Functionalization of 4-Substituted Pyridines for Enantioselective Synthesis

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Abstract

Enantioselective synthesis using nitrogen containing heterocycles, such as pyridines, is extremely useful in drug discovery. The prevalence of pyridines in the drug market is well-documented and a mild, enantioselective method to functionalize pyridines would allow faster access to more structurally diverse pyridines, improving efficiency in the search of drug candidates. The Orellana group has developed a strategy for selective allylation of 4-substituted pyridines using mild conditions, which results in broad functional group tolerance. Reported herein are ways to expand the allyl fragment to larger linear and cyclic fragments, and attempts at the development of an enantioselective variant using palladium catalyzed decarboxylative allylation. The pathway for reductive elimination was also discovered through mechanistic experiments which revealed more of this palladium catalyzed decarboxylative allylation mechanism. Furthermore, a new method was investigated for arylation of the pyridylic position using a high-valent copper catalysis.

Acknowledgements

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List of Abbreviations

1D	one dimensional
2D	two dimensional
ACS	American Chemical Society
ADHP	alkylidene dihydropyridine
ANDEN	9,10-dihydro-9,10-ethanoanthracene
Ar	aryl
ATR	average true range
BINAP	2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
COSY	Correlation spectroscopy
DACH	diaminocyclohexane
DCC	N,N’-dicyclohexylcarbodiimide
dba	dibenzylidene acetone
DCM	dichloromethane
Di	dioxane
DMAP	4-dimethylaminopyridine
ee	enantiomeric excess
EtOAc	ethyl acetate
Eq.	equation
Equiv.	equivalents
FDA	Food and Drug Administration
h	hour
HMBC	Heteronuclear Multiple Bond Correlation
IR	infrared
KHMDS	potassium hexamethyldisilazide
LiHMDS	lithium hexamethyldisilazide
mCPBA	meta-chloroperoxybenzoic acid

Me	methyl
Mes	mesitylene
Min	minutes
MHz	megahertz
n-BuLi	n-butylithium
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
OAc	acetyloxy
OTf	triflate
Ph	phenyl
ppm	parts per million
RBF	round bottom flask
R_f	retention factor
r.t.	room temperature
SPhos	2-dicyclohexylphosphino-2’,6’-dimethoxybiphenyl
THF	tetrahydrofuran
TsCl	tosyl chloride
TMP	2,2,6,6-tetramethylpiperidine
UV	ultraviolet
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Chapter 1: Introduction

1.1 Importance of Heterocycles

Many of the most useful molecules for drug discovery contain highly coordinating, polar heterocycles that have a wide variety of functional groups. In 2002, an analysis of all marketed drugs revealed that pharmaceutical drugs containing heterocycles encompass 65% of the molecules that were in late development stages[1] and seven out of ten of the top selling drugs on the market.[2] Among these heterocycles, six-membered rings are used 59% of the time with pyridine being the second most common nitrogen containing heterocycle used among FDA approved pharmaceuticals.[3] These pyridine derivatives are commonly functionalized at the 2- and 3-positions, with the 2-position being the most common, such as the antihistamine in **Figure 1**. The methods to synthesize pyridines containing functionalizable handles is limited,[4] emphasizing the importance in development of new methods to synthesize substituted pyridines using techniques that can tolerate a wide variety of functional groups. Specifically, optically active pyridines containing stereogenic centres at the pyridylic position are extremely useful as they can lead to more selective drugs, and avoid possibly harmful effects arising from their antipodes.

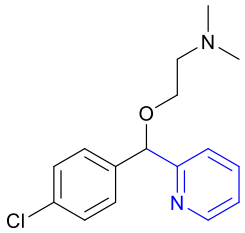
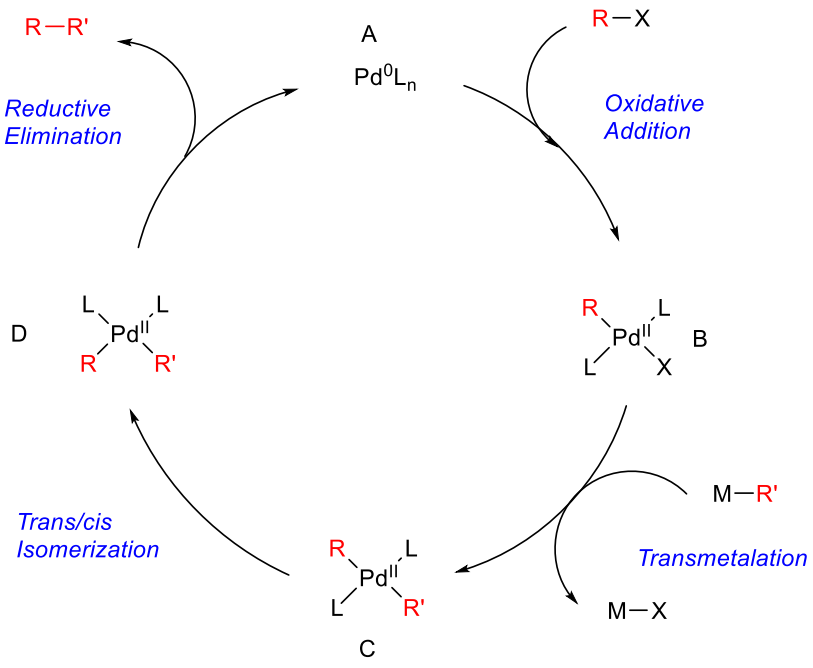


Figure 1: A pyridine-containing drug; Carbinoxamine.

1.2 Palladium catalyzed carbon-carbon bond formation

The use of catalysis allows organic chemists to accelerate reactions and synthesize new products that would not otherwise be accessible. Transition metals have been used for catalysis as they are able to easily move between oxidation states. Transition metal catalysts do not affect the thermodynamics of a reaction, but are able to increase the rate at which they proceed by lowering the activation energy of the rate determining step. Palladium catalysts in particular facilitate unique transformations that cannot be readily achieved using classical techniques.[5] The general

mechanism for C-C cross-coupling reactions using palladium catalysts is well understood (**Scheme 1)**. The cycle begins with Pd(0), which is either formed *in situ* by reduction of a Pd(II) precatalyst, or is introduced in the form of a stabilized Pd(0) source, such as $Pd_2(dba)_3$. Pd(0) undergoes oxidative addition with an electrophilic partner, R-X, to place the first carbon fragment on palladium, forming a Pd(II) complex (B). This electrophilic or oxidative addition partner can be aryl, alkenyl, or alkyl and bears a leaving group, which is generally a halogen or pseudohalogen group (e.g. triflate). The next step in the cycle is transmetallation where an organometallic species (C-M) bearing the second carbon fragment undergoes addition to the Pd(II) complex (B), replacing the leaving group (X) and forming complex C and a metal salt (MX). *Cis/trans* isomerization will then occur, placing both coupling partners adjacent to each other on Pd(II) to give complex D. The final step of the reaction is reductive elimination where the C-C bond is formed and Pd(0) is regenerated, allowing the cycle to repeat. There are a number of well-established palladium catalyzed C-C bond forming reactions that use this general cycle with a variety of organometallic reagents. These include the Kumada (R-MgX), Suzuki ($R-B(OH)_2$), Stille (R'-SnR_3), Negishi (R-ZnX), and Sonogashira (R-Cu, R= terminal alkyne).[5]



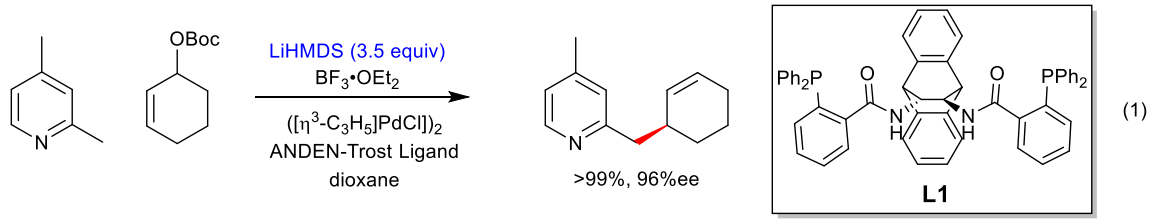
Scheme 1: General mechanism of palladium catalyzed cross-coupling reactions.

1.3 Palladium catalyzed allylation of alkylpyridines

The lateral allylation of alkylpyridines is a very useful drug synthesis method for organic chemists as it establishes a new stereogenic centre and provides a versatile synthetic handle that can be transformed to other groups. There are three main strategies that have been developed to produce these allylated alkylpyridines thus far. These include Lewis-acid activation and deprotonation of pyridines to form soft nucleophiles, activation of pyridine with a carboxylate group, and the use of benzylpyridines and a strong base to achieve allylation. Not only does this pyridylic allylation provide a starting point for further functionalization, but it also forms a stereogenic centre. These centres are an important part of drug development as forming one enantiomer selectively allows more specificity within the human body. Syntheses that incorporates highly enantioselective routes have proven to be extremely useful in the formation of new small molecules. Although two enantiomers will have the same constitution, they have differences in biological activities such as pharmacology, toxicology, and pharmacokinetics.[6] This is reflected in the pharmaceutical industry where over 56% of drugs are chiral products.[6]

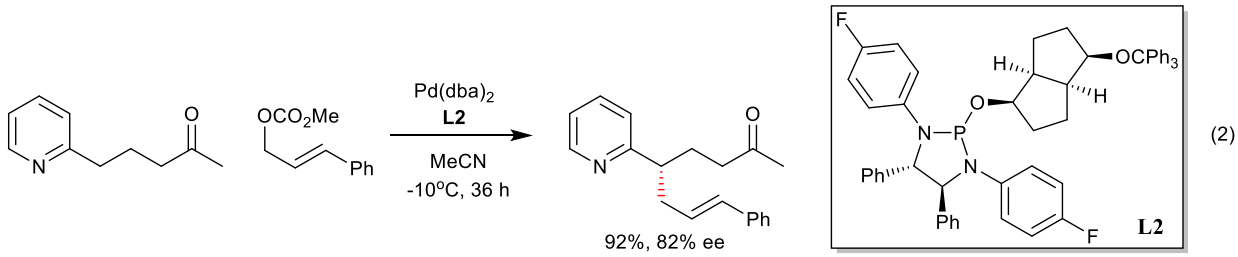
1.3.1 Lewis-acid activation of pyridine for palladium catalyzed allylation

Trost has shown that Lewis-acids can be used to activate alkylpyridines by coordination to the nitrogen. He has shown that the use of pyridine with boron trifluoride complexes softens the nucleophile, decreasing the density of the negative charge of the anion for enantioselective palladium catalyzed allylation reactions of pyridines (**Eq. 1**).[7] Strong bases are needed for deprotonation of the pyridine at the pyridylic site. Trost found that when using a pivalate ester protecting group, one equivalent of *n*-BuLi was necessary to deprotonate the HMDS, driving the reaction to completion. This pyridine nucleophile can then attack the electrophilic allyl group producing an allylated pyridine. These reactions show selectivity for allylation of the 2-position over the 4-position.[7] Trost has also used this method to gain high enantio- and diastereoselectivity. Strong bases are used to achieve this selectivity, incorporating multiple equivalents of LiHMDS. These harsh conditions diminish the functional group tolerance of this reaction.[7]



(1)

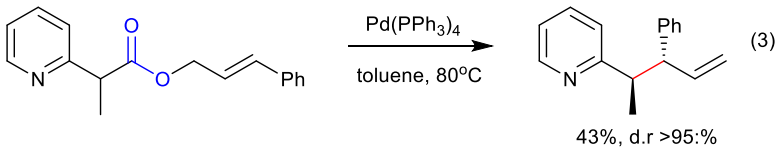
Similar to this work by Trost, Sawamura has used a Lewis-acid activation of pyridine (**Eq 2**) for allylation. In this type of reaction, the π-allylpalladium complex generated plays a dual role.[8] Firstly, it is used as an electrophile to form a new C-C bond in the allylation of the 2-pyridylic site. Secondly, it acts as a Lewis-acid to coordinate to nitrogen and facilitate 'soft enolization' by generating an alkoxide base, removing the need for a stoichiometric Lewis-acid. When using a cinnamyl group, Sawamura has been able to obtain enantioselectivity without requiring a base in the reaction conditions.[8] This work is completely selective for the 2-pyridylic position in the presence of a 4-pyridylic position, but cannot be selective for the 4-pyridylic position.



(2)

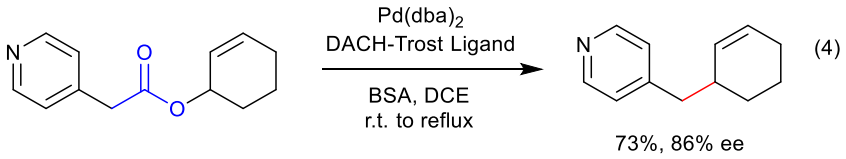
1.3.2 Activation of pyridine with a carboxylate group for palladium catalyzed allylation

Other groups have found conditions for pyridylic allylation by incorporating an activating group on the pyridine. Tunge has developed the palladium catalyzed decarboxylative allylation of allyl 2-pyridinecarboxylates (**Eq. 3**).[9] These types of reactions use esters to form a C-C bond with loss of CO_2. This decarboxylative technique is safer and cheaper than many other palladium catalysis methods as the major side product is CO_2, eliminating the production of stoichiometric metal waste generally formed during transmetallation. A particular class of compounds is created using decarboxylative allylation that is generally different from traditional cross-coupling reactions. This method can also be used to allylate other heterocycles. Contrary to the common mechanism of nucleophilic attack at the (π-allyl)Pd system, the pyridylic nucleophile was shown to intercept the π-allyl intermediate at the more substituted carbon,[9] and the resulting product is formed diastereoselectively. The substrate scope for this reaction is limited by the need for a carboxylate group at the pyridylic position in order to activate the pyridine.



(3)

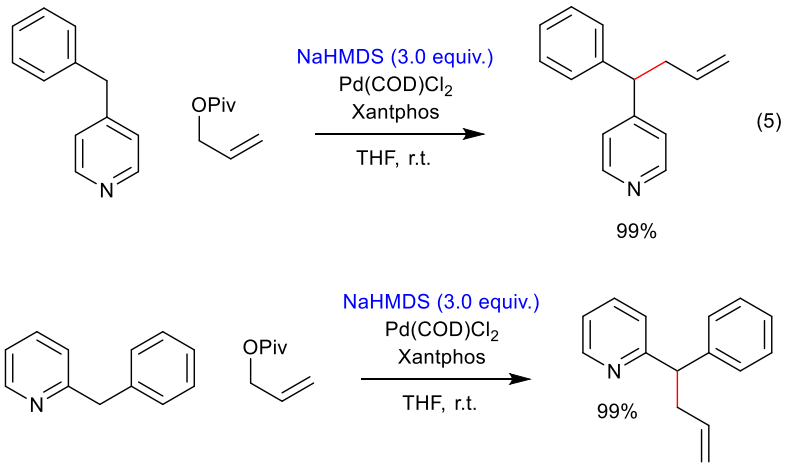
Lundgren has shown pyridylic functionalization using a similar type of activated pyridine to the one used by Tunge, with the use of an ester or carboxylic acid. This synthesis method uses palladium or iridium catalyzed decarboxylative allylation at the 2-position and 4-position of pyridine (**Eq. 4**).[10] Interestingly, the mechanistic hypothesis shows that the C-C bond is generated at the pyridylic site before decarboxylation, forming a functionalized carboxylic acid. The desired allylation product is then formed upon decarboxylation.[10] Very high levels of enantioselectivity is achieved through this type of allylative work. This reaction uses DBU as a mild base allowing a wider range of functional groups than that seen with Trost, Walsh, or You groups.[7,11,12] This reaction has no selectivity as both the 2- and 4-positions can be allylated. It is necessary to begin with a carboxylic acid at the pyridylic position, limiting the substrate scope to these types of substituted pyridines.[10]



(4)

1.3.3 Allylation of 4-benzylpyridine using palladium catalysis

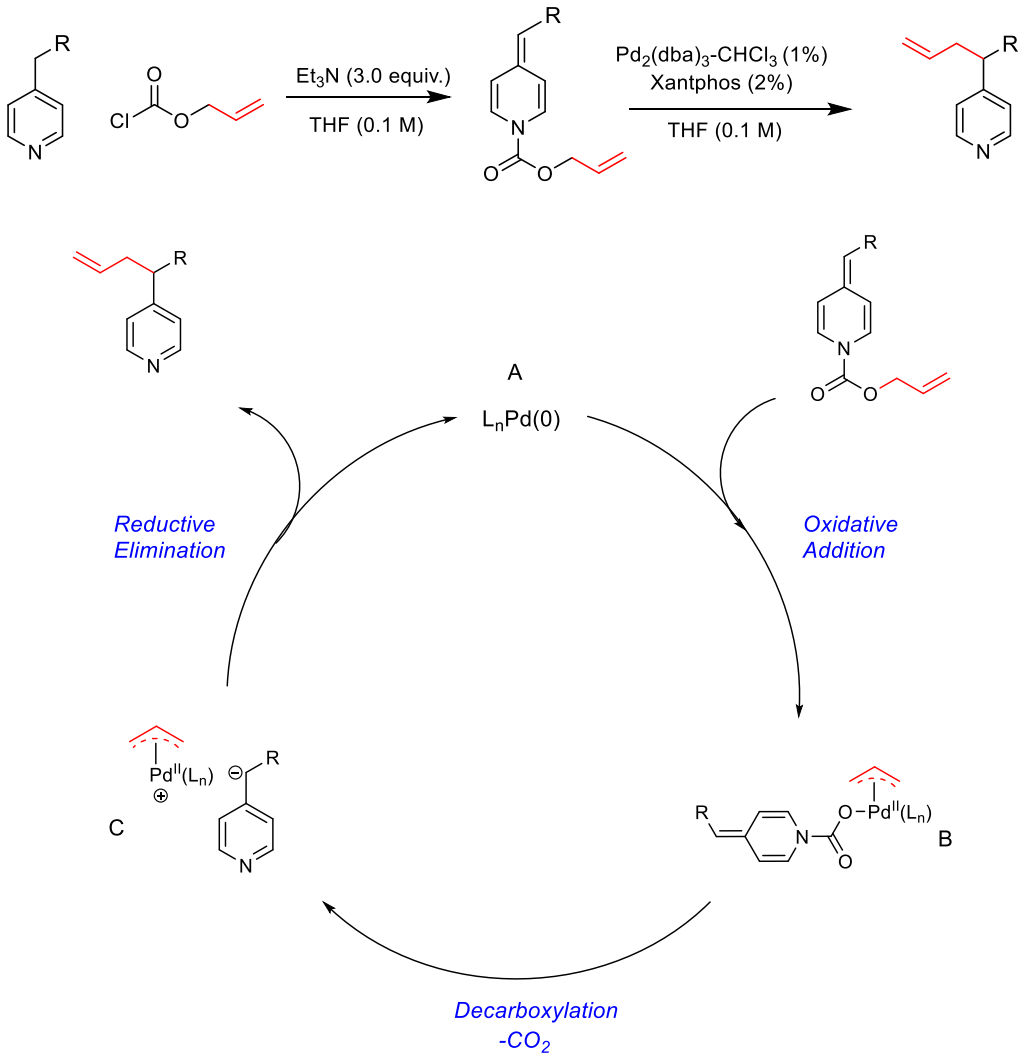
Walsh has shown the allylation of a variety of diarylmethanes, including benzylpyridines, with the use of multiple equivalents of strong base to deprotonate the pyridylic position, generating a pyridylic anion that can undergo palladium catalysis (**Eq 5, 6**).[11] These diarylmethane anions act as soft nucleophiles with a pKa of 32 to retain the stereochemistry in the electrophile through double inversion of configuration. This reaction enables pyridylic allylation at the 2-, 3-, and 4-positions, with both the 2- and 4-positions attaining allylation in excellent yields,[11] although Walsh has not shown examples of allylation selective for primarily the 4-position. The use of strong base in this reaction limits the functional group tolerance and can create selectivity issues in pyridines containing multiple pyridylic sites.



1.4 Allylating 4-alkylpyridines using a mild conditions as proposed by the Orellana Group

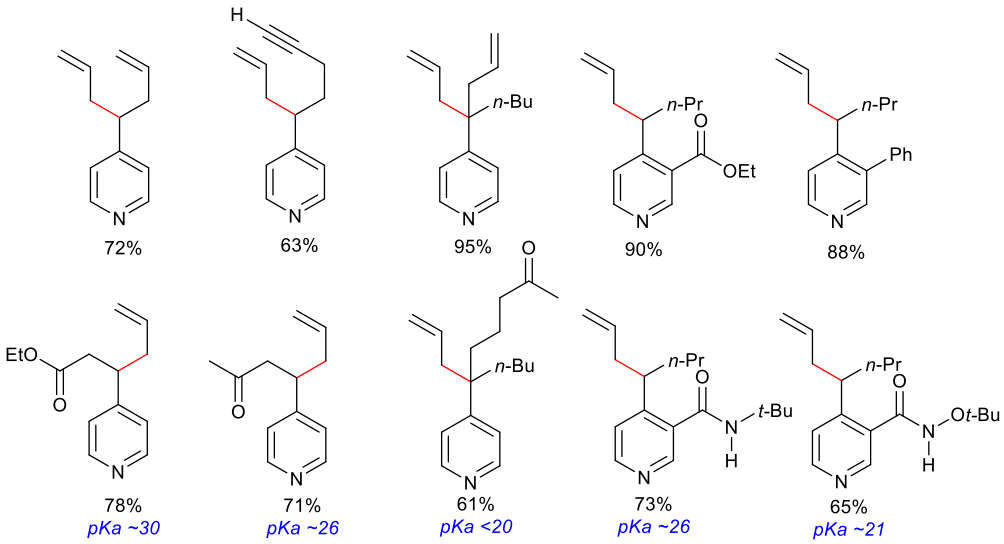
In the production of pharmaceutical drugs, the least wasteful techniques which can also incorporate a wide variety of functional groups are valuable from both a synthetic and production perspective. Considering this, the Orellana group has developed a low toxicity synthesis route to allylate pyridines, effectively adding a functionalizable handle to this useful heterocycle. We incorporate the Tsuji-Trost reaction which is a palladium catalyzed allylation method that occurs between a substrate with a leaving group at an allylic position and a nucleophile. This reaction type forms a π-allyl palladium complex after oxidative addition which is then attacked by a nucleophile. This decarboxylative mechanism along with the Tsuji-Trost type allylation provides a mild synthesis method that is fully selective for the 4-position.

We use chloroformates and triethylamine to activate and dearomatize pyridine forming an alkylidene dihydropyridine (ADHP) intermediate (**Scheme 2**). A side product of this reaction is a triethylammonium chloride salt which can be easily removed upon trituration with diethyl ether. Without further purification, this ADHP can then undergo oxidative addition in the presence of Pd(0) to form a π-allyl palladium complex. Upon loss of CO_2, pyridine is rearomatized and the positively charged palladium allyl fragment can migrate to the anion at the pyridylic position, to give complex C as seen in **Scheme 2**. The pyridylic anion and allyl fragment can then undergo reductive elimination to give the desired product, and regenerate Pd(0).



Scheme 2: Equation and mechanism for pyridylic allylation as proposed by the Orellana group.

The optimal ligand was found from the results of a ligand screen[13] which indicated that Xantphos produced both a high yield and stable catalyst due to the chelating effect from it being a bidentate ligand. These conditions allowed the reaction to run with as little as 1% palladium and Xantphos loading, giving moderate to excellent yields. Due to the use of mild conditions, a wide variety of functional groups are tolerated including alkynes, alkenes, halogens, protected and unprotected alcohols, nitrile groups, esters, amides, ketones, and substituents bearing acidic protons (**Scheme 3**).



Scheme 3: Substituted pyridines synthesized using the Orellana conditions, tolerating a variety of functional groups.

The dearomatization and allylation of pyridines only occurs with a substituent at the 4-position, there is no allylation of the pyridine if a substituent is at the 2- or 3-position. Even in molecules that contain multiple pyridylic sites, only those which have a 4-substituent will undergo dearomatization followed by palladium catalyzed allylation. As seen in **Figure 2**, the first two molecules (**A** and **B**) have substituents at the 3- and 4-position, but only the 4-position undergoes dearomatization to form the ADHP. Similarly, in example **C**, both the 2- and 4-position of the pyridine are functionalized but only the 4-position undergoes dearomatization.

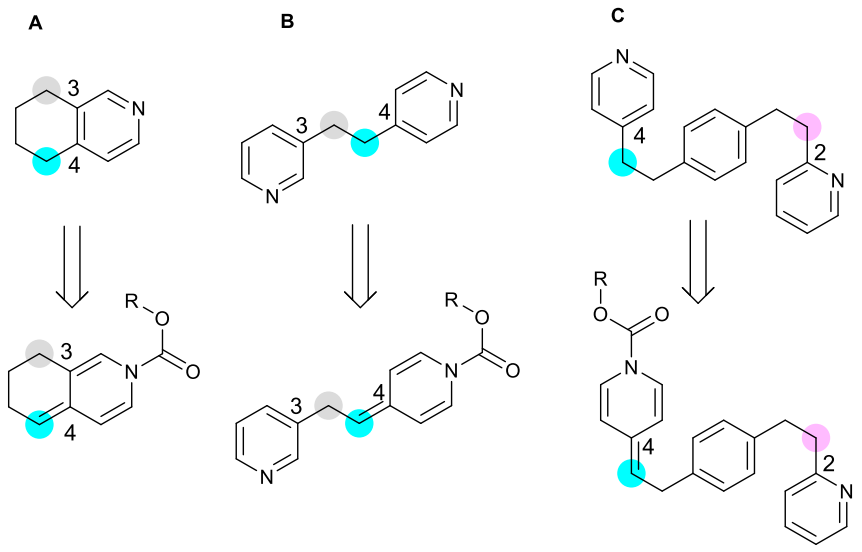


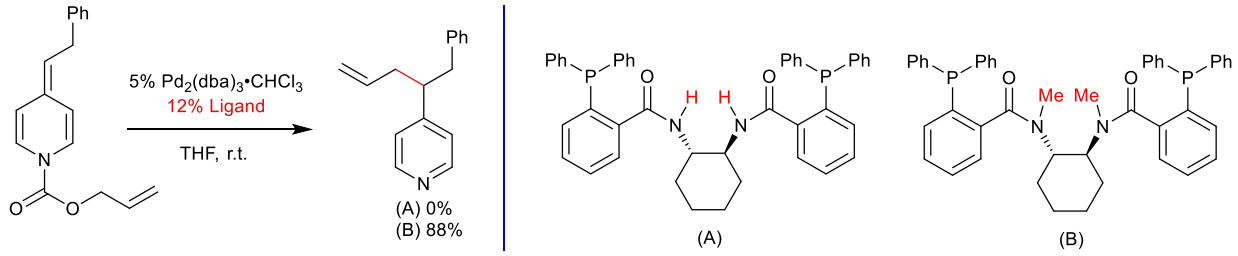
Figure 2: Pyridine-containing molecules that have two pyridylic sites to test selectivity. A) Pyridylic sites at the 3- and 4-position in a bicyclic molecule. B) Pyridylic sites at the 3- and 4-position with two pyridine rings. C) Pyridylic sites at the 2- and 4-position with two pyridine rings.

Unlike the previously stated pyridylic allylation methods, ours does not use harsh bases or Lewis-acidic groups tolerating a wide variety of functional groups. It is also not necessary for our substrate pyridines to contain an activating group at the pyridylic position, which would also limit our substrate scope. Thus far, this is the only pyridylic allylation method to be completely selective for the 4-position.

1.4.1 Mechanistic studies on the allylation of pyridines by the Orellana Group

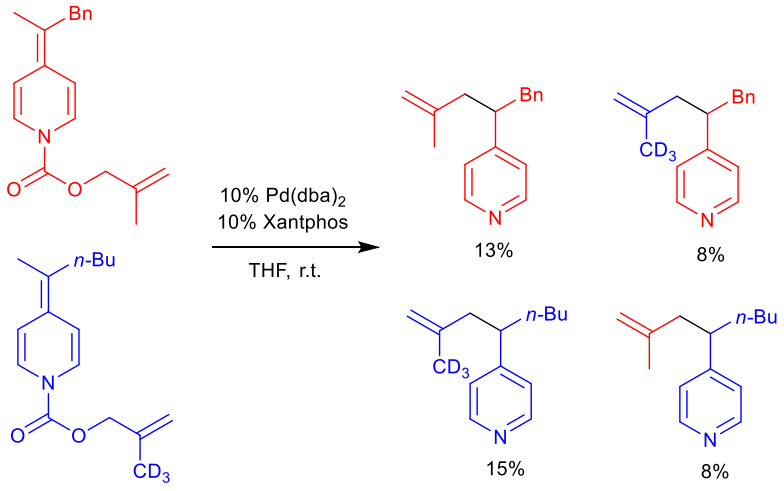
The Orellana group has done an extensive amount of work to investigate the mechanism of the palladium catalyzed allylation of pyridines with ADHPs. A discrepancy between our proposed mechanism and the reactivity patterns seen from our results prompted us to look for a deeper understanding of the reaction. The proposed mechanism invokes a pyridylic anion and a cationic palladium allyl species (**Scheme 2**, complex C). The anion in this ion pair should react with a number of the functional groups that were tolerated in the substrate scope. This anion should also react with the N-H group in the DACH-Trost ligand backbone, which incorporates a 1,2-*trans*-diamine (**Scheme 4**). Recent reactions have shown that 4-alkylpyridine did not undergo allylation when using the DACH-Trost ligand, but we found an 88% yield when an N-methylated version of

the ligand was used. This suggests that the pyridylic anion can deactivate the ligand by deprotonation.



Scheme 4: 4-Alkylpyridine allylation with the standard and methylated DACH-Trost ligand.

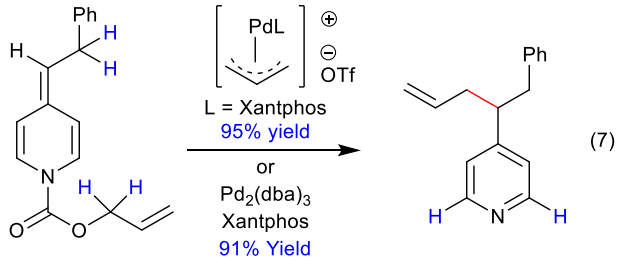
To test if this pyridylic anion and a cationic palladium allyl species was formed in the catalytic cycle, a cross over experiment was performed using ADHP intermediates prepared from two different alkylpyridines and two different methallyl chloroformates.[14] A 1:1 mixture of these ADHP intermediates were prepared and by using standard conditions with $Pd_2(dba)_3 \cdot CHCl_3$ and Xantphos, all possible products were observed (**Scheme 5**). This supports the formation of a separated ion pair.



Scheme 5: Crossover experiment to establish the formation of ion pairs.

To test if a pyridylic anion attack, from a separated ion pair, outcompetes an attack from an ADHP the relative rates of attack were measured.[14] This was directly tested by conducting a head-to-head comparison of the allylation reaction of using our standard conditions of $Pd_2(dba)_3 \cdot CHCl_3$ and Xantphos, and the allylpalladium(II) complex (**Eq. 7**). A kinetic study was completed and the reaction rates were compared by monitoring the disappearance of the 4-phenylethyl pyridine

substrate and appearance of product using ^{1}H NMR spectroscopy. The attack by the pyridylic anion was proved to be significantly faster than that with attack from a neutral ADHP. Thus, this kinetic study suggests that an anion attack would outcompete that of an ADHP *in situ*.



(7)

1.5 Copper catalysis

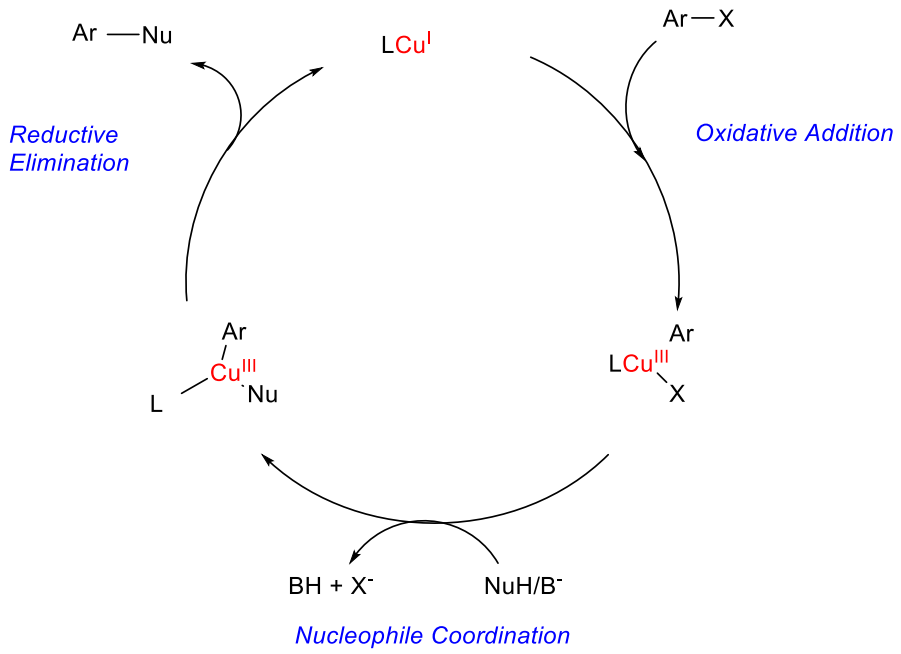
1.5.1 Copper catalysis in organic synthesis

Through the mechanistic work that had been done to elucidate the catalytic cycle in our allylation of pyridines, we had determined that an ADHP was nucleophilic enough to attack the allylpalladium(II) complex.[14] Due to this realization, we proposed that this pyridylic functionalization could extend to other transition metals. Copper is isoelectronic with palladium, therefore it would be logical to use a copper cycle to functionalize 4-alkylpyridines.

Similar to palladium, copper is another transition metal that is used as a catalyst in a wide variety of cross-coupling reactions and it is extremely useful for the formation of new C-C bonds. Copper surpasses other coupling transition metal catalysts, such as palladium and iridium, in natural abundance, cost effectiveness, and eco-friendliness.[15] Copper is easily coordinated to heteroatoms and π-bonds allowing cross coupling synthesis of C-C bonds, C-heteroatom bonds, and the formation of new allylic substrates.[16]

The mechanism of C-C bond forming using high valent copper catalysts were not well understood until recently. The increase in the use of Cu(III) species in a catalytic cycle warranted a deeper understanding of the cross-coupling mechanism when going between the oxidation states of Cu(I) and Cu(III). In earlier studies, the formation of Cu(III) was thought to occur from a disproportionation reaction between a Cu(II) ion and an arene substrate.[17] Following studies determined that high valent organometallic species ArCu(II) were never observed and ArCu(II)

compounds were actually precursors to ArCu(III) compounds.[18] This oxidation state was validated by experimental evidence from reaction kinetics, linear free energy relationships and kinetic isotope effects, and theoretical calculations.[17] The Cu(III) species was confirmed by observation using rapid-injection NMR spectroscopy at -100°C.[19] As seen in **Scheme 6** with the Ullmann-type cross-coupling reaction,[20] the catalytic cycle is now thought to begin as Cu(I) and undergo oxidative addition to become Cu(III). The Cu(III) species is then reduced back to Cu(I) upon reductive elimination where it can begin the catalytic cycle again. [19,21,22]



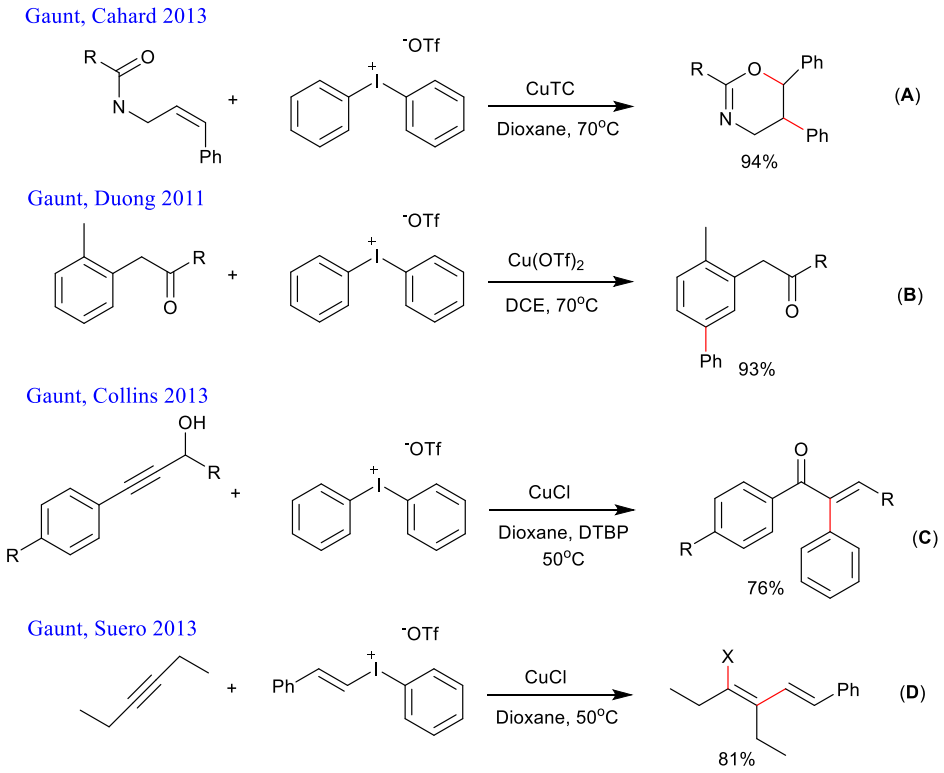
Scheme 6: General copper catalyzed mechanism in the Ullmann-type cross-coupling reactions, involving Cu(I) and Cu(III).

1.5.2 Cu(I) to Cu(III) catalytic cycle in arylation using biaryl iodonium salts

Recently there has been greater use of copper-catalyzed coupling reactions in organic chemistry. An emerging arylating technique with copper catalysts uses biaryl iodonium salts as the source for the aryl group. These iodonium species are in the +3 oxidation state which makes them strong electrophiles and powerful oxidants.[23] A major drawback of these reagents is that they create stoichiometric ArI as a wasteful byproduct, although it can potentially be isolated and reused. A wide variety of aryl groups can be incorporated into organic compounds aryl iodonium salts as a coupling partner in copper catalyzed reactions.[23] In these reactions, the least sterically hindered

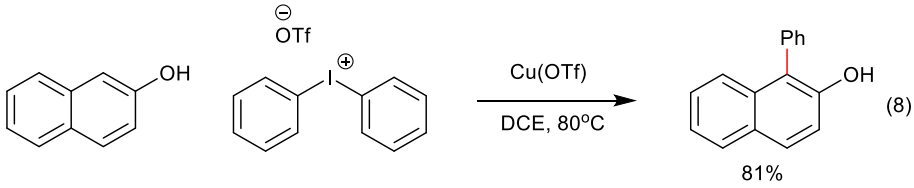
group will undergo oxidative addition more quickly.[22] These reactions are believed to follow the same catalytic cycle as other high valent copper species with Cu(I) being oxidized to Cu(III) and subsequently reduced to reform Cu(I) after reductive elimination. Lockhart performed a number of kinetic studies comparing Cu(I) to Cu(II) and showed that Cu(I) is the active copper species due to the rate of the reaction being faster when Cu(I) is used than Cu(II).[24] The ease of copper to go between the Cu(I) and Cu(II) oxidation state by reducing the starting compound *in situ* by electron transfer allows either Cu(I) or Cu(II) catalysts to be used as pre-catalysts. Electron transfer from Cu(I) to the iodonium salt followed by rapid homolysis of a phenyl-iodine bond generates a phenylcopper(III) intermediate.[24] This is an efficient aromatic electrophile that can readily undergo reductive elimination with a nucleophile to form the desired product.[24]

Although there has been copper-catalyzed arylation by a number of different groups, Gaunt has been the pioneer of these types of reactions and has arylated a very diverse set of reagents. He has shown through carbofunctionalization of allylicamides that the cyclization on an endo-selective alkene can be performed with complete diastereoselectivity (**Scheme 7, Eq. A**).[25] Gaunt has also shown meta-selective arylation on α-aryl carbonyl framework (**Scheme 7, Eq. B**).[26] He has found a copper catalyzed arylative rearrangement of propargylic alcohols (**Scheme 7, Eq. C**).[27] The iodonium salt is also able to bear an aryl group and allyl group with Gaunt's work involving carbotriflation of alkynes (**Scheme 7, Eq. D**).[28]



Scheme 7: A number of copper catalyzed reactions involving biphenyl iodonium salts from the Gaunt group.

Wang has also shown selective arylation of 2-napthol using biaryl iodonium salts (**Eq. 8**).[29] He has shown that a wide variety of iodonium salts could be tolerated in this type of reaction with both electron donating and electron withdrawing substituents. The counterion on the iodonium salt has a strong effect on the outcome of the reaction with OTf^- giving the highest yields. However, steric bulk on the aryl groups affects the reactivity, only a trace amount of product being formed when the ring was increasingly bulky.[29]



1.6 Research Proposal

1.6.1 Investigating more diverse allyl electrophiles

We have developed mild allylation conditions for both alkyl- and benzyl- pyridines that is completely selective for the 4-position. Thus far, pyridylic allylation has been achieved with a simple allyl fragment. This allyl group can be expanded to use both bulkier linear fragments, such as a cinnamyl group, and cyclic fragments, such as a cyclohexenyl group. The chloroformate from these allylic alcohols needs to be synthesized using phosgene or triphosgene as these types of fragments are not commercially available. This will hopefully form the ADHP and proceed through the same type of intramolecular mechanism as seen in **Scheme 2** where the nucleophile and electrophile begin on the same molecule. An intermolecular mechanism can also be used where the allyl electrophile and nucleophile begin on separate molecules and undergo palladium catalysis. In this case, the allyl electrophile would have to be synthesized with a leaving group that is non-coordinating to palladium and allows allylation of the pyridine. We believe that these bulkier allyl fragments can lead to an eventual enantioselective variant of this reaction as it will create more of a steric bias in the catalyst active site forming one enantiomer preferentially over the other.

1.6.2 Investigating an enantioselective allylation of 4-benzylpyridines

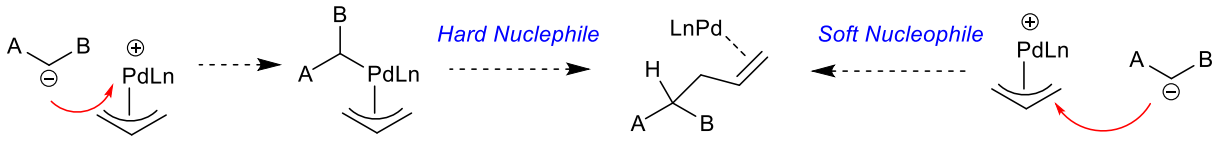
It was believed up until recently that nucleophiles with a pKa of less than 32 were considered soft nucleophiles and above this were considered hard nucleophiles. This would make 4-alkylpyridines (pKa ~ 35) hard nucleophiles and 4-benzylpyridines (pKa ~ 27) soft nucleophiles. Therefore, these two types of pyridines should proceed through different reductive elimination mechanisms. The study of 4-benzylpyridines would then be inherently different from that of 4-alkylpyridines and therefore, the enantioselective variants would need to be studied separately. The formation of a stereogenic centre at the pyridylic position makes these types of pyridines prime candidates for an enantioselective type of reaction.

Our group has shown that a number of alkylpyridines can be used for allylation at the pyridylic position but we were in need of a broadened substrate library for the allylation of 4-benzylpyridines. These needed to be synthesized under mild conditions to allow the testing of different electronic and steric properties. Once the allylation of 4-benzylpyridines has been

established with moderate to high yields, different conditions can be optimized for enantioselectivity.

1.6.3 Mechanistic studies on the mode of reductive elimination

The mode of reductive elimination for pyridylic allylation needed to be investigated as to determine if there was a difference between the mechanism of alkyl and benzyl pyridines. Due to the pKa difference between these two molecules we proposed that there would be a different reductive elimination mechanism for both. Determination of this mechanism could aid in development of an enantioselective variant. The route of reductive elimination depends on whether the nucleophile is acting as a soft nucleophile or a hard nucleophile (**Scheme 8**). Nucleophiles with a pKa of less than 32 were considered soft and therefore are prone to undergo outer-sphere reductive elimination. The soft nucleophile attacks the π-allyl moiety directly to undergo an outer-sphere mechanism. In this type of mechanism, ligands must reach beyond the allylic plane for stereoinduction.[7] This is in contrast with hard nucleophiles which were thought to have a pKa of greater than 32. The reductive elimination mechanism with hard nucleophiles begins with direct attack of the metal centre and proceeds through an inner-sphere mechanism. Ligands impart stereoinduction more readily in this type of mechanism.[7]



Scheme 8: Reductive elimination step of palladium catalysis either proceeding through an inner-sphere or outer-sphere mechanism.

1.6.4 Exploring the reactivity of ADHP intermediates in other transition metal-catalyzed reactions

Due to the nucleophilicity of the ADHP intermediates, we had hypothesized that this type of pyridylic functionalization could extend to other transition metals. Copper is a candidate for further pyridylic functionalization as copper and palladium are isoelectronic. We proposed that a synthetic method could be developed to arylate pyridines using copper catalysis and biaryl iodonium salts as coupling partners.

Chapter 2: Results and Discussion

2.1 Expanding the scope of allyl fragments

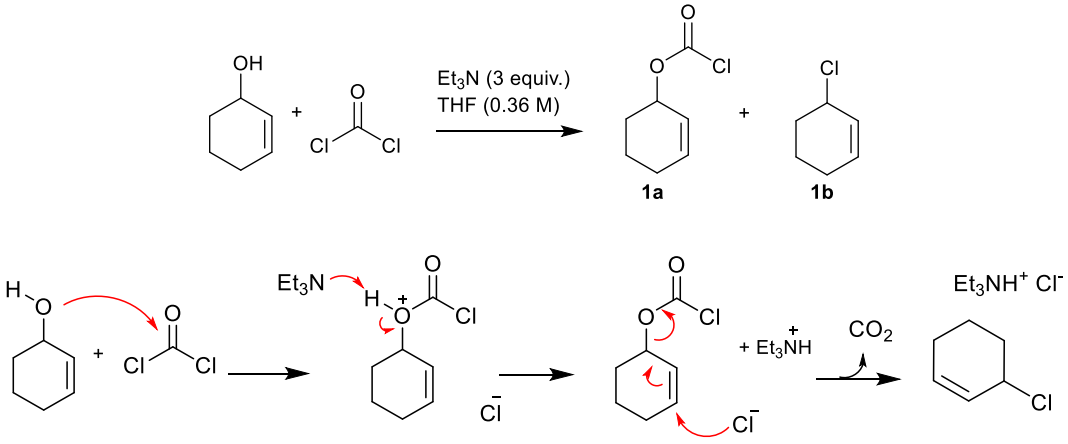
2.1.1 Synthesis of allylic chloroformates

In our allylation of pyridines, commercially available allyl chloroformate is used to activate the pyridine and form the ADHP intermediate. We proposed that a substituted allyl fragment could lead to more differentiation between transition states in the chiral pocket of the catalyst and generate increased enantioselectivity. In order to test larger allyl fragments such as cyclohexenyl or cinnamyl fragments, a chloroformate from the respective alcohol first had to be synthesized to form the corresponding ADHP.

We began by using cyclohexenol as a substrate and testing a number of different reaction conditions with both phosgene and triphosgene to produce the chloroformate (**1a**). These reaction conditions included testing a number of different bases, solvents, and equivalent ratios of each reactant (**Table 1**). Synthesizing this chloroformate proved difficult, as either there was very little conversion to product, or an unwanted chloride side product (**1b**) was formed as shown by ^{1}H NMR and ^{13}C NMR. This chloride side product is thought to be formed from free chloride anions in solution which can attack the alkene and displace the chloroformate. Cyclopentanol was tested as a substrate because it does not contain an alkene, so therefore it is less likely to proceed through the same mechanism of side product formation. After investigating various conditions, optimal results were found with cyclopentanol, phosgene, and silver tetrafluoroborate in THF. The final product was formed with very little starting material remaining as the silver additive worked as a chloride scavenger decreasing the possibility of side product formation. When the same conditions were used with cyclohexenol there was incomplete conversion of the starting material to product and a large amount of chloride side product formation. After further testing without a silver additive, it was determined that the optimal conditions for chloroformate synthesis with cyclohexenol included using triethylamine as a base (**Table 1, Entry 3**). It was necessary to add triethylamine to the mixture before the addition of phosgene. This allowed the formation of the triethylammonium chloride salt as the chloride anion could be coordinated to the protonated triethylamine immediately upon release from phosgene. The phosgene needed to be added very slowly at 0°C and the reaction had to stir for exactly 3 hours, purge for 20 minutes through sodium hydroxide with argon, and triturated using pentane. Leaving the reaction for a longer or shorter

amount of time formed mainly chloride side product or incomplete conversion respectively. After a thorough investigation of various conditions, this reaction still did not cleanly form the desired cyclohexene chloroformate, and further tests using this chloroformate in our palladium-catalysis allylation did not produce an allylated pyridine.

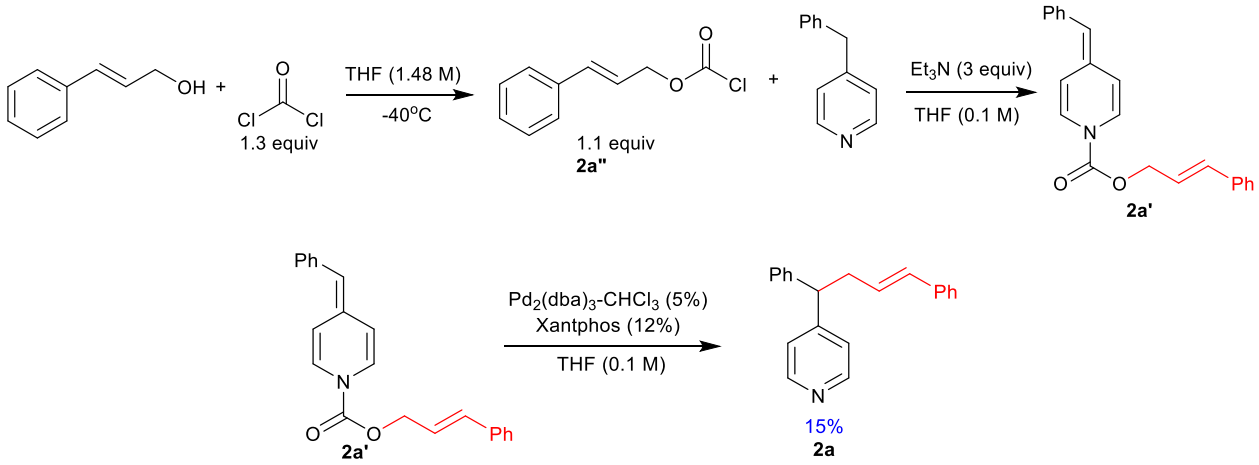
Table 1: Optimization of reaction conditions for the synthesis of cyclohexene chloroformate with the mechanism of side product formation.



Entry	Base / Additive	Solvent	Phosgene or Triphosgene	Product Formed
1	NA	THF	Phosgene	No
2*	Pyridine	DCM	Phosgene	No
3	Triethylamine	THF	Phosgene	Yes
4	Triethylamine	THF	Triphosgene	No
5	Pyridine	DCM	Triphosgene	No
6*	Triethylamine	Diethyl Ether	Phosgene	Yes
7	Sodium Bicarbonate	THF	Triphosgene	No
8*	Silver tetrafluoroborate	THF	Phosgene	Yes
9	Sodium Hydroxide	THF	Phosgene	No
10	N, N-dimethylamine	THF	Phosgene	No

* Cyclopentanol also subjected to reaction conditions, product formed in cyclopentanol but not cyclohexenol

Due to the difficulty in forming the chloroformate from cyclohexenol and the incomplete conversion, we subsequently tested chloroformate synthesis of an allyl fragment using cinnamyl alcohol. We began by testing conditions as seen in **Table 1** entries 1, 2, and 3, with cinnamyl alcohol as the substrate, but these were unsuccessful in forming primarily the chloroformate. We found that the reaction did not go to completion or there was formation of large amounts of chloride side product. We discovered that when using the cinnamyl group, the absence of base improved the outcome of the reaction. After testing different equivalents of phosgene, concentrations, and temperatures we identified that 1.3 equivalents of phosgene, 1.48 M in THF, and a temperature of -40°C gave the best results. Treatment of 4-benzylpyridine with triethylamine and 1.1 equivalents of cinnamyl chloroformate (**2a"**) provided the expected ADHP intermediate (**2a'**) in approximately an 80% yield although this could not be fully purified. As always, the triethylammonium chloride salt could be removed by trituration with diethyl ether. When the ADHP was subjected to our previously developed conditions for pyridylic allylation of $Pd_2(dba)_3 \cdot CHCl_3$ and Xantphos, it formed the expected allylated product pyridine in a 15% yield (**2a**).



Scheme 9: Cinnamyl chloroformate synthesis and subsequent allylation of 4-benzylpyridine.

It is reasonable to expect that that this reaction could be performed enantioselectively with the use of a chiral ligand instead of Xantphos (**L5**). However, when using the same reaction conditions used in **Scheme 9**, there was no product observed when (*S*)-BINAP (**L6**), ANDEN-Trost ligand (**L7**), and DACH-Trost ligand (**L8**) (**Figure 3**) were used instead of Xantphos. The reasons for this remain unclear.

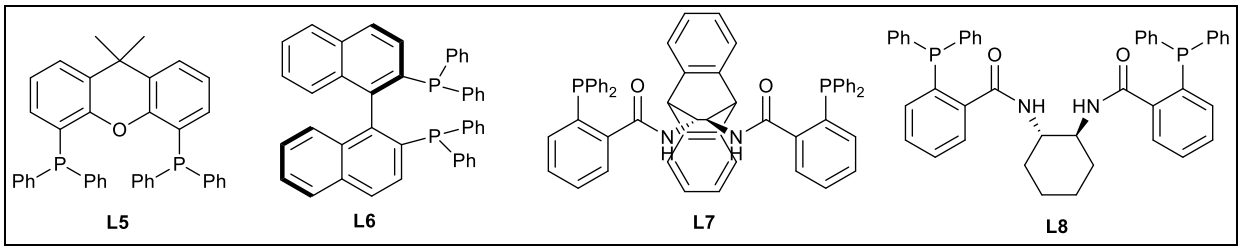
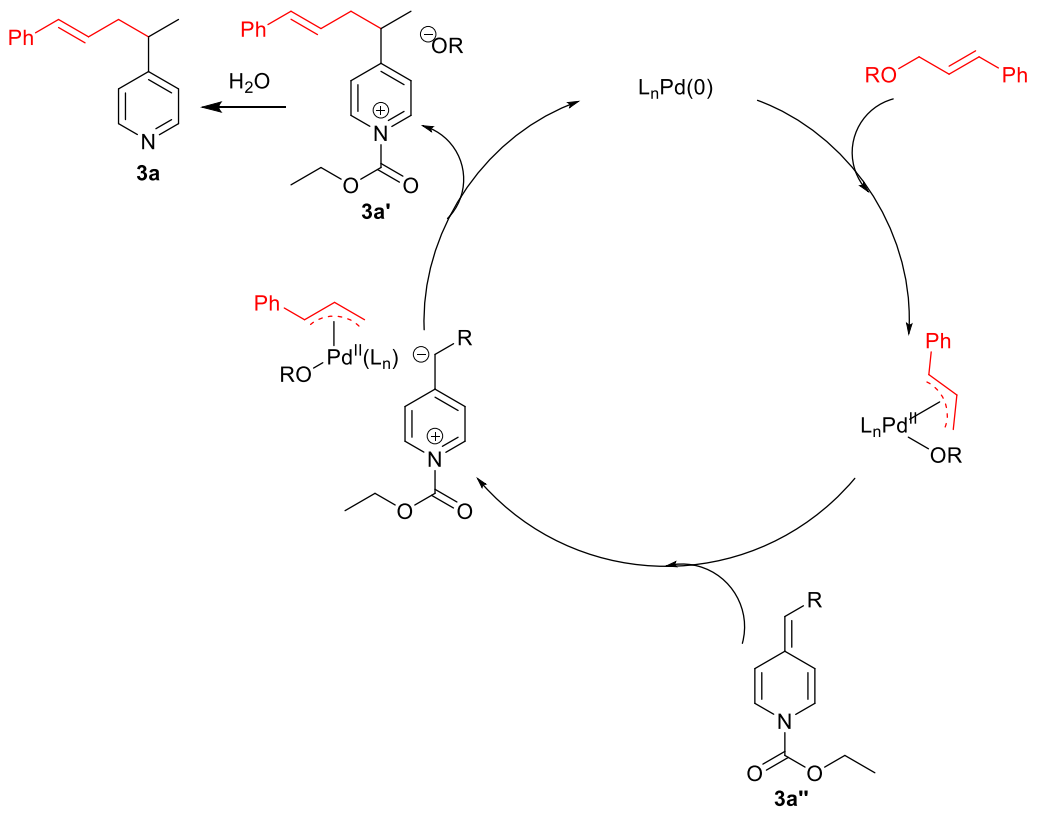


Figure 3: Ligand screen for allylation of a cinnamyl fragment to the pyridylic position.

2.1.2 Allylating pyridine by using substituted allyl electrophiles

In our proposed mechanism for the allylation of pyridines, the palladium-allyl fragment and ADHP dissociate to form two ions. Therefore, the allyl fragment did not have to be attached to the ADHP as a carbamate but could instead be introduced as a separate reagent to undergo oxidative addition with palladium. As seen in **Scheme 10,** the ADHP (**3a"**) could instead be formed using ethyl chloroformate, where there would be no allyl group on the carbamate to form a complex with palladium. The allyl fragment could be introduced to the reaction as a separate reagent and if the allyl palladium intermediate is sufficiently electrophilic, the neutral ADHP could be nucleophilic enough to attack the allyl fragment. After oxidative addition, the allyl fragment would then be coordinated to palladium and could undergo migratory insertion and reductive elimination. Since carbon dioxide is not released during oxidative addition to palladium and a pyridinium salt is formed instead (**3a'**), the reaction would have to be quenched with water to reform pyridine (**3a**).



Scheme 10: Palladium catalyzed allylation of pyridine with an exogenous allyl fragment.

The leaving group on the allyl fragment needed optimization to increase the ease of the π-allyl palladium complex formation. We proposed that a tosylate would be an optimal leaving group as it is easily synthesized, and stable. The negative charge from anion formation can be delocalized over resonance structures and it is a highly polar molecule. Tosylates are commonly used with palladium catalysis as they behave as weakly coordinating leaving groups, allowing the allyl-palladium intermediate to be sufficiently electrophilic to attack the nucleophile. After several attempts to initiate this reaction, mixing the cinnamyl reagent with the ADHP, there was no formation of the desired product when subjected to the standard catalysis conditions of $Pd_2(dba)_3 \cdot CHCl_3$ and Xantphos.

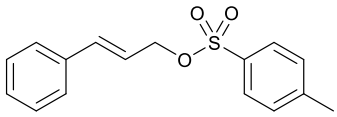
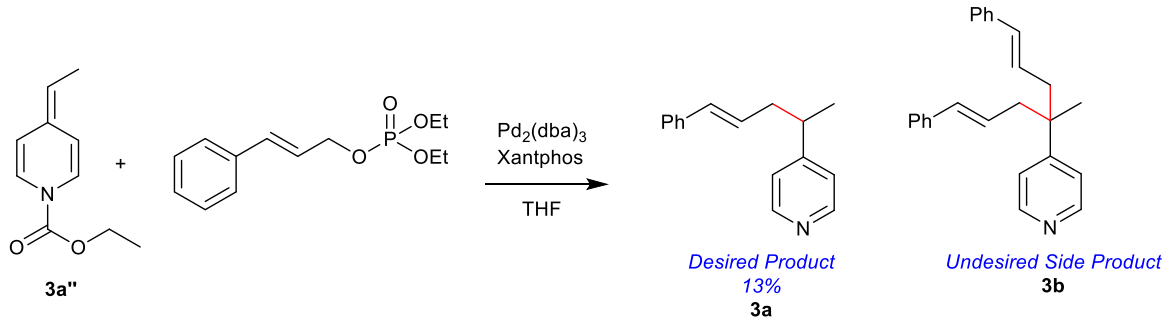


Figure 4: Cinnamyl alcohol with tosyl group.

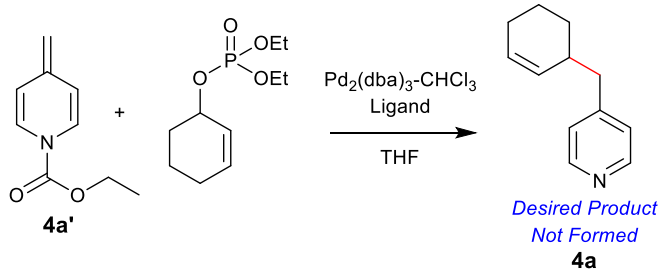
A phosphonate could also be a suitable leaving group on cinnamyl alcohol. When cinnamyl alcohol with a phosphonate group[30] was subjected to the standard catalysis conditions using 4-ethyl chloroformate to activate the ADHP (**12a"**), the desired allylated product (**12a**) was formed in a 13% yield but an undesired product with double allyl addition at the pyridylic position (**12b**) was

also formed in approximately a 1:1 ratio (**Scheme 11**). To test if this reaction could form the desired product enantioselectively, the ANDEN-Trost ligand (**L7**) was used but no product was formed.



Scheme 11: Allylation of pyridine using cinnamyl phosphonate and the resulting products.

Since there was formation of a modest amount of the desired product when using an allyl fragment with a phosphonate leaving group, we believed that a bulkier allyl fragment could block the double addition of the allyl group. A phosphonate was synthesized with a cyclohexene allyl fragment using similar conditions to the formation of the cinnamyl phosphonate.[30] The cyclohexene electrophile was tested with a number of different ADHPs, made from 4-ethylpyridine, 4-methylpyridine (**Scheme 12**), and 3-benzyl-4-methyl pyridine, and none of these pyridine precursors formed the desired product. We thought that the ligand may need to be optimized to allow formation of the desired product. A number of ligands with different electronic and steric properties were tested (**Figure 5**) in a screen using 4-methylpyridine to make the ADHP (**4a'**) and $Pd_2(dba)_3 \cdot CHCl_3$. These did not form the desired product (**4a**).



Scheme 12: Allylation of pyridine using cyclohexene phosphonate.

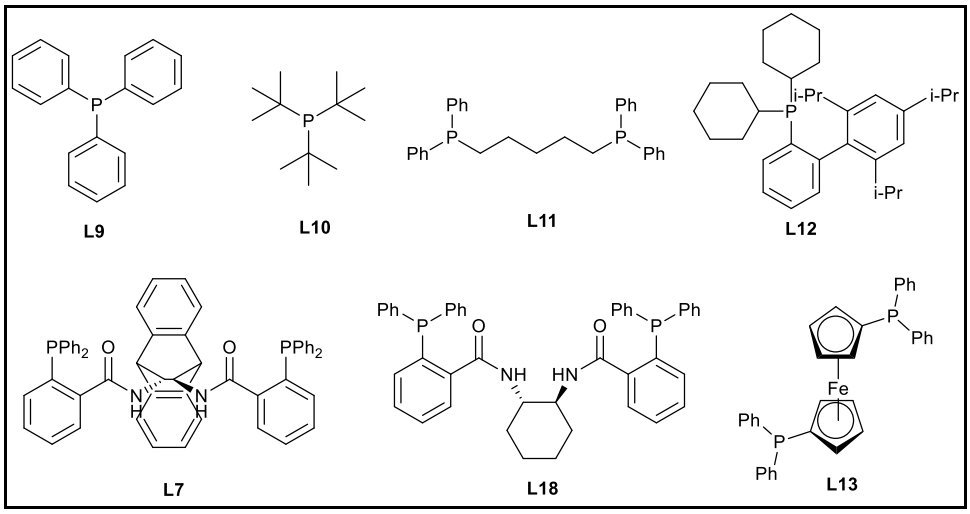
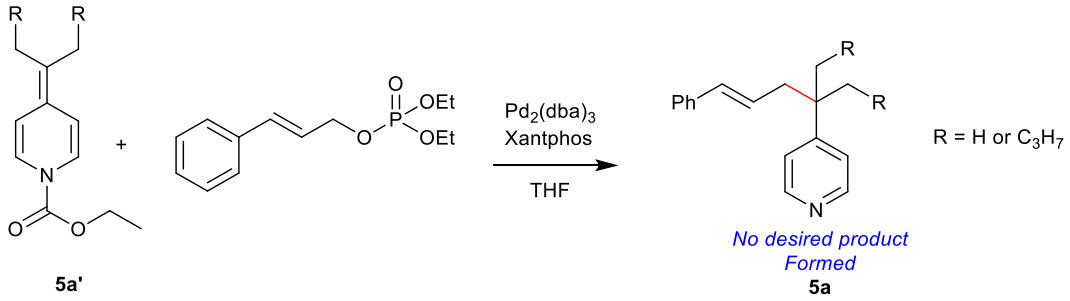


Figure 5: Ligands used in a ligand screen for allylation of a cyclohexene fragment to the pyridylic position.

The original allylation reaction using the electrophile cinnamyl phosphonate (**Scheme 11**) was low yielding, in part, due to the formation of a product with double allylation at the pyridylic site. If this site was blocked allowing only a single addition, this would hopefully allow the reaction to be higher yielding. We first attempted to block this double allylation by using a pyridine with two alkyl groups at the pyridylic position (**Scheme 13**). When the cinnamyl phosphonate was added to the ADHP formed from 4-isononyl pyridine, no product was formed. The same results were found when using 4-ispropyl pyridine.



Scheme 13: Allylation of pyridines that are disubstituted at the pyridylic position using cinnamyl phosphonate.

Since two alkyl groups at this position seemed to be too bulky for the addition of a cinnamyl fragment, we thought that a fluorine may be less bulky and allow this addition while still blocking double allylation. When this reaction was performed with the fluorinated ADHP seen in **Figure 6**,

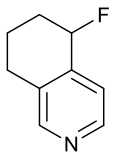


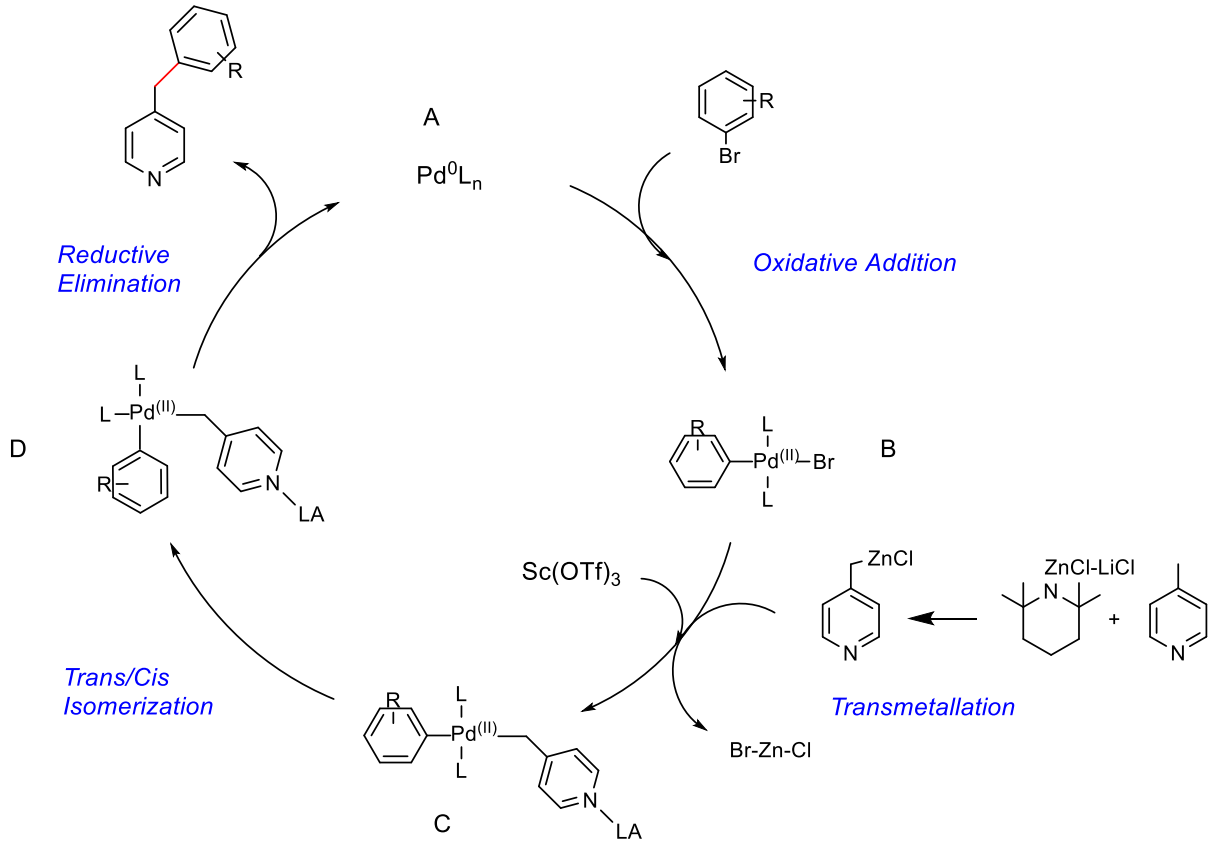
Figure 6: Fluorinated Pyridine.

a small amount of the desired allylated product appeared to be formed as seen by crude ^{1}H NMR, but a number of unidentified side products were also formed and the product could not be isolated.

2.2 Developing an enantioselective allylation of 4-benzylpyridines

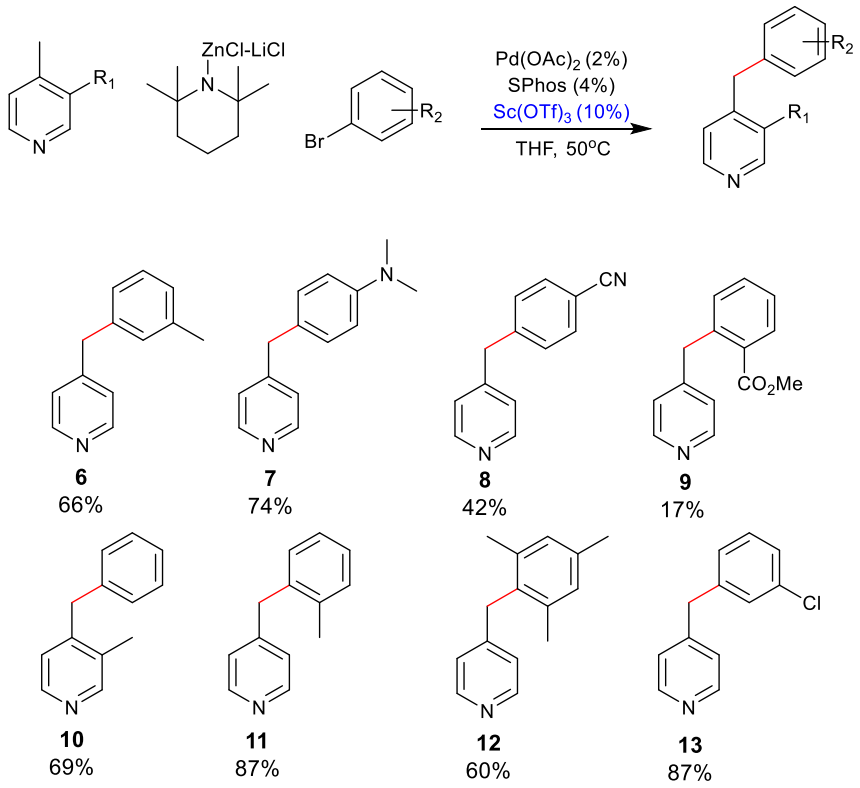
2.2.1 Substituted 4-benzylpyridine substrate synthesis

The Orellana group has developed a palladium catalyzed method for the pyridylic allylation of 4-alkylpyridines. A number of functional groups can be tolerated with our mild allylation techniques when using alkylpyridines as substrates. The substrate scope could be even further expanded to include substituted benzylpyridines. Due to the need for functional group tolerance, a mild synthesis of these 4-benzylpyridines was sought after. Many of the known methods for 4-benzylpyridine formation use strong acids or bases, or otherwise harsh conditions that do not tolerate these functional groups.[31,32] For this reason, we synthesized 4-benzylpyridine substrates by employing the palladium catalyzed arylation of 4-picoline (**Scheme 14**) as proposed by Knochel *et al*.[33] The proposed mechanism of this arylation follows the classic palladium catalyzed Negishi cross-coupling reaction. This type of palladium catalyzed Negishi reaction requires the formation of the transmetallation agent with a base that is mild enough to tolerate other functional groups. Thus, Knochel proposed that a LiCl solubilized TMP base such as TMPZnCl·LiCl can be used in combination with a Lewis-acid to promote Negishi cross-coupling.[33,34] This base deprotonates 4-methylpyridine allowing it to be sufficiently nucleophilic for attack on a functionalized aryl bromide. When the aryl bromide contains an electron withdrawing group, it is reluctant to undergo reductive elimination with 4-picoline (complex D) and therefore requires a Lewis-acid to accelerate this step of the reaction.[35] After testing a number of Lewis-acids, $Sc(OTf)_3$ was determined to give the highest yields. This reaction proceeds through palladium catalysis with a pre-stirred mixture of $Pd(OAc)_2$ (2 mol%) and SPhos (4 mol%) in THF to generate the functionalized 4-benzylpyridine.[33]



Scheme 14: Palladium catalyzed Negishi cross-coupling to form substituted 4-benzylpyridines.

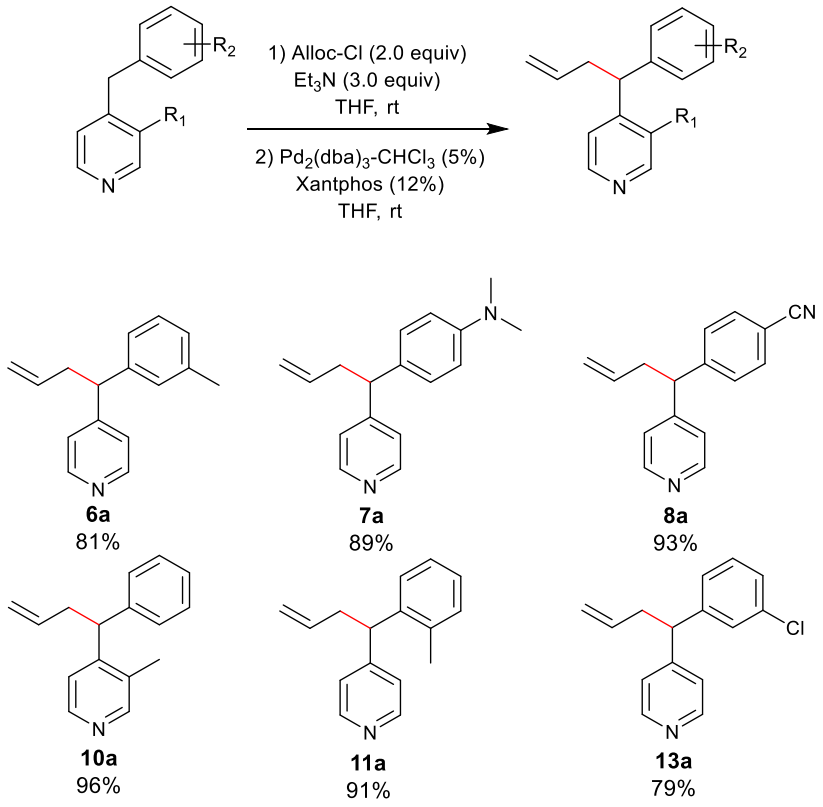
Using this method, the substrate library which can be subjected to the allylation conditions, was expanded to include 4-benzylpyridines with dimethyl amino, nitrile, ester, and chlorine functional groups (**Scheme 15** (**7, 8, 9, 13**)). A number of substrates were also synthesized to have steric hindrance at the pyridylic position (**Scheme 15** (**10, 11, 12**)).



Scheme 15: Substrate synthesis of 4-benzyl pyridines with various substituents.

2.2.2 Allylation of 4-benzyl pyridines

The synthesis of these substituted 4-benzylpyridines, allowed us to expand the scope of allylation by subjecting these substrates to our standard conditions. Upon forming the ADHP with these substituted benzyl pyridines, using our standard conditions, they were subjected to $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol%) with Xantphos (12 mol%) which produced the allylated pyridine after ~3 hours. This reaction was proved to be high yielding, expanding the substrate scope to include functionalized 4-benzylpyridines. Both aryl groups with electron donating (**Scheme 16** (**7a**)) and electron withdrawing groups (**Scheme 16** (**8a, 13a**)) are tolerated and high yielding. We also found high yields in substrates that had steric hindrance at the pyridylic position potentially making allylation more challenging (**Scheme 16** (**10a, 11a**)).



Scheme 16: Substrate scope of substituted 4-benzyl pyridines for pyridylic allylation.

2.2.3 Enantioselective allylation with a simple allyl group on 4-benzylpyridine

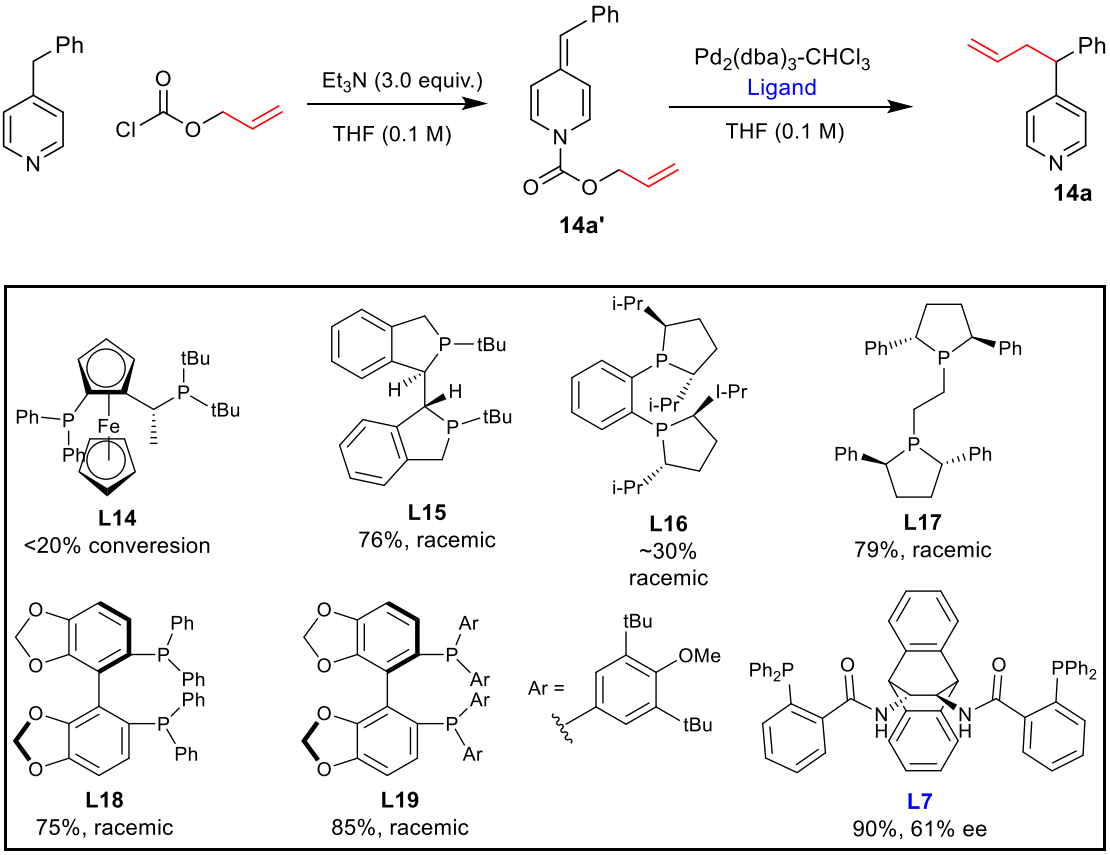
The presence of a stereogenic centre in an organic molecule makes enantioselective synthetic routes accessible. This is often exploited in chemical synthesis due to its usefulness in drug discovery. The allylation of 4-alkyl- or 4-benzylpyridines creates a stereogenic centre at the pyridylic position. The use of Xantphos as a ligand creates a racemic product, but with the use of a chiral ligand that is optically active, and optimization of the reaction conditions, this stereogenic centre can be exploited to produce one enantiomer selectively.

In general, the extent of enantioselectivity in a given reaction is determined by the chiral pocket that is formed from the metal centre and the chosen chiral ligands. Thus, in principle, the enantioselectivity can be tuned by changing the ligand effects. These effects include changing the steric bulk around the metal centre, the electronic properties of the metal, and enforcing a bite angle preferred by the ligand.[36] In a study by Dierkes, it was determined that larger bridges of

bidentate ligands resulted in a more effective embracing of the allyl group.[36] In addition, if the steric bulk is too large, the rate and regioselectivity of the reaction drop but steric effects can also be used to steer the nucleophile to one side of the allyl group.

A common chiral ligand that is used in enantioselective reactions with allyl groups are the Trost ligands which have large bite angles, allowing certain steps of the catalytic cycle to be accelerated. We have discovered that 4-alkylpyridines (pKa ~ 35) are too basic and deprotonate the nitrogen atoms on the amide of the DACH-Trost ligand backbone. In contrast, 4-benzylpyridines (pKa ~ 27) do not have the same basicity to deprotonate the nitrogen, allowing the possibility for an enantioselective synthesis with these types of ligands.

Using this knowledge of ligand effects, a number of chiral, bidentate ligands were tested in a ligand screen (**Scheme 17**)[13] to determine the optimal steric bulk and bite angle to gain enantioselectivity. The ligands that were tested were selected because they represent different chiral frameworks. Most of the ligands were found to give varying yields, but only the ANDEN-Trost ligand showed any enantioselectivity with 61% ee.[13] Therefore, we moved forward in our studies optimizing further conditions using the ANDEN-Trost ligand to gain optimal enantioselectivity.



Scheme 17: Ligand screen data for palladium catalyzed enantioselective allylation of pyridine. These structures represent the ligands used along with the yield of the reaction.

To further optimize the reaction conditions when using this the ANDEN-Trost ligand, a solvent screen was conducted. THF, dioxane, and toluene were found to give enantioselectivity with moderate to high yields. To enhance the selectivity, the reactions were conducted at 0°C with the exception of dioxane which has a melting point of 11°C. Of the solvents that were tested, dioxane was found to give the highest amount of enantioselectivity with an ee of 67%. Due to the limitations involving the melting point of dioxane, further reactions at lower temperatures were run using THF. When cooling the reaction in THF to -35°C there was no increase in the enantioselectivity. There was also no improvement when using a mixture of THF/ dioxane at 0°C.

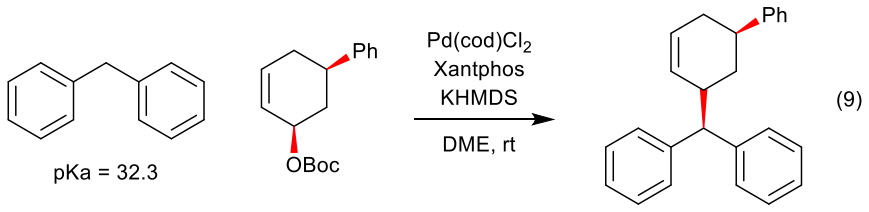
Table 2: Solvent screen for enantioselective allylation of 4-benzylpyridine.

Solvent	Temperature (°C)	Yield (%)	Enantiomeric Excess (ee)
THF	0	97	61
Dioxane	25	68	67
Toluene	0	83	64
Diethyl Ether	0	79	47
DCM	0	NA	NA

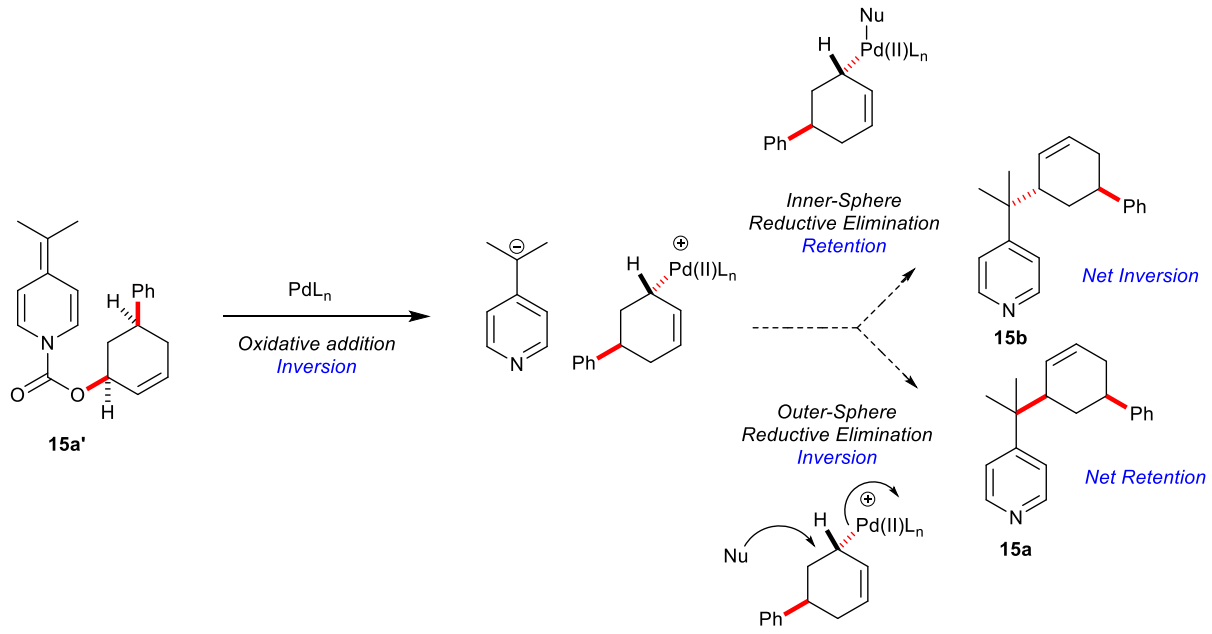
We were hopeful that steric bulk at the pyridylic position would force the allyl group into one conformation to relieve steric clash. Substrates **10** and **11** both contain a methyl group which increases the steric bulk around the pyridylic position over 4-benzylpyridine. These substrates were tested using the ANDEN-Trost ligand at 0°C but contrary to expectations there was no increase in the ee of these reactions past 67% as both were ~66%.

2.3 Elucidating the mode of reductive elimination in the allylation of 4-alkylpydidines

When using a mechanistic probe, generally containing two stereocentres with one being at an allylic position, the mechanism of a hard nucleophile can be distinguished from that of a soft nucleophile by the relative stereochemistry at the beginning and end of the reaction. It is generally understood that oxidative addition of palladium goes through an inversion of stereochemistry. Soft nucleophiles also go through an inversion of stereochemistry in the reductive elimination step leading to an overall retention of stereochemistry. In contrast, hard nucleophiles retain their stereochemistry during reductive elimination leading to an overall inversion of stereochemistry. The pKa limit for soft nucleophiles was believed to be 25 until Walsh coupled a nucleophile with a pKa of 32 and a stereoprobe and determined that this nucleophile behaved as a soft nucleophile.[11] The stereoprobe used was a *cis*-disubstituted cyclohexene with a phenyl group and a protected alcohol that retained a *cis* conformation at the end of the reaction proving it went through an outer-sphere reductive elimination pathway (**Eq. 9**).[11]



Our mechanism of the allylation of pyridine that proceeds under palladium catalysis has been explored to gain mechanistic insight. The next aspect in need of determination is whether reductive elimination proceeds through an inner- or outer-sphere mechanism. We had proposed that this would go through an inner-sphere mechanism as the pKa threshold for soft nucleophiles was believed to be ~32 and alkylpyridines have a pKa of 35 without taking electronic effects of substituents into account. We tested the mechanism by using a mechanistic probe similar to the one used by Walsh[11] which has a *cis* relationship between the two substituents. As shown in **Scheme 18,** if the alkylpyridine behaved as a hard nucleophile, it would proceed through an inner-sphere mechanism where the alkylpyridine would attack the π-allyl palladium complex directly and produce a diastereomer with inverted stereochemistry to that of the starting material (**15b**). This is due to inversion of stereochemistry during oxidative addition, followed by retention of stereochemistry in the reductive elimination step. If the alkylpyridine behaved as a soft nucleophile it would proceed through an outer-sphere reductive elimination mechanism and attack the allyl group directly, producing a diastereomer with retention of stereochemistry (**15a**) due to inversion over both the oxidative addition and reductive elimination steps.

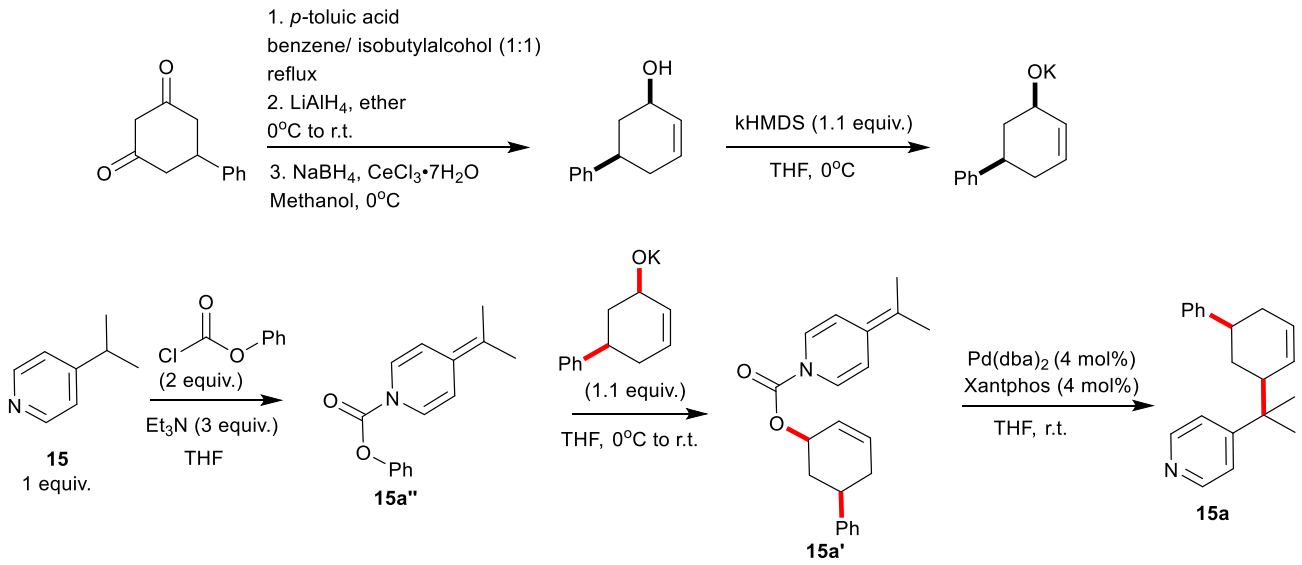


Scheme 18: Both possible pathways for the reductive elimination step of palladium catalysis with alkylpyridines and a mechanistic probe.

We began by preparing the mechanistic probe from a procedure that begins with 5-phenyl-1,3-cyclohexanedione which is reduced to form an enone and ultimately undergoes a Luche reduction to form the *cis*-disubstituted cyclohexenol (**Scheme 19**).[37] This relative *cis* stereochemistry was confirmed using 1D and 2D NMR spectroscopy, but the main evidence came from the correlation between the protons at the two stereocentres as both were in the *cis* orientation (**Scheme 20**).

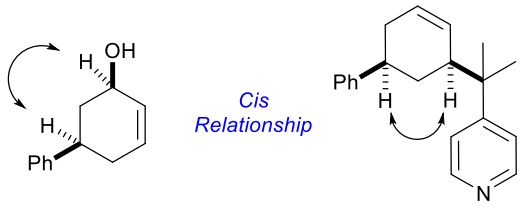
The next task was to form the ADHP using this mechanistic probe. Since the formation of a cyclohexene chloroformate had been very difficult and there was regularly a large amount of unwanted chloride side product formation, we believed that forming a chloroformate from this mechanistic probe would also prove to be difficult. After attempting several variations of conditions, we found that this chloride decomposition product was also prominent in the formation of the chloroformate.[14] Using another approach for making the ADHP with the mechanistic probe (**Scheme 19**) was to form an ADHP using a commercial chloroformate such as phenyl chloroformate (**14a"**) and attack this carbamate with an alkoxide formed from the alcohol of the mechanistic probe. When the mechanistic probe was subjected to KHMDS, the deprotonated alcohol formed an alkoxide with potassium. This alkoxide was then added to a solution of the ADHP **15a"**, the ADHP **15a'** was formed as well as the byproduct phenoxide-potassium salt. After

testing a number of solvents, we found that this crude ADHP could be triturated with toluene to remove the potassium phenoxide and allow palladium catalysis with the standard conditions to form the desired product (**15a**). It is understood that the oxidative addition step always goes through inversion of stereochemistry. At the end of the reaction the product was found to have a *cis* relationship between the two stereocentres. This contrasts our proposed mechanism and suggests that the alkylpyridine behaves as a soft nucleophile and proceeds through an outer-sphere reductive elimination, going through double inversion during the palladium catalysis cycle. As previously mentioned, the pKa threshold for soft nucleophiles was believed to be ~32 but these results set a new pKa threshold of 35 for soft nucleophiles.



Scheme 19: Synthesis of the mechanistic probe, and testing the mechanism of reductive elimination using this mechanistic probe as proposed by the Orellana Group.

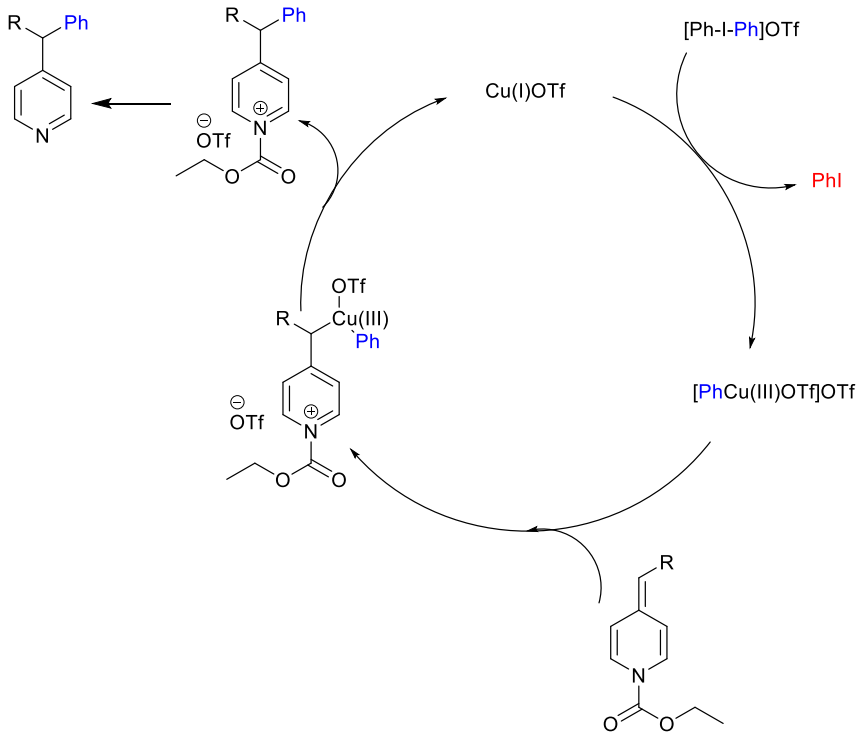
This retention of stereochemistry in the allylated product was confirmed by 1D and 2D NMR experiments. The main evidence was from the *cis* relationship between the hydrogens at the two stereocentres as mentioned for the formation of the mechanistic probe. This relationship can be seen in **Scheme 20**.



Scheme 20: *Cis* stereochemistry between both stereocentres in the mechanistic probe and allylated alkylpyridine product.

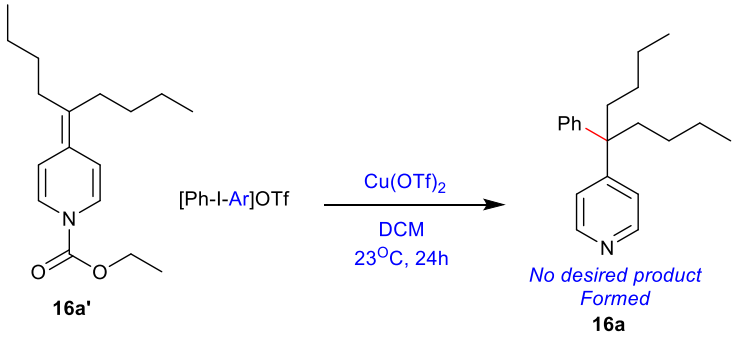
2.4 Copper Catalyzed Arylation of Pyridines

The extensive research by Gaunt shows arylation of a wide variety of substrates using a copper cycle and iodonium salts. We believed that the formation of the ADHP could be used for arylation, in a similar way that Gaunt showed the arylation of indoles.[38] It was found that using $Cu(OTf)_2$ as the precatalyst, and iodonium triflates as the oxidative addition partners provided the best results for Gaunt.[38] The mechanism of this reaction is proposed to undergo oxidative addition of the biaryl iodine(III) reagent to the Cu(I) salt to generate the Cu(III) aryl intermediate, which is then attacked by the indole.[38] We proposed that the highly electrophilic Cu(III) intermediates could be attacked by the nucleophilic ADHP intermediate (**Scheme 21**), and reductive elimination would form an arylated pyridinium salt. A mildly basic workup would remove the carbamate and produce the desired product. This mechanism is believed to allow the arylation of pyridine using a range of different functional groups under mild conditions and ultimately arylate pyridines enantioselectively.



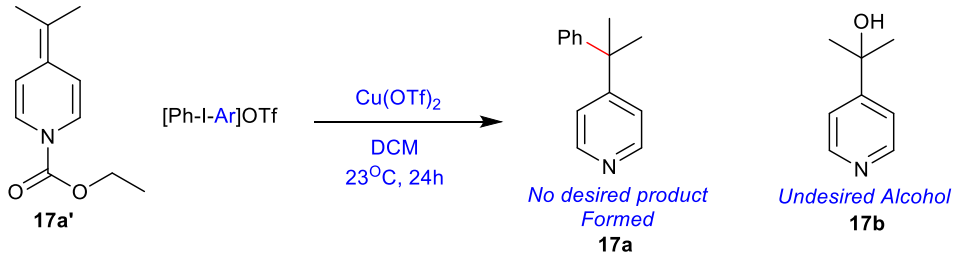
Scheme 21: Proposed copper catalyzed arylation of pyridines via ADHP intermediates.

We began by using 4-isononylpyridine as a substrate to form the ADHP (**16a'**). When this ADHP was added to a mixture of $Cu(OTf)_2$ and biphenyl iodonium triflate there was no conversion to the arylated product (**Scheme 22**). We hypothesized that this could be due to the alkyl chains blocking both faces of the pyridylic nucleophile to avoid a *syn*-pentane-type interaction.



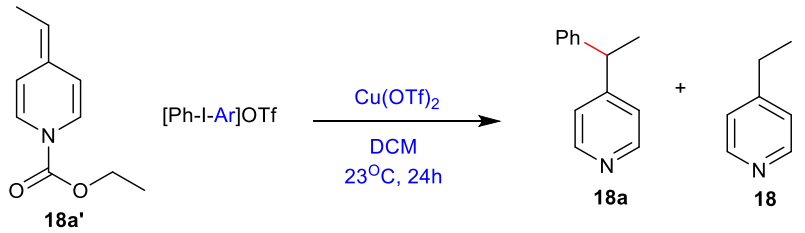
Scheme 22: Copper catalyzed arylation of 4-isononylpyridine.

We next shortened the alkyl chains on the pyridylic position using isopropylpyridine to reduce this type of strain. This reaction appeared to result in formation of an alcohol at the pyridylic position (**17b**) as opposed to arylation (**Scheme 23**).



Scheme 23: Copper catalyzed arylation of 4-isopropylpyridine and the undesired alcohol side product.

We then investigated ethylpyridine as a substrate since two alkyl groups at the pyridylic position created too much steric bulk for arylation. The desired product (**18a**) was formed in low yield using 10% $Cu(OTf)_2$ loading and 1.1 equivalents of the biphenyl iodonium triflate (**Scheme 24**). There were a number of unidentified side products formed, and the starting pyridine (**18**) could be seen by ^1H NMR. This was proposed to occur because the ADHP (**18a'**) was not consumed fully in the reaction and upon workup, the starting pyridine was reformed.



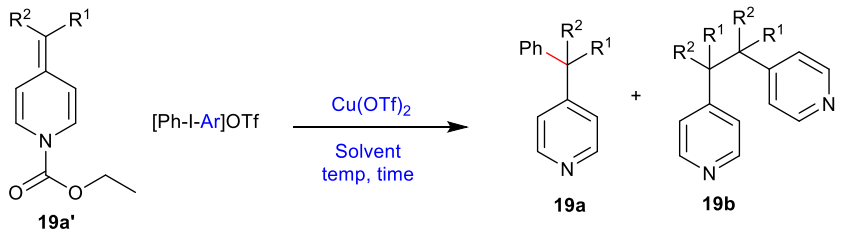
Scheme 24: Copper catalyzed arylation of 4-ethylpyridine.

To test the impact that solvent had on the outcome of the reaction a solvent screen was performed. Instead of using a simple biphenyl iodonium triflate, a biaryl iodonium triflate was synthesized using a phenyl group and mesitylene to simplify the analysis of the ^1H NMR spectrum. Due to the side product now being iodo-mesitylene instead of iodo-benzene, the benzene region of the spectrum only contains one proton signal from this side product. The most commonly used solvents in literature of these types of copper catalyzed coupling reactions are DCM, dioxane, and toluene.[17,19,21,23] These solvents along with THF were run in the solvent screen. DCM and dioxane formed a modest amount of product but no increase from the initial reaction run in DCM (**Scheme 24**). In an attempt to push the reaction to completion, it was heated to 50°C and 70°C. At 70°C the ADHP (**19a'**) decomposed. At 50°C there was an increase in the amount of product (**19a**), a

decrease in recovered pyridine starting material, and a large amount of a pyridine dimer (**19b**) was formed. This result could be due to copper coupling two pyridines together, or it could be the result of a background reaction that is occurring.

To reduce the statistical likelihood of dimer (**19b**) formation we hypothesized that adding a solution of the ADHP (**19a'**) slowly to a mixture of copper and iodonium salt would couple the aryl group and pyridine preferentially. This would create an environment with limited amount of pyridine and excess of the aryl reagent making it easier for the catalyst to undergo oxidative addition with an aryl group and couple this to pyridine. When this reaction was performed with addition of the ADHP (**19a'**) solution being added dropwise over 30 minutes to a mixture of the copper and iodonium salt, there was no change in the amounts of arylated product or dimer produced. When this addition was slowed further to 2 hours, there was still no change in the ratio of products that were created. Since heating the reaction appeared to form a large amount of dimer (**19b**), running the reaction at room temperature but over a longer period of time could hopefully allow the consumption of the ADHP (**19a'**) with decreased formation of the dimer (**19b**). When the reaction was run over 72 hours there appeared to be some decomposition along with formation of the dimer (**19b**).

Table 3: Conditions for arylation of pyridine and undesired dimer side product.



Entry	R^1	R^2	Ar	Solvent	temp, °C	$Cu(OTf)_2$ (mol%)	Time (h)	Approx. Yield (%)	Dimer (%)
1	Butyl	Butyl	Ph	DCM	23	15	24	NA	NA
2	Me	Me	Ph	DCM	23	15	24	NA	NA
3	Me	H	Ph	DCM	23	15	24	18	NA
4	Butyl	H	Ph	DCM	23	15	24	25	NA
5*	CH_2-Ph	H	Mes	THF	23	15	24	NA	NA
6	CH_2-Ph	H	Mes	Dioxane	50	40	24	40	26
7‡	CH_2-Ph	H	Mes	Dioxane	50	40	24	Not isolated	Not isolated
8	CH_2-Ph	H	Mes	Dioxane	70	40	24	Decomposed	Decomposed
9	Me	H	Mes	DCM	23	15	72	NA	Not Isolated

*Part of a solvent screen with THF, Toluene, DCM, and dioxane. THF and toluene did not produce any product, and there was no increase in yield seen with DCM and dioxane.

‡The ADHP solution was added dropwise over 30 minutes and 2 hours in two separate reactions.

2.5 Conclusion

In conclusion, using the methodology that has been developed for the palladium catalyzed pyridylic allylation of 4-substituted pyridines, we have been able to expand the allyl electrophile used in the reaction in low yields. We have attempted the synthesis of bulkier allyl chloroformates including cyclohexene and cinnamyl fragments to form the ADHP and ultimately the allylated pyridine. Success was only found in forming the cinnamyl chloroformate in a racemic fashion. When enantioselective allylation is attempted with this ADHP under our standard conditions with a number of different chiral ligands, the desired product could not be formed. We further tested this cinnamyl fragment as an exogenous source, exploring an intermolecular mechanism in contrast with the standard intramolecular mechanism. After testing both a tosyl group and phosphonate group on the cinnamyl fragment, the phosphonate was found to be the better leaving group and this allowed formation of the racemic allylated pyridine, but could not convert to an enantioselective variant.

We have also studied an enantioselective synthesis of the pyridylic allylation of 4-benzylpyridine. We began by expanding the substrate scope to include a number of substituted 4-benzylpyridines. The mild conditions allow many substrate groups with varying steric and electronic properties to be tolerated. We have also found moderate enantioselectivity allylating the pyridylic position using a chiral ligand. The best results were found when using the ANDEN-Trost ligand with a simple allyl group, but after testing many different conditions the ee could not be increased past 67%.

Delving into the mechanism, we have determined the mode of reductive elimination occurs through an outer-sphere mechanism. An allylic electrophile with two stereocentres undergoes an inversion of stereochemistry during both oxidative addition and reductive elimination to give an overall retention of stereochemistry when coupled with an ADHP. This suggests that both 4-alkyl- and 4-benzylpyridines proceed through an outer-sphere reductive elimination, effectively raising the pKa threshold for soft nucleophiles to 35 for alkylpyridines.

We have also begun developing a new synthesis method for functionalizing the pyridylic position with an aryl group using copper catalysis. This arylation method uses biaryl iodonium salts in a Cu(I) to Cu(III) type mechanism and has afforded modest yields thus far. Hopefully, this type of synthesis will allow an enantioselective variant by using chiral ligands. We anticipate that this work will provide building blocks for further enantioselectivity in pyridylic functionalization.

Chapter 3: Experimental

3.1 General Experimental

All reactions were conducted in flame- or oven-dried glassware under an atmosphere of argon using freshly distilled solvents unless specified otherwise. Dichloromethane (DCM), and toluene were distilled from CaH_2 prior to use. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Commercial reagents were used as received. Thin-layer chromatography was performed on Merck silica gel 60 F254 plates. Visualization was carried out using UV light (254 nm) and/or KMnO4, $(NH_4)_2Ce(NO_3)_6$ solutions. Hexanes (ACS grade) and ethyl acetate (ACS grade) were used as received. Flash column chromatography was carried out using Aldrich silica gel (230-400 mesh, 40- 63 μ, 60 Å pore size). ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AV 400 or Bruker AV 300 spectrometer in chloroform-d (99.8 % deuterated). Spectra recorded using chloroform was calibrated to 7.24 ppm ^{1}H and 77.23 ppm ^{13}C. Chemical shifts (δ) are reported in ppm and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), m (multiplet), br (broad). Coupling constants J are reported in Hertz (Hz).

3.2 Preparation of Substrates: Procedures and Structural Data

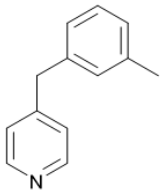
General Procedure 1: Preparation of the reagent TMPZnCl·LiCl

A dry, argon flushed RBF was equipped with a magnetic stirrer and a septum. This RBF was charged with 2,2,6,6-tetramethylpiperidine dissolved in THF. This solution was cooled to -40°C and *n*-BuLi (1.6 M in hexane) was added dropwise. After the addition was complete, the reaction mixture was allowed to warm up slowly to -10°C for 1 h. Sublimed $ZnCl_2$ (1.0 M in THF) was added dropwise and the resulting solution was stirred for 30 min at -10°C and then for 30 min at 25°C. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added to a concentration of 1.3 M in THF.

General Procedure 2: Metalation of pyridines and related *N*-heterocycles with TMPZnCl·LiCl.

In a dry and argon flushed RBF with a stir bar, 4-methylpyridine was dissolved in dry THF. Then, TMPZnCl·LiCl (1.3 M in THF) was added dropwise and the reaction mixture was stirred at the desired temperature for 10 min.

Synthesis of 4-(3-methylbenzyl)pyridine (6, CAS 130406-95-0**):**



TMPZnCl·LiCl (1.3 M in THF, 6.00 mL, 7.2 mmol) was added to a solution of 4-methylpyridine (559 mg, 6.00 mmol, 1.00 equiv) in THF (9.23 mL) at 25°C and the reaction mixture was then stirred at this temperature for 1 h according to **General Procedure 2**. $Pd(OAc)_2$ (27 mg, 2 mol%), SPhos (99 mg, 4 mol%) and 1-bromo-3-methylbenzene (821 mg, 4.80 mmol, 0.80 equiv) were stirred in a separate flask for 30 min and were added to the reaction mixture dropwise. The resulting mixture was stirred for 1 h at 50°C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 6.70 mL), extracted with EtOAc and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by column chromatography (hexane/ EtOAc, 2:3) (R_f = 0.4) furnished 4-(3-methylbenzyl)pyridine (581 mg, 66%) as a colourless oil. Spectral data obtained is consistent with that previously reported.[33]

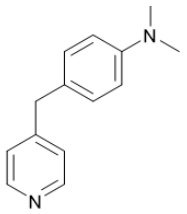
^{1}H-NMR (400MHz, $CDCl_3$)

δ 8.47 (d, *J* = 5.6 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.08 (d, *J* = 5.6 Hz, 2H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 7.6 Hz, 2H), 2.31 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 150.1, 149.9, 138.8, 138.4, 129.8, 128.6, 127.4, 126.1, 124.2, 41.2, 21.4

Synthesis of *N,N*-dimethyl-4-(pyridine-4-ylmethyl)aniline (7 CAS 131416-55-2**):**



TMPZnCl·LiCl (1.3 M in THF, 6.00 mL, 7.02 mmol) was added to a solution of 4-methylpyridine (559 mg, 6.00 mmol, 1.00 equiv) in THF (9.23 mL) at 25°C and the reaction mixture was then stirred at this temperature for 1 h according to **General Procedure 2**. $Pd(OAc)_2$ (27 mg, 2 mol%), SPhos (99 mg, 4 mol%) and 4-bromo-*N*,-*N*-dimethylaniline (821 mg, 4.80 mmol, 0.80 equiv) stirred in a separate flask for 30 min and were added to the reaction mixture dropwise. The resulting mixture was stirred for 1 h at 50°C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 6.70 mL), extracted with EtOAc and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by column chromatography (hexane/ EtOAc, 1:1) (R_f = 0.4) furnished *N,N*-dimethyl-4-(pyridine-4-ylmethyl)aniline (581 mg, 66%) as a yellow oil. Spectral data obtained is consistent with that previously reported.[33]

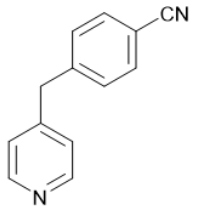
^{1}H-NMR (400MHz, $CDCl_3$)

δ 8.36 (d, *J* = 5.2Hz, 2H), 6.98 (d, *J* = 5.6Hz, 2H), 6.93 (d, *J* = 8.4Hz , 2H), 6.58 (d, *J* = 8.4 Hz, 2H), 3.74 (s, 2H), 2.80 (s, 6H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 150.9, 149.5, 149.3, 149.2, 129.5, 126.5, 123.9, 112.7, 40.4, 40.1

Synthesis of 4-(pyridine-4-ylmethyl)benzonitrile (8 CAS 146040-04-2**):**



TMPZnCl·LiCl (1.3 M in THF, 6.00 mL, 7.20 mmol) was added to a solution of 4-methylpyridine (559 mg, 6.00 mmol, 1.00 equiv) in THF (9.23 mL) at 25°C and the reaction mixture was then stirred at this temperature for 1 h according to **General Procedure 2**. $Sc(OTf)_3$ (30 mg, 0.60 mmol, 0.10 equiv.) was added at 25°C and stirred for 15 min. $Pd(OAc)_2$ (27 mg, 2 mol%), SPhos (99 mg, 4 mol%) and 4-bromobenzonitrile (874 mg, 4.80 mmol, 0.80 equiv) stirred in a separate flask for 30 min and were added to the reaction mixture dropwise. The resulting mixture was stirred for 1 h at 50°C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 6.70 mL), extracted with EtOAc and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by column chromatography (hexanes/ EtOAc, 1:4) (R_f = 0.3) furnished 4-(pyridine-4-ylmethyl)benzonitrile (489 mg, 42%) as a yellow oil. Spectral data obtained is consistent with that previously reported.[33]

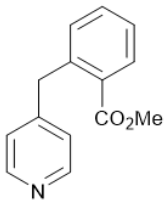
^{1}H-NMR (400MHz, $CDCl_3$)

δ 8.49 (d, *J* = 5.2Hz, 2H), 7.57 (d, *J* = 8.0Hz, 2H), 7.26 (d, *J* = 8.4Hz, 2H), 7.06 (d, *J* = 5.6Hz, 2H), 4.00 (s, 2H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 150.0, 148.1, 144.3, 132.4, 129.7, 124.0, 118.6, 110.5, 41.0

Synthesis of methyl 4-(pyridine-2-ylmethyl)benzoate (9):

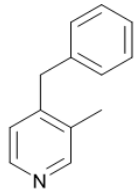


TMPZnCl·LiCl (1.3 M in THF, 6.00 mL, 7.20 mmol) was added to a solution of 4-methylpyridine (559 mg, 6.00 mmol, 1.00 equiv) in THF (9.23 mL) at 25°C and the reaction mixture was then stirred at this temperature for 1 h according to **General Procedure 2**. $Sc(OTf)_3$ (30 mg, 0.60 mmol, 0.10 equiv.) was added at 25°C and stirred for 15 min. $Pd(OAc)_2$ (27 mg, 2 mol%), SPhos (99 mg, 4 mol%) and methyl 2-bromobenzoate (1.03 g, 4.80 mmol, 0.80 equiv) stirred in a separate flask for 30 min and were added to the reaction mixture dropwise. The resulting mixture was stirred for 1 h at 50°C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 6.70 mL), extracted with EtOAc and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by column chromatography (hexanes/ EtOAc, 1:4) (R_f = 0.2) furnished methyl 4-(pyridine-2-ylmethyl)benzoate (231 mg, 17%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$)

δ 8.44, (d, *J* = 4.4Hz, 2H), 7.95 (d, *J* = 8Hz, 1H), 7.47 (t, *J* = 7.2Hz, 1H), 7.33 (t, *J* = 7.6Hz, 1H), 7.23 (d, *J* = 10.4Hz, 1H), 7.02 (d, *J* = 4.8Hz, 2H), 4.37 (s, 2H), 3.78 (s, 3H)

Synthesis of 4-benzyl-3-methylpyridine (10 CAS 24015-80-3**):**



TMPZnCl·LiCl (1.3 M in THF, 6.00 mL, 7.20 mmol) was added to a solution of 3,4-lutidine (643 mg, 6.00 mmol, 1.00 equiv) in THF (9.23 mL) at 25°C and the reaction mixture was then stirred at this temperature for 1 h according to **General Procedure 2**. $Pd(OAc)_2$ (27 mg, 2 mol%), SPhos (99 mg, 4 mol%) and bromobenzene (754 mg, 4.80 mmol, 0.80 equiv) stirred in a separate flask for 30 min and were added to the reaction mixture dropwise. The resulting mixture was stirred for 1 h at 50°C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 6.70 mL), extracted with EtOAc and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by column chromatography (hexane/ EtOAc, 2:3) (R_f = 0.4) furnished 4-benzyl-3-methylpyridine (758 mg, 69%) as a colourless oil. Spectral data obtained is consistent with that previously reported.[39]

^{1}H-NMR (400MHz, $CDCl_3$)

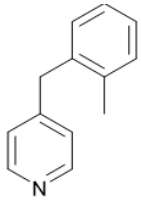
δ 8.35-8.33 (m, 2H), 7.73-7.21 (m, 3H), 7.10 (d, *J* = *5.6*Hz, 2H),

6.95 (d, *J* = 5.2Hz, 1H), 3.94 (s, 2H), 2.23 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 149.9, 149.6, 136.5, 130.5, 130.0, 127.0, 126.2, 124.0, 38.8, 19.5

Synthesis of 4-(2-methylbenzyl)pyridine (11 CAS 36995-46-7**):**



TMPZnCl·LiCl (1.3 M in THF, 6.00 mL, 7.20 mmol) was added to a solution of 4-methylpyridine (559 mg, 6.00 mmol, 1.00 equiv) in THF (9.23 mL) at 25°C and the reaction mixture was then stirred at this temperature for 1 h according to **General Procedure 2**. $Pd(OAc)_2$ (27 mg, 2 mol%), SPhos (99 mg, 4 mol%) and 1-bromo-2-methylbenzene (821 mg, 4.8 mmol, 0.80 equiv) stirred in a separate flask for 30 min and were added to the reaction mixture dropwise. The resulting mixture was stirred for 1 h at 50°C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 6.70 mL), extracted with EtOAc and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by column chromatography (hexane/ EtOAc, 2:3) (R_f = 0.4) furnished 4-(2-methylbenzyl)pyridine (957 mg, 87%) as a colourless oil. Spectral data obtained is consistent with that previously reported.[40]

^{1}H-NMR (400MHz, $CDCl_3$)

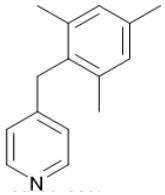
δ 8.51 (d, *J* = 5.6Hz, 2H), 7.22-7.20 (m, 3H), 7.14-7.12 (m, 1H),

7.07 (d, *J* = 5.6Hz, 2H), 4.01 (s, 2H), 2.23 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 149.9, 149.6, 136.5, 130.5, 130.0, 127.0, 126.2, 124.0, 38.8, 19.5

Synthesis of 4-(2,4,6-methylbenzyl)pyridine (12 CAS 43136-90-9**):**



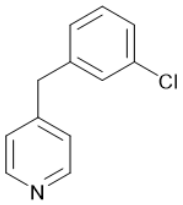
TMPZnCl·LiCl (1.3 M in THF, 6.00 mL, 7.20 mmol) was added to a solution of 4-methylpyridine (559 mg, 6.00 mmol, 1.00 equiv) in THF (9.23 mL) at 25°C and the reaction mixture was then stirred at this temperature for 1 h according to **General Procedure 2**. $Pd(OAc)_2$ (27 mg, 2 mol%), SPhos (99 mg, 4 mol%) and 1-bromo-2,4,6-methylbenzene (956 mg, 4.80 mmol, 0.80 equiv) stirred in a separate flask for 30 min and were added to the reaction mixture dropwise. The resulting mixture was stirred for 1 h at 50°C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 6.70 mL), extracted with EtOAc and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by column chromatography (hexane/ EtOAc, 2:3) (R_f = 0.2) furnished 4-(2,4,6-methylbenzyl)pyridine (761 mg, 60%) as a colourless oil.

^{1}H-NMR (300MHz, $CDCl_3$)

δ 8.42 (d, *J*= 6.3Hz, 2H), 6.92 (d, *J* =6Hz, 2H), 6.89 (s, 2H), 3.98 (s, 2H),

2.28 (s, 3H), 2.16 (s, 6H)

Synthesis of 4-(3-chlorobenzyl)pyridine (13 CAS 134869-90-2 **):**



TMPZnCl·LiCl (1.3 M in THF, 6.00 mL, 7.20 mmol) was added to a solution of 4-methylpyridine (559 mg, 6.00 mmol, 1.00 equiv) in THF (9.23 mL) at 25°C and the reaction mixture was then stirred at this temperature for 1 h according to **General Procedure 2**. $Sc(OTf)_3$ (30 mg, 0.60 mmol, 0.10 equiv.) was added at 25°C and stirred for 15 min. $Pd(OAc)_2$ (27 mg, 2 mol%), SPhos (99 mg, 4 mol%) and 1-bromo-2-chlorobenzene (919 mg, 4.80 mmol, 0.80 equiv) stirred in a separate flask for 30 min and were added to the reaction mixture dropwise. The resulting mixture was stirred for 1 h at 50°C. The reaction mixture was then quenched with a mixture of saturated aqueous NH_4Cl and NH_3 (10:1, 6.70 mL), extracted with EtOAc and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by column chromatography (hexanes/ EtOAc, 1:4) (R_f = 0.3) furnished 4-(3-chlorobenzyl)pyridine (733 mg, 60%) as a yellow oil.

^{1}H-NMR (300MHz, $CDCl_3$)

δ 8.50 (d, *J* = 6Hz, 2H), 7.22-7.21 (m, 2H), 7.14 (s, 1H), 7.08-7.02 (m, 3H), 3.92 (s, 2H)

^{13}C-NMR (100MHz, $CDCl_3$)

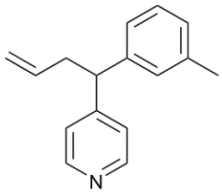
δ 150.0, 149.0, 140.9, 134.5, 130.0, 129.1, 127.2, 126.9, 124.1, 40.8

3.3 Palladium catalyzed pyridylic allylation: Procedures and Structural Data

General Procedure 3: Palladium catalyzed pyridylic allylation

Triethylamine (1.77 mmol, 3.00 equiv.) was added to a solution of 4-benzylpyridine (100 mg, 0.59 mmol, 1.00 equiv.) in dry THF (5.91 mL) in a flame dried RBF under argon. The resulting solution was stirred at reflux for 2 min and allyl chloroformate (142 mg, 1.18 mmol, 2.00 equiv.) was added dropwise. After 30 min, the solvent was evaporated under reduced pressure. The resulting mixture of the ADHP intermediate and triethylammonium chloride was triturated using diethyl ether and filtered through a cotton plug. The filtrate was concentrated *in vacuo*. The crude intermediate was dissolved in THF (3.00 mL) and was kept under an inert atmosphere of argon. To an oven-dried RBF, Xantphos (41 mg, 0.071 mmol, 12 mol%), and $Pd_2(dba)_3 \cdot CHCl_3$ (30 mg, 0.0030 mmol, 5 mol%), were added under argon. To this flask, THF (2.90 mL) was added and the resulting solution was allowed to stir for 20 min at room temperature. This solution was then added dropwise to the flask containing the crude intermediate and stirred at room temperature. After 3 h, the reaction mixture was concentrated *in vacuo* and the product was afforded as a yellow oil after column chromatography purification.

Synthesis of (6a):



Using the **General Procedure 3**, 4-(3-methylbenzyl)pyridine (108 mg, 0.59 mmol, 1.00 equiv) afforded **6a** in (107 mg, 81%) as a yellow oil in 3 h. Purification by column chromatography (hexanes/ EtOAc, 1:3) (R_f = 0.3).

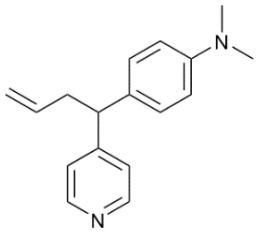
^{1}H-NMR (300MHz, $CDCl_3$)

δ 8.46 (d, *J* = 1.8Hz, 2H), 7.20-7.12 (m, 3H), 7.02-6.99 (m, 3H), 5.73-5.60 (m, 1H), 5.05-4.93 (m, 2H), 3.92 (t, *J* = 7.8Hz, 1H), 2.80-2.75 (m, 2H), 2.30 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 153.3, 149.9, 142.6, 138.3, 135.9, 128.7, 128.6, 127.6, 124.9, 123.3, 117.0, 50.6, 39.2, 21.5

Synthesis of (7a):



Using the **General Procedure 3**, *N*,*N*-dimethyl-4-(pyridine-4-ylmethyl)aniline (118 mg, 0.59 mmol, 1.00 equiv.) afforded **7a** (139 mg, 89%) as an orange solid in 3 h. Purification by column chromatography (hexanes/ EtOAc, 1:9) (R_f = 0.3).

^{1}H-NMR (300MHz, $CDCl_3$)

δ 8.45 (d, *J* = 6.0Hz, 2H), 7.10 (d, *J* = 6.3Hz, 2H), 6.66 (d, *J* = 8.7Hz, 2H),

5.68 (d, *J* = 8.7Hz, 2H), 5.75-5.61 (m, 1H), 5.04-4.93 (m, 2H),

3.87 (t, *J* = 7.8Hz, 1H), 2.90 (s, 6H), 2.77-2.72 (m, 2H)

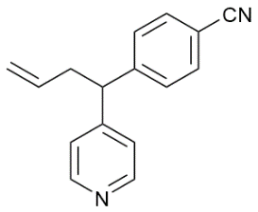
^{13}C-NMR (100MHz, $CDCl_3$)

δ 154.2, 149.8, 149.4, 136.3, 130.4, 128.5, 123.3, 116.7, 112.7, 49.7, 40.6, 39.4

IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 2977, 1594, 1518, 1346, 912, 811, 552

Synthesis of (8a):



Using the **General Procedure 3**, 4-(pyridine-4-ylmethyl)benzonitrile (115 mg, 0.59 mmol, 1.00 equiv.) afforded **8a** (121 mg, 93%) as a dark orange oil in 3 h. Purification by column chromatography (EtOAc) (R_f = 0.3).

^{1}H-NMR (300MHz, $CDCl_3$)

δ 8.42 (d, *J* = 6Hz, 2H), 7.58 (d, *J* = 8.1Hz, 2H), 7.30 (d, *J* = 8.4Hz, 2H),

7.10 (d, *J* = 6.0Hz, 2H), 5.70-5.56 (m, 1H), 5.05-4.98 (m, 2H),

4.03 (t, *J* = 7.8Hz, 1H), 2.82-2.76 (m, 2H)

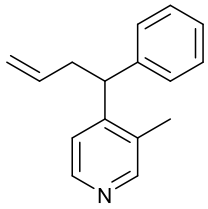
^{13}C-NMR (100MHz, $CDCl_3$)

δ 151.6, 150.2, 148.0, 134.7, 132.5, 128.8, 123.2, 118.6, 117.6, 110.9, 50.5, 38.8

IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 3027, 2226, 1593, 1412, 993, 872, 815, 561

Synthesis of (10a):



Using the **General Procedure 3**, 4-benzyl-3-methylpyridine (75 mg, 0.41 mmol, 1.00 equiv.) afforded **10a** (91 mg, 96%) as a yellow oil in 3 h. Purification by column chromatography (hexanes/ EtOAc, 1:3) (R_f = 0.3).

^{1}H-NMR (300MHz, $CDCl_3$)

δ 8.40 (d, *J* = 6.8Hz, 1H), 8,31 (s, 1H), 7.28-7.18 (m, 6H), 5.75-5.62 (m, 1H), 5.04-4.94 (m, 1H), 4.13 (t, *J* = 10.4Hz, 2H), 2.20 (s, 3H)

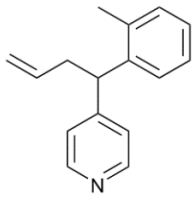
^{13}C-NMR (100MHz, $CDCl_3$)

δ 151.2, 150.9, 147.8, 142.2, 135.9, 131.9, 128.6, 128.2, 126.6, 121.6, 117.0, 46.6, 39.5, 16.6

IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 3025, 1589, 1402, 913, 699, 557

Synthesis of (11a):



Using the **General Procedure 3**, 4-(2-methylbenzyl)pyridine (108 mg, 0.59 mmol, 1.00 equiv.) afforded **11a** (120mg, 91%) as a yellow oil in 3 h. Purification by column chromatography (hexanes/ EtOAc, 1:3) (R_f = 0.3).

^{1}H-NMR (300MHz, $CDCl_3$)

δ 8.45 (d, *J* = 7.0Hz, 2H), 7.26-7.14 (m, 2H), 7.13 (d, *J* = 3.6Hz, 2H),

7.07 (d, *J* = 7.0Hz, 2H), 5.77-5.63 (m, 1H), 5.04-4.95 (m, 2H),

4.16 (t, *J* = 7.8Hz, 1H), 2.79-2.72 (m, 2H), 2.22 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$)

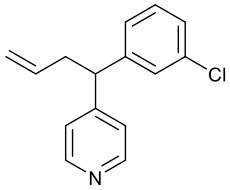
δ 153.1, 149.8, 140.5, 136.3, 135.9, 130.7, 126.9, 126.7, 126.3, 123.6, 117.2, 46.3,

39.6, 19.9

IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 3021, 1594, 1411, 993, 848, 748, 640, 559

Synthesis of (13a):



Using the **General Procedure 3**, 4-(3-chlorobenzyl)pyridine (80 mg, 0.39 mmol, 1.00 equiv.) afforded **13a** (92 mg, 79%) as a yellow oil in 3 h. Purification by column chromatography (hexanes/ EtOAc, 1:4) (R_f = 0.4).

^{1}H-NMR (300MHz, $CDCl_3$)

δ 8.50 (d, *J* = 6.0Hz, 2H), 7.22-7.17 (m, 3H), 7.11 (d, *J* = 6.4Hz, 2H), 7.08-7.06 (m, 1H), 5.68-5.59 (m, 1H), 5.04-4.96 (m, 1H), 3.94 (t, *J* = 8.0Hz, 1H), 2.79-2.75 (m, 2H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 152.4, 150.0, 144.7, 135.2, 134.5, 129.9, 128.1, 127.1, 126.2, 123.2, 117.5, 50.2, 39.0

IR Alpha-Platinum ATR, Bruker, diamond crystal

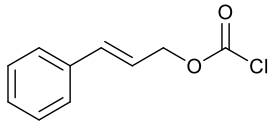
ν = 3024, 1592, 1475, 1412, 993, 915, 694

3.4 Chloroformate variants study

General Procedure 4: Synthesis of cyclohexene chloroformate.

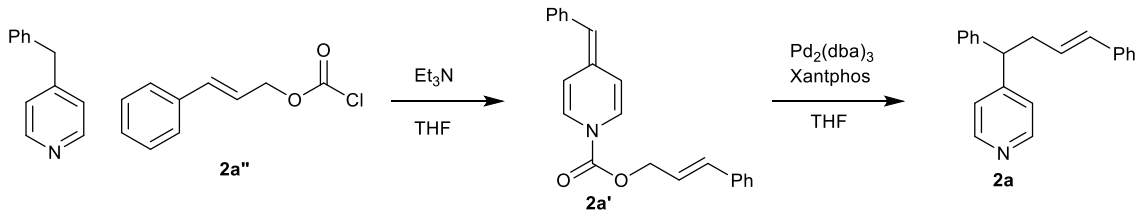
A dry and argon flushed RBF, equipped with a magnetic stirrer and a septum was charged with 2-cyclohexen-1-ol dissolved in THF. This solution was cooled to 0°C and distilled triethylamine (3.00 equiv.) was added. Phosgene (1.50 equiv.) was then added dropwise and the reaction was left to stir at 0°C for 3 h. The flask was then flushed with argon through a solution of NaOH (1.0 M) for 20 mins. The solvents were then removed under vacuum leaving a white solid. This was triturated using diethyl ether, which was removed under vacuum to produce a colourless liquid.

Synthesis of cinnamyl chloroformate:



Cinnamyl alcohol (105 mg, 0.78 mmol, 1.00 equiv.) and THF (0.53 mL) were added to a RBF and cooled to -45°C. The solution was added to a flask containing phosgene (100 mg, 1.01 mmol, 1.30 equiv.) dropwise at this temperature and stirred for 1 h. The solution was then warmed to 0°C for 5 mins and purged through a solution of NaOH at 0°C for 30 mins. This crude cinnamyl chloroformate was then used in the following step without further purification.

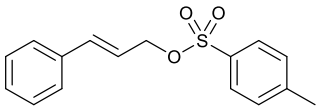
General Procedure 5: Synthesis of 4-[(3*E*)-1,4-diphenyl-3-buten-1-yl]-pyridine



4-Benzylpyridine (120 mg, 0.71 mmol, 1.00 equiv.), triethylamine (216 mg, 2.13 mmol, 3.00 equiv.) and THF (7.10 mL) were added to a RBF. This mixture was cooled to 0°C and cinnamyl chloroformate was added dropwise. This mixture was stirred at r.t. for 1 h and concentrated under reduced pressure. The crude solid was then diluted with diethyl ether and filtered over a cotton plug. The resulting solution was concentrated under reduced pressure and used in the next step without further purification. The yellow oil was dissolved in THF (3.50 mL). In a second flask, $Pd_2(dba)_3 \cdot CHCl_3$ (26 mg, 0.028, 0.04 equiv.) and Xantphos (37 mg, 0.064 mmol, 0.090 equiv.) in THF (3.60 mL) were stirred at r.t. for 20 mins. The contents of this second flask were added to the first flask dropwise and allowed to stir at r.t. overnight. This mixture was then concentrated under reduced pressure and purified by column chromatography (hexanes: EtOAc, 3:1) (R_f = 0.2) to afford 4-[(3*E*)-1,4-diphenyl-3-buten-1-yl]-pyridine (30 mg, 15%) as a white solid.

3.5 Allyl electrophile variants study

Synthesis of Cinnamyl Tosylate (CAS 19627-30-6)**:**



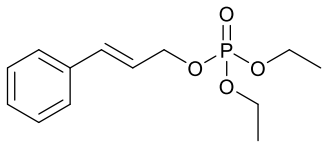
A mixture of cinnamyl alcohol (200 mg, 1.50 mmol, 1.00 equiv.) and KOH (421 mg, 7.50 mmol, 5.00 equiv.) in THF (3.75 mL) were cooled to 0°C. A solution of TsCl (355 mg, 1.90 mmol, 1.25 equiv.) was added dropwise and the resulting mixture was allowed to warm to r.t. overnight. This mixture was quenched with $NaHCO_3$ and extracted 3x, washed once with brine, and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The resulting material was left on the high-vacuum line overnight to furnish cinnamyl tosylate (406 mg, 90%) as a beige powder. Spectral data obtained is consistent with that previously reported.[41]

^{1}H-NMR (400MHz, $CDCl_3$)

δ 7.79 (t, *J* = 8.4Hz, 3H), 7.33-7.27 (m, 6H), 6.57 (d, *J* = 16 Hz, 1H),

6.11 (dt, *J* = 16, 6.8Hz, 1H), 4.69 (d, *J* = 8.0Hz, 2H), 2.41 (s, 3H)

Synthesis of Diethyl cinnamylphosphonate (CAS 85669-63-2)**:**



Cinnamyl alcohol (300 mg, 2.20 mmol, 1.00 equiv.), triethylamine (557 mg, 5.50 mmol, 2.50 equiv.), DMAP (108 mg, 0.90 mmol, 0.40 equiv.), and DCM (11.00 mL) were added to a RBF at r.t. Diethyl phosphorochloridate (456 mg, 2.64 mmol, 1.20 equiv.) was added dropwise at 0°C and warmed to r.t. overnight. This reaction mixture was quenched with cold H_2O after dilution with DCM. This was extracted with DCM (3x), washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by column chromatography (hexanes / EtOAc, 1:2) furnished diethyl cinnamylphosphonate (450 mg, 76%) as a yellow oil. Spectral data obtained is consistent with that previously reported.[30]

^{1}H-NMR (400MHz, $CDCl_3$)

δ 7.39 (t, *J* = 1.6Hz, 2H), 7.32 (t, *J* = 2.0Hz, 2H), 7.27-7.23 (m, 1H),

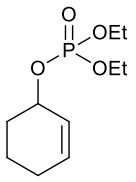
6.67 (d, *J* = 16.0Hz, 1H), 6.29 (dt, *J* = 16.0, 6.0Hz, 1H), 4.70-4.66 (m, 2H),

4.16-4.08 (m, 4H), 1.34-1.31 (m, 6H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 136.2, 134.0, 128.8, 128.3, 126.8, 123.7, 68.1, 64.0, 16.3

Synthesis of Phosphoric acid, 2-cyclohexen-1-yl diethyl ester (CAS 68735-62-6)**:**



Cyclohexenol (200 mg, 2.03 mmol, 1.00 equiv.), triethylamine (514 mg, 5.10 mmol, 2.50 equiv.), DMAP (99 mg, 0.81 mmol, 0.40 equiv.), and DCM (20.00 mL) were added at r.t. to a RBF. Diethyl phosphorochloridate (422 mg, 2.44 mmol, 1.20 equiv.) was added dropwise at 0°C and warmed to r.t. overnight. The reaction mixture was quenched with cold H_2O after dilution with DCM. This mixture was extracted with DCM (3x), washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. Purification by column chromatography (pentane/ Et_2O, Et_3N, 33:65:2) (R_f = 0.3) furnished phosphoric acid, 2-cyclohexen-1-yl diethyl ester (322 mg, 68%) as a yellow oil. Spectral data obtained is consistent with that previously reported.[37]

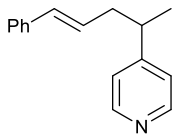
^{1}H-NMR (400MHz, $CDCl_3$)

δ 5.94 (m, 1H), 5.79-5.75 (m, 1H), 4.87-4.84 (m, 1H), 4.12-4.05 (m, 4H), 2.04-2.02 (m, 1H), 1.98-1.87 (m, 3H), 1.77-1.74 (m, 1H), 1.62-1.58 (m, 1H), 1.33-1.26 (m, 6H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 132.7, 126.3, 72.0, 63.5, 63.4, 29.7, 24.6, 18.3, 16.0, 15.9

Synthesis of 3a



4-Ethylpyridine (50 mg, 0.47 mmol, 1.00 equiv.), triethylamine (143 mg, 1.41 mmol, 3.00 equiv.) and THF (4.70 mL) were added to an RBF under argon. Ethyl chloroformate (102 mg, 0.94 mmol, 2.00 equiv.) was added dropwise and the mixture was stirred at room temperature for 30 mins. The solvent was evaporated under reduced pressure and the resulting solid was triturated with diethyl ether. The resulting solution was concentrated under reduced pressure and the ADHP was used in the next step without further purification. The yellow oil was dissolved in THF (2.0 mL) and diethyl cinnamylphosphonate (152 mg, 0.56 mmol, 1.20 equiv.) was added dropwise at r.t. and allowed to stir. In a second flask, $Pd_2(dba)_3 \cdot CHCl_3$ (24 mg, 0.024 mmol, 0.050 equiv.) and Xantphos (33 mg, 0.056 mmol, 0.12 equiv.) in THF (2.70 mL) were stirred at r.t. for 20 mins. The contents of this second flask were added to the first flask dropwise and allowed to stir at r.t. overnight. This mixture was then quenched with cold NaOH and extracted with EtOAc (3x), washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting crude oil was then purified by column chromatography (hexanes/ EtOAc, 1:1) (R_f = 0.4) to afford 3a (14 mg, 13%) as a yellow oil.

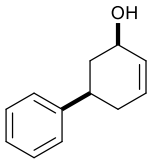
^{1}H-NMR (400MHz, $CDCl_3$)

δ 8.47 (d, *J* = 4.2 Hz, 2H), 7.38-7.37 (m, 4H), 7.22-7.17 (m, 1H),

7.11 (d, *J* = 6.0 Hz, 2H), 6.33 (d, *J* = 15.9 Hz, 1H), 6.08-5.98 (m, 1H),

2.84 (sextet, *J* = 6.9 Hz, 1H), 2.52-2.39 (m, 2H), 1.29-1.26 (m, 2H)

Synthesis of *cis*-5-Phenyl-2-cyclohexen-1-ol (CAS 26114-87-4):



5-phenyl-1,3-cyclohexanedione (200mg, 1.10 mmol, 1.00 equiv), *p*-toluic acid (2 mg, 0.016 mmol, 0.0015 equiv.) and a benzene/ isobutylalcohol mixture (1:1, 4.66 mL) were added to a RBF. The flask was fitted with a Dean-Stark trap and heated to reflux for 3 h. The solution was cooled to r.t. and the solvent was evaporated under reduced pressure to afford an oil. This oil was dissolved in diethyl ether (8.00 mL), washed with 2.0 M NaOH (3x), washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was dissolved in diethyl ether (12.00 mL) and transferred to a flame-dried RBF. The solution was cooled to 0°C and $LiAlH_4$ (31 mg, 0.82 mmol, 0.77 equiv.) was added portion-wise and the resulting mixture was stirred at r.t. for 2 h. The reaction was quenched with 10% aq. HCl, extracted with diethyl ether, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting oil was then dissolved in methanol (16.00 mL), $CeCl_3 \cdot 7H_2O$ (394 mg, 1.60 mmol, 1.50 equiv.) was added, and $NaBH_4$ was added portion-wise (40 mg, 1.06 mmol, 1.00 equiv.). This reaction mixture was stirred at 0°C for 3 h and concentrated under reduced pressure. It was then washed with 1.0 M HCl (3x), brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (hexanes/ EtOAc, 5:1) (R_f = 0.4) furnished *cis*-5-Phenyl-2-cyclohexen-1-ol (142mg, 77%) as a white solid. Spectral data obtained is consistent with that previously reported.[37]

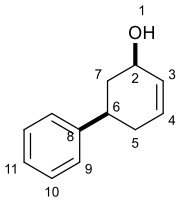
^{1}H-NMR (300MHz, $CDCl_3$)

δ 7.33-7.29 (m, 2 H), 7.23-7.18 (m, 3 H), 5.84-5.81 (m, 1 H), 5.77-5.73 (m, 1 H), 4.47 (br, 1 H), 2.96-2.83 (m, 1 H), 2.37-2.21 (m, 2 H), 2.19-2.04 (m, 1 H), 1.78-1.68 (m, 1 H), 1.58 (d, *J* = 5.1Hz, 1 H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 145.6, 131.1, 128.7, 128.6, 126.8, 126.4, 68.6, 39.6, 39.3, 33.8

***cis*-5-Phenyl-2-cyclohexen-1-ol**



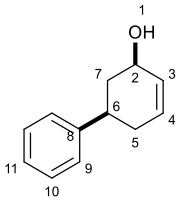
Proton No.	^{1}H δ (ppm) (mult: *J* (Hz))[a, b,c,d]	COSY Correlation
H-1	1.58 (d, *J* = 5.1Hz, 1H)	H-2, H-7a, H-7b
H-2	4.47 (s, 1H)	H-1, H-5a H-7a, H-7b
H-3	5.77-5.73 (m, 1H)	H-4
H-4	5.84-5.81 (m, 1H)	H-4, H-5b, H-7b
H-5	H-5a: 2.19-2.04 (m, 1H) H-5b: part of the m at 2.37-2.21	H-2, H-4, H-6, H-7a, H-7b
H-6	2.96-2.83 (m, 1H)	H-5a, H-5b, H-7a, H-7b
H-7	H-7a: 1.78-1.68 (m, 1H) H-7b: part of the m at 2.37-2.21	H-1, H-2, H-4, H-5a, H-5b, H-6
H-9	Part of the m at 7.23-7.18	H-10, H-11
H-10	7.33-7.29 (m, 2H)	H-9, H-11
H-11	Part of the m at 7.23-7.18	H-9, H-19

[a] Recorded at 600 MHz. [b] Assignments based on HSQC-DEPT and HMBC data

[c] Methylene protons are designated H-Xa and H-Xb arbitrarily

[d] Only those correlations which could be unambiguously assigned are reported.

***cis*-5-Phenyl-2-cyclohexen-1-ol**



Proton No.	^{1}H δ (ppm) (mult: *J* (Hz))[a, b,c,d]	NOESY Correlation
H-1	1.58 (d, *J* = 5.1Hz, 1H)	H-2
H-2	4.47 (s, 1H)	H-1, H-6, H-7a, H-7b
H-3	5.77-5.73 (m, 1H)	H-4, H-7a
H-4	5.84-5.81 (m, 1H)	H-3, H-5a, H-5b, H-7b
H-5	H-5a: 2.19-2.04 (m, 1H) H-5b: part of the m at 2.37-2.21	H-2, H-4, H-6, H-7a, H-7b, H-9
H-6	2.96-2.83 (m, 1H)	H-2, H-5a, H-5b, H-7a, H-7b, H-9
H-7	H-7a: 1.78-1.68 (m, 1H) H-7b: part of the m at 2.37-2.21	H-2, H-3, H-4, H-5a, H-5b, H-6, H-9
H-9	Part of the m at 7.23-7.18	H-5a, H-5b, H-7a, H-7b, H-10, H-11
H-10	7.33-7.29 (m, 2H)	H-9, H-11
H-11	Part of the m at 7.23-7.18	H-9, H-10

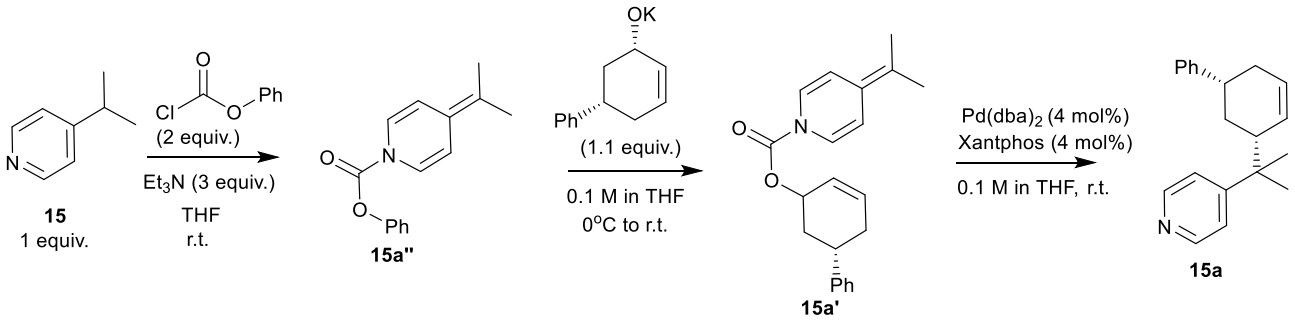
[a] Recorded at 600 MHz. [b] Assignments based on HSQC-DEPT and HMBC data

[c] Methylene protons are designated H-Xa and H-Xb arbitrarily

[d] Only those correlations which could be unambiguously assigned are reported.

3.6 Mechanistic insight: Procedures and Structural Data

General Procedure 6: Synthesis of 2-cyclohexene, 1-[1-4(pyridinyl)ethyl]-



*Intermediate **15a"** Formation* – Using **General Procedure 3**, phenyl chloroformate (438 mg, 2.80 mmol, 1.00 equiv.) was added to a mixture of triethylamine (850 mg, 8.40 mmol, 3.00 equiv.) and pyridine **15** (340 mg, 2.80 mmol, 1.00 equiv.) in dry THF (28.00 mL). The ADHP intermediate was isolated according to **General Procedure 3**.

*Intermediate **15a'** Formation* – 5-phenyl-2-cyclohexen-1-ol (520 mg, 3.00 mmol, 1.10 equiv.) was dissolved in dry THF (25.00 mL) at 0°C under an argon atmosphere. KHMDS (0.50 M in toluene, 6.20 mL, 1.10 equiv.) was then added dropwise and the mixture was allowed to stir at 0°C for 30 mins. This solution was added dropwise to intermediate **15a"** suspended in dry THF (5.00 mL) at 0°C and allowed to warm to r.t. over 1.5 h. The mixture was concentrated *in vacuo* and the resulting crude mass was suspended in toluene and filtered through a plug of cotton to remove the phenyl alkoxide salt. The filtrate was concentrated *in vacuo* to afford a yellow oil which was carried forward to the next step without further purification.

Palladium catalyzed decarboxylative allyation – Using **Procedure 3**, intermediate **15a'** was added to a mixture of Xantphos (12 mol%) and $Pd(dba)_2$ (5 mol%) in dry THF (0.1 M) which had been pre-stirred for 20 minutes. The resulting mixture was left to stir at room temperature overnight. Purification by column chromatography (hexanes/ EtOAc, 3:1) (R_f = 0.3) furnished **15a** (70 mg, 44%) as a yellow solid.

Melting Point: 103.8°C – 104.6°C

^{1}H-NMR (400 MHz, $CDCl_3$)

δ 8.50 (d, *J* = 6.0 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 4.7 Hz, 2H), 7.19-7.15 (m, 3H), 5.81-5.77 (m, 1H), 5.48 (d, *J* = 10.4 Hz, 1H), 2.83-2.77 (m, 1H), 2.76-2.64 (m, 1H), 2.19-2.03 (m, 2H), 1.69-1.68 (m, 1H), 1.43 (q, *J* = 12.4 Hz, 1H), 1.30 (s, 1H), 1.26 (s, 1H)

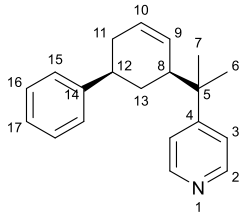
^{13}C-NMR (100 MHz, $CDCl_3$)

δ 158.5, 149.6, 146.8, 128.7, 128.4, 127.8, 126.8, 126.2, 121.6, 47.4, 40.8, 40.4, 33.6, 32.1, 29.7, 24.8, 24.2

IR Alpha-Platinum ATR, Bruker, diamond crystal

ν = 2893, 1592, 1442, 1148, 822, 760, 699, 578

2-cyclohexene, 1-[1-4(pyridinyl)ethyl]- **15a**

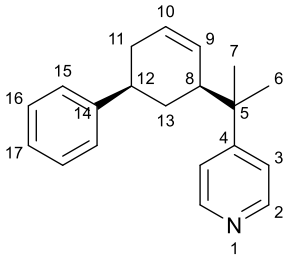


Carbon No.	**^{13}C δ (ppm)[a]**	**^{1}H δ (ppm) (mult: *J* (Hz))[b,c,d]**	**HMBC Correlation**
2	149.6	H-2 : 8.50 (d, *J* = 6.0 Hz, 2H)	H-3
3	121.6	H-3 : 7.25 (d, 4.7 Hz, 2H)	H-16, H-15, H-6, H-7
4	158.5		H-2, H-6, H-7
5	40.4		H-2, H-3, H-6, H-7
6	24.2	H-6 : 1.30 (s, 1H)	H-7
7	24.8	H-7 : 1.26 (s, 1H)	H-6
8	47.4	H-8 : 2.76-2.64 (m, 1H)	H-10, H-12, H-13a, H-13b, H-6, H-7
9	127.8	H-9 : 5.48 (d, *J* = 10.4 Hz, 1H)	H-13a, H-13b
10	128.7	H-10 : 5.81-5.77 (m, 1H)	H-11
11	33.6	H-11 : 2.19-2.03 (m, 2H)	H-10, H-12, H-13a, H-13b
12	40.8	H-12 : 2.83-2.77 (m, 1H)	H-15, H-10, H-8, H-11, H-13a, H-13b
13	29.7	H-13a : 1.69-1.68 (m, 1H) H-13b : 1.43 (q, *J* = 12.4 Hz, 1H)	H-9, H-12, H-11
14	146.8		H-16, H-15, H-12, H-13a, H-13b
15	126.8	H-15: part of the m at 7.19-7.15	H-16, H-17, H-12
16	128.4	H-16: 7.28 (t, *J* = 7.5 Hz, 2H)	H-17
17	126.2	H-17 : part of the m at 7.19-7.15	H-16, H-15

[a] Recorded at 600 MHz. [b] Assignments based on HSQC-DEPT and HMBC data

[c] Methylene protons are designated H-Xa and H-Xb arbitrarily

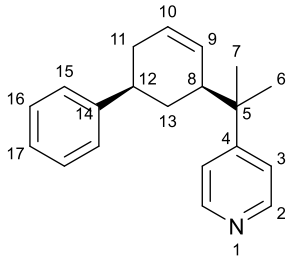
[d] Only those correlations which could be unambiguously assigned are reported.



Proton No.	^{1}H δ (ppm) (mult: *J* (Hz))[b,c,d]	COSY Correlation
H-2	8.50 (d, *J* = 6.0 Hz, 2H)	H-3
H-3	7.25 (d, *J* = 4.7 Hz, 2H)	H-2
H-6	1.30 (s, 1H)	H-7
H-7	1.26 (s, 1H)	H-6
H-8	2.76-2.64 (m, 1H)	H-10, H-11, H-13a, H-13b
H-9	5.48 (d, *J* = 10.4 Hz, 1H)	H-10
H-10	5.81-5.77 (m, 1H)	H-9, H-11
H-11	2.19-2.03 (m, 2H)	H-10, H-12
H-12	2.83-2.77 (m, 1H)	H-11, H-13b
H-13	H-13a : 1.69-1.68 (m, 1H) H-13b : 1.43 (q, *J* = 12.4 Hz, 1H)	H-8
H-15	part of the m at 7.19-7.15	H-17, H-16
H-16	7.28 (t, *J* = 7.5 Hz, 2H)	H-17, H-15
H-17	part of the m at 7.19-7.15	H-16, H-15

[a] Recorded at 600 MHz. [b] Methylene protons are designated H-Xa and H-Xb arbitrarily

[c] Only those correlations which could be unambiguously assigned are reported.



Proton No.	^{1}H δ (ppm) (mult: *J* (Hz))[b,c,d]	NOESY Correlation
H-3	7.25 (d, *J* = 4.7 Hz, 2H)	H-6, H-7, H-8
H-6	1.30 (s, 1H)	H-8, H-3, H-9
H-7	1.26 (s, 1H)	H-8, H-3, H-9
H-8	2.76-2.64 (m, 1H)	H-6, H-7, H-13a, H-13b
H-9	5.48 (d, *J* = 10.4 Hz, 1H)	H-6, H-7
H-10	5.81-5.77 (m, 1H)	H-11
H-11	2.19-2.03 (m, 2H)	H-10, H-12, H-15
H-12	2.83-2.77 (m, 1H)	H-13a, H-13b, H-11
H-13	H-13a : 1.69-1.68 (m, 1H) H-13b : 1.43 (q, *J* = 12.4 Hz, 1H)	H-8, H-15
H-15	part of the m at 7.19-7.15	H-13, H-11, H-12

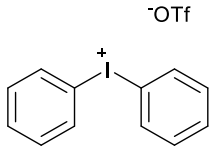
[a] Recorded at 600 MHz. [b] Assignments based on HSQC and HMBC data

[c] Methylene protons are designated H-Xa and H-Xb arbitrarily

[d] Only those correlations which could be unambiguously assigned are reported.

3.7 Copper catalyzed pyridylic arylation: Procedures and Structural Data

Synthesis of diphenyliodoniuim triflate (CAS 16668-99-8)**:**



A solution of iodobenzene (800 mg, 3.90 mmol, 1.00 equiv.), benzene (398 mg, 5.10 mmol, 1.30 equiv.), and DCM (16.00 mL) was cooled to 0°C and stirred for 5 mins. mCPBA (744 mg, 4.30 mmol, 1.10 equiv.) was added portion wise. Triflic acid (1.18 g, 7.84 mmol, 2.00 equiv.) was added dropwise and the mixture was allowed to warm to r.t. and stir overnight. The solvent was evaporated under reduced pressure. Diethyl ether was added and the crystals were collected by filtration, and purified by washing with diethyl ether. These crystals were then dried to afford diphenyliodonium triflate (1.46 g, 86%) as white crystals. Spectral data obtained is consistent with that previously reported.[42]

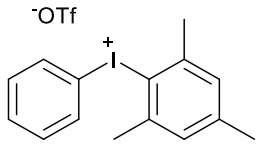
^{1}H-NMR (400MHz, $CDCl_3$)

δ 7.97 (d, *J* = 9.2Hz, 2H), 7.62 (t, *J* = 7.6Hz, 1H), 7.46 (t, *J* = 15.6Hz, 2H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 136.4, 133.7, 133.2, 121.8, 115.9

Synthesis of mesityl(phenyl)iodonium triflate (CAS 144930-50-7)**:**



A solution of iodobenzene (600 mg, 2.90 mmol, 1.00 equiv.), mesitylene (460 mg, 3.82 mmol, 1.30 equiv), and DCM (11.60 mL) was cooled to 0°C and stirred for 5 mins. mCPBA (660 mg, 3.82 mmol, 1.30 equiv.) was added portion wise. Triflic acid (870 mg, 5.80 mmol, 2.00 equiv.) was added dropwise and the mixture was allowed to warm to r.t. and stir overnight. The solvent was evaporated under reduced pressure. Diethyl ether was added and the solvent was removed under reduced pressure, and this procedure was repeated several times. The solution was then stored at 0°C for 1 h. The resulting crystals were filtered, washed with diethyl ether, and dried to afford mesityl(phenyl)iodonium triflate (909 mg, 69%) as white crystals. Spectral data obtained is consistent with that previously reported.[43]

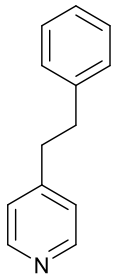
^{1}H-NMR (400MHz, $CDCl_3$)

δ 7.65 (d, *J* = 7.6Hz, 2H), 7.55 (t, *J* = 10.0Hz, 1H), 7.42 (t, *J* = 10.4Hz, 2H), 7.12 (s, 2H), 2.61 (s, 6H), 2.36 (s, 3H)

^{13}C-NMR (100MHz, $CDCl_3$)

δ 144.4, 142.5, 133.0, 132.2, 131.7, 130.3, 120.3 111.7, 27.0, 21.0

Synthesis of 4-phenylethylpyridine (CAS 2116-64-5)**:**



Diisopropylamine (606 mg, 3.54 mmol, 1.10 equiv.) and THF (3.57 mL) were cooled to -78°C and n-BuLi (1.6 M in hexane, 2.00 mL, 3.22 mmol) was added dropwise. This was stirred for 15 mins. and 4-methylpyridine (300 mg, 3.22 mmol, 1.00 equiv.) in THF (3.57 mL) was added dropwise and stirred for 15 min. This solution was then added dropwise to a flask containing bromobenzene (441 mg, 3.22 mmol, 1.00 equiv.) in THF (3.57 mL). The resulting mixture was stirred for 1 h at -78°C and warmed to r.t. overnight. The reaction mixture was quenched with water, extracted with EtOAc (3x) and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The crude solid was dissolved in minimal DCM and treated with pentane. The suspension was filtered through a cotton plug and the concentrated to afford 4-phenylethylpyridine (489 mg, 83%) as white crystals. Spectral data obtained is consistent with that previously reported.[44]

^{1}H-NMR (400MHz, $CDCl_3$)

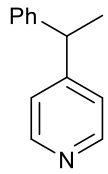
δ 8.46 (d, *J* = 6.0Hz, 2H), 7.26 (m, 2H), 7.19 (m, 1H), 7.13 (d, *J* = 7.2Hz, 2H),

7.06 (d, *J* = 6.0 Hz, 2H), 2.91, (s, 4H)

General Procedure 8: Copper catalyzed pyridylic arylation.

A dry and argon flushed RBF, equipped with a magnetic stirrer and a septum was charged with triethylamine (198 mg, 1.96 mmol, 3.00 equiv.), the pyridine species (1.00 equiv.), and THF (6.50 mL). The resulting solution was stirred at r.t. for 2 mins and ethyl chloroformate (142 mg, 1.31 mmol, 2.00 equiv.) was added dropwise. After 30 mins the solvent was evaporated under reduced pressure. The resulting mixture of the ADHP intermediate and triethylammonium chloride salt was triturated using diethyl ether and filtered through a cotton plug and the filtrate was concentrated *in vacuo*. The crude intermediate was dissolved in THF (1.00 mL) and was kept under an inert atmosphere of argon. To an oven-dried RBF $Cu(OTf)_2$ (23 mg, 0.0064 mmol, 0.10 equiv.), biphenyl iodonium triflate (303 mg, 0.70, 1.10 equiv.), and DCM (5.40 mL) were added under argon. The resulting solution was allowed to stir at r.t. for 20 mins. The solution of ADHP was then transferred to the flask containing the copper species and this was left to stir overnight. The mixture was then quenched with 15% NH_4OH in water and extracted with DCM (3x). It was then washed with brine and dried over anhydrous $MgSO_4$. After filtration, the solution was concentrated under reduced pressure and purified by column chromatography.

Synthesis of 4-(1-Phenylethyl)pyridine (18a CAS 42362-47-0**):**



Using the **General Procedure 8,** 4-ethylpyridine (70 mg, 0.65 mmol, 1.00 equiv.) afforded 4-(1-Phenylethyl)pyridine (18 mg, 15%) purified by column chromatography (hexanes/ EtOAc, 3:1) (R_f = 0.2) as a yellow oil. Spectral data obtained is consistent with that previously reported.[45]

^{1}H-NMR (400MHz, $CDCl_3$)

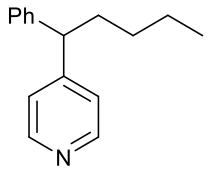
δ 8.47 (d, *J* = 6.0Hz, 2H), 7.29 (t, *J* = 7.2Hz, 2H), 7.22-7.21 (m, 3H),

7.11 (d, *J* = 6.0Hz, 2H), 4.10 (q, *J* = 6.0Hz, 1H), 1.62 (d, *J* = 7.2Hz, 3H)

^{13}C-NMR (100MHz, $CDCl_3$)

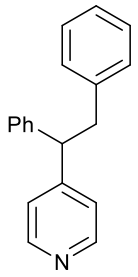
δ 154.9, 149.5, 144.3, 128.7, 127.6, 126.4, 122.8, 44.8, 21.0

Synthesis of 4-(1-Phenylpentyl)pyridine (CAS 857221-78-4)**:**



Using the **General Procedure 8,** 4-pentylpyridine (70 mg, 0.47, 1.00 equiv.) afforded 4-(1-Phenylpentyl)pyridine (27 mg, 25%) purified by column chromatography (hexanes/ EtOAc, 2:1) (R_f = 0.2) as a yellow oil.

Synthesis of 4-(1,2-Diphenylethyl)pyridine (CAS 6634-61-3)**:**



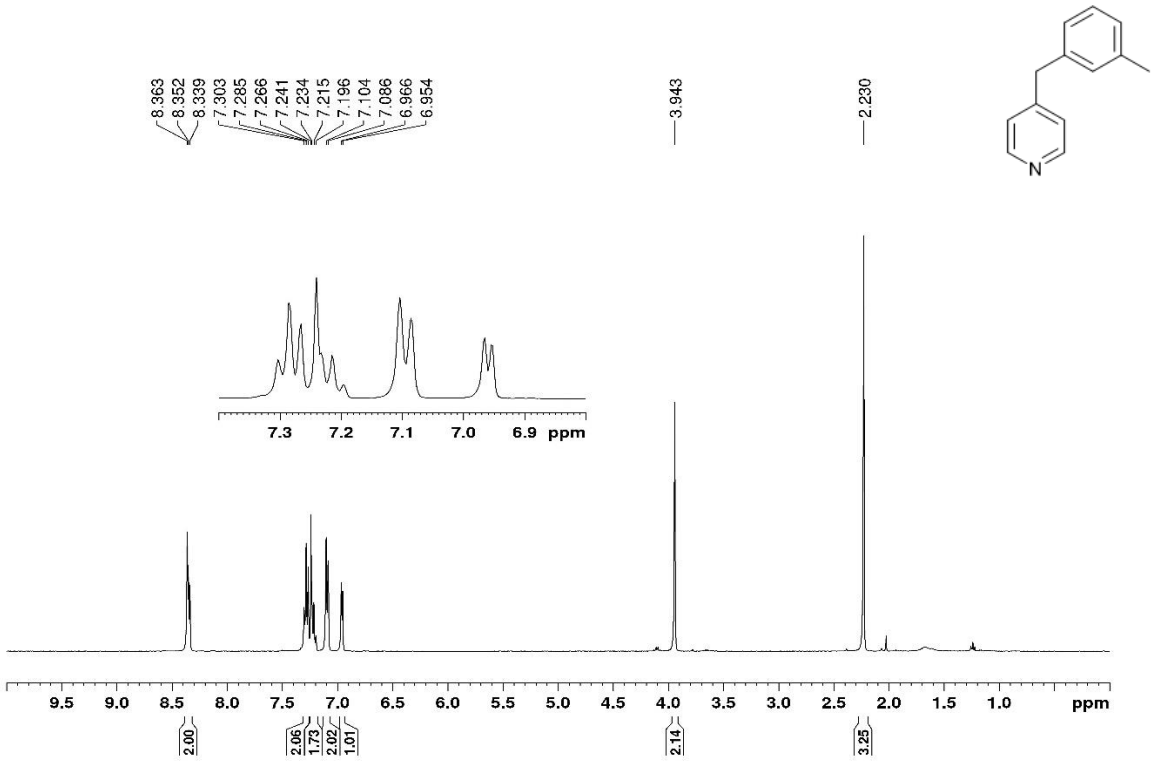
Using the **General Procedure 8,** 4-phenylethylpyridine (60 mg, 0.33, 1.00 equiv.) afforded 4-(1,2-Diphenylethyl)pyridine (40 mg, 40%) purified by column chromatography (hexanes/ EtOAc, 1:1) (R_f = 0.2) as a yellow solid.

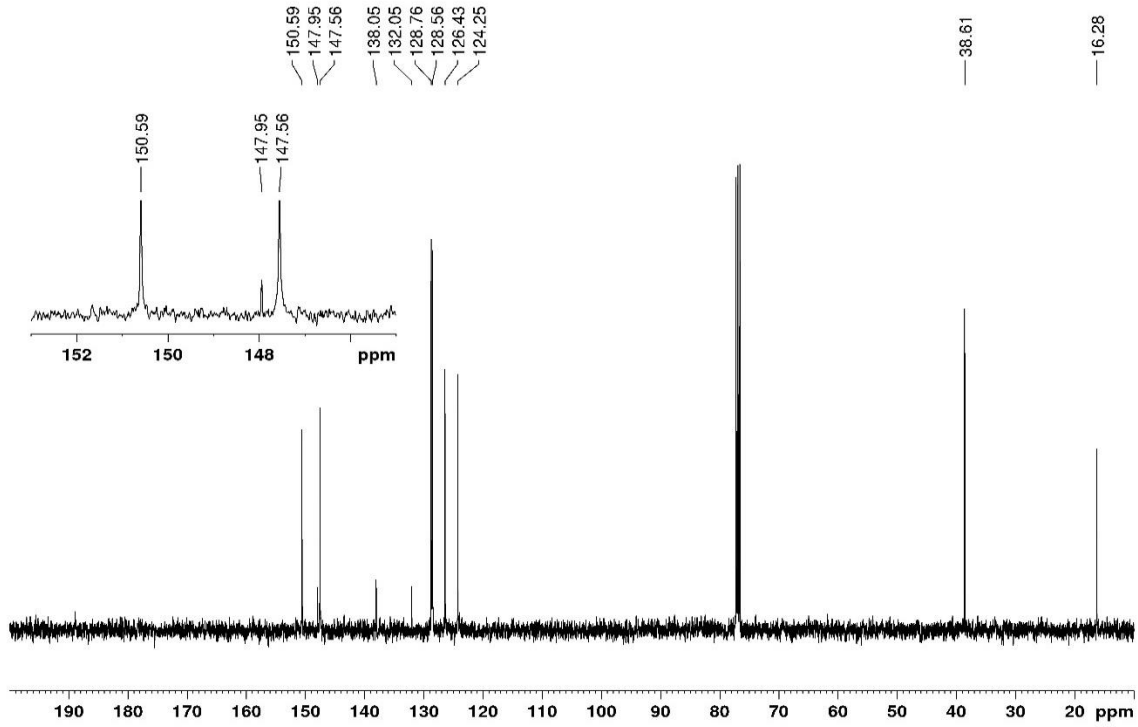
References

1. Janvier, P.; Sun, X.; Bienayme, H.; Zhu, J. *J. Am. Chem. Soc* **2002**, *124*, 2560.
2. Mills, A. D.; Nazer, M. .; Kurth, M. . *J. Org. Chem.* **2006**, *71*, 2687.
3. Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem* **2014**, *57*, 10257.
4. Foley, D. J.; Nelson, A.; Marsdon, S. P. *Angew. Chemie. Int. Ed.* **2016**, *55*, 13650.
5. Wolfe, J.; Li, J. *Tetrahedron Lett.* **2007**, *26*, 1.
6. Nguyen, L.; He, H.; Pham-Huy, C. *Int. J. Biomed. Sci.* **2006**, *2*, 85.
7. Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc* **2008**, *130*, 14092.
8. Murakami, R.; Sano, K.; Iwai, T.; Taniguchi, T.; Monde, K.; Sawamura, M. *Angew. Chemie. Int. Ed.* **2018**, *57*, 9465.
9. Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc* **2007**, *129*, 4138.
10. Moon, P. J.; Wei, Z.; Lundgren, R. J. *J. Am. Chem. Soc* **2018**, *140*, 17418.
11. Sha, S.; Zhang, J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc* **2013**, *135*, 17602.
12. Liu, X.; You, S. *Angew. Chemie. Int. Ed.* **2017**, *56*, 4002.
13. Rasheed, F. Mild and Selective Palladiuim-Catalyzed Pyridylic Allylation of 4-Alkylpyridines, York University, **2019**.
14. Wasfy, N. Palladium-Catalyzed Functionalization of 4-Alkylpyridines: Pyridylic Dehydrogenation & Mechanistic Investigation of Pyridylic Allylation, York University, **2020**.
15. Yao, B.; Liu, Y.; Zhao, L.; Wang, D.; Wang, M. *J. Org. Chem.* **2014**, *79*, 11139.
16. Chemler, S. *Beilstein J. Org. Chem.* **2015**, *11*, 2252.
17. Ribas, X.; Jackson, D. A.; Donnadieu, B.; Mahia, J.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. *Angew. Chemie. Int. Ed.* **2002**, *41*, 2991.
18. King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc* **2010**, *132*, 12068.
19. Hickman, A.; Sanford, M. *Nature* **2012**, *484*, 177.
20. Ribas, X.; Guell, I. *Pure Appl. Chem.* **2014**, *86*, 345.
21. Chen, B.; Hou, X.; Li, Y.; Wu, Y. *J. Am. Chem. Soc* **2011**, *133*, 7668.
22. Phipps, R.; Gaunt, M. *Science (80-.).* **2009**, *323*, 1593.
23. Deprez, N.; Sanford, M. *Inorg. Chem.* **2007**, *46*, 1924.
24. Lockhart, T. *J. Am. Chem. Soc* **1983**, *105*, 1940.

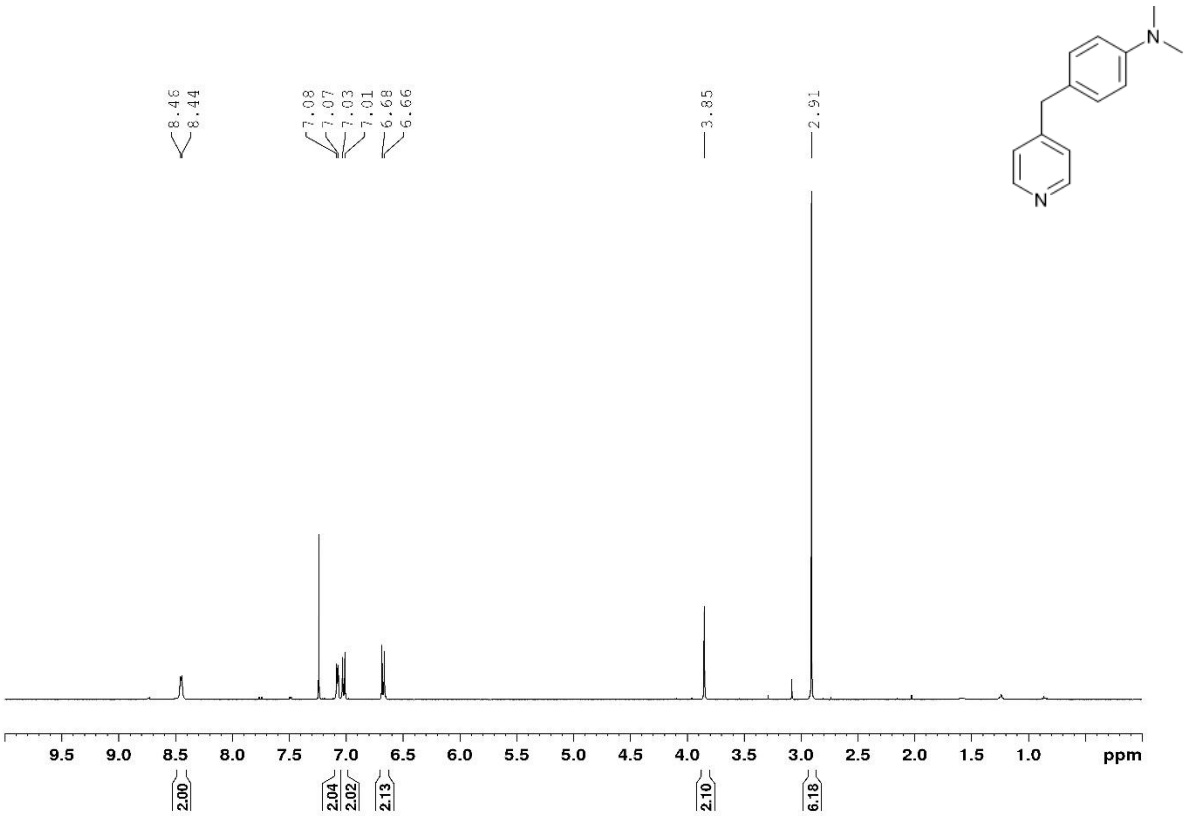
25. Cahard, E.; Bremeyer, N.; Gaunt, M. *Angew. Chemie. Int. Ed.* **2013**, *52*, 9284.
26. Duong, H.; Gilligan, R.; Cooke, M.; Phipps, R.; Gaunt, M. *Angew. Chemie. Int. Ed.* **2011**, *50*, 463.
27. Collins, B.; Suero, M.; Gaunt, M. *Angew. Chemie. Int. Ed.* **2013**, *52*, 5799.
28. Suero, M.; Bayle, E.; Collins, B.; Gaunt, M. *J. Am. Chem. Soc* **2013**, *135*, 5332.
29. Qian, X.; Han, J.; Wang, L. *Tetrahedron Lett.* **2016**, *57*, 607.
30. Yurino, T.; Ryutaro, T.; Ohkuma, T. *ACS Catal.* **2019**, *9*, 4434.
31. Panda, S.; Coffin, A.; Nguyen, N.; Tantillo, D.; Ready, J. *Angew. Chemie. Int. Ed.* **2016**, *55*, 2205.
32. Henry, N.; Enguehard-Gueiffier, C.; Thery, I.; Gueffier, A. *Eur. J. Org. Chem* **2008**, 4824.
33. Duez, S.; Steib, A. K.; Manolikakes, S. M.; Knochel, P. *Angew. Chemie. Int. Ed.* **2011**, *50*, 7686.
34. Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc* **1973**, *95*, 292.
35. Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc* **2007**, *129*, 7734.
36. van Leeuwen, P.; Kamer, P.; Reek, J.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741.
37. Rideau, E.; You, H.; Sidera, M.; Claridge, T. D.; Fletcher, S. P. *J. Am. Chem. Soc* **2017**, *139*, 5614.
38. Phipps, R.; Grimster, N.; Gaunt, M. *J. Am. Chem. Soc* **2008**, *130*, 8172.
39. Shing, T.; Chia, W.; Shiao, M.; Chau, T. *Synthesis (Stuttg).* **1991**, *10*, 849.
40. Wu, J.; Want, D.; Chen, X.; Gui, Q.; Li, H.; Tan, Z.; Huang, G.; Wang, G. *Org. Biol. Chem.* **2017**, *15*, 7509.
41. Velusamy, S.; Kumar, J.; Punniyamurthy, T. *Tetrahedron Lett.* **2004**, *45*, 203.
42. Soldatova, N.; Postnikov, P.; Yusubov, M.; Wirth, T. *Eur. J. Chem.* **2019**, *2019*, 2081.
43. Mayer, R.; Ofial, A.; Mayr, H.; Legault, C. *J. Am. Chem. Soc* **2020**, *142*, 5221.
44. Schmaunz, C. E.; Pabel, J.; Wanner, K. T. *Synthesis (Stuttg).* **2010**, *13*, 2147.
45. Sterckx, H.; Sambiagio, C.; Lemiere, F.; Tehrani, K.; Maes, B. *Synlett* **2017**, *28*, 1564.

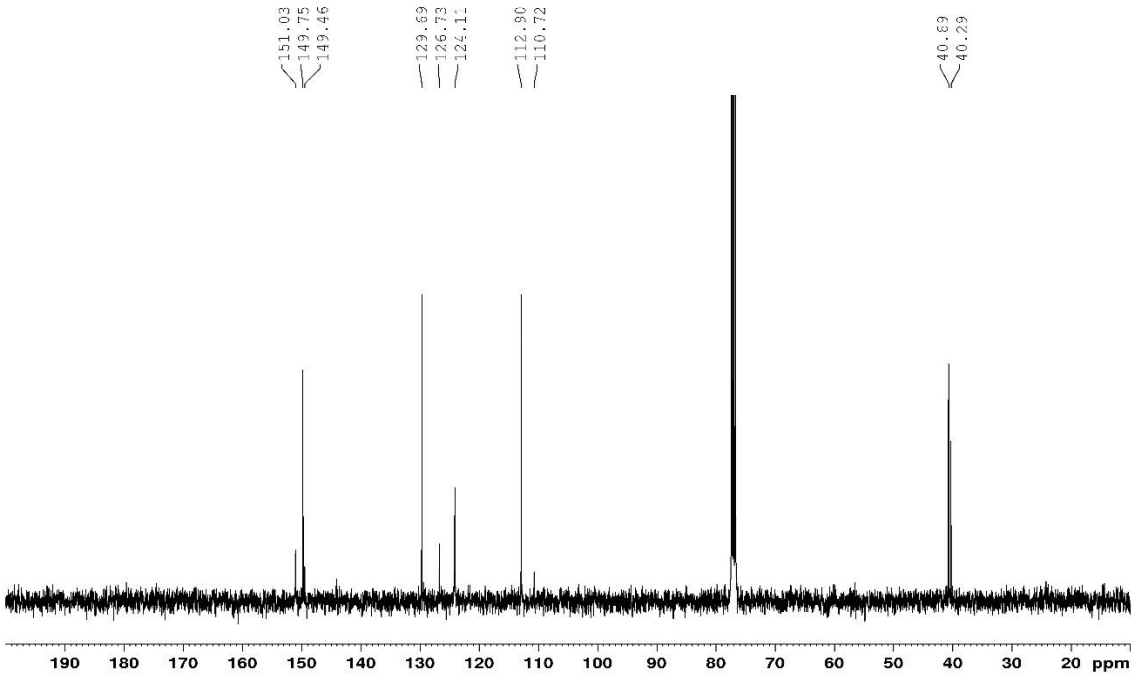
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **6**



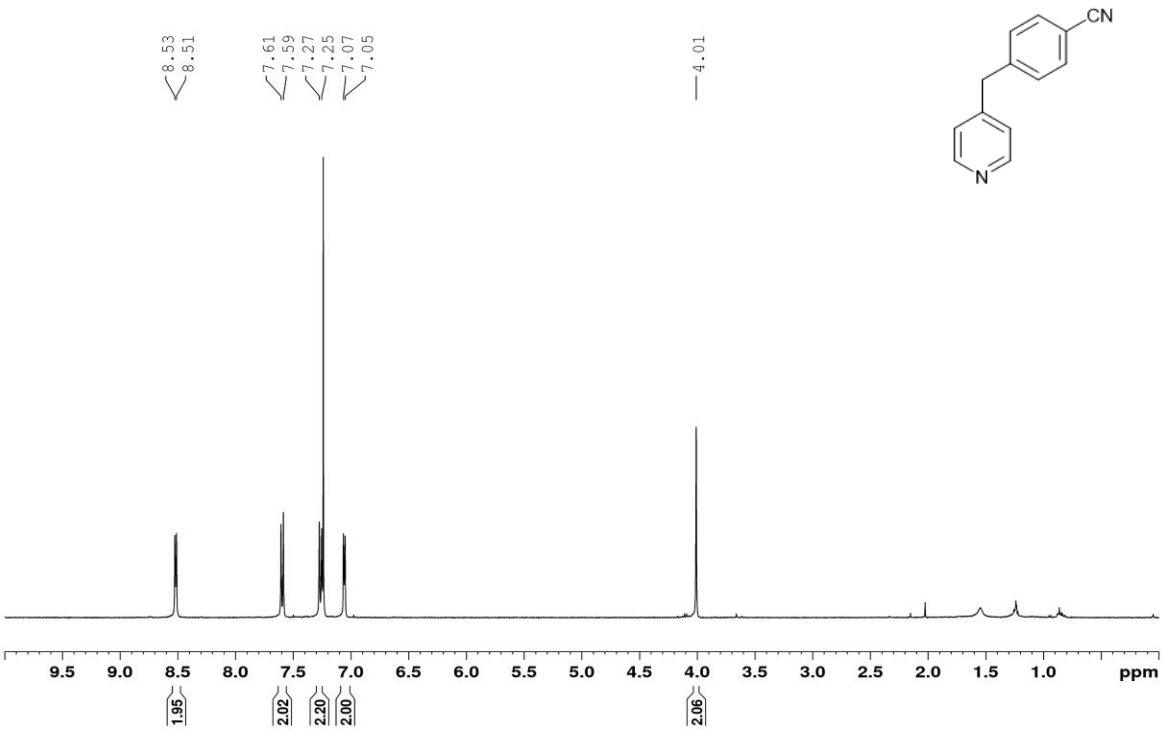


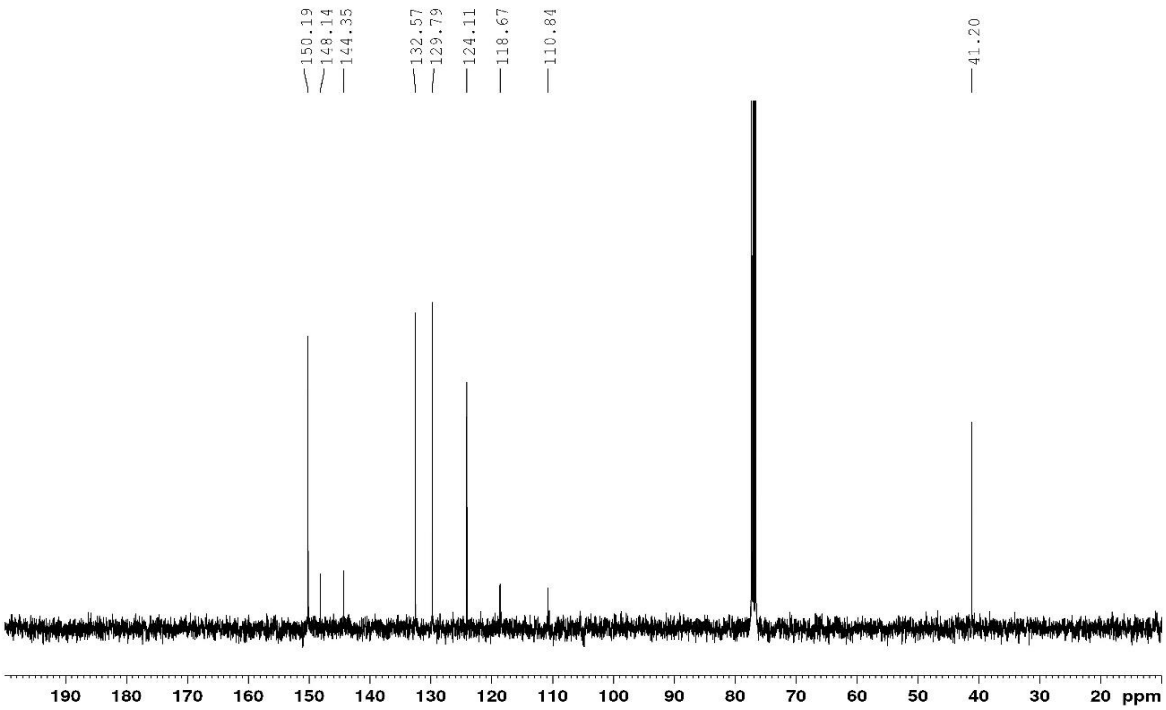
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **7**



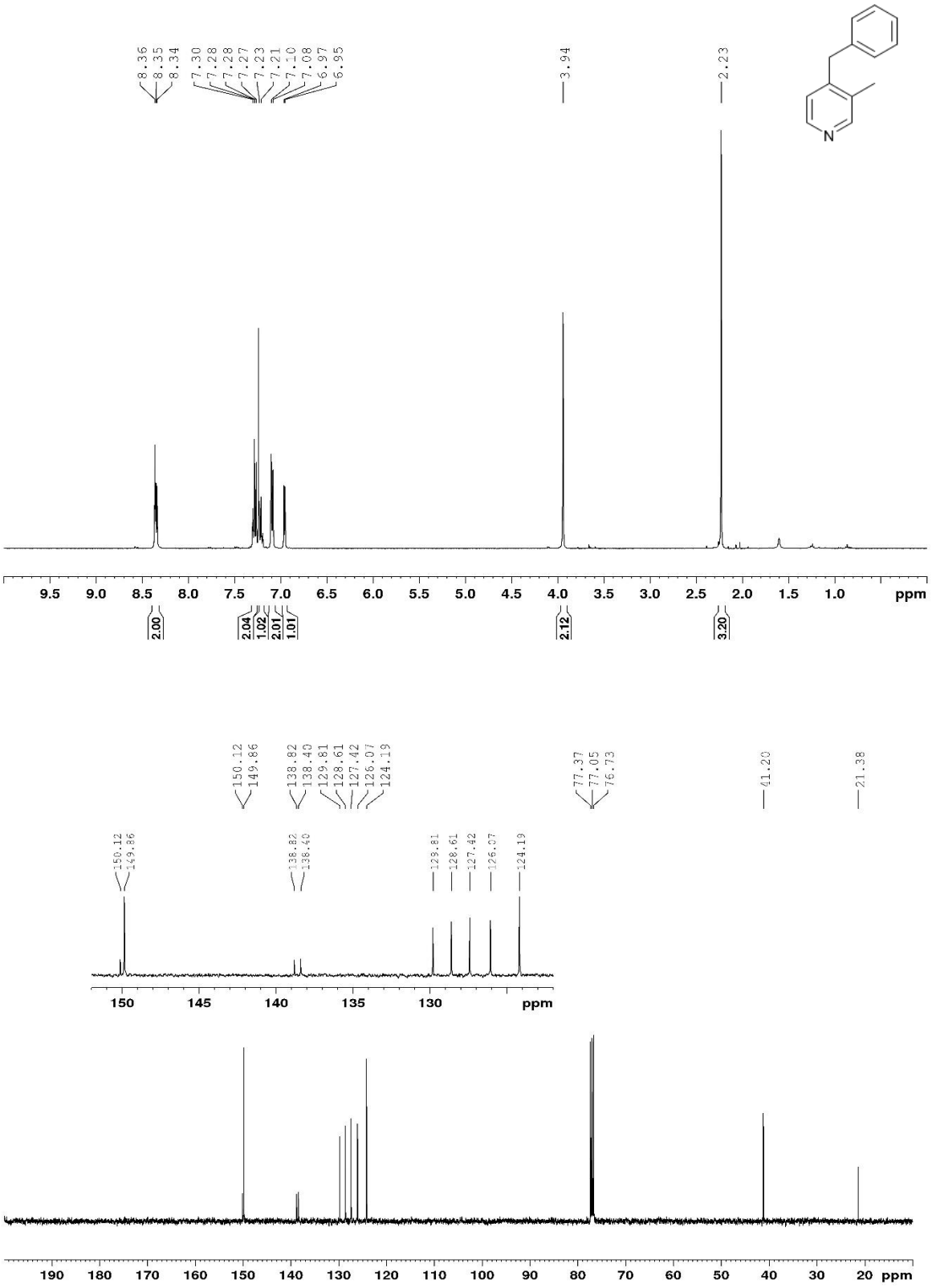


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **8**

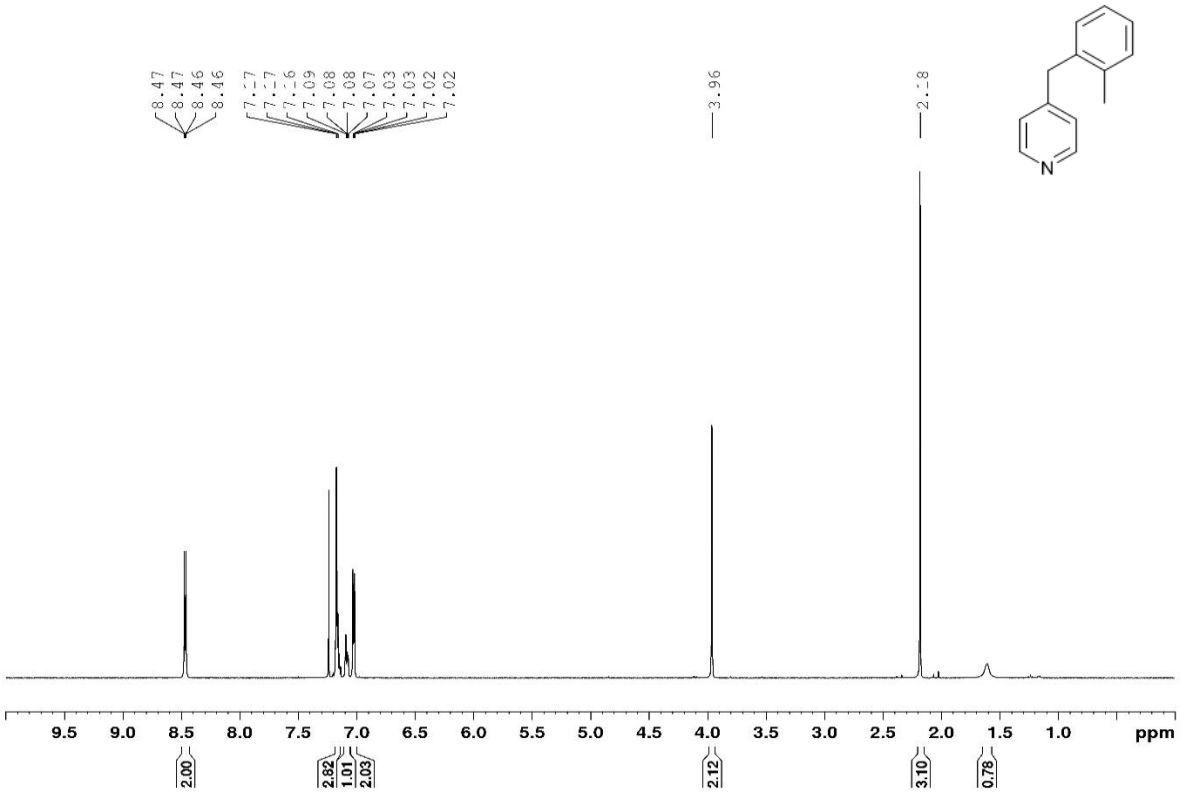


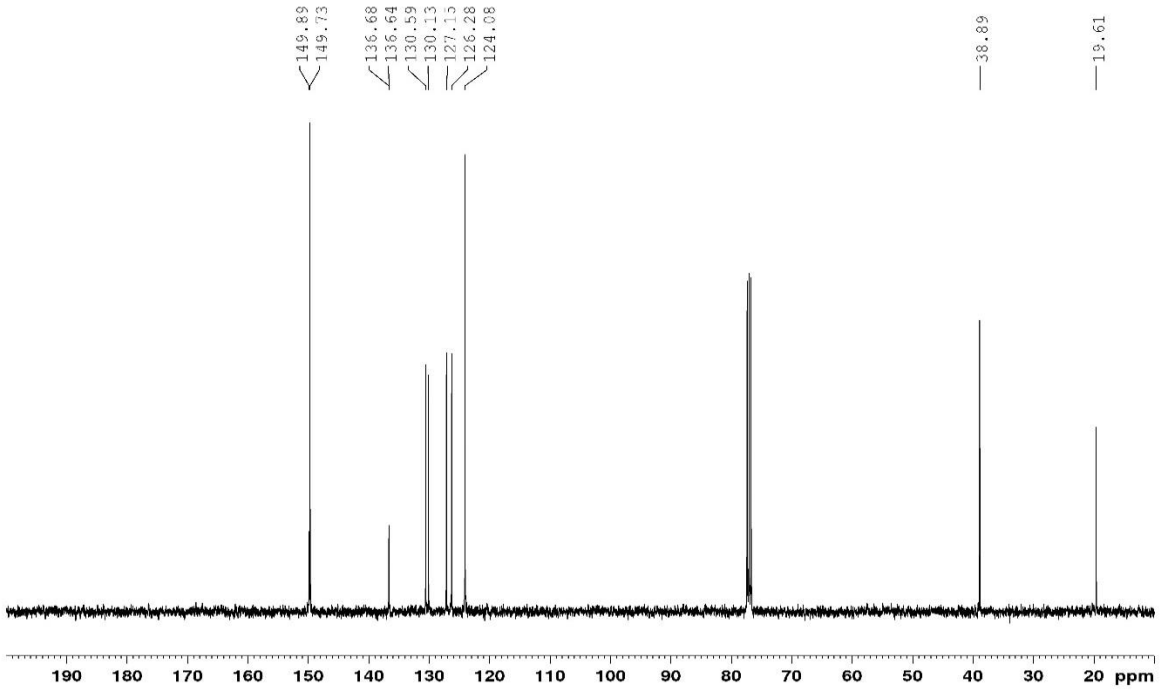


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **10**

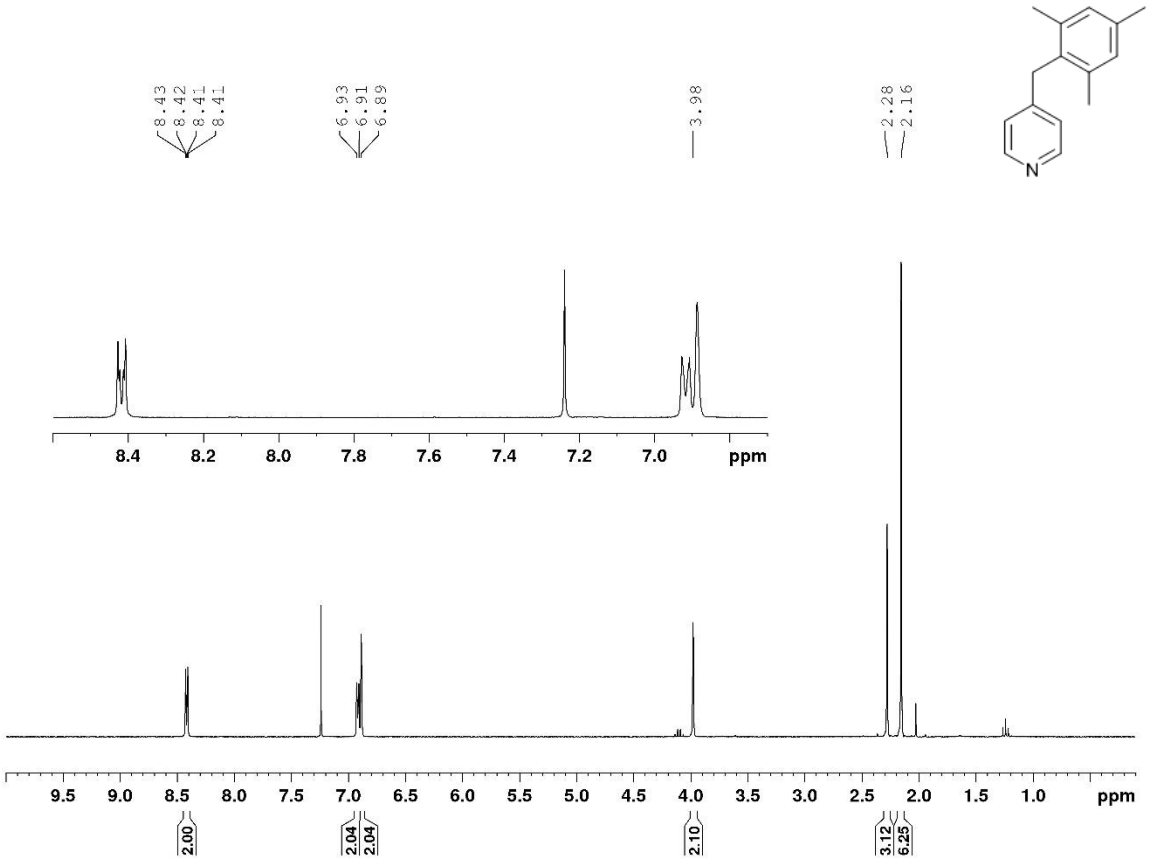


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **11**

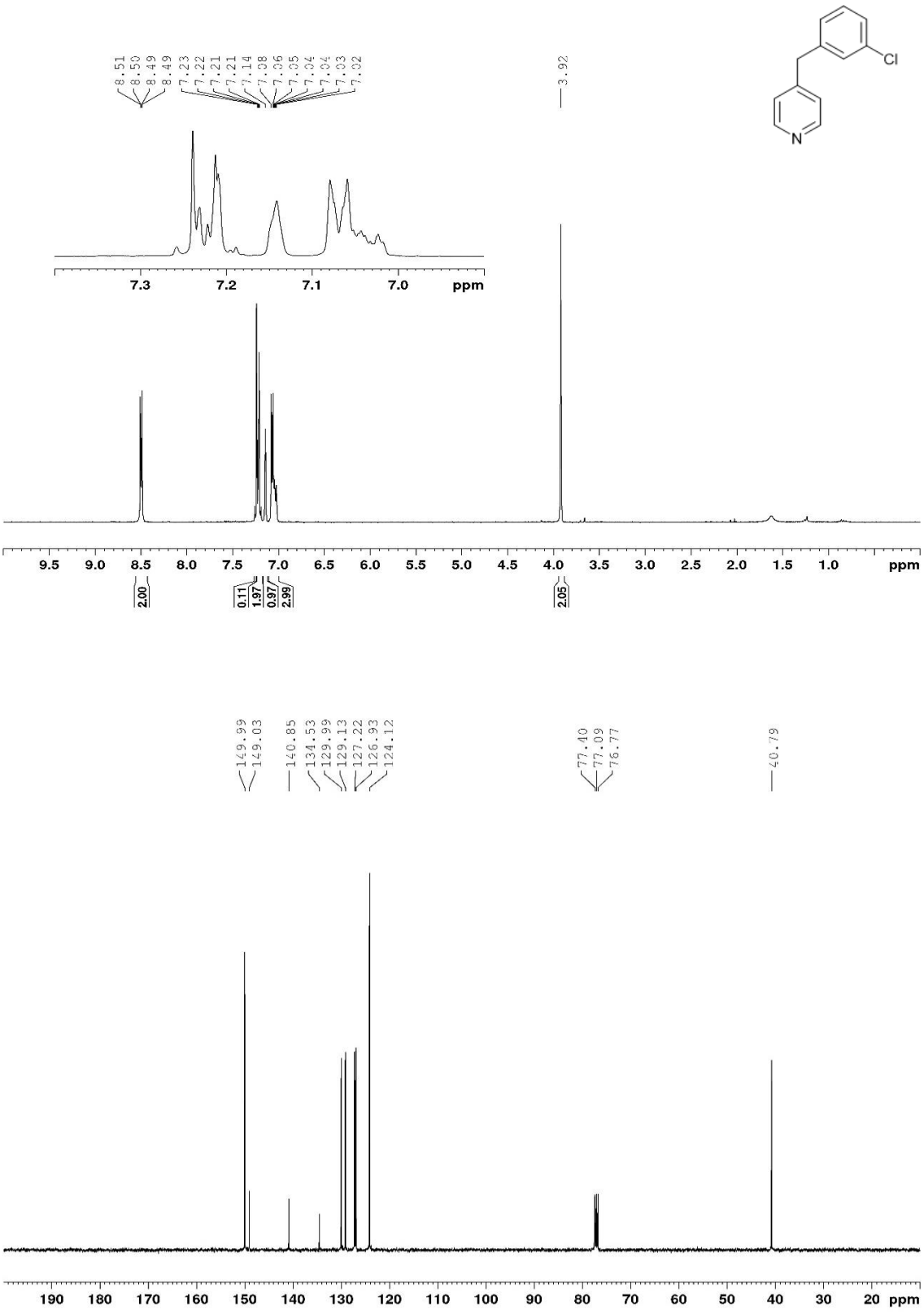




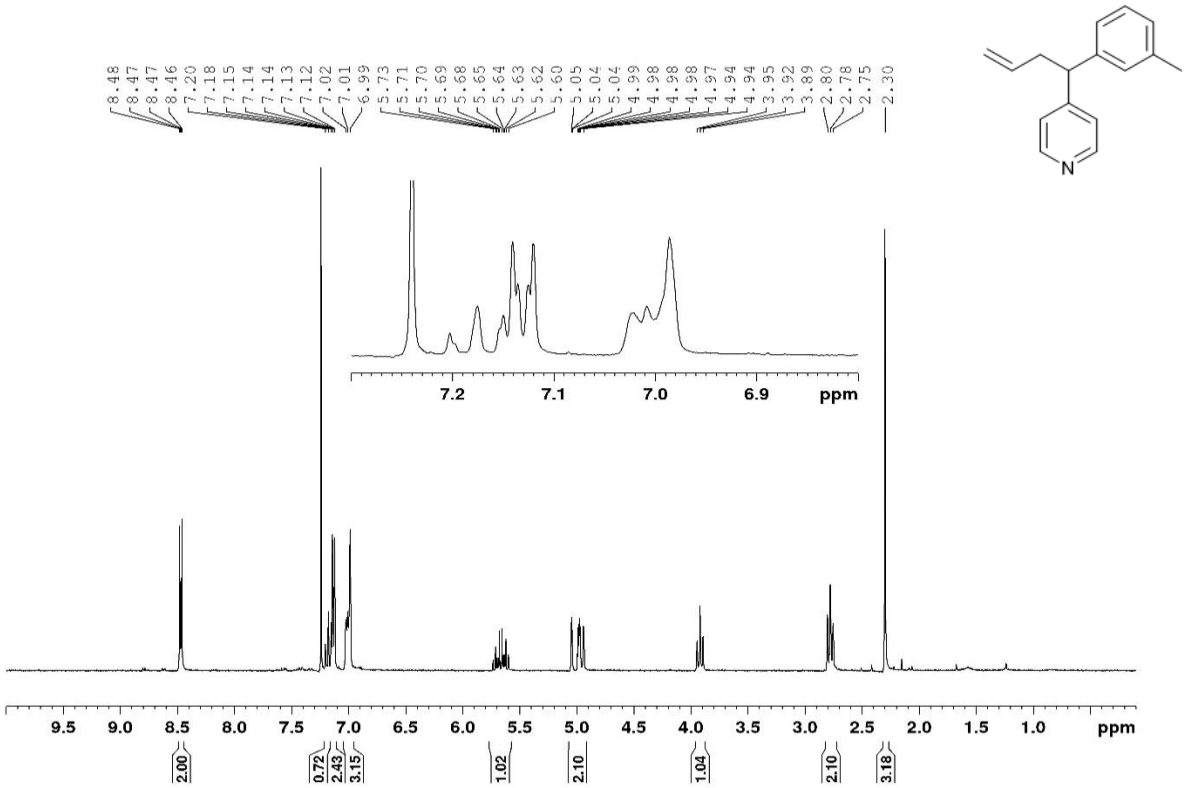
^{1}H (400 MHz, $CDCl_3$) – NMR spectra for **12**

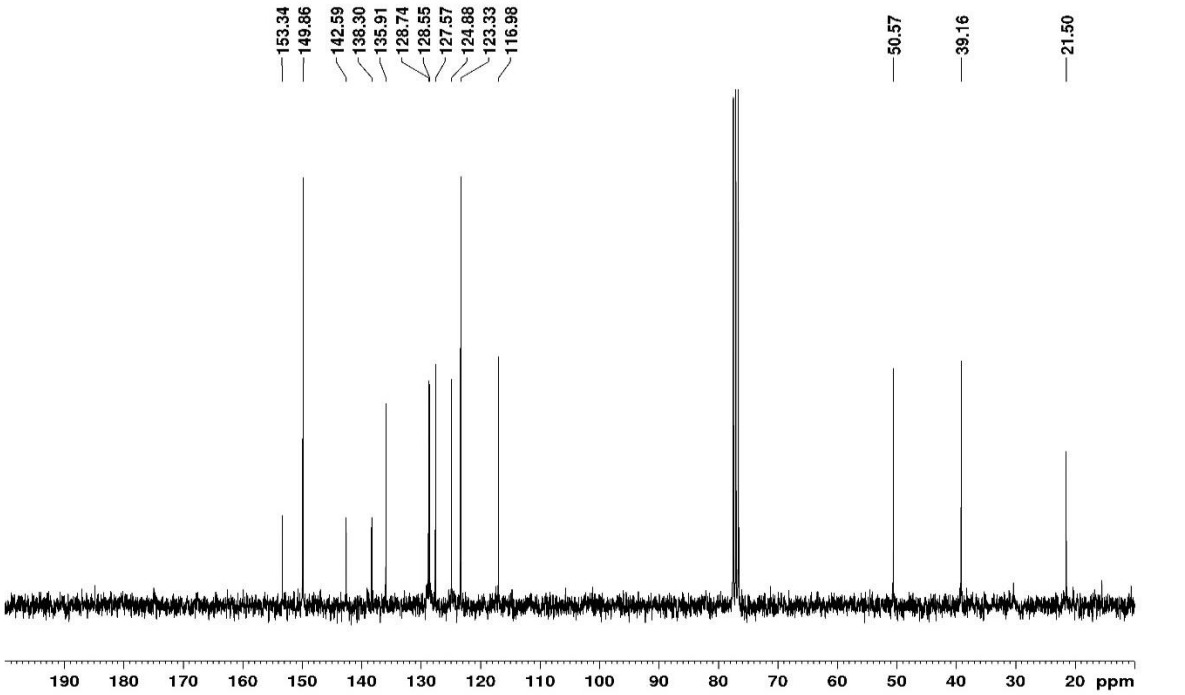


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **13**

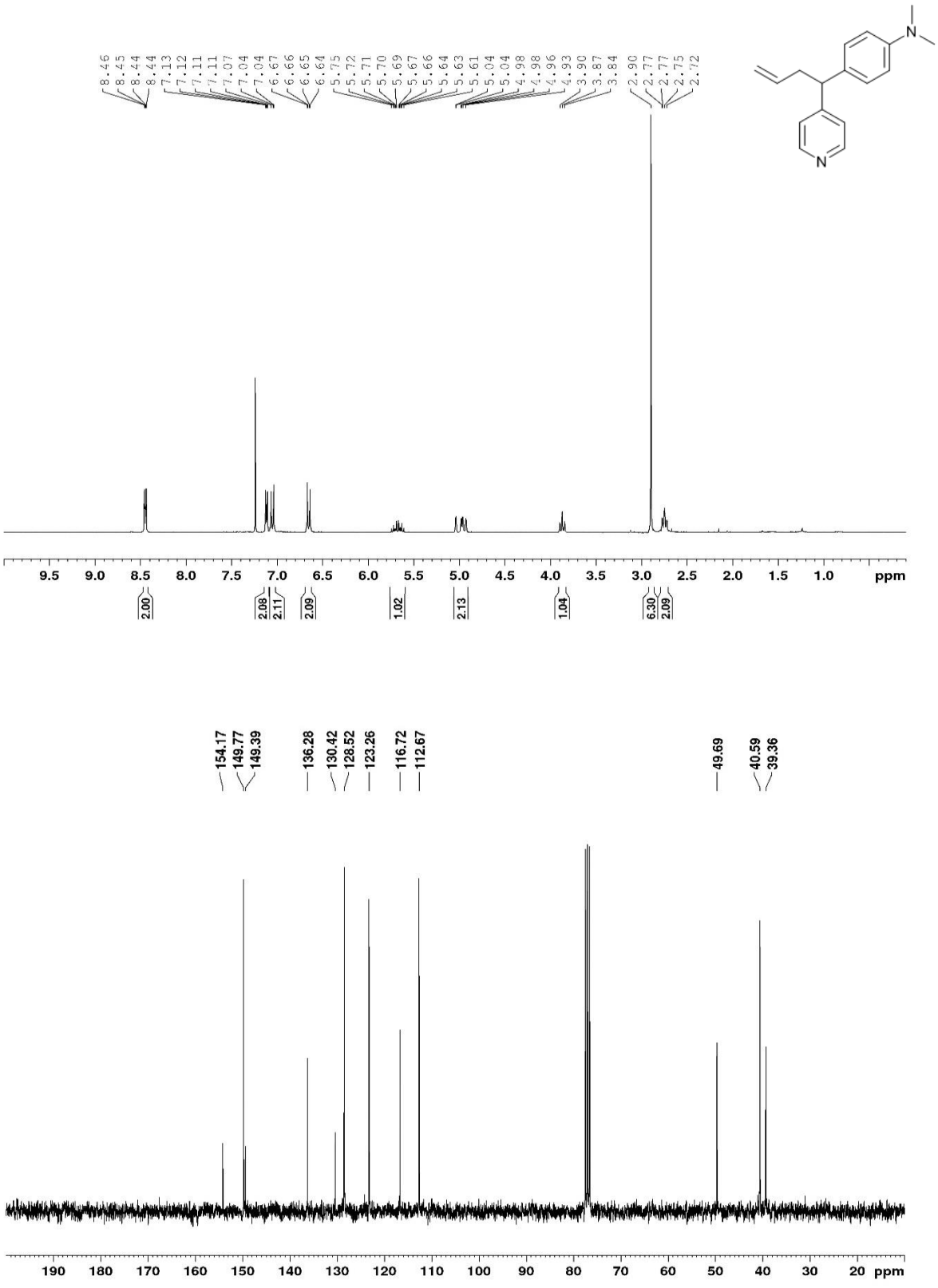


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **6a**

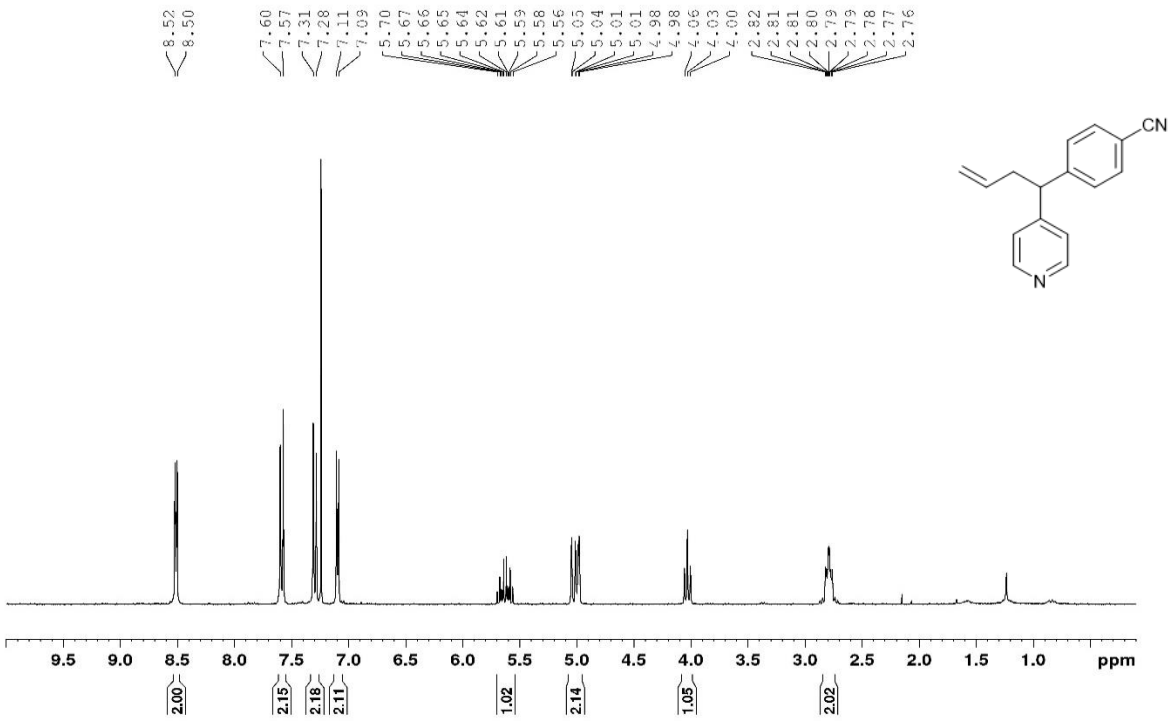


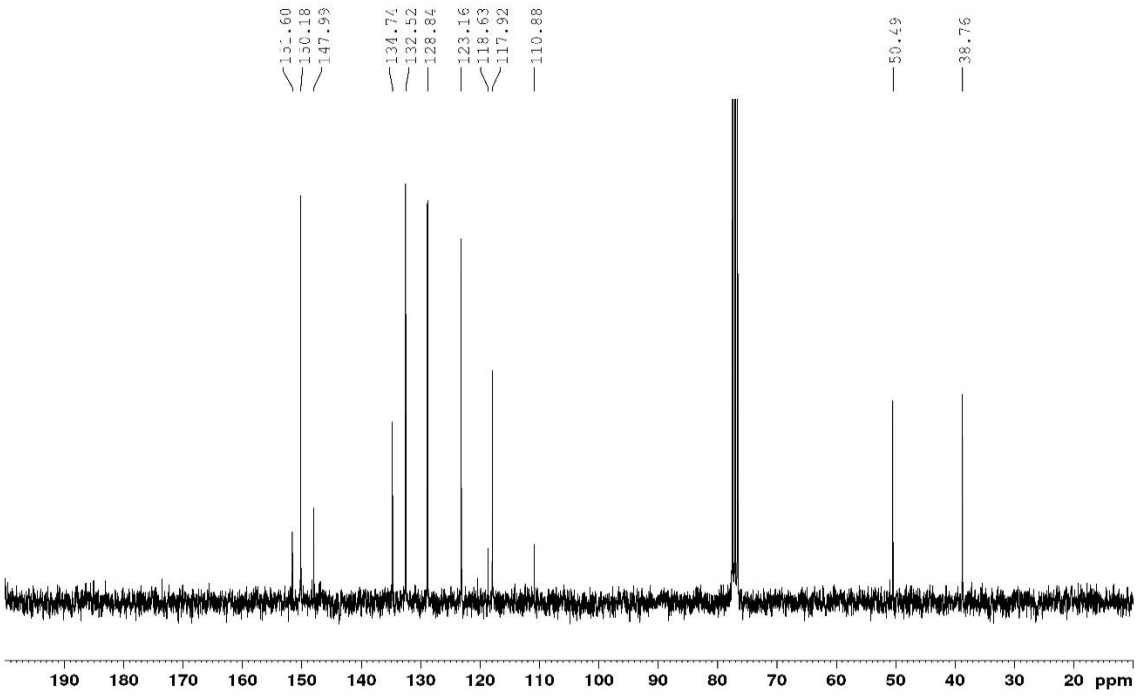


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **7a**

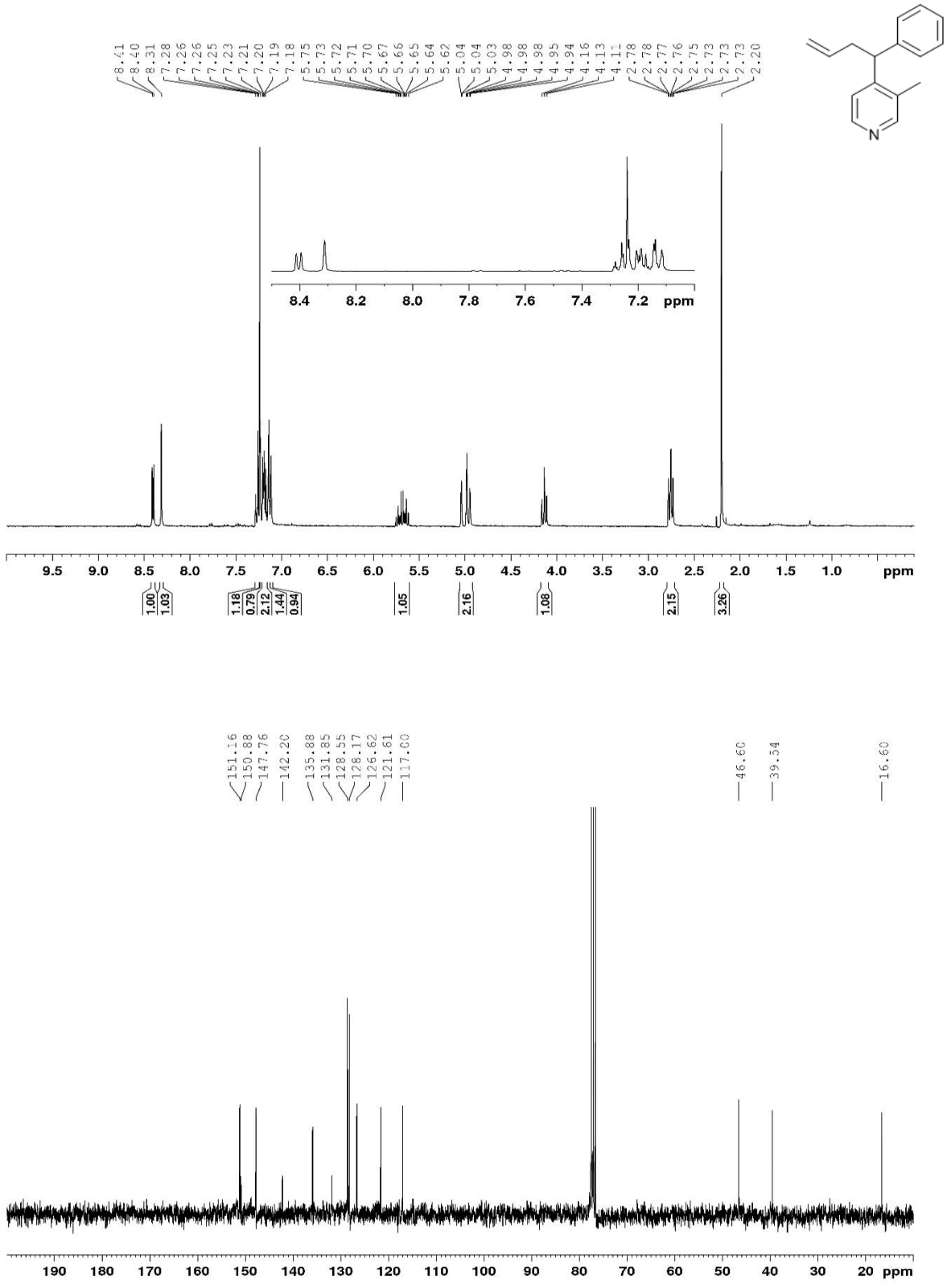


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **8a**

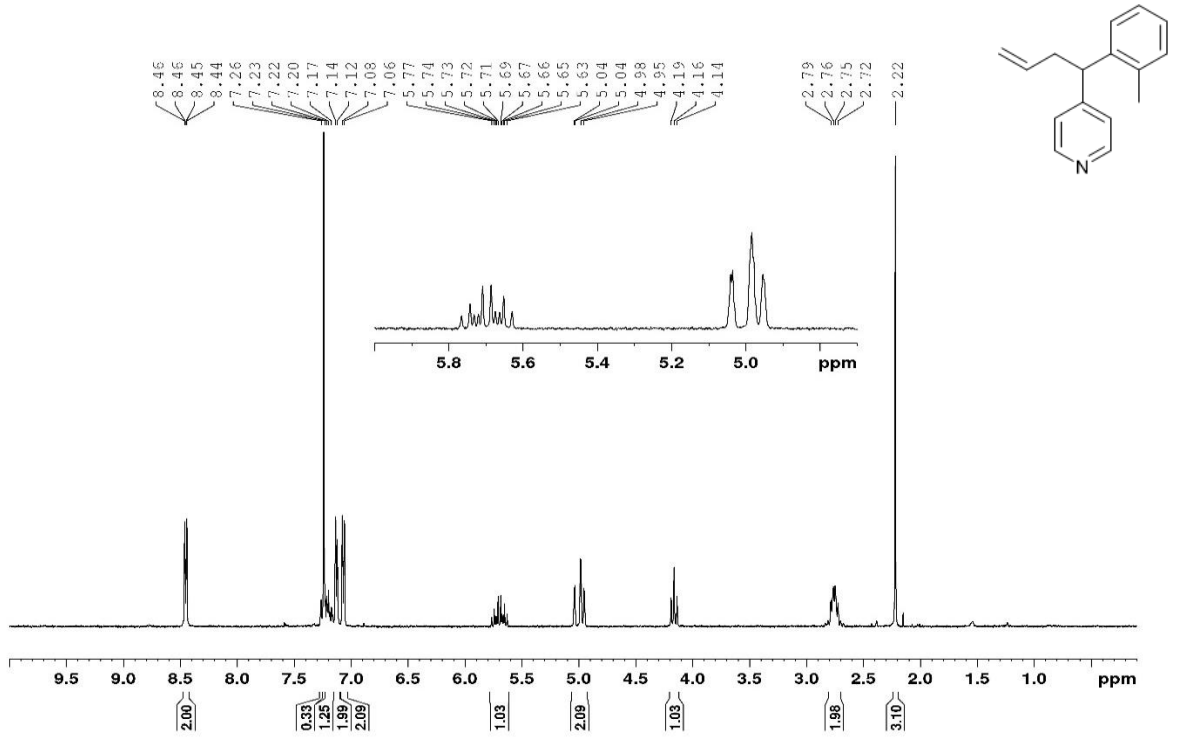


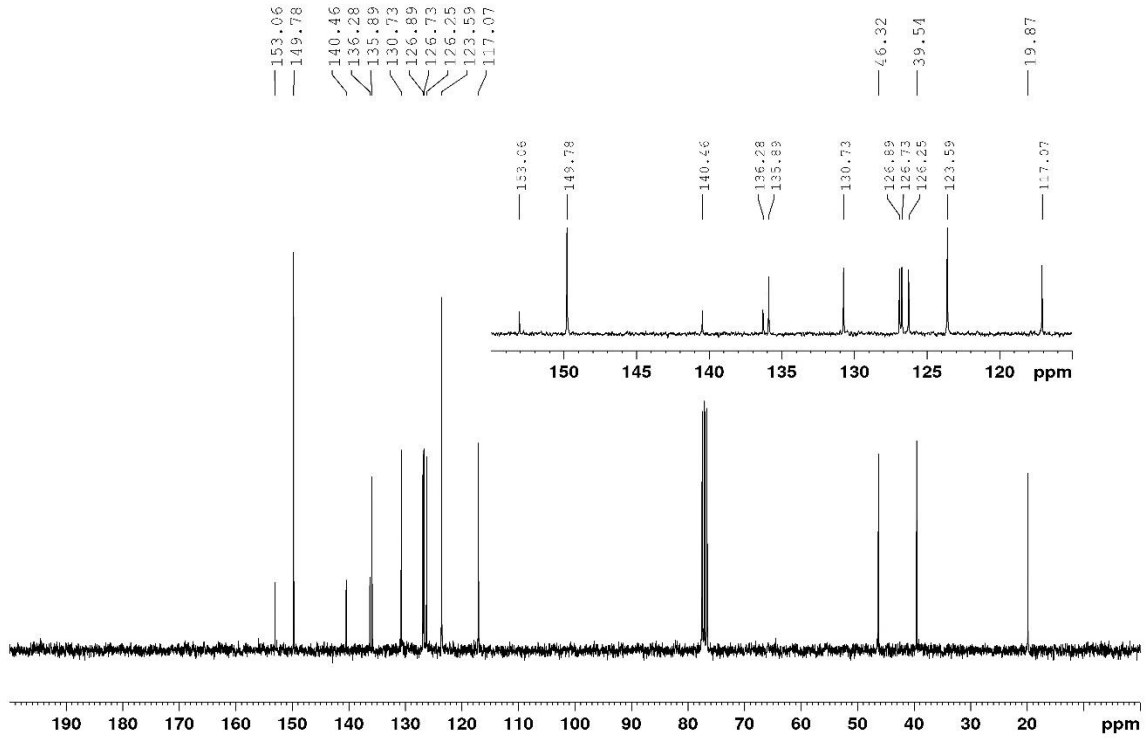


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **10a**

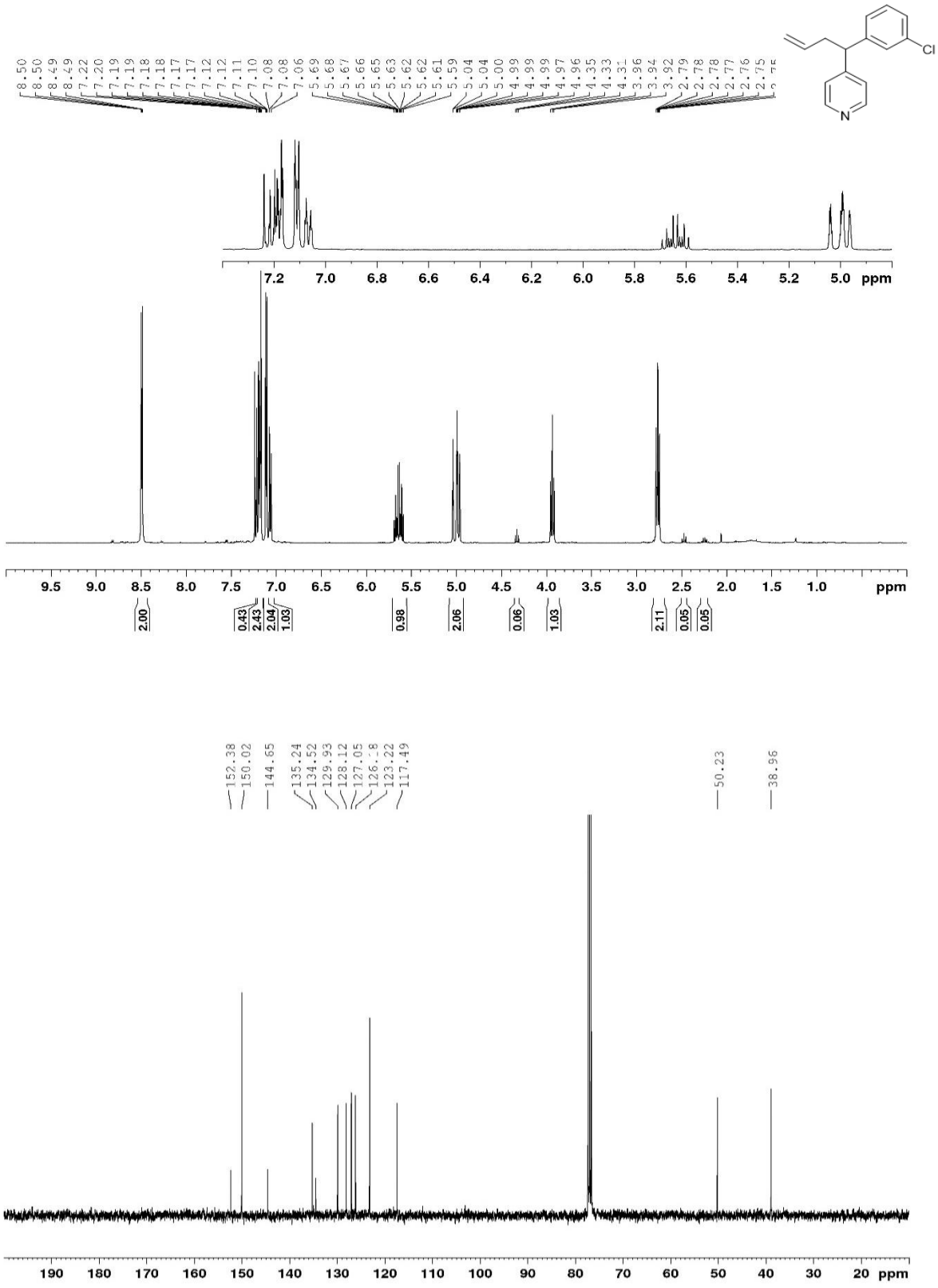


^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **11a**

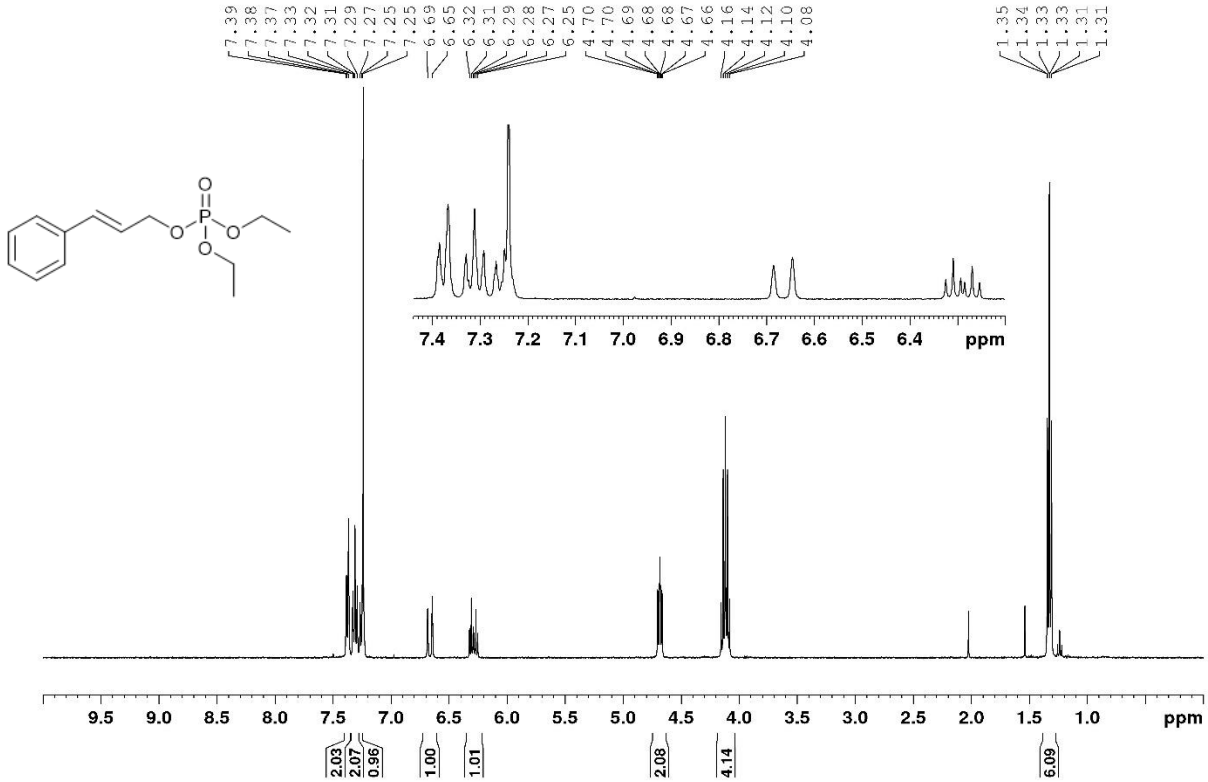




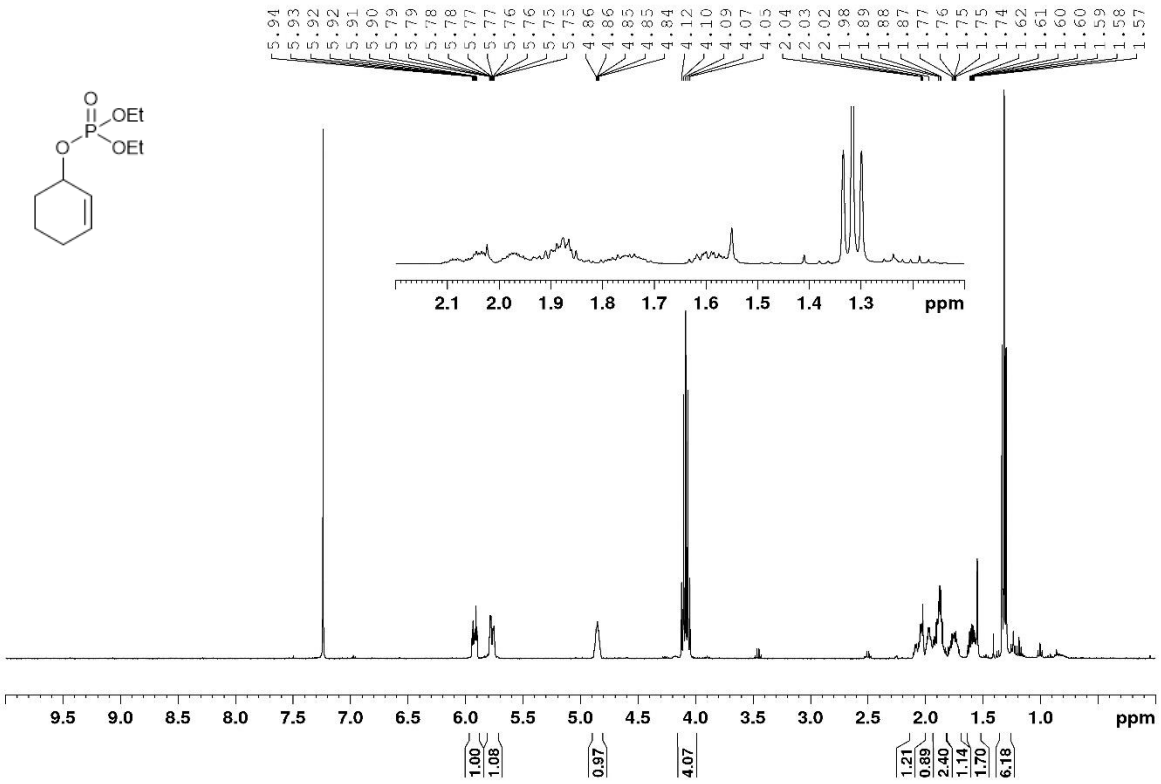
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **13a**



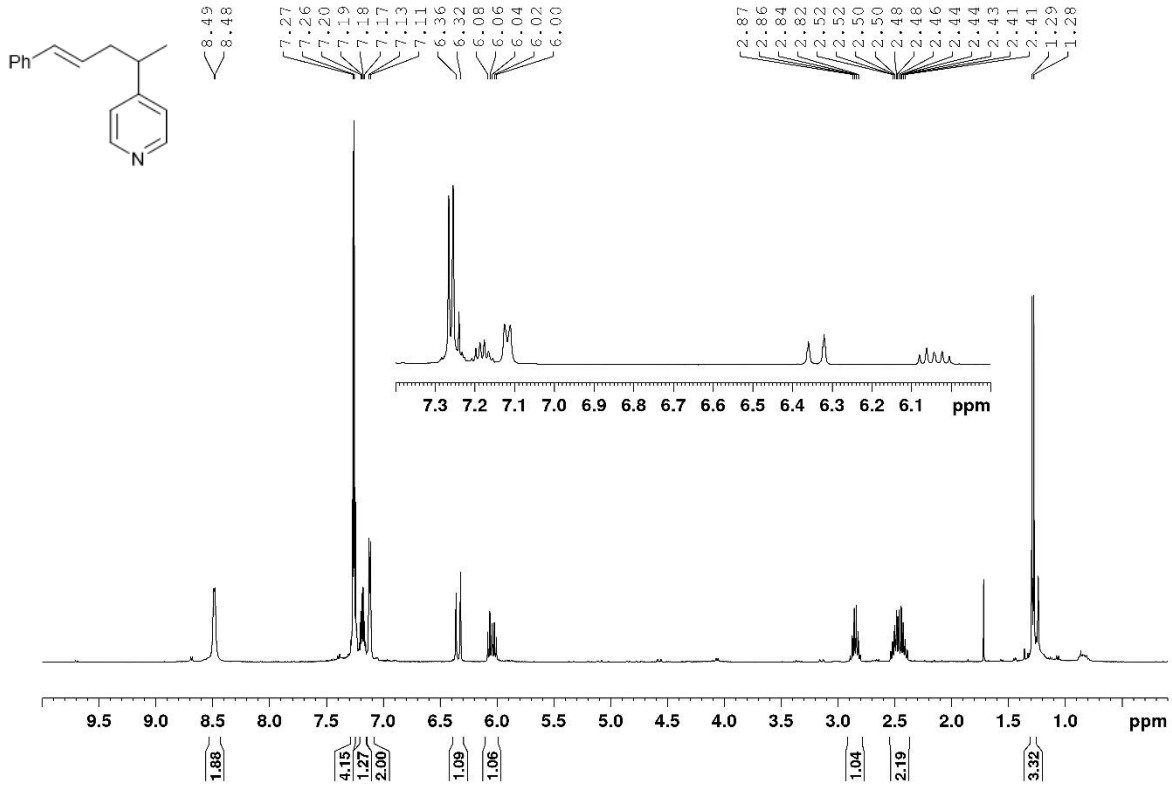
^{1}H (400 MHz, $CDCl_3$) – NMR spectra for **Cinnamyl Phosphonate**



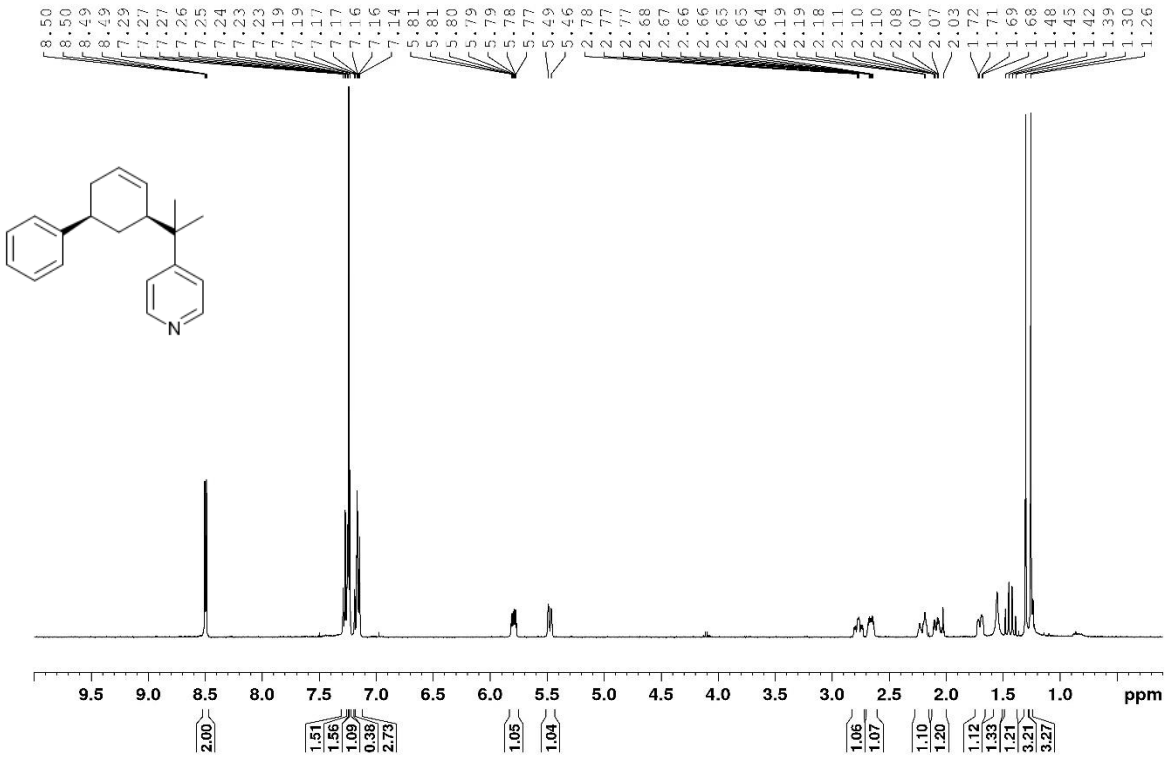
^{1}H (400 MHz, $CDCl_3$) – NMR spectra for **Phosphoric acid, 2-cyclohexen-1-yl diethyl ester**

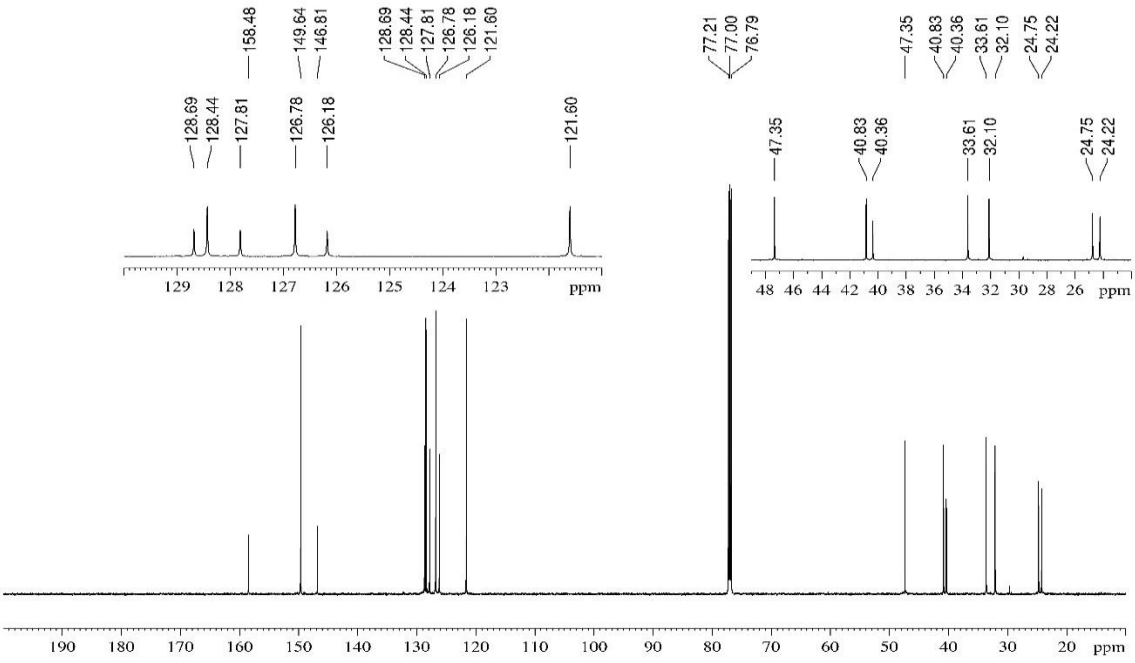


^{1}H (400 MHz, $CDCl_3$) – NMR spectra for **3a**

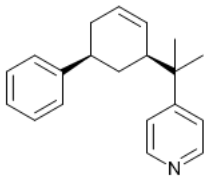


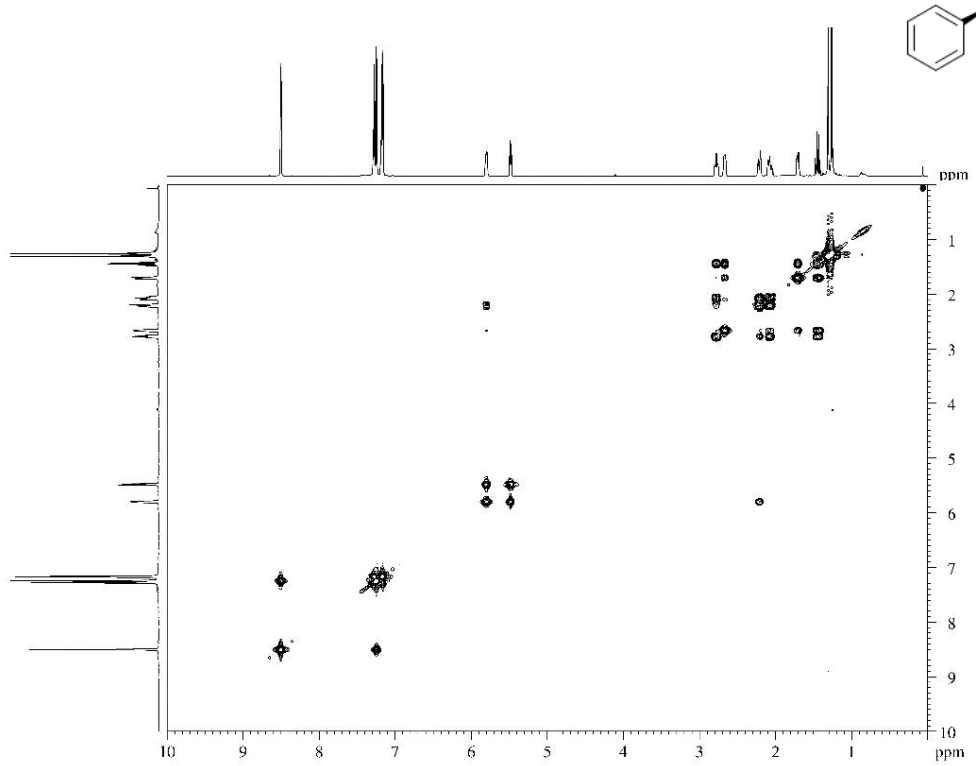
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for **15a**

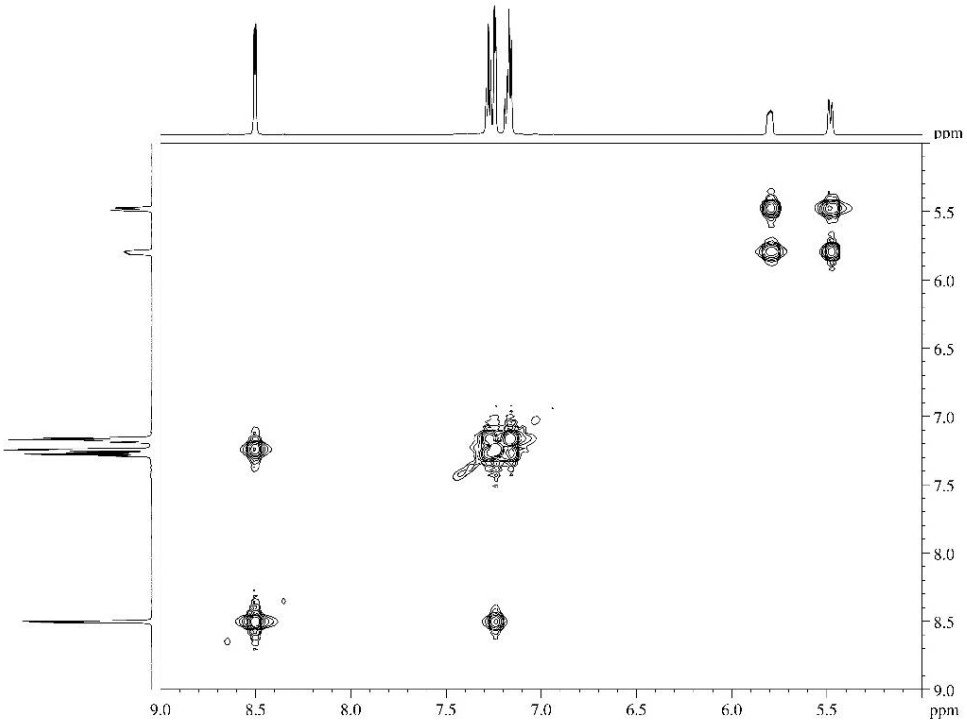




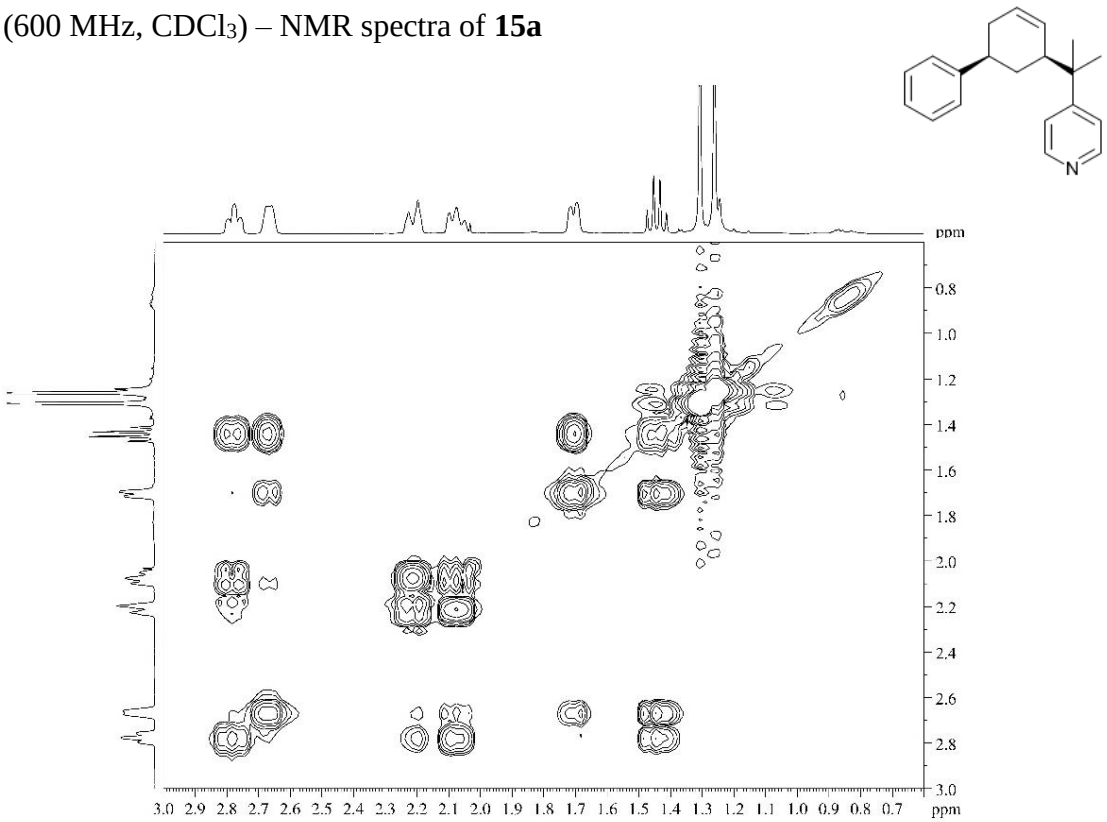
2D-COSY (600 MHz, $CDCl_3$) – NMR spectra of **15a**



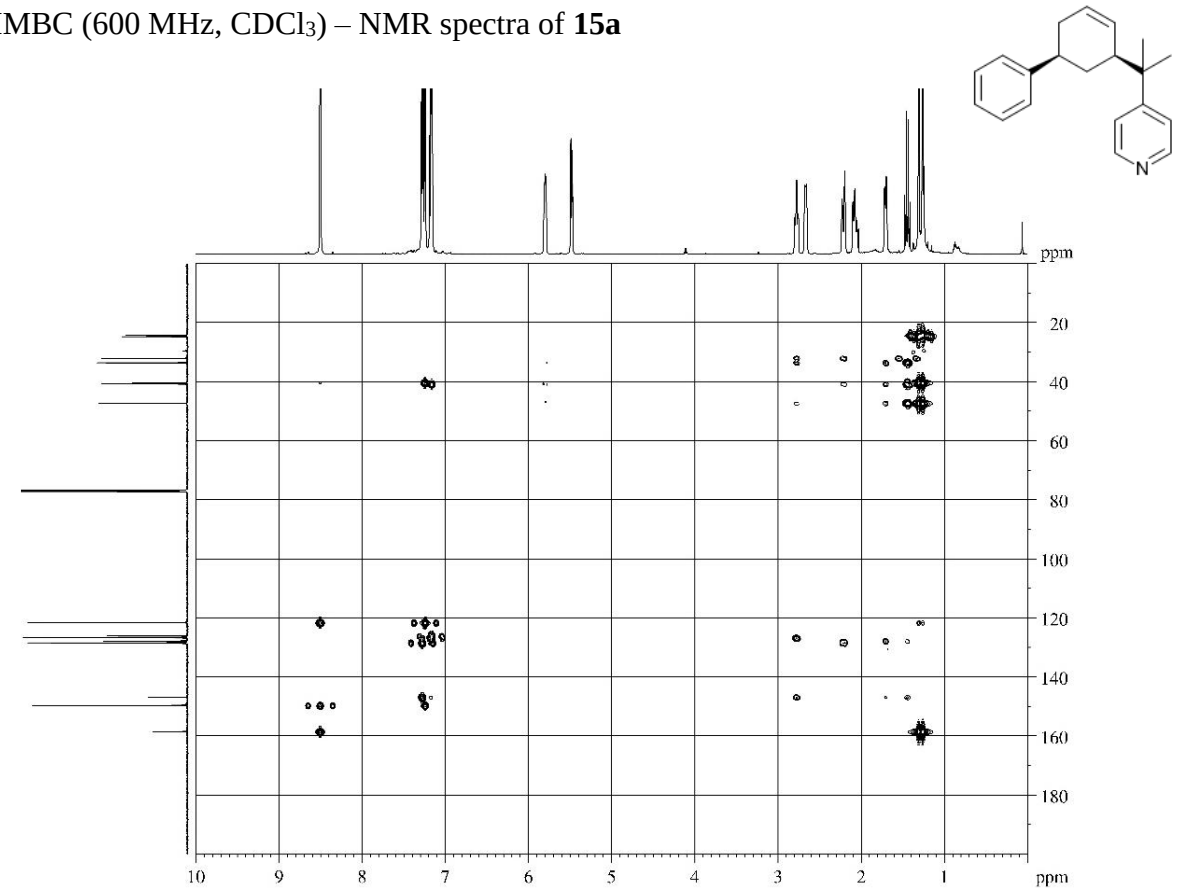


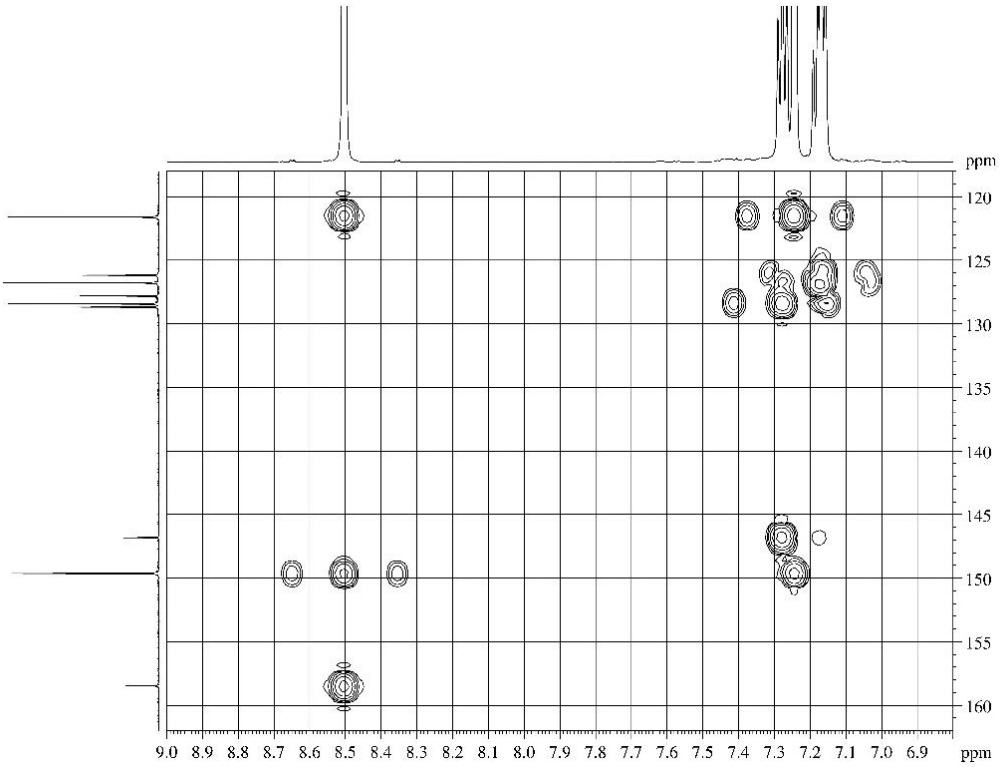


2D-COSY (600 MHz, $CDCl_3$) – NMR spectra of **15a**

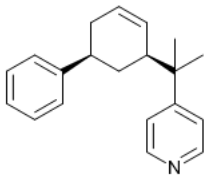


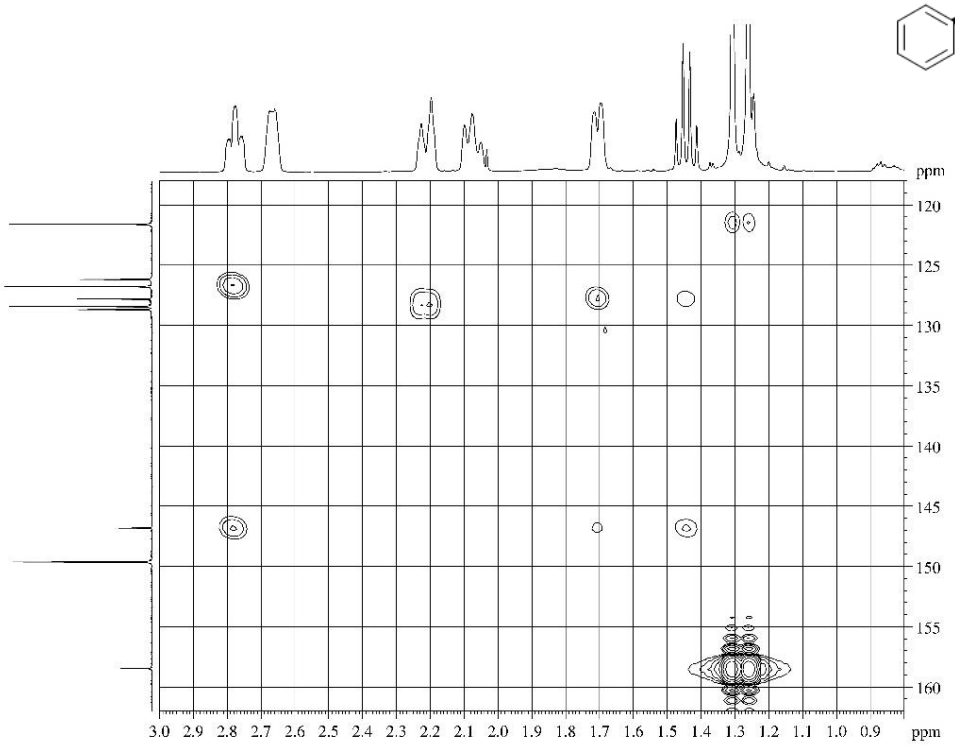
2D-HMBC (600 MHz, $CDCl_3$) – NMR spectra of **15a**

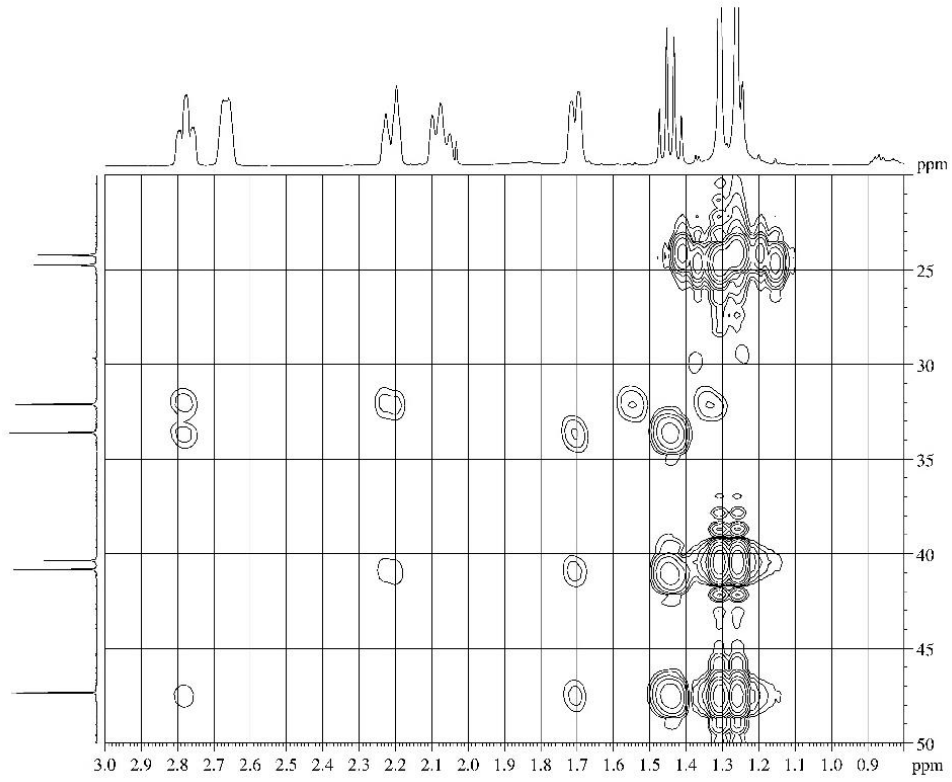




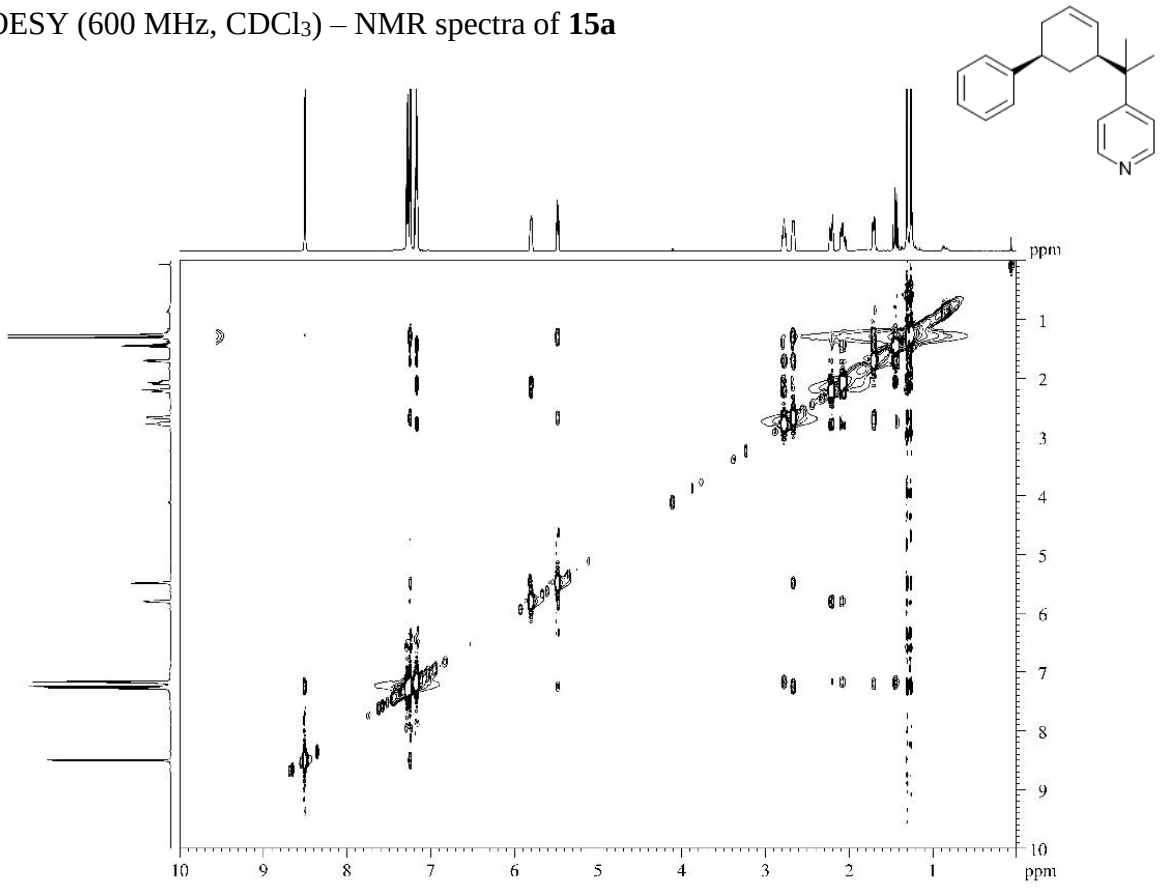
2D-HMBC (600 MHz, $CDCl_3$) – NMR spectra of **15a**

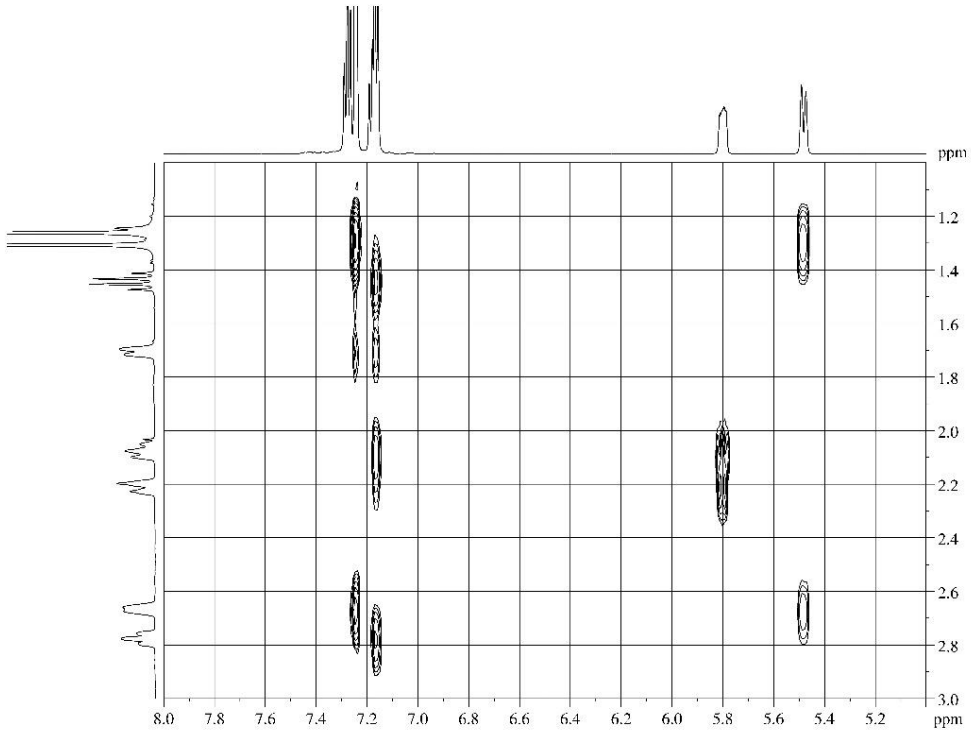




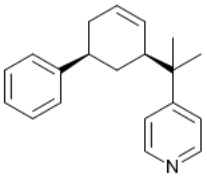


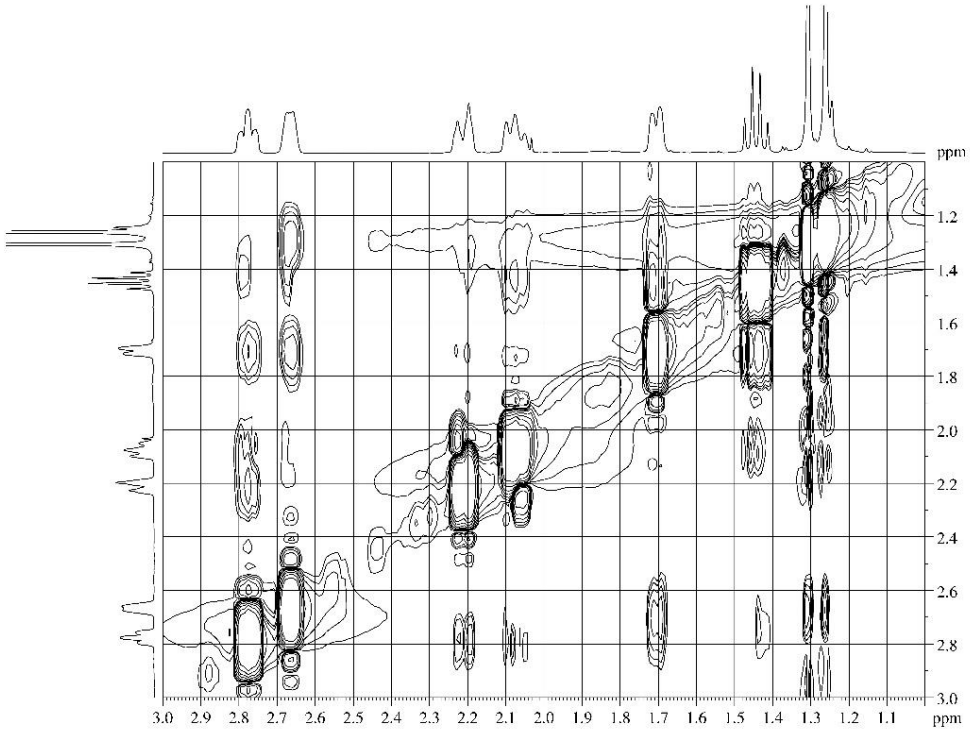
2D-NOESY (600 MHz, $CDCl_3$) – NMR spectra of **15a**



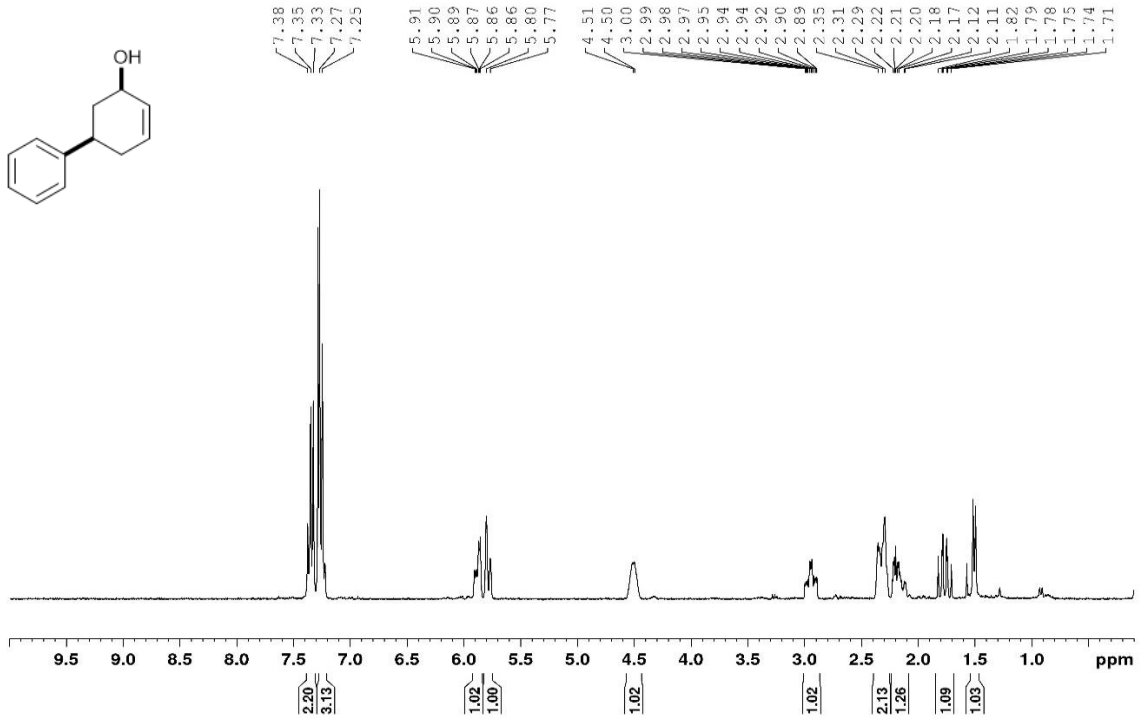


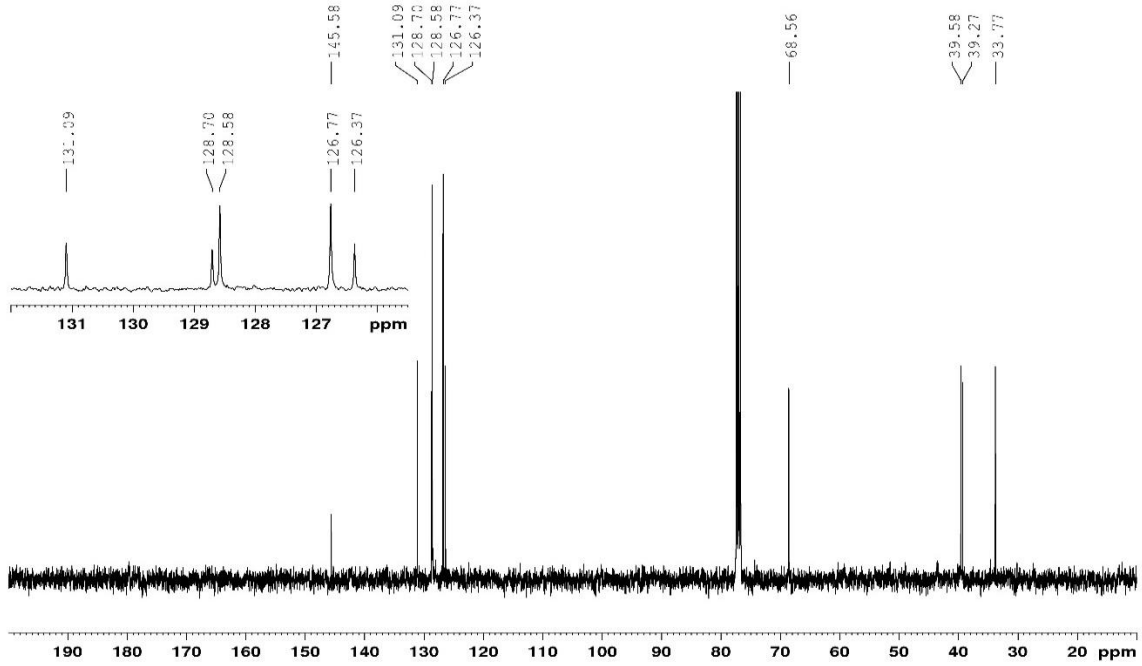
2D-NOESY (600 MHz, $CDCl_3$) – NMR spectra of **15a**



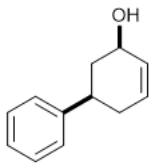


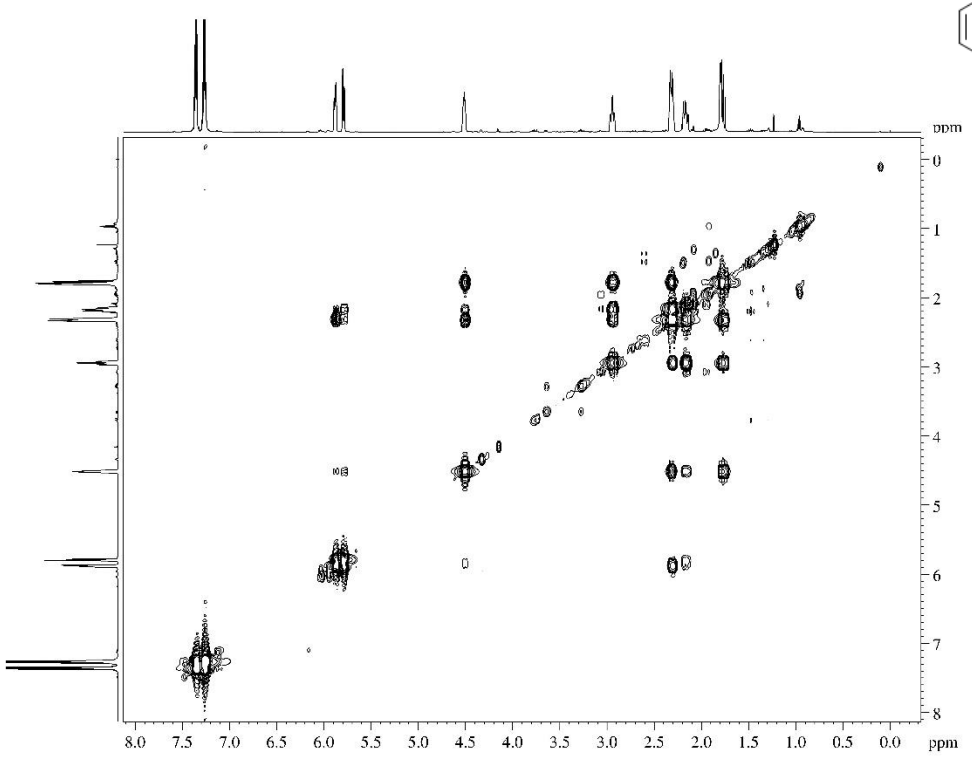
^{1}H (400 MHz, $CDCl_3$) and ^{13}C (400 MHz, $CDCl_3$) – NMR spectra for ***cis*-5-Phenyl-2-cyclohexen-1-ol**

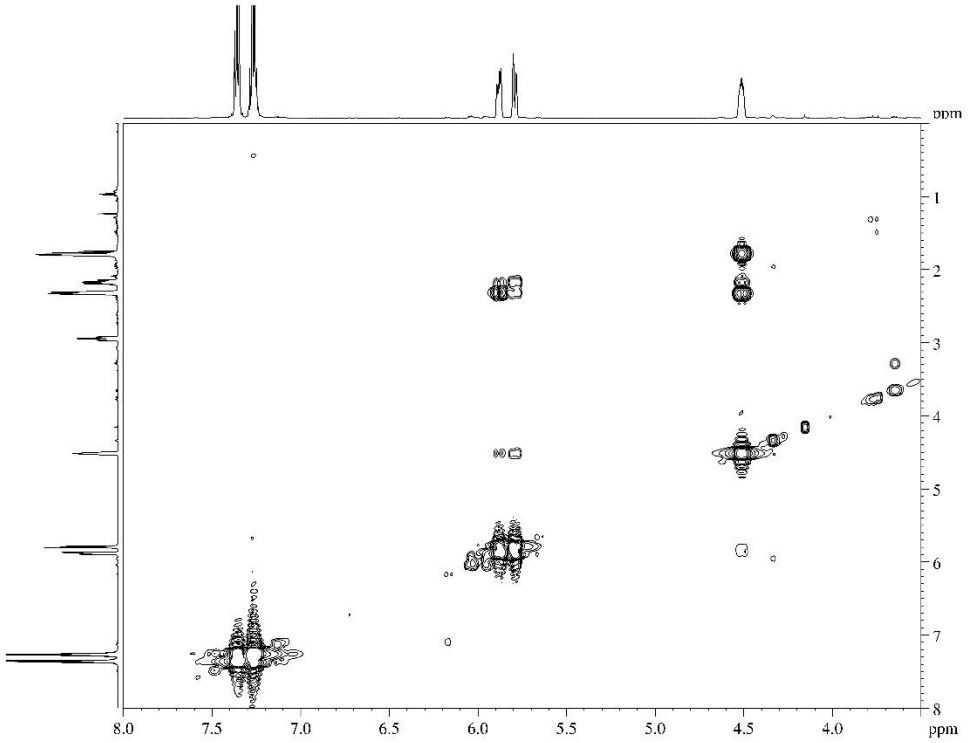




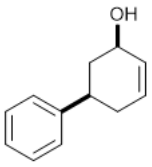
2D COSY (600 MHz, $CDCl_3$) – NMR spectra of ***cis*-5-Phenyl-2-cyclohexen-1-ol**

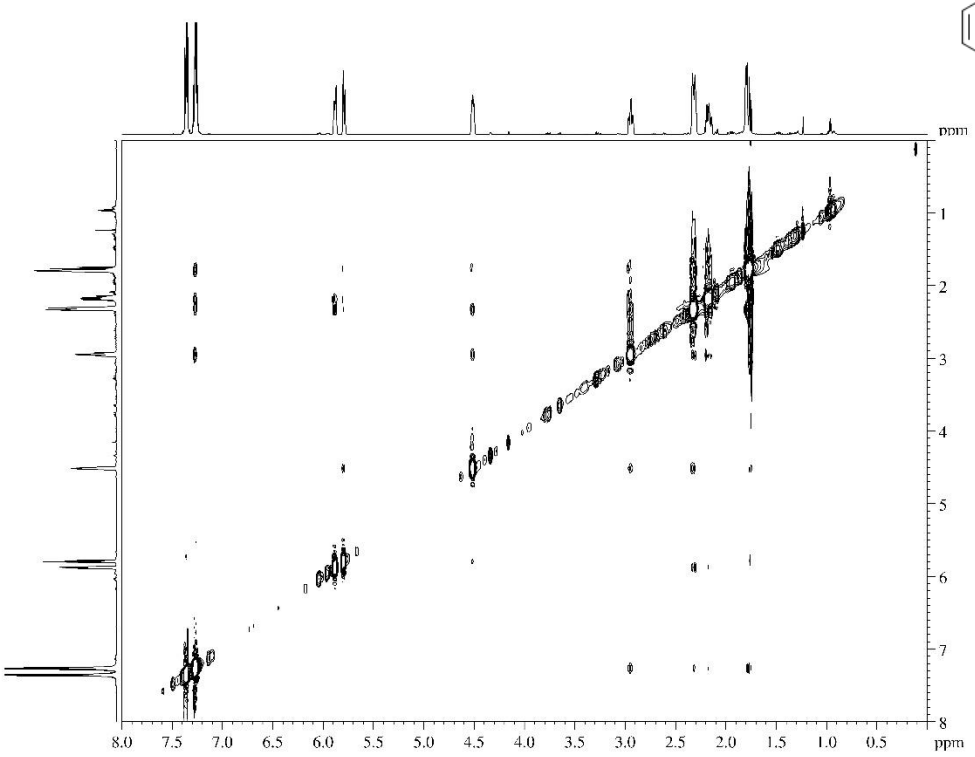


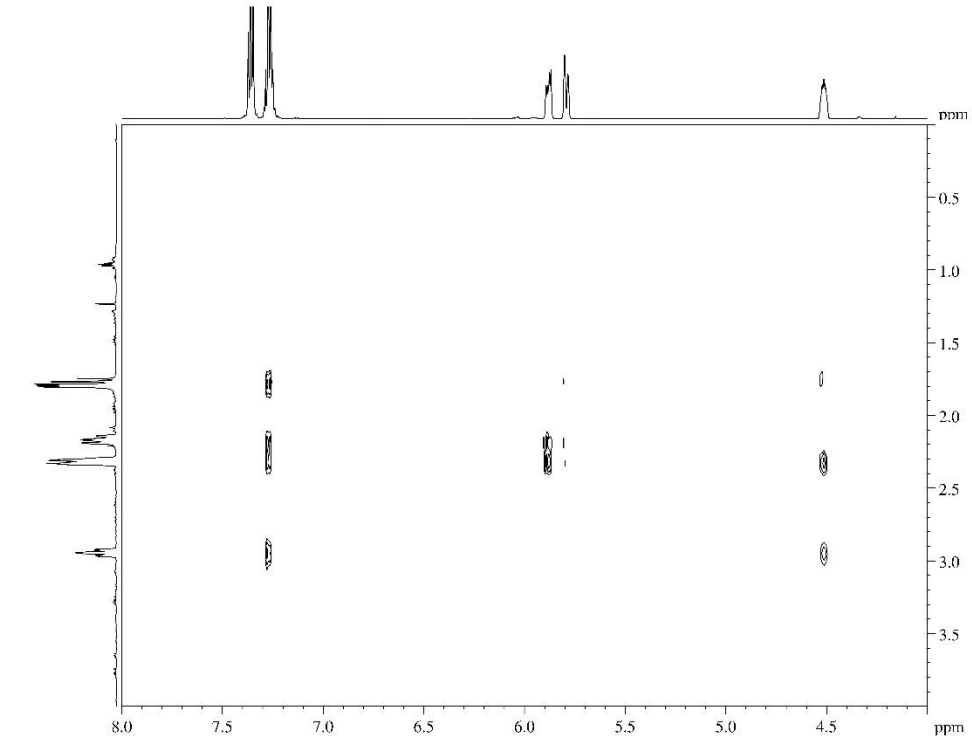




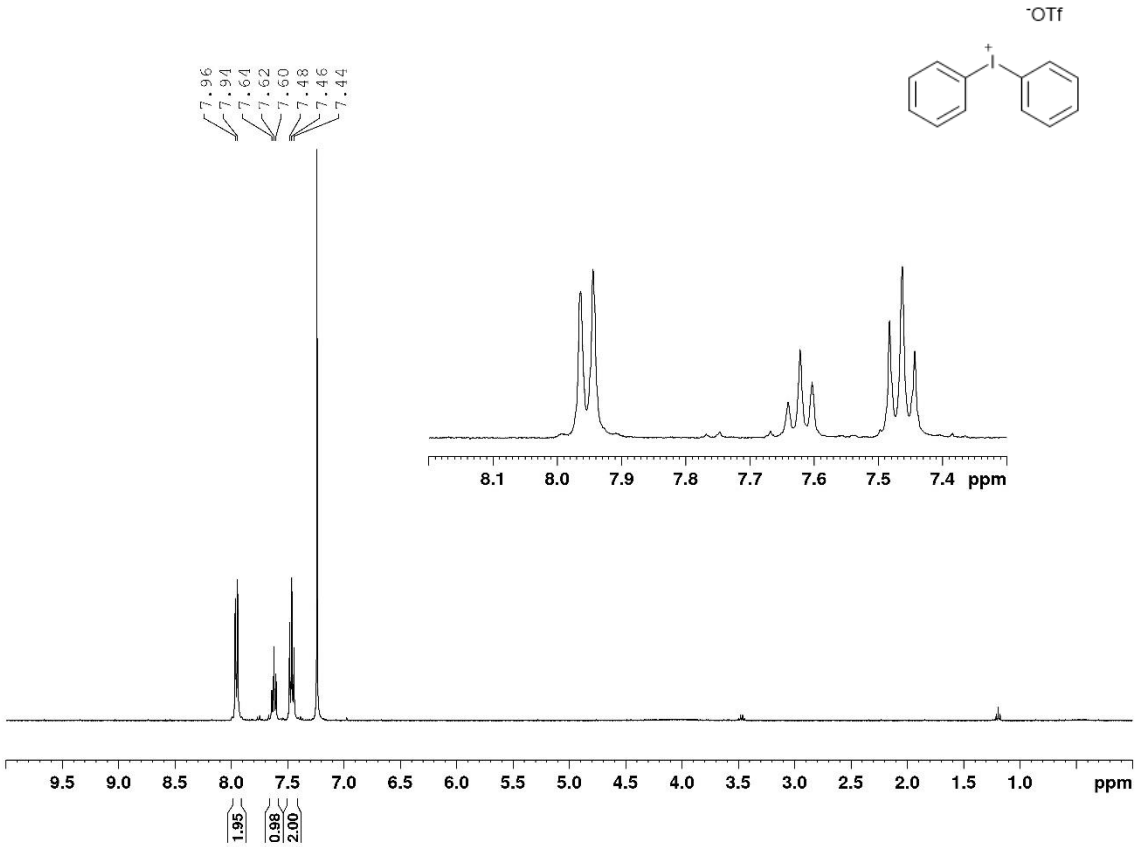
2D NOESY (600 MHz, $CDCl_3$) – NMR spectra of ***cis*-5-Phenyl-2-cyclohexen-1-ol**



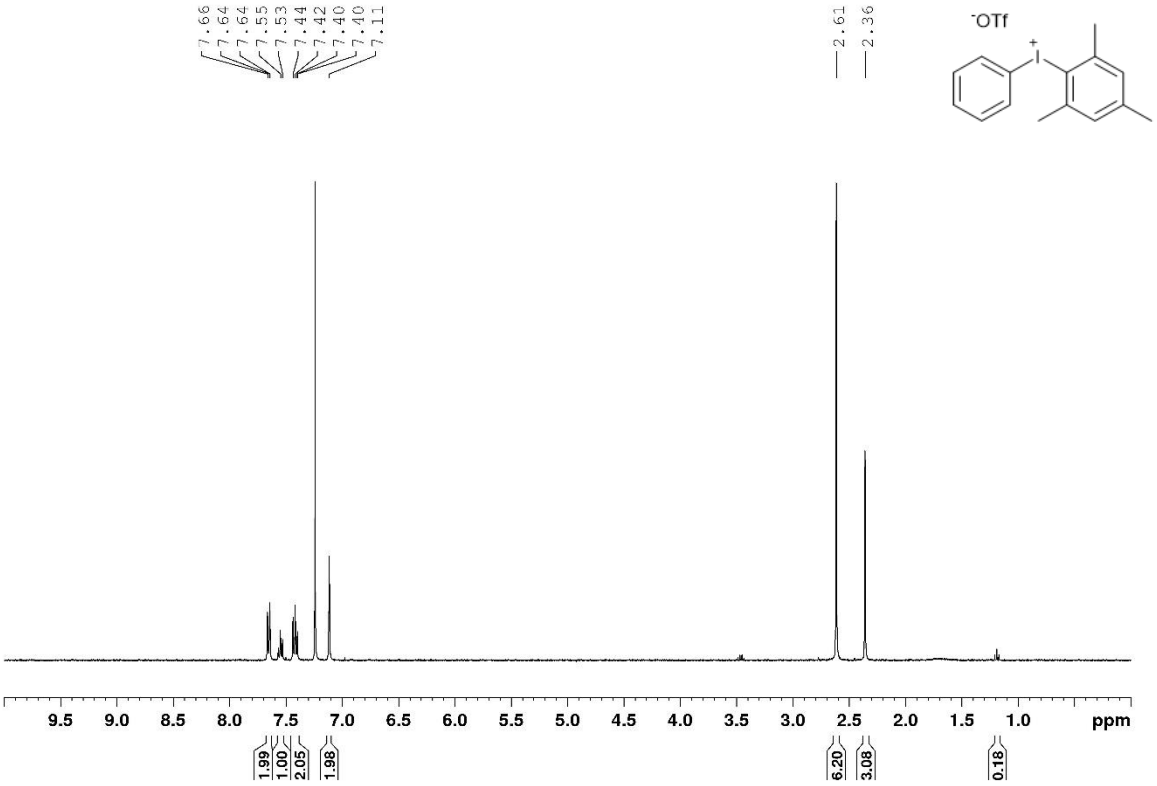




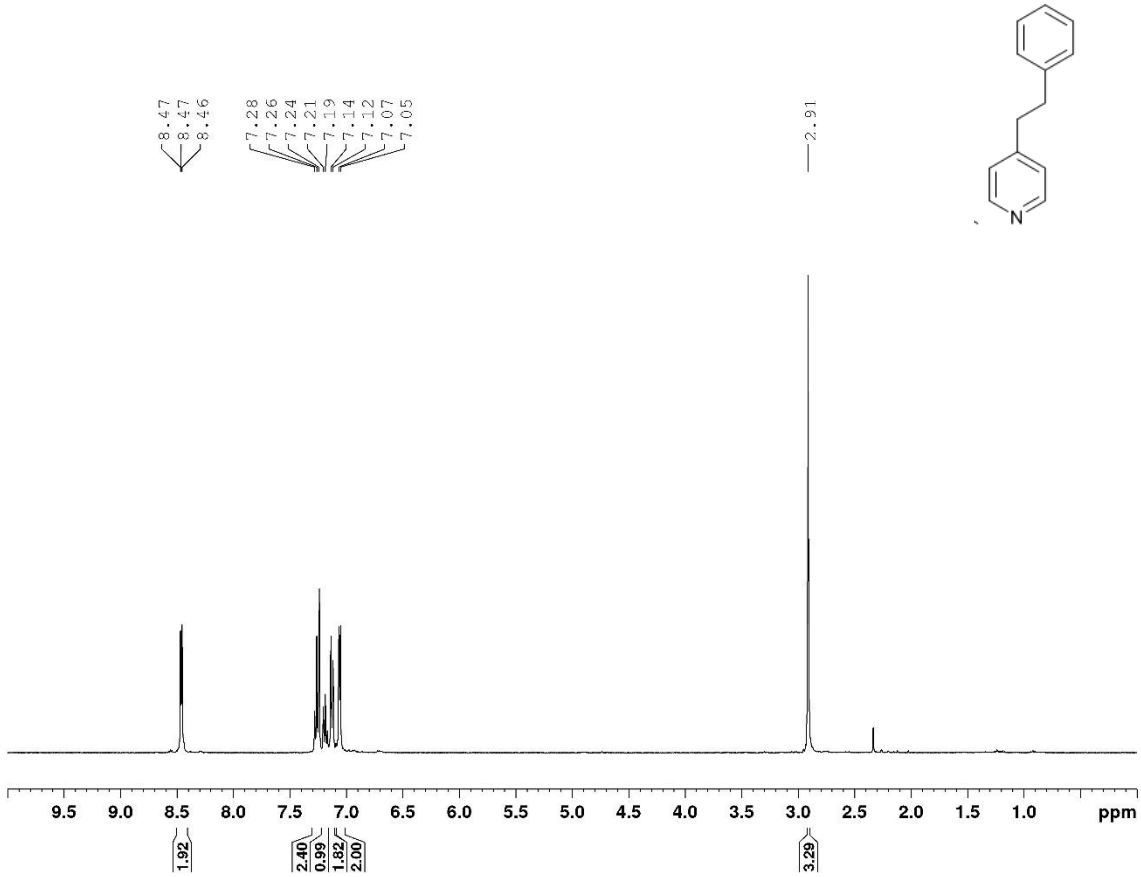
^{1}H (400 MHz, $CDCl_3$) – NMR spectra for **diphenyliodonium triflate**



^{1}H (400 MHz, $CDCl_3$) – NMR spectra for **mesityl(phenyl)iodonium triflate**



^{1}H (400 MHz, $CDCl_3$) – NMR spectra for **4-phenylethylpyridine**



^{1}H (400 MHz, $CDCl_3$) – NMR spectra for **18a**