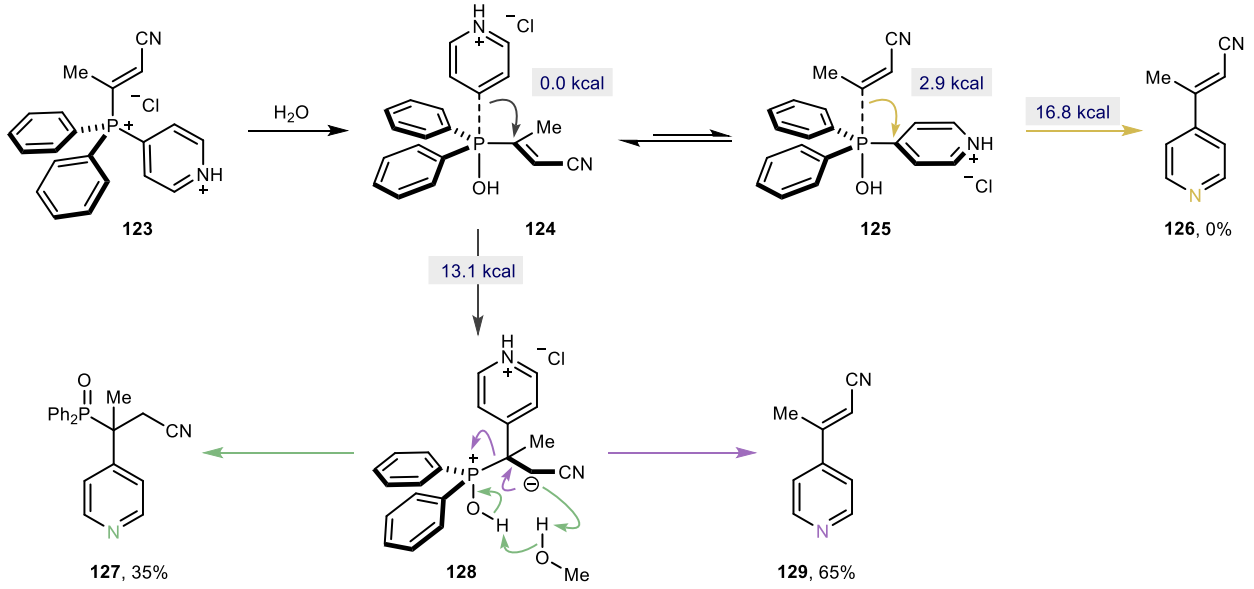


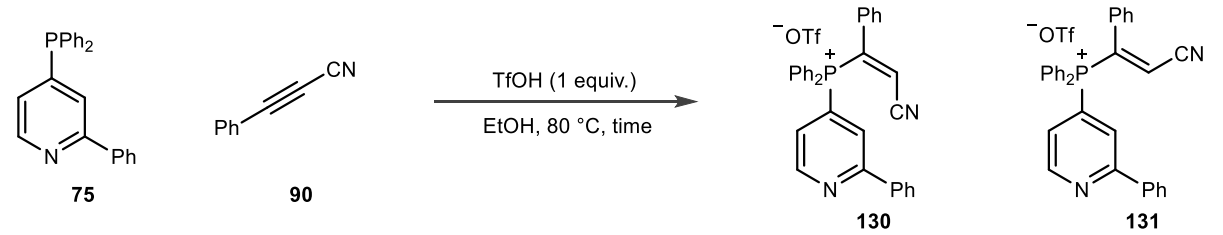
Figure 3.18 Predicted outcomes of the molecular dynamics simulation for coupling from phosphorane **124**. Relevant G_{rel} values are provided for both intermediates (next to structures) and transition states (on reaction arrows) and are reported in kcal mol^{-1}.

3.6.3 Rationalization of Alkene Product Geometry

We hypothesized that the alkene geometry for alkenylation was determined during addition of the phosphine to the alkyne acceptor and set out to provide evidence for this hypothesis. Under the reaction conditions with water excluded, the alkenylphosphonium forms, but does not decompose via a phosphorane (**Table 3.3**). Early in the reaction, the sole phosphonium isomer is the *Z* isomer based on the alkene coupling to phosphorus (40 Hz), which should lead to *Z* product based on our proposed mechanism. As the reaction progresses over 24 hours, isomerization to the *E* isomer occurs, and a 4:1 Z:E ratio is obtained. After 48 hours, the ratio becomes 1:1, where it appears to reach an equilibrium point. This suggests that the *Z* isomer is the kinetic product, and that both isomers are thermodynamically similar. Because the ligand-coupling reaction is typically

complete in 24 hours, it is likely that the minor amounts of *E* isomer observed in the reaction are a result of this thermodynamic phosphonium isomerization.

Table 3.3 Time study of alkenylphosphonium salt isomerization.



Time	% 1	% 2	% 3	130:131 (^{1}H NMR)	130:131 (^{31}P NMR)
30 min	76	24	0	n/a	n/a
1 hour	64	40	1.4	29:1	33:1
2 hours	31	64	2	32:1	33:1
5 hours	19	75	2	38:1	33:1
7 hours	14	82	2	41:1	29:1
12 hours	8	84	6	15:1	14:1
24 hours	6	77	18	5:1	4:1
48 hours	6	52	42	1.2:1	1:1
72 hours	6	52	42	1.2:1	1:1

3.7 Conclusion

In summary, a new pyridine alkenylation protocol was developed using phosphorus ligand-coupling. The reaction functions on a range of pyridyl phosphines and aryl-cyanoalkynes to deliver alkenylpyridines with high diastereoselectivity. Mechanistic studies indicate that both steric and electronic factors arising from alkyne substitution are responsible for selective olefin migration over pyridine migration from the phosphorane intermediate, and further studies are ongoing to determine if additional factors can be exploited to expand the scope of this transformation.

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CHAPTER FOUR

A DISTINCT NUCLEOPHILE DELIVERY SYSTEM FOR PYRIDONE AND AMINOPYRIDINE SYNTHESIS VIA PHOSPHORUS LIGAND- COUPLING

4.1 Introduction to Pyridone Synthesis

4.1.1 Pyridones in Bioactive Compounds

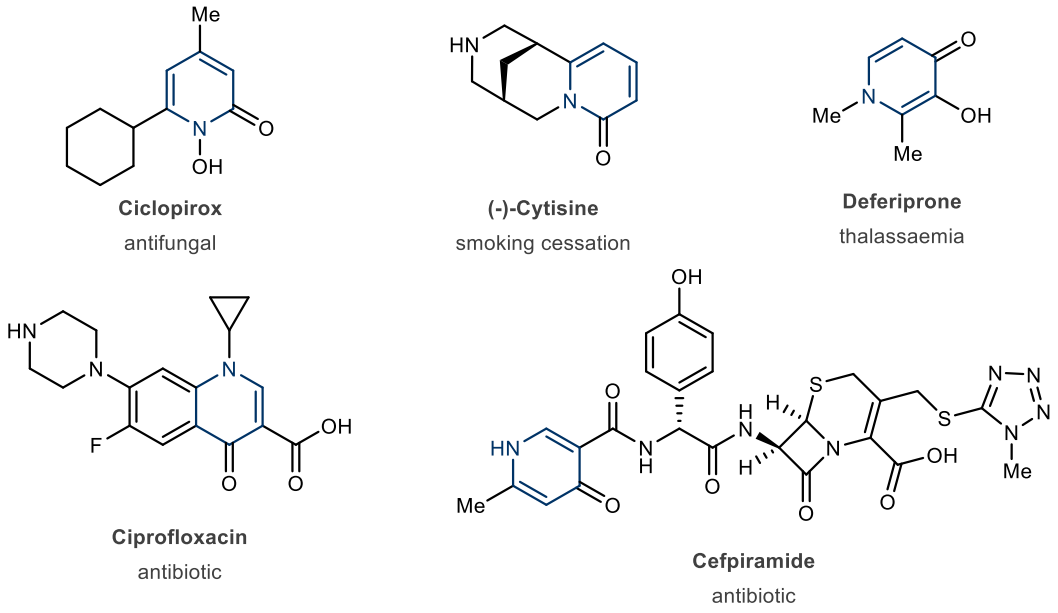


Figure 4.1 Pyridone-containing natural products and pharmaceuticals.

Pyridones are prevalent subunits in natural products, pharmaceutical targets, and agrochemicals.[1–3] Compounds containing this core scaffold have been found with biological activity ranging from antimicrobial, anti-inflammatory, antitumor, neurotrophic to insecticidal properties.[4–11] Such compounds include ciclopirox, (-)-cytisine, deferiprone, cefpiramide, and ciprofloxacin, one of the many members of the 4-quinolone family of antibiotics (**Figure 4.1**).[12,13] When the nitrogen is unsubstituted in both 2- and 4-pyridones, tautomerization between the hydroxypyridine and pyridone can occur (**Figure 4.2a**). Generally, the pyridone tautomer **2** is preferred in both the solid state and in solution. In medicinal chemistry, this motif is common for

its ability to serve as both a hydrogen bond donor and acceptor, as well as act as an isostere for amides, pyridines, and other N- or O-containing heterocycles.[1] The synthesis of these motifs is therefore of long-standing interest to the chemistry community. Generally, pyridones can be prepared by three distinct strategies: ring synthesis from acyclic precursors, conversion of pyrones to pyridones, and conversion of pyridyl halides to pyridones (**Figure 4.2b-d**).[14–19]

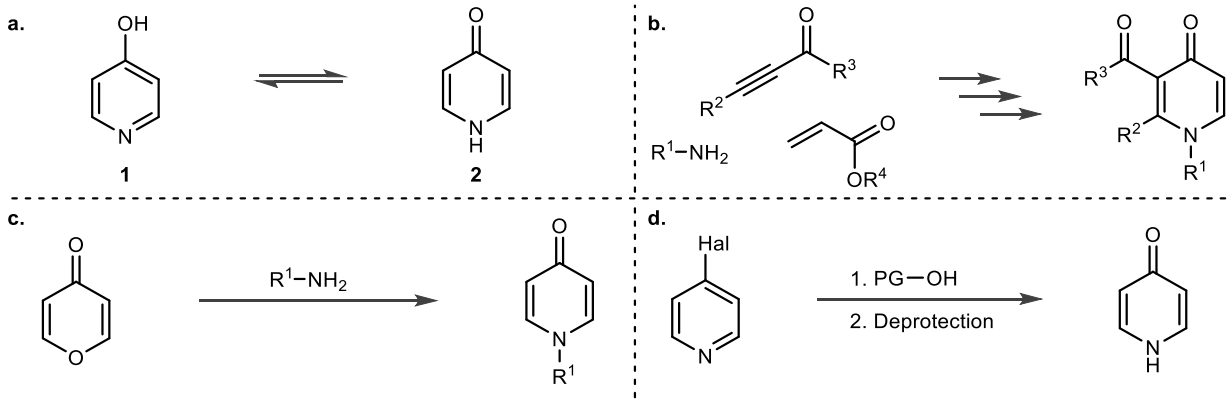


Figure 4.2 Properties and synthesis of pyridones.

4.2 Investigation of Pyridone Formation via Alkenylphosphonium Decomposition

The discovery of the reaction shown in **Figure 3.12e** during the examination of alkyne acceptors for pyridine alkenylation was intriguing to us for two reasons. The first is that previous attempts in our group to achieve pyridone synthesis via phosphorus ligand-coupling were unsuccessful. During our previous study of pyridyl ether synthesis, in which pyridyl phosphonium salts were treated with alkoxide nucleophiles to form the desired product, we found that addition of hydroxide to the phosphonium did not result in the pyridone product. Instead, the reaction exclusively produces the pyridine starting material, likely by the ligand-exchange pathway shown in **Figure 4.3a**. Additionally, attempts to achieve ligand-coupling under acidic conditions were also unsuccessful. When heating a set of phosphoniums with water in acidic *n*-butanol at reflux, no reaction of the phosphonium was observed (**Figure 4.3b**). We hypothesize that the

phosphonium is not sufficiently electrophilic enough for phosphorane formation to occur via attack by water in these systems.

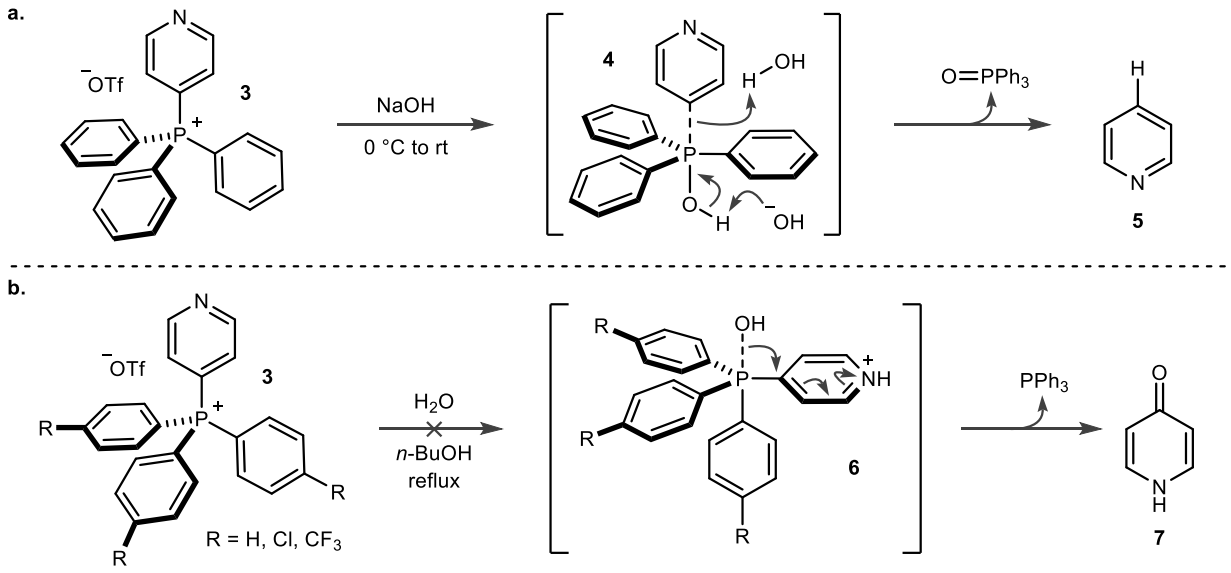


Figure 4.3 Previous attempts at pyridone synthesis from phosphonium salts.

We were also intrigued by the result in **Figure 3.12e** in the context of the decomposition of alkenylphosphonium salts. This reaction outcome had never previously been reported in these systems, so we set out to determine the mechanism leading to the pyridone product. In the initial reaction of phosphine **8** with trifluoromethyl ynone **13**, we observed the formation of byproduct phosphine **12** (R = Ph, X = CF_3, **Figure 4.4**). Trifluoromethyl ynones are well-known for reacting readily with water to form hydrates, and we realized that hydrate formation likely played a role in facilitating the hydroxylation pathway. We began to examine other acceptors to determine what components of the acceptor were necessary to retain the pathway to hydroxylation. Removal of the trifluoromethyl group to form ynal **14** lead to a diminished yield of the pyridone product, but the only reaction byproduct was 2-phenylpyridine resulting from protonation. Removal of the phenyl substituent (**15**) led to further a reduced yield, but again, hydroxylation was the only ligand-

coupling pathway observed. Finally, testing acrolein (**16**) in the reaction still gave the hydroxylation product despite the decreased electrophilicity of phosphonium **10**.

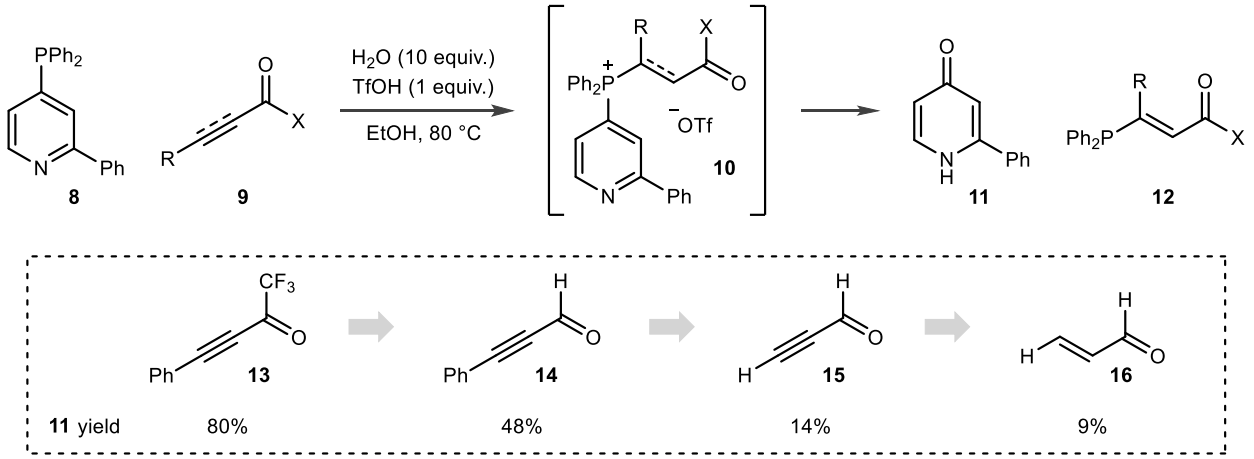


Figure 4.4 Exploration of acceptors for hydroxylation.

4.3 Proposed Mechanism for Hydroxylation

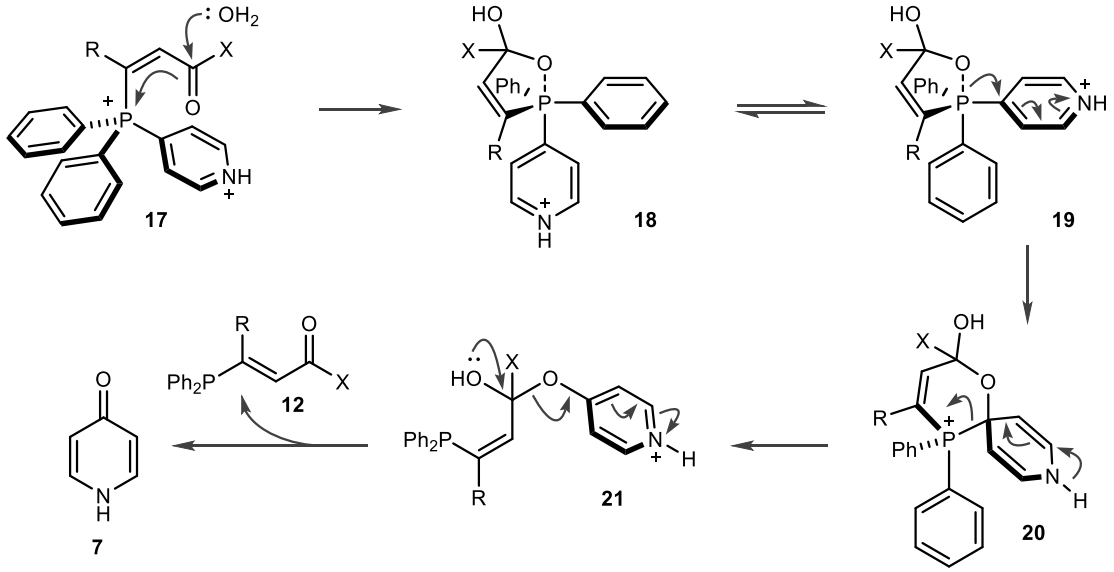


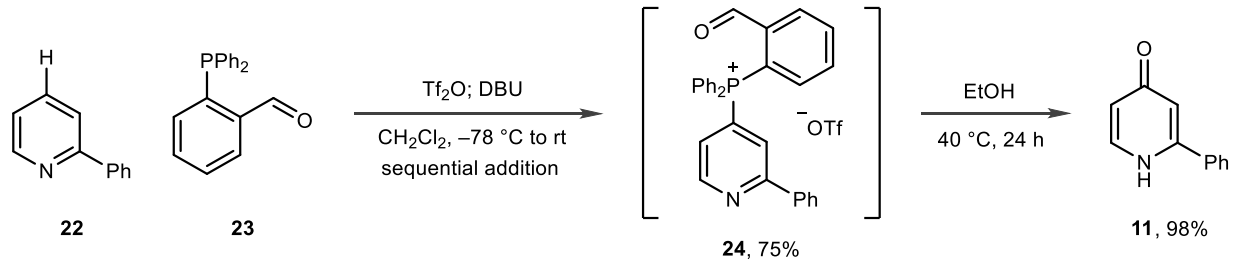
Figure 4.5 Proposed ligand-coupling mechanism for hydroxylation.

The studies outlined above led us to propose the mechanism shown in **Figure 4.5**. Upon formation of phosphonium **17**, we propose that the carbonyl undergoes attack by water and cyclizes to form phosphorane **18**. This pathway is similar to hydrate formation, and the phosphonium can serve as a Lewis acid to activate the carbonyl oxygen. Phosphorane formation

is typically the rate-limiting step in the coupling reactions that we have developed previously, and this cyclization approach should assist in lowering the energy barrier to that process. Upon formation of phosphorane **19**, ligand-coupling of the apical alkoxy ligand onto the equatorial pyridinium occurs to provide Meisenheimer-like **20**, which can rapidly rearomatize and eject phosphine. The resulting hemiacetal **21** then decomposes to provide the 4-pyridone product and generates phosphine **12**.

4.4 Design of a System for Pyridine to Pyridone Interconversion

We next set out to develop a more practical system for pyridone synthesis that met the criteria in our proposed mechanism. Our goal was to design a phosphine that could be selectively installed at the 4-position as the phosphonium salt, and then decomposed via ligand-coupling to produce the 4-pyridone. We wanted a reaction which could be performed in one pot with no isolation of the phosphonium intermediate, similar to the fluoroalkylation reaction developed previously. To achieve this, we focused on developing a phosphine which was readily accessible and bench stable, to ensure the method would be applicable in medicinal chemistry contexts. Based on the proposed mechanism, we hypothesized that forcing a *cis* relationship between the carbonyl and phosphonium and enabling the 5-membered cyclic transition state (**17**) would facilitate the desired reactivity.



22 **23** **24**, 75% **11**, 98%

Figure 4.6 Pyridine to pyridone interconversion through phosphorus ligand-coupling.

Ultimately we found that phosphine **23** fit the criteria outlined in our proposed method (**Figure 4.6**). This phosphine is commercially available but can also be synthesized in two steps from commodity chemicals. The reaction of phosphine **23** with 2-phenylpyridine gave phosphonium **23a** in 75% yield. Furthermore, simply heating this phosphonium in EtOH at 40 °C provided the pyridone product in nearly quantitative yield. Unfortunately, examination of the pyridine scope for phosphonium preparation with aldehyde **23** found that it was sub-optimal on many of the substrates that typically perform well in the salt-forming reaction (**Figure 4.7**). We hypothesized that the aldehyde participated in deleterious side reactions and found that protecting the aldehyde as acetal **26** alleviated these issues.

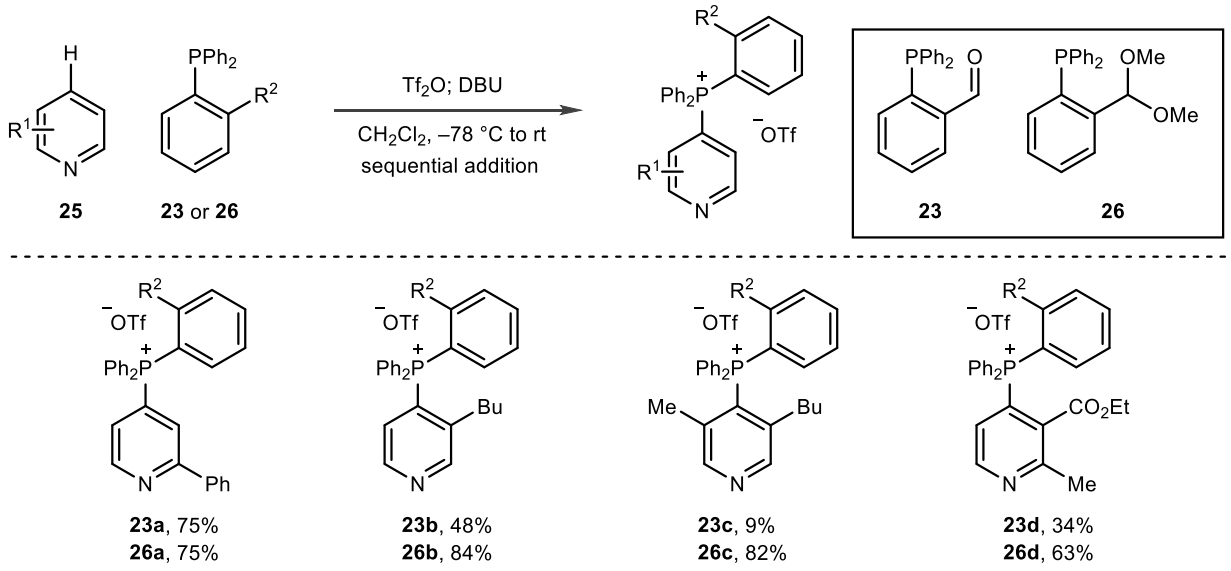
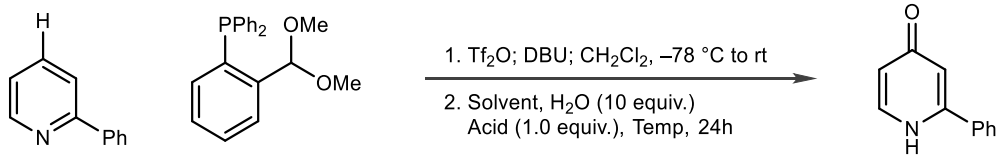


Figure 4.7 Initial phosphonium scope with aldehyde and acetal-containing phosphines.

Efforts then focused on optimizing the one-pot hydroxylation reaction with acetal phosphine **26** and 2-phenylpyridine (**Table 4.1**). Triflic acid (TfOH), trifluoroacetic acid (TFA), *p*-toluenesulfonic acid (TsOH) and methanesulfonic acid (MsOH) were all identified as viable acids to facilitate *in situ* deprotection of the acetal at 80 °C (entries 1-6). Polar solvents such as acetone, acetonitrile, and ethanol all delivered the coupled product in ~75% yield (entries 10 and

11). Attempts to lower the reaction temperature found that at higher concentration, the reaction still proceeded at a reasonable rate at 40 °C; later studies of the substrate scope found that 60 °C was more general, so this temperature was chosen for the general procedure (entries 12-16). Alternative conditions ($LiBF_4$, H_2O, MeCN, 60 °C) were also identified which allow for coupling on substrates which are acid-sensitive or prone to ethanolysis (entry 17).

Table 4.1 Optimization of one-pot hydroxylation of pyridine.



22 **26** **11**

Entry	Acid	Solvent	Temp °C	Concentration (M)	11 yield (%)
1	AcOH	EtOH	80	0.1	n.d.
2	Citric	EtOH	80	0.1	40
3	TFA	EtOH	80	0.1	65
4	TfOH	EtOH	80	0.1	75
5	MsOH	EtOH	80	0.1	73
6	TsOH	EtOH	80	0.1	74
7	TsOH	THF	80	0.1	n.d.
9	TsOH	CH_2Cl_2	80	0.1	n.d.
10	TsOH	MeCN	80	0.1	75
11	TsOH	Acetone	80	0.1	74
12	TsOH	EtOH	40	0.1	29
13	TsOH	EtOH	60	0.1	57
15	TsOH	EtOH	40	0.4	73
16	TsOH	EtOH	60	0.4	74
17	$LiBF_4$	MeCN	60	0.4	74

4.5 Investigation of Scope for Pyridone Synthesis

4.5.1 Building Block Scope

An investigation of the scope for this transformation is currently ongoing, but so far the functional group tolerance of the reaction is promising (**Figure 4.8**). 2- and 3-substituted alkyl and aryl pyridines deliver pyridone products in high yield under the one-pot coupling procedure (**27a**-**27d**). Withdrawing groups, which are sometimes problematic for ligand-coupling reactions

developed previously, are well tolerated, including substrates **27e** and **27f**. Both 2-OMe and 3-OMe pyridines (**27g** and **27h**) are also viable in the reaction but require higher temperatures to reach completion in 24 hours. Other heterocycles also function in the reaction; quinoline **27i**, as well as pyrimidine **27k** and pyridazine **27l** all gave good to high conversion. Notably, when the 4-position is blocked on pyridine and phosphonium formation occurs at the 2-position, no hydroxylation product is observed in the reaction. Instead, the ligand exchange pathway is favored and pyridine starting material is observed. However, with 4-substituted quinolines, hydroxylation proceeds at the 2-position in excellent yield (**27j**).

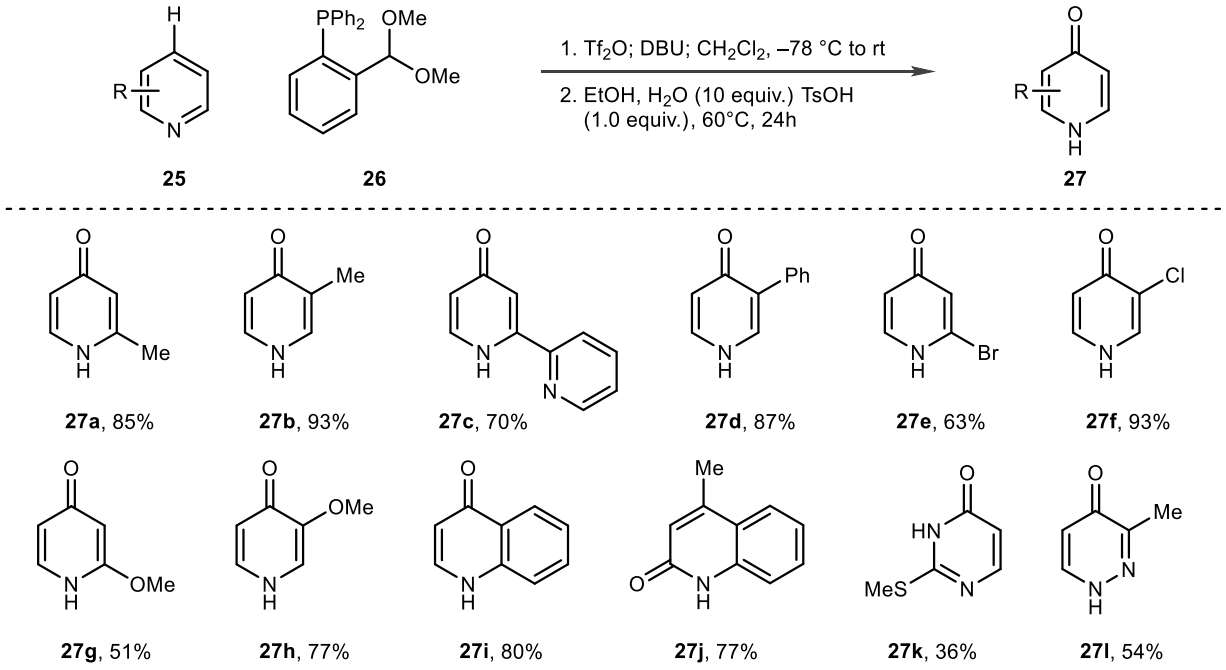


Figure 4.8 Preliminary building block scope for pyridine hydroxylation.

4.5.2 Fragment and Drug Scope

Preliminary studies of the drug-like fragment and pharmaceutical scope are also encouraging (**Figure 4.9**). So far, 5 fragments and 10 drugs have performed well in the pyridone-forming reaction (**27m**-**27aa**). The polarity of pyridones makes them difficult to isolate and carry

through an entire drug candidate synthesis, so we envision this will be a practical method for pyridone incorporation late in a synthetic strategy.

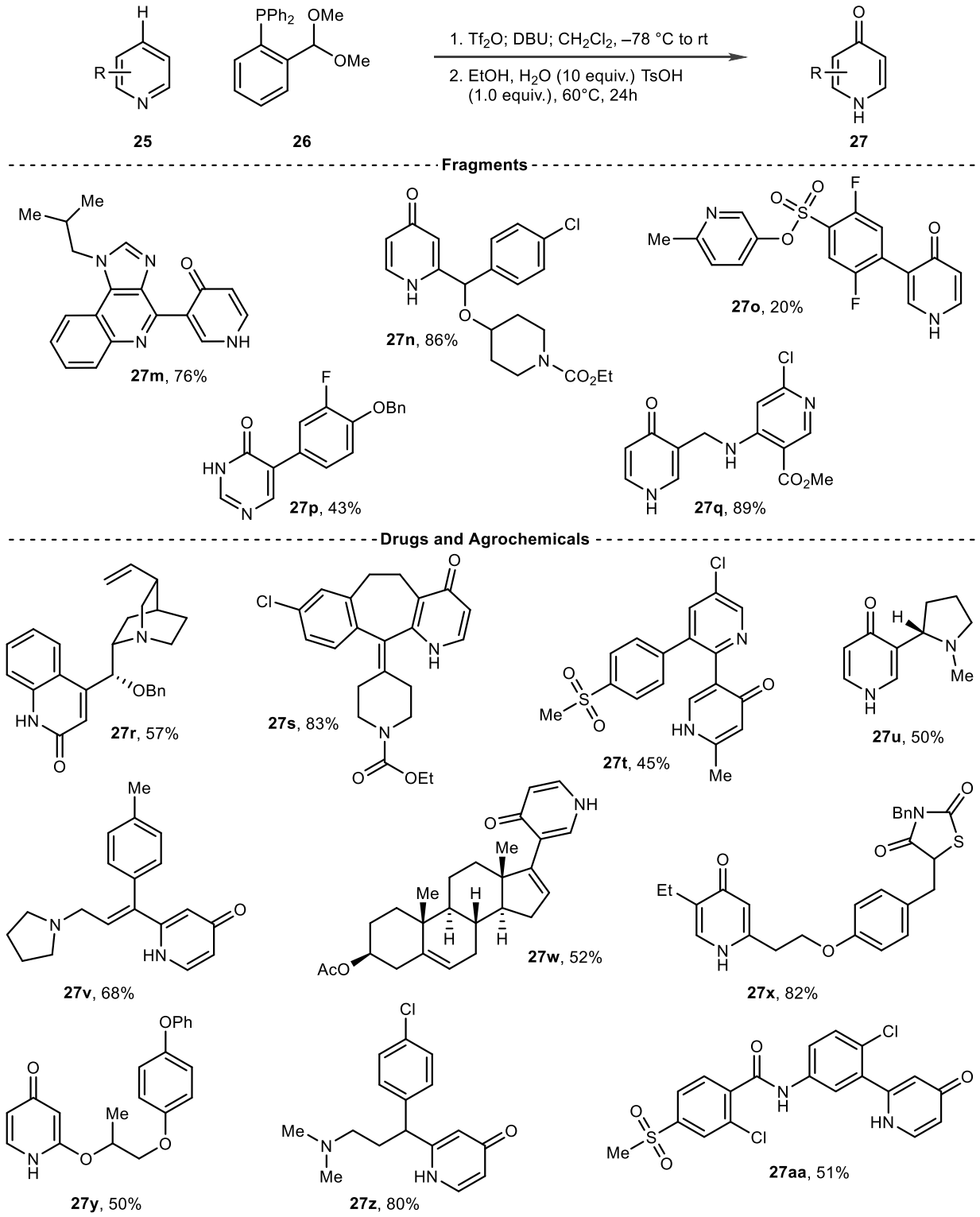


Figure 4.9 Late-stage hydroxylation of complex fragments, pharmaceuticals, and agrochemicals.

Additionally, the pyridone products can be converted to fluoropyridines in one step via deoxofluorination – currently, there are no general methods for direct 4-position fluorination on pyridine, so this approach will be valuable.[20]

4.5.3 Current Limitations

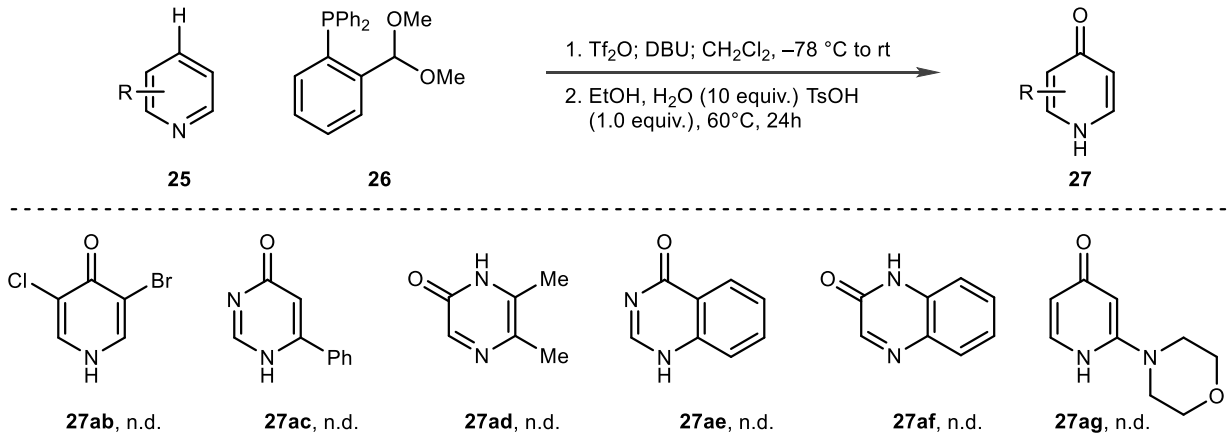


Figure 4.10 Representative examples of substrate limitations for hydroxylation.

Limitations for phosphonium formation were described in **Section 2.4.3** of Chapter 2. Current limitations for the ligand-coupling step of hydroxylation are similar to those encountered for the difluoromethylation and trifluoromethylation reactions (**Figure 4.10**). 3,5-disubstituted pyridines (**27ab**) yield none of the desired product, instead preferring protonation of the pyridine from the phosphorane intermediate. Certain diazines, such as pyrimidine **27ac**, pyrazine **27ad** and their benzo-fused counterparts (**27ae** and **27af**) favor this ligand exchange pathway as well. Investigation of substituent effects on the competition between ligand-coupling and ligand exchange is ongoing. Strongly electron-donating substituents such as in amine-substituted **27ag** are also not well-tolerated in the reaction.

4.6 Mechanistic Studies

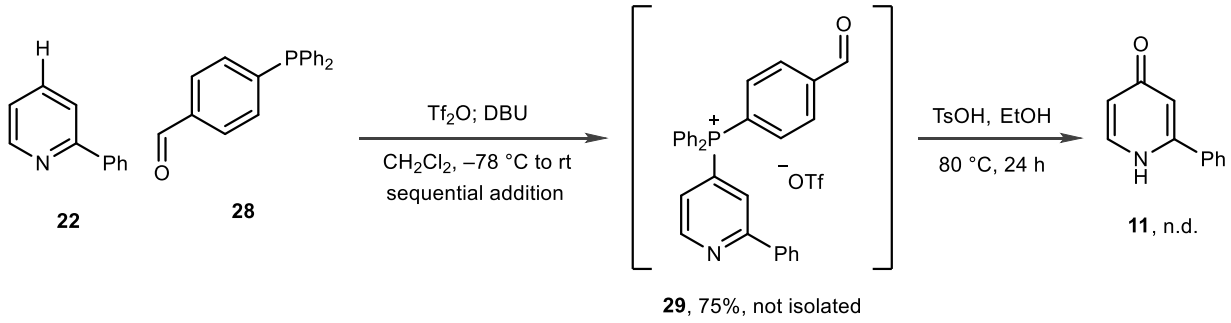


Figure 4.11 Attempt to achieve hydroxylation with *p*-substituted phosphine **28**.

To provide support for our proposed mechanism for phosphorane formation, we prepared phosphine **28** with the aldehyde at the *para* position (**Figure 4.11**). If the aldehyde substituent in phosphine **23** allowed for phosphorane formation on purely an electronics basis, phosphine **28** should also provide pyridone product under our reaction conditions. However, if our proposed cyclization mechanism is operative, the aldehyde in **28** is unlikely to form a cyclic phosphorane, and thus should not provide the hydroxylation product. Subjecting phosphonium **29** to the reaction conditions gave none of pyridone **11**, and the phosphonium persisted in the reaction, indicating that no phosphorane formation occurred and supporting our proposed cyclization pathway.

Further support for the proposed mechanism of hydroxylation was provided through a computational study in collaboration with the Paton lab. The barrier to the proposed migration of the apical alkoxy ligand in **32** is 15.5 kcal mol^{-1} and is easily achievable under the reaction conditions. Interestingly, the highest energy structure in the whole reaction pathway is the transition state for the elimination step between intermediate **33** and hemiacetal **34**. This is due to the high energy (10.6 kcal mol^{-1}) of intermediate **33** in comparison to equivalent intermediates observed for alkoxide coupling (–21 kcal mol^{-1}), fluoroalkylation (–10 kcal mol^{-1}) and bipyridine (–17 kcal mol^{-1}) synthesis, presumably due to its spirocyclic nature. Nonetheless, all of the

observed reaction energies are consistent with reactivity at room temperature, implying that phosphorane formation, while substantially faster in this system, is still the reaction bottleneck.

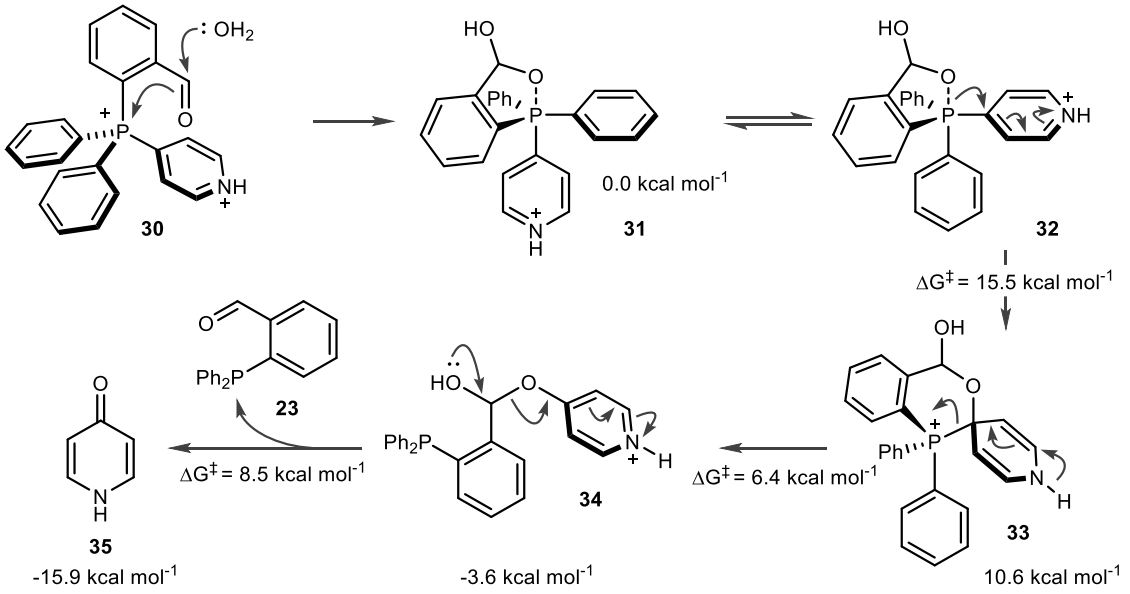


Figure 4.12 Proposed mechanism for hydroxylation and associated energy values.

4.7 Other transformations

4.7.1 Aminopyridine Synthesis

Based on our proposed mechanism involving formation of cyclic oxyphosphorane **32**, we hypothesized that a pyridine amination reaction could be feasible with minor modifications to the reaction system (**Figure 4.13**). Condensation of ammonia with the benzaldehyde ligand on phosphonium **24** provides imine **36**, which can form cyclic phosphorane **37**. Migration of the apical amino ligand in **37** and elimination of phosphine should results in aminopyridine **38**.

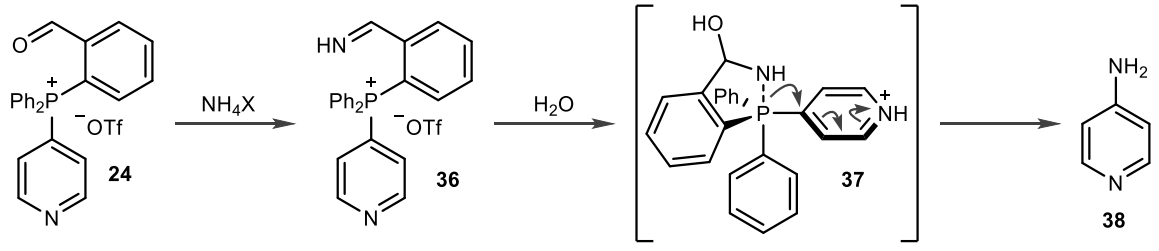


Figure 4.13 Proposed aminopyridine synthesis via phosphorus ligand-coupling.

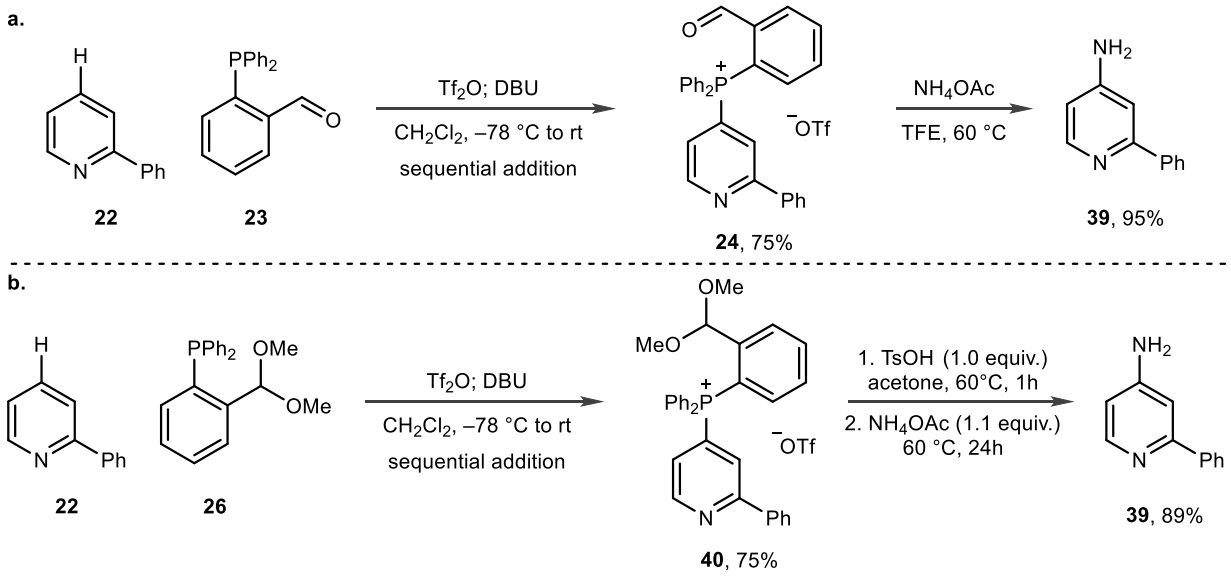


Figure 4.14 One-pot amination of pyridine via phosphorus ligand-coupling.

An initial screen for reactivity revealed that ammonium acetate in TFE provided the ligand-coupled product from aldehyde-containing phosphonium **24** in 24 hours at 60 °C (**Figure 4.14a**). Additional efforts determined that coupling could be achieved from acetal phosphonium **40** to improve the phosphonium scope of the transformation (**Figure 4.14b**). A two-stage process consisting of deprotection at a lower pH, followed by imine formation and ligand-coupling at a higher pH, provided the aminated product in 89% yield. Notably, it was determined that acetone helps to sequester methanol formed in the deprotection step, which we speculate can attack aldehyde intermediate **24** and lead to undesired pyridone product. Initial studies for the scope of this transformation are promising in a one-pot process (**Figure 4.15**). Additional efforts are ongoing to explore this scope and achieve amination with primary amines.

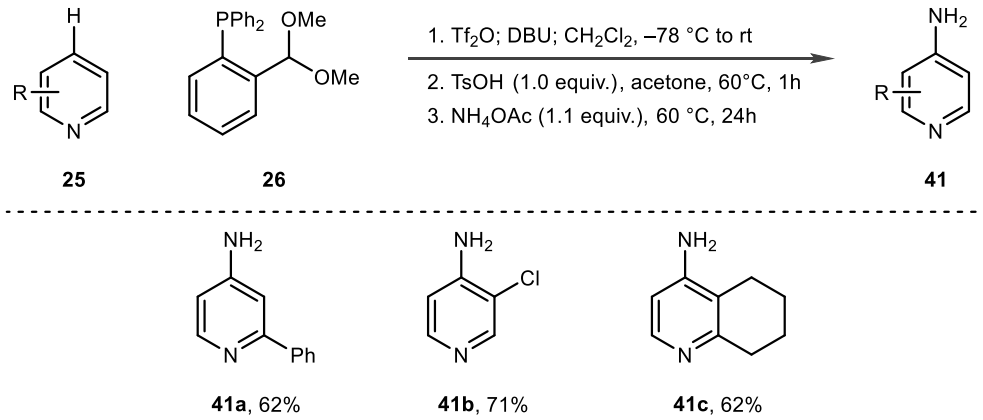


Figure 4.15 Preliminary scope for the one-pot amination of pyridines.

4.7.2. α-Pyridyl Amine Synthesis

We were also curious about the capacity of this distinct nucleophile delivery system to enable C–C bond formation through phosphorus ligand-coupling. Previous efforts to facilitate C–C coupling either required a significant electronic bias, as was the case for fluoroalkylation, or addition of aryl organolithium compounds, which often posed challenges to achieving selective coupling between the two desired ligands from an all-carbon phosphorane. Inspired by aza-allyl anion chemistry developed to functionalize α-stabilized amines, we proposed the transformation outlined in **Figure 4.16**.[21] Deprotonation of imine-containing phosphonium **42** by a sufficient base forms aza-allyl anion **43**, which can cyclize to form phosphorane **44**. We hypothesized that ring expansion, as well as the deficient nature of the α-amino ligand might provide a reasonable bias for selective ligand-coupling to pyridine over migration of one of the phenyl ligands and lead to product **46**. After hydrolysis of the resulting imine, α-pyridyl amine **47** would form.

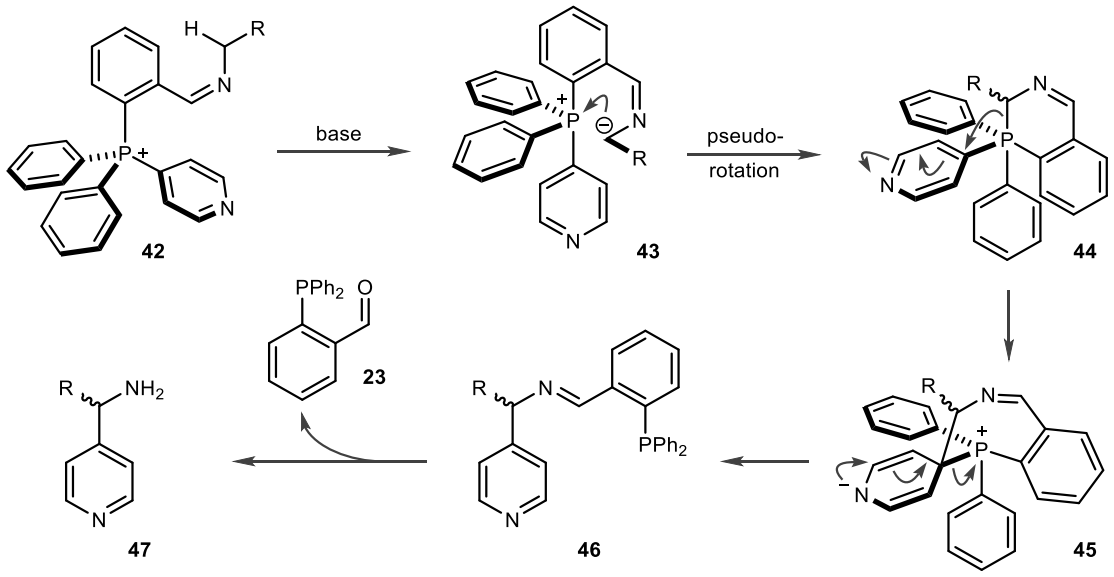


Figure 4.16 Proposed α-pyridyl amine synthesis via phosphorus ligand-coupling.

Synthesis of phosphonium **42** is possible by condensation from aldehyde **24**, but to address concerns about the phosphonium scope, an alternative approach was developed. Condensation of benzylamines **48** and **49** with phosphine **23** is achieved in 30 minutes when the reaction is run at 2 M in methanol at reflux (**Figure 4.17a**). Notably, the product precipitates from the reaction and can be collected by filtration in high yield and purity with no further purification necessary. This new imine-containing phosphine was then tested in the phosphonium forming reaction on substrates which were problematic for the aldehyde; in every case, substantial improvements in yield were observed (**Figure 4.17b**).

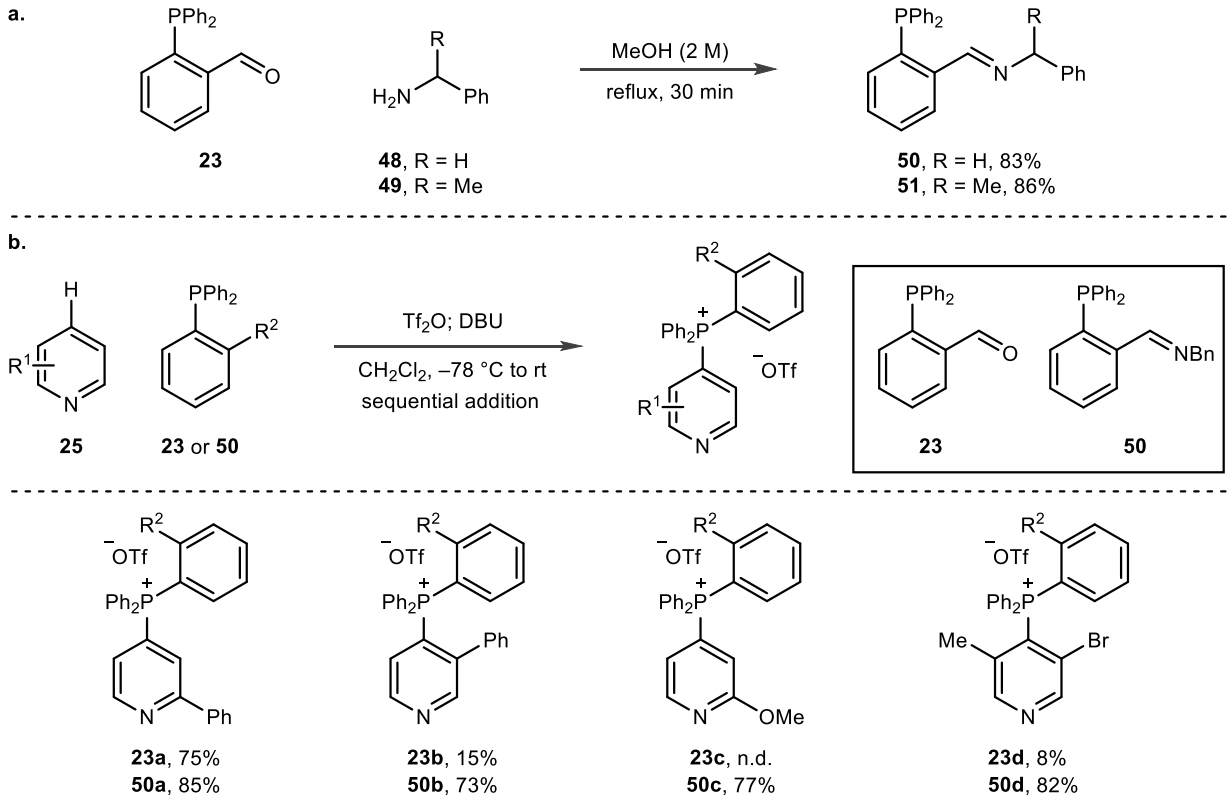


Figure 4.17 Comparison of phosphonium scope for aldehyde phosphine **23** and imine phosphine **50**.

Phosphoniums **52** and **53** were both isolated and subjected to conditions previously used to form aza-allyl anions (**Figure 4.18**). LDA and KHMDS gave none of the desired product and multiple decomposition products. However, potassium *tert*-butoxide gave **54** in 82% yield with only phosphonium salt as the remaining byproduct. Additionally, synthesis of α-quaternary imine **55** was achieved in 55%. These unoptimized conditions are a promising starting point for further investigation of the scope for this transformation.

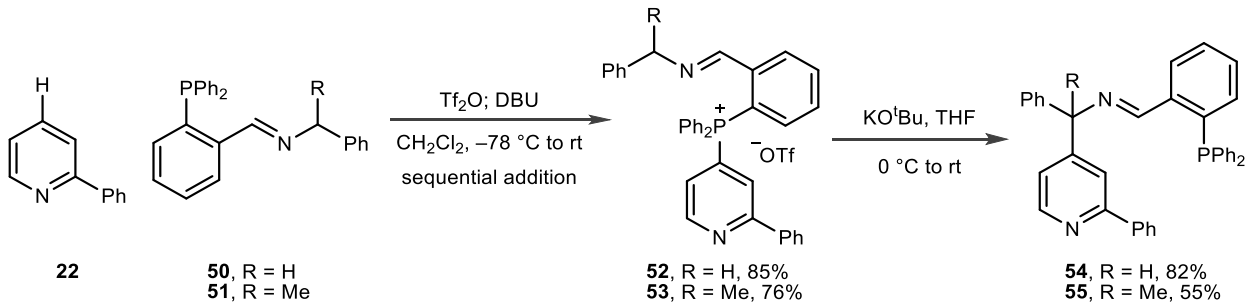


Figure 4.18 Initial results for α-pyridyl amine synthesis via phosphorus ligand-coupling.

4.8 Conclusion

A distinct nucleophile delivery strategy was discovered and developed to achieve C–O, C–N, and C–C bond-formation through phosphorous ligand-coupling. These strategies enable the synthesis of pharmaceutically-relevant pyridine compounds from C–H precursors in good yields on a range of substrates, including approved drug compounds. Computational studies and mechanistic studies support the formation of a cyclic phosphorane intermediate which undergoes ring expansion to provide selectivity during the ligand-coupling step. Studies are ongoing to develop the scopes of these transformations.

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APPENDIX ONE

PHOSPHORUS LIGAND-COUPLING AND ITS SYNTHETIC UTILITY: EXPERIMENTAL

A1.1 General Methods and Materials

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (400 MHz), an Agilent Inova 400 (400 MHz) spectrometer, an Agilent Inova 500 (500 MHz) spectrometer, or a Bruker AV-111 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.1 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm) or $(CD_3)_2SO$ (2.05 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (multiplicity, coupling constants, number of protons). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (100 MHz), an Agilent Inova 400 (100 MHz) spectrometer, an Agilent Inova 500 spectrometer (125 MHz) or a Bruker AV-111 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.01 ppm relative to the residual solvent peaks in $CDCl_3$ (77.16 ppm), $(CD_3)_2SO$ (39.51 ppm), CD_3OD (49.00 ppm) or CD_3CN (1.32 ppm).

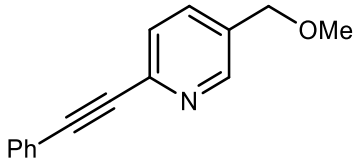
Low-resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. High-resolution mass spectra (HRMS) were measured on an Agilent 6224 TOF

LC/MS ("OTOF") interfaced to an Agilent 1200 HPLC with multi-mode (combined ESI and APCI) and Direct Analysis in Real Time (DART) sources. (IR) spectra were recorded on a Nicolet IS-50 FT-IR spectrometer as either solids or neat films, either through direct application or deposited in CHCl3, with absorptions reported in wavenumbers (cm-1). Analytical thin layer chromatography (TLC) was performed using pre-coated Silicycle glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Silicycle silica gel Siliaflash P60 40-63 um (230-400 mesh) under a positive pressure of air unless otherwise stated. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or basic potassium permanganate solutions as appropriate. Melting points (mp) were recorded using a Büchi B-450 melting point apparatus and are reported uncorrected.

Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] Methanol, 1,2-dichloroethane (DCE), 1,4-dioxane, ethyl acetate, chloroform, and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest commercial quality and used without further purification. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated. All reactions were monitored by TLC, ^{1}H NMR spectra taken from reaction samples, and liquid chromatography mass spectrometry (LCMS) using an Agilent 6310 Quadrupole Mass Spectrometer for MS analysis. Tf_2O (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. 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.

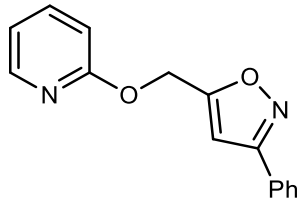
A1.2 Preparation of Heterocyclic Precursors

5-(Methoxymethyl)-2-(phenylethynyl)pyridine



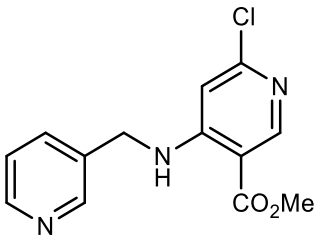
A 100 mL flask equipped with a magnetic stirring bar was charged with $PdCl_2(PPh_3)_2$ (140 mg, 0.20 mmol) and CuI (76 mg, 0.40 mmol) dissolved in diisopropylamine (20 mL) and *N*,*N*-dimethylformamide (15 mL). The resultant solution was stirred under nitrogen at room temperature for 10 minutes before adding 2-bromo-5-(methoxymethyl)pyridine (2.02 g, 10.00 mmol) in diisopropylamine (10 mL) and phenylacetylene (1.22 g, 12.00 mmol). Then, stirring was continued at room temperature for an additional hour. After this time, the reaction mixture was diluted with EtOAc and washed with a saturated NH_4Cl solution and with brine. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a light brown oil (2.12 g, 9.50 mmol, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, *J* = 2.2 Hz, 1H), 7.69 (dd, *J* = 2.2, 8.0 Hz, 1H), 7.62–7.59 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.40–7.33 (m, 3H), 4.50 (s, 2H), 3.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.33, 142.74, 135.60, 133.05, 132.12, 129.06, 128.47, 126.93, 122.32, 89.38, 88.58, 71.87, 58.52; IR υ_{max}/cm^{-1} (film): 3055, 2986, 2926, 2892, 2817, 2220, 1725, 1590, 1559, 1491, 1470, 1442, 1394, 1356, 1314, 1279, 1191, 1153, 1098, 1024, 966, 914, 863, 839, 755, 689; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_{14}NO^+$ = 224.1070, found 224.1079.

3-Phenyl-5-((pyridin-2-yloxy)methyl)isoxazole



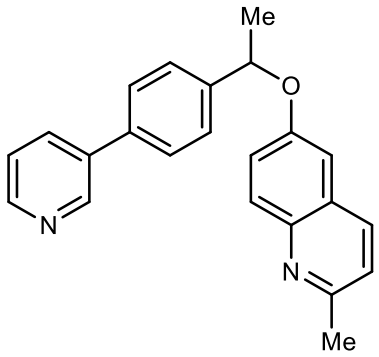
(3-Phenylisoxazol-5-yl)methanol (1.75 g, 10.00 mmol) was added portion wise under N_2 to a suspension of NaH (60%) (480 mg, 12.00 mmol) in anhydrous DMF (25 mL). After stirring at rt for 30 min, 2-fluoropyridine (1.03 mL, 12.00 mmol) was added dropwise and the mixture was stirred at room temperature overnight. The reaction mixture was quenched with cold H_2O and extracted with EtOAc (3 x 50 mL). The organic extracts were washed with H_2O (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes) to provide the title compound as a yellow oil (2.26 g, 8.90 mmol, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (dd, J = 1.6, 5.1 Hz, 1H), 7.82–7.79 (m, 2H), 7.64–7.60 (m, 1H), 7.48–7.43 (m, 3H), 6.95–6.92 (m, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.64 (s, 1H), 5.54 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.15, 162.61, 162.55, 146.85, 139.14, 130.14, 129.12, 129.03, 126.99, 117.80, 111.38, 101.67, 58.30; IR υ_{max}/cm^{-1} (film): 3128, 3059, 2961, 1611, 1600, 1573, 1469, 1433, 1422, 1403, 1365, 1309, 1284, 1263, 1249, 1221, 1167, 1140, 1044, 1014, 993, 946, 910, 826, 772, 759, 738, 731, 689, 678; m/z HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_{13}N_2O_2^+$ = 253.0972, found 253.0971.

Methyl 6-chloro-4-((pyridin-3-ylmethyl)amino)nicotinate



An oven dried 50 mL flask was charged with pyridin-3-ylmethanamine (611 μL, 6.00 mmol), methyl 4,6-dichloronicotinate (1.03 g, 5.00 mmol), *N*,*N*-diisopropylethylamine (2.09 mL, 12.00 mmol) and EtOH (10 mL). The mixture was stirred at reflux for overnight. After cooling to room temperature, the mixture was poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: EtOAc) to provide the title compound as a white solid (1.19 g, 3.55 mmol, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (s, 1H), 8.62–8.57 (m, 3H), 7.66–7.63 (m, 1H), 7.32 (ddd, J = 0.9, 4.8, 7.2 Hz, 1H), 6.53 (s, 1H), 4.47 (d, J = 5.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.06, 156.21, 155.84, 153.22, 149.46, 148.86, 134.99, 132.45, 124.04, 107.33, 105.14, 52.20, 44.24; IR υ_{max}/cm^{-1} (film): 3320, 3070, 3036, 2961, 1687, 1592, 1576, 1565, 1501, 1484, 1465, 1442, 1428, 1408, 1363, 1324, 1297, 1280, 1223, 1191, 1113, 1065, 1026, 928, 842, 791, 712, 607; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{13}ClN_3O_2^+$ = 278.0691, found 278.0704.

2-Methyl-6-(1-(4-(pyridin-3-yl)phenyl)ethoxy)quinoline

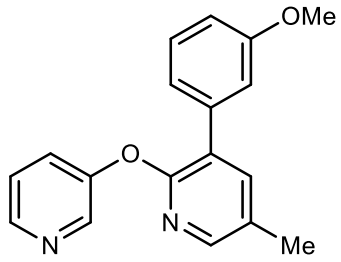


To a mixture of 1-(4-(pyridin-3-yl)phenyl)ethan-1-ol (598 mg, 3.00 mmol), Et_3N (544 µL, 3.30 mmol) and CH_2Cl_2 (6.6 mL) was added MsCl (256 µL, 3.30 mmol) in one portion at –10 °C for 30 minutes under nitrogen. After the reaction completed, the mixture was poured into cold water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to give the product 1-(4-(pyridin-3-yl)phenyl)ethyl methanesulfonate, which was used without further purification.

2-methylquinolin-6-ol (477 mg, 3.00 mmol) was added portion wise under N_2 to a suspension of NaH (60%) (144 mg, 3.60 mmol) in anhydrous DMF (4.5 mL). After stirring at room temperature for 30 min, 1-(4-(pyridin-3-yl)phenyl)ethyl methanesulfonate (prepared accordingly) in anhydrous DMF (4.5 mL) was added dropwise and the mixture was stirred at rt overnight. The reaction mixture was quenched with cold H_2O and extracted with EtOAc (3 x 50 mL). The organic extracts were washed with H_2O (3 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: EtOAc) to provide the title compound as a colorless oil (130 mg, 0.38 mmol, 13% yield over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (dd, *J* = 0.8, 2.4 Hz, 1H), 8.58 (dd, *J* = 1.6, 4.8 Hz, 1H), 7.90 (d, J = 9.2 Hz, 1H), 7.86–7.81 (m, 2H), 7.58–7.52 (m, 4H), 7.40 (dd, *J* = 2.8, 9.2 Hz, 1H), 7.34 (ddd, *J* = 0.9, 4.8,

8.0 Hz, 1H), 7.18 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 2.8 Hz, 1H), 5.50 (q, J = 6.4 Hz, 1H), 2.67 (s, 3H), 1.74 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.54, 155.37, 148.59, 148.33, 143.78, 142.94, 137.22, 136.25, 135.25, 134.32, 130.08, 127.60, 127.25, 126.40, 123.64, 122.71, 122.23, 108.58, 76.05, 25.06, 24.53; IR υ_{max}/cm^{-1} (film): 3029, 2976, 2925, 1621, 1599, 1497, 1476, 1429, 1395, 1376, 1342, 1304, 1266, 1223, 1167, 1112, 1071, 1023, 1000, 967, 940, 897, 832, 802, 710; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{21}N_2O^+$ = 341.1648, found 341.1662.

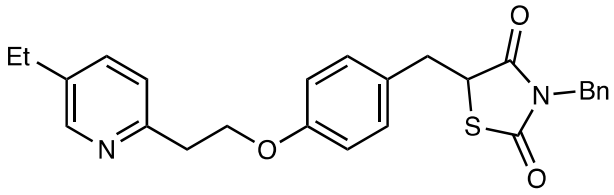
3-(3-Methoxyphenyl)-5-methyl-2-(pyridin-3-yloxy)pyridine



To a mixture of (3-methoxyphenyl)boronic acid (547 mg, 3.60 mmol), 3-bromo-5-methyl-2-(pyridin-3-yloxy)pyridine (795 mg, 3.00 mmol), $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) and Na_2CO_3 (636 mg, 6.00 mmol) was added a degassed mixture of THF (14.4 mL) and H_2O (3.6 mL). The mixture was stirred at 70 °C for 24 hours under nitrogen. After cooling to room temperature, the mixture was poured into water (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 67% EtOAc in hexanes to 75% EtOAc in hexanes) to provide the title compound as a colorless oil (778 mg, 2.64 mmol, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.46 (d, J = 2.6 Hz, 1H), 8.40 (dd, J = 1.4, 4.7 Hz, 1H), 7.94 (dd, J = 0.7, 2.4 Hz, 1H), 7.61 (dd, J = 0.7, 2.4 Hz, 1H), 7.47–7.44 (m, 1H), 7.43 (dd, J = 2.8, 9.2 Hz, 1H),

7.37 (ddd, *J* = 0.9, 4.8, 8.0 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 2.8 Hz, 1H), 5.53 (q, *J* = 6.4 Hz, 1H), 2.69 (s, 3H), 1.76 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.61, 157.67, 151.37, 146.00, 145.14, 143.27, 140.98, 137.32, 129.51, 129.33, 128.28, 125.36, 123.94, 121.61, 115.09, 113.37, 55.37, 17.57. IR υ_{max}/cm^{-1} (film): 3029, 2976, 2925, 1621, 1599, 1497, 1476, 1429, 1395, 1376, 1342, 1304, 1266, 1223, 1167, 1112, 1071, 1023, 1000, 967, 940, 897, 832, 802, 710; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{17}N_2O_2^+$ = 293.3414, found 293.3428.

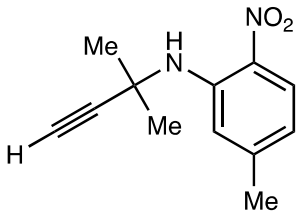
3-benzyl-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione



To a mixture of 5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (535 mg, 1.5 mmol) in DMF (15 mL) was added NaH (60% dispersion in oil) (66 mg, 1.65 mmol) at 0 °C. The reaction was warmed to room temperature over 15 minutes, then benzyl bromide (196 μL, 1.65 mmol) was added. The reaction was stirred at room temperature for 25 hours and then concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: hexanes to 25% EtOAc in hexanes) to provide the title compound as a light-yellow solid (625 mg, 1.40 mmol, 93% yield). m.p. 94-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (d, *J*= 2.2 Hz, 1H), 7.48 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.32 –7.23 (m, 5H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 4.79 –4.59 (m, 2H), 4.43 (dd, *J* = 8.7, 4.0 Hz, 1H), 4.31 (t, *J* = 6.6 Hz, 2H), 3.38 (dd, *J* = 14.1, 4.0 Hz, 1H), 3.24 (t, *J* = 6.6 Hz, 2H), 3.09 (dd, *J* = 14.1, 8.7 Hz, 1H), 2.64 (q, *J* = 7.6 Hz, 2H), 1.25 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.78, 171.03, 158.32, 155.73, 149.02, 137.24, 136.01, 135.09, 130.49, 128.72, 128.16, 127.45, 123.47, 115.98,

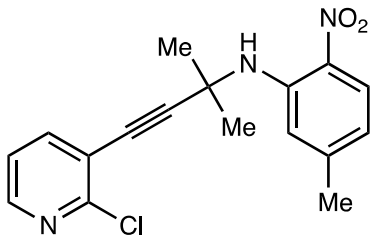
114.83, 67.32, 51.73, 45.22, 37.64, 37.62, 25.82, 15.44. IR υ_{max}/cm^{-1} (film): 3033, 2966, 2931, 2874, 2360, 2342, 1749, 1680, 1611, 1512, 1490, 1430, 1382, 1330, 1247, 1179, 1146, 1029, 908, 730, 700. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{26}H_{27}N_2O_3S^+$= 447.1737, found 447.1748.

5-methyl-*N*-(2-methylbut-3-yn-2-yl)-2-nitroaniline



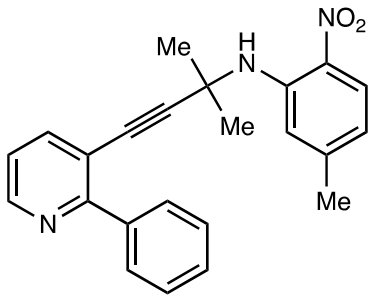
To a mixture of 2-fluoro-4-methyl-1-nitrobenzene (776 mg, 5 mmol) and K_2CO_3 (1.38 g, 10 mmol) in DMF was added 2-methylbut-3-yn-2-amine (2.63 mL, 25 mmol), and the reaction was heated to 60 °C for 72 hours. After cooling to room temperature, the reaction was poured into water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 5% CH_2Cl_2 in hexanes) to provide the title compound as a yellow solid (562 mg, 2.57 mmol, 51% yield). m.p. 104-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 – 8.20 (m, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.34 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.51 (dd, *J* = 8.8, 1.7 Hz, 1H), 2.47 (s, 1H), 2.37 (s, 3H), 1.73 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 147.01, 143.60, 131.22, 127.03, 117.81, 116.26, 86.22, 71.92, 47.61, 30.51, 22.42. IR υ_{max}/cm^{-1} (film): 3331, 3288, 2994, 2979, 2938, 2360, 2342, 1619, 1582, 1486, 1414, 1334, 1276, 1237, 1209, 1177, 1076, 988, 940, 753, 679, 647. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_{15}N_2O_2^+$ = 219.1128, found 219.1119.

***N*-(4-(2-chloropyridin-3-yl)-2-methylbut-3-yn-2-yl)-5-methyl-2-nitroaniline**



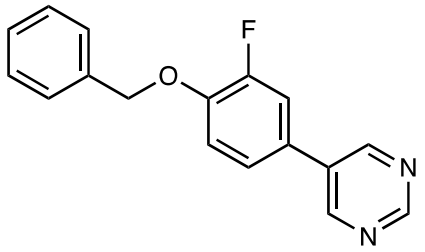
To a mixture of 3-bromo-2-chloropyridine (620 mg, 3.22 mmol), CuI (37 mg, 0.19 mmol), $PdCl_2(PPh_3)_2$ (68 mg, 0.097 mmol) and Et_3N (6.5 mL) was added 5-methyl-*N*-(2-methylbut-3-yn-2-yl)-2-nitroaniline (704 mg, 3.22 mmol). The reaction was heated to 100 °C for 24 hours. After cooling to room temperature, EtOAc (20 mL) and water (20 mL) was added, the organic layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a yellow oil (692 mg, 2.10 mmol, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.36 (s, 1H), 8.30 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.72 (dd, *J* = 7.7, 2.0 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.19 (dd, *J* = 7.6, 4.8 Hz, 1H), 6.51 (dd, *J* = 8.7, 1.7 Hz, 1H), 2.36 (s, 3H), 1.83 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 152.48, 148.57, 147.11, 143.42, 141.51, 131.20, 126.92, 121.97, 119.95, 117.93, 116.31, 99.29, 78.80, 48.28, 30.32, 22.39. IR υ_{max}/cm^{-1} (film): 3352, 2984, 2938, 2360, 2342, 2253, 1618, 1578, 1491, 1394, 1335, 1270, 1236, 1215, 1188, 1079, 908, 754, 730. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{17}H_{17}ClN_3O_2^+$ = 330.1004, found 330.1011.

5-methyl-*N*-(2-methyl-4-(2-phenylpyridin-3-yl)but-3-yn-2-yl)-2-nitroaniline



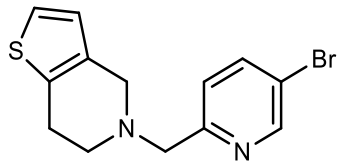
To a mixture of *N*-(4-(2-chloropyridin-3-yl)-2-methylbut-3-yn-2-yl)-5-methyl-2-nitroaniline (241 mg, 0.73 mmol), phenylboronic acid (98 mg, 0.80 mmol), $Pd(PPh_3)_4$ (85 mg, 0.073 mmol) and Na_2CO_3 (164 mg, 1.55 mmol) was added toluene (6 mL) and EtOH (6 mL). The reaction was heated to 110 °C for 24 hours. After cooling to room temperature, the reaction was filtered through celite, EtOAc (20 mL) and water (20 mL) was added, the organic layer was separated, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 10% CH_2Cl_2 in hexanes) to provide the title compound as a yellow oil (252 mg, 0.678 mmol, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (d, 1H), 8.32 (s, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.88 (dd, *J* = 6.7, 2.9 Hz, 2H), 7.78 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.39 – 7.29 (m, 3H), 7.21 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.15 (s, 1H), 6.52 – 6.39 (m, 1H), 2.13 (s, 3H), 1.73 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.97, 148.89, 146.99, 143.57, 140.99, 139.26, 131.05, 129.21, 129.08, 127.89, 126.93, 121.46, 117.73, 117.32, 116.14, 96.73, 81.84, 48.30, 30.18, 22.29. IR υ_{max}/cm^{-1} (film): 3351, 3058, 2980, 2932, 2360, 2342, 1618, 1578, 1490, 1422, 1334, 1265, 1237, 1186, 1077, 743. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{22}N_3O_2^+$ = 372.1707, found 372.1719.

5-(4-(benzyloxy)-3-fluorophenyl)pyrimidine



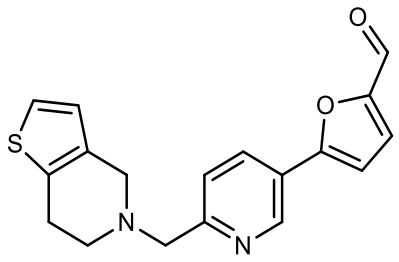
To a mixture of 5-bromopyrimidine (795 mg, 5.0 mmol), (4-(benzyloxy)-3-fluorophenyl)boronic acid (1.85 g, 7.5 mmol), Pd/C (10 % w/w) (160 mg, 0.15 mmol) and K_2CO_3 (691 mg, 5.0 mmol) was added EtOH (30 mL) and H_2O (10 mL). The reaction was heated to 80 °C for 18 hours. After cooling to room temperature, the reaction was filtered through celite, EtOAc (50 mL) and water (50 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a white solid (1.135 g, 4.05 mmol, 81 % yield). m.p. 103-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.18 (s, 1H), 8.89 (s, 2H), 7.49 – 7.44 (m, 2H), 7.41 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 2H), 7.38 – 7.34 (m, 1H), 7.33 (d, *J* = 2.2 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.13 (t, *J* = 8.4 Hz, 1H), 5.22 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.54, 154.64, 152.18, 147.67 (d, *J* = 10.7 Hz), 136.17, 133.12 (d, *J* = 1.9 Hz), 128.87, 128.47, 127.70 (d, *J* = 6.8 Hz), 127.55, 122.99 (d, *J* = 3.6 Hz), 116.45 (d, *J* = 2.4 Hz), 114.99 (d, *J* = 19.6 Hz), 71.52; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -131.81 (dd, *J* = 11.8, 8.4 Hz). IR υ_{max}/cm^{-1} (film): 3050, 3035, 2941, 2883, 2578, 2360, 2341, 1618, 1585, 1559, 1522, 1417, 1403, 1389, 1302, 1275, 1257, 1203, 1146, 1052, 1012, 1001, 898, 873, 855, 791, 749, 722, 699, 635, 625. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{17}H_{14}FN_2O^+$ = 281.1085, found 281.1105.

5-((5-bromopyridin-2-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine



An oven-dried 200 mL round bottom flask was charged with 5-bromopicolinaldehyde (2.68 g, 14.4 mmol), 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (2.20 g, 15.8 mmol), and sodium triacetoxyhydroborate (6.1 g, 28.8 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill. DCM (72 mL) was added to the reaction flask along with glacial AcOH (1.65 mL). After 19 hours at room temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl (30 mL), diluted with CH_2Cl_2, and the organic layer was separated. The aqueous layer was basified with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 40 % EtOAc in hexanes) to provide the title compound as a white solid (4.17 g, 13.5 mmol, 94 % yield). mp 88-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (d, *J* = 2.2 Hz, 1H), 7.79 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.07 (d, *J* = 5.1 Hz, 1H), 6.69 (d, *J* = 5.1 Hz, 1H), 3.83 (s, 2H), 3.62 (s, 2H), 2.95 – 2.88 (m, 2H), 2.88 – 2.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.67, 150.33, 139.28, 133.71, 133.42, 125.30, 124.54, 122.88, 119.22, 63.16, 53.31, 50.98, 25.57. IR υ_{max}/cm^{-1} (film): 2962, 2901, 2826, 2771, 2360, 2342, 1573, 1468, 1446, 1376, 1365, 1320, 1171, 1108, 1086, 1001, 982, 843, 703, 652. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{14}BrN_2S^+$ = 309.0056, found 309.0041.

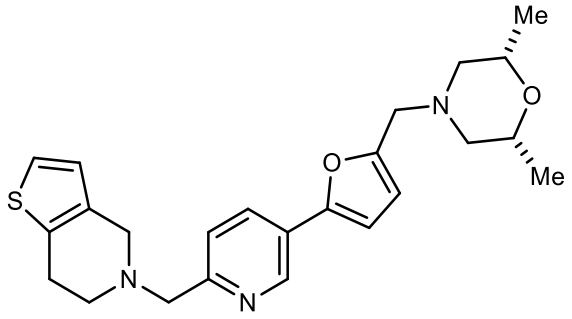
5-(6-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)pyridin-3-yl)furan-2-carbaldehyde



An oven dried 200 mL pressure tube was charged with 5-((5-bromopyridin-2-yl)methyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (4.02 g, 13.0 mmol), (5-formylfuran-2-yl)boronic acid (1.65 g, 11.8 mmol), K_2CO_3 (4.89 g, 35.4 mmol), $Pd(OAc)_2$ (132 mg, 0.59 mmol), triphenylphosphine (619 mg, 2.36 mmol) and subjected to three cycles of vacuum/nitrogen backfill. H_2O (43 mL) and dimethoxyethane (41 mL) were charged to the tube. The mixture was heated at 85 ºC for 18 hours then diluted with CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted 2x with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 2 % MeOH in CH_2Cl_2) to provide the title compound as a slightly impure white solid. Further purification was achieved by dissolving the compound in CH_2Cl_2 and adding an excess of 1M HCl. The aqueous phase was extracted with CH_2Cl_2, separated, and treated with sat. aq. $NaHCO_3$. The aqueous phase was then extracted with CH_2Cl_2 and the combined organic layers were washed with brine then dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as pure white solid (1.45 g, 4.5 mmol, 38 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.68 (s, 1H), 8.99 (d, *J* = 2.1 Hz, 1H), 8.10 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 3.7 Hz, 1H), 7.08 (d, *J* = 5.1 Hz, 1H), 6.92 (d, *J* = 3.7 Hz, 1H), 6.70 (d, *J* = 5.1 Hz, 1H), 3.94 (s, 2H), 3.68 (s, 2H), 3.00 – 2.83 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.43, 160.18, 156.71, 152.67, 146.18, 133.69, 133.42, 133.03, 125.31, 123.96, 123.28, 122.91, 108.62, 63.55, 53.36, 51.04, 25.55. IR υ_{max}/cm^{-1} (film):

3109, 2913, 2813, 2360, 2342, 1690, 1600, 1584, 1519, 1467, 1403, 1376, 1357, 1340, 1259, 1019, 965, 797, 768, 754, 700, 637. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{17}N_2O_2S^+$ = 325.1005, found 325.1014.

5-(6-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)pyridin-3-yl)furan-2-carbaldehyde

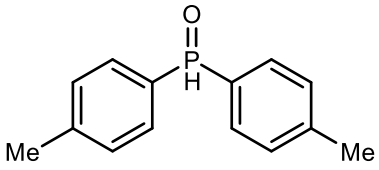


An oven-dried 100 mL round bottom flask was charged with 5-(6-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)pyridin-3-yl)furan-2-carbaldehyde (0.973 g, 3.00 mmol), *cis*-2,6,-dimethylmorpholine (0.406 mL, 3.30 mmol), and sodium triacetoxyhydroborate (1.27 g, 6.00 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill. DCM (15 mL) was added to the reaction flask along with glacial AcOH (0.343 mL). After 3 hours stirring at room temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), diluted with CH_2Cl_2, and the organic layer was separated. The aqueous layer was basified with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel, gradient elution: 90 % EtOAc in hexanes to 5 % MeOH in CH_2Cl_2) to provide the title compound as an amber oil (1.17 g, 2.8 mmol, 92 % yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.85 (d, *J* = 1.9 Hz, 1H), 7.91 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 5.1 Hz, 1H), 6.68 (dd, *J* = 10.6, 4.2 Hz, 2H), 6.33 (d, *J* = 3.3 Hz, 1H), 3.89 (s, 2H), 3.71 (ddq, *J* = 12.5, 6.3, 3.1, 1.7 Hz, 2H), 3.63 (d, *J* = 17.5 Hz, 4H), 2.99 – 2.83 (m,

4H), 2.78 (d, J = 10.5 Hz, 2H), 1.86 (t, J = 10.8 Hz, 2H), 1.15 (d, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.28, 152.06, 150.82, 144.70, 133.73, 133.34, 131.39, 125.48, 125.21, 122.94, 122.66, 111.19, 106.81, 71.63, 63.52, 58.94, 54.81, 53.20, 50.85, 25.47, 19.15. IR υ_{max}/cm^{-1} (film): 2970, 2929, 2811, 2771, 2360, 2342, 1591, 1566, 1477, 1453, 1397, 1374, 1300, 1197, 1141, 1082, 1065, 1018, 981, 837, 788, 733, 700. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{24}H_{30}N_3O_2S^+$ = 424.2053, found 424.2062.

A1.3 Preparation of Phosphines

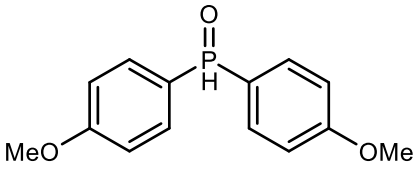
Di-p-tolylphosphine oxide



An oven-dried 200 mL round bottom flask was charged with 4-bromotoluene (11.4 g, 66.6 mmol) and 70 mL THF. The resulting solution was added dropwise to a separate oven-dried 200 mL round bottom flask containing magnesium turnings (1.70 g, 70 mmol) at 0 °C. Upon completion of the addition, the flask was allowed to warm to room temperature. After stirring for 2 hours at room temperature the mixture was cooled with an ice bath and a solution of diethyl phosphite (2.6 mL, 20 mmol) in 7.0 mL THF was added. The mixture was allowed to warm to room temperature and stirred for two hours. Subsequently 60 mL 0.1 N HCl was added drop wise over a period of 5 minutes at 0 °C, followed by addition of 60 mL methyl *tert*-butyl ether (MTBE) and stirring for further 5 minutes. The upper organic phase was decanted from the formed gel. 60 mL CH_2Cl_2 was added to the remaining gel and the mixture agitated well for additional 5 minutes. The resultant mixture was then filtered through a frit equipped with Celite. After washing the Celite with CH_2Cl_2 (2 x 60 mL) the organic phases were combined, dried over Na_2SO_4 and the solvent was removed

in vacuo. The crude product was purified by flash chromatography (silica gel: 90 % EtOAc in Hexanes) to give the product di-p-tolylphosphine oxide as a white solid (4.35 g, 18.9 mmol, 94 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (d, J = 480 Hz, 1H), 7.57 (dd, J = 13.5, 7.9 Hz, 4H), 7.29 (dd, J = 8.0, 2.7 Hz, 4H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.04 (d, J = 3.2 Hz), 130.70 (d, J = 11.9 Hz), 129.56 (d, J = 13.4 Hz), 128.32 (d, J = 104.0 Hz), 21.64 (d, J = 1.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 21.53. The spectroscopic data is in agreement with the previous reported synthesis.[2]

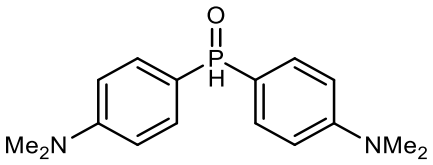
Bis(4-methoxyphenyl)phosphine oxide



An oven-dried 200 mL round bottom flask was charged with 4-bromoanisole (8.3 mL, 66.6 mmol) and 70 mL THF. The resulting solution was added dropwise to a separate oven-dried 200 mL round bottom flask containing magnesium turnings (1.70 g, 70 mmol) at 0 °C. Upon completion of the addition, the flask was allowed to warm to room temperature. After stirring for 2 hours at room temperature the mixture was cooled with an ice bath and a solution of diethyl phosphite (2.6 mL, 20 mmol) in 7.0 mL THF was added. The mixture was allowed to warm to room temperature and stirred for two hours. Subsequently 60 mL 0.1 N HCl was added drop wise over a period of 5 minutes at 0 °C, followed by addition of 60 mL methyl *tert*-butyl ether (MTBE) and stirring for further 5 minutes. The upper organic phase was decanted from the formed gel. 60 mL CH_2Cl_2 was added to the remaining gel and the mixture agitated well for additional 5 minutes. The resultant mixture was then filtered through a frit equipped with Celite. After washing the Celite with CH_2Cl_2 (2 x 60 mL) the organic phases were combined, dried over Na_2SO_4 and the solvent was removed

in vacuo. The crude product was purified by flash chromatography (silica gel: 1 % MeOH in EtOAc) to give the product bis(4-methoxyphenyl)phosphine oxide as a white solid (4.72 g, 18.0 mmol, 90 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J = 476 Hz, 1H), 7.61 (dd, J = 13.2, 8.6 Hz, 4H), 6.99 (dd, J = 8.7, 2.3 Hz, 4H), 3.85 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.88 (d, J = 2.8 Hz), 132.63 (d, J = 12.9 Hz), 123.01 (d, J = 107.9 Hz), 114.43 (d, J = 13.9 Hz), 55.36; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 20.56. The spectroscopic data is in agreement with the previous reported synthesis.[2]

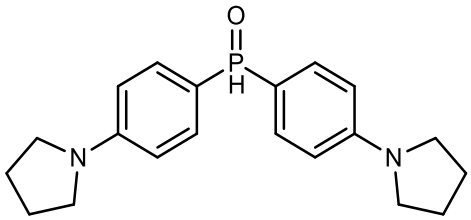
Bis(4-(dimethylamino)phenyl)phosphine oxide



An oven-dried 100 mL round bottom flask was charged with 4-bromo-*N*,*N*-dimethylaniline (4.00 g, 20.00 mmol) and 20 mL THF. The resulting solution was added dropwise to a separate oven-dried 100 mL round bottom flask containing magnesium turnings (504 mg, 21.00 mmol) at 0 °C. After stirring for four hours at room temperature, the mixture was cooled with an ice bath and a solution of diethyl phosphite (773 µL, 6.00 mmol) in 2 mL THF was added. The mixture was allowed to warm to room temperature and stirred for two hours. Subsequently 16 mL 0.1 N HCl was added drop wise over a period of 5 minutes at 0 °C, followed by addition of 16 mL methyl *tert*-butyl ether (MTBE) and stirring for further 5 minutes. The upper organic phase was decanted from the formed gel. 20 mL CH_2Cl_2 were added to the remaining gel and the mixture agitated well for additional 5 minutes. The resultant mixture was then filtered through a frit equipped with Celite. After washing the Celite with CH_2Cl_2 (2 x 30 mL) the organic phases were combined, dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash

chromatography (silica gel: EtOAc to 2% MeOH in EtOAc) to give the product bis(4-(dimethylamino)phenyl)phosphine oxide as a white solid (1.38 g, 16 .00mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, J = 468 Hz, 1H), 7.50 (dd, J = 13.0, 8.8 Hz, 4H), 6.71 (dd, J = 8.9, 2.2 Hz, 4H), 3.01 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.64 (d, J = 2.4 Hz), 132.21 (d, J = 12.6 Hz), 117.18 (d, J = 111.9 Hz), 111.41 (d, J = 13.4 Hz), 39.96; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.11. The spectroscopic data is in agreement with previous reported synthesis.[2]

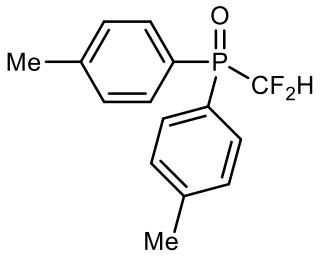
Bis(4-(pyrrolidin-1-yl)phenyl)phosphine oxide



An oven-dried 500 mL round bottom flask was charged with 1-(4-bromophenyl)pyrrolidine (31.0 g, 137 mmol) and 140 mL THF. The resulting solution was added dropwise to a separate oven-dried 500 mL round bottom flask containing magnesium turnings (3.51 g, 144 mmol) at 0 °C. Upon completion of the addition, the flask was allowed to warm to room temperature. After stirring for 2 hours at room temperature the mixture was cooled with an ice bath and a solution of diethyl phosphite (5.31 mL, 41.2 mmol) in 14.0 mL THF was added. The mixture was allowed to warm to room temperature and stirred for two hours. Subsequently 140 mL 0.1 N HCl was added drop wise over a period of 5 minutes at 0 °C, followed by addition of 140 mL methyl *tert*-butyl ether (MTBE) and stirring for further 5 minutes. The upper organic phase was decanted from the formed gel. 140 mL CH_2Cl_2 was added to the remaining gel and the mixture agitated well for additional 5 minutes. The resultant mixture was then filtered through a frit equipped with Celite. After washing the Celite with CH_2Cl_2 (2 x 100 mL) the organic phases were combined, dried over

Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica gel: 3 % MeOH in CH_2Cl_2) to give the product bis(4-(pyrrolidin-1-yl)phenyl)phosphine oxide as a white solid (11.9 g, 34.8 mmol, 84 % yield). mp 176-178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 468.6 Hz, 1H), 7.48 (dd, *J* = 13.0, 8.7 Hz, 4H), 6.56 (dd, *J* = 8.8, 2.3 Hz, 4H), 3.40 – 3.20 (m, 8H), 2.11 – 1.92 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.27 (d, *J* = 2.3 Hz), 132.50 (d, *J* = 12.9 Hz), 116.72 (d, *J* = 112.6 Hz), 111.45 (d, *J* = 13.6 Hz), 47.57, 25.56; ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.61. IR υ_{max}/cm^{-1} (film): 2953, 2850, 2270, 1594, 1542, 1482, 1459, 1385, 1283, 1175, 1125, 1003, 961, 927, 802, 708. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{20}H_{26}N_2OP^+$ = 341.1777, found 341.1769.

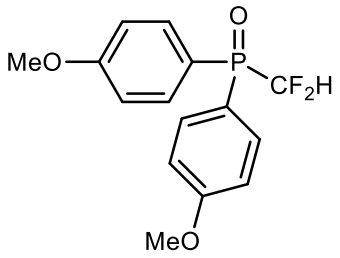
(Difluoromethyl)di-p-tolylphosphine oxide



Prepared according to a previous report.[3] An oven-dried 300 mL round bottom flask was charged with di-p-tolylphosphine oxide (3.45 g, 15 mmol) and K_2CO_3 (10.4 g, 75 mmol) and subjected to three cycles of vacuum/nitrogen backfill. CH_2Cl_2 (30 mL) and H_2O (90 mL) were added and the mixture was stirred until all solids dissolved. The flask was cooled to 0 °C and a solution of bromodifluoromethyl)trimethylsilane (6.92 mL, 45 mmol) in CH_2Cl_2 (15 mL) was added. After being stirred at 0 °C for 16 h, the reaction was quenched by adding water (150 mL), followed by extraction with EtOAc (2 × 100 mL). The organic layers were combined and dried over anhydrous $MgSO_4$ and filtered. After removal of the solvents *in vacuo*, the crude material was purified by

flash chromatography (silica gel: 50 % EtOAc in petroleum ether) to provide the title compound as a white solid (2.92 g, 10.4 mmol, 69 % yield). mp 127-128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75 (dd, *J* = 11.6, 8.0 Hz, 4H), 7.35 (dd, *J* = 7.9, 2.5 Hz, 4H), 6.29 (td, *J* = 49.2, 22.0 Hz, 1H), 2.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.20 (d, *J* = 2.9 Hz), 132.20 (d, *J* = 10.0 Hz), 129.80 (d, *J* = 12.7 Hz), 123.45 (d, *J* = 104.8 Hz), 115.51 (td, *J* = 266.1, 104.6 Hz), 21.85 (d, *J* = 1.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -132.25 (dd, *J* = 69.5, 49.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 23.08 (t, *J* = 69.4 Hz). IR υ_{max}/cm^{-1} (film): 3041, 2967, 2360, 2342, 1602, 1384, 1347, 1220, 1200, 1194, 1121, 1080, 1040, 805, 664, 641, 629. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_{16}F_2OP^+$ = 281.0901, found 281.0913.

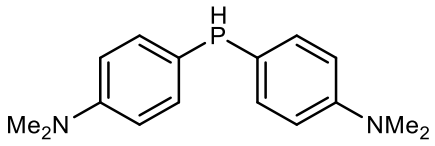
(Difluoromethyl)bis(4-methoxyphenyl)phosphine oxide



Prepared according to a modified version of a previous report.[4] An oven-dried round 100 mL round bottom flask was charged with bis(4-methoxyphenyl)phosphine oxide (13.1 g, 50 mmol) and brought into a nitrogen-filled glovebox. LiH (0.48 g, 60 mmol) and LiCl (8.5 g, 200 mmol) were added and the flask was brought out of the glovebox and equipped with a nitrogen line. After cooling to 0 °C, the flask was charged with DMF while stirring and allowed to warm to room temperature. After 30 minutes, trifluoromethyltrimethylsilane (30 mL, 200 mmol) was added dropwise at 0 °C, and the reaction mixture was allowed to warm to room temperature. After 20 minutes, the solution was cooled to 0 °C and a 1M solution of aqueous K_2CO_3 was added slowly,

and the reaction was allowed to warm to room temperature. After 2 hours, the solution was treated with 60 mL of 1M HCl and extracted (3x) with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 25 % EtOAc in CH_2Cl_2) to provide the title compound as white solid (12.3 g, 39.5 mmol, 79 % yield). mp 87-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (dd, *J* = 11.1, 8.7 Hz, 4H), 7.04 (dd, *J* = 8.8, 2.2 Hz, 4H), 6.27 (td, *J* = 49.3, 21.9 Hz, 1H), 3.87 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.62 (d, *J* = 2.9 Hz), 134.15 (d, *J* = 10.9 Hz), 117.74 (d, *J* = 109.4 Hz), 115.58 (td, *J* = 265.7, 105.7 Hz), 114.67 (d, *J* = 13.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -132.26 (dd, *J* = 69.4, 49.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 22.84 (t, *J* = 69.4 Hz). IR υ_{max}/cm^{-1} (film): 3012, 2964, 2845, 2360, 2342, 1594, 1567, 1499, 1458, 1411, 1318, 1294, 1256, 1199, 1185, 1123, 1107, 1081, 1024, 828, 815, 800, 670, 640, 575. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_{16}F_2O_3P^+$ = 313.0800, found 313.0812.

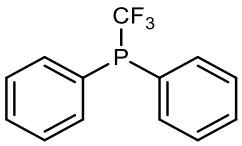
4,4'-Phosphanediylbis(N,N-dimethylaniline)



A 100 mL flask was equipped with a gas inlet, a bubbler and an addition funnel. The addition funnel was charged with a solution of the bis(4-(dimethylamino)phenyl)phosphine oxide (577 mg, 2.00 mmol) in 4 mL THF. This solution was added over a period of 15 minutes to a 1M solution of DIBAL-H in hexane (6 mL, 6.00 mmol) and stirred for overnight at room temperature (caution: gas evolution). Subsequently 7 mL freshly degassed MTBE was added via the addition funnel over ten minutes. After cooling the solution to 0 °C, 4 mL 2N aq. NaOH (freshly degassed) was added via the addition funnel over 15 minutes (caution: vigorous gas evolution), followed by 2 mL sat.

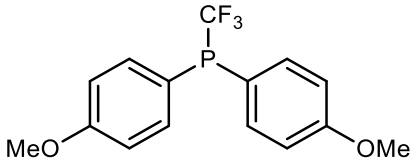
aq. NaCl over 5 minutes. The solution was stirred for additional 5 minutes and warmed to room temperature. Stirring was subsequently stopped, and the layers allowed to separate. The organic layer was then transferred via cannula to a second 250 mL flask charged with Na_2SO_4 (4.00 g). After stirring for 10 minutes the mixture was filtered under N_2 atmosphere and the solvent removed *in vacuo* yielding 4,4'-phosphanediylbis(N,N-dimethylaniline) as a white solid (495 mg, 1.82 mmol, 91% yield) (caution: the phosphine is air sensitive and stored in glovebox). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (t, *J* = 7.8 Hz, 4H), 6.67 (d, *J* = 7.1 Hz, 4H), 5.16 (d, *J* = 218.8 Hz, 1H), 2.94 (s, 12H). ^{31}P NMR (162 MHz, $CDCl_3$) δ: -46.13. The spectroscopic data is in agreement with previous reported synthesis.[2]

Diphenyl(trifluoromethyl)phosphane



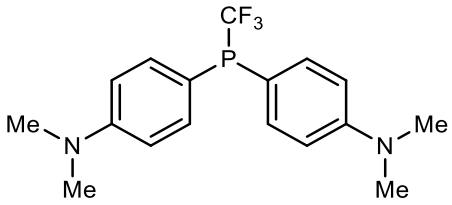
Prepared according to a previous report.[5] An oven dried 100 mL round bottom flask was charged with CsF, diethyl ether, and phenoxydiphenylphosphane under nitrogen. Trifluoromethyltrimethylsilane was added and the reaction was stirred for 16 hours at room temperature, then the solvent was removed *in vacuo*. The crude product was purified by flash chromatography (silica gel: 2 % EtOAc in hexanes) to yield the title compound as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47 (t, J = 8.2 Hz, 4H), 7.40 – 7.27 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.09 (d, J = 21.0 Hz), 130.52, 129.54 (dq, J = 9.9, 3.2 Hz), 128.90 (d, J = 7.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 2.54 (q, J = 73.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -55.16 (d, *J* = 73.4 Hz). The spectroscopic data is in agreement with previous reported synthesis.[5]

Bis(4-methoxyphenyl)(trifluoromethyl)phosphane



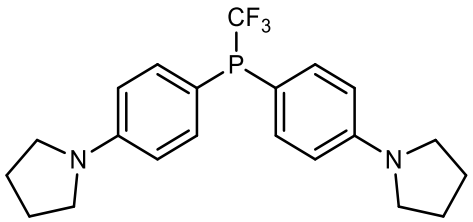
Prepared according to a modified version of a previous report.[4] An oven-dried 300 mL round bottom flask was charged with bis(4-methoxyphenyl)phosphine oxide (5.24 g, 20.0 mmol) and 18-crown-6 (6.34 g, 24.0 mmol) and then subjected to 3 cycles of vacuum/nitrogen backfill. THF (400 mL) was added and the reaction was cooled to 0 °C. KH (2.65 g, 24.0 mmol, 36% dispersion in paraffin) was added in one portion, and the reaction was stirred at room temperature for 30 minutes. Trimethyl(trifluoromethyl)silane (12.0 mL, 80.0 mmol) was added dropwise, and the reaction was stirred at room temperature for 10 minutes. The reaction was quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 20 % CH_2Cl_2 in hexanes) to provide the title compound as a pale yellow oil (1.34 g, 4.2 mmol, 21 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 – 7.49 (m, 4H), 7.00 – 6.92 (m, 4H), 3.84 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.54, 135.74 (d, J = 22.1 Hz), 120.36 (dq, J = 6.7, 3.3 Hz), 114.57 (d, J = 9.1 Hz), 55.24; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -0.54 (q, J = 73.3 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ: -56.23 (d, J = 72.8 Hz). The spectroscopic data is in agreement with previous reported synthesis.[6]

4,4'-((Trifluoromethyl)phosphanediyl)bis(*N*,*N*-dimethylaniline)



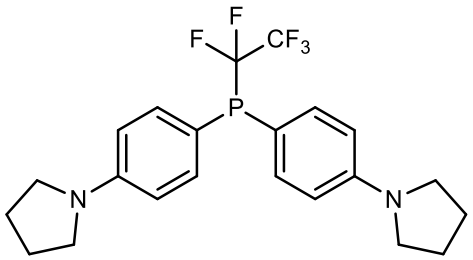
To a stirred solution of 4,4'-phosphanediylbis(*N*,*N*-dimethylaniline) (495 mg, 1.82 mmol) and pyridine (147 µL, 1.82 mmol) in 7.5 mL of DMF was added 2,8-difluoro-*S*-(trifluoromethyl) dibenzothiophenium triflate (760 mg, 1.73 mmol) under N_2 atmosphere. The mixture was stirred at rt for overnight. After the reaction was completed, the mixture was poured into water (20 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 5% EtOAc in Hexanes) to give 4,4'-((trifluoromethyl)phosphanediyl)bis(*N*,*N*-dimethylaniline) as a white powder (366 mg, 1.07 mmol, 62% yield). mp 79–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 (t, *J* = 8.5 Hz, 4H), 6.72 (dd, *J* = 1.2, 9.0 Hz, 4H), 2.99 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.68, 135.54 (d, *J* = 22.3 Hz), 131.65 (dq, *J* = 33.0, 319.9 Hz), 114.89, 112.21 (d, *J* = 8.8 Hz), 40.11; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -56.54 (d, *J* = 71.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -1.02 (q, *J* = 71.3 Hz); IR υ_{max}/cm^{-1} (film): 3087, 2895, 2820, 1593, 1544, 1513, 1481, 1443, 1365, 1230, 1199, 1176, 1144, 1100, 1078, 999, 946, 800; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{17}H_{21}F_3N_2P^+$ = 341.1389, found 341.1360.

1,1'-(((Trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine



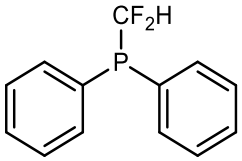
Prepared according to a modified version of a previous report.[4] An oven-dried 300 mL round bottom flask was charged with bis(4-(pyrrolidin-1-yl)phenyl)phosphine oxide (6.81 g, 20.0 mmol) and 18-crown-6 (6.34 g, 24.0 mmol) and then subjected to 3 cycles of vacuum/nitrogen backfill. THF (136 mL) was added and the reaction was cooled to 0 °C. KHMDS (1.0 M in THF) (24 mL, 24.0 mmol) was added dropwise, and the reaction was stirred at room temperature for 30 minutes. Trimethyl(trifluoromethyl)silane (11.82 mL, 80.0 mmol) was added dropwise, and the reaction was stirred at room temperature for 10 minutes. The reaction was quenched with water (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 20 % CH_2Cl_2 in hexanes) to provide the title compound as a peach solid (5.08 g, 12.9 mmol, 65 % yield). m.p. 163-165 ^oC; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.48 (t, J = 8.4 Hz, 4H), 6.58 (d, J = 8.3 Hz, 4H), 3.38 – 3.22 (m, 8H), 2.07 – 1.94 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.13, 135.66 (d, J = 22.5 Hz), 113.82 – 113.51 (m), 47.56, 25.62; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -0.42 (q, J = 71.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -56.83 (d, J = 71.4 Hz). IR υ_{max}/cm^{-1} (film): 2974, 2847, 1594, 1543, 1511, 1484, 1460, 1381, 1277, 1148, 1100, 1084, 1000, 962, 803, 716, 698. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{21}H_{25}F_3N_2P^+$ = 393.1702, found 393.1702.

1,1'-(((Perfluoroethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine



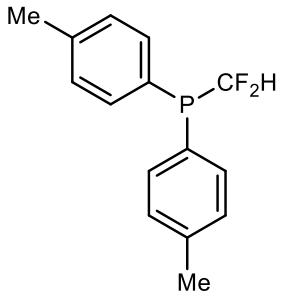
Prepared according to a modified version of a previous report.[4] An oven-dried 300 mL round bottom flask was charged with bis(4-(pyrrolidin-1-yl)phenyl)phosphine oxide (681 mg, 2.0 mmol) and 18-crown-6 (634 mg, 2.4 mmol) and then subjected to 3 cycles of vacuum/nitrogen backfill. THF (13.6 mL) was added and the reaction was cooled to 0 °C. KHMDS (1.0 M in THF) (2.4 mL, 2.4 mmol) was added dropwise, and the reaction was stirred at room temperature for 30 minutes. Trimethyl(perfluoroethyl)silane (1.41 mL, 8.0 mmol) was added dropwise, and the reaction was stirred at room temperature for 10 minutes. The reaction was quenched with water (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 20 % CH_2Cl_2 in hexanes) to provide the title compound as a yellow solid (93 mg, 0.210 mmol, 11 % yield). m.p. 149-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (t, J = 8.6 Hz, 4H), 6.70 – 6.50 (m, 4H), 3.43 – 3.22 (m, 8H), 2.09 – 1.96 (m, 8H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 149.23, 136.51 (d, J = 24.3 Hz), 122.37 – 119.90 (m), 119.32 – 118.33 (m), 112.60 (q, J = 4.0 Hz), 111.77 (d, J = 9.8 Hz), 47.48, 25.59; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -4.89 (td, J = 56.5, 17.1 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ: -80.51 (dt, J = 17.2, 3.4 Hz), -113.74 (dq, J = 56.5, 3.4 Hz). IR υ_{max}/cm^{-1} (film): 2847, 1593, 1543, 1510, 1484, 1384, 1323, 1279, 1248, 1229, 1187, 1098, 1077, 947, 809, 742, 714, 699. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{22}H_{25}F_5N_2P^+$ = 443.1670, found 443.1689.

(Difluoromethyl)diphenylphosphane



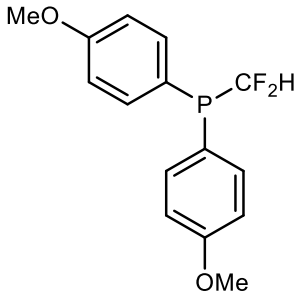
An oven-dried 300 mL round bottom flask was charged with $LiBF_4$ (1.12 g, 12.0 mmol), LiH (95 mg, 12.0 mmol), DMF (50 mL) and then subjected to 3 cycles of vacuum/nitrogen backfill. The reaction was cooled to 0 °C, then diphenylphosphane (1.74 mL, 10.0 mmol) was added and the reaction was stirred for 5 minutes. Trimethyl(trifluoromethyl)silane (7.4 mL, 50.0 mmol) was added, and the reaction was stirred at room temperature for 24 hours. TBAF (1 M in THF) (40 mL, 40 mmol) was added, and the reaction was stirred at room temperature for 10 minutes. The reaction was quenched with water (100 mL) and extracted with EtOAc (2 x 100 mL). The combined organic layer was washed with water (3 x 200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 100 % hexanes) to provide the title compound as a colorless oil (1.075 g, 4.55 mmol, 46 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 – 7.52 (m, 4H), 7.51 – 7.39 (m, 6H), 6.55 (td, J = 51.7, 14.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.92 (d, J = 18.9 Hz), 131.41 (dt, J = 10.3, 5.8 Hz), 130.05, 128.95 (d, J = 7.1 Hz), 122.35 (td, J = 264.7, 12.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -10.09 (t, J = 117.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -117.40 (dd, J = 117.5, 51.7 Hz). IR υ_{max}/cm^{-1} (film): 3075, 3056, 2933, 2360, 2342, 1483, 1435, 1307, 1288, 1064, 1022, 734, 692. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{12}F_2P^+$ = 237.0639, found 237.0638.

(Difluoromethyl)di-p-tolylphosphine



An oven-dried 300 mL round bottom flask was charged with (difluoromethyl)di-p-tolylphosphine oxide (2.80 g, 10 mmol) and subjected to 3 cycles of vacuum/nitrogen backfill. Toluene (120 mL) was added and the flask was cooled to 0 °C. Trichlorosilane (4.04 mL, 40 mmol) and TfOH (0.132 mL, 1.5 mmol) were added and the reaction was immediately warmed to 70 °C. After 22 h, the reaction was quenched with saturated aqueous sodium carbonate (500 mL) at 0 °C while stirring vigorously. The mixture was allowed to warm to room temperature and filtered through a pad of celite, rinsing liberally with EtOAc. The organic layer was separated and dried with anhydrous MgSO4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 10 % EtOAc in hexanes) to provide the title compound as a colorless oil (2.28 g, 8.6 mmol, 86 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44 (t, *J* = 7.8 Hz, 4H), 7.28 – 7.21 (m, 4H), 6.49 (td, *J* = 51.9, 13.9 Hz, 1H), 2.40 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.20, 133.90 (d, *J* = 19.2 Hz), 129.75 (d, *J* = 7.4 Hz), 128.00 (dt, *J* = 8.9, 5.8 Hz), 122.56 (td, *J* = 264.6, 12.7 Hz), 21.48; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -117.62 (dd, *J* = 117.5, 51.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -11.58 (t, *J* = 117.5 Hz). IR υ_{max}/cm^{-1} (film): 3073, 3019, 2922, 2866, 2361, 2342, 1599, 1498, 1448, 1398, 1307, 1287, 1188, 1094, 1065, 1019, 804, 627. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_{16}F_2P^+$ = 265.0952, found 265.0968.

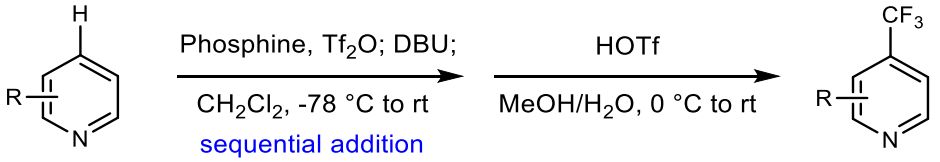
(Difluoromethyl)bis(4-methoxyphenyl)phosphine



An oven-dried 2 L round bottom flask was charged with (difluoromethyl)bis(4-methoxyphenyl)phosphine oxide (20.6 g, 66 mmol) and subjected to 3 cycles of vacuum/nitrogen backfill. Toluene (800 mL) was added and the flask was cooled to 0 °C. Trichlorosilane (26.7 mL, 264 mmol) and TfOH (0.874 mL, 9.9 mmol) were added and the reaction was immediately warmed to 70 °C. After 22 h, the reaction was quenched with saturated aqueous sodium carbonate (1 L) at 0 °C while stirring vigorously. The mixture was allowed to warm to room temperature and filtered through a pad of celite, rinsing liberally with EtOAc. The organic layer was separated and dried with anhydrous MgSO4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 7.5 % EtOAc in hexanes) to provide the title compound as a white solid (13.8 g, 46.5 mmol, 70 % yield). mp 34-35 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 (tt, *J* = 7.5, 2.3 Hz, 4H), 7.01 – 6.85 (m, 4H), 6.45 (td, *J* = 51.9, 14.9 Hz, 1H), 3.83 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.21, 135.48 (d, *J* = 20.6 Hz), 122.59 (td, *J* = 264.8, 13.5 Hz), 122.17 (q, *J* = 6.0 Hz), 114.65 (d, *J* = 8.1 Hz), 55.32; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -118.06 (dd, *J* = 116.0, 51.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -12.74 (t, *J* = 116.0 Hz). IR υ_{max}/cm^{-1} (film): 3012, 2969, 2947, 2932, 2840, 2361, 2342, 1590, 1568, 1497, 1281, 1249, 1217, 1186, 1108, 1095, 1066, 1024, 842, 827, 812, 798. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_{16}F_2O_2P^+$ = 297.0850, found 297.0878.

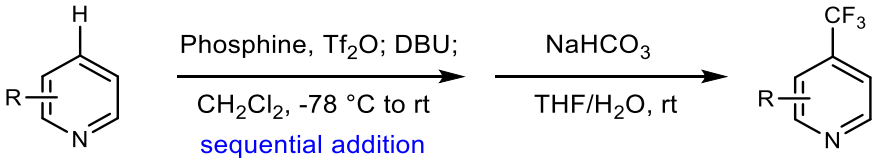
A1.4 Trifluoromethylation of Heterocycles

General Procedure A



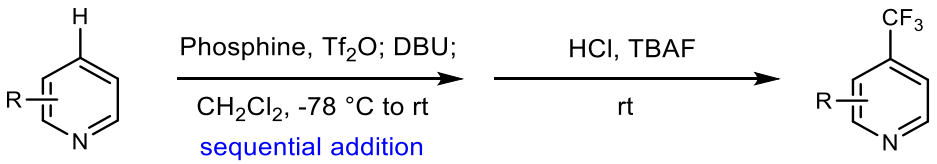
An oven dried 8 mL vial (≤ 0.30 mmol scale) or a round bottom flask (> 0.30 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). 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 1 hour before DBU (1.0 equiv) was added dropwise via syringe, the cooling bath was removed and the reaction warmed to room temperature while stirring (approximately 15–30 minutes). Then, the reaction mixture was cooled to 0 °C, HOTf (1.5 equiv), MeOH (0.2 M) and H_2O (10 equiv) were added sequentially. The mixture was warmed to room temperature and stirred for 12 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the trifluoromethylated heterocycle.

General Procedure B



An oven dried 8 mL vial (≤ 0.30 mmol scale) or a round bottom flask (> 0.30 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). 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 1 hour before DBU (1.0 equiv) was added dropwise via syringe, the cooling bath was removed and the reaction warmed to room temperature while stirring (approximately 15–30 minutes). Then, the mixture was stirred for additional 30 minutes after $NaHCO_3$ (3 equiv), THF (0.2 M) and H_2O (10 equiv) were added sequentially. The reaction was quenched with H_2O and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the trifluoromethylated heterocycle.

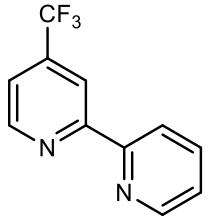
General Procedure C



An oven dried 8 mL vial (≤ 0.30 mmol scale) or a round bottom flask (> 0.30 mmol scale) equipped with a stir bar was charged with the heterocycle (1.0 equiv) and 1,1'-

(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). 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 1 hour before DBU (1.0 equiv) was added dropwise via syringe, the cooling bath was removed and the reaction warmed to room temperature while stirring (approximately 15–30 minutes). Then, the reaction mixture was cooled to 0 °C, HOTf (1.5 equiv) and TBAF (1M in THF, 1 equiv) were added sequentially. The mixture was warmed to room temperature and stirred for 12 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the trifluoromethylated heterocycle.

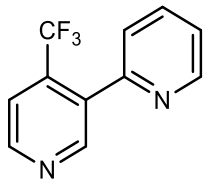
4-(Trifluoromethyl)-2,2'-bipyridine



Prepared according to general procedure A using 2,2'-bipyridine (78 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (111 μL, 1.25 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes to 33% EtOAc in hexanes) to provide the title compound as a white solid (83 mg, 0.37 mmol, 74% yield). ^1H NMR (400 MHz, $CDCl_3$)

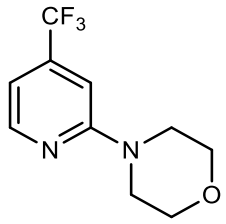
δ: 8.83 (d, *J* = 5.0 Hz, 1H), 8.71–8.68 (m, 2H), 8.44 (td, *J* = 1.2, 7.9 Hz, 1H), 7.84 (dt, *J* = 1.8, 7.7 Hz, 1H), 7.51 (dd, *J* = 1.7, 5.1 Hz, 1H), 7.35 (ddd, *J* = 1.2, 4.8, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.69, 154.81, 150.16, 149.47, 139.39 (q, *J* = 33.9 Hz), 137.19, 124.60, 123.11 (q, *J* = 271.6 Hz), 121.40, 119.17 (q, *J* = 3.5 Hz), 116.98 (q, *J* = 3.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.78. The spectroscopic data is in agreement with previous reported synthesis.[7]

4'-(Trifluoromethyl)-2,3'-bipyridine



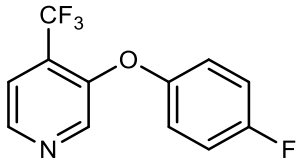
Prepared according to general procedure A using 2,3'-bipyridine (78 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (111 μL, 1.25 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 24 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes to 33% EtOAc in hexanes) to provide the title compound as a light-yellow oil (83 mg, 0.37 mmol, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83–8.81 (m, 2H), 8.72 (td, *J* = 1.4, 4.8 Hz, 1H), 7.79 (dt, *J* = 1.8, 7.8 Hz, 1H), 7.63 (d, *J* = 5.2 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.38–7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.52, 152.45, 150.27, 149.74, 136.45, 135.81 (q, *J* = 32.3 Hz), 134.18 (q, *J* = 0.9 Hz), 124.34 (q, *J* = 2.2 Hz), 123.27, 122.88 (q, *J* = 273.2 Hz), 119.73 (q, *J* = 4.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -59.29. The spectroscopic data is in agreement with previous reported synthesis.[8]

4-(4-(Trifluoromethyl)pyridin-2-yl)morpholine



Prepared according to general procedure A (except that the reaction was done in a pressure tube), using 4-(pyridin-2-yl)morpholine (82 mg, 0.50 mmol), Tf_2O (84 µL, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (68 µL, 0.77 mmol), MeOH (2.5 mL), and H_2O (90 µL, 5.00 mmol) at 60 °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 colorless oil (19 mg, 0.08 mmol, 16% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (d, *J* = 5.1 Hz, 1H), 6.82 (d, *J* = 5.2 Hz, 1H), 6.79 (s, 1H), 3.85 – 3.81 (m , 4H), 3.59 – 3.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.73, 149.37, 139.94 (q, *J* = 32.9 Hz), 123.30 (q, *J* = 273.0 Hz), 108.87 (q, *J* = 3.3 Hz), 102.51 (q, *J* = 4.4 Hz), 66.75, 45.43; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -65.16, IR υ_{max}/cm^{-1} (film): 2925, 1610, 1320, 1040, 957, 761, 667, 531. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_{12}F_3N_2O^+$ = 233.0902, found 233.0898.

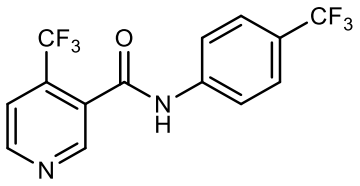
3-(4-Fluorophenoxy)-4-(trifluoromethyl)pyridine



Prepared according to general procedure A using 3-(4-fluorophenoxy)pyridine (95 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55

mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 12 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes) to provide the title compound as a light-yellow oil (106 mg, 0.41 mmol, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (d, *J* = 5.0 Hz, 1H), 8.29 (s, 1H), 7.55 (d, *J* = 4.9 Hz, 1H), 7.13–7.02 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.80 (d, *J* = 242.7 Hz), 151.56 (d, *J* = 2.7 Hz), 151.23, 144.49, 141.39, 127.97 (q, *J* = 32.8 Hz), 122.21 (q, *J* = 272.1 Hz), 121.02 (d, *J* = 8.4 Hz), 120.44 (q, *J* = 3.1 Hz), 117.00 (d, *J* = 23.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.66, -117.55; IR υ_{max}/cm^{-1} (film): 3047, 1599, 1572, 1501, 1489, 1411, 1322, 1290, 1257, 1218, 1181, 1138, 1090, 1069, 1057, 1011, 881, 832, 823, 769, 732, 649, 617; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_8F_4NO^+$ = 258.0537, found 258.0551.

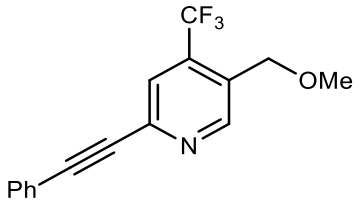
4-(Trifluoromethyl)-*N*-(4-(trifluoromethyl)phenyl)nicotinamide



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using *N*-(4-(trifluoromethyl)phenyl)nicotinamide (133 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (20 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a light-yellow solid (58 mg, 0.18 mmol, 35% yield). mp 167–171 °C; ^{1}H NMR (400

MHz, $CDCl_3$) δ: 8.93 (br s, 2H), 7.88 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.66–7.64 (m, 3H); ^{13}C NMR (100 MHz, d_6-Acetone) δ: 164.61, 153.24, 150.29, 143.05, 135.40 (q, *J* = 33.3 Hz), 130.86, 127.11–127.07 (m), 126.40 (q, *J* = 32.3 Hz), 125.35 (q, *J* = 269.1 Hz), 123.64 (q, *J* = 272.4 Hz), 121.08–120.92 (m), 120.72–120.53 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.24, -62.31; IR υ_{max}/cm^{-1} (film): 3255, 1649, 1605, 1548, 1413, 1404, 1317, 1289, 1272, 1190, 1141, 1065, 1048, 1019, 898, 841, 703, 658; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{14}H_9F_6N_2O^+$ = 335.0614, found 335.0621.

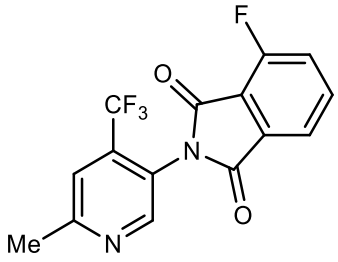
5-(Methoxymethyl)-2-(phenylethynyl)-4-(trifluoromethyl)pyridine



Prepared according to general procedure A using 5-(methoxymethyl)-2-(phenylethynyl)pyridine (112 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 20 hours. The crude material was purified by flash chromatography (silica gel: 9% EtOAc in hexanes to 17% EtOAc in hexanes) to provide the title compound as an off-white solid (117 mg, 0.40 mmol, 80% yield). mp 65–68 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.91 (s, 1H), 7.72 (s, 1H), 7.62–7.60 (m, 2H), 7.42–7.35 (m, 3H), 4.67 (s, 2H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.37, 143.72, 135.75 (q, *J* = 32.7 Hz), 132.24, 129.95 (q, *J* = 1.6 Hz), 129.51, 128.56, 122.81 (q, *J* = 273.5 Hz), 122.62 (q, *J* = 5.2 Hz), 121.75, 91.04, 87.71, 68.69 (q, *J* = 2.5 Hz), 58.98; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.62; IR υ_{max}/cm^{-1} (film): 3064, 2984, 2920, 2888, 2825, 2226, 1600, 1496, 1471,

1458, 1445, 1392, 1299, 1283, 1270, 1204, 1185, 1165, 1136, 1117, 1054, 971, 932, 922, 905, 894, 760, 690, 678; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{16}H_{13}F_3NO^+$ = 292.0944, found 292.0973.

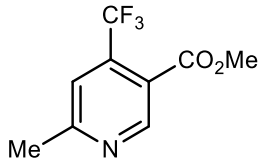
4-Fluoro-2-(6-methyl-4-(trifluoromethyl)pyridin-3-yl)isoindoline-1,3-dione



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 4-fluoro-2-(6-methylpyridin-3-yl)isoindoline-1,3-dione (128 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 43 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes to 50% EtOAc in hexanes) to provide the title compound as an off-white solid (141 mg, 0.44 mmol, 87% yield). mp 163–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (s, 1H), 7.86–7.78 (m, 2H), 7.58 (s, 1H), 7.49 (dt, *J* = 1.1, 8.4 Hz, 1H), 2.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.76 (d, *J* = 2.9 Hz), 163.45 (d, *J* = 1.5 Hz), 162.17, 158.05 (d, *J* = 265.7 Hz), 151.58, 137.51 (d, *J* = 7.7 Hz), 137.21 (q, *J* = 32.4 Hz), 133.84 (d, *J* = 1.3 Hz), 123.19 (d, *J* = 19.4 Hz), 122.21 (q, *J* = 2.0 Hz), 121.86 (q, *J* = 273.0 Hz), 120.64 (q, *J* = 4.2 Hz), 120.46 (d, *J* = 3.8 Hz), 117.74 (d, *J* = 12.4 Hz), 24.58; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.14, -110.89; IR υ_{max}/cm^{-1} (film): 3501, 3083, 1784, 1724, 1664, 1610, 1495, 1479, 1442, 1391, 1294, 1267, 1251, 1216, 1197, 1169, 1135, 1099, 1062, 1040, 968,

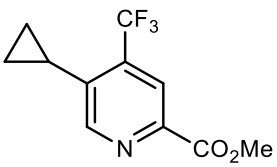
915, 892, 869, 822,794, 781, 743, 704, 670, 635, 607, 557; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{15}H_9F_4N_2O_2^+$ = 325.0595, found 325.0621.

Methyl 6-methyl-4-(trifluoromethyl)nicotinate



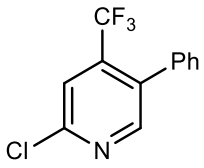
Prepared according to general procedure B using methyl 6-methylnicotinate (76 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), $NaHCO_3$ (126 mg, 1.50 mmol), THF (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 30 minutes. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a light-yellow solid (92 mg, 0.42 mmol, 84% yield). mp 31–33 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.00 (s, 1H), 7.49 (s, 1H), 3.96 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.19, 163.59, 151.53, 137.10 (q, *J* = 34.0 Hz), 122.30 (q, *J* = 1.7 Hz), 122.26 (q, *J* = 272.8 Hz), 119.96 (q, *J* = 5.1 Hz), 53.09, 24.90; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.98; IR υ_{max}/cm^{-1} (film): 3453, 3078, 2964, 2858, 1733, 1694, 1602, 1569, 1442, 1384, 1367, 1257, 1232, 1214, 1147, 1125, 1050, 956, 890, 817, 790, 732, 671; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_9H_9F_3NO_2^+$ = 220.0580, found 220.0587.

Methyl 5-cyclopropyl-4-(trifluoromethyl)picolinate



Prepared according to general procedure A using methyl 5-cyclopropylpicolinate (89 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 48 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes to 33% EtOAc in hexanes) to provide the title compound as a white solid (115 mg, 0.47 mmol, 93% yield). mp 76–78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (s, 1H), 8.29 (s, 1H), 4.02 (s, 3H), 2.25–2.19 (m, 1H), 1.25–1.20 (m, 2H), 1.00–0.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.73, 148.52, 146.02, 140.71, 138.10 (q, J = 31.9 Hz), 123.05 (q, J = 273.3 Hz), 120.78 (q, J = 5.1 Hz), 53.11, 10.87, 9.67; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.60; IR υ_{max}/cm^{-1} (film): 3424, 3029, 2963, 1718, 1680, 1601, 1558, 1491, 1456, 1442, 1323, 1310, 1258, 1154, 1124, 1069, 1042, 1017, 986, 923, 909, 879, 863, 806, 788, 754, 746, 669, 629; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{11}H_{11}F_3NO_2^+$ = 246.0736, found 246.0752.

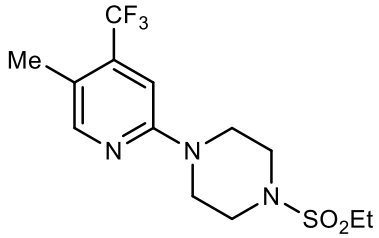
2-Chloro-5-phenyl-4-(trifluoromethyl)pyridine



Prepared according to general procedure A using 2-chloro-5-phenylpyridine (95 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), THF (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 80 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 33% CH_2Cl_2 in hexanes) to provide the title compound as a colorless oil (92 mg, 0.37 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.43 (s, 1H), 7.67 (s,

1H), 7.48–7.43 (m, 3H), 7.34–7.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.64, 151.36, 138.59 (q, *J* = 32.1 Hz), 134.67 (q, *J* = 1.8 Hz), 134.55, 129.26 (q, *J* = 1.5 Hz), 128.94, 128.44, 122.19 (q, *J* = 273.7 Hz), 120.67 (q, *J* = 5.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -59.70; IR υ_{max}/cm^{-1} (film): 3061, 1586, 1463, 1445, 1303, 1284, 1253, 1215, 1122, 1076, 1035, 885, 840, 775, 757, 699, 684, 665; *m*/*z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_8ClF_3N^+$ = 258.0292, found 258.0297.

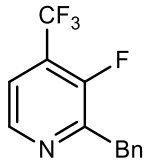
1-(Ethylsulfonyl)-4-(5-methyl-4-(trifluoromethyl)pyridin-2-yl)piperazine



Prepared according to general procedure A using 1-(ethylsulfonyl)-4-(5-methylpyridin-2-yl)piperazine (135 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as an off-white solid (28 mg, 0.08 mmol, 16% yield). mp 103–106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (s, 1H), 6.83 (s, 1H), 3.65–3.63 (m, 4H), 3.41–3.38 (m, 4H), 2.98 (q, *J* = 7.4 Hz, 2H), 2.30 (q, *J* = 1.8 Hz, 3H), 1.38 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.79, 150.94, 138.26 (q, *J* = 30.7 Hz), 123.55 (q, *J* = 273.0 Hz), 119.74 (q, *J* = 1.6 Hz), 103.46 (d, *J* = 5.5 Hz), 45.63, 45.54, 44.10, 15.18 (q, *J* = 1.5 Hz), 7.88; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.34; IR υ_{max}/cm^{-1} (film): 2980, 2926, 2870, 1726, 1612, 1499, 1433, 1386, 1354, 1342, 1326, 1303, 1276, 1244, 1219, 1193, 1138, 1117, 1067, 1048, 1005, 957, 937,

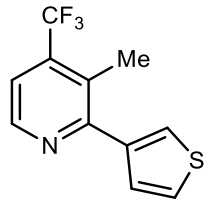
868, 847, 837, 779, 753, 715, 678; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{19}F_3N_3O_2S^+$ = 338.1145, found 338.1149.

2-Benzyl-3-fluoro-4-(trifluoromethyl)pyridine



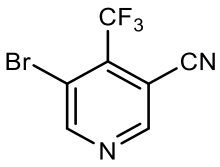
Prepared according to general procedure B, using 2-benzyl-3-fluoropyridine (94 mg, 0.50 mmol), Tf_2O (84 µL, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (5 mL), $NaHCO_3$ (126 mg, 1.50 mmol), H_2O (90 µL, 5.00 mmol), THF (2.5 mL) at rt for 30 minutes. The crude material was purified by flash chromatography (silica gel: 50% EtOAc in hexanes) to provide the title compound as a colorless oil (75 mg, 0.29 mmol, 58% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, *J* = 4.9 Hz, 1H), 7.39 – 7.21 (m, 6H), 4.27 (d, *J* = 3.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.77 (dq, *J* = 267.0, 2.3 Hz), 151.46 (d, *J* = 15.0 Hz), 145.54 (d, *J* = 7.2 Hz), 137.51, 129.12, 128.81, 126.94, 125.64 (qd, *J* = 34.0, 11.1 Hz), 121.62 (q, *J* = 273.6 Hz), 119.0 (qd, *J* = 4.0, 1.2 Hz), 38.08; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.72 (*J* = 12.5 Hz, 3F), -127.75 – (-127.61) (m, 1F), IR υ_{max}/cm^{-1} (film): 3032, 2932, 1430, 1226, 1149, 907, 728. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{10}F_4N^+$ = 256.0749, found 256.0772.

3-Methyl-2-(thiophen-3-yl)-4-(trifluoromethyl)pyridine



Prepared according to general procedure A, using 3-methyl-2-(thiophen-3-yl)pyridine (88 mg, 0.50 mmol), Tf_2O (84 µL, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (68 µL, 0.77 mmol), H_2O (90 µL, 5.00 mmol), MeOH (2.5 mL) at rt for 20 hours. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes) to provide the title compound as a colorless oil (72 mg, 0.29 mmol, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (d, *J* = 5.0 Hz, 1H), 7.55 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.46 (d, *J* = 5.0 Hz, 1H), 7.43 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.36 (dd, *J* = 5.0, 1.3 Hz, 1H), 2.53 (d, *J* = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.79, 147.37, 140.62, 137.76 (q, *J* = 30.8 Hz), 128.84 (m), 128.78, 125.87, 125.61, 123.50 (q, *J* = 275.1 Hz), 118.23 (q, *J* = 5.3 Hz), 16.24 (q, *J* = 1.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.10, IR υ_{max}/cm^{-1} (film): 2928, 2359, 1425, 1317, 1129, 1057, 907, 732, 530. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{11}H_9F_3NS^+$ = 244.0408, found 244.0404.

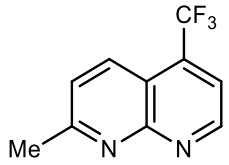
5-Bromo-4-(trifluoromethyl)nicotinonitrile



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –30 °C) using 5-bromonicotinonitrile (92 mg, 0.50 mmol), 1,1'-

(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 80% CH_2Cl_2 in hexanes) to provide the title compound as a white solid (65 mg, 0.26 mmol, 51% yield). mp 40–43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.11 (s, 1H), 8.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.07, 153.44, 138.75 (q, J = 32.9 Hz), 122.71 (q, J = 275.9 Hz), 119.11, 113.23, 108.54 (q, J = 1.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -60.76; IR υ_{max}/cm^{-1} (film): 3070, 2923, 2240, 1547, 1535, 1407, 1277, 1233, 1208, 1196, 1171, 1148, 1057, 916, 850, 757, 687, 609; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_7H_3BrF_3N_2^+$ = 250.9426, found 250.9429.

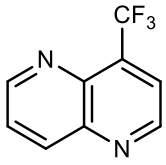
2-Methyl-5-(trifluoromethyl)-1,8-naphthyridine



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 2-methyl-1,8-naphthyridine (72 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (111 μL, 1.25 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 2% Et_3N in hexanes) to provide the title compound as a brown solid (55 mg, 0.26 mmol, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.21 (d, J = 4.4 Hz, 1H), 8.39 (qd, J = 1.9, 8.7 Hz, 1H), 7.72 (d, J = 4.4 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 2.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.21, 156.26, 152.75, 135.34 (q, J = 32.2 Hz), 133.18 (q,

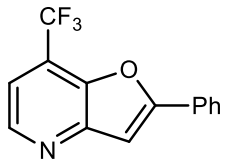
J = 2.2 Hz), 124.43, 123.01 (q, J = 272.8 Hz), 118.13 (q, J = 5.0 Hz), 116.13 (q, J = 0.5 Hz), 25.67; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -60.81. The spectroscopic data is in agreement with previous reported synthesis.[8]

4-(Trifluoromethyl)-1,5-naphthyridine



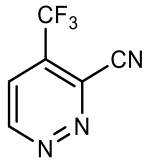
Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 1,5-naphthyridine (65 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (111 μL, 1.25 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at 40 °C for 16 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a white solid (41 mg, 0.21 mmol, 41% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.15–9.13 (m, 2H), 8.51 (dd, J = 1.8, 8.6 Hz, 1H), 7.93 (d, J = 4.3 Hz, 1H), 7.77 (dd, J = 4.2, 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.22, 150.77, 144.75, 139.46, 137.86, 135.58 (q, J = 31.2 Hz), 125.32, 122.97 (q, J = 273.1 Hz), 121.29 (q, J = 5.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.68. The spectroscopic data is in agreement with previous reported synthesis.[8]

2-Phenyl-7-(trifluoromethyl)furo[3,2-b]pyridine



Prepared according to general procedure A using 2-phenylfuro[3,2-b]pyridine (98 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes to 33% EtOAc in hexanes) to provide the title compound as a light yellow solid (112 mg, 0.43 mmol, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (d, *J* = 5.0 Hz, 1H), 7.95–7.92 (m, 2H), 7.53–7.43 (m, 3H), 7.38 (d, *J* = 5.0 Hz, 1H), 7.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.36, 151.27, 146.32, 142.78, 130.28, 129.06, 128.84, 125.64, 122.28 (q, *J* = 271.4 Hz), 120.71 (q, *J* = 35.6 Hz), 114.36, 102.21; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.06. The spectroscopic data is in agreement with previous reported synthesis.[8]

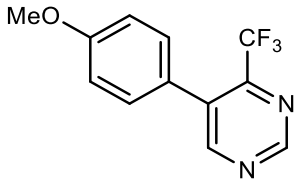
4-(Trifluoromethyl)pyridazine-3-carbonitrile



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using pyridazine-3-carbonitrile (53 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), THF (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 12 hours. The crude material was purified by flash

chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a light-yellow oil (32 mg, 0.19 mmol, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.64 (d, *J* = 5.4 Hz, 1H), 7.93 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.62, 135.72 (q, *J* = 0.9 Hz), 132.56 (q, *J* = 36.2 Hz), 122.85 (q, *J* = 4.1 Hz), 120.65 (q, *J* = 273.6 Hz), 112.47; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.21; IR υ_{max}/cm^{-1} (film): 3078, 1555, 1435, 1344, 1307, 1194, 1149, 1108, 1072, 1028, 867, 834, 783, 750, 663; *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_6H_3F_3N_3^+$ = 174.0, found 174.0.

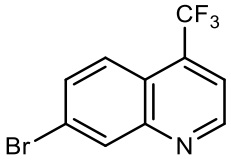
5-(4-Methoxyphenyl)-4-(trifluoromethyl)pyrimidine



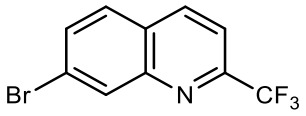
Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 5-(4-methoxyphenyl)pyrimidine (93 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 μL, 0.50 mmol), DBU (75 μL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 μL, 0.75 mmol), MeOH (2.5 mL) and H_2O (90 μL, 5.00 mmol) at rt for 30 hours. The crude material was purified by flash chromatography (silica gel: 17% EtOAc in hexanes to 33% EtOAc in hexanes) to provide the title compound as an off-white solid (100 mg, 0.39 mmol, 78% yield). mp 66–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.31 (s, 1H), 8.84 (s, 1H), 7.29–7.26 (m, 2H), 7.02–6.98 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.97, 160.48, 156.98, 151.96 (q, *J* = 33.9 Hz), 133.64, 130.29 (q, *J* = 1.6 Hz), 125.31, 121.05 (q, *J* = 275.2 Hz), 114.23, 55.42; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.60; IR υ_{max}/cm^{-1} (film): 3021, 2966, 2934, 2839, 1612, 1572, 1548, 1515, 1459, 1450, 1440,

1416, 1398, 1326, 1308, 1294, 1251, 1231, 1180, 1166, 1132, 1110, 1085, 1032, 1018, 997, 930, 833, 819, 800, 786, 730, 658; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_{10}F_3N_2O^+$ = 255.0740, found 255.0739.

7-Bromo-4-(trifluoromethyl)quinoline



16.8



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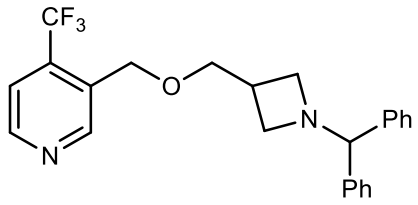
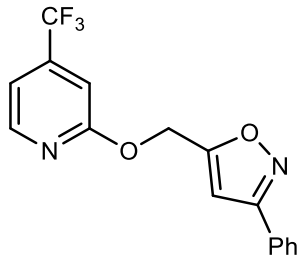
Prepared according to general procedure A using 7-bromoquinoline (104 mg, 0.50 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (216 mg, 0.55 mmol), Tf_2O (84 µL, 0.50 mmol), DBU (75 µL, 0.50 mmol), CH_2Cl_2 (5 mL), HOTf (67 µL, 0.75 mmol), THF (2.5 mL) and H_2O (90 µL, 5.00 mmol) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes to 50% EtOAc in hexanes) to provide the mixture of compounds as a light-brown solid (122 mg, 0.44 mmol, 88% yield). Major, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.03 (d, *J* = 4.4 Hz, 1H), 8.40 (s, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 4.1 Hz, 1H); Major, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.75, 149.68, 134.60 (d, *J* = 32.0 Hz), 132.87, 132.01, 125.44 (q, *J* = 2.3 Hz), 124.74, 123.27 (q, *J* = 273.0 Hz), 121.71, 118.31 (d, *J* = 5.2 Hz); Major, ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.44; IR υ_{max}/cm^{-1} (film): 3055, 3023, 2923, 1606, 1499, 1443, 1347, 1323, 1287, 1271, 1252, 1187, 1145, 1113, 1092, 1062, 977, 886, 856, 824, 775, 739, 653, 623, 610; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_6BrF_3N^+$ = 275.9630, found 275.9616.

3-(((1-Benzhydrylazetidin-3-yl)methoxy)methyl)-4-(trifluoromethyl)pyridine



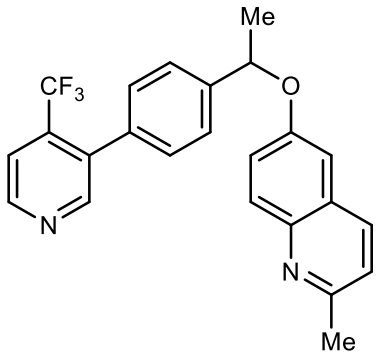
Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 3-(((1-benzhydrylazetidin-3-yl)methoxy)methyl)pyridine (86 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 2% Et_3N in hexanes) to provide the title compound as an off-white solid (77 mg, 0.19 mmol, 75% yield). mp 56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (s, 1H), 8.70 (d, J = 5.1 Hz, 1H), 7.48 (d, J = 5.1 Hz, 1H), 7.40–7.37 (m, 4H), 7.27–7.23 (m, 4H), 7.18–7.13 (m, 2H), 4.69 (s, 2H), 4.33 (s, 1H), 3.69 (d, J = 6.5 Hz, 2H), 3.29 (t, J = 7.5 Hz, 2H), 2.93 (t, J = 7.5 Hz, 2H), 2.81–2.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.16, 149.83, 142.32, 135.37 (q, J = 32.5 Hz), 131.02 (q, J = 1.7 Hz), 128.50, 127.60, 127.13, 123.12 (q, J = 273.2 Hz), 119.23 (q, J = 5.1 Hz), 78.13, 73.70, 67.31 (q, J = 2.2 Hz), 56.43, 29.82; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.39; IR υ_{max}/cm^{-1} (film): 3031, 2942, 2911, 2853, 1731, 1724, 1596, 1489, 1451, 1404, 1368, 1348, 1318, 1301, 1235, 1205, 1181, 1151, 1129, 1067, 1036, 976, 840, 821, 808, 780, 747, 707, 659, 638, 614; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{24}H_{24}F_3N_2O^+$ = 413.1835, found 413.1864.

3-Phenyl-5-(((4-(trifluoromethyl)pyridin-2-yl)oxy)methyl)isoxazole



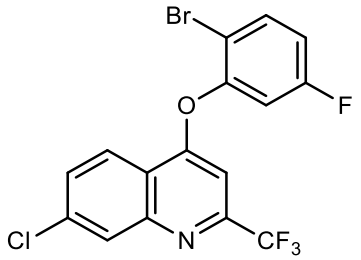
Prepared according to general procedure A using 3-phenyl-5-((pyridin-2-yloxy)methyl)isoxazole (63 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (90 μL, 5.00 mmol) at 80 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: CH_2Cl_2) to provide the title compound as an off-white solid (56 mg, 0.18 mmol, 70% yield). mp 56–59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (d, J = 5.4 Hz, 1H), 7.83–7.79 (m, 2H), 7.49–7.43 (m, 3H), 7.16 (dd, J = 1.0, 5.4 Hz, 1H), 7.08 (s, 1H), 6.65 (s, 1H), 5.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.32, 162.96, 162.64, 148.31, 141.49 (q, J = 33.8 Hz), 130.23, 129.05, 128.94, 126.96, 122.64 (q, J = 271.6 Hz), 113.42 (q, J = 3.2 Hz), 108.07 (q, J = 4.0 Hz), 101.90, 58.81; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.96; IR υ_{max}/cm^{-1} (film): 3120, 3053, 2920, 2850, 1622, 1569, 1490, 1473, 1426, 1407, 1337, 1289, 1271, 1231, 1170, 1160, 1131, 1081, 1037, 1002, 985, 951, 908, 884, 838, 826, 786, 766, 689, 667; m/z HRMS (DART): $[M+H]^+$ calculated for $C_{16}H_{12}F_3N_2O_2^+$ = 321.0845, found 321.0862.

2-Methyl-6-(1-(4-(4-(trifluoromethyl)pyridin-3-yl)phenyl)ethoxy)quinoline



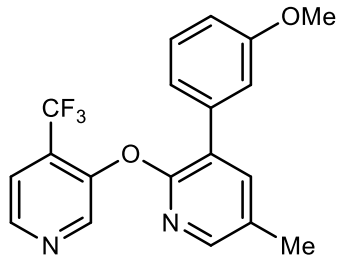
Prepared according to general procedure A using 2-methyl-6-(1-(4-(pyridin-3-yl)phenyl)ethoxy)quinoline (85 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 2% Et_3N in hexanes to 33% EtOAc, 5% Et_3N in hexanes) to provide the title compound as a colorless oil (45 mg, 0.11 mmol, 44% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.75 (d, J = 5.2 Hz, 1H), 8.63 (s, 1H), 7.91 (d, J = 9.2 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 5.2 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.40 (dd, J = 2.8, 9.2 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 2.8 Hz, 1H), 5.50 (q, J = 6.4 Hz, 1H), 2.67 (s, 3H), 1.74 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.64, 155.35, 152.70, 149.48, 143.95, 143.37, 135.91 (q, J = 31.6 Hz), 135.18, 135.05, 130.18, 129.67 (q, J = 1.7 Hz), 127.30, 125.52, 122.94 (q, J = 273.3 Hz), 122.71, 122.29, 119.55 (q, J = 4.8 Hz), 108.69, 76.13, 25.14, 24.33; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -59.25; IR υ_{max}/cm^{-1} (film): 3031, 2979, 2929, 1622, 1601, 1563, 1497, 1478, 1443, 1398, 1376, 1342, 1320, 1304, 1255, 1224, 1179, 1134, 1064, 1001, 968, 940, 908, 831, 730, 659, 615; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{24}H_{20}F_3N_2O^+$ = 409.1522, found 409.1541.

4-(2-Bromo-5-fluorophenoxy)-7-chloro-2-(trifluoromethyl)quinoline



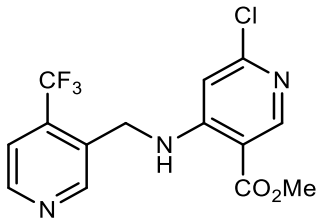
Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 4-(2-bromo-5-fluorophenoxy)-7-chloroquinoline (88 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (33 μL, 0.38 mmol), THF (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 22 hours. The crude material was purified by flash chromatography (silica gel: 5% EtOAc in hexanes) to provide the title compound as a white solid (90 mg, 0.22 mmol, 86% yield). mp 150–153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (d, J = 8.9 Hz, 1H), 8.24 (d, J = 2.0 Hz, 1H), 7.75–7.67 (m, 2H), 7.08–7.03 (m, 2H), 6.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.60 (d, J = 249.8 Hz), 161.89, 151.01 (d, J = 10.5 Hz), 150.11 (q, J = 34.8 Hz), 149.40, 138.05, 135.33 (d, J = 9.0 Hz), 129.58, 128.97, 123.40, 121.09 (q, J = 273.9 Hz), 119.74, 115.73 (d, J = 22.2 Hz), 111.36 (d, J = 24.8 Hz), 110.83 (d, J = 4.2 Hz), 99.91 (q, J = 2.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -67.87, -109.55; IR υ_{max}/cm^{-1} (film): 3101, 3081, 1614, 1588, 1569, 1478, 1438, 1424, 1412, 1372, 1285, 1244, 1197, 1158, 1147, 1128, 1118, 1102, 1073, 1038, 963, 950, 925, 914, 880, 865, 842, 829, 815, 739, 621, 600; m/z HRMS (DART): $[M+H]^+$ calculated for $C_{16}H_8BrClF_4NO^+$ = 419.9408, found 419.9420.

3-(3-Methoxyphenyl)-5-methyl-2-((4-(trifluoromethyl)pyridin-3-yl)oxy)pyridine



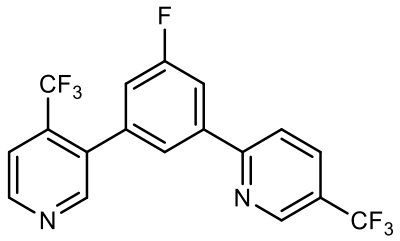
Prepared according to general procedure A using 3-(3-methoxyphenyl)-5-methyl-2-(pyridin-3-yloxy)pyridine (73 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 2% Et_3N in hexanes) to provide the title compound as a colorless oil (66 mg, 0.18 mmol, 73% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55–8.53 (m, 2H), 7.90 (dd, J = 0.8, 2.4 Hz, 1H), 7.63 (dd, J = 0.8, 2.4 Hz, 1H), 7.56 (d, J = 5.0 Hz, 1H), 7.39–7.35 (m, 1H), 7.22–7.20 (m, 2H), 6.94 (ddd, J = 1.4, 2.2, 8.2 Hz, 1H), 3.85 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.62, 157.51, 147.69, 146.57, 145.82, 145.53, 141.19, 136.95, 129.83 (q, J = 32.6 Hz), 129.73, 129.51, 125.05, 122.28 (q, J = 272.2 Hz), 121.66, 120.26 (q, J = 4.5 Hz), 114.69, 114.09, 55.31, 17.54; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.10; IR υ_{max}/cm^{-1} (film): 2938, 2836, 1571, 1490, 1456, 1440, 1407, 1322, 1288, 1231, 1184, 1137, 1068, 1056, 1040, 937, 869, 836, 820, 784, 743, 698, 649, 615; m/z HRMS (DART): $[M+H]^+$ calculated for $C_{19}H_{16}F_3N_2O_2^+$ = 361.1158, found 361.1173.

Methyl 6-chloro-4-(((4-(trifluoromethyl)pyridin-3-yl)methyl)amino)nicotinate



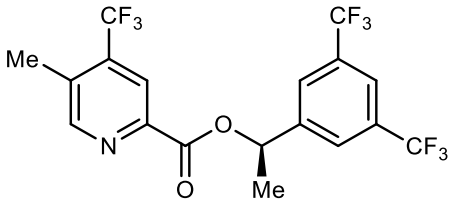
Prepared according to general procedure A using methyl 6-chloro-4-((pyridin-3-ylmethyl)amino)nicotinate (70 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes to 33% EtOAc, 2% Et_3N in hexanes) to provide the title compound as a white solid (77 mg, 0.22 mmol, 89% yield). mp 115–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.78–8.73 (m, 3H), 8.66 (t, *J* = 5.9 Hz, 1H), 7.59 (d, *J* = 5.1 Hz, 1H), 6.47 (s, 1H), 4.67 (d, *J* = 5.9 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.89, 156.25, 155.61, 153.19, 150.53, 150.44, 135.99 (q, *J* = 32.5 Hz), 129.21, 123.05 (q, *J* = 273.2 Hz), 119.81 (q, *J* = 5.0 Hz), 107.44, 104.89, 52.18, 41.25 (q, *J* = 2.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.47; IR υ_{max}/cm^{-1} (film): 3310, 3009, 2955, 2846, 1710, 1586, 1559, 1500, 1448, 1436, 1419, 1393, 1358, 1309, 1275, 1261, 1244, 1215, 1182, 1152, 1109, 1062, 977, 960, 934, 888, 838, 786, 776, 750, 717, 661, 613; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{14}H_{12}ClF_3N_3O_2^+$ = 346.0565, found 346.0570.

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



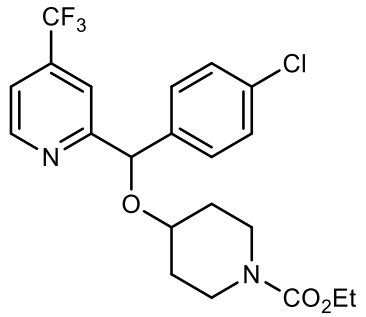
Prepared according to general procedure A using 2-(3-fluoro-5-(pyridin-3-yl)phenyl)-5-(trifluoromethyl)pyridine (80 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (56 μL, 0.63 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a white solid (84 mg, 0.22 mmol, 87% yield). mp 87–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.96–8.95 (m, 1H), 8.86 (d, *J* = 5.2 Hz, 1H), 8.73 (s, 1H), 8.02 (dd, *J* = 2.4, 4.4 Hz, 1H), 7.91–7.83 (m, 3H), 7.67 (d, *J* = 5.1 Hz, 1H), 7.19 (dt, *J* = 8.5, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.14, 161.67, 158.56 (m), 152.36, 150.31, 146.93 (q, J = 4.0 Hz), 140.25 (d, J = 8.1 Hz), 138.39 (d, J = 8.3 Hz), 136.05 (q, J = 32.0 Hz), 134.37 (q, J = 3.5 Hz), 133.83, 125.88 (q, J = 33.2 Hz), 124.01 (d, J = 1.5 Hz), 119.68 (q, J = 4.6 Hz), 118.02 (dd, J = 22.9, 1.6 Hz), 114.59 (d, J = 23.1 Hz), 77.16 (t, *J* = 32.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -59.27, -62.37, -111.82; IR υ_{max}/cm^{-1} (film): 3046, 2924, 2360, 1599, 1573, 1492, 1430, 1399, 1384, 1330, 1316, 1279, 1239, 1183, 1170, 1153, 1135, 1113, 1081, 1067, 1042, 1014, 938, 922, 882, 840, 769, 697, 658, 633, 616; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{10}F_7N_2^+$ = 387.0727, found 387.0748.

(*R*)-1-(3,5-Bis(trifluoromethyl)phenyl)ethyl 5-methyl-4-(trifluoromethyl)picolinate



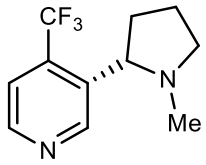
Prepared according to general procedure A using (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl 5-methylpicolinate (76 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (18 μL, 0.20 mmol), TBAF (0.2 mL, 0.20 mmol, 1M in THF) at rt for 24 hours. The crude material was purified by flash chromatography (silica gel: 50% DCM in hexanes to 80% DCM in hexanes) to provide the title compound as a white solid (76 mg, 0.17 mmol, 85% yield). mp 55–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (s, 1H), 8.28 (s, 1H), 7.93 (s, 2H), 7.83 (s, 1H), 6.28 (q, *J* = 6.7 Hz, 1H), 2.57 (s, 3H), 1.80 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.59, 153.46, 146.63, 143.76, 137.73 (q, *J* = 32.2 Hz), 135.51 (q, *J* = 1.7 Hz), 132.23 (q, *J* = 33.2 Hz), 126.72 (q, *J* = 3.8 Hz), 123.28 (q, *J* = 271.0 Hz), 122.87 (q, *J* = 273.1 Hz), 122.42–122.23 (m), 121.18 (q, *J* = 5.1 Hz), 72.93, 22.05, 16.51 (q, *J* = 1.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.90, -64.10; IR υ_{max}/cm^{-1} (film): 1746, 1382, 1370, 1361, 1321, 1303, 1283, 1268, 1243, 1200, 1163, 1114, 1103, 1067, 1059, 1005, 915, 900, 857, 841, 816, 787, 744, 728, 707, 683, 677; LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{13}F_9NO_2^+$ = 446.1, found 446.2.

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



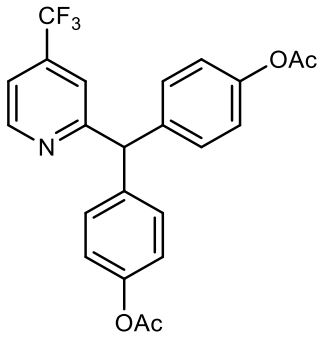
Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using ethyl 4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (94 mg, 0.25 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (108 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HOTf (33 μL, 0.38 mmol), MeOH (1.25 mL) and H_2O (45 μL, 2.50 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a colorless oil (85 mg, 0.19 mmol, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (d, J = 5.1 Hz, 1H), 7.77 (s, 1H), 7.39–7.35 (m, 3H), 7.32–7.28 (m, 2H), 5.67 (s, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.80–3.76 (m, 2H), 3.66–3.60 (m, 1H), 3.22–3.15 (m, 2H), 1.87–1.81 (m, 2H), 1.71–1.62 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.79, 155.59, 150.05, 139.35, 139.34 (q, J = 33.8 Hz), 133.94, 128.90, 128.31, 122.87 (q, J = 271.7 Hz), 118.21 (q, J = 3.6 Hz), 116.08 (q, J = 3.7 Hz), 80.60, 73.08, 61.40, 41.18, 41.09, 31.39, 30.89, 14.76; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.73; IR υ_{max}/cm^{-1} (film): 2931, 1692, 1488, 1473, 1432, 1407, 1383, 1331, 1273, 1227, 1204, 1167, 1135, 1083, 1029, 1014, 964, 921, 832, 767, 723, 665; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{21}H_{23}ClF_3N_2O_3^+$ = 443.1344, found 443.1347.

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



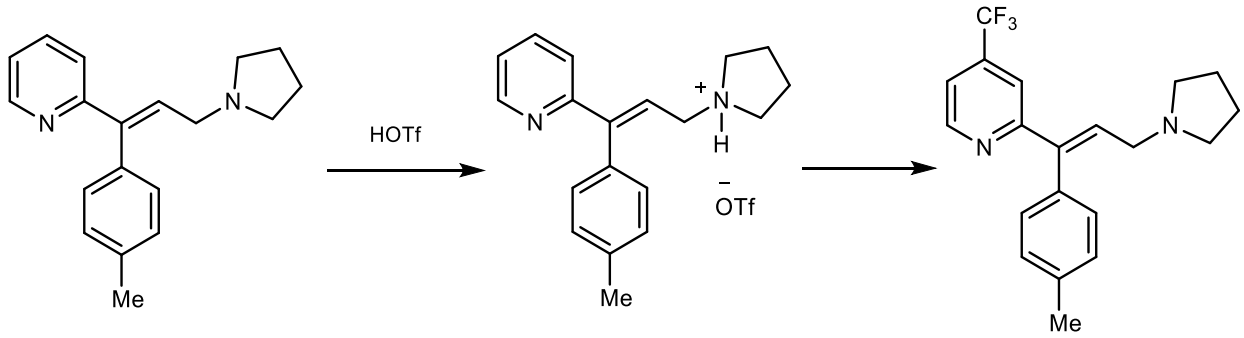
Prepared according to general procedure A using (*S*)-3-(1-methylpyrrolidin-2-yl)pyridine (33 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (44 μL, 0.50 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: EtOAc) to provide the title compound as a light-yellow oil (30 mg, 0.13 mmol, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.18 (s, 1H), 8.64 (s, 1H), 7.43 (d, *J* = 5.1 Hz, 1H), 3.53 (t, *J* = 7.9 Hz, 1H), 3.27 (t, *J* = 7.9 Hz, 1H), 2.38–2.24 (m, 2H), 2.18 (m, 3H), 2.05–1.93 (m, 1H), 1.88–1.78 (m, 1H), 1.71–1.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.88, 148.71, 137.15, 136.03 (q, *J* = 31.5 Hz), 123.34 (q, *J* = 273.2 Hz), 118.57, 64.85, 56.88, 40.39, 35.91, 23.04; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -60.50; IR υ_{max}/cm^{-1} (film): 2944, 2779, 1454, 1409, 1315, 1290, 1235, 1170, 1128, 1062, 1043, 900, 835, 659, 614; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{11}H_{14}F_3N_2^+$ = 231.1104, found 231.1106.

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



Prepared according to general procedure B using (pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate (72 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), $NaHCO_3$ (50 mg, 0.60 mmol), THF (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 50 minutes. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a white solid (78 mg, 0.18 mmol, 90% yield). mp 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.78 (d, J = 5.0 Hz, 1H), 7.39–7.37 (m, 2H), 7.19 (d, J = 8.6 Hz, 4H), 7.05 (d, J = 8.6 Hz, 4H), 5.71 (s, 1H), 2.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.49, 164.31, 150.80, 149.68, 139.25, 139.06 (q, J = 33.7 Hz), 130.32, 122.86 (q, J = 271.7 Hz), 121.80, 119.31 (q, J = 3.6 Hz), 117.48 (q, J = 3.5 Hz), 58.14, 21.23; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.65; IR υ_{max}/cm^{-1} (film): 3053, 2926, 1749, 1607, 1570, 1503, 1479, 1403, 1367, 1330, 1269, 1216, 1201, 1162, 1140, 1107, 1087, 1046, 1015, 958, 919, 879, 862, 848, 838, 800, 777, 750, 697, 677, 657, 644, 630, 593; HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{19}F_3NO_4^+$ = 430.1261, found 430.1271.

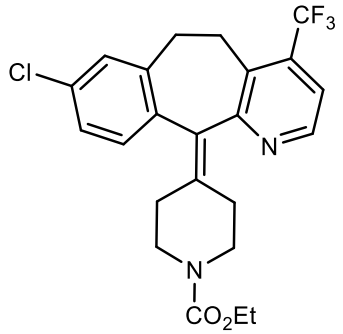
(*E*)-2-(3-(Pyrrolidin-1-yl)-1-(p-tolyl)prop-1-en-1-yl)-4-(trifluoromethyl)pyridine



(*E*)-2-(3-(pyrrolidin-1-yl)-1-(p-tolyl)prop-1-en-1-yl)pyridine (56 mg, 0.20 mmol) was dissolved in Et2O (1 mL) and cooled to 0 °C. Trifluoromethanesulfonic acid (18 μL, 0.20 mmol) was added dropwise, the ice bath was removed, and the solution was stirred for 10 minutes at room temperature. The solution was concentrated *in vacuo* and the resulting acid salt was subjected to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (2 mL), HOTf (44 μL, 0.50 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 2% Et_3N in EtOAc) to provide the title compound as a light-yellow solid (43 mg, 0.12 mmol, 62% yield). mp 39–41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (d, *J* = 5.0 Hz, 1H), 7.31 (dd, *J* = 1.6, 5.1 Hz, 1H), 7.24–7.22 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 6.8 Hz, 1H), 3.23 (d, *J* = 6.9 Hz, 2H), 2.56–2.51 (m, 4H), 2.40 (s, 3H), 1.79–1.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.26, 150.18, 141.11, 138.65 (q, *J* = 33.4 Hz), 137.55, 134.64, 132.76, 129.76, 129.48, 123.01 (q, *J* = 271.5 Hz), 117.40 (q, *J* = 3.7 Hz), 117.25 (q, *J* = 3.4 Hz), 54.84, 54.29, 23.64, 21.42; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.83; IR υ_{max}/cm^{-1} (film): 3386, 3024, 2969, 2877, 2790, 1630, 1605, 1568, 1512, 1460, 1434, 1397, 1327, 1233, 1168, 1139,

1083, 957, 932, 902, 878, 839, 816, 782, 750, 729, 711, 690, 659, 641; HRMS (DART): $[M+H]^+$ calculated for $C_{20}H_{22}F_3N_2^+$ = 347.1730, found 347.1735.

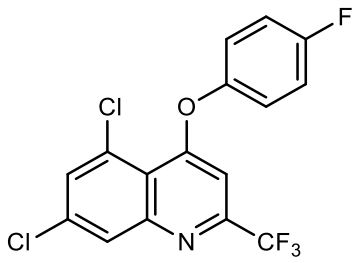
Ethyl 4-(8-chloro-4-(trifluoromethyl)-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate



Prepared according to general procedure A using ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate (77 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (27 μL, 0.30 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 16 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes to 50% EtOAc in hexanes) to provide the title compound as a colorless oil (75 mg, 0.17 mmol, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, *J* = 5.2 Hz, 1H), 7.41 (d, *J* = 5.2 Hz, 1H), 7.11–7.09 (m, 3H), 4.14 (q, *J* = 7.0 Hz, 2H), 3.82–3.75 (m, 2H), 3.44–3.36 (m, 2H), 3.29–3.13 (m, 3H), 2.97–2.88 (m, 1H), 2.51–2.33 (m, 3H), 2.14–2.08 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.47, 155.57, 147.72, 138.37, 137.83, 136.35 (q, *J* = 31.4 Hz), 134.63, 133.64, 133.47, 131.89, 131.31, 130.32, 126.23, 123.33 (q, *J* = 273.5 Hz), 118.59 (q, *J* = 5.2 Hz), 61.52, 44.89, 44.64, 31.92, 30.86, 30.62, 26.18, 14.77; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.88; IR υ_{max}/cm^{-1} (film): 2980, 2909, 1692, 1590, 1476,

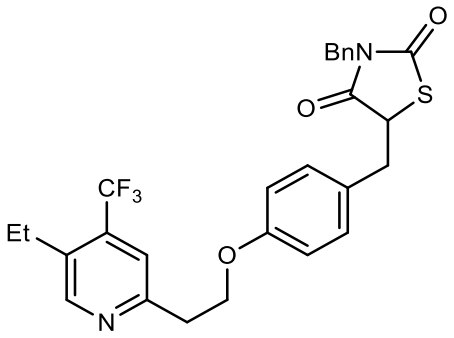
1430, 1406, 1326, 1300, 1278, 1222, 1155, 1119, 1092, 1061, 1028, 999, 981, 907, 844, 813, 766, 729, 690, 682; HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{23}ClF_3N_2O_2^+$ = 451.1395, found 451.1412.

5,7-Dichloro-4-(4-fluorophenoxy)-2-(trifluoromethyl)quinoline



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 5,7-dichloro-4-(4-fluorophenoxy)quinoline (62 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (27 μL, 0.30 mmol), THF (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 22 hours. The crude material was purified by flash chromatography (silica gel: 5% EtOAc in hexanes) to provide the title compound as a white solid (68 mg, 0.18 mmol, 90% yield). mp 82–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (s, 1H), 7.70 (s, 1H), 7.26–7.15 (m, 4H), 6.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.61, 160.67 (d, J = 244.6 Hz), 150.88, 150.39 (q, J = 35.0 Hz), 149.15 (d, J = 2.8 Hz), 136.63, 131.53, 130.68, 128.55, 122.61 (d, J = 8.5 Hz), 120.85 (q, J = 274.0 Hz), 118.50, 117.68 (q, J = 23.4 Hz), 102.15 (q, J = 2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -68.35, -115.41; IR υ_{max}/cm^{-1} (film): 3103, 1750, 1599, 1586, 1565, 1503, 1431, 1386, 1366, 1330, 1316, 1266, 1241, 1214, 1186, 1139, 1123, 1099, 1070, 1014, 964, 926, 855, 835, 770, 738, 724, 694, 611; HRMS (DART): $[M+H]^+$ calculated for $C_{16}H_8Cl_2F_4NO^+$ = 375.9914, found 375.9930.

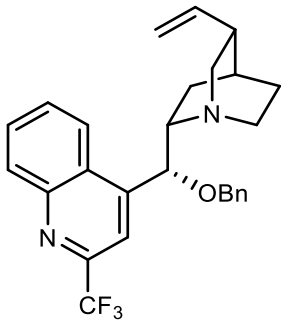
3-Benzyl-5-(4-(2-(5-ethyl-4-(trifluoromethyl)pyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione



Prepared according to general procedure B using 3-benzyl-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (89 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), $NaHCO_3$ (50 mg, 0.60 mmol), THF (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 30 minutes. The crude material was purified by flash chromatography (silica gel: 33% EtOAc in hexanes) to provide the title compound as a white solid (50 mg, 0.10 mmol, 49% yield). mp 111–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 (s, 1H), 7.45 (s, 1H), 7.25 (s, 5H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 4.72–4.64 (m, 2H), 4.42 (dd, *J* = 4.0, 8.8 Hz, 1H), 4.32 (t, *J* = 6.4 Hz, 2H), 3.38 (dd, *J* = 4.0, 14.2 Hz, 1H), 3.28 (t, *J* = 6.4 Hz, 2H), 3.38 (dd, *J* = 8.8, 14.2 Hz, 1H), 2.81 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.79, 171.02, 158.17, 157.13, 152.07, 136.14 (q, *J* = 31.0 Hz), 135.12, 134.66 (q, *J* = 1.6 Hz), 130.55, 128.73, 128.17, 127.70, 123.52 (q, *J* = 273.1 Hz), 119.50 (q, *J* = 5.2 Hz), 114.83, 66.82, 51.70, 45.24, 37.68, 37.62, 23.14 (q, *J* = 1.8 Hz), 15.76; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -62.14; IR υ_{max}/cm^{-1} (film): 3032, 2921, 1740, 1679, 1610, 1582, 1514, 1493, 1467, 1456, 1436, 1380, 1335, 1324, 1308, 1296, 1279, 1265, 1247, 1198, 1180, 1146, 1122, 1080,

1069, 1054, 1029, 964, 899, 879, 824, 810, 790, 745, 722, 696, 678, 668, 626, 601; HRMS (DART): $[M+H]^+$ calculated for $C_{27}H_{26}F_3N_2O_3S^+$ = 515.1611, found 515.1646.

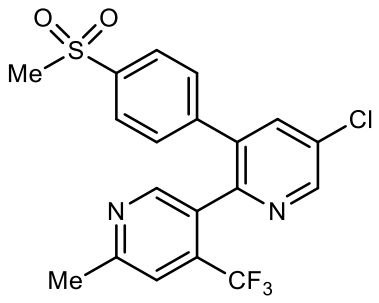
(1*R*,4*R*,5*R*)-2-((*R*)-(Benzyloxy)(2-(trifluoromethyl)quinolin-4-yl)methyl)-5-vinylquinuclidine



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using (1*R*,4*R*,5*R*)-2-((*R*)-(benzyloxy)(quinolin-4-yl)methyl)-5-vinylquinuclidine (77 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (44 μL, 0.50 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at 40 °C for 20 hours. The crude material was purified by flash chromatography (silica gel: 2% Et_3N in EtOAc) to provide the title compound as a colorless oil (48 mg, 0.11 mmol, 53% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, *J* = 8.1 Hz, 1H), 8.22 (d, *J* = 8.6 Hz, 1H), 7.86–7.81 (m, 2H), 7.72–7.68 (m, 1H), 7.37–7.27 (m, 5H), 5.79–5.70 (m, 1H), 5.33 (s, 1H), 4.98–4.90 (m, 2H), 4.42 (dd, *J* = 1.1, 13.1 Hz, 2H), 3.38–3.31 (m, 1H), 3.18–3.03 (m, 2H), 2.71–2.57 (m, 2H), 2.29–2.24 (m, 1H), 1.84–1.65 (s, 4H), 1.55–1.48 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.87, 147.86 (q, *J* = 34.2 Hz), 147.77, 141.88, 137.41, 131.33, 130.54, 128.79, 128.66, 128.15, 128.14, 127.35, 123.41, 121.78 (q, *J* = 273.8 Hz), 119.89, 114.51, 81.06, 72.00, 61.14, 57.09, 43.19, 40.03, 27.93, 27.79, 22.85; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -67.43; IR υ_{max}/cm^{-1} (film): 3066, 2934, 2864,

1636, 1596, 1569, 1511, 1467, 1454, 1423, 1363, 1320, 1251, 1212, 1180, 1132, 1095, 1046, 1027, 990, 905, 807, 761, 732, 698, 669; HRMS (DART): $[M+H]^+$ calculated for $C_{27}H_{28}F_3N_2O^+$ = 453.2148, found 453.2177.

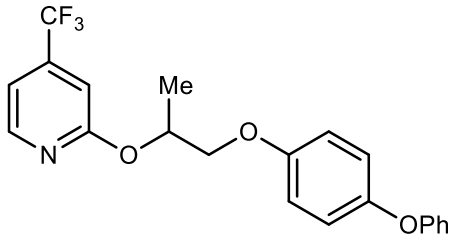
5-Chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-4'-(trifluoromethyl)-2,3'-bipyridine



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 5-chloro-6'-methyl-3-(4-(methylsulfonyl)phenyl)-2,3'-bipyridine (72 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (44 μL, 0.50 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 60 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in CH_2Cl_2 to 33% EtOAc in CH_2Cl_2) to provide the title compound as a colorless oil (68 mg, 0.16 mmol, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (d, *J* = 1.9 Hz, 1H), 8.25 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 2.4 Hz, 1H), 7.42 (s, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.02 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.09, 151.81, 150.96, 148.02, 142.68, 140.36, 137.47, 136.81 (q, *J* = 32.0 Hz), 136.59, 132.15, 130.33, 129.04, 127.82, 122.77 (q, *J* = 273.5 Hz), 120.04 (q, *J* = 3.5 Hz), 44.48, 24.48; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -60.13; IR υ_{max}/cm^{-1} (film): 3054, 2926, 1601, 1573, 1538, 1493, 1431, 1386, 1367, 1310, 1268, 1218, 1140, 1089, 1033, 1012, 956,

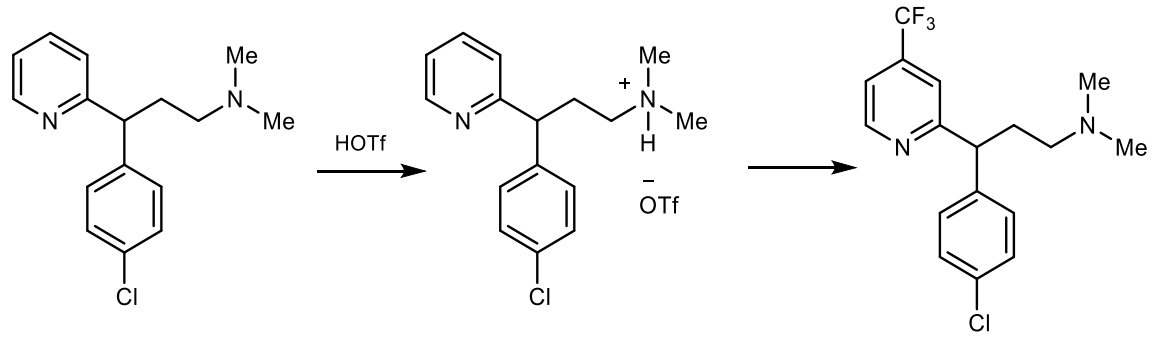
906, 888, 836, 790, 771, 728, 674, 661, 646, 593; HRMS (DART): $[M+H]^+$ calculated for $C_{19}H_{15}ClF_3N_2O_2S^+$ = 427.0489, found 427.0503.

2-((1-(4-Phenoxyphenoxy)propan-2-yl)oxy)-4-(trifluoromethyl)pyridine



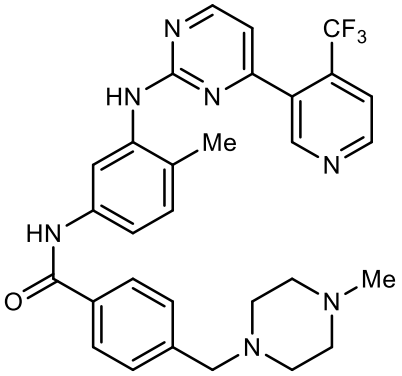
Prepared according to general procedure A using 2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine (64 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (27 μL, 0.30 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at 60 °C for 68 hours. The crude material was purified by flash chromatography (silica gel: 33% CH_2Cl_2 in hexanes to 50% CH_2Cl_2 in hexanes) to provide the title compound as a colorless oil (55 mg, 0.14 mmol, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (d, *J* = 5.3 Hz, 1H), 7.33–7.28 (m, 2H), 7.08–7.03 (m, 2H), 7.00–6.90 (m, 7H), 5.67–5.62 (m, 1H), 4.20 (dd, *J* = 5.6, 10.0 Hz, 1H), 4.09 (dd, *J* = 4.6, 10.0 Hz, 1H), 1.50 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.78, 158.57, 155.18, 150.60, 148.33, 141.17 (q, *J* = 33.6 Hz), 129.76, 122.80 (q, *J* = 271.6 Hz), 122.64, 120.90, 117.81, 115.90, 112.42 (q, *J* = 3.2 Hz), 108.46 (q, *J* = 4.0 Hz), 71.01, 70.54, 16.93; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -65.01; IR υ_{max}/cm^{-1} (film): 3041, 2934, 1615, 1589, 1569, 1503, 1488, 1416, 1335, 1306, 1217, 1171, 1135, 1073, 1045, 989, 966, 872, 826, 767, 748, 690, 668; HRMS (DART): $[M+H]^+$ calculated for $C_{21}H_{19}F_3NO_3^+$ = 390.1312, found 390.1338.

3-(4-Chlorophenyl)-N,N-dimethyl-3-(4-(trifluoromethyl)pyridin-2-yl)propan-1-amine

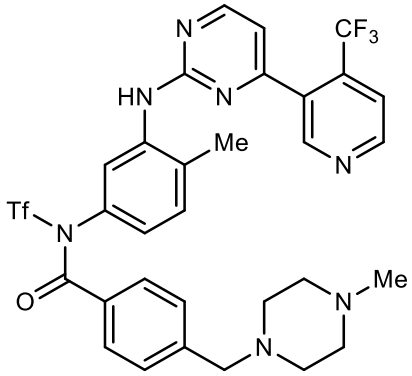


3-(4-chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine (55 mg, 0.20 mmol) was dissolved in Et2O (1 mL) and cooled to 0 °C. Trifluoromethanesulfonic acid (18 μL, 0.20 mmol) was added dropwise, the ice bath was removed, and the solution was stirred for 10 minutes at room temperature. The solution was concentrated *in vacuo* and the resulting acid salt was subjected to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (60 μL, 0.40 mmol), CH_2Cl_2 (2 mL), HOTf (44 μL, 0.50 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 5% Et_3N in EtOAc) to provide the title compound as a light-yellow oil (52 mg, 0.15 mmol, 76% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.75 (d, J = 5.2 Hz, 1H), 7.37–7.26 (m, 6H), 4.25–4.22 (m, 1H), 2.48–2.36 (m, 1H), 2.26–2.15 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.86, 150.54, 141.35, 138.80 (q, J = 33.7 Hz), 132.73, 129.57, 128.91, 122.93 (q, J = 271.6 Hz), 118.64 (q, J = 3.7 Hz), 117.22 (q, J = 3.5 Hz), 57.45, 50.57, 45.52, 33.05; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.75; IR υ_{max}/cm^{-1} (film): 2943, 2858, 2817, 2767, 1609, 1570, 1490, 1460, 1403, 1328, 1264, 1238, 1167, 1135, 1088, 1043, 1014, 895, 842, 828, 744, 721, 667; HRMS (DART): $[M+H]^+$ calculated for $C_{17}H_{19}ClF_3N_2^+$ = 343.1183, found 343.1187.

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



13

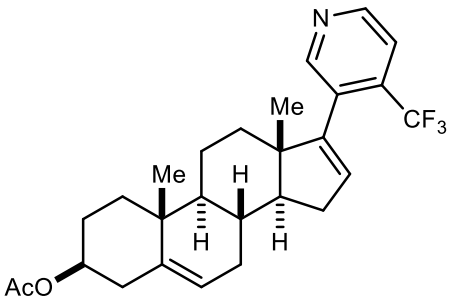


1

An oven dried 8 mL vial with a stir bar was charged with *N*-(4-methyl-3-((4-(pyridin-3-yl)pyrimidin-2-yl)amino)phenyl)-4-((4-methylpiperazin-1-yl)methyl)benzamide (74 mg, 0.15 mmol) and placed under a nitrogen atmosphere. CH_2Cl_2 (3.8 mL) was added, the reaction vessel cooled to –78 °C and Tf_2O (26 μL, 0.15 mmol) was added dropwise over 5 minutes. The reaction was stirred for 2 hours before 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (65 mg, 0.17 mmol) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred further for 1 hour at –50 °C. The DBU (23 μL, 0.15 mmol) was added dropwise via syringe at the same temperature and stirred for another 2 hours. Then HOTf (47 μL, 0.53 mmol), MeOH (0.75 mL) and H_2O (27 μL, 1.50 mmol) were added sequentially at –50 °C, the cooling bath was removed and the reaction was allowed to warm to room temperature and stirred for 5 additional hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 30% toluene, 3% MeOH and 2% Et_3N in CH_2Cl_2) to provide the mixture of compounds as a yellow

oil (36 mg, 0.06 mmol, 42% yield). Major, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.87–8.86(m, 2H), 8.52 (d, *J* = 5.0 Hz, 1H), 8.25 (s, 1H), 7.89 (s, 1H), 7.80 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 5.2 Hz, 1H), 7.50 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.10 (s, 1H), 6.87 (d, *J* = 5.0 Hz, 1H), 3.55 (s, 2H), 2.47 (br s, 8H), 2.30–2.29 (m, 6H); Major, ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.61, 163.29, 160.37, 158.67, 151.87, 151.21, 142.60, 137.38, 136.70, 135.71 (d, *J* = 32.6 Hz), 133.97, 132.11 (q, *J* = 2.0 Hz), 130.99, 129.37, 127.13, 124.94, 122.77 (q, *J* = 273.2 Hz), 119.95 (d, *J* = 4.9 Hz), 116.18, 113.74, 112.58, 62.61, 55.18, 53.18, 46.08, 17.64; Major, ^{19}F NMR (376 MHz, $CDCl_3$) δ: -59.03; IR υ_{max}/cm^{-1} (film): 3246, 2937, 2801, 1656, 1572, 1505, 1449, 1402, 1316, 1185, 1136, 1066, 1009, 908, 815, 727, 660, 613; *m*/*z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{30}H_{31}F_3N_7O^+$ = 562.3, found 562.3.

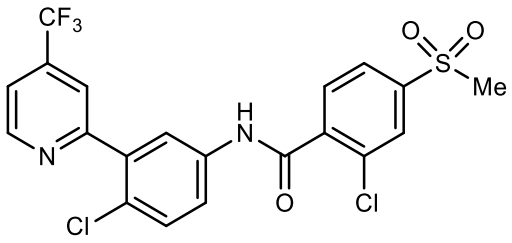
(3*S*,9*S*,10*R*,13*S*,14*S*)-10,13-Dimethyl-17-(4-(trifluoromethyl)pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl acetate



Prepared according to general procedure A using (3*S*,9*S*,10*R*,13*S*,14*S*)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (78 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (18 μL, 0.20 mmol), TBAF (0.2 mL, 0.20 mmol, 1M in THF) at rt for 24 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in

hexanes) to provide the title compound as a white solid (51 mg, 0.11 mmol, 55% yield). mp 145–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64–8.61 (m, 2H), 7.53 (d, *J* = 5.0 Hz, 1H), 5.81 (s, 1H), 5.41 (d, *J* = 5.1 Hz, 1H), 4.64–4.56 (m, 1H), 2.37–2.69 (m, 3H), 2.14–2.01 (m, 5H), 1.88–1.44 (m, 10H), 1.18–1.04 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.64, 151.30, 148.59, 147.95, 140.13, 136.59 (q, *J* = 30.5 Hz), 133.13 (q, *J* = 2.5 Hz), 131.89, 123.01 (q, *J* = 273.2 Hz), 122.40, 119.97 (q, *J* = 4.9 Hz), 73.97, 57.06, 50.36, 49.67, 38.24, 37.02, 36.93, 34.56, 32.57, 31.65, 30.83, 27.84, 21.53, 20.77, 19.34, 17.10; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -58.61; IR υ_{max}/cm^{-1} (film): 3060, 2941, 2912, 2853, 2836, 1731, 1724, 1597, 1429, 1402, 1368, 1317, 1291, 1236, 1181, 1152, 1135, 1061, 1036, 963, 876, 839, 821, 808, 739, 653; HRMS (DART): $[M+H]^+$ calculated for $C_{27}H_{33}F_3NO_2^+$ = 460.2458, found 460.2446.

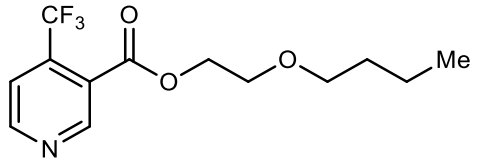
2-Chloro-*N*-(4-chloro-3-(4-(trifluoromethyl)pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide



Prepared according to general procedure A (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –50 °C) using 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (84 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (27 μL, 0.30 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in CH_2Cl_2 to 25% EtOAc in CH_2Cl_2) to provide the title compound as a white solid (75 mg, 0.15

mmol, 76% yield). mp 147–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.90 (s, 1H), 8.82 (d, *J* = 5.2 Hz, 1H), 7.92–7.90 (m, 2H), 7.83 (t, *J* = 1.1 Hz, 1H), 7.76 (dd, *J* = 2.7, 8.7 Hz, 1H), 7.70 (d, *J* = 1.1 Hz, 2H), 7.52 (dd, *J* = 0.9, 5.1 Hz, 1H), 7.48 (d, *J* = 8.7 Hz, 1H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.68, 157.54, 150.49, 142.63, 140.62, 138.61 (q, *J* = 34.1 Hz), 138.24, 136.83, 132.51, 131.09, 130.50, 128.97, 127.90, 125.86, 123.04, 122.77 (q, *J* = 271.8 Hz), 122.16, 120.84 (q, *J* = 3.8 Hz), 118.46 (q, *J* = 3.4 Hz), 44.48; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.70; IR υ_{max}/cm^{-1} (film): 3299, 3066, 3025, 2926, 1675, 1605, 1584, 1534, 1485, 1462, 1430, 1371, 1335, 1301, 1280, 1246, 1211, 1167, 1150, 1137, 1098, 1084, 1049, 1032, 965, 883, 851, 817, 795, 757, 725, 667, 642, 591, 559; HRMS (DART): $[M+H]^+$ calculated for $C_{20}H_{14}Cl_2F_3N_2O_3S^+$ = 489.0049, found 489.0062.

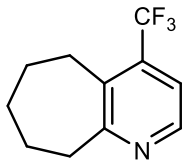
2-Butoxyethyl 4-(trifluoromethyl)nicotinate



Prepared according to general procedure B (except that after Tf_2O added, the reaction mixture was stirred for 1 hour at –30 °C) using 2-butoxyethyl nicotinate (45 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 µL, 0.20 mmol), DBU (30 µL, 0.20 mmol), CH_2Cl_2 (2 mL), $NaHCO_3$ (50 mg, 0.60 mmol), THF (1 mL) and H_2O (36 µL, 2.00 mmol) at rt for 50 minutes. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a light-yellow oil (45 mg, 0.16 mmol, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.10 (s, 1H), 8.90 (d, *J* = 5.2 Hz, 1H), 7.63 (d, *J* = 5.2 Hz, 1H), 4.50 (t, *J* = 4.8 Hz, 2H), 3.73 (t, *J* = 4.8 Hz, 2H), 3.48 (t, *J* = 6.6 Hz, 2H), 1.59–1.52 (m, 2H), 1.40–1.30 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100

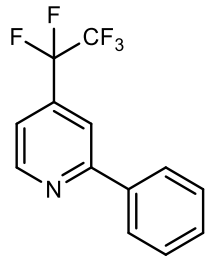
MHz, $CDCl_3$) δ: 164.60, 153.31, 151.72, 136.79 (q, *J* = 34.2 Hz), 125.39 (q, *J* = 1.9 Hz), 122.17 (q, *J* = 272.9 Hz), 120.22 (q, *J* = 5.0 Hz), 71.31, 68.20, 65.61, 31.74, 19.30, 13.94; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.73; IR υ_{max}/cm^{-1} (film): 2959, 2934, 2870, 1739, 1593, 1458, 1405, 1383, 1306, 1265, 1232, 1145, 1067, 1050, 844, 790, 660, 612; *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{17}F_3NO_3^+$ = 292.1155, found 292.1161.

4-(Trifluoromethyl)-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine



Prepared according to trifluoromethylation general procedure A using 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (30 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (86 mg, 0.22 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (27 μL, 0.30 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 24 hours. The crude material was purified by flash chromatography (silica gel: DCM) to provide the title compound as a colorless oil (8.6 mg, 0.04 mmol, 20% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.42 (d, *J* = 5.3 Hz, 1H), 7.31 (d, *J* = 5.2 Hz, 1H), 3.17–3.14 (m, 2H), 2.96–2.93 (m, 2H), 1.89–1.85 (m, 2H), 1.73–1.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.18, 146.61, 136.10, 135.67 (q, *J* = 30.3 Hz), 123.67 (q, *J* = 273.2 Hz), 117.39 (q, *J* = 4.2 Hz), 39.13, 32.01, 29.18 (q, *J* = 2.2 Hz), 26.94, 26.18; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.08; IR υ_{max}/cm^{-1} (film): 2929, 2856, 1411, 1315, 1159, 1133, 1110, 907, 841, 832, 730, 709; LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{11}H_{13}F_3N^+$ = 216.1, found 216.1.

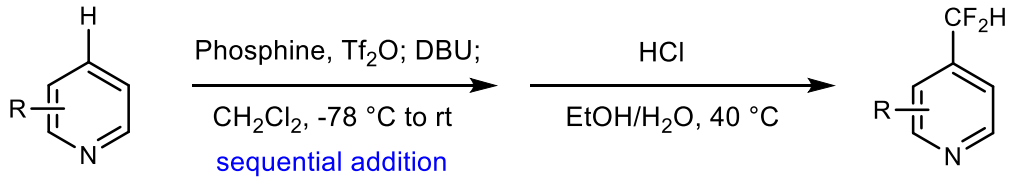
4-(Perfluoroethyl)-2-phenylpyridine



Prepared according to general procedure A using 2-phenylpyridine (29 μL, 0.2 mmol), 1,1'-(((perfluoroethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (97 mg, 0.22 mmol), Tf_2O (34 μL, 0.2 mmol), DBU (30 μL, 0.2 mmol), CH_2Cl_2 (2 mL), TfOH (18 μL, 0.2 mmol), MeOH (1 mL) and H_2O (36 μL, 2 mmol) at rt for 22 hours. The crude material was purified by flash chromatography (silica gel: 3 % EtOAc in hexanes) to provide the title compound as a colorless oil (40 mg, 0.148 mmol, 74 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (d, *J* = 5.1 Hz, 1H), 8.09 – 7.99 (m, 2H), 7.92 (s, 1H), 7.57 – 7.45 (m, 3H), 7.44 (dd, *J* = 5.1, 1.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 158.88, 150.65, 138.17, 137.94 – 137.70 (m), 130.03, 129.13, 127.23, 120.31 (t, *J* = 37.9 Hz), 118.87 (t, *J* = 5.8 Hz), 117.37 (t, *J* = 6.1 Hz), 115.44 – 114.57 (m), 112.58 (q, *J* = 38.7 Hz), 110.63 – 109.86 (m); ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.47, -117.05. IR υ_{max}/cm^{-1} (film): 2957, 2923, 2853, 2360, 1558, 11471, 1457, 1214, 760, 667. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_9F_5N^+$ = 274.0650, found 274.0662.

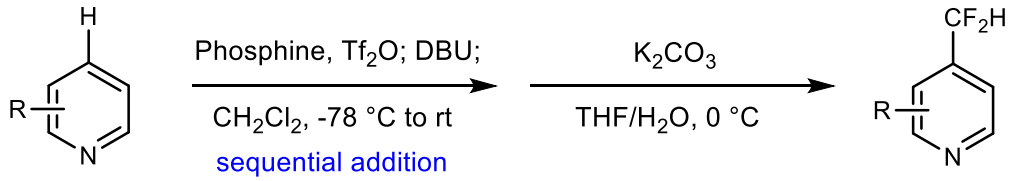
A1.5 Difluoromethylation of Heterocycles

General Procedure A



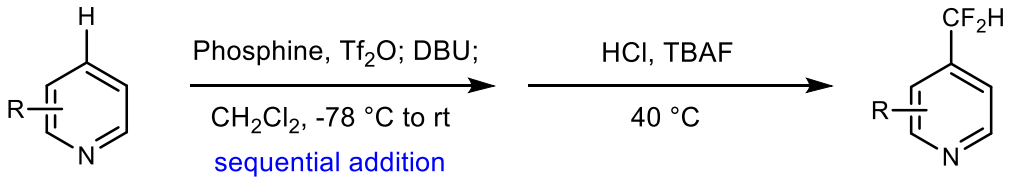
An oven dried 8 mL vial or 25 mL round bottom flask was charged with the heterocycle (1.0 equiv) and phosphine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 °C and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before DBU (1.0 equiv) was added dropwise (note – addition should be performed with vigorous stirring to ensure the DBU is readily homogenized; at –78 °C it tends to freeze and stick to the stir bar, preventing stirring). After the addition was complete, the reaction was warmed to 0 °C in an ice bath over 5 minutes. A 10 % H_2O in EtOH (v/v) solution was added to the reaction, bringing the final concentration to 0.05 M, and HCl in dioxane was added (1.0 equiv). The reaction was heated to 40 °C and allowed to run for 24 h, then quenched with a saturated aqueous solution of $NaHCO_3$ 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 to provide the difluoromethylated heteroarene.

General Procedure B



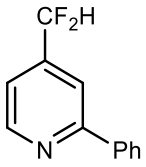
An oven dried 8 mL vial or 25 mL round bottom flask was charged with the heterocycle (1.0 equiv) and phosphine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). CH_2Cl_2 (0.1 M) was added, the reaction vessel cooled to –78 °C and Tf_2O (1.0 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before DBU (1.0 equiv) was added dropwise (note – addition should be performed with vigorous stirring to ensure the DBU is readily homogenized; at –78 °C it tends to freeze and stick to the stir bar, preventing stirring). After the addition was complete, the reaction was warmed to 0 °C in an ice bath over 5 minutes. The solvent was removed under vacuum, and THF and H_2O (1:1, 0.1 M) were added to the residue. The solution was vigorously stirred and solid K_2CO_3 (1.5 eq.) was added in one portion. After 1 h, the reaction mixture was extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography to provide the difluoromethylated heteroarene.

General Procedure C



An oven dried 8 mL vial or 25 mL round bottom flask was charged with the heterocycle (1.0 equiv) and phosphine (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). 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 DBU (1.0 equiv) was added dropwise (note – addition should be performed with vigorous stirring to ensure the DBU is readily homogenized; at –78 °C it tends to freeze and stick to the stir bar, preventing stirring). After the addition was complete, the reaction was warmed to 0 °C in an ice bath over 5 minutes. HCl in dioxane was added (1.0 equiv), followed by TBAF (1.0 equiv.), and the reaction was heated to 40 °C for 24 h, then quenched with a saturated aqueous solution of $NaHCO_3$ 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 to provide the difluoromethylated heteroarene.

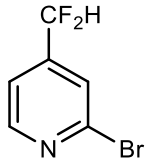
4-(Difluoromethyl)-2-phenylpyridine



Prepared according to general procedure A using 2-phenylpyridine (71.5 µL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol),

DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 60 % CH_2Cl_2 in hexanes) to provide the title compound as a colorless oil (83 mg, 0.40 mmol, 80 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (d, J = 5.3 Hz, 1H), 8.09 – 7.91 (m, 2H), 7.84 (s, 1H), 7.60 – 7.39 (m, 3H), 7.39 – 7.31 (m, 1H), 6.69 (t, J = 55.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.43, 150.38, 142.97 (t, J = 23.3 Hz), 138.48, 129.57, 128.90, 127.00, 118.20 (t, J = 5.7 Hz), 116.62 (t, J = 6.0 Hz), 113.14 (t, J = 240.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.56 (d, J = 55.8 Hz). IR υ_{max}/cm^{-1} (film): 3054, 2360, 1609, 1583, 1564, 1476, 1409, 1380, 1302, 1198, 1114, 1038, 837, 774, 692, 635, 548. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_{10}F_2N^+$ = 206.0776, found 206.0792.

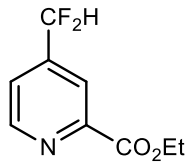
2-Bromo-4-(difluoromethyl)pyridine



Prepared according to general procedure B using 2-bromopyridine (48.6 μL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), K_2CO_3 (69 mg, 0.5 mmol), THF (2.5 mL) and H_2O (2.5 mL) at rt for 16 hours. The crude material was purified by flash chromatography (silica gel: 75 % CH_2Cl_2 in hexanes) to provide the title compound as a colorless oil (68 mg, 0.33 mmol, 65 % iso. yield, 78 % ^{1}H NMR yield). Note that the product evaporates during solvent evaporation. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.51 (d, J = 5.1 Hz, 1H), 7.62 (s, 1H), 7.38 (d, J = 5.1 Hz, 1H), 6.60 (t, J = 55.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.09, 144.83 (t, J = 23.7 Hz), 142.91, 124.87 (t, J = 6.2 Hz), 119.17 (t, J = 5.6 Hz), 112.01 (t, J = 242.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -

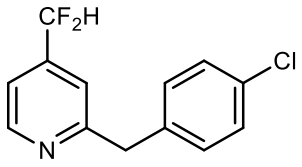
116.15 (d, J = 55.4 Hz). IR υ_{max}/cm^{-1} (film): 3067, 2979, 1598, 1557, 1464, 1397, 1363, 1286, 1218, 1125, 1078, 1043, 830, 739, 708, 671. *m/z* LRMS (ESI + APCI): $[M]^+$ calculated for $C_6H_4BrF_2N$ = 208.0, found 208.0.

Ethyl 4-(difluoromethyl)picolinate



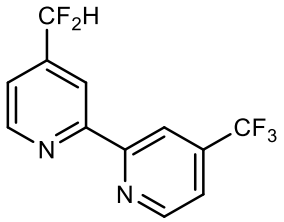
Prepared according to general procedure A using ethyl picolinate (67.5 μL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 30 % EtOAc in hexanes) to provide the title compound as a colorless oil (67 mg, 0.33 mmol, 67 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (d, J = 4.6 Hz, 1H), 8.23 (s, 1H), 7.59 (d, J = 4.0 Hz, 1H), 6.69 (t, J = 55.4 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 1.44 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.53, 150.74, 149.37, 143.62 (t, J = 23.9 Hz), 123.02 (t, J = 5.7 Hz), 121.63 (t, J = 6.0 Hz), 112.56 (t, J = 241.6 Hz), 62.47, 14.40; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.95 (d, J = 55.5 Hz). IR υ_{max}/cm^{-1} (film): 2985, 2940, 2360, 1720, 1609, 1471, 1367, 1300, 1275, 1206, 1131, 1040, 1022, 913, 863, 783, 668. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_9H_{10}F_2NO_2^+$ = 202.0674, found 202.0689.

2-(4-Chlorobenzyl)-4-(difluoromethyl)pyridine (37)



Prepared according to general procedure A using 2-(4-chlorobenzyl)pyridine (74 μL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 5 % EtOAc in CH_2Cl_2) to provide the title compound as a colorless oil (104 mg, 0.41 mmol, 82 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (d, *J* = 5.1 Hz, 1H), 7.34 – 7.24 (m, 3H), 7.24 – 7.13 (m, 3H), 6.58 (t, *J* = 55.7 Hz, 1H), 4.18 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.68, 150.37, 142.98 (t, *J* = 23.3 Hz), 137.35, 132.71, 130.57, 128.99, 119.29 (t, *J* = 5.9 Hz), 117.83 (t, *J* = 5.7 Hz), 113.06 (t, *J* = 240.9 Hz), 44.07; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.63 (d, *J* = 55.7 Hz). IR υ_{max}/cm^{-1} (film): 3028, 2928, 2360, 2341, 2222, 1611, 1570, 1491, 1407, 1365, 1174, 1089, 1043, 1016, 907, 848, 797, 729, 686. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{11}ClF_2N^+$ = 254.0543, found 254.0563.

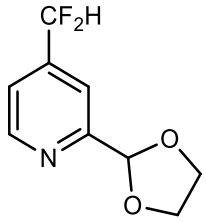
4-(Difluoromethyl)-4'-(trifluoromethyl)-2,2'-bipyridine



Prepared according to general procedure A using 4-(trifluoromethyl)-2,2'-bipyridine (112 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH

(4.5 mL) and H_2O (0.5 mL) at 60 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 3 % EtOAc in CH_2Cl_2) to provide the title compound as a white solid (83 mg, 0.30 mmol, 60 % yield). mp 74-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.85 (dd, *J* = 14.3, 4.2 Hz, 2H), 8.72 (s, 1H), 8.60 (s, 1H), 7.53 (dd, *J* = 24.8, 4.5 Hz, 2H), 6.73 (t, *J* = 55.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.70, 155.82, 150.29 (d, *J* = 11.7 Hz), 143.62 (t, *J* = 23.6 Hz), 139.69 (q, *J* = 34.2 Hz), 124.39, 121.67, 121.18 – 120.39 (m), 119.82, 117.97 (t, *J* = 6.3 Hz), 117.25 (d, *J* = 3.7 Hz), 113.15 (t, *J* = 241.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.85, -115.58 (d, *J* = 55.7 Hz). IR υ_{max}/cm^{-1} (film): 3080, 2925, 2360, 2342, 1603, 1568, 1465, 1392, 1367, 1332, 1287, 1263, 1164, 1129, 1080, 1068, 1038, 908, 849, 667. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{12}H_8F_5N_2^+$ = 275.0602, found 275.0608.

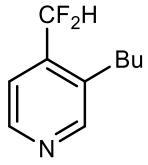
4-(Difluoromethyl)-2-(1,3-dioxolan-2-yl)pyridine



Prepared according to general procedure C using 2-(1,3-dioxolan-2-yl)pyridine (76 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), and TBAF (1 M in THF, 500 µL, 0.5 mmol), at 60 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 10 % EtOAc in CH_2Cl_2) to provide the title compound as a colorless oil (68 mg, 0.34 mmol, 68 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (d, *J* = 5.0 Hz, 1H), 7.66 (s, 1H), 7.40 (d, *J* = 4.8 Hz, 1H), 6.64 (t, *J* = 55.7 Hz, 1H), 5.89 (s, 1H), 4.23 – 4.04 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.44, 150.22, 143.18 (t, *J* = 23.5 Hz), 120.26 (t, *J* = 5.7 Hz), 117.23 (t, *J* = 6.0 Hz), 112.97 (t, *J* = 241.2

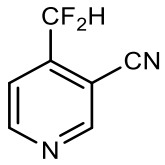
Hz), 103.30, 65.80; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.73 (d, *J* = 55.7 Hz). IR υ_{max}/cm^{-1} (film): 2962, 2893, 2360, 2341, 2252, 1614, 1383, 1173, 1119, 1080, 1041, 982, 907, 855, 728, 647. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_9H_{10}F_2NO_2^+$ = 202.0674, found 202.0687.

3-Butyl-4-(difluoromethyl)pyridine



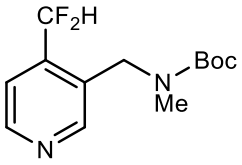
Prepared according to general procedure A using 3-butylpyridine (74 μL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15 % EtOAc in CH_2Cl_2) to provide the title compound as a colorless oil (56 mg, 0.28 mmol, 55 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 – 8.37 (m, 2H), 7.41 (d, *J* = 5.0 Hz, 1H), 6.77 (t, *J* = 54.8 Hz, 1H), 2.80 – 2.63 (m, 2H), 1.60 (tt, *J* = 7.9, 6.4 Hz, 2H), 1.41 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.68, 148.01, 139.36 (t, *J* = 22.0 Hz), 135.36, 119.37 (t, *J* = 6.6 Hz), 112.20 (t, *J* = 239.6 Hz), 33.45, 29.32, 22.55, 13.77; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -114.97 (d, *J* = 55.0 Hz). IR υ_{max}/cm^{-1} (film): 2960, 2934, 2874, 1466, 1411, 1379, 1347, 1237, 1166, 1089, 1035, 833, 730. *m/z* LRMS (ESI-APCI): $[M]^+$ calculated for $C_{10}H_{13}F_2N$ = 186.1, found 186.2.

4-(Difluoromethyl)nicotinonitrile



Prepared according to general procedure A using 3-cyanopyridine (52 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 2 % EtOAc in CH_2Cl_2) to provide the title compound as a white solid (13 mg, 0.08 mmol, 17 % iso. yield, 40 % ^{1}H NMR yield). Note that the product evaporates during solvent evaporation. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.02 (s, 1H), 8.98 (d, J = 4.8 Hz, 1H), 7.68 (d, J = 5.1 Hz, 1H), 6.89 (t, J = 54.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.72, 147.33, 139.88 (t, J = 21.5 Hz), 129.96, 117.17 (t, J = 7.1 Hz), 112.61 (t, J = 239.6 Hz), 33.05, 24.90, 22.52, 22.32; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -116.21 (d, J = 54.0 Hz). IR υ_{max}/cm^{-1} (film): 3037, 2924, 2236, 1593, 1407, 1381, 1235, 1191, 1164, 1090, 1042, 836, 790, 734, 660. *m/z* LRMS (ESI-APCI): $[M]^+$ calculated for $C_7H_4F_2N_2$ = 154.0, found 154.0.

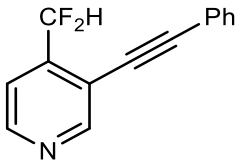
Tert-butyl ((4-(difluoromethyl)pyridin-3-yl)methyl)(methyl)carbamate



Prepared according to general procedure A using tert-butyl methyl(pyridin-3-ylmethyl)carbamate (111 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL,

0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 55 % EtOAc in hexanes) to provide the title compound as a colorless oil (85 mg, 0.31 mmol, 62 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (d, *J* = 5.0 Hz, 1H), 8.57 (s, 1H), 7.48 (d, *J* = 5.0 Hz, 1H), 6.91 (br t, *J* = 54.1 Hz, 1H), 4.58 (s, 2H), 2.82 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.06 – 154.49 (m), 152.70 – 150.30 (m), 149.93, 141.44 – 138.84 (m), 130.85, 119.89, 112.22 (t, *J* = 239.2 Hz), 80.67, 51.80 – 44.51 (m), 34.13, 29.82, 28.43; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.47 (d, *J* = 53.3 Hz). IR υ_{max}/cm^{-1} (film): 2978, 2933, 2360, 2341, 1686, 1480, 1414, 1391, 1367, 1240, 1147, 1084, 1038, 980, 911, 730, 663. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{13}H_{19}F_2N_2O_2^+$ = 273.1409, found 273.1417.

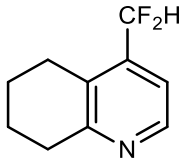
4-(Difluoromethyl)-3-(phenylethynyl)pyridine



Prepared according to general procedure A using 3-(phenylethynyl)pyridine (90 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 20 % EtOAc in hexanes) to provide the title compound as a yellow solid (89 mg, 0.39 mmol, 78 % yield). mp 44-45 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.85 (s, 1H), 8.68 (d, *J* = 5.1 Hz, 1H), 7.59 – 7.52 (m, 3H), 7.40 (qd, *J* = 4.7, 1.6 Hz, 3H), 7.00 (t, *J* = 54.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.21, 149.37, 142.40 (t, *J* = 23.2 Hz), 131.90, 129.57, 128.70, 121.90, 119.01 (t, *J* = 5.1 Hz), 118.44 (t, *J* = 5.7 Hz), 111.98 (t, *J* = 239.8 Hz), 98.26,

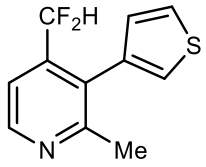
81.91; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -117.10 (d, *J* = 54.7 Hz). IR υ_{max}/cm^{-1} (film): 3068, 3021, 3001, 2926, 2854, 2360, 2341, 2221, 1598, 1496, 1442, 1365, 1233, 1211, 1168, 1143, 1076, 1031, 869, 848, 825, 749, 720, 686, 664. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{14}H_{10}F_2N^+$ = 230.0776, found 230.0787.

4-(Difluoromethyl)-5,6,7,8-tetrahydroquinoline



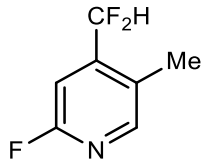
Prepared according to general procedure A using 5,6,7,8-tetrahydroquinoline (64.7 μL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol) (125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 40 % EtOAc in hexanes) to provide the title compound as a colorless oil (46 mg, 0.25 mmol, 50 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (d, *J* = 5.0 Hz, 1H), 7.24 (d, *J* = 5.0 Hz, 1H), 6.71 (t, *J* = 54.7 Hz, 1H), 2.99 (t, *J* = 6.2 Hz, 2H), 2.84 (t, *J* = 6.1 Hz, 2H), 1.98 – 1.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.56, 147.18, 139.72 (t, *J* = 21.5 Hz), 129.80, 117.01 (t, *J* = 7.1 Hz), 112.46 (t, *J* = 239.6 Hz), 32.89, 24.74, 22.36, 22.17; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -117.77 (d, *J* = 54.7 Hz). IR υ_{max}/cm^{-1} (film): 2941, 2864, 2360, 2341, 2213, 1574, 1438, 1412, 1374, 1263, 1249, 1232, 1112, 1036, 908, 872, 843, 728, 644. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_{12}F_2N^+$ = 184.0932, found 184.0941.

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



Prepared according to general procedure A using 2-methyl-3-(thiophen-3-yl)pyridine (87.6 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 60 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 25 % EtOAc in hexanes) to provide the title compound as a colorless oil (86 mg, 0.38 mmol, 76 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.63 (d, J = 5.1 Hz, 1H), 7.56 – 7.37 (m, 2H), 7.22 (dd, J = 2.9, 1.1 Hz, 1H), 7.01 (dd, J = 4.9, 1.1 Hz, 1H), 6.29 (t, J = 54.7 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.60, 148.98, 140.76 (t, J = 22.8 Hz), 134.91, 130.22 (t, J = 6.3 Hz), 128.80, 126.73, 125.17, 116.69 (t, J = 5.1 Hz), 111.98 (t, J = 238.4 Hz), 23.52; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -106.33 – -117.12 (m). IR υ_{max}/cm^{-1} (film): 3107, 2997, 2220, 1576, 1423, 1394, 1355, 1268, 1242, 1105, 1038, 908, 860, 845, 785, 729, 705, 658. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{11}H_{10}F_2NS^+$ = 226.0497, found 226.0518.

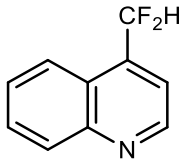
4-(Difluoromethyl)-2-fluoro-5-methylpyridine



Prepared according to general procedure B using 2-fluoro-5-methylpyridine (52 μL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), K_2CO_3 (69 mg, 0.5 mmol), THF (2.5 mL) and H_2O (2.5 mL) at rt for 2 hours. The crude material was purified by flash chromatography (silica gel: 80 %

CH_2Cl_2 in hexanes) to provide the title compound as a colorless oil (44 mg, 0.27 mmol, 27 % iso. yield, 70 % ^{1}H NMR yield) Note that the product evaporates during solvent evaporation. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (s, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.69 (t, *J* = 54.4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.69 (d, *J* = 238.1 Hz), 149.46 (d, *J* = 14.2 Hz), 145.18 (td, *J* = 22.2, 7.2 Hz), 128.49 (q, *J* = 4.6 Hz), 111.85 (td, *J* = 240.9, 2.9 Hz), 106.06 (dt, *J* = 40.1, 7.7 Hz), 14.85; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -70.09, -118.49 (d, *J* = 54.4 Hz). IR υ_{max}/cm^{-1} (film): 2973, 2360, 2342, 1612, 1582, 1490, 1456, 1387, 1348, 1269, 1156, 1049, 967, 881, 820, 735, 691. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_7H_7F_3N^+$ = 162.0525, found 162.0535.

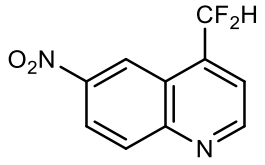
4-(Difluoromethyl)quinoline



Prepared according to general procedure A using quinoline (59.2 µL, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 5 % EtOAc in CH_2Cl_2) to provide the title compound as colorless crystals (69 mg, 0.39 mmol, 77 % yield). mp 53-55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.01 (d, *J* = 4.3 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.12 – 8.01 (m, 2H), 7.78 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.64 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.57 (d, *J* = 4.3 Hz, 1H), 7.15 (t, *J* = 54.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.11, 148.75, 137.88 (t, *J* = 21.8 Hz), 130.55, 130.03, 127.92, 124.25 (t, *J* = 2.5 Hz), 123.40, 118.05 (t, *J* = 7.7 Hz), 113.41 (t, *J* = 240.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.10 (d, *J* = 54.5 Hz). IR υ_{max}/cm^{-1} (film): 3059, 2983, 2923, 2851, 2360, 2342, 1602, 1515,

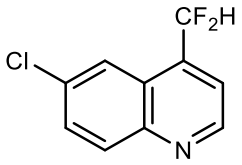
1501, 1466, 1407, 1359, 1310, 1245, 1171, 1147, 1115, 1074, 1031, 1022, 999, 986, 865, 851, 767, 816, 777, 752, 665, 625. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_8F_2N^+$ = 180.0619, found 180.0632.

4-(Difluoromethyl)-6-nitroquinoline



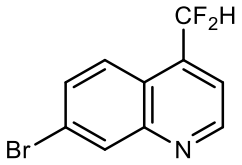
Prepared according to general procedure A using 6-nitroquinoline (87 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 4 % EtOAc in CH_2Cl_2) to provide the title compound as a white solid (61 mg, 0.27 mmol, 54 % yield). mp 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.20 (d, *J* = 4.4 Hz, 1H), 9.05 (s, 1H), 8.55 (dd, *J* = 9.2, 2.4 Hz, 1H), 8.35 (d, *J* = 9.2 Hz, 1H), 7.74 (d, *J* = 4.3 Hz, 1H), 7.20 (t, *J* = 54.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.58, 150.63, 146.30, 139.97 (t, *J* = 22.5 Hz), 132.49, 123.61, 123.21 (t, *J* = 2.5 Hz), 120.71 (t, *J* = 1.9 Hz), 120.06 (t, *J* = 7.6 Hz), 112.95 (t, *J* = 241.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -114.34 (d, *J* = 54.1 Hz). IR υ_{max}/cm^{-1} (film): 3118, 3084, 3059, 3027, 2923, 2840, 2359, 2342, 1620, 1609, 1574, 1421, 1392, 1344, 1300, 1264, 1235, 1221, 1145, 1120, 1100, 1046, 1009, 910, 894, 867, 805, 742, 736, 657. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_7F_2N_2O_2^+$ = 225.047, found 225.0478.

6-Chloro-4-(difluoromethyl)quinoline



Prepared according to general procedure A using 6-chloroquinoline (82 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 5 % EtOAc in CH_2Cl_2) to provide the title compound as pale yellow crystals (75 mg, 0.35 mmol, 70 % yield). mp 65-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (d, *J* = 4.3 Hz, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 8.06 (d, *J* = 1.7 Hz, 1H), 7.72 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.58 (d, *J* = 4.3 Hz, 1H), 7.07 (t, *J* = 54.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.27, 147.17, 137.20 (t, *J* = 22.1 Hz), 134.09, 132.09, 131.11, 124.81 (t, *J* = 2.8 Hz), 122.66, 119.00 (t, *J* = 7.7 Hz), 113.25 (t, *J* = 240.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -114.91 (d, *J* = 54.3 Hz). IR υ_{max}/cm^{-1} (film): 2925, 2360, 2342, 1602, 1498, 1453, 1386, 1346, 1301, 1240, 1119, 1068, 1036, 851, 790. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_7ClF_2N^+$ = 214.023, found 214.0233.

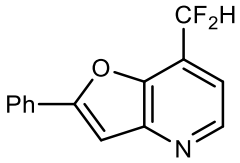
7-Bromo-4-(difluoromethyl)quinoline



Prepared according to general procedure A using 8-bromoquinoline (104 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 µL, 0.5 mmol), DBU (75 µL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (4.5

mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 3 % EtOAc in CH_2Cl_2) to provide the title compound as colorless crystals (104 mg, 0.40 mmol, 81 % yield). mp 77-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.99 (d, *J* = 4.3 Hz, 1H), 8.36 (d, *J* = 2.0 Hz, 1H), 7.94 (dt, *J* = 9.0, 1.3 Hz, 1H), 7.72 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.57 (d, *J* = 4.3 Hz, 1H), 7.09 (t, *J* = 54.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.13, 149.39, 138.11 (t, *J* = 22.0 Hz), 132.83, 131.44, 124.88, 124.33, 122.84 (t, *J* = 2.9 Hz), 118.46 (t, *J* = 7.7 Hz), 113.29 (t, *J* = 240.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -114.66 (d, *J* = 54.4 Hz). IR υ_{max}/cm^{-1} (film): 3068, 3040, 2975, 2923, 2852, 2360, 2333, 1600, 1494, 1442, 1362, 1305, 1238, 1166, 1120, 1080, 1066, 1041, 1001, 899, 858, 821, 778, 769, 672. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{10}H_7BrF_2N^+$ = 257.9724, found 257.9745.

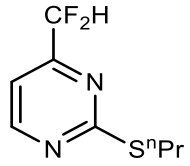
7-(Difluoromethyl)-2-phenylfuro[3,2-b]pyridine



Prepared according to general procedure A using 2-phenylfuro[3,2-b]pyridine (195 mg, 1.0 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (326 mg, 1.1 mmol), Tf_2O (168 µL, 1.0 mmol), DBU (150 µL, 1.0 mmol), CH_2Cl_2 (10 mL), HCl (4 M in dioxane, 125 µL, 0.5 mmol), EtOH (9 mL) and H_2O (1.0 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 5 % EtOAc in CH_2Cl_2) to provide the title compound as a pale yellow solid (46 mg, 0.19 mmol, 19 % yield). mp 93-94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.64 (d, *J* = 4.4 Hz, 1H), 7.96 – 7.85 (m, 2H), 7.56 – 7.39 (m, 3H), 7.35 (d, *J* = 4.9 Hz, 1H), 7.27 (s, 1H), 7.15 (t, *J* = 54.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.92, 150.48, 146.60, 144.71 – 143.57 (m), 130.21, 129.21, 129.15, 125.66, 124.47 (t, *J* = 24.9 Hz), 115.32 – 114.04 (m), 110.90 (t, *J* = 240.0

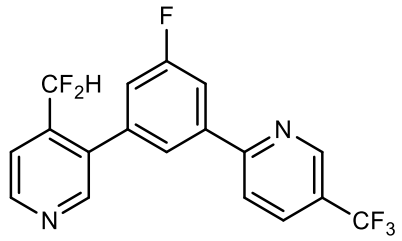
Hz), 102.49; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -116.04 (d, *J* = 54.7 Hz). IR υ_{max}/cm^{-1} (film): 3117, 3068, 3037, 2979, 2924, 2853, 2360, 2341, 1577, 1494, 1448, 1398, 1375, 1362, 1282, 1267, 1257, 1215, 1114, 1080, 1034, 1015, 992, 917, 840, 800, 771, 756, 698, 686, 659. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{14}H_{10}F_2NO^+$ = 246.0725, found 246.0748.

4-(Difluoromethyl)-2-(propylthio)pyrimidine



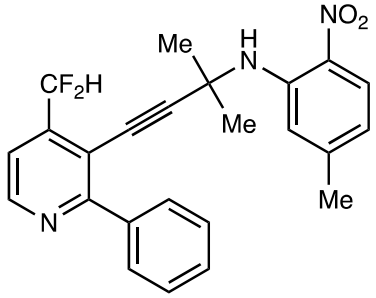
Prepared according to general procedure A using 2-(propylthio)pyrimidine (77 mg, 0.5 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (163 mg, 0.55 mmol), Tf_2O (84 μL, 0.5 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (5 mL), HCl (4 M in dioxane, 125 μL, 0.5 mmol), EtOH (4.5 mL) and H_2O (0.5 mL) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 10 % EtOAc in hexanes) to provide the title compound as a colorless oil (32 mg, 0.16 mmol, 32 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (d, *J* = 5.0 Hz, 1H), 7.22 (d, *J* = 5.0 Hz, 1H), 6.44 (t, *J* = 54.8 Hz, 1H), 3.23 – 3.05 (m, 2H), 1.77 (h, *J* = 7.3 Hz, 2H), 1.05 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.68, 160.52 (t, *J* = 26.9 Hz), 159.00, 112.59 (t, *J* = 242.3 Hz) 111.64 (t, *J* = 2.9 Hz), 33.09, 22.55, 13.58; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -119.57 (d, *J* = 54.8 Hz). IR υ_{max}/cm^{-1} (film): 2966, 2933, 2874, 2360, 2342, 1560, 1458, 1436, 1363, 1325, 1262, 1202, 1182, 1110, 1052, 835, 751, 735. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_8H_{11}F_2N_2S^+$ = 205.0606, found 205.0624.

2-(3-(4-(Difluoromethyl)pyridin-3-yl)-5-fluorophenyl)-5-(trifluoromethyl)pyridine



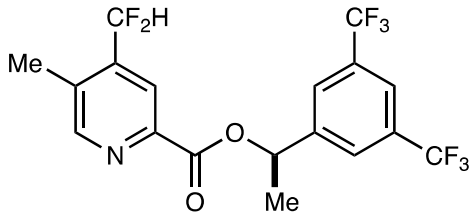
Prepared according to general procedure A using 2-(3-fluoro-5-(pyridin-3-yl)phenyl)-5-(trifluoromethyl)pyridine (80 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (37 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 23 hours. The crude material was purified by flash chromatography (silica gel: 20 % EtOAc in toluene) to provide the title compound as a white solid (57 mg, 0.155 mmol, 62 % yield). m.p. 120-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.02 – 8.92 (m, 1H), 8.83 (d, *J* = 5.1 Hz, 1H), 8.72 (s, 1H), 8.04 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.94 – 7.83 (m, 3H), 7.69 (d, *J* = 5.1 Hz, 1H), 7.22 (dt, *J* = 8.5, 2.0 Hz, 1H), 6.58 (t, *J* = 54.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 164.53, 162.05, 159.25 – 157.72 (m), 151.00, 150.37, 147.02 (d, *J* = 4.0 Hz), 140.89 (d, *J* = 8.1 Hz), 139.35 (t, *J* = 23.1 Hz), 137.73 (d, *J* = 8.1 Hz), 134.67 – 134.33 (m), 126.05 (q, *J* = 33.2 Hz), 124.98, 124.29, 120.28, 119.53 (t, *J* = 5.3 Hz), 118.20 (d, *J* = 22.6 Hz), 114.77 (d, *J* = 23.0 Hz), 111.65 (t, *J* = 239.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ: -62.38, -110.80 (t, *J* = 9.1 Hz), -111.59 (d, *J* = 54.1 Hz). IR υ_{max}/cm^{-1} (film): 3080, 3036, 2923, 1600, 1571, 1492, 1432, 1046, 1329, 1237, 1164, 1177, 1138, 1076, 1020, 920, 886, 842, 771, 697, 670, 553, 532. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{11}F_6N_2^+$ = 369.0821, found 369.0846.

***N*-(4-(4-(Difluoromethyl)-2-phenylpyridin-3-yl)-2-methylbut-3-yn-2-yl)-5-methyl-2-nitroaniline**



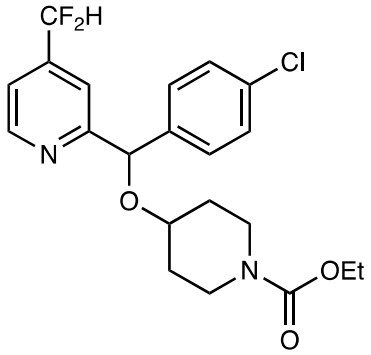
Prepared according to general procedure A using 5-methyl-*N*-(2-methyl-4-(2-phenylpyridin-3-yl)but-3-yn-2-yl)-2-nitroaniline (70 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (37 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 5 % EtOAc in hexanes) to provide the title compound as a yellow oil (64 mg, 0.152 mmol, 61 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (d, *J* = 5.0 Hz, 1H), 8.31 (s, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.83 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.50 (d, *J* = 4.9 Hz, 1H), 7.43 – 7.31 (m, 3H), 7.08 (d, *J* = 1.6 Hz, 1H), 6.91 (t, *J* = 54.8 Hz, 1H), 6.49 (dd, *J* = 8.7, 1.7 Hz, 1H), 2.19 (s, 3H), 1.73 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 161.31, 149.15, 147.37, 144.16 (t, *J* = 22.9 Hz), 143.34, 138.57, 131.18, 129.47, 129.34, 127.99, 127.04, 118.01, 117.33 (t, *J* = 5.4 Hz), 115.71, 115.19 (d, *J* = 5.8 Hz), 112.20 (t, *J* = 240.0 Hz), 103.06, 48.35, 29.99, 22.14; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -116.97 (d, *J* = 54.8 Hz). IR υ_{max}/cm^{-1} (film): 3352, 2983, 2932, 2360, 2342, 1617, 1578, 1491, 1405, 1335, 1237, 1187, 1128, 1073, 1048, 908, 843, 751, 732, 697. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{24}H_{22}F_2N_3O_2^+$ = 422.1675, found 422.1682.

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



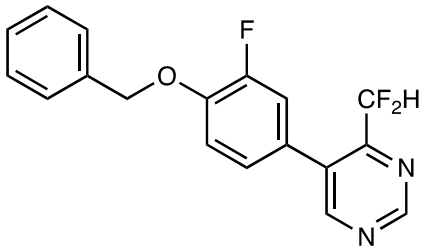
Prepared according to general procedure A using (*R*)-1-(3,5-bis(trifluoromethyl)phenyl)ethyl 5-methylpicolinate (94 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (37 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 60 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 1 % EtOAc in CH_2Cl_2) to provide the title compound as a colorless oil (57 mg, 0.133 mmol, 53 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (t, *J* = 0.9 Hz, 1H), 8.20 (s, 1H), 7.92 (d, *J* = 1.7 Hz, 2H), 7.82 (t, *J* = 1.7 Hz, 1H), 6.76 (t, *J* = 54.4 Hz, 1H), 6.27 (q, *J* = 6.7 Hz, 1H), 2.49 (d, *J* = 1.6 Hz, 3H), 1.78 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.78, 152.49, 146.39, 143.75, 140.99 (t, *J* = 22.4 Hz), 135.33 (t, *J* = 4.3 Hz), 132.05 (q, *J* = 33.4 Hz), 126.58 (q, *J* = 3.6 Hz), 123.15 (q, *J* = 272.8 Hz), 122.38 – 122.00 (m), 121.30 (t, *J* = 7.1 Hz), 112.20 (t, *J* = 240.9 Hz), 72.59, 21.97, 15.81; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -62.90, -117.64 (d, *J* = 54.7 Hz). IR υ_{max}/cm^{-1} (film): 2989, 2360, 2342, 1726, 1456, 1384, 1278, 1247, 1222, 1174, 1134, 1054, 907, 845, 755, 730, 705, 682, 669. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{14}F_8NO_2^+$ = 428.0891, found 428.0907.

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



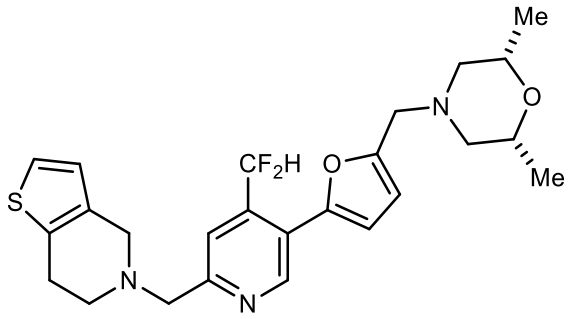
Prepared according to general procedure A using ethyl 4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (94 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (37 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 45 hours. The crude material was purified by flash chromatography (silica gel: 30 % EtOAc in toluene) to provide the title compound as a colorless oil (69 mg, 0.162 mmol, 65 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.58 (d, *J* = 5.1 Hz, 1H), 7.62 (s, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.28 – 7.21 (m, 3H), 6.58 (t, *J* = 55.7 Hz, 1H), 5.62 (s, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.82 – 3.66 (m, 2H), 3.59 (tt, *J* = 7.7, 3.7 Hz, 1H), 3.21 – 3.08 (m, 2H), 1.89 – 1.72 (m, 2H), 1.61 (td, *J* = 8.4, 4.1 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.25, 155.60, 149.79, 143.28 (t, *J* = 23.4 Hz), 139.63, 133.79, 128.83, 128.28, 118.80 (t, *J* = 5.7 Hz), 116.77 (t, *J* = 6.1 Hz), 113.05 (t, *J* = 241.1 Hz), 80.75, 72.96, 61.40, 41.15 (d, *J* = 7.4 Hz), 31.16 (d, *J* = 34.4 Hz), 14.79; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -115.57 (dd, *J* = 55.8, 10.1 Hz). IR υ_{max}/cm^{-1} (film): 2982, 2931, 2870, 1687, 1609, 1571, 1489, 1474, 1433, 1383, 1274, 1229, 1164, 1113, 1077, 1032, 1015, 828, 751, 666, 548, 531. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{21}H_{24}ClF_2N_2O_3^+$ = 425.1438, found 425.1463.

5-(4-(Benzyloxy)-3-fluorophenyl)-4-(difluoromethyl)pyrimidine



Prepared according to general procedure A using 5-(4-(benzyloxy)-3-fluorophenyl)pyrimidine (70 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (37 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 17 hours. The crude material was purified by flash chromatography (silica gel: 30 % EtOAc in hexanes) to provide the title compound as a white solid (32 mg, 0.096 mmol, 39 % yield). m.p. 73-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.81 (s, 1H), 7.51 – 7.33 (m, 5H), 7.22 – 7.04 (m, 3H), 6.58 (t, J = 53.6 Hz, 1H), 5.22 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.46, 157.84, 155.64 (t, J = 23.5 Hz), 153.97, 151.50, 147.90 (d, J = 10.5 Hz), 136.08, 132.83 (d, J = 2.2 Hz), 128.90, 128.52, 127.57, 125.96 – 125.44 (m), 117.53 (dt, J = 19.7, 1.8 Hz), 115.78 (d, J = 2.5 Hz), 111.90 (t, J = 242.5 Hz), 71.48; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -114.77 (d, J = 53.8 Hz), -131.97 (dd, J = 11.4, 8.1 Hz). IR υ_{max}/cm^{-1} (film): 3038, 2923, 2851, 1618, 1573, 1555, 1520, 1511, 1455, 1435, 1384, 1371, 1348, 1300, 1272, 1211, 1134, 1093, 1059, 1009, 993, 926, 906, 883, 817, 756, 746, 698, 668, 637, 630, 558. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{14}F_3N_2O^+$ = 331.1053, found 331.1058.

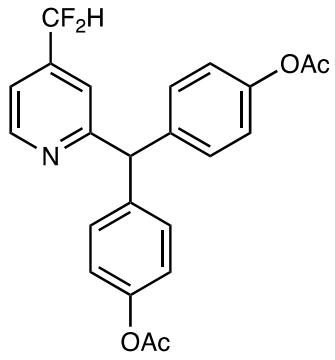
(2R,6S)-4-((5-(4-(Difluoromethyl)-6-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)pyridin-3-yl)furan-2-yl)methyl)-2,6-dimethylmorpholine



Prepared according to general procedure A except the reaction was allowed to warm to –50 °C after DBU addition and stirred for 5 minutes, then HCl was added and the reaction heated to 60 °C using (2R,6S)-4-((5-(6-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)pyridin-3-yl)furan-2-yl)methyl)-2,6-dimethylmorpholine (106 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (81.5 mg, 0.28 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (38 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 190 μL, 0.75 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 60 °C for 72 hours. The crude material was purified by flash chromatography (silica gel: 1 % MeOH in CH_2Cl_2) to provide the title compound as a pale yellow oil (60 mg, 0.13 mmol, 52 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (s, 1H), 7.82 (s, 1H), 7.08 (d, *J* = 5.1 Hz, 1H), 7.02 (t, *J* = 54.6 Hz, 1H), 6.70 (dd, *J* = 11.2, 4.2 Hz, 2H), 6.38 (d, *J* = 3.3 Hz, 1H), 3.94 (s, 2H), 3.77 – 3.66 (m, 4H), 3.62 (s, 2H), 2.99 – 2.85 (m, 4H), 2.77 (d, *J* = 10.5 Hz, 2H), 1.86 (t, *J* = 10.7 Hz, 2H), 1.16 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.92, 153.65, 148.50, 148.20, 137.64 (t, *J* = 22.8 Hz), 133.74, 133.48, 125.36, 123.32 (t, *J* = 5.8 Hz), 122.85, 118.84 (t, *J* = 6.8 Hz), 111.82 (t, *J* = 239.0 Hz), 111.53, 111.45 – 111.16 (m), 71.80, 63.44, 59.06, 54.84, 53.38, 50.98, 25.54, 19.27; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.13 (d, *J* = 54.6 Hz). IR υ_{max}/cm^{-1} (film): 2971, 2931, 2871, 2813, 2360, 2342, 1474, 1454, 1376, 1355, 1321, 1162, 1142, 1080, 1044, 1023,

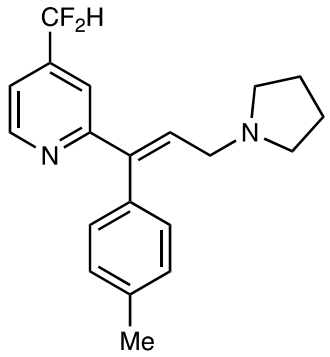
906, 837, 795, 730, 702. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{25}H_{30}F_2N_3O_2S^+$ = 474.2021, found 474.2025.

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



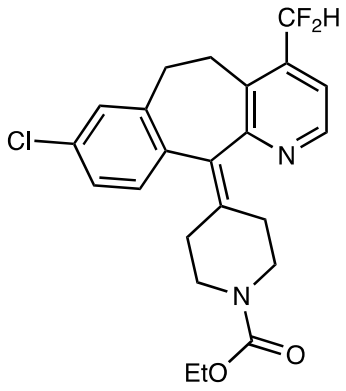
Prepared according to general procedure C using (pyridin-2-ylmethylene)bis(4,1-phenylene) diacetate (90 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 µL, 0.25 mmol), DBU (37 µL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 µL, 0.25 mmol), and TBAF (1 M in THF, 250 µL, 0.25 mmol) at 40 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 20 % EtOAc in toluene) to provide the title compound as a yellow oil (86 mg, 0.208 mmol, 83 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (d, *J* = 5.0 Hz, 1H), 7.29 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.23 (s, 1H), 7.21 – 7.15 (m, 4H), 7.08 – 7.00 (m, 4H), 6.58 (t, *J* = 55.7 Hz, 1H), 5.70 (s, 1H), 2.28 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.52, 163.85, 150.53, 149.60, 142.97 (t, *J* = 23.3 Hz), 139.53, 130.36, 121.74, 120.04 (t, *J* = 6.1 Hz), 117.99 (t, *J* = 5.7 Hz), 113.04 (t, *J* = 241.0 Hz), 58.20, 21.26; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -115.50 (d, *J* = 55.9 Hz). IR υ_{max}/cm^{-1} (film): 3023, 1754, 1608, 1571, 1504, 1412, 1369, 1165, 1044, 1018, 909, 847, 751, 730, 665, 650, 549, 531. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{20}F_2NO_4^+$ = 412.1355, found 412.1367.

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



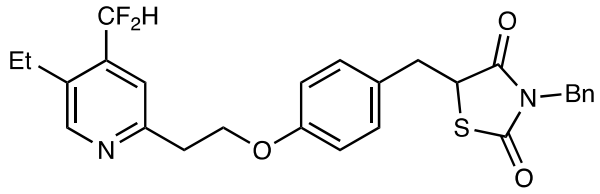
Prepared according to general procedure A (except (*E*)-2-(3-(pyrrolidin-1-yl)-1-(*p*-tolyl)prop-1-en-1-yl)pyridine was protonated using TfOH (22 μL, 0.25 mmol) before the salt reaction) using (*E*)-2-(3-(pyrrolidin-1-yl)-1-(*p*-tolyl)prop-1-en-1-yl)pyridine (70 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 25 hours. The crude material was purified by flash chromatography (silica gel: 5 % MeOH in CH_2Cl_2) to provide the title compound as a brown oil (66 mg, 0.200 mmol, 80 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (d, *J* = 4.9 Hz, 1H), 7.33 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.11 – 7.00 (m, 4H), 6.52 (t, *J* = 55.6 Hz, 1H), 3.79 (d, *J* = 7.3 Hz, 2H), 3.25 (s, 4H), 2.43 (s, 3H), 2.15 – 2.01 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.67, 150.02, 142.50 (t, *J* = 23.2 Hz), 141.90, 137.50, 134.80, 131.15, 129.76, 129.46, 118.33 (t, *J* = 6.2 Hz), 117.93 (t, *J* = 5.6 Hz), 113.23 (t, *J* = 240.7 Hz), 54.63, 54.11, 23.63, 21.43; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -115.28 (d, *J* = 55.9 Hz). IR υ_{max}/cm^{-1} (film): 2966, 2927, 2878, 2796, 1605, 1568, 1513, 1462, 1413, 1379, 1216, 1157, 1110, 1046, 908, 823, 731, 666, 549, 531. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{20}H_{23}F_2N_2^+$ = 329.1824, found 329.1832.

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



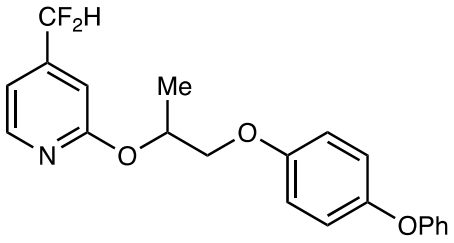
Prepared according to general procedure A using ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (96 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 µL, 0.25 mmol), DBU (37 µL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 µL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 20 hours. The crude material was purified by flash chromatography (silica gel: 50 % EtOAc in toluene) to provide the title compound as a yellow oil (93 mg, 0.216 mmol, 86 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.53 (d, *J* = 5.0 Hz, 1H), 7.32 (d, *J* = 5.1 Hz, 1H), 7.12 (d, *J* = 2.5 Hz, 3H), 6.76 (t, *J* = 54.7 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.80 (d, *J* = 12.5 Hz, 2H), 3.49 – 3.30 (m, 2H), 3.26 – 3.11 (m, 2H), 3.10 – 2.99 (m, 1H), 2.94 – 2.83 (m, 1H), 2.53 – 2.32 (m, 3H), 2.27 – 2.10 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.34, 155.48, 147.54, 139.97 (t, *J* = 21.8 Hz), 138.65, 137.80, 135.81, 133.75, 133.25, 131.24, 131.11 (t, *J* = 4.0 Hz), 129.69, 126.24, 118.79 (t, *J* = 7.2 Hz), 112.71 (t, *J* = 240.4 Hz), 61.40, 44.71 (d, *J* = 15.6 Hz), 31.59, 30.66 (d, *J* = 7.2 Hz), 26.31, 14.69; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -112.76 – -118.16 (m). IR υ_{max}/cm^{-1} (film): 2981, 2911, 2870, 1734, 1591, 1478, 1434, 1386, 1374, 1227, 1119, 1043, 909, 757, 733, 561. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{23}H_{24}ClF_2N_2O_2^+$ = 433.1489, found 433.1515.

3-Benzyl-5-(4-(2-(4-(difluoromethyl)-5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione



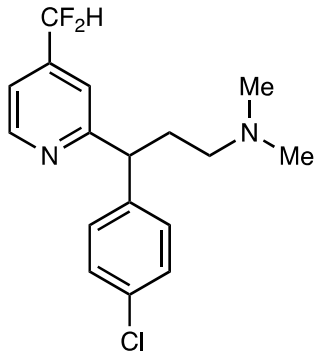
Prepared according to general procedure A using 3-benzyl-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione (112 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (37 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 15 % EtOAc in toluene) to provide the title compound as a colorless oil (31 mg, 0.061 mmol, 25 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (s, 1H), 7.40 (s, 1H), 7.26 (d, *J* = 1.2 Hz, 6H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.91 – 6.61 (m, 3H), 4.78 – 4.60 (m, 2H), 4.42 (dd, *J* = 8.8, 3.9 Hz, 1H), 4.32 (t, *J* = 6.5 Hz, 2H), 3.38 (dd, *J* = 14.2, 3.9 Hz, 1H), 3.27 (t, *J* = 6.5 Hz, 2H), 3.08 (dd, *J* = 14.2, 8.7 Hz, 1H), 2.75 (q, *J* = 7.6 Hz, 2H), 1.27 (t, *J* = 7.6 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.82, 171.05, 158.26, 157.12, 150.97, 139.71 (t, *J* = 21.8 Hz), 135.12, 134.58, 130.53, 128.76, 128.20, 127.63, 119.55 (t, *J* = 6.8 Hz), 114.87, 112.58 (d, *J* = 238.9 Hz), 67.01, 51.75, 45.27, 37.81, 37.68, 22.65, 15.74; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -115.09 (d, *J* = 54.8 Hz). IR υ_{max}/cm^{-1} (film): 3017, 2971, 2935, 2878, 1749, 1679, 1610, 1512, 1382, 1330, 1302, 1244, 1216, 1179, 1147, 1036, 908, 699, 667, 561, 530. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{27}H_{27}F_2N_2O_3S^+$ = 497.1705, found 497.1720.

4-(Difluoromethyl)-2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine



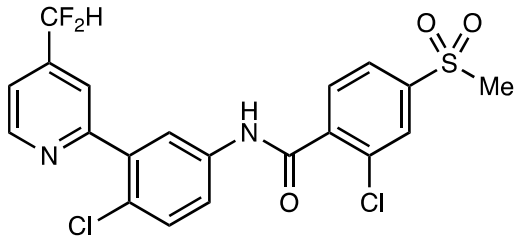
Prepared according to general procedure B using 2-((1-(4-phenoxyphenoxy)propan-2-yl)oxy)pyridine (80 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (2.5 mL), K_2CO_3 (35 mg, 0.25 mmol), THF (0.625 mL) and H_2O (0.625 mL) at rt for 30 minutes. The crude material was purified by flash chromatography (silica gel: 100 % toluene) to provide the title compound as a colorless oil (18 mg, 0.048 mmol, 19 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.25 (d, *J* = 5.2 Hz, 1H), 7.29 (dd, *J* = 8.6, 7.3 Hz, 2H), 7.08 – 7.01 (m, 1H), 7.01 – 6.88 (m, 7H), 6.87 (s, 1H), 6.56 (t, *J* = 55.8 Hz, 1H), 5.67 – 5.56 (m, 1H), 4.13 (ddd, *J* = 42.4, 9.9, 5.1 Hz, 2H), 1.48 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 163.74, 158.59, 155.25, 150.54, 147.97, 145.21, 129.76, 122.62, 120.91, 117.79, 115.92, 115.54 – 110.51 (m), 108.68, 71.09, 70.20, 17.01; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -115.62 (d, *J* = 55.8 Hz). IR υ_{max}/cm^{-1} (film): 2985, 1617, 1590, 1569, 1504, 1489, 1422, 1380, 1317, 1221, 1078, 1047, 909, 759, 734, 582, 560. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{21}H_{20}F_2NO_3^+$ = 372.1406, found 372.1420.

3-(4-Chlorophenyl)-3-(4-(difluoromethyl)pyridin-2-yl)-*N*,*N*-dimethylpropan-1-amine



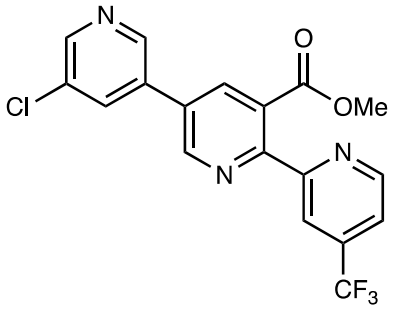
Prepared according to general procedure A (except 3-(4-chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine was protonated using TfOH (22 μL, 0.25 mmol) before the salt reaction) using 3-(4-chlorophenyl)-*N*,*N*-dimethyl-3-(pyridin-2-yl)propan-1-amine (69 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (75 μL, 0.5 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 20 hours. The crude material was purified by flash chromatography (neutral silica gel: 2 % MeOH in CH_2Cl_2) to provide the title compound as a brown oil (53 mg, 0.163 mmol, 65 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (d, *J* = 5.0 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 7H), 6.54 (t, *J* = 55.7 Hz, 1H), 4.24 (t, *J* = 6.6 Hz, 1H), 2.68 (s, 3H), 2.57 (s, 6H), 2.47 – 2.37 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.69, 150.25, 143.10 (t, *J* = 23.3 Hz), 140.45, 133.21, 129.42, 129.20, 119.80 (t, *J* = 6.0 Hz), 118.27 (t, *J* = 5.7 Hz), 112.92 (t, *J* = 241.1 Hz), 56.89, 50.04, 43.90, 30.44.; ^{19}F NMR (377 MHz, $CDCl_3$) δ: -115.59 (dd, *J* = 55.6, 3.7 Hz). IR υ_{max}/cm^{-1} (film): 2953, 1681, 1611, 1570, 1420, 1410, 1383, 1090, 1039, 1015, 832. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{17}H_{20}ClF_2N_2^+$ = 325.1278, found 325.1297.

2-Chloro-N-(4-chloro-3-(4-(difluoromethyl)pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide



Prepared according to general procedure A using 2-chloro-*N*-(4-chloro-3-(pyridin-2-yl)phenyl)-4-(methylsulfonyl)benzamide (105 mg, 0.25 mmol), (difluoromethyl)bis(4-methoxyphenyl)phosphane (82 mg, 0.275 mmol), Tf_2O (42 μL, 0.25 mmol), DBU (37 μL, 0.25 mmol), CH_2Cl_2 (2.5 mL), HCl (4 M in dioxane, 63 μL, 0.25 mmol), EtOH (2.25 mL) and H_2O (0.25 mL) at 40 °C for 25 hours. The crude material was purified by flash chromatography (silica gel: 60 % EtOAc in toluene) to provide the title compound as a yellow solid (71 mg, 0.151 mmol, 60 % yield). m.p. 124-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.21 (s, 1H), 8.63 (d, *J* = 5.1 Hz, 1H), 7.90 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.83 (d, *J* = 1.7 Hz, 1H), 7.80 (s, 1H), 7.78 (d, *J* = 2.7 Hz, 1H), 7.68 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.40 – 7.32 (m, 1H), 6.71 (t, *J* = 55.7 Hz, 1H), 3.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.02, 157.28, 150.30, 143.54 – 142.75 (m), 140.92, 138.63, 137.31, 132.71, 131.54, 130.70, 129.33, 128.03, 126.22, 123.25, 122.40, 121.92 (t, *J* = 6.1 Hz), 119.50 (t, *J* = 5.7 Hz), 113.15 (t, *J* = 241.4 Hz), 44.75; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -116.15 (d, *J* = 55.8 Hz). IR υ_{max}/cm^{-1} (film): 3015, 2932, 1678, 1609, 1546, 1488, 1469, 1367, 1310, 1155, 1095, 1033, 959, 892, 875, 749, 676, 607, 550. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{20}H_{15}Cl_2F_2N^+$ = 471.0143, found 471.0138.

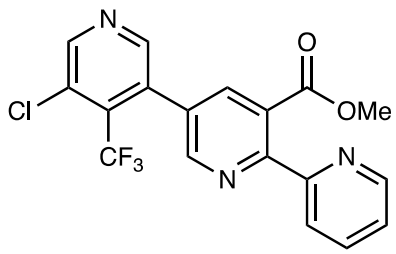
Methyl 5''-chloro-4-(trifluoromethyl)-[2,2':5',3''-terpyridine]-3'-carboxylate



An oven dried 8 mL vial equipped with a stir bar was charged with methyl 5''-chloro-[2,2':5',3''-terpyridine]-3'-carboxylate (65 mg, 0.20 mmol), 1,1'-(((trifluoromethyl) phosphanediyl)bis(4,1-phenylene))dipyrrolidine (157 mg, 0.40 mmol), and placed under a nitrogen atmosphere. CH_2Cl_2 (2 mL) was added, the reaction vessel was cooled to –50 °C and Tf_2O (67 µL, 0.40 mmol) was added dropwise. After stirring for 1 hour, the reaction was cooled to –78 °C and Et_3N (56 µL, 0.40 mmol) was added dropwise via syringe. The cooling bath was removed, and the reaction was allowed to warm 0 °C while stirring (approximately 20-30 minutes). At 0 °C, TfOH (27 µL mg, 0.31 mmol), H_2O (36 µL, 2.00 mmol), MeOH (1 mL) were added and the reaction was stirred at room temperature for 40 hours. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 25% EtOAc in hexanes) to provide the title compound as a yellow solid (53 mg, 0.13 mmol, 67% yield). mp 185 – 189 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.98 (d, J = 2.2 Hz, 1H), 8.82 – 8.79 (m, 2H), 8.68 (d, J = 2.2 Hz, 1H), 8.51 (s, 1H), 8.16 (d, J = 2.3 Hz, 1H), 7.96 (app t, J = 2.1 Hz, 1H), 7.57 (dd, J = 5.0, 1.0 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.76, 156.77, 153.68, 149.56, 149.01, 148.54, 145.95, 139.54 (q, J = 34.1 Hz), 135.60, 134.26, 133.32, 132.83, 132.14, 129.20, 122.91 (q, J = 273.5 Hz), 119.64 (q, J = 3.6 Hz), 118.90 (q, J = 3.8 Hz), 52.86; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.76, IR υ_{max}/cm^{-1} (film): 3021, 2925,

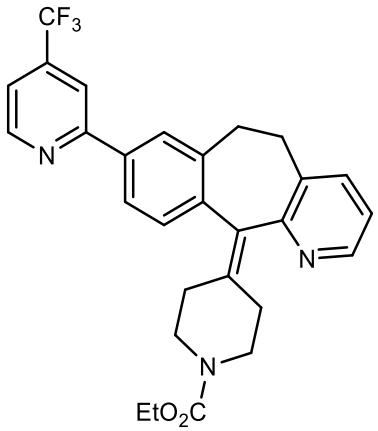
1733, 1336, 1262, 1142, 891, 667. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{12}ClF_3N_3O_2^+$ = 394.0570, found 394.0559.

Methyl 5''-chloro-4''-(trifluoromethyl)-[2,2':5',3''-terpyridine]-3'-carboxylate



Prepared according to trifluoromethylation general procedure A using methyl 5''-chloro-[2,2':5',3''-terpyridine]-3'-carboxylate (65 mg, 0.20 mmol), Tf_2O (34 µL, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (84 mg, 0.22 mmol), DBU (30 µL, 0.20 mmol), CH_2Cl_2 (2 mL), then TfOH (27 µL mg, 0.31 mmol), H_2O (36 µL, 2.00 mmol), MeOH (1 mL) were added at 0 °C and the reaction was stirred at room temperature for 24 hours. The crude material was purified by flash chromatography (silica gel: 35% EtOAc in hexanes) to provide the title compound as an amorphous solid (25 mg, 0.06 mmol, 31% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.86 (s, 1H), 8.69 – 8.63 (m, 2H), 8.51 (s, 1H), 8.23 (d, *J* = 7.9 Hz, 1H), 7.93 – 7.85 (m, 2H), 7.36 (ddd, *J* = 7.6, 5.0, 0.9 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.43, 155.51, 155.36, 152.17, 150.71, 149.47 (d, *J* = 2.0 Hz), 148.68, 137.17, 136.95 (d, *J* = 1.5 Hz), 133.92 (q, *J* = 30.8 Hz), 132.49 (q, *J* = 2.0 Hz), 131.42, 130.40 (q, *J* = 1.4 Hz), 128.16, 124.25, 123.02, 122.10 (q, *J* = 276.2 Hz), 52.79; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -55.55, IR υ_{max}/cm^{-1} (film): 2950, 2359, 1728, 1284, 1144, 1034, 750, 667. *m/z* HRMS (DART): $[M+H]^+$ calculated for $C_{18}H_{12}ClF_3N_3O_2^+$ = 394.0570, found 394.0590.

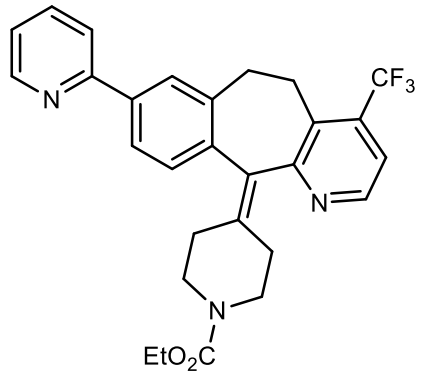
Ethyl 4-(8-(4-(trifluoromethyl)pyridin-2-yl)-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)piperidine-1-carboxylate



An oven dried 8 mL vial with a stir bar was charged with ethyl 4-(8-(pyridin-2-yl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (85 mg, 0.20 mmol) and placed under a nitrogen atmosphere. CH_2Cl_2 (3.8 mL) was added, the reaction vessel cooled to –78 ºC and Tf_2O (68 µL, 0.40 mmol) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (157 mg, 0.40 mmol) was added in one portion. The reaction was subjected to three rapid cycles of vacuum/nitrogen backfill and was stirred for a further 30 minutes at –78 °C. Then Et_3N (56 µL, 0.40 mmol) was added dropwise via syringe, the cooling bath was removed and the reaction was allowed to warm to room temperature while stirring (approximately 15 minutes). Then, the reaction mixture was cooled to 0 ºC, HOTf (45 µL, 0.5 mmol), MeOH (1 mL) and H_2O (36 µL, 2.00 mmol) were added sequentially. The mixture was warmed to room temperature and stirred for 12 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3x). The combined organic extracts were washed with a saturated aqueous solution of brine, dried (Na_2SO_4), filtered and concentrated in vacuo. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 10% Et_3N in hexanes) to

provide the title compound as a light-yellow oil (72 mg, 0.15 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (d, *J* = 5.1 Hz, 1H), 8.41 (dd, *J* = 1.7, 4.8 Hz, 1H), 7.88 (s, 2H), 7.79 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.45 (dd, *J* = 1.7, 7.7 Hz, 1H), 7.42 (dd, *J* = 0.7, 5.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.10 (dd, *J* = 4.8, 7.7 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.83 (br s, 2H), 3.55–3.47 (m, 1H), 3.44–3.36 (m, 1H), 3.19–3.12 (m, 2H), 2.99–2.87 (m, 2H), 2.55–2.48 (m, 1H), 2.42–2.32 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.55, 157.13, 155.61, 150.71, 146.79, 141.19, 139.20 (q, *J* = 33.7 Hz), 138.69, 137.66, 137.59, 137.23, 134.90, 133.70, 130.05, 127.83, 124.80, 123.02 (q, *J* = 271.6 Hz), 122.35, 117.56 (q, *J* = 3.6 Hz), 115.98 (q, *J* = 3.7 Hz), 61.40, 44.95, 44.93, 32.04, 31.83, 30.95, 30.67, 14.78; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -64.84; IR υ_{max}/cm^{-1} (film): 2911, 1690, 1608, 1570, 1471, 1423, 1384, 1333, 1277, 1227, 1168, 1134, 1113, 1088, 1059, 1026, 996, 889, 835, 790, 766, 726, 666; HRMS (DART): $[M+H]^+$ calculated for $C_{28}H_{27}F_3N_3O_2^+$ = 494.2050, found 494.2084.

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



Prepared according to trifluoromethylation general procedure A using ethyl 4-(8-(pyridin-2-yl)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)piperidine-1-carboxylate (85 mg, 0.20 mmol), 1,1'-(((trifluoromethyl)phosphanediyl)bis(4,1-phenylene))dipyrrolidine (79 mg,

0.20 mmol), Tf_2O (34 μL, 0.20 mmol), DBU (30 μL, 0.20 mmol), CH_2Cl_2 (2 mL), HOTf (45 μL, 0.50 mmol), MeOH (1 mL) and H_2O (36 μL, 2.00 mmol) at rt for 12 hours. The crude material was purified by flash chromatography (silica gel: 33% EtOAc, 10% Et_3N in hexanes) to provide the title compound as a colorless oil (70 mg, 0.14 mmol, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (d, *J* = 4.6 Hz, 1H), 8.56 (d, *J* = 5.1 Hz, 1H), 7.78 (s, 1H), 7.74–7.65 (m, 3H), 7.40 (d, *J* = 5.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.21–7.18 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.83–3.80 (m, 2H), 3.56–3.42 (m, 2H), 3.30–3.16 (m, 3H), 3.11–3.02 (m, 1H), 2.55–2.52 (m, 2H), 2.44–2.37 (m, 1H), 2.18–2.12 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.61, 156.86, 155.57, 149.76, 147.56, 138.84, 137.48, 137.00, 136.92, 136.83, 136.27 (q, *J* = 31.1 Hz), 134.42, 131.62, 131.04, 128.98, 124.45, 123.37 (q, *J* = 273.2 Hz), 122.28, 120.47, 118.46 (q, *J* = 5.1 Hz), 61.45, 44.95, 44.70, 32.15, 30.88, 30.69, 26.45, 14.76; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -61.86; IR υ_{max}/cm^{-1} (film): 2911, 2868, 1708, 1585, 1484, 1463, 1431, 1407, 1328, 1302, 1279, 1215, 1149, 1122, 1065, 1028, 1000, 985, 893, 857, 781, 759, 736, 687; HRMS (DART): $[M+H]^+$ calculated for $C_{28}H_{27}F_3N_3O_2^+$ = 494.2050, found 494.2080.

A1.6 References

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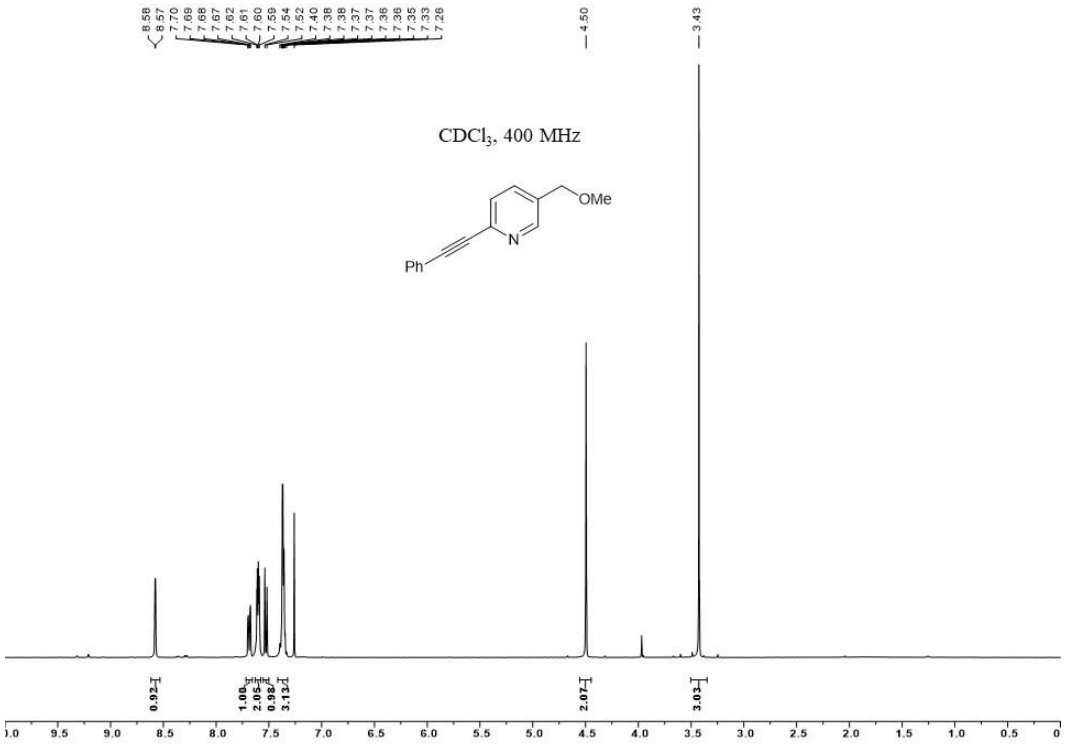
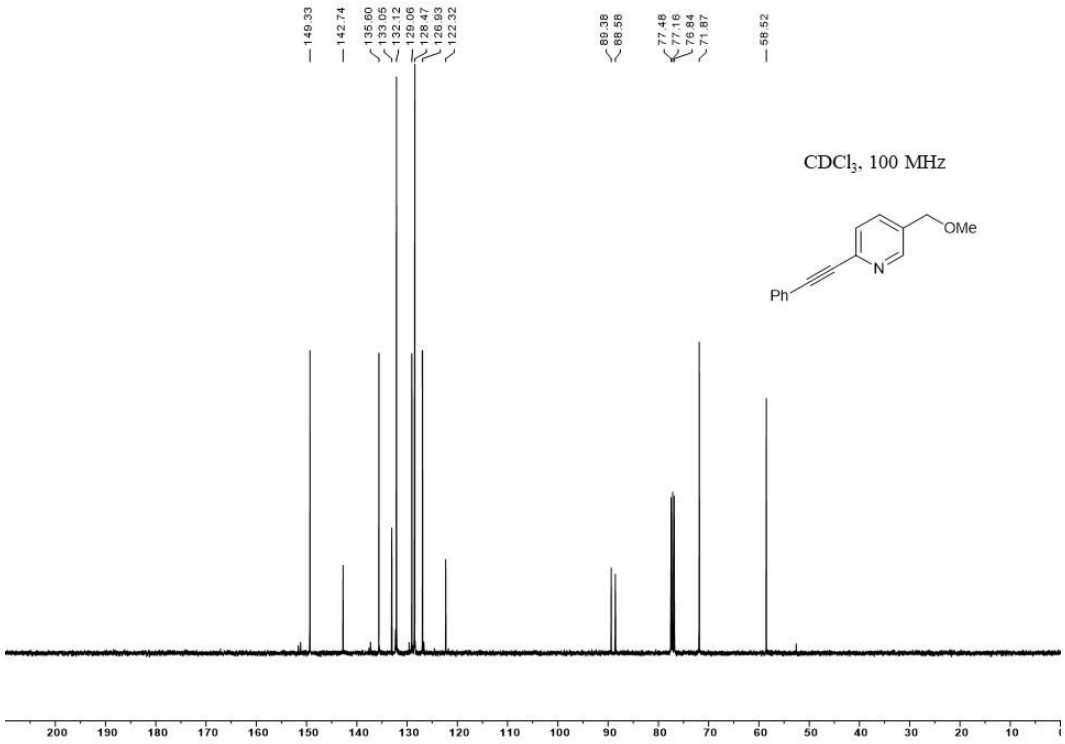
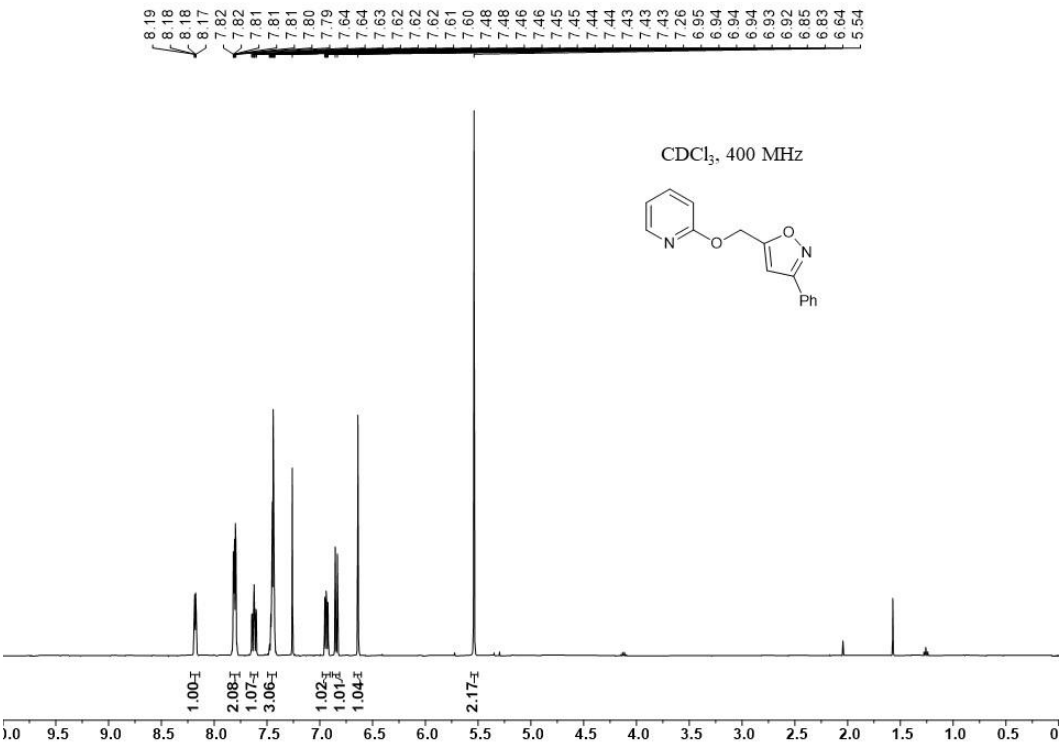
A1.7 Experimental Spectra



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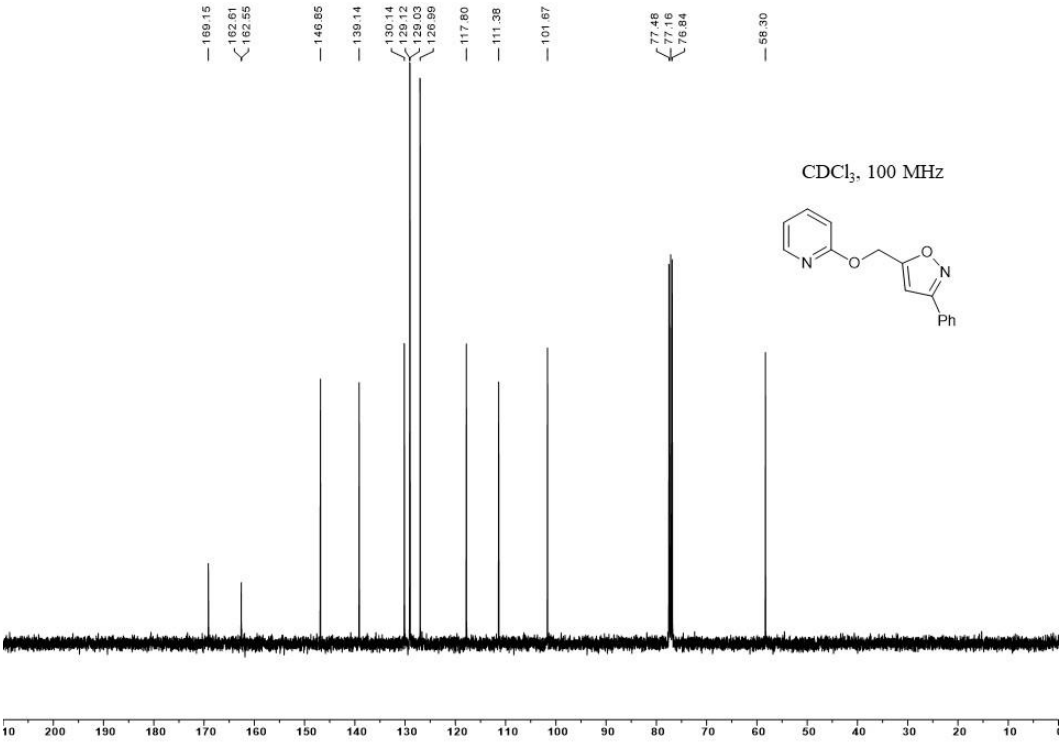
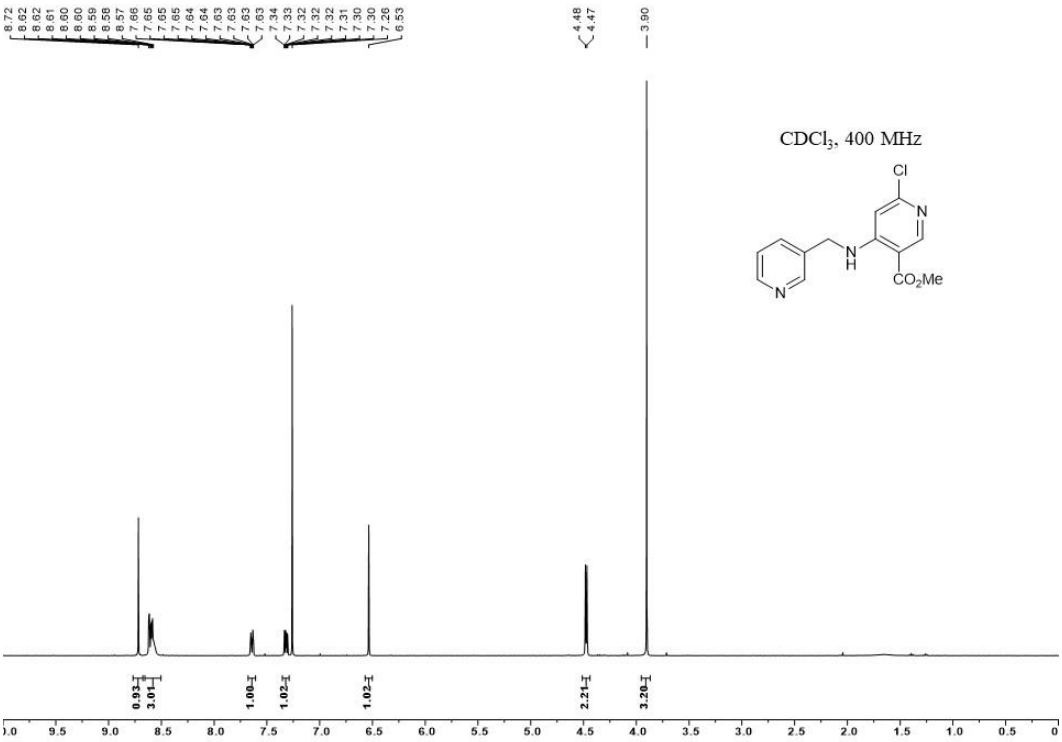
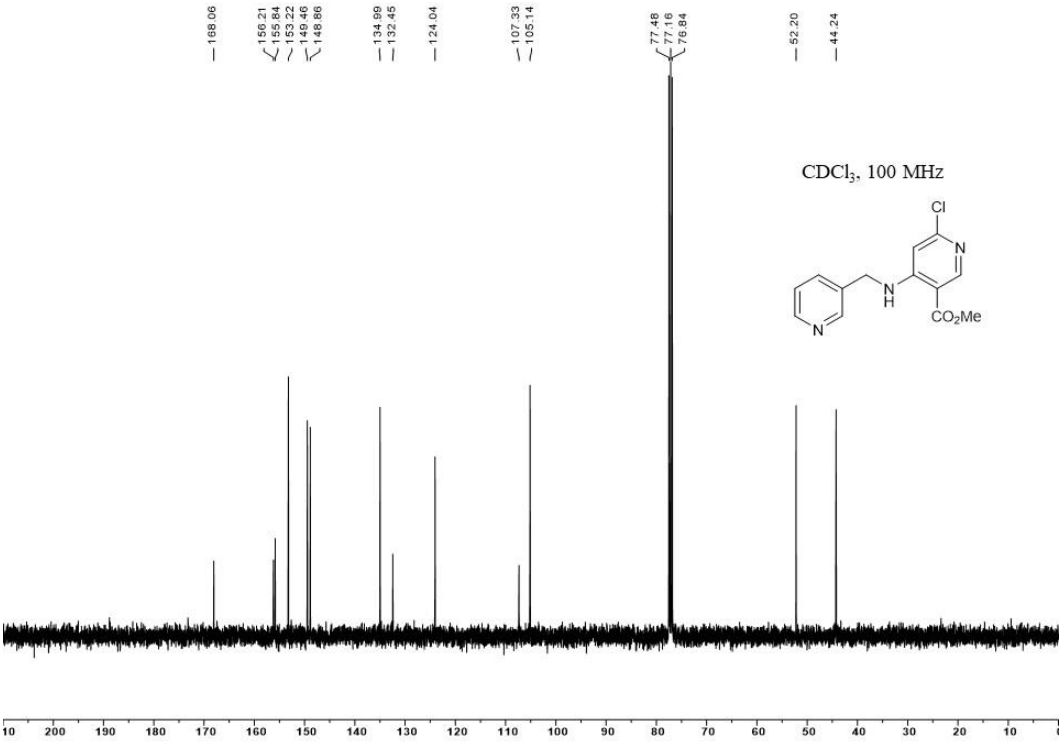
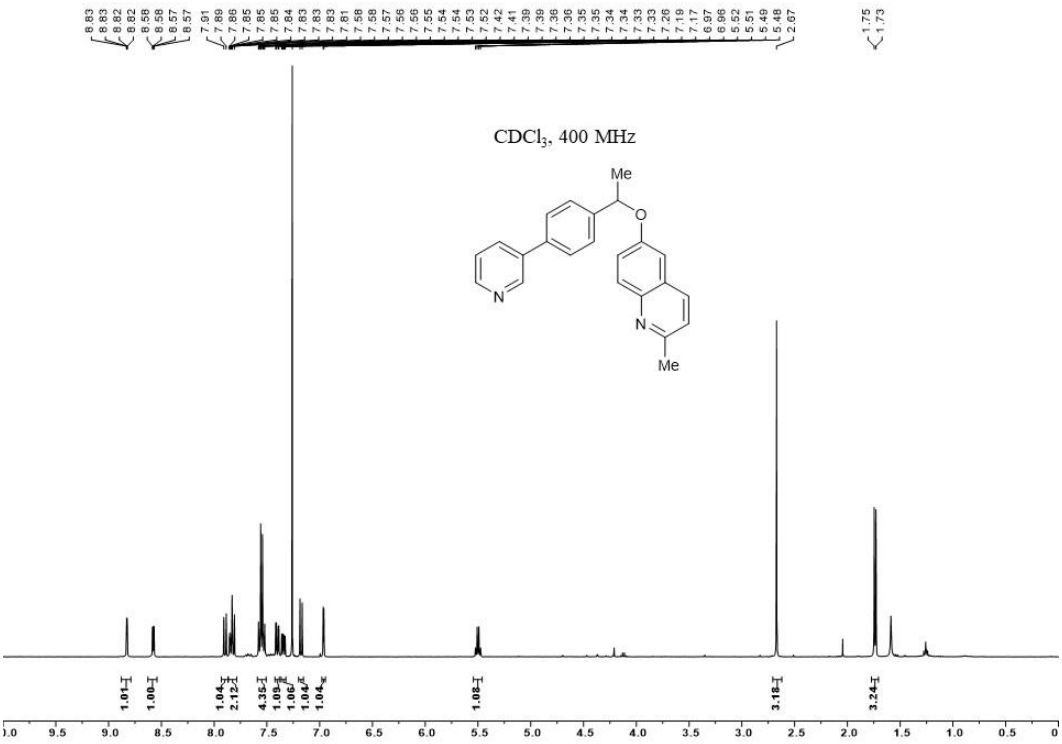
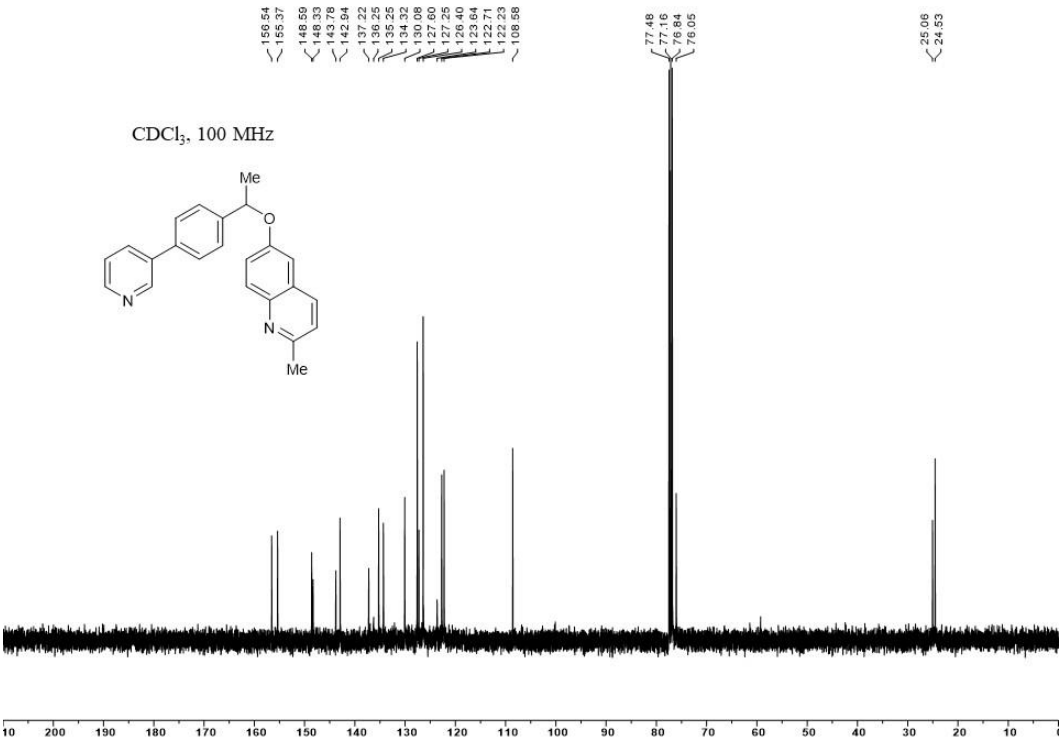
0.5
0

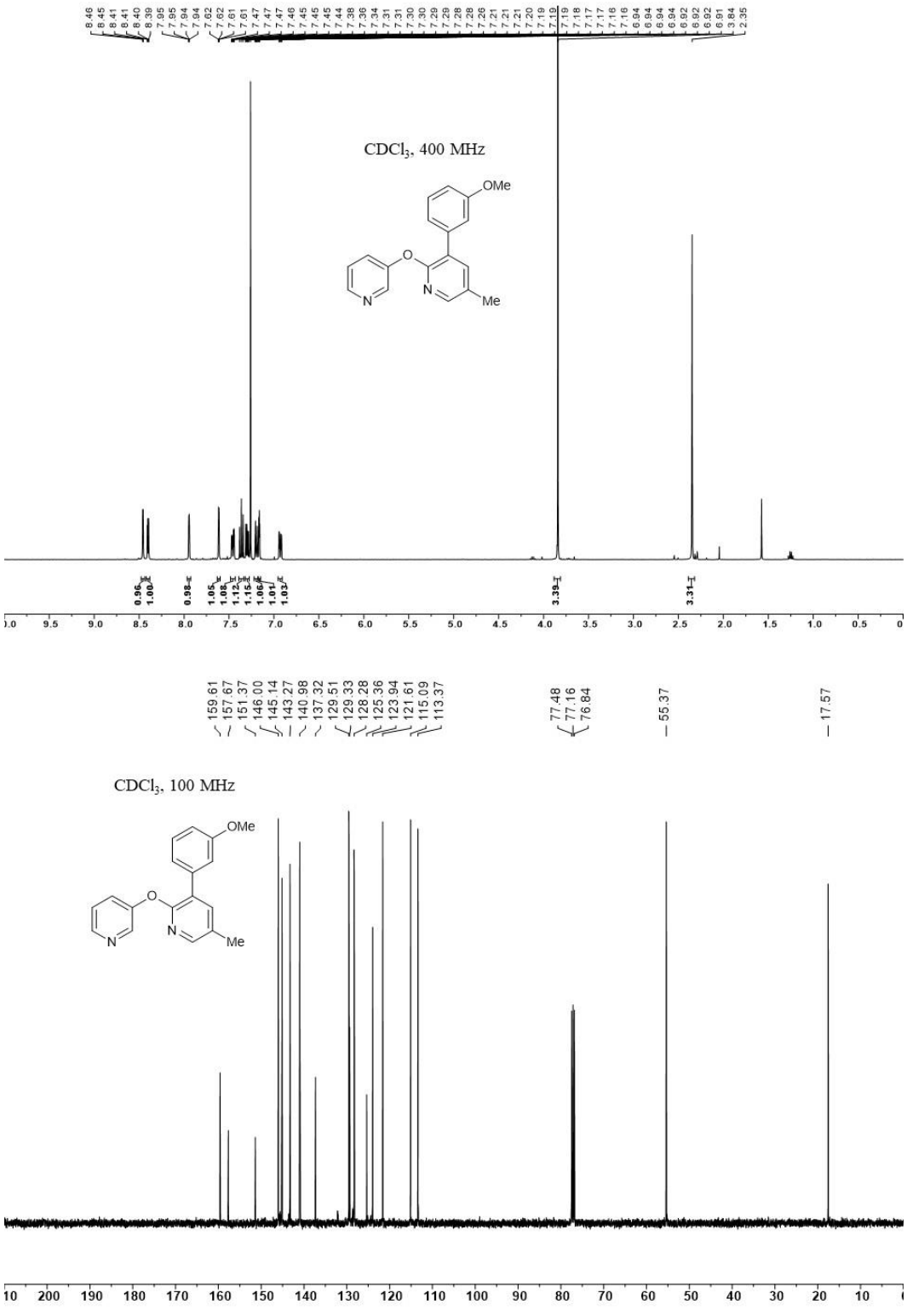

169.15
162.61
162.55
146.85
139.14
130.14
129.12
129.03
126.99
117.80
111.38
101.67
77.48
77.16
76.84
58.30
CDCl3, 100 MHz
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

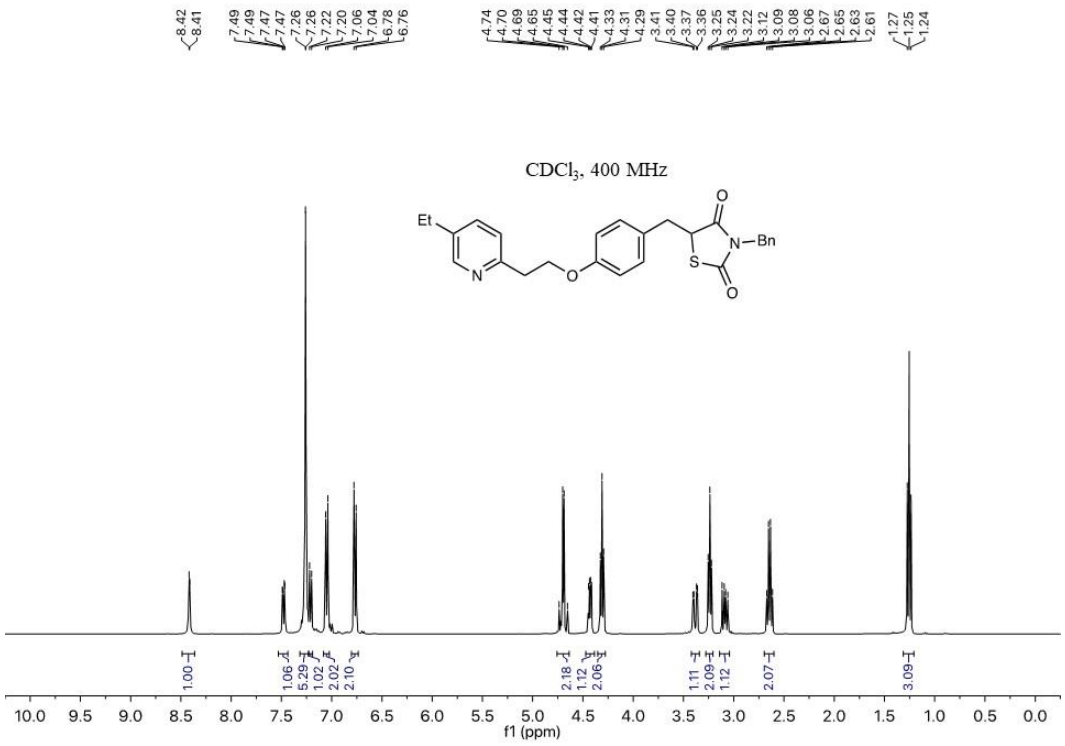

8.72
8.62
8.62
8.61
8.61
8.60
8.60
8.59
8.58
8.57
7.66
7.65
7.65
7.64
7.64
7.63
7.63
7.63
7.34
7.33
7.32
7.32
7.32
7.31
7.30
7.30
7.26
6.53
4.48
4.47
3.90
CDCl3, 400 MHz
Cl
N
N
H
N
CO2Me
0.93
3.01
1.08
1.02
1.02
2.21
3.20

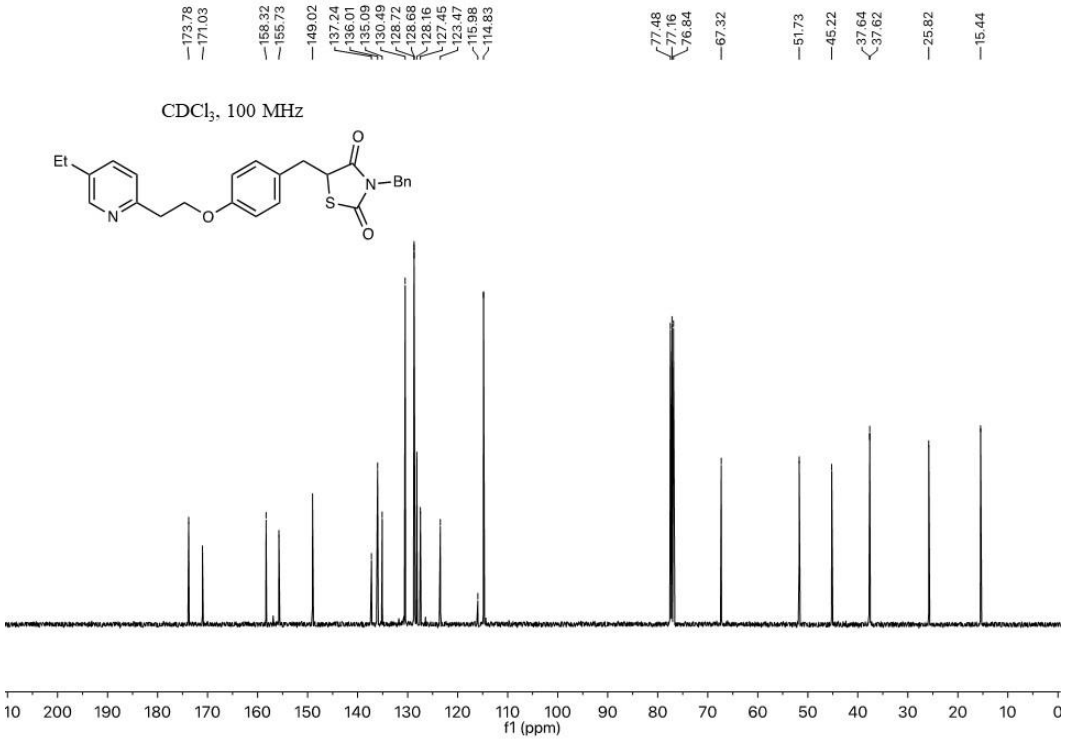

168.06
156.21
155.84
153.22
149.46
148.86
134.99
132.45
124.04
107.33
105.14
77.48
77.16
76.84
52.20
44.24
CDCl3, 100 MHz
Cl
N
N
H
N
CO2Me

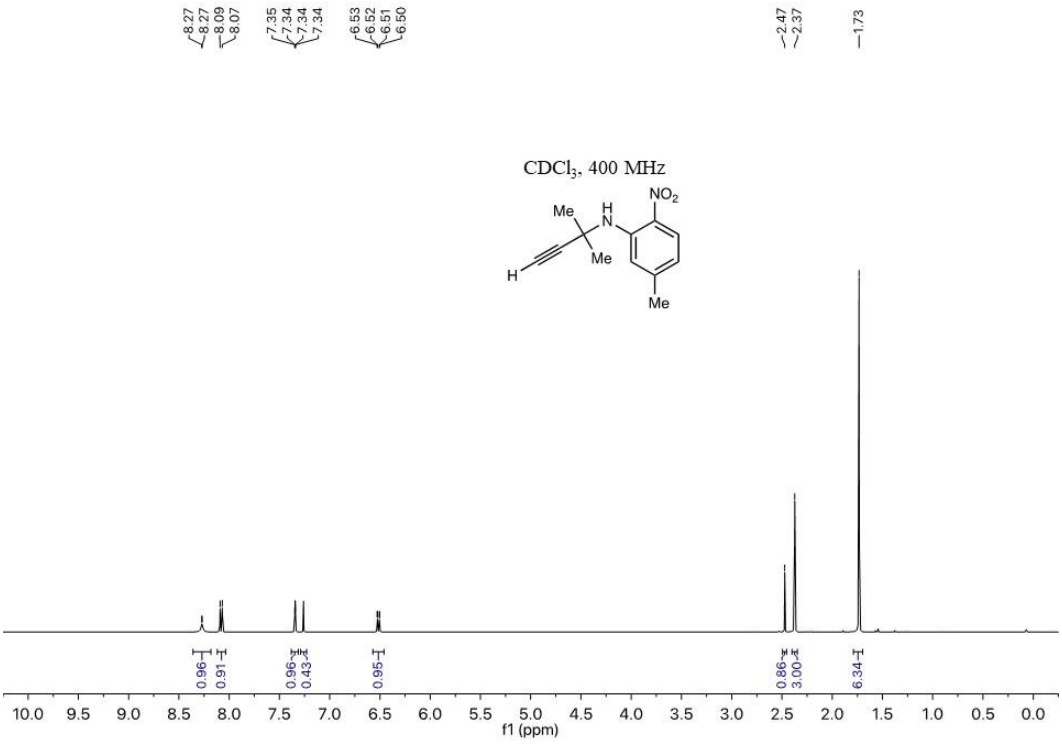

CDCl3, 400 MHz
Me
O
N
N
Me

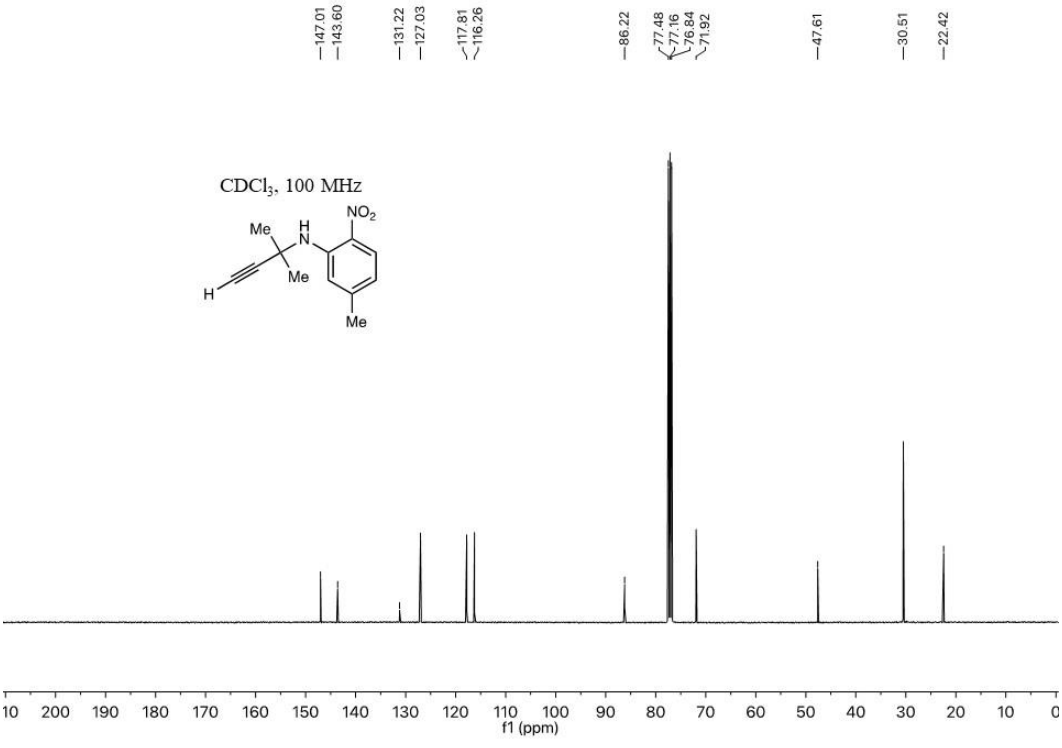

CDCl3, 100 MHz
Me
O
N
N
Me

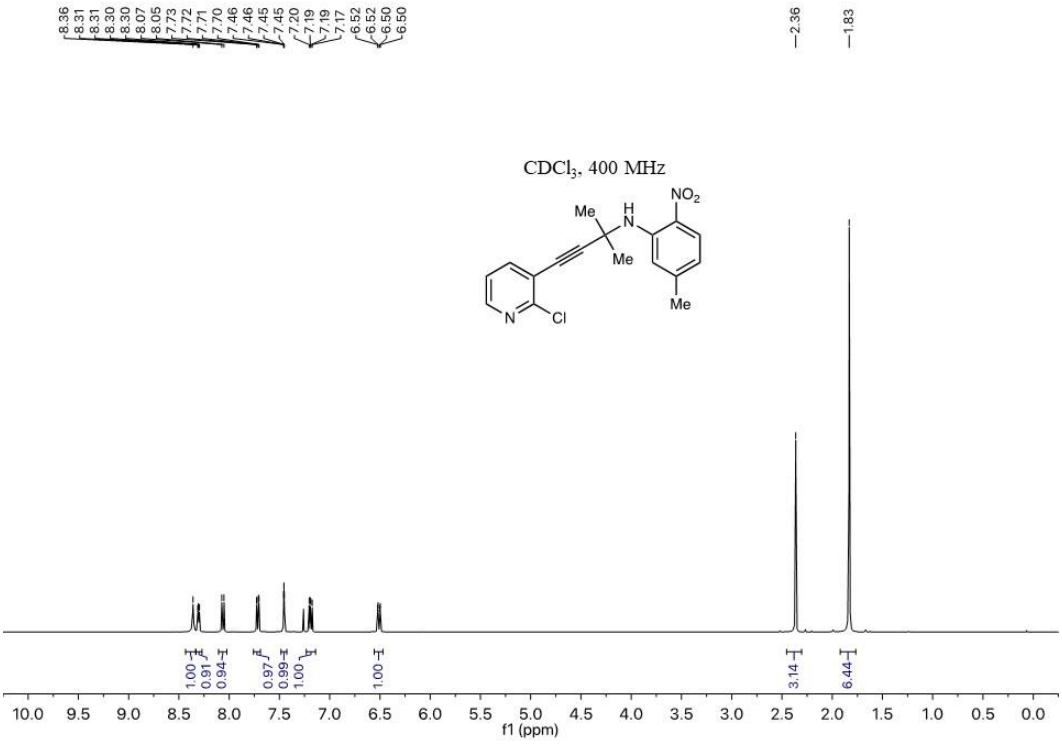

CDCl3, 400 MHz
OMe
Me
CDCl3, 100 MHz
OMe
Me

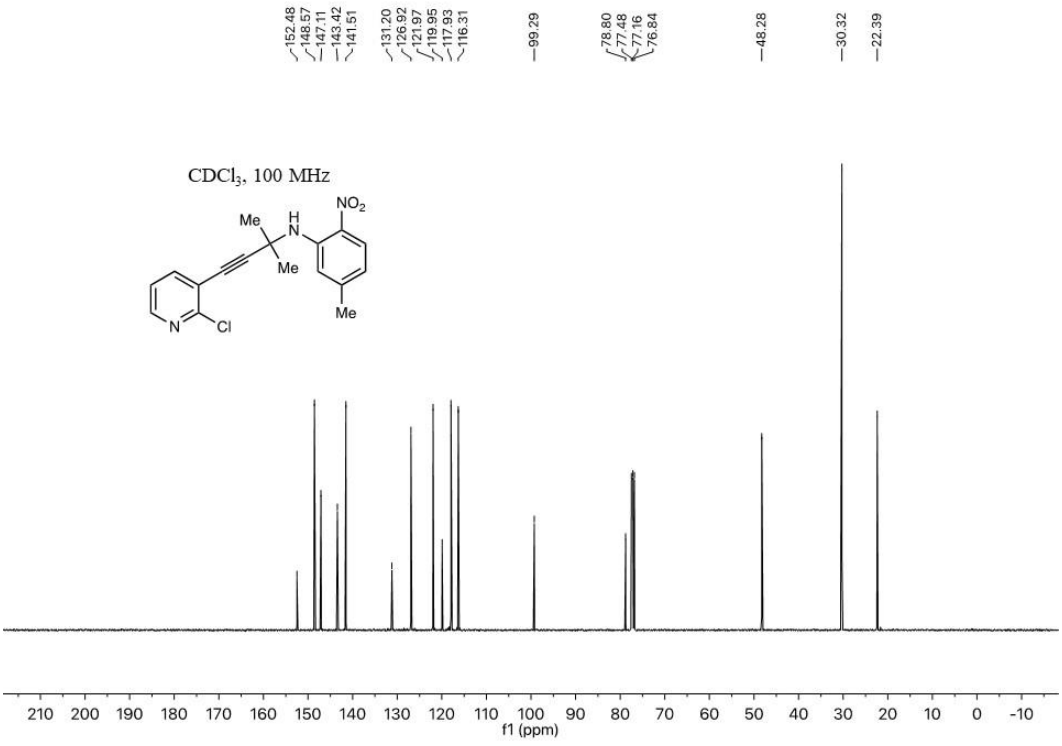

8.42
8.41
7.49
7.49
7.47
7.47
7.26
7.26
7.22
7.20
7.06
7.04
6.78
6.76
4.74
4.70
4.69
4.65
4.45
4.44
4.42
4.41
4.33
4.31
4.29
3.41
3.40
3.37
3.36
3.25
3.24
3.22
3.12
3.09
3.08
3.06
2.67
2.65
2.63
2.61
1.27
1.25
1.24
CDCl3, 400 MHz
Et
N
O
S
N–Bn
O
O
1.00
1.06
5.29
1.02
2.02
2.10
2.18
1.12
2.06
1.11
2.09
1.12
2.07
3.09
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

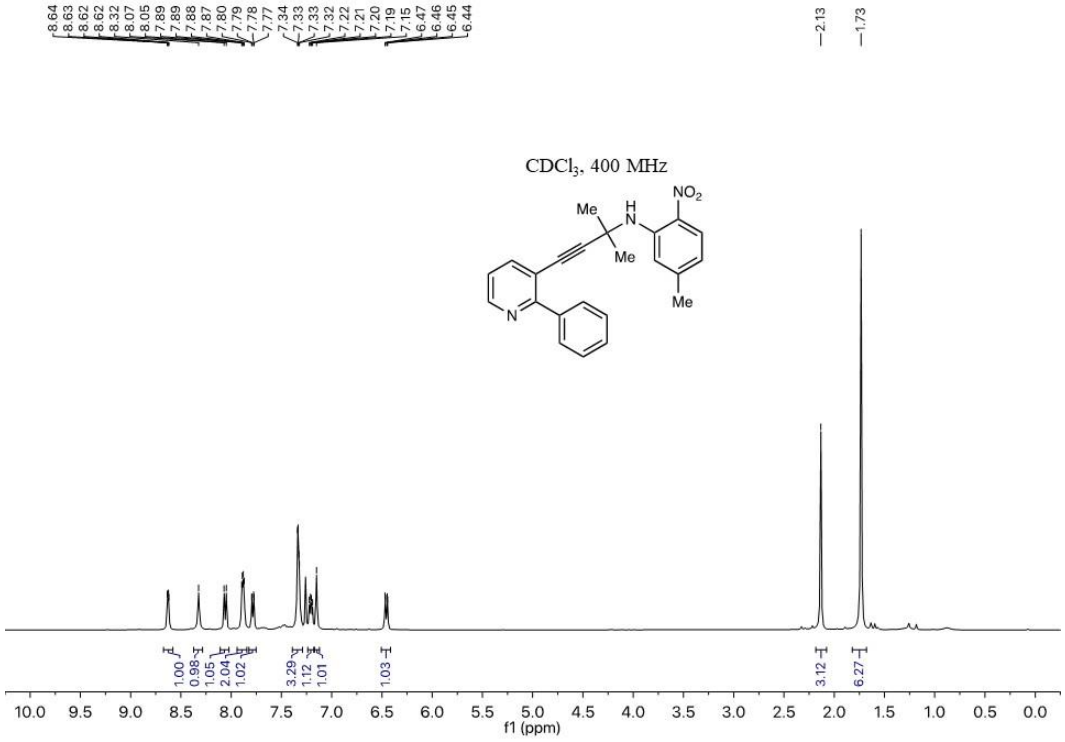

173.78
171.03
158.32
155.73
149.02
137.24
136.01
135.09
130.49
128.72
128.68
128.16
127.45
123.47
115.98
114.83
77.48
77.16
76.84
67.32
51.73
45.22
37.64
37.62
25.82
15.44
CDCl3, 100 MHz
Et
N
O
S
N–Bn
O
O
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

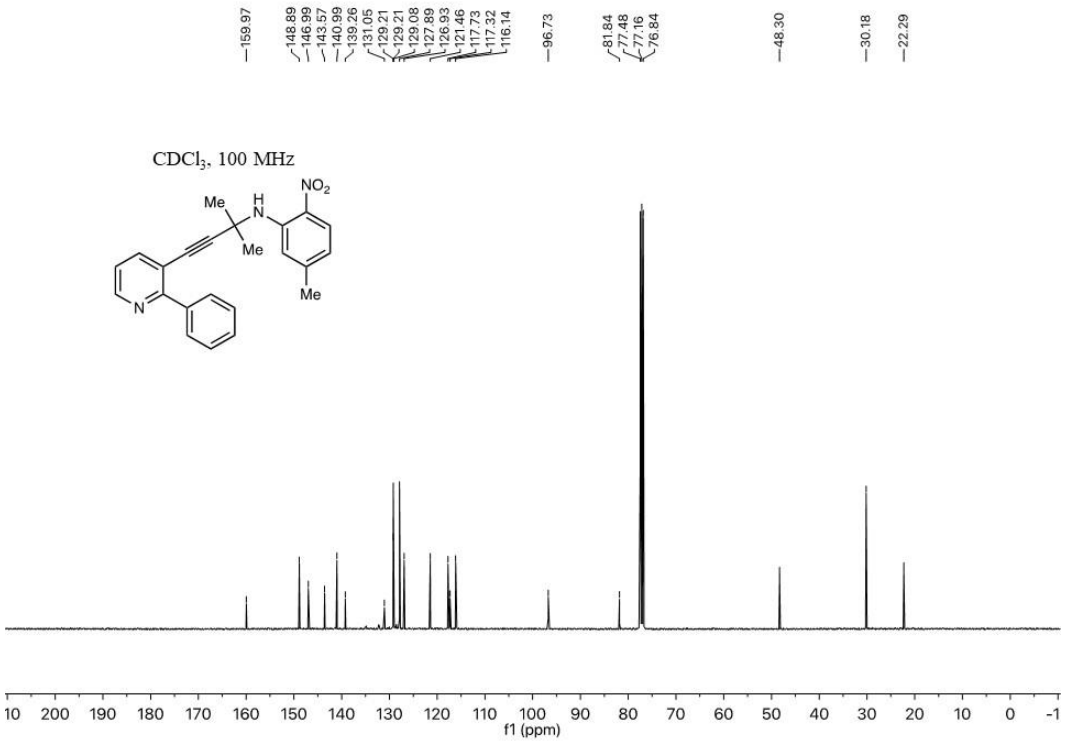

8.27
8.27
8.09
8.07
7.35
7.34
7.34
7.34
6.53
6.52
6.51
6.50
2.47
2.37
1.73
CDCl3, 400 MHz
NO2
Me
H
N
Me
H
Me
0.96
0.91
0.96
0.43
0.95
0.86
3.00
6.34
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


147.01
143.60
131.22
127.03
117.81
116.26
86.22
77.48
77.16
76.84
71.92
47.61
30.51
22.42
CDCl3, 100 MHz
NO2
Me
H
N
Me
H
Me
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

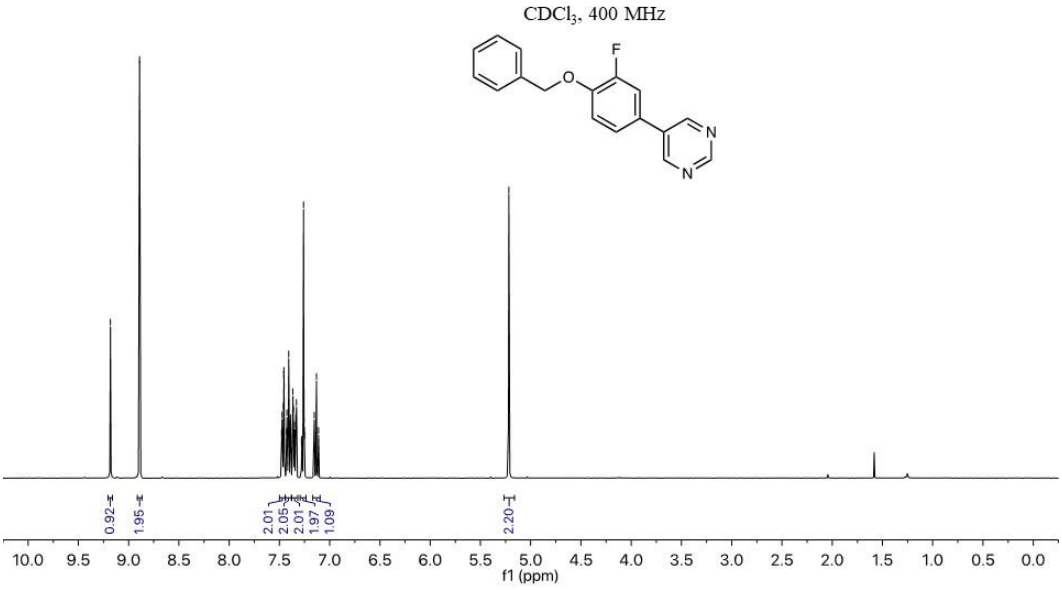

8.36
8.31
8.31
8.30
8.30
8.07
8.05
7.73
7.72
7.71
7.70
7.46
7.46
7.45
7.45
7.20
7.19
7.19
7.17
6.52
6.52
6.50
6.50
2.36
1.83
CDCl3, 400 MHz
Me
H
N
NO2
Me
Me
N
Cl
1.00
0.91
0.94
0.97
0.99
1.00
1.00
3.14
6.44
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

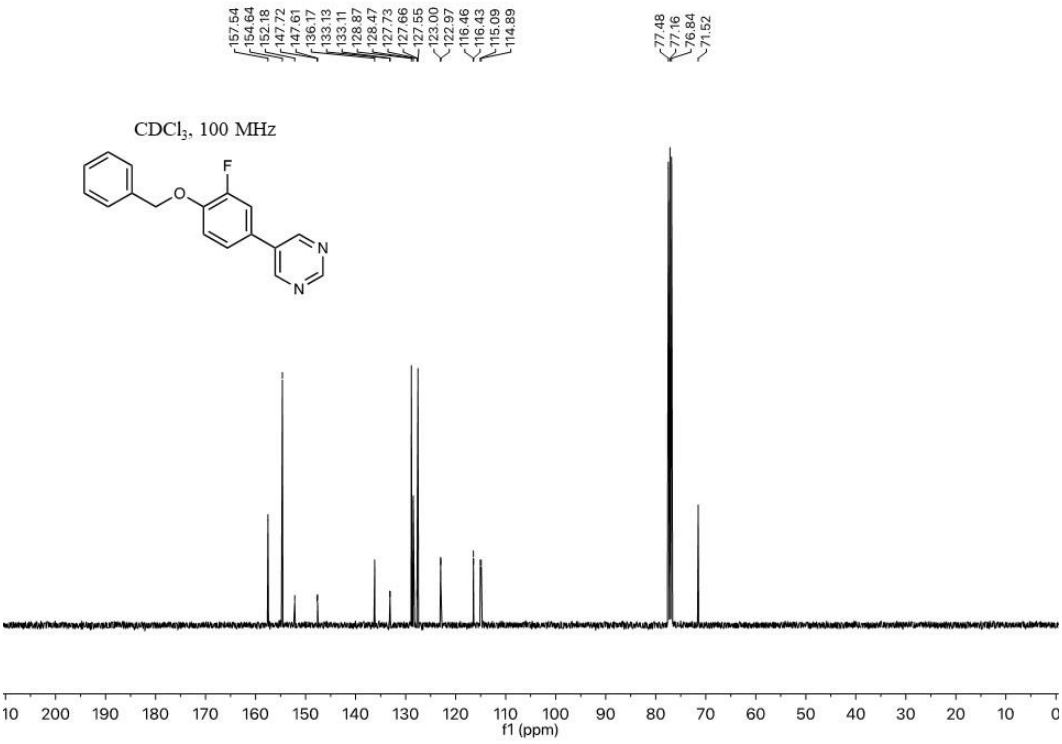

152.48
148.57
147.11
143.42
141.51
131.20
126.92
121.97
119.95
117.93
116.31
99.29
78.80
77.48
77.16
76.84
48.28
30.32
22.39
CDCl3, 100 MHz
Me
H
N
NO2
Me
Me
N
Cl
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

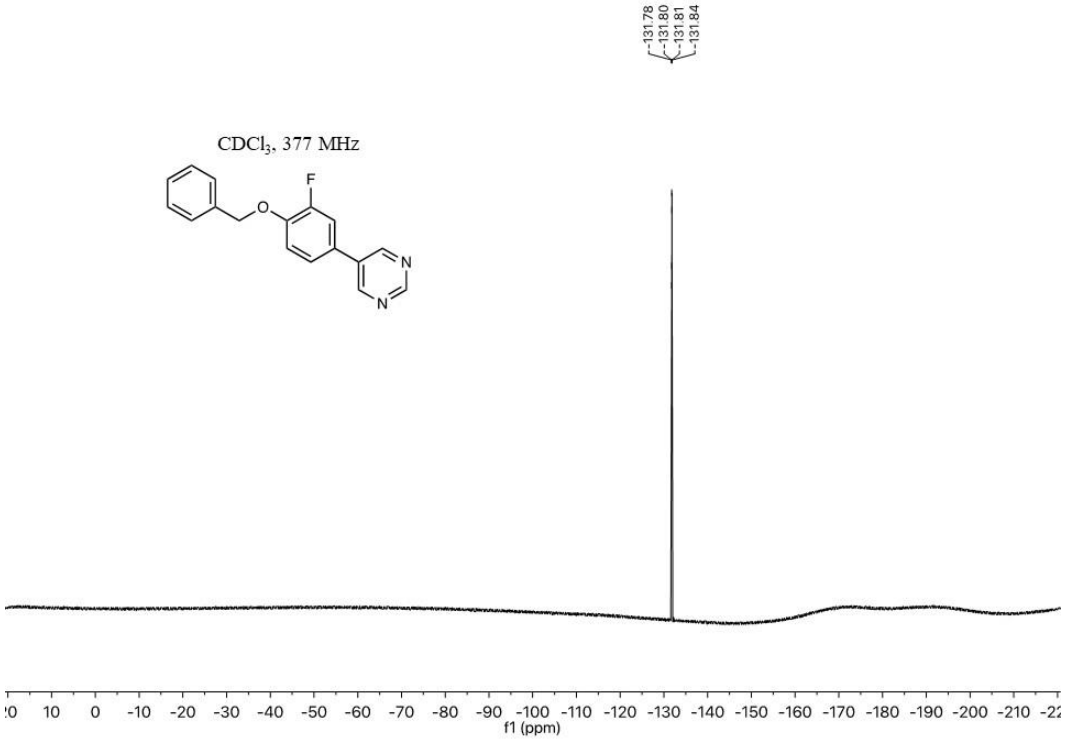

8.64
8.63
8.62
8.62
8.32
8.07
8.05
7.89
7.89
7.88
7.87
7.80
7.79
7.78
7.77
7.34
7.33
7.33
7.32
7.22
7.21
7.20
7.19
7.15
6.47
6.46
6.45
6.44
2.13
1.73
CDCl3, 400 MHz
Me
H
N
NO2
Me
Me
N
Me
1.00
0.98
1.05
2.04
1.02
3.29
1.12
1.01
1.03
3.12
6.27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

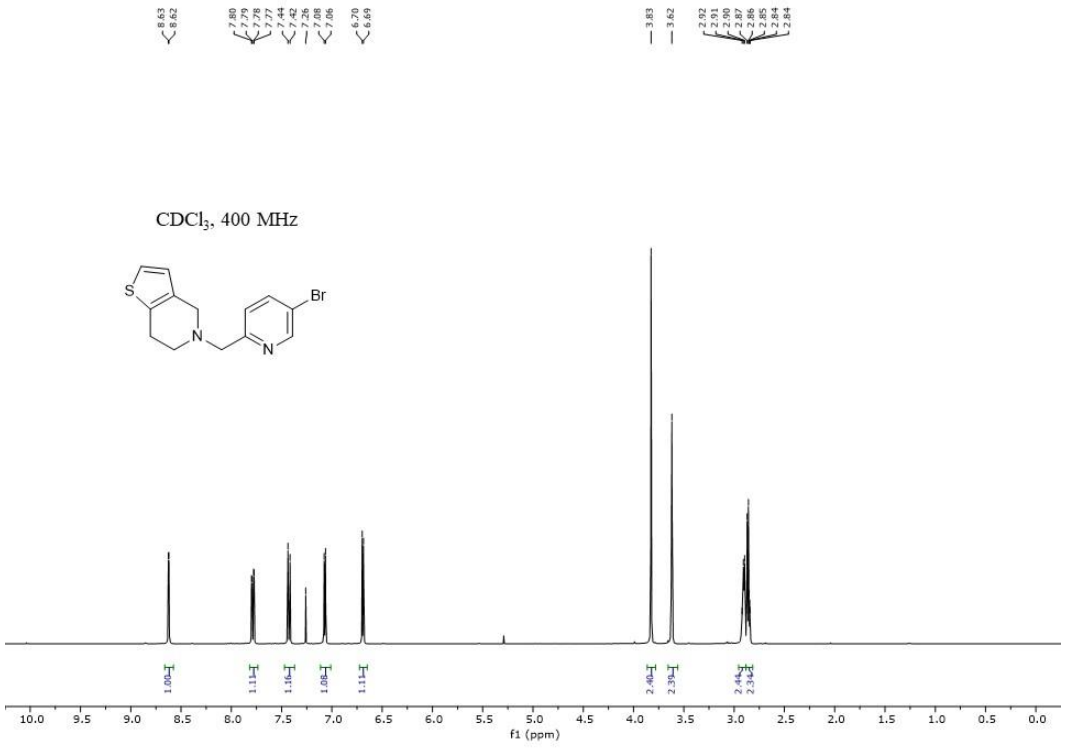

159.97
148.89
146.99
143.57
140.99
139.26
131.05
129.21
129.21
129.08
127.89
126.93
121.46
117.73
117.32
116.14
96.73
81.84
77.48
77.16
76.84
48.30
30.18
22.29
CDCl3, 100 MHz
Me
H
N
NO2
Me
Me
N
Me
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

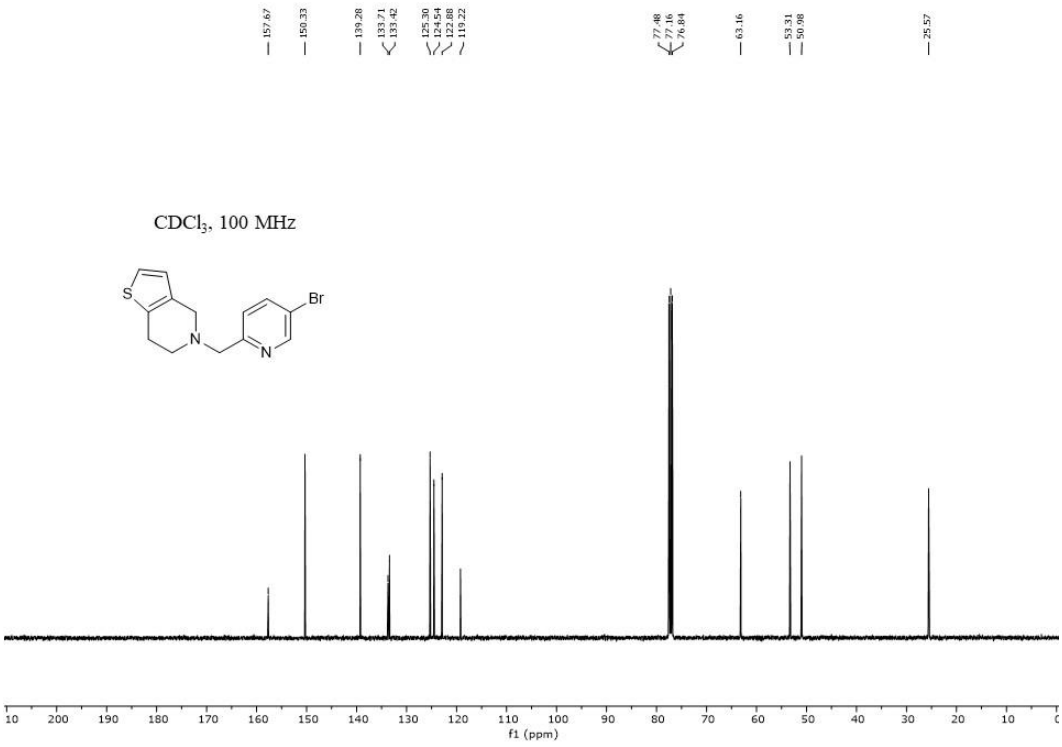

9.18
8.89
7.48
7.47
7.46
7.46
7.46
7.46
7.45
7.43
7.43
7.41
7.41
7.40
7.39
7.39
7.37
7.36
7.35
7.34
7.33
7.28
7.28
7.27
7.27
7.26
7.26
7.25
7.25
7.15
7.13
7.11
5.22

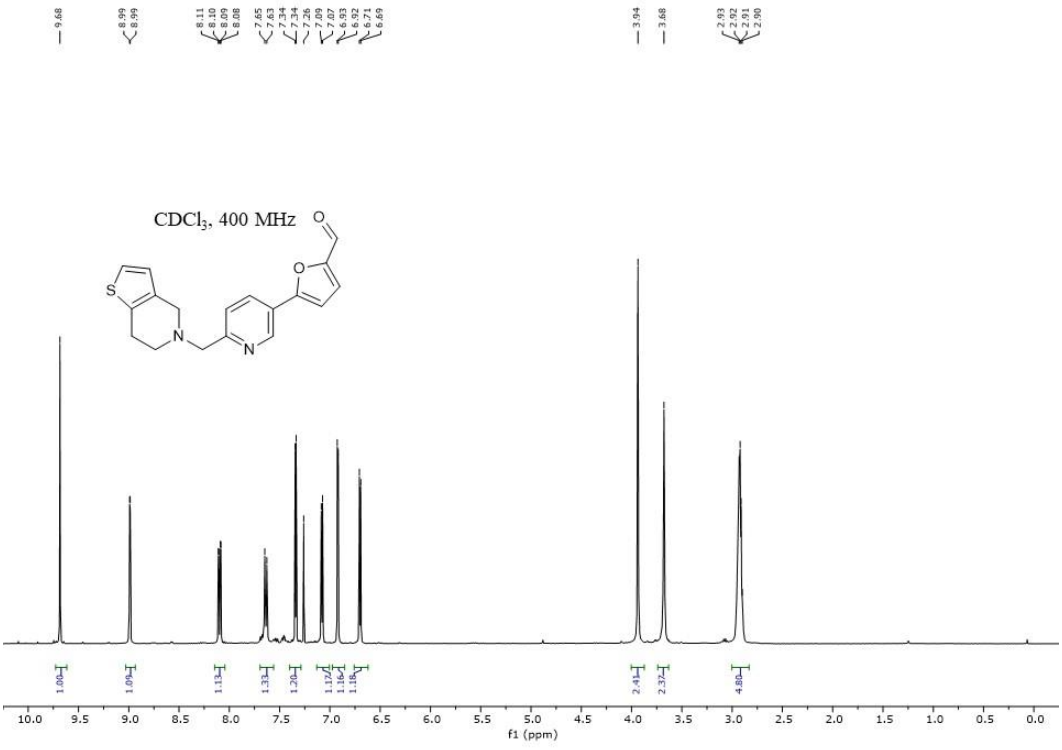

CDCl3, 400 MHz
F
O
N
N
0.92
1.95
2.01
2.05
2.01
1.97
1.09
2.20
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

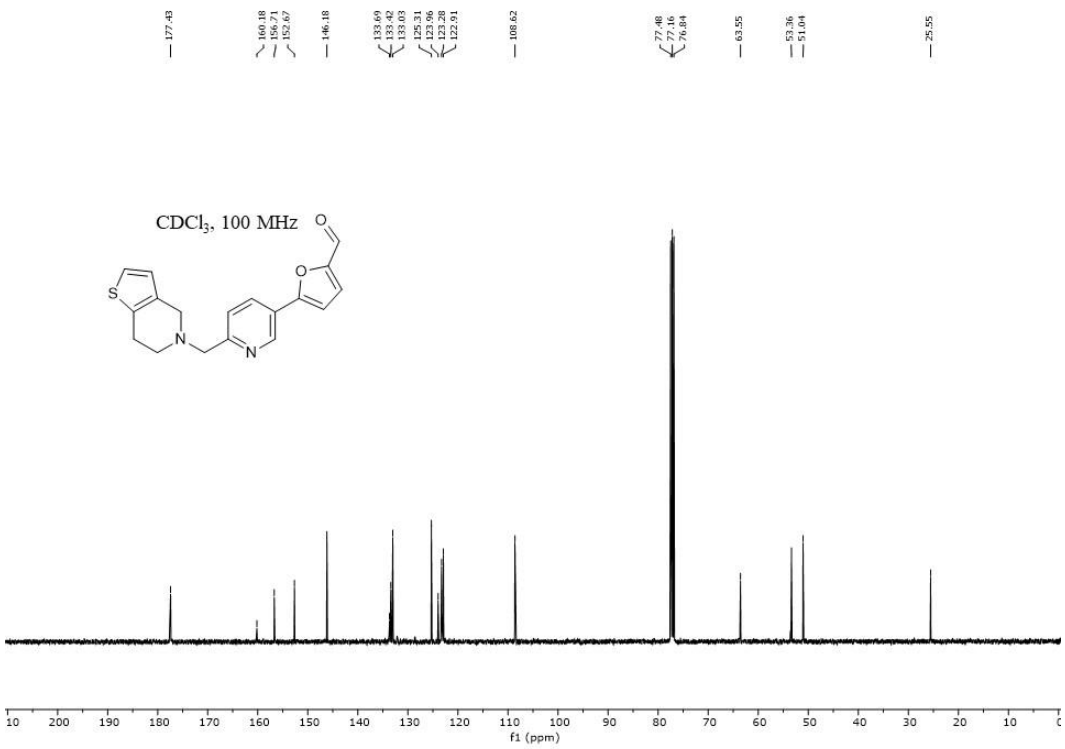

157.54
154.64
152.18
147.72
147.61
136.17
133.13
133.11
128.87
128.47
127.73
127.66
127.55
123.00
122.97
116.46
116.43
115.09
114.89
77.48
77.16
76.84
71.52
CDCl3, 100 MHz
F
O
N
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

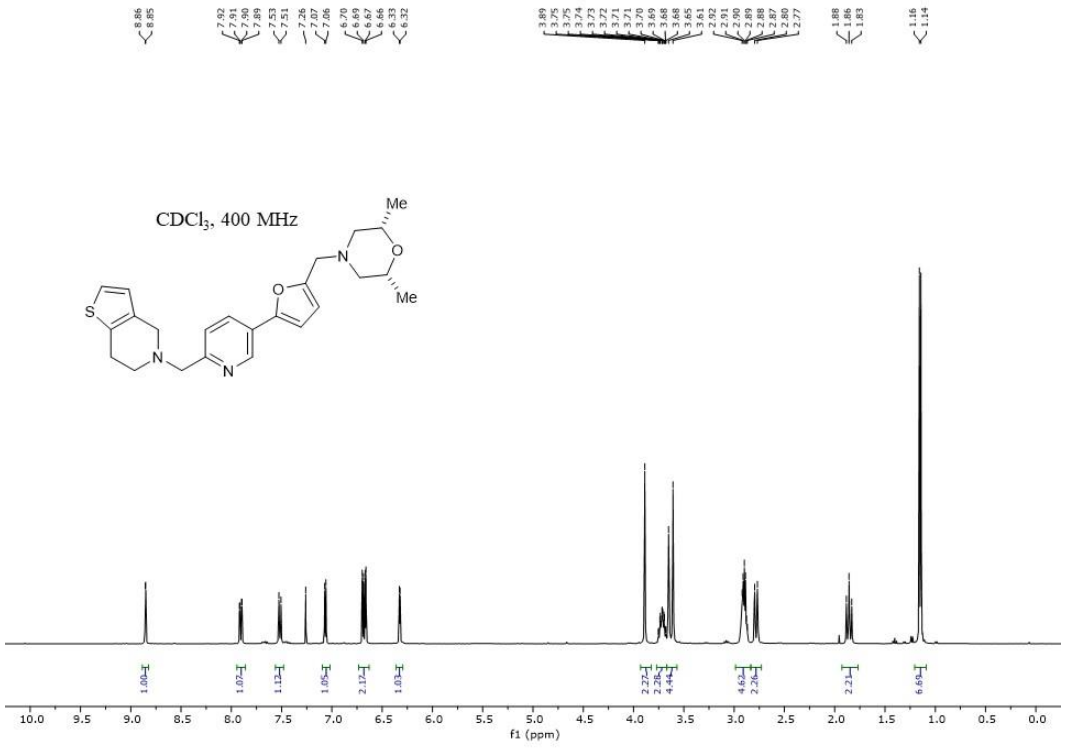

-131.78
-131.80
-131.81
-131.84
CDCl3, 377 MHz
F
O
N
N
f1 (ppm)

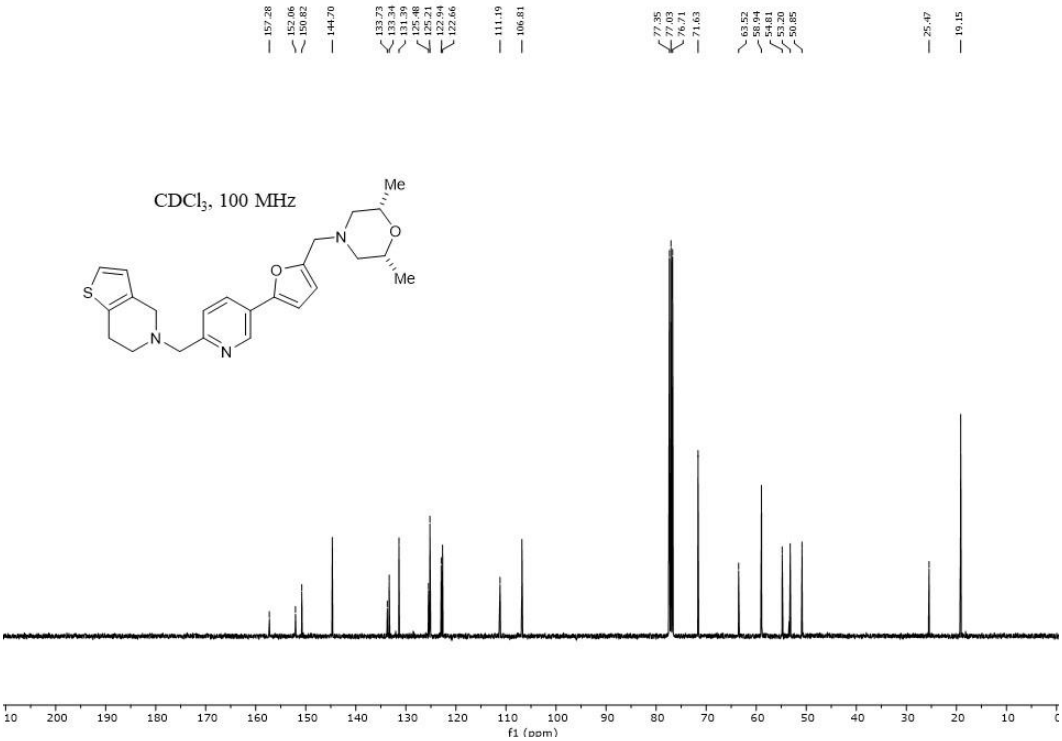

8.63
8.62
7.80
7.79
7.78
7.77
7.44
7.42
7.26
7.08
7.06
6.70
6.69
3.83
3.62
2.92
2.91
2.90
2.87
2.86
2.85
2.84
2.84
CDCl3, 400 MHz
S
N
N
Br
1.00
1.11
1.16
1.08
1.11
2.40
2.39
2.44
2.34
f1 (ppm)

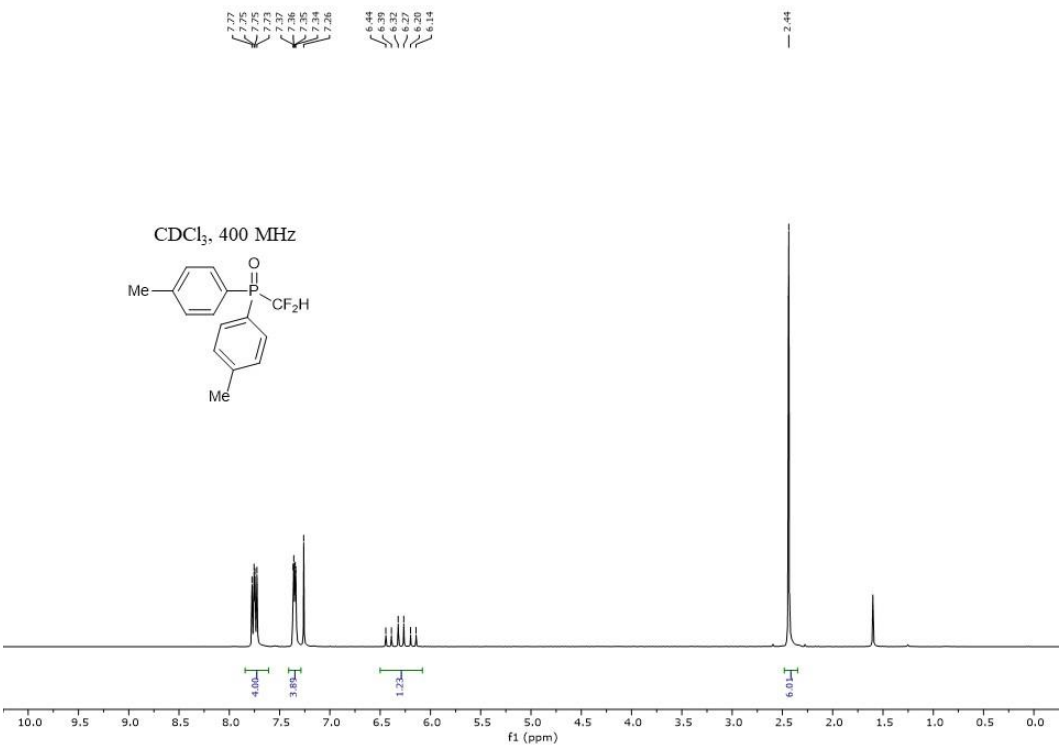

157.67
150.33
139.28
133.71
133.42
125.30
124.54
122.88
119.22
77.48
77.16
76.84
63.16
53.31
50.98
25.57
CDCl3, 100 MHz
S
N
N
Br
f1 (ppm)

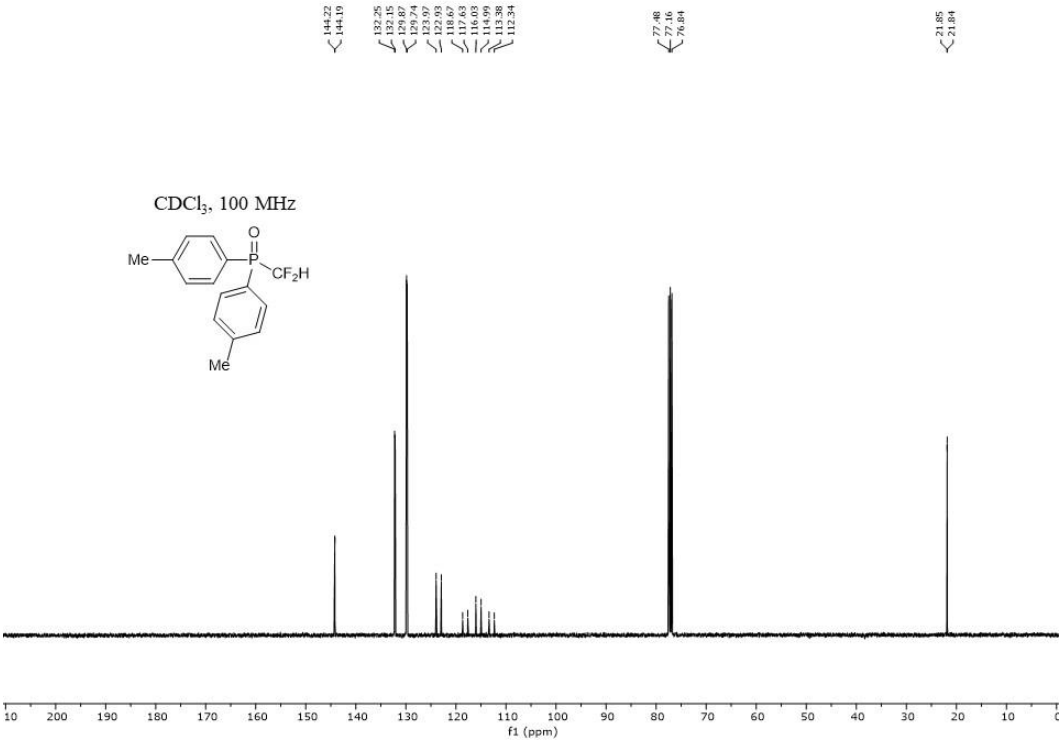

9.68
8.99
8.99
8.11
8.10
8.09
8.08
7.65
7.63
7.34
7.34
7.26
7.09
7.07
6.93
6.92
6.71
6.69
3.94
3.68
2.93
2.92
2.91
2.90
CDCl3, 400 MHz
O
O
S
N
N
1.00
1.09
1.13
1.33
1.20
1.12
1.16
1.18
2.41
2.37
4.80
f1 (ppm)

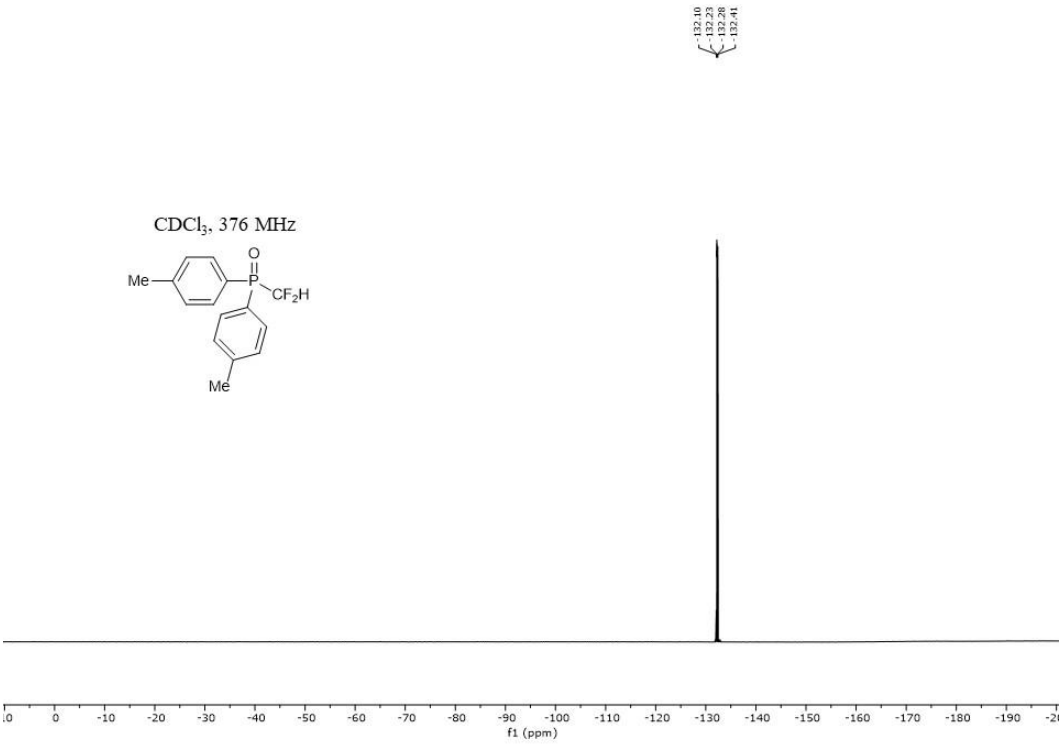

177.43
160.18
156.71
152.67
146.18
133.69
133.42
133.03
125.31
123.96
123.28
122.91
108.62
77.48
77.16
76.84
63.55
53.36
51.04
25.55
CDCl3, 100 MHz
f1 (ppm)


8.86
8.85
7.92
7.91
7.90
7.89
7.53
7.51
7.26
7.07
7.06
6.70
6.69
6.67
6.66
6.33
6.32
3.89
3.75
3.75
3.74
3.73
3.72
3.71
3.71
3.70
3.69
3.68
3.68
3.65
3.61
2.92
2.91
2.90
2.89
2.88
2.87
2.80
2.77
1.88
1.86
1.83
1.16
1.14
CDCl3, 400 MHz
Me
Me
1.00
1.07
1.12
1.05
2.12
1.03
2.27
2.26
4.44
4.62
2.26
2.21
6.69
f1 (ppm)

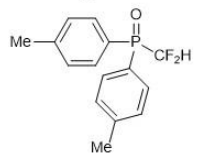

157.28
152.06
150.82
144.70
133.73
133.34
131.39
125.46
125.21
122.94
122.66
111.19
106.81
77.35
77.03
76.71
71.63
63.52
58.94
54.81
53.20
50.85
25.47
19.15
CDCl3, 100 MHz
Me
Me
S
N
O
O
N
N
f1 (ppm)


7.77
7.75
7.75
7.73
7.37
7.36
7.35
7.34
7.26
6.44
6.39
6.32
6.27
6.20
6.14
2.44
CDCl3, 400 MHz
Me
O
P
CF2H
Me
4.00
3.89
1.23
6.01
f1 (ppm)

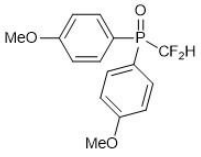

144.22
144.19
132.25
132.15
129.87
129.74
123.97
122.93
118.67
117.63
116.03
114.99
113.38
112.34
77.48
77.16
76.84
21.85
21.84
CDCl3, 100 MHz
Me
O
P
CF2H
Me
f1 (ppm)

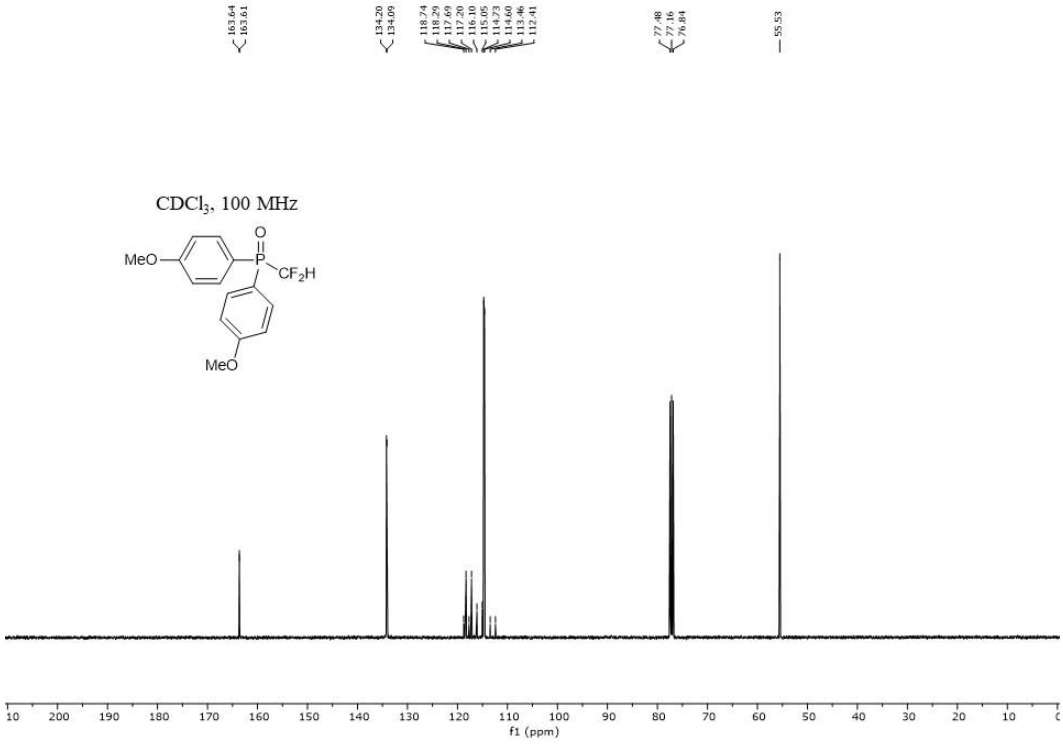

-132.10
-132.33
-132.58
-132.81
CDCl3, 376 MHz
Me
O
P
CF2H
Me
f1 (ppm)

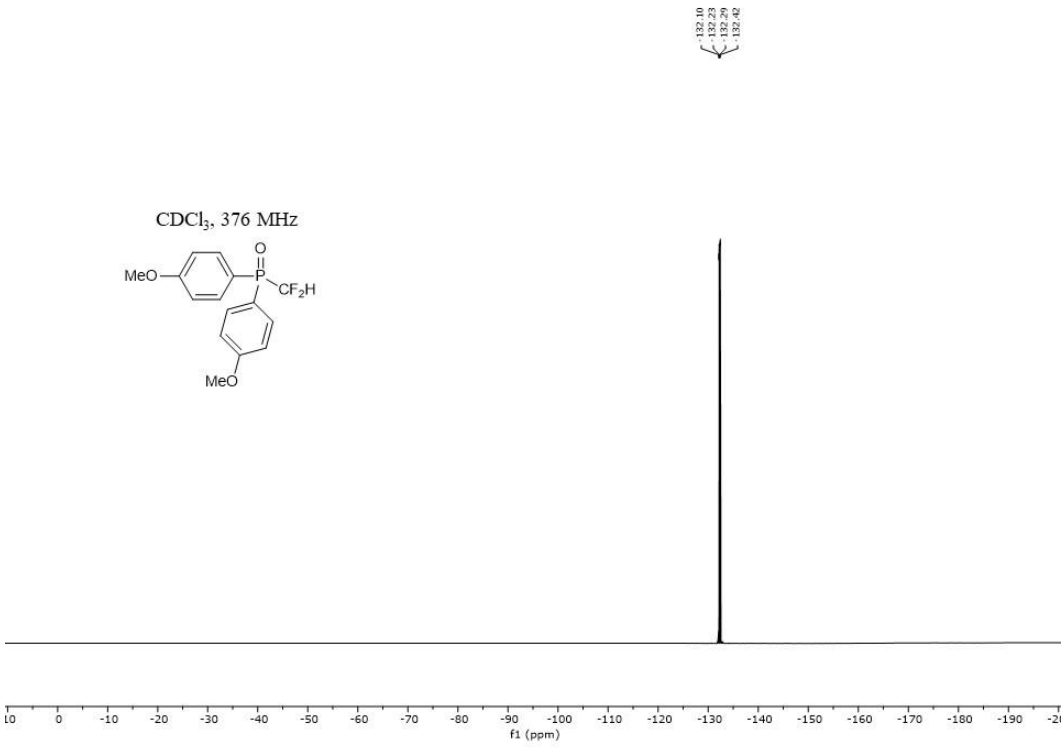
$CDCl_3$, 162 MHz

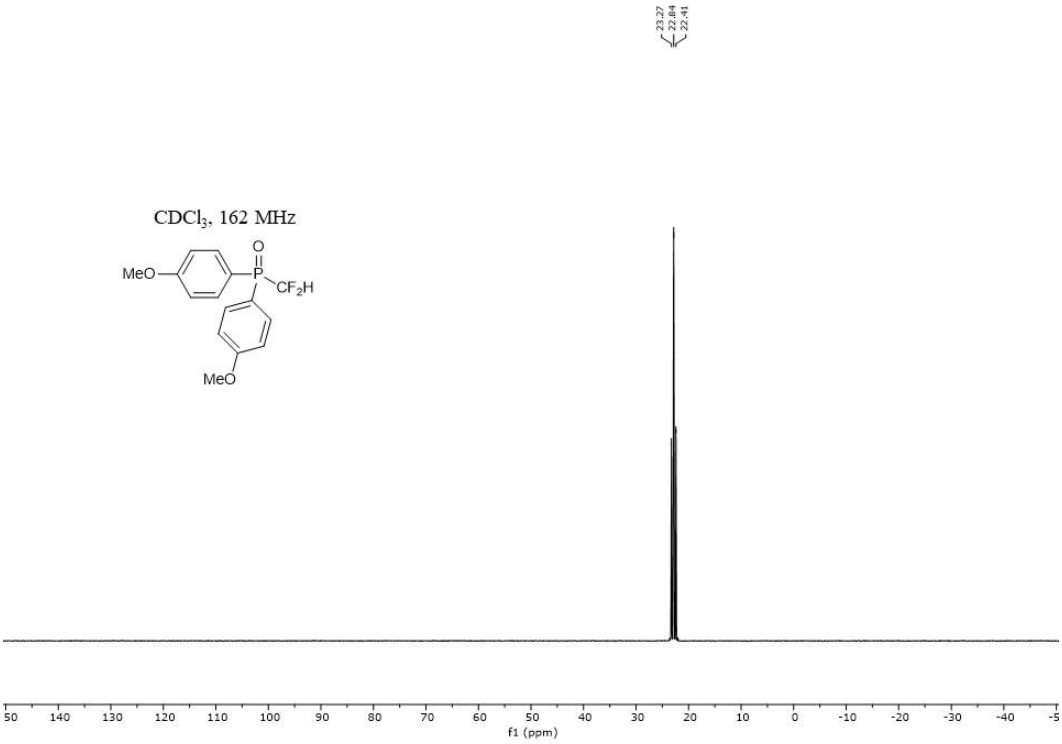


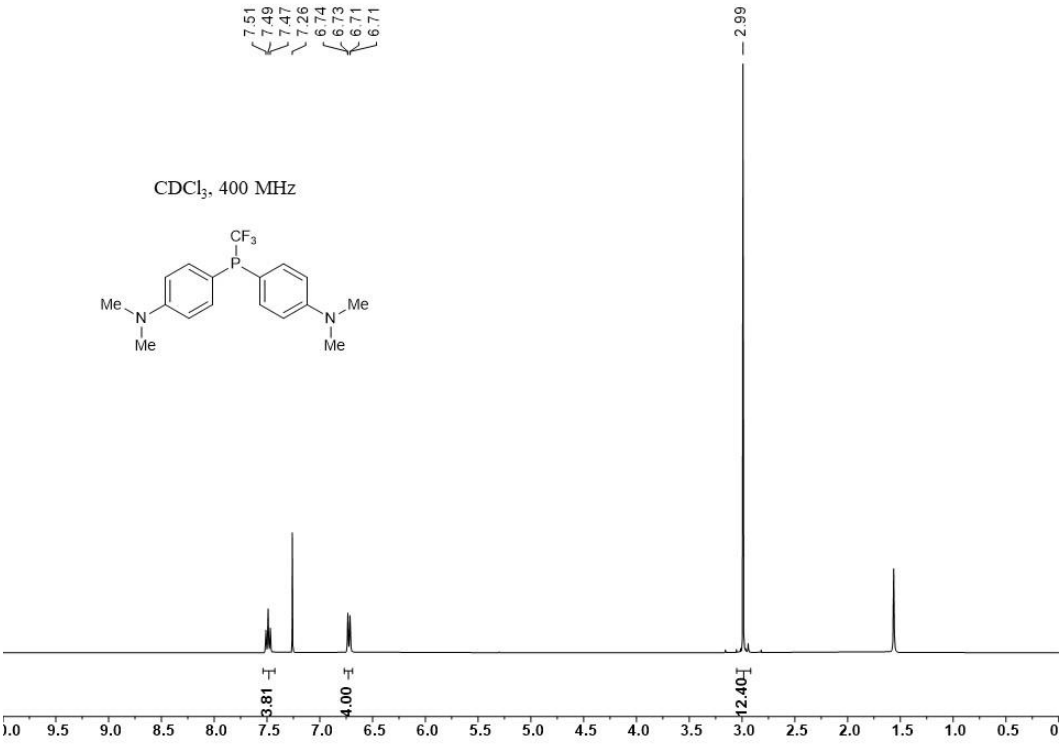
$CDCl_3$, 400 MHz

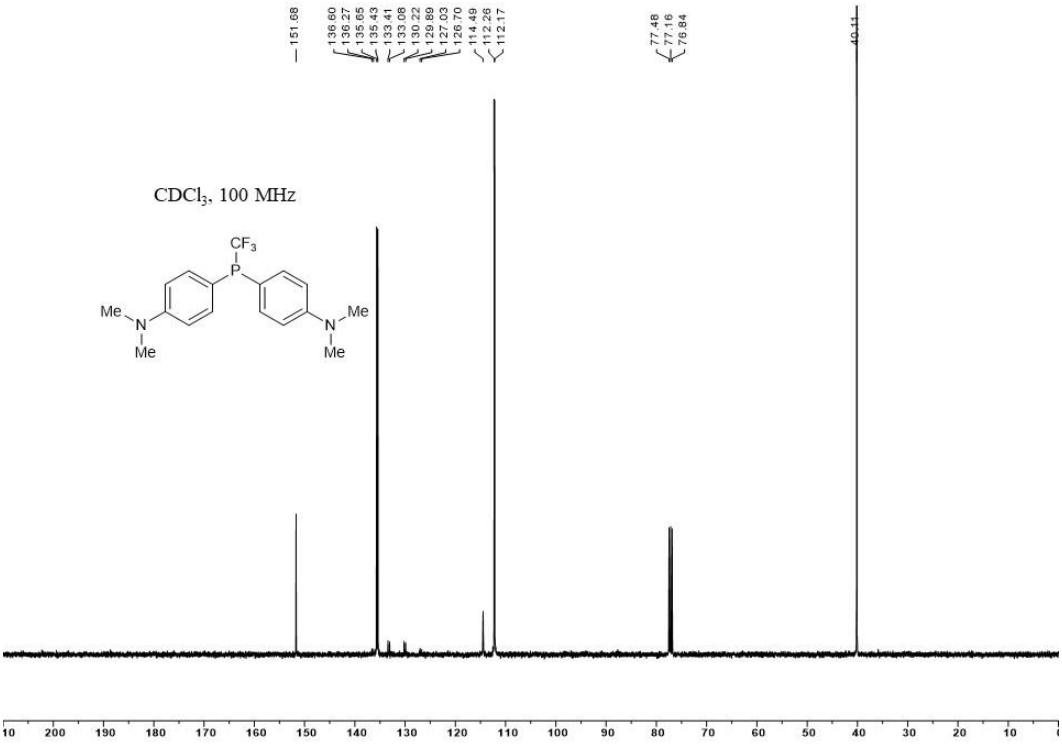


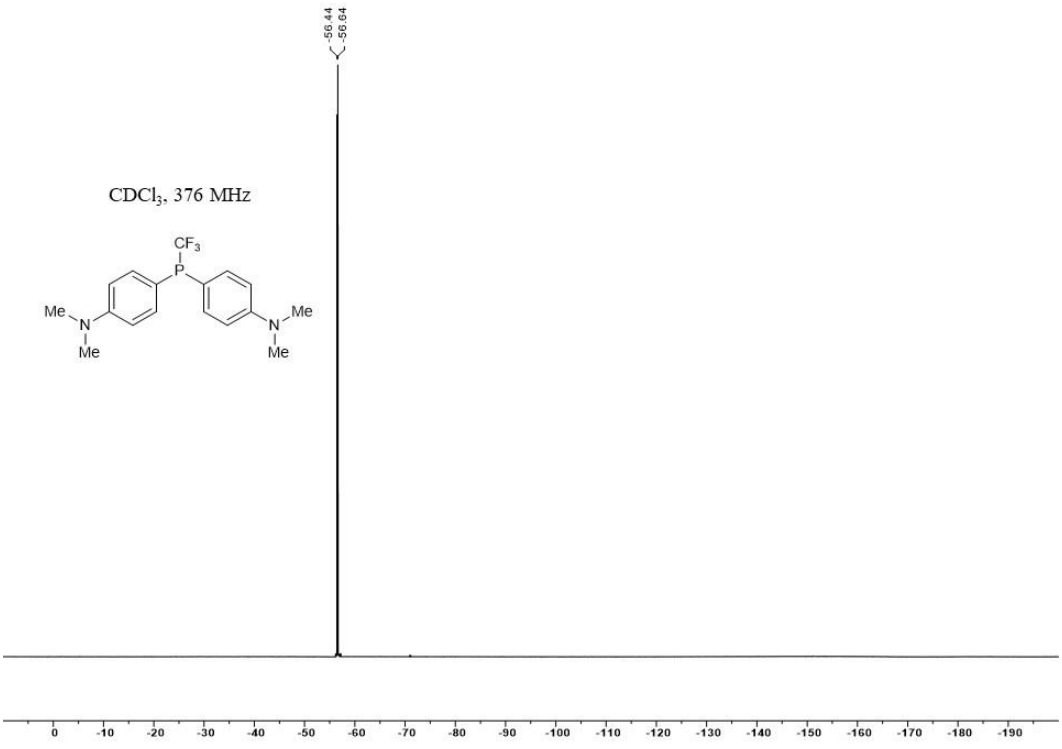

163.64
163.61
134.20
134.09
118.74
118.29
117.69
117.20
116.10
115.05
114.73
114.60
113.46
112.41
77.48
77.16
76.84
55.53
CDCl3, 100 MHz
MeO
O
P
CF2H
MeO
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

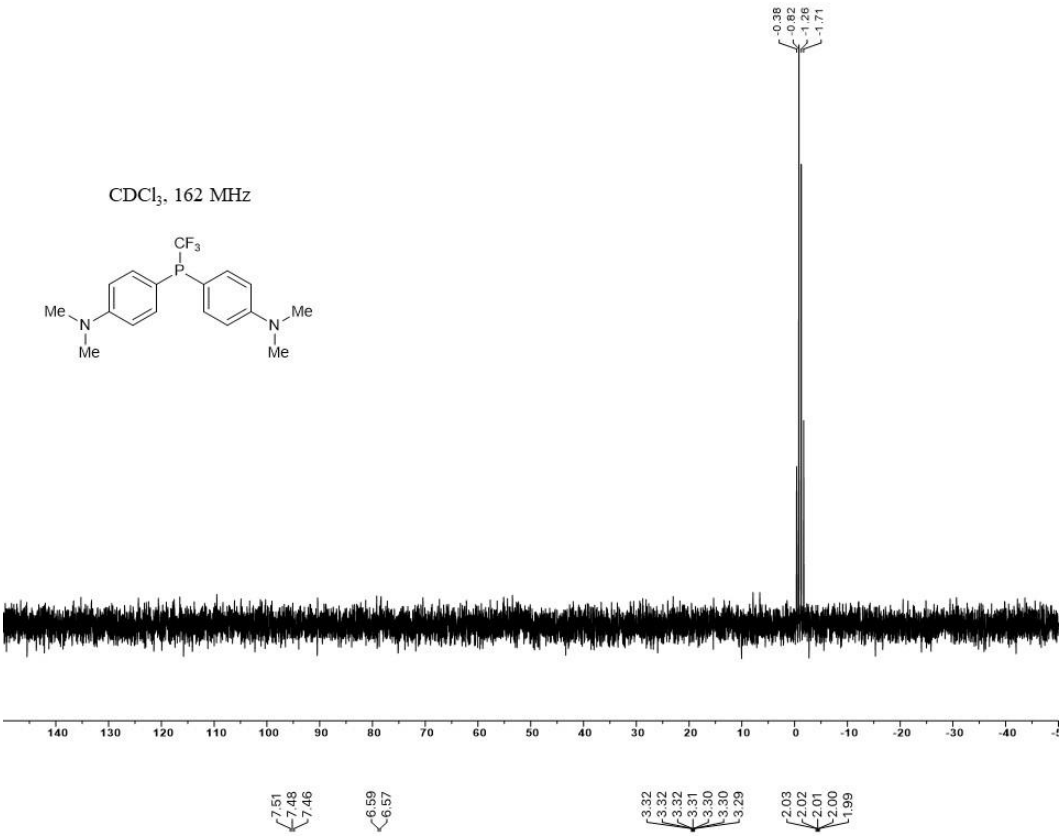

132.10
132.23
132.29
132.42
CDCl3, 376 MHz
MeO
O
P
CF2H
MeO
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

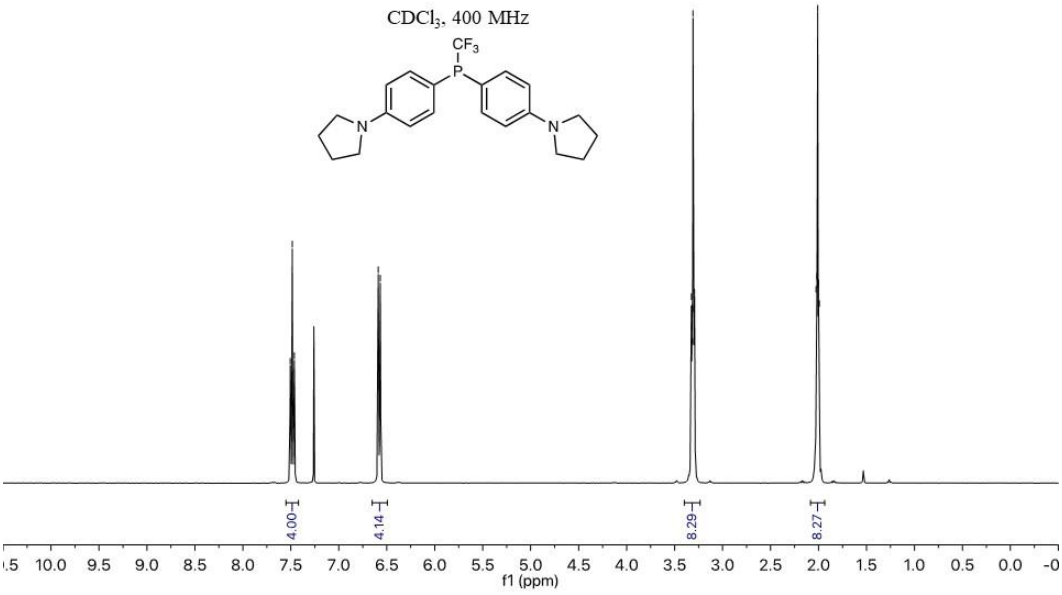

23.27
22.84
22.41
CDCl3, 162 MHz
MeO
O
P
CF2H
MeO
f1 (ppm)

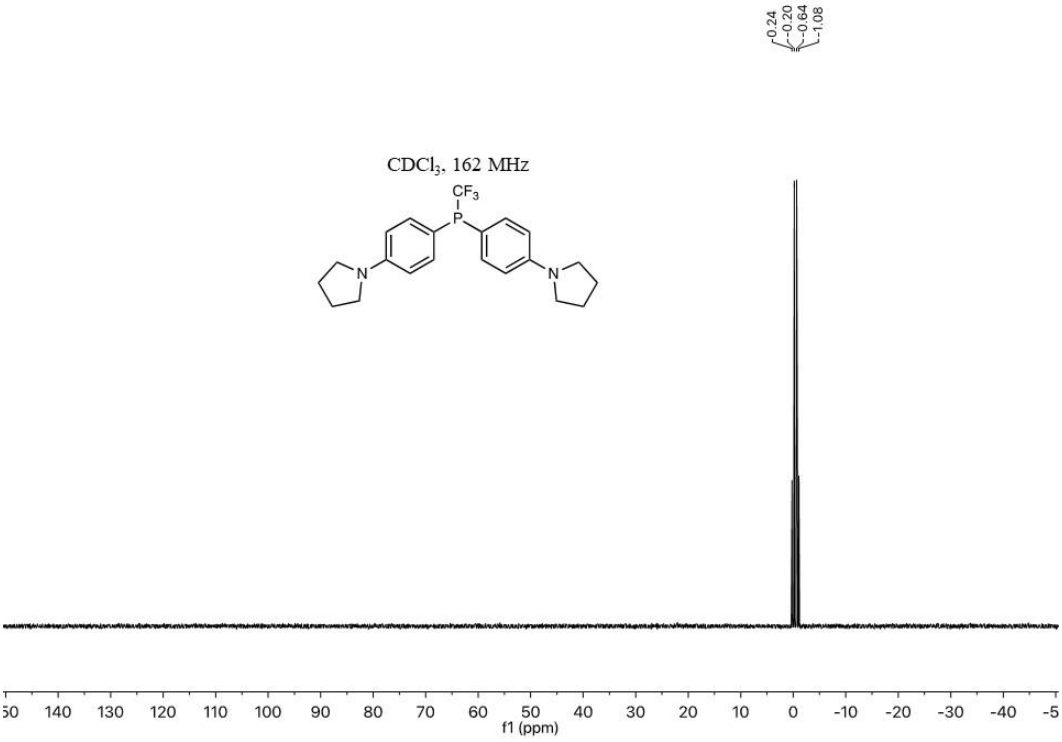

7.51
7.49
7.47
7.26
6.74
6.73
6.71
6.71
2.99
CDCl3, 400 MHz
CF3
P
Me
N
Me
Me
N
Me
3.81
4.00
12.40

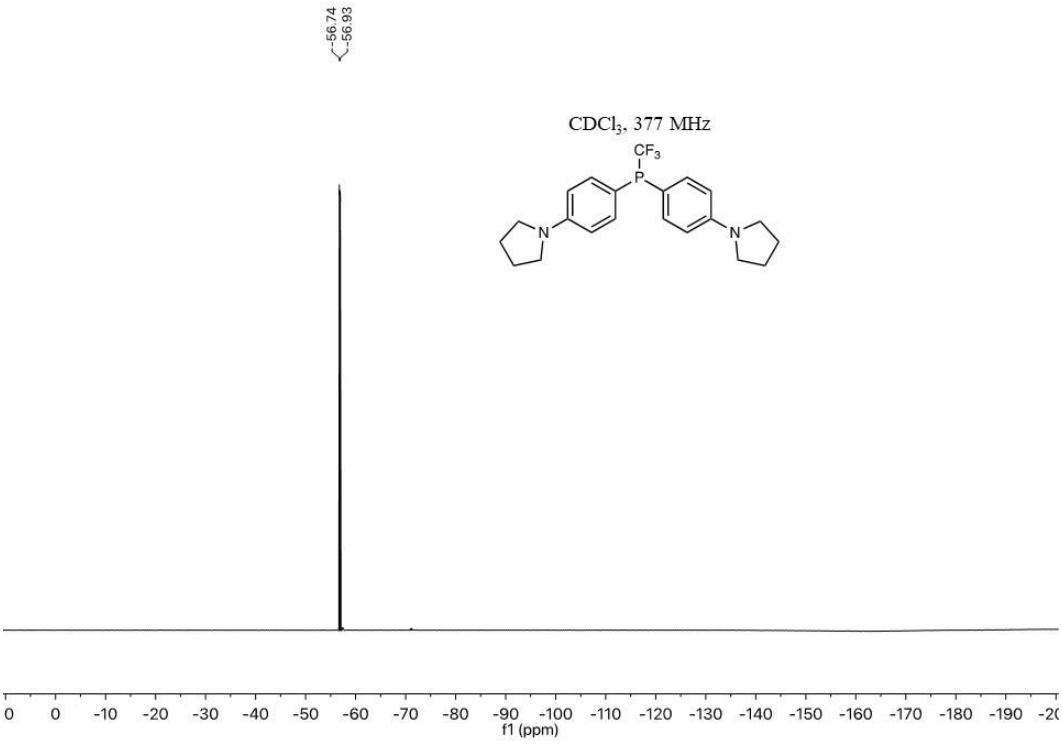

151.68
136.60
136.27
135.65
135.43
133.41
133.08
130.22
129.89
127.03
126.70
114.49
112.26
112.17
77.48
77.16
76.84
40.11
CDCl3, 100 MHz
CF3
P
Me
N
Me
Me
N
Me
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

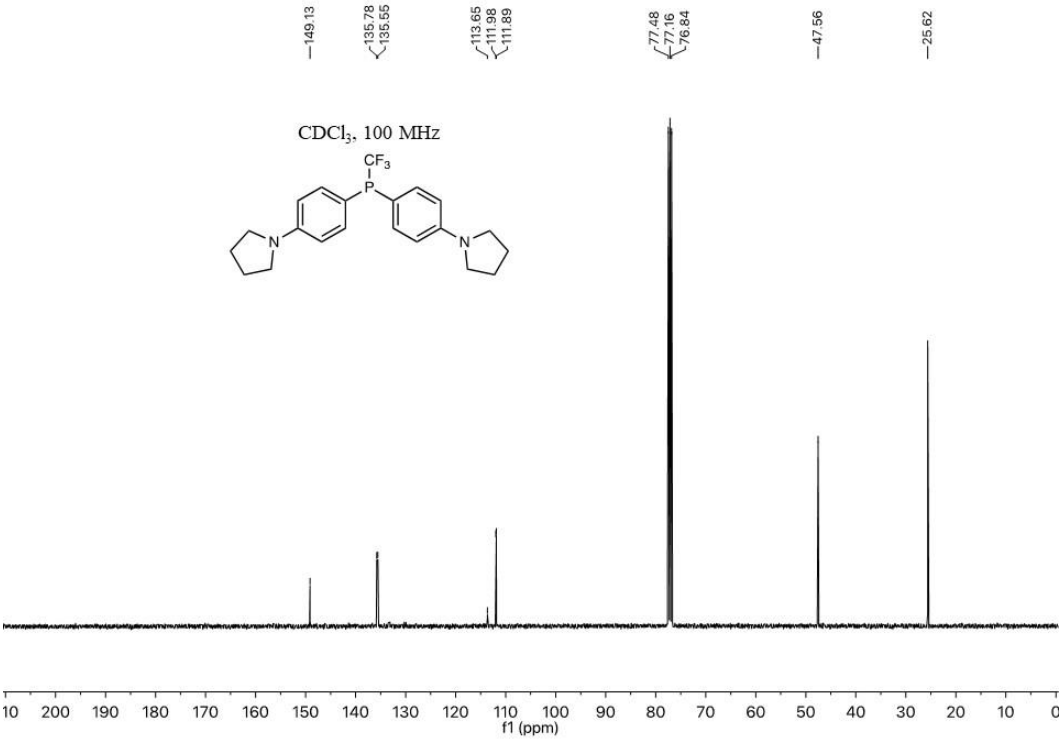

-56.44
-56.64
CDCl3, 376 MHz
CF3
P
Me
N
Me
Me
N
Me
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

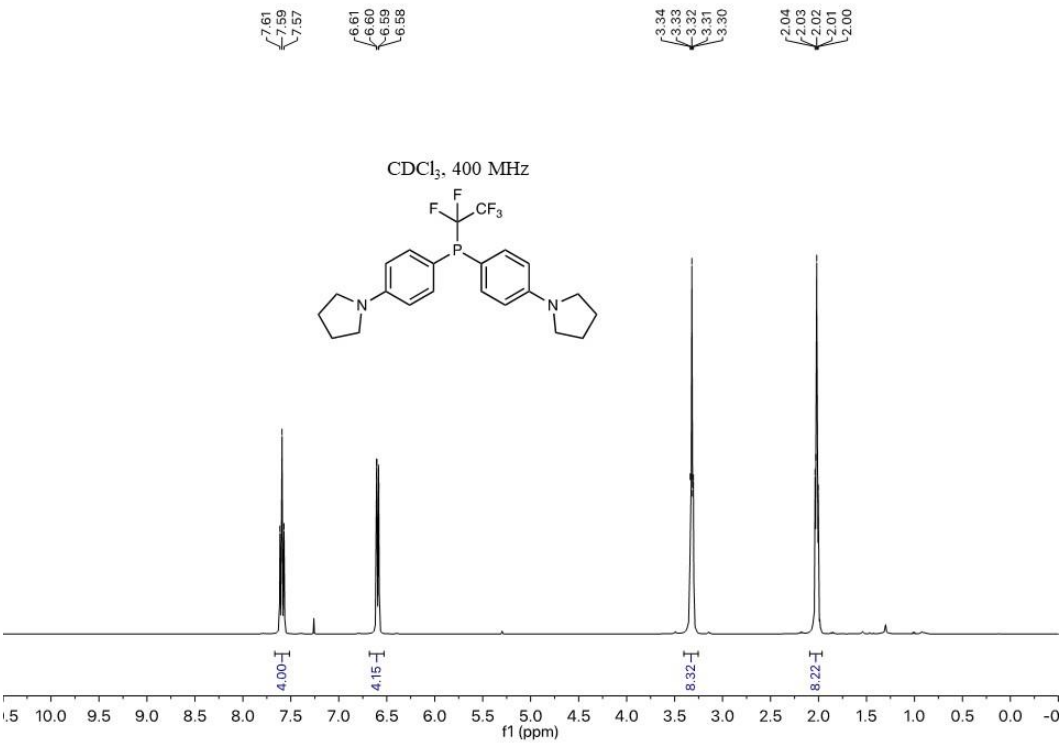

CDCl3, 162 MHz
CF3
P
Me
N
Me
Me
N
Me
-0.36
-0.82
-1.26
-1.71
140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
7.51
7.48
7.46
6.59
6.57
3.32
3.32
3.32
3.31
3.30
3.30
3.29
2.03
2.02
2.01
2.00
1.99

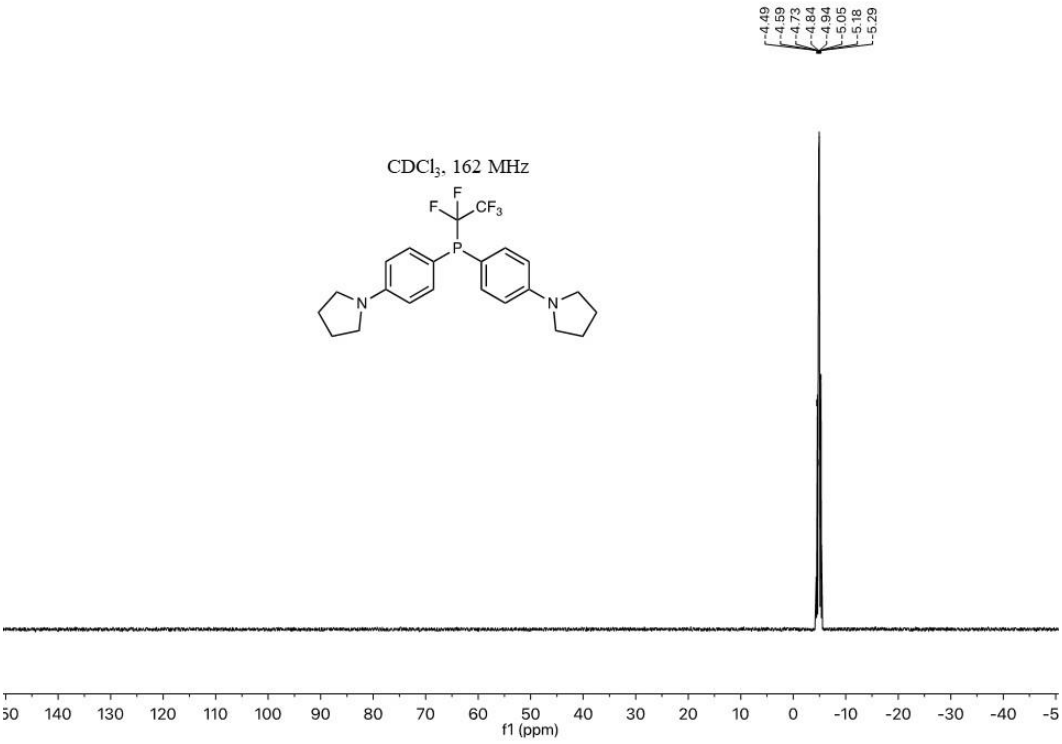

CDCl3, 400 MHz
CF3
P
N
N
4.00
4.14
8.29
8.27
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

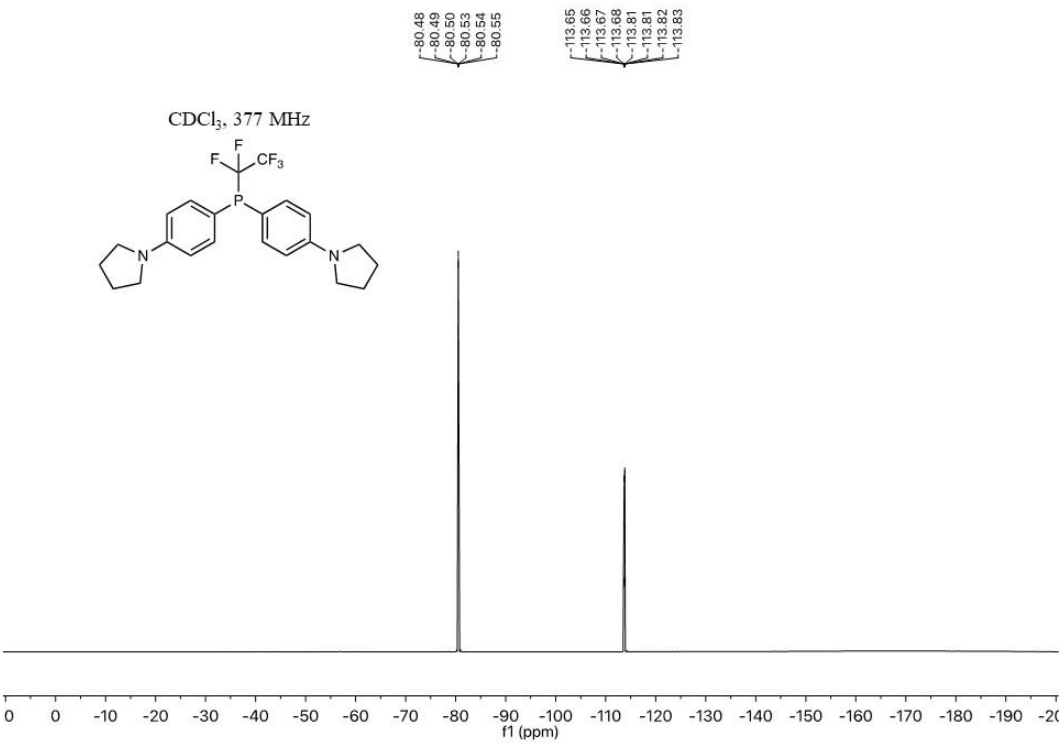

0.24
0.20
0.64
1.08
CDCl3, 162 MHz
CF3
P
N
N
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -5
f1 (ppm)

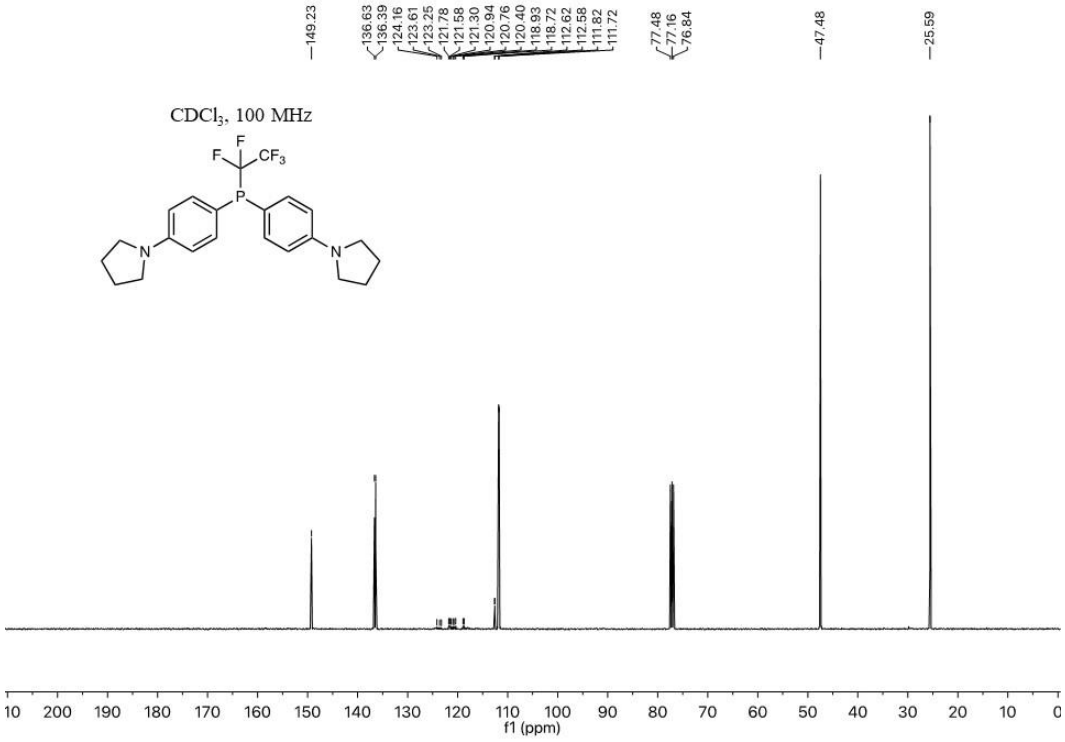

56.74
56.93
CDCl3, 377 MHz
CF3
P
N
N
0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2(
f1 (ppm)

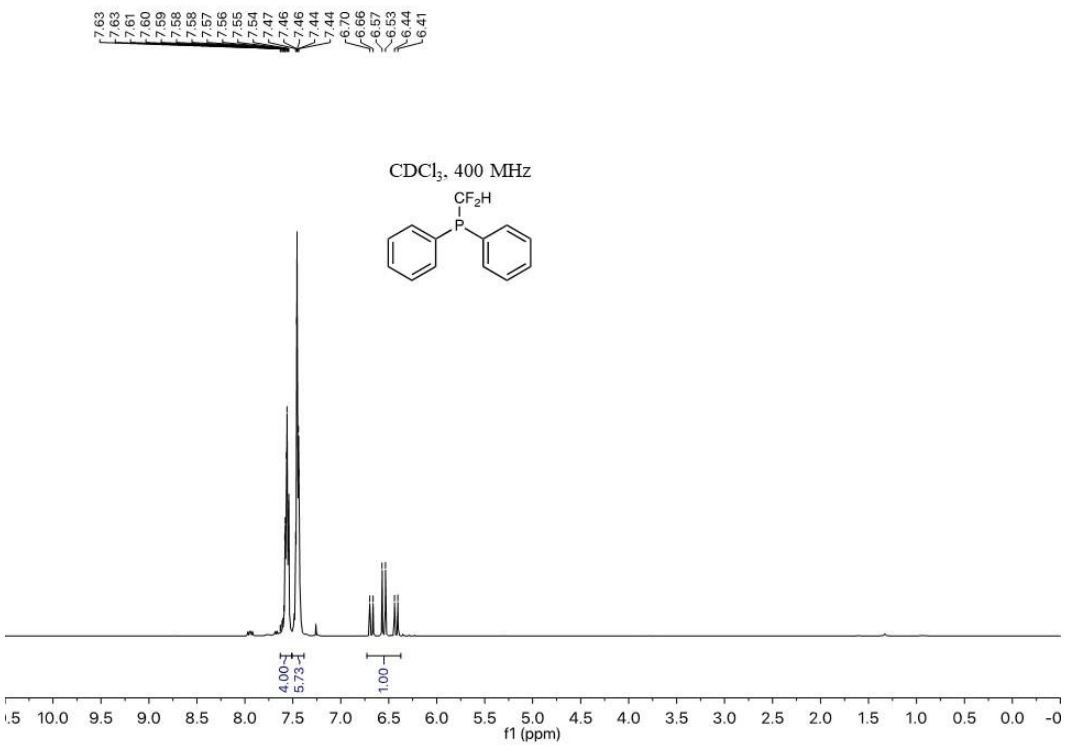

149.13
135.78
135.55
113.65
111.98
111.89
77.48
77.16
76.84
47.56
25.62
CDCl3, 100 MHz
CF3
P
N
N
f1 (ppm)

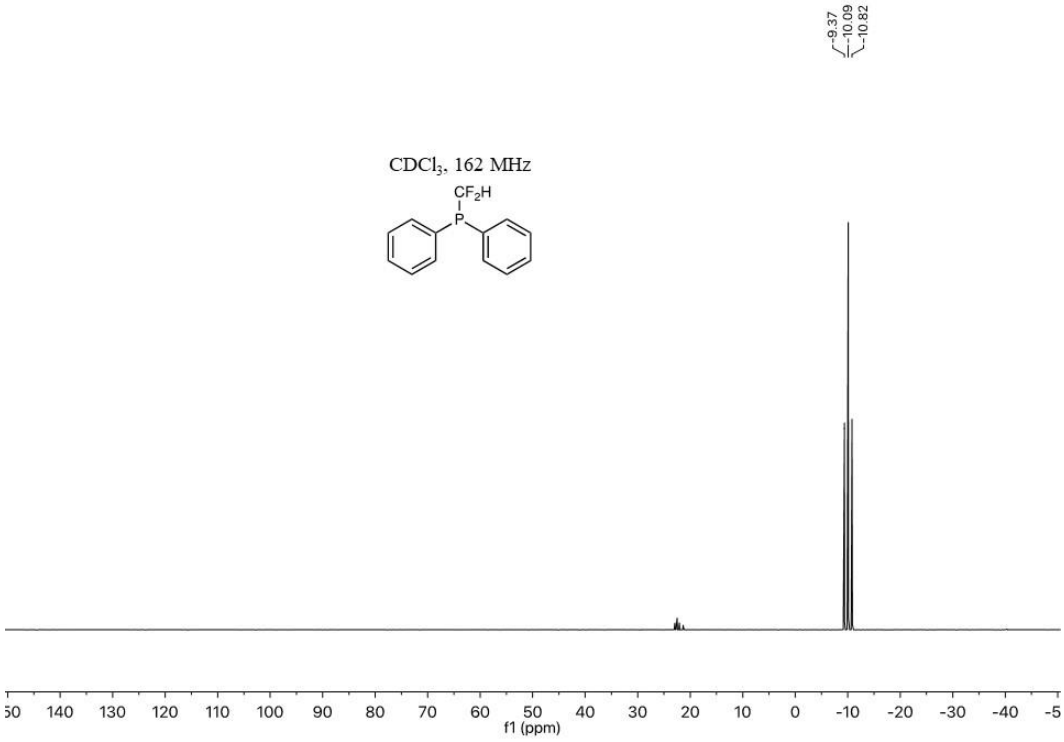

7.61
7.59
7.57
6.61
6.60
6.59
6.58
3.34
3.33
3.32
3.31
3.30
2.04
2.03
2.02
2.01
2.00
CDCl3, 400 MHz
F
F
CF3
P
N
N
4.00
4.15
8.32
8.22
f1 (ppm)

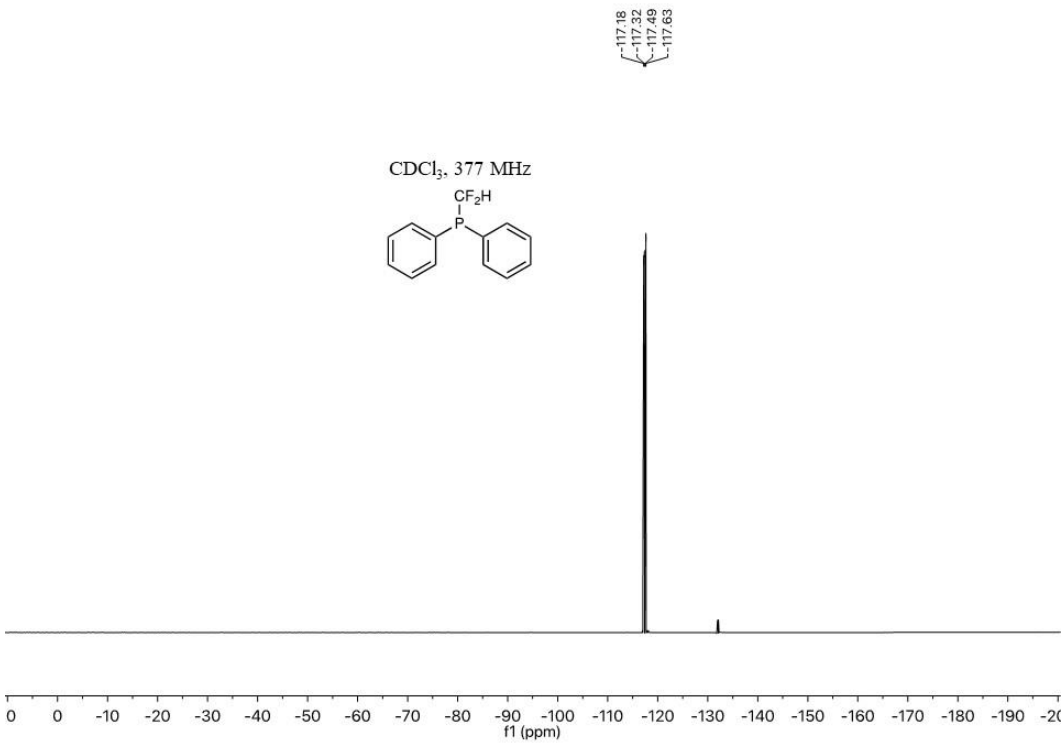

-4.49
-4.59
-4.73
-4.84
-4.94
-5.05
-5.18
-5.29
CDCl3, 162 MHz
F
F
CF3
P
N
N
f1 (ppm)

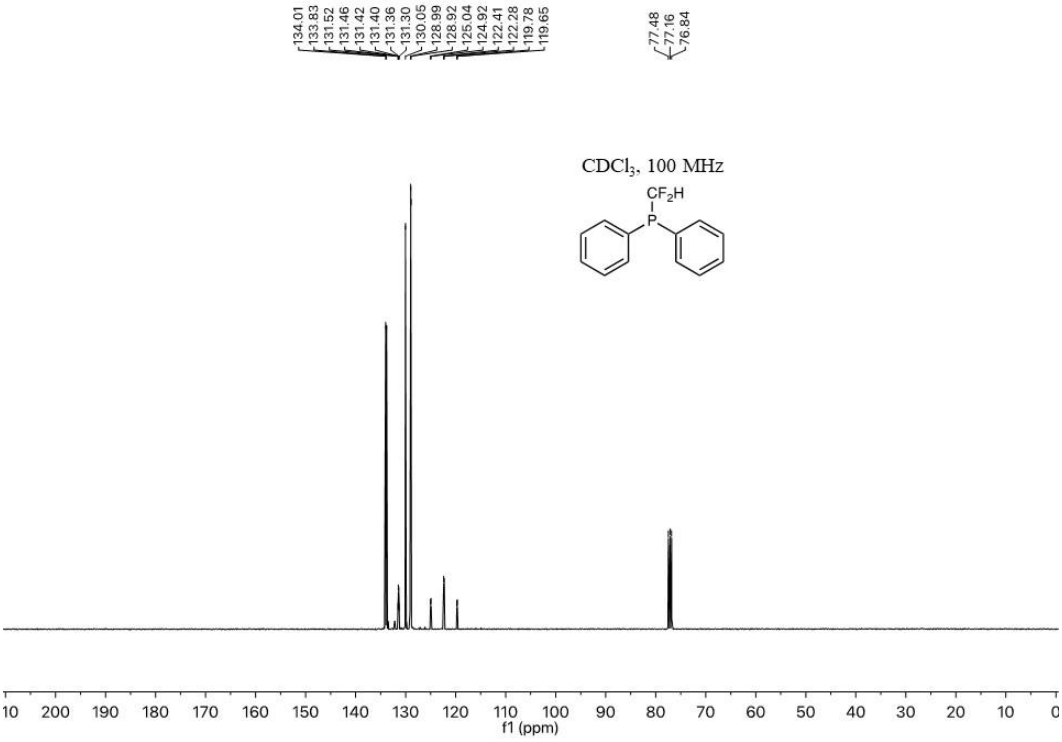

-80.48
-80.49
-80.50
-80.53
-80.54
-80.55
-113.65
-113.66
-113.67
-113.68
-113.81
-113.81
-113.82
-113.83
CDCl3, 377 MHz
F
F
CF3
P
N
N
f1 (ppm)

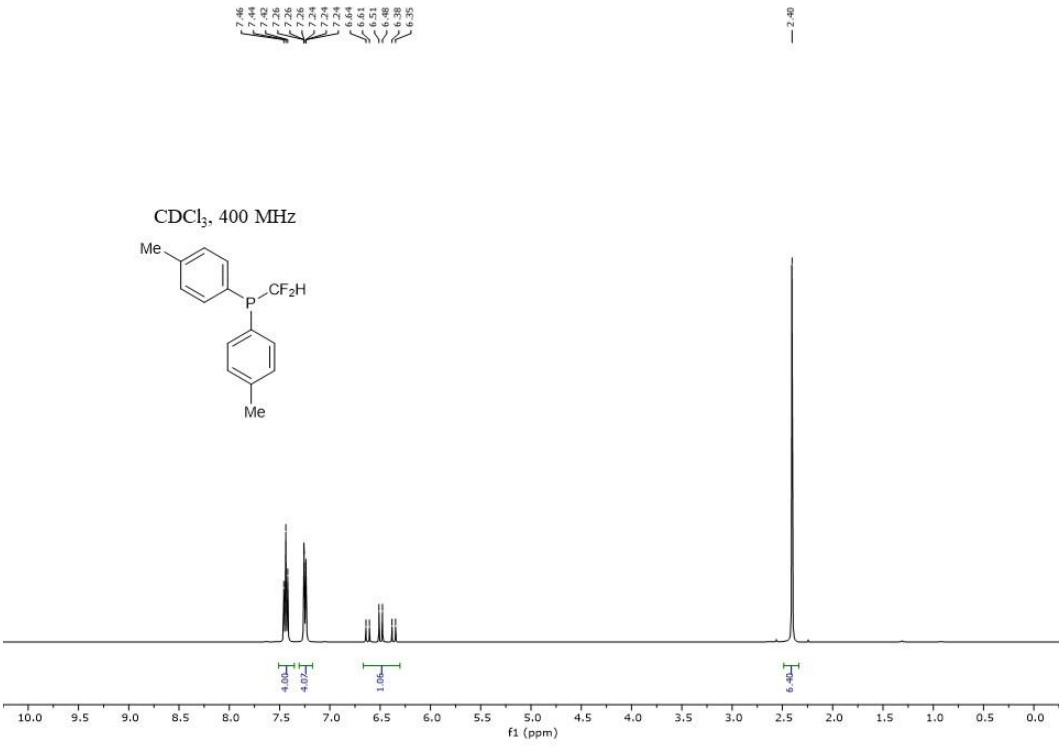

149.23
136.63
136.39
124.16
123.61
123.25
121.78
121.58
121.30
120.94
120.76
120.40
118.93
118.72
112.62
112.58
111.82
111.72
77.48
77.16
76.84
47.48
25.59
CDCl3, 100 MHz
F
F
CF3
P
N
N
f1 (ppm)

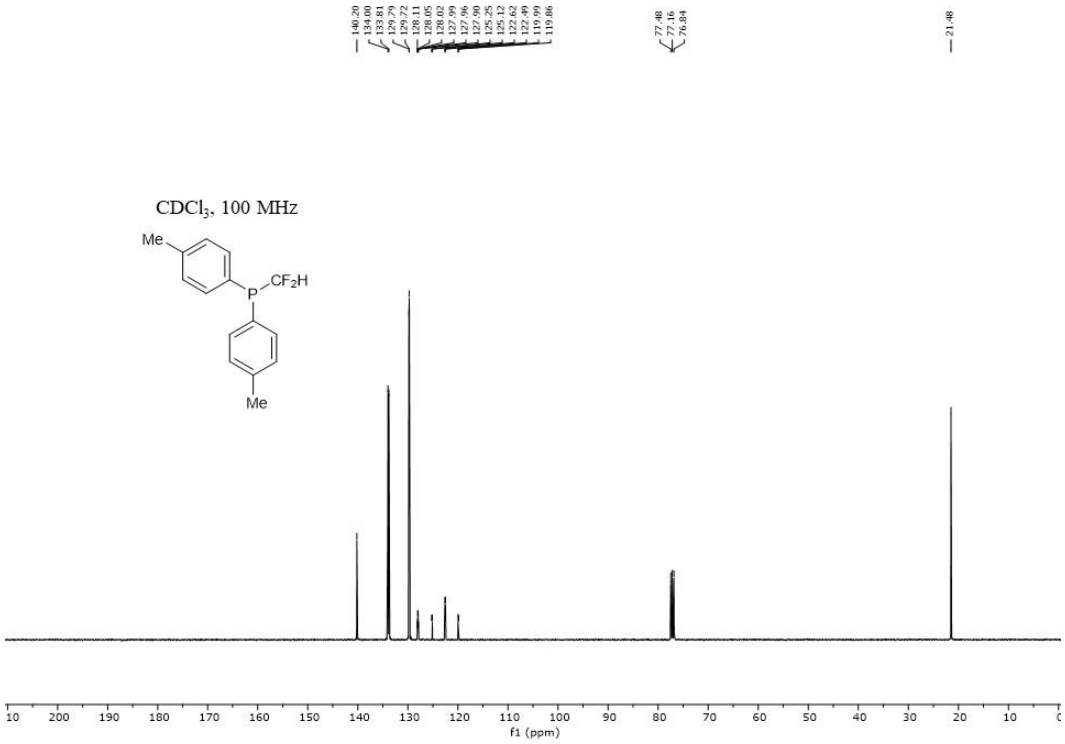

7.63
7.63
7.61
7.60
7.59
7.58
7.58
7.57
7.56
7.55
7.54
7.47
7.46
7.46
7.44
7.44
6.70
6.66
6.57
6.53
6.44
6.41
CDCl3, 400 MHz
CF2H
P
4.00
5.73
1.00
f1 (ppm)


-9.37
-10.09
-10.82
CDCl3, 162 MHz
CF2H
P
f1 (ppm)


-117.18
-117.32
-117.49
-117.63
CDCl3, 377 MHz
CF2H
P
f1 (ppm)

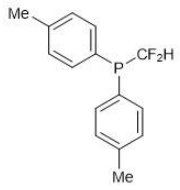

134.01
133.83
131.52
131.46
131.42
131.40
131.36
131.30
130.05
128.99
128.92
125.04
124.92
122.41
122.28
119.78
119.65
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
P
f1 (ppm)


7.46
7.44
7.42
7.26
7.26
7.26
7.24
7.24
7.24
6.64
6.61
6.51
6.48
6.38
6.35
2.40
CDCl3, 400 MHz
Me
P
CF2H
Me
4.00
4.07
1.06
6.40
f1 (ppm)

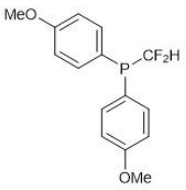

140.20
134.00
133.81
129.79
129.72
128.11
128.05
128.02
127.99
127.96
127.90
125.25
125.12
122.62
122.49
119.99
119.86
77.48
77.16
76.84
21.48
CDCl3, 100 MHz
Me
P
CF2H
Me
f1 (ppm)

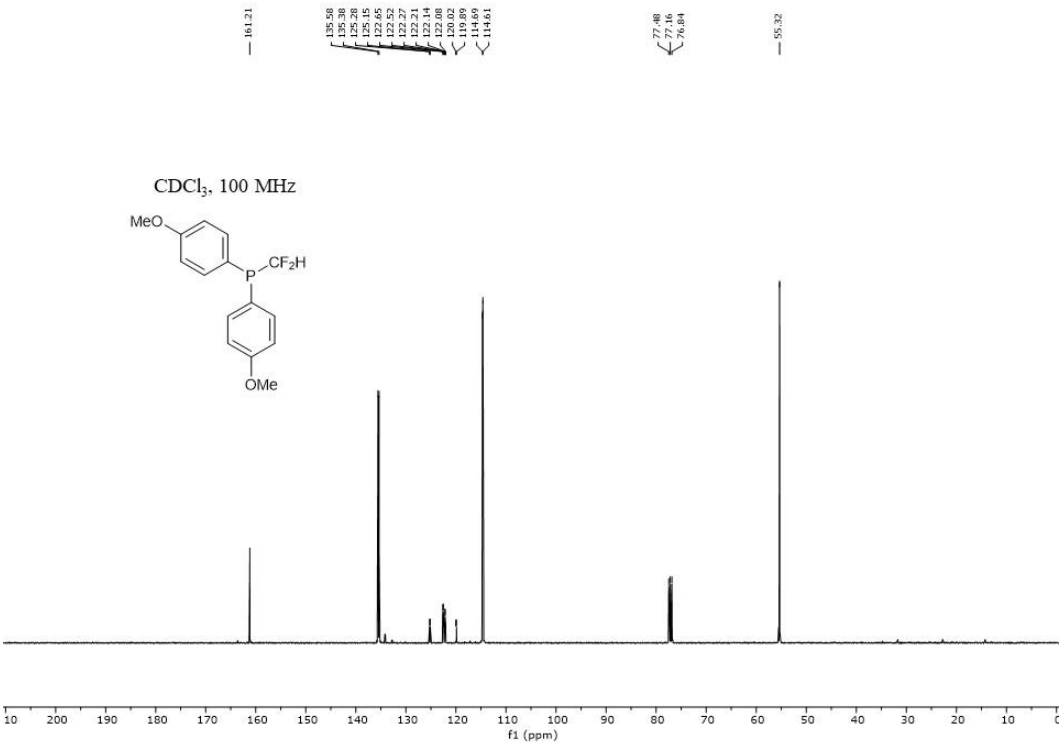

-117.39
-117.53
-117.70
-117.84
CDCl3, 376 MHz
Me
P
CF2H
Me
f1 (ppm)

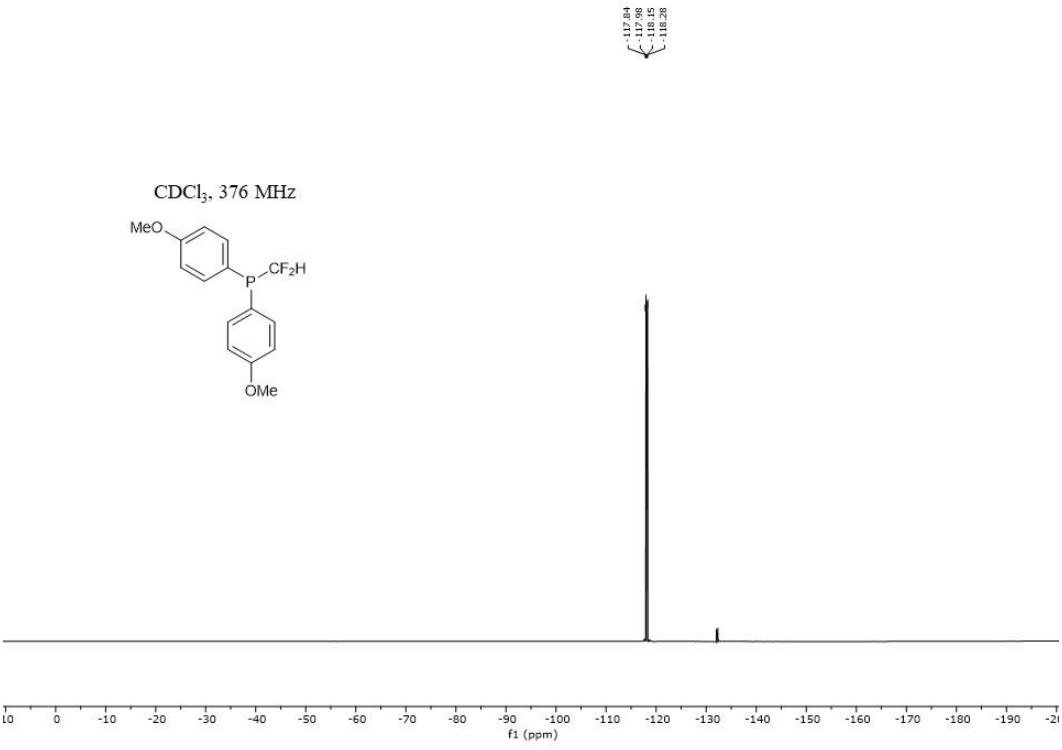
$CDCl_3$, 162 MHz



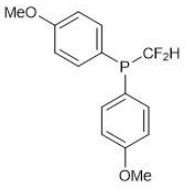
$CDCl_3$, 400 MHz



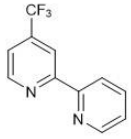

161.21
135.58
135.38
125.28
125.15
122.65
122.52
122.27
122.21
122.14
122.08
120.02
119.89
114.69
114.61
77.48
77.16
76.84
55.32
CDCl3, 100 MHz
MeO
P
CF2H
OMe
f1 (ppm)

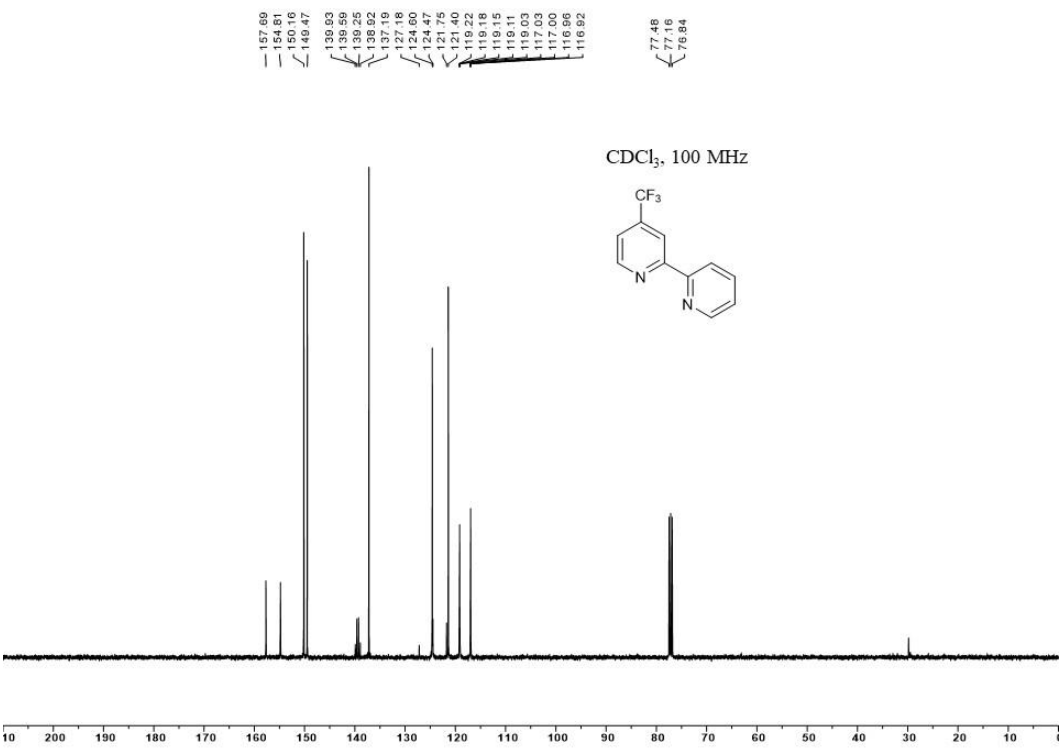

-117.84
-117.86
-118.15
-118.28
CDCl3, 376 MHz
MeO
P
CF2H
OMe
f1 (ppm)

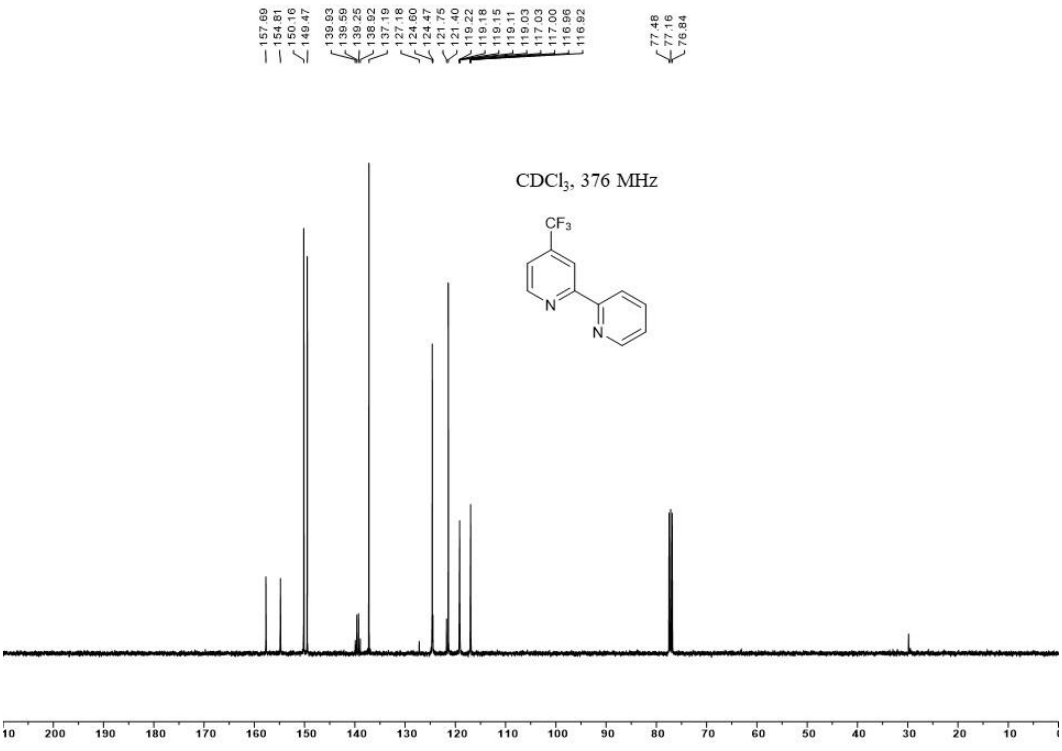
$CDCl_3$, 162 MHz

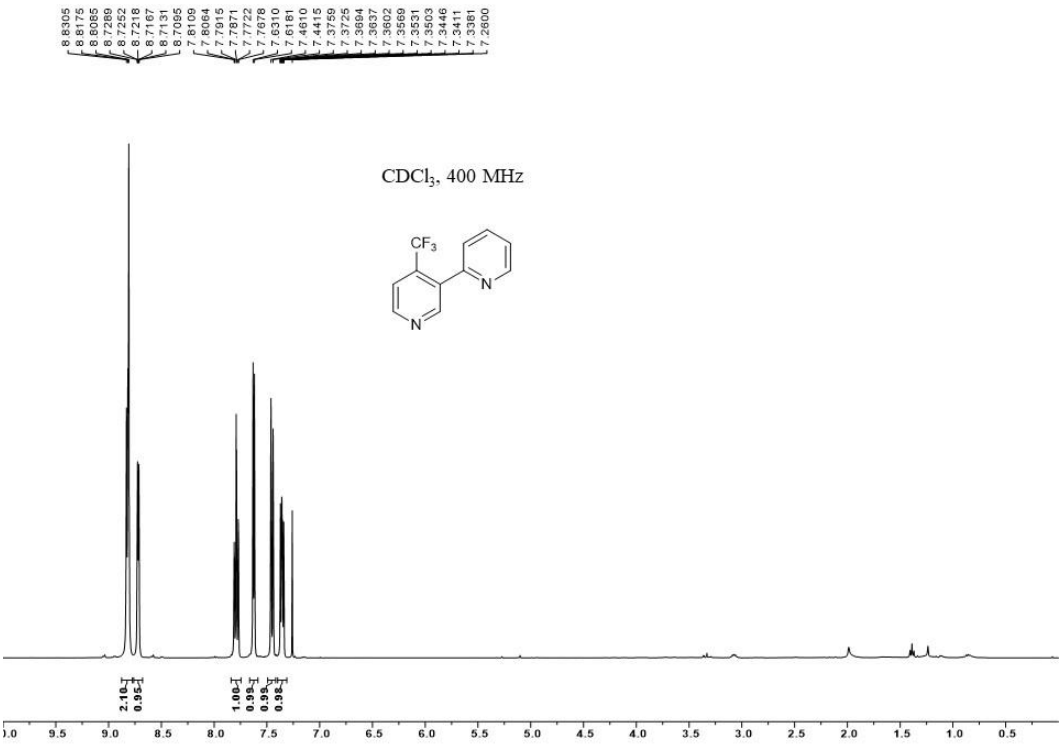


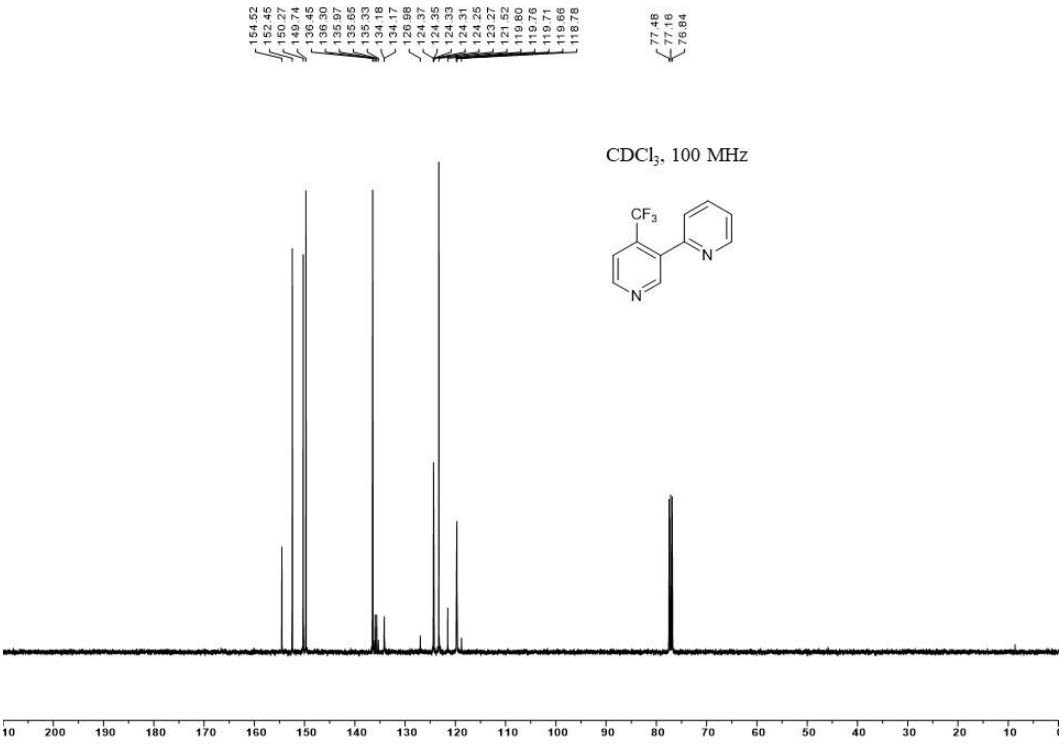
$CDCl_3$, 400 MHz

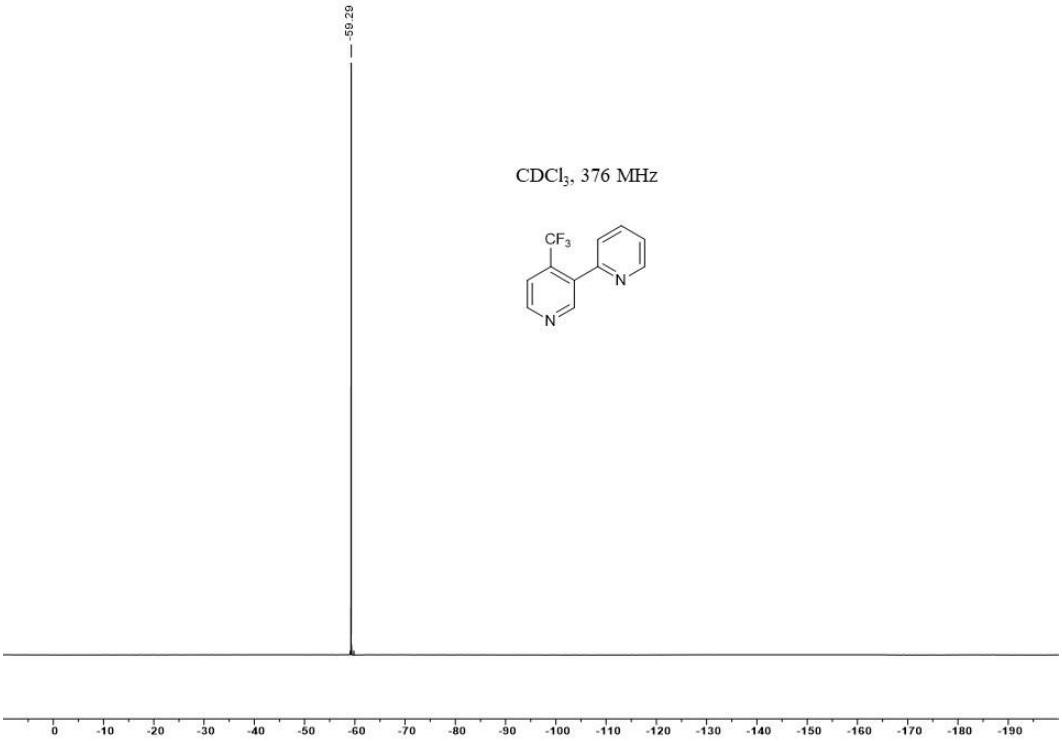



157.69
154.81
150.16
149.47
139.93
139.59
139.25
138.92
137.19
127.18
124.60
124.47
121.75
121.40
119.22
119.18
119.15
119.11
119.03
117.03
117.00
116.96
116.92
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
N
N
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

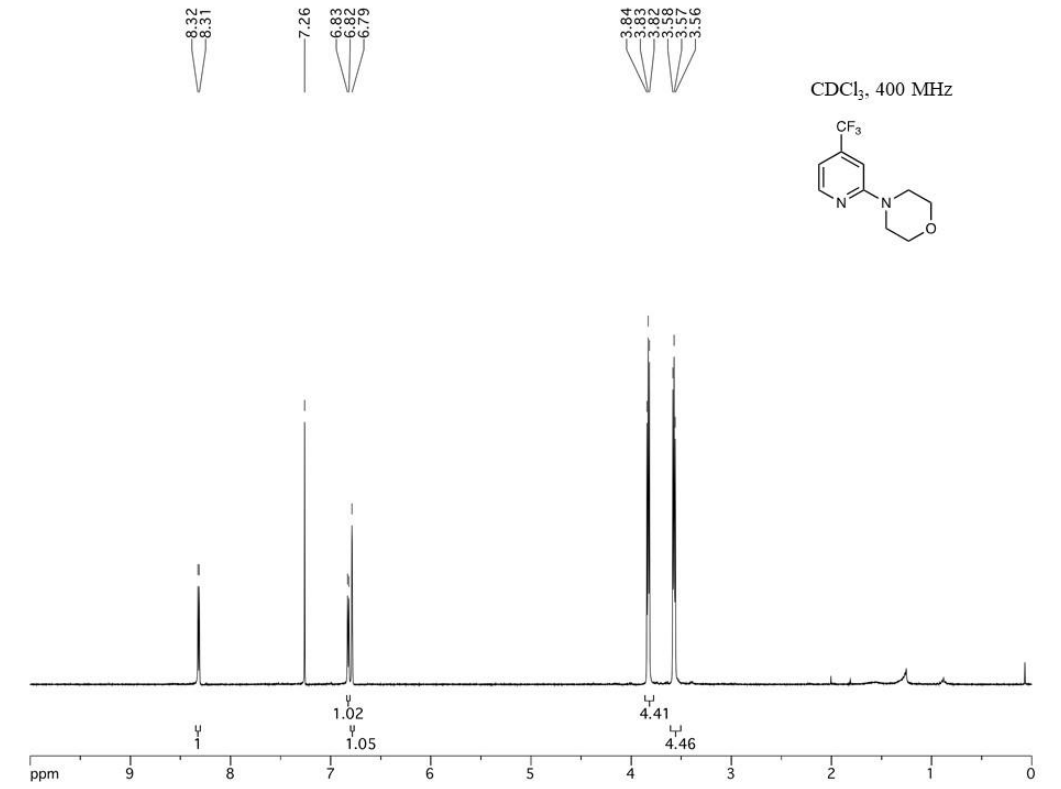

157.69
154.81
150.16
149.47
139.93
139.59
139.25
138.92
137.19
127.18
124.60
124.47
121.75
121.40
119.22
119.18
119.15
119.11
119.03
117.03
117.00
116.96
116.92
77.48
77.16
76.84
CDCl3, 376 MHz
CF3
N
N
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10


8.8305
8.8175
8.8085
8.7289
8.7252
8.7218
8.7167
8.7131
8.7095
7.8109
7.8064
7.7915
7.7871
7.7722
7.7678
7.6310
7.6181
7.4610
7.4415
7.3759
7.3725
7.3694
7.3637
7.3602
7.3569
7.3551
7.3503
7.3446
7.3411
7.3381
7.2600
CDCl3, 400 MHz
CF3
N
N
2.10
0.95
1.00
0.99
0.99
0.98

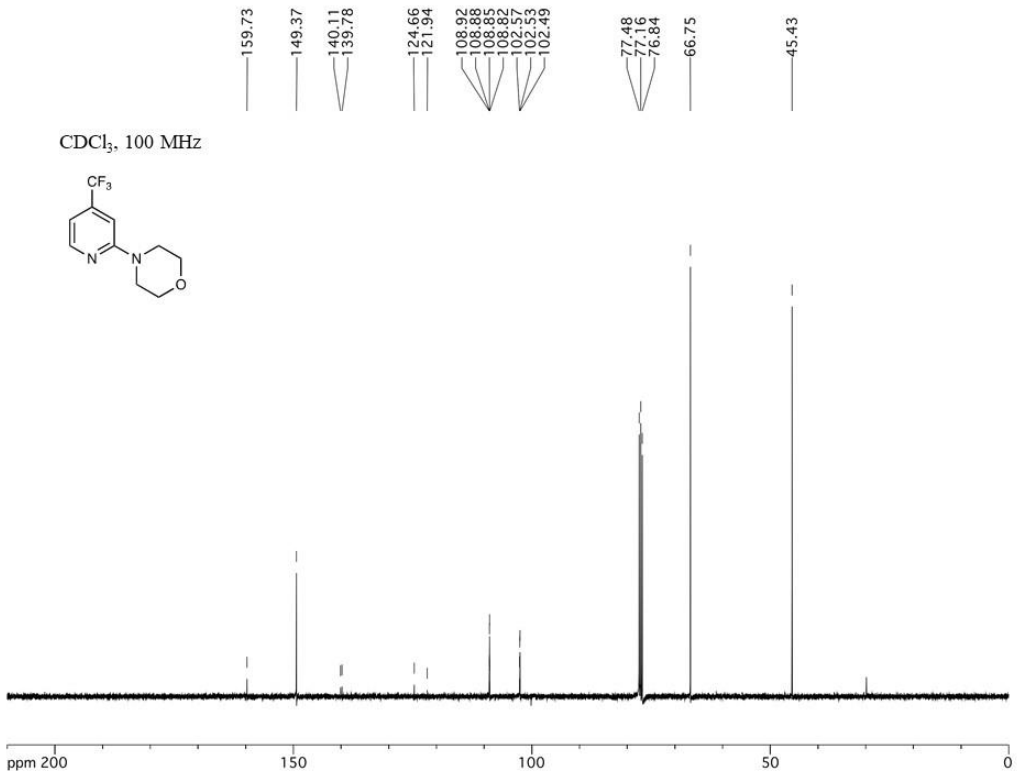

154.52
152.45
150.27
149.74
136.45
136.30
135.97
135.65
135.33
134.18
134.17
126.98
124.37
124.35
124.33
124.31
124.25
123.27
121.52
119.80
119.76
119.71
119.66
118.78
77.46
77.16
76.84
CDCl3, 100 MHz
CF3
N
N

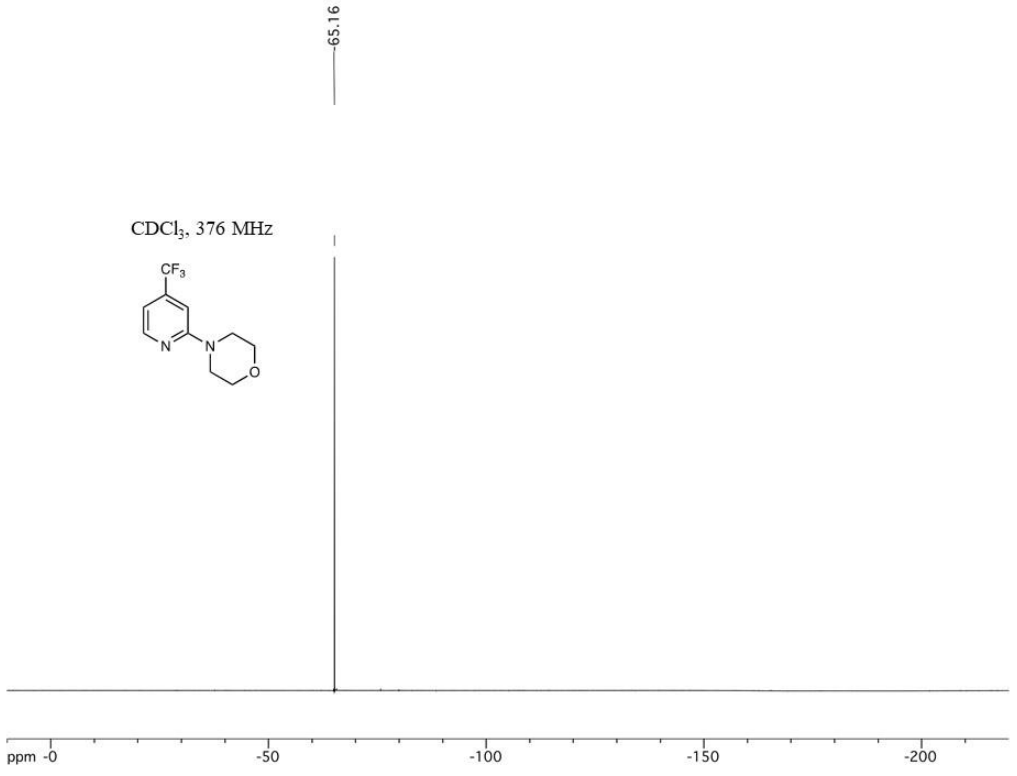


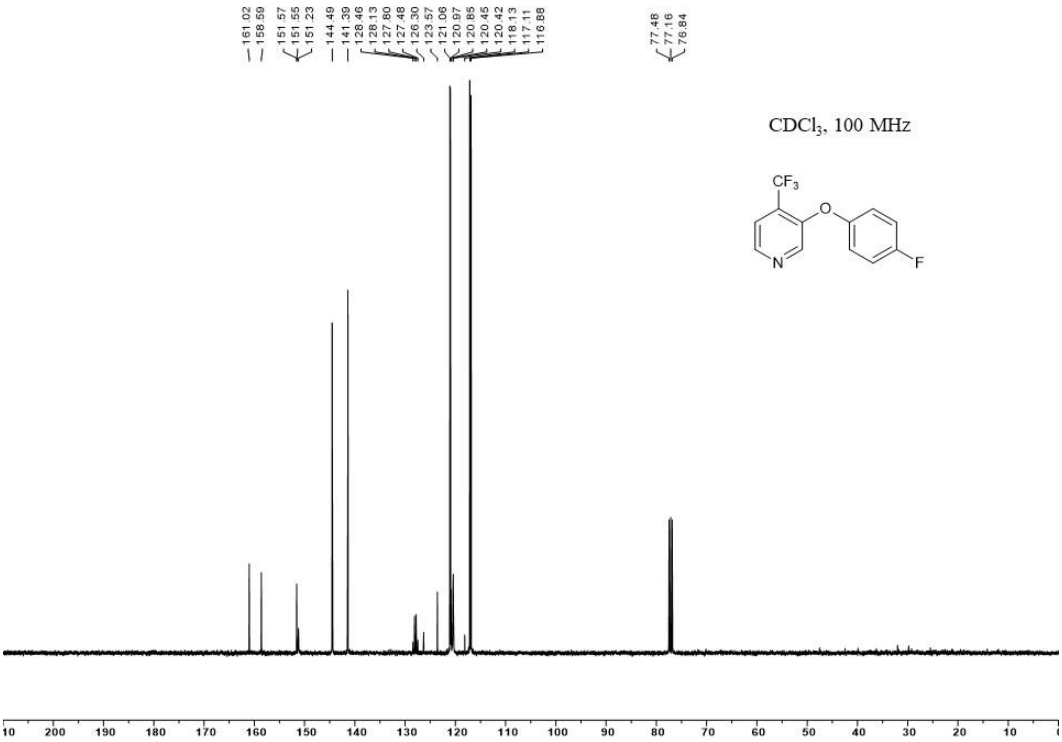
$CDCl_3$, 376 MHz

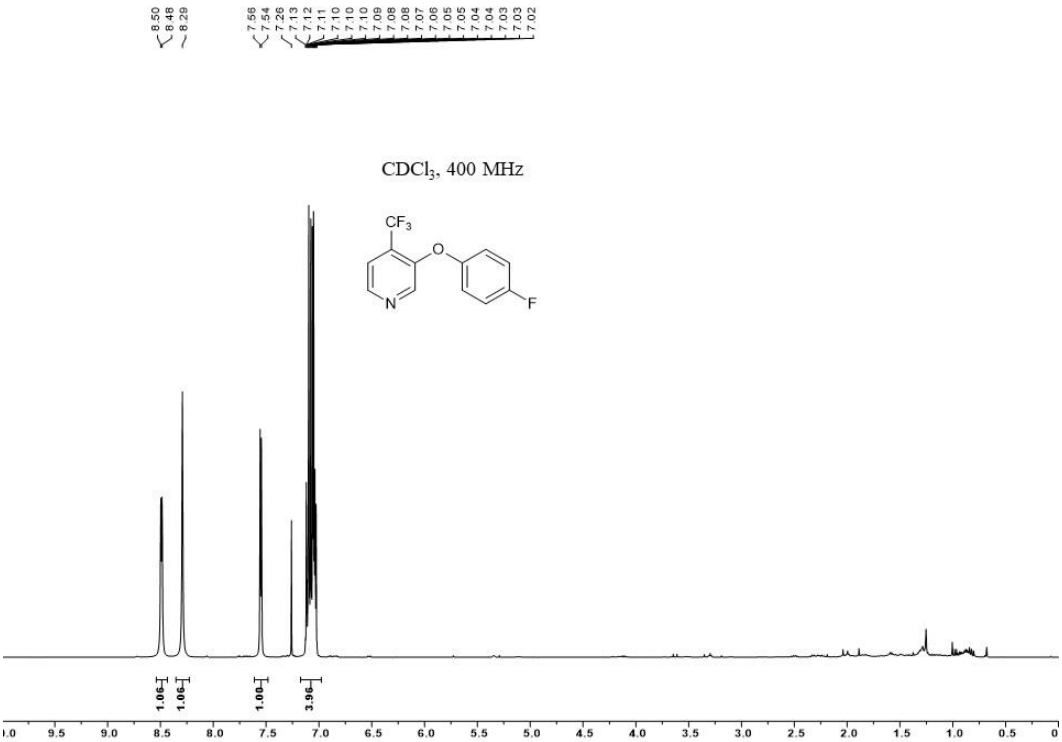


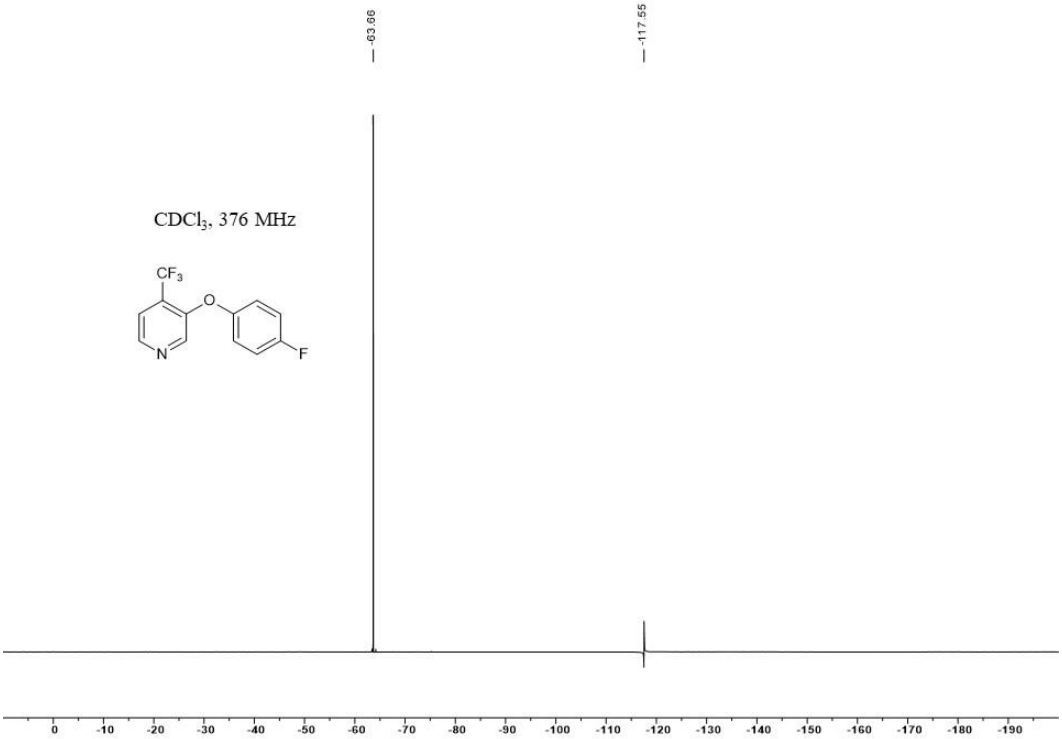
$CDCl_3$, 400 MHz

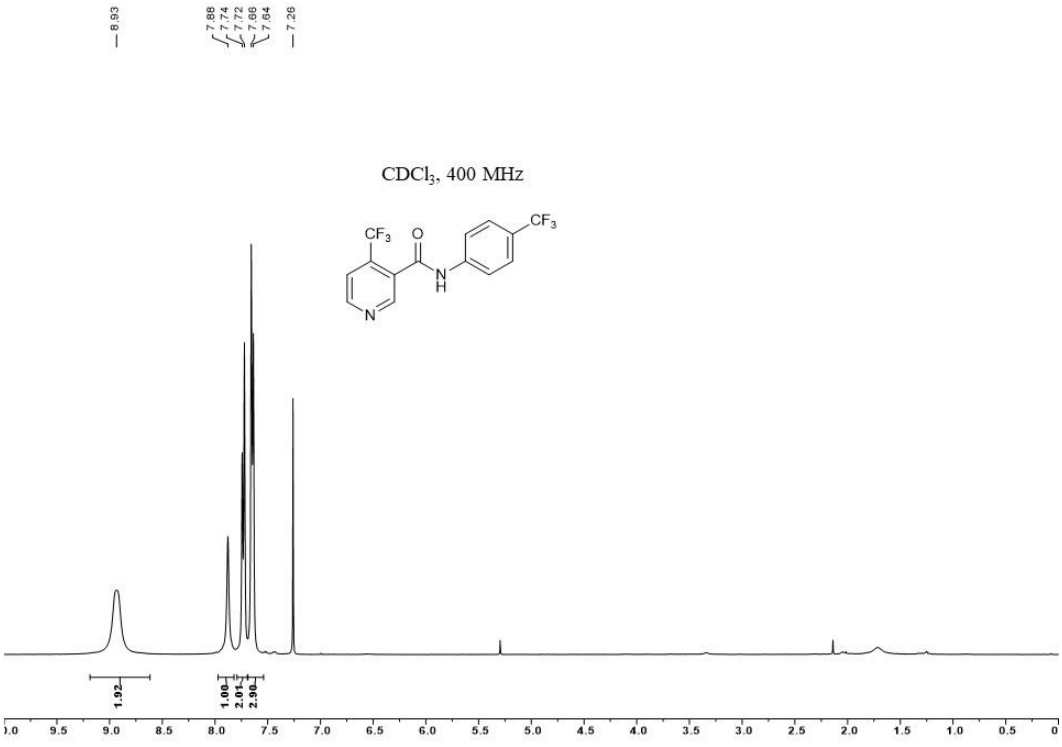

159.73
149.37
140.11
139.78
124.66
121.94
108.92
108.88
108.85
108.82
102.57
102.53
102.49
77.48
77.16
76.84
66.75
45.43
CDCl3, 100 MHz
CF3
N
N
O
ppm 200
150
100
50
0

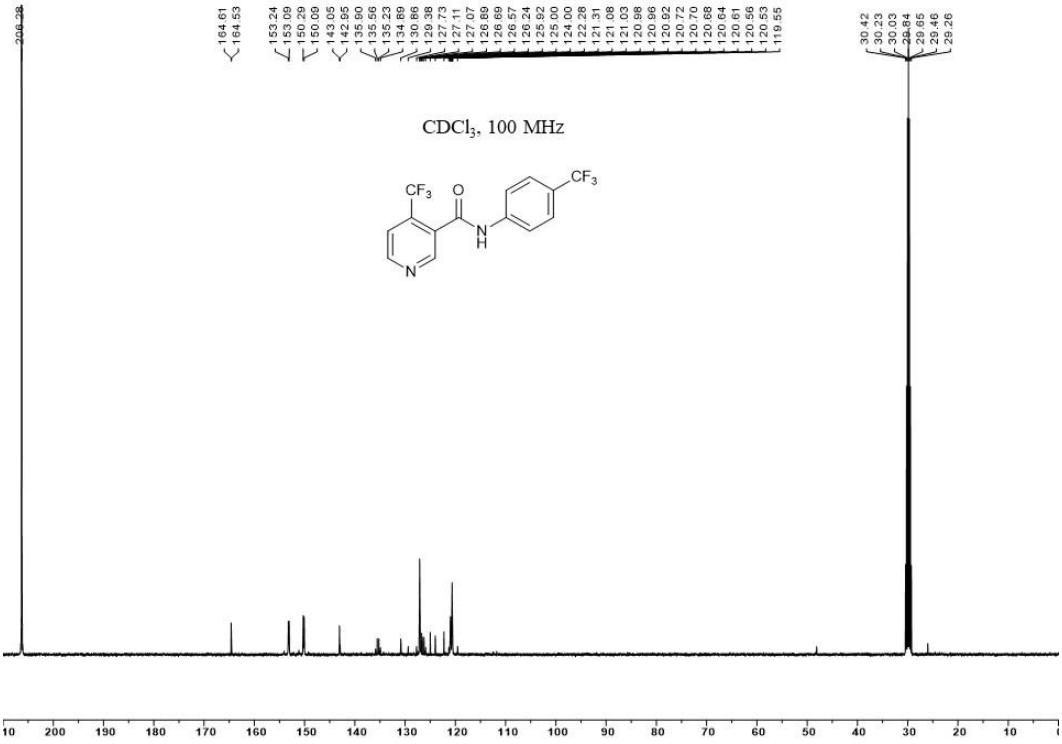

-65.16
CDCl3, 376 MHz
CF3
N
N
O
ppm -0
-50
-100
-150
-200

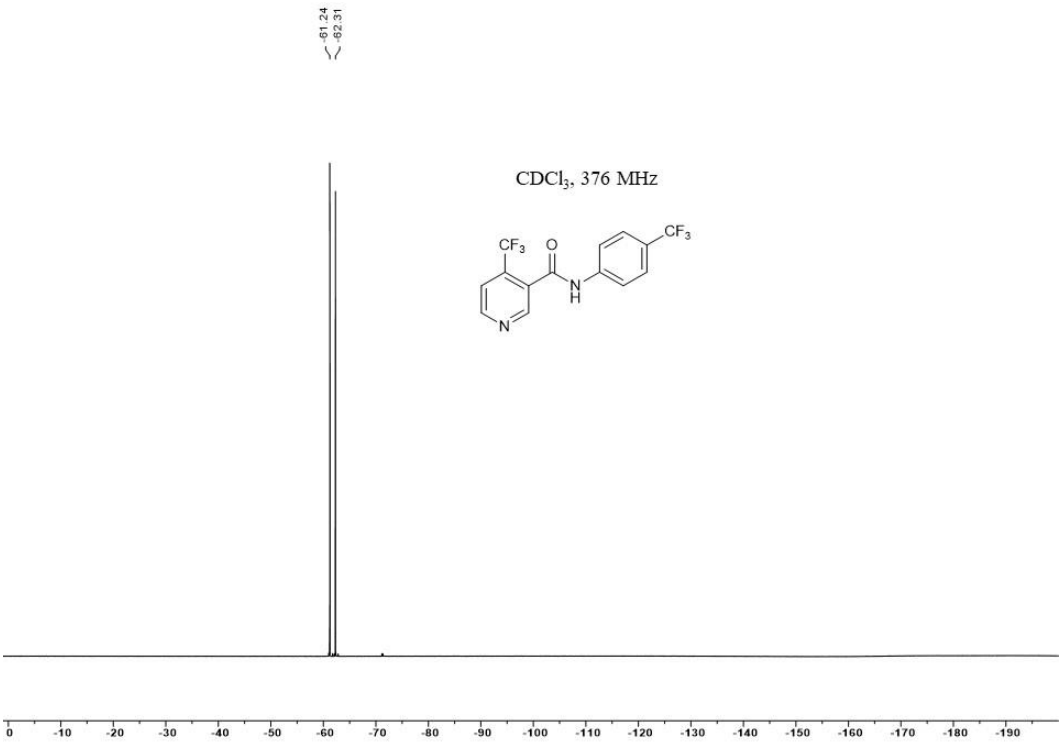

161.02
158.59
151.57
151.55
151.23
144.49
141.39
128.46
128.13
127.90
127.48
127.30
123.97
121.06
120.97
120.85
120.45
120.42
118.13
117.11
116.88
77.46
77.16
76.84
CDCl3, 100 MHz
CF3
O
N
F
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

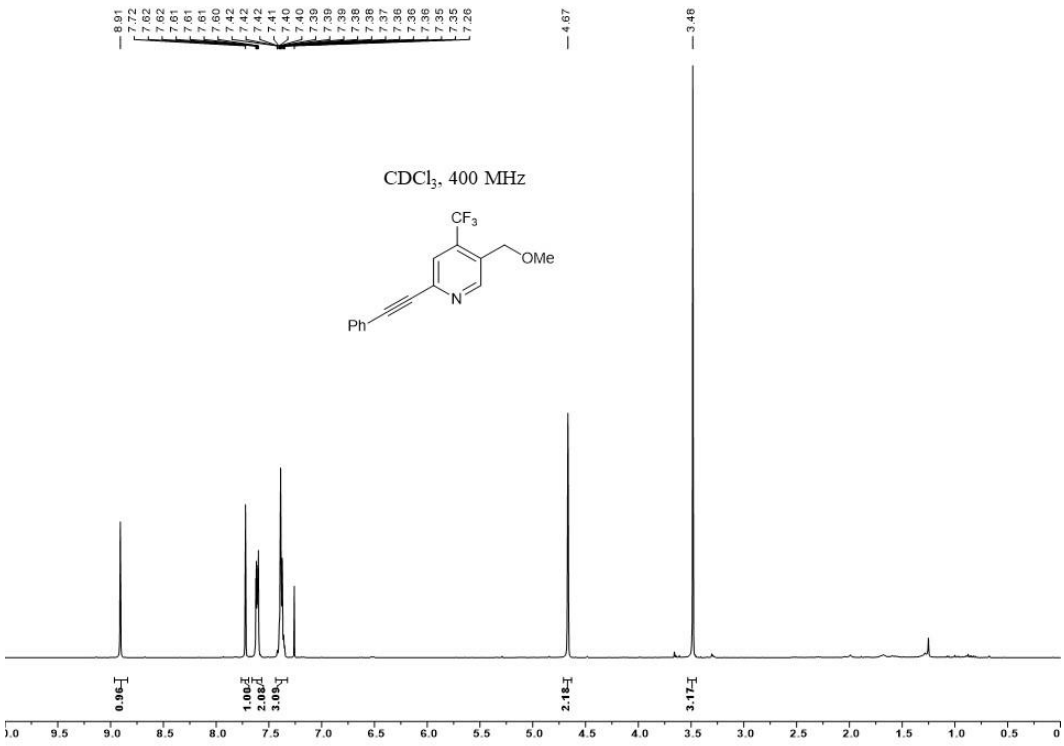

8.50
8.48
8.29
7.56
7.54
7.26
7.13
7.12
7.11
7.10
7.10
7.10
7.09
7.08
7.08
7.07
7.06
7.05
7.05
7.04
7.04
7.03
7.03
7.02
CDCl3, 400 MHz
CF3
O
N
F
1.06
1.06
1.00
3.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

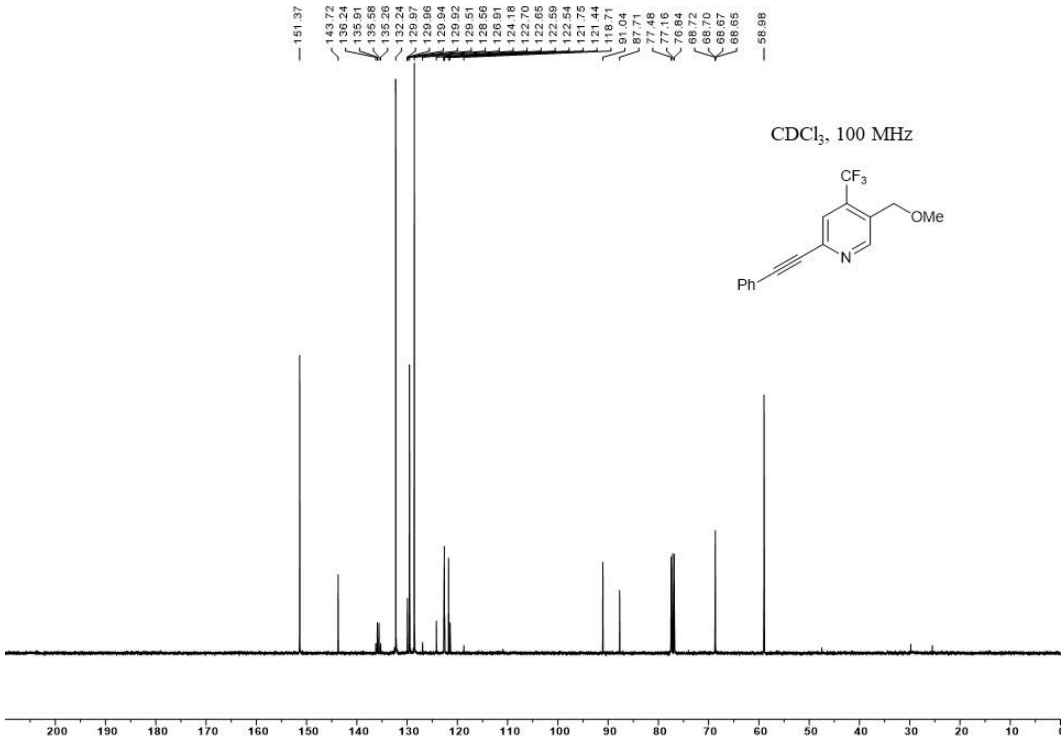

-63.66
-117.55
CDCl3, 376 MHz
CF3
O
N
F
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

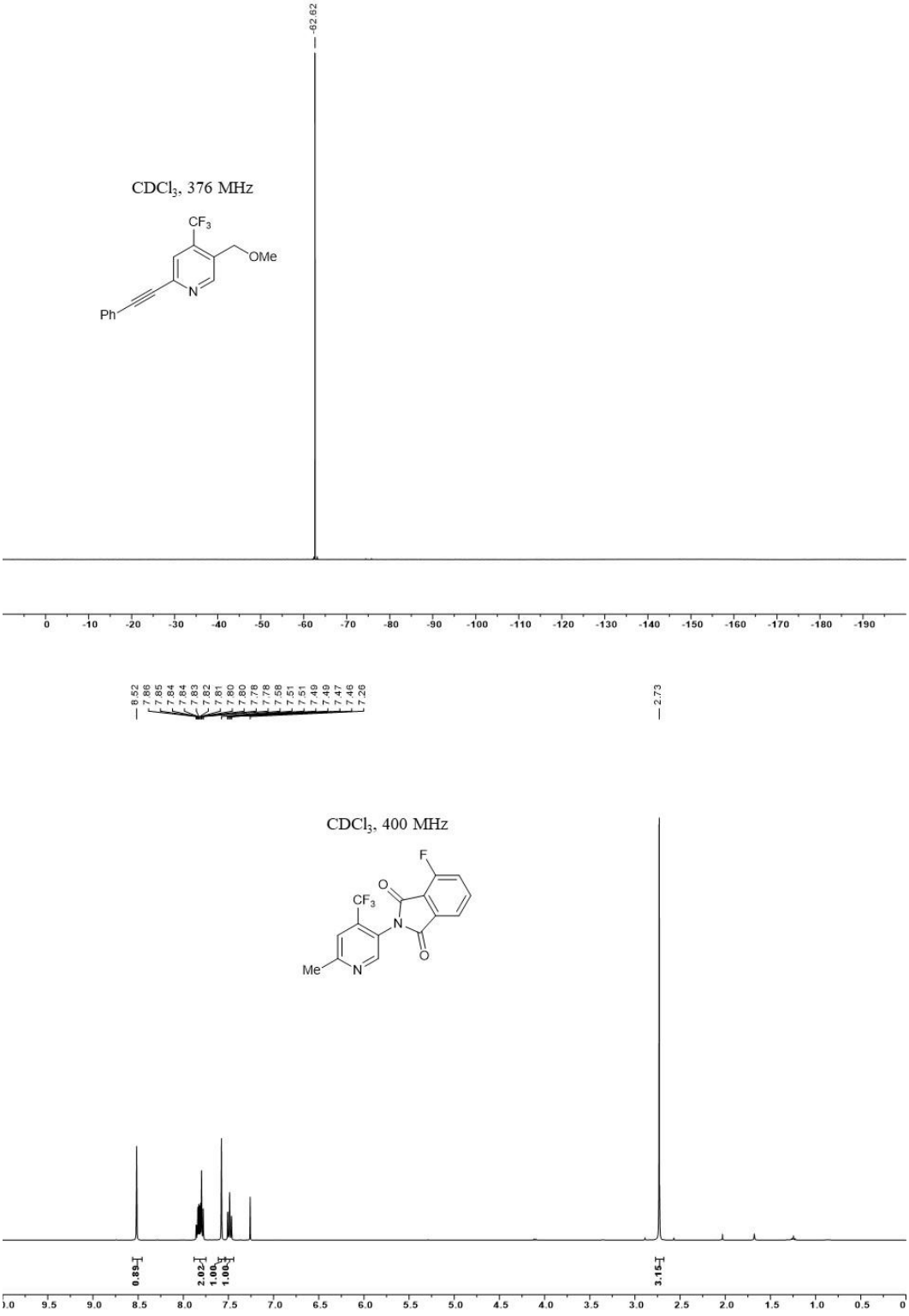

8.93
7.88
7.74
7.72
7.66
7.64
7.26
CDCl3, 400 MHz
CF3
O
N
H
CF3
1.92
1.00
2.01
2.90
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

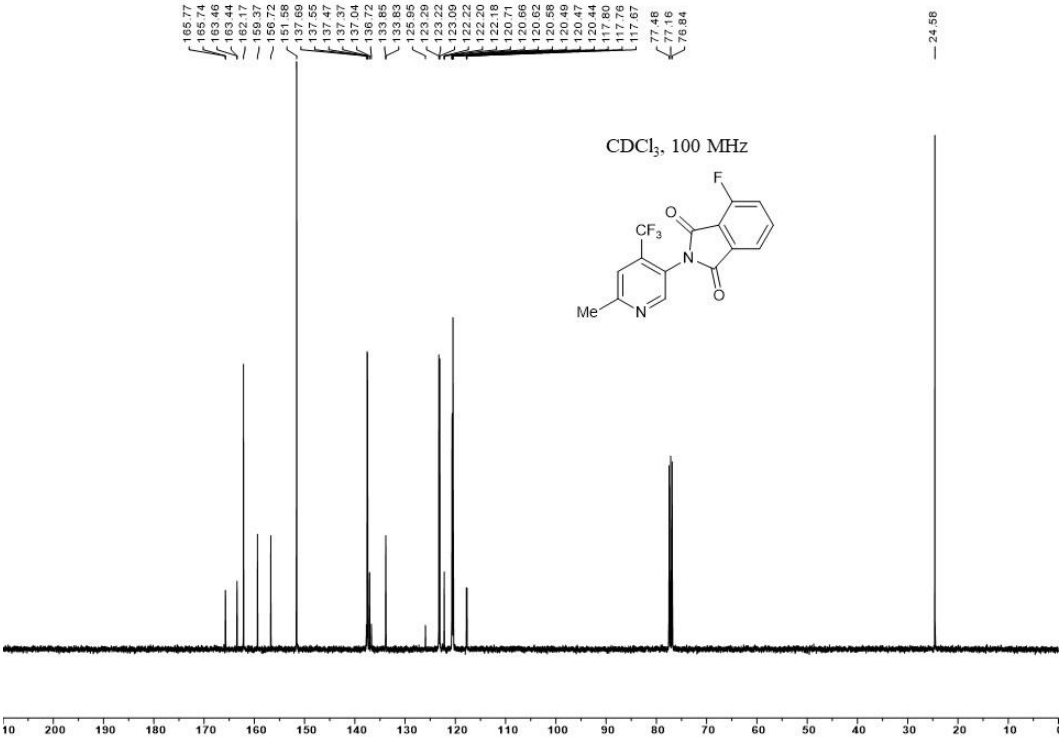

164.61
164.53
153.24
153.09
150.29
150.09
143.05
142.95
135.90
135.66
135.23
134.89
134.86
129.38
127.73
127.11
127.07
126.89
126.69
126.67
126.24
125.92
125.00
124.00
122.28
121.31
121.08
121.03
120.98
120.96
120.92
120.72
120.70
120.68
120.64
120.61
120.56
120.53
119.55
30.42
30.23
30.03
29.84
29.65
29.46
29.26
CDCl3, 100 MHz
CF3
O
N
H
CF3
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

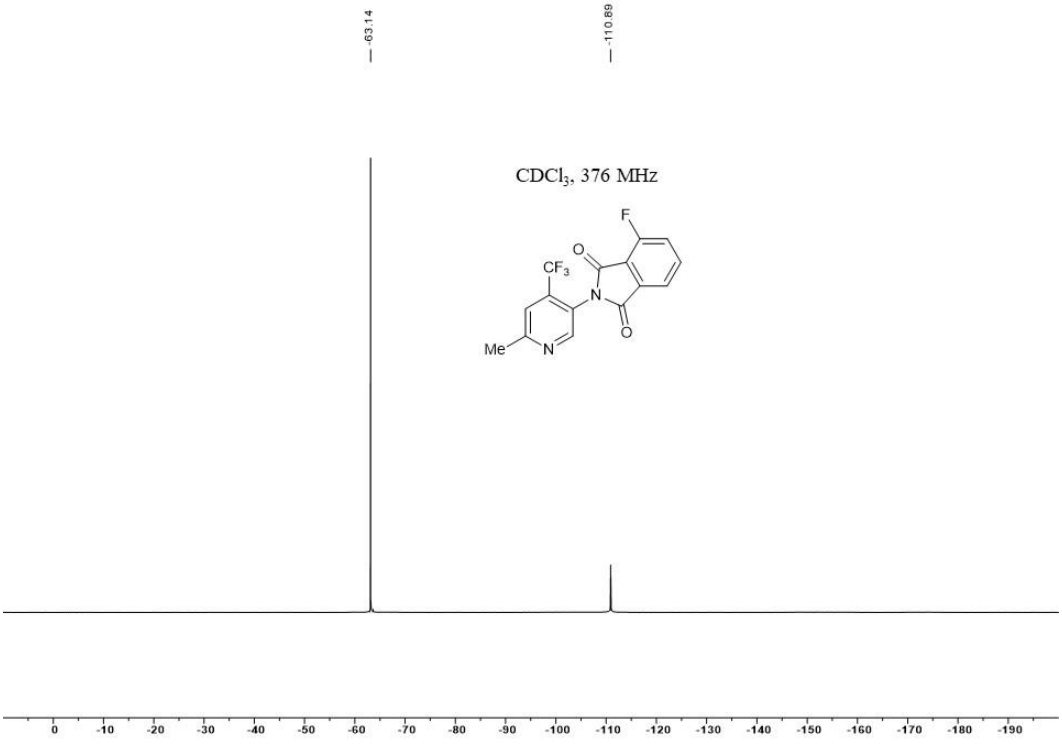

-61.24
-62.31
CDCl3, 376 MHz
CF3
O
N
H
CF3
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

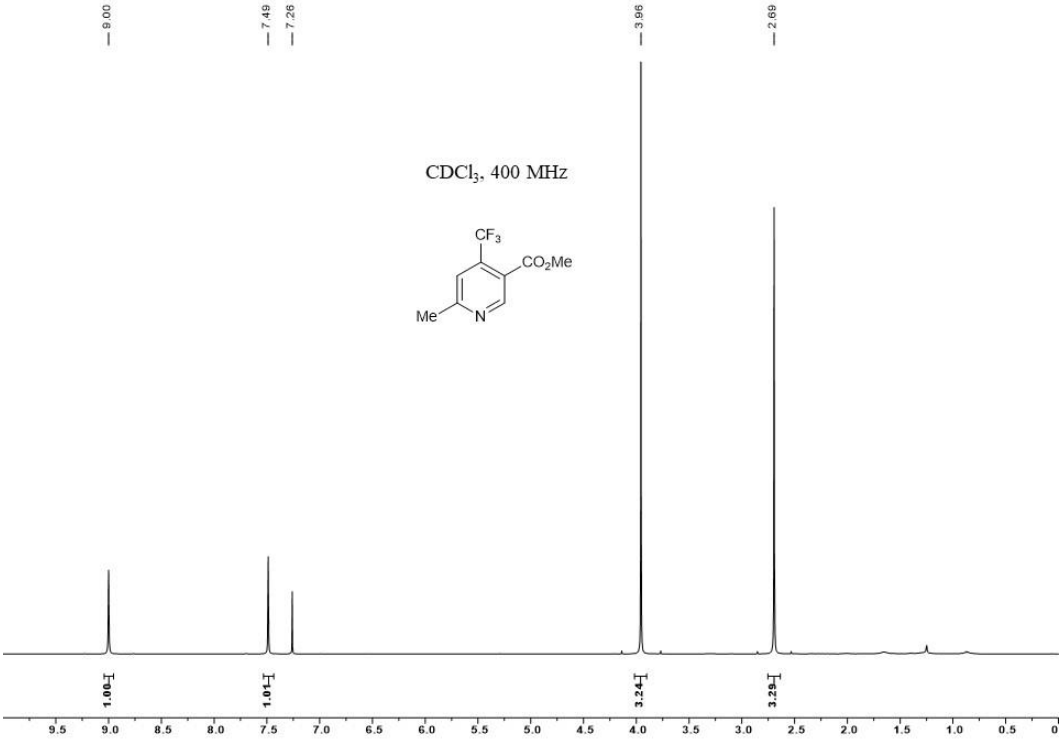

8.91
7.72
7.62
7.62
7.62
7.61
7.61
7.61
7.60
7.42
7.42
7.42
7.42
7.41
7.40
7.40
7.39
7.39
7.39
7.38
7.38
7.37
7.36
7.36
7.36
7.35
7.35
7.26
4.67
3.48
CDCl3, 400 MHz
CF3
OMe
N
Ph
0.96
1.00
2.02
3.05
2.18
3.17

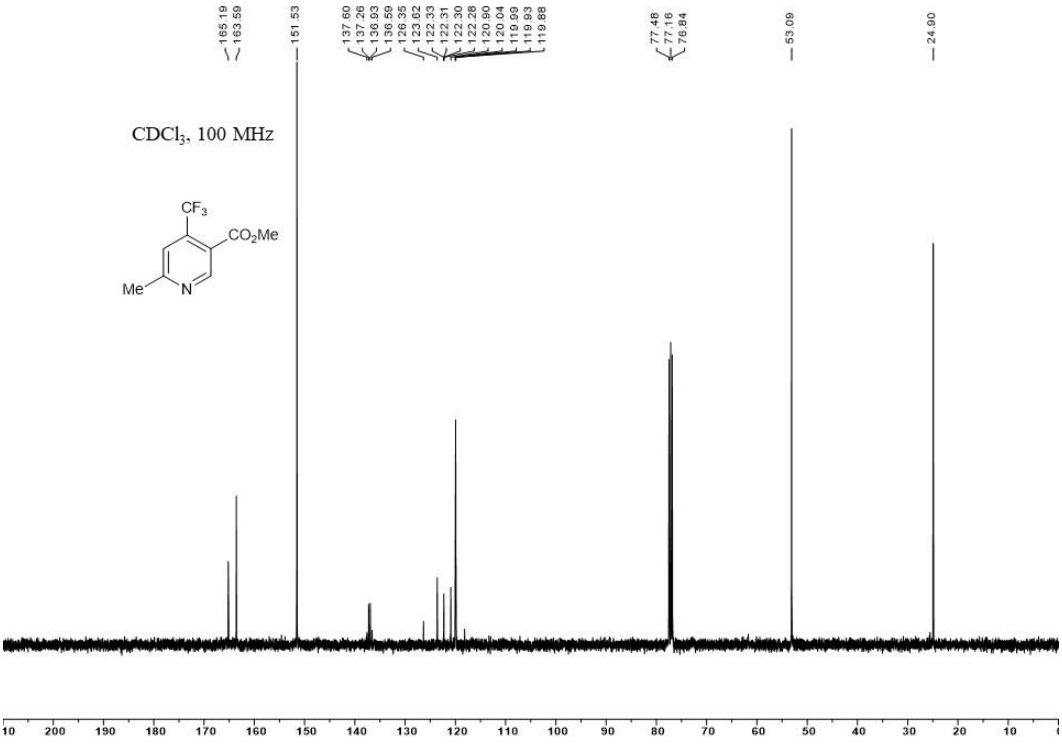

151.37
143.72
136.24
135.91
135.58
135.26
132.24
129.97
129.96
129.94
129.92
129.51
128.56
126.91
124.18
122.70
122.65
122.59
122.54
121.75
121.44
118.71
91.04
87.71
77.48
77.16
76.84
68.72
68.70
68.67
68.65
58.98
CDCl3, 100 MHz
CF3
OMe
N
Ph

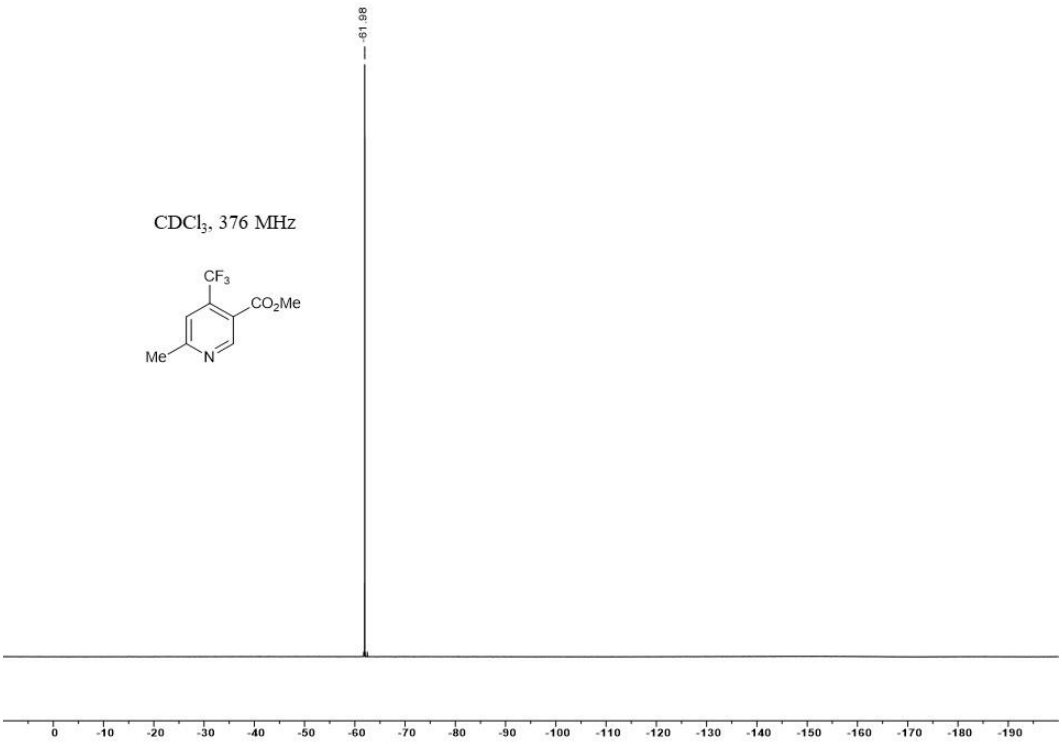

CDCl3, 376 MHz
CF3
OMe
N
Ph
-62.62
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
8.52
7.86
7.85
7.84
7.84
7.83
7.82
7.81
7.80
7.80
7.78
7.78
7.58
7.51
7.51
7.49
7.49
7.47
7.46
7.26
2.73
CDCl3, 400 MHz
F
O
CF3
N
O
Me
N
0.83
2.02
1.06
1.06
3.15
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

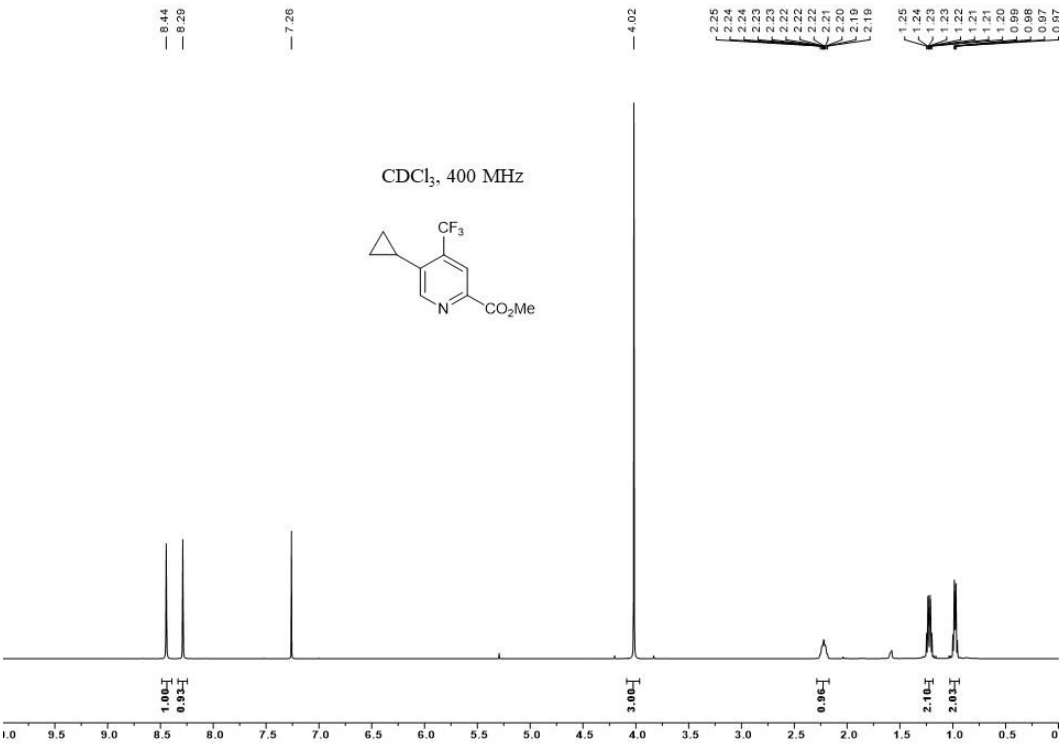

165.77
165.74
163.46
163.44
162.17
159.37
156.72
151.58
137.69
137.55
137.47
137.37
137.04
136.72
133.85
133.83
125.95
123.29
123.22
123.09
122.22
122.20
122.18
120.71
120.66
120.62
120.58
120.49
120.47
120.44
117.80
117.76
117.67
77.46
77.16
76.84
24.58
CDCl3, 100 MHz
F
O
CF3
N
O
Me
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

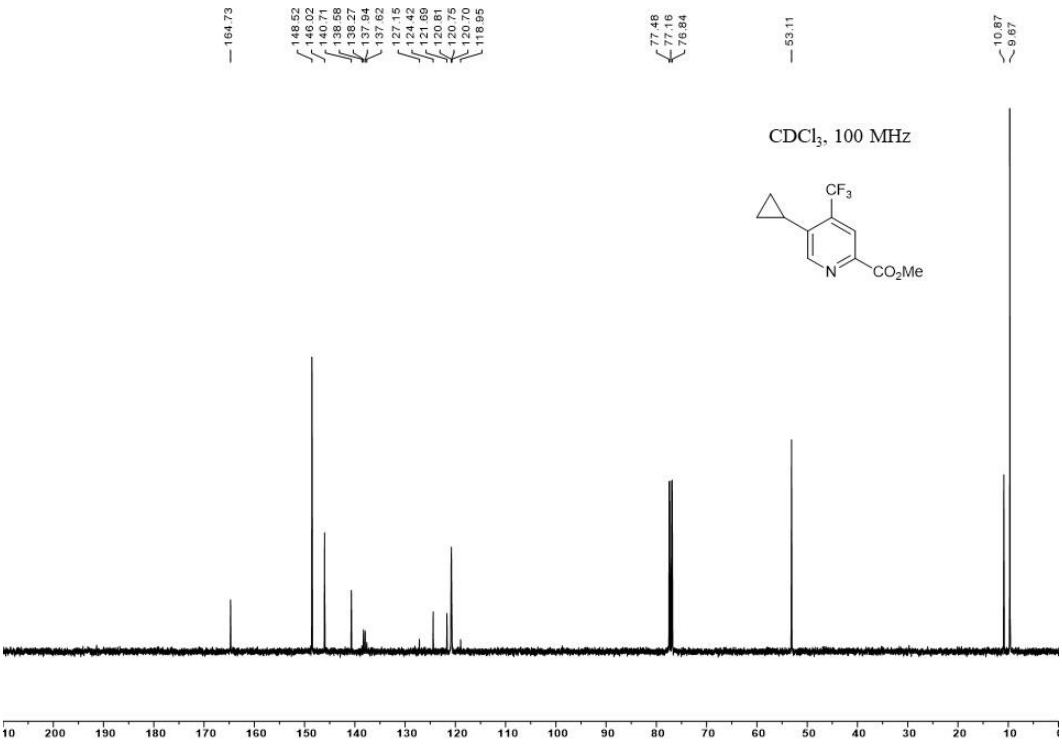

-63.14
-110.89
CDCl3, 376 MHz
F
O
CF3
N
O
Me
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

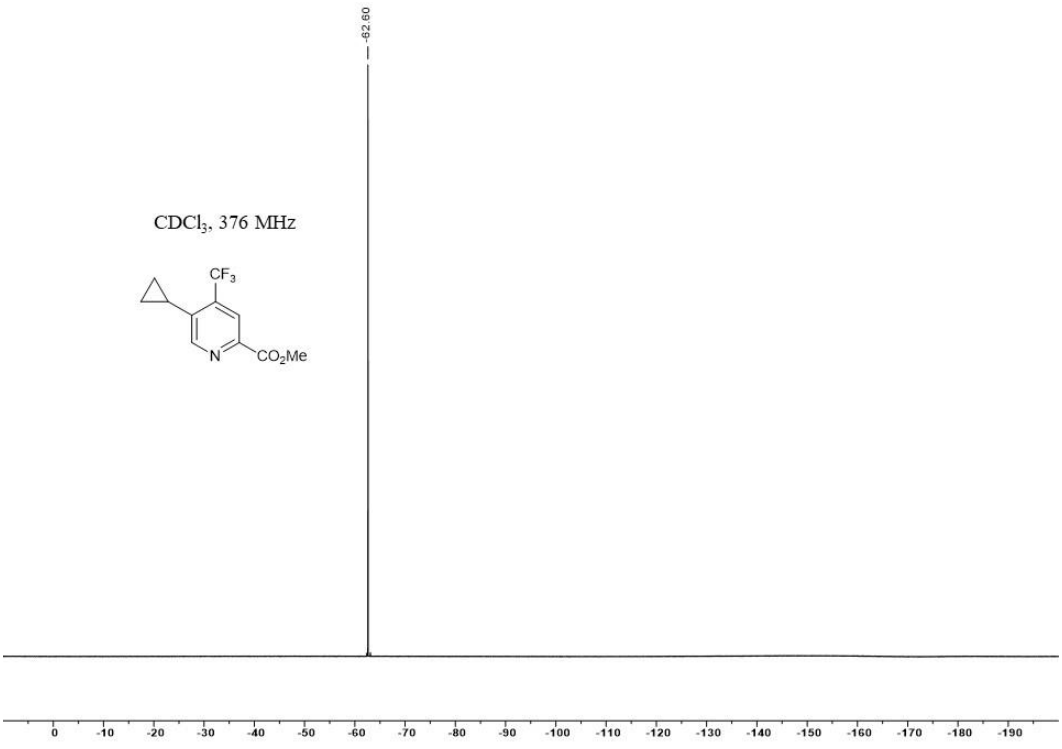

9.00
7.49
7.26
3.96
2.69
CDCl3, 400 MHz
CF3
CO2Me
Me
N
1.00
1.01
3.24
3.29

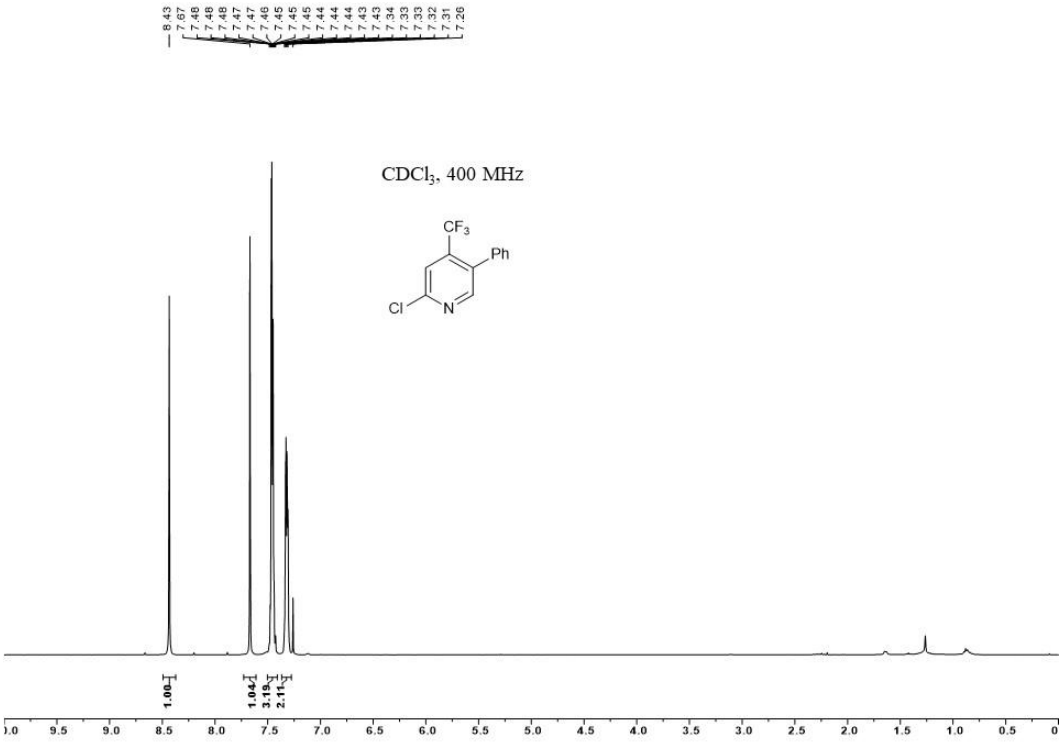

165.19
163.59
151.53
137.60
137.26
136.93
136.59
126.35
123.62
122.33
122.31
122.30
122.28
120.90
120.04
119.99
119.93
119.88
77.46
77.16
76.84
53.09
24.90
CDCl3, 100 MHz
CF3
CO2Me
Me
N

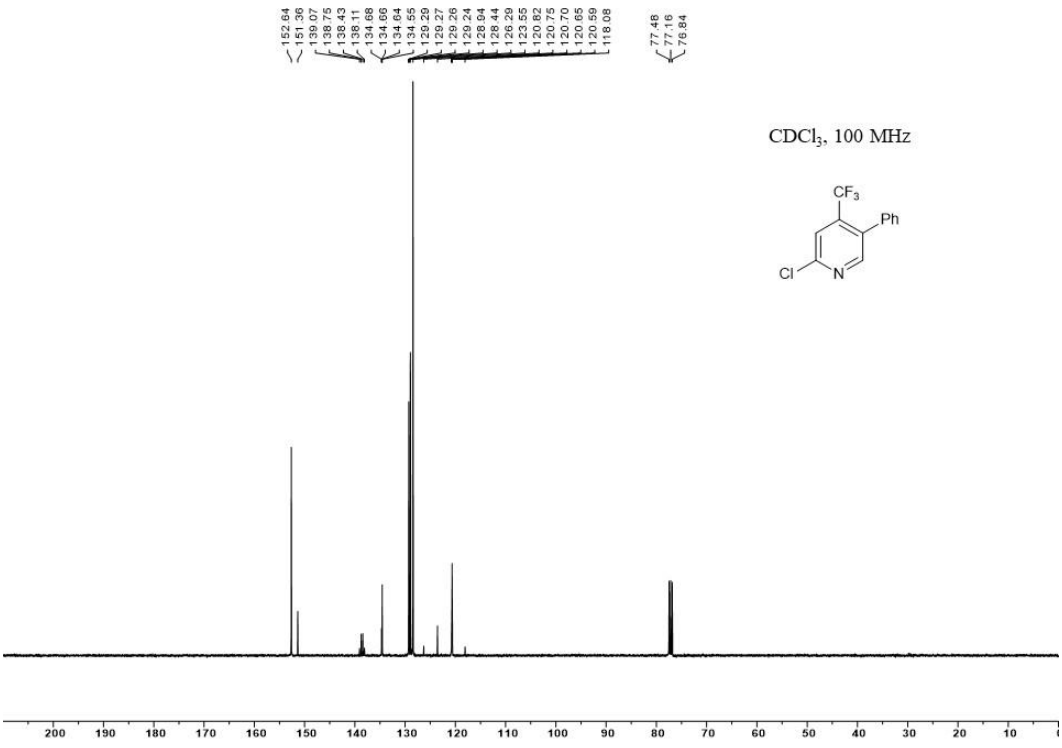

-61.98
CDCl3, 376 MHz
CF3
CO2Me
Me
N
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

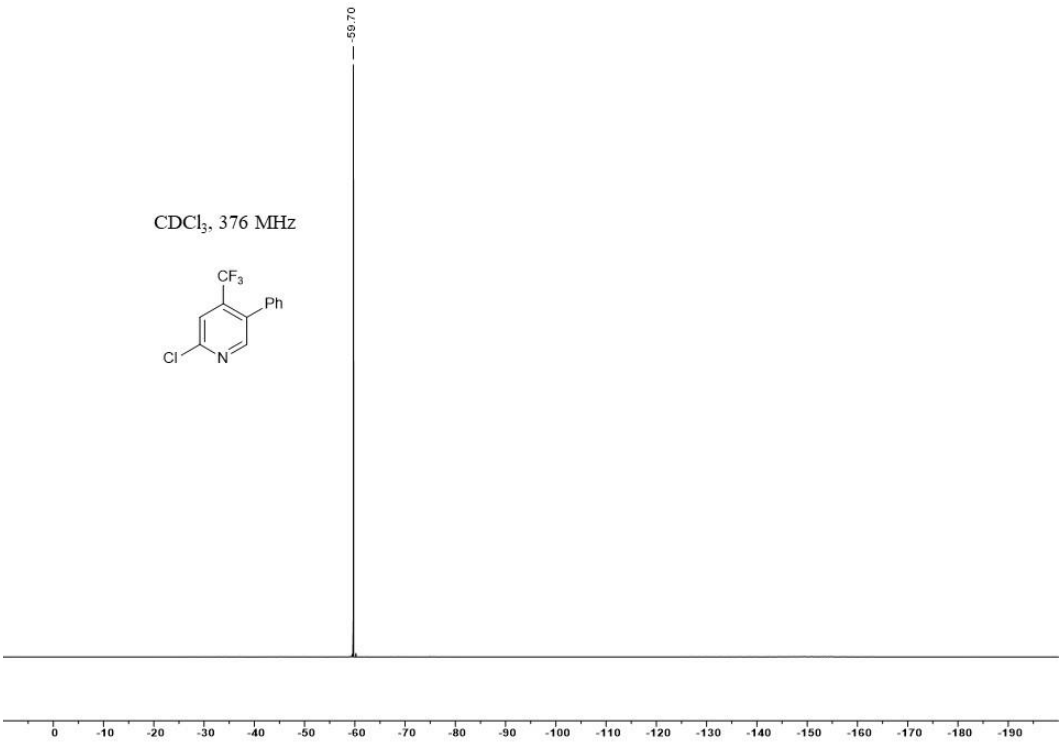

8.44
8.29
7.26
4.02
2.25
2.24
2.24
2.23
2.23
2.22
2.22
2.22
2.21
2.20
2.19
2.19
1.25
1.24
1.23
1.23
1.22
1.21
1.21
1.20
0.69
0.68
0.67
0.67
CDCl3, 400 MHz
CF3
N
CO2Me
1.00
0.93
3.00
0.96
2.10
2.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

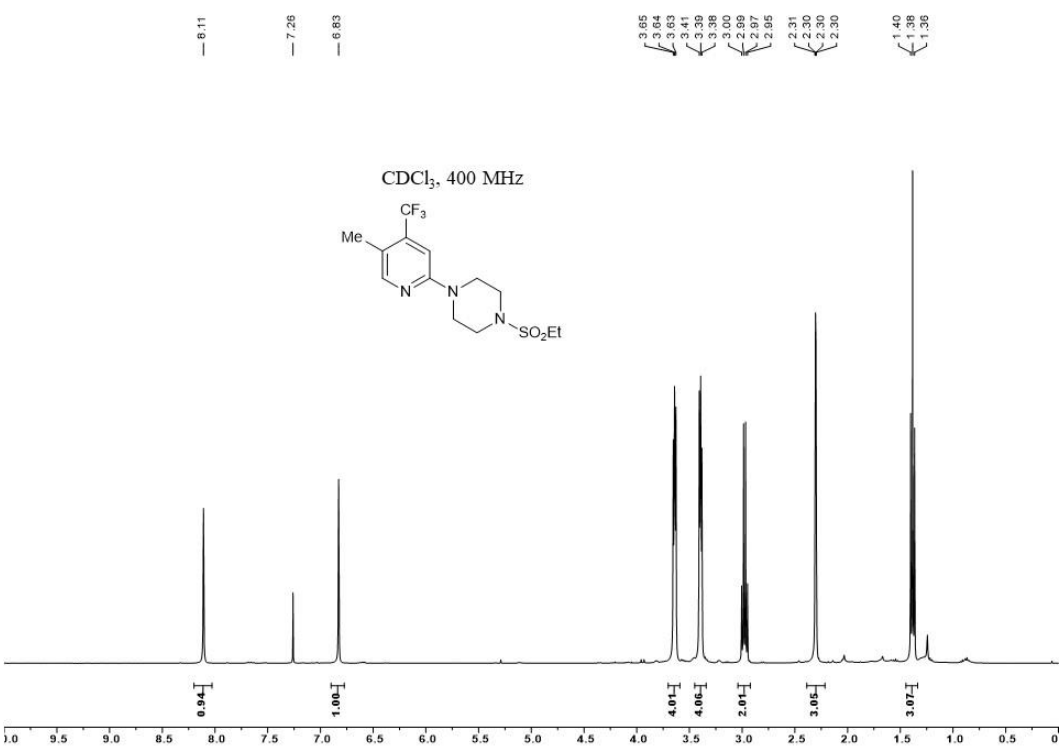

164.73
148.52
146.02
140.71
138.58
138.27
137.94
137.62
127.15
124.42
121.69
120.81
120.75
120.70
118.95
77.46
77.16
76.84
53.11
10.87
9.67
CDCl3, 100 MHz
CF3
N
CO2Me
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

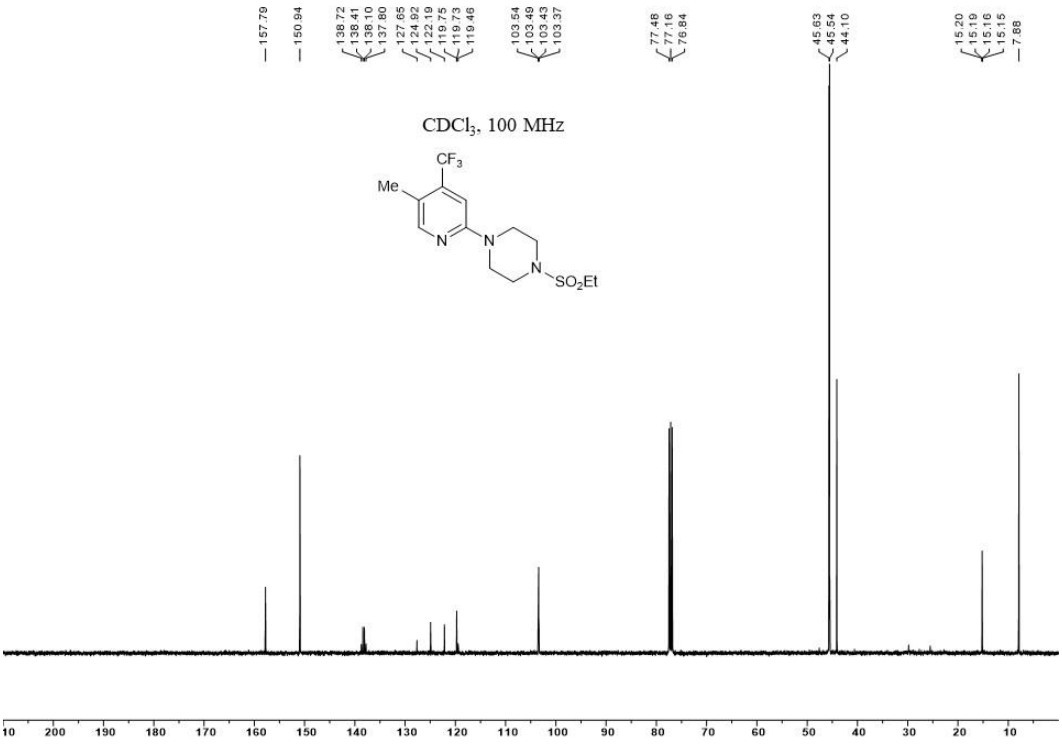

-62.60
CDCl3, 376 MHz
CF3
N
CO2Me
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

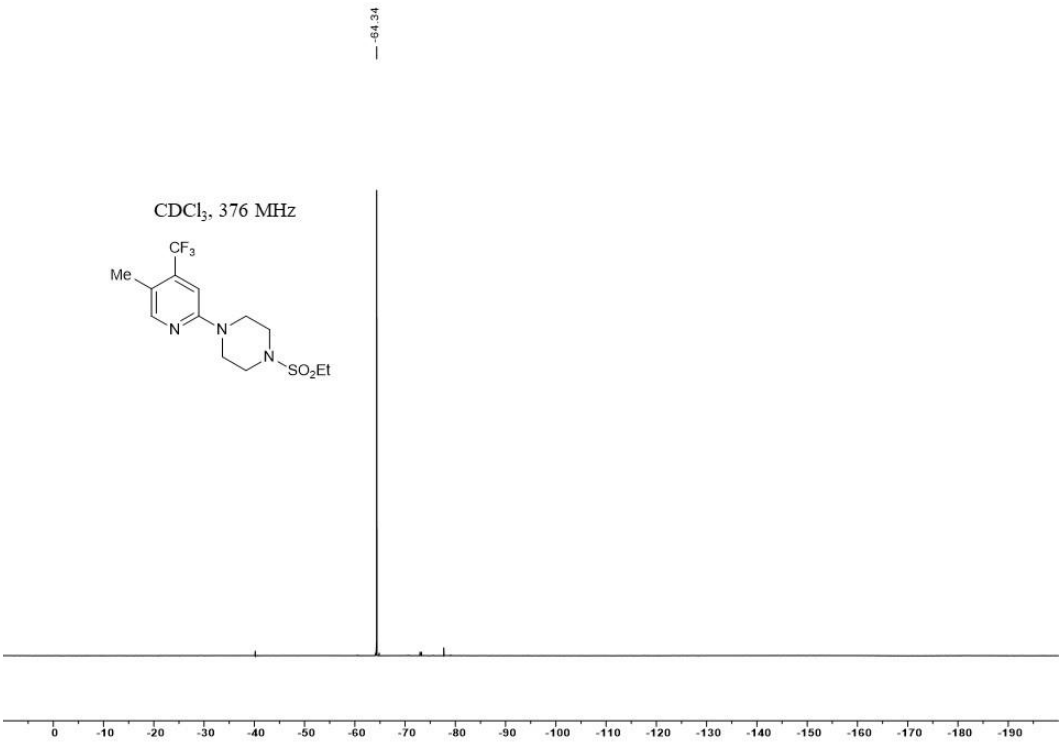

8.43
7.67
7.48
7.48
7.48
7.48
7.47
7.47
7.46
7.45
7.45
7.44
7.44
7.44
7.43
7.43
7.34
7.33
7.33
7.32
7.31
7.26
CDCl3, 400 MHz
CF3
Ph
Cl
N
1.00
1.04
3.19
2.11

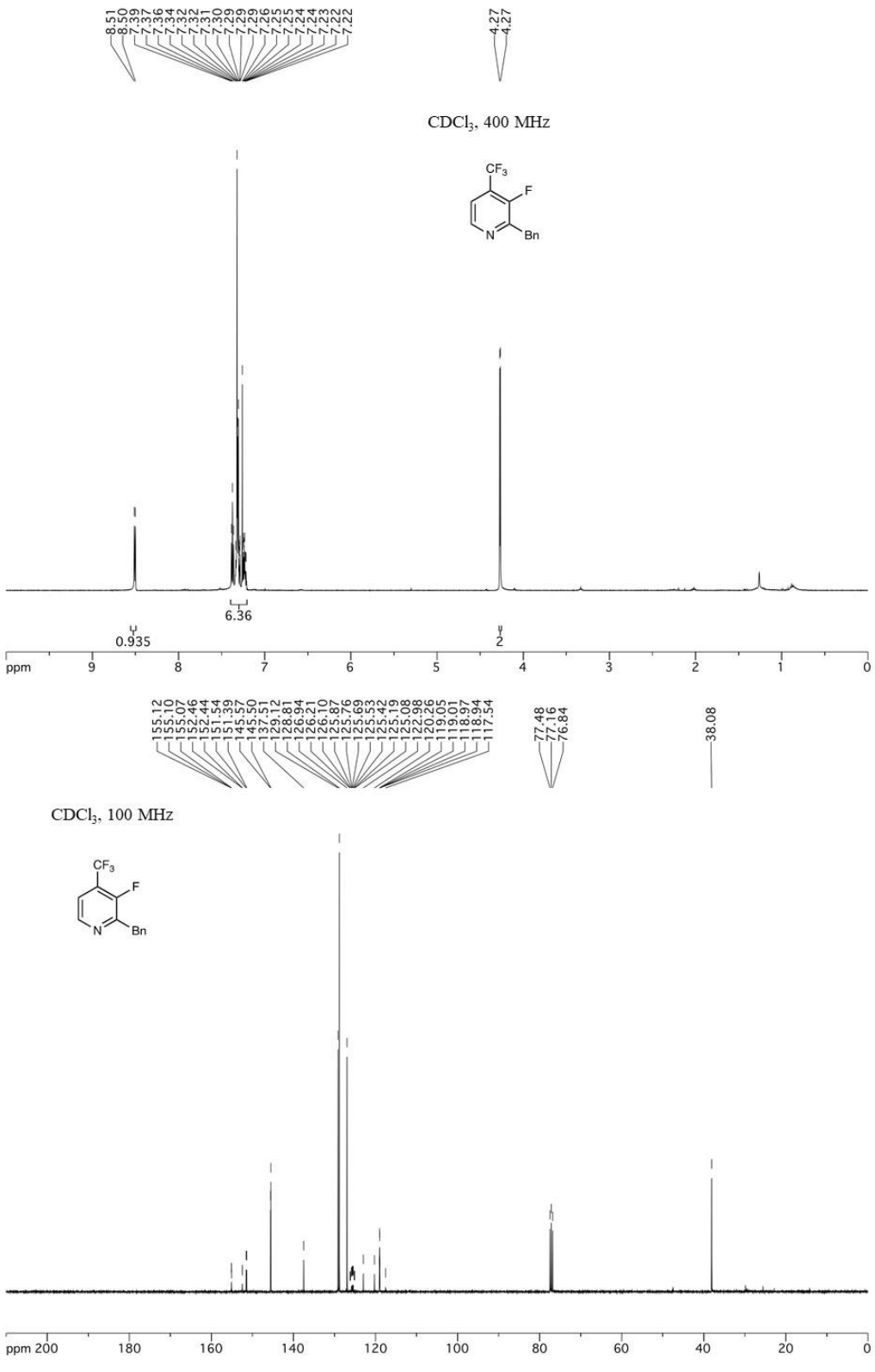

152.64
151.36
139.07
138.75
138.43
138.11
134.68
134.66
134.64
134.55
129.29
129.27
129.26
129.24
128.94
128.44
126.29
123.55
120.82
120.75
120.70
120.65
120.59
118.08
77.46
77.16
76.84
CDCl3, 100 MHz
CF3
Ph
Cl
N

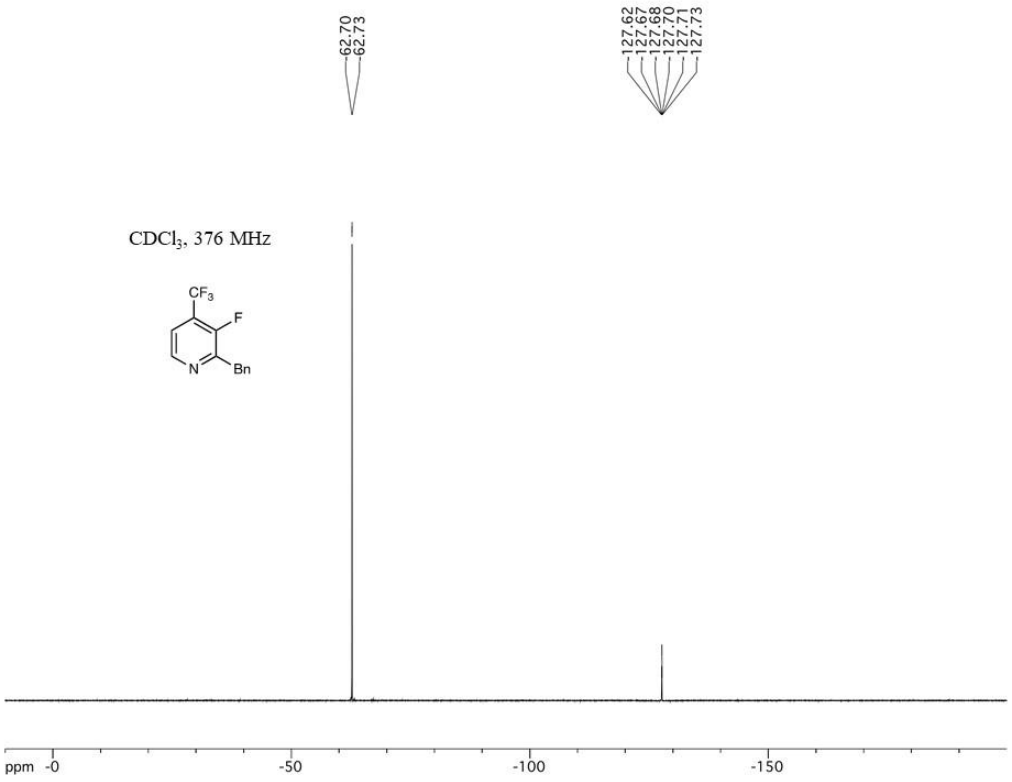

-59.70
CDCl3, 376 MHz
CF3
Ph
Cl
N
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

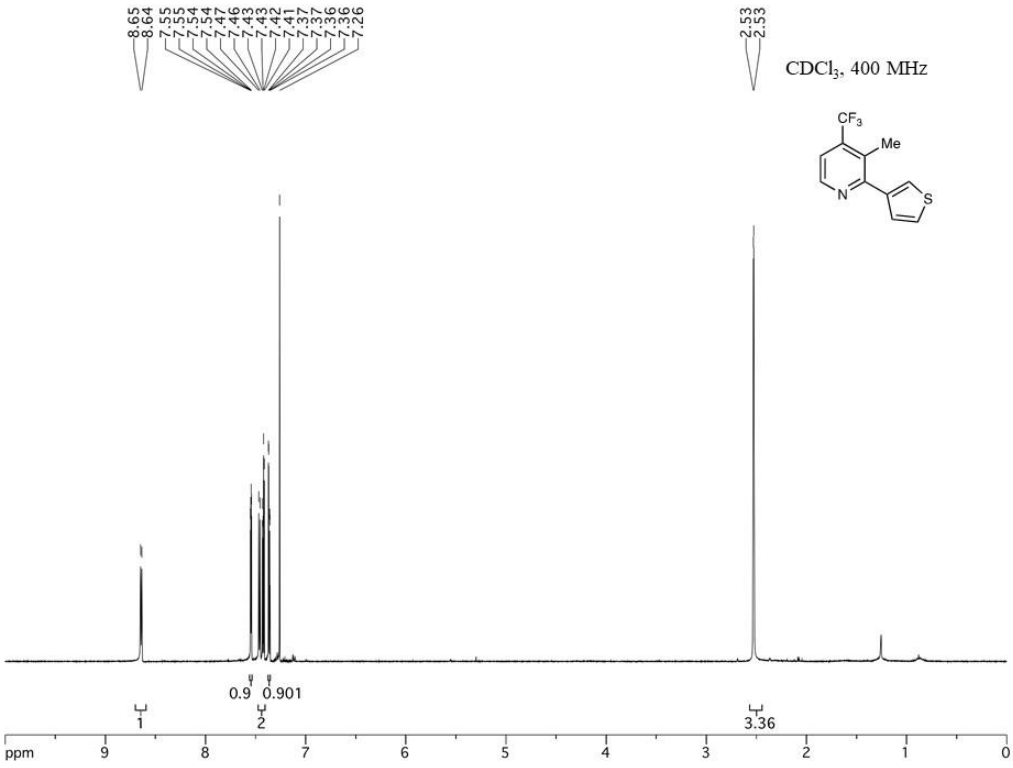

8.11
7.26
6.83
3.65
3.64
3.63
3.41
3.39
3.38
3.00
2.99
2.97
2.95
2.31
2.30
2.30
2.30
1.40
1.38
1.36
CDCl3, 400 MHz
CF3
Me
N
N
N
SO2Et
0.94
1.00
4.01
4.06
2.01
3.05
3.07
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

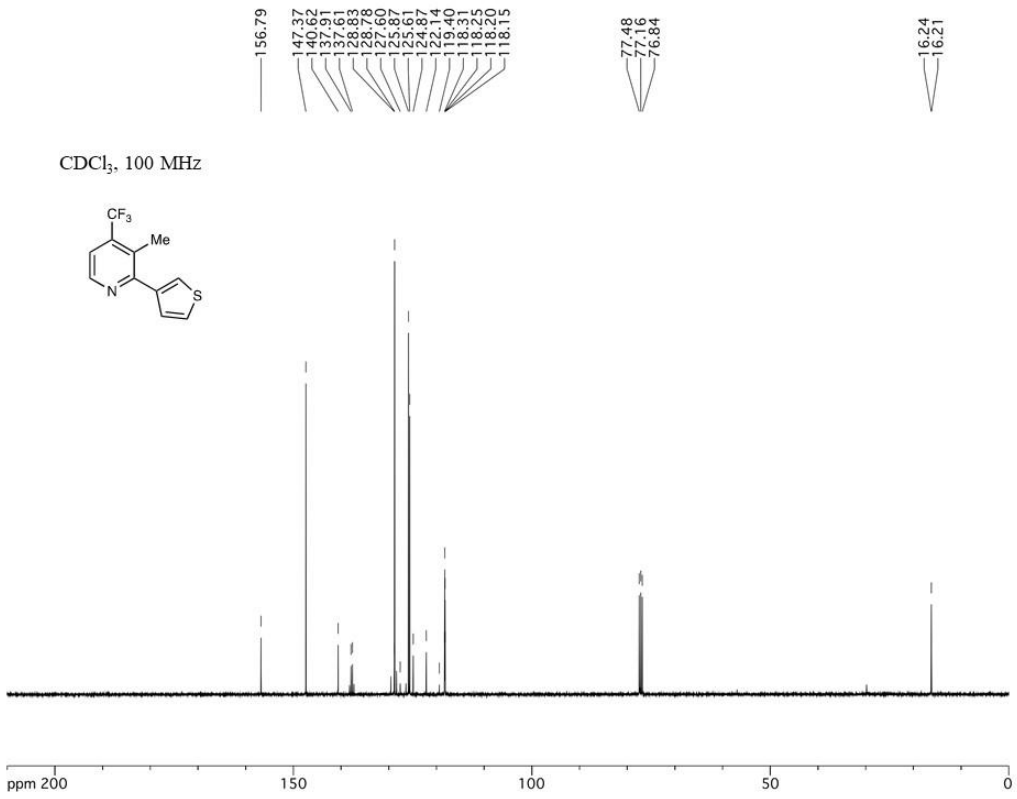

157.79
150.94
138.72
138.41
138.10
137.80
127.65
124.92
122.19
119.75
119.73
119.46
103.54
103.49
103.43
103.37
77.48
77.16
76.84
45.63
45.54
44.10
15.20
15.19
15.16
15.15
7.88
CDCl3, 100 MHz
CF3
Me
N
N
N
SO2Et
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

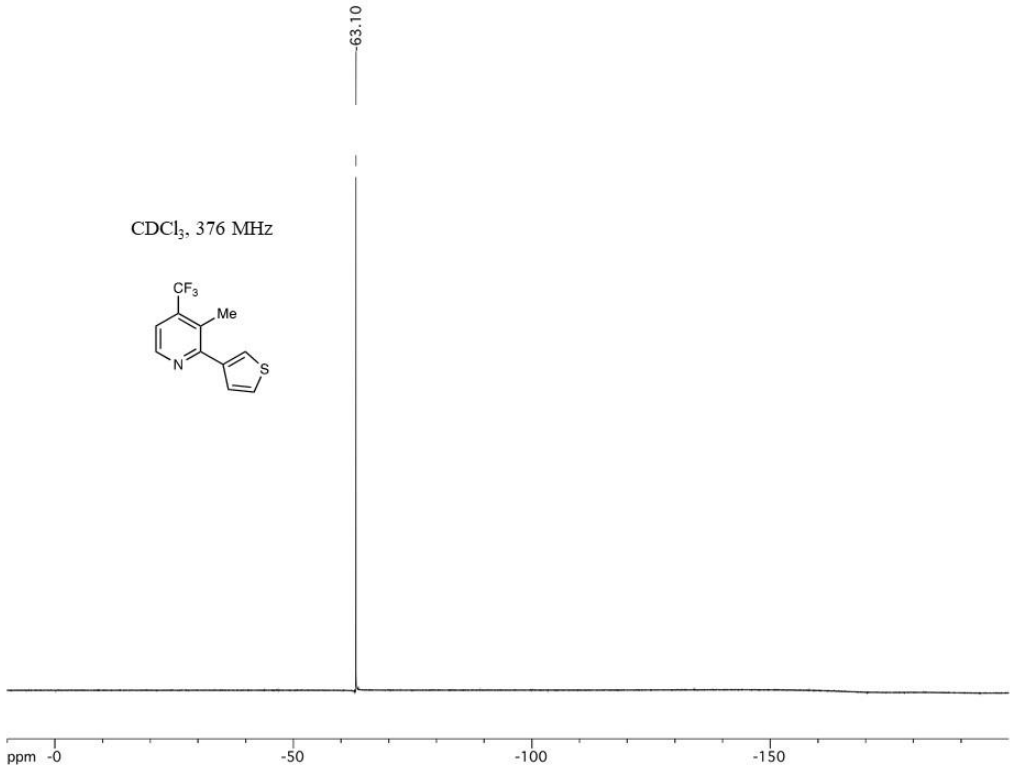

-64.34
CDCl3, 376 MHz
CF3
Me
N
N
N
SO2Et
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

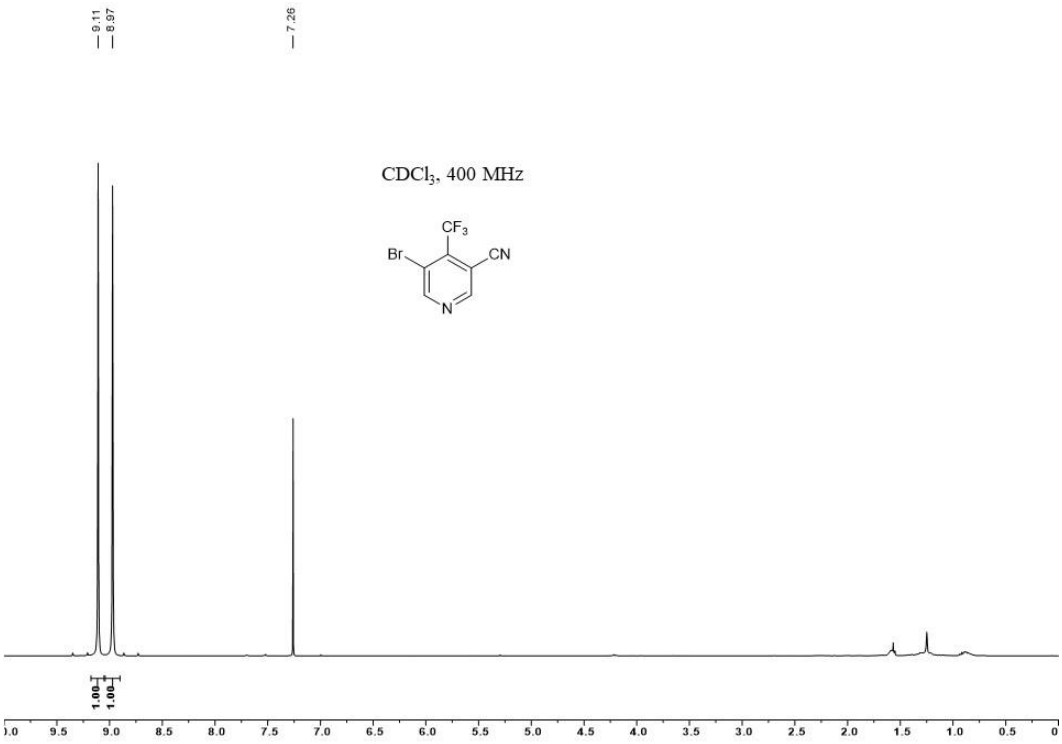

8.51
8.50
7.39
7.37
7.36
7.34
7.32
7.32
7.31
7.30
7.29
7.29
7.29
7.26
7.25
7.25
7.24
7.24
7.23
7.22
7.22
4.27
4.27
CDCl3, 400 MHz
CF3
F
N
Bn
6.36
0.935
2
ppm
9
8
7
6
5
4
3
2
1
0
155.12
155.10
155.07
155.04
152.46
152.44
151.54
151.39
145.57
145.50
137.51
129.12
128.81
126.94
126.21
126.10
125.87
125.76
125.69
125.53
125.42
125.19
125.08
122.98
120.26
119.05
119.01
118.97
118.94
117.54
77.48
77.16
76.84
38.08
CDCl3, 100 MHz
CF3
F
N
Bn
ppm 200
180
160
140
120
100
80
60
40
20
0

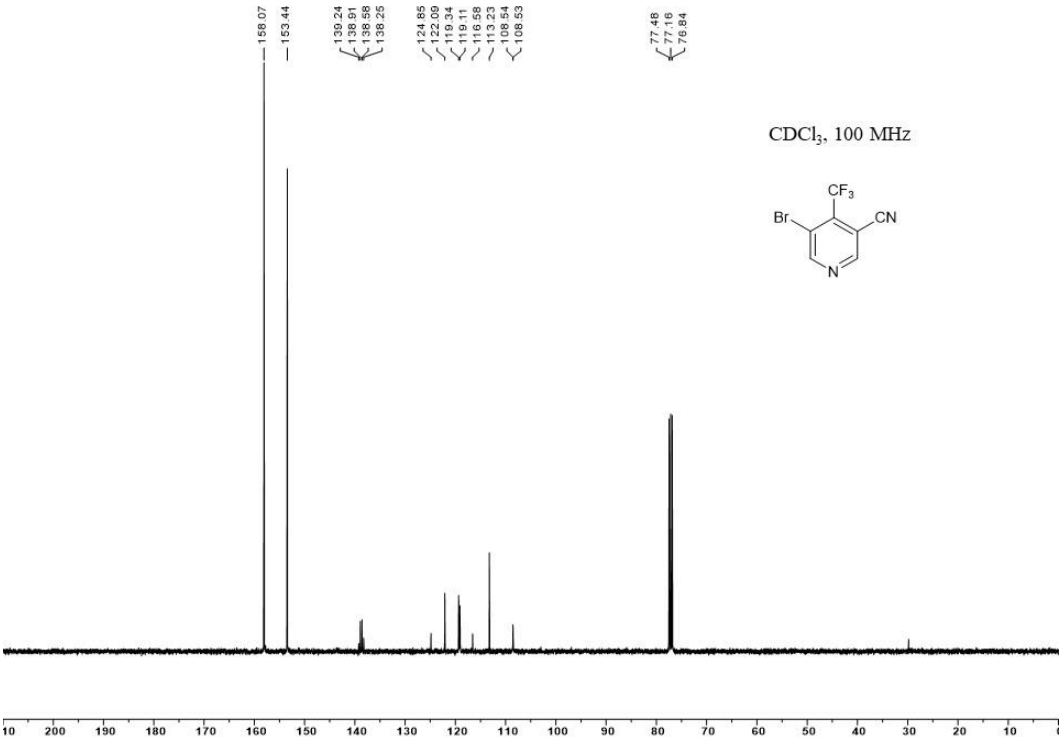

62.70
62.73
127.62
127.67
127.68
127.70
127.71
127.73
CDCl3, 376 MHz
CF3
F
N
Bn
ppm -0
-50
-100
-150

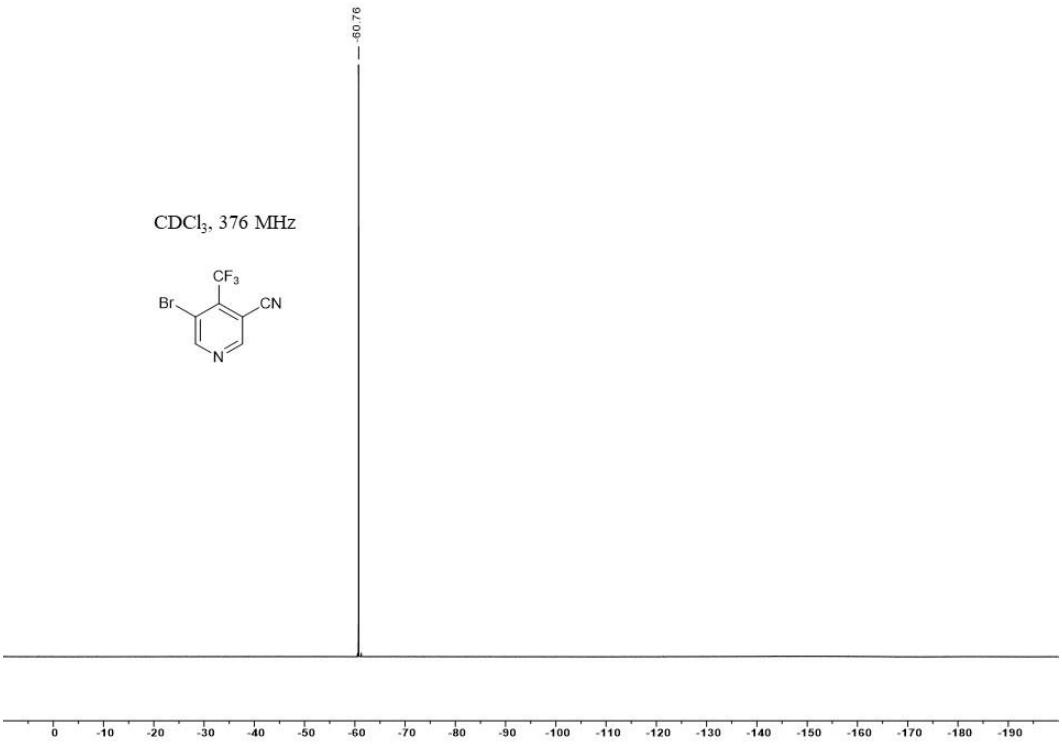

8.65
8.64
7.55
7.54
7.54
7.47
7.46
7.43
7.42
7.41
7.37
7.37
7.36
7.36
7.26
2.53
2.53
CDCl3, 400 MHz
CF3
Me
N
S
0.9
0.901
1
2
3.36
ppm 9
8
7
6
5
4
3
2
1
0

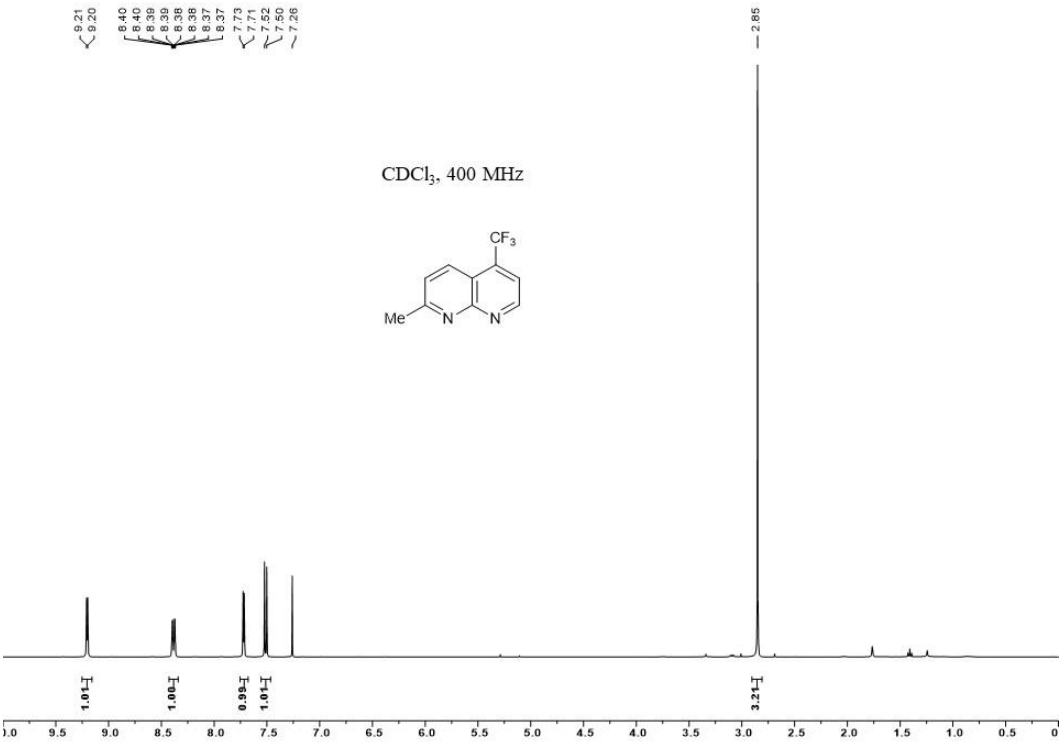

156.79
147.37
140.62
137.91
137.61
128.83
128.78
127.60
125.87
125.61
124.87
122.14
119.40
118.31
118.25
118.20
118.15
77.48
77.16
76.84
16.24
16.21
CDCl3, 100 MHz
CF3
Me
N
S
ppm 200
150
100
50
0

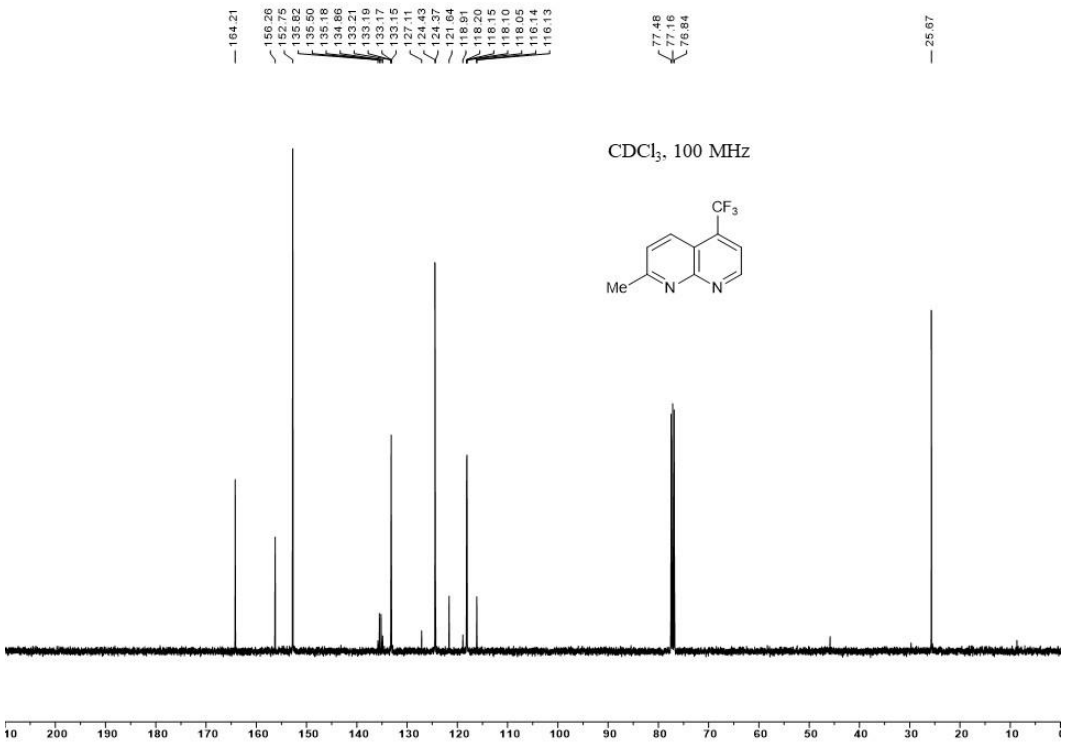

63.10
CDCl3, 376 MHz
CF3
Me
N
S
ppm -0
-50
-100
-150

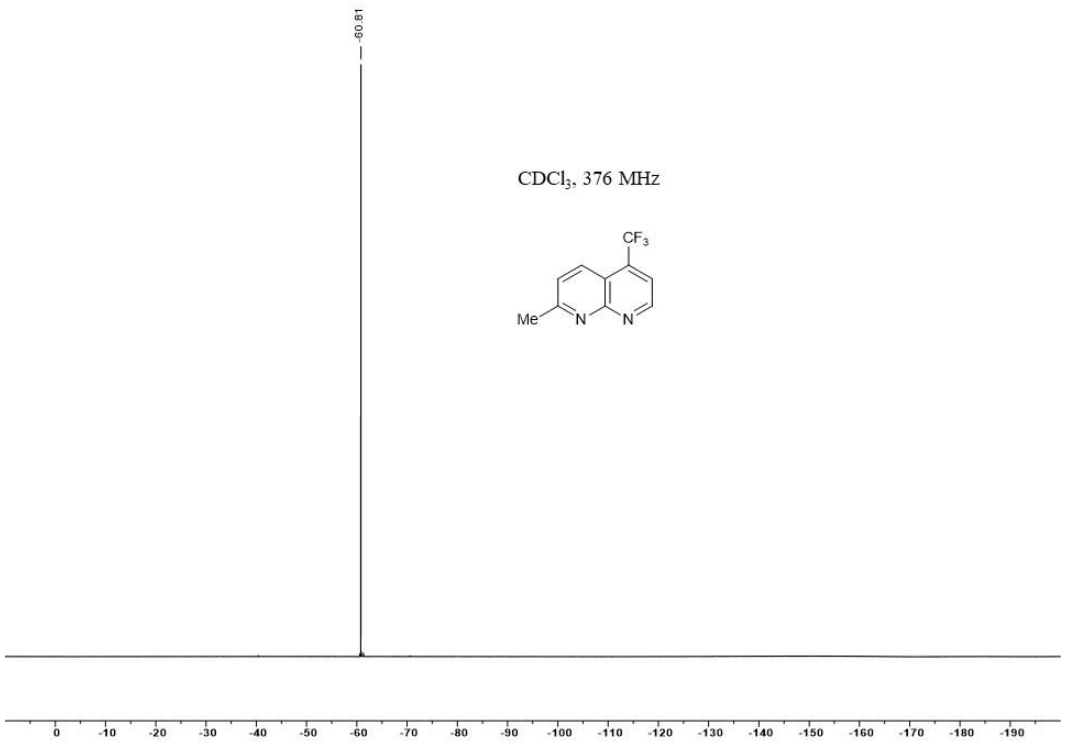

9.11
8.97
7.26
CDCl3, 400 MHz
CF3
Br
CN
N
1.00
1.00


158.07
153.44
139.24
138.91
138.58
138.25
124.85
122.09
119.34
119.11
116.58
113.23
108.54
108.53
77.46
77.16
76.84
CDCl3, 100 MHz
CF3
Br
CN
N

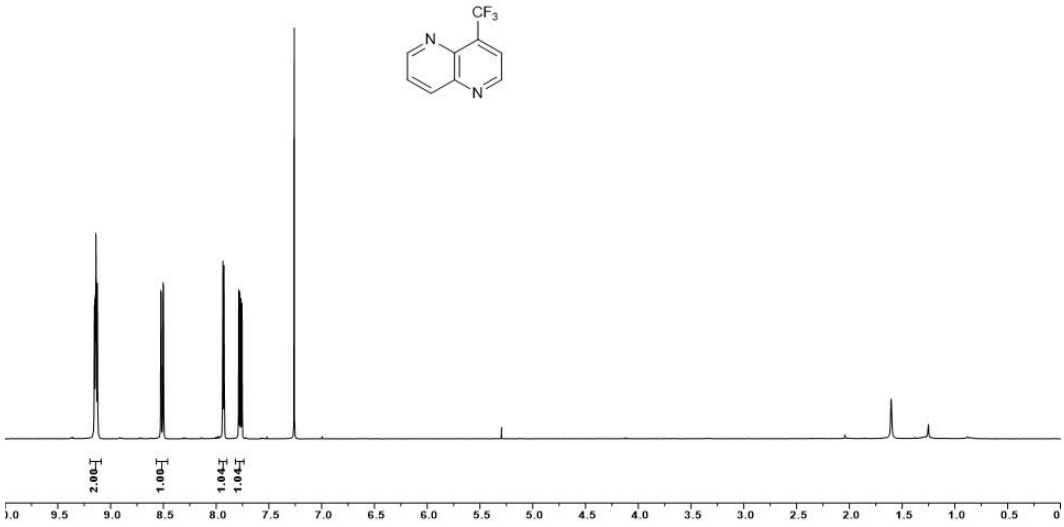

-60.76
CDCl3, 376 MHz
CF3
Br
CN
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190


9.21
9.20
8.40
8.40
8.39
8.39
8.38
8.38
8.37
8.37
7.73
7.71
7.52
7.50
7.26
2.85
CDCl3, 400 MHz
CF3
Me
N
N
1.01
1.00
0.99
1.01
3.21
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

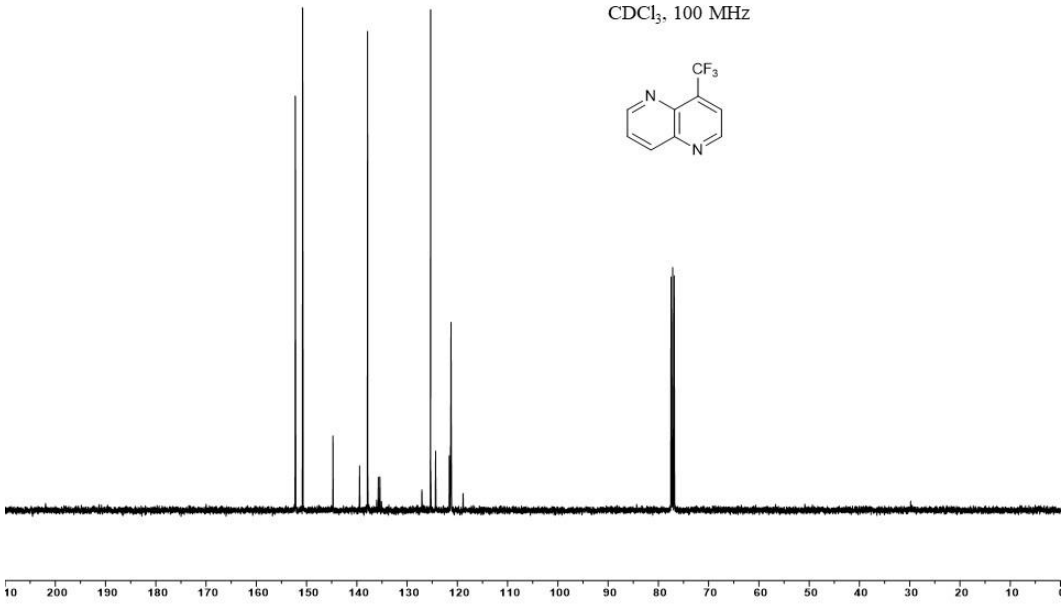

164.21
156.26
152.75
135.82
135.50
135.18
134.86
133.21
133.19
133.17
133.15
127.11
124.43
124.37
121.64
118.91
118.20
118.15
118.10
118.05
116.14
116.13
77.48
77.16
76.84
25.67
CDCl3, 100 MHz
CF3
Me
N
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

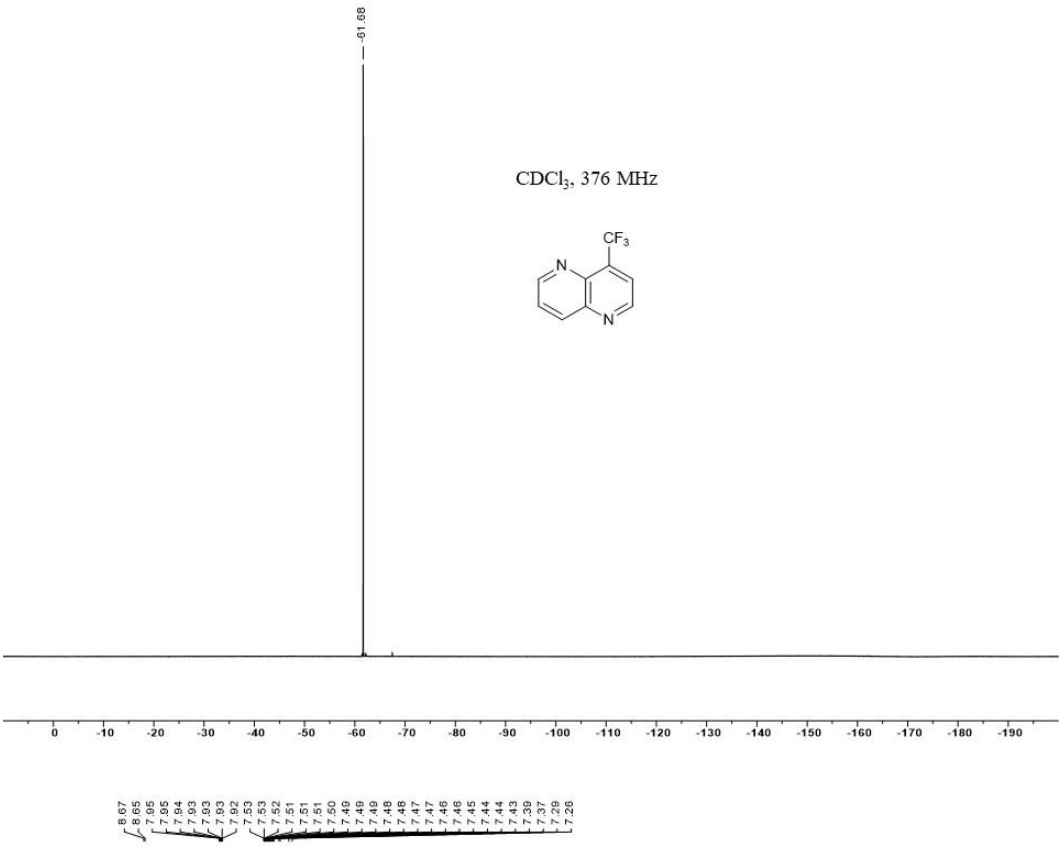

-60.61
CDCl3, 376 MHz
CF3
Me
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

$CDCl_3$, 400 MHz



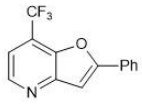
$CDCl_3$, 100 MHz

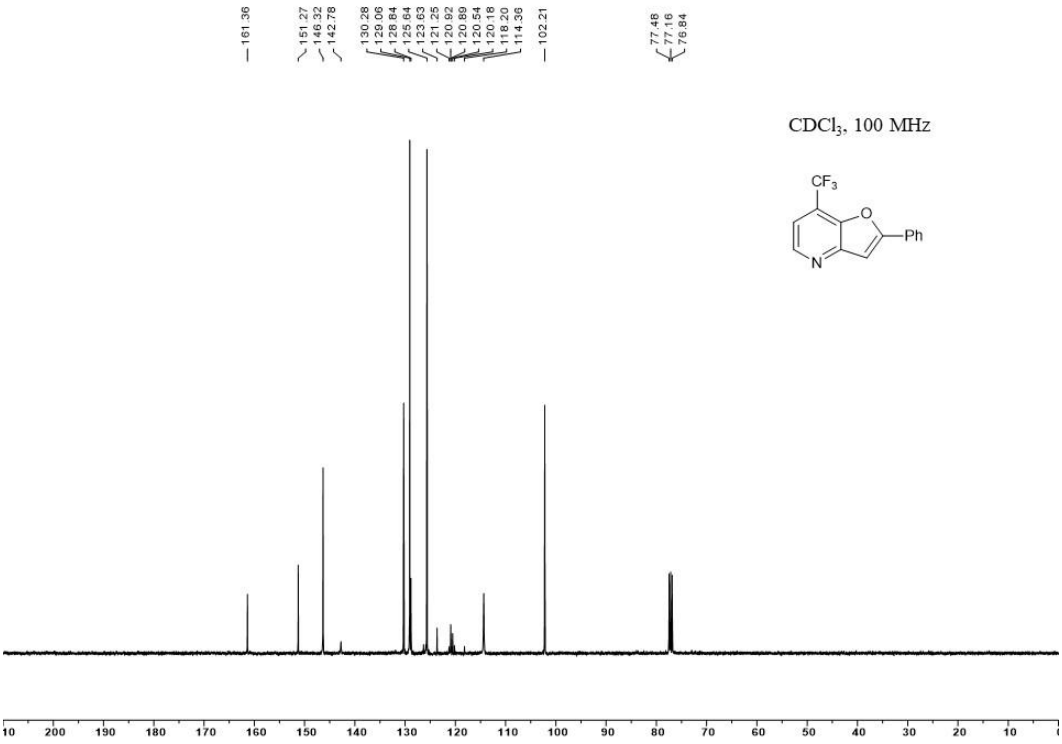


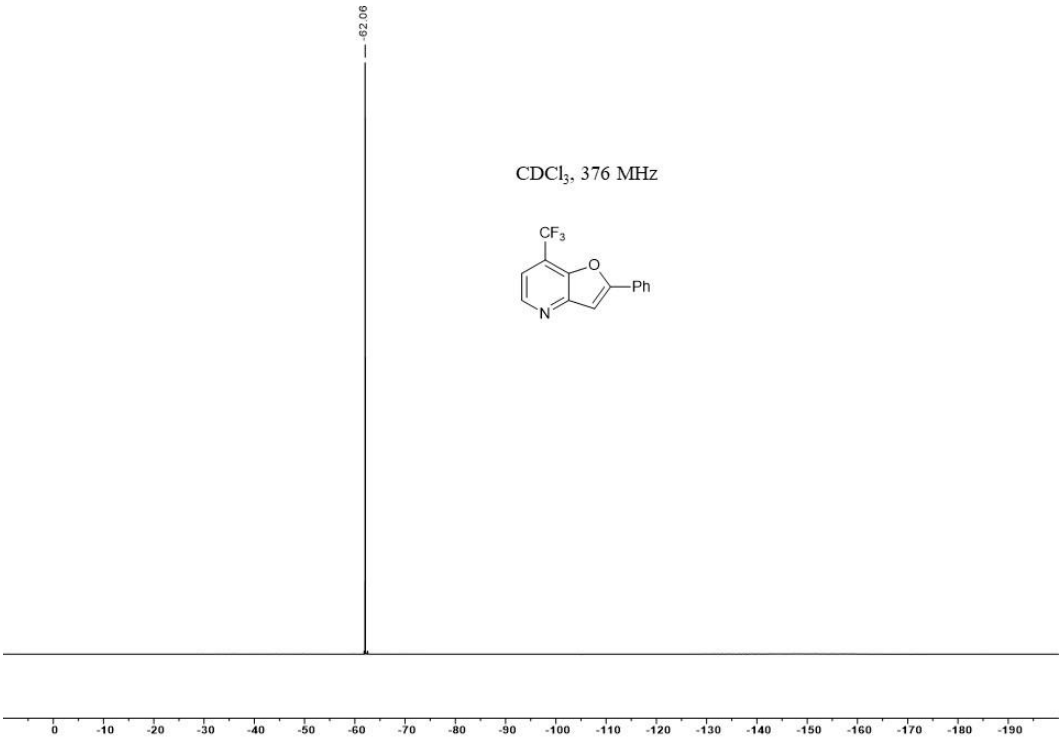


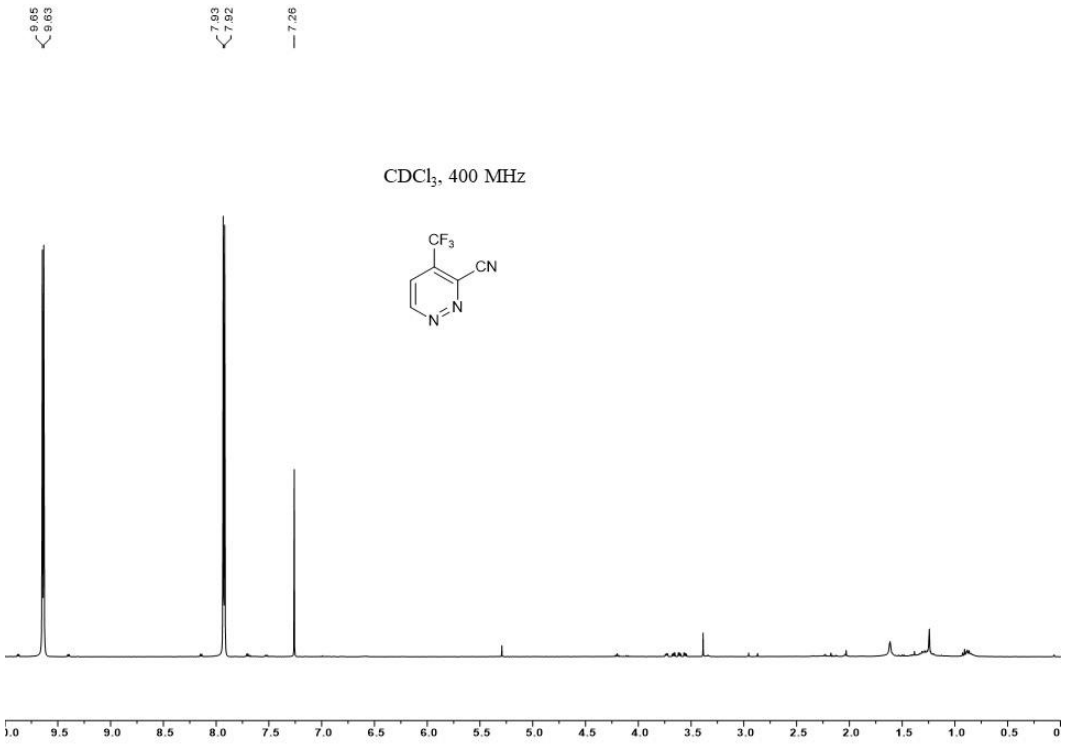
$CDCl_3$, 376 MHz

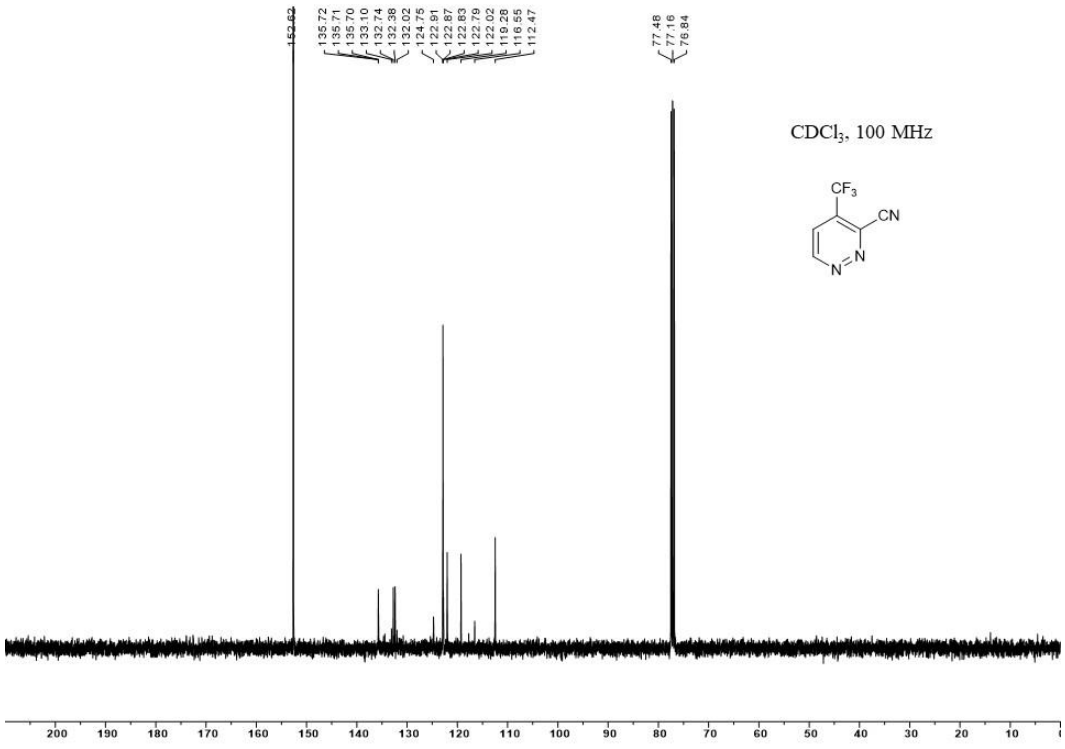
$CDCl_3$, 400 MHz

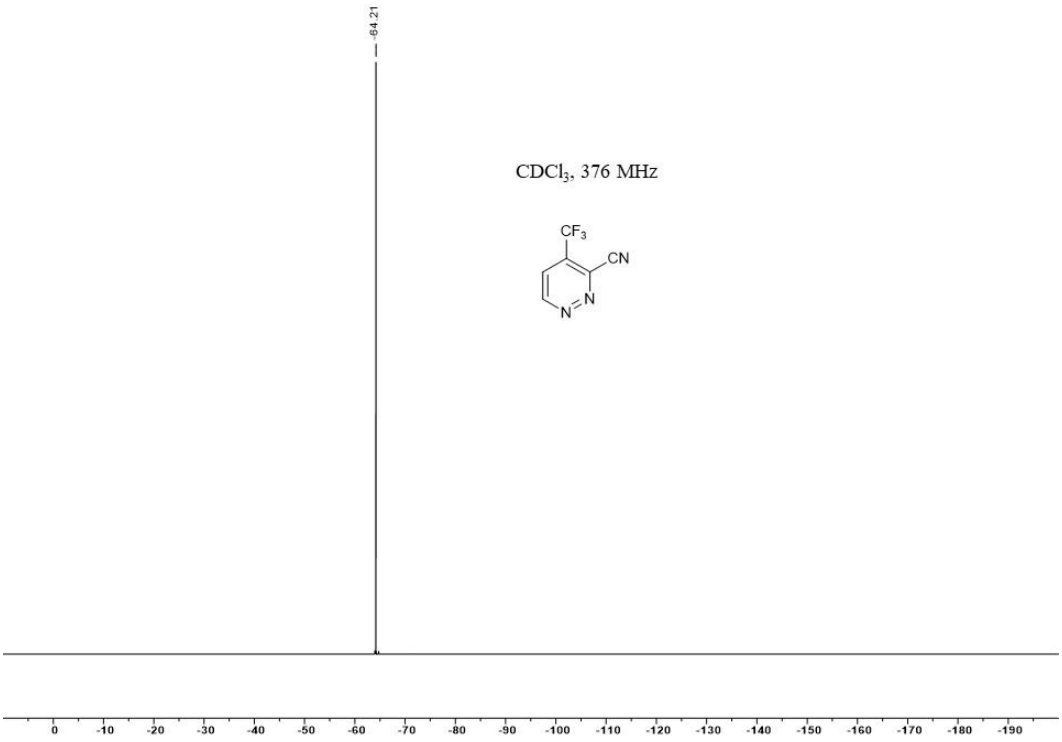


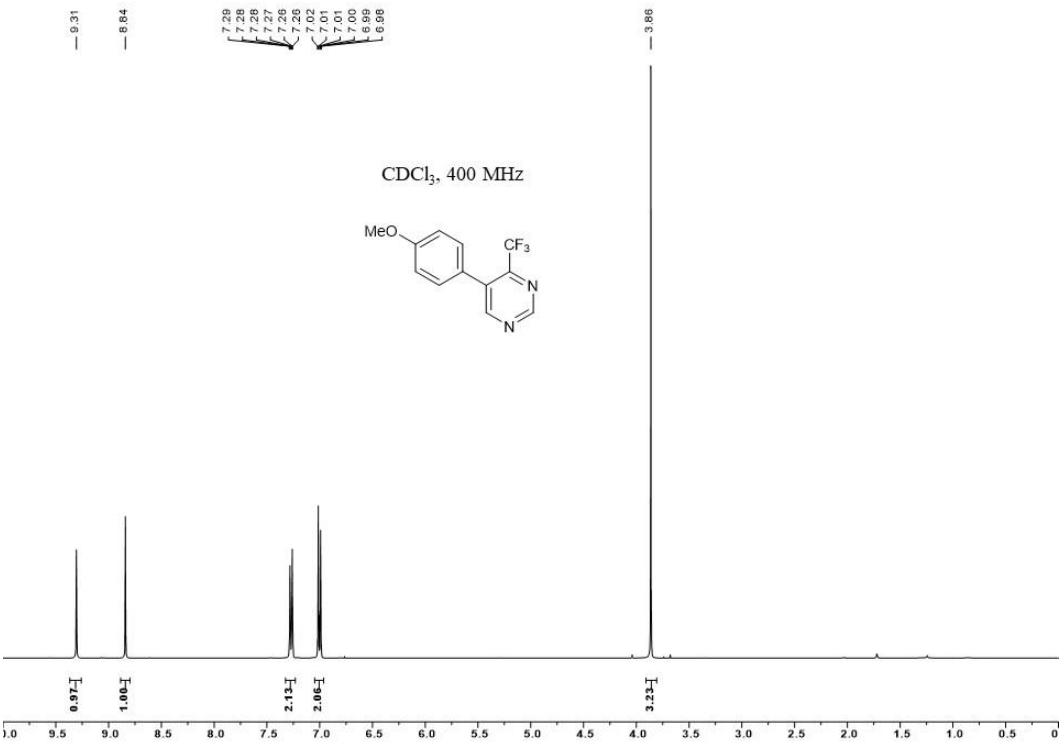

161.36
151.27
146.32
142.78
130.28
129.06
128.84
125.64
123.63
121.25
120.92
120.89
120.54
120.18
118.20
114.36
102.21
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
O
Ph
N

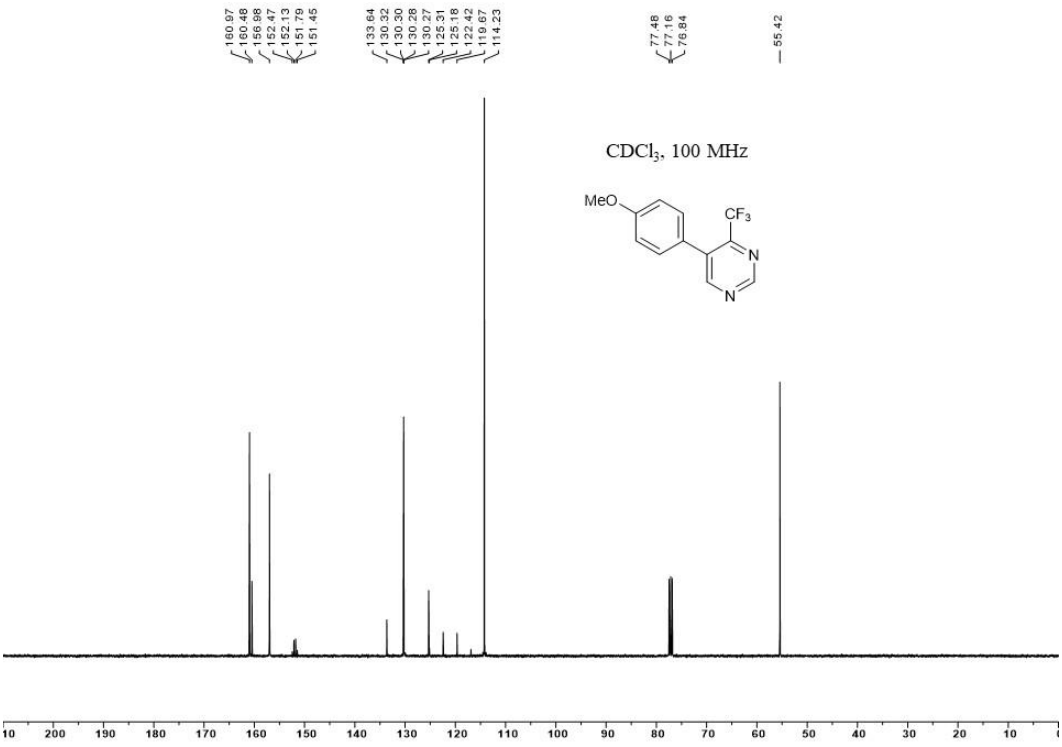

-62.06
CDCl3, 376 MHz
CF3
O
Ph
N

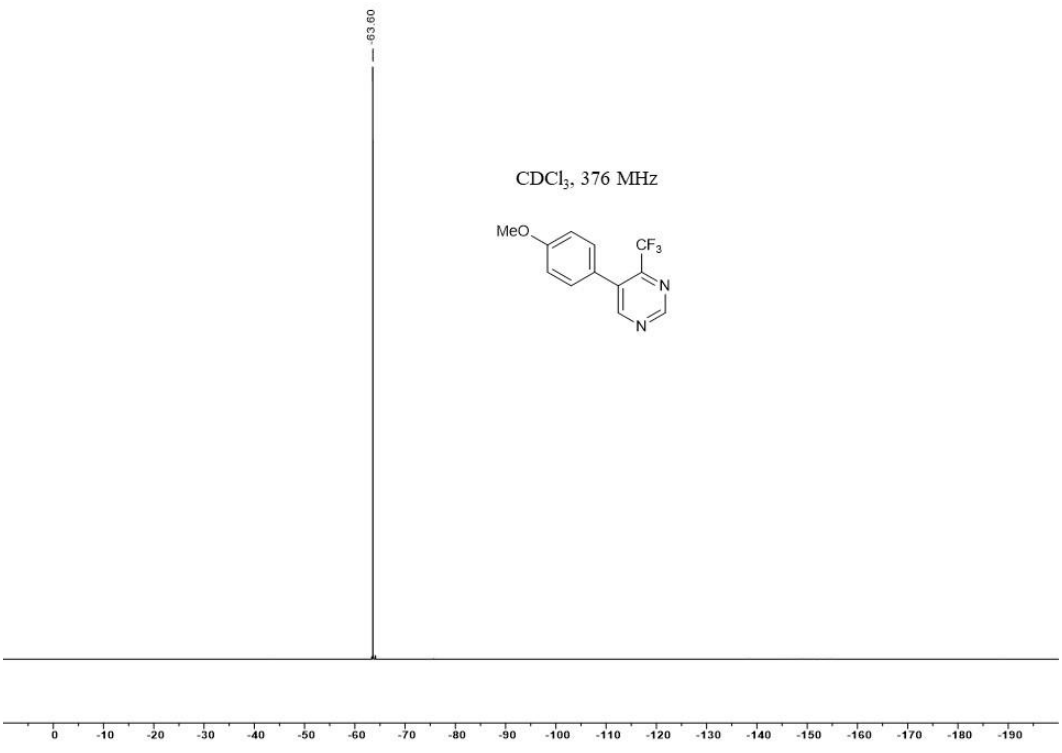

9.65
9.63
7.93
7.92
7.26
CDCl3, 400 MHz
CF3
CN
N
N

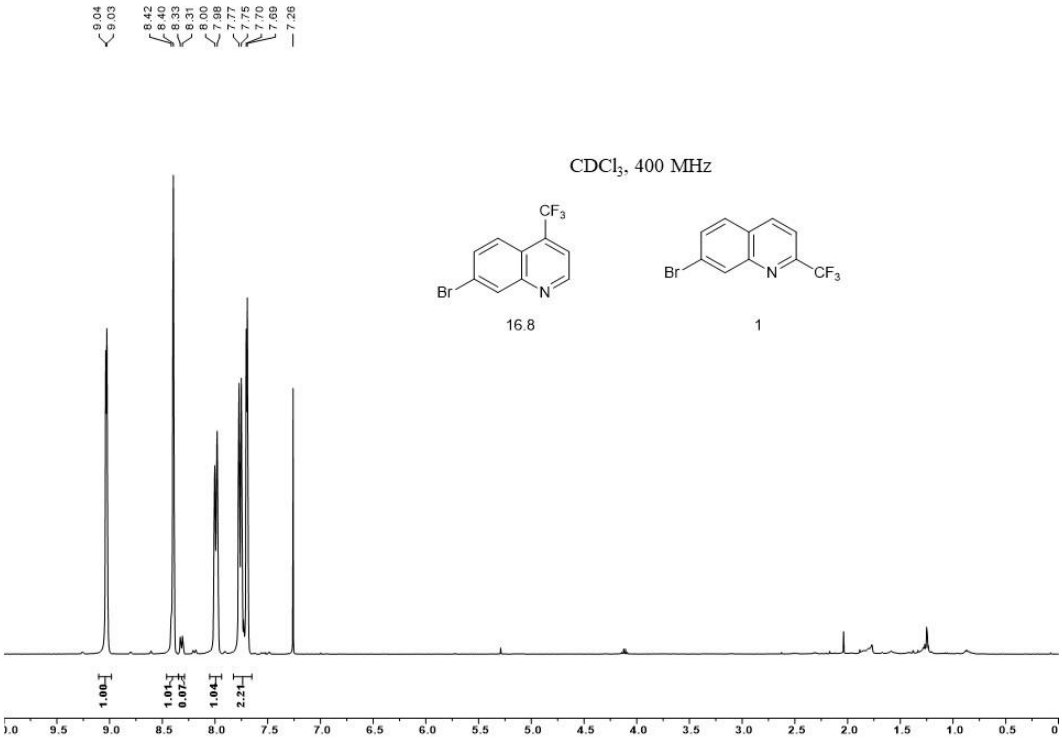

152.62
135.72
135.71
135.70
133.10
132.74
132.38
132.02
124.75
122.91
122.87
122.83
122.79
122.02
119.28
116.55
112.47
77.48
77.16
76.84
CDCl3, 100 MHz
CF3
CN
N
N

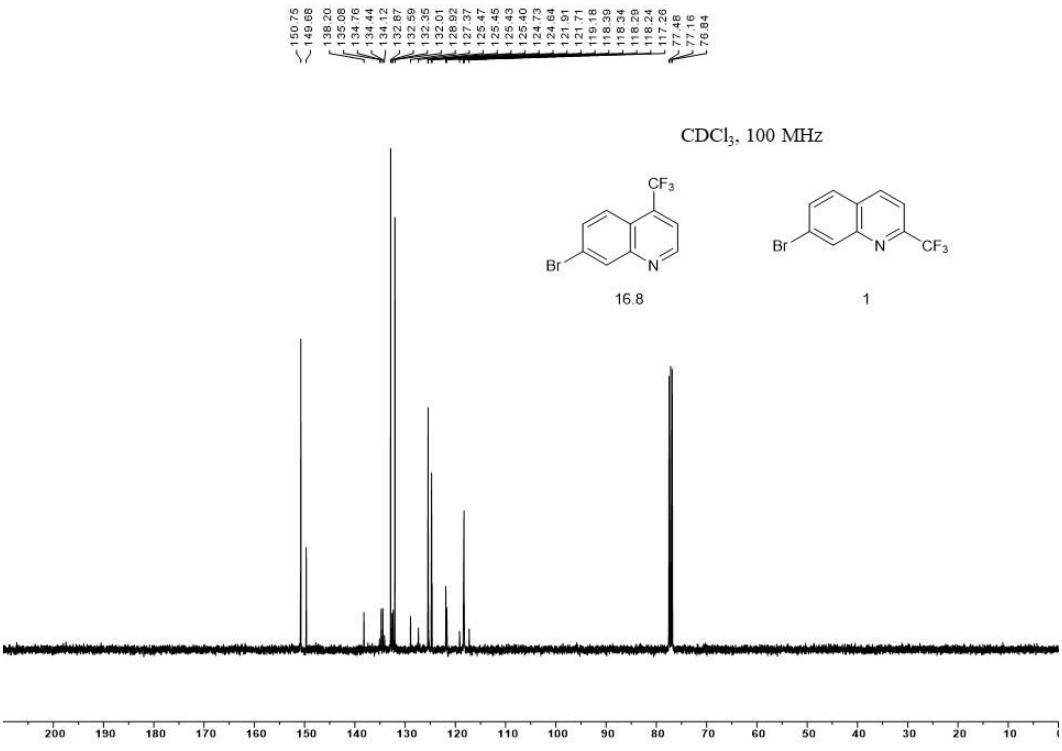

-64.21
CDCl3, 376 MHz
CF3
CN
N
N
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

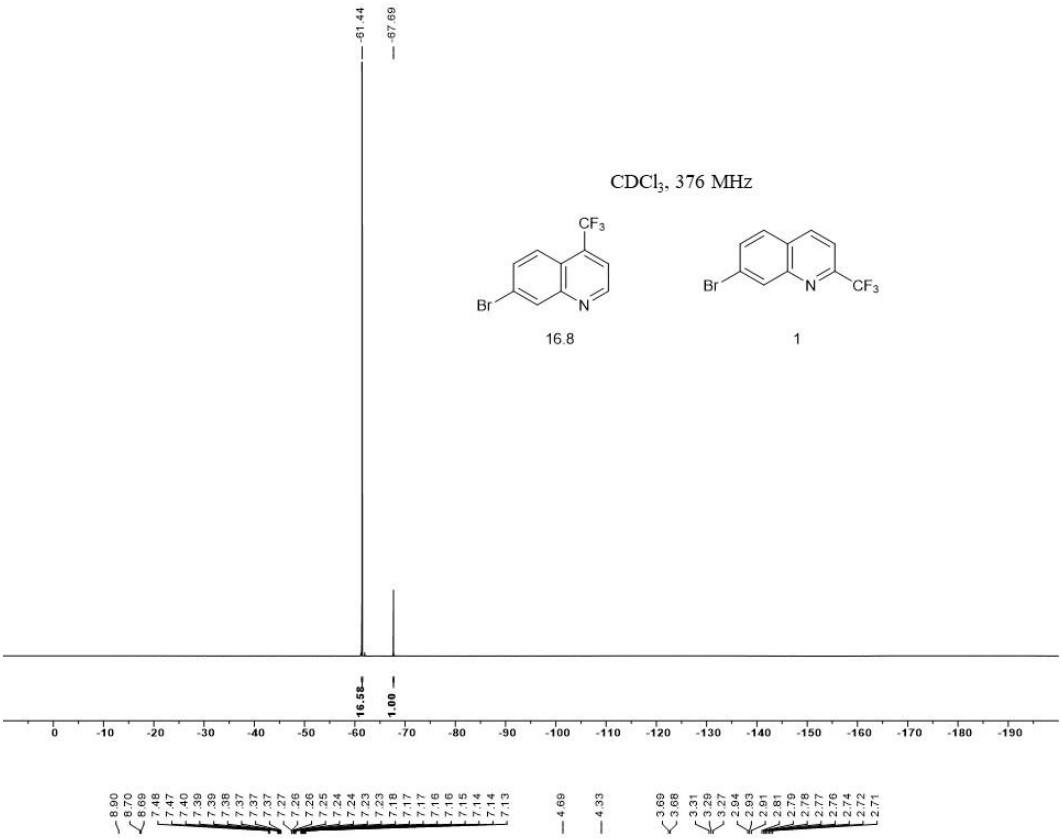

9.31
8.84
7.29
7.28
7.28
7.27
7.26
7.26
7.02
7.01
7.01
7.00
6.99
6.98
3.86
CDCl3, 400 MHz
MeO
CF3
N
N
0.97
1.00
2.13
2.06
3.23
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

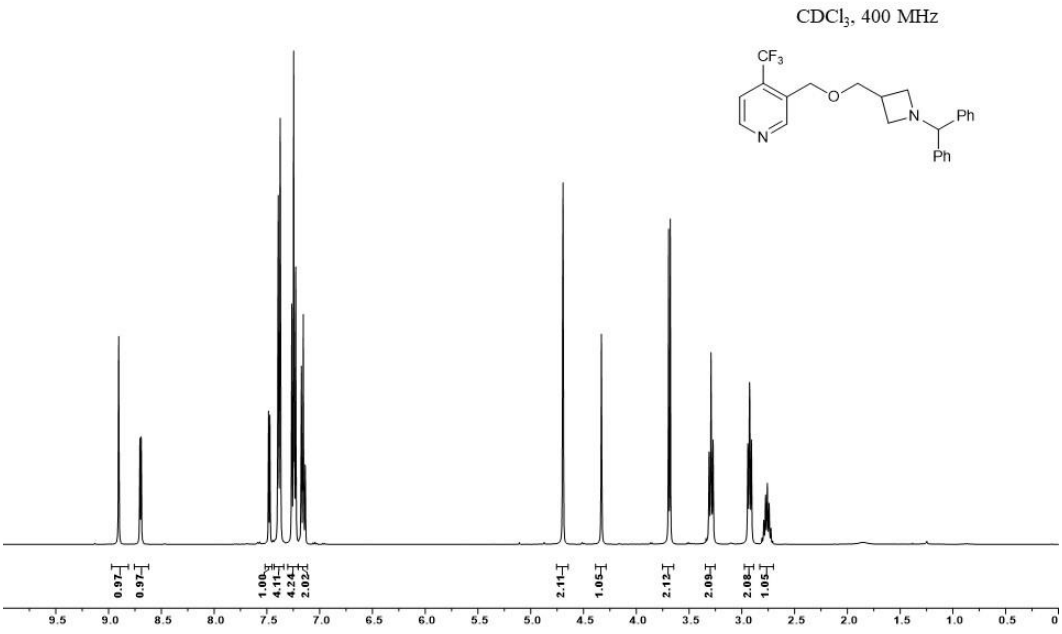

160.97
160.48
156.98
152.47
152.13
151.79
151.45
133.64
130.32
130.30
130.28
130.27
125.31
125.18
122.42
119.67
114.23
77.48
77.16
76.84
55.42
CDCl3, 100 MHz
MeO
CF3
N
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

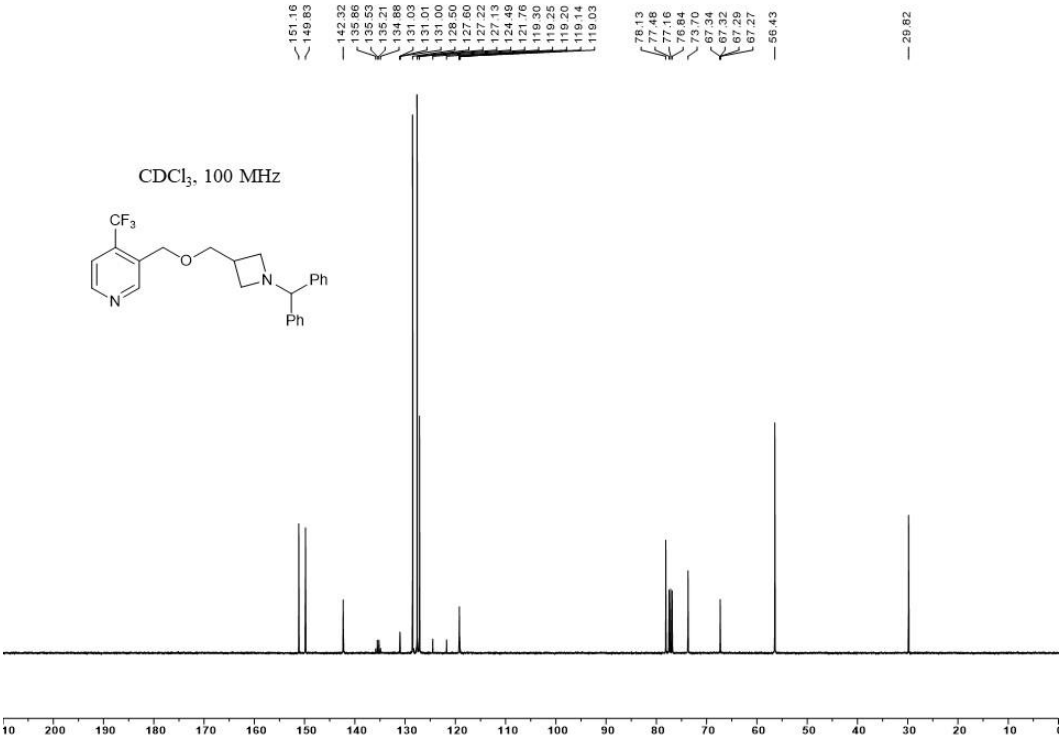

-63.60
CDCl3, 376 MHz
MeO
CF3
N
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

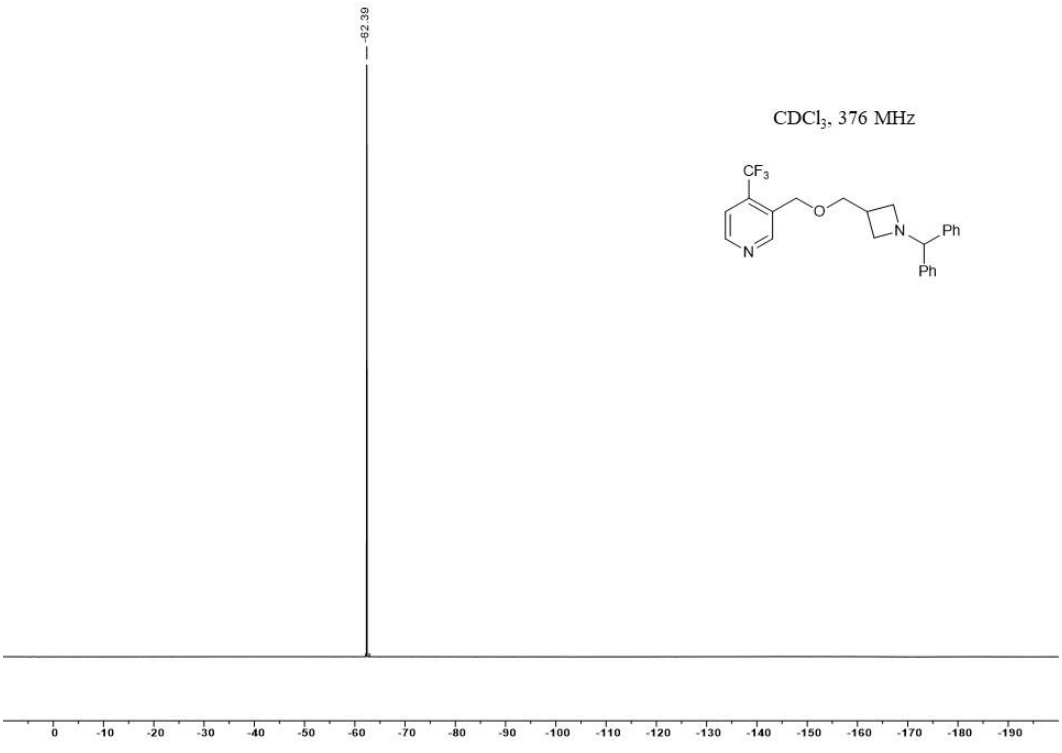

9.04
9.03
8.42
8.40
8.33
8.31
8.00
7.98
7.77
7.75
7.70
7.69
7.26
CDCl3, 400 MHz
CF3
Br
N
16.8
Br
N
CF3
1
1.00
1.01
0.07
1.04
2.21

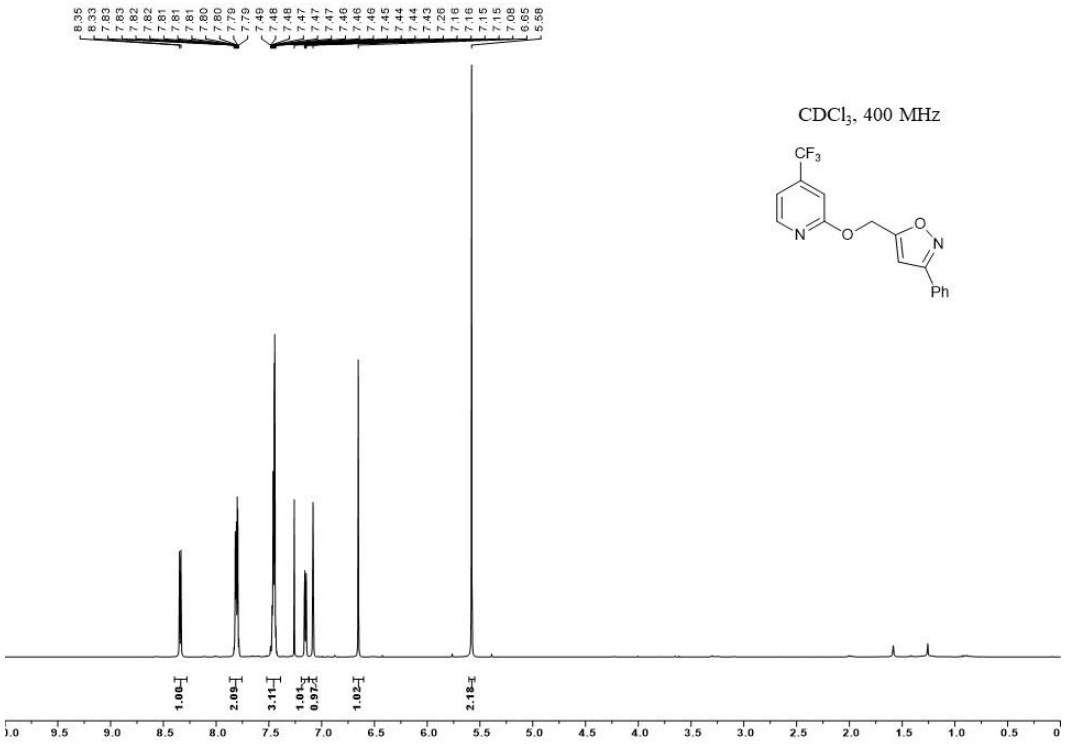

150.75
149.68
138.20
135.08
134.76
134.44
134.12
132.87
132.59
132.35
132.01
128.92
127.37
125.47
125.45
125.43
125.40
124.73
124.64
121.91
121.71
119.18
118.39
118.34
118.29
118.24
117.26
77.46
77.16
76.84
CDCl3, 100 MHz
CF3
Br
N
16.8
Br
N
CF3
1

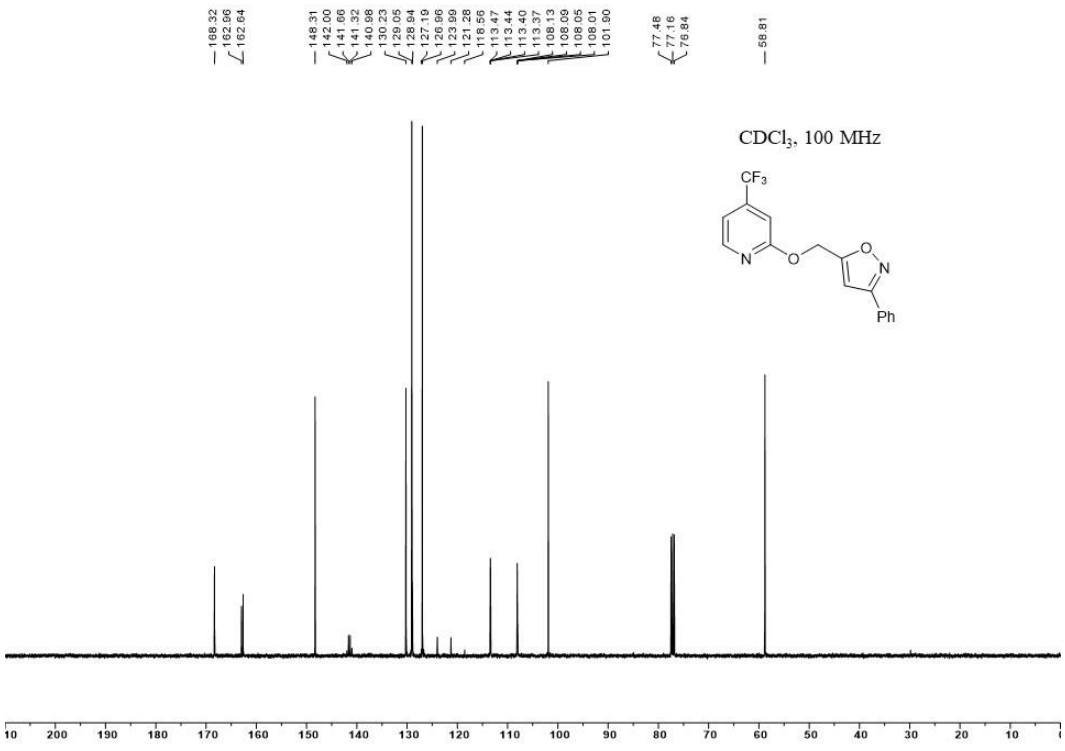

-61.44
-67.69
CDCl3, 376 MHz
CF3
Br
N
16.8
Br
N
CF3
1
16.58
1.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
8.90
8.70
8.69
7.48
7.47
7.40
7.39
7.39
7.38
7.37
7.37
7.37
7.27
7.26
7.26
7.25
7.24
7.24
7.23
7.23
7.18
7.17
7.17
7.16
7.16
7.15
7.14
7.14
7.13
4.69
4.33
3.69
3.68
3.31
3.29
3.27
2.94
2.93
2.91
2.81
2.79
2.78
2.77
2.76
2.74
2.72
2.71

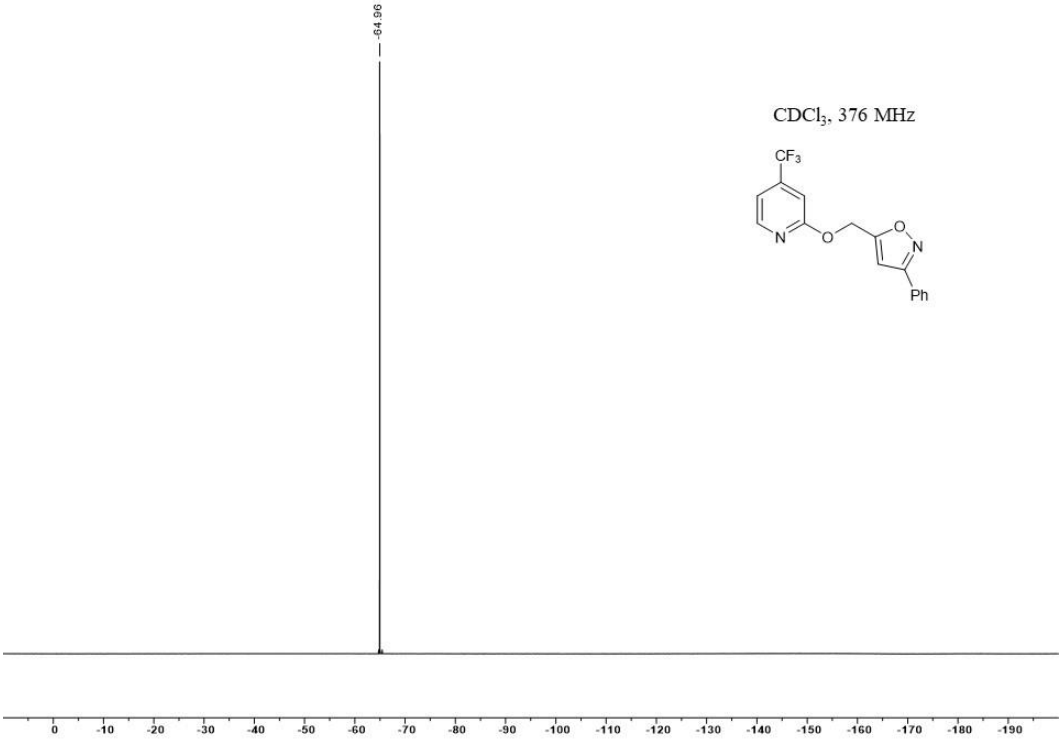

CDCl3, 400 MHz
CF3
O
N
N
Ph
Ph
0.97
0.97
1.00
4.11
4.24
2.02
2.11
1.05
2.12
2.09
2.08
1.05
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

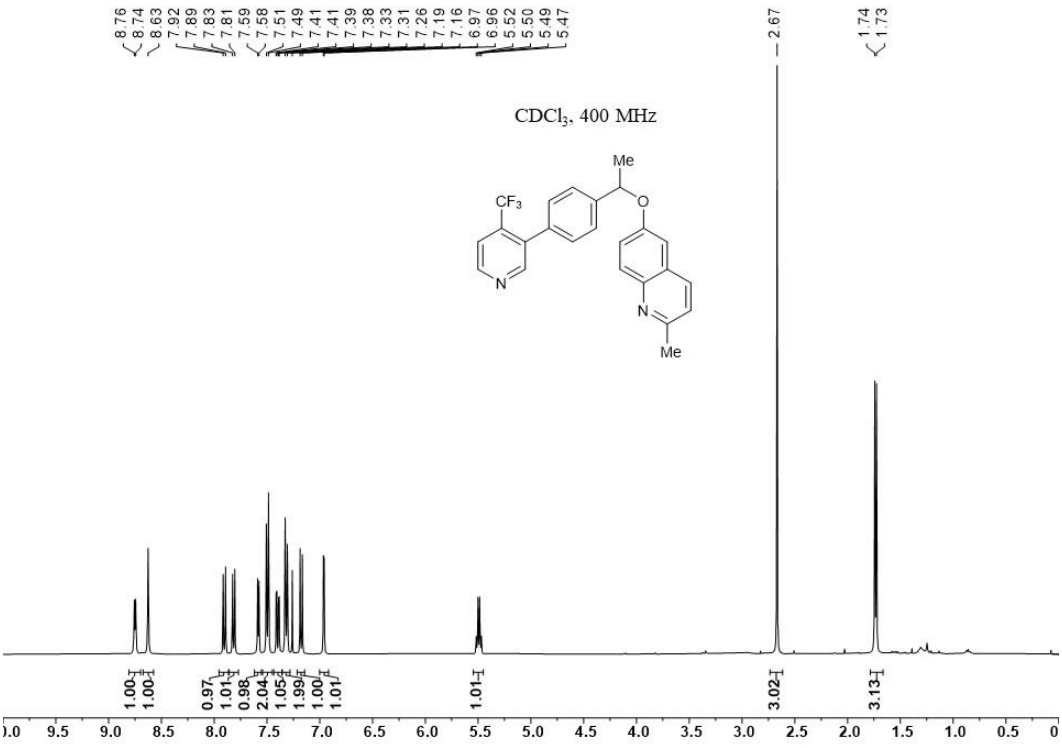

151.16
149.83
142.32
135.86
135.53
135.21
134.88
131.03
131.01
131.00
128.50
127.60
127.22
127.13
124.49
121.76
119.30
119.25
119.20
119.14
119.03
78.13
77.48
77.16
76.84
73.70
67.34
67.32
67.29
67.27
56.43
29.62
CDCl3, 100 MHz
CF3
O
N
Ph
Ph
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

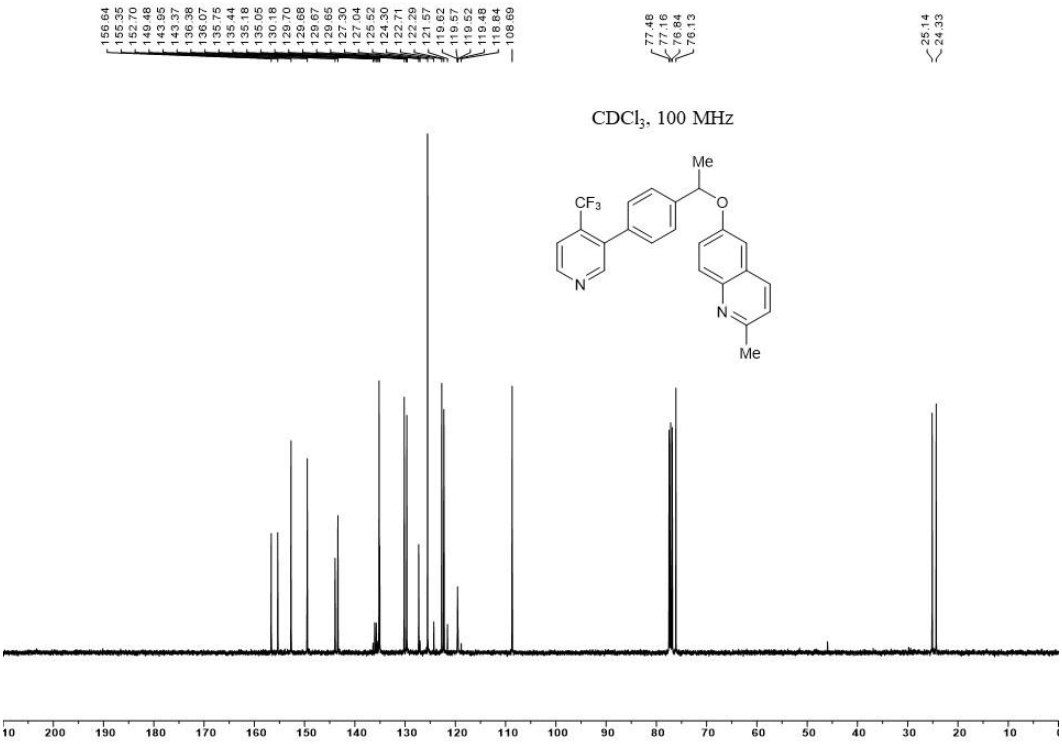

-62.39
CDCl3, 376 MHz
CF3
O
N
Ph
Ph
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

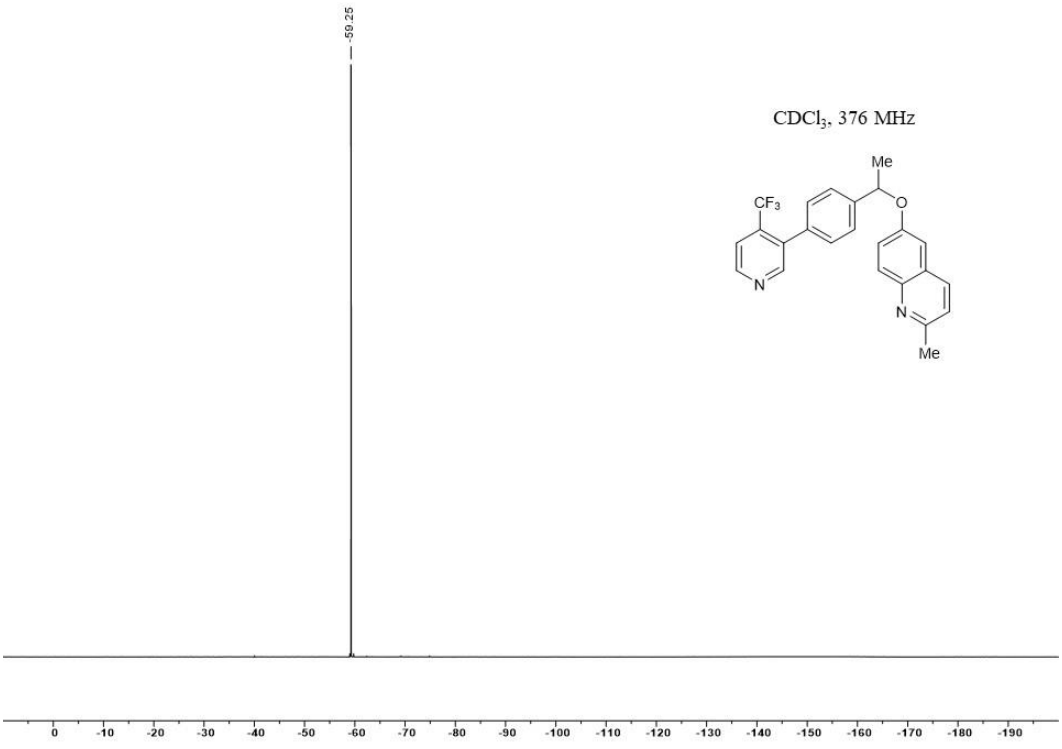

8.35
8.33
7.83
7.82
7.82
7.81
7.81
7.80
7.80
7.79
7.79
7.49
7.48
7.48
7.47
7.47
7.47
7.46
7.46
7.46
7.45
7.44
7.44
7.43
7.26
7.16
7.16
7.15
7.15
7.08
6.65
5.58
CDCl3, 400 MHz
CF3
N
O
O
N
Ph
1.00
2.05
3.11
1.01
0.97
1.02
2.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

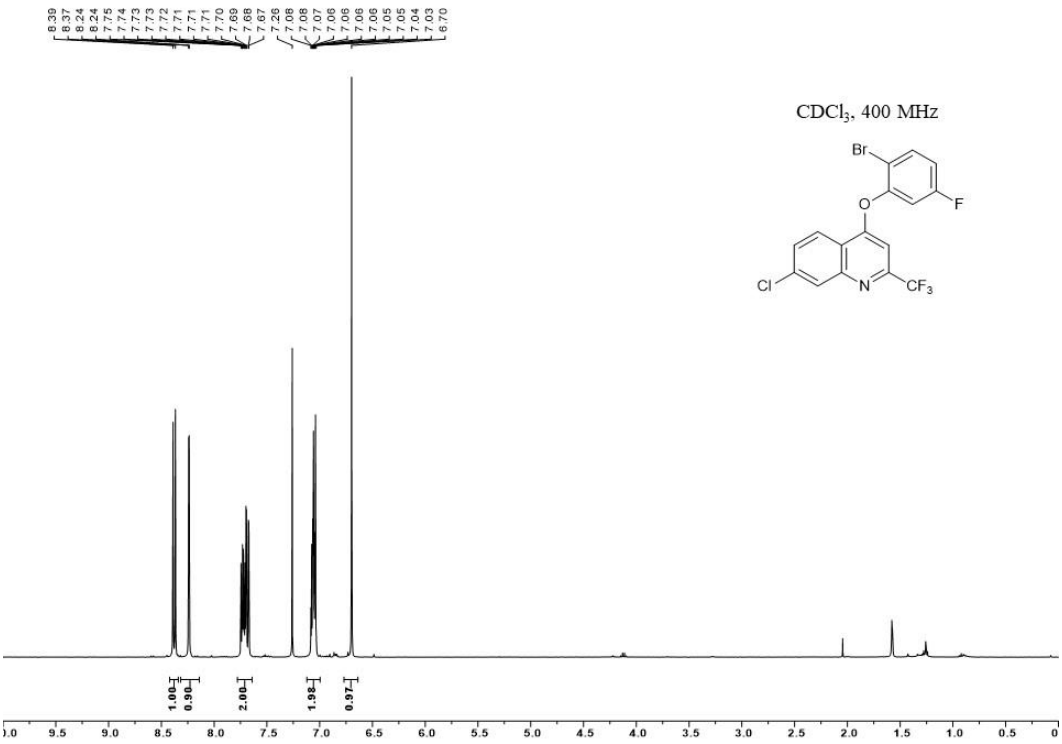

168.32
162.96
162.64
148.31
142.00
141.66
141.32
140.98
130.23
129.05
128.94
127.19
126.86
123.99
121.28
118.56
113.47
113.44
113.40
113.37
108.13
108.09
108.05
108.01
101.90
77.48
77.16
76.84
58.81
CDCl3, 100 MHz
CF3
N
O
O
N
Ph
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

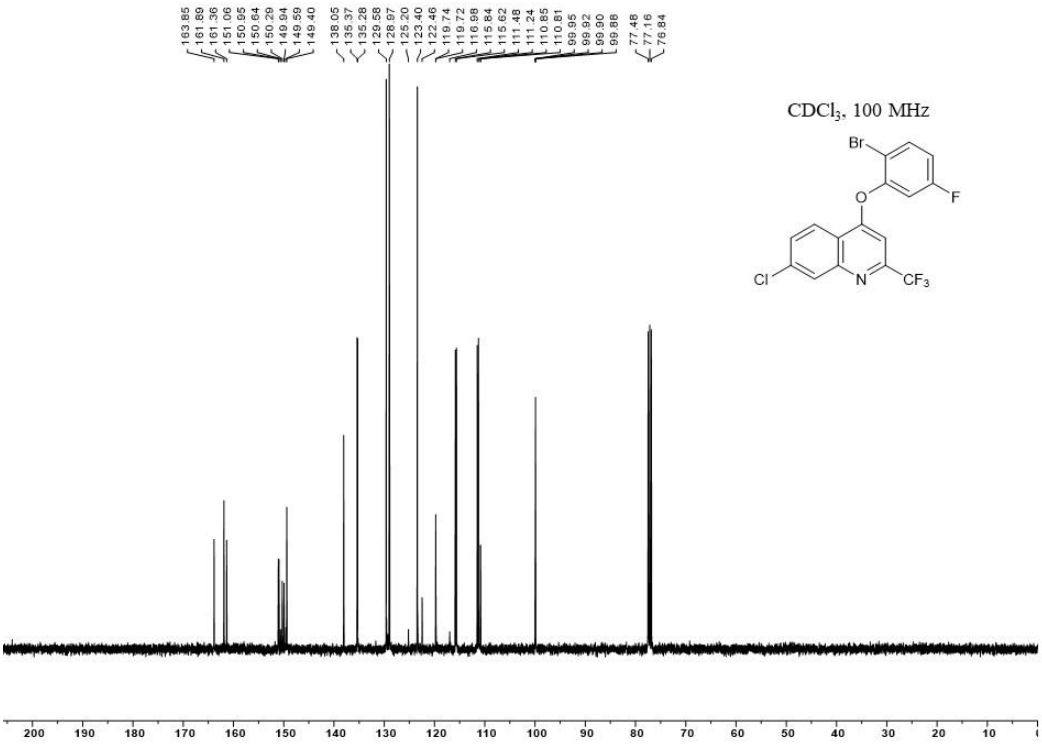

-64.96
CDCl3, 376 MHz
CF3
N
O
O
N
Ph
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

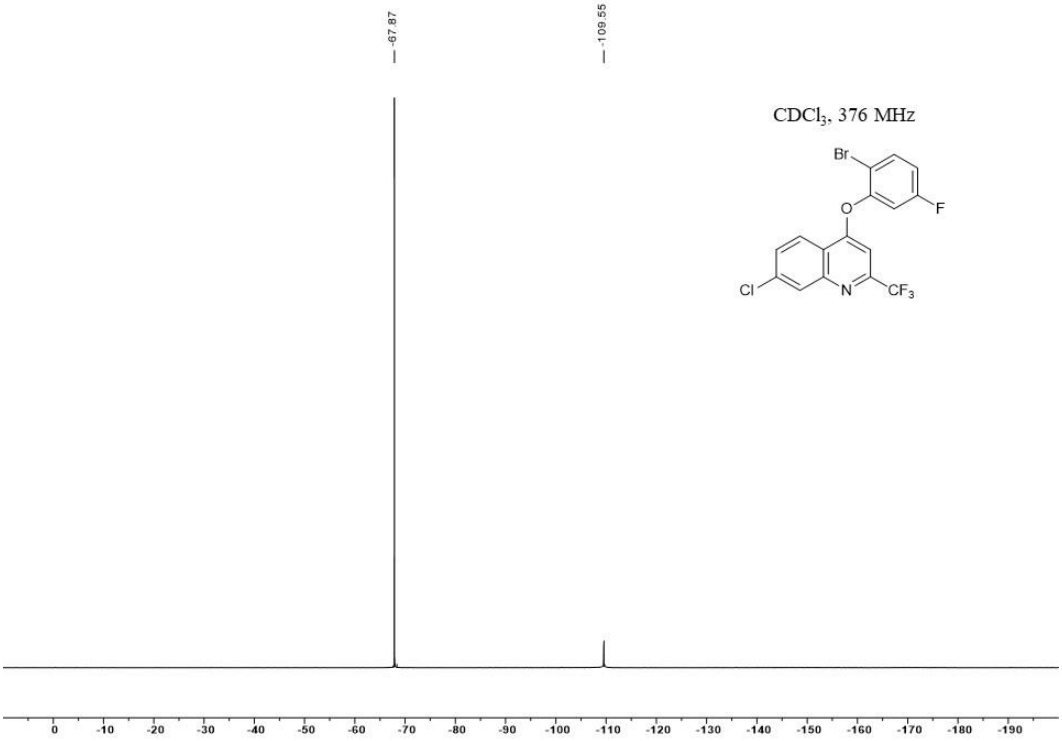

8.76
8.74
8.63
7.92
7.89
7.83
7.81
7.59
7.58
7.51
7.49
7.41
7.41
7.39
7.38
7.33
7.31
7.26
7.19
7.16
6.97
6.96
5.52
5.50
5.49
5.47
2.67
1.74
1.73
CDCl3, 400 MHz
Me
CF3
O
N
N
Me
1.00
1.00
0.97
1.01
0.98
2.04
1.05
1.99
1.00
1.01
1.01
3.02
3.13
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

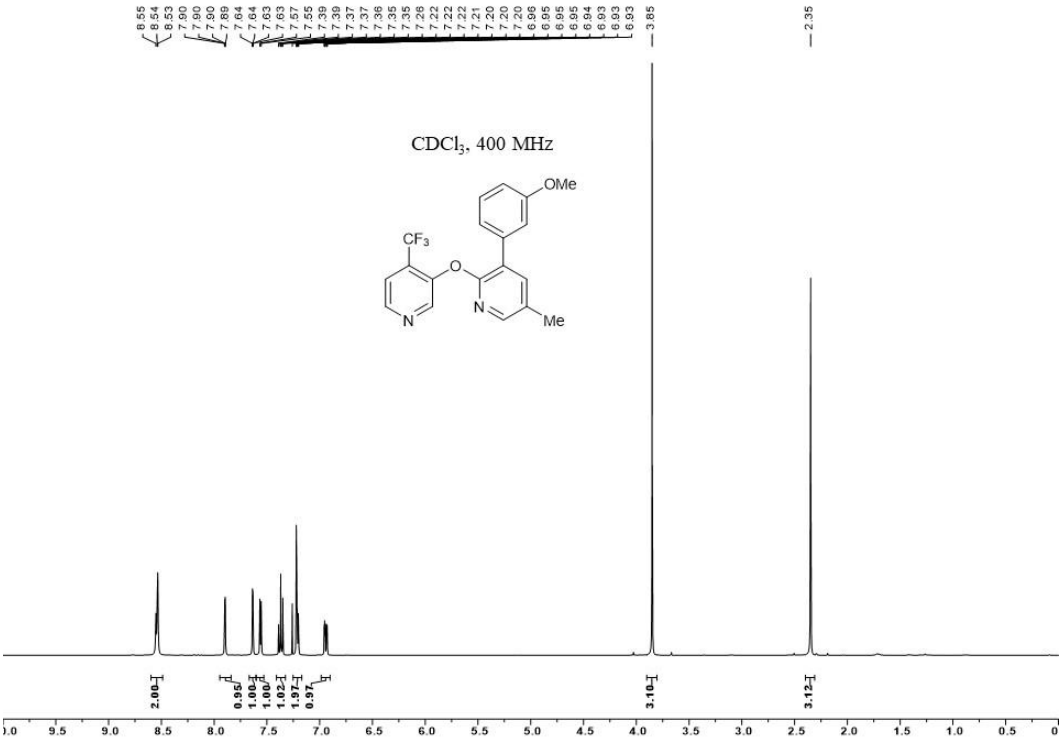

156.64
155.35
152.70
149.48
143.95
143.37
136.38
136.07
135.75
135.44
135.18
135.05
130.18
129.70
129.68
129.67
129.65
127.30
127.04
125.52
124.30
122.71
122.29
121.57
119.62
119.57
119.52
119.48
118.84
108.69
77.48
77.16
76.84
76.13
25.14
24.33
CDCl3, 100 MHz
Me
CF3
O
N
N
Me
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

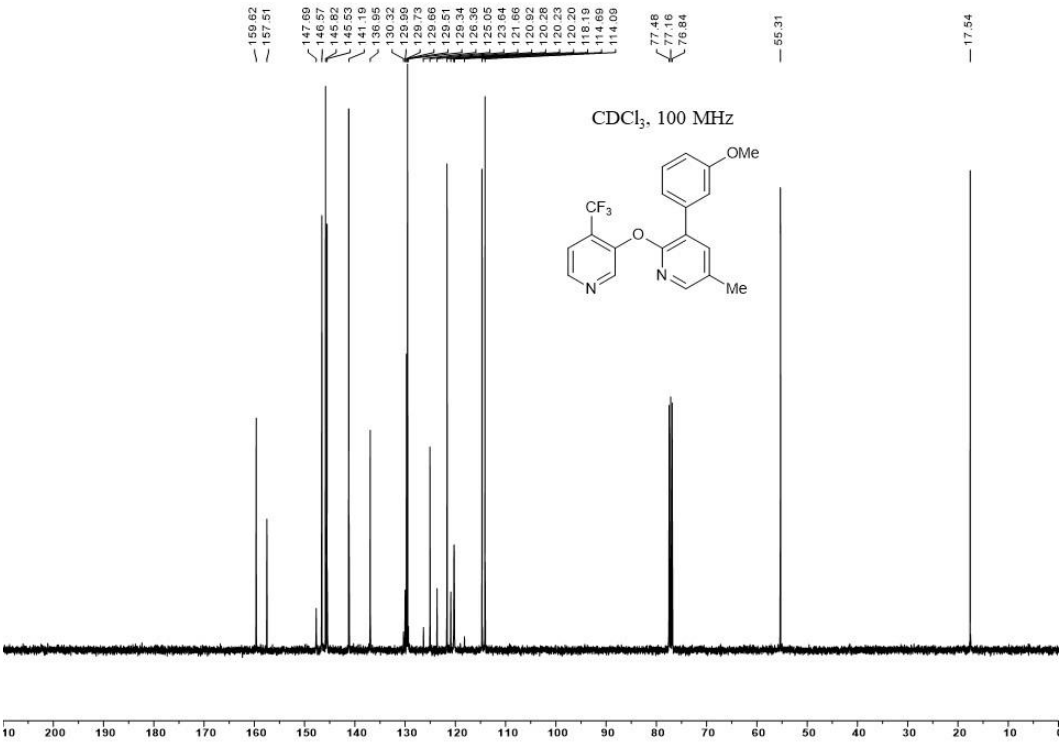

-59.25
CDCl3, 376 MHz
Me
CF3
O
N
N
Me
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

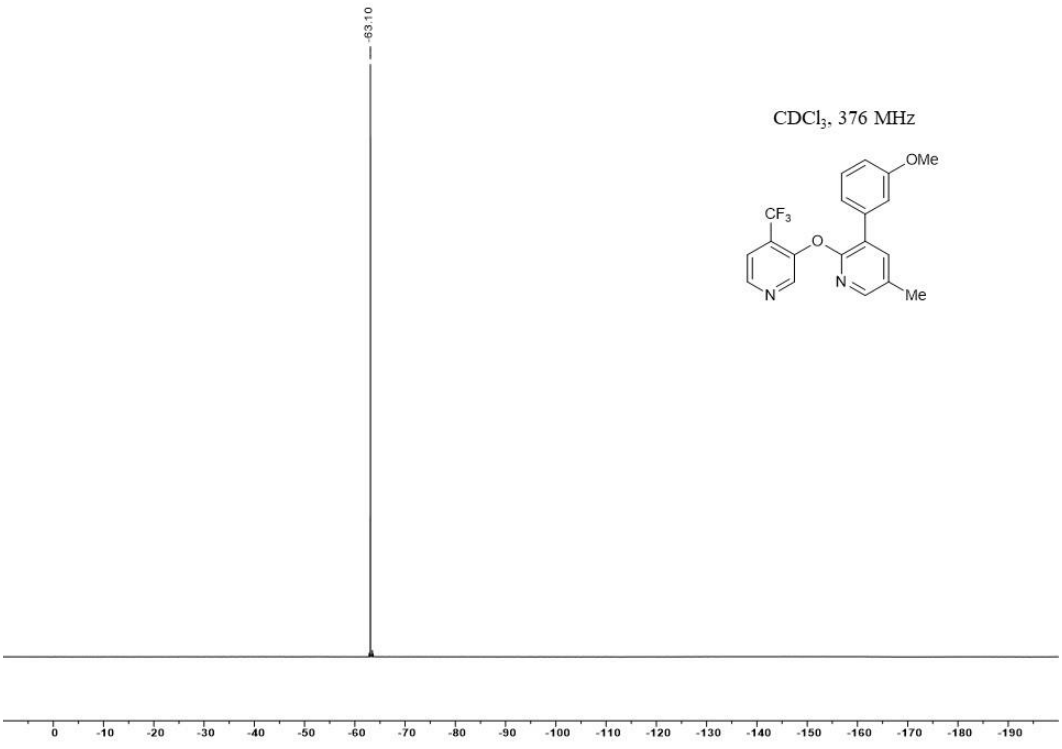

8.39
8.37
8.24
8.24
7.75
7.74
7.73
7.73
7.72
7.71
7.71
7.71
7.70
7.69
7.68
7.67
7.28
7.08
7.08
7.07
7.07
7.06
7.06
7.06
7.06
7.05
7.05
7.04
7.03
6.70
CDCl3, 400 MHz
Br
O
F
Cl
N
CF3
1.00
0.90
2.00
1.98
0.97
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

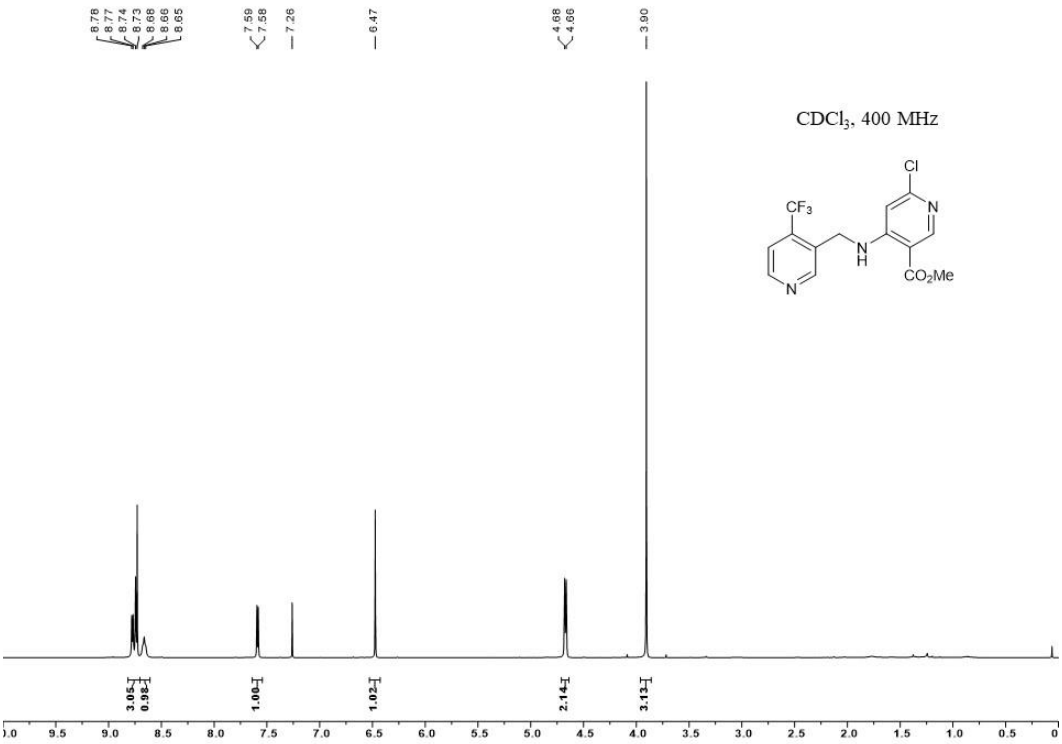

163.85
161.89
161.36
151.06
150.95
150.64
150.29
149.94
149.59
149.40
138.05
135.37
135.28
129.58
128.97
125.20
123.40
122.46
119.74
119.72
116.98
115.84
115.62
111.48
111.24
110.85
110.81
99.95
99.92
99.90
99.88
77.48
77.16
76.84
CDCl3, 100 MHz
Br
O
F
Cl
N
CF3
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

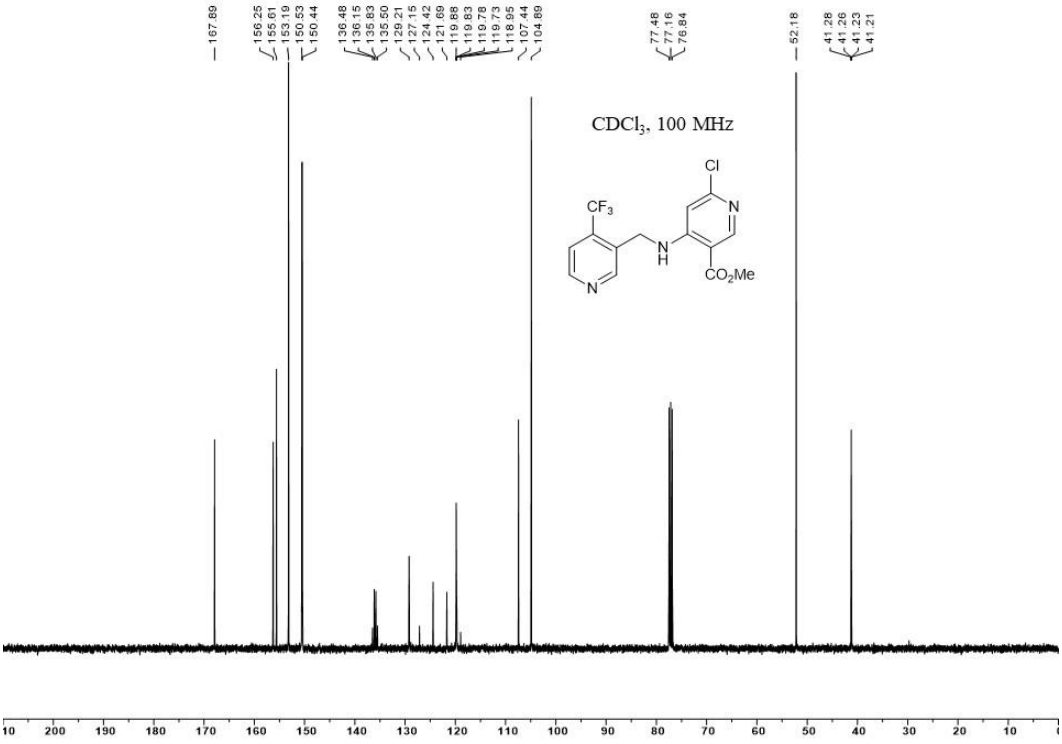

-67.87
-108.55
CDCl3, 376 MHz
Br
O
F
Cl
N
CF3
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

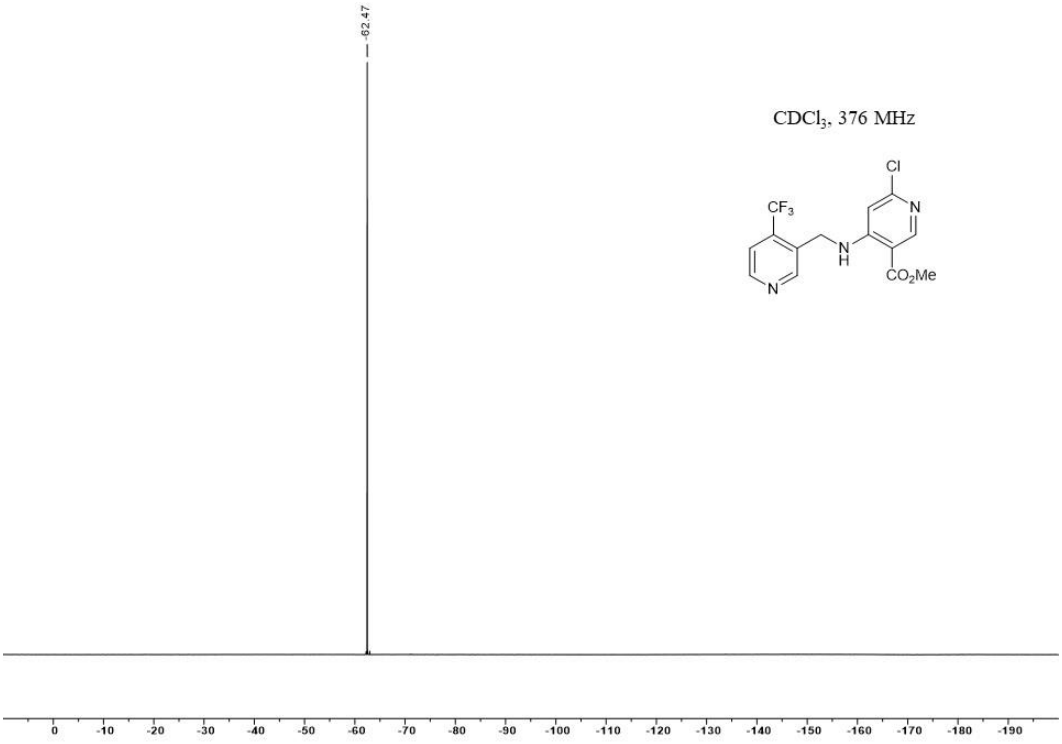

8.55
8.54
8.53
7.90
7.90
7.90
7.89
7.64
7.64
7.63
7.63
7.57
7.55
7.39
7.39
7.37
7.37
7.36
7.35
7.35
7.28
7.22
7.22
7.22
7.21
7.20
7.20
7.20
6.96
6.95
6.95
6.95
6.94
6.93
6.93
6.93
3.85
2.35
CDCl3, 400 MHz
OMe
CF3
O
N
N
Me
2.00
0.95
1.00
1.00
1.02
1.97
0.97
3.10
3.12
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

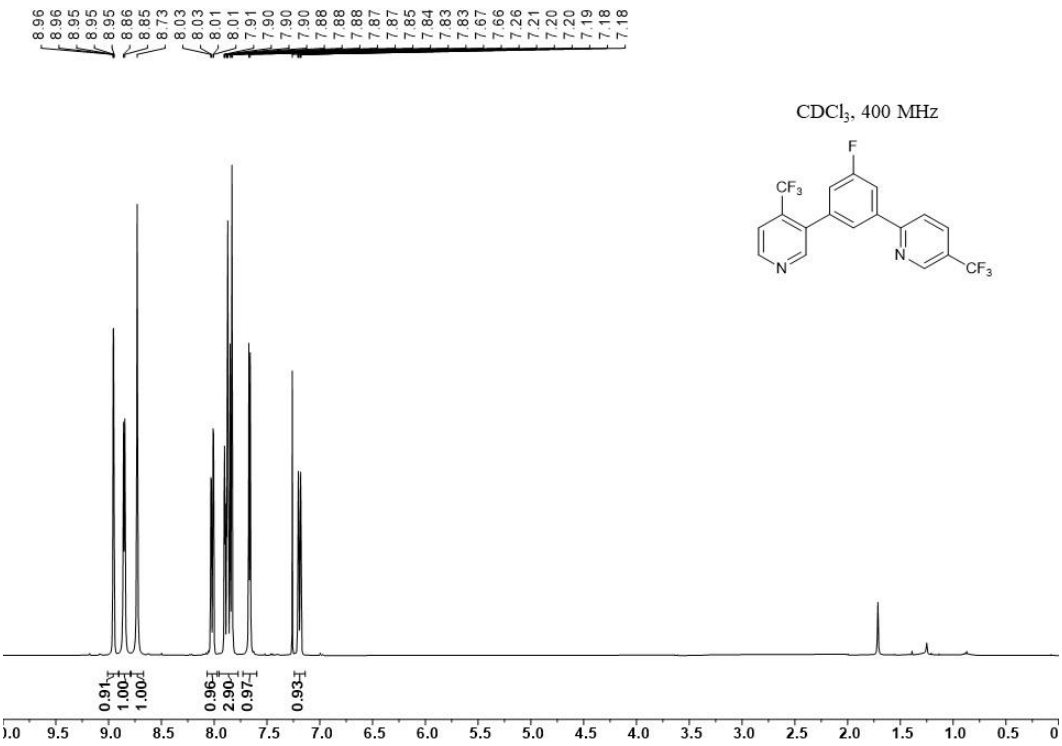

159.62
157.51
147.69
146.57
145.82
145.53
141.19
136.95
130.32
129.99
129.73
129.66
129.51
129.34
126.36
125.05
123.64
121.66
120.92
120.28
120.23
120.20
118.19
114.69
114.09
77.48
77.16
76.84
55.31
17.54
CDCl3, 100 MHz
OMe
CF3
O
N
N
Me
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

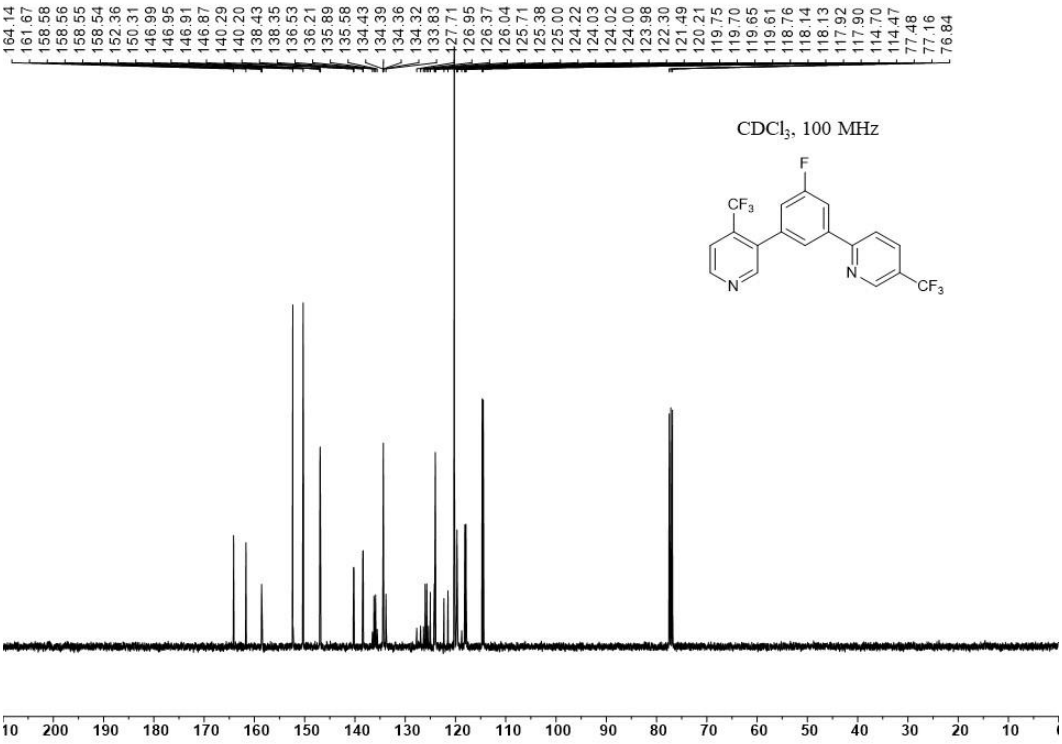

-63.10
CDCl3, 376 MHz
OMe
CF3
O
N
N
Me
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

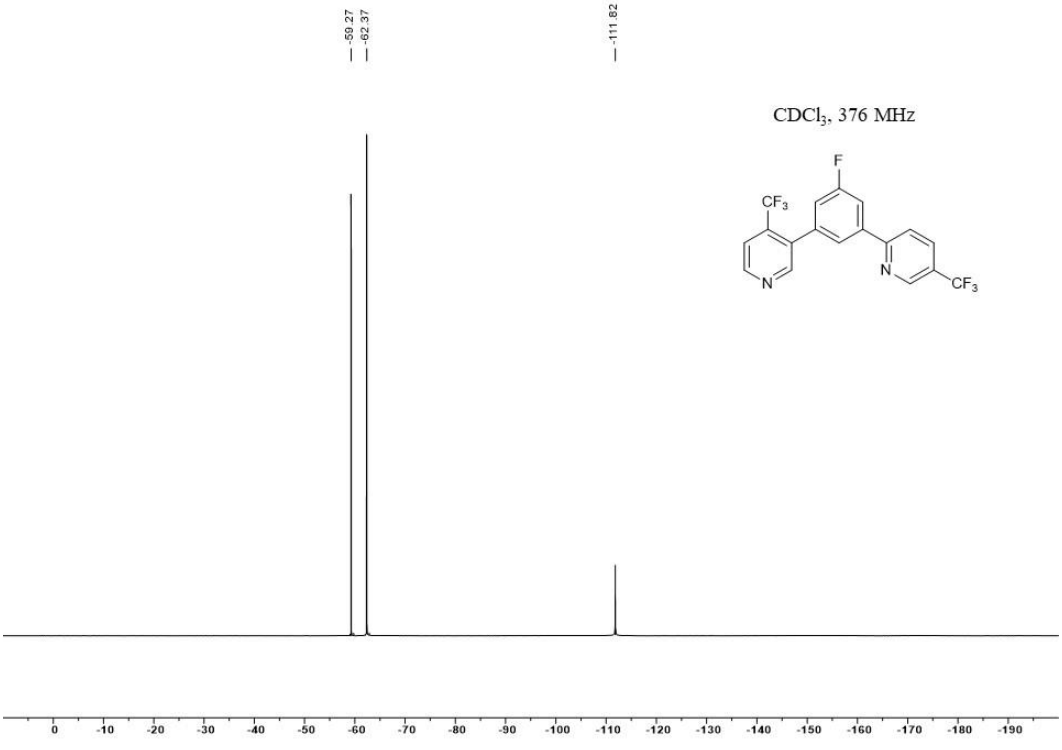

8.78
8.77
8.74
8.73
8.68
8.66
8.65
7.59
7.58
7.26
6.47
4.68
4.66
3.90
CDCl3, 400 MHz
Cl
CF3
N
N
H
CO2Me
N
3.05
0.93
1.06
1.02
2.14
3.13

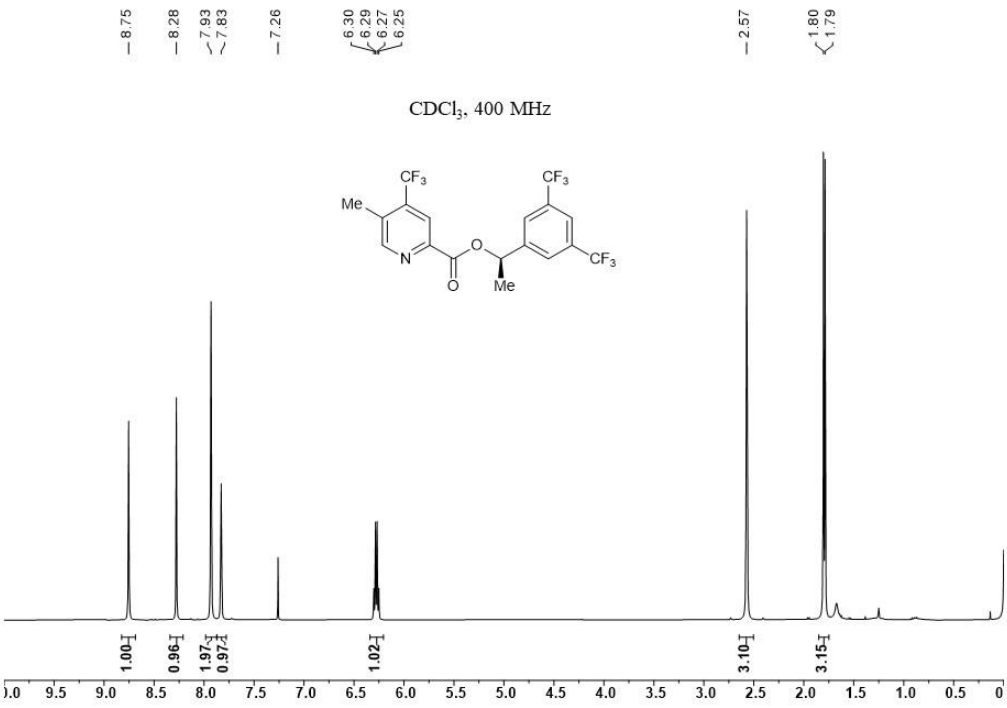

167.89
156.25
155.61
153.19
150.53
150.44
136.48
136.15
135.83
135.50
129.21
127.15
124.42
121.69
119.88
119.83
119.78
119.73
118.95
107.44
104.89
77.46
77.16
76.84
52.18
41.28
41.26
41.23
41.21
CDCl3, 100 MHz
Cl
CF3
N
N
H
CO2Me
N

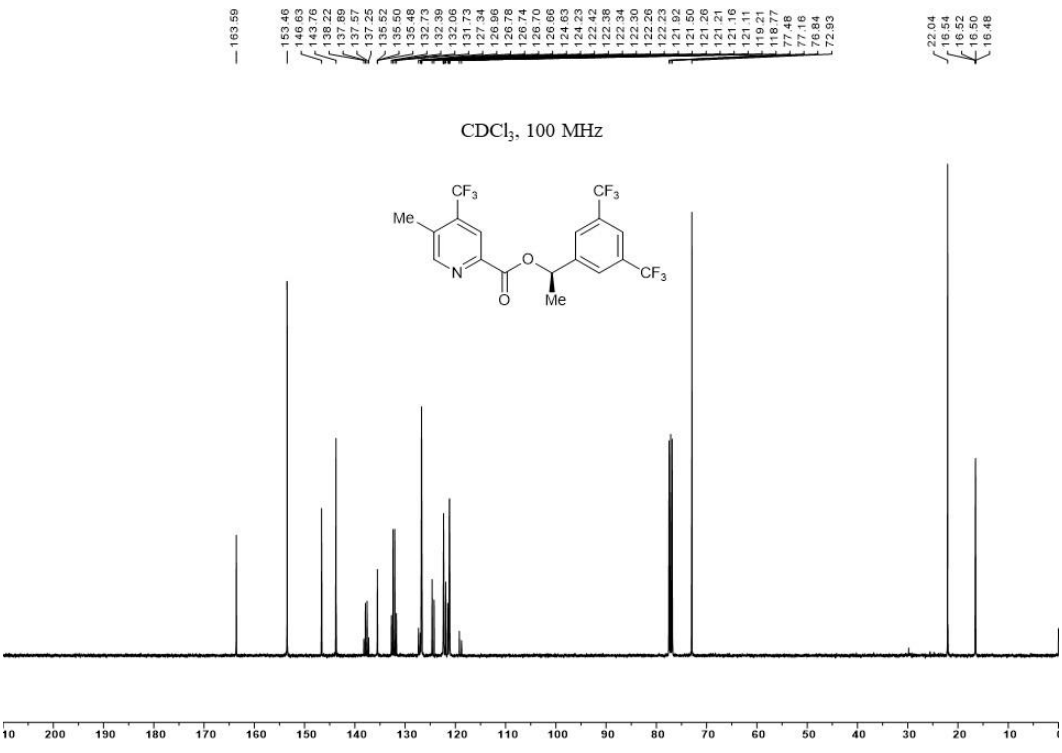

-62.47
CDCl3, 376 MHz
Cl
CF3
N
N
H
N
CO2Me
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

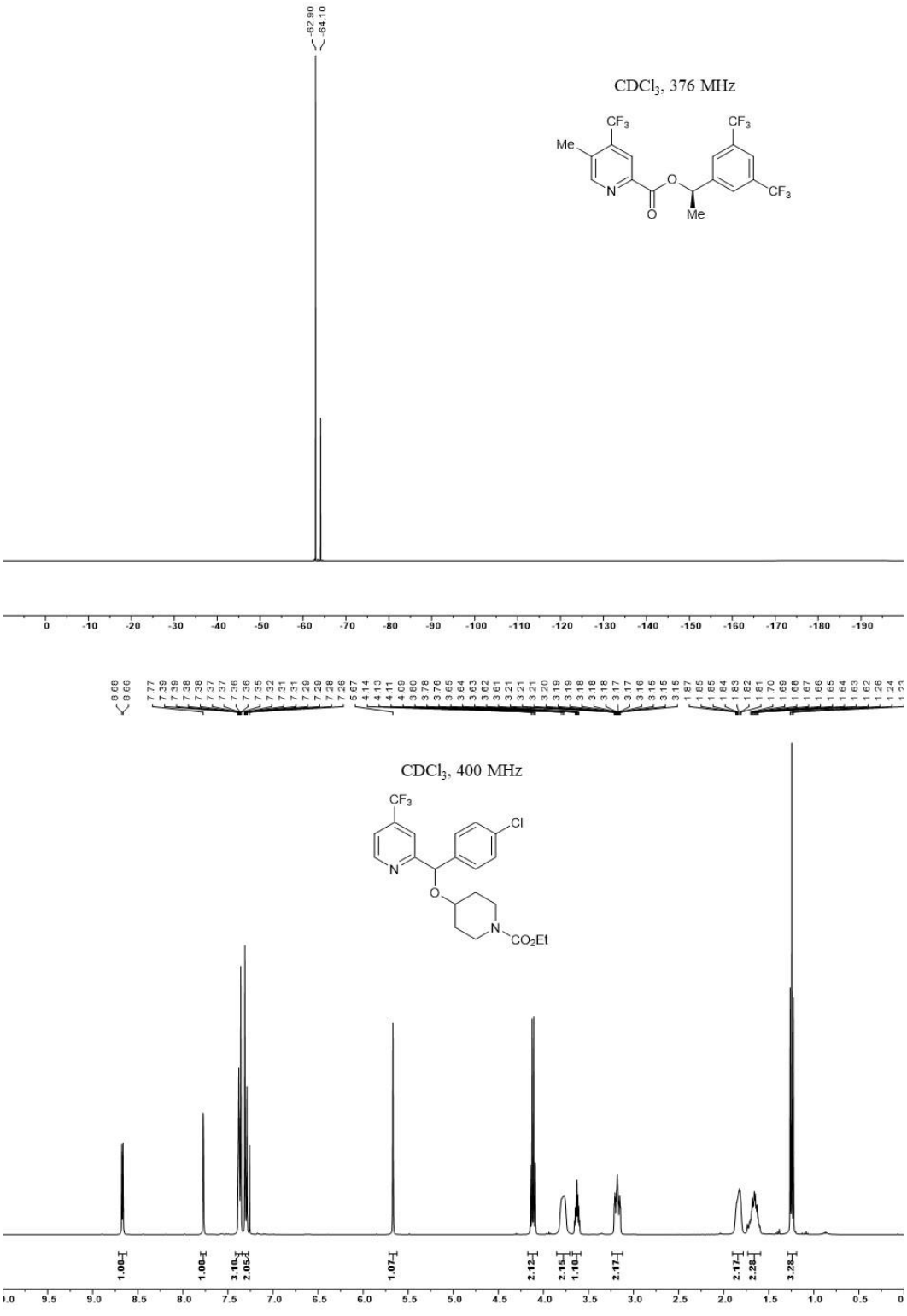

8.96
8.96
8.95
8.95
8.95
8.86
8.85
8.73
8.03
8.03
8.01
8.01
7.91
7.90
7.90
7.90
7.88
7.88
7.88
7.87
7.87
7.85
7.84
7.83
7.83
7.67
7.66
7.26
7.21
7.20
7.20
7.19
7.18
7.18
CDCl3, 400 MHz
F
CF3
N
N
CF3
0.91
1.00
1.00
0.96
2.90
0.97
0.93
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

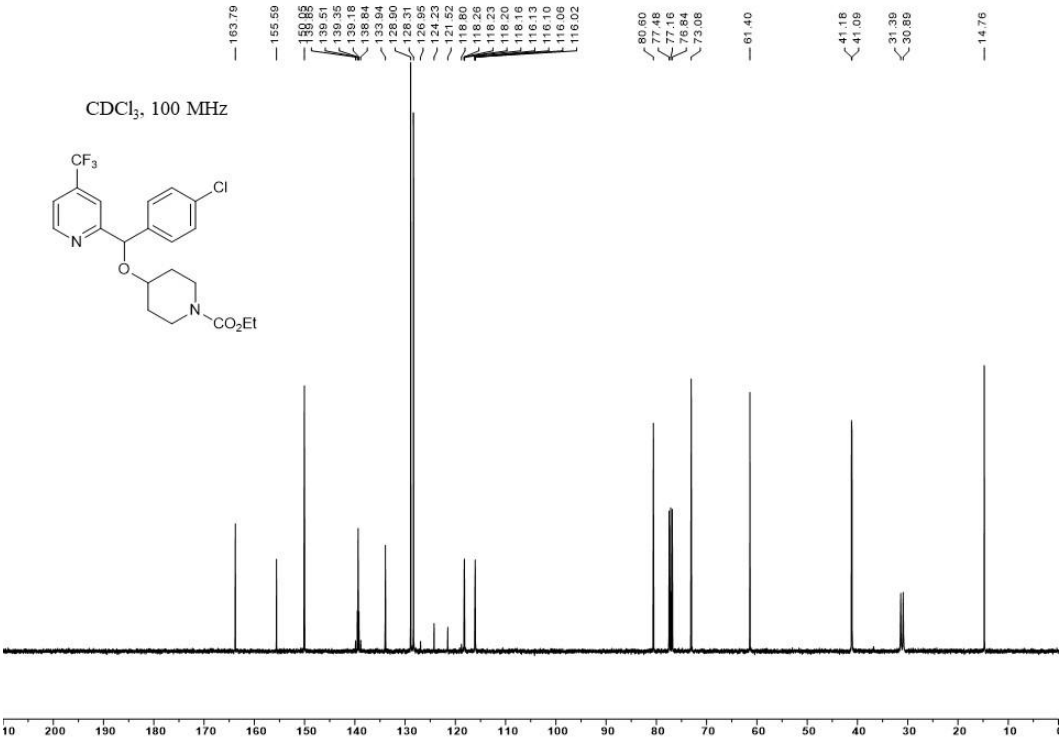

164.14
161.67
158.58
158.56
158.55
158.54
152.36
150.31
146.99
146.95
146.91
146.87
140.29
140.20
138.43
138.35
136.53
136.21
135.89
135.58
134.43
134.39
134.36
134.32
133.83
127.71
126.95
126.37
126.04
125.71
125.38
125.00
124.22
124.03
124.02
124.00
123.98
122.30
121.49
120.21
119.75
119.70
119.65
119.61
118.76
118.14
118.13
117.92
117.90
114.70
114.47
77.48
77.16
76.84
CDCl3, 100 MHz
F
CF3
N
N
CF3
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

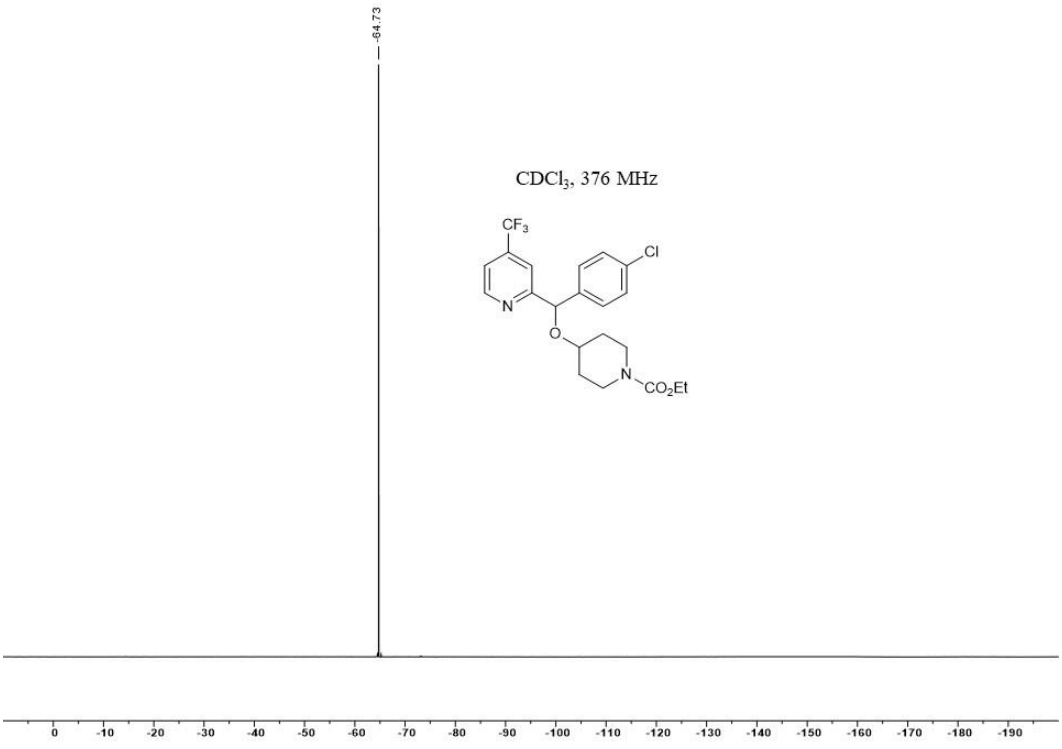

-59.27
-62.37
-111.82
CDCl3, 376 MHz
F
CF3
N
N
CF3
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

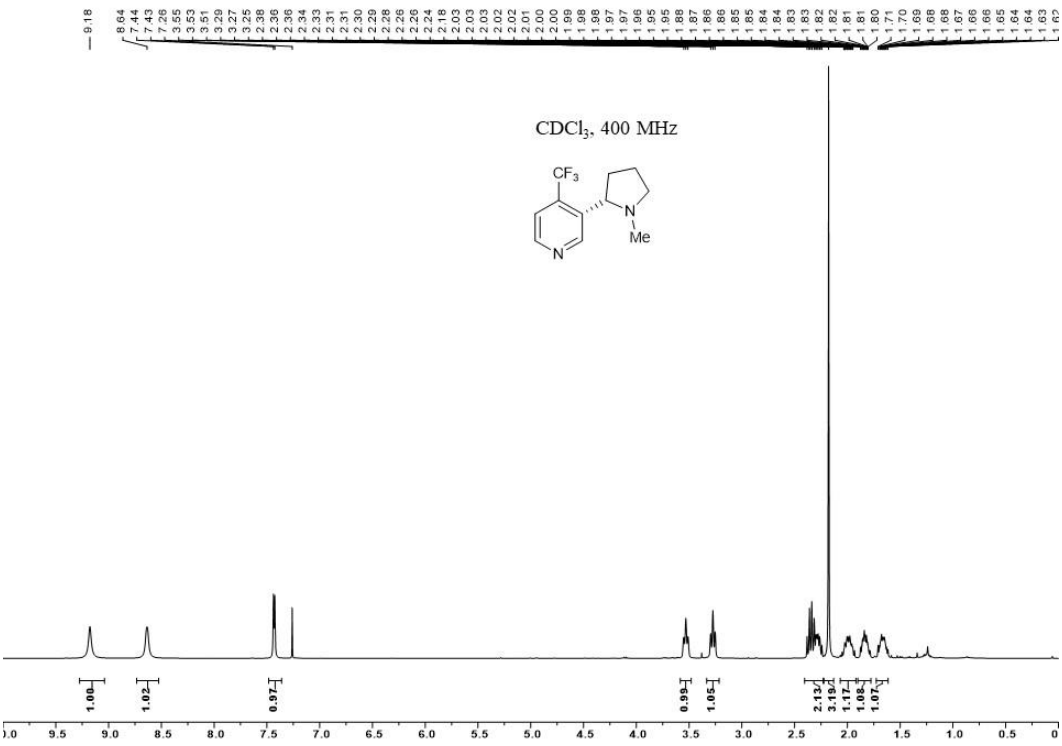

8.75
8.28
7.93
7.83
7.26
6.30
6.29
6.27
6.25
2.57
1.80
1.79
CDCl3, 400 MHz
CF3
CF3
Me
N
O
O
CF3
Me
1.00
0.96
1.97
0.97
1.02
3.10
3.15

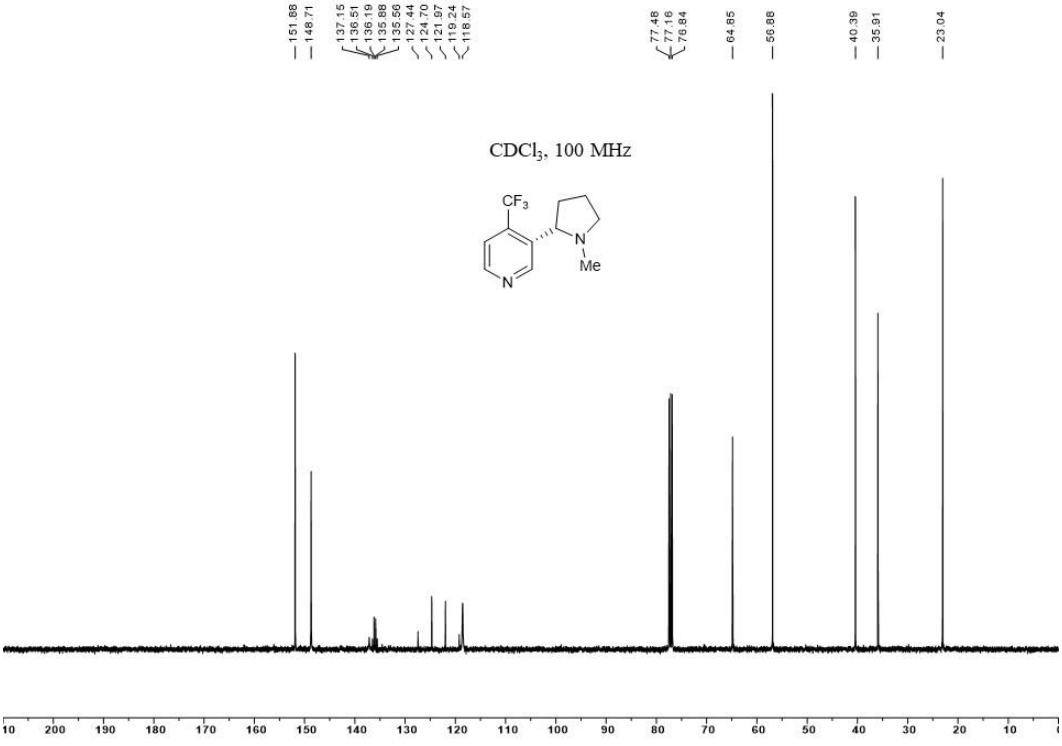

163.59
153.46
146.63
143.76
138.22
137.89
137.57
137.25
135.52
135.50
135.48
132.73
132.39
132.06
131.73
127.34
126.96
126.78
126.74
126.70
126.66
124.63
124.23
122.42
122.38
122.34
122.30
122.26
122.23
121.92
121.50
121.26
121.21
121.16
119.21
118.77
77.48
77.16
76.84
72.93
22.04
16.54
16.52
16.50
16.48
CDCl3, 100 MHz
CF3
CF3
Me
N
O
O
CF3
Me

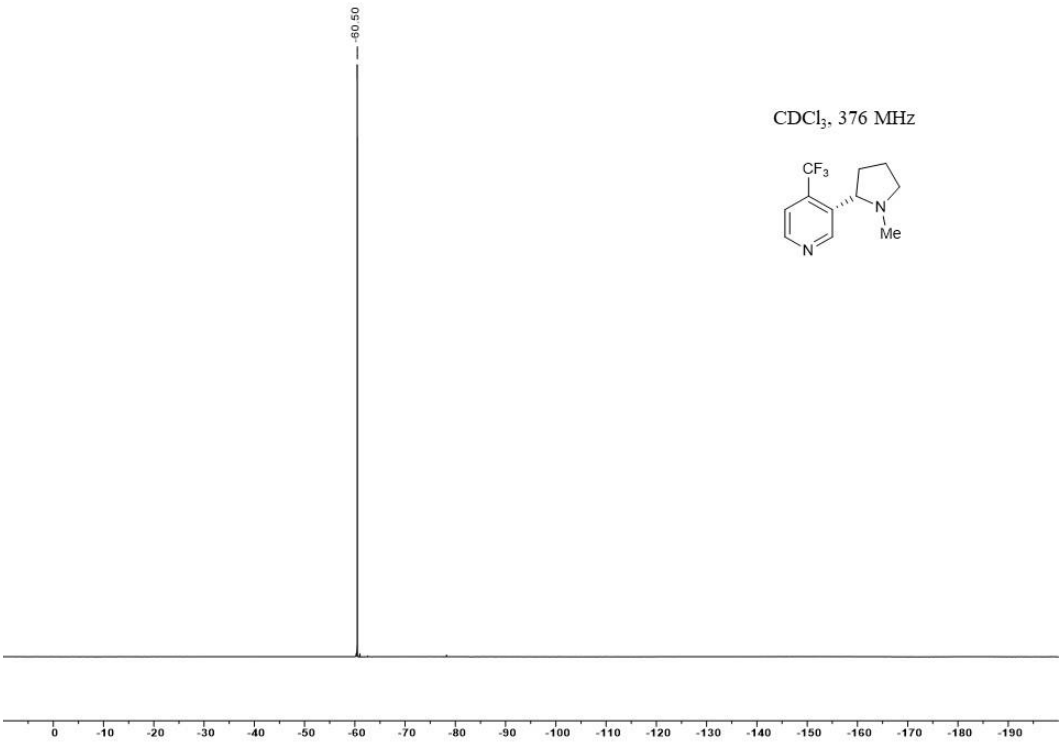

-62.90
-64.10
CDCl3, 376 MHz
CF3
CF3
Me
N
O
O
CF3
Me
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
8.68
8.66
7.77
7.39
7.38
7.38
7.37
7.37
7.36
7.35
7.32
7.31
7.31
7.29
7.29
7.28
7.26
5.67
4.14
4.13
4.11
4.09
3.80
3.78
3.76
3.65
3.64
3.63
3.62
3.61
3.21
3.21
3.21
3.20
3.19
3.19
3.18
3.18
3.18
3.17
3.17
3.16
3.15
3.15
3.15
1.87
1.85
1.85
1.84
1.83
1.82
1.81
1.70
1.69
1.68
1.67
1.66
1.65
1.64
1.63
1.62
1.26
1.24
1.23
CDCl3, 400 MHz
CF3
Cl
N
O
N
CO2Et
1.00
1.00
3.10
2.05
1.07
2.12
2.15
1.10
2.17
2.17
2.28
3.28
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

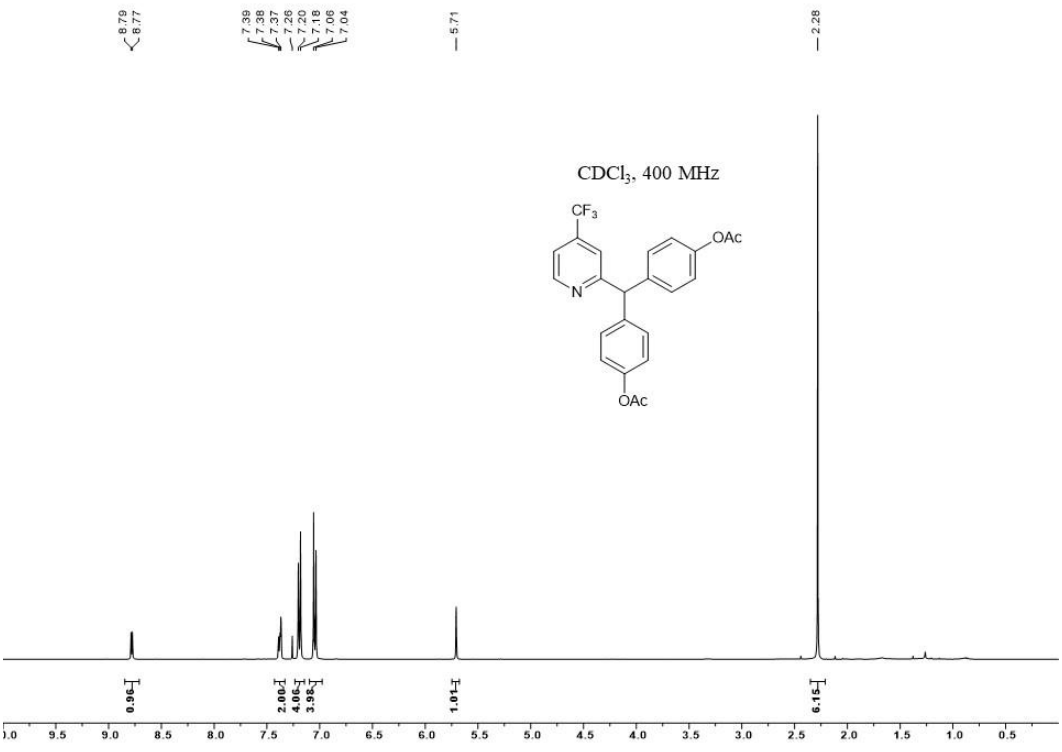

163.79
155.59
150.05
139.51
139.35
139.18
138.84
133.94
128.90
128.31
126.95
124.23
121.52
118.80
118.26
118.23
118.20
118.16
116.13
116.10
116.08
116.02
80.60
77.48
77.16
76.84
73.08
61.40
41.16
41.09
31.39
30.89
14.76
CDCl3, 100 MHz
CF3
Cl
N
O
N
CO2Et
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

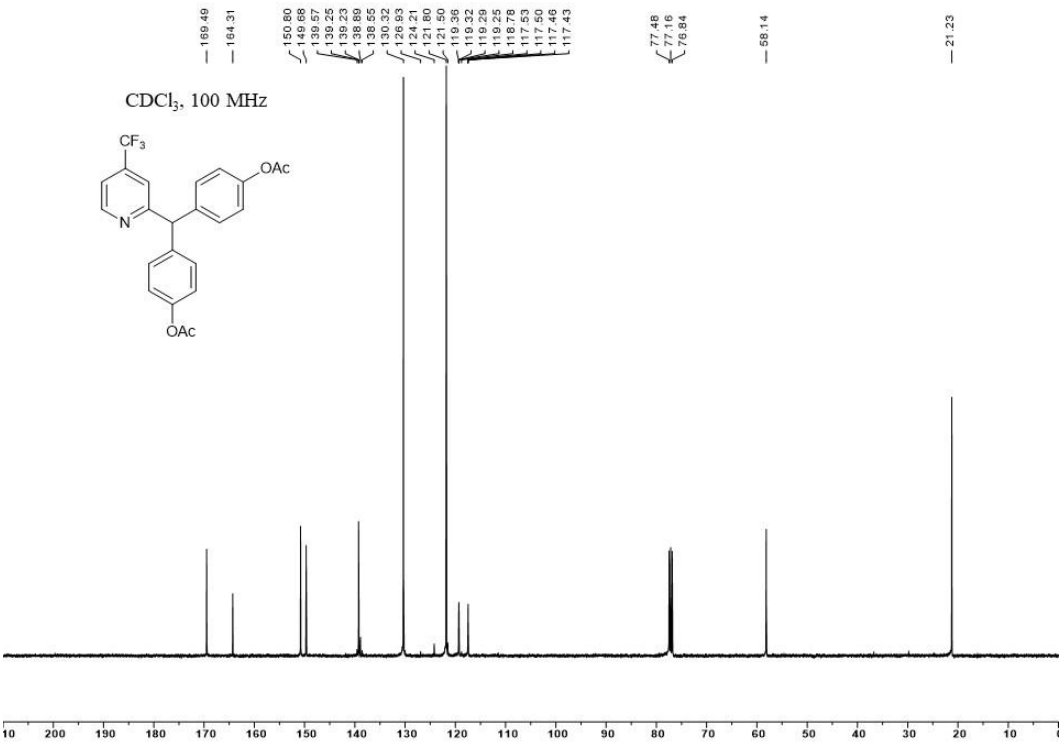

-64.73
CDCl3, 376 MHz
CF3
Cl
N
O
N
CO2Et
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

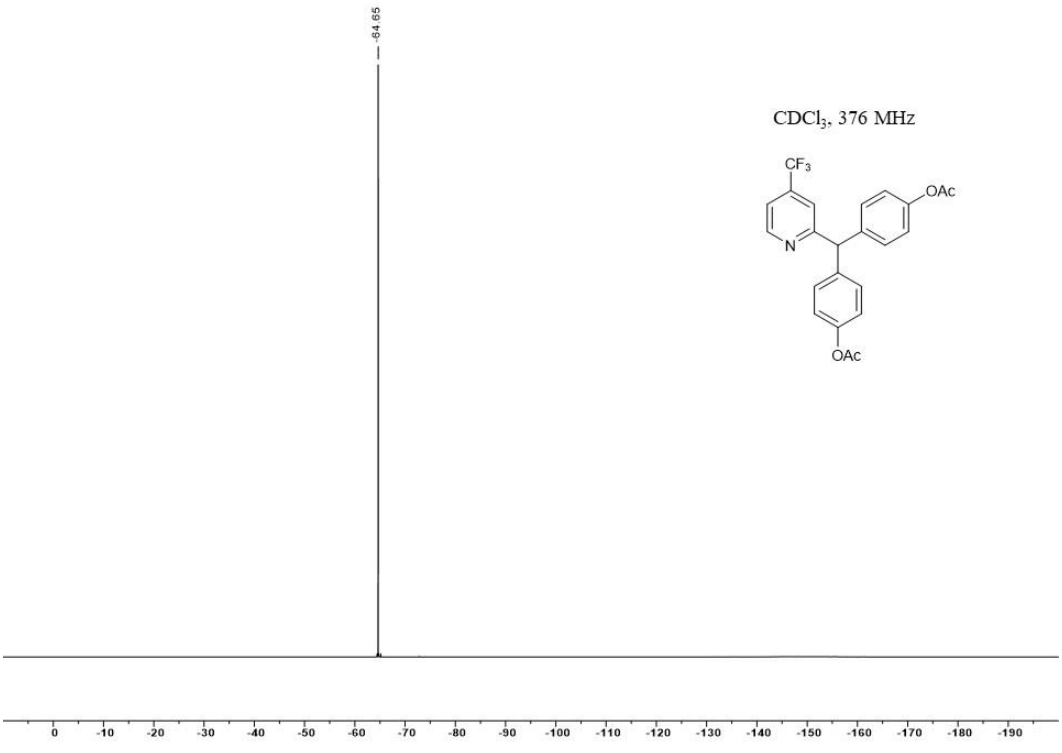

CDCl3, 400 MHz
CF3
N
Me
N
1.00
1.02
0.97
0.99
1.05
2.13
3.19
1.17
1.08
1.07

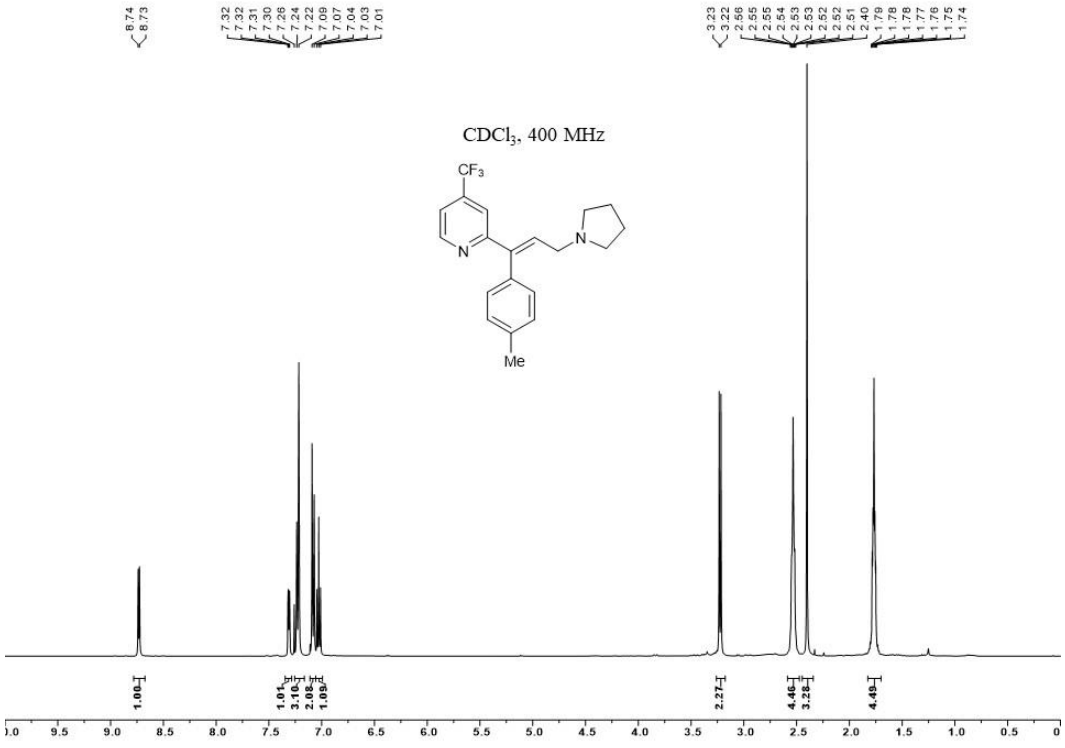

CDCl3, 100 MHz
CF3
N
Me
N

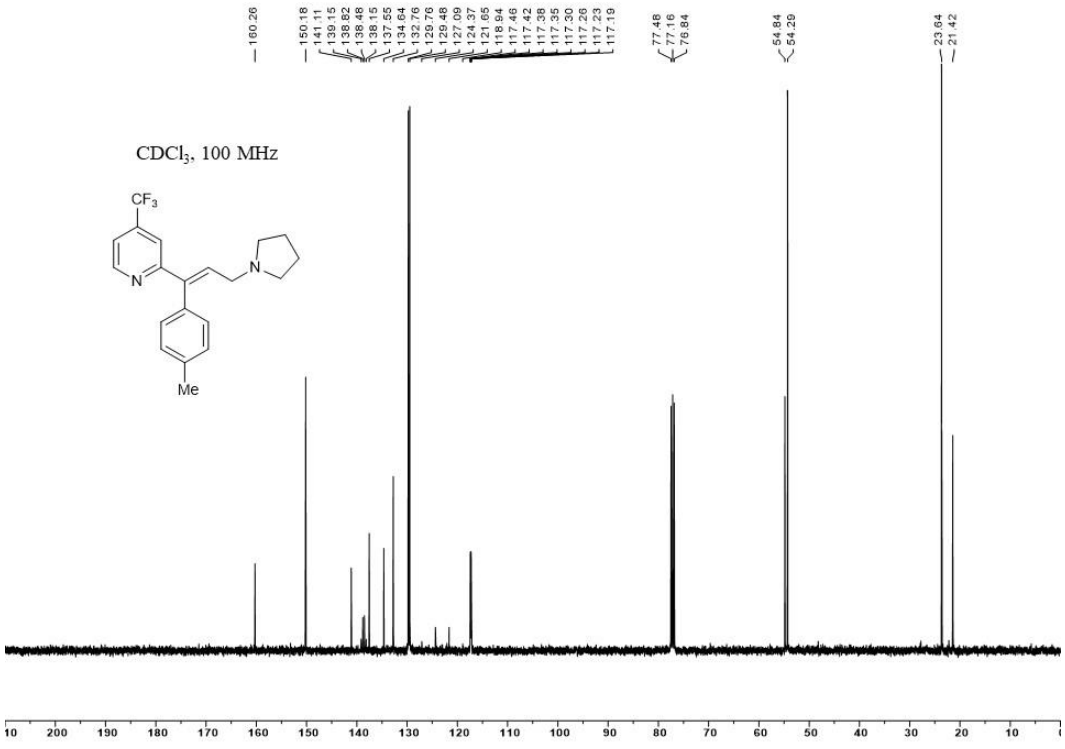

-60.50
CDCl3, 376 MHz
CF3
N
Me
N
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

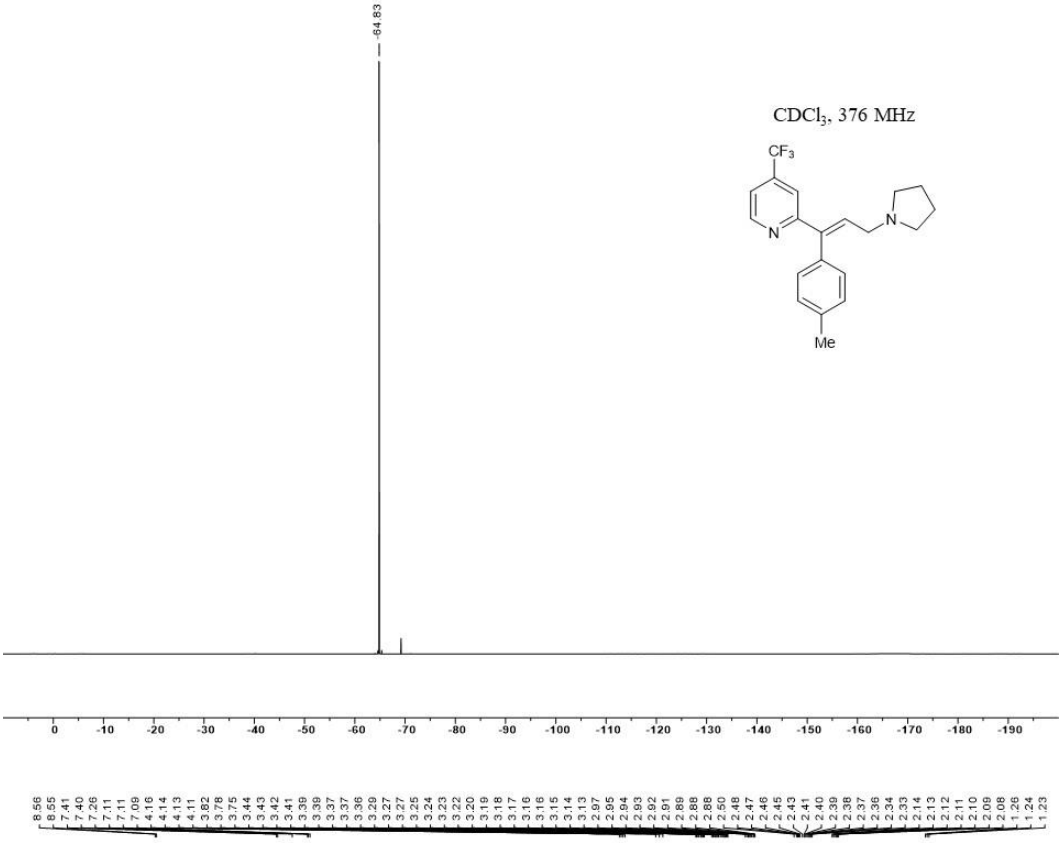

8.79
8.77
7.39
7.38
7.37
7.26
7.20
7.18
7.06
7.04
5.71
2.28
CDCl3, 400 MHz
CF3
OAc
N
OAc
0.96
2.00
4.06
3.98
1.01
6.15
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

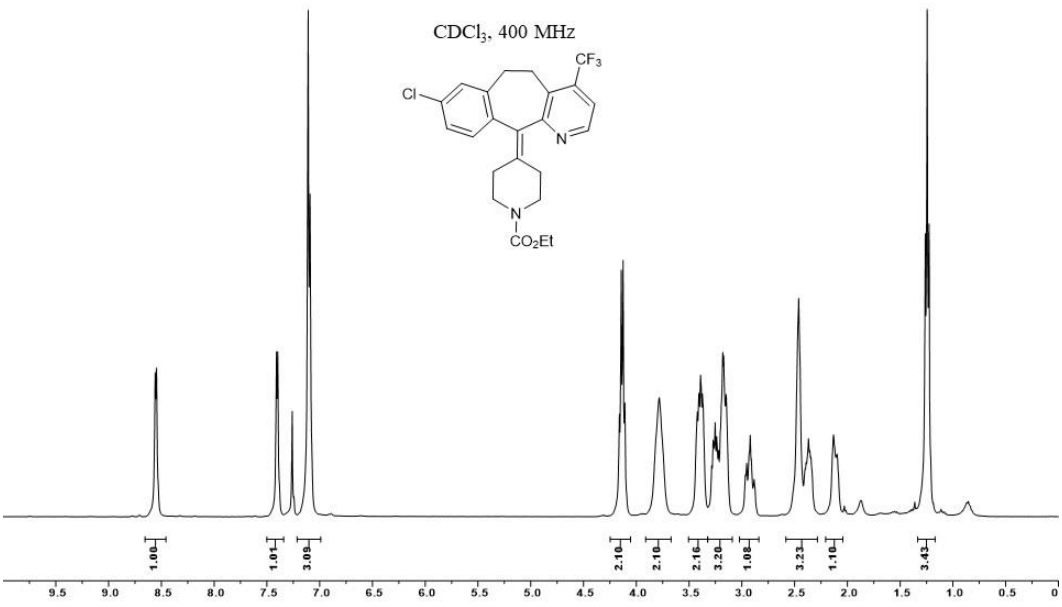

169.49
164.31
150.80
149.68
139.57
139.25
139.23
138.89
138.55
130.32
126.93
124.21
121.80
121.50
119.36
119.32
119.29
119.25
118.78
117.53
117.50
117.46
117.43
77.48
77.16
76.84
58.14
21.23
CDCl3, 100 MHz
CF3
OAc
N
OAc
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

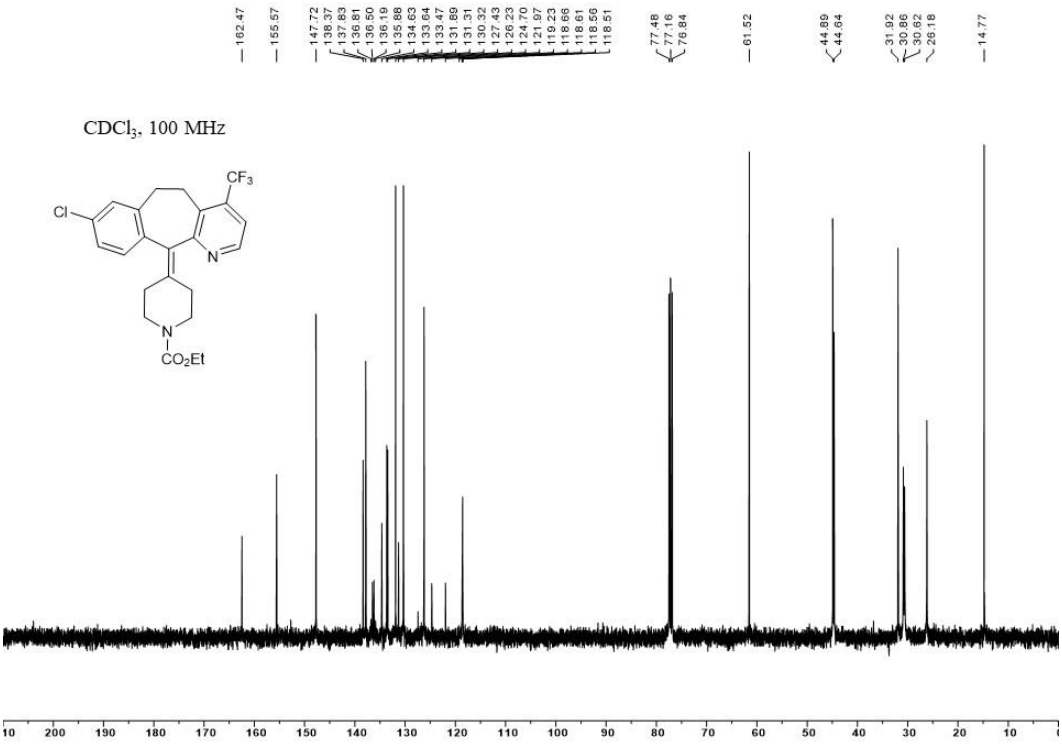

-64.65
CDCl3, 376 MHz
CF3
OAc
N
OAc
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

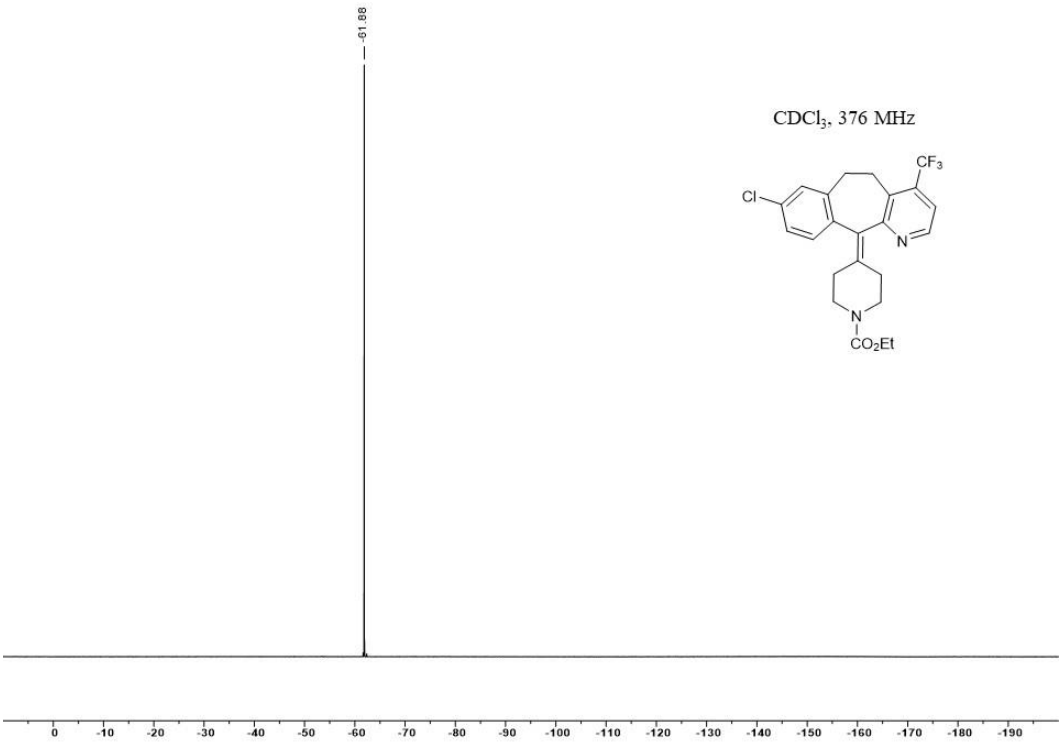

CDCl3, 400 MHz
CF3
N
N
Me

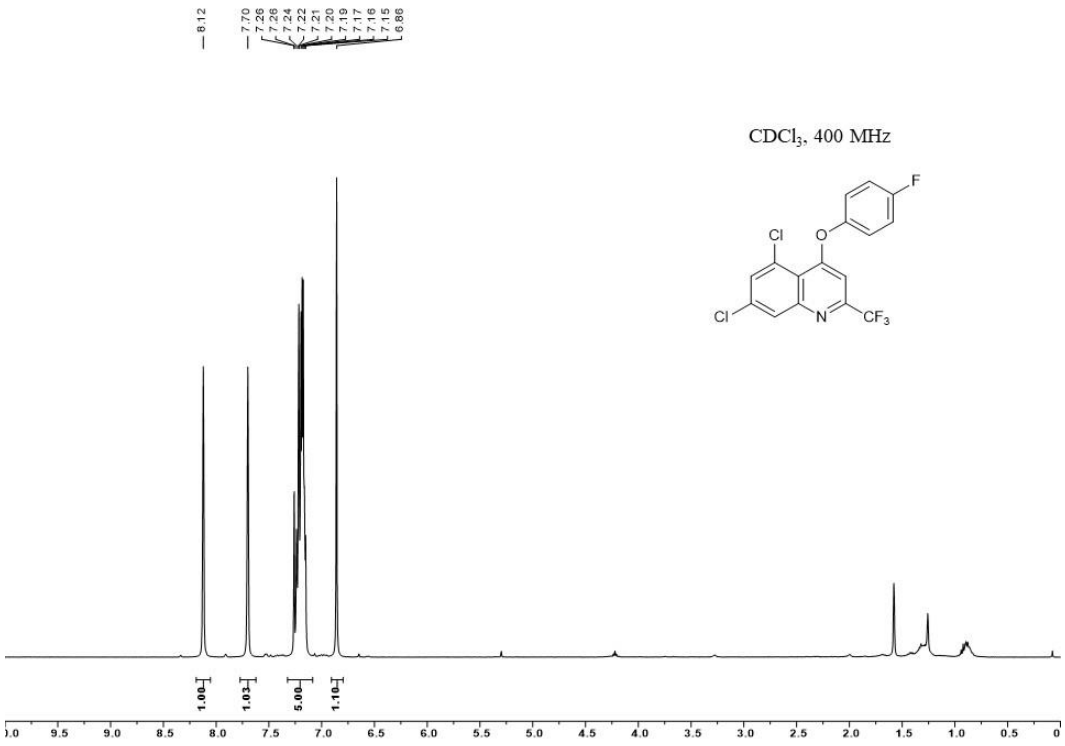

CDCl3, 100 MHz
CF3
N
N
Me

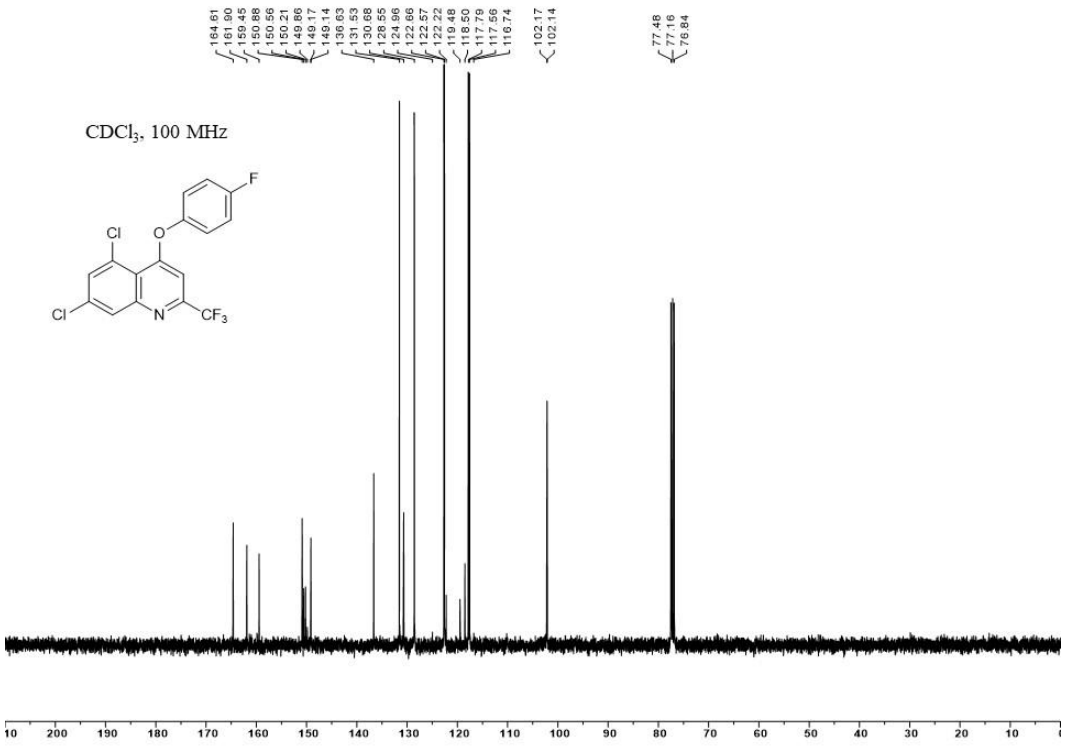

-64.83
CDCl3, 376 MHz
CF3
N
N
Me
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

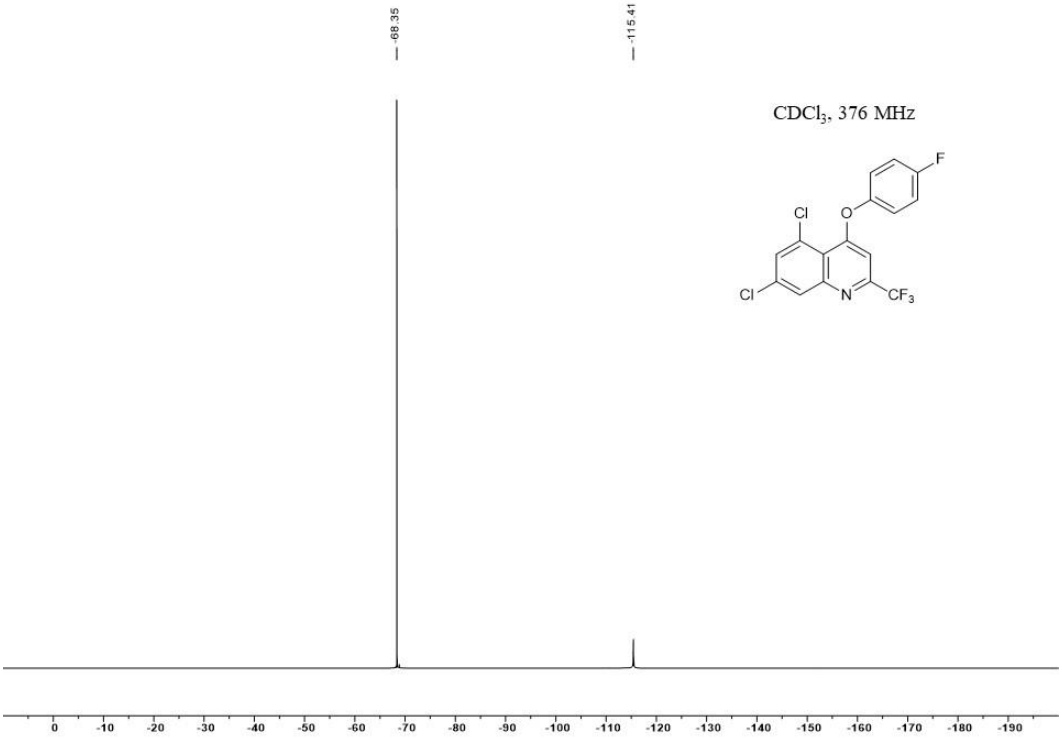

CDCl3, 400 MHz
CF3
Cl
N
N
CO2Et
1.00 1.01 3.09 2.10 2.10 2.16 3.20 1.08 3.23 1.10 3.43
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

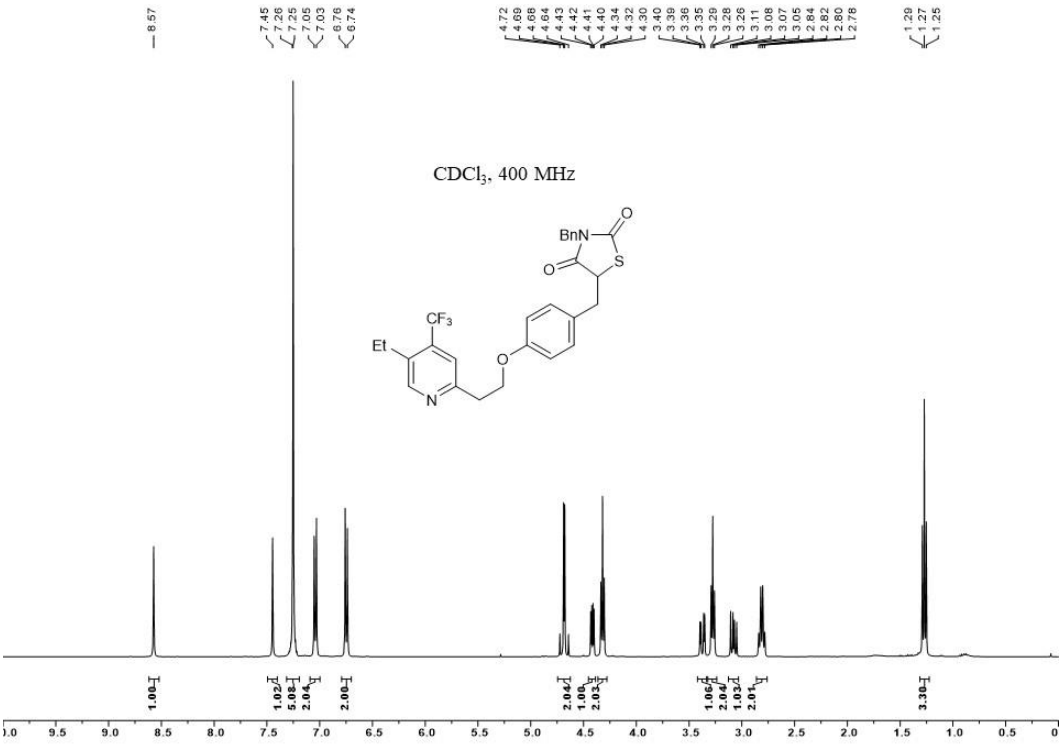

162.47
155.57
147.72
138.37
137.83
136.81
136.50
136.19
135.88
134.63
133.64
133.47
131.89
131.31
130.32
127.43
126.23
124.70
121.97
119.23
118.66
118.61
118.56
118.51
77.48
77.16
76.84
61.52
44.89
44.64
31.92
30.86
30.62
26.18
14.77
CDCl3, 100 MHz
CF3
Cl
N
N
CO2Et
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

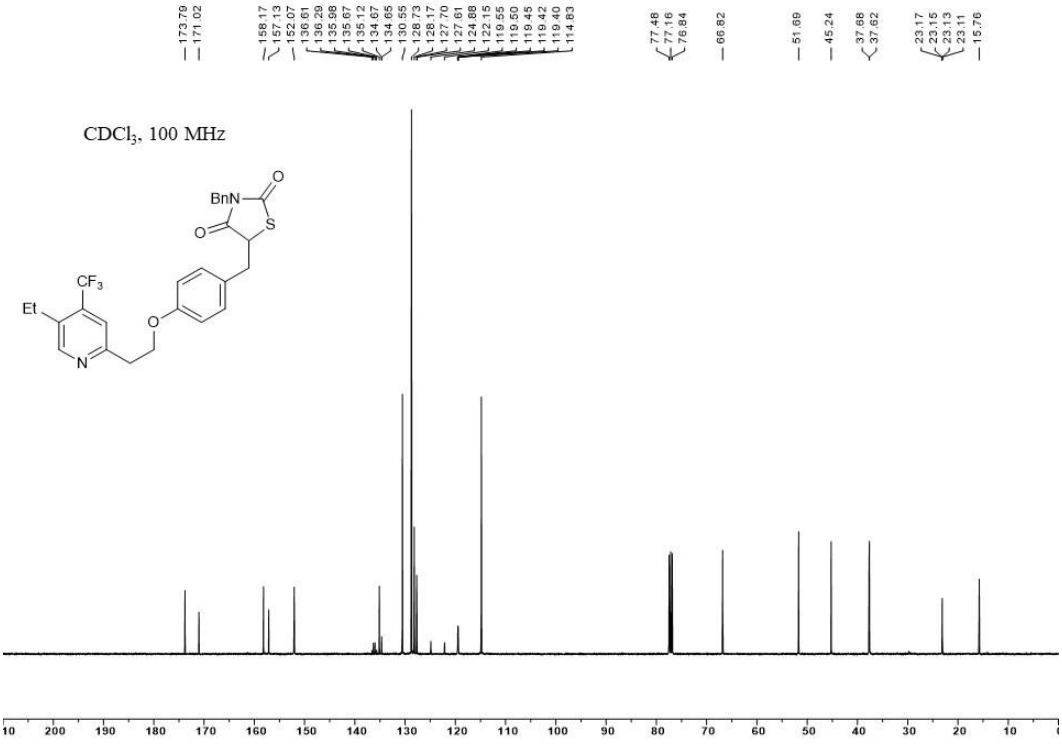

-61.88
CDCl3, 376 MHz
CF3
Cl
N
N
CO2Et
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

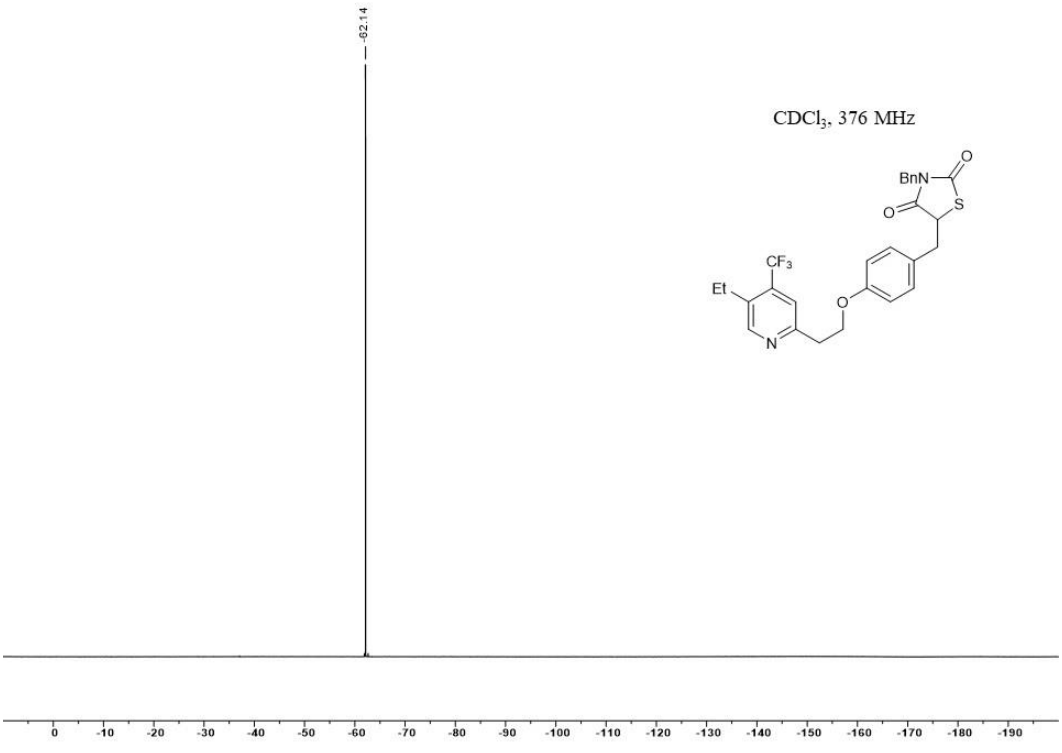

8.12
7.70
7.26
7.26
7.24
7.22
7.21
7.20
7.19
7.17
7.16
7.15
6.86
CDCl3, 400 MHz
F
Cl
O
Cl
N
CF3
1.00
1.03
5.00
1.10

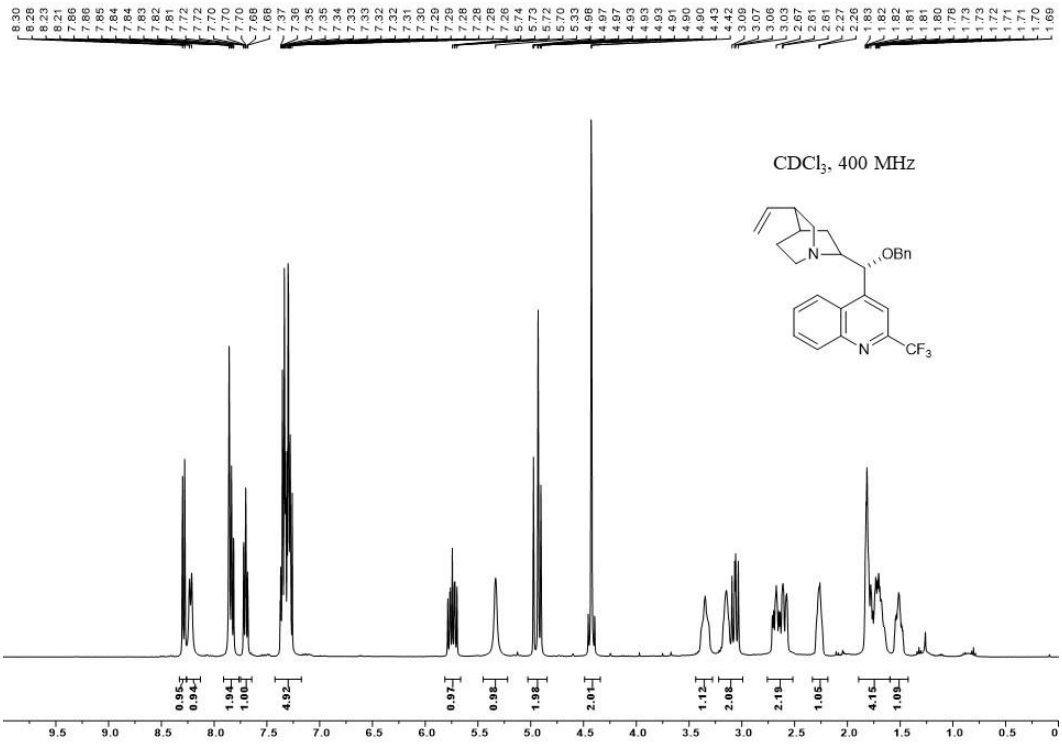

164.61
161.90
159.45
150.88
150.56
150.21
149.86
149.17
149.14
136.63
131.53
130.68
128.55
124.96
122.66
122.57
122.22
119.48
118.50
117.79
117.56
116.74
102.17
102.14
77.48
77.16
76.84
CDCl3, 100 MHz
F
Cl
O
Cl
N
CF3

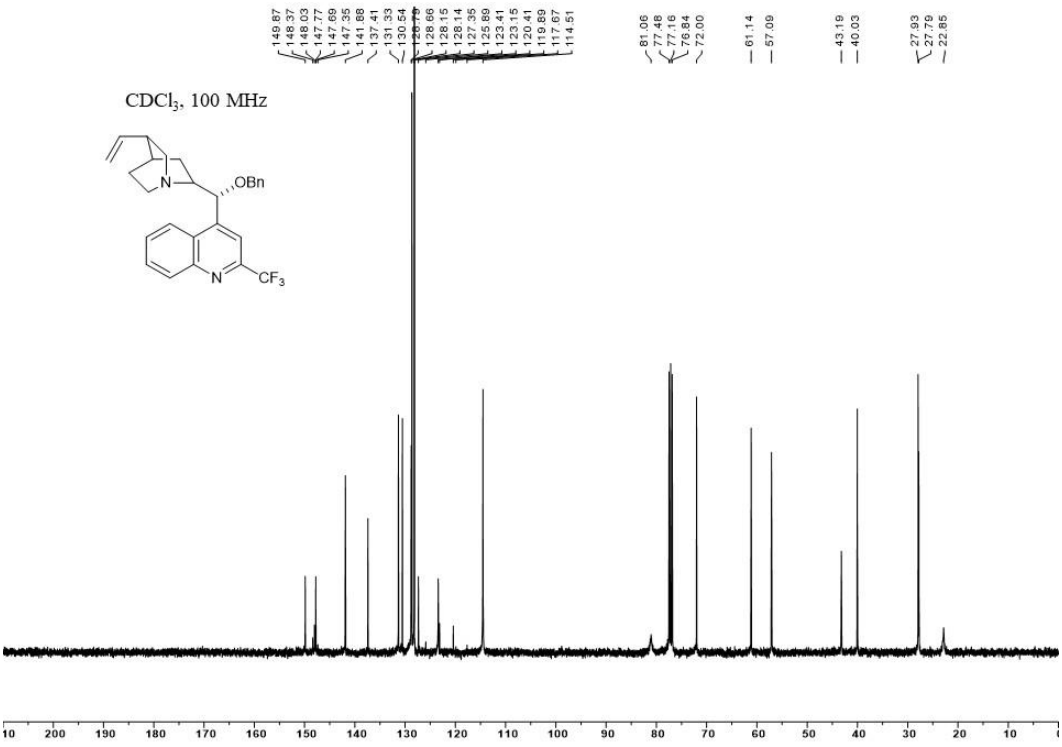

-68.35
-115.41
CDCl3, 376 MHz
F
O
Cl
Cl
N
CF3

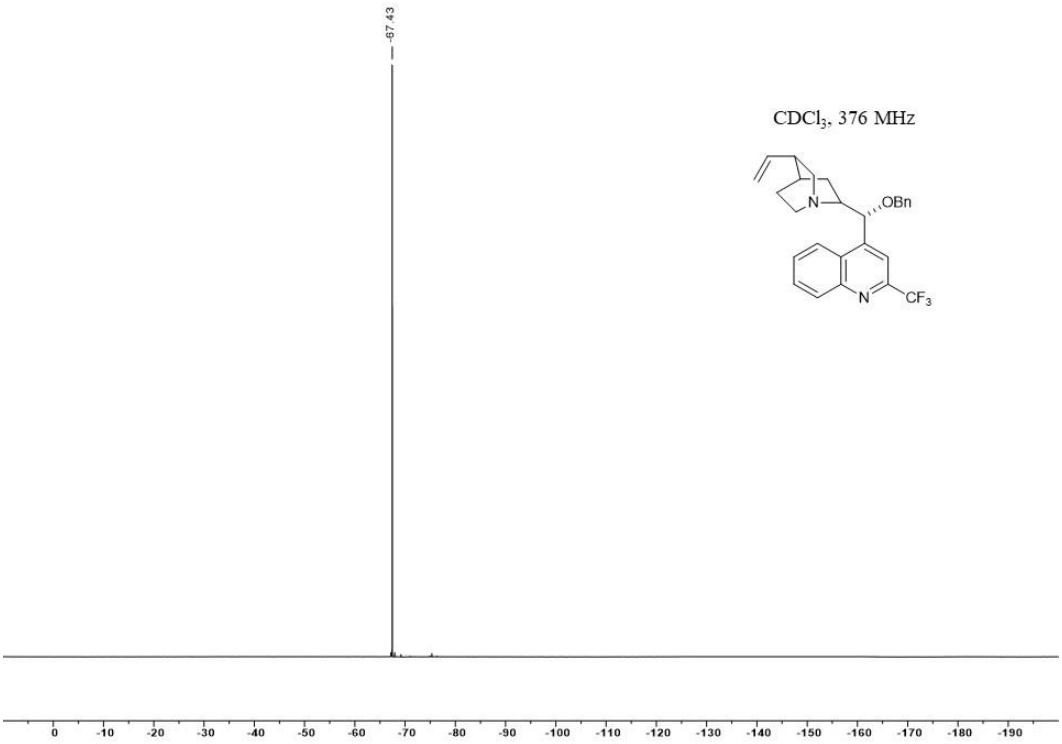

8.57
7.45
7.26
7.25
7.05
7.03
6.76
6.74
4.72
4.69
4.68
4.64
4.43
4.42
4.41
4.40
4.34
4.32
4.30
3.40
3.39
3.36
3.35
3.29
3.28
3.26
3.11
3.08
3.07
3.05
2.84
2.82
2.80
2.78
1.29
1.27
1.25
CDCl3, 400 MHz
BnN
O
O
S
CF3
Et
O
N
1.00
1.02
5.08
2.04
2.00
2.04
1.00
2.03
1.06
2.04
1.03
2.01
3.38

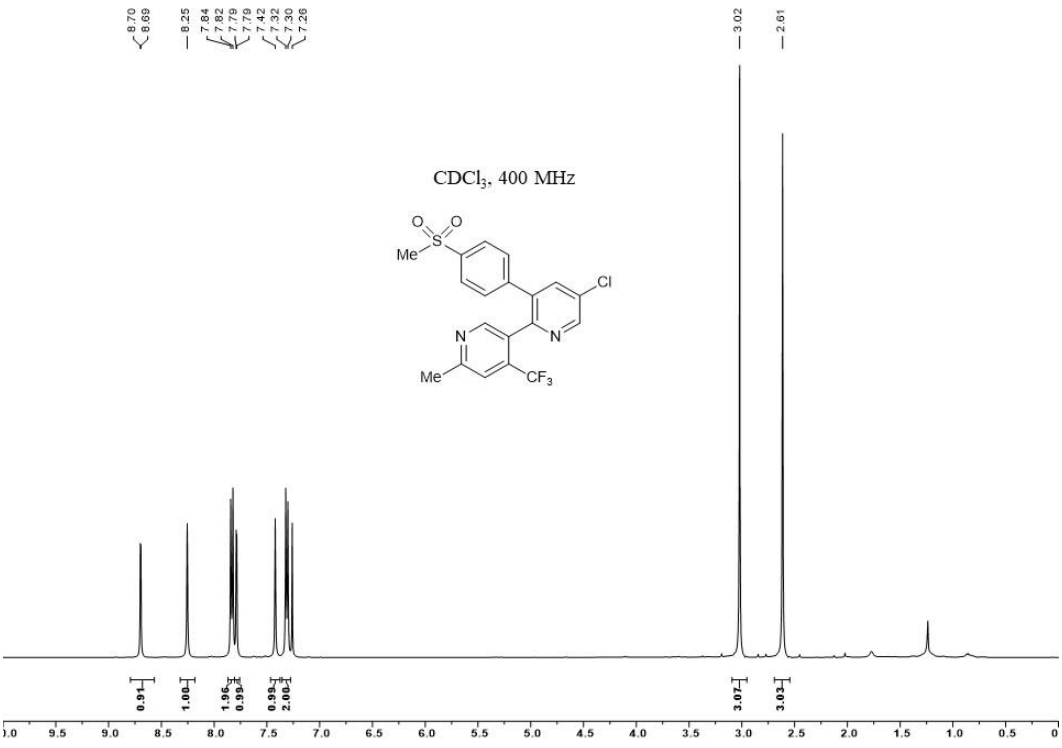

173.79
171.02
158.17
157.13
152.07
136.61
136.29
135.98
135.67
135.12
134.67
134.65
130.55
128.73
128.17
127.70
127.61
124.88
122.15
119.55
119.50
119.45
119.42
119.40
114.83
77.48
77.16
76.84
66.82
51.69
45.24
37.68
37.62
23.17
23.15
23.13
23.11
15.76
CDCl3, 100 MHz
BnN
O
O
S
CF3
Et
O
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

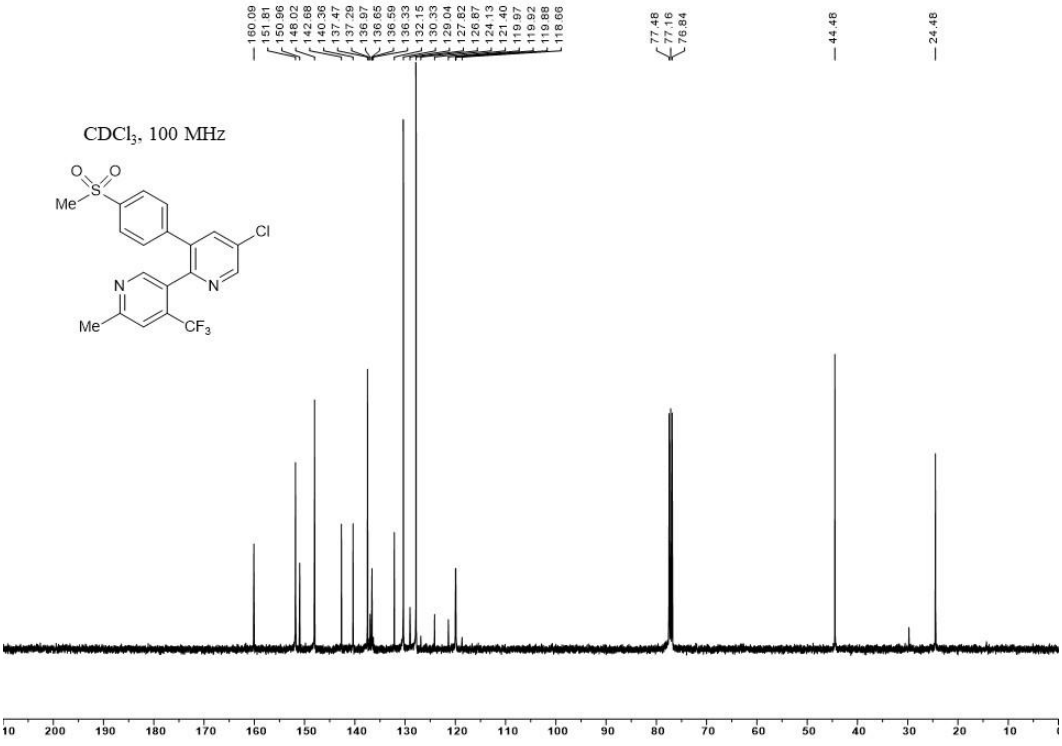

-62.14
CDCl3, 376 MHz
BnN
O
O
S
CF3
Et
O
N
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

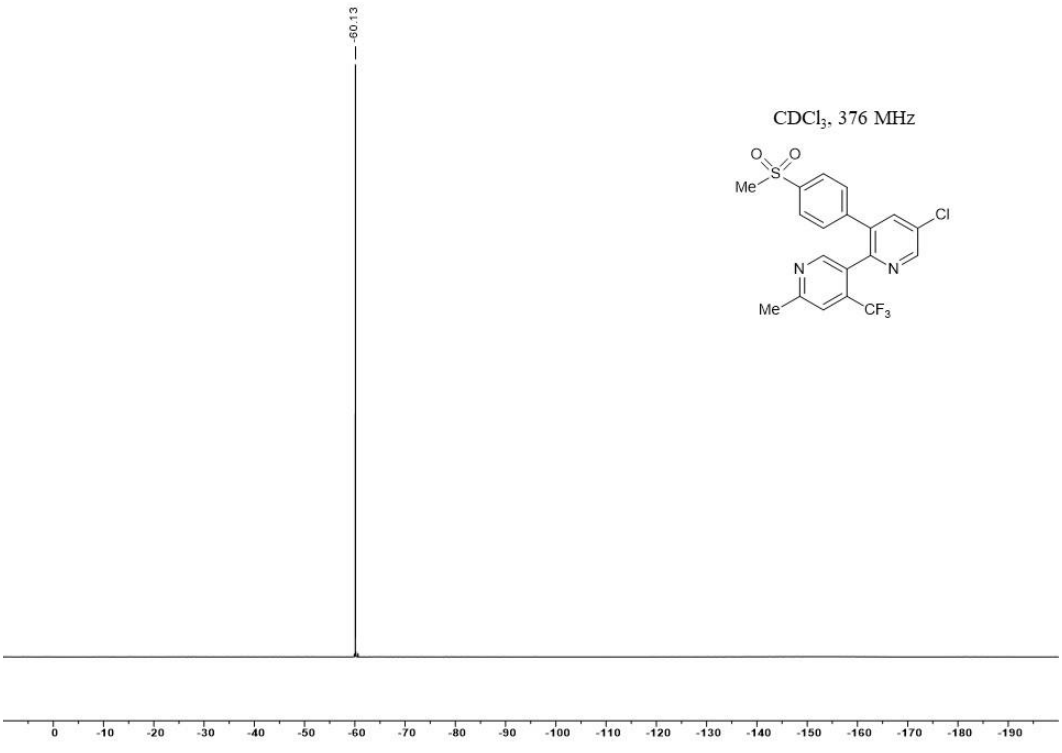

CDCl3, 400 MHz
OBn
N
CF3

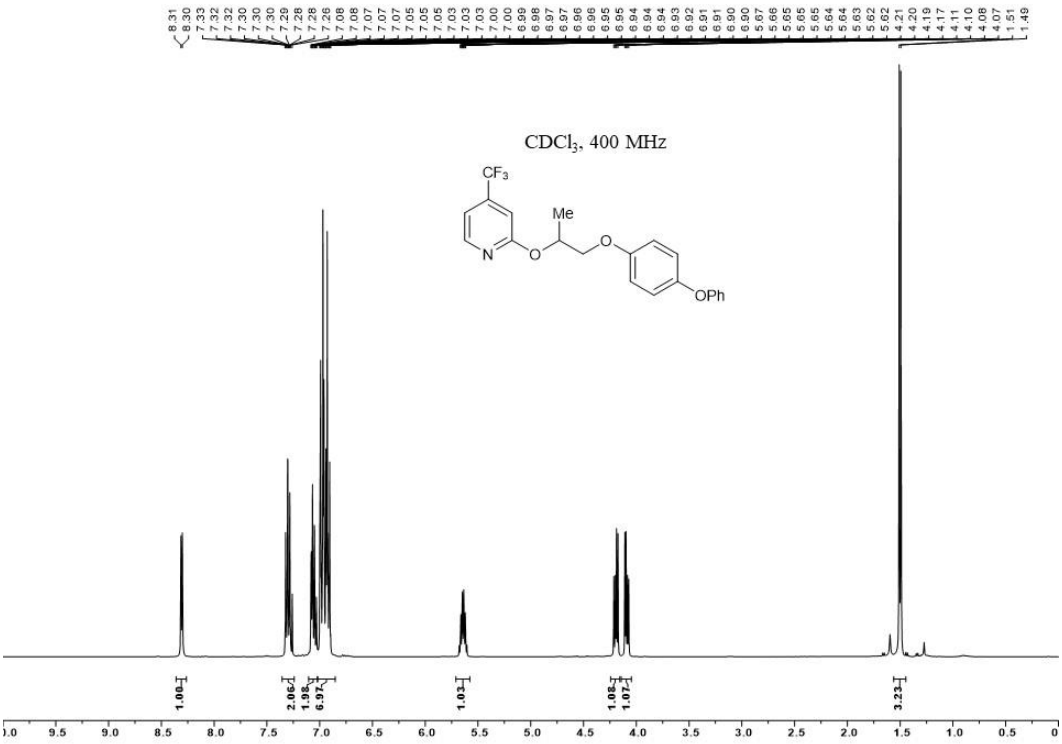

CDCl3, 100 MHz
OBn
N
CF3

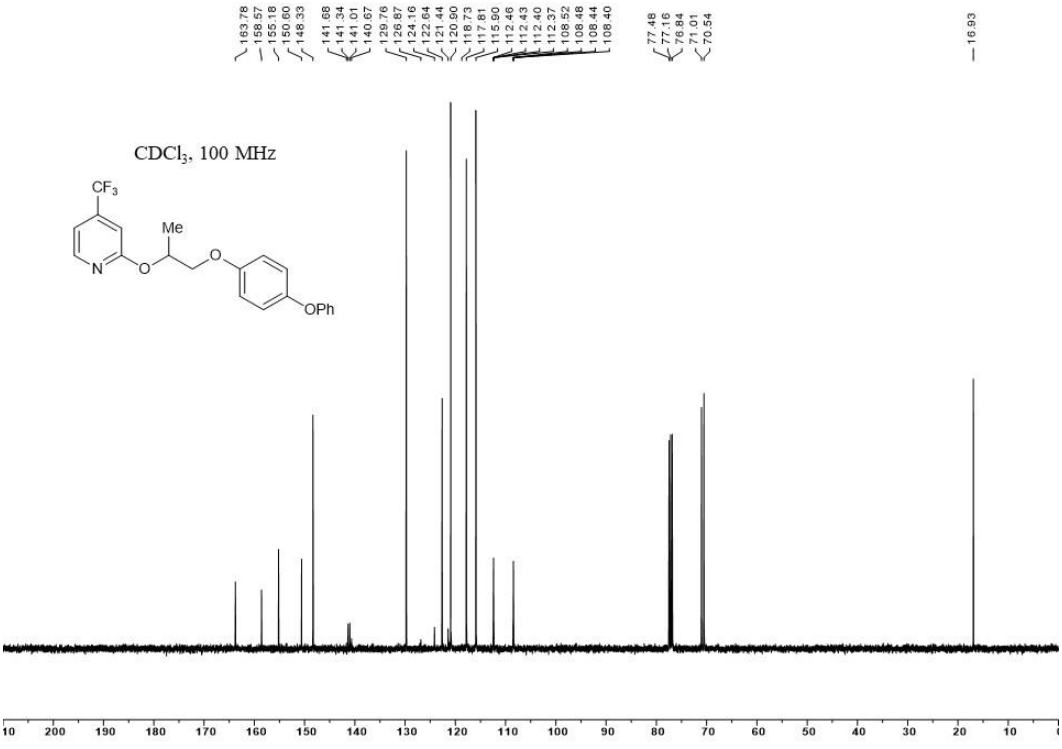

-67.43
CDCl3, 376 MHz
OBn
N
CF3
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

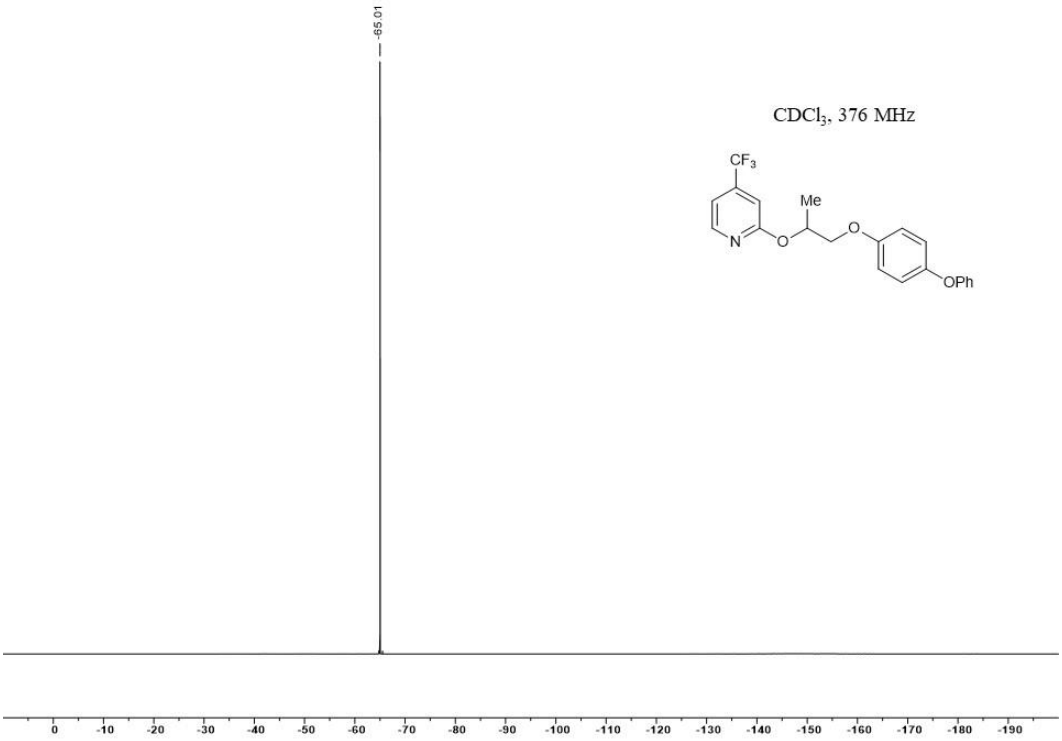

8.70
8.69
8.25
7.84
7.82
7.79
7.79
7.42
7.32
7.30
7.26
3.02
2.61
CDCl3, 400 MHz
O
O
S
Me
Cl
N
N
Me
CF3
0.91
1.00
1.96
0.99
2.00
3.07
3.03
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0

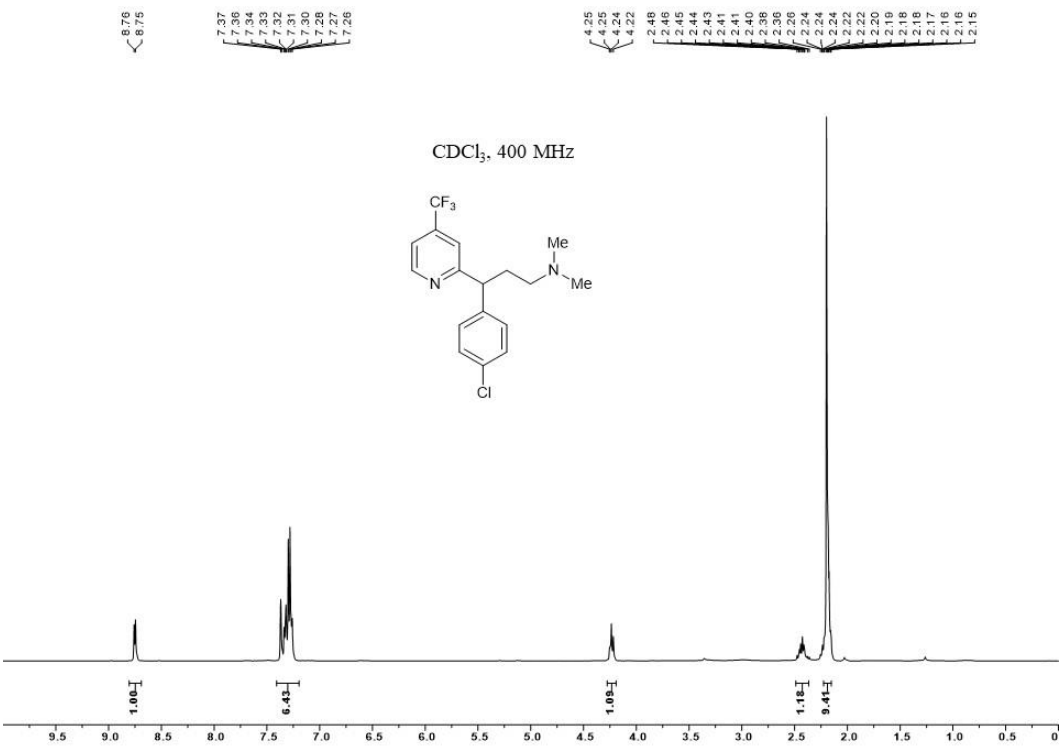

160.09
151.81
150.96
148.02
142.68
140.36
137.47
137.29
136.97
136.65
136.59
136.33
132.15
130.33
129.04
127.82
126.87
124.13
121.40
119.97
119.92
119.88
118.66
77.48
77.16
76.84
44.48
24.48
CDCl3, 100 MHz
Me
S
O
O
Cl
N
N
Me
CF3
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

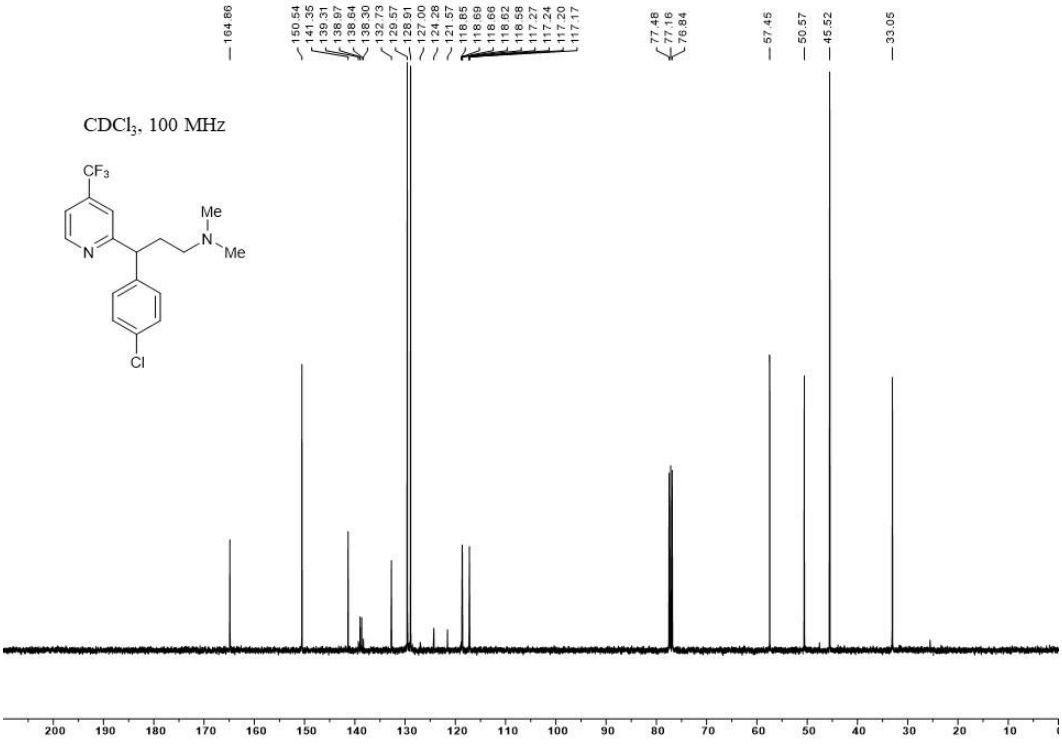

-60.13
CDCl3, 376 MHz
Me
S
O
O
Cl
N
N
Me
CF3
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

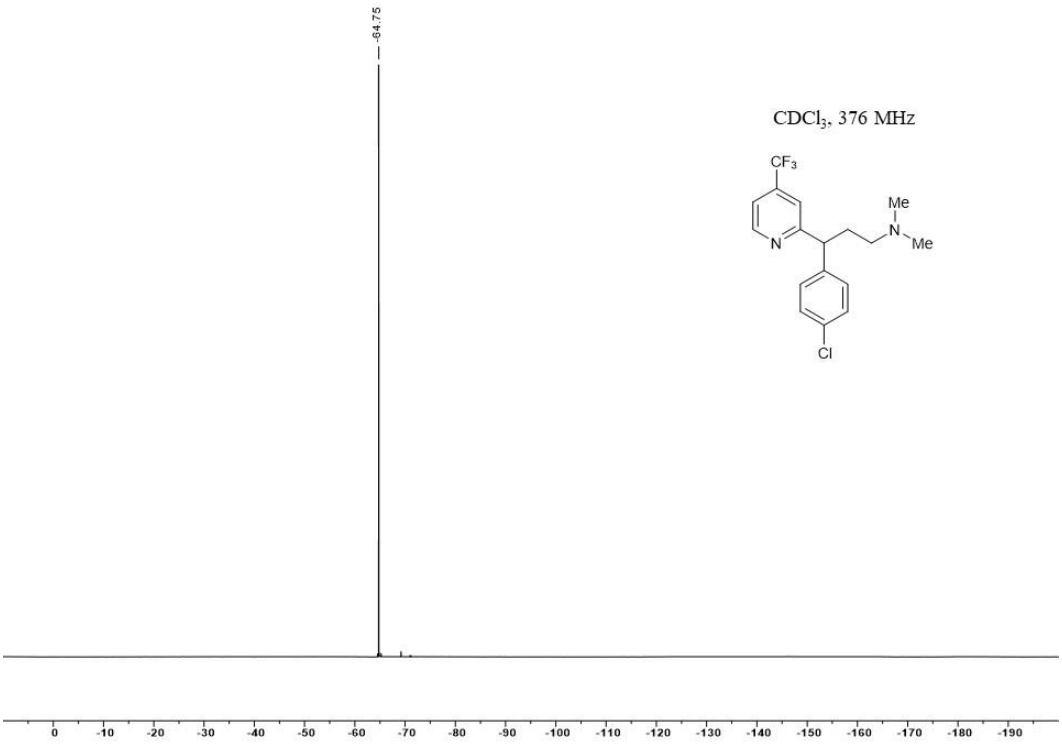

CDCl3, 400 MHz
CF3
Me
N
O
O
OPh

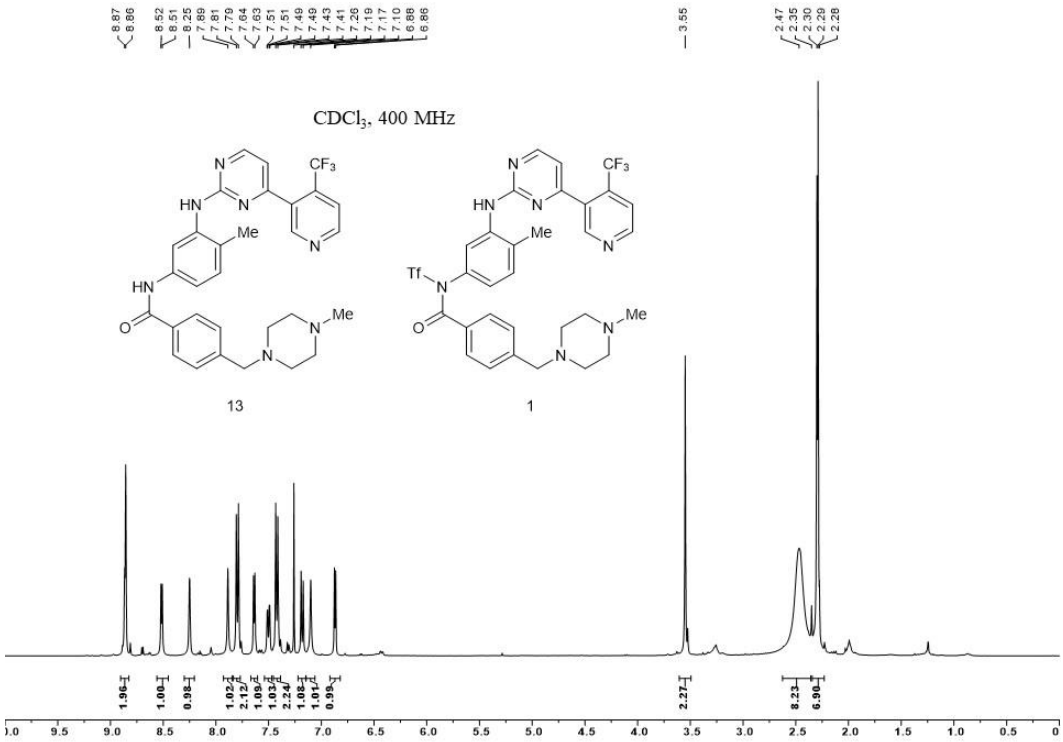

CDCl3, 100 MHz
CF3
Me
N
O
O
OPh

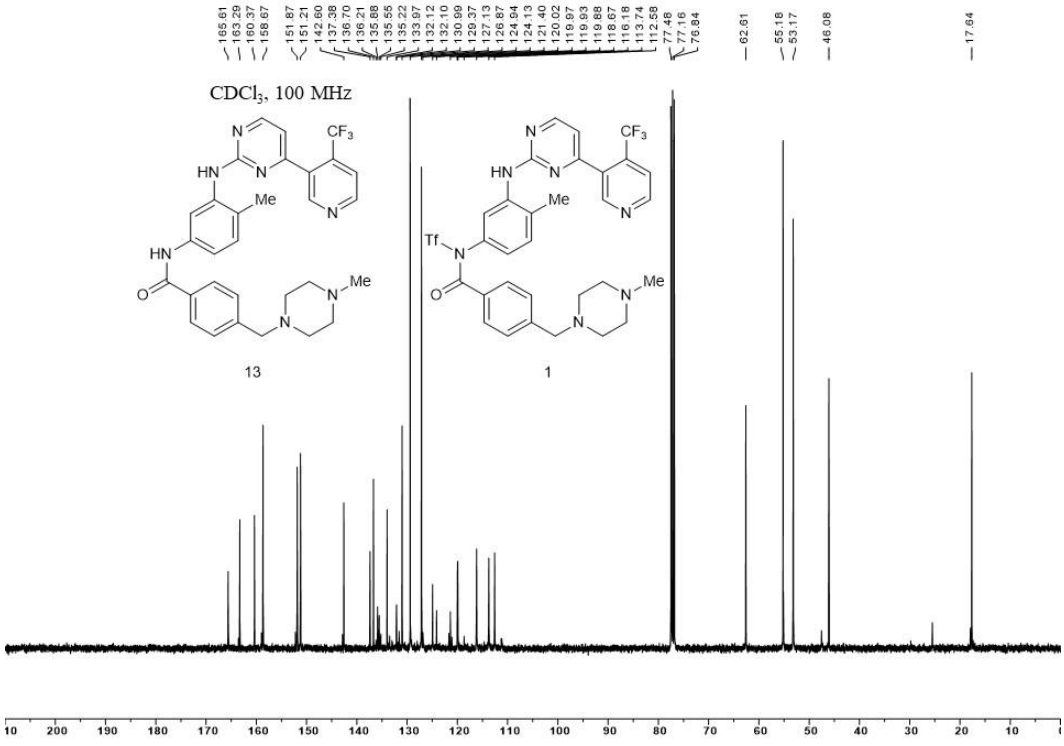

-65.01
CDCl3, 376 MHz
CF3
Me
N
O
O
OPh
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

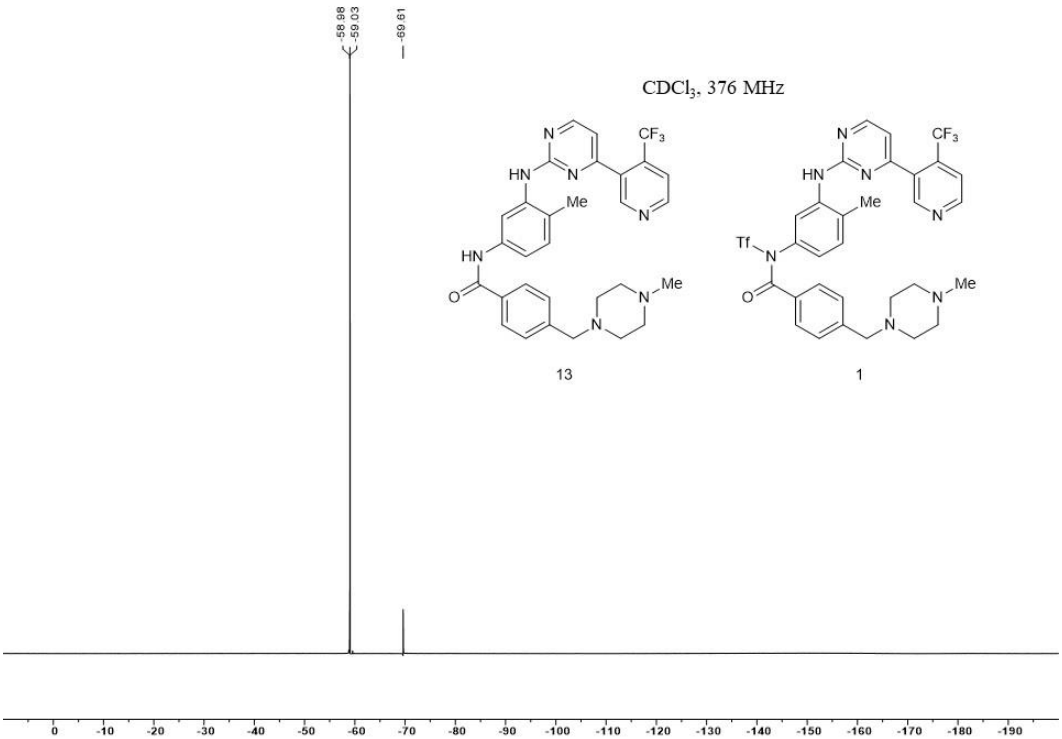

8.76
8.75
7.37
7.36
7.34
7.33
7.32
7.31
7.30
7.28
7.27
7.26
4.25
4.25
4.24
4.22
2.48
2.46
2.45
2.44
2.43
2.41
2.41
2.40
2.38
2.36
2.26
2.24
2.24
2.22
2.22
2.20
2.19
2.18
2.18
2.17
2.16
2.16
2.15
CDCl3, 400 MHz
CF3
Me
N
Me
N
Cl
1.00
6.43
1.09
1.18
9.41
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0

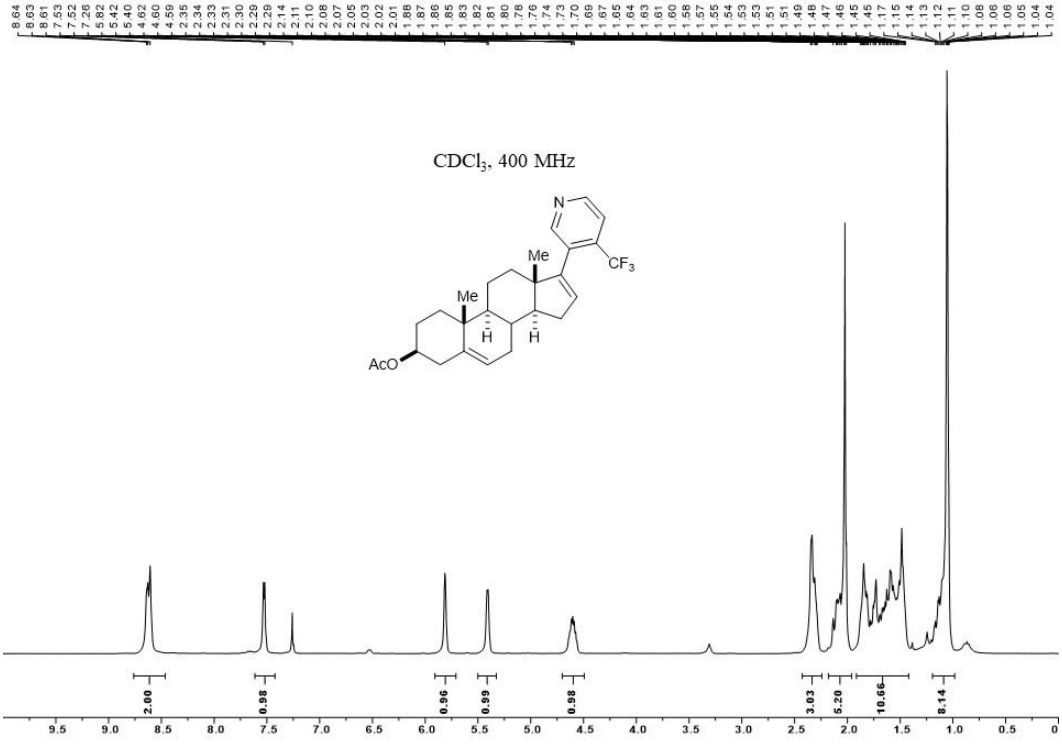

164.86
150.54
141.35
139.31
138.97
138.64
138.30
132.73
129.57
128.91
127.00
124.28
121.57
118.85
118.69
118.66
118.62
118.58
117.27
117.24
117.20
117.17
77.48
77.16
76.84
57.45
50.57
45.52
33.05
CDCl3, 100 MHz
CF3
Me
N
Me
N
Cl
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

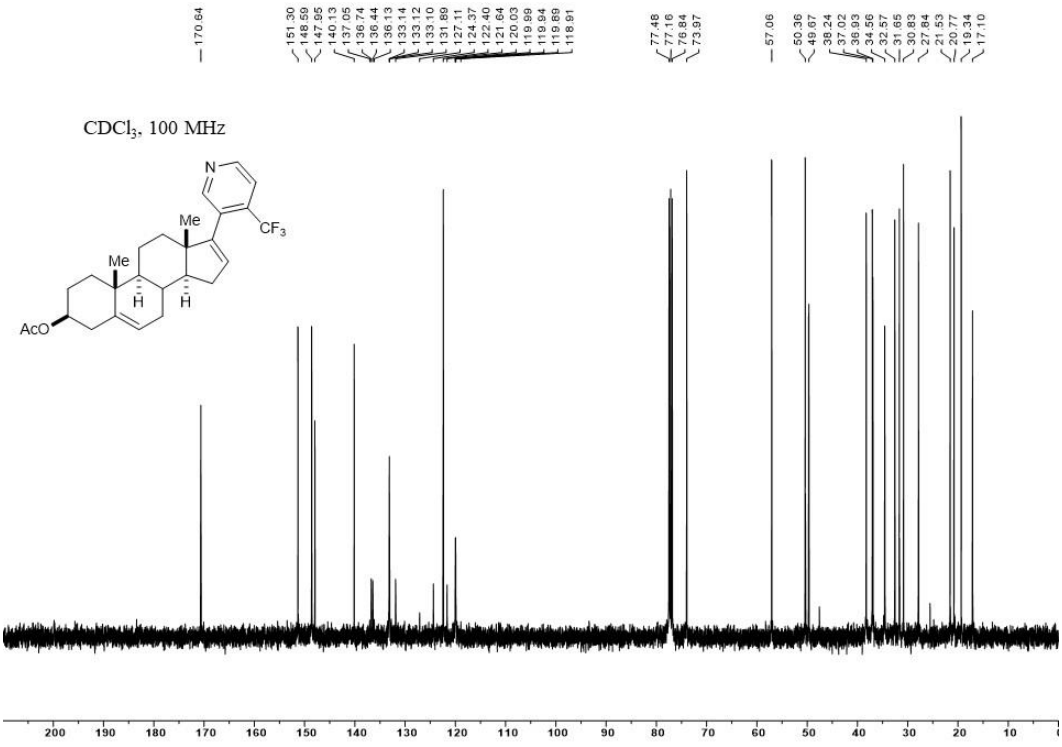

-64.75
CDCl3, 376 MHz
CF3
Me
N
Me
N
Cl
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190

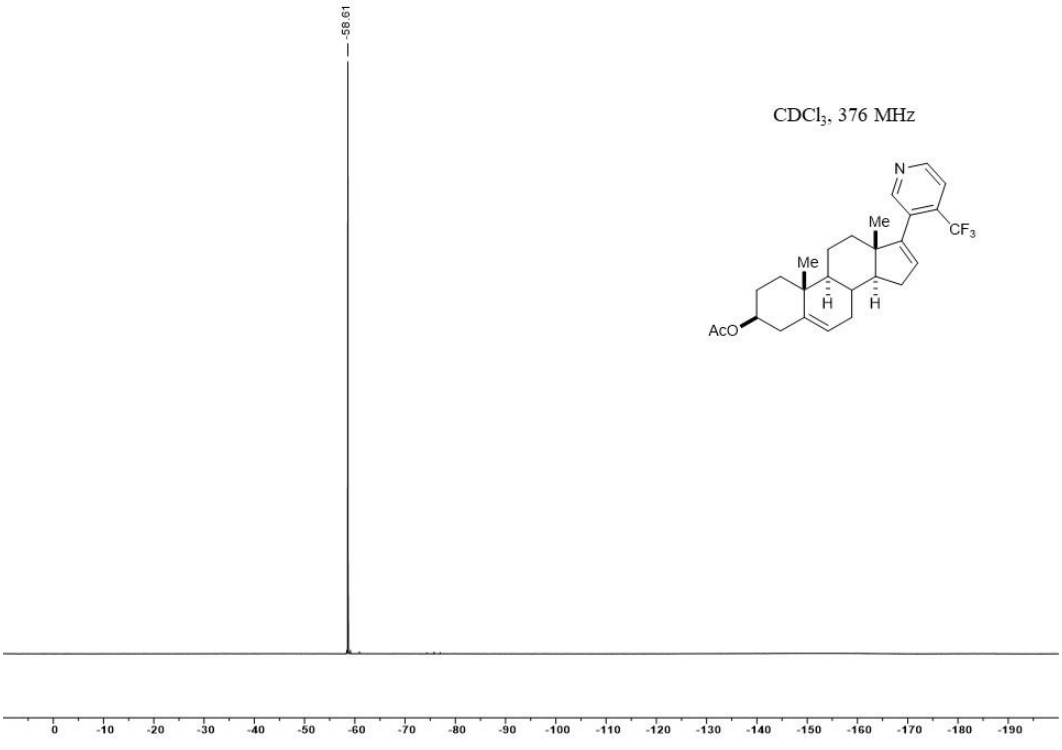

CDCl3, 400 MHz
13
1

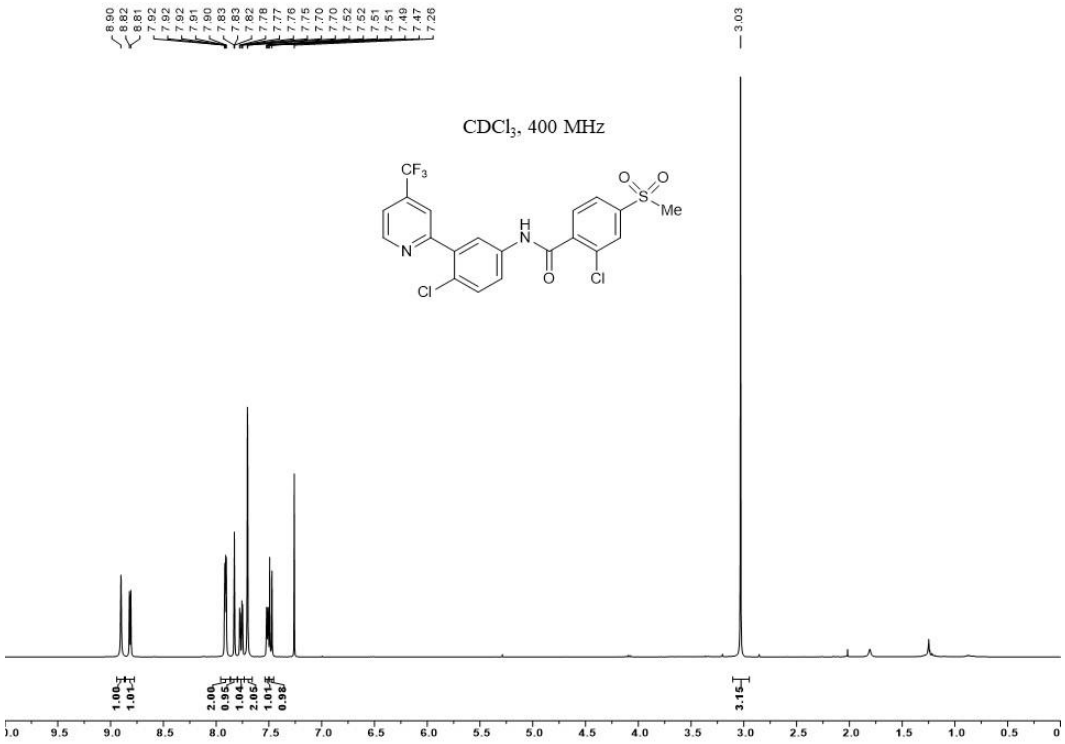

CDCl3, 100 MHz
13
1

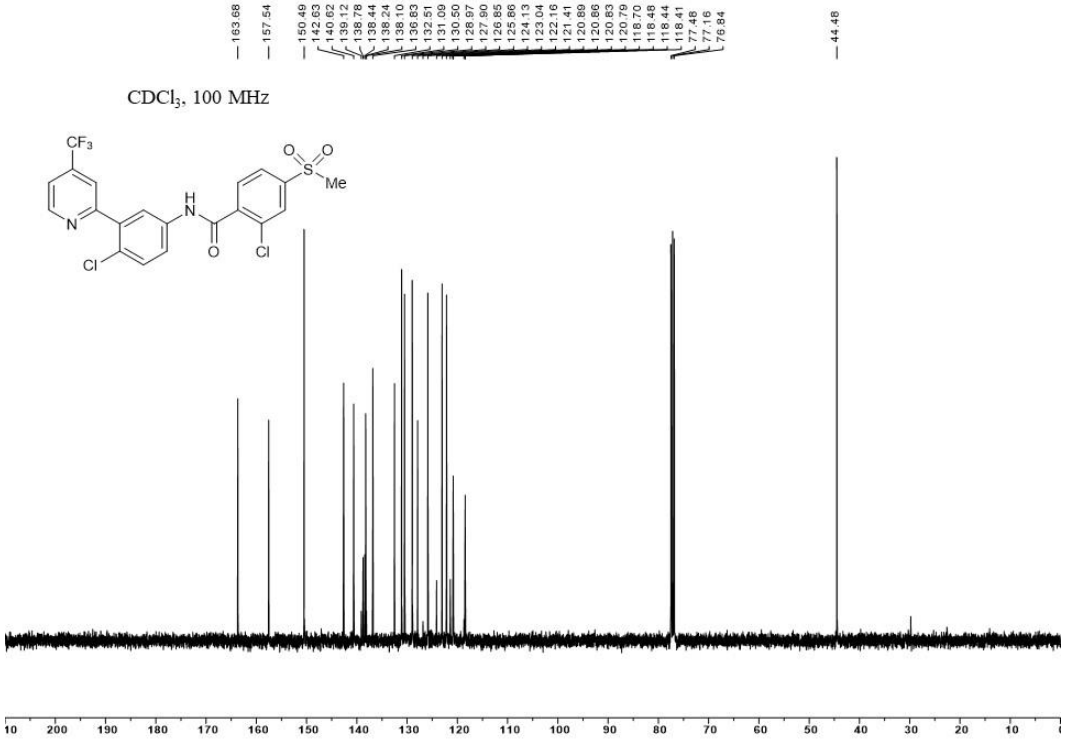

-58.98
-59.03
-69.61
CDCl3, 376 MHz
13
1

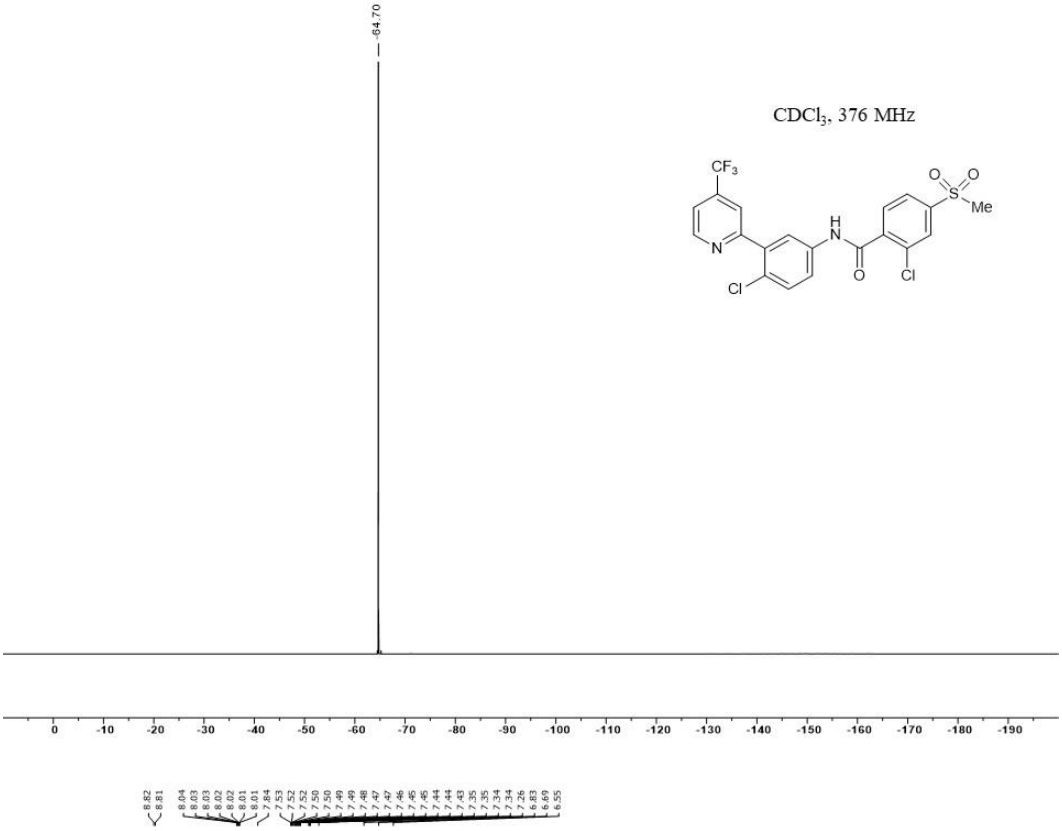

CDCl3, 400 MHz
2.00
0.98
0.96
0.99
0.98
3.03
5.20
10.66
8.14

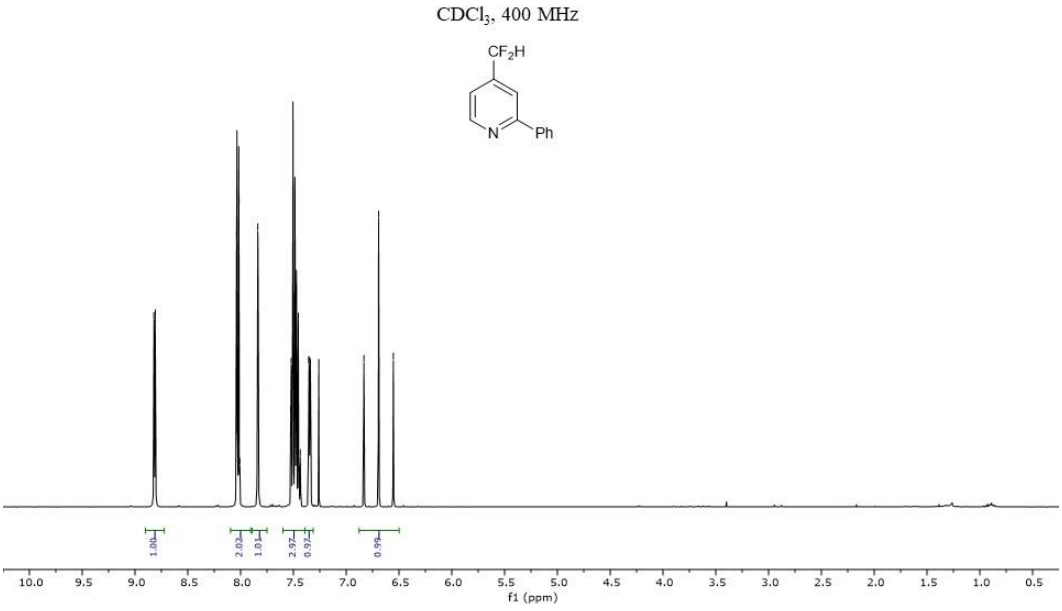

170.64
151.30
148.59
147.95
140.13
137.05
136.74
136.44
136.13
133.14
133.12
133.10
131.89
127.11
124.37
122.40
121.64
120.03
119.99
119.94
119.69
118.91
77.48
77.16
76.84
73.97
57.06
50.36
49.67
38.24
37.02
36.93
34.56
32.57
31.65
30.83
27.84
21.53
20.77
19.34
17.10
CDCl3, 100 MHz
N
Me
CF3
Me
H
H
AcO
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10

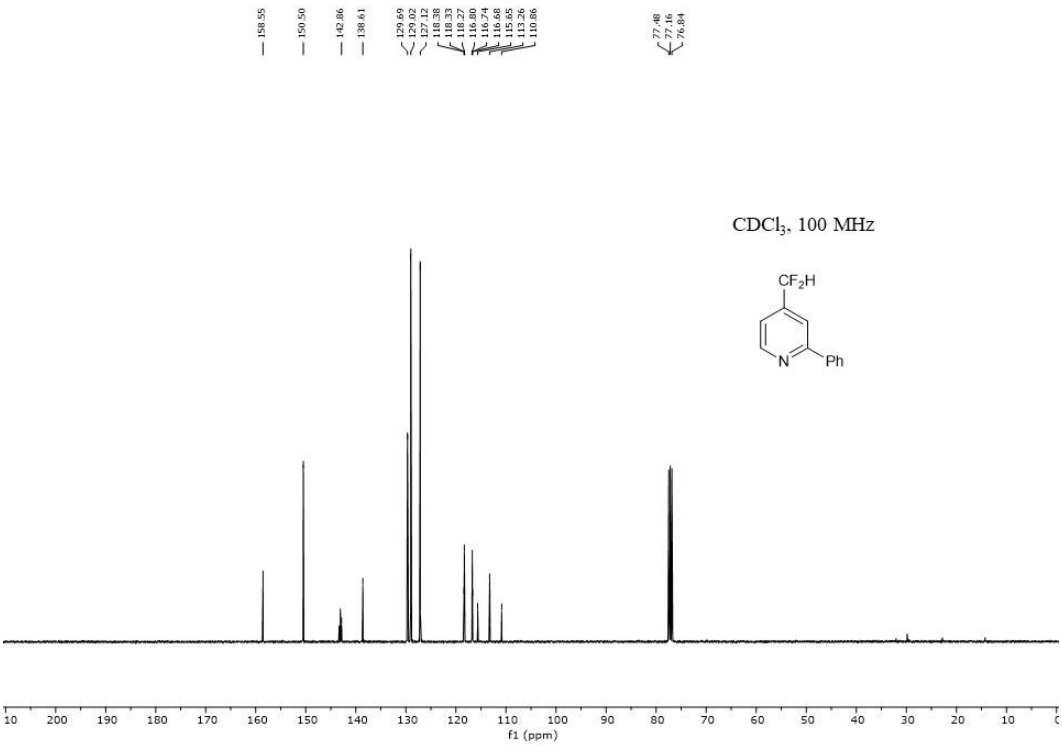

-58.61
CDCl3, 376 MHz
N
Me
CF3
Me
H
H
AcO
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

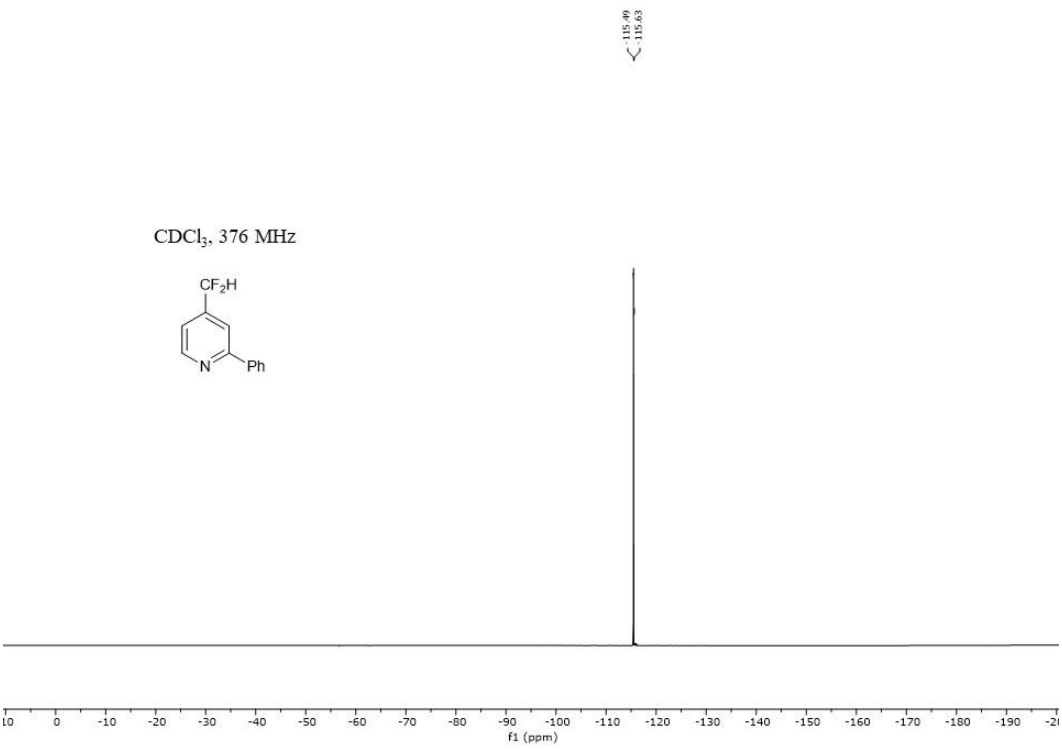

8.90
8.82
8.81
7.92
7.92
7.92
7.91
7.90
7.83
7.82
7.78
7.77
7.76
7.75
7.70
7.70
7.52
7.52
7.51
7.51
7.49
7.47
7.26
3.03
CDCl3, 400 MHz
CF3
N
H
N
O
S
O
O
Me
Cl
O
Cl
1.00
1.01
2.00
0.95
1.04
2.05
1.01
0.98
3.15

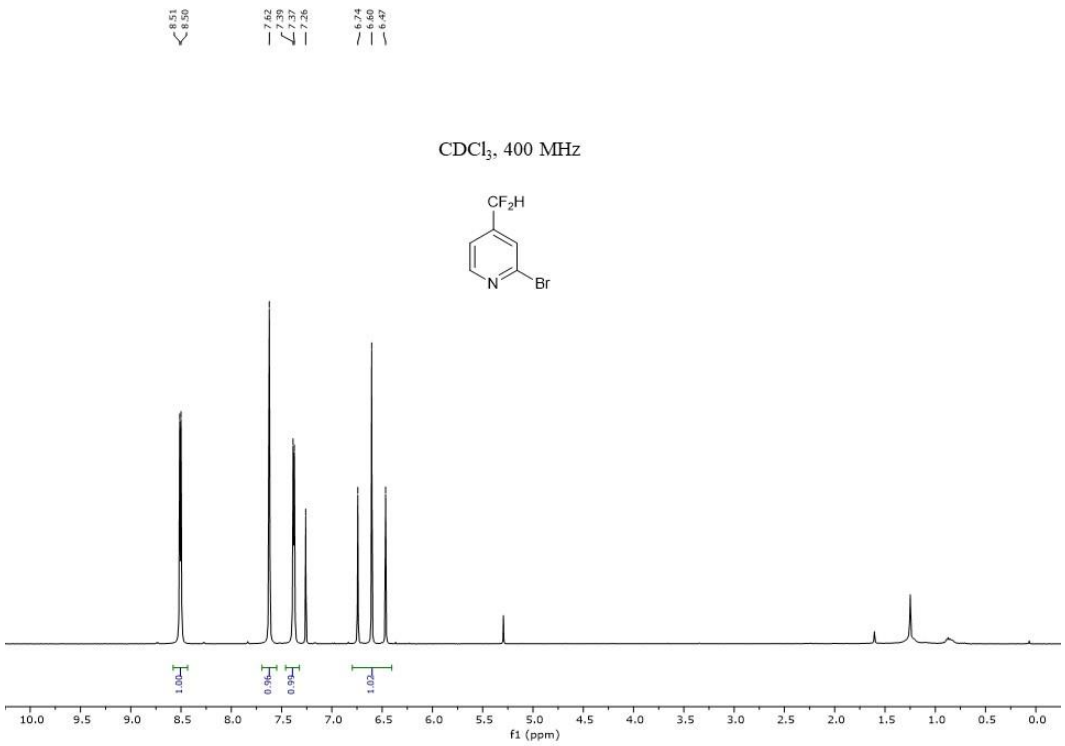

163.68
157.54
150.49
142.63
140.62
139.12
138.78
138.44
138.24
138.10
136.83
132.51
131.09
130.50
128.97
127.90
126.85
125.86
124.13
123.04
122.16
121.41
120.89
120.86
120.83
120.79
118.70
118.48
118.44
118.41
77.48
77.16
76.84
44.48
CDCl3, 100 MHz
CF3
N
H
N
O
S
O
O
Me
Cl
O
Cl

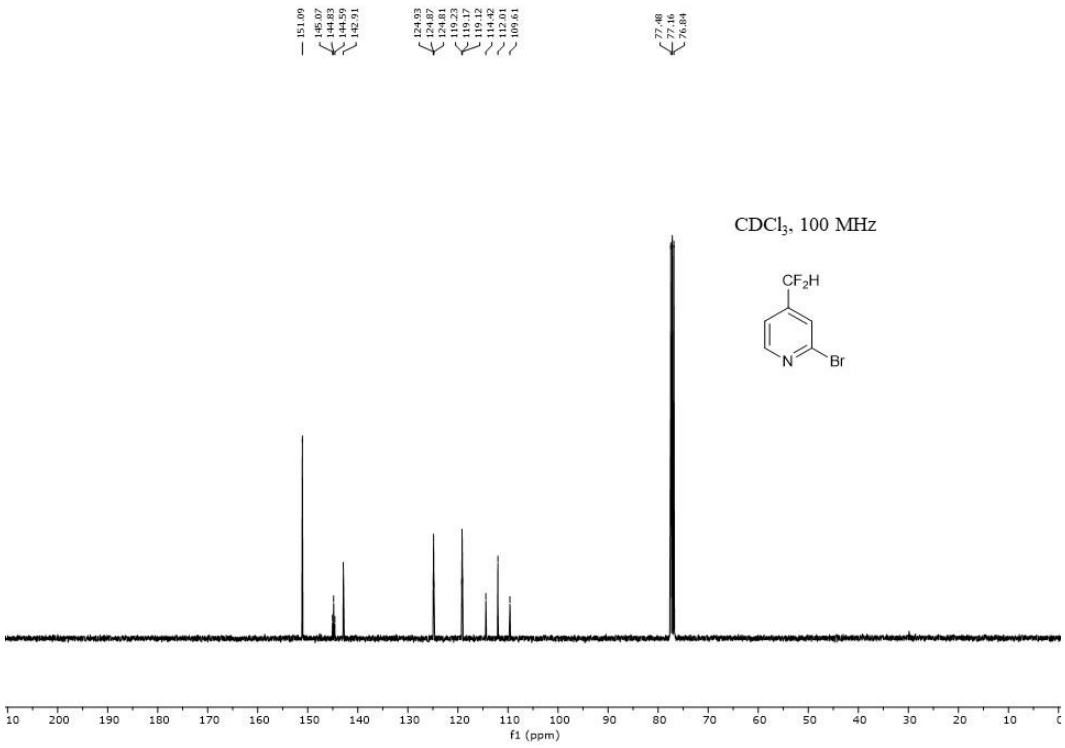

-64.70
CDCl3, 376 MHz
CF3
O
S
O
Me
H
N
N
O
Cl
Cl
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
8.82
8.81
8.04
8.03
8.03
8.02
8.02
8.01
8.01
7.84
7.53
7.52
7.52
7.50
7.50
7.49
7.49
7.48
7.47
7.47
7.46
7.46
7.45
7.44
7.44
7.43
7.35
7.35
7.34
7.26
6.83
6.69
6.55


CDCl3, 400 MHz
CF2H
N
Ph
1.00
2.02
1.01
2.97
0.92
0.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

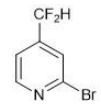

158.55
150.50
142.86
138.61
129.69
129.02
127.12
118.38
118.33
118.27
116.80
116.74
116.68
115.65
113.26
110.86
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
N
Ph
f1 (ppm)


115.49
115.63
CDCl3, 376 MHz
CF2H
N
Ph
f1 (ppm)

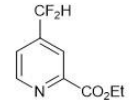

8.51
8.50
7.62
7.39
7.37
7.26
6.74
6.60
6.47
CDCl3, 400 MHz
CF2H
N
Br
1.00
0.96
0.99
1.02
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

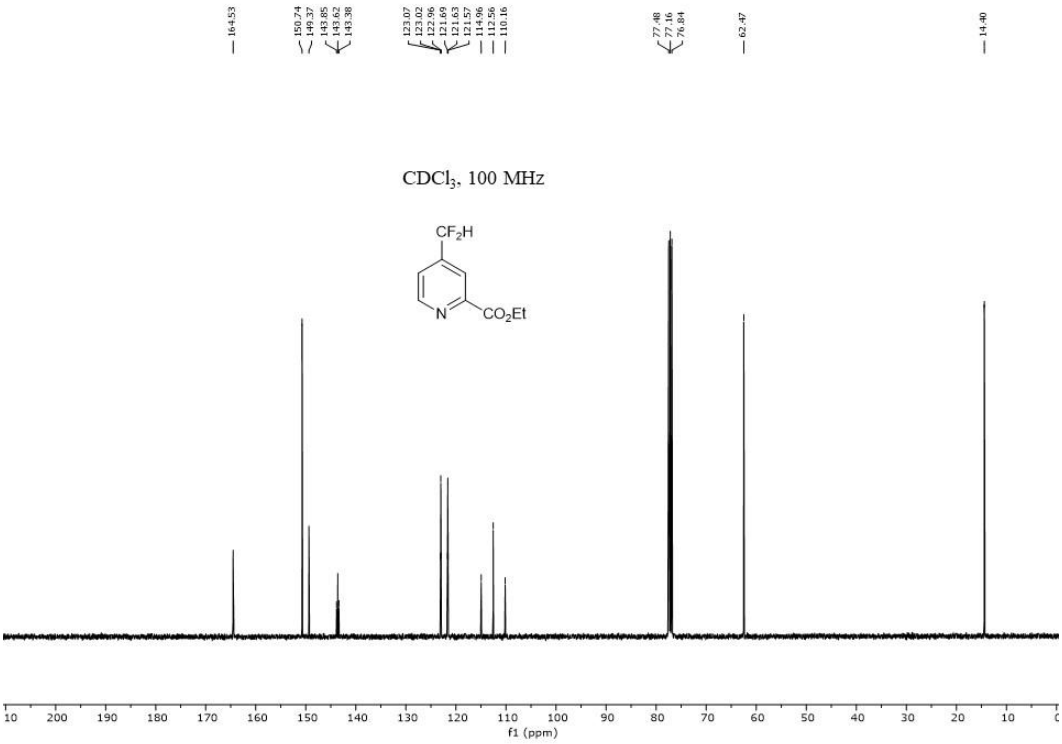

151.09
145.07
144.83
144.59
142.91
124.83
124.57
124.81
119.23
119.17
119.12
114.42
112.01
109.61
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
N
Br
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

$CDCl_3$, 376 MHz

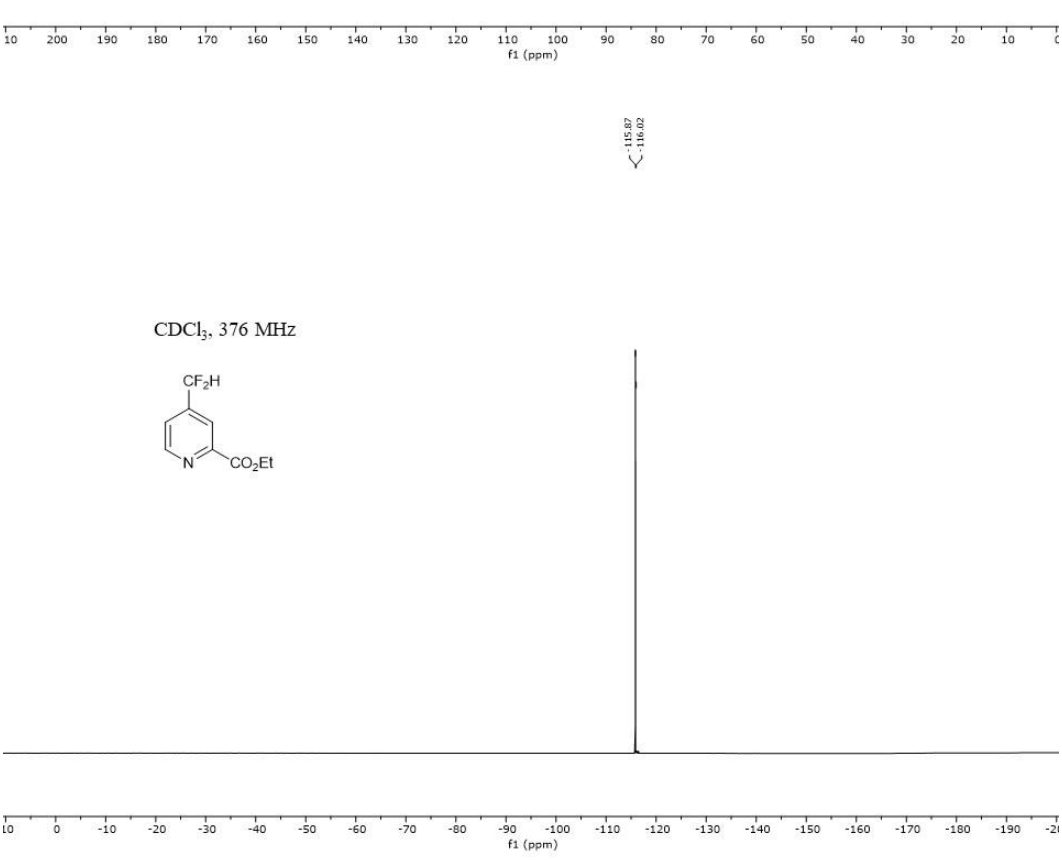


$CDCl_3$, 400 MHz



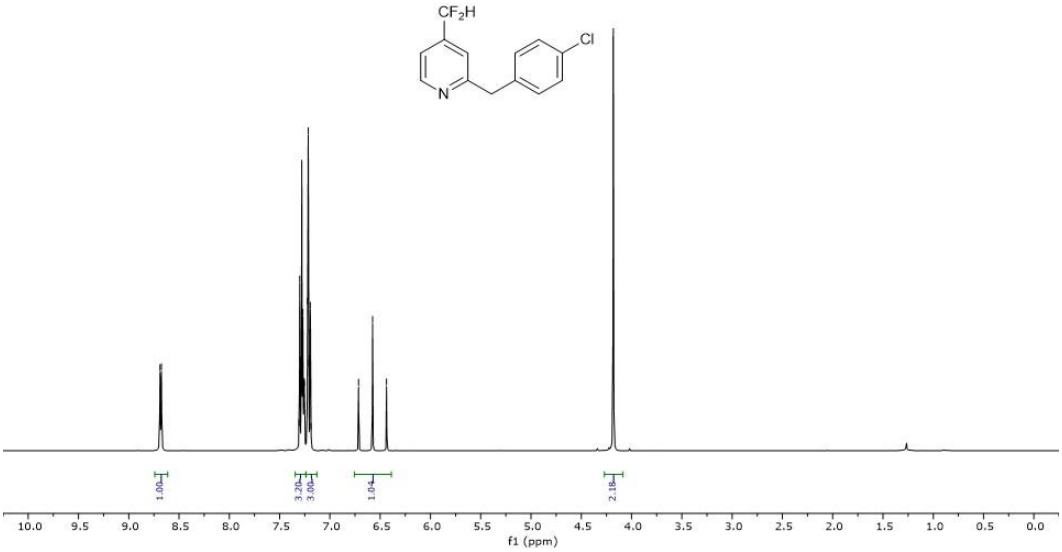


$CDCl_3$, 100 MHz

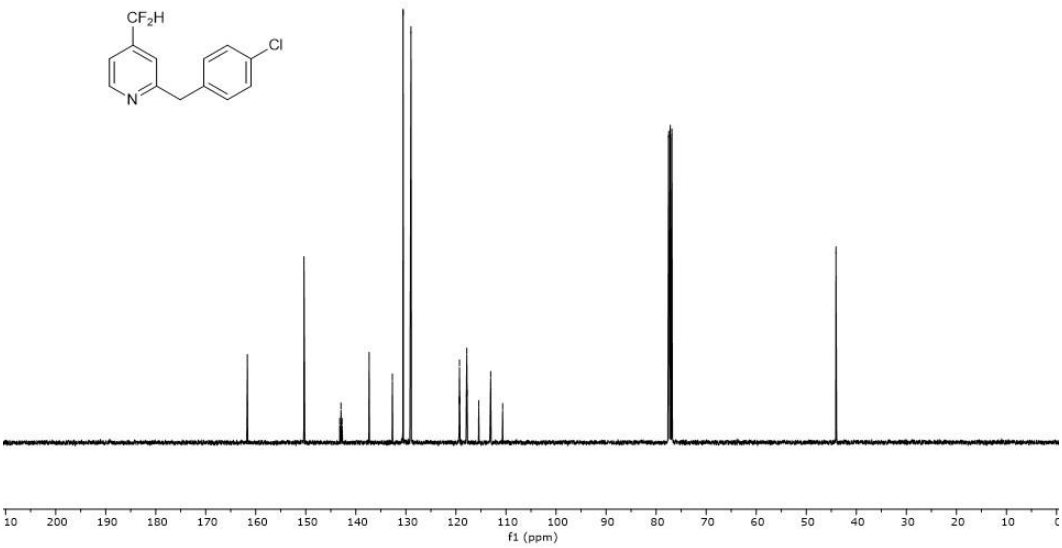


$CDCl_3$, 376 MHz

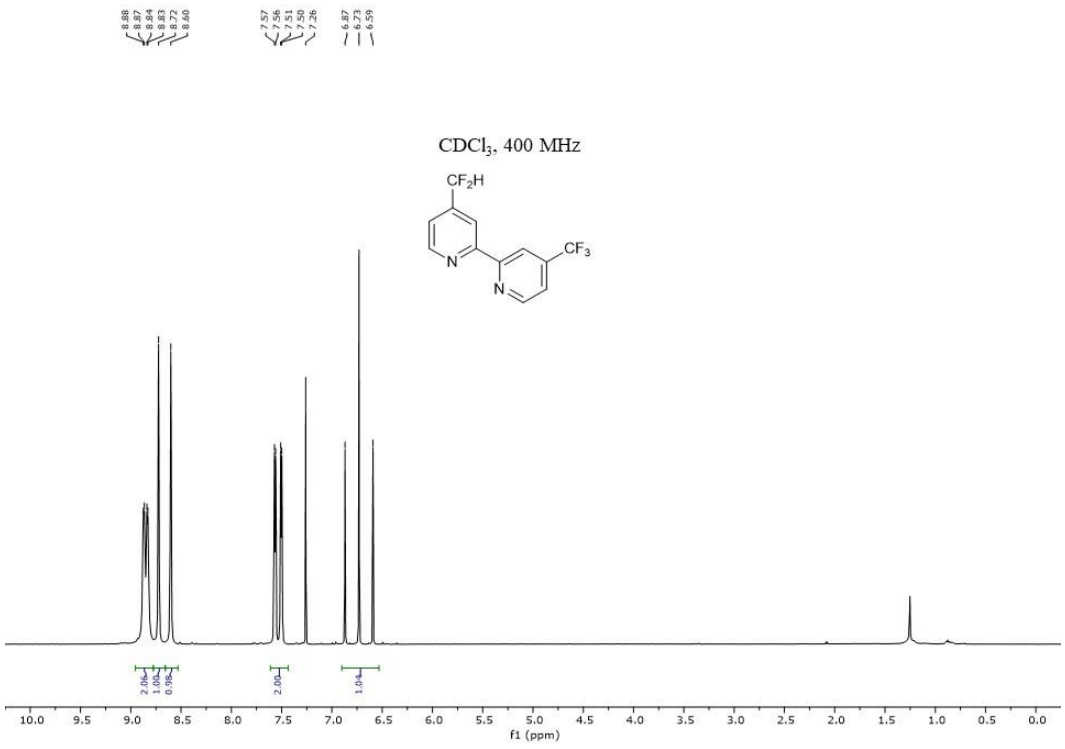
$CDCl_3$, 400 MHz

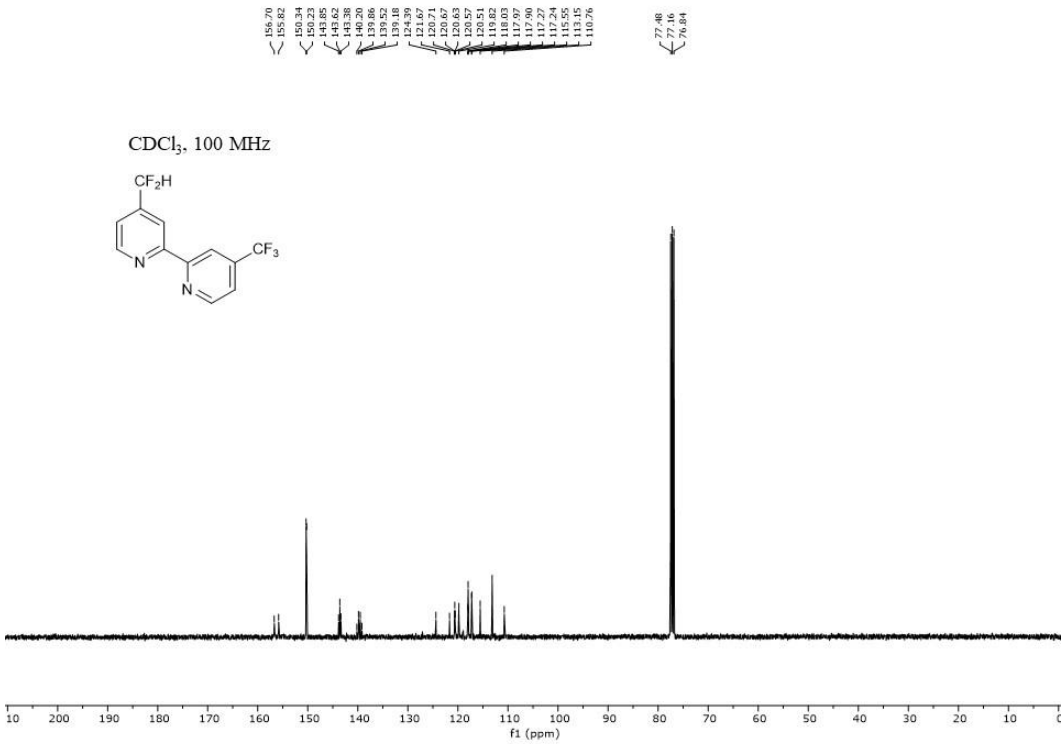


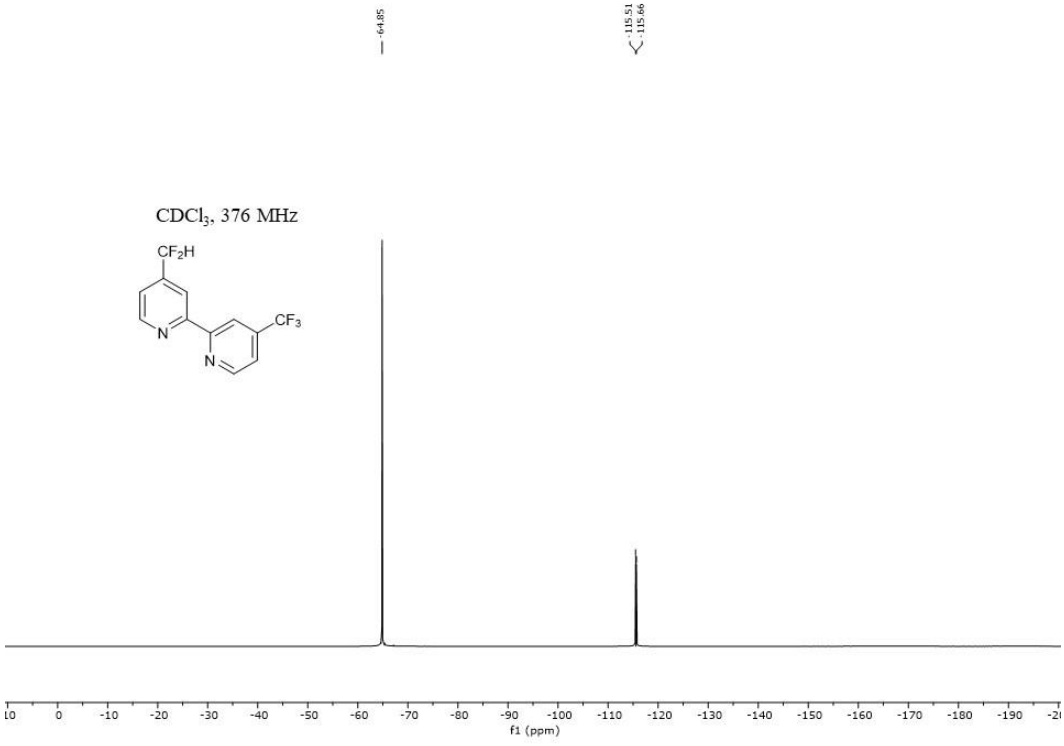
$CDCl_3$, 100 MHz

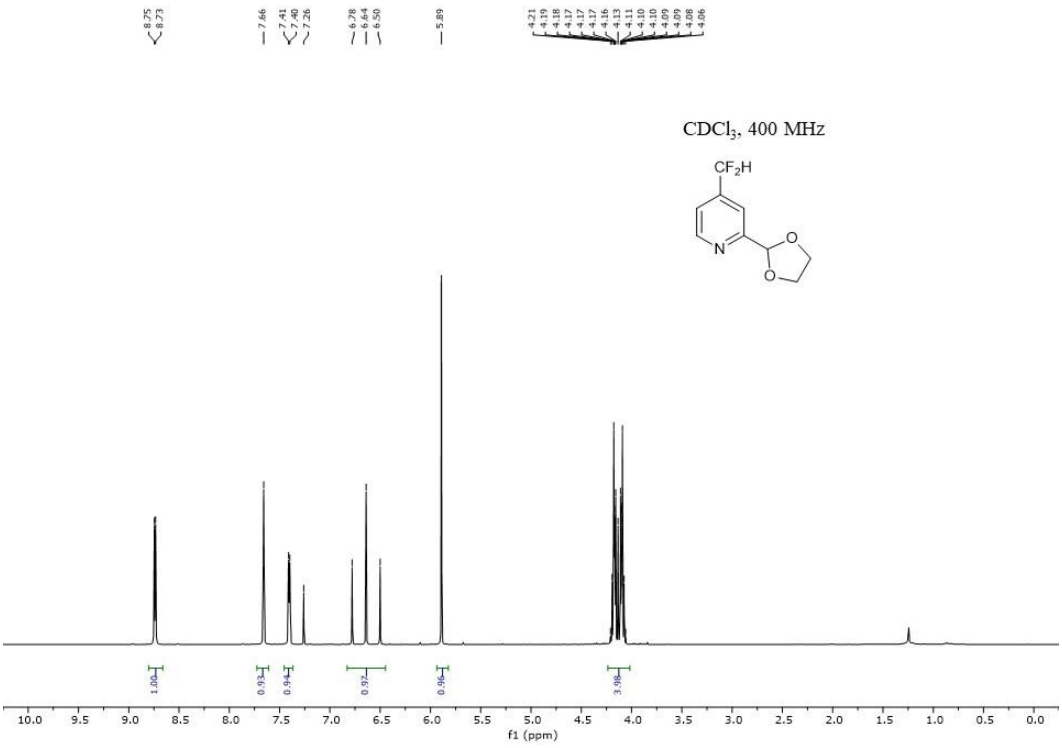


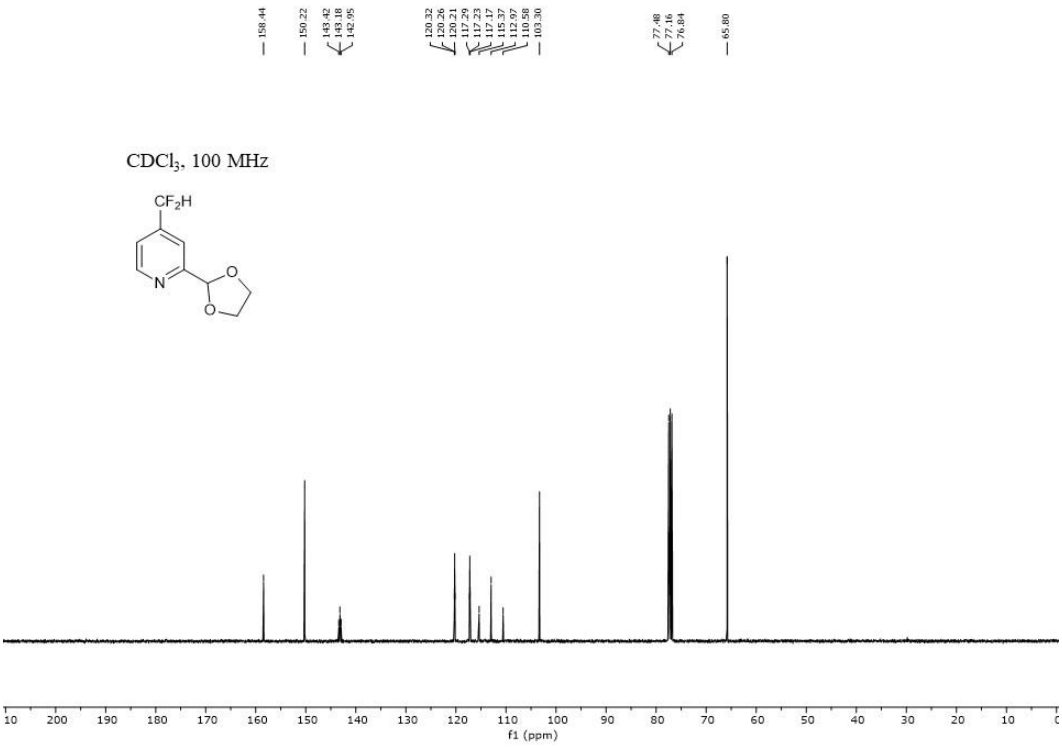

115.56
115.71
CDCl3, 376 MHz
CF2H
Cl
N
f1 (ppm)


8.88
8.87
8.84
8.83
8.72
8.60
7.57
7.56
7.51
7.50
7.26
6.87
6.73
6.59
CDCl3, 400 MHz
CF2H
CF3
N
N
2.00
1.00
0.98
2.00
1.04
f1 (ppm)

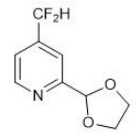

156.70
155.82
150.34
150.23
143.85
143.62
143.38
140.20
139.86
139.52
139.18
124.39
121.67
120.71
120.67
120.63
120.57
120.51
119.82
118.03
117.97
117.90
117.27
117.24
115.55
113.15
110.76
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
CF3
N
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-64.85
-115.51
-115.66
CDCl3, 376 MHz
CF2H
CF3
N
N
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

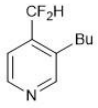

8.75
8.73
7.66
7.41
7.40
7.26
6.78
6.64
6.50
5.89
4.21
4.19
4.18
4.17
4.17
4.17
4.17
4.16
4.13
4.11
4.10
4.10
4.09
4.09
4.08
4.06
CDCl3, 400 MHz
CF2H
N
O
O
1.00
0.93
0.94
0.97
0.96
3.98
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

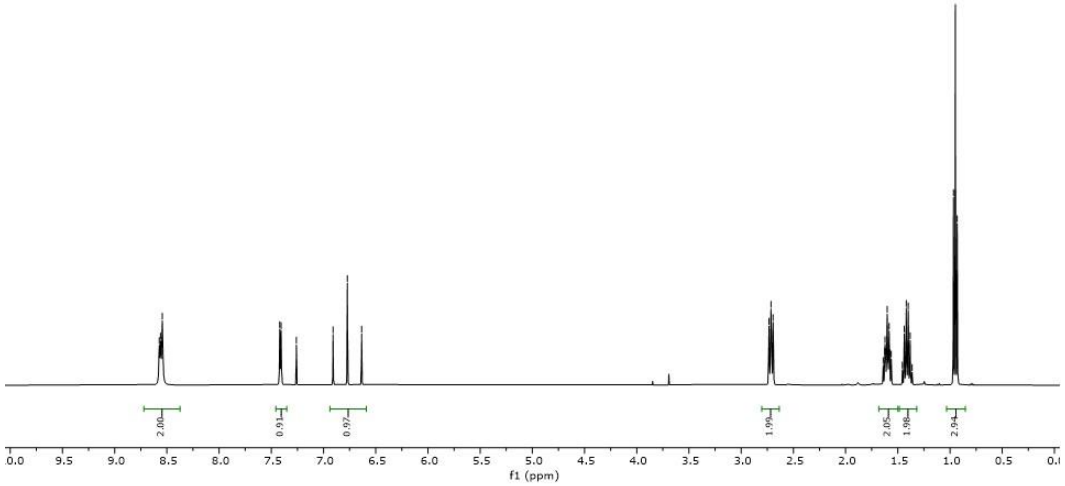

158.44
150.22
143.42
143.18
142.95
120.32
120.26
120.21
117.29
117.23
117.17
115.37
112.07
110.58
103.30
77.48
77.16
76.84
65.80
CDCl3, 100 MHz
CF2H
N
O
O
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

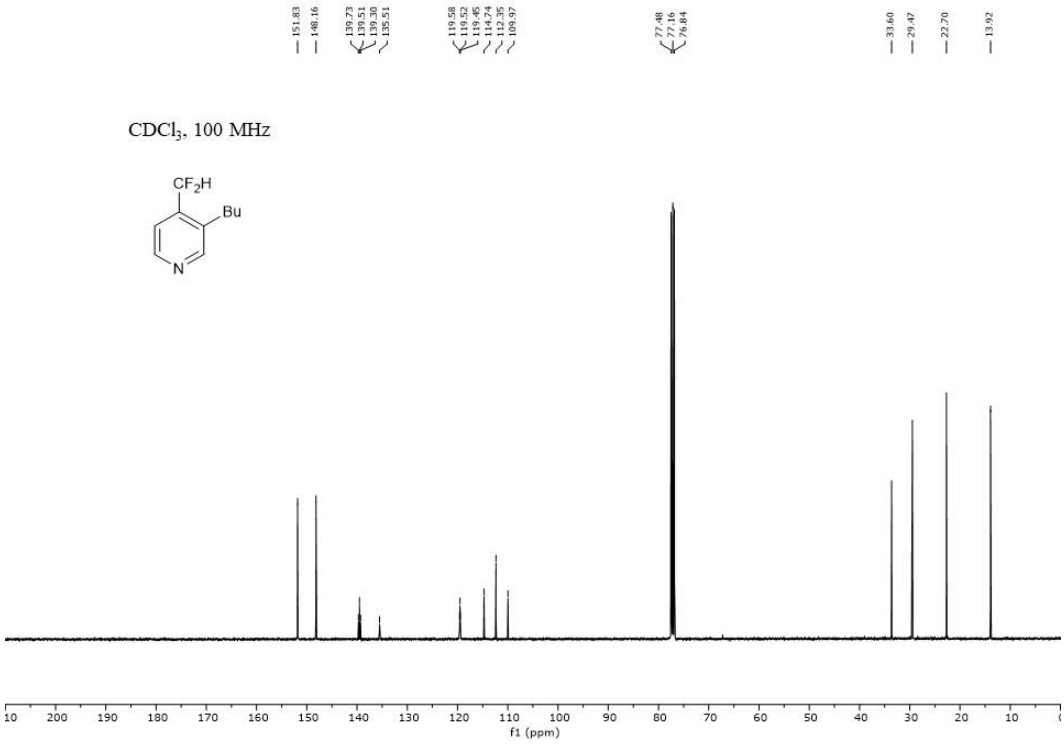
$CDCl_3$, 376 MHz

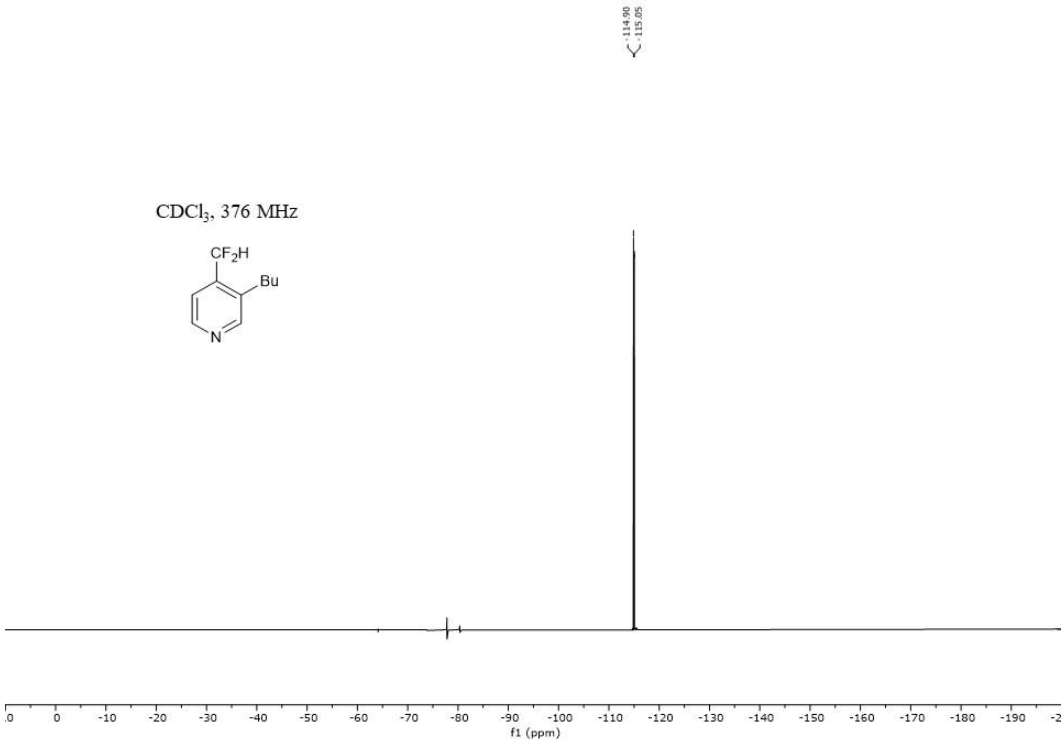


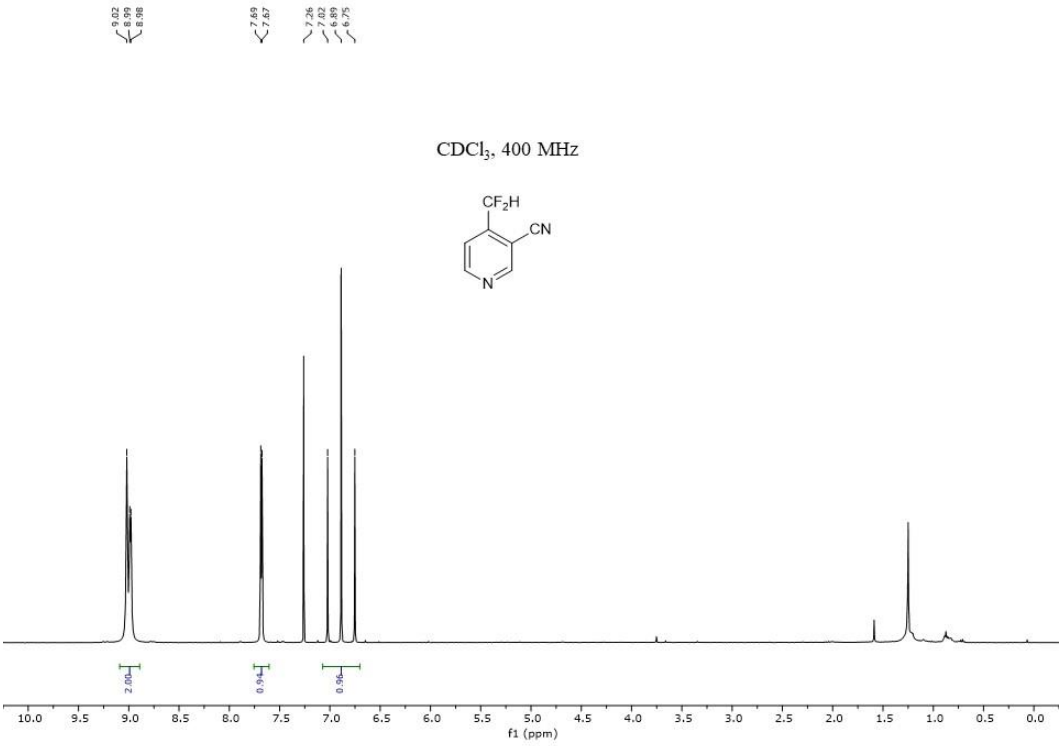
$CDCl_3$, 400 MHz

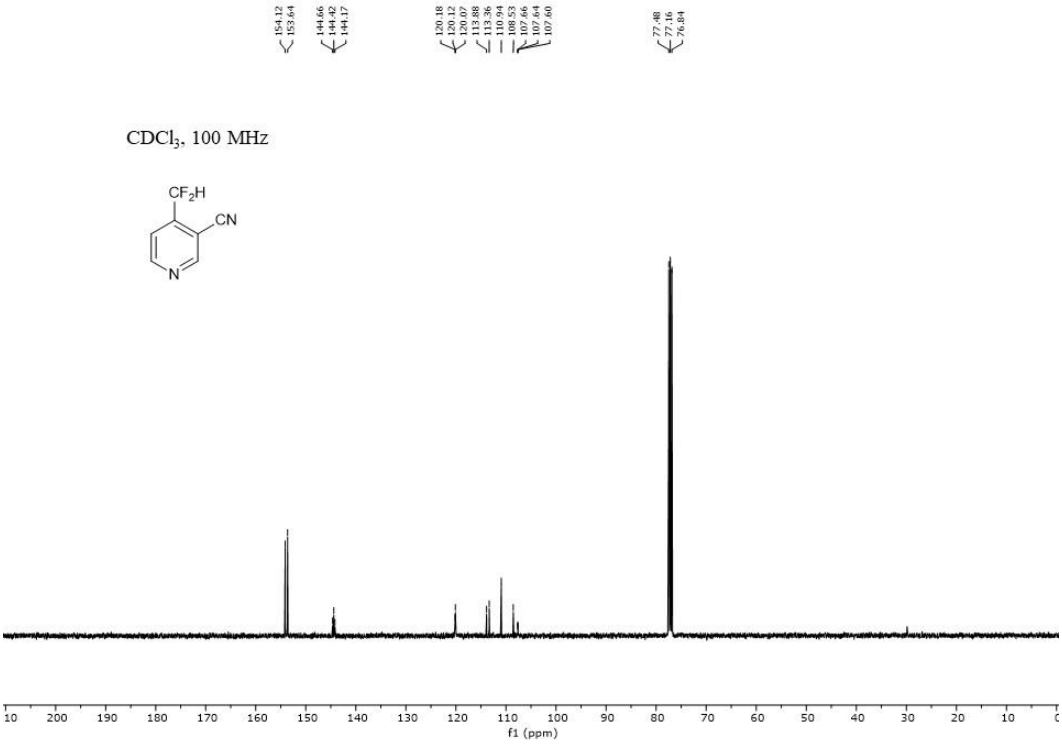




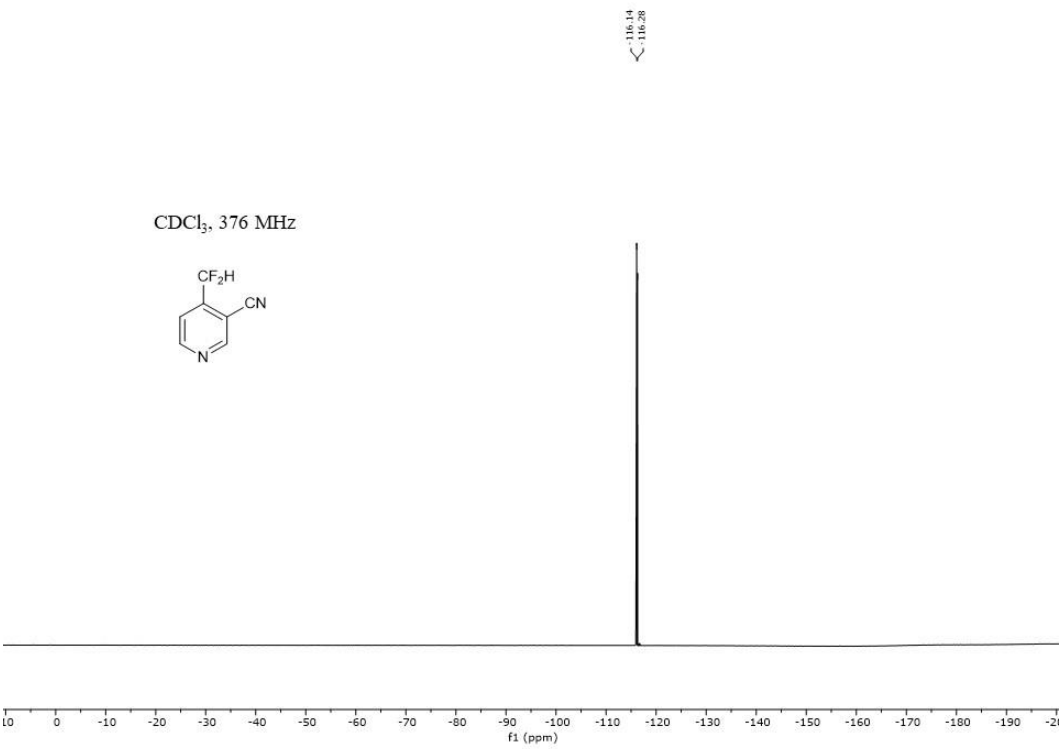

151.83
148.16
139.73
139.51
139.30
135.51
119.58
119.52
119.46
114.74
112.35
109.97
77.48
77.16
76.84
33.60
29.47
22.70
13.92
CDCl3, 100 MHz
CF2H
Bu
N
f1 (ppm)


-114.90
-115.05
CDCl3, 376 MHz
CF2H
Bu
N
f1 (ppm)

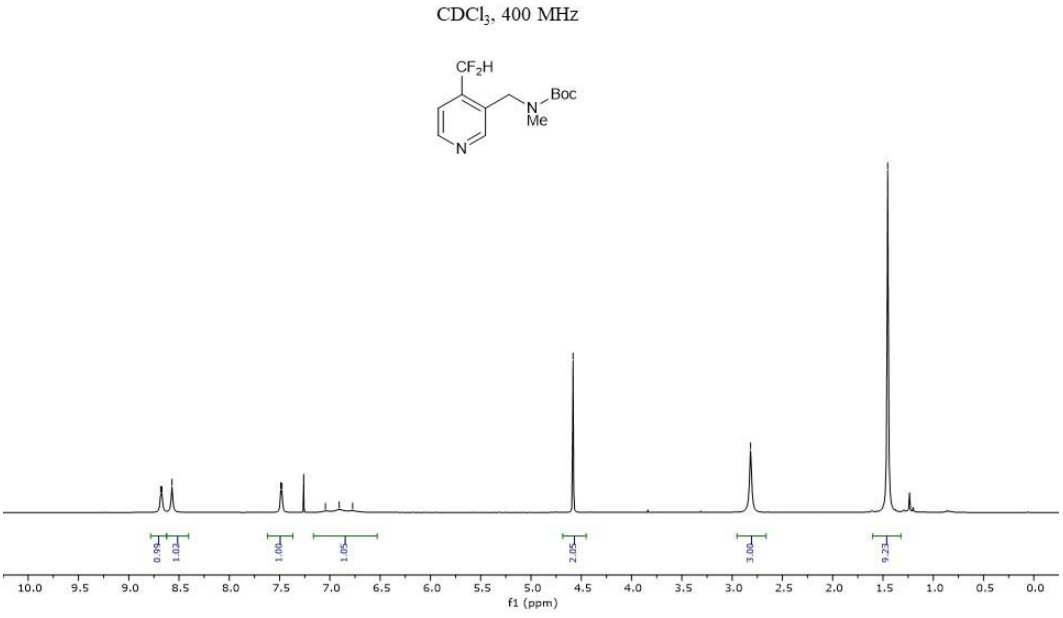

9.02
8.99
8.98
7.69
7.67
7.26
7.02
6.89
6.75
CDCl3, 400 MHz
CF2H
CN
N
2.00
0.94
0.96
f1 (ppm)

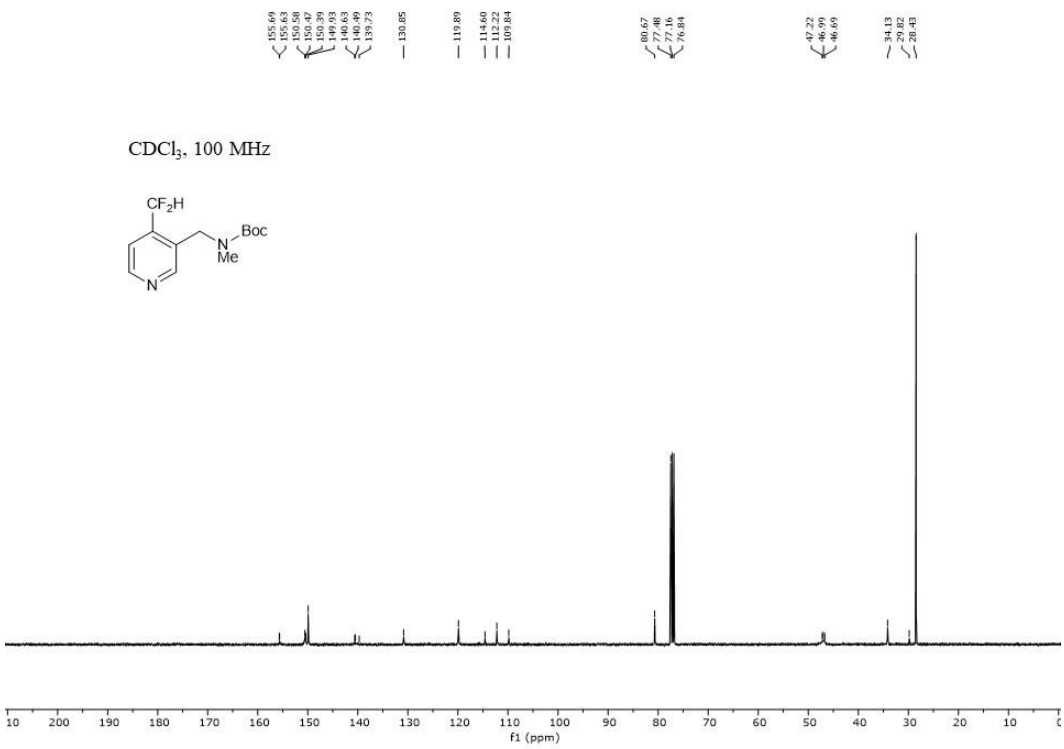

154.12
153.64
144.66
144.42
144.17
120.18
120.12
120.07
113.88
113.36
110.94
108.55
107.66
107.64
107.60
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
CN
N
f1 (ppm)

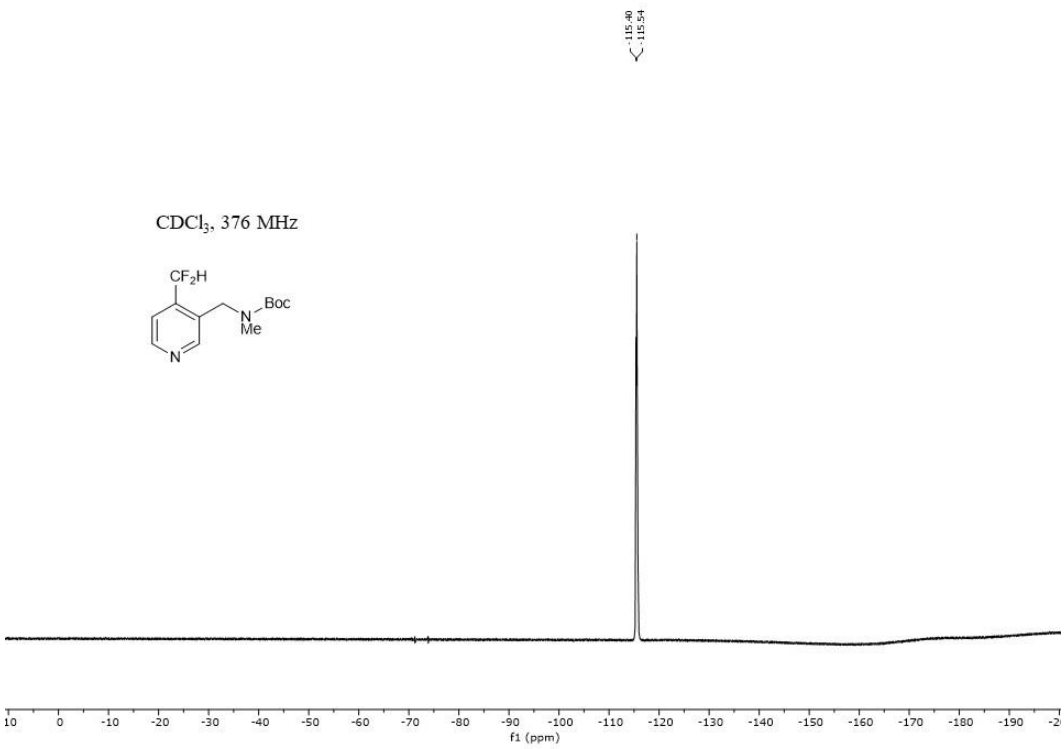
$CDCl_3$, 376 MHz



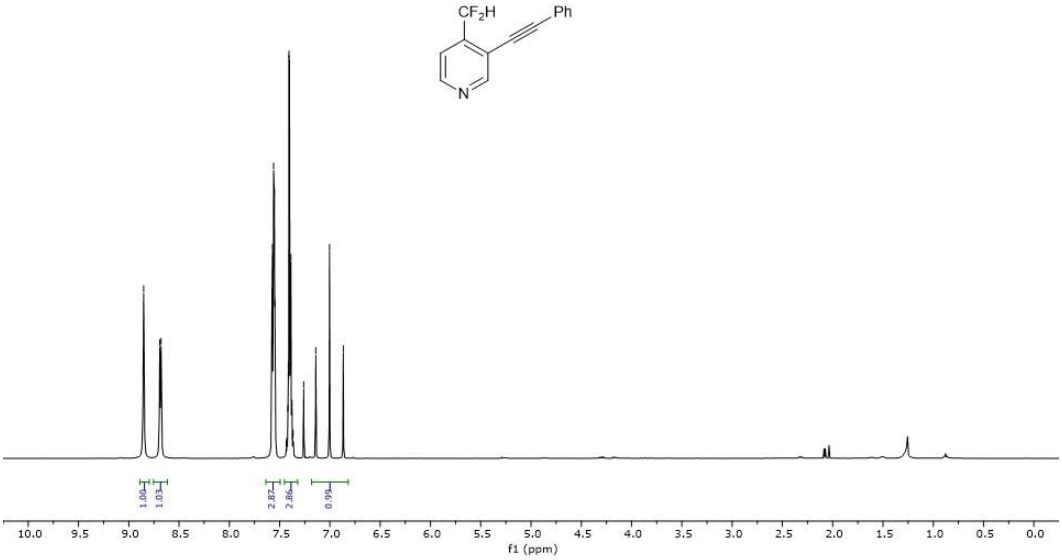
$CDCl_3$, 400 MHz

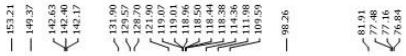



155.69
155.63
150.58
150.47
150.39
140.63
140.63
140.49
139.73
130.85
119.89
114.60
112.22
109.84
80.67
77.48
77.16
76.84
47.22
46.99
46.69
34.13
29.82
28.43
CDCl3, 100 MHz
CF2H
N
Boc
Me
N
f1 (ppm)

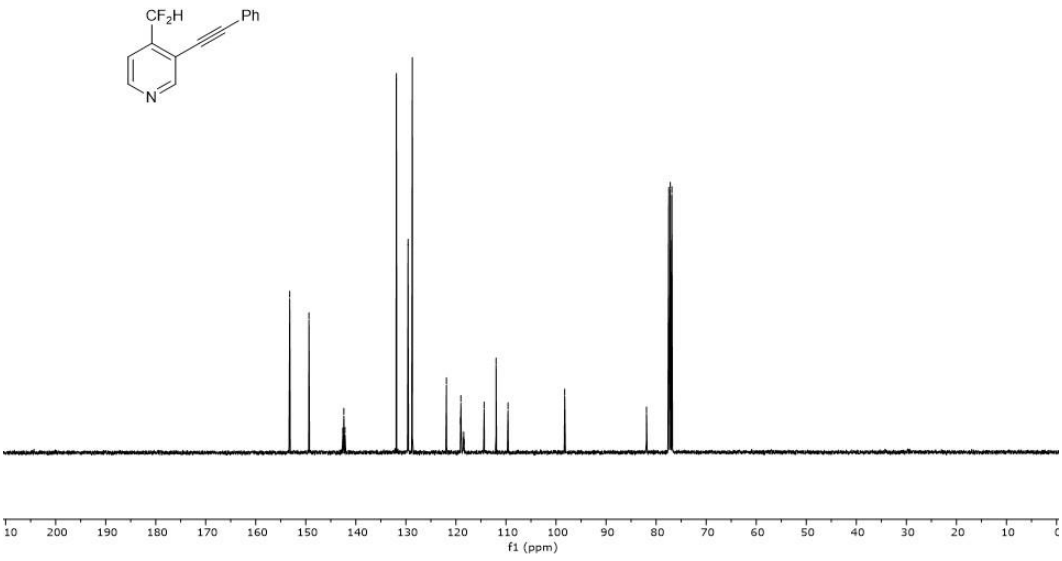

-115.40
-115.54
CDCl3, 376 MHz
CF2H
N
Boc
Me
N
f1 (ppm)

$CDCl_3$, 400 MHz

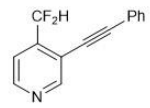




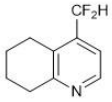
$CDCl_3$, 100 MHz

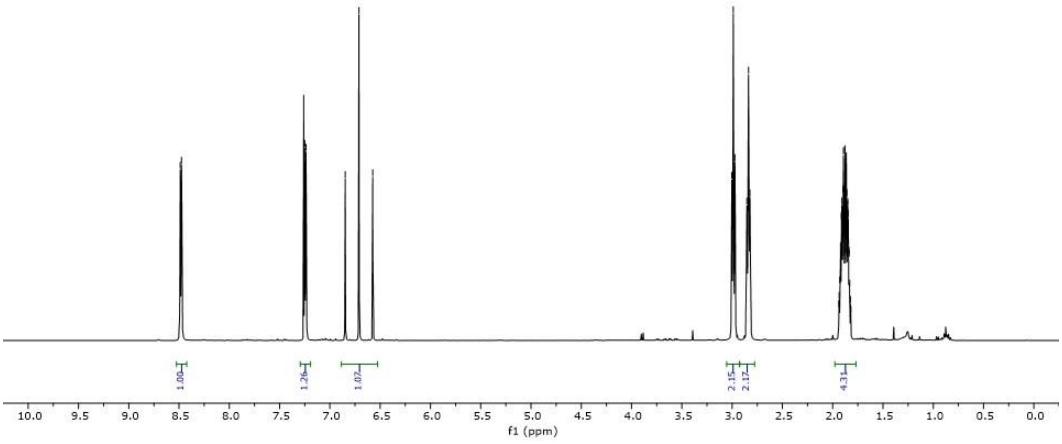


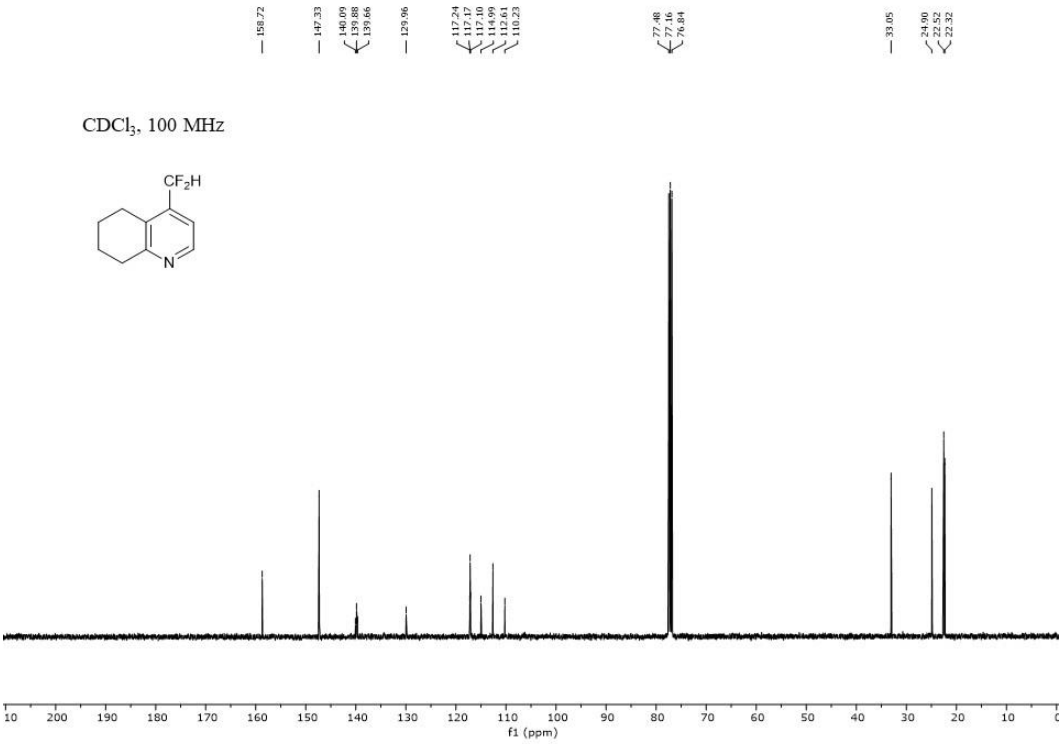
$CDCl_3$, 376 MHz

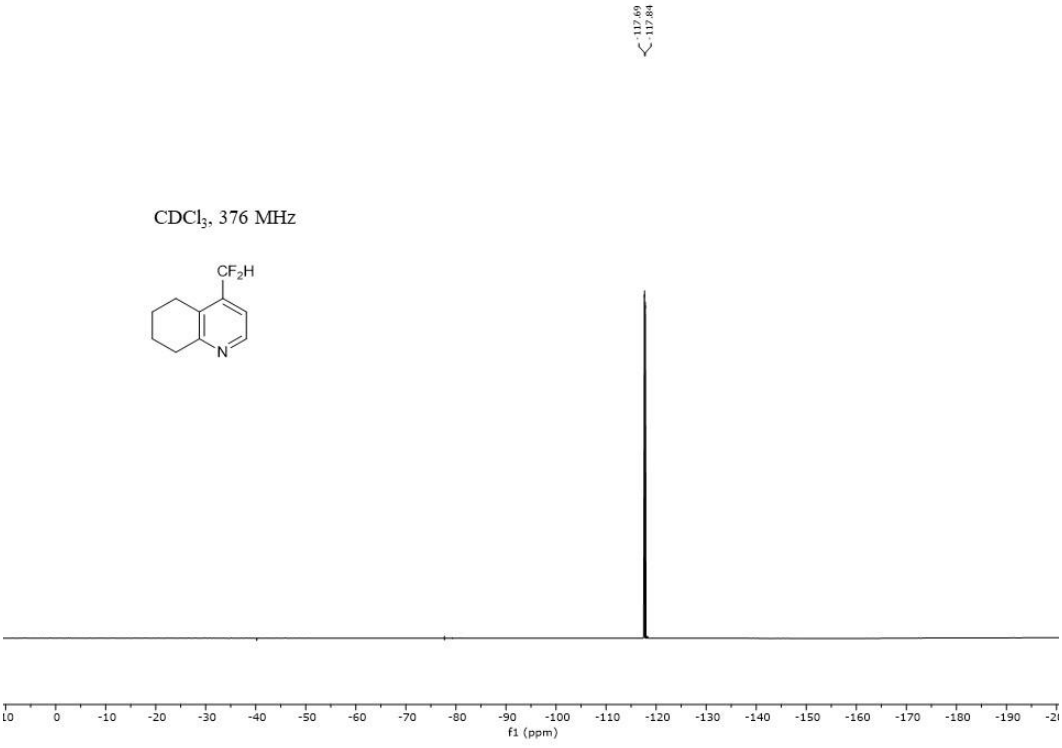


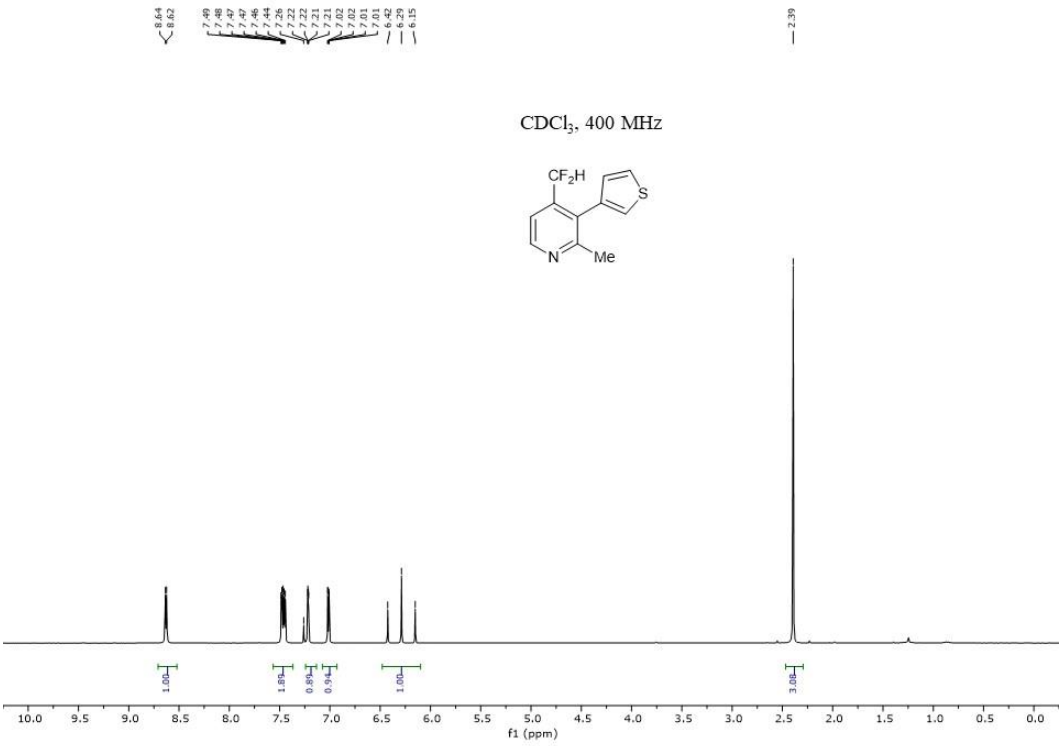
$CDCl_3$, 400 MHz

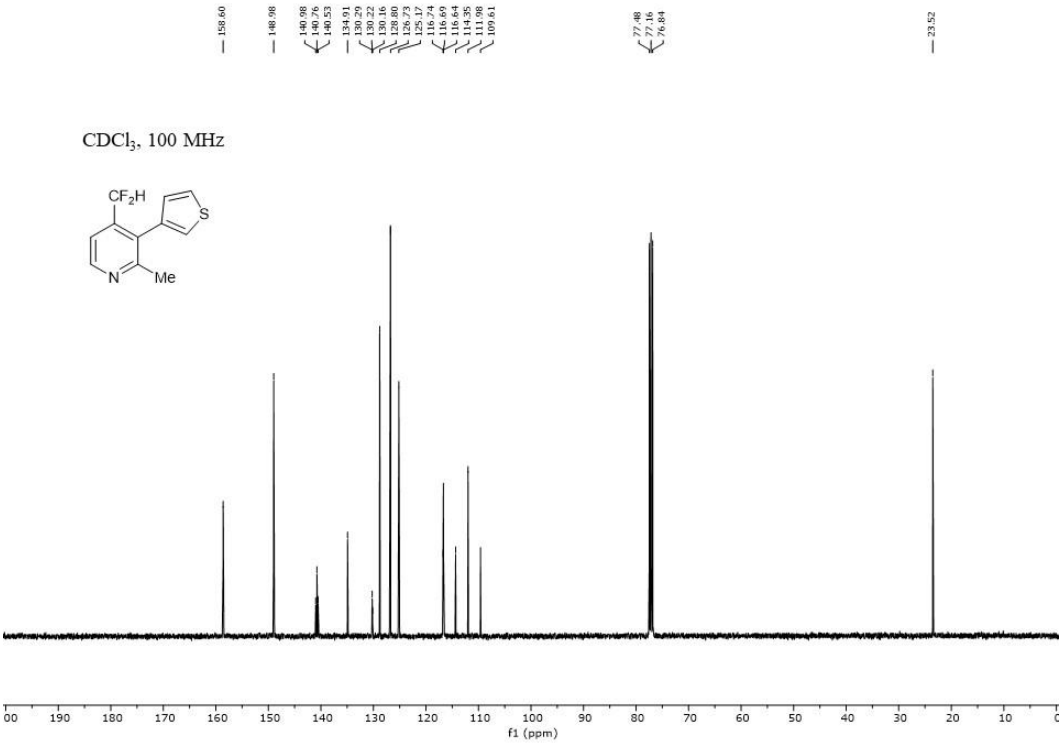




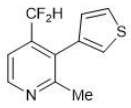

158.72
147.33
140.09
139.88
139.66
129.96
117.24
117.17
117.10
114.99
112.61
110.23
77.48
77.16
76.84
33.05
24.90
22.52
22.32
CDCl3, 100 MHz
CF2H
N
f1 (ppm)

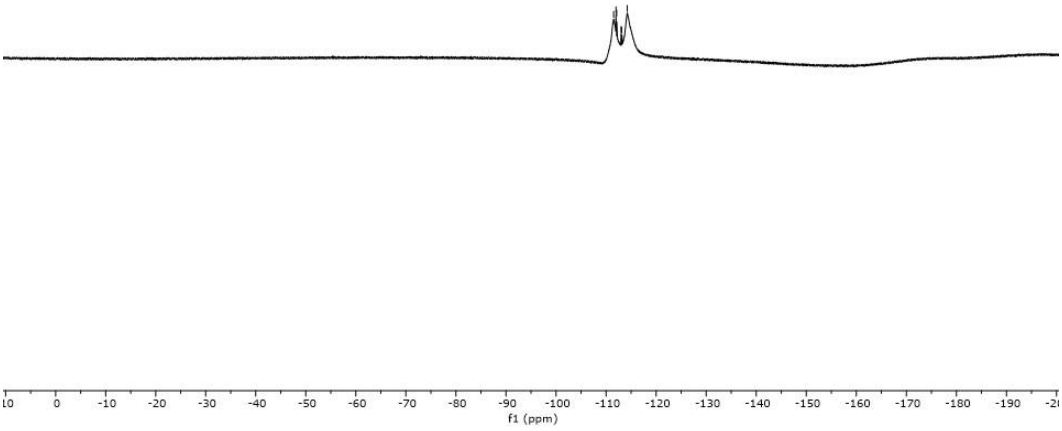

-117.69
-117.84
CDCl3, 376 MHz
CF2H
N
f1 (ppm)


8.64
8.62
7.49
7.48
7.47
7.47
7.46
7.44
7.26
7.22
7.22
7.21
7.21
7.02
7.02
7.01
7.01
6.42
6.28
6.15
2.39
CDCl3, 400 MHz
CF2H
S
N
Me
1.00
1.86
0.89
0.94
1.00
3.08
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

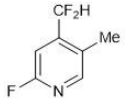

158.60
148.98
140.98
140.76
140.53
134.91
130.29
130.22
130.16
128.80
126.73
125.17
116.74
116.69
116.64
114.35
111.98
109.61
77.48
77.16
76.84
23.52
CDCl3, 100 MHz
CF2H
S
N
Me
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

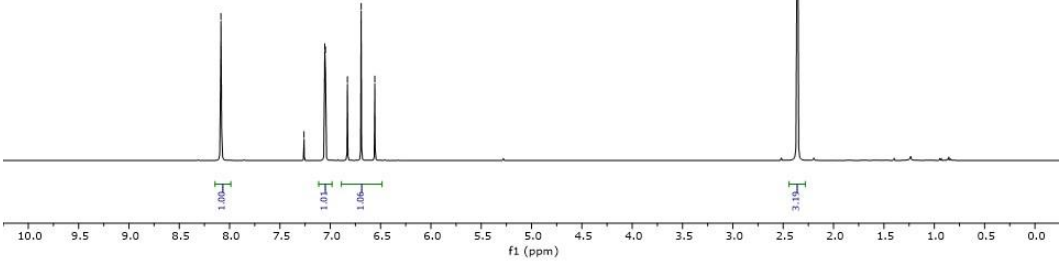
$CDCl_3$, 376 MHz

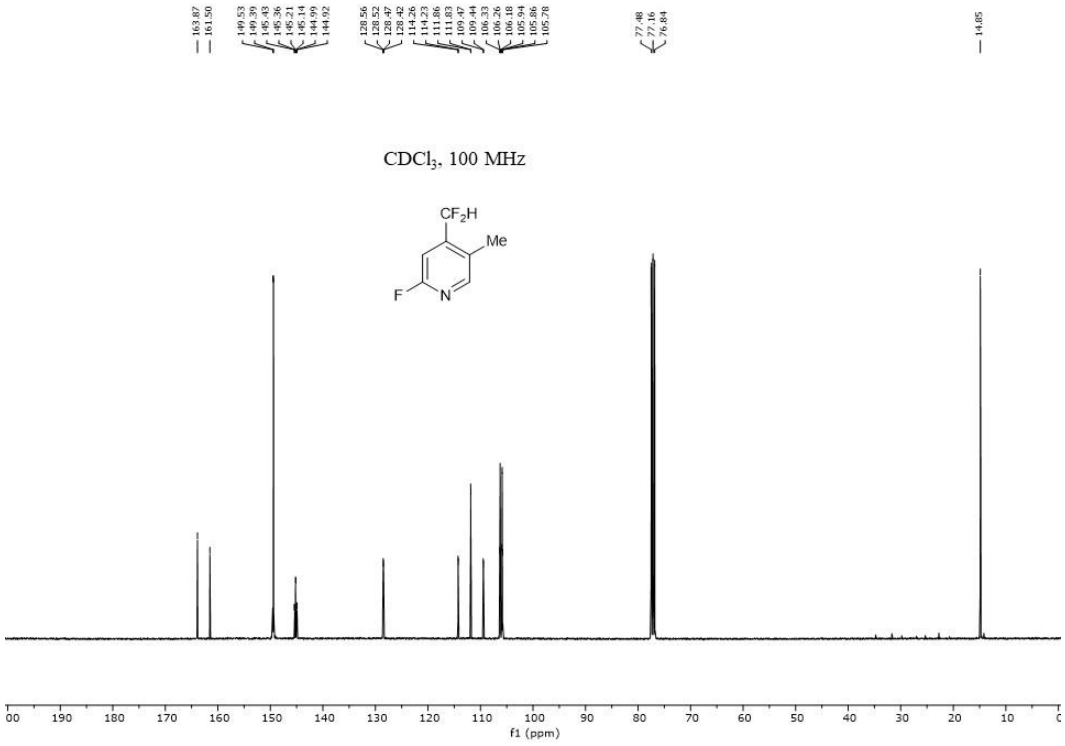


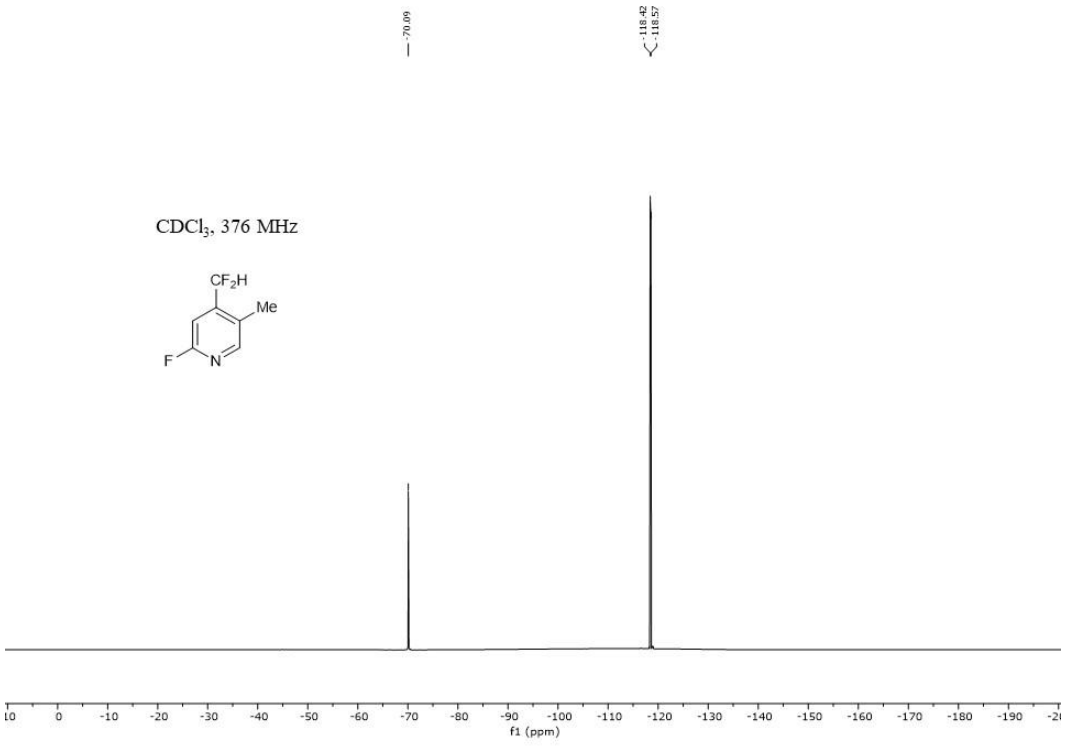


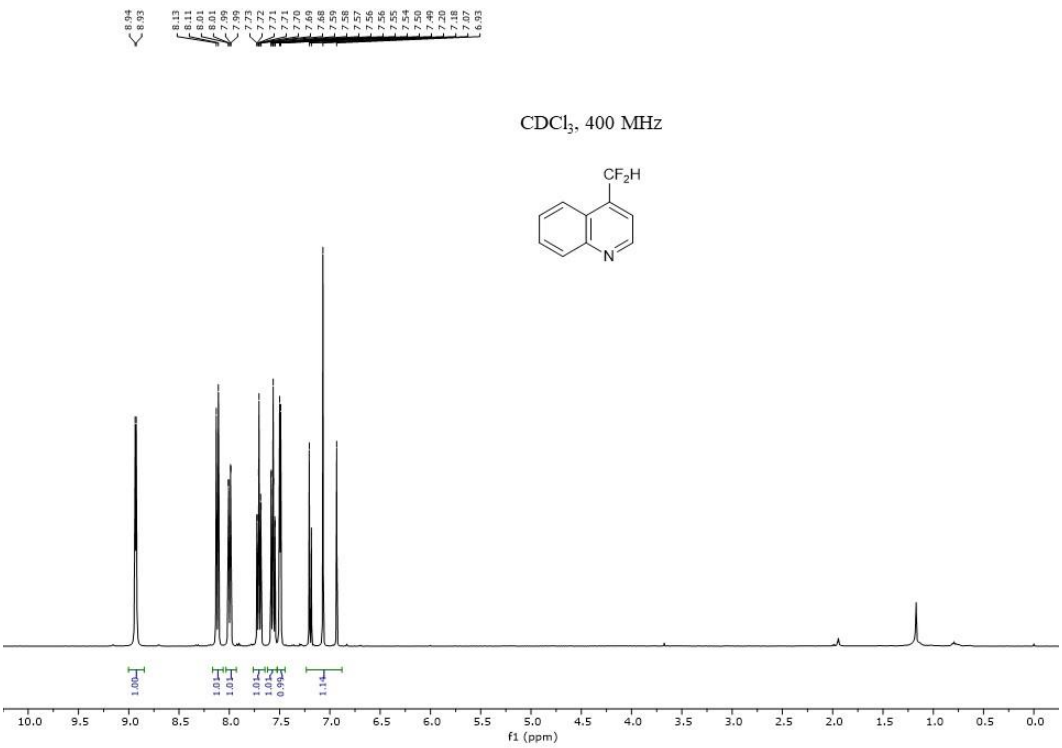
$CDCl_3$, 400 MHz



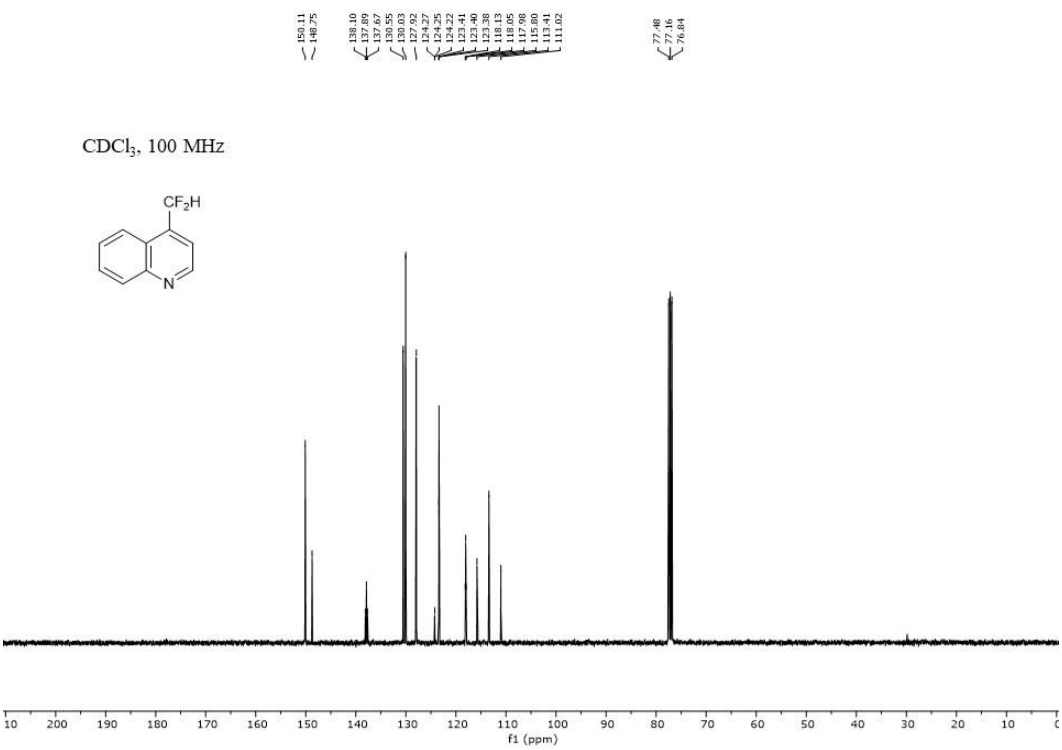



163.87
161.50
149.53
149.39
146.43
146.36
145.21
145.14
144.99
144.92
128.56
128.52
128.47
128.42
114.26
114.23
111.86
111.83
109.47
109.44
106.35
106.26
106.18
105.94
105.86
105.78
77.48
77.16
76.84
14.85
CDCl3, 100 MHz
CF2H
Me
F
N
f1 (ppm)

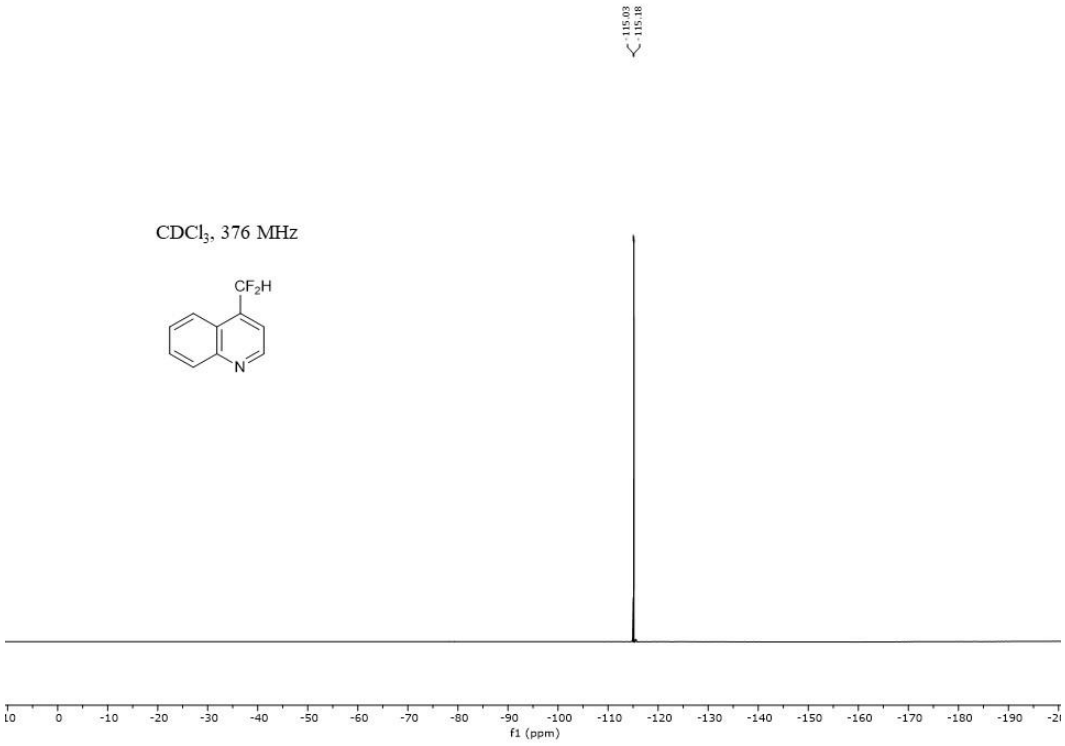

-70.09
-118.42
-118.57
CDCl3, 376 MHz
CF2H
Me
F
N
f1 (ppm)

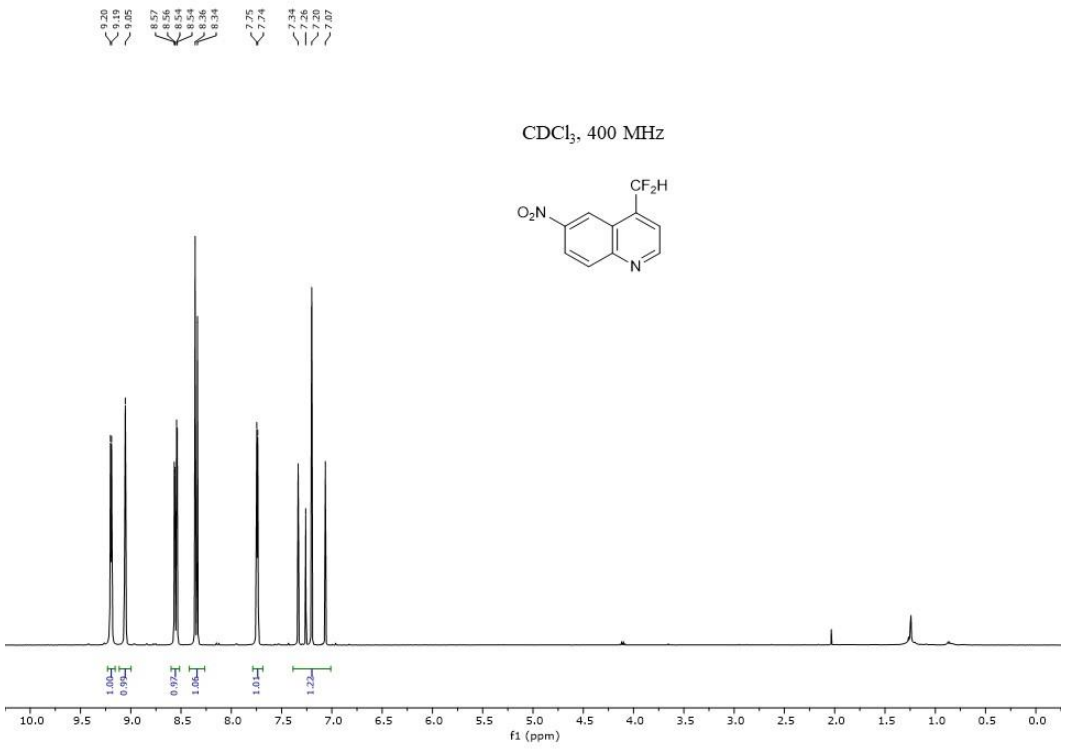


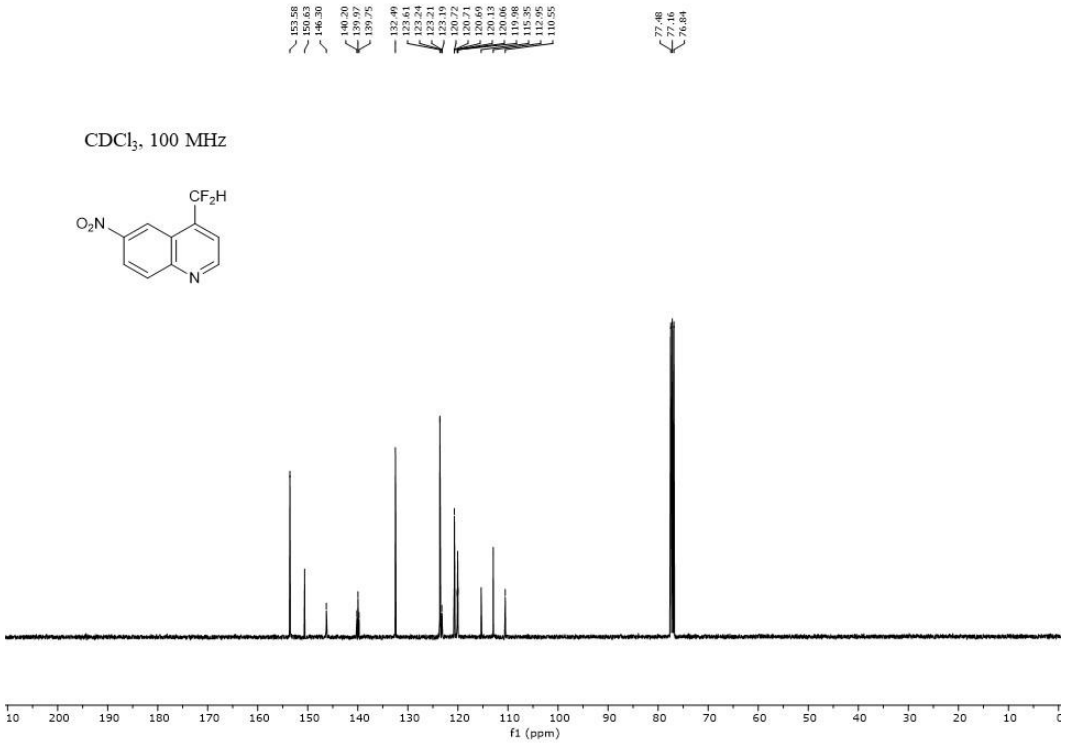
$CDCl_3$, 400 MHz



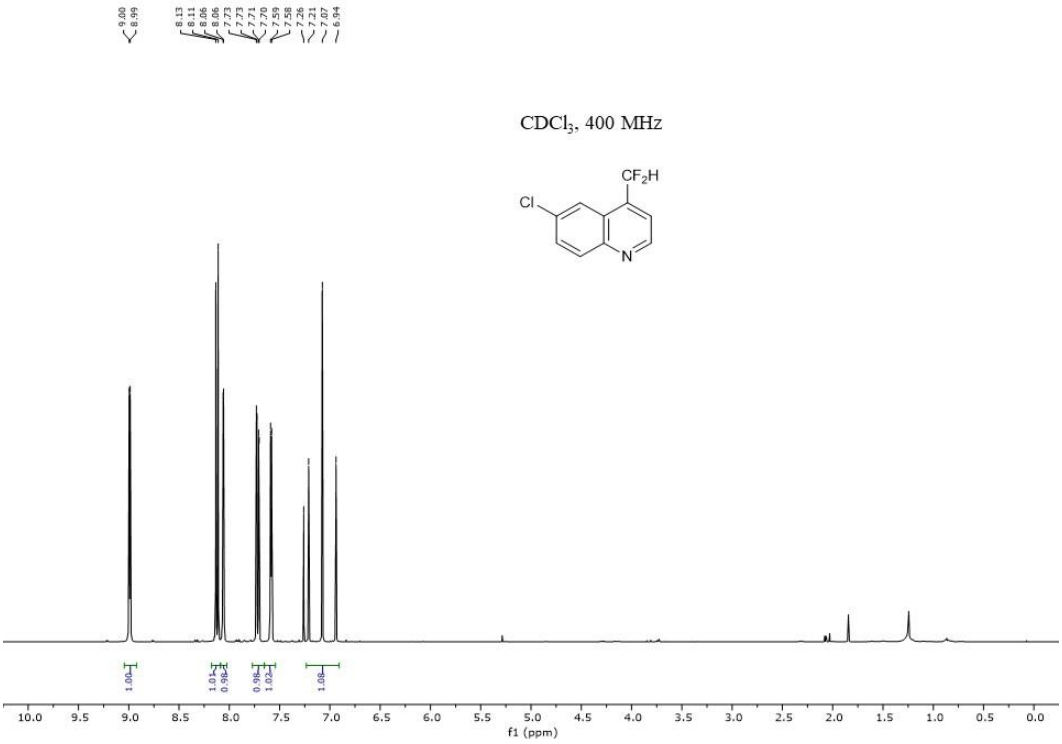
$CDCl_3$, 100 MHz

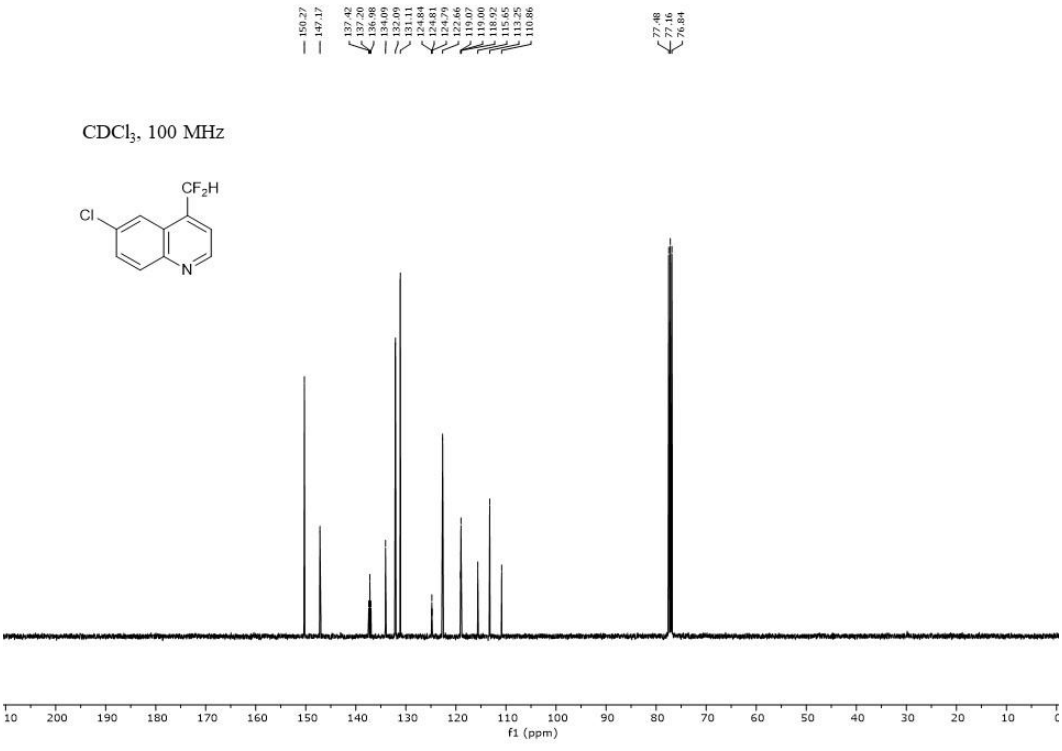

-115.03
-115.18
CDCl3, 376 MHz
CF2H
N
f1 (ppm)

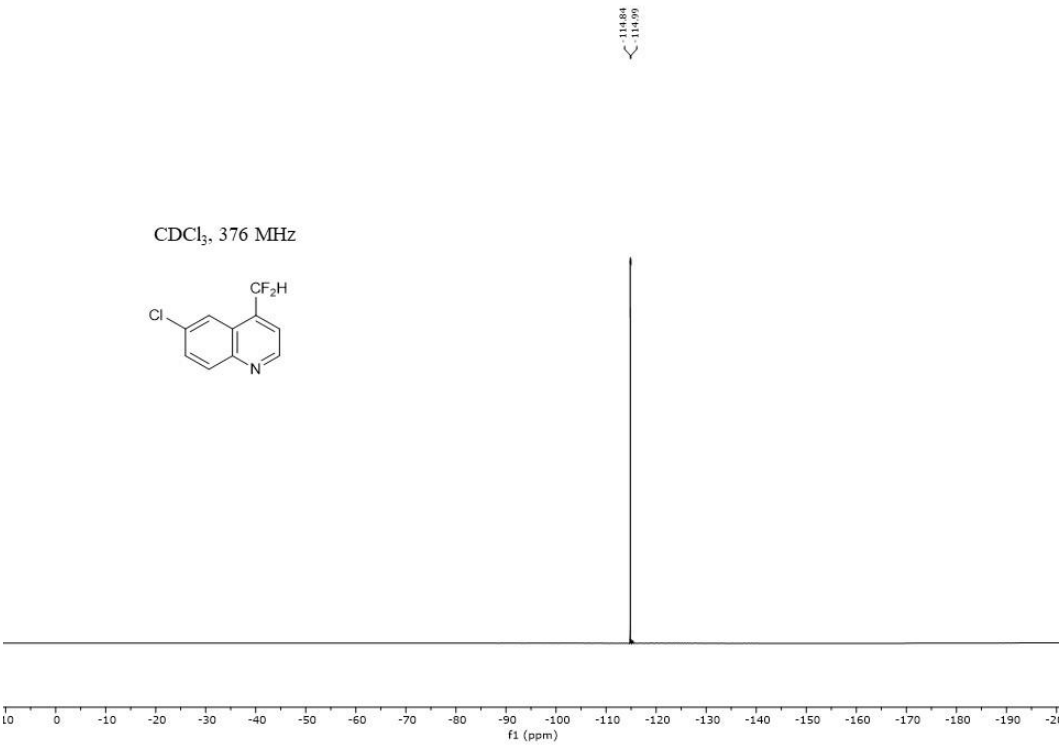

9.20
9.19
9.05
8.57
8.56
8.54
8.54
8.36
8.34
7.75
7.74
7.34
7.26
7.20
7.07
CDCl3, 400 MHz
CF2H
O2N
N
1.00
0.99
0.97
1.06
1.01
1.22
f1 (ppm)

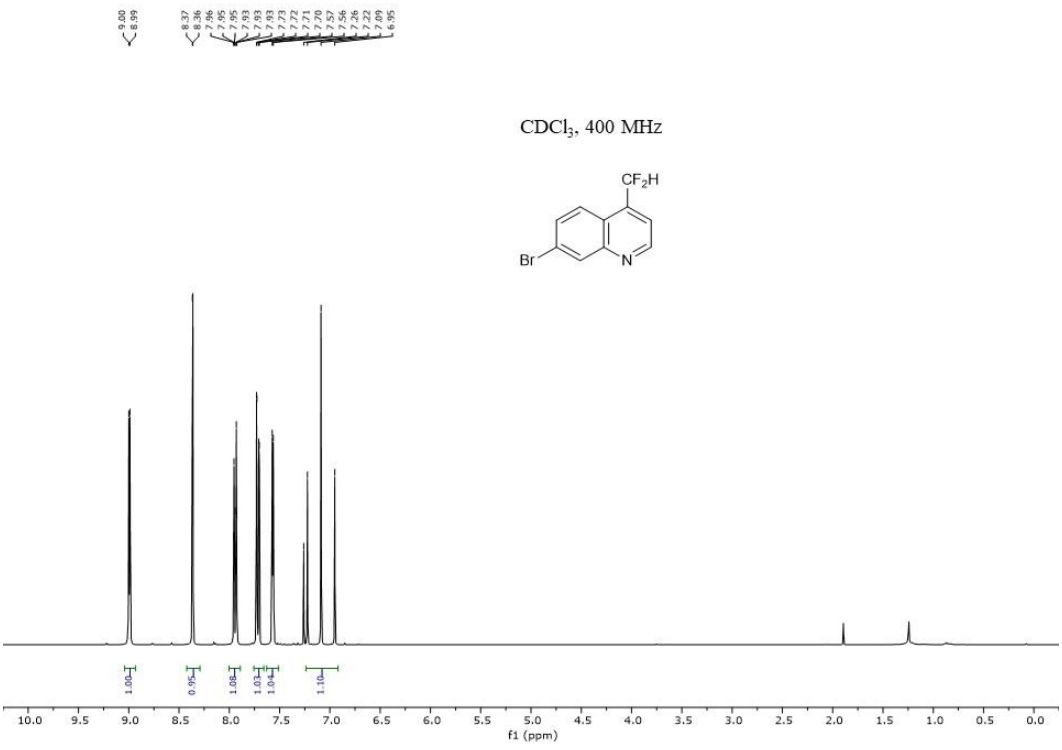

153.58
150.63
146.30
140.20
139.97
139.75
132.49
123.61
123.24
123.21
123.19
120.72
120.71
120.69
120.13
120.06
119.98
115.35
112.95
110.55
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
O2N
N
f1 (ppm)

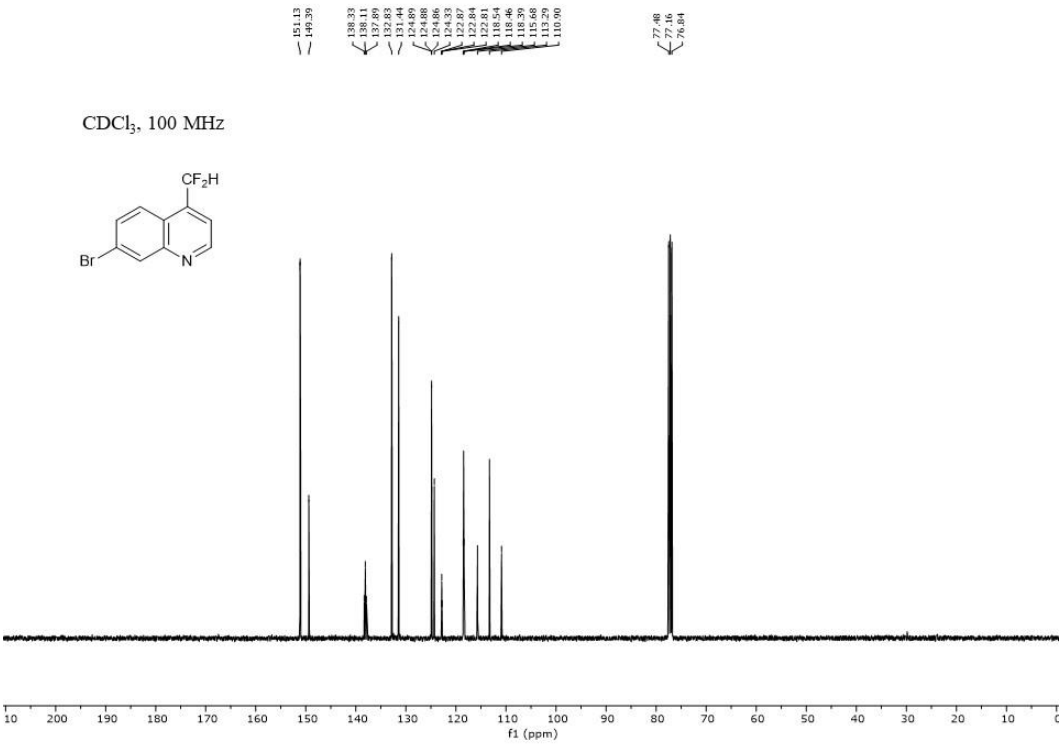

-114.27
-114.42
CDCl3, 376 MHz
CF2H
O2N
N
f1 (ppm)


9.00
8.99
8.13
8.11
8.06
8.06
7.73
7.73
7.71
7.70
7.59
7.58
7.26
7.21
7.07
6.94
CDCl3, 400 MHz
CF2H
Cl
N
1.00
1.01
0.98
0.98
1.03
1.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


150.27
147.17
137.92
137.20
136.08
134.09
132.09
131.11
124.84
124.81
124.79
122.66
119.07
119.00
118.92
115.65
113.25
110.86
77.48
77.16
76.84
CDCl3, 100 MHz
CF2H
Cl
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-114.84
-114.99
CDCl3, 376 MHz
CF2H
Cl
N
f1 (ppm)


8.99
8.37
8.36
7.96
7.95
7.95
7.93
7.93
7.93
7.73
7.72
7.71
7.70
7.57
7.56
7.26
7.22
7.09
6.95
CDCl3, 400 MHz
CF2H
Br
N
1.00
0.95
1.08
1.03
1.04
1.10
f1 (ppm)


151.13
149.39
138.33
138.11
137.89
132.83
131.44
124.89
124.88
124.86
124.33
122.87
122.84
122.81
118.54
118.46
118.39
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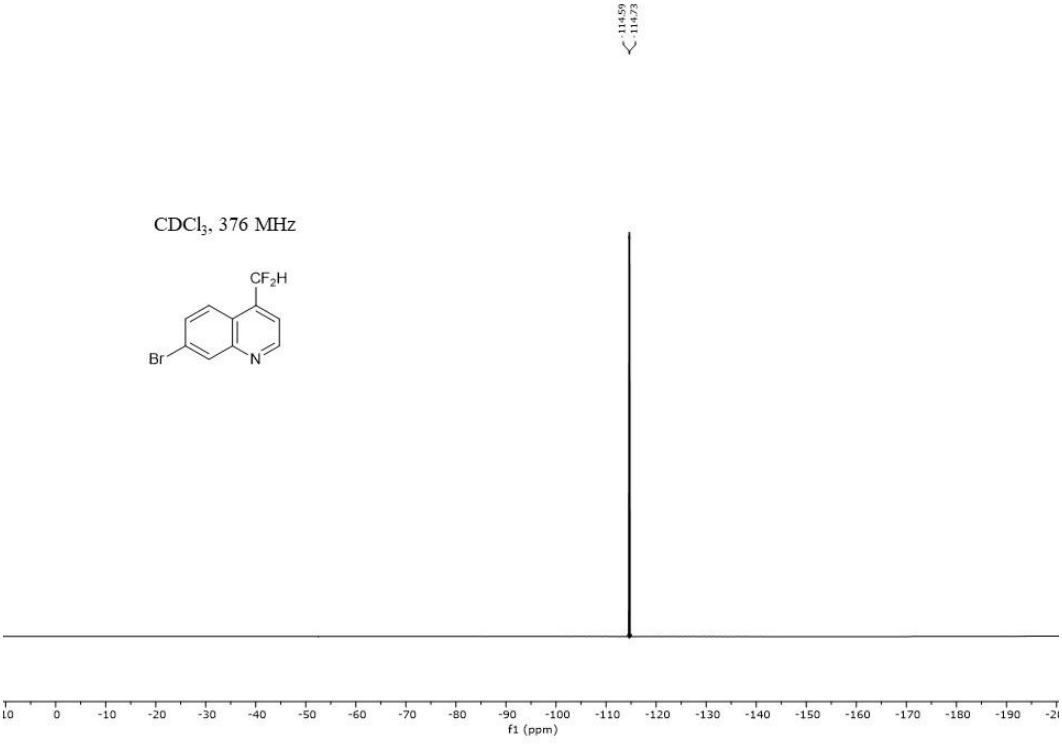
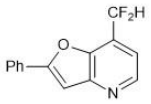
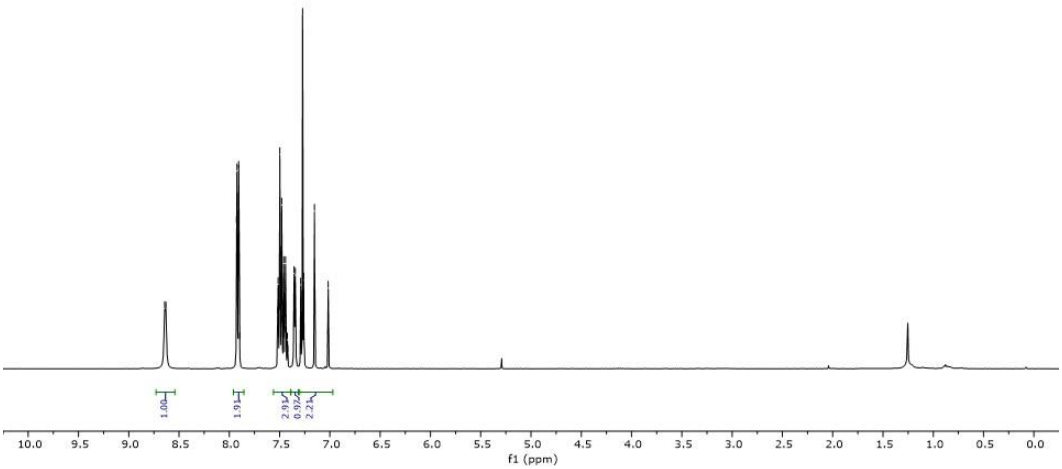
77.16
76.84
CDCl3, 100 MHz
CF2H
Br
N
f1 (ppm)

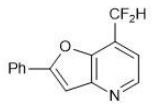

-114.59
-114.73
CDCl3, 376 MHz
CF2H
Br
N
f1 (ppm)

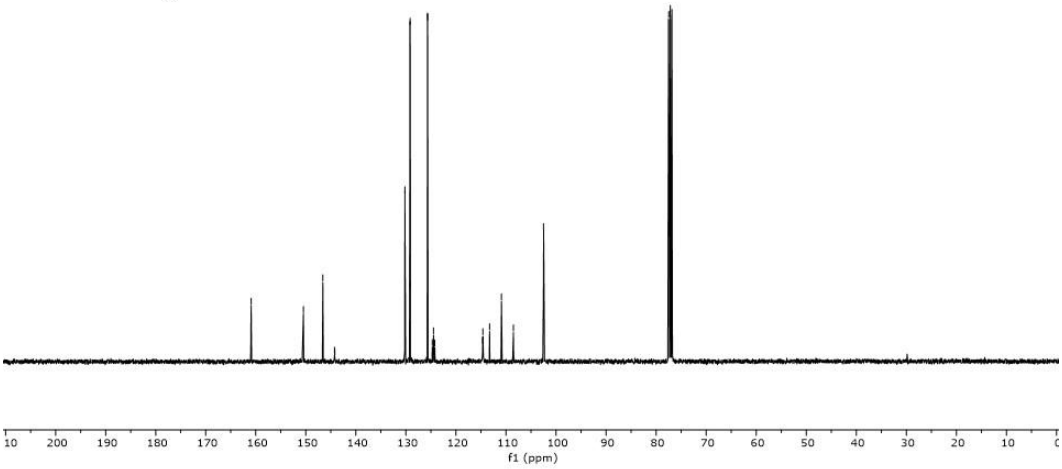
$CDCl_3$, 400 MHz

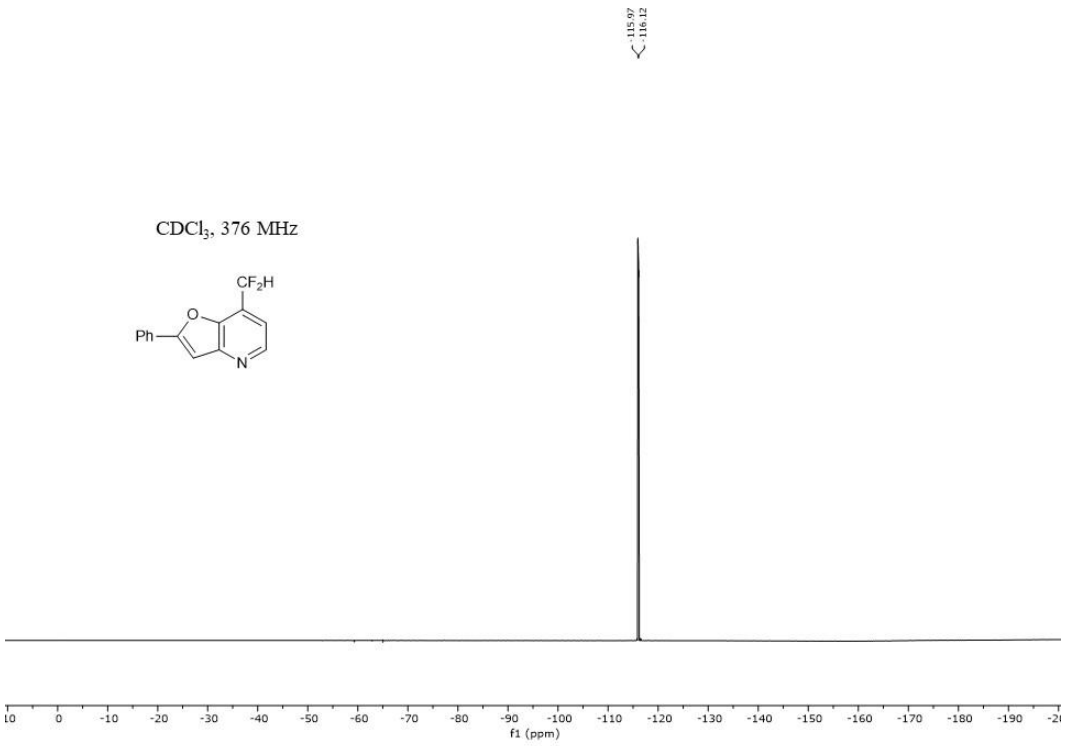


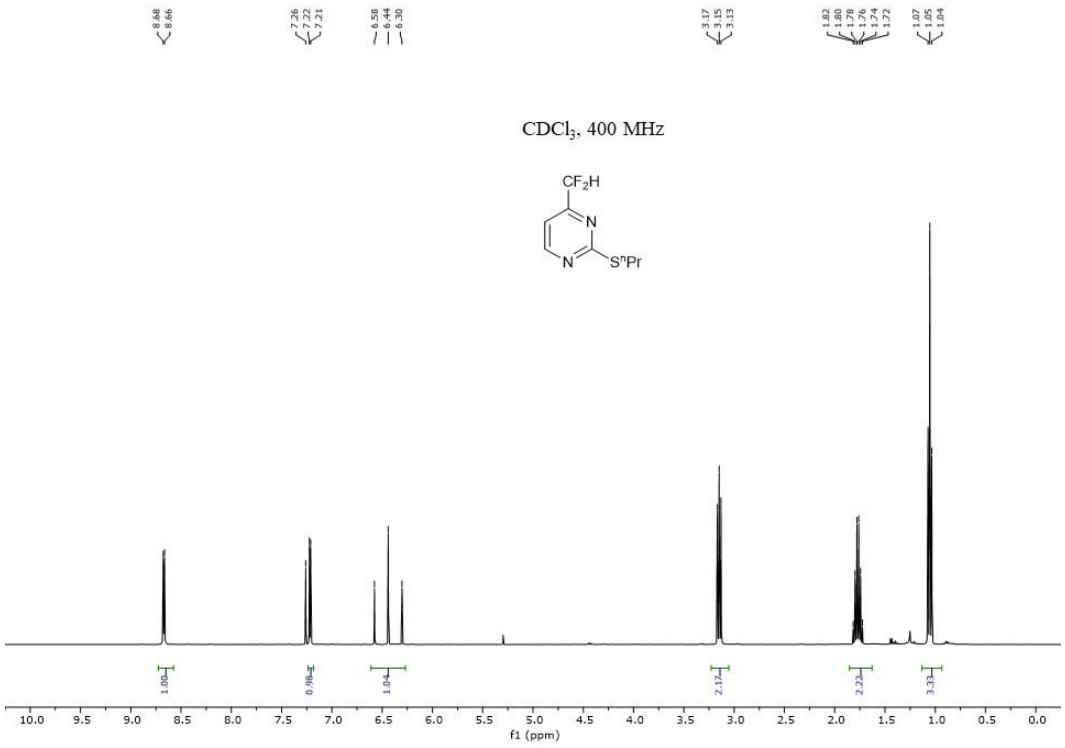


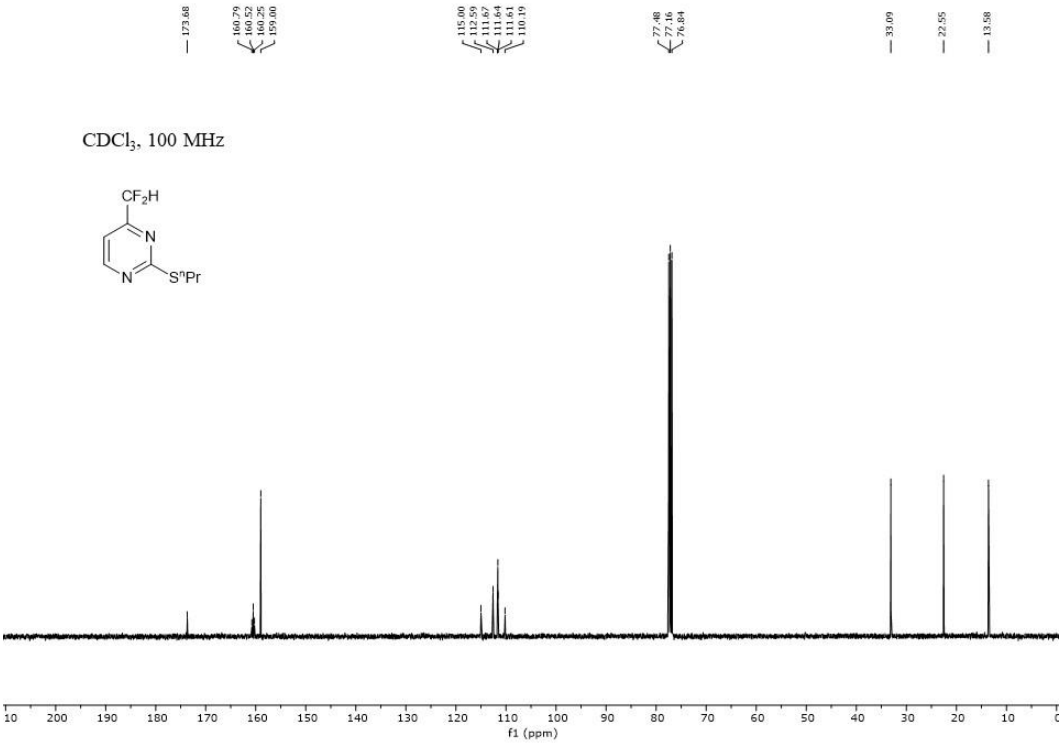
$CDCl_3$, 100 MHz

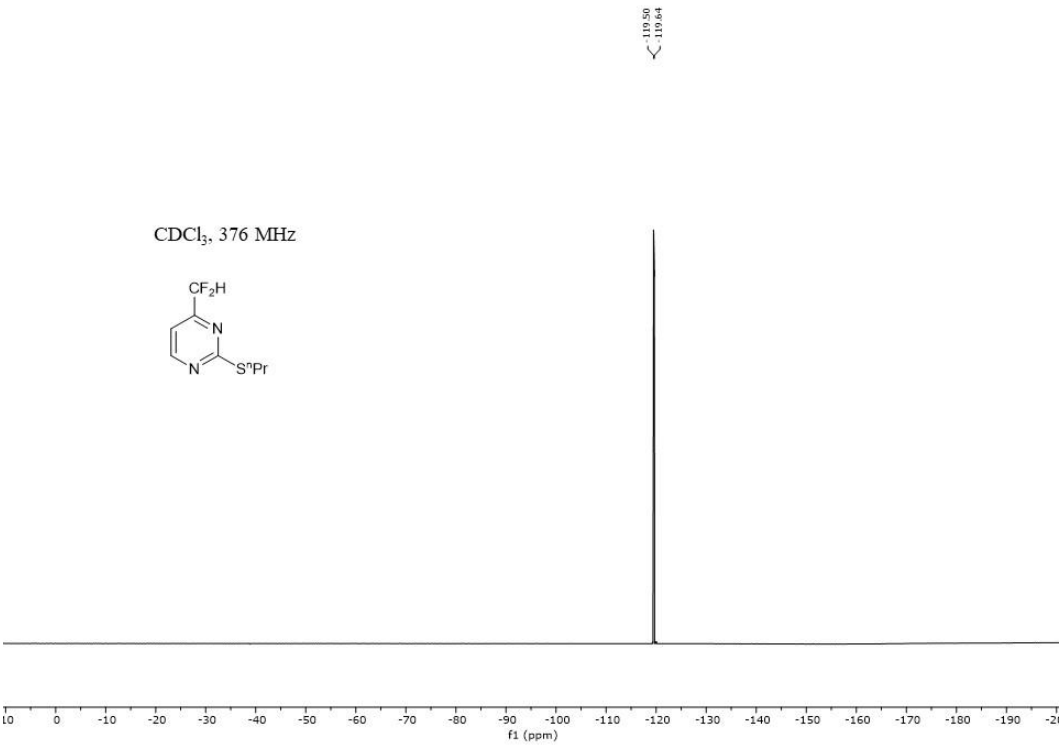


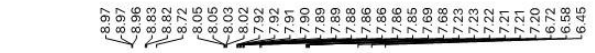


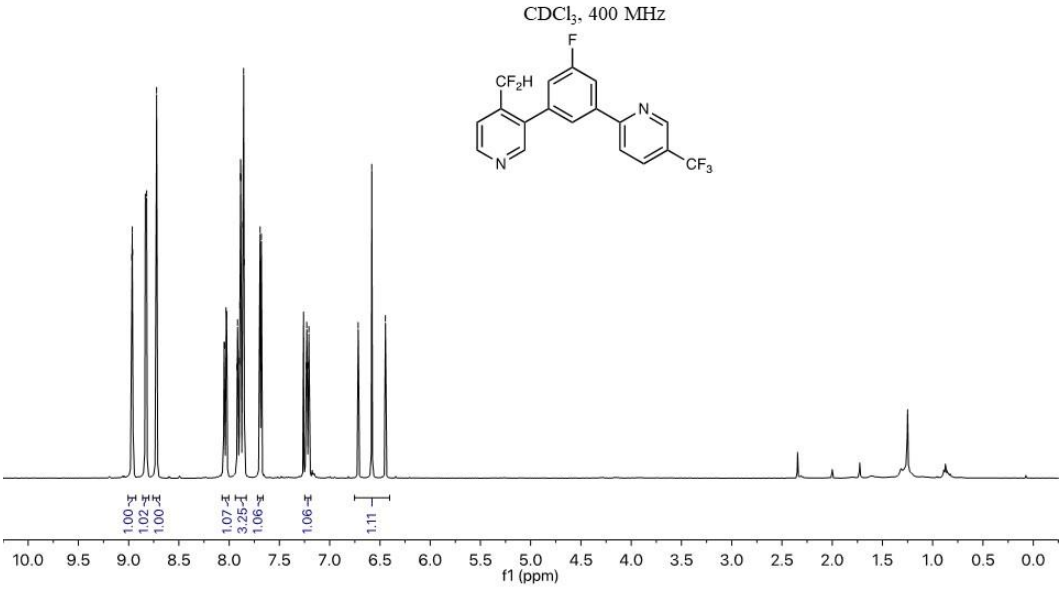

-115.97
-116.12
CDCl3, 376 MHz
CF2H
Ph
O
N
f1 (ppm)


8.68
8.66
7.26
7.22
7.21
6.58
6.44
6.30
3.17
3.15
3.13
1.82
1.80
1.78
1.76
1.74
1.72
1.07
1.05
1.04
CDCl3, 400 MHz
CF2H
N
N
SnPr
1.00
0.98
1.04
2.17
2.22
3.33
f1 (ppm)

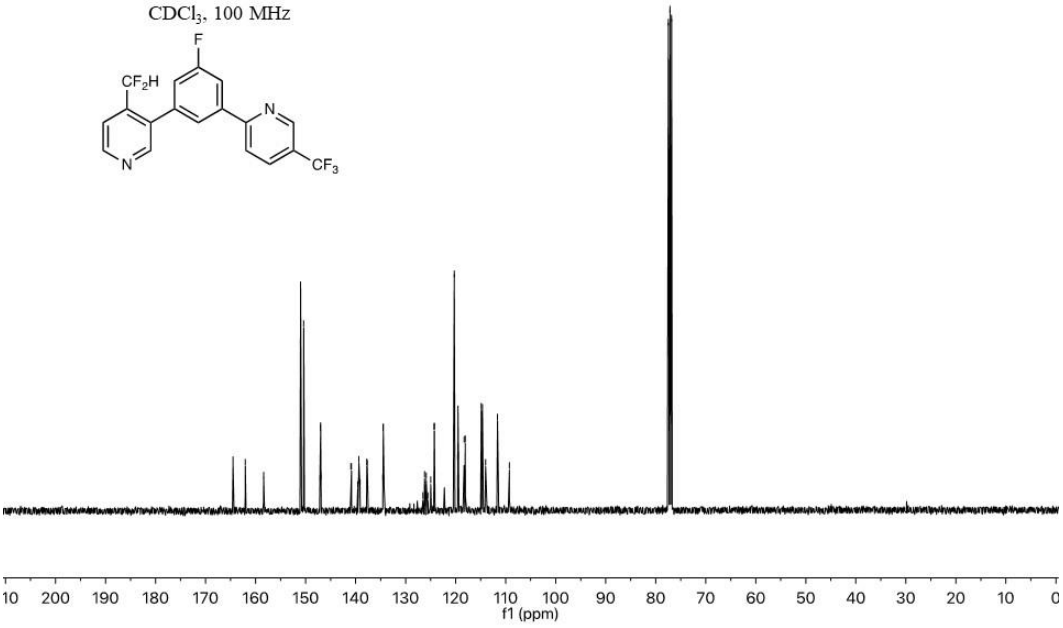

173.68
160.79
160.52
160.25
159.00
115.00
112.59
111.67
111.64
111.61
110.19
77.48
77.16
76.84
33.09
22.55
13.58
CDCl3, 100 MHz
CF2H
N
N
SnPr
f1 (ppm)

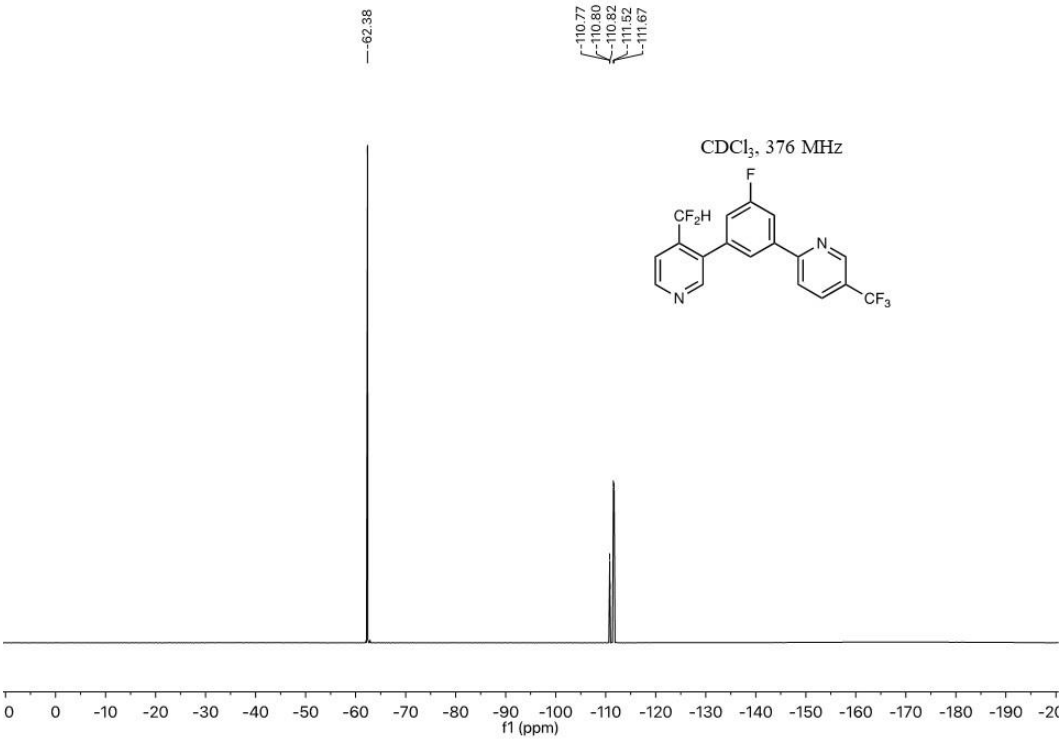

-119.50
-119.64
CDCl3, 376 MHz
CF2H
N
N
SnPr
f1 (ppm)

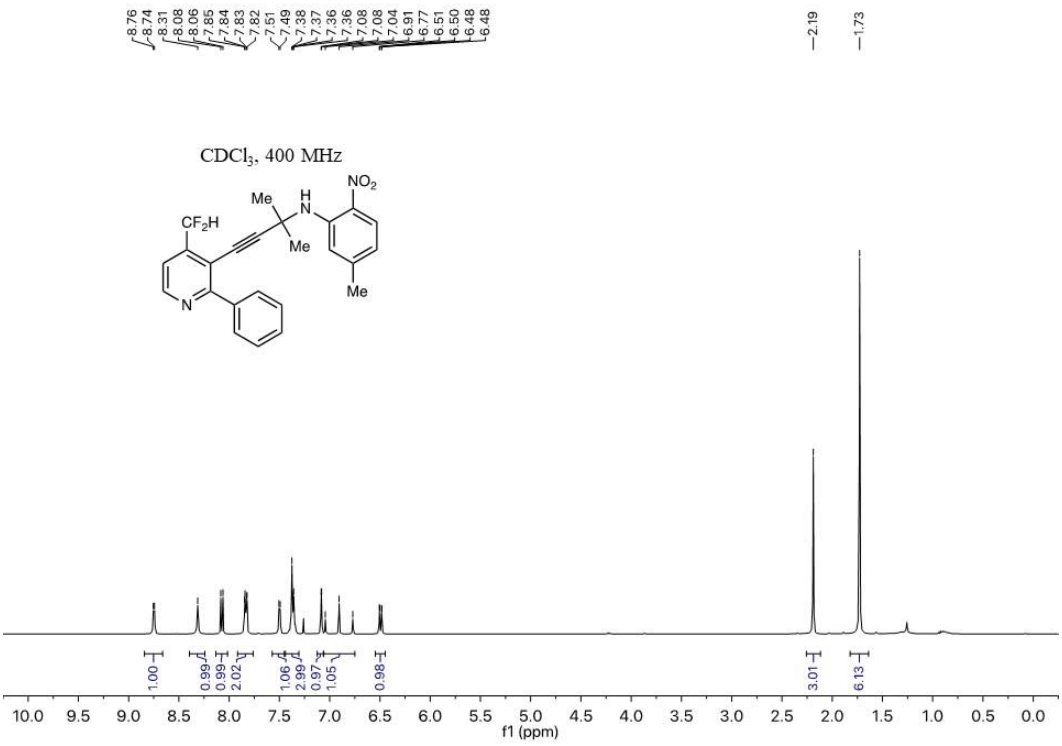

8.97
8.97
8.96
8.83
8.82
8.72
8.05
8.05
8.03
8.02
7.92
7.92
7.91
7.90
7.89
7.89
7.88
7.86
7.86
7.86
7.85
7.69
7.68
7.23
7.23
7.22
7.21
7.21
7.20
6.72
6.58
6.45

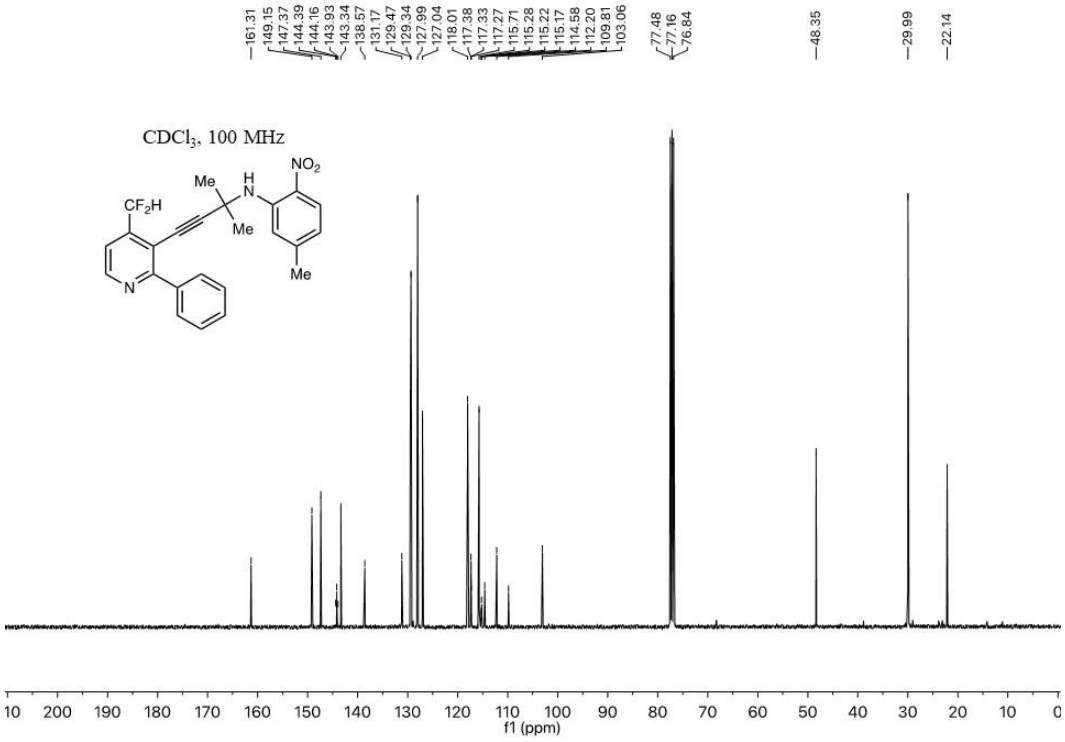

CDCl3, 400 MHz
F
CF2H
N
N
CF3
1.00
1.02
1.00
1.07
3.25
1.06
1.06
1.11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

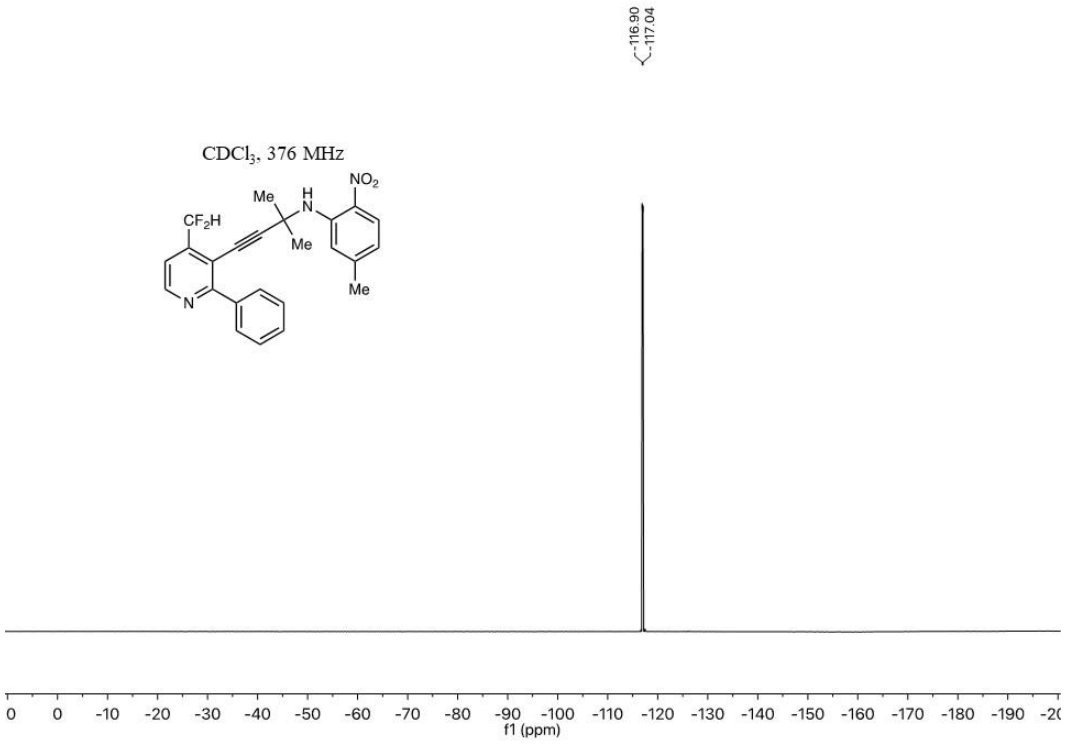

164.52
162.05
158.40
151.00
150.37
147.08
147.04
147.00
146.96
140.93
140.85
139.58
139.35
139.12
137.76
137.68
134.55
134.52
134.48
134.45
126.55
126.22
125.89
125.56
124.98
124.29
124.26
120.28
119.58
119.53
119.47
118.31
118.08
114.89
114.66
114.02
111.64
109.27
77.48
77.16
76.84

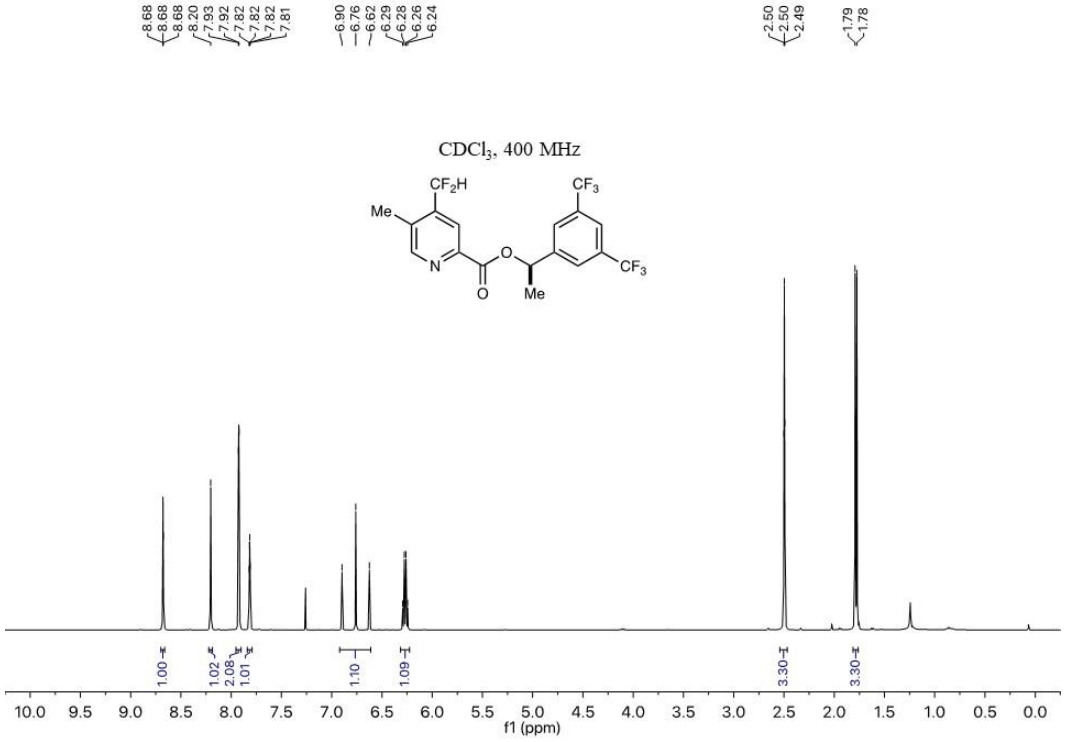

CDCl3, 100 MHz
F
CF2H
N
N
CF3
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

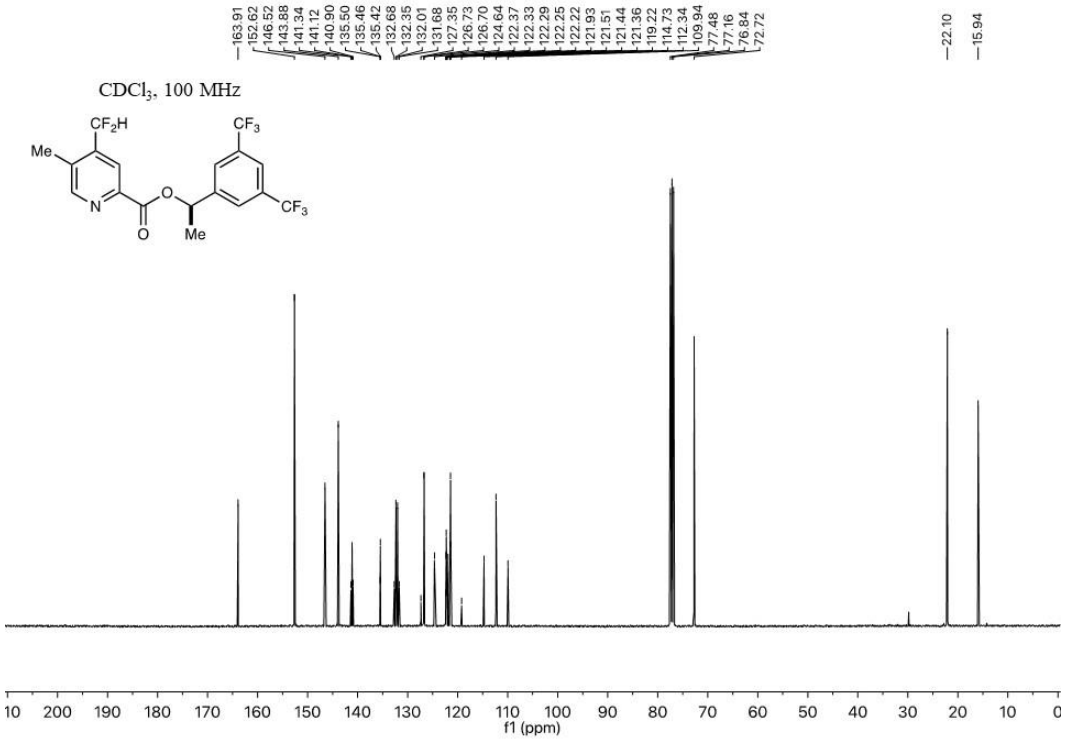

-62.38
-110.77
-110.80
-110.82
-111.52
-111.67
CDCl3, 376 MHz
F
CF2H
N
N
CF3
f1 (ppm)

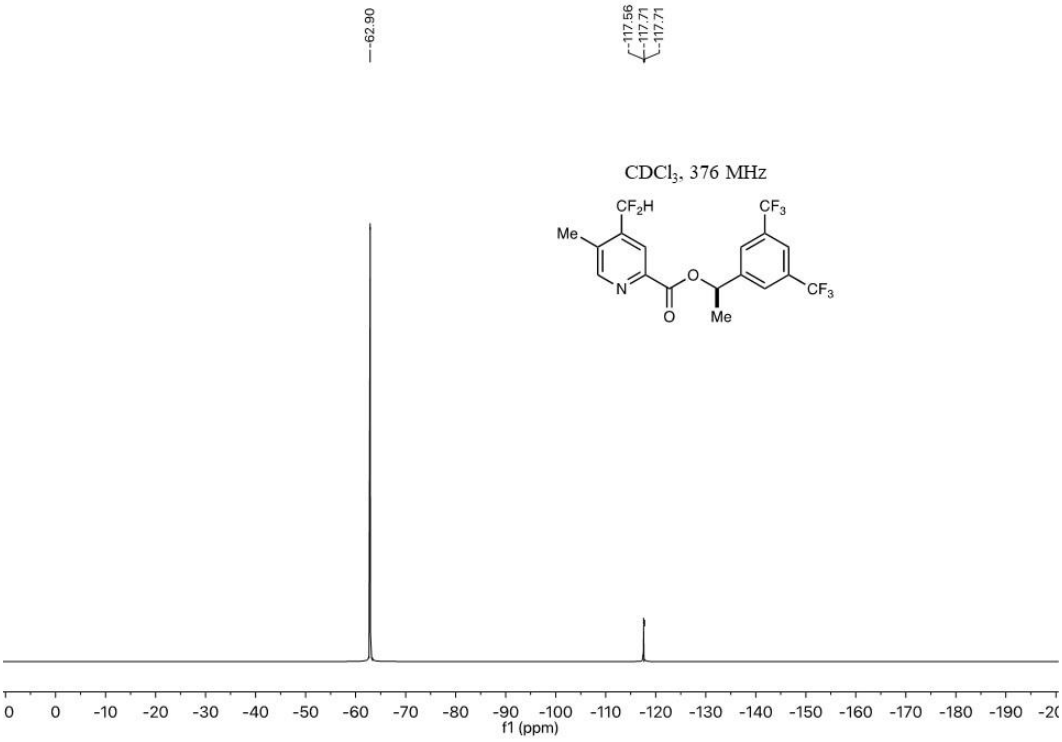

8.76
8.74
8.31
8.08
8.06
7.85
7.84
7.83
7.82
7.51
7.49
7.38
7.37
7.36
7.36
7.08
7.08
7.04
6.91
6.77
6.51
6.50
6.48
6.48
2.19
1.73
CDCl3, 400 MHz
Me
H
N
NO2
CF2H
Me
Me
N
Me
1.00
0.99
0.99
2.02
1.06
2.99
0.97
1.05
0.98
3.01
6.13
f1 (ppm)

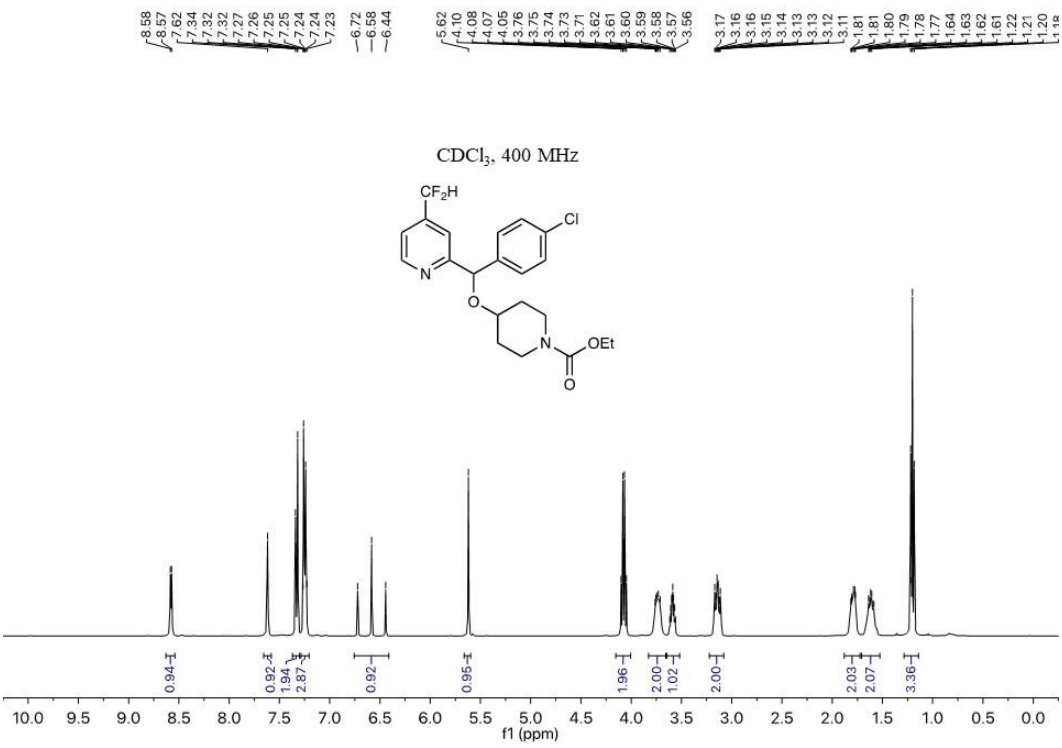

161.31
149.15
147.37
144.39
144.16
143.93
143.34
138.57
131.17
129.47
129.34
127.99
127.04
118.01
117.38
117.33
117.27
115.71
115.28
115.22
115.17
114.58
112.20
109.81
103.06
77.48
77.16
76.84
48.35
29.99
22.14
CDCl3, 100 MHz
NO2
Me
H
N
CF2H
Me
Me
N
f1 (ppm)

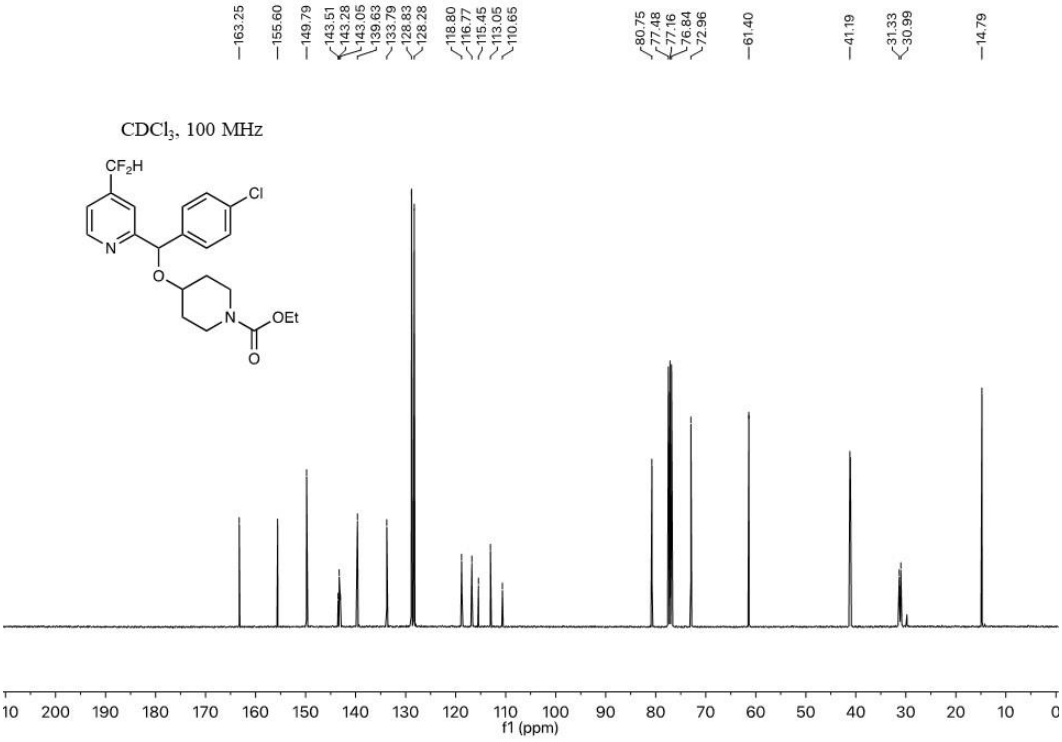

116.90
117.04
CDCl3, 376 MHz
NO2
Me
H
N
CF2H
Me
Me
N
f1 (ppm)

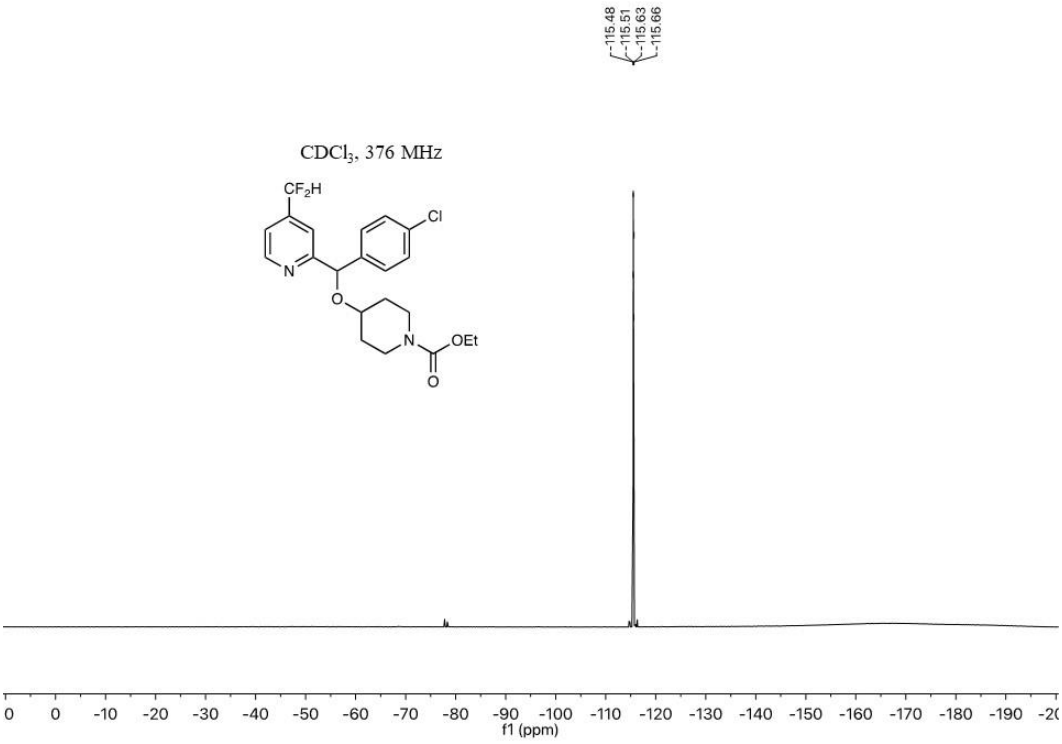

8.68
8.68
8.68
8.20
7.93
7.92
7.82
7.82
7.82
7.81
6.90
6.76
6.62
6.29
6.28
6.26
6.24
2.50
2.50
2.49
1.79
1.78
CDCl3, 400 MHz
CF2H
CF3
Me
N
O
O
Me
CF3
1.00
1.02
2.08
1.01
1.10
1.09
3.30
3.30
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

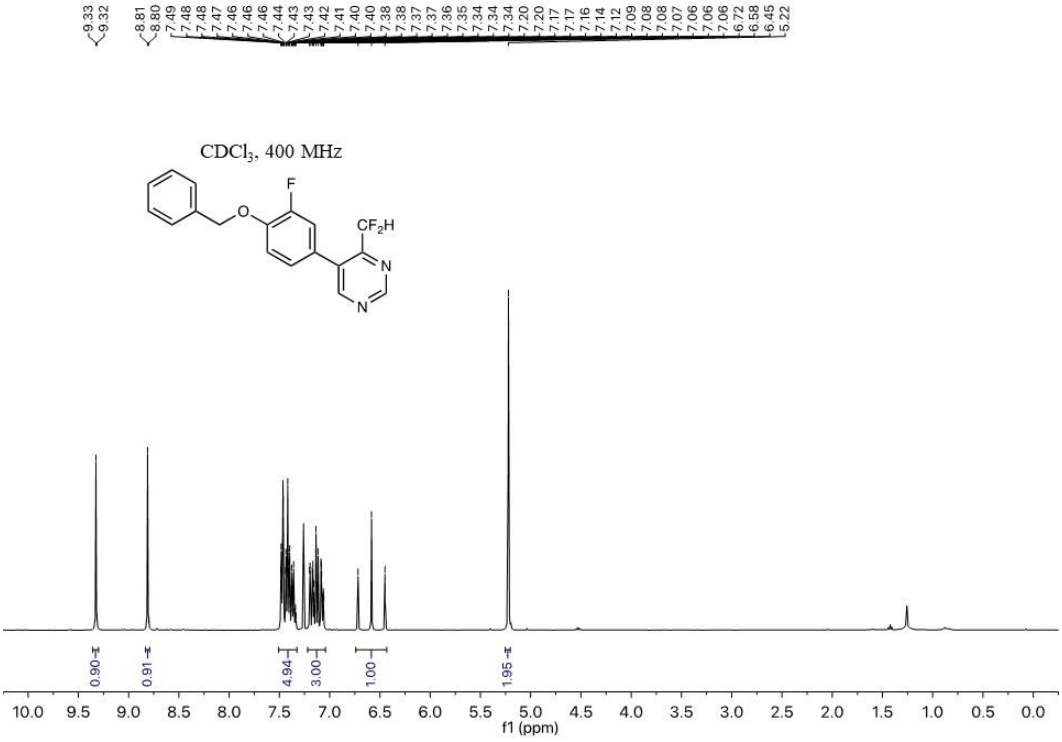

163.91
152.62
146.52
143.88
141.34
141.12
140.90
135.50
135.46
135.42
132.68
132.35
132.01
131.68
127.35
126.73
126.70
124.64
122.37
122.33
122.29
122.25
122.22
121.93
121.51
121.44
121.36
119.22
114.73
112.34
109.94
77.48
77.16
76.84
72.72
22.10
15.94
CDCl3, 100 MHz
CF2H
CF3
Me
N
O
O
Me
CF3
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

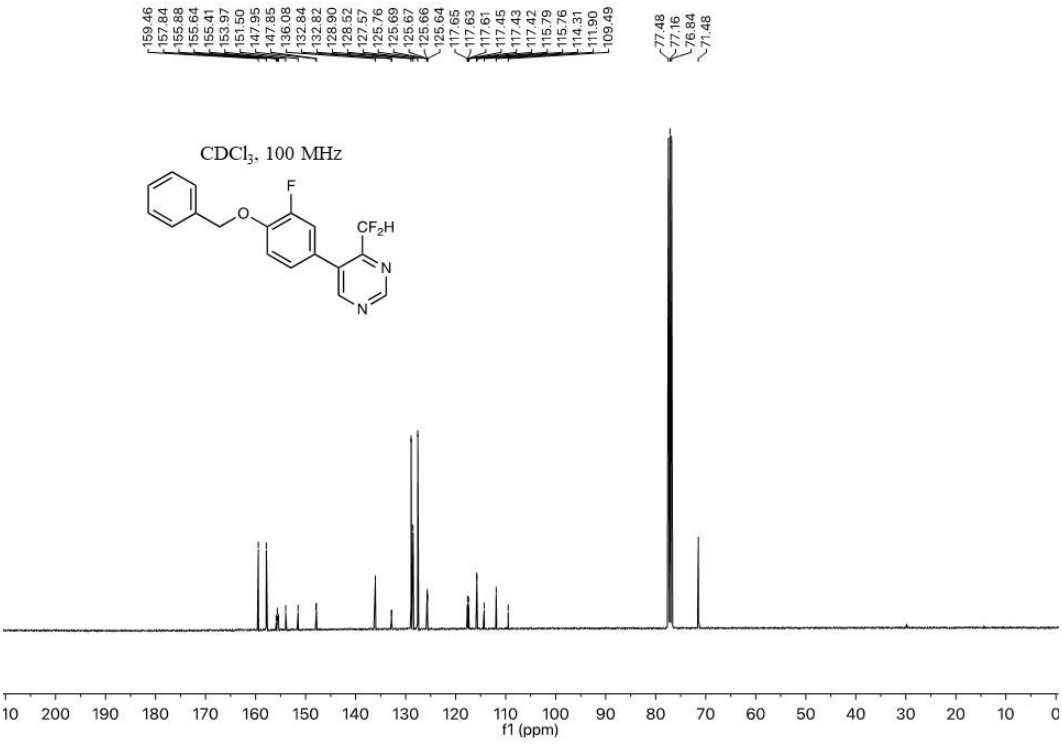

-62.90
-117.56
-117.71
-117.71
CDCl3, 376 MHz
CF2H
CF3
Me
N
O
O
Me
CF3
f1 (ppm)

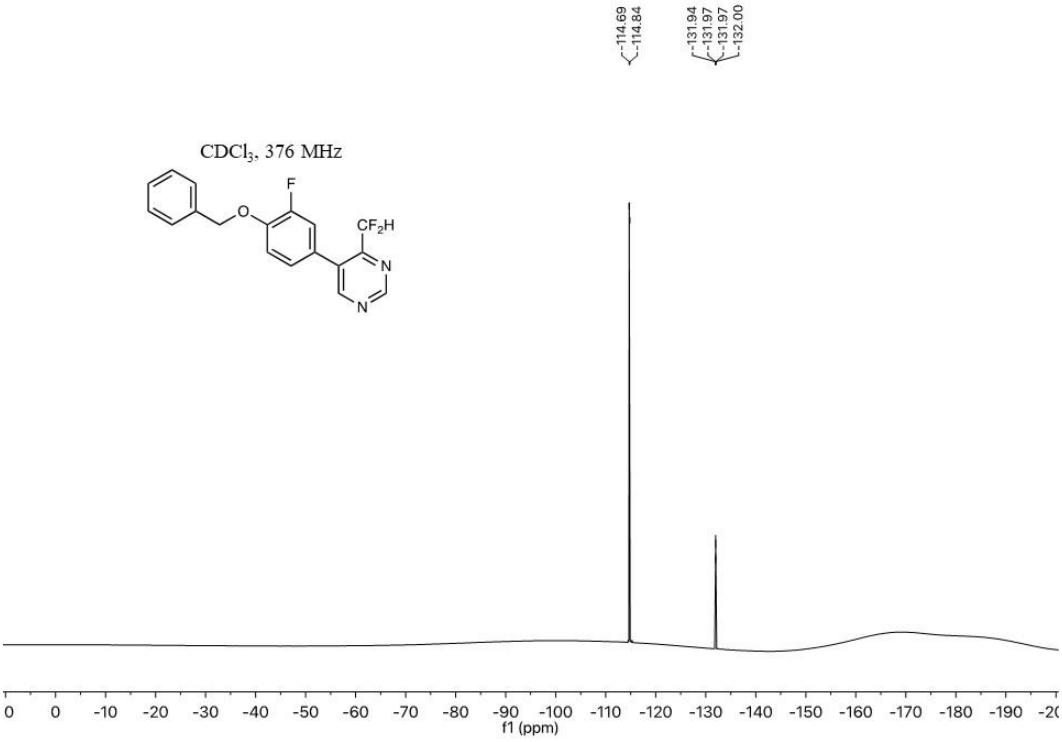

CDCl3, 400 MHz
CF2H
Cl
N
O
N
OEt
O
0.94
0.92
1.94
2.87
0.92
0.95
1.96
2.00
1.02
2.00
2.03
2.07
3.36
f1 (ppm)

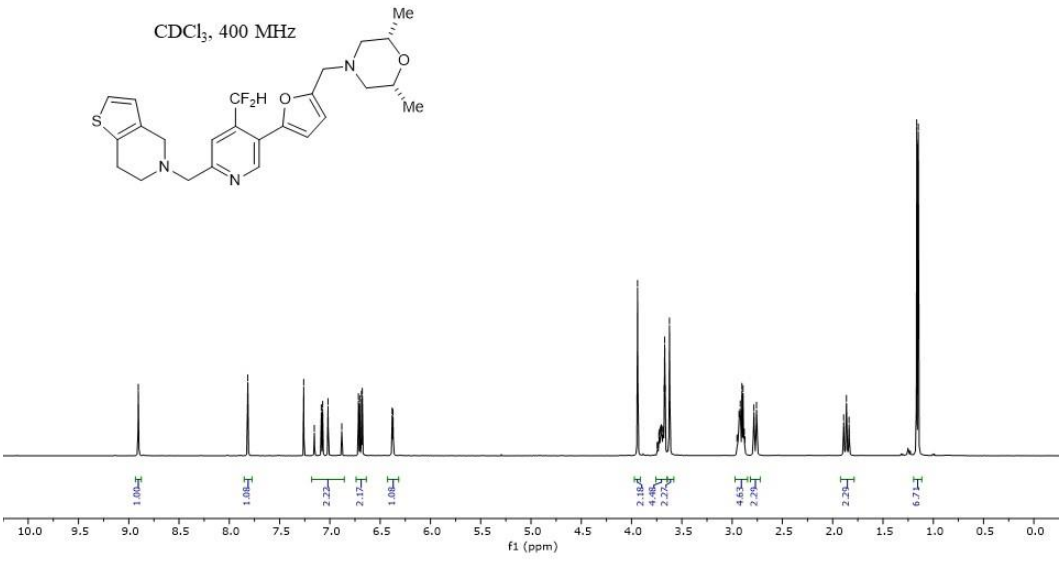

163.25
155.60
149.79
143.51
143.28
143.05
139.63
133.79
128.83
128.28
118.80
116.77
115.45
113.05
110.65
80.75
77.48
77.16
76.84
72.96
61.40
41.19
31.33
30.99
14.79
CDCl3, 100 MHz
CF2H
Cl
N
O
N
OEt
O
f1 (ppm)

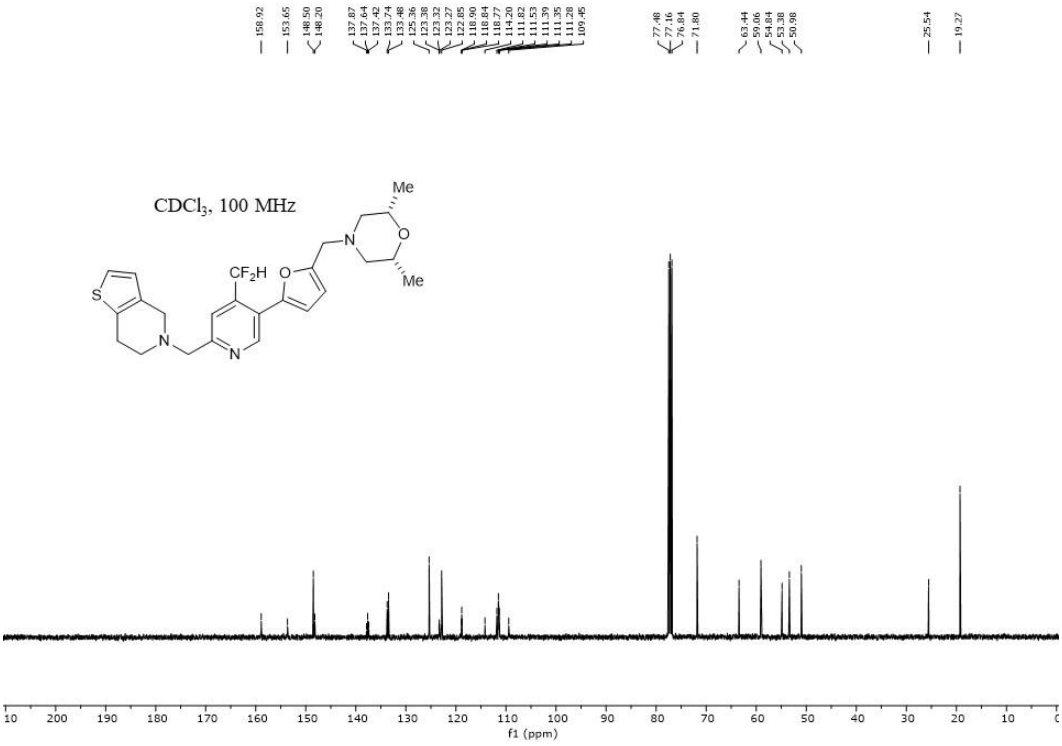

115.48
115.51
115.63
115.66
CDCl3, 376 MHz
CF2H
Cl
N
O
N
OEt
O
f1 (ppm)

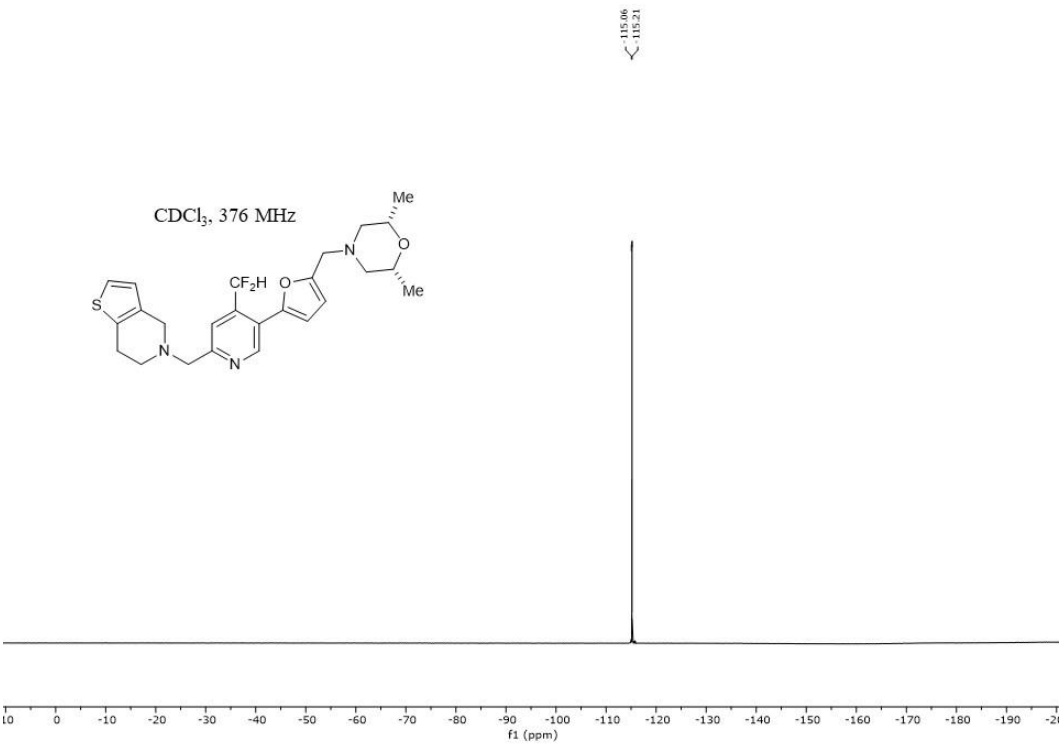

9.33
9.32
8.81
8.80
7.49
7.48
7.48
7.47
7.46
7.46
7.46
7.44
7.43
7.43
7.42
7.41
7.40
7.40
7.38
7.38
7.37
7.37
7.36
7.35
7.34
7.34
7.34
7.20
7.17
7.17
7.16
7.14
7.12
7.09
7.08
7.08
7.07
7.06
7.06
7.06
6.72
6.58
6.45
5.22
CDCl3, 400 MHz
F
O
CF2H
N
N
0.90
0.91
4.94
3.00
1.00
1.95
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

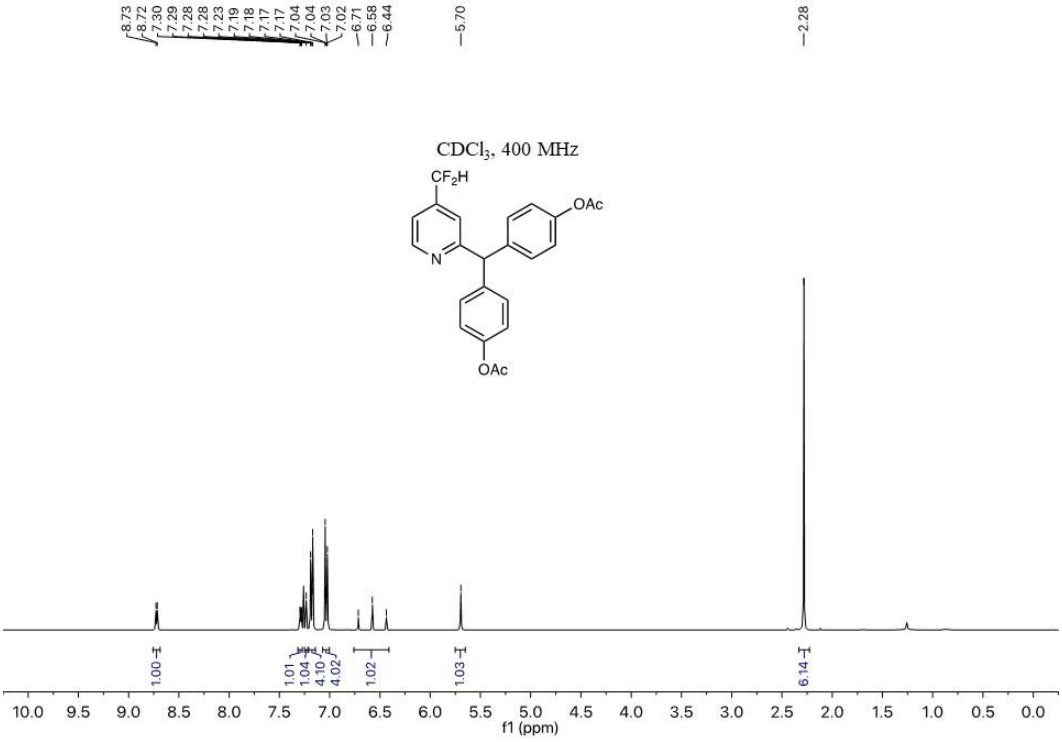

159.46
157.84
155.88
155.64
155.41
153.97
151.50
147.95
147.85
136.08
132.84
132.82
128.90
128.52
127.57
125.76
125.69
125.67
125.66
125.64
117.65
117.63
117.61
117.45
117.43
117.42
115.79
115.76
114.31
111.90
109.49
77.48
77.16
76.84
71.48
CDCl3, 100 MHz
F
O
CF2H
N
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

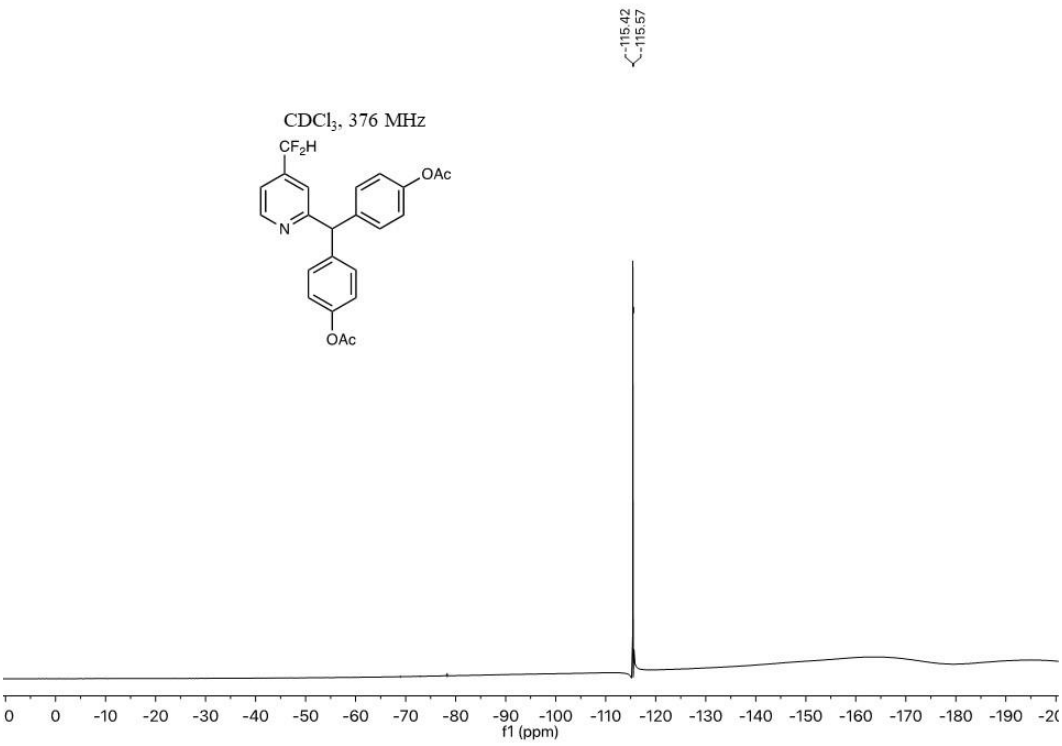

CDCl3, 376 MHz
F
O
CF2H
N
N
-114.69
-114.84
-131.94
-131.97
-131.97
-132.00
f1 (ppm)

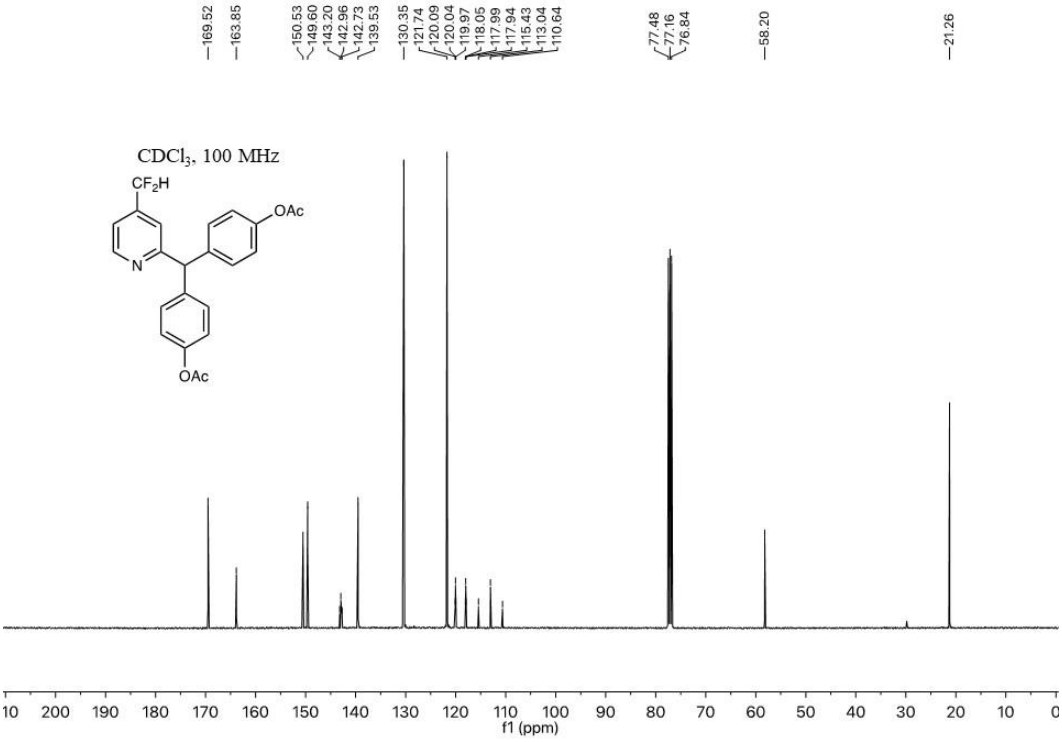

CDCl3, 400 MHz
Me
N
O
Me
CF2H
O
S
N
N
f1 (ppm)

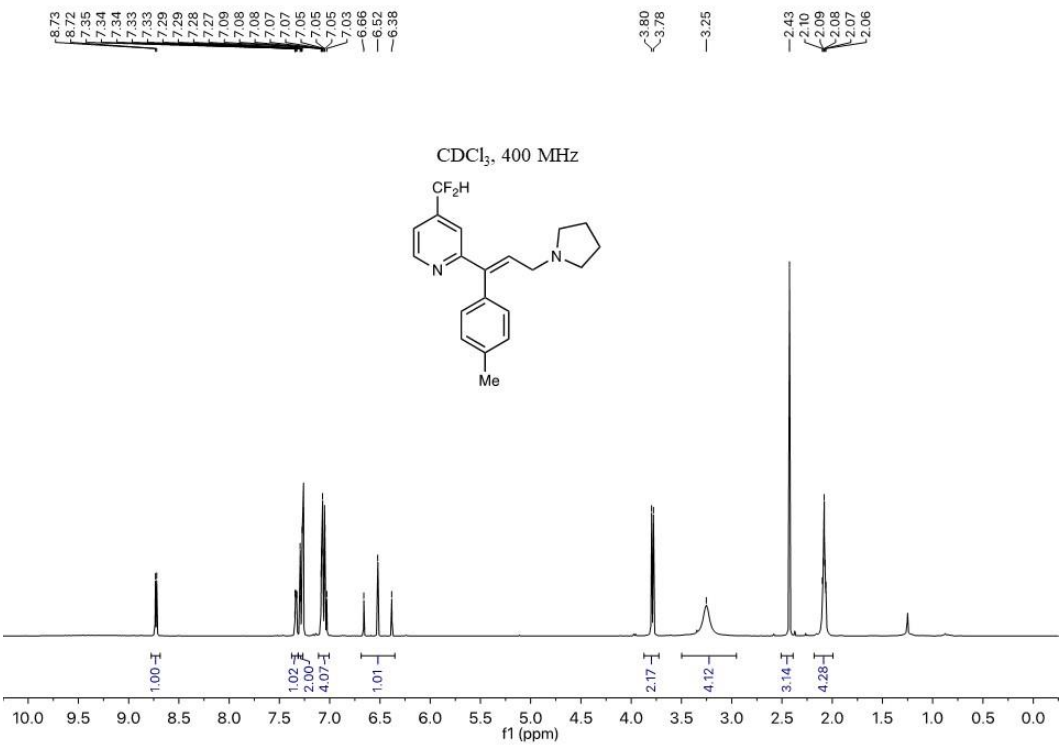

158.92
153.65
148.50
148.20
137.87
137.64
137.42
133.74
132.48
125.36
123.38
123.32
123.27
122.85
118.90
118.64
118.37
114.20
111.82
111.53
111.39
111.35
111.28
109.45
77.48
77.16
76.84
71.80
63.44
59.06
54.84
53.38
50.98
25.54
19.27
CDCl3, 100 MHz
Me
Me
CF2H
S
N
O
N
f1 (ppm)

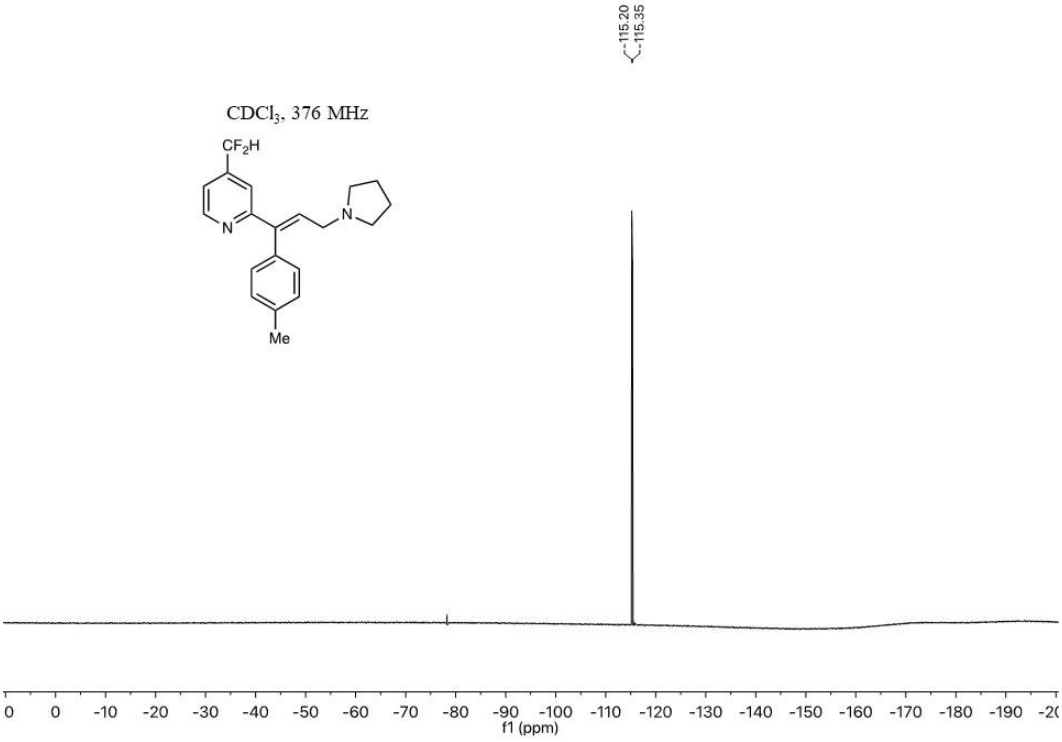

115.06
115.21
CDCl3, 376 MHz
Me
Me
CF2H
S
N
O
N
f1 (ppm)

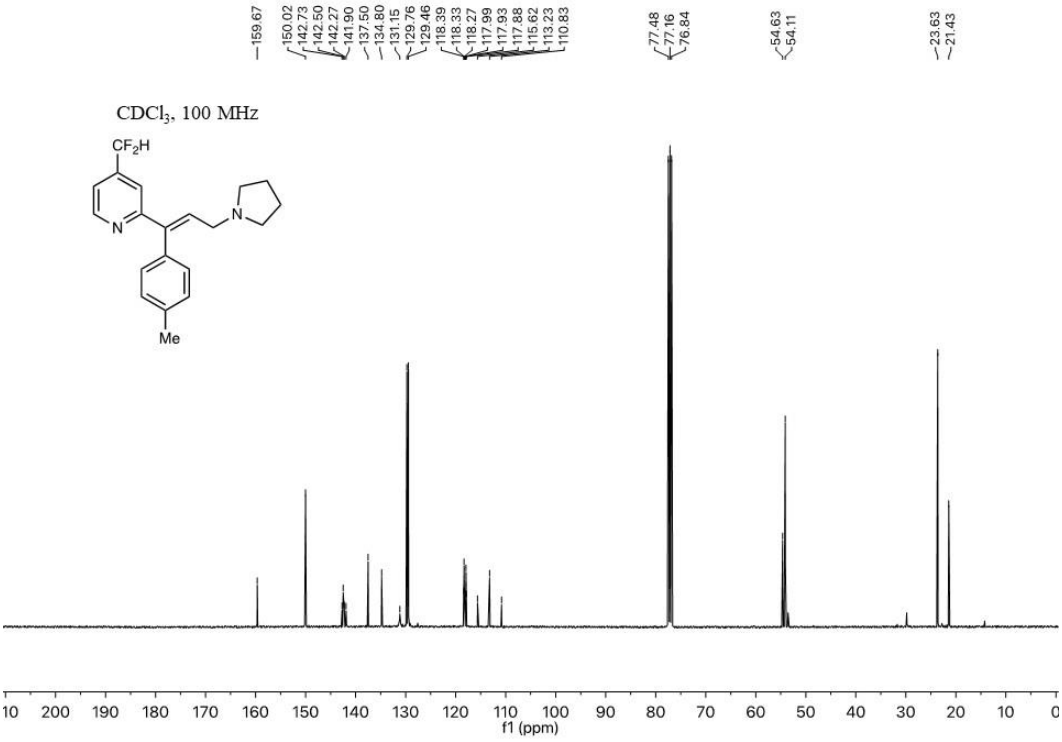

8.73
8.72
7.30
7.29
7.28
7.28
7.23
7.19
7.18
7.17
7.17
7.04
7.04
7.03
7.02
6.71
6.58
6.44
5.70
2.28
CDCl3, 400 MHz
CF2H
OAc
N
OAc
1.00
1.01
1.04
4.10
4.02
1.02
1.03
6.14
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


-115.42
-115.57
CDCl3, 376 MHz
CF2H
OAc
N
OAc
0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)

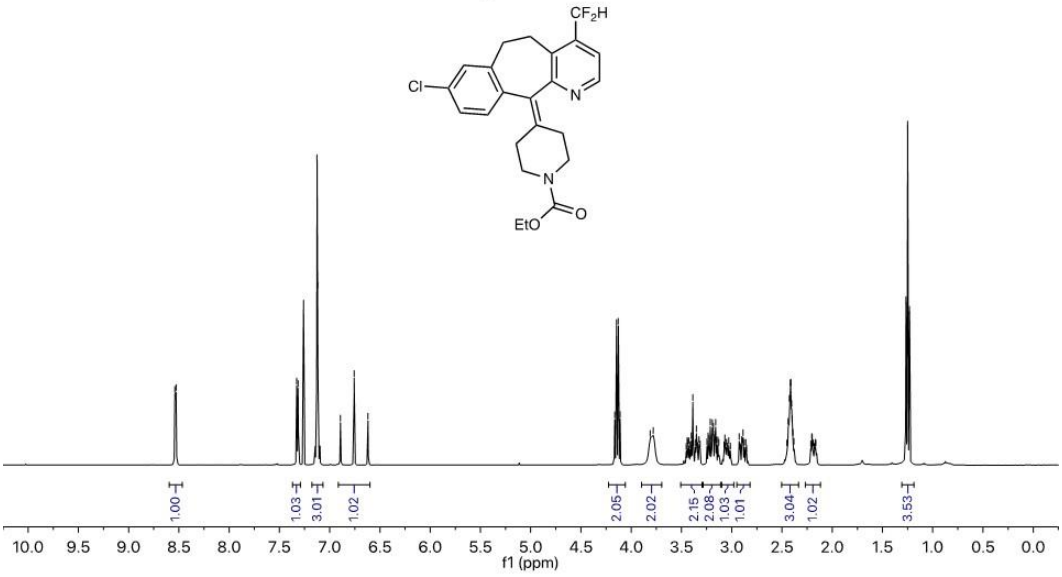

169.52
163.85
150.53
149.60
143.20
142.96
142.73
139.53
130.35
121.74
120.09
120.04
119.97
118.05
117.99
117.94
115.43
113.04
110.64
77.48
77.16
76.84
58.20
21.26
CDCl3, 100 MHz
CF2H
OAc
N
OAc
f1 (ppm)

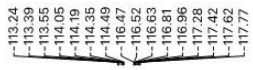

8.73
8.72
7.35
7.34
7.34
7.33
7.33
7.29
7.29
7.28
7.27
7.09
7.08
7.08
7.07
7.07
7.05
7.05
7.05
7.03
6.66
6.52
6.38
3.80
3.78
3.25
2.43
2.10
2.09
2.08
2.07
2.06
CDCl3, 400 MHz
CF2H
N
N
Me
1.00
1.02
2.00
4.07
1.01
2.17
4.12
3.14
4.28
f1 (ppm)


-115.20
-115.35
CDCl3, 376 MHz
CF2H
N
N
Me
0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -20
f1 (ppm)

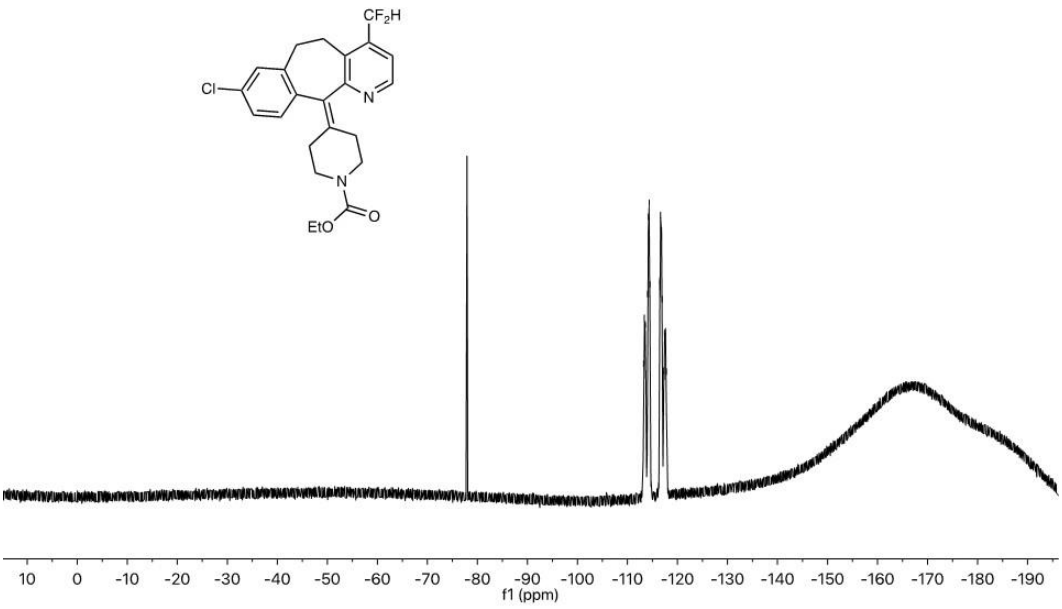

159.67
150.02
142.73
142.50
142.27
141.90
137.50
134.80
131.15
129.76
129.46
118.39
118.33
118.27
117.99
117.93
117.88
115.62
113.23
110.83
77.48
77.16
76.84
54.63
54.11
23.63
21.43
CDCl3, 100 MHz
CF2H
N
N
Me
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

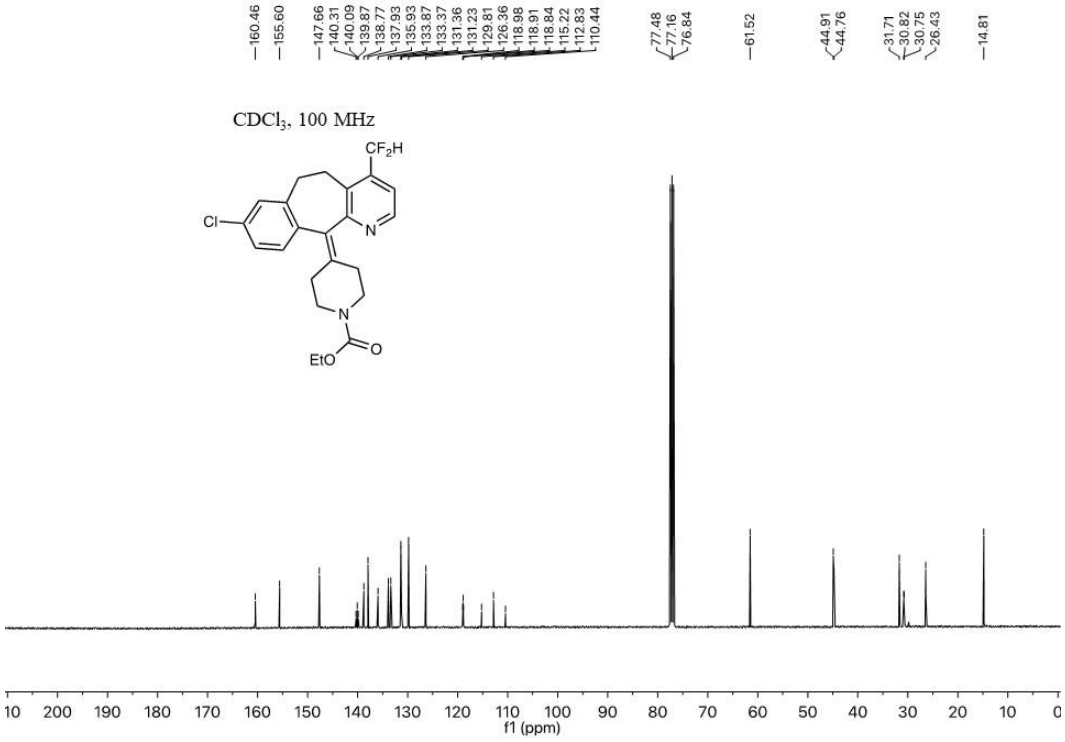
$CDCl_3$, 400 MHz

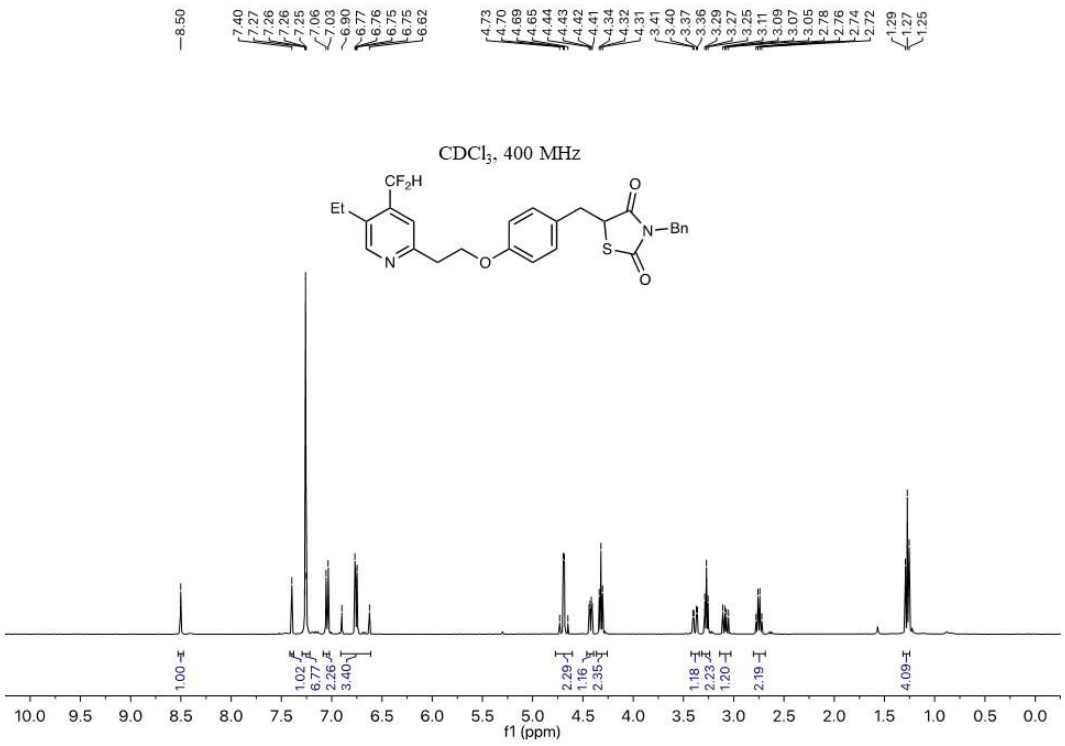


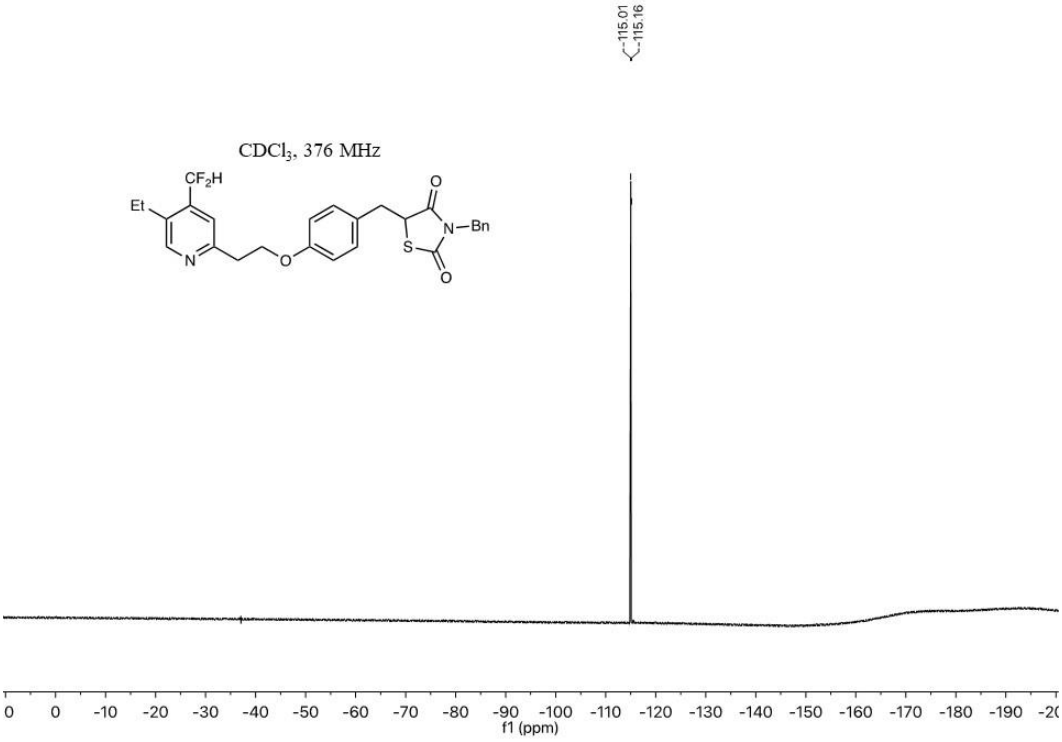


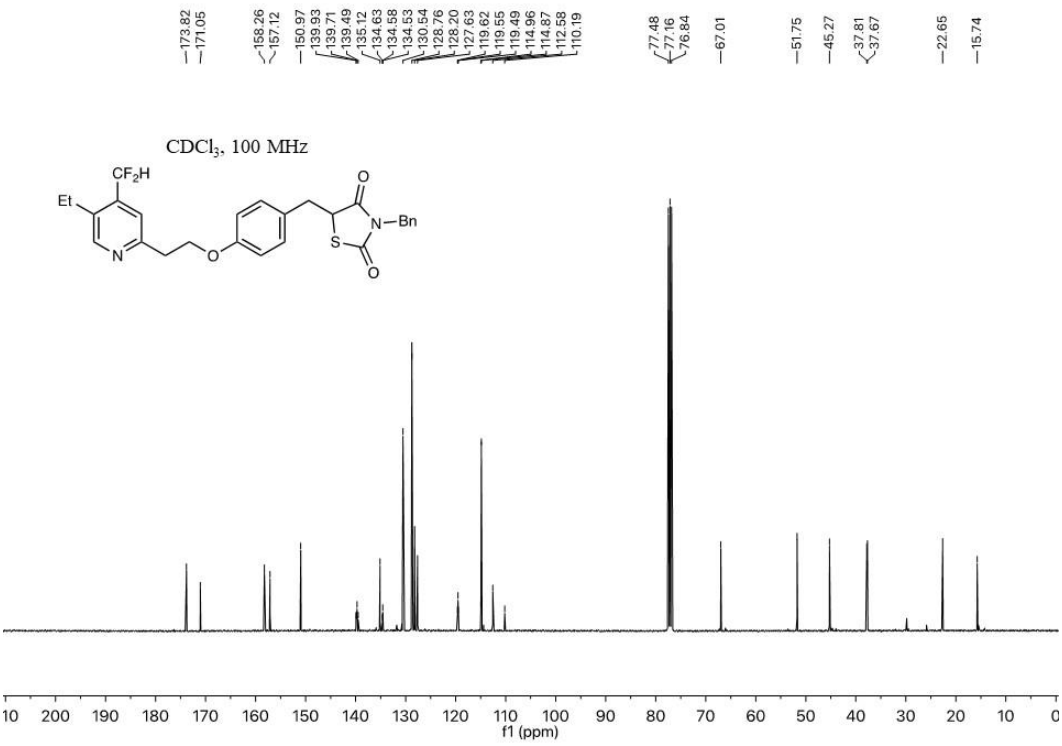
$CDCl_3$, 376 MHz

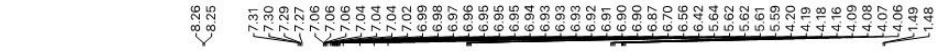



160.46
155.60
147.66
140.31
140.09
139.87
138.77
137.93
135.93
133.87
133.37
131.36
131.23
129.81
126.36
118.98
118.91
118.84
115.22
112.83
110.44
77.48
77.16
76.84
61.52
44.91
44.76
31.71
30.82
30.75
26.43
14.81
CDCl3, 100 MHz
CF2H
Cl
N
N
EtO
O
f1 (ppm)

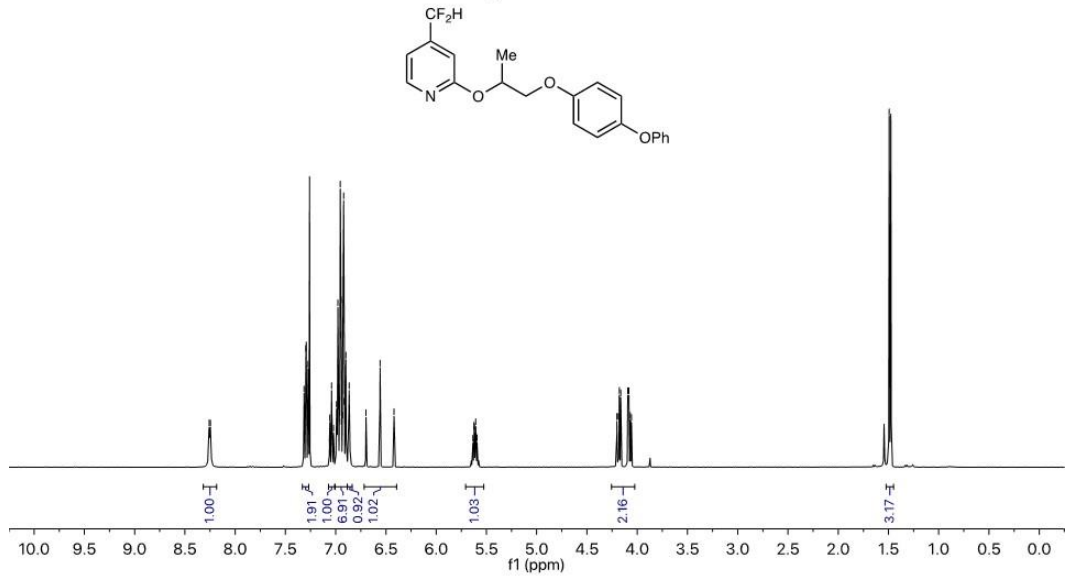

8.50
7.40
7.27
7.26
7.26
7.25
7.06
7.03
6.90
6.77
6.76
6.75
6.75
6.62
4.73
4.70
4.69
4.65
4.44
4.43
4.42
4.41
4.34
4.32
4.31
3.41
3.40
3.37
3.36
3.29
3.27
3.25
3.11
3.09
3.07
3.05
2.78
2.76
2.74
2.72
1.29
1.27
1.25
CDCl3, 400 MHz
CF2H
Et
N
O
O
N
Bn
S
O
1.00
1.02
6.77
2.26
3.40
2.29
1.16
2.35
1.18
2.23
1.20
2.19
4.09
f1 (ppm)


-115.01
-115.16
CDCl3, 376 MHz
CF2H
Et
N
O
S
N
Bn
O
O
f1 (ppm)

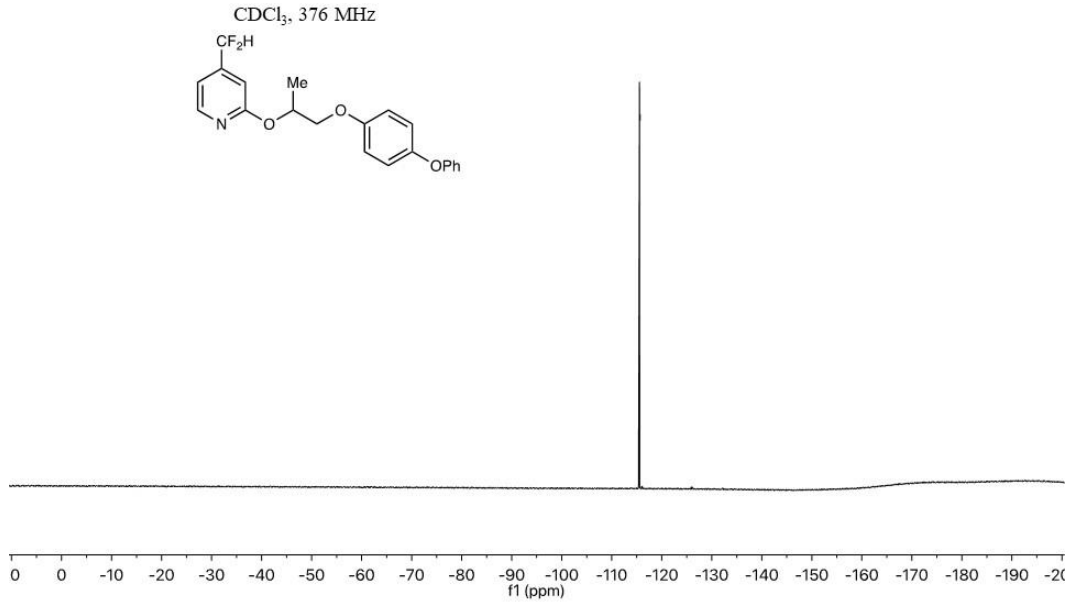

173.82
171.05
158.26
157.12
150.97
139.93
139.71
139.49
135.12
134.63
134.58
134.53
130.54
128.76
128.20
127.63
119.62
119.55
119.49
114.96
114.87
112.58
110.19
77.48
77.16
76.84
67.01
51.75
45.27
37.81
37.67
22.65
15.74
CDCl3, 100 MHz
CF2H
Et
N
O
S
N
Bn
O
O
f1 (ppm)

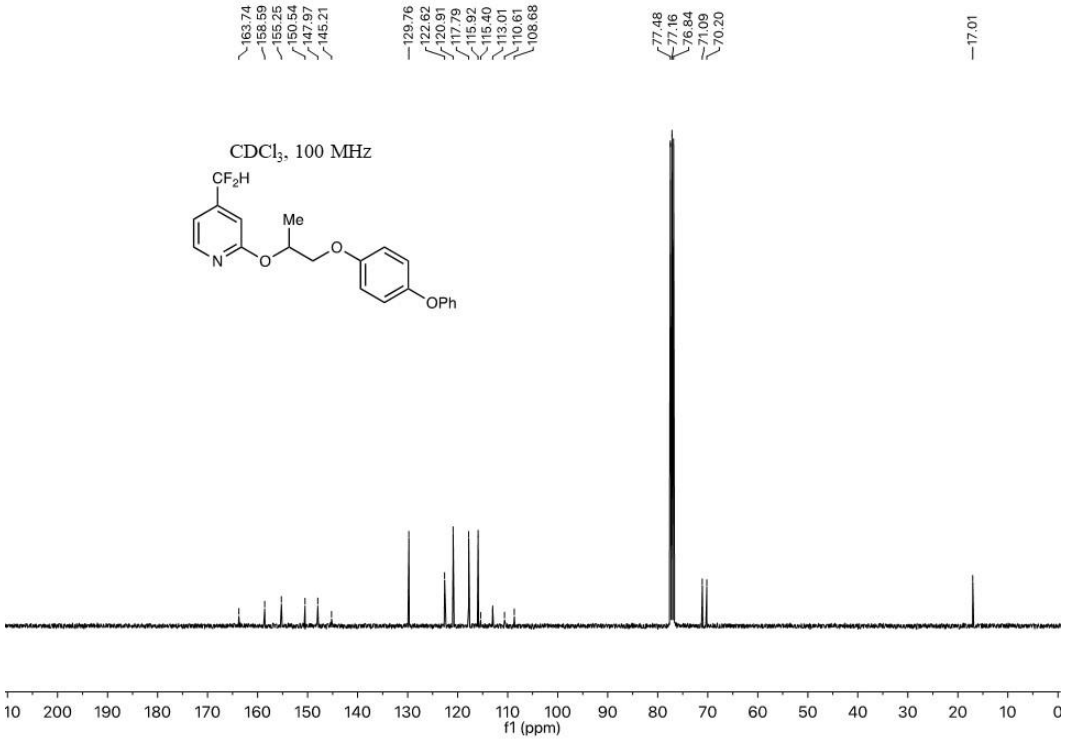


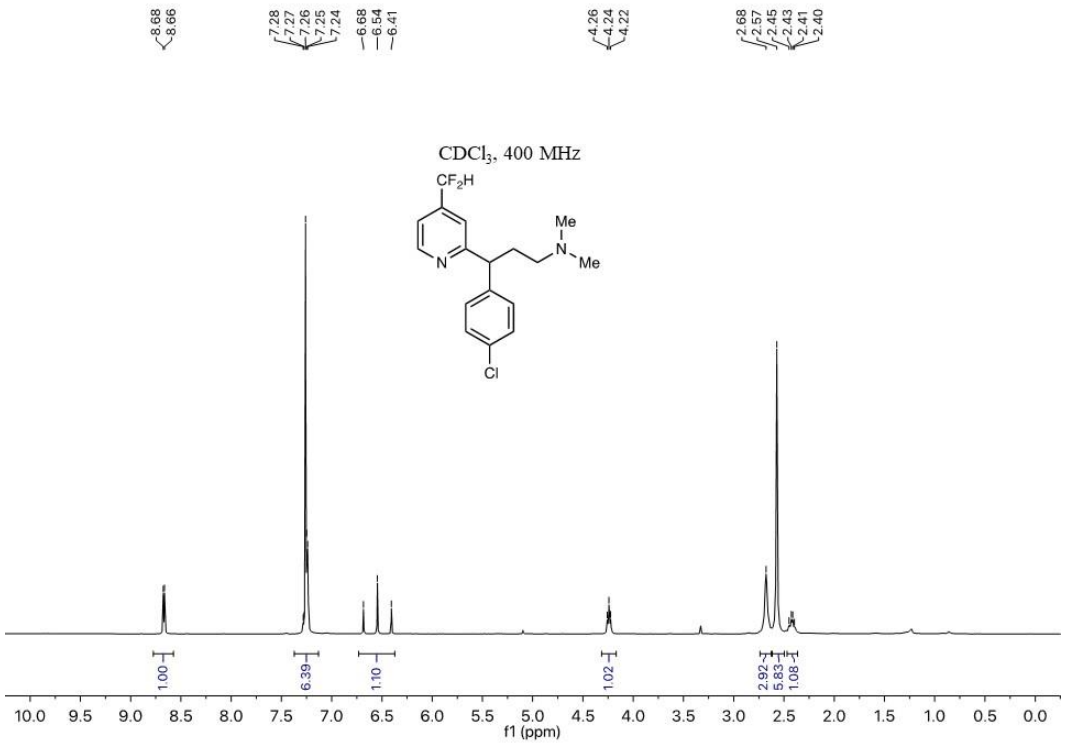
$CDCl_3$, 400 MHz

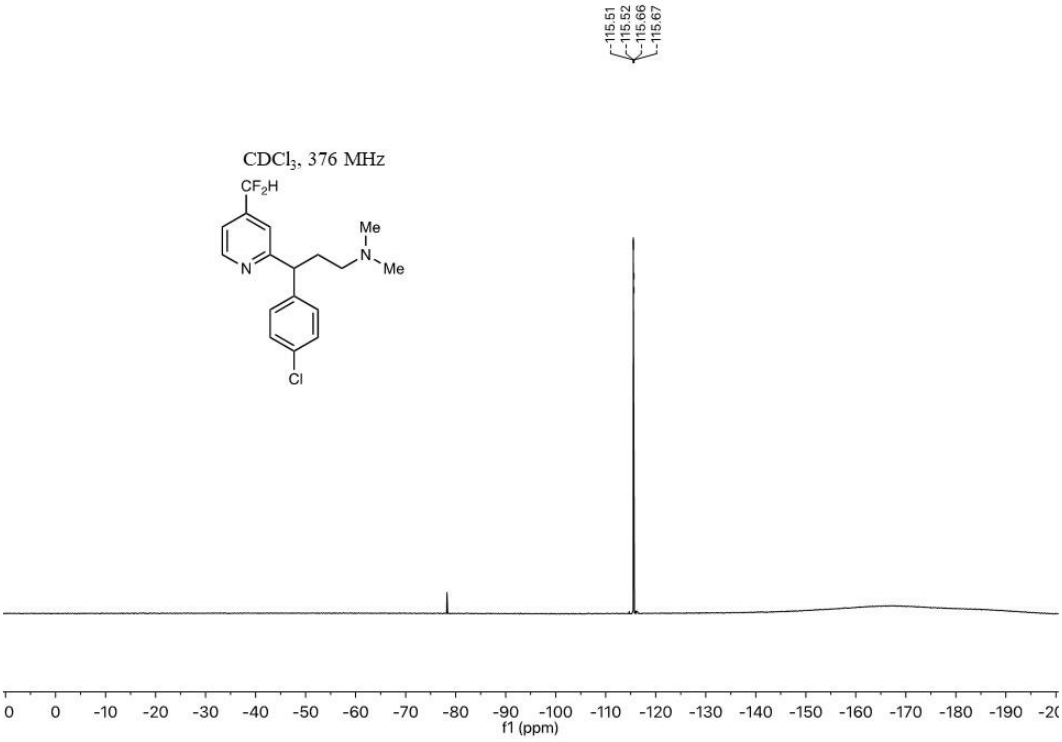


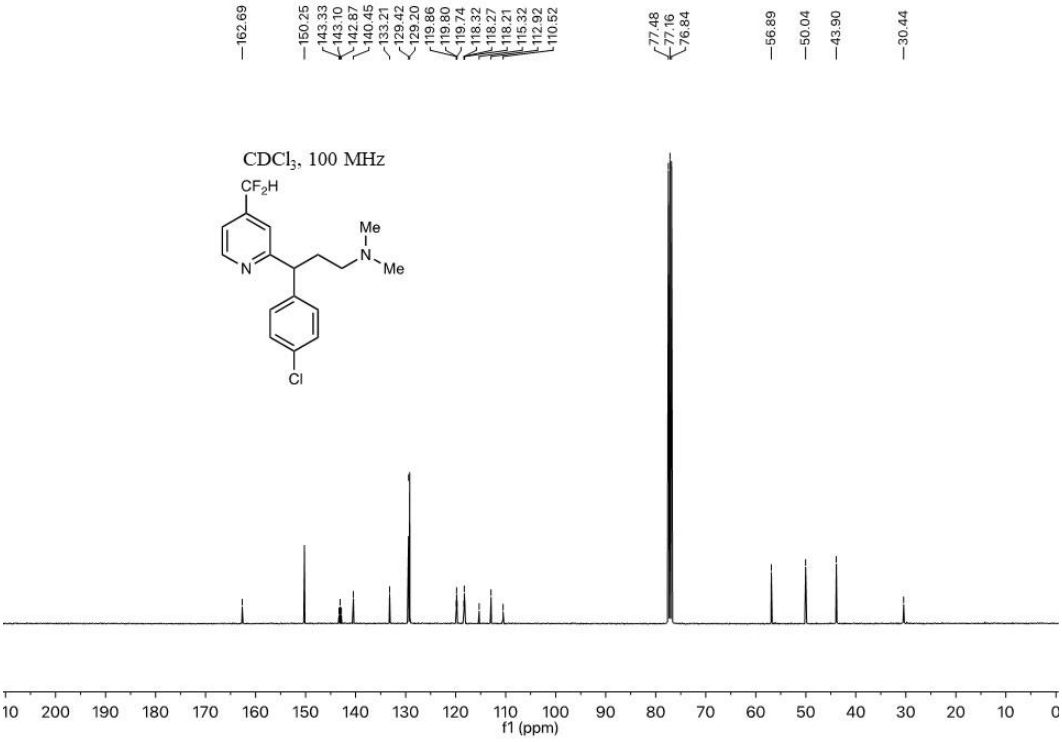
$CDCl_3$, 376 MHz

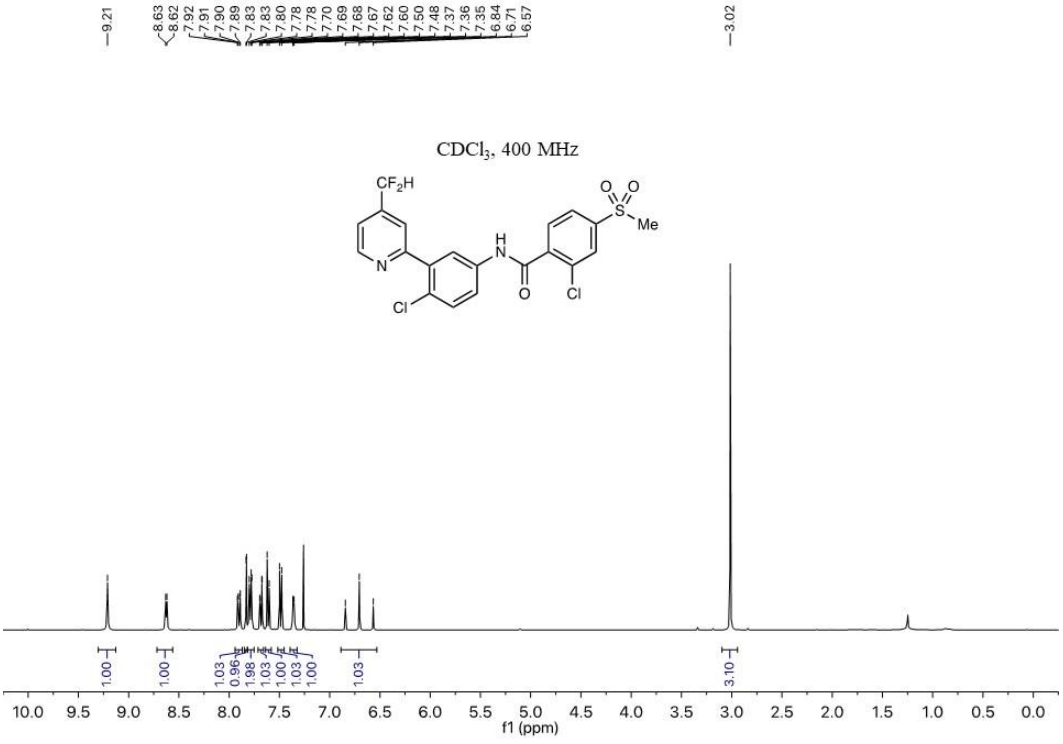


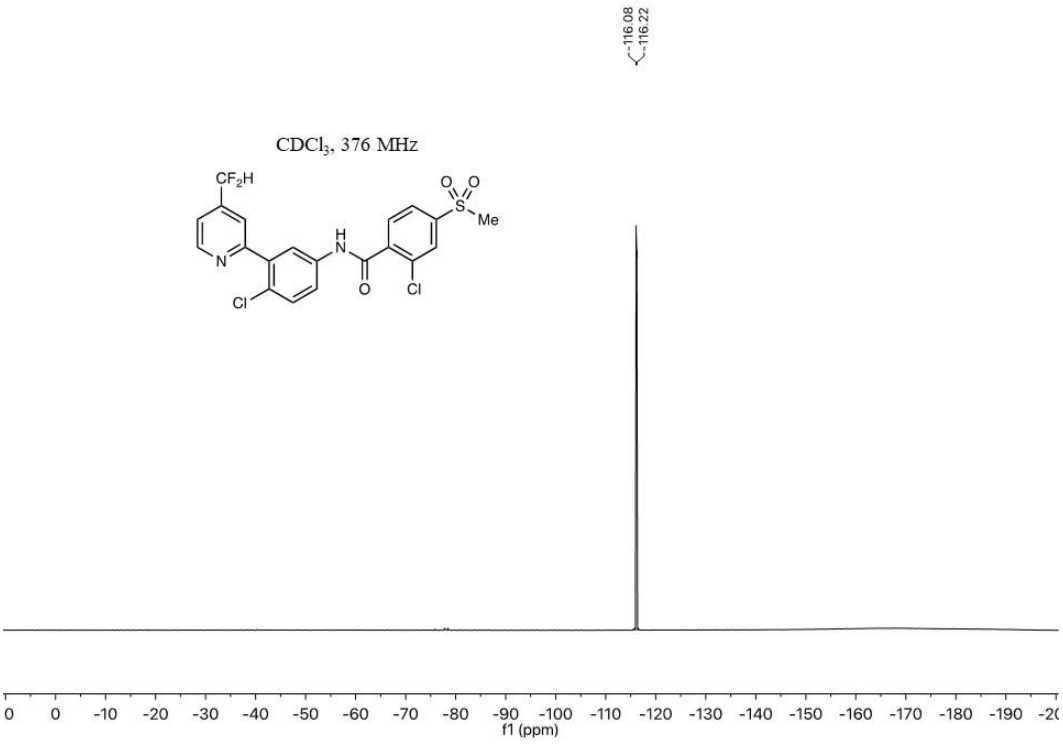

163.74
158.59
155.25
150.54
147.97
145.21
129.76
122.62
120.91
117.79
115.92
115.40
113.01
110.61
108.68
77.48
77.16
76.84
71.09
70.20
17.01
CDCl3, 100 MHz
CF2H
Me
N
O
O
OPh
f1 (ppm)

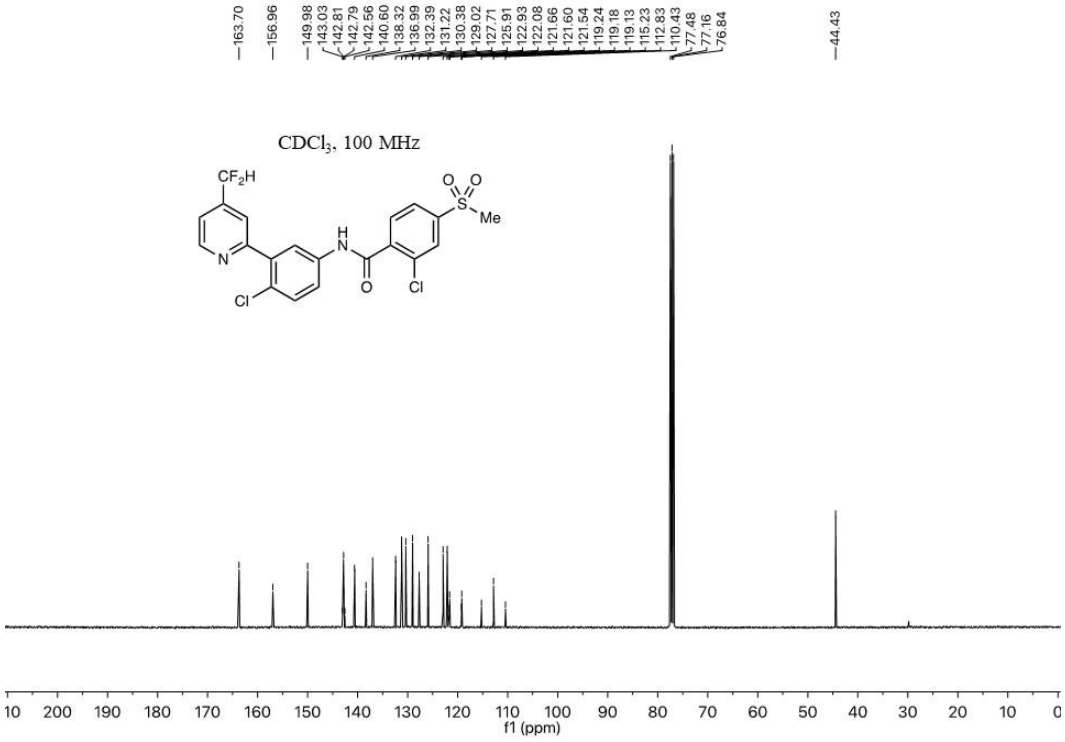

8.68
8.66
7.28
7.27
7.26
7.25
7.24
6.68
6.54
6.41
4.26
4.24
4.22
2.68
2.57
2.45
2.43
2.41
2.40
CDCl3, 400 MHz
CF2H
Me
N
Me
N
Cl
1.00
6.39
1.10
1.02
2.92
5.83
1.08
f1 (ppm)

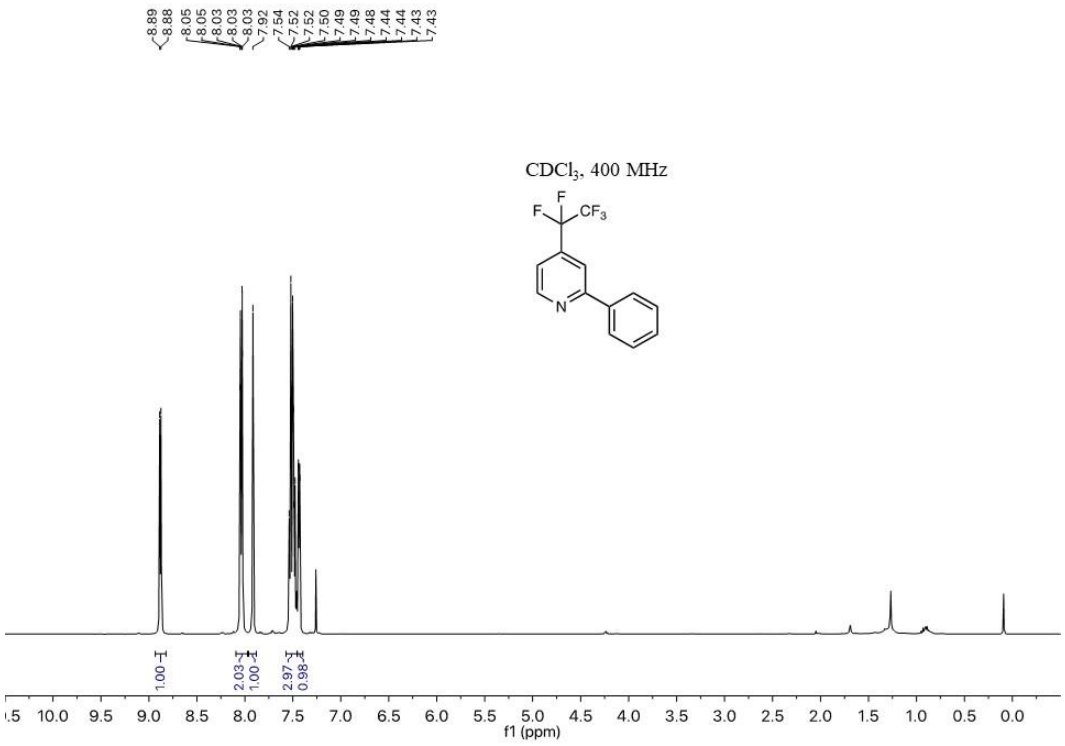

-115.51
-115.52
-115.66
-115.67
CDCl3, 376 MHz
CF2H
Me
N
Me
Cl
0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -20
f1 (ppm)

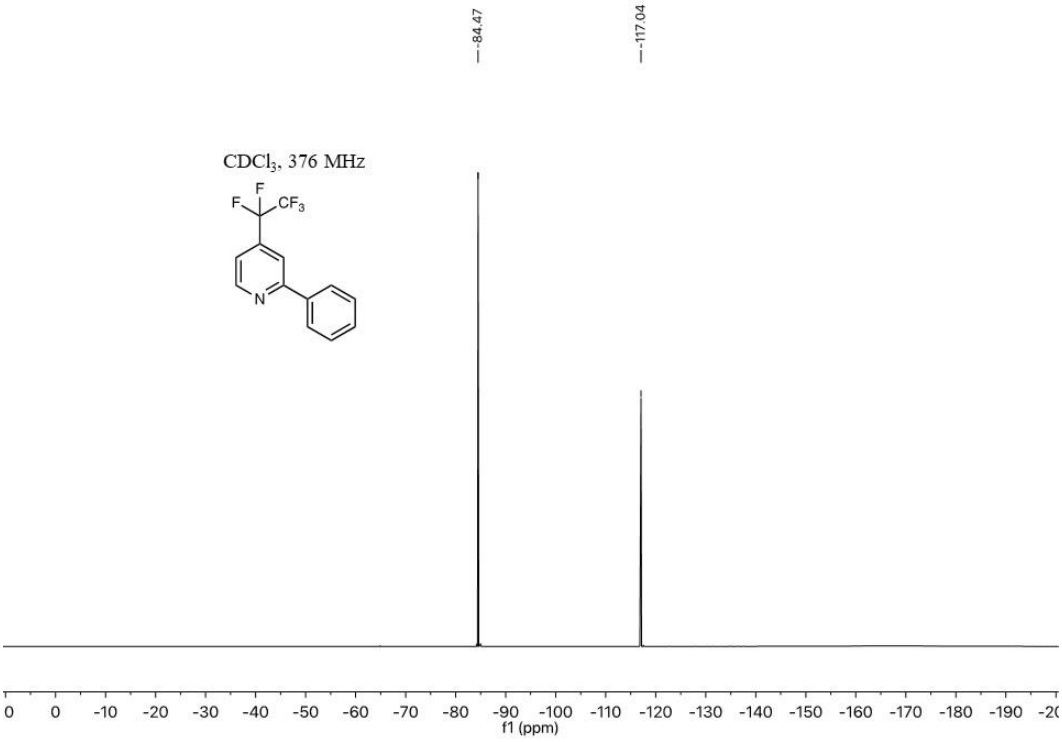

162.69
150.25
143.33
143.10
142.87
140.45
133.21
129.42
129.20
119.86
119.80
119.74
118.32
118.27
118.21
115.32
112.92
110.52
77.48
77.16
76.84
56.89
50.04
43.90
30.44
CDCl3, 100 MHz
CF2H
Me
N
Me
Cl
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

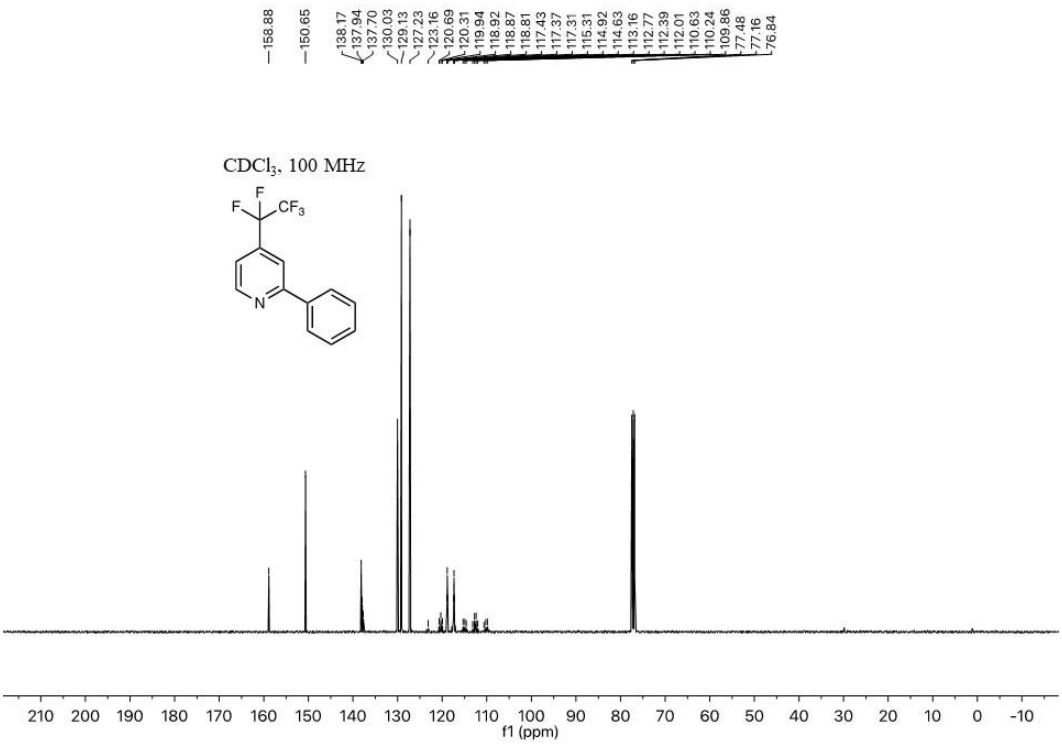

9.21
8.63
8.62
7.92
7.91
7.90
7.89
7.83
7.83
7.80
7.78
7.78
7.70
7.69
7.68
7.67
7.62
7.60
7.50
7.48
7.37
7.36
7.35
6.84
6.71
6.57
3.02
CDCl3, 400 MHz
CF2H
N
H
N
O
O
S
O
O
Me
Cl
Cl
1.00
1.00
1.03
0.96
1.98
1.03
1.00
1.03
1.00
1.03
3.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

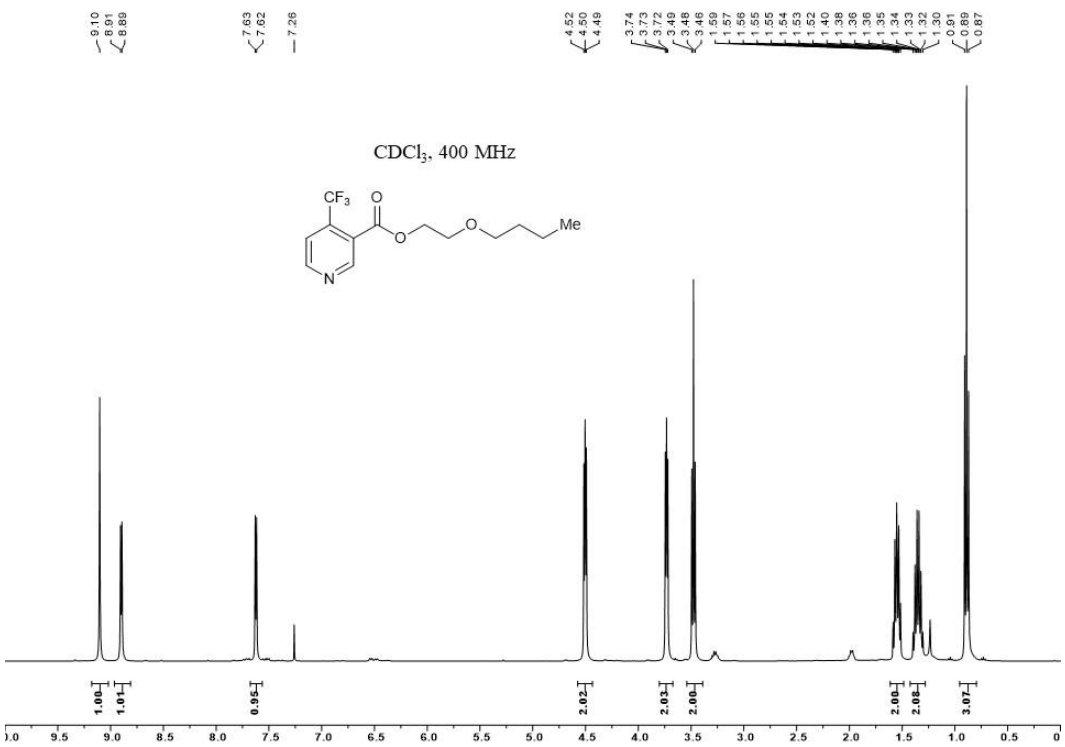

-116.08
-116.22
CDCl3, 376 MHz
CF2H
N
H
N
O
O
S
O
O
Me
Cl
Cl
0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2(
f1 (ppm)

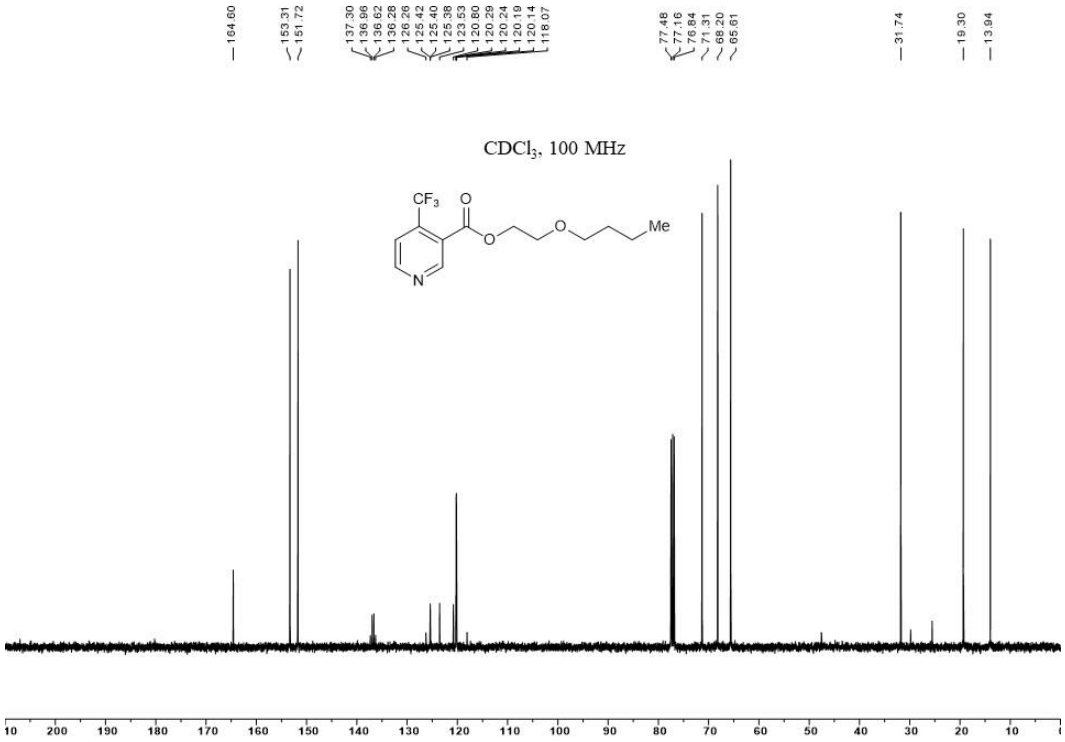

163.70
156.96
149.98
143.03
142.81
142.79
142.56
140.60
138.32
136.99
132.39
131.22
130.38
129.02
127.71
125.91
122.93
122.08
121.66
121.60
121.54
119.24
119.18
119.13
115.23
112.83
110.43
77.48
77.16
76.84
44.43
CDCl3, 100 MHz
CF2H
N
H
N
O
O
S
O
O
Me
Cl
Cl
f1 (ppm)

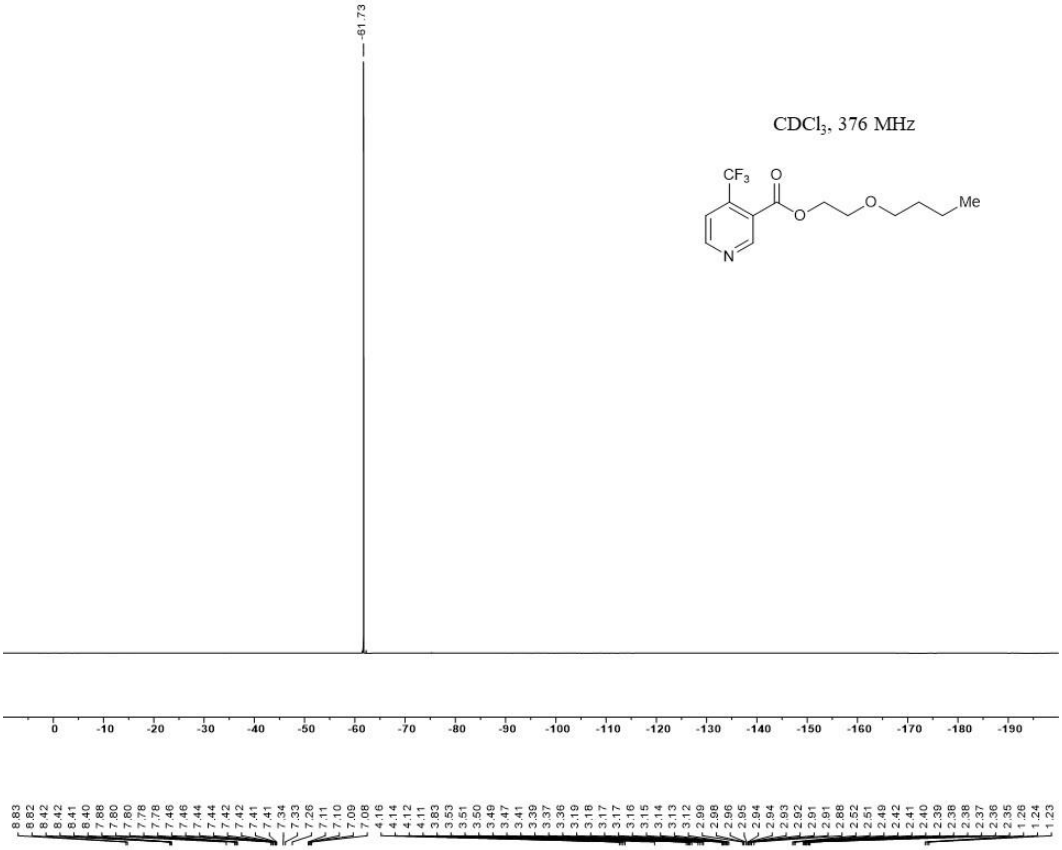

8.89
8.88
8.05
8.03
8.03
8.03
7.92
7.54
7.52
7.52
7.50
7.49
7.49
7.48
7.44
7.44
7.43
7.43
CDCl3, 400 MHz
F
F
CF3
N
1.00
2.03
1.00
2.97
0.98
f1 (ppm)

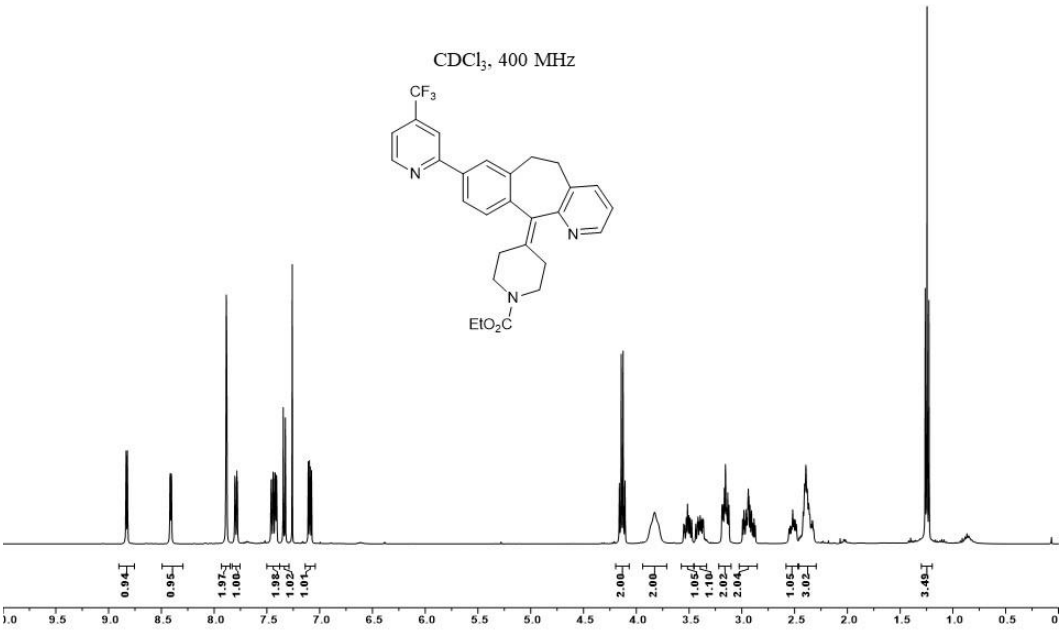

-84.47
-117.04
CDCl3, 376 MHz
F
F
CF3
N
0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -20
f1 (ppm)

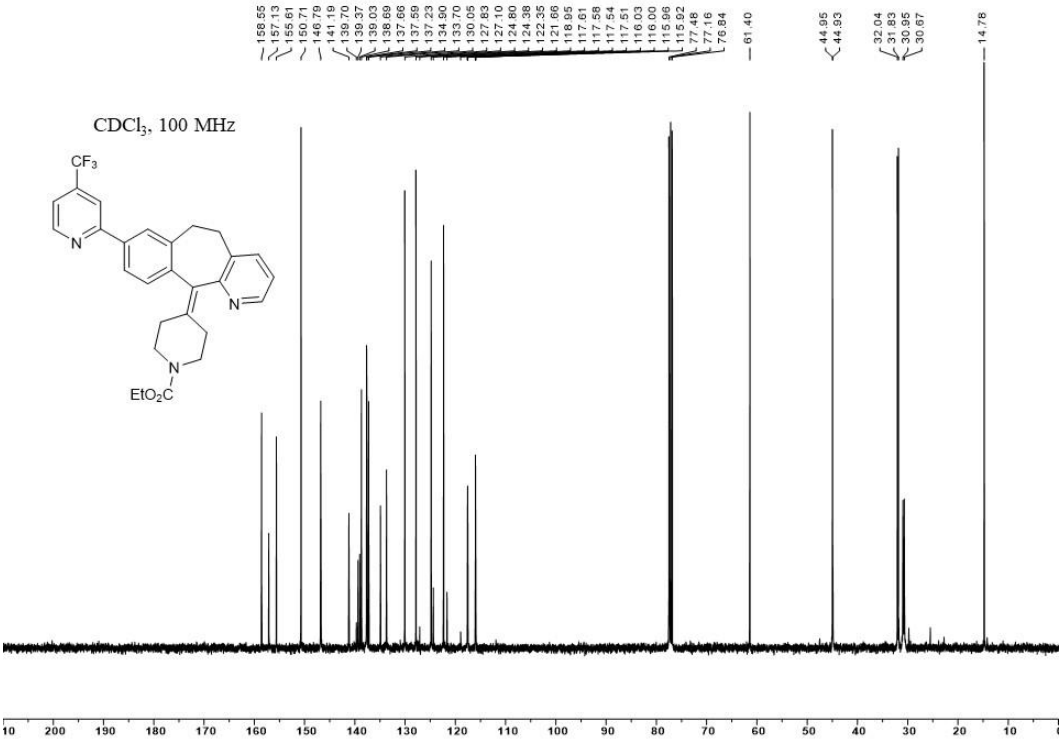

158.88
150.65
138.17
137.94
137.70
130.03
129.13
127.23
123.16
120.69
120.31
119.94
118.92
118.87
118.81
117.43
117.37
117.31
115.31
114.92
114.63
113.16
112.77
112.39
112.01
110.63
110.24
109.86
77.48
77.16
76.84
CDCl3, 100 MHz
F
F
CF3
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

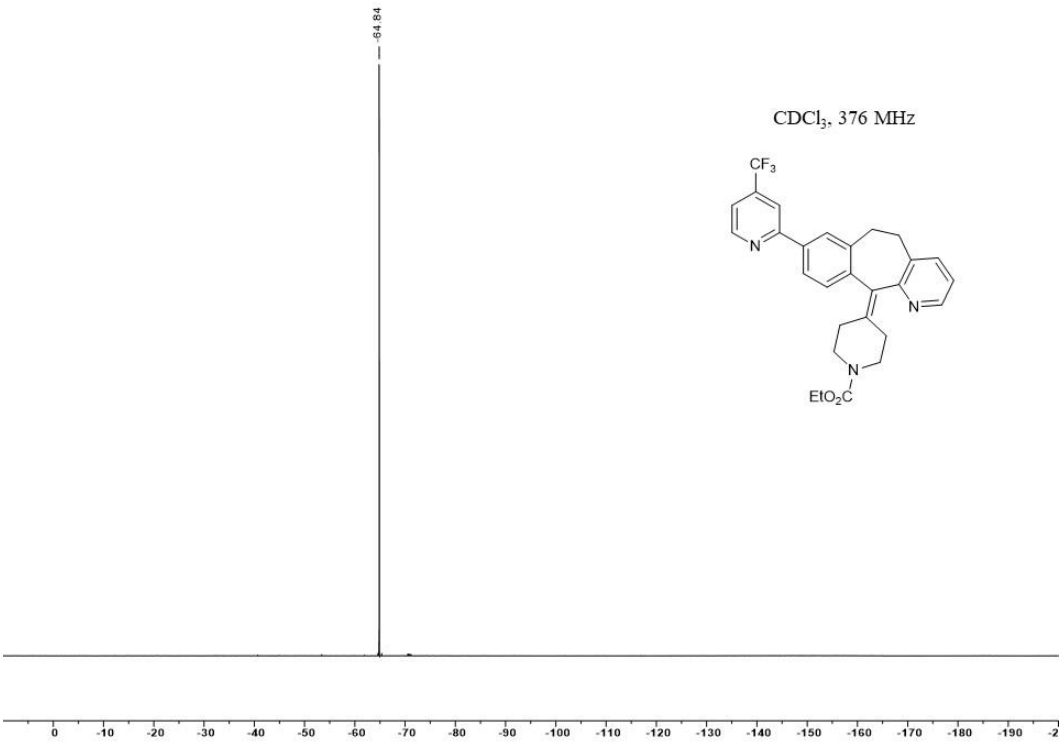

9.10
8.91
8.89
7.63
7.62
7.28
4.52
4.50
4.49
3.74
3.73
3.72
3.49
3.48
3.46
1.59
1.57
1.56
1.55
1.54
1.53
1.52
1.40
1.38
1.36
1.35
1.34
1.33
1.32
1.30
0.91
0.89
0.87
CDCl3, 400 MHz
CF3
O
O
O
Me
N
1.00
1.01
0.95
2.02
2.03
2.00
2.00
2.08
3.07

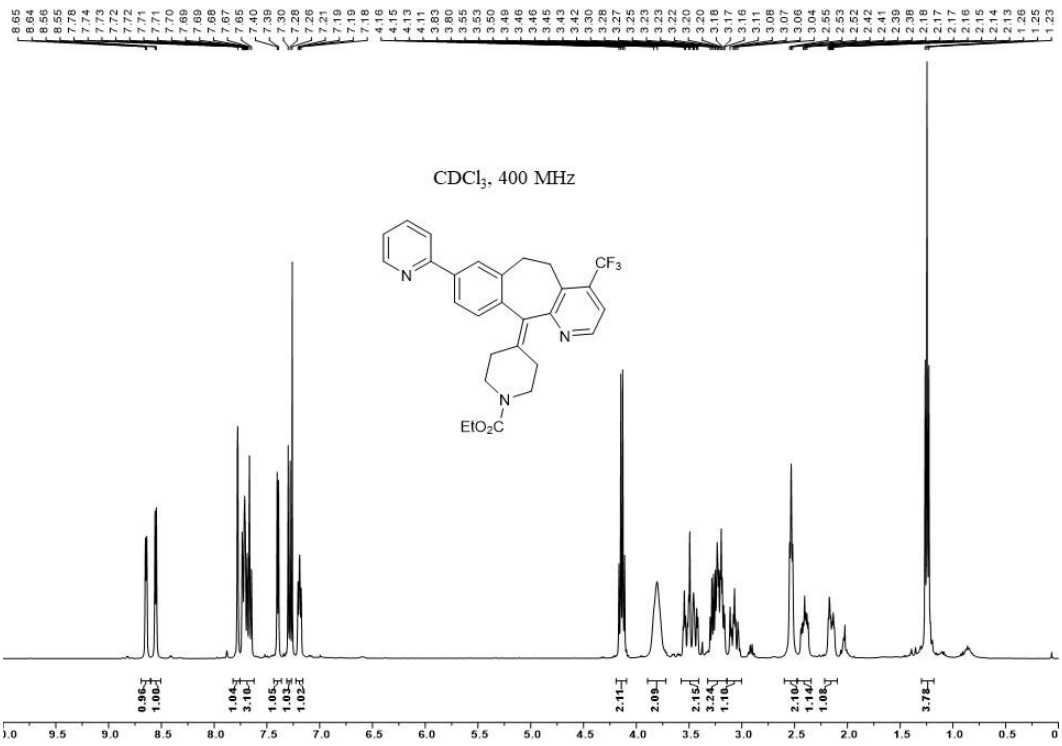

164.60
153.31
151.72
137.30
136.96
136.62
136.28
126.26
125.42
125.40
125.38
123.53
120.80
120.29
120.24
120.19
120.14
118.07
77.48
77.16
76.84
71.31
68.20
65.61
31.74
19.30
13.94
CDCl3, 100 MHz
CF3
O
O
O
Me
N

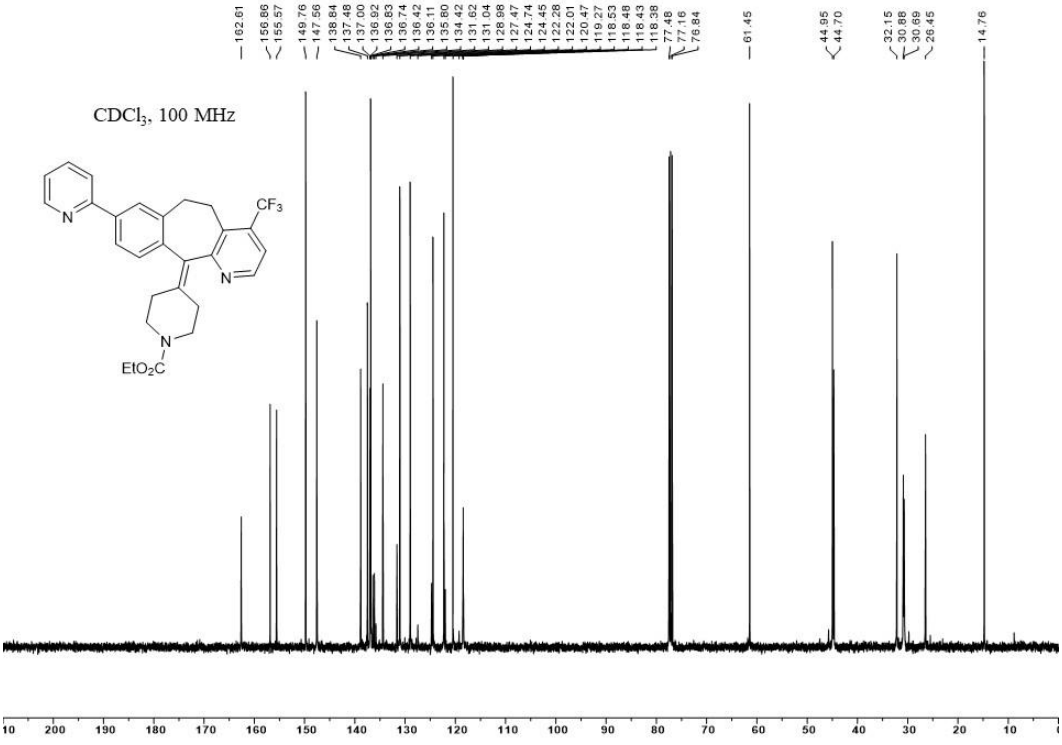

-61.73
CDCl3, 376 MHz
CF3
O
O
O
Me
N
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190

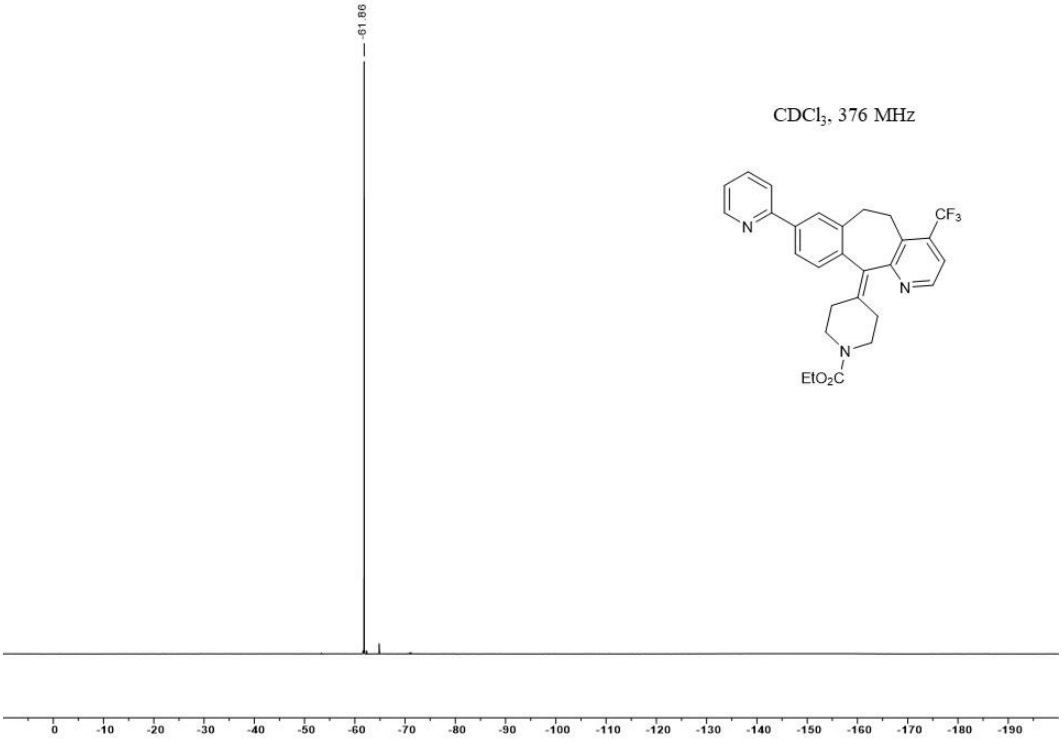

CDCl3, 400 MHz
CF3
N
N
N
EtO2C
0.94
0.95
1.97
1.08
1.98
1.02
1.01
2.00
2.00
1.05
1.16
2.02
2.04
1.05
3.02
3.48
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0


158.55
157.13
155.61
150.71
146.79
144.19
139.70
139.37
139.03
138.69
137.66
137.59
137.23
134.90
133.70
130.05
127.63
127.10
124.60
124.38
122.35
121.66
118.95
117.61
117.58
117.54
117.51
116.03
116.00
115.99
115.92
77.48
77.16
76.84
61.40
44.95
44.93
32.04
31.83
30.95
30.67
14.78
CDCl3, 100 MHz
CF3
N
N
N
EtO2C
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10


-64.84
CDCl3, 376 MHz
CF3
N
N
N
EtO2C
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2


CDCl3, 400 MHz
CF3
N
N
N
EtO2C


CDCl3, 100 MHz
CF3
N
N
N
EtO2C


-61.86
CDCl3, 376 MHz
CF3
N
N
N
EtO2C
0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
8.42
8.41
7.32
7.30
7.28
3.17
3.15
3.14
2.96
2.94
2.93
1.89
1.88
1.86
1.85
1.85
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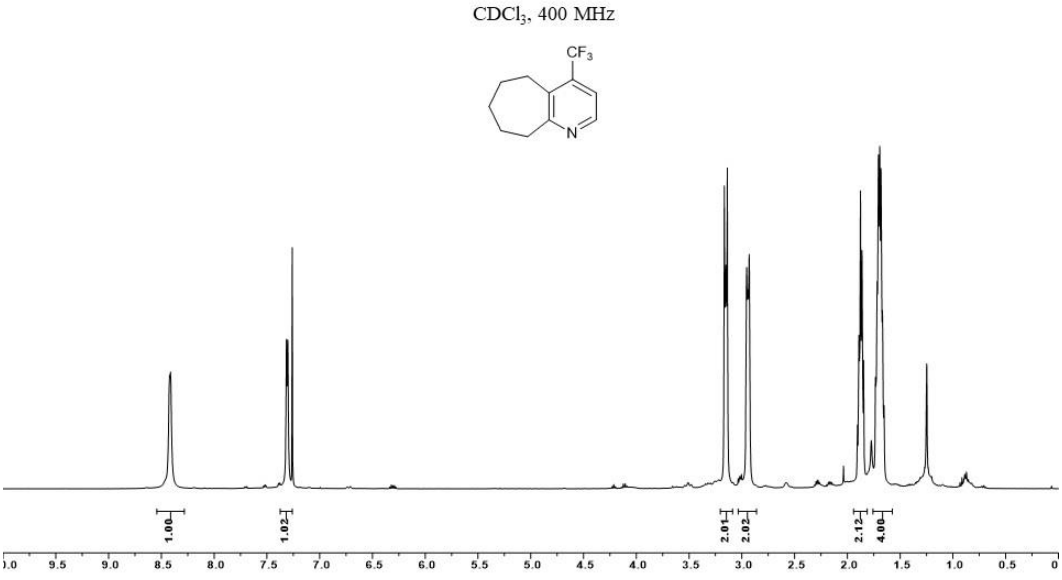
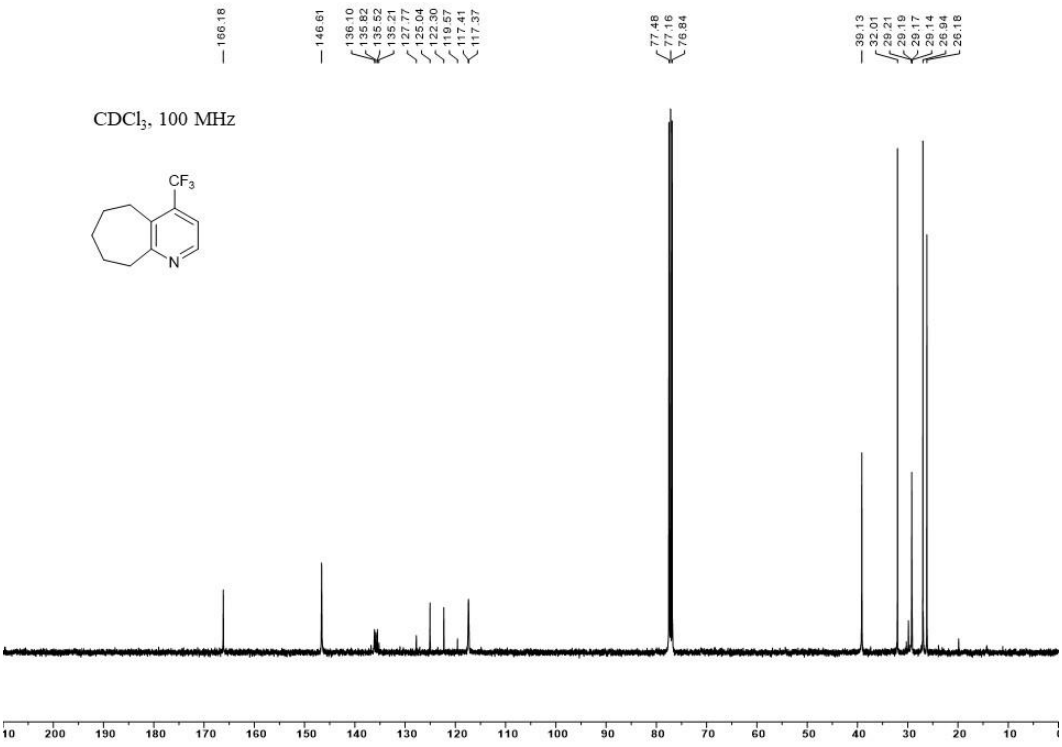
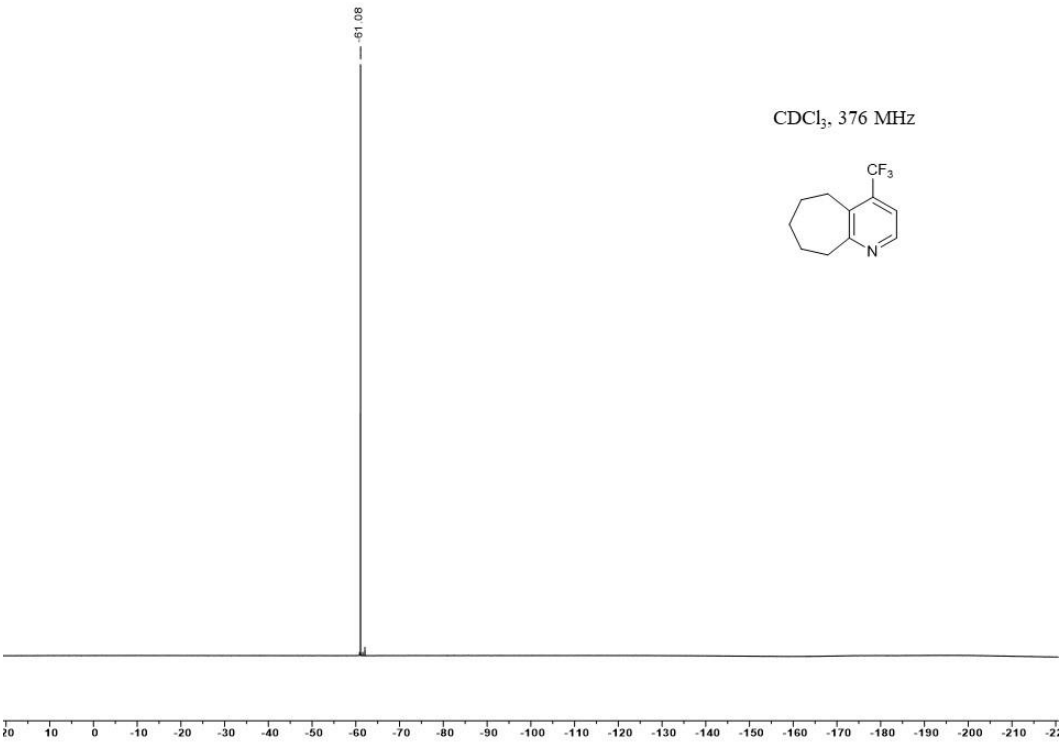
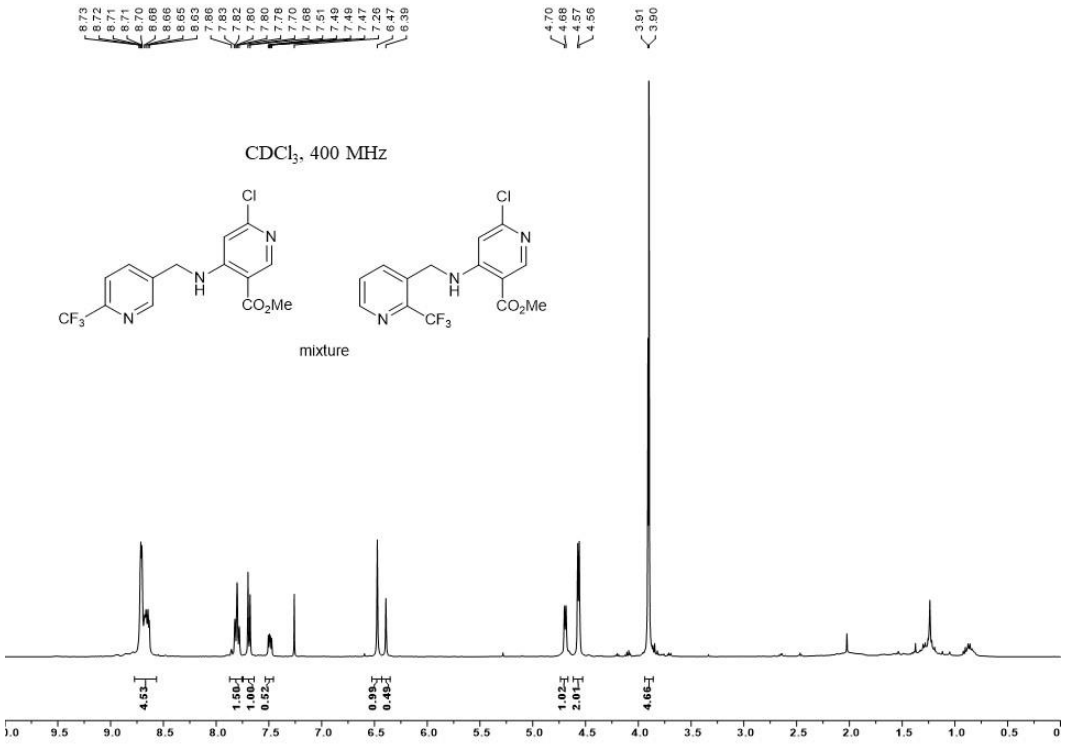
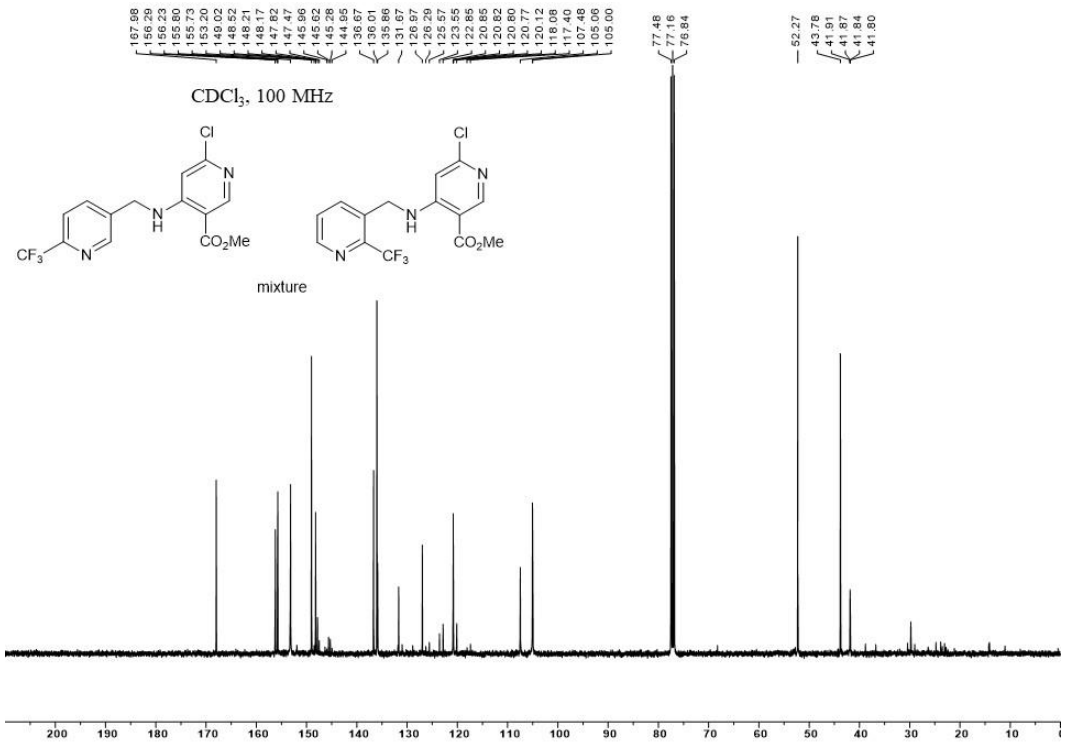
1.73
1.72
1.71
1.69
1.68
1.67
1.65


CDCl3, 400 MHz
CF3
N
1.00
1.02
2.01
2.02
2.12
4.00
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0


166.18
146.61
136.10
135.82
135.52
135.21
127.77
125.04
122.30
119.57
117.41
117.37
77.48
77.16
76.84
39.13
32.01
29.21
29.19
29.17
29.14
26.94
26.18
CDCl3, 100 MHz
CF3
N


-61.08
CDCl3, 376 MHz
CF3
N


8.73
8.72
8.71
8.71
8.70
8.68
8.66
8.65
8.63
7.86
7.83
7.82
7.80
7.80
7.78
7.70
7.68
7.51
7.49
7.49
7.47
7.26
6.47
6.39
4.70
4.68
4.57
4.56
3.91
3.90
CDCl3, 400 MHz
Cl
N
N
H
CO2Me
CF3
N
mixture
4.53
1.58
1.06
0.52
0.99
0.49
1.02
2.01
4.66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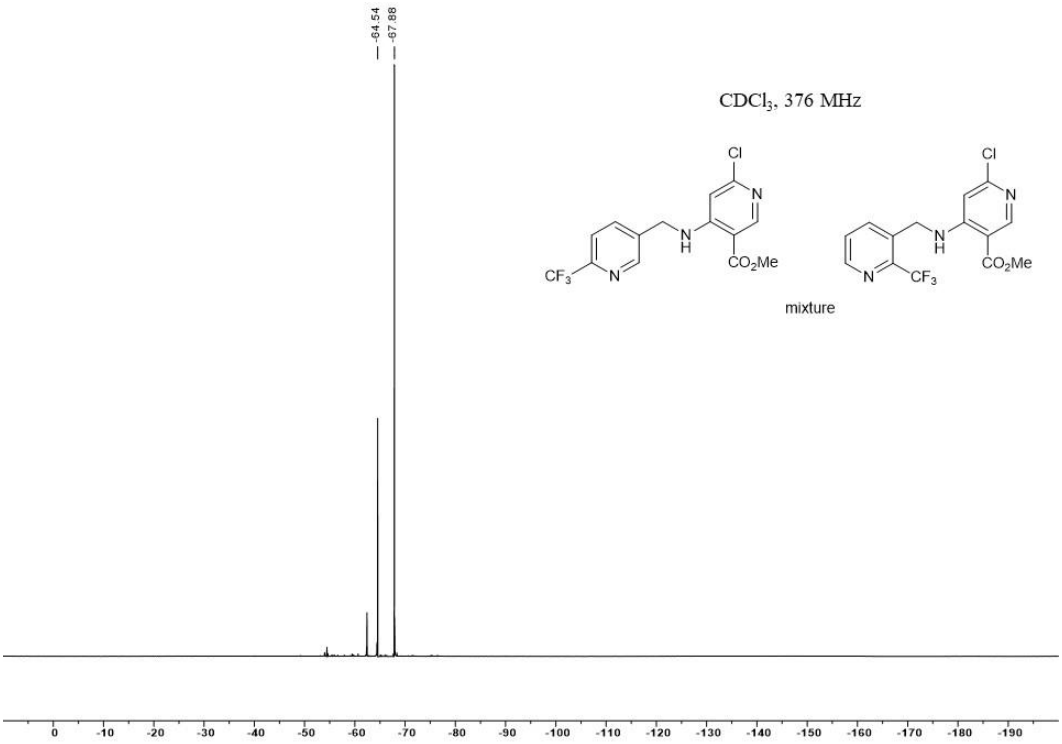
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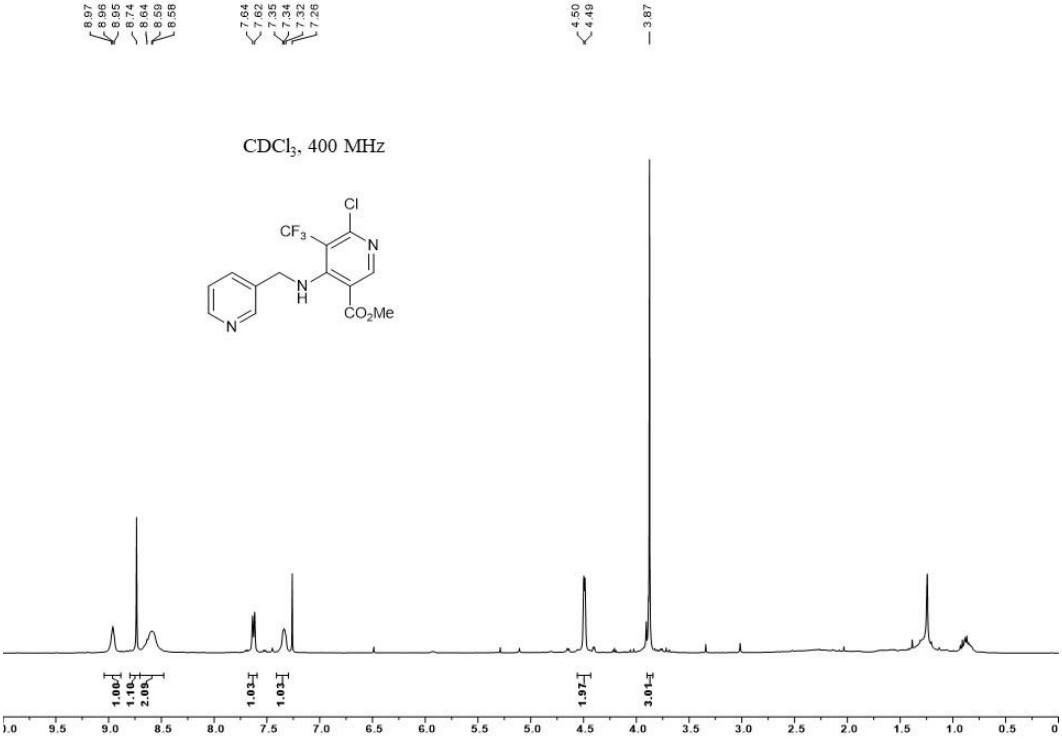
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3.01
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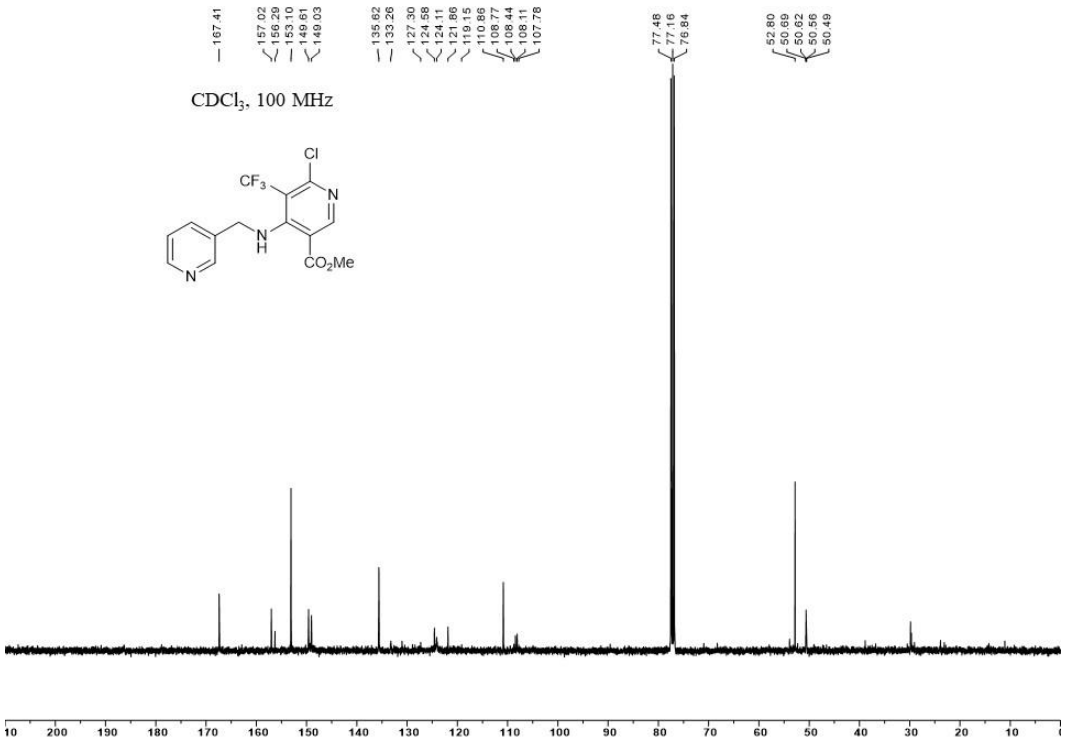
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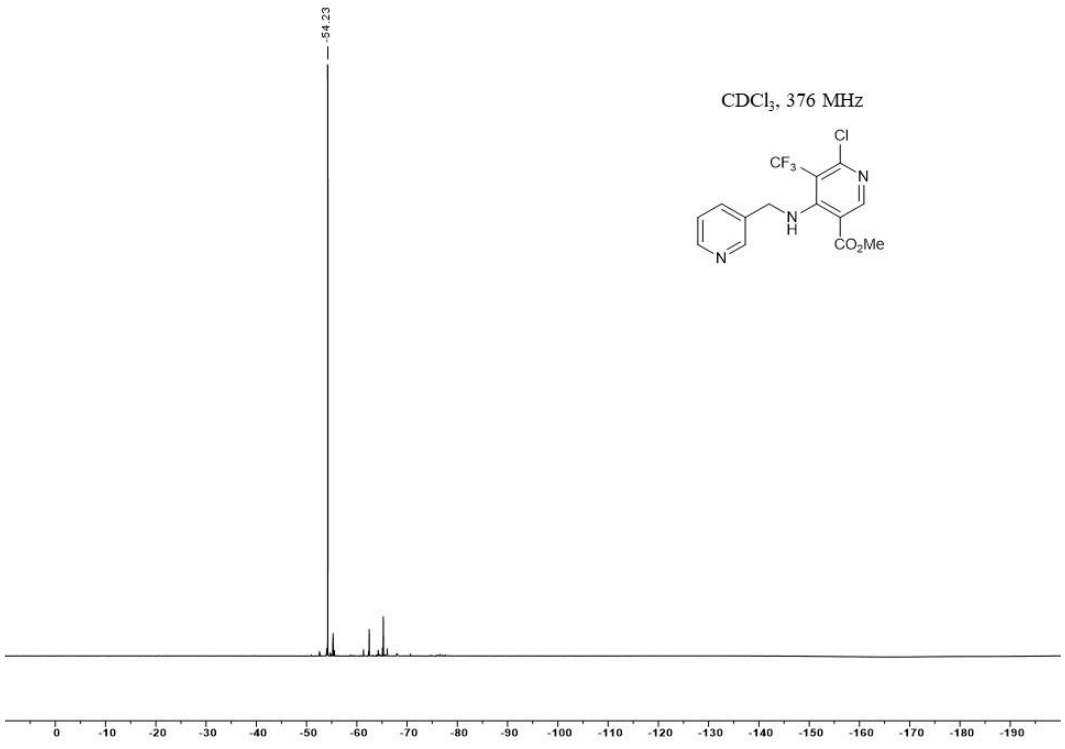
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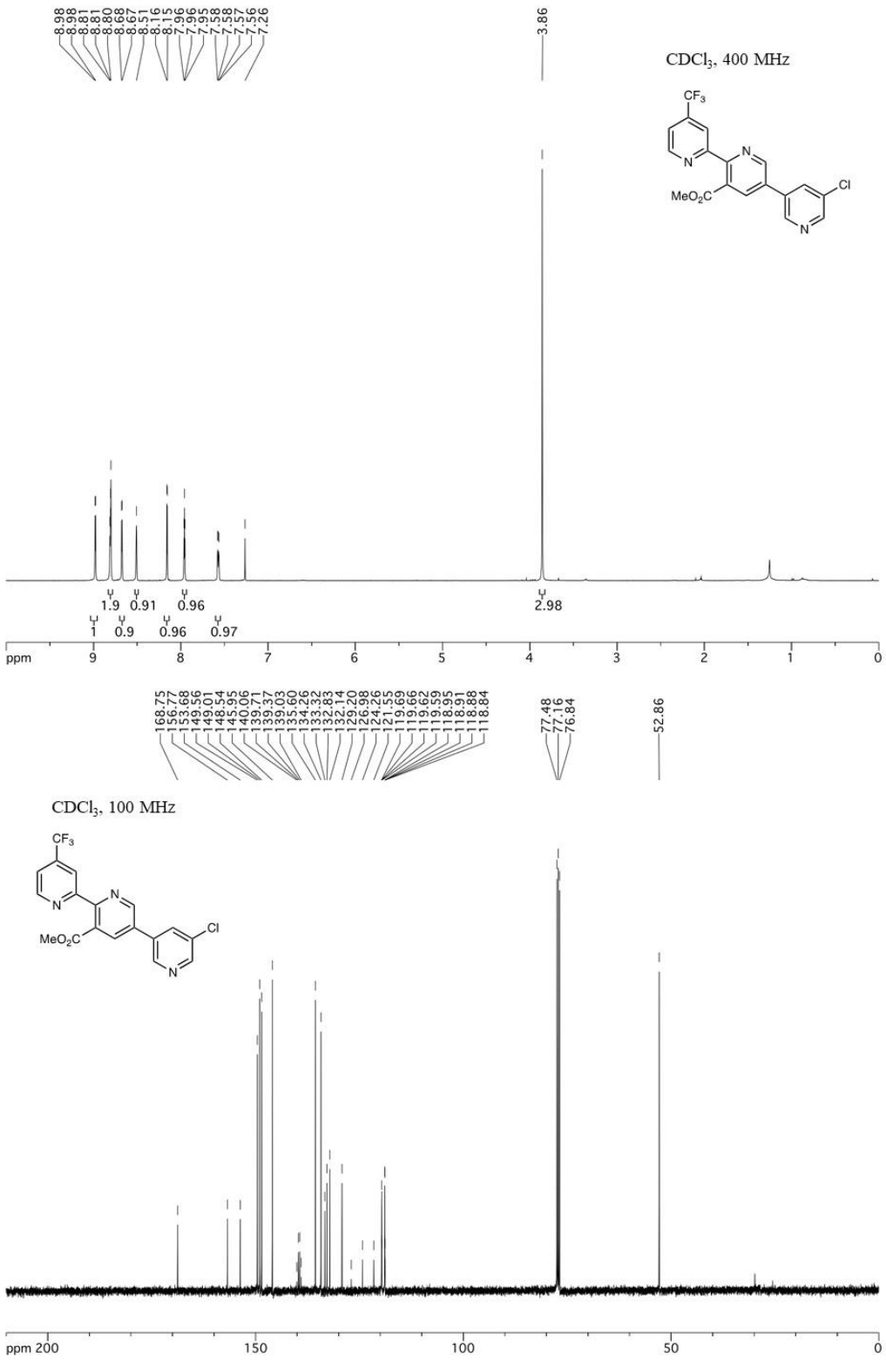
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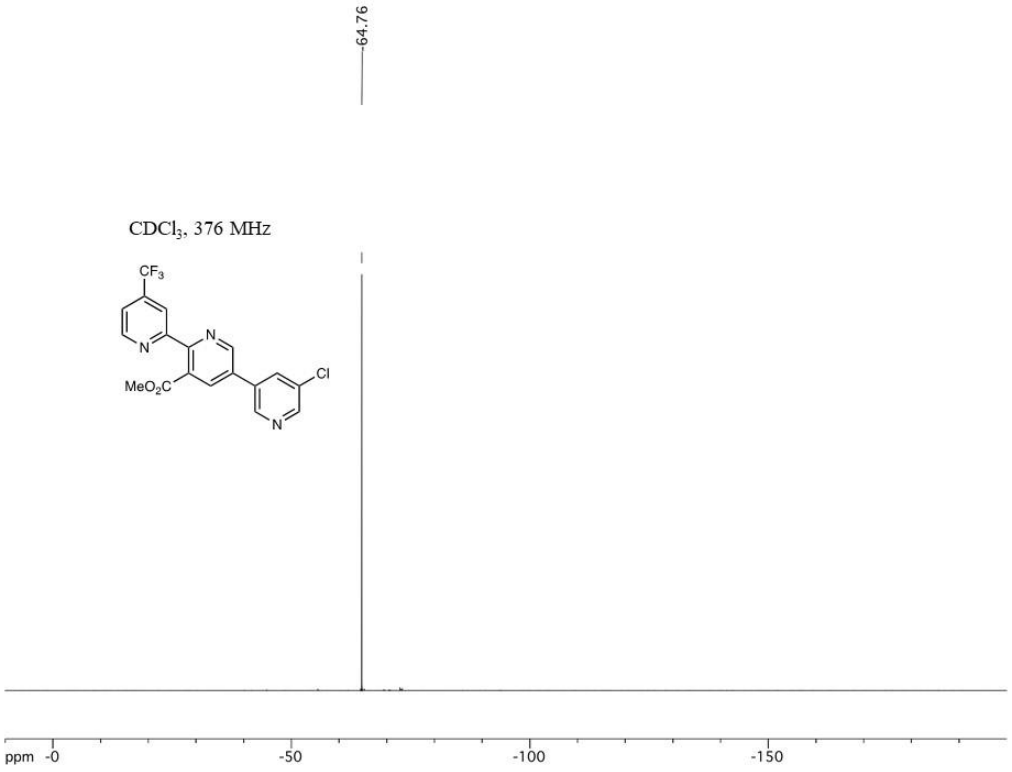
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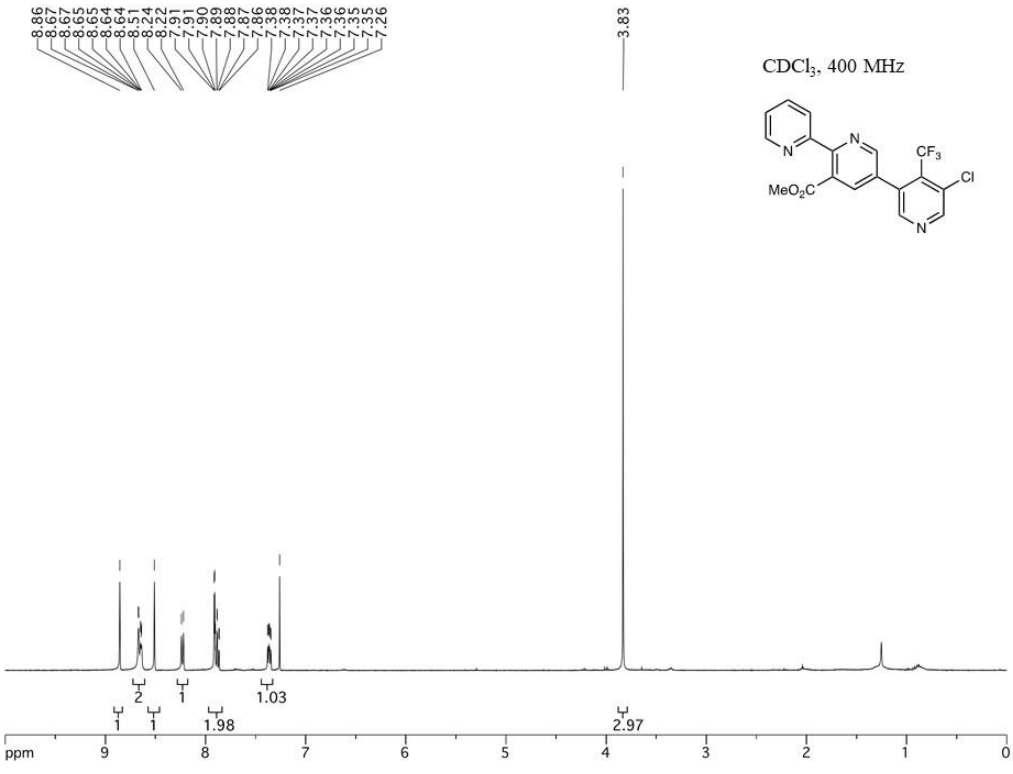
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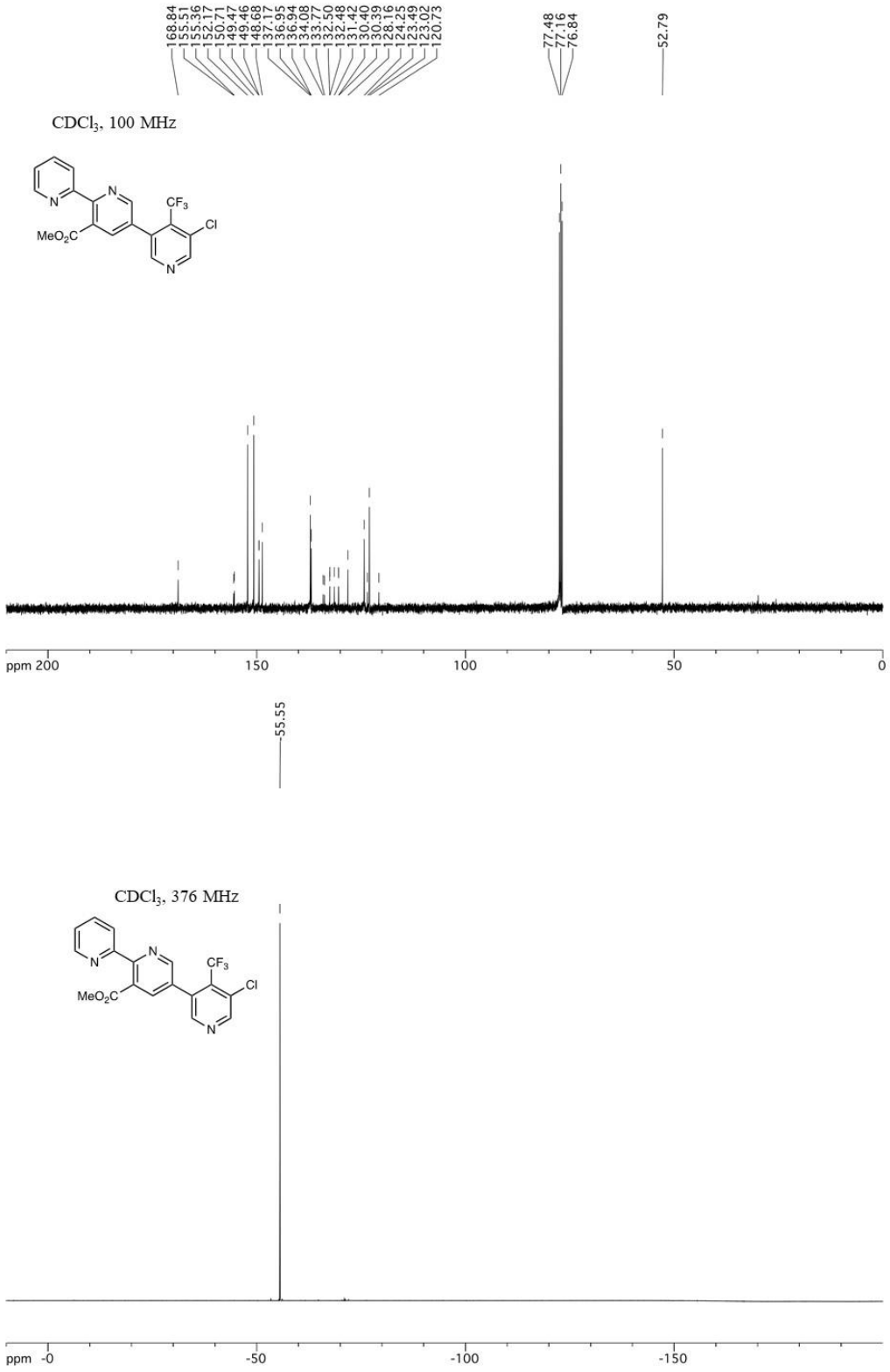
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123.49
123.02
120.73
77.48
77.16
76.84
52.79
CDCl3, 100 MHz
MeO2C
CF3
Cl
N
ppm 200
150
100
50
0
55.55
CDCl3, 376 MHz
MeO2C
CF3
Cl
N
ppm -0
-50
-100
-150

APPENDIX TWO

INVESTIGATION OF MIGRATION SELECTIVITY FROM P^V SPECIES FOR THE ALKENYLATION OF PYRIDINES: EXPERIMENTAL

A2.1 General Methods and Materials

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (400 MHz), an Agilent Inova 400 (400 MHz) spectrometer, an Agilent Inova 500 (500 MHz) spectrometer, or a Bruker AV-111 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.1 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm) or $(CD_3)_2SO$ (2.05 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (multiplicity, coupling constants, number of protons). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (100 MHz), an Agilent Inova 400 (100 MHz) spectrometer, an Agilent Inova 500 spectrometer (125 MHz) or a Bruker AV-111 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.01 ppm relative to the residual solvent peaks in $CDCl_3$ (77.16 ppm), $(CD_3)_2SO$ (39.51 ppm), CD_3OD (49.00 ppm) or CD_3CN (1.32 ppm).

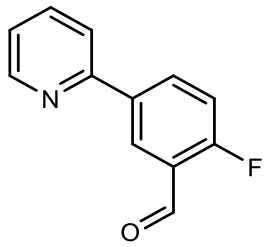
Low-resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. High-resolution mass spectra (HRMS) were measured on an Agilent 6224 TOF

LC/MS ("OTOF") interfaced to an Agilent 1200 HPLC with multi-mode (combined ESI and APCI) and Direct Analysis in Real Time (DART) sources. (IR) spectra were recorded on a Nicolet IS-50 FT-IR spectrometer as either solids or neat films, either through direct application or deposited in CHCl3, with absorptions reported in wavenumbers (cm-1). Analytical thin layer chromatography (TLC) was performed using pre-coated Silicycle glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Silicycle silica gel Siliaflash P60 40-63 um (230-400 mesh) under a positive pressure of air unless otherwise stated. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or basic potassium permanganate solutions as appropriate. Melting points (mp) were recorded using a Büchi B-450 melting point apparatus and are reported uncorrected.

Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] Methanol, 1,2-dichloroethane (DCE), 1,4-dioxane, ethyl acetate, chloroform, and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest commercial quality and used without further purification. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated. All reactions were monitored by TLC, ^{1}H NMR spectra taken from reaction samples, and liquid chromatography mass spectrometry (LCMS) using an Agilent 6310 Quadrupole Mass Spectrometer for MS analysis. Tf_2O (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. 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.

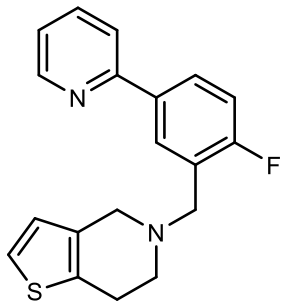
A2.2 Preparation of Heterocyclic Precursors

2-fluoro-5-(pyridin-2-yl)benzaldehyde



An oven dried 100 mL pressure tube was charged with 2-bromopyridine (477 μL, 5.00 mmol), (4-fluoro-3-formylphenyl)boronic acid (1.01 g, 6.00 mmol), K_2CO_3 (2.07 g, 15.00 mmol), $Pd(OAc)_2$ (56 mg, 0.25 mmol), triphenylphosphine (262 mg, 1.00 mmol) and subjected to three cycles of vacuum/nitrogen backfill. Degassed H_2O (20 mL) and dimethoxyethane (20 mL) were charged to the tube. The mixture was heated at 85 ºC for 18 hours then diluted with CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted 2x with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a white solid (933 mg, 4.65 mmol, 93% yield). mp 65-67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.37 (s, 1H), 8.64 (d, *J* = 4.8 Hz, 1H), 8.39 (dd, *J* = 6.6, 2.6 Hz, 1H), 8.30 (ddd, *J* = 8.5, 5.1, 2.5 Hz, 1H), 7.77 – 7.64 (m, 2H), 7.25 – 7.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 187.13 (d, J = 6.1 Hz), 165.18 (d, J = 260.9 Hz), 155.13, 149.91, 137.18, 136.31 (d, J = 3.5 Hz), 135.01 (d, J = 9.4 Hz), 127.10 (d, J = 2.3 Hz), 124.23 (d, J = 8.6 Hz), 122.83, 120.43, 117.17 (d, J = 21.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -122.02. IR υ_{max}/cm^{-1} (film): 3054, 2861, 2769, 1685, 1607, 1587, 1568, 1500, 1465, 1439, 1395, 1309, 1262, 1208, 1184, 1153, 1114, 1058, 1036, 992, 908, 848, 809, 796, 780, 746, 716. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{12}H_9FNO^+$ = 202.1, found 202.1.

5-(2-fluoro-5-(pyridin-2-yl)benzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

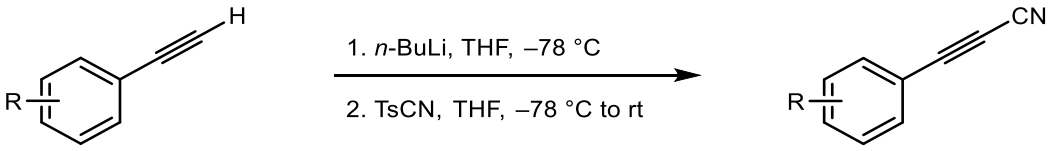


An oven-dried 200 mL round bottom flask was charged with 2-fluoro-5-(pyridin-2-yl)benzaldehyde (0.80 g, 4.00 mmol), 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (0.613 g, 4.40 mmol), and sodium triacetoxyhydroborate (1.70 g, 8.00 mmol). The flask was subjected to three cycles of vacuum/nitrogen backfill. DCM (20 mL) was added to the reaction flask along with glacial AcOH (0.46 mL). After 22 hours at room temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl (30 mL), diluted with CH_2Cl_2, and the organic layer was separated. The aqueous layer was basified with a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a pale-yellow oil (1.05 g, 3.24 mmol, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.67 (dt, J = 4.8, 1.5 Hz, 1H), 8.09 (dd, J = 7.1, 2.4 Hz, 1H), 7.92 (ddd, J = 8.7, 5.0, 2.4 Hz, 1H), 7.79 – 7.63 (m, 2H), 7.22 (ddd, J = 6.7, 4.8, 1.6 Hz, 1H), 7.16 (dd, J = 9.5, 8.6 Hz, 1H), 7.06 (d, J = 5.1 Hz, 1H), 6.71 (d, J = 5.1 Hz, 1H), 3.86 (s, 2H), 3.65 (s, 2H), 2.89 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.26 (d, J = 248.9 Hz), 156.63, 149.77, 136.90, 135.66 (d, J = 3.5 Hz), 133.92, 133.48, 130.25 (d, J = 4.8 Hz), 127.73 (d, J = 8.7 Hz), 125.42 (d, J = 14.8 Hz), 125.39, 122.76, 122.16, 120.52, 115.85 (d, J = 22.8 Hz), 54.71 (d, J = 1.7

Hz), 53.03, 50.64, 25.63. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -117.79. IR υ_{max}/cm^{-1} (film): 2920, 2775, 1587, 1566, 1501, 1464, 1433, 1403, 1356, 1304, 1263, 1228, 1169, 1153, 1113, 1098, 1079, 1053, 1015, 991, 957, 895, 832, 779, 774, 701, 666. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{19}H_{18}FN_2S^+$ = 325.1, found 325.2.

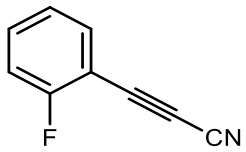
A2.3 Preparation of Cyanoalkynes

General Procedure A



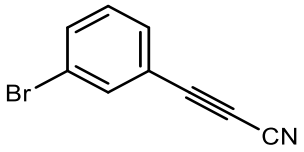
An oven dried round bottom flask equipped with a stir bar was charged with the alkyne (1.0 equiv) and placed under a nitrogen atmosphere. THF (0.15 M) was added, the reaction vessel was cooled to –78 ºC and *n*-BuLi (1.1 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes before a solution of tosyl cyanide (1.2 equiv) in THF (0.3 M) was added dropwise, and the resulting mixture was allowed to stir for 30 minutes at –78 ºC. The cooling bath was removed, and the reaction was allowed to warm to room temperature while stirring for approximately 2 hours. The reaction was treated with a saturated solution of aqueous ammonium chloride and extracted with Et_2O (3x). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the cyanoalkyne product.

3-(2-Fluorophenyl)propiolonitrile



Prepared according to general procedure A, using 1-ethynyl-2-fluorobenzene (567 μL, 5.00 mmol), THF (30 mL), *n*-BuLi (1.6 M in hexanes, 3.40 mL, 5.50 mmol), TsCN (1.10 g, 6.00 mmol), THF (20 mL). The crude material was purified by flash chromatography (silica gel: 5% Et_2O in hexanes) to provide the title compound as a white solid (406 mg, 3.65 mmol, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 – 7.47 (m, 2H), 7.24 – 7.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.75 (d, *J* = 257.6 Hz), 135.08, 134.13 (d, *J* = 8.3 Hz), 124.74 (d, *J* = 3.7 Hz), 116.32 (d, *J* = 19.9 Hz), 106.79 (d, *J* = 15.0 Hz), 105.27, 67.59 (d, *J* = 3.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -106.04

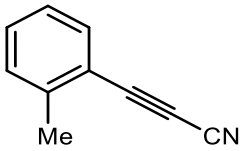
3-(3-Bromophenyl)propiolonitrile



An oven dried pressure tube equipped with a stir bar was charged with 1-bromo-3-ethynylbenzene (362 μL, 3.00 mmol) and placed under a nitrogen atmosphere. THF (30 mL) was added, followed by copper (II) perchlorate hexahydrate (4.45 g, 12.0 mmol), 1-methylimidazole (240 μL, 3.00 mmol), sodium cyanide (1.18 g, 24.0 mmol), and diisopropylethyl-amine (1.05 mL, 6.00 mmol) sequentially. The vessel was sealed and heated to 40 °C for 24 h. After cooling to rt, the reaction was diluted with Et_2O and washed with 30% aqueous ammonia solution followed by saturated brine (2x). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude

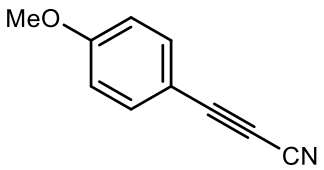
material was purified by flash chromatography (silica gel: 10% Et_2O in hexanes) to provide the title compound as a white solid (177 mg, 0.87 mmol, 29% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.76 (t, *J* = 1.8 Hz, 1H), 7.67 (ddd, *J* = 8.1, 2.0, 1.1 Hz, 1H), 7.55 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.06, 135.29, 132.12, 130.45, 122.74, 119.62, 105.21, 81.10, 64.15.

3-(o-Tolyl)propiolonitrile



Prepared according to general procedure A, using 1-ethynyl-2-methylbenzene 630 μL, 5.00 mmol), THF (30 mL), *n*-BuLi (1.6 M in hexanes, 3.40 mL, 5.5 mmol), TsCN (1.10 g, 6.00 mmol), THF (20 mL). The crude material was purified by flash chromatography (silica gel: 1% Et_2O in hexanes) to provide the title compound as a colorless oil (278 mg, 1.95 mmol, 39% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.57 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.41 (td, *J* = 7.6, 1.4 Hz, 1H), 7.31 – 7.15 (m, 2H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.53, 134.14, 131.92, 130.20, 126.21, 117.53, 105.68, 82.44, 66.51, 20.61.

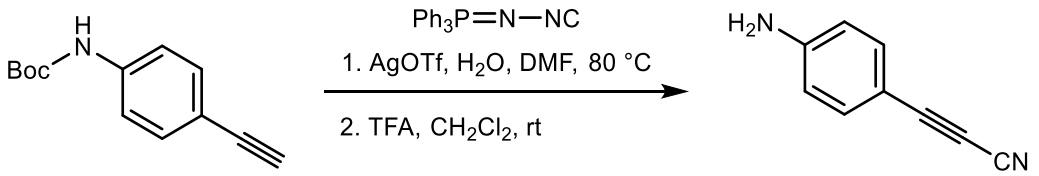
3-(4-Methoxyphenyl)propiolonitrile



Prepared according to general procedure A, using 1-ethynyl-4-methoxybenzene (660 mg, 5.00 mmol), THF (30 mL), *n*-BuLi (1.6 M in hexanes, 3.40 mL, 5.5 mmol), TsCN (1.10 g, 6.00 mmol),

THF (20 mL). The crude material was purified by flash chromatography (silica gel: 10% Et_2O in hexanes) to provide the title compound as a white solid (406 mg, 2.60 mmol, 52% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.61 – 7.50 (m, 2H), 6.96 – 6.84 (m, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.45, 135.49, 114.71, 109.06, 105.92, 83.83, 62.45, 55.58.

3-(4-Aminophenyl)propiolonitrile

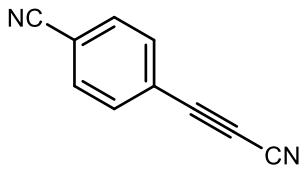


An oven dried pressure tube equipped with a stir bar was charged with tert-butyl (4-(ethynyl)phenyl)carbamate (652 mg, 3.00 mmol), *N*-isocyanoiminotriphenylphosphorane (1.80 g, 6.00 mmol), AgOTf (771 mg, 3.00 mmol), and placed under a nitrogen atmosphere. DMF (15 mL) and H_2O (550 µL, 30 mmol) were added and the reaction was heated to 80 °C. After 22 h, the reaction mixture was treated with water, the organic layer separated, and the aqueous layer extracted with ethyl acetate (3x). The combined organic extracts were washed with water, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 10% EtOAc, 0.25% NEt_3 in hexanes) to provide tert-butyl (4-(cyanoethynyl)phenyl)carbamate as a white solid (330 mg, 1.35 mmol, 45% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.61 – 7.48 (m, 2H), 7.48 – 7.34 (m, 2H), 6.65 (s, 1H), 1.52 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.10, 141.97, 134.86, 118.12, 111.11, 105.92, 83.61, 81.75, 62.81, 28.36.

An oven-dried round bottom flask equipped with a stir bar was charged with tert-butyl (4-(cyanoethynyl)phenyl)carbamate (242 mg, 1.00 mmol) and placed under a nitrogen atmosphere.

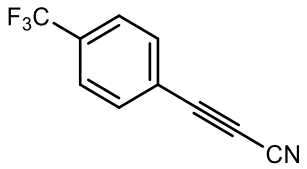
DCM (5 mL) was added followed by TFA (1.5 mL) and the reaction was stirred at room temperature. After 3 h, the solvent was removed *in vacuo* and the resulting residue was dissolved in EtOAc and quenched with sat. aq. Na_2CO_3 solution. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3x). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the pure title compound as a white solid (78 mg, 0.55 mmol, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46 – 7.35 (m, 2H), 6.66 – 6.53 (m, 2H), 4.12 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.79, 135.45, 113.78, 106.31, 105.62, 85.21, 62.05.

4-(Cyanoethynyl)benzonitrile



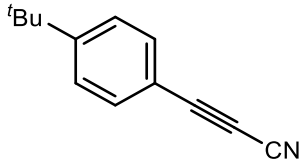
An oven dried pressure tube equipped with a stir bar was charged with 4-ethynylbenzonitrile (381 mg, 3.00 mmol) and placed under a nitrogen atmosphere. THF (30 mL) was added, followed by copper (II) perchlorate hexahydrate (4.45 g, 12.0 mmol), sodium cyanide (1.18 g, 24.0 mmol), and diisopropylethyl-amine (1.05 mL, 6.00 mmol) sequentially. The vessel was sealed and heated to 40 °C for 22 h. After cooling to rt, the reaction was diluted with Et_2O and washed with 30% aqueous ammonia solution followed by saturated brine (2x). The organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (silica gel: 20% Et_2O in hexanes) to provide the title compound as a tan solid (198 mg, 1.29 mmol, 43% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.72 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.94, 132.46, 122.21, 117.39, 115.38, 104.77, 80.24, 66.16.

3-(4-(Trifluoromethyl)phenyl)propiolonitrile



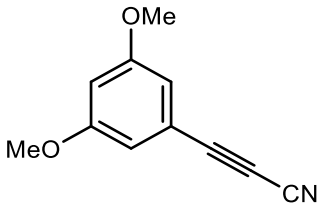
Prepared according to general procedure A, using 1-ethynyl-4-(trifluoromethyl)benzene (816 μL, 5.00 mmol), THF (30 mL), *n*-BuLi (1.6 M in hexanes, 3.40 mL, 5.5 mmol), TsCN (1.10 g, 6.00 mmol), THF (20 mL). The crude material was purified by flash chromatography (silica gel: 2.5% Et_2O in hexanes) to provide the title compound as a white solid (634 mg, 3.25 mmol, 65% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.79 – 7.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.96, 133.51 (q, J = 33.2 Hz), 125.95 (q, J = 4.0 Hz), 123.38 (q, J = 272.8 Hz), 121.47 (d, J = 1.8 Hz), 105.06, 80.99, 64.88. ^{19}F NMR (376 MHz, $CDCl_3$) δ: -63.42.

3-(4-(tert-Butyl)phenyl)propiolonitrile



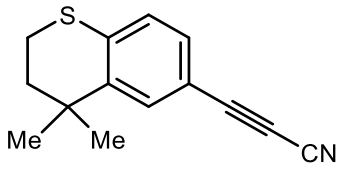
Prepared according to general procedure A, using 1-(tert-butyl)-4-ethynylbenzene (541 μL, 3.00 mmol), THF (20 mL), *n*-BuLi (1.6 M in hexanes, 2.06 mL, 3.3 mmol), TsCN (652 mg, 3.6 mmol), THF (12 mL). The crude material was purified by flash chromatography (silica gel: 1% Et_2O in hexanes) to provide the title compound as a white solid (316 mg, 2.00 mmol, 67% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.58 – 7.50 (m, 2H), 7.47 – 7.38 (m, 2H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.94, 133.49, 126.08, 114.48, 105.79, 83.61, 62.81, 35.35, 31.06.

3-(3,5-Dimethoxyphenyl)propiolonitrile



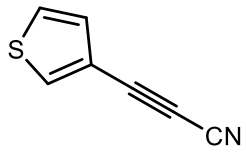
Prepared according to general procedure A, using 1-ethynyl-3,5-dimethoxybenzene (487 mg, 3.00 mmol), THF (20 mL), *n*-BuLi (1.6 M in hexanes, 2.06 mL, 3.3 mmol), TsCN (652 mg, 3.6 mmol), THF (12 mL). The crude material was purified by flash chromatography (silica gel: 5% Et_2O in hexanes) to provide the title compound as a white solid (377 mg, 2.00 mmol, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.73 (d, *J* = 2.4 Hz, 2H), 6.61 (t, *J* = 2.3 Hz, 1H), 3.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.87, 118.70, 111.17, 105.52, 105.43, 83.10, 62.51, 55.69.

3-(4,4-Dimethylthiochroman-6-yl)propiolonitrile



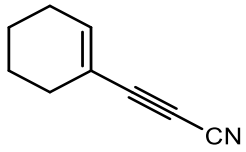
Prepared according to general procedure A, using 6-ethynyl-4,4-dimethylthiochromane (607 mg, 3.00 mmol), THF (20 mL), *n*-BuLi (1.6 M in hexanes, 2.06 mL, 3.3 mmol), TsCN (652 mg, 3.6 mmol), THF (12 mL). The crude material was purified by flash chromatography (silica gel: 4% Et_2O in hexanes) to provide the title compound as a white solid (521 mg, 2.28 mmol, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, *J* = 1.9 Hz, 1H), 7.23 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 3.10 – 3.01 (m, 2H), 1.98 – 1.87 (m, 2H), 1.32 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.71, 138.97, 131.43, 130.37, 126.98, 112.22, 105.90, 84.13, 62.84, 36.55, 33.03, 29.72, 23.39.

3-(Thiophen-3-yl)propiolonitrile



Prepared according to general procedure A, using 3-ethynylthiophene (296 μL, 3.00 mmol), THF (20 mL), *n*-BuLi (1.6 M in hexanes, 2.06 mL, 3.3 mmol), TsCN (652 mg, 3.6 mmol), THF (12 mL). The crude material was purified by flash chromatography (silica gel: 4% Et_2O in hexanes) to provide the title compound as a white solid (289 mg, 2.16 mmol, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.87 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.37 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.25 (dd, *J* = 5.1, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.21, 130.19, 126.86, 116.81, 105.65, 78.54, 63.22.

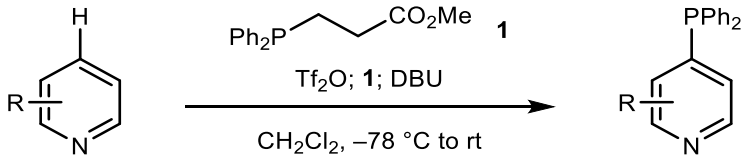
3-(Cyclohex-1-en-1-yl)propiolonitrile



Prepared according to general procedure A, using 1-ethynylcyclohex-1-ene (588 μL, 5.00 mmol), THF (30 mL), *n*-BuLi (1.6 M in hexanes, 3.40 mL, 5.5 mmol), TsCN (1.10 g, 6.00 mmol), THF (20 mL). The crude material was purified by flash chromatography (silica gel: 4% Et_2O in hexanes) to provide the title compound as a yellow oil (506 mg, 3.85 mmol, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.61 (tt, *J* = 3.9, 1.6 Hz, 1H), 2.30 – 2.02 (m, 4H), 1.77 – 1.57 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.07, 117.19, 105.82, 85.07, 60.98, 27.50, 26.21, 21.66, 20.87.

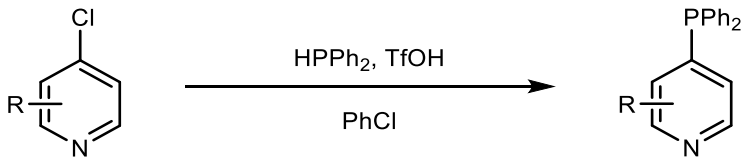
A2.4 Preparation of Heteroaryl Phosphines

General Procedure B



An oven dried 100 mL round bottom flask 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 was cooled to –78 ºC 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 ºC and methyl 3-(diphenylphosphaneyl)propanoate (1.1 equiv) was added 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 ºC. The reaction was cooled to –78 ºC 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 H_2O and then extracted with CH_2Cl_2 (3x). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography under the stated conditions to provide the heteroaryl phosphine product.

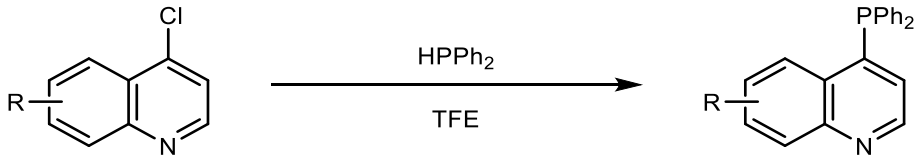
General Procedure C



An 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,

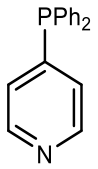
followed by diphenylphosphine (1.2 equiv), and trifluoromethanesulfonic acid (1.0 equiv). The reaction was heated to 130 °C and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of Na_2CO_3 and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined 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.

General Procedure D



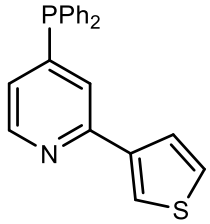
A 15 mL pressure tube equipped with a stir bar was charged with the heterocycle (1.0 equiv). The vial was subjected to three rapid cycles of vacuum/nitrogen backfill, and TFE (0.4 M) was added, followed by diphenylphosphine (1.2 equiv). The reaction was heated to 80 °C and allowed to stir for the stated time. The reaction was quenched with a saturated aqueous solution of 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.

4-(Diphenylphosphaneyl)pyridine



Prepared according to general procedure C except that no TfOH was added, using 4-chloropyridine hydrochloride, (302 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and chlorobenzene (1.0 mL) at 130 ºC for 24 hours. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a white solid (510 mg, 1.94 mmol, 97% yield). mp 105-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.57 – 8.45 (m, 2H), 7.46 – 7.30 (m, 10H), 7.10 (ddd, *J* = 6.3, 4.4, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.39 (d, *J* = 4.3 Hz), 149.00 (d, *J* = 17.8 Hz), 134.98 (d, *J* = 10.0 Hz), 134.28 (d, *J* = 20.4 Hz), 129.62, 128.92 (d, *J* = 7.6 Hz), 127.29 (d, *J* = 15.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -7.01. IR υ_{max}/cm^{-1} (film): 3029, 1576, 1535, 1475, 1434, 1400, 1322, 1307, 1224, 1180, 1159, 1091, 1069, 1024, 1000, 989, 975, 921, 853, 813, 749, 743, 735, 692. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{17}H_{15}NP^+$ = 264.1, found 264.1.

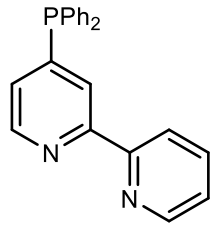
4-(Diphenylphosphaneyl)-2-(thiophen-3-yl)pyridine



Prepared according to general procedure B, using 2-(thiophen-3-yl)pyridine (484 mg, 3.00 mmol), trifluoromethanesulfonic anhydride (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

(30 mL). The crude material was purified by flash chromatography (silica gel: 3.5% Et_2O in toluene) to provide the title compound as a white solid (712 mg, 2.07 mmol, 69% yield). mp 103-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (ddd, *J* = 5.0, 2.5, 0.9 Hz, 1H), 7.81 (dd, *J* = 3.1, 1.3 Hz, 1H), 7.52 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.46 (dt, *J* = 7.3, 1.2 Hz, 1H), 7.44 – 7.31 (m, 11H), 6.97 (ddd, *J* = 6.3, 5.0, 1.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.03 (d, *J* = 5.3 Hz), 149.76 (d, *J* = 17.1 Hz), 149.19 (d, *J* = 4.3 Hz), 141.92, 135.05 (d, *J* = 10.1 Hz), 134.31 (d, *J* = 20.3 Hz), 129.69, 128.98 (d, *J* = 7.5 Hz), 126.37 (d, *J* = 16.9 Hz), 125.40 (d, *J* = 13.6 Hz), 124.17, 123.99; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -6.62. IR υ_{max}/cm^{-1} (film): 3115, 3065, 2919, 1576, 1531, 1519, 1475, 1430, 1419, 1378, 1353, 1326, 1305, 1281, 1267, 1190, 1180, 1158, 1114, 1104, 1089, 1068, 1049, 1026, 998, 987, 919, 908, 890, 869, 843, 830, 793, 745, 694, 670. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{17}NPS^+$ = 346.1, found 346.1.

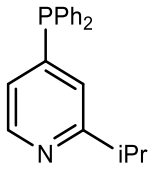
4-(Diphenylphosphaneyl)-2,2'-bipyridine



Prepared according to general procedure B, using 2,2'-bipyridine (470 mg, 3.00 mmol), trifluoromethanesulfonic anhydride (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 (30 mL). The crude material was purified by flash chromatography (silica gel: 10% Et_2O in toluene) to provide the title compound as an amber oil (833 mg, 2.46 mmol, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.62 (ddd, *J* = 4.8, 1.9, 0.9 Hz, 1H), 8.59 (ddd, *J* = 4.9, 2.2, 0.9 Hz, 1H), 8.40 (dt, *J* = 8.0, 1.2 Hz, 1H), 8.36 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.79 (td, *J* = 7.7, 1.8 Hz, 1H), 7.46 –

7.34 (m, 9H), 7.30 – 7.22 (m, 1H), 7.22 – 7.15 (m, 1H), 7.05 (td, J = 5.3, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.96, 155.57 (d, J = 5.9 Hz), 149.99 (d, J = 17.9 Hz), 149.25, 148.84 (d, J = 3.3 Hz), 136.84, 135.16 (d, J = 10.3 Hz), 134.24 (d, J = 20.4 Hz), 132.49 (d, J = 2.8 Hz), 132.10 (d, J = 9.9 Hz), 129.47, 128.85 (d, J = 7.4 Hz), 127.02 (d, J = 10.9 Hz), 125.12 (d, J = 21.5 Hz), 123.73, 121.31; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -6.32. IR υ_{max}/cm^{-1} (film): 3050, 1576, 1562, 1532, 1477, 1452, 1434, 1375, 1308, 1278, 1243, 1199, 1118, 1091, 1069, 1026, 1044, 994, 916, 842, 791, 742, 693, 660. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{22}H_{18}N_2P$+ = 341.1, found 341.2.

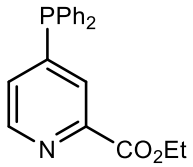
4-(Diphenylphosphaneyl)-2-isopropylpyridine



Prepared according to general procedure B, using 2-isopropylpyridine (251 μL, 3.00 mmol), trifluoromethanesulfonic anhydride (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 (30 mL). The crude material was purified by flash chromatography (silica gel: 5% Et_2O in toluene) to provide the title compound as a white solid (304 mg, 1.00 mmol, 33% yield). mp 80-81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (ddd, J = 5.1, 2.5, 0.9 Hz, 1H), 7.43 – 7.30 (m, 10H), 7.05 (dt, J = 7.6, 1.2 Hz, 1H), 6.88 (ddd, J = 6.4, 5.0, 1.5 Hz, 1H), 2.99 (hept, J = 6.9 Hz, 1H), 1.24 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.82 (d, J = 5.1 Hz), 149.02 (d, J = 16.8 Hz), 148.69 (d, J = 4.0 Hz), 135.34 (d, J = 10.1 Hz), 134.23 (d, J = 20.4 Hz), 129.51, 128.86 (d, J = 7.4 Hz), 124.83, 124.67 (d, J = 3.8 Hz), 124.56, 36.33, 22.59. ^{31}P NMR (162 MHz, $CDCl_3$) δ: -6.59. IR υ_{max}/cm^{-1} (film): 3059, 2971, 2927, 2868, 1576, 1533, 1469, 1480, 1456, 1432, 1389, 1374,

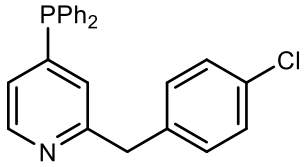
1310, 1287, 1225, 1200, 1151, 1124, 1093, 1056, 1031, 999, 989, 979, 927, 892, 839, 746, 726, 717, 695. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{20}H_{21}NP^+$ = 306.1, found 306.2.

Ethyl 4-(diphenylphosphaneyl)picolinate



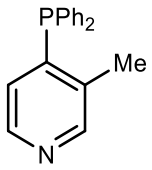
Prepared according to general procedure B, using ethyl picolinate (405 μL, 3.00 mmol), trifluoromethanesulfonic anhydride (500 μL, 3.00 mmol), methyl-3-(diphenylphosphaneyl)propanoate (900 mg, 3.30 mmol), DBU (1.35 mL, 9.00 mmol), and CH_2Cl_2 (30 mL). The crude material was purified by flash chromatography (silica gel: 15% Et_2O in toluene) to provide the title compound as a colorless oil (462 mg, 1.38 mmol, 46% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.66 (ddd, *J* = 4.9, 2.1, 0.8 Hz, 1H), 8.02 (ddd, *J* = 6.7, 1.6, 0.8 Hz, 1H), 7.48 – 7.31 (m, 10H), 7.31 – 7.22 (m, 2H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.21, 151.55 (d, *J* = 20.0 Hz), 149.28 (d, *J* = 3.6 Hz), 147.68 (d, *J* = 4.7 Hz), 134.35 (d, *J* = 20.7 Hz), 134.34 (d, *J* = 9.4 Hz), 130.13 (d, *J* = 12.7 Hz), 129.94, 129.12 (d, *J* = 8.0 Hz), 128.61 (d, *J* = 18.2 Hz), 62.15, 14.39; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -6.53. IR υ_{max}/cm^{-1} (film): 3051, 2980, 1716, 1572, 1536, 1479, 1461, 1435, 1400, 1384, 1364, 1294, 1270, 1227, 1140, 1094, 1020, 991, 914, 857, 782, 743, 694. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{20}H_{19}NO_2P^+$ = 336.1, found 336.1.

2-(4-Chlorobenzyl)-4-(diphenylphosphaneyl)pyridine



Prepared according to general procedure C, using 2-(4-chlorobenzyl)pyridine (522 μL, 3.00 mmol), trifluoromethanesulfonic anhydride (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 (30 mL). The crude material was purified by flash chromatography (silica gel: 7% Et_2O in toluene) to provide the title compound as a colorless oil (909 mg, 2.34 mmol, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.44 (dt, *J* = 4.5, 2.0 Hz, 1H), 7.46 – 7.27 (m, 10H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 6.92 (d, *J* = 6.4 Hz, 2H), 4.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.96 (d, *J* = 4.7 Hz), 149.93 (d, *J* = 17.8 Hz), 148.98 (d, *J* = 4.0 Hz), 137.79, 134.99 (d, *J* = 9.8 Hz), 134.24 (d, *J* = 20.3 Hz), 132.34, 130.48, 129.65, 128.92 (d, *J* = 7.6 Hz), 128.77, 126.77 (d, *J* = 16.7 Hz), 124.99 (d, *J* = 13.8 Hz), 43.90; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -6.59. IR υ_{max}/cm^{-1} (film): 3051, 1575, 1533, 1489, 1433, 1407, 1382, 1308, 1179, 1089, 1070, 1026, 1015, 999, 919, 846, 824, 798, 742, 694, 662. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{24}H_{20}ClNP^+$ = 388.1, found 388.1.

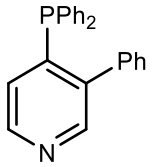
4-(Diphenylphosphaneyl)-3-methylpyridine



Prepared according to general procedure B, using 3-methylpyridine (292 μL, 3.00 mmol), trifluoromethanesulfonic anhydride (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 (30 mL). The crude material was purified by flash chromatography (silica gel: 20% Et_2O in toluene) to provide the title compound as a pale-yellow oil (692 mg, 2.49 mmol, 83% yield). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.30 (d, *J* = 5.2 Hz, 1H), 8.22 (d, *J* = 5.0 Hz, 1H), 7.36 – 7.24 (m, 6H), 7.24 – 7.14 (m, 4H), 6.55 (t, *J* = 4.6 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.15 (d, *J* = 3.3 Hz), 147.36 (d, *J* = 18.5 Hz), 147.30, 136.70 (d, *J* = 21.4 Hz), 134.33 (d, *J* = 20.3 Hz), 134.12 (d, *J* = 8.7 Hz), 129.55, 128.99 (d, *J* = 7.6 Hz), 126.15, 18.20 (d, *J* = 17.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -14.60. IR υ_{max}/cm^{-1} (film): 3051, 1572, 1532, 1475, 1433, 1398, 1377, 1294, 1240, 1189, 1157, 1092, 1060, 1026, 999, 917, 828, 743, 722, 694. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{17}NP^+$ = 278.1, found 278.2.

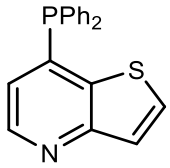
4-(Diphenylphosphaneyl)-3-phenylpyridine



Prepared according to general procedure B, using 3-phenylpyridine (1.43 mL, 10.0 mmol), trifluoromethanesulfonic anhydride (1.68 mL, 10.0 mmol), methyl-3-(diphenylphosphaneyl)propanoate (2.90 g, 11.0 mmol), DBU (4.50 mL, 30.0 mmol), and CH_2Cl_2 (100 mL). The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a white solid (2.63 g, 7.75 mmol, 78% yield). mp 84-86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.47 (ddd, *J* = 8.1, 5.0, 0.8 Hz, 2H), 7.41 – 7.09 (m, 16H), 6.89 (ddd, *J* = 5.1, 3.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.87 (d, *J* = 2.9 Hz), 148.25, 147.50 (d, *J* = 21.2 Hz), 142.40 (d, *J* = 23.0 Hz), 138.01 (d, *J* = 4.6 Hz), 135.23 (d, *J* = 10.5 Hz), 134.35 (d, *J* = 20.6 Hz), 129.76 (d, *J* = 3.5 Hz), 129.30, 128.74 (d, *J* = 7.4 Hz), 128.02, 127.90,

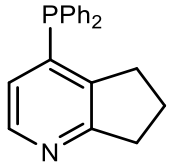
127.02. ; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -13.64. IR υ_{max}/cm^{-1} (film): 3039, 1575, 1480, 1457, 1442, 1434, 1394, 1301, 1270, 1177, 1088, 1071, 1027, 1006, 996, 977, 923, 909, 855, 831, 766, 749, 742, 692, 680. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{23}H_{19}NP^+$ = 340.1, found 340.2.

7-(Diphenylphosphaneyl)thieno[3,2-b]pyridine



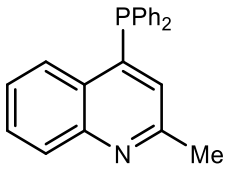
Prepared according to general procedure C using 7-chlorothieno[3,2-*b*]pyridine, (339 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), trifluoromethanesulfonic acid (177 µL, 2.00 mmol), and chlorobenzene (1.0 mL) at 130 ºC for 3 hours. The crude material was purified by flash chromatography (silica gel: 35% EtOAc in hexanes) to provide the title compound as a pale-yellow solid (615 mg, 1.93 mmol, 96% yield). mp 138-139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.59 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.67 (d, *J* = 5.5 Hz, 1H), 7.56 (dd, *J* = 5.6, 3.2 Hz, 1H), 7.46 – 7.32 (m, 10H), 6.80 (t, *J* = 4.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 155.63 (d, *J* = 3.7 Hz), 147.11, 142.84 (d, *J* = 18.4 Hz), 137.32 (d, *J* = 23.4 Hz), 134.42 (d, *J* = 20.4 Hz), 133.29 (d, *J* = 8.7 Hz), 131.08 (d, *J* = 3.1 Hz), 129.86, 128.99 (d, *J* = 7.7 Hz), 124.98 (d, *J* = 2.1 Hz), 121.62 (d, *J* = 1.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -10.95. IR υ_{max}/cm^{-1} (film): 3107, 1539, 1529, 1499, 1474, 1447, 1432, 1356, 1329, 1271, 1231, 1178, 1113, 1084, 1069, 1038, 1025, 998, 959, 928, 894, 857, 837, 808, 786, 747, 713, 696, 675. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{19}H_{15}NPS^+$ = 320.1, found 320.1.

4-(Diphenylphosphaneyl)-6,7-dihydro-5H-cyclopenta[b]pyridine



Prepared according to general procedure B, using 6,7-dihydro-5H-cyclopenta[b]pyridine (351 μL, 3.00 mmol), trifluoromethanesulfonic anhydride (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 (30 mL). The crude material was purified by flash chromatography (silica gel: 20% Et_2O in toluene) to provide the title compound as a white solid (710 mg, 2.34 mmol, 78% yield). mp 75-77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.46 – 7.27 (m, 10H), 6.54 – 6.43 (m, 1H), 3.02 (t, *J* = 7.7 Hz, 2H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.04 (p, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.67 (d, *J* = 4.3 Hz), 147.53, 144.11 (d, *J* = 17.5 Hz), 140.58 (d, *J* = 22.1 Hz), 134.36, 134.22 – 134.10 (m), 129.45, 128.86 (d, *J* = 7.5 Hz), 123.23, 34.16 (d, *J* = 1.7 Hz), 30.69 (d, *J* = 8.8 Hz), 22.73; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -14.28. IR υ_{max}/cm^{-1} (film): 3046, 2949, 1567, 1545, 1475, 1460, 1432, 1381, 1308, 1201, 1178, 1091, 1069, 1027, 1000, 958, 909, 846, 827, 794, 750, 740, 694. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{20}H_{19}NP^+$ = 304.1, found 304.2.

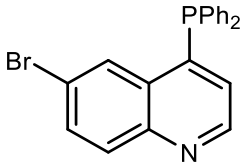
4-(Diphenylphosphaneyl)-2-methylquinoline



Prepared according to general procedure D using 4-chloro-2-methylquinoline (403 μL, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and TFE (5.0 mL) at 80 °C for 3 hours. The

crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a white solid (642 mg, 1.96 mmol, 98% yield). mp 164-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.17 (ddd, *J* = 8.4, 3.5, 1.4 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.65 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.45 – 7.28 (m, 11H), 6.70 (d, *J* = 4.5 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.26, 147.39 (d, *J* = 3.5 Hz), 146.53 (d, *J* = 20.5 Hz), 134.65, 134.46 (d, *J* = 20.4 Hz), 129.53, 129.34 (d, *J* = 1.9 Hz), 128.94 (d, *J* = 7.6 Hz), 128.22 (d, *J* = 19.2 Hz), 126.23, 126.06, 125.89 (d, *J* = 1.9 Hz), 125.84, 25.54; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -14.76. IR υ_{max}/cm^{-1} (film): 1574, 1555, 1492, 1480, 1434, 1395, 1327, 1307, 1295, 1208, 1183, 1159, 1123, 1093, 1070, 1026, 999, 920, 883, 867, 851, 823, 787, 763, 755, 745, 737, 695. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{22}H_{19}NP^+$ = 328.1, found 328.2.

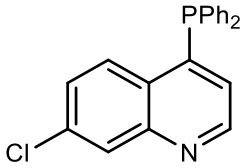
6-Bromo-4-(diphenylphosphaneyl)quinoline



Prepared according to general procedure B, using 6-bromoquinoline (406 μL, 3.00 mmol), trifluoromethanesulfonic anhydride (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 (30 mL). The crude material was purified by flash chromatography (silica gel: 10% Et_2O in toluene) to provide the title compound as a pale brown solid (363 mg, 0.93 mmol, 31% yield). mp 160-161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (d, *J* = 4.4 Hz, 1H), 8.44 (dd, *J* = 3.8, 2.2 Hz, 1H), 7.99 (d, *J* = 8.9 Hz, 1H), 7.75 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.46 – 7.27 (m, 10H), 6.87 (t, *J* = 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.04, 146.34 (d, *J* = 3.2 Hz), 146.13 (d, *J* = 22.2 Hz), 134.39 (d, *J* = 20.3 Hz), 133.99 (d, *J* = 8.5 Hz), 133.14, 131.91 (d, *J* = 1.9 Hz), 131.37 (d, *J* = 20.1

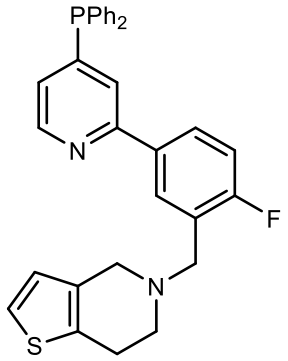
Hz), 129.78, 129.10 (d, J = 7.5 Hz), 128.38 (d, J = 23.6 Hz), 126.25, 121.10 (d, J = 1.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: -16.01. IR υ_{max}/cm^{-1} (film): 1596, 1558, 1479, 1432, 1412, 1337, 1281, 1214, 1184, 1155, 1135, 1095, 1068, 1055, 1029, 1000, 979, 917, 862, 852, 843, 818, 768, 752, 743, 695, 669. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{16}BrNP^+$ = 393.0, found 393.1.

7-Chloro-4-(diphenylphosphaneyl)quinoline



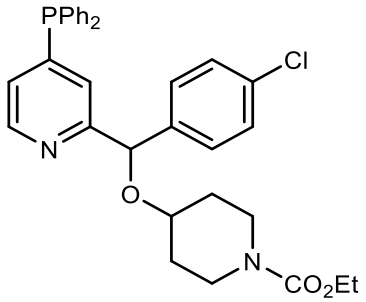
Prepared according to general procedure D using 7-chloroquinoline (396 mg, 2.00 mmol), diphenylphosphane (0.42 mL, 2.40 mmol), and TFE (5.0 mL) at 80 °C for 15 hours. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a white solid (443 mg, 1.28 mmol, 64% yield). mp 154-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (dd, J = 4.4, 1.2 Hz, 1H), 8.15 (dd, J = 9.0, 3.5 Hz, 1H), 8.12 (d, J = 2.2 Hz, 1H), 7.47 – 7.33 (m, 7H), 7.30 (ddt, J = 8.1, 6.5, 1.6 Hz, 4H), 6.81 (t, J = 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.75, 148.17 (d, J = 3.0 Hz), 147.24 (d, J = 22.0 Hz), 135.43 (d, J = 1.4 Hz), 134.48 (d, J = 20.4 Hz), 134.08 (d, J = 8.4 Hz), 129.80, 129.12, 129.10 (d, J = 7.7 Hz), 128.43 (d, J = 19.3 Hz), 127.77 (d, J = 2.0 Hz), 127.57 (d, J = 22.2 Hz), 125.50; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -14.98. IR υ_{max}/cm^{-1} (film): 1598, 1556, 1478, 1431, 1404, 1364, 1337, 1287, 1200, 1184, 1156, 1144, 1095, 1074, 1026, 1000, 979, 892, 878, 863, 851, 818, 769, 749, 742, 694. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{16}ClNP^+$ = 348.1, found 348.1.

5-(5-(4-(Diphenylphosphaneyl)pyridin-2-yl)-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine



Prepared according to general procedure B, using 5-(2-fluoro-5-(pyridin-2-yl)benzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (1.02 g, 3.15 mmol), trifluoromethanesulfonic anhydride (529 μL, 3.15 mmol), methyl-3-(diphenylphosphaneyl)propanoate (953 mg, 3.50 mmol), DBU (1.42 mL, 9.50 mmol), and CH_2Cl_2 (32 mL). The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as an orange amorphous solid (954 mg, 1.89 mmol, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (dd, *J* = 5.0, 2.4 Hz, 1H), 8.29 (dd, *J* = 7.1, 2.5 Hz, 1H), 8.11 (ddd, *J* = 8.2, 5.0, 2.4 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 3.3 Hz, 10H), 7.47 – 7.28 (m, 3H), 7.01 (d, *J* = 5.1 Hz, 1H), 4.13 (s, 2H), 3.93 (s, 2H), 3.16 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.48, 161.00, 156.06 (d, *J* = 5.1 Hz), 149.83 (d, *J* = 17.6 Hz), 149.23 (d, *J* = 4.1 Hz), 135.34 (d, *J* = 3.3 Hz), 135.02 (d, *J* = 10.1 Hz), 134.28 (d, *J* = 20.4 Hz), 133.88, 133.41, 130.27 (d, *J* = 5.0 Hz), 129.66, 128.95 (d, *J* = 7.4 Hz), 127.71 (d, *J* = 8.7 Hz), 125.58 (d, *J* = 13.5 Hz), 125.34, 124.11 (d, *J* = 18.2 Hz), 122.69, 115.79 (d, *J* = 22.8 Hz), 54.63 (d, *J* = 1.7 Hz), 52.94, 50.55, 25.60.; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -6.46; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -117.48. IR υ_{max}/cm^{-1} (film): 3052, 2919, 2816, 1594, 1573, 1530, 1499, 1461, 1433, 1407, 1375, 1362, 1320, 1246, 1169, 1096, 1049, 1015, 999, 982, 899, 822, 792, 742, 694, 667. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{31}H_{27}FN_2PS^+$ = 509.2, found 509.3.

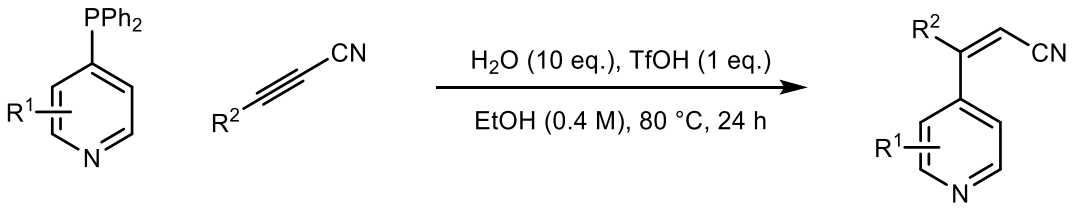
Ethyl 4-((4-chlorophenyl)(4-(diphenylphosphaneyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate



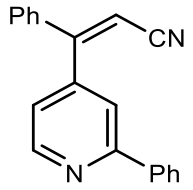
Prepared according to general procedure B, using ethyl 4-((4-chlorophenyl)(pyridin-2-yl)methoxy)piperidine-1-carboxylate (1.12 g, 3.00 mmol), trifluoromethanesulfonic anhydride (500 μL, 3.00 mmol), methyl-3-(diphenylphosphaneyl)propanoate (900 mg, 3.30 mmol), DBU (1.35 mL, 9.00 mmol), and CH_2Cl_2 (30 mL). The crude material was purified by flash chromatography (silica gel: 40% EtOAc in hexanes) to provide the title compound as a colorless amorphous solid (929 mg, 1.66 mmol, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.42 (dd, *J* = 5.0, 2.5 Hz, 1H), 7.47 – 7.33 (m, 11H), 7.33 – 7.24 (m, 4H), 7.00 (ddd, *J* = 6.3, 4.9, 1.5 Hz, 1H), 5.56 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.70 – 3.48 (m, 3H), 3.32 – 3.10 (m, 2H), 1.85 – 1.70 (m, 1H), 1.70 – 1.42 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.24 (d, *J* = 4.1 Hz), 155.56, 150.41 (d, *J* = 18.0 Hz), 148.56 (d, *J* = 4.3 Hz), 140.01, 134.97 (dd, *J* = 10.1, 3.4 Hz), 134.26 (dd, *J* = 20.5, 11.4 Hz), 133.50, 129.70 (d, *J* = 2.8 Hz), 128.91 (d, *J* = 7.6 Hz), 128.48 (d, *J* = 31.9 Hz), 125.94 (d, *J* = 14.9 Hz), 124.01 (d, *J* = 15.7 Hz), 80.93, 72.40, 61.33, 40.87, 30.97, 30.84, 14.82.; ^{31}P NMR (162 MHz, $CDCl_3$) δ: -6.20. IR υ_{max}/cm^{-1} (film): 2929, 1691, 1588, 1571, 1488, 1469, 1432, 1382, 1355, 1334, 1273, 1226, 1171, 1132, 1083, 1029, 1014, 993, 964, 939, 872, 843, 805, 765, 749, 724. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{32}H_{33}ClN_2O_3P^+$ = 559.2, found 559.3.

A2.5 Alkenylation of Pyridines and Quinolines

General Procedure E

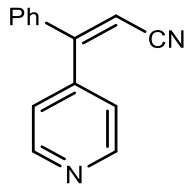


(Z)-3-Phenyl-3-(2-phenylpyridin-4-yl)acrylonitrile



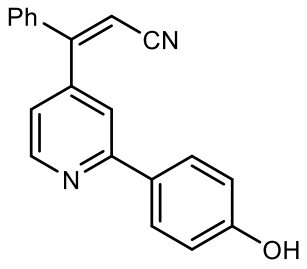
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a colorless oil (70 mg, 0.25 mmol, 83% yield, Z/E = >20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (d, *J* = 5.1 Hz, 1H), 8.00 (d, *J* = 7.1 Hz, 2H), 7.77 (s, 1H), 7.55 – 7.37 (m, 6H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.30 – 7.23 (m, 1H), 5.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.73, 158.43, 150.31, 145.64, 138.83, 137.30, 131.15, 129.55, 129.15, 128.97, 128.32, 127.29, 122.18, 120.82, 117.11, 96.98. IR υ_{max}/cm^{-1} (film): 3054, 2215, 1593, 1541, 1493, 1473, 1446, 1398, 1351, 1265, 1223, 1153, 1109, 1074, 1028, 1000, 989, 893, 848, 776, 762, 733, 693. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{20}H_{15}N_2^+$ = 283.1, found 283.1.

(Z)-3-Phenyl-3-(pyridin-4-yl)acrylonitrile



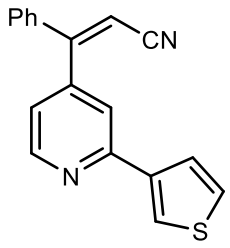
Prepared according to general procedure E using 4-(diphenylphosphaneyl)pyridine (79 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a green solid (36 mg, 0.17 mmol, 58% yield, Z/E = >20:1). mp 134-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (d, *J* = 5.5 Hz, 2H), 7.51 – 7.44 (m, 1H), 7.44 – 7.38 (m, 2H), 7.38 – 7.31 (m, 2H), 7.30 – 7.23 (m, 2H), 5.89 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.41, 150.48, 144.77, 137.25, 131.12, 129.11, 128.26, 123.79, 116.96, 97.00. IR υ_{max}/cm^{-1} (film): 3014, 2924, 2211, 1601, 1586, 1573, 1544, 1491, 1448, 1413, 1360, 1325, 1262, 1216, 1162, 1082, 1069, 1032, 992, 923, 855, 870, 825, 765, 735, 689, 654. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{14}H_{11}N_2^+$ = 207.1, found 207.2.

(Z)-3-(2-(4-Hydroxyphenyl)pyridin-4-yl)-3-phenylacrylonitrile



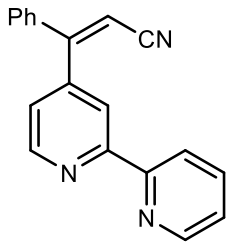
Prepared according to general procedure E using 4-(4-(diphenylphosphaneyl)pyridin-2-yl)phenol (107 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 50% EtOAc in hexanes) to provide the title compound as a pale-yellow solid (73 mg, 0.24 mmol, 81% yield). mp 205-206 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 9.81 (s, 1H), 8.73 (dd, *J* = 4.9, 0.8 Hz, 1H), 8.02 – 7.92 (m, 2H), 7.83 (t, *J* = 1.2 Hz, 1H), 7.55 – 7.36 (m, 5H), 7.20 (dd, *J* = 5.0, 1.5 Hz, 1H), 6.93 – 6.80 (m, 2H), 6.58 (s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 159.58, 158.92, 156.80, 149.88, 145.77, 136.34, 130.86, 128.98, 128.95, 128.19, 128.00, 121.00, 118.69, 117.63, 115.60, 97.62. IR υ_{max}/cm^{-1} (film): 2922, 2853, 2573, 2211, 1743, 1606, 1582, 1444, 1379, 1316, 1282, 1225, 1174, 1109, 1002, 903, 872, 828, 813, 755, 692. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{20}H_{15}N_2O^+$ = 299.1, found 299.2.

(Z)-3-Phenyl-3-(2-(thiophen-3-yl)pyridin-4-yl)acrylonitrile



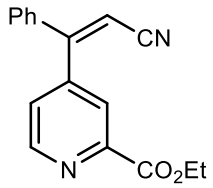
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-(thiophen-3-yl)pyridine (104 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 22 hours. The crude material was purified by flash chromatography (silica gel: 25% EtOAc in hexanes) to provide the title compound as a yellow amorphous solid (76 mg, 0.26 mmol, 88% yield, Z/E = 15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.75 (d, *J* = 5.1 Hz, 1H), 7.98 (d, *J* = 1.4 Hz, 1H), 7.72 – 7.63 (m, 2H), 7.54 – 7.46 (m, 1H), 7.42 (m, 3H), 7.36 – 7.28 (m, 2H), 7.21 (dd, *J* = 5.1, 1.7 Hz, 1H), 5.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.58, 154.33, 150.31, 145.54, 141.63, 137.21, 131.13, 129.13, 128.27, 126.66, 126.33, 124.52, 121.81, 120.30, 117.03, 96.91. IR υ_{max}/cm^{-1} (film): 3049, 2926, 2217, 1600, 1587, 1572, 1532, 1491, 1477, 1443, 1426, 1379, 1349, 1287, 1251, 1193, 1156, 1080, 1059, 999, 919, 900, 869, 884, 833, 796, 772, 758, 746, 698, 683. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{13}N_2S^+$ = 289.1, found 289.1.

(Z)-3-([2,2'-Bipyridin]-4-yl)-3-phenylacrylonitrile



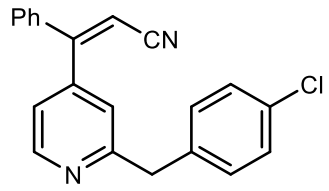
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2,2'-bipyridine (102 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (54 μL, 0.60 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 100 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 65% EtOAc in hexanes) to provide the title compound as a green amorphous solid (41 mg, 0.14 mmol, 48% yield, Z/E = 15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (d, *J* = 5.0 Hz, 1H), 8.64 (d, *J* = 4.5 Hz, 1H), 8.45 (d, *J* = 8.1 Hz, 1H), 8.42 (s, 1H), 7.83 (td, *J* = 7.8, 1.8 Hz, 1H), 7.46 (m, 1H), 7.43 – 7.35 (m, 3H), 7.35 – 7.27 (m, 3H), 5.92 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 160.85, 157.02, 155.53, 149.90, 149.35, 145.97, 137.23, 137.16, 131.08, 129.12, 128.26, 124.23, 123.69, 121.53, 121.15, 117.00, 96.95. IR υ_{max}/cm^{-1} (film): 3056, 2216, 1583, 1542, 1493, 1459, 1447, 1392, 1352, 1265, 1150, 1092, 1070, 1044, 1031, 991, 897, 852, 792, 762, 733, 695, 664. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{19}H_{14}N_3^+$ = 284.1, found 284.2.

Ethyl (Z)-4-(2-cyano-1-phenylvinyl)picolinate



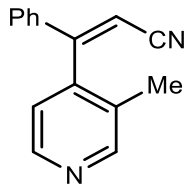
Prepared according to general procedure E using ethyl 4-(diphenylphosphaneyl)picolinate (101 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 45% EtOAc in hexanes) to provide the title compound as a yellow amorphous solid (51 mg, 0.18 mmol, 61% yield, Z/E = 15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.91 (d, *J* = 4.9 Hz, 1H), 8.11 (s, 1H), 7.57 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.42 (dd, *J* = 8.5, 6.7 Hz, 2H), 7.30 – 7.19 (m, 2H), 5.95 (s, 1H), 4.50 (q, *J* = 7.1 Hz, 2H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.80, 159.60, 150.63, 149.18, 146.21, 136.76, 131.37, 129.28, 128.16, 126.77, 125.16, 116.63, 97.66, 62.41, 14.43. IR υ_{max}/cm^{-1} (film): 3039, 2991, 2916, 2213, 1734, 1589, 1575, 1545, 1446, 1386, 1364, 1299, 1244, 1176, 1125, 1099, 1022, 992, 925, 864, 839, 778, 763, 690, 656. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{17}H_{15}N_2O_2^+$ = 279.1, found 279.1.

(Z)-3-(2-(4-Chlorobenzyl)pyridin-4-yl)-3-phenylacrylonitrile



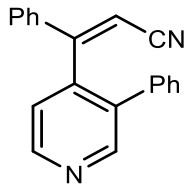
Prepared according to general procedure E using 2-(4-chlorobenzyl)-4-(diphenylphosphaneyl)pyridine (116 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 22 hours. The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a brown solid (77 mg, 0.23 mmol, 78% yield, Z/E = 20:1). mp 109-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (d, *J* = 5.1 Hz, 1H), 7.57 – 7.44 (m, 1H), 7.45 – 7.34 (m, 2H), 7.33 – 7.18 (m, 7H), 7.15 (dd, *J* = 5.1, 1.7 Hz, 1H), 5.86 (s, 1H), 4.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.33, 160.42, 150.18, 145.46, 137.46, 137.17, 132.51, 131.10, 130.58, 129.07, 128.88, 128.22, 123.11, 121.58, 116.99, 96.93, 44.00. IR υ_{max}/cm^{-1} (film): 3036, 2926, 2212, 1589, 1572, 1542, 1490, 1490, 1445, 1430, 1401, 1343, 1253, 1193, 1144, 1088, 1014, 996, 908, 869, 858, 833, 802, 762, 718, 689. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{16}ClN_2^+$ = 331.1, found 331.2.

(Z)-3-(3-Methylpyridin-4-yl)-3-phenylacrylonitrile



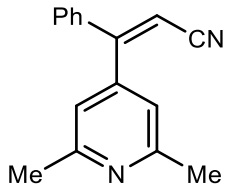
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-3-methylpyridine (83 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 25% EtOAc in hexanes) to provide the title compound as an orange amorphous solid (18 mg, 0.08 mmol, 28% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.60 (s, 2H), 7.52 – 7.32 (m, 3H), 7.29 – 7.14 (m, 3H), 6.05 (s, 1H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.01, 151.80, 147.83, 144.76, 135.73, 131.32, 129.37, 127.07, 123.44, 116.62, 97.13, 16.57. IR υ_{max}/cm^{-1} (film): 3050, 2922, 2852, 2215, 1586, 1548, 1493, 1444, 1404, 1380, 1347, 1300, 1252, 1191, 1154, 1080, 1057, 1030, 999, 929, 835, 816, 765, 718, 693, 653. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{15}H_{13}N_2^+$ = 221.1, found 221.2.

(Z)-3-Phenyl-3-(3-phenylpyridin-4-yl)acrylonitrile



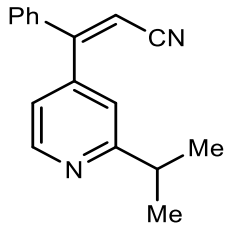
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-3-phenylpyridine (102 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 25% EtOAc in hexanes) to provide the title compound as a yellow amorphous solid (18 mg, 0.06 mmol, 21 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 – 8.65 (m, 2H), 7.43 – 7.31 (m, 2H), 7.31 – 7.15 (m, 7H), 7.15 – 7.06 (m, 2H), 5.87 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.41, 151.22, 148.84, 143.76, 136.87, 136.62, 136.48, 130.82, 129.07, 128.86, 128.35, 128.13, 127.34, 124.12, 116.89, 97.92. IR υ_{max}/cm^{-1} (film): 3008, 2215, 1587, 1494, 1475, 1446, 1402, 1352, 1253, 1209, 1185, 1076, 1033, 1008, 973, 922, 871, 845, 773, 763, 751, 705, 692, 663, 653. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{20}H_{15}N_2^+$ = 283.1, found 283.2.

(Z)-3-(2,6-Dimethylpyridin-4-yl)-3-phenylacrylonitrile



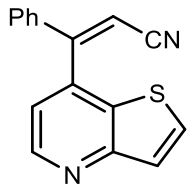
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2,6-dimethylpyridine (87 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a white solid (57 mg, 0.24 mmol, 81 % yield). mp 105-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.55 – 7.34 (m, 3H), 7.26 (d, *J* = 7.1 Hz, 2H), 6.97 (s, 2H), 5.83 (s, 1H), 2.58 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.06, 158.67, 145.45, 137.47, 130.95, 129.01, 128.20, 120.22, 117.09, 96.43, 24.69. IR υ_{max}/cm^{-1} (film): 3059, 2924, 2213, 1606, 1590, 1556, 1492, 1445, 1402, 1385, 1373, 1246, 1220, 1187, 1141, 1080, 1030, 1001, 976, 929, 882, 832, 764, 740, 696, 674, 654. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{16}H_{15}N_2^+$ = 235.1, found 235.1.

(Z)-3-(2-Isopropylpyridin-4-yl)-3-phenylacrylonitrile



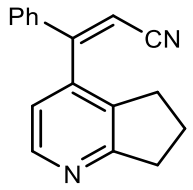
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-isopropylpyridine (92 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a white solid (68 mg, 0.27 mmol, 91 % yield). mp 95-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.44 – 7.37 (m, 2H), 7.31 – 7.22 (m, 4H), 7.11 (dd, *J* = 5.1, 1.7 Hz, 1H), 5.86 (s, 1H), 3.14 (hept, *J* = 6.9 Hz, 1H), 1.34 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.28, 161.01, 149.67, 145.08, 137.45, 131.01, 129.05, 128.28, 121.14, 120.94, 117.14, 96.68, 36.54, 22.57. IR υ_{max}/cm^{-1} (film): 3038, 2967, 2922, 2868, 2208, 1599, 1587, 1570, 1547, 1480, 1444, 1402, 1377, 1356, 1326, 1295, 1265, 1207, 1150, 1121, 1102, 1079, 1058, 1029, 999, 978, 924, 905, 884, 849, 819, 770, 701, 655. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{17}H_{17}N_2^+$ = 249.1, found 249.2.

(Z)-3-Phenyl-3-(thieno[3,2-b]pyridin-7-yl)acrylonitrile



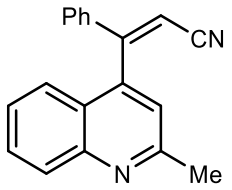
Prepared according to general procedure E using 7-(diphenylphosphaneyl)thieno[3,2-b]pyridine (96 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (54 μL, 0.60 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 100 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a green solid (44 mg, 0.17 mmol, 57% yield, Z/E = >20:1). mp 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.86 (d, J = 4.8 Hz, 1H), 7.71 (d, J = 5.5 Hz, 1H), 7.62 (d, J = 5.6 Hz, 1H), 7.52 – 7.44 (m, 1H), 7.45 – 7.35 (m, 3H), 7.35 – 7.28 (m, 2H), 6.06 (s, 1H). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 4.8 Hz, 1H), 7.71 (d, *J* = 5.5 Hz, 1H), 7.62 (d, *J* = 5.6 Hz, 1H), 7.52 – 7.44 (m, 1H), 7.45 – 7.35 (m, 3H), 7.35 – 7.28 (m, 2H), 6.06 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.05, 157.35, 147.87, 139.69, 135.45, 131.70, 131.50, 129.32, 127.97, 125.32, 118.97, 116.46, 98.28. IR υ_{max}/cm^{-1} (film): 3090, 3011, 2215, 1728, 1601, 1559, 1545, 1493, 1457, 1447, 1376, 1352, 1267, 1238, 1161, 1126, 1090, 1037, 956, 917, 893, 872, 838, 816, 791, 774, 763, 716, 687. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{16}H_{11}N_2S^+$ = 263.1, found 263.1.

(Z)-3-(6,7-Dihydro-5H-cyclopenta[b]pyridin-4-yl)-3-phenylacrylonitrile



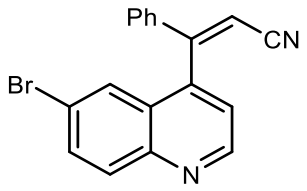
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-6,7-dihydro-5H-cyclopenta[b]pyridine (91 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 40% EtOAc in hexanes) to provide the title compound as a brown oil (45 mg, 0.18 mmol, 61% yield, Z/E = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.49 (d, *J* = 5.1 Hz, 1H), 7.54 – 7.42 (m, 4H), 7.26 (s, 1H), 7.06 (d, *J* = 5.1 Hz, 1H), 5.95 (s, 1H), 3.11 (t, *J* = 7.8 Hz, 2H), 2.63 (t, *J* = 7.4 Hz, 2H), 2.08 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.10, 160.11, 148.11, 141.33, 136.25, 135.61, 131.11, 129.23, 129.01, 120.96, 116.93, 96.86, 34.47, 29.93, 22.83. IR υ_{max}/cm^{-1} (film): 3055, 2954, 2215, 1720, 1582, 1555, 1494, 1437, 1388, 1356, 1312, 1254, 1199, 1119, 1078, 1029, 999, 911, 825, 763, 723, 695. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{17}H_{15}N_2^+$ = 247.1, found 247.2.

(Z)-3-(2-Methylquinolin-4-yl)-3-phenylacrylonitrile



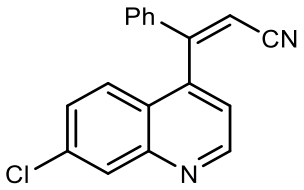
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-methylquinoline (98 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (54 μL, 0.60 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 100 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a pale-yellow solid (77 mg, 0.29 mmol, 95% yield). mp 187-188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 8.5 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.49 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.40 – 7.32 (m, 3H), 7.33 – 7.27 (m, 3H), 6.21 (s, 1H), 2.83 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ: 159.41, 158.79, 148.34, 143.26, 136.51, 131.12, 129.94, 129.39, 129.17, 127.06, 126.54, 124.84, 124.03, 122.26, 116.53, 98.00, 25.43. IR υ_{max}/cm^{-1} (film): 3057, 2213, 1602, 1584, 1571, 1560, 1507, 1493, 1445, 1409, 1382, 1356, 1331, 1251, 1218, 1185, 1151, 1126, 1076, 1030, 999, 954, 901, 866, 847, 835, 816, 790, 752, 716, 686, 657. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{19}H_{15}N_2^+$ = 271.1, found 271.2.

(Z)-3-(6-Bromoquinolin-4-yl)-3-phenylacrylonitrile



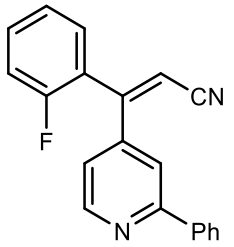
Prepared according to general procedure E using 6-bromo-4-(diphenylphosphaneyl)quinoline (118 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (54 μL, 0.60 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 100 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 25% EtOAc in hexanes) to provide the title compound as a yellow amorphous solid (69 mg, 0.21 mmol, 68% yield, Z/E = 15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.66 (d, *J* = 4.4 Hz, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.41 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.31 (d, *J* = 2.3 Hz, 1H), 7.10 – 7.02 (m, 2H), 7.02 – 6.94 (m, 2H), 6.91 – 6.84 (m, 2H), 5.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.46, 150.52, 147.37, 142.44, 136.03, 133.74, 132.09, 131.57, 129.46, 127.24, 127.14, 122.28, 121.95, 116.39, 98.71. IR υ_{max}/cm^{-1} (film): 3020, 2214, 1601, 1583, 1561, 1490, 1447, 1417, 1370, 1337, 1263, 1213, 1197, 1160, 1139, 1083, 1061, 999, 968, 921, 885, 877, 861, 847, 830, 781, 757, 691, 681. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{12}BrN_2^+$ = 335.0, found 335.1.

(Z)-3-(7-Chloroquinolin-4-yl)-3-phenylacrylonitrile



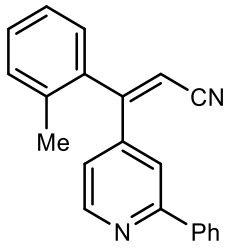
Prepared according to general procedure E using 7-chloro-4-(diphenylphosphaneyl)quinoline (104 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (54 μL, 0.60 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 100 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a white solid (62 mg, 0.21 mmol, 71% yield, Z/E = 15:1). mp 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.07 (d, *J* = 4.4 Hz, 1H), 8.21 (d, *J* = 2.4 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.48 – 7.40 (m, 3H), 7.40 – 7.34 (m, 2H), 7.30 – 7.23 (m, 2H), 6.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.75, 151.30, 149.19, 143.34, 136.31, 136.11, 131.50, 129.43, 129.32, 128.70, 127.15, 126.50, 124.26, 121.78, 116.42, 98.59. IR υ_{max}/cm^{-1} (film): 3044, 2212, 1591, 1574, 1562, 1491, 1416, 1379, 1388, 1260, 1208, 1189, 1154, 1088, 1033, 1000, 962, 949, 913, 886, 879, 852, 831, 797, 763, 730, 696, 662. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{12}ClN_2^+$ = 291.1, found 291.1.

(Z)-3-(2-Fluorophenyl)-3-(2-phenylpyridin-4-yl)acrylonitrile



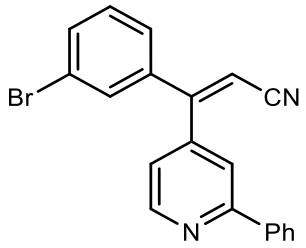
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-(2-fluorophenyl)propiolonitrile (65 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a colorless oil (82 mg, 0.27 mmol, 91% yield, Z/E = 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.80 (dd, *J* = 5.0, 0.8 Hz, 1H), 8.02 – 7.96 (m, 2H), 7.78 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.52 – 7.39 (m, 5H), 7.28 – 7.23 (m, 1H), 7.21 – 7.16 (m, 2H), 6.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.36 (d, *J* = 253.2 Hz), 158.54, 155.20, 150.38, 145.53, 138.85, 132.59 (d, *J* = 8.7 Hz), 131.31 (d, *J* = 2.2 Hz), 129.55, 128.98, 127.32, 124.83 (d, *J* = 3.6 Hz), 121.41, 120.08, 116.89 (d, *J* = 21.8 Hz), 116.63, 101.08 (d, *J* = 6.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ: -111.20. IR υ_{max}/cm^{-1} (film): 3048, 2217, 1594, 1579, 1542, 1487, 1473, 1446, 1401, 1351, 1266, 1249, 1213, 1158, 1104, 1073, 1028, 989, 948, 892, 847, 825, 801, 774, 760, 735, 694, 657. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{20}H_{14}FN_2^+$ = 301.1, found 301.2.

(Z)-3-(2-Phenylpyridin-4-yl)-3-(o-tolyl)acrylonitrile



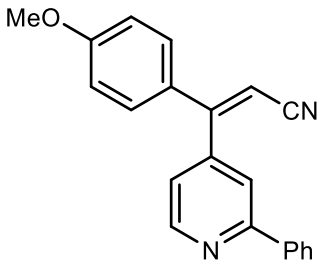
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-(o-tolyl)propiolonitrile (64 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 100 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 12% EtOAc in hexanes) to provide the title compound as a white solid (57 mg, 0.20 mmol, 65 % yield, Z/E = 1:1). mp 111-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (d, *J* = 5.1 Hz, 1H), 8.02 – 7.94 (m, 2H), 7.86 (s, 1H), 7.53 – 7.42 (m, 3H), 7.38 (td, *J* = 7.4, 1.8 Hz, 1H), 7.30 (t, *J* = 6.9 Hz, 1H), 7.24 (dt, *J* = 5.3, 2.4 Hz, 3H), 5.69 (s, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.37, 158.45, 150.40, 145.18, 138.78, 138.05, 135.96, 131.13, 130.02, 129.56, 129.41, 128.86, 127.15, 126.35, 120.90, 119.42, 116.75, 99.87, 77.24, 20.41. IR υ_{max}/cm^{-1} (film): 3064, 2922, 2852, 2219, 1610, 1593, 1580, 1541, 1485, 1475, 1445, 1400, 1295, 1228, 1185, 1157, 1108, 1030, 987, 926, 899, 853, 827, 785, 774, 756, 734, 693, 679, 657. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{17}N_2^+$ = 297.1, found 297.2.

(Z)-3-(3-Bromophenyl)-3-(2-phenylpyridin-4-yl)acrylonitrile



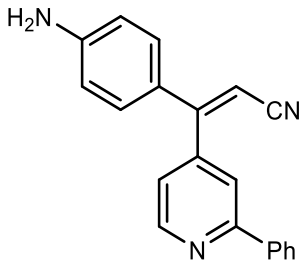
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-(3-bromophenyl)propiolonitrile (93 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a white amorphous solid (97 mg, 0.27 mmol, 90 % yield, Z/E = 11:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.84 (d, *J* = 5.0 Hz, 1H), 8.02 (d, *J* = 7.0 Hz, 2H), 7.77 (s, 1H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.54 – 7.44 (m, 4H), 7.35 – 7.27 (m, 1H), 7.27 – 7.18 (m, 2H), 5.91 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.21, 158.58, 150.49, 144.87, 139.35, 138.69, 134.01, 131.07, 130.62, 129.64, 128.99, 127.27, 127.01, 123.34, 121.92, 120.52, 116.62, 98.29. IR υ_{max}/cm^{-1} (film): 3033, 3005, 2212, 1605, 1587, 1556, 1545, 1471, 1445, 1405, 1390, 1352, 1317, 1249, 1230, 1175, 1151, 1107, 1096, 1073, 1023, 991, 964, 937, 925, 886, 845, 830, 786, 777, 743, 732, 698, 671. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{20}H_{14}BrN_2^+$ = 361.0, found 361.1.

(Z)-3-(4-Methoxyphenyl)-3-(2-phenylpyridin-4-yl)acrylonitrile



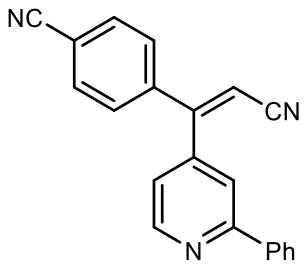
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-(4-methoxyphenyl)propiolonitrile (71 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a colorless amorphous solid (50 mg, 0.16 mmol, 54% yield, Z/E = 15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (d, *J* = 5.0 Hz, 1H), 7.99 – 7.90 (m, 2H), 7.67 (s, 1H), 7.44 – 7.35 (m, 3H), 7.25 – 7.11 (m, 3H), 6.89 – 6.78 (m, 2H), 5.75 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.09, 160.19, 158.36, 150.31, 145.96, 138.93, 129.92, 129.51, 128.96, 127.28, 122.26, 120.86, 117.55, 114.55, 94.54, 55.62. IR υ_{max}/cm^{-1} (film): 3051, 2213, 1599, 1541, 1511, 1462, 1444, 1422, 1398, 1357, 1299, 1250, 1180, 1152, 1118, 1074, 1028, 894, 843, 818, 775, 733, 695. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{17}N_2O^+$ = 313.1, found 313.2.

(Z)-3-(4-Aminophenyl)-3-(2-phenylpyridin-4-yl)acrylonitrile



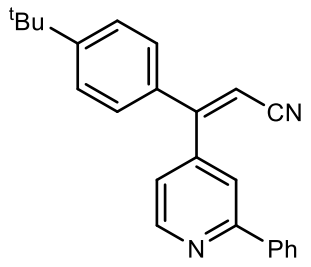
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-(4-aminophenyl)propiolonitrile (64 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 100 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 40% EtOAc in hexanes) to provide the title compound as an orange amorphous solid (44 mg, 0.15 mmol, 50% yield, Z/E = 1.3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (d, *J* = 6.0 Hz, 1H), 8.04 – 7.98 (m, 2H), 7.74 (s, 1H), 7.48 (td, *J* = 7.1, 1.8 Hz, 3H), 7.38 – 7.30 (m, 1H), 7.15 – 7.08 (m, 2H), 6.67 – 6.59 (m, 2H), 5.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.41, 158.20, 150.16, 146.34, 138.98, 129.88, 129.43, 128.93, 127.27, 126.51, 122.40, 120.99, 118.05, 114.72, 92.22. IR υ_{max}/cm^{-1} (film): 3370, 3217, 3046, 2207, 1623, 1595, 1540, 1516, 1473, 1444, 1397, 1357, 1307, 1259, 1230, 1179, 1154, 1074, 1027, 990, 894, 833, 811, 775, 732, 695, 658. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{20}H_{16}N_3^+$ = 298.1, found 298.2.

(Z)-4-(2-Cyano-1-(2-phenylpyridin-4-yl)vinyl)benzonitrile



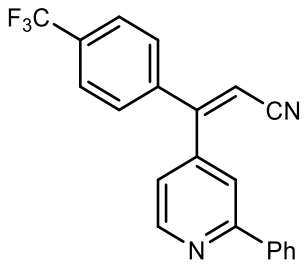
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 4-(cyanoethynyl)benzonitrile (69 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a white amorphous solid (79 mg, 0.26 mmol, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.84 (d, *J* = 5.0 Hz, 1H), 7.99 (dd, *J* = 8.1, 1.8 Hz, 2H), 7.77 – 7.63 (m, 3H), 7.52 – 7.34 (m, 5H), 7.21 (dd, *J* = 5.0, 1.9 Hz, 1H), 5.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.76, 158.68, 150.65, 144.34, 141.45, 138.52, 132.87, 129.77, 129.03, 128.93, 127.23, 121.75, 120.38, 117.89, 116.27, 114.68, 99.84. IR υ_{max}/cm^{-1} (film): 3042, 2230, 2216, 1595, 1539, 1503, 1477, 1445, 1399, 1344, 1273, 1225, 1180, 1151, 1115, 1074, 1020, 990, 909, 898, 856, 840, 824, 778, 760, 746, 736, 722, 698. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{14}N_3^+$ = 308.1, found 308.2.

(Z)-3-(4-(tert-Butyl)phenyl)-3-(2-phenylpyridin-4-yl)acrylonitrile



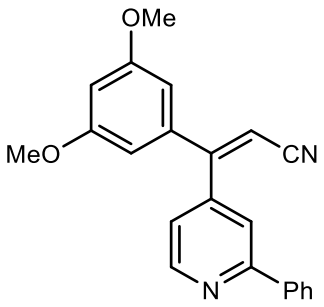
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-(4-(tert-butyl)phenyl)propiolonitrile (82 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes) to provide the title compound as a white solid (55 mg, 0.16 mmol, 54% yield). mp 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.74 (d, *J* = 5.1 Hz, 1H), 7.93 (d, *J* = 7.0 Hz, 2H), 7.69 (s, 1H), 7.44 – 7.30 (m, 5H), 7.22 – 7.12 (m, 3H), 5.82 (s, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.60, 158.38, 154.90, 150.30, 145.81, 138.95, 134.29, 129.51, 128.97, 128.08, 127.32, 126.15, 122.25, 120.82, 117.36, 95.95, 35.07, 31.24. IR υ_{max}/cm^{-1} (film): 2964, 2922, 2853, 2211, 1600, 1587, 1542, 1508, 1475, 1443, 1409, 1389, 1363, 1269, 1203, 1159, 1127, 1110, 1073, 1024, 1014, 972, 921, 886, 853, 820, 776, 743, 713, 697, 674. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{24}H_{23}N_2^+$ = 339.2, found 339.2.

3-(4-(Trifluoromethyl)phenyl)propiolonitrile



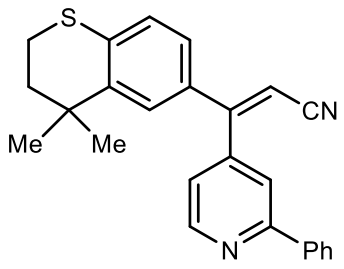
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-(4-(trifluoromethyl)phenyl)propiolonitrile (88 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a colorless amorphous solid (87 mg, 0.25 mmol, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.84 (dd, *J* = 5.1, 0.9 Hz, 1H), 8.05 – 7.93 (m, 2H), 7.76 (dd, *J* = 1.8, 1.0 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.54 – 7.39 (m, 5H), 7.24 (dd, *J* = 5.1, 1.7 Hz, 1H), 5.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.25, 158.73, 150.60, 144.77, 140.78 (d, *J* = 1.8 Hz), 138.66, 132.85 (q, *J* = 33.1 Hz), 129.72, 129.04, 128.76, 127.28, 126.19 (q, *J* = 4.0 Hz), 123.68 (q, *J* = 272.7 Hz), 121.90, 120.52, 116.51, 99.11. IR υ_{max}/cm^{-1} (film): 3053, 2219, 1594, 1542, 1474, 1446, 1412, 1323, 1265, 1170, 1128, 1069, 1016, 895, 855, 826, 777, 733, 697. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{14}F_3N_2^+$ = 351.1, found 351.2.

(Z)-3-(3,5-Dimethoxyphenyl)-3-(2-phenylpyridin-4-yl)acrylonitrile



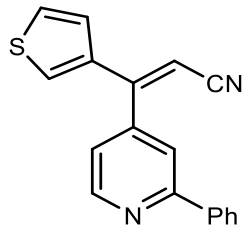
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-(3,5-dimethoxyphenyl)propiolonitrile (84 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 100 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 20% EtOAc in hexanes) to provide the title compound as a yellow amorphous solid (86 mg, 0.25 mmol, 84% yield, Z/E = 7:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (d, *J* = 5.0 Hz, 1H), 8.08 – 7.98 (m, 2H), 7.78 (s, 1H), 7.53 – 7.43 (m, 3H), 7.26 (dd, *J* = 5.0, 2.0 Hz, 1H), 6.56 (t, *J* = 2.3 Hz, 1H), 6.42 (d, *J* = 2.3 Hz, 2H), 5.90 (s, 1H), 3.77 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.16, 160.68, 158.33, 150.25, 145.41, 139.30, 138.83, 129.52, 128.95, 127.26, 122.10, 120.70, 117.01, 106.75, 102.54, 97.38, 55.65. IR υ_{max}/cm^{-1} (film): 2937, 2839, 2214, 1583, 1541, 1454, 1424, 1399, 1353, 1319, 1298, 1266, 1204, 1156, 1064, 1030, 989, 927, 894, 837, 776, 759, 736, 719, 694. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{22}H_{19}N_2O_2^+$ = 343.1, found 343.2.

(Z)-3-(4,4-Dimethylthiochroman-6-yl)-3-(2-phenylpyridin-4-yl)acrylonitrile



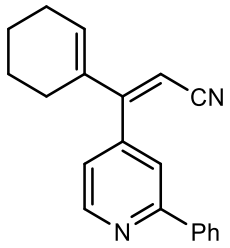
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-(4,4-dimethylthiochroman-6-yl)propiolonitrile (102 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 100 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a yellow amorphous solid (91 mg, 0.24 mmol, 79% yield, Z/E = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (d, *J* = 5.0 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.78 (s, 1H), 7.56 – 7.44 (m, 3H), 7.37 – 7.24 (m, 2H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.97 (d, *J* = 8.3, 2.9 Hz, 1H), 5.86 (s, 1H), 3.20 – 3.01 (m, 2H), 2.08 – 1.90 (m, 2H), 1.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.45, 158.30, 150.23, 145.70, 142.63, 138.85, 137.20, 132.71, 129.50, 128.94, 127.23, 127.12, 126.15, 125.70, 122.25, 120.84, 117.50, 94.89, 37.04, 33.19, 30.02, 23.28. IR υ_{max}/cm^{-1} (film): 3050, 2960, 2210, 1593, 1579, 1541, 1472, 1445, 1389, 1364, 1347, 1307, 1248, 1180, 1154, 1117, 1055, 988, 892, 848, 810, 775, 721, 694. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{25}H_{23}N_2S^+$ = 383.2, found 383.2.

(Z)-3-(2-Phenylpyridin-4-yl)-3-(thiophen-3-yl)acrylonitrile



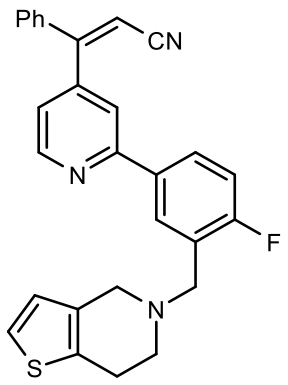
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-(thiophen-3-yl)propiolonitrile (60 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 15% EtOAc in hexanes) to provide the title compound as a colorless amorphous solid (67 mg, 0.23 mmol, 77% yield, Z/E = X:X). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.83 (dd, *J* = 5.0, 1.0 Hz, 1H), 8.05 – 7.99 (m, 2H), 7.78 (dd, *J* = 1.7, 1.0 Hz, 1H), 7.53 – 7.40 (m, 4H), 7.30 (dd, *J* = 5.0, 1.7 Hz, 1H), 7.26 – 7.20 (m, 2H), 5.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.39, 154.54, 150.35, 145.54, 138.87, 138.81, 129.56, 128.97, 128.92, 127.89, 127.25, 125.59, 121.78, 120.35, 117.11, 95.33. IR υ_{max}/cm^{-1} (film): 3050, 2213, 1586, 1541, 1474, 1445, 1418, 1385, 1332, 1265, 1147, 1073, 1029, 988, 893, 849, 824, 787, 778, 733, 719, 693. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{18}H_{13}N_2S^+$ = 289.1, found 289.1.

(Z)-3-(Cyclohex-1-en-1-yl)-3-(2-phenylpyridin-4-yl)acrylonitrile



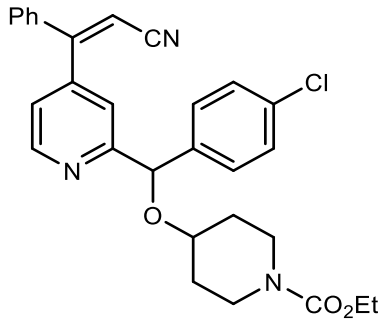
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), 3-(cyclohex-1-en-1-yl)propiolonitrile (59 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 100 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 10% EtOAc in hexanes) to provide the title compound as a white solid (17 mg, 0.06 mmol, 20% yield, Z/E = 17:1). mp 115-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.76 (d, *J* = 5.0 Hz, 1H), 8.05 – 7.97 (m, 2H), 7.59 (d, *J* = 1.2 Hz, 1H), 7.54 – 7.38 (m, 3H), 7.12 (dd, *J* = 5.0, 1.6 Hz, 1H), 5.84 (t, *J* = 4.3 Hz, 1H), 5.48 (s, 1H), 2.27 (ddt, *J* = 6.3, 4.2, 1.9 Hz, 2H), 2.17 (h, *J* = 4.0 Hz, 2H), 1.85 – 1.74 (m, 2H), 1.67 – 1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.57, 157.97, 149.95, 146.01, 139.73, 139.03, 135.39, 129.42, 128.93, 127.26, 122.25, 120.76, 117.59, 93.49, 26.69, 25.39, 22.36, 21.52. IR υ_{max}/cm^{-1} (film): 3047, 2922, 2210, 1680, 1615, 1599, 1570, 1538, 1474, 1444, 1423, 1403, 1383, 1331, 1274, 1247, 1223, 1138, 1080, 1028, 990, 930, 914, 852, 842, 813, 797, 775, 743, 727, 710, 695. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{20}H_{19}N_2^+$ = 287.2, found 287.2.

(Z)-3-(2-(3-((6,7-Dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)-4-fluorophenyl)pyridin-4-yl)-3-phenylacrylonitrile



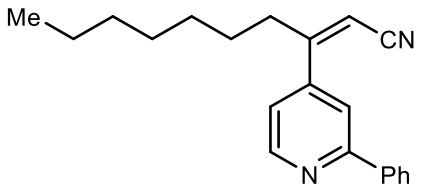
Prepared according to general procedure E using 5-(5-(4-(diphenylphosphaneyl)pyridin-2-yl)-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine (153 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 30% EtOAc in hexanes) to provide the title compound as a green amorphous solid (54 mg, 0.12 mmol, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 5.0 Hz, 1H), 8.03 (d, *J* = 4.4 Hz, 1H), 7.85 (tt, *J* = 5.0, 2.5 Hz, 1H), 7.65 (s, 1H), 7.36 (dt, *J* = 28.3, 7.4 Hz, 3H), 7.27 – 7.12 (m, 3H), 7.08 (t, *J* = 9.0 Hz, 1H), 6.97 (d, *J* = 5.1 Hz, 1H), 6.62 (d, *J* = 5.1 Hz, 1H), 5.83 (s, 1H), 3.78 (s, 2H), 3.58 (s, 2H), 2.81 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.74, 161.25, 160.67, 157.40, 150.33, 145.70, 137.21, 135.06 (d, *J* = 3.3 Hz), 133.43, 131.17, 130.55 (d, *J* = 4.7 Hz), 129.17, 128.30, 128.11 (d, *J* = 8.7 Hz), 125.38, 122.80, 122.10, 120.48, 117.08, 116.10, 115.87, 97.00, 54.55, 52.96, 50.55, 25.51; ^{19}F NMR (376 MHz, $CDCl_3$) δ: -116.98. IR υ_{max}/cm^{-1} (film): 3057, 2920, 2214, 1595, 1541, 1501, 1469, 1446, 1409, 1432, 1382, 1356, 1248, 1226, 1169, 1112, 1098, 1079, 1051, 1015, 982, 903, 826, 784, 761, 726, 694, 667. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{28}H_{23}FN_3S^+$ = 452.2, found 452.3.

Ethyl (Z)-4-((4-chlorophenyl)(4-(2-cyano-1-phenylvinyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate



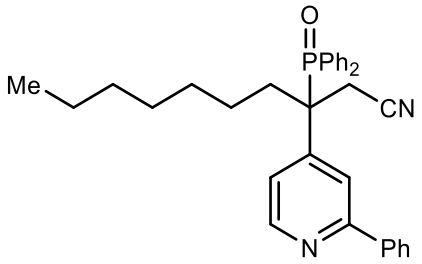
Prepared according to general procedure E using ethyl 4-((4-chlorophenyl)(4-(diphenylphosphaneyl)pyridin-2-yl)methoxy)piperidine-1-carboxylate (168 mg, 0.30 mmol), 3-phenylpropiolonitrile (57 mg, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude material was purified by flash chromatography (silica gel: 50% EtOAc in hexanes) to provide the title compound as an amber amorphous solid (100 mg, 0.20 mmol, 52% ^{1}H NMR yield with 14% of an unknown impurity). IR υ_{max}/cm^{-1} (film): 3057, 2922, 2214, 1688, 1594, 1542, 1501, 1469, 1446, 1432, 1408, 1382, 1356, 1227, 1170, 1113, 1079, 1051, 1014, 1000, 904, 827, 783, 761, 726, 694. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{29}H_{29}ClN_3O_3^+$ = 502.2, found 502.2.

(Z)-3-(2-phenylpyridin-4-yl)dec-2-enenitrile



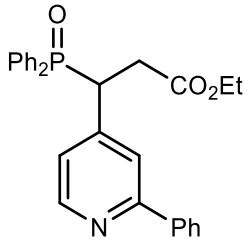
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (170 mg, 0.50 mmol), dec-2-ynenitrile (112 mg, 0.75 mmol), trifluoromethanesulfonic acid (44 μL, 0.50 mmol), H_2O (90 μL, 5.00 mmol), and EtOH (1.25 mL, 0.4 M) at 100 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 1% MeOH in CH_2Cl_2) to provide the title compound as a colorless oil (31 mg, 0.10 mmol, 20% yield, Z/E = 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.78 (d, J = 5.1 Hz, 1H), 8.01 (d, J = 7.3 Hz, 2H), 7.75 (s, 1H), 7.48 (dt, J = 14.5, 6.9 Hz, 3H), 7.24 (d, J = 3.1 Hz, 1H), 5.51 (s, 1H), 2.60 (t, J = 7.5 Hz, 2H), 1.43 (p, J = 7.2 Hz, 2H), 1.37 – 1.16 (m, 8H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.74, 158.39, 150.28, 146.05, 138.90, 129.40, 128.87, 127.18, 119.95, 118.80, 116.63, 97.46, 37.59, 31.62, 28.92, 28.87, 27.45, 22.56, 14.03. IR υ_{max}/cm^{-1} (film): 2926, 2855, 2218, 1594, 1580, 1540, 1467, 1445, 1401, 1271, 1228, 1180, 1114, 1074, 1027, 989, 892, 845, 775, 740, 722, 694. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{21}H_{25}N_2^+$ = 305.2, found 305.3.

3-(diphenylphosphoryl)-3-(2-phenylpyridin-4-yl)decanenitrile



Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (170 mg, 0.50 mmol), dec-2-ynenitrile (112 mg, 0.75 mmol), trifluoromethanesulfonic acid (44 μL, 0.50 mmol), H_2O (90 μL, 5.00 mmol), and EtOH (1.25 mL, 0.4 M) at 100 °C for 48 hours. The crude material was purified by flash chromatography (silica gel: 1% MeOH in CH_2Cl_2) to provide the title compound as a colorless oil (48 mg, 0.10 mmol, 20% yield). IR υ_{max}/cm^{-1} (film): 3055, 2928, 2856, 1593, 1545, 1467, 1438, 1395, 1265, 1184, 1109, 1074, 1027, 997, 908, 847, 775, 731, 694. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{33}H_{36}N_2OP^+$ = 507.3, found 507.4.

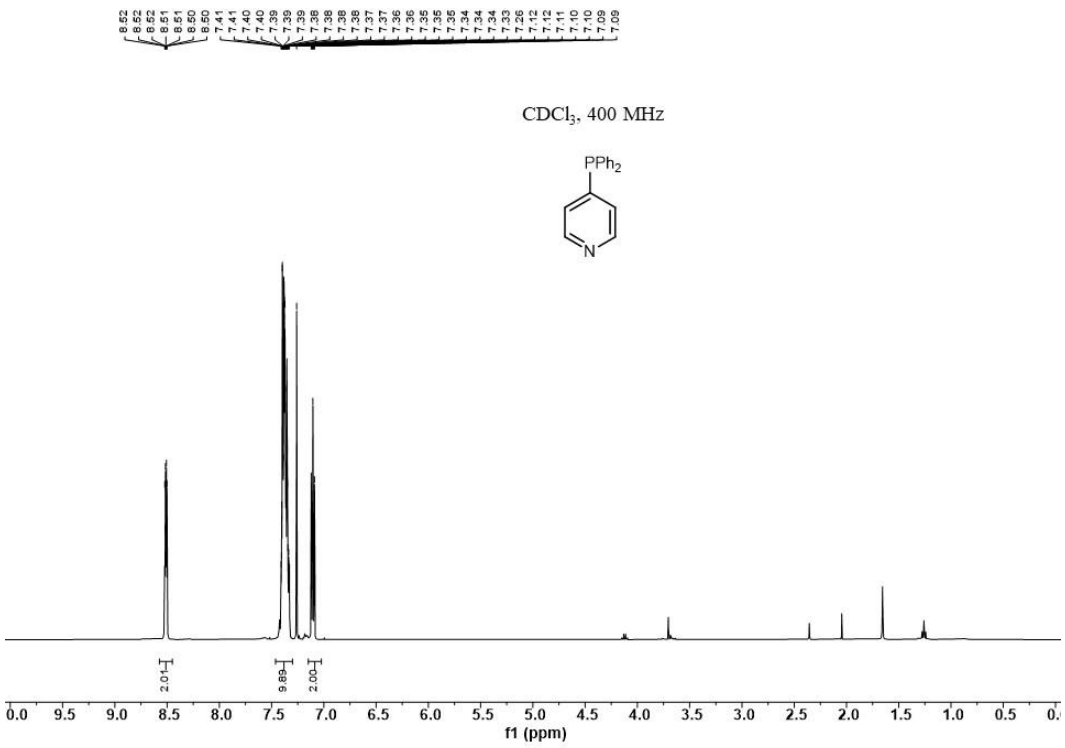
Ethyl 3-(diphenylphosphoryl)-3-(2-phenylpyridin-4-yl)propanoate

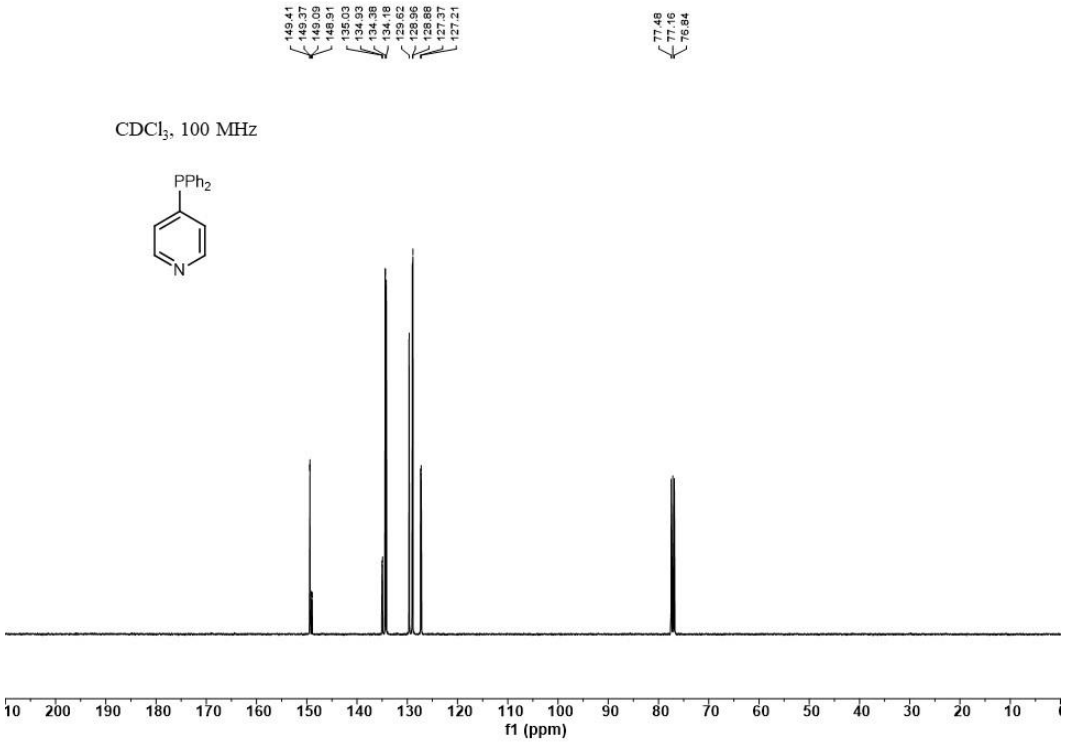


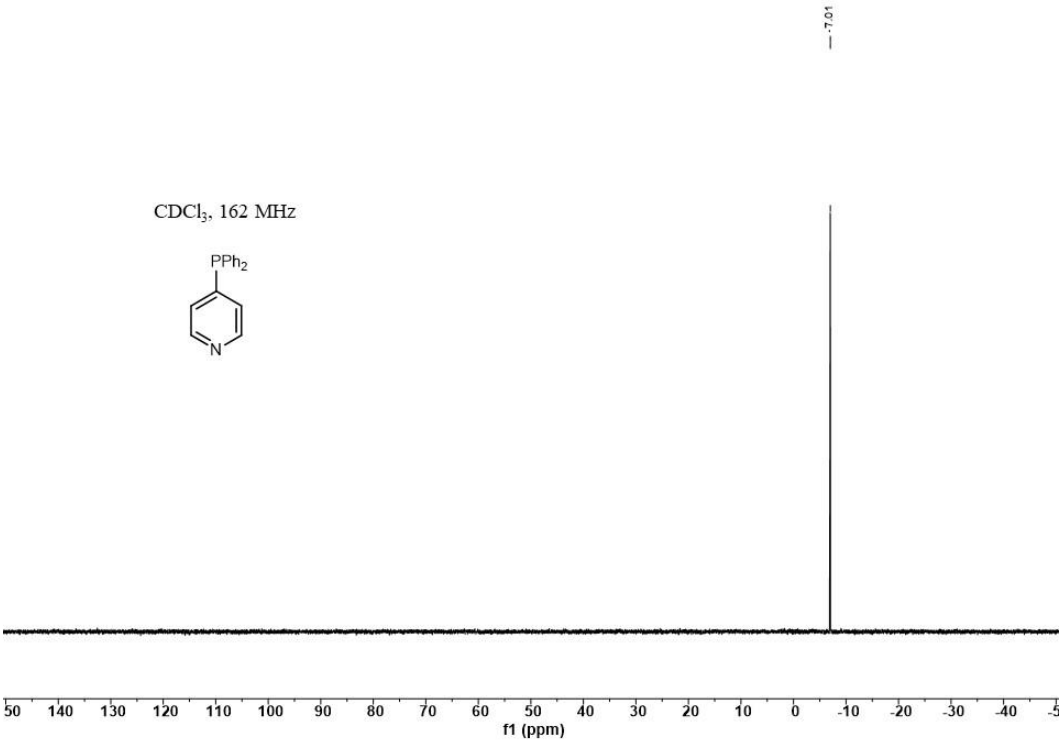
Prepared according to general procedure E using 4-(diphenylphosphaneyl)-2-phenylpyridine (102 mg, 0.30 mmol), ethyl propiolate (46 μL, 0.45 mmol), trifluoromethanesulfonic acid (27 μL, 0.30 mmol), H_2O (54 μL, 3.00 mmol), and EtOH (0.75 mL, 0.4 M) at 80 °C for 24 hours. The crude

material was purified by flash chromatography (silica gel: 2% MeOH in CH_2Cl_2) to provide the title compound as a pale-yellow solid (77 mg, 0.17 mmol, 56% yield). mp 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.48 (d, J = 5.1 Hz, 1H), 8.05 – 7.91 (m, 2H), 7.83 (d, J = 6.8 Hz, 2H), 7.67 – 7.48 (m, 6H), 7.48 – 7.33 (m, 4H), 7.29 (td, J = 9.3, 8.5, 3.9 Hz, 2H), 7.15 (d, J = 4.9 Hz, 1H), 4.13 (ddd, J = 11.3, 7.9, 3.4 Hz, 1H), 3.93 (q, J = 7.1 Hz, 2H), 3.15 (ddd, J = 17.1, 11.2, 6.0 Hz, 1H), 2.92 (ddd, J = 16.8, 9.3, 3.4 Hz, 1H), 1.04 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.99 (d, J = 16.5 Hz), 157.42 (d, J = 1.7 Hz), 149.56, 145.56 (d, J = 5.0 Hz), 139.11, 132.51 (d, J = 2.8 Hz), 132.10 (d, J = 2.8 Hz), 131.46 (d, J = 8.6 Hz), 131.25, 131.08 (d, J = 8.8 Hz), 131.06, 130.17 (d, J = 14.9 Hz), 129.20 (d, J = 11.6 Hz), 129.12, 128.75, 128.55 (d, J = 11.9 Hz), 127.09, 123.22 (d, J = 5.0 Hz), 121.88 (d, J = 5.1 Hz), 61.21, 43.04 (d, J = 65.6 Hz), 34.32, 14.06. IR υ_{max}/cm^{-1} (film): 2983, 1726, 1594, 1554, 1474, 1437, 1407, 1371, 1346, 1319, 1297, 1221, 1198, 1184, 1172, 1143, 1119, 1101, 1073, 1050, 1031, 1016, 907, 896, 850, 838, 793, 775, 762, 742, 725, 709, 693. *m/z* LRMS (ESI + APCI): $[M+H]^+$ calculated for $C_{28}H_{27}NO_3P^+$ = 456.2, found 456.2.

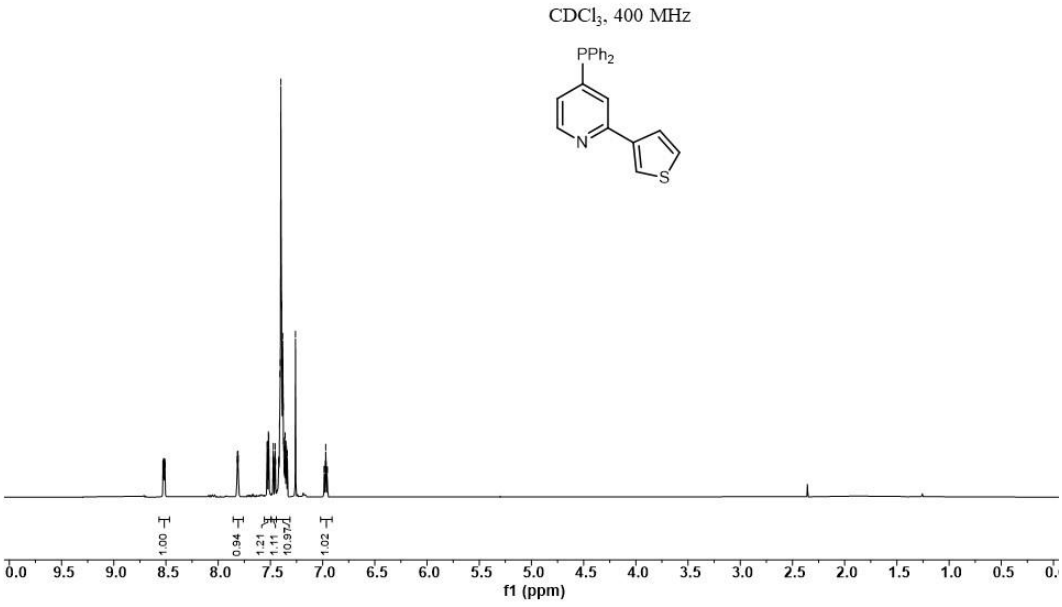
A2.6 Experimental Spectra

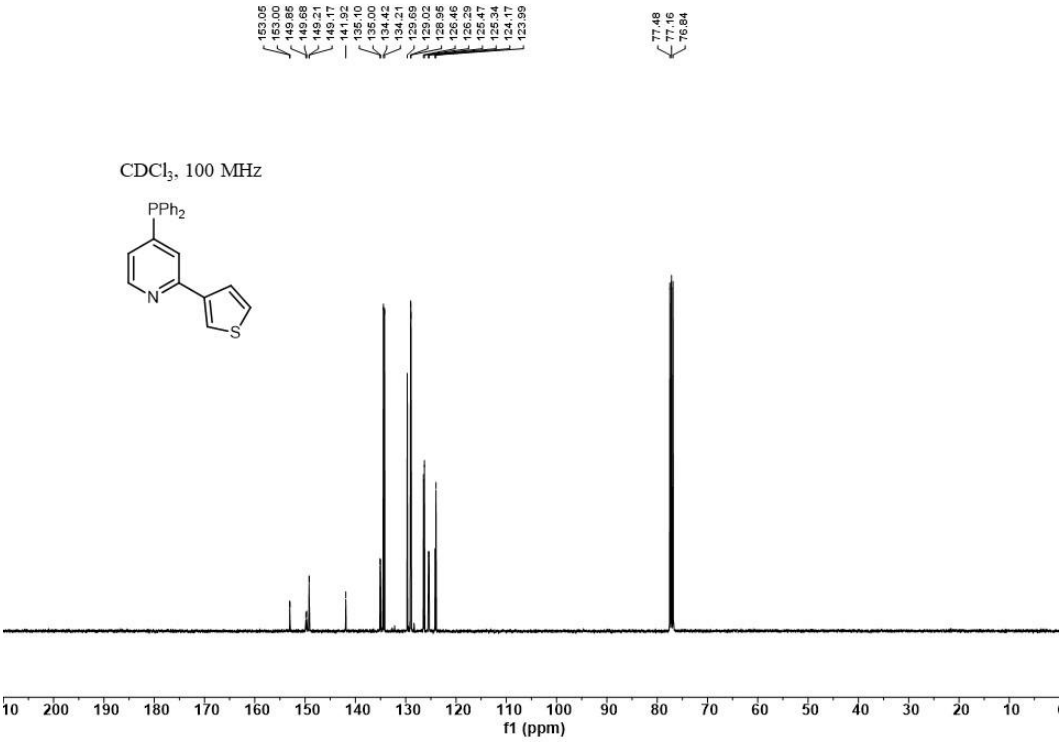


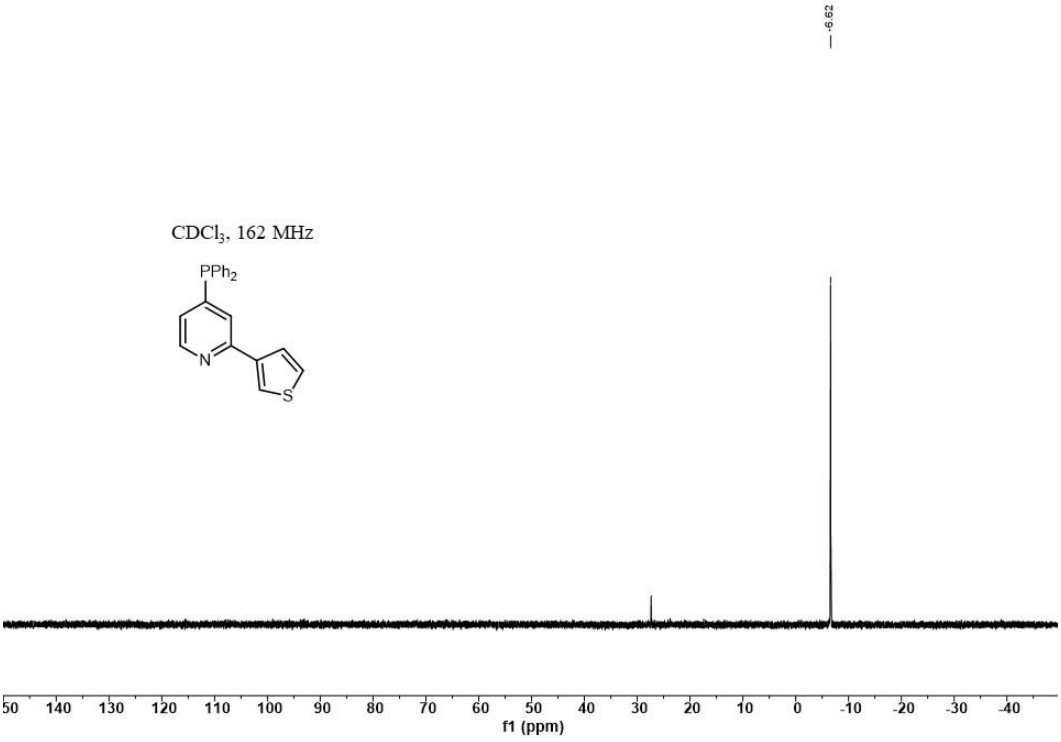



-7.01
CDCl3, 162 MHz
PPh2
N
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

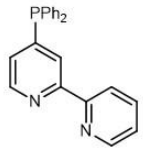

8.63
8.63
8.62
8.62
8.62
8.61
8.61
7.82
7.82
7.81
7.81
7.53
7.53
7.52
7.52
7.48
7.47
7.47
7.46
7.45
7.45
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.39
7.38
7.38
7.37
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.25
6.99
6.98
6.97
6.97
6.96
6.95

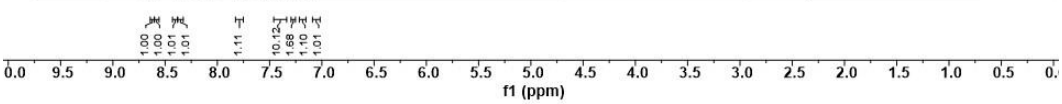

CDCl3, 400 MHz
PPh2
N
S
1.00
0.94
1.21
1.11
10.97
1.02
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


153.06
153.00
149.85
149.68
149.71
149.17
141.92
135.10
135.00
134.42
134.21
129.69
129.02
128.95
126.46
126.29
125.47
125.34
124.17
123.99
77.48
77.16
76.84
CDCl3, 100 MHz
PPh2
N
S
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

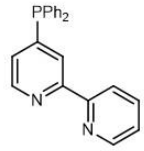

-6.62
CDCl3, 162 MHz
PPh2
N
S
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

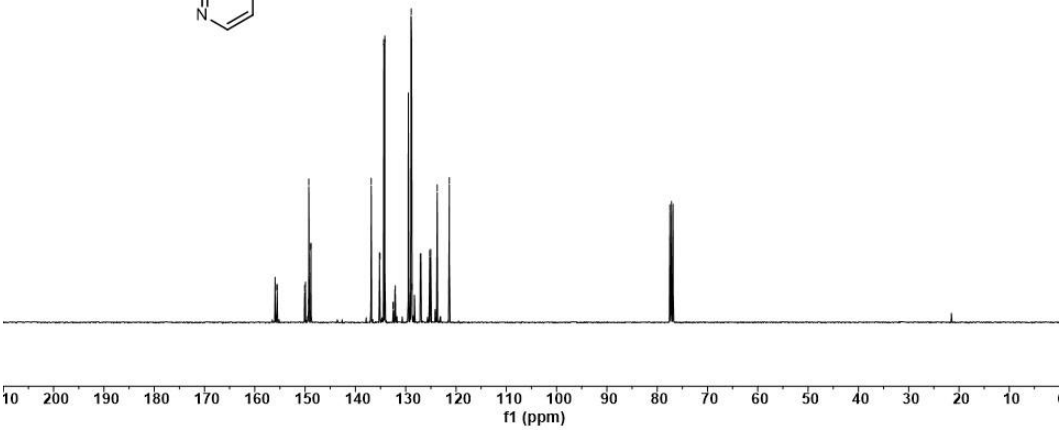
$CDCl_3$, 400 MHz



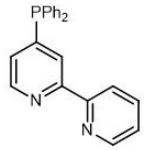


$CDCl_3$, 100 MHz

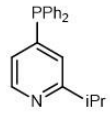


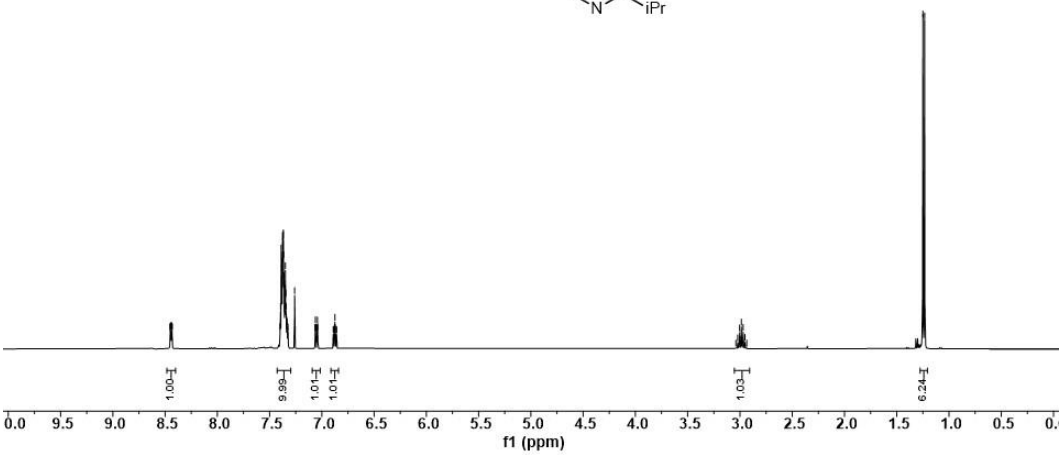


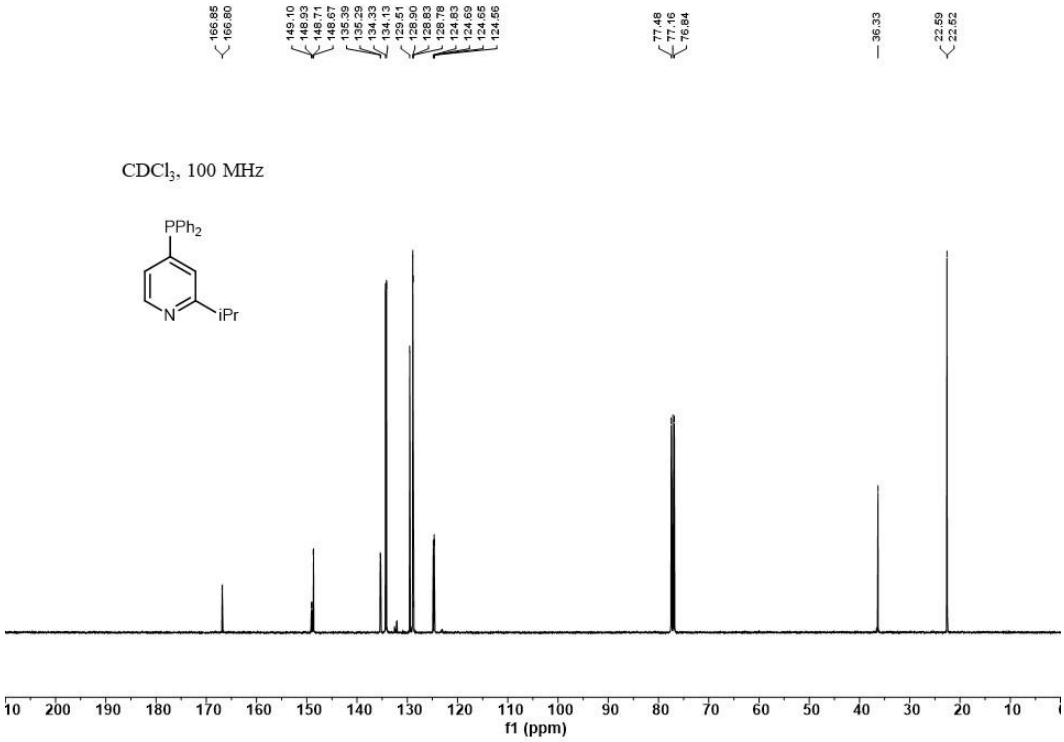
$CDCl_3$, 162 MHz

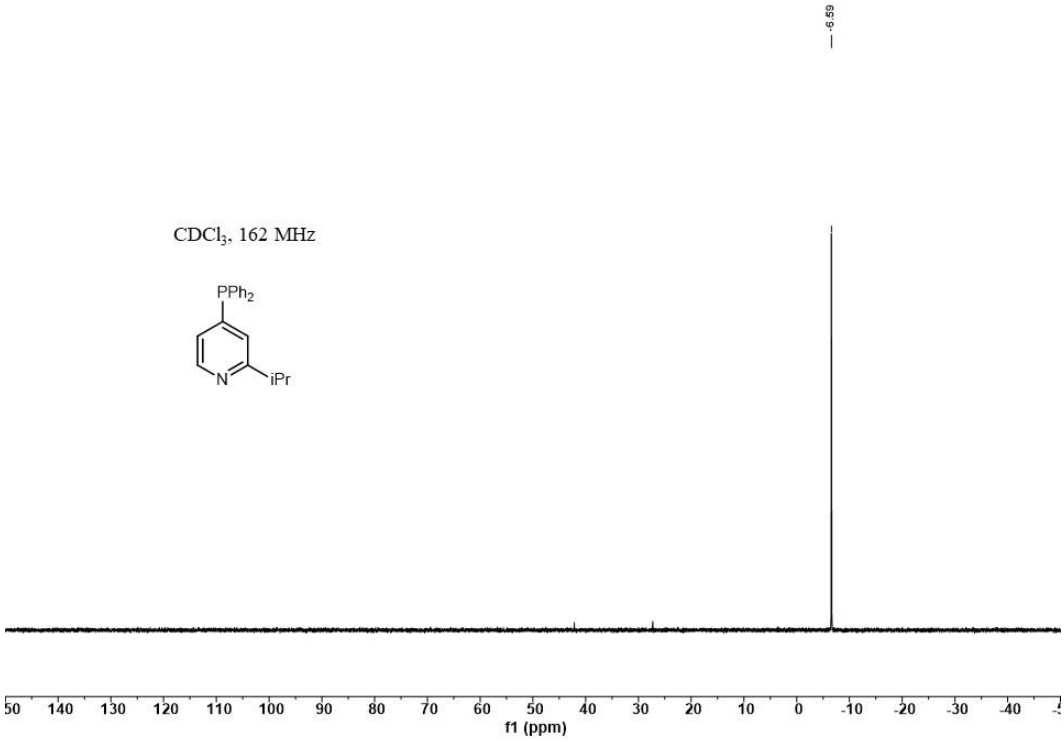


$CDCl_3$, 400 MHz

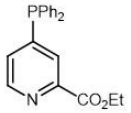


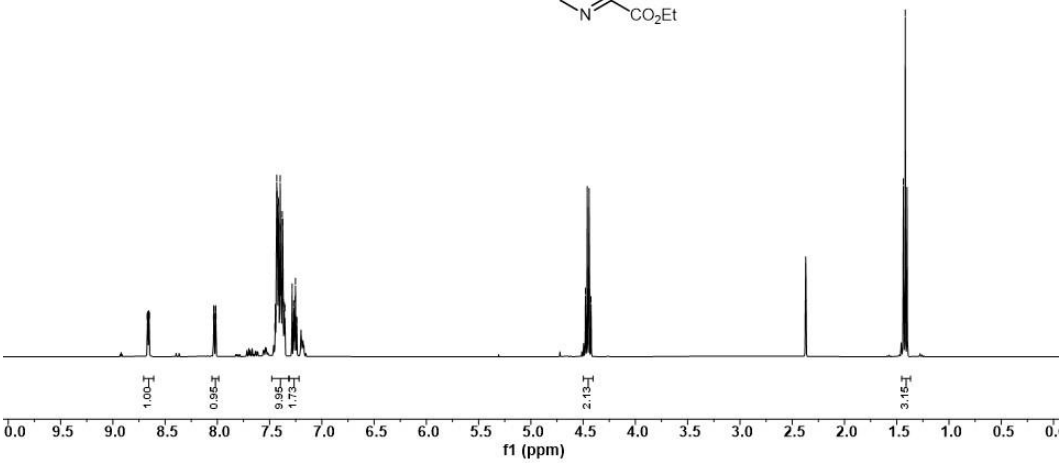



166.85
166.80
149.10
148.93
148.71
148.67
135.39
135.29
134.33
134.13
129.51
128.90
128.83
128.79
124.83
124.69
124.65
124.56
77.48
77.16
76.84
36.33
22.59
22.52
CDCl3, 100 MHz
PPh2
N
iPr
f1 (ppm)

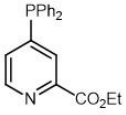

-6.59
CDCl3, 162 MHz
PPh2
N
iPr
f1 (ppm)

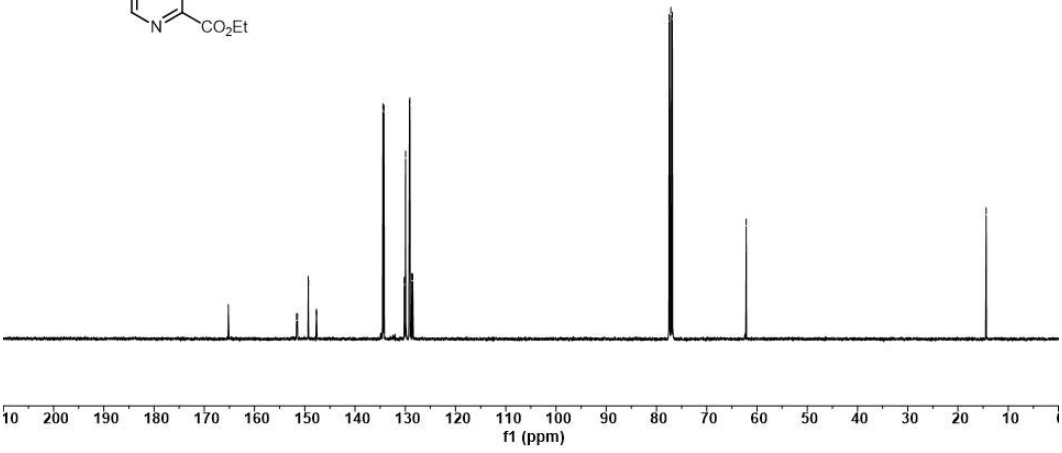
$CDCl_3$, 400 MHz

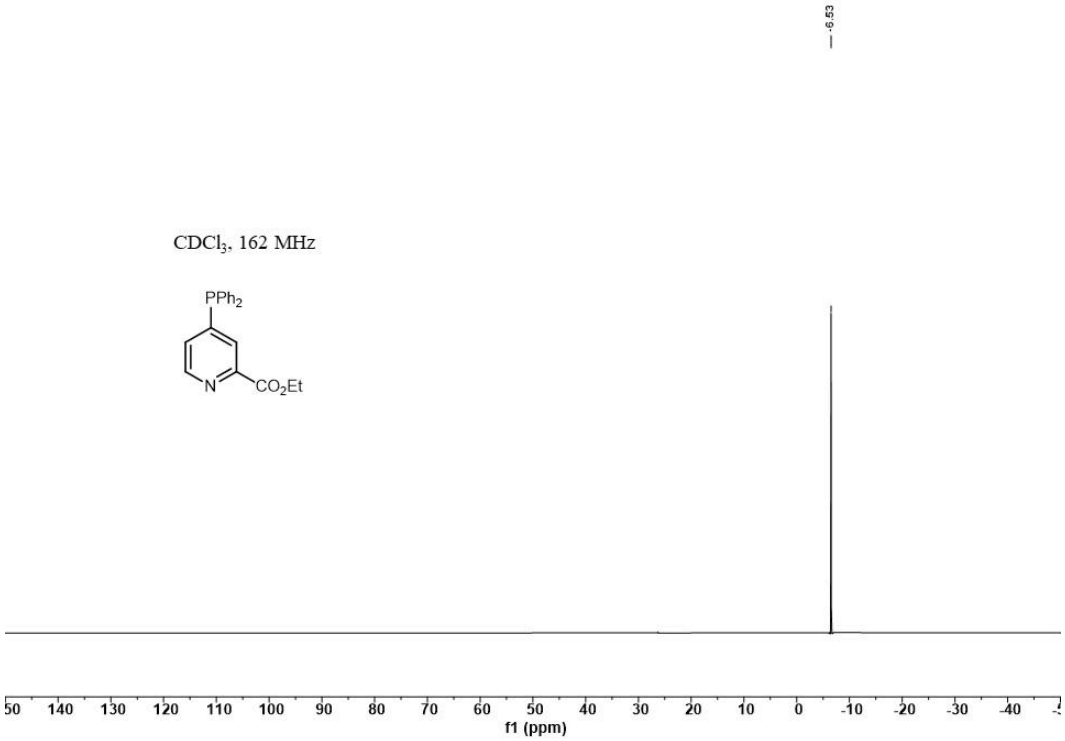


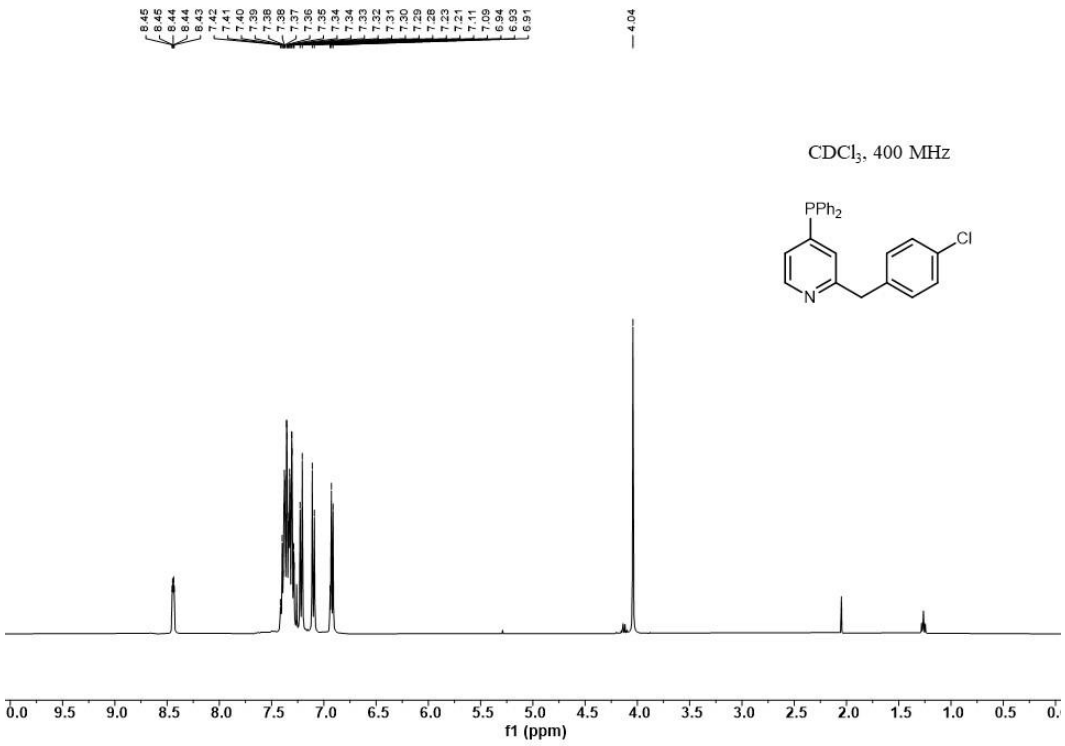


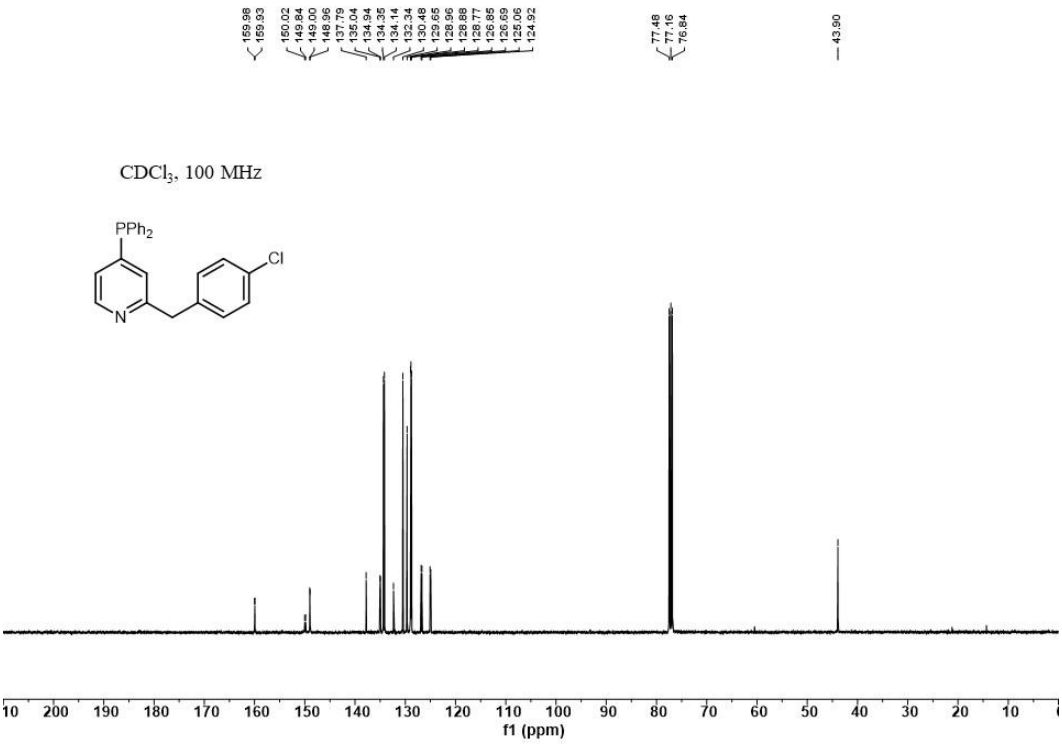
$CDCl_3$, 100 MHz

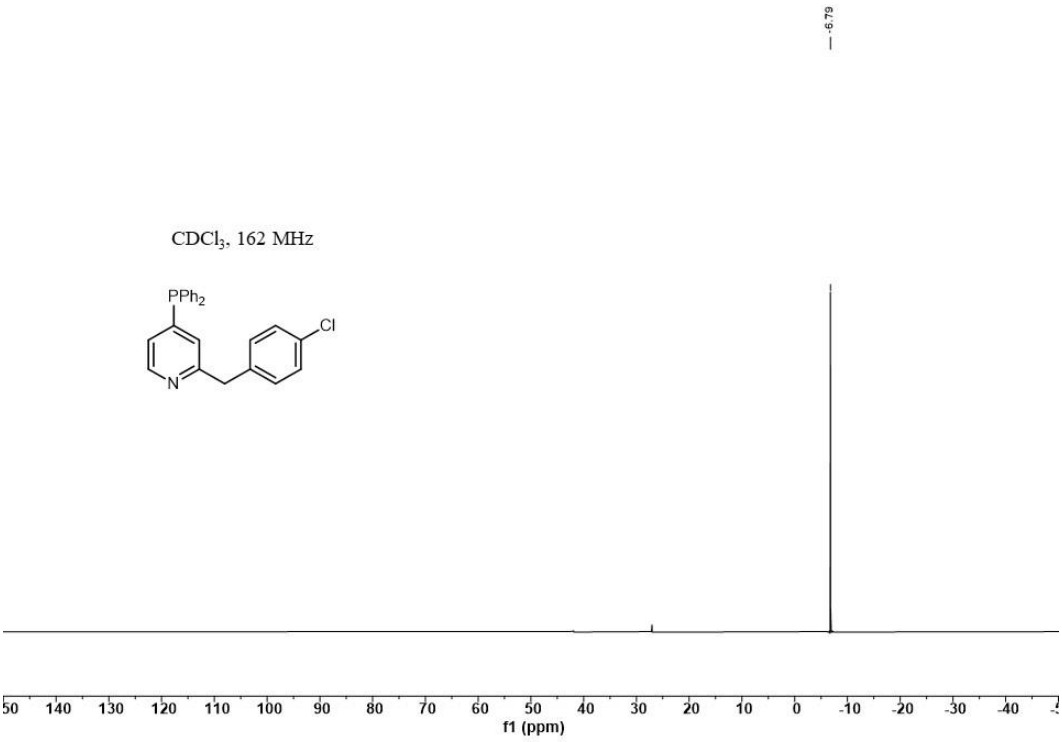




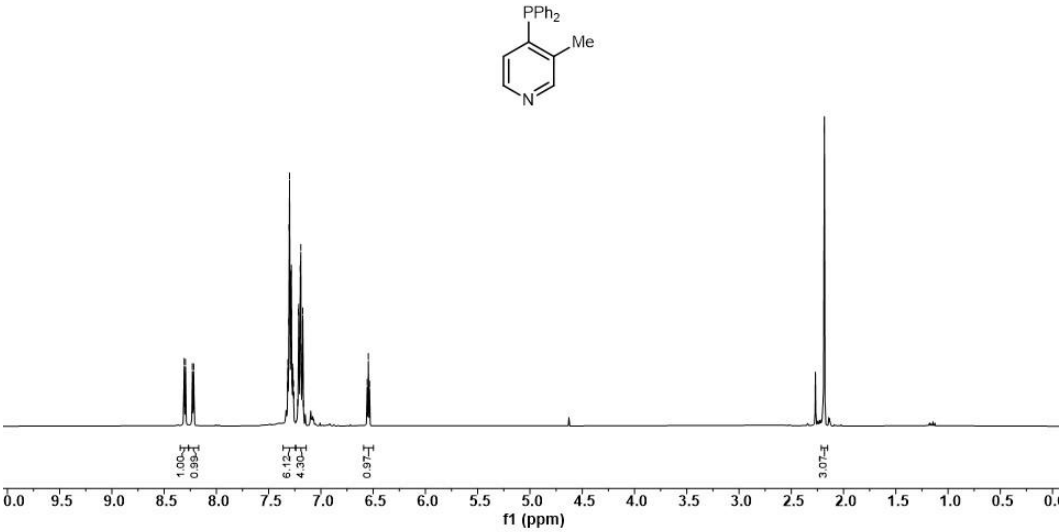

-6.53
CDCl3, 162 MHz
PPh2
N
CO2Et
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

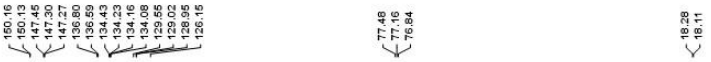

8.45
8.45
8.44
8.44
8.43
7.42
7.41
7.40
7.39
7.38
7.38
7.37
7.36
7.35
7.34
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.23
7.21
7.11
7.09
6.94
6.93
6.91
4.04
CDCl3, 400 MHz
PPh2
Cl
N
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


159.98
159.93
150.02
149.84
149.00
148.96
137.79
135.04
134.94
134.35
134.14
132.34
130.48
129.65
128.96
128.88
128.77
126.85
126.69
125.06
124.92
77.48
77.16
76.84
43.90
CDCl3, 100 MHz
PPh2
Cl
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

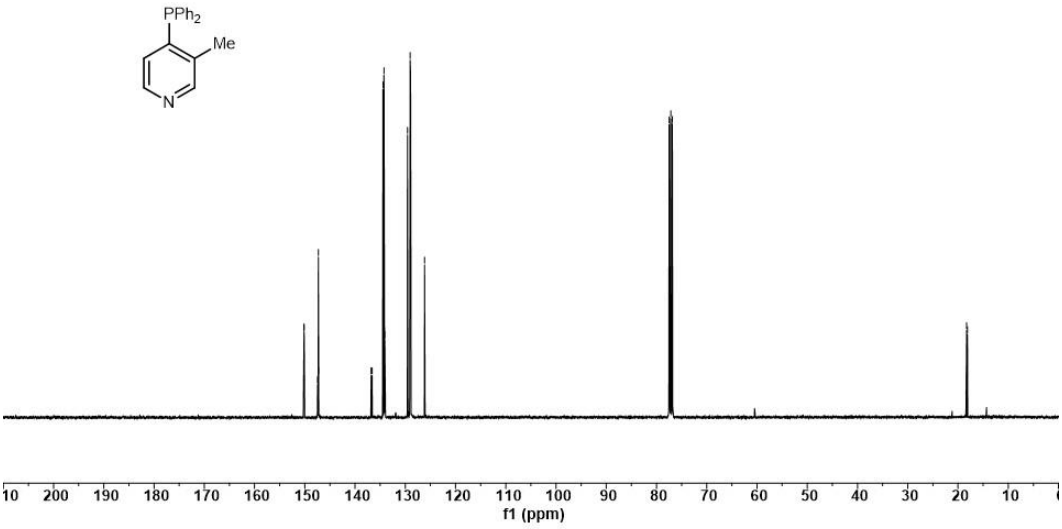

-6.79
CDCl3, 162 MHz
PPh2
Cl
N
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

$CDCl_3$, 400 MHz

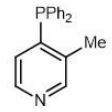




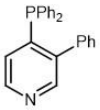
$CDCl_3$, 100 MHz

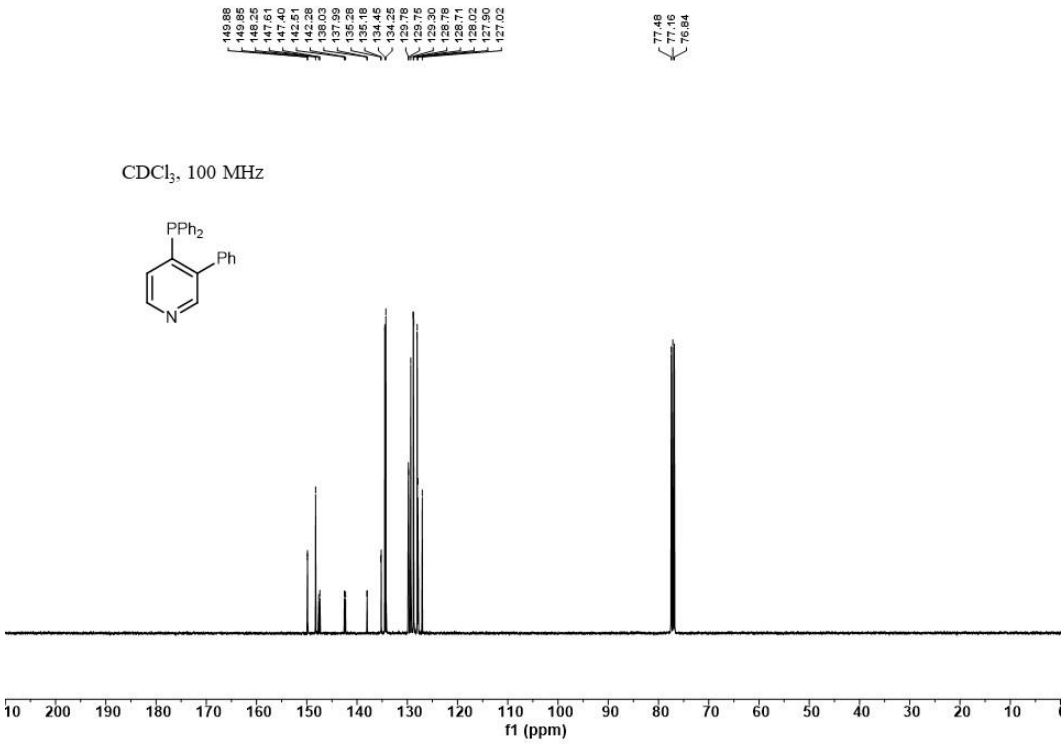


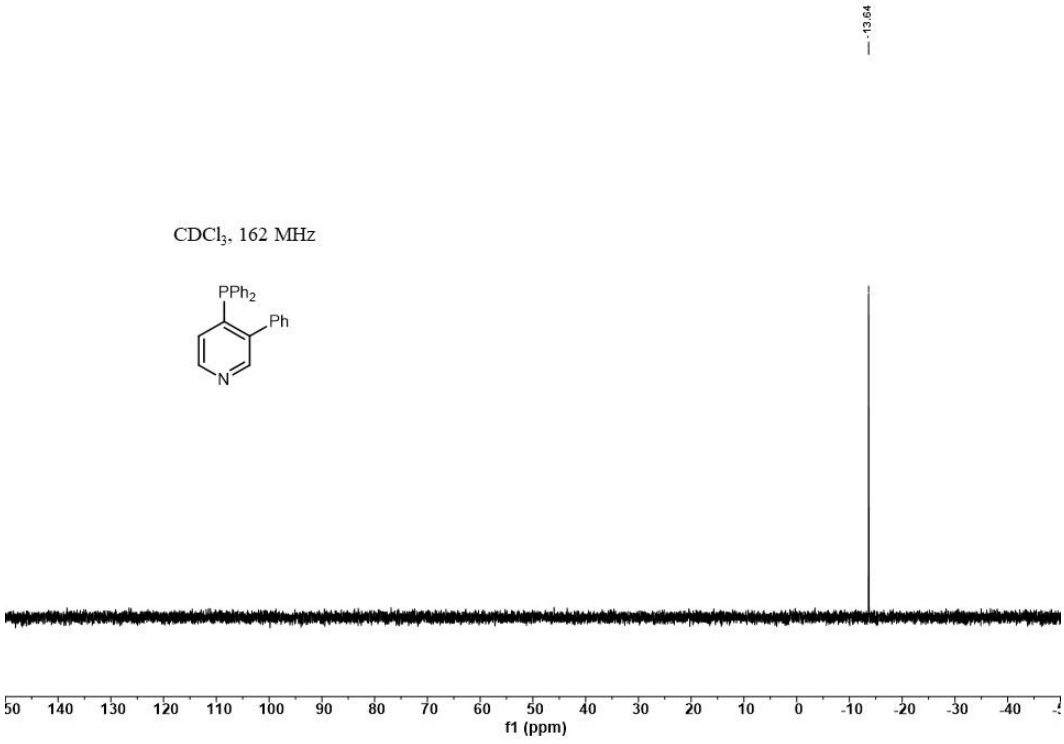
$CDCl_3$, 162 MHz



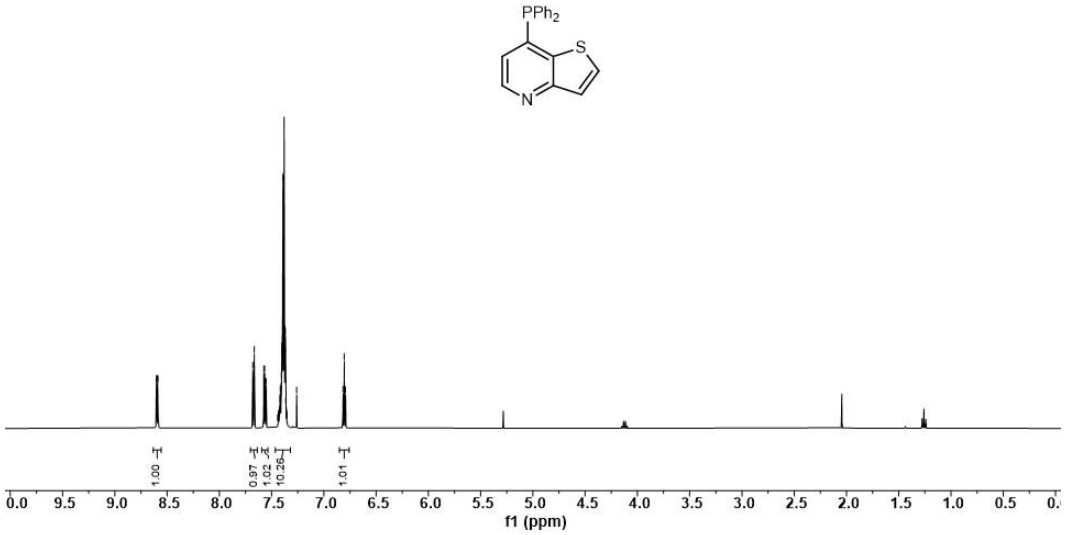
$CDCl_3$, 400 MHz



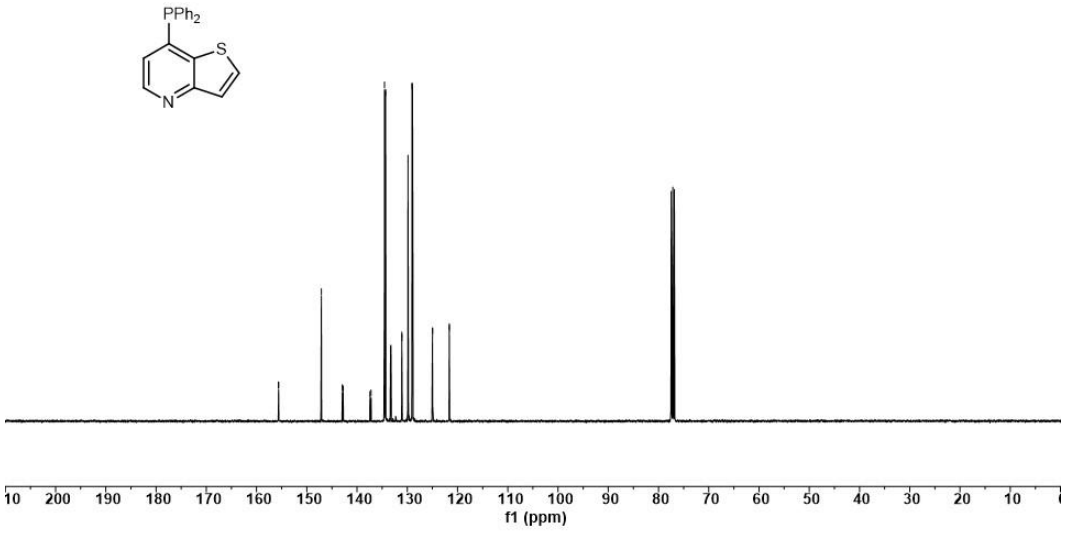

149.88
149.85
148.25
147.61
147.40
142.51
142.28
138.03
137.99
135.28
135.18
134.45
134.25
129.78
129.75
129.30
128.78
128.71
128.02
127.90
127.02
77.48
77.16
76.84
CDCl3, 100 MHz
PPh2
Ph
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-13.64
CDCl3, 162 MHz
PPh2
Ph
N
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

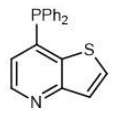
$CDCl_3$, 400 MHz



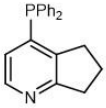
$CDCl_3$, 100 MHz

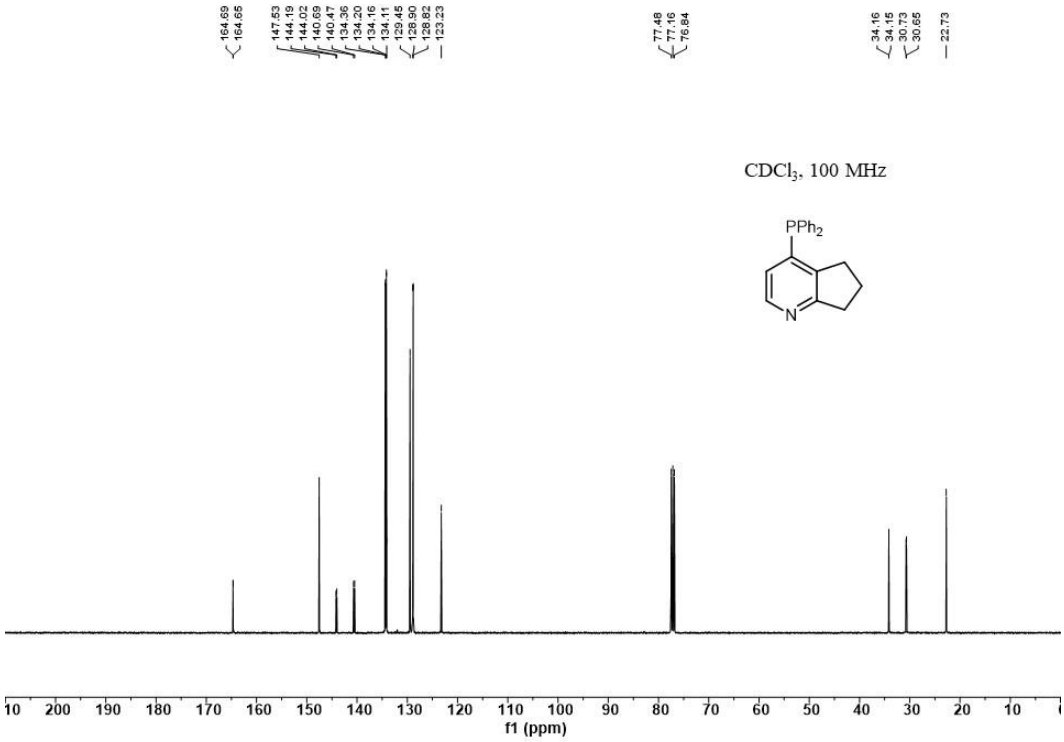


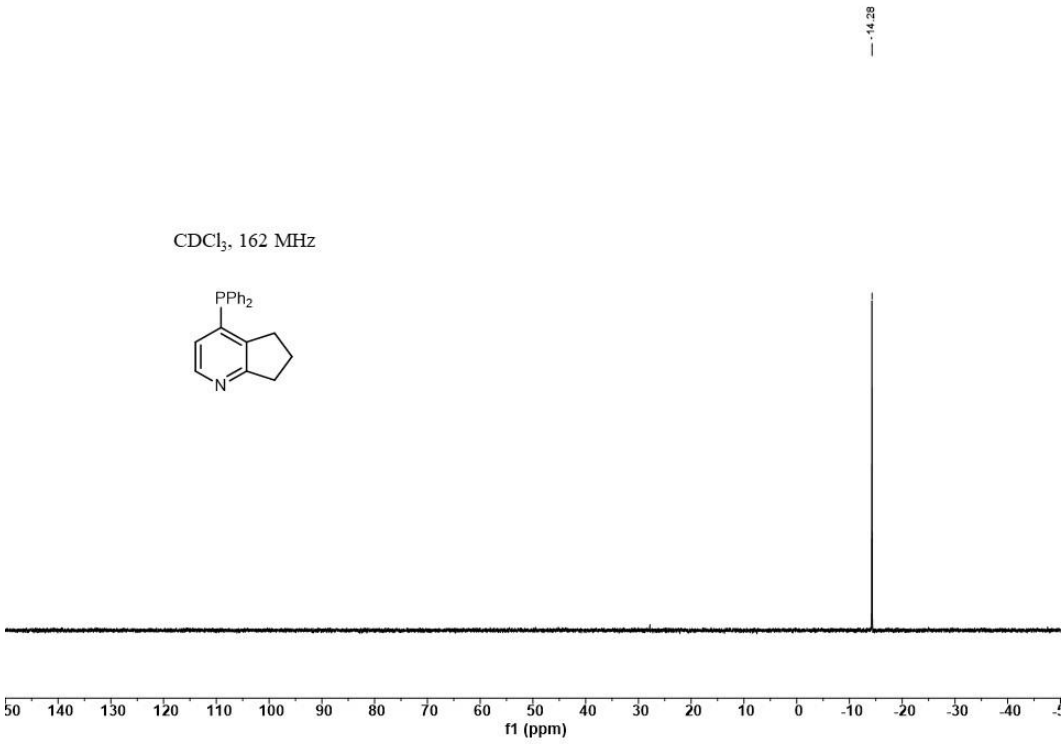
$CDCl_3$, 162 MHz



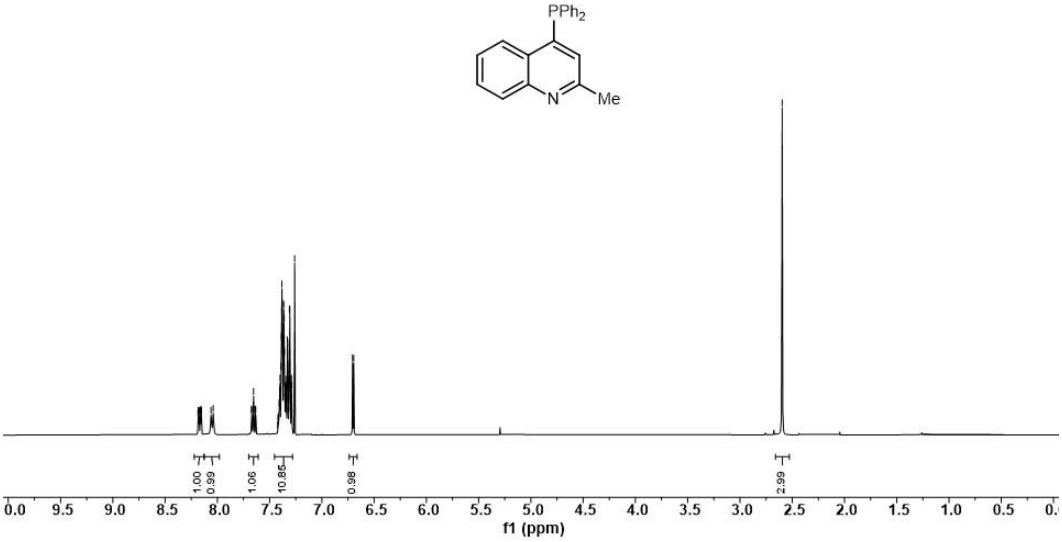
$CDCl_3$, 400 MHz



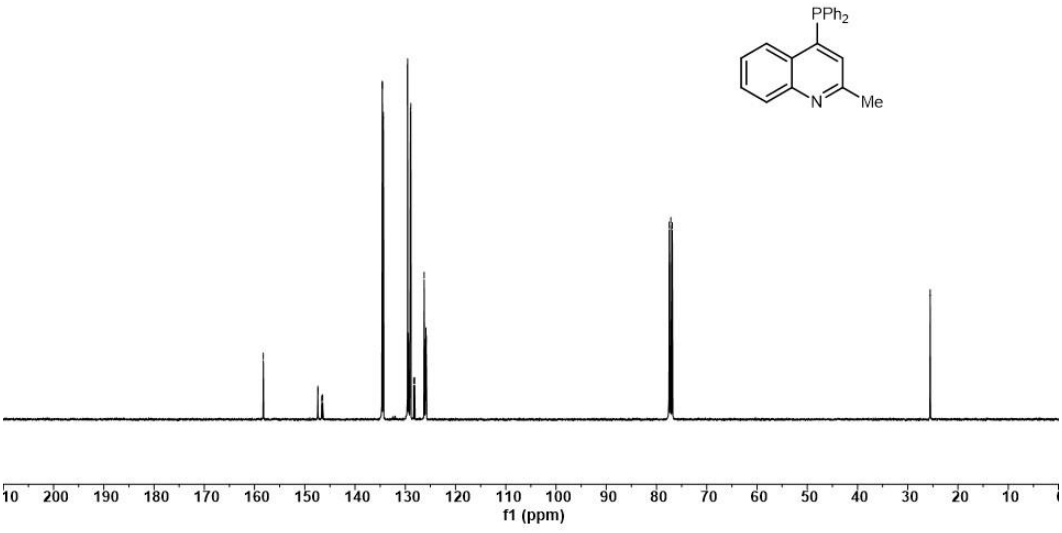

164.69
164.65
147.53
144.19
144.02
140.69
140.47
134.36
134.20
134.16
134.11
129.45
128.90
128.82
123.23
77.48
77.16
76.84
34.16
34.15
30.73
30.65
22.73
CDCl3, 100 MHz
PPh2
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

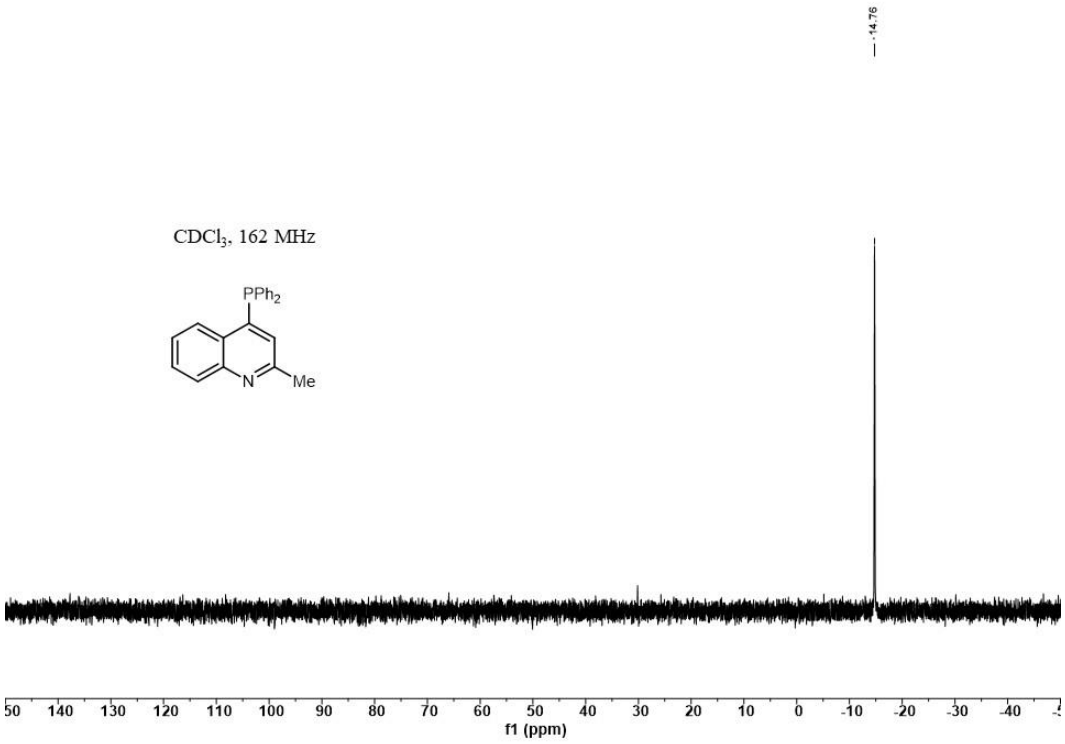

-14.28
CDCl3, 162 MHz
PPh2
N
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

$CDCl_3$, 400 MHz



$CDCl_3$, 100 MHz




-14.76
CDCl3, 162 MHz
PPh2
N
Me
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)


8.76
8.75
8.45
8.44
8.44
8.43
8.00
7.98
7.77
7.76
7.75
7.74
7.43
7.42
7.41
7.39
7.39
7.37
7.37
7.36
7.35
7.35
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7.32
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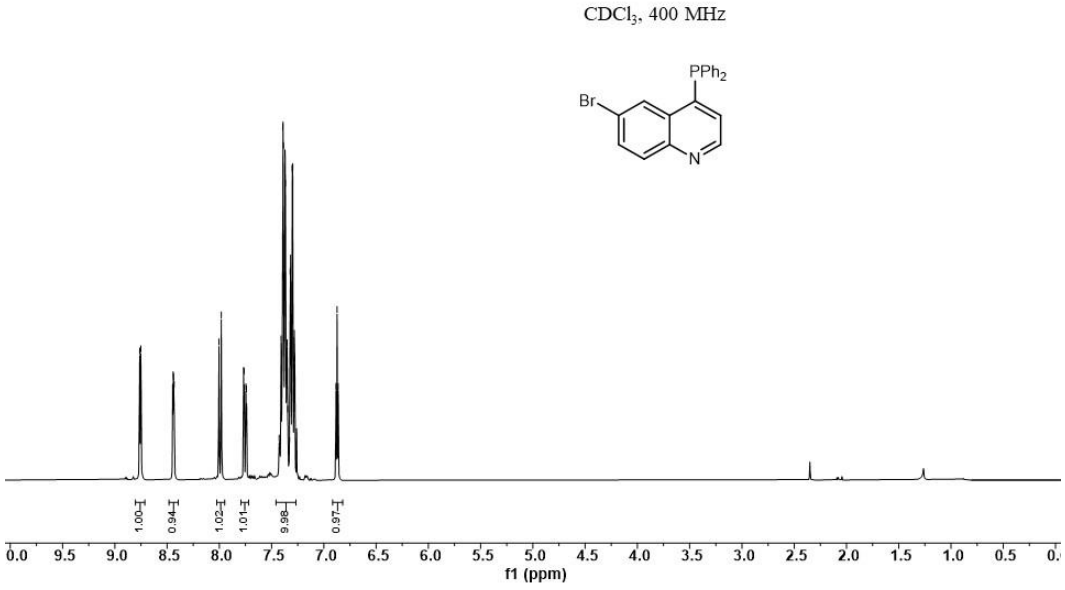
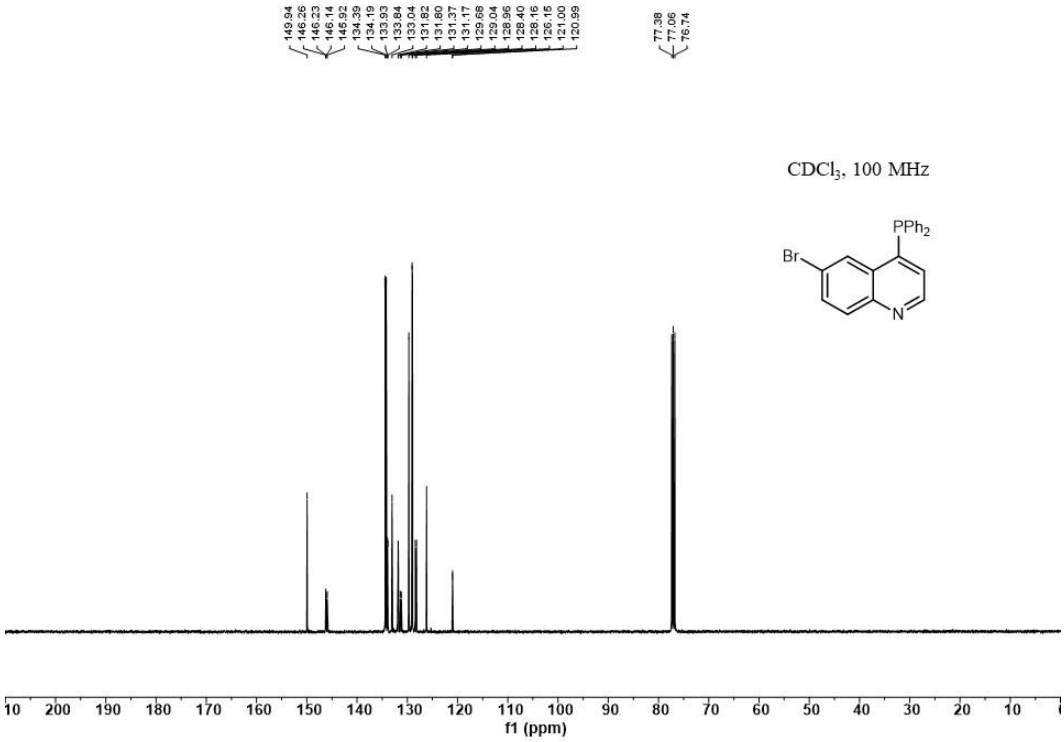
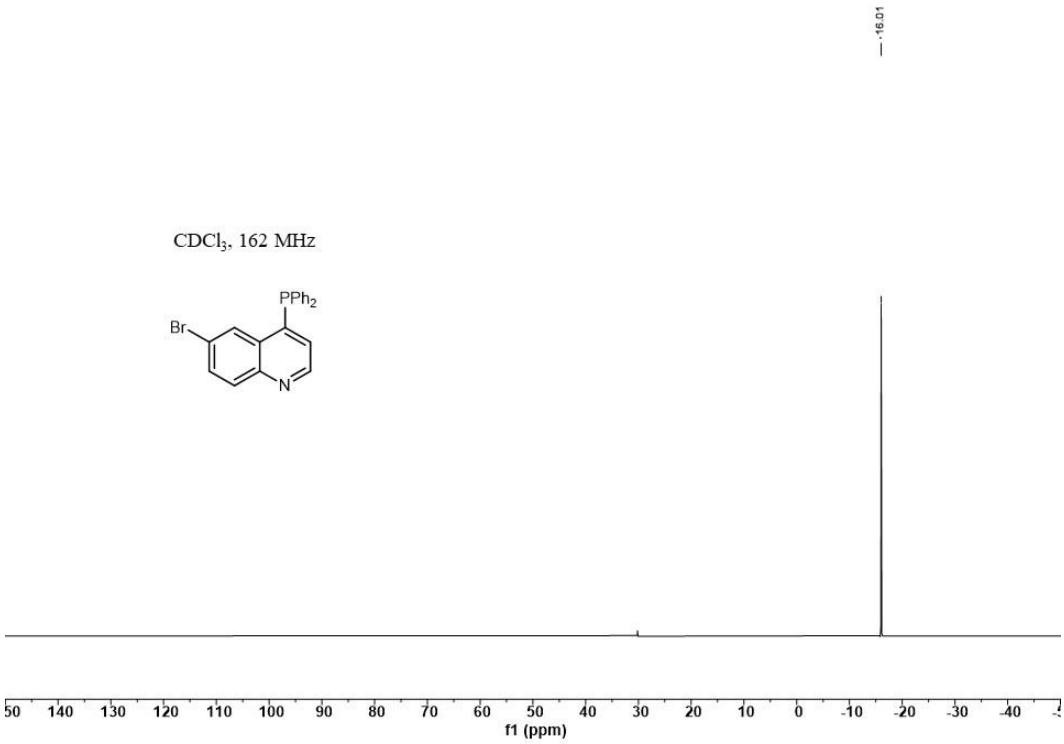
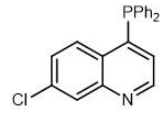
7.30
7.30
7.28
7.28
6.88
6.87
6.86

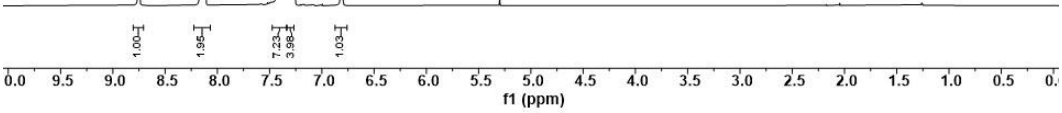

CDCl3, 400 MHz
PPh2
Br
N
1.00
0.94
1.02
1.01
9.98
0.97
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

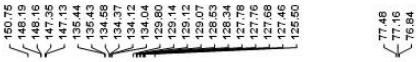

149.94
146.26
146.23
146.14
145.92
134.39
134.19
133.93
133.84
133.04
131.82
131.80
131.37
131.17
129.68
129.04
128.96
128.40
128.16
126.15
121.00
120.99
77.38
77.06
76.74
CDCl3, 100 MHz
PPh2
Br
N
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-16.01
CDCl3, 162 MHz
PPh2
Br
N
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

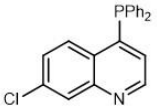
$CDCl_3$, 400 MHz

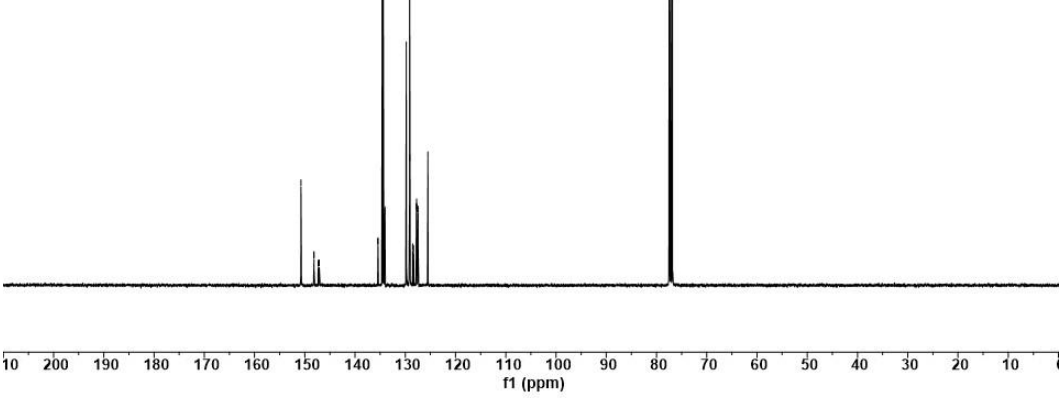




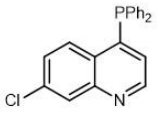


$CDCl_3$, 100 MHz

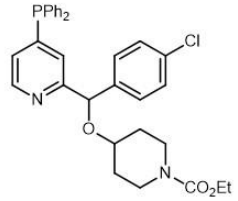


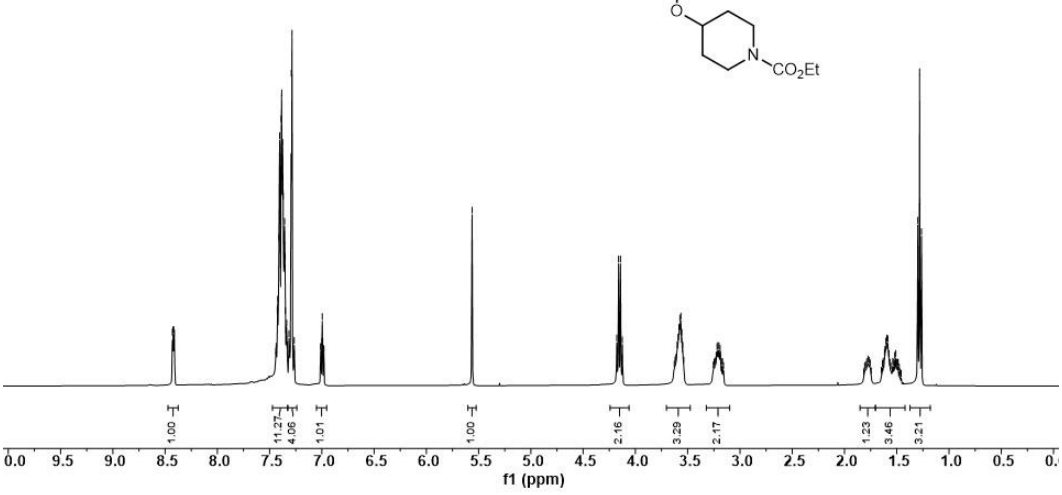


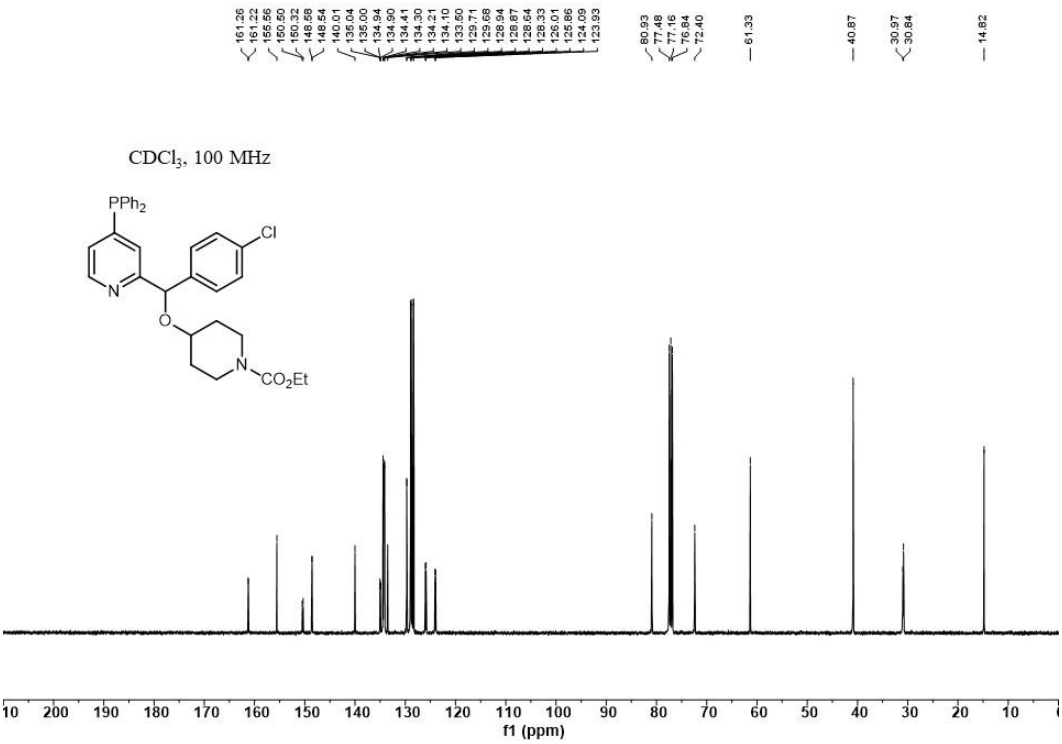
$CDCl_3$, 162 MHz

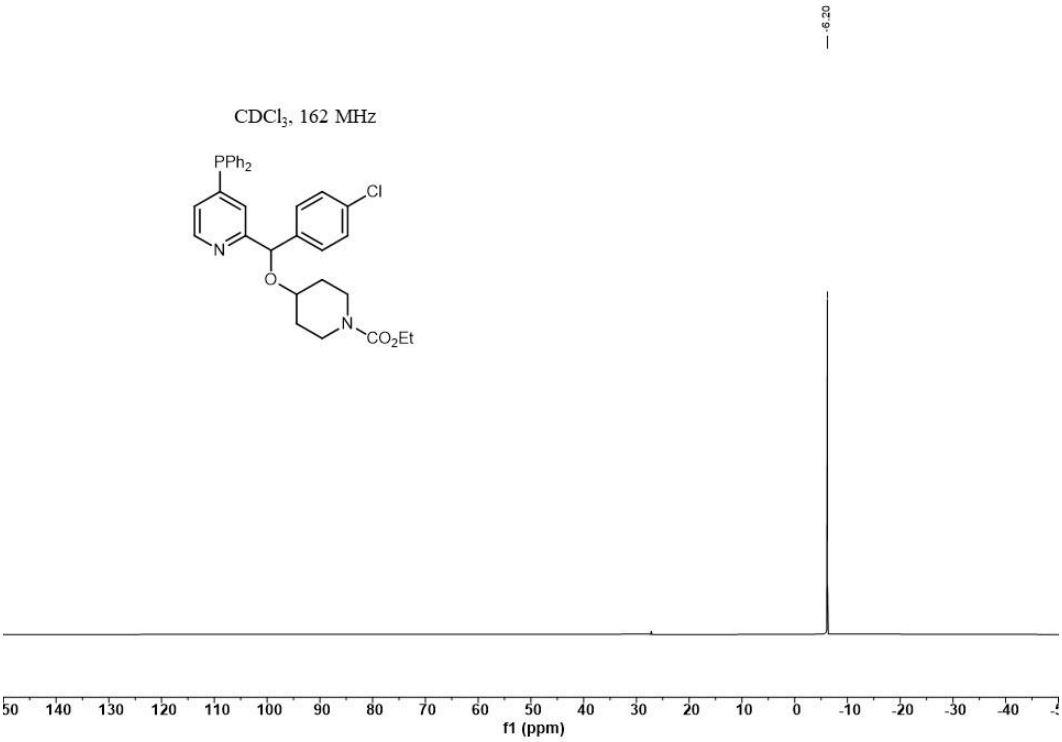


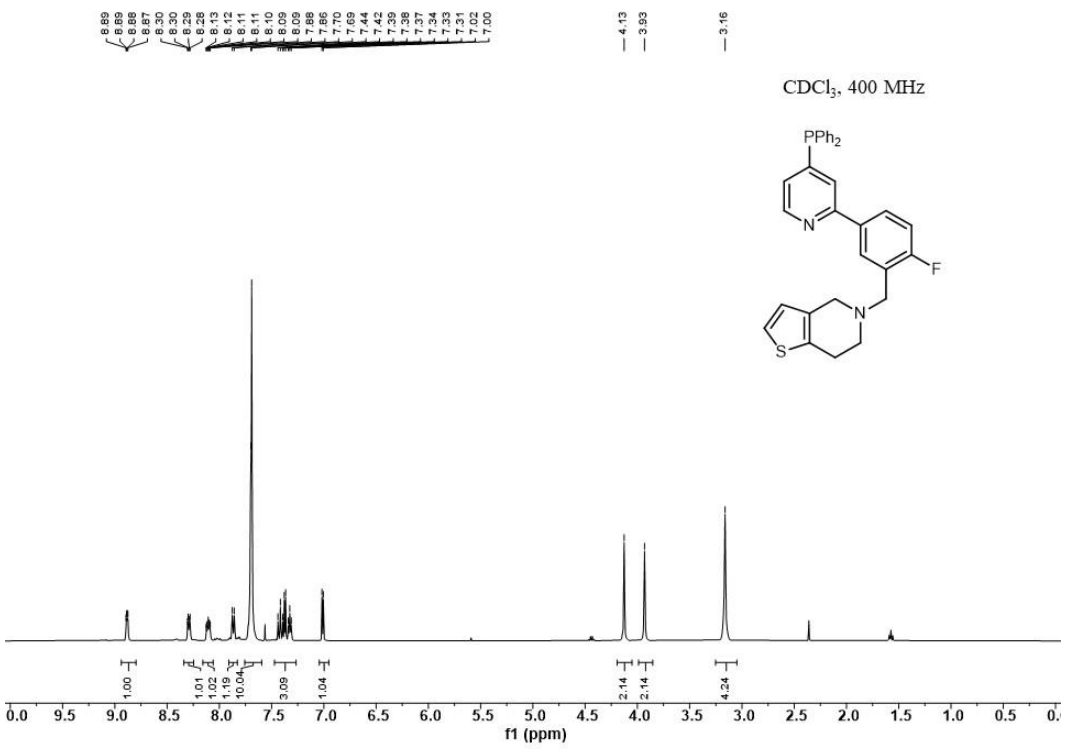
$CDCl_3$, 400 MHz

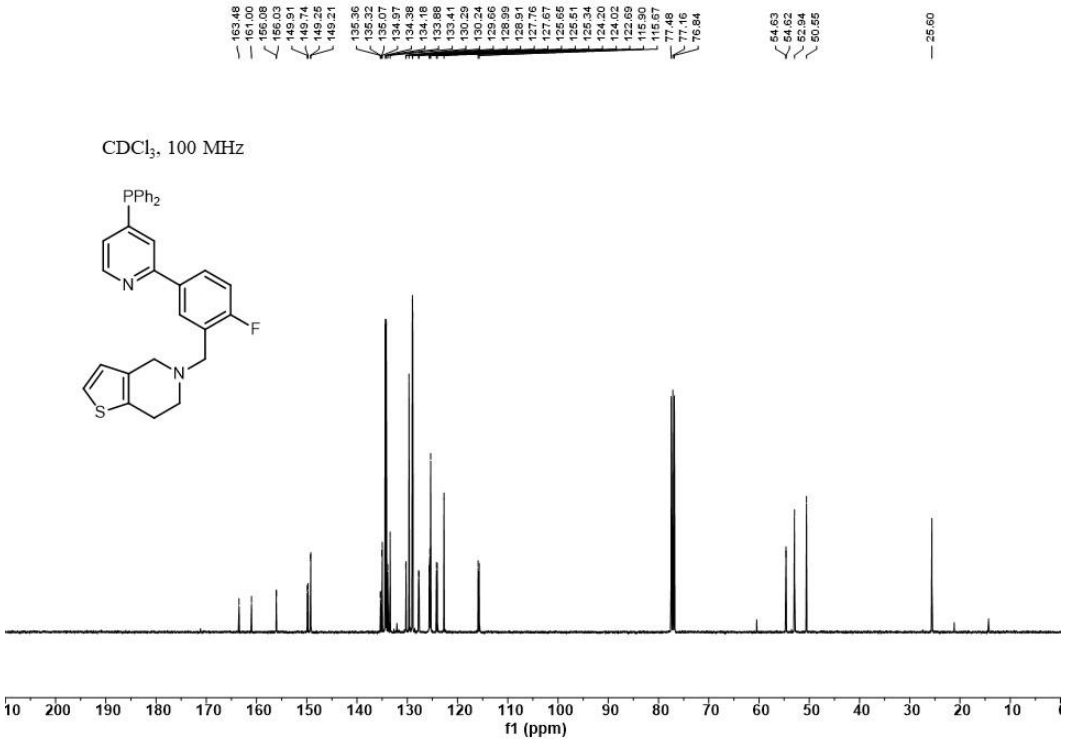




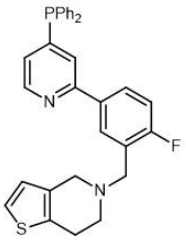

161.26
161.22
155.56
150.50
150.32
148.58
148.54
140.01
135.04
135.00
134.94
134.90
134.41
134.30
134.21
134.10
133.50
129.71
129.68
128.94
128.87
128.64
128.33
126.01
125.86
124.09
123.93
80.93
77.48
77.16
76.84
72.40
61.33
40.87
30.97
30.84
14.82
CDCl3, 100 MHz
PPh2
Cl
N
O
N
CO2Et
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-6.20
CDCl3, 162 MHz
PPh2
Cl
N
O
N
CO2Et
50 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

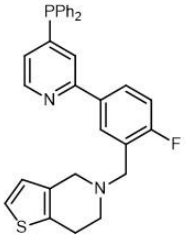

8.89
8.89
8.88
8.87
8.30
8.30
8.29
8.28
8.13
8.12
8.11
8.11
8.10
8.09
8.09
8.09
7.88
7.86
7.70
7.69
7.44
7.42
7.39
7.38
7.37
7.34
7.33
7.31
7.02
7.00
4.13
3.93
3.16
CDCl3, 400 MHz
PPh2
N
F
N
S
1.00
1.01
1.02
1.19
10.04
3.09
1.04
2.14
2.14
4.24
f1 (ppm)

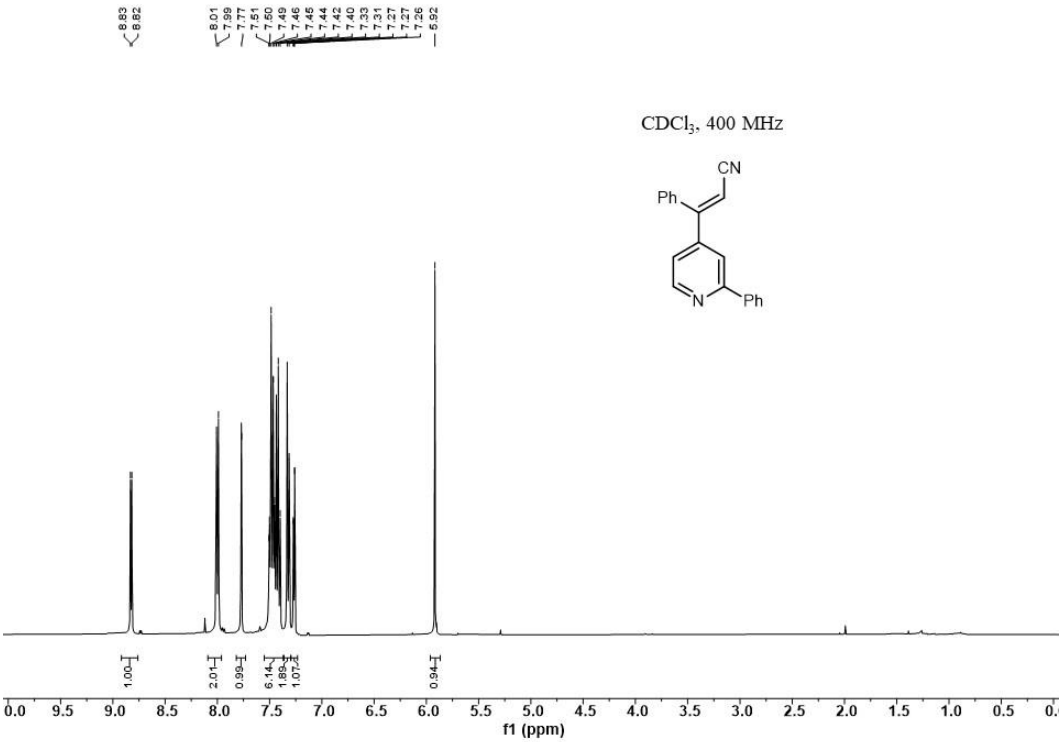

163.48
161.00
156.08
156.03
149.91
149.74
149.26
149.21
135.36
135.32
135.07
134.97
134.38
134.18
133.88
133.41
130.29
130.24
129.66
128.99
128.91
127.76
127.67
126.66
125.51
125.34
124.20
124.02
122.69
116.90
115.67
77.48
77.16
76.84
54.63
54.62
52.94
50.55
25.60
CDCl3, 100 MHz
PPh2
N
F
N
S
f1 (ppm)

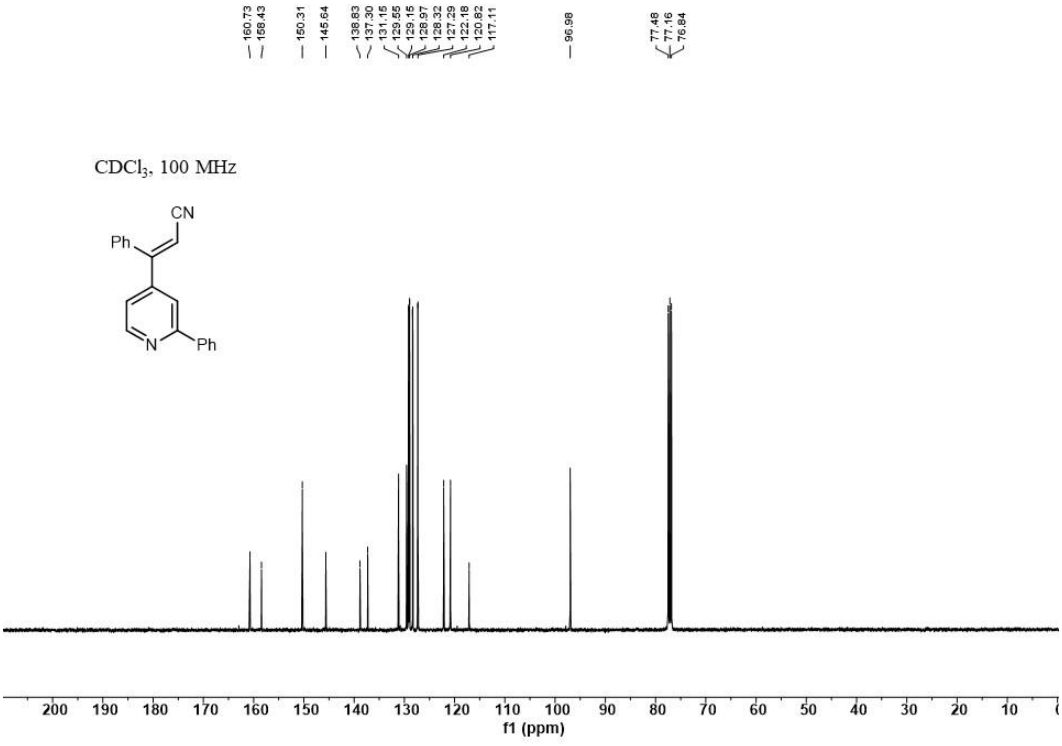
$CDCl_3$, 162 MHz

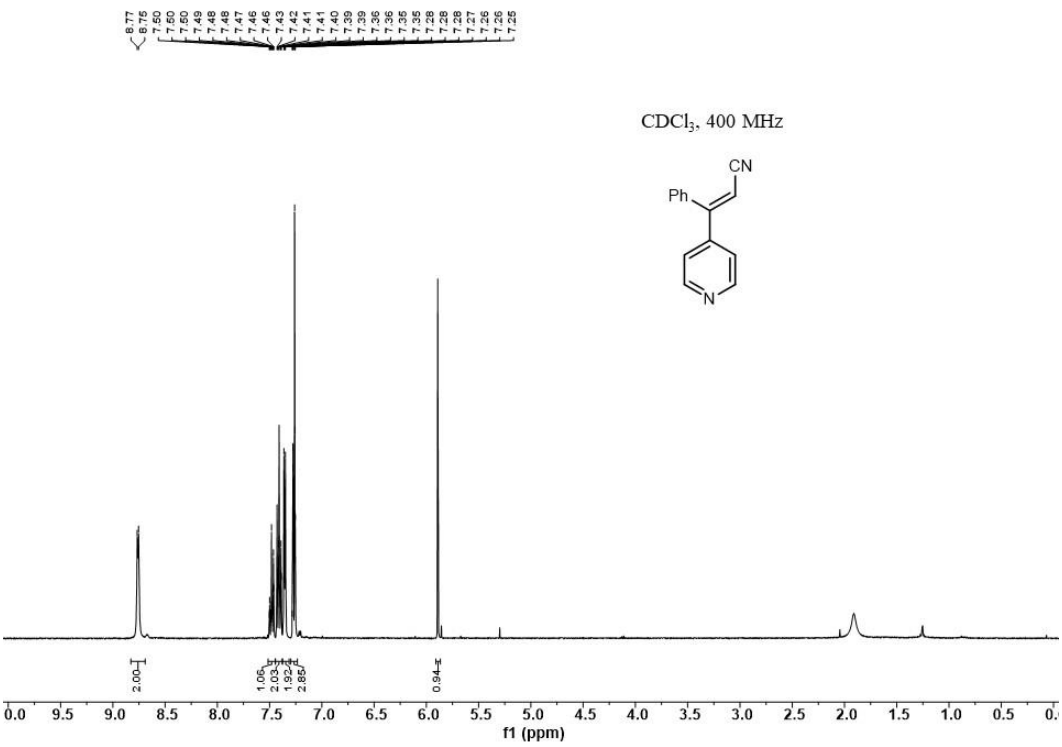


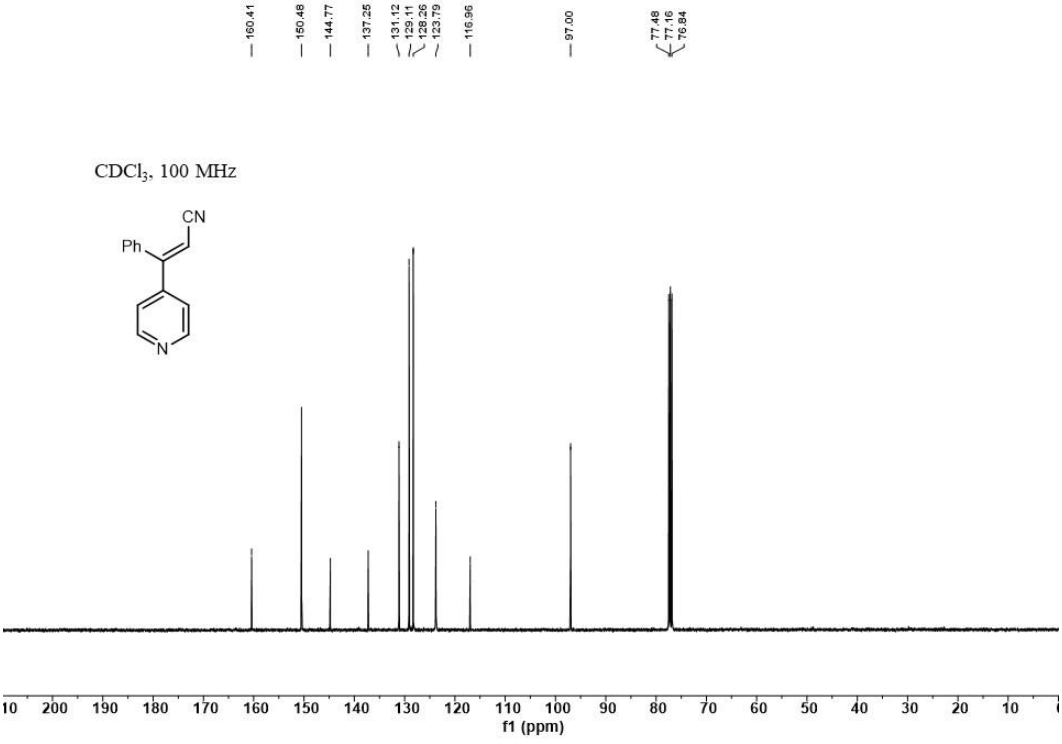
$CDCl_3$, 376 MHz



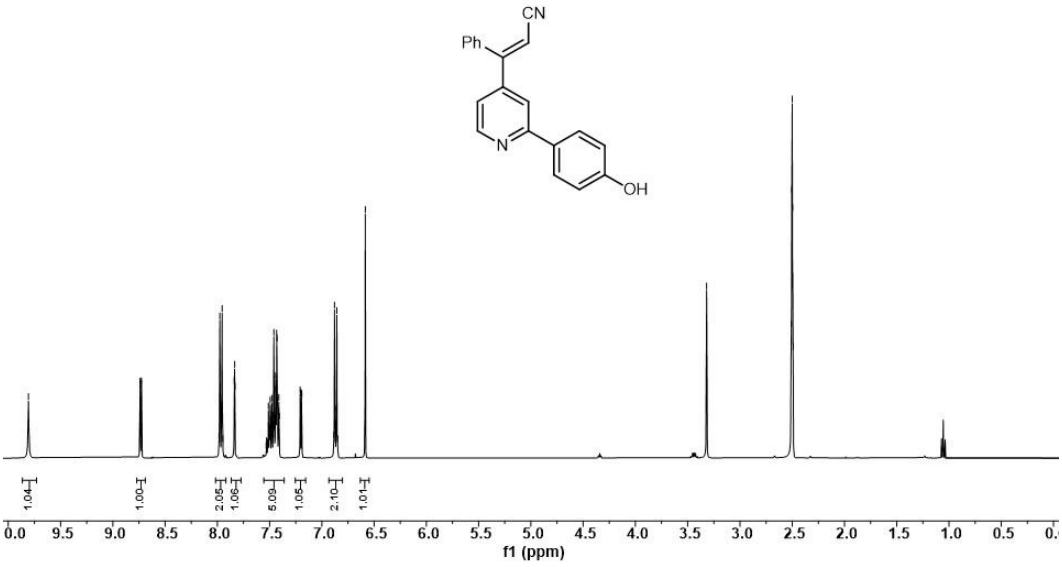

8.83
8.82
8.01
7.99
7.77
7.51
7.50
7.49
7.46
7.45
7.44
7.42
7.40
7.33
7.31
7.27
7.27
7.27
7.26
6.92
CDCl3, 400 MHz
CN
Ph
N
Ph
1.00
2.01
0.99
6.14
1.89
1.07
0.94
f1 (ppm)

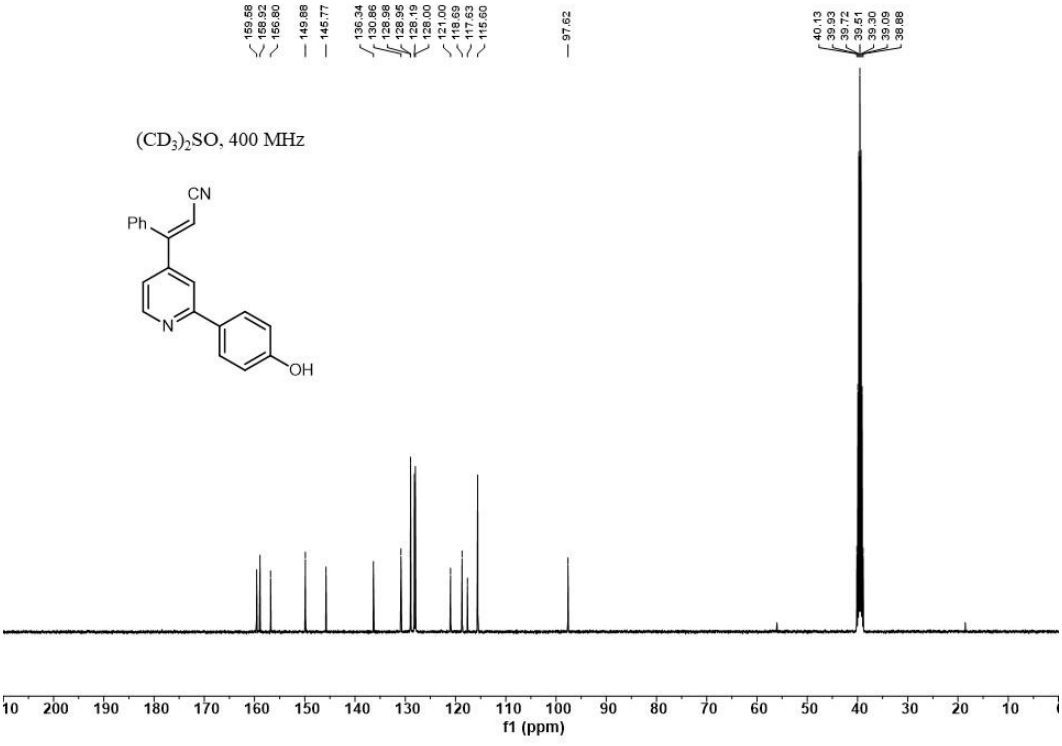

160.73
158.43
150.31
145.64
138.83
137.30
131.15
129.55
129.15
128.97
128.32
127.29
122.18
120.82
117.11
96.98
77.48
77.16
76.84
CDCl3, 100 MHz
CN
Ph
N
Ph
f1 (ppm)


8.77
8.75
7.50
7.50
7.50
7.49
7.48
7.48
7.47
7.46
7.46
7.43
7.42
7.41
7.41
7.40
7.39
7.39
7.36
7.36
7.35
7.28
7.28
7.28
7.27
7.26
7.26
7.25
CDCl3, 400 MHz
CN
Ph
N
2.00
1.06
2.03
1.92
2.85
0.94
f1 (ppm)


160.41
150.48
144.77
137.25
131.12
129.11
128.26
123.79
116.96
97.00
77.48
77.16
76.84
CDCl3, 100 MHz
CN
Ph
N
f1 (ppm)

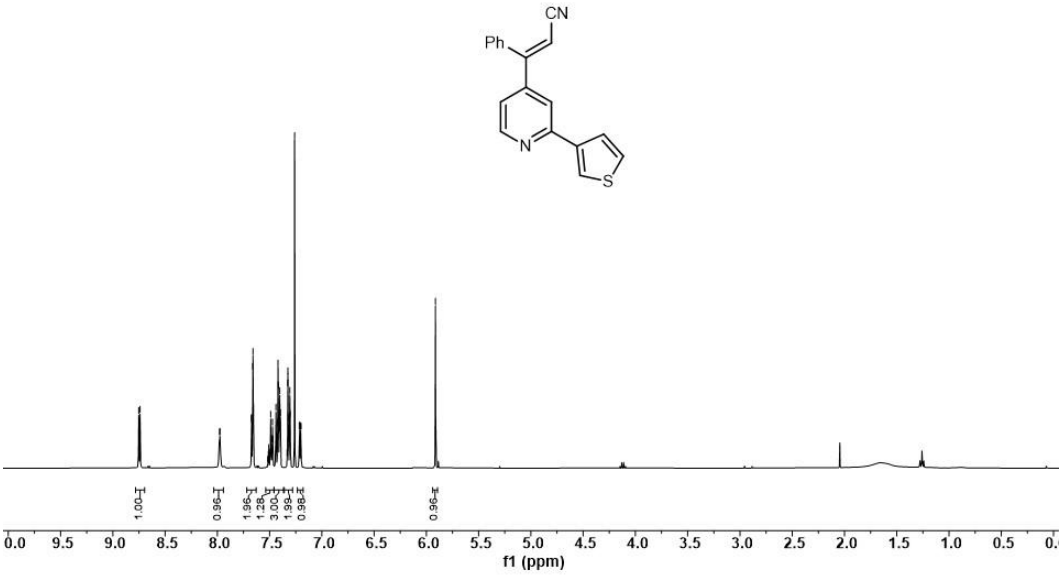
$(CD_3)_2SO$, 400 MHz



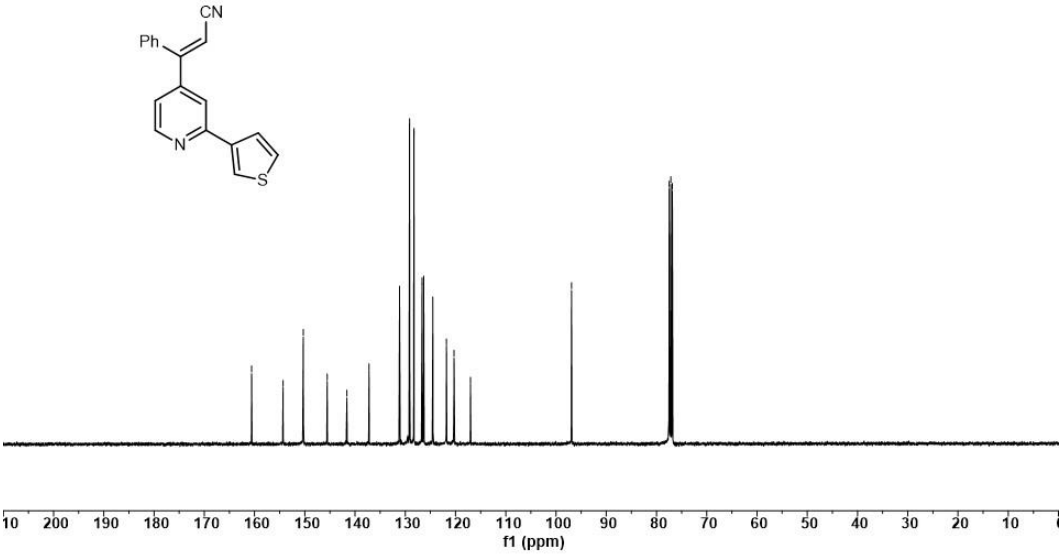


$(CD_3)_2SO$, 400 MHz

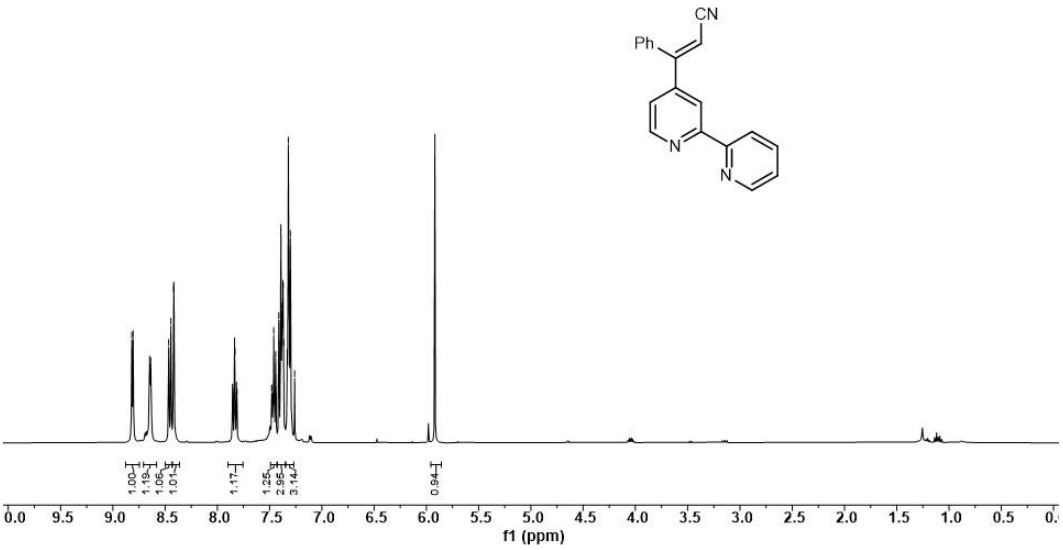
$CDCl_3$, 400 MHz



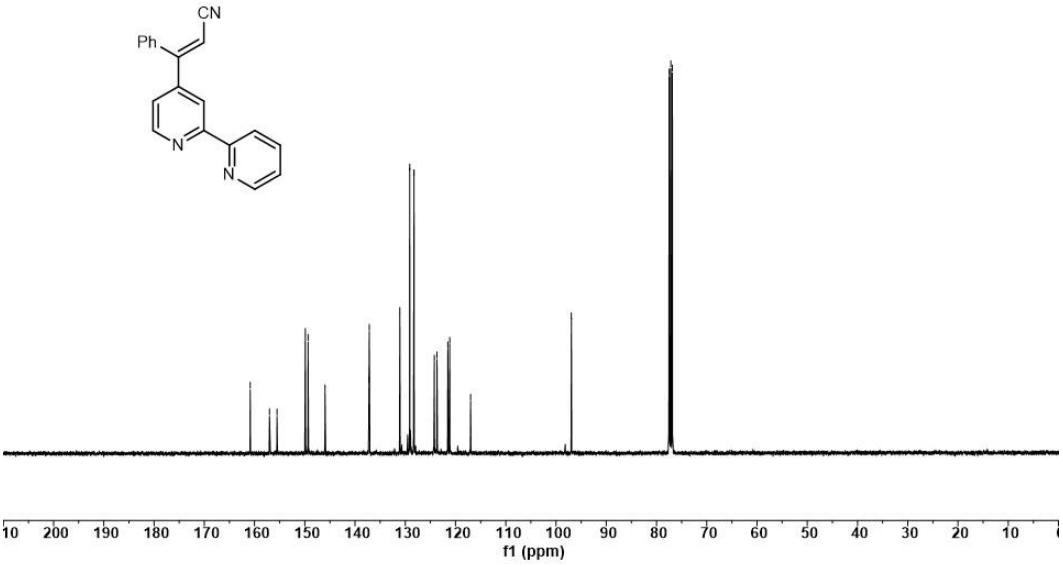
$CDCl_3$, 100 MHz

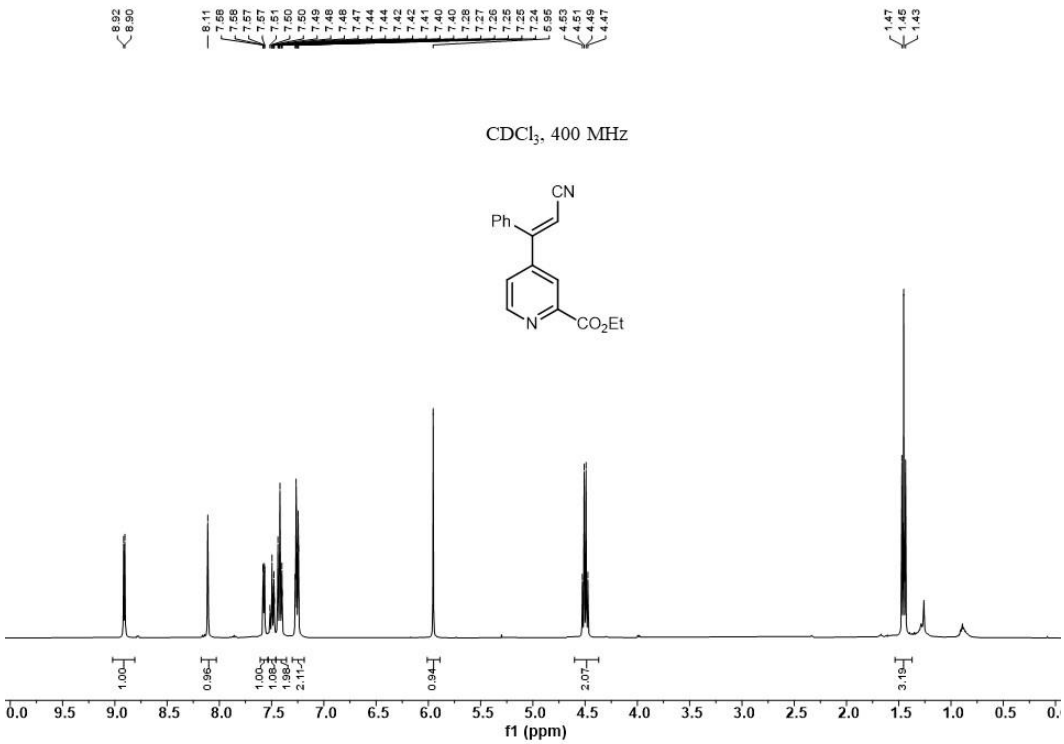


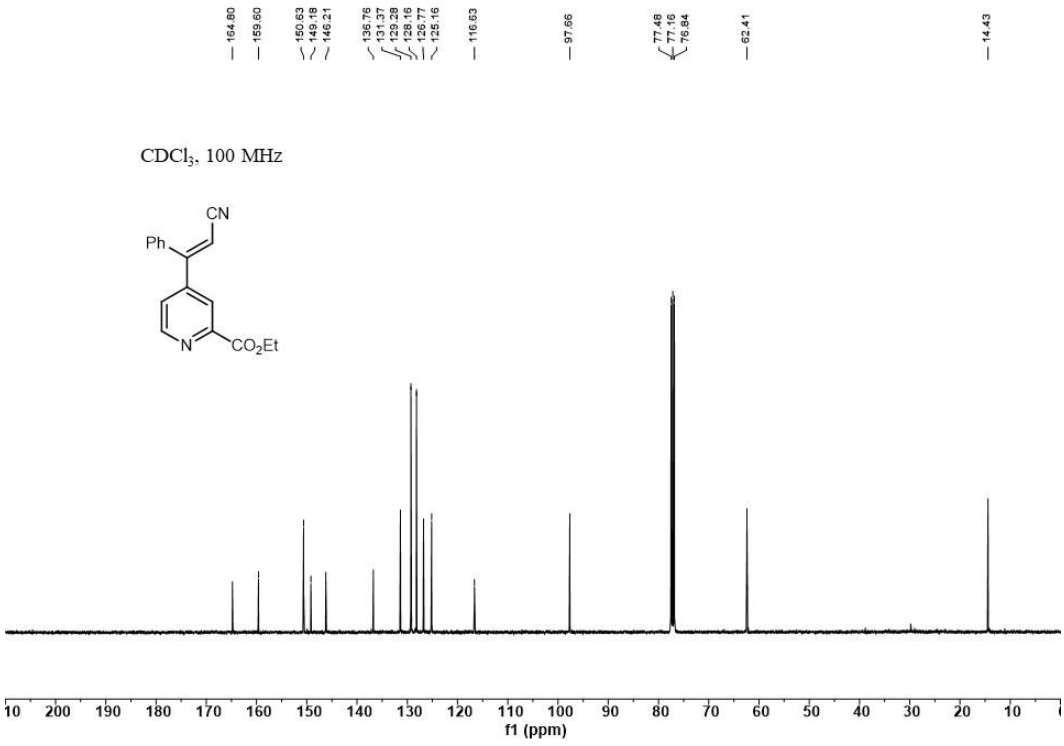
$CDCl_3$, 400 MHz



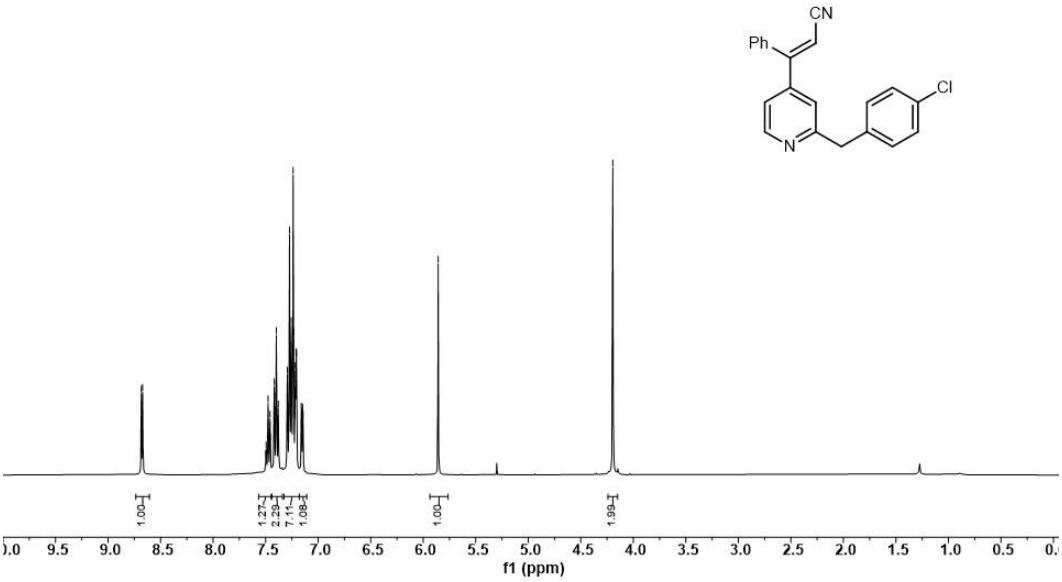
$CDCl_3$, 100 MHz



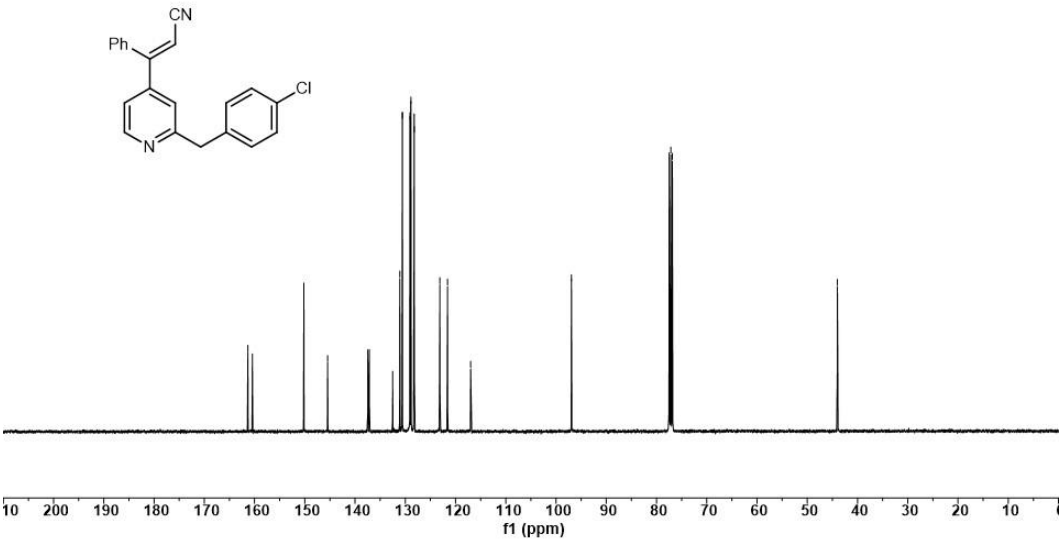

8.92
8.90
8.11
7.68
7.68
7.67
7.67
7.51
7.50
7.50
7.49
7.48
7.48
7.47
7.44
7.44
7.42
7.42
7.41
7.40
7.40
7.28
7.27
7.26
7.25
7.25
7.24
5.96
4.53
4.51
4.49
4.47
1.47
1.45
1.43
CDCl3, 400 MHz
CN
Ph
N
CO2Et
1.00
0.96
1.00
1.08
1.98
2.11
0.94
2.07
3.19
f1 (ppm)

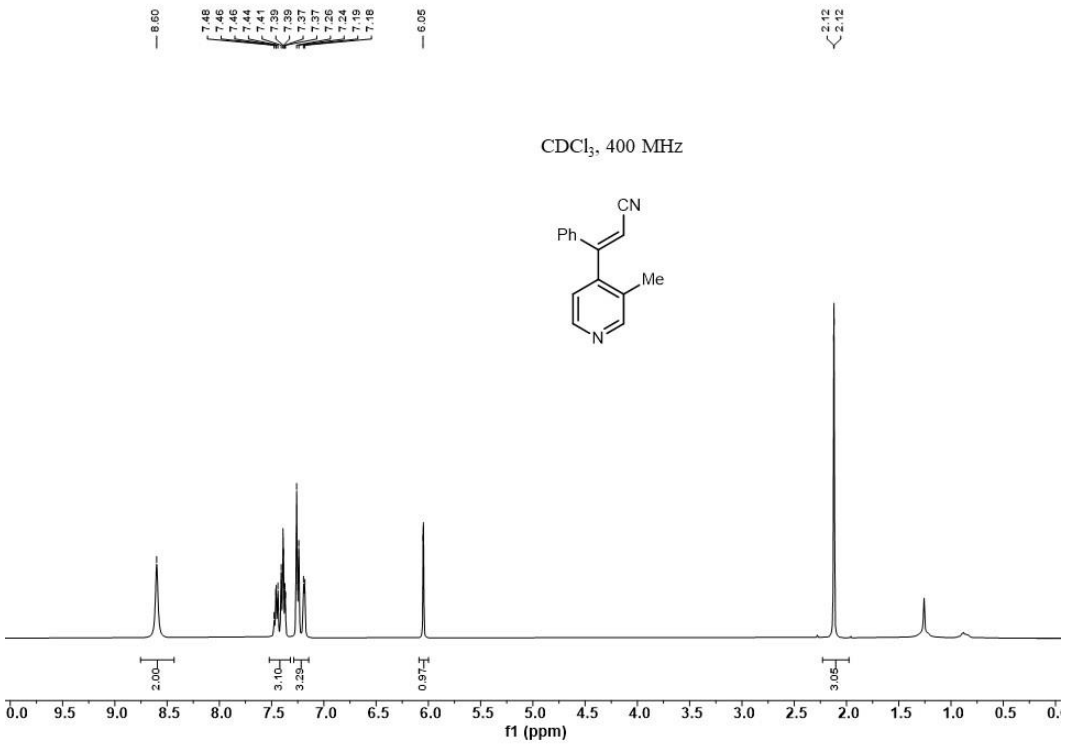

164.80
159.60
150.63
149.18
146.21
136.76
131.37
129.28
128.16
126.77
125.16
116.63
97.66
77.48
77.16
76.84
62.41
14.43
CDCl3, 100 MHz
CN
Ph
N
CO2Et
f1 (ppm)

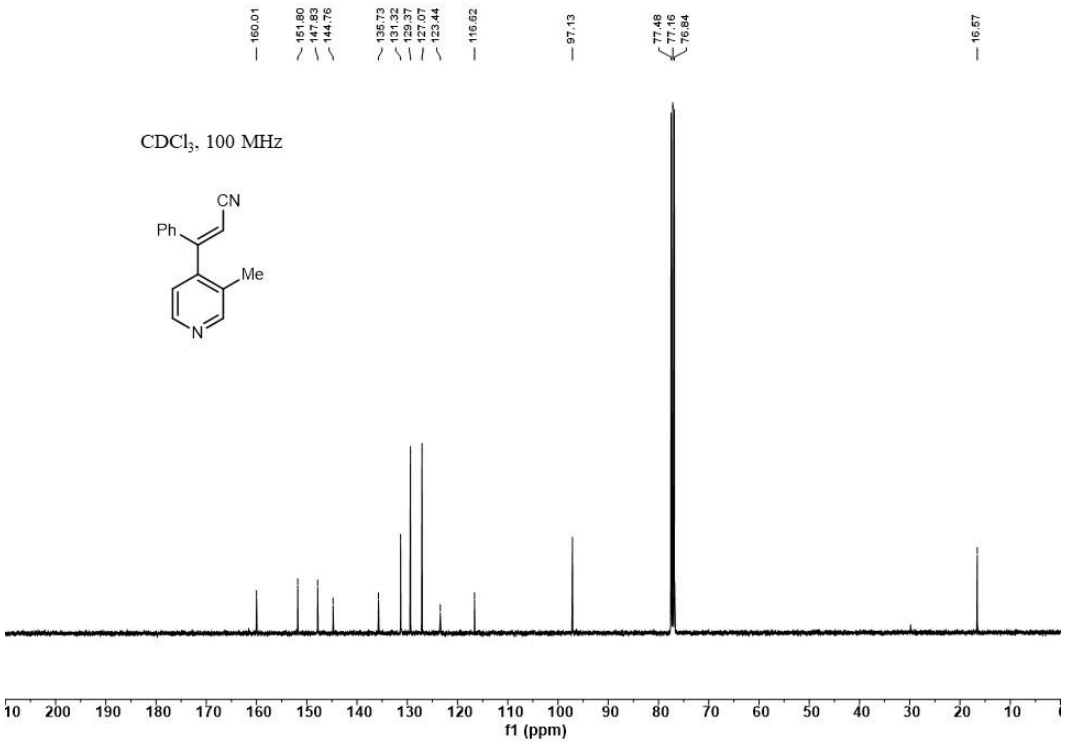
$CDCl_3$, 400 MHz



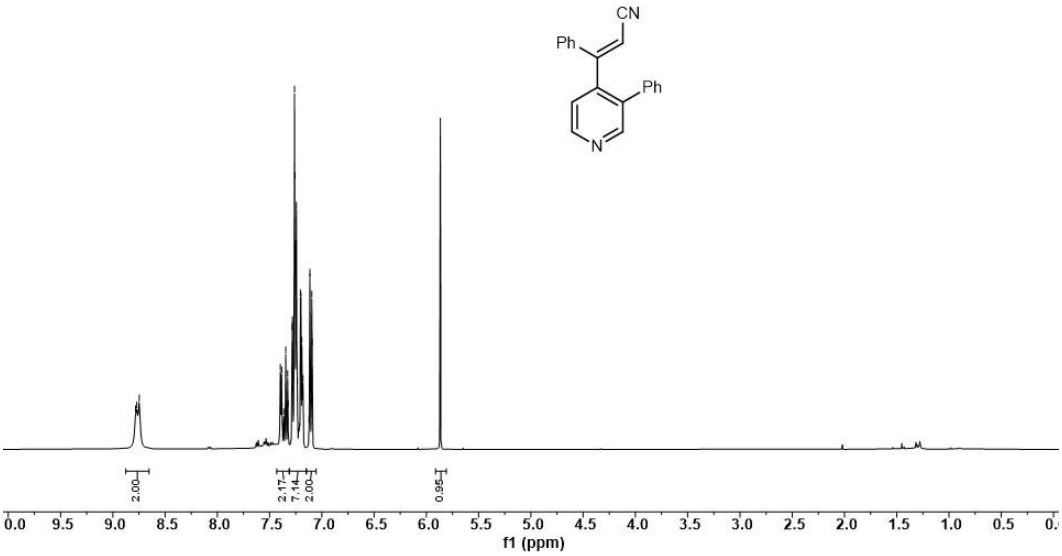
$CDCl_3$, 100 MHz



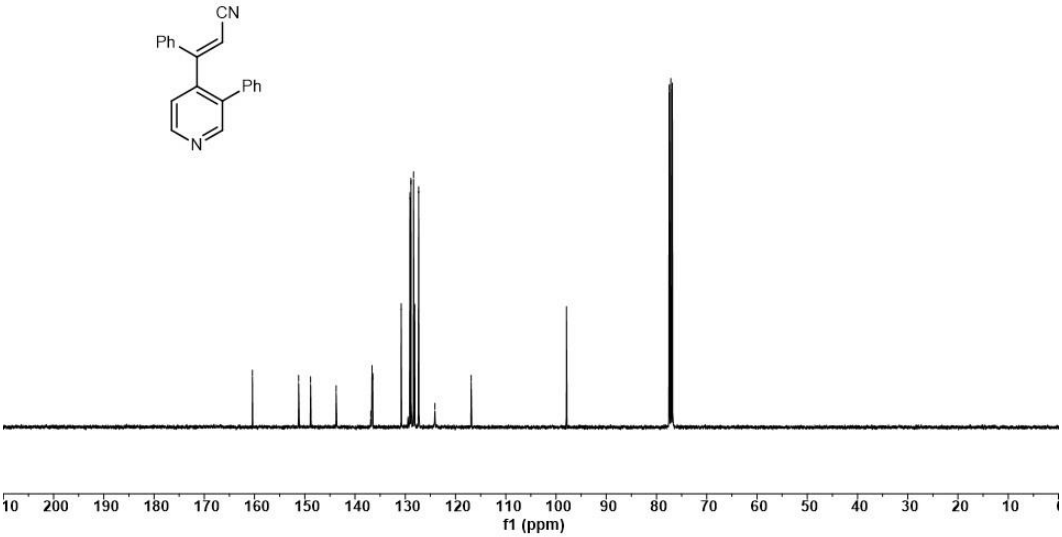

8.60
7.48
7.46
7.46
7.44
7.41
7.39
7.39
7.37
7.37
7.26
7.24
7.19
7.18
6.05
2.12
2.12
CDCl3, 400 MHz
CN
Ph
Me
N
2.00
3.10
3.29
0.97
3.05
f1 (ppm)

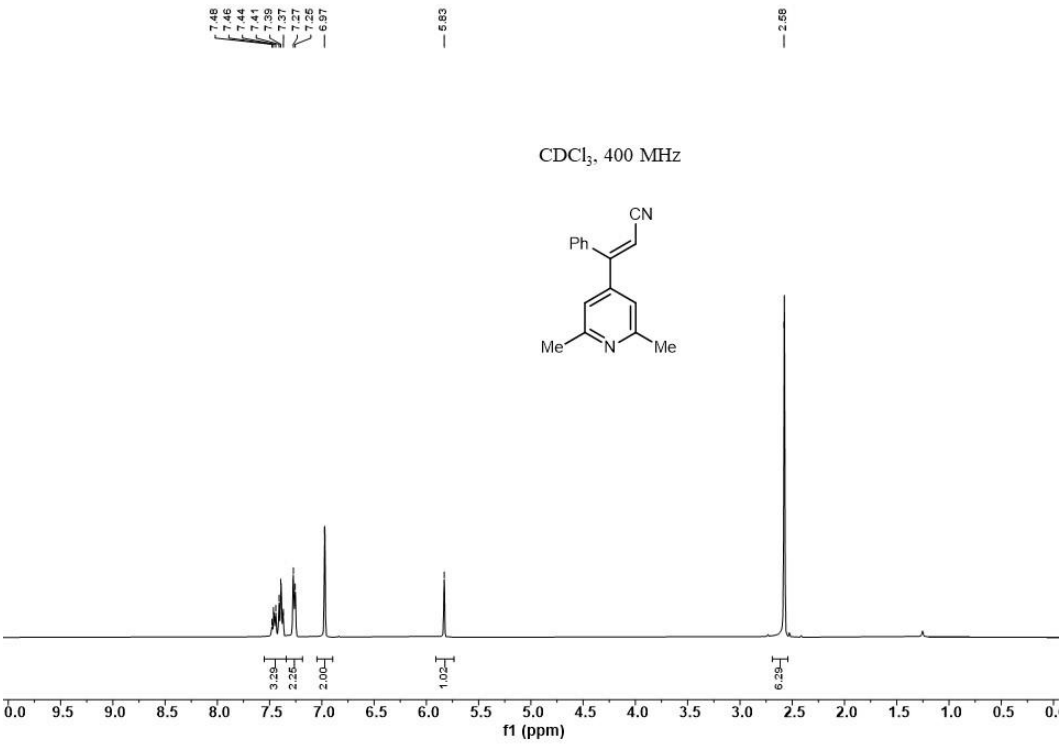

160.01
151.80
147.83
144.76
135.73
131.32
129.37
127.07
123.44
116.62
97.13
77.48
77.16
76.84
16.57
CDCl3, 100 MHz
CN
Ph
Me
N
f1 (ppm)

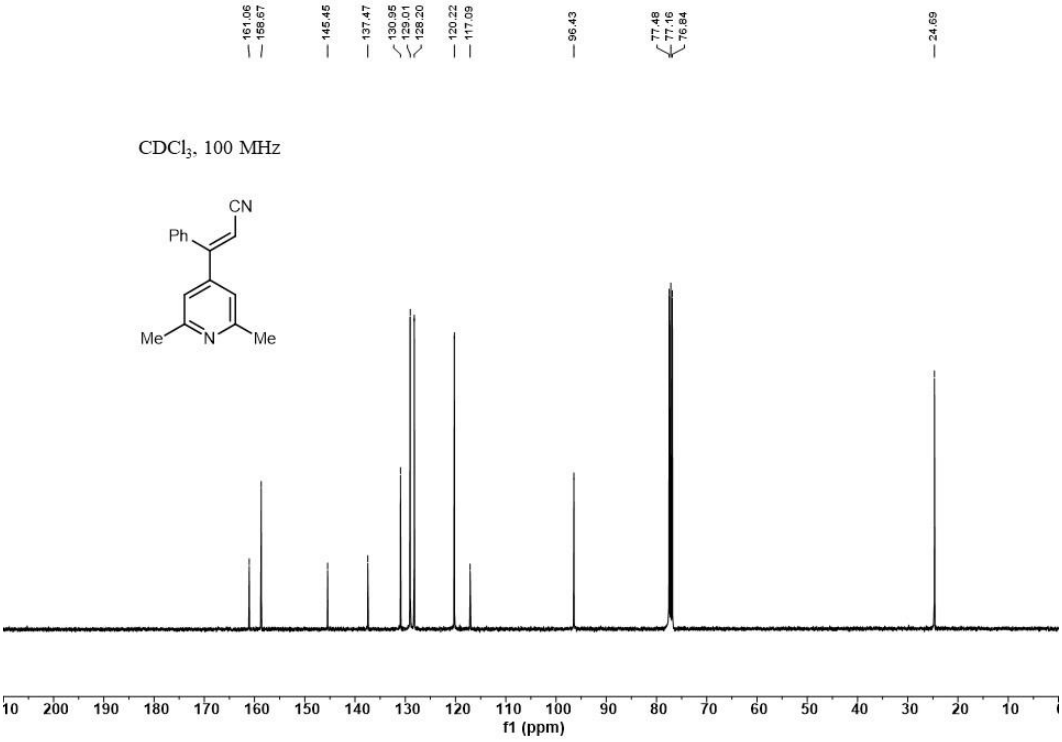
$CDCl_3$, 400 MHz



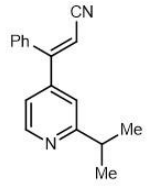
$CDCl_3$, 100 MHz

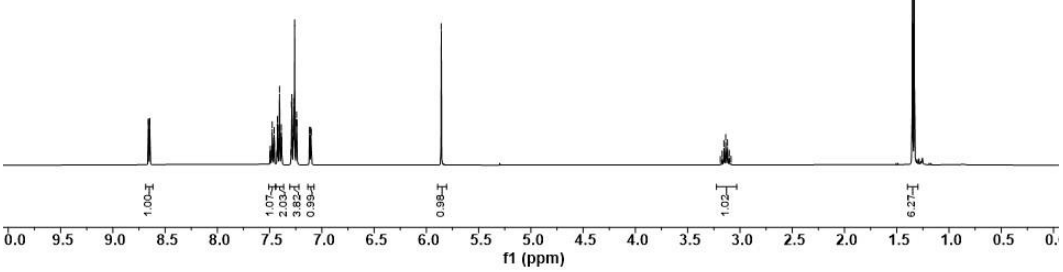



7.48
7.46
7.44
7.41
7.39
7.37
7.27
7.25
6.97
5.83
2.58
CDCl3, 400 MHz
CN
Ph
Me
N
Me
3.29
2.25
2.00
1.02
6.29
f1 (ppm)

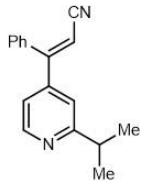

161.06
158.67
145.45
137.47
130.95
129.01
128.20
120.22
117.09
96.43
77.48
77.16
76.84
24.69
CDCl3, 100 MHz
CN
Ph
Me
N
Me
f1 (ppm)

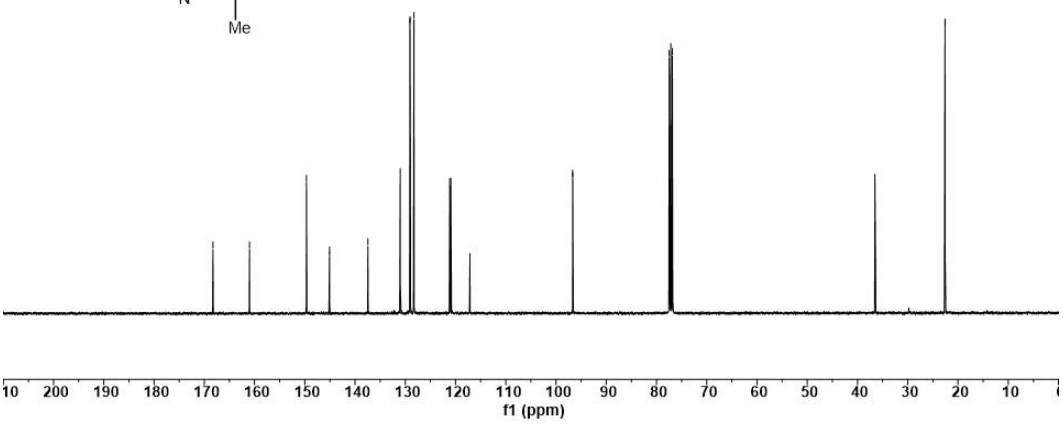
$CDCl_3$, 400 MHz



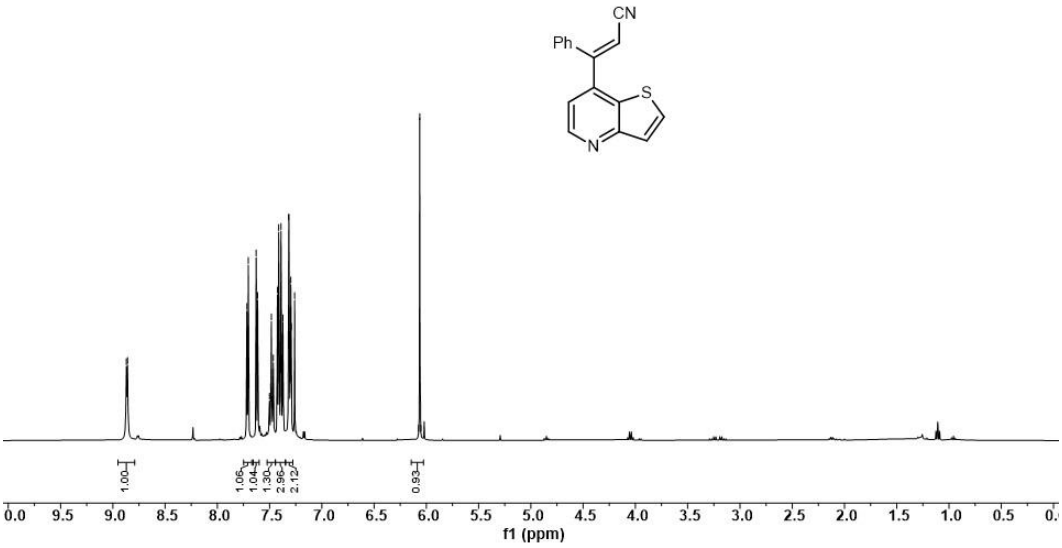


$CDCl_3$, 100 MHz

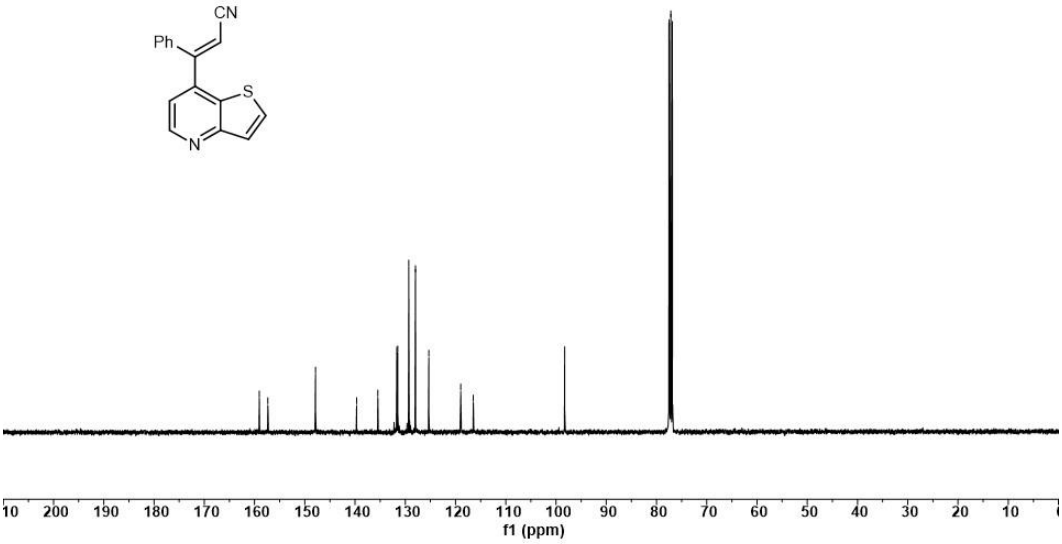


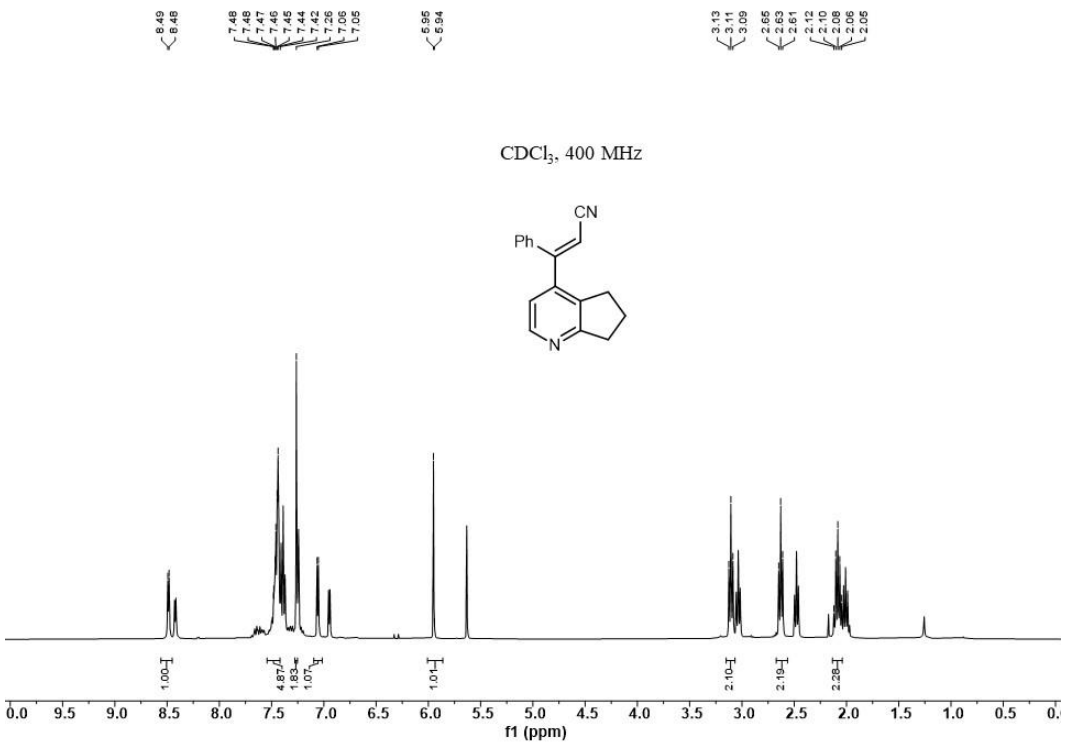


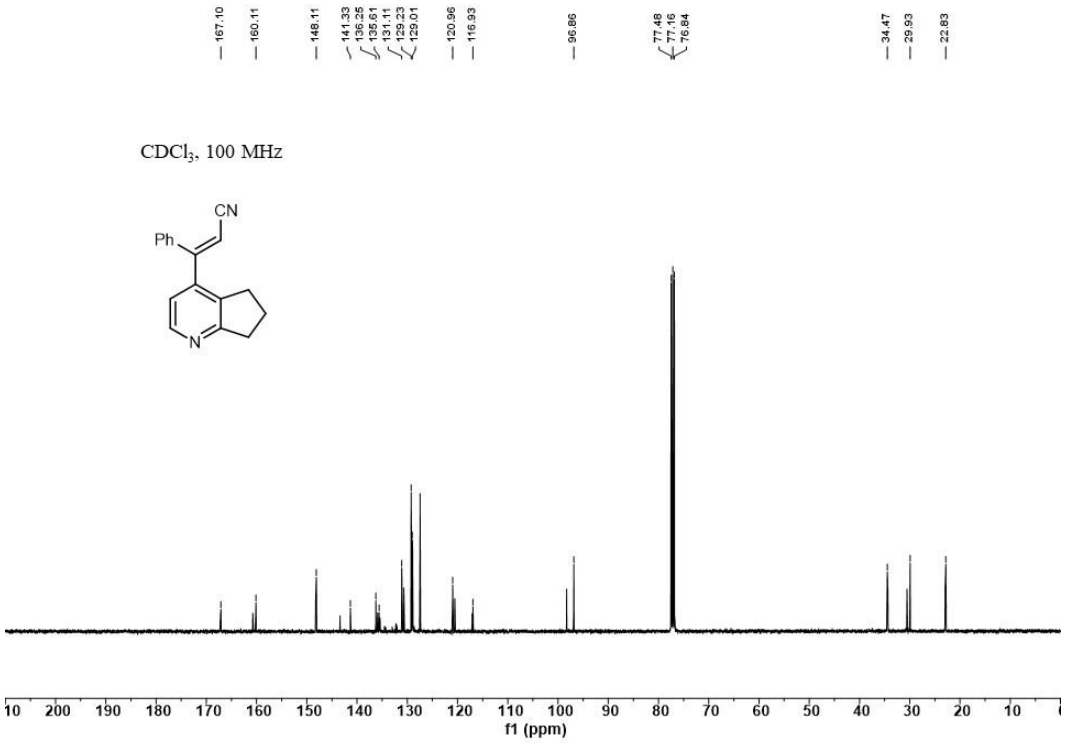
$CDCl_3$, 400 MHz



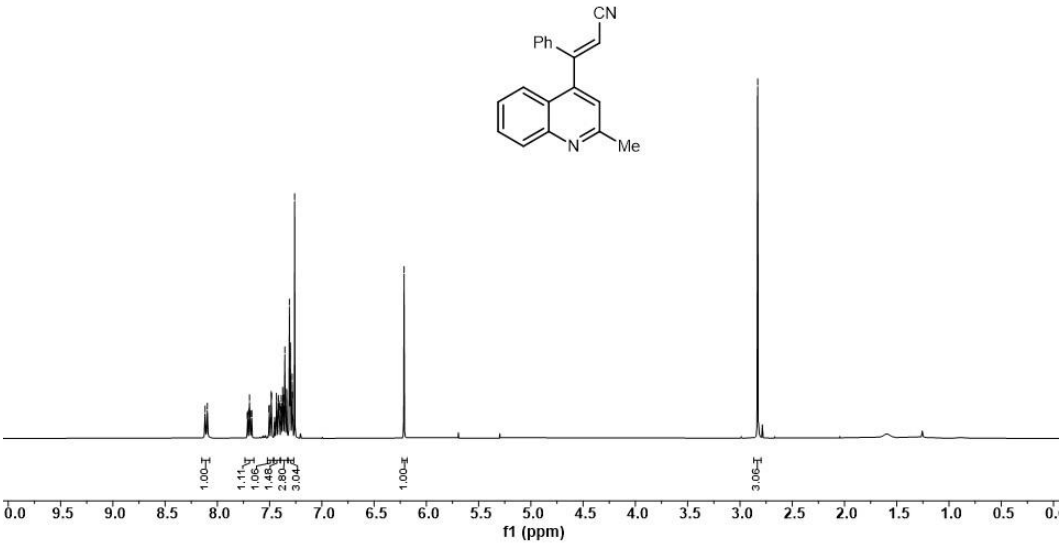
$CDCl_3$, 100 MHz



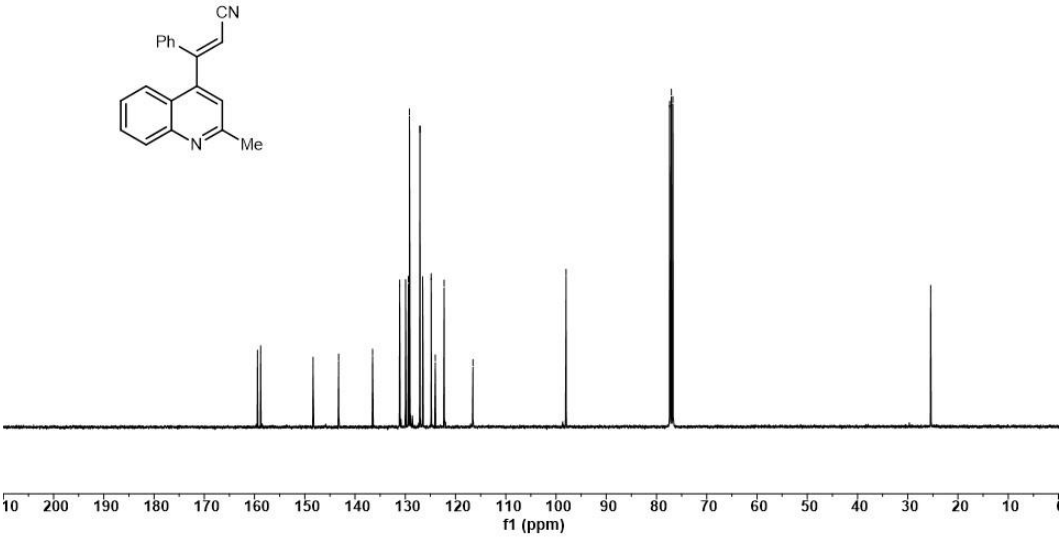

8.49
8.48
7.48
7.48
7.47
7.46
7.45
7.44
7.42
7.26
7.06
7.05
5.95
5.94
3.13
3.11
3.09
2.65
2.63
2.61
2.12
2.10
2.08
2.06
2.05
CDCl3, 400 MHz
CN
Ph
N
1.00
4.87
1.83
1.07
1.01
2.10
2.19
2.28
f1 (ppm)


167.10
160.11
148.11
141.33
136.25
135.61
131.11
129.23
129.01
120.96
116.93
96.86
77.48
77.16
76.84
34.47
29.93
22.83
CDCl3, 100 MHz
CN
Ph
N
f1 (ppm)

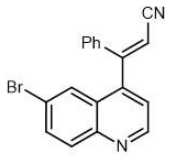
$CDCl_3$, 400 MHz

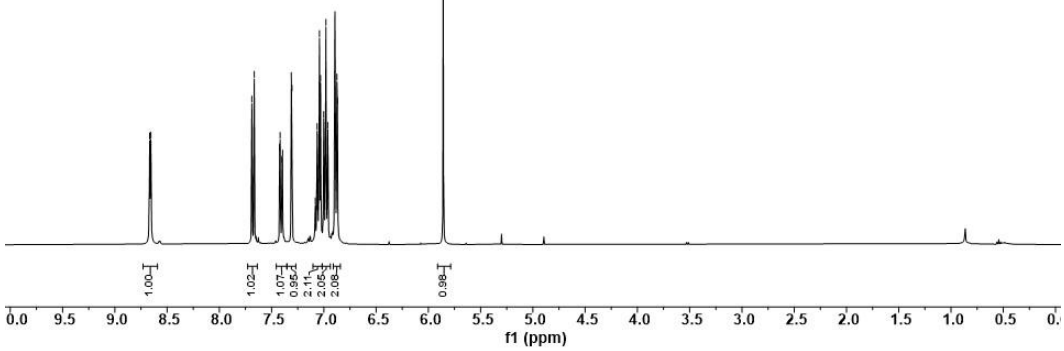


$CDCl_3$, 100 MHz

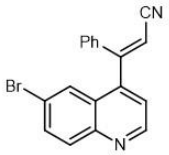


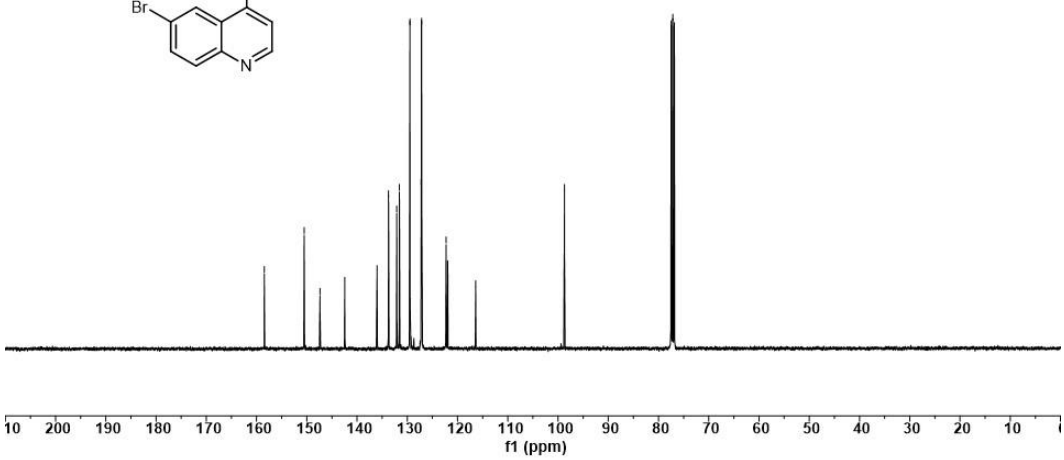
$CDCl_3$, 400 MHz

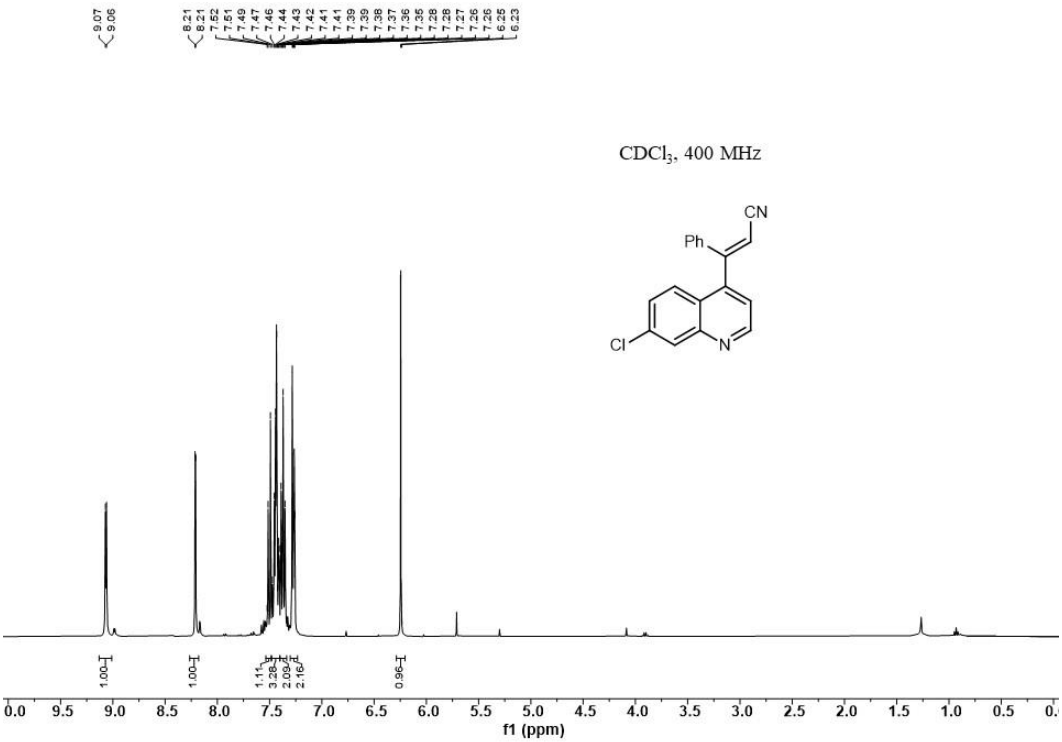


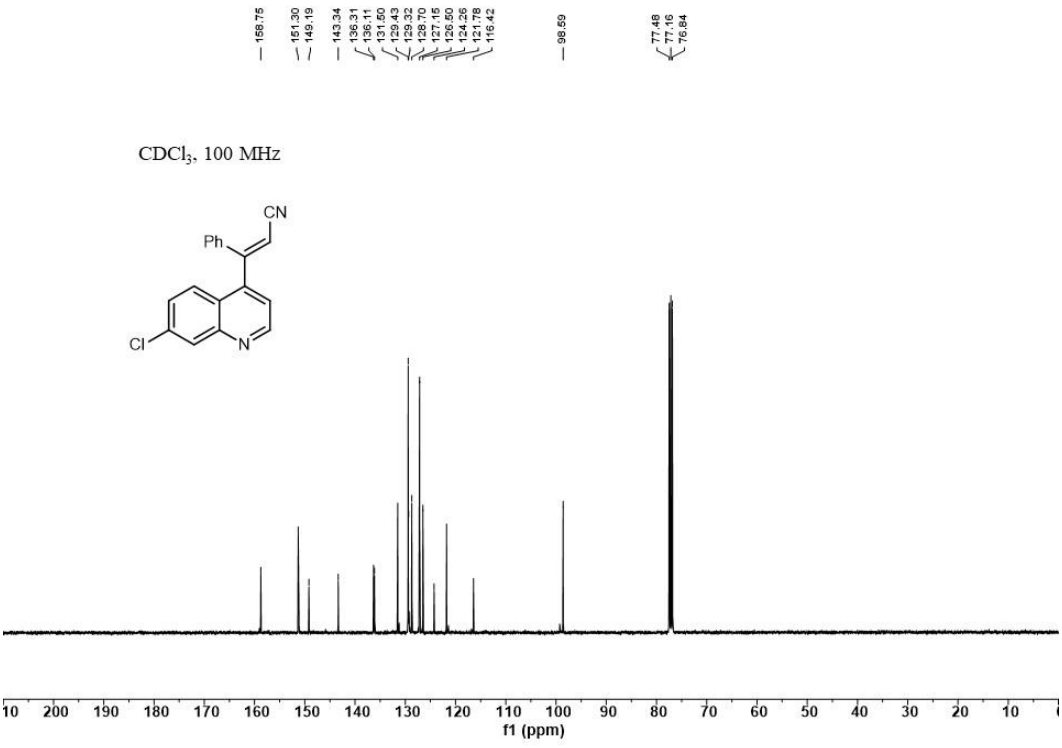


$CDCl_3$, 100 MHz

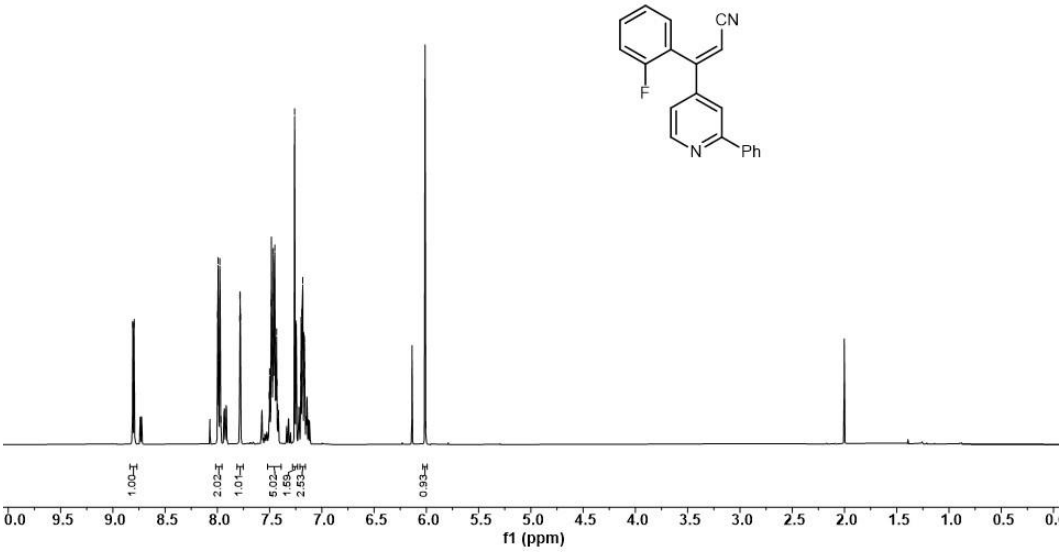




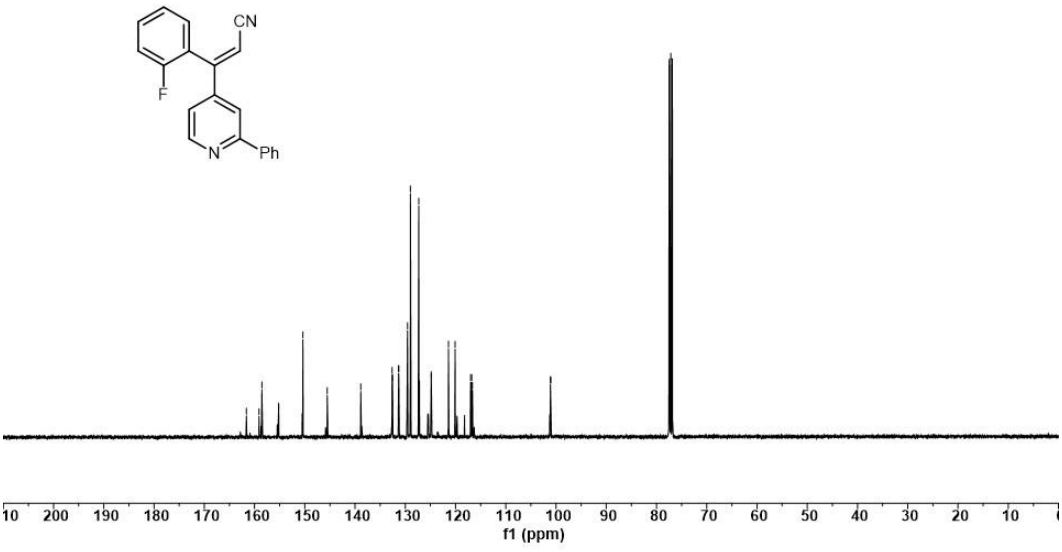

9.07
9.06
8.21
8.21
7.52
7.51
7.49
7.47
7.46
7.44
7.43
7.42
7.41
7.41
7.39
7.39
7.38
7.37
7.36
7.35
7.28
7.28
7.27
7.26
7.26
6.25
6.23
CDCl3, 400 MHz
CN
Ph
Cl
N
1.00
1.00
1.11
3.29
2.09
2.16
0.96
f1 (ppm)

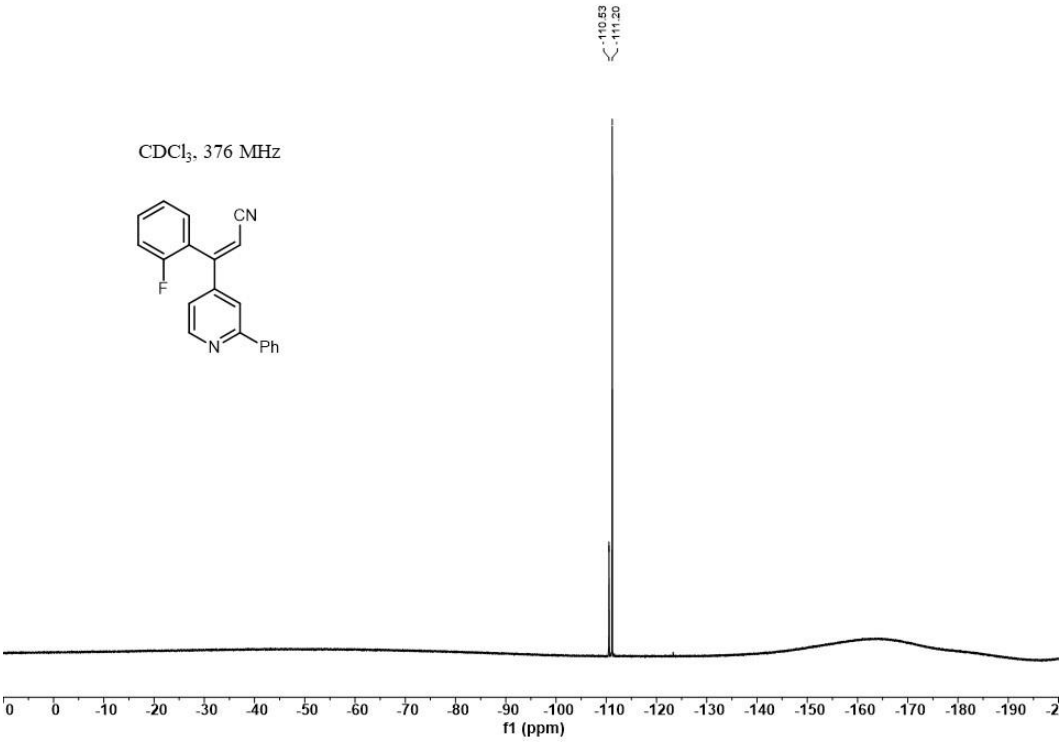

158.75
151.30
149.19
143.34
136.31
136.11
131.50
129.43
129.32
128.70
127.15
126.50
124.26
121.78
116.42
98.59
77.48
77.16
76.84
CDCl3, 100 MHz
CN
Ph
Cl
N
f1 (ppm)

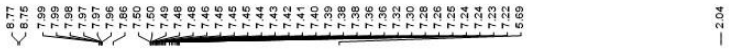
$CDCl_3$, 400 MHz

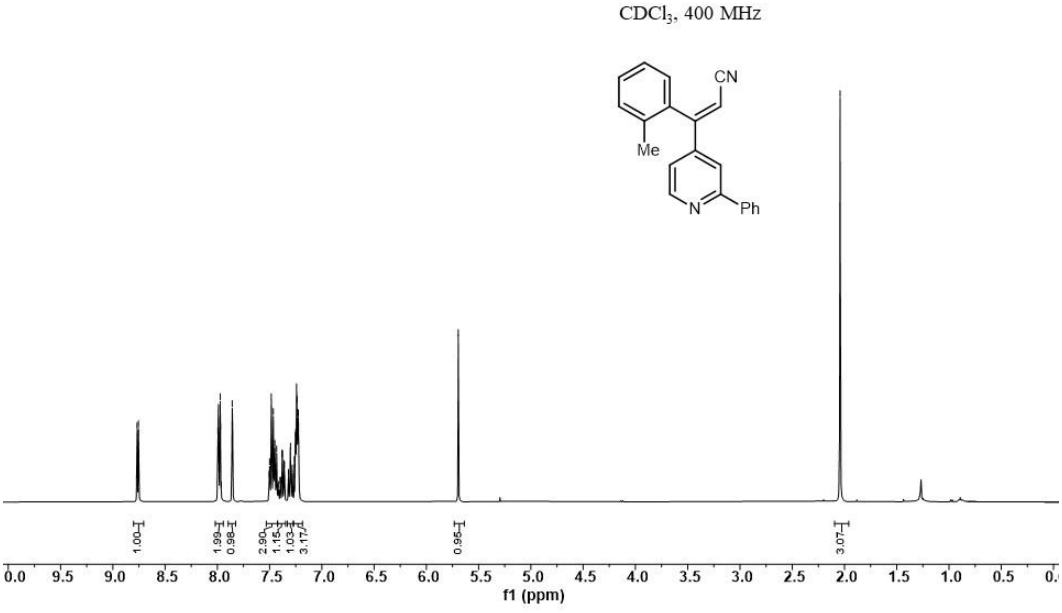


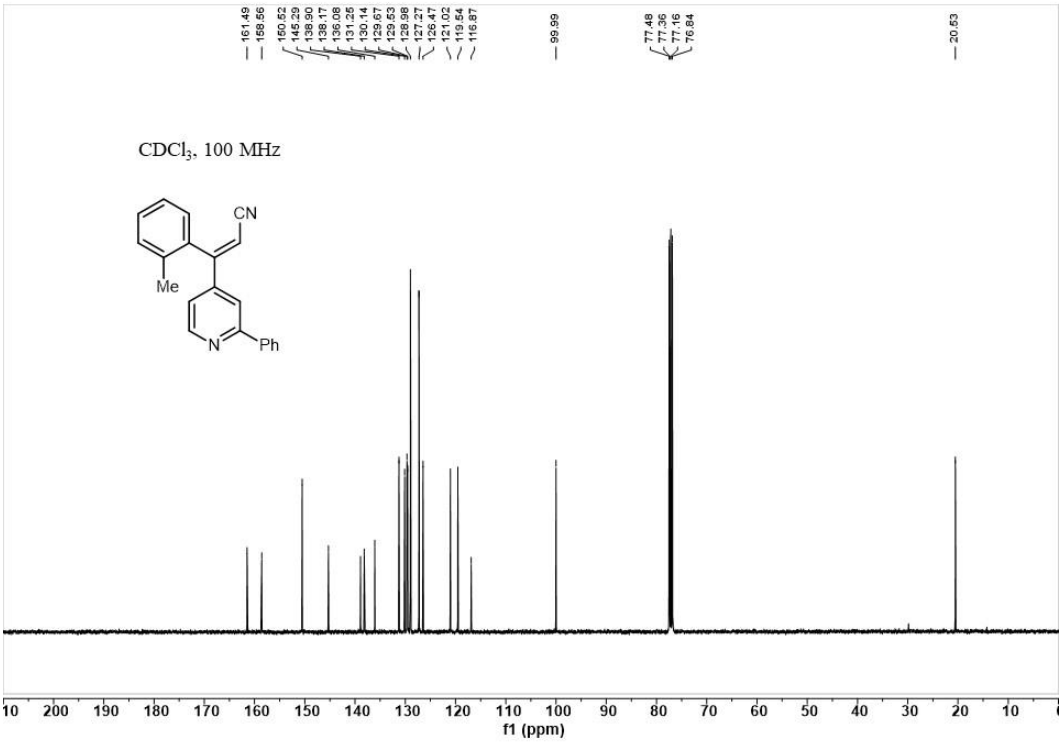
$CDCl_3$, 100 MHz

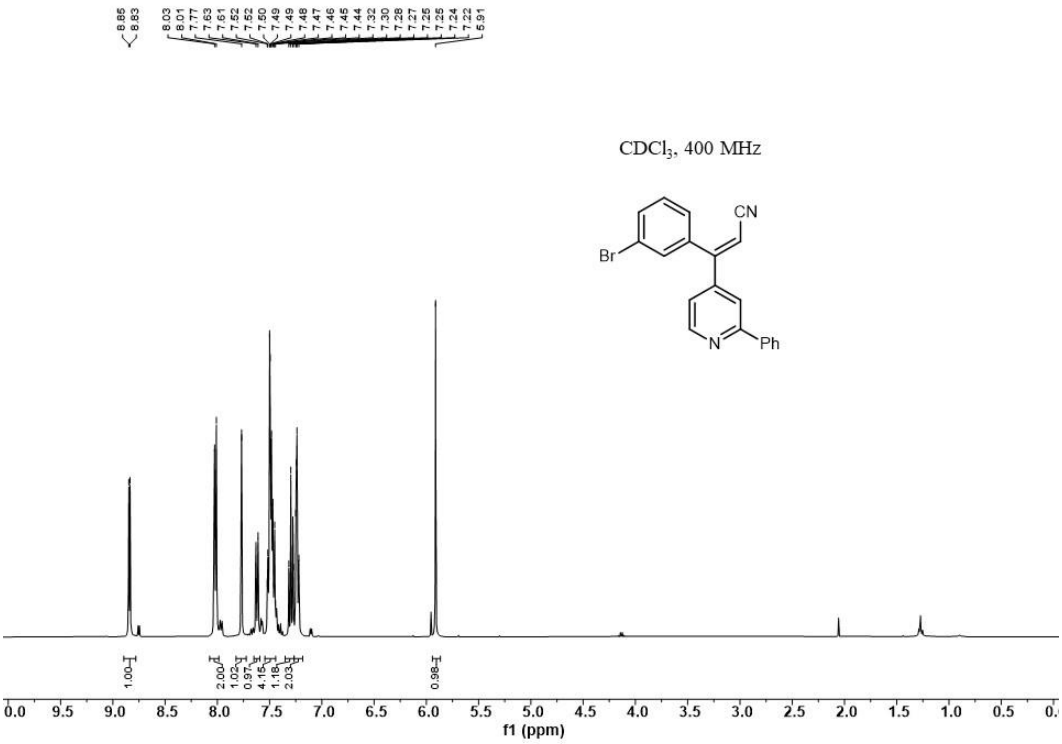


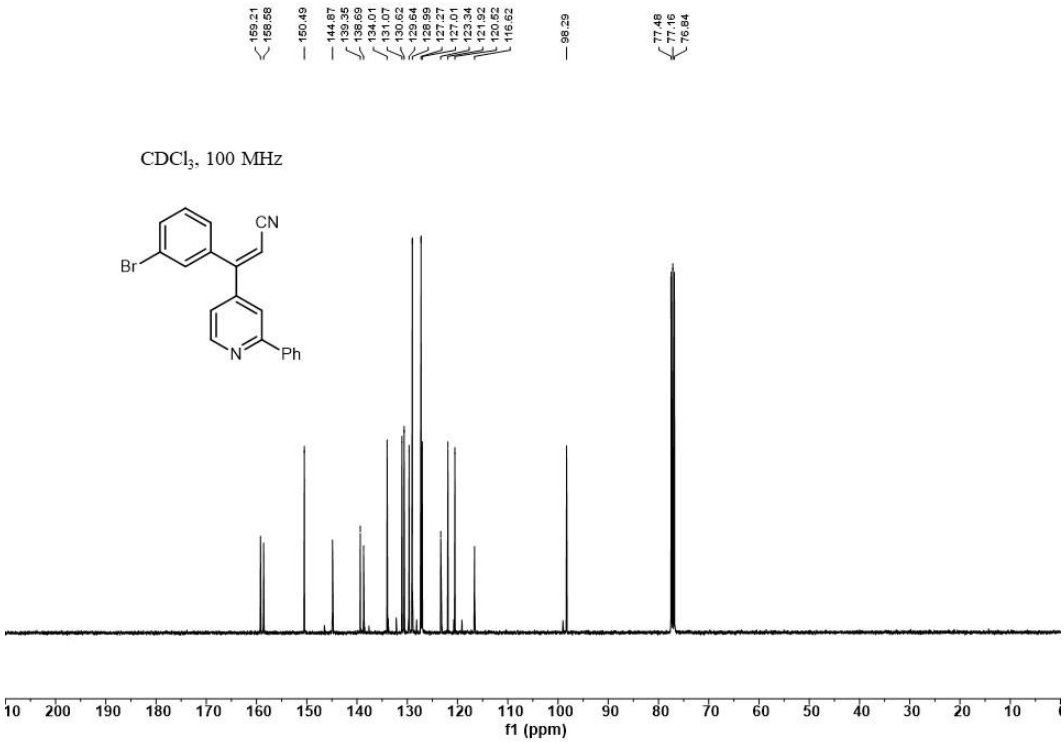

-110.63
-111.20
CDCl3, 376 MHz
CN
F
N
Ph
0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2
f1 (ppm)

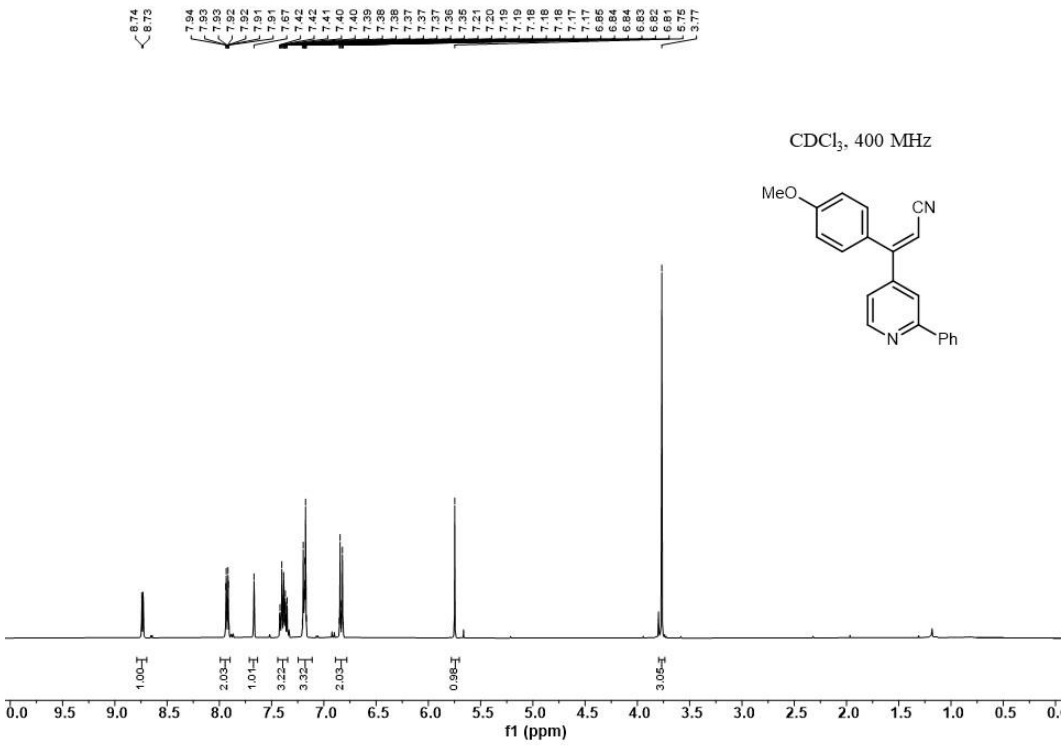

8.77
8.75
7.99
7.99
7.98
7.97
7.97
7.96
7.86
7.50
7.49
7.48
7.48
7.46
7.45
7.45
7.45
7.44
7.43
7.42
7.41
7.40
7.39
7.38
7.38
7.36
7.36
7.32
7.30
7.28
7.26
7.25
7.24
7.24
7.23
7.22
6.69
2.04

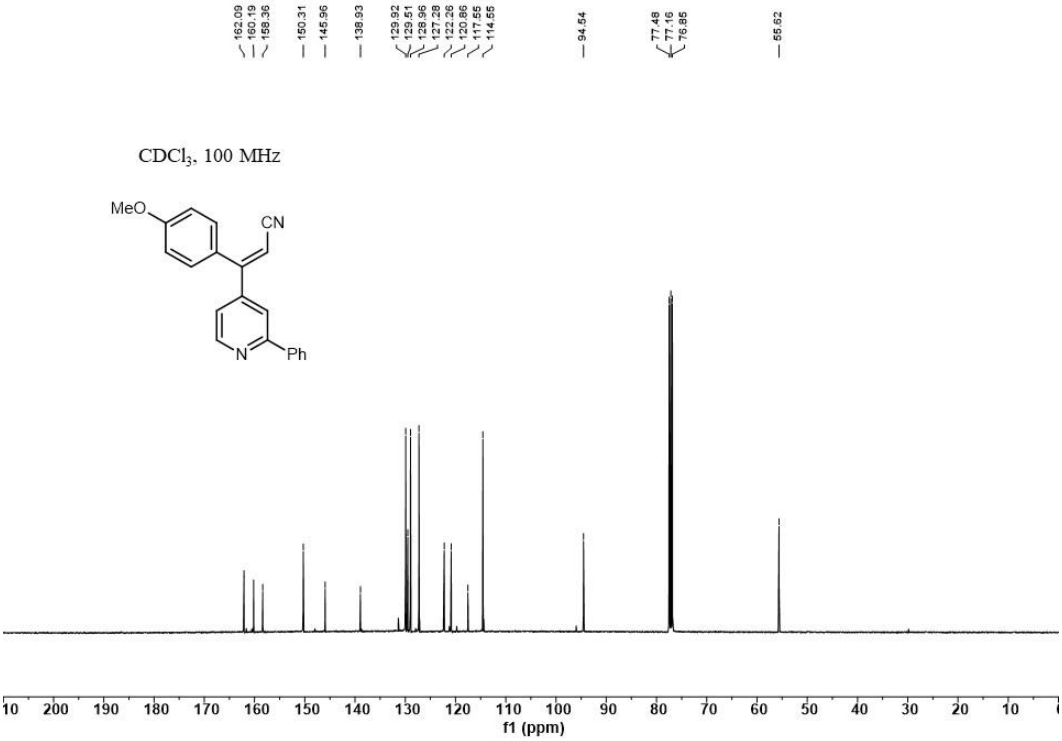

CDCl3, 400 MHz
CN
Me
N
Ph
1.00
1.90
0.98
2.90
1.15
1.03
3.17
0.95
3.07
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)

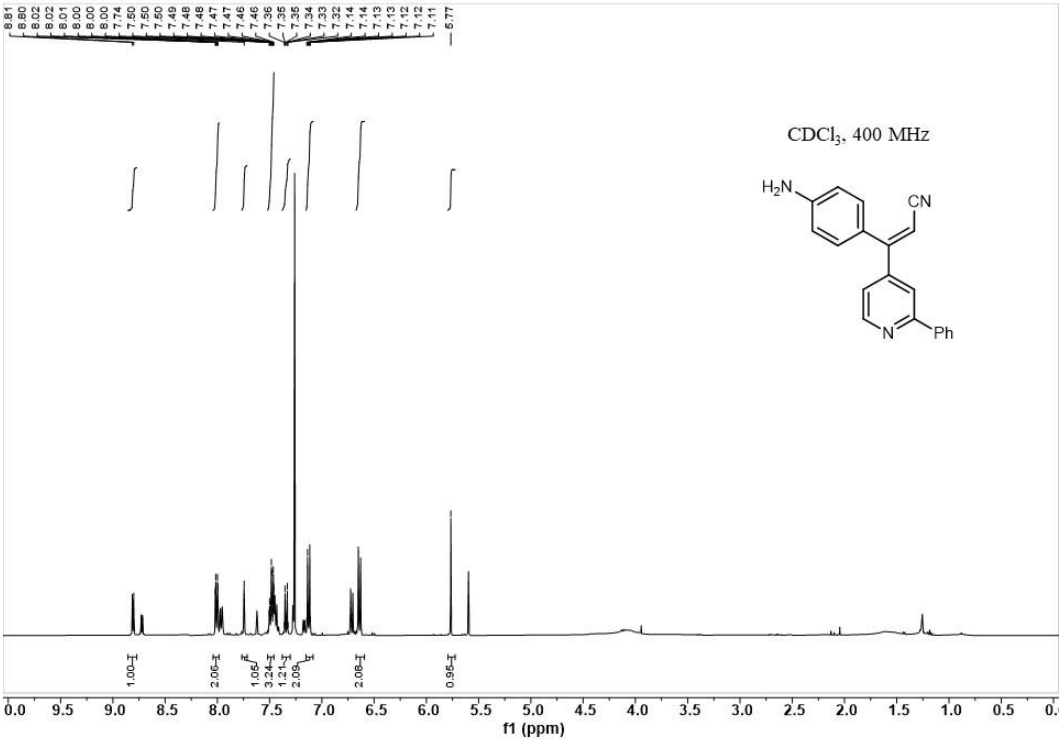

161.49
158.56
150.52
145.29
138.90
138.17
136.08
131.26
130.14
129.67
129.53
128.98
127.27
126.47
121.02
119.54
116.87
99.99
77.48
77.36
77.16
76.84
20.53
CDCl3, 100 MHz
CN
Me
N
Ph
f1 (ppm)

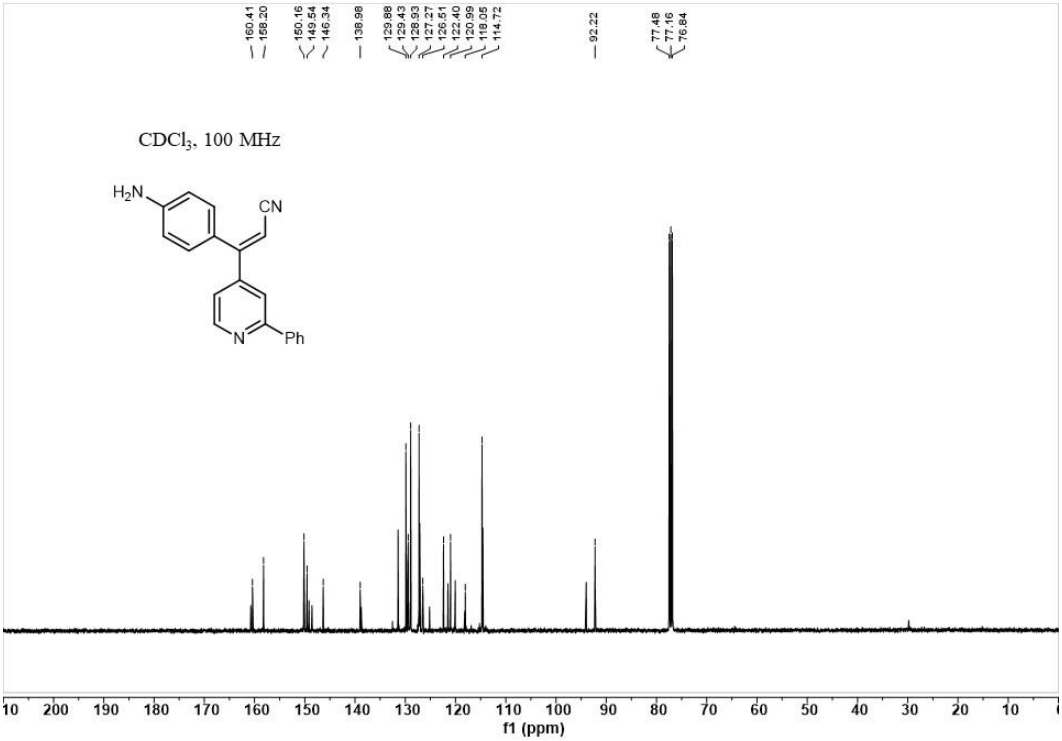

8.85
8.83
8.03
8.01
7.77
7.63
7.61
7.52
7.52
7.50
7.49
7.49
7.48
7.47
7.46
7.45
7.44
7.32
7.30
7.28
7.27
7.25
7.25
7.24
7.22
5.91
CDCl3, 400 MHz
CN
Br
N
Ph
1.00
2.00
1.02
0.97
4.15
1.18
2.03
0.98
f1 (ppm)

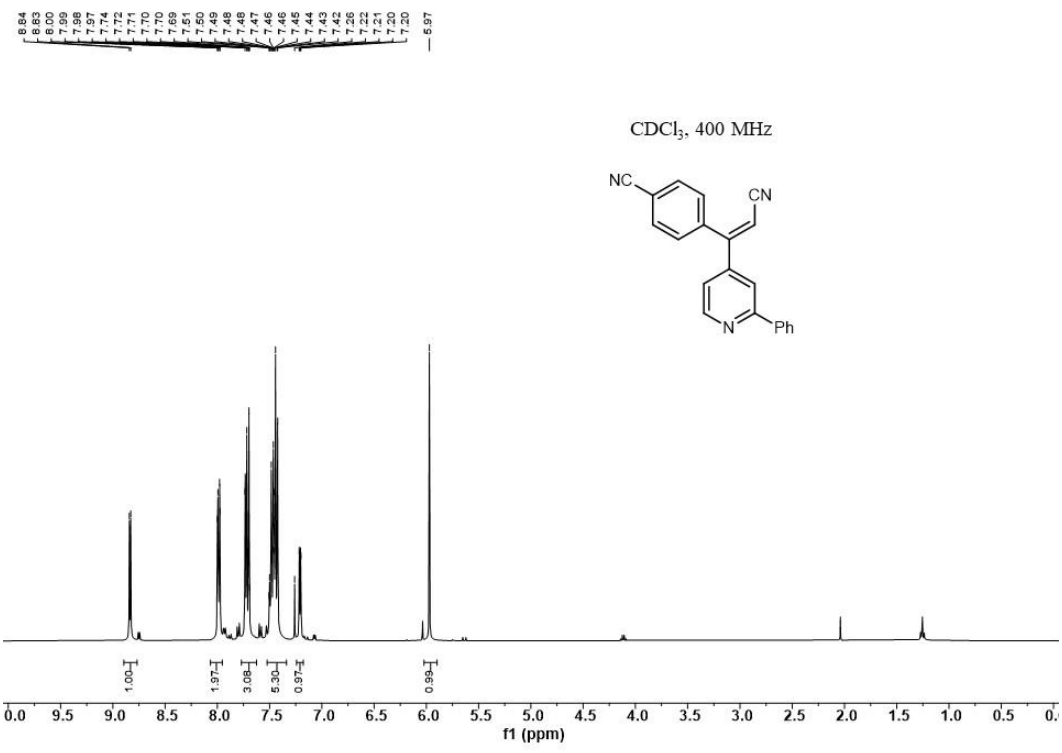

159.21
158.58
150.49
144.87
139.35
138.69
134.01
131.07
130.62
129.64
128.99
127.27
127.01
123.34
121.92
120.62
116.62
98.29
77.48
77.16
76.84
CDCl3, 100 MHz
CN
Br
N
Ph
f1 (ppm)

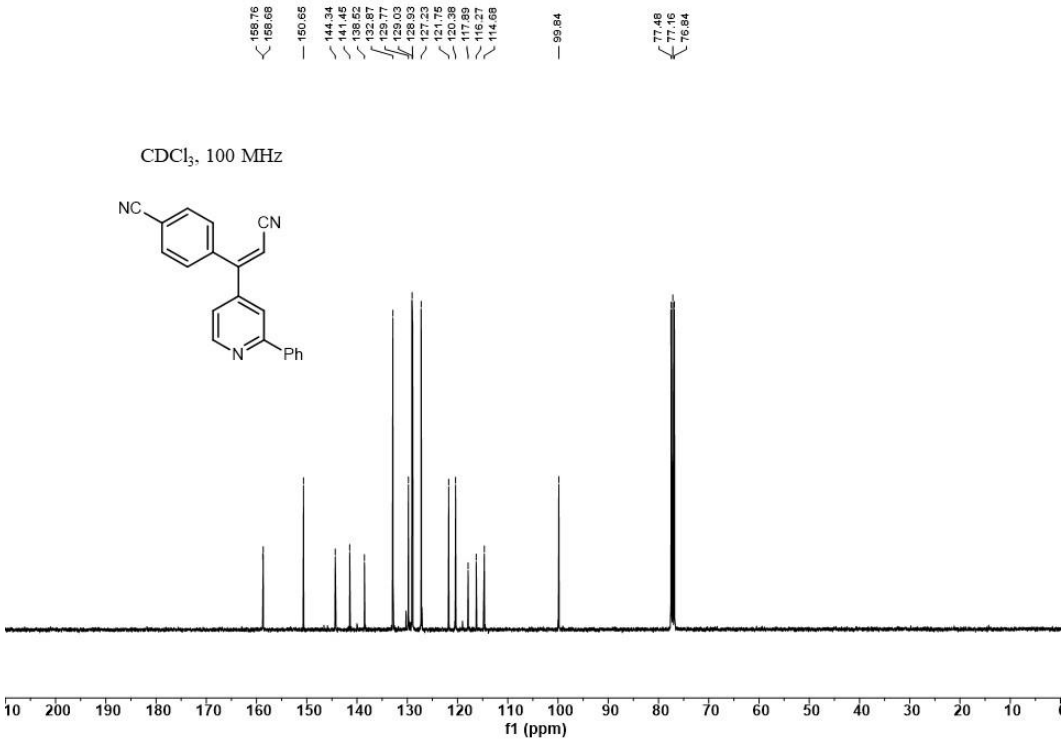

8.74
8.73
7.94
7.93
7.93
7.92
7.92
7.91
7.91
7.67
7.42
7.42
7.41
7.40
7.40
7.39
7.38
7.38
7.37
7.37
7.37
7.36
7.35
7.21
7.20
7.19
7.19
7.18
7.18
7.16
7.16
7.17
7.17
6.85
6.84
6.84
6.83
6.82
6.81
5.75
3.77
CDCl3, 400 MHz
MeO
CN
N
Ph
1.00
2.03
1.01
3.22
3.32
2.03
0.98
3.05
f1 (ppm)

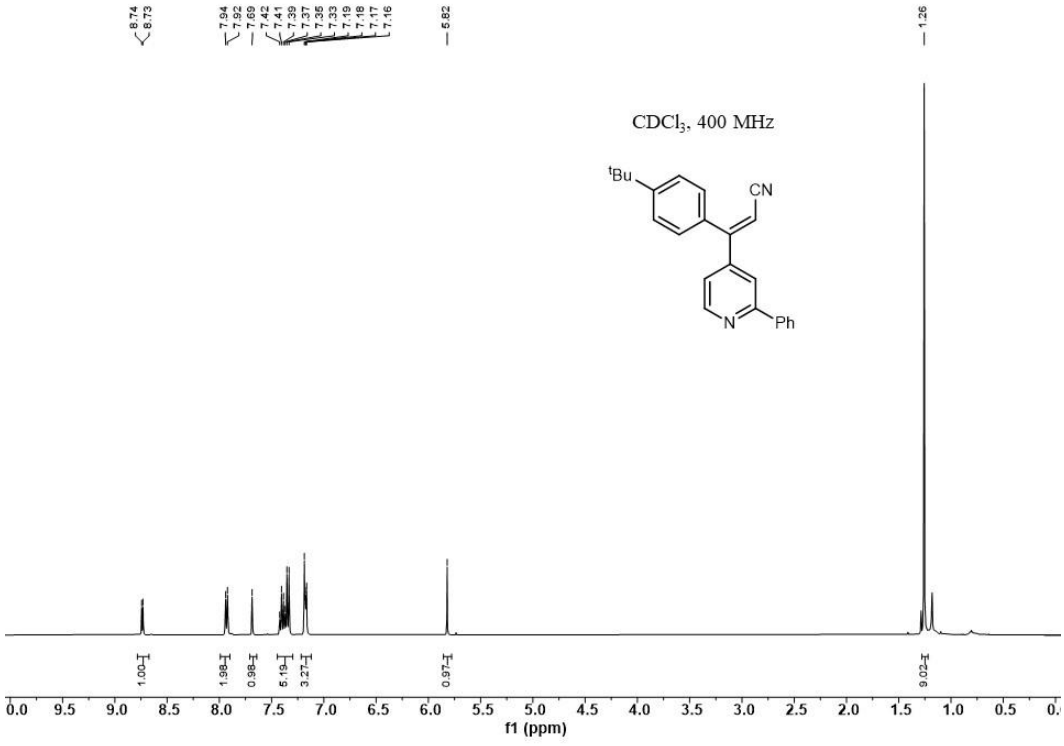

162.09
160.19
158.36
150.31
145.96
138.93
129.92
129.51
128.96
127.28
122.26
120.86
117.55
114.55
94.54
77.48
77.16
76.85
55.62
CDCl3, 100 MHz
MeO
CN
N
Ph
f1 (ppm)

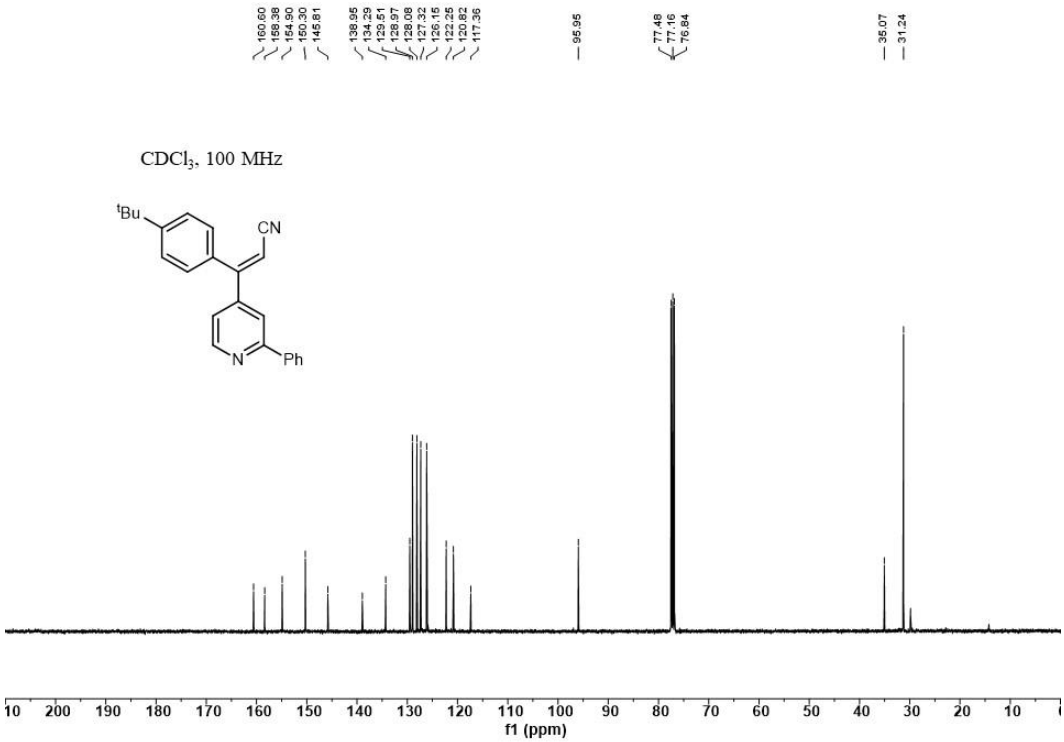

8.81
8.80
8.02
8.02
8.01
8.00
8.00
8.00
7.74
7.50
7.50
7.49
7.48
7.47
7.47
7.46
7.46
7.36
7.35
7.35
7.34
7.33
7.32
7.14
7.14
7.13
7.12
7.12
7.11
5.77
CDCl3, 400 MHz
H2N
CN
N
Ph
1.00
2.06
1.05
3.24
1.21
2.09
2.08
0.95
f1 (ppm)

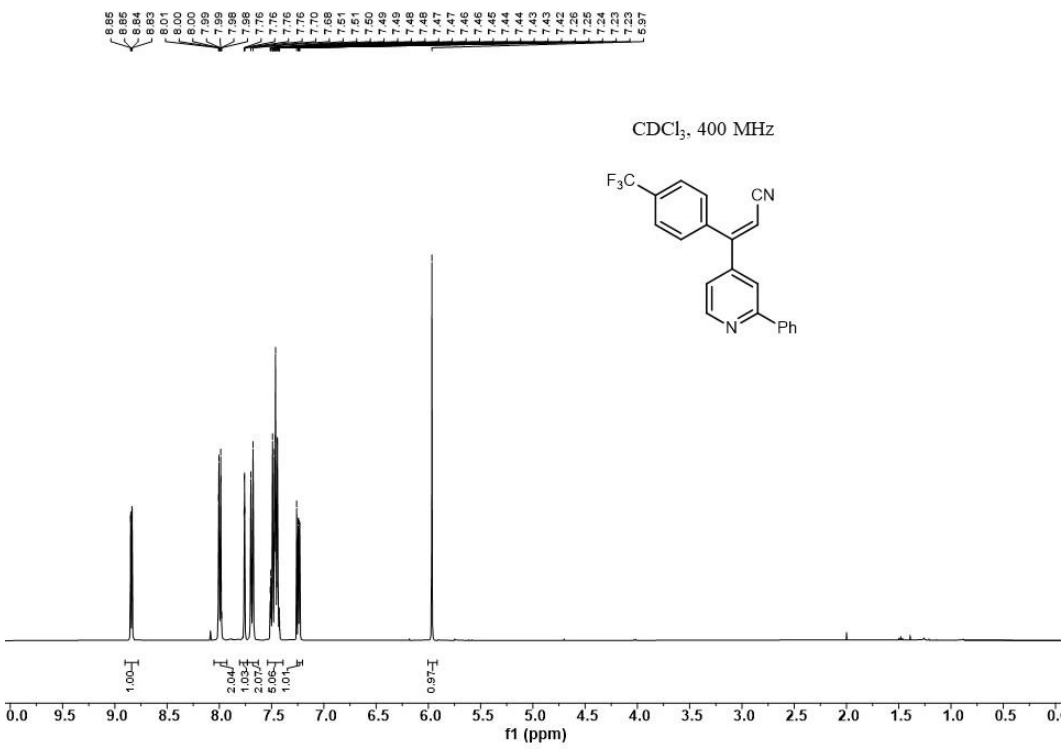

160.41
158.20
150.16
149.54
146.34
138.98
129.98
129.43
128.93
127.27
125.51
122.40
120.99
118.05
114.72
92.22
77.48
77.16
76.84
CDCl3, 100 MHz
H2N
CN
N
Ph
f1 (ppm)


8.84
8.83
8.00
7.99
7.98
7.97
7.74
7.72
7.71
7.70
7.70
7.69
7.51
7.50
7.49
7.48
7.48
7.47
7.46
7.46
7.45
7.44
7.43
7.42
7.26
7.22
7.21
7.20
7.20
5.97
CDCl3, 400 MHz
NC
CN
N
Ph
1.00
1.97
3.08
5.30
0.97
0.99
f1 (ppm)


158.76
158.68
150.65
144.34
141.45
138.52
132.87
129.77
129.03
128.93
127.23
121.75
120.38
117.89
116.27
114.68
99.84
77.48
77.16
76.84
CDCl3, 100 MHz
NC
CN
N
Ph
f1 (ppm)


8.74
8.73
7.94
7.92
7.69
7.42
7.41
7.39
7.37
7.36
7.33
7.19
7.18
7.17
7.16
5.82
1.26
CDCl3, 400 MHz
tBu
CN
N
Ph
1.00
1.98
0.98
5.19
3.27
0.97
9.03
f1 (ppm)


160.60
159.38
154.90
150.30
145.81
138.95
134.29
129.51
128.97
128.08
127.32
126.15
122.25
120.82
117.36
95.95
77.48
77.16
76.84
35.07
31.24
CDCl3, 100 MHz
tBu
CN
N
Ph
f1 (ppm)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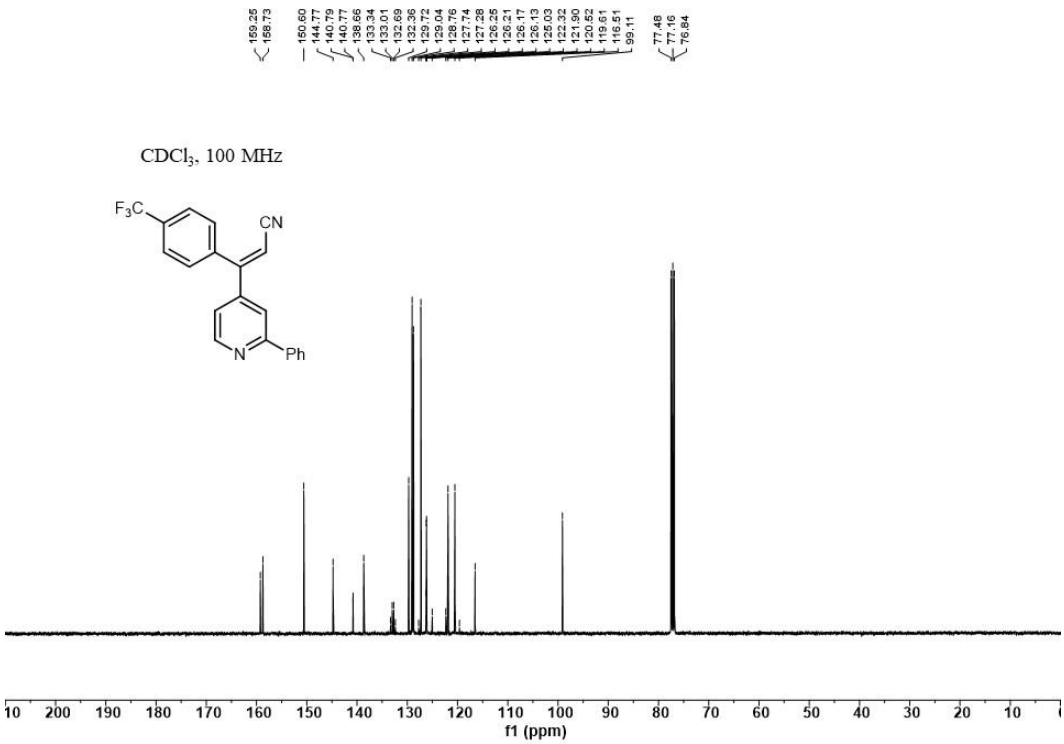
8.85
8.84
8.83
8.01
8.00
8.00
7.99
7.99
7.98
7.98
7.76
7.76
7.76
7.76
7.70
7.68
7.51
7.51
7.50
7.49
7.49
7.48
7.48
7.47
7.47
7.46
7.46
7.45
7.44
7.44
7.43
7.43
7.42
7.26
7.25
7.24
7.23
7.23
5.97
CDCl3, 400 MHz
F3C
CN
N
Ph
1.00
2.04
1.03
2.07
5.06
1.01
0.97
f1 (ppm)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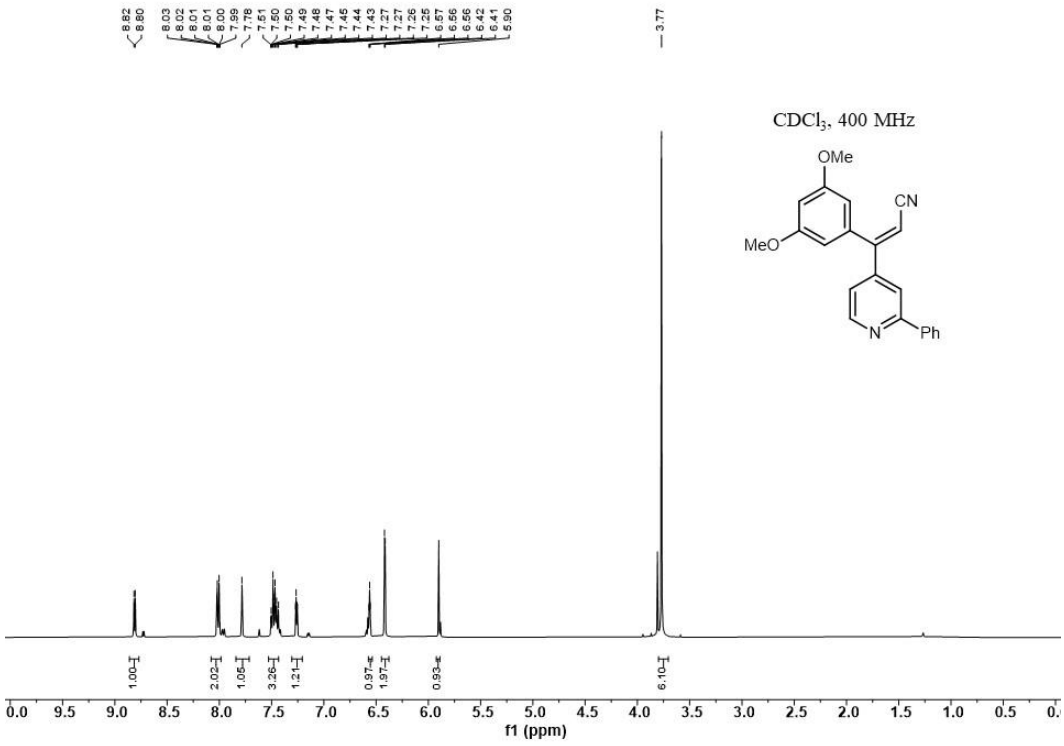
158.73
150.60
144.77
140.79
140.77
138.66
133.34
133.01
132.69
132.36
129.72
129.04
128.76
127.74
127.28
126.25
126.21
126.17
126.13
125.03
122.32
121.90
120.52
119.61
116.51
99.11
77.48
77.16
76.84
CDCl3, 100 MHz
F3C
CN
N
Ph
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)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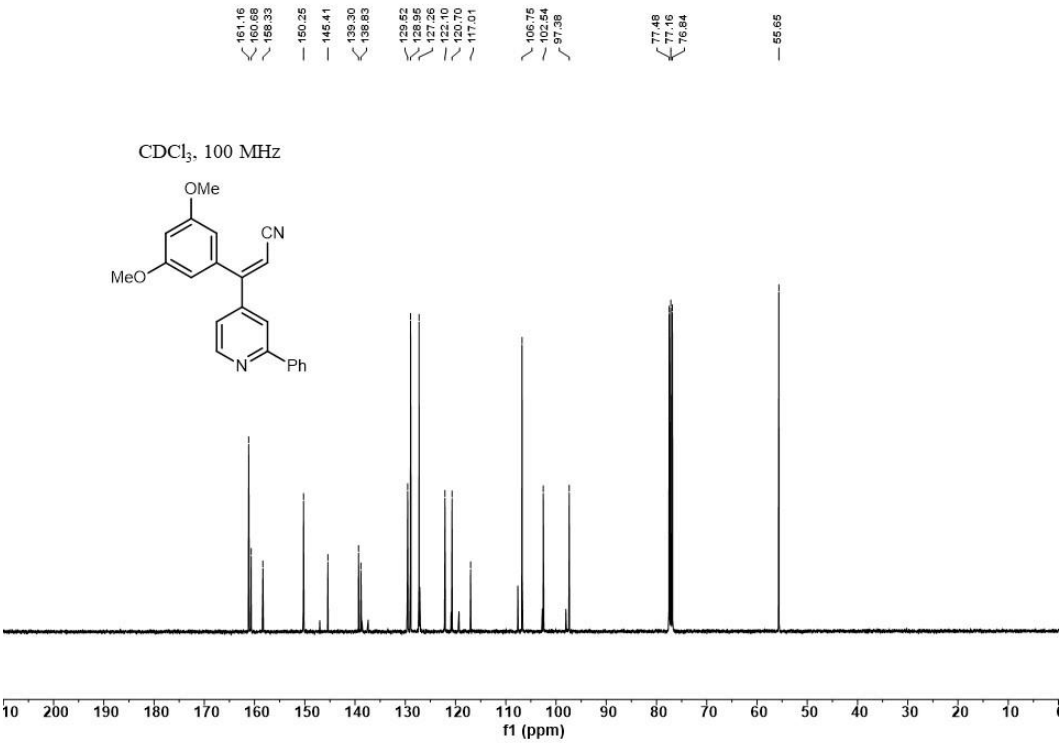
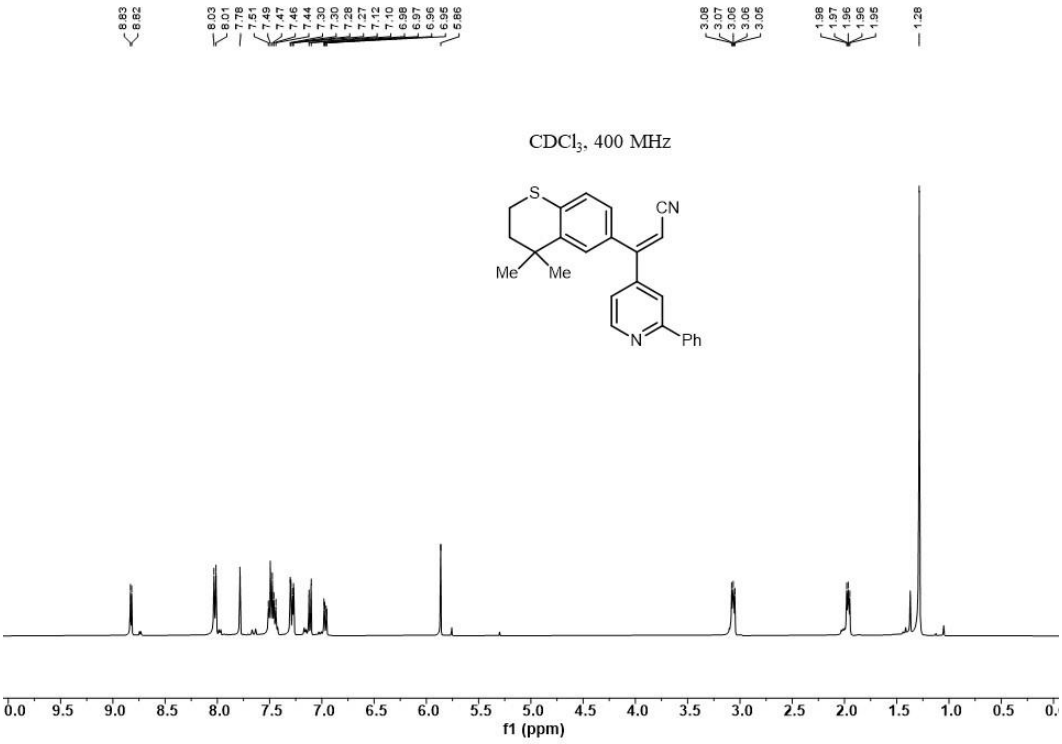
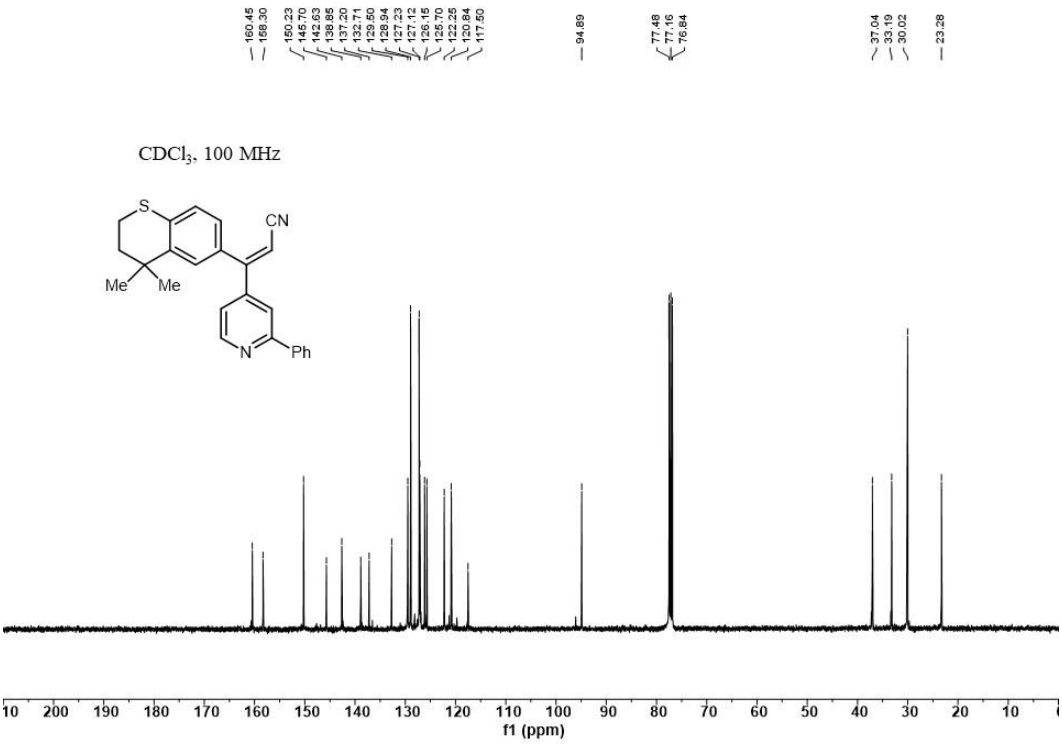
8.80
8.03
8.02
8.01
8.01
8.00
7.99
7.78
7.51
7.50
7.50
7.49
7.48
7.47
7.45
7.44
7.43
7.27
7.27
7.26
7.25
6.57
6.56
6.56
6.42
6.41
5.90
3.77
CDCl3, 400 MHz
OMe
CN
MeO
N
Ph
1.00
2.02
1.05
3.26
1.21
0.97
1.97
0.93
6.10
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


161.16
160.68
158.33
150.25
145.41
139.30
138.83
129.52
128.95
127.26
122.10
120.70
117.01
106.75
102.54
97.38
77.48
77.16
76.84
55.65
CDCl3, 100 MHz
OMe
CN
MeO
N
Ph
f1 (ppm)


8.83
8.82
8.03
8.01
7.78
7.51
7.49
7.47
7.46
7.44
7.30
7.30
7.28
7.27
7.12
7.10
6.98
6.97
6.96
6.95
5.86
3.08
3.07
3.06
3.06
3.05
1.98
1.97
1.96
1.96
1.95
1.28
CDCl3, 400 MHz
S
CN
Me
Me
N
Ph
f1 (ppm)


160.45
158.30
150.23
145.70
142.63
138.85
137.20
132.71
129.50
128.94
127.23
127.12
126.15
125.70
122.25
120.84
117.50
94.89
77.48
77.16
76.84
37.04
33.19
30.02
23.28
CDCl3, 100 MHz
S
CN
Me
Me
N
Ph
f1 (ppm)


8.84
8.84
8.83
8.82
8.03
8.03
8.02
8.01
8.01
8.01
8.00
7.79
7.79
7.78
7.78
7.51
7.51
7.50
7.49
7.48
7.47
7.47
7.46
7.46
7.46
7.45
7.44
7.44
7.43
7.42
7.42
7.41
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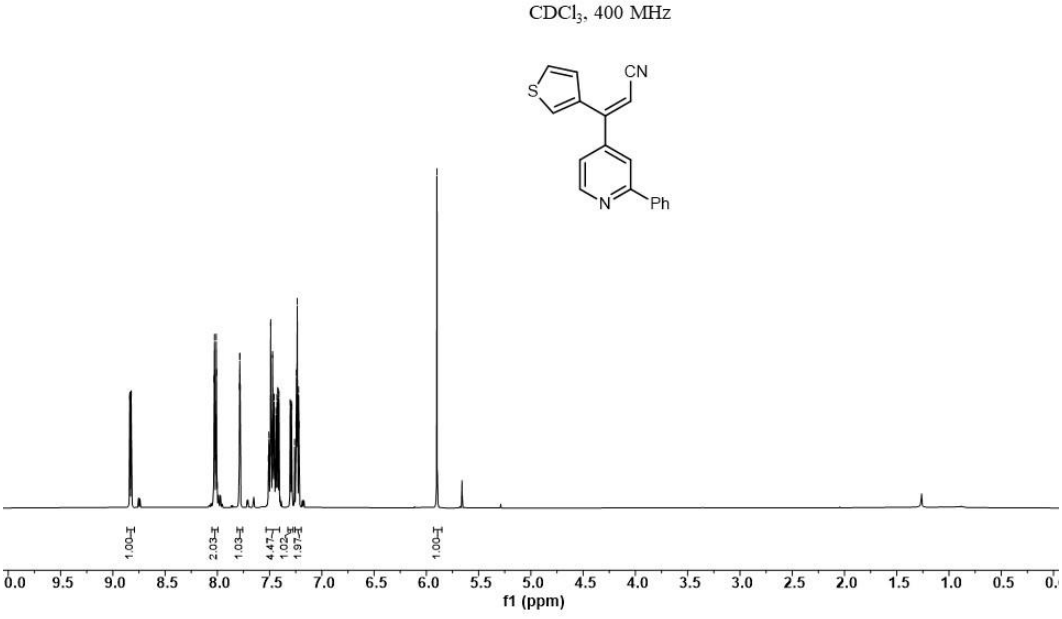
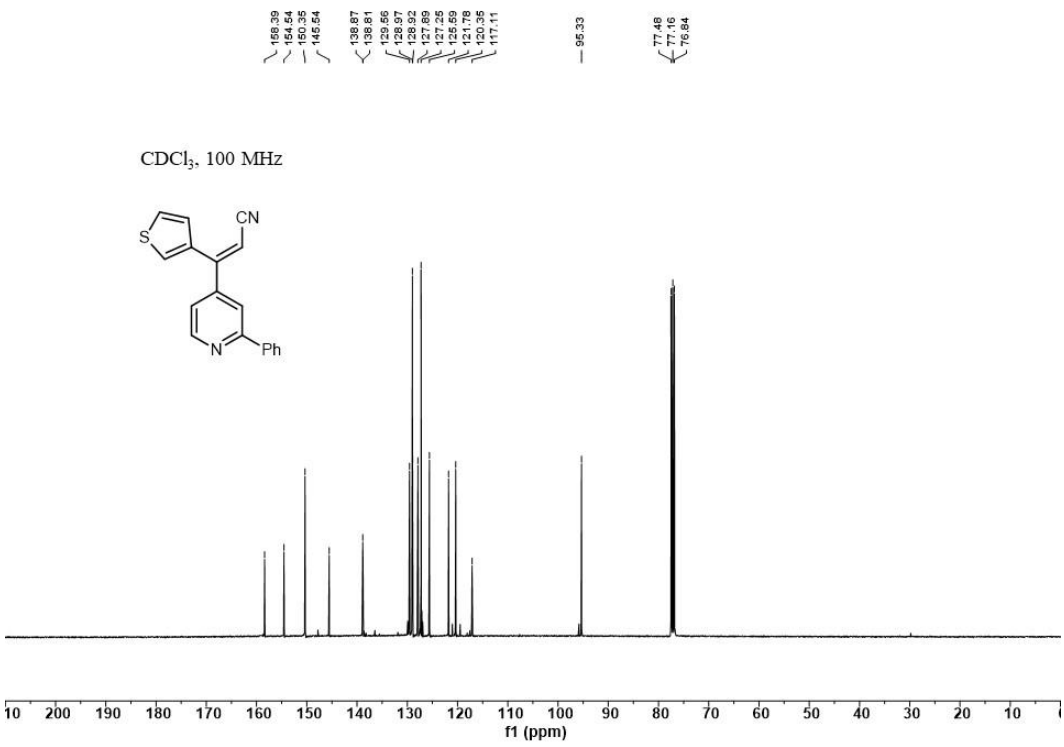
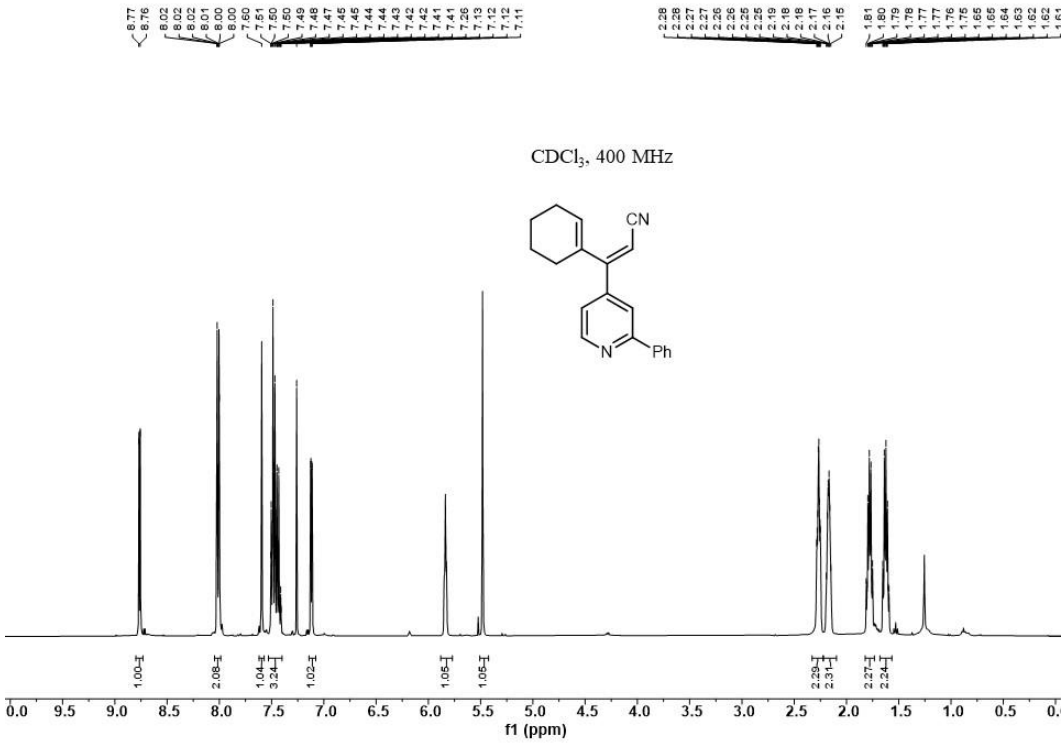
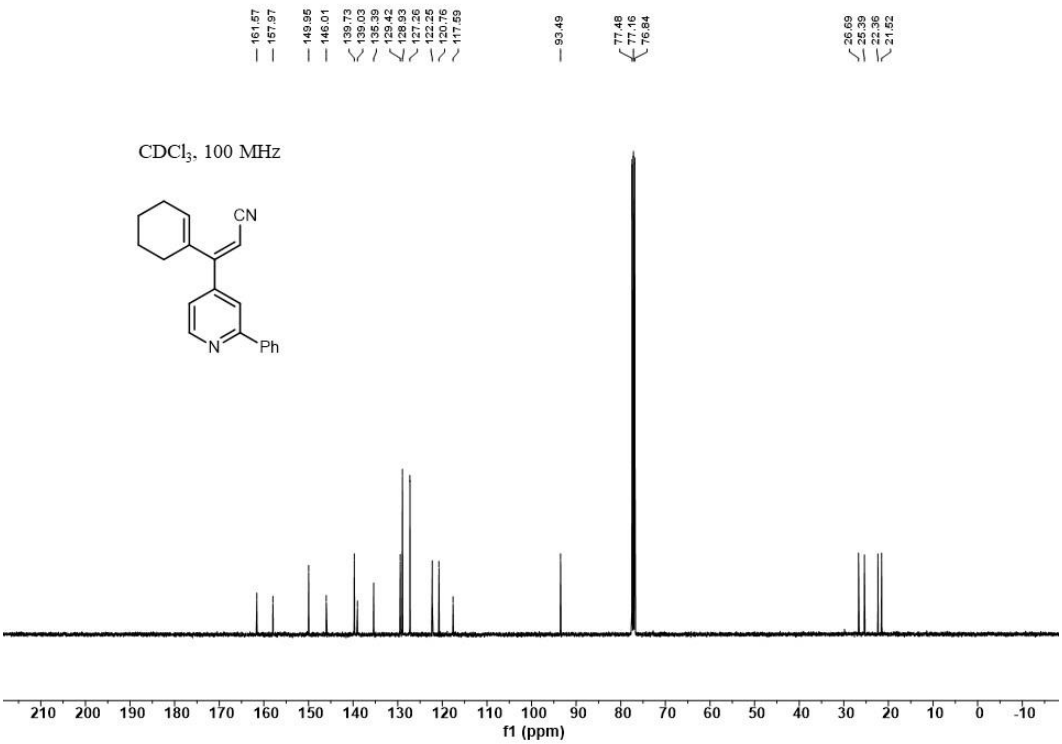
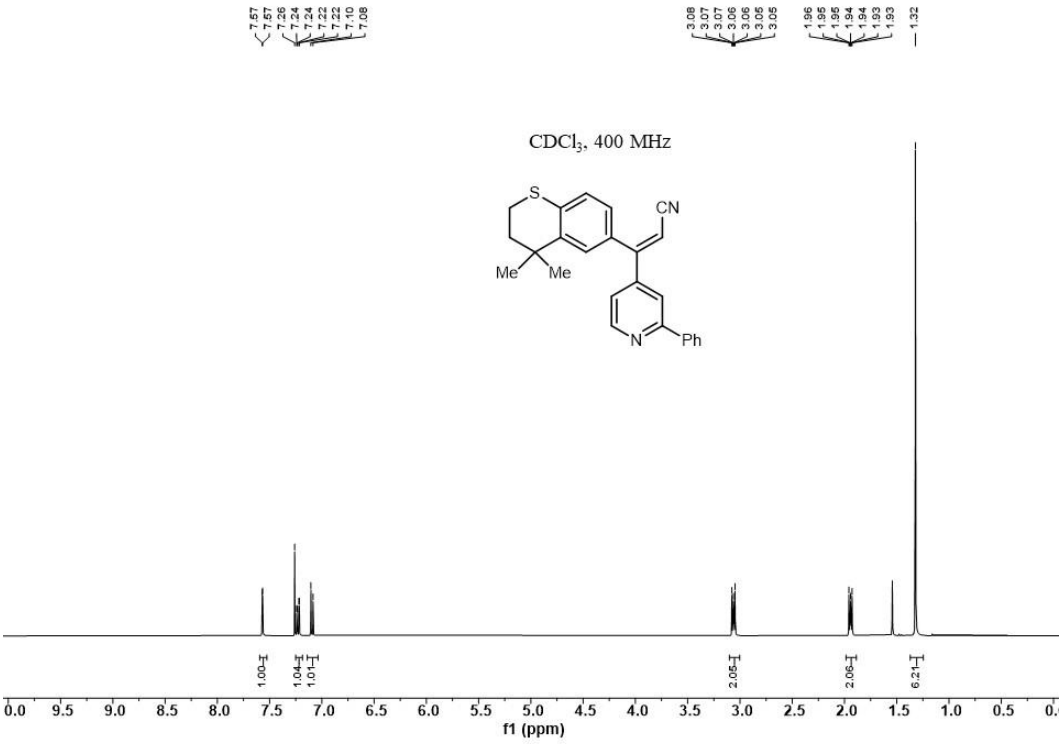
7.24
7.23
7.23
7.22
7.22
6.90

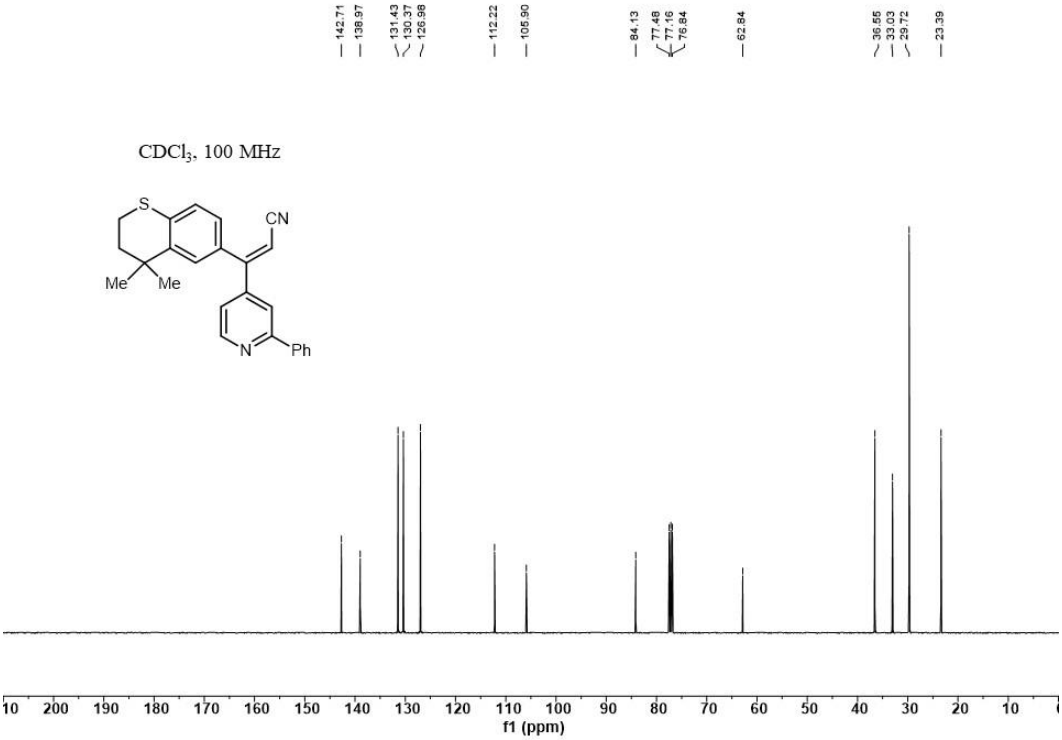

CDCl3, 400 MHz
S
CN
N
Ph
1.00
2.03
1.03
4.47
1.02
1.97
1.00
f1 (ppm)

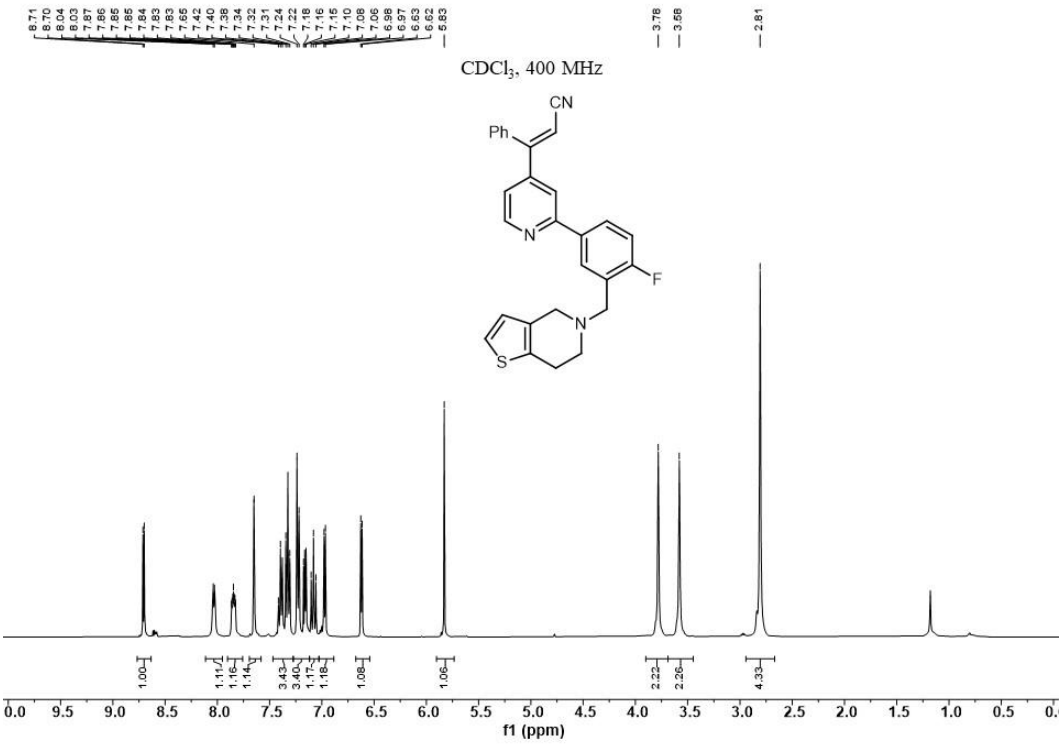

158.39
154.54
150.35
145.54
138.87
138.81
129.56
128.97
128.92
127.89
127.25
125.59
121.78
120.35
117.11
95.33
77.48
77.16
76.84
CDCl3, 100 MHz
CN
S
N
Ph
f1 (ppm)

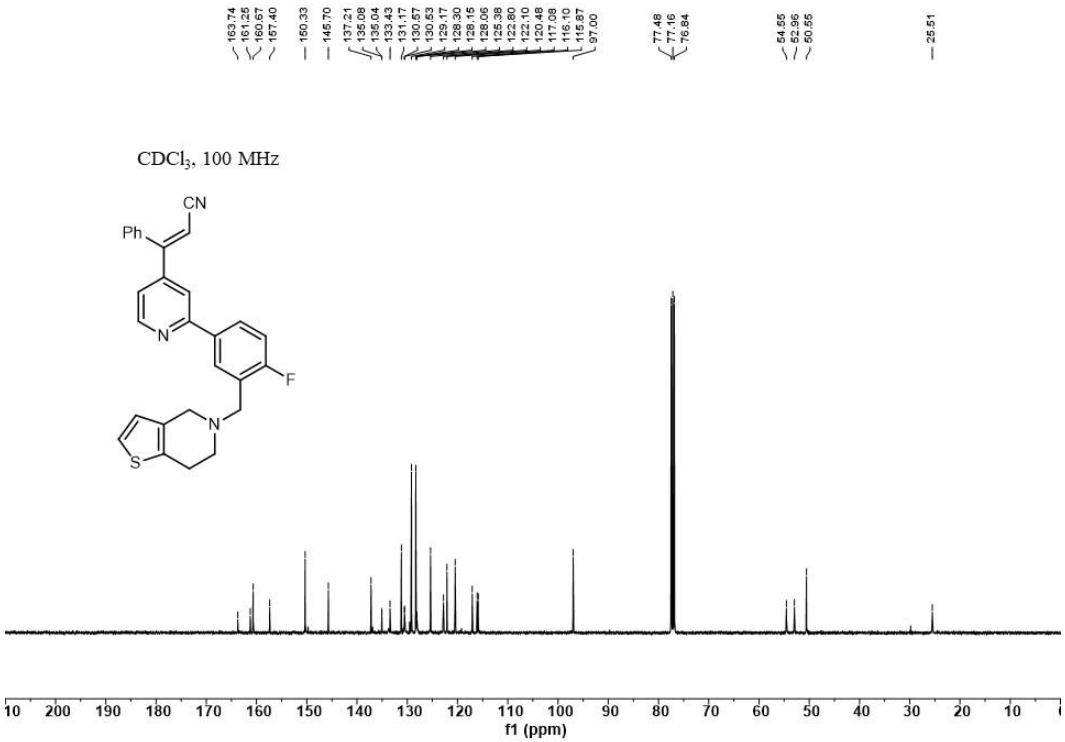

8.77
8.76
8.02
8.02
8.02
8.01
8.00
8.00
7.60
7.51
7.50
7.50
7.49
7.48
7.47
7.45
7.45
7.44
7.44
7.43
7.42
7.42
7.41
7.41
7.26
7.13
7.12
7.12
7.11
2.28
2.28
2.27
2.27
2.26
2.26
2.25
2.25
2.19
2.18
2.18
2.17
2.16
2.15
1.81
1.80
1.79
1.78
1.77
1.77
1.76
1.75
1.65
1.65
1.64
1.63
1.62
1.62
CDCl3, 400 MHz
CN
N
Ph
1.00
2.08
1.04
3.24
1.02
1.05
1.05
2.29
2.31
2.27
2.24
f1 (ppm)

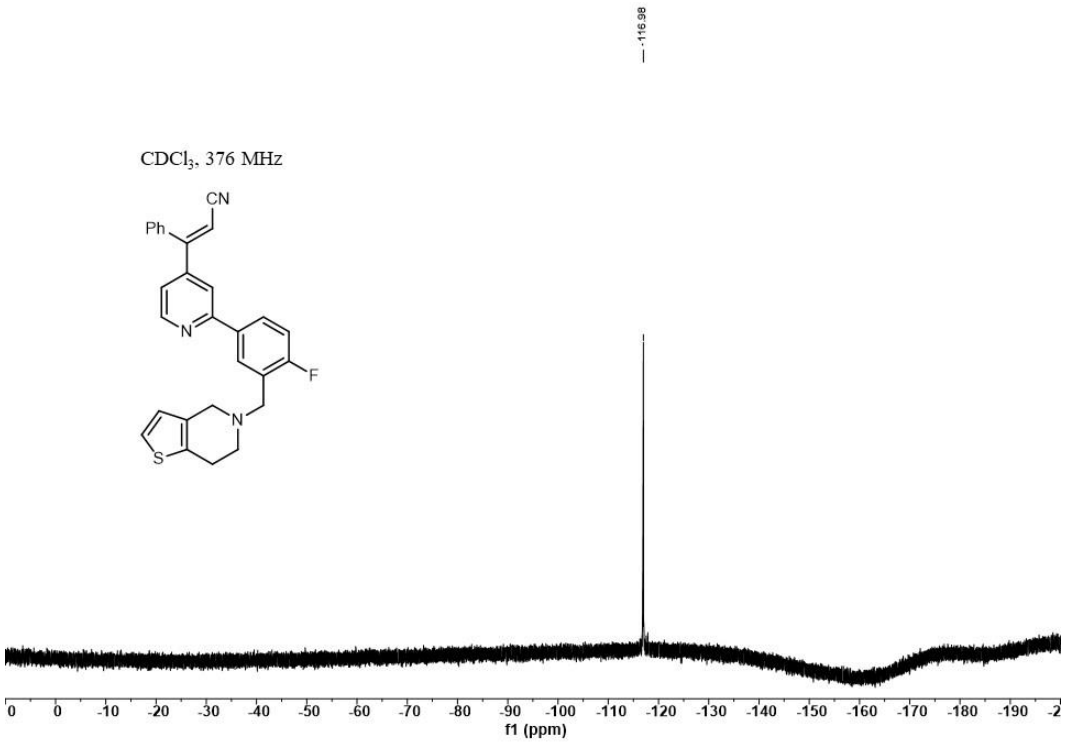

161.57
157.97
149.95
146.01
139.73
139.03
135.39
129.42
128.93
127.26
122.25
120.76
117.59
93.49
77.48
77.16
76.84
26.69
25.39
22.36
21.62
CDCl3, 100 MHz
CN
N
Ph
f1 (ppm)

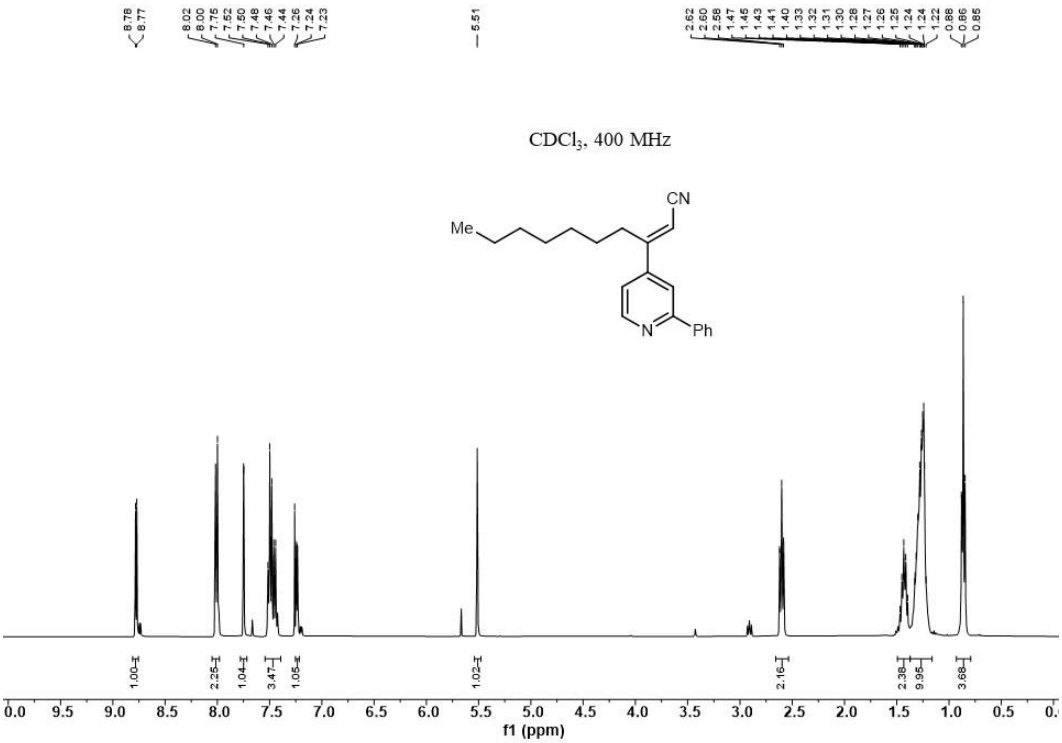

7.57
7.57
7.26
7.24
7.24
7.22
7.22
7.10
7.08
3.08
3.07
3.07
3.06
3.06
3.05
3.05
1.96
1.95
1.95
1.94
1.94
1.93
1.93
1.32
CDCl3, 400 MHz
S
CN
Me
Me
N
Ph
1.00
1.04
1.01
2.05
2.06
6.21
f1 (ppm)

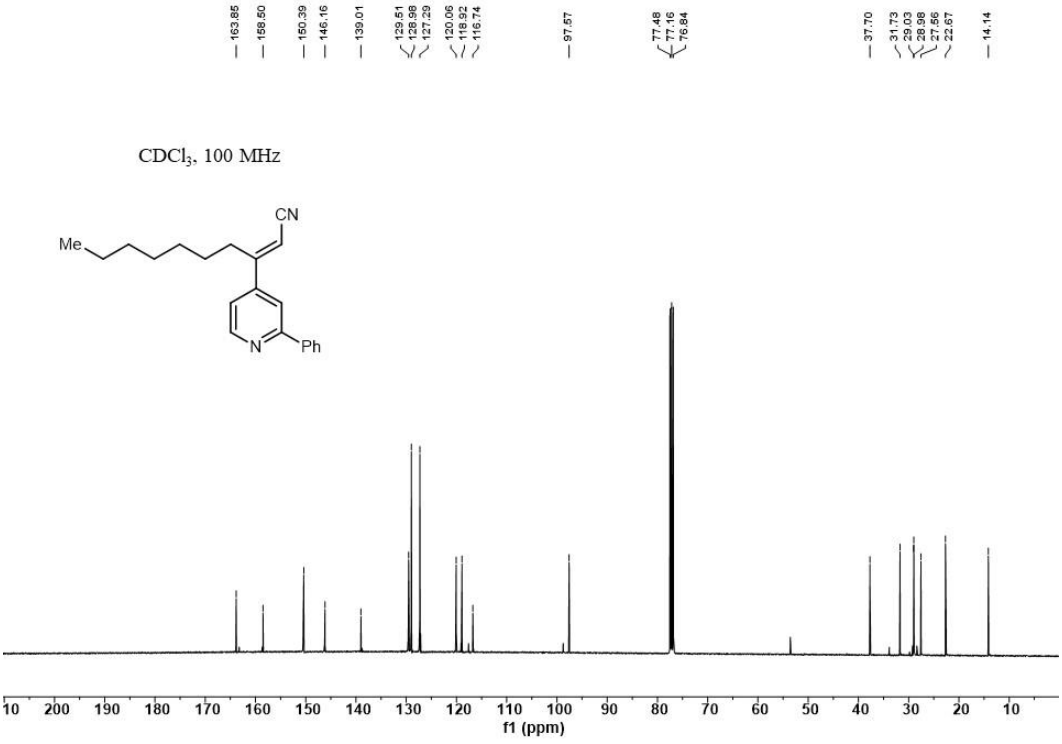

142.71
138.97
131.43
130.37
126.98
112.22
105.90
84.13
77.48
77.16
76.84
62.84
36.55
33.03
29.72
23.39
CDCl3, 100 MHz
S
CN
Me
Me
N
Ph
f1 (ppm)


8.71
8.70
8.04
8.03
7.87
7.86
7.85
7.85
7.84
7.83
7.83
7.65
7.42
7.40
7.38
7.34
7.32
7.31
7.24
7.22
7.18
7.16
7.15
7.10
7.08
7.06
6.98
6.97
6.63
6.62
5.83
3.78
3.56
2.81
CDCl3, 400 MHz
CN
Ph
N
F
N
S
1.00
1.11
1.16
1.14
3.43
3.40
1.17
1.18
1.08
1.06
2.23
2.26
4.33
f1 (ppm)

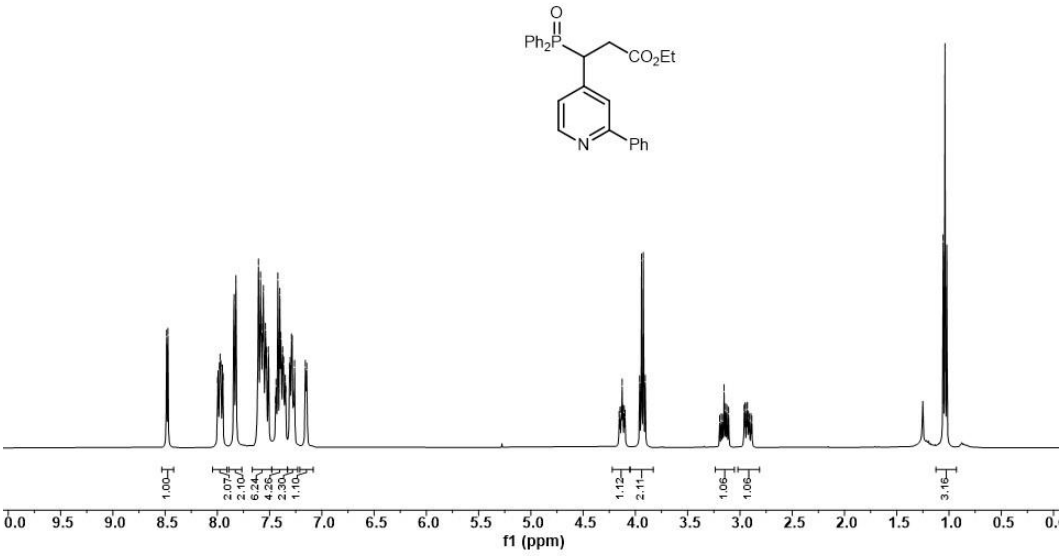

163.74
161.25
160.67
157.40
150.33
145.70
137.21
136.08
135.04
133.43
131.17
130.57
130.53
129.17
128.30
128.15
128.06
125.38
122.80
122.10
120.48
117.08
116.10
115.87
97.00
77.48
77.16
76.84
54.55
52.96
50.55
25.51
CDCl3, 100 MHz
CN
Ph
N
F
N
S
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-116.98
CDCl3, 376 MHz
CN
Ph
N
F
N
S
0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2
f1 (ppm)

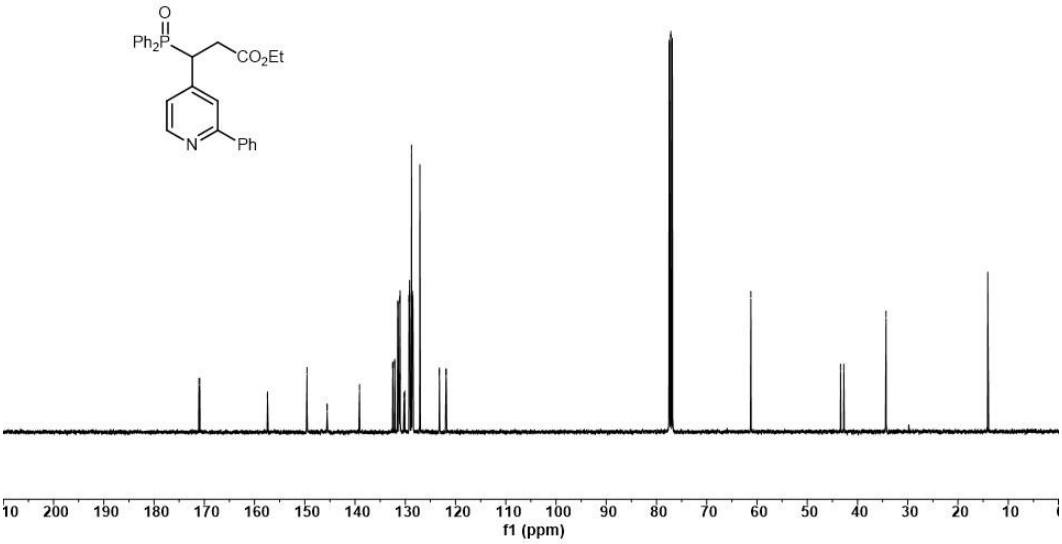

8.78
8.77
8.02
8.00
7.75
7.52
7.50
7.48
7.46
7.44
7.26
7.24
7.23
5.51
2.62
2.60
2.58
1.47
1.45
1.43
1.41
1.40
1.33
1.32
1.31
1.30
1.28
1.27
1.26
1.25
1.24
1.24
1.22
0.88
0.86
0.85
CDCl3, 400 MHz
CN
Me
N
Ph
1.00
2.25
1.04
3.47
1.05
1.02
2.16
2.38
9.95
3.68
f1 (ppm)

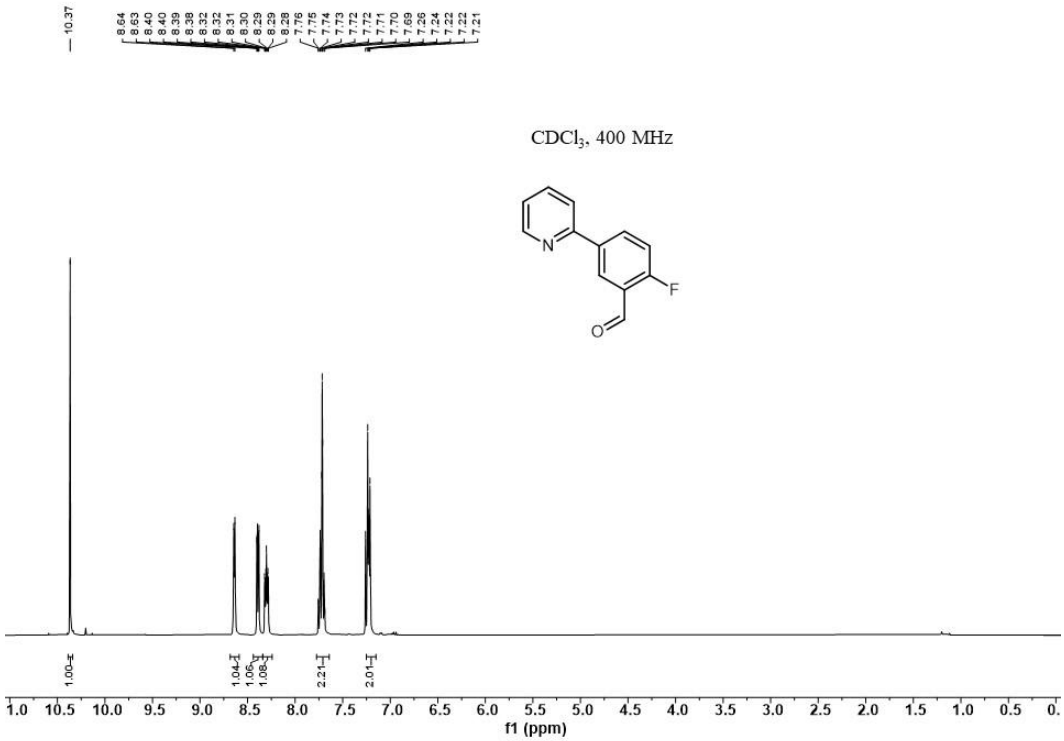

163.85
158.60
150.39
146.16
139.01
129.51
128.98
127.29
120.06
118.92
116.74
97.57
77.48
77.16
76.84
37.70
31.73
29.03
28.98
27.56
22.67
14.14
CDCl3, 100 MHz
CN
Me
N
Ph
f1 (ppm)

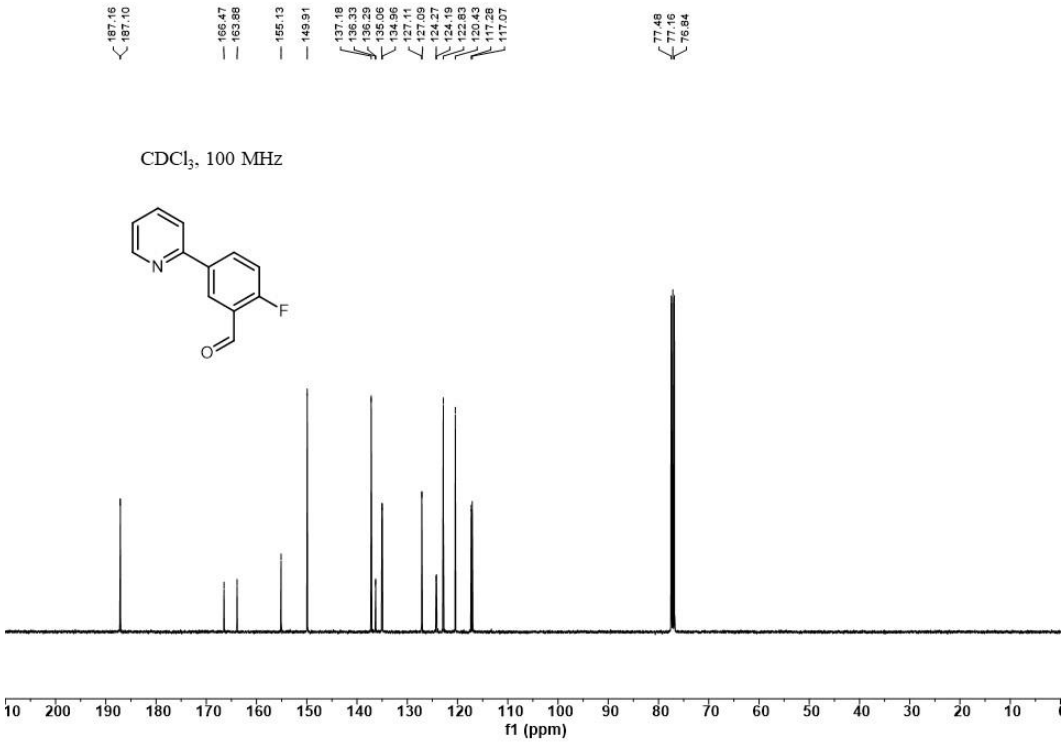
$CDCl_3$, 400 MHz



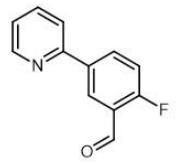
$CDCl_3$, 100 MHz



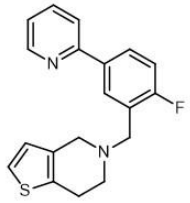

10.37
8.64
8.63
8.40
8.40
8.39
8.38
8.32
8.31
8.30
8.29
8.29
8.28
7.76
7.75
7.74
7.73
7.72
7.72
7.71
7.70
7.69
7.26
7.24
7.22
7.22
7.21
CDCl3, 400 MHz
N
F
O
1.00
1.04
1.06
1.08
2.21
2.01
f1 (ppm)

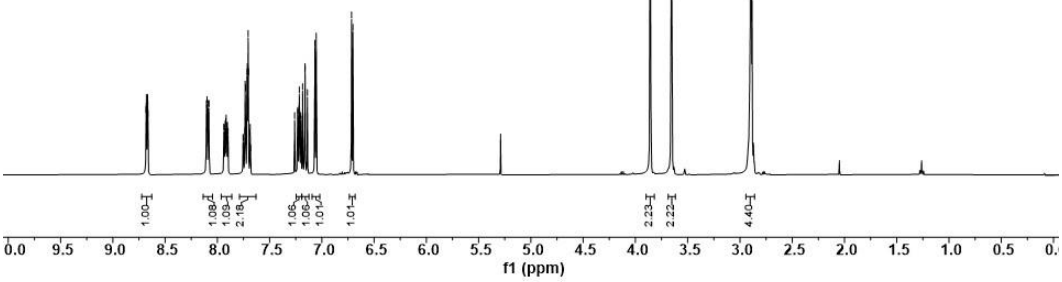

187.16
187.10
166.47
163.88
155.13
149.91
137.18
136.33
136.29
135.06
134.96
127.11
127.09
124.27
124.19
122.83
120.43
117.28
117.07
77.48
77.16
76.84
CDCl3, 100 MHz
N
F
O
f1 (ppm)

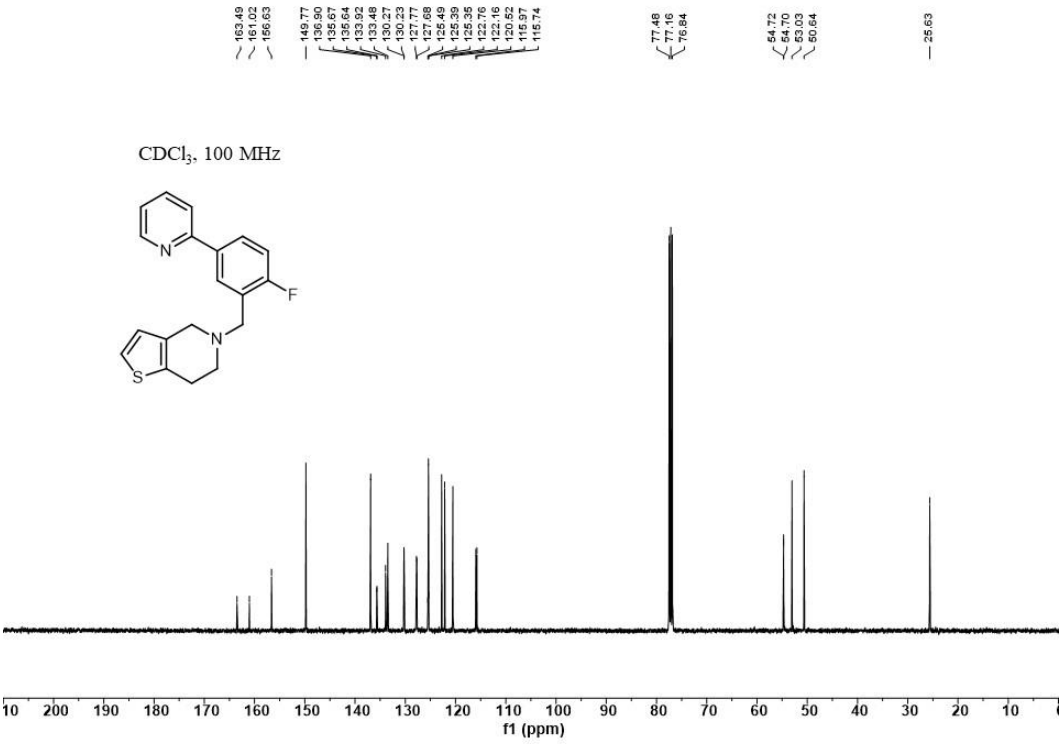
$CDCl_3$, 376 MHz

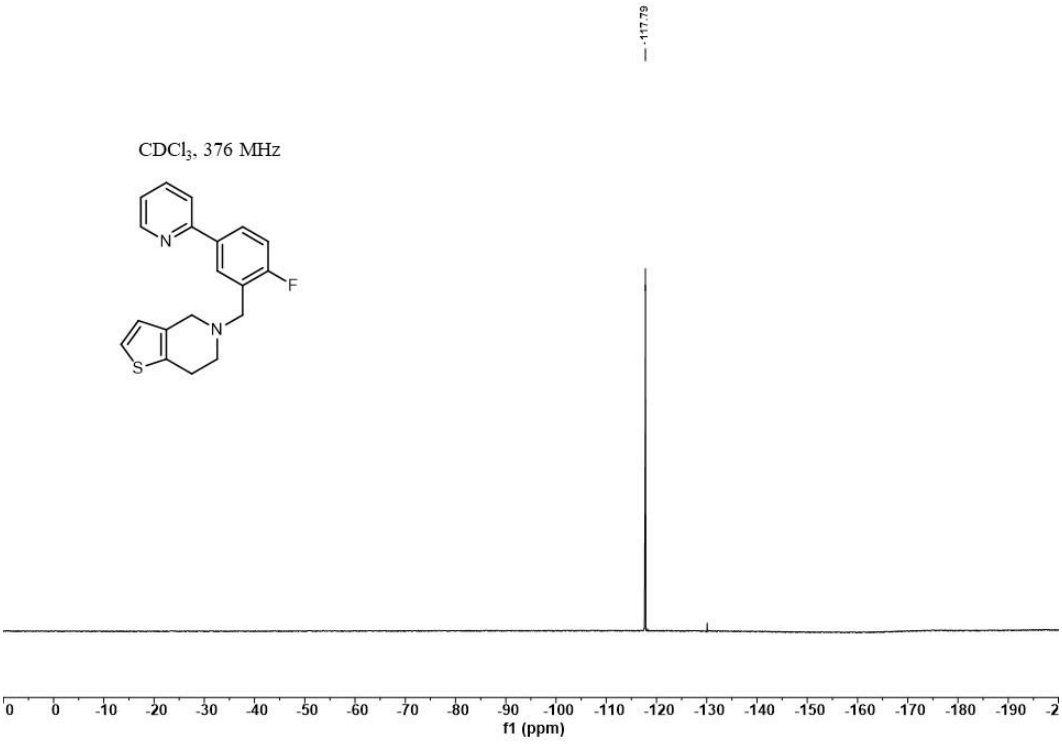


$CDCl_3$, 400 MHz






163.49
161.02
156.63
149.77
136.90
135.67
135.64
133.62
133.48
130.27
130.23
127.77
127.68
125.49
125.39
125.35
122.76
122.16
120.52
115.97
115.74
77.48
77.16
76.84
54.72
54.70
53.03
50.64
25.63
CDCl3, 100 MHz
N
F
N
S
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-117.79
CDCl3, 376 MHz
N
F
N
S
0 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -2
f1 (ppm)

APPENDIX THREE

A DISTINCT NUCLEOPHILE DELIVERY SYSTEM FOR PYRIDONE AND AMINOPYRIDINE SYNTHESIS VIA PHOSPHORUS LIGAND- COUPLING: EXPERIMENTAL

A3.1 General Methods and Materials

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (400 MHz), an Agilent Inova 400 (400 MHz) spectrometer, an Agilent Inova 500 (500 MHz) spectrometer, or a Bruker AV-111 400 (400 MHz) spectrometer. Chemical shifts (δ) are reported in ppm and quoted to the nearest 0.1 ppm relative to the residual protons in $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm) or $(CD_3)_2SO$ (2.05 ppm) and coupling constants (*J*) are quoted in Hertz (Hz). Data are reported as follows: Chemical shift (multiplicity, coupling constants, number of protons). Coupling constants were quoted to the nearest 0.1 Hz and multiplicity reported according to the following convention: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextet, sp = septet, m = multiplet, br = broad. Where coincident coupling constants have been observed, the apparent (app) multiplicity of the proton resonance has been reported. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at ambient temperature on a Varian 400 MR spectrometer (100 MHz), an Agilent Inova 400 (100 MHz) spectrometer, an Agilent Inova 500 spectrometer (125 MHz) or a Bruker AV-111 400 (100 MHz) spectrometer. Chemical shift (δ) was measured in ppm and quoted to the nearest 0.01 ppm relative to the residual solvent peaks in $CDCl_3$ (77.16 ppm), $(CD_3)_2SO$ (39.51 ppm), CD_3OD (49.00 ppm) or CD_3CN (1.32 ppm).

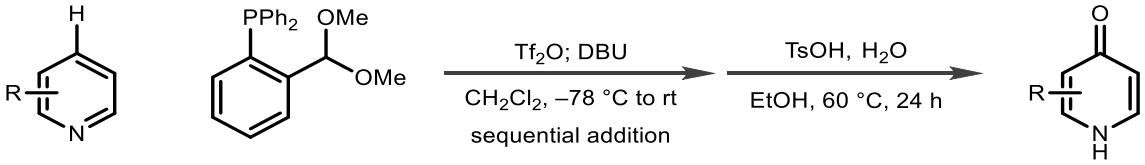
Low-resolution mass spectra (LRMS) were measured on an Agilent 6310 Quadrupole Mass Spectrometer. High-resolution mass spectra (HRMS) were measured on an Agilent 6224 TOF

LC/MS ("OTOF") interfaced to an Agilent 1200 HPLC with multi-mode (combined ESI and APCI) and Direct Analysis in Real Time (DART) sources. (IR) spectra were recorded on a Nicolet IS-50 FT-IR spectrometer as either solids or neat films, either through direct application or deposited in CHCl3, with absorptions reported in wavenumbers (cm-1). Analytical thin layer chromatography (TLC) was performed using pre-coated Silicycle glass backed silica gel plates (Silicagel 60 F254). Flash column chromatography was undertaken on Silicycle silica gel Siliaflash P60 40-63 um (230-400 mesh) under a positive pressure of air unless otherwise stated. Visualization was achieved using ultraviolet light (254 nm) and chemical staining with ceric ammonium molybdate or basic potassium permanganate solutions as appropriate. Melting points (mp) were recorded using a Büchi B-450 melting point apparatus and are reported uncorrected.

Tetrahydrofuran (THF), toluene, hexane, diethyl ether and dichloromethane were dried and distilled using standard methods.[1] Methanol, 1,2-dichloroethane (DCE), 1,4-dioxane, ethyl acetate, chloroform, and acetone were purchased anhydrous from Sigma Aldrich chemical company. All reagents were purchased at the highest commercial quality and used without further purification. Reactions were carried out under an atmosphere of nitrogen unless otherwise stated. All reactions were monitored by TLC, ^{1}H NMR spectra taken from reaction samples, and liquid chromatography mass spectrometry (LCMS) using an Agilent 6310 Quadrupole Mass Spectrometer for MS analysis. Tf_2O (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. 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.

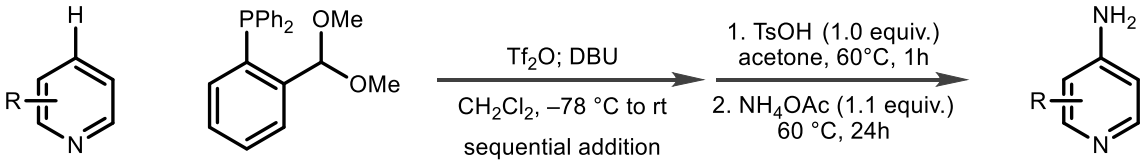
A3.2 Hydroxylation of Heterocycles

General Procedure A



An oven dried 8 mL vial equipped with a stir bar was charged with the heterocycle (1.0 equiv) and (2-(dimethoxymethyl)phenyl)diphenylphosphane (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). 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 DBU (1.0 equiv) was added dropwise via syringe, the cooling bath was removed, and the reaction was warmed to room temperature while stirring (approximately 5 minutes). Then, the reaction mixture was concentrated *in vacuo* and EtOH (0.4 M), TsOH (1.0 equiv), and H_2O (10 equiv) were added sequentially. The mixture was heated to 60 °C and stirred for 24 hours. To the crude reaction was added triphenylmethane (1.0 equiv) as an internal standard, and a 0.1 mL aliquot of the reaction was diluted to 0.7 mL with $CDCl_3$ for ^1H NMR analysis.

A3.2 Amination of Heterocycles



An oven dried 8 mL vial equipped with a stir bar was charged with the heterocycle (1.0 equiv) and (2-(dimethoxymethyl)phenyl)diphenylphosphane (1.1 equiv) and placed under a nitrogen atmosphere (vacuum/nitrogen backfill, 3 cycles). 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 DBU (1.0 equiv) was added dropwise via syringe, the cooling bath was removed, and the reaction was warmed to room temperature while stirring (approximately 5 minutes). Then, the reaction mixture was concentrated *in vacuo* and acetone (0.4 M) and TsOH (1.0 equiv) were added sequentially. The mixture was heated to 60 °C and stirred for 1 hour, then NH_4OAc (1 equiv) was added followed by heating at 60 °C for 24 h. To the crude reaction was added triphenylmethane (1.0 equiv) as an internal standard, and a 0.1 mL aliquot of the reaction was diluted to 0.7 mL with $CDCl_3$ for ^1H NMR analysis.