Regio- and Enantioselective Synthesis of N-alkyl 1,2- and 1,6-dihydropyridines through Rhodium-Catalyzed Nucleophilic Dearomatization

by

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Abstract

Nonaromatic nitrogen heterocycles, particularly the ones containing one or multiple stereogenic centers, are common structural motifs in bioactive natural products and continue to be challenging synthetic targets. The dihydropyridine motif is an attractive intermediate in the synthesis of such heterocycles. Prior syntheses of such molecules usually involve linear syntheses or highly specialized starting materials. Dihydropyridines can be converted to other (partially) saturated nitrogen heterocycles such as tetrahydropyridines and piperidines through hydrogenation and functionalization reactions. Here, we discuss the synthesis of 1,6- and 1,4 dihydropyridines as synthetic intermediates to small molecule synthesis.

First, we investigated boronic acids as nucleophiles due to their commercial availability and functional group tolerance. We have reported the formation of 1,6-dihydropyridines containing fully substituted stereogenic centers using phenyl and alkenyl boronic acids with a variety of functional groups including alkenes, free alcohols, ethers, amides, esters, halides, and heterocycles.

Next, we explored the use of boronic acid pinacol esters (Bpins) as nucleophiles due to their higher stability, which enabled us to increase the yield of heterocycle addition, as well as expand the scope of N-heteroarene starting materials. We were also able to employ our strategy to complete an enantioselective total synthesis of the natural product nuphar indolizidine.

Finally, we are currently developing the regioselective addition of boronic acids and their pinacol esters to N-alkyl pyridinium salts. We found that different ligands bound to the metal provide different selectivity, particularly to the C-2 electrophilic site on the heteroarenium salt.

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List of Schemes

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List of Abbreviations

Ac	Acetyl
acac	Acetylacetonate
BINAP	([1,1'-binaphthalene]-2,2'-diyl)bis(diphenylphosphane)
Bn	Benzyl
Bz	Benzoyl
Cbz	Benzyl chloroformyl
COD	Cyclooctodiene
coe	Cyclooctene
Cy	Cyclohexyl
DCE	1,2-dichloroethane
DHP	Dihydropyridine
DME	1,2-dimethoxyethane
Equiv	equivalents
Et	Ethyl
i-Bu	Isobutyl
i-Pr	Isopropyl
Me	Methyl
Ph	Phenyl
PhMe	Toluene
Pr	Propyl
py	Pyridine
TBDMS	Tert-Butyldimethylsilyl
t-Bu	Tert-butyl
TIPS	Triisopropylsilyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl

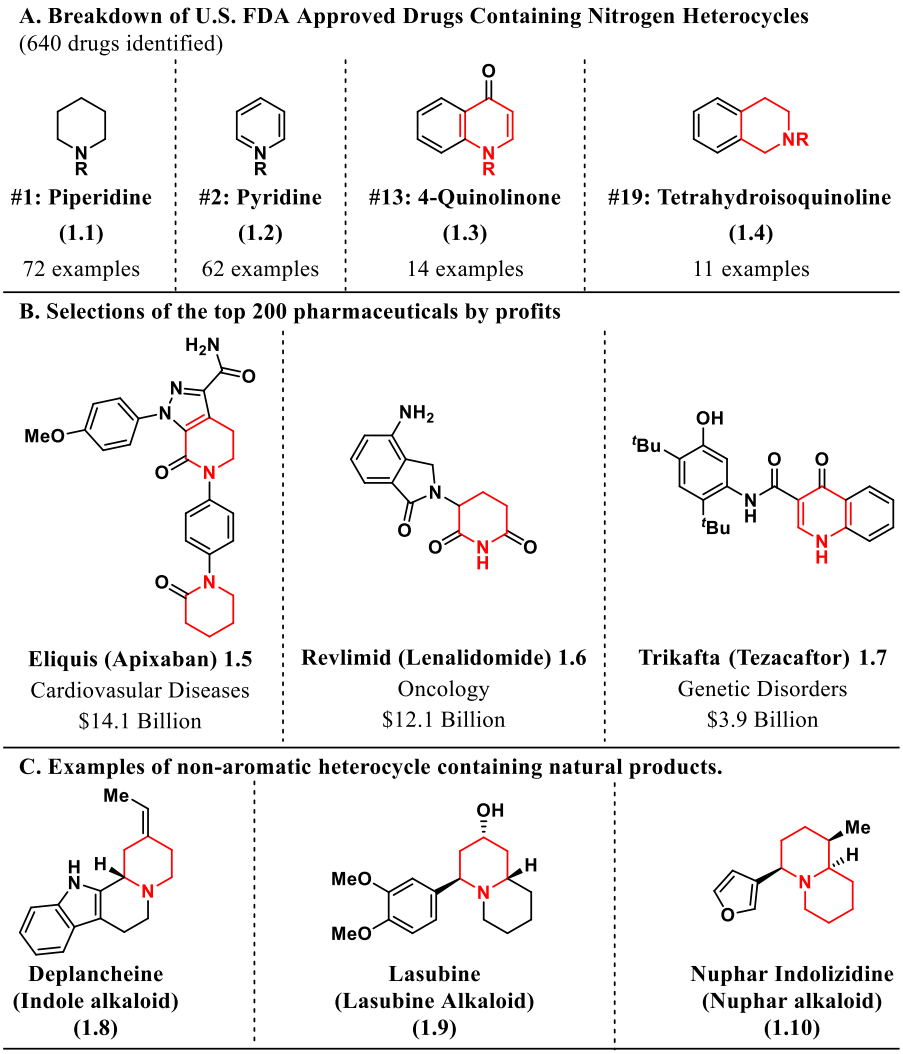
Chapter 1: Introduction

1.1. Importance of azaheterocycles and dihydropyridines for their synthesis:

An analysis of U.S. FDA-approved small-molecule therapeutics found that the most common structural motifs, accounting for 59% of all structures, are six-membered azaheterocycles such as piperidine (**1.1**), and pyridine (**1.2**) (Figure 1.1.A).[1] A more recent analysis of molecules containing six-membered azaheterocycles shows that molecules containing these scaffolds continue to bring in hundreds of billions of dollars in profit for the pharmaceutical industry (Figure 1.1.B).[2] In addition to FDA approved therapeutic drugs, these heterocyclic moieties are prevalent in agrochemicals and alkaloid natural products such as indole (**1.8**), lasubine (**1.9)**, and nuphar alkaloids (**1.10**) (Figure 1.1.C). A common structural feature in such natural products is a stereogenic center alpha to the ring nitrogen. Considering their importance, the synthesis of azaheterocycles has attracted significant attention of the synthetic community. However, despite past efforts, the asymmetric synthesis of azaheterocycles, especially those containing stereogenic centers alpha to the nitrogen, remains challenging.

Dihydropyridines (DHPs) are versatile synthetic intermediates for the synthesis of six membered nitrogen heterocycles. This versatility is due to the fact that (1) DHPs contain unsaturation in synthetically useful locations, allowing for their chemoselective and stereoselective fuctionalizations for the synthesis of tetrahydropyridines and piperidines[3,4]; and (2) DHPs can be oxidized to the corresponding aromatic azaheterocycles.[5]

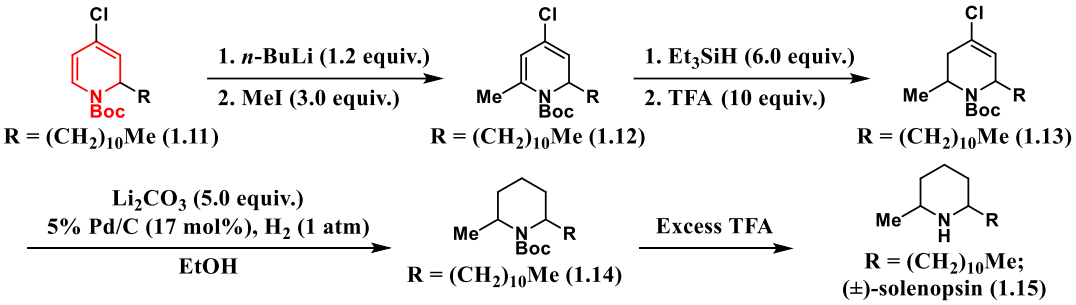
Figure 1.1:Importance and prevalence of six-membered azaheterocycles.



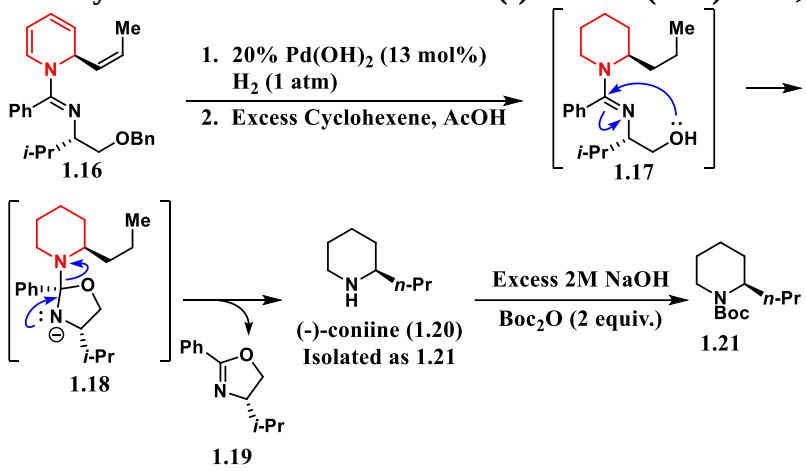
There is a plethora of examples using DHPs as synthetic intermediates, showcasing the DHP's utility for the synthesis of various nitrogen heterocycles. Comins and coworkers have used DHPs as intermediates in their synthesis of more than 40 alkaloids.[6–14] For example, DHP **1.11** was used as a key intermediate in their synthesis of (±)-solenopsin (**1.15**) (Scheme 1.1)[15]. In addition to the Comins research group, Charette and others have also significantly contributed to the synthesis of alkaloids using DHPs as key intermediates. For example, DHPs **1.16** and **1.22** were used as key intermediates in the synthesis of hemlock toxin coniine (**1.20**) (Scheme 1.2) and

alkaloid (+)-julifloridine (**1.26**) respectively (Scheme 1.3).[16,17] Select examples of alkaloids that have been prepared utilizing DHPs as key examples are shown in Figure 1.4.[18–23]

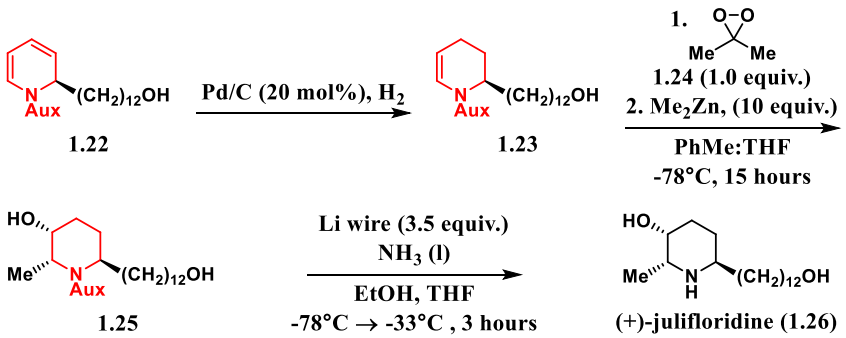
Scheme 1.1: Synthesis of (±)-solenopsin (1.15) via 1,2-DHP intermediate.



Scheme 1.2: Synthesis of the hemlock toxin (-)-coniine (1.20) via 1,2-DHP.

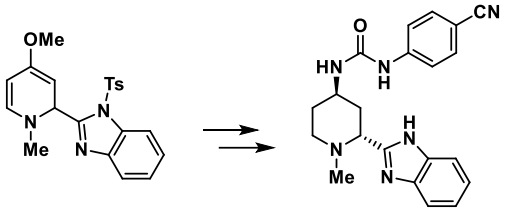


Scheme 1.3: Synthesis of (+)-julifluoridine (1.26) *via* 1,2-DHP intermediate 1.22.



In addition to their application in natural product synthesis DHPs have been actively used by medicinal chemists for the synthesis of active pharmaceutical ingredients containing six-membered nitrogen heterocycles.[24] For example, DHP **1.27** was a key intermediate during the process scale synthesis of FDA approved drug glasdegib (brand name Darismo) (**1.28**) which is used to treat acute myeloid leukemia in adults over 75 (Figure 1.2).[25]

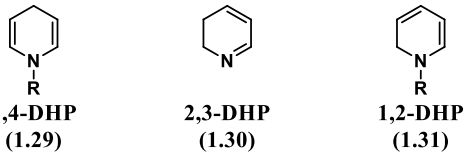
Figure 1.2: DHP (1.27) as an intermediate in the process synthesis of glasdegib (1.28).



1.2. Methods for the synthesis of DHPs:

DHPs include three main classes of constitutional isomers: 1,4 (**1.29**); 2,3 (**1.30**); and 1,2.(**1.31**) (Figure 1.3). All these constitutional isomers have been used in medicinal chemistry and natural product synthesis. Significant research interest has been focused on the synthesis of these compounds. Mainly, these past efforts can be grouped into two general areas. The first of these has focused on cyclization and cycloaddition reactions and while the second has focused on dearomatization reactions of pyridines. Below we summarize these past strategies for the synthesis of DHPs. It is worth noting that this is not a comprehensive summary and emphasis has been placed on different strategies rather than listing all previous methods. A more detailed summary of methods for the synthesis of DHPs could be found in appropriate reviews.[26–29]

Figure 1.3: Common constitutional isomers of DHP.



1.2.1. Cyclization and cycloaddition reactions for the synthesis DPHs:

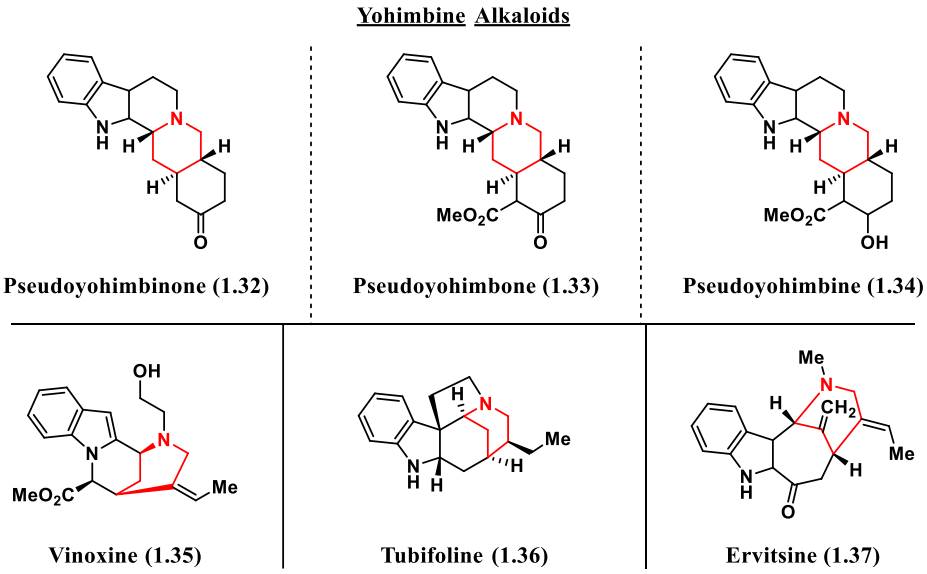
1.2.1.1. Synthesis of 1,4-DHPs:

The 1,4-dihydropyridine scaffold is one of the most studied isomers of DHPs. Discovered through the pioneering work of Arthur Hantzsch, 1,4-DHPs are useful reagents and intermediates in organic synthesis.[27,30] As the 1,4-DHP resembles NADH, this scaffold is highly attractive in drug design and has been extensively used as a reductant in organic synthesis.[31] In particular, analogues of Hantzsch esters have been known for their selective inhibition of L-type Ca^{2+} channels and several drugs with this structural motif has been approved by the FDA for treating hypertension.[31] In organic synthesis 1,4-DHPs primarily have been used as a hydride or hydrogen atom source.[32–36] Recently, reagents that contain this motif have been developed to generate various radicals for cross-coupling reactions.[37–39]

In addition to their uses as medicines and reagents for organic synthesis, 1,4-DHPs have also been used as synthetic intermediates for the synthesis of natural products. (Figure 1.4). For example, yohimbine (**1.32-34**), vinoxine (**1.35**), strychnos (**1.36**), and ervitsine (**1.37**) alkaloids were all synthesized via 1,4-DHP intermediates.[19–23]

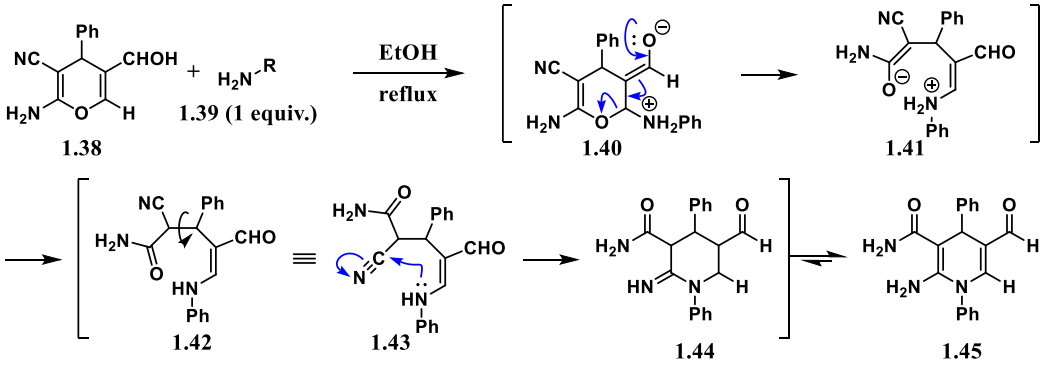
Due to their importance in organic synthesis and medicinal chemistry, there have been a multitude of reports for the synthesis of 1,4-DHPs. Below we summarize general strategies for the synthesis of 1,4-DHPs using cyclization and cycloaddition reactions.

Figure 1.4: Examples of alkaloids synthesized using 1-4,DHPs as intermediates.



4-H-pyrans (**1.38**) were utilized by De Lucas et al. to produce 1,4-DHPs (**1.45**) (Scheme 1.4).[40] In this strategy, the pyran (**1.38**) opens in the presence of primary amine **1.39** in refluxing ethanol. After a proton transfer forms **1.42**, an intramolecular nucleophilic attack by the amine on the nitrile forms intermediate **1.44**, which forms 1,4-DHP **1.45** upon another proton transfer.

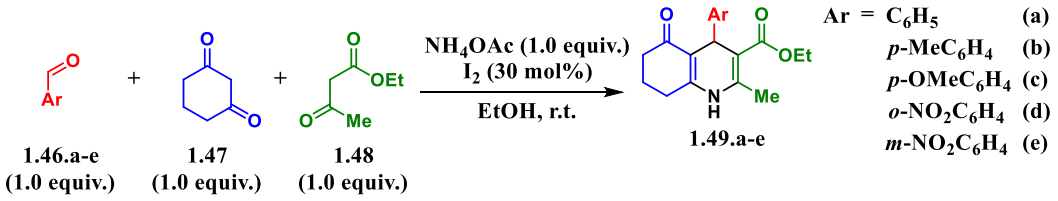
Scheme 1.4: Synthesis of 1,4-DHPs via pyran cleavage and 6-exo-dig cyclization.



The inexpensive synthesis of 1,4-DHPs at room temperature was reported by Ko et al. (Scheme 1.5).[41] In this reaction, aryl aldehydes (**1.46.a-e**), cyclohexanediones (**1.47**), and ethyl acetoacetates (**1.48**) in the presence of ammonium acetate and catalytic iodine produced substituted

1,4-DHPs (**1.49.a-e**) in high yield. In this fashion, 1,4-DHPs could be synthesized with high structural diversity.

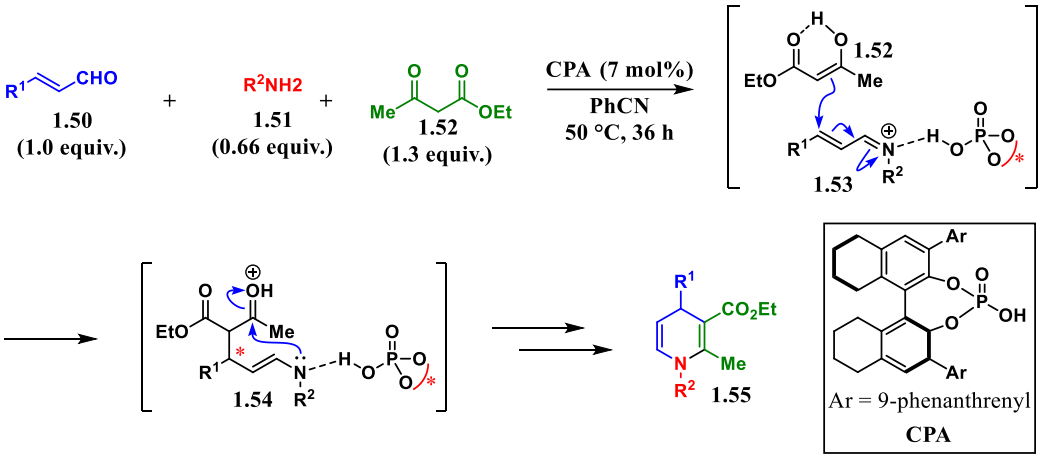
Scheme 1.5: I_2-catalyzed synthesis of 1,4-DHPs.



Unfortunately, the strategies discussed above deliver racemic mixtures of 1,4-DHPs. As access to single enantiomers of complex molecules is important to drug discovery,[42–45] strategies for accessing chiral 1,4-DHPs have been developed. One such strategy is the chiral resolution of the target DHP by treating it with enantiopure alkaloids, which form a mixture of quasi-diastereomeric salts, that were separated by recrystallization.[46–49] Another strategy employs chiral esters in the starting materials, forming diastereomeric mixtures of DHPs. After separation and transesterification, the enantioenriched target DHP can be isolated.[50–53]

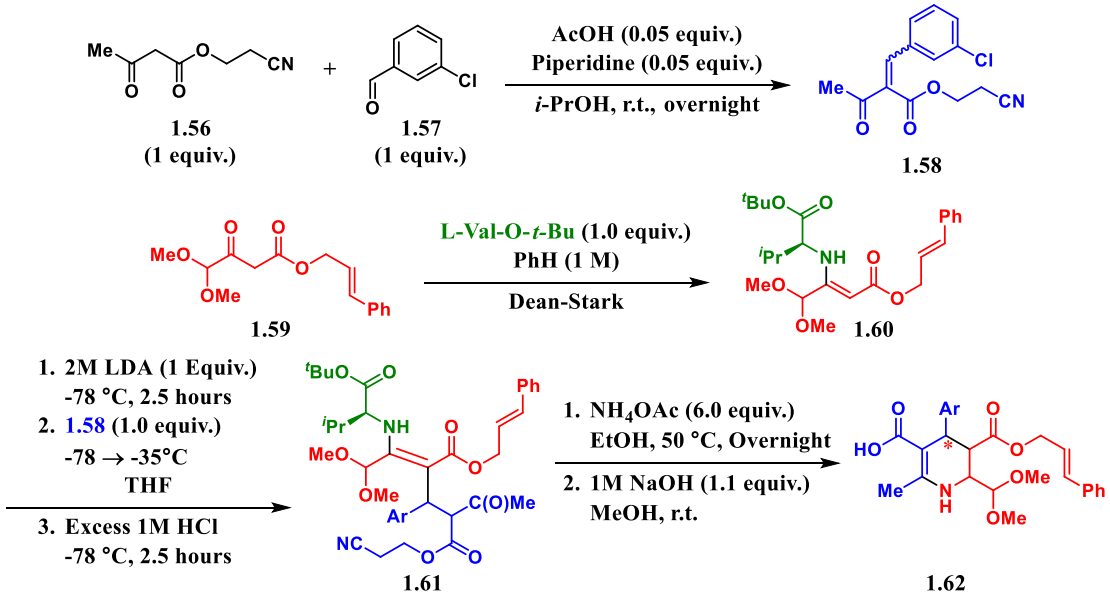
In synthetic and medicinal chemistry, the ability to establish enantioselectivity and structural diversity in a single step remains a problematic transformation in the synthesis of 1,4-DHPs. One strategy to address this problem used chiral phosphoric acids to facilitate the room temperature cyclization between cinnamaldehyde (**1.50**), primary aniline derivative **1.51**, and 1,3-dicarbonyl **1.52** (Scheme 1.6: Asymmetric synthesis of 1,4-DHPs utilizing chiral phosphoric acid catalysts.).[54] The key steps in the proposed mechanism are the Michael addition of the dicarbonyl compound **1.50** to the vinylogous imine **1.53,** which is coordinated to the chiral phosphoric acid (**CPA**), and the cyclization driven by nucleophilic attack of the nitrogen of the enamine (**1.54**) to the protonated ketone. Thus, 1,4-DHP **1.55** was synthesized enantioselectively.

Scheme 1.6: Asymmetric synthesis of 1,4-DHPs utilizing chiral phosphoric acid catalysts.



Yammamoto et al., used the *t*-butyl ester of the amino acid L-valine (L-Val-O-*t*-Bu) as the nitrogen source and as a chiral auxiliary (Scheme 1.7). Aldol condensation of keto-ester **1.56** and benzaldehyde **1.57** gave access to Michael acceptor **1.58.** The condensation of L-Val-O-*t*-Bu onto dicarbonyl **1.59** gave a chiral Michael donor (**1.60**), which can be added to Michael acceptor **1.58**. Subsequent cyclization of **1.61** and deprotection of the nitrogen affords an enantioenriched 1,4-DHP (**1.62**).[55]

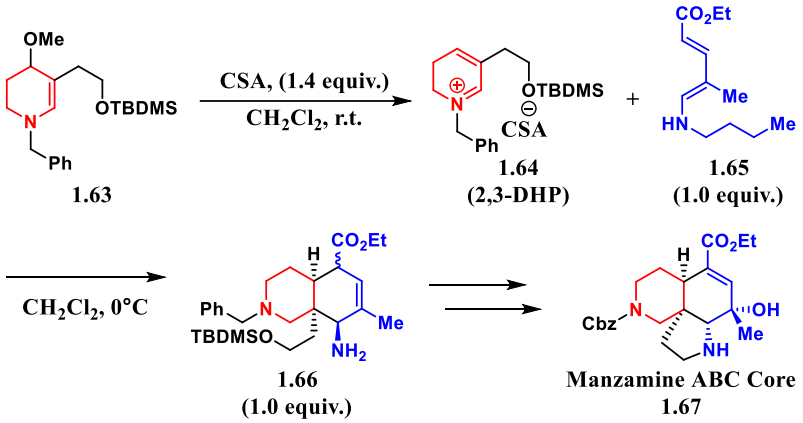
Scheme 1.7: Asymmetric synthesis of 1,4-DHPs utilizing amino acid derivatives as chiral auxiliaries.



1.2.1.2. Synthesis of 2,3-DHPs:

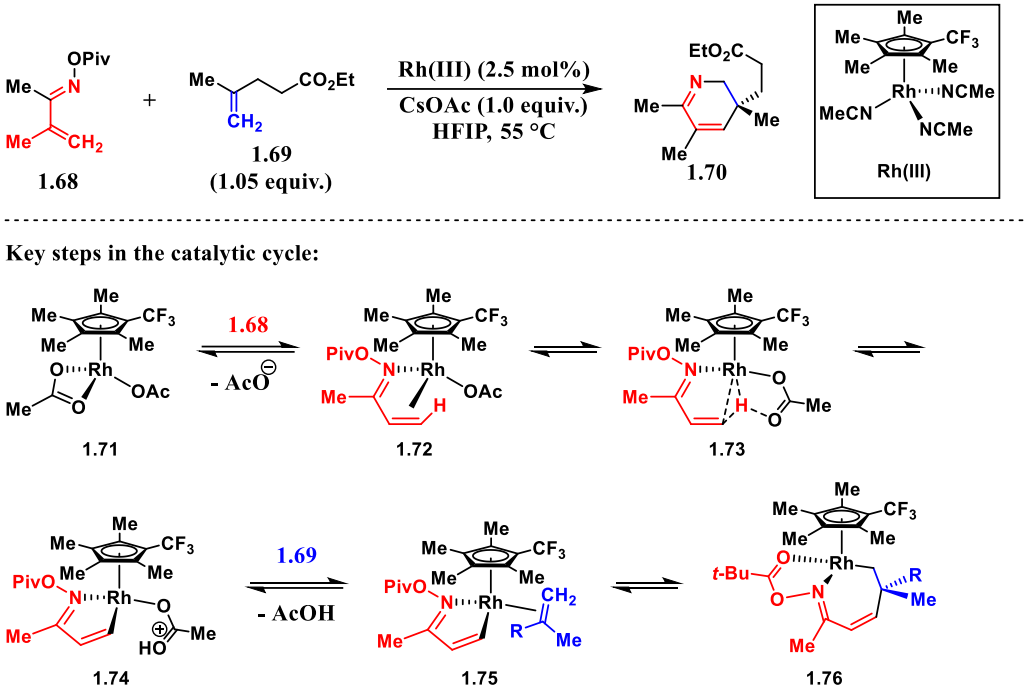
2,3-dihydropyridines are attractive intermediates in the synthesis of saturated six-membered azaheterocycles. Such DHPs must generally be protected as N-alkyl or N-acyl pyridinium salts, due to the facile oxidation of unprotected 2,3-DHPs to the corresponding pyridines.[56] N-alkyl-2,3-DHPs were used extensively in the synthesis of Manzamine natural products, which were found to have cytotoxic, antibiotic, insecticidal, and antimalarial activity after their isolation in 1986 (Scheme 1.8: Enantioselective synthesis of the manzmine ABC core.).[57–63] A general strategy for forming the manzamine core was developed by the Marazano research group. Tetrahydropyridine **1.63** underwent elimination of the methoxide to form 2,3-dhiyropyridinium **1.64,** which was subsequently reacted with vinylogous carbamate **1.65** at 0°C to give **1.66**. Further synthetic steps produced the tricyclic carbon skeleton core of manzamine alkaloids (**1.67**) and this method provides several opportunities for potential derivatization.[57]

Scheme 1.8: Enantioselective synthesis of the manzmine ABC core.



The Rovis group employed a Rh-catalyzed C-H activation strategy to couple oxime pivalates (**1.68**) with alkenes (**1.69**) to produce 2,3-DHPs (**1.70**) (Scheme 1.9).[64] The key to this reaction was the formation of Rh metallocycle **1.74**, which undergoes a migratory insertion in the presence of 1,1-disubsttuted alkenes to give **1.76**. The catalytic cycle closes with a reductive elimination of the product (**1.70**) and cleavage of the N-O bond to give the 2,3-DHP **1.70**.[65]

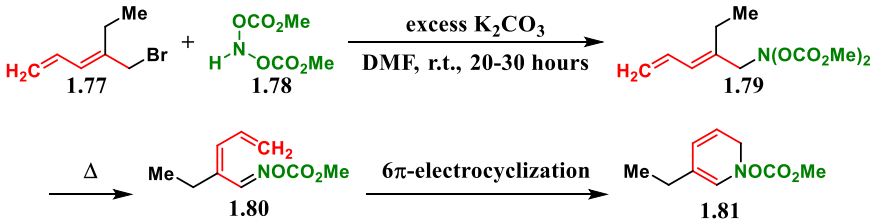
Scheme 1.9: 2,3-DHP synthesis by Rh(III)-catalyzed C-H activation.



1.2.1.3. Synthesis of 1,2-DHPs:

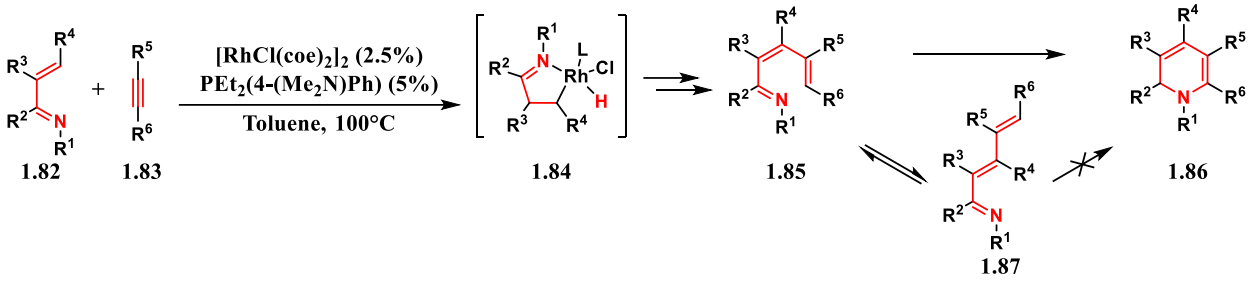
The syntheses of 1,2-DHPs have involved reactions such as cyclization, cycloaddition reactions, and multicomponent cascades. Wyle and Fowler reported multiple methods for the synthesis of 1,2-DHPs, including the 6π-electrocyclization of azatrienes (**1.80**) generated from hydroxamic acid esters (**1.79**) which form the 1,2-DHP upon heating (Scheme 1.10).[66] Structural diversity could be achieved in the initial step by using substituted dienes.

Scheme 1.10: Azatriene cyclization strategy for the synthesis of 1,2-DHPs.



A strategy involving the Rh-catalyzed C-H activation of substituted imines was developed by the Ellman research group. A wide scope of substituted imines (**1.82**) and alkynes (**1.83**) gave 1,2-DHPs in good yield after reaction optimization (Scheme 1.11).[67] The C-H activated metallocycle intermediate **1.84** was isolated and characterized in the mechanistic investigation. The azatriene **1.85** proceeded through a 6π-electrocyclization, forming the 1,2-DHP **1.86**. An alkene isomerization of **1.85** produced **1.87**, which could not cyclize. At room temperature, this isomerization was not reversable, thus elevated temperatures were found to be crucial to the formation of the DHP by increasing the rate of the electrocyclization and reversibility of the isomerization.

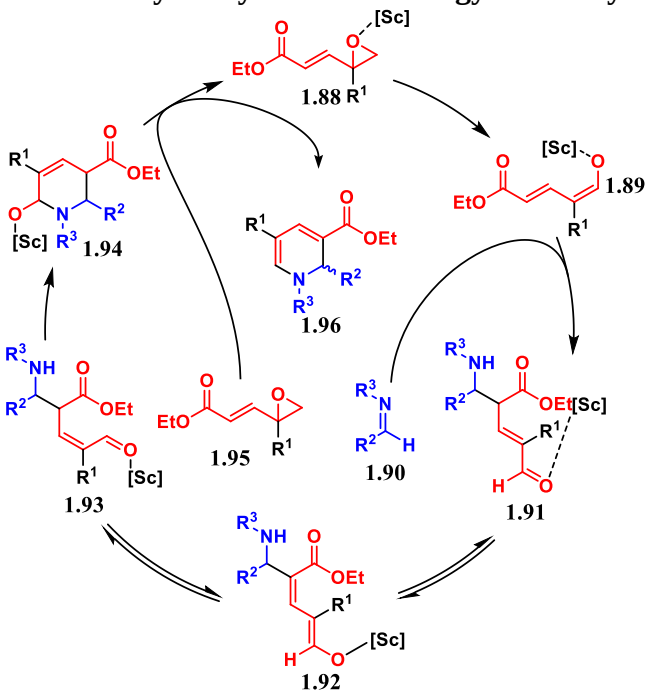
Scheme 1.11: Rh-catalyzed C-H activation strategy for the synthesis of 1,2-DHPs.



1.82 **1.83** **1.84** **1.85** **1.87** **1.86**

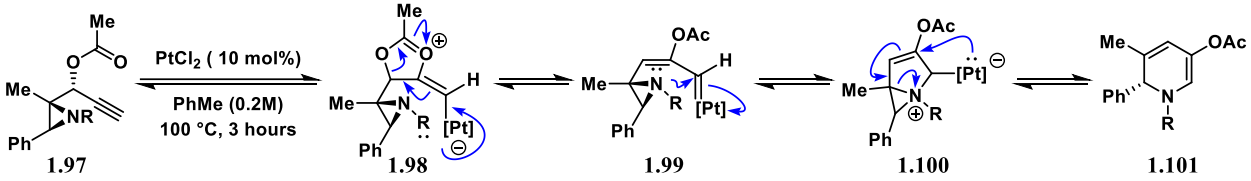
The synthesis of 1,2-DHPs *via* vinylogous imino-aldol reactions between vinyloxiranes (**1.88**) and imines (**1.90**) in the presence of catalytic scandium triflate were developed in 2006 by Brunner et al. (Scheme 1.12).[64] Electron withdrawing group-substituted vinyloxiranes (**1.88**) function as precursors for enolates (**1.89**) in the presence of Lewis acids, attacking N-alkyl and aryl imines (**1.90**). E- to Z-isomerization of the addition intermediates (**1.91** to **1.93**) allows the cyclization of **1.93** to **1.94**, which loses an equivalent of water upon addition of an equivalent of vinyloxirane **1.88** to restart the catalytic cycle.

Scheme 1.12: Scandium-catalyzed cyclization strategy for the synthesis of 1,2-DHPs.



The first Pt catalyzed cycloisomerization of aziridinyl propargylic esters (**1.97**) to form 1,2-DHPs was reported by the Sarpong group in 2007 (Scheme 1.13).[68] The Pt catalyzed cycloisomerization gives 1,2-DHPs (**1.101**) in good yield while retaining the stereochemistry present in the aziridine ring of (**1.97**).

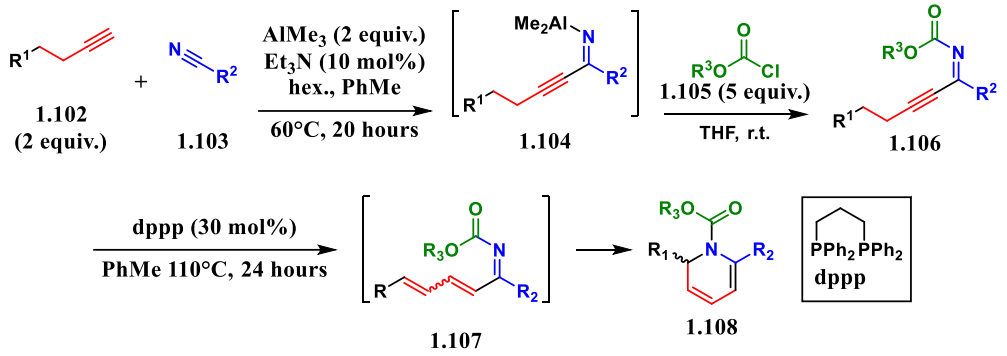
Scheme 1.13: Cycloisomerization of aziridinyl propargylic esters to form 1,2-DHPs.



A cycloisomerization strategy for the synthesis of 1,2-DHPs developed by Trost began with a one-pot procedure for the formation of ynimines (**1.106**) by treating a mixture of terminal alkynes (**1.102**) and nitriles (**1.103**) with trimethyl aluminum, then adding chloroformate **1.105** (Scheme 1.14).[69] 1,3-Bis-(diphenylphosphino) propane served as a catalyst for the isomerization of the of the ynimine (**1.106**) to the azatriene (**1.107**), which allowed a 6π-electrocyclization to

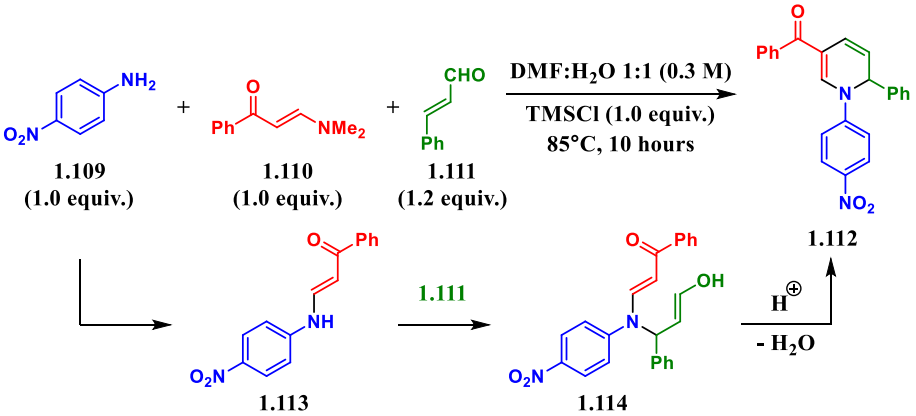
1,2-DHPs (**1.108**). 1,2-DHP **1.108**, was proposed as an intermediate for preparing several histamine H_3 receptor agonists, which are used as analgesics and to treat sleeping disorders.[70–72]

Scheme 1.14: Cycloisomerization of ynimines for the synthesis of 1,2-DHPs.



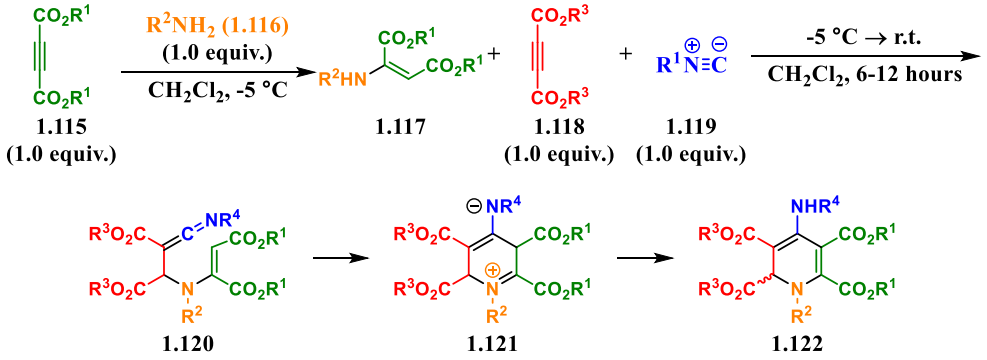
Multi-component reactions are highly efficient methods for introducing structural diversity into target molecules. Wan et al. reported the three-component cascade reaction of anilines (**1.109**), vinylogous amides (**1.110**), and α,β-unsaturated aldehydes (**1.111**) to produce 1,4- and 1,2-DHPs (**1.112**) (Scheme 1.15).[73] In this example, 1,2-DHPs were obtained when the aniline was bulky, or featured highly electron withdrawing groups such as NO_2. After mechanistic investigations, Wan et al. proposed that the cascade begins with the coupling of **1.109** and **1.110** in the presence of TMSCl to form vinylogous amide **1.113.** The amide nitrogen then attacks the β-position of **1.111** to form intermediate **1.114**, which then cyclizes and dehydrates to form 1,2-DHP **1.112**.

Scheme 1.15: Multicomponent cascade strategy for the synthesis of 1,2-DHPs.



A strategy to synthesize 1,2-DHPs from the Souri research group combined acetylenic esters (**1.115** and **1.118**), primary amines (**1.116**), and alkyl isocyanides (**1.119**) to produce 4-amino-1,2-DHPs (**1.122**) in good yield (Scheme 1.16).[74] In the event, the reaction of primary amine **1.116** with acetylenic ester **1.115** at -5 °C in CH_2Cl_2 forms vinylogous carbamate **1.117**. Upon addition of a second acetylenic ester (**1.118**) and isocyanide **1.119**, the reaction was allowed to warm to room temperature, promoting the formation of ketenimine **1.119**. The ketenimine cyclizes to form 2,5-dihydropyridinium **1.121**, which undergoes a proton transfer to afford 1,2-DHP **1.122**. This method allows convergent synthesis of 1,2-DHPs with various ester and amine substituents.

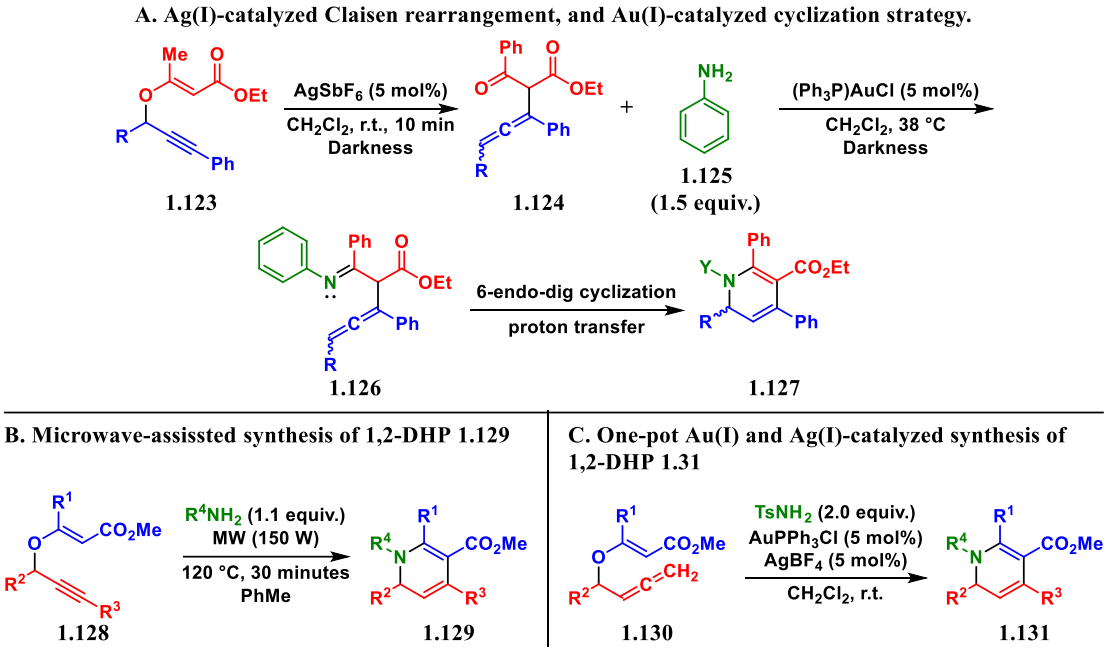
Scheme 1.16: One-pot 1,2-DHP synthesis from alkylamines, isocyanides, and acetylenic esters.



A common strategy for forming 1,2-DHPs from propargyl enol ethers was discovered in 2005 (Scheme 1.17.A). The Kirsch group from the Munich Technical University found that a silver (I) salt catalyzed a propargyl Claisen rearrangement of the enol ether **1.123** to give allene **1.124**. Treatment of **1.124** with a substituted aniline (**1.125**) in the presence of a gold (I) salt produced imine **1.126**, which underwent a 6-endo-dig cyclization and proton transfer to give 1,2-DHP **1.127**.[75–77] Following this report, several research groups improved on this strategy. For example, Tejedor et al. developed a strategy utilizing microwave reactions to produce substituted 1,2-DHPs

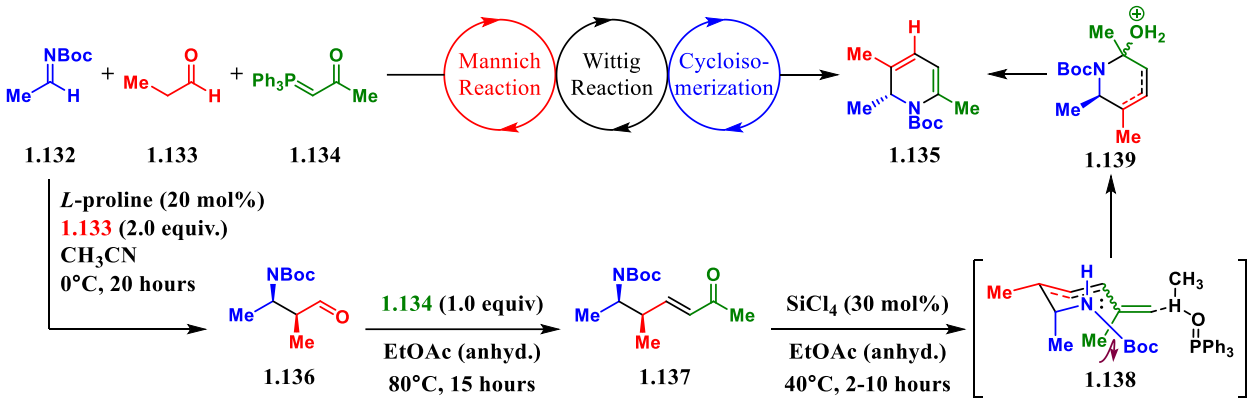
(**1.129**) in good yields and short reaction times (Scheme 1.17.B),[78–80] and the starting material scope was expanded by Wei et al. to include allenic vinyl ethers (**1.130**) (Scheme 1.17.C).[81]

Scheme 1.17: Synthesis of 1,2-DHPs via Claisen rearrangement and 6-endo-dig cyclization.



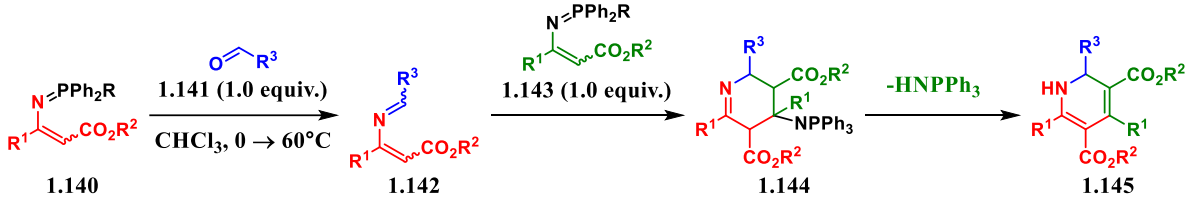
Mu et al. recently reported a Mannich-Wittig-cycloisomerization cascade for the synthesis of 1,2-DHPs (Scheme 1.18). In this strategy, imine **1.132** and aldehyde **1.133** were mixed in the presence of a catalytic amount of *L*-proline at 0°C. The crude Mannich product **1.136** was then heated to 80 °C with phosphorous ylide **1.134**. Upon consumption of **1.134**, the reaction was cooled to room temperature, $SiCl_4$ added, and the reaction heated to 40 °C. In the presence of triphenylphosphine oxide from the Wittig step, **1.137** adopted a 6-membered, chair-like transition state **1.138**, which facilitates the cyclization to **1.139**, forming the 1,2-DHP **1.135** upon dehydration.

Scheme 1.18: Mannich-Wittig-Cycloisomerization cascade for 1,2-DHP synthesis.



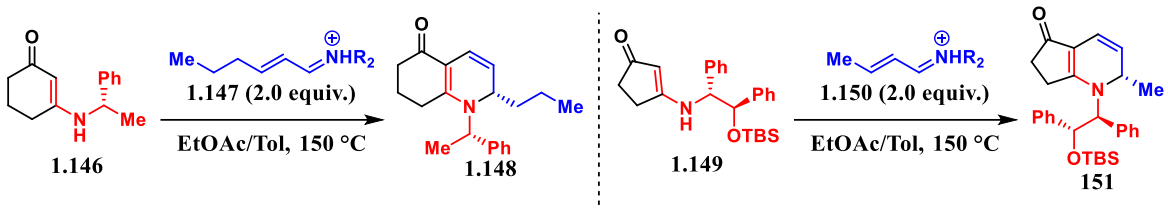
Cycloaddition reactions are another useful strategy for forming 1,2-DHPs, employing a variety of substrates. A 4+2 cyclization strategy was developed by Palacios et al. (Scheme 1.19).[82] Phosphazines (**1.140**) and aldehydes (**1.141**) formed azadienes (**1.142**) which reacted with an equivalent of **1.143** forming substituted tetrahydropyridines (**1.144**) which gave 1,2-DHPs (**1.145**) after elimination of the phosphazine ylide.

Scheme 1.19: 4+2 cycloaddition strategy for the synthesis of 1,2-DHPs.



Gerasyuto, with Sklenicka and Wei, developed a 3+3 cycloaddition strategy coupling vinylogous amides (**1.146**/**1.149**) and α,β-unsaturated iminiums (**1.147**/**1.150**) (Scheme 1.20).[83,84] These methods are highly stereoselective, employing chiral auxiliaries to induce diastereoselective addition of the iminiums.

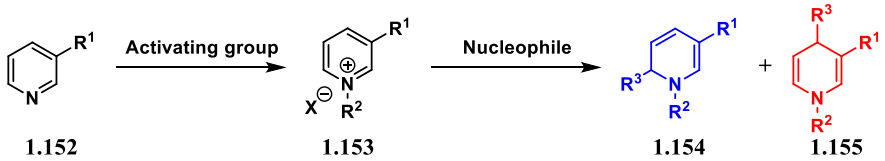
Scheme 1.20: Formal 3+3 cycloaddition strategy for the synthesis of 1,2-DHPs.



1.2.2. Nucleophilic dearomatization of azaheteroarenes for the synthesis of DHPs:

The cyclization, multicomponent reaction, and cycloaddition strategies described above have significant limitations, such as substrates with specific substituents to enable reactivity. For example, substrates for multicomponent reactions often contain multiple ester and other electron withdrawing groups, and pericyclic reactions such as cycloadditions and 6π-electrocyclizations have limitations resulting from electronic requirements for such transformations. A promising strategy to overcome these drawbacks is the dearomatization of pyridinium salts (Scheme 1.21). This dearomatization strategy is a particularly attractive method in DHP synthesis because: (1) pyridines are feedstock chemicals that can be readily purchased or synthesized; (2) activated pyridines are reactive coupling partners for nucleophiles; (3) pyridines can be activated with a variety of electrophiles to control the regio- and stereoselectivity of dearomatization reactions; (4) Both 1,2- and 1,4- DHPs (**1.154** and **1.155**, respectively) could be synthesized using this strategy from the same starting materials (**1.152** and **1.53**).

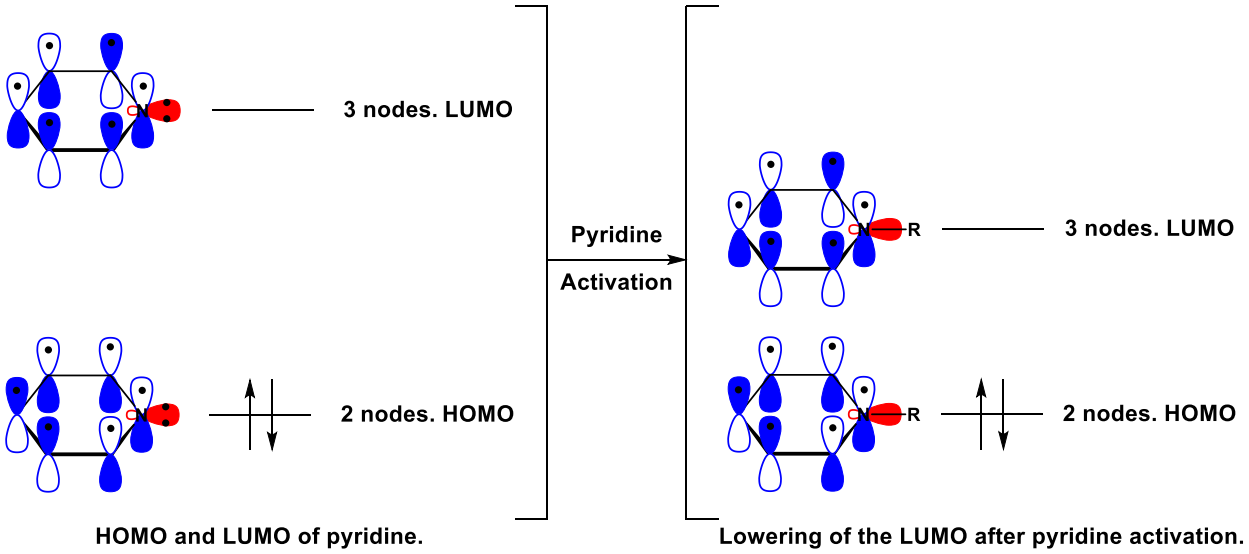
Scheme 1.21: General dearomatization strategy for the synthesis of 1,2- and 1,4-DHPs.



In general, the dearomatization event occurs in activated pyridines due to changes in hybridization and bond order. Pyridine is aromatic because it: (1) is cyclic; (2) contains 4n+2 π electrons; (3) contains atoms that are all in conjugation; (4) and contains atoms that are all sp^2

hybridized. As an aromatic molecule, pyridine is a poor electrophilic partner; the resonance stabilization energy of pyridine is less than that of benzene (150 kJ/mol vs 117 kJ/mol, respectively).[85] When the pyridine is activated, the energy of the LUMO in the aromatic ring is lowered (Figure 1.5), and the energy release from hybridizing two sp^2 atoms (C and N) to sp^3, breaking one π-bond, and forming one sigma bond, drives the reaction forward.

Figure 1.5: The change in the energies of pyridine molecular orbitals after activation.

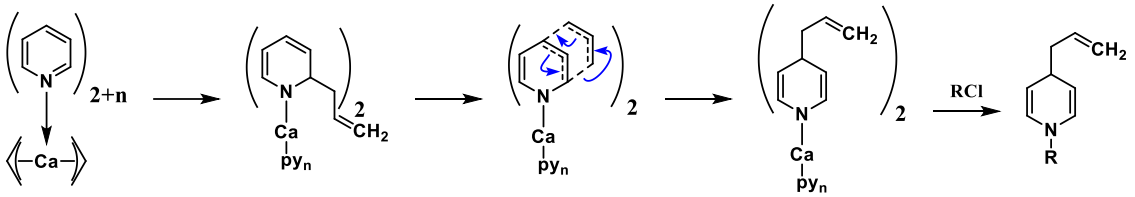


1.2.2.1. Nitrogen activating agents for the synthesis of DHPs from pyridines:

Dearomatization reactions of pyridines are usually categorized into two main pathways: reductive and nucleophilic, the latter being the focus of my studies. Due to the pyridine aromaticity, pyridines are generally poor electrophilic partners, requiring the activation of the nitrogen. Described below, is a selection of N-activation strategies for the synthesis of DHPs.

One such class of activators for nucleophilic dearomatization involves the activation of the pyridine through N-metal coordination. In 2010, the groups of Maron and Okuda utilized a calcium allyl complex to activate pyridine (Scheme 1.22).[86] Allyl insertion occurred at the C2 position in complex **1.156**, followed by a Cope rearrangement to form complex **1.159.** Upon addition of an electrophilic group, the product is released as the 1,4-diydropyridine (**1.160**).

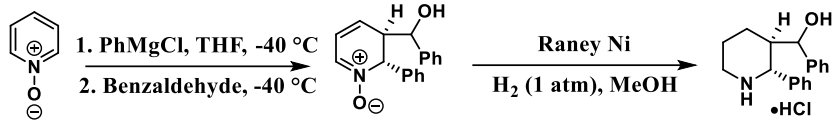
Scheme 1.22: N-calcium transient activation strategy to synthesize 1,4-DHP 1.158.



1.156 **1.157** **1.158** **1.159** **1.160**

The Almqvist group found that pyridine-N-oxides (**1.161**) could be attacked by Grignard reagents to form 2,3-dihydropyridiniums (**1.162**) after the addition of an aldehyde (Scheme 1.23).[87] After the dearomatization event, Raney nickel reduction produced trans-substituted piperidines (**1.163**).

Scheme 1.23: N-O activation strategy for the synthesis of 1,2-DHPs.

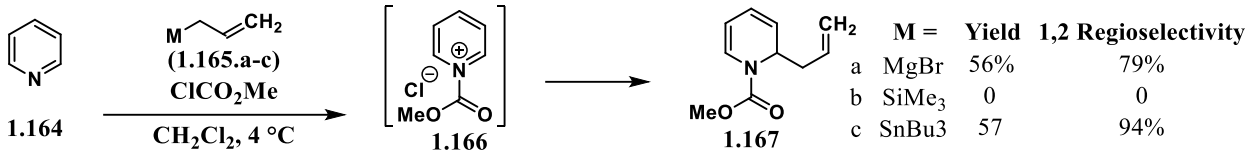


1.161 **1.162** **1.163**

The most common activators for heteroarenium dearomatization include N-acyl and N-alkyl groups.[26,27] N-acyl heteroarenium salts are generally unstable at ambient temperature as the activation step is in equilibrium.[26] As such, the salt must usually be prepared *in situ*, either by formation before the addition of organometallics, or by introducing the acylating agents in the presence of the pyridine and the organometallic reagent. Yamaguchi and coworkers pioneered the use of N-acyl pyridiniums to affect the α-selective addition of organometallic reagents (Scheme 1.24).[88] Pyridine (**1.164**) was acylated with methyl chloroformate, and the dearomatized with a

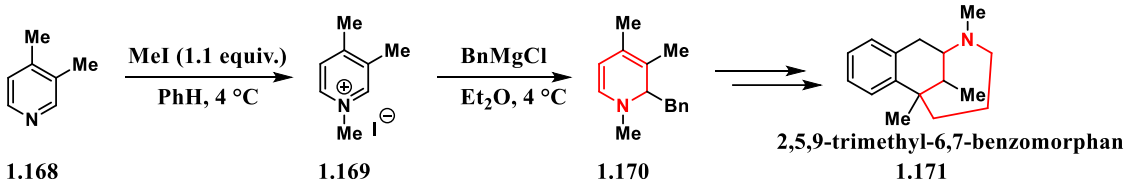
variety of allyl organometallics (**1.165.a-c**). Interestingly, Yamaguchi discovered that different organometallic reagents displayed different regioselectivities (**1.167.a** vs **1.167.c**).

Scheme 1.24: N-acyl activation strategy for the synthesis of 1,2-DHPs.



In contrast to N-acyl heteroarenium salts, N-alkyl heteroarenium salts are made in a prior step to the dearomatization and are bench stable at room temperature. Unfortunately, N-alkyl DHP is not as stable as N-acyl DHP, and such reactions are more efficient when using more electron poor azaheterocycles such as nicotinates, picolinates, and quinolines.[26] N-alkyl heteroarenium salts are particularly attractive because N-alkyl DHPs can be easily transformed into synthetic intermediates for total synthesis[3–5,25,89,90]. Notably, N-alkyl pyridinium salts were key in May's approaches toward morphine analogues (**1.171**) (Scheme 1.25).[90–94] Activation of 3,4-lutidine (**1.168**) with methyl iodide formed pyridinium salt **1.169**, which was dearomatized to 1,2-DHP **1.170**. Further synthetic steps produced benzomorphan (**1.171**).

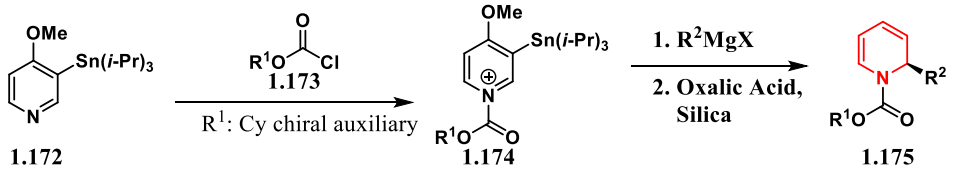
Scheme 1.25: N-alkyl activation strategy for the synthesis of 1,2-DHP 1.168.



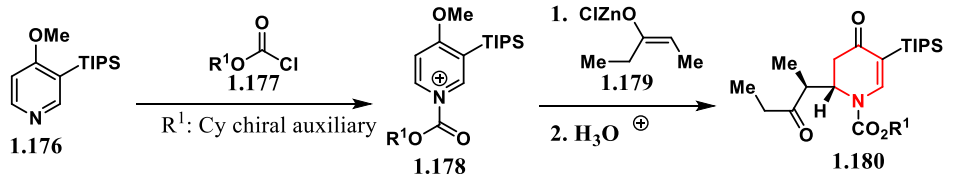
1.2.2.2. Nucleophiles for the dearomatization of N-activated pyridines:

After the of activation of pyridines as described above, a variety of nucleophiles are useful for forming carbon-carbon bonds to prepare 1,2- and 1,4-DHPs. A selection of such reagents is described here. The Comins group has extensively used Grignard reagents in the nucleophilic dearomatization, using chiral auxiliaries to direct the regio- and enantioselectivity of the addition (Scheme 1.26). Using a chiral chloroformate ester (**1.173**) to activate pyridine **1.172**, pyridinium salt **1.174** could be dearomatized using Grignard reagents. The removal of methoxide and triisopropyl stannyl groups after the dearomatization event afforded 1,2-DHP **1.175**. This strategy requires the tin blocking group to influence the regioselectivity of the addition. Comins and coworkers have also reported the addition of metaloenolates (**1.179**) to the same heteroarenium substrates (Scheme 1.27).[95–97]

Scheme 1.26: Grignard addition strategy for the synthesis of 1,2-DHPs.



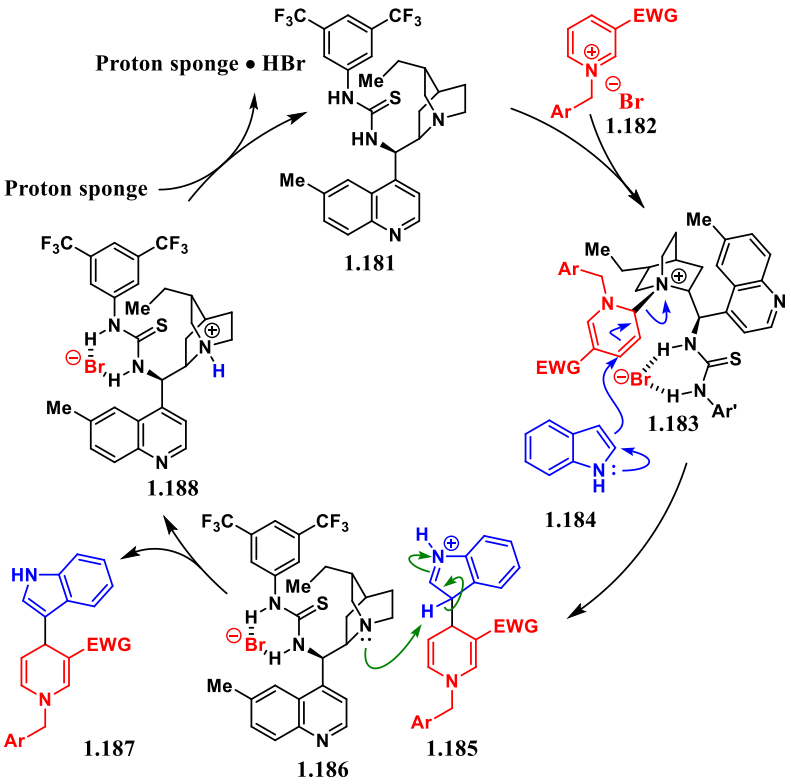
Scheme 1.27: An Metalo-enolate addition strategy for forming 1,2-DHPs.



Recently, catalytic strategies for the dearomatization of pyridinium salts utilizing organo- and transition-metal catalysts have been developed. One such approach utilized a bifunctional organocatalyst to synthesize 1,4-DHPs enantioselectively (Scheme 1.28).[98] N-benzylpyridinium salts (**1.182**) bearing strongly electron withdrawing groups on the C-3 position were reacted with variously substituted indoles (**1.184**). The use of a catalyst containing a tertiary amine as well as a thiourea motif such as **1.181** with a stoichiometric amount of proton sponge facilitated the

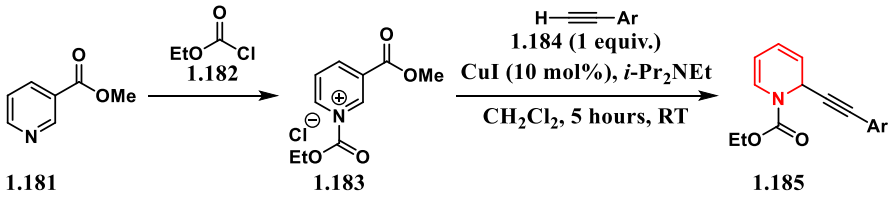
enantioselective C-4 dearomatization of the pyridinium salt at the C-3 position of the indole. Upon addition of the tertiary amine component of the catalyst to the pyridinium C-6 position (**1.183** is observable via NMR), the thiourea component sequestered the bromide counter-ion. Through an $SN^{2'}$-like mechanism, the indole (**1.184**) added to the pyridine C-4 carbon, releasing the organocatalyst. Rearomatization of the indole motif caused the release of an equivalent of HBr, which is bound to the catalyst (**1.188**). An equivalent of proton sponge removes the HBr and regenerates the catalyst.

Scheme 1.28: Proposed catalytic cycle for the organocatalytic addition of indole to pyridine, a strategy for the synthesis of 1,4-DHPs.



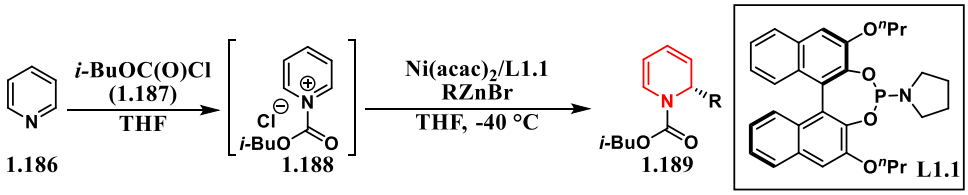
Sathiaiah and coworkers have reported a copper-catalyzed strategy using alkynes (**1.184**) as nucleophiles (Scheme 1.29).[99–102] Activating a variety of pyridine-based substrates such as nicotinic acid esters (**1.181**) with chloroformates (**1.182**) followed by copper-catalyzed addition of electron rich and poor alkynes (**1.184**) formed the 1,2-DHPs (**1.185**).

Scheme 1.29: Cu(I)-catalyzed alkyne addition strategy for the synthesis of 1,2-DHPs.



The Doyle group has investigated the use of nickel catalysis to add arylzinc reagents to N-acyl pyridinium salts (**1.188**) (Scheme 1.30).[103,104] While they were able to form C-C bonds α to the nitrogen asymmetrically, the use of non-symmetric pyridines caused a decrease in regio- and enantioselectivity and yield.

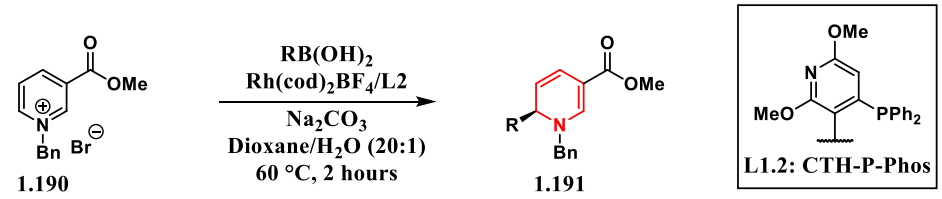
Scheme 1.30: Nickel-catalyzed arylzinc addition strategy for the synthesis of 1,2-DHPs.



The Merck process group reported the asymmetric addition of arylboronic acid nucleophiles to N-benzyl nicotinate salts (**1.188**) (Scheme 1.31).[105] Boronic acids are attractive nucleophiles for this transformation for a two main reasons; 1) there is a variety of commercially available boronic acids, and they are easily synthesized; 2) reactions utilizing boronic acids typically have a higher functional-group tolerance than that of more basic nucleophiles such as organometallic reagents and enolates. This allows addition reactions with substrates that contain

electrophilic and acidic groups such as aldehydes, ketones, secondary amides, and unprotected alcohols, to be present in the reaction.

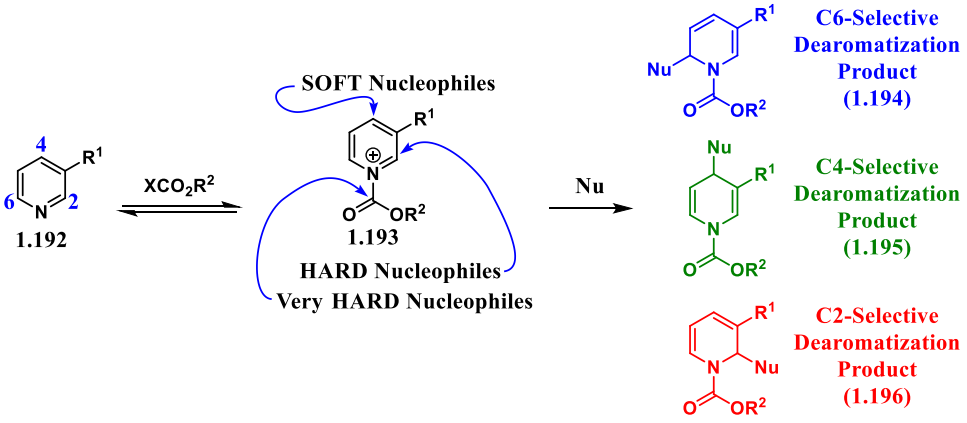
Scheme 1.31: Rh-catalyzed boronic acid addition strategy for the synthesis of 1,2-DHPs.



1.3. The Regioselectivity of Nucleophilic Dearomatization:

Since pyridinium salts (**1.193**) have three electrophilic sites (C-2, C-4, and C-6), one general problem with dearomatization is that the regioselective outcomes of the addition is difficult to predict, often resulting in mixtures of isomers (**1.194**, **1.195**, **1.196**) (Scheme 1.32).

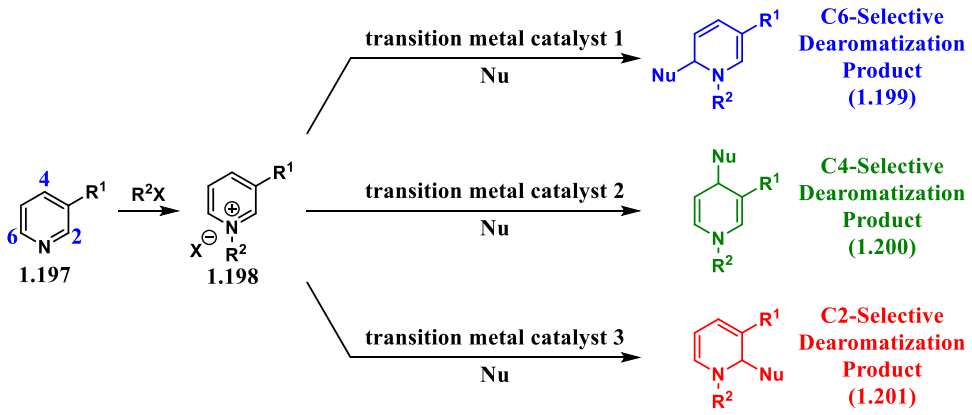
Scheme 1.32: Regioselectivity outcomes for nucleophilic addition to N-acylpyridinium salts.



A recent investigation into the regioselective addition of various Grignard reagents to N-alkyl pyridinium salts showed only slight substrate dependence on the site of the nucleophilic attack.[106] Common solutions to this problem involve the use of directing and blocking groups. Unfortunately, such groups add steps to the synthesis due to the need to install and remove them.

The approach taken by the Karimov lab involves the use of transition-metal catalysis to control the site of the addition (Scheme 1.33). While activated pyridinium salts (**1.198**) have three electrophilic cites, such sites are not equally reactive. Calculations undertaken by our group show that in certain organometallic systems, we can influence the hardness and softness of the nucleophile and attack the desired pyridinium site. Our hypothesis is that different organometallic species will attack different pyridinium electrophilic sites. Our investigations began with rhodium-catalyzed addition of boronic acid nucleophiles to N-methyl nicotinate salts, forming the fully substituted stereogenic center as reported in our 2020 publication.

Scheme 1.33: Proposed strategy for the regioselective nucleophilic addition to N-alkylpyridinium salts.



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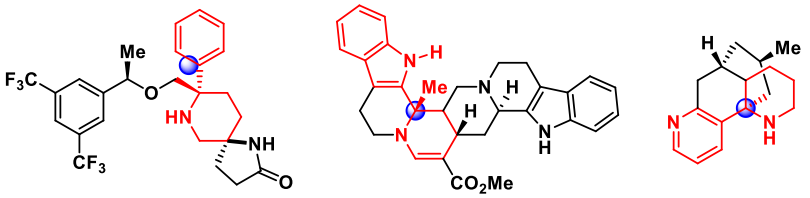
Chapter 2: Synthesis of 1,6-DHPs *via* Enantioselective Addition of Boronic Acids

This chapter is reproduced from Robinson, D. J.; Spurlin, S. S.; Gorden, J. D.; and Karimov, R. R. *ACS Catal.* **2020,** 10, 51−55.

2.1. Introduction:

Nonaromatic 6-membered azaheterocycles are the most common nitrogen heterocycles in FDA approved small molecule drugs.[1] In addition to their abundance in drug molecules, these heterocycles are common in agrochemicals and alkaloid natural products.[2] Often sp^3 carbons of these heterocycles, especially the ones in natural products, are functionalized to contain stereogenic centers. A number of these compounds contain a fully substituted stereogenic center alpha to the ring nitrogen atom. Examples of such molecules include rolapitant (**2.1**), a NK1 receptor antagonist that has recently been approved for treating delayed phase of chemotherapy-induced nausea and vomiting, and alkaloids roxburghine (**2.2**) and lycodine (**2.3**) (Figure 2.1). Despite the wide abundance of these azaheterocycles in bioactive molecules, methods for their synthesis, especially the ones that contain fully substituted stereocenters, are limited as the synthesis of quaternary centers in general remains one of the great challenges in organic chemistry.[3–7]

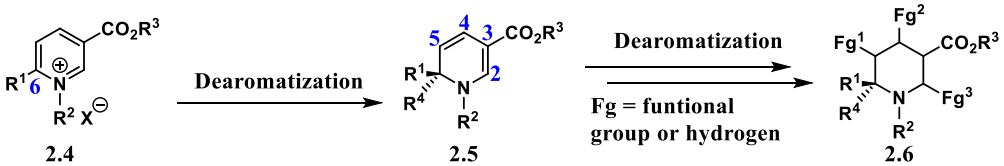
Figure 2.1: Examples of bioactive molecules containing six-membered azaheterocycles with a fully substituted stereocenter.



Rolapitant (2.1) **Roxburghine D (2.2)** **Lycodine (2.3)**

Catalytic dearomatization of electron deficient pyridines is an attractive approach toward the synthesis of 6-membered nonaromatic azaheterocycles because of the following: (1) pyridines are widely available commercially and through chemical synthesis; (2) initial dearomatization yields dihydropyridines (**2.5**) that contain a stereocenter and two double bonds that subsequently could be sequentially functionalized in a diastereoselective manner for the synthesis of highly substituted tetrahydropyridines and piperidines (Scheme 2.1).[8–20] Previous efforts on the catalytic enantioselective dearomatization of pyridines have focused on the hydrogenation of the heteroarene double bonds[21–31] and addition of nucleophiles to activated pyridines[32–41] and related heteroarenes.[42–44] Despite the surge of research interest in asymmetric heteroarene hydrogenation, complete reduction of highly substituted pyridines is still challenging, and the hydrogenation method cannot establish a fully substituted stereogenic center as one of the substituents introduced is hydrogen. Catalytic nucleophilic additions to activated pyridines on the other hand have mainly focused on the dearomatization reactions of unsubstituted or symmetrically substituted N-acyl and N-alkylpyridiniums. Examples of these reactions include addition of arylboronic acids,[32,42] alkynes,[33,34] aryl and alkyl zinc reagents,[35–37] indoles,[38,43] and other nucleophiles[39–41,44,45] to pyridinium and quinolinium salts. Despite these advances in heteroarene dearomatization, there is no general method reported for the dearomative formation of the fully substituted stereocenters starting from either N-alkyl or N-acylpyridinium salts with practical yield and enantioselectivity.

Scheme 2.1: Dearomatization approach to the synthesis of highly substituted piperidines.



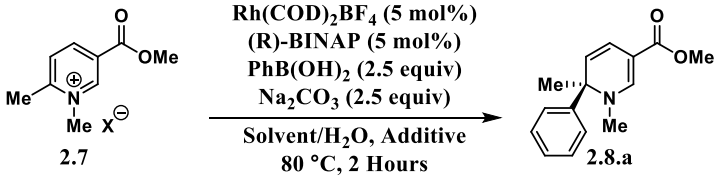
Herein we report rhodium catalyzed dearomatization of N-alkyl nicotinic acid esters (**2.4**) for the synthesis of dihydropyridines that contain a fully substituted stereocenter at the C-6 position (Scheme 2.1). We have chosen nicotinic acid ester-derived pyridinium salts, as the regioselective dearomatization of these salts lead to DHPs (**2.5**) that contain two double bonds with distinct reactivities. One of these double bonds, C4=C5, typically reacts as a C=C double bond while the C2=C3 bond is part of the vinylogous carbamate, and thus resembles the reactivity of that functional group.[46] Together these reactivities would provide a versatile reactivity profile for the dearomatization products (**2.5**) to synthesize functionalized nonaromatic azaheterocycles where at least one of the stereocenters is fully substituted.

2.2. Optimization of Reaction Conditions:

We initiated our studies using N-methylpyridinium triflate **2.7** as a substrate, which is readily available from the reaction of methyl 6-methylnicotinate and methyl triflate (Table 2.1). Initial reactions were conducted at 80 °C in a 2:1 THF/water mixture as the solvent, phenyl boronic acid as the nucleophile, and $Rh(COD)_2BF_4$/(R)-BINAP as the catalyst. We were delighted to find out that under these conditions dihydropyridine (**2.8.a**) was formed in excellent enantioselectivity and regioselectivity albeit in low yield (Table 2.1, entry 1). In order to improve the yield, we evaluated several solvents and found that ethereal solvents gave a higher yield than that of toluene and 1,2-dichloroethane (Table 2.1, entries 1−5). To further improve the yield of the reaction, we investigated KPF_6 as an additive with the idea that a more soluble anion PF_6 may improve solubility of the pyridinium salts in organic solvents. In fact, addition of 2 equiv. of KPF_6 improved the yield in all solvents tested while the highest yield was obtained in 1,4-dioxane (Table 2.1, entries 6−8). Lastly, we evaluated the impact of amount of water on the yield of the reaction (Table 2.1, entries 9−11). Increasing the amount of water from 0.5 to 1 mL yielded only a trace

amount dearomatization product, while decreasing the amount of water to 0.25 or 0.1 mL significantly improved the yield. As the *ee* slightly decreased for the 0.1 mL water case, we decided to go with the 0.25 mL water as the optimal reaction conditions. It is worth noting that the reaction did not work without the addition of $Rh(COD)_2BF_4$ or (R)- BINAP (Table 2.1: Optimization of reaction conditions., entries 12 and 13) and gave only trace amounts of the product without addition of the water (Table 2.1, entry 14).

Table 2.1: Optimization of reaction conditions.



Entry	Solvent	H_2O	Additive	Yield (%)[a]	*ee* (%)[b]
1	THF	0.50 mL	none	27	96
2	1,4-dioxane	0.50 mL	none	39	ND
3	DME	0.50 mL	none	27	ND
4	DCE	0.50 mL	none	24	ND
5	PhMe	0.50 mL	none	25	ND
6	1,4-dioxane	0.50 mL	KPF_6	52	ND
7	THF	0.50 mL	KPF_6	45	ND
8	DME	0.50 mL	KPF_6	47	ND
9	1,4-dioxane	1.0 mL	none	< 5	ND
10	**1,4-dioxane**	**0.25 mL**	**none**	**84**	**94**
11	**1,4-dioxane**	**0.10 mL**	**none**	**86**	**92**
12[c]	1,4-dioxane	0.25 mL	none	0	ND
13[d]	1,4-dioxane	0.25 mL	none	0	ND
14	1,4-dioxane	0 mL	none	< 5	ND

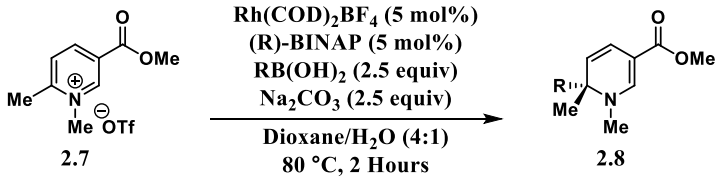
[a]Yield of **2.8.a** was reported based on ^1H NMR spectra analysis of crude reaction mixtures using 1,3,5-trimethoxybenzene as in internal standard. [b]Enantiomeric excess (*ee*) was determined by chiral HPLC. [c]No $Rh(COD)_2BF_4$ was added. [d]No (R)-BINAP was added.

2.3. Reaction Scope:

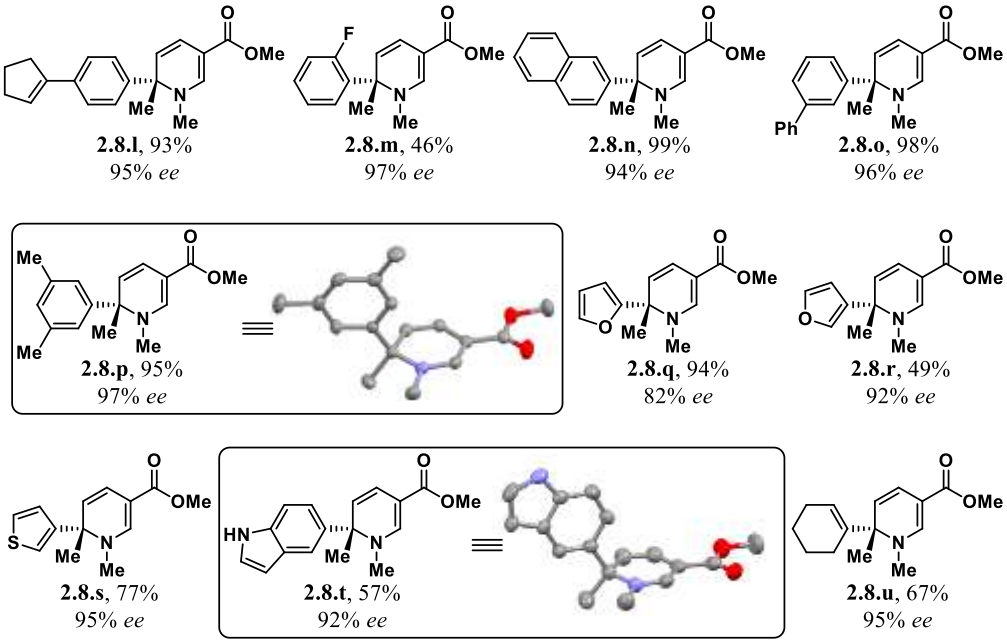
2.3.1. Scope of Boronic Acids:

With the optimal reaction conditions in hand, we investigated the scope of the boronic acids in this reaction. Boronic acids containing ester, amide, ether, olefin, alcohol, halide functional groups reacted to give the corresponding dearomatization products (**2.8**) in good to excellent yield and excellent enantioselectivities (Table 2.2). Regioselectivity of the addition was also high where no C-4 addition product was observed, while the ratio of the C-6 versus C-2 addition products was greater than 15:1 favoring the C-6 addition product. Both electron-donating and electron-withdrawing groups are well tolerated, although boronic acids containing electron-withdrawing groups gave dihydropyridines in slightly diminished yields and enantioselectivities (Table 2.2, **2.8.b** and **2.8.c**). Substituents at the ortho and meta positions of aryl boronic acids also tolerated delivering the expected products without erosion of enantioselectivity (Table 2.2, **2.8.b−l,** and **2.8.n−p**). The yield of the reaction was lower for the ortho-substituted boronic acid (Table 2.2, **2.8.m**), while the enantioselectivity remained high. Heterocycles are important building blocks in medicinal chemistry. Considering this, we have evaluated a number of heteroarene boronic acids under the optimal reaction conditions. Furan-, thiophene-, and indole-containing boronic acids reacted to give the corresponding dearomatized products in good to excellent yield and excellent enantioselectivities (Table 2.2, **2.8.q−t**) with only slight erosion of enantioselectivity when furan-2-boronic acid was used (Table 2.2, **2.8.q**). Finally, an alkenyl boronic acid also reacted to give the corresponding dihydropyridine derivative in excellent enantioselectivity (Table 2.2, **2.8.u**). Absolute stereochemistry of the two products (**2.8.p** and **2.8.t**) was determined to be (R) using X-ray crystallography.

Table 2.2: : Scope of Rhodium-catalyzed synthesis of dihydropyridines containing a fully substituted stereocenter.[a]



Entry	R =	Yield	*ee*
2.8.a	H	82%	94%
2.8.b	CF_3	63%	91%
2.8.c	CO_2Me	76%	81%
2.8.d	OMe	85%	91%
2.8.e	F	99%	94%
2.8.f	Cl	90%	91%
2.8.g	Br	80%	95%
2.8.h	Me	88%	94%
2.8.i	CH_2OH	70%	86%[b]
2.8.j	Ph	99%	93%
2.8.k	NHAc	75%	93%[c]



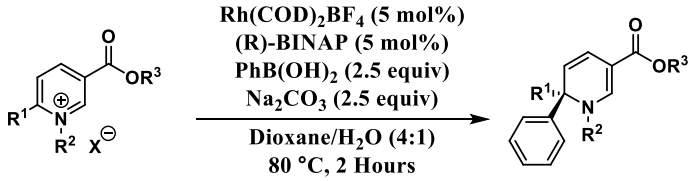
[a]Isolated yield is reported. Enantiomeric excess (*ee)* was measured by chiral HPLC analysis. [b]*ee* was measured by converting the alcohol to the corresponding methyl ether. [c]*ee* was measured after N-acylation of the free N-H using Boc_2O. See supporting information for details. The pictured X-ray structures are shown with thermal elipsoids at 30% probability. CCDC 1921656 (**2.8.p**) and 1920061 (**2.8.t**) contain the crystalographic data for this publication.

2.3.2. Substitutions to the Nicotinate Salt:

After establishing the scope of the boronic acids, we turned our attention to investigate the influence of pyridinium substituents and counter-anions on the yield and stereoselectivity of this reaction by systematically varying the ester, C-6, and N-alkyl substituents and counter-anions (Table 2.3). In our optimization studies, we have observed that pyridinium salts that are more soluble in organic solvents give the dearomatization product in higher yield compared with the less soluble pyridinium salts (Table 2.3, entries 6−8). This trend was further evidenced by the fact that more hydrophobic pyridiniums, which contain larger alkyl substituents or more hydrophobic

counter-anions consistently gave higher yields than those that are less hydrophobic (Table 2.3: Evaluation of substituent and counter anion effects on the yield and enantioselectivity of the dearomatization., entry 1 vs entry 2 and entry 2 vs entries 3 and 4). Altering the C-6 substituent (Table 2.3, entry 8 vs Table 2.2, **2.8.a**) or ester group (Table 2.3, entry 3 vs Table 2.2, **2.8.a**) did not significantly influence the enantioselectivity of the reactions. However, substituents that are sterically bulkier than the methyl group at the N-alkyl site resulted in diminished *ee*s (Table 2.3, entries 6 and 7).

Table 2.3: Evaluation of substituent and counter anion effects on the yield and enantioselectivity of the dearomatization.



2.S.4-2.S.10 2.S.13-2.S.16

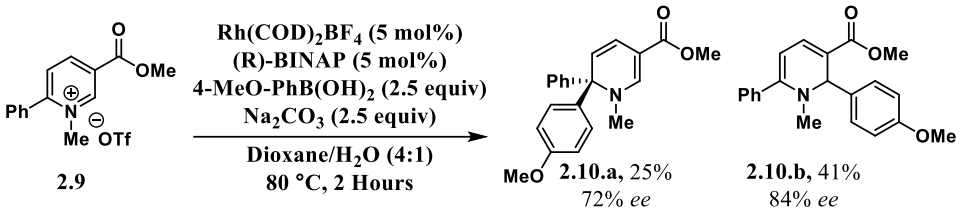
Entry	R^1	R^2	R^3	X	yield (%)[a]	*ee* (%)[b]
1	Me	Me	Me	I	6	96
2	Me	Me	*t*-Bu	I	75	95
3	Me	Me	*t*-Bu	OTf	80	93
4	Me	Me	*t*-Bu	PF_6	99	91
5	Me	Me	*t*-Bu	BF_4	75	93
6	Me	Et	Me	Br	31	84
7	Me	Bn	Me	Br	56	66
8	Et	Me	Me	OTf	67	97

[a]Isolated yield is reported. [b]Enantiomeric excess (*ee)* was determined by chiral HPLC.

In general, dearomative nucleophilic addition to pyridinium salts takes place at C-2, C-4, and C-6 positions. In all reactions described in Table 2.2 and Table 2.3, formation of a small amount (<5%) of constitutional isomer of the major product where the addition occurred at the C-

2 position instead of the C-6 position was observed. No C-4 addition product was detected in any of these reactions. Presumably this is due to the fact that C-2 or C-6 are closer to the electron-withdrawing nitrogen atom; thus, these two positions are more activated. In order to further probe the steric influence of the C-6 substituent on the regioselectivity of the reaction, we synthesized pyridinium salt **2.9** which contains a sterically bulky phenyl group at the C-6 position (Scheme 2.2: : Dearomatization of pyridinium salt with sterically hindered C-6 substituent.). When this pyridinium salt was subjected to the standard reaction conditions, C-2 addition product **2.10.b** was observed as the major product. Enantioselectivity of the reaction was still good, giving the highly sterically hindered C-6 addition product **2.10.a** in 72% *ee* and constitutional isomer **2.10.b** in 84% *ee*.

Scheme 2.2: : Dearomatization of pyridinium salt with sterically hindered C-6 substituent.

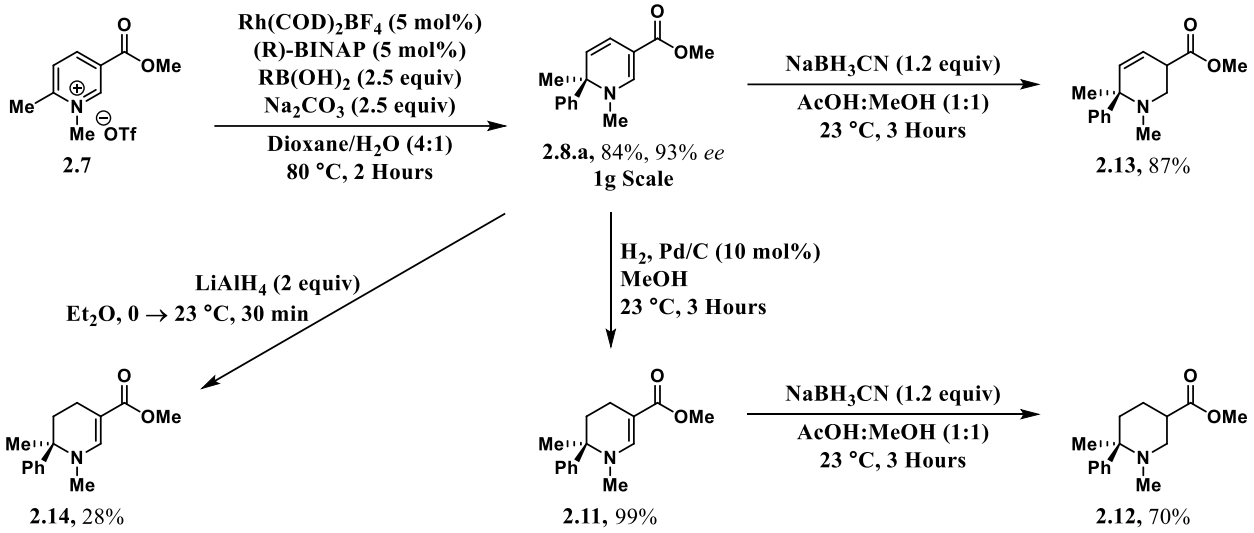


2.4. Functionalization of the 1,6-DHP Product:

In order to demonstrate that the two double bonds of the dihydropyridines **2.8.a** can be selectively functionalized, we carried out several reductive derivatization reactions (Scheme 2.3). To do this, we first carried out the initial dearomatization reaction on a 1 g scale. At this scale, yield and enantioselectivity remained essentially the same compared to the standard 0.2 mmol scale reaction, which demonstrates the scalability of this dearomatization reaction. Hydrogenation of the dihydropyridine **2.8.a** resulted in the vinylogous carbamate **2.11** in excellent yield and purity. This carbamate can be further reduced to piperidine **2.12** using sodium cyanoborohydride.

Treatment of **2.8a** with cyanoborohydride selectively reduces the C2=C3 double bond delivering **2.13** as a 1.0:1.0 mixture of diastereomers in 87% overall yield. Interestingly, when $LiAlH_4$ was used as a reductant, instead of complete reduction of the C2=C3 double bond and ester group to primary alcohol, aldehyde **2.14** was obtained in 28% yield as the major product.

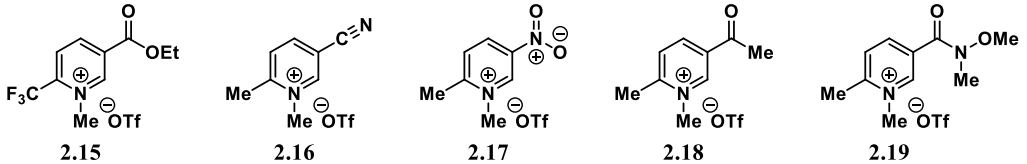
Scheme 2.3: Gram-scale synthesis and derivatization of dihydropyridine 2.8.a.



2.5. Method Shortcomings:

Although the method developed by us show a broad scope, dearomatization of certain pyridinium salts proved to be challenging. particularly, highly electrophilic pyridinium salts such as **2.15**−**2.18** did not produce the corresponding dearomatization products (Figure 2.2). The main side product observed in these reactions was the product of addition of hydroxide to the pyridinium

Figure 2.2: Pyridinium salts that did not yield corresponding dearomatization products.

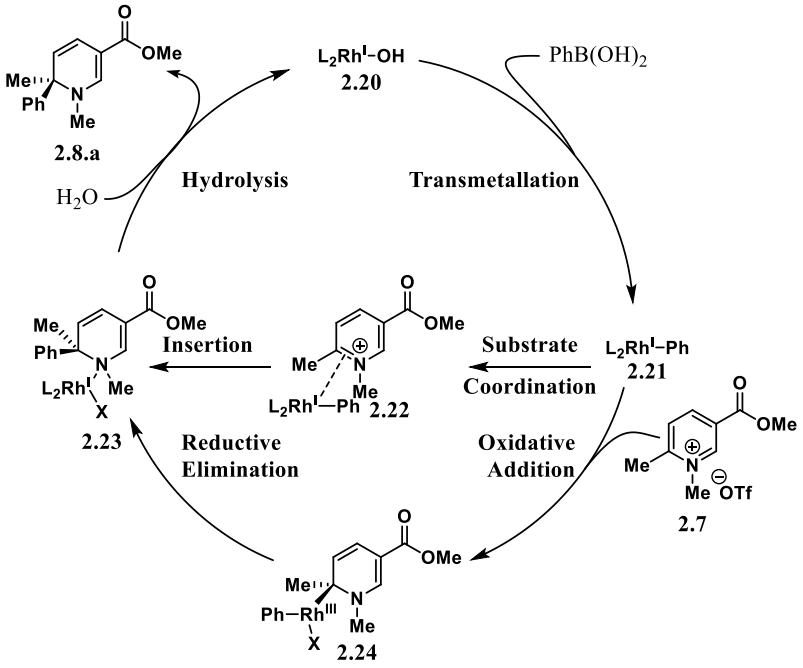


salts under basic reaction conditions. The amide **2.19** gave some product, although the yield was again low. We are currently working toward overcoming these limitations to further expand the substrate scope for this important reaction.

2.6. Mechanism Proposal:

Mechanistically, two possible catalytic cycles could be envisioned for this transformation (Scheme 2.4: Possible catalytic cycles for Rh-catalyzed dearomatization of N-Alkyl nicotinate salts.). The first one involves a reactivity that resembles the rhodium-catalyzed conjugate addition reactions of boronic acids with Michael acceptors. The key steps in this mechanism involve (1) transmetalation of ligated Rh(I) **2.20** to give aryl rhodium species **2.21**; (2) coordination of the pyridinium salt; (3) insertion of the C=N bond into the Rh−Ar bond; and (4) hydrolysis of the product **2.8a** from **2.23** to regenerate the catalyst **2.20**. An alternative mechanism has a resemblance to the rhodium-catalyzed allylic substitution reactions and involves (1) transmetalation of ligated Rh(I) **2.20** to give aryl rhodium species **2.21**; (2) oxidative addition of

Scheme 2.4: Possible catalytic cycles for Rh-catalyzed dearomatization of N-Alkyl nicotinate salts.



Rh(I)-Ar species **2.21** to pyridinium salts to form **2.24**; (3) reductive elimination; and (4) hydrolysis of the product **2.8a** from **2.23** to regenerate the catalyst **2.20**. Experimental and computational studies to understand detailed mechanism of this reaction are currently ongoing in our laboratory.

2.7. Conclusion:

In conclusion, we report a practical method for the dearomatization of pyridinium salts using boronic acid nucleophiles and readily available Rh/BINAP catalyst system to access dihydropyridines that contain a fully substituted stereogenic center. The dearomatization reaction proceeded with high yield and enantioselectivity and demonstrated excellent functional group tolerance. We have also demonstrated that this dearomatization reaction can be carried out in gram scale, and the dearomatization products can be selectively functionalized to deliver tetrahydropyridine and piperidine derivatives.

2.8. Experimental Section:

2.8.1. Materials and Methods:

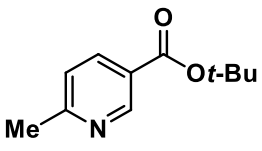
Reactions were performed in flame-dried sealed tubes or modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of nitrogen or inside nitrogen filled glovebox using 1 dram or 4 dram vials unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe. The appropriate starting materials and reagents were dried via azeotropic removal of water with toluene. Molecular sieves were activated at 350 °C then flame-dried under vacuum immediately prior to use. Organic solutions were concentrated by rotary evaporation below 40 °C. Flash column chromatography was performed employing 230–400 mesh silica gel. Thin-layer chromatography was performed using glass plates pre-coated to a depth of 0.25 mm with 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm) and visualized under UV light (254 and 360 nm), or stained with Ceric Ammonium Molybdate in concentrated H_2SO_4.

Dichloromethane, tetrahydrofuran, diethyl ether, dimethylformamide, dimethoxyethane and toluene were purified by passage through two packed columns of neutral alumina under an argon atmosphere.[47] Methanol was dried by storing over 3A molecular sieves for at least 36 hours. Amines were distilled from CaH_2 at 760 torr. All other chemicals were obtained from commercial vendors and were used without further purification unless otherwise noted.

Automated flash chromatography was performed with a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns. Infrared (IR) spectra were obtained using a *Thermo Scientific™ Nicolet™ iS50* FTIRspectrophotometer. Data are presented as the frequency of absorption (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were acquired on commercial instruments (400 and 600 MHz) at Auburn University NMR facility. Carbon-13

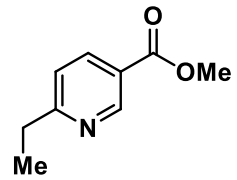
nuclear magnetic resonance (^{13}C NMR) spectra were acquired at 100 and 151MHz. Fluorine-19 nuclear magnetic resonance (19F NMR) spectra were acquired at 235 MHz. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual peaks in the NMR solvent (d-chloroform: δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR; d4-methanol: δ 3.31 for ^{1}H NMR, δ 49.00 for ^{13}C NMR). Data are presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration.

2.8.2. Synthesis of Pyridine Starting Materials:



tert-Butyl 6-methylpyridine-3-carboxylate (2.S.1)

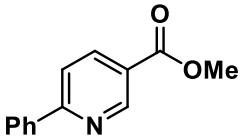
To a stirred solution of 6-methylpyridine carboxylic acid (6.86 g, 50.0 mmol, 1.0 equiv.) in CH_2Cl_2 (85 mL) under nitrogen atmosphere was added (in this order) *t*-BuOH (7.12 mL, 75.0 mmol, 1.5 equiv.), DMAP (2.45 g, 20.0 mmol, 0.40 equiv.), and DCC (20.6 g, 100 mmol, 2.0 equiv.). The solution was stirred for 20 hours at 23 °C and filtered through celite. The solids and celite were further washed with CH_2Cl_2 (100 mL) and the solvent was evaporated under reduced pressure. The residue was purified via flash column chromatography to yield **2.S.1** as a colorless oil. **Yield** 7.50 g (78%); **TLC** R_f 0.19 (hexanes:EtOAc 9:1). The ^{1}H and ^{13}C spectral data match those of the reported molecule.[48] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.04 (dd, *J* = 7.8, 2.1 Hz, 1H), 7.12 (dd, *J* = 7.9, 3.7 Hz, 1H), 2.52 (d, *J* = 4.1 Hz, 3H), 1.51 (d, *J* = 4.5 Hz, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.57, 162.47, 150.35, 137.17, 124.87, 122.74, 81.67, 28.11, 24.67.



Methyl 6-phenylpyridine-3-carboxylate (2.S.2)

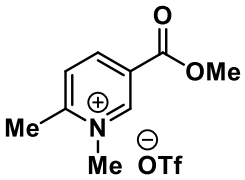
In a N_2 filled glove box, dppf (91.5 mg, 0.165 mmol, 0.11 equiv.) and $Pd(OAc)_2$ (34 mg, 0.15 mmol, 0.10 equiv.) were dissolved in 4 mL of dioxane

in a 4-dram vial and allowed to stir for 10 min to prepare the solution of the catalyst. This solution was then added to a flame dried Schlenk tube (25 mL) that contained a stir bar and methyl-6-bromonicotinate (324 mg, 1.50 mmol, 1.0 equiv.) and stirred until homogenous solution was obtained. 1 M solution of Et_2Zn in PhMe (1.80 mL, 1.80 mmol, 1.20 equiv.) was added dropwise. The Schlenk tube was sealed and transferred to a Schlenk line where it was then heated at 80 °C with stirring for 16 hours. The reaction mixture was cooled to ambient temperature, diluted to 25 mL with Et_2O, filtered through a plug of silica gel and then celite, and concentrated *in vacuo*. The brown crude mixture was purified via automated flash chromatography to afford **2.S.2**. **Yield:** 210 mg (85%) The ^1H and ^{13}C spectral data match those of the reported molecule.[49] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.13 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 3.87 (s, 3H), 2.83 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.88, 165.67, 150.22, 137.25, 123.19, 121.54, 52.03, 31.33, 13.4; **HRMS** (ESI) *m/z* calc'd for $C_9H_{12}NO_2$ $[M+H]^+$: 166.0863, found 166.0869.



Methyl 6-phenylpyridine-3-carboxylate (2.S.3)

To a flame dried Schlenk tube (25 mL) charged with stir bar and methyl-6-bromonicotinate (432 mg, 2.00 mmol, 1.0 equiv.), $PhB(OH)_2$ (366 mg, 3.00 mmol, 1.5 equiv.) was added under N_2. The reaction vessel was transferred to a N_2 filled glove box where $Pd(PPh_3)_4$ (116 mg, 0.100 mmol, 0.05 equiv.) was added followed by PhMe (10 mL). The tube was sealed and transferred to a Schlenk line where degassed 2M Na_2CO_3(aq) (2 mL, 4 mmol, 2 equiv.) was added under N_2. The reaction vessel was sealed and heated at 80° C for 16 hours. The reaction mixture was cooled to ambient temperature, diluted to 25 mL with EtOAc, filtered through silica and then celite, and concentrated *in vacuo*. The orange crude mixture was purified via automated flash chromatography to give **2.S.3**. **Yield:** 373 mg (87%). The ^1H and ^{13}C spectral data match those of



the reported molecule.[50] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.28 (d, *J* = 1.3 Hz, 1H), 8.35 (dd, *J* = 8.3, 2.1 Hz, 1H), 8.06 (d, *J* = 6.7 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.53 – 7.44 (m, 3H), 3.98 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 165.74, 160.65, 150.84, 138.03, 137.89, 130.01, 128.90, 127.32, 124.08, 119.83, 52.36; **HRMS** (ESI) *m/z* calc'd for $C_{13}H_{12}NO_2$ $[M+H]^+$: 214.0863, found 214.0864.

2.8.3. Synthesis of N-Alkyl Pyridinium Salts:

General procedure for pyridinium salts using MeOTf (GP):

In a Schlenk flask, specified nicotinic ester (1.0 equiv) was dissolved in CH_2Cl_2 (10 mL/g) and cooled in an ice water bath. MeOTf (1.1 equiv) was added slowly via syringe and the reaction mixture was stirred overnight allowing it to warm to ambient temperature. ~1/3 of the CH_2Cl_2 was removed under reduced pressure to obtain light yellow oil. Pyridinium salt was isolated from this oil according to the general isolation protocol described below.

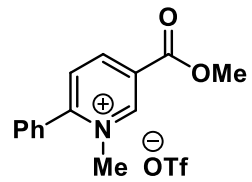
General procedure for isolation of pyridinium salts (GIP):

Crude pyridinium salt solution was slowly added to a beaker containing rapidly stirring Et_2O (50 mL/g). Stirring was continued for additional 30 min at which point, pyridinium salt precipitated out. This precipitate was filtered off and washed with Et_2O (3 x 10 mL/g) to give pyridinium salt as white to off white solid unless otherwise noted.

5-(methoxycarbonyl)-1,2-dimethylpypiridin-1-ium triflate (2.7)

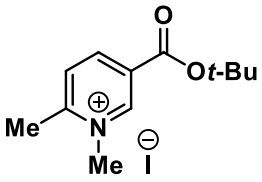
Prepared from methyl 6-methylpyridine carboxylate (3.02 g, 20.0 mmol, 1.0 equiv,) according to GP and isolated according to GIP to give **2.7** as a white solid. **Yield:** 5.80 g (87%); **FTIR** 3014.96, 2969.35, 1732.49, 1637.39; **^{1}H NMR** (600 MHz, CD_3OD) δ 7.83 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 2.75 (s, 3H), 2.41 (s, 3H), 1.29 (s, 3H); **^{13}C NMR** (151 MHz, CD_3OD) δ 163.50, 161.50, 148.79, 145.72, 130.75, 129.48, 121.67 (q, *J* = 318.6 Hz), 53.93, 46.85; **^{19}F NMR**

(235 MHz, CD_3OD) δ -80.02; **HRMS** (ESI) *m/z* calc'd for $C_{10}H_{14}NO_2$ $[M]^+$ 166.0863, found 166.0870.



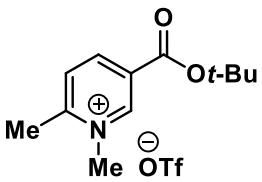
5-(methoxycarbonyl)-1-methyl-2-phenylpyridin-1-ium triflate (2.9)

Prepared from **2.S.3** (350 mg, 1.64 mmol, 1.0 equiv.) according to GP and isolated according to GIP to give **2.9** as a white solid. **Yield:** 539 mg (87%). **FTIR:** 2994, 2944, 2842, 1715, 1592**; ^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.92 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.60 (m, 5H), 4.36 (s, 3H), 4.04 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.69, 159.20, 148.65, 144.82, 132.21, 130.65, 129.90, 129.72, 129.25, 128.90, 53.92, 48.48; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -78.44. **HRMS** (ESI) *m/z* calc'd for $C_{14}H_{14}NO_2$ $[M]^+$: 228.1019, found 228.1018.



5-(*tert*-butoxycarbonyl)-1,2-dimethylpypiridin-1-ium iodide (2.S.4)

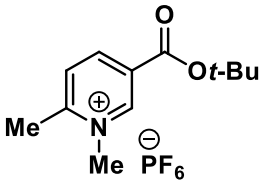
To a vial charged with a stir bar and **2.S.1** (1.00 g, 1.0 equiv, 5.18 mmol), was added MeI (0.484 mL, 7.77 mmol, 1.5 equiv.). The vial was fitted with a Teflon lined cap and stirred at 23 °C for 16 hours. The reaction was worked up following GIP to afford **2.S.4** as a white powder. **Yield** 905 mg (52%); **FTIR** 3035.68, 2989.08, 2973.70, 1718.41, 1641.31; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.73 (d, *J* = 8.1 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.26 (s, 1H), 4.62 (s, 3H), 3.11 (s, 3H), 1.64 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.00, 159.64, 147.12, 144.84, 130.40, 130.23, 85.53, 48.72, 28.22, 22.96; **HRMS** (ESI) *m/z* calc'd for $C_{12}H_{18}NO_2^+$ $[M]^+$ 208.1332, found 208.1329.



5-(*tert*-butoxycarbonyl)-1,2-dimethylpypiridin-1-ium triflate (2.S.5)

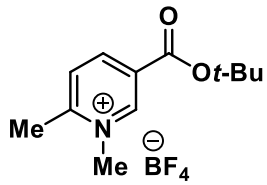
To a stirred solution of **2.S.4** (200 mg, 0.596 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) in a 50 mL round-bottomed flask was added solution of NaOTf (102 mg, 0.596 mmol, 1.0 equiv.) in H_2O (10 mL). The biphasic solution was stirred vigorously

for 1 hour at 23 °C. The CH_2Cl_2 layer was separated and dried over $MgSO_4$. Solids were filtered off and CH_2Cl_2 layer was concentrated to afford **2.S.5** as a dark purple solid. **Yield** 171 mg (80%); **FTIR** 2982.45, 2251.38, 1724.75, 1640.84; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.72 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 4.48 (s, 3H), 2.99 (s, 3H), 1.62 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.06, 159.46, 147.08, 144.55, 129.95, 129.93, 123.64, 121.52, 120.46 (q, *J* = 320.6 Hz), 119.40, 117.27, 85.14, 47.60, 27.98, 21.69; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -78.53; **HRMS** (ESI) *m/z* calc'd for $C_{12}H_{18}NO_2^+$ $[M]^+$ 208.1332, found 208.1337.



5-(*tert*-butoxycarbonyl)-1,2-dimethylpypiridin-1-ium hexafluoro-phosphate (2.S.6)

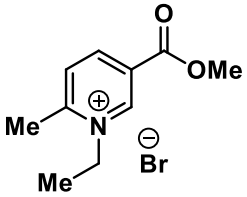
To a stirred solution of **2.S.4** (200 mg, 0.596 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL). in a 50 mL round-bottomed flask was added a solution of KPF_6 (109 mg, 0.596 mmol, 1.0 equiv.) in H_2O (10 mL). The biphasic solution was stirred vigorously for 1 hour at 23 °C. The CH_2Cl_2 layer was separated and dried over $MgSO_4$. Solids were filtered off and CH_2Cl_2 layer was concentrated to afford **2.S.6** as an off green solid. **Yield** 188 mg (90%); **FTIR** 3100.51, 2976.93, 1718.41, 1641.31; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.70 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 4.33 (s, 3H), 2.89 (s, 3H), 1.61 (s, 9H); **^{13}C NMR** (151 MHz, CD_3OD) δ 161.95, 160.99, 148.55, 145.62, 131.04, 130.59, 85.48, 46.77, 28.12, 20.70; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -73.37 (d, *J* = 711.9 Hz); **^{31}P NMR** (101 MHz, $CDCl_3$) δ -144.38 (hept, *J* = 711.5 Hz); **HRMS** (ESI) *m/z* calc'd for $C_{12}H_{18}NO_2^+$ $[M]^+$ 208.1332, found 208.1330.



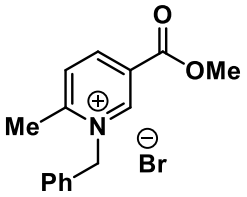
5-(*tert*-butoxycarbonyl)-1,2-dimethylpypiridin-1-ium tetrafluoro-borate (2.S.7)

To a stirred solution of **2.S.4** (200 mg, 0.596 mmol, 1.0 equiv.) and CH_2Cl_2 (10 mL) in a 50 mL round-bottomed flask was added a solution of KBF_4 (75.1 mg, 0.596

mmol, 1.0 equiv.) in H_2O (10 mL). The biphasic solution was stirred vigorously for 1 hour at 23 °C. The CH_2Cl_2 layer was separated and dried over $MgSO_4$. Solids were filtered off and CH_2Cl_2 layer was concentrated to afford **2.S.7** as a light green solid. **Yield** 87.9 mg (50%); **FTIR** 3041.48, 3105.54, 2982.77, 1719.96, 1642.98, 1565.21; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.72 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 4.51 (s, 3H), 3.02 (s, 3H), 1.63 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 160.09, 159.57, 147.11, 144.61, 130.04, 129.84, 85.20, 47.25, 28.01, 21.38; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -153.00; **HRMS** (ESI) *m/z* calc'd for $C_{12}H_{18}NO_2^+$ $[M]^+$ 208.1332, found 208.1344.

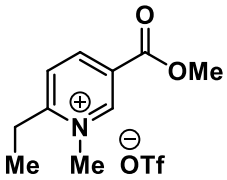


5-(methoxycarbonyl)-1-ethyl-2-methylpypiridin-1-ium bromide (2.S.8) To a 4 dram vial charged with stir bar and methyl 6-methyl-nicotinate (756 mg, 5.00 mmol, 1.0 equiv.) was added ethyl bromide (0.45 mL, 6.0 mmol, 1.2 equiv.). The vial was fitted with a Teflon-lined cap and heated at 80 °C for 12 hours. The reaction was worked up following GIP to afford **2.S.8** as a light brown solid. **Yield** 360.3 mg (28%); **FTIR** 3438.4, 301.92, 3003.28, 1729.83; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.80 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 5.06 (q, *J* = 6.9 Hz, 2H), 4.04 (s, 3H), 3.15 (s, 3H), 1.69 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 161.80, 159.15, 146.06, 144.60, 131.33, 128.45, 54.95, 53.74, 21.47, 15.62; **HRMS** (ESI) *m/z* calc'd $C_9H_{12}NO_2$ $[M]^+$ 180.1019, found 180.1024.



5-(methoxycarbonyl)-1-benzyl-2-methylpypiridin-1-ium bromide (2.S.9) Compound **2.S.9** was synthesized according to a reported procedure and the ^{1}H and ^{13}C spectral data match those of the reported molecule.[51] **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.47 (s, 1H), 8.80 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.37 – 7.29 (m, 2H), 6.28 (s, 2H), 3.99 (s, 3H), 3.12 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$)

δ 161.77, 160.51, 146.73, 144.91, 131.05, 130.92, 129.91, 129.88, 128.51, 128.33, 62.96, 53.89, 22.46.



2-ethyl-5-(methoxycarbonyl)-1-methylpyridin-1-ium triflate (2.S.10)

To a 25 mL Schlenk tube charged with stir bar and solution of methyl 6-ethylpyridine-3-carboxylate (200 mg, 1.21 mmol, 1.00 equiv) in CH_2Cl_2 (3.1 mL), MeOTf (238 mg, 1.45 mmol, 1.20 equiv) was added dropwise under N_2 at 4 °C, and the reaction was gradually warmed to ambient temperature after addition of methyl triflate. After 12 hours, the reaction mixture was added dropwise to 400 mL of stirring 1:1 Et_2O/Hex. After an hour of additional stirring, the precipitate was collected and washed with 5 mL of cold ether to afford **2.S.10**. **Yield:** 380 mg (95%). **FTIR:** **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.83 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 4.43 (s, 3H), 4.03 (s, 3H), 3.22 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.94, 161.85, 147.93, 144.75, 127.98, 127.18, 123.63, 121.51, 119.39, 117.27, 77.28, 77.07, 76.85, 53.65, 53.49, 46.57, 26.61, 10.88; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -78.61 (s); **HRMS** (ESI) *m/z* calc'd for $C_{10}H_{14}NO_2$ $[M]^+$: 180.1019, found 180.1024.

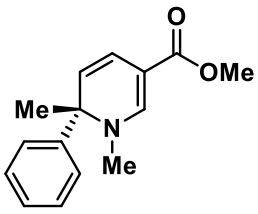
2.8.4. Dearomative Synthesis of Dihydropyridines:

Preparation of the Rh catalyst stock solution:

In a nitrogen filled glove box $Rh(COD)_2BF_4$ (64 mg, 0.16 mmol, 1.0 equiv) and (R)-BINAP (99 mg, 0.16 mmol, 1.0 equiv) was weighed into a 4-dram vial and dissolved in dioxane (16 mL). This solution was used in the dearomatization reactions below. To prepare the racemic dearomatization products racemic BINAP was used to prepare the catalyst.

General procedure for dearomatization of *n*-alkyl pyridinium salts:

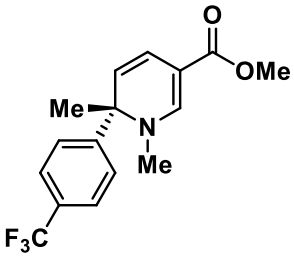
The specified pyridinium salt (0.20 mmol, 1.0 equiv), aryl boronic acid (0.50 mmol, 2.5 equiv), and Na_2CO_3 (53 mg, 0.50 mmol, 2.5 equiv), were measured into a 1 dram scintillation vial on the benchtop. The vial was then transferred into the glovebox where 1.0 mL of the solution of the catalyst was added into the vial. The vial was sealed with a Teflon lined septa cap and brought outside the glovebox. Degassed water (250 µL) was added to the reaction mixture via syringe and the reaction mixture was heated at 80 °C for 2 hours. The vial was then removed from the heating block and diluted with 2 mL of EtOAc. The reaction mixture was dried with 1.0 g of $MgSO_4$ and filtered through basic Al_2O_3. Al_2O_3 was washed with additional EtOAc (2 x 4 mL) and the combined filtrate was concentrated to give brown residue. The residue was purified by flash column chromatography on a Teledyne Isco Combiflash® R_f system with Redi*Sep* Gold™ columns (24-gram silica gel column) using a hexanes:EtOAc gradient (0 to 100% EtOAc) to give **8-10** as a light yellow oil unless otherwise noted.



Methyl (6S)-1,6-dimethyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (2.8.a)

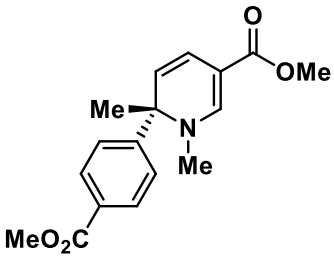
Dihydropyridine **2.8.a** was synthesized from pyridinium **2.7** and phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 40 mg **(**82%); The **enantiomeric excess** was determined by HPLC analysis to be 94%ee (254 nm, 25℃); t_{minor} = 14.7 min, t_{major} = 16.3 min [(Chiralpak ID) hexane/i-PrOH, 90:10, 1.0 mL/min]; **TLC** R_f 0.56 (Hex:EtOAc 1:1); **FTIR:** 3055, 3025, 2976, 2947, 1677, 1634, 1588; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -0.3728 (c 0.046 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.32 (s, 1H), 7.29 – 7.25 (m, 1H), 6.31 (d, *J* = 9.8 Hz, 1H), 4.77 (d, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 2.72 (s, 3H), 1.75 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.12, 147.67,

145.61, 128.51, 127.57, 126.52, 120.00, 118.03, 94.61, 63.22, 50.76, 38.40, 24.81; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{18}NO_2$ $[M+H]^+$ 244.1332, found 244.1347.



Methyl (6*S*)-1,6-dimethyl-6-[4-(trifluoromethyl)phenyl]-1,6-dihydro-pyridine-3-carboxylate (2.8.b)

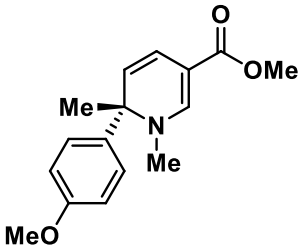
Dihydropyridine **2.8.b** was synthesized from pyridinium **2.7** and 4-(trifluoromethyl)phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 39 mg **(**63%); The **enantiomeric excess** was determined by HPLC analysis to be 91%ee (254 nm, 25℃); t_{minor} = 13.1 min, t_{major} = 13.8 min [(Chiralpak IG) hexane/*i*-PrOH, 90:10, 1.0 mL/min]; **TLC** R_f 0.57 (Hex:EtOAc 1:1); **FTIR:** 2978, 2948, 1681, 1637, 1569; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** 0.2700 (c 0.020 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.34 (s, 1H), 6.32 (d, *J* = 9.9 Hz, 1H), 4.75 (d, *J* = 10.0 Hz, 1H), 3.70 (s, 3H), 2.73 (s, 3H), 1.78 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.94, 149.39, 147.61, 129.68 (q, *J* = 32.5 Hz), 126.78, 125.55 (q, *J* = 3.6 Hz), 124.01 (q, *J* = 272.2 Hz), 119.40, 118.73, 95.15, 63.19, 50.85, 38.44, 24.97; **^{19}F NMR** (235 MHz, $CDCl_3$) δ -62.55; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{19}H_{17}F_3NO$ $[M+H]^+$ 312.1206, found 312.1196.



Methyl (6*S*)-6-(4-methoxycarbonylphenyl) -1,6-dihydropyridine-3-carboxylate (2.8.c)

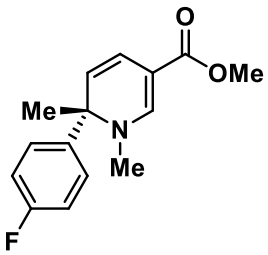
Dihydropyridine **2.8.c** was synthesized from pyridinium **2.7** and 4-methoxycarbonylphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 46 mg **(**76%); The **enantiomeric excess** was determined by HPLC analysis to be 81%ee (254 nm, 25℃); t_{minor} = 26.8 min, t_{major} = 23.4 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.44 (Hex:EtOAc 1:1); **FTIR:** 2949, 1720, 1678, 1636, 1567; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** 0.2288 (c 0.090 $CHCl_3$); **^{1}H NMR** (600 MHz,

$CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.33 (s, 1H), 6.30 (d, *J* = 9.9 Hz, 1H), 4.74 (d, *J* = 10.0 Hz, 1H), 3.90 (s, 3H), 3.69 (s, 3H), 2.71 (s, 3H), 1.77 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.03, 166.80, 150.36, 147.71, 129.91, 129.29, 126.50, 119.49, 118.61, 95.04, 63.36, 52.35, 50.87, 38.49, 25.00; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{17}H_{20}NO_4$ $[M+H]^+$ 302.1387, found 302.1381.



Methyl (6*S*)-6-(4-methoxyphenyl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (2.8.d)

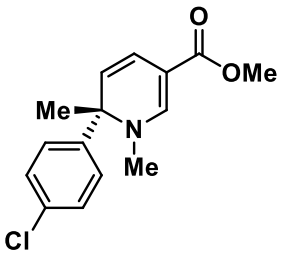
Dihydropyridine **2.8.d** was synthesized from pyridinium **2.7** and 4-methoxyphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 52 mg **(**95%); The **enantiomeric excess** was determined by HPLC analysis to be 91%ee (254 nm, 25℃); t_{minor} = 13.3 min, t_{major} = 14.3min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.50 (Hex:EtOAc 1:1); **FTIR:** 3050, 2946, 2836, 1676, 1635, 1568; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$**:** -1.2092 (c 0.086 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H), 7.30 (s, 1H), 6.91 – 6.83 (m, 2H), 6.30 (d, *J* = 10.0 Hz, 1H), 4.75 (d, *J* = 10.0 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 2.70 (s, 3H), 1.71 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.18, 158.83, 147.56, 138.02, 127.91, 120.10, 117.90, 113.63, 94.45, 62.69, 55.36, 50.77, 38.30, 24.92; **HRMS:** (ESI) *m/z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$ 274.1438, found 274.1437.



Methyl (6*S*)-6-(4-methoxyphenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.e)

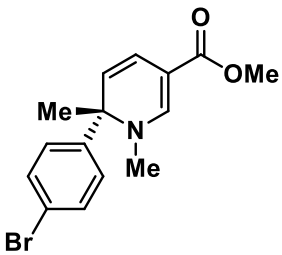
Dihydropyridine **2.8.e** was synthesized from pyridinium **2.7** and 4-fluorophenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 52 mg **(**99%); The **enantiomeric excess** was determined by HPLC analysis to be 94%ee (254 nm, 25℃); t_{minor} = 9.8 min, t_{major} = 10.5 min

[(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.37 (Hex:EtOAc 4:1); **FTIR:** 3052, 2977, 2947, 1677, 1636, 1569; $[\alpha]_D^{20}$**:** -0.6176 (c 0.057 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.31 (s, 1H), 7.04 (t, *J* = 8.5 Hz, 2H), 6.31 (d, *J* = 9.7 Hz, 1H), 4.75 (d, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 2.71 (s, 3H), 1.73 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.07, 162.83, 161.19, 147.50, 141.62 (d, *J* = 3.1 Hz), 128.37 (d, *J* = 8.1 Hz). 119.83, 118.22, 115.34, 115.20, 94.73, 62.74, 50.82, 38.29, 24.99. **^{19}F NMR** (235 MHz, $CDCl_3$) δ -114.95; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{18}H_{17}FNO$ $[M+H]^+$ 262.1238, found 262.1237.



Methyl (6*S*)-6-(4-chlorophenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.f)

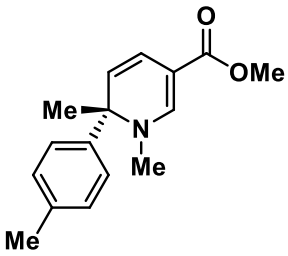
Dihydropyridine **2.8.f** was synthesized from pyridinium **2.7** and 4-chlorophenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 50 mg (90%); The **enantiomeric excess** was determined by HPLC analysis to be 91%ee (254 nm, 25℃); t_{minor} = 18.3 min, t_{major} = 18.9 min [(Chiralpak IG) hexane/*i*-PrOH, 90:10, 1.0 mL/min]; **TLC** R_f 0.77 (Hex:EtOAc 1:1); **FTIR:** 3051, 2975, 2946, 1677, 1636, 1567; $[\alpha]_D^{20}$**:** -0.4905 (c 0.057 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 – 7.39 (7.40 (d, *J* = 6.8 Hz, 2H), 7.33 (s, 1H), 7.31 (d, *J* = 6.6 Hz, 2H), 6.30 (d, *J* = 10.0 Hz, 1H), 4.73 (d, *J* = 10.0 Hz, 1H), 3.69 (s, 3H), 2.71 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.03, 147.57, 144.23, 133.50, 128.66, 128.01, 119.64, 118.43, 94.88, 62.89, 50.85, 38.37, 24.91; **HRMS:** (ESI) *m/z* calc'd for $C_{15}H_{17}ClNO_2$ $[M+H]^+$ 278.0942, found 278.0951.



Methyl (6*S*)-6-(4-bromophenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.g)

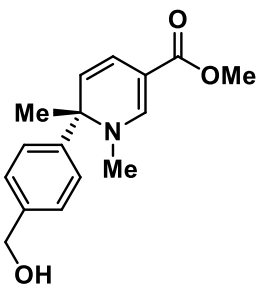
Dihydropyridine **2.8.g** was synthesized from pyridinium **2.7** and 4-bromophenylboronic acid according to the general procedure for

dearomatization of *n*-alkyl pyridinium salts. **Yield** 51.4 mg (80%); The **enantiomeric excess** was determined by HPLC analysis to be 95%ee (254 nm, 25℃); t_{minor} = 17.7 min, t_{major} = 16.2 min [(Chiralpak IE) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.48 (hexanes:EtOAc, 3:2); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ - 3.16 (*c* 0.095 $CHCl_3$); **FTIR** 1949.06, 1736.57, 1678.07, 1636.69; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.30 (s, 1H), 6.30 (d, *J* = 9.9 Hz, 1H), 4.73 (d, *J* = 9.9 Hz, 1H), 3.69 (s, 3H), 2.71 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.07, 147.57, 144.82, 131.70, 128.42, 121.83, 119.65, 118.59, 95.14, 63.05, 50.87, 38.39, 24.89; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{17}NO_2$ $[M+H]^+$ 322.0437, found 322.0455.



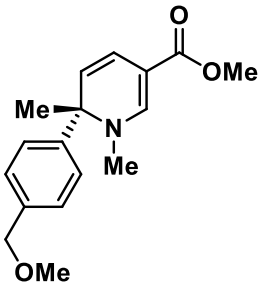
Methyl (6*S*)-6-(4-methylphenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.h)

Dihydropyridine **2.8.h** was synthesized from pyridinium **2.7** and 4-methylphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 45.2 mg (88%); The **enantiomeric excess** was determined by HPLC analysis to be 94%ee (254 nm, 25℃); t_{minor} = 9.1 min, t_{major} = 9.8 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.55 (hexanes:EtOAc, 3:2); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ - 8.06 (*c* 0.783 $CHCl_3$); **FTIR** 3050, 2974, 2945, 2922, 1677, 1639, 1567; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.8 Hz, 2H), 7.32 (s, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.29 (d, *J* = 9.8 Hz, 1H), 4.75 (d, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 2.71 (s, 3H), 2.34 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ = 167.17, 147.66, 142.78, 137.34, 129.17, 126.48, 120.10, 117.89, 94.49, 62.97, 50.75, 38.36, 24.86, 21.14; **HRMS** (ESI) *m/z* calc'd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found 258.1502.



Methyl (6*S*)-6-(4-hydroxymethylphenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.i)

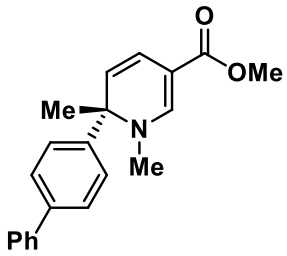
Dihydropyridine **2.8.i** was synthesized from pyridinium **2.7** and 4-hydroxymethylphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 38.2 mg (70%); **ee:** We were not able to achieve acceptable separation for this compound on chiral HPLC. For ee see derivative **S11; TLC** R_f 0.1 (hexanes:EtOAc, 3:2); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -4.24 (*c* 0.726 $CHCl_3$); **FTIR** 3414, 3051, 2973, 2946, 2872, 1664; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.31 (s, 1H), 6.27 (d, *J* = 9.8 Hz, 1H), 4.72 (t, *J* = 12.2 Hz, 1H), 4.68 (s, 2H), 3.68 (s, 3H), 2.70 (s, 3H), 1.73 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.22, 147.69, 145.68, 138.03, 129.18, 124.38, 120.16, 117.74, 94.38, 63.15, 50.75, 38.46, 24.92, 21.56; **HRMS** (ESI) *m/z* calc'd for $C_{16}H_{20}NO_3$ $[M+H]^+$ 274.1438, found 274.1438.



Methyl (6*S*)-6-(4-methoxymethylphenyl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (2.S.11)

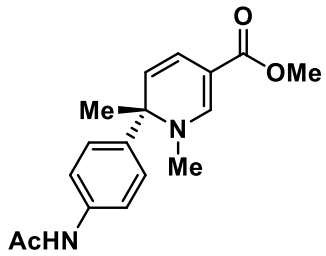
In order to determine the enantiomeric excess of dihydropyridine **2.8.i**, it was converted to the methyl ether **2.S.11** through the following procedure: To a stirred solution of **2.8.i** (12.1 mg, 0.0440 mmol, 1.0 equiv.) in dry DMF (1.0 mL) in a Schlenk flask at 0 °C was added sodium hydride (60% dispersion in mineral oil) (2.25 mg, 0.0530 mmol, 1.2 equiv.) in one addition. The solution was stirred for 30 minutes. Methyl Iodide (4.65 µl, 0.066 mmol, 1.5 equiv.) was added via syringe. The solution was warmed to 23 °C and stirred for 3 hours. The reaction was quenched with NH_4Cl (1.0 ml) and then diluted with H_2O (5.0 ml) and extracted three times with diethyl ether (3 x 5.0 ml). The combined ether layers were dried over sodium sulfate. Solids were filtered off and the filtrate was evaporated to give a residue. This

residue was purified via flash column chromatography to afford **2.S.11** as a colorless oil. **Yield** 8.6 mg (68%); The **enantiomeric excess** was determined by HPLC analysis to be 86% ee (254 nm, 25℃); t_{minor} = 15.5 min, t_{major} = 16.8 min [(Chiralpak ID) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.45 (hexanes:EtOAc, 3:2); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -0.011 (*c* 0.055 $CHCl_3$); **FTIR** 3055.94, 2976.93, 2849.30, 2818.91, 1677.98, 1635.91; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.5 Hz, 2H), 7.35 – 7.30 (m, 3H), 6.31 (d, *J* = 9.7 Hz, 1H), 4.76 (d, *J* = 9.8 Hz, 1H), 4.45 (s, 2H), 3.70 (s, 3H), 3.41 (s, 3H), 2.71 (s, 3H), 1.74 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.07, 147.56, 145.11, 137.56, 127.86, 126.64, 119.95, 118.11, 94.79, 74.32, 63.10, 58.38, 50.70, 38.33, 24.81; **HRMS** (ESI) *m/z* calc'd for $C_{17}H_{22}NO_3$ $[M+H]^+$ 288.1594, found 288.1610.



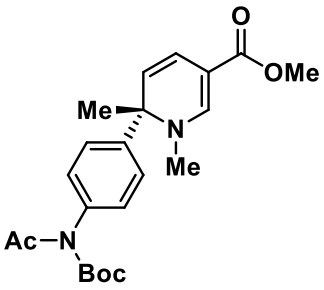
Methyl (6*S*)-6-(4-biphenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.j)

Dihydropyridine **2.8.j** was synthesized from pyridinium **2.7** and 4-biphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 43.4 mg (99%); The **enantiomeric excess** was determined by HPLC analysis to be 93% ee (254 nm, 25℃); t_{minor} = 14.7 min, t_{major} = 15.7 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.26 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -6.64 (*c* 1.456, $CHCl_3$); **FTIR** 3041, 3025, 2991, 2966, 2941, 1682; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.0 Hz, 3H), 7.55 (d, *J* = 7.1 Hz, 2H), 7.45 (t, *J* = 6.9 Hz, 2H), 7.37 (s, 2H), 6.35 (d, *J* = 9.8 Hz, 1H), 5.29 (s, 1H), 4.82 (d, *J* = 9.9 Hz, 1H), 3.72 (s, 3H), 2.77 (s, 3H), 1.79 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.14, 147.73, 144.62, 140.48, 140.40, 128.91, 127.55, 127.24, 127.17, 126.99, 119.95, 118.21, 94.71, 63.11, 50.81, 38.49, 24.99; **HRMS** (ESI) *m/z* calc'd for $C_{19}H_{23}NO_2$ $[M+H]^+$ 320.1645, found 320.1626.



Methyl (6*S*)-6-(4-acetamidophenyl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (2.8.k)

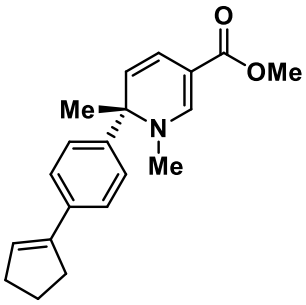
Dihydropyridine **2.8.k** was synthesized from pyridinium **2.7** and 4-acetamidophenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield**: 45 mg (75%); **ee:** We were not able to achieve acceptable separation for this compound on chiral HPLC. For ee see derivative **S12; TLC** R_f 0.12 (Hex:EtOAc 1:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -0.9158 (c 0.227 $CHCl_3$); **FTIR:** 3052, 2976, 2947, 1668, 1633, 1600, 1568, 1530; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.23 (d, *J* = 9.9 Hz, 1H), 4.69 (d, *J* = 9.9 Hz, 1H), 3.66 (s, 3H), 2.63 (s, 3H), 2.12 (d, *J* = 15.0 Hz, 3H), 1.67 (s, 3H).; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.28, 167.44, 147.87, 141.02, 137.76, 127.11, 120.12, 119.74, 117.76, 94.17, 62.90, 50.87, 38.37, 24.96, 24.5.**; HRMS:** (ESI) *m/z* calc'd $C_{17}H_{20}N_2O_3Na$ $[M+Na]^+$ 323.1366, found 323.1382.



Methyl (6S)-6-[*p*-(N-acetyl-N-tert-butoxycarbonylamino)phenyl]-1-methyl-6-methyl-1,6-dihydropyridine-3-carboxylate (2.S.12)

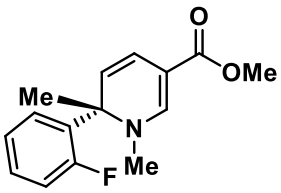
To a 500 µL Schlenk tube charged with stir bar, dihydropyridine **2.8.k** (20.0 mg, 0.066, 1 equiv), and DMAP (4.00 mg, 0.033 mmol, 0.50 equiv), DMF (75 µL) was added. Boc_2O (22 mg, 0.098 mmol, 1.5 equiv) was then added and the reaction mixture was stirred for 1.5 hours at ambient temperature. The reaction was quenched into H_2O (5 mL), extracted with EtOAc. EtOAc layer was dried over $MgSO_4$. Solids were removed through a filtration over a pad of silica then celite, and concentrated. Crude mixture was purified via automated flash chromatography to yield **2.S.12.** Y**ield:** 25 mg **(**96%). The **enantiomeric excess** was determined by HPLC analysis to be 93% ee (254 nm, 25℃); t_{minor} = 22.8 min, t_{major} = 25.3 min [(Chiralpak ID) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.57 (Hex:EtOAc 1:1);

$[\alpha]_D^{20}$**:** -0.4642 (c 0.063 $CHCl_3$); **FTIR:** 3053, 2977, 2947, 1736, 1682, 1637, 1570; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.25 (d, *J* = 9.9 Hz, 1H), 4.72 (d, *J* = 9.9 Hz, 1H), 3.64 (s, 3H), 2.65 (s, 3H), 2.53 (s, 3H), 1.69 (s, 3H), 1.31 (s, 9H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 173.14, 167.11, 152.65, 147.53, 144.98, 138.12, 128.17, 127.37, 119.79, 118.23, 94.75, 83.48, 63.02, 50.82, 38.34, 27.82, 26.73, 24.75.; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{20}H_{30}N_2O_5Na$ $[M+Na]^+$ 401.2071, found 401.2060.



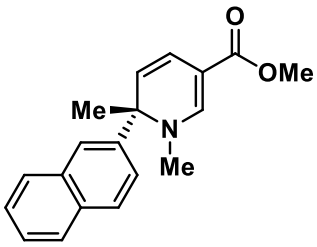
Methyl (6*S*)-6-[4-(cyclopent-1-en-1-yl)phenyl]-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.l)

Dihydropyridine **2.8.l** was synthesized from pyridinium **2.7** and (4-cyclopent-1-en-1-yl)phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 58 mg (93%); The **enantiomeric excess** was determined by HPLC analysis to be 95% ee (254 nm, 25℃); t_{minor} = 13.2 min, t_{major} = 14.6 min [(Chiralpak IA) hexane/*i*-PrOH, 95:5, 1.0 mL/min]; **TLC** R_f 0.79 (Hex:EtOAc 1:1); $[\alpha]_D^{20}$**:**-0.780 (c 0.003 $CHCl_3$); **FTIR:** 3050, 2949, 2845, 1735, 1679, 1636, 1572; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (q, *J* = 8.5 Hz, 3H), 7.32 (s, 1H), 7.26 (s, 1H), 6.31 (d, *J* = 9.9 Hz, 1H), 6.21 (s, 1H), 4.76 (d, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 2.80 – 2.67 (m, 5H), 2.59 – 2.46 (m, 2H), 2.07 – 1.92 (m, 2H), 1.74 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.16, 147.66, 144.02, 141.78, 136.03, 126.90, 126.51, 125.60, 119.94, 118.02, 94.55, 63.05, 50.78, 38.39, 33.43, 33.16, 24.81, 23.36**; HRMS:** (ESI) *m/z* calc'd for $C_{20}H_{24}NO_2$ $[M+H]^+$ 310.1802, found 310.1807.



Methyl (6*S*)-6-(2-fluorophenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.m)

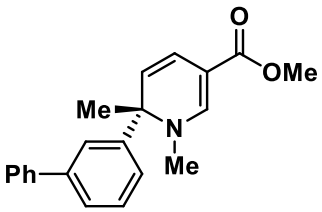
Dihydropyridine **2.8.m** was synthesized from pyridinium **2.7** and 2-fluorophenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 24 mg **(**46%); The **enantiomeric excess** was determined by HPLC analysis to be 94% ee (254 nm, 25℃); t_{minor} = 20.8 min, t_{major} = 21.9 min [(Chiralpak ID) hexane/*i*-PrOH, 90:10, 1.0 mL/min]; **TLC** R_f 0.71 (Hex:EtOAc 1:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** 0.6886 (c 0.070 $CHCl_3$); **FTIR:** 3057, 2978, 2946, 1678, 1636, 1567; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 3H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.09 (dd, *J* = 11.7, 8.2 Hz, 1H), 6.35 (d, *J* = 9.8 Hz, 1H), 4.93 (d, *J* = 9.8 Hz, 1H), 3.72 (s, 3H), 2.88 (s, 3H), 1.85 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.06, 161.46, 159.80, 147.59, 131.03 (d, *J* = 10.7 Hz), 129.80 (d, *J* = 8.7 Hz), 127.81 (d, *J* = 3.4 Hz), 124.06 (d, *J* = 3.6 Hz), 119.05, 117.86, 117.08, 116.92, 95.51, 62.09, 50.78, 38.72, 26.34 (d, *J* = 3.3 Hz); **HRMS:** (ESI) *m/z* **c**alc'd for $C_{15}H_{17}NO_2F$ $[M+H]^+$: 262.1239 found: 262.1240.



Methyl (6*S*)-6-(2-napthalen-2-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.n)

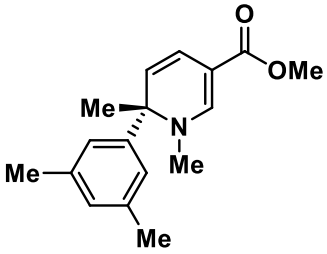
Dihydropyridine **2.8.n** was synthesized from pyridinium **2.7** and 2-napthalen-2-ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 58.0 (99%); The **enantiomeric excess** was determined by HPLC analysis to be 94% ee (254 nm, 25℃); t_{minor} = 14.6 min, t_{major} = 12.0 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.26 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -1.14 (*c* 2.686 $CHCl_3$); **FTIR** 3053, 2974, 2945, 1675, 1634; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 14.6, 7.9 Hz, 3H), 7.78 – 7.73 (m, *J* = 10.9 Hz, 2H), 7.54 – 7.47 (m, 2H), 7.39 (s, 1H), 6.36 (d, *J* = 9.8 Hz, 1H), 4.81 (d, *J* = 9.9 Hz, 1H), 3.73 (s, 3H), 2.72 (s, 3H), 1.87 (s, 3H); **^{13}C**

NMR (151 MHz, $CDCl_3$) δ 167.16, 147.82, 142.72, 132.77, 132.59, 128.66, 128.44, 127.61, 126.50, 126.44, 125.74, 123.87, 119.82, 118.44, 94.71, 63.46, 50.82, 38.44, 24.86; **HRMS** (ESI) *m*/*z* Calc'd for $C_{19}H_{20}NO_2$ $[M+H]^+$ 294.1489, found 294.1485.



Methyl (6*S*)-6-([1,1'-biphenyl]-3-yl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (2.8.o)

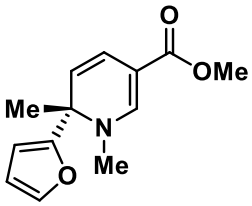
Dihydropyridine **2.8.o** was synthesized from pyridinium **2.7** and 1,1'-biphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 62.5 mg (98%); The **enantiomeric excess** was determined by HPLC analysis to be 96% ee (254 nm, 25℃); t_{minor} = 13.9 min, t_{major} = 10.5 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.29 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -5.32 (*c* 1.003 $CHCl_3$); **FTIR** 3054, 3029, 2974, 2945, 2246, 1677, 1635; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.59 (d, *J* = 7.1 Hz, 2H), 7.52 (d, *J* = 6.4 Hz, 1H), 7.49 – 7.43 (m, 4H), 7.40 – 7.35 (m, 2H), 6.35 (d, *J* = 9.8 Hz, 1H), 4.83 (d, *J* = 9.8 Hz, 1H), 3.72 (s, 3H), 2.77 (s, 3H), 1.81 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.16, 147.69, 146.27, 141.53, 140.98, 129.00, 128.93, 127.59, 127.34, 126.45, 125.49, 119.99, 118.19, 94.73, 63.38, 53.59, 50.82, 38.52, 24.93; **HRMS** (ESI) *m*/*z* calc'd for $C_{21}H_{22}O_2$ $[M+H]^+$ 320.1645, found 320.1642.



Methyl (6*S*)-6-(3,5-dimethylphenyl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (2.8.p)

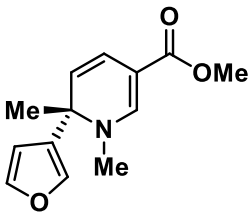
Dihydropyridine **2.8.p** was synthesized from pyridinium **2.7** and 3,5-dimethylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 51.5 mg (95%); The **enantiomeric excess** was determined by HPLC analysis to be 97% ee (254 nm, 25℃); t_{minor} = 7.2 min, t_{major} = 8.6 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC**

R_f 0.35 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -6.65 (*c* 0.526 $CHCl_3$); **FTIR** 3050, 2980, 2940, 2910, 2850; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.06 (s, 2H), 6.91 (s, 1H), 6.28 (d, *J* = 9.8 Hz, 1H), 4.74 (d, *J* = 9.9 Hz, 1H), 3.71 (s, 3H), 2.72 (s, 3H), 2.32 (s, 6H), 1.71 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.32 147.80, 145.75, 138.11, 129.24, 124.44, 120.23, 117.78, 94.41, 63.22, 50.84, 38.54, 25.00, 21.64; **HRMS** (ESI) *m/z* calc'd for $C_{17}H_{22}NO_2$ $[M+H]^+$ 272.1645, found 272.1653. Single crystals suitable for **X-Ray** analysis were obtained by slow evaporation of diethylether from a solution of **8p** in a mixture of diethylether and hexanes. CCDC registry number 1921656.



Methyl (6*S*)-6-(furan-2-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.q)

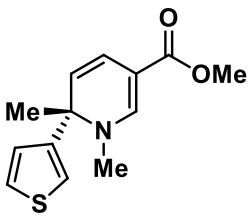
Dihydropyridine **2.8.q** was synthesized from pyridinium **2.7** and furan-2-ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 44 mg (94%); The **enantiomeric excess** was determined by HPLC analysis to be 82% ee (254 nm, 25℃); t_{minor} = 23.0 min, t_{major} = 23.9 min [(Chiralpak IG) hexane/*i*-PrOH, 90:10, 1.0 mL/min]; **TLC** R_f 0.74 (Hex:EtOAc 1:1); **FTIR:** 2980, 2947, 1677, 1637, 1568; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -1.8176 (c 0.057 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.30 (s, 1H), 6.48 (d, *J* = 9.6 Hz, 1H), 6.37 (d, *J* = 1.1 Hz, 1H), 6.28 (d, *J* = 1.1 Hz, 1H), 4.85 (d, *J* = 9.8 Hz, 1H), 3.71 (s, 3H), 2.84 (s, 3H), 1.68 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.99, 156.91, 147.16, 142.86, 120.53, 116.16, 110.32, 107.63, 95.36, 59.18, 50.80, 38.45, 24.28; **HRMS:** (ESI) *m/z* calc'd for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1125, found 234.1141.



Methyl (6*S*)-6-(furan-3-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.r)

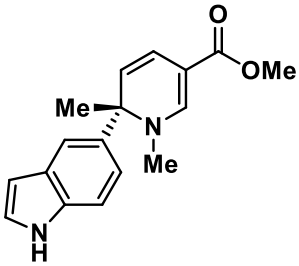
Dihydropyridine **2.8.r** was synthesized from pyridinium **2.7** and furan-3-ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts.

Yield: 23 mg **(**49%); The **enantiomeric excess** was determined by HPLC analysis to be 92% ee (254 nm, 25℃); t_{minor} = 10.2 min, t_{major} = 11.1 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.71 (Hex:EtOAc 1:1); **FTIR:** 3051, 2976, 2947, 1676, 1636, 1568; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -0.9525 (c 0.026 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.33 (s, 1H), 7.31 – 7.28 (m, 2H), 6.50 (s, 1H), 6.37 (d, *J* = 9.8 Hz, 1H), 4.81 (d, *J* = 9.9 Hz, 1H), 3.72 (s, 3H), 2.85 (s, 3H), 1.66 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.15, 147.62, 143.88, 138.58, 131.00, 119.42, 118.53, 110.09, 95.24, 57.93, 50.86, 38.20, 25.50; **HRMS:** (ESI) *m/z* calc'd for $C_{13}H_{16}NO_3$ $[M+H]^+$ 234.1125, found 234.1131.



Methyl (6*S*)-6-(thiophen-3-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.s)

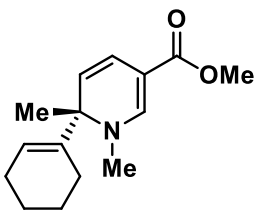
Dihydropyridine **2.8.s** was synthesized from pyridinium **2.7** and thiophen-3-ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 38.3 mg (77%); The **enantiomeric excess** was determined by HPLC analysis to be 95% ee (254 nm, 25℃); t_{minor} = 11.1 min, t_{major} = 12.6 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.29 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -11.21 (*c* 0.616 $CHCl_3$); **FTIR** 3100, 3049, 2975, 2945, 1673, 1634; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.27 (s, *J* = 1.5 Hz, 1H), 7.17 (s, 1H), 6.38 (d, *J* = 9.8 Hz, 1H), 4.86 (d, *J* = 9.9 Hz, 1H), 3.75 (s, 3H), 2.83 (s, *J* = 14.4 Hz, 3H), 1.79 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.09, 147.49, 147.32, 127.56, 126.39, 120.78, 119.11, 118.73, 94.94, 60.68, 50.77, 38.28, 25.78; **HRMS** (ESI) *m*/*z* calc'd for $C_{13}H_{16}NO_2S$ $[M+H]^+$ 250.0896, found 250.0896.



Methyl (6*S*)-6-(1*H*-indol-5-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.t)

Dihydropyridine **2.8.t** was synthesized from pyridinium **2.7** and 1*H*-indol-5-ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 32.1 (57%); The **enantiomeric excess** was determined by HPLC analysis to be 92% ee (254 nm, 25℃); t_{minor} = 20.7 min, t_{major} = 10.0 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.32 (hexanes:EtOAc, 3:2); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ - 0.71 (*c* 20.953 $CHCl_3$); **FTIR** 3390, 3310, 2940, 2480; **^{1}H NMR** (600 MHz, $_{CD3OD}$) δ 7.62 (s, 1H), 7.42 (s, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.33 (s, 1H), 7.24 (s, 1H), 6.45 (s, 1H), 6.22 (d, *J* = 9.2 Hz, 1H), 4.82 (d, *J* = 9.1 Hz, 1H), 3.68 (s, 3H), 2.73 (s, 3H), 1.81 (s, 3H); **^{13}C NMR** (151 MHz, CD_3OD) δ 168.20, 148.25, 136.34, 135.49, 127.73, 125.01, 120.83, 120.79, 117.39, 116.54, 110.95, 101.53, 93.33, 63.47, 49.87, 37.38, 24.21; **HRMS** (ESI) *m*/*z* calc'd for $C_{17}H_{19}N_2O_2$ $[M+H]^+$ 283.1441, found 283.1442.

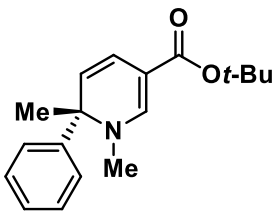
Single crystals suitable for **X-Ray** analysis were obtained by slow evaporation of diethylether from a solution of **8t** in a mixture of diethylether and hexanes. CCDC registry number 1920061.



Methyl (6*S*)-6-(cyclohex-1-ene-1-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.8.u)

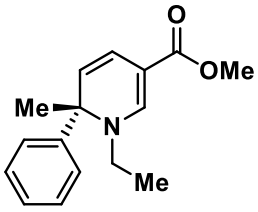
Dihydropyridine **2.8.u** was synthesized from pyridinium **2.7** and cyclohex-1-ene-1ylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield** 33.1 (67%); The **enantiomeric excess** was determined by HPLC analysis to be 95% ee (254 nm, 25℃); t_{minor} = 16.3 min, t_{major} = 17.3 min [(Chiralpak IE) hexane/*i*-PrOH, 90:10, 1.0 mL/min]; **TLC** R*f* 0.33 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ - 0.005 (*c* 0.310 $CHCl_3$); **FTIR** 2925.19, 2855.26, 1681.86, 1634.24; **^{1}H NMR** (600 MHz, $CDCl_3$)

δ 7.26 (s, 1H) 6.28 (d, *J* = 9.8 Hz, 1H), 5.61 (s, 1H), 4.54 (d, *J* = 9.8 Hz, 1H), 3.66 (s, 3H), 2.78 (s, 3H), 2.24 (d, *J* = 16.8 Hz, 1H), 2.07 (s, 2H), 1.89 (d, *J* = 16.8 Hz, 1H), 1.67 – 1.56 (m, 2H), 1.55 (d, *J* = 5.4 Hz, 2H), 1.42 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.10, 148.53, 140.23, 122.50, 120.00, 118.88, 94.28, 64.35, 50.58, 37.51, 25.34, 25.23, 24.17, 23.00, 22.23; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2$ $[M+H]^+$ 248.1645, found 248.1651.



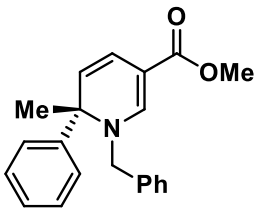
***Tert*-butyl (6*S*)-6-(phenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (2.S.13)**

Dihydropyridine **2.S.13** was synthesized from pyridinium salts **2.S.4**, **2.S.5**, **2.S.6**, **2.S.7** and phenyl boronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. Yields and enantiomeric excess for each case was as follows: from **2.S.4** (67.0 mg, 75% yield, 95% ee), from **2.S.5** (71.4 mg, 80% yield, 93% ee), from **2.S.6** (70.6 mg, 99% yield, 91% ee), and from **2.S.7** (59.0 mg, 75% yield, 90% ee). The **enantiomeric excess** was determined by HPLC analysis (254 nm, 25℃); t_{minor} = 5.2 min, t_{major} = 5.6 min [(Chiralpak ID) hexane/*i*-PrOH, 80:20, 1.0 mL/min];**TLC** R_f 0.63 (hexanes:EtOAc, 4:1), $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -2.11 (*c* 0.060 $CHCl_3$); **FTIR** 2973.91, 2929.11, 1729.93, 1673.98; **^{1}H NMR** (600 MHz, CDCl3) δ 7.51 (d, J = 7.6 Hz, 2H), 7.40 (t, J = 7.7 Hz, 2H), 7.32 – 7.28 (m, 1H), 6.30 (d, J = 9.8 Hz, 1H), 4.78 (d, J = 9.9 Hz, 1H), 2.73 (s, 3H), 1.77 (s, 3H), 1.52 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.48, 147.13, 145.93, 128.52, 127.53, 126.66, 119.83, 118.43, 96.25, 78.62, 63.23, 38.40, 28.65, 24.84; **HRMS** (ESI) calc'd for $C_{18}H_{23}NO_2Na$ $[M+Na]^+$ 308.1621, found 308.1625.



Methyl (6*S*)-1-ethyl-6-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (2.S.14)

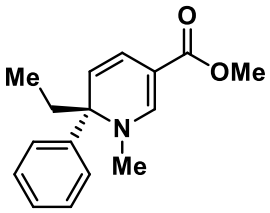
Dihydropyridine **2.S.14** was synthesized from pyridinium **2.S.8** and phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield**: 16 mg (31%); The **enantiomeric excess** was determined by HPLC analysis to be 84% ee (254 nm, 25℃); t_{minor} = 9.1 min, t_{major} = 8.2 min [(Chiralpak ID) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.28 (Hex:EtOAc 4:1);); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -0.675 (*c* 0.027 $CHCl_3$) **FTIR:** 2977, 2945, 1678, 1636, 1566; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.13 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 3.87 (s, 3H), 2.83 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.15, 146.44, 145.35, 128.40, 127.57, 126.79, 120.27, 117.82, 94.87, 63.83, 50.77, 44.43, 26.09, 16.32. **HRMS:** (ESI) *m/z* calc'd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found 258.1503.



Methyl (6*S*)-1-benzyl-6-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (2.S.15)

Dihydropyridine **2.S.15** was synthesized from pyridinium **2.S.9** and phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 36 mg (56%); The **enantiomeric excess** was determined by HPLC analysis to be 66% ee (254 nm, 25℃); t_{minor} = 8.8 min, t_{major} = 8.1 min [(Chiralpak ID) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **R**f: 0.30 (Hex:EtOAc 4:1)**; FTIR:** 3059, 2979, 2946, 1679, 1637, 1566; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 3H), 7.33 (t, *J* = 7.6 Hz, 3H), 7.30 – 7.26 (m, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 6.41 (d, *J* = 10.0 Hz, 1H), 4.91 (d, *J* = 10.0 Hz, 1H), 4.12 (s, 2H), 3.71 (s, 3H), 1.73 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.06, 146.30, 146.02, 137.60,

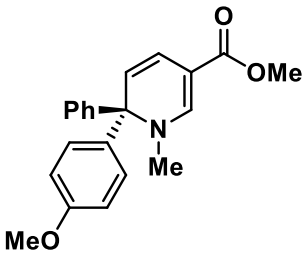
128.80, 128.51, 127.80, 127.72, 127.46, 126.94, 121.01, 118.08, 95.96, 63.87, 53.72, 50.83, 26.28; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{21}H_{22}NO_2$ $[M+H]^+$ 320.1645, found 320.1647.



Methyl (6*S*)-6-ethyl-1-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (2.S.16)

Dihydropyridine **2.S.16** was synthesized from pyridinium **2.S.10** and phenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts. **Yield:** 34 mg **(**67%); The **enantiomeric excess** was determined by HPLC analysis to be 97% ee (254 nm, 25℃); t_{minor} = 8.4 min, t_{major} = 8.8 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.26 (Hex:EtOAc 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -0.3225 (c 0.053 $CHCl_3$); **FTIR:** 3054, 2968, 2943, 1677, 1635, 1568; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.44 (s, 1H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.29 (dd, *J* = 8.5, 6.1 Hz, 1H), 6.43 (d, *J* = 10.0 Hz, 1H), 4.61 (d, *J* = 10.1 Hz, 1H), 3.73 (s, 3H), 2.70 (s, 3H), 2.33 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.74 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.16 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.21, 148.85, 146.04, 128.51, 127.57, 126.67, 119.69, 118.31, 94.15, 67.21, 50.74, 37.96, 29.08, 8.38; **HRMS:** (ESI) *m/z* **c**alc'd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found 258.1492.

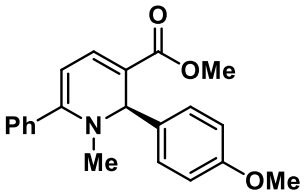
Compounds **2.10.a** and **2.10.b** were synthesized by reacting pyridinium salt **2.9** with 4-methoxyphenylboronic acid according to the general procedure for dearomatization of *n*-alkyl pyridinium salts.



Methyl (6*S*)-6-phenyl-6-(4-methoxyphenyl)-1-methyl-1,6-dihydro-pyridine-3-carboxylate (2.10.a)

Yield 16.8 mg (25 %); The **enantiomeric excess** was determined by HPLC analysis to be 72% ee (254 nm, 25℃); t_{minor} = 14.2 min, t_{major} =

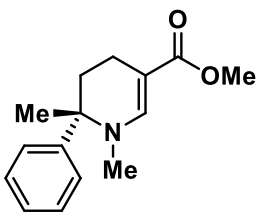
11.9 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.23 (hexanes:EtOAc, 4:1); $[\alpha]_D^{20}$ -12.667 (c 0.060 $CHCl_3$); **FTIR** 2946.96, 2835.69, 1679.37, 1607.34; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.34 – 7.27 (m, 5H), 6.90 (d, *J* = 8.5 Hz, 2H), 6.40 (d, *J* = 9.8 Hz, 1H), 5.08 (d, *J* = 9.8 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H), 2.71 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.17, 158.80, 147.00, 143.06, 135.08, 130.02, 128.53, 127.86, 127.34, 119.82, 117.98, 113.58, 95.54, 70.58, 55.46, 50.92, 40.68 ; **HRMS** (ESI) calc'd for $C_{21}H_{22}NO_3$ $[M+H]^+$ 336.1594, found 336.1599.



Methyl (6*S*)-6-phenyl-1-(4-methoxyphenyl)-1-methyl-1,2-dihydro-pyridine-3-carboxylate (2.10.b)

Yield 27.5 mg **(**41 %); The **enantiomeric excess** was determined by HPLC analysis to be 84% ee (254 nm, 25℃); t_{minor} = 10.6 min, t_{major} = 8.8 min [(Chiralpak IG) hexane/*i*-PrOH, 80:20, 1.0 mL/min]; **TLC** R_f 0.41 (hexanes:EtOAc, 4:1); $[\alpha]_D^{20}$ 16.000 (c 0.060 $CHCl_3$); **FTIR** 2946.88, 1732.67, 1684.96, 1607.07,; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.32 (m, *J* = 3.7 Hz, 3H), 7.30 – 7.24 (m, 3H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.46 (s, 1H), 5.01 (d, *J* = 6.4 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 2.93 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.20, 159.27, 153.15, 136.80, 135.10, 134.53, 129.19, 128.54, 128.20, 127.86, 113.82, 109.87, 97.75, 62.49, 55.34, 51.43, 40.80; **HRMS** (ESI) calc'd for $C_{21}H_{22}NO_3$ $[M+H]^+$ 336.1594, found 336.1616.

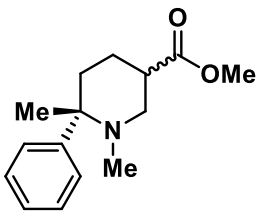
2.8.5. Derivatizations of 2.8.a:



Methyl (6S)-1,6-dimethyl-6-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (2.11)

To a septa-capped vial charged with **2.8.a** (24.5 mg, 0.100 mmol, 1.0 equiv) and 10% Pd/C (10.6 mg, 0.01 mmol, 0.1 equiv) was added MeOH (1 mL).

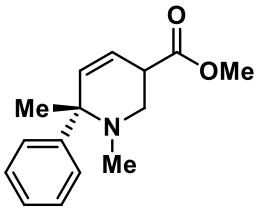
A balloon filled with hydrogen was inserted through the septum via a needle. The reaction was stirred for 3 hours at 23 °C and filtered through celite. The celite was rinsed with a further 5 mL of MeOH and the filtrate concentrated to afford **2.11** as a colorless oil. **Yield** 24.4 mg (99%); **TLC** R_f 0.4 (CH_2Cl_2); **FTIR** 2943.78, 2849.73, 1676.47, 1606.26; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -2.400 (c 0.075 $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.27 – 7.20 (m, *J* = 21.0, 7.9 Hz, 3H), 3.67 (s, 3H), 2.81 (s, 3H), 2.30 – 2.23 (m, 1H), 2.00 – 1.92 (m, 2H), 1.85 – 1.76 (m, 1H), 1.61 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 169.14, 148.00, 144.31, 128.66, 127.05, 125.64, 94.69, 59.87, 50.76, 38.59, 38.18, 23.77, 18.34; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{20}NO_2$ $[M+H]^+$ 246.1489, found 246.1494.



Methyl (6S)-1,6-dimethyl-6-phenylpiperidine-3-carboxylate (2.12)

To a Teflon lined septa-capped vial charged with **2.11** (24.4 mg, 0.100 mmol, 1.0 equiv) was added 0.5 mL of glacial acetic acid. A solution of $NaBH_3CN$ (7.54 mg, 0.12 mmol, 1.2 equiv) in MeOH (1.0 mL) was then added to the stirring solution of **2.11**. The mixture was stirred for three hours, diluted with diethyl ether and acidified with 3 mL of 1M HCl. The ether layer was removed and washed with 3 times with 2 mL of 1M HCl. The combined aqueous layer was neutralized with saturated $NaHCO_3$, extracted with EtOAc (3 x 5 mL). The combined organic layers were concentrated to afford a colorless oil residue. The residue was purified by flash chromatography to afford **2.12** as an inseparable 1.3:1 mixture of C3 diastereomers. Isomers were characterized as a pair of diastereomers, NMR shifts are reported using HSQC to determine which peaks belong to the major and minor products. Indeterminable peaks are reported as the mixture. Yield 16.1 mg (65%) **TLC** R_f 0.55 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ 9.778 (c 0.030 $CHCl_3$); **FTIR:** 2947.78, 2844.76, 2798.44, 1732.10, 1600.06; **^{1}H NMR** (600 MHz, $CDCl_3$) (for major diastereomer) δ 7.59 – 7.53 (m, 2H),

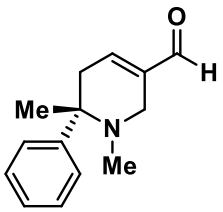
3.01 – 2.97 (m, *J* = 11.4 Hz, 1H), 1.96 (s, 3H), 1.37 (s, 3H); (for minor diastereomer) 7.51 (d, *J* = 7.2 Hz, 2H), 3.12 – 3.08 (m, *J* = 12.6 Hz, 1H), 2.15 (s, 3H), 1.31 (s, 3H); (for the mixture of diastereomers) 7.35 – 7.28 (m, 2H), 7.21 (dd, *J* = 15.6, 7.0 Hz, 1H), 3.70 (s, 3H) 2.83 – 2.62 (m, 2H), 2.03 – 1.88 (m, 2H), 1.79 – 1.49 (m, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ (for major diastereomer) 126.21, 51.51, 39.28, 11.21; (for minot diastereomer) 126.33, 51.43, 38.53, 22.75; (for the mixture of diastereomers) 175.15, 174.99, 149.48, 149.02, 128.22, 126.44, 59.39, 59.24, 51.57, 42.67, 24.17, 41.99; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1645, found 248.1651.



Methyl (6S)-1,6-dimethyl-6-phenyl-1,2,3,6-tetrahydropyridine-3-carboxylate (2.13)

To a 4 mL Schlenk tube charged with stir bar and solution of **2.8a** (46.0 mg, 0.20 mmol, 1.00 equiv) in AcOH (500 µL), $NaBH_3CN$ (15 mg, 0.24 mmol, 1.2 equiv) in MeOH (1 mL) was added under N_2. The reaction was stirred for four hours, diluted to 4 mL with EtOAc, quenched with 10% HCl (250 µL), and neutralized with $NaHCO_3$. The organics were filtered through basic alumina and then celite, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude mixture was purified via automated flash chromatography to yield a 1:1 mixture of diasteriomers. **Yield: 42** mg (85%) **^{1}H NMR** (600 MHz, $CDCl_3$) δ (for 1:1 mixture of diastereomers) 7.50 – 7.42 (m, 5H), 7.32 (ddd, *J* = 10.8, 9.5, 5.4 Hz, 5H), 5.86 (dd, *J* = 9.9, 4.1 Hz, 1H), 5.82 (dd, *J* = 9.9, 1.8 Hz, 1H), 5.65 (dd, *J* = 9.9, 1.7 Hz, 1H), 5.59 (dd, *J* = 10.0, 2.6 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.54 – 3.49 (m, 1H), 3.25 (d, *J* = 4.1 Hz, 1H), 3.01 – 2.85 (m, 4H), 2.09 (s, 6H), 1.47 (s, 3H), 1.45 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) (for 1:1 mixture of diastereomers) δ 173.34, 138.01, 137.40, 128.31, 128.04, 127.90, 127.66, 127.21, 126.85, 126.41,

120.05, 119.85, 60.36, 57.41, 52.13, 51.75, 49.91, 48.74, 48.67, 42.08, 41.27, 38.34, 38.27, 16.27; **HRMS** (ESI) *m/z* calc'd for $C_{15}H_{20}NO_2$ $[M+H]^+$ 246.1489, found 246.1500.



(6S)-1,6-dimethyl-6-phenyl-1,2,5,6-tetrahydropyridine-3-carbaldehyde (2.14)

To a stirred solution of $LiAlH_4$ (37.9 mg, 1.00 mmol, 10.0 equiv) in dry Et_2O (1.0 mL), in a 1-dram vial fitted with a Teflon lined septa cap, was added a solution of **2.8a** in dry Et_2O at 23 °C. After 30 minutes of vigorous stirring, the reaction was diluted with 2 mL of Et_2O and cooled to 0 °C. To this solution was sequentially added H_2O (40 µl), 15% NaOH (aq.) (40 µl), and further H_2O (120 µl). The reaction was warmed to 23 °C, stirred for 15 minutes, dried over $MgSO_4$, filtered, and concentrated. The pale-yellow oil was purified by flash column chromatography to afford **2.14** as a clear oil. **Yield** 6.2 mg (28%); **TLC** R_f 0.19 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ 17.333 (*c* 0.03, $CHCl_3$); **FTIR** 2975.22, 2929.10, 2850.7, 2787.1, 2116.61, 1678.05; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.31 – 7.22 (m, 2H), 6.95 (s, 1H), 3.47 (d, *J* = 17.9 Hz, 1H), 3.28 (d, *J* = 17.8 Hz, 1H), 2.88 (dd, *J* = 19.6, 2.3 Hz, 1H), 2.44 (d, *J* = 19.6 Hz, 1H), 2.06 (s, 3H), 1.34 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 192.73, 148.17, 145.99, 138.89, 128.47, 127.05, 126.48, 58.31, 47.89, 38.38, 17.95, 1.17; **HRMS** (ESI) *m/z* calc'd for $C_{14}H_{18}NO$ $[M+H]^+$ 215.1383, found 216.1379.

2.9. References:

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Chapter 3: Synthesis of 1,6-DHPs *via* Enantioselective Addition of Boronic Acid Pinacol Esters: Application to the Total Synthesis of a Nuphar Alkaloid:

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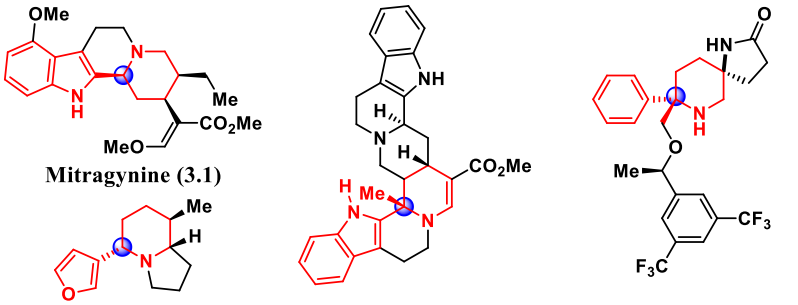
3.1. Introduction:

As discussed in Chapters 1 and 2, nitrogen heterocycles are common structural motifs in natural products and active pharmaceutical ingredients.[1–4] In particular, indole alkaloids contain 2-indolesubstituted piperidines such as in mitragynine (**3.1**) and roxburghine D (**3.2**) (Figure 3.1). The latter contains a fully substituted stereogenic center at the C-2 position of the piperidine. Nuphar alkaloids contain 2-furan-substituted piperidine. These alkaloids demonstrate significant biological activities as anticancer agents, immunosuppressants, etc.[5,6] For example, rolapitant (**3.4**) is an FDA-approved small molecule used for the treatment of chemotherapy induced nausea and vomiting that contains such an aryl-substituted piperidine structural motif, as well.

Figure 3.1: Structures of natural products and a drug molecule containing (hetero)aryl-substituted nonaromatic azaheterocycles.



In Chapter 2, we established the utility of a Rh-catalyzed nucleophilic dearomatization strategy for the synthesis of saturated azaheterocycles. With regard to the asymmetric dearomative arylation of pyridiniums and related heteroarenium salts, recently our group and others have reported that N-alkyl- and N-acylpyridinium salts can undergo asymmetric dearomatization using aryl boronic acids, aryl zinc, and electron rich aryl nucleophiles.[6-10] During our studies of the asymmetric addition of aryl boronic acids to pyridinium salts, we have observed that the addition of indole-2-boronic acid to pyridinium salts under rhodium catalysis did not yield any of the corresponding dihydropyridine product while addition of furan-3-boronic acid gave the corresponding DHP in moderate yield.[10] This was due to the competing protodeboronation side reaction of these boronic acids under basic conditions.[11] Successful asymmetric and high-yield addition of such a boronic acid is an important synthetic challenge as it could enable efficient synthesis of nuphar and indole alkaloids.

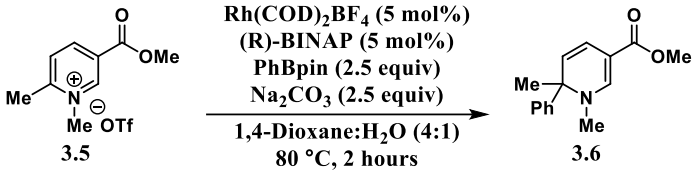
Pinacol esters of aryl boronic acids are more stable alternatives to arylboronic acids under basic conditions.[12,13] In addition to their increased stability compared to that of aryl boronic acids, ArBpins are also easier to access through direct C−H borylation of arenes[14] or Miyaura[15] and Masuda[16] borylation of aryl and alkenyl halides and triflates.[17] Considering their improved stability and availability when compared to that of aryl boronic acids, we thought to develop a rhodium-catalyzed dearomative arylation of heteroarenium salts using aryl boronic acid pinacol esters as aryl nucleophiles. Herein, we report the results from these studies, which shows that ArylBpins are competent nucleophiles for Rh-catalyzed dearomatization reactions that tolerate a wide range of functional groups and enable addition of challenging heteroarenes such as indoles. The

methodology reported herein has been applied to the synthesis of a bioactive nuphar alkaloid **2** to illustrate its efficiency for the synthesis of alkaloid natural products.

3.2. Optimization of Reaction Conditions:

Optimization of reaction conditions started by using reaction conditions developed for aryl boronic acids. Under these conditions, dearomatization product (**3.6**) was obtained in 50% yield as measured by analysis of ^{1}H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard (Table 3.1, entry 1). Changing the base from Na_2CO_3 to Et_3N or NaOH resulted in a decreased yield (Table 3.1, entries 2 and 3). Increasing or decreasing the reaction temperature resulted in diminished yields, as well (Table 3.1, entries 3 and 4). 1,4-Dioxane was found to be the best solvent for this reaction as other solvents gave inferior yields (Table 3.1, entries 6−9). Finally, we found that the water content in the reaction had a crucial impact on the reaction yield. Thus, while dry dioxane or a 2:1 dioxane/water mixture as a solvent gave low yields, using a 20:1 dioxane/water mixture gave the dearomatization product in 85% yield and 94% ee (Table 3.1, entries 10−12).

Table 3.1: Optimization of reaction conditions.



Entry	Deviation from above	Yield (%)[a]
1	none	50
2	Et_3N instead of Na_2CO_3	41
3	NaOH instead of Na_2CO_3	30
4	40 °C instead of 80 °C	30
5	100 °C instead of 80 °C	43
6	PhMe instead of 1,4-dioxane	2
7	DME instead of 1,4-dioxane	38
8	DCE instead of 1,4-dioxane	8
9	THF instead of 1,4-dioxane	28
10	no H_2O	14
11	20:1 1,4-dioxane:H_2O	85
12	2:1 1,4-dioxane:H_2O	16

Yields are reported based on ^1H NMR analysis of crude reactiuon mixtures using 1,3,5-trimethoxybenzene as an internal standard.

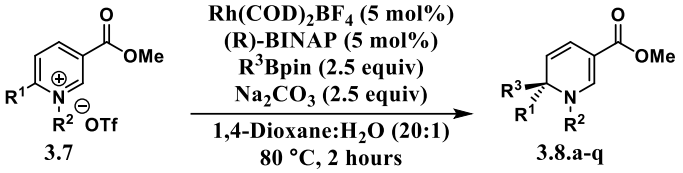
3.3. Dearomatization Substrate Scope:

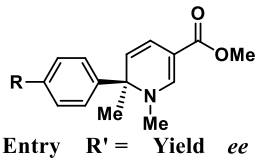
3.3.1. Scope of Bpins for the Dearomatization Reaction Forming Fully Substituted Stereogenic Centers:

With the optimized reaction conditions in hand, we explored the scope of ArBPins. Electron rich, electron neutral, and electron deficient pinacol esters reacted with the pyridinium **3.7** and gave the corresponding dihydropyridines **3.8.a−i** in good to excellent yields and *ee*. In general, both the yields and the enantioselectivities of dihydropyridines were lower when the ArBpins contained an electron-withdrawing group at the para position (Table 3.2, **3.8.b**, **3.8.h**, and **3.8.i**). The reaction tolerated a wide range of functional groups such as halogens (Table 3.2, **3.8.d−f**), a perfluoroalkyl group (Table 3.2, **3.8.b**), an ester (Table 3.2, **3.8.h**), a ketone (Table 3.2, **3.8.i**), and an unprotected primary alcohol (Table 3.2, **3.8.g**). While C-6 ethyl substitution was still

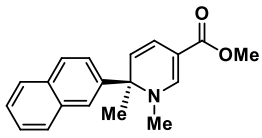
tolerated and gave the corresponding DHP **3.8.m** in 62% yield and 97% *ee*, substituents larger than an ethyl group at the C-6 position of the pyridinium salt were not well tolerated giving DHPs **3.8.n** and **3.8.o** in low yield. Finally, increased sterics of the N-alkyl group resulted in diminished enantioselectivities for DHPs **3.8.p** and **3.8.q** when compared to those of N-methylsubstituted pyridinium salts (Table 3.2).

Table 3.2: Scope of aryl, heteroaryl, and vinyl boron pinacol esters for the dearomatization of pyridinium salt 7.

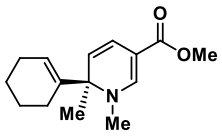




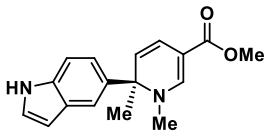
Entry	R' =	Yield	*ee*
3.8.a	OMe	89%	91%
3.8.b	CF_3	56%	74%
3.8.c	Me	82%	90%
3.8.d	Br	65%	89%
3.8.e	Cl	78%	94%
3.8.f	F	86%	94%
3.8.g	CH_2OH	92%	94%
3.8.h	CO_2Me	64%	92%
3.8.i	C(O)Me	61%	91%[a]



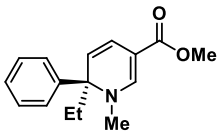
3.8.j, 94%, 76% *ee*



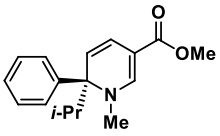
3.8.k, 34%, 88% *ee*



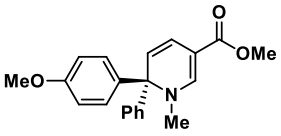
3.8.l, 92%, 92% *ee*



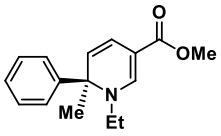
3.8.m, 62%, 98% *ee*



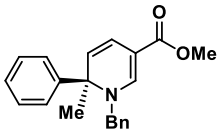
3.8.n, 10%, 91% *ee*



3.8.o, 29%, 62% *ee*



3.8.p, 69%, 82% *ee*



3.8.q, 64%, 71% *ee*

Isolated yields are reported. Enantiomeric excess (*ee*) was determined using chiral HPLC. [a]*ee* was measured after subjecting **3.8.h** to Wittig conditions. See suporting information for details.

3.3.2. Scope of Bpins for the Dearomatization Reaction forming Tertiary Stereogenic Centers:

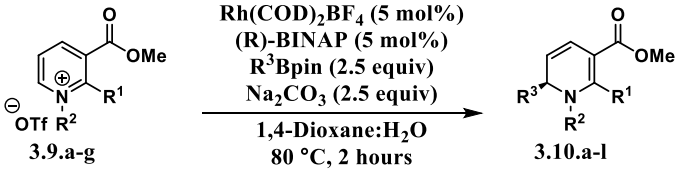
Next, we focused on exploring the scope of the heteroarenium salts for the synthesis of DHPs containing tertiary stereocenters (Table 3.3). Thus, N-benzyl nicotinate salt **3.9** reacted with various heteroarene nucleophiles to afford dihydropyridines **3.10.a–j** in excellent yield and *ee*. We were pleased to find that heteroaryl Bpin nucleophiles gave improved yields of the corresponding

DHPs compared to that of the heteroarylboronic acid nucleophiles (yields with aryl boronic acids are shown in parentheses in Table 3.3: Scope of ArBpins and heteroarenes for the synthesis of dihydroheteroarenes containing tertiary stereocenters.). The most drastic difference in the yield of the corresponding DHP was observed for the addition of the indole group. While indole-2-boronic acid failed to yield any of the DHP **3.10.c**, the corresponding aryl Bpin gave **3.10.c** in 71% yield and 91% *ee*. Dihydropyridine **3.10.c** represents the core of many indole alkaloids. Substitutions at positions C-2 and C-5 of the pyridinium salts were tolerated, albeit the corresponding products **3.10.g−i** were obtained in diminished yields compared to unsubstituted nicotinic acid esters. The N-methyl salt of N,N-diisopropyl nicotinamide underwent dearomatization to give DHP **3.10.j** in moderate yield and *ee*. Finally, N-alkyl quinolinium salts underwent dearomatization, affording **3.10.k** and **3.10.l** in 71% and 39% yields, respectively.

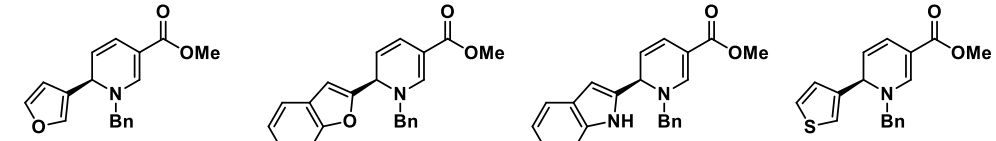
3.4. Synthesis of Nuphar Indolizidine:

To demonstrate the utility of the method detailed herein, we pursued synthesis of a nuphar alkaloid **2**. This indolizidine alkaloid is a minor component of the alkaloids isolated from beaver castoreum.[18] The synthesis of alkaloid **3.2** commenced with a Sonogoshira coupling between pyridine **3.11** and propargyl alcohol, which gave alkyne **3.12** in 91% yield (Scheme 3.1). Hydrogenation of alkyne **3.12** followed by the activation of alcohol **3.13** as the corresponding mesylate gave pyridinium salt **3.14** after anion exchange. Pyridinium **3.14** underwent dearomatization under the standard reaction conditions developed by us to give dihydropyridine **3.15** in 79% yield over two steps starting from alcohol **3.13** and in 94% *ee*. The two double bonds of the dihydropyridine were sequentially reduced to give ester **3.17** as a 2.4:1 mixture of

Table 3.3: Scope of ArBpins and heteroarenes for the synthesis of dihydroheteroarenes containing tertiary stereocenters.



3.9.a-g → 3.10.a-l

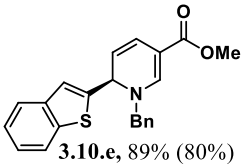


3.10.a, 87% (51%) 95% *ee*

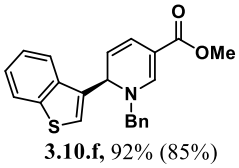
3.10.b, 87% (24%) 92% *ee*

3.10.c, 71% (0%) 91% *ee*

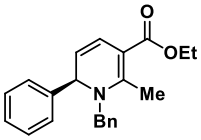
3.10.d, 74% (78%) 95% *ee*



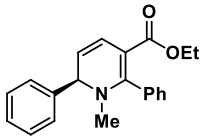
3.10.e, 89% (80%) 87% *ee*



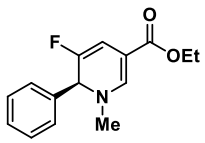
3.10.f, 92% (85%) 82% *ee*



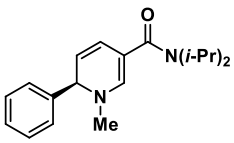
3.10.g, 62% 95% *ee*



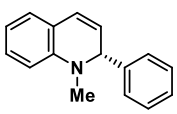
3.10.h, 49% 94% *ee*



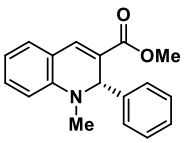
3.10.i, 20% 92% *ee*



3.10.j, 41% 45% *ee*



3.10.k, 71% 91% *ee*

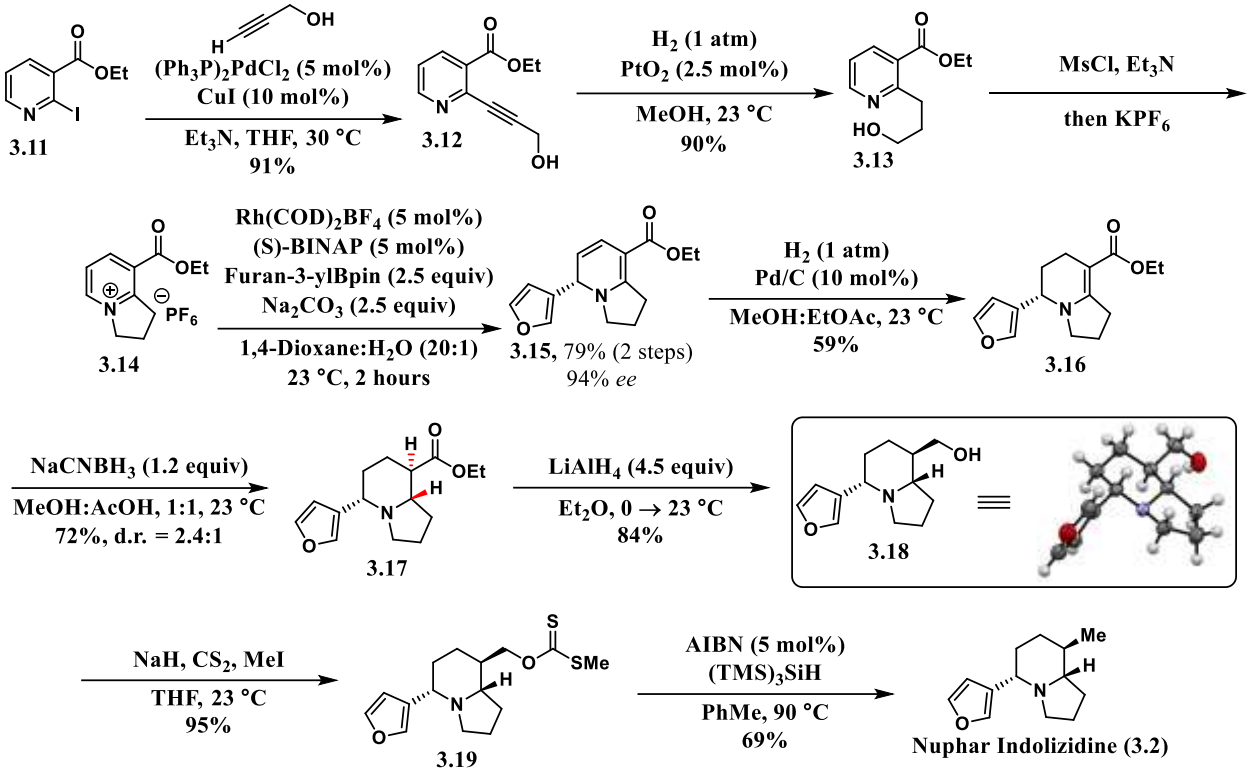


3.10.l, 39% 82% *ee*

Isolated yields are reported. Yields for reactions run using boronic acids are shown in parentheses. Enantiomeric excess (*ee*) was determined using chiral HPLC.

diastereomers favoring the desired diastereomer. Reduction of ester **3.17** gave primary alcohol **3.18** in 84% yield. The relative and absolute stereochemistry of alcohol **3.18** was unambiguously assigned by X-ray analysis of the corresponding single crystals. Alcohol **3.18** was converted to xanthate **3.19** in high yield, and subsequent deoxygenation delivered nuphar alkaloid **3.2** in nine overall steps starting from commercially available pyridine **3.11**. The synthetic route executed by us would allow efficient synthesis of analogues of this compound for structure−activity relationship studies as using this route, the furan moiety can be modified to probe different aryl groups at position C-6 and dihydropyridine **3.15** would allow modifications within the piperidine ring of alkaloid 2 through functionalization of the two C=C bonds.

Scheme 3.1: Dearomative approach for the total synthesis of nuphar indolizidine (2).



Isolated yields are reported. Enantiomeric excess (*ee*) was determined using chiral HPLC. [a] The pictured X-ray structure of **3.18** is shown with thermal elipsoids at 50% probability. CCDC 2084950 contains the crystalographic data for this publication.

3.5. Conclusion:

In conclusion, herein we report the Rh-catalyzed dearomatization of pyridinium and quinolinium salts with ArBpin nucleophiles. ArBpins are easier to access than ArB(OH)2 through C−H borylation of arenes as well as from aryl halides and triflates through Miyaura and Matsuda borylations correspondingly. ArBPins have significantly improved stability toward protodeboronation under basic conditions, which in this case led to the successful addition of heteroarenes to pyridiniums. Addition of heteroarenes to hetearoniums is potentially important for the synthesis of natural products that contain heteroarene-substituted piperidines. We demonstrate application of the dearomatization strategy to the synthesis of a bioactive alkaloid from the nuphar alkaloid family.

3.6. Experimental Section:

3.6.1. Materials and Methods:

Reactions were performed in flame-dried sealed tubes or modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of nitrogen or inside nitrogen filled glovebox using 1-dram vials unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe. The appropriate starting materials and reagents were dried *via* azeotropic removal of water with toluene. Molecular sieves were activated at 350 °C and were crushed immediately prior to use, then flame-dried under vacuum. Organic solutions were concentrated by rotary evaporation below 40 °C. Flash column chromatography was performed employing 230–400 mesh silica gel.

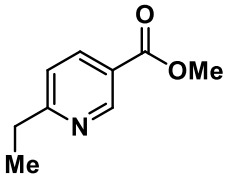
Dichloromethane, tetrahydrofuran, diethyl ether, DMF and toluene were purified by passage through two packed columns of neutral alumina under an argon atmosphere.[18] Methanol was distilled from magnesium at 760 Torr. Amines were distilled from CaH_2 at 760 torr. Mesyl Chloride was distilled from P_2O_5 at 760 torr. All other chemicals were obtained from commercial vendors and were used without further purification unless otherwise noted.

Automated flash chromatography was performed with a Teledyne Isco Combiflash® R*f* system with Redi*sep* Gold™ silica columns. Thin-layer chromatography was performed using glass plates pre-coated to a depth of 0.25 mm with 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm) and visualized under UV light (254 and 360 nm), or stained with Ceric Ammonium Molybdate in conc. H_2SO_4, vanillin in acidic EtOH, or I_2 on SiO_2.

Proton, carbon-13, and fluorine-19 nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR, and ^{19}F NMR) spectra were recorded on a Bruker Avance III instrument; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual isotopes

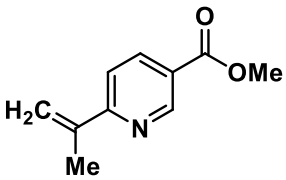
in the NMR solvent (d-chloroform: δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR; d4-methanol: δ 3.31 for ^{1}H NMR, δ 49.00 for ^{13}C NMR; d6-benzene: δ 7.16 for ^{1}H NMR, δ 128.06 for ^{13}C NMR). Data are presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration. HPLC analysis for the determination of enantiomeric access (*ee*) was performed using a Waters 1515 isocratic solvent pump, 2489 UV-Vis detector, and CHIRALPAK® columns (IA, IC, ID, and IG columns), or Agilent Technologies 1260 Infinity II HPLC system and InfinityLab Poroshell 120 column (Chiral-CD). Optical rotations are calculated and reported in concentrations of g/mL, and were recorded using a Rudolph Research Analytical Autopol® IV Automatic Polarimeter with a 0.5 dm path length. High resolution mass spectrometry (HRMS) was performed using an Orbitrap Exploris 120 quadrupole orbitrap.

3.6.2. Synthesis of Pyridine Starting Materials:



Methyl 6-Ethylpyridine-3-carboxylate (3.S.1)

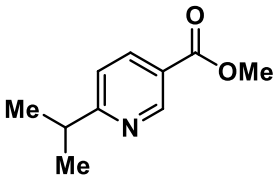
Compound **3.S.1** was prepared according to a reported procedure.[40] ^{1}H and ^{13}C spectral data matched those of the reported compound. **Yield:** 129.8 mg (52%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.91 (d, J = 2.2 Hz, 1H), 7.98 (dd, J = 8.1, 2.2 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 3.72 (s, 3H), 2.67 (q, J = 7.6 Hz, 2H), 1.11 (t, J = 7.6 Hz, 3H).; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.9, 165.7, 150.2, 137.3, 123.2, 121.5, 52.0, 31.3, 13.4.



Methyl 6-isopropenylpyridine-3-carboxylate (3.S.2)

To a flame dried Schlenk tube (25 mL) charged with N_2 and a magnetic stirbar was added methyl-6-bromonicotinate (324.0 mg, 1.50 mmol, 1.0 equiv.), and 2-propenyl boronic acid pinacol ester (378.2 mg, 2.25 mmol, 1.5 equiv.). The vessel was sealed and transferred to the N_2 filled glovebox where $Pd(PPh_3)_4$ (86.7 mg, 0.08 mmol, 0.05

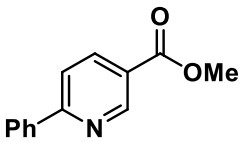
equiv.) and toluene (5.0 mL) were added. The vessel was sealed and removed to the Schlenk line, where degassed 2M K_2CO_3(aq) (1.5 mL, 3.0 mmol, 2.0 equiv.) was added under N_2. The vessel was sealed and heated in an oil bath to 80 °C with vigorous stirring for 16 hours. The reaction mixture was cooled to ambient temperature, diluted to 25 mL with EtOAc, filtered through silica, then celite, and concentrated *in vaccuo*. The crude mixture was purified *via* automated flash column chromatography to give a mixture of **S2** and Methyl-6-bromonicotinate (10%). **Yield:** 221.3 mg (75 % for **S2**). **TLC:** R*f* 0.50 (EtOAc:Hexanes 1:4); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.22 (d, J = 1.6 Hz, 1H), 8.34 (d, J = 7.0 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 6.11 (s, 1H), 5.52 (s, 1H), 3.97 (s, 3H), 2.27 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.9, 161.8, 150.2, 142.6, 137.5, 124.2, 119.2, 118.2, 52.3, 20.3; **HRMS** (ESI) *m/*z Calcd for $C_{10}H_{12}O_2N$ $[M+H]^+$: 178.0863, found 178.0862.



Methyl 6-isopropylpyridine-3-carboxylate (3.S.3)

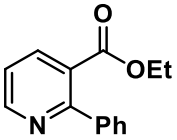
To a 50 ml round bottomed flask charged with a magnetic stirbar was added **S2** (132.5 mg, 0.75 mmol, 1.0 equiv.), then Pd/C (5%) (159.6 mg, 0.0.08 mmol, 0.1 equiv.) which were then dissolved in MeOH (5.0 mL). The flask was capped with a rubber septum. With stirring, the solution was purged with H_2 by applying a light vacuum on the flask and back-filling with H_2 from a balloon with a needle attached. The reaction was stirred at ambient temperature for 1 hour. After TLC analysis showed complete consumption of the starting material, the reaction mixture filtered over a silica plug, which was washed with MeOH (5.0 mL). The collected washes were concentrated *in vacuo* and the crude reaction mixture was purified *via* flash column and the solvents removed under reduced pressure to afford **S3** as a clear to light yellow oil. **Yield:** 71.3 mg (35%); **TLC:** R*f* 0.36 (EtOAc:Hexanes, 1:4); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.12 (dd, J = 2.2, 0.9 Hz, 1H), 8.19 (dd, J = 8.2, 2.3 Hz, 1H), 7.24 (dd, J = 8.2, 0.9

Hz, 1H), 3.92 (s, 3H), 3.12 (hept, J = 6.9 Hz, 1H), 1.31 (d, J = 6.9 Hz, 7H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.1, 166.1, 150.6, 137.7, 123.7, 120.4, 52.4, 36.7, 22.5; **HRMS** (ESI) *m/*z Calcd for $C_{10}H_{14}O_2N$ $[M+H]^+$: 180.1019, found 180.1019.



Methyl 6-phenylpyridine-3-carboxylate (3.S.4)

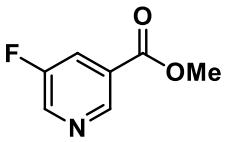
Compound **S4** was prepared according to a reported procedure.[10] ^{1}H and ^{13}C spectral data matched those of the reported compound. **Yield:** 287.7 mg (54%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.27 (d, J = 2.4 Hz, 1H), 8.33 (dd, J = 8.3, 2.2 Hz, 1H), 8.08 – 8.02 (m, 2H), 7.79 (d, J = 8.3 Hz, 1H), 7.53 – 7.42 (m, 3H), 3.96 (s, 3H).; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.94, 160.98, 151.02, 138.32, 137.98, 130.06, 128.99, 127.44, 124.28, 119.93, 52.43.



Ethyl 2-phenylpyridine-3-carboxylate (3.S.5)

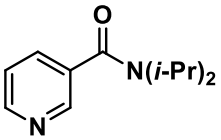
A 100 mL Schlenk tube charged with ethyl-2-chloro-3-carboxylate (1.0 g, 5.39 mmol, 1.0 equiv.) and phenylboronic acid (0.9 g, 8.09 mmol, 1.5 equiv.) was transferred to a N_2-filled glovebox. $Pd(PPh_3)_4$ (62.4 mg, 0.05 mmol, 1 mol%) was added and the mixture was dissolved in dry, degassed THF (22.5 mL). The Schlenk tube was sealed and removed to a Schlenk line where degassed 2.0 M K_2CO_3 (aq.) (10.7 mL, 10.78 mmol, 2.0 equiv.) was added. The tube was sealed, and the reaction heated in an oil bath to 65 °C with vigorous stirring overnight (18 hours). The reaction was cooled to room temperature and filtered over celite. The celite filter was rinsed with EtOAc (10.0 mL) and the combined organic solvent was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude reaction mixture was purified via flash column and the solvent removed under reduced pressure to give **S5** as a yellow oil. **Yield:** 929.7 mg (76%); **TLC:** R*f* 0.39 (EtOAc:Hexanes, 20:80); **^{1}H NMR** (500 MHz, CDCl3) δ 8.73 (dd, J = 5.1, 1.7 Hz, 1H), 8.07 (dd, J = 7.9, 1.7 Hz, 1H), 7.52 (dt, J = 6.6, 2.6 Hz, 2H), 7.46 – 7.34 (m, 3H), 7.29 (dd, J = 7.8, 4.8 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 1.01 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, CDCl3)

δ 168.1, 158.8, 151.1, 140.2, 137.8, 128.6, 128.5, 128.1, 127.4, 121.6, 61.4, 13.6; **HRMS** (ESI) *m/z* Calcd for $C_{14}H_{14}O_2N$ $[M+H]^+$: 228.1019, found 228.1012.



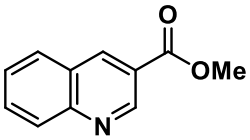
Methyl-5-fluoropyridine-3-carboxylate (3.S.6)

Compound **3.S.6** was prepared according to a reported procedure.[20] ^1H and ^{13}C spectral data matched those of the reported compound. **Yield:** 113.2 mg (73%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.65 (d, J = 2.9 Hz, 1H), 7.99 (ddd, J = 8.6, 2.7, 1.6 Hz, 1H), 3.97 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 164.82 (d, J = 2.1 Hz), 159.25 (d, J = 258.5 Hz), 146.80 (d, J = 4.3 Hz), 142.30 (d, J = 23.2 Hz), 127.55, 123.75 (d, J = 19.5 Hz), 52.90.



N,N-di(propan-2-yl)pyridine-3-carboxamide (3.S.7)

Compound **3.S.5** was prepared according to a reported procedure.[21] ^1H and ^{13}C spectral data matched those of the reported compound. **Yield:** 2.2 g (66%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.55 (d, J = 5.0 Hz, 1H), 8.51 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.26 (dd, J = 7.8, 4.8 Hz, 1H), 3.61 (d, J = 102.5 Hz, 2H), 1.28 (d, J = 162.0 Hz, 5H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.2, 149.9, 146.7, 134.6, 133.6, 123.5, 51.2, 46.2, 20.8.



Methyl quinoline-3-carboxylate (3.S.8)

Compound **3.S.8** prepared from quinoline-3-carboxylic acid (1.0 g, 5.35 mmol, 1.0 equiv.) using a modified procedure[4]. **3.S.8** was used without further purification. **Yield:** 1.10 g (50%). ^1H and ^{13}C spectra match those of the reported compound.[22] **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.85 (d, J = 2.0 Hz, 1H), 8.17 (d, J = 8.5 Hz, 1H), 7.94 (dd, J = 8.1, 1.4 Hz, 1H), 7.84 (t, J = 7.7 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 4.02 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.0, 150.1, 150.0, 139.0, 132.1, 129.6, 129.3, 127.6, 127.0, 123.2, 52.7.

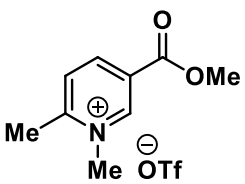
3.6.3. Synthesis of N-Alkyl Pyridinium Salts:

3.6.3.1. General procedure for pyridinium salts using MeOTf (GP 1):

In a Schlenk flask, the specified nicotinic ester (1.0 equiv.) was dissolved in CH_2Cl_2 (0.1M) and cooled to 4 °C in an ice water bath. MeOTf (1.1 equiv.) was added slowly *via* syringe and the reaction mixture was stirred overnight allowing it to warm to ambient temperature. ~1/3 of the CH_2Cl_2 was removed under reduced pressure and obtained oil was slowly added to a beaker containing rapidly stirring Et_2O (50 mL). Stirring was continued for additional 30 min at which point, the initial thick oil solidified. This solid was filtered and washed with Et_2O (50 mL) to give pyridinium salt as white to brown solid.

3.6.3.2. General procedure for pyridinium salts using benzyl bromide and AgOTf (GP 2):

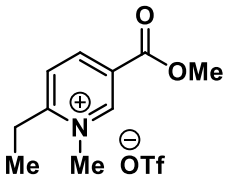
In a Schlenk tube, the specified nicotinic ester (2.0 g, 1.0 equiv.) was dissolved in *i*-PrOH (0.2M). BnBr (2.0 equiv.) was added slowly *via* syringe, the tube was sealed, and the reaction mixture was stirred overnight. The solvents were evaporated under reduced pressure and the obtained oil was dissolved in acetone (0.2M). In a 20 ml scintillation vial, AgOTf (1.0 equiv.) was dissolved in acetone (1.0M). The solution of AgOTf was added to the bromide dropwise with stirring. The resulting AgBr was filtered out over celite, and the filtrate was added slowly to a beaker containing rapidly stirring Et_2O (100 mL). Stirring was continued for additional 30 min at which point, the initial thick oil solidified. This solid was filtered and washed with Et_2O (50 mL) to give pyridinium salt as white to brown solid.



5-(methoxycarbonyl)-1,2-dimethylpypiridin-1-ium triflate (3.5)

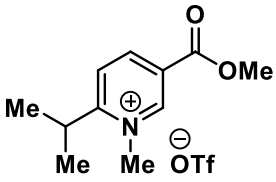
Prepared from methyl 6-methylpyridine carboxylate (10.0 g, 66.00 mmol, 1 equiv.) and according to GP1. ^{1}H and ^{13}C spectral data matched those of a

reported compound.[10] **Yield:** 16.8 g (81%); **^{1}H NMR** (600 MHz, CD_3OD) δ 7.83 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 2.75 (s, 3H), 2.41 (s, 3H), 1.29 (s, 3H); **^{13}C NMR** (151 MHz, CD_3OD) δ 163.5, 161.5, 148.8, 145.7, 130.8, 129.5, 121.7 (q, *J* = 318.6 Hz), 53.93, 46.9.



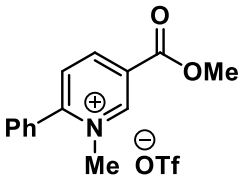
2-ethyl-5-(methoxycarbonyl)-1-methylpyridin-1-ium triflate (3.7.m)

Prepared from **3.S.4** (165.0 mg, 1.00 mmol, 1.0 equiv.) via GP1. ^{1}H and ^{13}C spectral data match those of a reported compound.[10] **Yield:** 188.4 mg (58%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.83 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 4.43 (s, 3H), 4.03 (s, 3H), 3.22 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 163.9, 161.9, 147.9, 144.8, 128.0, 127.2, 123.6, 121.5, 119.4, 117.3, 77.3, 77.1, 76.9, 53.7, 53.5, 46.6, 26.6, 10.9.



5-(methoxycarbonyl)-1-methyl-2-(propan-2-yl)-pyridin-1-ium triflate (3.7.n)

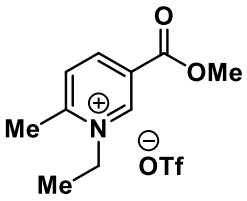
Prepared from **3.S.3** (57.4 mg, 0.32 mmol, 1.0 equiv.) according to GP1. **Yield:** 90.2 mg (82%); **^{1}H NMR** (500 MHz, C6D6) δ 9.11 (d, J = 1.6 Hz, 1H), 8.16 (dd, J = 8.4, 1.7 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 3.70 (s, 3H), 3.16 (dt, J = 13.5, 6.7 Hz, 1H), 0.99 (d, J = 6.7 Hz, 6H), 0.56 (s, 6H) **^{13}C NMR** (126 MHz, CDCl3) δ 168.0, 161.8, 148.3, 145.1, 128.1, 125.6, 120.6 (q, J = 320.2 Hz), 53.6, 46.7, 31.0, 21.4; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -78.52; **HRMS** (ESI) *m/z* Calcd for $C_{11}H_{16}O_2N$ $[M\text{-}OTf]^+$: 194.1176, found 194.1175.



5-(methoxycarbonyl)-1-methyl-2-phenylpyridin-1-ium triflate (7o)

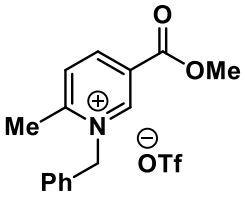
Prepared from **3.S.4** (287.9 mg, 1.35 mmol, 1.0 equiv.) *via* GP1. ^{1}H and ^{13}C spectral data match those of a reported molecule.[10] **Yield:** 447.7 mg (88%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.92 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.60 (m, 5H), 4.36 (s, 3H), 4.04 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.8, 159.2, 148.6,

144.9, 132.1, 130.9, 130.1, 129. 7, 129. 6, 129.1, 120.6 (q, J = 320.4 Hz), 53. 8, 48.4. 128.9, 53.9, 48.5.



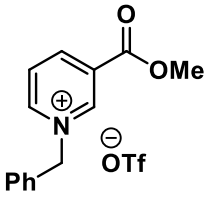
1-ethyl-5-(methoxycarbonyl)-2-methylpyridin-1-ium triflate (3.7.p)

In a 20 mL scintillation vial charged with a Teflon-coated stir bar, methyl 6-methylpyridine carboxylate (2.000 g, 13.2 mmol, 1.0 equiv.) was dissolved in bromoethane (1.10 mL, 14.5 mmol, 1.1 equiv.). The vial was sealed with a Teflon-coated cap and heated in an aluminum heating block to 60°C overnight. The reaction was cooled to 23°C and a few drops (less than 1.0 mL) of methanol was added to the resulting slurry until all solids were dissolved. The resulting solution was treated with AgOTf according to GP2 to furnish the N-ethyl triflate salt **3.7.p**. **Yield**: 1.2 g (28% over two steps); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.77 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.2 Hz, 1H), 4.79 (q, J = 7.3 Hz, 2H), 4.04 (s, 3H), 3.00 (s, 3H), 1.67 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.8, 159.2, 146.1, 144.7, 130.8, 129.1, 125.0 – 116.2 (m); 55.0, 53.9, 20.9, 15.3, 0.1; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -78.48; **HRMS** (ESI) *m/z* Calcd for $C_{10}H_{14}O_2N$ [M-OTf]$^+$: 180.1019, found 180.1012.



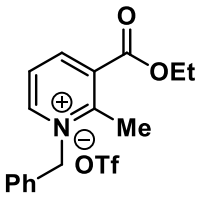
1-benzyl-5-(methoxycarbonyl)-2-methylpyridin-1-ium triflate (3.7.q)

Prepared from methyl 6-methylpyridine carboxylate (2.000 g, 13.2 mmol, 1 equiv.) according to GP2. **Yield**: 2.9 g (56% over two steps); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.14 (d, J = 1.7 Hz, 1H), 8.81 (dd, J = 8.2, 1.8 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.26 – 7.19 (m, 2H), 5.93 (s, 2H), 4.00 (s, 3H), 2.97 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.8, 160.3, 146.5, 145.1, 131.0, 130.9, 130.1, 130.1, 128.7, 128.3, 125.4 – 116.3 (m), 62.6, 53.9, 21.5; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -78.42; **HRMS** (ESI) *m/z* Calcd for $C_{15}H_{16}O_2N$ [M-OTf]$^+$: 242.1175, found 242.1169.



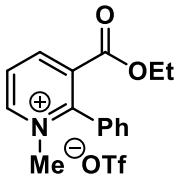
1-benzyl-3-(methoxycarbonyl)pyridin-1-ium triflate (3.9.a)

Prepared from methyl nicotinate (480.0 mg, 3.5 mmol, 1.0 equiv.) according to GP2. **Yield**: 1.0 g (79% over two steps); **^{1}H NMR** (500 MHz, D_2O) δ 9.52 (s, 1H), 9.12 (d, J = 6.2 Hz, 1H), 9.06 (d, J = 8.0 Hz, 1H), 8.23 (t, J = 7.2 Hz, 1H), 7.52 (m, 5H), 5.93 (s, 2H), 4.05 (s, 3H); **^{13}C NMR** (126 MHz, D_2O) δ 164.9, 149.0, 147.7, 147.3, 133.8, 132.6, 131.8, 131.3, 130.9, 130.4, 126.6 – 115.2 (m), 66.8, 55.5; **^{19}F NMR** (471 MHz, D2O) δ -78.82. **HRMS** (ESI) *m/z* Calcd for $C_{14}H_{14}O_2N$ [M-OTf]$^+$: 228.1019, found 228.1010.



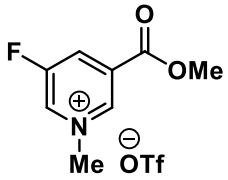
1-benzyl-3-(ethoxycarbonyl)-2-methylpyridin-1-ium triflate (3.9.g)

Prepared from ethyl 2-methyl nicotinate (1.863 g, 8.2 mmol, 1.0 equiv.) according to GP2. **Yield**: 2.350 g (71% over two steps); **^{1}H NMR** (500 MHz, D_2O) δ 9.21 – 9.04 (m, 1H), 8.82 (dd, J = 8.2, 1.5 Hz, 1H), 8.03 (dd, J = 8.1, 6.3 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.19 (dd, J = 7.4, 2.1 Hz, 2H), 5.93 (s, 2H), 4.43 (q, J = 7.1 Hz, 2H), 3.02 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, D_2O) δ 163.0, 157.4, 149.5, 146.7, 132.5, 131.6, 129.9, 129.7, 127.9, 125.8, 126.6 – 115.2 (m), 63.6, 63.1, 18.2, 14.1.; **^{19}F NMR** (471 MHz, D2O) δ -78.82. **HRMS** (ESI) *m/z* Calcd for $C_{16}H_{18}O_2N$ [M-OTf]$^+$: 256.1332, found 256.1324.s



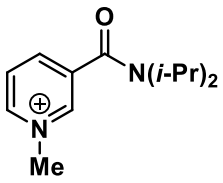
3-(ethoxycarbonyl)-1-methyl-2-phenylpyridin-1-ium triflate (3.9.h)

Prepared from **3.S.6** (1.0 g, 4.40 mmol, 1.0 equiv.) according to GP1.**Yield:** 802.6 mg, (98%); **^{1}H NMR** (500 MHz, D_2O) δ 9.01 (dd, J = 6.2, 1.5 Hz, 1H), 8.93 (dd, J = 8.1, 1.5 Hz, 1H), 8.06 (dd, J = 8.1, 6.3 Hz, 1H), 7.53 – 7.45 (m, 3H), 7.33 – 7.21 (m, 2H), 4.49 (q, J = 7.2 Hz, 2H), 2.97 (s, 3H), 1.41 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (126 MHz, D_2O) δ 166.5, 158.7, 149.8, 148.4, 134.5, 133.4, 131.2, 131.1, 129.3, 127.0, 121.3 (q, J = 317.4 Hz), 65.7, 63.7, 19.3, 14.8; **^{19}F NMR** (471 MHz, D_2O) δ -78.80; **HRMS** (ESI) m/z Calcd for $C_{15}H_{16}O_2N$ [M-OTf]$^+$: 242.1175, found 242.1167.



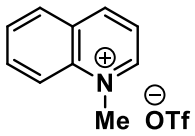
3-fluoro-5-(methoxycarbonyl)-1-methylpyridin-1-ium triflate (3.9.i)

Prepared from methyl 5-fluoro-pyridine-3-carboxylate (1.8 g, 11.60 mmol, 1.0 equiv.) according to GP1. **Yield** 3.6 g (97%); **^{1}H NMR** (600 MHz, CDCl3) δ 9.20 (s, 1H), 9.17 (s, 1H), 8.68 (d, J = 6.4 Hz, 1H), 4.68 (s, 1H), 4.09 (s, 1H); **^{13}C NMR** (126 MHz, MeOD) δ 162.7, 162.4 (d, J = 2.3 Hz), 160.7, 145.2, 140.3 (d, J = 38.4 Hz), 133.9 (d, J = 20.2 Hz), 133.5(d, J = 7.2 Hz), 121.8 (q, J = 318.7 Hz), 54.4, 49.8; **^{19}F NMR** (471 MHz, CDCl3) δ -76.20, -113.07. **HRMS** (ESI) *m/z* Calcd for $C_8H_9O_2NF$ $[M\text{-}OTf]^+$: 170.0612, found 170.0611.



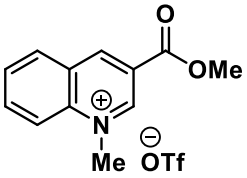
3-[di(propan-2-yl)carbamoyl]-1-methylpyridin-1-ium triflate (3.9.j)

Prepared from **3.S.5** (1.0 g, 4.85 mmol, 1.0 equiv.) according to GP1. **Yield:** 90.2 mg (82%.) **^{1}H NMR** (600 MHz, CDCl3) δ 8.89 (d, J = 6.0 Hz, 1H), 8.60 (s, 1H), 8.24 (d, J = 7.9 Hz, 1H), 8.09 – 8.01 (m, 1H), 4.53 (s, 3H), 3.83 (s, 1H), 3.61 (s, 1H), 1.38 (d, J = 174.7 Hz, 12H); **^{13}C NMR** (126 MHz, MeOD) δ 165.4, 147.0, 144.4, 143.1, 139.6, 129.5, 121.8 (q, J = 318.7 Hz), 53.5, 48.0, 20.6; **^{19}F NMR** (471 MHz, CDCl3) δ -76.13.δ. **HRMS** (ESI) *m/z* Calcd for $C_8H_9O_2N$ $[M\text{-}OTf]^+$: 170.0612, found 170.0611.



1-methylquinolin-1-ium triflate (3.9.k)

Prepared from quinoline (1.2 mL, 10 mmol, 1.0 equiv.) according to GP1. **Yield** 2.6 g (89%). **^{1}H NMR** (600 MHz, CDCl3) δ 9.65 (d, J = 5.7 Hz, 1H), 8.98 (d, J = 8.4 Hz, 1H), 8.38 (d, J = 8.9 Hz, 1H), 8.25 (ddd, J = 12.3, 10.1, 4.7 Hz, 2H), 8.08 (dd, J = 8.3, 5.8 Hz, 1H), 8.00 (t, J = 7.6 Hz, 1H), 4.79 (s, 3H); **^{13}C NMR** (126 MHz, MeOD) δ 151.1, 148.8, 140.3, 137.2, 131.7, 131.4, 131.3, 122.9, 121.8 (q, J = 318.4 Hz), 119.8, 46.2; **^{19}F NMR** (471 MHz, CDCl3) δ -76.16. **HRMS** (ESI) *m/z* Calcd for $C_{10}H_{10}N$ $[M\text{-}OTf]^+$: 144.0808, found 144.0808.



3-(methoxycarbonyl)-1-methylquinolin-1-ium triflate (3.9.l)

Prepared from **3.S.8** (965.2 mg, 5.16 mmol, 1.0 equiv.) according to GP1. **^{1}H NMR** (500 MHz, D_2O) δ 9.80 (d, J = 1.9 Hz, 1H), 9.75 – 9.64 (m, 1H), 8.59 – 8.45 (m, 2H), 8.41 (ddd, J = 8.8, 7.0, 1.5 Hz, 1H), 8.13 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H), 4.74 (s, 3H), 4.12 (s, 3H); **^{13}C NMR** (126 MHz, D_2O, ref DMSO D6) δ 165.6, 151.2, 150.2, 141.5, 140.0, 133.6, 132.7, 130.4, 125.4, 121.2 (q, J = 317.4 Hz), 120.2, 55.4, 47.4; **^{19}F NMR** (471 MHz, D_2O) δ -78.86; **HRMS** (ESI) *m/z* Calcd for $C_{12}H_{12}O_2NF$ $[M\text{-}OTf]^+$: 202.0862, found 202.0857.

3.6.4. Synthesis of Dihydropyridines:

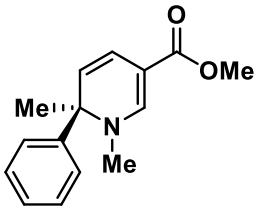
3.6.4.1. Preparation of Rh catalyst stock solution for dearomatization reactions:

In a nitrogen filled glovebox, $Rh(COD)_2BF_4$ (64 mg, 0.16 mmol, 1 equiv.) and BINAP (99 mg, 0.16 mmol, 1.0 equiv.) were weighed into a 4-dram vial and dissolved in dioxane (16 mL, 0.01M). This solution was stirred for 15 minutes to promote the formation of the catalyst. The solution is a clear red color. This solution was used in the dearomatization reactions below. For racemic dearomatization products, racemic BINAP was used.

3.6.4.2. General procedure for dearomatization of *n*-alkyl pyridinium salts:

The specified pyridinium salt (1.0 equiv.), boronic acid pinacol ester (Bpin) (2.5 equiv.), and Na_2CO_3 (2.5 equiv.), were measured into a 1 dram scintilation vial on the benchtop.The vials containing pyridinium salt, Bpin, and Na_2CO_3 were transferred into the nitrogen filled glovebox where the Rh/BINAP stock solution of catalyst was added into each vial (0.2 M) . The vials were then sealed and brought outside the glovebox. A specified amount of degassed water was added to each reaction mixture *via* syringe and the reaction mixture was heated to the specified temerature for 2 hours using an aluminum heating block. The vials were then removed from the heating block

and cooled to room temperature. **Workup:** room temperature solutions were diluted with 1 mL of EtOAc and dried with 1.0 g of $MgSO_4$. The reactions were filtered through Al_2O_3 and the filtrate was concentrated. The residue was purified by manual or automatic flash column chromatography to give **3.6**, **3.8.a-q**, and **3.10.a-l**. **^{1}H** and **^{13}C** spectra for compounds **3.6, 3.8.a-h, 3.8.j-m**, and **3.8.o-q** match those of reported compounds.[10]



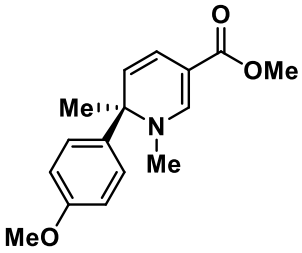
Methyl (6S)-1,6-dimethyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (3.6)

Dihydropyridine **6** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and phenyl Bpin (102.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water at 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield:** 41.3 mg (85%); The **enantiomeric excess** was determined by HPLC analysis to be 95% *ee*. **HPLC** (Chiral-CD, water/acetonitrile = gradient from 90:10 to 5:95, flow rate = 1.0 mL/min, l = 250 nm) tR = 13.9 min (major), 14.4 min (minor); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.32 (s, 1H), 7.29 – 7.25 (m, 1H), 6.31 (d, *J* = 9.8 Hz, 1H), 4.77 (d, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 2.72 (s, 3H), 1.75 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 147.7, 145.6, 128.5, 127.6, 126.5, 120.0, 118.0, 94.6, 63.2, 50.8, 38.4, 24.8.

Representative scaleup of 6:

To demonstrate the scalability of the dearomatization of n-alkyl pyridinium salts, pyridinium **3.5** (315 mg, 1.00 mmol, 1.0 equiv.), phenyl Bpin (510 mg, 2.50 mmol, 2.5 equiv.), and Na_2CO_3 (265 mg, 2.50 mmol, 2.5 equiv.) were added to a 25 ml Schlenk tube charged with a magnetic stirbar.

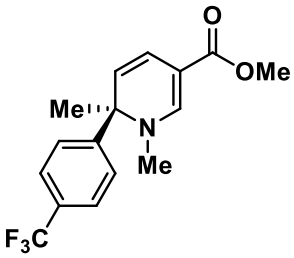
The contents of the tube were placed under N_2 by evacuating under vacuum and back-filling with N_2 three times. In an N_2-filled glovebox, $Rh(COD)_2BF_4$ (20.3 mg, 0.050 mmol, 5 mol%) and (R)-Binap (31.1 mg, 0.050 mmol, 5 mol%) were added to a 20 ml scintillation vial and dissolved in 5 ml of dioxane. The resulting solution was stirred for 15 minutes to promote the formation of the catalyst. The Schlenk tube was transferred to the glovebox, where the catalyst solution was added. The Schlenk tube was sealed and transferred to a Schlenk line, where degassed H_2O (250 µl) was added. The Schlenk tube was sealed and heated in an oil bath to 80°C. After two hours, the reaction was cooled to room temperature and worked up according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts.** The crude reaction mixture was purified via flash column chromatography to give **3.6** as a light yellow oil. **Yield:** 153.1 mg (63%). The **enantiomeric excess** was determined by HPLC analysis to be 92% *ee*. **HPLC** (Chiral-CD, water/acetonitrile = gradient from 90:10 to 5:95, flow rate = 1.0 mL/min, l = 250 nm) tR = 14.4 min (major), 14.7 min (minor).



Methyl (6*S*)-6-(4-methoxyphenyl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (3.8.a)

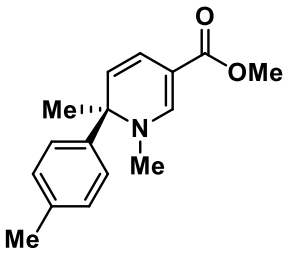
Dihydropyridine **3.8.a** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 4-methoxyphenyl Bpin (117.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield:** 48.6 mg **(**89%); The **enantiomeric excess** was determined by HPLC analysis to be 91% *ee.* **HPLC** (Chiral-CD, water/acetonitrile = Gradient from 90:10 to 5:95, flow rate 1 mL/min, l = 250 nm) tR = 11.6 min (major), 12.1 min (minor); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 – 7.35 (m, 2H), 7.30 (s, 1H), 6.91 – 6.83 (m, 2H), 6.30 (d, *J* = 10.0 Hz, 1H), 4.75 (d, *J* = 10.0

Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 2.70 (s, 3H), 1.71 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 158.8, 147.6, 138.0, 127.9, 120.1, 117.9, 113.6, 94.5, 62.7, 55.4, 50.8, 38.3, 24.9.



Methyl (6*S*)-1,6-dimethyl-6-[4-(trifluoromethyl)phenyl]-1,6-dihydropyridine-3-carboxylate (3.8.b)

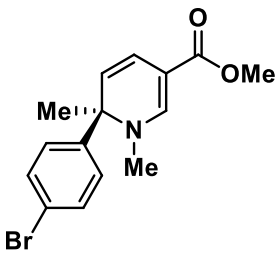
Dihydropyridine **3.8.b** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 4-(trifluoromethyl)phenyl Bpin (136.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield:** 34.9 mg **(**56%); The **enantiomeric excess** was determined by HPLC analysis to be 74% *ee*. **HPLC** (Chiralpak-IA, 2-propanol/*n*-hexane = 90:10, flow rate = 1 ml/min, l = 250 nm) tR = 8.35 min (major), 9.18 min (minor); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.34 (s, 1H), 6.32 (d, *J* = 9.9 Hz, 1H), 4.75 (d, *J* = 10.0 Hz, 1H), 3.70 (s, 3H), 2.73 (s, 3H), 1.78 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 166.9, 149.4, 147.6, 129.7 (q, *J* = 32.5 Hz), 126.8, 125.6 (q, *J* = 3.6 Hz), 124.0 (q, *J* = 272.2 Hz), 119.4, 118.7, 95.2, 63.2, 50.9, 38.4, 25.0.



Methyl (6*S*)-6-(4-methylphenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (3.8.c)

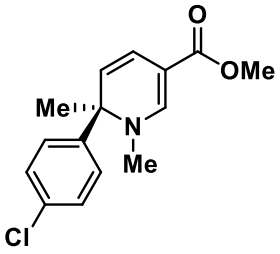
Dihydropyridine **3.8.c** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 4-methylphenyl Bpin (109.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield** 33.7 mg (66 %); The **enantiomeric excess** was determined by HPLC analysis to be 90% *ee*. **HPLC** (Chiral-CD, water/acetonitrile = gradient from 90:10 to 5:95, flow rate = 1.0

ml/min, l = 250 nm) tR = 14.4 min (major), 14.9 min (minor); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.8 Hz, 2H), 7.32 (s, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 6.29 (d, *J* = 9.8 Hz, 1H), 4.75 (d, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 2.71 (s, 3H), 2.34 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 147.7, 142.8, 137.3, 129.2, 126.5, 120.1, 117. 9, 94.5, 63.0, 50.8, 38.4, 24.9, 21.1.



Methyl (6*S*)-6-(4-bromophenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (3.8.d)

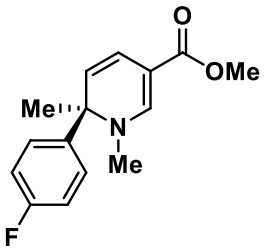
Dihydropyridine **3.8.d** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 4-bromophenyl Bpin (141.5 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield** 41.9 mg (65%); The **enantiomeric excess** was determined by HPLC analysis to be 89% *ee;* **HPLC** (Chiral-CD, water:acetonitrile = gradient from 90:10 to 5:95, flow rate = 1 ml/min, l = 250 nm) tR = 11.2 min (major), 11.5 min (minor); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.30 (s, 1H), 6.30 (d, *J* = 9.9 Hz, 1H), 4.73 (d, *J* = 9.9 Hz, 1H), 3.69 (s, 3H), 2.71 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 147.6, 144.8, 131.7, 128.4, 121.8, 119.7, 118.5, 95.1, 63.1, 50.9, 38.4, 24.9.



Methyl (6*S*)-6-(4-chlorophenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (3.8.e)

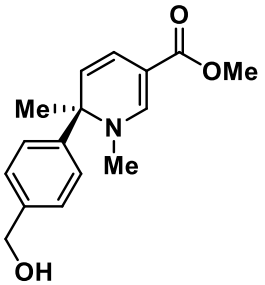
Dihydropyridine **3.8.e** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 4-chlorophenyl Bpin (119.3 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield:** 43.3 mg (78%); The **enantiomeric excess** was determined by HPLC analysis

to be 94% *ee*. **HPLC** (Chiral-CD, water:acetonitrile = gradient from 80:20 to 5:95, flow rate = 0.5 ml/min, l = 250 nm) tR = 10.2 min (major), 10.5 min (minor); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 – 7.39 (7.40 (d, *J* = 6.8 Hz, 2H), 7.33 (s, 1H), 7.31 (d, *J* = 6.6 Hz, 2H), 6.30 (d, *J* = 10.0 Hz, 1H), 4.73 (d, *J* = 10.0 Hz, 1H), 3.69 (s, 3H), 2.71 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.0, 147.6, 144.2, 133.5, 128.7, 128.0, 119.6, 118.4, 94.9, 62.9, 50.9, 38.4, 24.9.



Methyl (6*S*)-6-(4-methoxyphenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (8f)

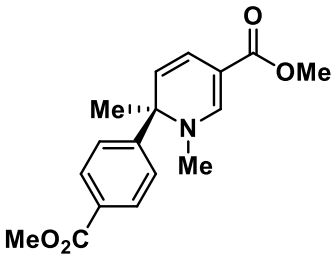
Dihydropyridine **3.8.f** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 4-fluorophenyl Bpin (111.0 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield:** 44.9 mg **(**86%); The **enantiomeric excess** was determined by HPLC analysis to be 94% *ee*. **HPLC** (Chiral-CD, water:acetonitrile = gradient from 90:10 to 5:95, flow rate = 1 ml/min, l = 250 nm) tR = 15.9 min (major), 16.7 min (minor); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -24.3° (*c* 4.33 mg/mL $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 2H), 7.31 (s, 1H), 7.04 (t, *J* = 8.5 Hz, 2H), 6.31 (d, *J* = 9.7 Hz, 1H), 4.75 (d, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 2.71 (s, 3H), 1.73 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 162.8, 161.2, 147.5, 141.6 (d, *J* = 3.1 Hz), 128.4 (d, *J* = 8.1 Hz). 119.8, 118.2, 115.3, 115.2, 94.7, 62.7, 50.8, 38.3, 25.0.



Methyl (6*S*)-6-(4-hydroxymethylphenyl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (3.8g)

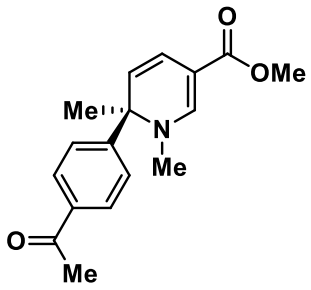
Dihydropyridine **3.8.g** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 4-hydroxymethylphenyl Bpin (117.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for**

dearomatization of *n*-alkyl pyridinium salts. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield:** 50.3 mg (92%); The **enantiomeric excess** was determined by HPLC analysis to be 94% *ee;* **HPLC** (Chiral-CD, water:acetonitrile = gradient from 90:10 to 5:95, flow rate = 1 ml/min, l = 250 nm) tR = 10.6 min (major), 11.0 min (minor); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.31 (s, 1H), 6.27 (d, *J* = 9.8 Hz, 1H), 4.72 (t, *J* = 12.2 Hz, 1H), 4.68 (s, 2H), 3.68 (s, 3H), 2.70 (s, 3H), 1.73 (s, 3H); **^{13}C NMR** (151 MHz, CDCl3) δ 167.2, 147.7, 145.7, 138.0, 129.2, 124.4, 120.2, 117.7, 94.4, 63.2, 50.8, 38.5, 24.9, 21.4.



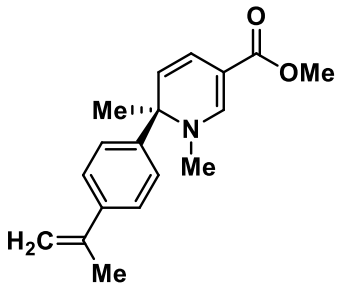
Methyl (6*S*)-6-(4-methoxycarbonylphenyl) -1,6-dihydropyridine-3-carboxylate (3.8.h)

Dihydropyridine **3.8.h** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 4-methoxycarbonylphenyl Bpin (131.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield:** 33.6 mg **(**64%); The **enantiomeric excess** was determined by HPLC analysis to be 92% *ee*; **HPLC** (Chiralpak-IG; 2-propanol:n-hexane = 1:4, flow rate = 1 ml/min, l = 250 nm) tR = 25.7 min (major), 29.0 min (minor); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.33 (s, 1H), 6.30 (d, *J* = 9.9 Hz, 1H), 4.74 (d, *J* = 10.0 Hz, 1H), 3.90 (s, 3H), 3.69 (s, 3H), 2.71 (s, 3H), 1.77 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.0, 166.8, 150.4, 147.7, 129.9, 129.3, 126.5, 119.5, 118.6, 95.0, 63.4, 52.4, 50.9, 38.5, 25.0.



Methyl 6-(4-acetylphenyl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (3.8.i)

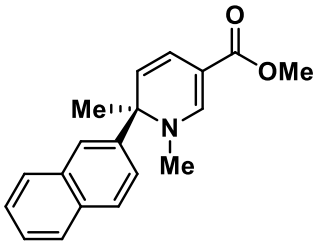
Dihydropyridine **3.8.i** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 4-acetylphenyl Bpin (123.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield** 34.8 mg (61%); ***ee*:** We were not able to achieve acceptable separation for this compound on Chiral HPLC. For *ee*: see derivative **S9**; **TLC:** R_f 0.14 (hexanes:EtOAc, 3:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +376.3° (*c* 0.001 mg/mL $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.27 (s, 1H), 6.26 (dd, *J* = 9.9, 1.2 Hz, 1H), 4.69 (d, *J* = 9.9 Hz, 1H), 3.64 (s, 3H), 2.67 (s, 3H), 2.54 (s, 3H), 1.72 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 197.8, 167.0, 150.6, 147.7, 136.4, 128. 8, 126.8, 119.5, 118.9, 95.5, 63.5, 50.9, 38.5, 26.8, 25.1; **HRMS** (ESI) *m/z* Calcd for $C_{17}H_{20}NO_0$ $[M+H]^+$ 286.1437, found 286.1437.



Methyl (6S)-1,6-dimethyl-6-[4-(prop-1-en-2-yl)phenyl]-1,6-dihydropyridine-3-carboxylate (3.S.9)

3.S.9 was synthesized from dihydropyridine **3.8.i** *via* the following procedure. To a 4 mL vial charged with a magnetic stir bar was added Ph_3PCH_3Br (71.44 mg, 0.20 mmol, 2.0 equiv.). To a separate vial charged with a stir bar was added **3.8.i** (28.5 mg, 0.10 mmol, 1.0 equiv.). Both vials and a third 4 mL vial were pumped into a glovebox. The Ph_3PCH_3Br and **3.8.i** were dissolved in THF (1.0 mL and 0.5 mL, respectively). To the third vial was added K^{t}OBu (23.6 mg, 0.21 mmol, 2.1 equiv.) and THF (1.0 mL). All vials were then removed from the glovebox and cooled to 0 ^{o}C. The solution of K^{t}OBu was added to the solution of Ph_3PCH_3Br and allowed to stir for one hour. The solution of Wittig reagent was added to the solution of **3.8.i** and allowed to warm to room temperature overnight. After 18 hours,

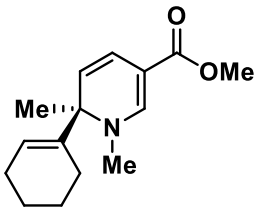
the reaction was diluted to 5 mL with ethyl acetate and filtered over celite. The reaction vials were rinsed with 5 mL of ethyl acetate, and the rinse was filtered over the celite. The filter was then rinsed with an additional 5 mL of ethyl acetate. The filtrate was concentrated under reduced pressure to afford a yellow oil. The oil was adsorbed onto celite and purified *via* automated flash column. The fractions were concentrated under reduced pressure to give **3.S.9** as a clear oil. **Yield** 14.1 mg (50%, 80% BRSM); The **enantiomeric excess** was determined by HPLC analysis to be 92% *ee*; **HPLC** (Chiral-CD; water/acetonitrile = gradient from 90:10 to 5:95, flow rate = 1 ml/min, l = 250 nm) tR = 11.8 min (major), 12.3 min (minor); **TLC:** R*f* 0.15 (hexanes:EtOAc, 9:1); **[α]$_D^{20}$** -568.7° (*c* 0.001 mg/mL $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (dd, J = 21.8, 8.4 Hz, 4H), 7.32 (s, 1H), 6.32 (d, J = 9.9 Hz, 1H), 5.38 (s, 1H), 5.10 (s, 1H), 4.77 (d, J = 9.9 Hz, 1H), 3.71 (s, 3H), 2.74 (s, 3H), 2.15 (s, 3H), 1.75 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 147.6, 144.8, 142.8, 140.6, 126.6, 125.7, 120.0, 118.4, 113.0, 95.1, 63.2, 50.8, 38.4, 24.9, 21.9; **HRMS** (ESI) *m/z* Calcd for $C_{18}H_{22}NO_2$ $[M+H]^+$ 284.1645, found 284.1646.



Methyl (6*S*)-6-(2-napthalen-2-yl)-1,6-dimethyl-1,6-dihydro-pyridine-3-carboxylate (3.8.j)

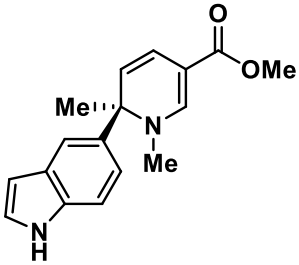
Dihydropyridine **3.8.j** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 2-napthyl Bpin (127.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield** 55.2 (94%); The **enantiomeric excess** was determined by HPLC analysis to be 76% *ee*; **HPLC** (Chiral-CD; water:acetonitrile = gradient from 80:20 to 5:95, flow rate = 1 ml/min, l = 250 nm) tR = 13.7 min (major), 14.9 min (minor); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 14.6, 7.9 Hz, 3H), 7.78 – 7.73 (m, *J* = 10.9 Hz, 2H), 7.54 – 7.47 (m, 2H), 7.39 (s, 1H),

6.36 (d, *J* = 9.8 Hz, 1H), 4.81 (d, *J* = 9.9 Hz, 1H), 3.73 (s, 3H), 2.72 (s, 3H), 1.87 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 147.8, 142.7, 132.8, 132.6, 128.7, 128.4, 127.6, 126.5, 126.4, 125.7, 123.9, 119.8, 118.4, 94.7, 63.5, 50.8, 38.4, 24.9.



Methyl (6*S*)-6-(cyclohex-1-ene-1-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (3.8.k)

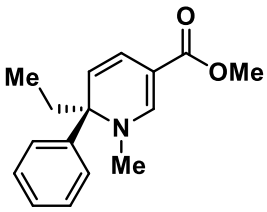
Dihydropyridine **3.8.k** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 1-cyclohexen-1-yl Bpin (104.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield** 16.8 mg (34%); The **enantiomeric excess** was determined by HPLC analysis to be 88% *ee* (250 nm, 25 °C); **HPLC** (Chiral-CD, water/acetonitrile = gradient from 90:10 to 5:95, flow rate = 1 ml/min, l = 250 nm) tR = 14.2 min (major), 14.4 min (minor); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.26 (s, 1H) 6.28 (d, *J* = 9.8 Hz, 1H), 5.61 (s, 1H), 4.54 (d, *J* = 9.8 Hz, 1H), 3.66 (s, 3H), 2.78 (s, 3H), 2.24 (d, *J* = 16.8 Hz, 1H), 2.07 (s, 2H), 1.89 (d, *J* = 16.8 Hz, 1H), 1.67 – 1.56 (m, 2H), 1.55 (d, *J* = 5.4 Hz, 2H), 1.42 (s, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.1, 148.5, 140.2, 122.5, 120.0, 118.9, 94.3, 64.4, 50.6, 37.5, 25.3, 25.2, 24.2, 23.0, 22.2.



Methyl (6*S*)-6-(1*H*-indol-5-yl)-1,6-dimethyl-1,6-dihydropyridine-3-carboxylate (3.8.l)

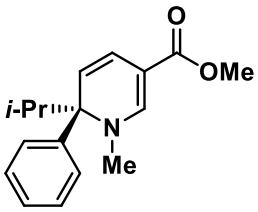
Dihydropyridine **3.8.l** was synthesized from pyridinium **3.5** (63.1 mg, 0.20 mmol, 1.0 equiv.) and 5-indole Bpin (121.6 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield** 42.6 mg (92%); The **enantiomeric excess** was determined by HPLC analysis

to be 92% *ee*; **HPLC** (Chiral-CD; water:acetonitrile = gradient from 90:10 to 5:95, flow rate = 1 ml/min, l = 250 nm) tR = 12.7 min (major), 13.3 min (minor); **^{1}H NMR** (600 MHz, CD_3OD) δ 7.62 (s, 1H), 7.42 (s, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.33 (s, 1H), 7.24 (s, 1H), 6.45 (s, 1H), 6.22 (d, *J* = 9.2 Hz, 1H), 4.82 (d, *J* = 9.1 Hz, 1H), 3.68 (s, 3H), 2.73 (s, 3H), 1.81 (s, 3H); **^{13}C NMR** (151 MHz, CD_3OD) δ 168.2, 148.3, 136.3, 135.5, 127.7, 125.0, 120.8, 120.8, 117.4, 116.5, 111.0, 101.5, 93.3, 63.5, 49.9, 37.4, 24.2.



Methyl (6*S*)-6-ethyl-1-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (3.8.m)

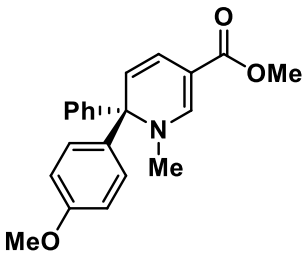
Dihydropyridine **3.8.m** was synthesized from pyridinium **3.7.m** (65.8 mg, 0.20 mmol, 1.0 equiv.) and phenyl Bpin (102.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield:** 32.0 mg **(**62%); The **enantiomeric excess** was determined by HPLC analysis to be 98% *ee;* **HPLC** (Chiral-CD; water:acetonitrile = gradient from 90:10 to 5:95, flow rate = 1 ml/min, l = 250 nm) tR = 11.7 min (major, 12.6 min (minor); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.44 (s, 1H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.29 (dd, *J* = 8.5, 6.1 Hz, 1H), 6.43 (d, *J* = 10.0 Hz, 1H), 4.61 (d, *J* = 10.1 Hz, 1H), 3.73 (s, 3H), 2.70 (s, 3H), 2.33 (dq, *J* = 14.4, 7.2 Hz, 1H), 1.74 (dq, *J* = 14.6, 7.4 Hz, 1H), 1.16 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (151 MHz, $CDCl_3$) δ 167.2, 148.9, 146.0, 128.5, 127.6, 126.7, 119.7, 118.3, 94.2, 67.2, 50.7, 38.0, 29.1, 8.4.



Methyl 1-methyl-6-phenyl-6-(propan-2-yl)-1,6-dihydropyridine-3-carboxylate (3.8.n)

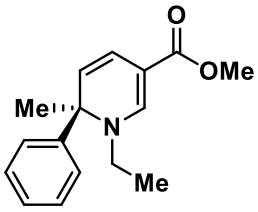
Dihydropyridine **3.8.n** was synthesized from pyridinium **3.7.n** (68.7 mg, 0.20 mmol, 1.0 equiv.) and phenyl Bpin (102.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water

and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield** 5.2 mg (10%); The **enantiomeric excess** was determined by HPLC analysis to be 91% *ee*; **HPLC** (Chiral-CD; water:acetonitrile = gradient from 90:10 to 5:95, flow rate = 1 ml/min, l = 250 nm) tR = 7.76 min (major), 7.58 min (minor); **TLC** R_f 0.15 (hexanes:EtOAc, 3:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +256.0° (*c* 0.002, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.2 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.30 – 7.23 (m, 3H), 7.20 (s, 1H), 6.65 (d, J = 10.4 Hz, 1H), 4.81 (d, J = 10.3 Hz, 1H), 3.70 (s, 3H), 2.89 (p, J = 6.7 Hz, 1H), 2.62 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.3, 147.9, 142.6, 129.0, 128.9, 128.3, 127.6, 122.2, 112.6, 94.5, 50.7, 37.9, 30.6, 17.9, 15.8; **HRMS** (ESI) *m*/*z* Calcd for $C_{17}H_{22}O_2N$ $[M+H]^+$ 272.1645, found 272.1646.



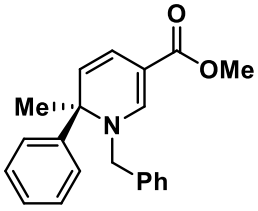
Methyl 6-(4-methoxyphenyl)-1-methyl-6-phenyl-1,6-dihydro-pyridine-3-carboxylate (3.8.o)

Dihydropyridine **3.8.o** was synthesized from pyridinium **3.7.o** (74.5 mg, 0.20 mmol, 1.0 equiv.) and phenyl Bpin (102.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield** 12.7 mg (19 %); The **enantiomeric excess** was determined by HPLC analysis to be 62% *ee*; **HPLC** (Chiralpak-IG; 2-propanol:n-hexane = 1:4, flow rate = 1 ml/min, l = 250 nm) tR = 12.3 min (major), 13.6 min (minor); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -294.3° (*c* 1.47 mg/mL $CHCl_3$); **^{1}H NMR** (600 MHz, CDCl3) δ 7.45 – 7.34 (m, 9H), 7.30 (dd, J = 9.6, 4.3 Hz, 2H), 6.44 (dd, J = 9.9, 1.2 Hz, 1H), 5.12 (d, J = 9.9 Hz, 1H), 3.70 (s, 3H), 2.72 (s, 3H); **^{13}C NMR** (151 MHz, CDCl3) δ 167.2, 158.8, 147.0, 143.1, 135.1, 130.0, 128.5, 127.9, 127.3, 119.8, 118.0, 113.6, 95.5, 70.6, 55.5, 50.9, 40.7.



Methyl (6S)-1-ethyl-6-methyl-6-phenyl-1,6-dihydropyridine-3-Carboxylate (3.8.p)

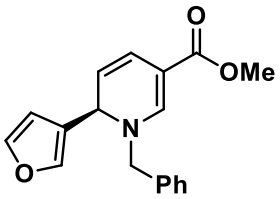
Dihydropyridine **3.8.p** was synthesized from pyridinium **3.7.p** (65.9 mg, 0.20 mmol, 1.0 equiv.) and phenyl Bpin (102.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield** 21.9 mg (69%); The **enantiomeric excess** was determined by HPLC analysis to be 82% *ee*; **HPLC** (Chiral-CD; water:acetonitrile = gradient from 90:10 to 5:95, flow rate = 0.5 ml/min, l = 250 nm) tR = 15.6 min (major), 15.2 min (minor); **^{1}H NMR** (600 MHz, CDCl3) δ 7.46 (d, J = 7.6 Hz, 2H), 7.43 (s, 1H), 7.34 (t, J = 7.7 Hz, 2H), 7.24 (t, J = 3.6 Hz, 1H), 6.30 (dd, J = 9.9, 1.0 Hz, 1H), 4.75 (d, J = 9.9 Hz, 1H), 3.69 (s, 3H), 3.02 – 2.85 (m, 2H), 1.71 (s, 3H), 1.05 (t, J = 7.3 Hz, 3H) **^{13}C NMR** (151 MHz, CDCl3) δ 167.2, 146.4, 145.4, 128.4, 127.6, 126.8, 120.3, 117.8, 94.9, 63.8, 50.8, 44.4, 26.1, 16.3.



Methyl (6S)-1-benzyl-6-methyl-6-phenyl-1,6-dihydropyridine-3-Carboxylate (3.8.q)

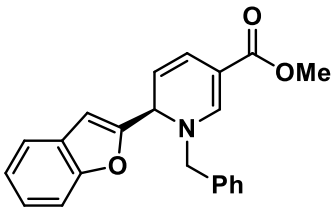
Dihydropyridine **3.8.q** was synthesized from pyridinium **3.7.q** (78.3 mg, 0.20 mmol, 1.0 equiv.) and phenyl Bpin (102.1 mg, 0.50 mmol, 2.5 equiv.) with 50 µL of water and heated to 80°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **^{1}H** and **^{13}C** spectra match those of a reported compound.[10] **Yield** 20.4 mg (64%); The **enantiomeric excess** was determined by HPLC analysis to be 71% *ee*; **HPLC** (Chiralpak-ID; 2-propanol:*n*-hexane = 20:80, flow rate = 1.0 ml/min, l = 250 nm) tR = 8.4 min (major), 9.2 min (minor); **^{1}H NMR** (500 MHz, CDCl3) δ 7.51 (d, J = 7.4 Hz, 2H), 7.35 (t, J = 7.7 Hz, 3H), 7.26 (m, 4H), 7.07 (d, J = 7.1 Hz, 2H), 6.35 (dd, J = 10.0, 1.1 Hz, 1H), 4.85 (d, J = 10.0 Hz, 1H), 4.06 (s,

2H), 3.65 (s, 3H), 1.67 (s, 3H); **^{13}C NMR** (151 MHz, CDCl3) δ 167.1, 146.3, 146.0, 137.6, 128.8, 128.5, 127.8, 127.7, 127.5, 126.9, 121.0, 118.1, 96.0, 63.9, 53.7, 50.8, 26.3.



Methyl 1-benzyl-6-(furan-3-yl)-1,6-dihydropyridine-3-carboxylate (3.10.a)

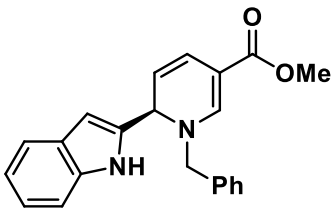
Dihydropyridine **3.10.a** was synthesized from pyridinium **3.9.a** (37.7 mg, 0.10 mmol, 1.0 equiv.) and 3-furanyl Bpin (38.8 mg, 0.25 mmol, 2.5 equiv.) with 50 µL of water and heated to 60°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield:** 25.6 mg (87 %); The **enantiomeric excess** was determined by HPLC analysis to be 95% *ee*; **HPLC** (Chiralpak-ID; 2-propanol:n-hexane = 20:80, flow rate = 1 ml/min, l = 250 nm) tR = 8.9 min (major), 8.3 min (minor); **TLC** R_f 0.22 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ - 225.8° (*c* 0.009, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (d, J = 1.5 Hz, 1H), 7.44 – 7.31 (m, 4H), 7.31 – 7.25 (m, 3H), 6.47 (dd, J = 9.1, 1.6 Hz, 2H), 5.07 – 4.94 (m, 2H), 4.28 (d, J = 2.7 Hz, 2H), 3.72 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 146.9, 144.2, 139.4, 135.5, 129.1, 128.4, 128.0, 126.0, 121.2, 113.0, 109.9, 96.7, 57.4, 51.9, 50.9; **HRMS** (ESI) *m/z* Calcd for $C_{18}H_{18}NO_3$ $[M+H]^+$ 296.1281, found 296.1281.



Methyl 6-(1-benzofuran-2-yl)-1-benzyl-1,6-dihydropyridine-3-carboxylate (3.10.b)

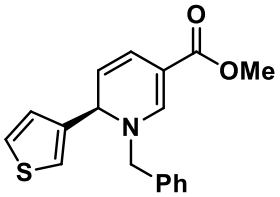
Dihydropyridine **10b** was synthesized from pyridinium **9a** (37.7 mg, 0.10 mmol, 1.0 equiv.) and 2-benzofuranyl Bpin (48.8 mg, 0.25 mmol, 2.5 equiv.) with 50 µL of water and heated to 60°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield:** 30.0 mg (87 %); The **enantiomeric excess** was determined by HPLC analysis to be 92% *ee;* **HPLC** (Chiralpak-ID; 2-propanol:n-hexane = 20:80, flow rate = 1 ml/min, l = 250 nm) tR = 9.6 min (major), 8.8 min (minor); **TLC** R_f 0.25 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -

222.2° (*c* 0.012, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.58 – 7.52 (m, 1H), 7.51 – 7.46 (m, 2H), 7.45 – 7.27 (m, 6H), 7.23 (t, J = 7.5 Hz, 1H), 6.66 – 6.60 (m, 2H), 5.25 (d, J = 4.7 Hz, 1H), 5.10 (dd, J = 9.7, 4.8 Hz, 1H), 4.50 (d, J = 15.1 Hz, 1H), 4.40 (d, J = 15.1 Hz, 1H), 3.73 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.1, 156.5, 155.3, 146.4, 135.5, 129.1, 128.4, 128.1, 128.1, 124.7, 123.1, 123.1, 121.4, 111.7, 109.9, 105.3, 97.6, 58.4, 54.2, 51.0; **HRMS** (ESI) *m/z* Calcd for $C_{22}H_{20}NO_3$ $[M+H]^+$ 346.1438, found 346.1437.



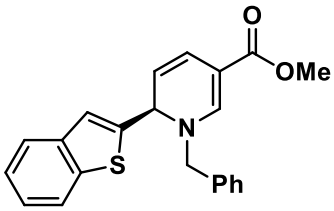
Methyl 1-benzyl-6-(1H-indol-2-yl)-1,6-dihydropyridine-3-carboxylate (3.10.c)

Dihydropyridine **3.10.c** was synthesized from pyridinium **3.9.a** (37.7 mg, 0.10 mmol, 1.0 equiv.) and indole-2 Bpin (48.6 mg, 0.25 mmol, 2.5 equiv.) with 50 µL of water and heated to 60°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield:** 48.6 mg (71 %); The **enantiomeric excess** was determined by HPLC analysis to be 91% *ee*; **HPLC** (Chiralpak-ID; 2-propanol:n-hexane = 20:80, flow rate = 1 ml/min, l = 250 nm) tR = 8.1 min (major), 6.4 min (minor); **TLC** R_f 0.16 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ - 75.5° (*c* 0.005, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.52 (s, 0H), 7.44 – 7.34 (m, 4H), 7.33 – 7.28 (m, 2H), 7.22 (t, J = 8.2 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.64 (d, J = 9.9 Hz, 1H), 6.34 (s, 1H), 5.23 (d, J = 4.6 Hz, 1H), 5.11 (dd, J = 9.9, 4.6 Hz, 1H), 4.35 (d, J = 15.0 Hz, 1H), 4.25 (d, J = 15.1 Hz, 1H), 3.76 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.1, 146.9, 136.9, 136.8, 135.2, 129.2, 128.5, 128.1, 127.8, 122.9, 122.2, 121.0, 120.3, 111.7, 111.4, 101.2, 96.4, 57.5, 54.2, 51.1. **HRMS** (ESI) *m/z* Calcd for $C_{22}H_{21}N_2O_2$ $[M+H]^+$ 345.1598, found 345.1597.



Methyl 1-benzyl-6-(thiophen-3-yl)-1,6-dihydropyridine-3-carboxylate (3.10.d)

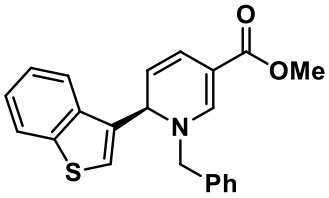
Dihydropyridine **3.10.d** was synthesized from pyridinium **3.9.a** (37.7 mg, 0.10 mmol, 1.0 equiv.) and thiophene-3 Bpin (42.0 mg, 0.25 mmol, 2.5 equiv.) with 50 µL of water and heated to 60°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield:** 23.1 mg (74 %); The **enantiomeric excess** was determined by HPLC analysis to be 95% *ee*; **HPLC** (Chiralpak-ID; 2-propanol:n-hexane = 20:80, flow rate = 1 ml/min, l = 250 nm) tR = 9.1 min (major), 8.6 min (minor); **TLC** R_f 0.25 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -270.3° (*c* 0.009, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.42 – 7.28 (m, 5H), 7.17 (dd, J = 5.0, 1.3 Hz, 1H), 7.11 (d, J = 1.7 Hz, 1H), 6.46 (d, J = 9.8 Hz, 1H), 5.13 (d, J = 4.5 Hz, 1H), 5.05 (dd, J = 9.9, 4.5 Hz, 1H), 4.27 (d, J = 15.1 Hz, 1H), 4.21 (d, J = 15.1 Hz, 1H), 3.72 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 146.8, 143.1, 135.5, 129.1, 129.1, 128.3, 128.0, 127.1, 127.0, 122.3, 120.7, 113.8, 96.5, 57.7, 56.0, 50.9; **HRMS** (ESI) *m/z* Calcd for $C_{18}H_{18}NO_2S$ $[M+H]^+$ 312.1052, found 312.1053.



Methyl 6-(1-benzothiophen-2-yl)-1-benzyl-1,6-dihydropyridine-3-carboxylate (3.10.e)

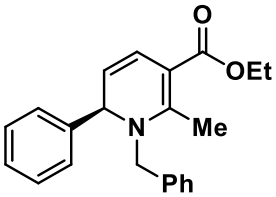
Dihydropyridine **3.10.e** was synthesized from pyridinium **3.9.a** (37.7 mg, 0.10 mmol, 1.0 equiv.) and benzothiophene-2 Bpin (52.0 mg, 0.25 mmol, 2.5 equiv.) with 50 µL of water and heated to 60°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield:** 32.3 mg (89 %); The **enantiomeric excess** was determined by HPLC analysis to be 87% *ee*; **HPLC** (Chiralpak-ID; 2-propanol:n-hexane = 80:20, flow rate = 1 ml/min, l = 250 nm) tR = 13.5 min (major), 11.1 min (minor); **TLC** R_f 0.26 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -314.8° (*c* 0.012, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, J = 6.9 Hz, 1H), 7.73 (d,

J = 7.1 Hz, 1H), 7.50 (s, 1H), 7.44 – 7.22 (m, 7H), 7.13 (s, 1H), 6.55 (d, J = 9.8 Hz, 1H), 5.39 (d, J = 4.5 Hz, 1H), 5.15 (dd, J = 9.8, 4.6 Hz, 1H), 4.39 (d, J = 15.1 Hz, 1H), 4.34 (d, J = 15.2 Hz, 1H), 3.74 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.0, 146.3, 146.0, 140.4, 139.3, 135.3, 129.2, 128.5, 128.1, 124.8, 124.6, 124.0, 122.8, 121.6, 121.5, 113.3, 97.3, 57.8, 56.6, 51.0; **HRMS** (ESI) *m/z* Calcd for $C_{22}H_{20}NO_2S$ $[M+H]^+$ 362.1209, found 362.1209.



Methyl 6-(1-benzothiophen-3-yl)-1-benzyl-1,6-dihydropyridine-3-carboxylate (3.10.f)

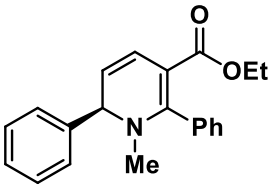
Dihydropyridine **3.10.f** was synthesized from pyridinium **3.9.a** (37.7 mg, 0.10 mmol, 1.0 equiv.) and benzothiophene-2 Bpin (52.0 mg, 0.25 mmol, 2.5 equiv.) with 50 µL of water and heated to 60°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield:** 33.4 mg (92 %); The **enantiomeric excess** was determined by HPLC analysis to be 82% *ee;* **HPLC** (Chiralpak-ID; 2-propanol:n-hexane = 20:80, flow rate = 1 ml/min, l = 250 nm) tR = 9.6 min (major), 8.6 min (minor); **TLC** R_f 0.23 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ -153.4° (*c* 0.015 $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 1H), 7.92 – 7.84 (m, 1H), 7.62 (s, 1H), 7.49 – 7.33 (m, 5H), 7.26 (s, 1H), 7.23 – 7.12 (m, 2H), 6.48 (dt, J = 10.0, 1.6 Hz, 1H), 5.59 (dd, J = 3.8, 1.6 Hz, 1H), 5.04 (dd, J = 10.1, 3.9 Hz, 1H), 4.23 (d, J = 15.2 Hz, 1H), 4.06 (d, J = 15.3 Hz, 1H), 3.77 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.3, 147.4, 141.3, 137.1, 136.8, 135.1, 129.1, 128.4, 128.0, 124.9, 124.8, 124.6, 123.2, 122.7, 121.2, 113.6, 96.0, 57.9, 56.7, 51.0; **HRMS** (ESI) *m/z* Calcd for $C_{22}H_{20}NO_2S$ $[M+H]^+$ 362.1209, found 362.1209.



Ethyl 1-benzyl-2-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (3.10.g)

Dihydropyridine **3.10.g** was synthesized from pyridinium **3.9.g** (40.5 mg, 0.10 mmol, 1.0 equiv.) and phenyl Bpin (51.1 mg, 0.25 mmol, 2.5 equiv.) with 100 µL of water

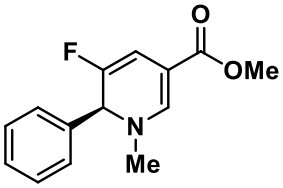
and heated to 60°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. Product was isolated on a manual flash column, 10% – 20% PhMe:Hexanes. Yield 20.7 mg (62%); The **enantiomeric excess** was determined by HPLC analysis to be 96% *ee;* **HPLC** (Chiralpak-ID; 2-propanol:n-hexane = 5:95, flow rate = 1 ml/min, l = 250 nm) tR = 10.7 min (major), 9.7 min (minor); **TLC** Rf 0.15 (hexanes:EtOAc 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -569.2° (*c* 0.010 $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 3H), 7.28 – 7.21 (m, 5H), 7.20 – 7.16 (m, 2H), 6.59 (d, J = 9.9 Hz, 1H), 5.10 (dd, J = 9.9, 5.1 Hz, 1H), 4.96 (d, J = 5.1 Hz, 1H), 4.78 (d, J = 17.0 Hz, 1H), 4.10 (qd, J = 7.1, 1.8 Hz, 2H), 2.48 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7, 156.4, 143.4, 136.9, 129.1, 129.0, 128.1, 127.7, 126.6, 126.4, 123.2, 112.6, 97.1, 64.0, 59.3, 52.4, 16.5, 14.7; **HRMS** (ESI) m/z Calcd for $C_{22}H_{24}O_2N$ [M+H]+ 334.1801, found 334.1794.



Ethyl 1-methyl-2,6-diphenyl-1,6-dihydropyridine-3-carboxylate (3.10.h)

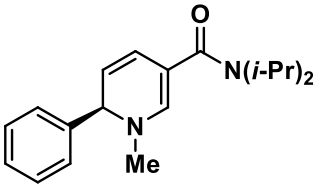
Dihydropyridine **3.10.h** was synthesized from pyridinium **3.9.h** (39.1 mg, 0.10 mmol, 1.0 equiv.) and phenyl Bpin (51.1 mg, 0.25 mmol, 2.5 equiv.) with 100 µL of water and heated to 40°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield:** 14.8 mg (49%); The **enantiomeric excess** was determined by HPLC analysis to be 94% *ee*; **HPLC** (Chiral-CD; water:acetonitrile = gradient from 90:10 to 5:95, flow rate = 1 ml/min, l = 250 nm) tR = 4.6 min (major), 5.0 min (minor); **TLC:** Rf 0.01 (hexanes:EtOAc 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -320.4° (*c* 0.007; $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 3H), 7.27 – 7.19 (m, 5H), 7.21 – 7.15 (m, 2H), 6.58 (d, J = 9.9 Hz, 1H), 5.08 (dd, J = 9.9, 5.1 Hz, 1H), 4.95 (d, J = 5.1 Hz, 1H), 4.77 (d, J = 17.0 Hz, 1H), 4.09 (qd, J = 7.1, 1.8 Hz, 2H), 2.47 (s, 3H), 1.22 (t, J = 7.1 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.7, 156.4, 143.4, 136.9, 129.1, 129.0, 128.1, 127.7,

126.7, 126.4, 123.2, 112.6, 97.1, 64.0, 59.3, 52.4, 16.5, 14.7; **HRMS** (ESI) *m/z* Calcd for $C_{21}H_{22}O_2N$ $[M+H]^+$ 320.1645, found 320.1636.



Methyl 5-fluoro-1-methyl-6-phenyl-1,6-dihydropyridine-3-carboxylate (3.10.i)

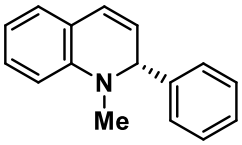
Dihydropyridine **3.10.i** was synthesized from pyridinium **3.9.i** (39.1 mg, 0.10 mmol, 1.0 equiv.) and phenyl Bpin (51.1 mg, 0.25 mmol, 2.5 equiv.) with 250 µL of water and stirred at 23°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield** 4.9 mg (20%); The **enantiomeric excess** was determined by HPLC analysis to be 92% *ee*; **HPLC** (Chiralpak-ID; 2-propanol:n-hexane = 10:90, flow rate = 1 ml/min, l = 250 nm) tR = 14.7 min (major), 11.6 min (minor); **TLC** R_f 0.31 (hexanes:EtOAc, 4:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -11.7° (*c* 0.001, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 5H), 7.27 (s, 2H), 6.17 (d, J = 13.2 Hz, 1H), 5.14 (d, J = 4.1 Hz, 1H), 3.72 (s, 3H), 2.84 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.7 (d, J = 3.5 Hz), 149.8, 147.8, 143.3, 138.7 (d, J = 3.3 Hz), 129.2, 129.0, 127.4, 99.5 (d, J = 17.9 Hz), 64.6 (d, J = 34.8 Hz), 51.0, 41.2 (d, J = 1.8 Hz); **^{19}F NMR** (471 MHz, $CDCl_3$) δ -122.87; **HRMS** (ESI) *m/z* Calcd for $C_{14}H_{15}O_2NF$ $[M+H]^+$ 248.1081, found 248.1082.



1-methyl-6-phenyl-N,N-di(propan-2-yl)-1,6-dihydropyridine-3-carboxamide (3.10.j)

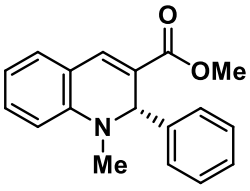
Dihydropyridine **3.10.j** was synthesized from pyridinium **3.9.j** (37.0 mg, 0.10 mmol, 1.0 equiv.) and phenyl Bpin (51.1 mg, 0.25 mmol, 2.5 equiv.) with 250 µL of water and heated to 60°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield** 24.4 mg (41%); The **enantiomeric excess** was determined by HPLC analysis to be 45% *ee*; **HPLC** (Chiralpak-IG; 2-propanol:n-hexane = 20:80, flow rate = 1 ml/min, l = 250 nm) tR = 10.2 min (major), 11.9 min (minor); **TLC** R_f 0.15 (hexanes:EtOAc, 3:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$:

-36.0° (*c* 0.009, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 6.84 (s, 1H), 5.98 (dt, *J* = 9.8, 1.3 Hz, 1H), 5.06 (d, *J* = 4.2 Hz, 1H), 4.97 – 4.93 (m, 1H), 3.77 – 3.69 (m, 2H), 2.71 (s, 3H), 1.30 (dd, *J* = 6.5, 5.2 Hz, 12H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.4, 143.8, 143.1, 128.9, 128.1, 126.9, 121.7, 112.9, 101.5, 75.1, 64.3, 48.1, 41.5, 25.0, 21.6, 21.5; **HRMS** (ESI) *m*/*z* Calcd for $C_{19}H_{27}ON_2$ $[M+H]^+$ 299.2117, found 299.2110.



1-methyl-2-phenyl-1,2-dihydroquinoline (3.10.k)

Dihydropyridine **3.10.k** was synthesized from pyridinium **3.9.k** (29.3 mg, 0.10 mmol, 1.0 equiv.) and phenyl Bpin (51.1 mg, 0.25 mmol, 2.5 equiv.) with 50 µL of water and heated to 40°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. Product was isolated on a manual flash column, EtOAc:Hexanes 10% – 20% PhMe:Hexanes. **Yield** 31.2 mg (71%); The **enantiomeric excess** was determined by HPLC analysis to be 91% *ee*; **HPLC** (Chiralpak-IC; 2-propanol:n-hexane = 10:90, flow rate = 1 ml/min, l = 250 nm) tR = 5.68 min (major), 6.75 min (minor); **TLC** R_f 0.38 (hexanes:PhMe, 80:20); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -198.1° (*c* 0.005, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 – 7.14 (m, 5H), 7.01 (td, *J* = 7.9, 1.6 Hz, 1H), 6.83 (dd, *J* = 7.3, 1.5 Hz, 1H), 6.53 (td, *J* = 7.4, 0.9 Hz, 1H), 6.36 (d, *J* = 8.1 Hz, 1H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.58 (dd, *J* = 9.8, 4.9 Hz, 1H), 5.07 (dd, *J* = 4.9, 1.2 Hz, 1H), 2.63 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.8, 142.6, 129.4, 128.7, 127.8, 126.9, 126.4, 125.5, 124.5, 120.8, 116.4, 109.5, 65.8, 36.0; **HRMS** (ESI) *m*/*z* Calcd for $C_{16}H_{16}N$ $[M+H]^+$ 222.1277, found 222.1278.

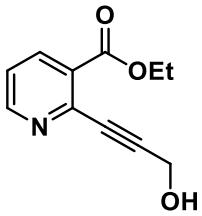


Methyl 1-methyl-2-phenyl-1,2-dihydroquinoline-3-carboxylate (3.10.l)

Dihydropyridine **3.10.l** was synthesized from pyridinium **3.9.l** (35.1 mg, 0.10 mmol, 1.0 equiv.) and phenyl Bpin (51.1 mg, 0.25 mmol, 2.5 equiv.) with 50 µL of water and heated to 40°C according to **the general procedure for dearomatization of *n*-alkyl pyridinium salts**. **Yield:** 26.1 mg (39%); The **enantiomeric excess** was determined by

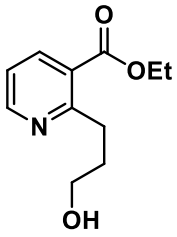
HPLC analysis to be 82% *ee*; **HPLC** (Chiralpak-IG; 2-propanol:n-hexane = 20:80, flow rate = 1 ml/min, l = 250 nm) tR = 6.9 min (major), 6.3 min (minor); **TLC** R_f *0*.45 (Toluene); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ -214.8° (*c* 0.012, $CHCl_3$); **^{1}H NMR** (500 MHz, CDCl3) δ 7.54 (s, 1H), 7.33 – 7.28 (m, 2H), 7.25 – 7.18 (m, 4H), 7.12 (d, J = 5.9 Hz, 1H), 6.67 (t, J = 6.9 Hz, 1H), 6.45 (d, J = 8.2 Hz, 1H), 5.45 (s, 1H), 3.72 (s, 3H), 2.80 (s, 3H); **^{13}C NMR** (126 MHz, CDCl3) δ 166.2, 146.1, 140.9, 134.7, 132.5, 130.0, 128.6, 128.2, 126.7, 124.1, 119.9, 116.9, 110.8, 63.7, 51.8, 36.4; **HRMS** (ESI) *m/z* Calcd for $C_{18}H_{18}NO_2$ $[M+H]^+$ 280.1332, found 280.1332. 334.1794.

3.6.5. Synthesis of Nuphar Indolizidine (3.2) :



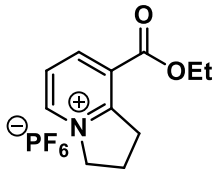
Ethyl 2-(3-hydroxyprop-1-yn-1-yl)pyridine-3-carboxylate (**3.12)**

The procedure was modified from a previously reported reaction.[24] To a Schlenk tube (10 mL) charged with N_2 and a magnetic stirbar was added ethyl-2-iodonicotinate (500.0 mg, 1.80 mmol, 1.0 equiv.), propargyl alcohol (0.13 mL, 2.16 mmol, 1.2 equiv.), Et_3N (1.00 mL, 7.2 mmol, 4.0 equiv.), CuI (34.3 mg, 0.18 mmol, 0.10 equiv.), $PdCl_2(Ph_3P)_2$ (63.1 mg, 0.09 mmol, 0.05 equiv.) and THF (3.6 mL) The reaction was stirred under N_2, at 30 °C for 2 hours. After cooling to room temperature, the reaction was filtered over silica and the solids were rinsed with EtOAc (50 mL). The filtrate was concentrated under reduced pressure and purified *via* flash column chromatography to afford **3.12** as a light orange solid. **Yield** 440.5 mg (91%); **TLC** R_f 0.22 (hexanes: EtOAc, 1:1.5); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.70 (dd, *J*=4.8, 1.7 Hz, 1H), 8.25 (dd, *J*=8.0, 1.7 Hz, 1H), 7.33 (dd, *J*=8.0, 4.8 Hz, 1H), 4.58 (d, *J*=5.4 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 2.03 (t, *J*=5.9 Hz, 1H), 1.42 (t, *J*=7.1 Hz, 3H); **^{13}C NMR (**126 MHz, $CDCl_3$) δ 165.0, 152.5, 142.3, 138.3, 128.7, 122.7, 93.1, 84.1, 62.0, 51.7, 14.3 **HRMS** (ESI) *m/z* Calcd for $C_{11}H_{11}NaNO_3$ $[M+Na]^+$: 228.0637 found: 228.0639. Both ^{1}H NMR and ^{13}C NMR matched previously reported spectral data of **(12)**.[24]



Ethyl 2-(3-hydroxypropyl)pyridine-3-carboxylate (3.13)

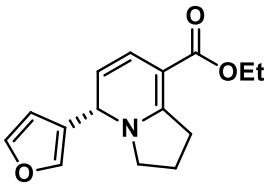
The procedure was modified from a previously reported reaction.[23] A sealed vial (20 mL) with magnetic stirbar was charged with **3.12** (1.04 g, 5.07 mmol, 1.0 equiv.), PtO_2 (28.8 mg, 0.13 mmol 0.025 equiv.), and MeOH (7.25 mL). The solution was stirred under H_2 (1 atm) at room temperature for 18 hours, after which additional PtO_2 (20.0 mg, 0.09 mmol, 0.015 equiv.) was added. After 5 hours the reaction was filtered over celite and the solids were rinsed with DCM (30 mL). The filtrate was concentrated under reduced pressure and purified *via* flash column chromatography to afford **3.13** as a light yellow oil**. Yield** 955 mg (90%); **TLC** R_f 0.31 (hexanes: EtOAc 1:9); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.63 (dd, J=4.7, 1.6 Hz, 1H), 8.17 (dd, J=7.9, 1.7 Hz, 1H), 7.23 (dd. J=7.9, 4.8 Hz, 1H), 4.39 (q, J=7.1 Hz, 2H), 3.64 (t, J=5.8 Hz, 2H), 3.42 (br s, 1H), 3.31 (t, J=6.9 Hz, 2H), 2.08 - 2.01 (m, 2H), 1.40 (t, J=7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.6, 162.5, 151.4, 138.6, 126.0, 120.9, 61.7, 61.5, 33.0, 32.1, 14.1; **HRMS** (ESI) *m/z* Calcd for $C_{11}H_{16}NO_3$ $[M+H]^+$: 210.1130 found: 210.1139.



8-(ethoxycarbonyl)-2,3-dihydro-1H-indolizin-4-ium hexafluorophosphate (3.14)

The procedure was modified from a previously reported reaction.[23] To a round-bottom flask (200 mL) charged with N_2 and a magnetic stirbar was added **3.13** (3.20 g, 15.5 mmol, 1.0 equiv.) and DCM (77.3 mL). The reaction was cooled to 0 °C, after which Et_3N (5.76 mL, 41.9 mmol, 2.67 equiv.) was added. Still at 0 °C, mesyl chloride was added dropwise. The reaction was allowed to stir and slowly warm to room temperature over 3 hours. The resulting mixture was concentrated under reduced pressure to give a dark purple waxy solid. The resulting solid was solvated in 50 mL of DCM and added to a 250 mL round-bottom flask. To the flask was added an aqueous solution of KPF_6 (5.71 g, 31.00 mmol, 2.00 equiv) in 50 mL of water. The biphasic

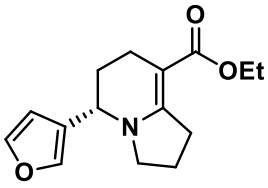
mixture was allowed to stir rapidly at room temperature for 16 hours. The resulting layers were separated, and the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 which was then removed by filtration. The resulting dark red solution was concentrated under reduced pressure to give a mixture of dark red and white solids. The solids were solvated in DCM (20 mL) and the resulting solution was added dropwise to rapidly stirring $CHCl_3$ (250 mL). The precipitated solids were removed by filtration and dried under reduced pressure. The resulting crude off-white solids were used as-is without further purification. **Yield** 5226.6 mg (100%); **^{1}H NMR** (500 MHz, DMSO-d6) δ 9.20 (d, J = 6.0 Hz, 1H), 8.90 (d, J = 7.9 Hz, 1H), 8.09 (t, J = 7.0 Hz, 1H), 4.86 (t, J = 7.8 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 3.73 (t, J = 7.7 Hz, 2H), 2.40 (p, J = 7.8 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (126 MHz, DMSO-d6) δ 162.74, 161.00, 146.00, 145.26, 127.33, 126.18, 62.94, 59.74, 34.10, 21.29, 14.37; **^{19}F NMR** (471 MHz, DMSO-d6) δ -69.40, -70.91; **^{31}P NMR** (203 MHz, DMSO-d6) δ -133.66, -137.17, -140.68, -144.19, -147.71, -151.22, -154.73; **HRMS** (ESI) m/z Calcd for $C_{11}H_{14}NO_2$ $[M\text{-}PF_6]^+$: 192.1019 found: 192.1020



Ethyl (5S)-5-(furan-3-yl)-1,2,3,5-tetrahydroindolizine-8-carboxylate (3.15)

In a glove box, to a vial (4 mL) charged with a magnetic stirbar, **3.14** (67.44 mg, 0.2 mmol, 1.0 equiv.), 3-furanboronic acid pinacol ester (97.00 mg, 0.50 mmol, 2.5 equiv.), and Na_2CO_3 (63.59 mg, 0.60 mmol, 3.0 equiv.) was added a solution of $Rh(COD)_2BF_4$ (4.87 mg, 0.012 mmol, 0.06 equiv.) and S-BINAP (8.71 mg, 0.014 mmol, 0.07 equiv.) in dioxane (2.00 mL). The Rh and BINAP in dioxane solution was stirred for 30 minutes in the glovebox before addition to the 4 mL vial with substrate. The 4 mL vial was sealed with a septa cap in the glove box, and on the bench-top, degassed H_2O (0.100 mL) was added. The reaction was let stir at room

temperature. After 12 hours, the reaction was diluted with EtOAc (1 mL) and $MgSO_4$ was added into the solution. The resulting mixture was filtered over Al_2O_3, and the solids were rinsed with EtOAc (5 mL). The filtrate was concentrated under reduced pressure and purified *via* flash column chromatography to afford **3.15** as a dark green oil**. Yield** 40.8 mg (79%); The **enantiomeric excess** was determined by HPLC to be 94% *ee*; **HPLC** (Chiral-CD Water:Acetonitrile = gradient from 75:25 to 95:5, flow rate = 1 ml/min, l = 250 nm) tR = 7.7 min (major), 8.2 min (minor); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** +17.4° (*c* 0.003 $CHCl_3$); **TLC** R_f 0.26 (hexanes:EtOAc 1:4); ^{1}**H NMR** (600 MHz, $CDCl_3$) δ 7.39 (t, J=1.5 Hz, 1H), 7.35 (s 1H). 6.57 (dd, J=9.9, 1.0 Hz, 1H), 6.43 (d, J=0.9 Hz, 1H), 5.27 (d, J=3.7 Hz, 1H), 4.94 (dd, J=9.9, 3.9 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.33 - 2.98 (m, 4H), 1.96 - 1.89 (m, 2H), 1.28 (t, J=7.1 Hz, 3H); **^{13}C NMR** (126 MHz, CDCl3) δ 166.9, 160.8, 144.0, 139.5, 126.7, 123.5, 110.2, 90.8, 58.9, 53.1, 51.2, 33.0, 20.3, 14.9; **HRMS** (ESI) *m/z* Calcd for $C_{15}H_{18}NO_3$ $[M+H]^+$: 260.1287 found: 260.1284.



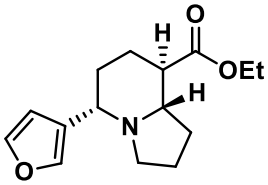
Ethyl (5S)-5-(furan-3-yl)-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (3.16)

The procedure was modified from a previously reported reaction.[10] A sealed vial (20 mL) with a magnetic stirbar was charged with **3.15** (122.3 mg, 0.472 mmol, 1.0 equiv.), 10% Pd/C (50.2 mg, 0.047 mmol, 0.1 equiv.), and 3:1 MeOH:EtOAc (1.5 mL:0.5 mL). The reaction was stirred under H_2 at room temperature for 1 hour and filtered over celite. The solids were rinsed with EtOAc (10 mL) and the resulting filtrate was concentrated under reduced pressure and purified *via* flash column chromatography to afford **3.16** as an orange oil. **Yield** 72.2 mg (59%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +76.4° (*c* 0.002 $CHCl_3$); **TLC** R_f 0.26 (hexanes:EtOAc 1:4); **^{1}H NMR** (600 MHz, C_6D_6) δ 7.01 (t, J=1.6 Hz, 1H), 6.89 (br s, 1H), 5.93 (d, J=0.9 Hz, 1H), 4.28 (qd, J=7.1, 0.6 Hz, 2H), 3.72 (t, J=4.8 Hz, 1H), 3.21 (t, J=7.7 Hz, 2H), 2.80 (ddd, J=9.1, 7.8, 5.9 Hz, 1H), 2.76 -

2.69 (m, 1H), 2.54 - 2.44 (m, 2H), 1.75 - 1.62 (m, 2H), 1.42 - 1.29 (m, 2H), 1.18 (t, J=7.1 Hz, 3H); **^{13}C NMR** (126 MHz, CD_3OD) δ 171.0, 161.3, 144.9, 141.0, 127.6, 109.9, 88.5, 59.9, 52.4, 51.8, 34.2, 29.4, 21.9, 19.9, 15.1; **HRMS** (ESI) *m/z* Calcd for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1443 found: 262.1437.

Ethyl (5S,8R,8aS)-5-(furan-3-yl)octahydroindolizine-8-carboxylate (3.17) & Ethyl (5S,8S,8aS)-5-(furan-3-yl)octahydroindolizine-8-carboxylate (3.S.10)

The procedure was modified from a previously reported reaction.[10] To a Schlenk tube (10 mL) charged with N_2, a magnetic stirbar, and **3.16** (121.7 mg, 0.466 mmol, 1.0 equiv.) was added a solution of $NaCNBH_3$ (35.13 mg, 0.559 mmol, 1.2 equiv.) in MeOH (4.66 mL). Acetic acid (2.33 mL) was added, and the solution was stirred for 3 hours at room temperature. The volatiles were removed under reduced pressure and the resulting mixture was diluted with DCM (8 mL). The solution was quenched slowly with $NaHCO_3$ (14 mL). The layers were separated, and the aqueous layer was extracted with DCM (3x10 mL). The organic layers were combined and after drying with $MgSO_4$ the mixture was filtered over celite. The solids were rinsed with DCM (10 mL) and the filtrate was concentrated under reduced pressure. The resulting diastereomers were purified and separated *via* flash column chromatography to afford **3.17** and **3.S.10** as yellow solids. **Yield** 62.2 mg **3.17** and 25.8 mg **3.S.10** (2.4:1 **17:10**, 72% overall yield).

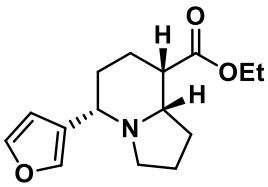


Ethyl (5S,8R,8aS)-5-(furan-3-yl)octahydroindolizine-8-carboxylate **(3.17)** $[\alpha]_D^{20}$: -98.1° (*c* 0.006g $CHCl_3$); **TLC** R_f 0.17 (DCM:MeOH 24:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 - 7.32 (m, 2H), 6.42 (s, 1H). 4.14 (q, J=7.1 Hz, 2H), 3.01 (dd, J=10.6, 1.8 Hz, 1H), 2.88 (t, J=8.4 Hz, 1H), 2.40 - 2.29 (m, 1H), 2.20 - 2.12 (m, 1H), 2.10 - 2.01 (m, 1H), 2.01 - 1.92 (m, 2H), 1.84 - 1.76 (m, 1H), 1.74 - 1.50 (m, 5H), 1.26 (t, J=7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.6, 143.0, 139.5, 127.9, 109.7, 65.9, 60.4, 59.2,

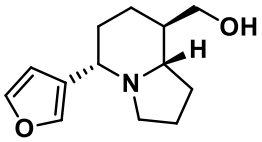
52.6, 47.9, 33.3, 29.3, 28.6, 20.2, 14.4; **HRMS** (ESI) *m/z* Calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1600 found: 264.1587.

Ethyl (5S,8S,8aS)-5-(furan-3-yl)octahydroindolizine-8-carboxylate (**3.S10)**

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +37.5° (*c* 0.005 $CHCl_3$); **TLC** R_f 0.11 (DCM:MeOH 24:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (s, 2H), 6.45 (s, 1H), 4.18 (q, J=7.1 Hz, 2H), 2.96 - 2.86 (m, 2H), 2.77 (s, 1H), 2.33 - 2.18 (m, 2H), 2.17 - 2.10 (m, 1H), 1.95 - 1.80 (m, 3H), 1.67 - 1.50 (m, 4H), 1.28 (t, J=7.1 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.1, 142.7, 139.2, 127.8, 109.9, 65.4, 60.4, 59.9, 53.3, 41.6, 30.2, 27.8, 27.2, 20.0, 14.4; **HRMS** (ESI) *m/z* Calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1600 found: 264.1589.

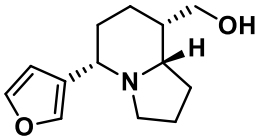


[(5S,8R,8aS)-5-(furan-3-yl)octahydroindolizin-8-yl]methanol (3.18)



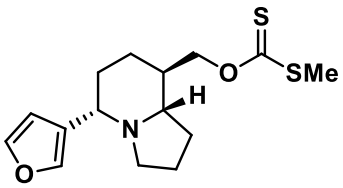
The procedure was modified from a previously reported reaction.[26] A Schlenk tube (10 mL), charged with N_2, a magnetic stirbar, and **3.17** (68.7 mg, 0.261, 1.0 equiv.) in Et_2O (1.31 mL), was cooled to 0 °C. A mixture of $LiAlH_4$ (44.4 mg, 1.17 mmol, 4.5 equiv.) in Et_2O (1.31 mL) was added and the resulting solution was allowed to warm to room temperature. After stirring for 3 hours, the solution was cooled to 0 °C and H_2O (0.05 mL), 15% aq. NaOH (0.05 mL), and H_2O (0.15 mL) were added dropwise in succession. The resulting mixture was allowed to warm to room temperature, after which $MgSO_4$ was added to the mixture. After stirring for 15 minutes, the mixture was filtered over celite and the solids were rinsed with DCM (10 mL). The filtrate was concentrated under reduced pressure and the resulting off-white solid **3.18** was used without further purification. **Yield** 48.4 mg (84%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$**:** -104.7° (*c* 0.004 $CHCl_3$); **TLC**: R_f 0.17 (DCM:MeOH:30% NH_4OH in H_2O 12.8:1.0:0.03) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 6.45 (s, 1H), 3.68 (dd, J=10.7, 4.6 Hz, 1H), 3.50 (dd, J=10.7, 6.7 Hz, 1H), 2.96 – 2.85 (m, 2H), 2.02 – 1.50 (m, 11H), 1.28 – 1.16 (m, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.8, 139.4,

128.0, 109.7, 66.9, 65.7, 59.6, 52.8, 44.2, 33.6, 29.1, 28.1, 20.4; **HRMS** (ESI) *m/z* Calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$: 222.1494 found: 222.1494. Single crystals suitable for **X-Ray** analysis were obtained by vapor diffusion recrystallization of dichloromethane from a solution of **18** in a mixture of dichloromethane and hexanes. CCDC registry number 2084950.



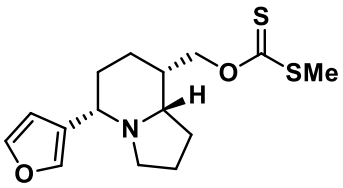
[(5S,8S,8aS)-5-(furan-3-yl)octahydroindolizin-8-yl]methanol (3.S.11)

The procedure was modified from a previously reported reaction.[50] A Schlenk tube (10 mL), charged with N_2, a magnetic stirbar, and **3.S.10** (21.3 mg, 0.081, 1.0 equiv.) in Et_2O (0.41 mL), was cooled to 0 °C. A mixture of $LiAlH_4$ (13.9 mg, 0.365 mmol. 4.5 equiv. in Et_2O (0.41 mL) was added and the resulting solution was allowed to warm to room temperature. After stirring for 3 hours, the solution was cooled to 0 °C and H_2O (0.015 mL), 15% aq. NaOH (0.015 mL), and H_2O (0.060 mL) were added dropwise in succession. The resulting mixture was allowed to warm to room temperature, after which $MgSO_4$ was added. After stirring for 15 minutes, the mixture was filtered over celite and the solids were rinsed with DCM (5 mL). The filtrate was concentrated under reduced pressure and purified *via* flash column chromatography to afford **3.S.11** as an off-white solid. **Yield** 10.0 mg (56%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -52.8° (*c* 0.003 $CHCl_3$). **TLC** R_f 0.55 (DCM:MeOH:30% NH_4OH in H_2O 12.8:1.0:0.03); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 6.38 (s, 1H), 4.28 (ddd, J=10.8, 4.0, 1.4 Hz, 1H), 3.81 (d, J=10.9 Hz, 1H), 3.06 (dd, J=11.6, 2.8 Hz, 1H), 2.85 (t, J=7.8 Hz, 1H), 2.46 (t, J=7.5 Hz, 1H), 2.27 – 2.16 (m, 1H), 2.05 – 1.93 (m, 2H), 1.90 – 1.77 (m, 3H), 1.76 – 1.61 (m, 5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.1, 139.1, 128.0, 109.2, 67.1, 65.8, 60.2, 53.0, 34.8, 31.8, 31.4, 26.3, 20.3; **HRMS** (ESI) m/z Calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$: 222.1488 found: 222.1489



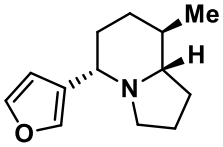
[(5S,8R,8aS)-5-(furan-3-yl)octahydroindolizin-8-yl]methyl xanthate (3.19)

The procedure was modified from a previously reported reaction.[27] In an N_2 glovebox, a 1 mL Schlenk tube was charged with NaH (6.31 mg, 0.263 mmol, 1.2 equiv.) and THF (0.365 mL). While stirring, a solution of **3.18** (48.4 mg, 0.219 mmol, 1.0 equiv.) in THF (0.365 mL) was added slowly to the Schlenk tube. The mixture was stirred at room temperature for 1 hour, after which, CS_2 (15.8 µL, 0.263 mmol, 1.2 equiv.) was added *via* syringe under N_2. After stirring for 1 hour, MeI (16.4 µL, 0.263 mmol, 1.2 equiv) was added under N_2 and the mixture stirred for an additional hour at room temperature. The reaction was diluted with EtOAc (3 mL) and quenched *via* dropwise addition of H_2O (2 mL). The resulting mixture was washed with H_2O (2x2 mL) and brine (4 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (1x1 mL). The organic layers were combined and filtered over $MgSO_4$. The $MgSO_4$ was removed by filtering over celite, and the solids were rinsed with EtOAc (1 mL). The resulting filtrate was concentrated under reduced pressure and purified *via* column chromatography to yield **3.19** as a yellow solid. **Yield** 64.8 mg (95%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -68.5° (*c* 0.003 $CHCl_3$); **TLC** R_f 0.17 (1:9 EtOAc:Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 2H), 6.44 (s, 1H), 4.58 (dd, J=10.9, 5.2 Hz, 1H), 4.49 (dd, J=11.0, 5.9 Hz, 1H), 2.97 (dd, J=11.0, 2.8 Hz, 1H), 2.89 (t, J=8.1 Hz, 1H), 2.57 (s, 3H), 2.02 – 1.54 (m, 10H), 1.28 (qd, J=12.9, 5.2 Hz, 1H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 215.9, 142.9, 139.3, 127.9, 109.6, 76.4, 66.9, 59.4, 52.7, 41.0, 33.5, 29.2, 28.3, 20.3, 19.0; **HRMS** (ESI) *m/z* Calcd for $C_{15}H_{22}NO_2S_2$ $[M+H]^+$: 312.1092 found: 312.1092.



[(5S,8S,8aS)-5-(furan-3-yl)octahydroindolizin-8-yl]methyl xanthate (3.S.12)

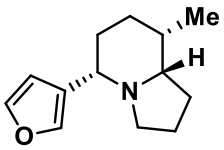
The procedure was modified from a previously reported reaction.[26] In an glovebox, a 4 mL vial was charged with NaH (0.864 mg, 0.0360 mmol, 1.2 equiv.) and THF (50.0 µL). While stirring a solution of **3.S.11** (6.70 mg, 0.0360 mmol, 1.0 equiv.) in THF (50.0 µL) was added slowly to the 4 mL vial. The mixture was stirred at room temperature for 1 hour, after which, CS_2 (2.16 µL, 0.036 mmol, 1.2 equiv.) was added *via* syringe. After stirring for 1 hour, MeI (5.11 µL, 0.036 mmol, 1.2 equiv.) was added, and the mixture stirred for an additional hour at room temperature. The reaction was quenched *via* dropwise addition of H_2O (1 mL). The resulting mixture was washed with H_2O (2x1 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3x1 mL). The organic layers were combined and filtered over $MgSO_4$ and the solids were rinsed with EtOAc (1 mL). The filtrate was concentrated under reduced pressure and purified *via* preparative TLC to yield **3.S.12** as a yellow oil. **Yield** 1.70 mg (25%); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -33.5° (*c* 0.001 $CHCl_3$); **TLC** R_f 0.48 (1:9 EtOAc:Hex); **^{1}H NMR** (600 MHz, CDCl3) δ 7.34 (s, 1H), 7.32 (s, 1H), 6.41 (s, 1H), 4.98 (dd, J = 11.0, 5.6 Hz, 1H), 4.87 (dd, J = 11.0, 7.6 Hz, 1H), 2.95 (dd, J = 11.2, 3.0 Hz, 1H), 2.90 – 2.84 (m, 1H), 2.37 (s, 1H), 2.26 (ddd, J = 10.1, 6.9, 2.8 Hz, 1H), 2.01 – 1.95 (m, 1H), 1.90 – 1.54 (m, 5H); **^{13}C NMR** (126 MHz, CDCl3) δ 216.0, 142.9, 139.2, 128.6, 109.7, 73.5, 66.0, 60.6, 53.3, 34.8, 30.0, 27.8, 27.1, 20.4, 19.1; **HRMS** (ESI) *m/z* Calcd for $C_{15}H_{22}NO_2S_2$ $[M+H]^+$: 312.1087 found: 312.1084.



Nuphar Indolizidine (3.2)

The procedure was modified from a previously reported reaction.[27] A 10 mL Schlenk tube was charged with **3.19** (32.4 mg, 0.104 mmol, 1.0 equiv.), $(TMS)_3SiH$ (64.2 µL, 0.208 mmol, 2.0 equiv.), AIBN (0.02 M solution in PhMe, 130 µL, 0.0026

mmol, 0.025 equiv) and PhMe (3.1 mL). After rigorously degassing *via* freeze-pump-thaw (x4), the solution was heated with an oil bath while stirring to 90 °C, under N_2. After 30 minutes, an additional portion of AIBN (0.02 M solution in PhMe, 130 µL, 0.0026 mmol, 0.025 equiv.) was added and the reaction was stirred at 90 °C. After 30 minutes the reaction was allowed to cool to room temperature. All volatiles were removed by evaporation under reduced pressure, and the resulting residue was purified *via* column chromotography to give **Nuphar Indolizidine** as a clear, colorless, oil. **Yield** 14.7 mg (69 %); **TLC** R_f 0.17 (1:9 EtOAc:Hex); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (d, J=4.9 Hz, 2H), 6.44 (s, 1H), 2.95 – 2.84 (m, 2H), 1.99 – 1.86 (m, 2H), 1.83 – 1.35 (m, 8H), 1.14 – 1.02 (m, 1H), 0.91 (d, J=6.5 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 142.8, 139.5, 128.4, 109.9, 71.6, 59.9, 53.3, 36.6, 34.3, 34.1, 29.2, 20.3, 19.0. The ^{1}H NMR and ^{13}C NMR spectra matched the previously reported spectral data of Nuphar Indolizidine.[28]



(5S,8S,8aS)-5-(furan-3-yl)-8-methyloctahydroindolizine (3.S.13)

The procedure was modified from a previously reported reaction.[28] A 1 mL Schlenk tube was charged with **3.S.12** (1.70 mg, 0.00550 mmol, 1.0 equiv.), $(TMS)_3SiH$ (3.4 µL, 0.0110 mmol, 2.0 equiv.), AIBN (0.005 M solution in PhMe, 55.0 µL, 0.000275 mmol, 0.05 equiv.) and PhMe (0.167 mL). After rigorously degassing *via* freeze-pump-thaw (x3), the solution was heated in an oil bath while stirring to 90 °C, under N_2. After 3 hours the reaction was allowed to cool to room temperature. All volatiles were removed by evaporation under reduced pressure. The resulting yellow oil was evaluated as the crude reaction mixture using quantitative NMR with 1,3,5-trimethoxybenzene as the internal standard. The 1H NMR and 13C NMR spectra matched previously reported spectral data.[29] **Yield (qNMR)** 0.415 mg (37%).

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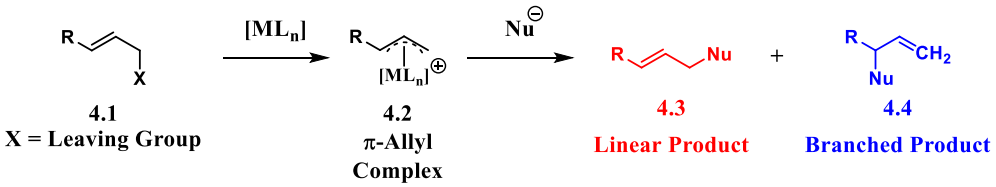
Chapter 4: Synthesis of 1,2-DHP *via* Nucleophilic Addition of Organoboron Nucleophiles to N-alkyl Nicotinate salts

4.1. Introduction:

4.1.1. Multidentate Electrophiles and Regioselectivity:

In the chemistry of nucleophilic additions, a common challenge is controlling the regioselectivity when using multidentate electrophiles. Such electrophiles have multiple electropositive sites that must be distinguished. In allylic substitutions, for example, the constitutional isomers are defined as linear (**4.3**), wherein the substituent is added to the less substituted carbon, and branched, wherein the substitution occurs on a higher substituted carbon (**4.4**) (Figure 4.1). These reactions generally proceed through π-allyl complexes (**4.2**) of transition metals such as Pd,[1–3] Ir,[4–9] Cu,[10,11] and Rh,[12] and while the metal is well known to control the linear/branched selectivity, there is evidence to support ligand control.[2]

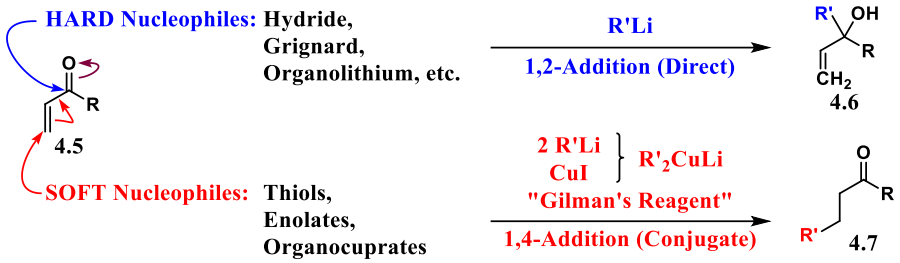
Figure 4.1: General regioselectivity of allylic substitution reactions.



Another example of multidentate electrophilic addition is the Michael addition, a ubiquitous organic reaction, properly defined as the 1,4- addition of doubly-stabilized enolates to α,β-unsaturated carbonyls (**4.5**) (Figure 4.2).[13] The Michael acceptor (**4.5**), an electron-poor vinylogous compound, is a multidentate electrophile, being able to accept a nucleophile at the 2- or 4-position. The nucleophilic addition is directed by the hard-soft nature of the nucleophile. In the classic example of an α,β-unsaturated carbonyl (**4.5**), the carbonyl carbon is hard while the 4, or β, carbon is soft, thus hard nucleophiles such as Grignard and organolithium reagents or

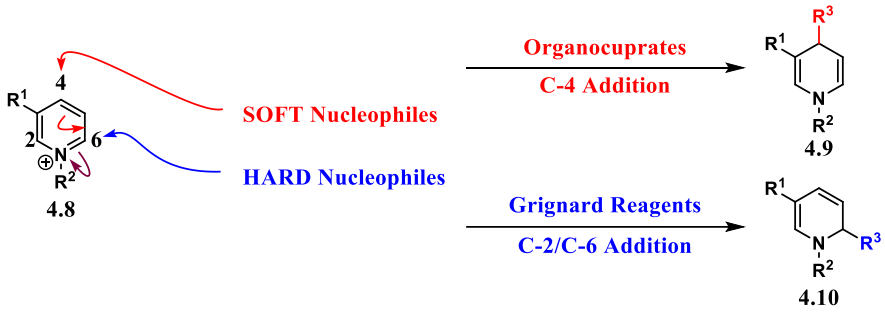
reductants add to the carbonyl carbon giving product **4.6**, while soft nucleophiles such as organocuprates and enolates add to the C-4 position, giving **4.7**.

Figure 4.2: General regioselectivity of nucleophilic additions to α,β-unsaturated carbonyls.



As discussed in Chapter 1, N-alkyl pyridinium salts (**4.8**) contain 3 electrophilic sites (C-2, C-4, and C-6) (Figure 4.3). In the regioselective nucleophilic addition to N-alkyl heteroarenium salts it is difficult to accurately predict the regioselectivity of the Nucleophilic attack. In general, hard nucleophiles add to the C-2 or C-6 position, forming product **4.10** while soft nucleophiles attack the C-4 position, giving **4.9**.[14]

Figure 4.3: General regioselectivity of nucleophilic addition to N-alkyl pyridinium salts.

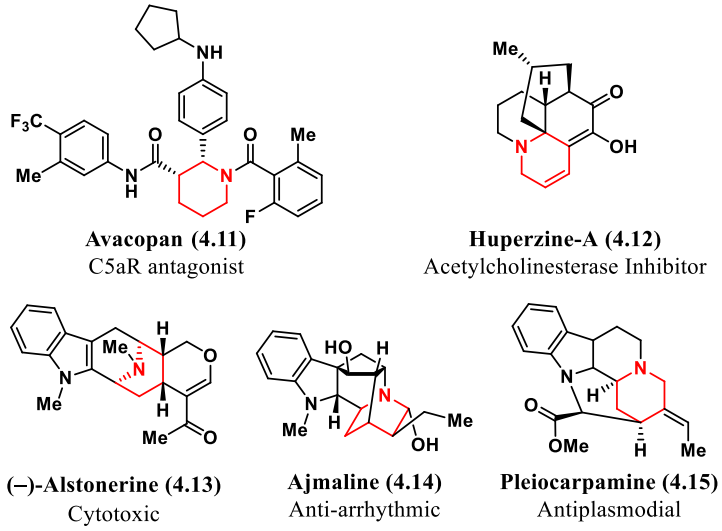


4.2. Importance of the regioselective synthesis of 1,2-DHPs:

We are concerned with C-2 site-selectivity due to the prevalence of bioactive natural products featuring piperidine moieties substituted in such a manner (Figure 4.4).[15–17] For example, avacopan (**4.11**), trade name Tavenos, is a recently FDA-approved treatment for adults with granulomatosis with polyangiitis, which is a rare condition causing the inflammation of blood

vessels.[18] huperzine-A (**4.12**) inhibits acetylcholinesterase and is used to treat conditions such as Alzheimer's.[19] There is also an extensive class of indole alkaloids with a variety of cytotoxic, anti-arrhythmic, and antiplasmodial activities such as (-)-alstonerine (**4.13**),[20,21] Ajmaline (**4.14**),[22] and pleiocarpamine (**4.15**),[21] respectively.

Figure 4.4:Bioactive natural products featuring C-2 substitution patterns.

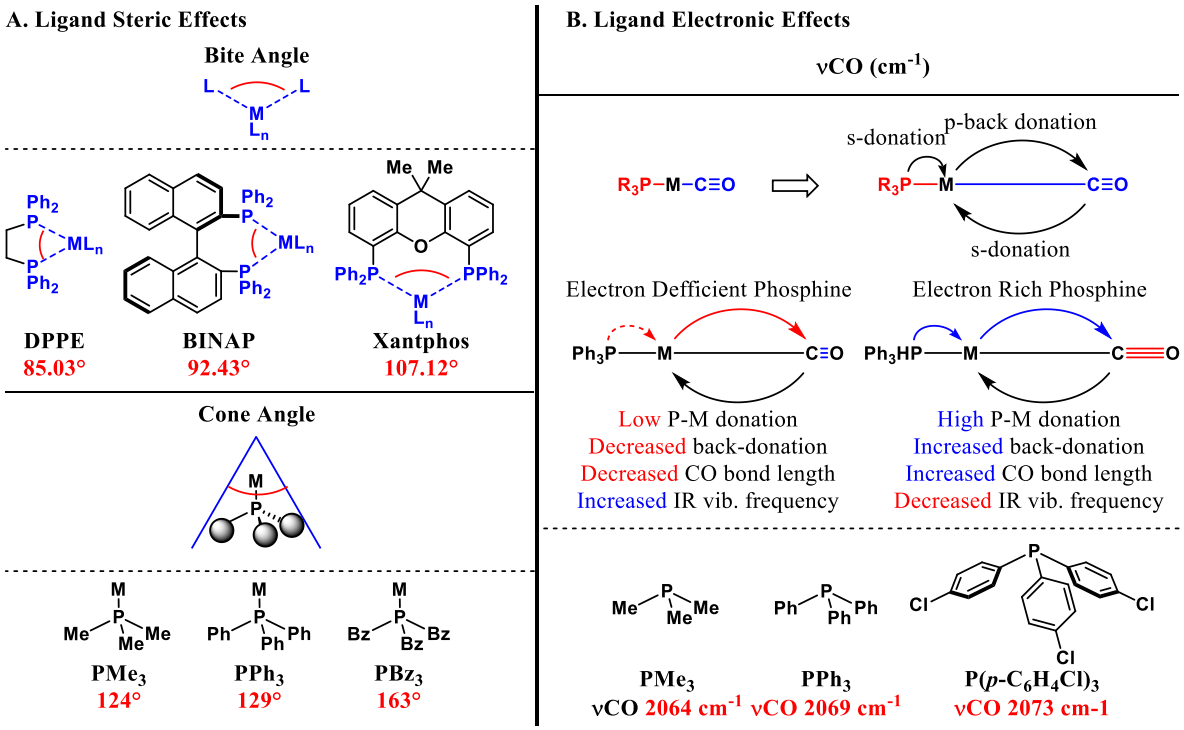


4.2.1. Statistical Analysis of Ligand Parameters:

We have previously described the C-6 regio- and enantioselective addition of boron nucleophiles to N-alkyl heteroarenium salts.[23,24] In each case, we observed the formation of side products, mainly the constitutional isomer resulting from addition to the C-2 position. As we investigated methods that gave the C-2 product selectively, we sought to discover what precisely causes such selectivity, the degree to which it can be controlled, and whether such selectivity can be predicted. The Sigman research group at the University of Utah has dedicated their organic methodology investigations to answering such questions, using statistical analyses such as linear regression[25–27] and multivariate pattern recognition[28] to develop predictive tools for organic catalysis.[29]

Databases, computer scripts, and machine learning toolkits have been thoroughly developed to model organic and inorganic complexes to provide a platform for the discovery of new reactivity in homo- and heterogeneous organic catalysis development.[30–35] The Sigman group have added to this body of work with their *kraken* system. By compiling the steric and electronic effects of phosphorous ligands, they built a database containing the computational and experimental data necessary for predicting ligand performance in transition-metal catalysis. In 1970, Tolman described the steric and electronic properties of phosphine ligands and their effect on specifically nickel catalysis (Figure 4.5).[36,37] Such properties as the Tolman bite and cone angles (Figure 4.5.A) and Tolman electronic parameter (Figure 4.5.B) were found to be the best predictors of ligand performance in our study. Herein, we describe the regioselective addition of organoboron nucleophiles to the C-2 position of N-alkyl nicotinate salts featuring a substituent on the C-6 position.

Figure 4.5: Tolman ligand parameters.



4.3. Development of Rh-catalyzed, C-2 regioselective, nucleophilic addition strategy for the synthesis of 1,2-DHPs:

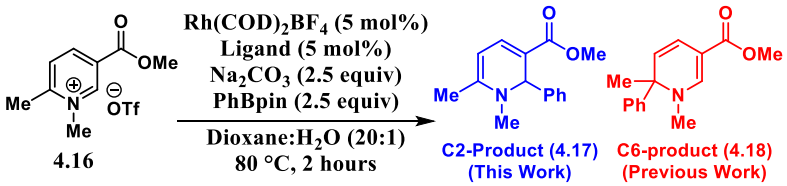
4.3.1. Ligand screenings for regioselective addition:

We began our investigations by screening our library of ligands bound to $Rh(COD)_2BF_4$ against several N-alkyl nicotinate salts, using PhBpin as the nucleophile (Table 4.1). We found that methyl N,6-dimethylnicotinate salt **4.16** gave consistently good yields and provided an effective model for ligand parameterization. To our delight, we discovered five ligands that gave the C-2 product (**4.17**) in good yield and actionable C-2:C-6 ratio (Table 4.1, Entries 6-10). From these, we identified two appropriate ligands that gave above 90% *ee* (Table 4.1, Entries 6 and 10). We selected the Ligand (S,S_{ax})-Bobphos (**Ligand J**) to continue method optimization due to the 7:1 regioisomeric ratio (Table 4.1, entry 10).

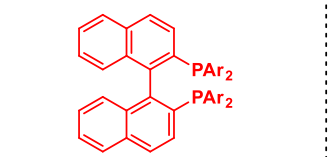
4.3.2. Optimization of Reaction Conditions:

Using the Rh/Bobphos system, nicotinate **4.16** as our electrophile, and PhBpin as our nucleophile, we began screening certain reaction parameters to increase the yield of the dearomatization (Table 4.2). Unlike in our previous studies, we found that the reaction was less sensitive to the ratio of organic solvent to water. From 20:1 to 10:1 dioxane:water, our yield remained almost unchanged, while increasing the amount of water lowered the yield by half (Table 4.2, entries 1-3). Temperature proved to be more critical to reaction yield; at lower temperatures, the overall reaction yield rises significantly (Table 4.2, entries 1, 4, and 5). We have also shown that a reaction time of two hours is still optimal (Table 4.2, entries 6 and 7). We have shown in other work that the complexed rhodium catalyst is necessary for reaction success.[23]

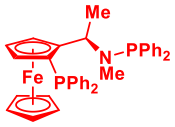
Table 4.1: Ligand screen for the dearomatization of pyridinium Salt 4.24.



Entry	Ligand	Yield (%)[a] C-6	C-2	Overall	6:2 Ratio	C-2 *ee*[b]
1	A	81	10	91	8:1	N.D.
2	B	78	4	82	20:1	N.D.
3	C	91	2	93	45:1	N.D.
4	D	36	10	46	4:1	N.D.
5	E	10	20	30	1:2	N.D.
6	F	34	60	94	1:2	91%
7	G	31	60	91	1:2	N.D.
8	H	2	39	42	1:20	36%
9	I	2	33	35	1:15	60%
10	J	11	67	78	1:7	91%

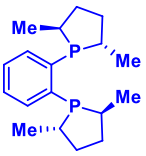


Ligand 4.A: Ar = Ph (BINAP)
Ligand 4.B: Ar = 3,5-Xyl (XylBINAP)

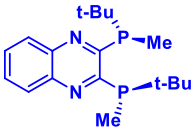


Ligand 4.C: BoPhoz™

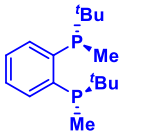
Ligand 4.D: JosiPhos



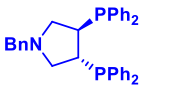
Ligand 4.E: Duphos



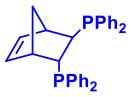
Ligand 4.F: Quinox P*



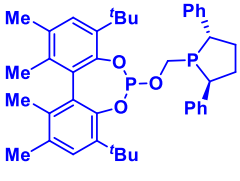
Ligand G: Benz P*



Ligand 4.H: CatAsium D



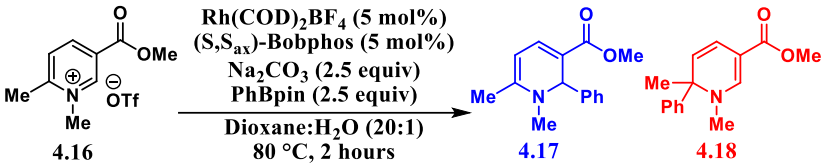
Ligand 4.I: Norphos



Ligand 4.J: BobPhos

[a]Reaction yield was determined via ^{1}H NMR analysis. product peaks were integrated vs the internal standard 1,3,5-trimethoxybenzene.
[b]Enantiomeric eccess was determined via chiral HPLC analysis.

Table 4.2: Optimization of the Rh/Bobphos system for the dearomatization of pyridinium salt 4.24.



4.16 4.17 4.18

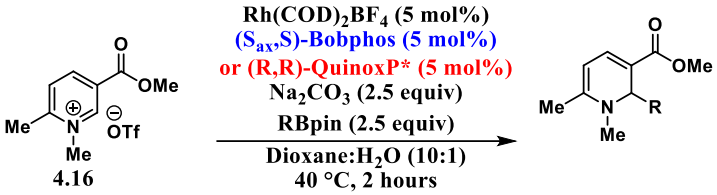
Entry	Change to above procedure	Yield of 7 (%)[a]	Overall yield (%)	*ee* (%)[b]
1	none	74	87	91
2	10:1 Solvent:H_2O	73	85	99
3	5:1 Solvent:H_2O	33	39	99
4	40 °C	86	99	99
5	60 °C	80	96	99
6	1 hour	59	68	99
7	3 hours	67	78	99

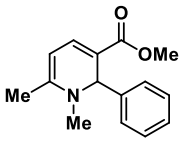
[a]Reaction yield was determined via ^{1}H NMR analysis. product peaks were integrated vs the internal standard 1,3,5-trimethoxybenzene.
[b]Enantiomeric eccess was determined via chiral HPLC analysis.

4.4. Reaction Scope:

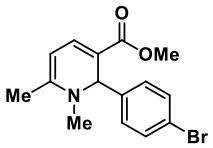
With optimized conditions in hand, we began developing a substrate scope of both nucleophiles (Table 4.3) and electrophiles (Table 4.4). Unfortunately, we found that some substrates do not react in the Rh/Bobphos system, even after re-optimization including water, temperature, and base screening. The Rh/Bobphos catalyst was effective with arylbpins that only contained alkyl or aryl functionality, except for the electron-donating methoxy ether (Table 4.3, **4.17**, **4.19.b-d**, **4.19.f**). All electron withdrawing group containing Bpins, as well as heterocyclic Bpins failed to react under Rh/Bobphos. Luckily, some of those substrates that failed to produce the dihydropyridine with Bobphos did so in a Rh/Quinox system under the previously optimal conditions including para-bromophenyl (**4.19.a**), para-trifluoromethylphenyl (**4.19.e**), and alkenyl Bpins (**4.19.g**) with good enantioselectivity, albeit in diminished yield (Table 4.3). It is important to note that the diminished C-2 yield was not associated with an increase in the C-6 constitutional isomer.

Table 4.3: Scope of C-2 regioselective dearomatization of N-Alkyl pyridinium salts.

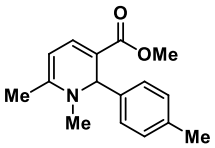




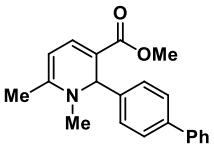
4.17, 77%, 97% *ee*



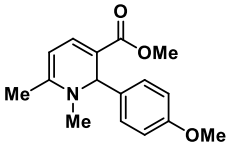
4.19.a, 47%, 90% *ee*



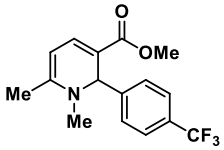
4.19.b, 84%, 98% *ee*



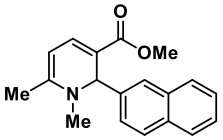
4.19.c, 59%, 98% *ee*



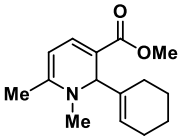
4.19.d, 51%, 94% *ee*



4.19.e, 35%, 81% *ee*



4.19.f, 70%, 99% *ee*

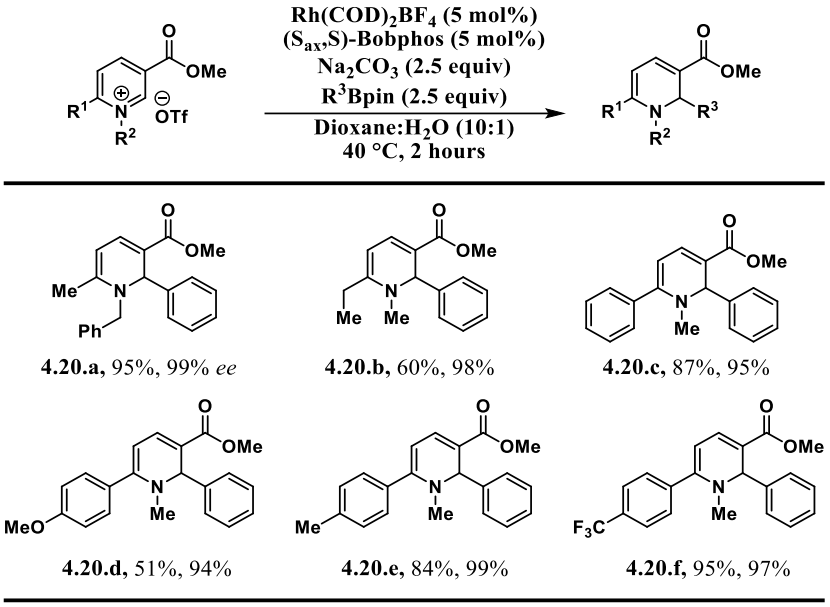


4.19.g, 31%, 90% *ee*

Isolated yield is reported. *ee* was determined by chiral HPLC analysis.

In our screen of nicotinate salts (Table 4.4), we found that increasing the size of the N-alkyl (**4.20.a**) and 6-alkyl (**4.20.b**) substituents was well tolerated, giving good yields and excellent *ee*s. To our delight, when the C-6 substituent was a substituted phenyl, the optimized Rh/Bobphos system gave 1,2-DHPs in good yield and *ee*, even when the substituents featured electron poor and rich phenyl groups on the C-6 position such as the methoxy ether (**4.20.d**) and trifluoromethyl groups (**4.20.f**) (Table 4.4).

Table 4.4: Scope of N-alkyl nicotinate salts for the synthesis of 1,2-DHPs.



Isolated yield is reported. *ee* was determined by chiral HPLC analysis.

4.5. Conclusion:

While this work is ongoing, we believe we have developed an effective method for the synthesis of 1,2-dihydropyridines with ligand control of the regioselectivity. Although the functional group tolerance is not ideal, we have shown a variety of ligands that are suitable for the enantioselective addition of organoboron nucleophiles to N-alkyl pyridinium salts. Our next steps are to expand our substrate scope and demonstrate the utility of the 1,2-DHP by functionalizing the C=C bonds. This work will be published in collaboration with the Sigman research group.

4.6. Experimental Section:

4.6.1. Materials and Methods:

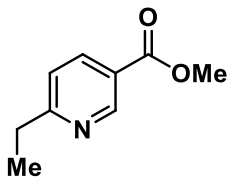
Reactions were performed in flame-dried sealed tubes or modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of nitrogen or inside nitrogen filled glovebox using 1-dram vials unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe. The appropriate starting materials and reagents were dried

via azeotropic removal of water with toluene. Organic solutions were concentrated by rotary evaporation below 40 °C. Flash column chromatography was performed employing 230–400 mesh silica gel.

Dichloromethane, tetrahydrofuran, diethyl ether, DMF and toluene were purified by passage through two packed columns of neutral alumina under an argon atmosphere.[48] Methanol was distilled from magnesium at 760 Torr. All other chemicals were obtained from commercial vendors and were used without further purification unless otherwise noted. $CDCl_3$ was stored over molecular sieves and passed through a plug of Al_2O_3 prior to use.

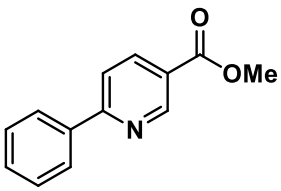
Thin-layer chromatography was performed using glass plates pre-coated to a depth of 0.25 mm with 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm) and visualized under UV light (254 and 360 nm), or stained with vanillin in acidic EtOH, or I_2 on SiO_2. Proton, carbon-13, and fluorine-19 nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR, and ^{19}F NMR) spectra were recorded on a Bruker Avance III instrument; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual isotopes in the NMR solvent (d-chloroform: δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR; d6-DMSO: δ 2.50 for ^{1}H NMR, δ 39.53 for ^{13}C NMR;). Data are presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), coupling constant in Hertz (Hz), integration. HPLC analysis for the determination of enantiomeric access (*ee*) was performed using an Agilent Technologies 1260 Infinity II HPLC system and InfinityLab Poroshell 120 column (Chiral-CD, or Chiral-V). Optical rotations are calculated and reported in concentrations of mg/mL and were recorded using a Rudolph Research Analytical Autopol® IV Automatic Polarimeter with a 0.5 dm path length. High resolution mass spectrometry (HRMS) was performed using an Orbitrap Exploris 120 quadrupole orbitrap.

4.6.2. Synthesis of Pyridine Starting Materials:



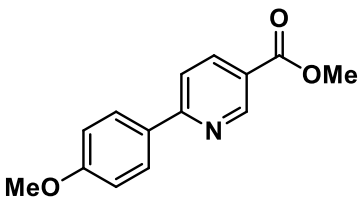
Methyl 6-Ethylpyridine-3-carboxylate (4.S.1)

Compound **4.S.1** was prepared from methyl 6-bromopyridine carboxylate (324 mg, 1.50 mmol, 1.0 equiv.) and a 1.0 M solution of Et_2Zn in toluene (1.80 mL, 1.80 mmol, 1.2 equiv.) according to a reported procedure.[49] ^1H and ^{13}C spectral data matched those of the reported compound. **Yield:** 159 mg (64%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.91 (d, J = 2.2 Hz, 1H), 7.98 (dd, J = 8.1, 2.2 Hz, 1H), 7.03 (d, J = 8.1 Hz, 1H), 3.72 (s, 3H), 2.67 (q, J = 7.6 Hz, 2H), 1.11 (t, J = 7.6 Hz, 3H).; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.9, 165.7, 150.2, 137.3, 123.2, 121.5, 52.0, 31.3, 13.4.



Methyl 6-phenylpyridine-3-carboxylate (4.S.2)

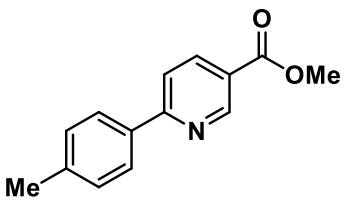
Compound **4.S.2** was prepared from methyl 6-bromopyridine carboxylate (2.0 g, 9.3 mmol, 1.0 equiv.) and $PhB(OH)_2$ (1.7 g, 14 mmol, 1.5 equiv.) according to a reported procedure. ^1H and ^{13}C spectral data matched those of the reported compound.[49] **Yield:** 287.7 mg (54%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.27 (d, J = 2.4 Hz, 1H), 8.33 (dd, J = 8.3, 2.2 Hz, 1H), 8.08 – 8.02 (m, 2H), 7.79 (d, J = 8.3 Hz, 1H), 7.53 – 7.42 (m, 3H), 3.96 (s, 3H).; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.9, 161.0, 151.0, 138.3, 138.0, 130.1, 129.0, 127.4, 124.3, 119.9, 52.4.



Methyl 6-(4-methoxyphenyl)pyridine-3-carboxylate (4.S.3)

Compound **4.S.3** was prepared *via* the following procedure. Methyl 6-bromopyridine carboxylate (211 mg, 0.99 mmol, 1.0 equiv.) and 4-MeO-$PhB(OH)_2$ (226 mg, 1.49 mmol, 1.5 equiv.) were added to a seal tube containing a magnetic stir bar. The vessel was evacuated and backfilled with N_2 on a Schlenk line. The tube was transferred to the glovebox, where $Pd(PPh_3)_4$ (57.2 mg, 0.0490 mmol, 5 mol%) and degassed

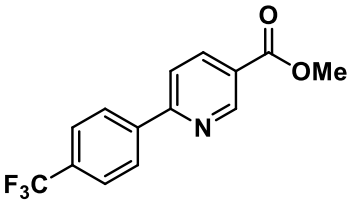
toluene (6.0 mL) were added. The seal tube was then transferred to the Schlenk line where a degassed, 2.0 M solution of Na_2CO_3 in H_2O (0.99 mL, 1.9 mmol, 2.0 equiv.) was added. The tube was sealed and stirred while heating in an oil bath to 80 °C. After 6 hours, the tube was cooled to room temperature, the solution diluted to 25 mL with EtOAc and filtered through a plug of silica, and then celite. The plug was rinsed with EtOAc (10 mL), and the solvents evaporated under reduced pressure. The crude oil was adsorbed onto celite and purified over silica *via* flash column (ethyl acetate : Hexanes, 10% to 20%). The solvents were evaporated to give **4.S.3** as an off-white powder. ^{1}H and ^{13}C NMR matched those of a reported compound.[50] **Yield:** 185.4 mg (77%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.23 (dd, J = 2.2, 0.9 Hz, 1H), 8.30 (dd, J = 8.3, 2.2 Hz, 1H), 8.07 – 8.01 (m, 2H), 7.74 (dd, J = 8.4, 0.9 Hz, 1H), 7.02 (d, J = 8.9 Hz, 2H), 3.96 (s, 3H), 3.88 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.2, 161.5, 160.7, 151.1, 138.0, 131.0, 129.0, 123.6, 119.2, 114.5, 55.6, 52.5.



Methyl 6-(4-methylphenyl)pyridine-3-carboxylate (4.S.4)

Compound **4.S.4** was prepared *via* the following procedure. Methyl 6-bromopyridine carboxylate (1.0 g, 4.6 mmol, 1.0 equiv.) and 4-Me-$PhB(OH)_2$ (0.95 g, 7.0 mmol, 1.5 equiv) were added to a seal tube containing a magnetic stir bar. The vessel was evacuated and backfilled with N_2 on a Schlenk line. The tube was transferred to the glovebox, where $Pd(PPh_3)_4$ (266 mg, 0.230 mmol, 5 mol%) and degassed toluene (23.0 mL) were added. The seal tube was then transferred to the Schlenk line where a degassed, 2.0 M solution of Na_2CO_3 in H_2O (4.6 mL, 9.2 mmol, 2.0 equiv.) was added. The tube was sealed and stirred while heating in an oil bath to 80 °C. After 16 hours, the tube was cooled to room temperature, the solution diluted to 100 mL with EtOAc and filtered through a plug of silica, and then celite. The plug was rinsed with EtOAc (10 mL), and the solvents evaporated under reduced

pressure. The crude oil was adsorbed onto celite and purified over silica *via* flash column (ethyl acetate : Hexanes, 10% to 20%). The solvents were evaporated to give **4.S.4** as a white powder. ^{1}H and ^{13}C NMR matched those of a reported compound.[51] **Yield:** 588.8 mg (56%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.26 (dd, J = 2.3, 0.9 Hz, 1H), 8.32 (dd, J = 8.3, 2.2 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.78 (dd, J = 8.3, 0.9 Hz, 1H), 7.33 – 7.28 (m, 2H), 3.97 (s, 3H), 2.42 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.1, 161.1, 151.1, 140.4, 138.0, 135.6, 129.8, 127.4, 124.0, 119.6, 52.5, 21.5.



Methyl 6-[4-(trifluoromethyl)phenyl]pyridine-3-carboxylate (4.S.5)

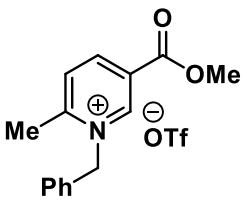
Compound **4.S.5** was prepared *via* the following procedure. Methyl 6-bromopyridine carboxylate (215 mg, 1.00 mmol, 1.0 equiv.), K_2CO_3 (415 mg, 3.00 mmol, 3.0 equiv.), and 4-CF_3-PhB$(OH)_2$ (209 mg, 1.10 mmol, 1.1 equiv.) were added to a seal tube containing a magnetic stir bar. The vessel was evacuated and backfilled with N_2 on a Schlenk line. The tube was transferred to the glovebox, where $Pd(PPh_3)_4$ (57.8 mg, 0.050 mmol, 5 mol%) and degassed toluene (4.0 mL) were added. The seal tube was then transferred to the Schlenk line where degassed MeOH (1 mL) was added. The tube was sealed and stirred while heating in an oil bath to 80 °C. After 5 hours, the tube was cooled to room temperature, the solution diluted to 25 mL with EtOAc and filtered through a plug of silica, and then celite. The plug was rinsed with EtOAc (10 mL), and the solvents evaporated under reduced pressure. The crude oil was adsorbed onto celite and purified *via* flash column (ethyl acetate : Hexanes, 10% to 20%). The solvents were evaporated to give **4.S.3** as an off-white solid. ^{1}H and ^{13}C NMR matched those of a reported compound.[52] **Yield:** 185.4 mg (77%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.28 (dd, J = 2.1, 0.8 Hz, 1H), 8.36 (dd, J = 8.3, 2.2 Hz, 1H), 8.15 (d, J = 8.1 Hz, 2H), 7.82 (dd, J = 8.3, 0.8 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H), 3.97 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.7, 159.3, 151.2, 141.6, 138.2,

131.8 (q, J = 32.5 Hz), 127.8, 125.9 (q, J = 3.8 Hz), 125.1, 124.1 (q, J = 272.2 Hz), 120.3, 52.6; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -62.7.

4.6.3. Synthesis of N-Alkyl Nicotinate Salts:

5-(methoxycarbonyl)-1,2-dimethylpypiridin-1-ium triflate (4.16)

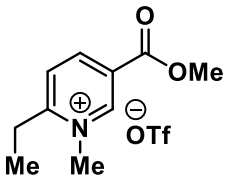
Pyridinium salt **6** was prepared from methyl 6-bromopyridine carboxylate (10.0 g, 66.00 mmol, 1 equiv.) according to a reported procedure. ^{1}H and ^{13}C spectral data matched those of a reported compound.[49] **Yield:** 16.8 g (81%); **^{1}H NMR** (600 MHz, CD_3OD) δ 7.83 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 8.2 Hz, 1H), 2.75 (s, 3H), 2.41 (s, 3H), 1.29 (s, 3H); **^{13}C NMR** (151 MHz, CD_3OD) δ 163.5, 161.5, 148.8, 145.7, 130.8, 129.5, 121.7 (q, *J* = 318.6 Hz), 53.93, 46.9.



1-benzyl-5-(methoxycarbonyl)-2-methylpyridin-1-ium triflate (4.S.6)

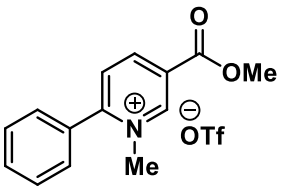
Prepared from methyl 6-methylpyridine carboxylate (2.000 g, 13.2 mmol, 1 equiv.) according to a reported procedure. ^{1}H and ^{13}C spectral data matched those of a reported compound.[49] **Yield**: 2.9 g (56% over two steps); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.14 (d, J = 1.7 Hz, 1H), 8.81 (dd, J = 8.2, 1.8 Hz, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.47 – 7.42 (m, 3H), 7.26 – 7.19 (m, 2H), 5.93 (s, 2H), 4.00 (s, 3H), 2.97 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.8, 160.3, 146.5, 145.1, 131.0, 130.9, 130.1, 130.1, 128.7, 128.3, 125.4 – 116.3 (m), 62.6, 53.9, 21.5.

2-ethyl-5-(methoxycarbonyl)-1-methylpyridin-1-ium triflate (4.S.7)



Prepared from **4.S.1** (165.0 mg, 1.00 mmol, 1.0 equiv.) according to a reported procedure. ^{1}H and ^{13}C spectral data matched those of a reported compound.[49] **Yield:** 188.4 mg (58%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.29 (s, 1H), 8.83 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 4.43 (s, 3H), 4.03 (s, 3H), 3.22 (q, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.2 Hz, 3H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.9, 161.9, 147.9, 144.8, 128.0, 127.2, 123.6, 121.5, 119.4, 117.3, 77.3, 77.1, 76.9, 53.7, 53.5, 46.6, 26.6, 10.9.



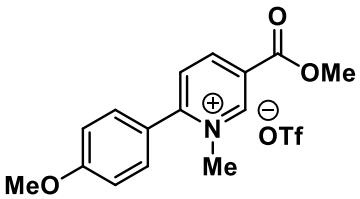
.5-(methoxycarbonyl)-1-methyl-2-phenylpyridin-1-ium triflate (4.S.8)

Prepared from **4.S.2** (287.9 mg, 1.35 mmol, 1.0 equiv.) according to a reported procedure. ^{1}H and ^{13}C spectral data matched those of a reported compound.[49]

Yield: 447.7 mg (88%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.92 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.60 (m, 5H), 4.36 (s, 3H), 4.04 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.8, 159.2, 148.6, 144.9, 132.1, 130.9, 130.1, 129. 7, 129. 6, 129.1, 120.6 (q, J = 320.4 Hz), 53. 8, 48.4. 128.9, 53.9, 48.5.

Pyridinium salts 9d-f were synthesized according to the following procedure:

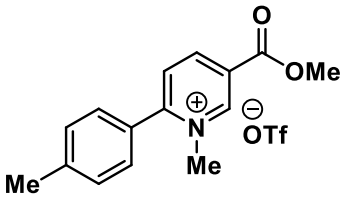
The specified nicotinic acid ester was dissolved in dry dichloromethane in a seal tube charged with a ptfe magnetic stirbar. MeOTf was added dropwise to the stirring solution and the vessel was sealed. After allowing the reaction to stir overnight, the contents were transferred to a 20 mL vial and around half of the CH_2CL_2 was evaporated under reduced pressure. The remaining residue was then triturated with diethyl ether (300 mL). The solids were filtered, and the filtrate was washed with Et_2O. the remaining residue was collected using MeOH into a 20 mL vial and the solvent evaporated under reduced pressure. The filtrate was added to the vial and the solids were dried under reduced pressure for 1 hour.



5-(methoxycarbonyl)-2-(4-methoxyphenyl)-1-methylpyridin-1-ium triflate (4.S.9)

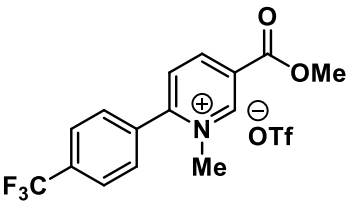
Prepared from **4.S.3** (184 mg, 0.760 mmol 1.0 equiv.) and methyl triflate (0.1 mL, 0.9 mmol, 1.2 equiv.) according to the above procedure. **Yield:** 183 mg, 59%; **^{1}H**

NMR (500 MHz, $CDCl_3$) δ 9.24 (dd, J = 2.2, 0.8 Hz, 1H), 8.31 (dd, J = 8.4, 2.2 Hz, 1H), 8.08 – 8.01 (m, 2H), 7.75 (dd, J = 8.4, 0.9 Hz, 1H), 7.05 – 6.99 (m, 2H), 3.97 (s, 3H), 3.88 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d6) δ 162.3, 161.8, 158.4, 148.0, 144.2, 131.4, 130.2, 127.5, 123.1, 120. 7 (q, J = 322.3 Hz), 114.6, 55.6, 53.6, 47.6; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -78.4; **HRMS:** Calcd for $C_{15}H_{16}NO_3^+$ [M] 258.1125, found 258.1127.



5-(methoxycarbonyl)-1-methyl-2-(4-methylphenyl) pyridin-1-ium triflate (4.S.10)

Prepared from **4.S.4** (454.2 mg 2.0 mmol 1.0 equiv.) and methyl triflate (0.22 mL 2.0 mmol, 1.0 equiv.) according to the above procedure. **Yield:** 693.0mg (88%); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.41 (d, J = 1.8 Hz, 1H), 8.86 (dd, J = 8.1, 1.8 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.49 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 7.7 Hz, 2H), 4.32 (s, 3H), 4.00 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.9, 159.2, 148.6, 144.9, 132.1, 130.9, 130.0, 129.7, 129.3, 129.0, 120.6 (q, J = 320.5 Hz), 53.8, 48.4; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -78.5. **HRMS:** Calcd for $C_{15}H_{16}NO_2^+$ [M] 242.1176, found 242.1180.



5-(methoxycarbonyl)-1-methyl-2-[4-(trifluoromethyl)phenyl] pyridine-1-ium triflate (4.S.11)

Prepared from **4.S.5** (214.2 mg, 0.76 mmol, 1.0 equiv.) and methyl triflate (0.9940 mL, 0.84 mmol, 1.1 equiv.) according to the above procedure. **Yield:** 284.9 mg (84%); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 9.46 (d, J = 1.8 Hz, 1H), 8.91 (dd, J = 8.2, 1.7 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 3.7 Hz, 4H), 4.34 (s, 3H), 4.03 (s, 3H); **^{13}C NMR** (126 MHz, DMSO-d6) δ 162.2, 156.8, 148.1, 145.0, 131.5 (q, J = 32.3 Hz), 130.3, 130.2, 128.8, 126.1 (d, J = 4.1 Hz), 127.3 – 116.8 (m, $2CF_3$), 53.7, 47.7; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -63.3, -78.4; **HRMS:** Calcd for $C_{15}H_{13}F_3NO_2^+$ [M] 296.0893, found 296.0889.

4.6.4. Synthesis of 1,2-Dihydropyridines:

Preparation of Rh catalyst stock solution for dearomatization reactions:

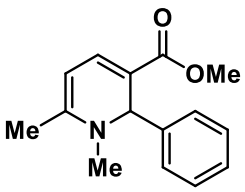
In a nitrogen filled glovebox, $Rh(COD)_2BF_4$ (64 mg, 0.16 mmol, 1 equiv.) was added to a vial containing the specified ligand (0.16 mmol, 1.0 equiv.) and dissolved in dioxane (16 mL, 0.01M). This solution was stirred for 15 minutes to promote the formation of the catalyst. The Rh(COD)(Bobphos) solution is a clear and orange in color. The Rh(COD)(Quinox-P*) solution is turbid and red in color. This solution was used in the dearomatization reactions below. For racemic dearomatization products, DPPBz was used, producing a turbid solution that is dark yellow in color.

General procedure for dearomatization of *n*-alkyl pyridinium salts using (S_{ax},S)-Bobphos ligand (GPA):

The specified pyridinium salt (0.2 mmol, 1.0 equiv.), boronic acid pinacol ester (Bpin) (0.5 mmol, 2.5 equiv.), and Na_2CO_3 (53 mg, 0.5 mmol, 2.5 equiv.), were measured into a 1 dram scintilation vial on the benchtop. The vials containing pyridinium salt, Bpin, and Na_2CO_3 were transferred into the nitrogen filled glovebox where the Rh/Bobphos stock solution of catalyst was added into each vial (1 mL, 0.2 M) . The vials were then sealed with a ptfe-lined septa cap and brought outside the glovebox. Degassed water (100 µL) was added to each reaction mixture *via* syringe and the reaction mixture was heated to 40 °C for 2 hours using an aluminum heating block. The vials were then removed from the heating block and cooled to room temperature. **Workup:** room temperature solutions were diluted with 1 mL of EtOAc and dried with 1.0 g of $MgSO_4$. The reactions were filtered through Al_2O_3 and the filtrate was concentrated. The residue was purified by flash column chromatography and the solvents removed under reuced pressure to give the products.

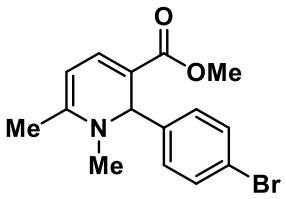
General procedure for dearomatization of *n*-alkyl pyridinium salts using (S,S)-Quinox-P* ligand (GPB):

The specified pyridinium salt (0.2 mmol, 1.0 equiv.), boronic acid pinacol ester (Bpin) (0.5 mmol, 2.5 equiv.), and Na_2CO_3 (53 mg. 0.5 mmol, 2.5 equiv.), were measured into a 1 dram scintilation vial on the benchtop. The vials containing pyridinium salt, Bpin, and Na_2CO_3 were transferred into the nitrogen filled glovebox where the Rh/Quinox stock solution of catalyst was added into each vial (1 mL, 0.2 M) . The vials were then sealed with a ptfe-lined septa cap and brought outside the glovebox. Degassed water (50 µL) was added to each reaction mixture *via* syringe and the reaction mixture was heated to 60 °C for 2 hours using an aluminum heating block. The vials were then removed from the heating block and cooled to room temperature. **Workup:** room temperature solutions were diluted with 1 mL of EtOAc and dried with 1.0 g of $MgSO_4$. The reactions were filtered through Al_2O_3 and the filtrate was concentrated. The residue was purified by flash column chromatography and the solvents removed under reuced pressure to give the products.



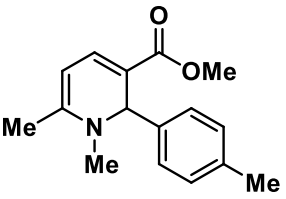
Methyl 1,6-dimethyl-2-phenyl-1,2-dihydropyridine-3-carboxylate (4.17) DHP **7** was synthesized using pyridinium salt **4.23** (63.0 mg) and PhBpin (102 mg) according to **GPA**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 37.5 mg (77%); The **enantiomeric excess** was determined by HPLC analysis to be 97% *ee*. **HPLC** (Chiral-V, water/methanol = gradient from 40:60 to 50:50 over 7 minutes, hold at 50:50, increase to 5:95 over 5 minutes, flow rate = 1.0 mL/min, l = 250 nm) tR = 17.84 min (major), 17.11 min (minor); **TLC:** R*f* = 0.18 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -0.378° (*c* 18.3 mg/mL, MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, J = 6.8 Hz, 2H), 7.32 – 7.21 (m, 3H), 7.11 (d, J = 6.5 Hz, 1H), 5.48 (s, 1H), 4.75 (d, J = 6.5 Hz, 1H), 3.65 (s, 3H), 2.99 (s,

3H), 2.01 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.3, 151.7, 142.5, 135.5, 128.6, 127.9, 126.8, 108.6, 94.5, 64.0, 51.2, 37.9, 20.6; **HRMS:** (ESI) *m/z* Calcd for $C_{15}H_{18}NO_2$ $[M+H]^+$ 244.1332, found 244.1332.



Methyl 2-(4-bromophenyl)-1,6-dimethyl-1,2-dihydropyridine-3-carboxylate (4.19.a)

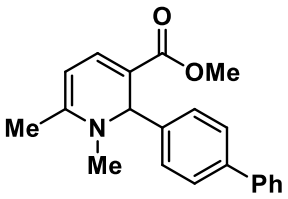
DHP **4.26a** was synthesized using pyridinium salt **4.23** (63.0 mg) and 4-bromophenyl Bpin (142 mg) according to **GPB**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 30.2 mg (47%); The **enantiomeric excess** was determined by HPLC analysis to be 90% *ee*. **HPLC** (Chiral-V, water/methanol = Gradient from 90:10 to 50:50 over 16 minutes, from 50:50 to 33:77 over 24 minutes, flow rate = 1.0 mL/min, l = 250 nm) tR = 31.94 min (major), 31.38 min (minor); **TLC:** R*f* = 0.12 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -0.250° (*c* 13.1 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.2, 1.5 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 6.6 Hz, 1H), 5.44 (s, 1H), 4.75 (d, J = 6.6 Hz, 1H), 3.65 (s, 3H), 2.97 (s, 3H), 2.00 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.0, 151.6, 141.3, 135.5, 131.7, 128.5, 121.8, 108.3, 94.5, 63.4, 51.2, 37.7, 20.5; **HRMS:** (ESI) *m/z* Calcd for $C_{15}H_{17}NO_2Br$ $[M+H]^+$ 322.0437, found 322.425.



Methyl 1,6-dimethyl-2-(4-methylphenyl)-1,2-dihydropyridine-3-carboxylate (4.19.b)

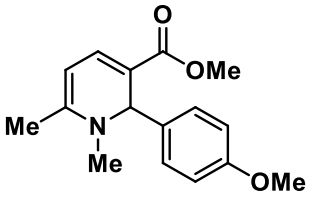
DHP **4.26.B** was synthesized using pyridinium salt **4.23** (63.0 mg) and 4-methylphenyl Bpin (109 mg) according to **GPA**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 43.1 mg (84%); The **enantiomeric excess** was determined by HPLC

analysis to be 98% *ee*. **HPLC** (Chiral-V, water/methanol = gradient from 60:40 to 50:50 over 5 minutes, to 5:95 over 35 minutes, flow rate = 1.0 mL/min, l = 250 nm) tR = 17.22 min (major), 16.67 min (minor); **TLC:** R*f* = 0.11 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +0.310° (*c* 19.4 mg/mL MeOH) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.1 Hz, 2H), 7.09 (m, 3H), 5.43 (s, 1H), 4.73 (d, J = 6.6 Hz, 1H), 3.64 (s, 3H), 2.98 (s, 3H), 2.30 (s, 3H), 1.99 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 151.6, 139.5, 137.5, 135.3, 129.2, 126.7, 108.5, 94.3, 63.6, 51.1, 37.7, 21.3, 20.6; **HRMS:** (ESI) *m/z* Calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found 258.1481.



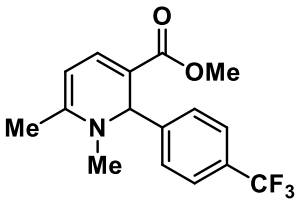
Methyl 2-([1,1'-biphenyl]-4-yl)-1,6-dimethyl-1,2-dihydropyridine-3-carboxylate (4.19.c)

DHP **4.26.c** was synthesized using pyridinium salt **4.23** (63.0 mg) and 4-biphenyl Bpin (140 mg) according to **GPA**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 37.9 mg (59%); The **enantiomeric excess** was determined by HPLC analysis to be 98% *ee*. **HPLC** (Chiral-V, water/methanol = gradient from 60:40 to 50:50 over 10 minutes, to 5:95 over 25 minutes, flow rate = 1.0 mL/min, l = 250 nm) tR = 24.43 min (major), 24.95 min (minor); **TLC:** R*f* = 0.17 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -0.267° (*c* 18.0 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (dt, J = 8.0, 1.4 Hz, 2H), 7.51 (dd, J = 8.3, 1.6 Hz, 2H), 7.47 (dd, J = 8.3, 1.6 Hz, 2H), 7.42 (td, J = 7.7, 1.6 Hz, 2H), 7.32 (td, J = 7.2, 1.4 Hz, 1H), 7.26 (s, 1H), 7.14 (dd, J = 6.6, 1.4 Hz, 1H), 5.53 (d, J = 1.4 Hz, 1H), 4.78 (d, J = 6.6 Hz, 1H), 3.67 (d, J = 1.4 Hz, 3H), 3.03 (d, J = 1.4 Hz, 3H), 2.04 (d, J = 1.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 151.7, 141.3, 141.1, 140.7, 135.5, 128.9, 127.4, 127.3, 127.2, 127.1, 108.3, 94.5, 63.6, 51.2, 37.8, 20.6; **HRMS:** (ESI) *m/z* Calcd for $C_{21}H_{22}NO_2$ $[M+H]^+$ 320.1645, found 320.1644.



Methyl 2-(4-methoxyphenyl)-1,6-dimethyl-1,2-dihydropyridine-3-carboxylate (4.19.d)

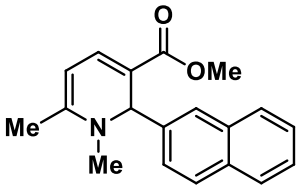
DHP **4.26.d** was synthesized using pyridinium salt **4.23** (63.0 mg) and 4-methoxyphenyl Bpin (107 mg) according to **GPA**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 34.1 mg (51%); The **enantiomeric excess** was determined by HPLC analysis to be 99% *ee*. **HPLC** (Chiral-V, water/methanol = gradient from 40:60 to 50:50 over 5 minutes, then to 5:95 over 35 minutes, flow rate = 1.0 mL/min, l = 250 nm) tR = 30.15 min (major), 28.16 min (minor); **TLC:** R*f* = 0.44 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$: -0.414° (*c* 16.5 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 6.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 2H), 5.41 (s, 1H), 4.73 (d, J = 6.5 Hz, 1H), 3.77 (s, 3H), 3.64 (s, 3H), 2.97 (s, 3H), 1.98 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 159.3, 151.5, 135.2, 134.9, 128.0, 113.8, 108.7, 94.1, 63.3, 55.3, 51.1, 37.5, 20.6; **HRMS:** (ESI) *m/z* Calcd for $C_{16}H_{20}NO_3$ $[M+H]^+$ 274.1438, found 274.1436.



Methyl 1,6-dimethyl-2-[4-(trifluoromethyl)phenyl]-1,2-dihydro-pyridine-3-carboxylate (4.19.e)

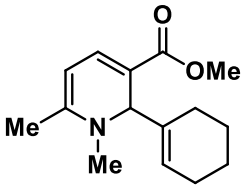
DHP **4.26.e** was synthesized using pyridinium salt **4.23** (63.0 mg) and 4-trifluoromethylphenyl Bpin (136 mg) according to **GPB**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 21.8 mg (35%); The **enantiomeric excess** was determined by HPLC analysis to be 81% *ee*. **HPLC** (Chiral-V, water/methanol= gradient from 60:40 to 50:50 over 5 minutes, hold for 20 minutes, then from 50:50 to 5:95 over 1 minute, flow rate = 1.0 mL/min, l = 250 nm) tR = 16.51 min (major), 15.61 min (minor); **TLC:** R*f* = 0.31

(Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -0.414° (*c* 7.70 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 4H), 7.11 (d, J = 6.6 Hz, 1H), 5.55 (s, 1H), 4.78 (d, J = 6.6 Hz, 1H), 3.66 (s, 3H), 2.99 (s, 3H), 2.03 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.0, 151.7, 146.0, 135.7, 129.9 (q, J = 32.3 Hz), 126.9, 125.6 (q, J = 3.8 Hz), 124.3 (q, J = 272.1 Hz), 108.1, 94.7, 63.5, 51.3, 37.9, 20.5; **^{19}F NMR** (471 MHz, $CDCl^3$) δ -62.49; **HRMS:** (ESI) *m/z* Calcd for $C_{16}H_{17}NO_2F_3$ $[M+H]^+$ 312.1206, found 312.1204.



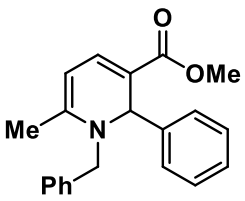
Methyl 1,6-dimethyl-2-(naphthalen-2-yl)-1,2-dihydropyridine-3-carboxylate (4.19.f)

DHP **4.26.f** was synthesized using pyridinium salt **4.23** (63.0 mg) and 2-napthyl Bpin (127 mg) according to **GPA**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%); **Yield:** 41.2 mg (70%); The **enantiomeric excess** was determined by HPLC analysis to be 99% *ee*. **HPLC** (Chiral-V, water/methanol = gradient from 60:40 to 50:50 over 5 minutes, then to 5:95 over 30 minutes, flow rate = 1.0 mL/min, l = 250 nm) tR = 21.64 min (major), 21.07 min (minor); **TLC:** R*f* = 0.18 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -0.113° (*c* 38.2 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 – 7.76 (m, 3H), 7.75 (s, 1H), 7.65 (dt, J = 8.5, 1.5 Hz, 1H), 7.44 (ddt, J = 8.3, 6.9, 5.2 Hz, 2H), 7.16 (d, J = 6.5 Hz, 1H), 5.64 (s, 1H), 4.79 (d, J = 6.6 Hz, 1H), 3.64 (s, 3H), 3.02 (s, 3H), 2.03 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 151.8, 139.6, 135.7, 133.3, 133.3, 128.6, 128.5, 127.7, 126.1, 125.9, 125.5, 125.0, 108.4, 94.4, 64.2, 51.2, 37.8, 20.6; **HRMS:** (ESI) *m/z* Calcd for $C_{19}H_{20}NO_2$ $[M+H]^+$ 294.1489, found 294.1487.



Methyl 2-(cyclohex-1-en-1-yl)-1,6-dimethyl-1,2-dihydropyridine-3-carboxylate (4.19.g)

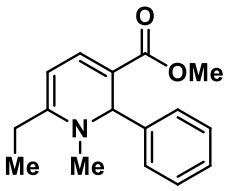
DHP **4.26.g** was synthesized using pyridinium salt **4.23** (63.0 mg) and cyclohex-1-ene-1-yl Bpin (104 mg) according to **GPB**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 15.5 mg (31%); The **enantiomeric excess** was determined by HPLC analysis to be 90% *ee*. **HPLC** (Chiral-V, water/methanol = gradient from 60:40 to 50:50 over 5 minutes, then to 5:95 over 30 minutes, flow rate = 1.0 mL/min, l = 250 nm) tR = 16.03 min (major), 15.53 min (minor); **TLC:** R*f* = 0.35 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -0.335° (*c* 3.80 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.05 (d, J = 6.5 Hz, 1H), 5.52 (qd, J = 3.0, 1.2 Hz, 1H), 4.86 (s, 1H), 4.61 (d, J = 6.6 Hz, 1H), 3.67 (s, 3H), 2.93 (s, 3H), 2.16 – 2.06 (m, 1H), 1.99 (dt, J = 6.0, 3.0 Hz, 2H), 1.61 – 1.53 (m, 3H), 1.50 (tdd, J = 12.4, 6.7, 4.6 Hz, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.4, 152.0, 136.3, 136.1, 122.3, 105.6, 94.2, 66.3, 51.0, 37.5, 25.1, 23.8, 22.8, 22.5, 20.3; **HRMS:** (ESI) *m/z* Calcd for $C_{15}H_{22}NO_2$ $[M+H]^+$ 248.1645, found 248.1644.



Methyl 1-benzyl-6-methyl-2-phenyl-1,2-dihydropyridine-3-carboxylate (4.20.a)

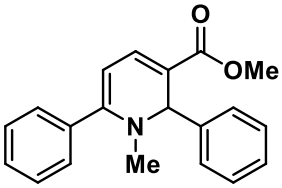
DHP **4.28.a** was synthesized using pyridinium salt **4.27.a** (78.3 mg) and phenyl Bpin (102 mg) according to **GPA**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 60.8 mg (95%); The **enantiomeric excess** was determined by HPLC analysis to be 99% *ee*. **HPLC** (Chiral-CD, water/acetonitrile = gradient from 75:25 to 5:95 over 7 minutes, hold for 2 minutes, flow rate = 1.0 mL/min, l = 250 nm) tR = 8.38 min (major), 7.89 min

(minor); **TLC:** R*f* = 0.31 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +1.41° (*c* 20.8 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.42 – 7.27 (m, 4H), 7.28 – 7.23 (m, 2H), 7.20 (d, J = 6.5 Hz, 1H), 5.58 (s, 1H), 4.87 (d, J = 6.5 Hz, 1H), 4.77 (d, J = 16.8 Hz, 1H), 4.31 (d, J = 16.8 Hz, 1H), 3.66 (s, 2H), 2.05 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.1, 151.0, 143.2, 137.6, 135.5, 129.0, 128.5, 127.8, 127.6, 126.8, 126.4, 109.6, 95.5, 61.6, 53.2, 51.1, 20.5; **HRMS:** (ESI) *m/z* Calcd for $C_{21}H_{22}NO_2$ $[M+H]^+$ 320.1645, found 320.1645.



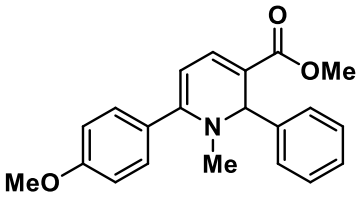
Methyl 6-ethyl-1-methyl-2-phenyl-1,2-dihydropyridine-3-carboxylate (4.20.b)

DHP **4.28.b** was synthesized using pyridinium salt **4.27.b** (65.9 mg) and phenyl Bpin (102 mg) according to **GPA**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 30.9 mg (60%); The **enantiomeric excess** was determined by HPLC analysis to be 98% *ee*. **HPLC** (Chiral-V, water/methanol = gradient from 60:40 to 50:50 over 30 minutes, to 5:95 over 5 minutes, flow rate = 0.75 mL/min, l = 250 nm) tR = 25.89 min (major), 24.22 min (minor); **TLC:** R*f* = 0.29 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -0.356 ° (*c* 14.4 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.35 – 7.23 (m, 3H), 7.19 (d, J = 6.5 Hz, 1H), 5.51 (s, 1H), 4.81 (d, J = 6.5 Hz, 1H), 3.69 (s, 3H), 3.04 (s, 3H), 2.34 (ddt, J = 18.9, 15.3, 7.7 Hz, 2H), 1.18 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 156.5, 142.5, 135.6, 128.6, 127.9, 126.8, 108.3, 92.8, 64.1, 51.2, 37.6, 26.5, 12.4; **HRMS:** (ESI) *m/z* Calcd for $C_{16}H_{20}NO_2$ $[M+H]^+$ 258.1489, found 258.1489.



Methyl 1-methyl-2,6-diphenyl-1,2-dihydropyridine-3-carboxylate (4.20.c)

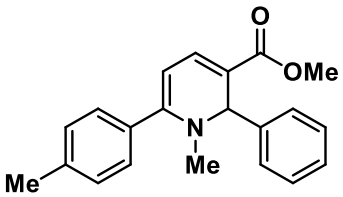
DHP **4.28.c** was synthesized using pyridinium salt **4.27.c** (75.5 mg) and phenyl Bpin (102 mg) according to **GPA**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 53.1 mg (87%); The **enantiomeric excess** was determined by HPLC analysis to be 95% *ee*. **HPLC** (Chiral-V, water/methanol = 50:50 for 30 minutes, 50:50 to 0:100 over 2 minutes, flow rate = 1.0 mL/min, l = 250 nm) tR = 29.09min (major), 25.88 min (minor); **TLC:** R*f* = 0.08 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +0.171° (*c* 33.8 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.36 (q, J = 3.4 Hz, 3H), 7.32 (td, J = 5.4, 3.3 Hz, 3H), 7.28 (dd, J = 6.7, 1.6 Hz, 2H), 5.55 (s, 1H), 5.05 (d, J = 6.4 Hz, 1H), 3.70 (s, 3H), 2.96 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 153.3, 142.7, 136.8, 134.7, 129.2, 128.6 (2C), 128.3, 127.9, 126.6, 109.9, 98.2, 63.1, 51.4, 40.9; **HRMS:** (ESI) *m/z* Calcd for $C_{20}H_{20}NO_2$ $[M+H]^+$ 306.1489, found 306.1489.



Methyl 6-(4-methoxyphenyl)-1-methyl-2-phenyl-1,2-dihydro-pyridine-3-carboxylate (4.20.d)

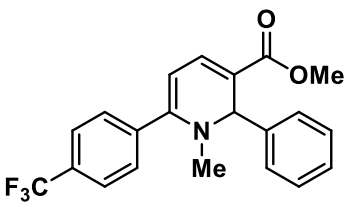
DHP **4.28.d** was synthesized using pyridinium salt **4.27.d** (81.5 mg) and phenyl Bpin (102 mg) according to **GPA**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 34.1 mg (51%); The **enantiomeric excess** was determined by HPLC analysis to be 94% *ee*. **HPLC** (Chiral-V, water/methanol = 50:50 for 30 minutes, flow rate = 1.0 mL/min, l = 250 nm) tR = 30.15 min (major), 28.16 min (minor); **TLC:** R*f* = 0.27 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: -0.318° (*c* 16.6 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.50

(m, 2H), 7.33 (dd, J = 8.1, 6.5 Hz, 2H), 7.31 – 7.26 (m, 4H), 6.93 – 6.87 (m, 2H), 5.55 (s, 1H), 5.06 (d, J = 6.4 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.00 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.3, 160.5, 153.1, 142.8, 134.9, 129.7, 129.2, 128.5, 127.8, 126.5, 114.0, 109.4, 98.1, 63.0, 55.5, 51.4, 41.1; **HRMS:** (ESI) *m/z* Calcd for $C_{21}H_{22}NO_3$ $[M+H]^+$ 336.1594, found 336.1594.



Methyl 1-methyl-6-(4-methylphenyl)-2-phenyl-1,2-dihydro-pyridine-3-carboxylate (4.20.e)

DHP **4.28.e** was synthesized using pyridinium salt **4.27.e** (78.3 mg) and phenyl Bpin (102 mg) according to **GPA**. The crude reaction mixture was purified by flash chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 53.6 mg (84%); The **enantiomeric excess** was determined by HPLC analysis to be 99% *ee*. **HPLC** (Chiral-V, water/methanol = 50:50 over 25 minutes, to 0:100 over 7 minutes, flow rate = 0.75 mL/min, l = 250 nm) tR = 32.57 min (major), 31.93 min (minor); **TLC:** R*f* = 0.31 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$: +0.251° (*c* 25.8 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 2H), 7.37 (t, J = 7.2 Hz, 2H), 7.34 – 7.29 (m, 2H), 7.27 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 5.60 (s, 1H), 5.09 (s, 1H), 3.75 (s, 3H), 3.02 (s, 3H), 2.41 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 153.5, 142.8, 139.4, 134.8, 133.9, 129.3, 128.6, 128.2, 127.9, 126.6, 109.6, 98.0, 63.1, 51.4, 41.0, 21.4; **HRMS:** (ESI) *m/z* Calcd for $C_{21}H_{22}NO_2$ $[M+H]^+$ 320.1645, found 320.1645; **HRMS:** (ESI) *m/z* Calcd for $C_{21}H_{22}NO_2$ $[M+H]^+$ 320.1645, found 320.1645.



Methyl 1-methyl-2-phenyl-6-[4-(trifluoromethyl)phenyl]-1,2-dihydropyridine-3-carboxylate (4.20.f)

DHP **4.28.f** was synthesized using pyridinium salt **4.27.f** (89.1 mg) and phenyl Bpin (102 mg) according to **GPA**. The crude reaction mixture was purified by flash

chromatography (ethyl acetate:hexanes 1:9 with 1% Et_3N) over silica treated with a solution of Et_3N in hexanes (1%). **Yield:** 70.7 mg (95%); The **enantiomeric excess** was determined by HPLC analysis to be 97% *ee*. **HPLC** (Chiral-V, water/methanol = 50:50 for 30 minutes, to 0:100 over 2 minutes flow rate = 1.0 mL/min, l = 250 nm) tR = 30.12 min (major), 28.24 min (minor); **TLC:** R*f* = 0.30 (Hexanes:Ethyl acetate, 9:1); $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$: +1.09° (*c* 6.80 mg/mL MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (d, J = 8.0 Hz, 2H), 7.54 – 7.49 (m, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.37 – 7.33 (m, 2H), 7.32 – 7.27 (m, 2H), 5.54 (s, 1H), 5.10 (d, J = 6.4 Hz, 1H), 3.71 (s, 3H), 2.94 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.0, 151.3, 142.4, 140.4, 134.9, 134.1, 131.1 – 122.5 (m), 128.7 (d, J = 10.5 Hz), 128.1, 126.62, 125.6 (q, J = 3.8 Hz), 111.5, 99.2, 83.9, 63.1, 51.5, 40.9; **^{19}F NMR** (471 MHz, $CDCl_3$) δ -62.7; **HRMS:** (ESI) *m/z* Calcd for $C_{21}H_{19}NO_2$ $[M+H]^+$ 374.1368, found 374.1362.

4.7. References:

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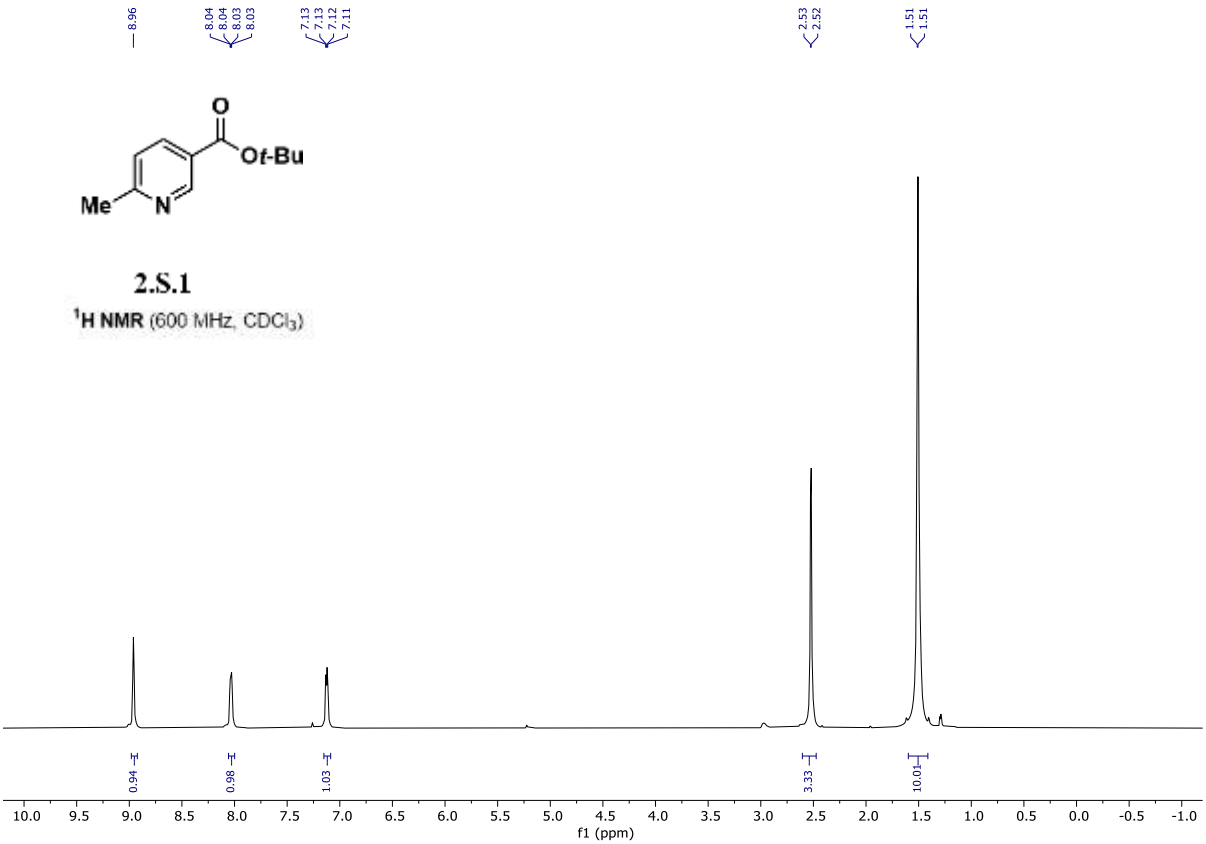
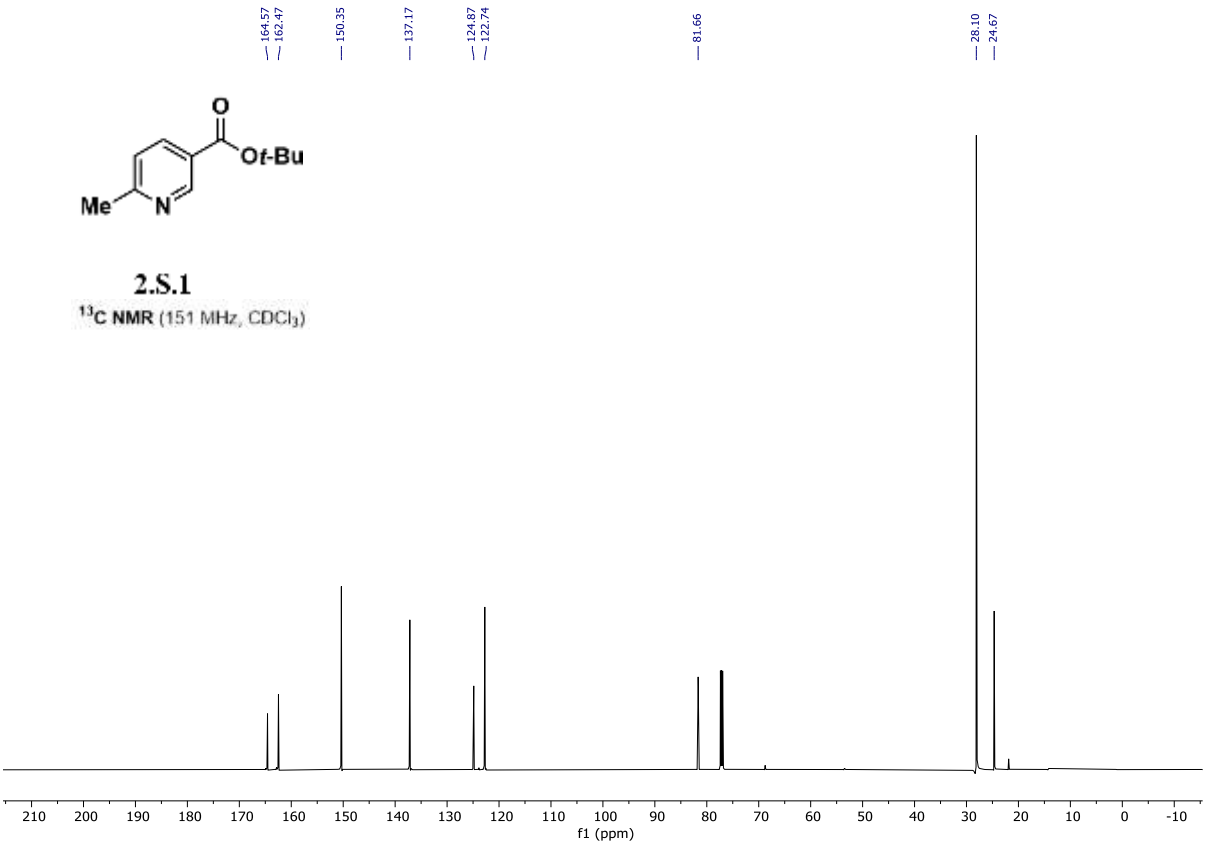
Appendix A: NMR Spectra for Chapter 2



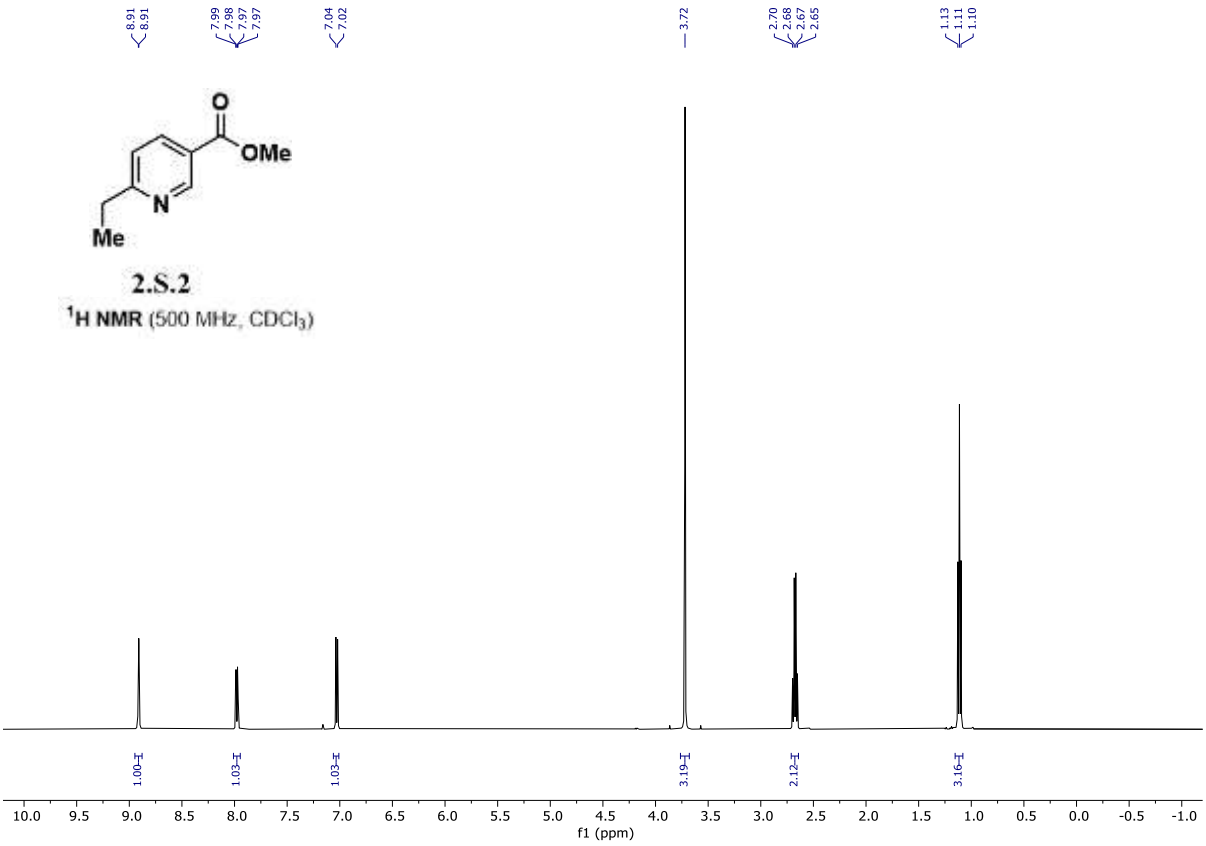
2.S.1

^{1}H NMR (600 MHz, $CDCl_3$)



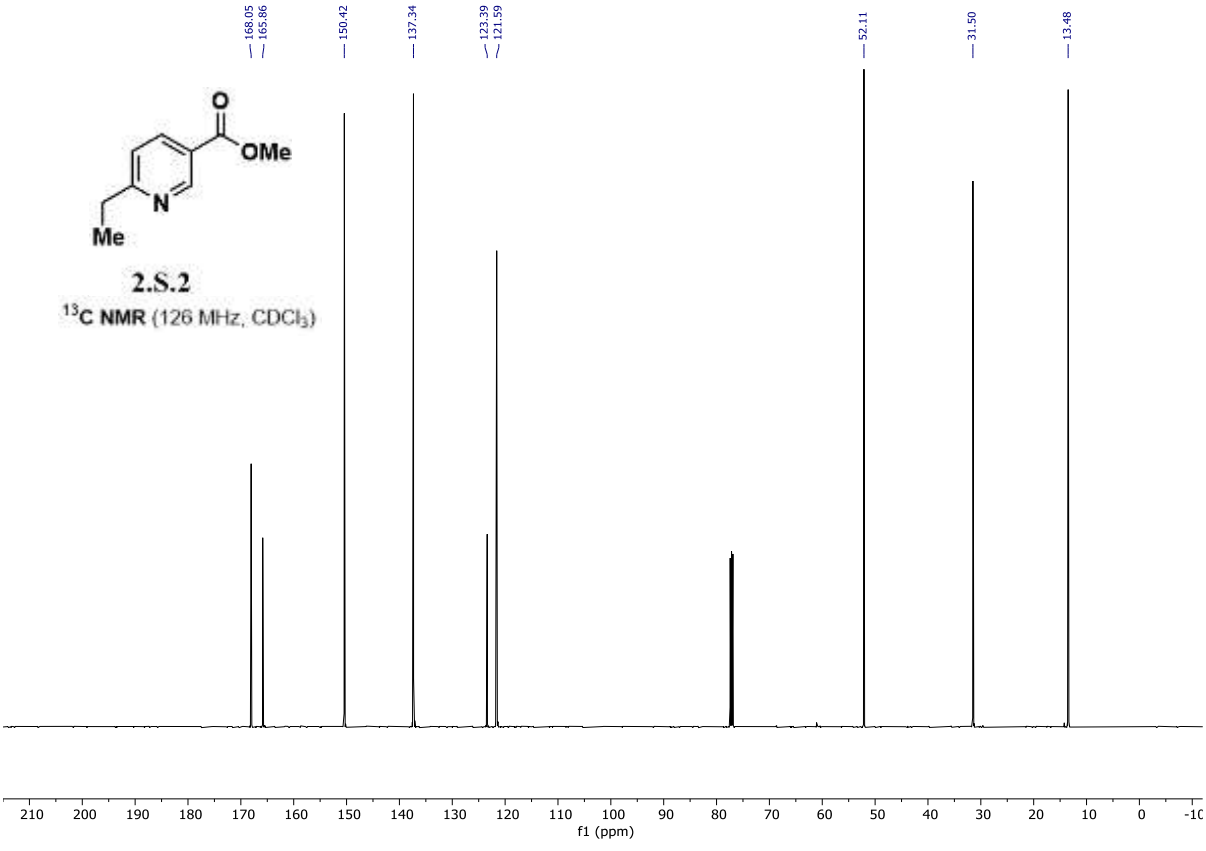
2.S.1

^{13}C NMR (151 MHz, $CDCl_3$)



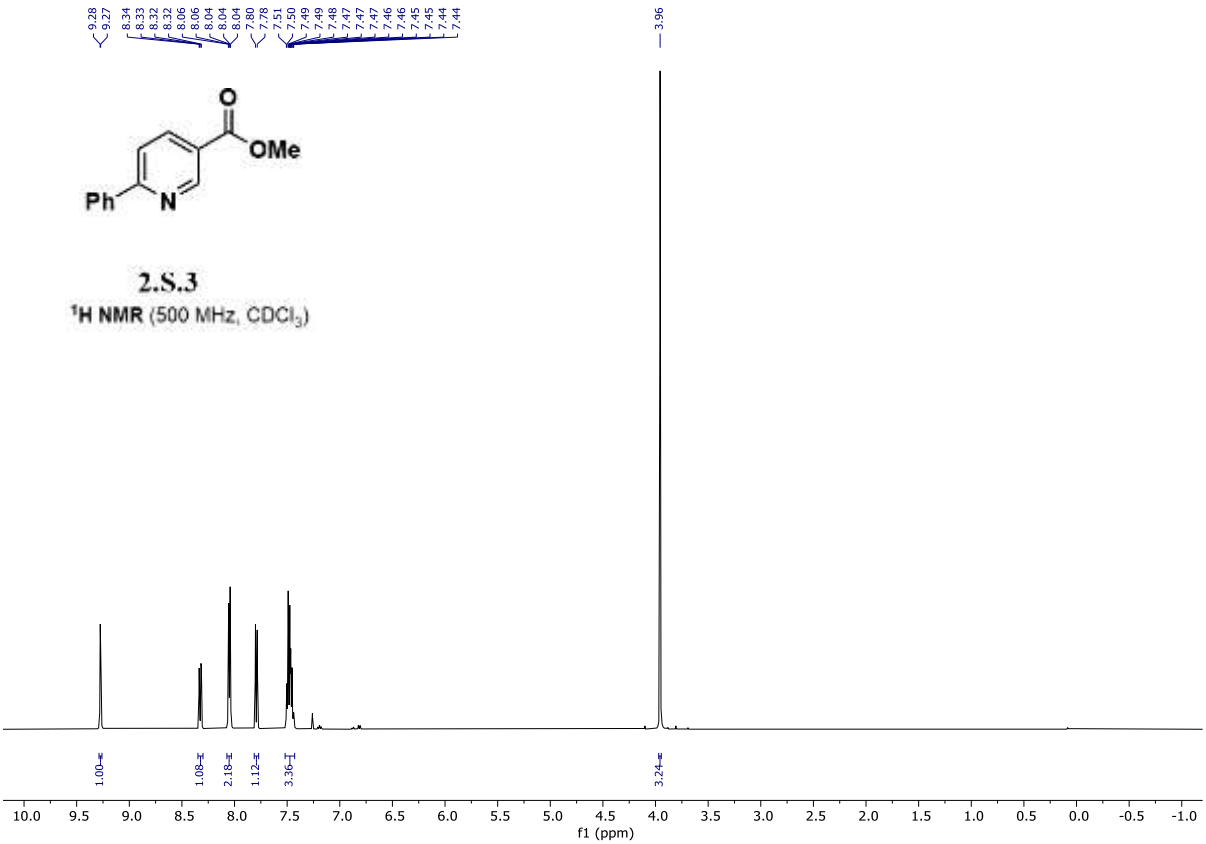
2.S.2

^{1}H NMR (500 MHz, $CDCl_3$)



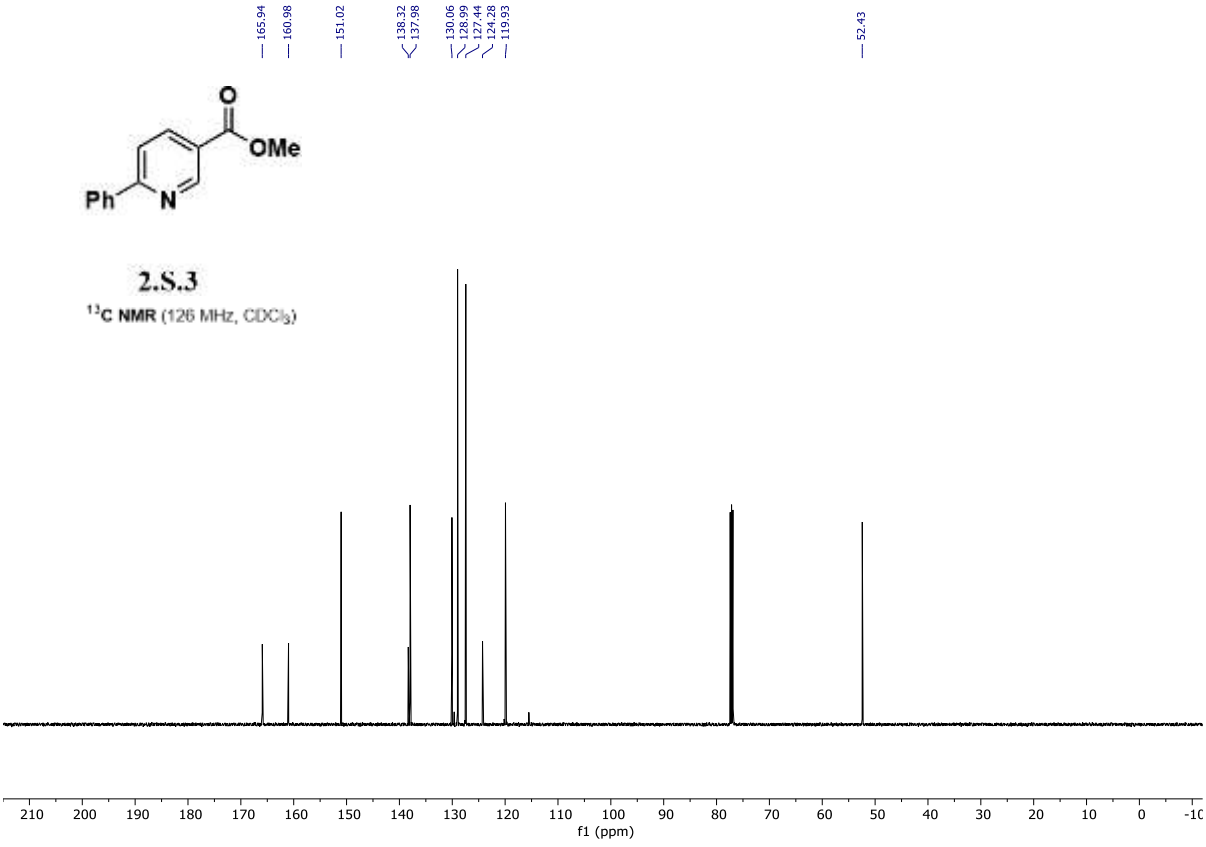
2.S.2

^{13}C NMR (126 MHz, $CDCl_3$)



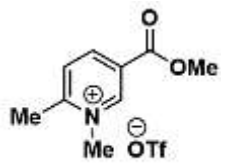
2.S.3

^{1}H NMR (500 MHz, $CDCl_3$)



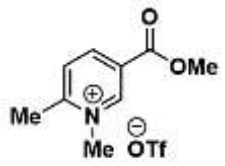
2.S.3

^{13}C NMR (126 MHz, $CDCl_3$)



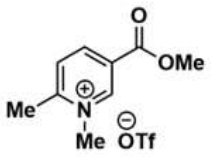
2.7

^{1}H NMR (500 MHz, CD_3OD)



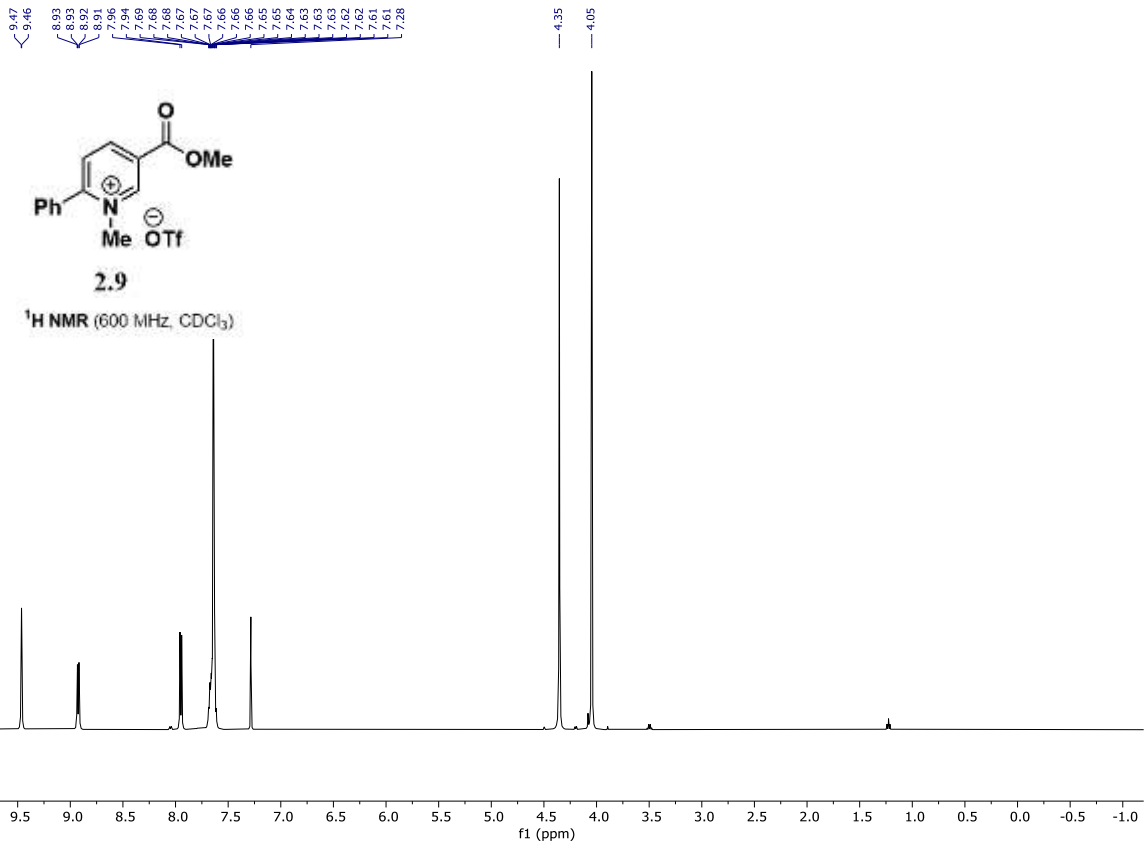
2.7

^{13}C NMR (126 MHz, CD_3OD)



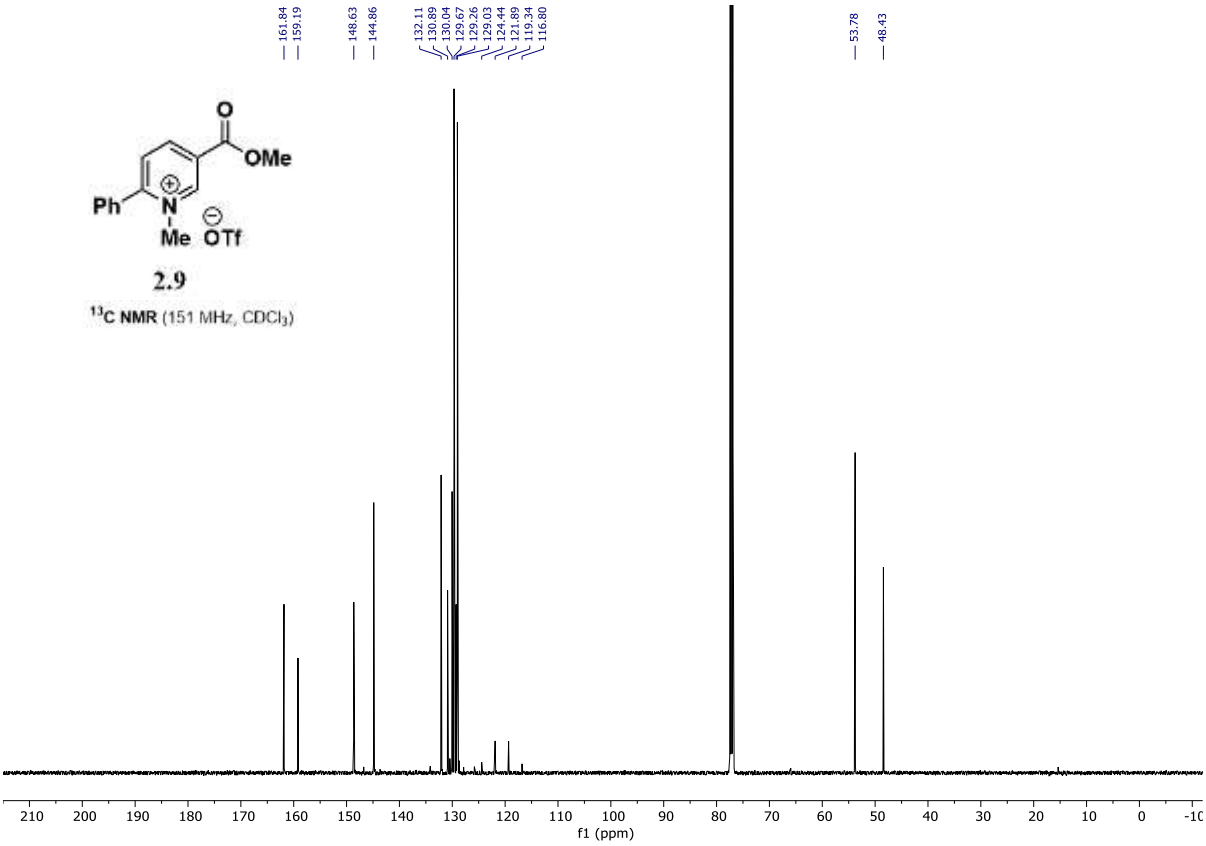
2.7

^{19}F NMR (235 MHz, $CDCl_3$)



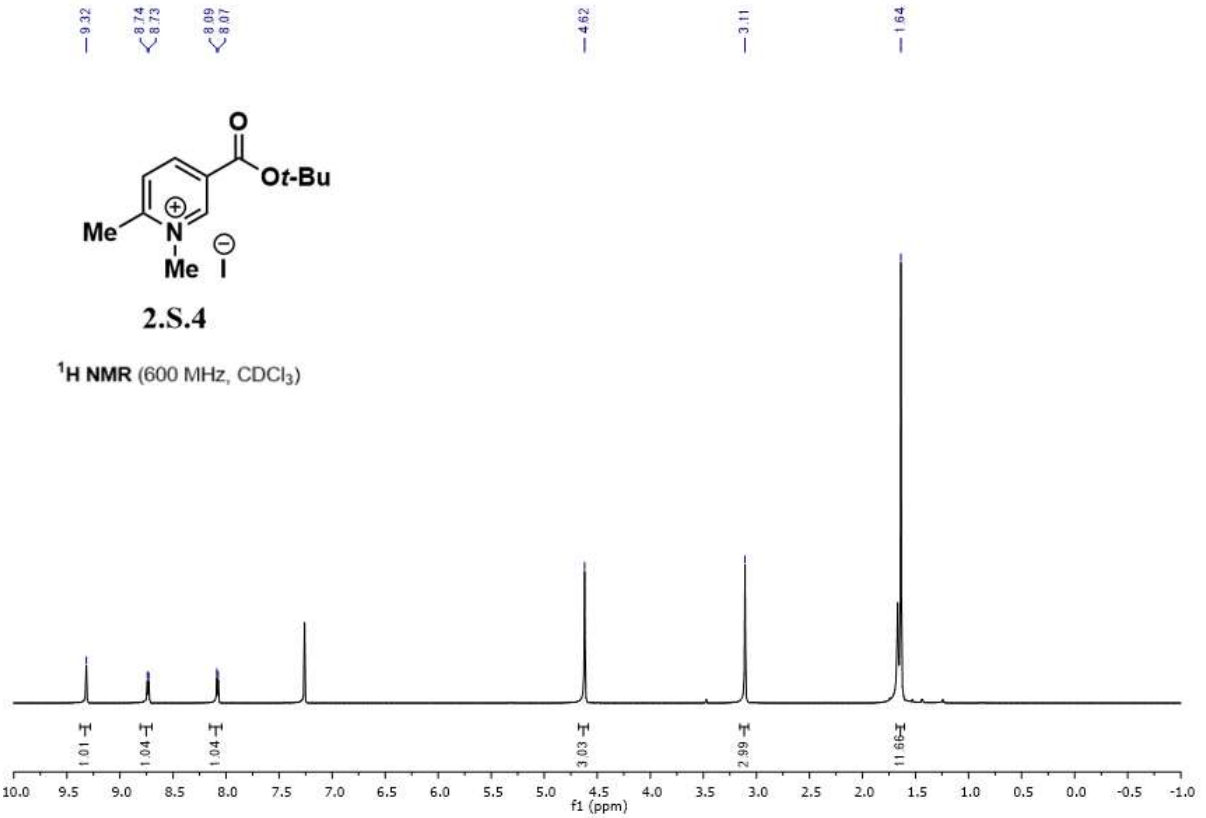
2.9

^{1}H NMR (600 MHz, $CDCl_3$)



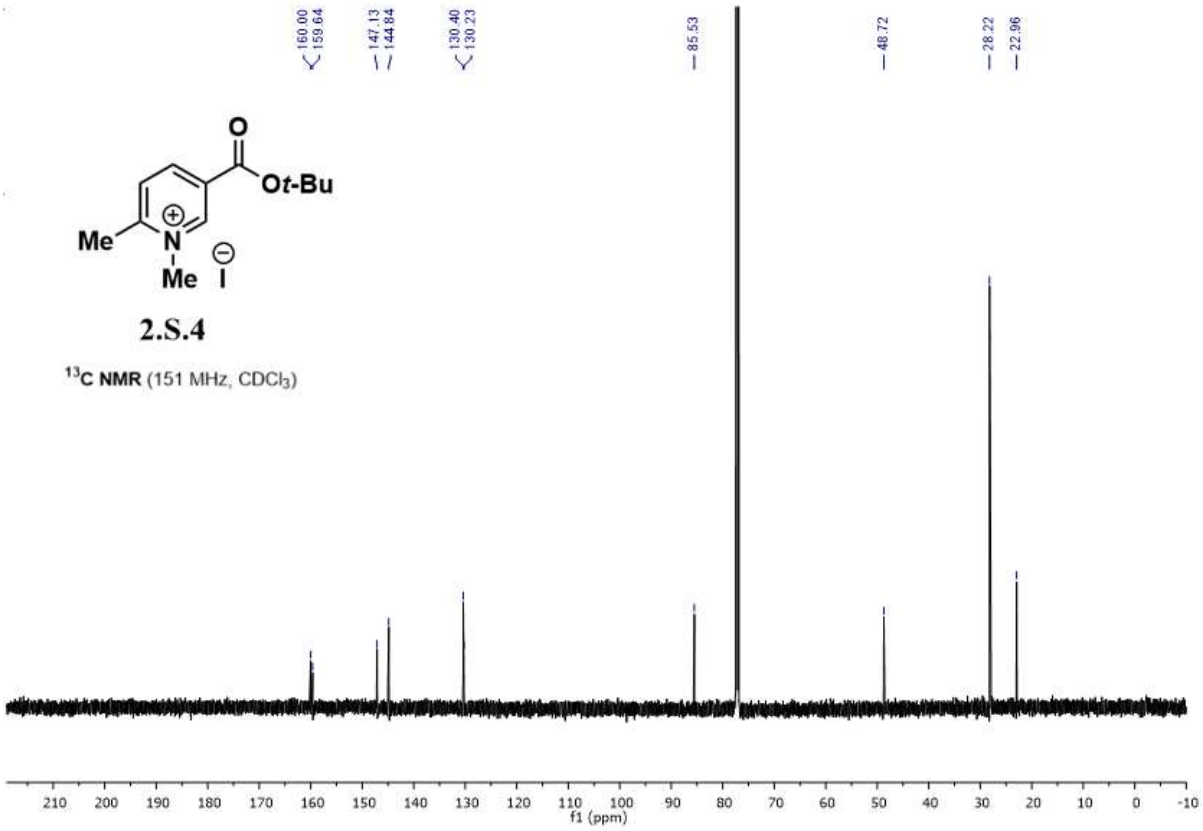
2.9

^{13}C NMR (151 MHz, $CDCl_3$)



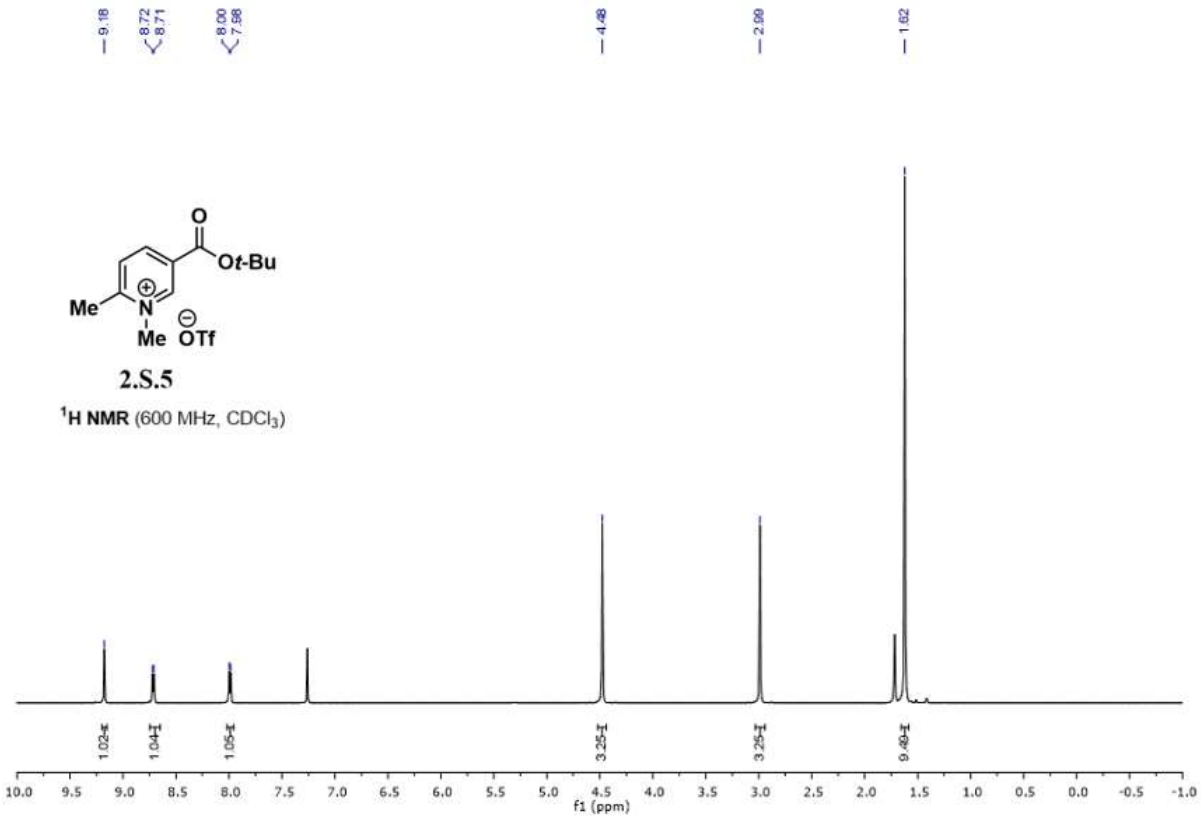
2.S.4

^{1}H NMR (600 MHz, $CDCl_3$)



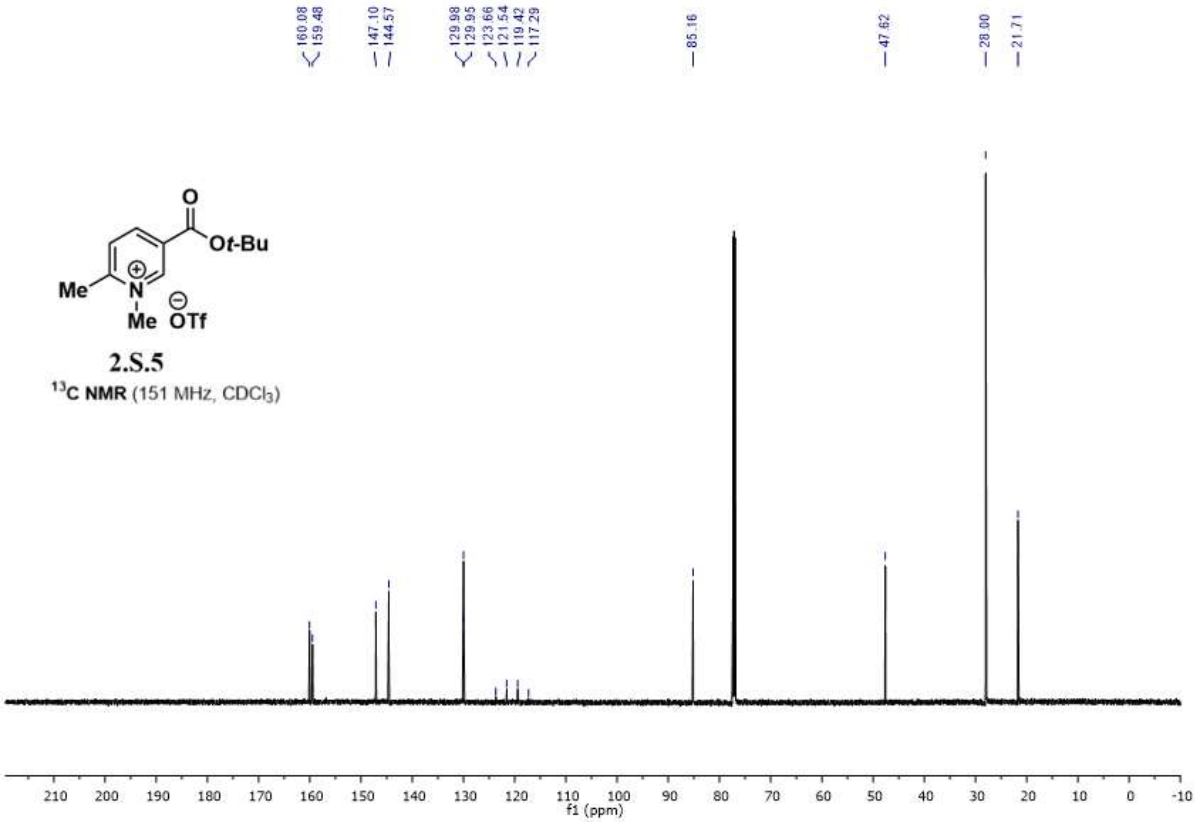
2.S.4

^{13}C NMR (151 MHz, $CDCl_3$)



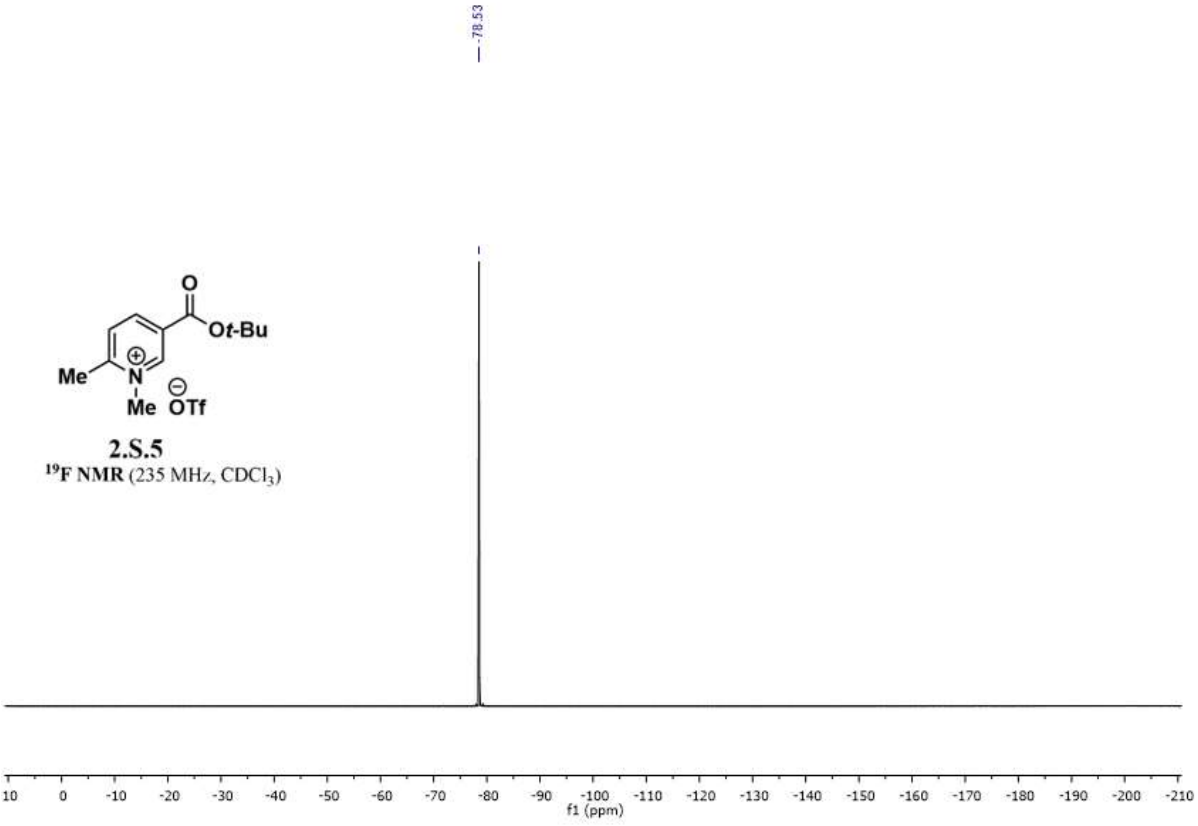
2.S.5

^{1}H NMR (600 MHz, $CDCl_3$)



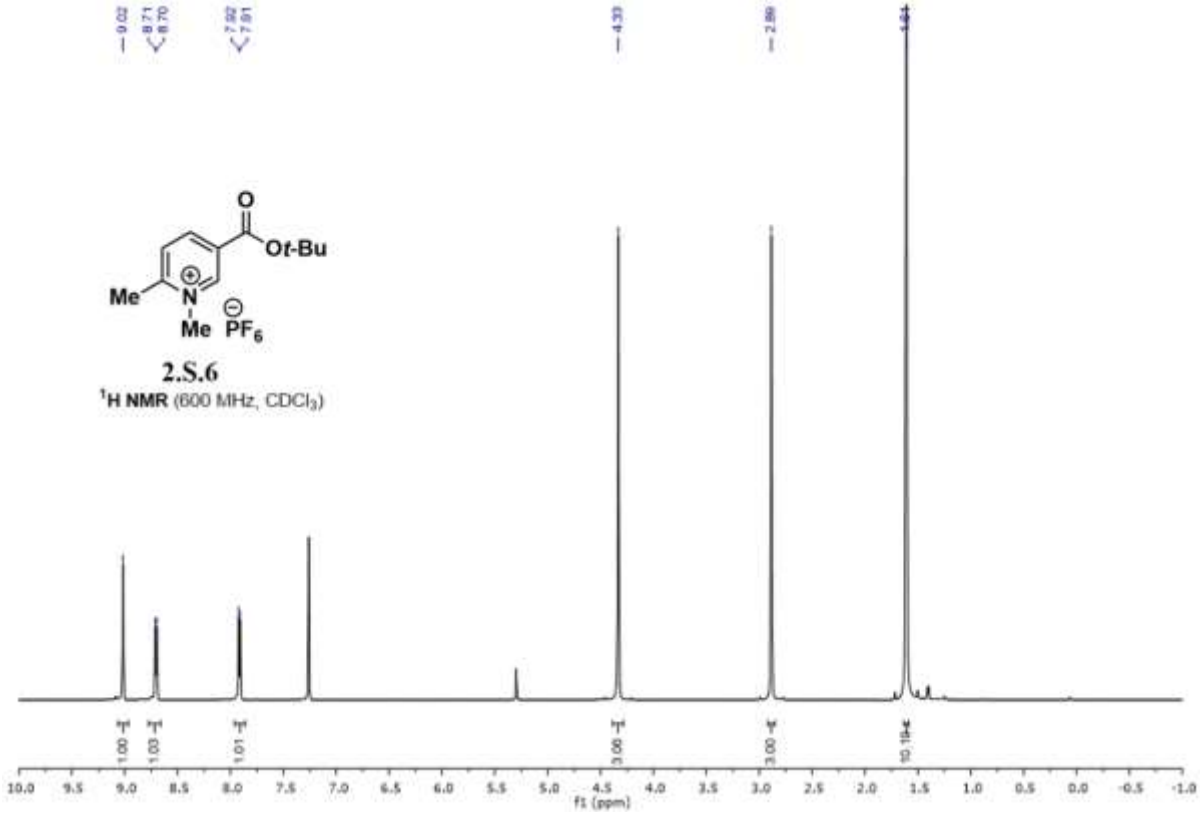
2.S.5

^{13}C NMR (151 MHz, $CDCl_3$)



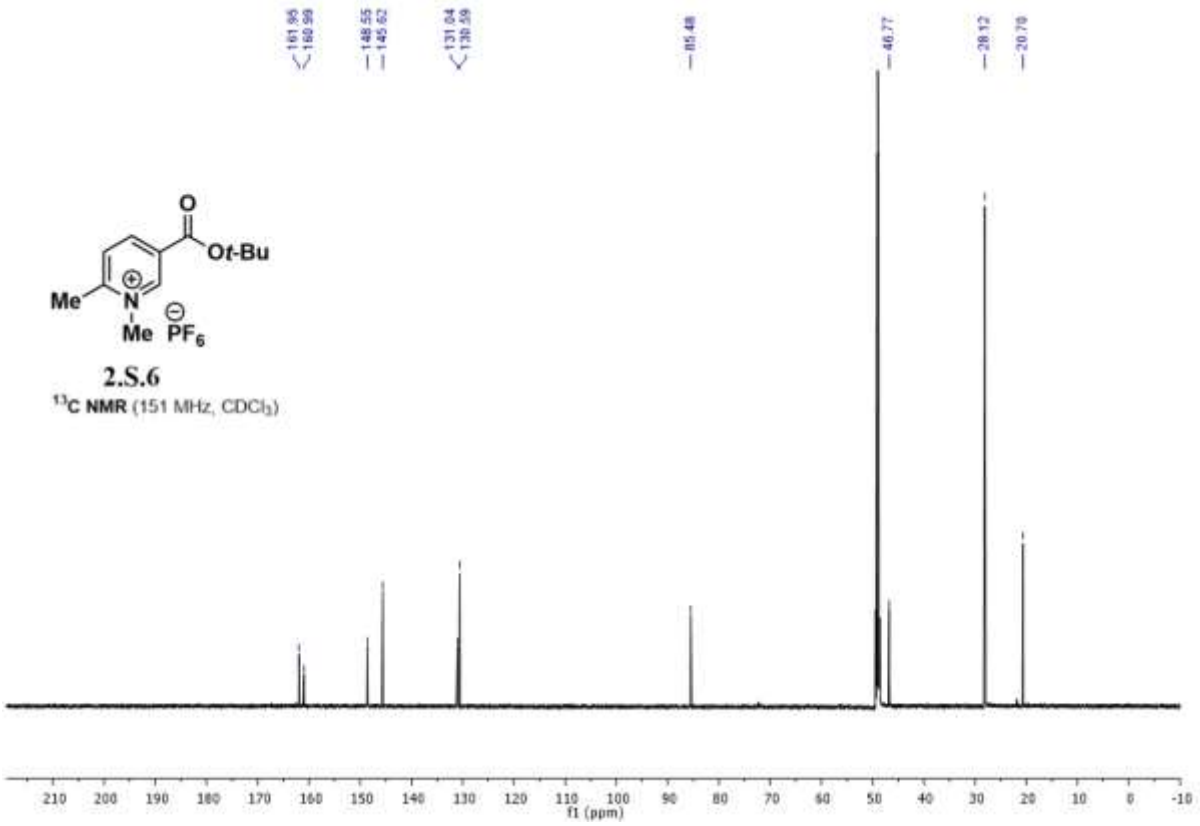
2.S.5

^{19}F NMR (235 MHz, $CDCl_3$)



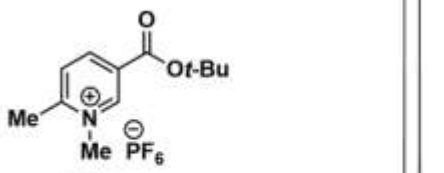
2.S.6

^{1}H NMR (600 MHz, $CDCl_3$)



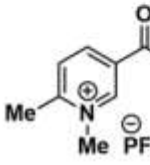
2.S.6

^{13}C NMR (151 MHz, $CDCl_3$)



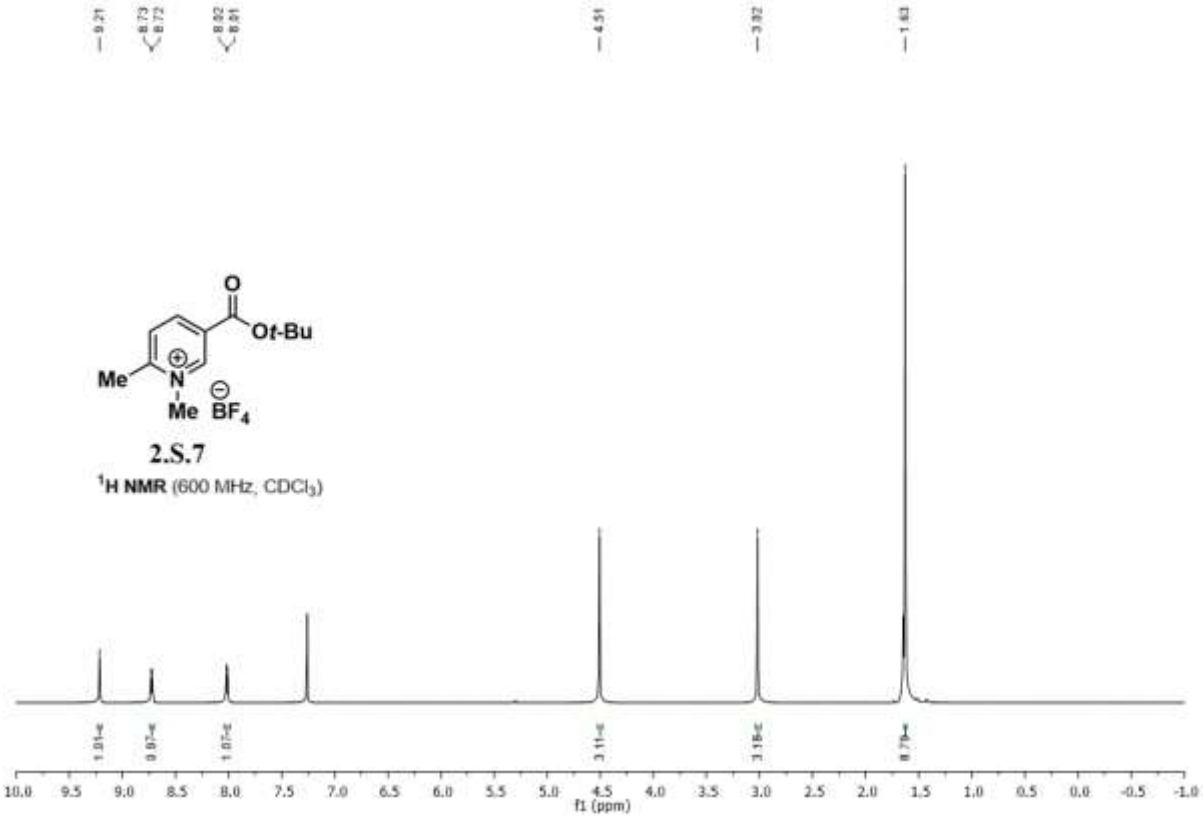
2.S.6

^{19}F NMR (235 MHz, $CDCl_3$)



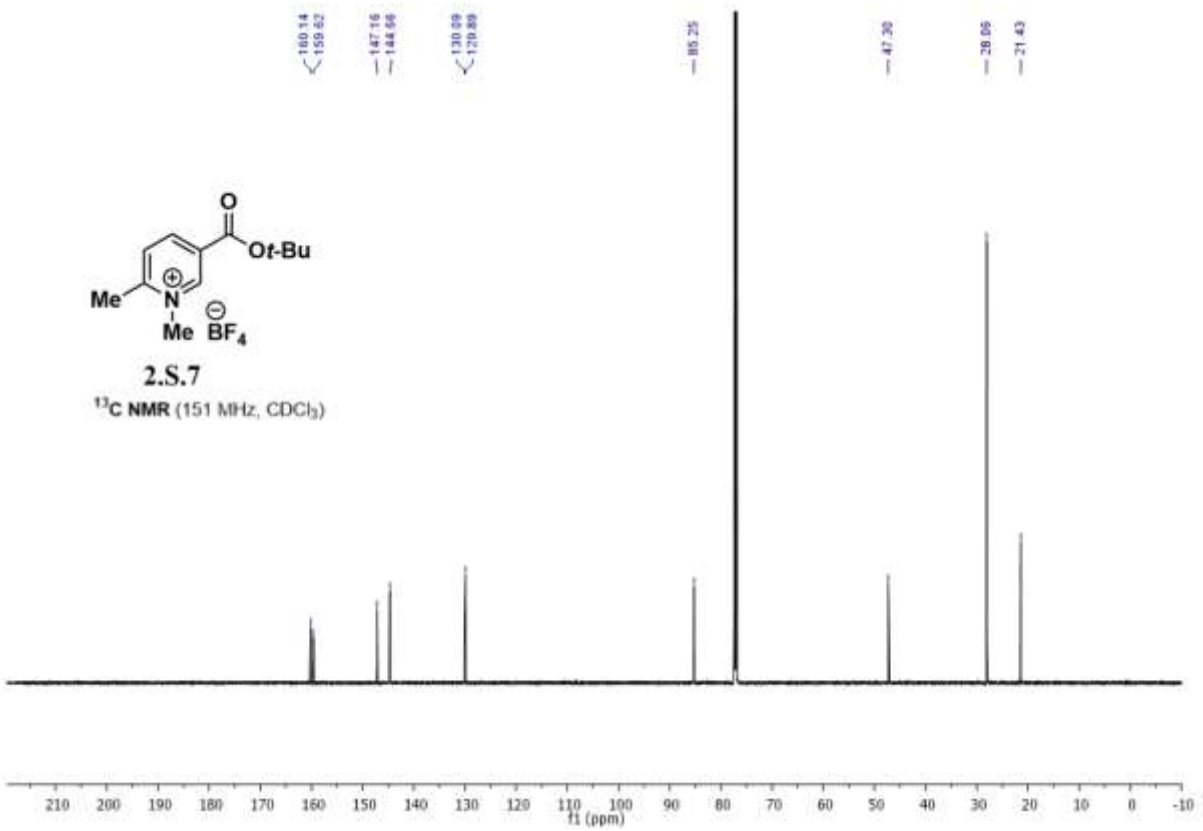
2.S.6

^{31}P NMR (101 MHz, $CDCl_3$)



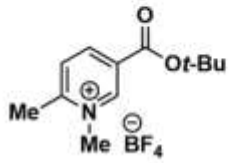
2.S.7

^{1}H NMR (600 MHz, $CDCl_3$)



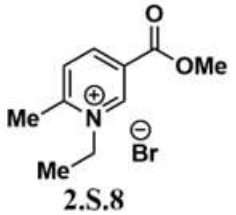
2.S.7

^{13}C NMR (151 MHz, $CDCl_3$)



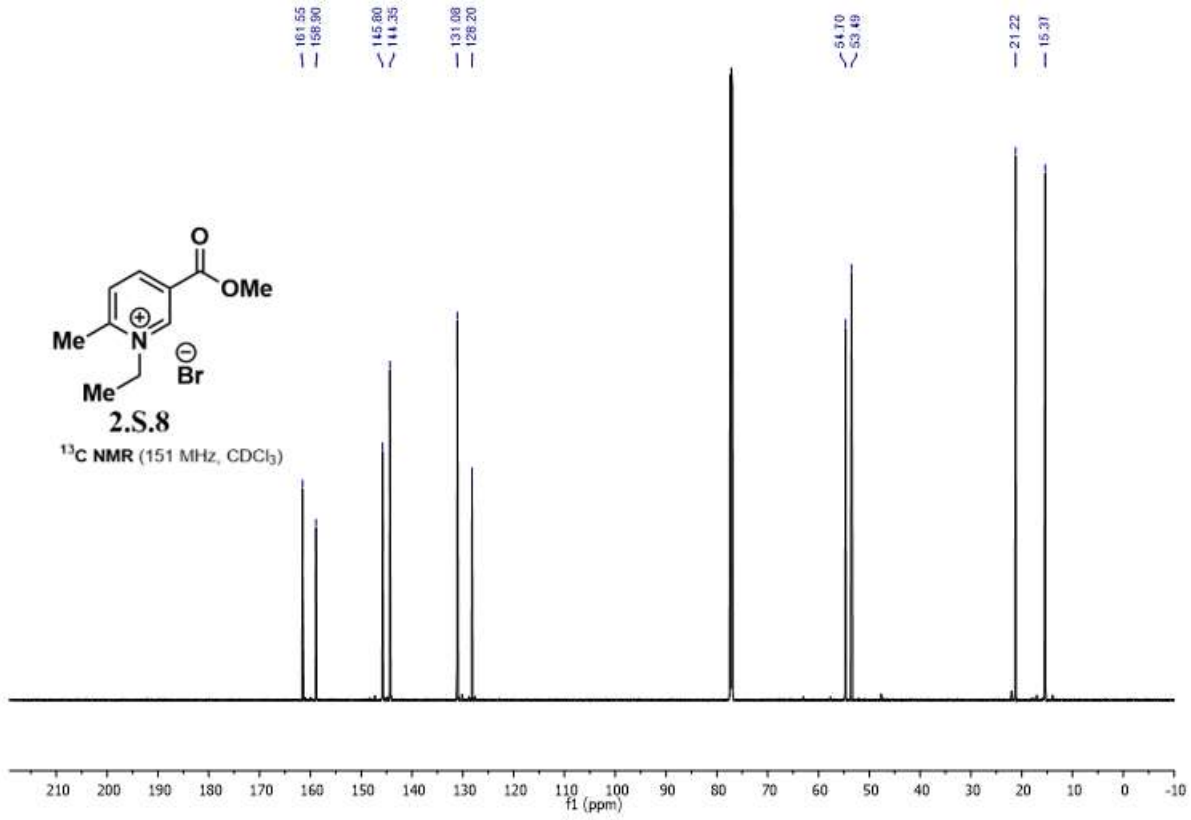
2.S.7

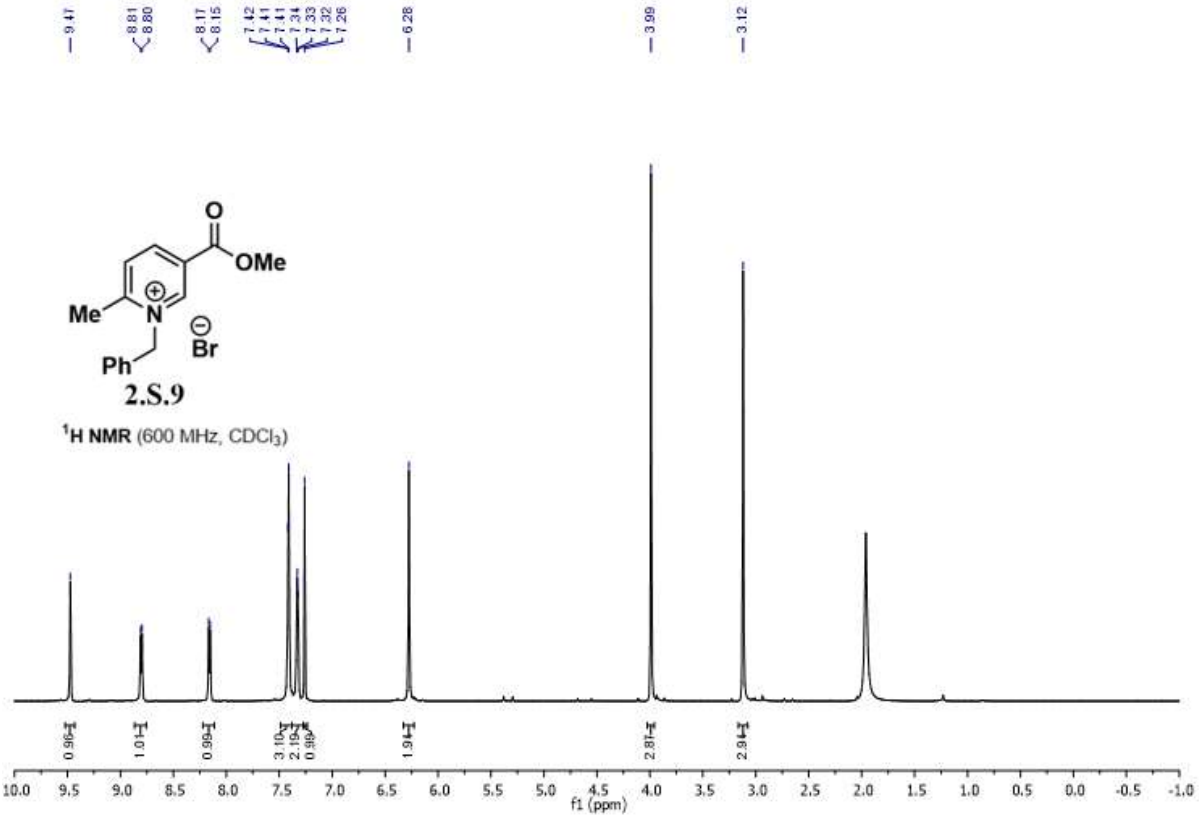
^{19}F NMR (235 MHz, $CDCl_3$)

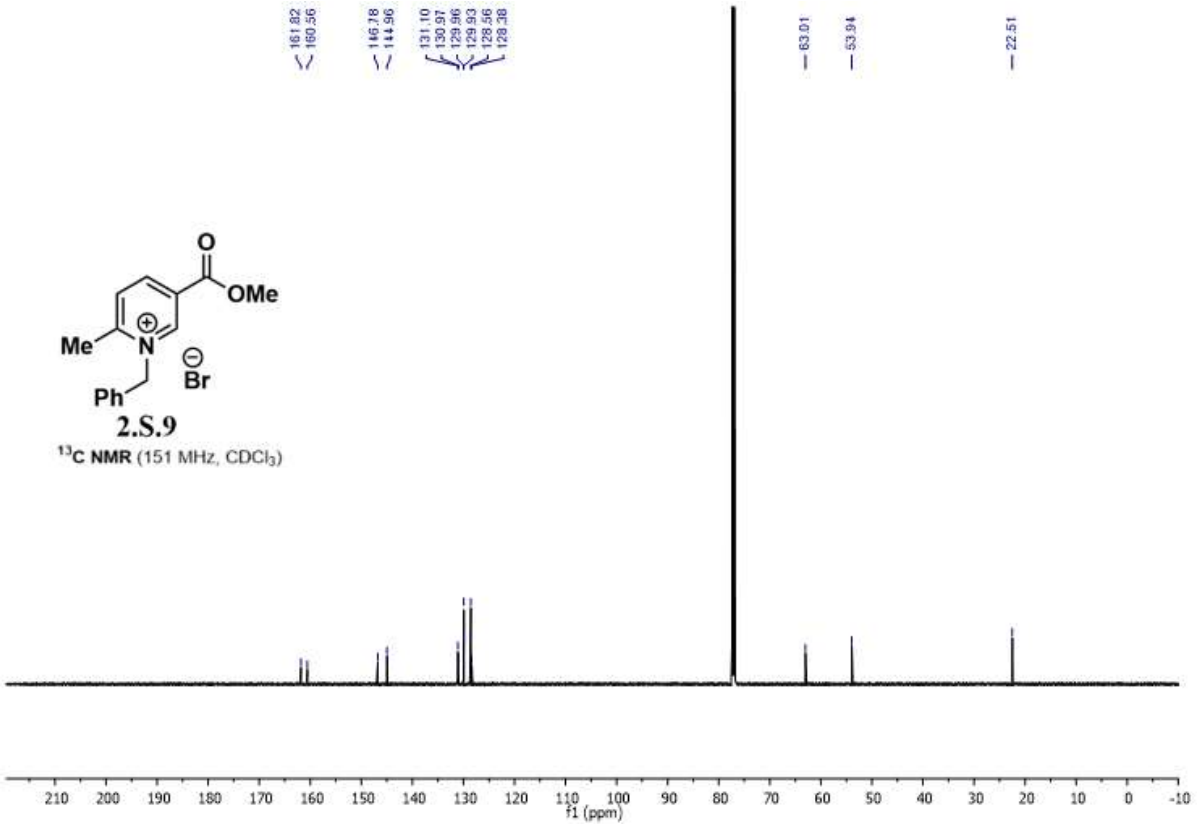


2.S.8

^{1}H NMR (600 MHz, $CDCl_3$)

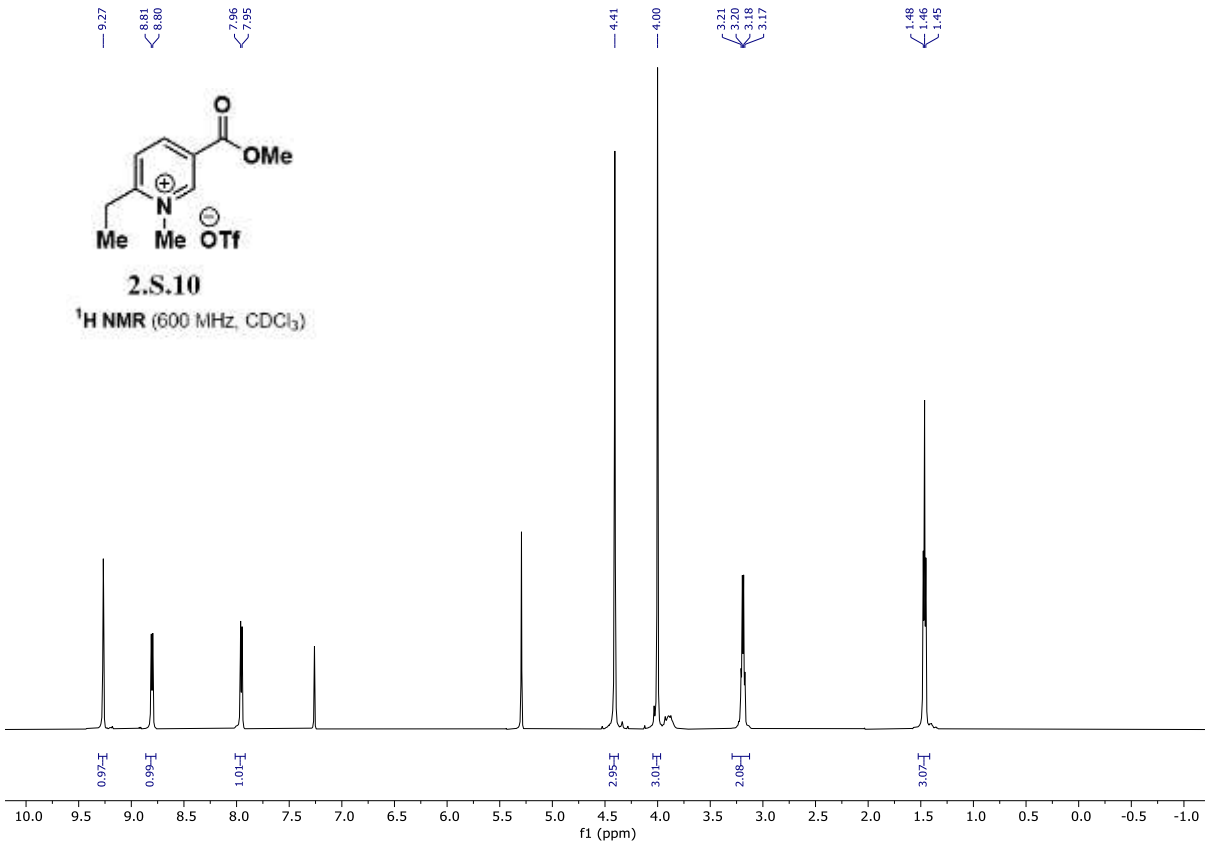

161.55
158.90
145.80
144.35
131.08
128.20
64.70
53.49
21.22
15.37
O
OMe
Me
N
Br
Me
2.S.8
13C NMR (151 MHz, CDCl3)
f1 (ppm)


9.47
8.81
8.80
8.17
8.15
7.42
7.41
7.41
7.34
7.33
7.32
7.26
6.28
3.99
3.12
O
OMe
Me
N
Br
Ph
2.S.9
1H NMR (600 MHz, CDCl3)
0.96
1.01
0.99
3.10
2.19
0.99
1.94
2.81
2.94
f1 (ppm)



2.S.9

^{13}C NMR (151 MHz, $CDCl_3$)



2.S.10

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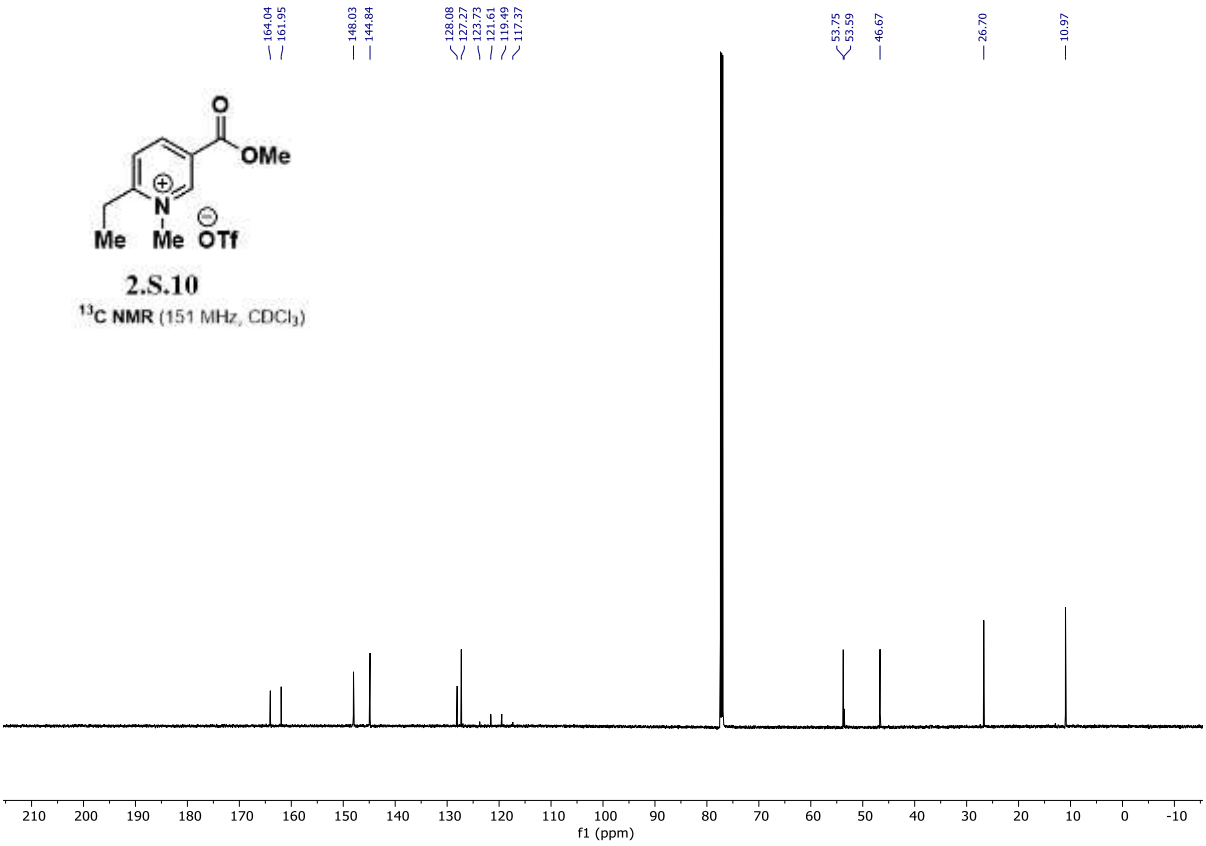
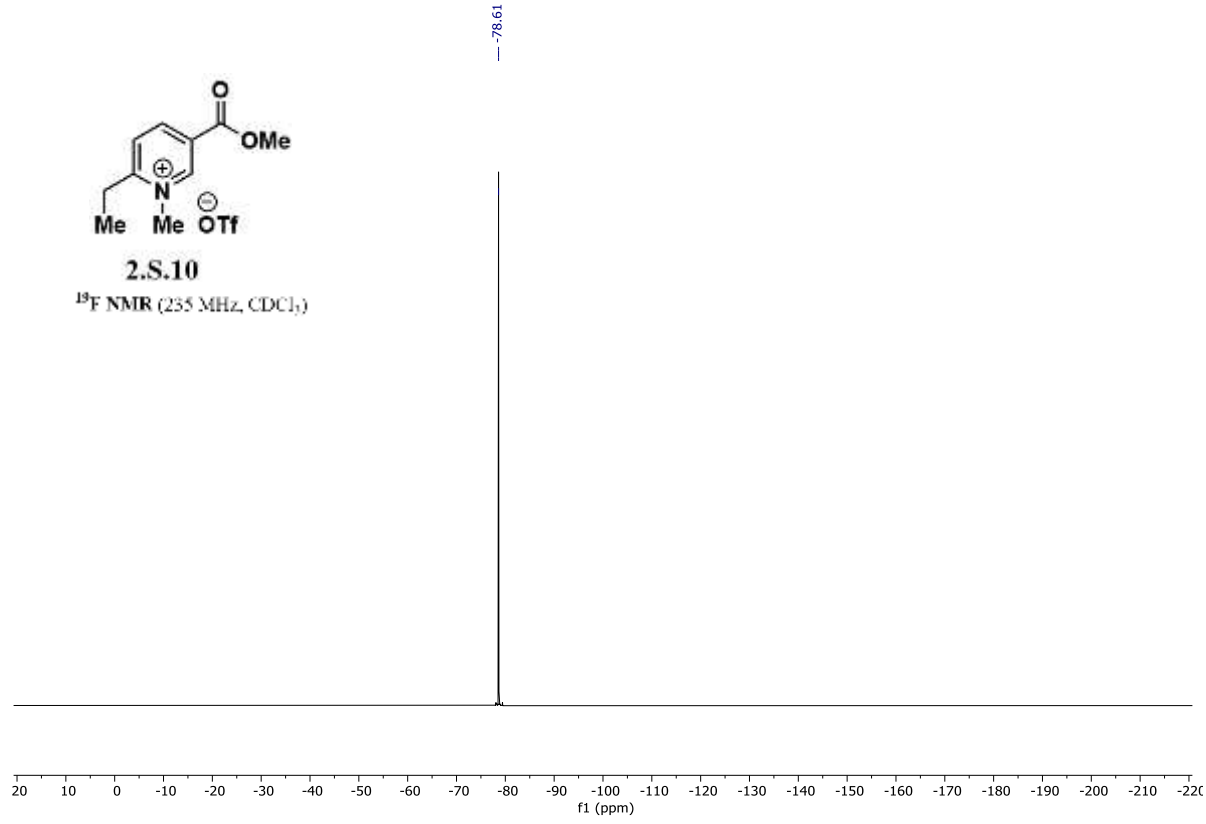


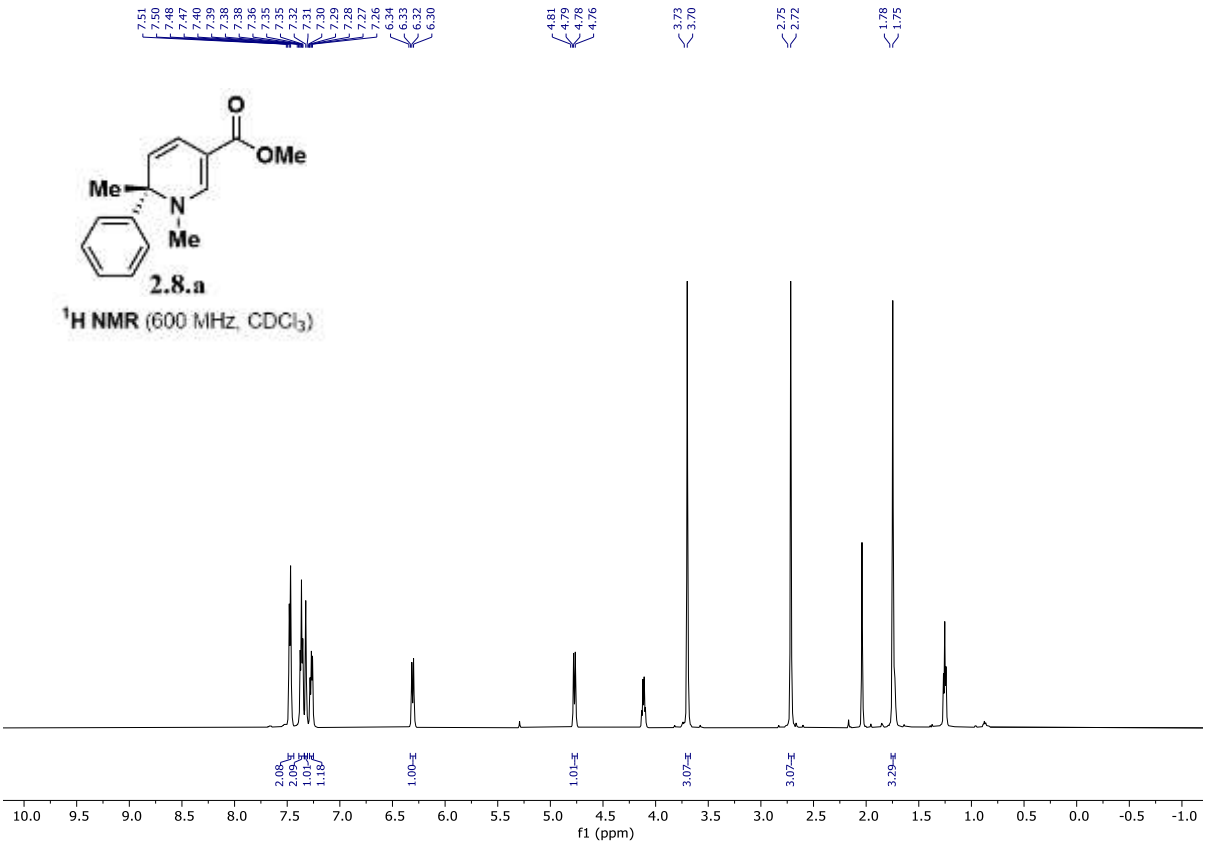
2.S.10

^{13}C NMR (151 MHz, $CDCl_3$)



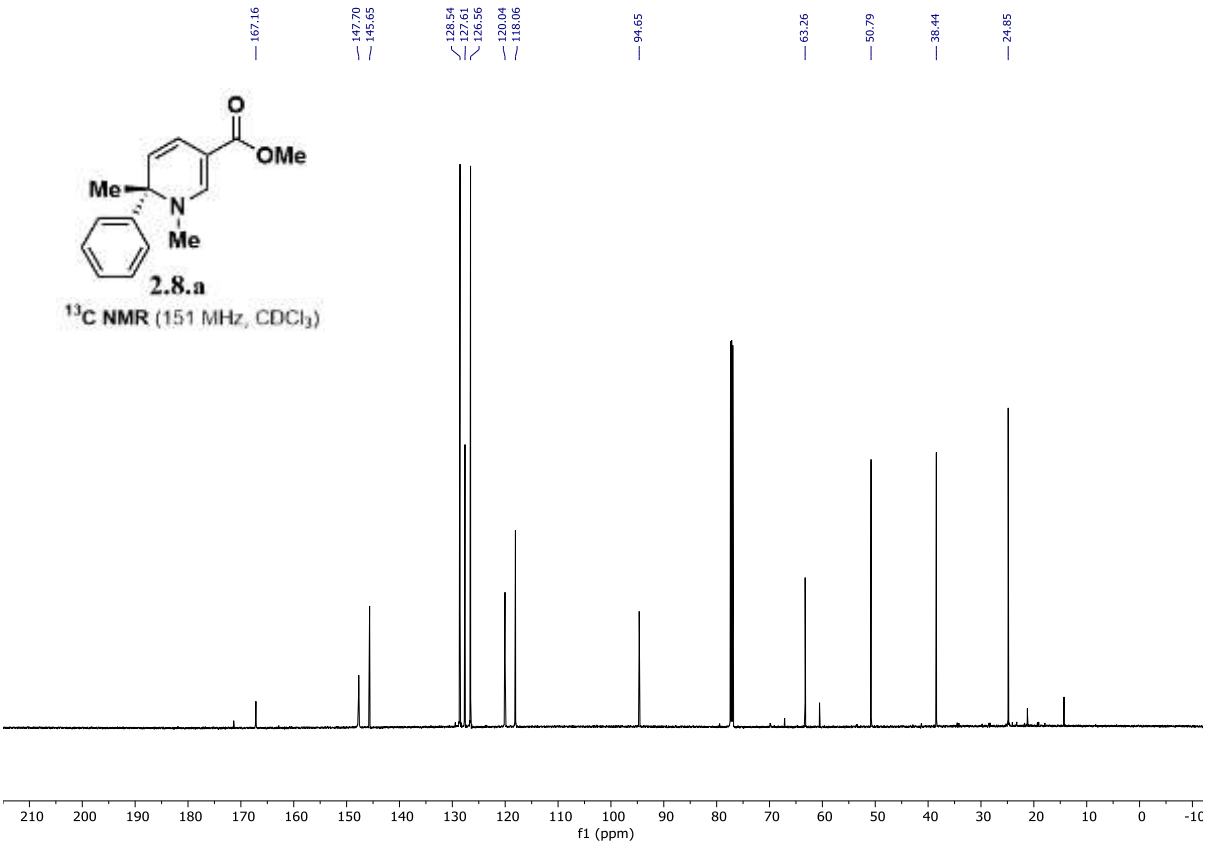
2.S.10

^{19}F NMR (235 MHz, $CDCl_3$)



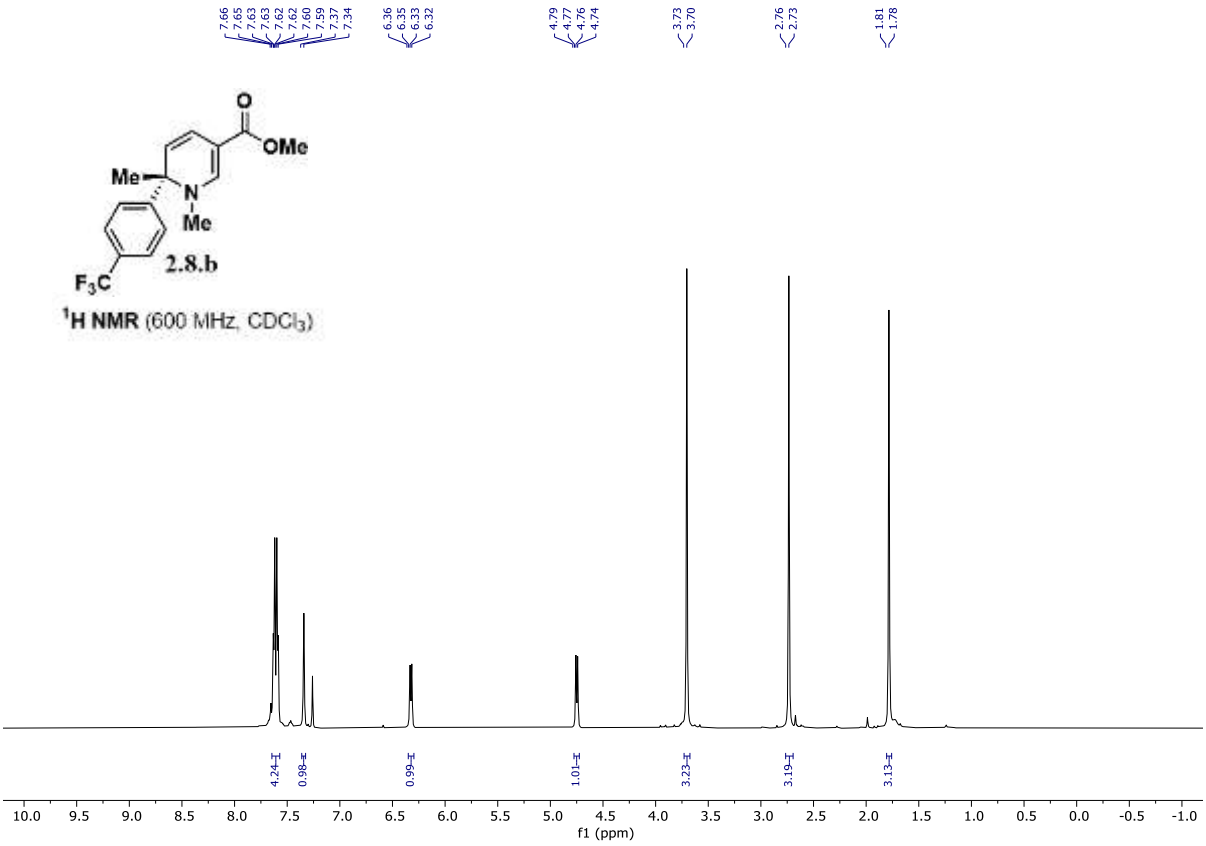
2.8.a

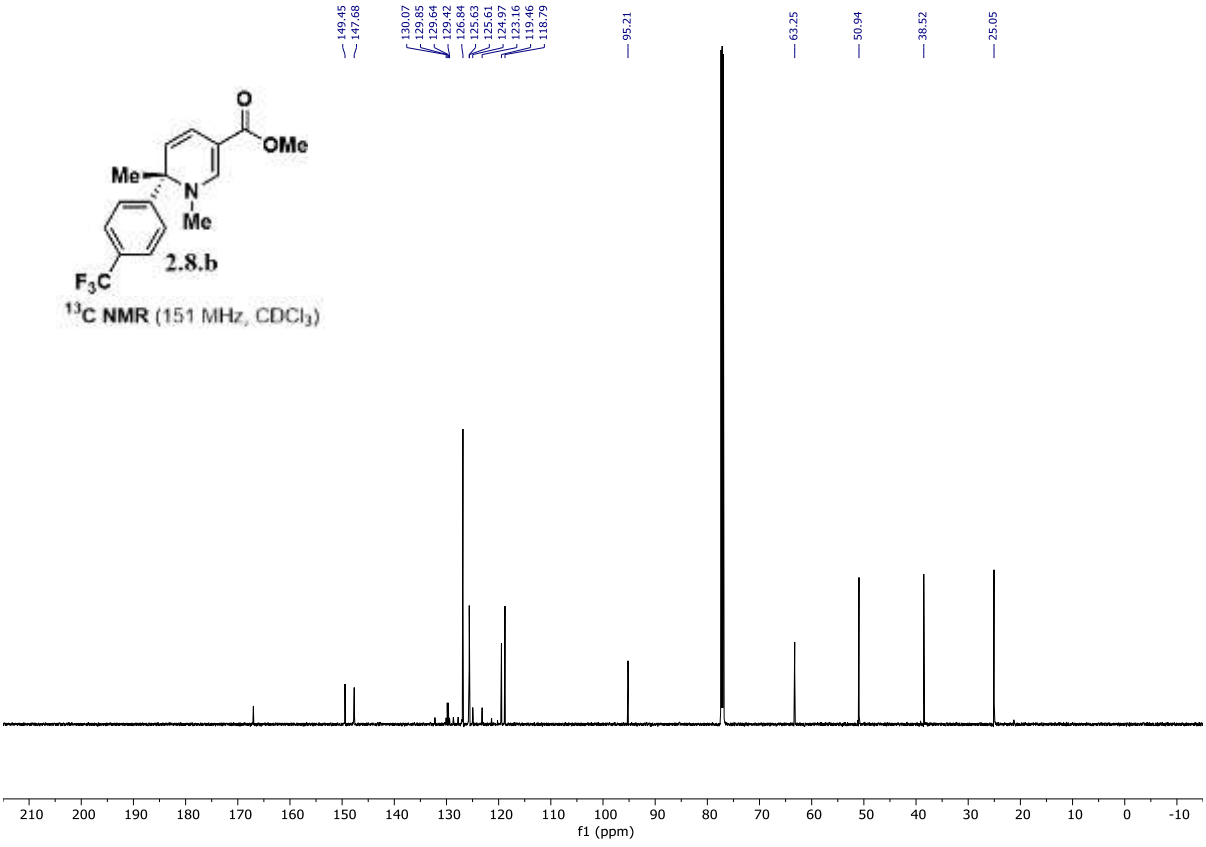
^{1}H NMR (600 MHz, $CDCl_3$)

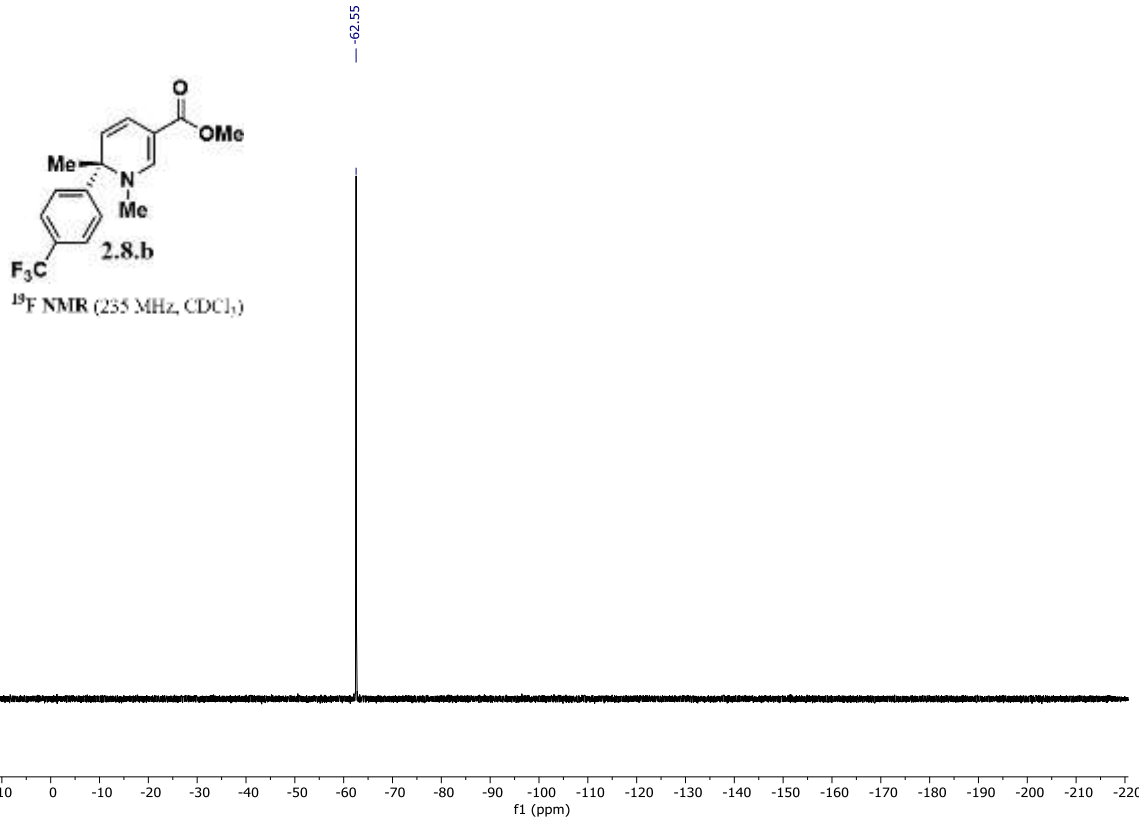


2.8.a

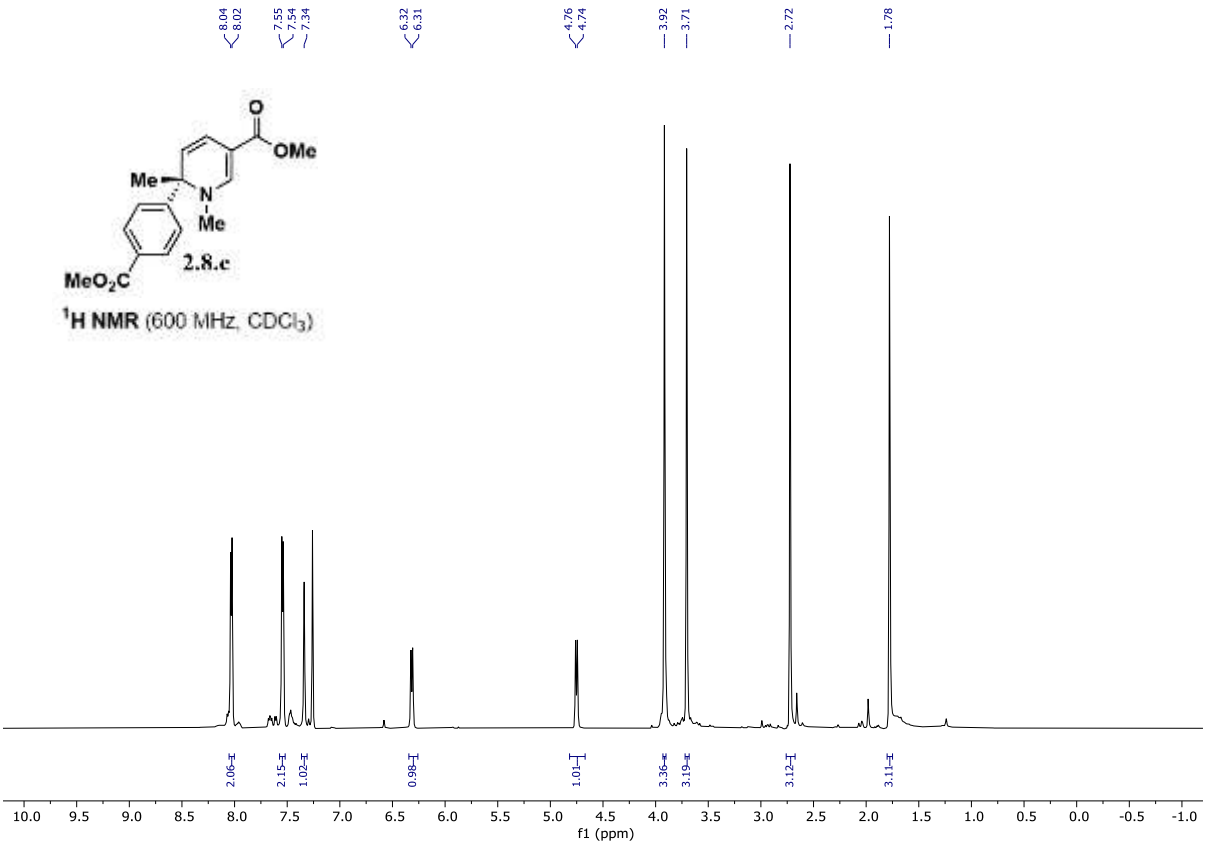
^{13}C NMR (151 MHz, $CDCl_3$)


7.66
7.65
7.63
7.63
7.62
7.62
7.60
7.59
7.37
7.34
6.36
6.35
6.33
6.32
4.79
4.77
4.76
4.74
3.73
3.70
2.76
2.73
1.81
1.78
O
OMe
Me
N
Me
2.8.b
F3C
1H NMR (600 MHz, CDCl3)
4.24
0.98
0.99
1.01
3.23
3.19
3.13
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 -0.5 -1.0
f1 (ppm)

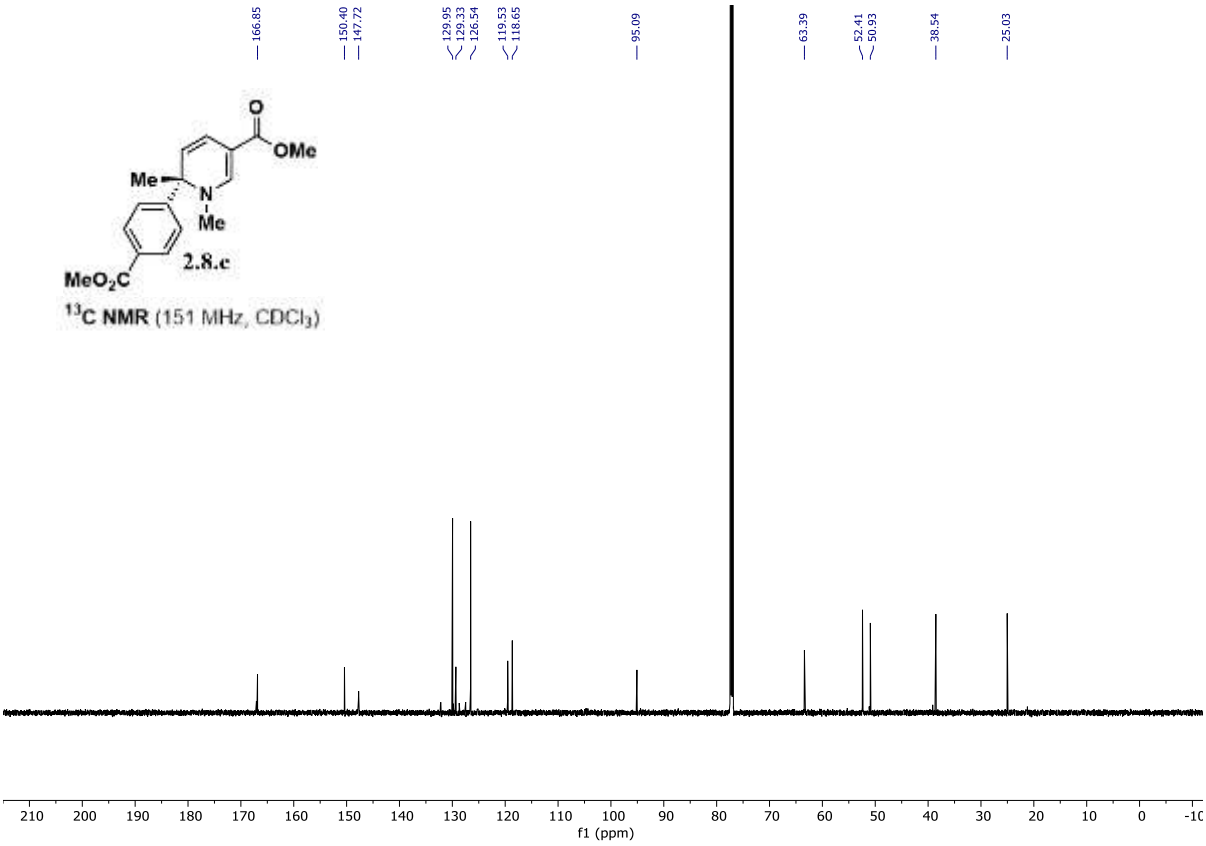

149.45
147.68
130.07
129.85
129.64
129.42
126.84
125.63
125.61
124.97
123.16
119.46
118.79
95.21
63.25
50.94
38.52
25.05
O
OMe
Me
N
Me
2.8.b
F3C
13C NMR (151 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

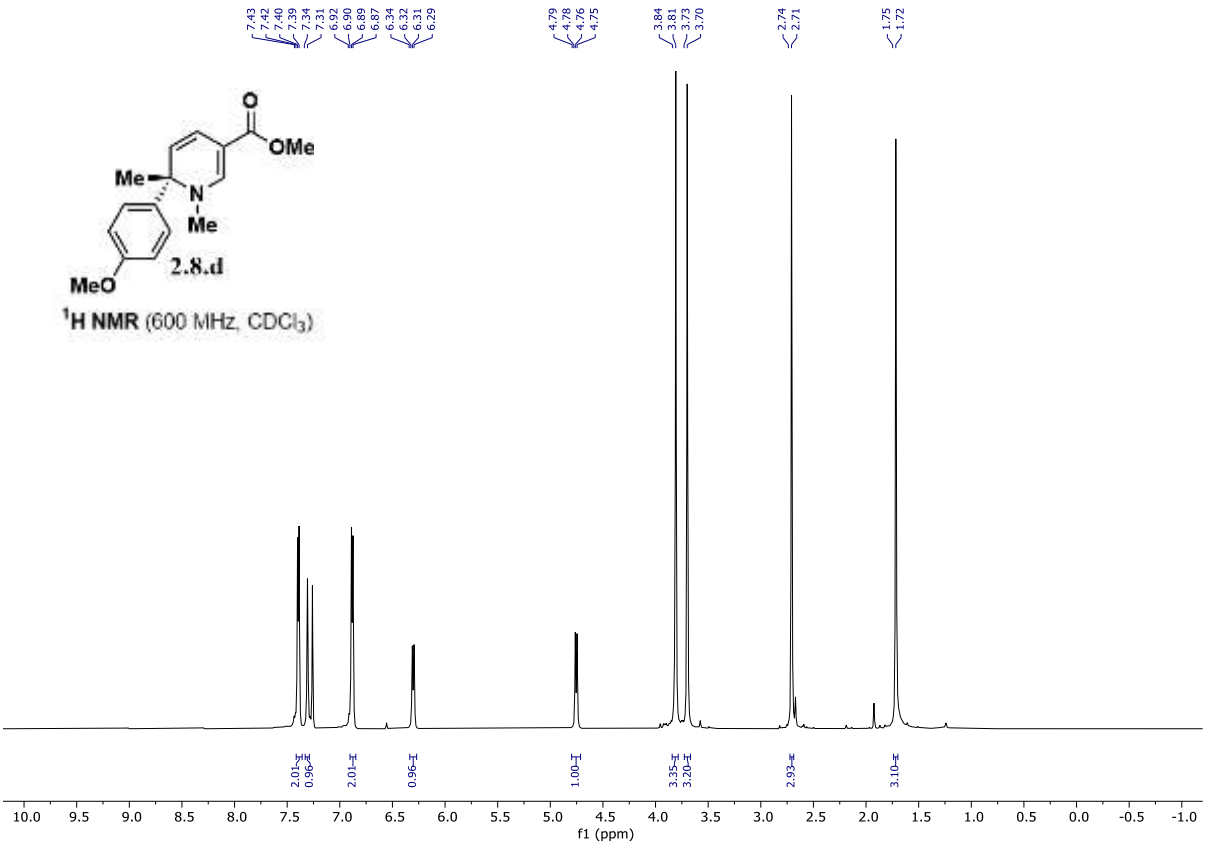


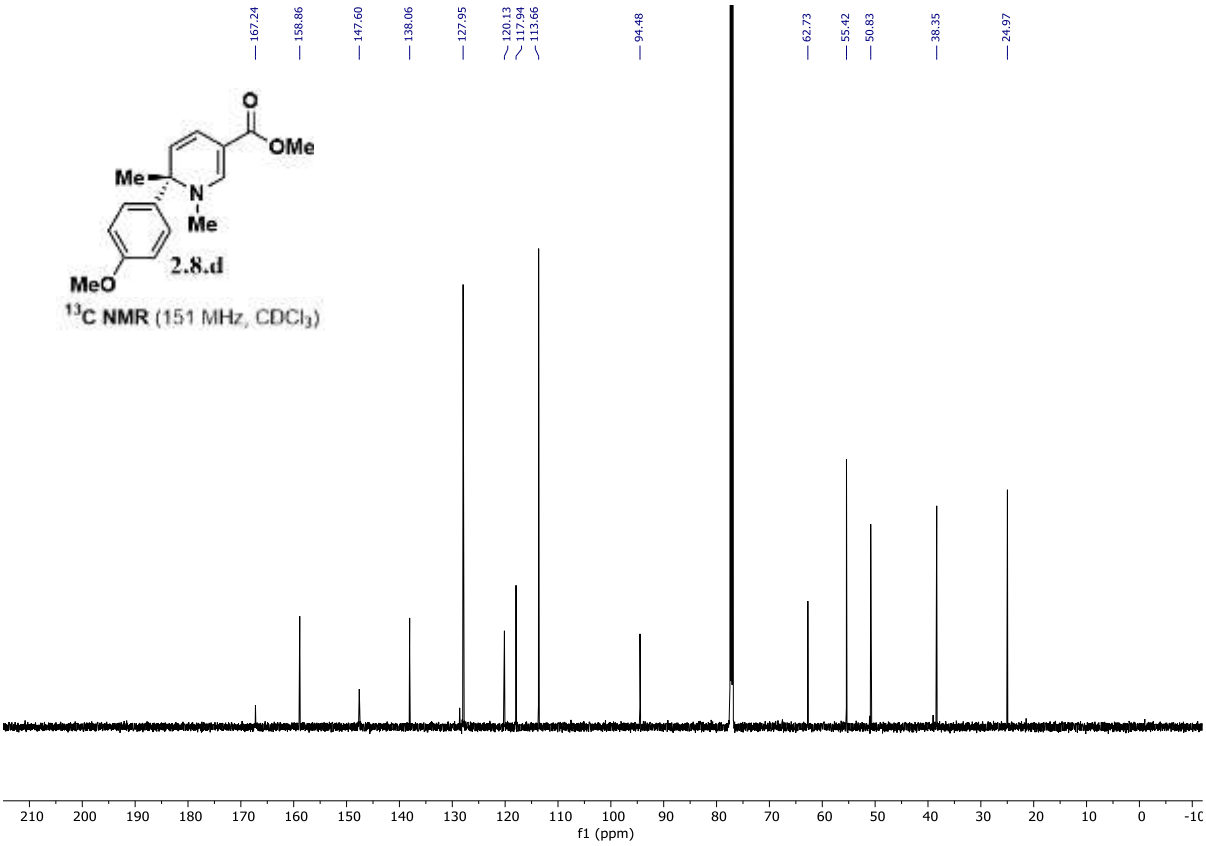
^{19}F NMR (235 MHz, $CDCl_3$)



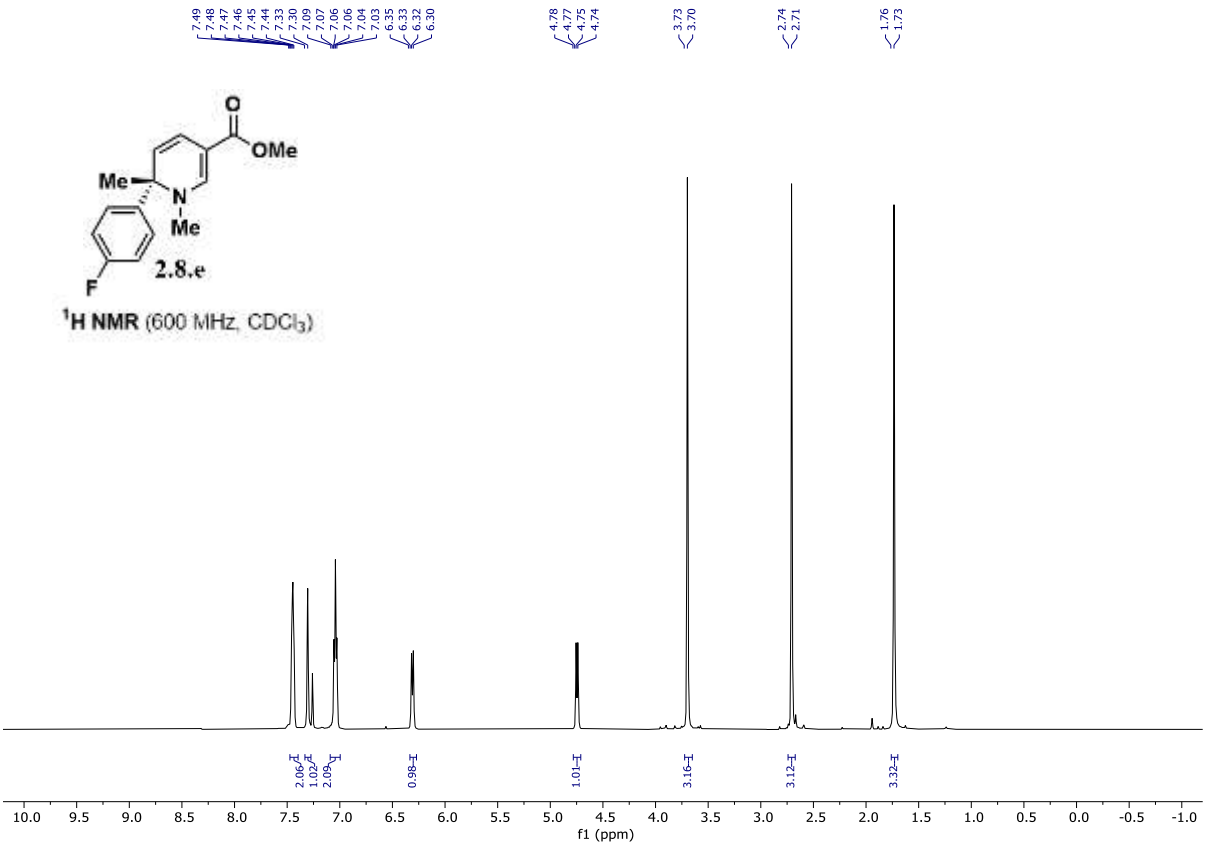
^{1}H NMR (600 MHz, $CDCl_3$)


166.85
150.40
147.72
129.95
129.33
126.54
119.53
118.65
95.09
63.39
52.41
50.93
38.54
25.03
O
OMe
Me
N
Me
MeO2C
2.8.c
13C NMR (151 MHz, CDCl3)
f1 (ppm)

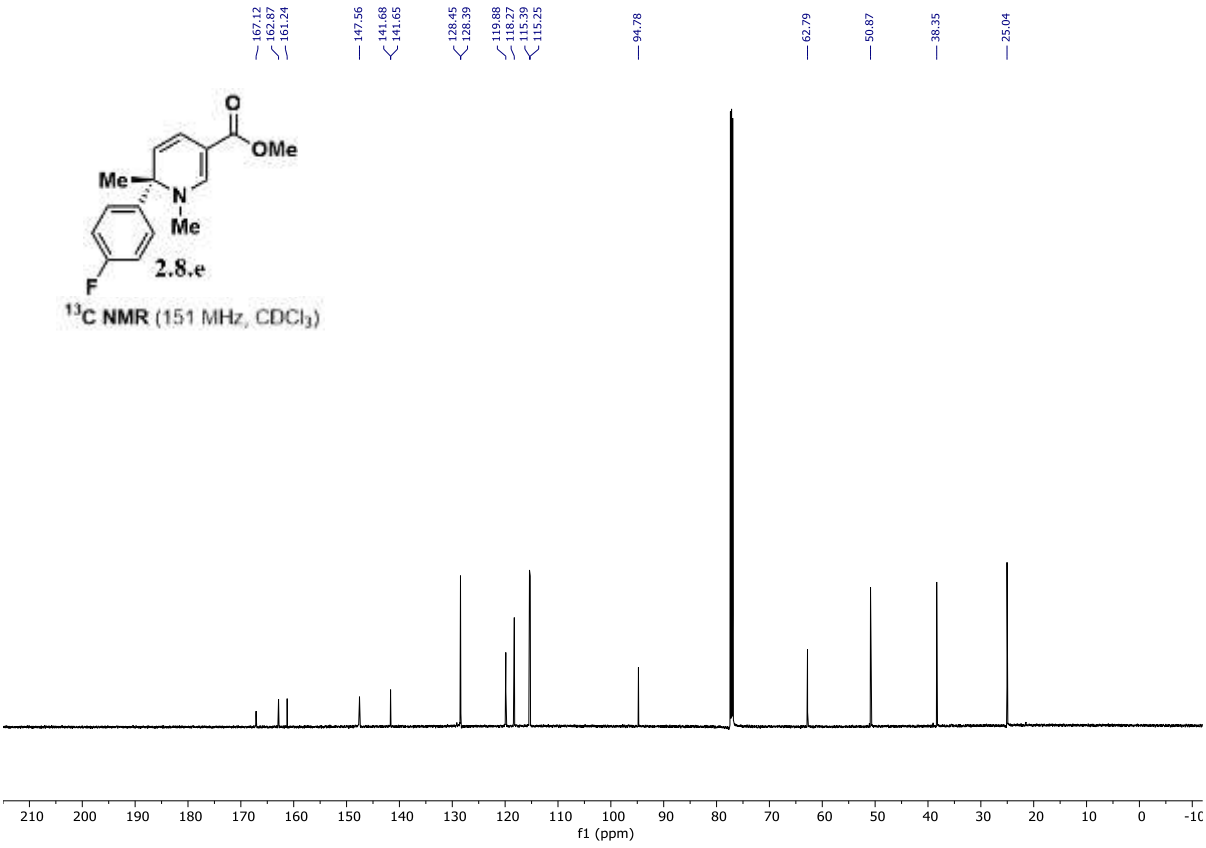

7.43
7.42
7.40
7.39
7.34
7.31
6.92
6.90
6.89
6.87
6.34
6.32
6.31
6.29
4.79
4.78
4.76
4.75
3.84
3.81
3.73
3.70
2.74
2.71
1.75
1.72
O
OMe
Me
N
Me
MeO
2.8.d
1H NMR (600 MHz, CDCl3)
2.01
0.96
2.01
0.96
1.00
3.35
3.20
2.93
3.10
f1 (ppm)



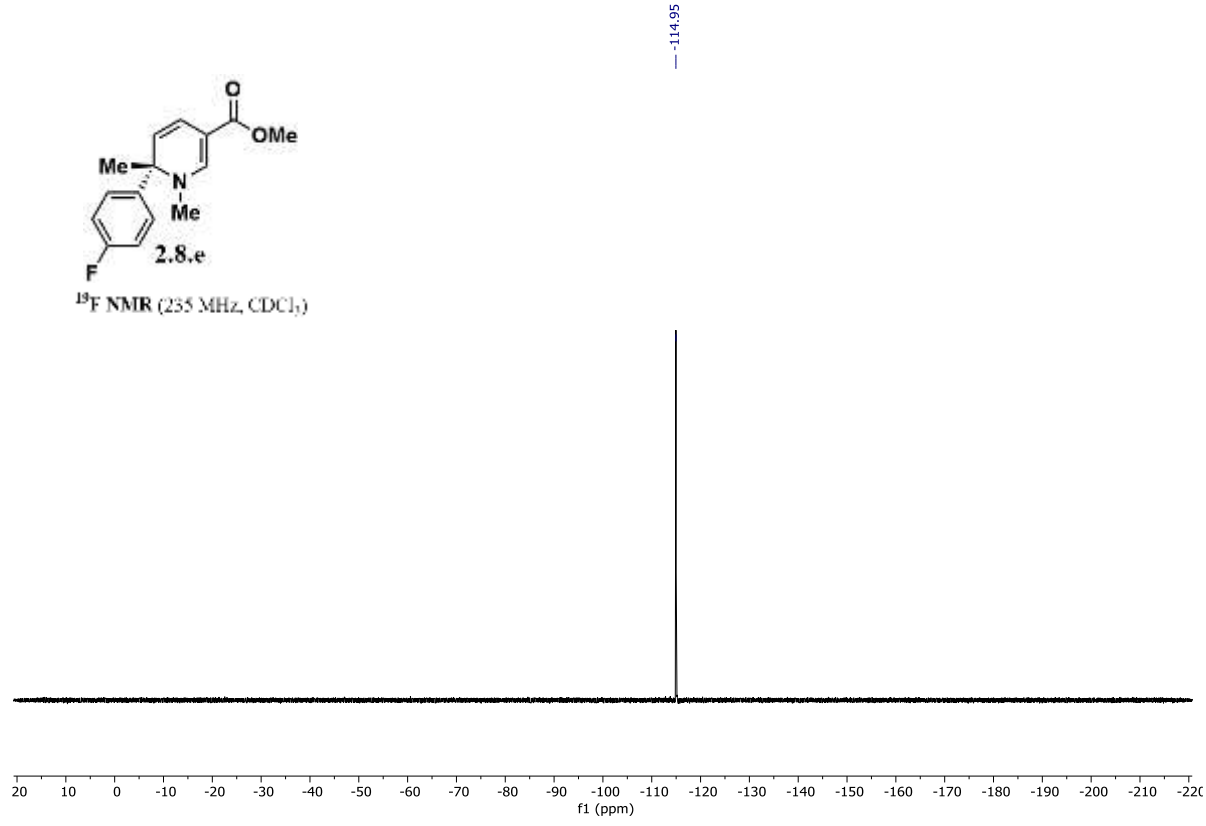
^{13}C NMR (151 MHz, $CDCl_3$)



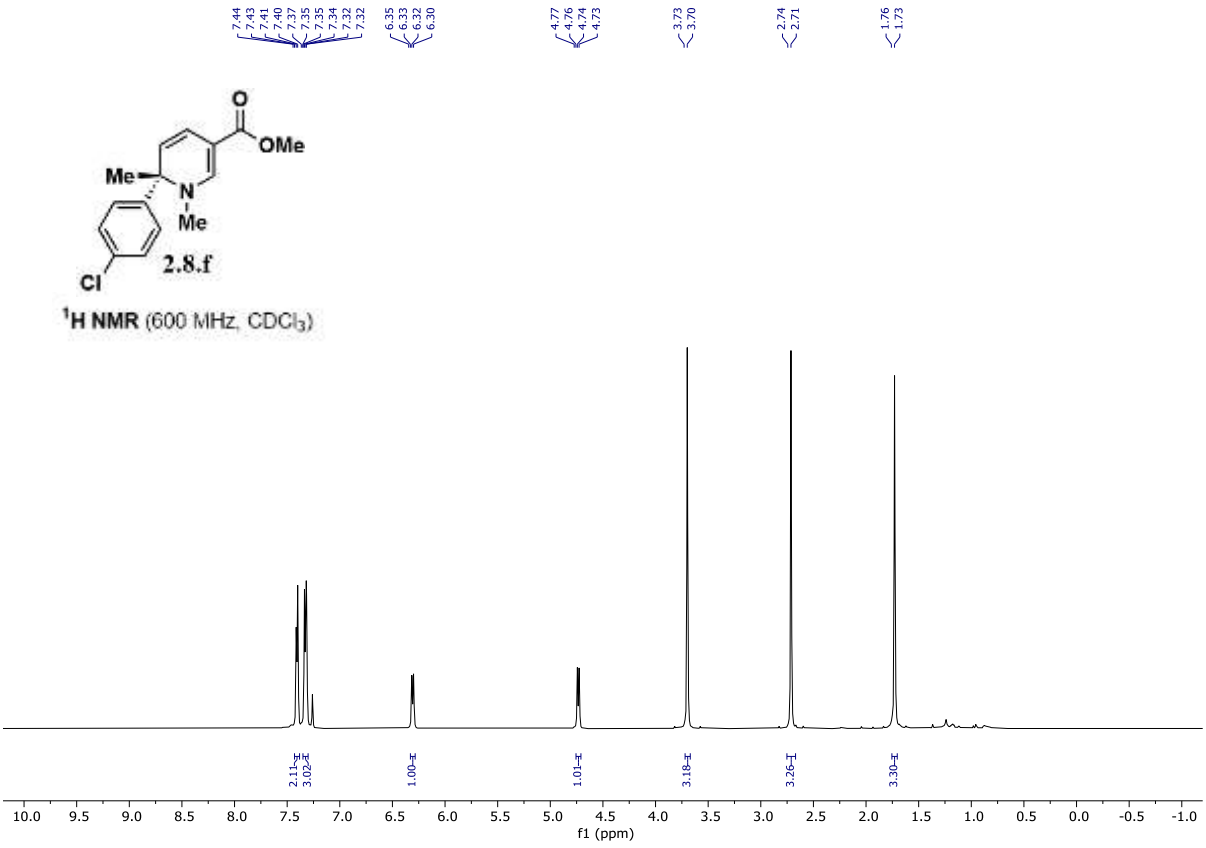
^{1}H NMR (600 MHz, $CDCl_3$)



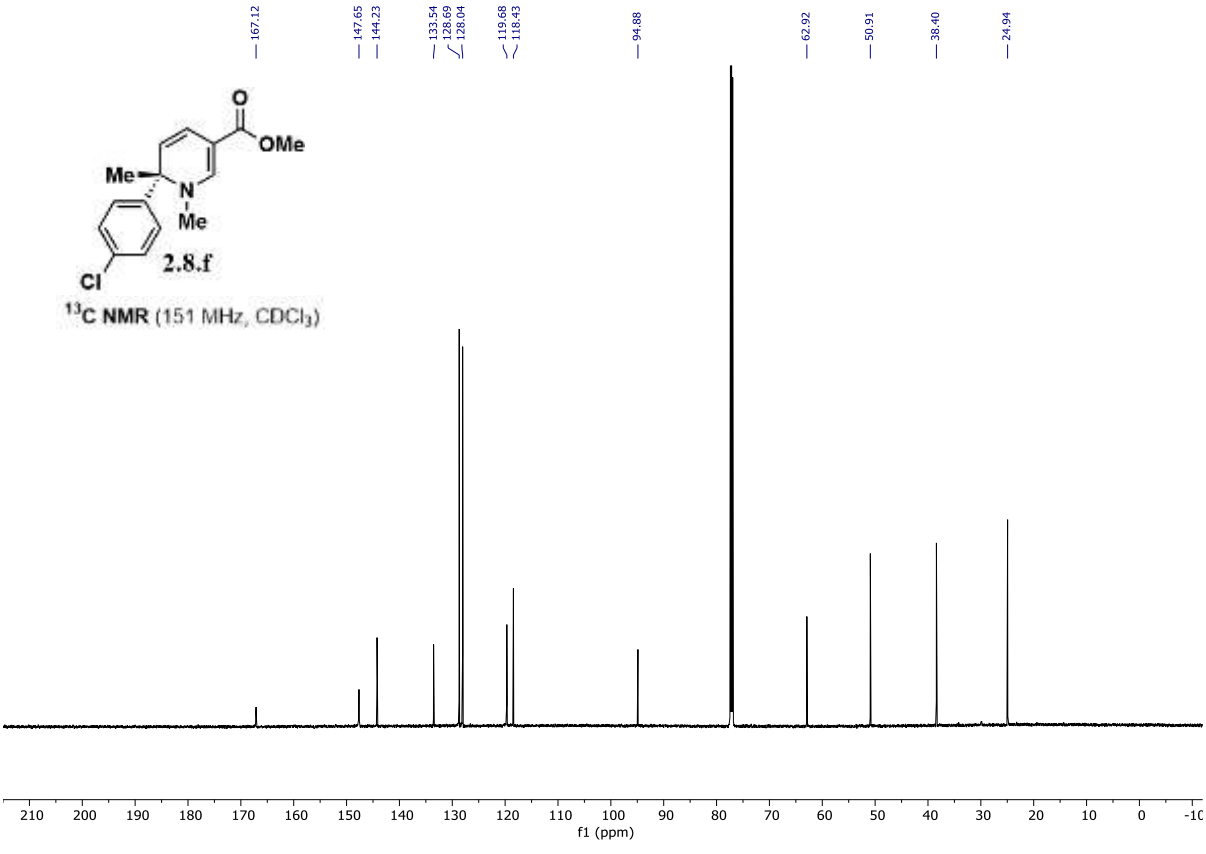
^{13}C NMR (151 MHz, $CDCl_3$)



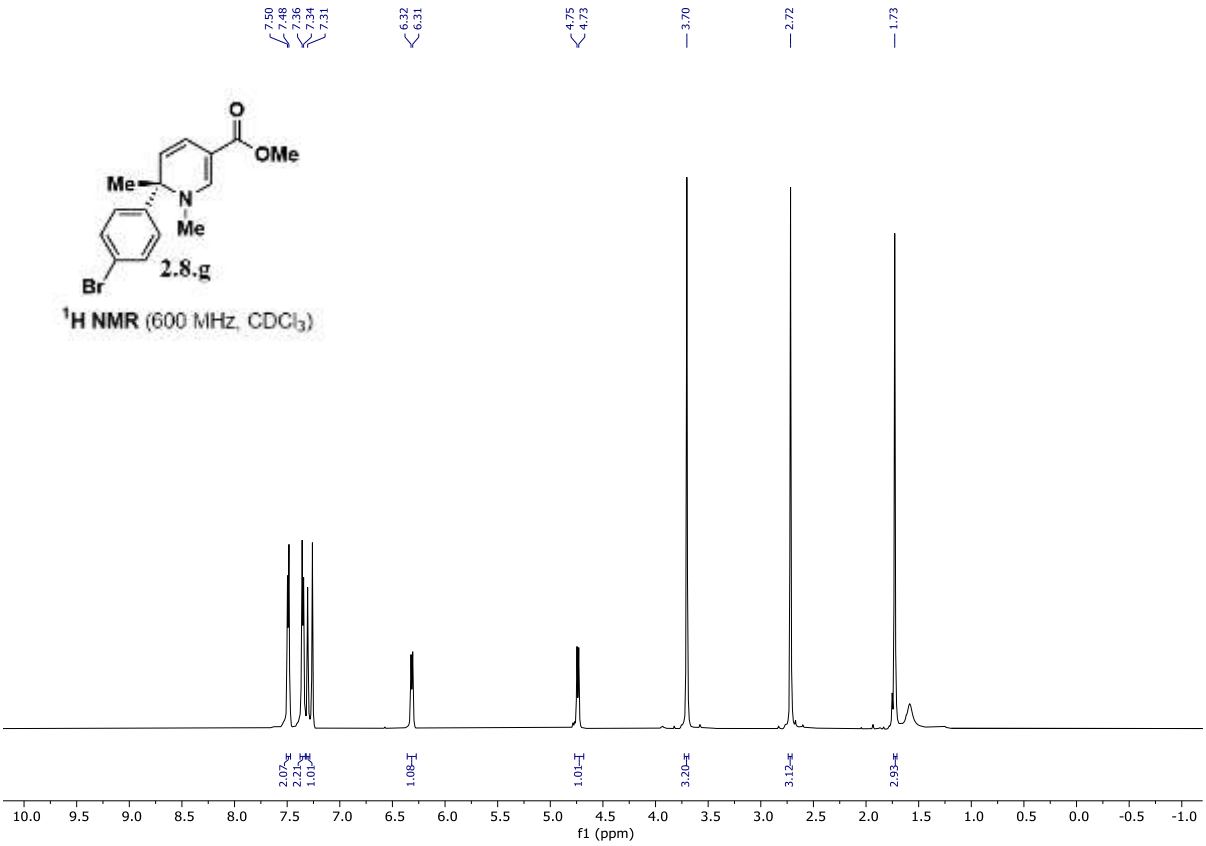
^{19}F NMR (235 MHz, $CDCl_3$)



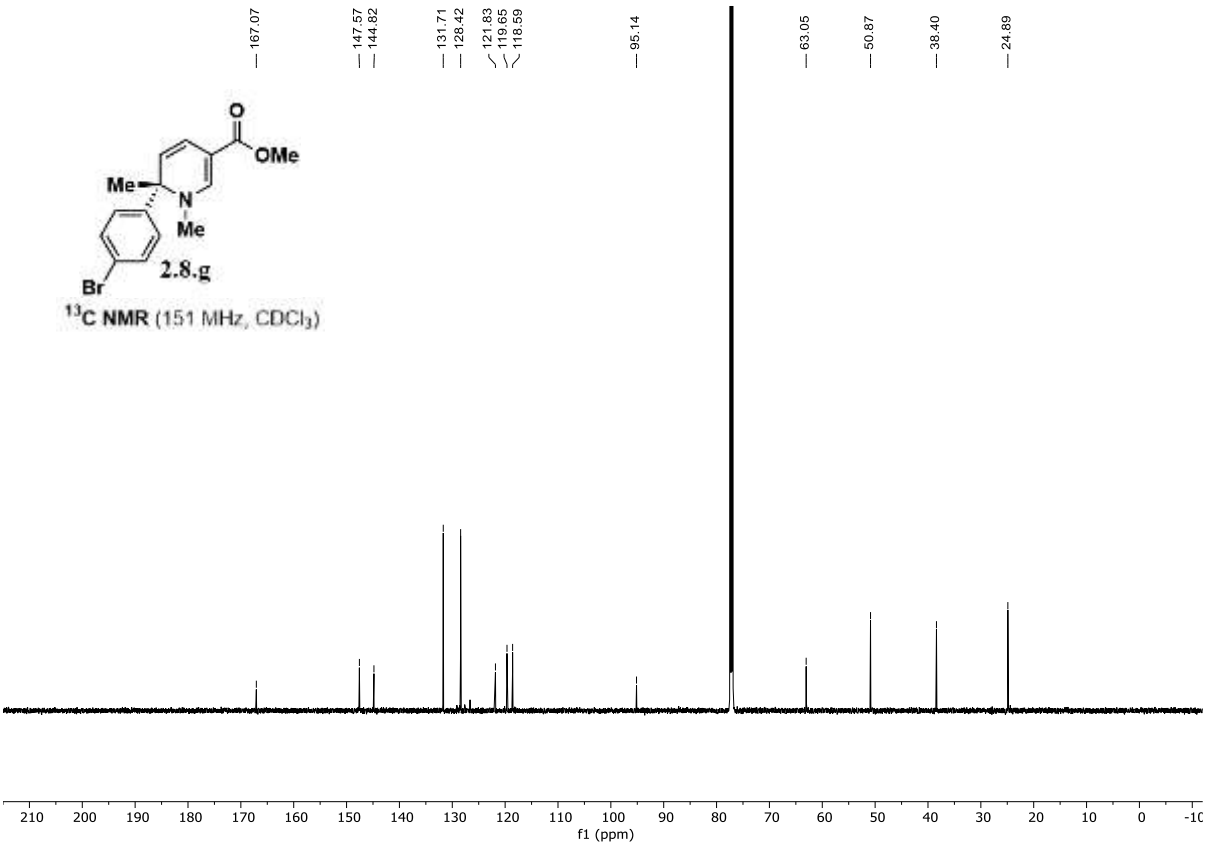
^{1}H NMR (600 MHz, $CDCl_3$)



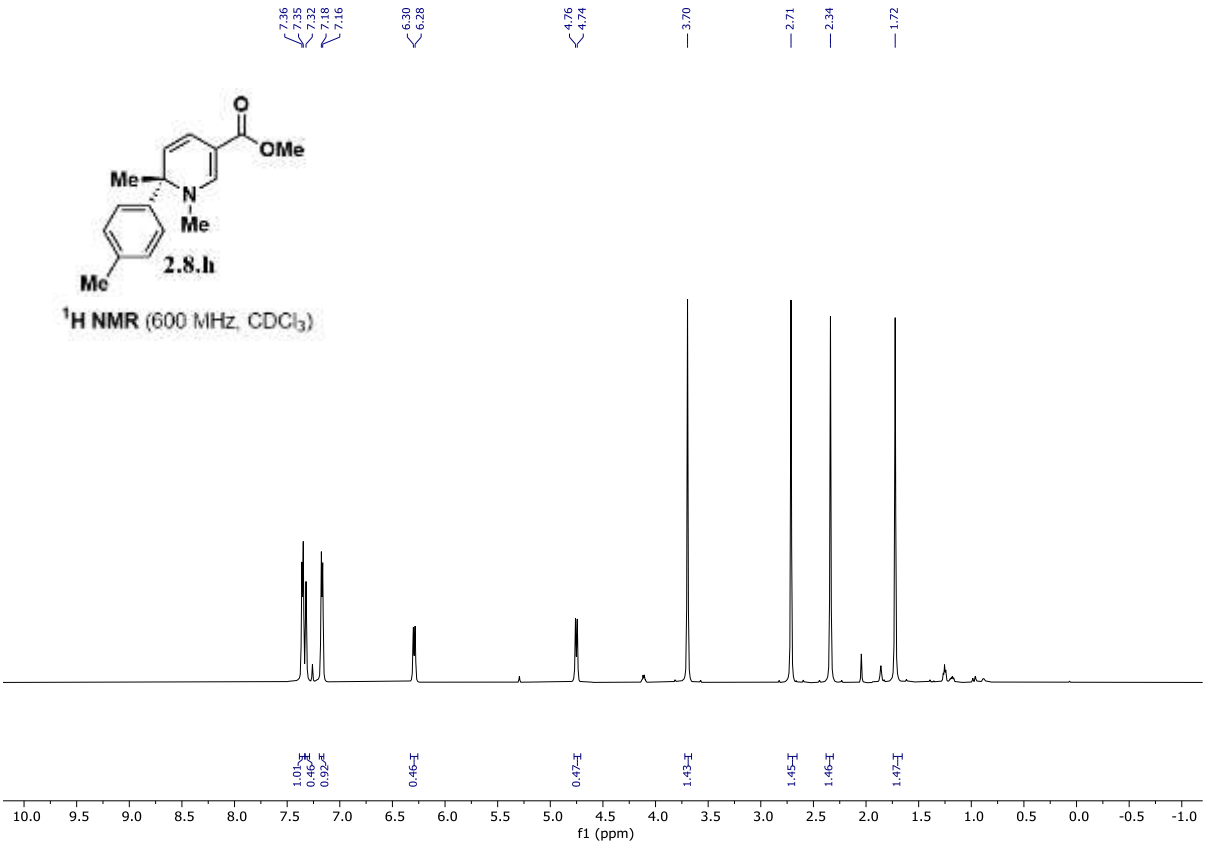
^{13}C NMR (151 MHz, $CDCl_3$)



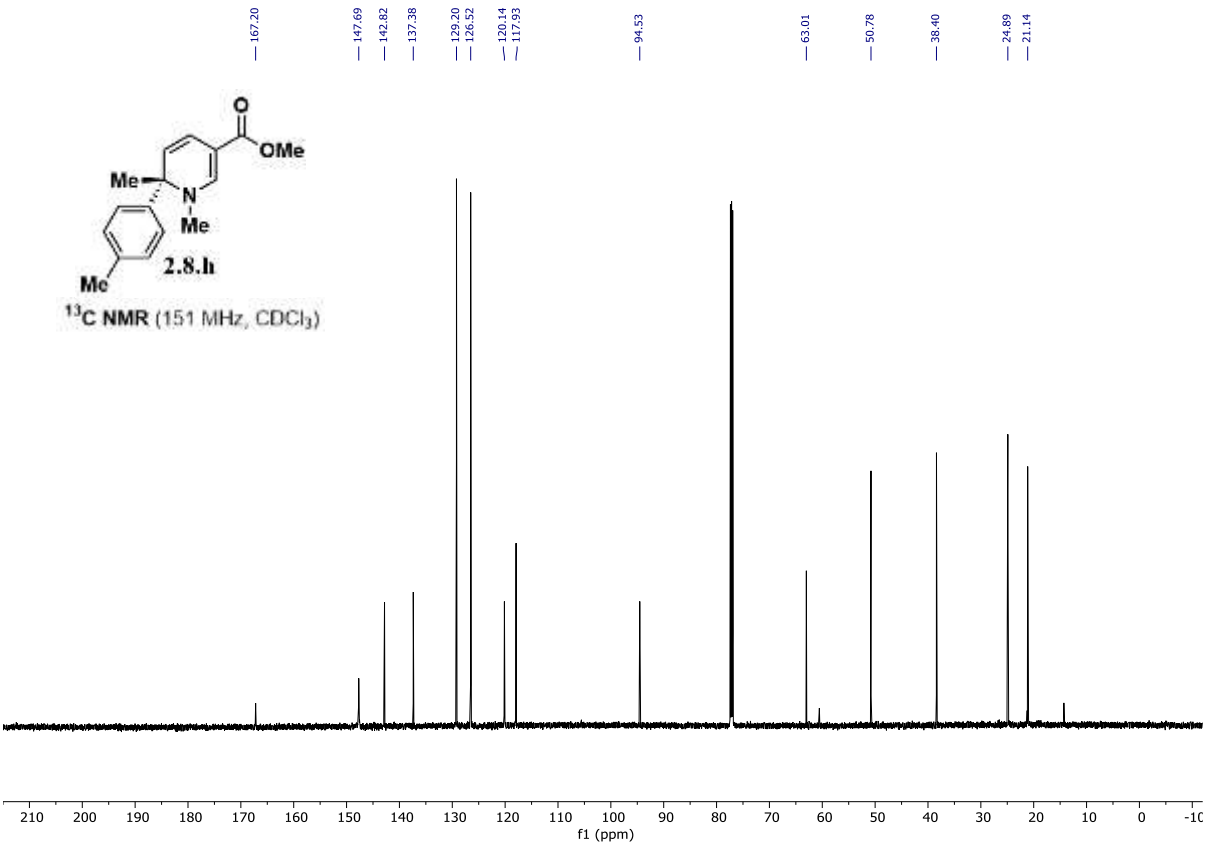
^{1}**H NMR** (600 MHz, $CDCl_3$)



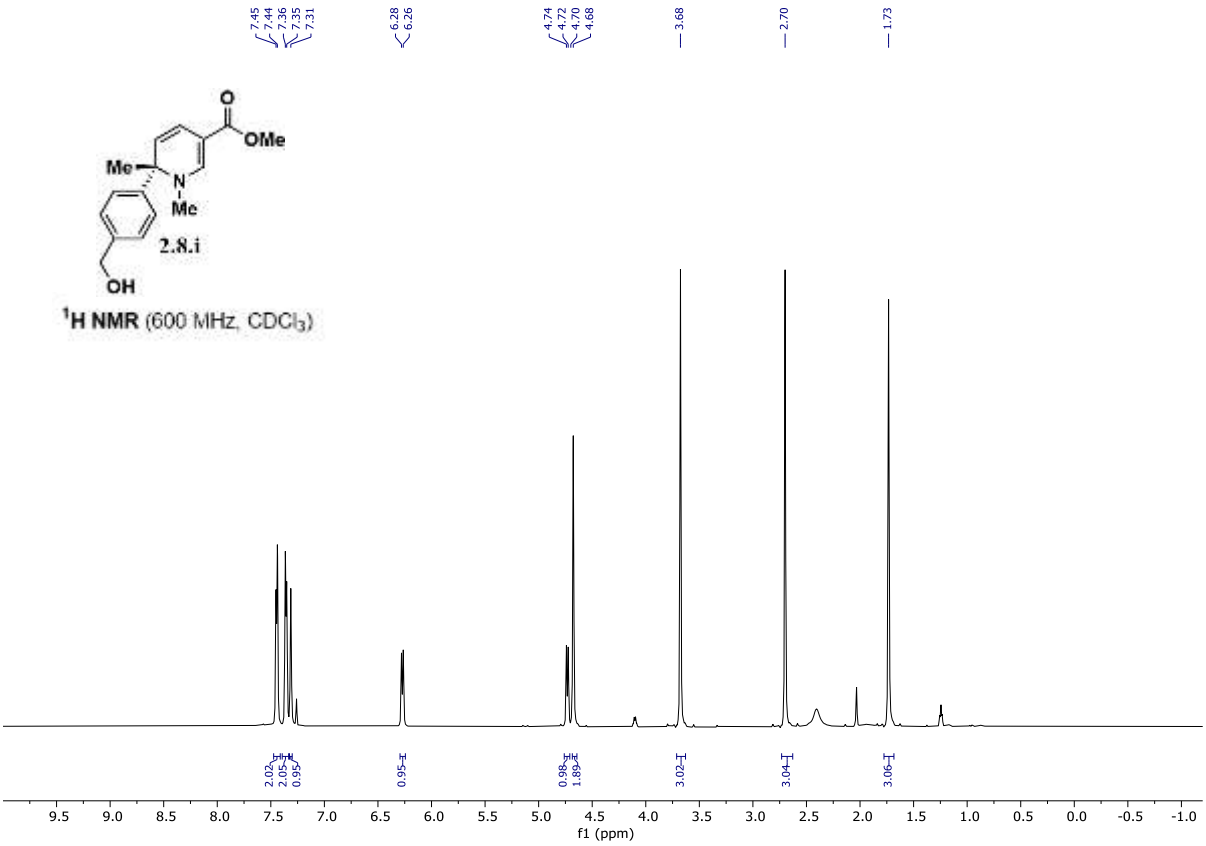
^{13}**C NMR** (151 MHz, $CDCl_3$)



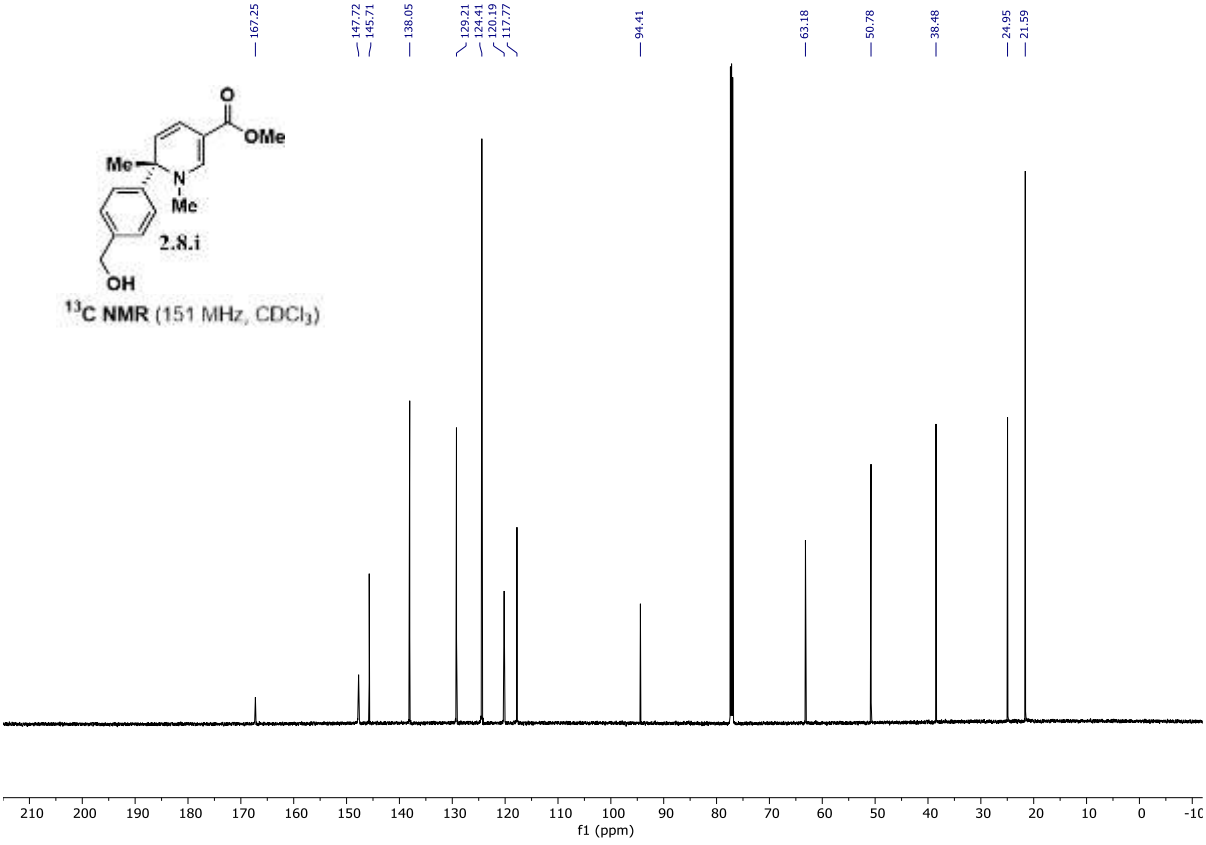
^{1}H NMR (600 MHz, $CDCl_3$)



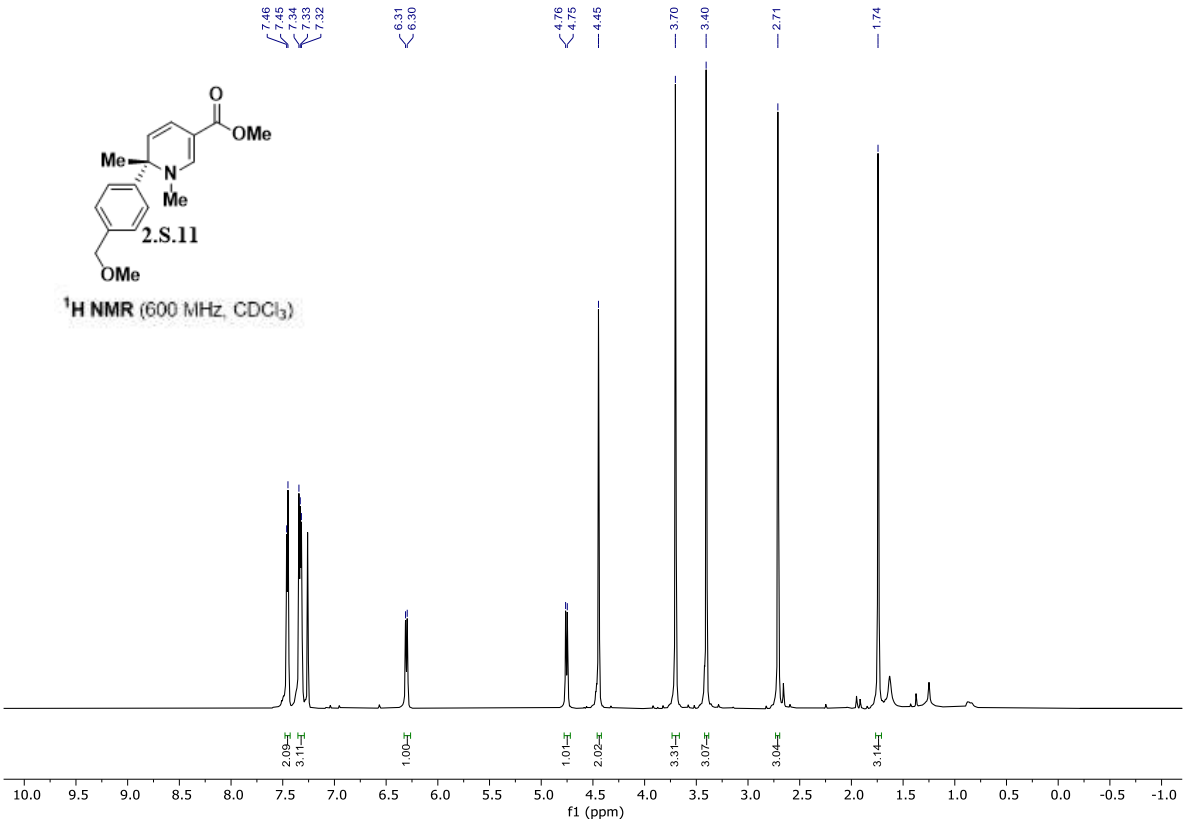
^{13}C NMR (151 MHz, $CDCl_3$)



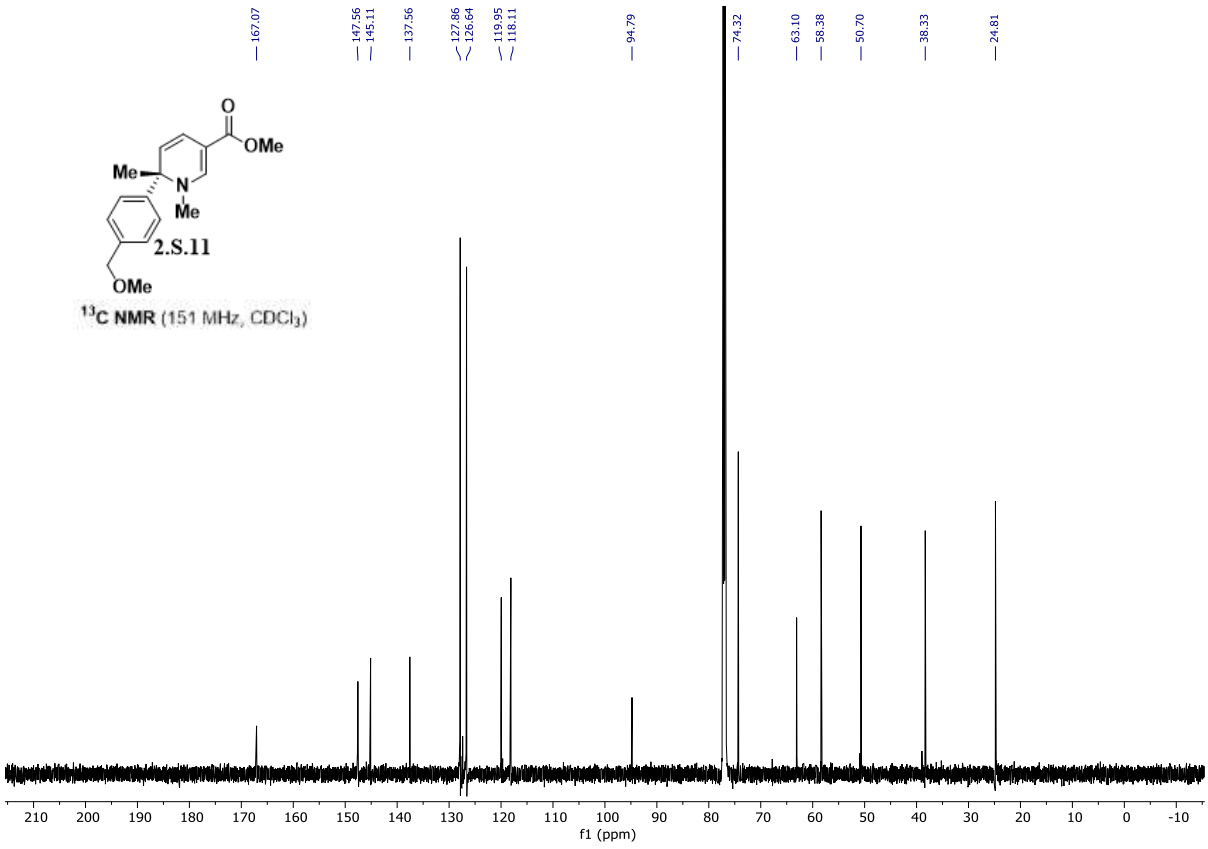
^{1}H NMR (600 MHz, $CDCl_3$)



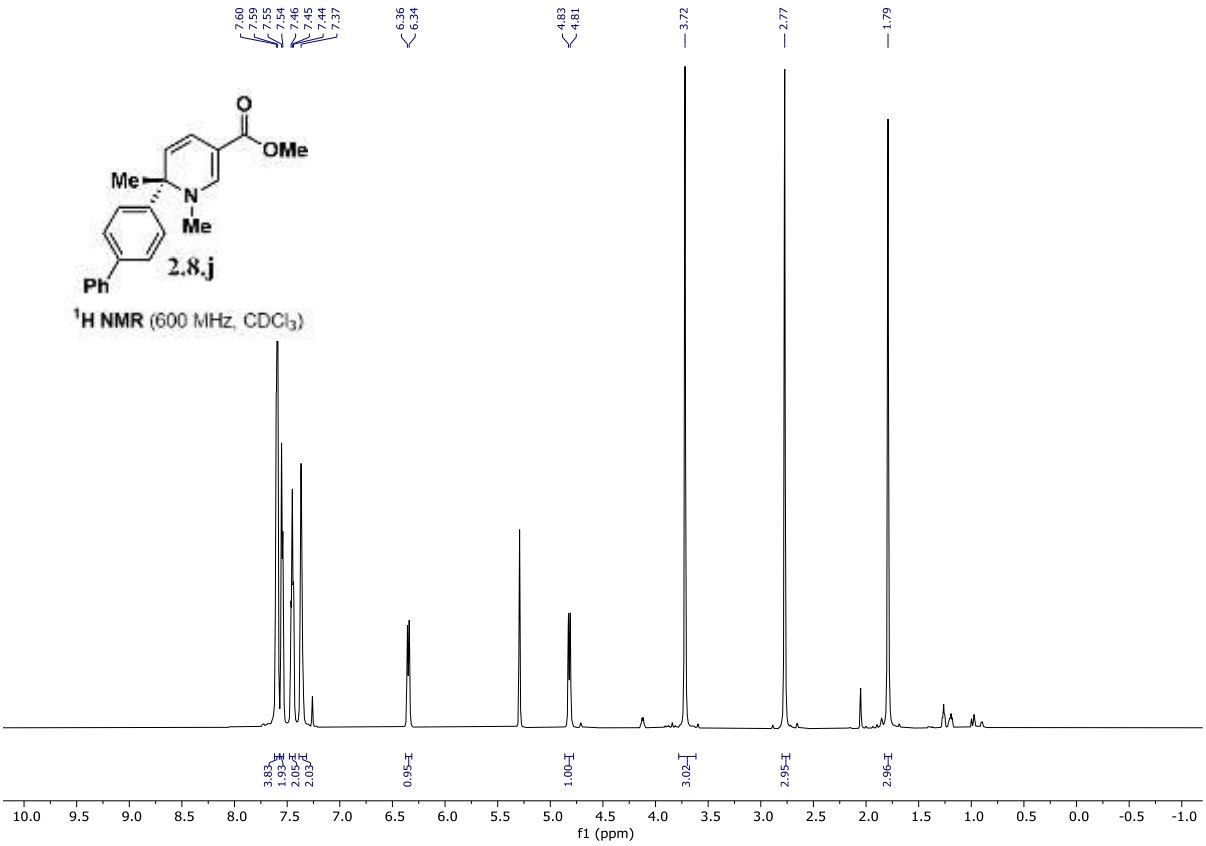
^{13}C NMR (151 MHz, $CDCl_3$)

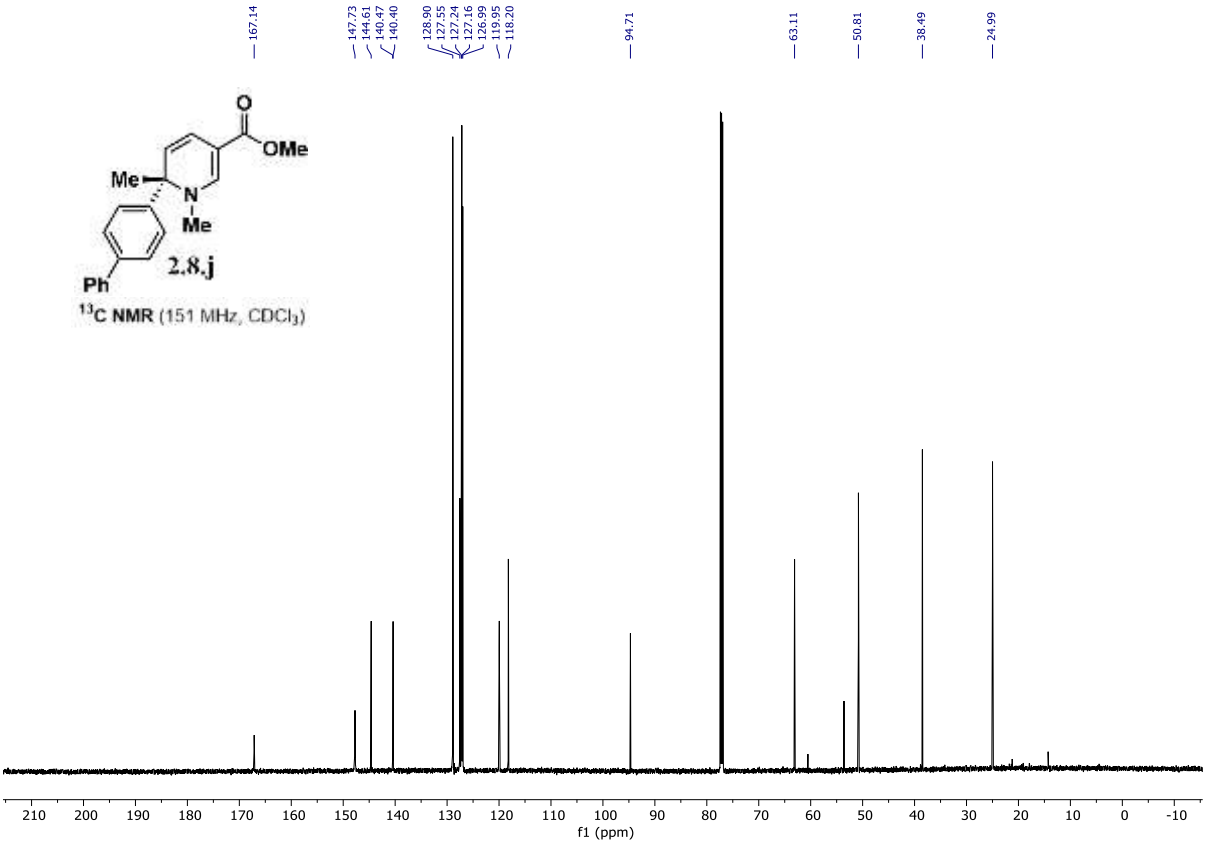


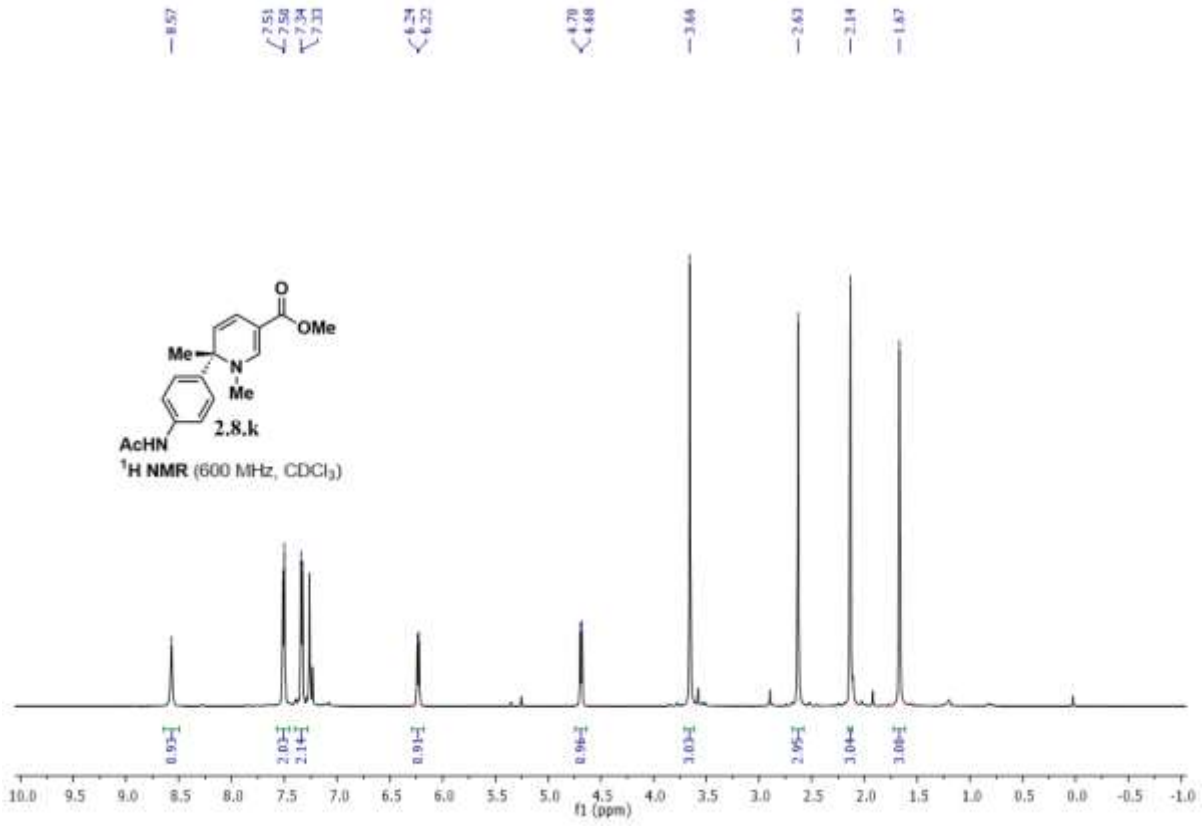
^{1}H NMR (600 MHz, $CDCl_3$)

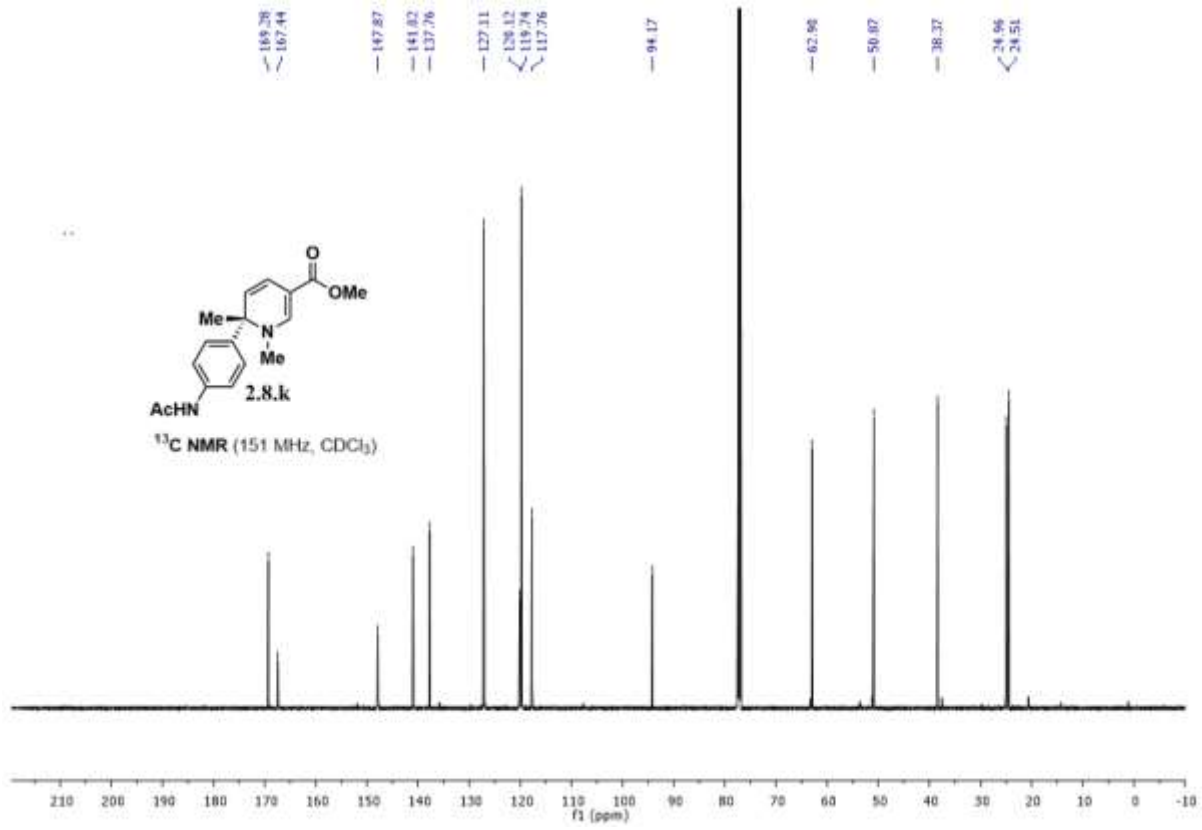


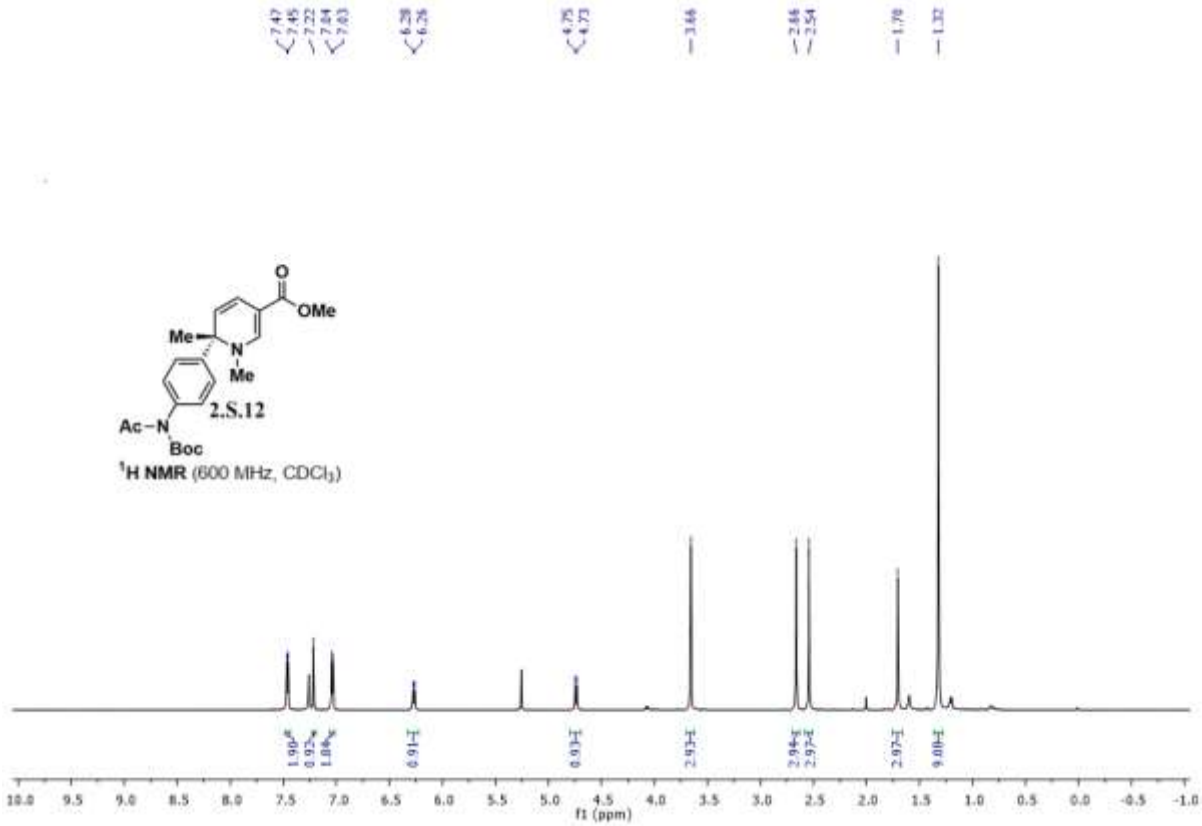
^{13}C NMR (151 MHz, $CDCl_3$)

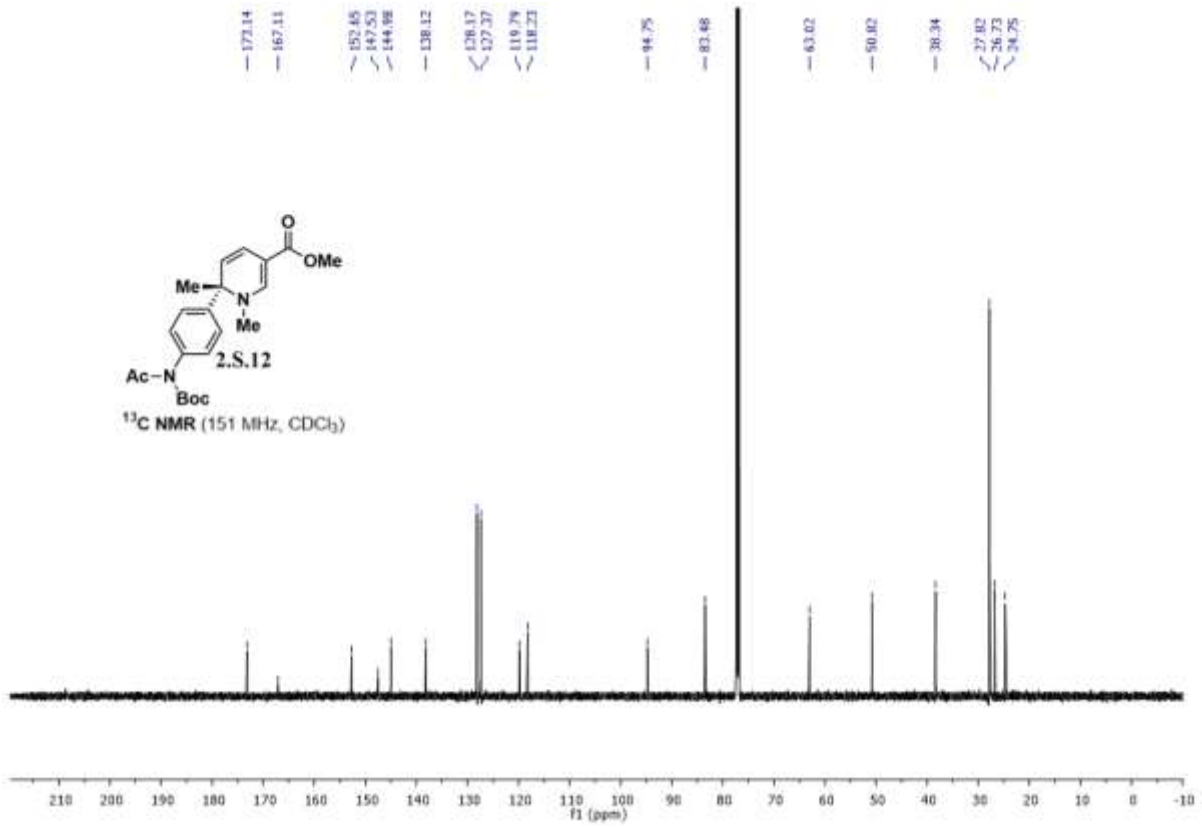

7.60
7.59
7.55
7.54
7.46
7.45
7.44
7.37
6.36
6.34
4.83
4.81
3.72
2.77
1.79
O
OMe
Me
N
Me
Ph
2.8.j
¹H NMR (600 MHz, CDCl₃)
3.83
1.93
2.05
2.03
0.95
1.00
3.02
2.95
2.96
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

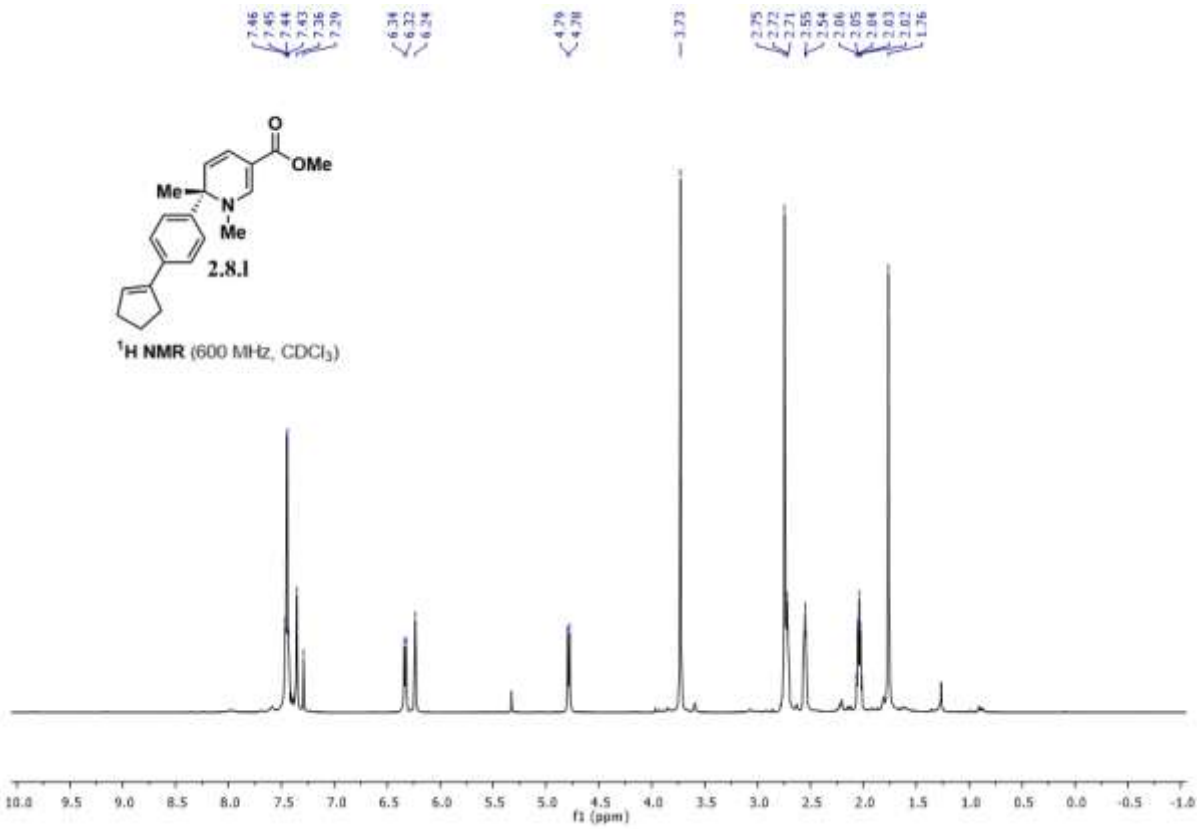

167.14
147.73
144.61
140.47
140.40
128.90
127.55
127.24
127.16
126.99
119.95
118.20
94.71
63.11
50.81
38.49
24.99
O
OMe
Me
N
Me
Ph
2.8.j
¹³C NMR (151 MHz, CDCl₃)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.57
7.51
7.50
7.34
7.33
6.24
6.22
4.70
4.68
3.66
2.63
2.14
1.67
O
OMe
Me
N
Me
AcHN
2.8.k
¹H NMR (600 MHz, CDCl₃)
0.93
2.03
2.14
0.91
0.96
3.03
2.95
3.04
3.08
f1 (ppm)

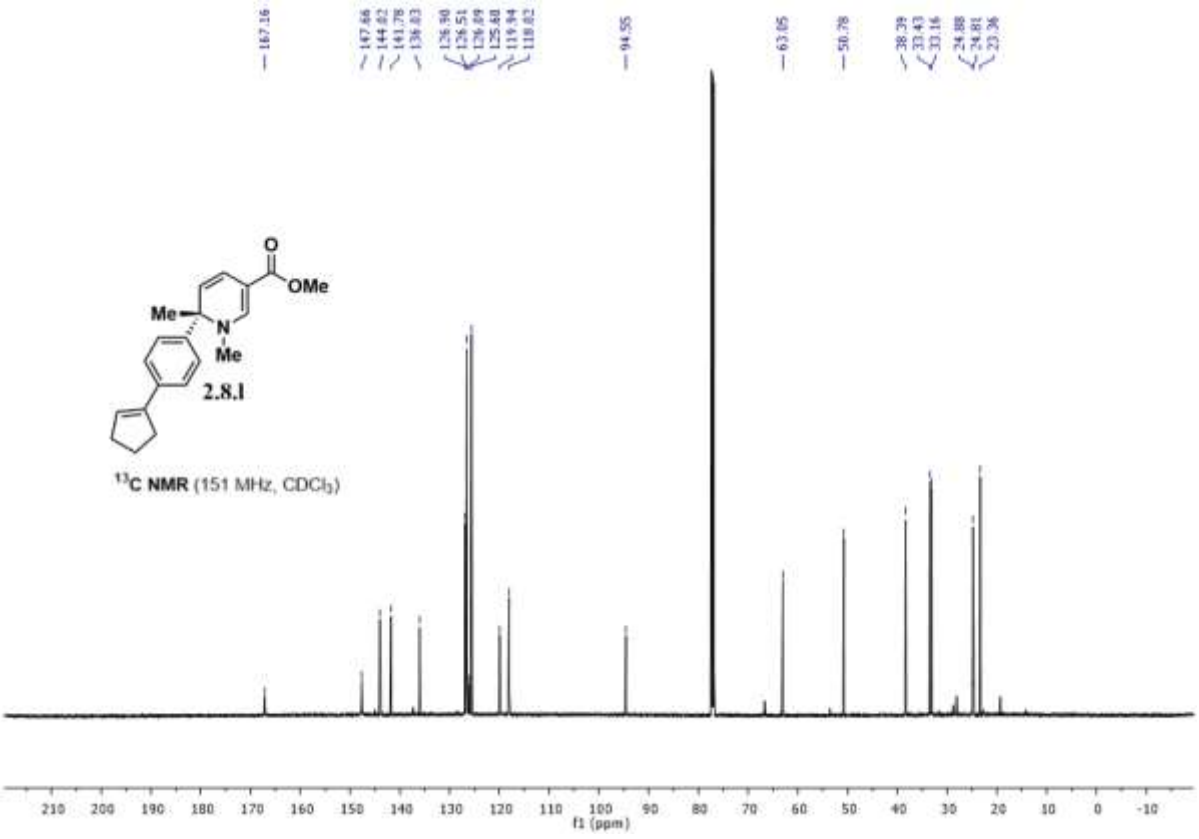

169.28
167.44
147.87
141.82
137.76
127.11
120.12
119.74
117.76
94.17
62.98
50.87
38.37
24.96
24.51
O
OMe
Me
N
Me
AcHN
2.8.k
¹³C NMR (151 MHz, CDCl₃)
f1 (ppm)


7.47
7.45
7.22
7.04
7.03
6.28
6.26
4.75
4.73
3.66
2.66
2.54
1.70
1.32
O
OMe
Me
N
Me
2.S.12
Ac–N
Boc
1H NMR (600 MHz, CDCl3)
1.90
0.93
1.04
0.91
0.93
2.93
2.94
2.92
2.97
9.00
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 -0.5 -1.0
f1 (ppm)

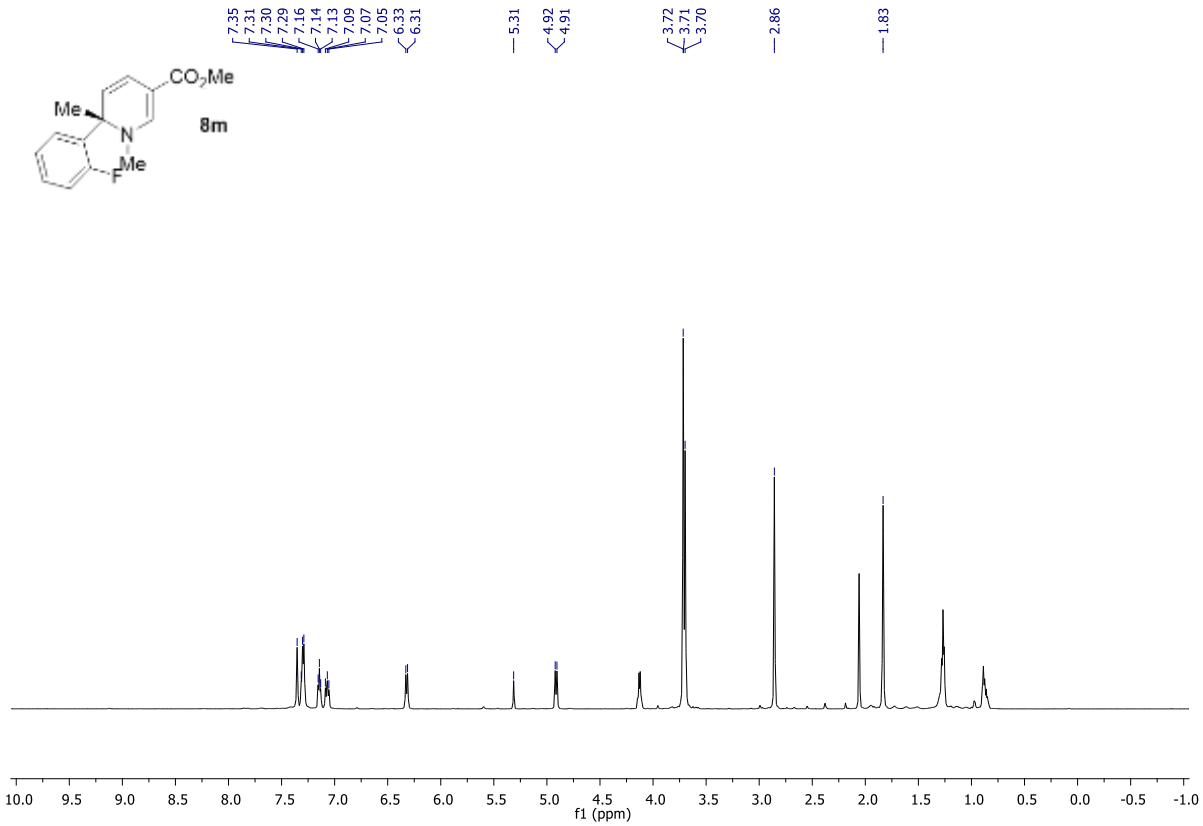

173.14
167.11
152.45
147.53
144.98
138.12
128.17
127.37
119.79
118.23
94.75
83.48
63.02
50.82
38.34
27.82
26.73
24.75
O
OMe
Me
N
Me
2.S.12
Ac–N
Boc
13C NMR (151 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



^{1}H NMR (600 MHz, $CDCl_3$)



^{13}C NMR (151 MHz, $CDCl_3$)


7.35
7.31
7.30
7.29
7.16
7.14
7.13
7.09
7.07
7.05
6.33
6.31
5.31
4.92
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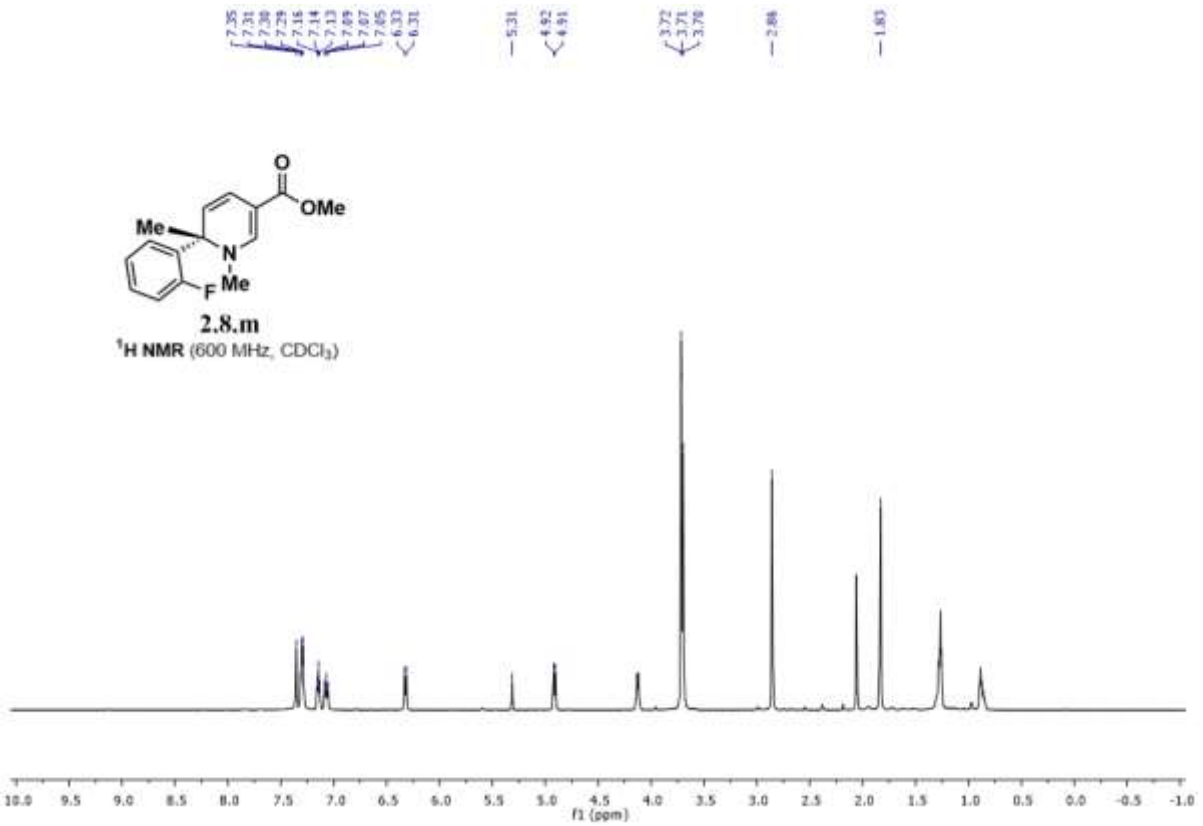
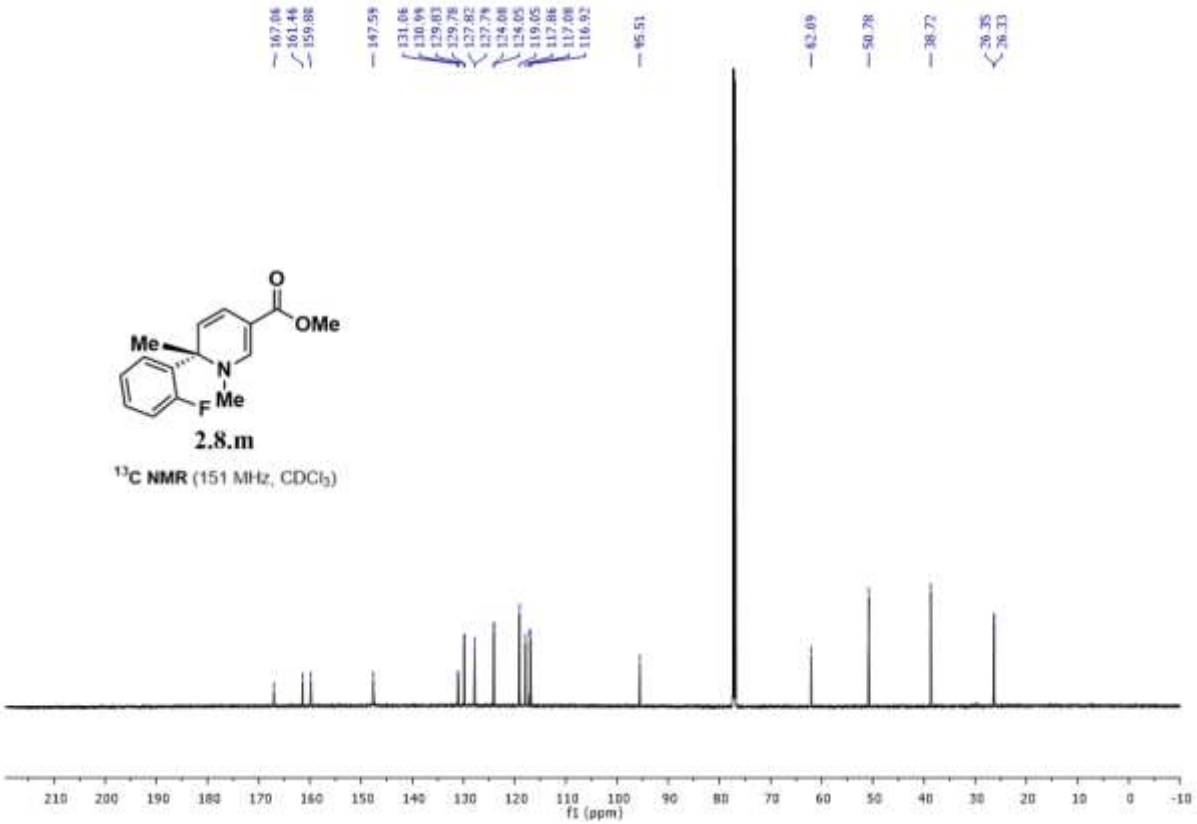
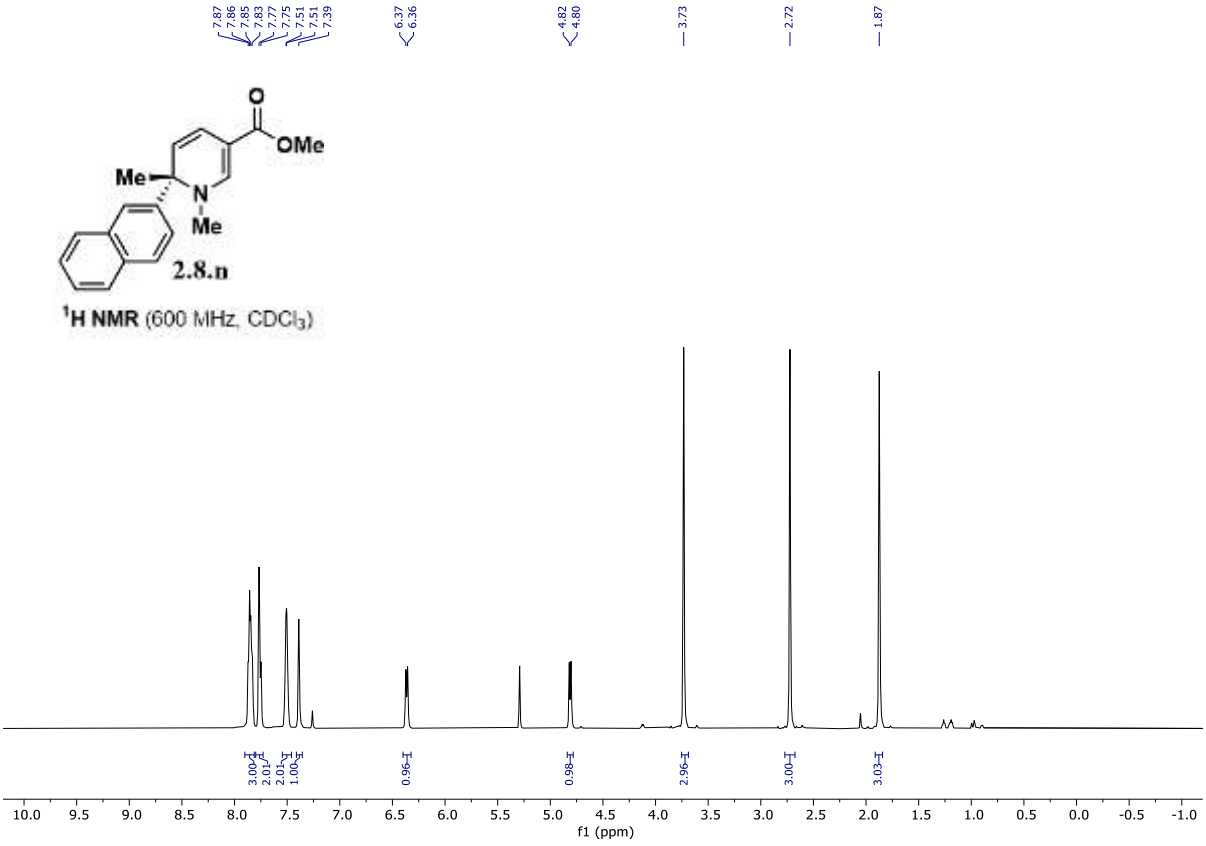
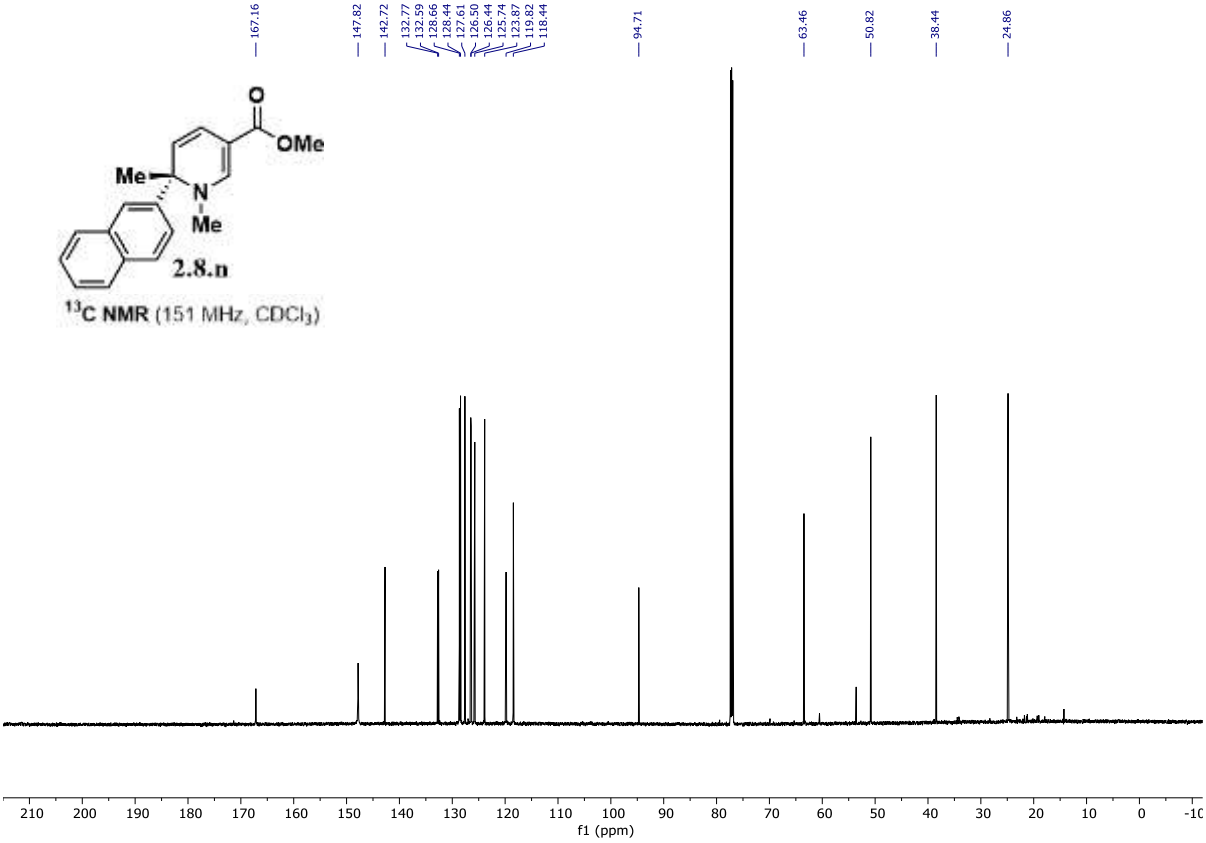
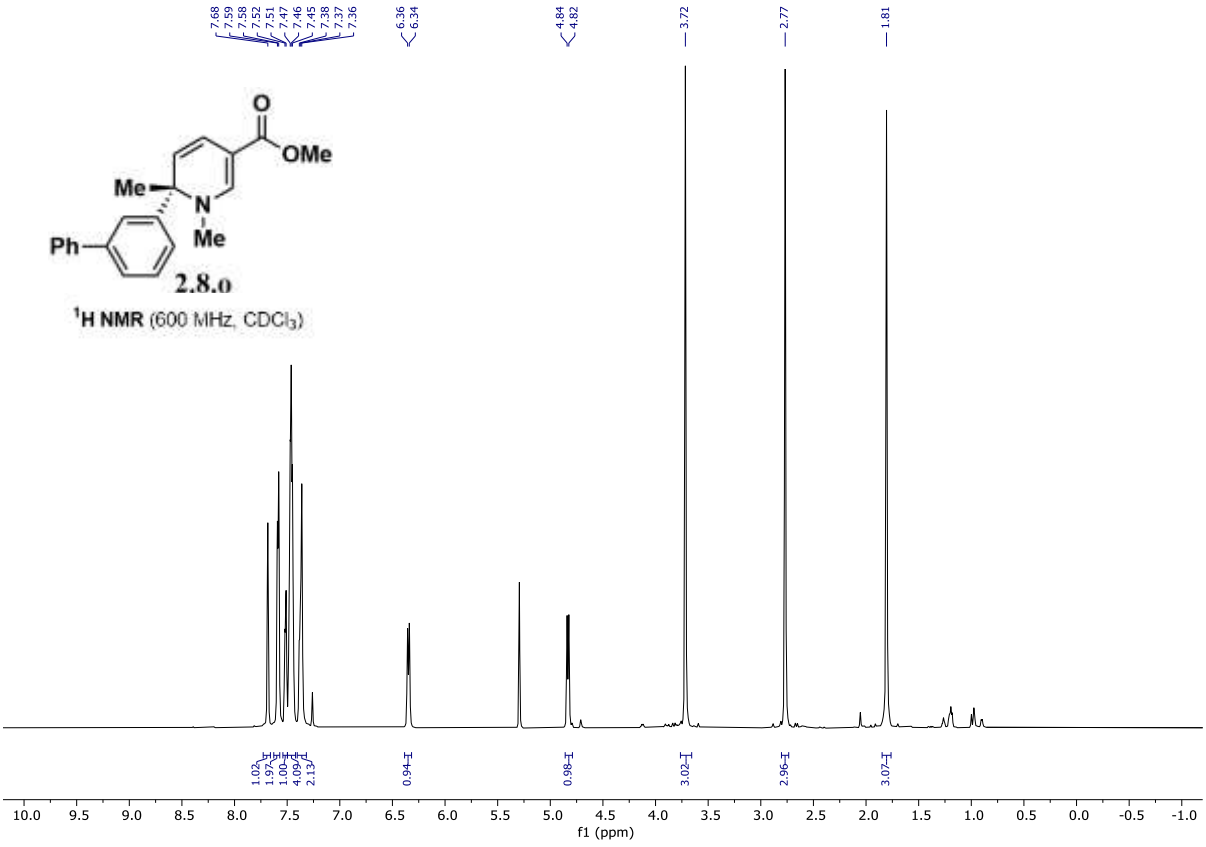
CO2Me
Me
N
Me
F
8m
f1 (ppm)

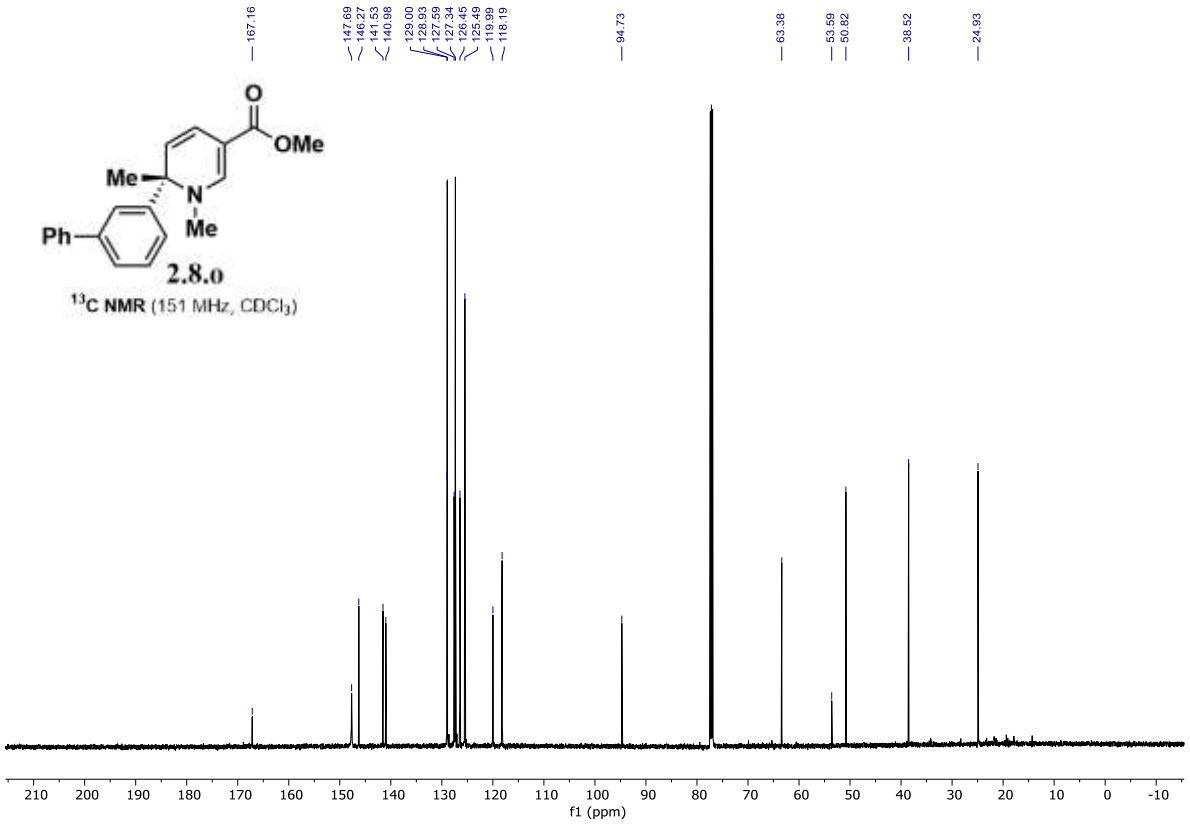

O
OMe
Me
N
Me
F
2.8.m
1H NMR (600 MHz, CDCl3)
f1 (ppm)

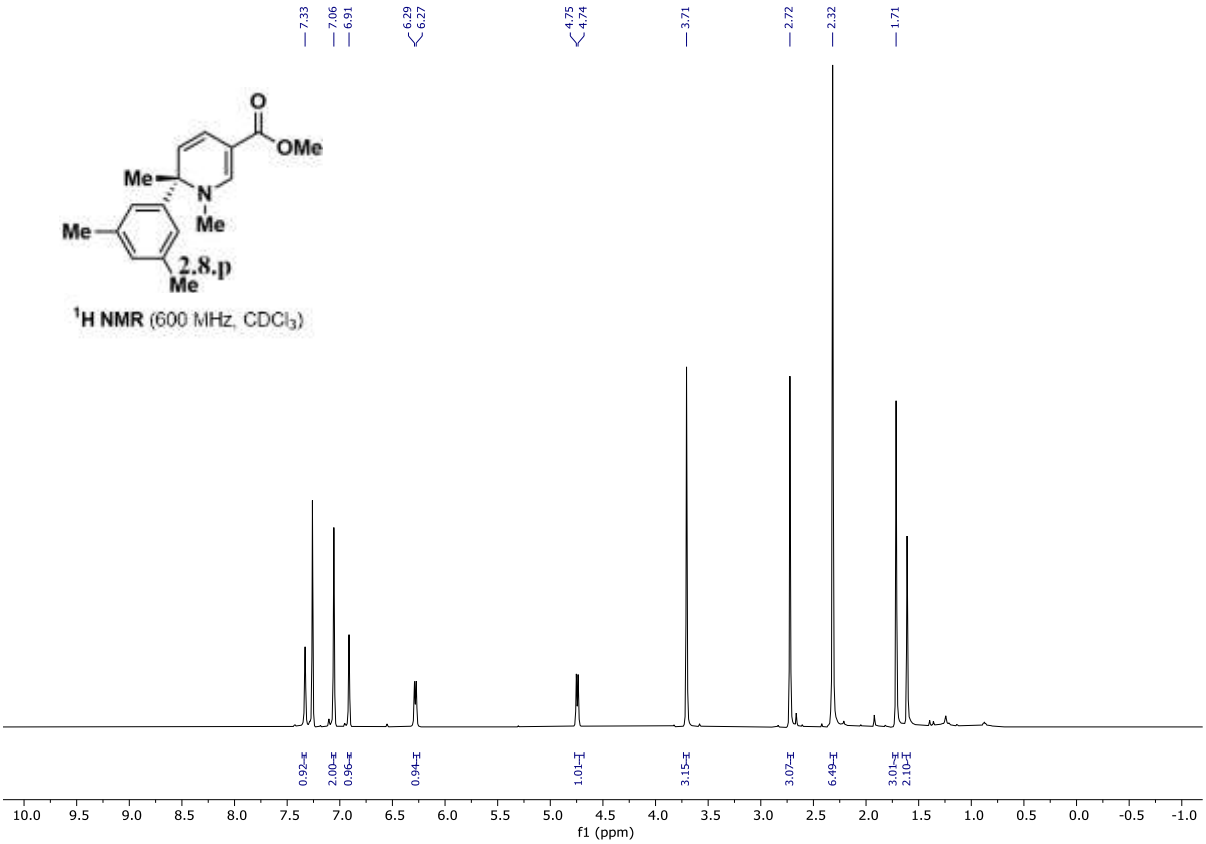

167.04
161.46
159.88
147.59
131.06
130.99
129.83
129.78
127.82
127.79
124.08
124.05
119.05
117.86
117.08
116.92
95.51
62.09
50.78
38.72
26.35
26.33
OMe
Me
N
Me
F
2.8.m
13C NMR (151 MHz, CDCl3)
f1 (ppm)

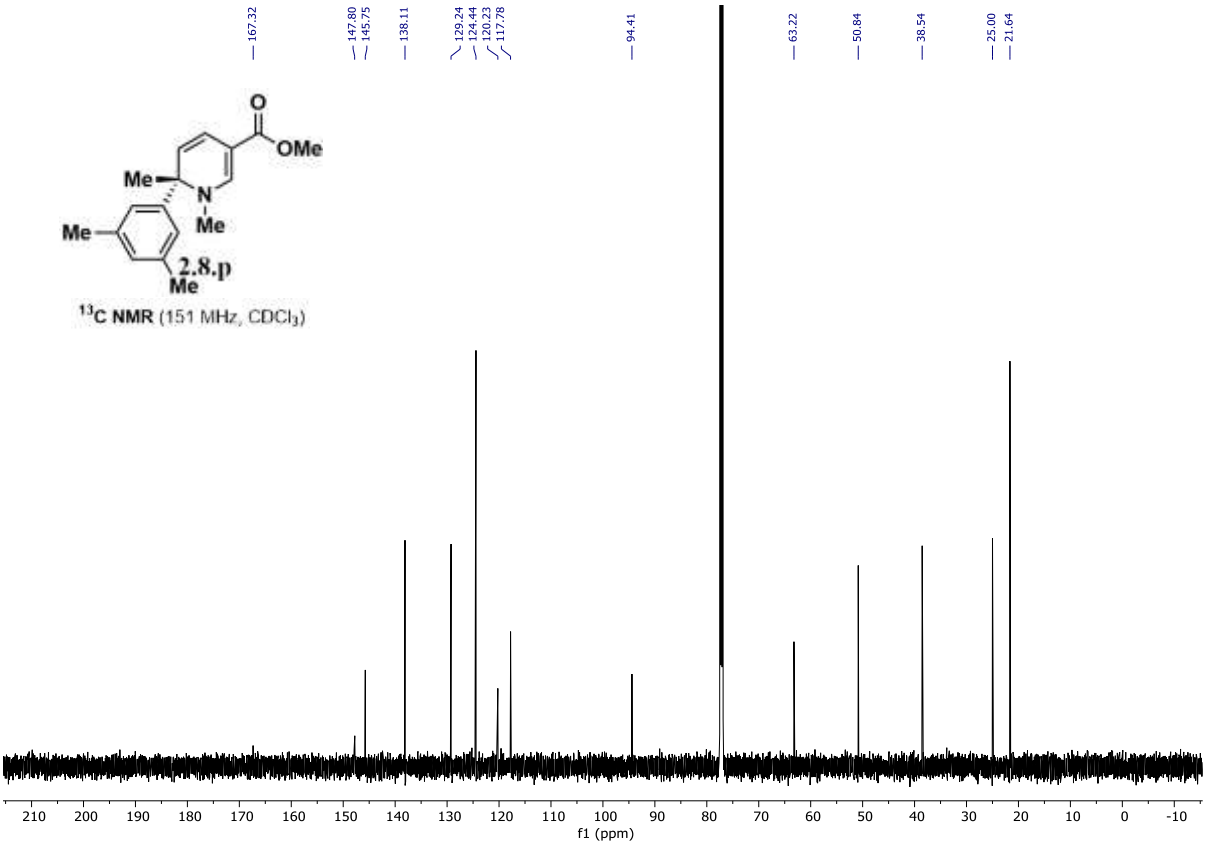

7.87
7.86
7.85
7.83
7.77
7.75
7.51
7.51
7.39
6.37
6.36
4.82
4.80
3.73
2.72
1.87
OMe
Me
N
Me
2.8.n
1H NMR (600 MHz, CDCl3)
3.00
2.01
2.01
1.00
0.96
0.98
2.96
3.00
3.03
f1 (ppm)


167.16
147.82
142.72
132.77
132.59
128.66
128.44
127.61
126.50
126.44
125.74
123.87
119.82
118.44
94.71
63.46
50.82
38.44
24.86
O
OMe
Me
N
Me
2.8.n
13C NMR (151 MHz, CDCl3)
f1 (ppm)

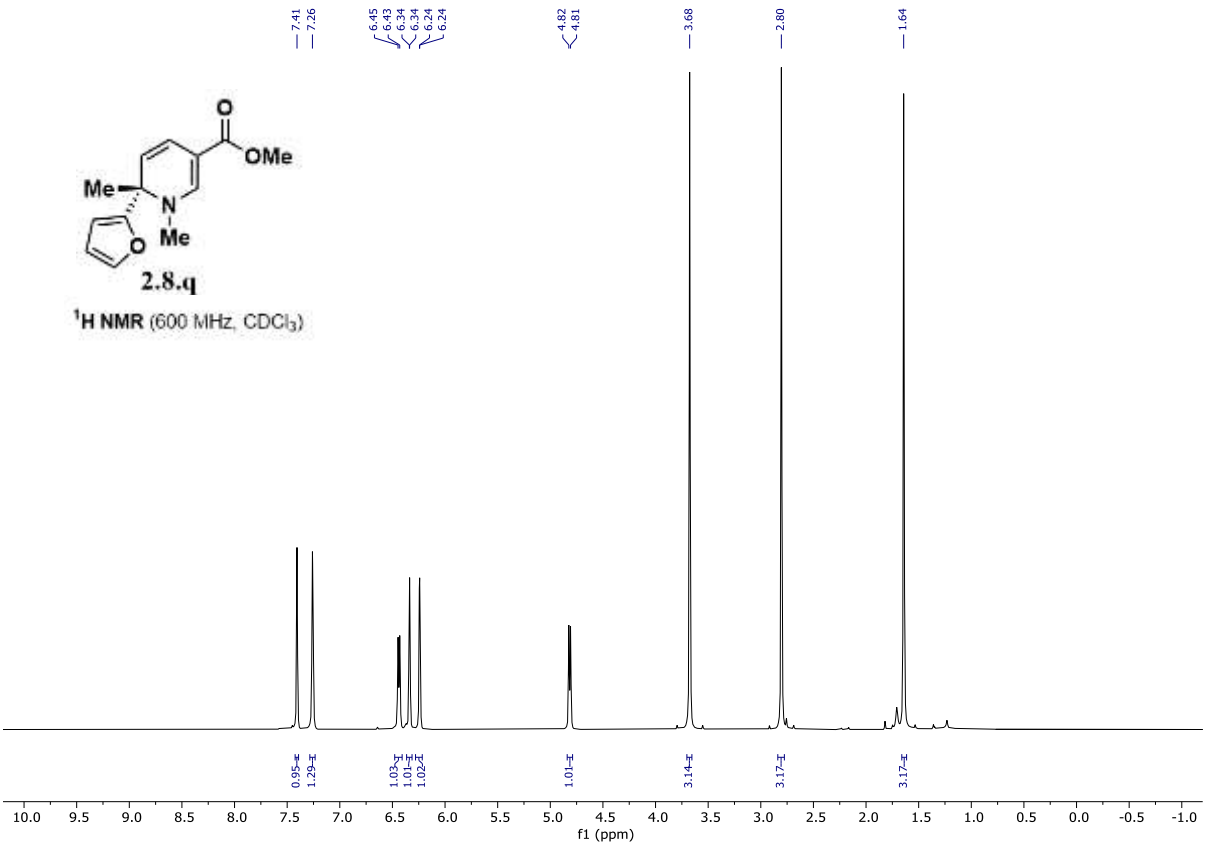

7.68
7.59
7.58
7.52
7.51
7.47
7.46
7.45
7.38
7.37
7.36
6.36
6.34
4.84
4.82
3.72
2.77
1.81
O
OMe
Me
N
Me
Ph
2.8.o
1H NMR (600 MHz, CDCl3)
1.02
1.97
1.00
4.09
2.13
0.94
0.98
3.02
2.96
3.07
f1 (ppm)


167.16
147.69
146.27
141.53
140.98
129.00
128.93
127.59
127.34
126.45
125.49
119.99
116.19
94.73
63.38
53.59
50.82
38.52
24.93
O
OMe
Me
N
Me
Ph
2.8.o
13C NMR (151 MHz, CDCl3)
f1 (ppm)

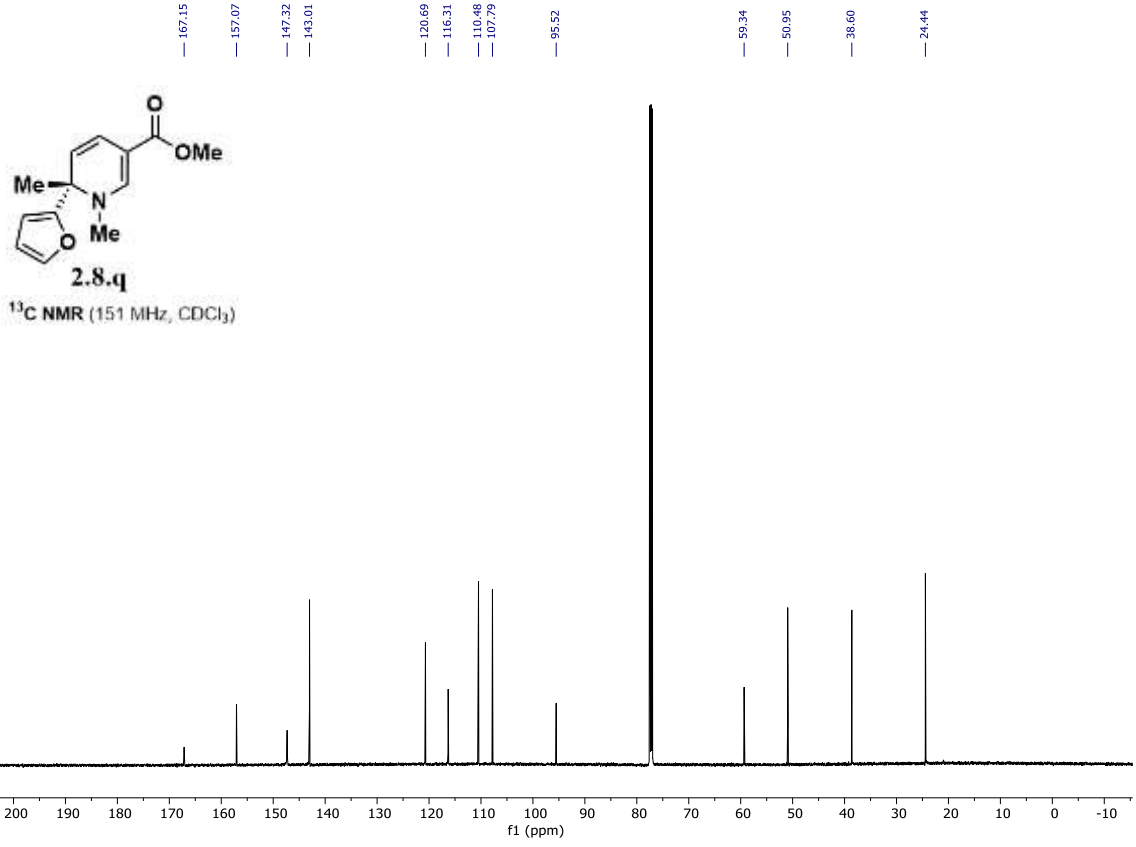

7.33
7.06
6.91
6.29
6.27
4.75
4.74
3.71
2.72
2.32
1.71
O
OMe
Me
N
Me
Me
2.8.p
Me
1H NMR (600 MHz, CDCl3)
0.92
2.00
0.96
0.94
1.01
3.15
3.07
6.49
3.01
2.10
f1 (ppm)

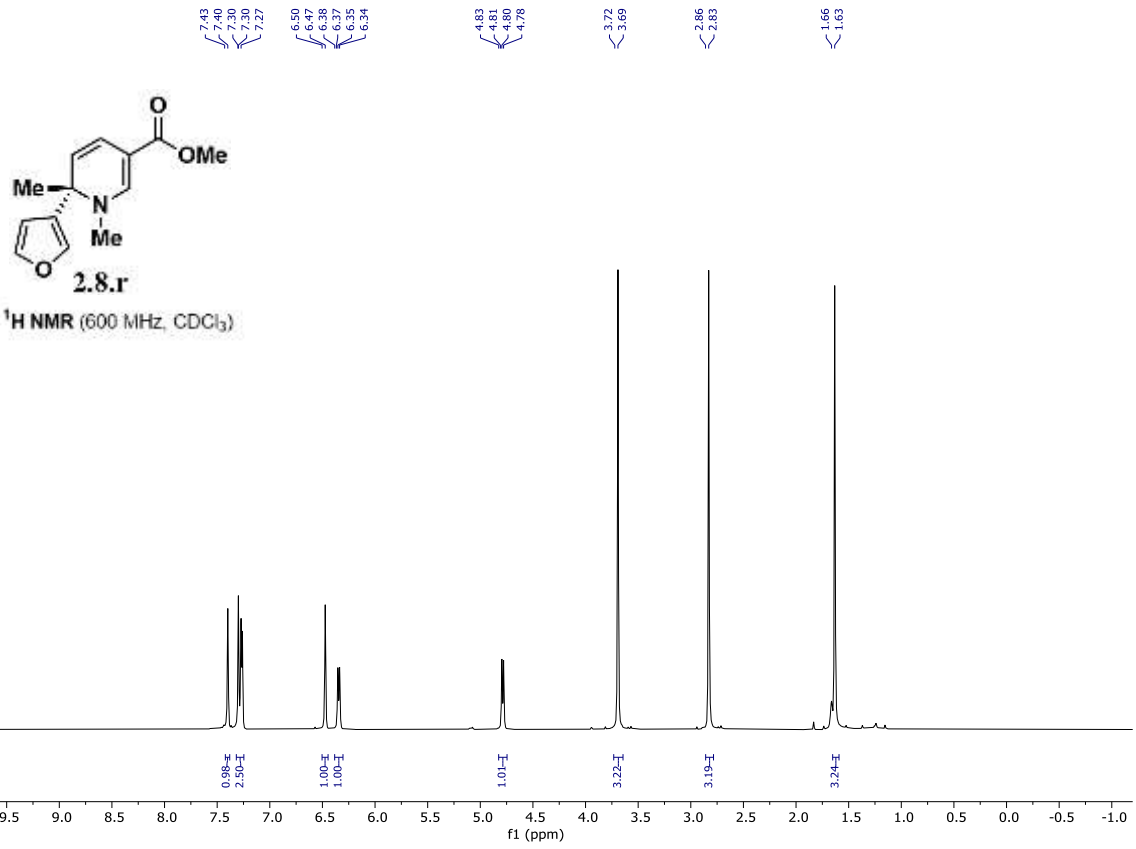


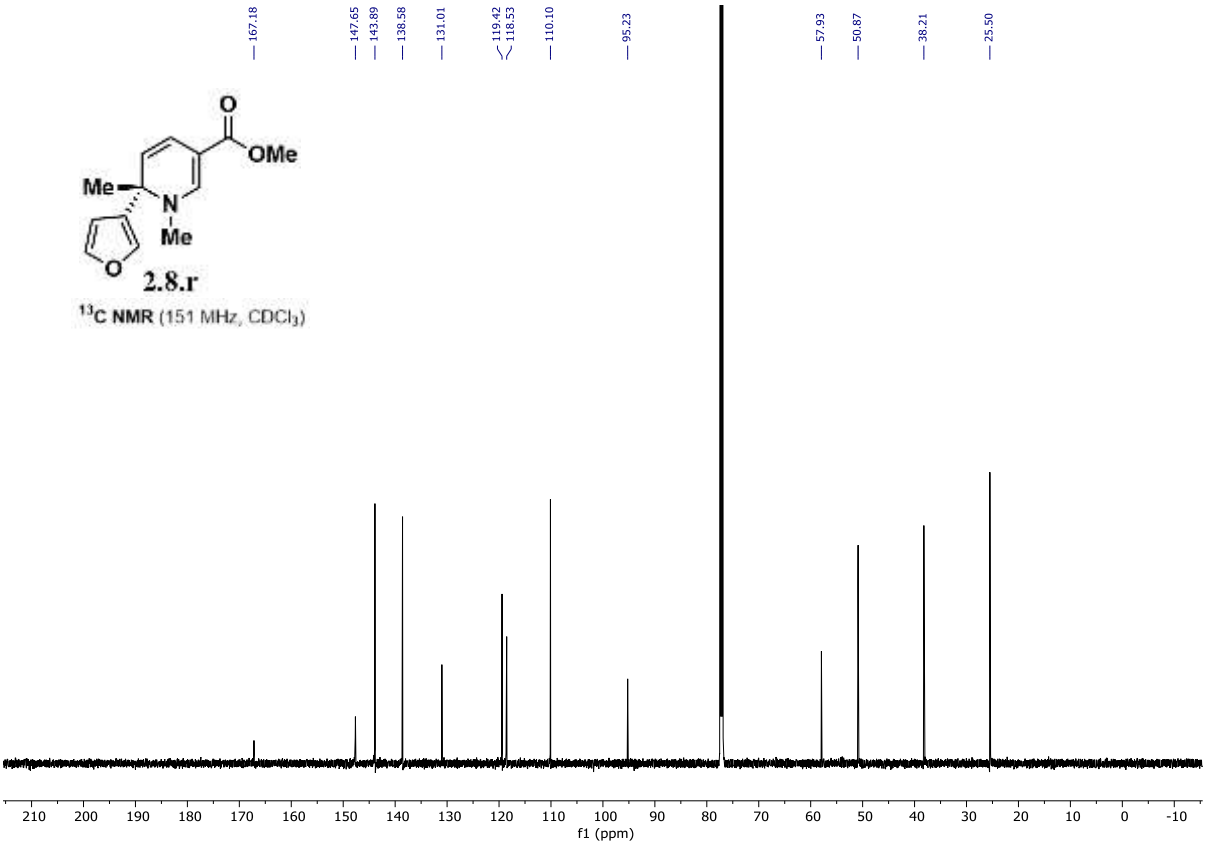
^{13}C NMR (151 MHz, $CDCl_3$)

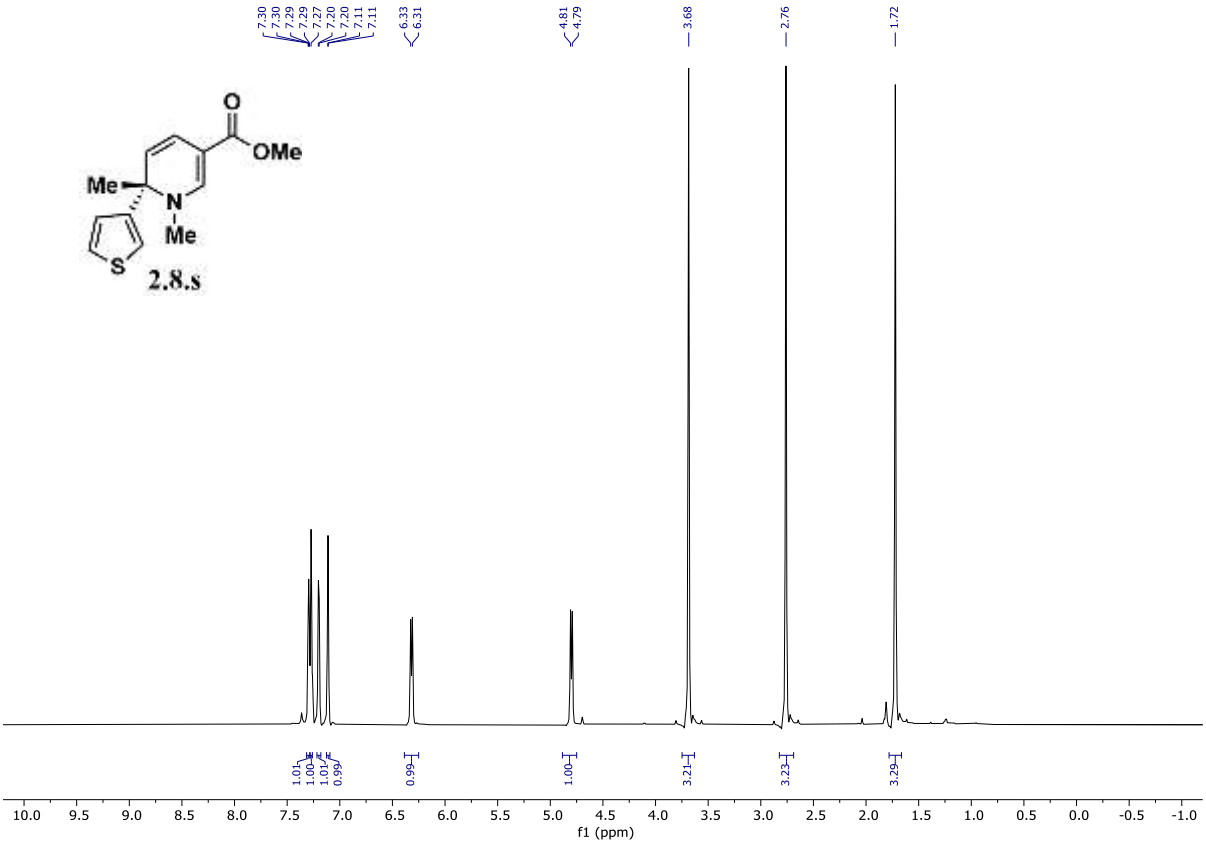


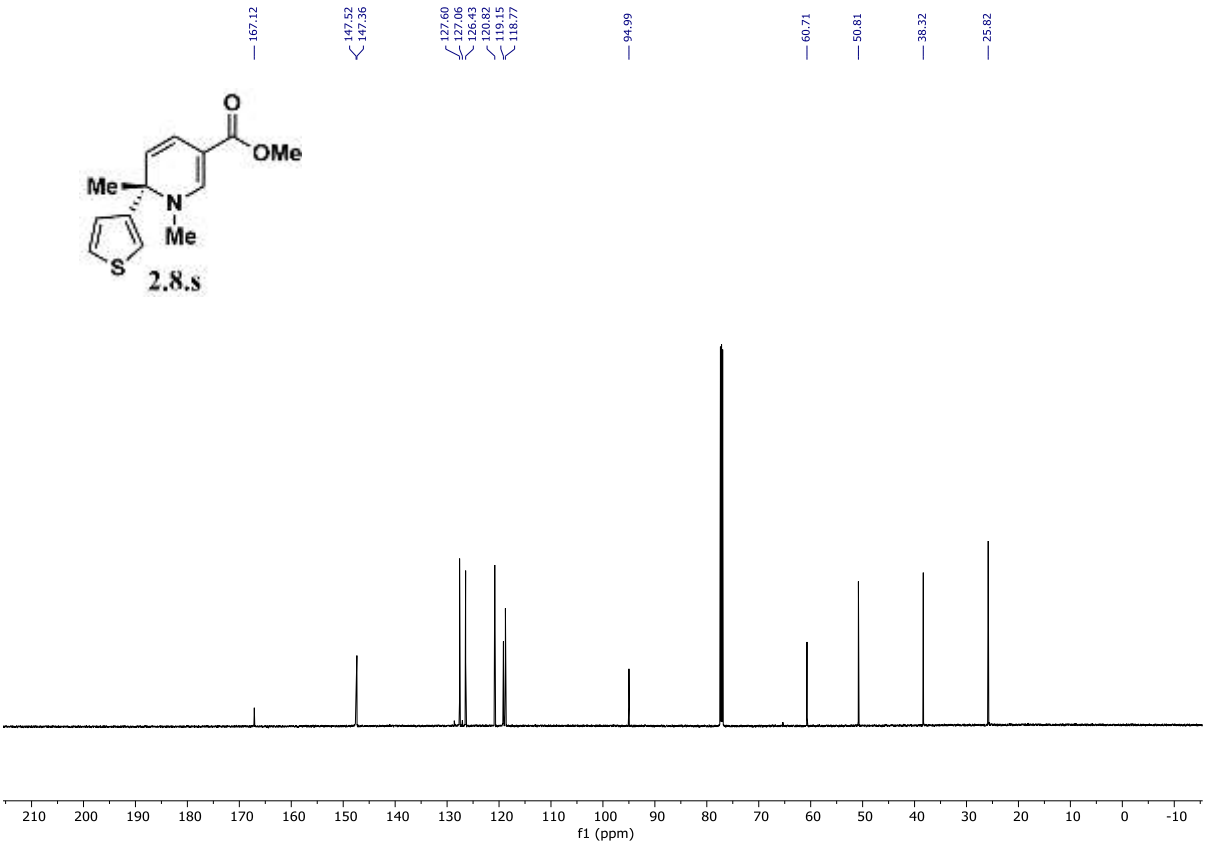
^{1}H NMR (600 MHz, $CDCl_3$)

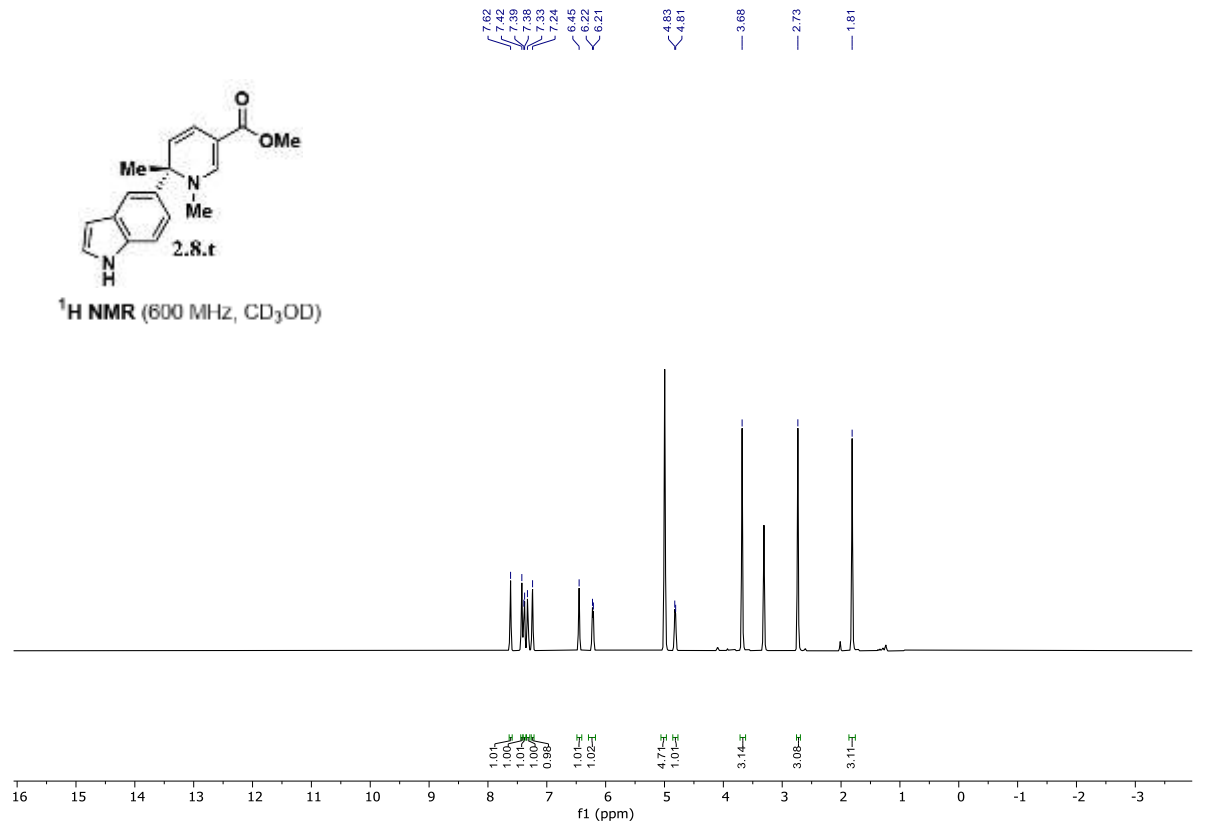

167.15
157.07
147.32
143.01
120.69
116.31
110.48
107.79
95.52
59.34
50.95
38.60
24.44
O
OMe
Me
N
Me
O
2.8.q
13C NMR (151 MHz, CDCl3)
f1 (ppm)


7.43
7.40
7.30
7.30
7.27
6.50
6.47
6.38
6.37
6.35
6.34
4.83
4.81
4.80
4.78
3.72
3.69
2.86
2.83
1.66
1.63
O
OMe
Me
N
Me
O
2.8.r
1H NMR (600 MHz, CDCl3)
0.98
2.50
1.00
1.00
1.01
3.22
3.19
3.24
f1 (ppm)

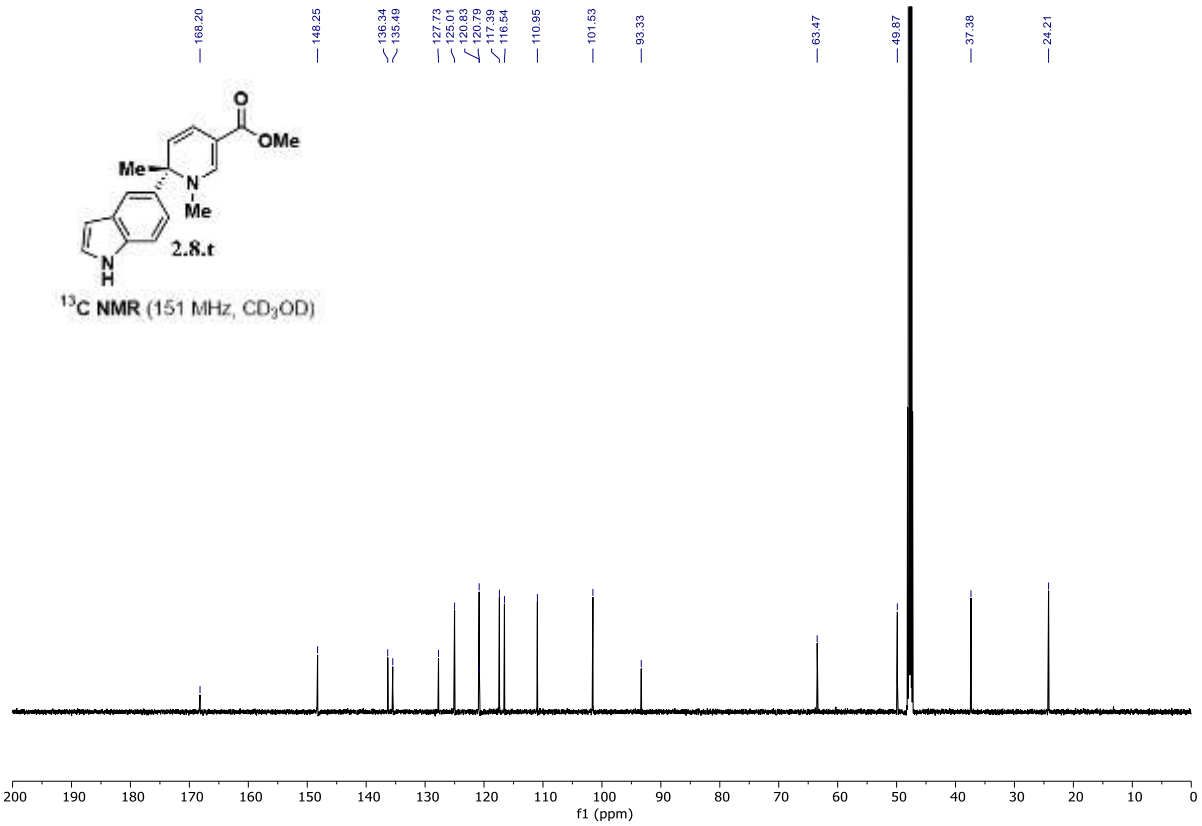

167.18
147.65
143.89
138.58
131.01
119.42
118.53
110.10
95.23
57.93
50.87
38.21
25.50
O
OMe
Me
N
Me
O
2.8.r
13C NMR (151 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.30
7.30
7.29
7.29
7.27
7.20
7.20
7.11
7.11
6.33
6.31
4.81
4.79
3.68
2.76
1.72
O
OMe
Me
N
Me
S
2.8.s
1.01
1.00
1.01
0.99
0.99
1.00
3.21
3.23
3.29
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 -0.5 -1.0
f1 (ppm)

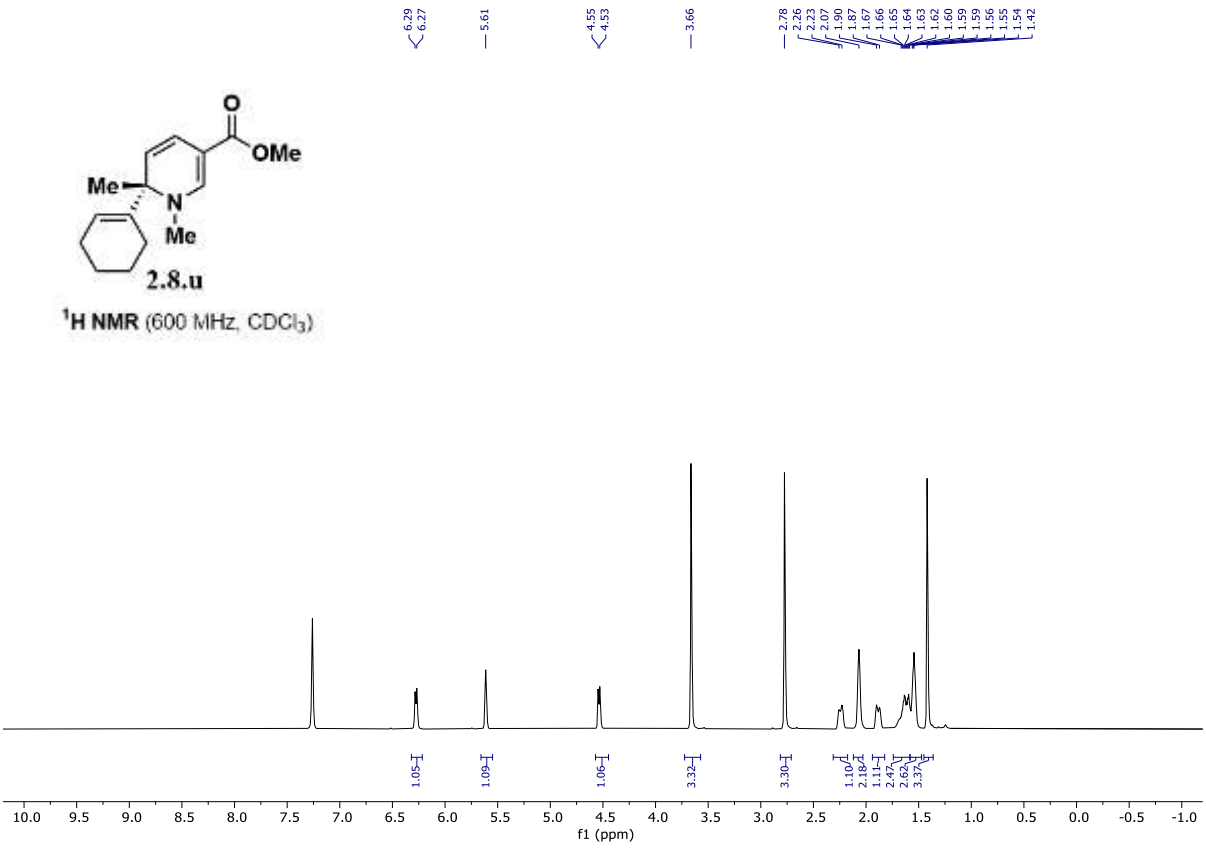




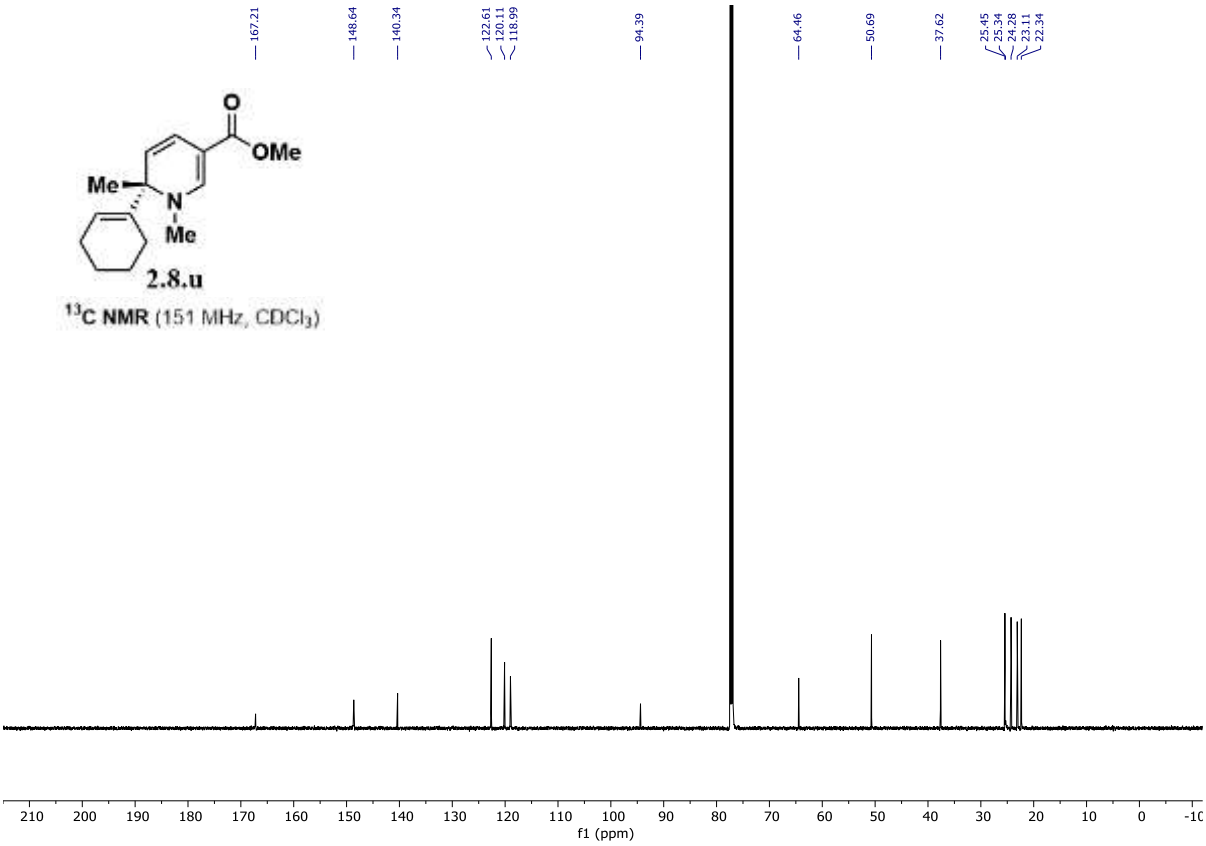
^{1}**H NMR** (600 MHz, CD_3OD)



^{13}C NMR (151 MHz, CD_3OD)

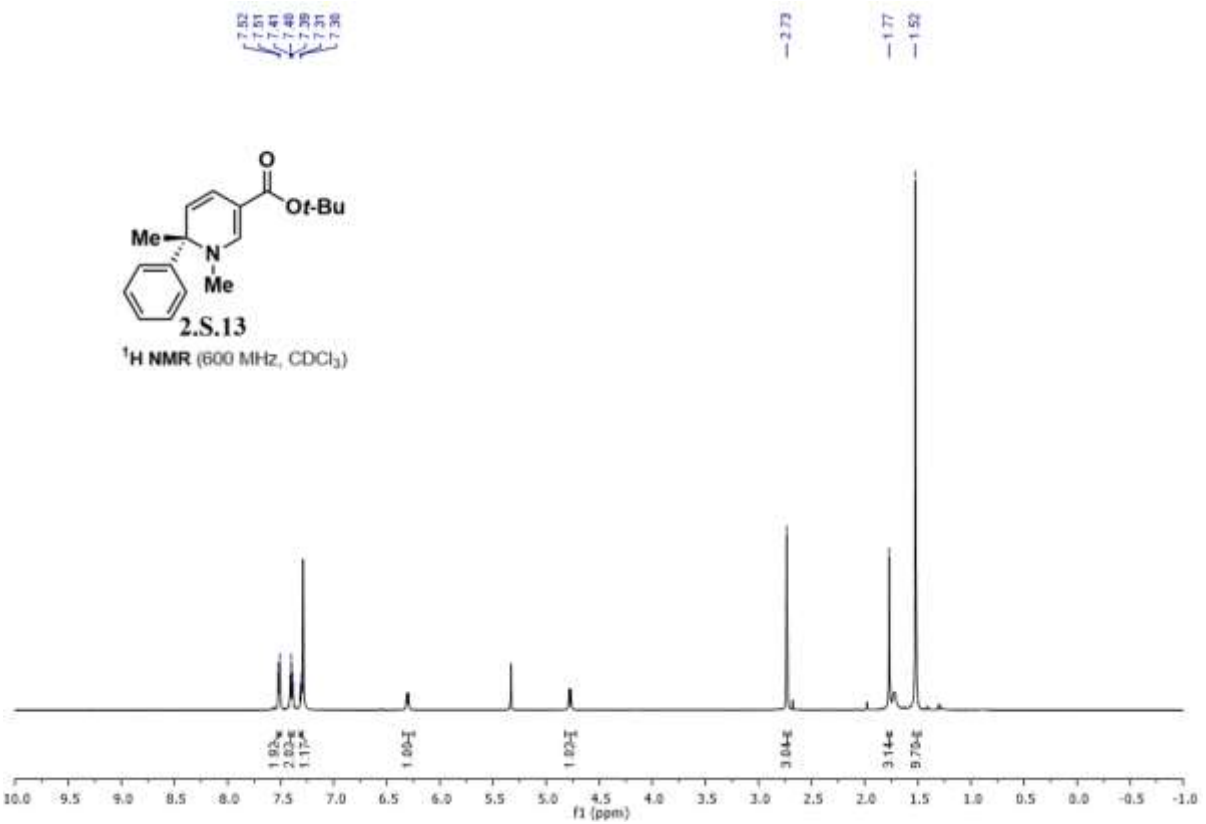


^{1}H NMR (600 MHz, $CDCl_3$)



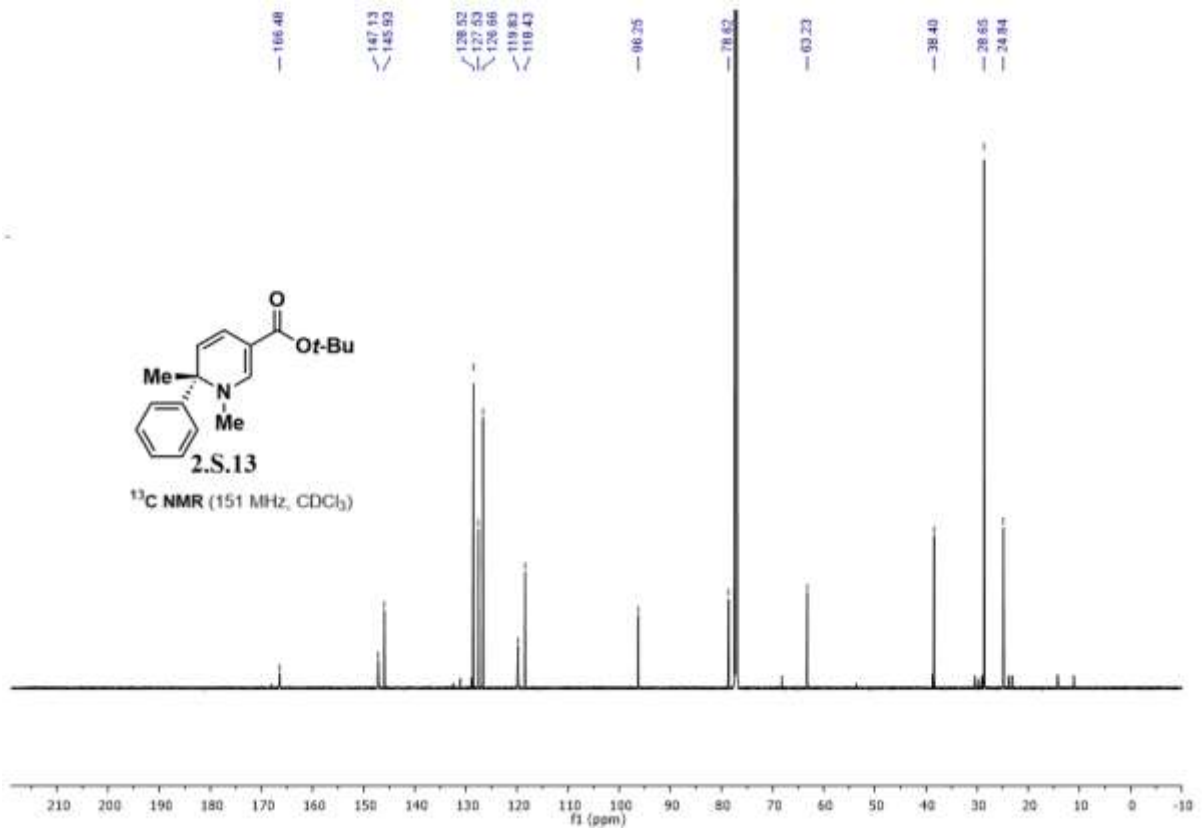
2.8.u

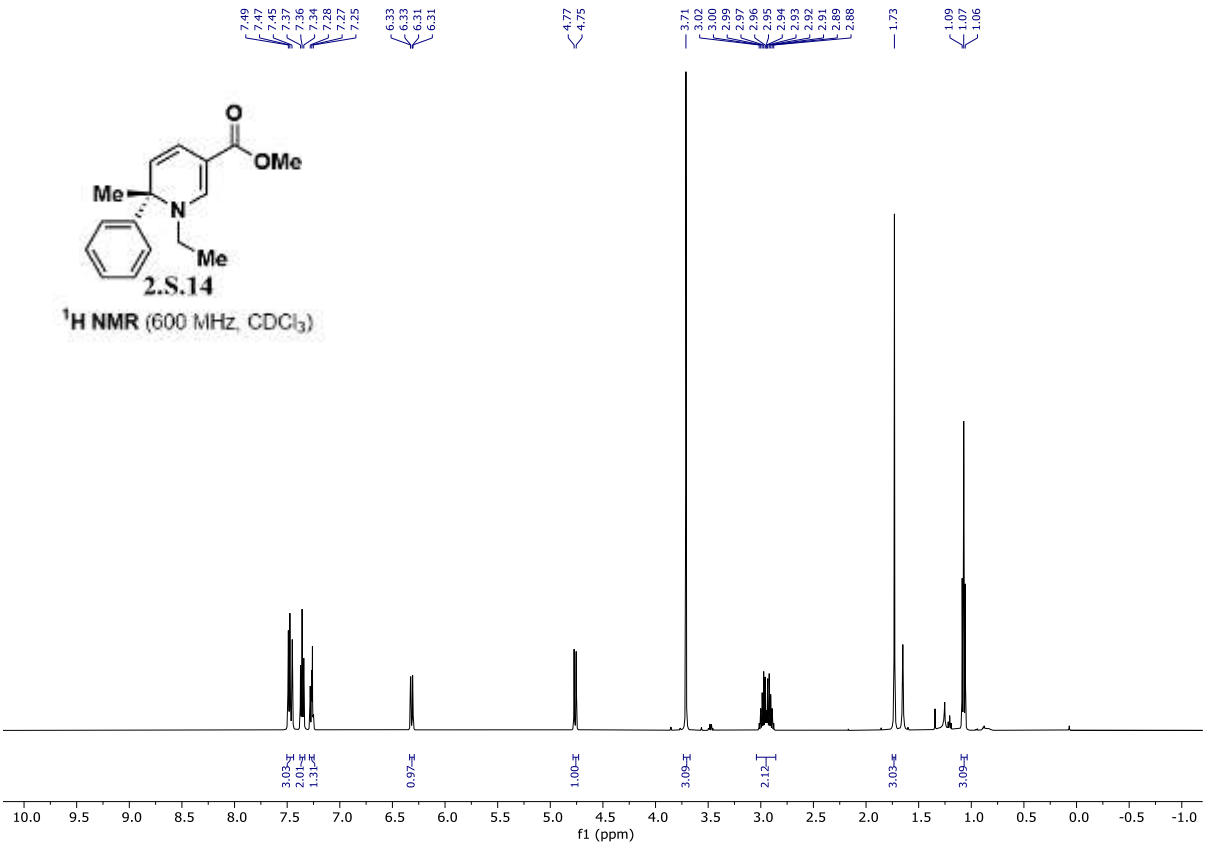
^{13}C NMR (151 MHz, $CDCl_3$)

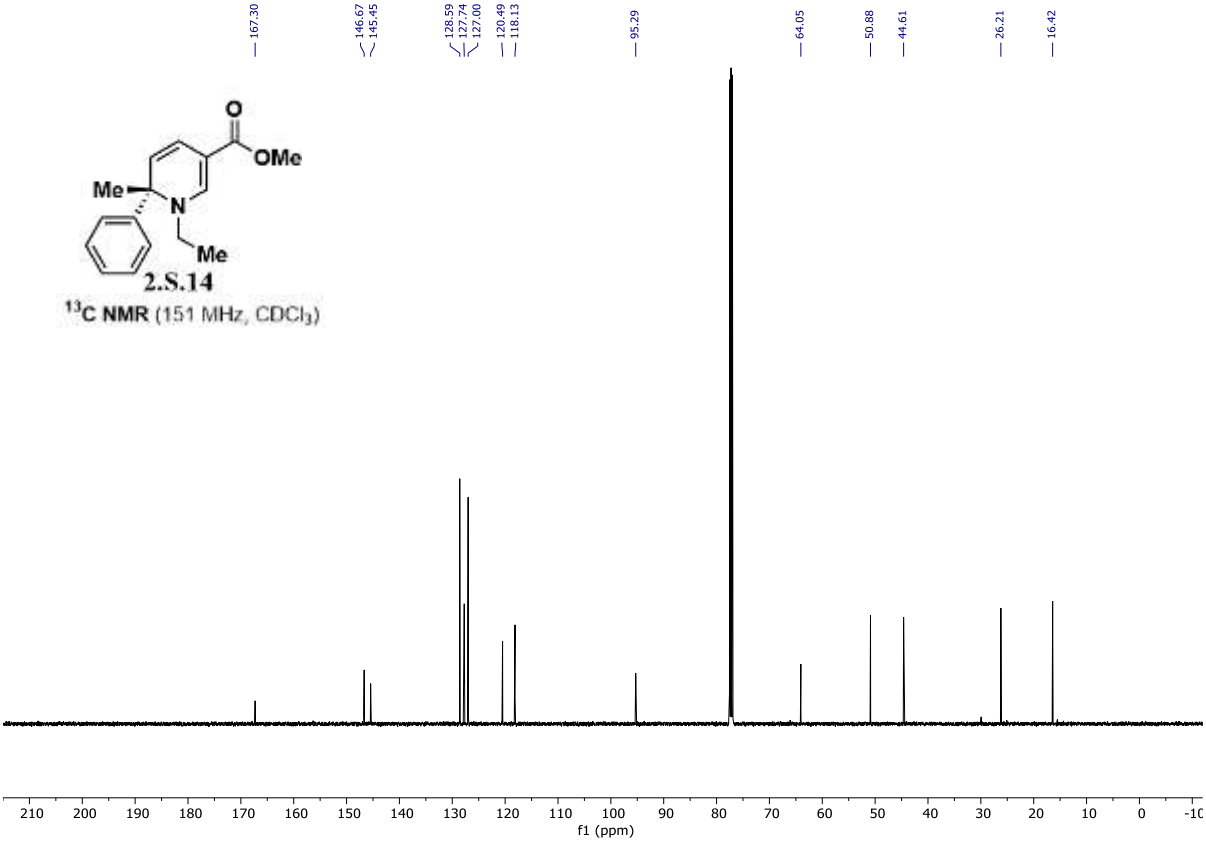


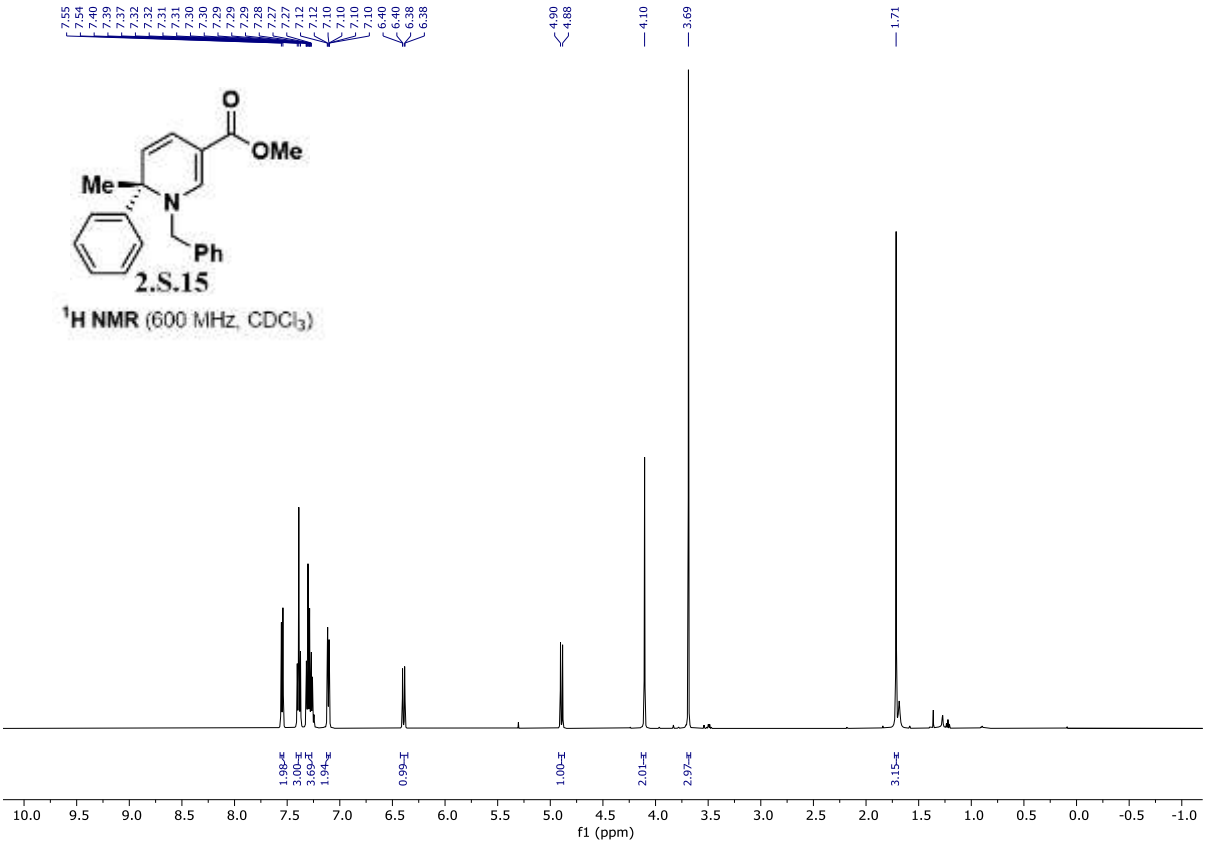
2.S.13

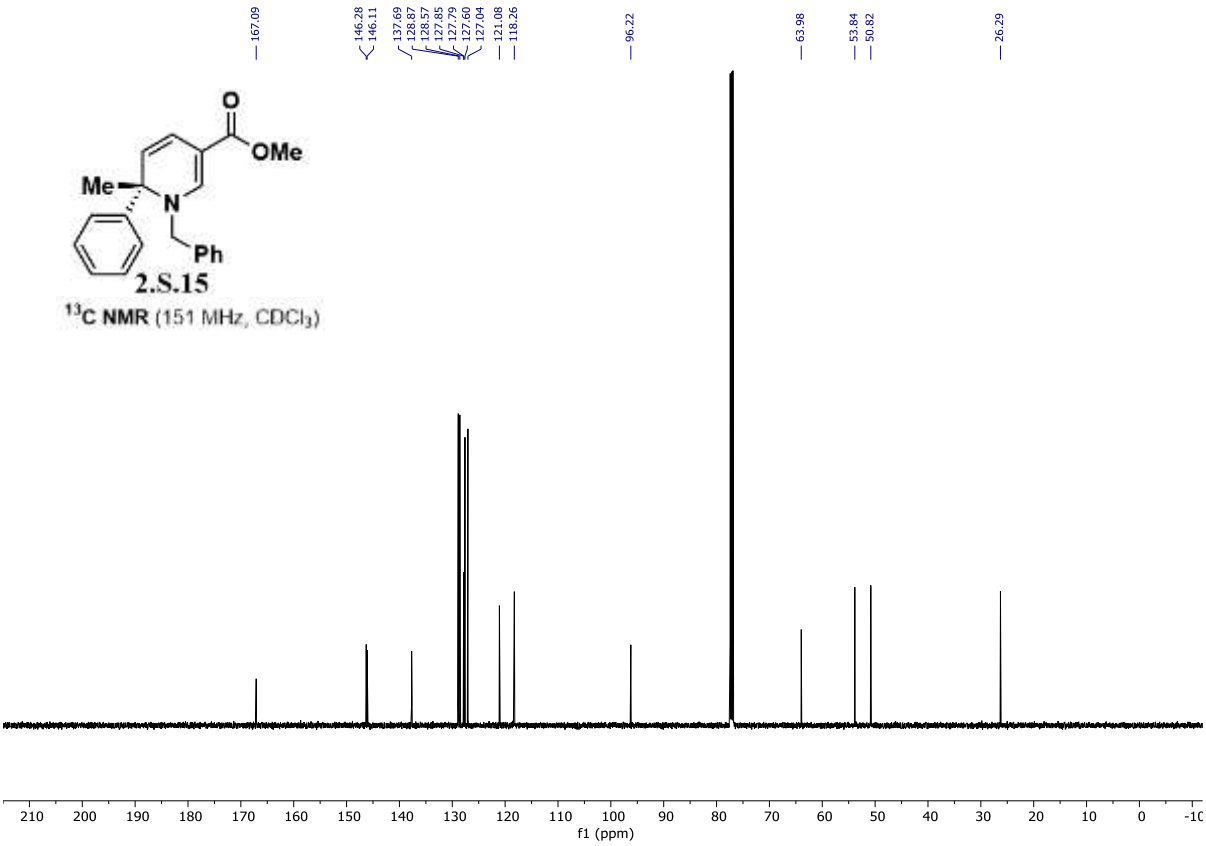
^{1}H NMR (600 MHz, $CDCl_3$)


O
Ot-Bu
Me
N
Me
2.S.13
13C NMR (151 MHz, CDCl3)
f1 (ppm)


O
OMe
Me
N
Me
2.S.14
1H NMR (600 MHz, CDCl3)
f1 (ppm)

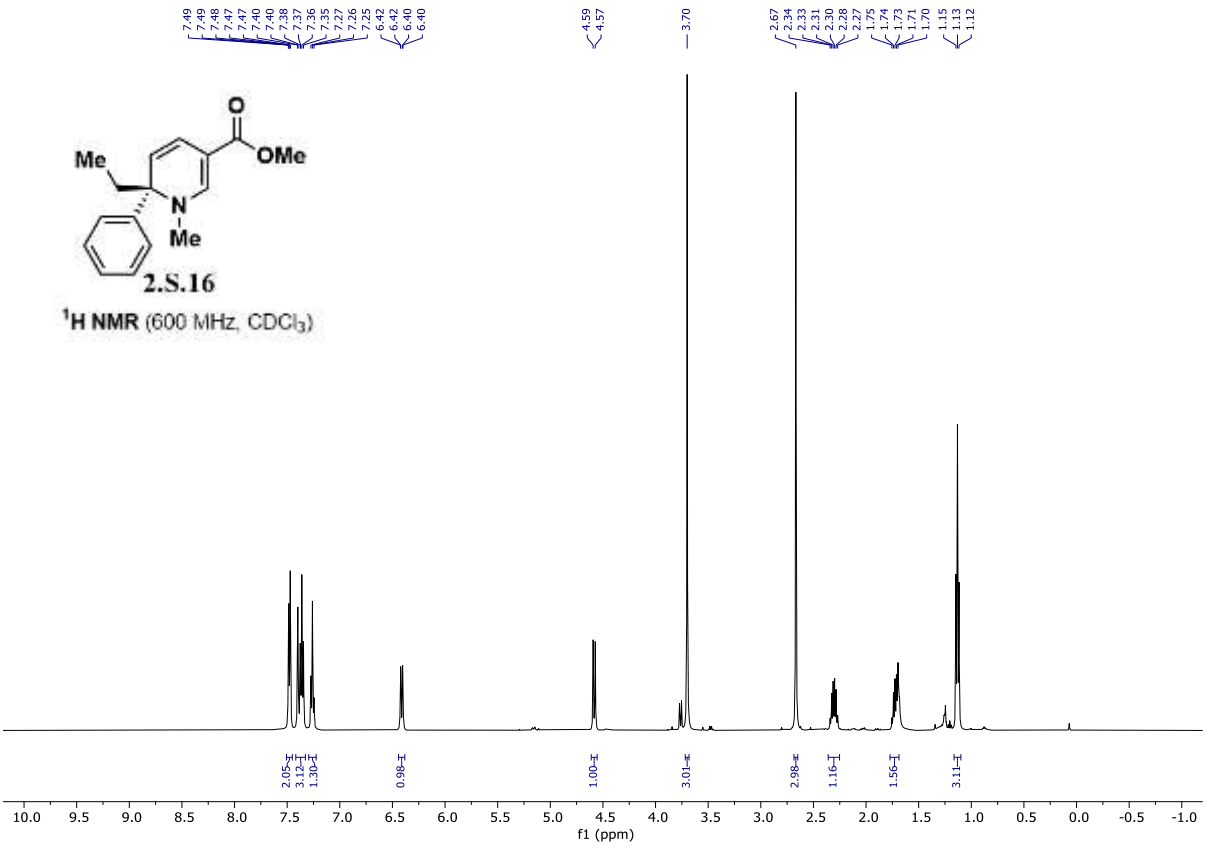

167.30
146.67
145.45
128.59
127.74
127.00
120.49
118.13
95.29
64.05
50.88
44.61
26.21
16.42
O
OMe
Me
N
Me
2.S.14
13C NMR (151 MHz, CDCl3)
f1 (ppm)


7.55
7.54
7.40
7.39
7.37
7.32
7.31
7.31
7.30
7.30
7.29
7.29
7.28
7.28
7.27
7.27
7.12
7.10
7.10
7.10
7.10
6.40
6.40
6.38
6.38
4.90
4.88
4.10
3.69
1.71
O
OMe
Me
N
Ph
2.S.15
1H NMR (600 MHz, CDCl3)
1.98
3.00
3.69
1.94
0.99
1.00
2.01
2.97
3.15
f1 (ppm)



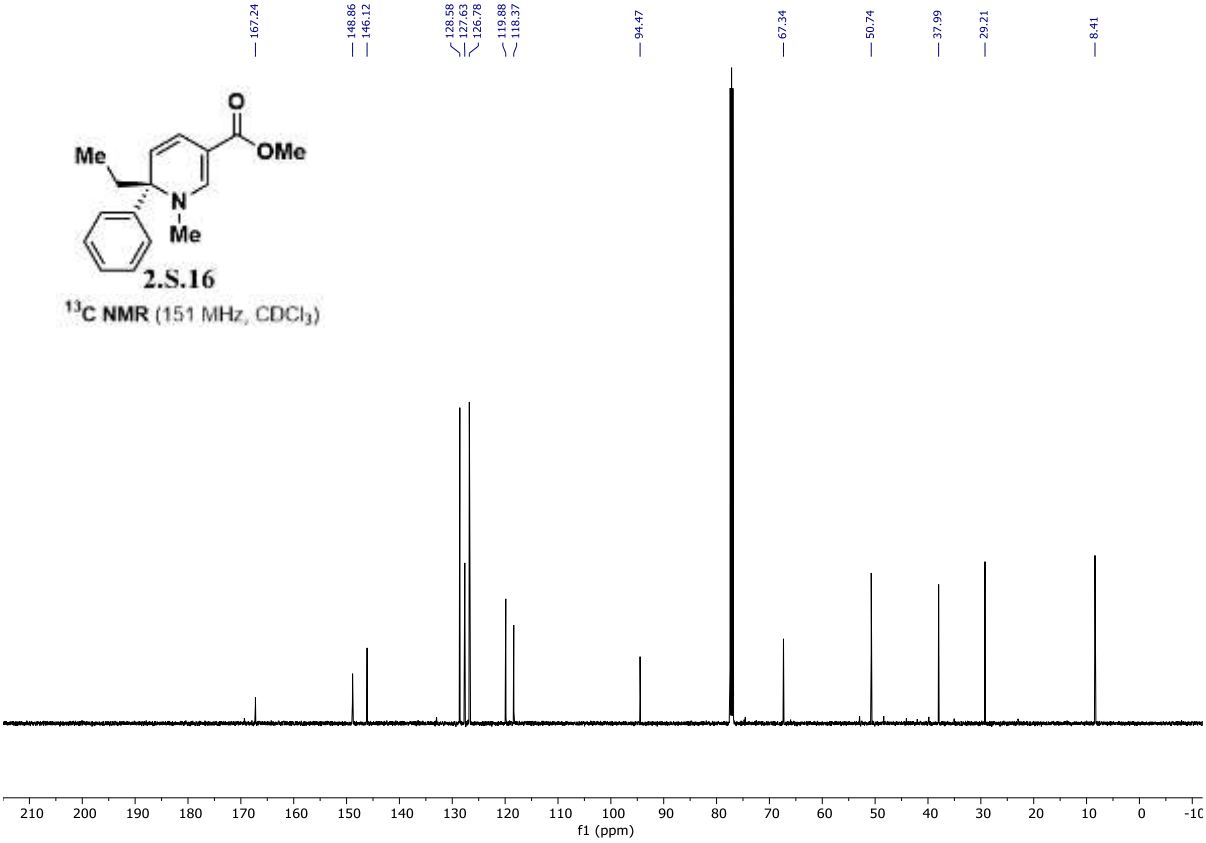
2.S.15

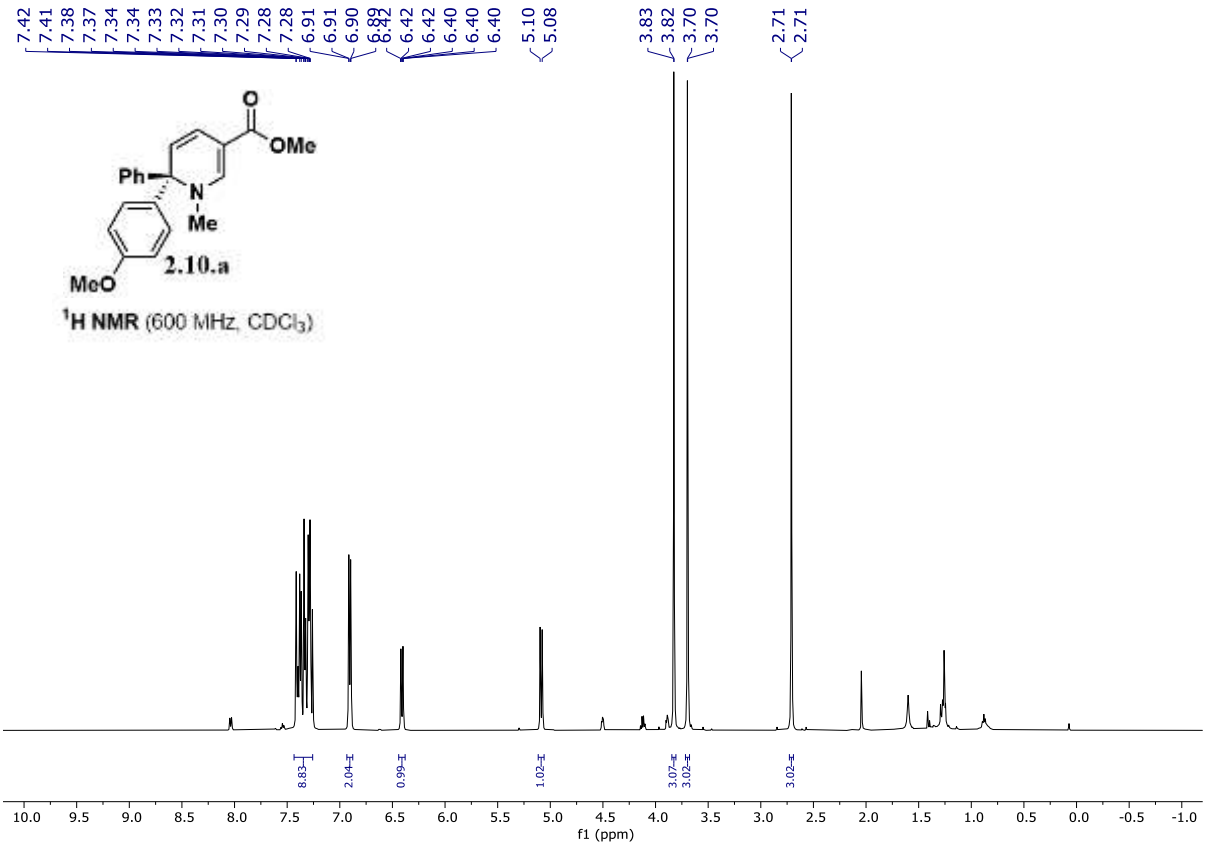
^{13}C NMR (151 MHz, $CDCl_3$)

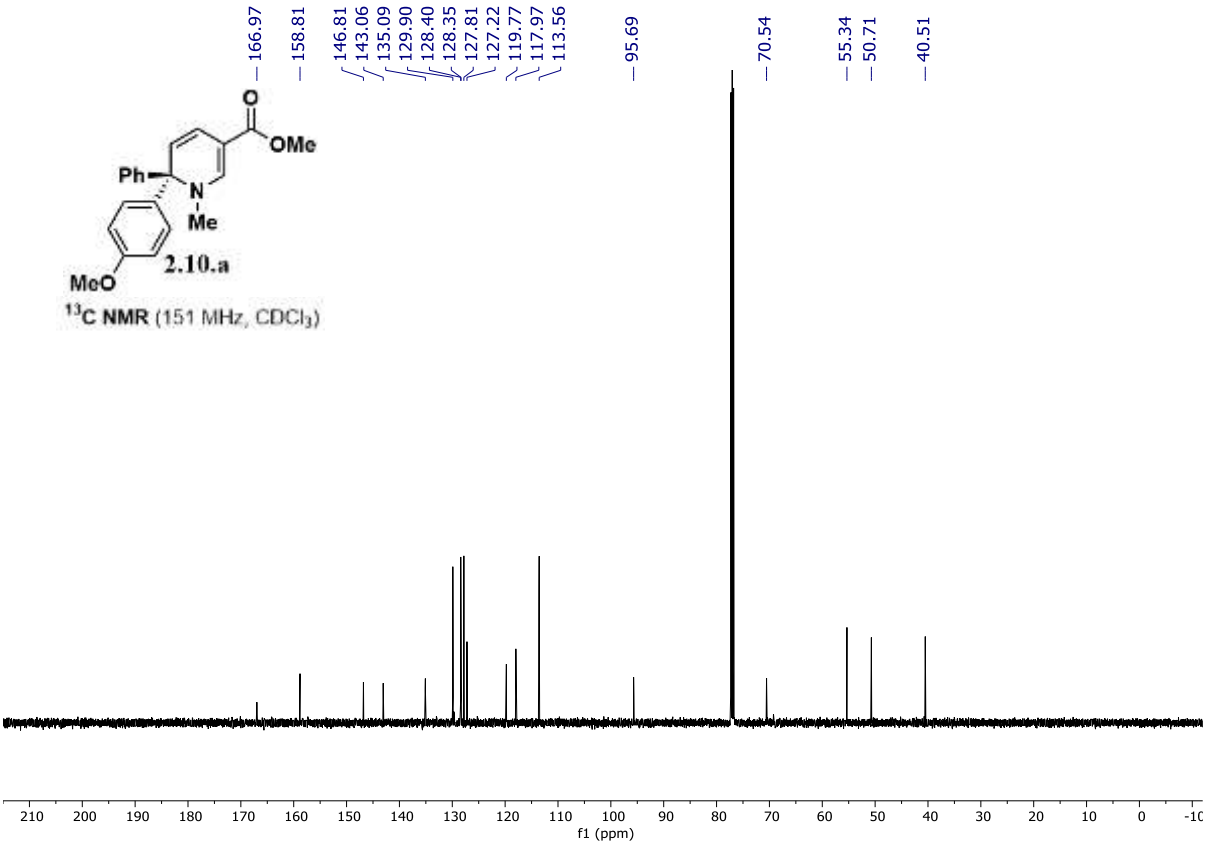


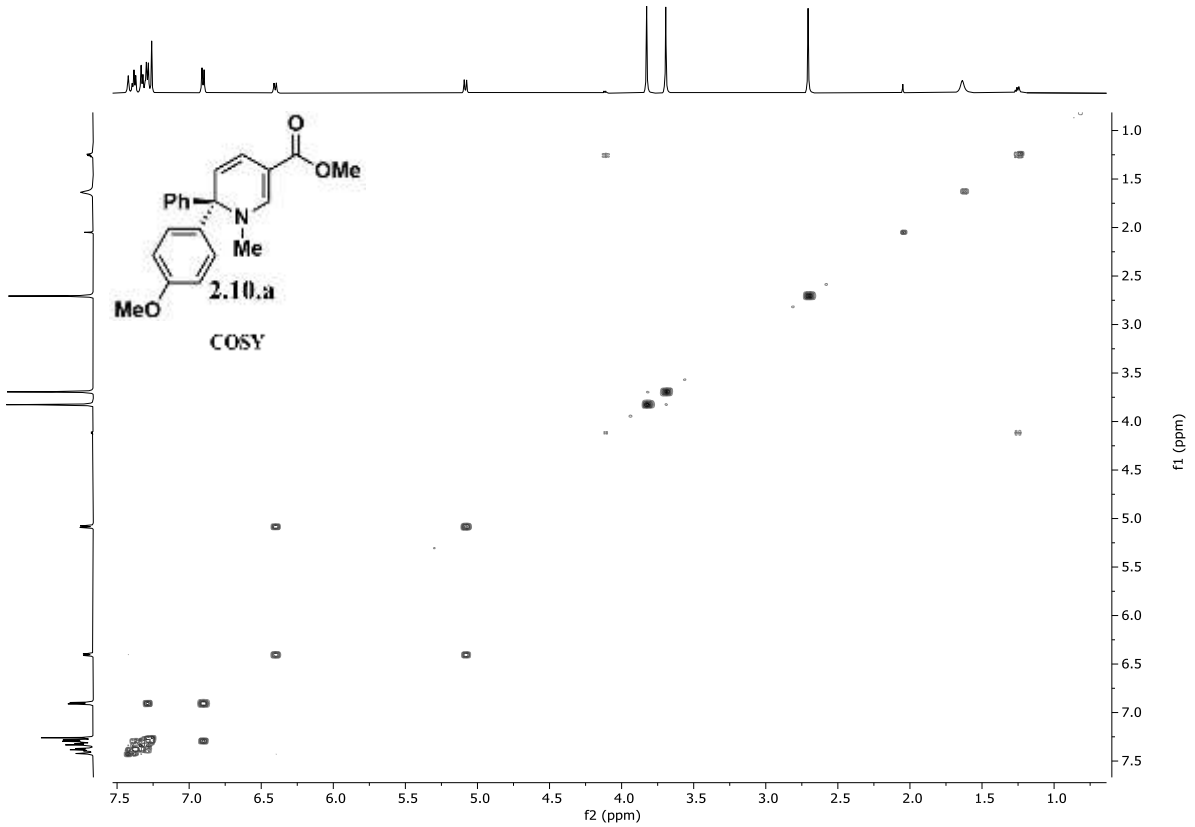
2.S.16

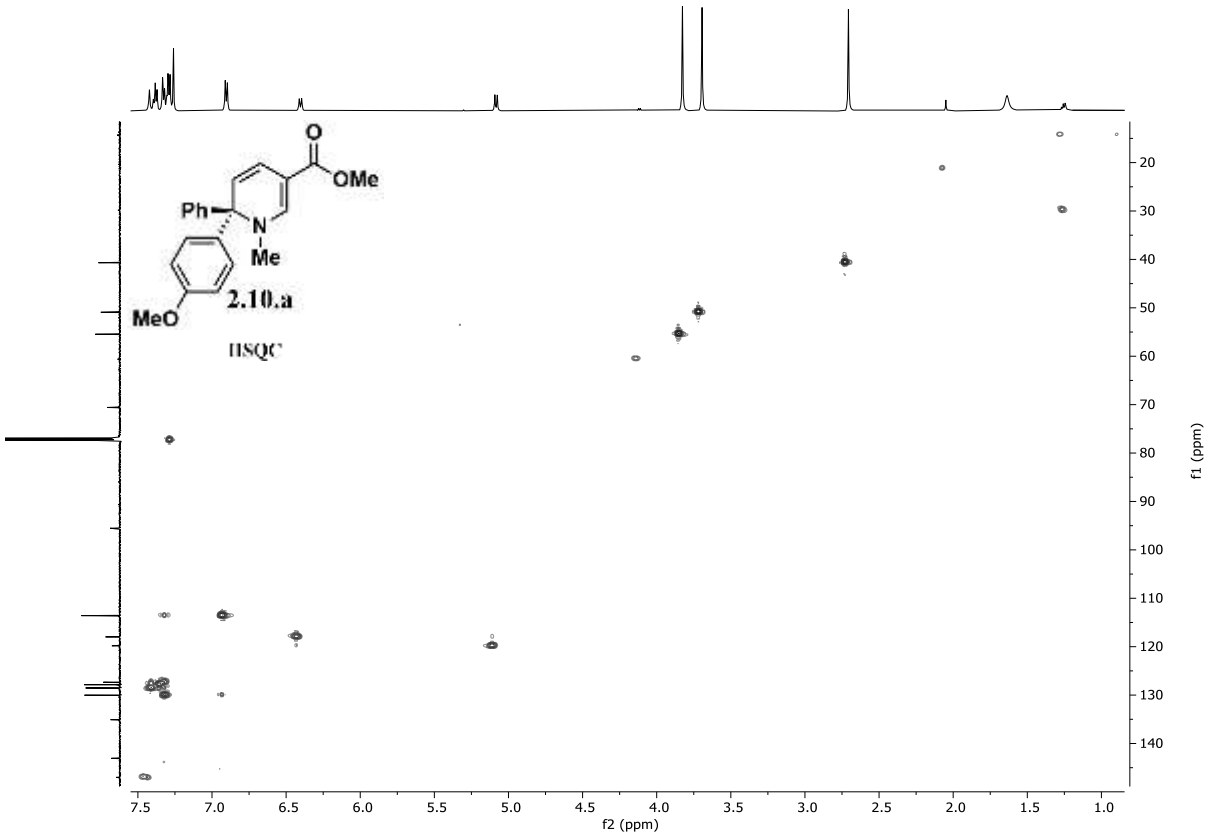
^{1}H NMR (600 MHz, $CDCl_3$)

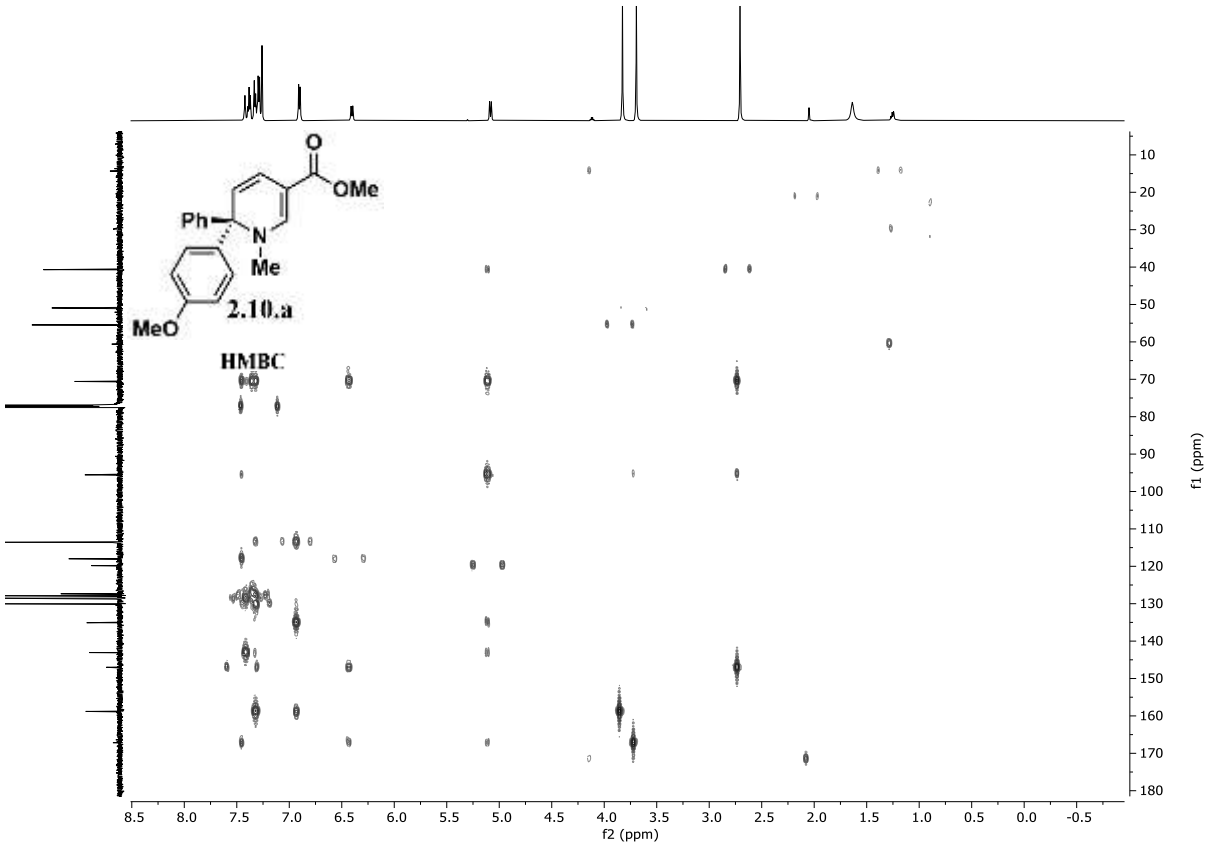

167.24
148.86
146.12
128.58
127.63
126.78
119.88
118.37
94.47
67.34
50.74
37.99
29.21
8.41
Me
O
OMe
N
Me
2.S.16
13C NMR (151 MHz, CDCl3)
f1 (ppm)

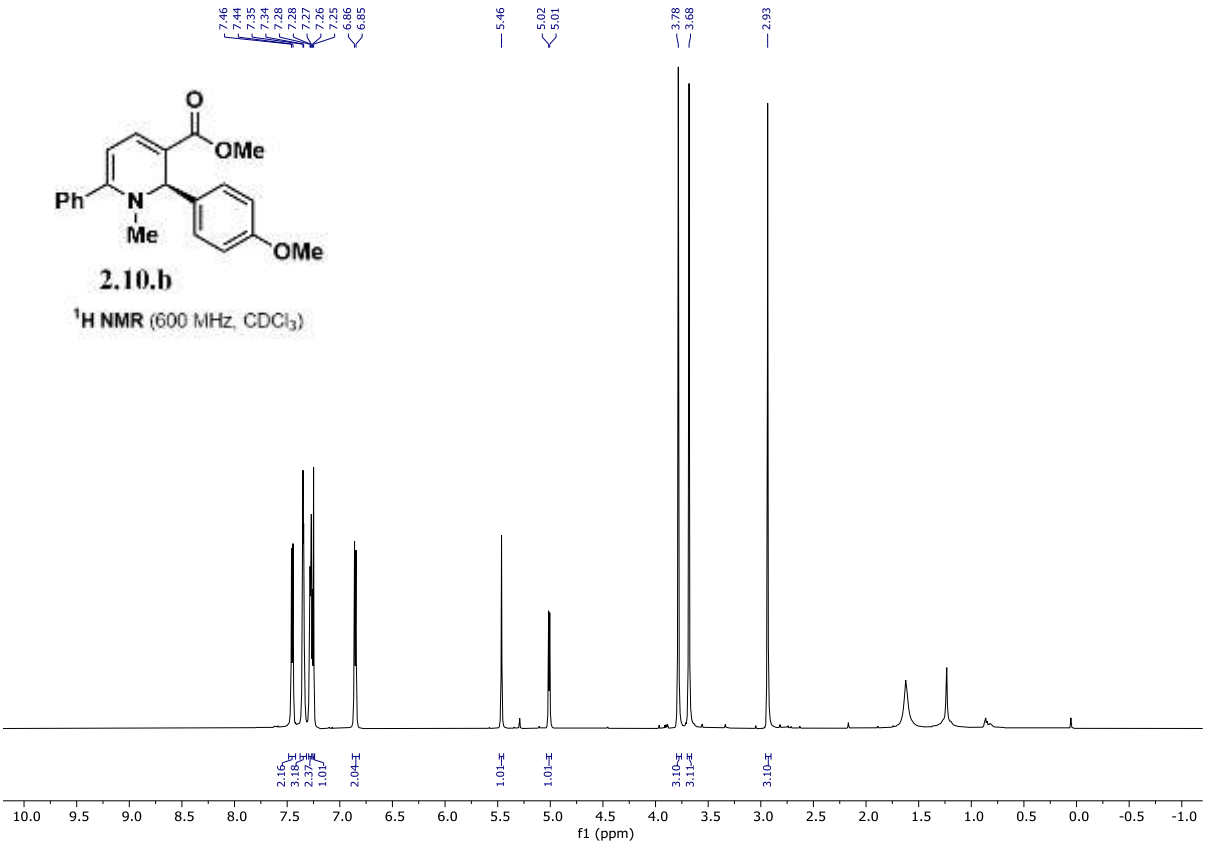

7.42
7.41
7.38
7.37
7.34
7.34
7.33
7.32
7.31
7.30
7.29
7.28
7.28
6.91
6.91
6.90
6.89
6.42
6.42
6.42
6.40
6.40
6.40
5.10
5.08
3.83
3.82
3.70
3.70
2.71
2.71
O
OMe
Ph
N
Me
MeO
2.10.a
1H NMR (600 MHz, CDCl3)
8.83
2.04
0.99
1.02
3.07
3.02
3.02
f1 (ppm)

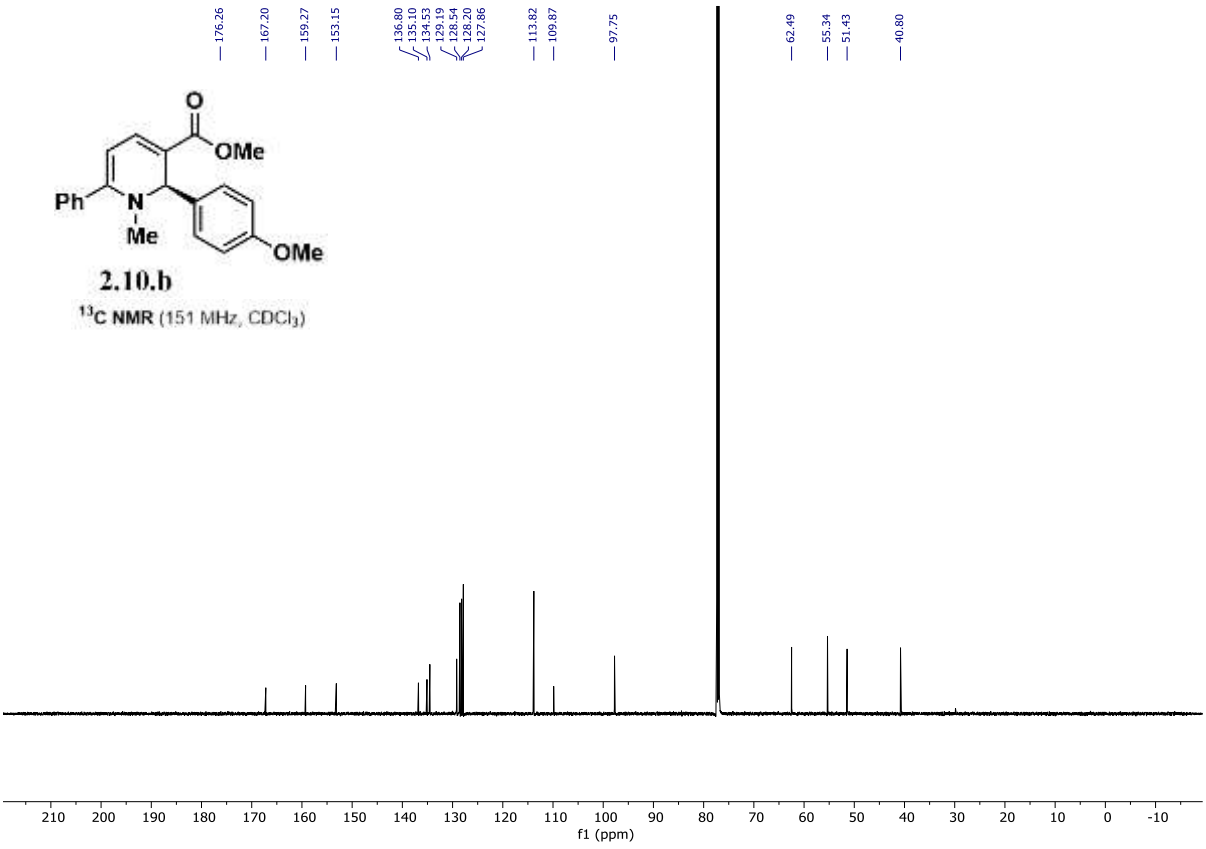

166.97
158.81
146.81
143.06
135.09
129.90
128.40
128.35
127.81
127.22
119.77
117.97
113.56
95.69
70.54
55.34
50.71
40.51
O
OMe
Ph
N
Me
MeO
2.10.a
13C NMR (151 MHz, CDCl3)
f1 (ppm)

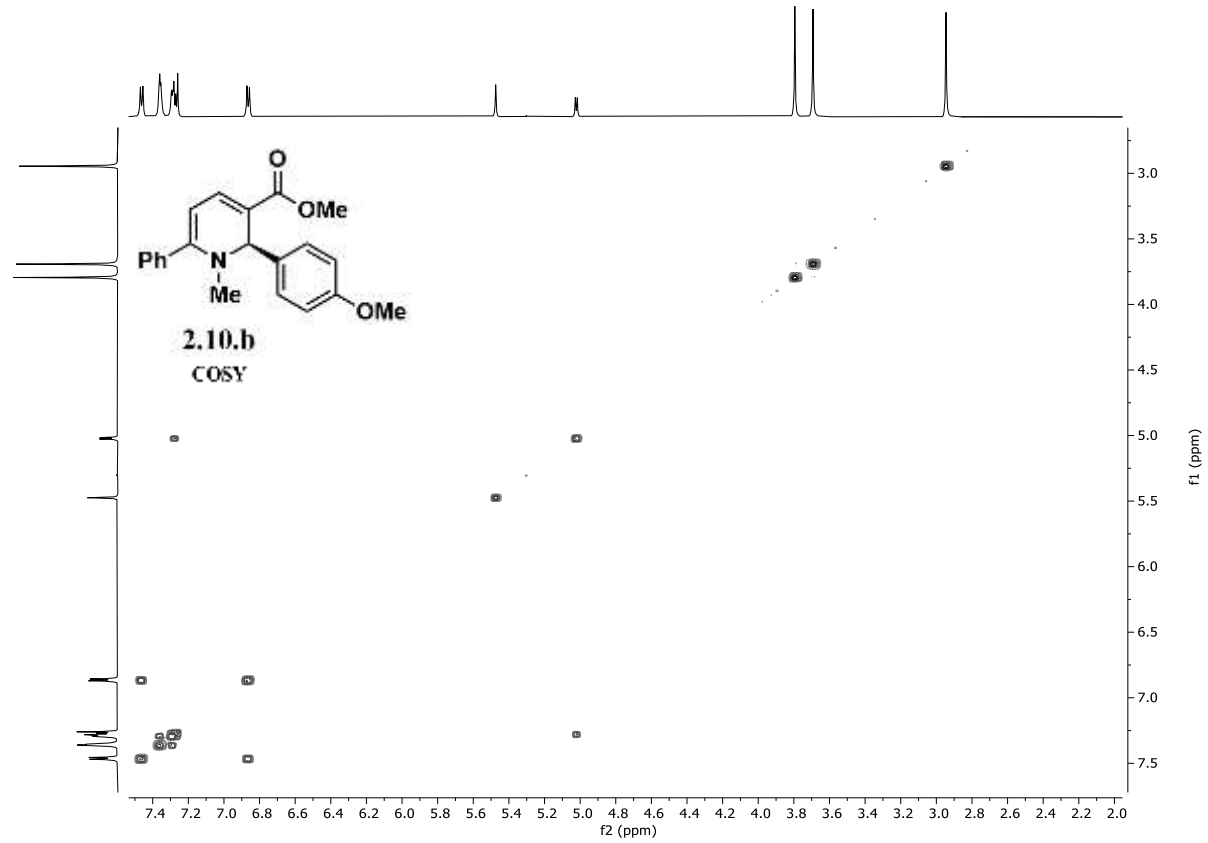

O
OMe
Ph
N
Me
MeO
2.10.a
COSY
f2 (ppm)
f1 (ppm)

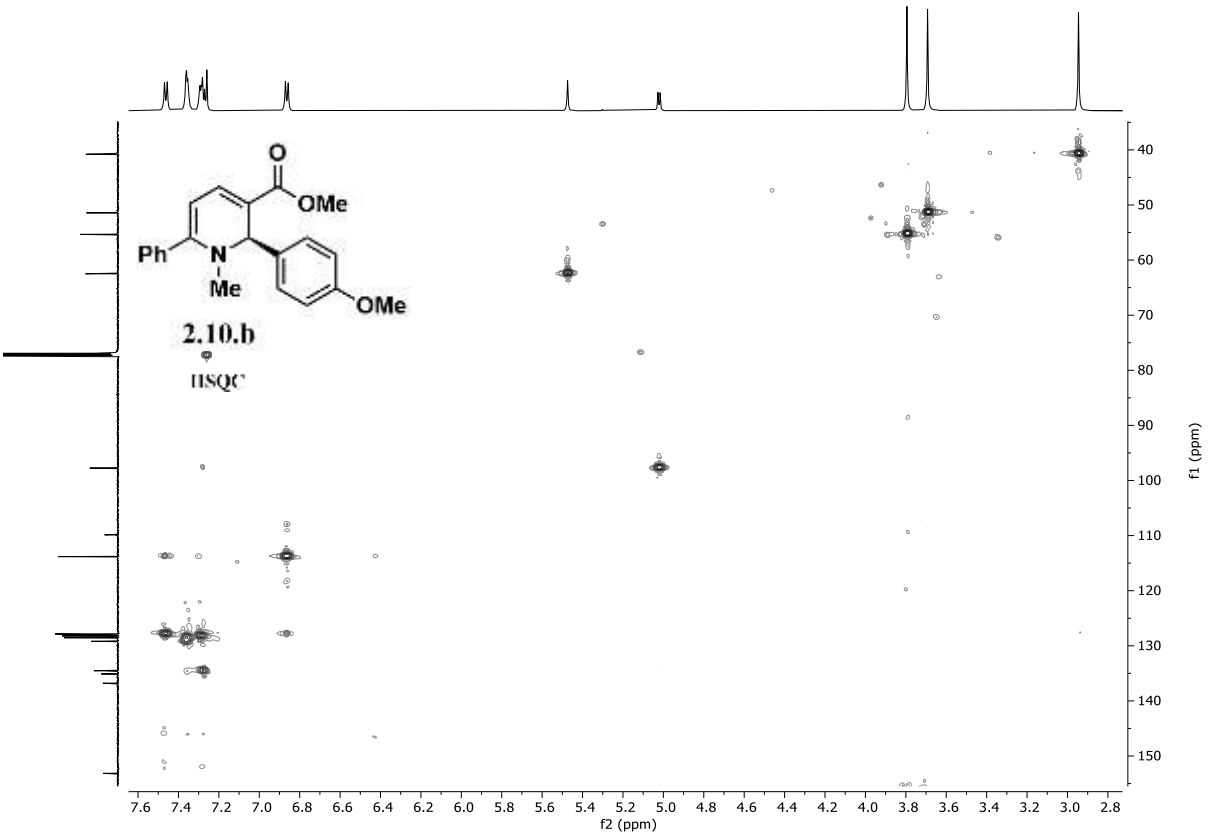

O
OMe
Ph
N
Me
2.10.a
MeO
HSQC
f2 (ppm)
f1 (ppm)

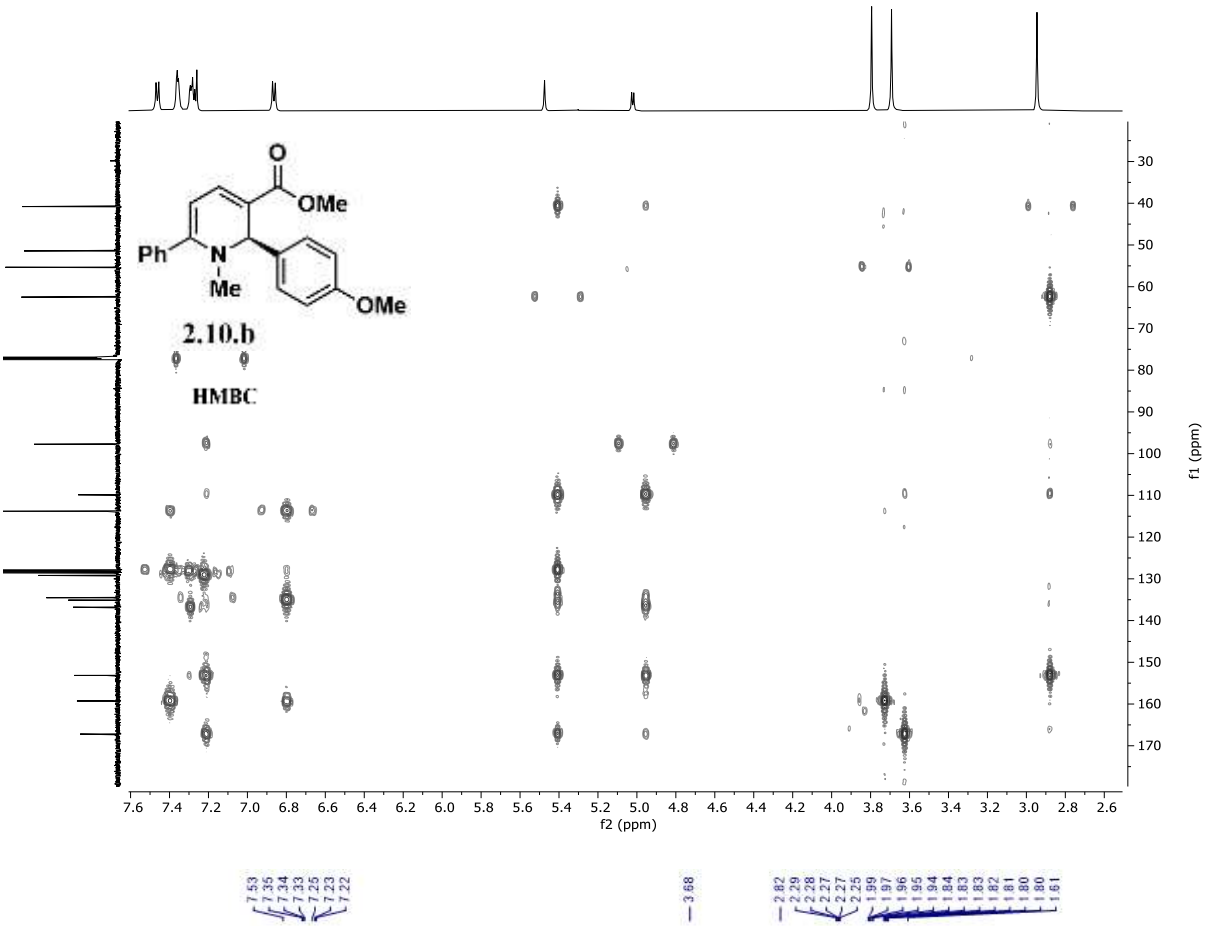

O
OMe
Ph
N
Me
2.10.a
MeO
HMBC
f2 (ppm)
f1 (ppm)

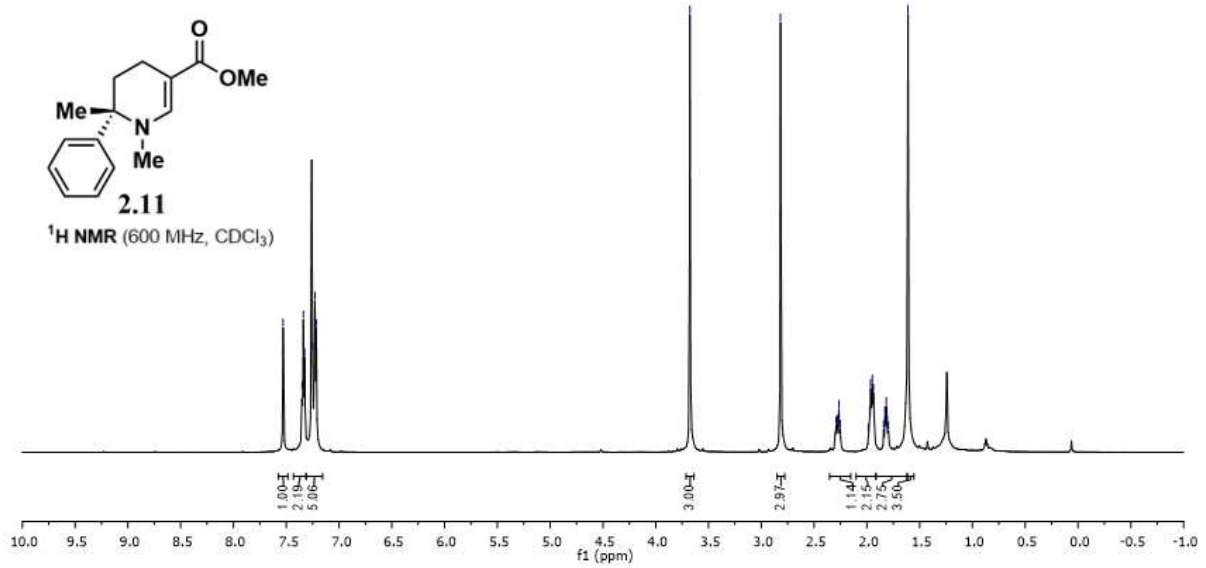

7.46
7.44
7.35
7.34
7.28
7.28
7.27
7.26
7.25
6.86
6.85
5.46
5.02
5.01
3.78
3.68
2.93
O
OMe
Ph
N
Me
OMe
2.10.b
1H NMR (600 MHz, CDCl3)
2.16
3.18
2.37
1.01
2.04
1.01
1.01
3.10
3.11
3.10
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

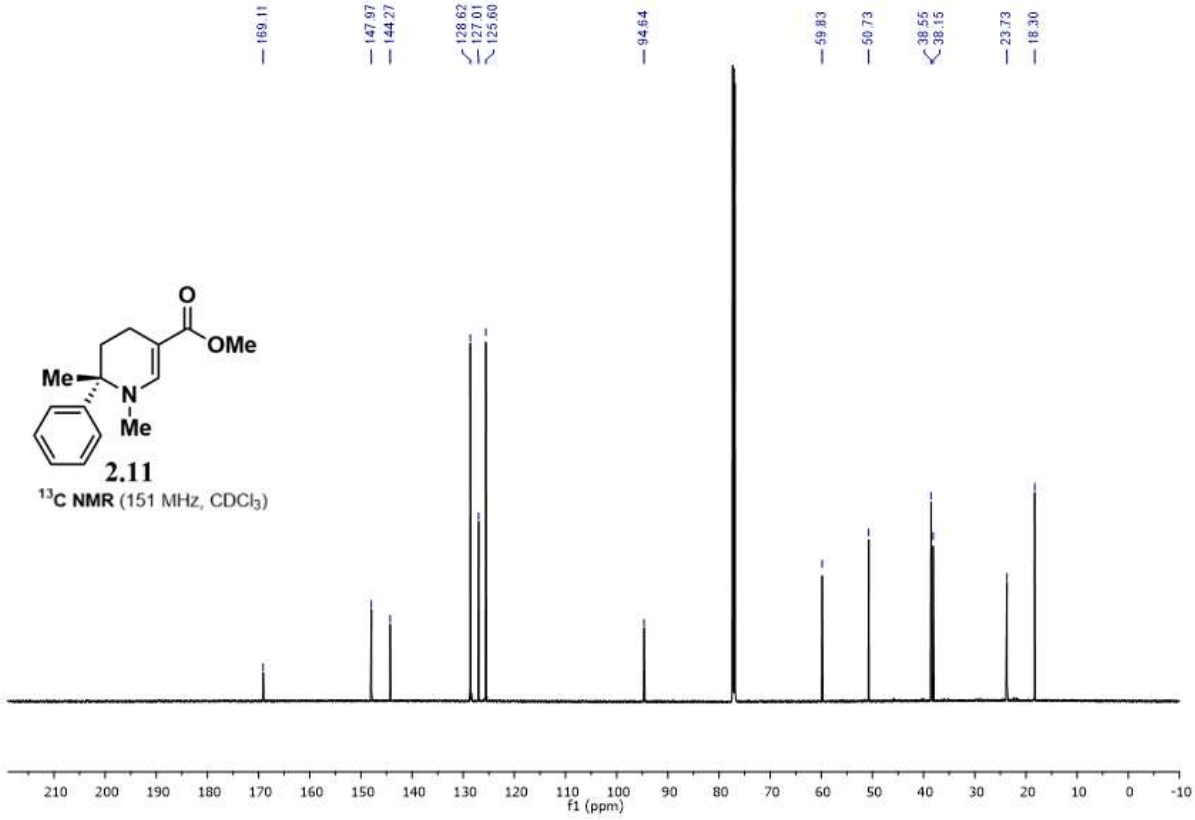

176.26
167.20
159.27
153.15
136.80
135.10
134.53
129.19
128.54
128.20
127.86
113.82
109.87
97.75
62.49
55.34
51.43
40.80
O
OMe
Ph
N
Me
OMe
2.10.b
13C NMR (151 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

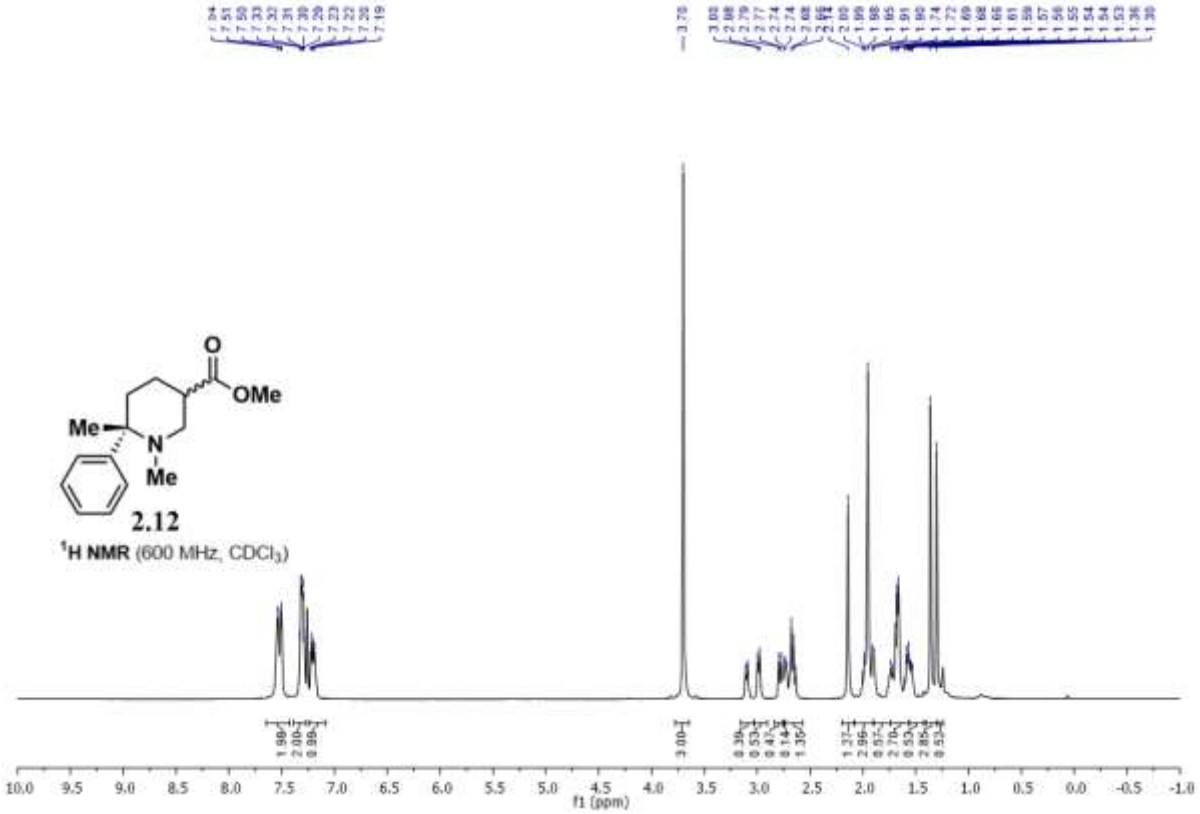

O
OMe
Ph
N
Me
OMe
2.10.b
COSY
f2 (ppm)
f1 (ppm)

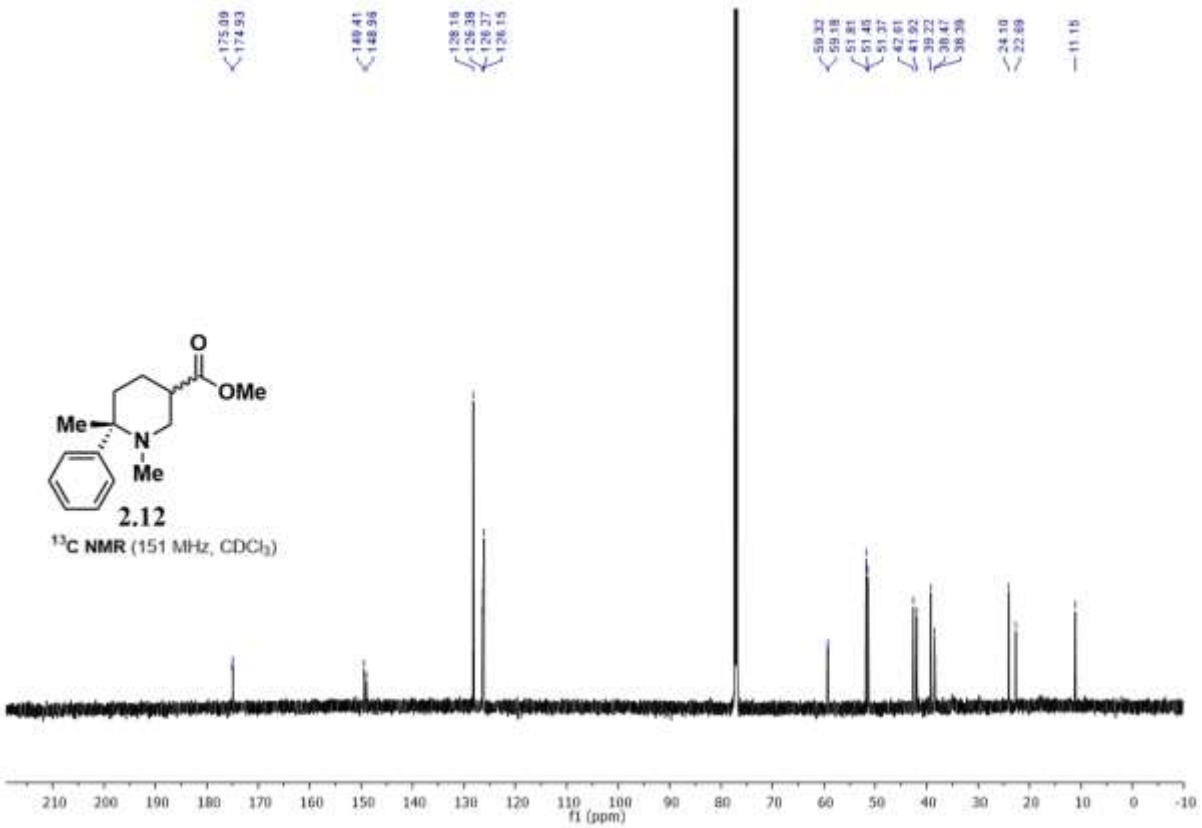

O
OMe
Ph
N
Me
OMe
2.10.b
HSQC
f2 (ppm)
f1 (ppm)

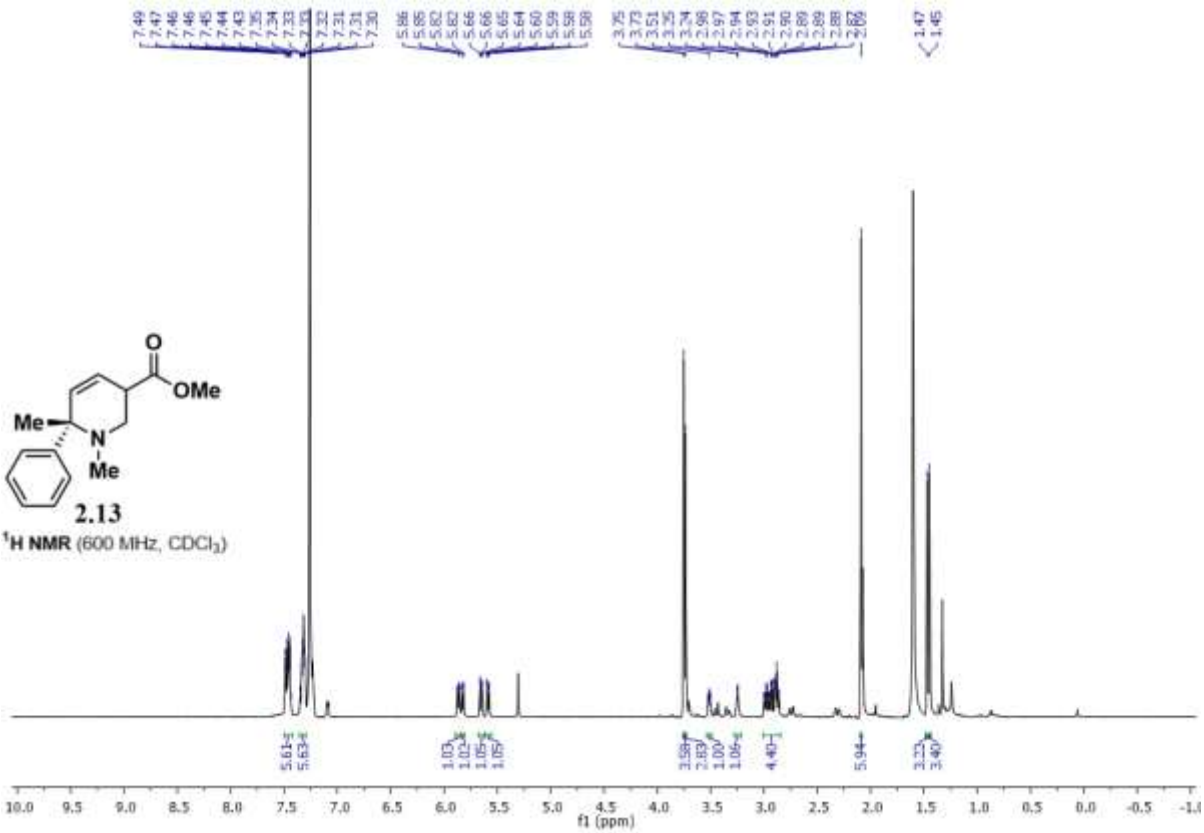

O
OMe
Ph
N
Me
OMe
2.10.b
HMBC
f2 (ppm)
f1 (ppm)
7.53
7.35
7.34
7.33
7.25
7.23
7.22
3.68
2.82
2.29
2.28
2.27
2.27
2.25
1.99
1.97
1.96
1.95
1.94
1.84
1.83
1.83
1.82
1.81
1.80
1.80
1.61

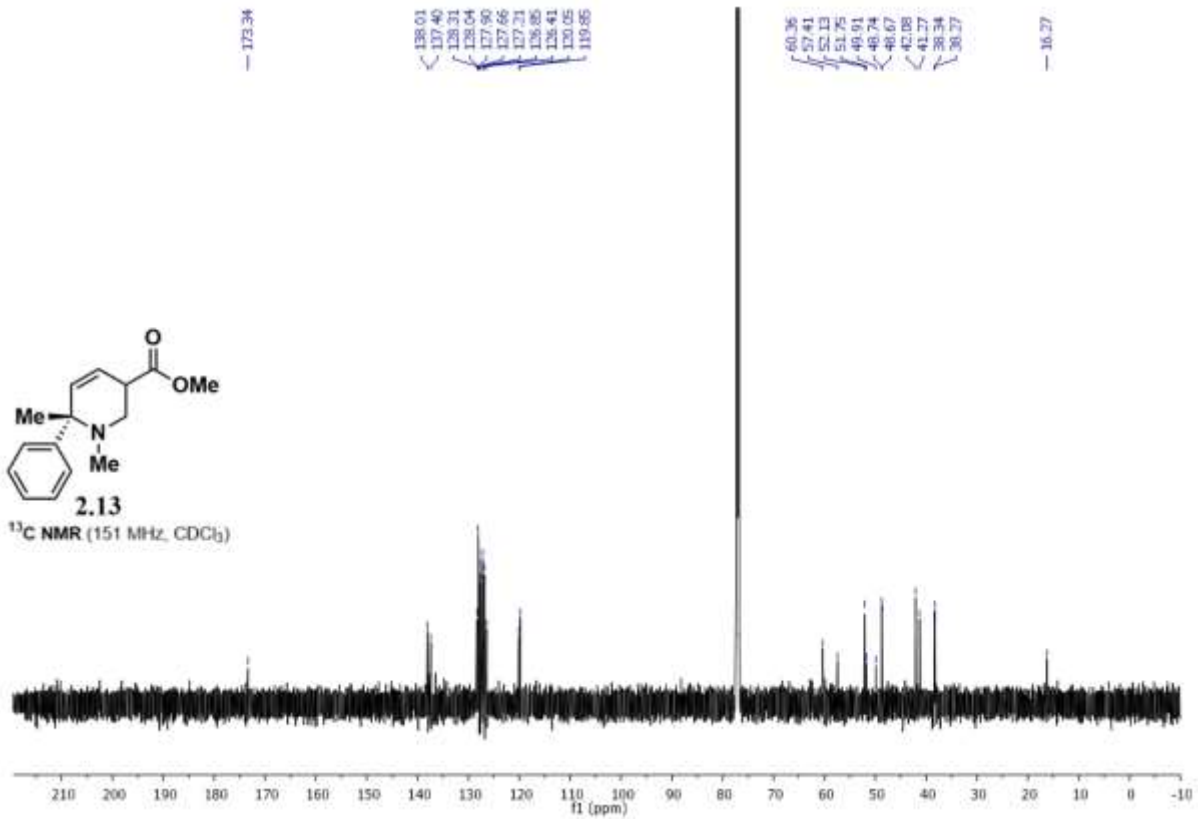

O
OMe
Me
N
Me
2.11
1H NMR (600 MHz, CDCl3)
1.00
2.19
5.06
3.00
2.97
1.14
2.15
2.75
3.50
f1 (ppm)

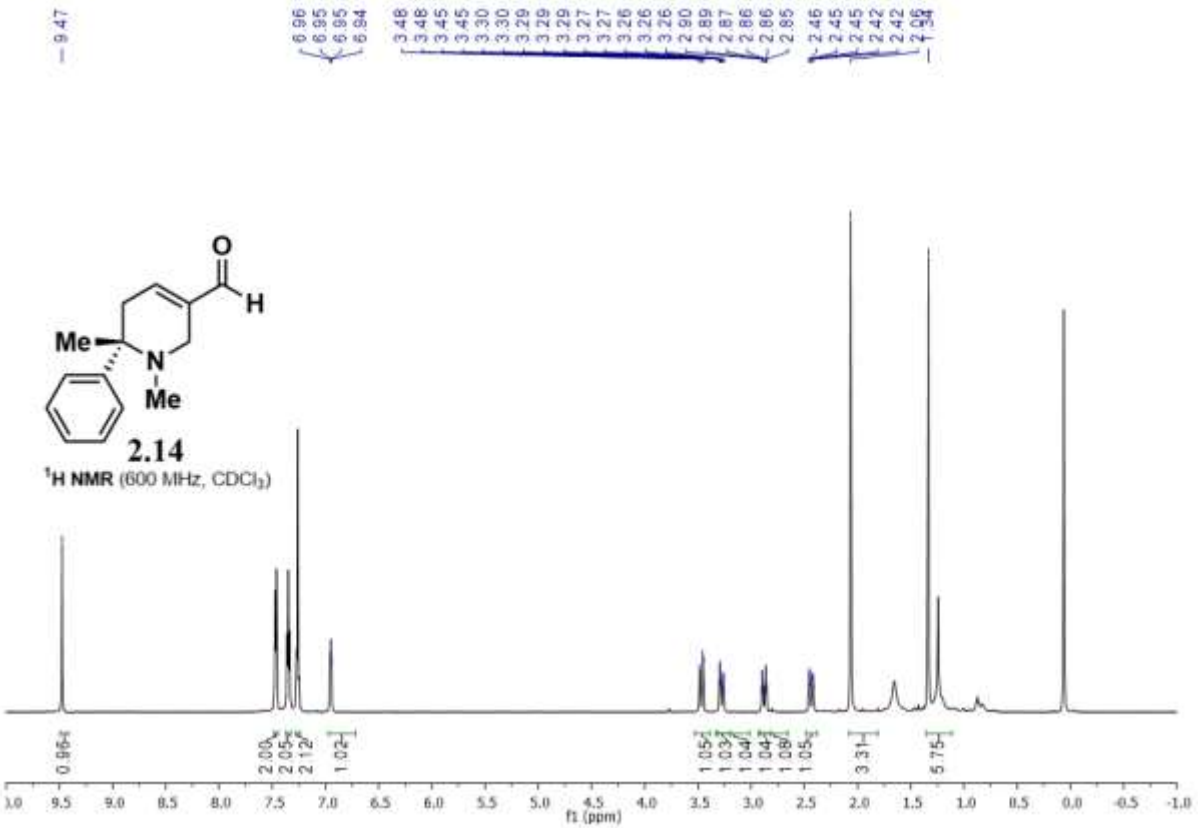

169.11
147.97
144.27
128.62
127.01
125.60
94.64
59.83
50.73
38.55
38.15
23.73
18.30
O
OMe
Me
N
Me
2.11
13C NMR (151 MHz, CDCl3)
f1 (ppm)

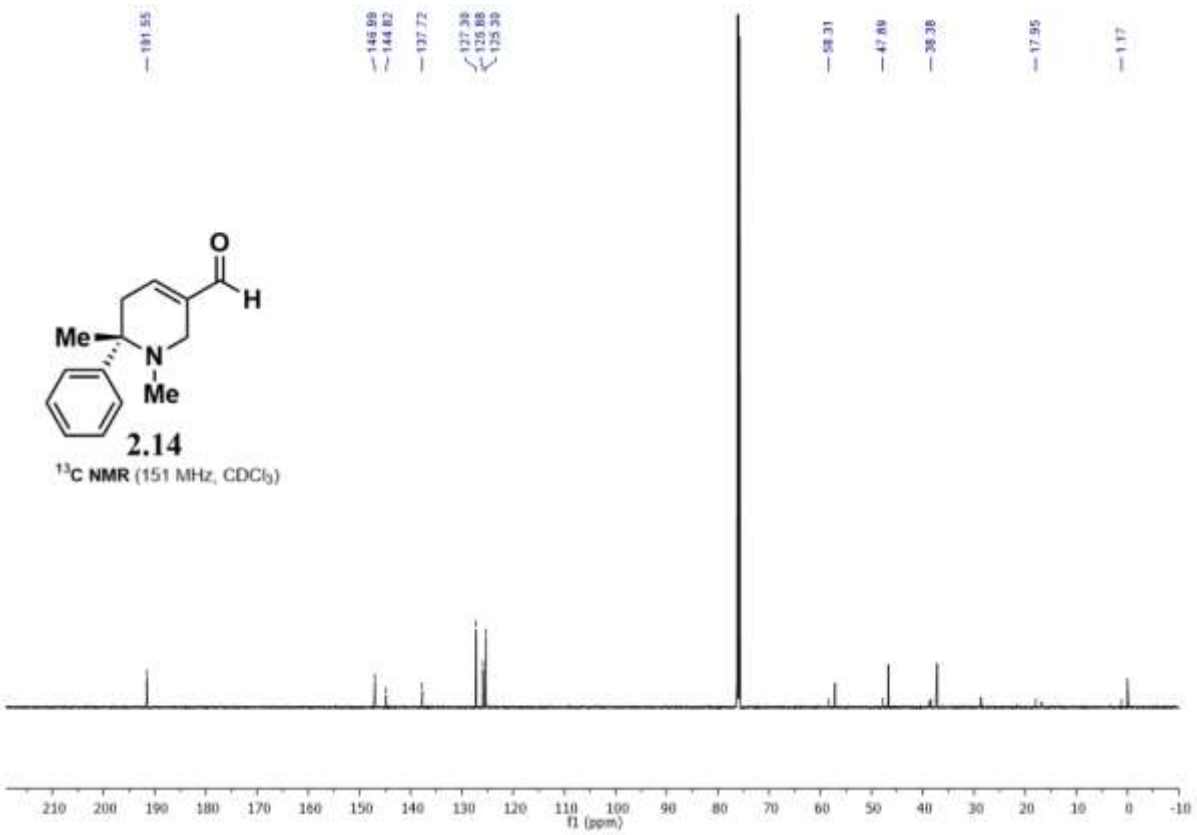

3.70
O
OMe
Me
N
Me
2.12
1H NMR (600 MHz, CDCl3)
f1 (ppm)


2.12
13C NMR (151 MHz, CDCl3)
f1 (ppm)

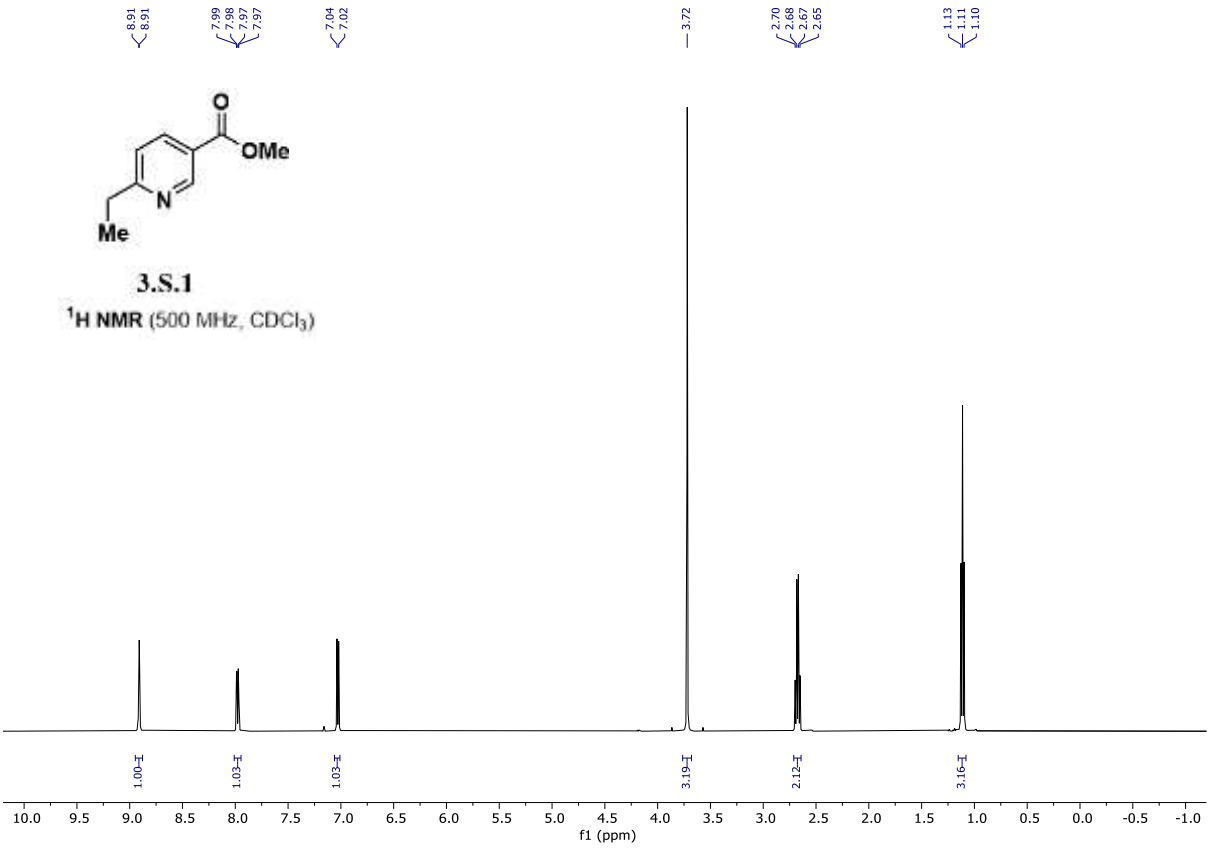

2.13
1H NMR (600 MHz, CDCl3)
f1 (ppm)


O
OMe
Me
N
Me
2.13
13C NMR (151 MHz, CDCl3)
f1 (ppm)


O
H
Me
N
Me
2.14
1H NMR (600 MHz, CDCl3)
f1 (ppm)

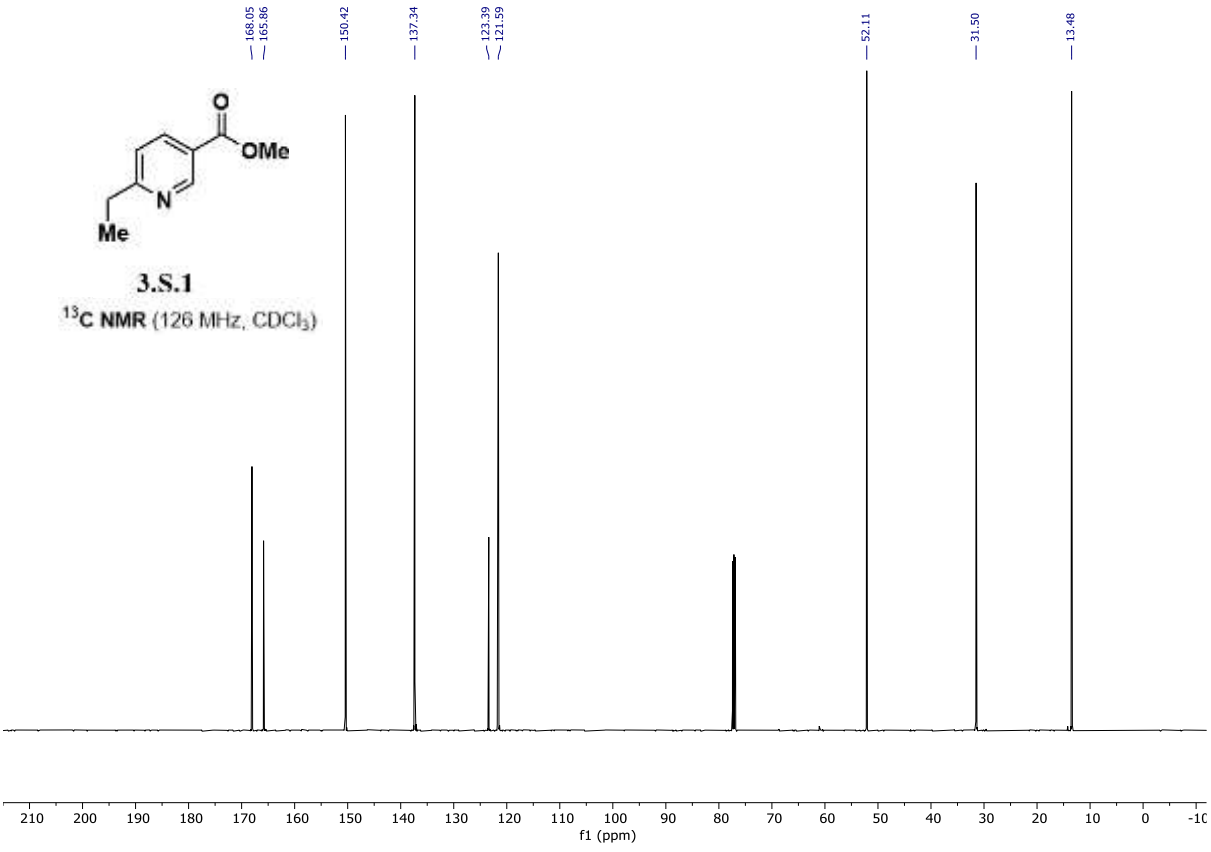

191.55
148.99
144.82
137.72
127.30
126.88
125.59
58.31
47.89
38.38
17.95
1.17
O
H
Me
N
Me
2.14
13C NMR (151 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Appendix B: NMR Spectra for Chapter 3



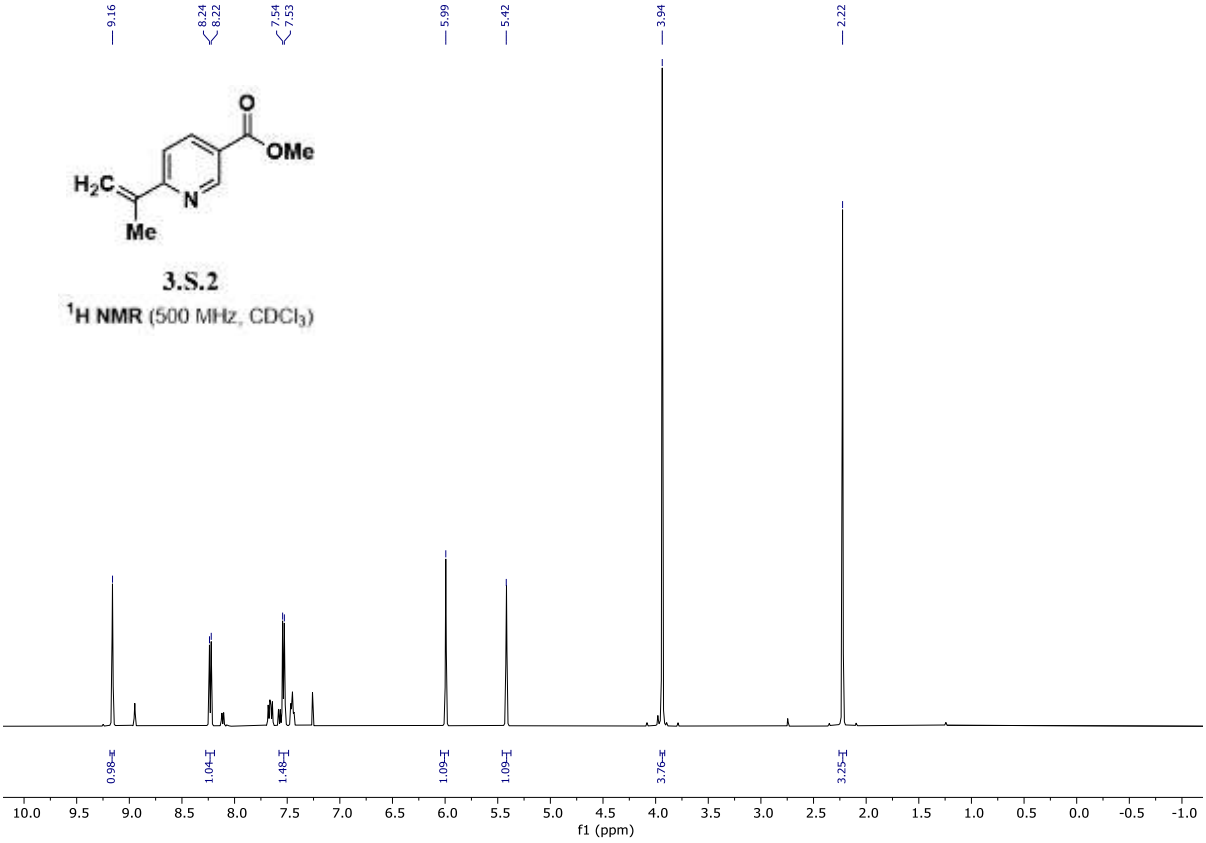
3.S.1

^{1}H NMR (500 MHz, $CDCl_3$)



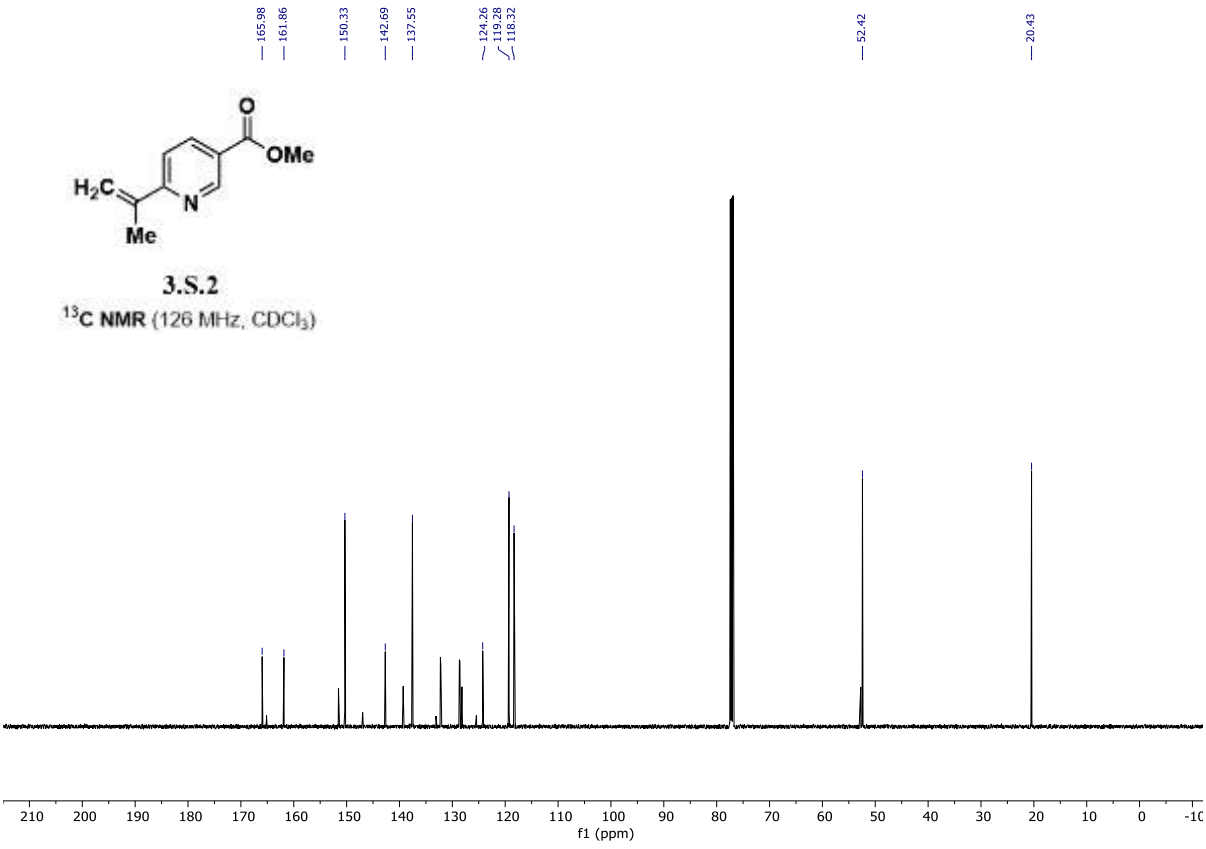
3.S.1

^{13}C NMR (126 MHz, $CDCl_3$)



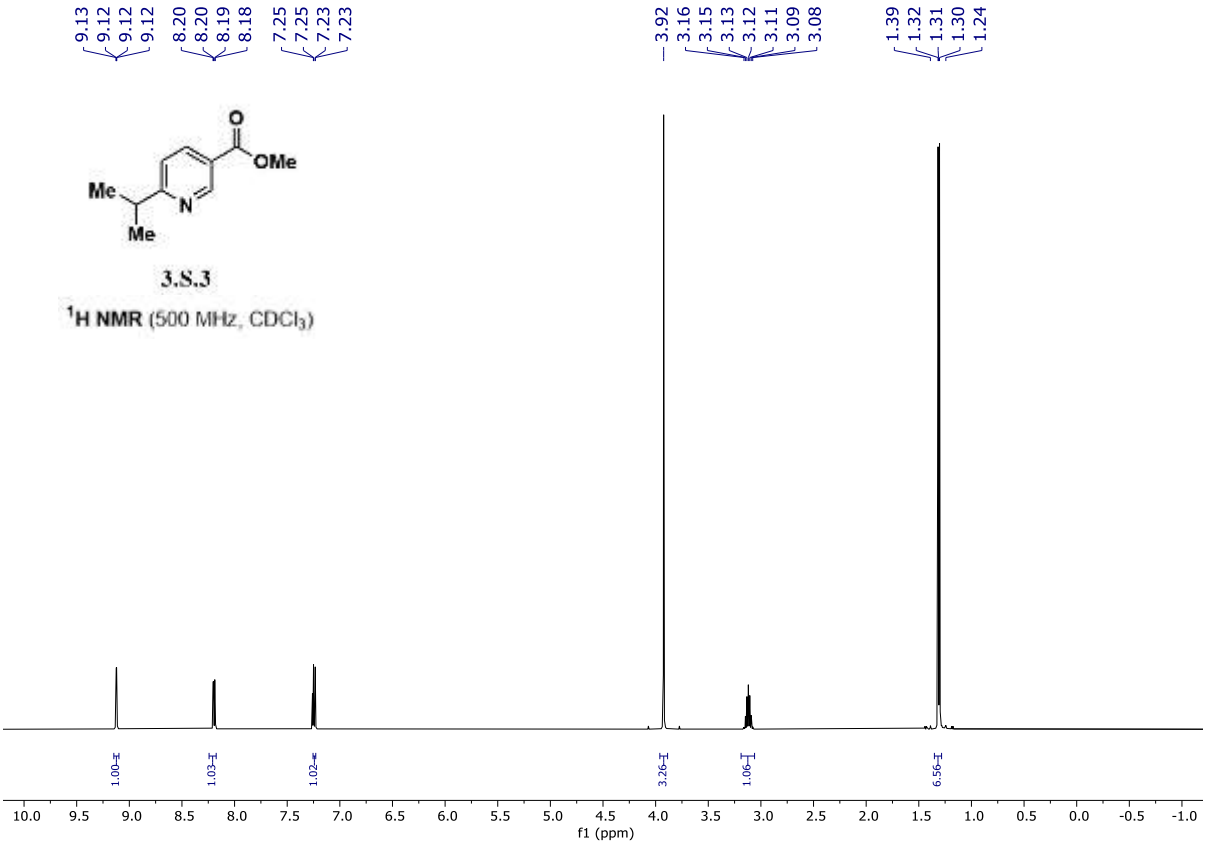
3.S.2

^{1}H NMR (500 MHz, $CDCl_3$)



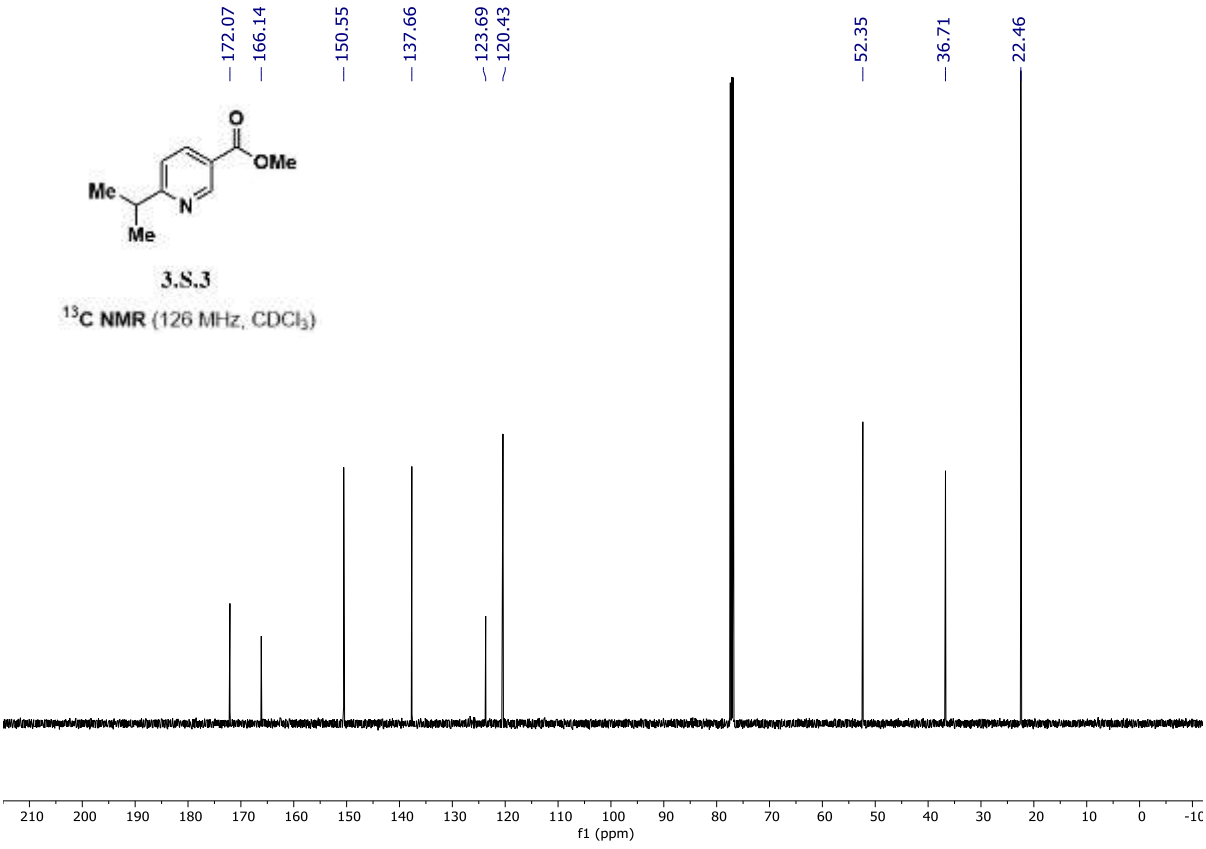
3.S.2

^{13}C NMR (126 MHz, $CDCl_3$)



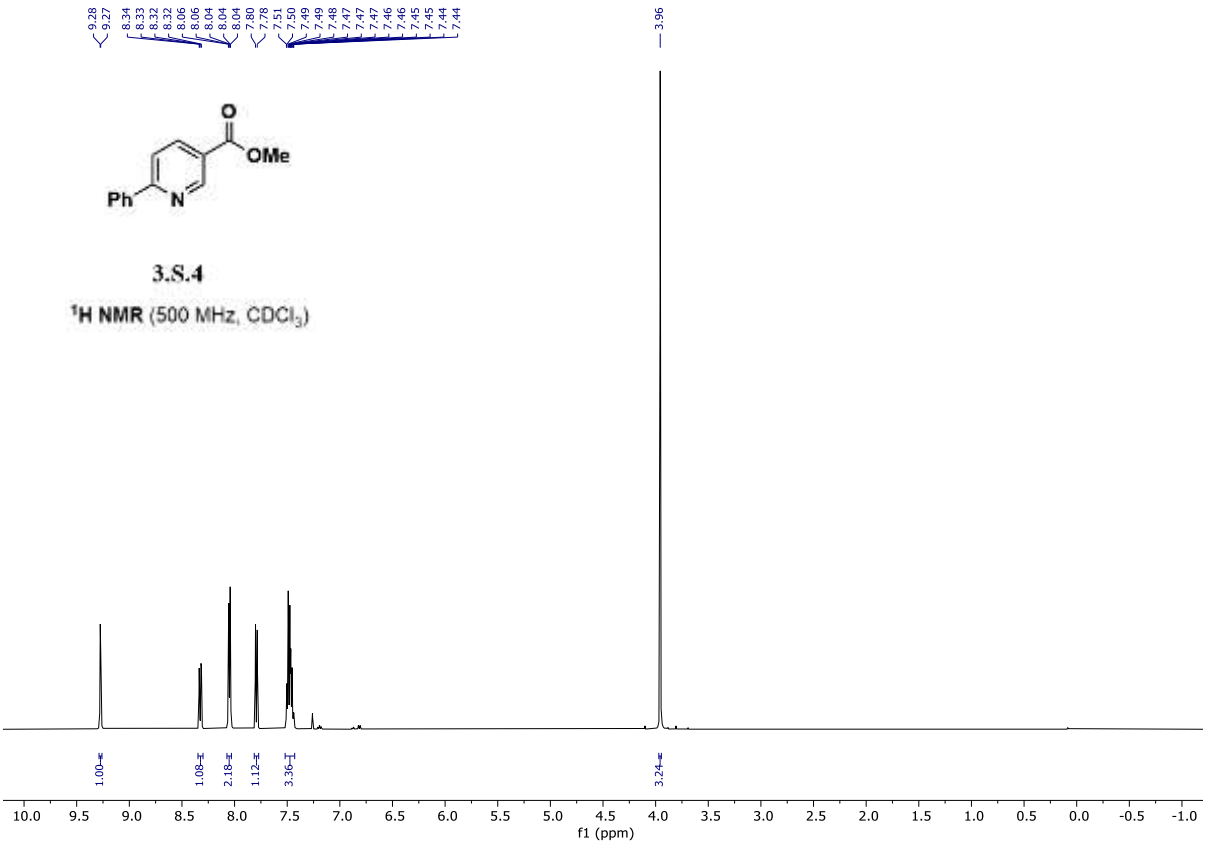
3.S.3

^{1}H NMR (500 MHz, $CDCl_3$)



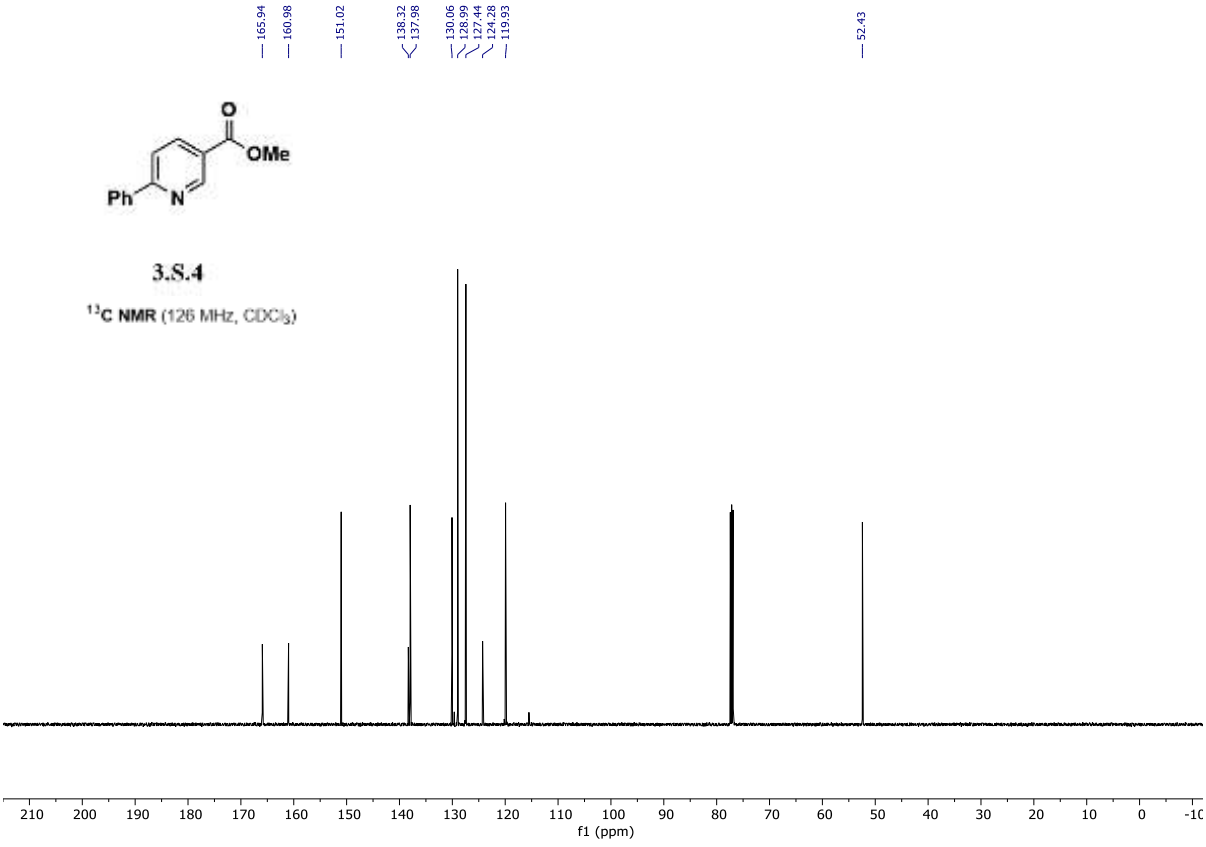
3.S.3

^{13}C NMR (126 MHz, $CDCl_3$)



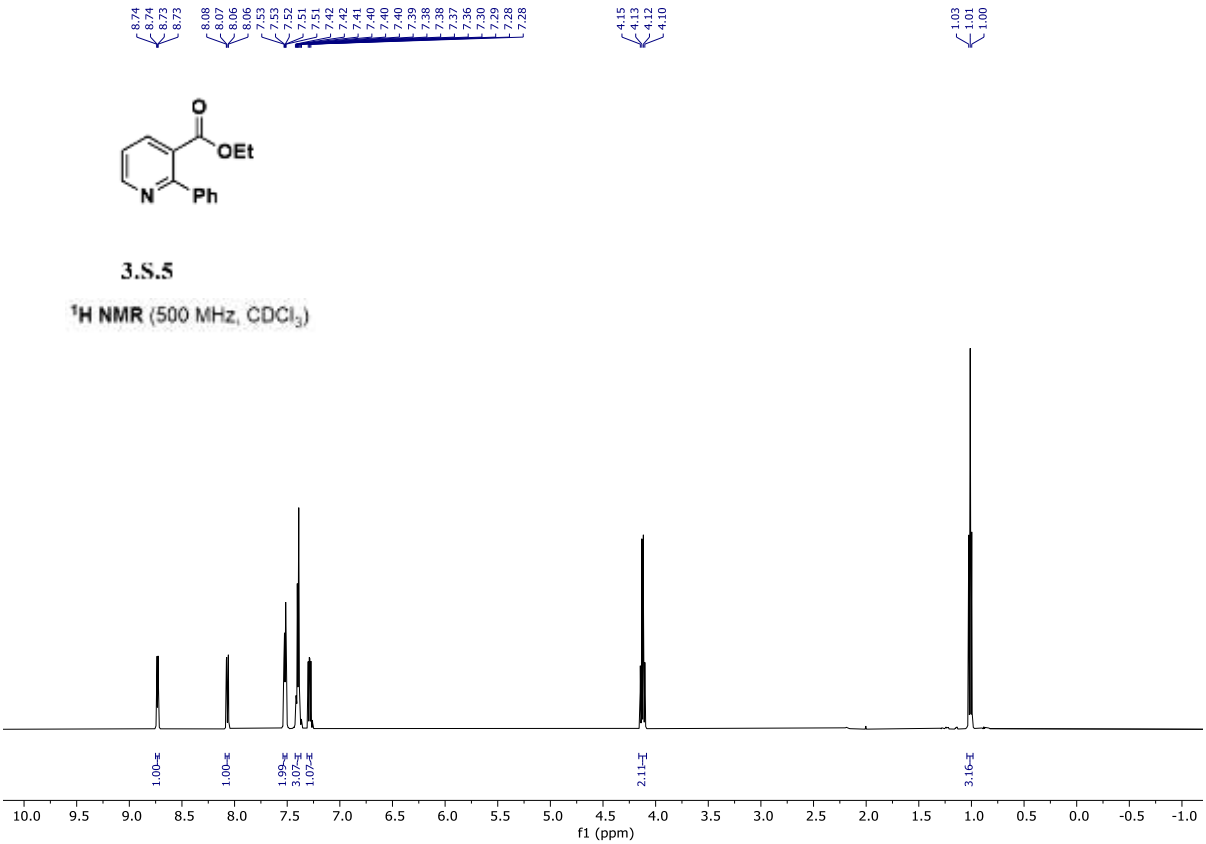
3.S.4

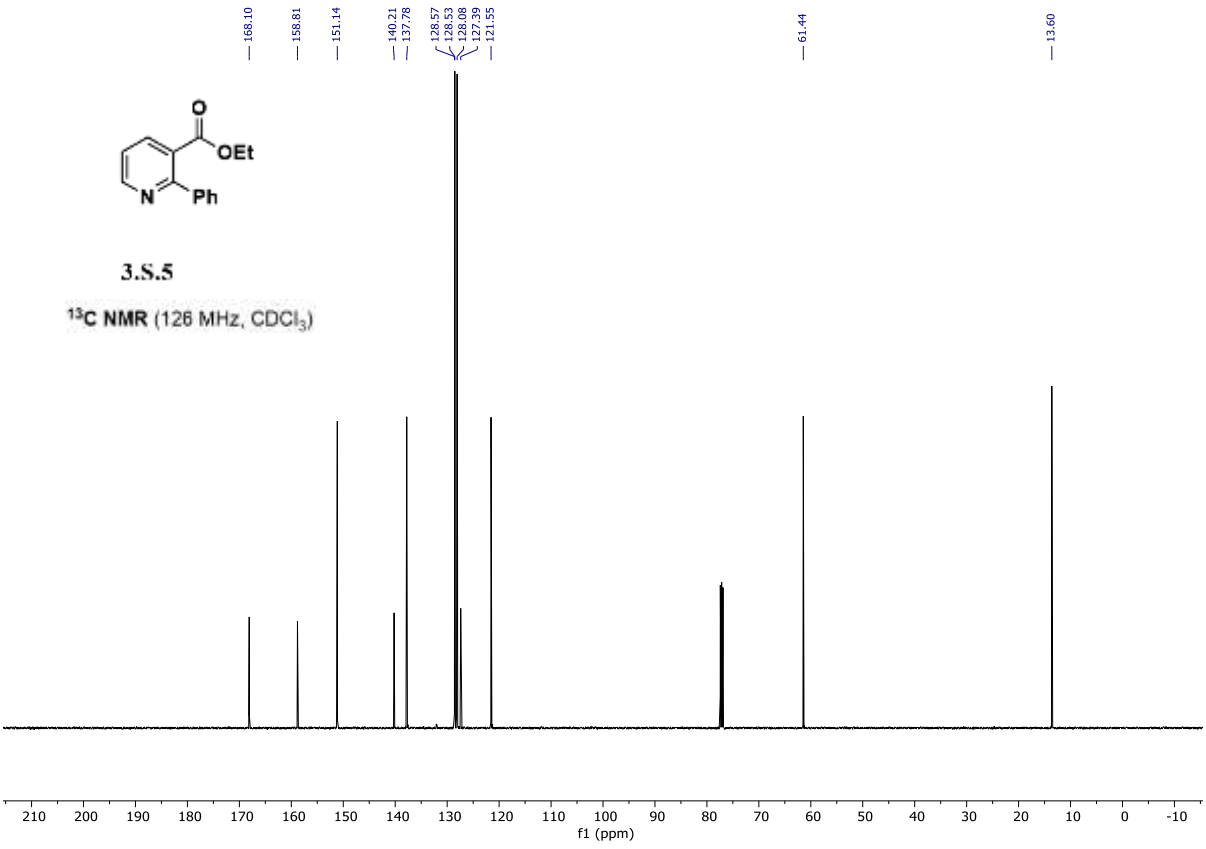
^{1}H NMR (500 MHz, $CDCl_3$)

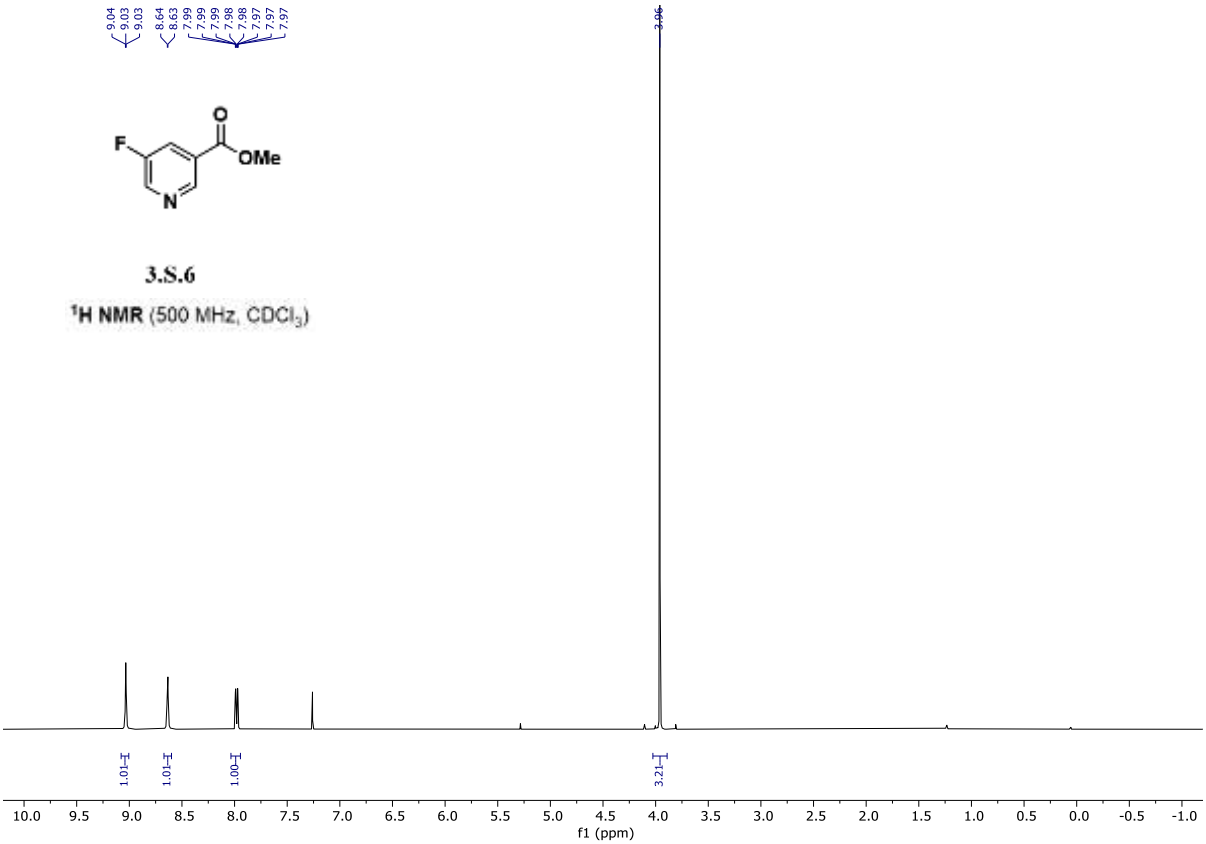


3.S.4

^{13}C NMR (126 MHz, $CDCl_3$)

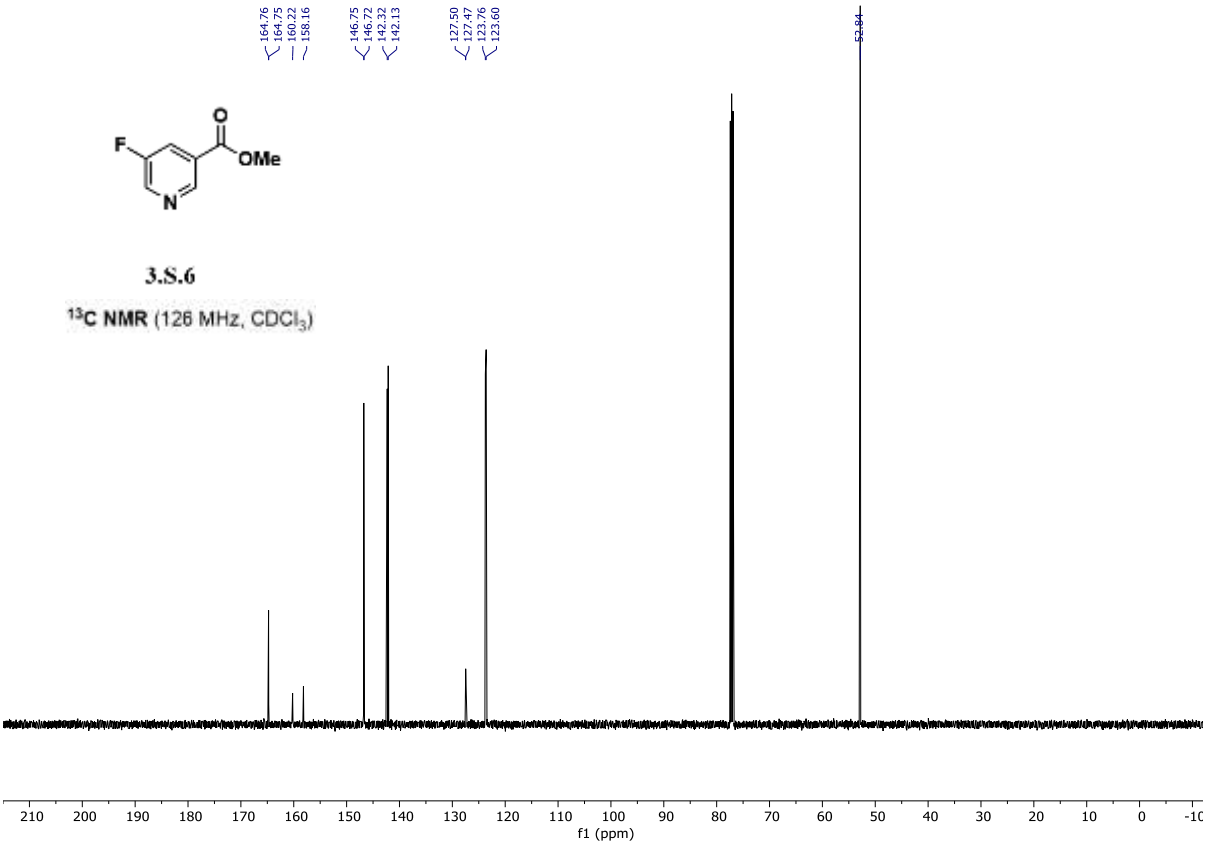

8.74
8.74
8.73
8.73
8.08
8.07
8.06
8.06
7.53
7.53
7.52
7.51
7.51
7.42
7.42
7.41
7.40
7.40
7.39
7.38
7.38
7.37
7.36
7.30
7.29
7.28
7.28
4.15
4.13
4.12
4.10
1.03
1.01
1.00
O
OEt
N
Ph
3.S.5
1H NMR (500 MHz, CDCl3)
1.00
1.00
1.99
3.07
1.07
2.11
3.16
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


168.10
158.81
151.14
140.21
137.78
128.57
128.53
128.08
127.39
121.55
61.44
13.60
O
OEt
N
Ph
3.S.5
13C NMR (126 MHz, CDCl3)
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)



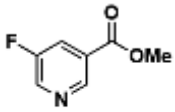
3.S.6

^{1}H NMR (500 MHz, $CDCl_3$)



3.S.6

^{13}C NMR (126 MHz, $CDCl_3$)

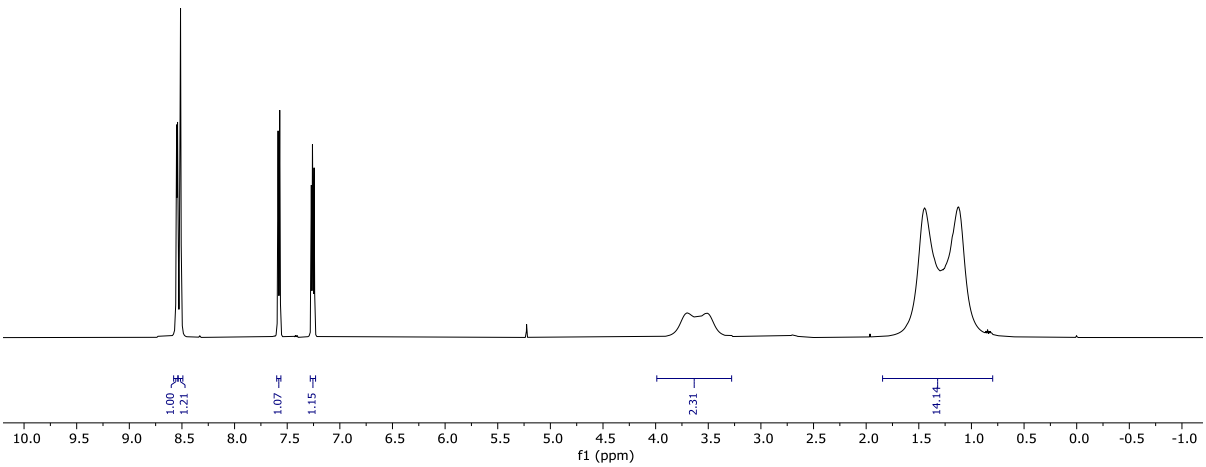


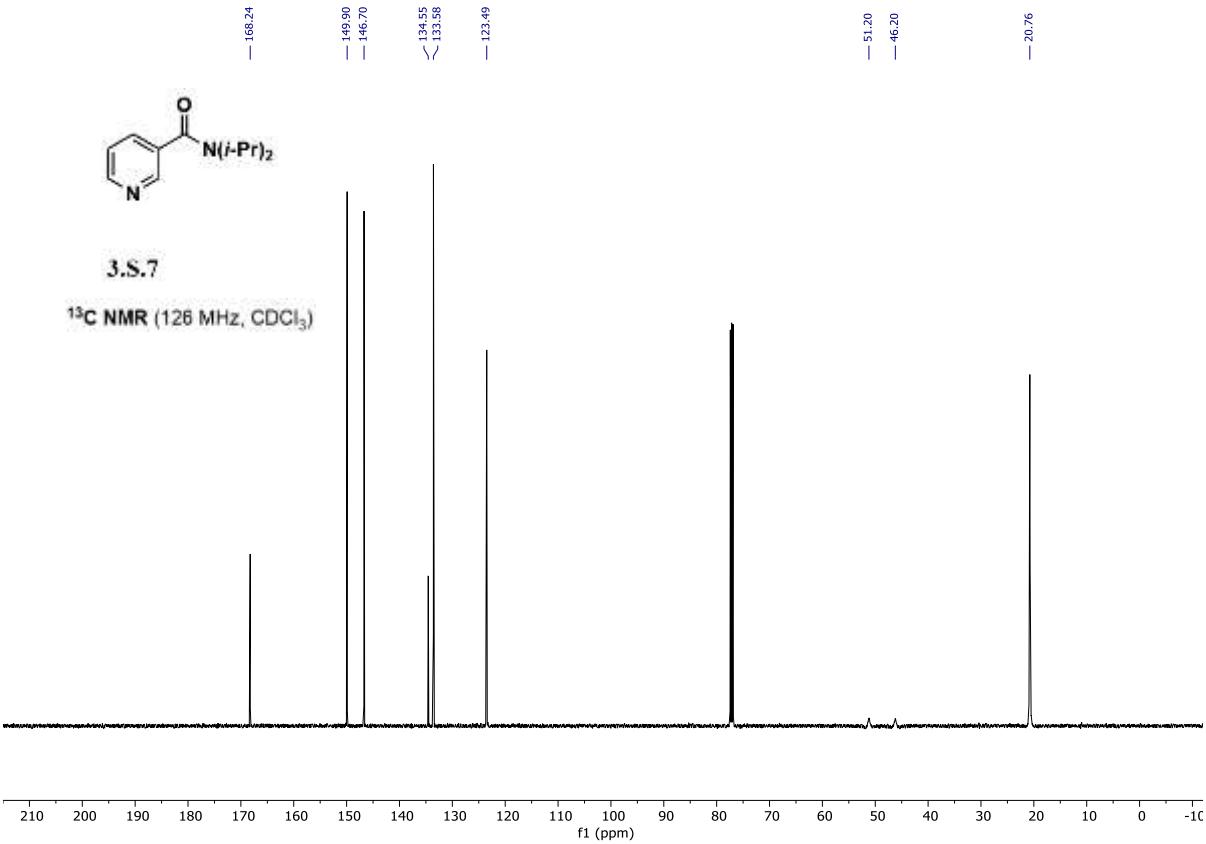
3.S.6

^{19}F NMR (471 MHz, D_2O)

3.S.7

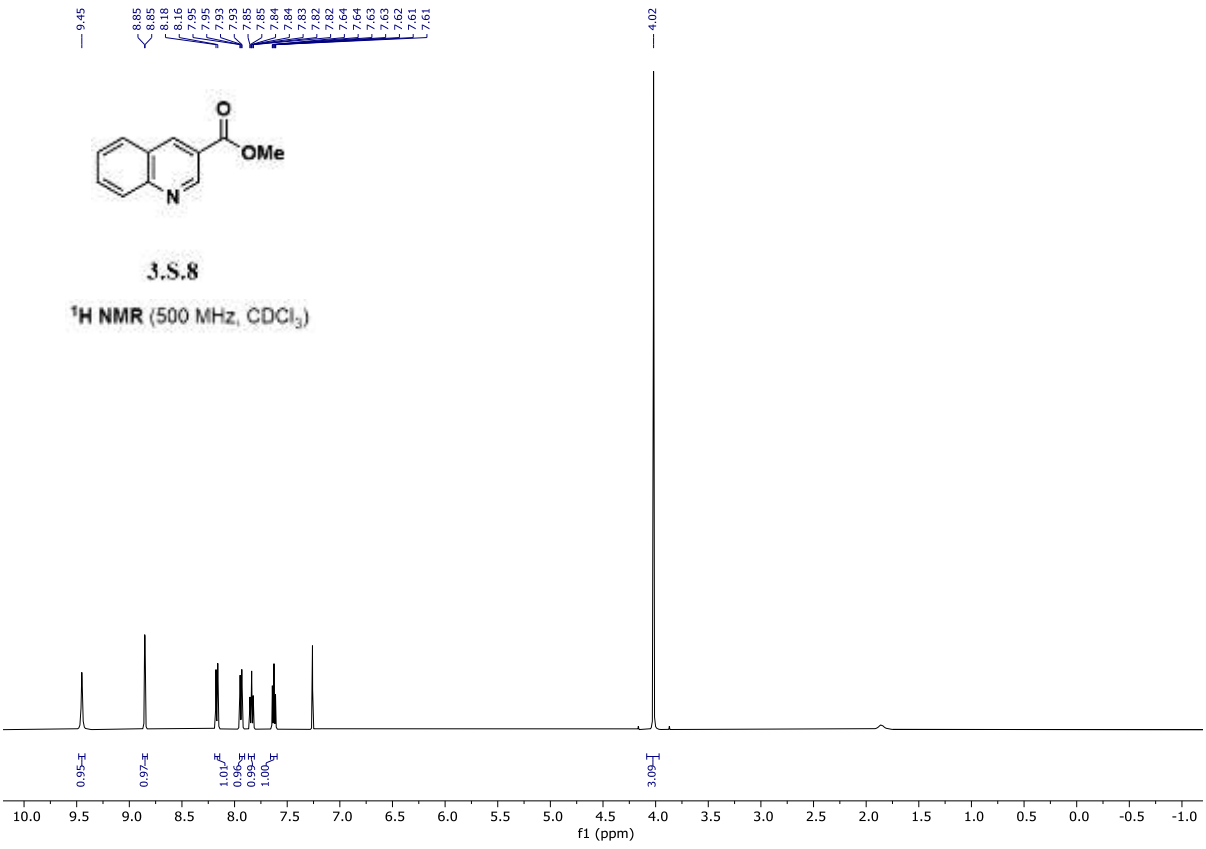
^{1}H NMR (500 MHz, $CDCl_3$)





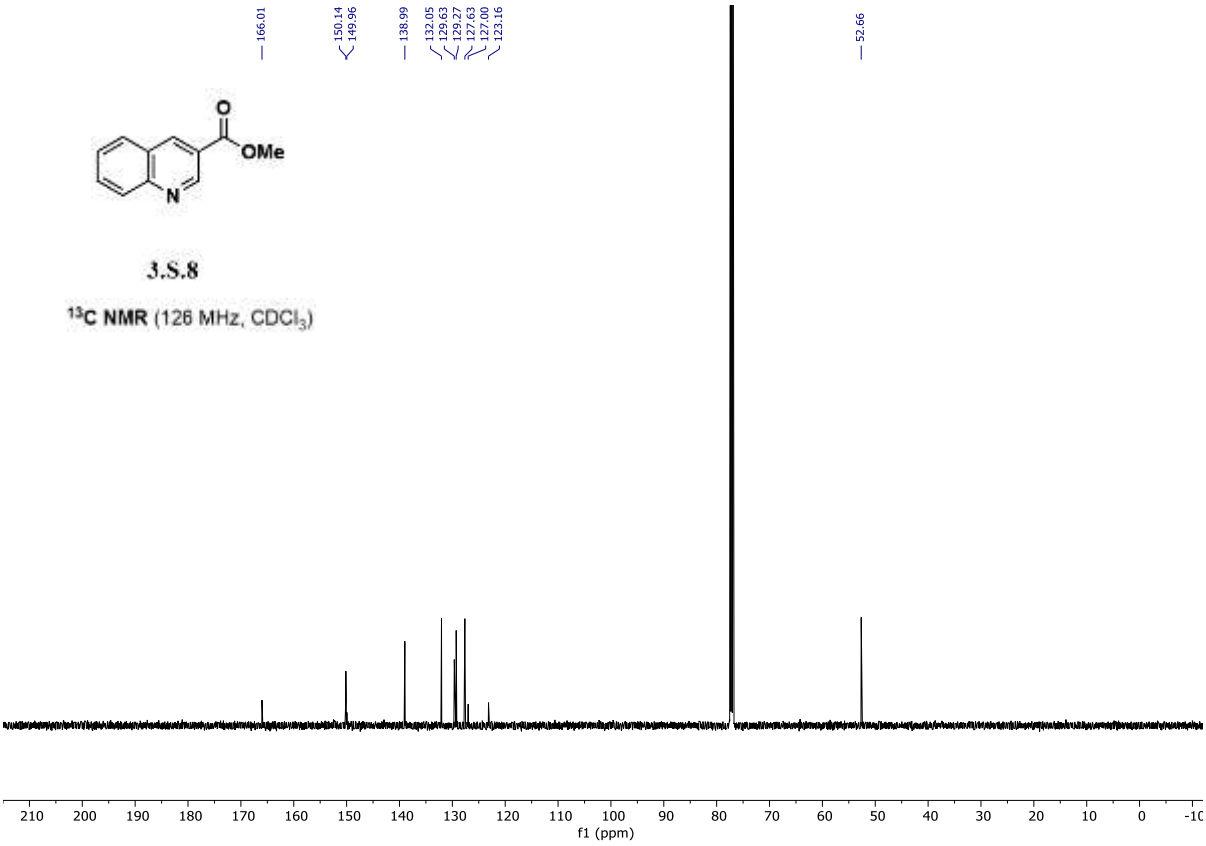
3.S.7

^{13}C NMR (126 MHz, $CDCl_3$)



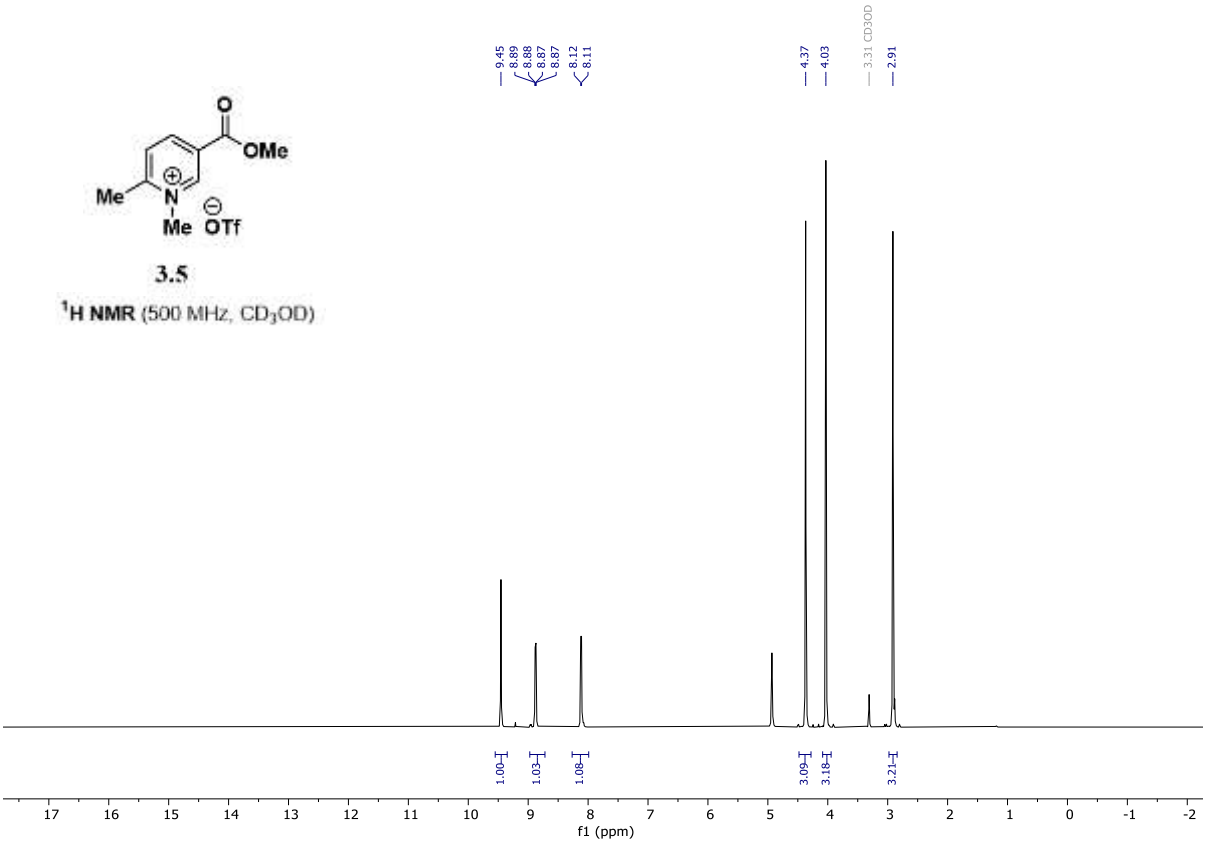
3.S.8

^{1}H NMR (500 MHz, $CDCl_3$)



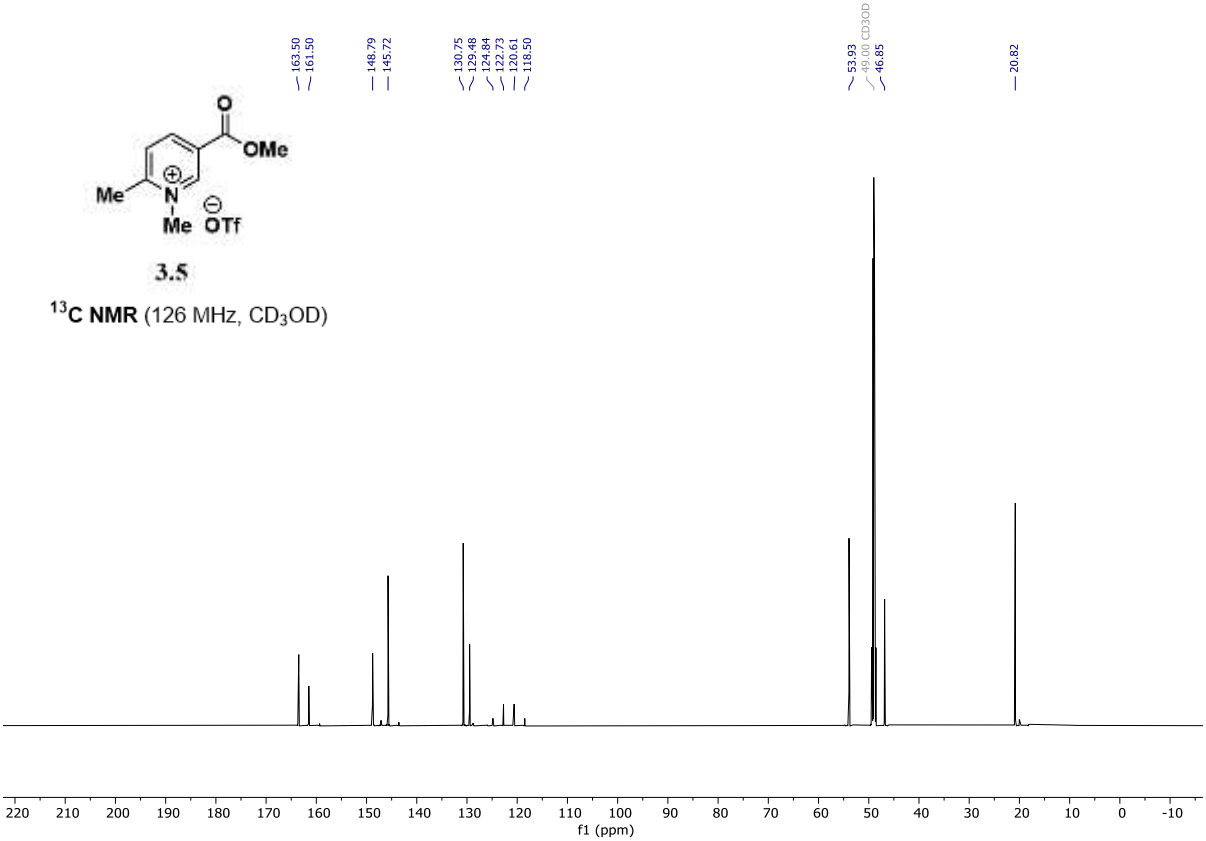
3.S.8

^{13}C NMR (126 MHz, $CDCl_3$)



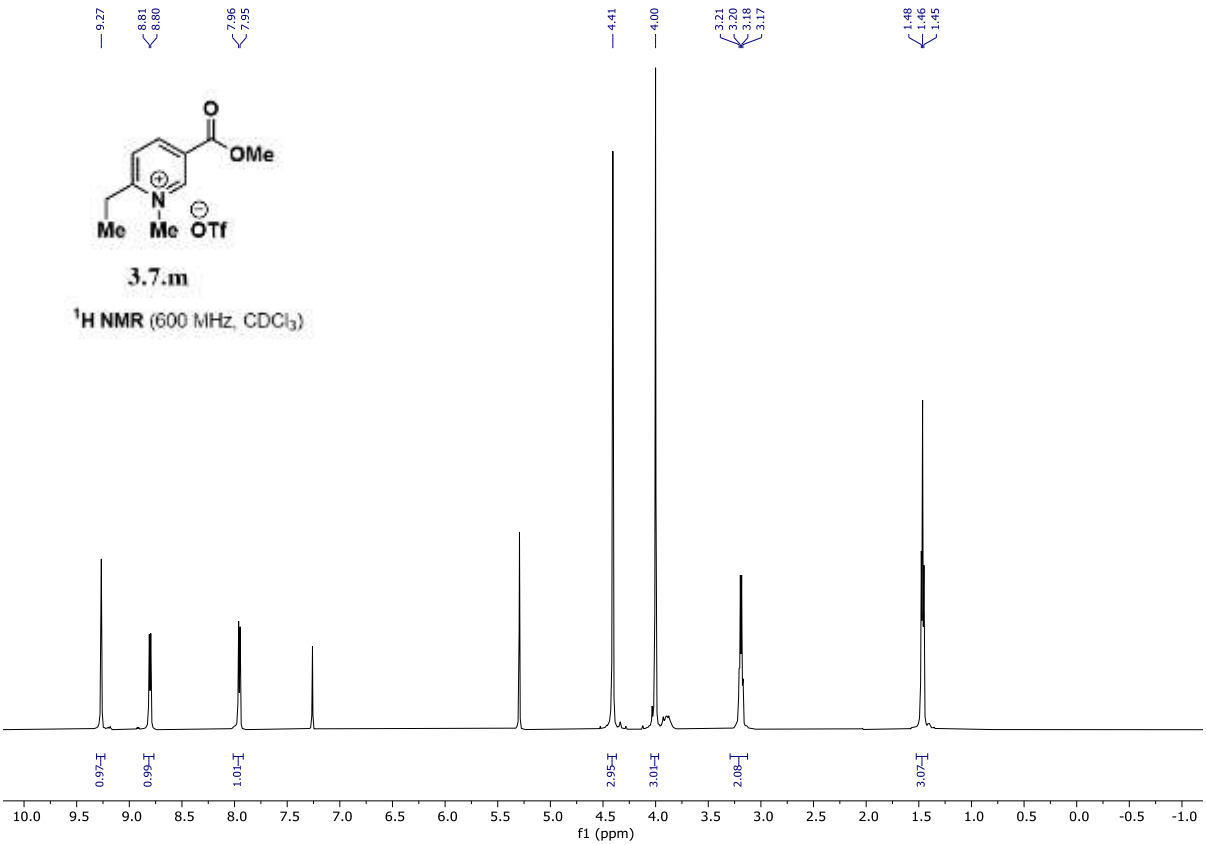
3.5

^{1}H NMR (500 MHz, CD_3OD)



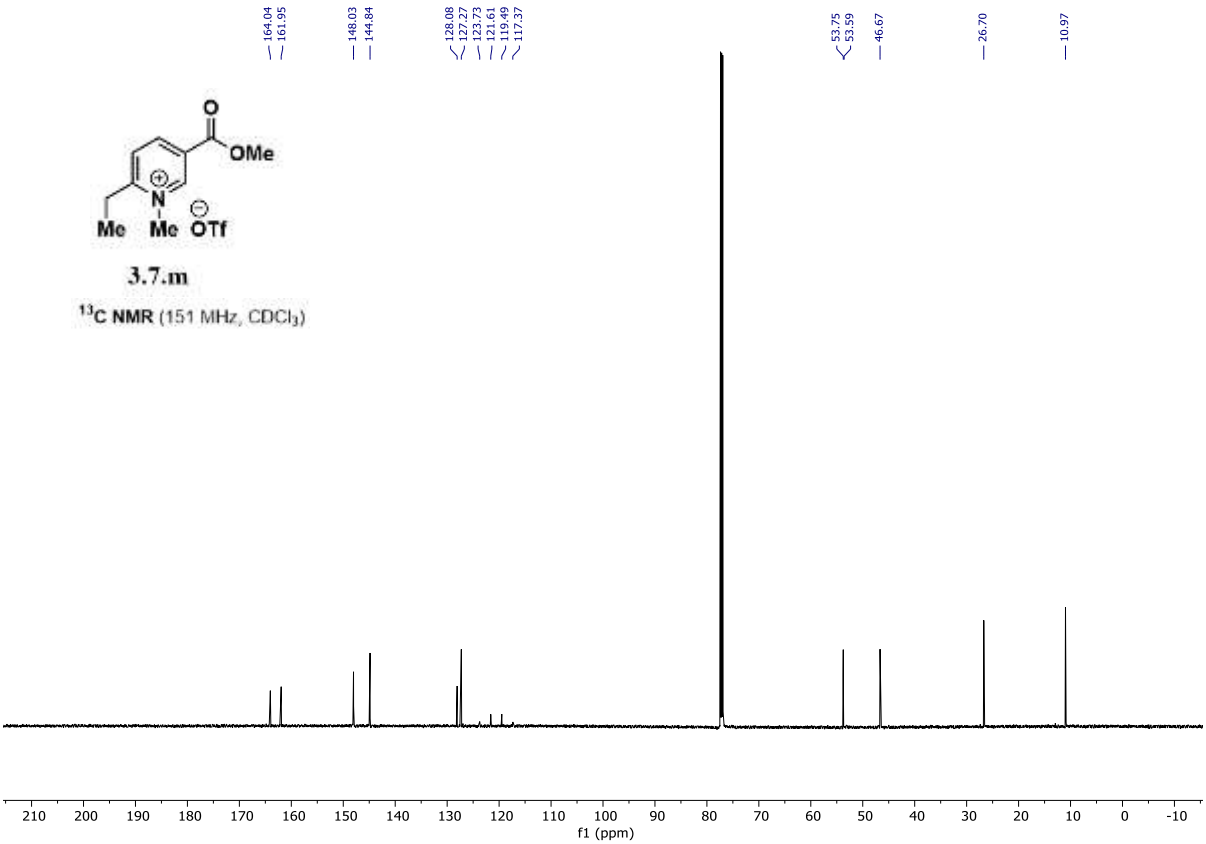
3.5

^{13}C NMR (126 MHz, CD_3OD)



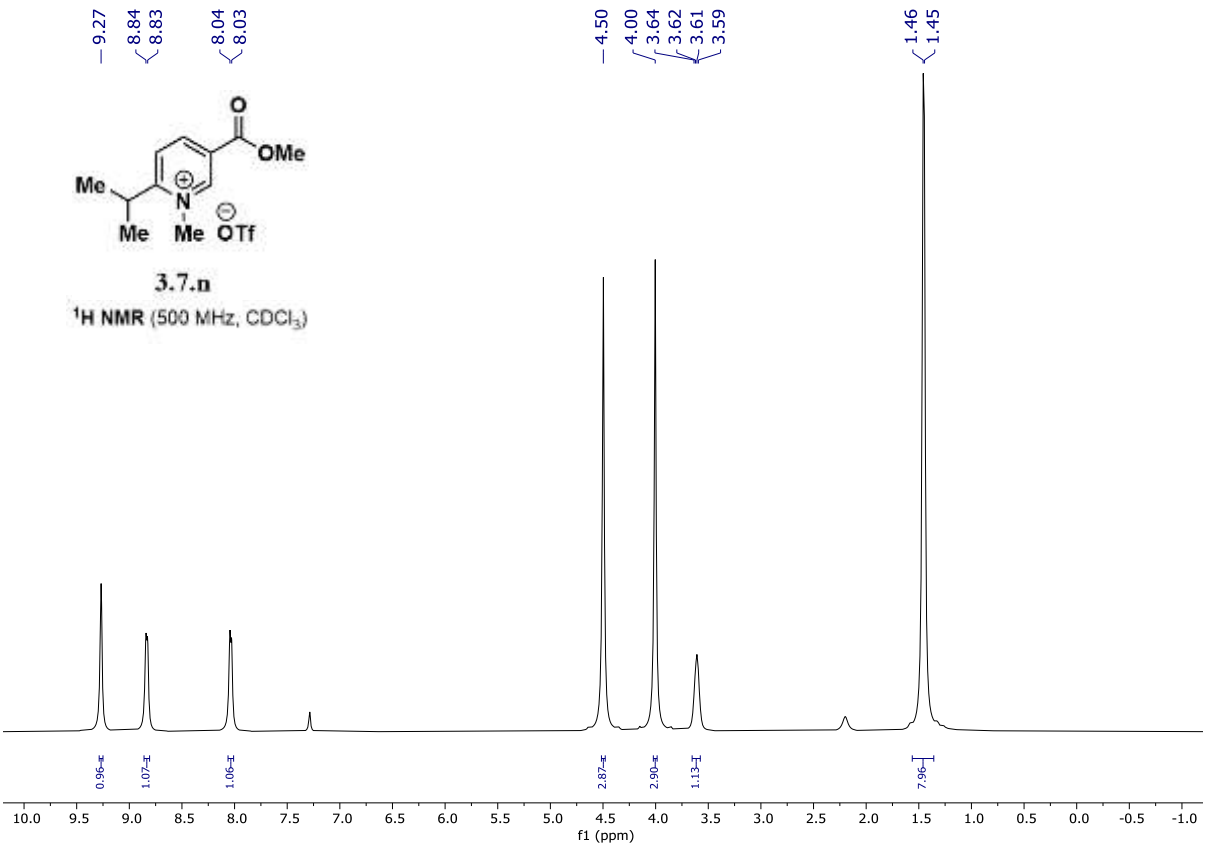
3.7.m

^{1}H NMR (600 MHz, $CDCl_3$)



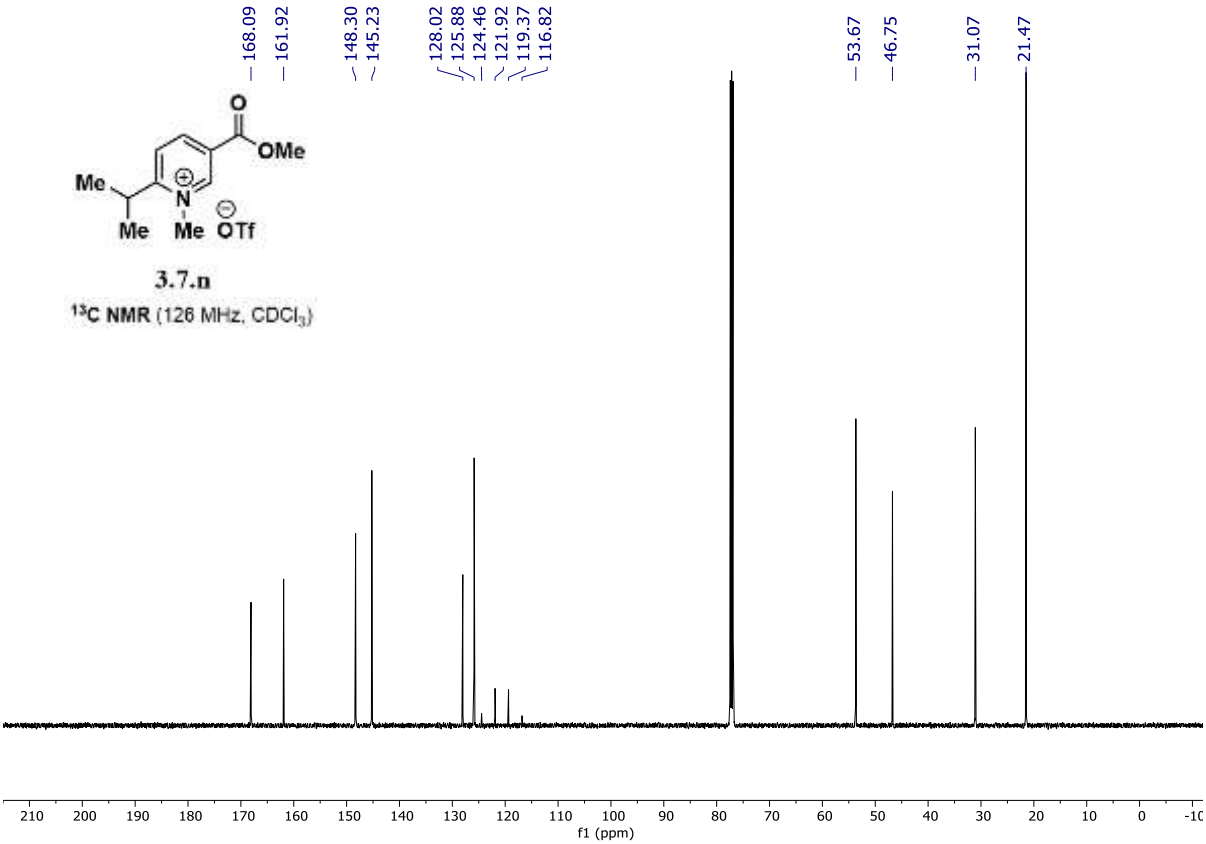
3.7.m

^{13}C NMR (151 MHz, $CDCl_3$)



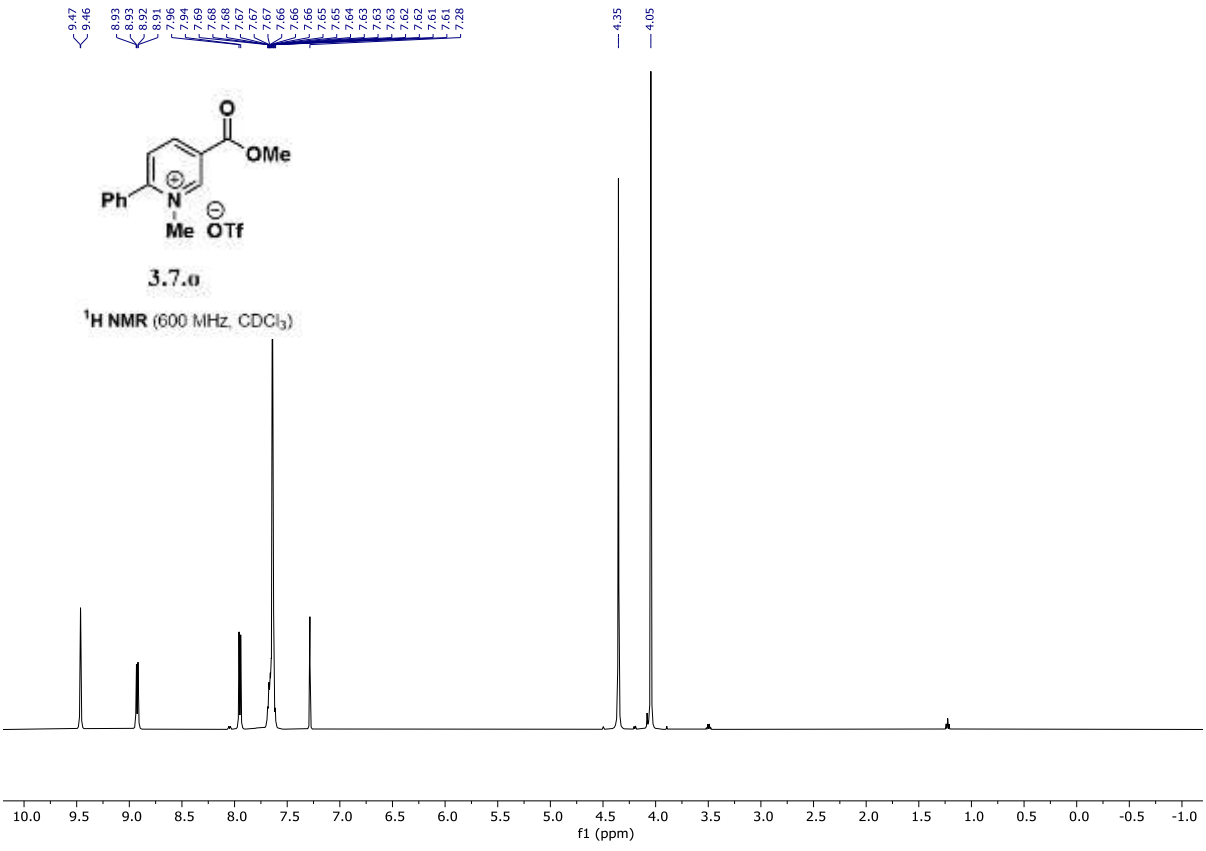
3.7.n

^{1}H NMR (500 MHz, $CDCl_3$)



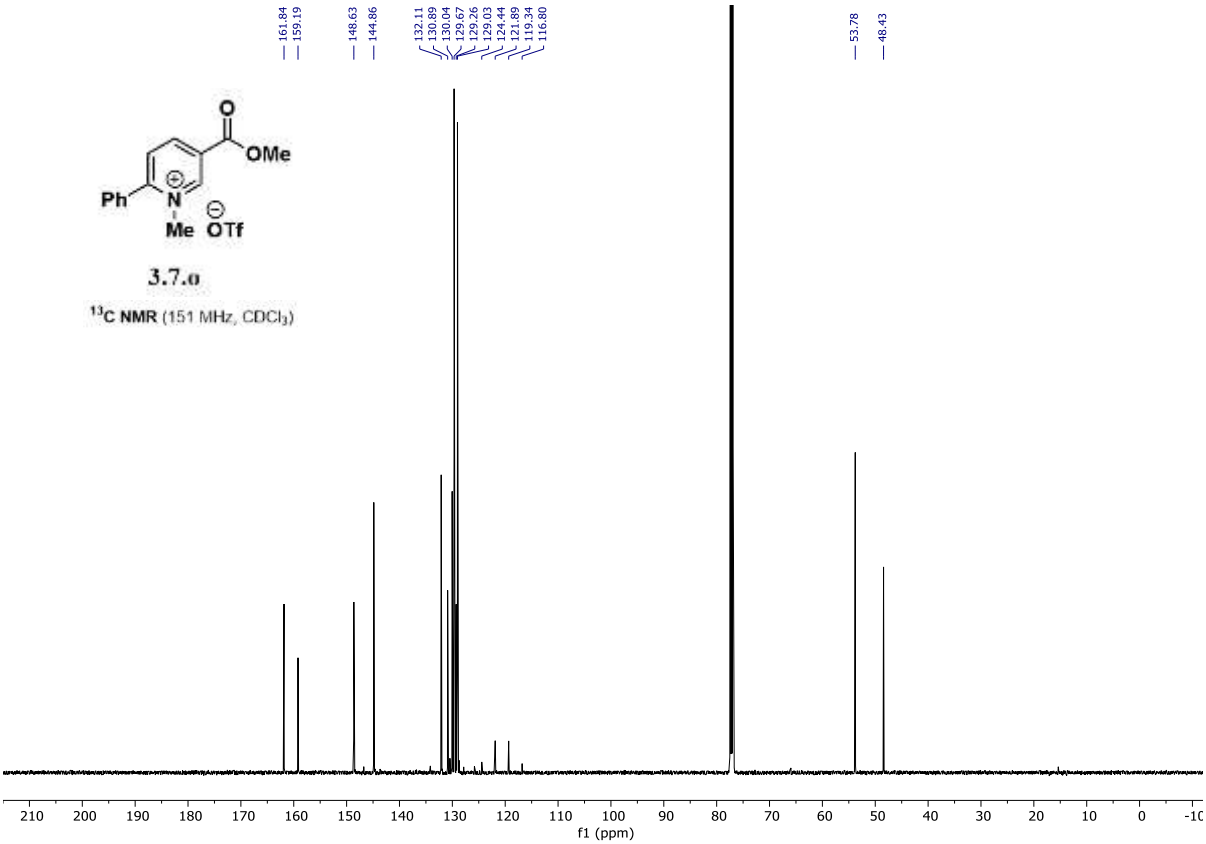
3.7.n

^{13}C NMR (126 MHz, $CDCl_3$)



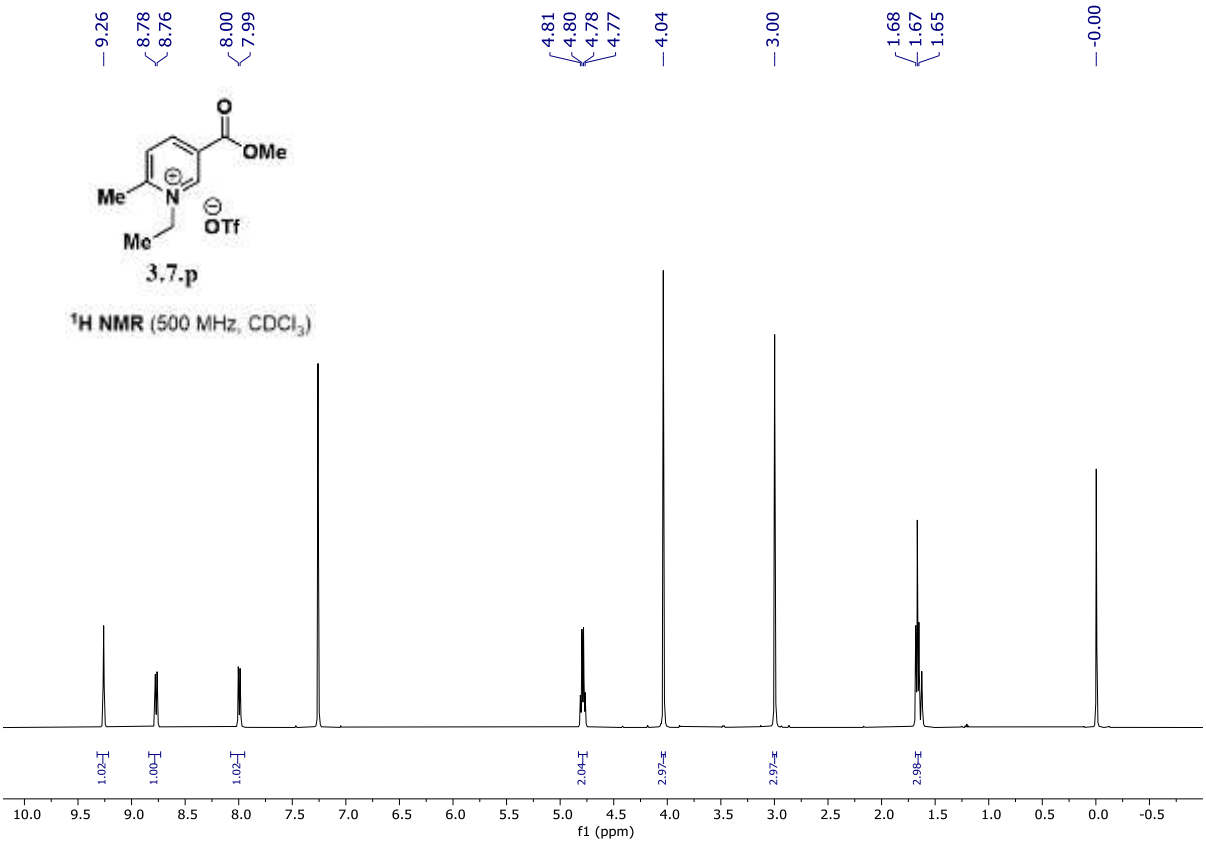
3.7.o

^{1}H NMR (600 MHz, $CDCl_3$)



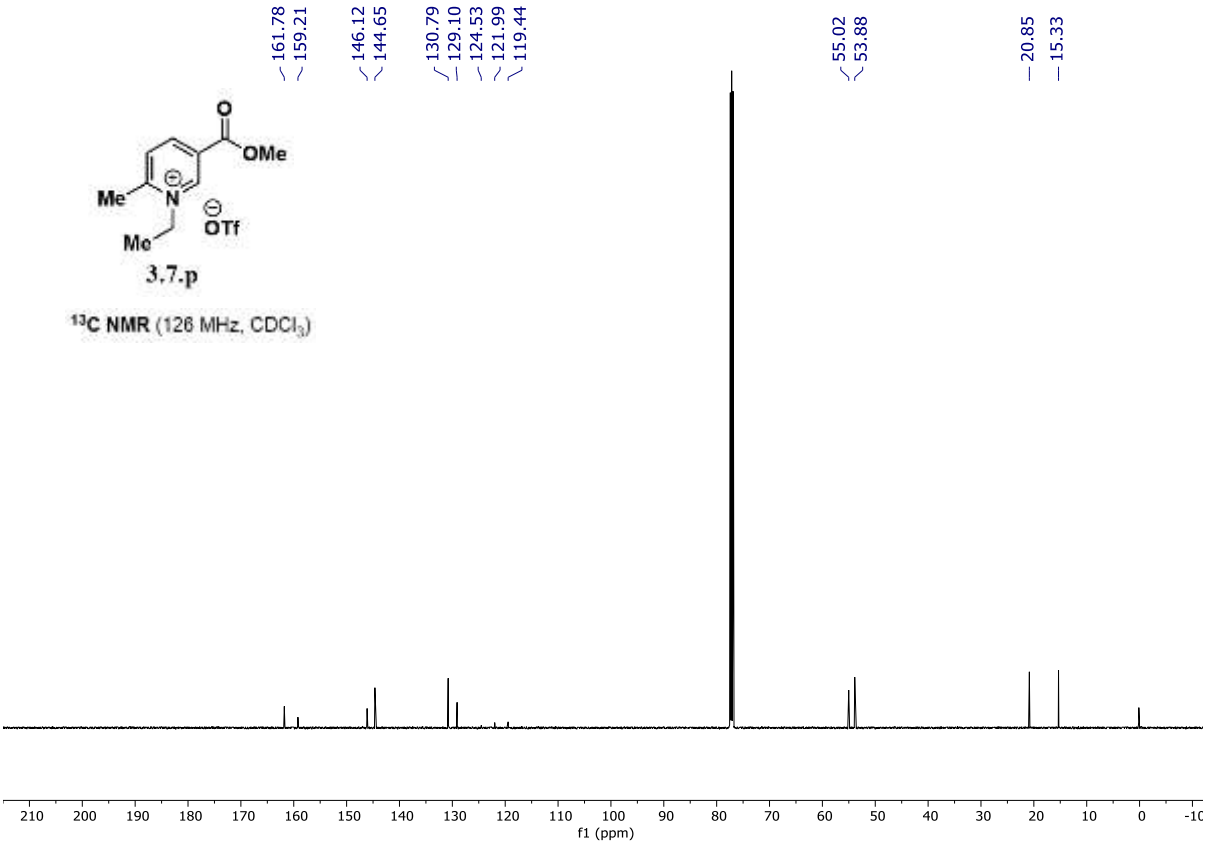
3.7.o

^{13}C NMR (151 MHz, $CDCl_3$)



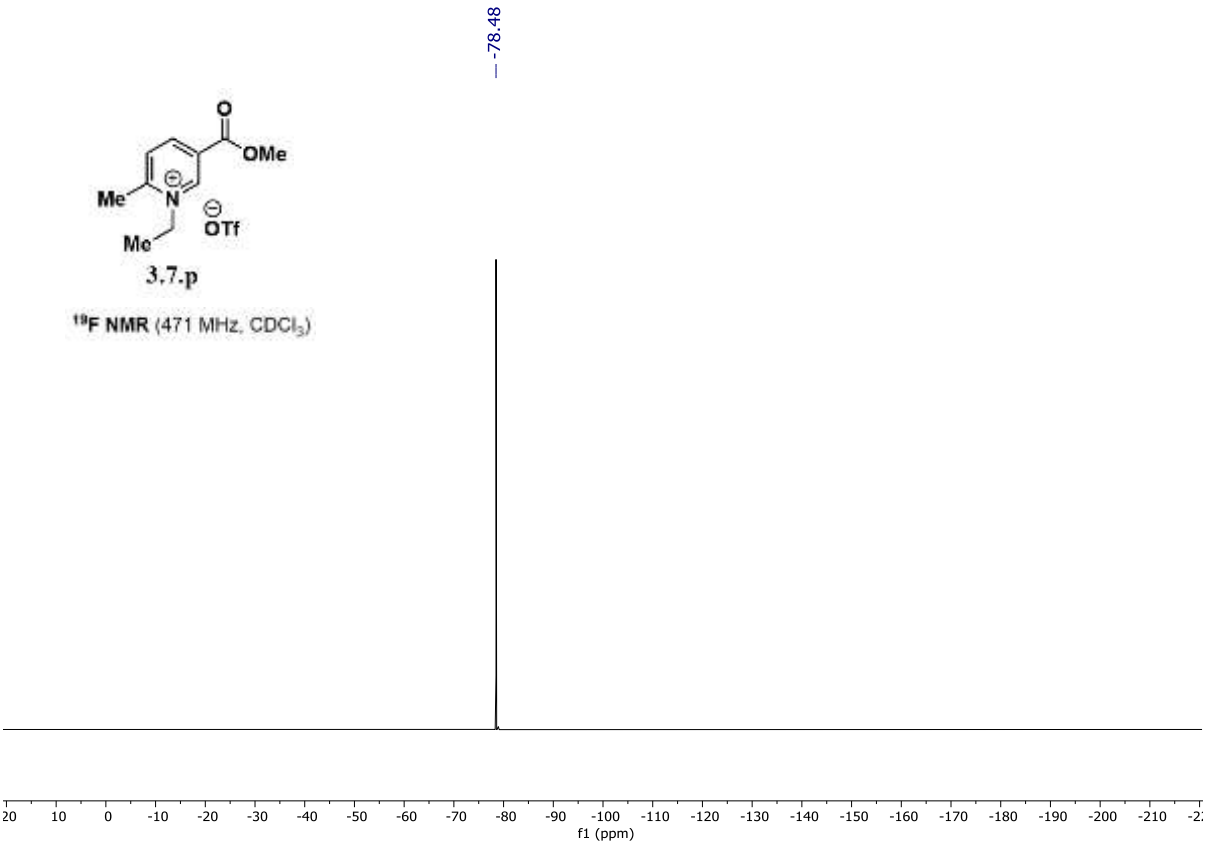
3.7.p

^{1}H NMR (500 MHz, $CDCl_3$)



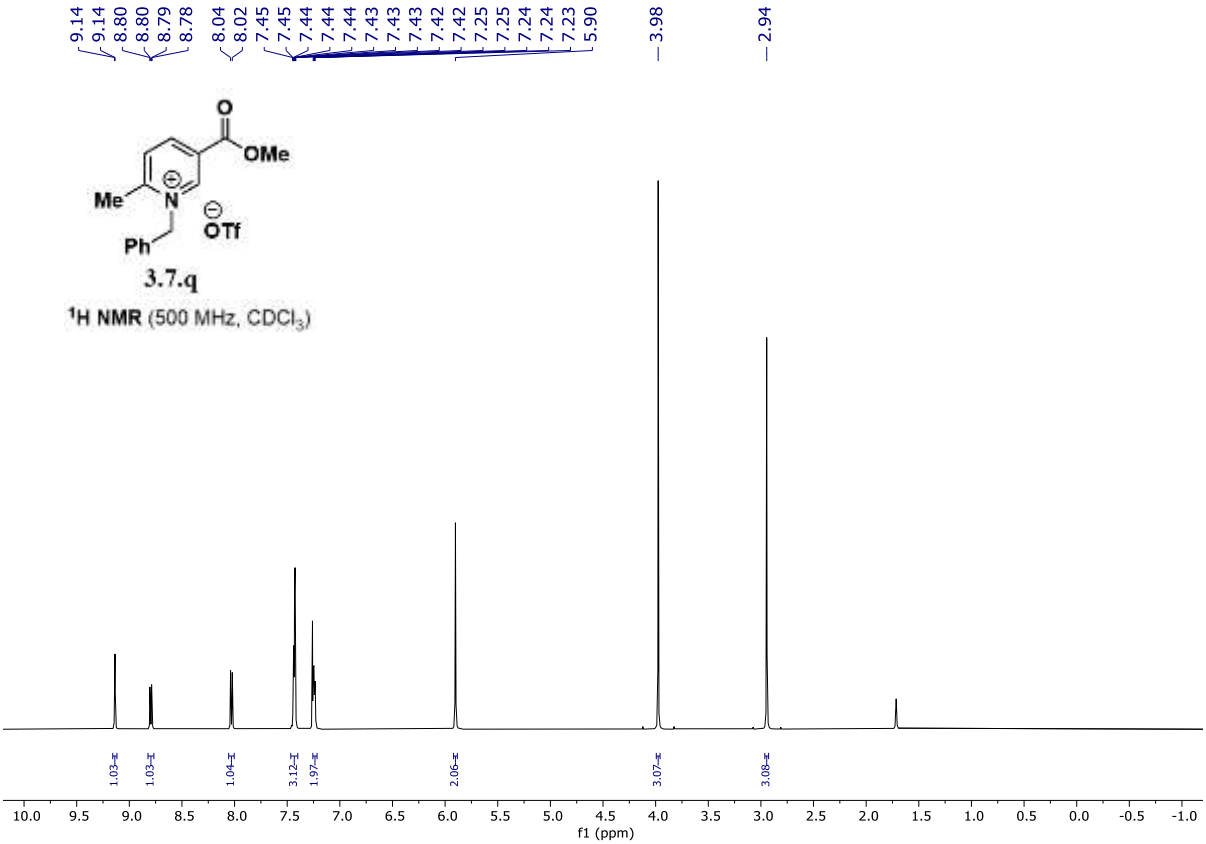
3.7.p

^{13}C NMR (126 MHz, $CDCl_3$)



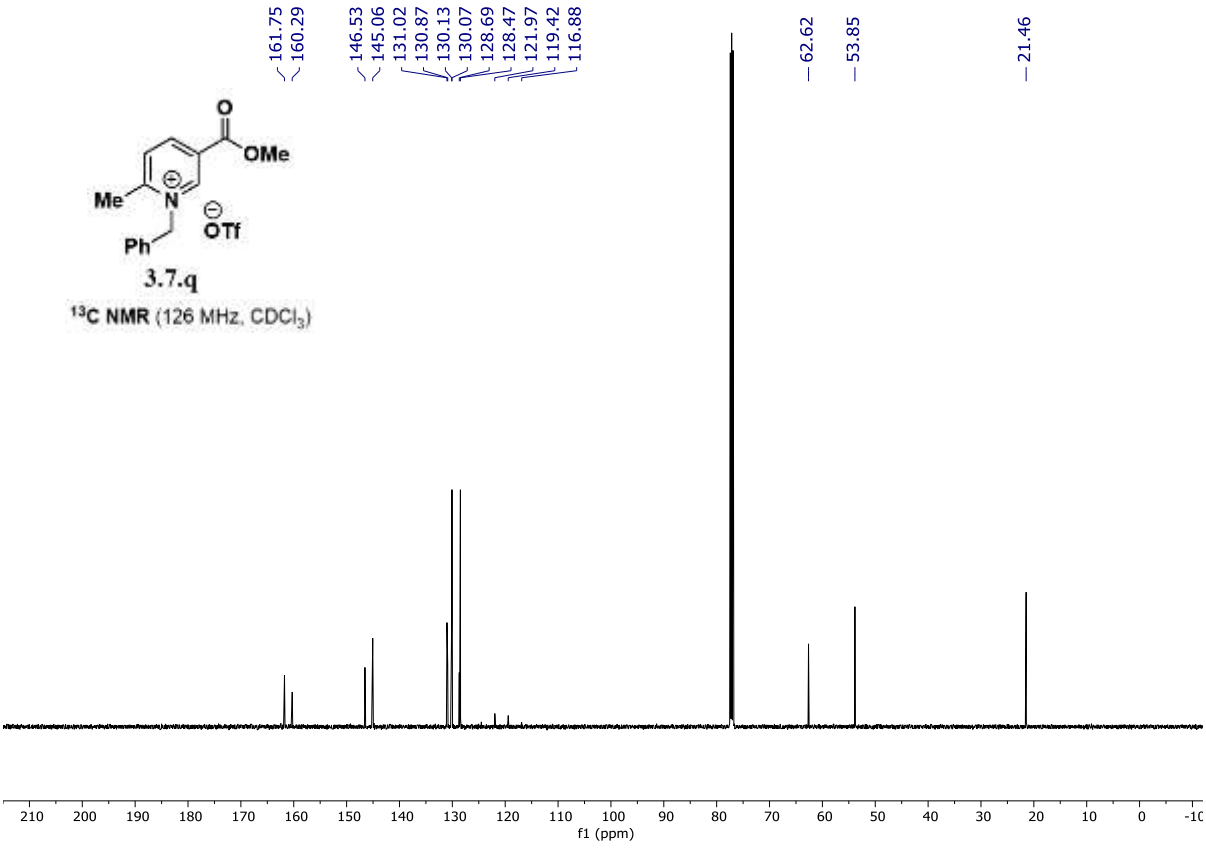
3.7.p

^{19}F NMR (471 MHz, $CDCl_3$)



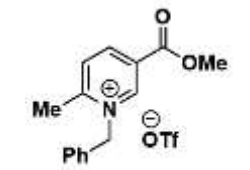
3.7.q

^{1}H NMR (500 MHz, $CDCl_3$)



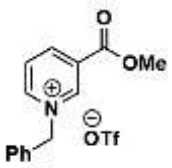
3.7.q

^{13}C NMR (126 MHz, $CDCl_3$)



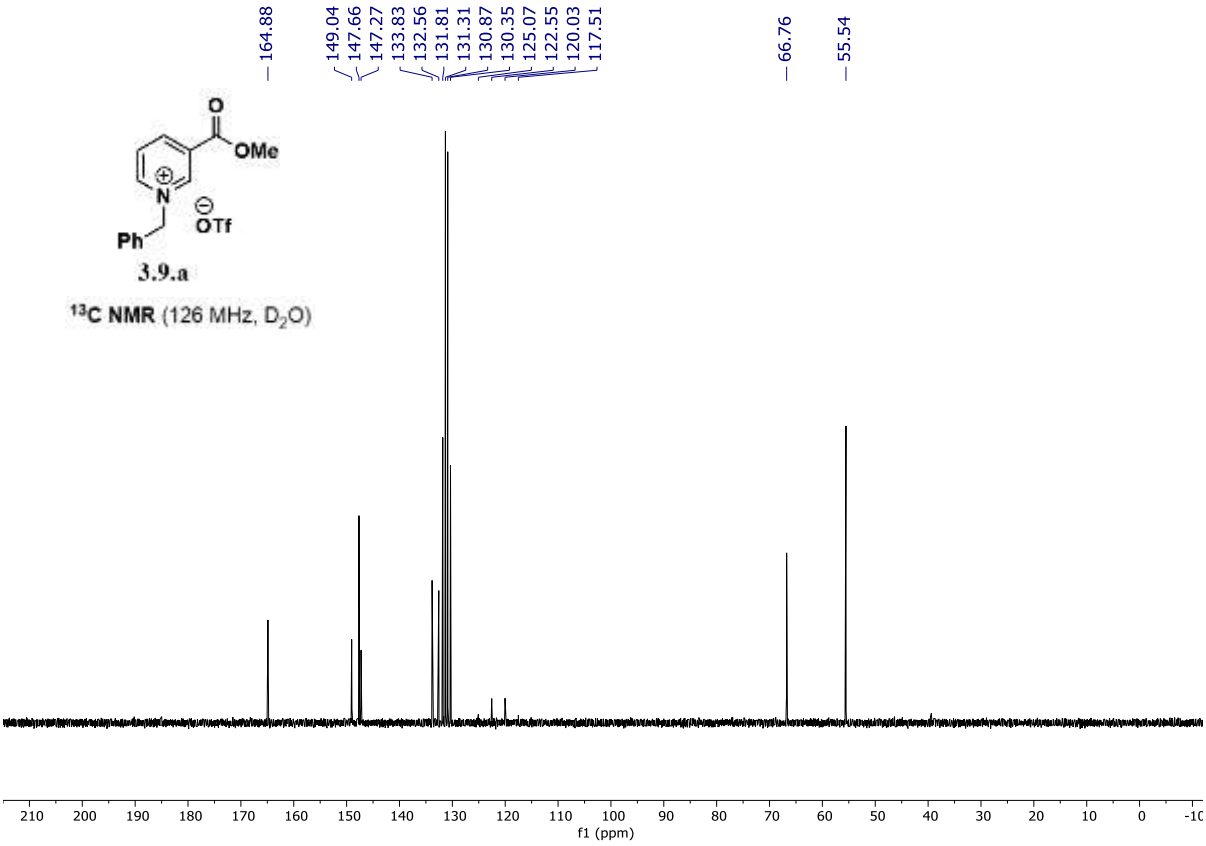
3.7.q

^{19}F NMR (471 MHz, $CDCl_3$)



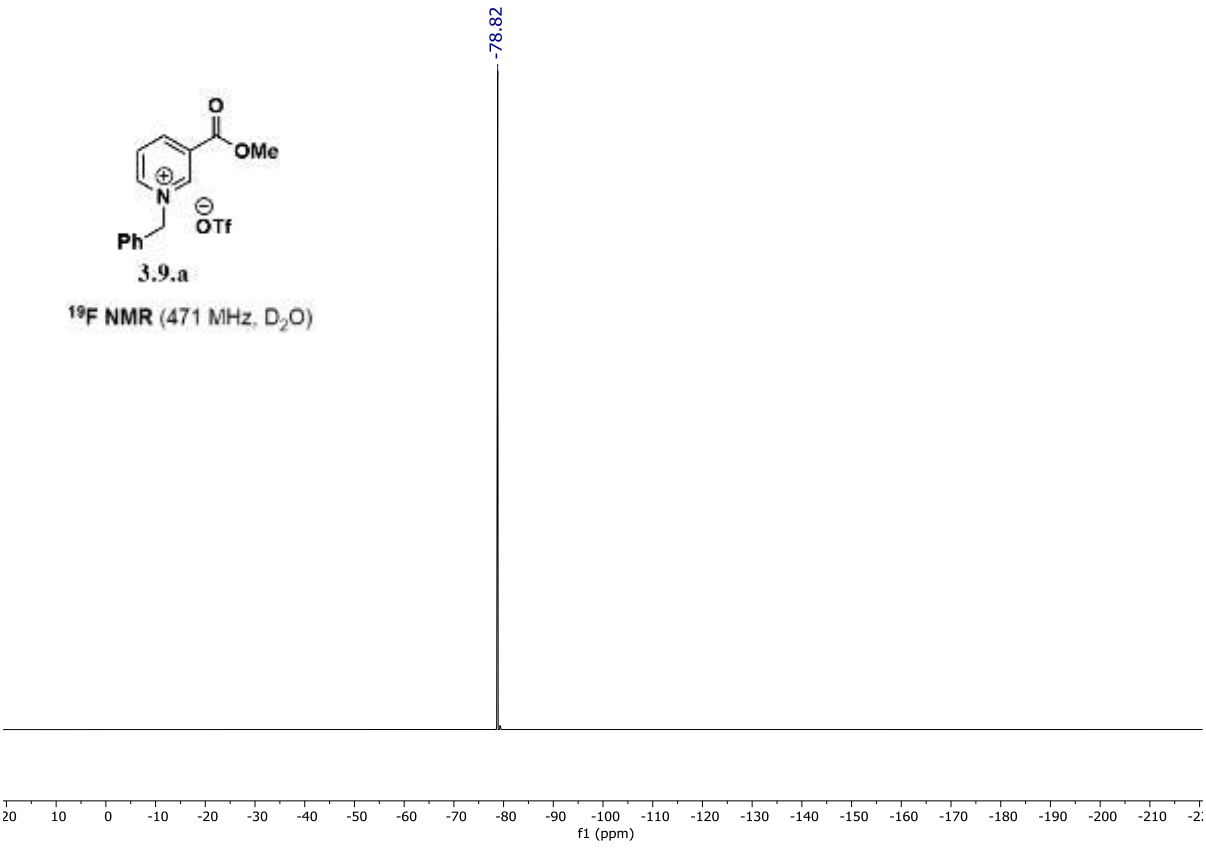
3.9.a

^{1}H NMR (500 MHz, D_2O)



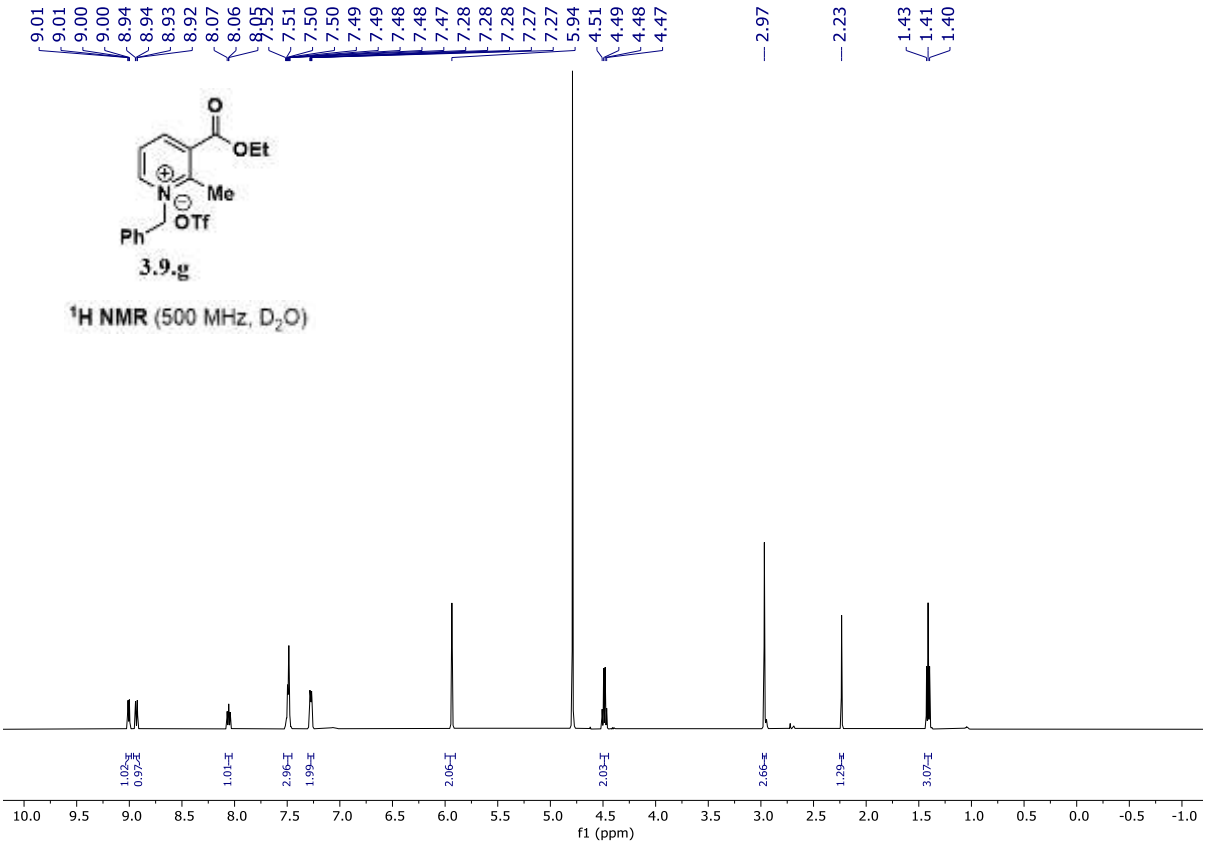
3.9.a

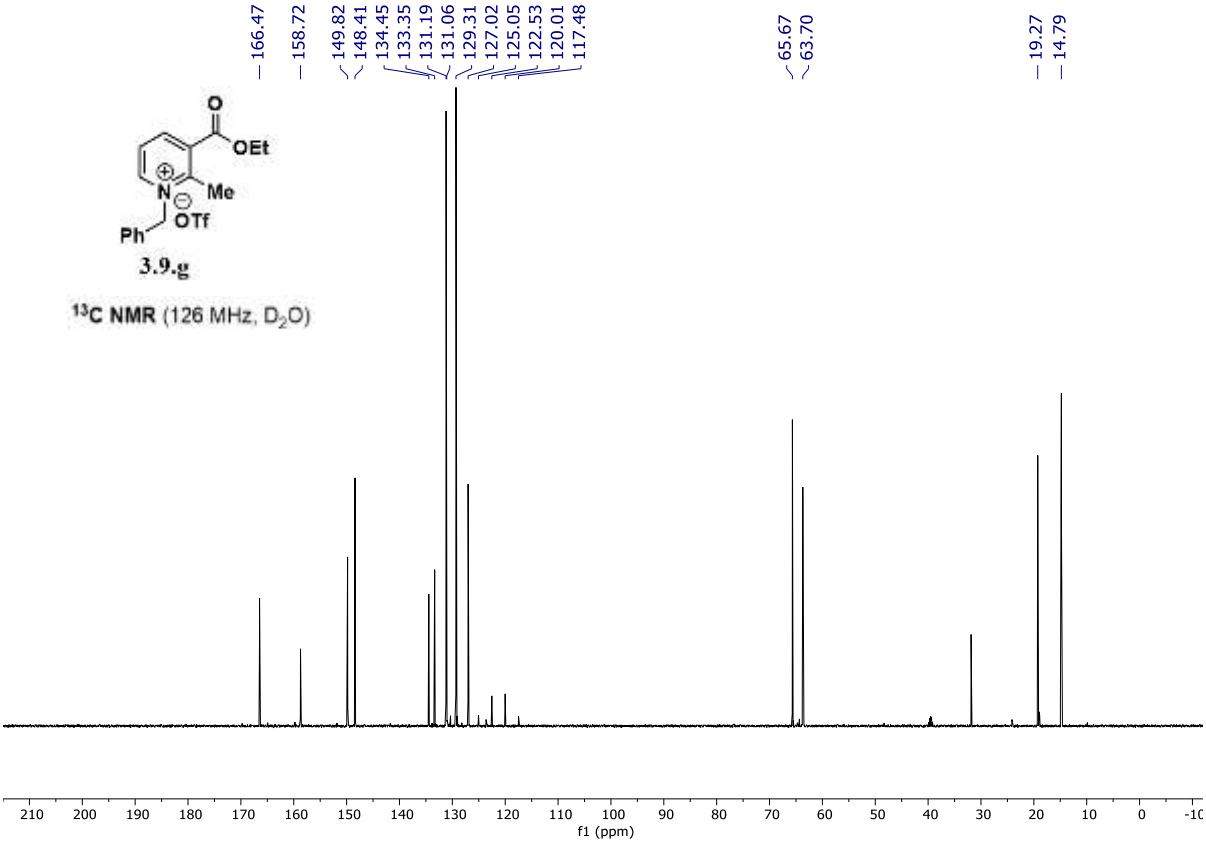
^{13}C NMR (126 MHz, D_2O)

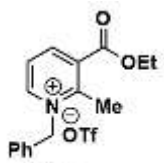


3.9.a

^{19}F NMR (471 MHz, D_2O)

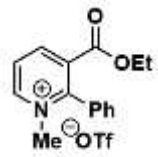

9.01
9.01
9.00
9.00
8.94
8.94
8.93
8.92
8.07
8.06
8.05
7.52
7.51
7.50
7.50
7.49
7.49
7.48
7.48
7.47
7.28
7.28
7.28
7.27
7.27
5.94
4.51
4.49
4.48
4.47
2.97
2.23
1.43
1.41
1.40
O
OEt
N
Me
OTf
Ph
3.9.g
1H NMR (500 MHz, D2O)
1.02
0.97
1.01
2.96
1.99
2.06
2.03
2.66
1.29
3.07
f1 (ppm)


166.47
158.72
149.82
148.41
134.45
133.35
131.19
131.06
129.31
127.02
125.05
122.53
120.01
117.48
65.67
63.70
19.27
14.79
O
OEt
N
Me
OTf
Ph
3.9.g
13C NMR (126 MHz, D2O)
f1 (ppm)



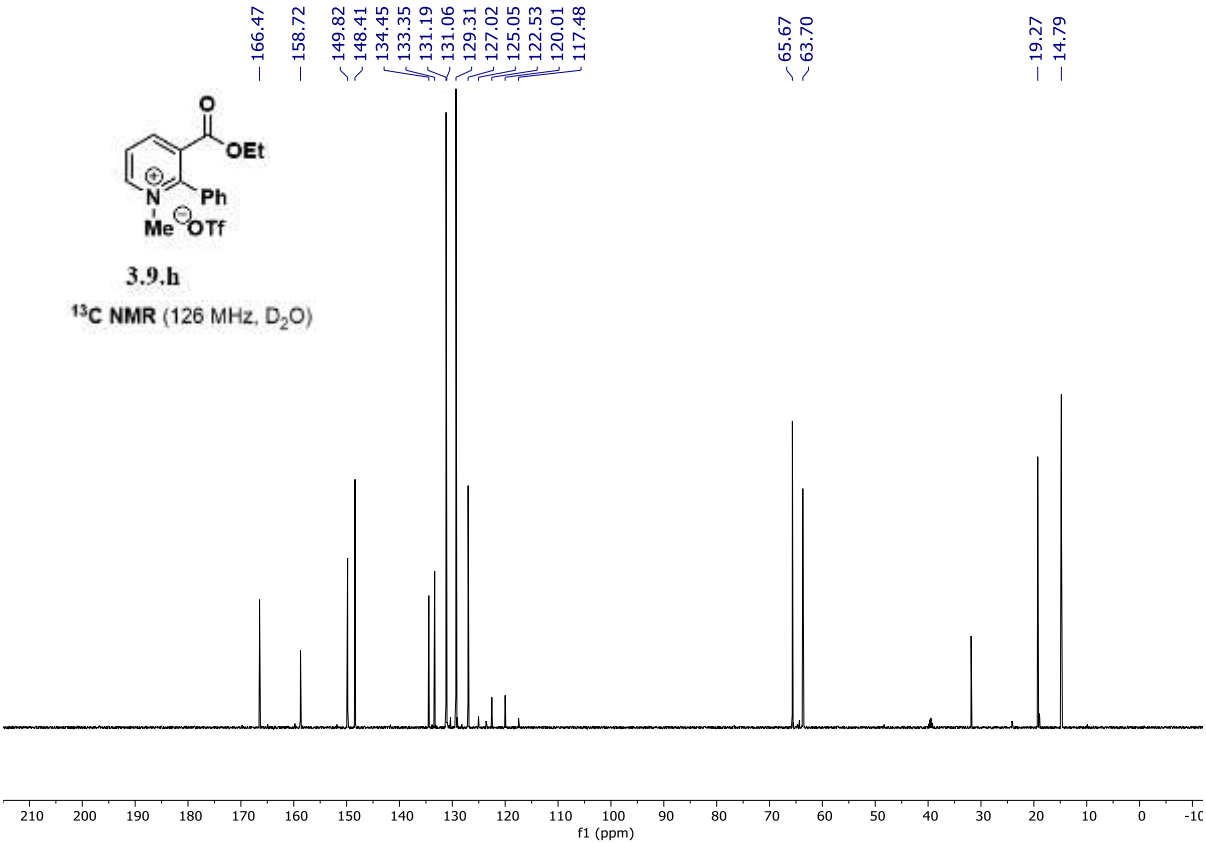
3.9.g

^{19}F NMR (471 MHz, D_2O)



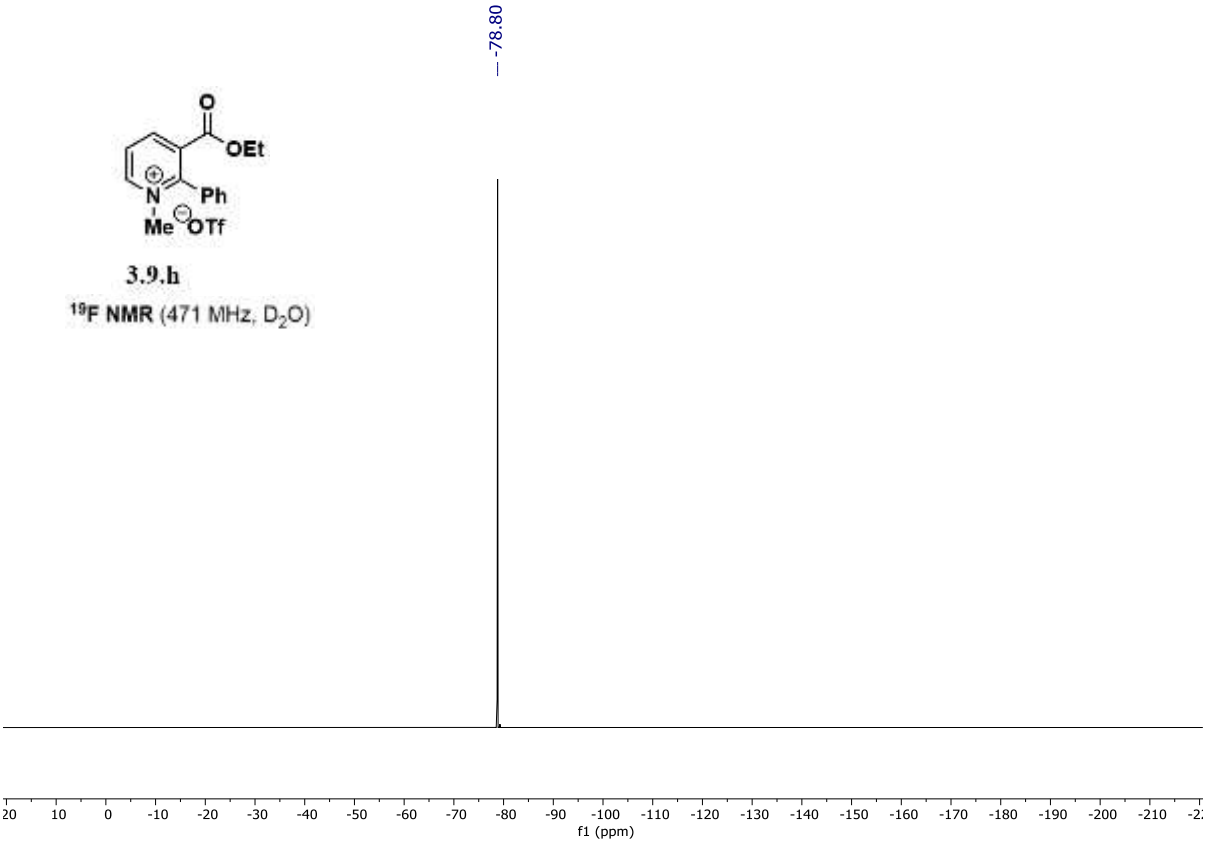
3.9.h

^{1}H NMR (500 MHz, D_2O)



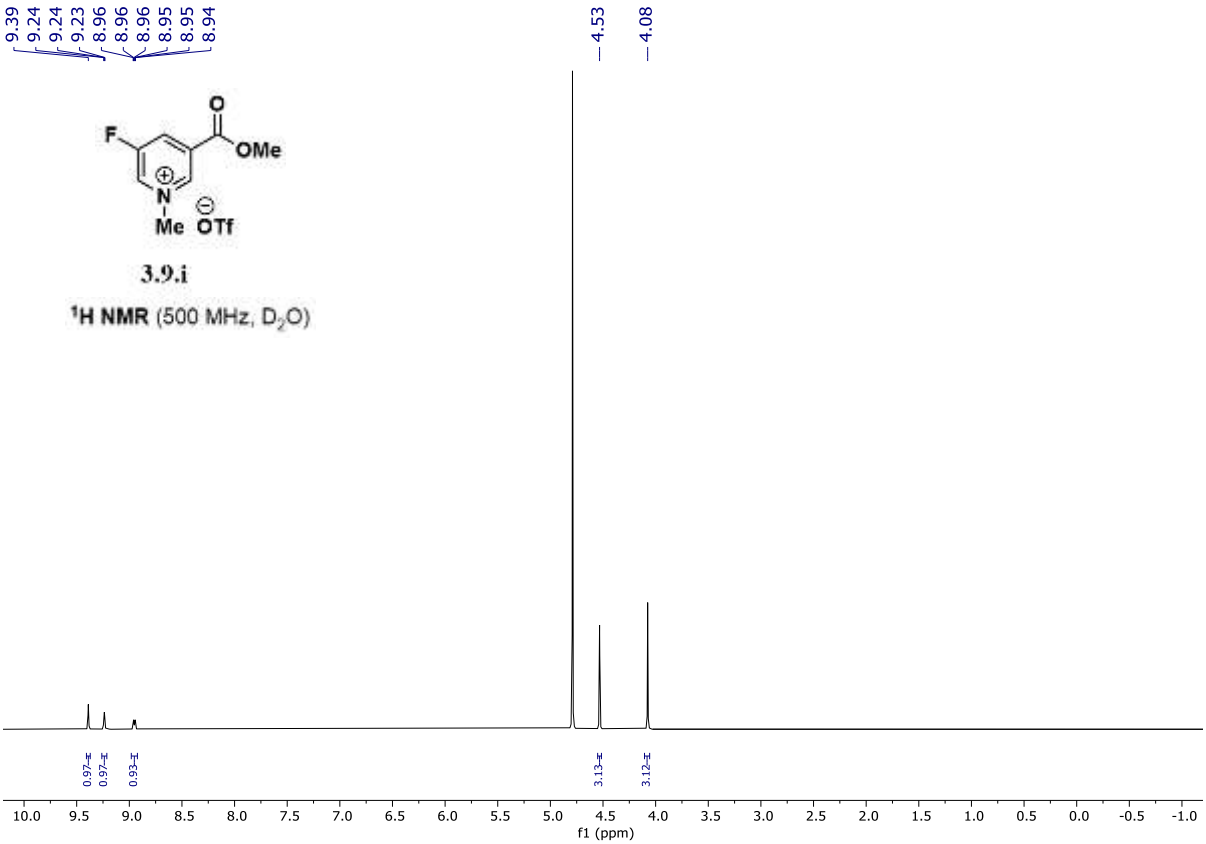
3.9.h

^{13}C NMR (126 MHz, D_2O)



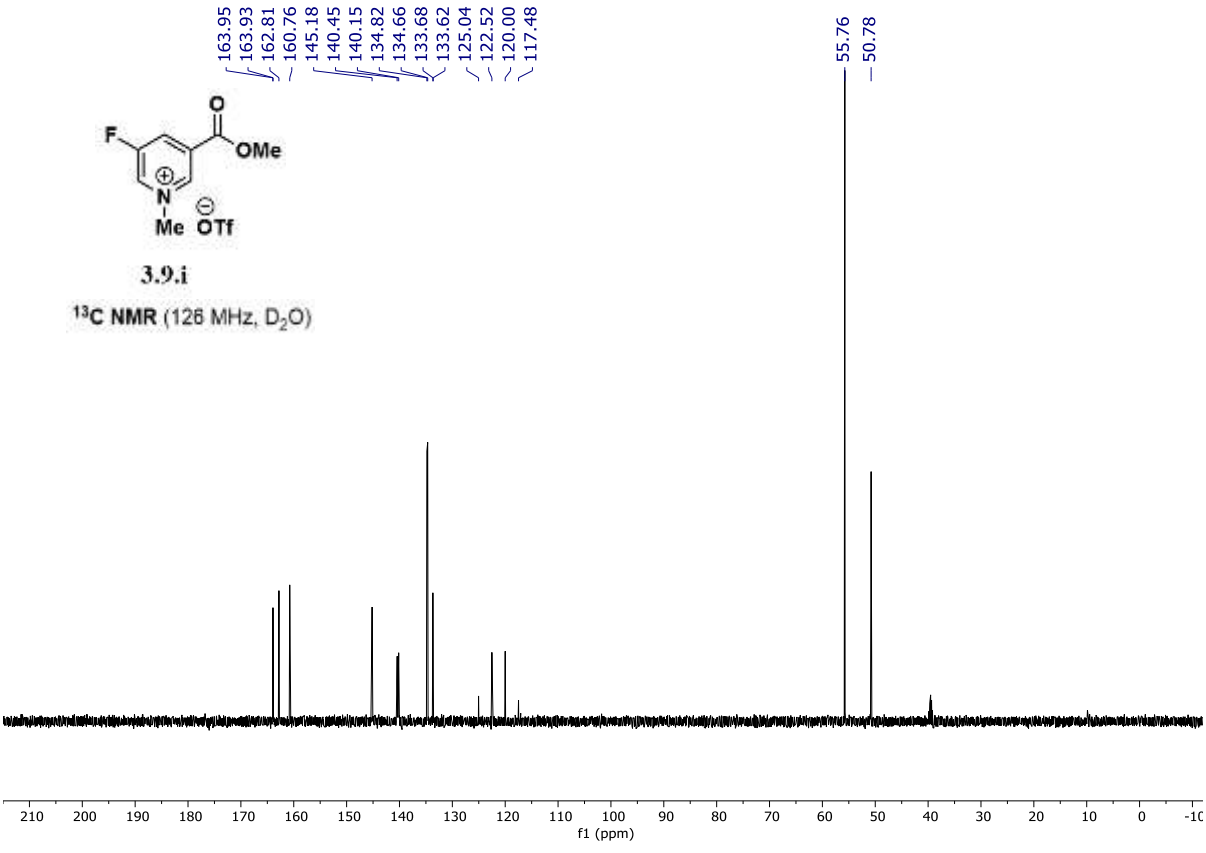
3.9.h

^{19}F NMR (471 MHz, D_2O)



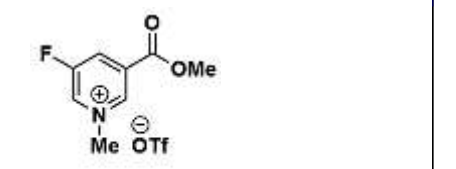
3.9.i

^{1}H NMR (500 MHz, D_2O)



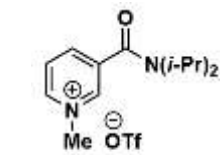
3.9.i

^{13}C NMR (126 MHz, D_2O)



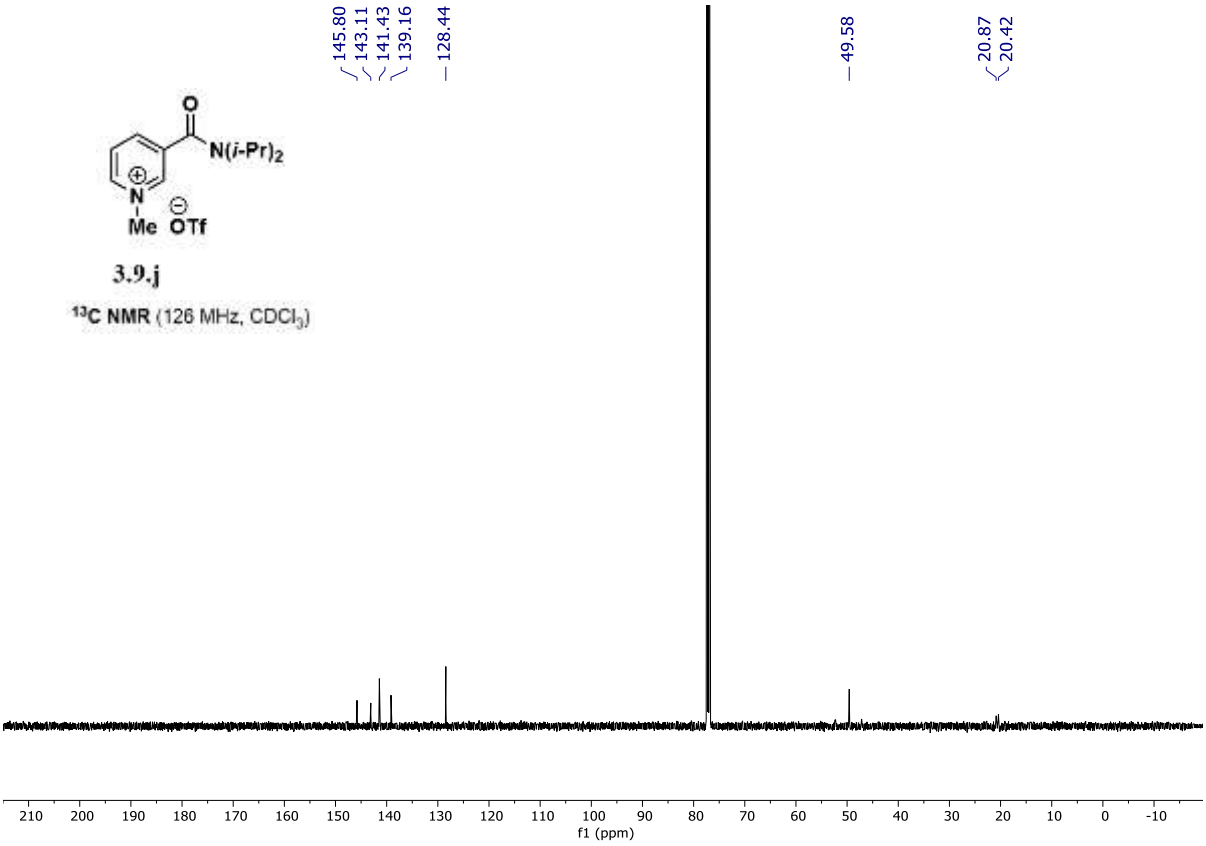
3.9.i

^{19}F NMR (471 MHz, D_2O)



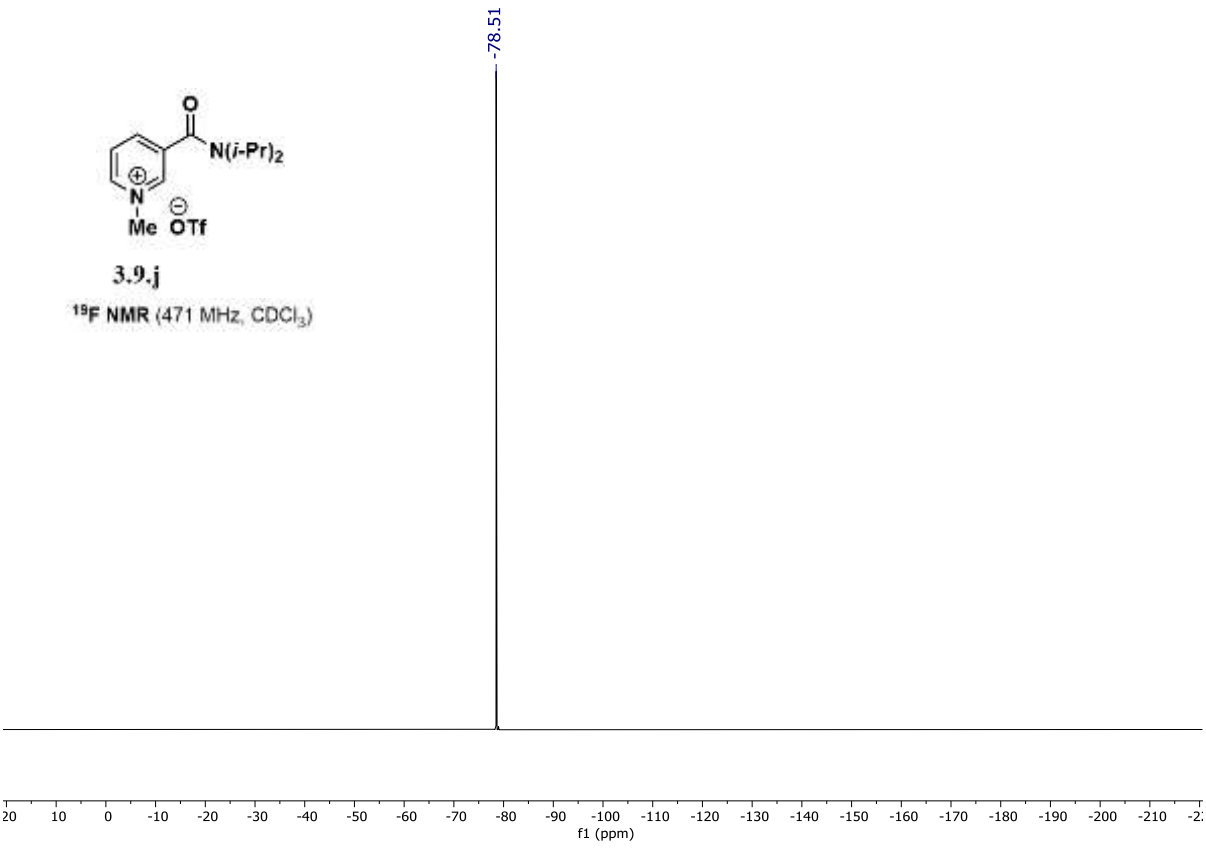
3.9.j

^{1}H NMR (500 MHz, $CDCl_3$)



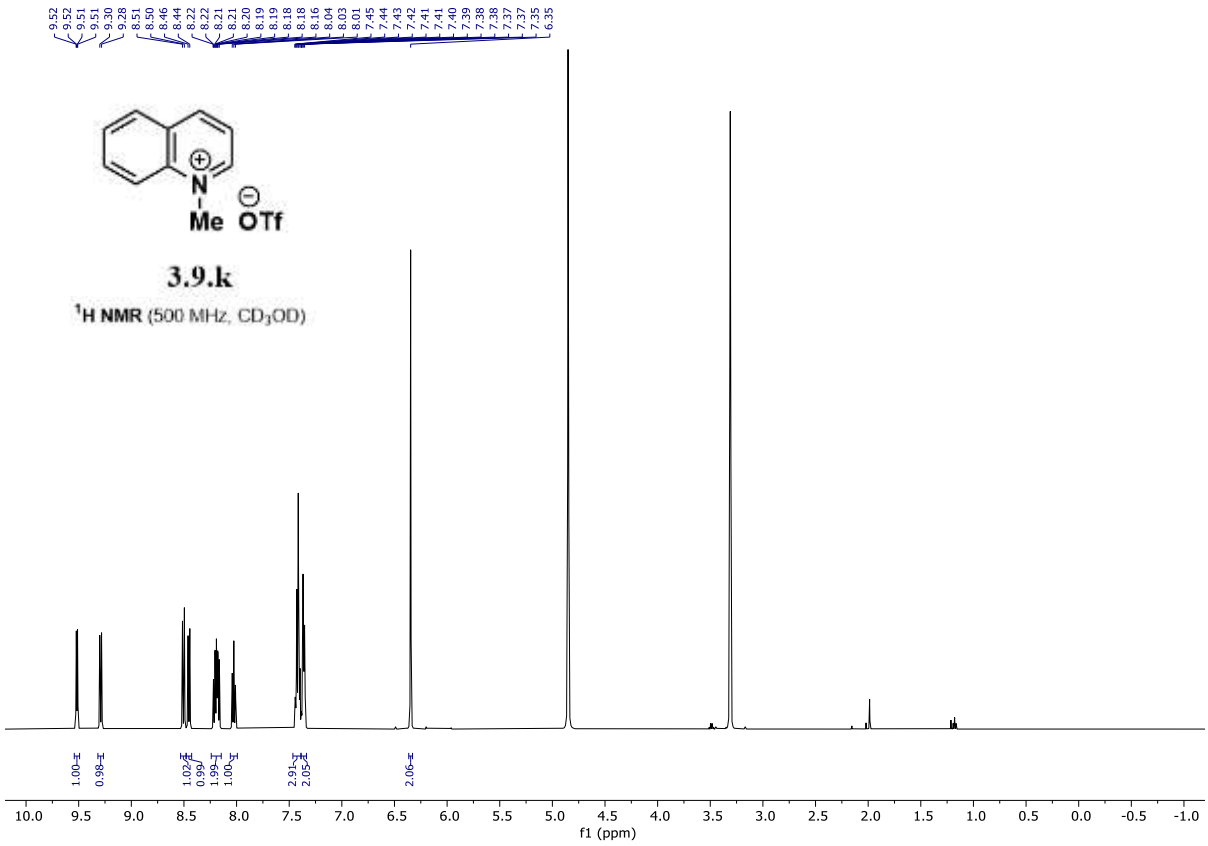
3.9.j

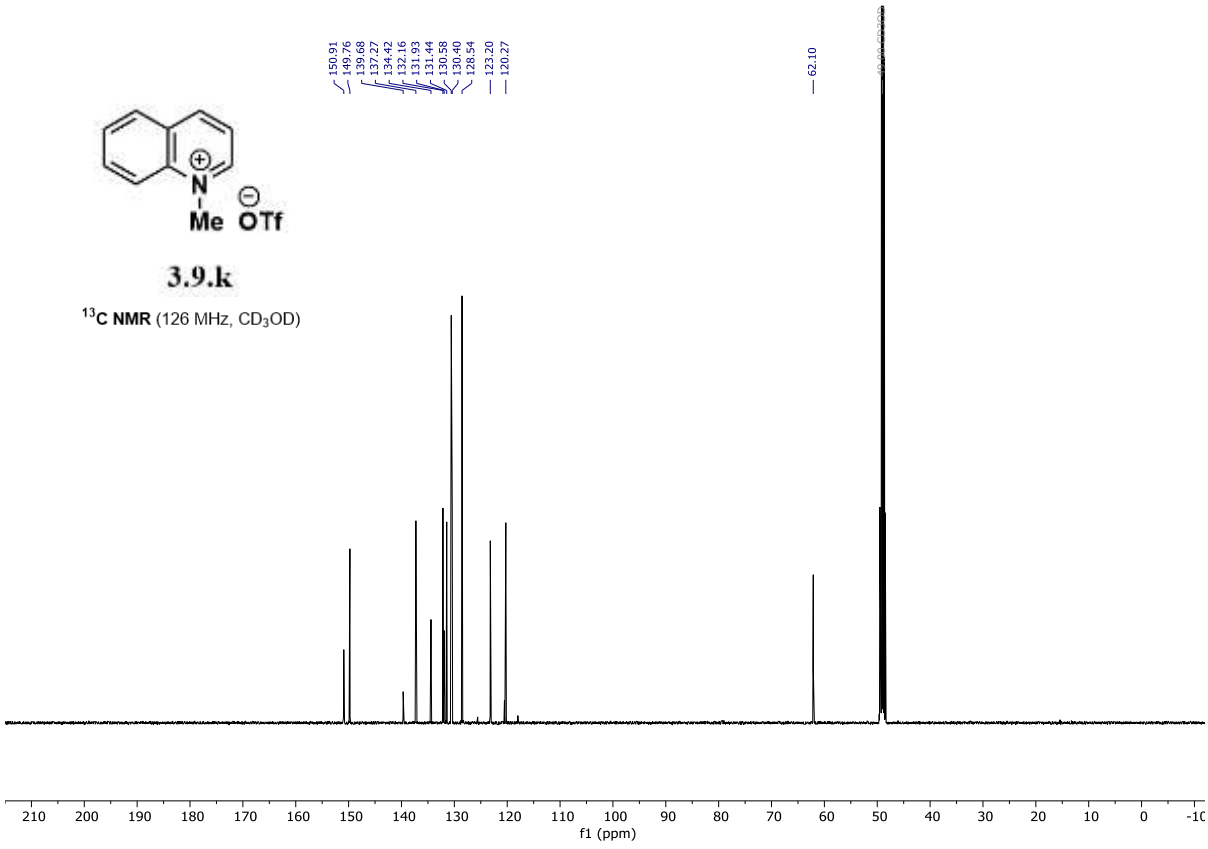
^{13}C NMR (126 MHz, $CDCl_3$)

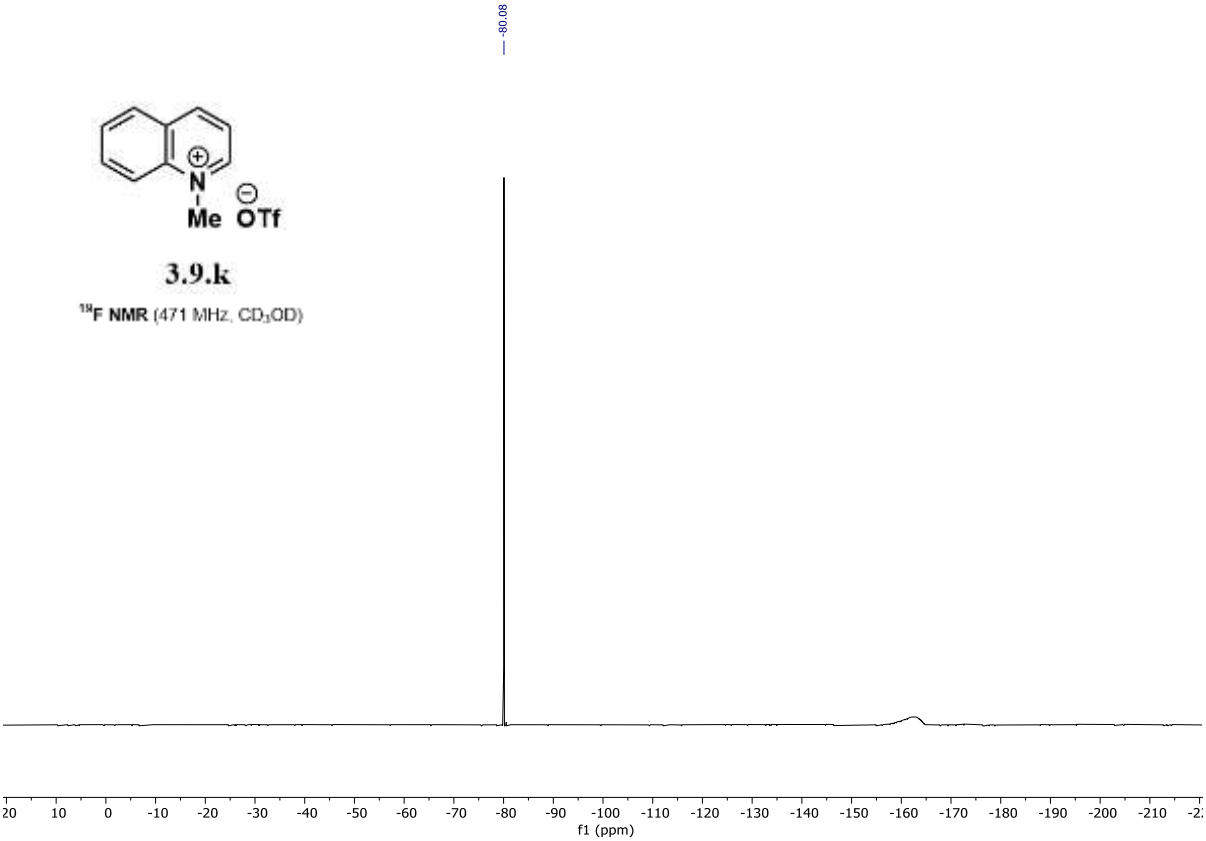


3.9.j

^{19}F NMR (471 MHz, $CDCl_3$)

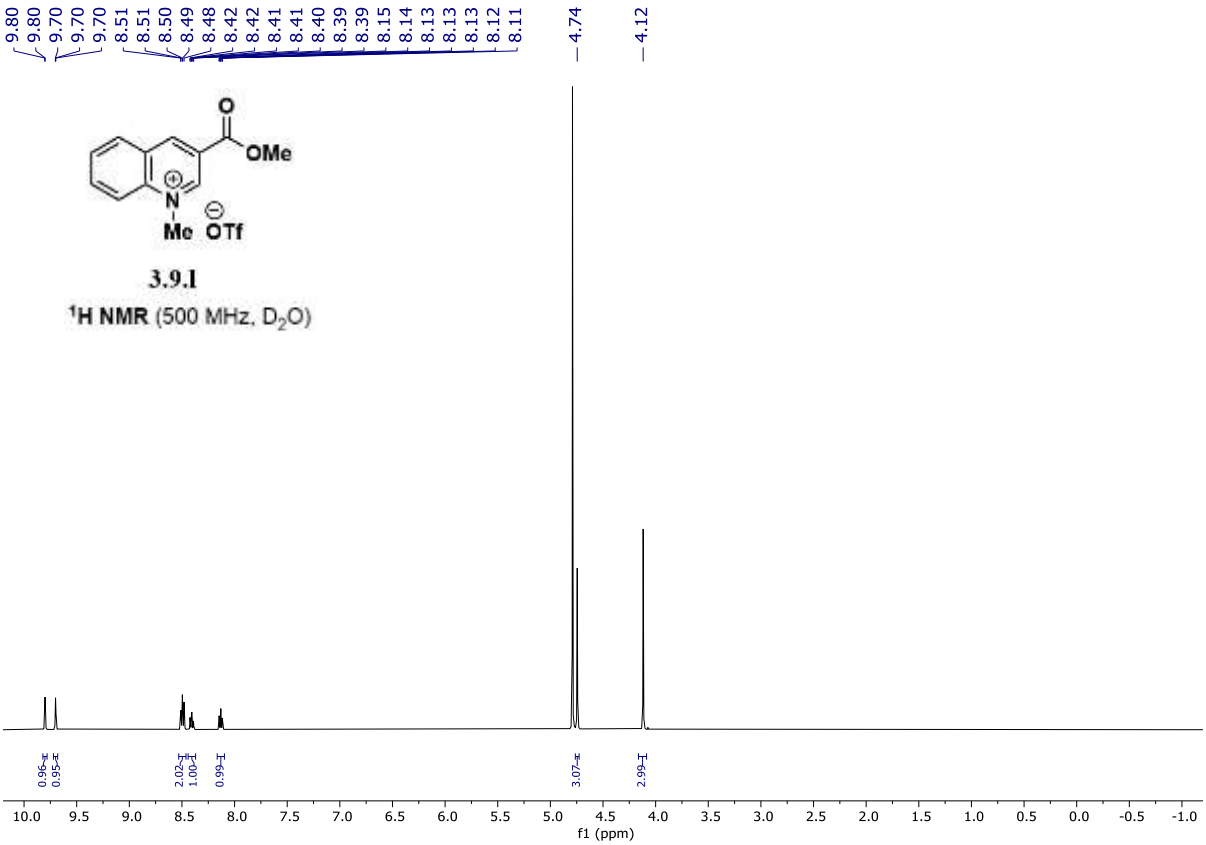

9.52
9.52
9.51
9.51
9.30
9.28
8.51
8.50
8.46
8.44
8.22
8.21
8.21
8.20
8.19
8.19
8.18
8.18
8.16
8.04
8.03
8.01
7.45
7.44
7.43
7.42
7.41
7.40
7.39
7.38
7.38
7.37
7.37
7.35
6.35
N
Me
OTf
3.9.k
1H NMR (500 MHz, CD3OD)
1.00
0.98
1.02
0.99
1.99
1.00
2.91
2.05
2.06
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


150.91
149.76
139.68
137.27
134.42
132.16
131.93
131.44
130.58
130.40
128.54
123.20
120.27
62.10
N
Me
OTf
3.9.k
13C NMR (126 MHz, CD3OD)
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)



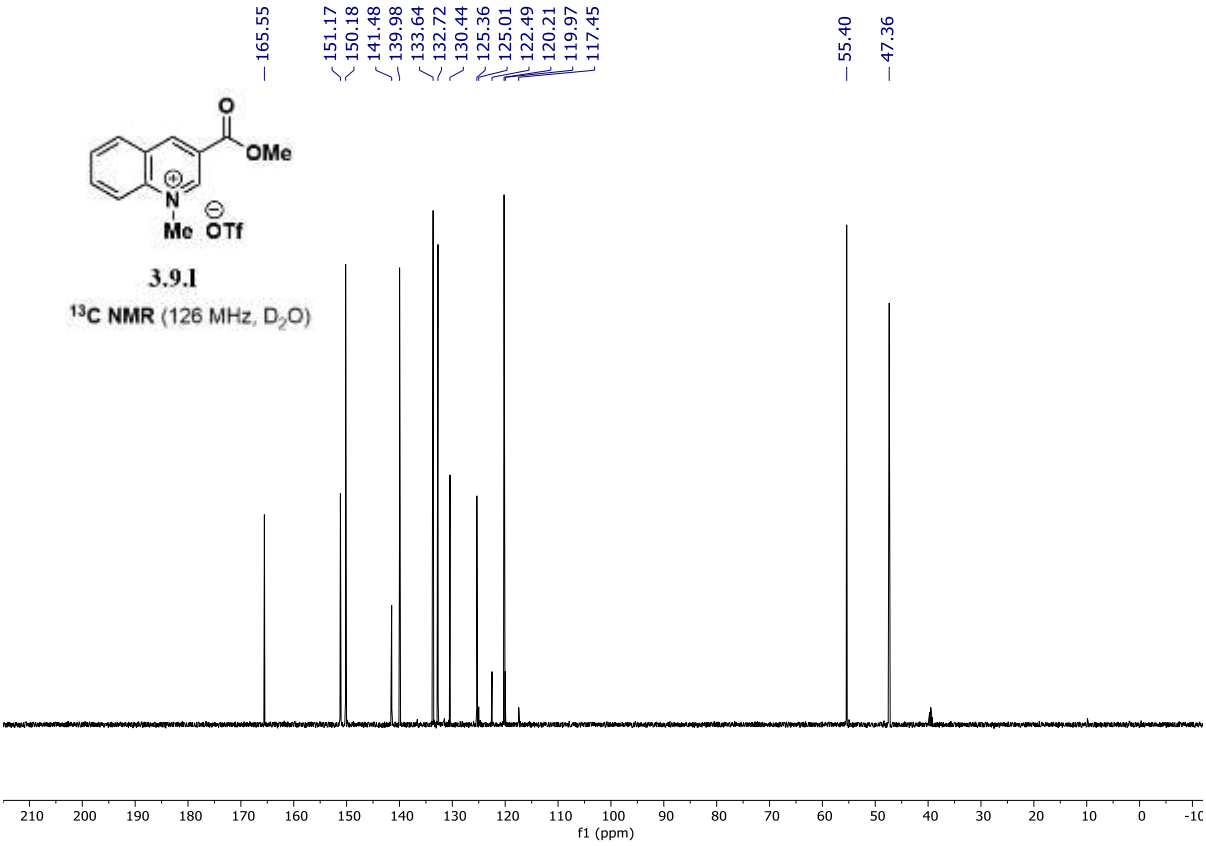
3.9.k

^{19}F NMR (471 MHz, CD_3OD)



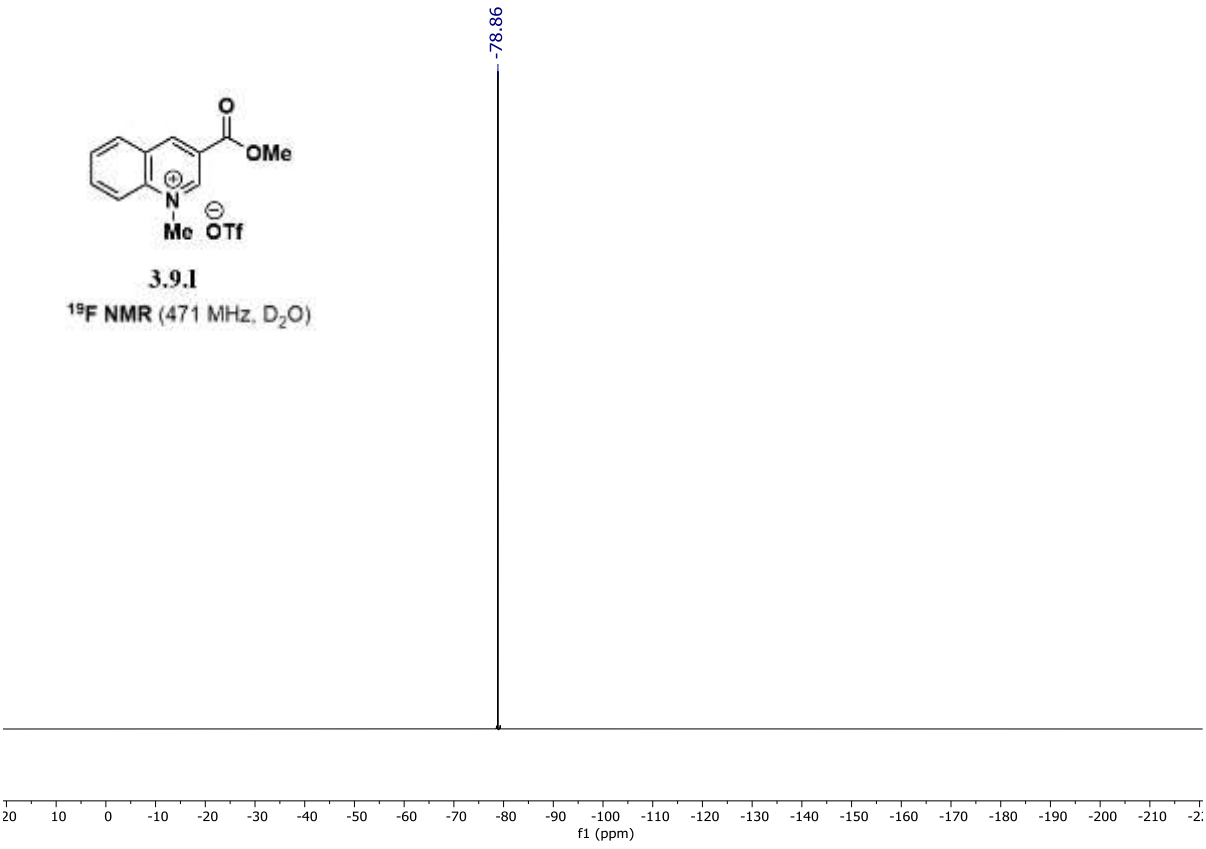
3.9.l

^{1}H NMR (500 MHz, D_2O)



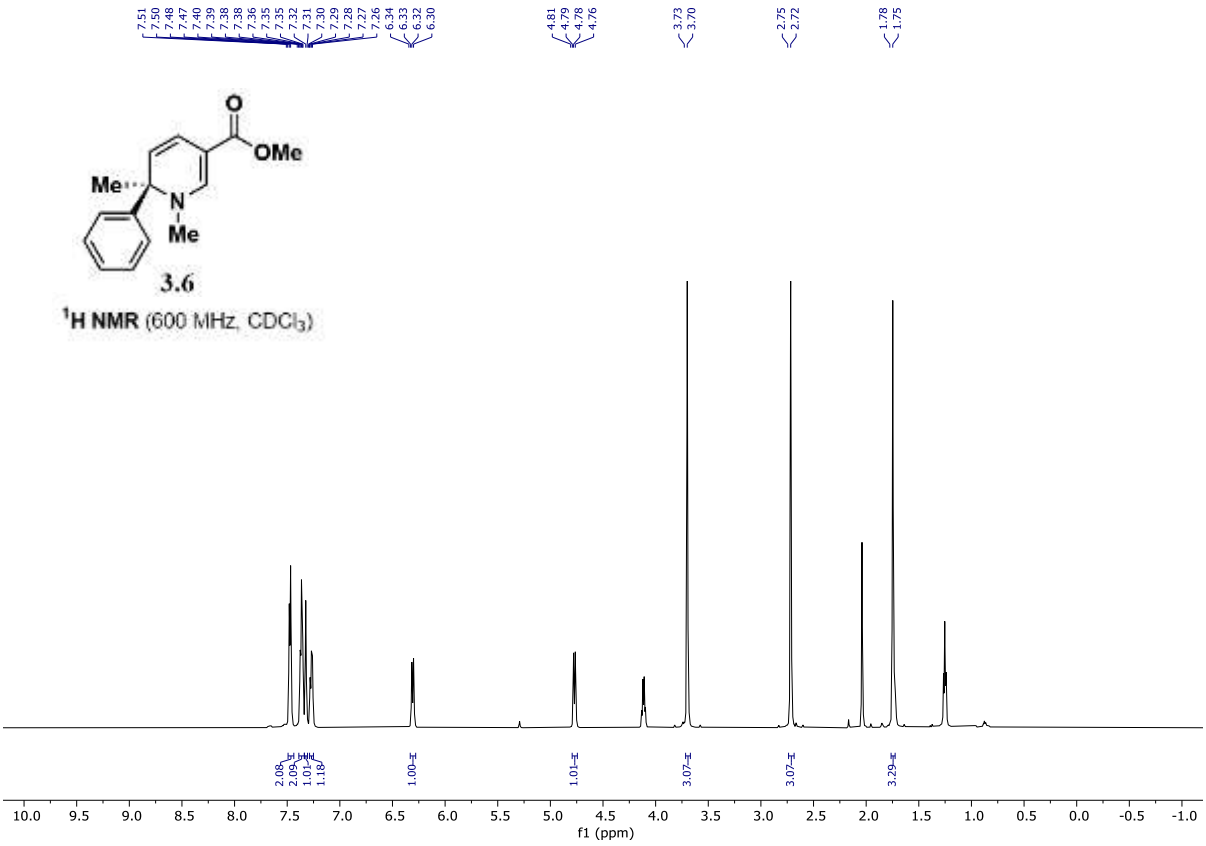
3.9.1

^{13}C NMR (126 MHz, D_2O)



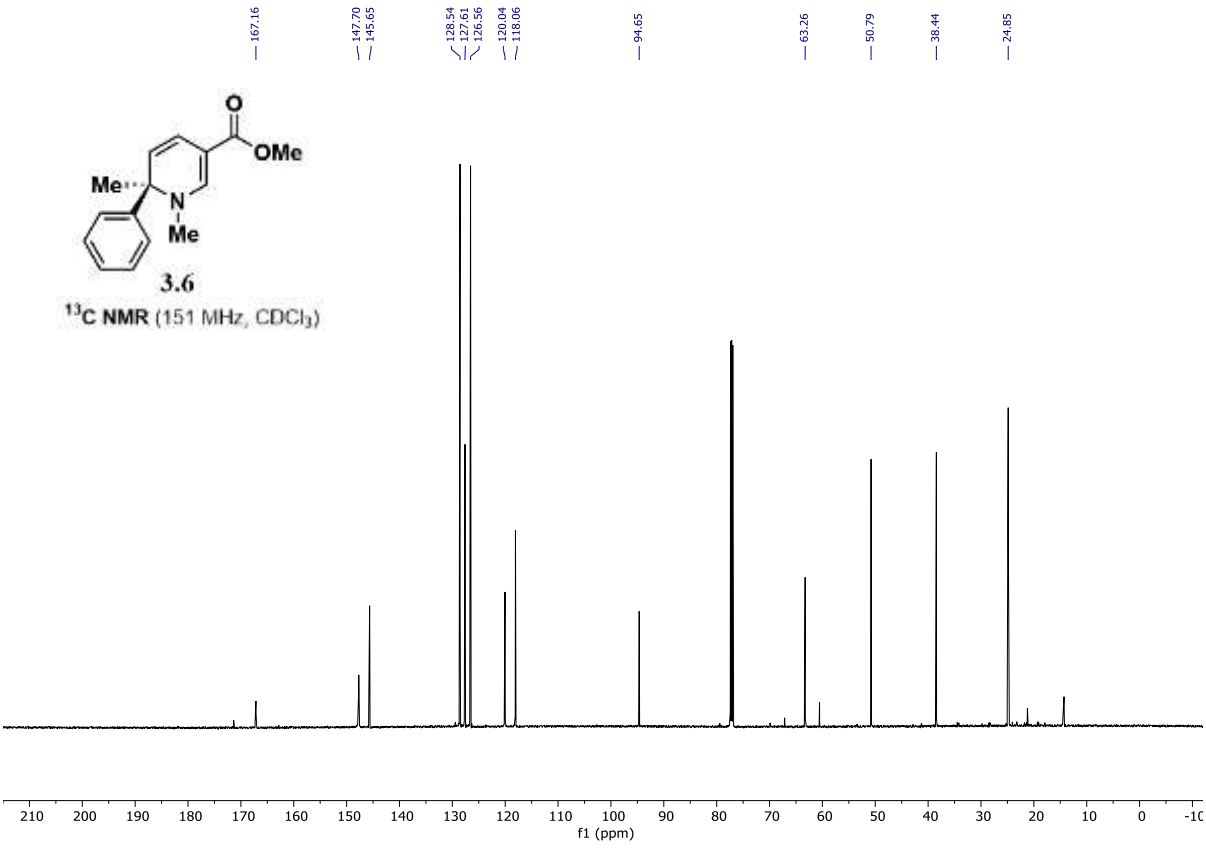
3.9.1

^{19}F NMR (471 MHz, D_2O)



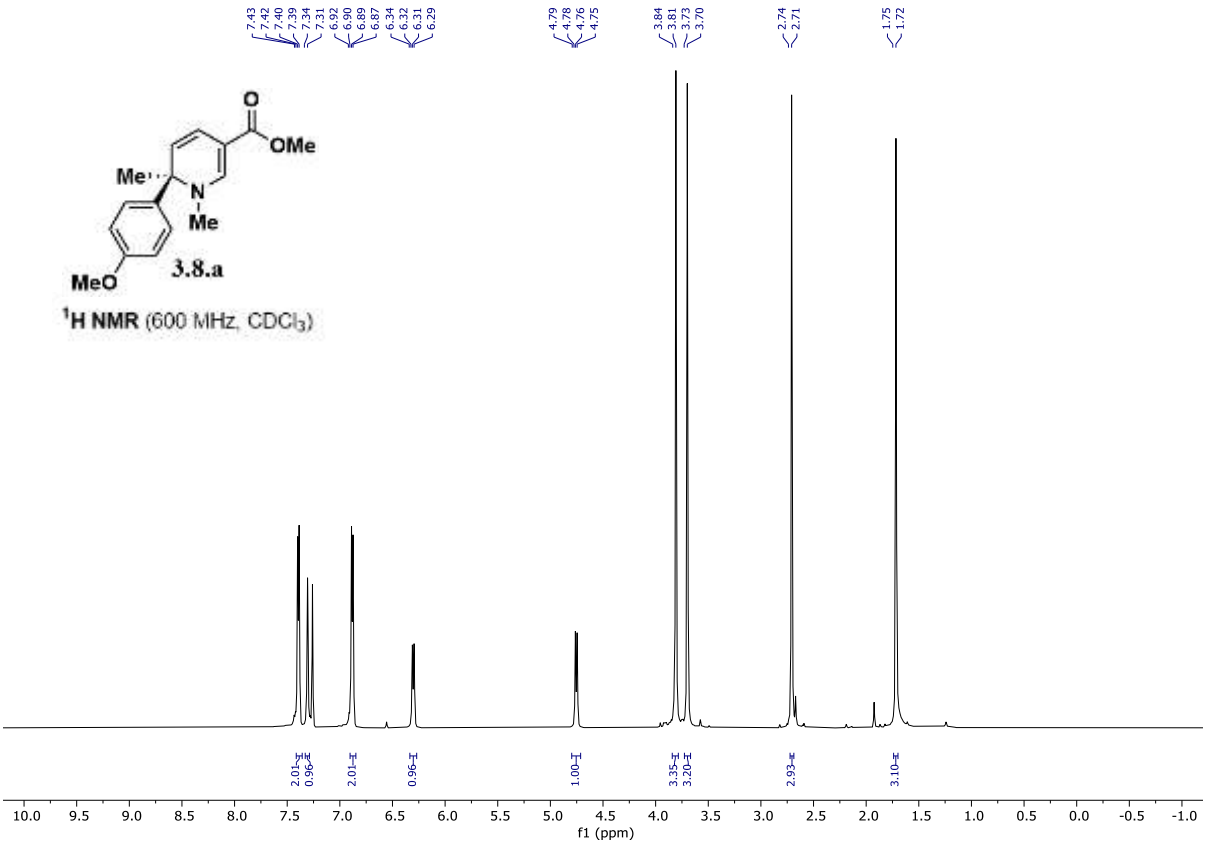
3.6

^{1}H NMR (600 MHz, $CDCl_3$)

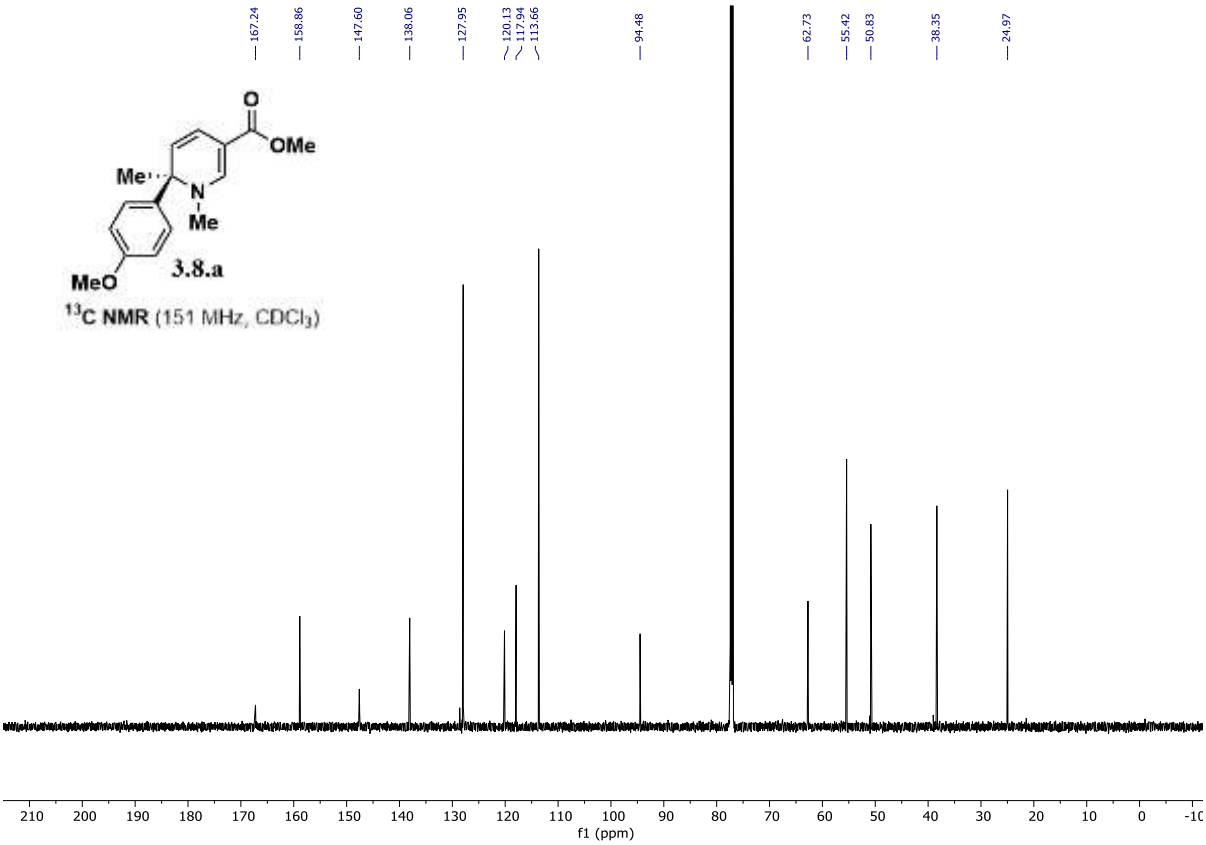


3.6

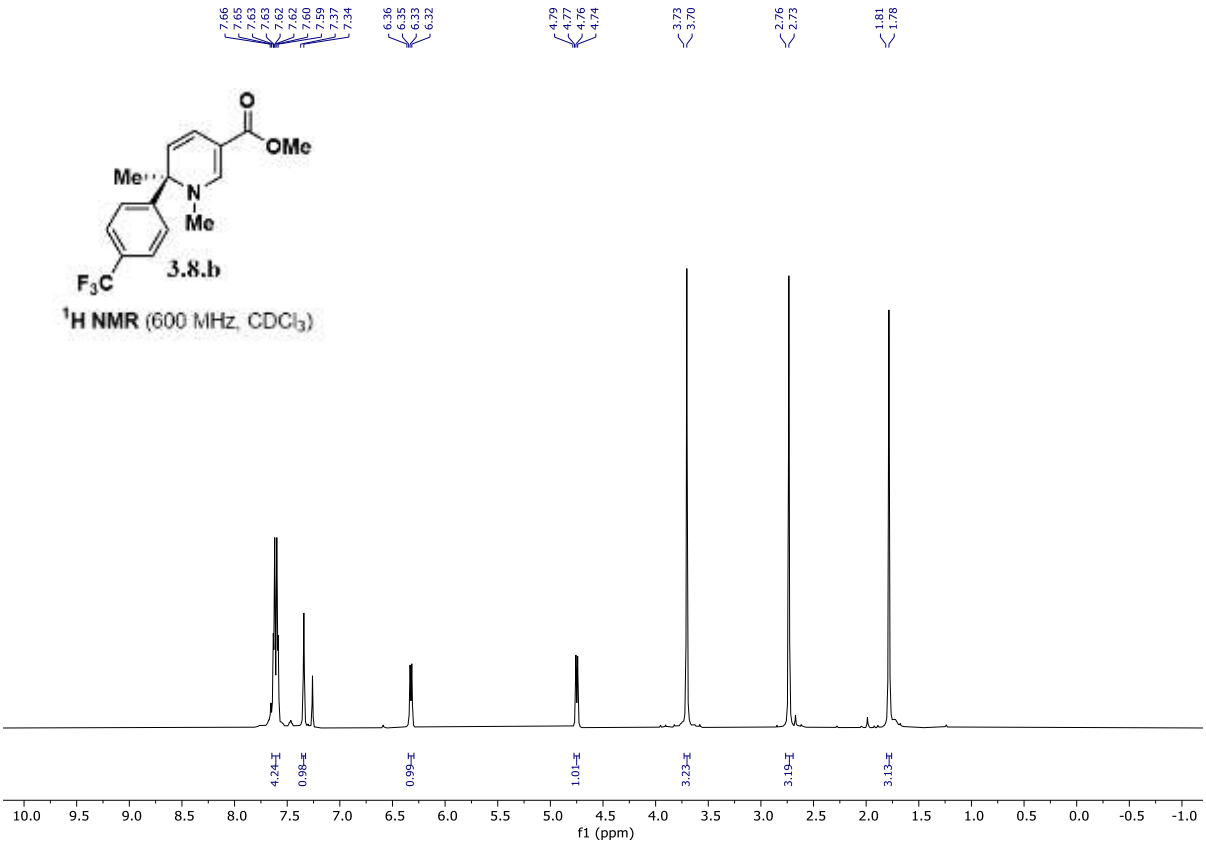
^{13}C NMR (151 MHz, $CDCl_3$)



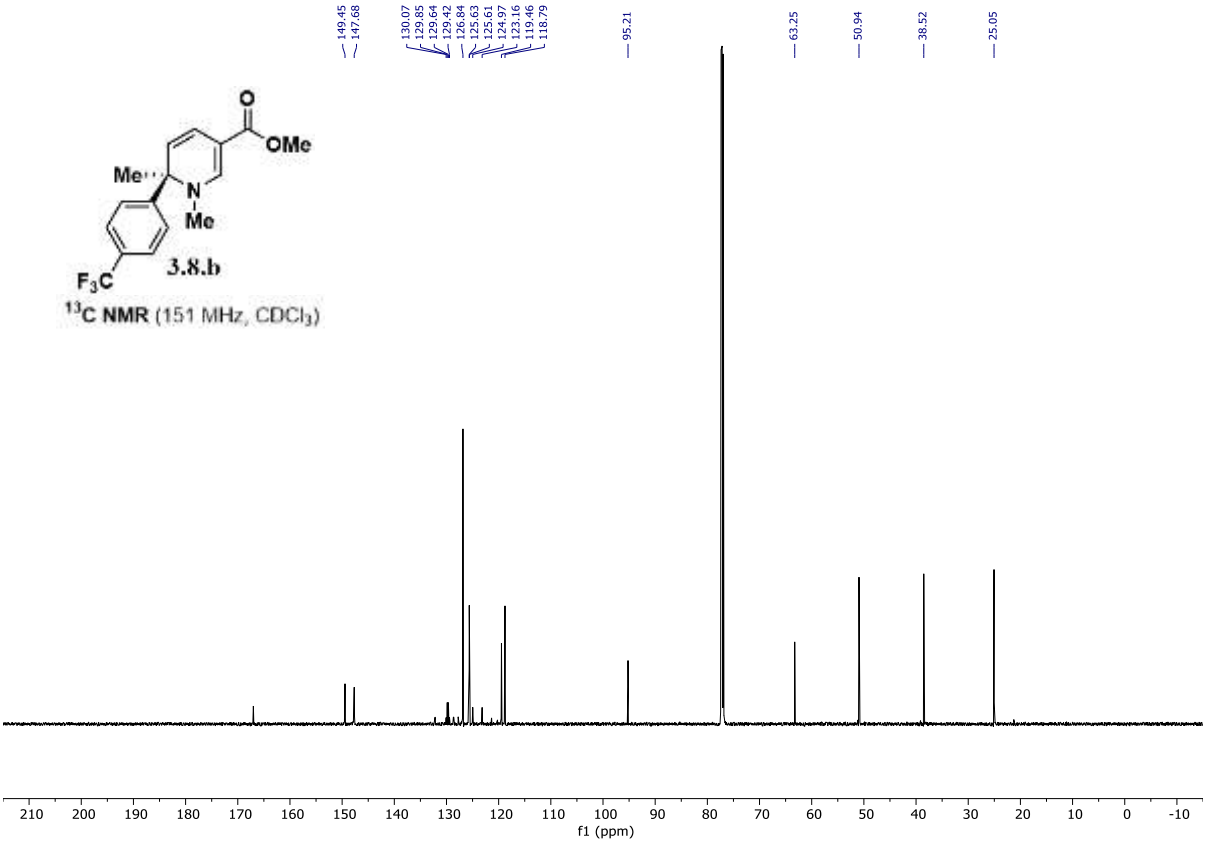
^{1}**H NMR** (600 MHz, $CDCl_3$)



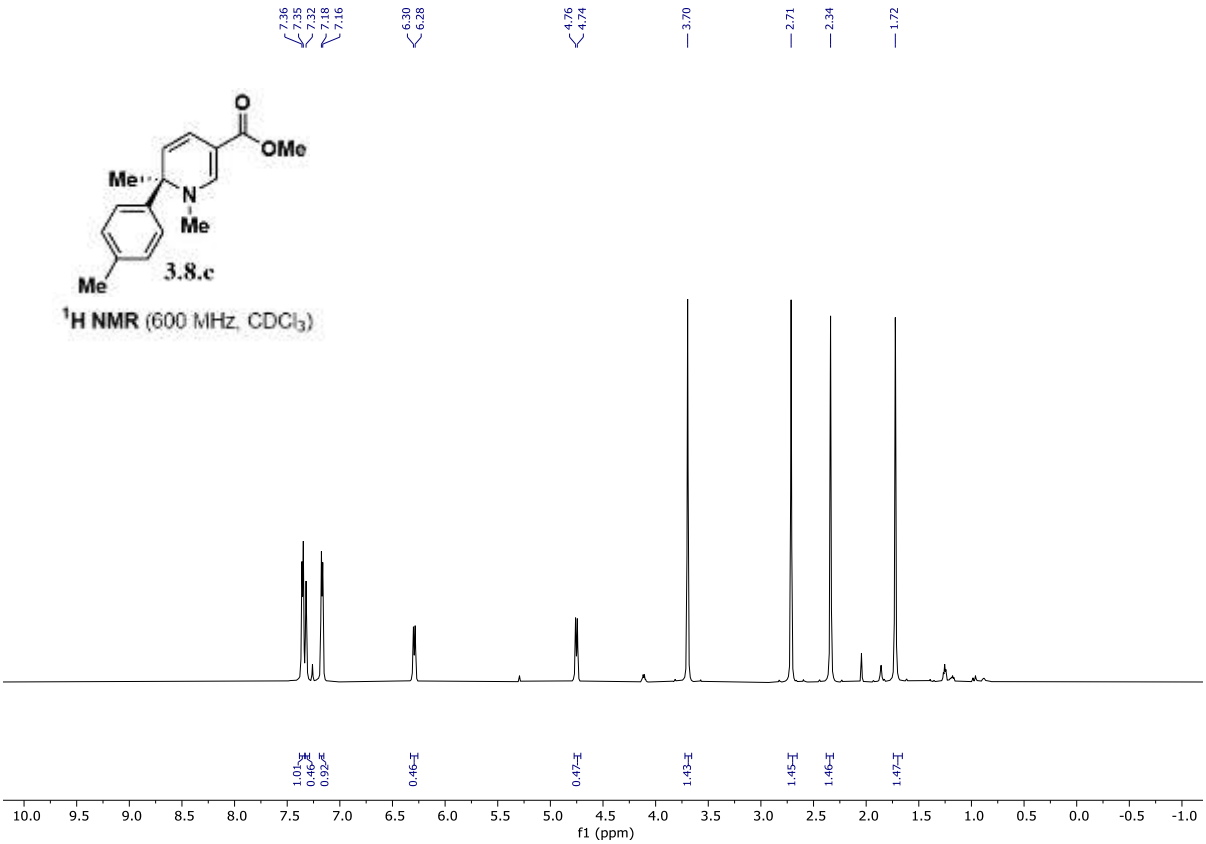
^{13}**C NMR** (151 MHz, $CDCl_3$)

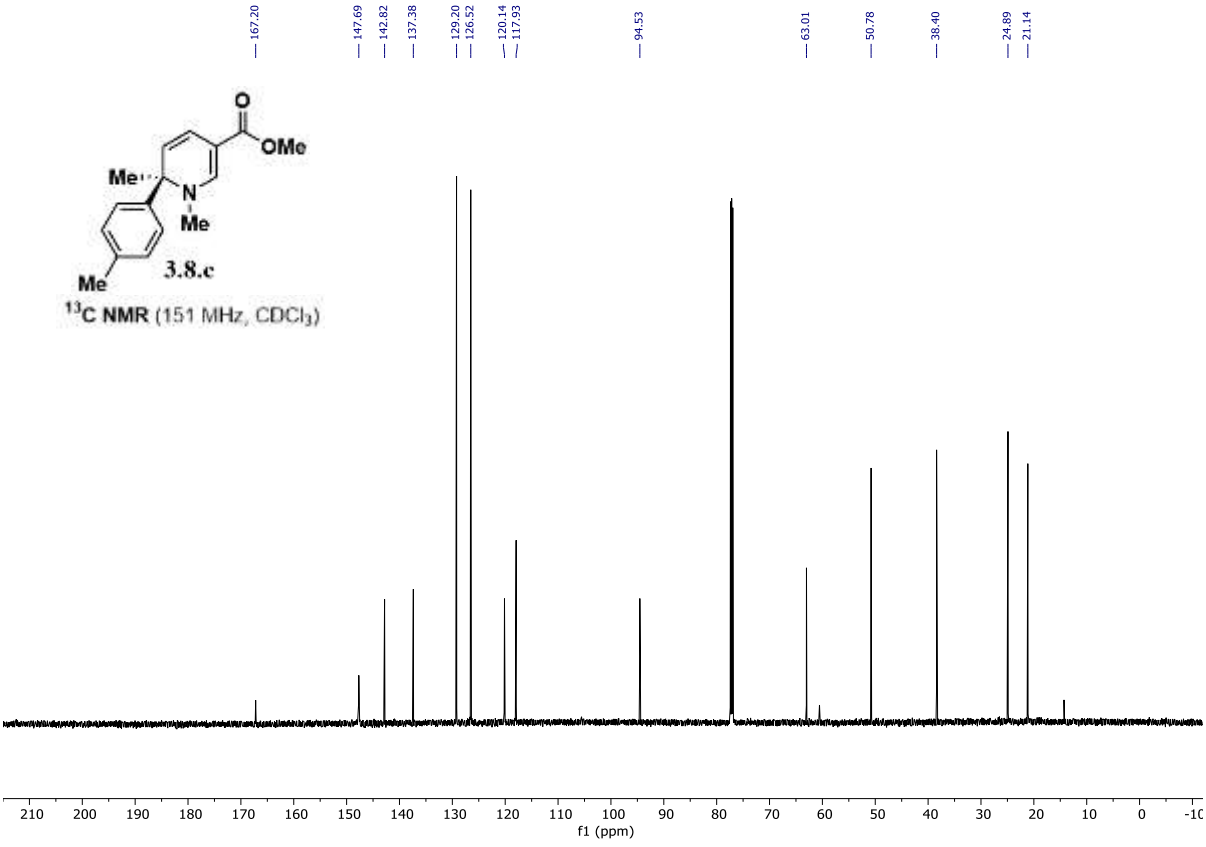


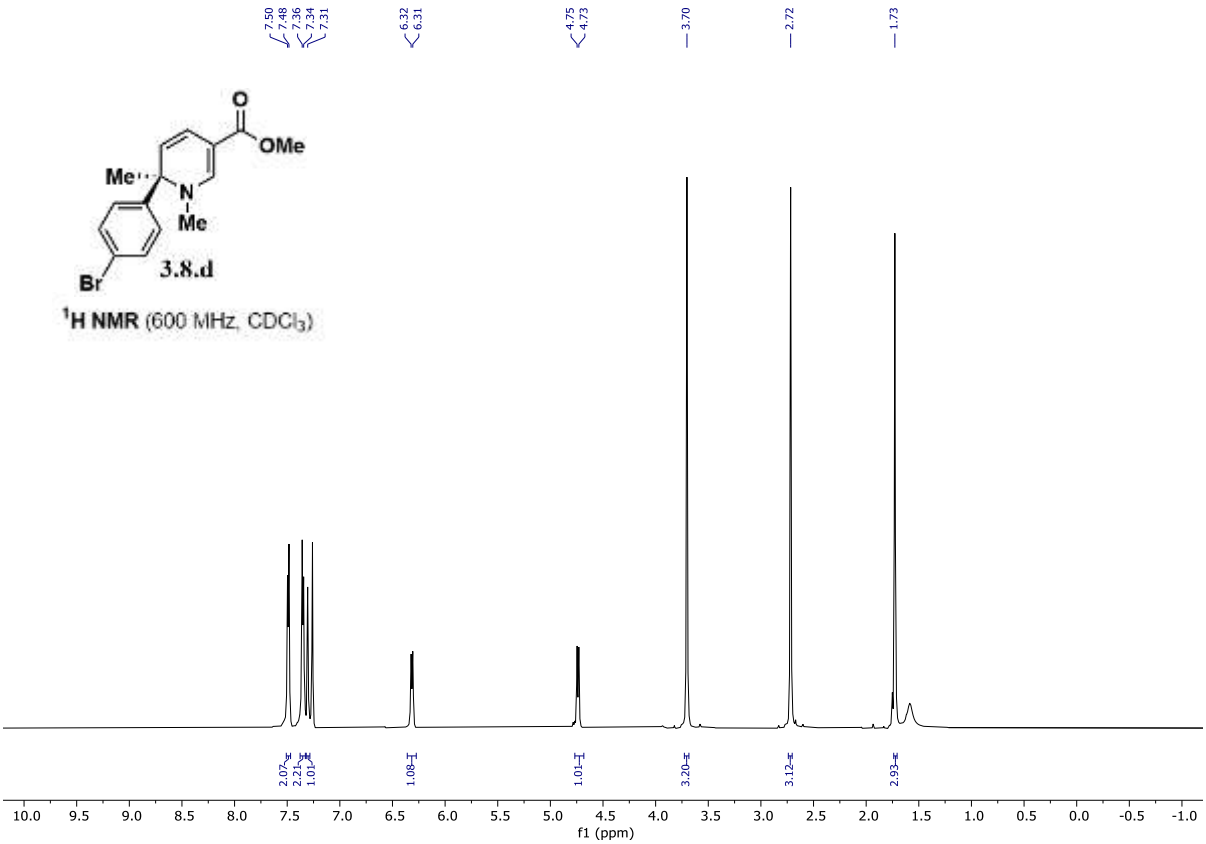
^{1}**H NMR** (600 MHz, $CDCl_3$)



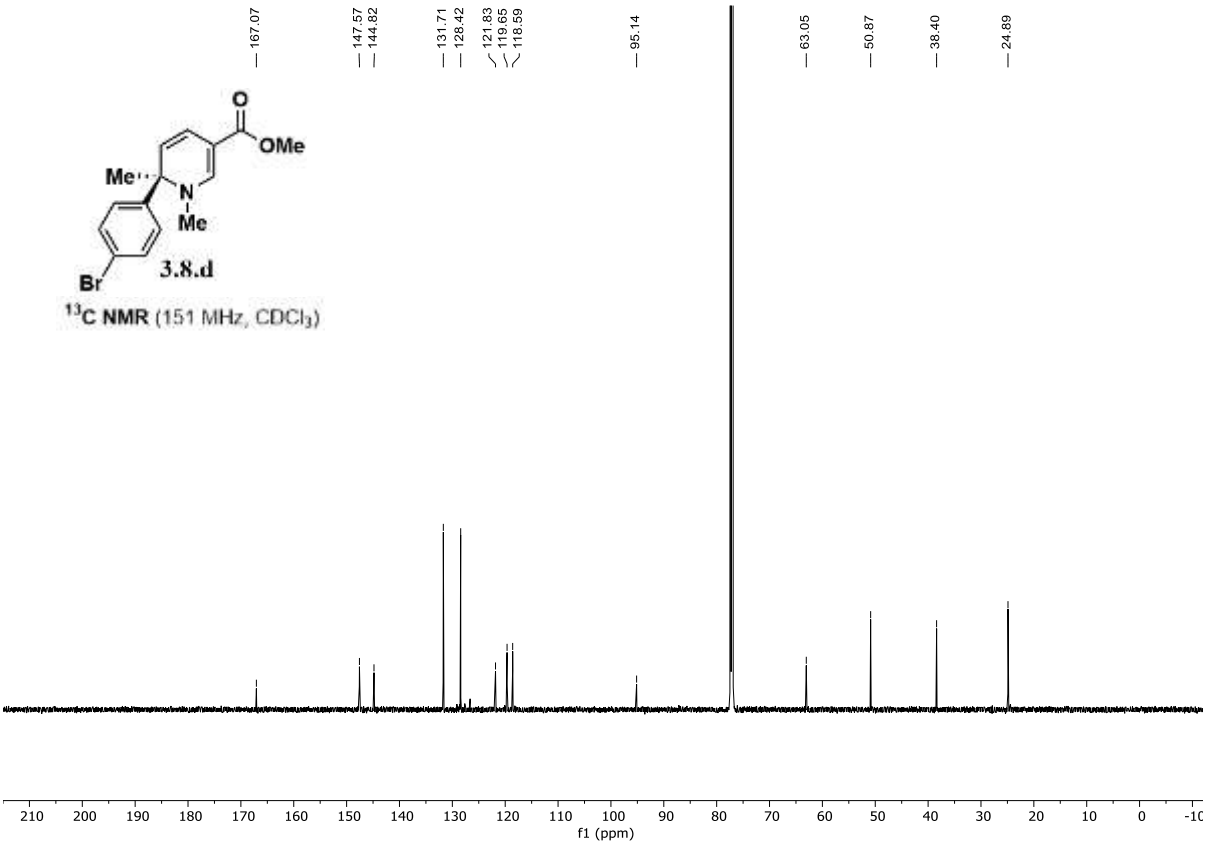
^{13}**C NMR** (151 MHz, $CDCl_3$)


7.36
7.35
7.32
7.18
7.16
6.30
6.28
4.76
4.74
3.70
2.71
2.34
1.72
OMe
Me
N
Me
Me
3.8.c
1H NMR (600 MHz, CDCl3)
1.01
0.46
0.92
0.46
0.47
1.43
1.45
1.46
1.47
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 -0.5 -1.0
f1 (ppm)

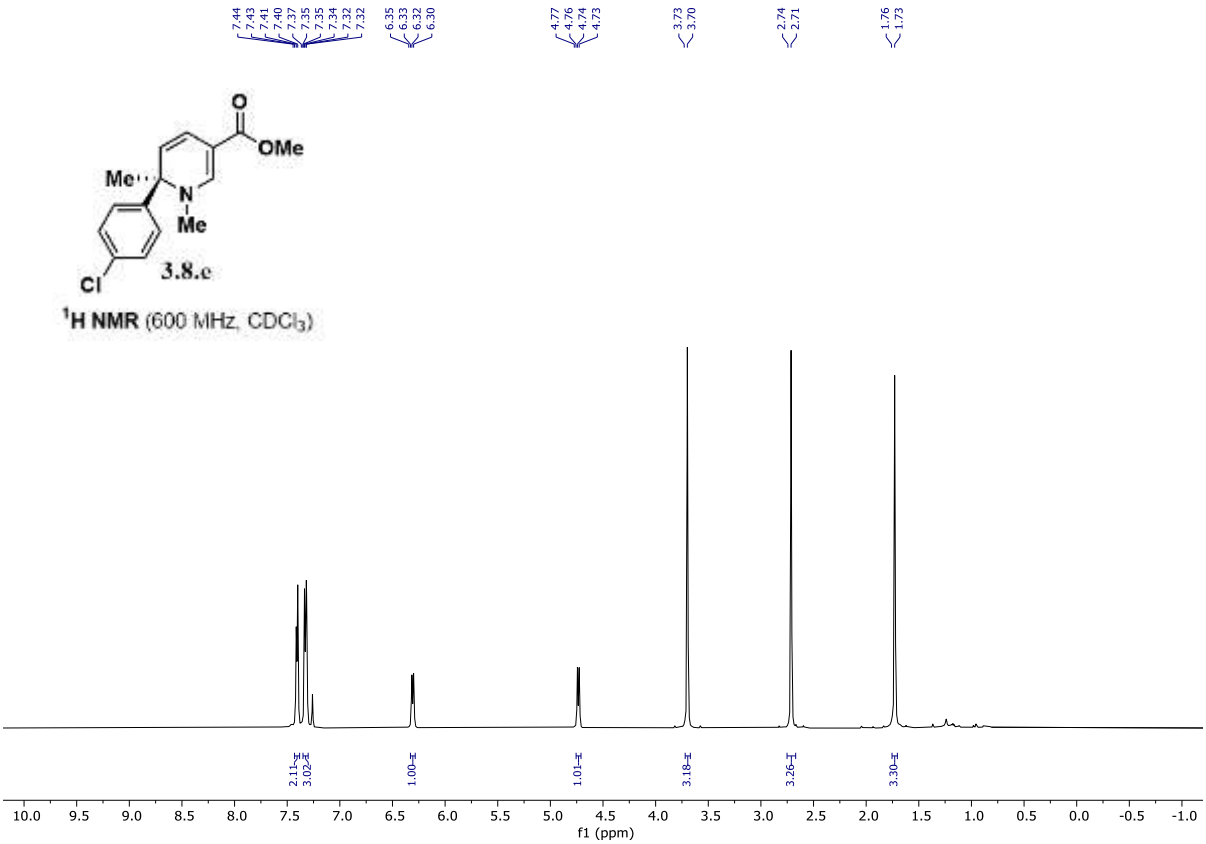

167.20
147.69
142.82
137.38
129.20
126.52
120.14
117.93
94.53
63.01
50.78
38.40
24.89
21.14
OMe
Me
N
Me
Me
3.8.c
13C NMR (151 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)



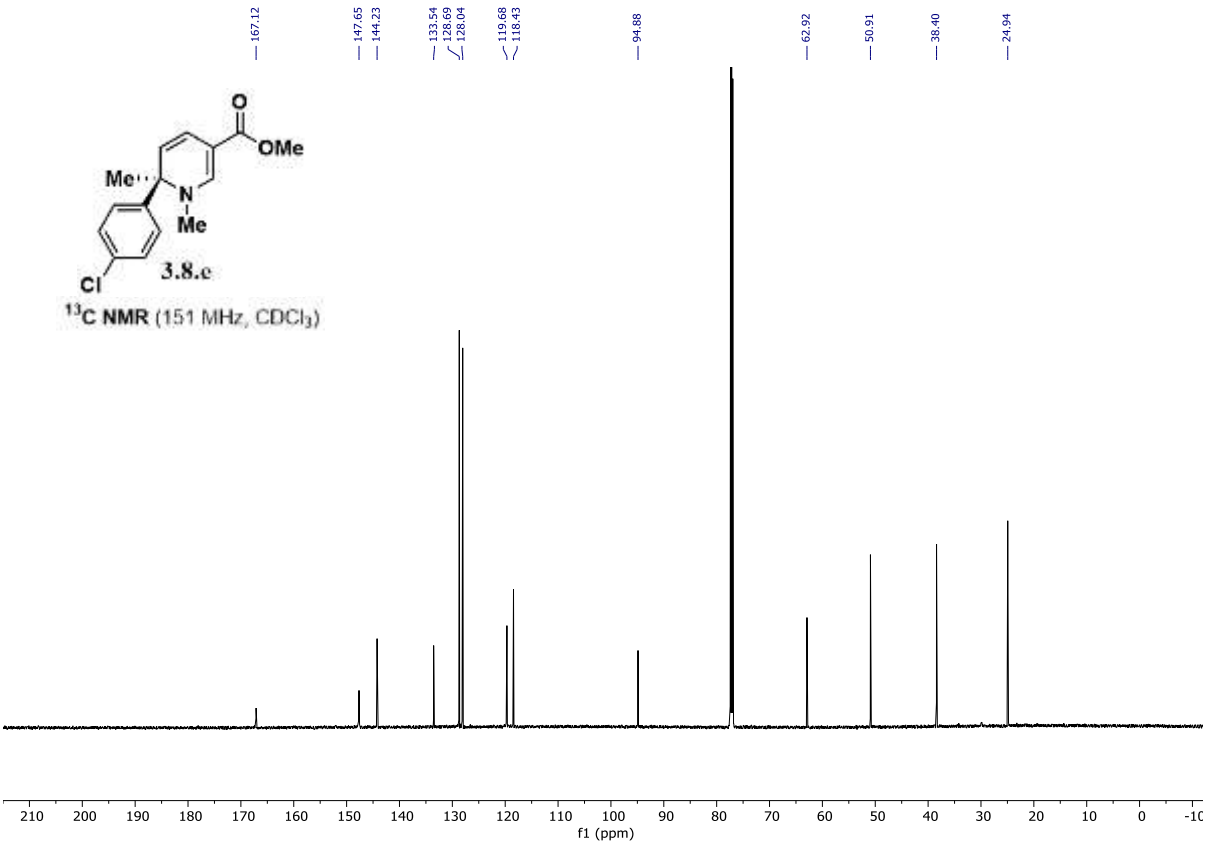
^{1}**H NMR** (600 MHz, $CDCl_3$)



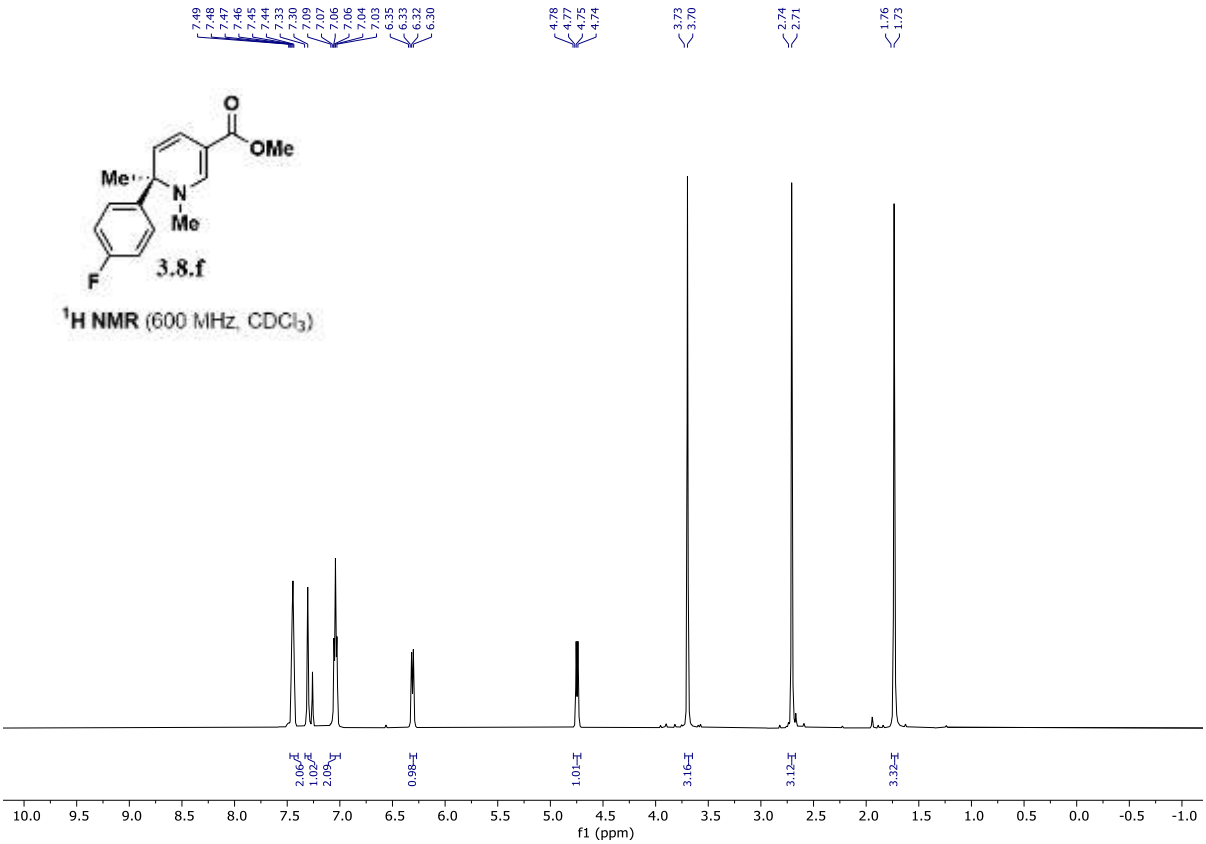
^{13}**C NMR** (151 MHz, $CDCl_3$)



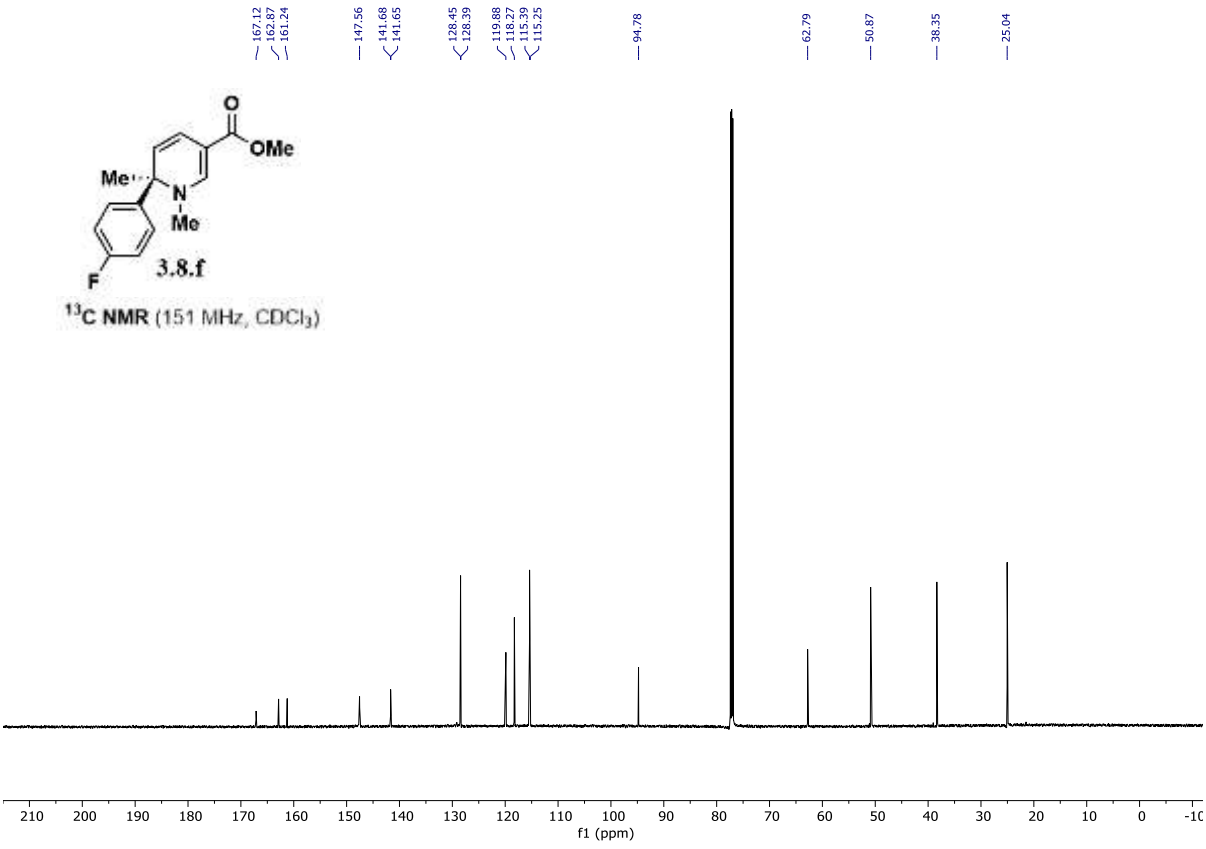
^{1}**H NMR** (600 MHz, $CDCl_3$)



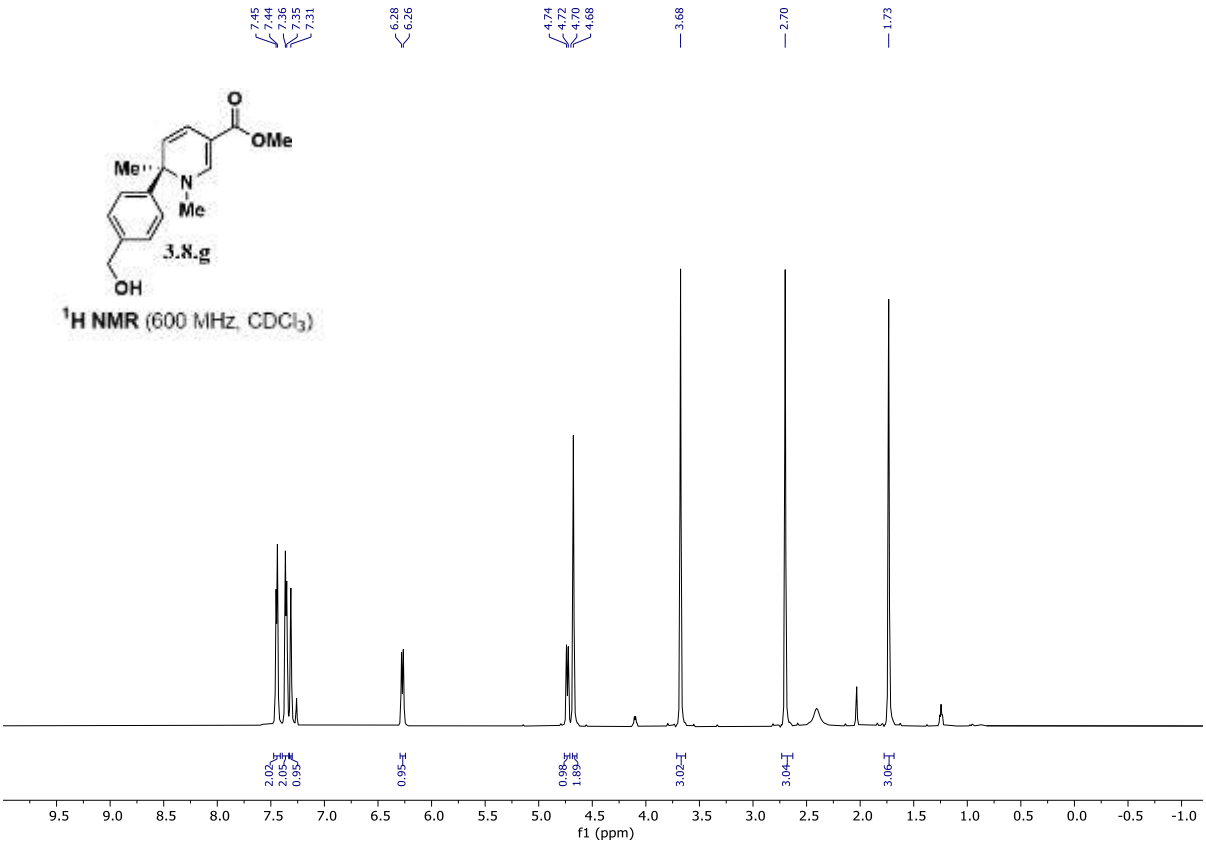
^{13}**C NMR** (151 MHz, $CDCl_3$)



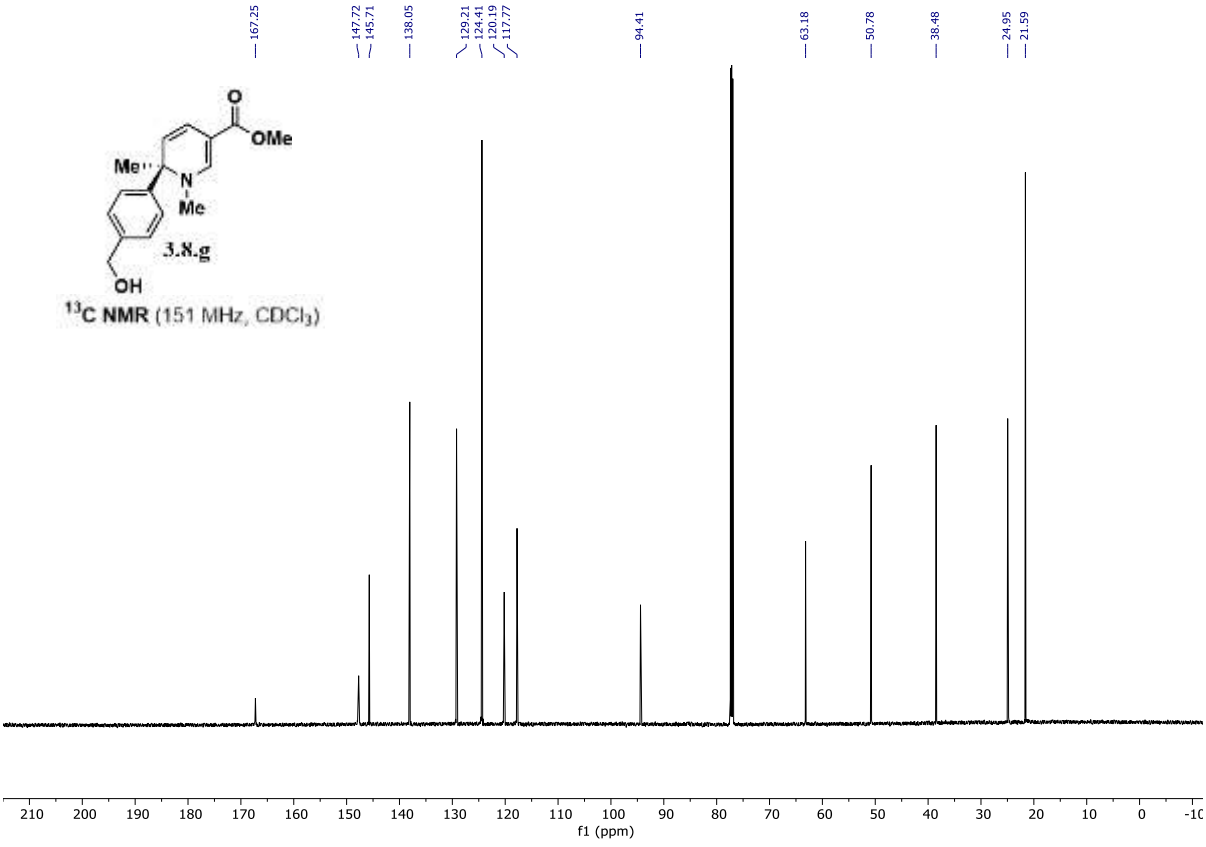
^{1}H NMR (600 MHz, $CDCl_3$)



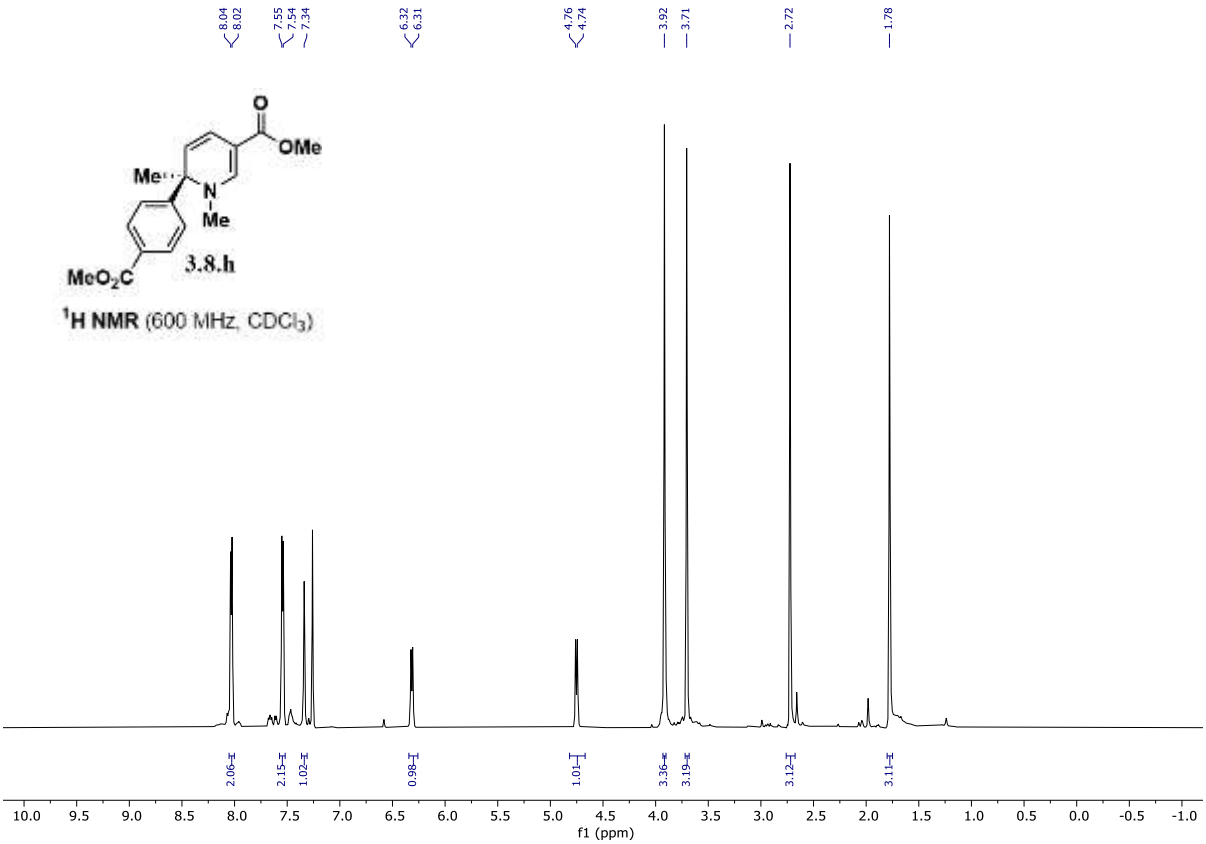
^{13}C NMR (151 MHz, $CDCl_3$)

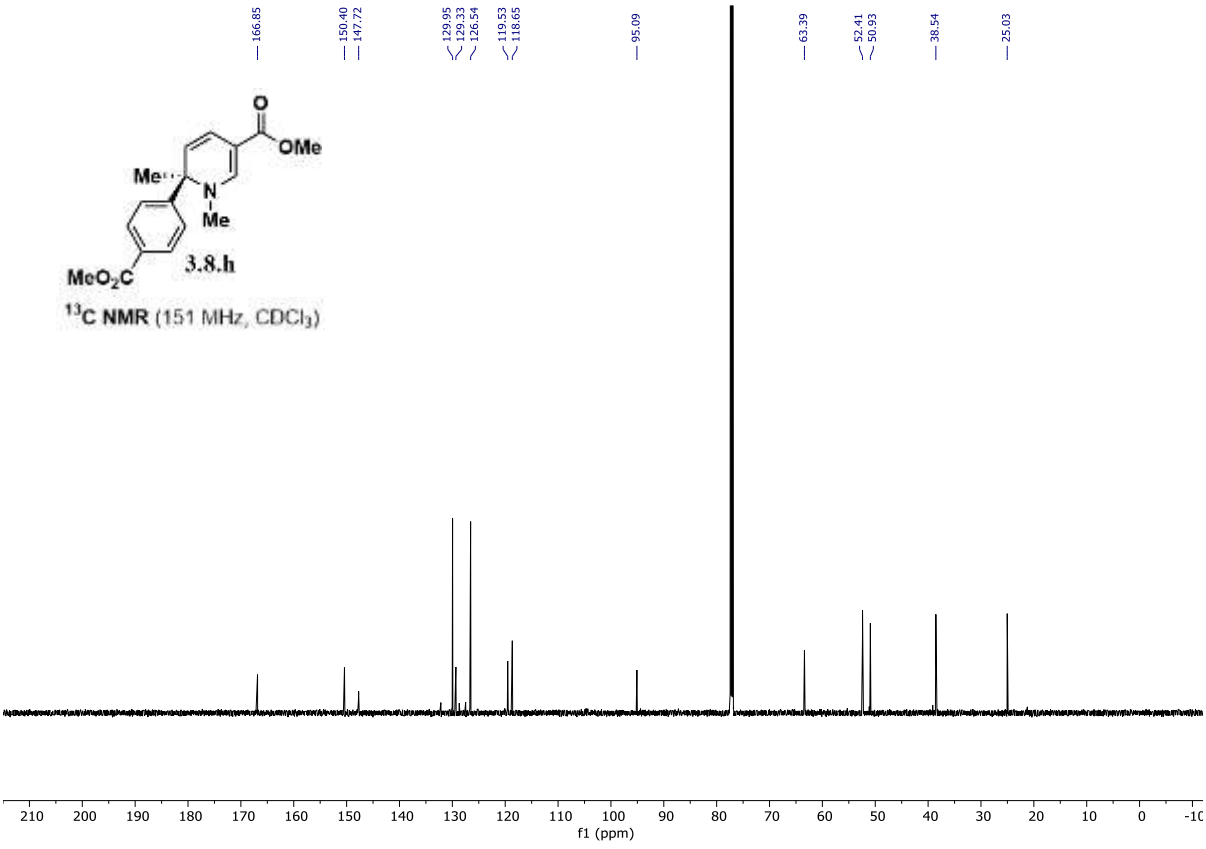


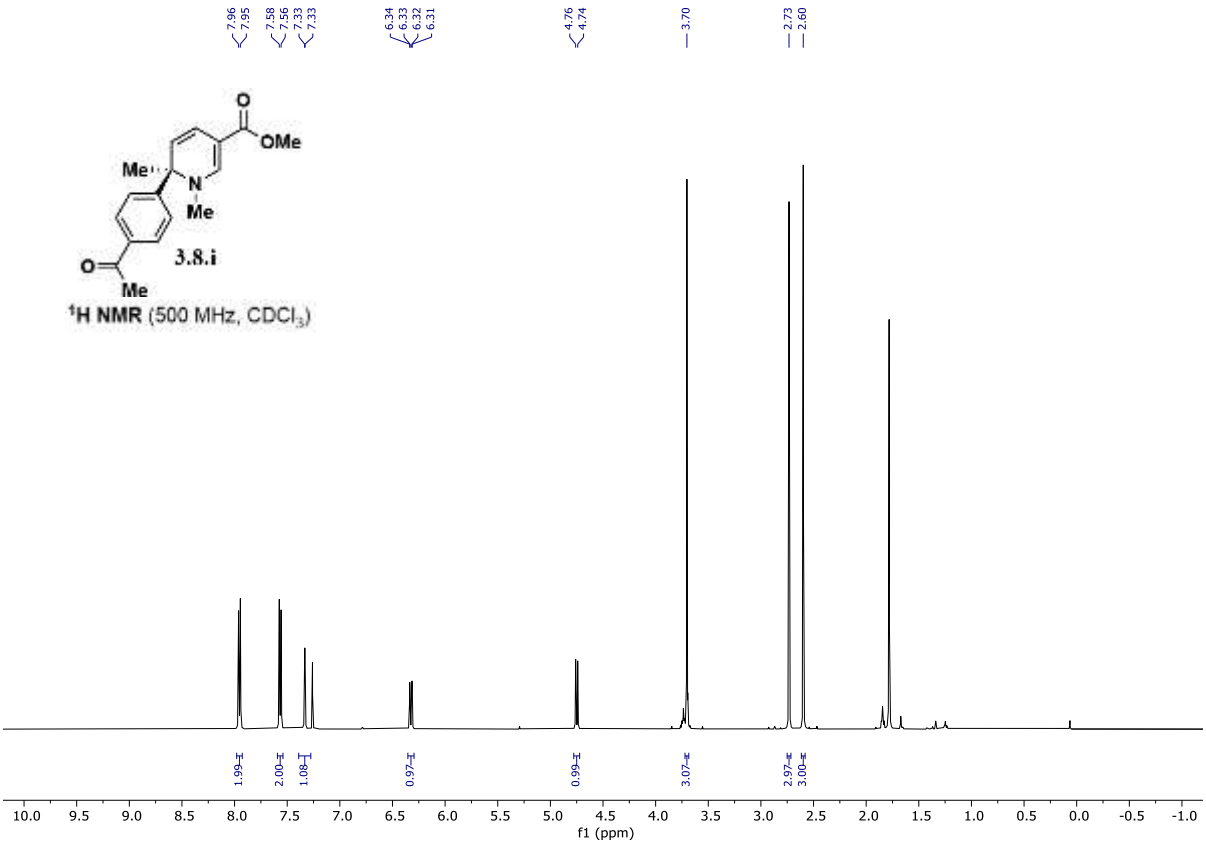
^{1}H NMR (600 MHz, $CDCl_3$)



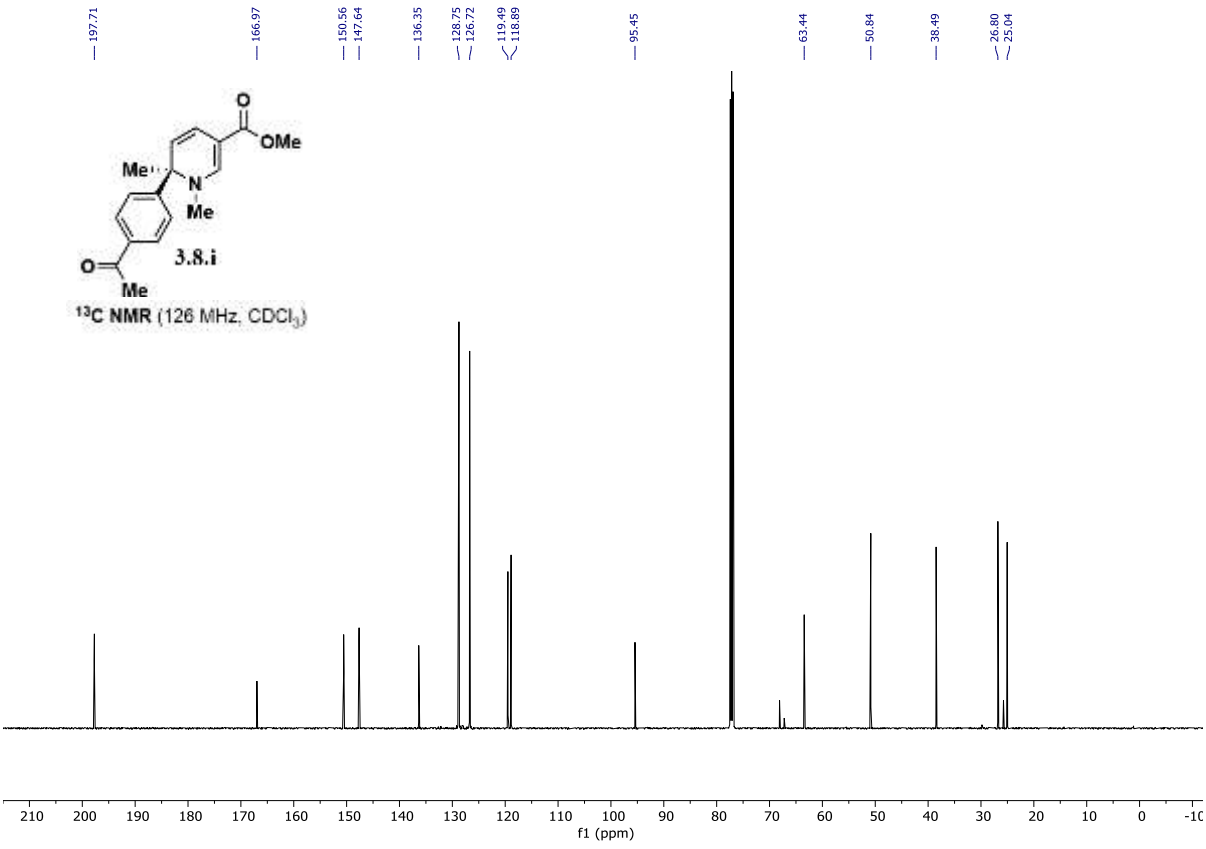
^{13}C NMR (151 MHz, $CDCl_3$)


8.04
8.02
7.55
7.54
7.34
6.32
6.31
4.76
4.74
3.92
3.71
2.72
1.78
O
OMe
Me
N
Me
MeO2C
3.8.h
1H NMR (600 MHz, CDCl3)
2.06
2.15
1.02
0.98
1.01
3.36
3.19
3.12
3.11
f1 (ppm)

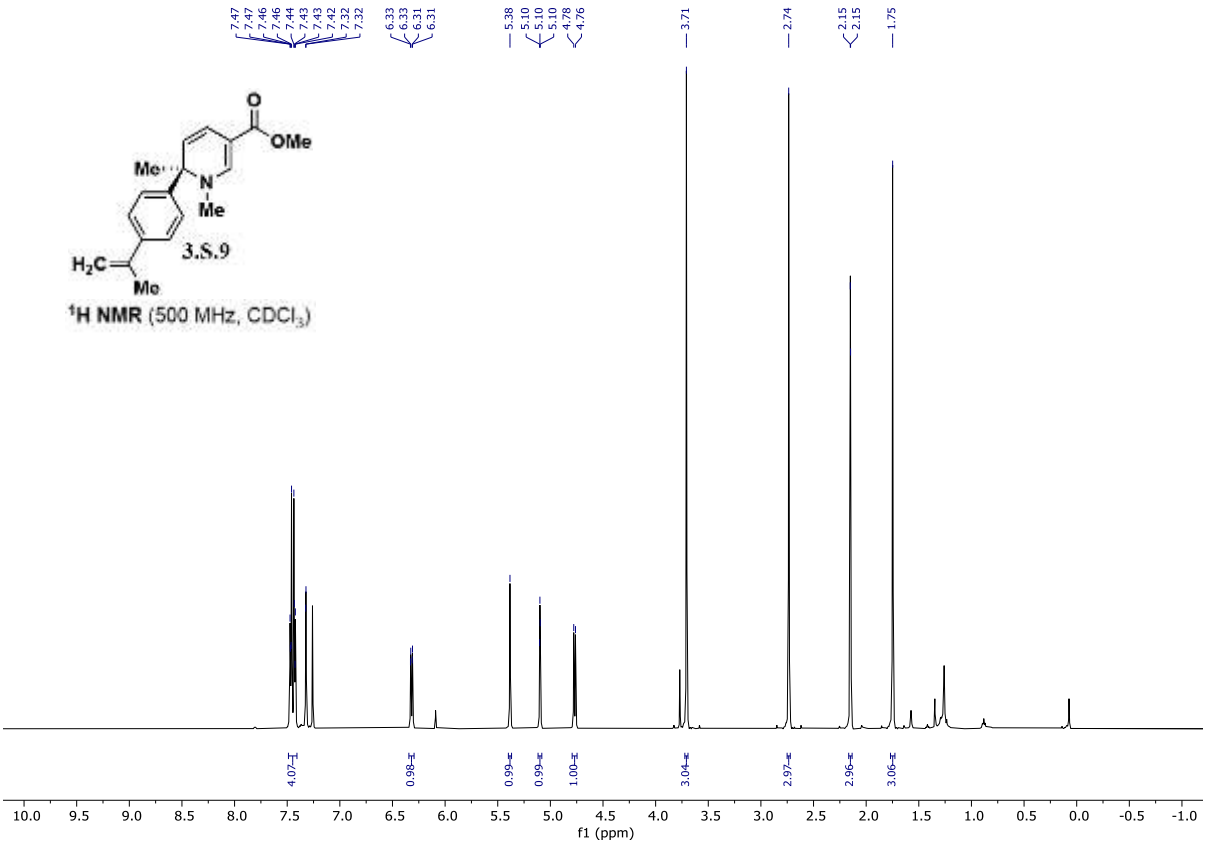

166.85
150.40
147.72
129.95
129.33
126.54
119.53
118.65
95.09
63.39
52.41
50.93
38.54
25.03
O
OMe
Me
N
Me
MeO2C
3.8.h
13C NMR (151 MHz, CDCl3)
f1 (ppm)



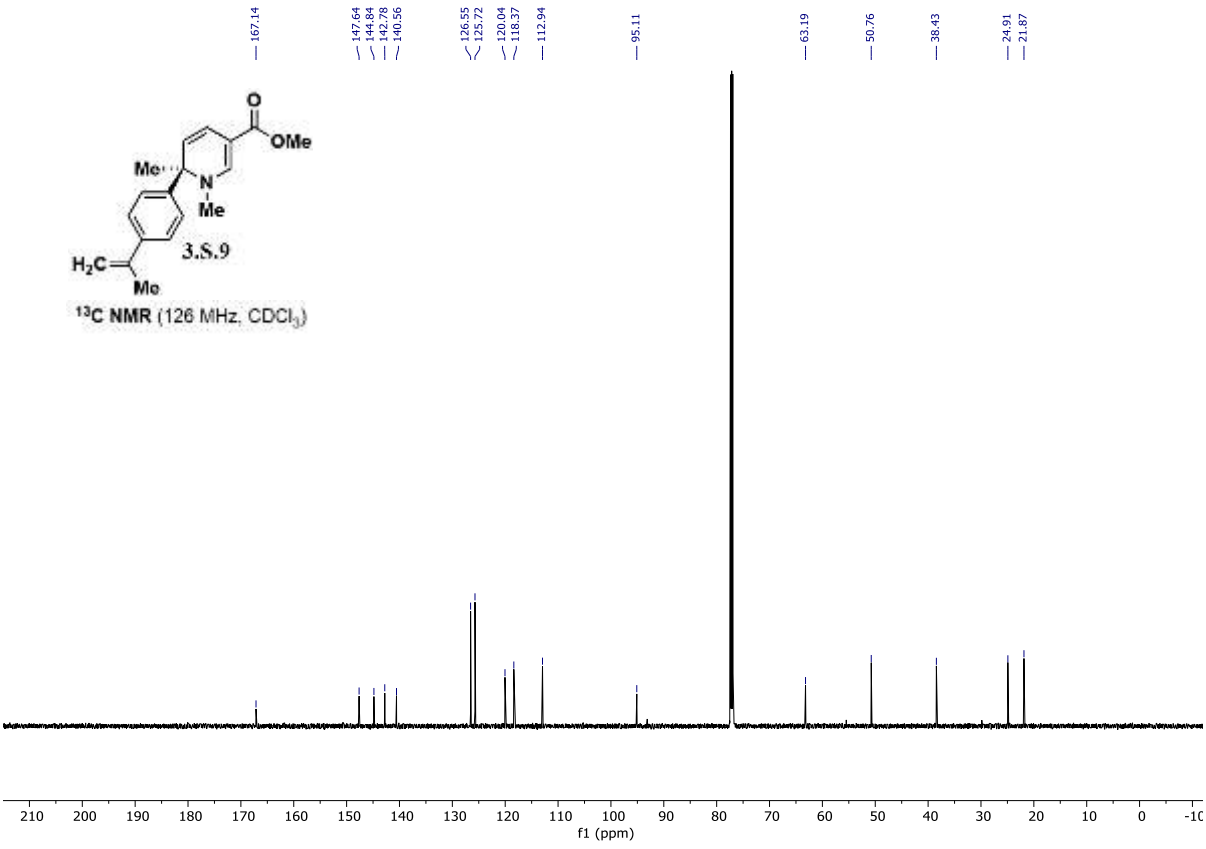
^{1}**H NMR** (500 MHz, $CDCl_3$)



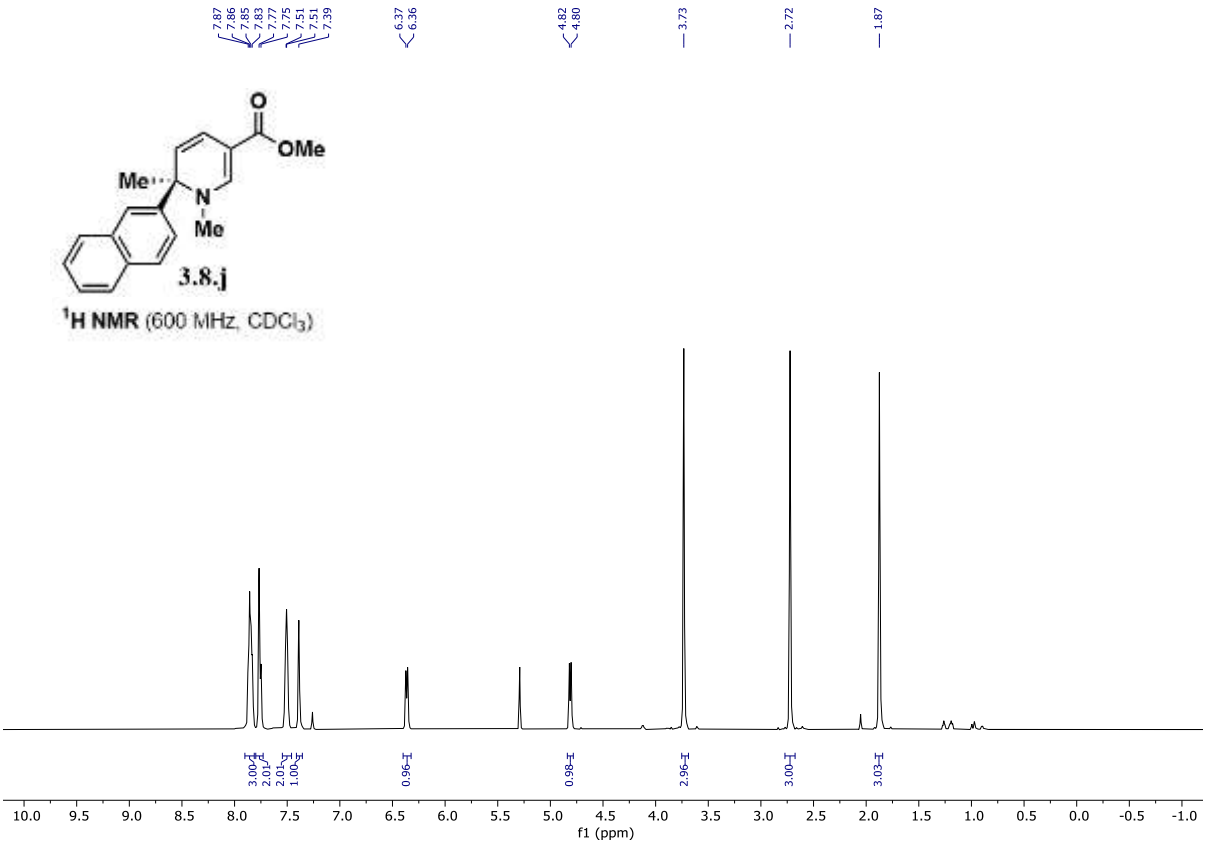
^{13}**C NMR** (126 MHz, $CDCl_3$)



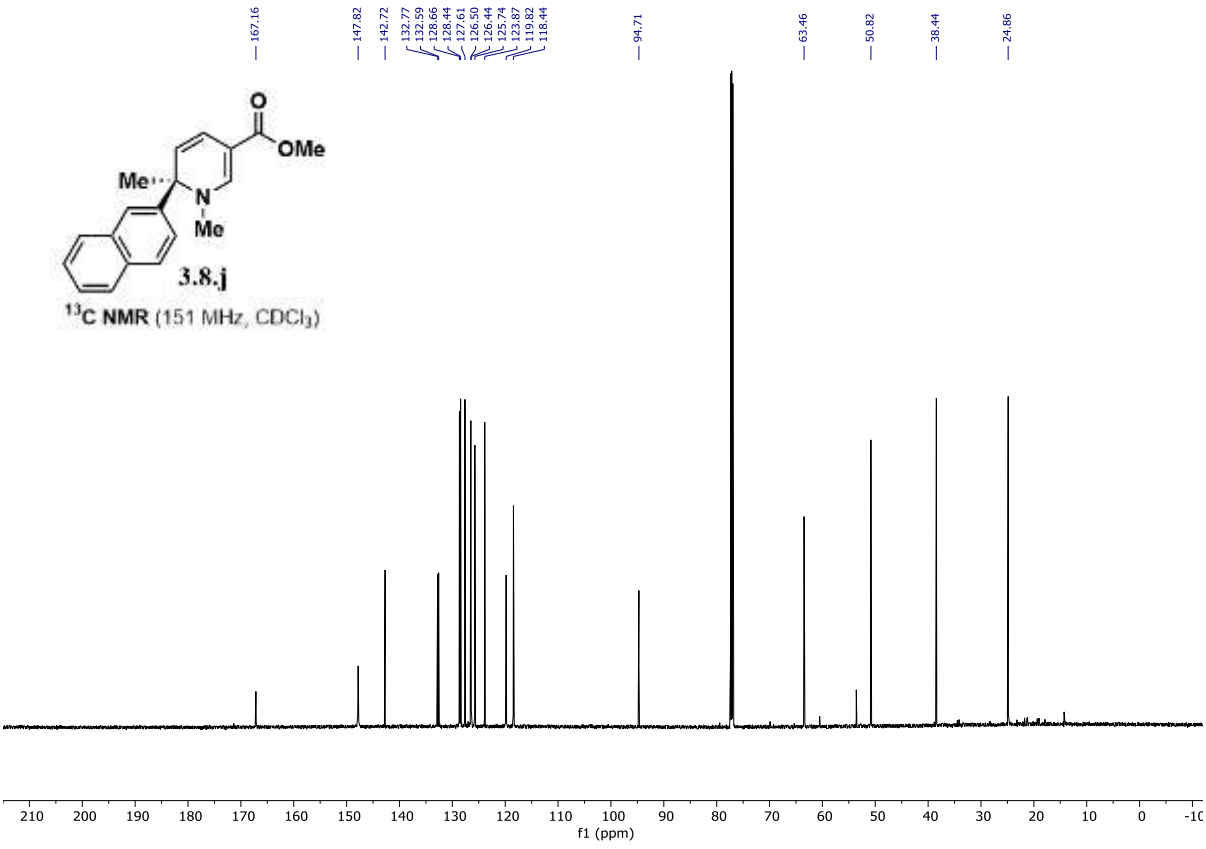
^{1}H NMR (500 MHz, $CDCl_3$)



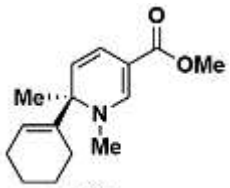
^{13}C NMR (126 MHz, $CDCl_3$)



^{1}H NMR (600 MHz, $CDCl_3$)

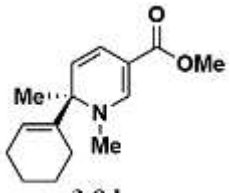


^{13}C NMR (151 MHz, $CDCl_3$)



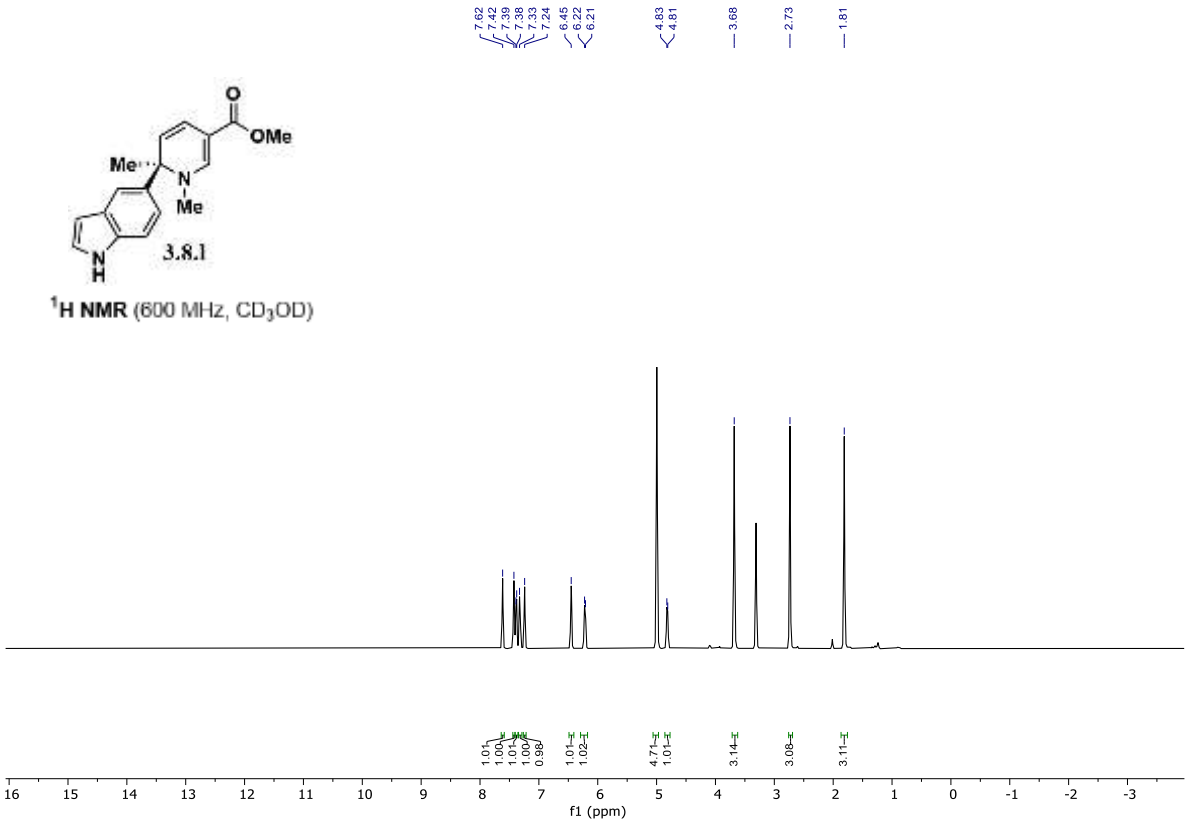
3.8.k

^{1}H NMR (600 MHz, $CDCl_3$)

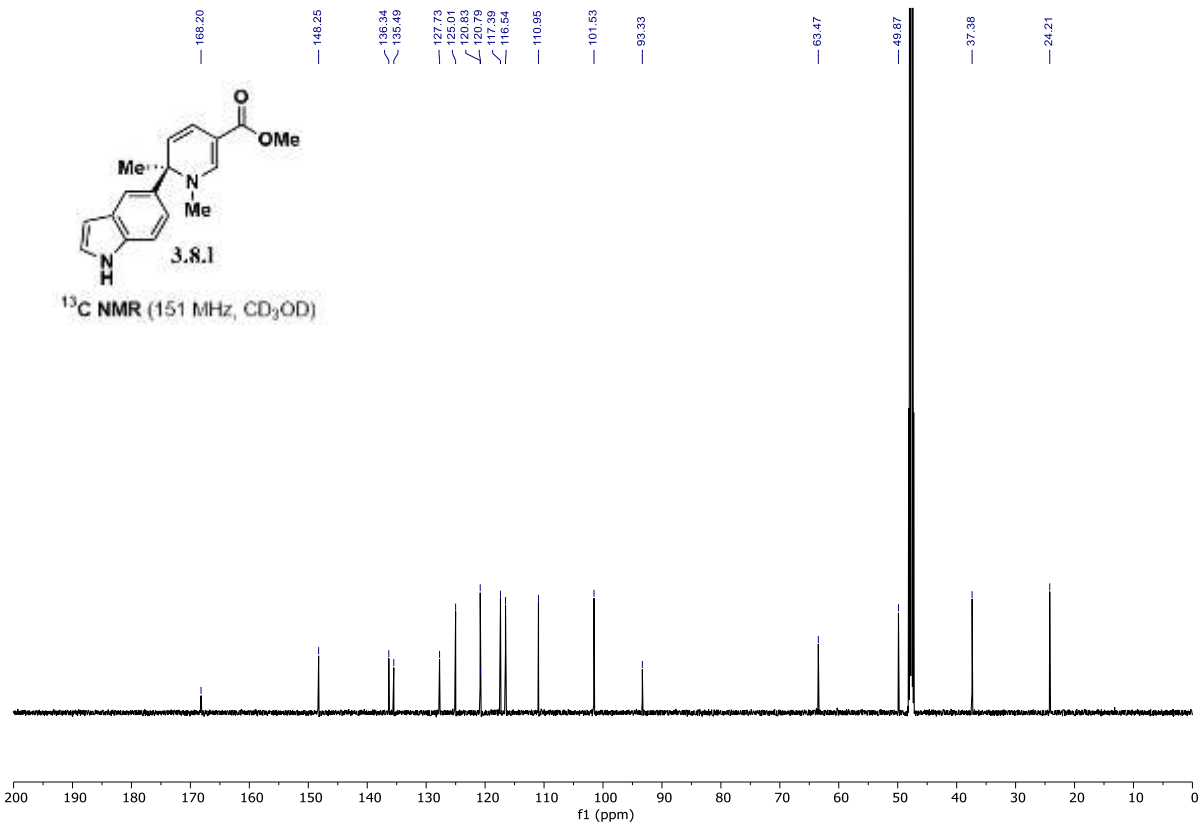


3.8.k

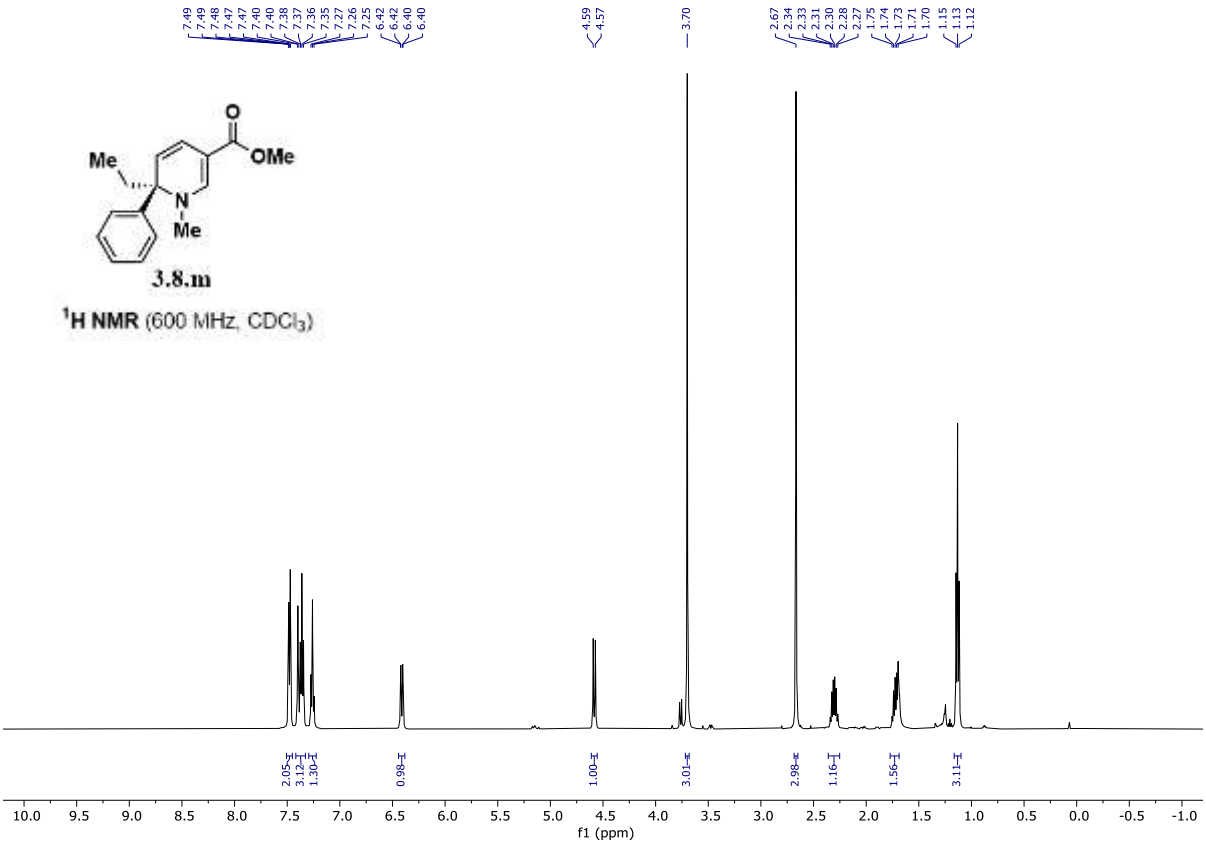
^{13}C NMR (151 MHz, $CDCl_3$)



^{1}**H NMR** (600 MHz, CD_3OD)

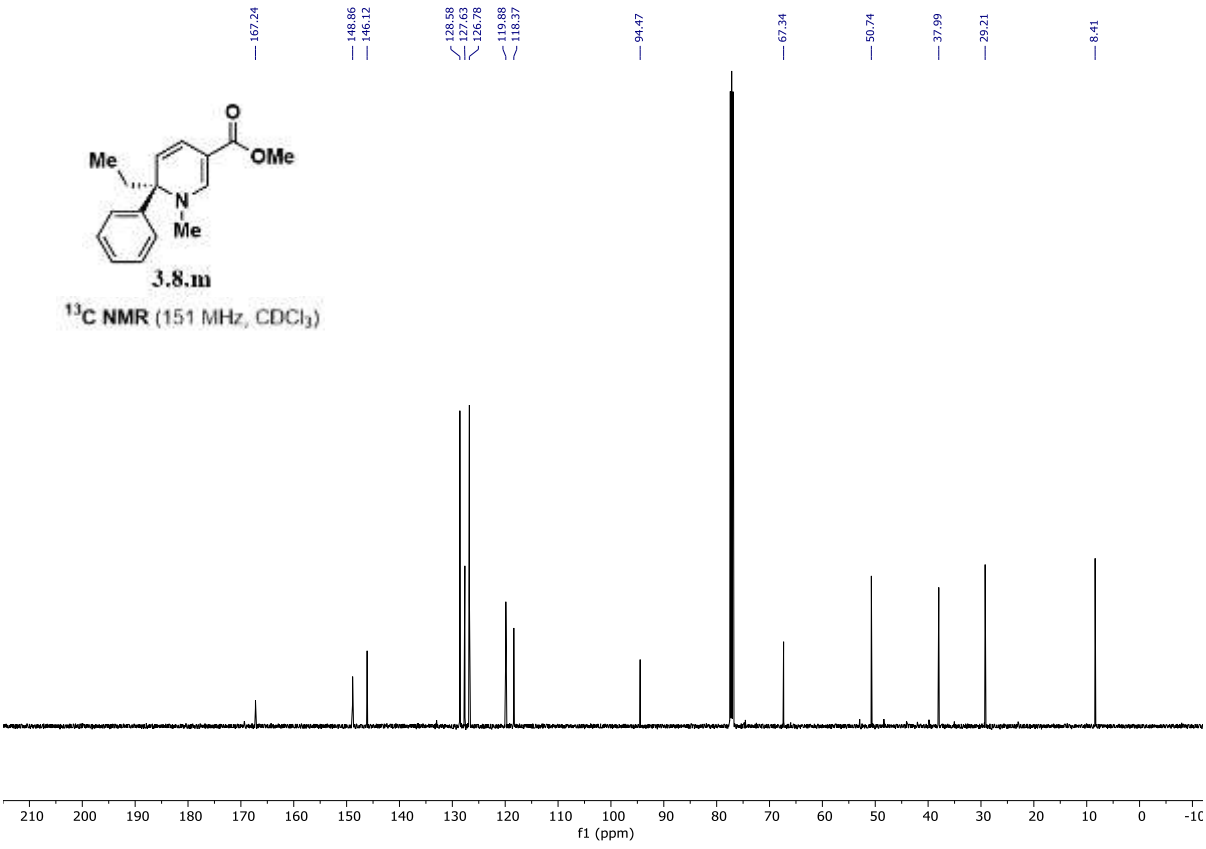


^{13}**C NMR** (151 MHz, CD_3OD)



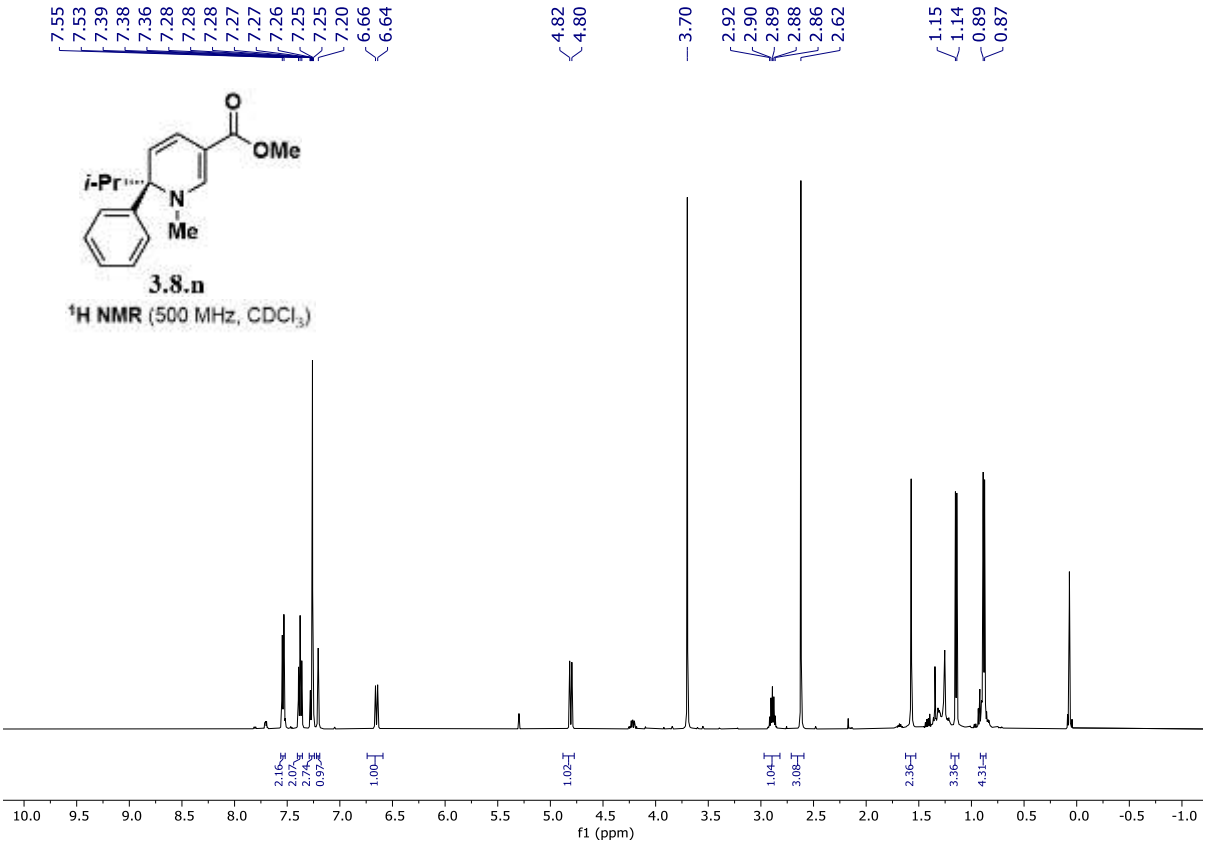
3.8.m

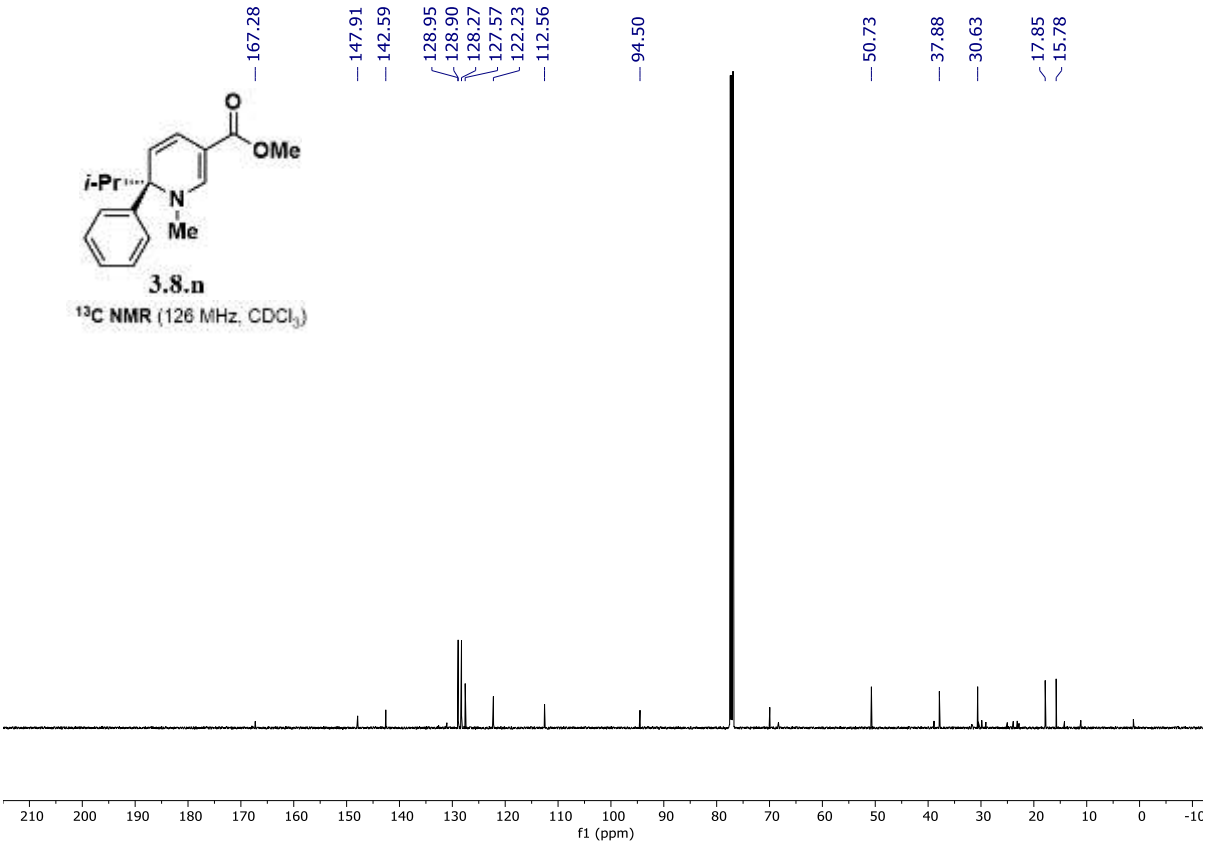
^{1}H NMR (600 MHz, $CDCl_3$)

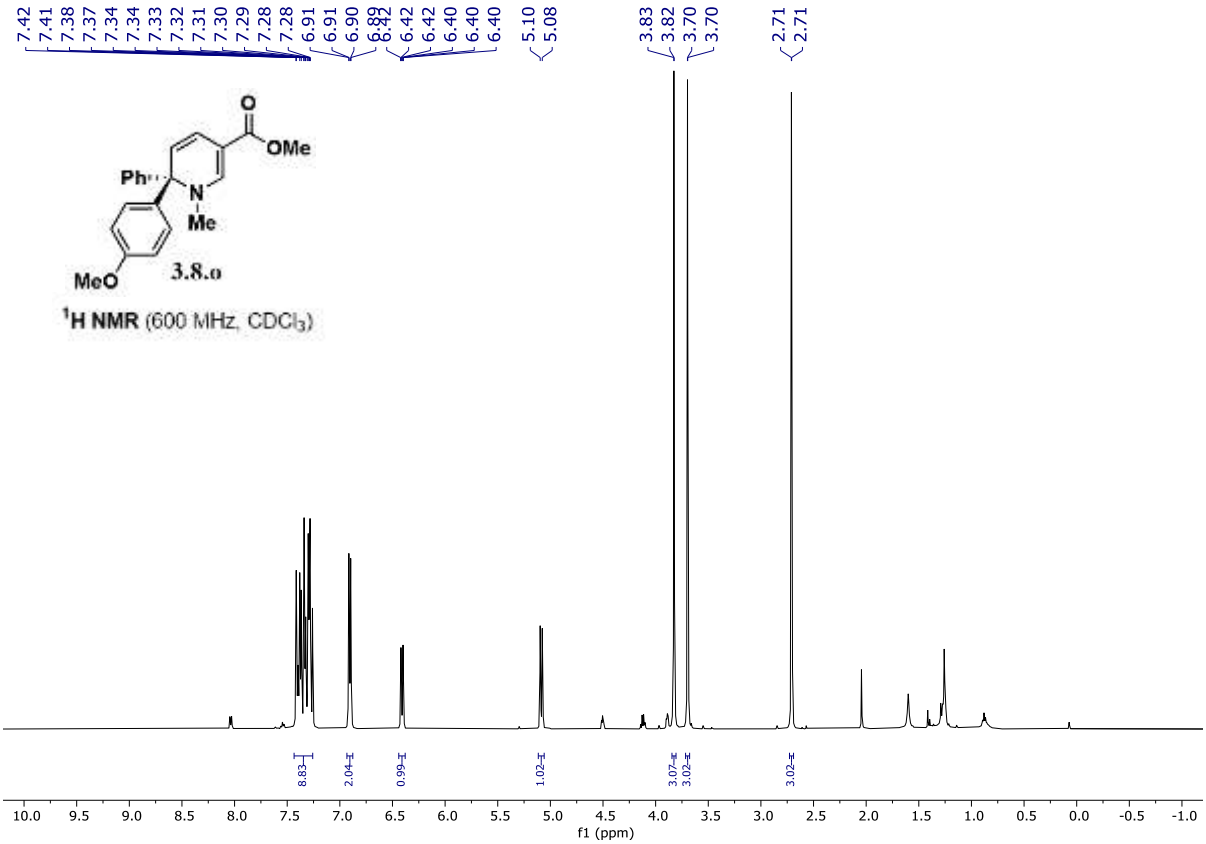


3.8.m

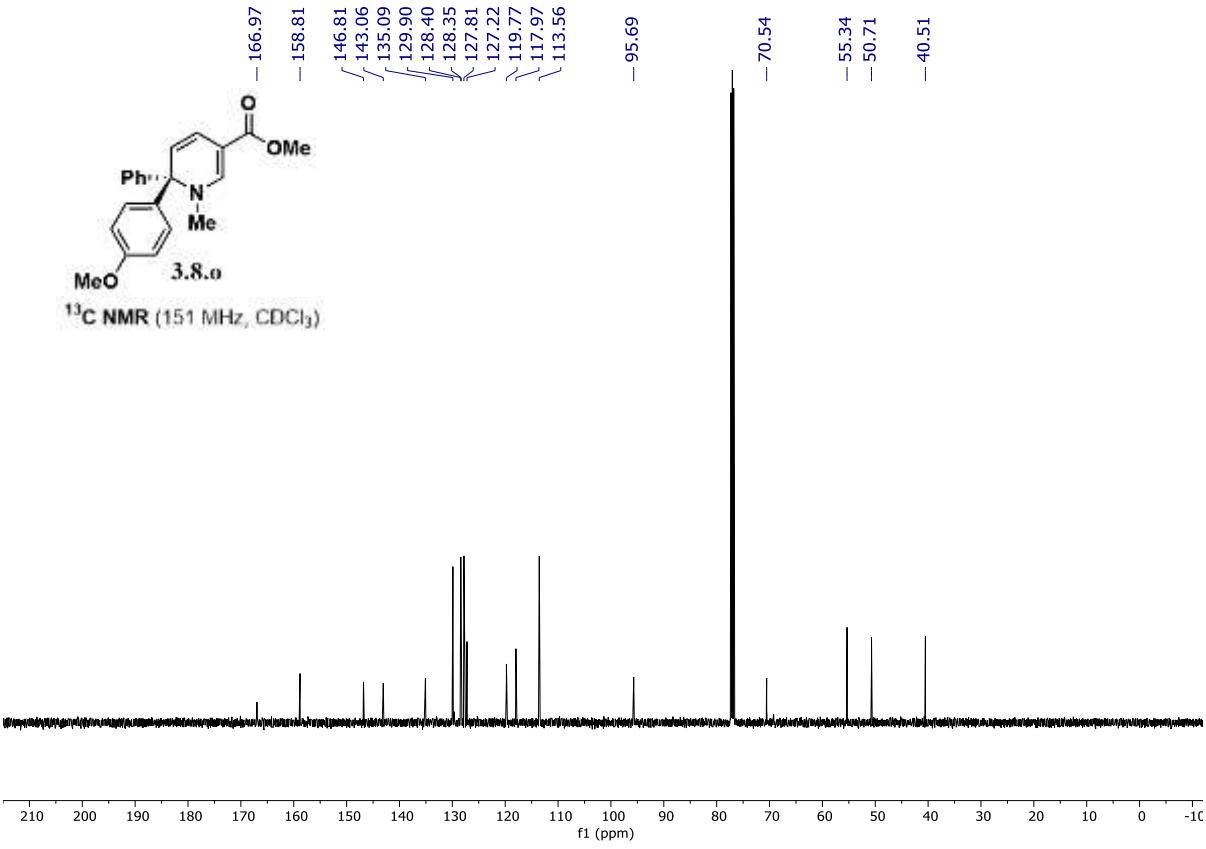
^{13}C NMR (151 MHz, $CDCl_3$)


7.55
7.53
7.39
7.38
7.36
7.28
7.28
7.28
7.27
7.27
7.26
7.25
7.20
6.66
6.64
4.82
4.80
3.70
2.92
2.90
2.89
2.88
2.86
2.62
1.15
1.14
0.89
0.87
OMe
i-Pr
N
Me
3.8.n
¹H NMR (500 MHz, CDCl3)
2.16
2.07
2.74
0.97
1.00
1.02
1.04
3.08
2.36
3.36
4.31
f1 (ppm)

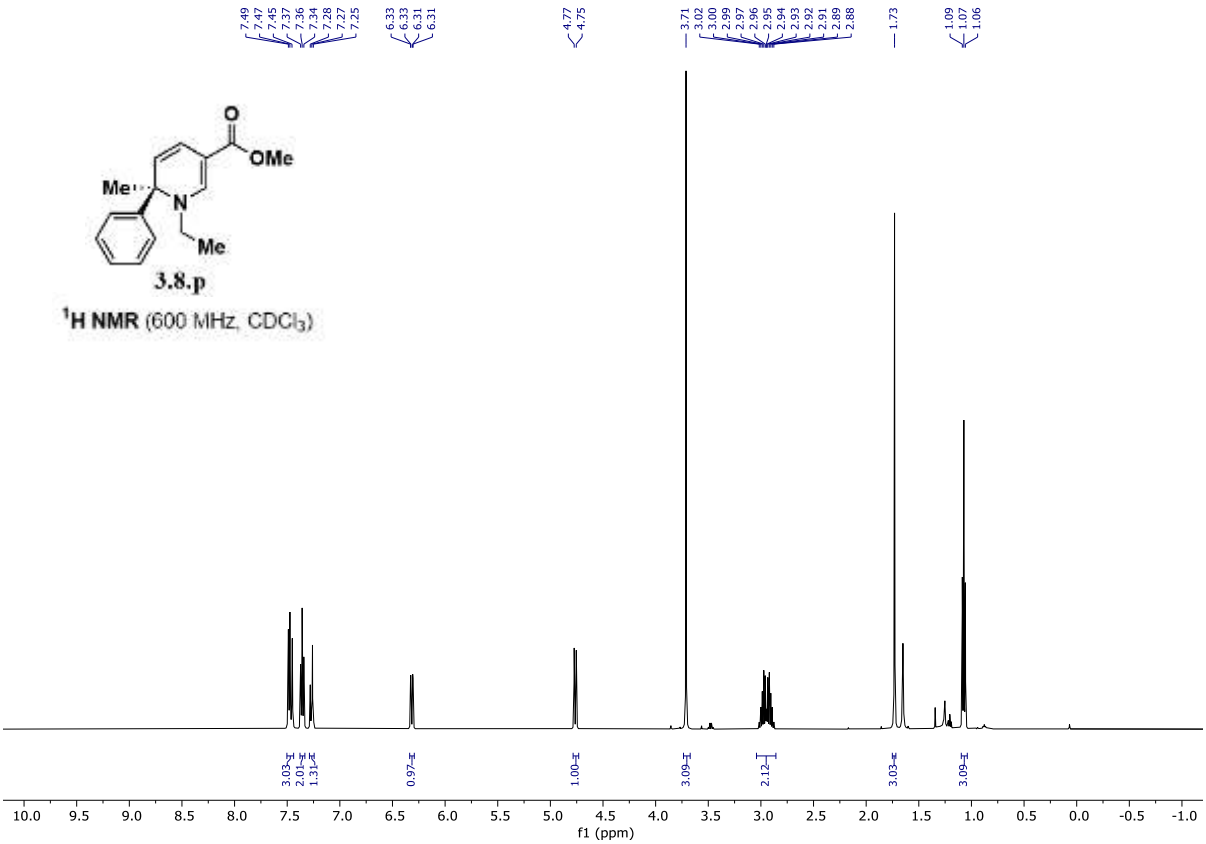

167.28
147.91
142.59
128.95
128.90
128.27
127.57
122.23
112.56
94.50
50.73
37.88
30.63
17.85
15.78
OMe
i-Pr
N
Me
3.8.n
¹³C NMR (126 MHz, CDCl3)
f1 (ppm)



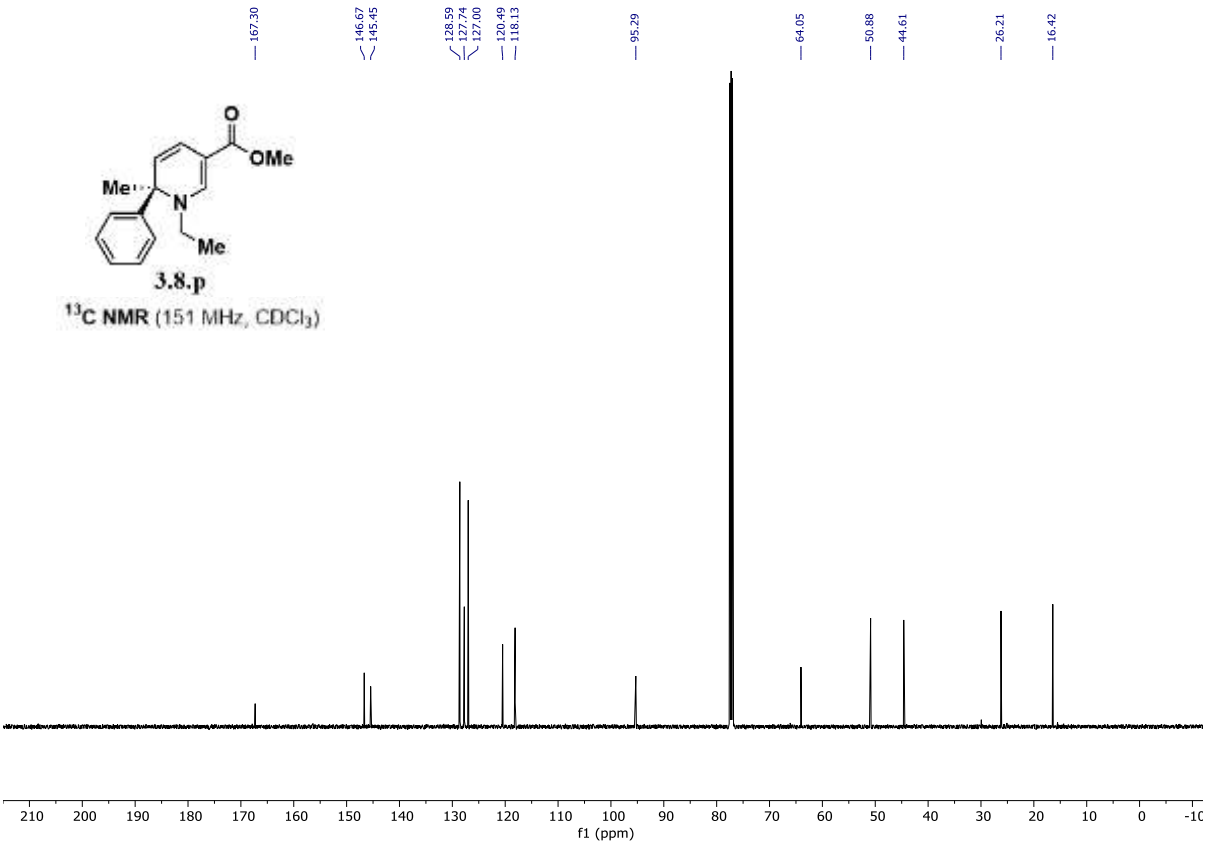
^{1}**H NMR** (600 MHz, $CDCl_3$)



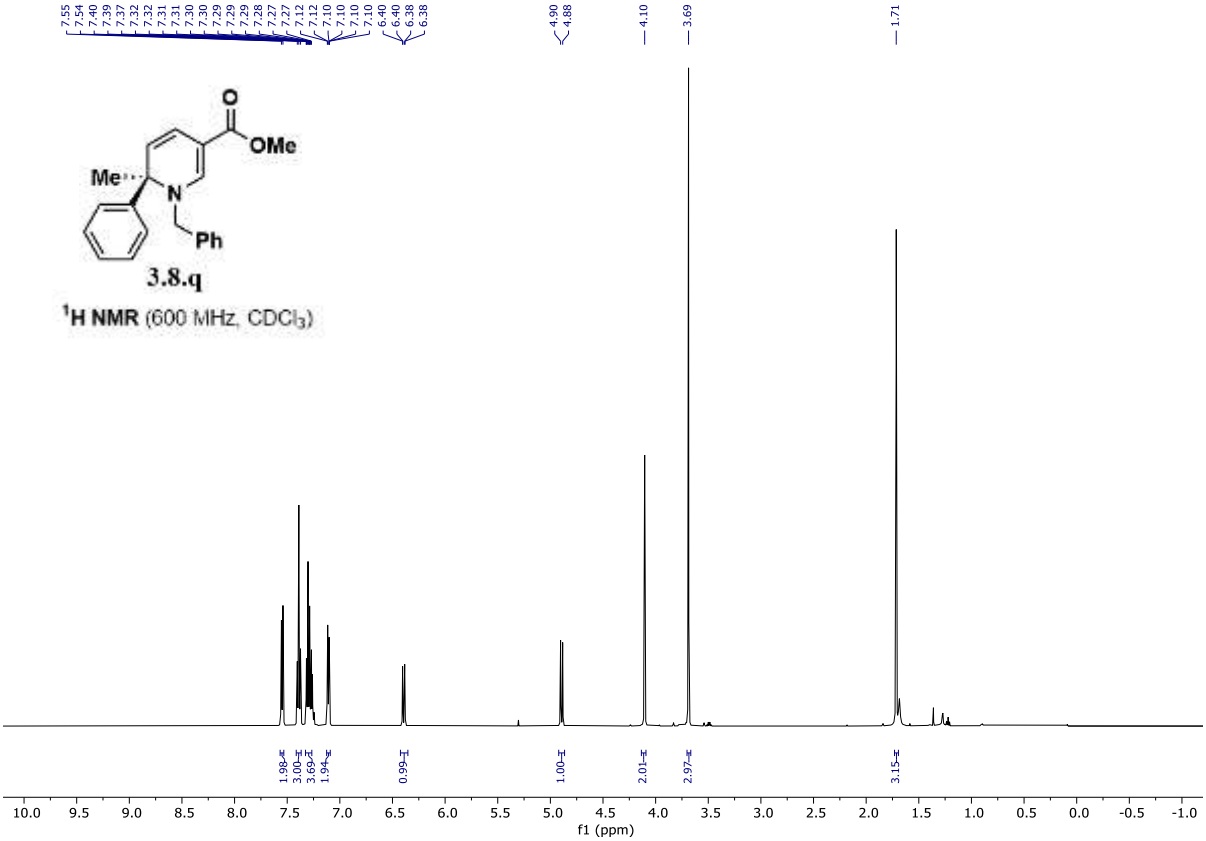
^{13}**C NMR** (151 MHz, $CDCl_3$)



^{1}H NMR (600 MHz, $CDCl_3$)

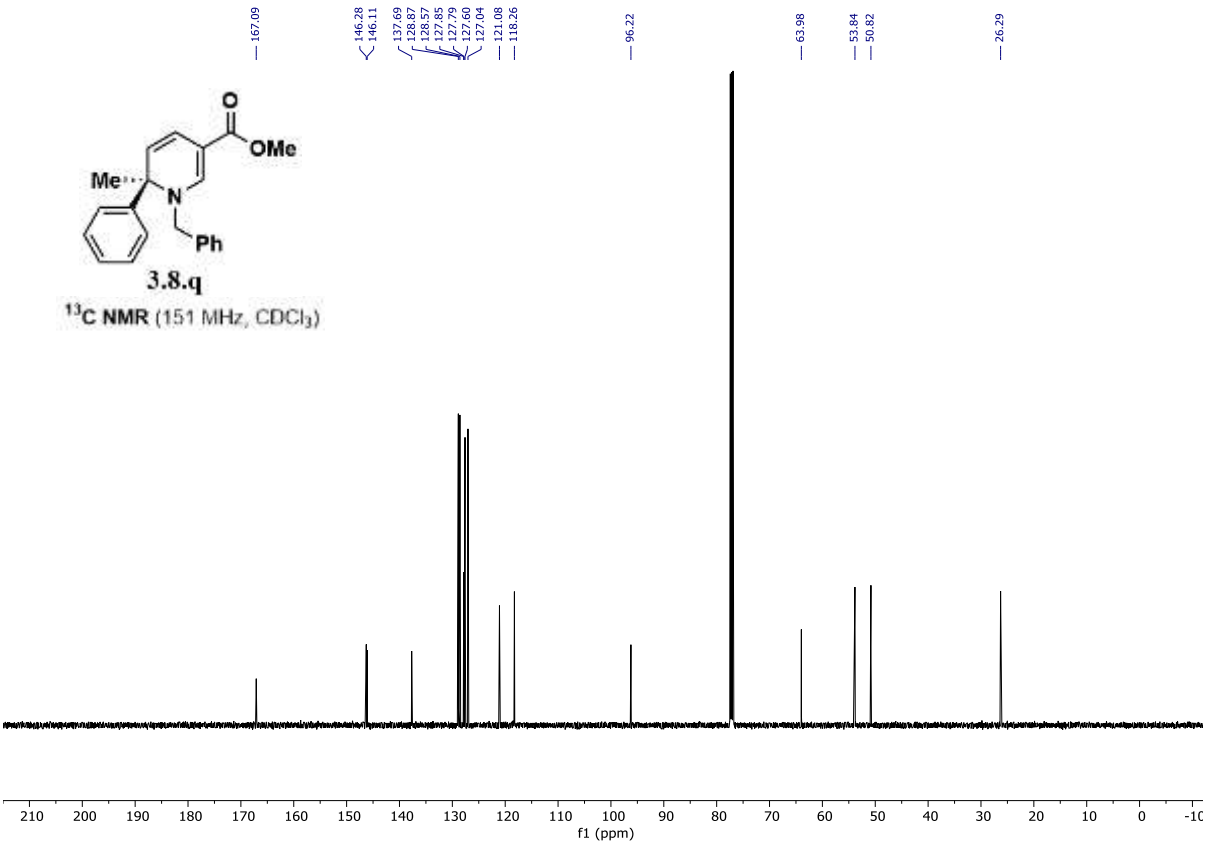


^{13}C NMR (151 MHz, $CDCl_3$)



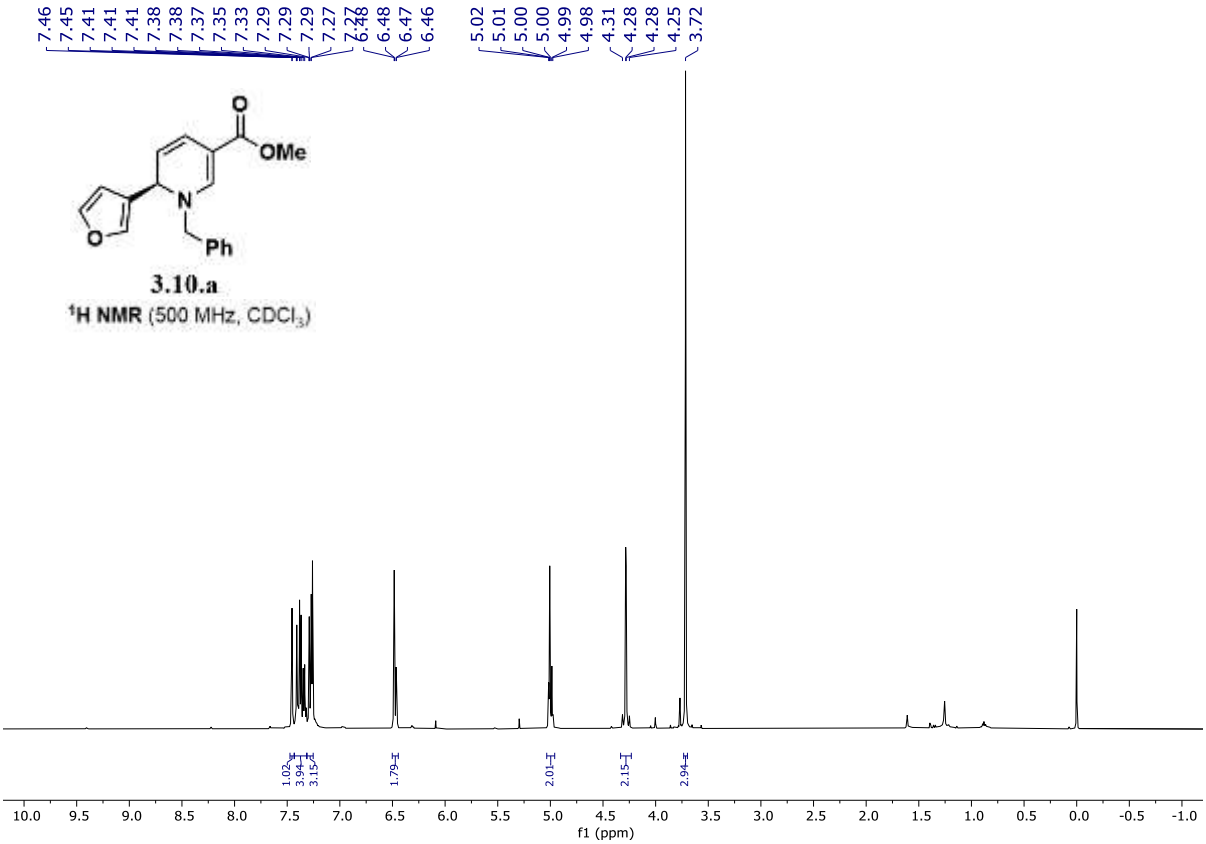
3.8.q

^{1}H NMR (600 MHz, $CDCl_3$)



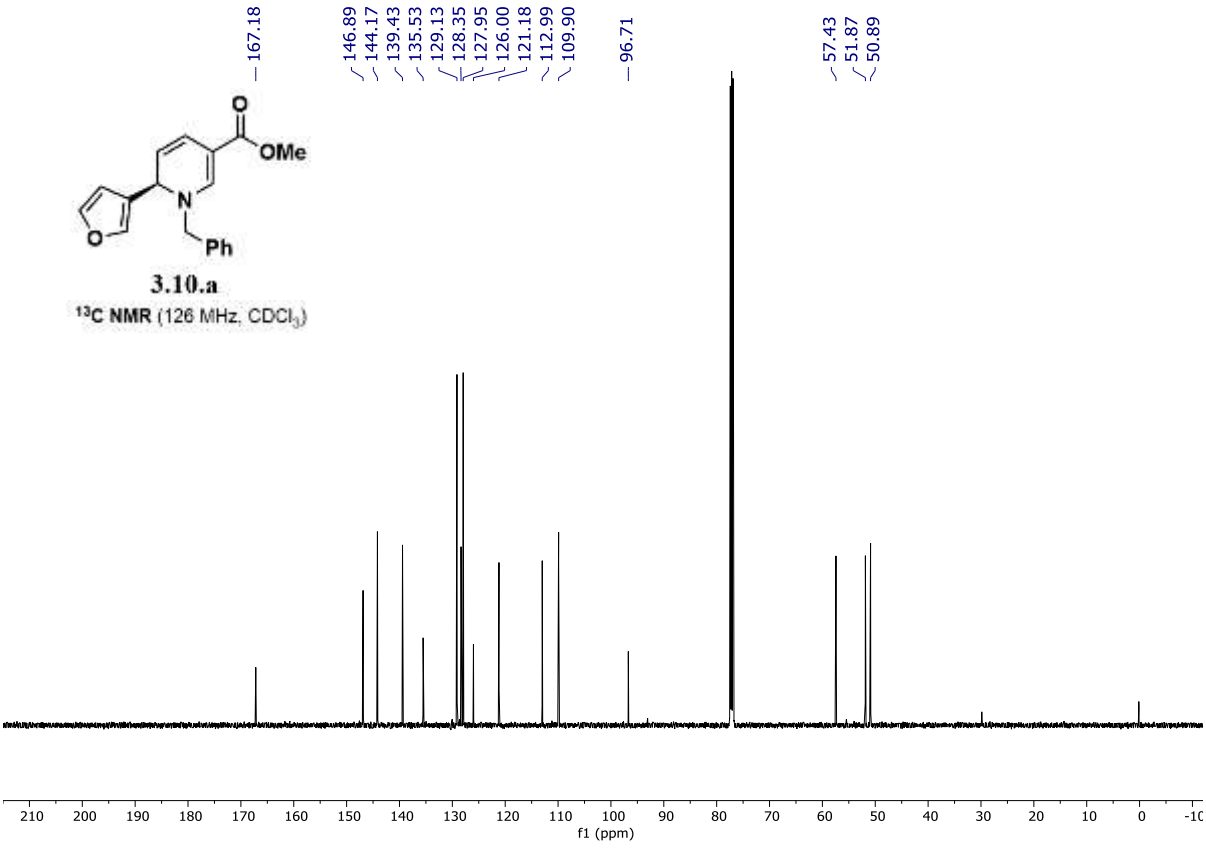
3.8.q

^{13}C NMR (151 MHz, $CDCl_3$)



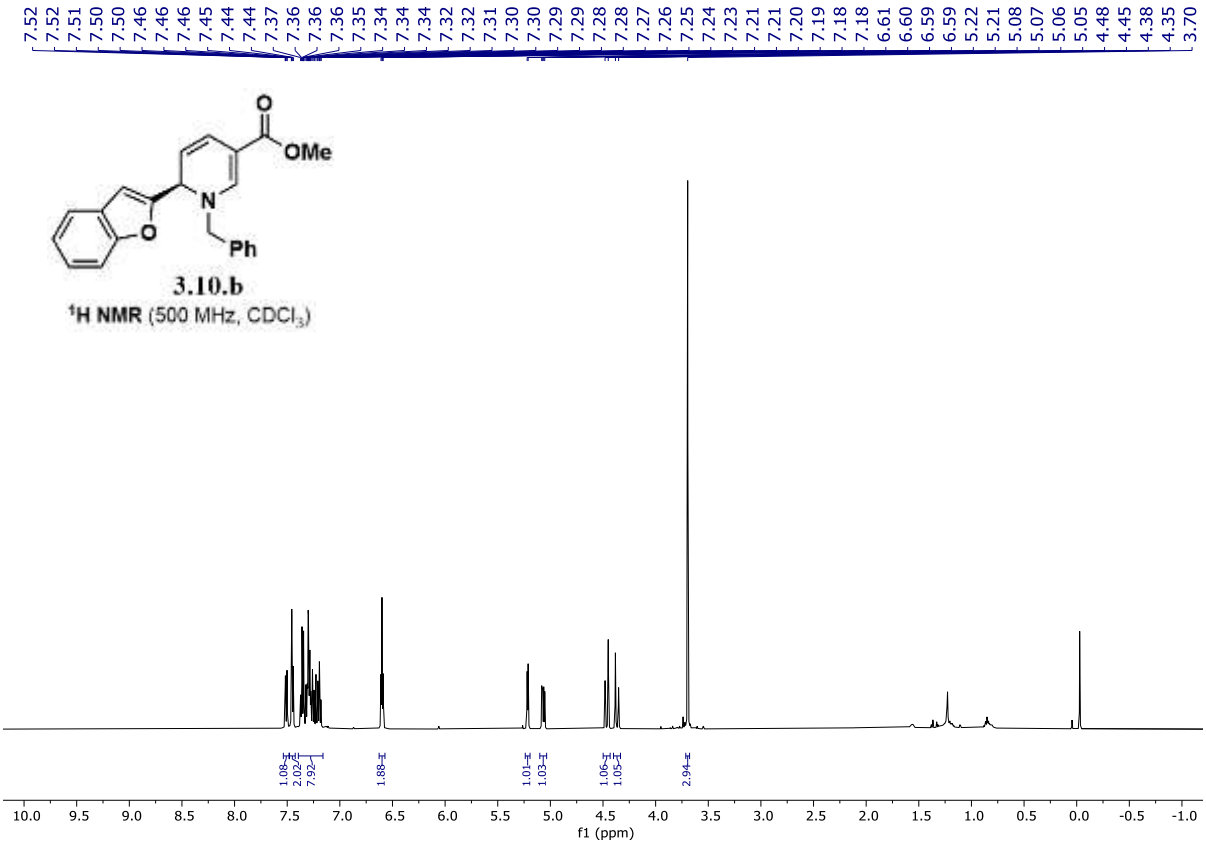
3.10.a

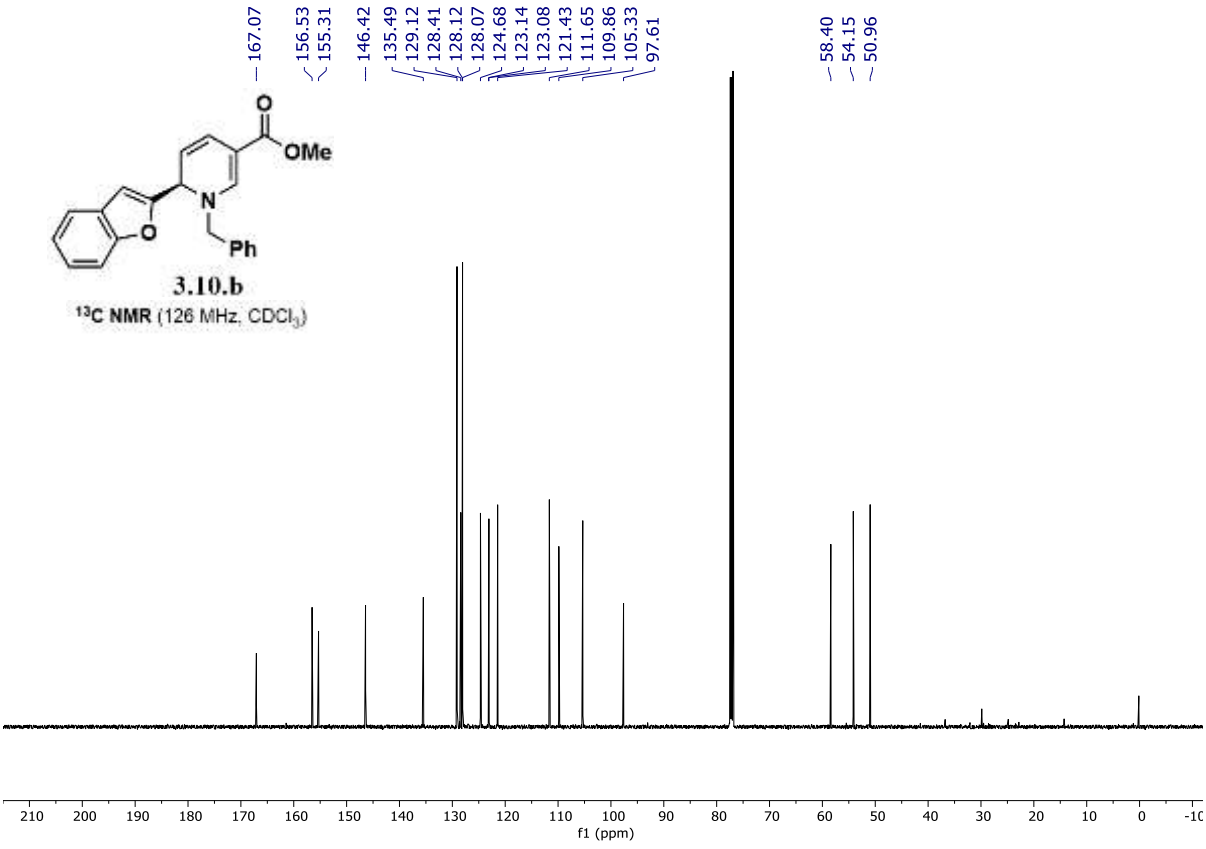
^{1}H NMR (500 MHz, $CDCl_3$)

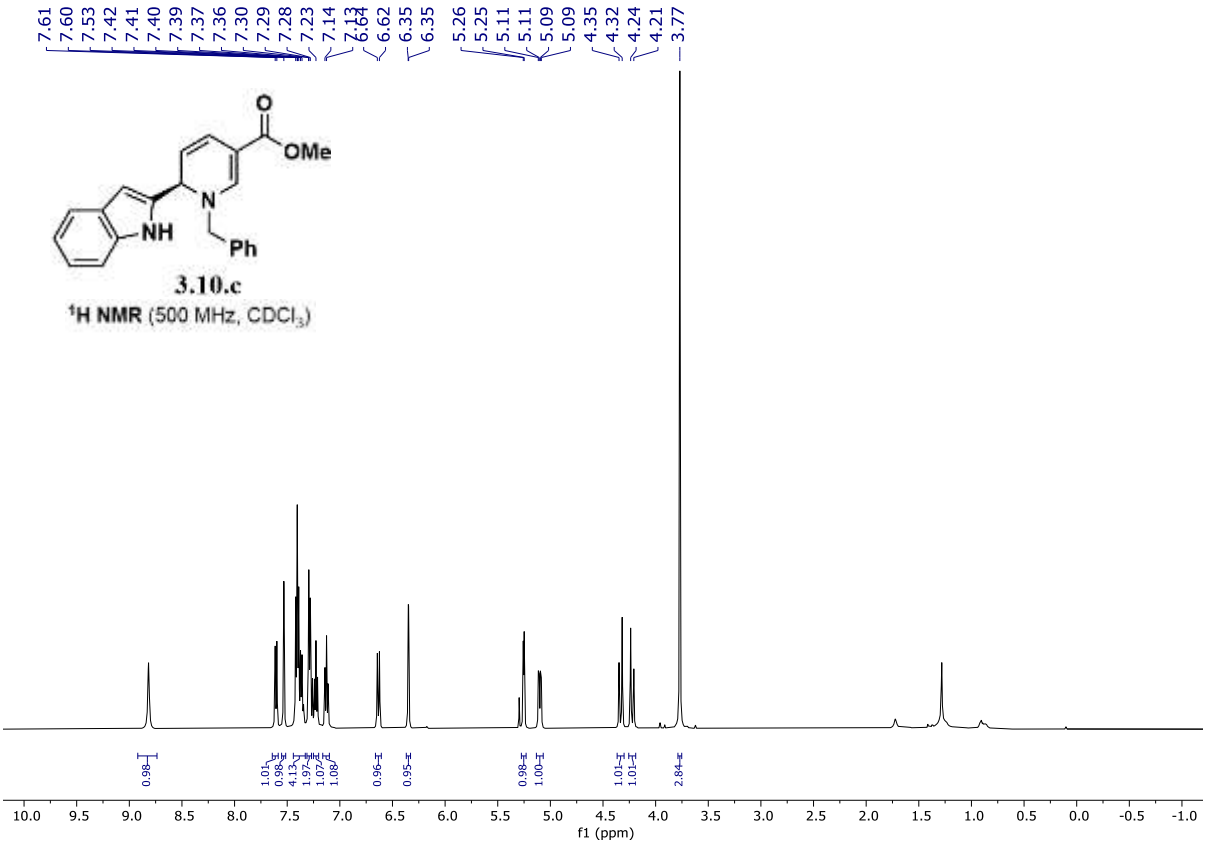


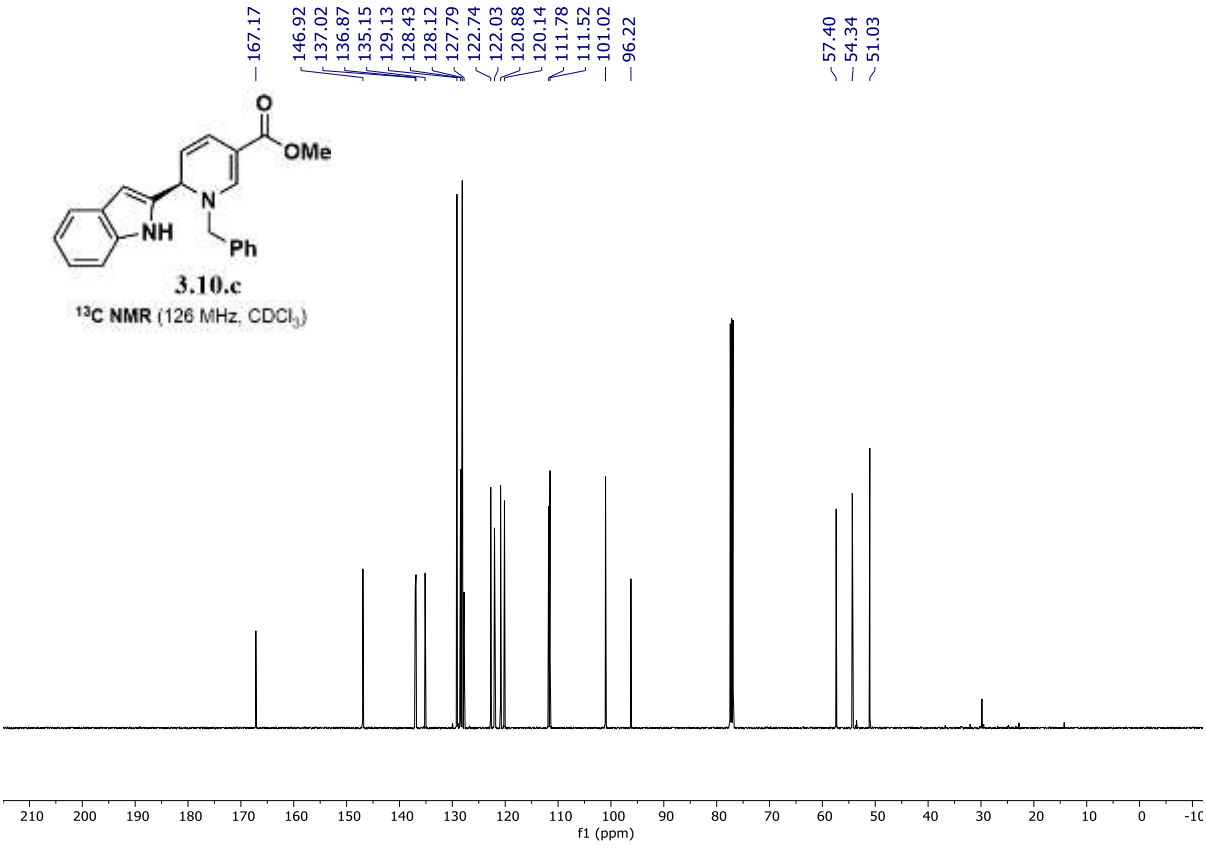
3.10.a

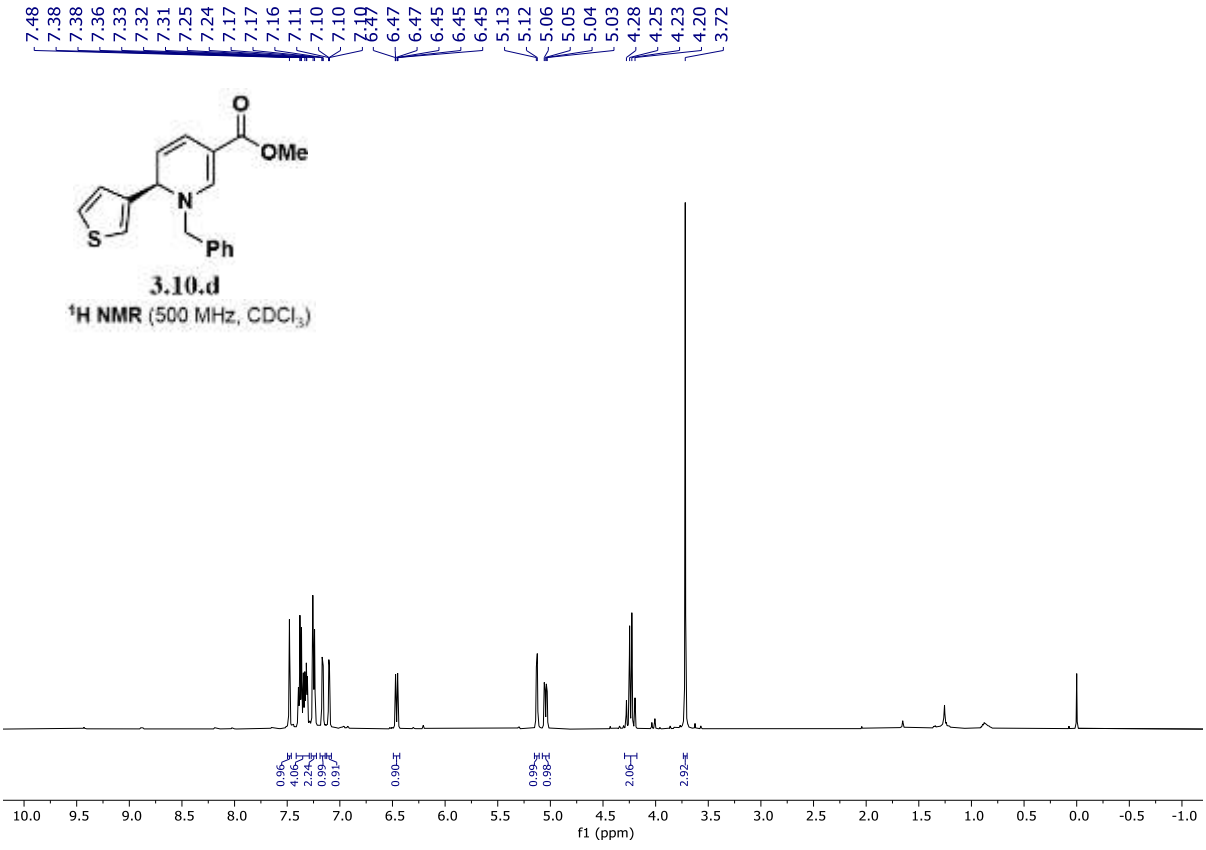
^{13}C NMR (126 MHz, $CDCl_3$)


7.52 7.52 7.51 7.50 7.50 7.46 7.46 7.46 7.45 7.44 7.44 7.37 7.36 7.36 7.36 7.35 7.34 7.34 7.34 7.32 7.32 7.31 7.30 7.30 7.29 7.29 7.28 7.28 7.27 7.26 7.25 7.24 7.23 7.21 7.21 7.20 7.19 7.18 7.18 6.61 6.60 6.59 6.59 5.22 5.21 5.08 5.07 5.06 5.05 4.48 4.45 4.38 4.35 3.70
O
OMe
N
O
Ph
3.10.b
1H NMR (500 MHz, CDCl3)
1.08
2.02
7.92
1.88
1.01
1.03
1.06
1.05
2.94
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 -0.5 -1.0
f1 (ppm)


167.07
156.53
155.31
146.42
135.49
129.12
128.41
128.12
128.07
124.68
123.14
123.08
121.43
111.65
109.86
105.33
97.61
58.40
54.15
50.96
O
OMe
N
O
Ph
3.10.b
13C NMR (126 MHz, CDCl3)
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)

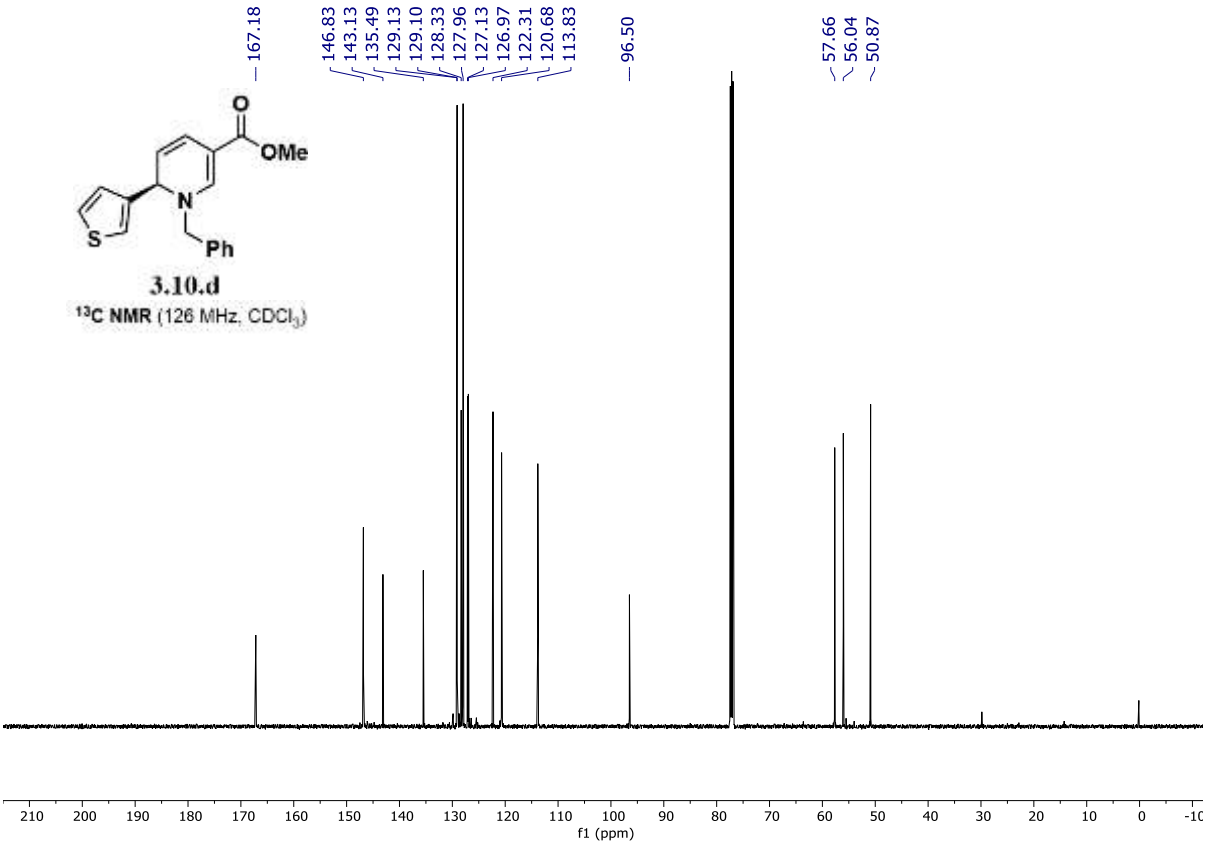

7.61
7.60
7.53
7.42
7.41
7.40
7.39
7.37
7.36
7.30
7.29
7.28
7.23
7.14
7.13
6.64
6.62
6.35
6.35
5.26
5.25
5.11
5.11
5.09
5.09
4.35
4.32
4.24
4.21
3.77
O
OMe
N
NH
Ph
3.10.c
¹H NMR (500 MHz, CDCl3)
0.98
1.01
0.98
4.13
1.92
1.07
1.08
0.96
0.95
0.98
1.00
1.01
1.01
2.84
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)


167.17
146.92
137.02
136.87
135.15
129.13
128.43
128.12
127.79
122.74
122.03
120.88
120.14
111.78
111.52
101.02
96.22
57.40
54.34
51.03
O
OMe
N
NH
Ph
3.10.c
¹³C NMR (126 MHz, CDCl3)
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)



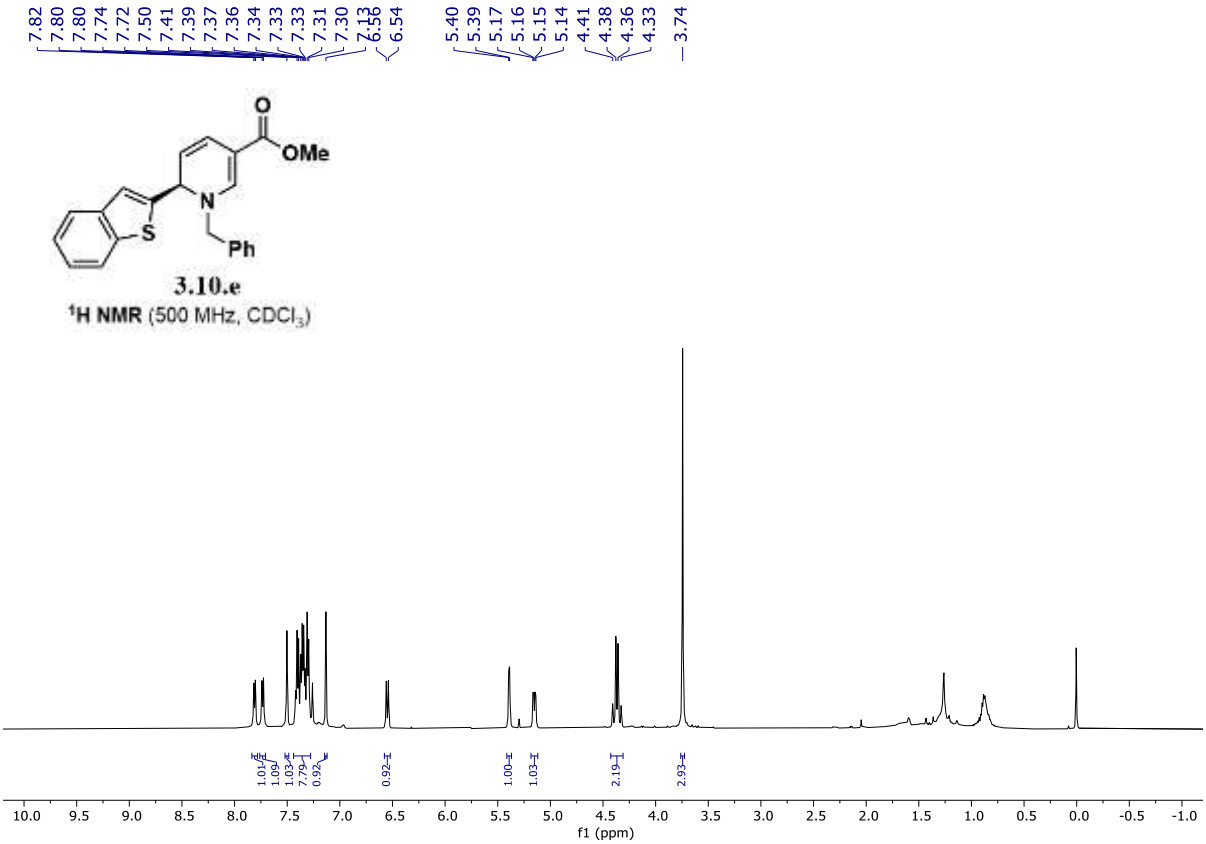
3.10.d

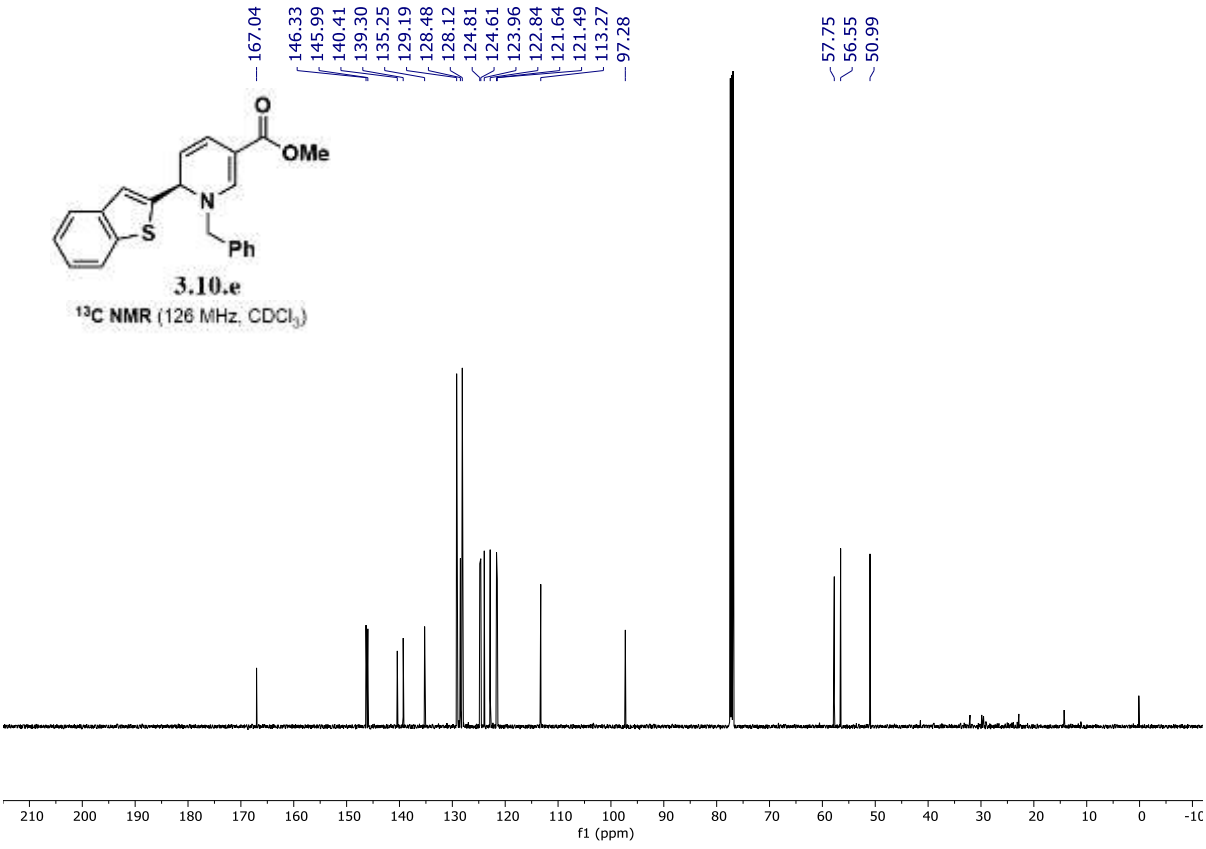
^{1}H NMR (500 MHz, $CDCl_3$)

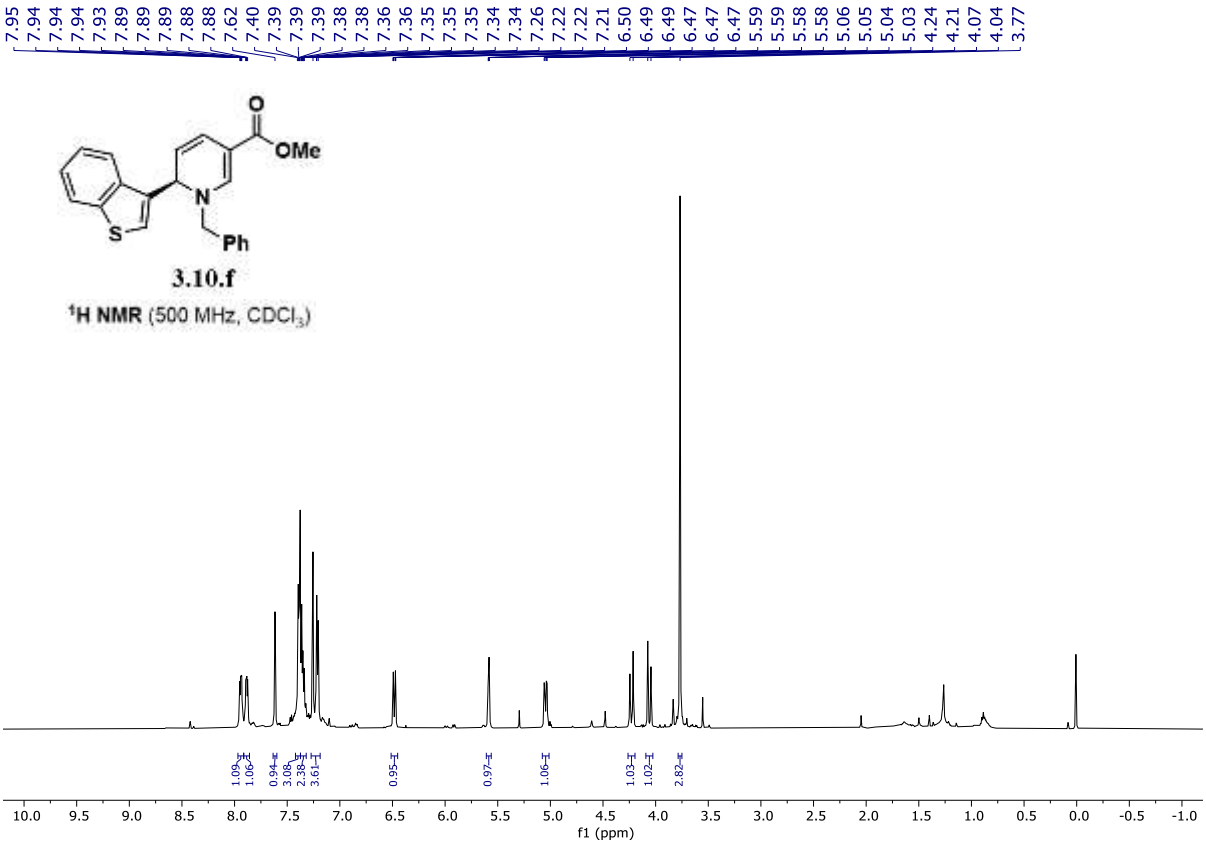


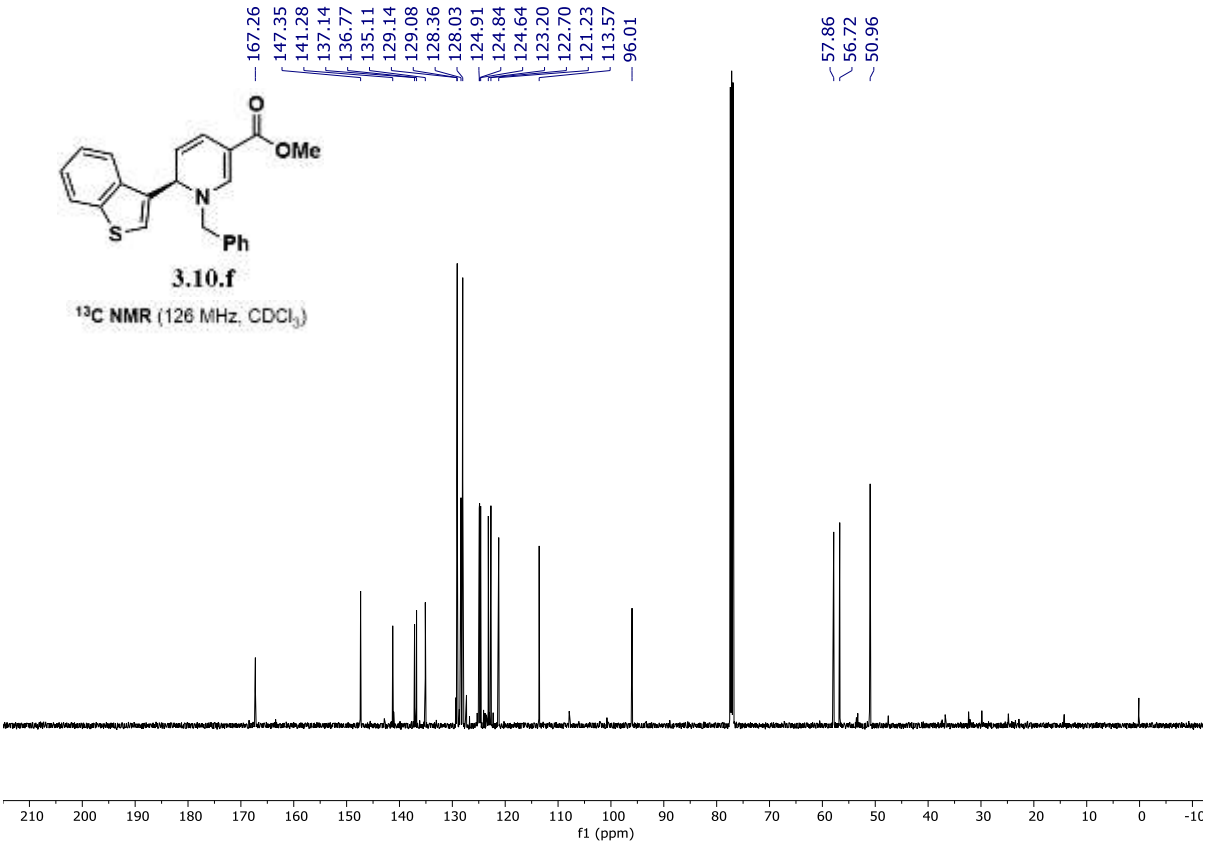
3.10.d

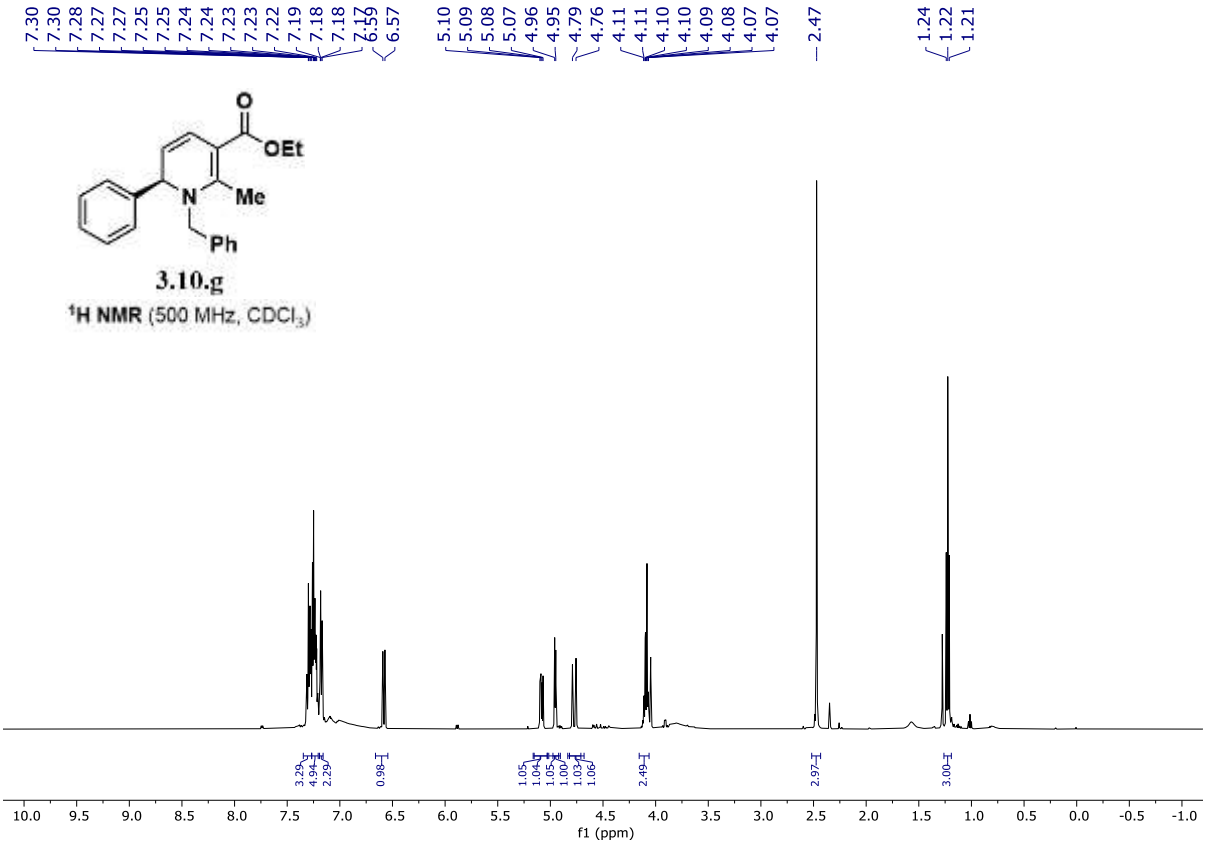
^{13}C NMR (126 MHz, $CDCl_3$)

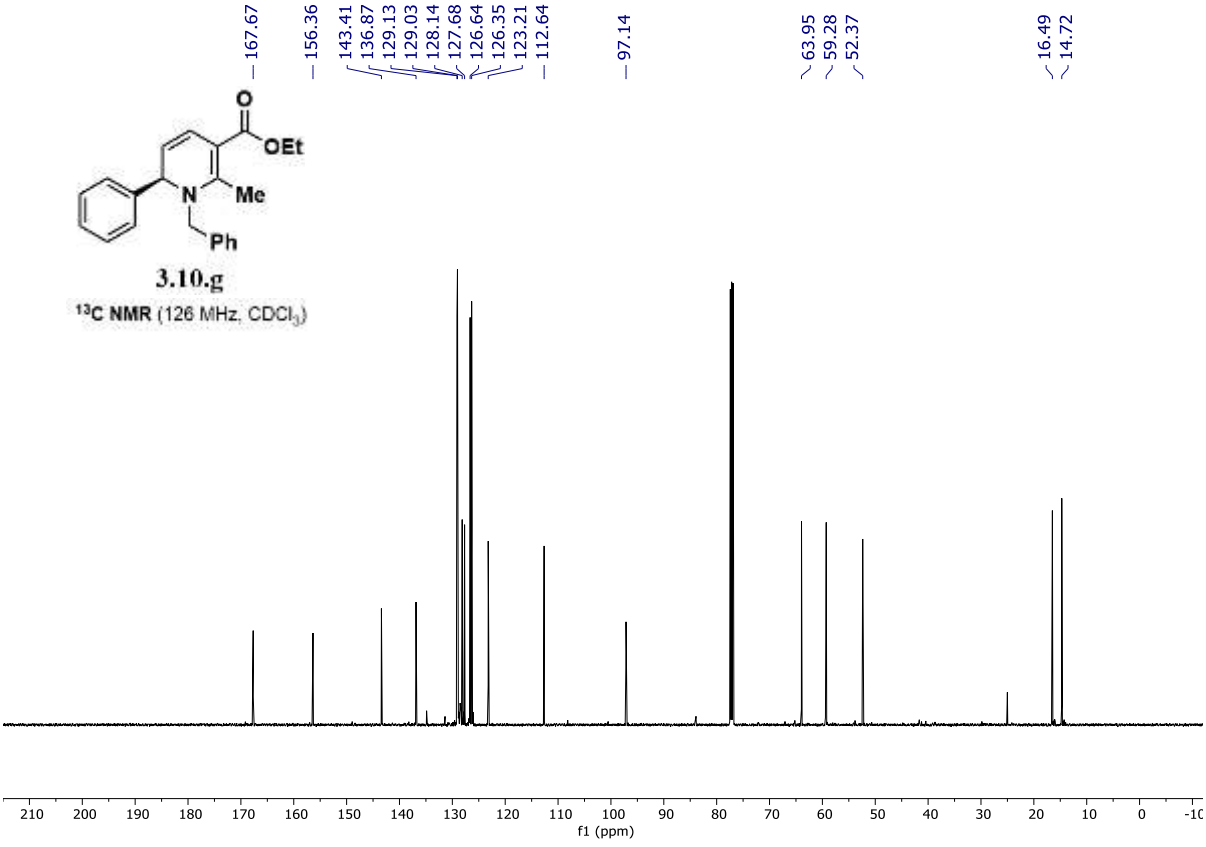

7.82
7.80
7.80
7.74
7.72
7.50
7.41
7.39
7.37
7.36
7.34
7.33
7.33
7.31
7.30
7.13
6.56
6.54
5.40
5.39
5.17
5.16
5.15
5.14
4.41
4.38
4.36
4.33
3.74
O
OMe
N
S
Ph
3.10.e
1H NMR (500 MHz, CDCl3)
1.01
1.09
1.03
7.79
0.92
0.92
1.00
1.03
2.19
2.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

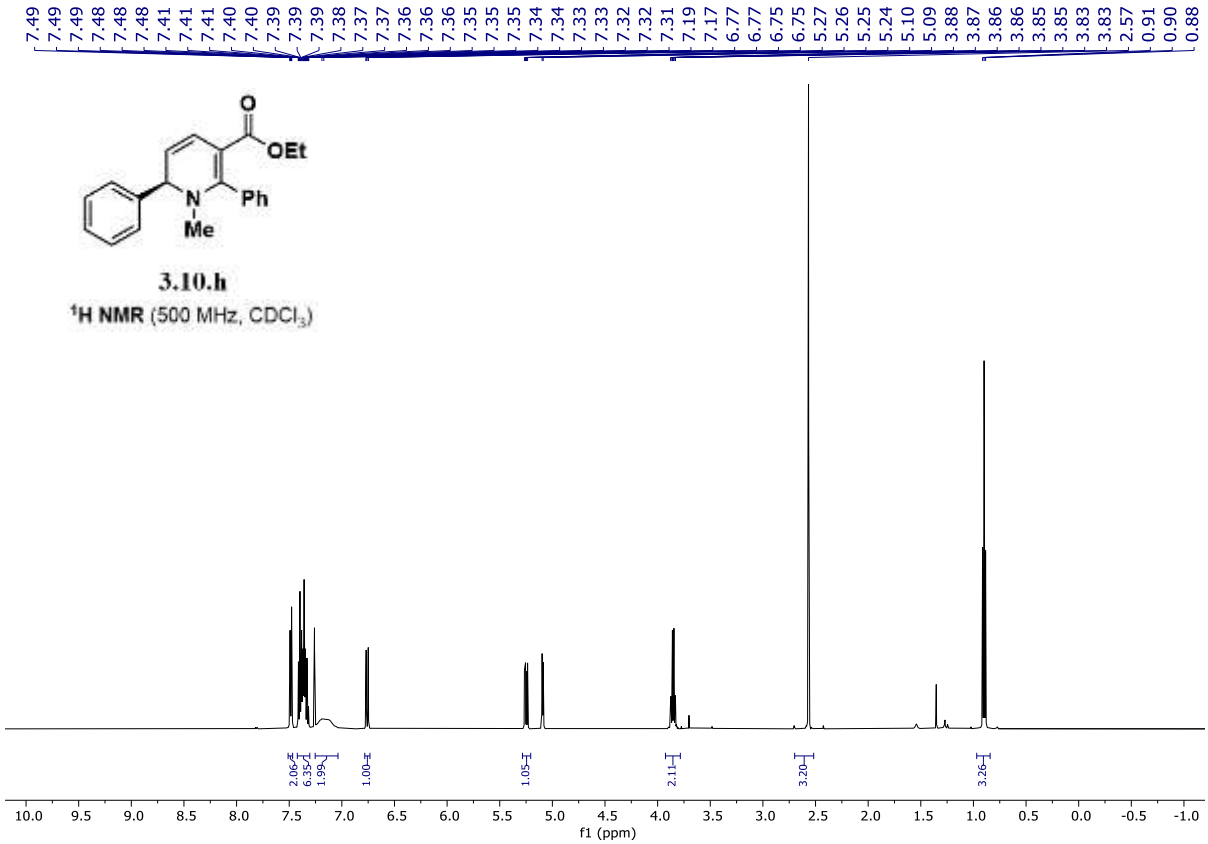

167.04
146.33
145.99
140.41
139.30
135.25
129.19
128.48
128.12
124.81
124.61
123.96
122.84
121.64
121.49
113.27
97.28
57.75
56.55
50.99
O
OMe
N
S
Ph
3.10.e
13C NMR (126 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


7.95 7.94 7.94 7.94 7.93 7.89 7.89 7.89 7.88 7.88 7.62 7.40 7.39 7.39 7.39 7.38 7.38 7.36 7.36 7.35 7.35 7.35 7.34 7.34 7.26 7.22 7.22 7.21 6.50 6.49 6.49 6.47 6.47 6.47 5.59 5.59 5.58 5.58 5.06 5.05 5.04 5.03 4.24 4.21 4.07 4.04 3.77
O
OMe
N
S
Ph
3.10.f
1H NMR (500 MHz, CDCl3)
1.09 1.06 0.94 3.08 2.38 3.61 0.95 0.97 1.06 1.03 1.02 2.82
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 -0.5 -1.0
f1 (ppm)


167.26 147.35 141.28 137.14 136.77 135.11 129.14 129.08 128.36 128.03 124.91 124.84 124.64 123.20 122.70 121.23 113.57 96.01
57.86 56.72 50.96
O
OMe
N
S
Ph
3.10.f
13C NMR (126 MHz, CDCl3)
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)

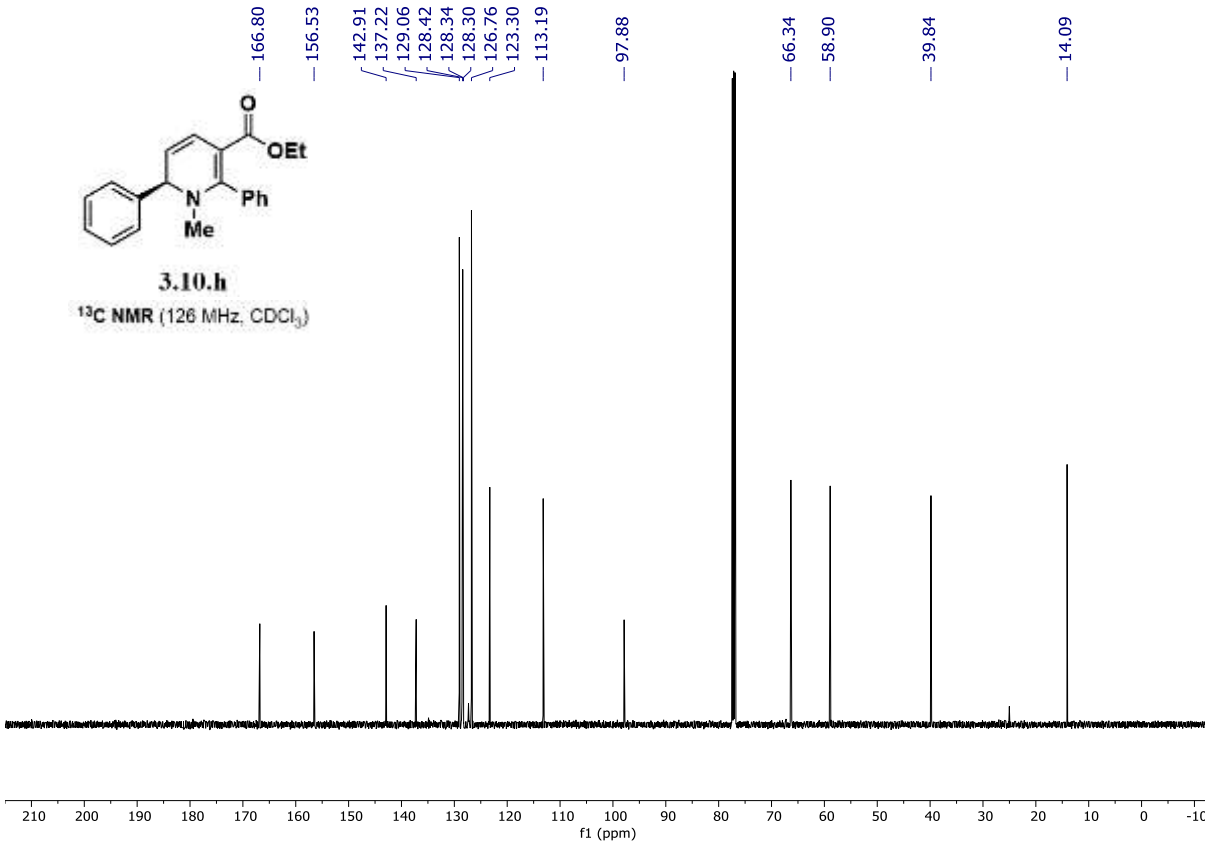

7.30
7.30
7.28
7.27
7.27
7.25
7.25
7.24
7.24
7.23
7.23
7.22
7.19
7.18
7.18
6.59
6.57
5.10
5.09
5.08
5.07
4.96
4.95
4.79
4.76
4.11
4.11
4.10
4.10
4.09
4.08
4.07
4.07
2.47
1.24
1.22
1.21
O
OEt
N
Me
Ph
3.10.g
¹H NMR (500 MHz, CDCl3)
3.29
4.94
2.29
0.98
1.05
1.04
1.05
1.00
1.03
1.06
2.49
2.97
3.00
10.0 9.5 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 -0.5 -1.0
f1 (ppm)


167.67
156.36
143.41
136.87
129.13
129.03
128.14
127.68
126.64
126.35
123.21
112.64
97.14
63.95
59.28
52.37
16.49
14.72
O
OEt
N
Me
Ph
3.10.g
¹³C NMR (126 MHz, CDCl3)
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)



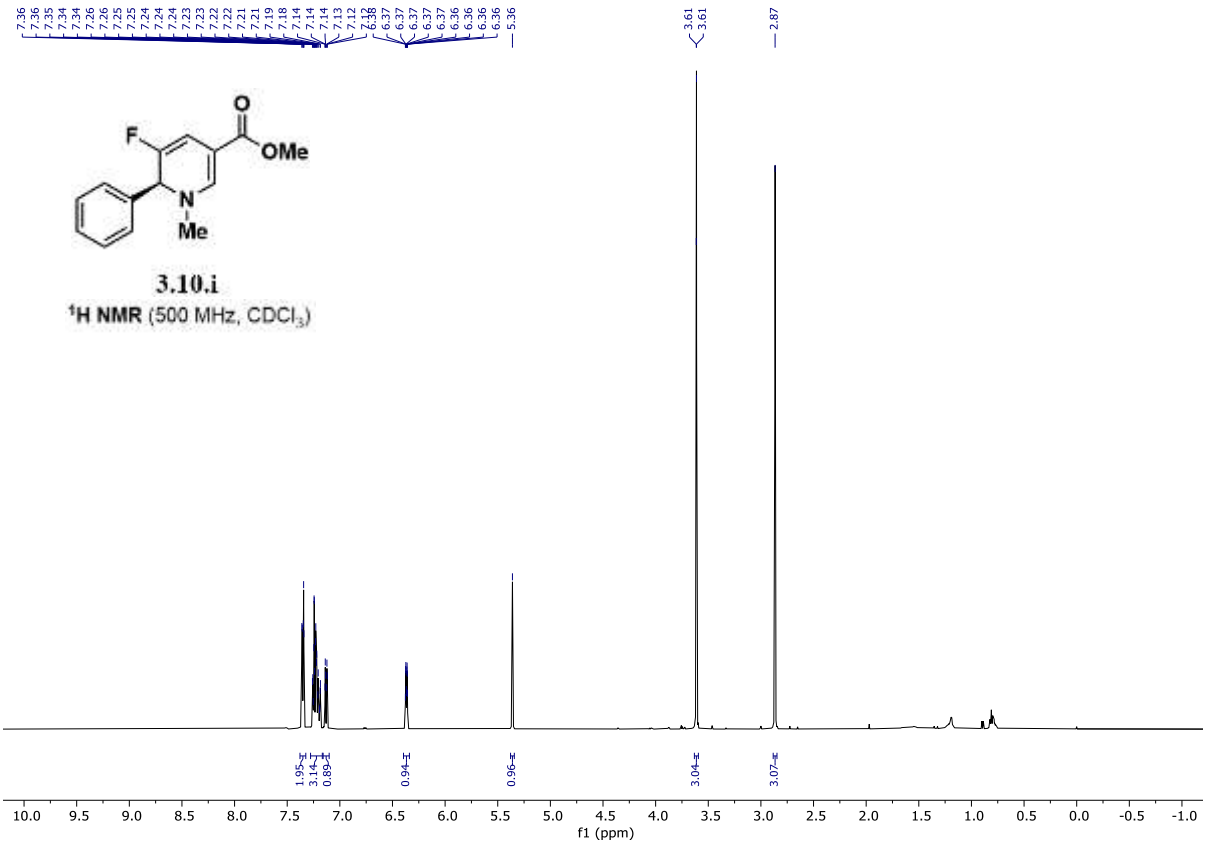
3.10.h

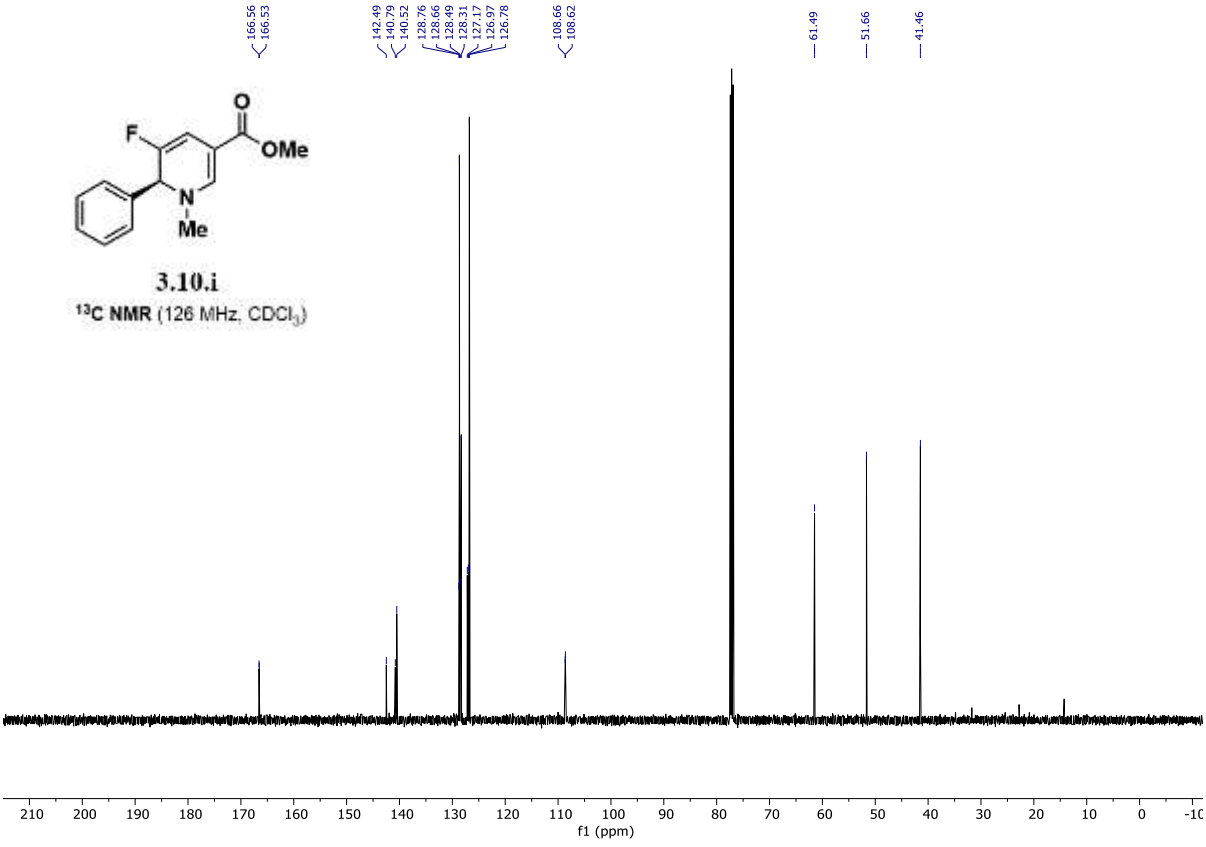
^{1}H NMR (500 MHz, $CDCl_3$)

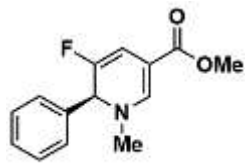


3.10.h

^{13}C NMR (126 MHz, $CDCl_3$)

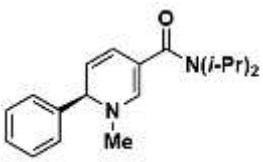

F
O
OMe
N
Me
3.10.i
¹H NMR (500 MHz, CDCl3)
f1 (ppm)


F
O
OMe
N
Me
3.10.i
¹³C NMR (126 MHz, CDCl3)
f1 (ppm)



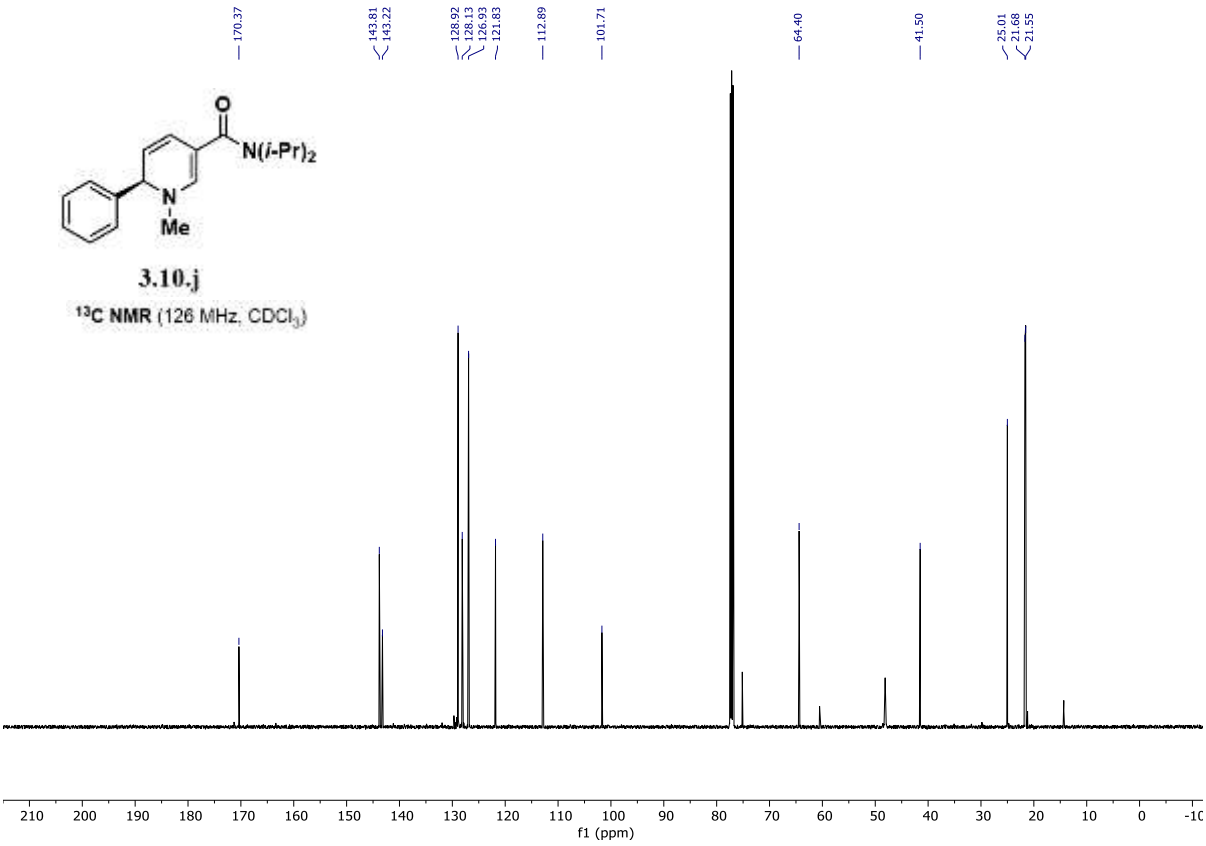
3.10.i

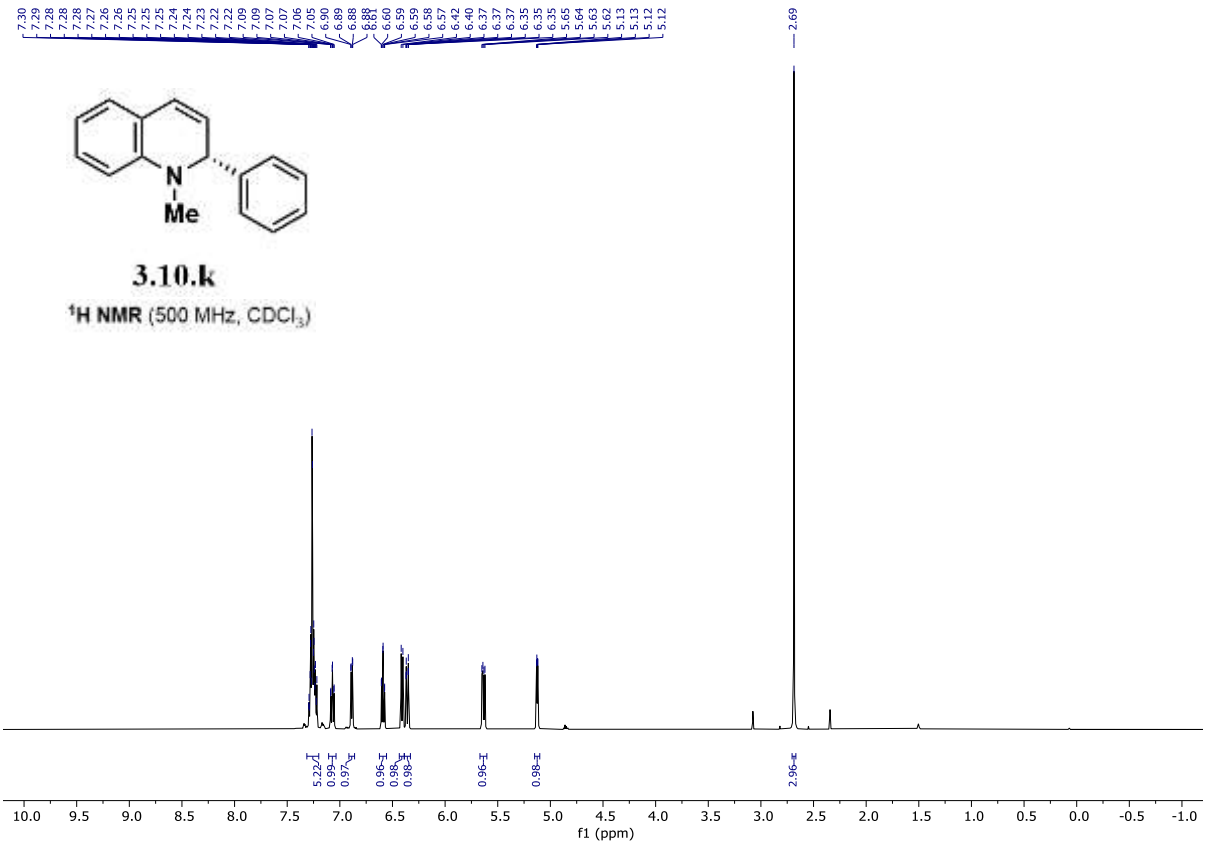
^{19}F NMR (471 MHz, $CDCl_3$)

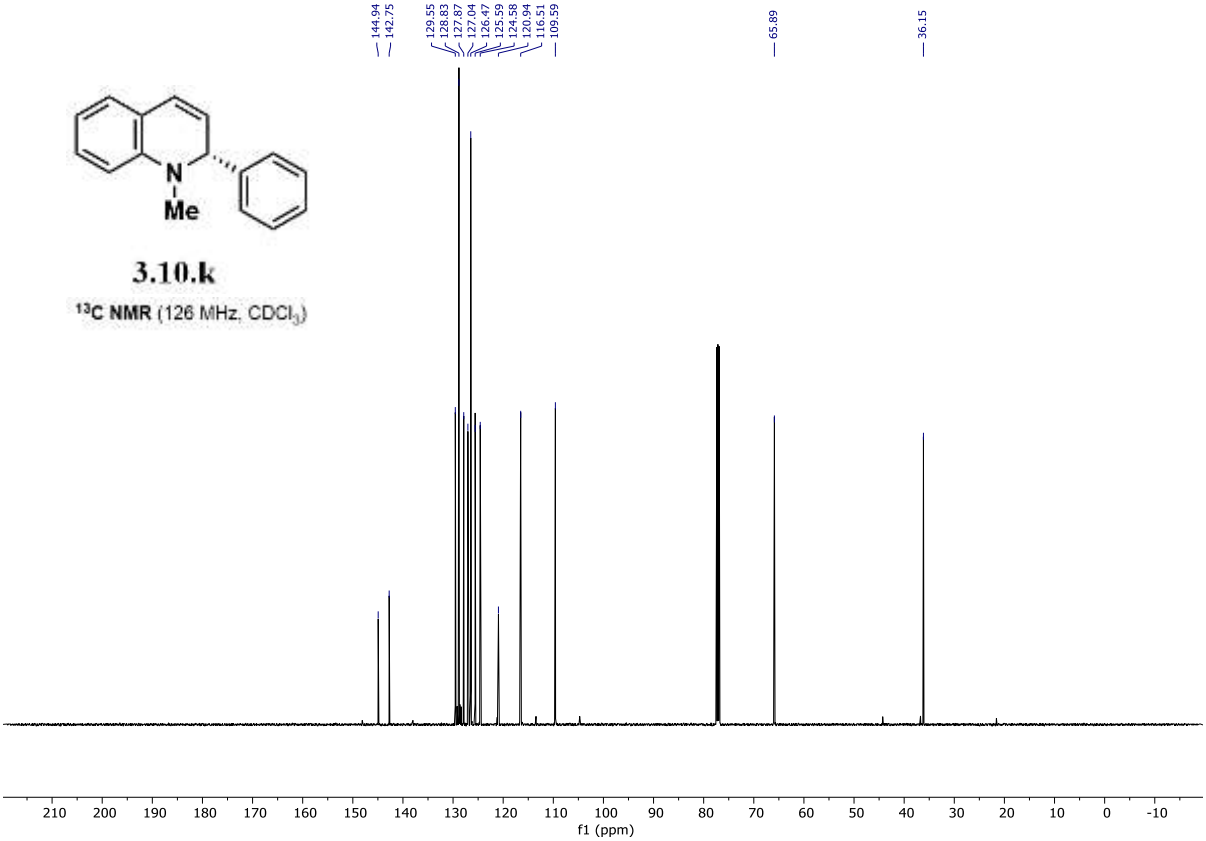


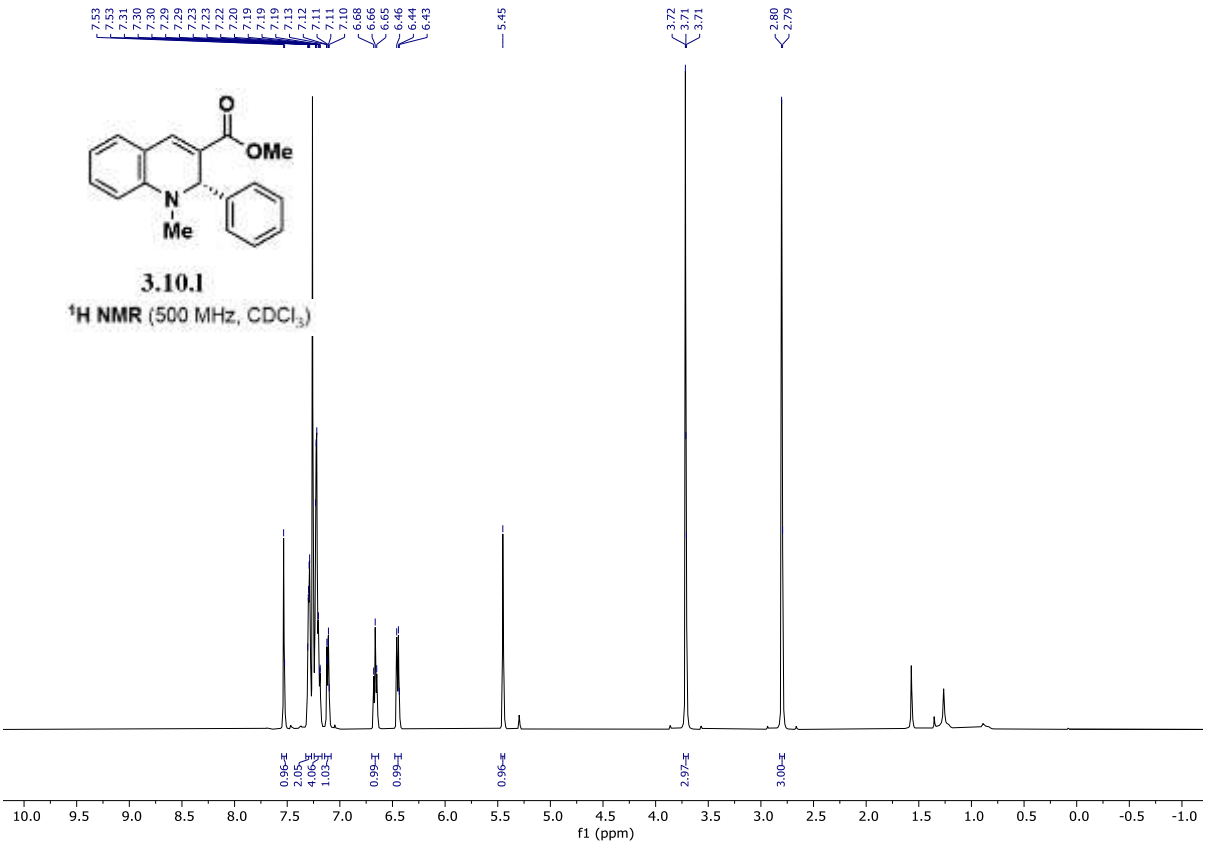
3.10.j

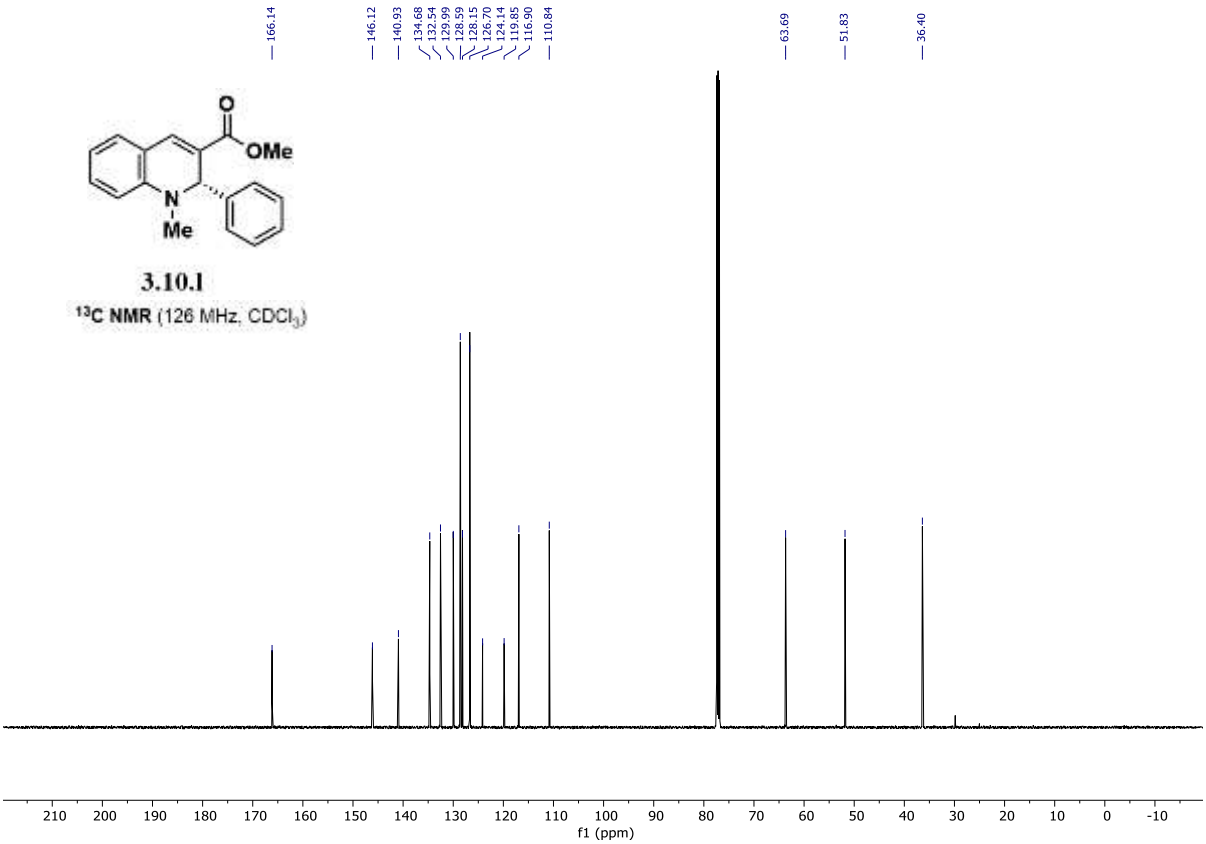
^{1}H NMR (500 MHz, $CDCl_3$)

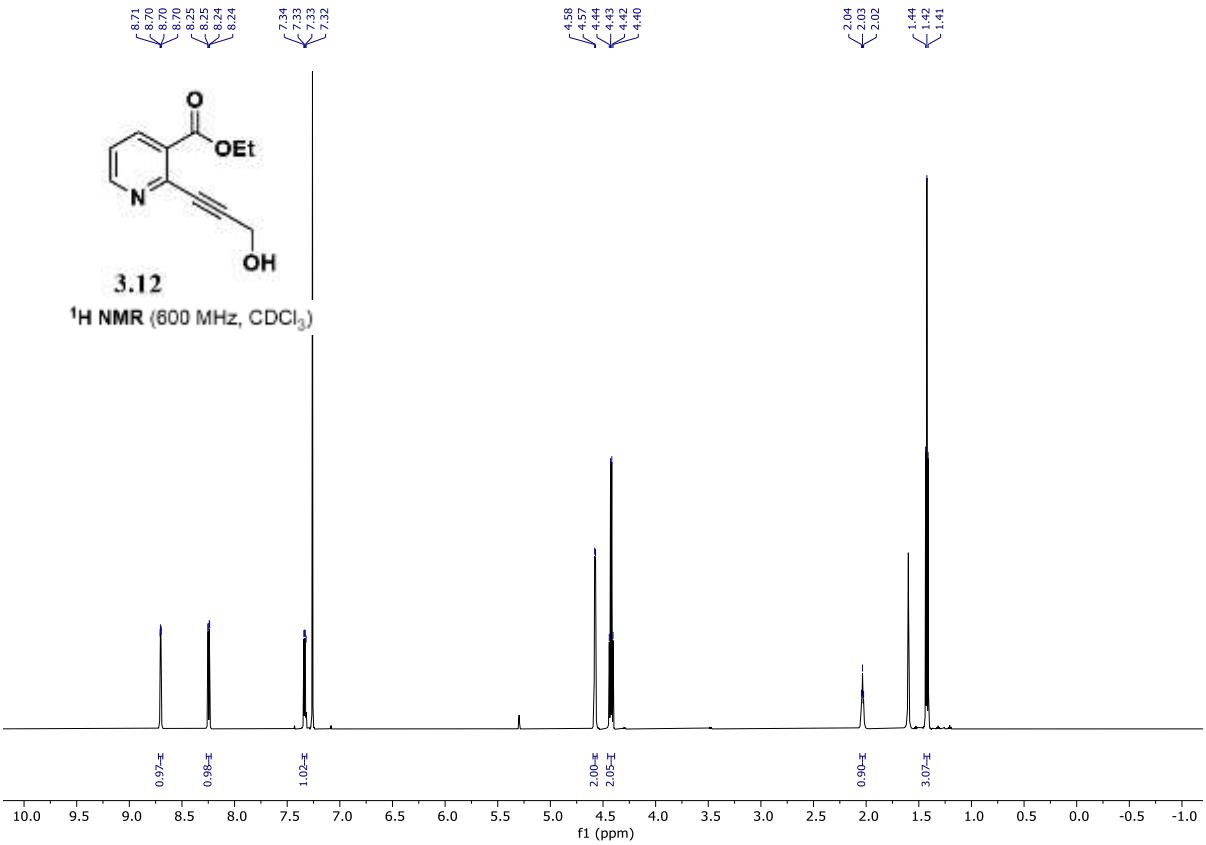

170.37
143.81
143.22
128.92
128.13
126.93
121.83
112.89
101.71
64.40
41.50
25.01
21.68
21.55
O
N(i-Pr)2
N
Me
3.10.j
13C NMR (126 MHz, CDCl3)
f1 (ppm)

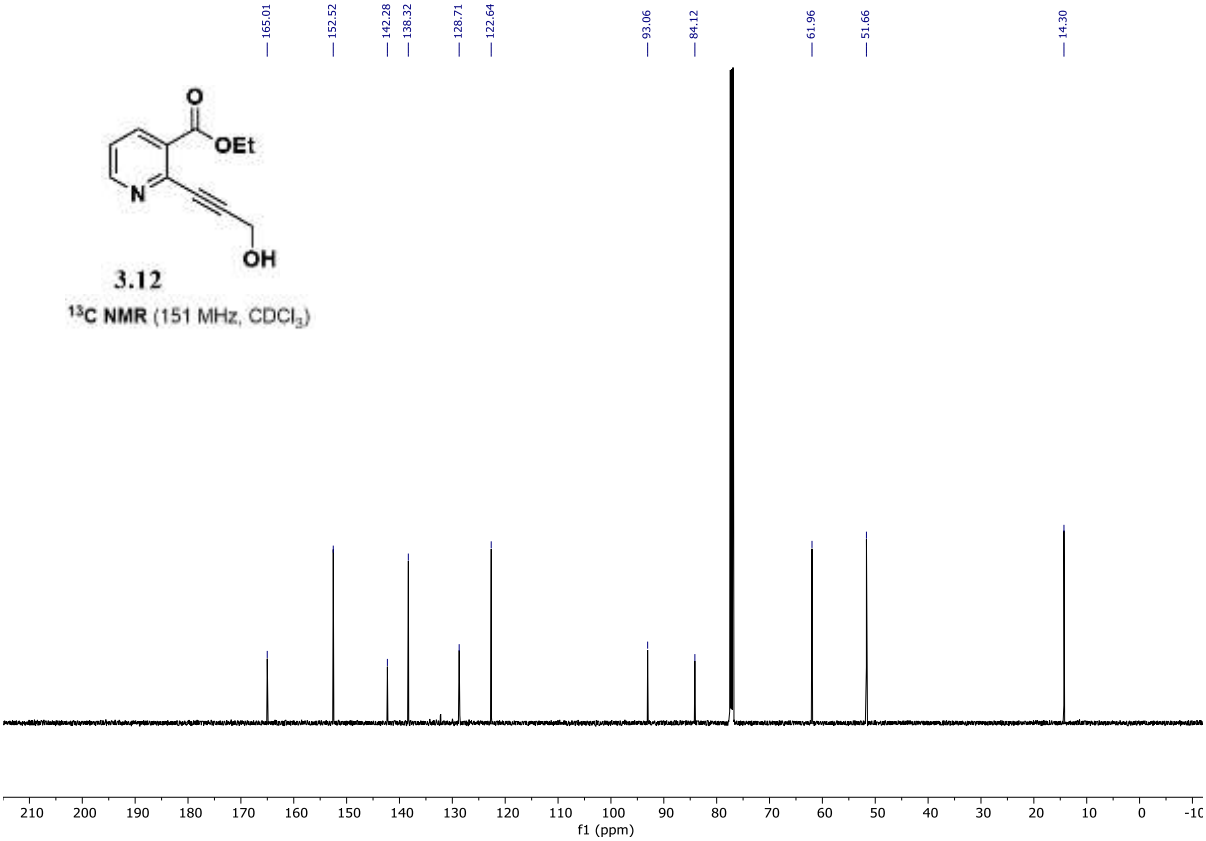

2.69
N
Me
3.10.k
1H NMR (500 MHz, CDCl3)
f1 (ppm)


144.94
142.75
129.55
128.83
127.87
127.04
126.47
125.59
124.58
120.94
116.51
109.59
65.89
36.15
N
Me
3.10.k
13C NMR (126 MHz, CDCl3)
f1 (ppm)


7.53
7.53
7.31
7.30
7.30
7.29
7.29
7.23
7.23
7.22
7.20
7.19
7.19
7.19
7.13
7.12
7.11
7.11
7.10
6.68
6.66
6.65
6.46
6.44
6.43
5.45
3.72
3.71
3.71
2.80
2.79
O
OMe
N
Me
3.10.l
1H NMR (500 MHz, CDCl3)
0.96
2.05
4.06
1.03
0.99
0.99
0.96
2.97
3.00
f1 (ppm)

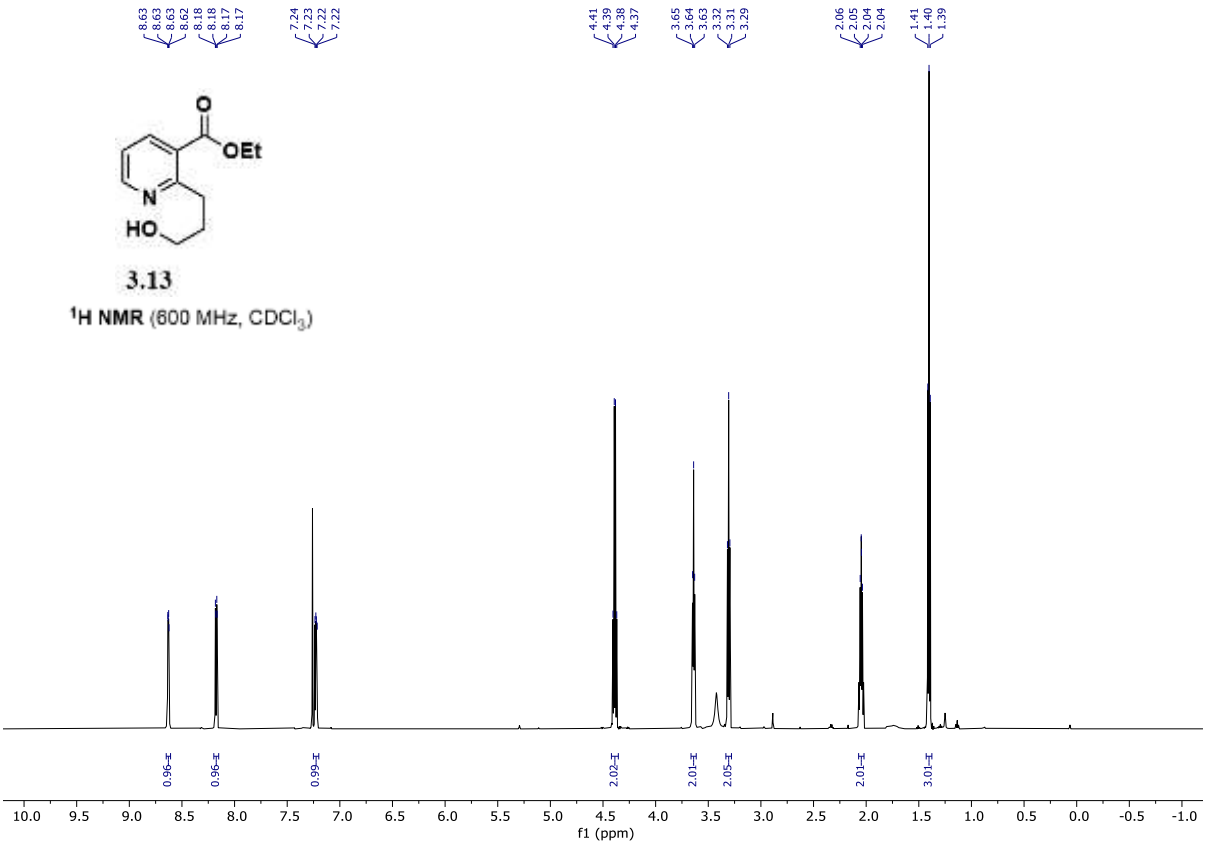

166.14
146.12
140.93
134.68
132.54
129.99
128.59
128.15
126.70
124.14
119.85
116.90
110.84
63.69
51.83
36.40
O
OMe
N
Me
3.10.1
13C NMR (126 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


8.71
8.70
8.70
8.70
8.25
8.25
8.24
8.24
7.34
7.33
7.33
7.32
4.58
4.57
4.44
4.43
4.42
4.40
2.04
2.03
2.02
1.44
1.42
1.41
O
OEt
N
OH
3.12
1H NMR (600 MHz, CDCl3)
0.97
0.98
1.02
2.00
2.05
0.90
3.07
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 -0.5 -1.0
f1 (ppm)



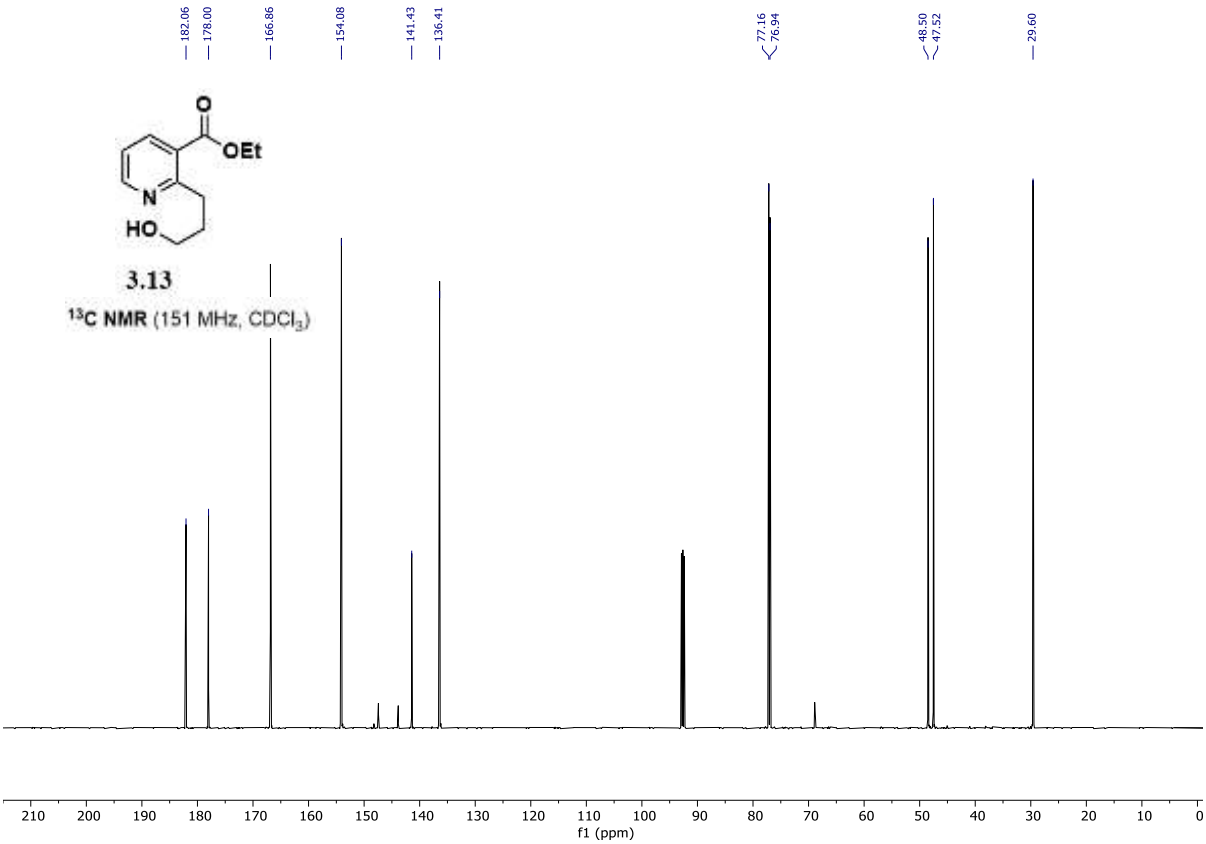
3.12

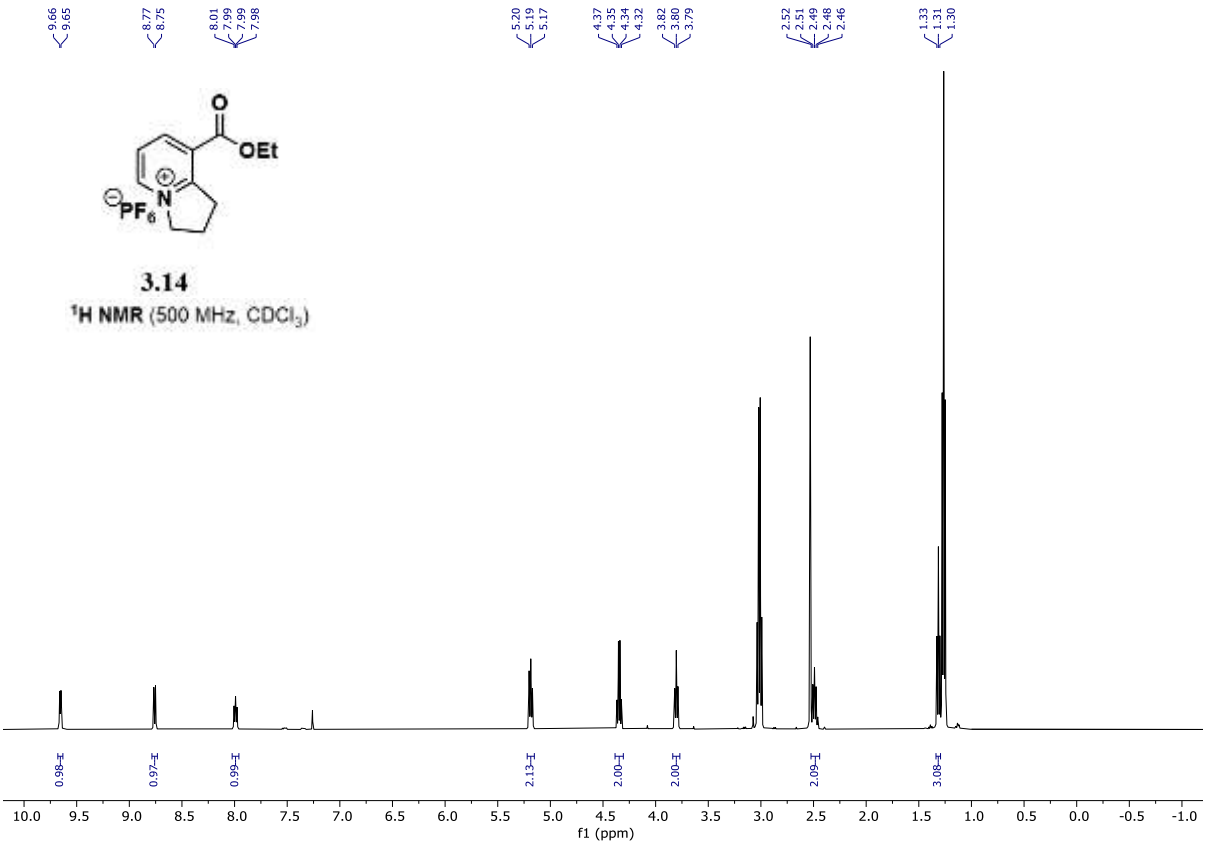
^{13}C NMR (151 MHz, $CDCl_3$)

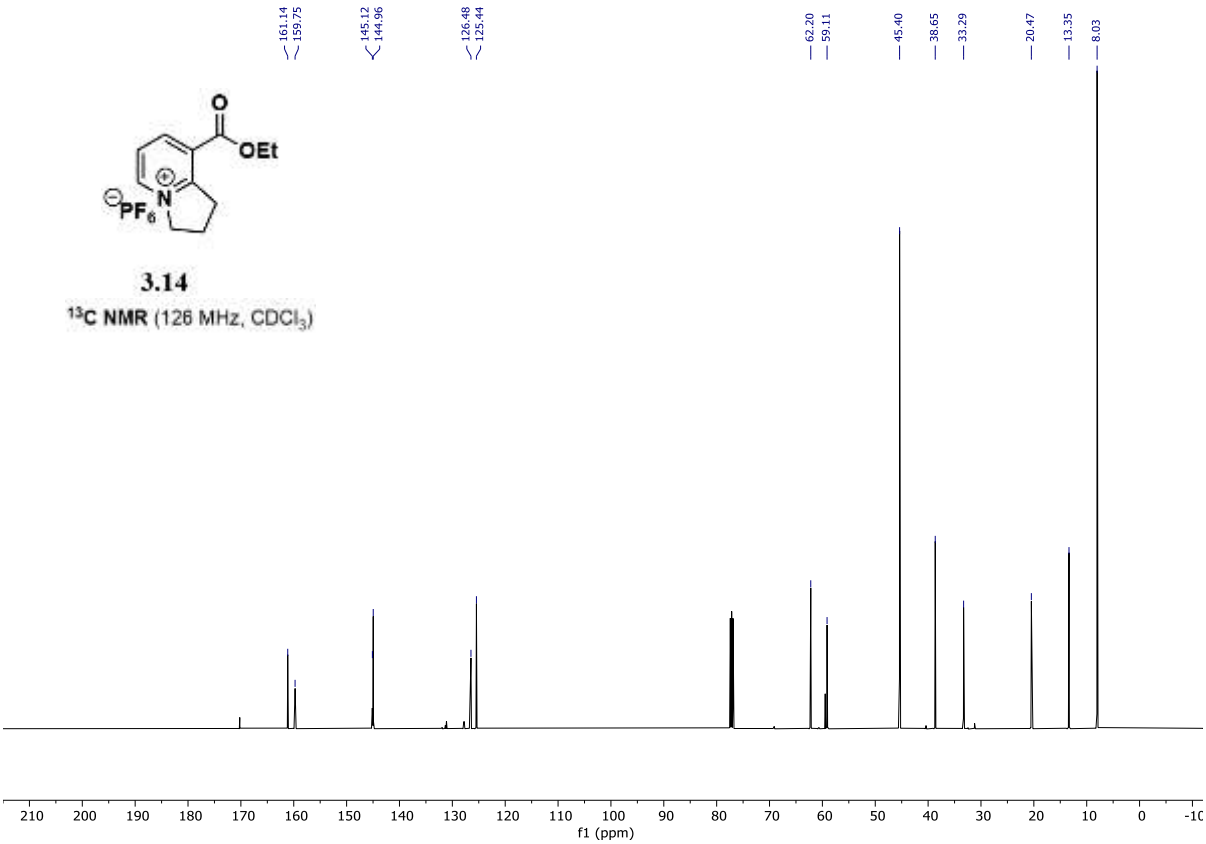


3.13

^{1}H NMR (600 MHz, $CDCl_3$)

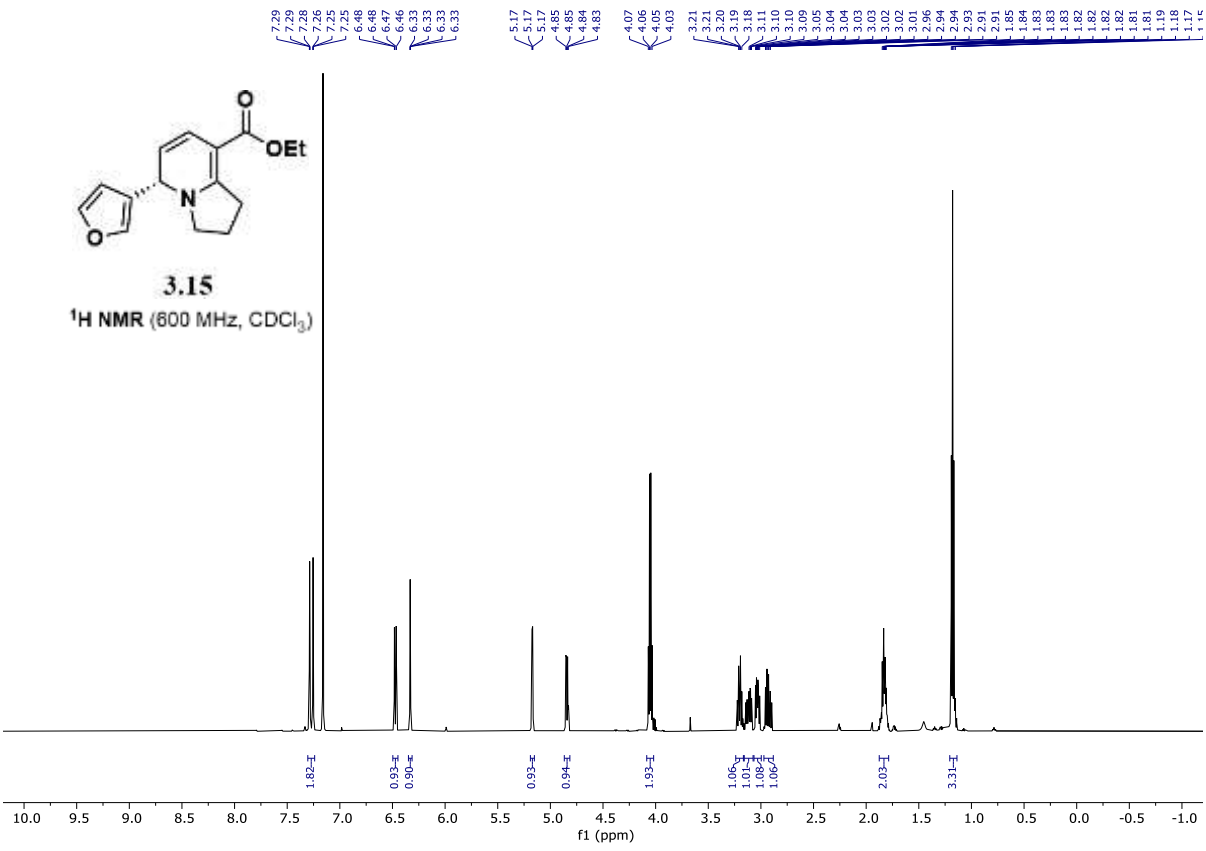

182.06
178.00
166.86
154.08
141.43
136.41
77.16
76.94
48.50
47.52
29.60
O
OEt
N
HO
3.13
13C NMR (151 MHz, CDCl3)
f1 (ppm)


9.66
9.65
8.77
8.75
8.01
7.99
7.99
7.98
5.20
5.19
5.17
4.37
4.35
4.34
4.32
3.82
3.80
3.79
2.52
2.51
2.49
2.48
2.46
1.33
1.31
1.30
O
OEt
N
PF6
3.14
1H NMR (500 MHz, CDCl3)
0.98
0.97
0.99
2.13
2.00
2.00
2.09
3.08
f1 (ppm)



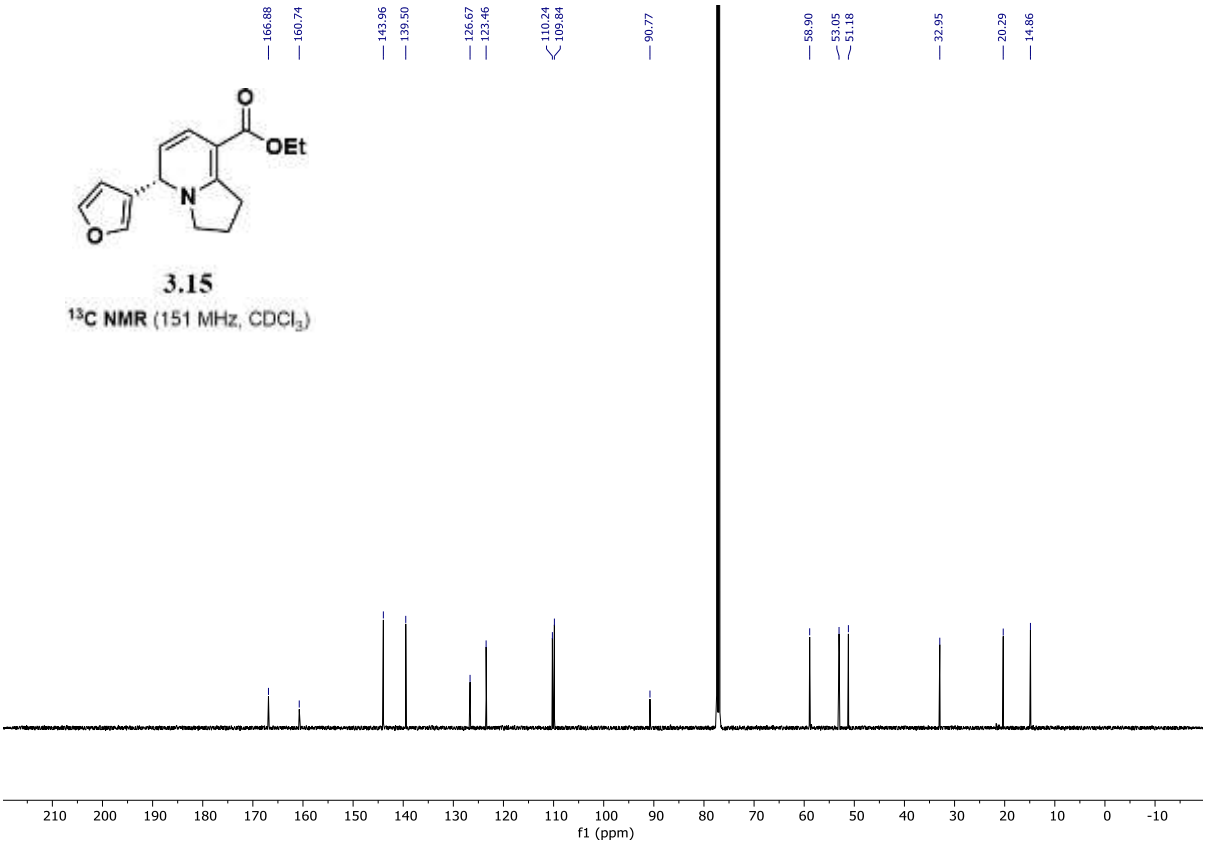
3.14

^{13}C NMR (126 MHz, $CDCl_3$)



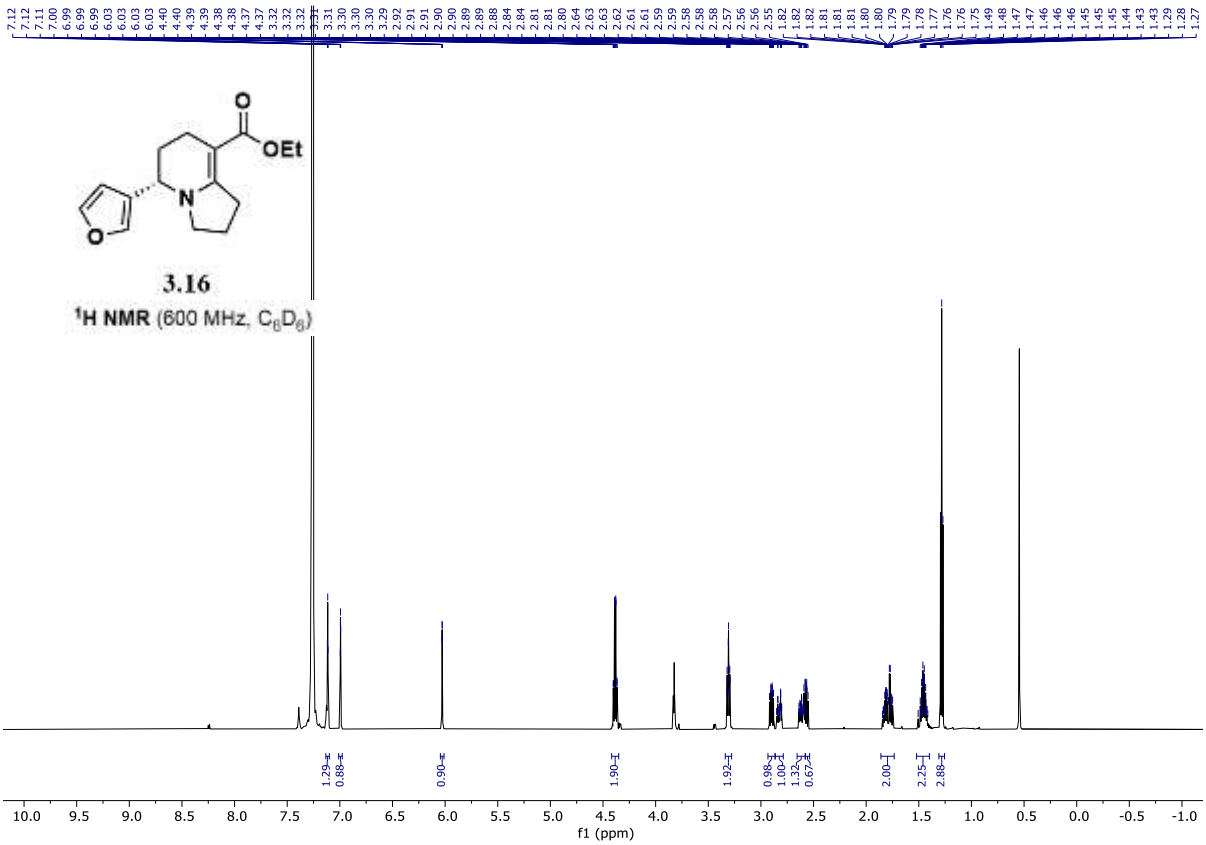
3.15

^{1}H NMR (600 MHz, $CDCl_3$)



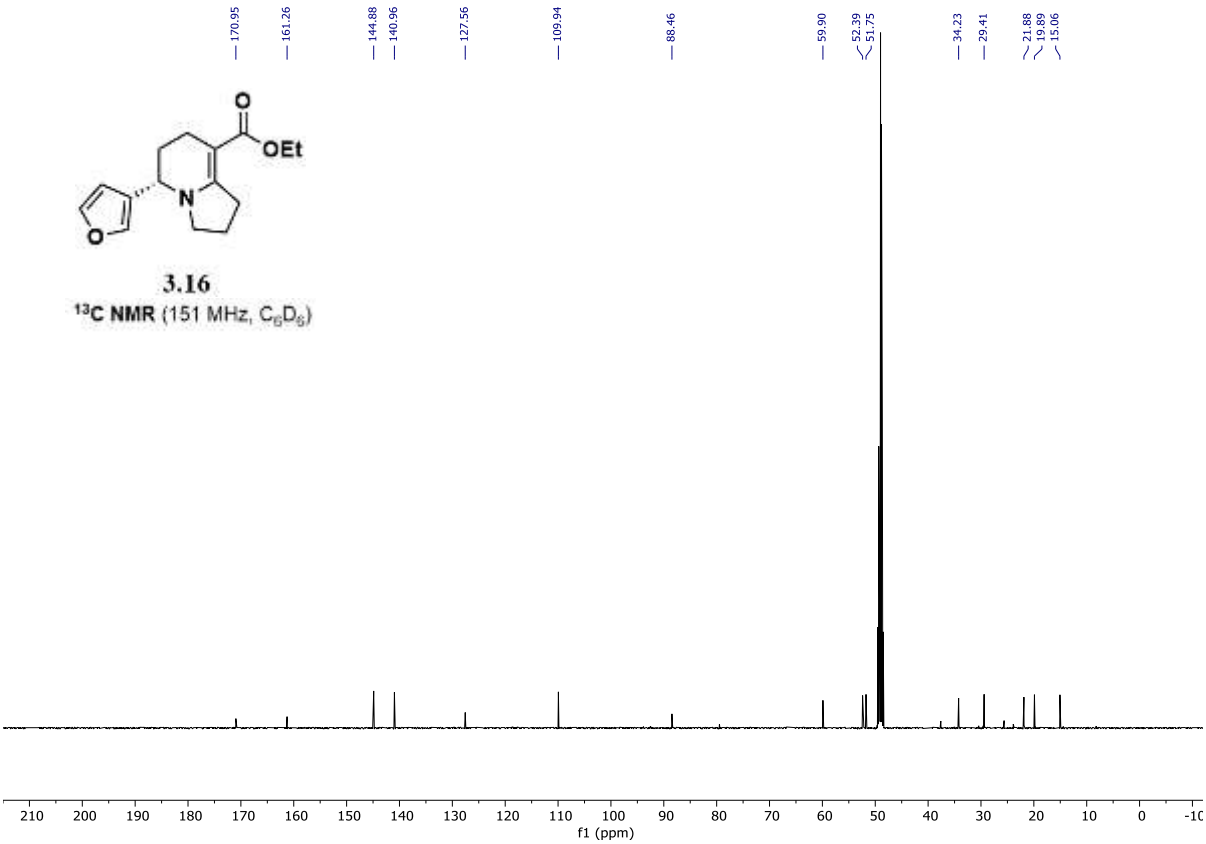
3.15

^{13}C NMR (151 MHz, $CDCl_3$)



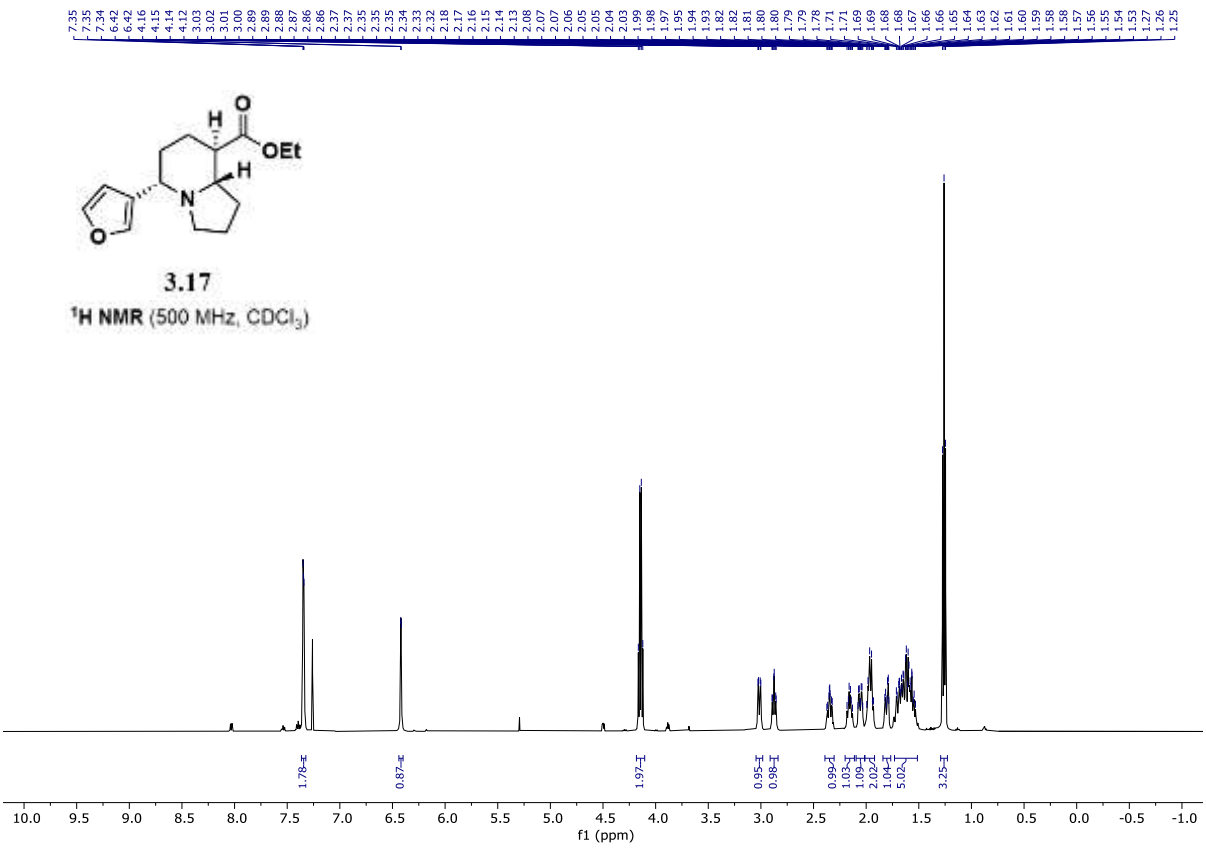
3.16

^{1}H NMR (600 MHz, C_6D_6)



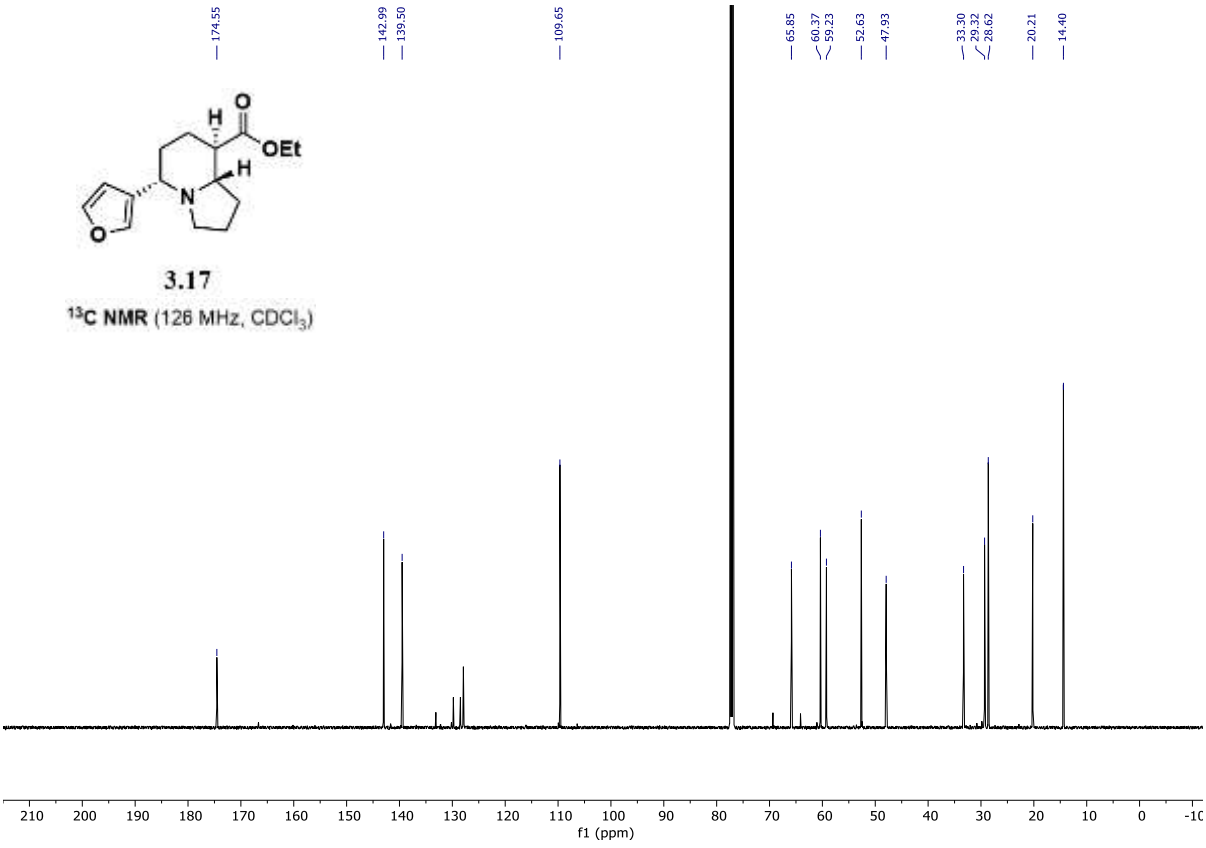
3.16

^{13}C NMR (151 MHz, C_6D_6)



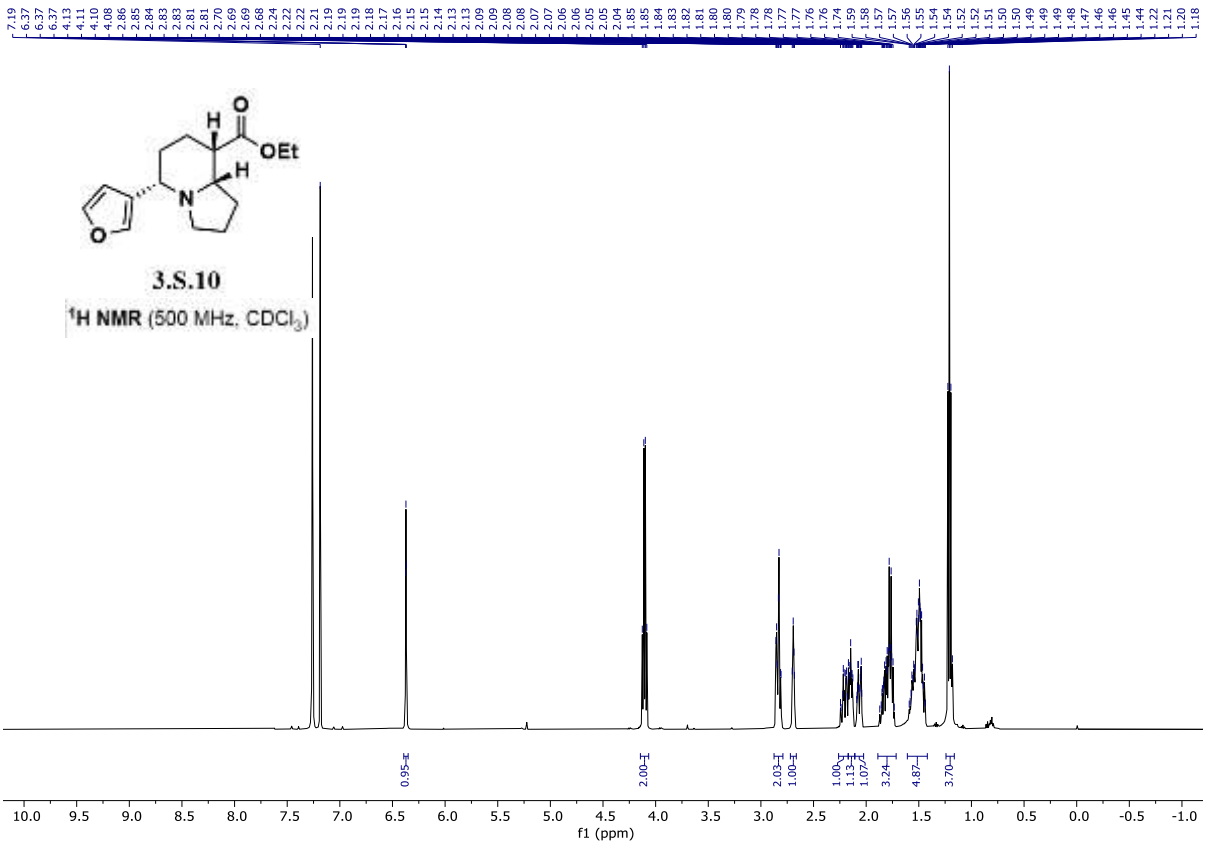
3.17

^{1}H NMR (500 MHz, $CDCl_3$)



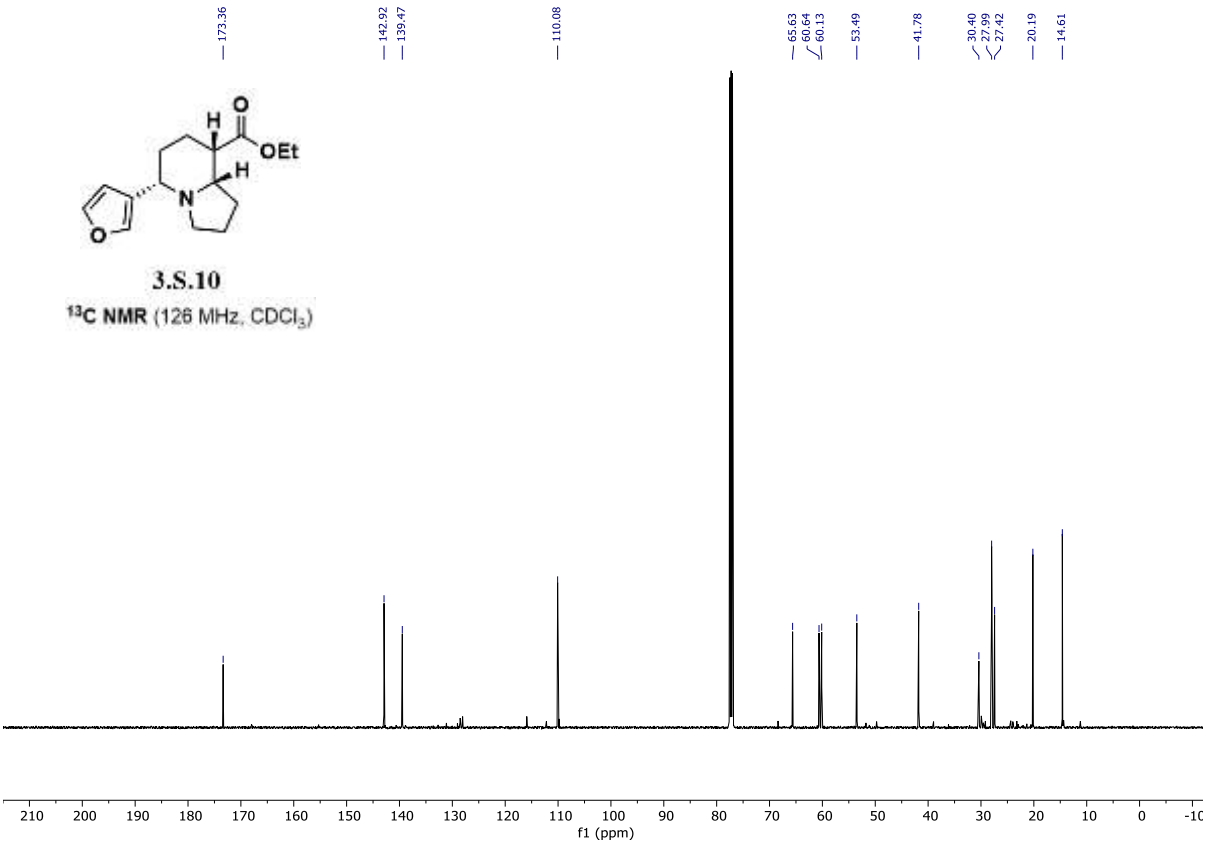
3.17

^{13}C NMR (126 MHz, $CDCl_3$)



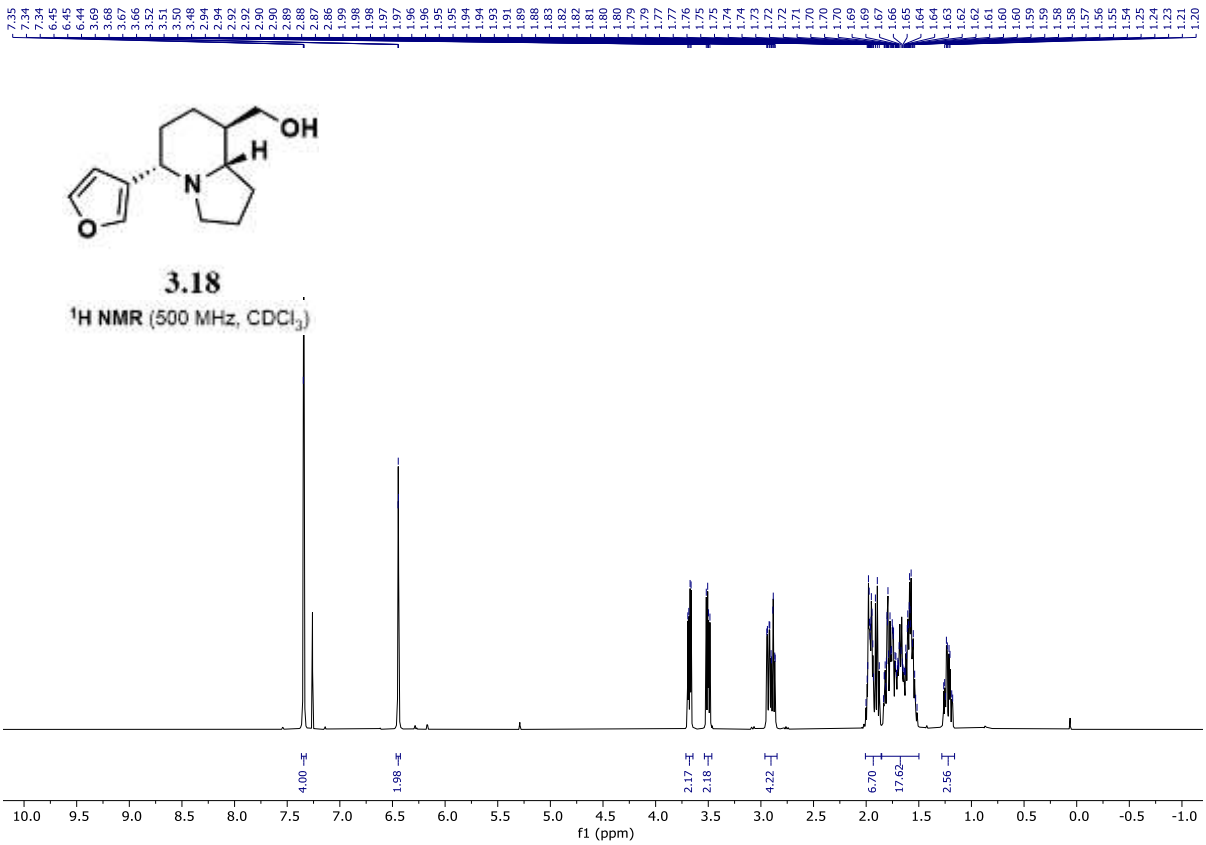
3.S.10

^{1}H NMR (500 MHz, $CDCl_3$)



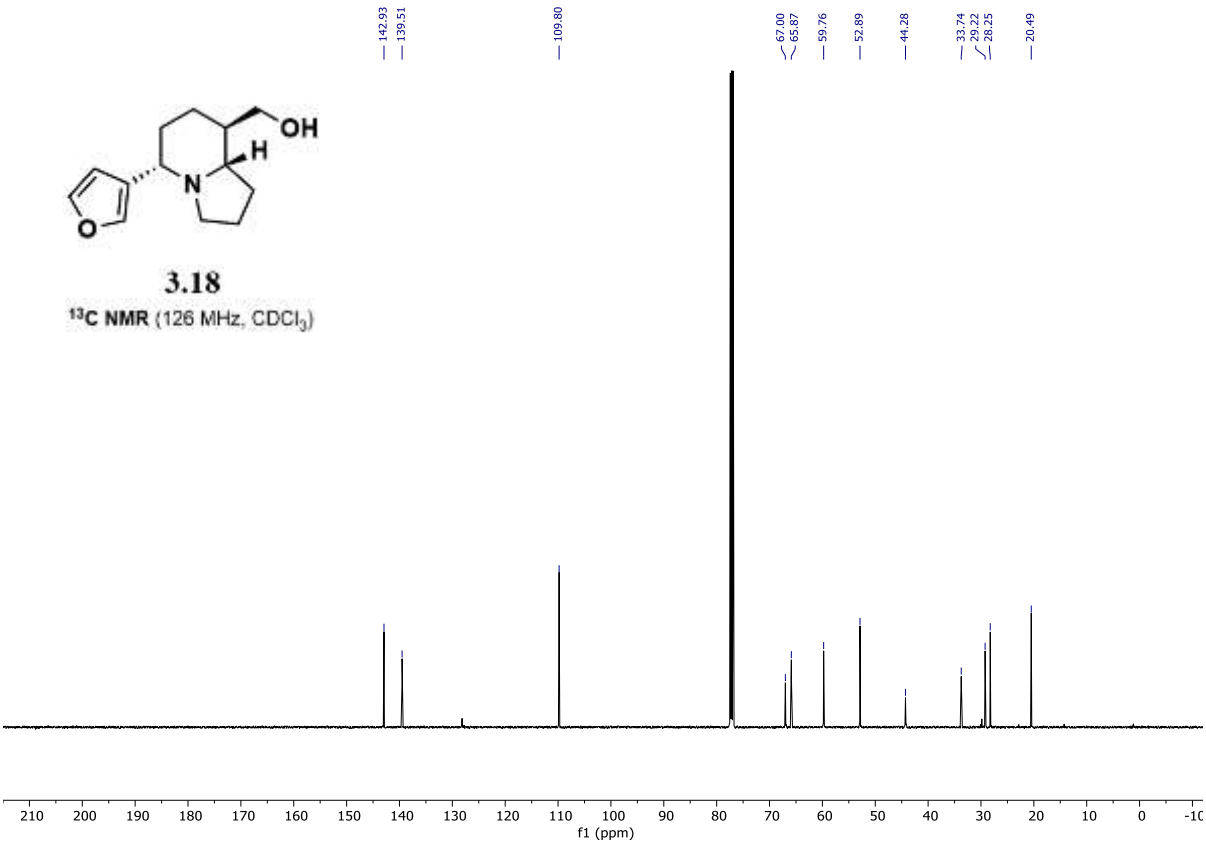
3.S.10

^{13}C NMR (126 MHz, $CDCl_3$)



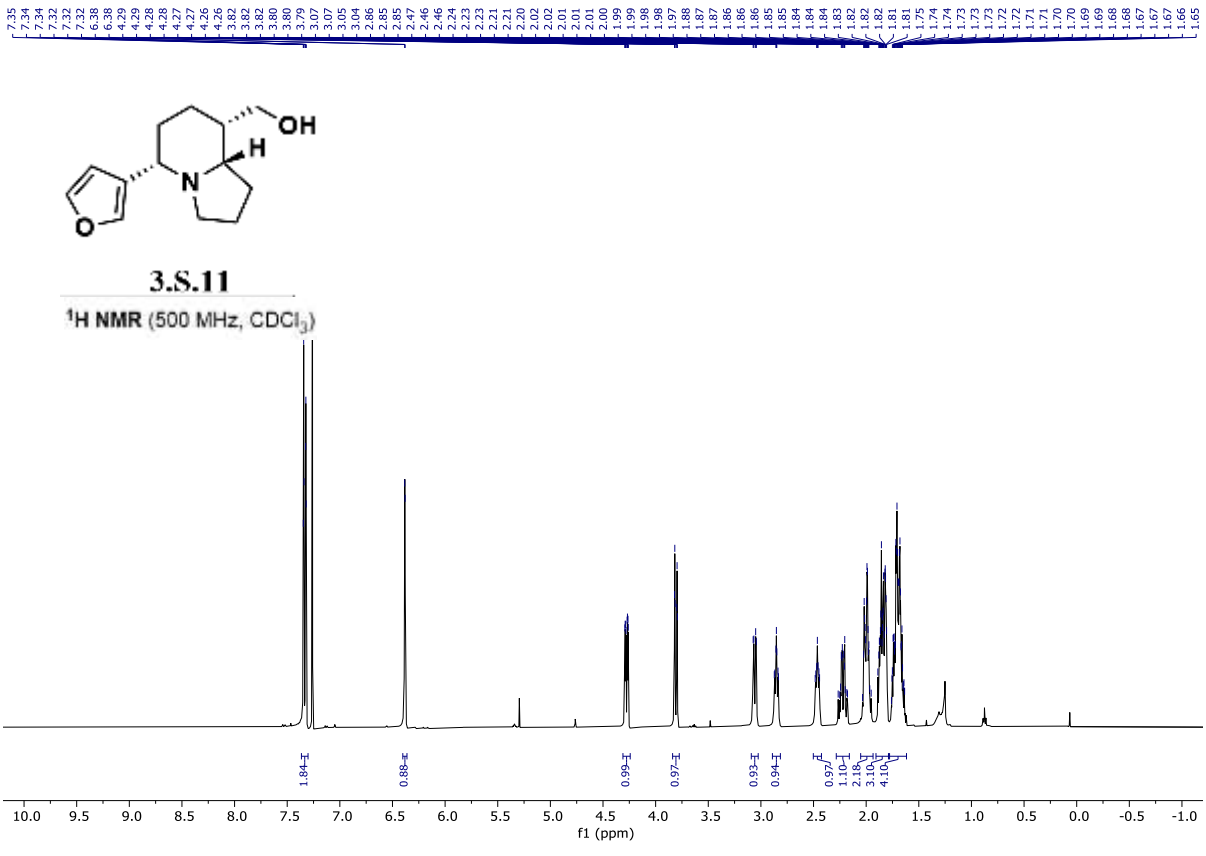
3.18

^{1}H NMR (500 MHz, $CDCl_3$)



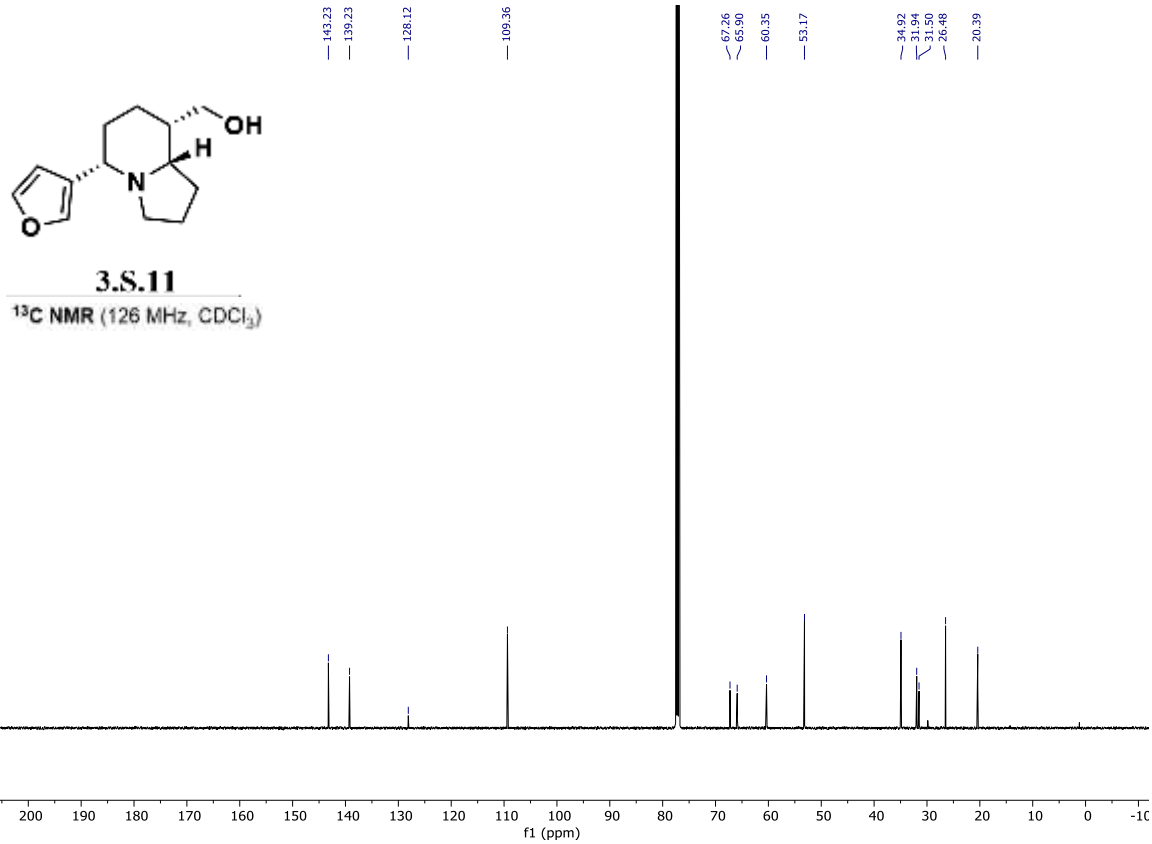
3.18

^{13}C NMR (126 MHz, $CDCl_3$)



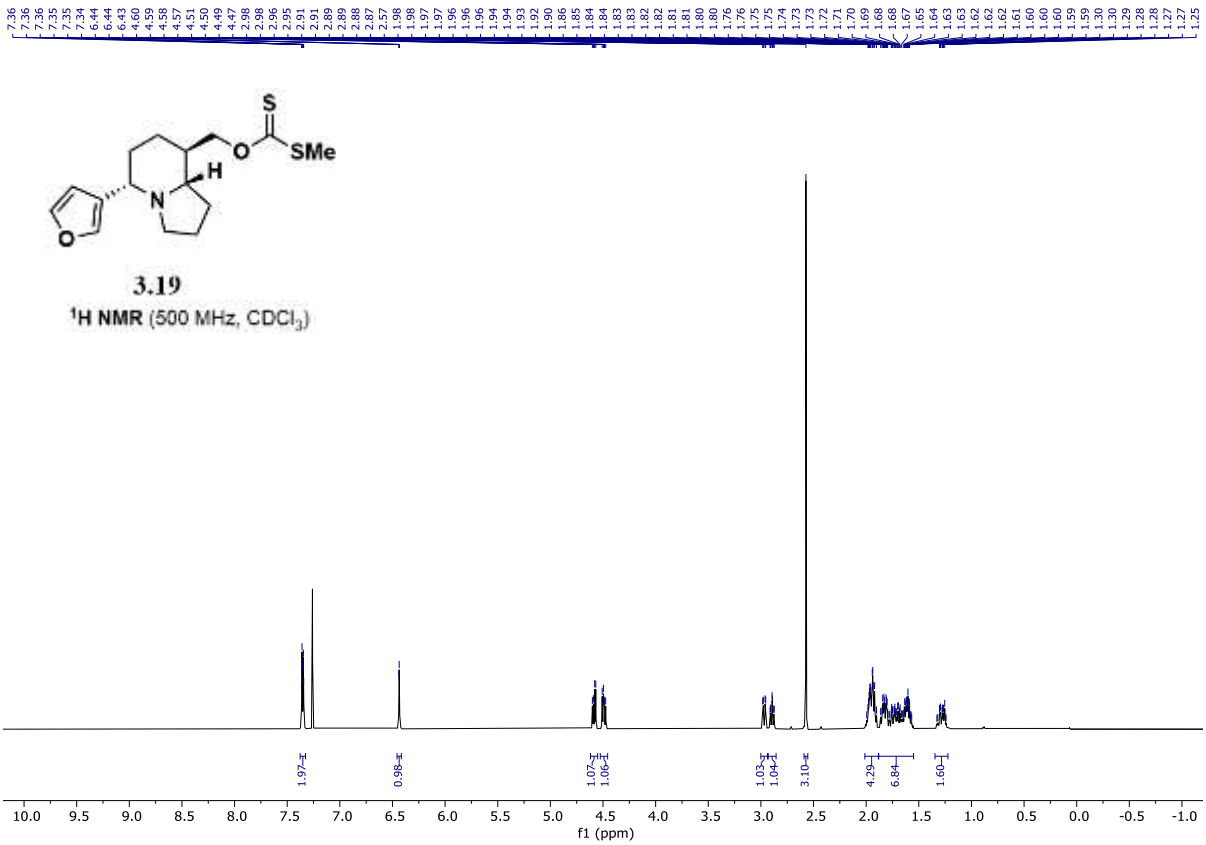
3.S.11

^{1}H NMR (500 MHz, $CDCl_3$)



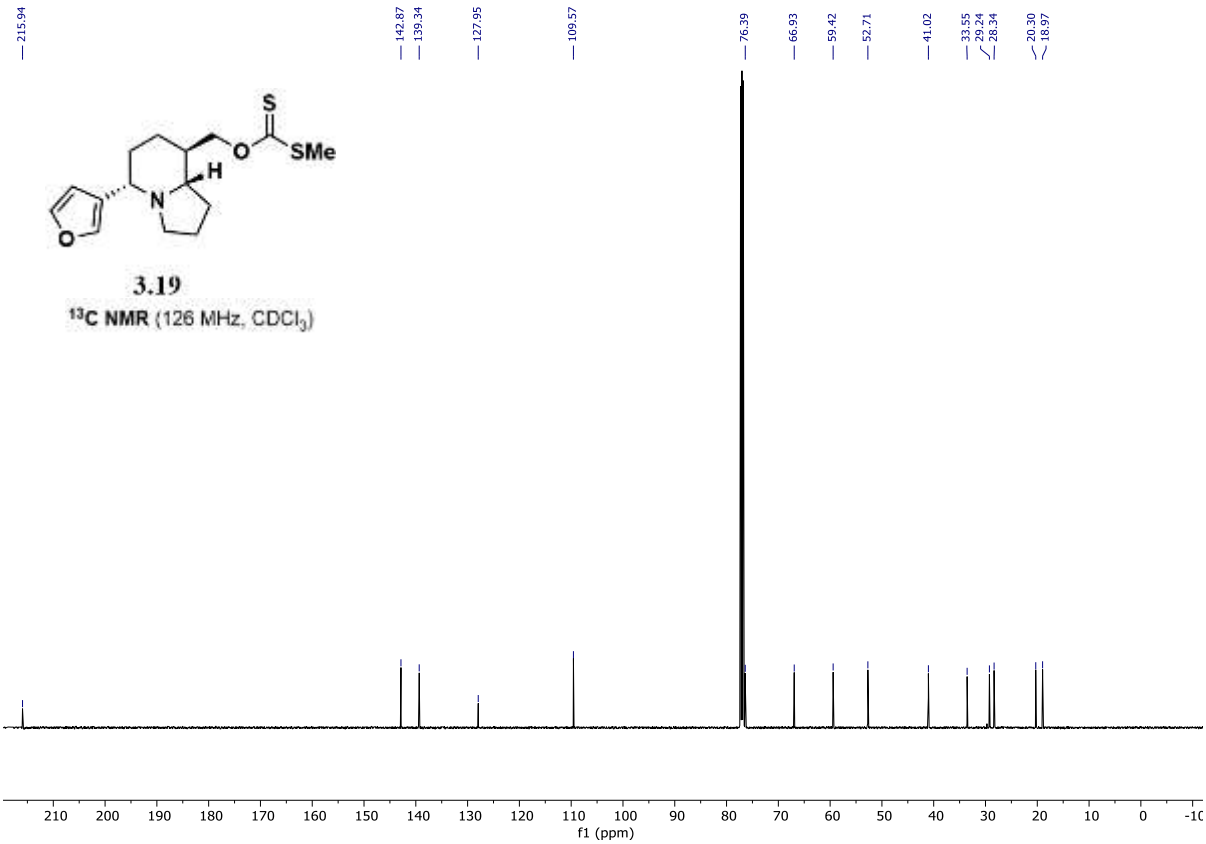
3.S.11

^{13}C NMR (126 MHz, $CDCl_3$)



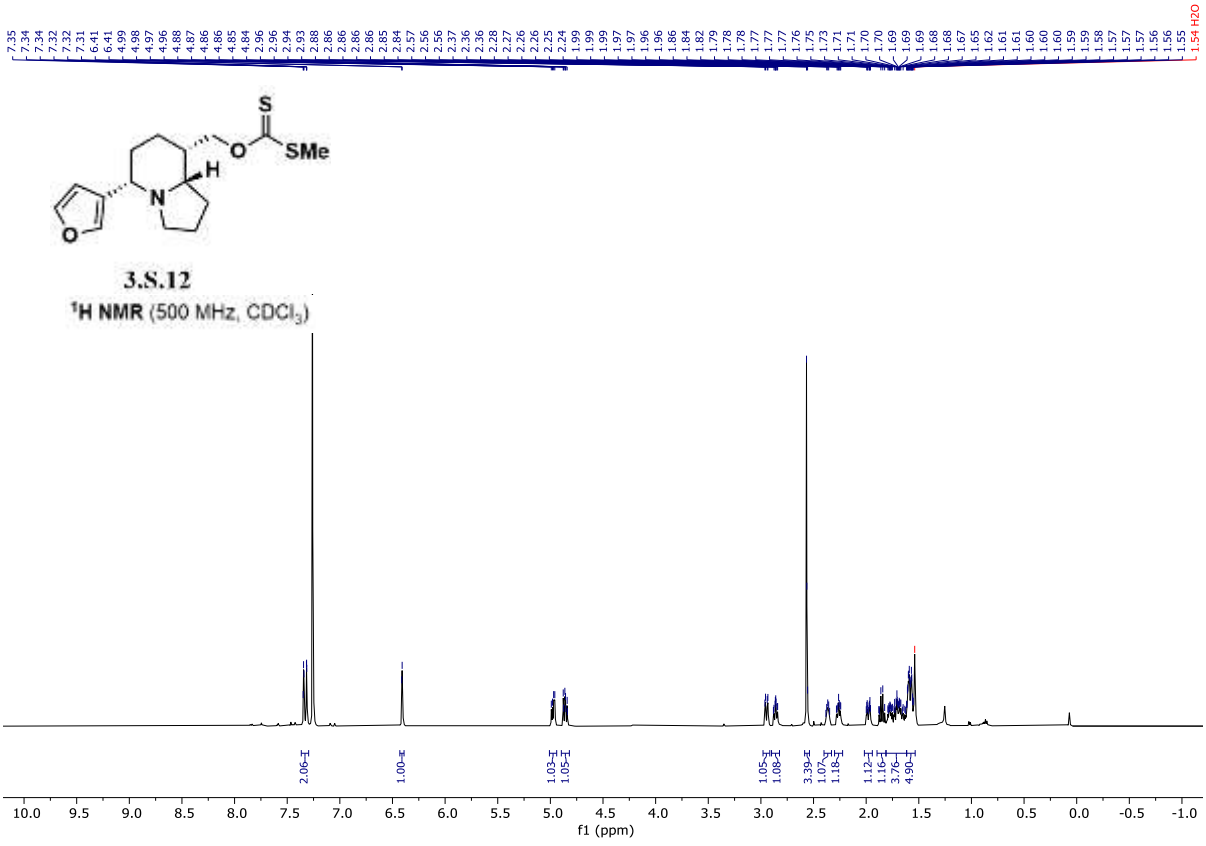
3.19

^{1}H NMR (500 MHz, $CDCl_3$)



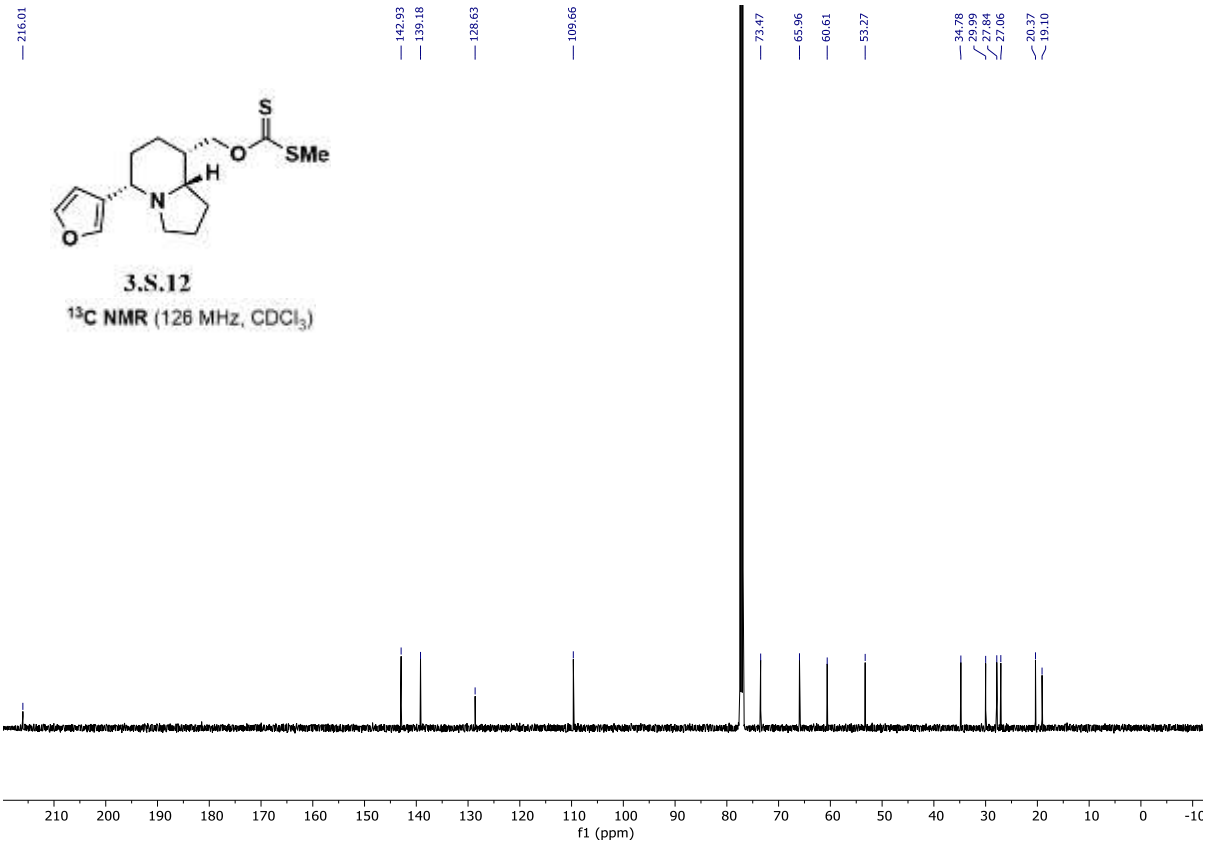
3.19

^{13}C NMR (126 MHz, $CDCl_3$)



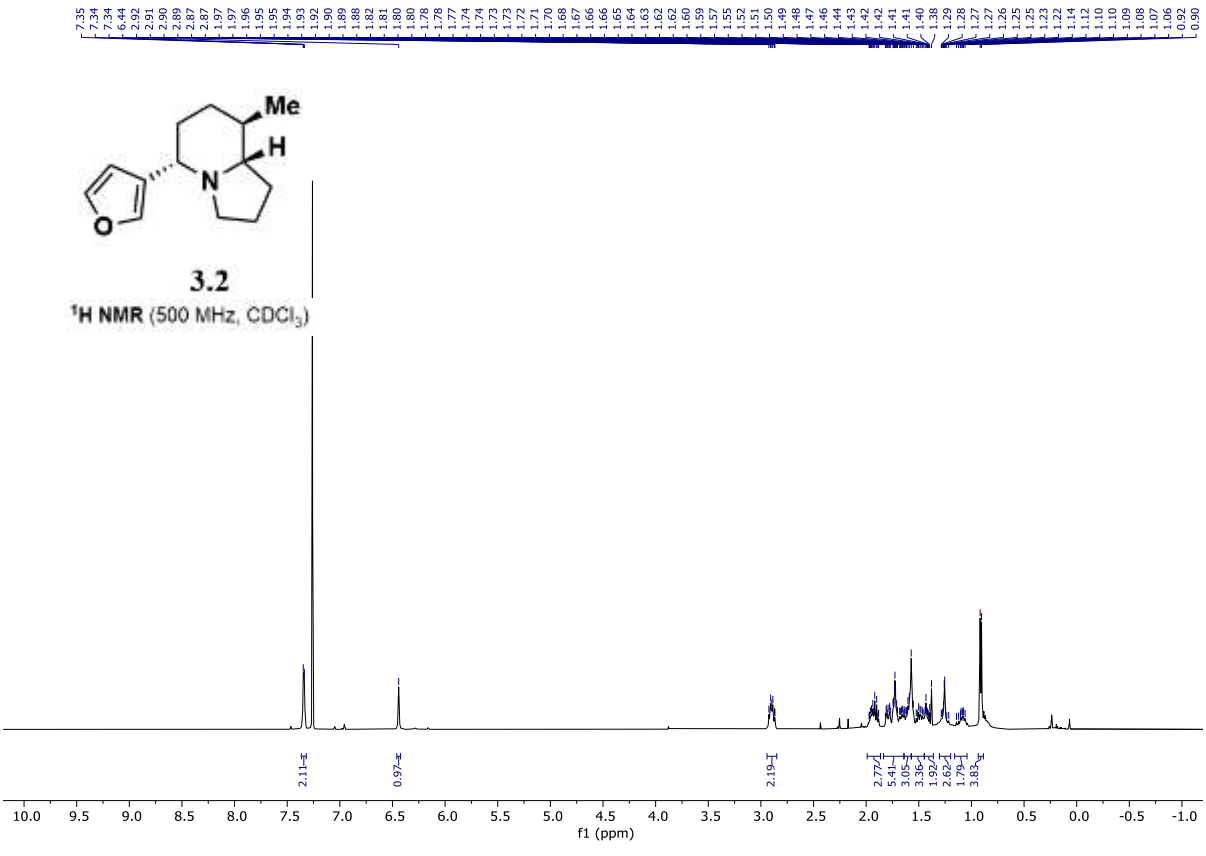
3.S.12

^{1}H NMR (500 MHz, $CDCl_3$)



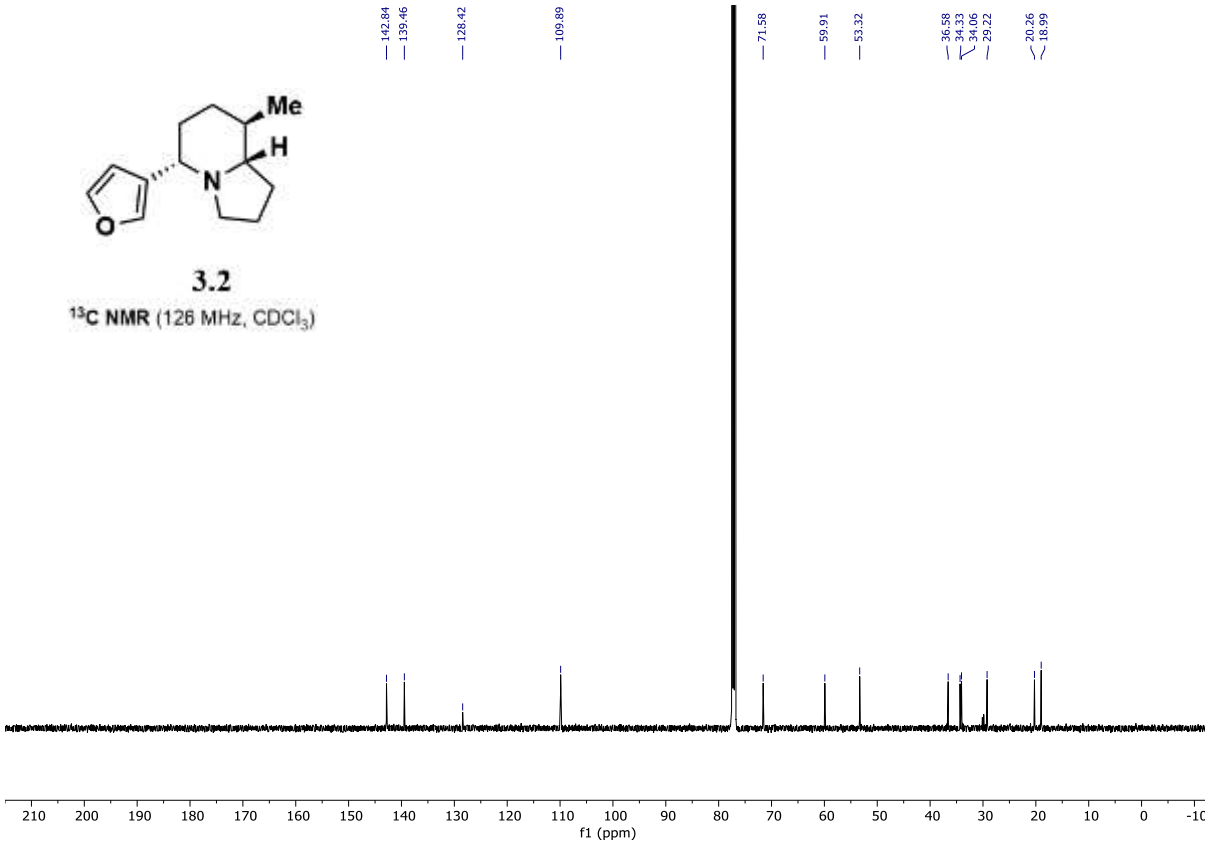
3.S.12

^{13}C NMR (126 MHz, $CDCl_3$)



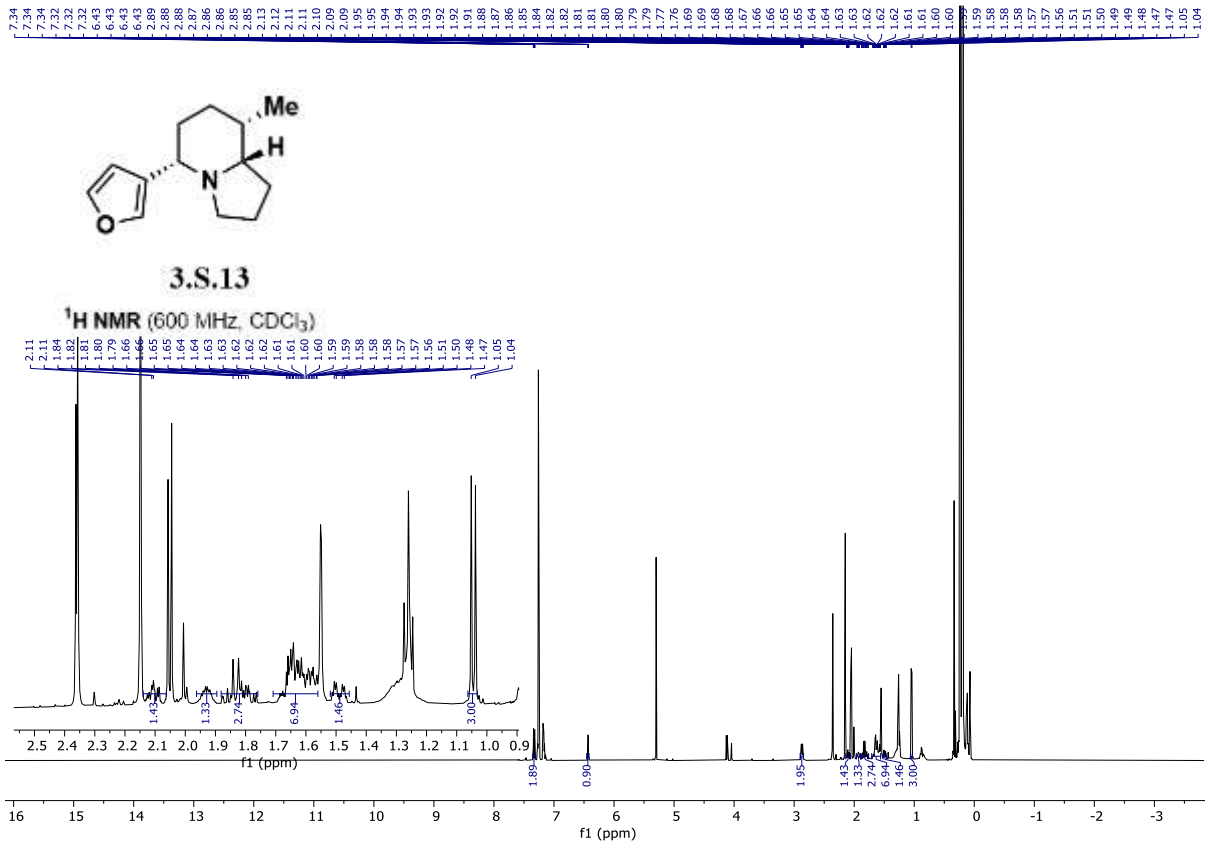
3.2

^{1}H NMR (500 MHz, $CDCl_3$)



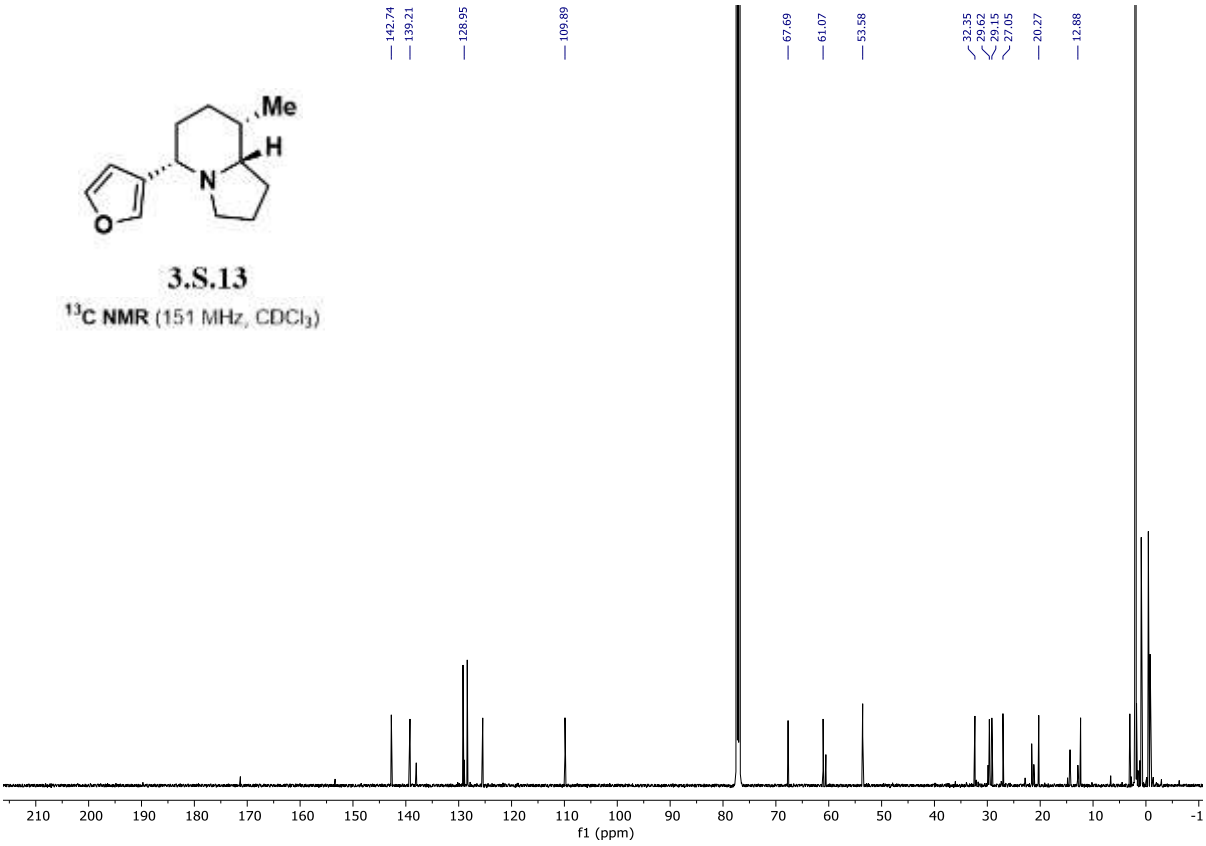
3.2

^{13}C NMR (126 MHz, $CDCl_3$)



3.S.13

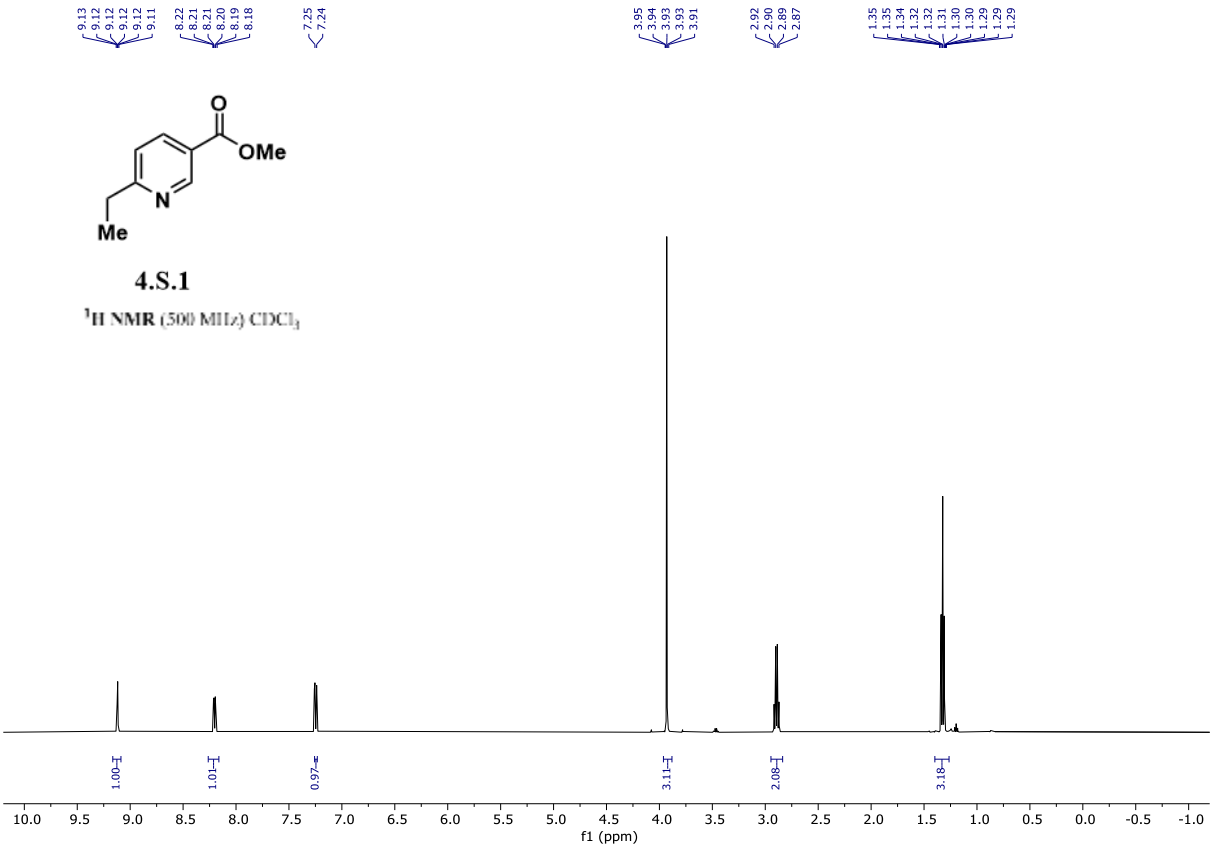
^{1}H NMR (600 MHz, $CDCl_3$)



3.S.13

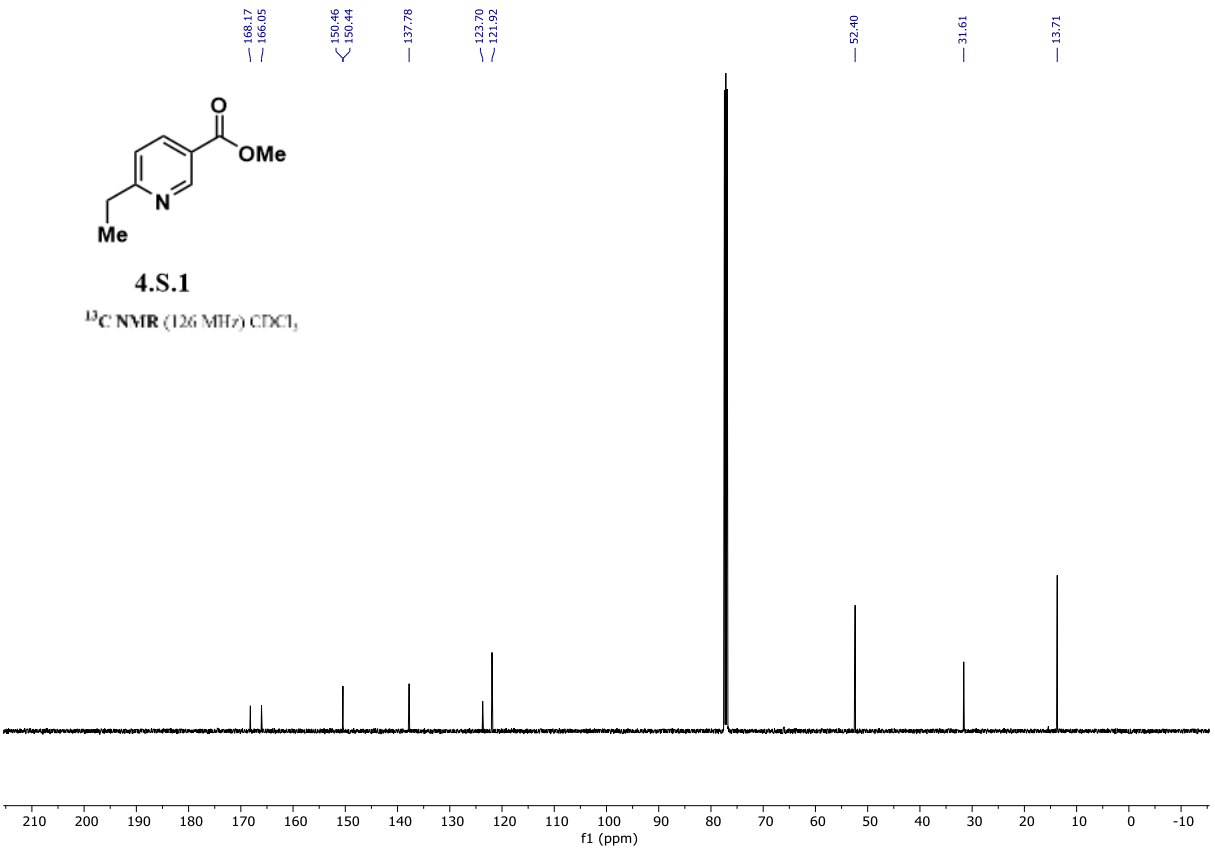
^{13}C NMR (151 MHz, $CDCl_3$)

Appendix C: NMR Spectra for Chapter 4



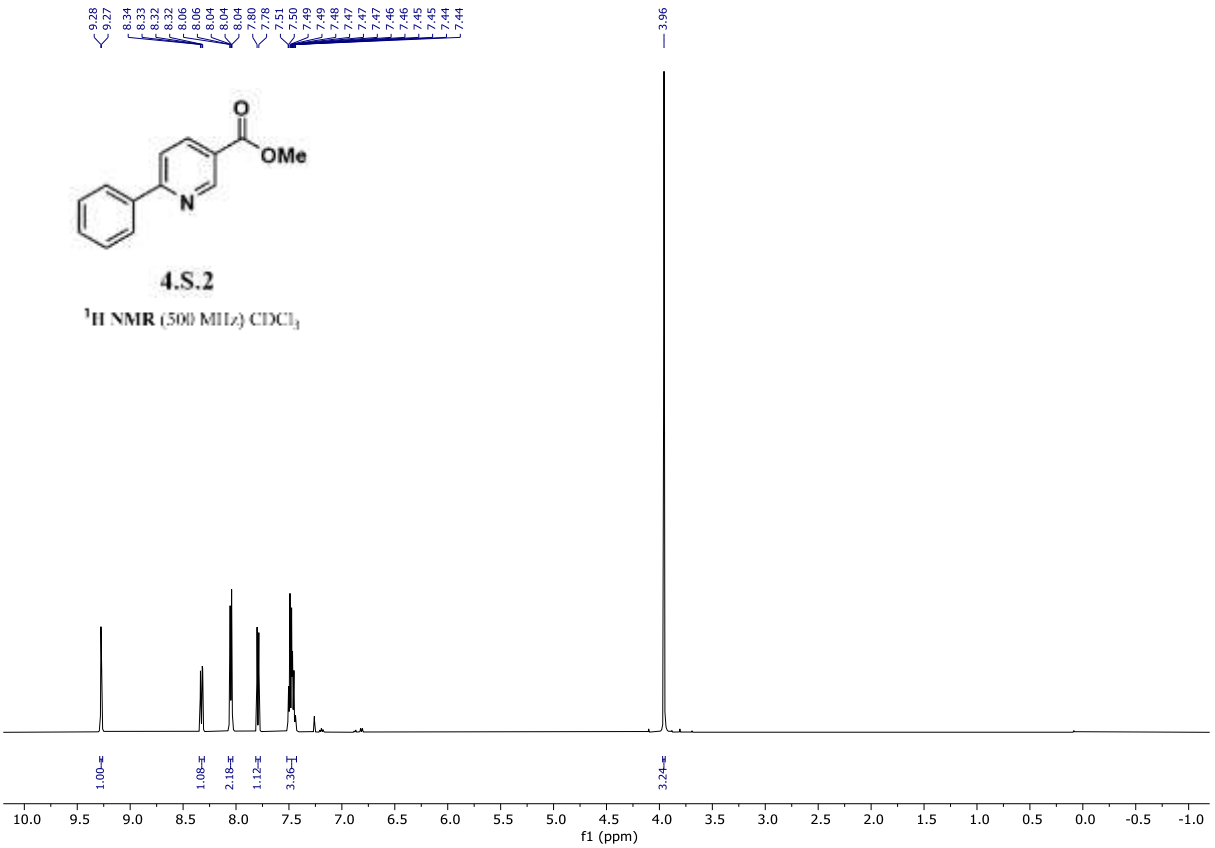
4.S.1

^{1}H NMR (500 MHz) $CDCl_3$



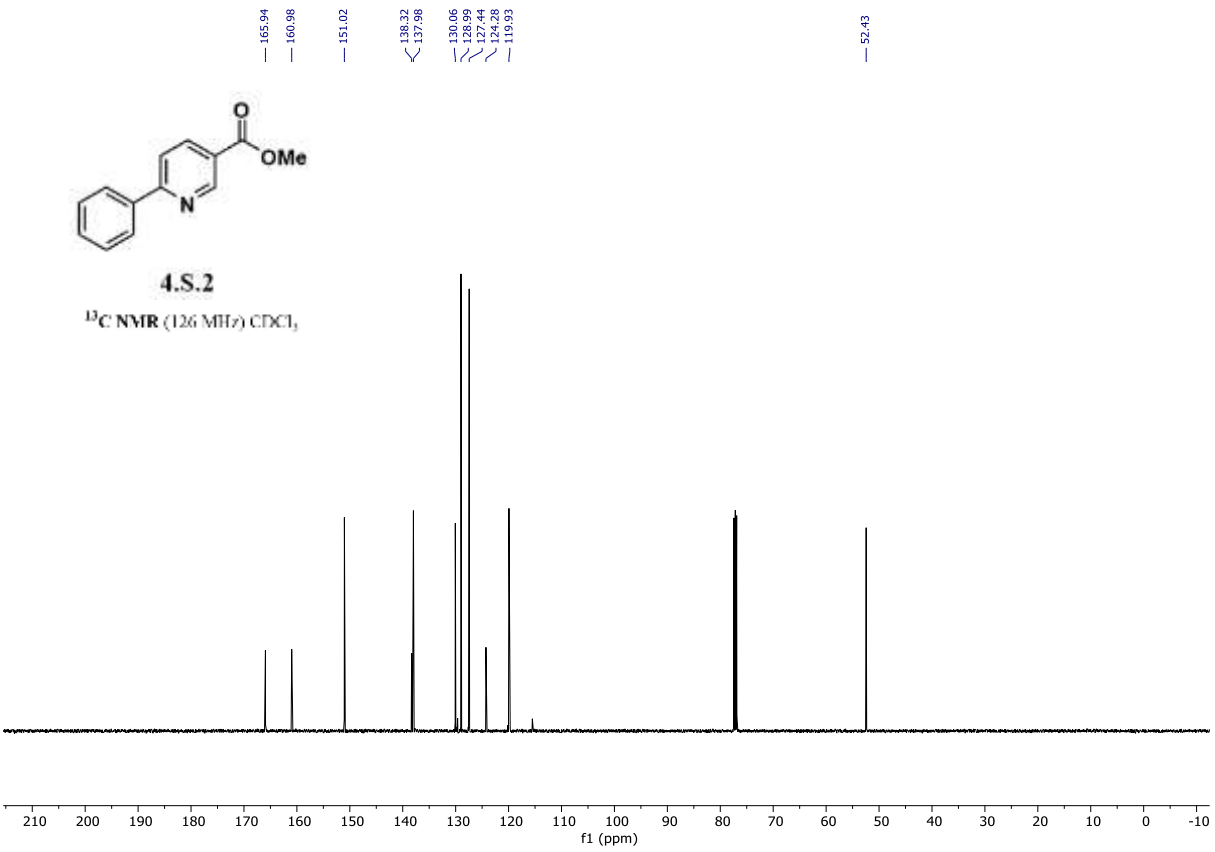
4.S.1

^{13}C NMR (126 MHz) $CDCl_3$



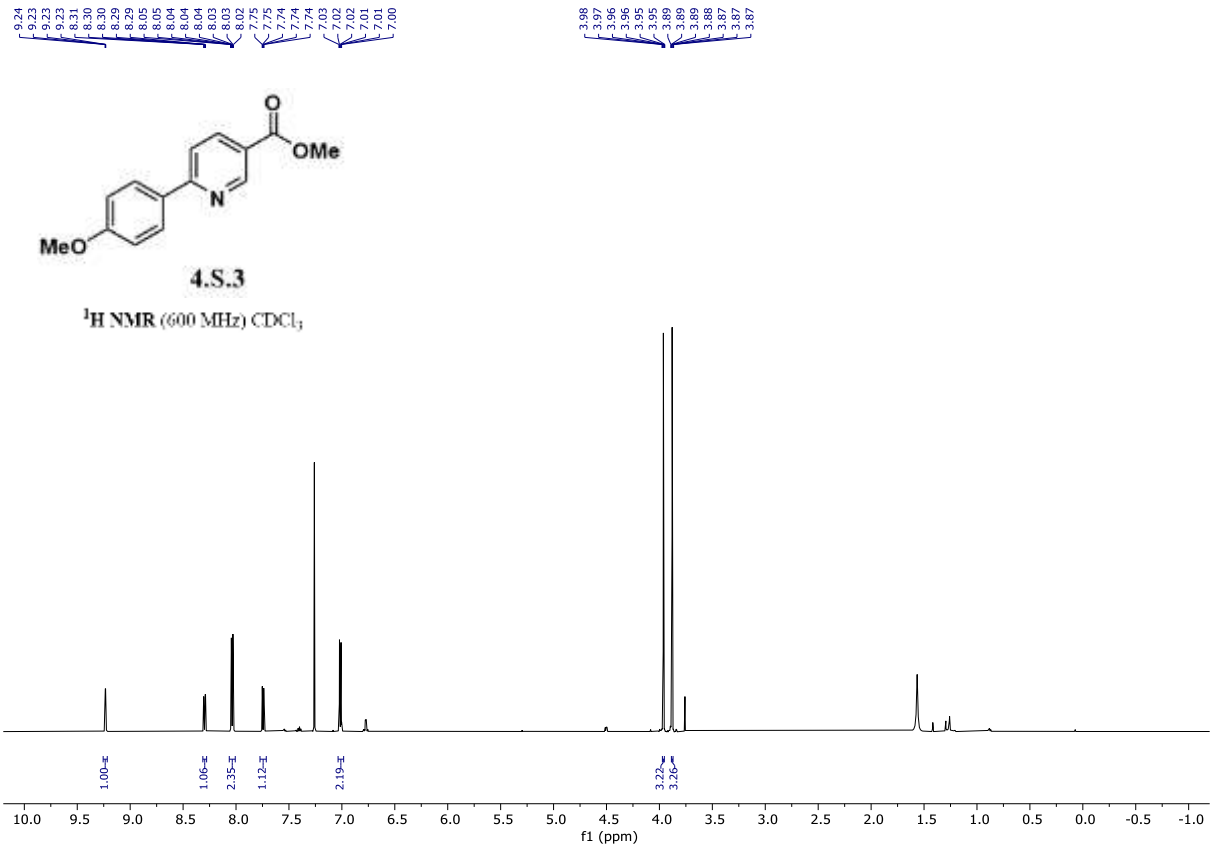
4.S.2

^{1}H NMR (500 MHz) $CDCl_3$



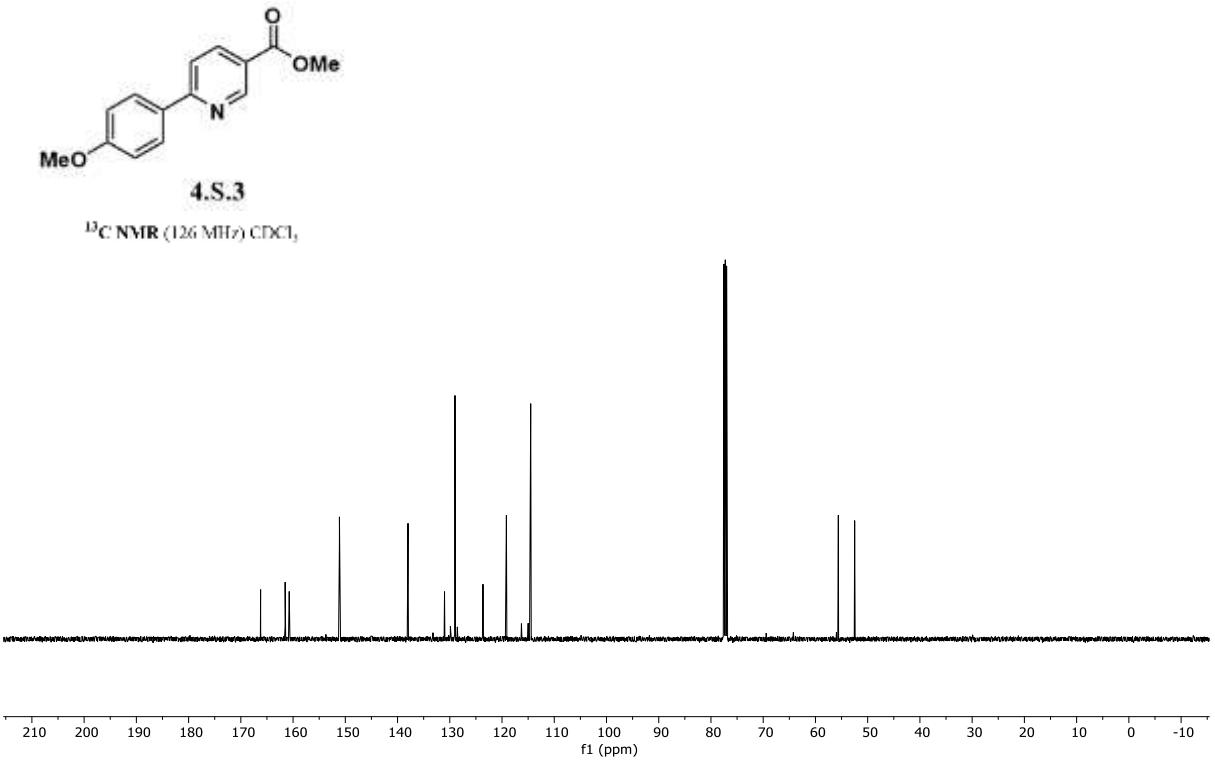
4.S.2

^{13}C NMR (126 MHz) $CDCl_3$



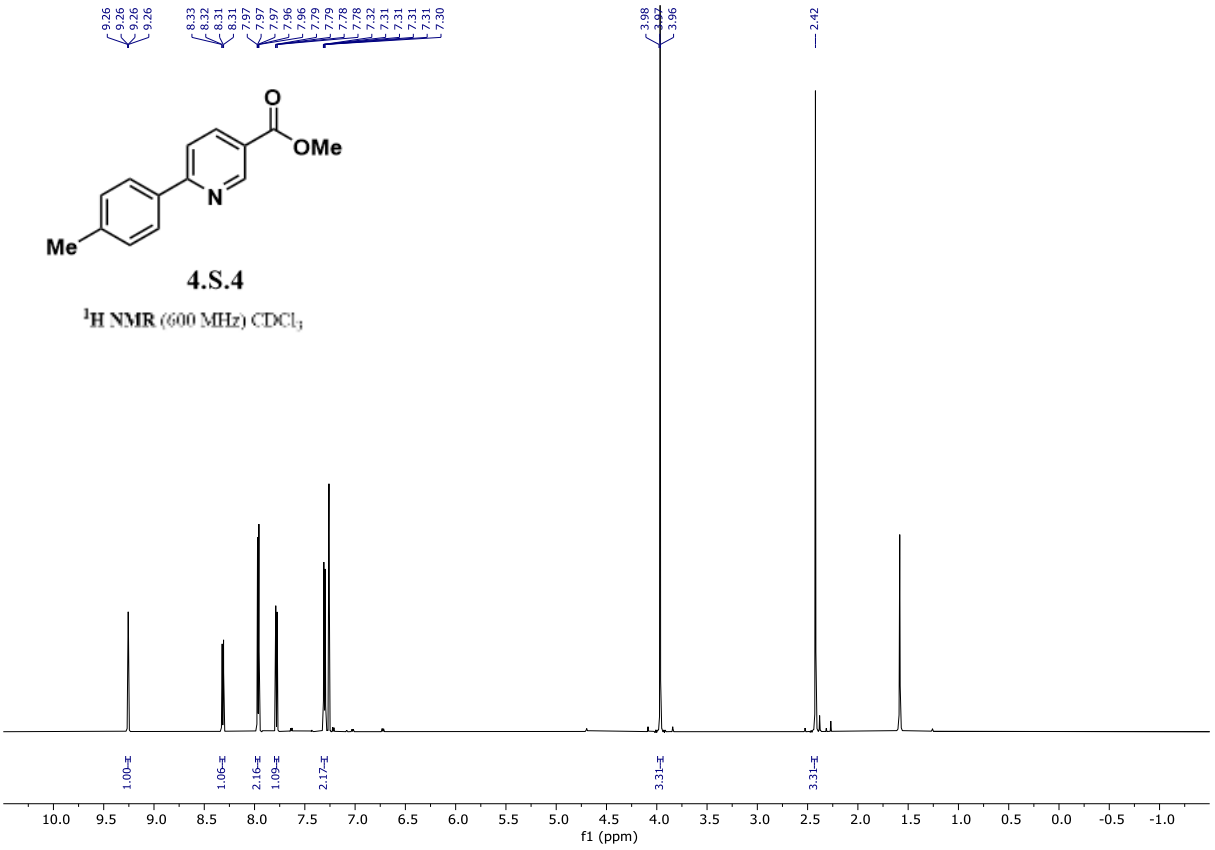
4.S.3

^{1}H NMR (600 MHz) $CDCl_3$



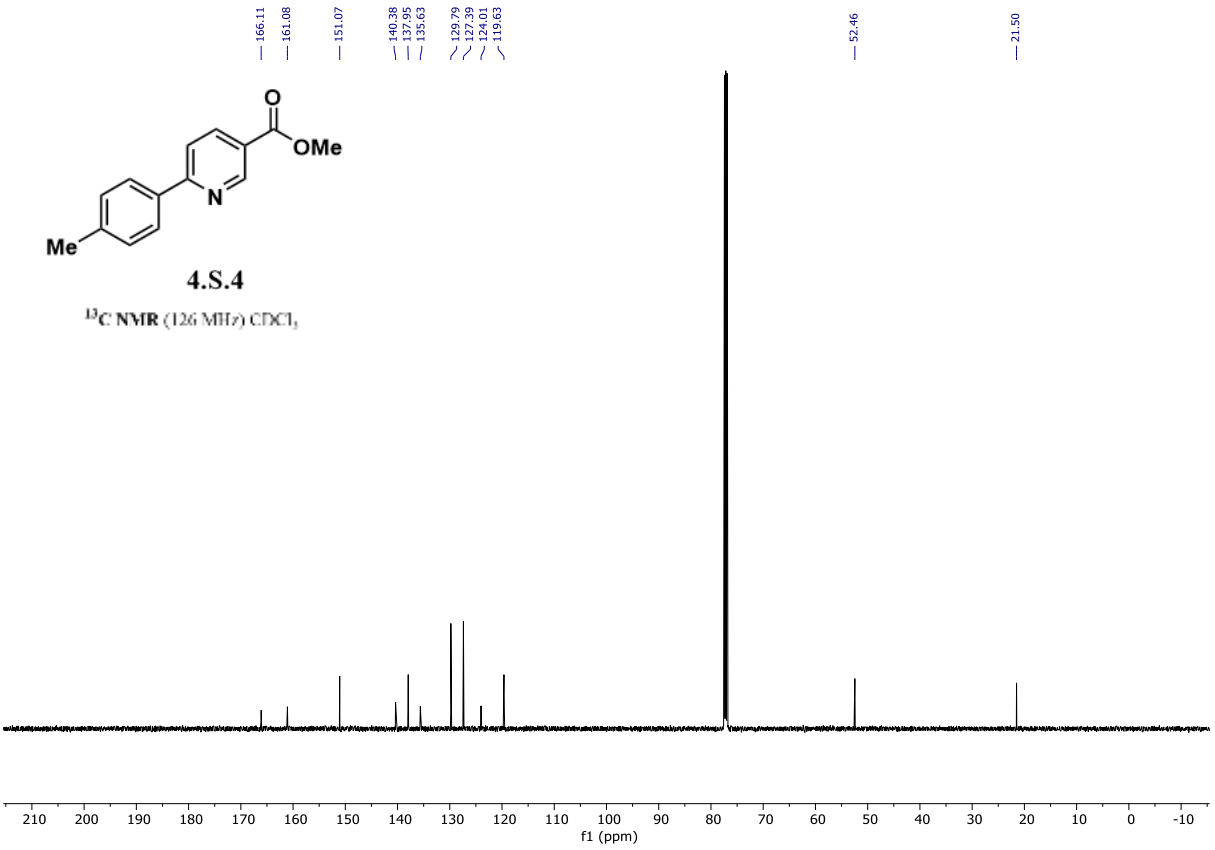
4.S.3

^{13}C NMR (126 MHz) $CDCl_3$



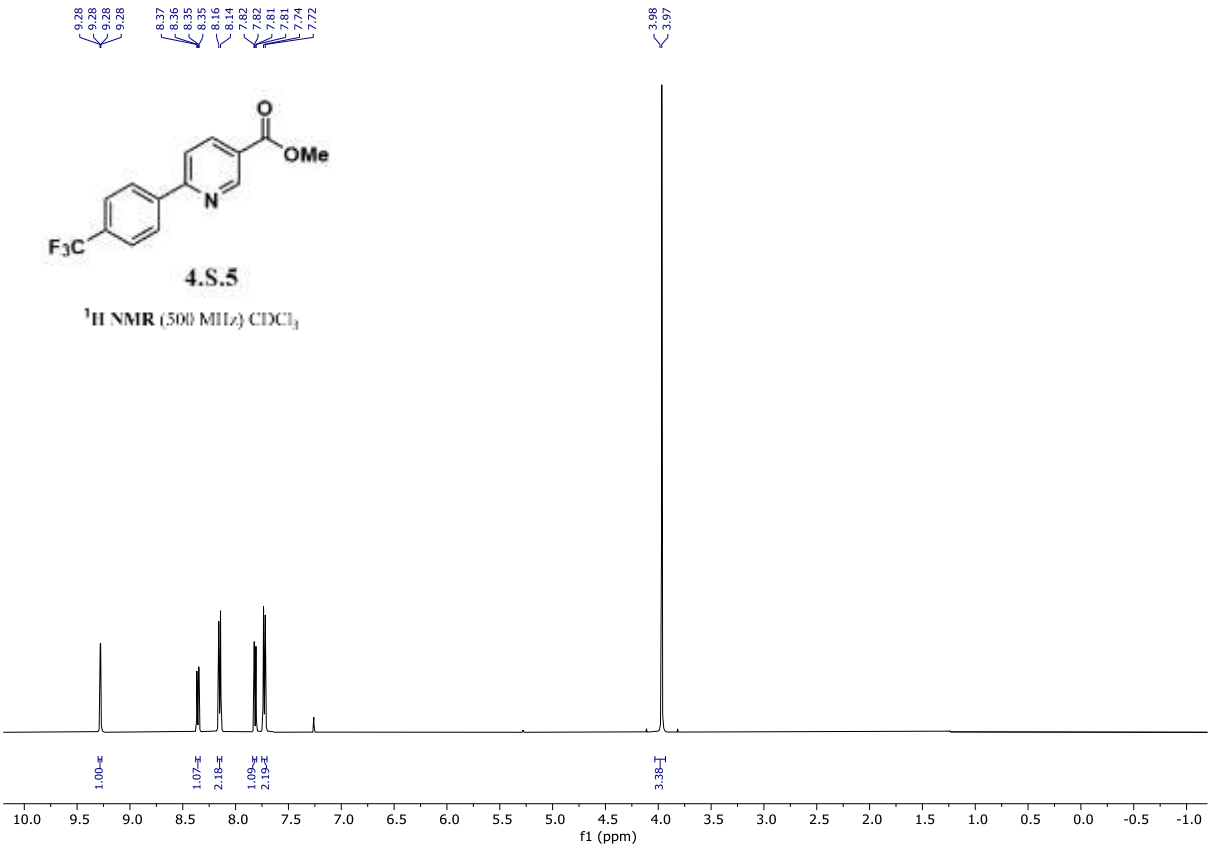
4.S.4

^{1}**H NMR** (600 MHz) $CDCl_3$



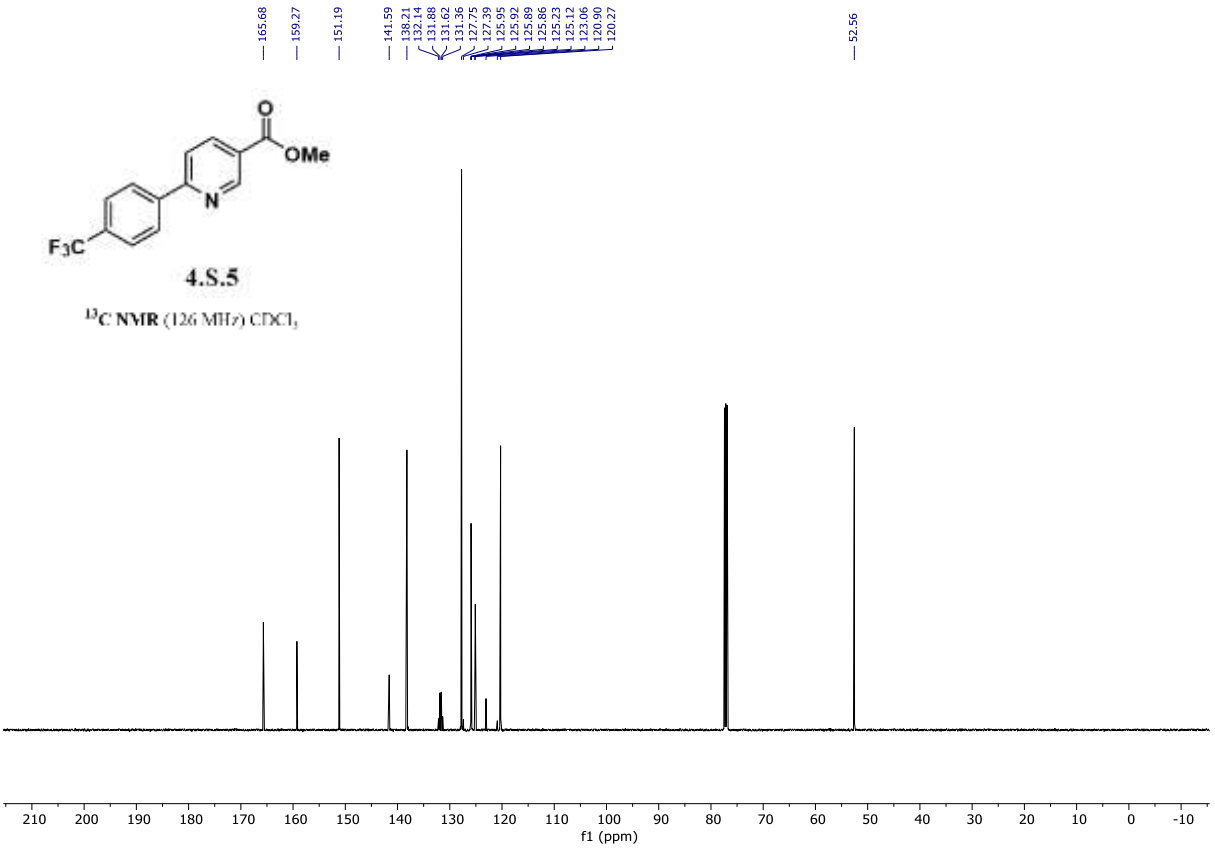
4.S.4

^{13}**C NMR** (126 MHz) $CDCl_3$



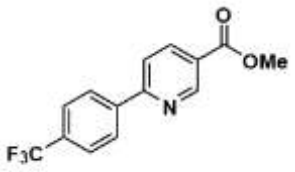
4.S.5

^{1}H NMR (500 MHz) $CDCl_3$



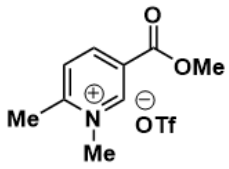
4.S.5

^{13}C NMR (126 MHz) $CDCl_3$



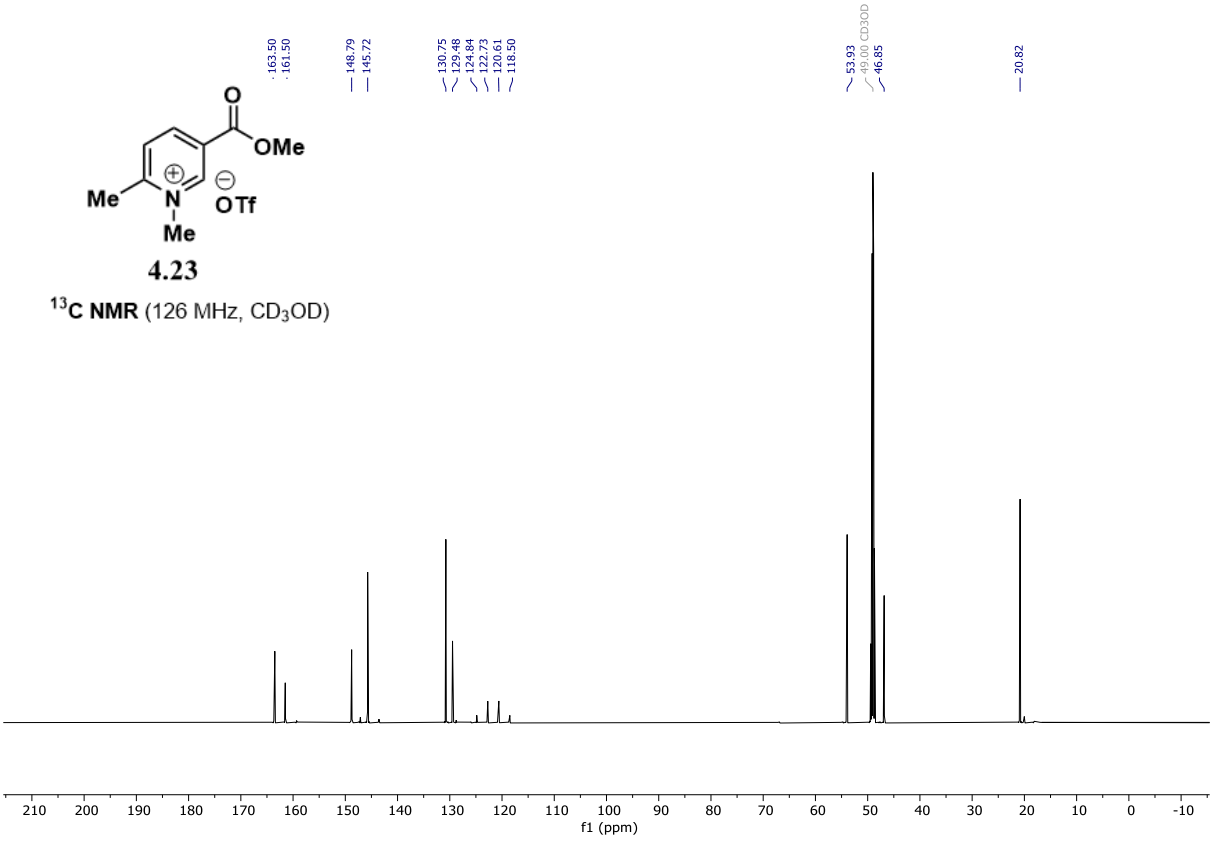
4.S.5

^{19}F NMR (471 MHz) $CDCl_3$



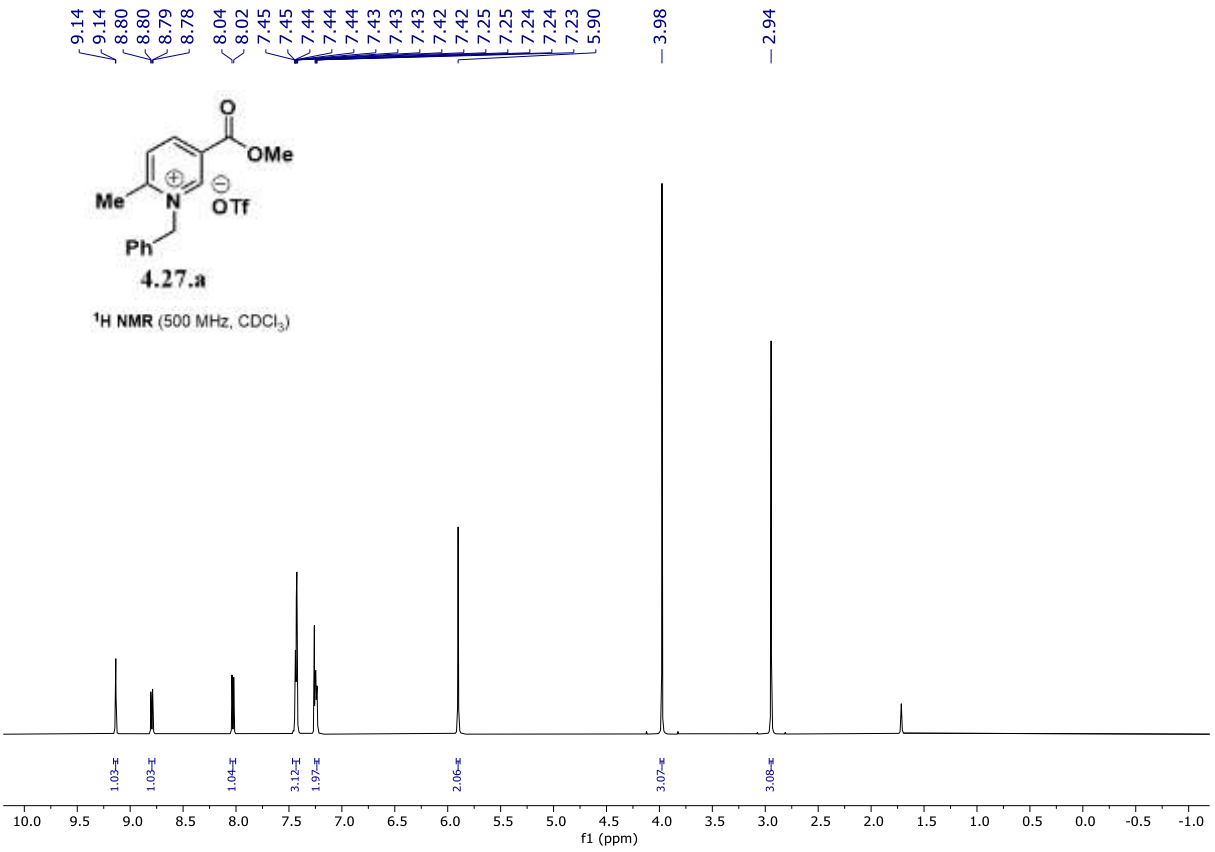
4.23

^{1}H NMR (500 MHz, CD_3OD)



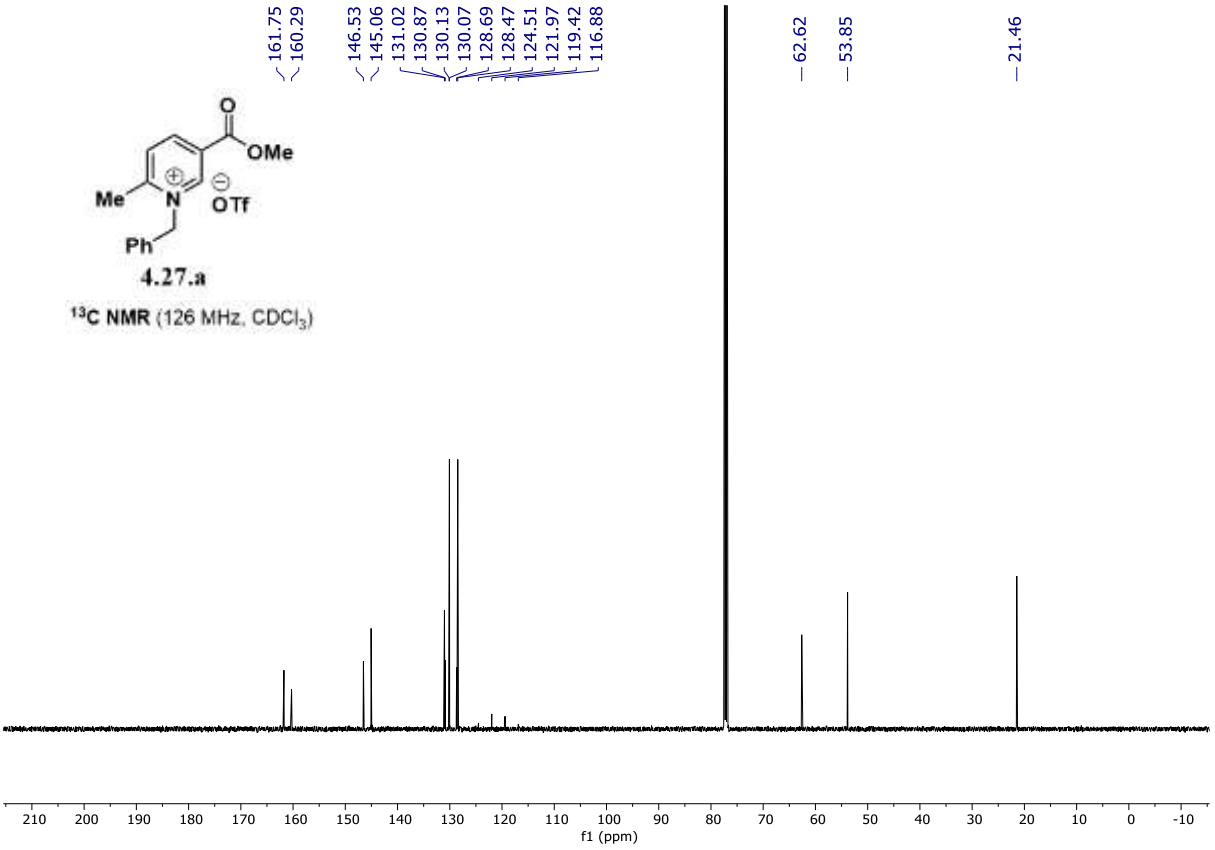
4.23

^{13}C NMR (126 MHz, CD_3OD)



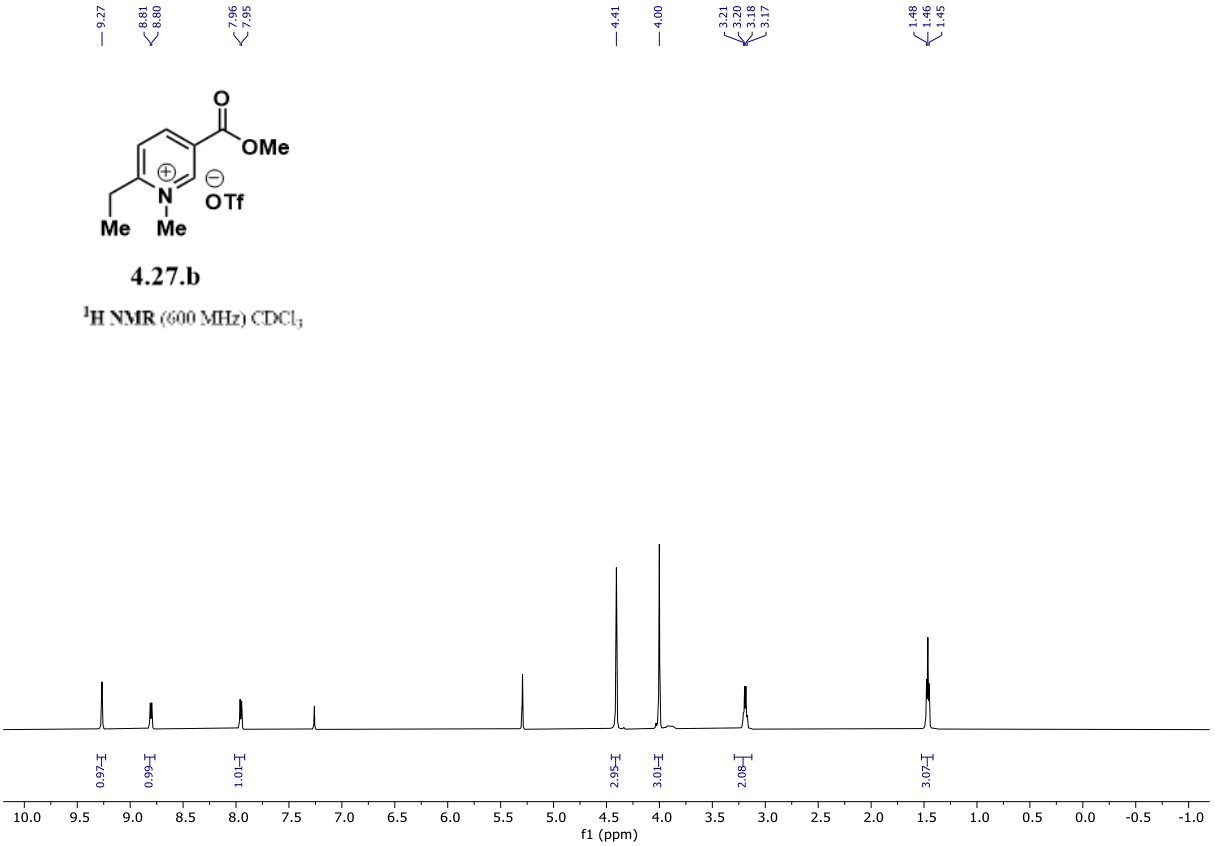
4.27.a

^{1}H NMR (500 MHz, $CDCl_3$)



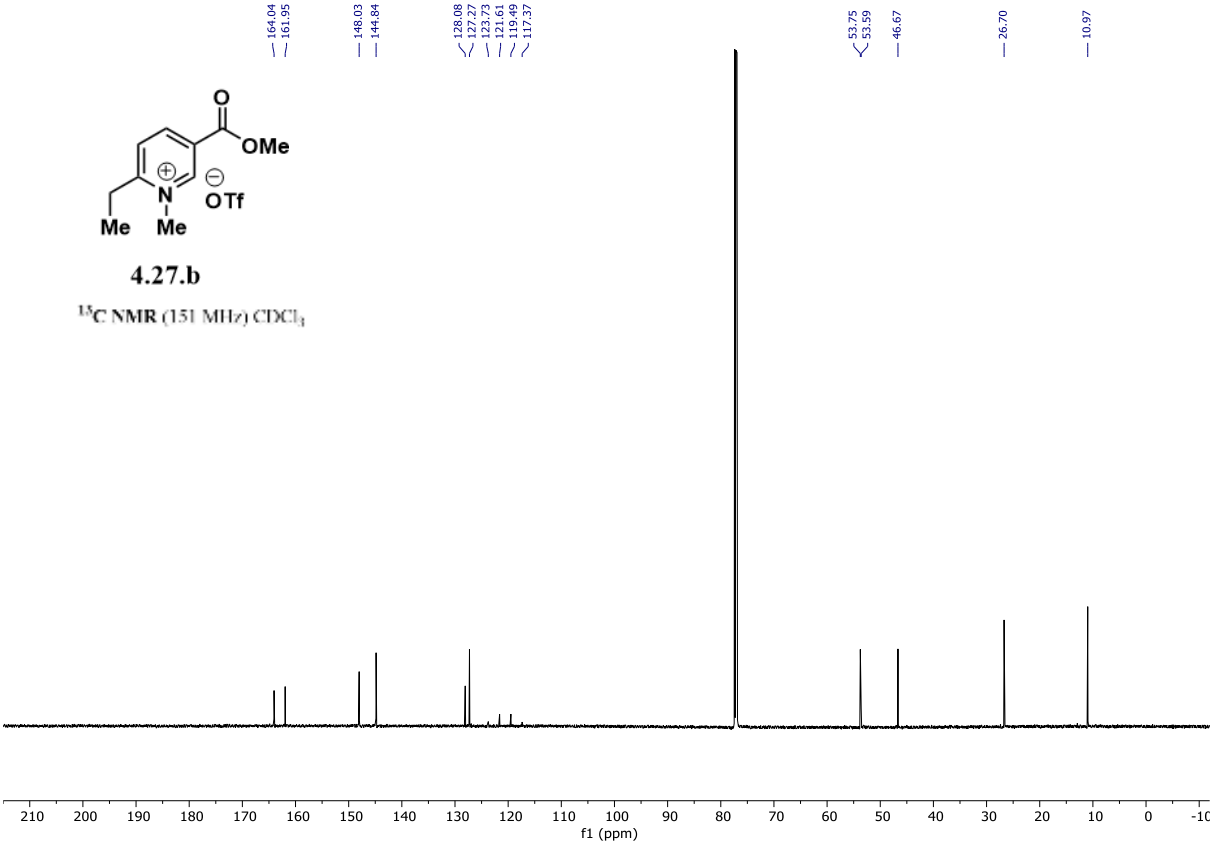
4.27.a

^{13}C NMR (126 MHz, $CDCl_3$)



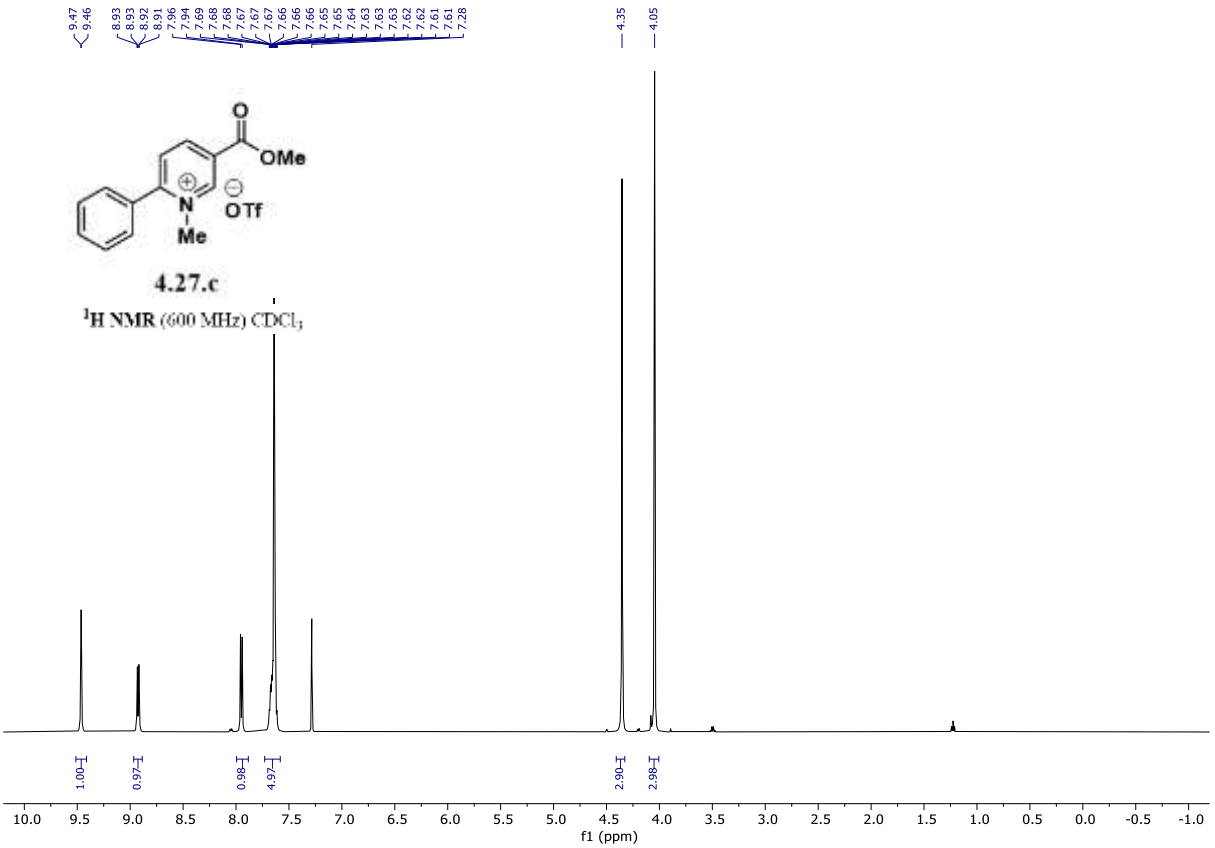
4.27.b

^{1}H NMR (600 MHz) $CDCl_3$



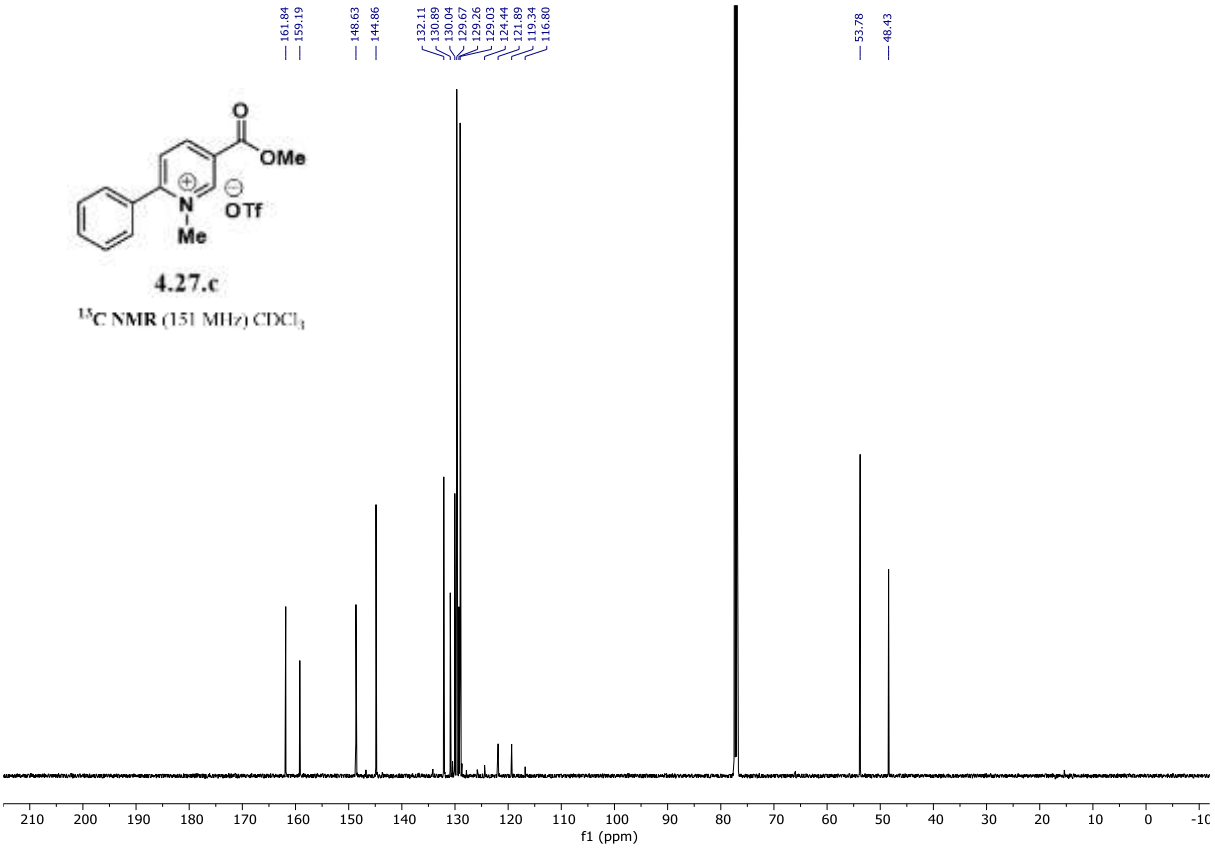
4.27.b

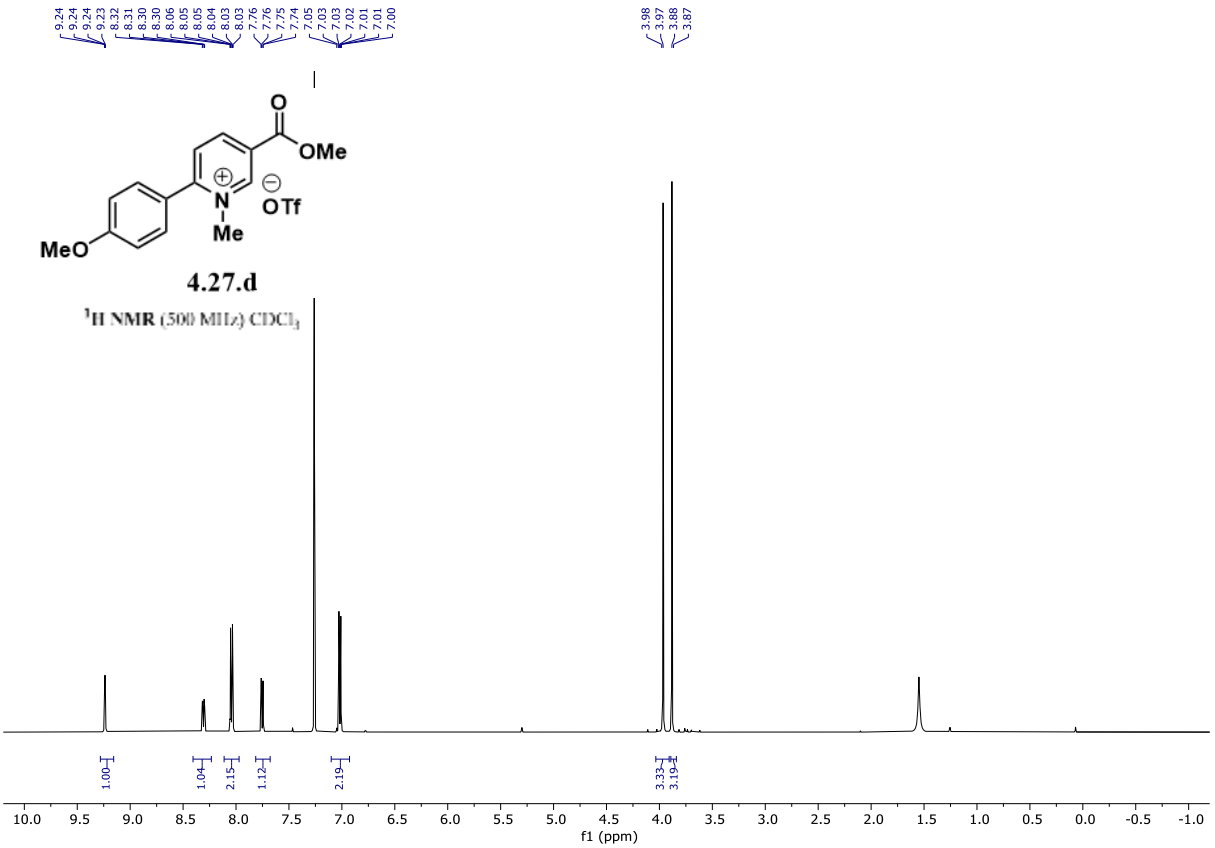
^{13}C NMR (151 MHz) $CDCl_3$

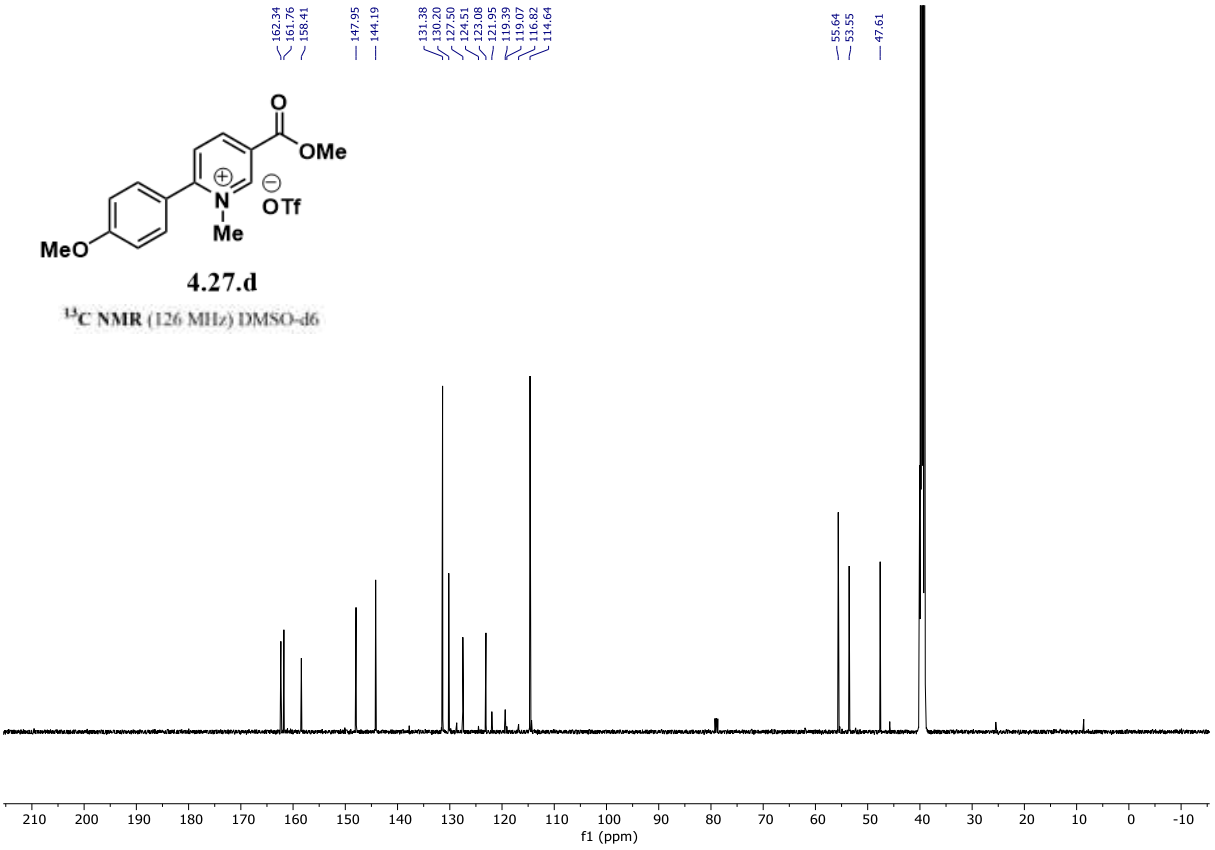


4.27.c

^{1}H NMR (600 MHz) $CDCl_3$

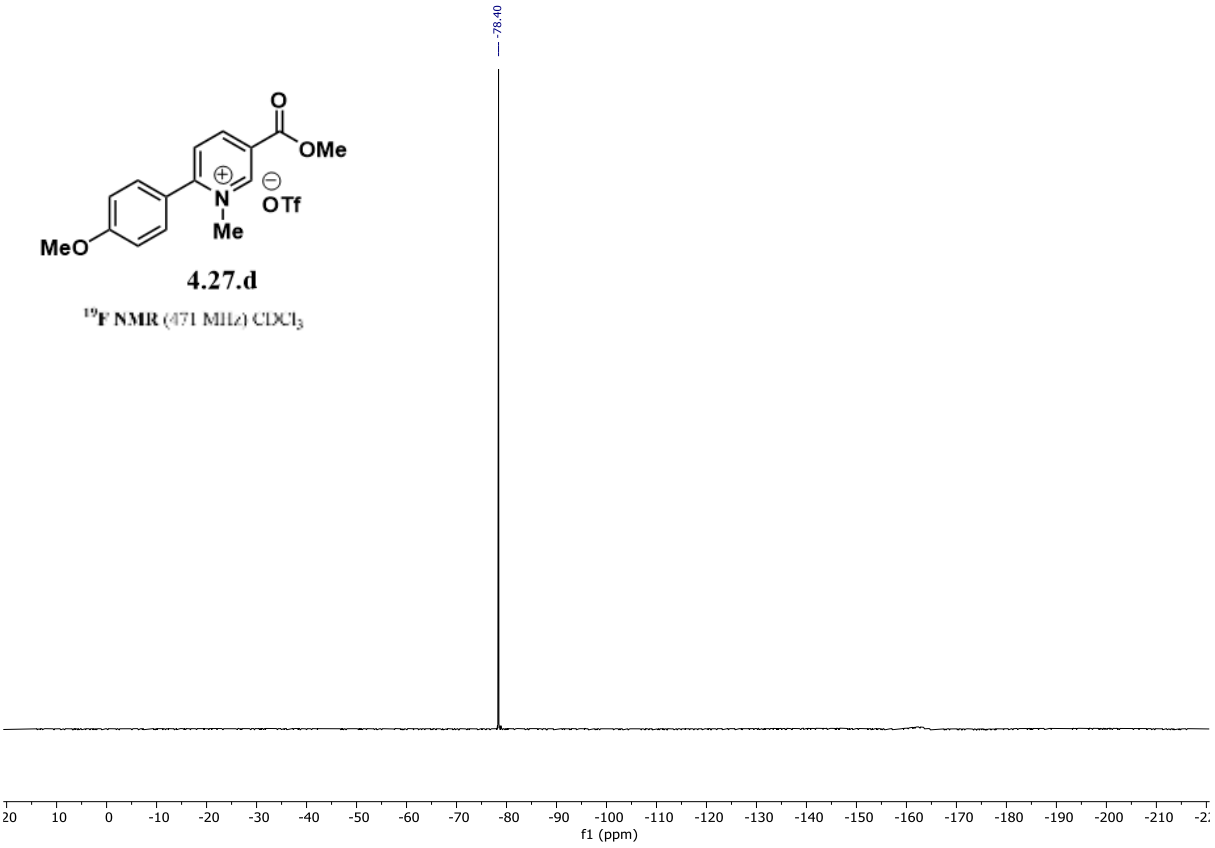

161.84
159.19
148.63
144.86
132.11
130.89
130.04
129.67
129.26
129.03
124.44
121.89
119.34
116.80
53.78
48.43
O
OMe
N
Me
OTf
4.27.c
^{13}C NMR (151 MHz) CDCl$_3$
f1 (ppm)


9.24
9.24
9.24
9.23
8.32
8.31
8.30
8.30
8.06
8.05
8.05
8.04
8.03
8.03
7.76
7.76
7.75
7.74
7.05
7.03
7.03
7.02
7.01
7.01
7.00
3.98
3.97
3.88
3.87
O
OMe
N
Me
OTf
MeO
4.27.d
^{1}H NMR (500 MHz) CDCl$_3$
1.00
1.04
2.15
1.12
2.19
3.33
3.19
f1 (ppm)



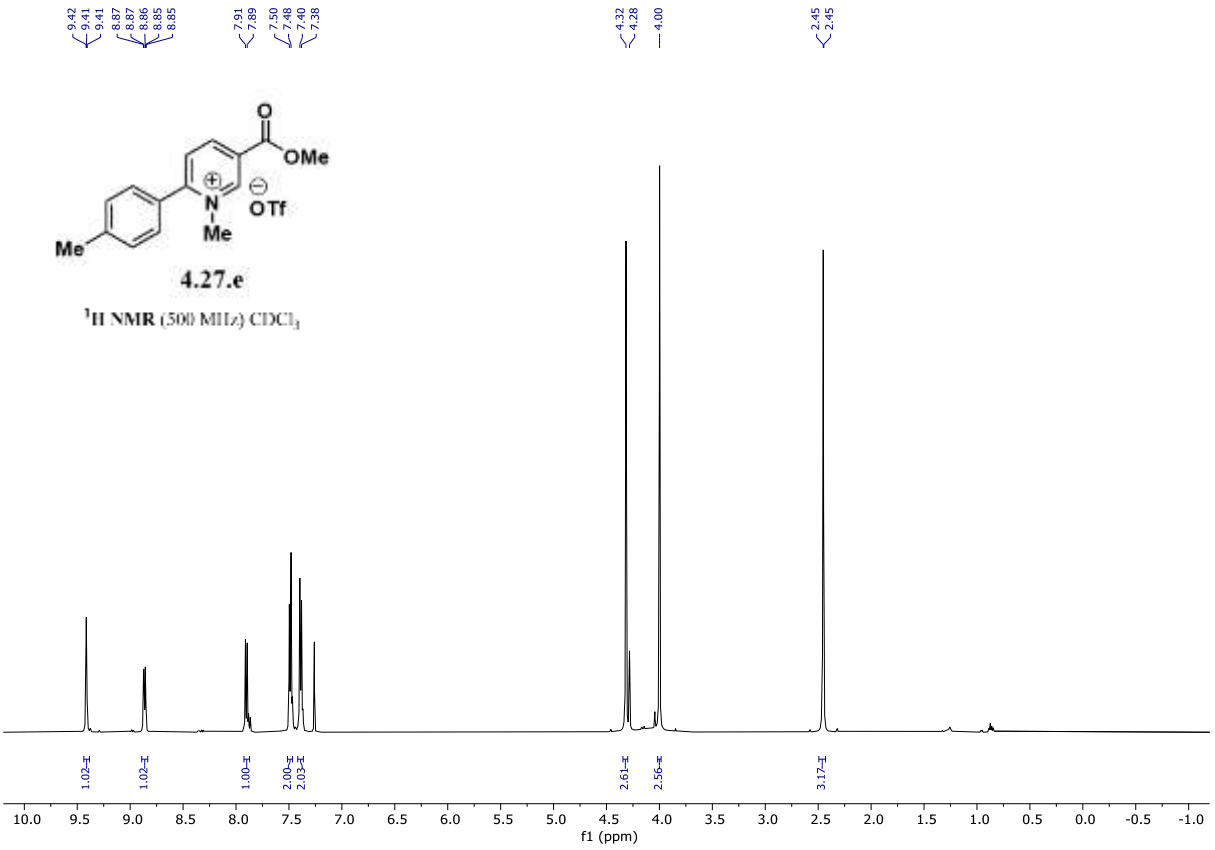
4.27.d

^{13}**C NMR** (126 MHz) DMSO-d6



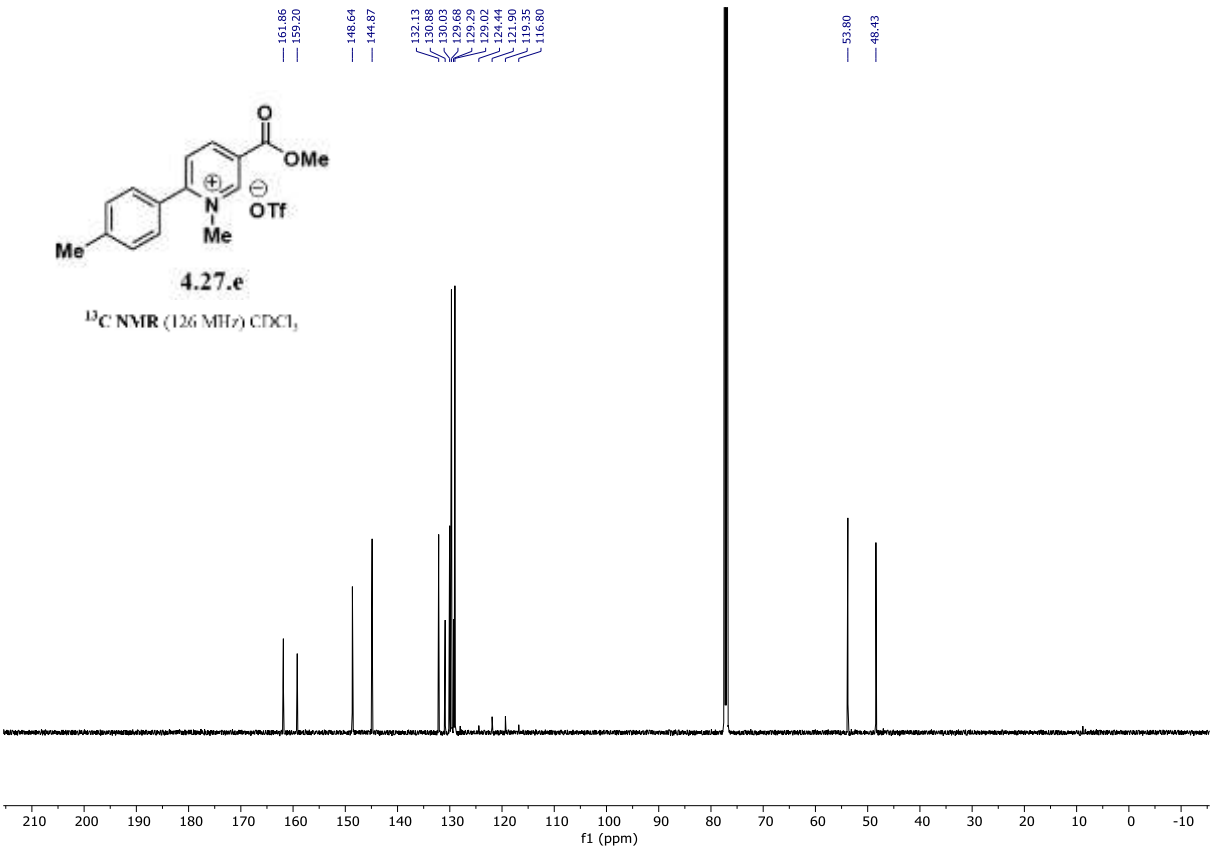
4.27.d

^{19}**F NMR** (471 MHz) $CDCl_3$



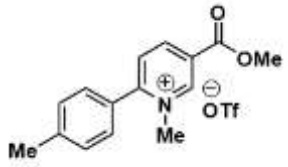
4.27.e

^{1}H NMR (500 MHz) $CDCl_3$



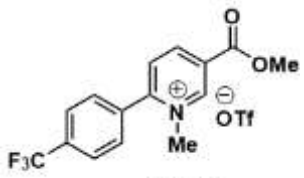
4.27.e

^{13}C NMR (126 MHz) $CDCl_3$



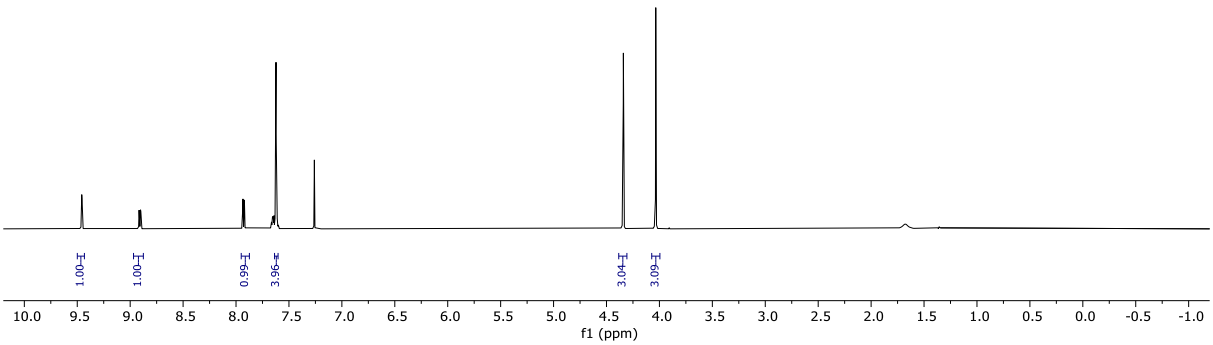
4.27.e

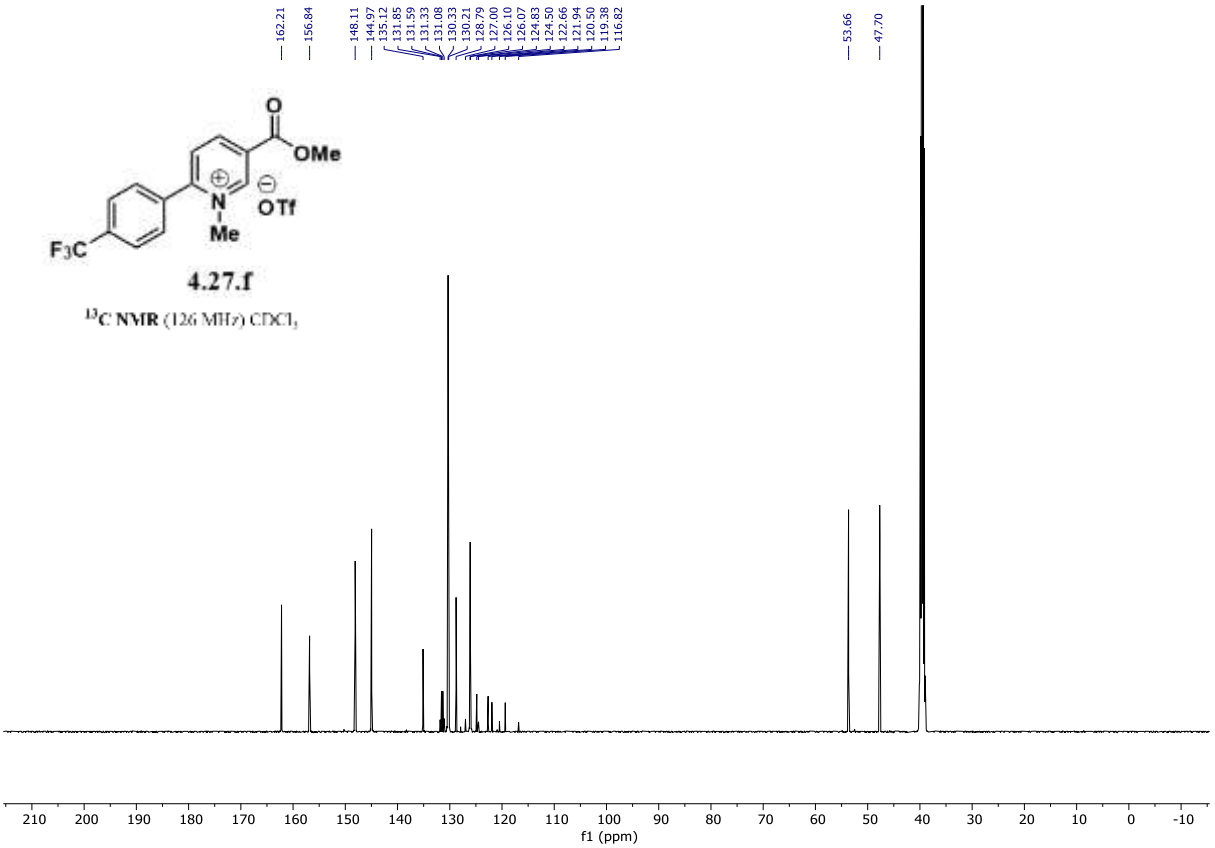
^{19}F NMR (471 MHz) $CDCl_3$



4.27.f

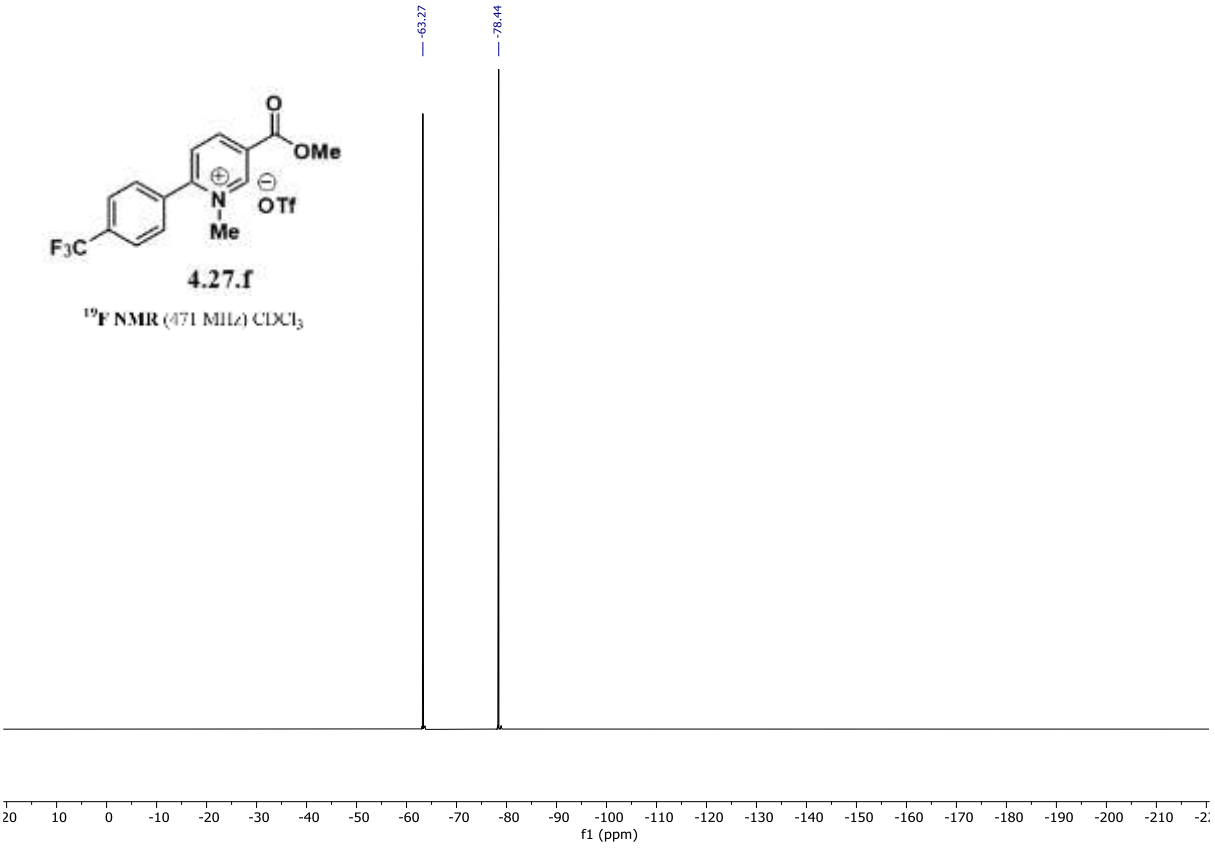
^{1}H NMR (600 MHz) $CDCl_3$





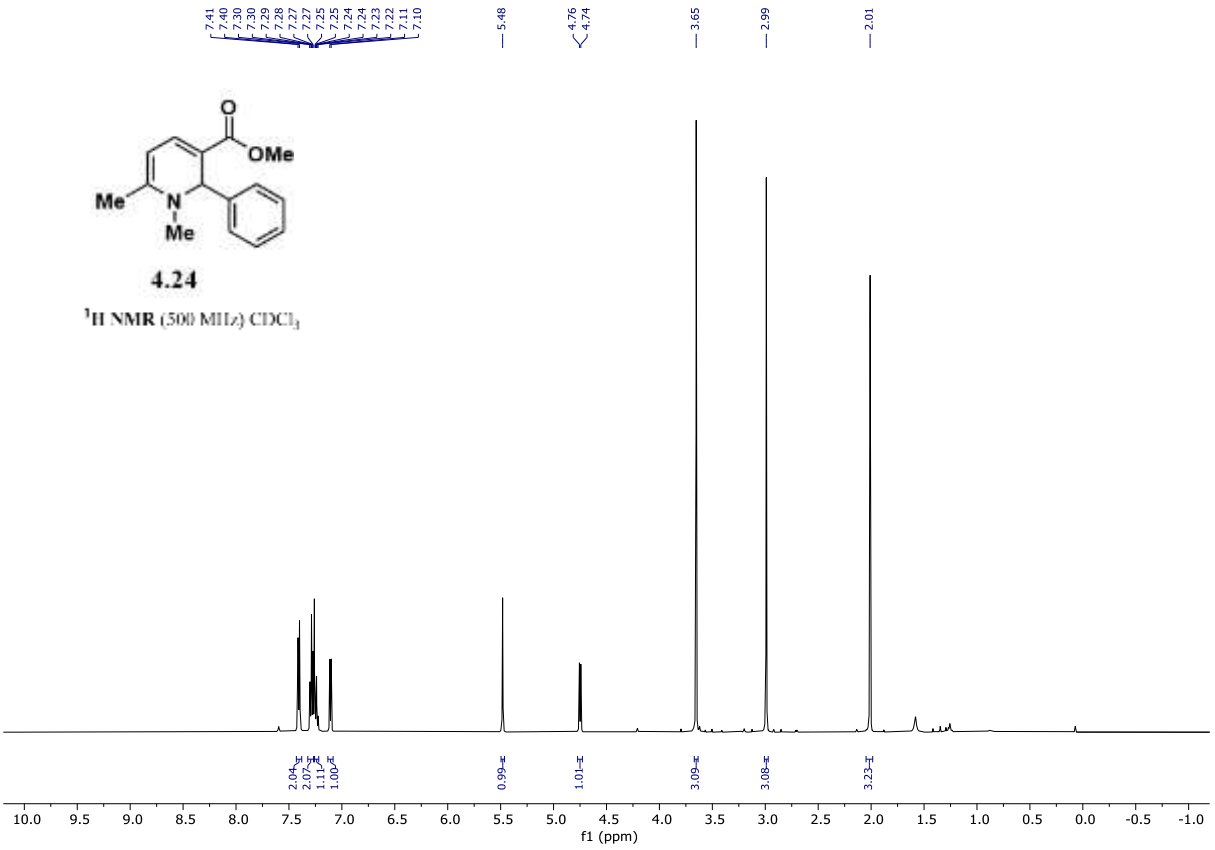
4.27.f

^{13}C NMR (126 MHz) $CDCl_3$



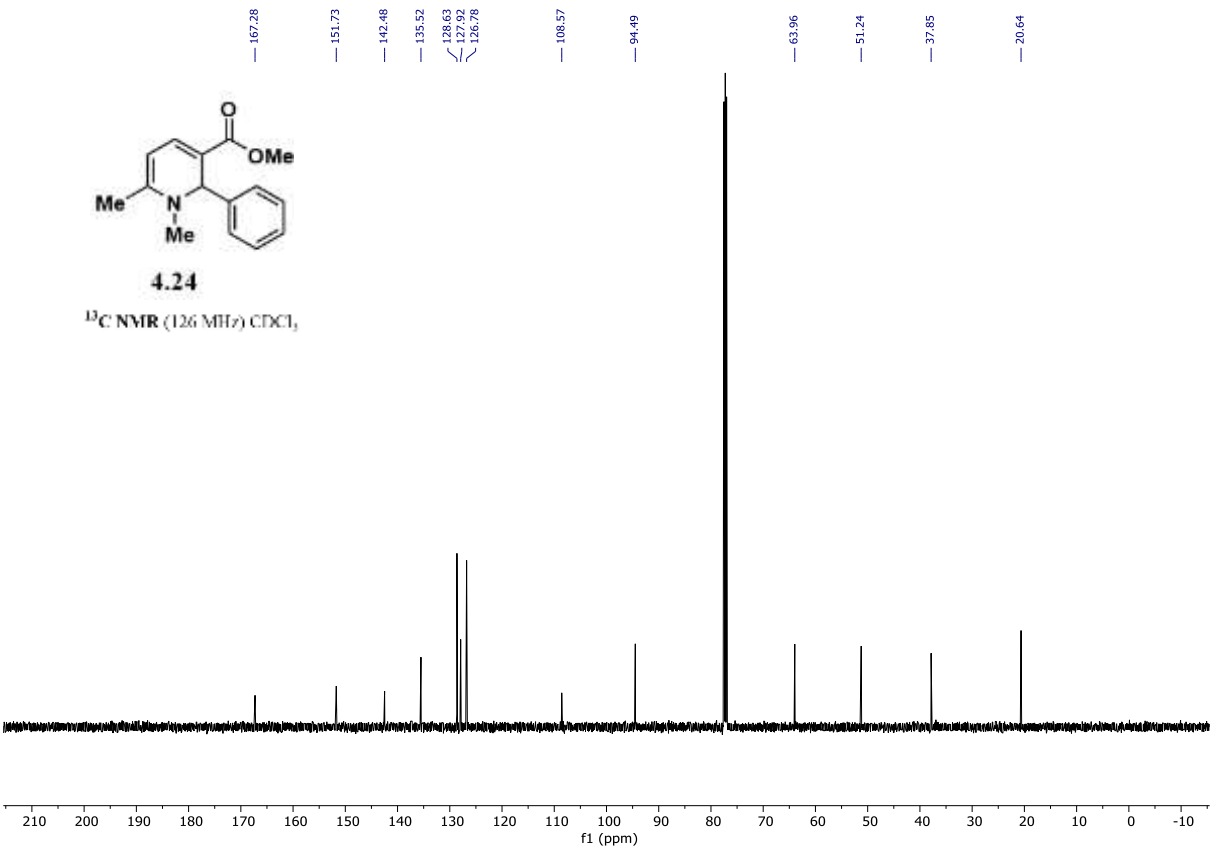
4.27.f

^{19}F NMR (471 MHz) $CDCl_3$



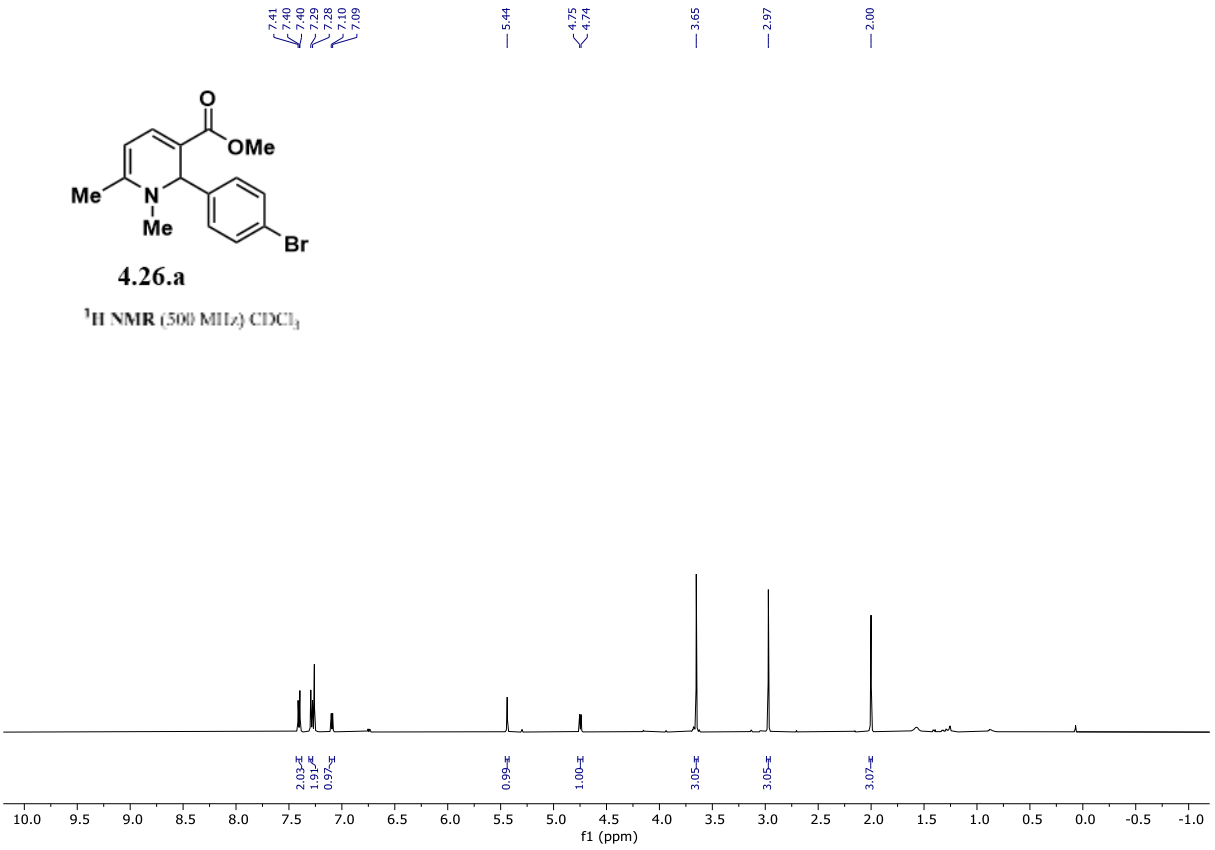
4.24

^{1}**H NMR** (500 MHz) $CDCl_3$



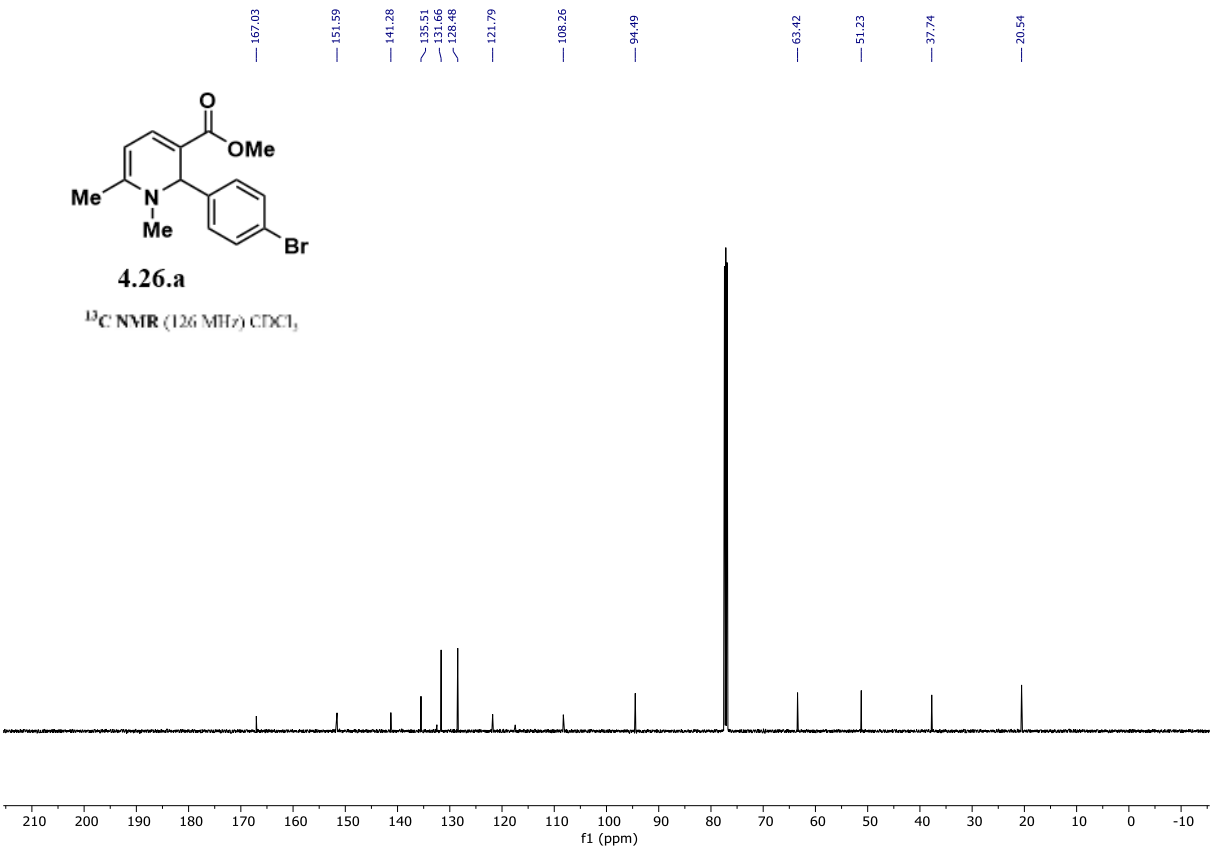
4.24

^{13}**C NMR** (126 MHz) $CDCl_3$



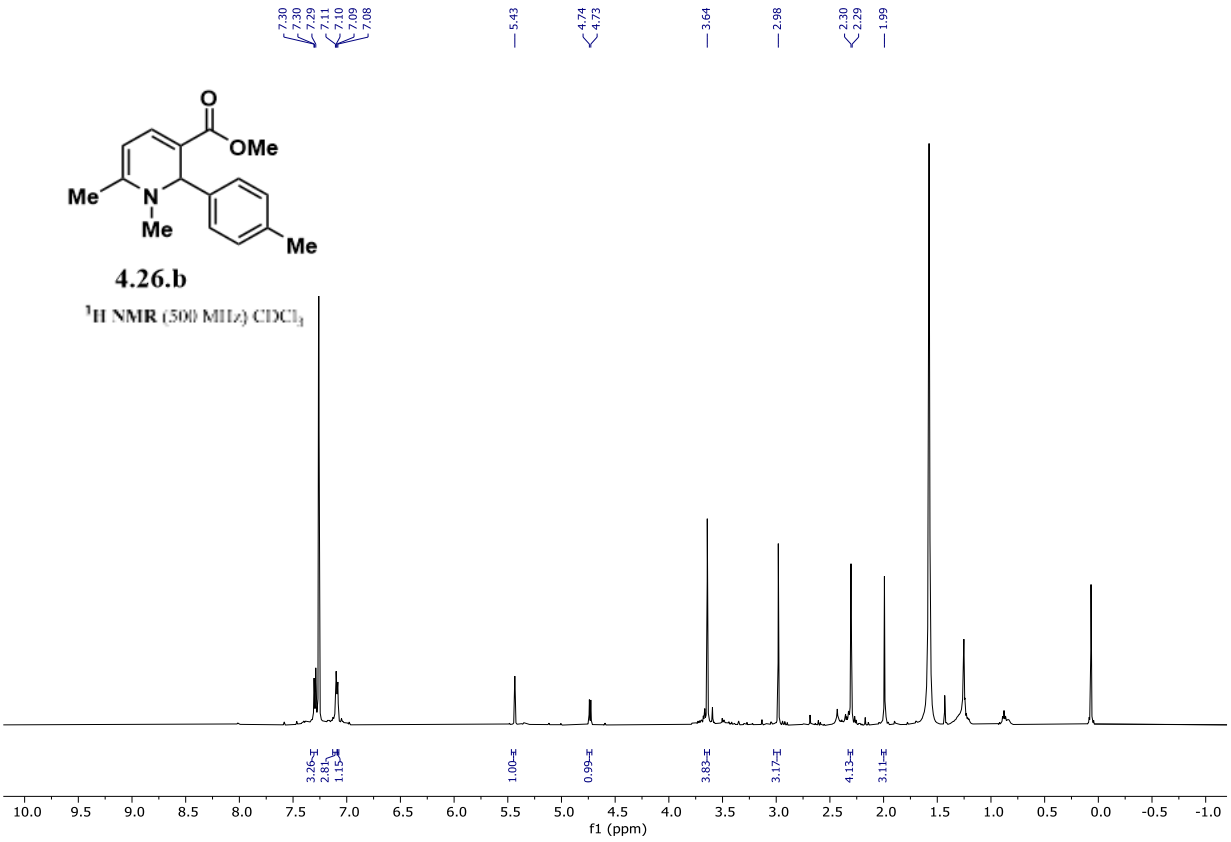
4.26.a

^{1}H NMR (500 MHz) $CDCl_3$



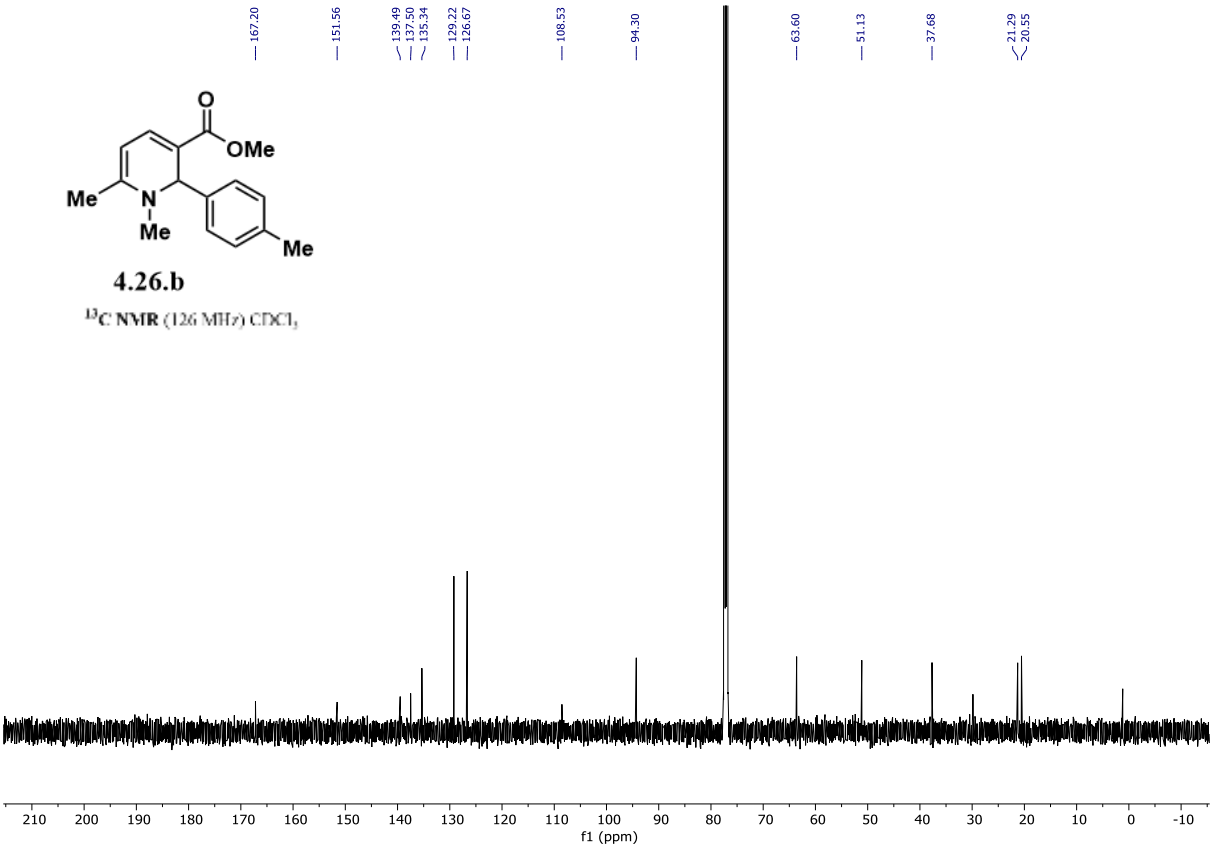
4.26.a

^{13}C NMR (126 MHz) $CDCl_3$



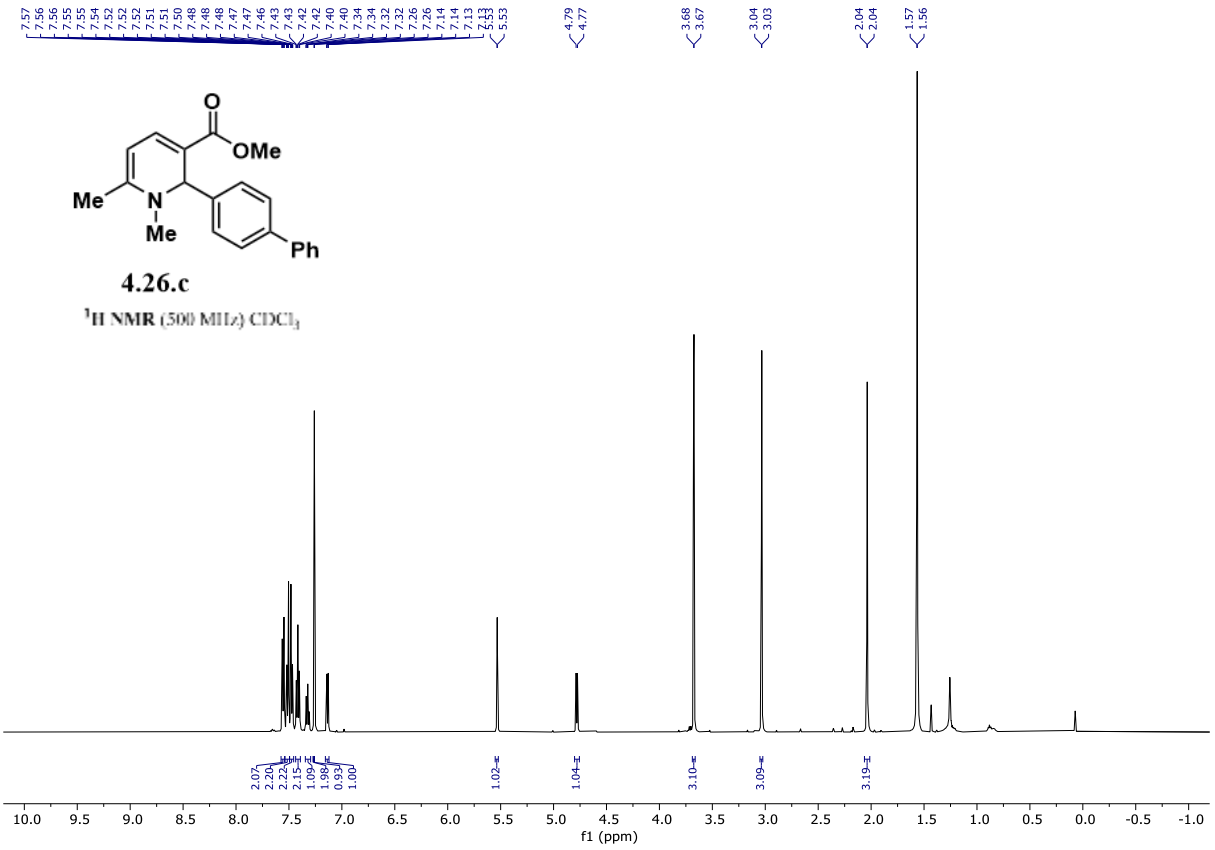
4.26.b

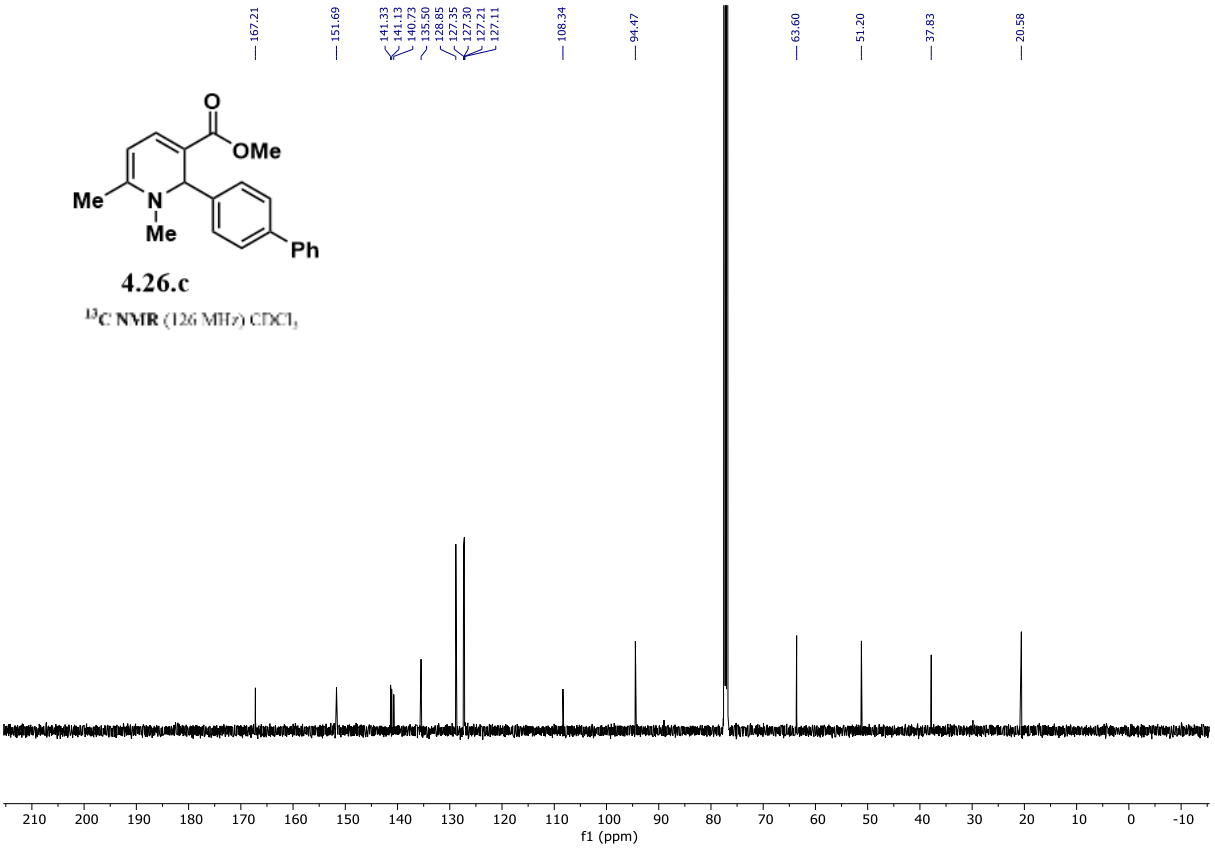
^{1}H NMR (500 MHz) $CDCl_3$

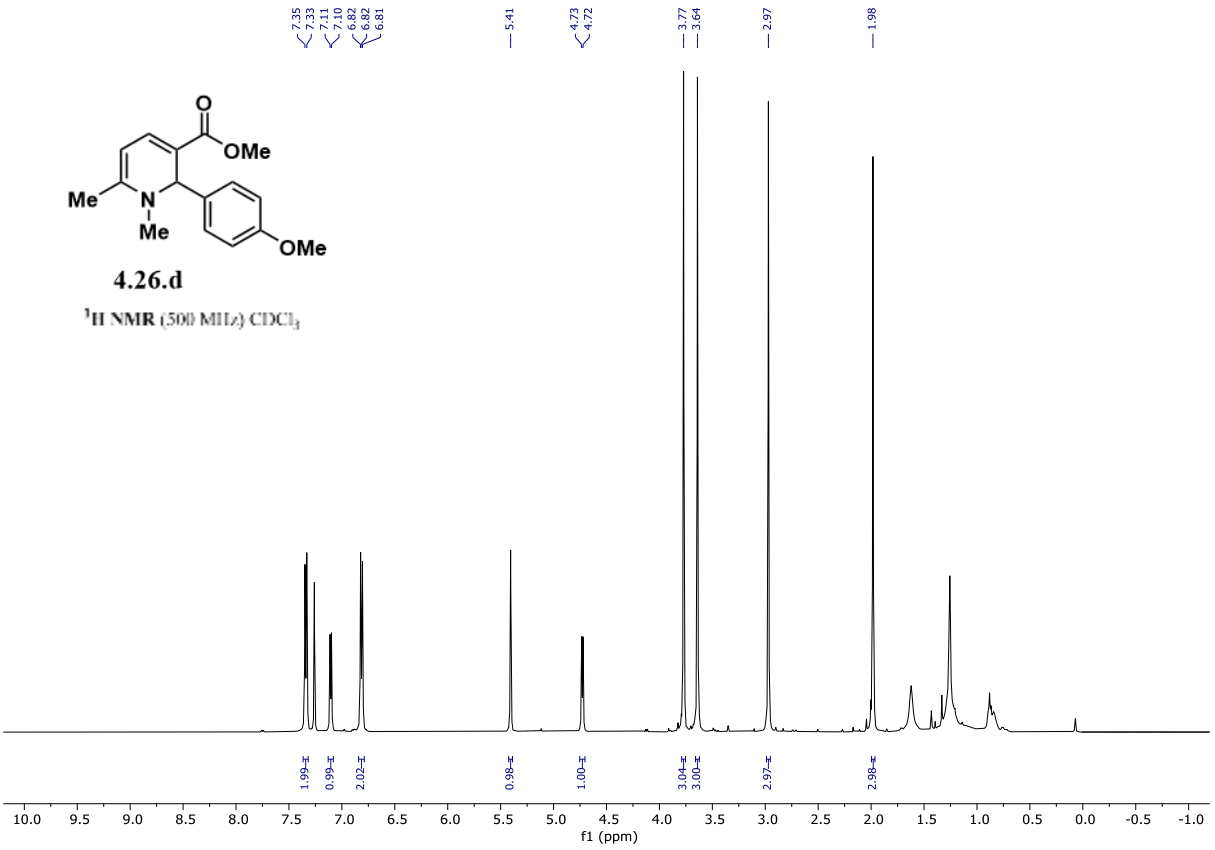


4.26.b

^{13}C NMR (126 MHz) $CDCl_3$

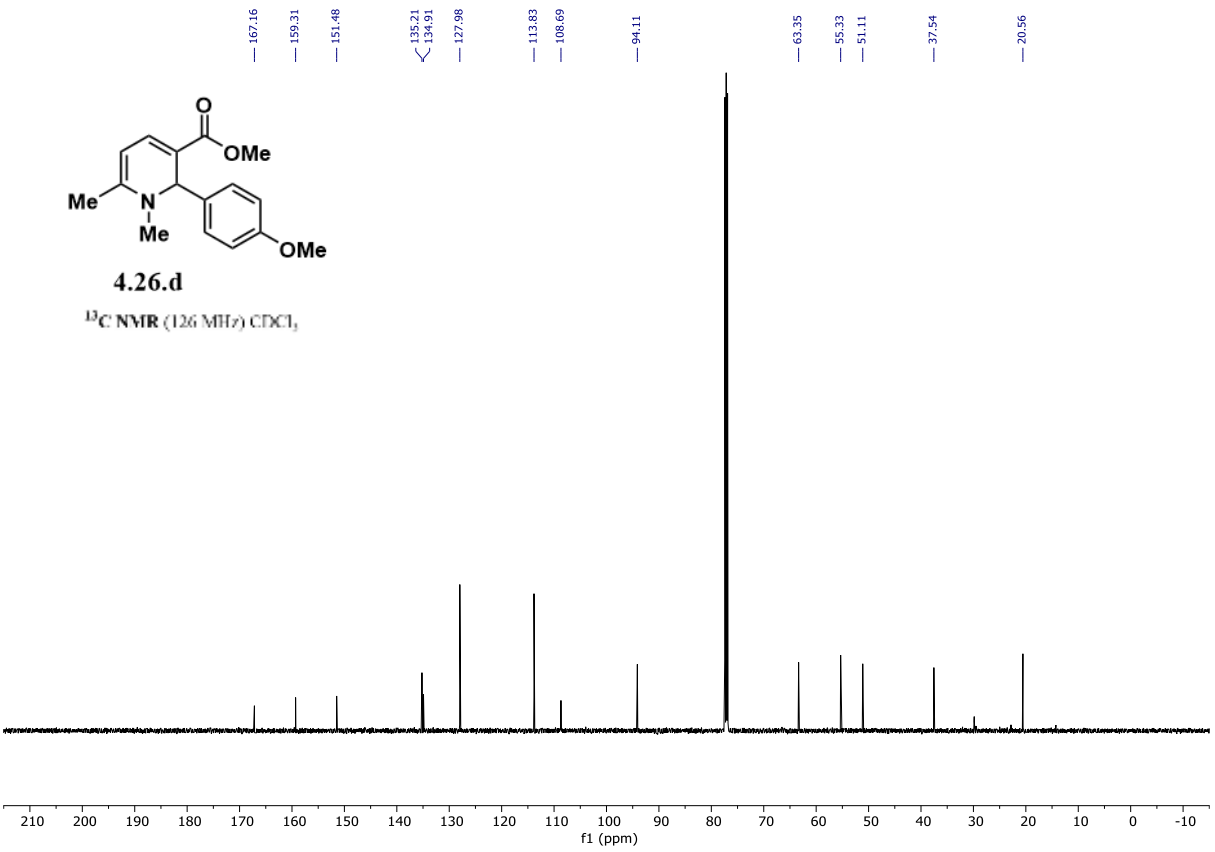

7.57 7.56 7.56 7.55 7.55 7.54 7.52 7.52 7.52 7.51 7.51 7.50 7.48 7.48 7.48 7.47 7.47 7.46 7.43 7.42 7.42 7.40 7.40 7.34 7.34 7.32 7.32 7.26 7.14 7.14 7.13 5.53 5.53
4.79 4.77
3.68 3.67
3.04 3.03
2.04 2.04
1.57 1.56
O
OMe
Me
N
Me
Ph
4.26.c
^{1}H NMR (500 MHz) CDCl$_3$
2.07 2.20 2.22 2.15 1.09 1.98 0.93 1.00
1.02 1.04 3.10 3.09 3.19
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 -0.5 -1.0
f1 (ppm)


167.21
151.69
141.33 141.13 140.73 135.50 128.85 127.35 127.30 127.21 127.11
108.34
94.47
63.60
51.20
37.83
20.58
O
OMe
Me
N
Me
Ph
4.26.c
^{13}C NMR (126 MHz) CDCl$_3$
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)



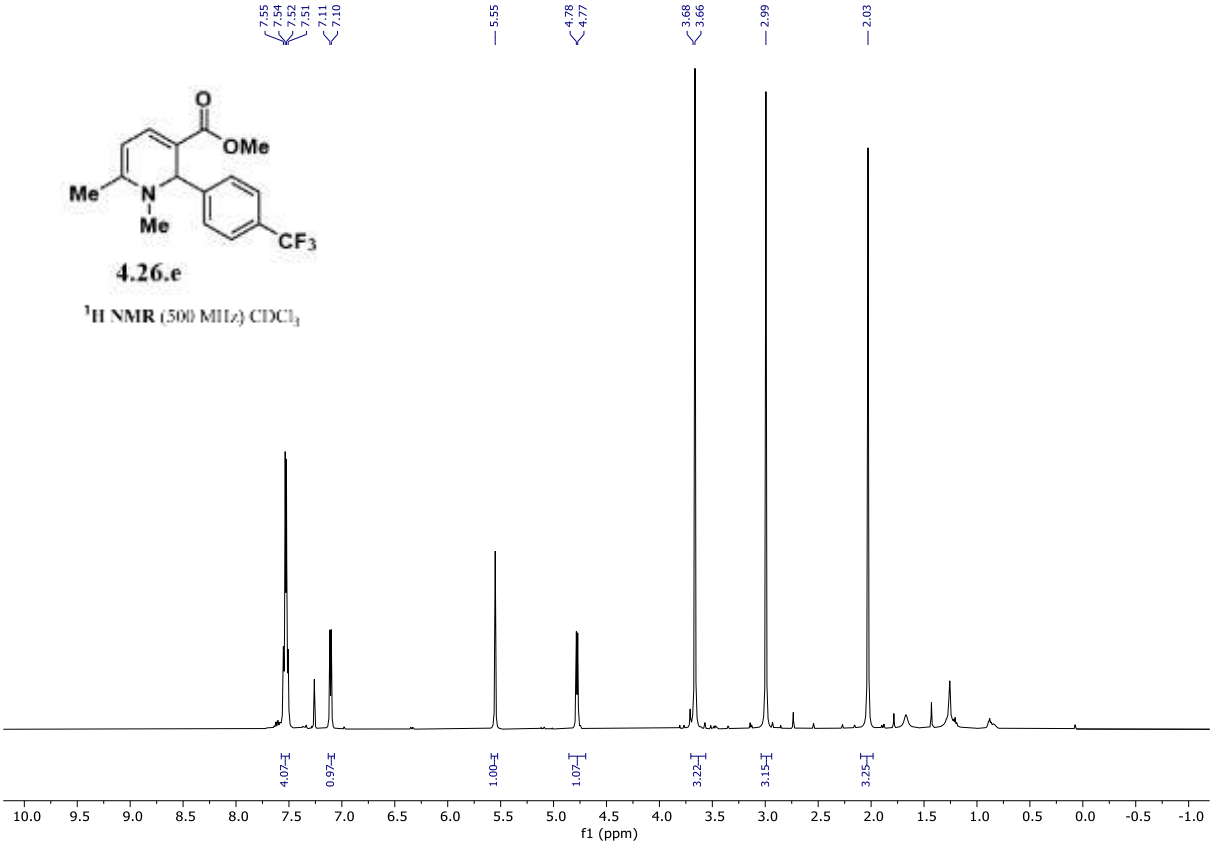
4.26.d

^{1}H NMR (500 MHz) $CDCl_3$



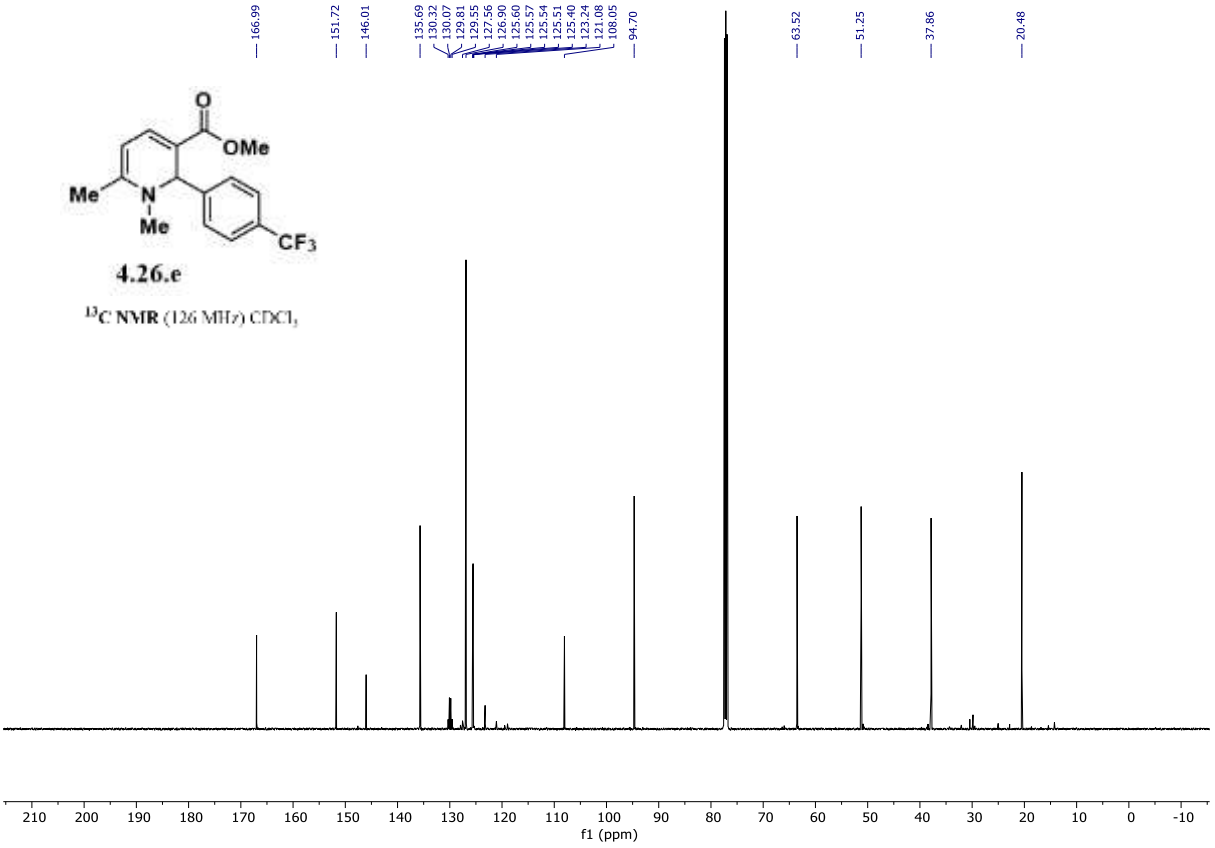
4.26.d

^{13}C NMR (126 MHz) $CDCl_3$



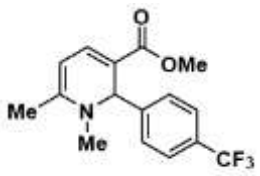
4.26.e

^{1}**H NMR** (500 MHz) $CDCl_3$



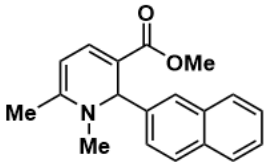
4.26.e

^{13}**C NMR** (126 MHz) $CDCl_3$



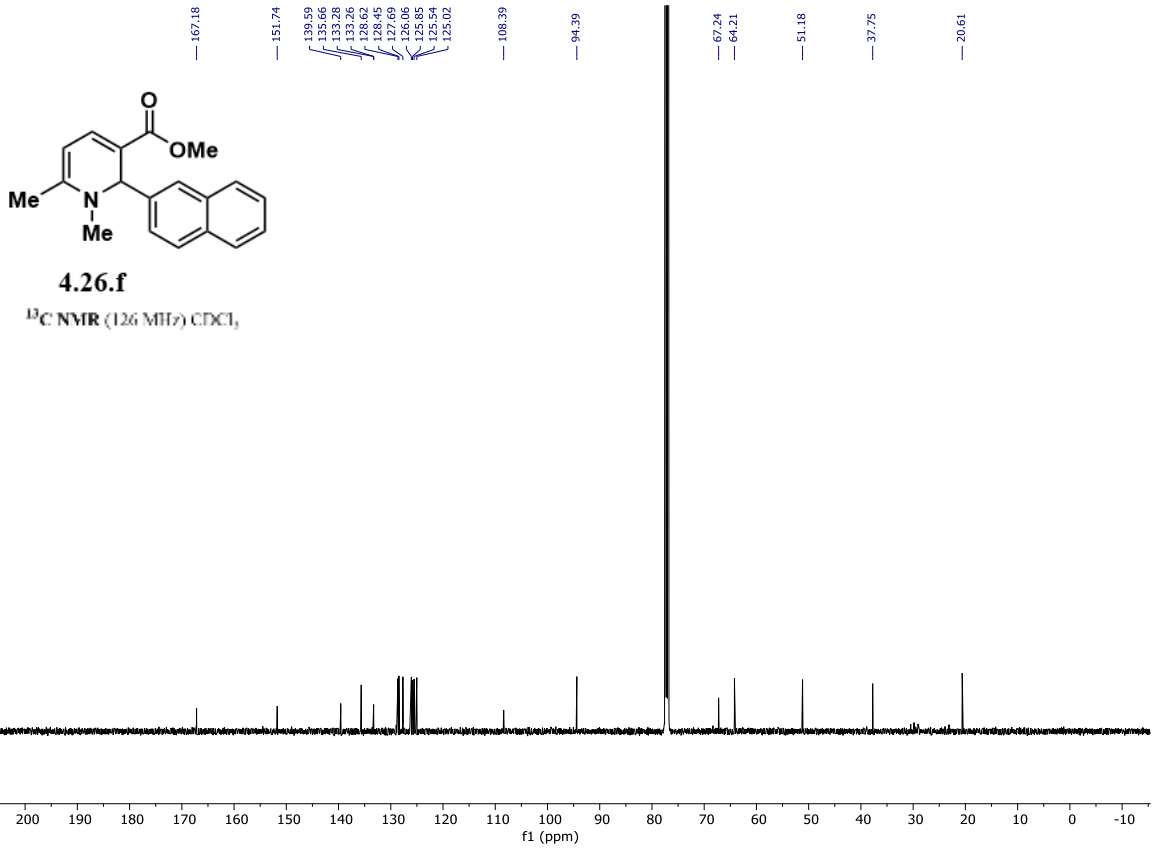
4.26.e

^{19}**F NMR** (471 MHz) $CDCl_3$



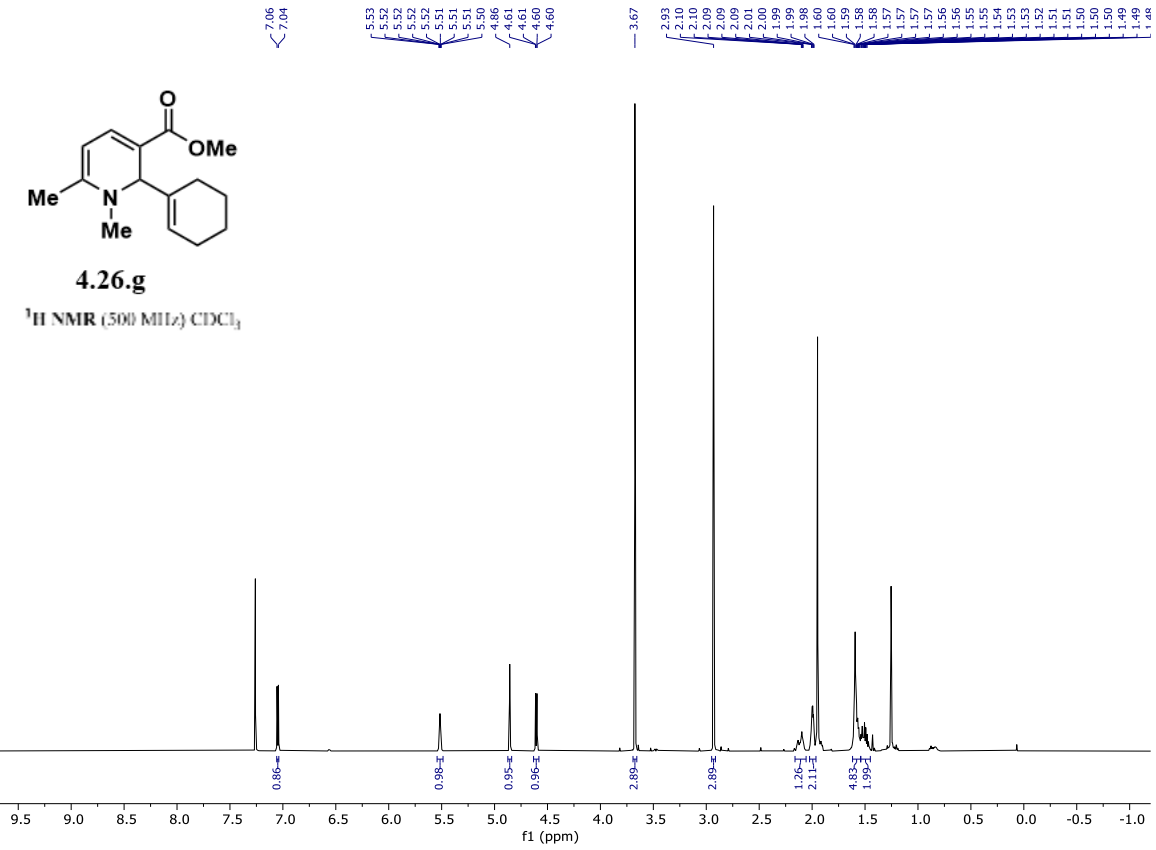
4.26.f

^{1}**H NMR** (500 MHz) $CDCl_3$



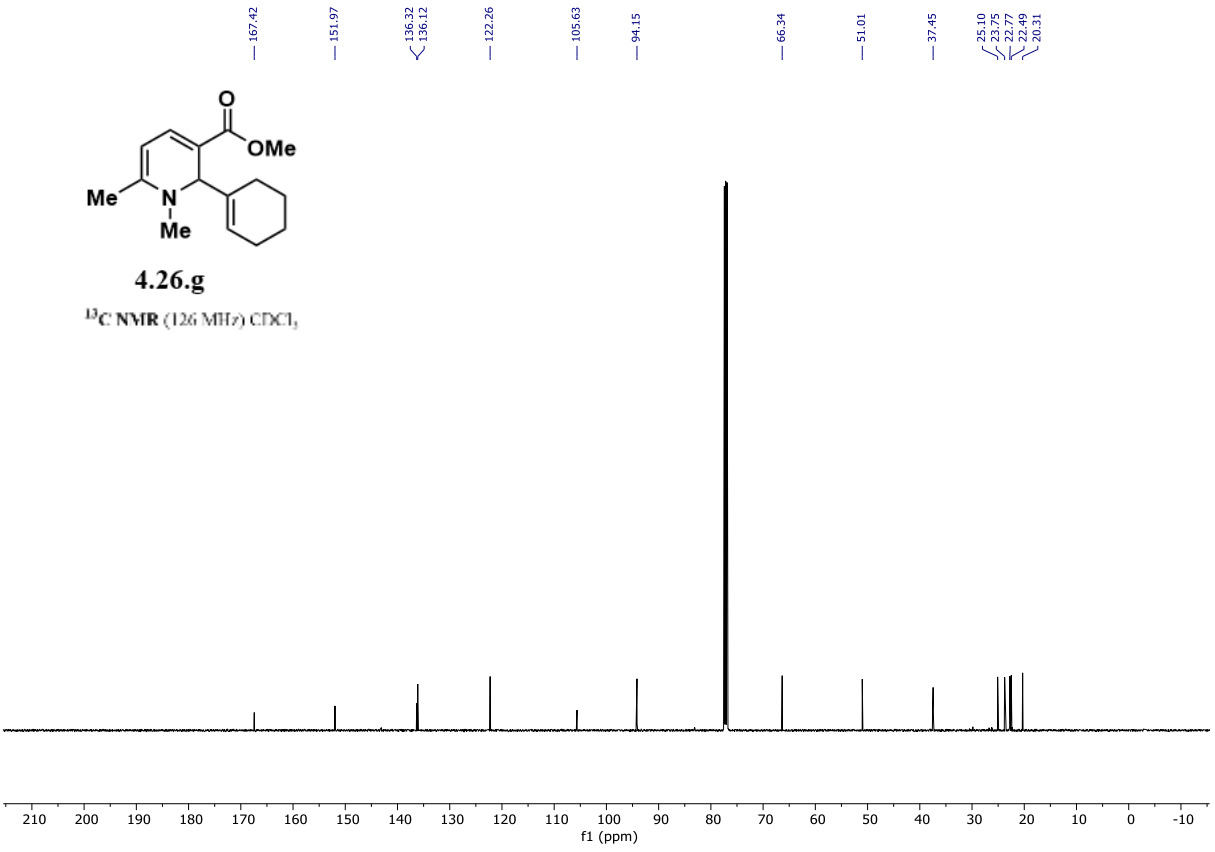
4.26.f

^{13}C NMR (126 MHz) $CDCl_3$



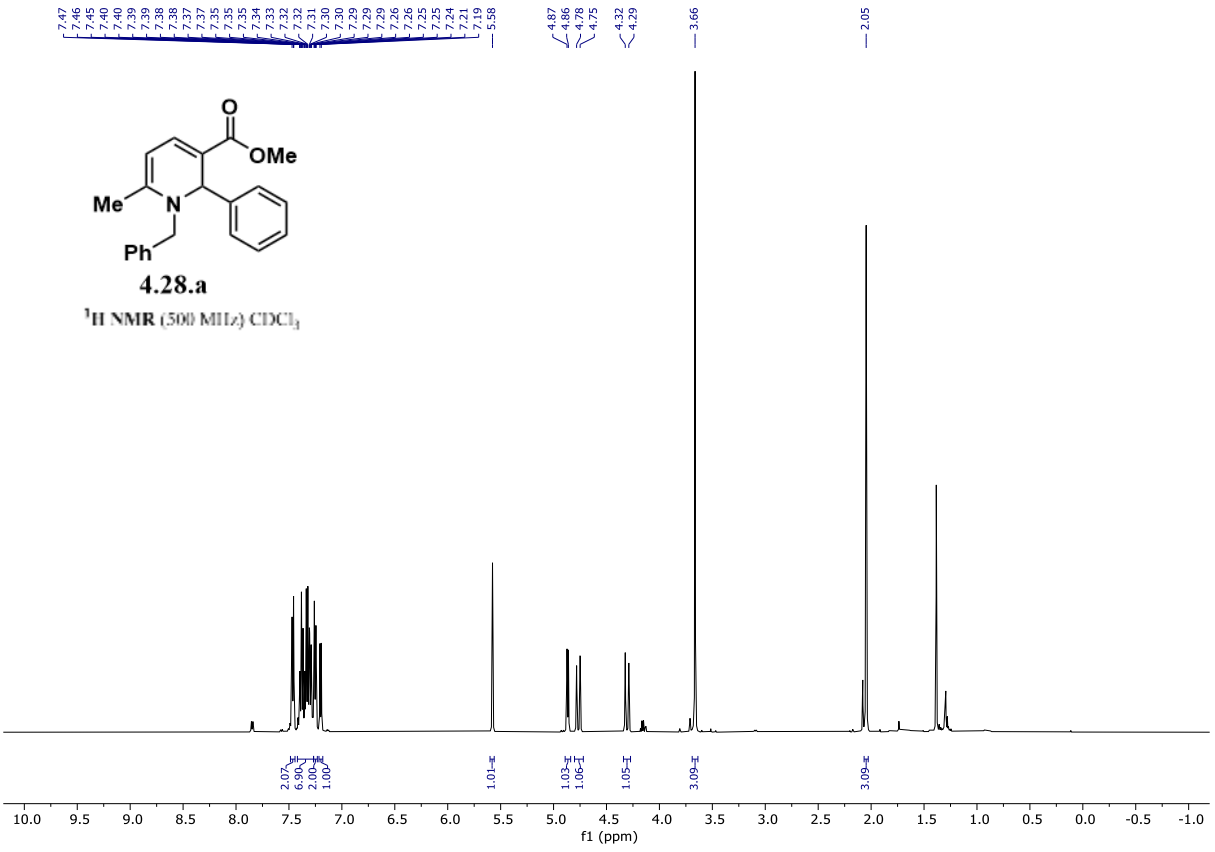
4.26.g

^{1}H NMR (500 MHz) $CDCl_3$



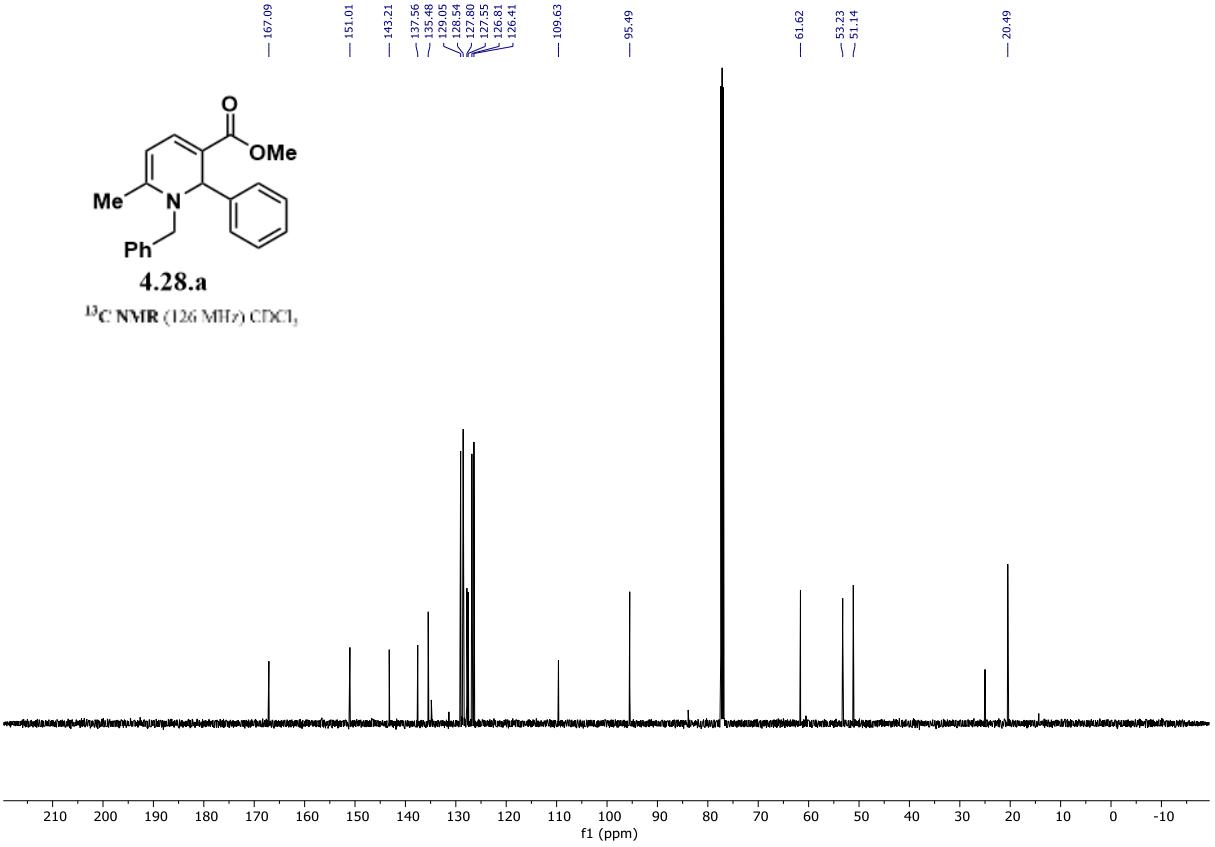
4.26.g

^{13}C NMR (126 MHz) $CDCl_3$



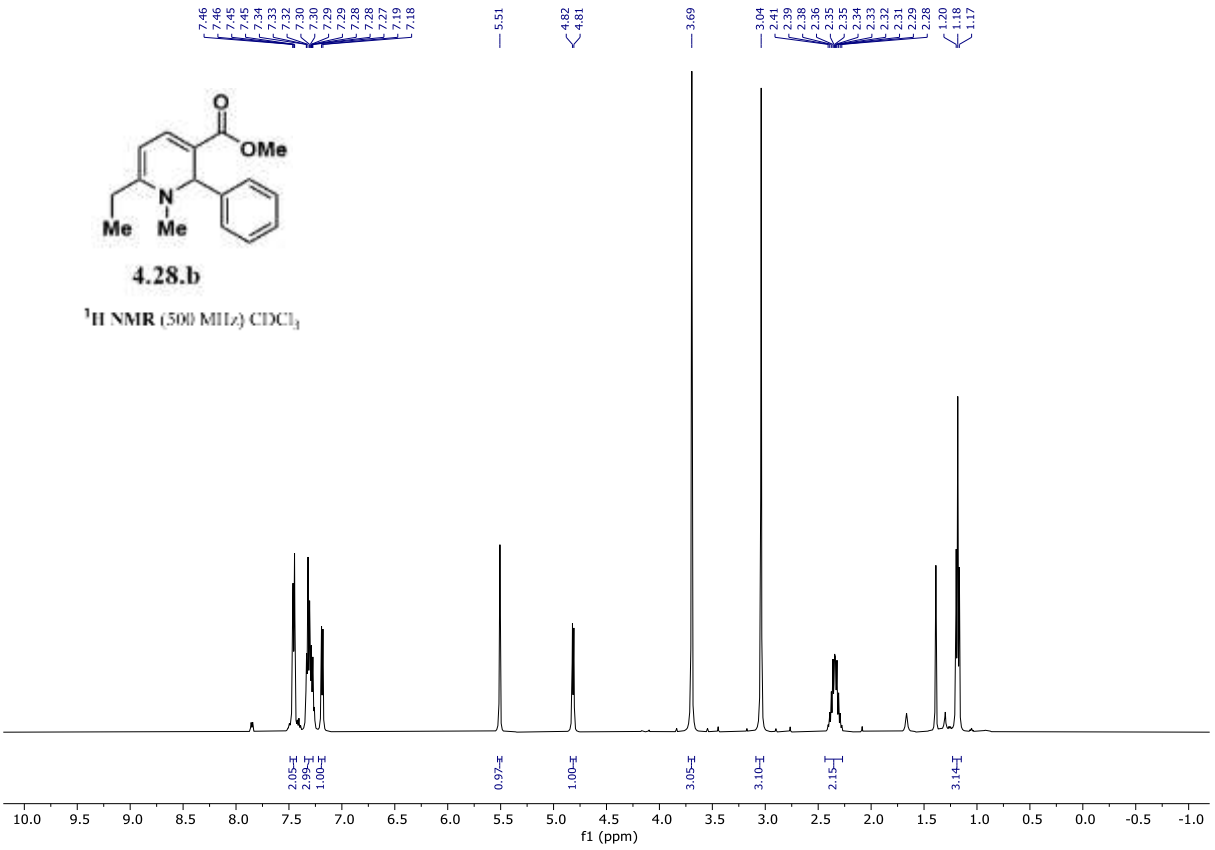
4.28.a

^{1}H NMR (500 MHz) $CDCl_3$



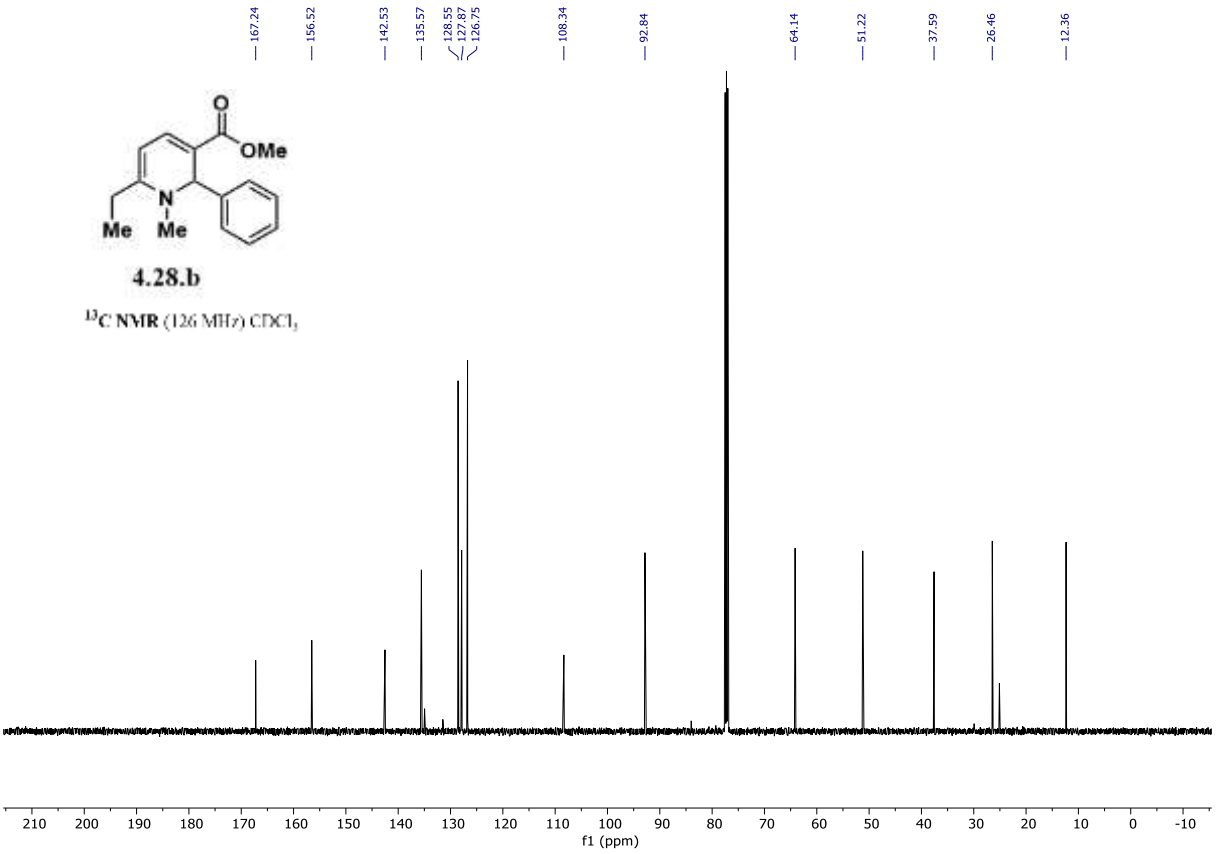
4.28.a

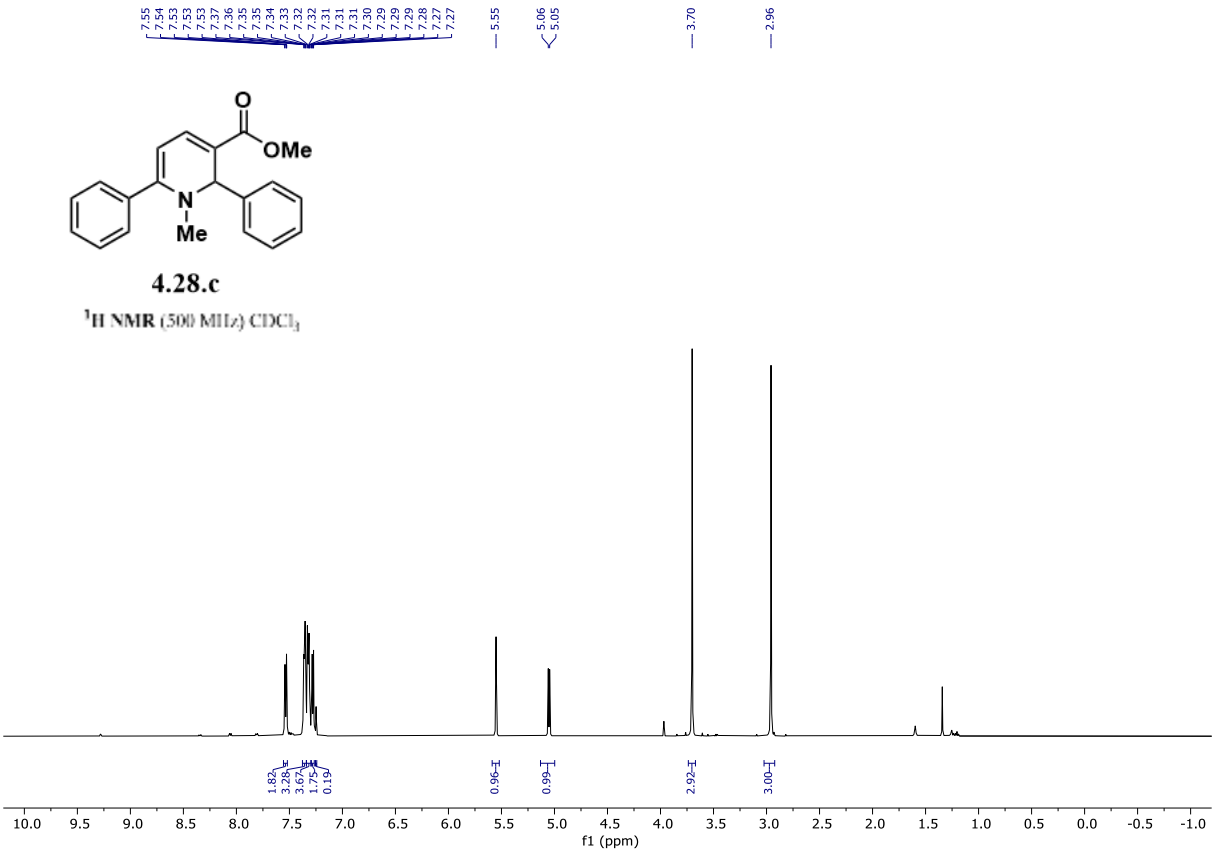
^{13}C NMR (126 MHz) $CDCl_3$



4.28.b

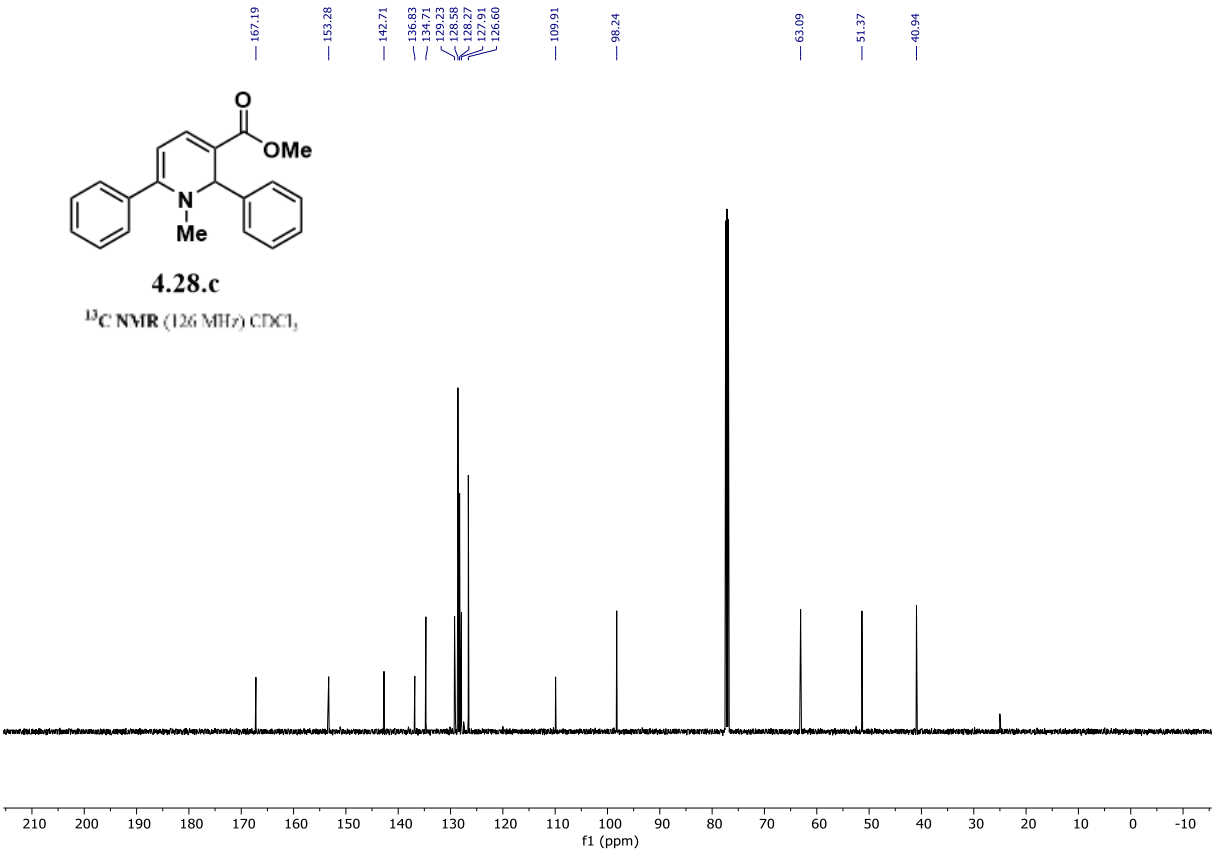
^{1}H NMR (500 MHz) $CDCl_3$

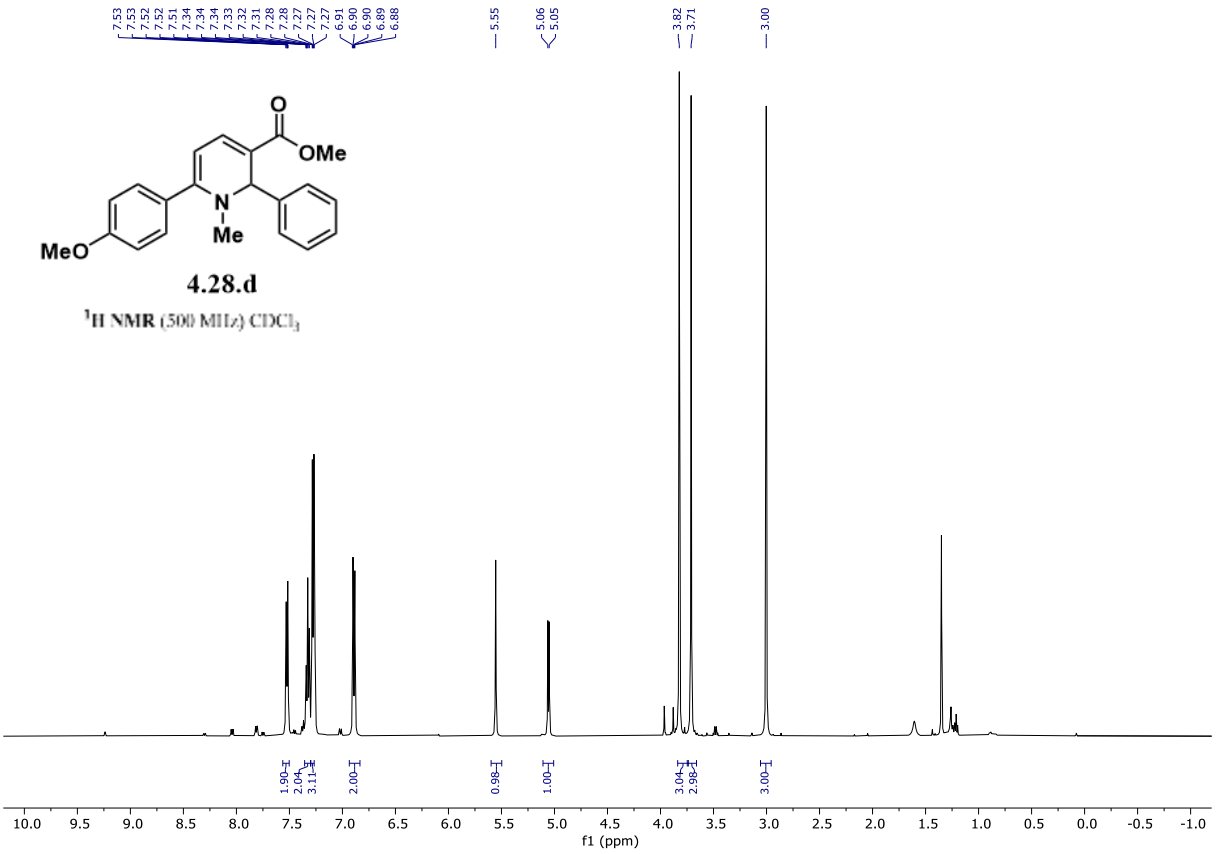

167.24
156.52
142.53
135.57
128.55
127.87
126.75
108.34
92.84
64.14
51.22
37.59
26.46
12.36
O
OMe
N
Me
Me
4.28.b
13C NMR (126 MHz) CDCl3
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



4.28.c

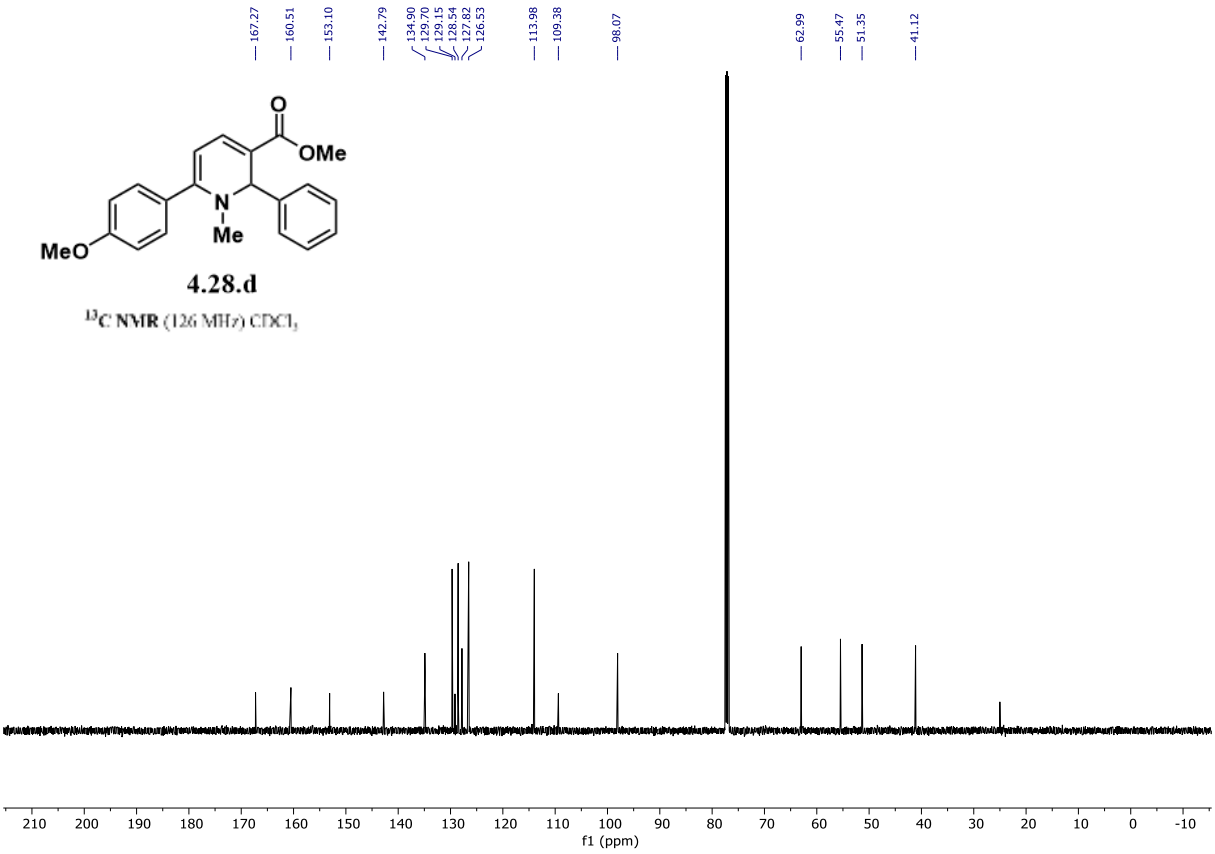
^{1}H NMR (500 MHz) $CDCl_3$


167.19
153.28
142.71
136.83
134.71
129.23
128.58
128.27
127.91
126.60
109.91
98.24
63.09
51.37
40.94
O
OMe
N
Me
4.28.c
13C NMR (126 MHz) CDCl3
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)



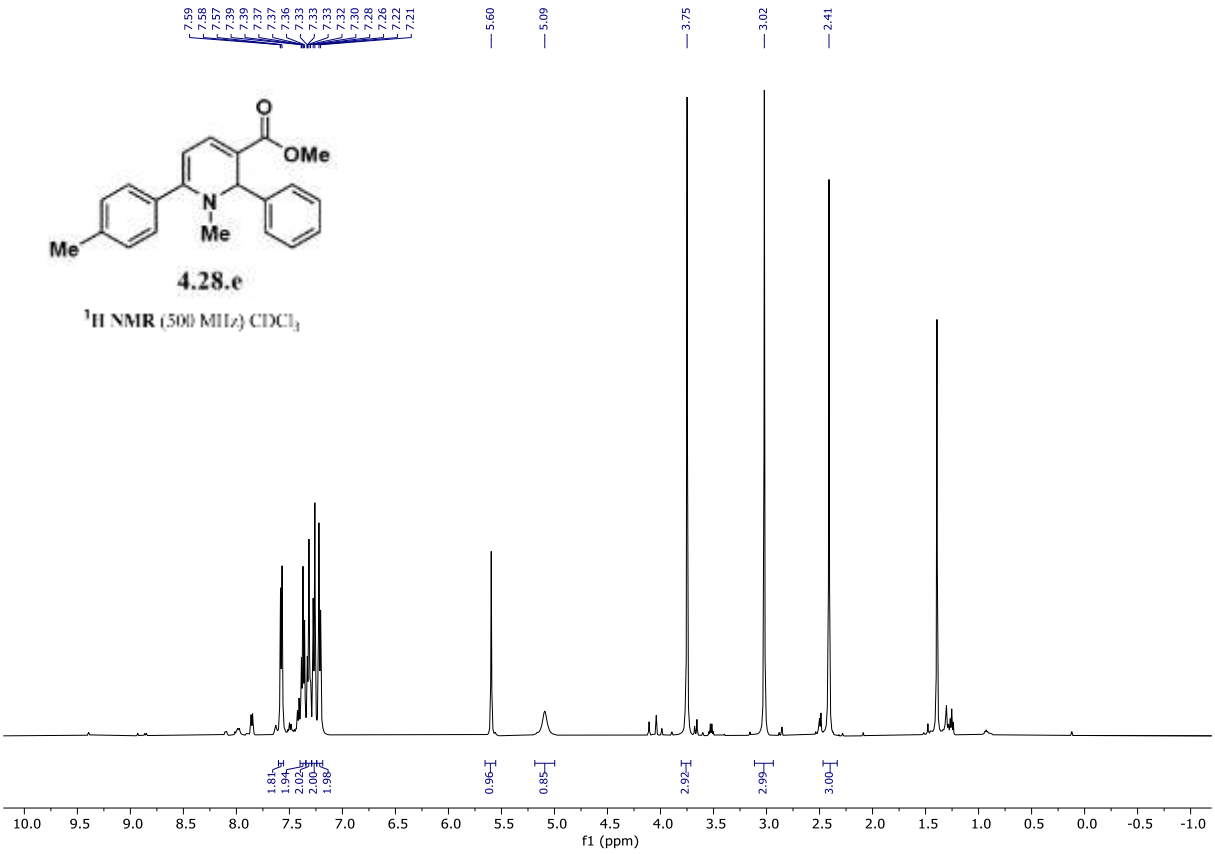
4.28.d

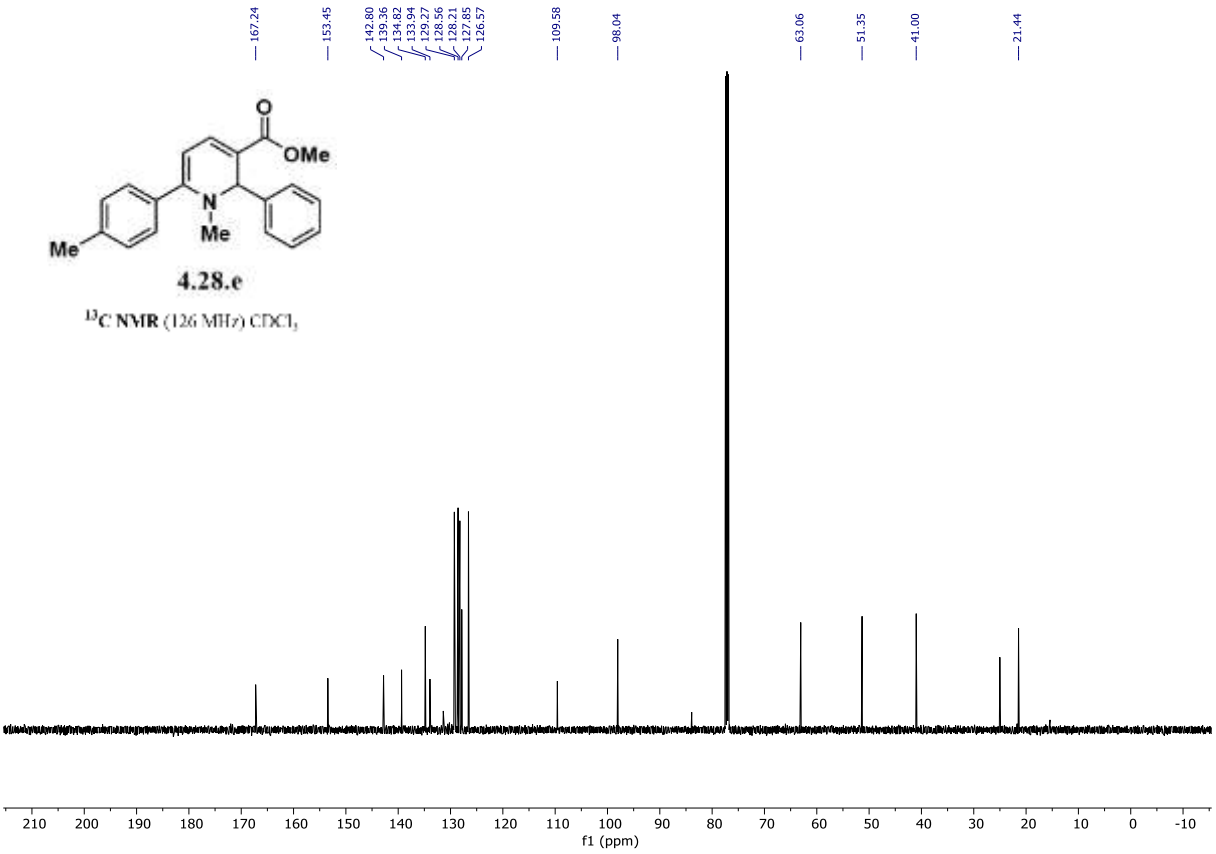
^{1}H NMR (500 MHz) $CDCl_3$



4.28.d

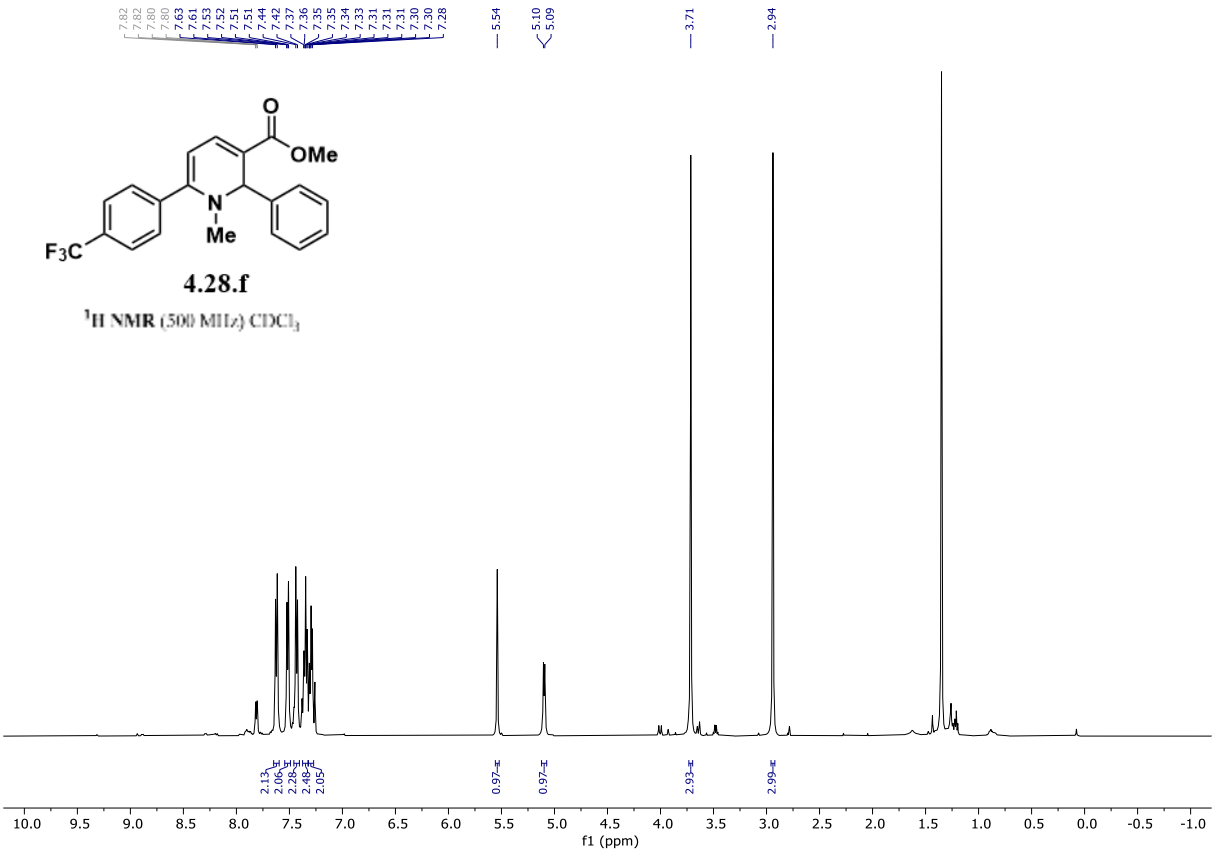
^{13}C NMR (126 MHz) $CDCl_3$

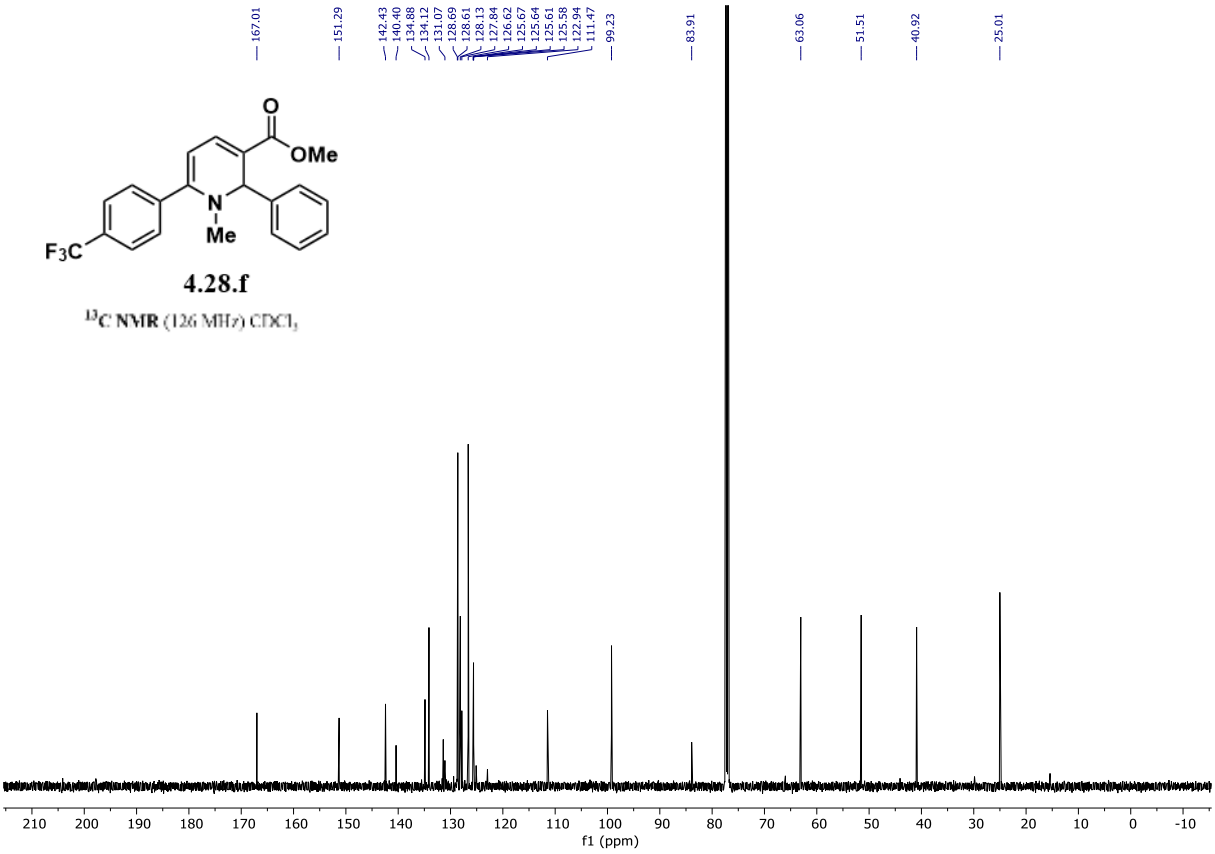

7.59
7.58
7.57
7.39
7.39
7.37
7.36
7.33
7.33
7.32
7.30
7.28
7.26
7.22
7.21
5.60
5.09
3.75
3.02
2.41
O
OMe
N
Me
Me
4.28.e
^{1}H NMR (500 MHz) $CDCl_3$
1.81
1.94
2.02
2.00
1.98
0.96
0.85
2.92
2.99
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

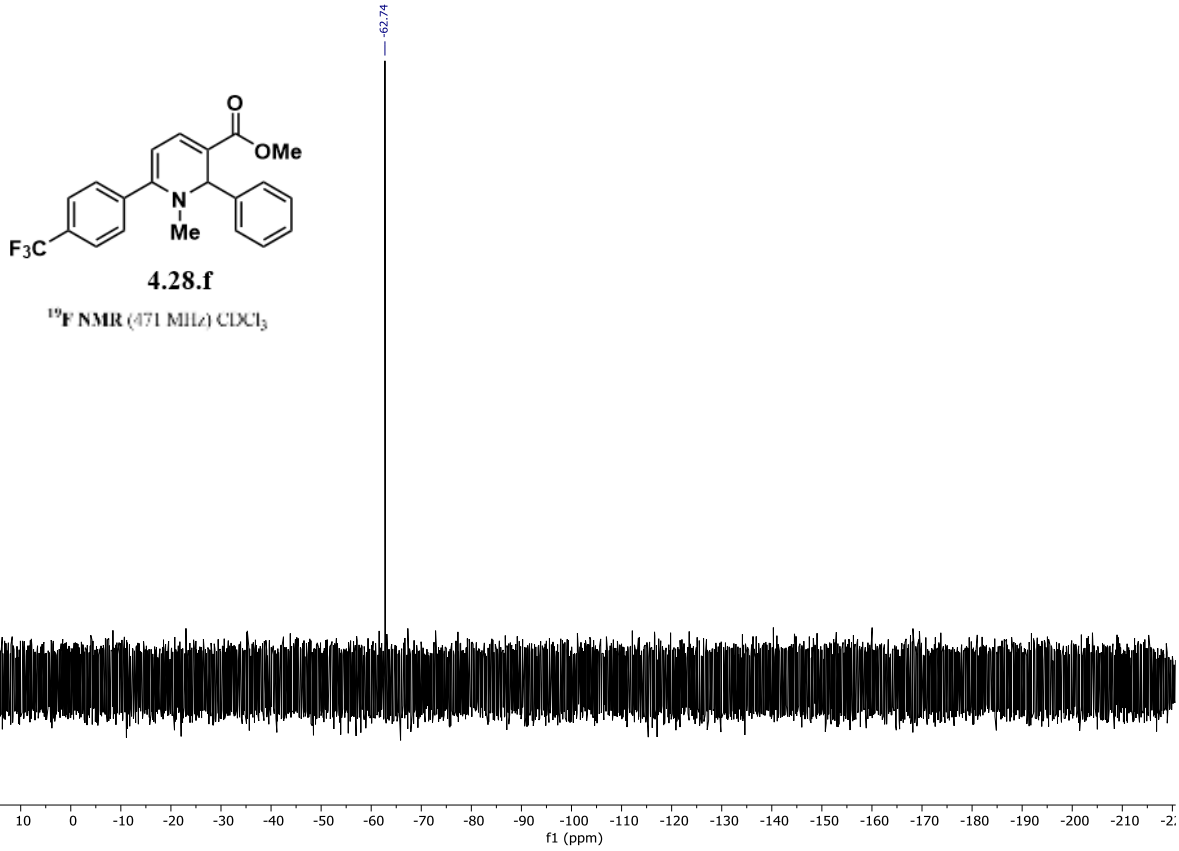


4.28.e

^{13}C NMR (126 MHz) $CDCl_3$


7.82
7.82
7.80
7.80
7.63
7.61
7.53
7.52
7.51
7.51
7.44
7.42
7.37
7.36
7.35
7.35
7.34
7.33
7.31
7.31
7.31
7.30
7.30
7.28
5.54
5.10
5.09
3.71
2.94
O
OMe
N
Me
F3C
4.28.f
1H NMR (500 MHz) CDCl3
2.13
2.06
2.28
2.48
2.05
0.97
0.97
2.93
2.99
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 0.0 -0.5 -1.0
f1 (ppm)


167.01
151.29
142.43
140.40
134.88
134.12
131.07
128.69
128.61
128.13
127.84
126.62
125.67
125.64
125.61
125.58
122.94
111.47
99.23
83.91
63.06
51.51
40.92
25.01
O
OMe
N
Me
F3C
4.28.f
13C NMR (126 MHz) CDCl3
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)



4.28.f

^{19}F NMR (471 MHz) $CDCl_3$