ALKYLIDENE DIHYDROPYRIDINES AS USEFUL INTERMEDIATES FOR FUNCTIONALIZATION OF 4-ALKYLPYRIDINES

JIAQI SHI

A DISSERTATION SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

GRADUATE PROGRAM IN CHEMISTRY
YORK UNIVERSITY
TORONTO, CANADA

JANUARY 2024

Abstract

Pyridines are widely used and extensively studied heterocyclic compounds in industry and academia. Developing mild and selective methods for functionalizing pyridines would facilitate the synthesis of more structurally diverse pyridine derivatives, which could aid the development of potential drug candidates and streamline the drug discovery process. Through a “soft-enolization” logic, 4-alkylpyridines can be readily converted to corresponding alkylidene dihydropyridines (ADHPs), enabling mild and selective palladium-catalyzed allylation and dehydrogenation, as previously shown by our group. During the mechanistic study of the allylation reaction, prompted by the low enantioselectivity of pyridine allylation using optically active ligands, our group demonstrated that ADHPs are “soft” nucleophiles towards the allylpalladium(II) complex. We thus began employing this class of intermediates as soft nucleophiles in other reactions. Here I will first discuss the work towards enantioselective allylation of 4-alkylpyridines. Then I will describe the conjugate addition of ADHPs to α,β-unsaturated ketones that are activated by triethylsilyl triflate. Finally, I will introduce the approach to unite piperidine and pyridine with a carbon atom through addition of ADHPs to protonated pyridines with subsequent transfer hydrogenation reaction.

Acknowledgements

This work could not be made possible without the supervision and guidance from Prof. Arturo Orellana. Thank you for providing me with the opportunity to conduct research on meaningful synthetic projects that bring real impact to the industry. Your knowledge in chemistry and constructive criticism motivated me to become a better chemist. Your unwavering support helped me go through difficult times in my research.

I would like to thank Prof. Ryan Hili and Prof. Christopher Caputo for being my committee members and their constructive feedback during my research evaluations. It is also an honor to take courses from both of you to expand my chemistry knowledge base.

Special thanks to Prof. Howard Hunter for his assistance with NMR experiments. Your expertise and support were essential to some of my NMR results.

I also would like to thank past and present group members for making the most memorable five-year period in my life. Dr. Ashik Sayyad, thank you for teaching me necessary skills and mindset needed for doing chemistry research. You are a mentor and friend that helped me during the most frustrating moments. Faizan Rasheed, it is a pleasure to work with you on several projects. Thank you for providing insightful suggestions whenever I run out of ideas. Anmol Dhesi, your sense of humor and talent in music make my research less stressful. Samira Komijani, Youxuan Guo, Matthew Puzhitsky, Nour Wasfy, Isabelle Hunter and Brian Doan, thank you all for creating an enjoyable and supportive working environment. Wish you all the best on your future endeavors.

Finally, I need to extend my gratitude to my mom for her moral and financial support. You have a kind and strong heart that encourages me to overcome obstacles in my life. To my wife, thank you for your love and patience. I am grateful to have you around to support me emotionally. To my sister, thank you for the joy you bring to our family.

Table of contents

Abstract ii

Acknowledgement iii

Table of contents iv

List of schemes vii

List of tables ix

List of figures x

List of symbols and abbreviations xi

Chapter 1: Introduction 1

1.1 The history and importance of organic synthesis 1

1.2 Overview of pyridine and its role in drug development 2

1.3 Conjugate addition and piperidine installation involving 4-alkylpyridines 3

1.3.1 Overview of conjugate addition involving 4-alkylpyridines 4

1.3.2 Overview of piperidine installation of 4-alkylpyridines 5

1.3.2.1 Piperidine in drug discovery 5

1.3.2.2 Current methods to connect piperidine with pyridine through a carbon atom 6

1.4 Alkylidene dihydropyridine as useful intermediates for 4-pyridylic functionalization 7

Chapter 2: Attempt towards enantioselective allylation of 4-alkylpyridines 8

2.1 Original understanding of the mechanism of allylation reaction 9

2.2 Ligand screen for asymmetric allylation of 4-alkylpyridines 9

2.3 Investigating the nature of pyridylic anion 10

2.4 Revealing the nucleophilicity of alkylidene dihydropyridine 11

Chapter 3: Conjugate addition of alkylidene dihydropyridines to α,β-unsaturated ketones 13

3.1 Conjugate addition involving activation of α,β-unsaturated ketones 15

3.2 Conjugate addition of alkylidene dihydropyridines to activated unsaturated ketones 15

3.2.1 Proof of concept and optimization 17

3.2.2 Substrate scope 17

3.2.3 Derivatization of the conjugate product 23

Chapter 4: Piperidine installation through addition of alkylidene dihydropyridines to pyridine hydrochloride 28

4.1 Nucleophilic addition to activated pyridine for piperidine synthesis 31

4.2 Addition of alkylidene dihydropyridine to *N*-triflyl pyridinium cation 31

4.3 Addition of alkylidene dihydropyridine to pyridine hydrochloride 31

4.4 Substrate Scope 33

4.5 Diversification of the piperidine product 39

Chapter 5: Conclusions 47

Chapter 6: Experimental and characterization of compounds 49

6.1 Substrate synthesis 50

6.2 General procedure (A) for synthesis of ADHPs 100

6.3 Attempts toward enantioselective allylation of 4-alkylpyridines 101

6.3.1 General procedure for allylation of 4-phenethylpyridine 101

6.3.2 HPLC chromatographs obtained from the ligand screen 102

6.4 Conjugate addition of ADHPs to unsaturated ketones 107

6.4.1 General procedure (B) for conjugate addition 107

6.4.2 Synthesis and characterization of compounds 108

6.5 Piperidine installation on 4-pyridylic carbon 226

6.5.1 General procedure (C) for addition of ADHP to activated pyridines 226

6.5.2 General procedure (D) for reduction of dihydropyridines 226

6.5.3 Synthesis and characterization of compounds 227

Reference 307

List of schemes

Scheme 1: Conjugate addition of 2-picoline as the key step for the synthesis of rac-cermizine C.

Scheme 2: Conjugate addition of 2,4,6-trimethylpyridine using Taber's method.

Scheme 3: Conjugate addition of 4-alkylpyridines that carry an electron-withdrawing group.

Scheme 4: Typical strategies to connect piperidine with pyridine through a carbon linker.

Scheme 5: General formation of alkylidene dihydropyridine.

Scheme 6: Functionalizing 4-pyridylic carbons through alkylidene dihydropyridine intermediates.

Scheme 7: Pyridylic allylation using DACH-Trost ligands.

Scheme 8: Two reductive elimination pathways for allylation reaction.

Scheme 9: Allylation of 4-alkylpyridines undergoes outer-sphere reductive elimination.

(Result obtained from Isabelle Hunter)

Scheme 10: Latent nucleophilicity of ADHPs at exocyclic carbon.

Scheme 11: Ethyl-ADHP as nucleophile in palladium-catalyzed allylation of 4-alkylpyridines.

(Result obtained from Nour Wasfy)

Scheme 12: Conjugate addition involving Lewis acid and neutral nucleophile.

Scheme 13: Examples of conjugate additions involving unsaturated ketones activated by Lewis acids.

Scheme 14: Proposed mechanism for conjugate addition of ADHP to activated α,β-unsaturated ketones.

Scheme 15: First attempt for conjugate addition of ADHP to activated 2-cyclopenten-1-one.

Scheme 16: Formation of acetonitrilium ion stabilizes the allyl triethylsilyloxy intermediate.

Scheme 17: Order of addition affects the yield of the reaction.

Scheme 18: Relationship between the amount of pyridine starting material and the final yield.

Scheme 19: Reverse reaction (highlighted in pink) may be the cause for low diastereoselectivity.

Scheme 20: Palladium-catalyzed allylation of 4-alkylpyridine synthesized through optimized conjugate addition of 4-(3-buten-1-yl)-pyridine with a neutral work-up procedure.

Scheme 21: Non-planar orientation of the pyridine ring and the alkoxycarbonyl group prevents the formation of ADHP.

Scheme 22: The use of silyl enol ether in synthesizing 2-substituted pyridine.

Scheme 23: Sample nucleophilic addition to *N*-activated pyridinium cation for piperidine synthesis.

Scheme 24: Proposed addition of ADHP to activated pyridine.

Scheme 25: Nucleophilic addition to *N*-triflyl pyridinium cation followed by oxidation.

Scheme 26: First attempt for addition of ADHP to *N*-triflyl pyridinium cation by following Corey's condition.

Scheme 27: Addition of ADHP to pyridine hydrochloride.

Scheme 28: Interaction between palladium with allyl-DHP leads to formation of pyridylic anion.

Scheme 29: Steric congestion amplifies the reverse reaction.

Scheme 30: Attempts for piperidine installation using 4-isopropyl- and 4-benzyl pyridine.

Scheme 31: Exploring regioselective piperidine installation on 4-methylpyridines.

Scheme 32: Addition of ADHP derived from 4-methylpyridine to substituted pyridinium chloride.

Scheme 33: Trans-dearomatization between 4-picoline-ADHP and 4-benzylpyridinium chloride.

Scheme 34: Further chemical transformations of piperidine product **4-4**.

List of tables

Table 1: Relationship between the product yield and the changes in reaction conditions

Table 2: Substrate scope for conjugate addition of ADHPs to unsaturated ketones

Table 3: Substrate scope for conjugated addition of 4-methyl-ADHP to α,β-unsaturated ketones

Table 4: Solvent screen for addition of ADHP to *N*-triflyl pyridinium cation

Table 5: Optimization for addition of alkylidene dihydropyridine to pyridinium chloride

Table 6: Optimization for hydrogenation of dihydropyridine

Table 7: Substrate scope for piperidine installation of piperidine on 4-alkylpyridines

List of figures

Figure 1: Replacing benzene with pyridine helps improve the permeability and solubility of the drug candidate for treating Parkinson's disease.

Figure 2: Replacing benzene with pyridine helps improve the metabolic stability of the drug candidate for treating Hepatitis C virus infection.

Figure 3: Natural product and drug candidates that involve 4-alkylpyridine fragment.

Figure 4: Sample natural products that contain piperidine moiety.

Figure 5: Examples of drug candidates containing pyridine and piperidine moieties.

Figure 6: Pyridine helps reduce lipophilicity of existing drug candidate.

Figure 7: Original proposed mechanism of allylation of 4-alkylpyridine.

Figure 8: Speculated structure for poisoned palladium catalyst that carries deprotonated DACH-Trost ligand **L1**.

Figure 9: Ligand screen for enantioselective allylation of 4-phenethylpyridine.

Figure 10: Overlapped proton NMR spectra for monitoring the conjugate addition of ADHP to activated 2-cyclopenten-1-one.

Figure 11: Overlapped carbon NMR spectra for compounds **3-1a** and **3-1b**.

Figure 12: NOE interactions that can help determine stereogenic configurations of the two diastereomers.

Figure 13: Overlapped proton NMR spectra for monitoring piperidine installation on 4-ethylpyridine.

Figure 14: Proton NMR spectrum for compound **4-4**.

Figure 15: Comparison of chemical shifts of exocyclic protons of ADHPs (highlighted with dotted circles) generated from 4-benzylpyridine (red) and 4-phenethylpyridine (blue).

Figure 16: NOE interaction (highlighted in red) between H_a (~1.6 ppm) and H_b (~ 4.05 ppm) confirmed the stereogenic configuration of compound **4-18**.

List of symbols and abbreviations

(*S*,*S*)-Ph-BPE	(+)-1,2-Bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane
ADHP	Alkylidene dihydropyridine
acac	Acetylacetonate
Bn	Benzyl group
DACH	Diaminocyclohexane
DCM	Dichloromethane
DCM-d_2	Deuterated dichloromethane
δ	Chemical shift
DHP	Dihydropyridine
DMF	Dimethyl formamide
DMMS	di-methoxy(methyl)silane
DMPU	*N*,*N*'-Dimethylpropylene urea
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
Equiv.	Equivalent(s)
Et	Ethyl group
FDA	Food and drug administration
HPLC	High-performance liquid chromatography
i-Pr	Isopropyl group
J	Coupling constant
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
Me	Methyl group
NMR	Nuclear magnetic resonance
n-Bu	Normal butyl group
υ	Wavenumber
OAc	Acetoxy group
OTf	Trifluoromethanesulfonate/Triflate
$Pd_2(dba)_3 \cdot CHCl_3$	Dipalladium-tris(dibenzylideneacetone)chloroform complex

Ph	Phenyl group
ppm	Parts per million
qNMR	Quantitative NMR experiment
r.t.	Room/Ambient temperature
R_f	Retention factor
TBS	Tert-butyl(dimethyl)silyl group
TES	Triethylsilyl group
THF	Tetrahydrofuran
TIPS	Triisopropyl silane
TMS	Trimethylsilyl group
TLC	Thin layer-chromatography
t-Bu	Tertiary butyl group
UV	Ultraviolet
XantPhos	4,5-Bis(diphenylphosphino)-9,9- dimethylxanthene

Chapter 1: Introduction

1.1 The history and importance of organic synthesis

The history of producing and obtaining organic compounds can be traced back thousands of years. Ancient civilizations such as the Egyptians and Romans prepared ethanol and acetic acid through fermentation. Similarly, they collected various chemicals, such as formic acid and salicylic acid, by extracting them from animals and plants. Up until the early 1800s, almost all organic substances discovered were obtained from living organisms. As a result, it was believed that a vital force is required to make organic compounds.[1]

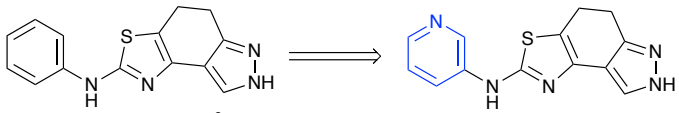
Friedrich Wöhler's groundbreaking synthesis of urea from inorganic ammonium cyanate in 1828 greatly challenged the belief of vital force.[2] In 1845, Kolbe synthesized acetic acid starting from elemental carbon and sulfur, which were considered "dead" things.[1,3] This discovery marked the demise of vitalism and the birth of organic synthesis. The dye industry was the first that enjoyed the fruit of organic synthesis with the development of mauveine by William Perkin.[4] In 1897, Felix Hoffmann synthesized acetylsalicylic acid (Aspirin®), which revolutionized the pharmaceutical industry.[5,6] Since the 20th century, developments in organic chemistry allowed the synthesis of natural products, including quinine, morphine, penicillin V, and vitamin B_{12}.[6]

One of the bedrocks for organic synthesis is the emergence of new methodologies that enable efficient and innovative chemical transformations. The pharmaceutical industry, in particular, relies on the breakthroughs in organic synthesis that empower them to better explore chemical space for drug discovery and accelerate the drug development process.[7] Because drug molecules generally contain a number of functional groups to form certain interactions with the biological target, it is of great advantage to develop synthetic methods that are chemoselective while tolerating a wide range of functional groups. In addition, regio- and stereoselective synthesis as well as the use of less expensive reagents will be valuable for both academia and industry.[8]

1.2 Overview of pyridine and its role in drug development

In medicinal chemistry, optimization on lead-like molecules or drug candidates often results in increased molecular weight and lipophilicity.[9] These will directly affect drug transport process and pose risks of promoting more off-target interactions, raising concerns about the overall efficacy and toxicity of drug candidates.[9] To mitigate these issues, heterocycles with hydrogen bond-forming ability can be used as key motifs in the lead-like compounds at the drug discovery stage, or as isosteres for the existing drug-like molecules during the optimization process.

In 2014, Njardarson's group conducted a comprehensive analysis on nearly two thousand FDA-approved drug molecules and found that pyridine was the most frequently used nitrogen-containing *aromatic* heterocycle.[10] Pyridine possesses hydrogen bond-forming ability and weak basicity due to the presence of an sp^2-hybridized nitrogen atom. It helps improve the pharmacological profiles, including permeability, solubility, and metabolic stability, of the existing drug candidates (**Figures 1** and **2**).[11–13] Moreover, pyridine can act as a valuable bio-isostere for several functional groups, including amide, amine, benzene, and other nitrogen-containing heterocycles.[14] These properties make pyridine an important synthetic scaffold in medicinal chemistry. Notably, pyridines can be converted to dihydropyridines and piperidines, which are useful in chemical synthesis and biological studies.[15]



permeability: < 0.1 x 10^{-6} cm/s
solubility: <0.1 μM (pH = 7.4)

permeability: 18.7 x 10^{-6} cm/s
solubility: 17 μM (pH = 7.4)

Figure 1: Replacing benzene with pyridine helps improve the permeability and solubility of the drug candidate for treating Parkinson's disease.

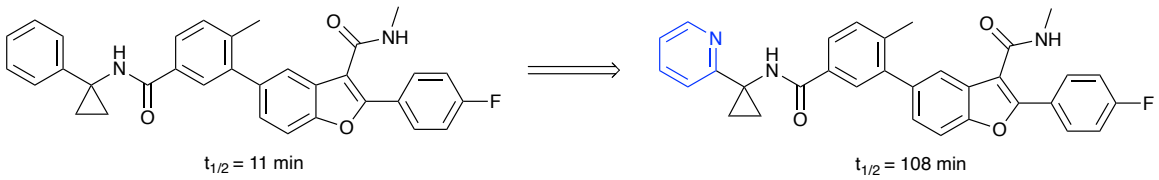


Figure 2: Replacing benzene with pyridine helps improve the metabolic stability of the drug candidate for treating Hepatitis C virus infection.

1.3 Conjugate addition and piperidine installation involving 4-alkylpyridines

Our group is dedicated to developing transformations that involve 4-alkylpyridines because they appear in natural products and display valuable biological activities (**Figure 3**).[16–18] More specifically, we would like our methods to have good functional group tolerance and be regioselective towards the 4-pyridylic carbon. The report herein will describe our recent developments on conjugate addition to α,β-unsaturated ketones and mild installation of piperidine on 4-alkylpyridines.

The high pKa value of the 4-pyridylic carbon, ranging from 26 to 35 in DMSO,[19] necessitates the use of strong bases for conventional pyridylic C—H transformation. An obvious limitation of this approach is the lack of functional group tolerance. The alternative is to install an activating group at the pyridylic site or on the pyridine ring to allow milder deprotonation condition. However, additional effort is required for the removal of these activating groups if they are not desired for subsequent reactions. Therefore, milder and more practical methods for pyridylic transformation would be of great value for drug discovery.

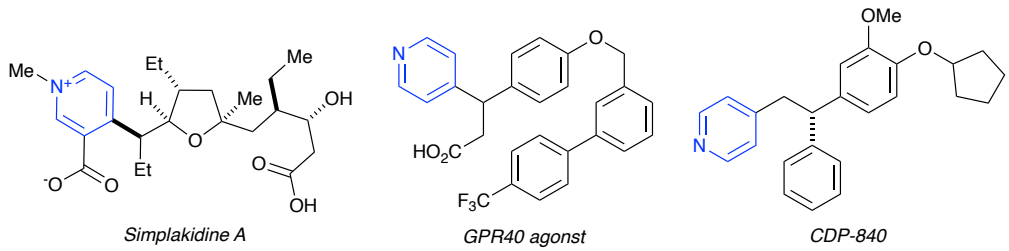
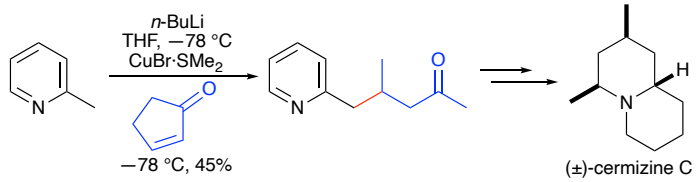


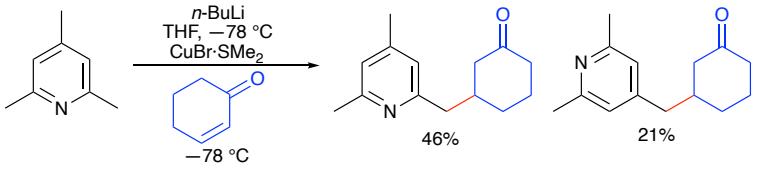
Figure 3: Natural product and drug candidates that involve 4-alkylpyridine fragment.

1.3.1 Overview of conjugate addition involving 4-alkylpyridines

Conjugate addition involving alkylpyridines plays an important role in making natural products and drug-like molecules. Methods for this transformation can be classified into three categories. The first strategy involves direct deprotonation of the alkylpyridine with a strong base, and it was highlighted by Taber's group in the synthesis of *rac*-cermizine C (**Scheme 1**).[20] They began by using *n*-butyl lithium (pKa ≈ 50) to deprotonate 2-methylpyridine, followed by the addition of copper(I) bromide dimethyl sulfide adduct, to generate the cuprate reagent to facilitate conjugate addition. However, when 2,4,6-trimethylpyridine was subjected to the reaction, this method displayed low regioselectivity towards the 4-pyridylic site (**Scheme 2**). More importantly, the use of a strong base limits overall functional group tolerance.



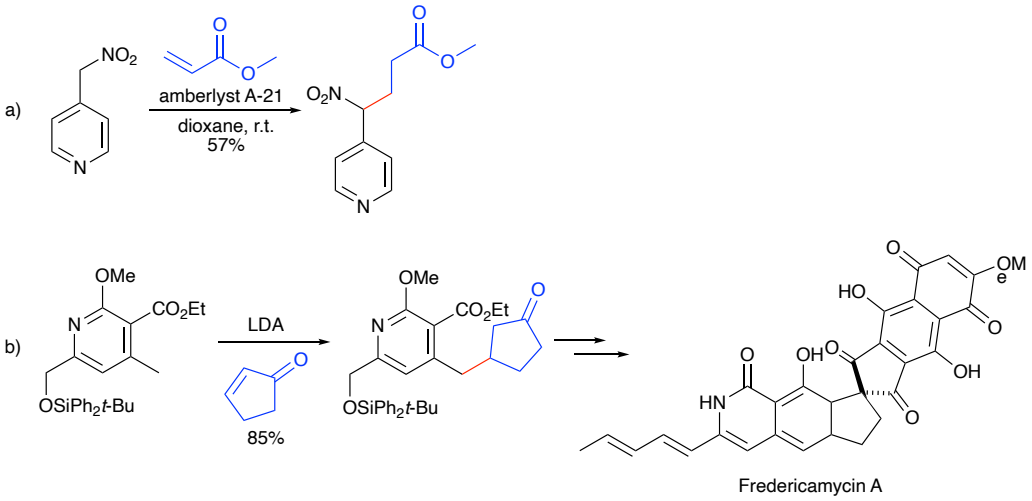
Scheme 1: Conjugate addition of 2-picoline as the key step for the synthesis of rac-cermizine C.



Scheme 2: Conjugate addition of 2,4,6-trimethylpyridine using Taber's method.

The second approach requires the use of an electron-withdrawing group that is pre-installed at the pyridylic carbon to enhance its acidity, so that a milder base can be used for deprotonation. For example, by having a nitro group installed on the pyridylic carbon, its acidity was increased significantly so that amberlyst A-21, a weakly basic polymeric resin, could deprotonate it and promote Michael addition (**Scheme 3**: equation **a**).[21] This strategy allowed the synthesis of valuable drug-like molecule for treating schizophrenia.[21] The third strategy is to have

an electron-withdrawing group on the pyridine ring to allow a milder deprotonation process. For instance, Clive's group took advantage of the vinylogous activating group to reduce the pKa of the pyridylic carbon so that a milder base could be used (**Scheme 3**: equation **b**).[22] This strategy was employed in the synthesis of Fredericamycin A, a natural product that displayed antitumor and antibiotic abilities.[22] A major drawback of these two strategies is the additional efforts on introducing and removing the activating groups. Overall, the notion that conjugate addition involving 4-alkylpyridines needs to proceed through the formation of charged pyridylic intermediates results in these limitations.



Scheme 3: Conjugate addition of 4-alkylpyridines that carry an electron-withdrawing group.

1.3.2 Overview of piperidine installation of 4-alkylpyridines

1.3.2.1 Piperidine in drug discovery

Piperidine is a six-membered heterocyclic amine that widely appears in natural products such as piperine and matrine (**Figure 4**).[23] Piperidine's sp^3 ring system can contribute to the three-dimensional character of organic compounds, making it a ubiquitous building block for synthesizing complex drug molecules. As a matter of fact, piperidine is the most frequently used heterocyclic fragment in FDA-approved pharmaceuticals.[10]

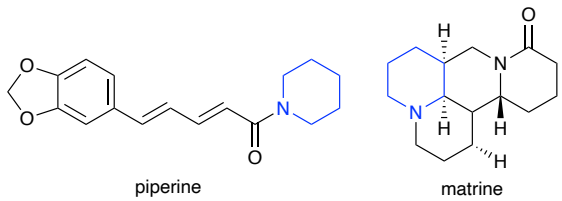


Figure 4: Sample natural products that contain piperidine moiety.

Recent report revealed that drug-like compound containing both pyridine and piperidine motifs exhibit the ability to inhibit γ-secretase, which is one of the targets in Alzheimer's disease research (**Figure 5**).[24] In addition, for existing drug candidate featuring a piperidine moiety, replacement of the benzene ring with a pyridine can reduce the lipophilicity while retaining pharmacological activity (**Figure 6**).[25] These molecules have a carbon linker that unites pyridine with piperidine.

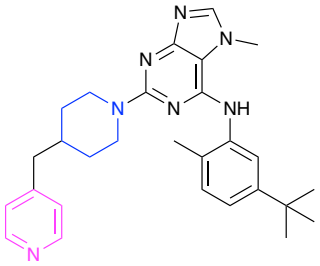


Figure 5: Examples of drug candidates containing pyridine and piperidine moieties.

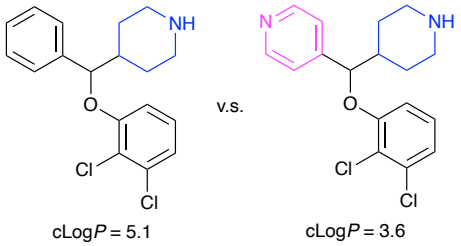
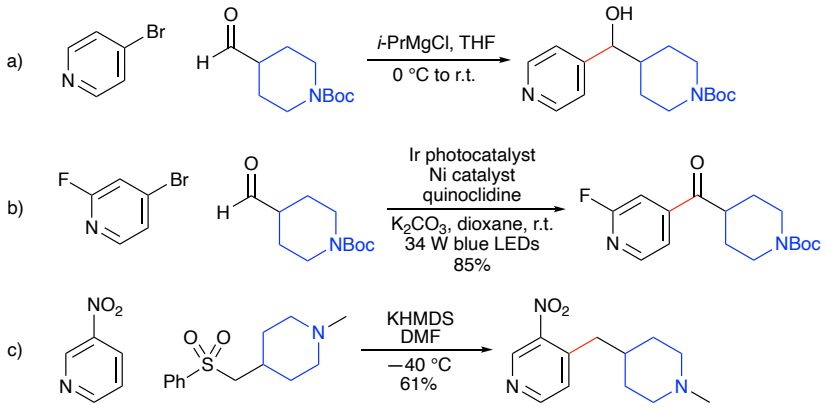


Figure 6: Pyridine helps reduce lipophilicity of existing drug candidate.

1.3.2.2 Current methods to connect piperidine with pyridine through a carbon atom

There are three main approaches to achieve the connection of piperidine with pyridine through a carbon atom. The first method is to convert 4-bromopyridine to its corresponding Grignard reagent, which will react with the electrophilic site of the piperidine aldehyde, to allow

formation of the corresponding alcohol product (**Scheme 4**: equation **a**).[25] An obvious limitation of this approach is the lack of functional group tolerance due to the use of the strong base. An alternative route is to transform the two starting materials into the ketone product through photo-redox chemistry using nickel and iridium catalysts (**Scheme 4**: equation **b**).[26] However, in the situation where the residual functional groups are not desired, additional steps are needed for their removal.[27] A third strategy was recently showcased by Barbasiewicz's group. They used an alkyl phenyl sulfone in conjunction with potassium bis-(trimethylsilyl)amide (KHMDS) as the base to conduct nucleophilic aromatic substitution with 3-nitropyridine (**Scheme 4**: equation **c**).[28] This method requires a pre-installed activating group on the pyridine ring to enhance its electrophilicity.

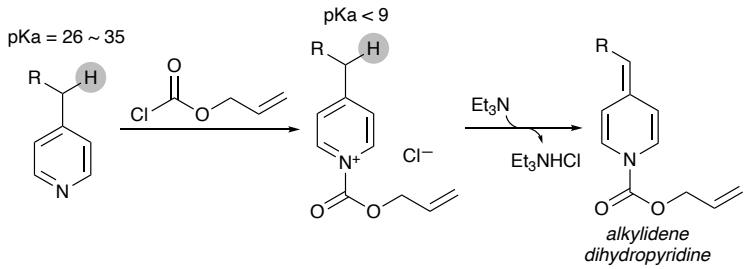


Scheme 4: Typical strategies to connect piperidine with pyridine through a carbon linker.

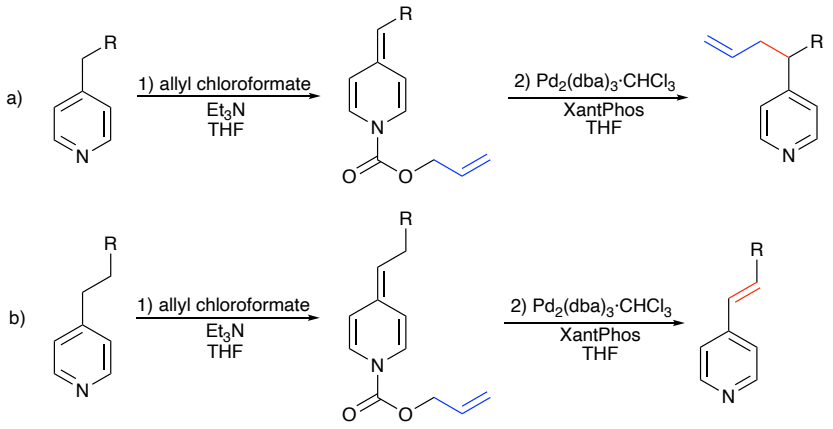
1.4 Alkylidene dihydropyridine as useful intermediates for 4-pyridylic functionalization

It was previously established that reaction of 4-alkylpyridine with chloroformate can substantially enhance its acidity so that a mild base, such as triethylamine (pKa = 9.0 in DMSO),[29] can deprotonate the pyridylic carbon and generate a semi-stable intermediate known as alkylidene dihydropyridine (ADHP) (**Scheme 5**).[30] This class of intermediates led to our developments of palladium-catalyzed allylation of 4-alkylpyridines as well as dehydrogenation reaction (**Scheme 6**: equations **a** and **b**).[31,32] These two methods are selective for the 4-pyridylic position and exhibit broad functional group tolerance. With respect to the allylation project, our

next focus was to develop an asymmetric variant to better serve the pharmaceutical industry. In this paper, I will first discuss some of our works related to this area.



Scheme 5: General formation of alkylidene dihydropyridine.



Scheme 6: Functionalizing 4-pyridylic carbons through alkylidene dihydropyridine intermediates.

4-Pyridylic functionalization using ADHP was once studied by Pigge's group, and they showcased some *intra*molecular pyridylic transformations, including aldol-like condensation and metal-catalyzed coupling reactions, by taking advantage of the alkene nature of the exocyclic carbon.[30,33–35] However, apart from the additional efforts required to attach the tethered electrophile to the pyridylic carbon, reactions that enable installation of meaningful synthetic handles through *inter*molecular functionalization remained largely underdeveloped. Recognizing the limitations of previously reported methods, I set out to explore the possibility of using ADHPs for conjugate addition and piperidine installation involving 4-alkylpyridines.

Chapter 2: Attempt towards enantioselective allylation of 4-alkylpyridines

2.1 Original understanding of the mechanism of allylation reaction

In 2018, our group had developed palladium-catalyzed allylation involving 4-alkylpyridines and conducted a substrate scope study to demonstrate its functional group tolerance and regioselectivity. While preparing for the publication of our allylation work, we simultaneously embarked on developing an enantioselective variant that could be more valuable for its use in pharmaceutical sector.

Our original mechanistic framework for this reaction was based on the Tsuji-Trost allylation reaction (**Figure 7**).[36] Palladium catalyst underwent decarboxylative oxidative addition with the allyl moiety of the ADHP to generate the allylpalladium(II) complex (**Figure 7**: complex **A**) and the pyridylic anion. As of 2018, it was thought that the pKa limit of soft nucleophiles was 32.[37] Therefore, 4-alkyl pyridylic carbon, with the pKa value of 35, was considered a "hard" nucleophile and would proceed through inner-sphere pathway to form a new palladium(II) complex **B** which, after reductive elimination, would produce the desired allylation product **C**.

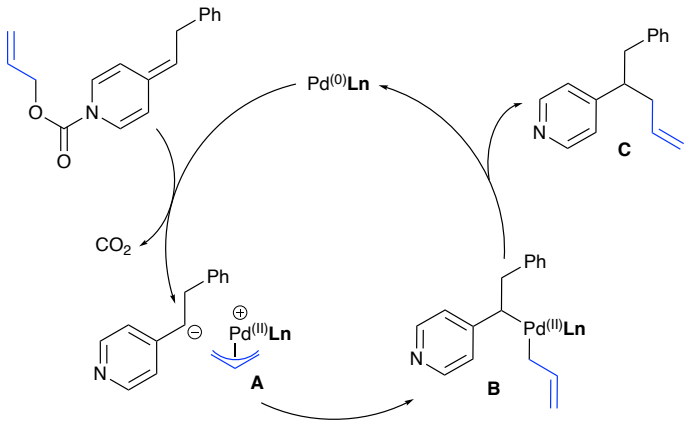
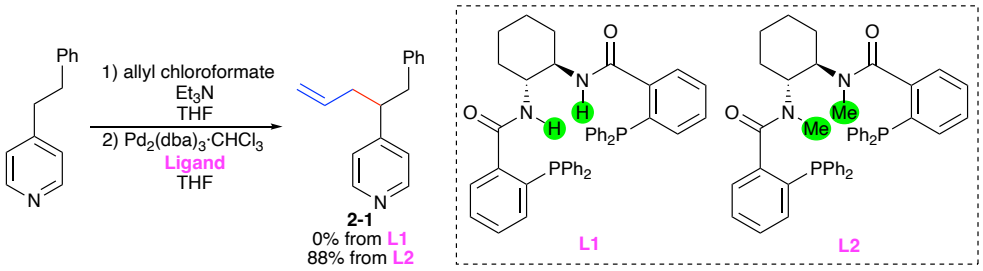


Figure 7: Original proposed mechanism of allylation of 4-alkylpyridine.

The formation of the pyridylic anion was indirectly confirmed from the allylation reactions using DACH-Trost ligands bearing the 1,2-*trans*-diamine backbone (**Scheme 7**). The reaction did not generate the desired product when the parent ligand **L1** was used. On the contrary, when its

N-methylated variant **L2** was employed, the allylation product was formed in 88% yield. We reasoned the side reaction between the pyridylic anion and the two amide groups (pKa ≈ 26) in the parent ligand deactivated the catalyst (**Figure 8**), resulting in unsuccessful reaction with **L1**.



Scheme 7: Pyridylic allylation using DACH-Trost ligands.

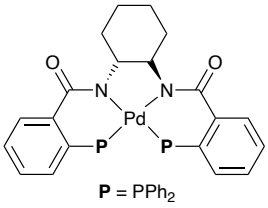


*Figure 8: Speculated structure for poisoned palladium catalyst that carries deprotonated DACH-Trost ligand **L1**.*

2.2 Ligand screen for asymmetric allylation of 4-alkylpyridines

According to our original proposed mechanism, it was thought that asymmetric allylation could be achieved by using a chiral ligand, because the stereochemical information of the ligand could directly affect the reductive elimination step. I screened a list of optically active ligands to find the optimal ligand for enantioselective allylation (**Figure 9**). These ligands featured different bite angles, substituents, and electron densities. To our surprise, most of the ligands delivered almost no influence towards stereoselectivity (**L2** to **L8**). Although I later managed to achieve greater enantiomeric excesses through phosphoramidites and bisphosphite (**L9** to **L11**), the research towards enantioselective allylation became strenuous. We thus questioned our original understanding of the mechanism and began a detailed investigation.

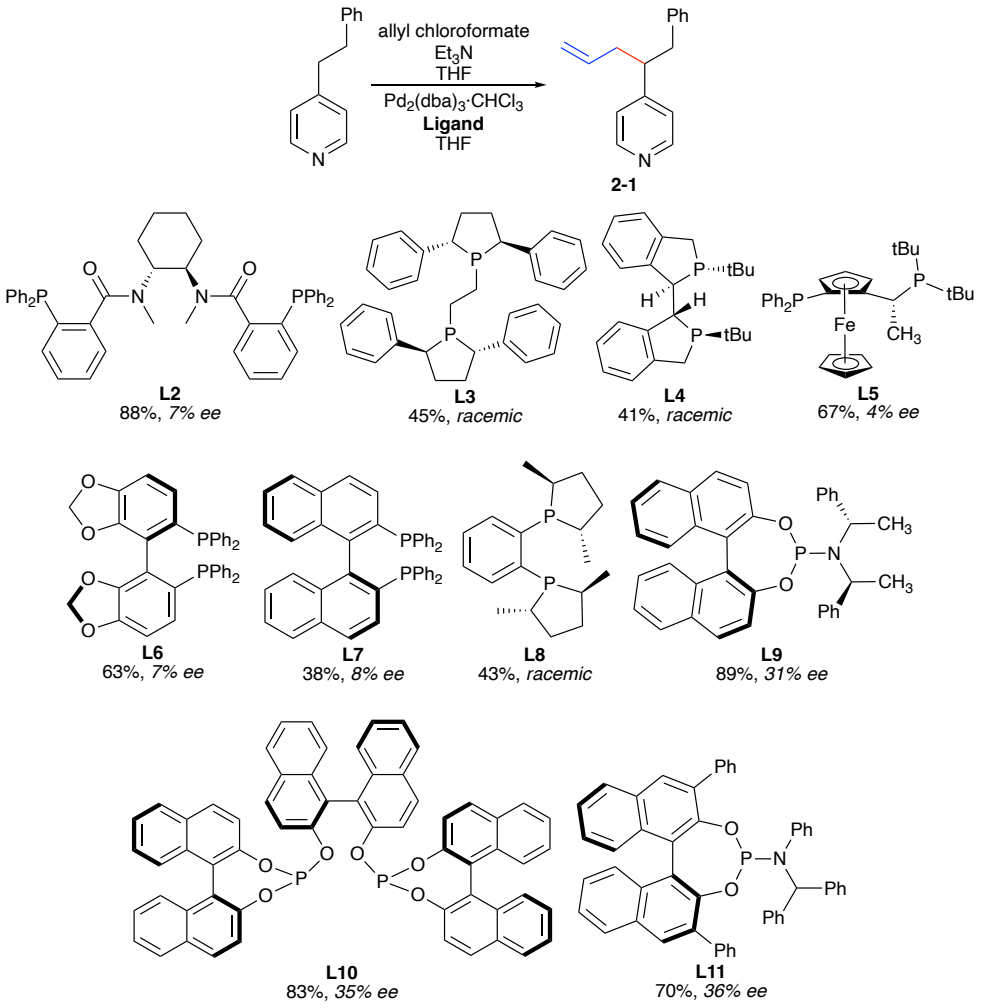
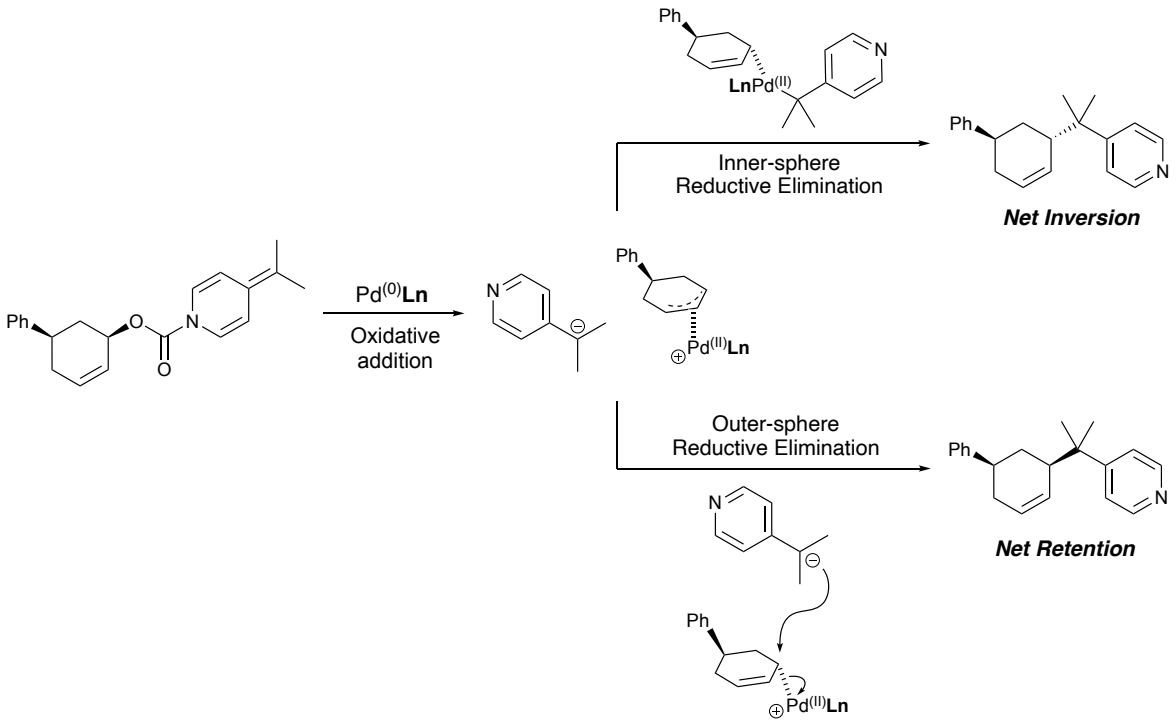


Figure 9: Ligand screen for enantioselective allylation of 4-phenethylpyridine.

2.3 Investigating the nature of pyridylic anion

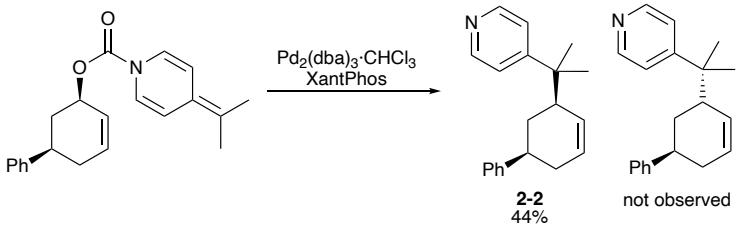
Our group performed a series of experiments to better understand the reductive elimination step, because it dictates the stereochemical outcome of the reaction. One of the mechanistic studies that our group conducted was to apply standard allylation condition to an ADHP, that contained a phenyl-cyclohexenoxy-carbonyl group, as a stereochemical probe to provide valuable insights into the reductive elimination pathway through which the allylation proceeded (**Scheme 8**). NOESY proton nuclear magnetic resonance (NMR) analysis would help us determine the stereo-configuration of the product. This, in turn, would help understand the nature the nucleophile. If our pyridylic anion behaved as a “hard” nucleophile, it would undergo

inner-sphere reductive elimination, resulting in a net inversion of stereochemistry. On the other hand, “soft” nucleophile would proceed through outer-sphere pathway and attack the allyl group in an S_N2 manner, leading to a net retention of stereochemistry.



Scheme 8: Two reductive elimination pathways for allylation reaction.

Upon applying the standard condition, our group member, Isabelle Hunter, observed the reaction proceeded with an overall retention of stereochemistry, suggesting that pyridylic anions undergo outer-sphere reductive elimination for allylation reaction (**Scheme 9**). This unexpected finding led us to establish a new pKa threshold for outer-sphere allylation.

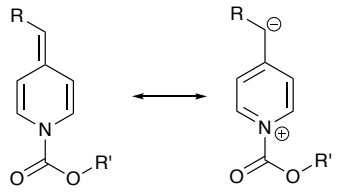


Scheme 9: Allylation of 4-alkylpyridines undergoes outer-sphere reductive elimination.

(Result obtained from Isabelle Hunter)

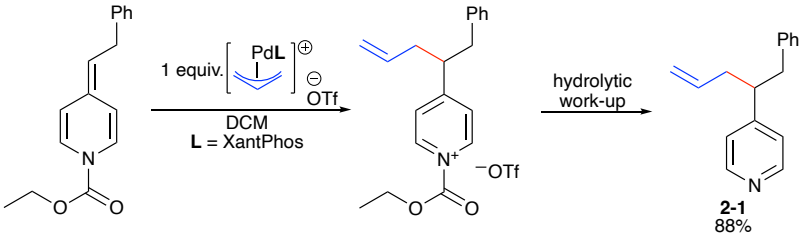
2.4 Revealing the nucleophilicity of alkylidene dihydropyridine

After discovering that pyridylic anion could attack the allyl group of the allylpalladium(II) species, we became interested in testing if ADHP itself could intercept with the complex in the same manner. Proton NMR analysis shows upfield shifts for the pyridyl protons (from 8.6 ~ 7.1 ppm to 6.9 ~ 5.5 ppm) when 4-alkylpyridines are converted to their corresponding ADHPs. This implies an increase in electron density in the system during the process. Moreover, ADHP possesses an enamine-like system, suggesting its latent nucleophilic nature (**Scheme 10**).



Scheme 10: Latent nucleophilicity of ADHPs at exocyclic carbon.

Our group member, Nour Wasfy, synthesized an ADHP carrying no allyl fragment and treated it with freshly prepared allylpalladium(II) complex (**Scheme 11**). Gratifyingly, the reaction produced the allylation compound in 88% yield through an aqueous work-up procedure, albeit a lower reaction rate.[31] This discovery encouraged us to explore reactions with other electrophiles using ADHP as the key intermediate, so that 4-pyridylic functionalization could be performed under milder conditions.



Scheme 11: Ethyl-ADHP as nucleophile in palladium-catalyzed allylation of 4-alkylpyridines.

(Result obtained from Nour Wasfy)

To summarize, although our efforts towards asymmetric allylation through ligand screening did not achieve the expected enantioselectivity, it motivated us to conduct detailed

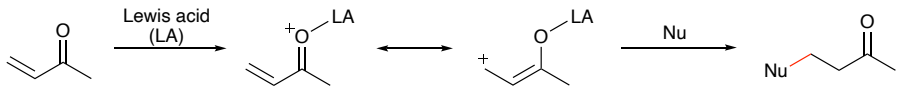
investigations on the reductive elimination step. Mechanistic study revealed that pyridylic anions underwent outer-sphere pathway, and this discovery helped established new pKa threshold for soft nucleophiles. Furthermore, we were delighted to demonstrate the nucleophilicity of ADHP with its reaction with an allylpalladium(II) complex. This encouraged us to explore other reactions using ADHP for milder functionalization at the 4-pyridylic site.

Chapter 3: Conjugate addition of alkylidene dihydropyridines to α,β-unsaturated ketones

3.1 Conjugate addition involving activation of α,β-unsaturated ketones

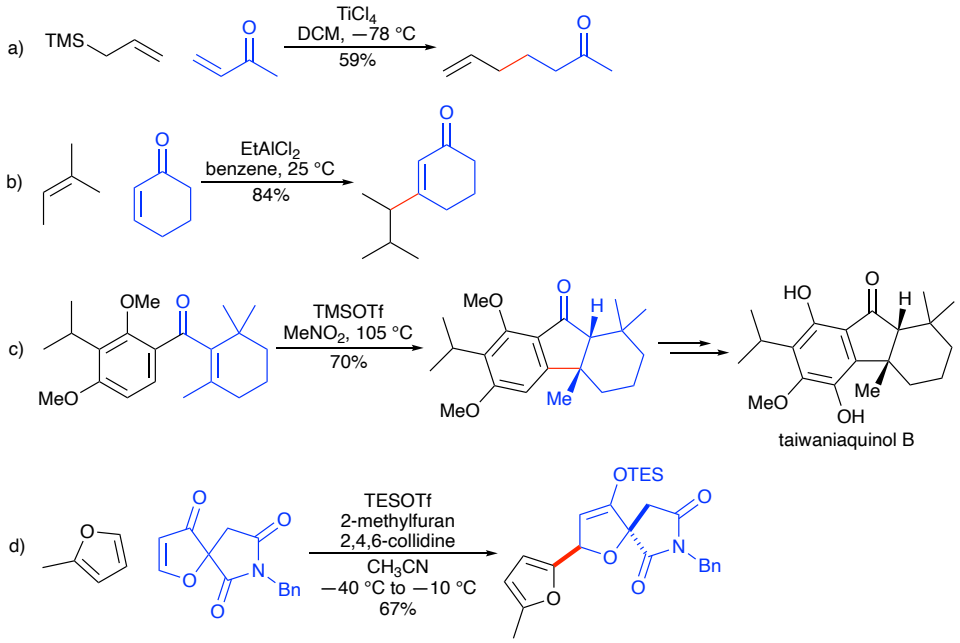
Inspired by the results obtained from the mechanistic study of the allylation reaction, we decided to exploit the reactivity of the ADHP in other chemical transformations. We first put our attention on developing the alternative way to conduct conjugate addition to α,β-unsaturated ketones because current methods have several limitations.

Besides the focus on activating the pro-nucleophiles through deprotonation, the use of Lewis acids to enhance the inherent electrophilicity of the β-carbon of α,β-unsaturated ketones can also facilitate conjugate addition (**Scheme 12**).[38] This is particularly useful when neutral nucleophiles are involved.



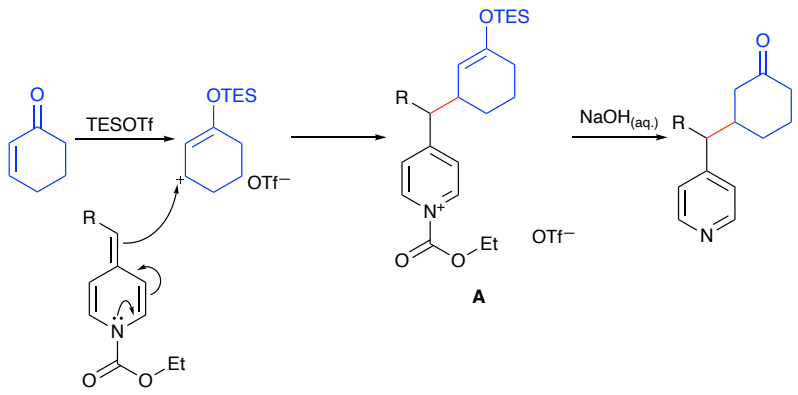
Scheme 12: Conjugate addition involving Lewis acid and neutral nucleophile.

Early developments by Sakurai's and Snider's groups used titanium tetrachloride and ethyl aluminum dichloride to activate unsaturated ketones by coordination of the Lewis acidic metal with a non-bonding electron pair on the ketone oxygen atom, allowing conjugate addition of allylsilanes and alkenes, respectively (**Scheme 13**: equations **a** and **b**).[39,40] Methods that use non-metal Lewis acids are also reported in the literature. For example, Trauner's group employed trimethylsilyl triflate (TMSOTf) to activate the unsaturated ketone to facilitate Friedel-Crafts type conjugate addition in the synthesis of natural product Taiwaniaquinol B (**Scheme 13**: equation **c**).[41] One of the advantages of using silicon-based Lewis acid in conjugate addition is the formation of a reasonably stable silyl enol ether, through a neutral work-up procedure, that can serve as a protecting group of the ketone moiety for further transformations. For instance, Rovis' group used triethylsilyl triflate (TESOTf) to form the corresponding silyl enol ether, which was then carried forward for the synthesis of antibiotic FD-838 (**Scheme 13**: equation **d**).[42]



Scheme 13: Examples of conjugate additions involving unsaturated ketones activated by Lewis acids.

We thus hypothesized that ADHPs could react with α,β-unsaturated ketones that are intercepted by a silyl triflate to generate the pyridinium species (**Scheme 14**: compound **A**). The intermediate could then undergo desilylation and hydrolysis under aqueous basic conditions to deliver the desired conjugate product. Such reaction would provide a mild alternative to the existing methods. Based on our previous works, we expected the new method to regioselectively functionalize the 4-pyridylic position.

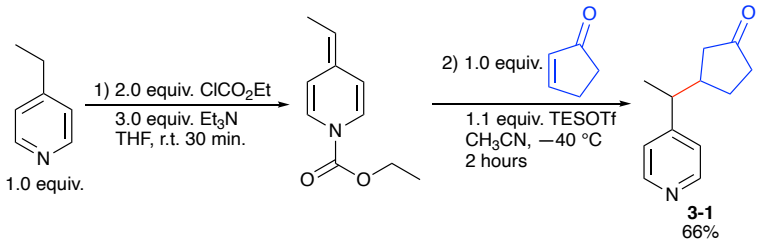


Scheme 14: Proposed mechanism for conjugate addition of ADHP to activated α,β-unsaturated ketones.

3.2 Conjugate addition of alkylidene dihydropyridines to activated unsaturated ketones

3.2.1 Proof of concept and optimization

I commenced the study by taking one equivalent of ADHP, formed with 4-ethylpyridine in quantitative yield, and mixing it with one equivalent of 2-cyclopenten-1-one, followed by the addition of 1.1 equivalents of TESOTf at –40 °C (**Scheme 15**). After stirring the reaction mixture for 2 hours, proton NMR showed the consumption of ADHP and the formation of a pyridinium intermediate (**Figure 10**: spectrum **B**). The reaction mixture was then quenched with 1 M aqueous sodium hydroxide at 0 °C. Through subsequent extraction and purification steps, we were delighted to observe pyridine signals at ~ 8.5 ppm and ~ 7.1 ppm from ^{1}H NMR spectra (**Figure 10**: spectra **C** and **D**), and ketone signal at ~ 218 ppm from ^{13}C NMR spectra (**Figure 11**: spectra **A** and **B**). After performing flash column chromatography, the two liquid products, **3-1a** and **3-1b**, were collected in 66% overall yield, with a diastereomeric ratio of 2:1 (**Table 1**: entry **1**). Unfortunately, I was not able to unambiguously assign their stereogenic configurations based on NOSEY NMR analysis, likely due to rapid rotation along the carbon-carbon bond (**Figure 12**, highlighted in red).



Scheme 15: First attempt for conjugate addition of ADHP to activated 2-cyclopenten-1-one.

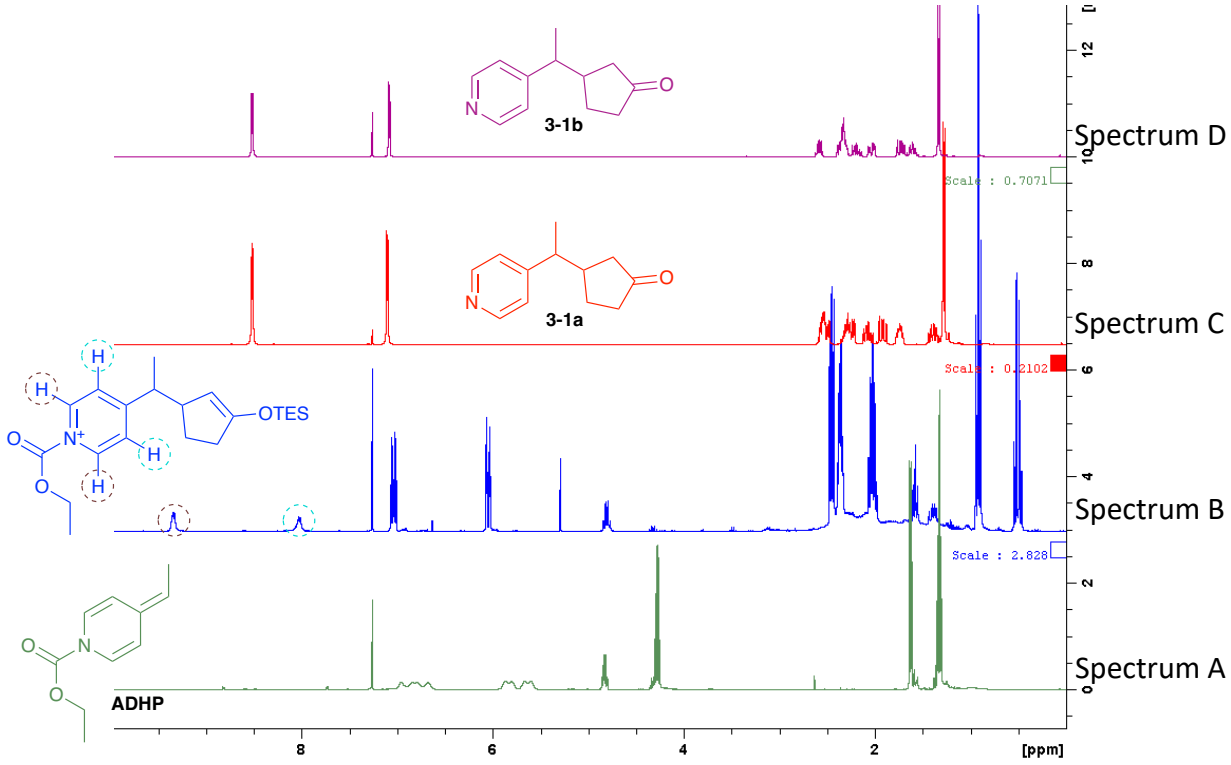


Figure 10: Overlapped proton NMR spectra for monitoring the conjugate addition of ADHP to activated 2-cyclopenten-1-one.

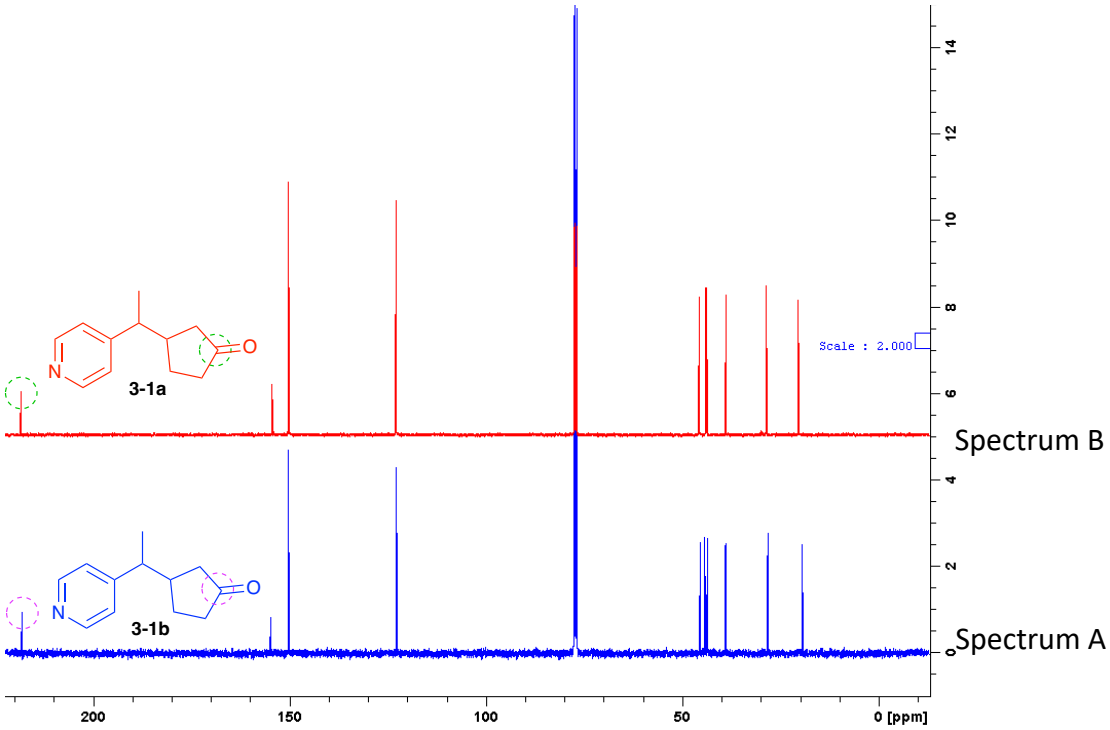


*Figure 11: Overlapped carbon NMR spectra for compounds **3-1a** and **3-1b**.*

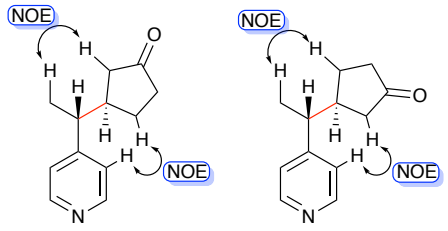
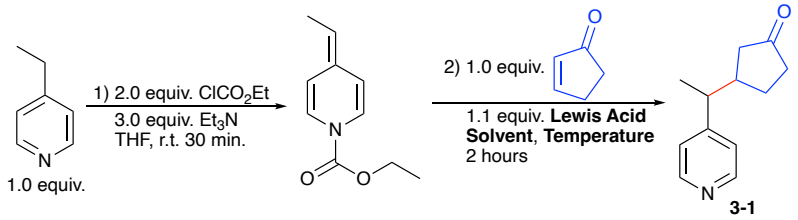


Figure 12: NOE interactions that can help determine stereogenic configurations of the two diastereomers.

A moderate yield obtained from the first attempt encouraged us to investigate the possibility of improving it to a higher level. Since the ADHP formation step generated quantitative yield with good purity, I focused more attention on the addition step. I started the optimization by testing different reaction conditions, including Lewis acids, temperatures and solvents (**Table 1**).

Table 1: Relationship between the product yield and the changes in reaction conditions

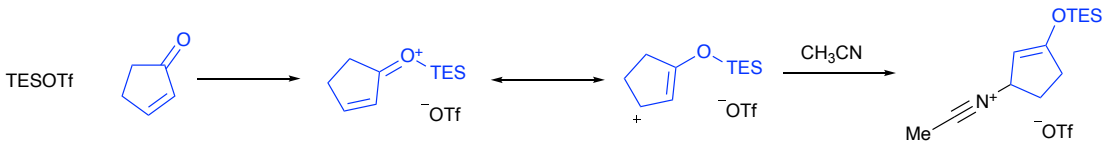


Entry	Lewis acid	Temperature	Solvent	Yield
1	**TESOTf**	**–40 °C**	**CH_3CN**	**66%[a]**
2	TESOTf	–40 °C to 0 °C	CH_3CN	50%
3	TESOTf	–40 °C to r.t.	CH_3CN	38%
4	TESOTf	–40 °C	THF	28%
5	TESOTf	–40 °C	DCM	55%
6	$BF_3{\cdot}OEt_2$	–40 °C	CH_3CN	59%
7	$Sc(OTf)_3$	–40 °C	CH_3CN	66%
8	$In(OTf)_3$	–40 °C	CH_3CN	37%
9	$Zn(OTf)_2$	–40 °C	CH_3CN	13%
10	$Al(OTf)_3$	–40 °C	CH_3CN	62%
11	$AlCl_3$	–40 °C	CH_3CN	48%
12	$Ga(OTf)_3$	–40 °C	CH_3CN	21%
13	HCl	–40 °C	CH_3CN	No Reaction
14	$Sc(OTf)_3$ (10 mol%)	–40 °C	CH_3CN	< 10%

a) Under optimized condition, the overall yield was 81% with d.r. = 2:1.

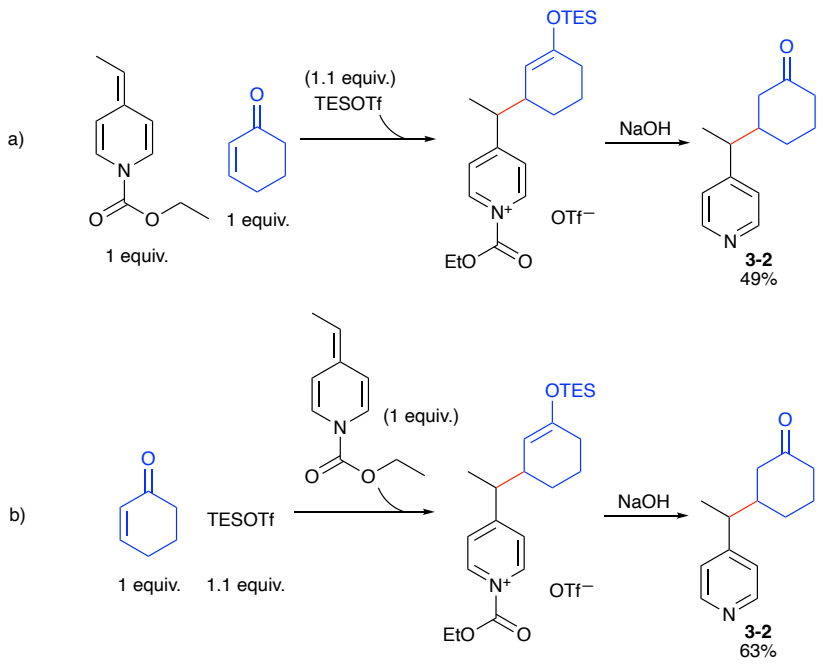
According to the data obtained, as listed in **Table 1**, we found that lower temperature helped minimize the decomposition of ADHP and pyridinium intermediate, thereby improved the overall yield (**Table 1**: entries **1** to **3**). In terms of solvents (**Table 1**: entries **1**, **4** and **5**), acetonitrile was confirmed to be a better solvent likely due to its ability to stabilize the allyl triethylsilyloxy

cation by forming the corresponding acetonitrilium ion (**Scheme 16**).[43] The use of the boron reagent generated the product with less yield (**Table 1**: entry **6**). Several Lewis acids were also tested (**Table 1**: entries **6** to **12**), and scandium triflate worked best by delivering the product in 66% yield. I eventually decided to use TESOTf as the Lewis acid activator as it provided the highest yield in Lewis acid screen and the potential use of silyl enol ether. I also tried to activate the unsaturated ketone using hydrochloric acid, but the reaction did not take place (**Table 1**: entry **13**). Lastly, I tested catalytic amount of scandium triflate, and the product was obtained in less than 10% yield (**Table 1**: entry **14**).

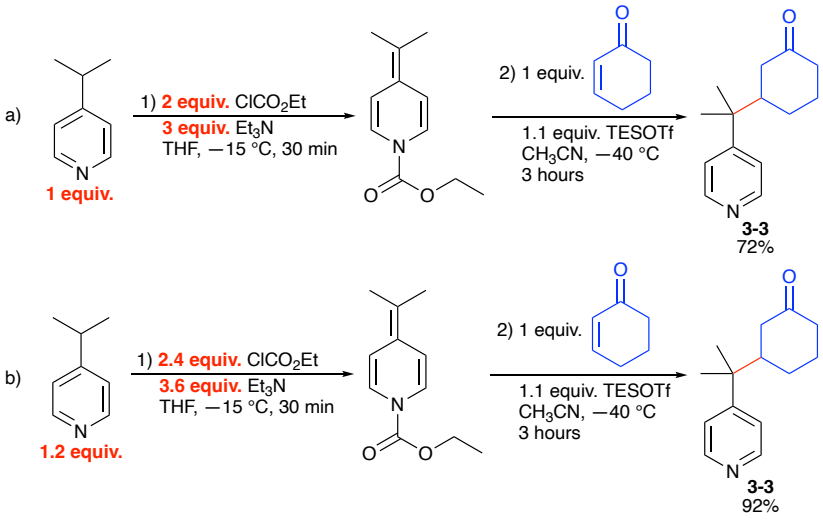


Scheme 16: Formation of acetonitrilium ion stabilizes the allyl triethylsilyloxy intermediate.

We observed that a certain amount of unsaturated ketone remained in the crude ^{1}H NMR spectrum (*e.g.*, **Figure 10**, spectrum **B**). We reasoned the Lewis acid could potentially interact with the carbamate group of the ADHP, leaving some of the unsaturated ketone inactive towards the desired reaction (**Scheme 17**, equation **a**). As a result, I started the reaction by mixing the unsaturated ketone with TESOTf first to ensure more complete activation, followed by the addition of ADHP (**Scheme 17.** equation **b**). This change in order of addition improved the yield to 63%. I also recognized that ADHP decomposed over a certain period. Therefore, I decided to use 1.2 equivalents of it for the reaction to maximize the consumption of the activated unsaturated ketone. These modifications led us to obtain the desired product in 92% yield using 4-isopropylpyridine as the starting material (**Scheme 18**, equation **b**).



Scheme 17: Order of addition affects the yield of the reaction.



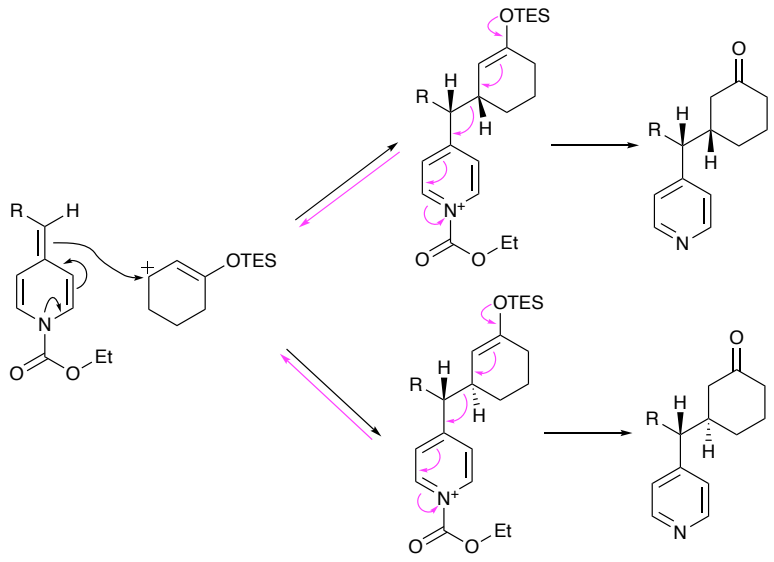
Scheme 18: Relationship between the amount of pyridine starting material and the final yield.

Overall, considering the potential instability of the ADHP, we maintained the reaction temperature at –40 °C to minimize its decomposition. In addition, we employed a slight excess of ADHP to ensure complete consumption of the unsaturated ketone. Furthermore, changing the order of addition minimized undesired interactions between TESOTf and ADHP and helped achieve more complete activation of the unsaturated ketone.

3.2.2 Substrate scope

Having developed the optimized condition, I conducted a series of experiments to explore the functional group tolerance of our method (**Table 2**). In most cases, I used 4-methylpyridine derivatives to avoid the formation of diastereomers and simplify the characterization process. It is worth noting that ADHPs generated from 4-methylpyridines are sensitive to acetonitrile at ambient temperature and will form insoluble substances. Therefore, THF was used as a co-solvent to dissolve these ADHPs for conjugate addition due to better solubility.

I began by testing various 4-alkylpyridines (**Table 2**: **3-2** – **3-7**) and obtained good yields. The method was shown to be regioselective toward the 4-pyridylic site (**3-7**). Our method generated compound **3-2** with a diastereomeric ratio of 2:1, while both compounds **3-5** and **3-6** were produced with a diastereomeric ratio of 1:1. The low diastereoselectivity may be the result of the reaction being reversible (**Scheme 19**), and the diastereomeric ratio was influenced by the thermodynamic stabilities of the isomers.

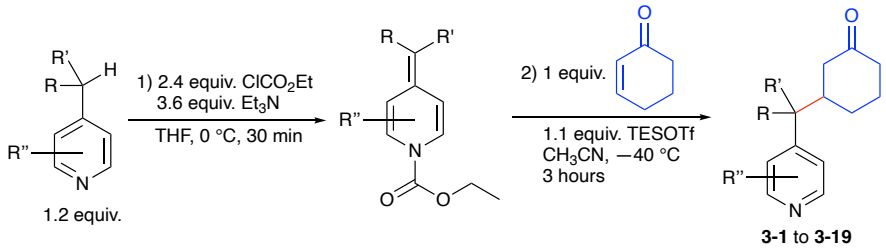


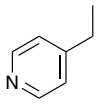
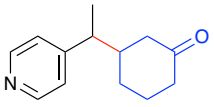
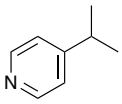
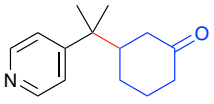
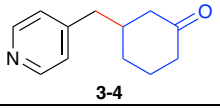
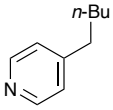
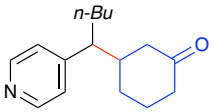
Scheme 19: Reverse reaction (highlighted in pink) may be the cause for low diastereoselectivity.

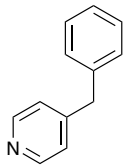
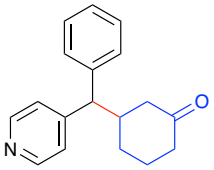
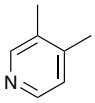
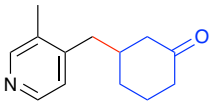
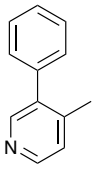
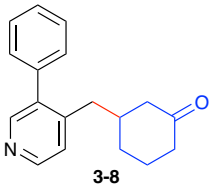
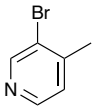
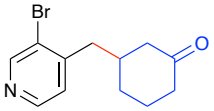
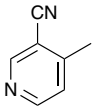
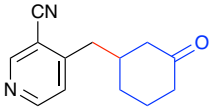
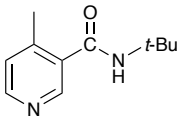
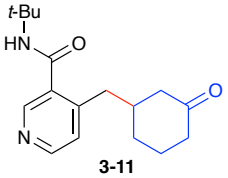
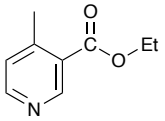
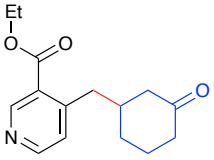
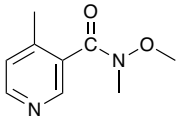
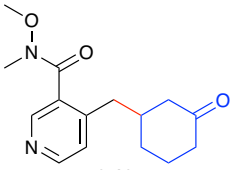
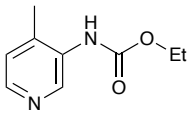
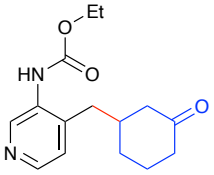
Our method generated high yields for ADHPs with various 4-alkylpyridines as well as relatively electron-rich systems (**Table 2**: **3-2** to **3-8**, **3-18**, **3-19**). Conversely, electron-withdrawing

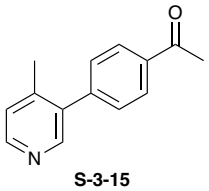
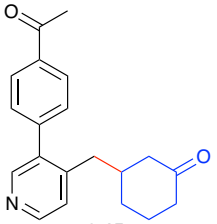
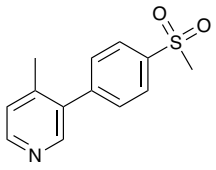
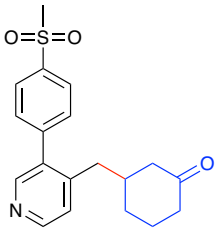
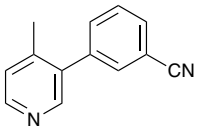
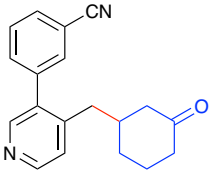
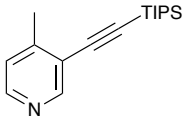
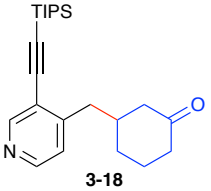
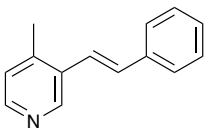
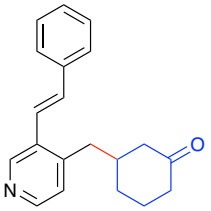
groups would decrease the nucleophilicity of ADHPs, resulting in lower yields (**3-9** to **3-12**). This was well demonstrated by compounds **3-10** and **3-17**. For **3-17**, the phenyl group was not co-planar with the pyridine ring, so the cyano group had less direct effect on the nucleophilicity of the ADHP. As a result, the yield was greatly improved. Because the ADHP formation and the addition steps did not require harsh conditions, our method could functionalize the 4-pyridylic site while leaving more activated carbons unreacted (**3-15**, **3-16**). More importantly, the mild transformation could tolerate various functional groups, including ketone, sulfone, ester, nitriles, and amides (**3-9** to **3-17**). Finally, when multiple heteroatoms were present the efficiency of our method was impacted significantly (**3-13**, **3-14**), likely because of their interactions with the Lewis acid.

Table 2: Substrate scope for conjugate addition of ADHPs to unsaturated ketones



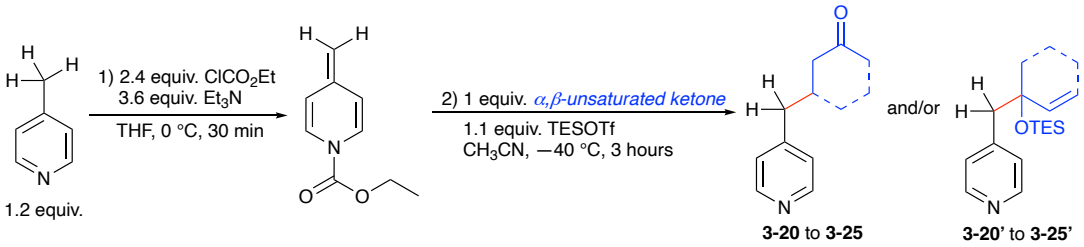
Entry	Substrate	Product	Yield
1		 **3-2**	89%, d.r = 2.1
2		 **3-3**	92%
3		 **3-4**	81%
4		 **3-5**	97%, d.r. = 1:1

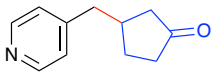
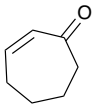
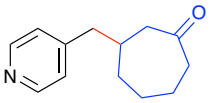
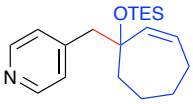
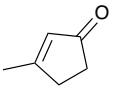
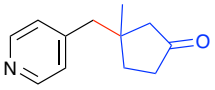
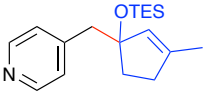
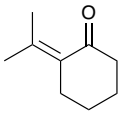
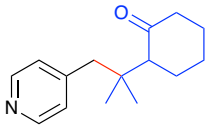
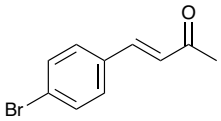
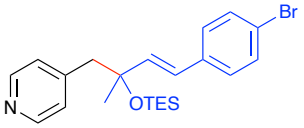
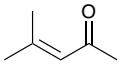
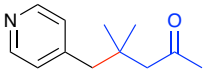
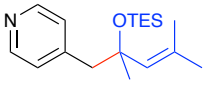
5		 **3-6**	80%, d.r. = 1:1
6		 **3-7**	92%
7		 **3-8**	85%
8		 **3-9**	76%
9		 **3-10**	35%
10	 **S-3-11**	 **3-11**	45%
11	 **S-3-12**	 **3-12**	54%
12	 **S-3-13**	 **3-13**	10%
13	 **S-3-14**	 **3-14**	29%

14	 S-3-15	 3-15	73%
15	 S-3-16	 3-16	59%
16	 S-3-17	 3-17	72%
17	 S-3-18	 3-18	83%
18	 S-3-19	 3-19	86%

I then examined various unsaturated ketones using the ADHP made from 4-methylpyridine (**Table 3**). The reactions with 2-cyclopenten-1-one and 2-isopropylidene cyclohexanone produced good yields (**3-20** and **3-23**). We found direct 1,2-addition took place when the carbonyl carbon became more accessible and/or the steric encumbrance around the β-carbon increased (**3-21'**, **3-22'**, and **3-25'**). In a more extreme case, direct addition became dominant when the β-carbon carried a large substituent (**3-24'**).

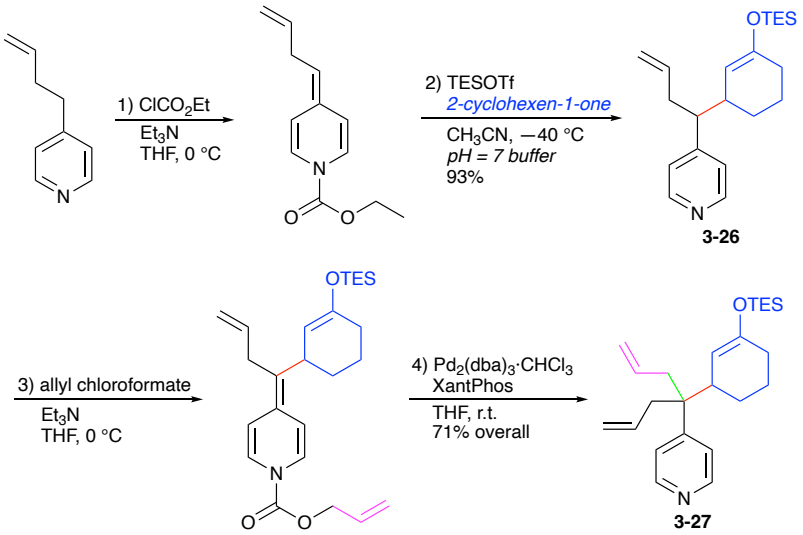
Table 3: Substrate scope for conjugated addition of 4-methyl-ADHP to α,β-unsaturated ketones



Entry	Unsaturated Ketone	Product(s)	Yield
1		 **3-20**	81%
2		 **3-21**	74%
		 **3-21'**	20%
3		 **3-22**	48%
		 **3-22'**	6%
4		 **3-23**	58%
5	 **S-3-24**	 **3-24'**	62%
6		 **3-25**	21%
		 **3-25'**	41%

3.2.3 Derivatization of the conjugate product

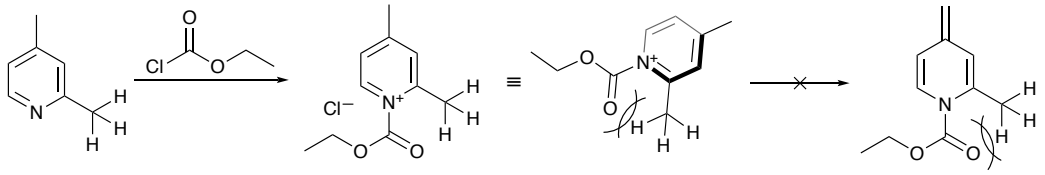
As mentioned earlier, the advantage of using silicon-based Lewis acid is the possible formation of the corresponding silyl enol ether in a regioselective manner through a neutral work-up procedure. This class of compounds can then be utilized for further transformations. For instance, the conjugate addition of ADHP, formed with 4-(3-buten-1-yl)-pyridine, delivered its corresponding silyl enol ether by following a neutral work-up using a pH = 7 buffer (**Scheme 20**: **3-26**). This intermediate could then be transformed into a second ADHP which, when subjected to palladium-catalyzed allylation condition, would generate the final product **3-27** with an overall yield of 71%.



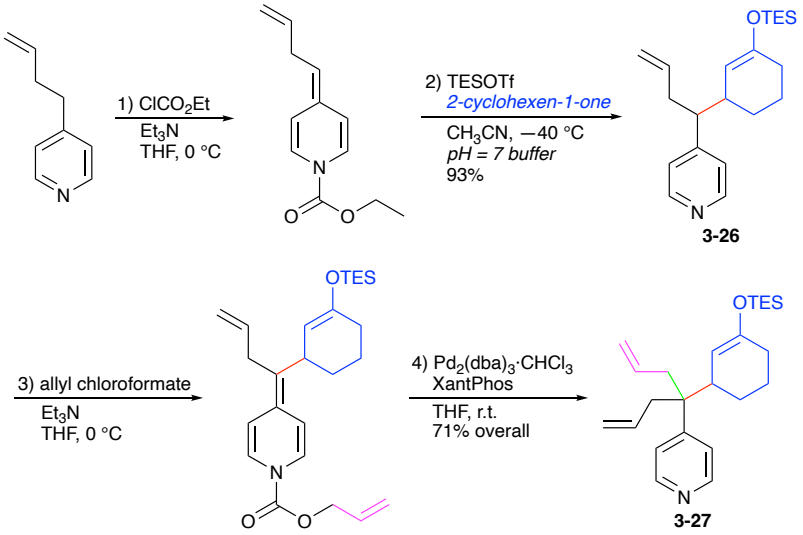
Scheme 20: Palladium-catalyzed allylation of 4-alkylpyridine synthesized through optimized conjugate addition of 4-(3-buten-1-yl)-pyridine with a neutral work-up procedure.

Generating the silyl enol ether also helps us overcome a limitation of our method. While 2,4-disubstituted pyridine can react with chloroformate, the resulting pyridinium cation cannot be deprotonated to form the corresponding ADHP to participate in conjugate addition, owing to the non-planar orientation of the pyridine ring and the alkoxycarbonyl group (**Scheme 21**).[32] To address this problem, I took the 4-substituted pyridine and applied the modified condition to generate the silyl enol ether (**Scheme 22**: compound **3-27**). This was then treated with allyl

chloroformate and a Grignard reagent to afford the corresponding dihydropyridine which, after palladium-catalyzed decarboxylative oxidation, was converted to the pyridine **3-29** with the substituent at the C-2 position. It is worth noting that the installation process would not be possible without the silyl enol ether because the carbonyl group would be affected by the Grignard reagent.



Scheme 21: Non-planar orientation of the pyridine ring and the alkoxycarbonyl group prevents the formation of ADHP.



Scheme 22: The use of silyl enol ether in synthesizing 2-substituted pyridine.

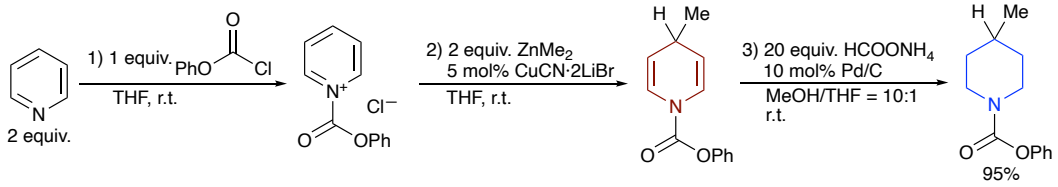
To summarize, we developed an alternative method to the current ones for conjugate addition of 4-alkylpyridines through the reaction of their corresponding alkylidene dihydropyridines to α,β-unsaturated ketones activated by TESOTf. The method uses mild condition and tolerates a wide array of functional groups. Substrate scope showed our method is regioselective towards the 4-pyridylic site. As for the electrophile, when the β-carbon carries a substituent and/or the carbonyl carbon becomes more accessible for nucleophilic attack, 1,2-addition could take place.

Additionally, the use of the silyl triflate facilitates the formation of silyl enol ether which enables further chemical transformations. In particular, it addresses the constraint posed by the inability to generate ADHP from 2,4-disubstituted pyridines.

Chapter 4: Piperidine installation through addition of alkylidene dihydropyridines to pyridine hydrochloride

4.1 Nucleophilic addition to activated pyridine for piperidine synthesis

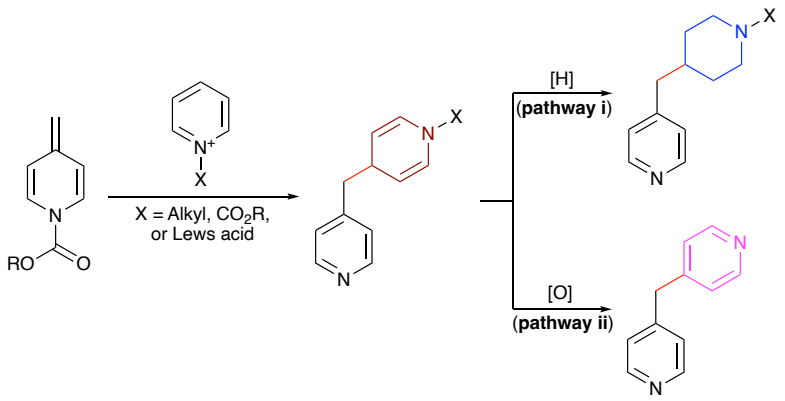
We then embarked on developing methods that can mildly unite the piperidine with pyridine through a carbon linker. Aside from the strategies that rely on combining existing piperidine and pyridine substrates, as mentioned in **Chapter 1**, literatures precedent have shown that addition to *N*-activated pyridinium cation can deliver the corresponding dihydropyridine adduct. This intermediate can then be hydrogenated to produce the desired piperidine product (**Scheme 23**).[44,45]



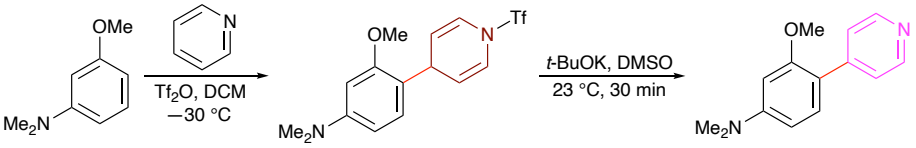
Scheme 23: Sample nucleophilic addition to N-activated pyridinium cation for piperidine synthesis.

4.2 Addition of alkylidene dihydropyridine to *N*-triflyl pyridinium cation

Building upon the success of the conjugate addition project, we envisioned that alkylidene dihydropyridine could also be intercepted with an activated pyridinium cation to generate its corresponding dihydropyridine. Subsequent hydrogenation would eventually achieve the goal of installing a piperidine moiety on 4-pyridylic position (**Scheme 24**: pathway **i**). One advantage of generating dihydropyridine through this logic is the possible oxidation pathway to form a bis-pyridine compound, which itself could be of great value (**Scheme 24**: pathway **ii**). For instance, Corey's group demonstrated a metal-free 4-arylation of activated pyridine to generate the *N*-triflyl dihydropyridine, which was then re-aromatized to pyridine using potassium *tert*-butoxide in DMSO (**Scheme 25**).[46]

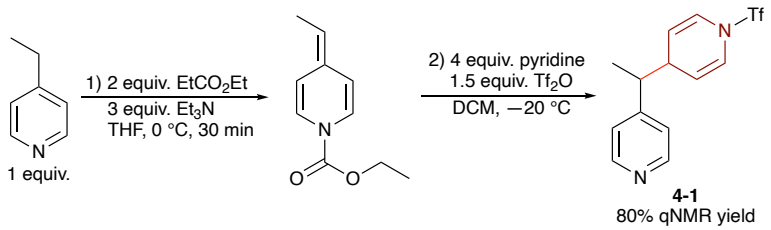


Scheme 24: Proposed addition of ADHP to activated pyridine.



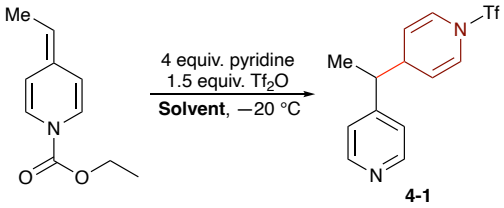
Scheme 25: Nucleophilic addition to N-triflyl pyridinium cation followed by oxidation.

Our exploration began by referring the reaction condition reported by Corey's group with one equivalent of 4-ethylpyridine as the starting material (**Scheme 26**). We were pleased to see the reaction generated the expected *N*-triflyl dihydropyridine compound in 80% qNMR yield (**Table 4**: entry **1**). However, although further solvent screen revealed that acetonitrile could increase the yield to 86% (entry **3**), we realized the reduction of such intermediate requires elevated hydrogen gas pressure,[47] making the method less practical for industrial use. Therefore, we began searching for different ways to activate the pyridine.



Scheme 26: First attempt for addition of ADHP to N-triflyl pyridinium cation by following Corey's condition.

Table 4: Solvent screen for addition of ADHP to N-triflyl pyridinium cation



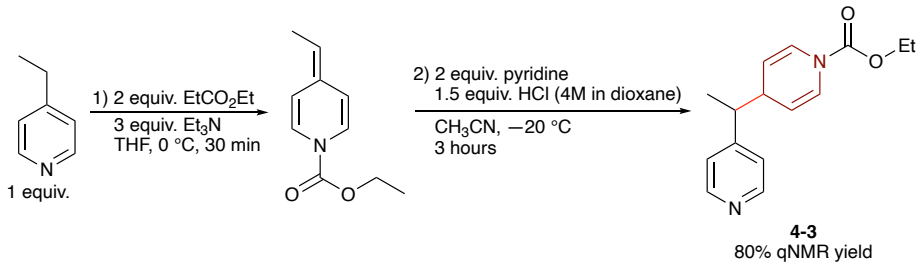
Entry	Solvent	qNMR Yield for *N*-triflyl Dihydropyridine[a]
1	DCM	80 %
2	THF	79 %
3	**CH_3CN**	**86 %**
4	Toluene	54 %
5	Ether	54 %

a) Quantitative NMR yield was obtained using 1,3,5-trimethoxybenzene as the internal standard. The relaxation time for protons was set to be 30 seconds.

4.3 Addition of alkylidene dihydropyridine to pyridine hydrochloride

Recognizing that pyridine contains an imine-like structure, I was tempted to activate it by simple protonation using a Brønsted acid and see if the addition could take place. Therefore, I conducted the experiment by preparing the pyridine hydrochloride *in situ* and treated it with the ADHP under –20 °C in acetonitrile (**Scheme 27**). Gratifyingly, proton NMR spectrum showed the consumption of ADHP after 3 hours (**Figure 13**: spectrum **B**). The reaction was then quenched

with saturated sodium bicarbonate, and the proton NMR spectrum showed two broad doublets at ~ 6.7 ppm and ~ 4.8 ppm, suggesting the hydrogen atoms on the dihydropyridine ring (**Figure 13**: spectrum **C**, compound **4-3**). There were also two signals at ~ 4.3 ppm and ~ 1.7 ppm, which indicated the existence of an ethoxycarbonyl group in the product. This implied a group transfer process was involved. It was later confirmed **4-3** was produced in 80% qNMR yield.



Scheme 27: Addition of ADHP to pyridine hydrochloride.

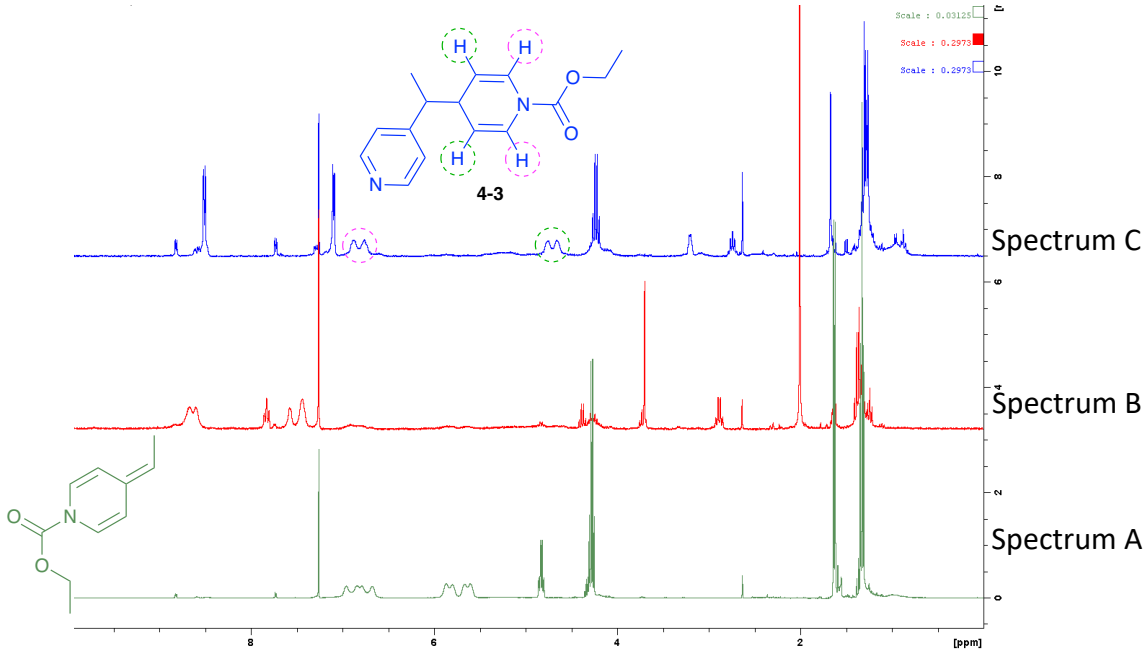
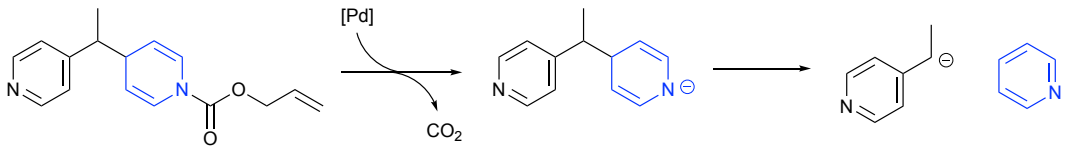


Figure 13: Overlapped proton NMR spectra for monitoring piperidine installation on 4-ethylpyridine.

To minimize the use of solvents during the extraction step, I decided to use four equivalents of triethylamine as the base, so that the newly formed triethylammonium chloride salt could be removed through simple filtration in ether medium. I was pleased to see the yield was

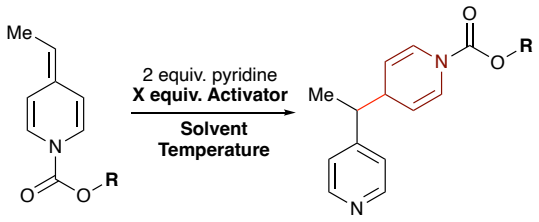
not affected. It is worth noting that the DHP intermediate is not fully recoverable from flash column chromatography. Therefore, quantitative NMR yield was used, with 1,3,5-trimethoxybenzene as the internal standard, to study the outcome of the addition step.

I started optimizing the addition of the ADHP by screening different solvents, temperatures as well as chloroformates (**Table 5**). The addition did not progress at –40 °C (entry **2**). It implied that pyridine hydrochloride was not as reactive as activated α,β-unsaturated ketones. More decomposition took place when the reaction was done at 0 °C (entry **3**), as confirmed by proton NMR analysis. I also observed that pyridine hydrochloride did not dissolve in THF at –20 °C, resulting in no reaction progress (entry **4**). The reaction still occurred with catalytic amount of HCl, but the yield was lower (entry **5**), possibly due to more decomposition over long reaction time. Interestingly, when the ADHP that was formed with allyl chloroformate was used, the yield of the DHP increased to 88% (entry **6**). It meant the substituent at the distal carbamate group could influence the reactivity of the ADHP. However, we planned to use palladium catalyst in the subsequent hydrogenation step, and it would form an allylpalladium complex with the allyl-DHP, resulting in decomposition of the dihydropyridine product and the formation of the pyridylic anion (**Scheme 28**). Therefore, we decided to maintain the use of ethyl chloroformate. Lastly, I tried to activate the pyridine electrophile using ethyl chloroformate directly, but the reaction generated the DHP in less than 20% qNMR yield (entry **7**).



Scheme 28: Interaction between palladium with allyl-DHP leads to formation of pyridylic anion.

Table 5: Optimization for addition of alkylidene dihydropyridine to pyridinium chloride



Entry	R	Activator	Solvent	Temperature	qNMR yield
1	**Ethyl**	**1.5 equiv. HCl**	**CH_3CN**	**–20 °C**	**80%**
2	Ethyl	1.5 equiv. HCl	CH_3CN	–40 °C	No reaction
3	Ethyl	1.5 equiv. HCl	CH_3CN	0 °C	58%
4	Ethyl	1.5 equiv. HCl	THF	–20 °C	No reaction
5	Ethyl	0.1 equiv. HCl	CH_3CN	–20 °C	67%
6	Allyl	1.5 equiv. HCl	CH_3CN	–20 °C	88%
7	Ethyl	1.5 equiv. ethyl chloroformate	CH_3CN	–20 °C	< 20%

I then focused the attention on the reduction step of the DHP intermediate using 10 mol% of palladium on carbon (10% w/w) as the catalyst (**Table 6**). I first applied one atmosphere of hydrogen pressure on a THF solution using hydrogen gas balloons. I then concentrated the reaction mixture and obtained tetrahydropyridine compound (**4-4'**) in 26% yield after purification through flash column chromatography (**Table 6**: entry **1**). I then employed the transfer hydrogenation approach by using forty equivalents of triethylamine and twenty equivalents of formic acid. After heating under reflux for three days, the piperidine product was obtained in 26% yield, alongside the tetrahydropyridine at a 67% yield (**Table 6**: entry **2**). I used twenty equivalents of ammonium formate salt as the alternative hydrogen source and stirred the mixture in methanol under ambient temperature. The piperidine product was isolated in 50% overall yield (**Table 6**:

entry **3**, **4-4**) and observed four signals at the regions of ~ 4.3 ppm and ~ 2.7 ppm on the proton NMR spectrum, suggesting the hydrogen atoms at the equatorial positions of a piperidine moiety (**Figure 14**).

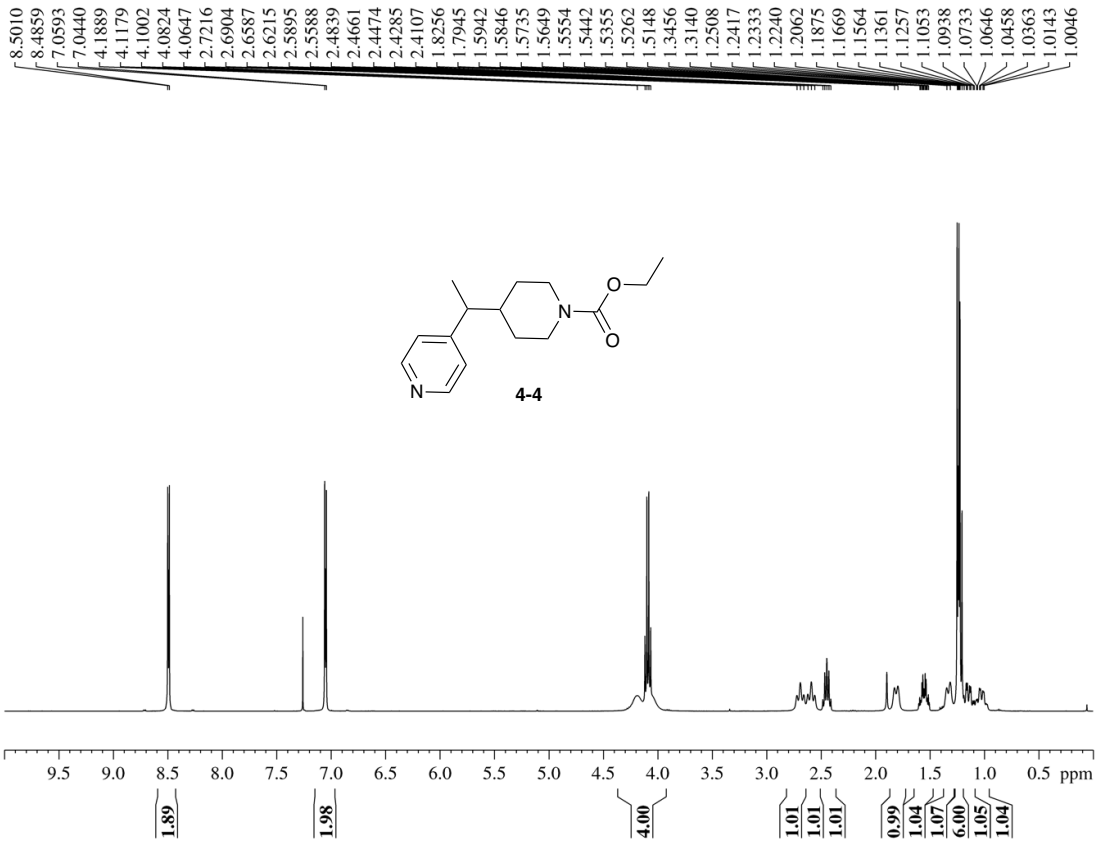
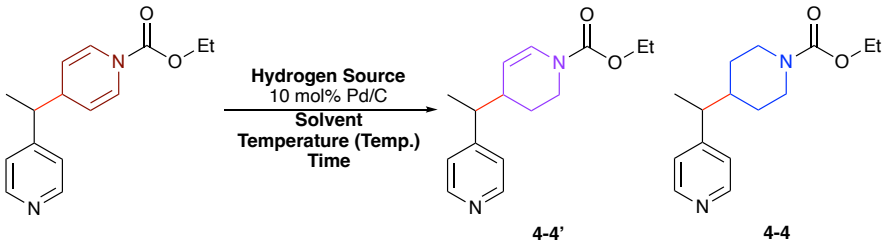


*Figure 14: Proton NMR spectrum for compound **4-4**.*

Notably, I observed DHP became a viscous substance upon mixing with methanol, which may explain the low yield. I thus used THF instead and found ammonium formate did not dissolve well, resulting in no reaction progress (**Table 6**: entry **4**). As a result, I experimented with different ratios of methanol and THF (**Table 6**: entries **5** to **7**). I observed 5% THF content in methanol was the optimal solvent condition for the hydrogenation step with the piperidine product being isolated in 84% overall yield (**Table 6**: entry **7**). I also attempted the use of ethanol and isopropanol and

observed a decrease in overall yield, as ammonium formate became less soluble in aliphatic solvents (**Table 6**: entries **8** and **9**). Finally, activating the pyridine with boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) or TESOTf led to the same product with less yields, while the use of diethyl maleate[48] as a covalent activating group for the pyridine electrophile did not provide the corresponding DHP product.

Table 6: Optimization for hydrogenation of dihydropyridine



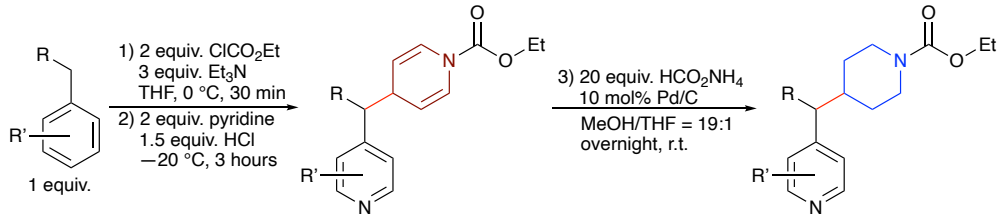
Entry	Hydrogen Sources	Solvent	Temp.	Times	Overall Yield 4-4'	Overall Yield 4-4
1	3 H_2 balloons	THF	r.t.	overnight	26%	0%
2	40 equiv. Et_3N 20 equiv. HCO_2H	THF	reflux	3 days	64%	27%
3	20 equiv. HCO_2NH_4	MeOH	r.t.	overnight	0%	50%
4	20 equiv. HCO_2NH_4	THF	r.t.	overnight	0%	0%
5	20 equiv. HCO_2NH_4	MeOH/THF 1:1	r.t.	overnight	0%	0%
6	20 equiv. HCO_2NH_4	MeOH/THF 3:1	r.t.	overnight	0%	64%
7	**20 equiv. HCO_2NH_4**	**MeOH/THF 19:1**	**r.t.**	**overnight**	**0%**	**84%**
8	20 equiv. HCO_2NH_4	EtOH	r.t.	overnight	0%	59%
9	20 equiv. HCO_2NH_4	*i*-PrOH	r.t.	overnight	0%	0%

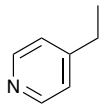
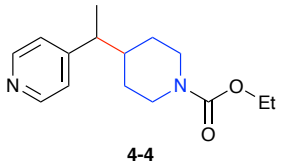
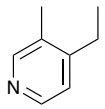
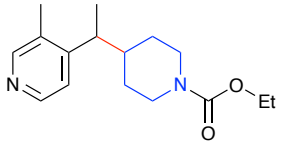
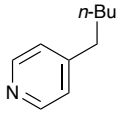
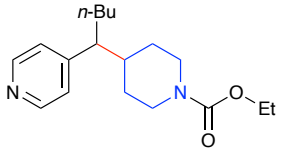
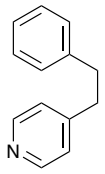
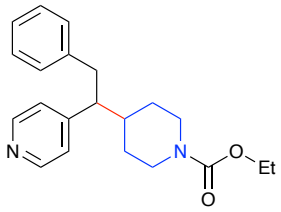
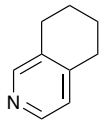
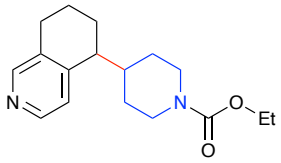
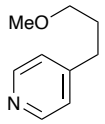
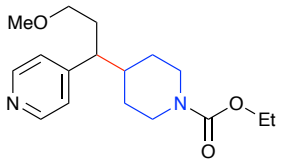
I later observed that ammonium formate is not soluble in ethyl acetate. Therefore, I modified the extraction procedure by performing concentration of the reaction mixture using a rotary evaporator, followed by trituration with ethyl acetate. This adjustment saved time and material while not impacting the overall yield of the reaction.

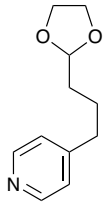
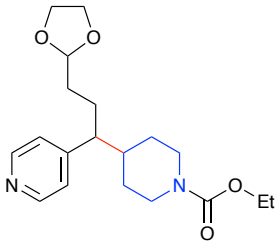
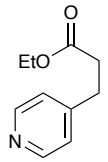
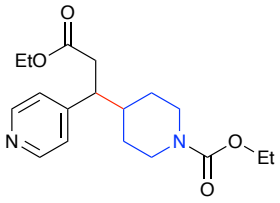
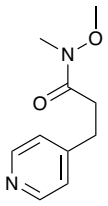
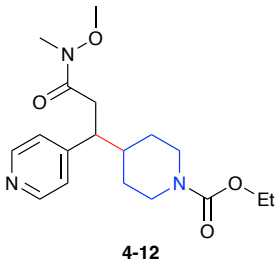
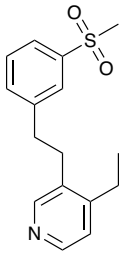
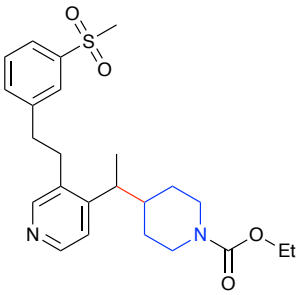
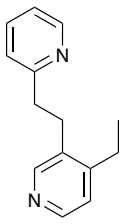
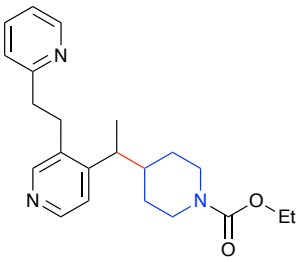
4.4 Substrate Scope

Having established the optimal conditions for the installation of piperidine, I conducted the substrate scope to examine its functional group tolerance and regioselectivity (**Table 7**). I first examined the method with several 4-alkylpyridines, and their corresponding piperidine products were isolated in good yields (**4-4** to **4-8**). Notably, our method was shown to be regioselective towards the 4-pyridylic carbon (**4-5**, **4-8** and **4-14**). However, the reaction involving 5,6,7,8-tetrahydroisoquinoline only gave a moderate yield (**4-8**). I speculated the steric congestion between the relatively rigid tetrahydroisoquinoline and the dihydropyridine ring systems amplified the reverse reaction (**Scheme 29**). It was later found catalytic amount of HCl helped obtain the best yield. The use of mild conditions allowed the piperidine installation to tolerate a wide range of functional groups, including ether and acetal groups (**4-9** and **4-10**). More importantly, our strategy could selectively functionalize the 4-pyridylic position in the presence of electrophilic and/or enolizable carbons (**4-11** to **4-13**), which was not possible through conventional ways.

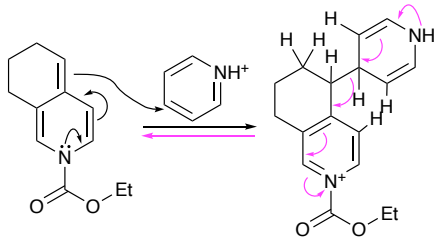
Table 7: Substrate scope for piperidine installation of piperidine on 4-alkylpyridines



Entry	Substrate	Product	Yield
1		 **4-4**	84%
2		 **4-5**	74%
3		 **4-6**	83%
4		 **4-7**	65%
5		 **4-8**	50%[a]
6	 **S-4-9**	 **4-9**	71%

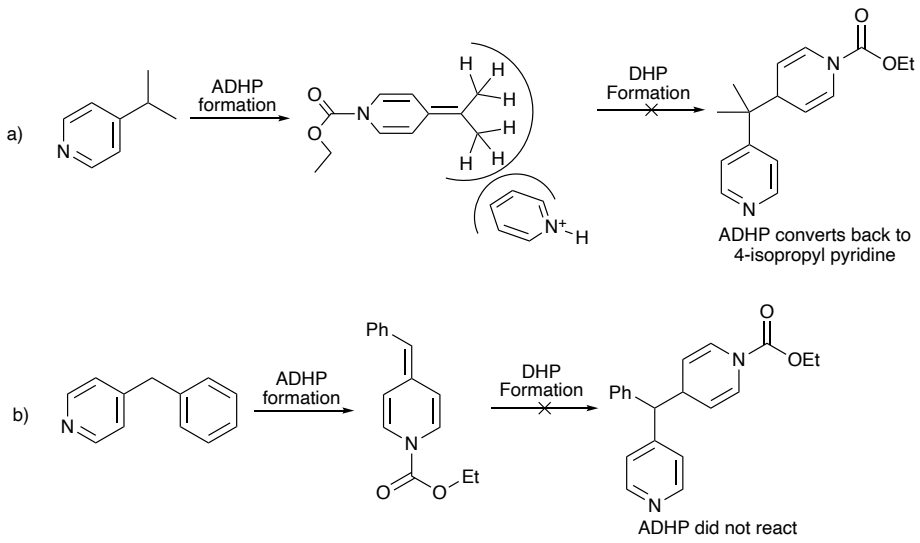
7		 **4-10**	74%
8		 **4-11**	63%
9	 **S-4-12**	 **4-12**	66%
10	 **S-4-13**	 **4-13**	61%
11	 **S-4-14**	 **4-14**	62%

a) Only 20% HCl was used to activate the pyridine electrophile.



Scheme 29: Steric congestion amplifies the reverse reaction.

Several substrates were found incompatible for piperidine installation through our approach. 4-alkylpyridines bearing a substituent at the C-2 position could not form corresponding ADHPs, as discussed in **Chapter 3**. Unexpectedly, even though both 4-isopropyl- and 4-benzyl pyridines could be converted to their corresponding ADHPs and undergo conjugate addition, their reactions with pyridine hydrochloride did not afford desired DHPs. In addition to pyridinium chloride being less electrophilic than the activated unsaturated ketones, we speculate the two exocyclic methyl groups from 4-isopropylpyridine experienced the steric congestion with the electrophile, leading to an unsuccessful addition (**Scheme 30**: equation **a**). As for 4-benzylpyridine, proton NMR analysis of its ADHP shows that the exocyclic carbon has less electron density than the one made from 4-phenethylpyridine (**Figure 15**, highlighted with dotted circles), indicating a less reactive nucleophile (**Scheme 30**: equation **b**).



Scheme 30: Attempts for piperidine installation using 4-isopropyl- and 4-benzyl pyridines.

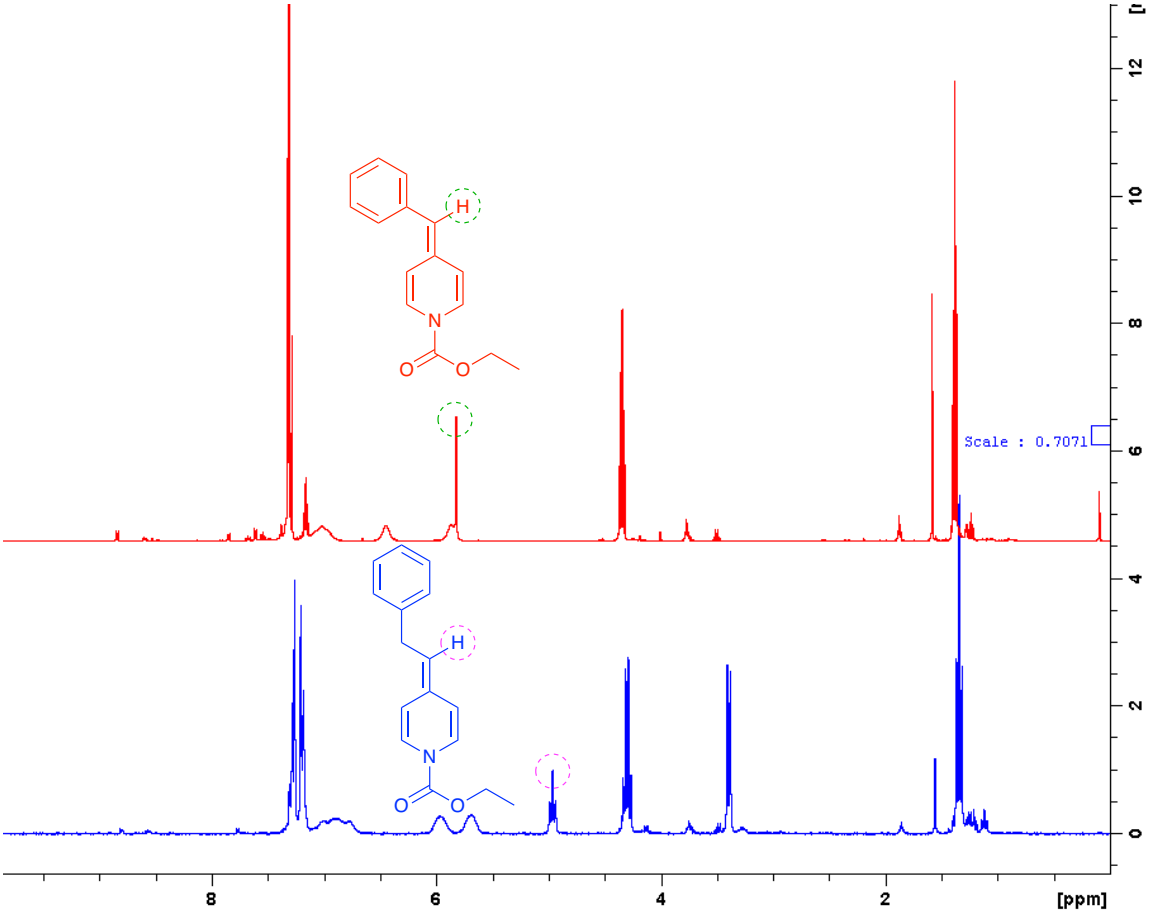
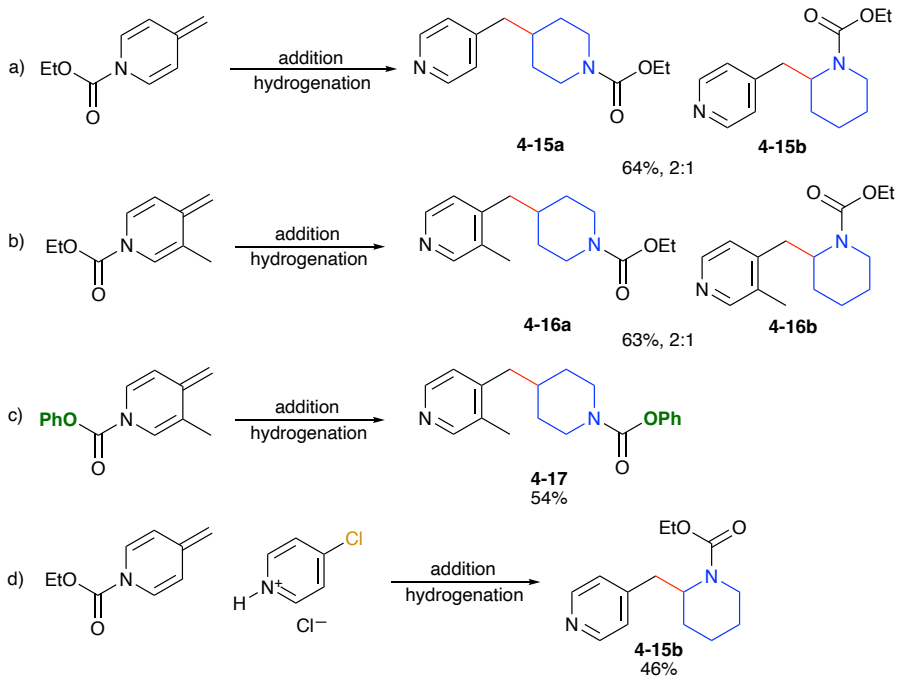


Figure 15: Comparison of chemical shifts of exocyclic protons of ADHPs (highlighted with dotted circles) generated from 4-benzylpyridine (red) and 4-phenethylpyridine (blue).

While our reaction exhibits good regioselectivity with respect to the nucleophile, we found the addition could take place at both 2- and 4-pyridyl positions when ADHPs carried no substituents on the nucleophilic carbon, albeit 4-addition being relatively favored (**Scheme 31**: equations **a** and **b**). It is also difficult to separate these products from one another, so we began exploring ways for regioselective addition.

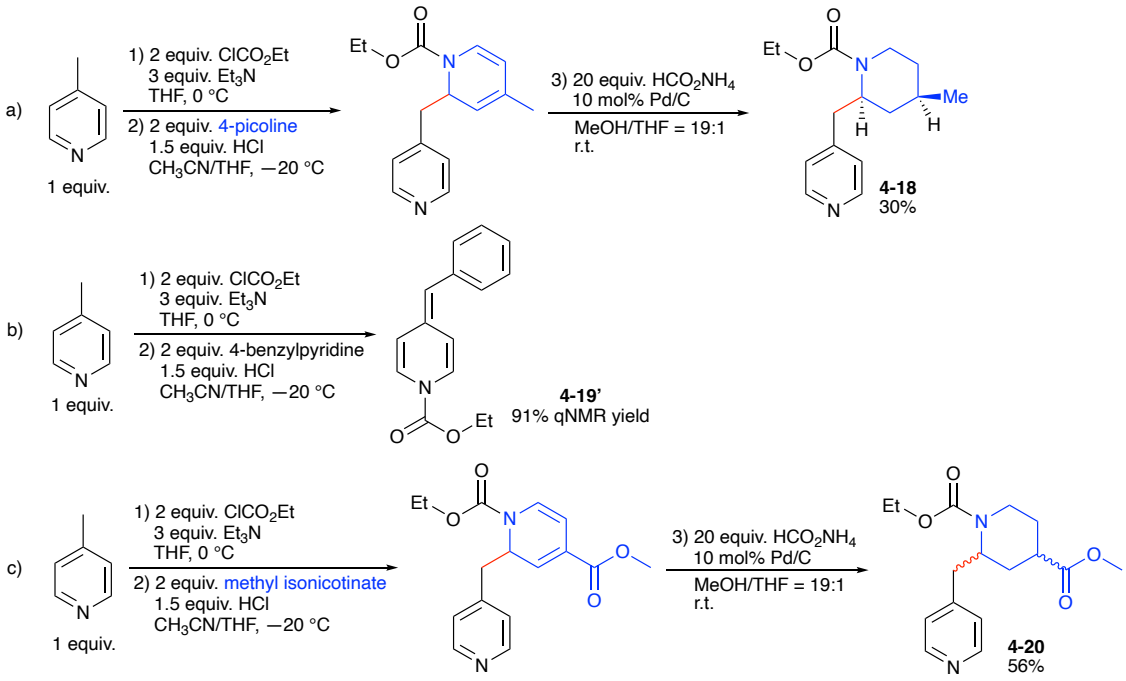
After revisiting the data obtained from the optimization process, we hypothesized that an electron-withdrawing group at the distal carbamate group could attenuate the overall reactivity of the ADHP, thereby making the 2-addition less likely to occur. Furthermore, a bulkier carbamate group would make the group transfer process more difficult for the 2-addition intermediate. Therefore, phenyl chloroformate was used instead, and we were delighted to see the 4-addition being the dominant pathway (**Scheme 31**: equation **c**). The above result then motivated us to develop a variant to selectively produce 2-substituted piperidine product. By "blocking" the 4-pyridyl position with a halogen atom, we expected the addition event to take place solely at the 2-pyridyl position. Dehalogenation could be achieved during the hydrogenation process. Indeed, when I employed 4-chloropyridine hydrochloride as the electrophile and applied our standard condition, 2-substituted piperidine was formed exclusively (**Scheme 31**: equation **d**).



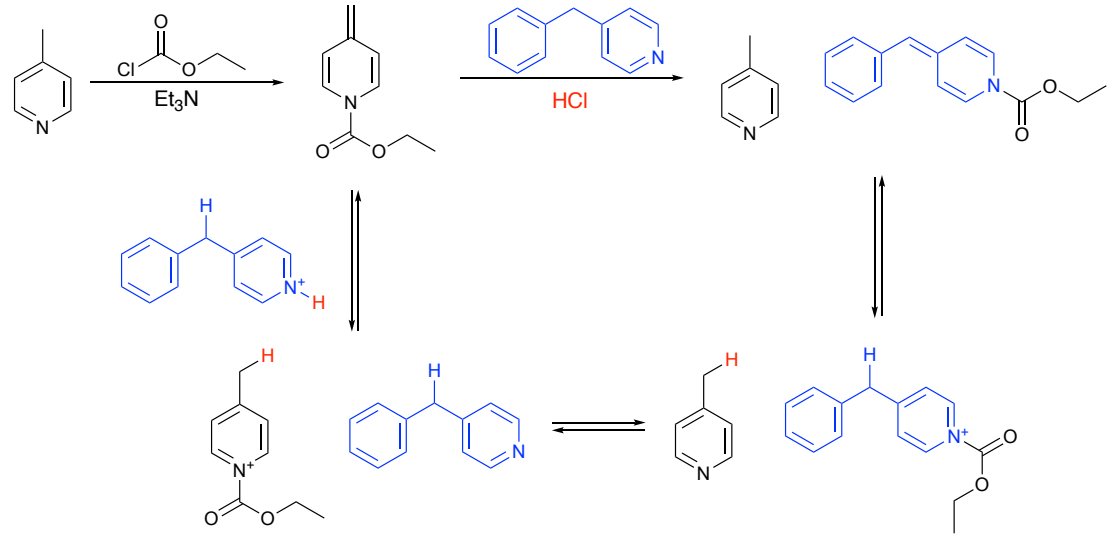
Scheme 31: Exploring regioselective piperidine installation on 4-methylpyridines.

I also briefly explored the possibility of generating piperidines with multiple stereogenic centers. The reaction with ADHP synthesized from 4-picoline to 4-picoline itself led to the formation of 2,4-disubstituted piperidine **4-18** as a single diastereomer in 30% yield (**Scheme 32**: equation **a**). 2D NOSEY NMR spectrum showed an NOE interaction between the two protons on the tertiary carbons, which confirmed the relative configurations (**Figure 16**). The low yield was caused by the ADHP being unstable as well as a decrease in electrophilicity for 4-picoline hydrochloride, due to the additional methyl group. Interestingly, when the similar reaction was performed using 4-benzylpyridinium chloride as the electrophile, the expected dihydropyridine did not form (**Scheme 32**: equation **b**), and "trans-dearomatization" event took place instead (**Scheme 33)**. ADHP that is generated from 4-picoline will start decomposing after several minutes of exposure in air, while the one made from 4-benzylpyridine can last for longer time in air. Therefore, this reaction was likely driven by the greater stability of ADHP generated from 4-benzylpyridine. Lastly, I employed methyl isonicotinate as the electrophile and obtained a mixture

of diastereomers in 56% overall yield (**Scheme 32**: equation **c**). This reaction implied how the electron density would affect the overall yield and the stereo-chemical outcome. Unfortunately, I was unable to separate the diastereomers and assign their relative configurations.



Scheme 32: Addition of ADHP derived from 4-methylpyridine to substituted pyridinium chloride.



Scheme 33: Trans-dearomatization between 4-picoline-ADHP and 4-benzylpyridinium chloride.

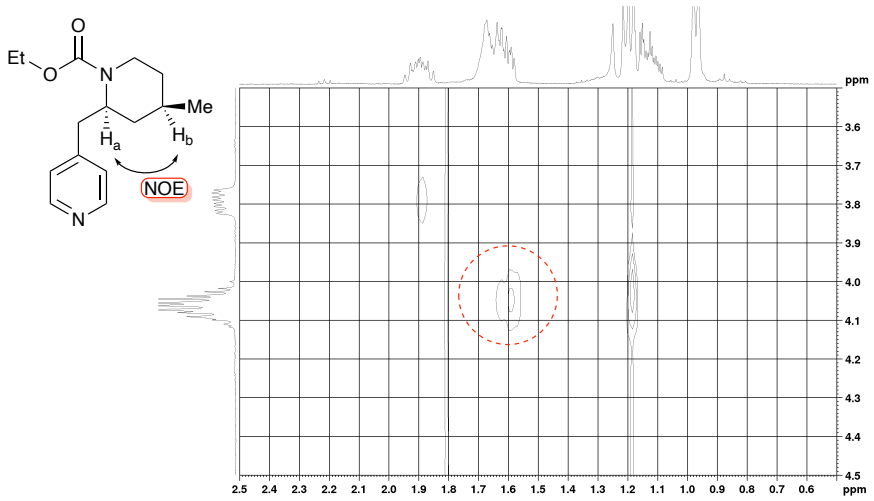
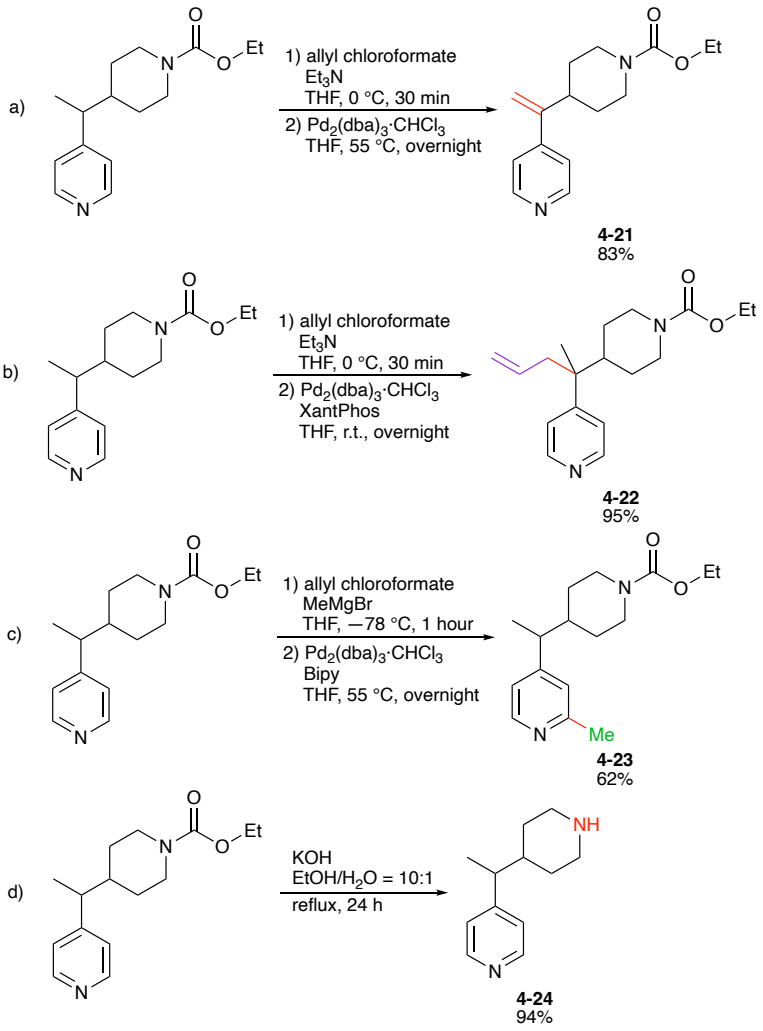


*Figure 16: NOE interaction (highlighted in red) between H_a (~1.6 ppm) and H_b (~ 4.05 ppm) confirmed the stereogenic configuration of compound **4-18**.*

4.5 Diversification of the piperidine product

I then performed a series of experiments to further functionalize the piperidine product (**Scheme 34**). For instance, by employing our previously reported dehydrogenation approach,[32] I converted the compound into its corresponding vinyl pyridine (**4-21**), which is a valuable electrophile. Furthermore, our palladium-catalyzed allylation condition not only provided the product with a quaternary carbon center, but also a useful synthetic handle (**4-22**). While 2,4-disubstituted pyridine cannot be used as the starting material under our standard condition, this limitation can be overcome by performing piperidine installation on the 4-alkylpyridines, followed by the addition of a Grignard reagent and palladium-catalyzed oxidation (**4-23**). Finally, the protected piperidine product could be hydrolyzed by heating under aqueous basic condition to reveal a free piperidine (**4-24**).



*Scheme 34: Further chemical transformations of piperidine product **4-4**.*

To summarize, we exploited the inherent electrophilicity of pyridines through activation with hydrochloric acid and developed their reactions with alkylidene dihydropyridines. The reactions generated the protected dihydropyridines, which were converted to their corresponding piperidines through a transfer hydrogenation process. The method is practical and simple to operate with no complex condition involved. It exhibited good functional group tolerance and displayed regioselectivity towards the 4-pyridylic position. In addition, we developed a synthetic variant for making 2-substituted piperidine using 4-chloropyridinium chloride as the electrophile.

Chapter 5: Conclusions

Our research was based upon the established works on palladium-catalyzed allylation and dehydrogenation of 4-alkylpyridines, using alkylidene dihydropyridines as the key intermediates. The attempts towards asymmetric allylation brought unexpected results and inspired our mechanistic study. Our group found pyridylic anions behaved as “soft” nucleophiles, and this discovery established a new pKa threshold for “outer-sphere” allylation. We then demonstrated the nucleophilic nature of ADHP through its reaction with the allylpalladium(II) complex and proton NMR analysis. This observation started a new chapter for our alkylpyridine research.

We first developed conjugate addition to activated α,β-unsaturated ketones. The method avoided the use of strong bases and displayed good functional group tolerance. In addition, the use of TESOTf and neutral work-up procedure could lead to the formation of silyl enol ethers, a versatile class of compounds that enabled further transformations.

We then developed a mild condition to unite pyridine with piperidine through a carbon atom. The reaction involved the addition of ADHPs to pyridine hydrochloride and the subsequent reduction step through transfer hydrogenation. The reaction was milder and more practical for industrial use, compared with previously reported methods. This approach exhibited good functional group tolerance and selectivity towards the 4-pyridylic carbon. Moreover, we designed a variant for making 2-substituted piperidines and discovered that distal substituent on the carbamate group could influence the reactivity of ADHPs.

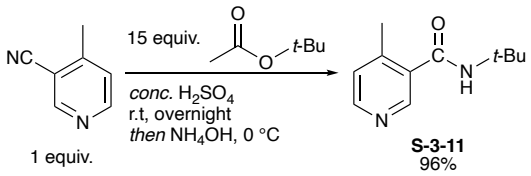
Functionalization of 4-pyridylic carbon has long been a challenge to chemists as it often requires harsh conditions or additional groups on the pyridylic carbon or the pyridine ring. The presented works on exploiting the reactivity of alkylidene dihydropyridines demonstrate the practicality for 4-pyridylic functionalization under milder conditions. We hope our study could inspire more research on alkylidene dihydropyridines to help unleash the potential of pyridine in medicinal chemistry.

Chapter 6: Experimental and characterization of compounds

Unless otherwise stated, all reactions were conducted in oven-dried glassware under an atmosphere of argon. Triethylamine (Et_3N) was distilled from calcium hydride prior to use. Tetrahydrofuran (THF), acetonitrile (CH_3CN) and toluene were dispensed from an INERT® PureSolv Solvent Purification System. Commercial reagents were used as received. Thin-layer chromatography (TLC) was performed on SiliCycle® silica gel 60 F254 plates. Visualization was carried out using UV light (254 nm), $KMnO_4$, DNP, *p*-anisaldehyde, as well as iodine stains. Hexanes, diethyl ether, methanol, ethanol, and ethyl acetate (all ACS grade) were used as received. Flash column chromatography was carried out using Silicycle® Silia*Flash®* silica gel (230 – 400 mesh, 40 – 63 µm, 60 Å pore size).[49] HPLC was conducted using Agilent 1200 Series purification system with isopropanol and heptane as eluents. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 400 AV or Bruker 300 AV spectrometer in chloroform-D (99.8% deuterated) or dichloromethane-D_2 (99.5% deuterated). Spectra recorded using chloroform-D were calibrated to 7.26 ppm ^{1}H and 77.16 ppm ^{13}C, and those that used dichloromethane-D_2 were calibrated to 5.30 ppm ^{1}H and 53.84 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), td (triplet of doublets), tt (triplet of triplets), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), qd (quartet of doublets), m (multiplet), and br (broad).[50,51] Structural assignments were made with additional information from gCOSY, gHSQC, and gHMBC experiments. Quantitative proton NMR was measured using 1,3,5-trimethoxybenzene as internal standard. The relaxation time was set to be 30 seconds. Coupling constants (*J*) are reported in Hertz (Hz). Infrared (IR) spectra were recorded as thin films neat using Alpha-Platinum ATR, Bruker, diamond crystal FT-IR instrument.

6.1 Substrate synthesis

Synthesis of compound **S-3-11**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with *tert*-butyl acetate (5 mL, 15 equiv., 3.75 mmol) and 3-cyano-4-methylpyridine (295.4 mg, 1.0 equiv., 2.5 mmol). 1 mL of concentrated sulfuric acid was added in a dropwise manner, and the resulting solution was stirred at ambient temperature overnight. The reaction mixture was then diluted with 10 mL of water and carefully neutralized with dropwise addition of 30% aqueous NH_4OH solution at 0 °C. The organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford compound **S-3-11** as white solid (460 mg, 96% yield).

Melting point: 93.6 – 94.7 °C

Chromatography: 70% EtOAc in Hexanes (R_f = 0.27).

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

δ 8.51 (s, 1H), 8.44 (d, *J* = 5.0 Hz, 1H), 7.13 (d, *J* = 5.0 Hz, 1H), 5.72 (bs, 1H), 2.44 (s, 3H), 1.47 (s, 9H).

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

δ 167.2, 150.5, 147.2, 145.7, 133.9, 125.9, 52.3, 29.0, 19.3.

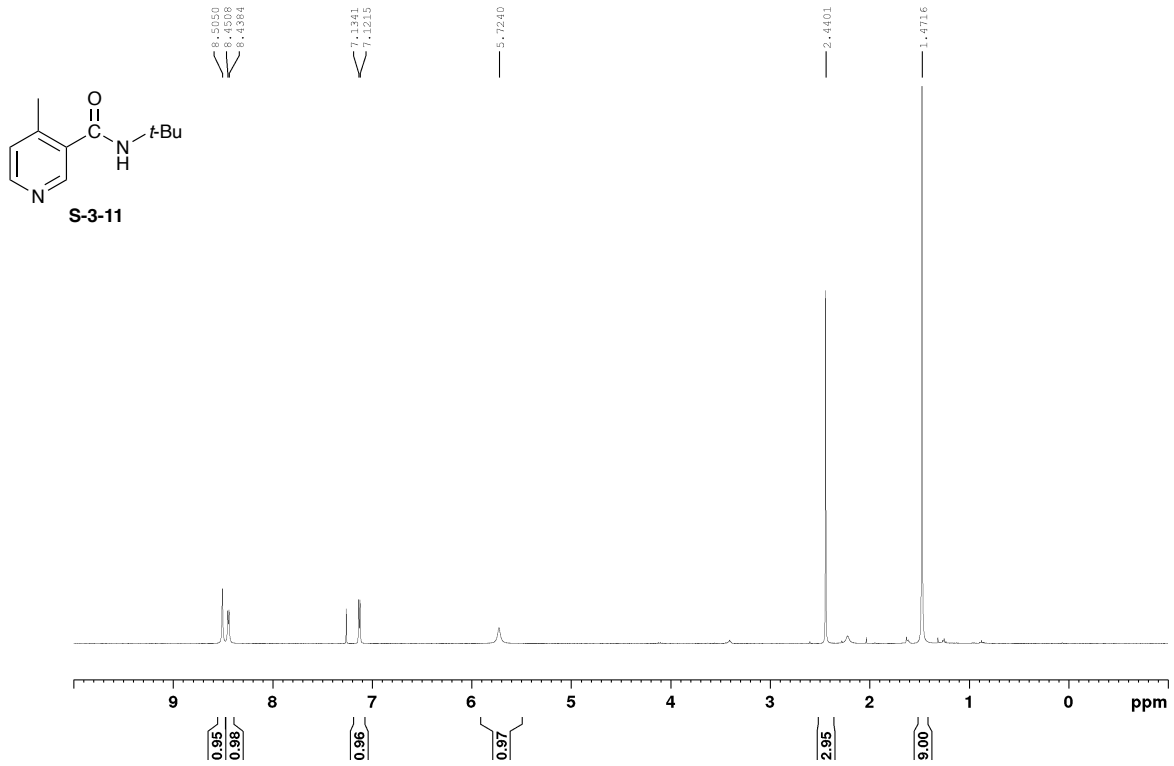
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3365, 3022, 2968, 1644, 1560, 1451 cm^{-1}.

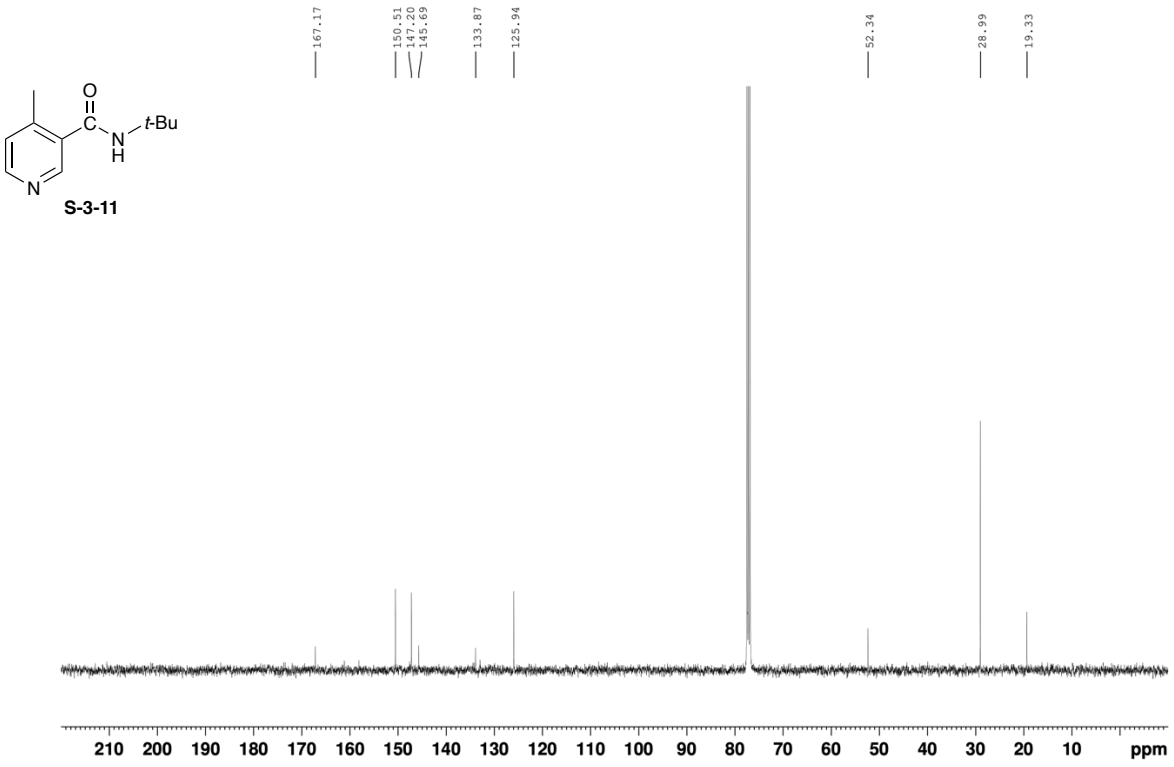
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{11}H_{17}N_2O$ is 193.1336; Found 193.1338.

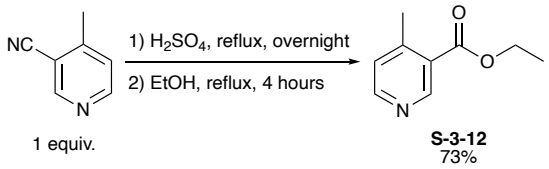
^1H NMR (400 MHz, $CDCl_3$) spectrum for **S-3-11**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-3-11**:



Synthesis of compound **S-3-12**:



1 equiv.

S-3-12
73%

An oven-dried round-bottomed flask equipped with a stir bar was charged with 3-cyano-4-methylpyridine (354.5 mg, 1 equiv., 3 mmol) and 6 mL of 75% sulfuric acid. The resulting mixture was placed in an oil bath, stirred, and heated to reflux overnight. The reaction mixture was then cooled to ambient temperature and 15 mL of 95% ethanol were added. The resulting mixture was placed in an oil bath, stirred, and heated to reflux for another 4 hours. The resulting mixture was then cooled to ambient temperature and 2 M aqueous Na_2CO_3 was added dropwise until the aqueous phase reached pH ~ 8. The reaction mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford compound **S-3-12** as pale-yellow oil (360 mg, 73% yield).

Chromatography: 20% EtOAc in Hexanes (R_f = 0.26).

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

δ 9.07 (s, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 7.17 (d, *J* = 5.1 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 2.62 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).

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

δ 166.3, 152.2, 151.7, 149.4, 126.5, 126.2, 61.3, 21.3, 14.4.

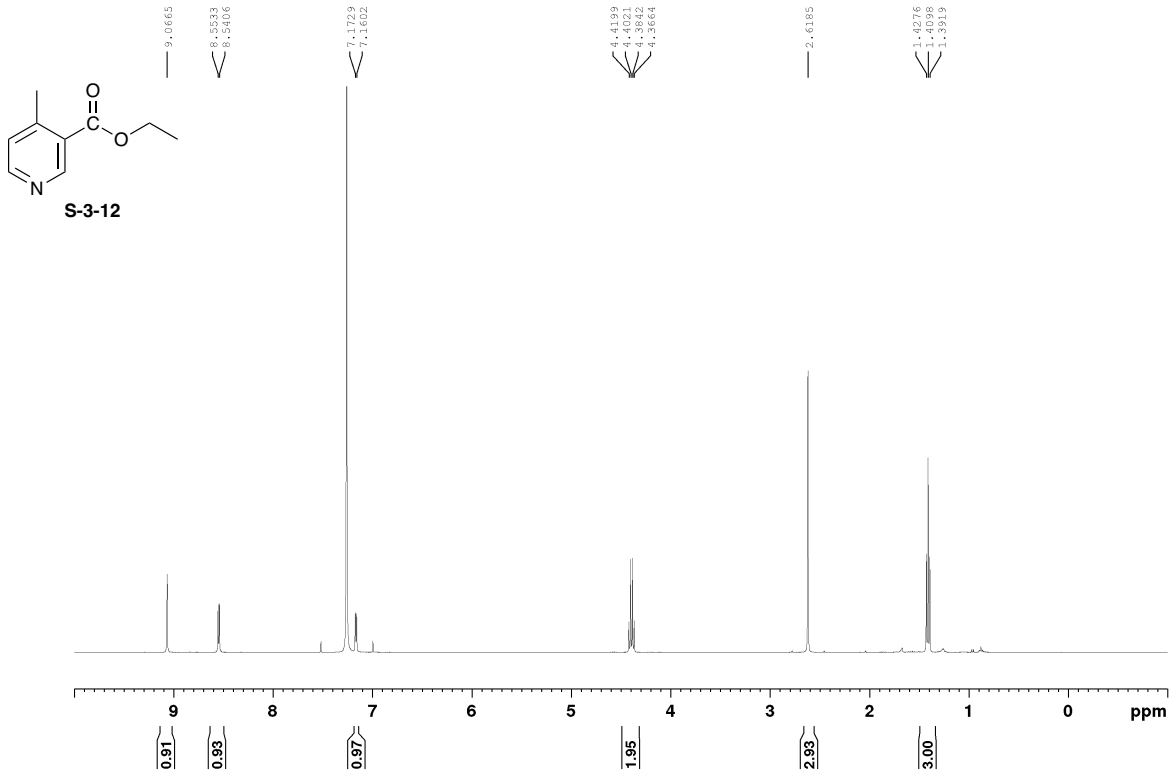
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3061, 2981, 2934, 1717, 1591, 1405, 1274 cm^{-1}.

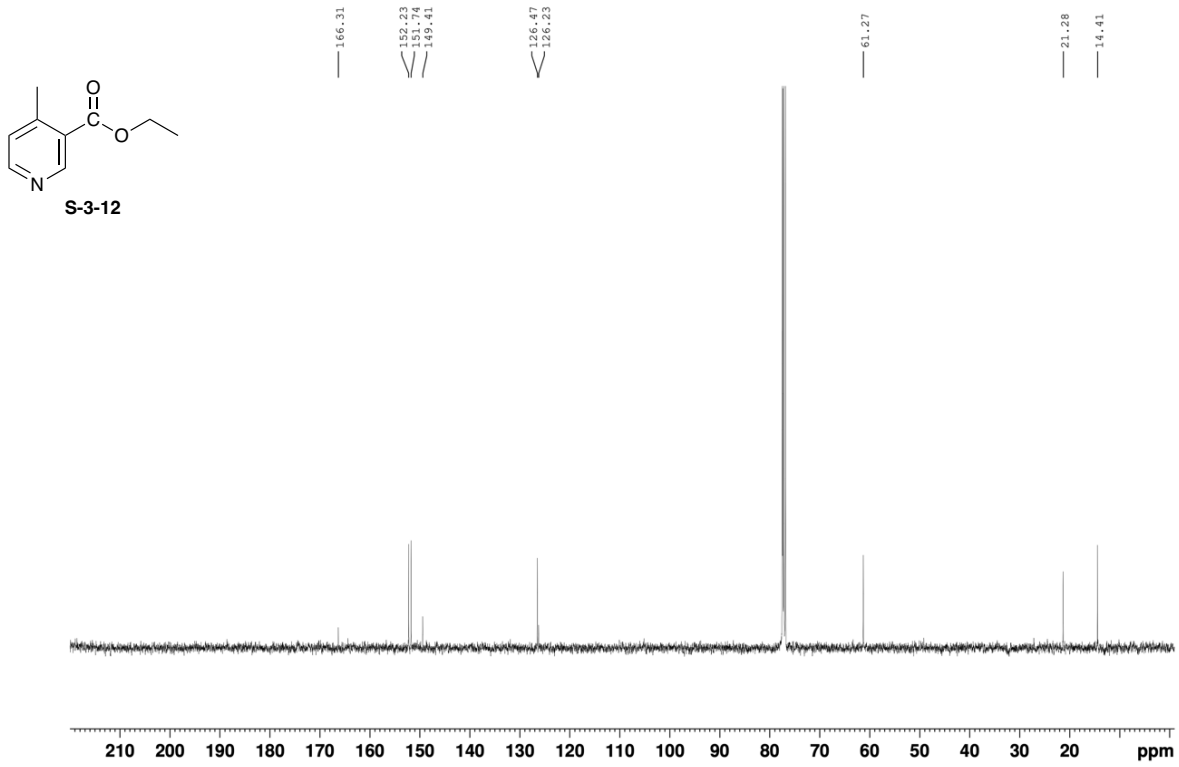
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_9H_{12}NO_2$ 166.0863; Found 166.0866.

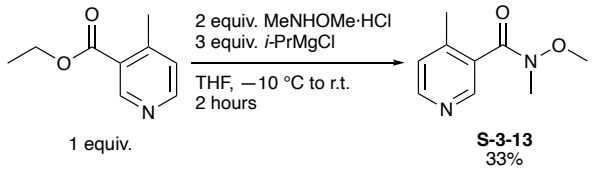
^1H NMR (400 MHz, $CDCl_3$) spectrum for **S-3-12**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-3-12**:



Synthesis of compound **S-3-13**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with pyridine **S-3-12** (826 mg, 1.0 equiv., 5 mmol), *N,O*-dimethylhydroxylamine hydrochloride (634 mg, 1.3 equiv., 6.5 mmol) and 10 mL of anhydrous THF. The reaction mixture was cooled to –10 °C and a solution of *i*-PrMgCl (7.5 mL, 2.0 M in THF, 3.0 equiv., 15 mmol) was added dropwise while stirring at –10 °C. The reaction mixture was stirred for 1 hour at –10 °C and for another hour at ambient temperature. The reaction was then quenched by dropwise addition of saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (4 x 20 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography with EtOAc/Et_3N to afford compound **S-3-13** as pale-yellow oil (297 mg, 33% yield).

Chromatography: 2.5% Et_3N in EtOAc (R_f = 0.20).

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

δ 8.50 (s, 1H), 8.48 (d, J = 5.1 Hz, 1H), 7.15 (d, J = 5.1 Hz, 1H), 3.47 (s, 3H), 3.35 (s, 3H), 2.34 (s, 3H).

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

δ 168.5, 150.2, 147.1, 144.9, 131.7, 125.2, 61.5, 32.7, 19.0.

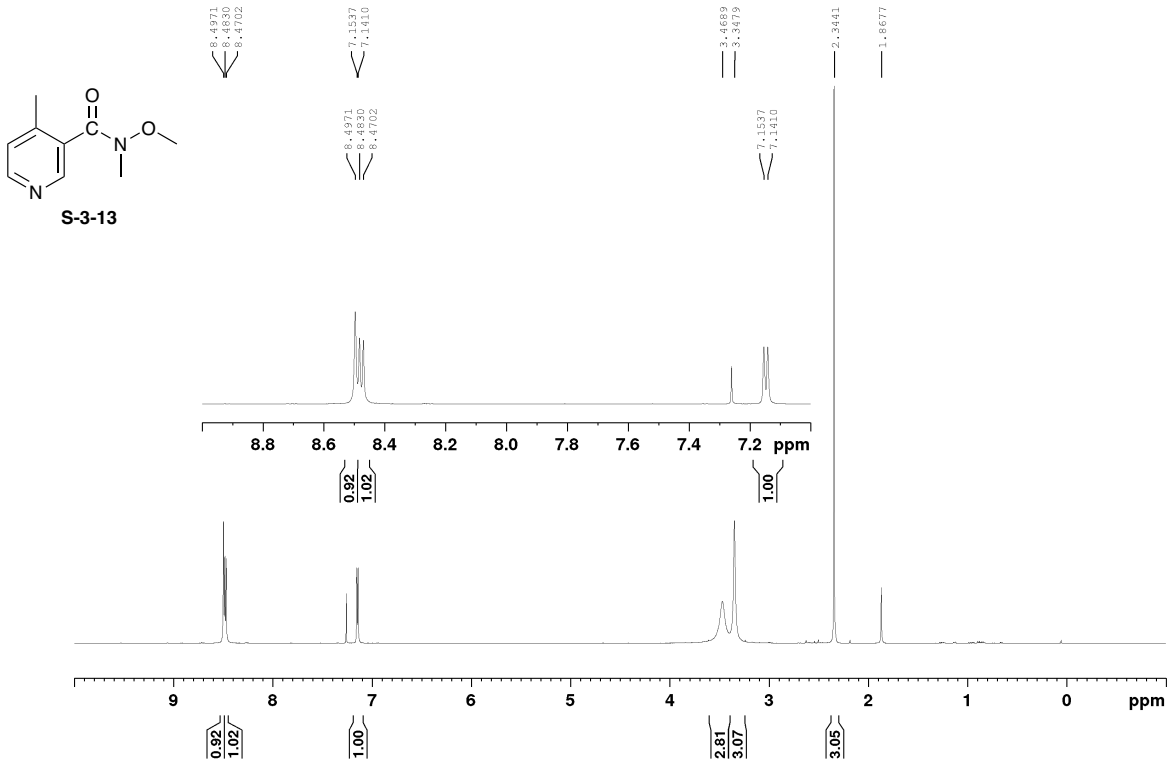
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3064, 2935, 1645, 1592, 1446, 1379, 1206 cm^{-1}.

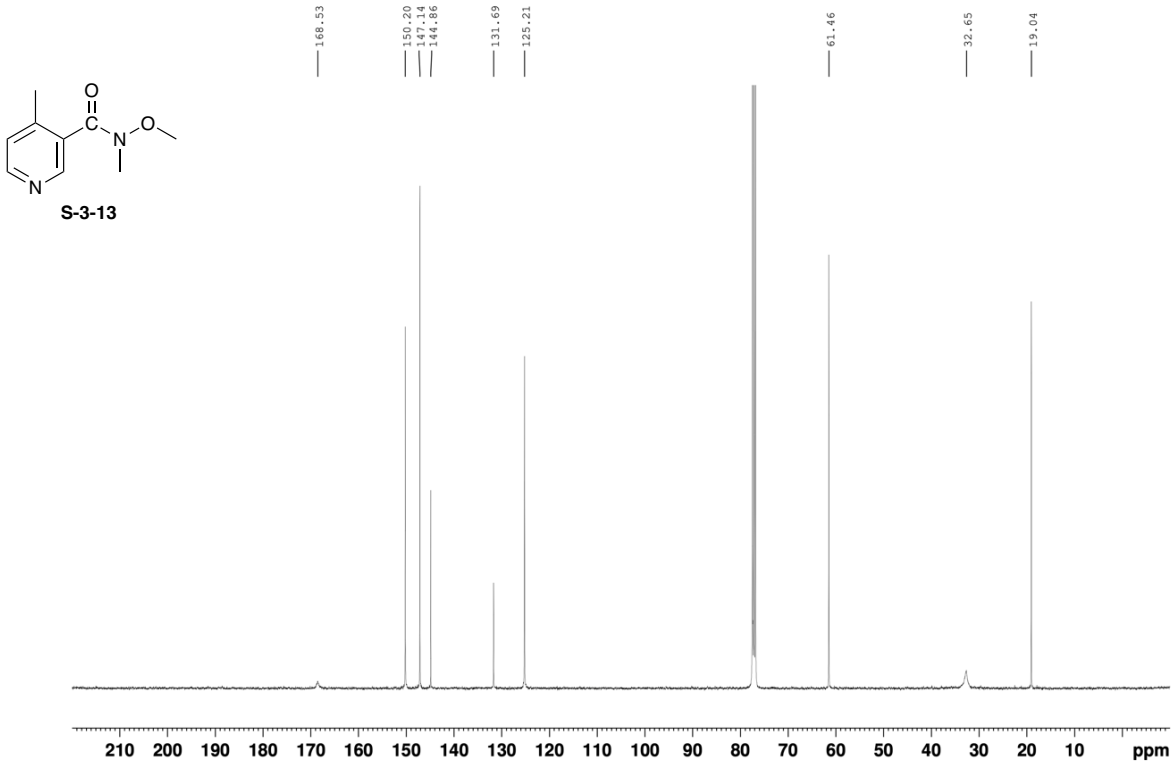
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_9H_{13}N_2O_2$ 181.0972; Found 181.0975.

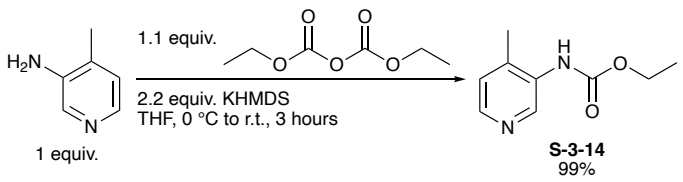
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **S-3-13**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-3-13**:



Synthesis of compound **S-3-14**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with 3-amino-4-methylpyridine (216.3 mg, 1.0 equiv., 2.0 mmol) and 20 mL of anhydrous THF. The resulting solution was cooled to 0 °C. A solution of potassium bis(trimethylsilyl)amide (4.4 mL, 2.2 equiv., 4.4 mmol, 1.0 M in THF) was added in a dropwise manner, and the resulting mixture was stirred for 30 minutes. Diethyl pyrocarbonate (0.33 mL, 1.1 equiv., 2.2 mmol) was added, and the reaction mixture was allowed to warm to ambient temperature while being stirred over three hours. The mixture was then concentrated using a rotary evaporator. The residue was dissolved in 10 mL of 0.1 M $HCl_{(aq.)}$, and the resulting mixture was extracted with DCM (3 x 20 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography with EtOAc to afford carbamate **S-3-14** as white solid (358 mg, 99% yield).

Melting point: 86.3 – 88.1 °C

Chromatography: 100% EtOAc (R_f = 0.34).

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

δ 8.88 (s, 1H), 8.27 (d, *J* = 4.9 Hz, 1H), 7.10 (d, *J* = 4.9 Hz, 1H), 6.38 (s, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.27 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

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

δ 154.1, 145.4, 144.3, 138.6, 133.1, 125.1, 61.5, 17.2, 14.4.

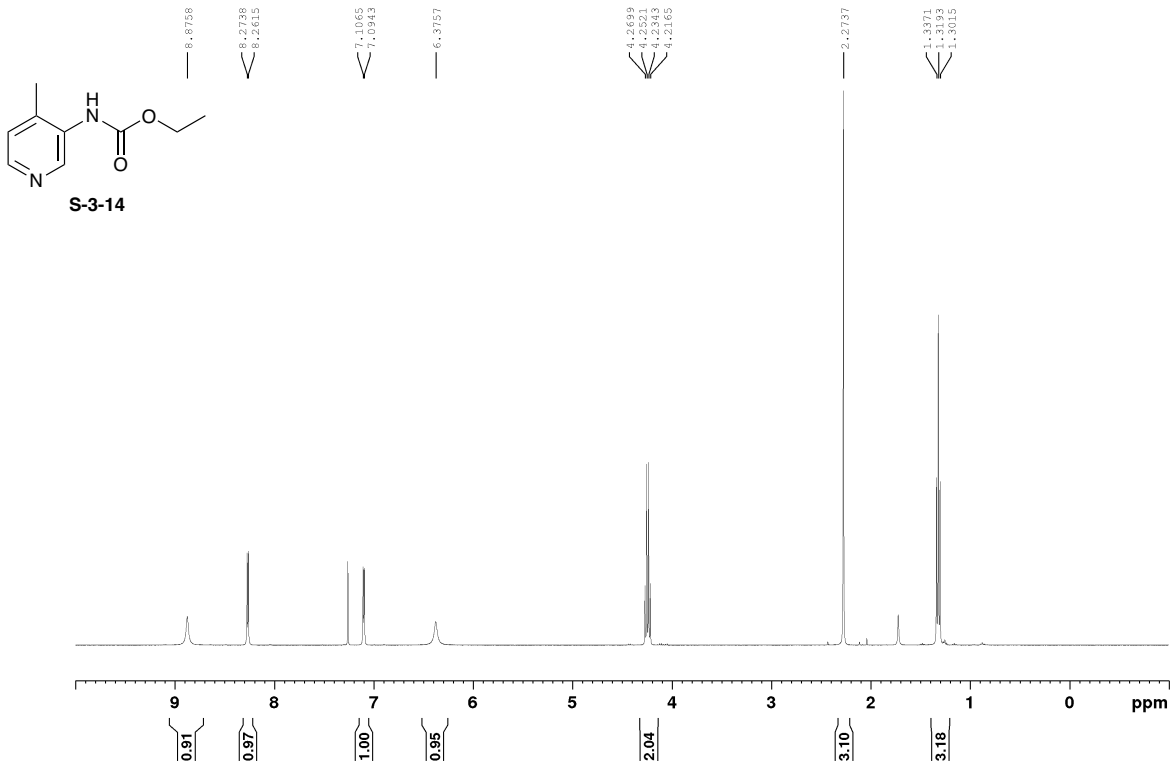
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ= 3199, 3026, 2990, 2932, 1727, 1610, 1422 cm^{-1}.

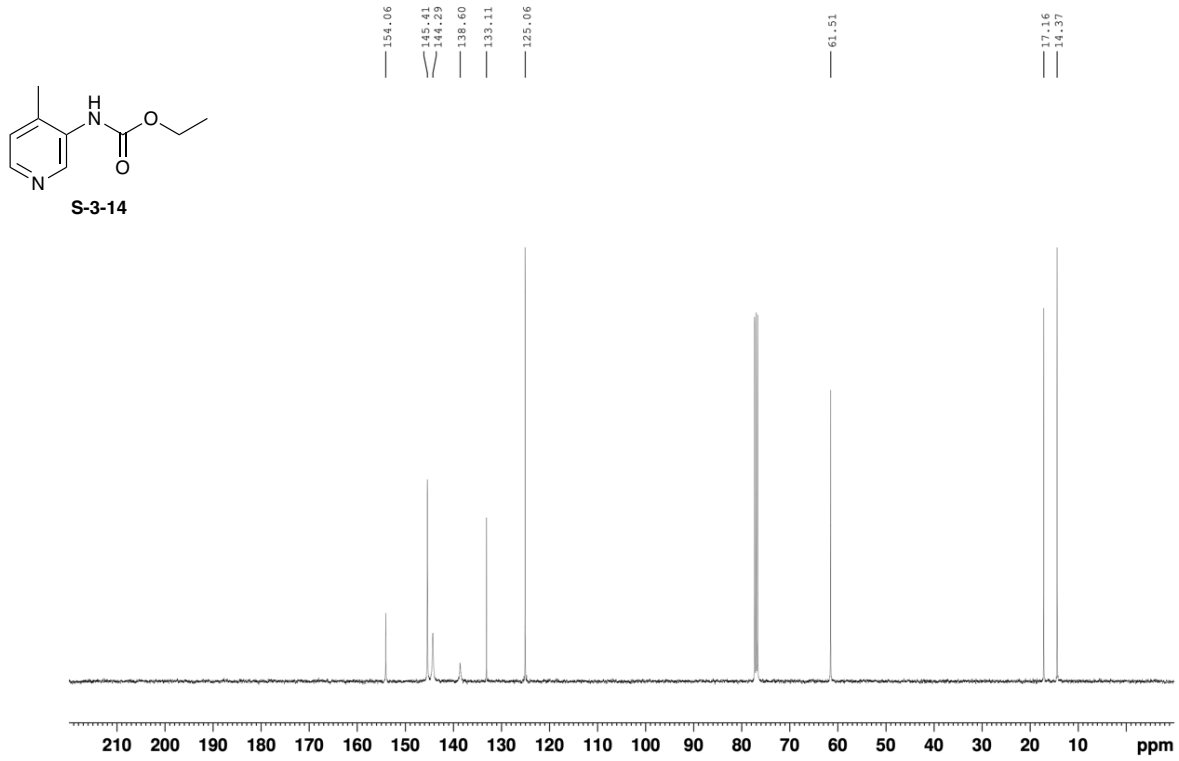
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_9H_{13}N_2O_2$ 181.0972; Found 181.0980.

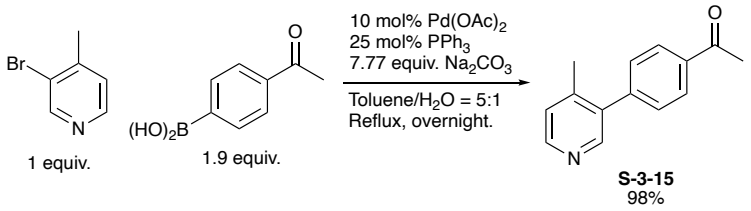
^1H NMR (400 MHz, $CDCl_3$) spectrum for **S-3-14**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-3-14**:



Synthesis of compound **S-3-15**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with 4 mL of water, 20 mL of toluene, triphenylphosphine (262.3 mg, 25 mol%, 1.0 mmol) and palladium acetate (89.8 mg, 10 mol%, 0.4 mmol). The resulting mixture was stirred for 15 minutes at ambient temperature. 3-Bromo-4-methylpyridine (0.45 mL, 1.0 equiv., 4.0 mmol), *p*-acetylphenylboronic acid (1.246 g, 1.9 equiv., 7.6 mmol) and sodium carbonate (3.29 g, 7.77 equiv., 31.1 mmol) were added, and the resulting mixture was placed in an oil bath, stirred, and heated to reflux overnight. The reaction mixture was then cooled to ambient temperature and filtered through a pad of Celite®. The filtrate was extracted with EtOAc (4 x 20 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford compound **S-3-15** as white solid (831 mg, 98% yield).

Melting point: 75.1 – 77.0 °C

Chromatography: 60% EtOAc in Hexanes (R_f = 0.30).

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

δ 8.48 (d, *J* = 5.0 Hz, 1H), 8.43 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 2H),

7.42 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 5.0 Hz, 1H), 2.65 (s, 3H), 2.29 (s, 3H).

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

δ 197.8, 149.8, 149.1, 144.5, 143.0, 136.8, 136.4, 129.7, 128.6, 125.4, 26.8, 19.9.

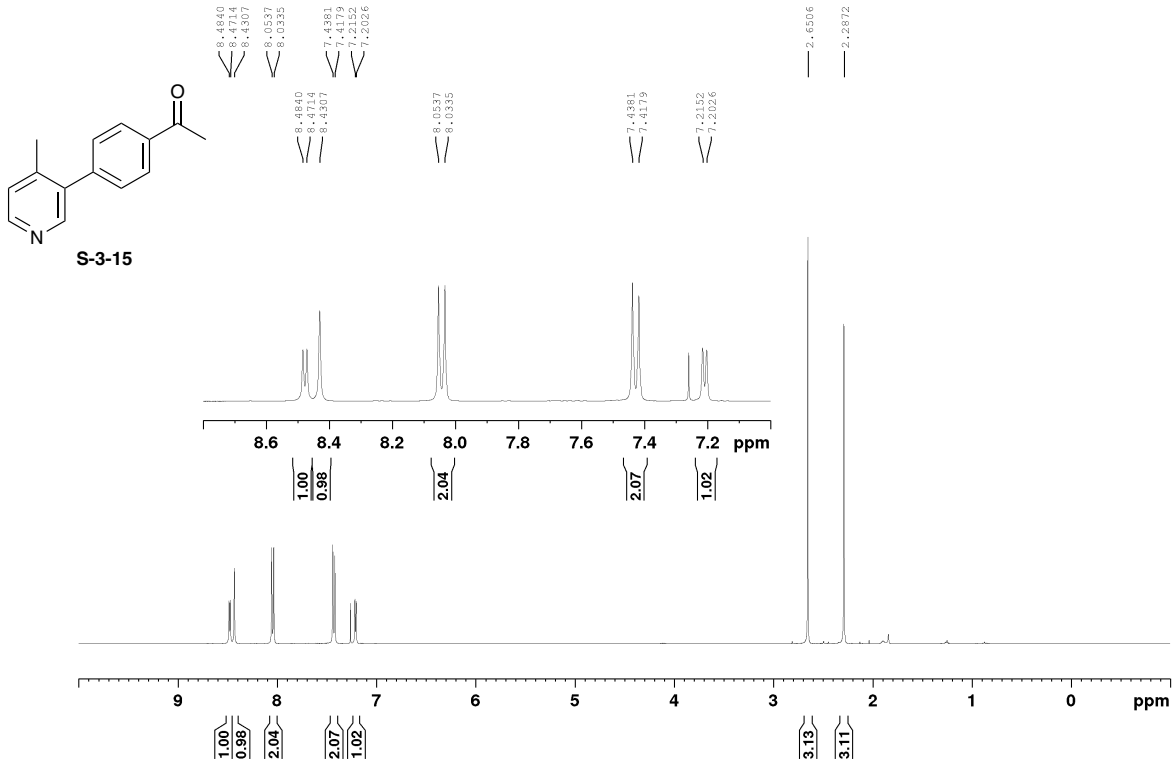
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3044, 2970, 2924, 1681, 1605, 1269 cm^{-1}.

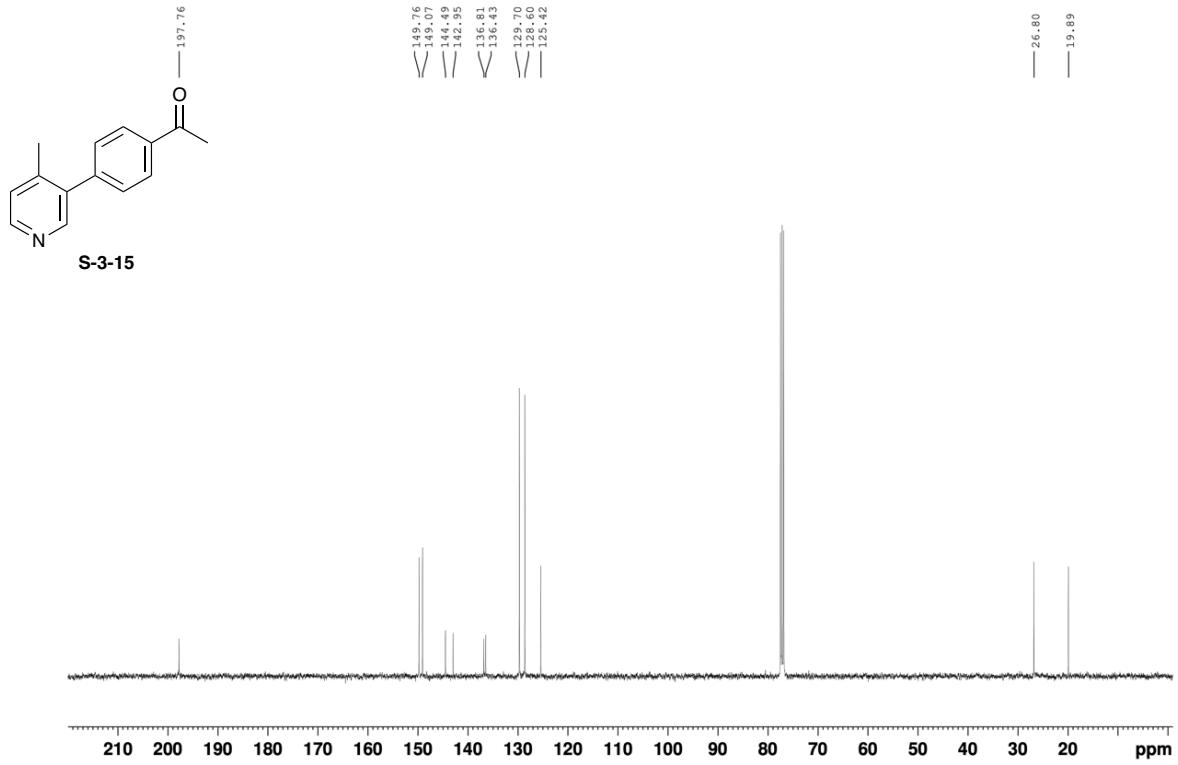
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{14}H_{14}NO$ 212.1070; Found 212.1070.

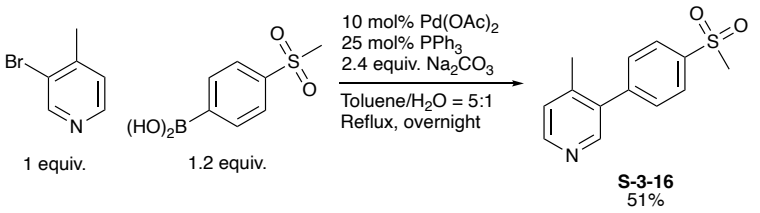
^1H NMR (400 MHz, $CDCl_3$) spectrum for **S-3-15**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-3-15**:



Synthesis of compound **S-3-16**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with 2 mL of water, 10 mL of toluene, triphenylphosphine (65.6 mg, 25 mol%, 0.25 mmol) and palladium acetate (23 mg, 10 mol%, 0.1 mmol). The resulting mixture was stirred for 15 minutes at ambient temperature. 3-Bromo-4-methylpyridine (0.11 mL, 1.0 equiv., 1.0 mmol), 4-(methanesulfonyl)-phenylboronic acid (240.0 mg, 1.2 equiv., 1.2 mmol) and sodium carbonate (254.4 mg, 2.4 equiv., 2.4 mmol) were added, and the resulting solution was placed in an oil bath, stirred, and heated to reflux overnight. The reaction mixture was then cooled to ambient temperature and filtered through a pad of Celite®. The filtrate was extracted with EtOAc (4 x 20 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford compound **S-3-16** as white solid (125 mg, 51% yield).

Melting point: 129.3 – 130.3 °C

Chromatography: 90% EtOAc in Hexanes (R_f = 0.26).

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

δ 8.51 (d, *J* = 5.0 Hz, 1H), 8.42 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 2H),

7.54 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 5.0 Hz, 1H), 3.13 (s, 3H), 2.29 (s, 3H).

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

δ 149.7, 149.5, 144.5, 143.9, 140.0, 136.1, 130.4, 127.8, 125.5, 44.7, 19.9.

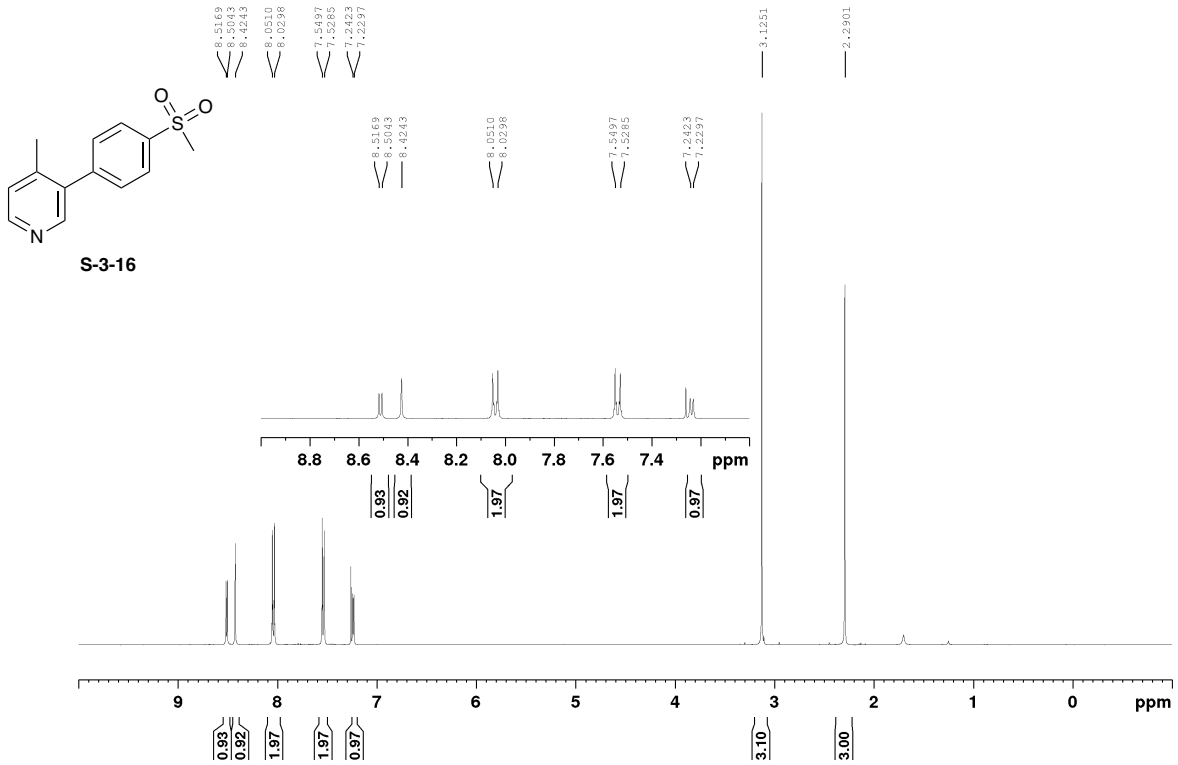
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3039, 3017, 2926, 1590, 1327, 1038 cm^{-1}.

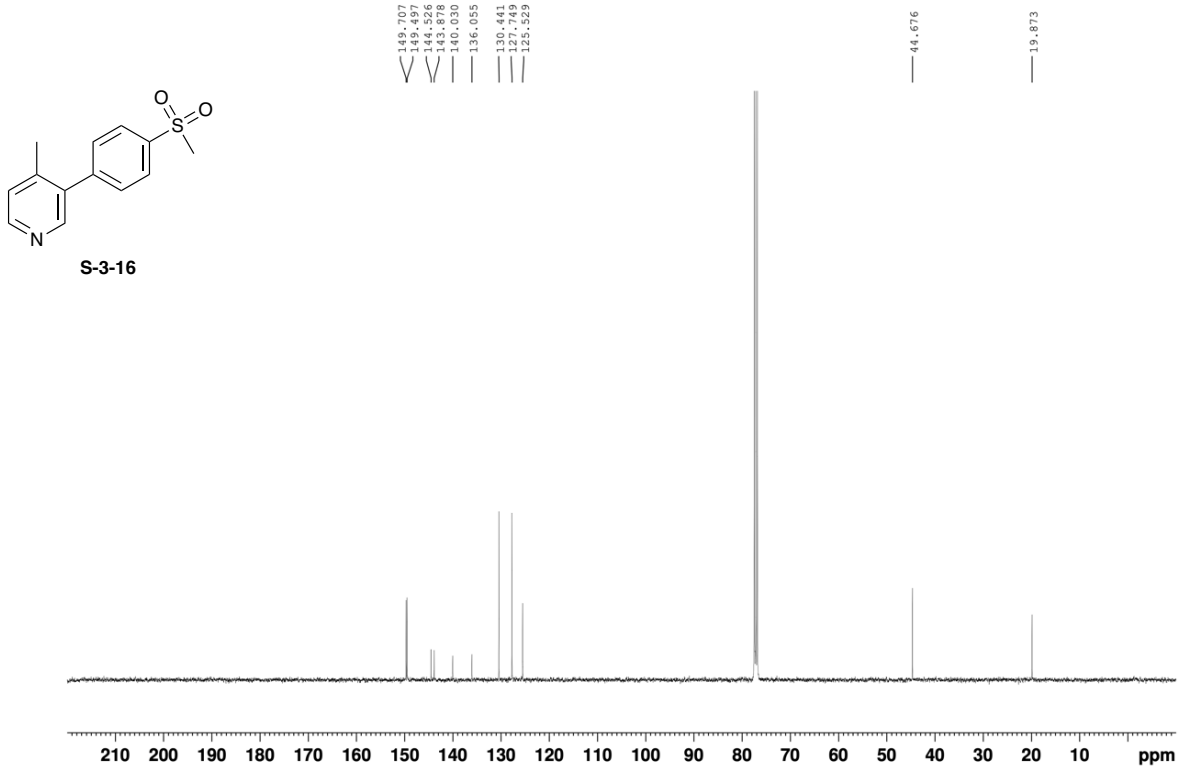
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{13}H_{14}NO_2S$ 248.0740; Found 248.1311.

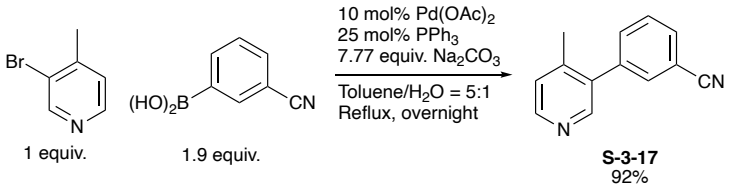
^1H NMR (400 MHz, $CDCl_3$) spectrum for **S-3-16**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-3-16**:



Synthesis of compound **S-3-17**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with 4 mL of water, 20 mL of toluene, triphenylphosphine (131.1 mg, 25 mol%, 0.5 mmol) and palladium acetate (45 mg, 10 mol%, 0.2 mmol). The resulting mixture was stirred for 15 minutes at ambient temperature. 3-Bromo-4-methylpyridine (0.22 mL, 1.0 equiv., 2.0 mmol), 3-cyanophenylboronic acid (558.2 mg, 1.9 equiv., 3.8 mmol) and sodium carbonate (1.65 g, 7.77 equiv., 15.5 mmol) were added, and the resulting mixture was placed in an oil bath, stirred, and heated to reflux overnight. The reaction mixture was then cooled to ambient temperature and filtered through a pad of Celite®. The filtrate was extracted with EtOAc (4 x 20 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **S-3-17** as white solid (358 mg, 92% yield).

Melting point: 63.4 – 64.1 °C

Chromatography: 40% EtOAc in Hexanes with 2% Et_3N (R_f = 0.24).

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

δ 8.44 (d, *J* = 5.1 Hz, 1H), 8.34 (s, 1H), 7.67 – 7.63 (m, 1H), 7.58 – 7.56 (m, 1H), 7.55 – 7.50 (m, 2H), 7.17 (d, *J* = 5.1 Hz, 1H), 2.23 (s, 3H).

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

δ 149.6, 149.2, 144.3, 139.2, 135.5, 133.7, 132.6, 131.3, 129.4, 125.3, 118.4, 112.7, 19.6.

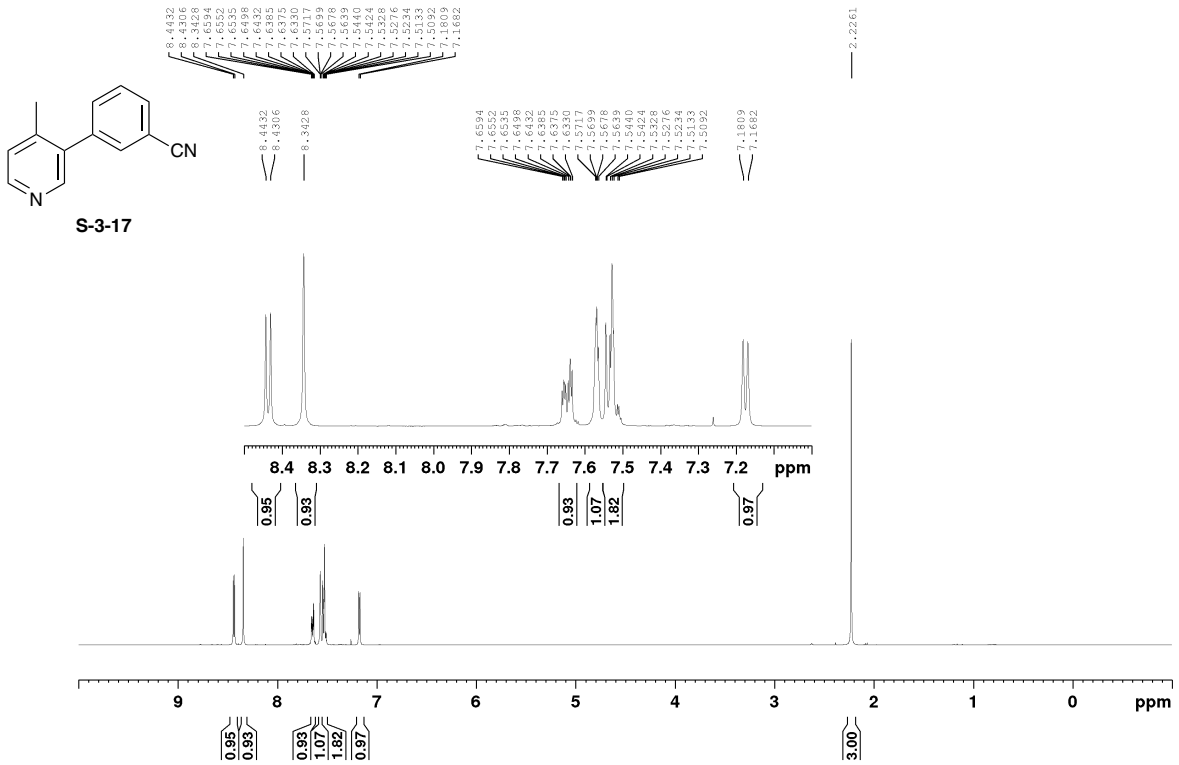
IR Alpha-Platinum ATR, Bruker, diamond crystal

u = 3026, 2956, 2854, 2227, 1592, 790 cm^{-1}.

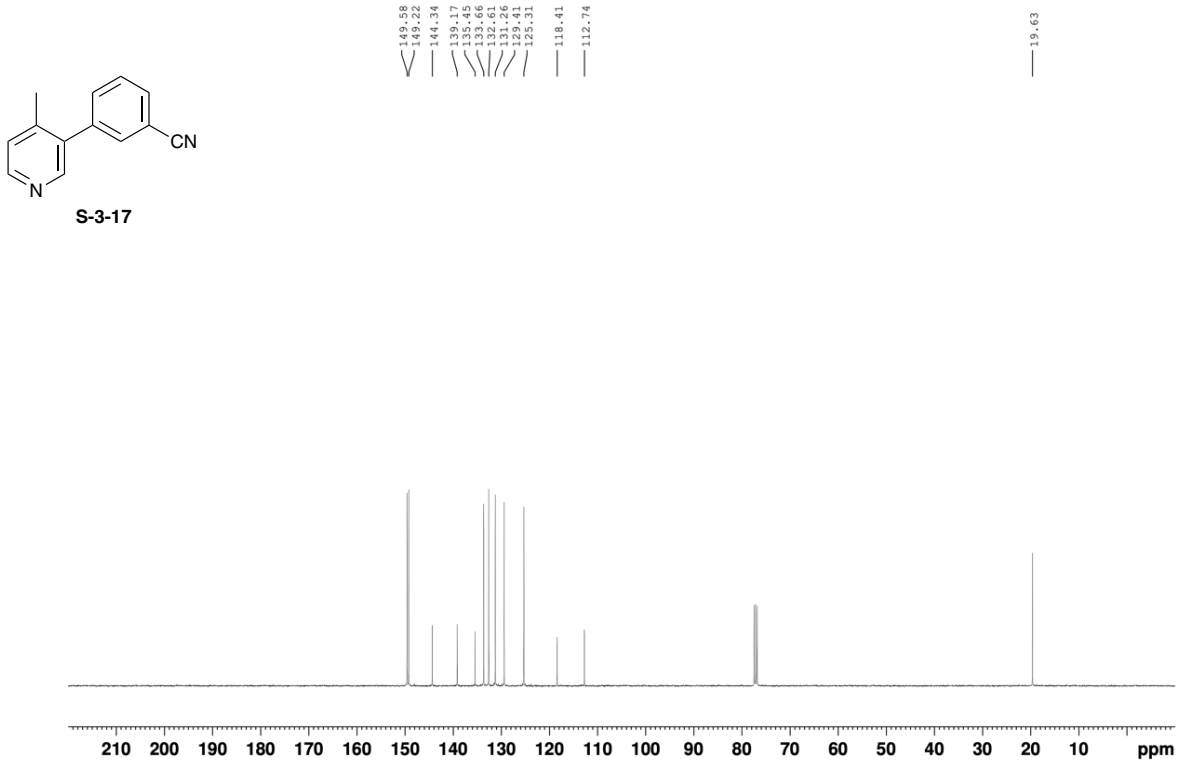
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{13}H_{11}N_2$ 195.0917; Found 195.0917.

^1H NMR (400 MHz, $CDCl_3$) spectrum for **S-3-17**:

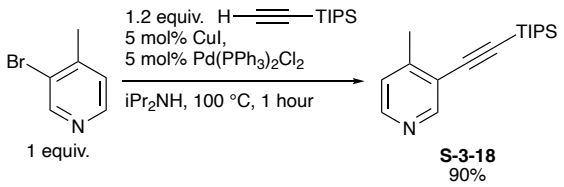


^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-3-17**:



S-3-17

Synthesis of compound **S-3-18**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with 24 mL of anhydrous diisopropylamine, 3-bromo-4-methylpyridine (0.58 mL, 1.0 equiv., 5.0 mmol), triisopropylacetylene (1.094 g, 1.2 equiv., 6.0 mmol), copper (I) iodide (48 mg, 5 mol%., 0.25 mmol) and bis(triphenylphosphine)-palladium (II) dichloride (175.5 mg, 5 mol%, 0.25 mmol). The resulting mixture was placed in an oil bath, stirred, and heated to reflux for 1 hour. The mixture was then cooled to ambient temperature and diluted with 100 mL of EtOAc, and the resulting suspension was filtered through a pad of Celite®. The filtrate was concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography by using EtOAC/Hexanes to afford compound **S-3-18** as colorless oil (1.24 g, 90% yield).

Chromatography: 10% EtOAc in Hexanes (R_f = 0.31).

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

δ 8.58 (s, 1H), 8.33 (d, J = 5.1 Hz, 1H), 7.07 (d, J = 5.1 Hz, 1H), 2.41 (s, 3H), 1.11 (s, 21H).

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

δ 152.8, 149.1, 148.4, 124.1, 121.0, 102.4, 98.5, 20.4, 18.7, 11.3.

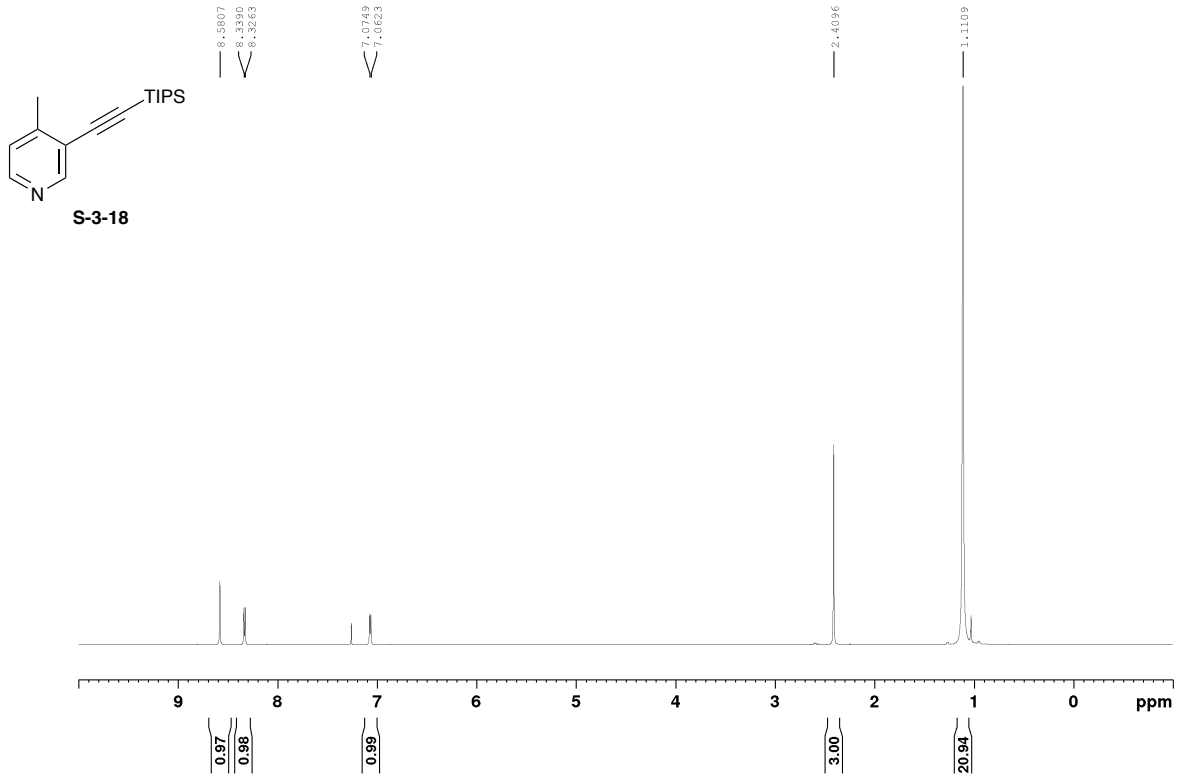
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3037, 2941, 2891, 2154, 1584, 1461, 1225 cm^{-1}.

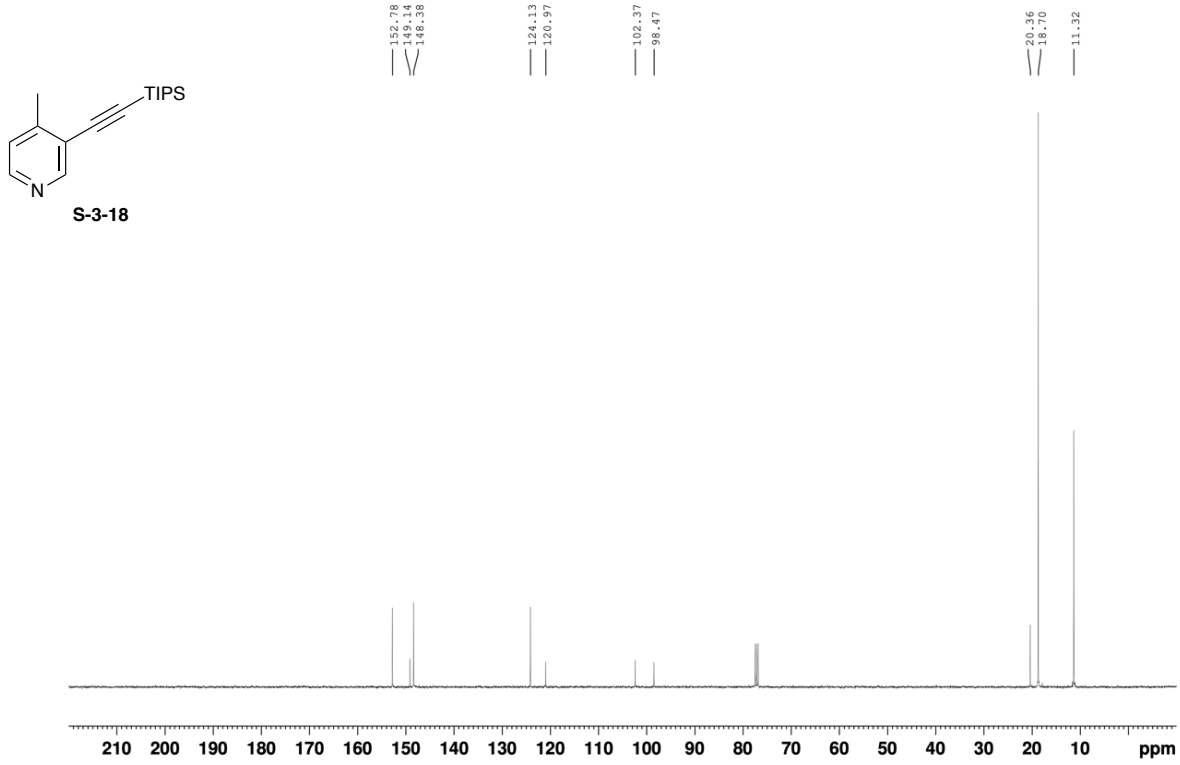
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{17}H_{28}NSi$ 274.1986; Found 274.2000.

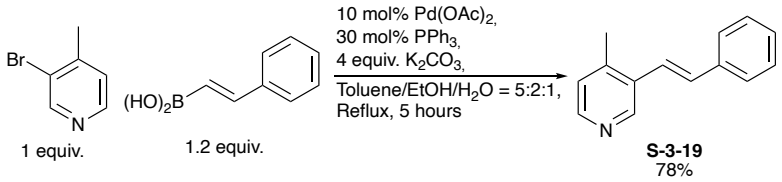
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **S-3-18**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-3-18**:



Synthesis of compound **S-3-19**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with 34 mL of toluene/ethanol/water (5:2:1), 3-bromo-4-methylpyridine (0.2 mL, 1.0 equiv., 1.7 mmol), *trans*-2-phenylvinylboronic acid (295.9 mg, 1.2 equiv., 2.0 mmol), palladium acetate (38.1 mg, 10 mol%, 0.17 mmol), triphenylphosphine (133.8 mg, 30 mol%, 0.51 mmol) and potassium carbonate (939.8 mg, 4.0 equiv., 6.8 mmol). The resulting mixture was placed in an oil bath, stirred, and heated to reflux for 5 hours. The mixture was then cooled to ambient temperature. Ethanol was removed using a rotary evaporator. The residue was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford compound **S-3-19** as light-yellow oil (259.4 mg, 78% yield).

Chromatography: 30% EtOAc in Hexanes (R_f = 0.23).

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

δ 8.74 (s, 1H), 8.36 (d, *J* = 4.9 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 2H), 7.40 – 7.35 (m, 2H), 7.32 – 7.27 (m, 1H), 7.21 (d, *J* = 16.2 Hz, 1H), 7.09 – 7.07 (m, 1H), 7.07 – 7.02 (m, 1H), 2.40 (s, 3H).

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

δ 148.3, 147.0, 144.3, 137.1, 132.9, 132.0, 128.9, 128.2, 126.8, 125.1, 123.3, 19.4.

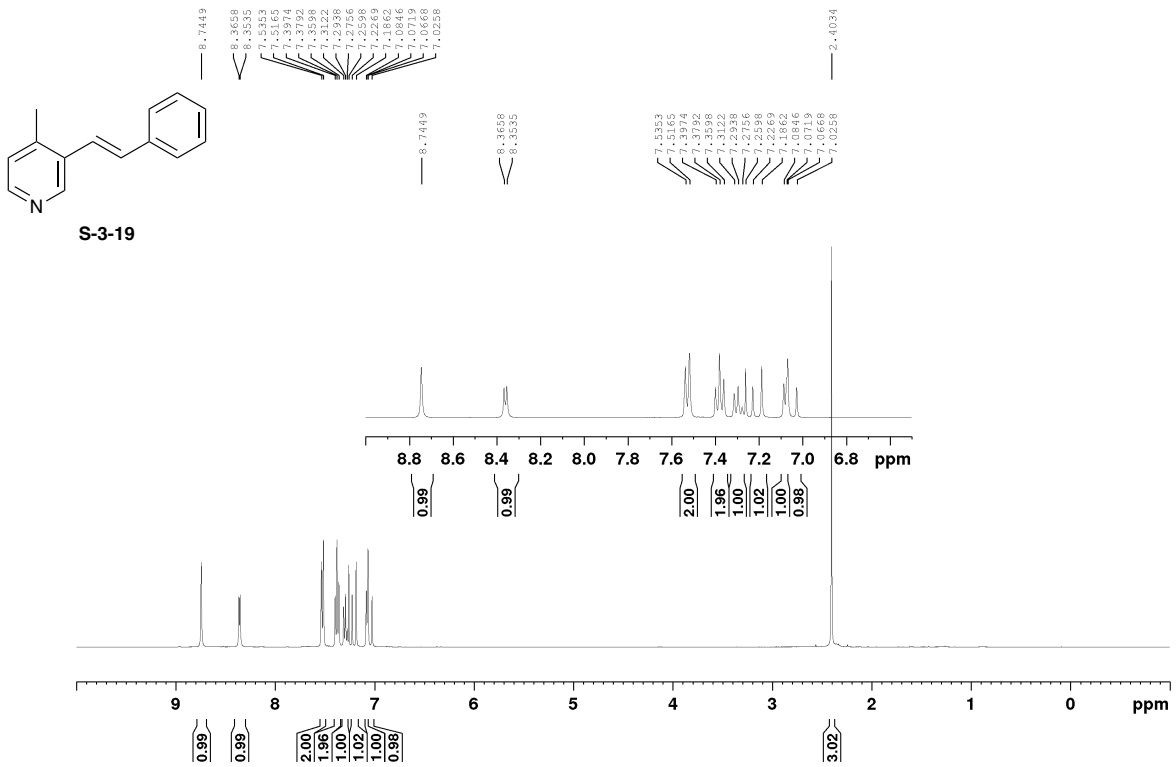
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3025, 2974, 2921, 1587, 1447, 960 cm^{-1}.

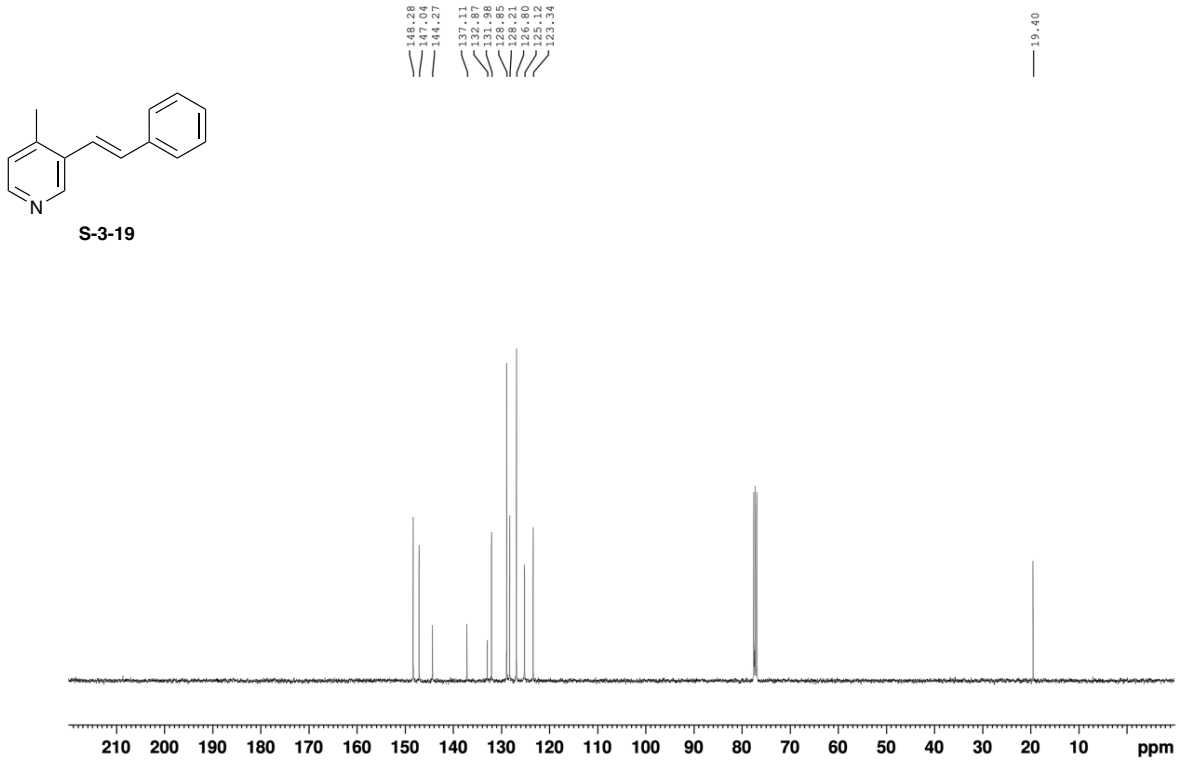
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{14}H_{14}N$ 196.1121; Found 196.1123.

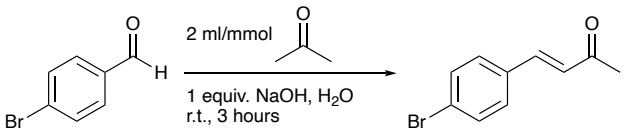
^1H NMR (400 MHz, $CDCl_3$) spectrum for **S-3-19**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-3-19**:



Synthesis of compound **S-3-24**:



An oven-dried round-bottomed flask equipped with a stir was charged with 4-bromobenzaldehyde (925 mg, 1 equiv., 5 mmol), 10 mL of acetone and 5 mL of 1 M aqueous NaOH. The resulting mixture was stirred at ambient temperature for 3 hours. The reaction mixture was then cooled to 0 °C and neutralized with dropwise addition of 1 M aqueous HCl. The resulting mixture was concentrated using a rotary evaporator to remove excess acetone. The residue was then extracted with EtOAc (4 x 20 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford compound **S-3-24** as white solid (782 mg, 70% yield). The NMR data was found to be consistent with the literature values.[52]

Chromatography: 10% EtOAc in Hexanes (R_f = 0.21).

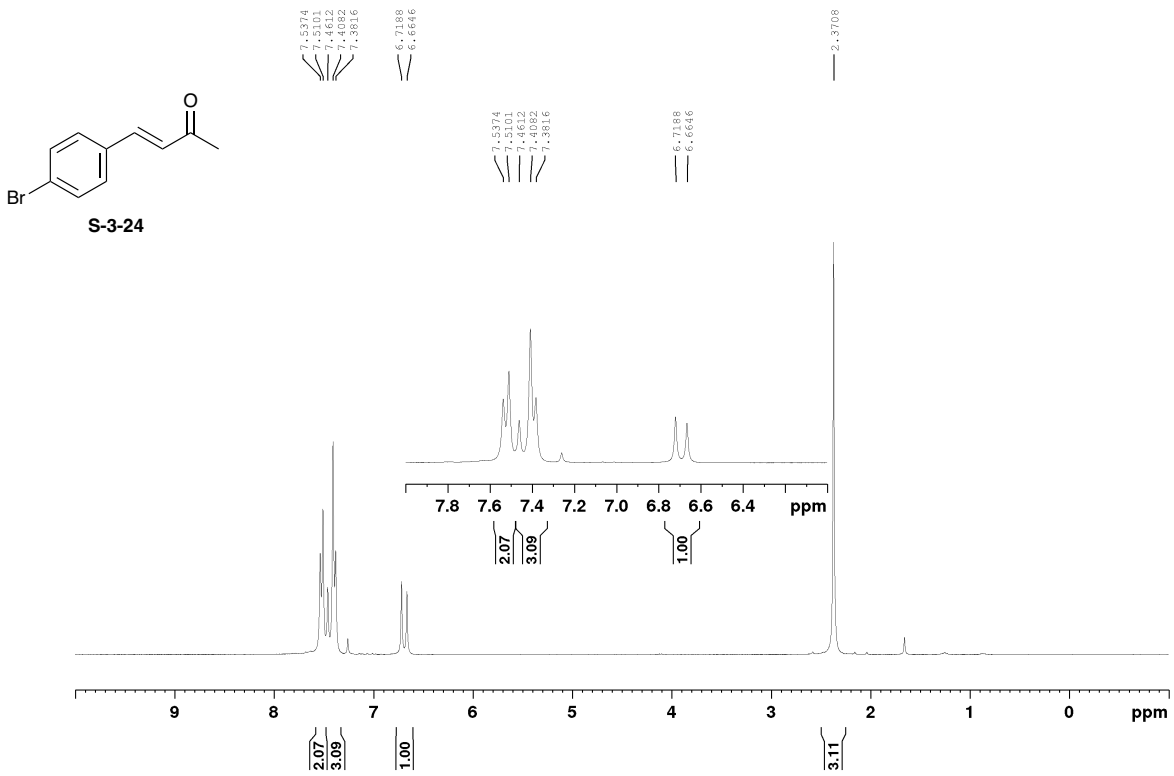
^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.54 –7.51 (m, 2H), 7.47 – 7.38 (m, 3H), 6.69 (d, J = 16.3 Hz, 1H), 2.37 (s, 3H).

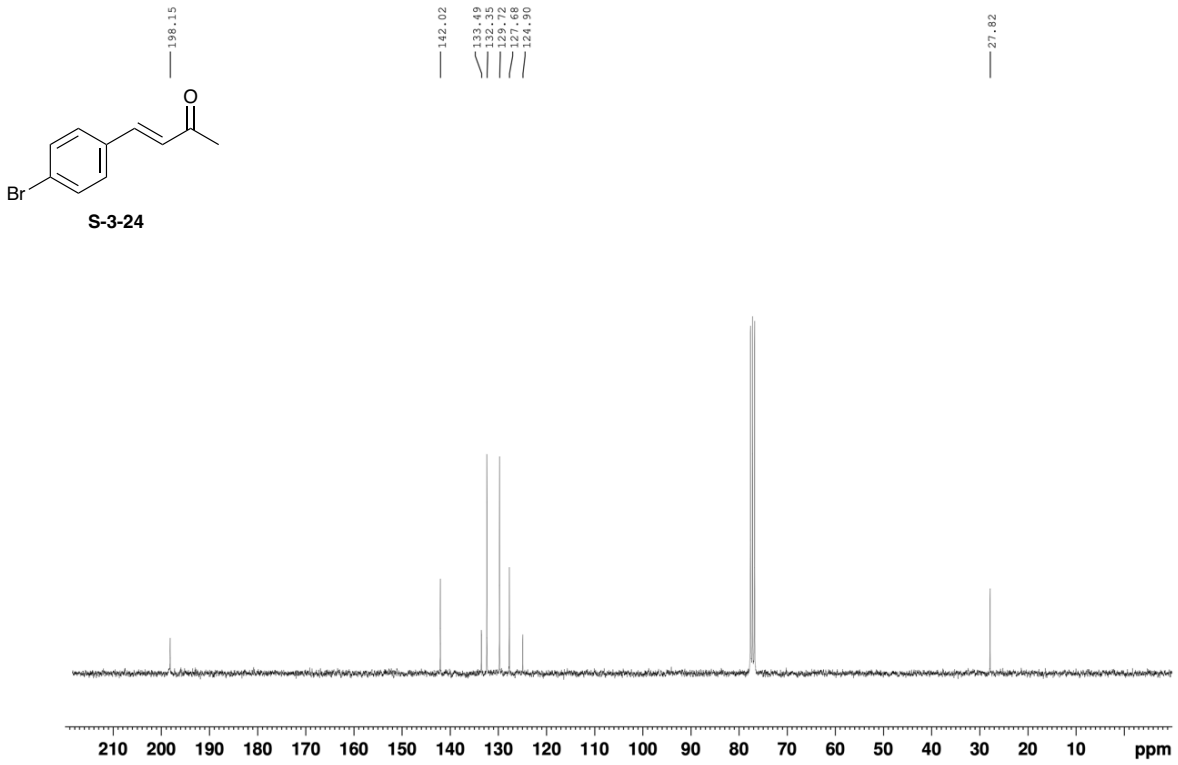
^{13}C NMR (75 MHz, $CDCl_3$)

δ 198.2, 142.0, 133.5, 132.4, 129.7, 127.7, 124.9, 27.8.

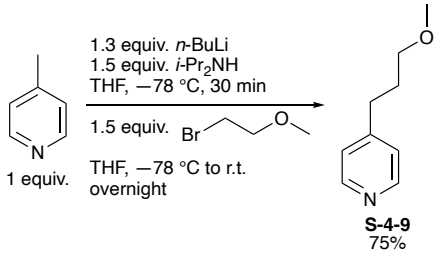
^{1}H NMR (300 MHz, $CDCl_3$) spectrum for **S-3-24**:



^{13}C NMR (75 MHz, $CDCl_3$) spectrum for **S-3-24**:



Synthesis of compound **S-4-9**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with freshly distilled diisopropylamine (1.05 mL, 1.5 equiv., 7.5 mmol) and 20 mL of anhydrous THF and cooled to –78 °C. *n*-Butyl lithium (4.06 mL, 1.3 equiv., 6.5 mmol, 1.6 M in hexanes) was added to the solution in a dropwise manner, and the resulting mixture was stirred for 15 min at –78 °C. A solution of 4-methylpyridine (0.49 mL, 1.0 equiv., 5.0 mmol) in 5 mL of anhydrous THF was added in a dropwise manner, and the resulting mixture was stirred for 30 min at –78 °C. The deprotonated picoline was cannulated to a dry round-bottomed flask containing 2-bromoethyl methyl ether (0.72 mL, 1.5 equiv., 7.5 mmol) in 7 mL of anhydrous THF. The mixture was stirred for additional 1 hour at –78 °C and allowed to warm slowly to ambient temperature overnight. The solution was quenched with water (20 mL), and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography using EtOAc/hexanes to afford compound **S-4-9** as colorless oil (563.7 mg, 75% yield).

Chromatography: 70% EtOAc in hexanes (R_f = 0.19).

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

δ 8.48 (d, *J* = 6.0 Hz, 2H), 7.11 (d, *J* = 6.0 Hz, 2H), 3.37 (t, *J* = 6.0 Hz, 2H), 3.34 (s, 3H), 2.67 (t, *J* = 8.0 Hz, 2H), 1.94 – 1.84 (m, 2H).

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

δ 151.1, 149.9, 124.1, 71.6, 58.8, 31.8, 30.3.

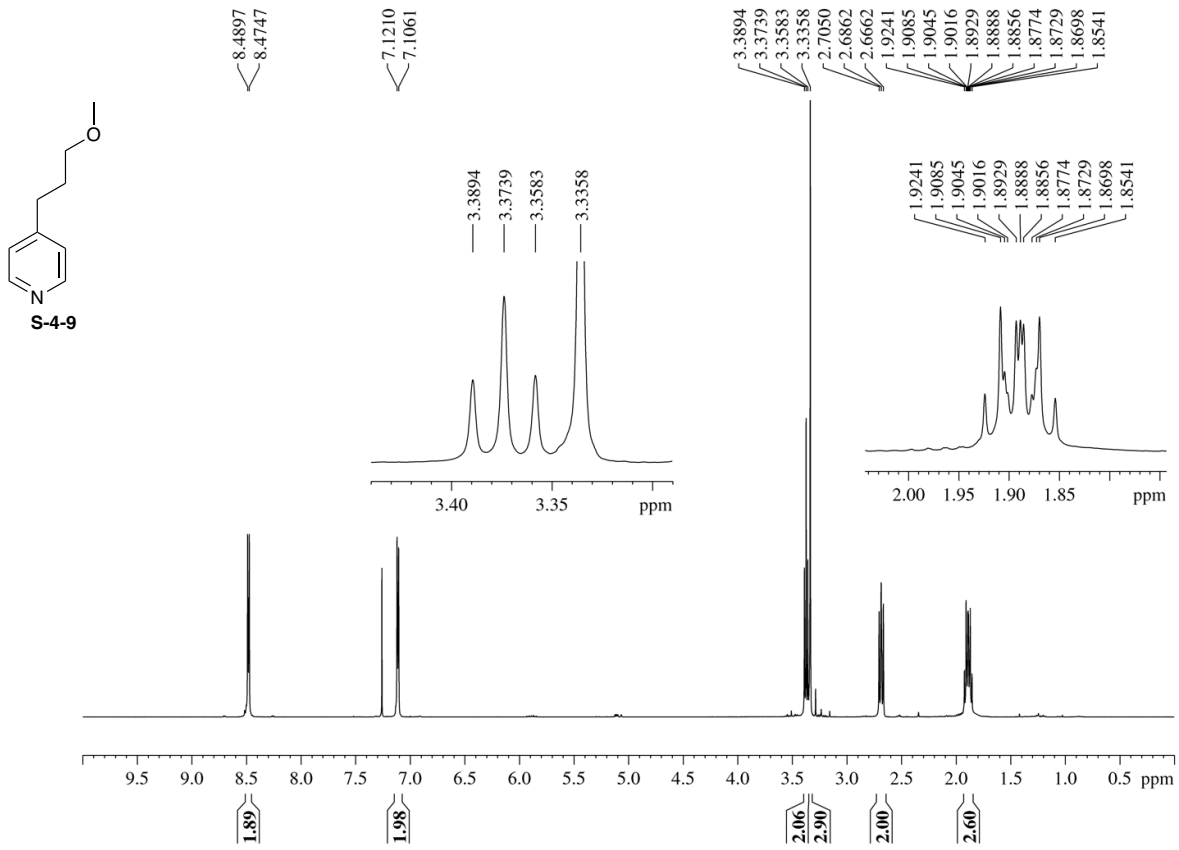
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3069, 2981, 2829, 1602, 1416 cm^{-1}.

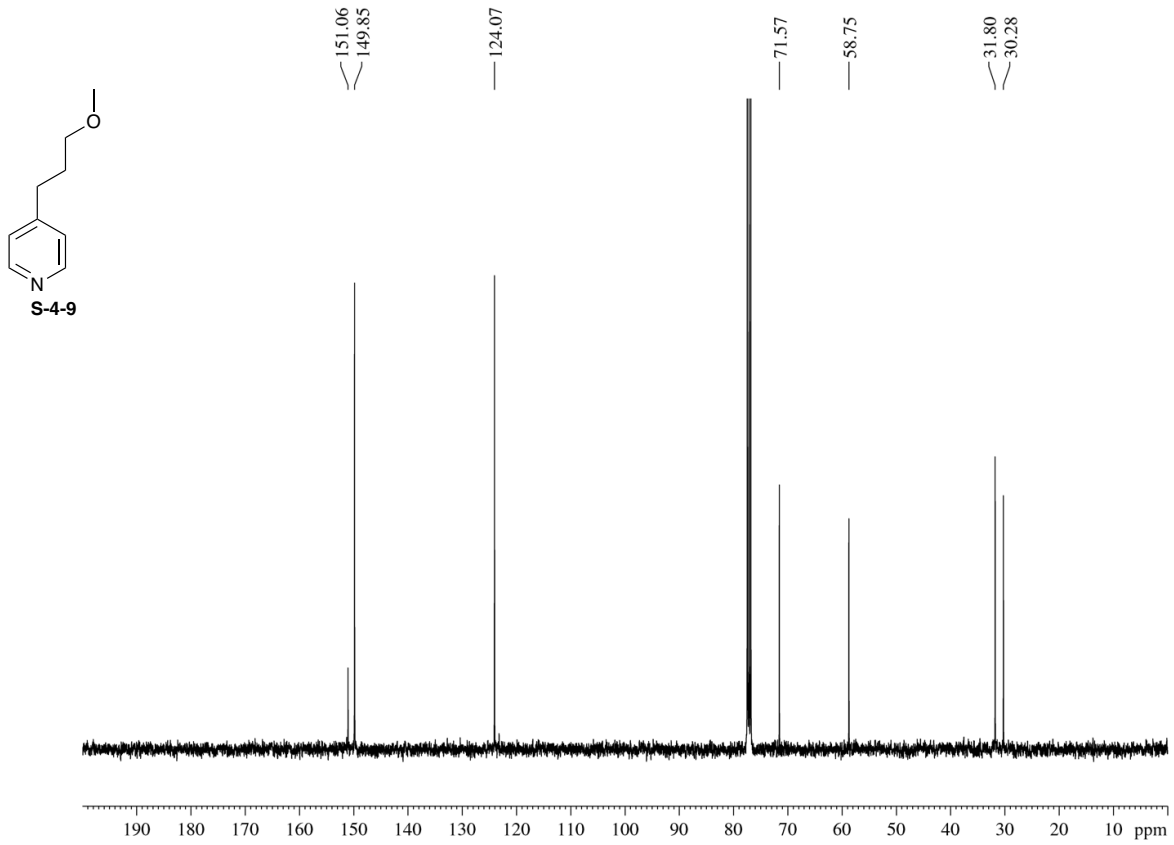
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_9H_{14}NO$ 152.1070; Found 152.1065.

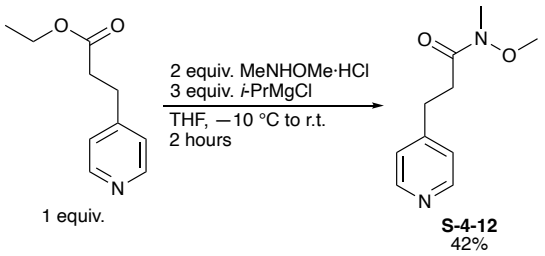
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **S-4-9**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-4-9**:



Synthesis of compound **S-4-12**:



A flame-dried round-bottomed flask equipped with a stir bar was charged with ethyl 3-(pyridin-4-yl)propanoate (1.0 equiv., 2 mmol, 360 mg), *N,O*-dimethylhydroxylamine hydrochloride (1.5 equiv., 3 mmol, 292.6 mg) and 10 mL of anhydrous THF. The reaction mixture was cooled to –10 °C, and isopropylmagnesium chloride (3.0 equiv., 6 mmol, 3.3 mL, 2.0 M in THF) was added dropwise while stirring at –10 °C. The reaction mixture was stirred for 1 hour at –10 °C and for another hour at ambient temperature. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (4 x 20 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography using EtOAc/Et_3N/Hexanes to afford compound **S-4-12** as colorless oil (164.2 mg, 42% yield).

Chromatography: 80% EtOAc and 5% Et_3N in Hexanes (R_f = 0.40).

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

δ 8.48 (d, *J* = 6.0 Hz, 2H), 7.15 (d, *J* = 6.0 Hz, 2H), 3.63 (s, 3H), 3.17 (s, 3H), 3.00 – 2.91 (t, *J* = 7.5 Hz, 2H), 2.81 – 2.70 (t, *J* = 7.5 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$):

δ 172.9, 150.4, 149.8, 123.9, 61.3, 32.3(1), 32.3, 29.7.

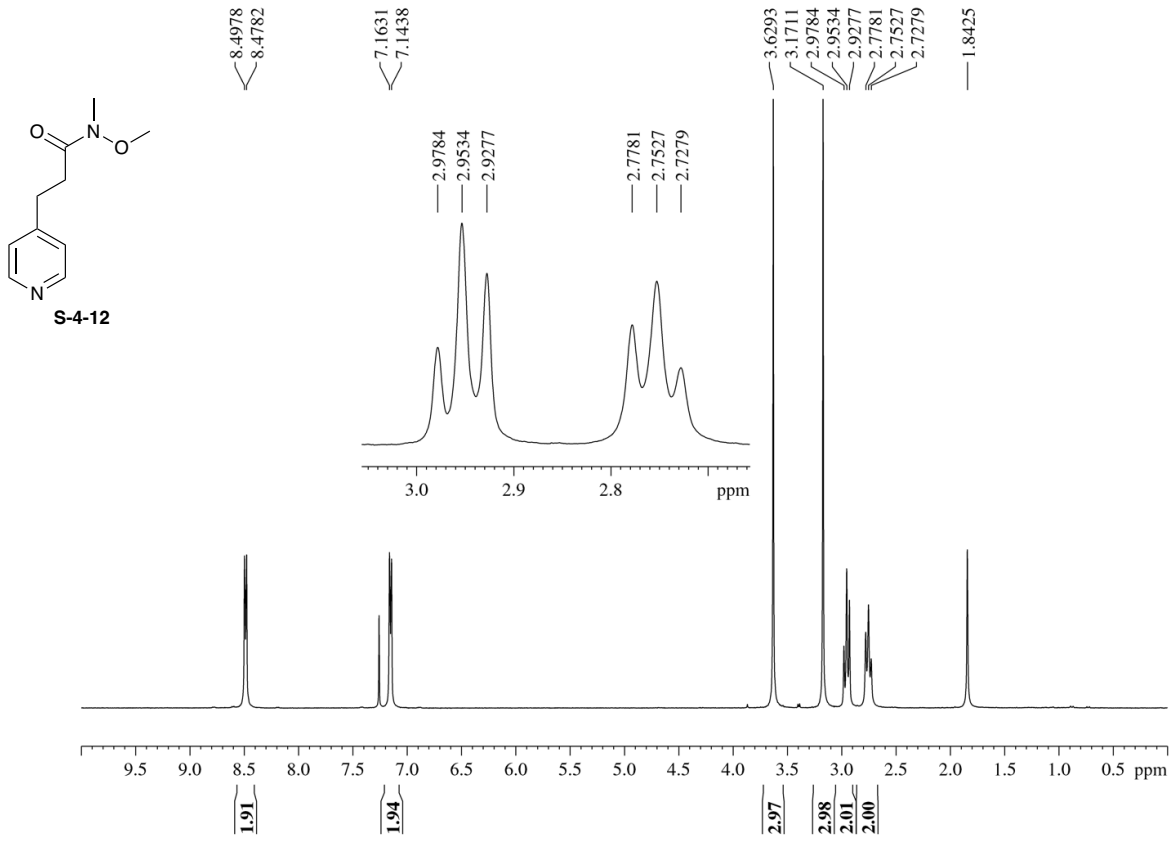
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3070, 2938, 2821, 1652, 1610, 1415 cm^{-1}.

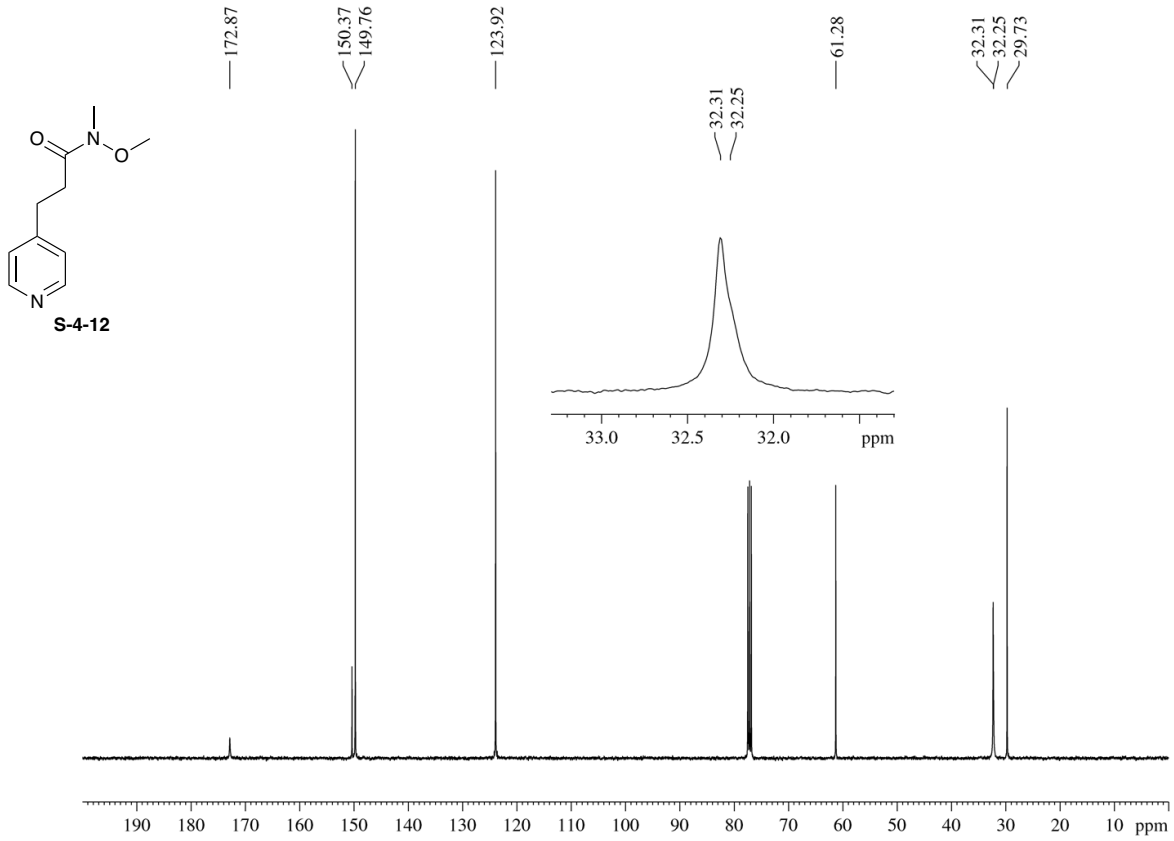
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{10}H_{15}N_2O_2$ 195.1128; Found 195.1121.

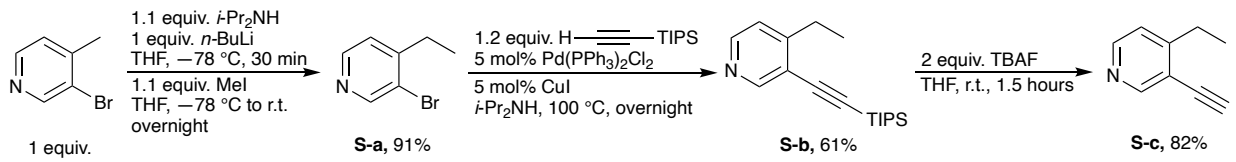
^1H NMR (300 MHz, $CDCl_3$) spectrum for **S-4-12**:



^{13}C NMR (75 MHz, $CDCl_3$) spectrum for **S-4-12**:



Synthesis of compound **S-c**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with freshly distilled diisopropylamine (4.47 mL, 1.1 equiv., 31.97 mmol) and 30 mL of anhydrous THF and cooled to –78 °C. *n*-Butyl lithium (18.16 mL, 1.0 equiv., 29.06 mmol, 1.6 M in hexanes) was added to the solution in a dropwise manner, and the resulting mixture was stirred for 15 min at –78 °C. A solution of 3-bromo-4-methylpyridine (3.23 mL, 1.0 equiv., 29.06 mmol) in 30 mL of anhydrous THF was introduced at the same temperature in a dropwise manner, and the resulting mixture was stirred for 30 min at –78 °C. The mixture was cannulated to a dry round-bottomed flask containing methyl iodide (1.81 mL, 1.1 equiv., 29.06 mmol) in 10 mL of anhydrous THF. The mixture was stirred for additional 1 hour at –78 °C and allowed to warm slowly to ambient tempeture overnight. The solution was quenched with water, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, filtered through a cotton plug and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography using EtOAc/hexanes to afford 3-bromo-4-ethylpyridine (**S-a**) as colorless oil (4.89 g, 91% yield).

An oven-dried round-bottomed flask equipped with a stir bar was charged with containing compound **S-a** (504.2 mg, 1.0 equiv. 2.71 mmol), triisopropylacetylene (0.79 mL, 1.2 equiv., 3.25 mmol), copper (I) iodide (25.8 mg, 5 mol%, 0.136 mmol), bis(triphenylphosphine)-palladium (II) dichloride (95.5 mg, 5 mol%, 0.136 mmol) and 24 mL of diisopropylamine. The resulting mixture was placed in an oil bath, heated at reflux overnight and then cooled to ambient temperature. The reaction mixture was diluted with 100 mL of EtOAc and the resulting suspension was filtered through a pad of Celite®. The filtrate was concentrated using a rotary evaporator. The resulting

residue was purified by flash column chromatography using EtOAC/hexanes to afford compound **S-b** as colorless oil (475 mg, 61% yield).

A round-bottomed flask equipped with a stir bar was charged with the compound **S-b** (450 mg, 1.0 equiv., 1.56 mmol) and 16 mL of THF at ambient temperature. Tetrabutylammonium fluoride (3.13 mL, 2.0 equiv., 3.13 mmol, 1 M in THF) was added, and stirred the reaction mixture 1.5 hours. The reaction mixture was concentrated using a rotary evaporator, and the resulting residue was purified by flash column chromatography using EtOAc/hexane to afford 3-ethynyl-4-ethylpyridine (**S-c**) as yellow oil (162 mg, 79% yield).

Chromatography: 10% EtOAc in Hexanes (R_f = 0.24).

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

δ 8.62 (s, 1H), 8.43 (d, *J* = 5.2 Hz, 1H), 7.12 (d, *J* = 5.2 Hz, 1H), 3.36 (s, 1H), 2.79 (q, *J* = 7.6 Hz, 2H), 1.24 (t, *J* = 7.6 Hz, 3H).

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

δ 155.2, 153.3, 149.3, 122.6, 118.9, 83.8, 79.2, 27.0, 13.7.

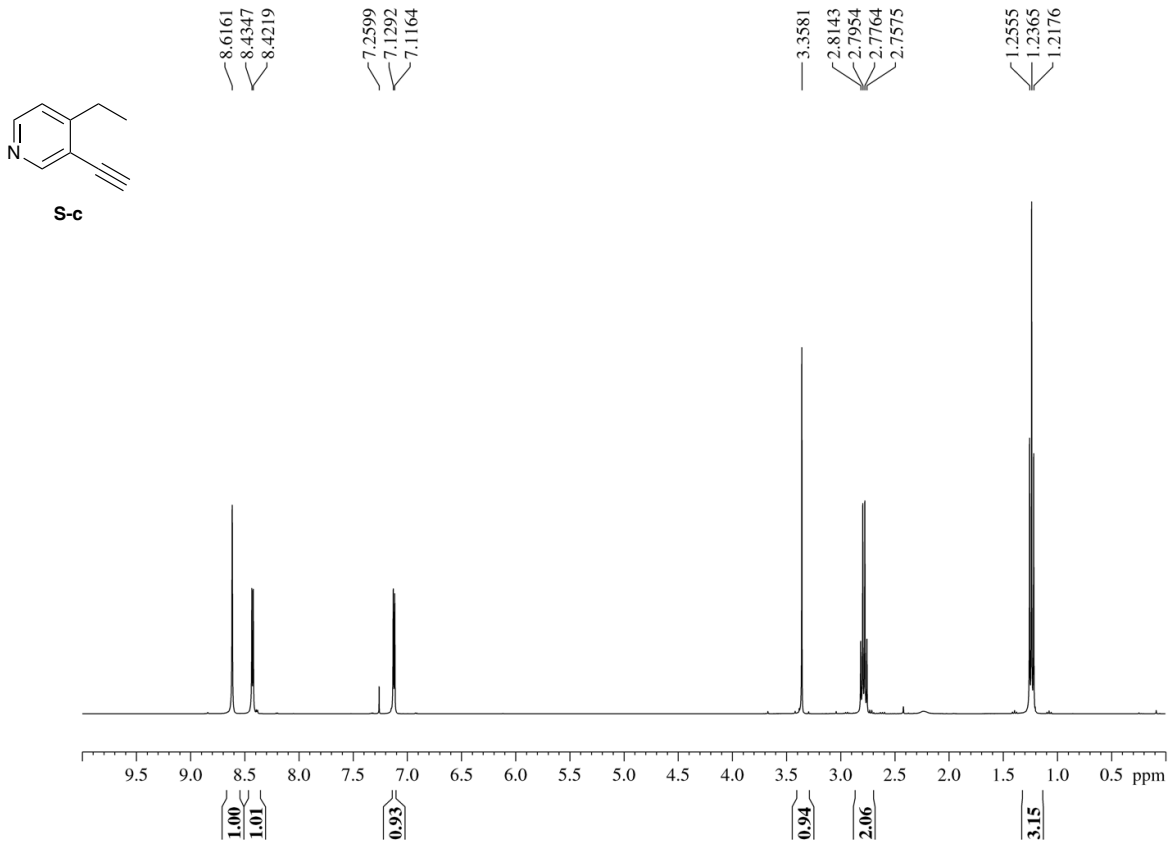
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2970, 2932, 2876, 1584, 1399, 837 cm^{-1}.

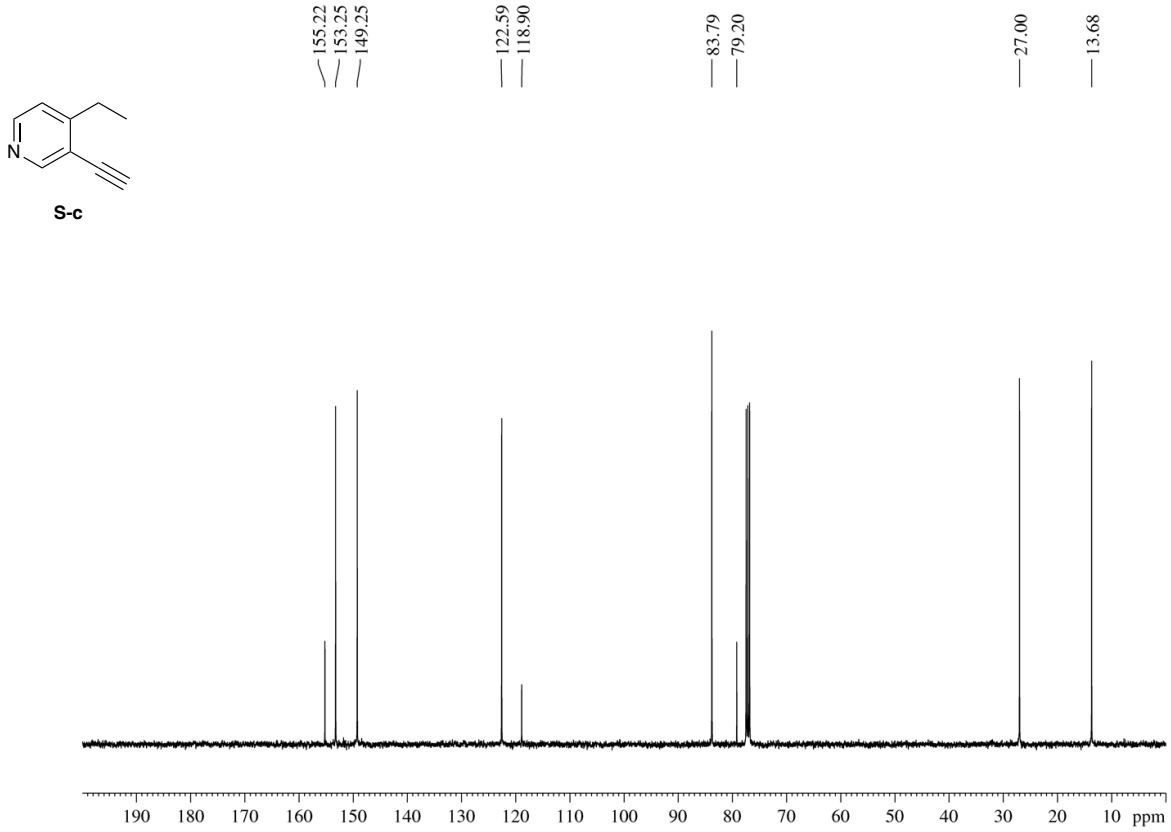
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_9H_{10}N$ 132.0808; Found 132.0805.

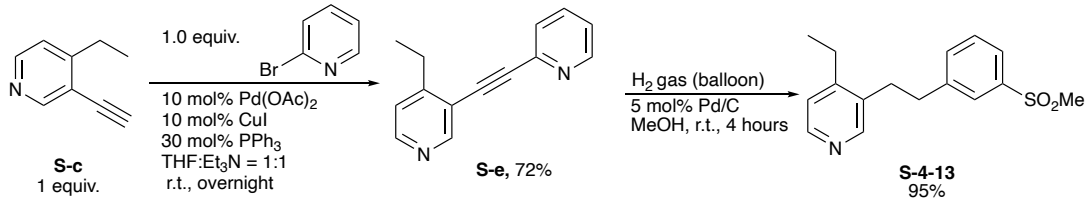
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **S-c**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-c**:



Synthesis of compound **S-4-13**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with compound **S-c** (199.4 mg, 1.0 equiv., 1.52 mmol), bis(triphenylphosphine)-palladium(II) dichloride (21.1 mg, 2 mol%, 0.03 mmol), copper(I) iodide (5.7 mg, 2 mol%, 0.03 mmol), 1-bromo-3-(methylsulfonyl)-benzene (357.5 mg, 1.0 equiv., 1.52 mmol), and triphenylphosphine (7.9 mg, 2 mol%, 0.03 mmol), along with 3 mL of anhydrous THF and 3 mL of freshly distilled triethylamine. The reaction mixture was stirred overnight at ambient temperature. The reaction mixture was then quenched with 10 mL of water and extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography using EtOAc/hexanes to afford compound **S-d** as colorless oil (290 mg, 67% yield).

A round-bottomed flask equipped with a stir bar was charged with compound **S-d** (350 mg, 1.0 equiv., 1.22 mmol) and 5 mL of MeOH. A slurry of Pd/C (64.9 mg, 5 mol%, 0.06 mmol, 10% w/w) in 2 mL of MeOH was added to the mixture, and the mixture was stirred under H_2 atmosphere at ambient temperature for 4 hours. The mixture was filtered through a pad of Celite®. The filtrate was concentrated using a rotary evaporator, and the resulting residue was purified by flash column chromatography using EtOAc/hexanes to afford compound **S-4-13** as colorless oil (334 mg, 95% yield).

Chromatography: 80% EtOAc in hexane (R_f = 0.13).

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

δ 8.36 (d, J = 5.2 Hz, 1H), 8.19 (s, 1H), 7.79 (dt, J = 7.6, 1.6 Hz, 1H),

7.67 – 7.62 (m, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.46 – 7.41 (m, 1H),

7.10 (d, J = 5.2 Hz, 1H), 3.01 (s, 3H), 2.99 – 2.92 (m, 4H), 2.62 (q, J = 7.6 Hz, 2H),

1.23 (t, J = 7.6 Hz, 3H).

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

δ 150.8, 150.4, 148.2, 142.8, 140.7, 134.0, 133.8, 129.7, 127.3, 125.4, 123.2,

44.6, 36.9, 31.6, 24.7, 14.2.

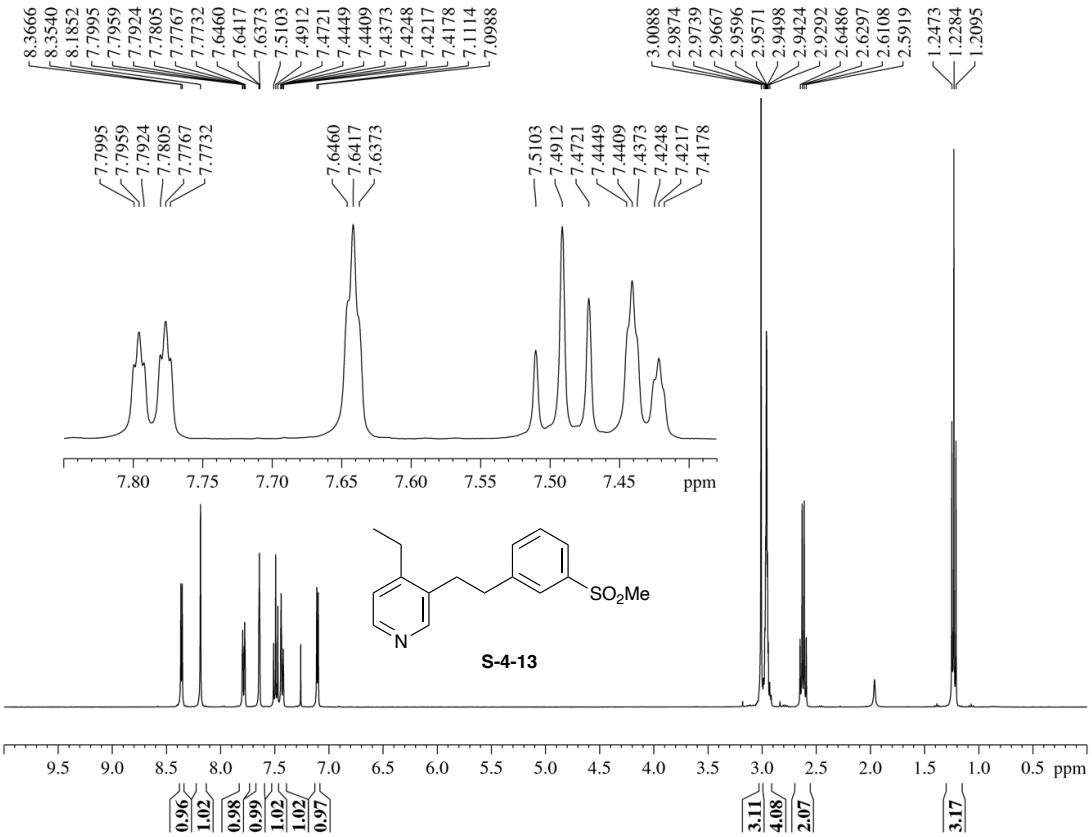
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2959, 2924, 2853, 1461, 1267, 1146, 759 cm^{-1}.

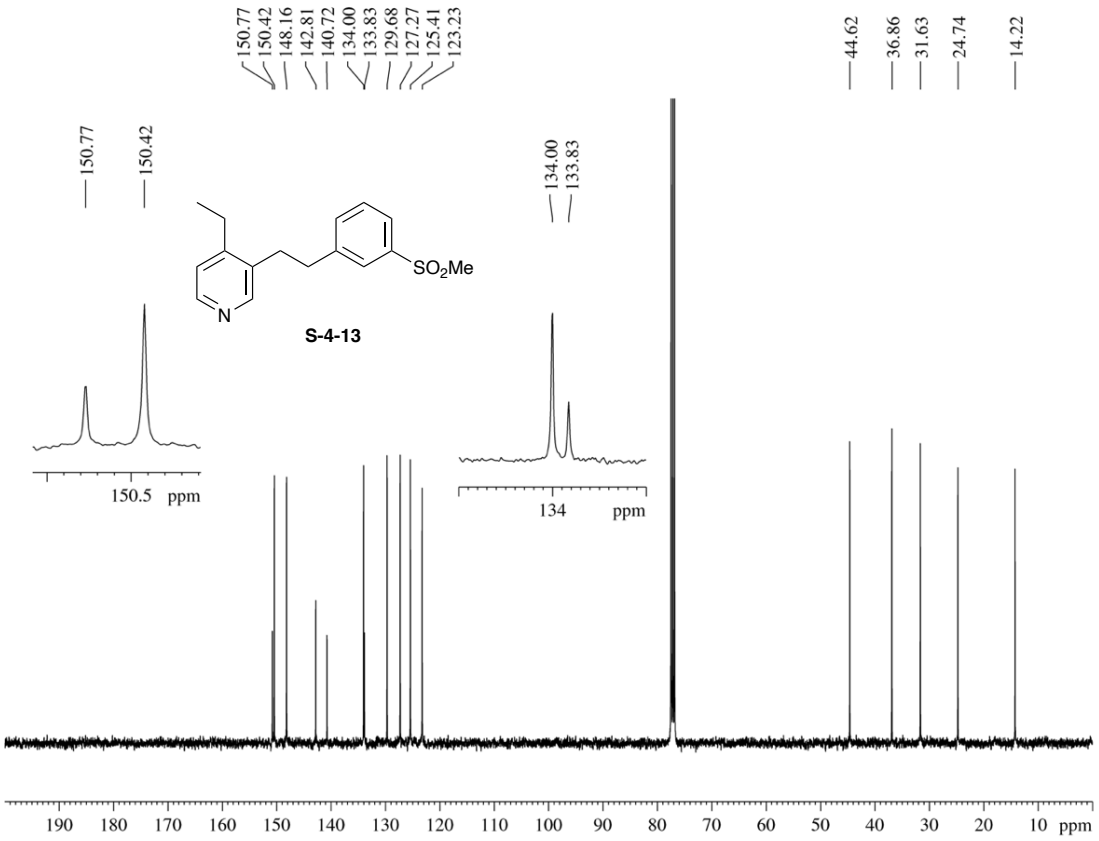
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{16}H_{20}NO_2S$ 290.1209; Found 290.1204.

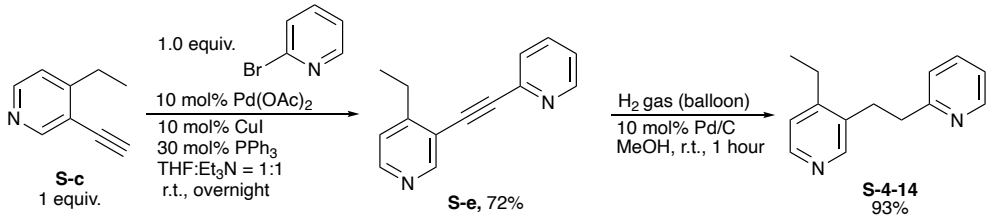
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **S-4-13**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-4-13**:



Synthesis of compound **S-4-14**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with palladium acetate (22.5 mg, 10 mol%, 0.1 mmol) and triphenylphosphine (78.7 mg, 30 mol%, 0.3 mmol), along with 5 mL of anhydrous THF and 5 mL of freshly distilled triethylamine. The mixture was stirred over 15 minutes at ambient temperature. 2-Bromopyridine (0.11 mL, 1.0 equiv., 1.0 mmol), copper(I) iodide (19.1 mg, 10 mol%, 0.1 mmol), and compound **S-c** (131.2 mg, 1.0 equiv., 1.0 mmol) were added sequentially to the solution, and the resulting mixture was stirred overnight at ambient temperature. The reaction mixture was filtered through a pad of Celite®, and the filtrate was concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography using EtOAc/hexanes to afford compound **S-e** as light-yellow oil (150.9 mg, 72% yield).

A round-bottomed flask equipped with a stir bar was charged with compound **S-e** (308 mg, 1.0 equiv., 1.48 mmol) and 10 mL of MeOH. A slurry of Pd/C (157 mg, 10 mol%, 0.148 mmol, 10% w/w) in 3 mL of MeOH was added to the mixture, and the resulting mixture was stirred under H_2 atmosphere at ambient temperature for 1 hour. The mixture was filtered through a pad of Celite®. The filtrate was concentrated using a rotary evaporator, and the resulting residue was purified by flash column chromatography using EtOAc to afford compound **S-4-14** as colorless oil (290.8 mg, 93% yield).

Chromatography: 100% EtOAc (R_f = 0.37).

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

δ 8.58 (d, J = 4.4 Hz, 1H), 8.35 (d, J = 4.8 Hz, 1H), 8.32 (s, 1H),

7.57 (td, *J* = 7.6, 1.2 Hz, 1H), 7.17 – 7.10 (m, 1H), 7.08 (d, *J* = 4.8 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 3.14 – 2.91 (m, 4H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H).

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

δ 160.7, 150.8, 150.4, 149.6, 147.9, 136.5, 134.7, 123.1, 123.0, 121.5, 39.4, 30.0, 24.7, 14.2.

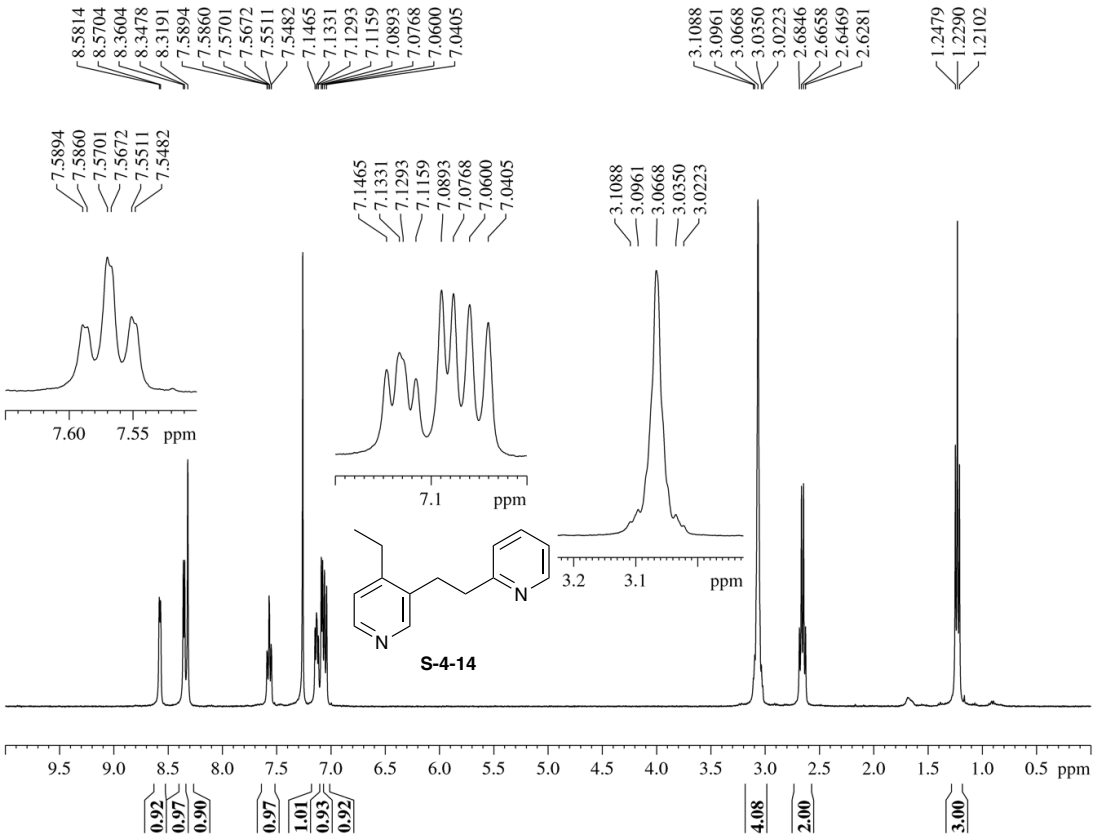
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3053, 2969, 2880, 1591, 1434, 1410, 765 cm^{-1}.

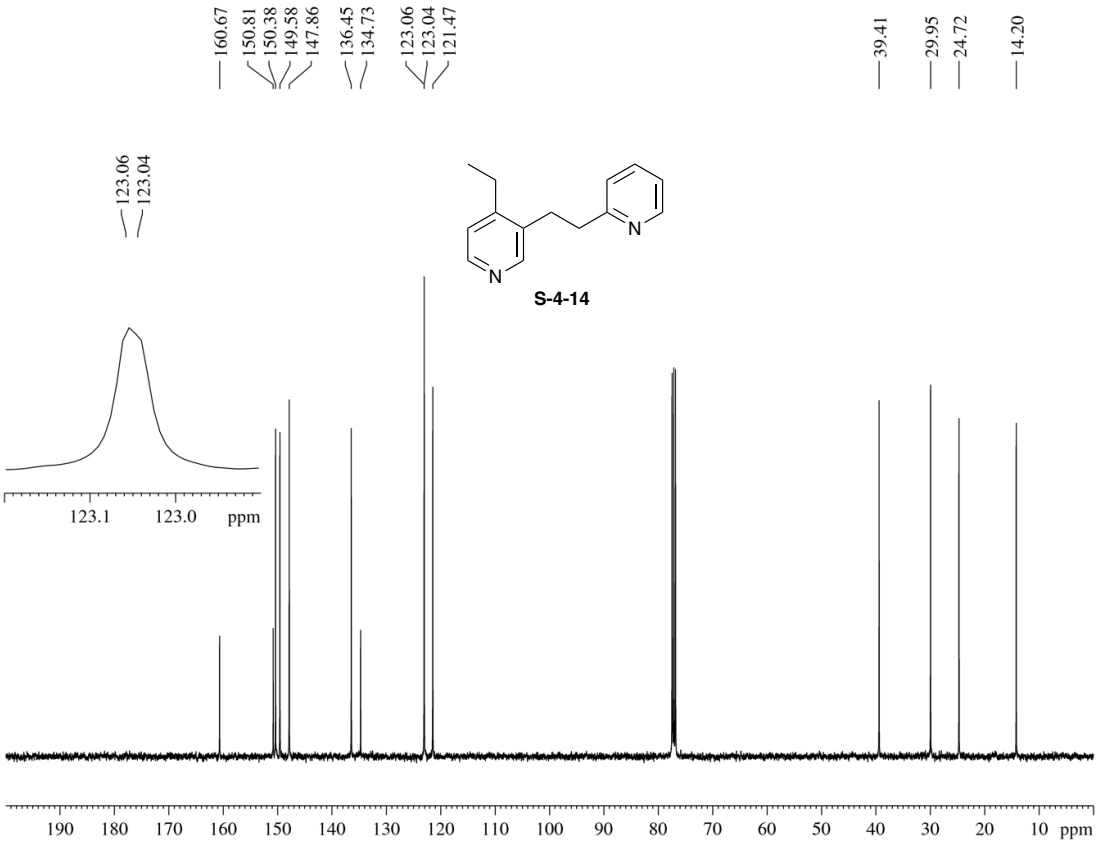
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{14}H_{17}N_2$ 213.1386; Found 213.1378.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **S-4-14**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **S-4-14**:



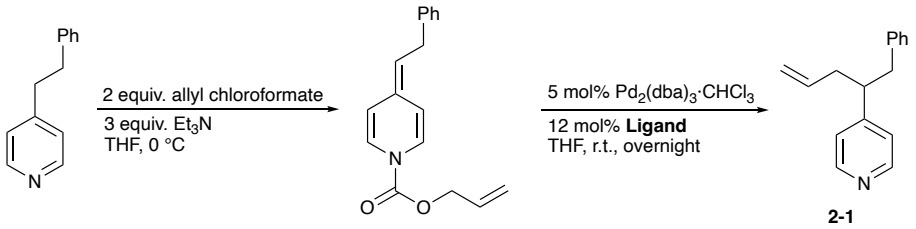
6.2 General procedure (A) for synthesis of ADHPs

An oven-dried round-bottomed flask equipped with a stir bar was charged with freshly distilled Et_3N (3.0 equiv.) and a 0.1 M solution of 4-alkylpyridine (1.0 equiv.) in anhydrous THF. The stirred mixture was cooled to 0 °C. Unless otherwise stated, 2.0 equiv. of ethyl chloroformate were added dropwise to the reaction mixture at 0 °C while stirring. The reaction mixture was allowed to warm slowly to ambient temperature while stirring over 30 minutes. The mixture was concentrated using a rotary evaporator. The resulting residue was suspended in diethyl ether for 2 – 3 minutes and filtered through a cotton plug to remove the precipitated triethylammonium chloride salt. The filtrate was concentrated using a rotary evaporator to obtain the ADHP, which was used in the next step without further purification.

Note: ADHP generated from 4-methylpyridine should be used quickly and not be exposed to air overtime due to its poor stability.

6.3 Attempts toward enantioselective allylation of 4-alkylpyridines

6.3.1 General procedure for allylation of 4-phenethylpyridine



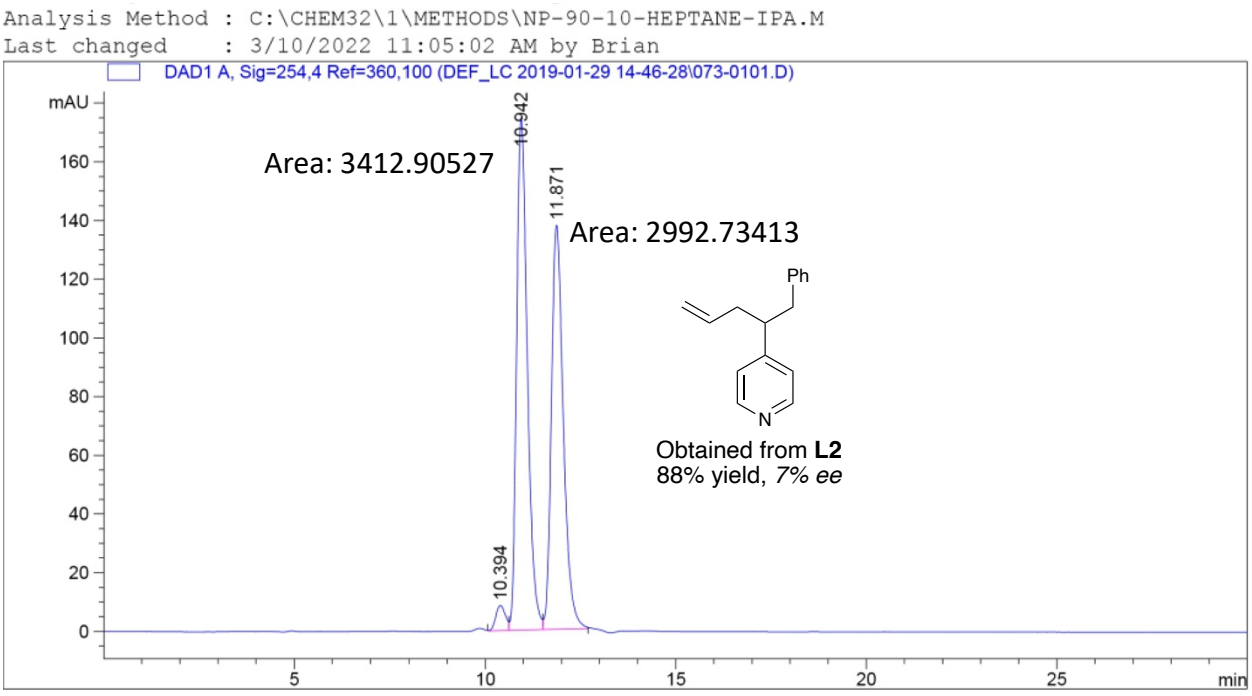
2-1

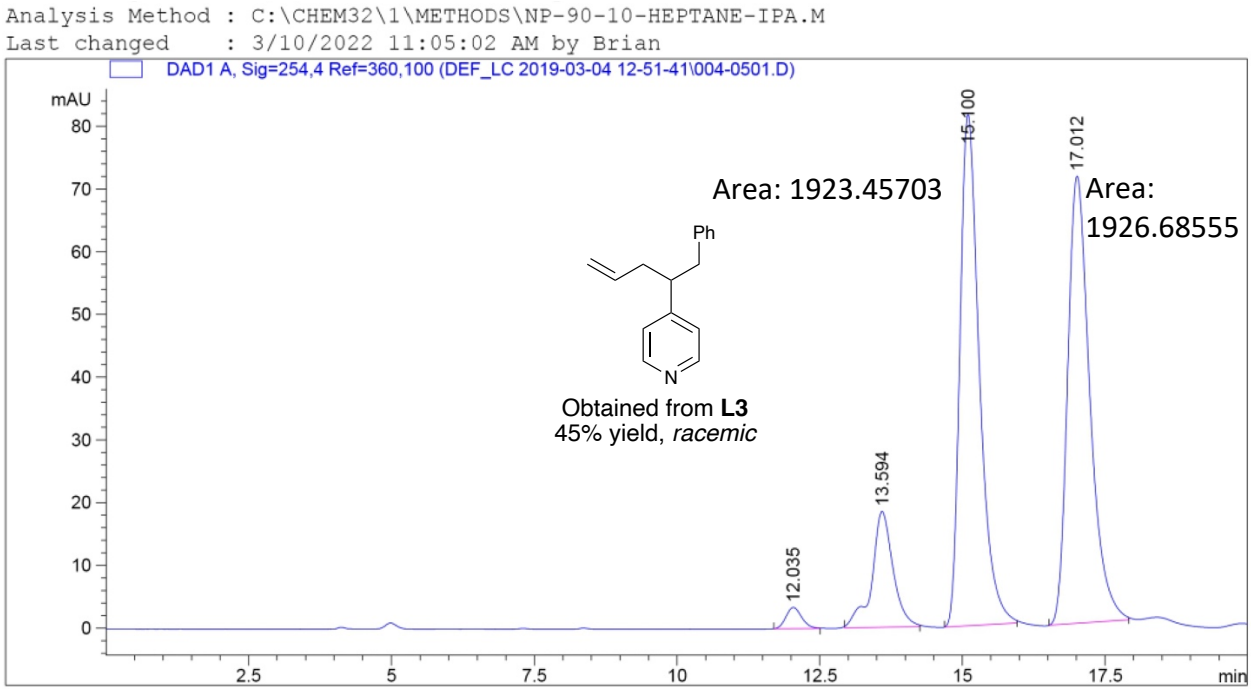
The ADHP was synthesized by following **General procedure A** using 4-phenethylpyridine. Allyl chloroformate (2.0 equiv.) was used instead of ethyl chloroformate.

An oven-dried scintillation vial equipped with a stir bar was charged with the chiral ligand (0.12 equiv.) and $Pd_2(dba)_3{\cdot}CHCl_3$ (0.05 equiv.) in anhydrous THF. The mixture was stirred for 30 minutes under ambient temperature. A solution of ADHP in THF (0.2 M) was added to the mixture in a dropwise manner, and the resulting mixture was stirred overnight under argon atmosphere at ambient temperature. The reaction mixture was concentrated using a rotary evaporator, and the resulting residue was purified using flash column chromatography to obtain the allylation product **2-1** as colorless oil.

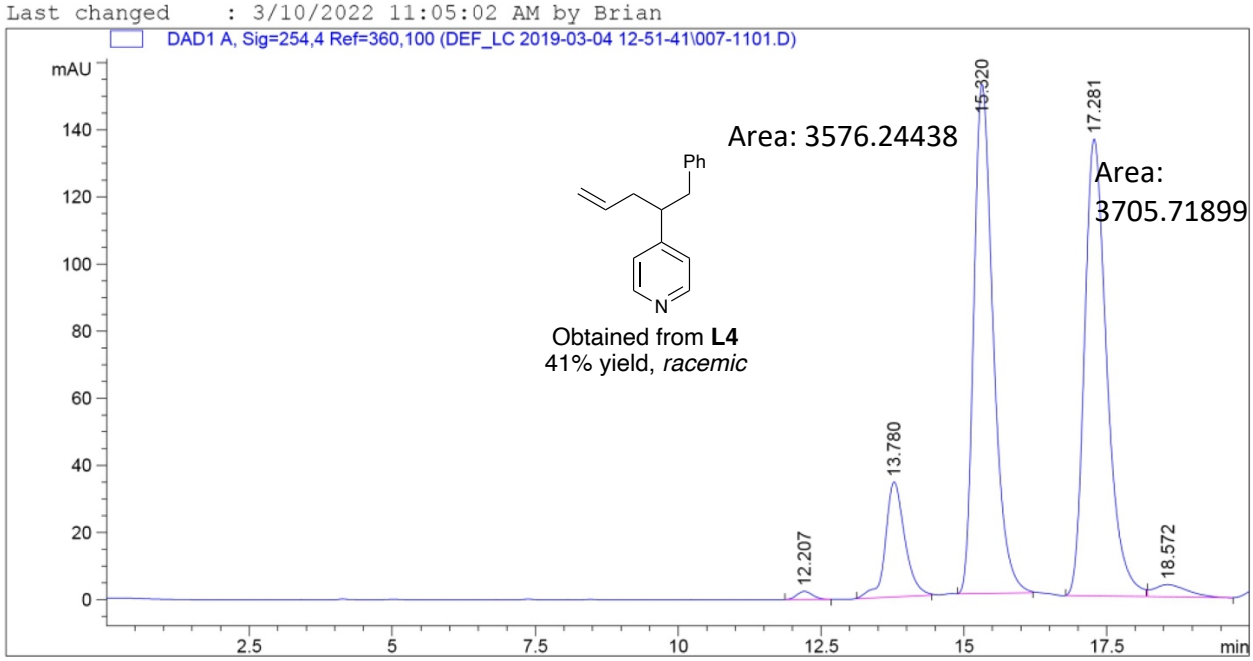
*Note: For **L9** and **L11**, 0.24 equiv. was used instead of 0.12 equiv.*

6.3.2 HPLC chromatographs obtained from the ligand screen

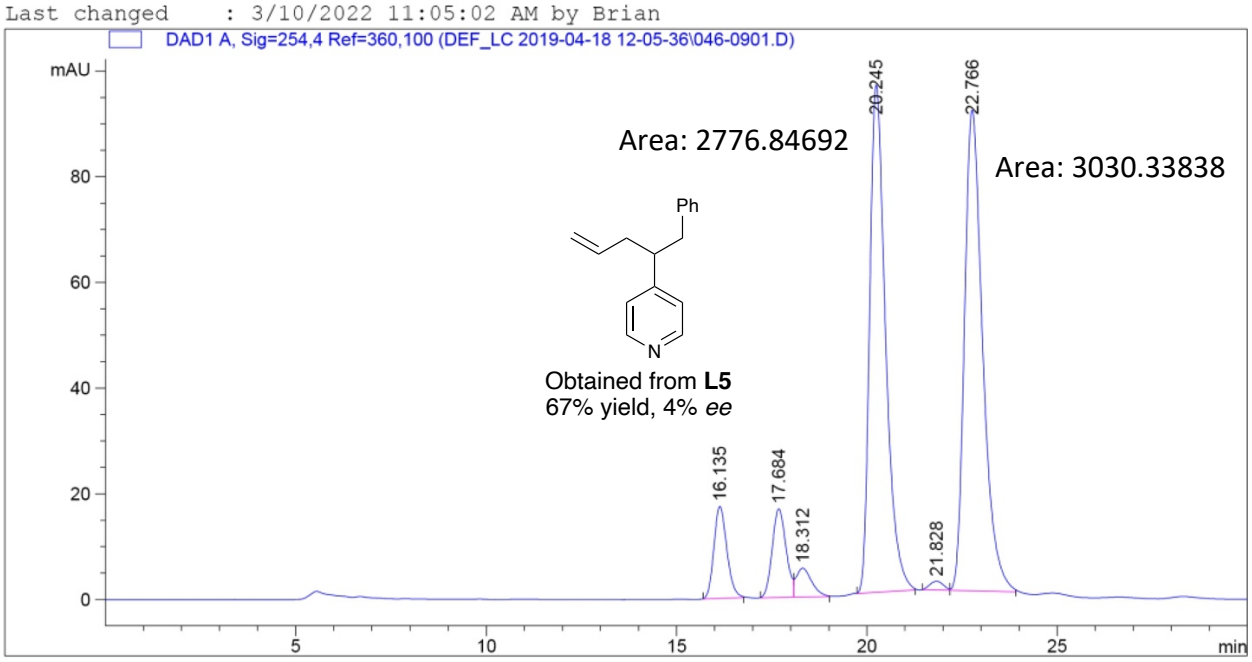




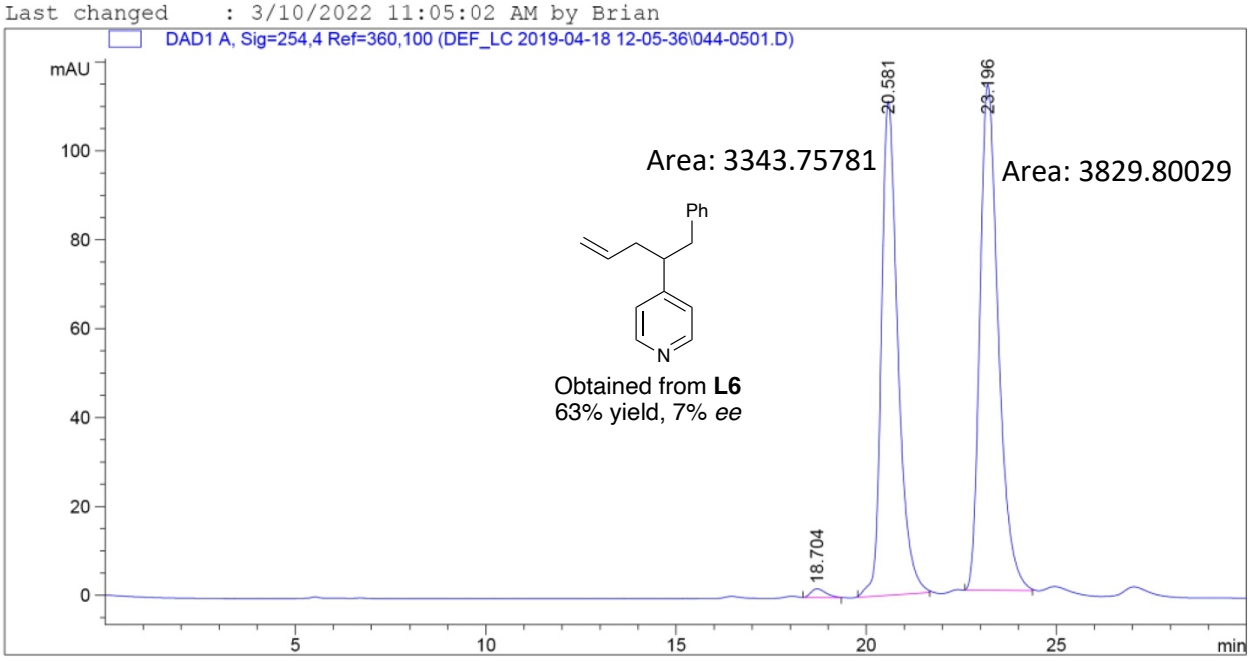
Analysis Method : C:\CHEM32\1\METHODS\NP-90-10-HEPTANE-IPA.M
Last changed : 3/10/2022 11:05:02 AM by Brian



Analysis Method : C:\CHEM32\1\METHODS\NP-90-10-HEPTANE-IPA.M
Last changed : 3/10/2022 11:05:02 AM by Brian

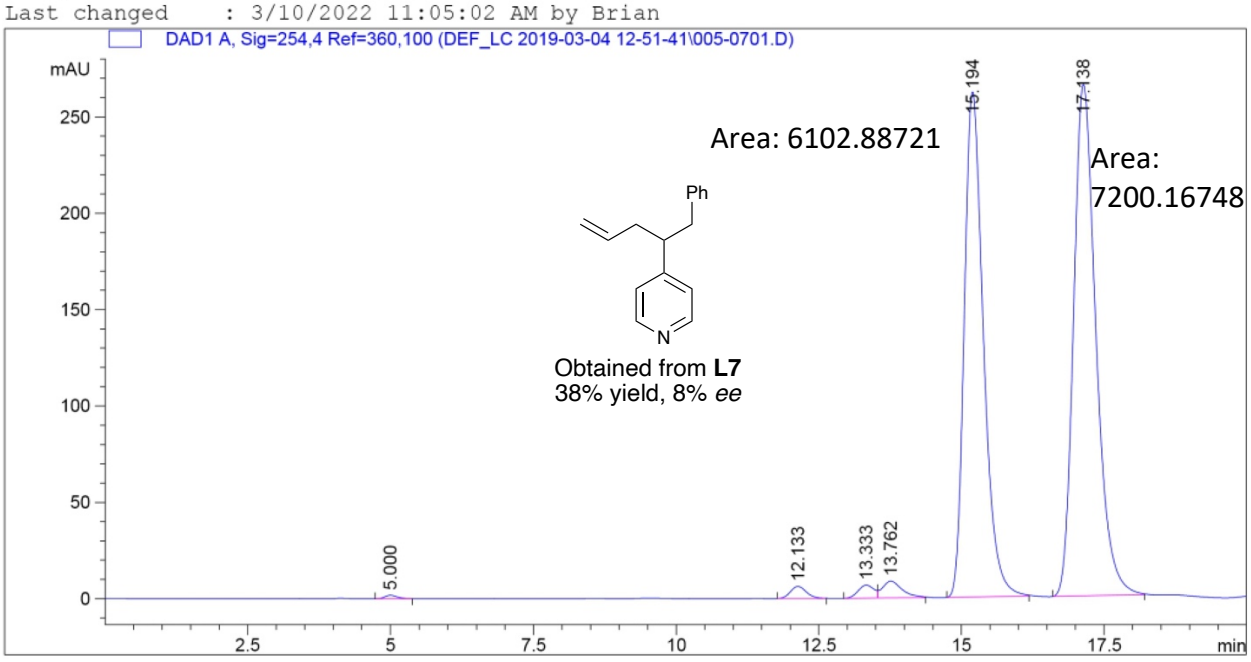


Analysis Method : C:\CHEM32\1\METHODS\NP-90-10-HEPTANE-IPA.M
Last changed : 3/10/2022 11:05:02 AM by Brian



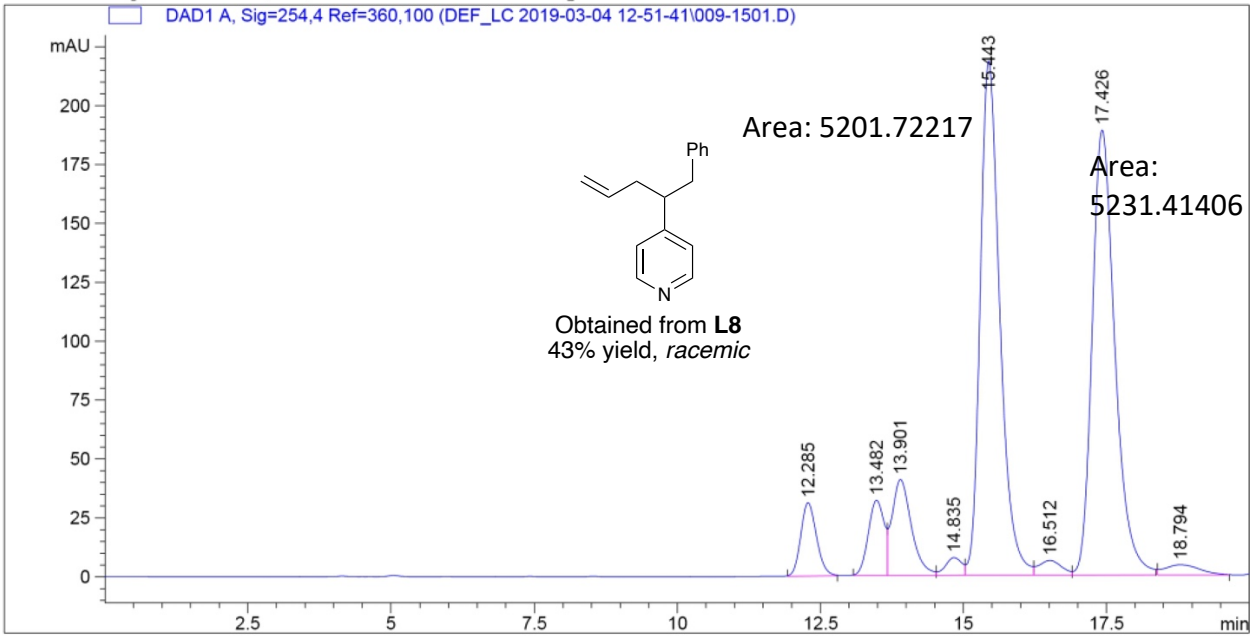
Obtained from **L6**
63% yield, 7% *ee*

Analysis Method : C:\CHEM32\1\METHODS\NP-90-10-HEPTANE-IPA.M
Last changed : 3/10/2022 11:05:02 AM by Brian

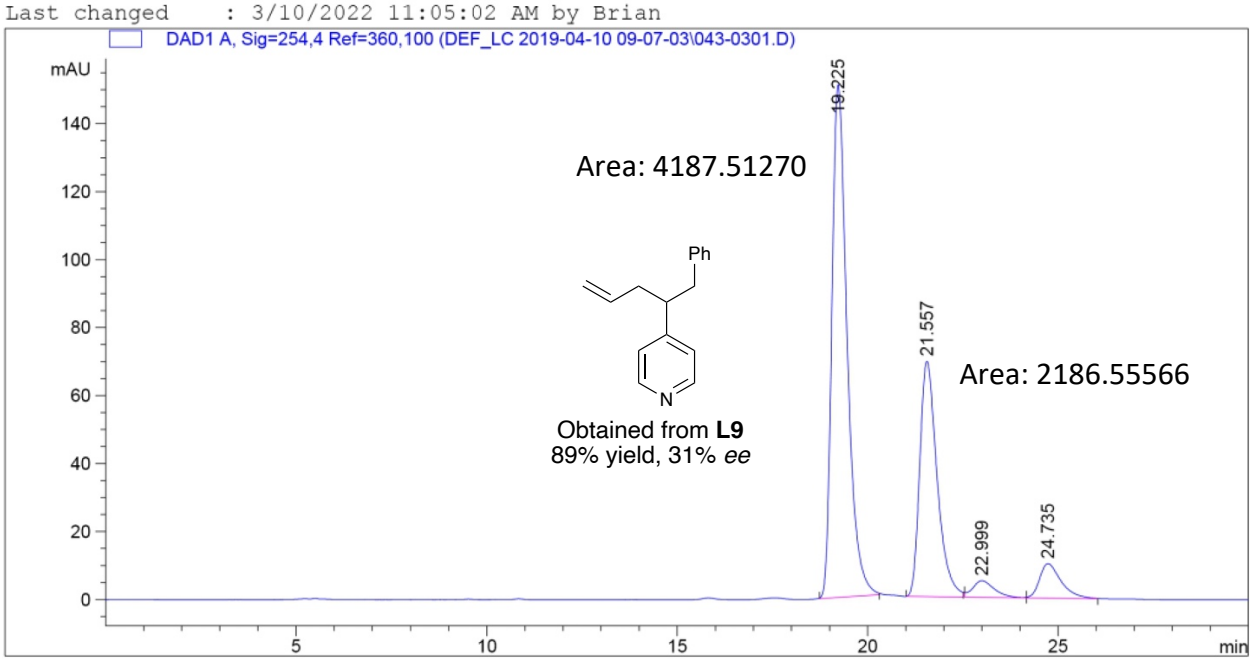


Obtained from **L7**
38% yield, 8% *ee*

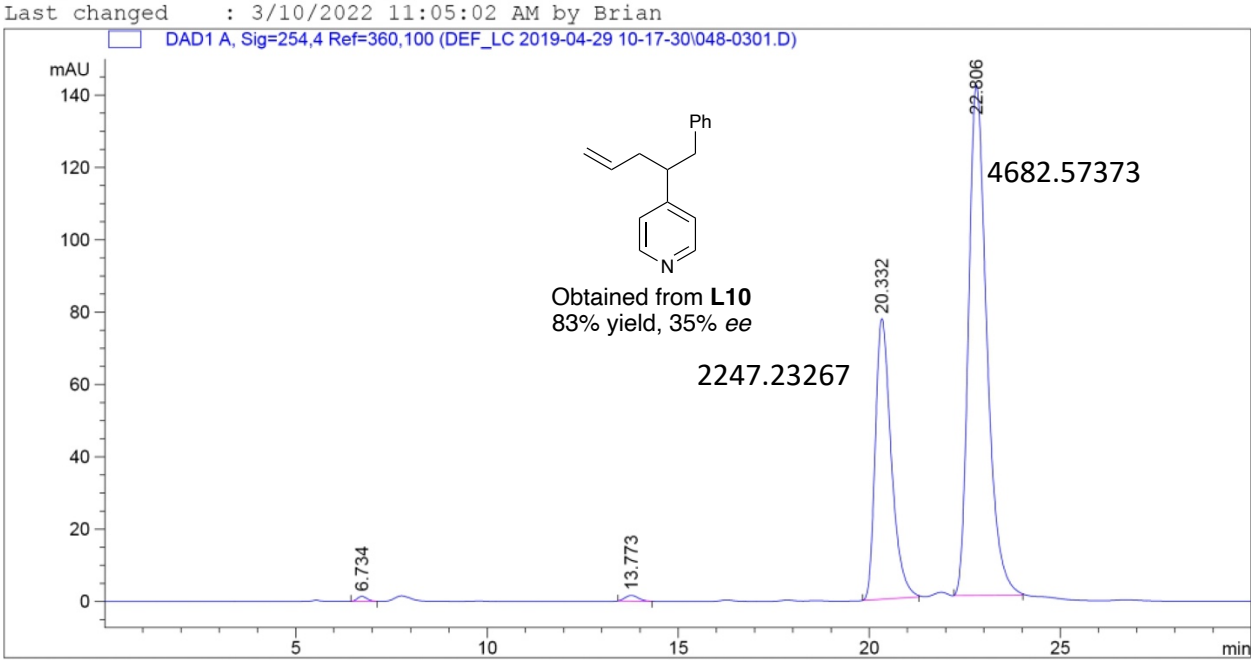
Analysis Method : C:\CHEM32\1\METHODS\NP-90-10-HEPTANE-IPA.M
Last changed : 3/10/2022 11:05:02 AM by Brian



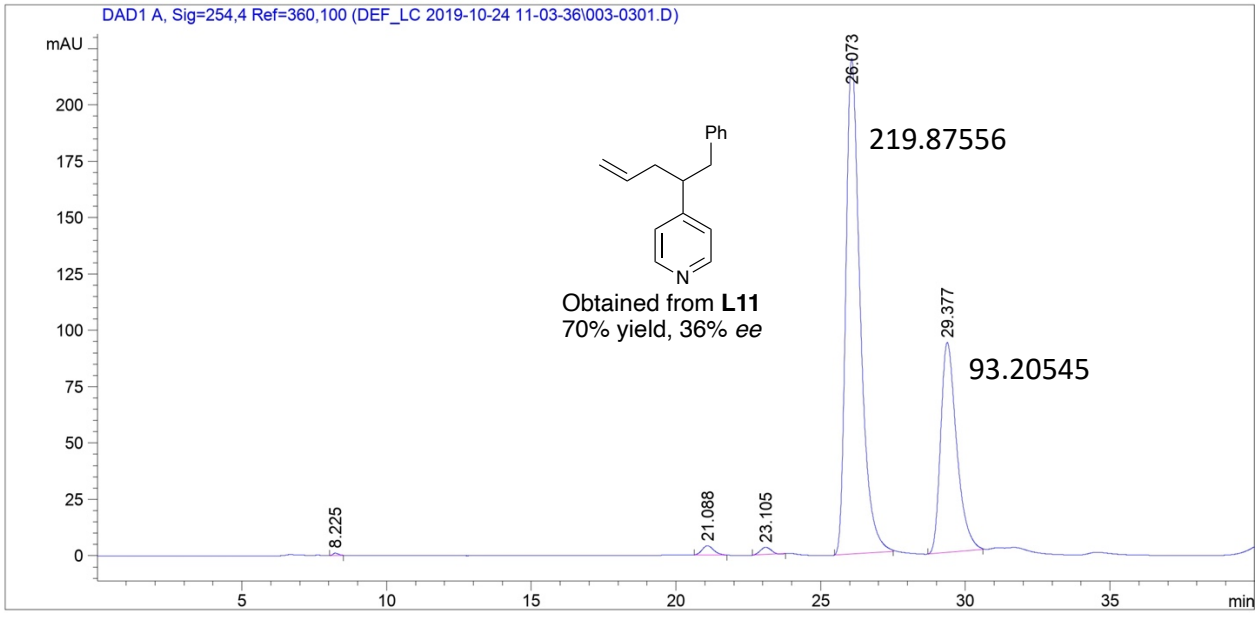
Analysis Method : C:\CHEM32\1\METHODS\NP-90-10-HEPTANE-IPA.M
Last changed : 3/10/2022 11:05:02 AM by Brian



Analysis Method : C:\CHEM32\1\METHODS\NP-90-10-HEPTANE-IPA.M
Last changed : 3/10/2022 11:05:02 AM by Brian



Analysis Method : C:\CHEM32\1\METHODS\NP-90-10-HEPTANE-IPA.M
Last changed : 3/10/2022 11:05:02 AM by Brian



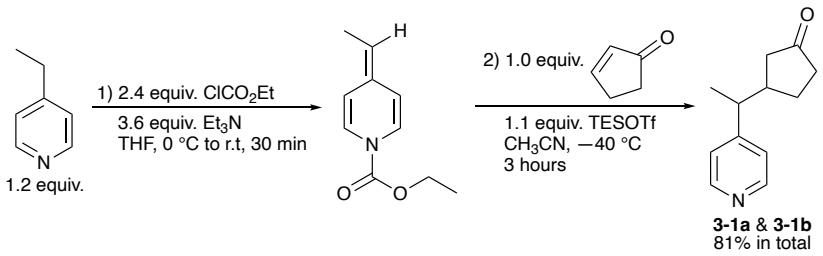
6.4 Conjugate addition of ADHPs to unsaturated ketones

6.4.1 General procedure (B) for conjugate addition

An oven-dried round-bottomed flask equipped with a stir bar was charged with a 0.2 M solution of the α,β-unsaturated ketone (1.0 equiv.) in anhydrous CH_3CN. The solution was cooled to –40 °C, 1.1 equiv. of TESOTf were added in a dropwise manner, and the resulting mixture was stirred for 15 minutes. Unless otherwise stated, the ADHP (1.2 equiv.) was dissolved in anhydrous CH_3CN (0.2 M) and added dropwise to the above reaction mixture while maintaining the temperature at –40 °C. The mixture was stirred at –40 °C, and the reaction progress was monitored by TLC and ^{1}H-NMR. Upon consumption of the ADHP, as shown by ^{1}H-NMR, the reaction mixture was placed in an ice-water bath and quenched with 1 M aqueous NaOH. The mixture was stirred vigorously until the hydrolysis of the carbamate and the deprotection of the silyl enol ether were complete, as indicated by TLC. The mixture was extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography to obtain the desired conjugate addition product.

6.4.2 Synthesis and characterization of compounds

Synthesis of compounds **3-1a** and **3-1b**:



By following the **general procedure A**, the corresponding ADHP was prepared from 4-ethyl-pyridine (0.14 mL, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** using 2-cyclopenten-1-one (0.1 mL, 1.0 equiv. 1.0 mmol) as the electrophile. The mixture of diastereomers was separated by flash column chromatography with MeCN/DCM/Hexanes to afford 102 mg of major diastereomer **3-1a** as a colorless oil and 51 mg of minor diastereomer **3-1b** as colorless oil, in 81% combined yield (d.r. = 2:1).

Data for diastereomer **3-1a**:

Chromatography: 14% MeCN, 36% DCM with 50% Hexanes (R_f = 0.24 after two runs).

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

δ 8.51 (d, *J* = 6.0 Hz, 2H), 7.10 (d, *J* = 6.0 Hz, 2H), 2.60 – 2.46 (m, 2H), 2.36 – 2.20 (m, 2H), 2.12 – 2.02 (m, 1H), 1.97 – 1.87 (m, 1H), 1.78 – 1.69 (m, 1H), 1.44 – 1.32 (m, 1H), 1.28 (d, *J* = 7.2 Hz, 3H)

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

δ 218.2, 154.3, 150.1, 122.8, 45.6, 44.0, 43.7, 38.9, 28.5, 20.4.

Data for diastereomer **3-1b**:

Chromatography: 14% MeCN, 36% DCM with 50% Hexanes (R_f = 0.2 after two runs).

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

δ 8.55 – 8.53 (m, 2H), 7.10 (d, *J* = 6.0 Hz, 2H), 2.65– 2.56 (m, 1H), 2.42 – 2.28 (m, 3H), 2.26 – 2.16 (m, 1H), 2.09 – 2.02 (m, 1H), 1.79 – 1.70 (m, 1H), 1.69 – 1.58 (m, 1H), 1.35 (d, *J* = 7.2 Hz, 3H).

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

δ 218.1, 154.8, 150.2, 122.7, 45.4, 44.2, 43.6, 38.9, 28.2, 19.4.

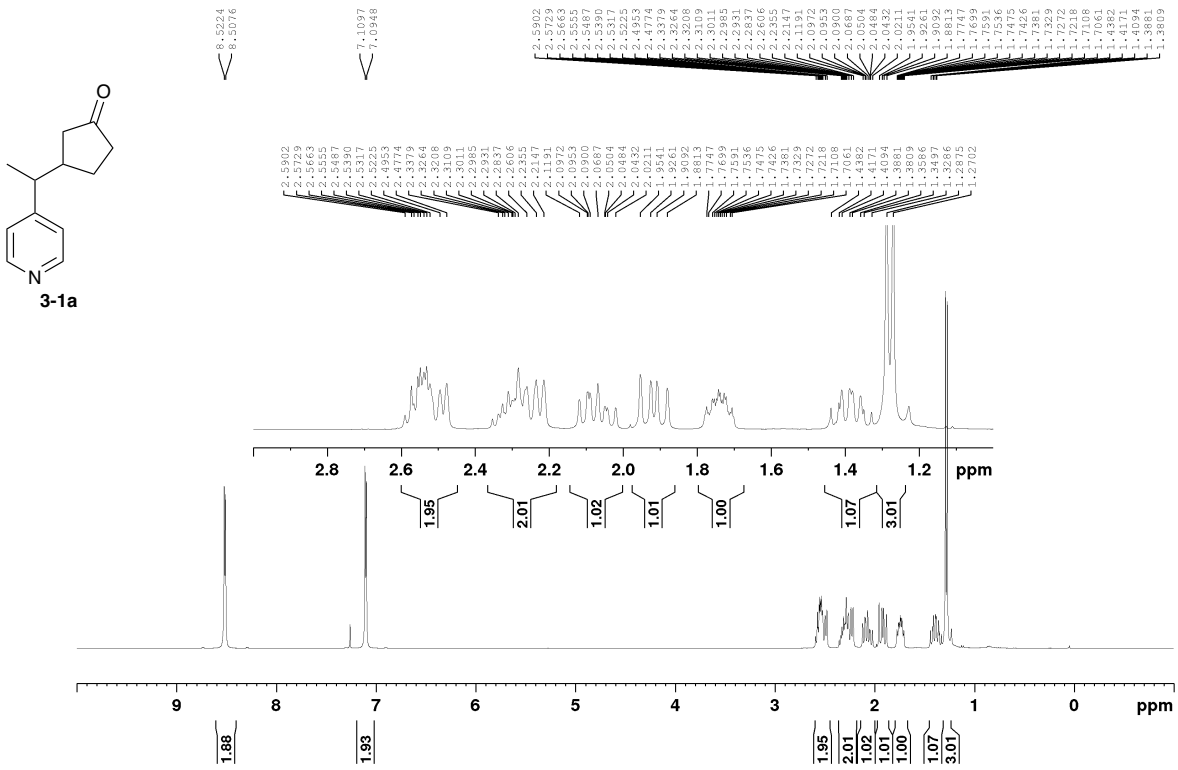
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3030, 2934, 2870, 1706, 1598, 1416 cm^{-1}.

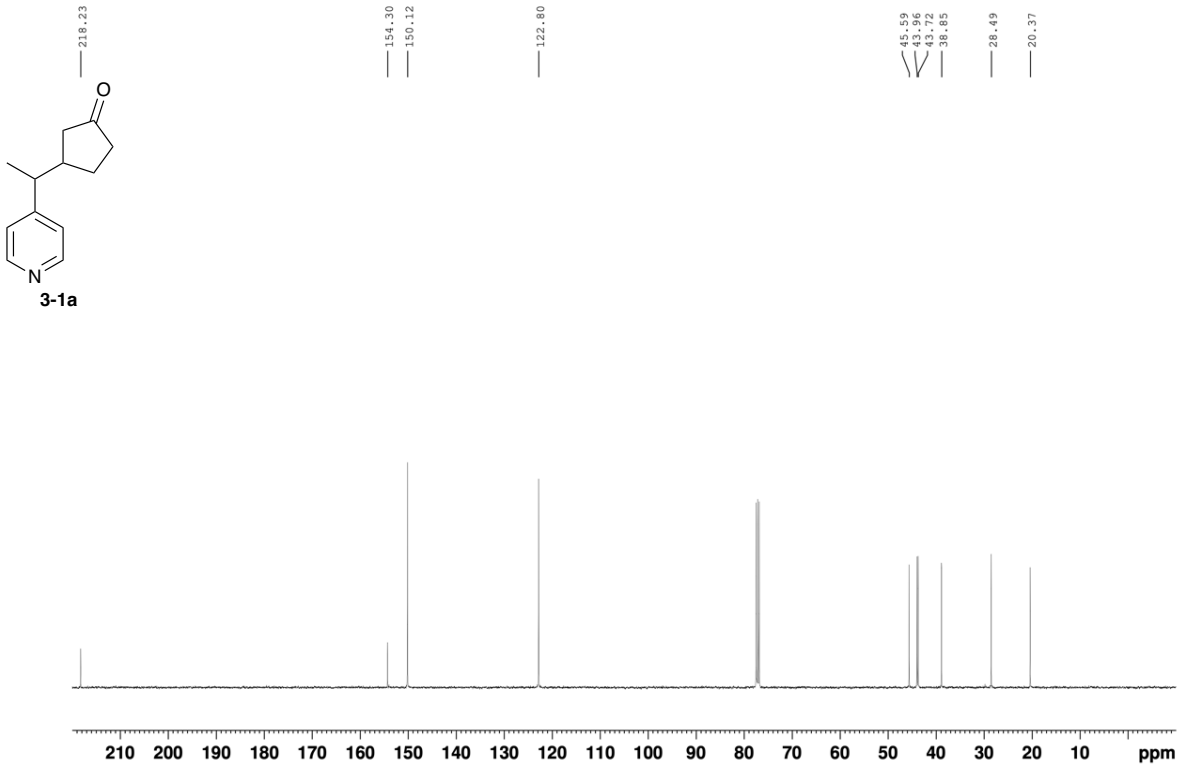
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{12}H_{16}NO$ 190.1227; Found 190.1234.

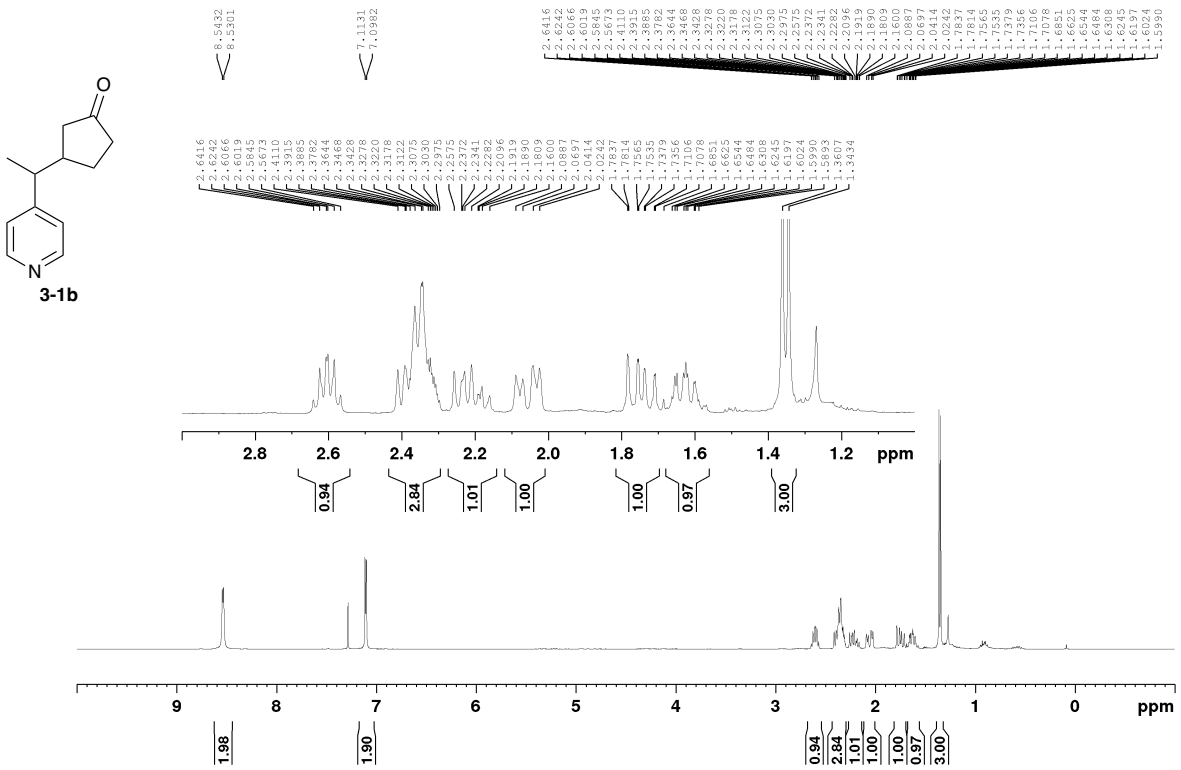
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-1a**:



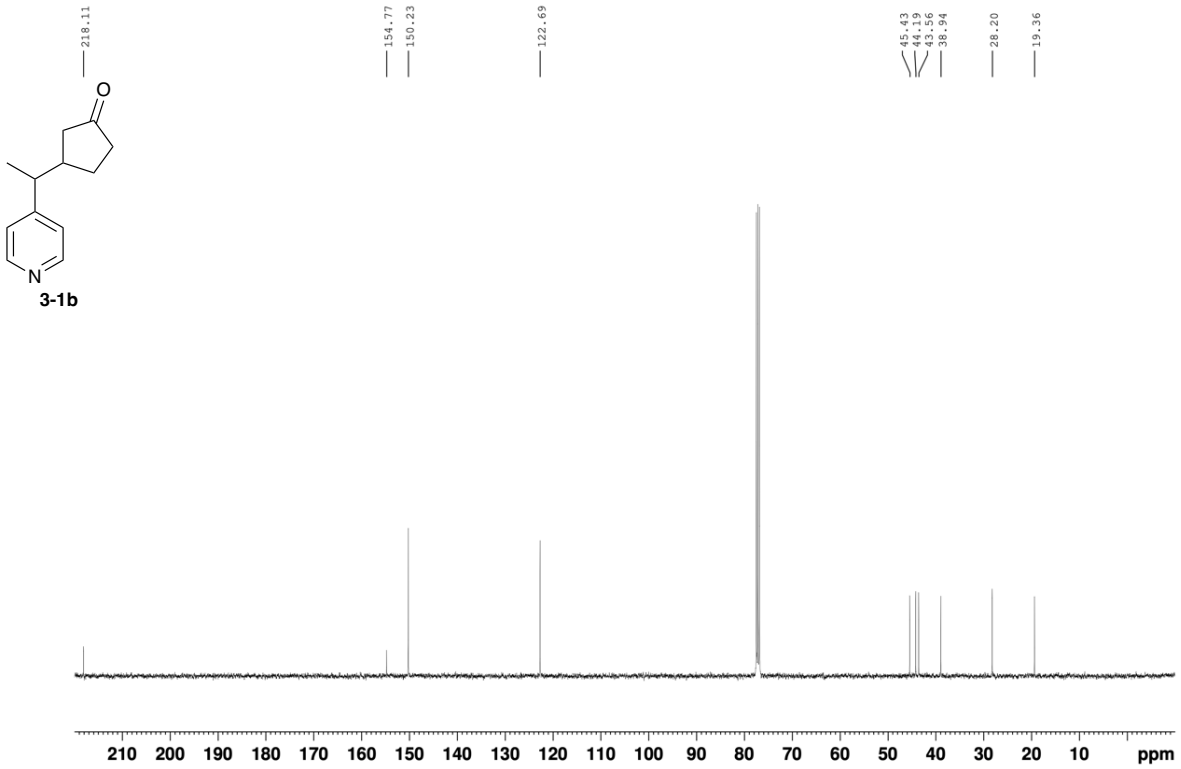
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-1a**:



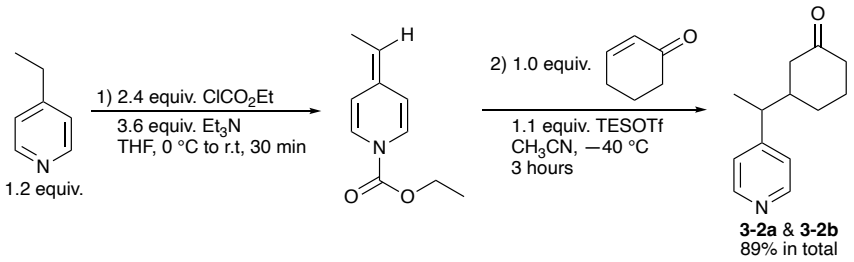
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-1b**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-1b**:



Synthesis of compounds **3-2a** and **3-2b**:



By following the **general procedure A**, the corresponding ADHP was prepared from 4-ethylpyridine (0.14 mL, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** using 2-cyclohexen-1-one (0.1 mL, 1.0 equiv. 1.0 mmol) as the electrophile. The mixture of diastereomers was separated by flash column chromatography with MeCN/DCM/Hexanes to afford 111 mg of major diastereomer **3-2a** as colorless oil and 69 mg of minor diastereomer **3-2b** as colorless oil, in 89% combined yield (d.r. ~ 2:1).

Data for diastereomer **3-2a**:

Chromatography: 14% MeCN, 36% DCM with 50% Hexanes (R_f = 0.25 after two runs).

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

δ 8.52 – 8.40 (m, 2H), 7.05 (d, *J* = 4.8 Hz, 2H), 2.62 – 2.54 (m, 1H), 2.54 – 2.49 (m, 1H), 2.37 – 2.29 (m, 1H), 2.26 – 2.16 (m, 1H), 2.08 – 2.01 (m, 1H), 2.01 – 1.87 (m, 2H), 1.67 – 1.59 (m, 1H), 1.58 – 1.45 (m, 1H), 1.29 – 1.16 (m, 4H).

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

δ 211.2, 154.2, 150.0, 123.1, 45.8, 45.0, 44.7, 41.4, 29.4, 25.1, 18.1.

Data for diastereomer **3-2b**:

Chromatography: 14% MeCN, 36% DCM with 50% Hexanes (R_f = 0.20 after two runs).

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

δ 8.52 – 8.51 (m, 2H), 7.05 (d, *J* = 5.2 Hz, 2H), 2.61 (p, *J* = 7.2 Hz, 1H),

2.39 – 2.31 (m, 1H), 2.27 – 2.20 (m, 1H), 2.20 – 2.15 (m, 1H),

2.12 – 2.06 (m, 1H), 2.06 – 1.98 (m, 1H), 1.98 – 1.87 (m, 2H),

1.69 – 1.57 (m, 1H), 1.44 – 1.33 (m, 1H), 1.29 (d, *J* = 7.2 Hz, 3H).

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

δ 211.2, 153.8, 150.1, 123.2, 46.2, 44.8, 44.7, 41.4, 28.8, 25.1, 18.1.

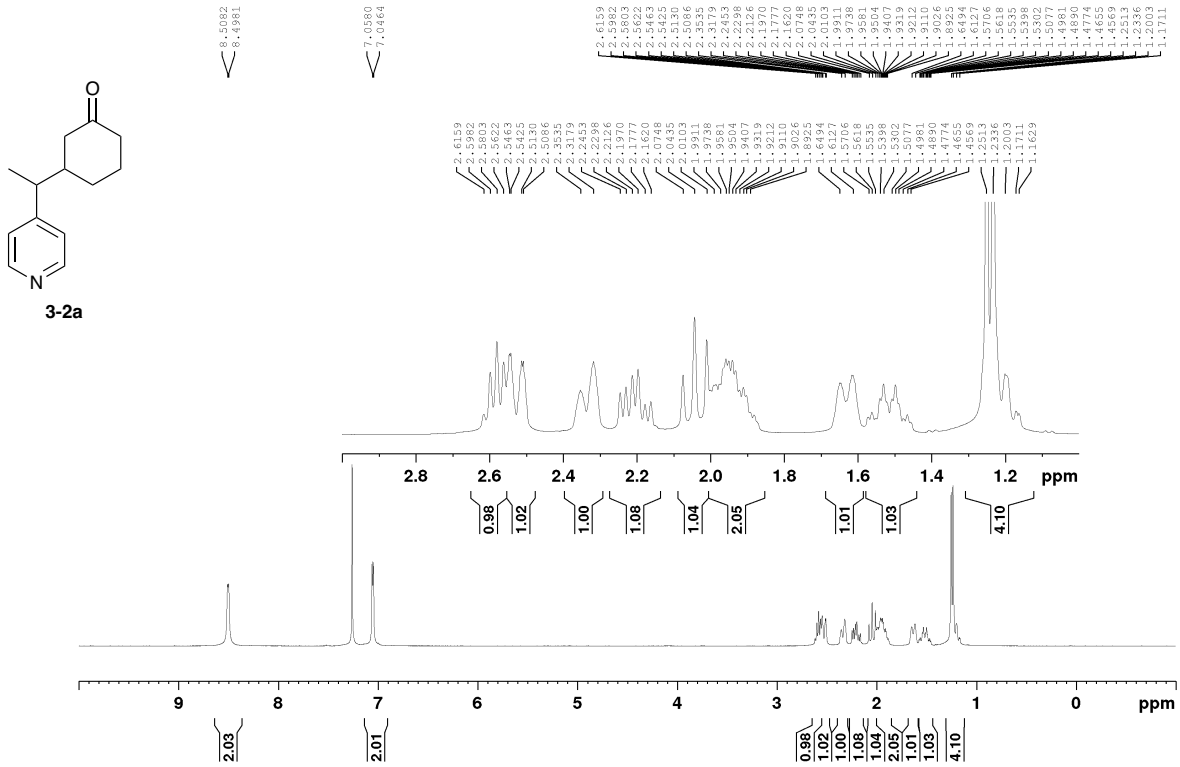
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3062, 2935, 2870, 1705, 1600, 1416 cm^{-1}.

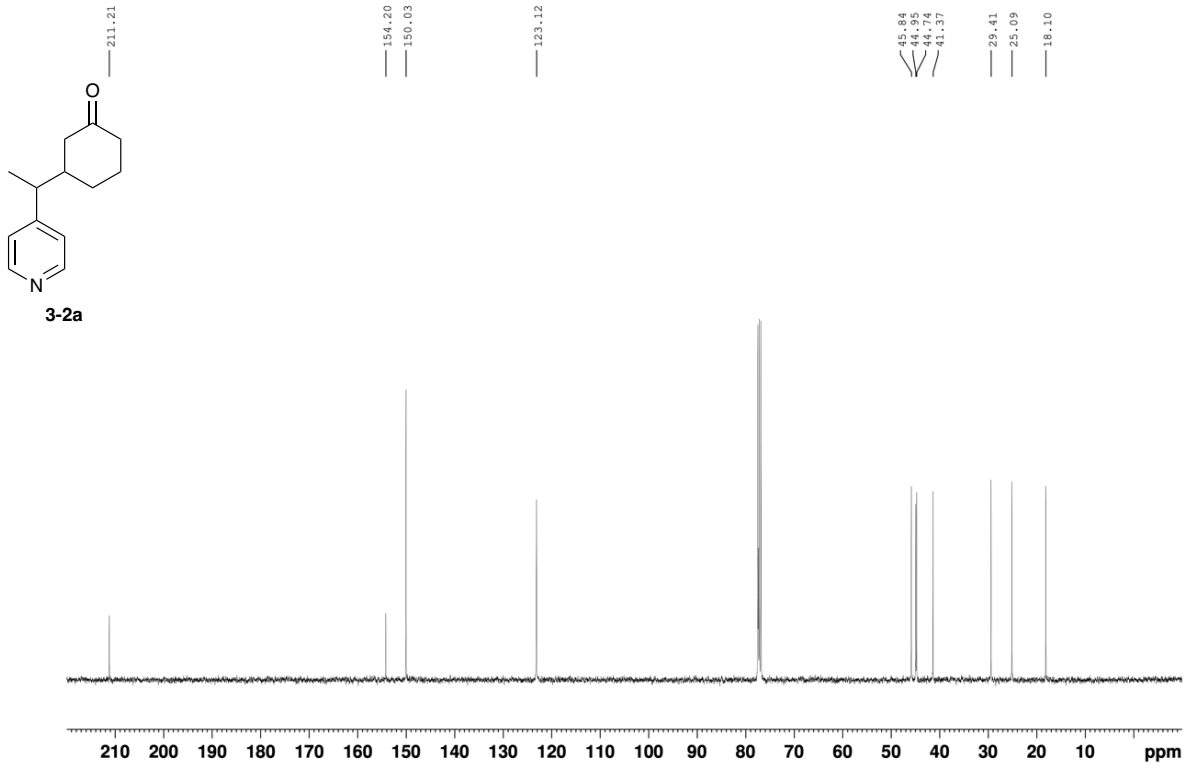
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{13}H_{18}NO$ 204.1383; Found 204.1391.

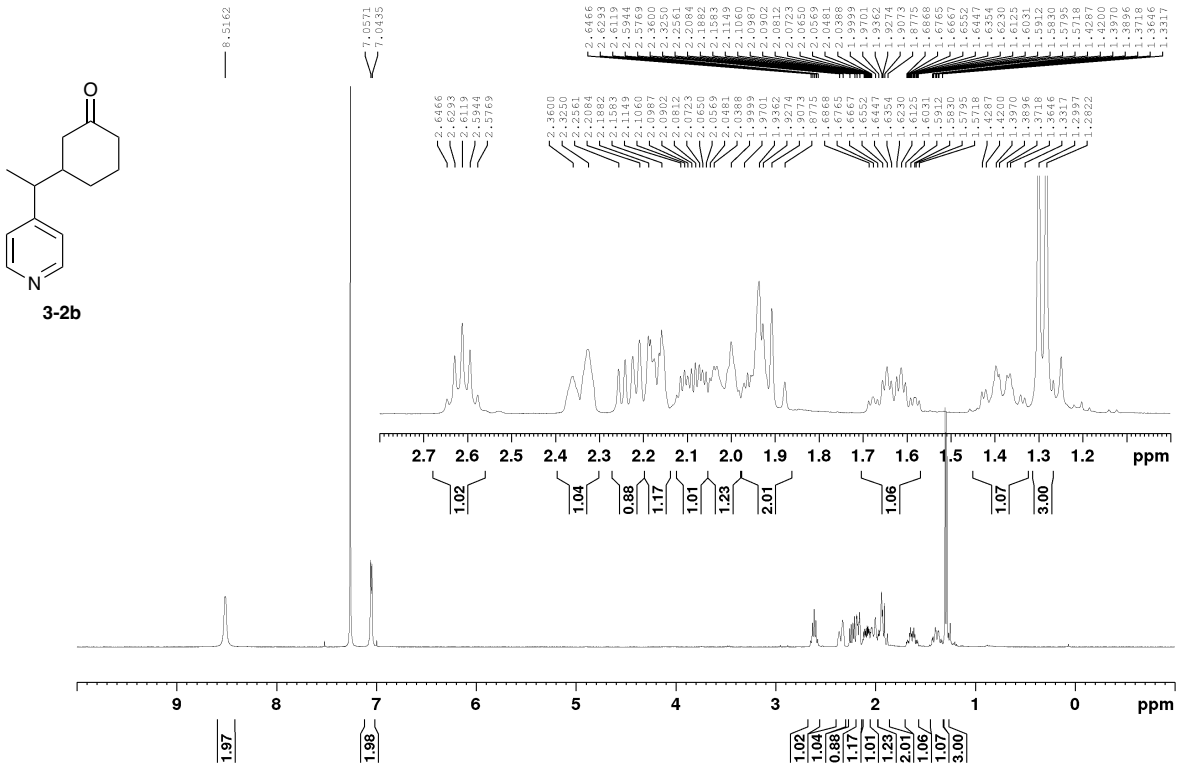
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-2a**:



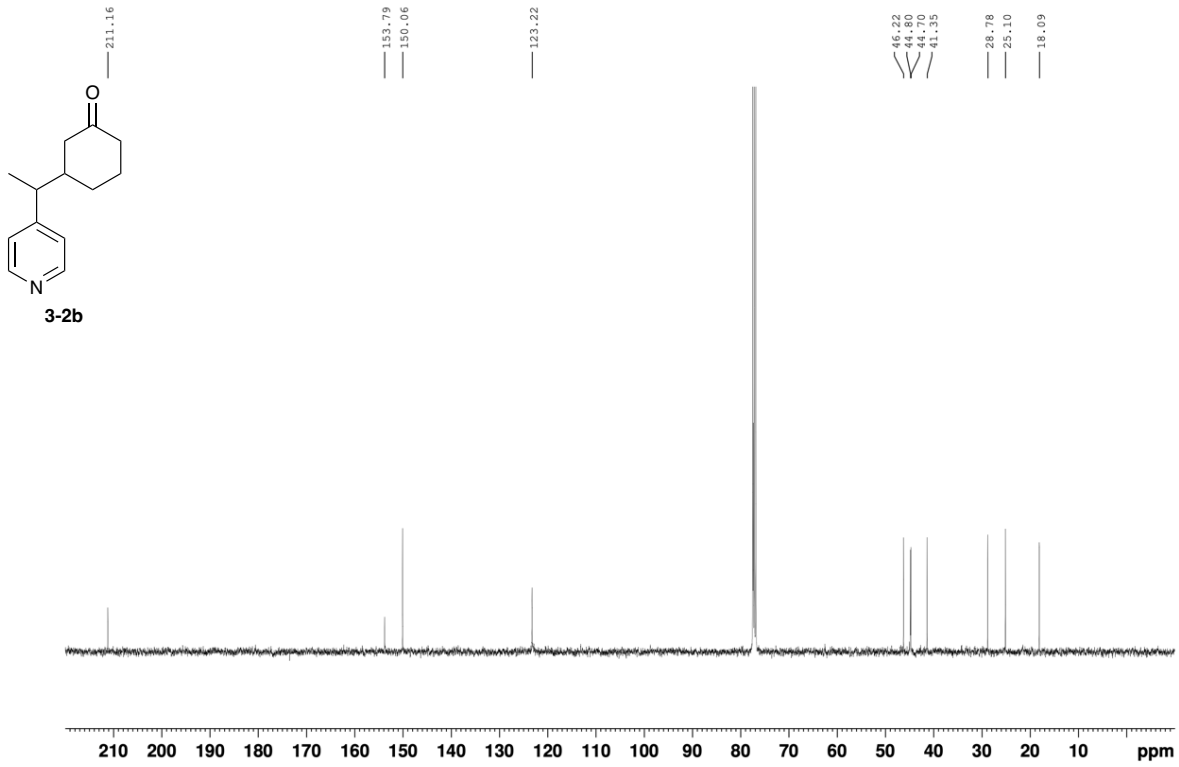
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-2a**:



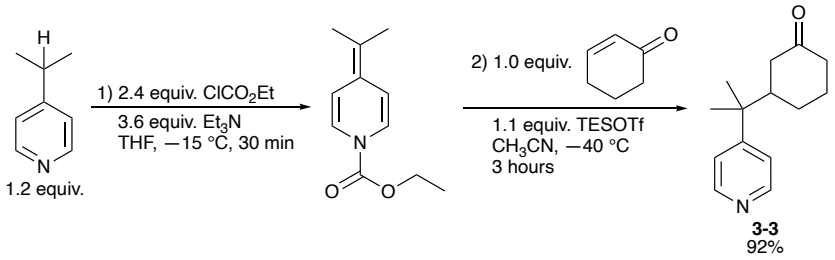
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-2b**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-2b**:



Synthesis of compound **3-3**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with 6 mL of anhydrous THF, 4-isopropylpyridine (145.4 mg, 1.2 equiv., 1.2 mmol) and triethylamine (0.50 mL, 3.6 equiv., 3.6 mmol). The resulting solution was cooled to –15 °C. A solution of ethyl chloroformate (0.23 mL, 2.4 equiv., 2.4 mmol) in 5.7 mL of THF was added to the above mixture using a syringe pump over 30 minutes while maintaining the temperature at –15 °C. The reaction mixture was allowed to warm to ambient temperature and then concentrated using a rotary evaporator. The residue was suspended in diethyl ether for 2 – 3 minutes and filtered through a cotton plug to remove the precipitated triethylammonium chloride salt. The filtrate was then concentrated using a rotary evaporator, and the corresponding ADHP was obtained and used immediately in the next step without further purification.

The final product was synthesized by following **general procedure B** using 2-cyclohexen-1-one (0.1 mL, 1.0 equiv. 1.0 mmol) as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford compound **3-3** as white solid (201 mg, 92% yield).

Melting point: 82.1 – 83.1 °C.

Chromatography: 70% EtOAc in Hexanes (R_f = 0.29).

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

δ 8.52 (d, *J* = 6.3 Hz, 2H), 7.18 (d, *J* = 6.3 Hz, 2H), 2.39 – 2.11 (m, 3H),

2.08 – 1.87 (m. 3H), 1.74 – 1.62 (m, 1H), 1.58 – 1.41 (m, 1H), 1.36 – 1.21 (m, 7H).

^{13}C NMR (75 MHz, $CDCl_3$)

δ 211.6, 157.4, 145.0, 121.6, 49.2, 43.7, 41.3, 40.5, 26.5, 25.4, 24.9, 24.1.

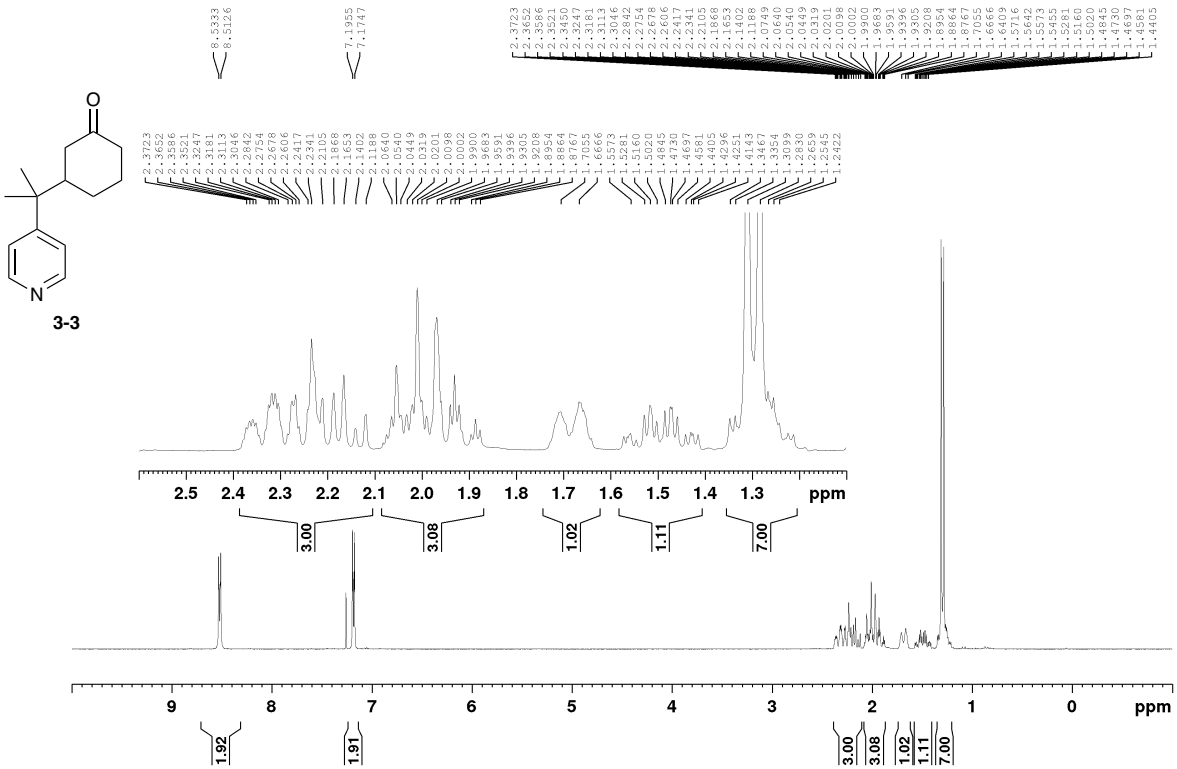
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3022, 2965, 2934, 1705, 1597, 1413 cm^{-1}.

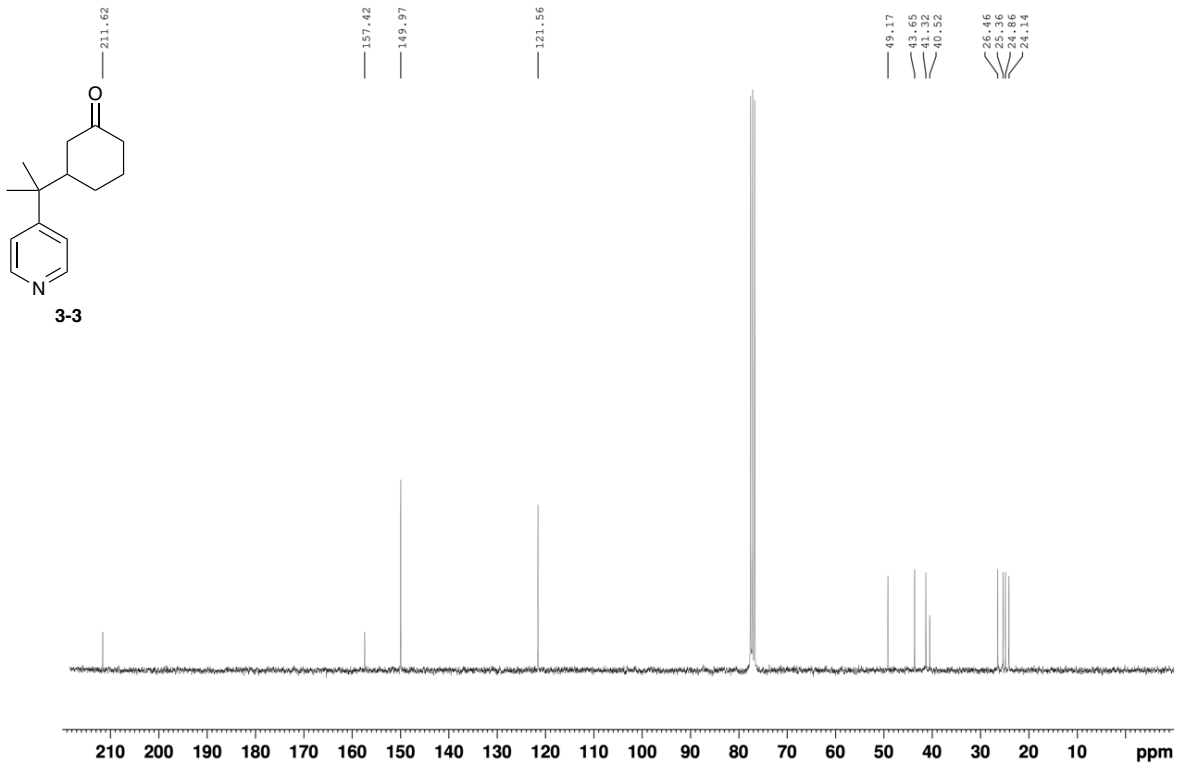
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{14}H_{20}NO$ 218.1540; Found 218.1545.

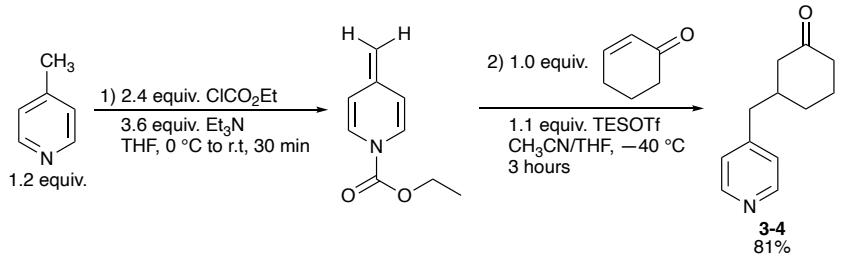
^{1}H NMR (300 MHz, $CDCl_3$) spectrum for **3-3**:



^{13}C NMR (75 MHz, $CDCl_3$) spectrum for **3-3**:



Synthesis of compound **3-4**:



By following the **general procedure A**, the corresponding ADHP was prepared from 4-picoline (0.12 mL, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.1 mL, 1.0 equiv. 1.0 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-4** as colorless oil (154 mg, 81% yield).

Chromatography: 70% EtOAc in Hexanes with 2% Et_3N (R_f = 0.37).

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

δ 8.49 (d, *J* = 5.8 Hz, 2H), 7.04 (d, *J* = 5.8 Hz, 2H), 2.66 – 2.55 (m, 2H), 2.39 – 2.31 (m, 2H), 2.30 – 2.19 (m, 1H), 2.13 – 1.98 (m, 3H), 1.89 – 1.81 (m, 1H), 1.68 – 1.54 (m, 1H), 1.43 – 1.31 (m, 1H).

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

δ 210.7, 149.9, 148.4, 124.5, 47.7, 42.3, 41.3, 40.0, 30.9, 25.0.

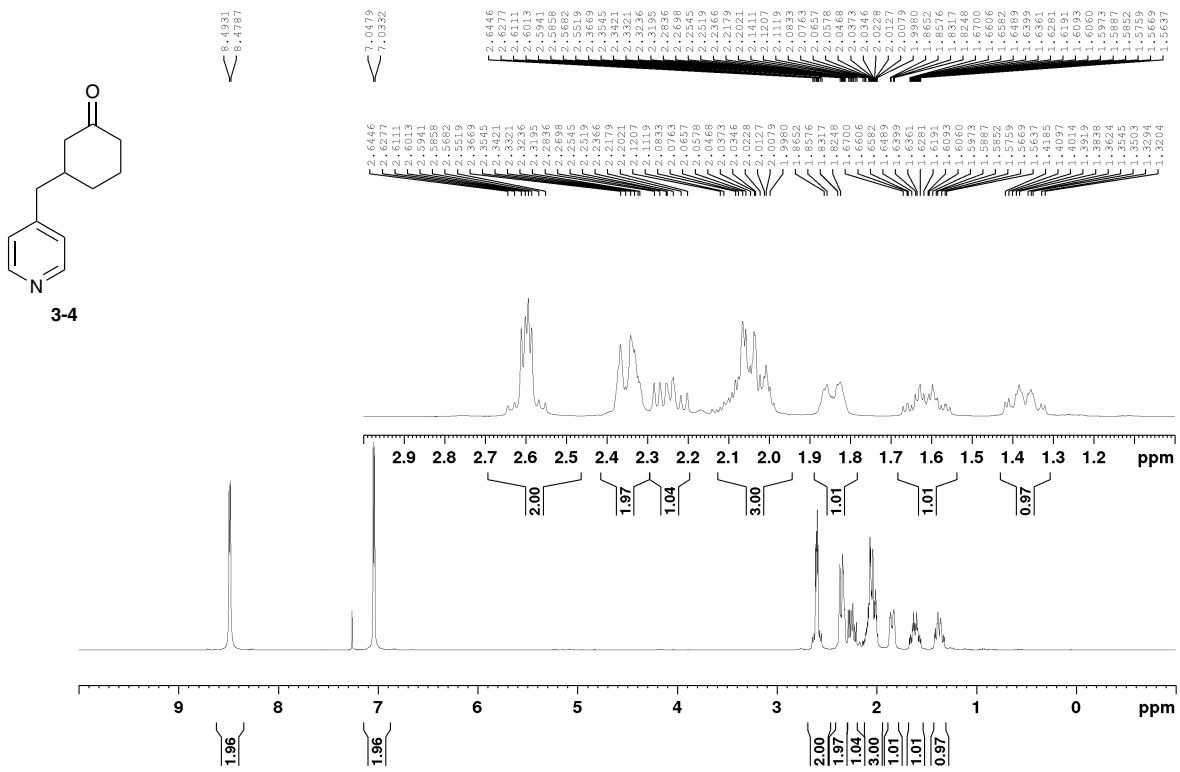
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3022, 2934, 2867, 1706, 1601, 1416 cm^{-1}.

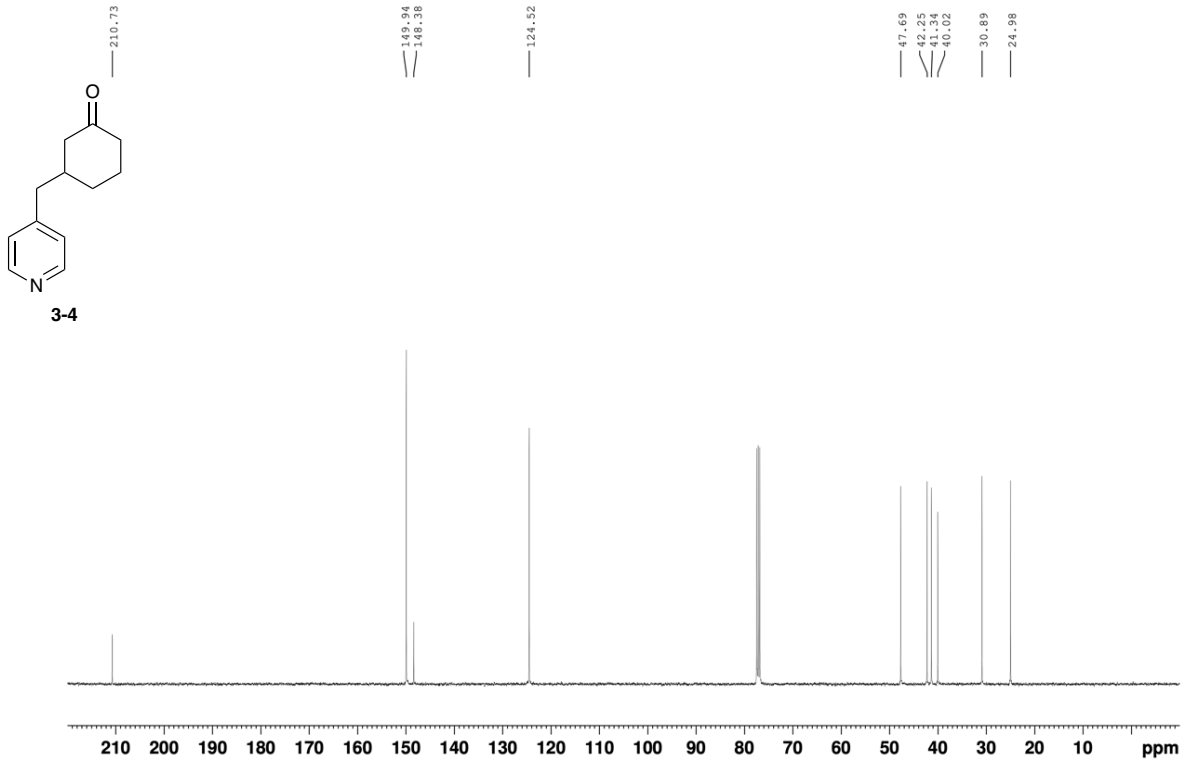
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{12}H_{16}NO$ 190.1227; Found 190.1233.

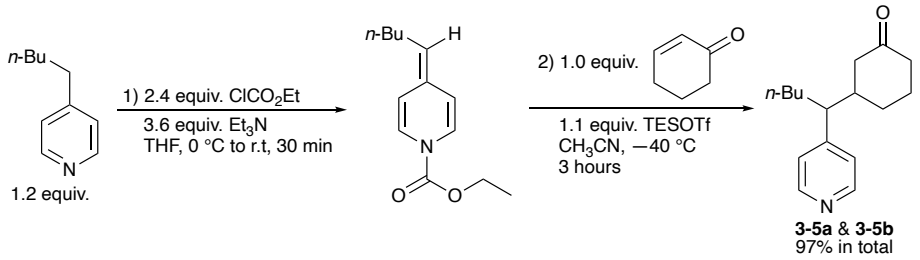
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-4**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-4**:



Synthesis of compounds **3-5a** and **3-5b**:



By following the **general procedure A**, the corresponding ADHP was prepared from 4-*n*-pentylpyridine[31] (179.1 mg, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** using 2-cyclohexen-1-one (0.1 mL, 1.0 equiv. 1.0 mmol) as the electrophile. The mixture of diastereomers was separated by flash column chromatography with MeCN/DCM/Hexanes to afford 124 mg of diastereomer **3-5a** as colorless oil and 133 mg of diastereomer **3-5b** as colorless oil, in 97% combined yield (d.r. ~ 1.1).

Data for diastereomer **3-5a**:

Chromatography: 14% MeCN, 36% DCM with 50% Hexanes (R_f = 0.35).

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

δ 8.52 (d, J = 5.6 Hz, 2H), 7.04 (d, J = 5.6 Hz, 2H), 2.59 – 2.53 (m, 1H), 2.43 – 2.38 (m, 1H), 2.38 – 2.30 (m, 1H), 2.25 – 2.14 (m, 1H), 2.06 – 1.93 (m, 3H), 1.79 – 1.70 (m, 1H), 1.68 – 1.45 (m, 3H), 1.32 – 1.12 (m, 3H), 1.09 – 0.96 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H).

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

δ 211.2, 152.4, 150.0, 124.1, 51.2, 46.7, 43.9, 41.5, 31.8, 29.7, 29.0, 25.1, 22.7, 14.0.

Data for diastereomer **3-5b**:

Chromatography: 14% MeCN, 36% DCM with 50% Hexanes (R_f = 0.28).

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

δ 8.52 (d, *J* = 6.0 Hz, 2H), 7.02 (d, *J* = 6.0 Hz, 2H), 2.50 – 2.43 (m, 1H), 2.37 – 2.29 (m, 1H), 2.23 – 2.12 (m, 2H), 2.11 – 1.93 (m, 3H), 1.92 – 1.84 (m, 1H), 1.83 – 1.72 (m, 1H), 1.70 – 1.55 (m, 2H), 1.39 – 1.15 (m, 3H), 1.12 – 0.95 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H).

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

δ 211.2, 151.9, 150.0, 124.1, 51.1, 45.8, 43.8, 41.4, 31.7, 29.8, 29.6, 25.2, 22.8, 14.0.

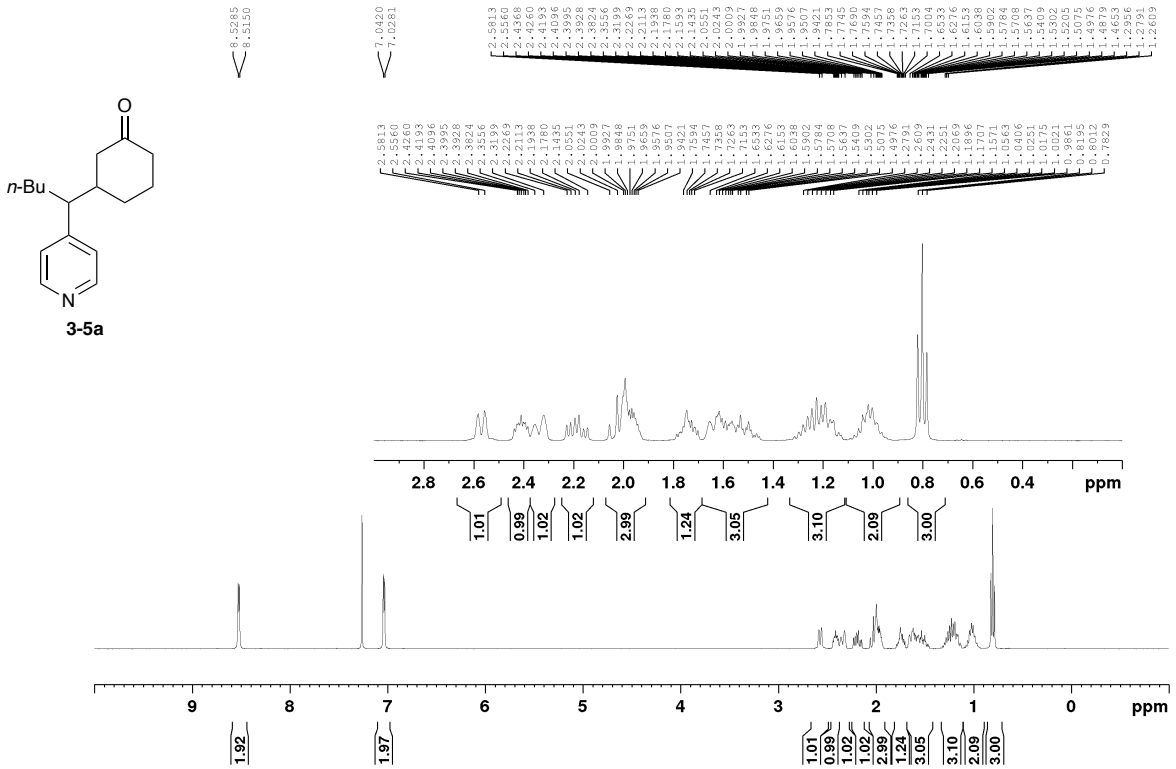
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3024, 2953, 2930, 1708, 1597, 1415 cm^{-1}.

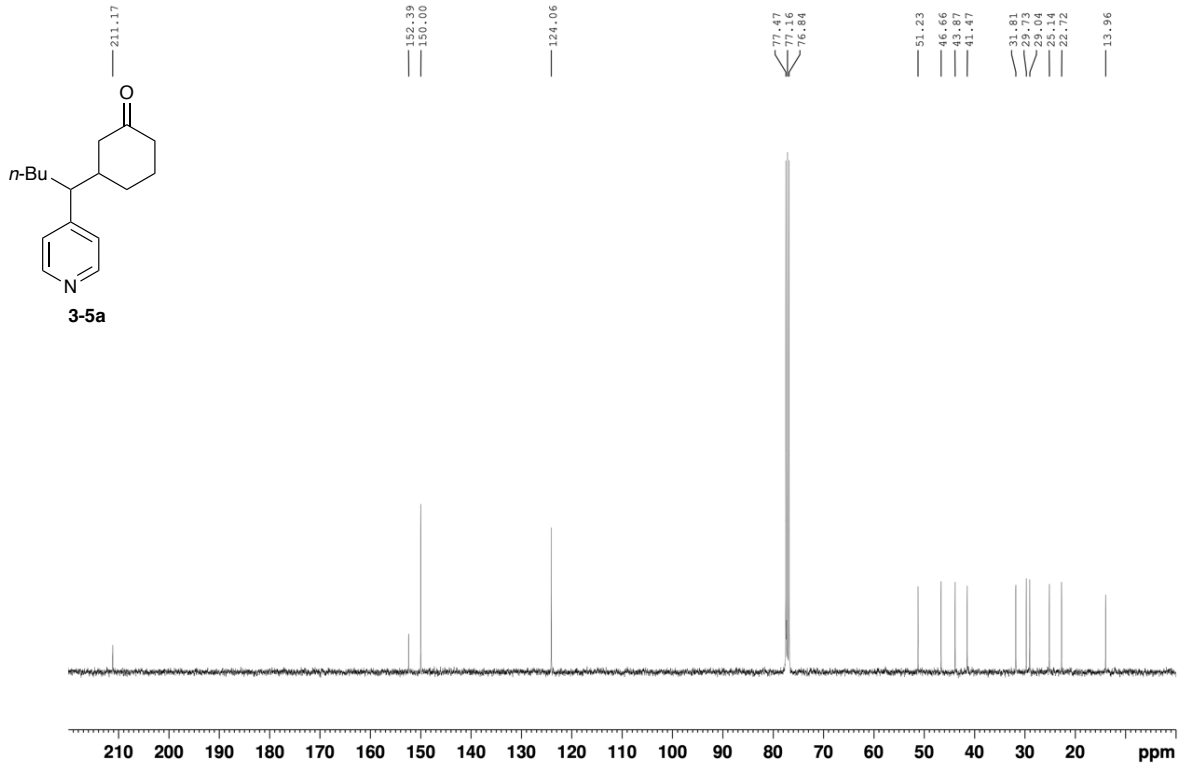
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{16}H_{24}NO$ 246.1853; Found 246.1863.

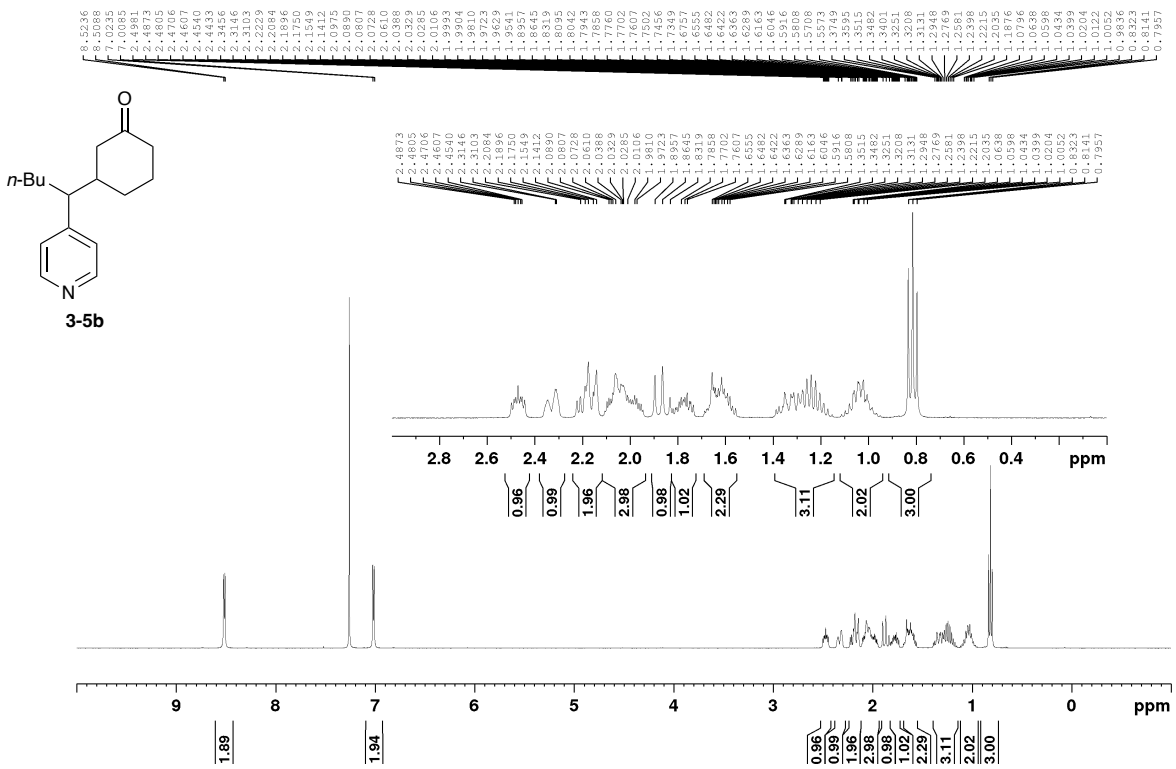
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-5a**:



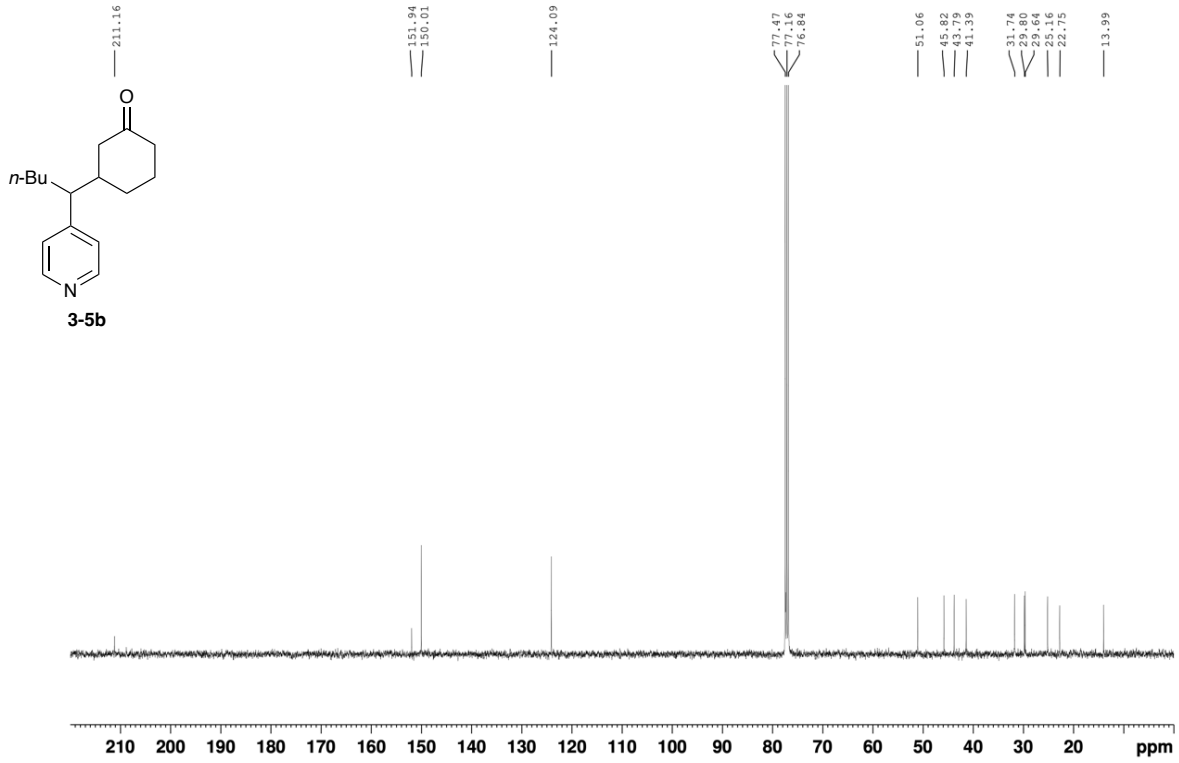
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-5a**:



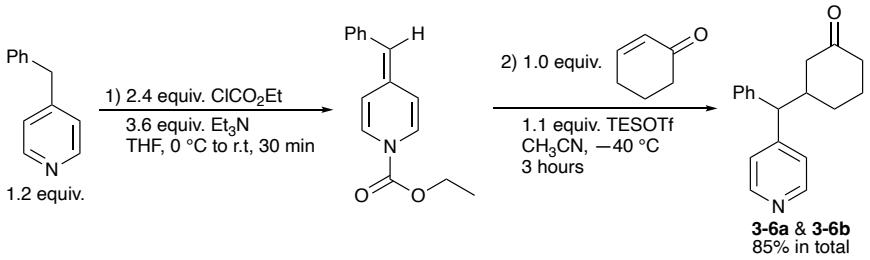
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-5b**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-5b**:



Synthesis of compounds **3-6a** and **3-6b**:



By following the **general procedure A**, the corresponding ADHP was prepared from 4-benzyl-pyridine (0.19 mL, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** using 2-cyclohexen-1-one (0.1 mL, 1.0 equiv. 1.0 mmol) as the electrophile. The mixture of diastereomers was separated by flash column chromatography with MeCN/DCM/Hexanes to afford 100 mg of *anti*-diastereomer **3-6a** as white solid and 112 mg of *syn*-diastereomer **3-6b** as colorless oil, in 85% combined yield (d.r. ~ 1.1).

Note – "*Syn*" and "*anti*" geometries of diastereomers **3-6a** and **3-6b** were assigned based on 2D-NMR studies.

Data for (*anti*-)diastereomer **3-6a**:

melting point: 156.3 – 157.6 °C

Chromatography: 10% MeCN in DCM (R_f = 0.38).

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

δ 8.70 – 8.40 (m, 2H), 7.31 – 7.25 (m, 2H), 7.24 – 7.17 (m, 5H),

3.61 (d, *J* = 10.8 Hz, 1H), 2.70 – 2.59 (m, 1H), 2.41 – 2.22 (m, 3H),

2.07 – 2.00 (m, 1H), 2.00 – 1.92 (m, 1H), 1.85 – 1.77 (m, 1H), 1.72 – 1.58 (m, 1H),

1.39 – 1.27 (m, 1H).

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

δ 210.8, 152.2, 150.3, 140.9, 129.2, 128.0, 127.3, 123.5, 58.4, 46.6, 42.0, 41.4,

30.2, 24.9.

Data for (*syn*-)diastereomer **3-6b**:

Chromatography: 10% MeCN in DCM (R_f = 0.28).

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

δ 8.53 – 8.46 (m, 2H), 7.34 – 7.28 (m, 2H), 7.27 – 7.20 (m, 3H), 7.17 (d, *J* = 5.6 Hz, 2 H), 3.62 (d, *J* = 10.8 Hz, 1H), 2.71 – 2.60 (m, 1H), 2.43 – 2.24 (m, 3H), 2.07 – 1.95 (m, 2H), 1.86 – 1.78 (m, 1H), 1.71 – 1.58 (m, 1H), 1.39 – 1.28 (m, 1H).

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

δ 210.7, 151.5, 150.3, 141.6, 129.1, 128.0, 127.3, 123.4, 58.2, 46.8, 42.0, 41.4, 29.9, 24.9.

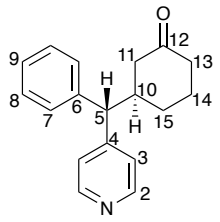
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ= 3022, 2964, 2931, 1701, 1593, 1415 cm^{-1}.

HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{18}H_{20}NO$ 266.1540; Found 266.1547.

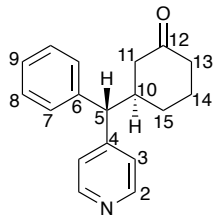
COSY (600 MHz, $CDCl_3/C_6D_6$, 10 °C) for **3-6a**:



Proton No.	^{1}H δ (ppm) (mult; *J* (Hz))	COSY Correlations
H-2	8.41 – 8.39 (m)	H-3
H-3	6.91 (d, *J* = 5.0 Hz)	H-2
H-5	3.28 (d, *J* = 10.8 Hz)	H-10
H-7	7.02 – 6.99 (m)	H-8
H-8	7.17 – 7.14 (m)	H-7, H-9
H-9	7.10 – 7.06 (m)	H-8
H-10	2.38 – 2.29 (m)	H-5; H-11; H-15
H-11a	1.68 – 1.63 (m)	H-10; H-11b
H-11b	2.20 – 2.17 (m)	H-10; H-11a
H-13a	2.03 – 1.95 (dt, *J* = 13.4, 6.2Hz)	H-13b; H-14
H-13b	2.26 – 2.01 (m)	H-13a; H-14
H-14a	1.42 – 1.33 (m)	H-13; H-14b; H-15
H-14b	1.75 – 1.69 (m)	H-13; H-14a; H-15
H-15a	0.99 – 0.95 (m)	H-10; H-15b
H-15b	1.52 – 1.46 (m)	H-10; H-15a

Methylene protons are designated H-Xa and H-Xb arbitrarily. Only those correlations which could be unambiguously assigned are reported.

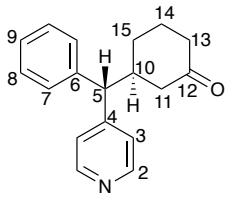
NOESY (600 MHz, $CDCl_3/C_6D_6$, 10 °C) for **3-6a**:



Proton No.	^{1}H δ (ppm) (mult; *J* (Hz))	NOESY Correlations
H-2	8.41 – 8.39 (m)	-
H-3	6.91 (d, *J* = 5.0 Hz)	H-5; H-10; H-15
H-5	3.28 (d, *J* = 10.8 Hz)	H-3; H-7; H-10; H-11; H-15
H-7	7.02 – 6.99 (m)	H-5; H-10; H-11
H-8	7.17 – 7.14 (m)	-
H-9	7.10 – 7.06 (m)	-
H-10	2.38 – 2.29 (m)	H-3; H-5; H-7
H-11a	1.68 – 1.63 (m)	H-5; H-7
H-11b	2.20 – 2.17 (m)	H-5; H-7
H-13a	2.03 – 1.95 (dt, *J* = 13.4, 6.2Hz)	-
H-13b	2.26 – 2.01 (m)	-
H-14a	1.42 – 1.33 (m)	-
H-14b	1.75 – 1.69 (m)	-
H-15a	0.99 – 0.95 (m)	H-3; H-5
H-15b	1.52 – 1.46 (m)	H-3; H-5

Methylene protons are designated H-Xa and H-Xb arbitrarily. Only those correlations which could be unambiguously assigned are reported.

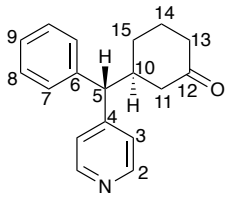
COSY (600 MHz, $CDCl_3/C_6D_6$, 10 °C) for **3-6b**:



Proton No.	^{1}H δ (ppm) (mult; *J* (Hz))	COSY Correlations
H-2	8.42 – 8.41 (m)	H-3
H-3	6.82 – 6.80 (m)	H-2
H-5	3.23 – 3.20 (m)	H-10
H-7	7.02 – 7.00 (m)	H-8
H-8	7.19 – 7.16 (m)	H-7, H-9
H-9	7.12 – 7.08 (m)	H-8
H-10	2.32 – 2.27 (m)	H-5; H-11; H-15
H-11a	1.60 – 1.55 (m)	H-10; H-11b
H-11b	2.22 – 2.13 (m)	H-10; H-11a
H-13a	1.96 – 1.88 (m)	H-13b; H-14
H-13b	2.24 – 2.13 (m)	H-13a; H-14
H-14a	1.35 – 1.26 (m)	H-13; H-14b; H-15
H-14b	1.66 – 1.60 (m)	H-13; H-14a; H-15
H-15a	0.95 – 0.84 (m)	H-10; H-15b
H-15b	1.54 – 1.47 (m)	H-10; H-15a

Methylene protons are designated H-Xa and H-Xb arbitrarily. Only those correlations which could be unambiguously assigned are reported.

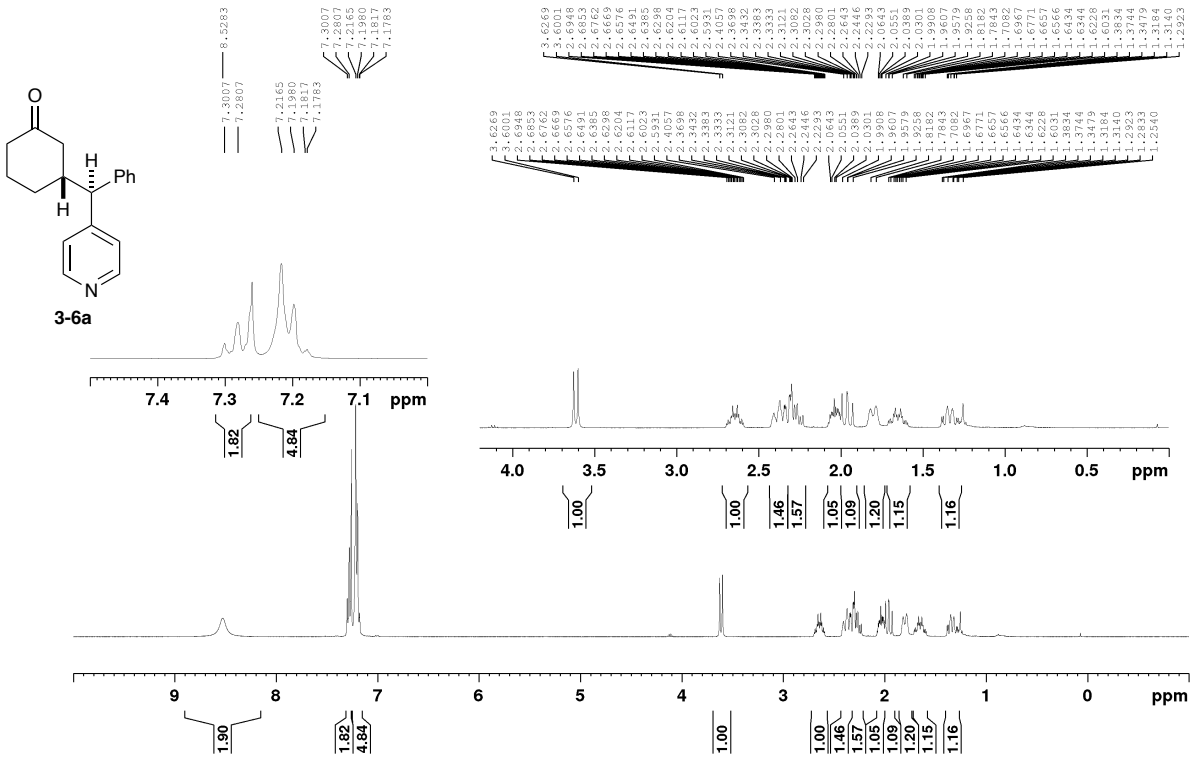
NOESY (600 MHz, $CDCl_3/C_6D_6$, 10 °C) for **3-6b**:



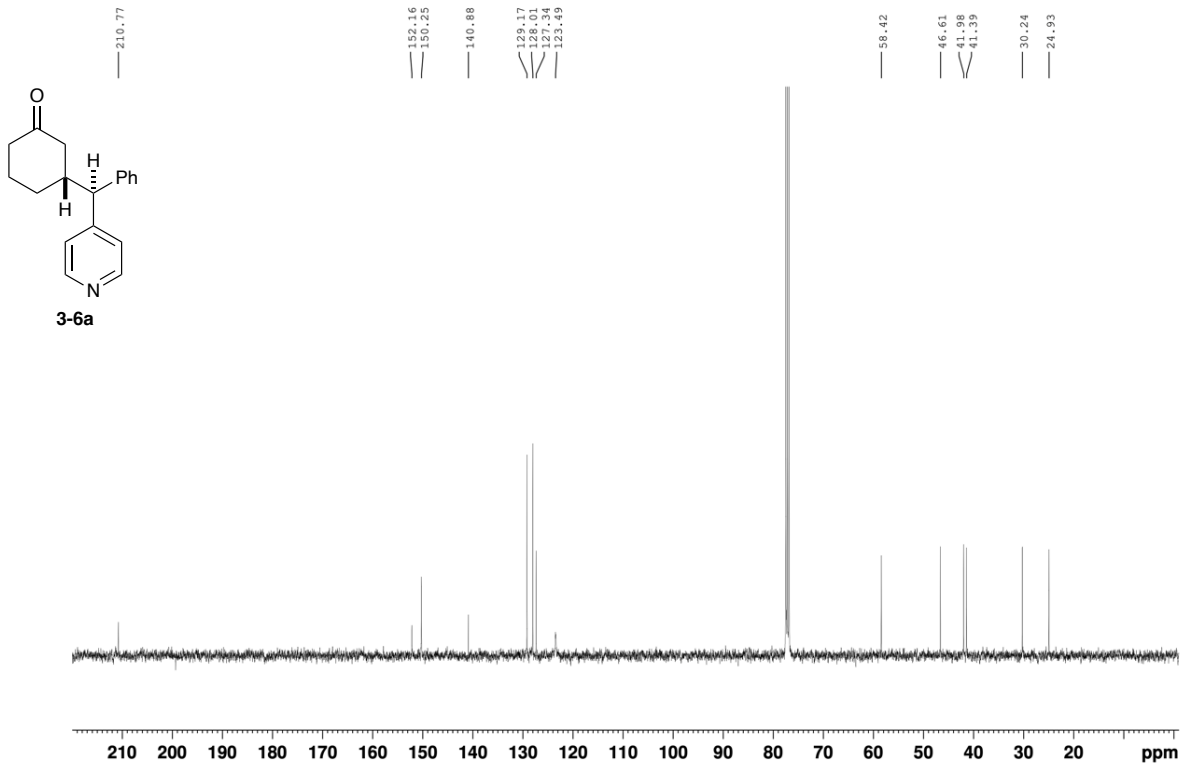
Proton No.	^{1}H δ (ppm) (mult; *J* (Hz))	NOESY Correlations
H-2	8.42 – 8.41 (m)	-
H-3	6.82 – 6.80 (m)	H-5; H-10; H-11
H-5	3.23 – 3.20 (m)	H-3; H-7; H-10; H-11; H-15
H-7	7.02 – 7.00 (m)	H-5; H-10; H-15
H-8	7.19 – 7.16 (m)	-
H-9	7.12 – 7.08 (m)	-
H-10	2.32 – 2.27 (m)	H-3; H-5; H-7
H-11a	1.60 – 1.55 (m)	H-3; H-5
H-11b	2.22 – 2.13 (m)	H-3; H-5
H-13a	1.96 – 1.88 (m)	-
H-13b	2.24 – 2.13 (m)	-
H-14a	1.35 – 1.26 (m)	-
H-14b	1.66 – 1.60 (m)	-
H-15a	0.95 – 0.84 (m)	H-3; H-5
H-15b	1.54 – 1.47 (m)	H-3; H-5

Methylene protons are designated H-Xa and H-Xb arbitrarily. Only those correlations which could be unambiguously assigned are reported.

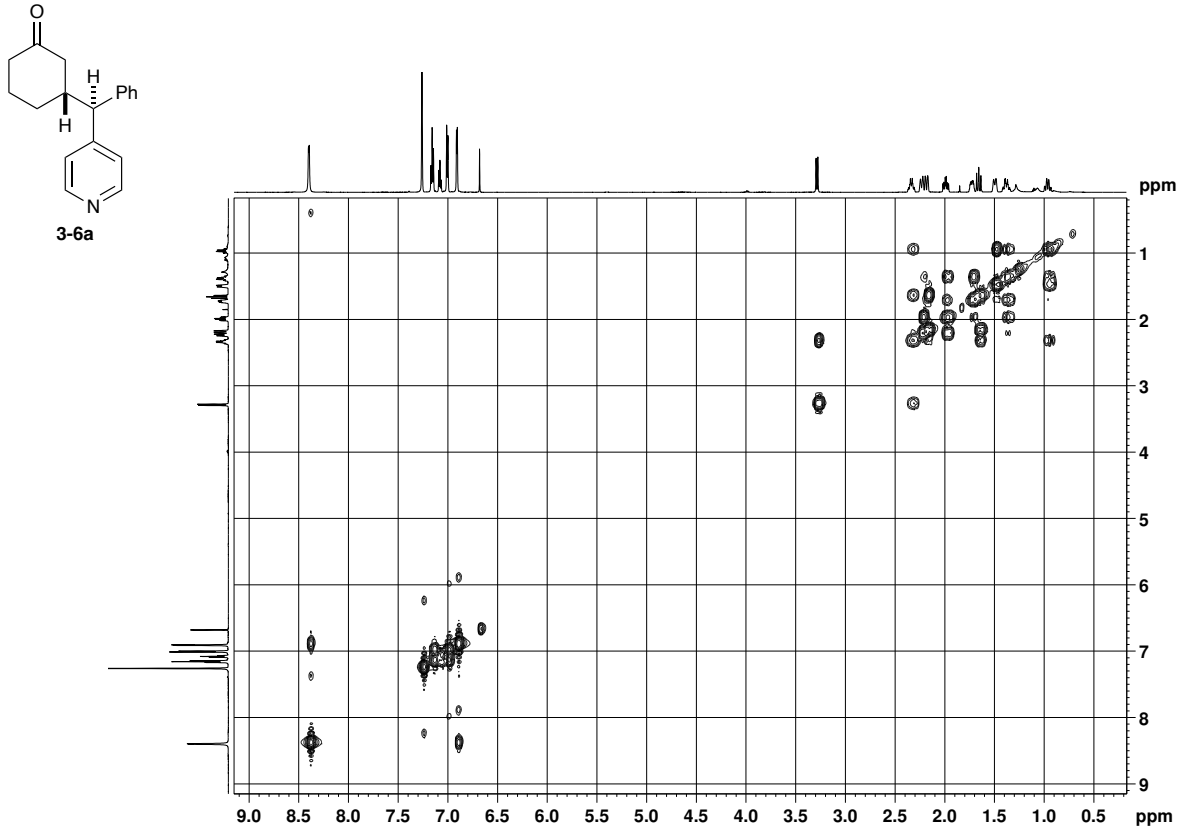
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-6a**:



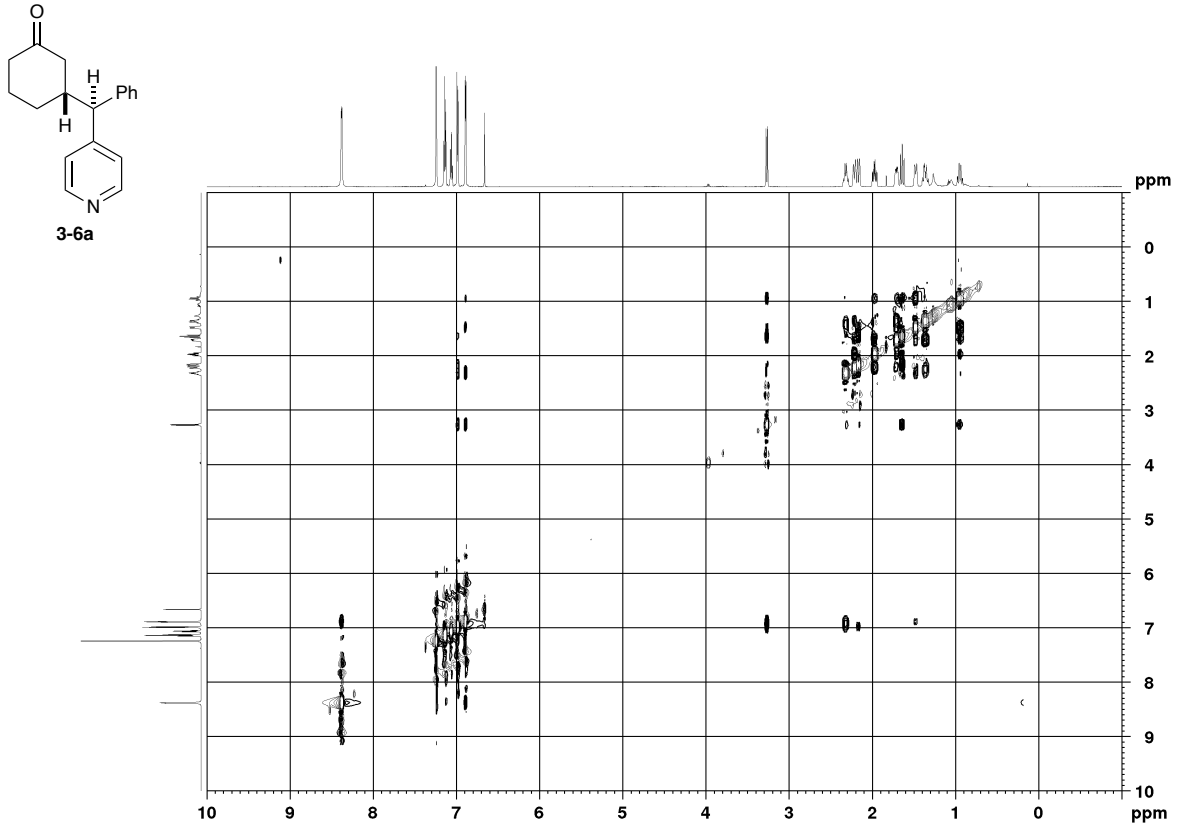
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-6a**:



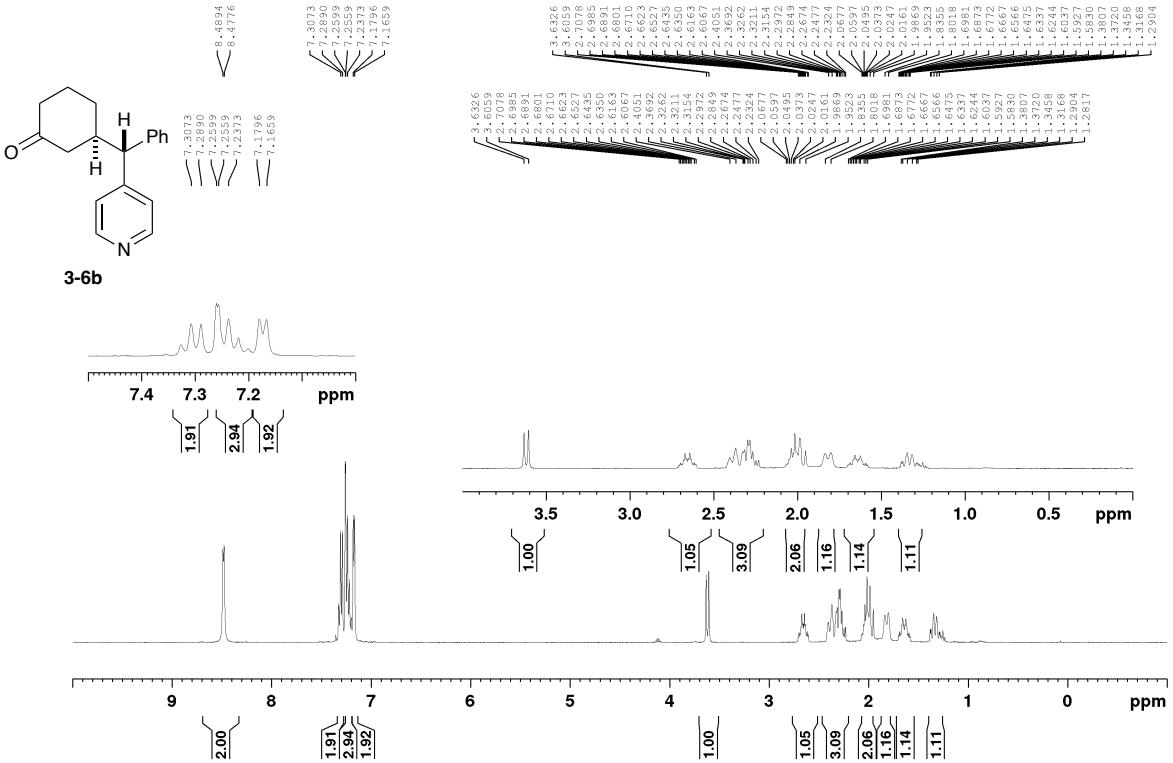
COSY (600 MHz, $C_6H_6/CDCl_3$, 10 °C) spectrum for **3-6a**:



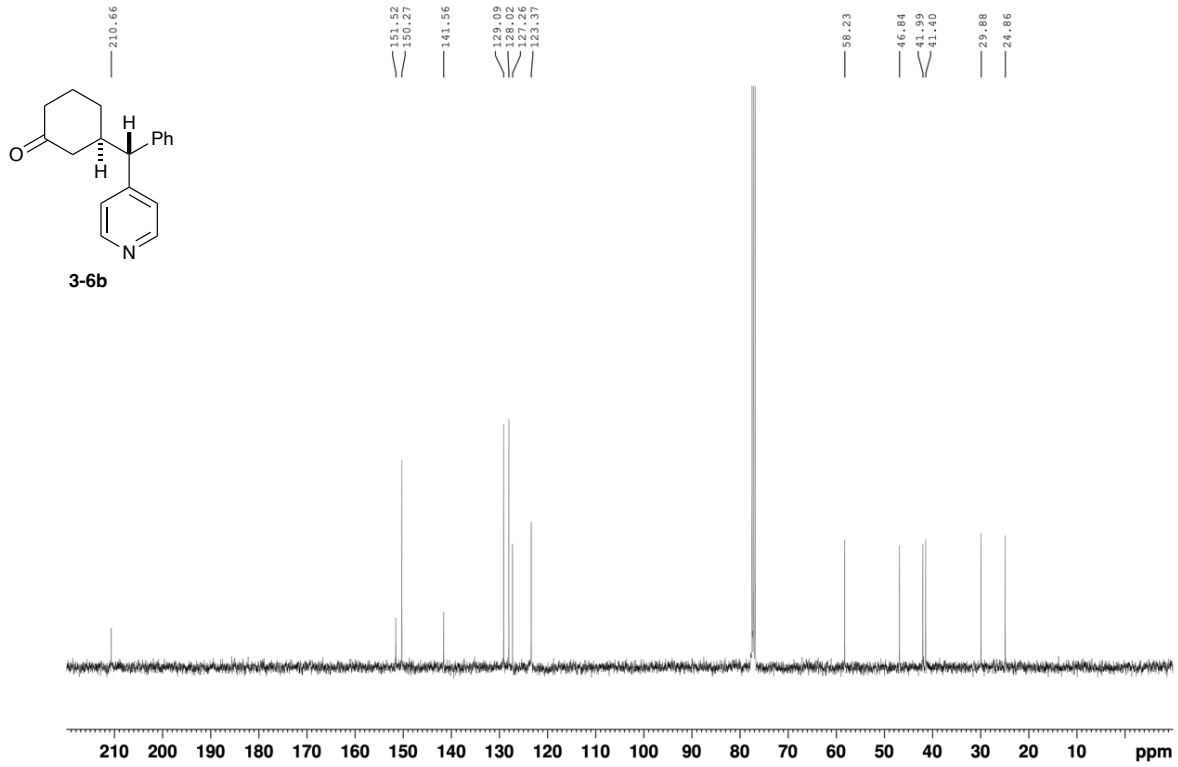
NOESY (600 MHz, in $C_6H_6/CDCl_3$, 10 °C) spectrum for **3-6a**:



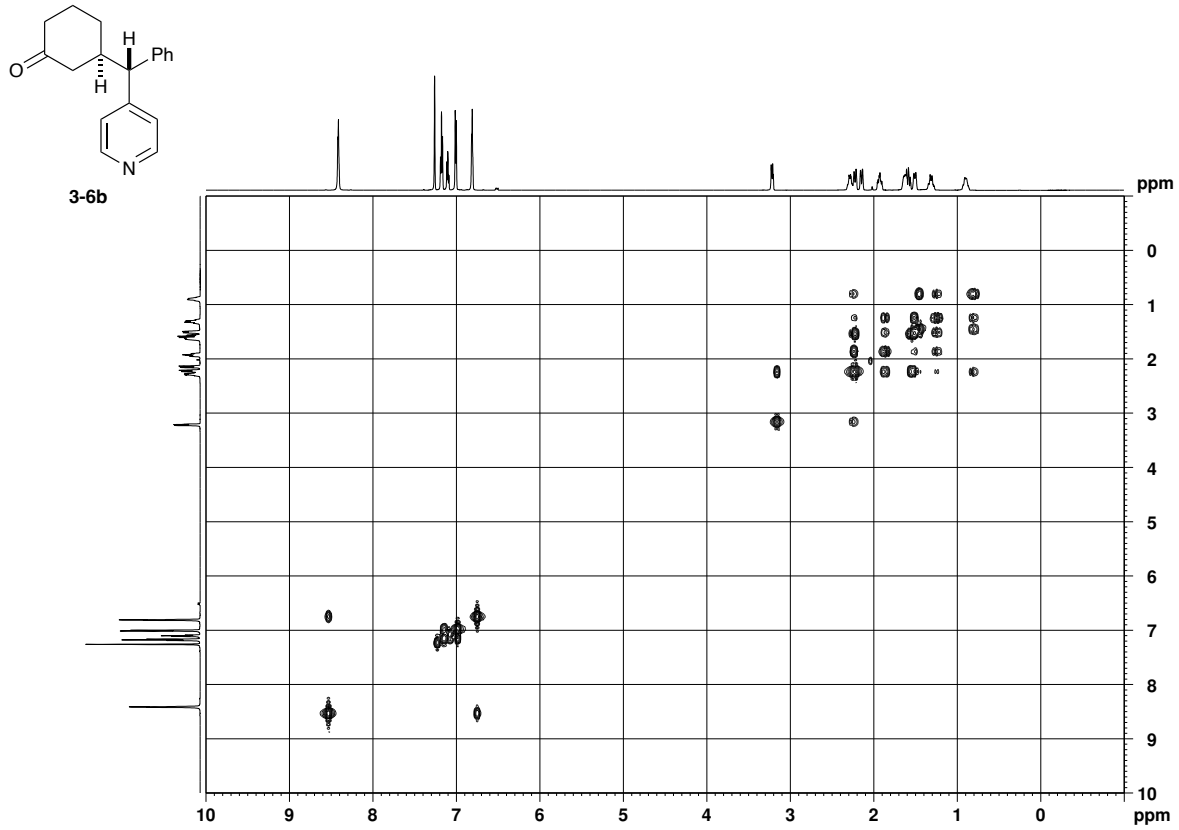
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-6b**:



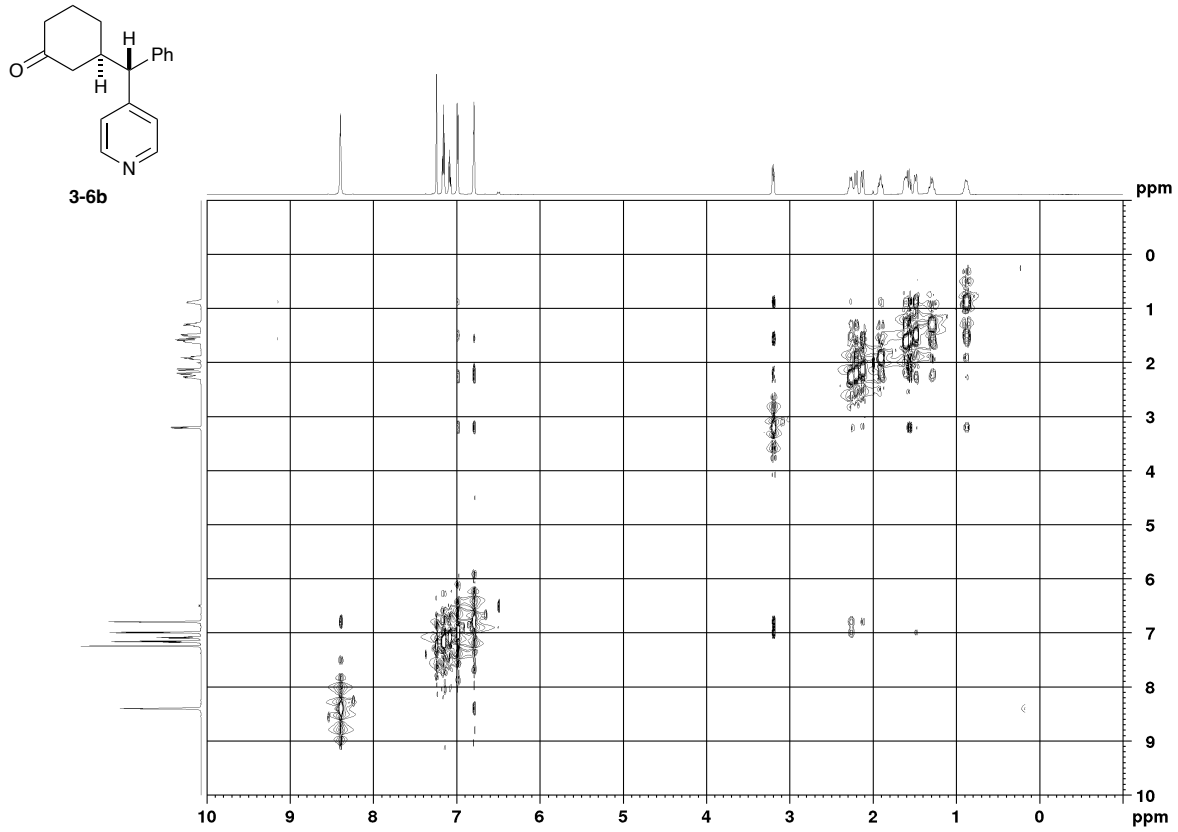
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-6b**:



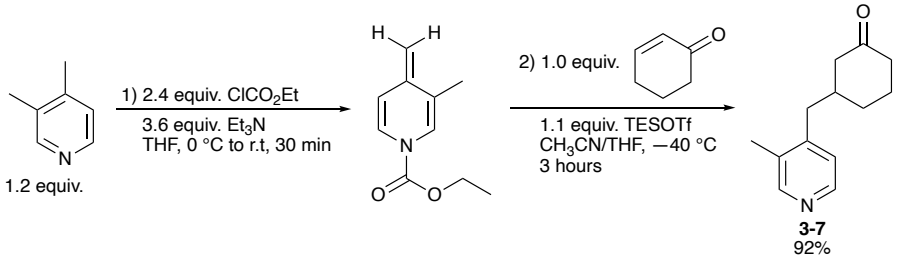
COSY (600 MHz, $C_6H_6/CDCl_3$, 10 °C) spectrum for **3-6b**:



NOSY (600 MHz, $C_6H_6/CDCl_3$, 10 °C) spectrum for **3-6b**:



Synthesis of compound **3-7**:



By following the **general procedure A**, the corresponding ADHP was prepared from 3,4-lutidine (0.14 mL, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.1 mL, 1.0 equiv., 1.0 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-7** as colorless oil (187 mg, 92% yield).

Chromatography: 70% EtOAc in Hexanes with 2% Et_3N (R_f = 0.34).

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

δ 8.35 (s, 1H), 8.32 (d, *J* = 4.8 Hz, 1H), 6.96 (d, *J* = 4.8 Hz, 1H),

2.66 – 2.55 (m, 2H), 2.41 – 2.32 (m, 2H), 2.32 – 2.23 (m, 4H),

2.14 – 2.00 (m, 3H), 1.89 – 1.82 (m, 1H), 1.68 – 1.55 (m, 1H), 1.48 – 1.36 (m, 1H).

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

δ 210.8, 151.3, 147.5, 146.6, 131.8, 124.5, 48.0, 41.4, 39.5, 39.2, 31.2, 25.1, 16.4.

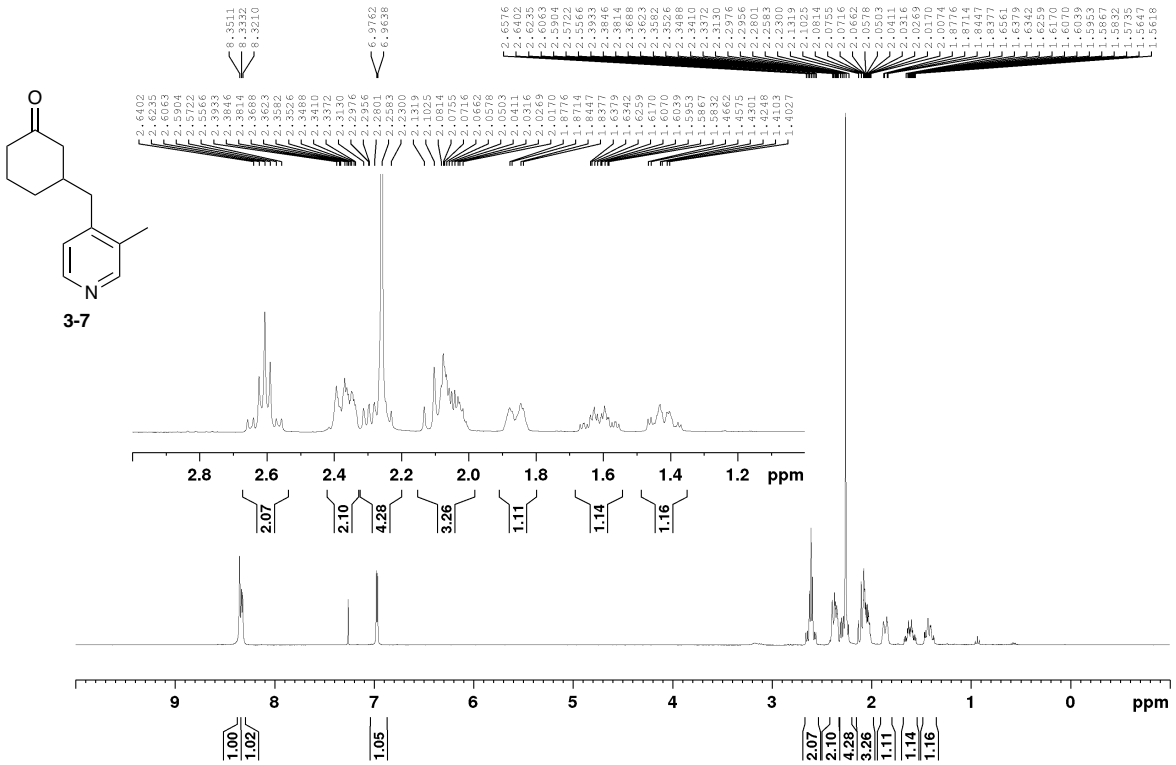
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3022, 2932, 2869, 1706, 1594, 1449 cm^{-1}.

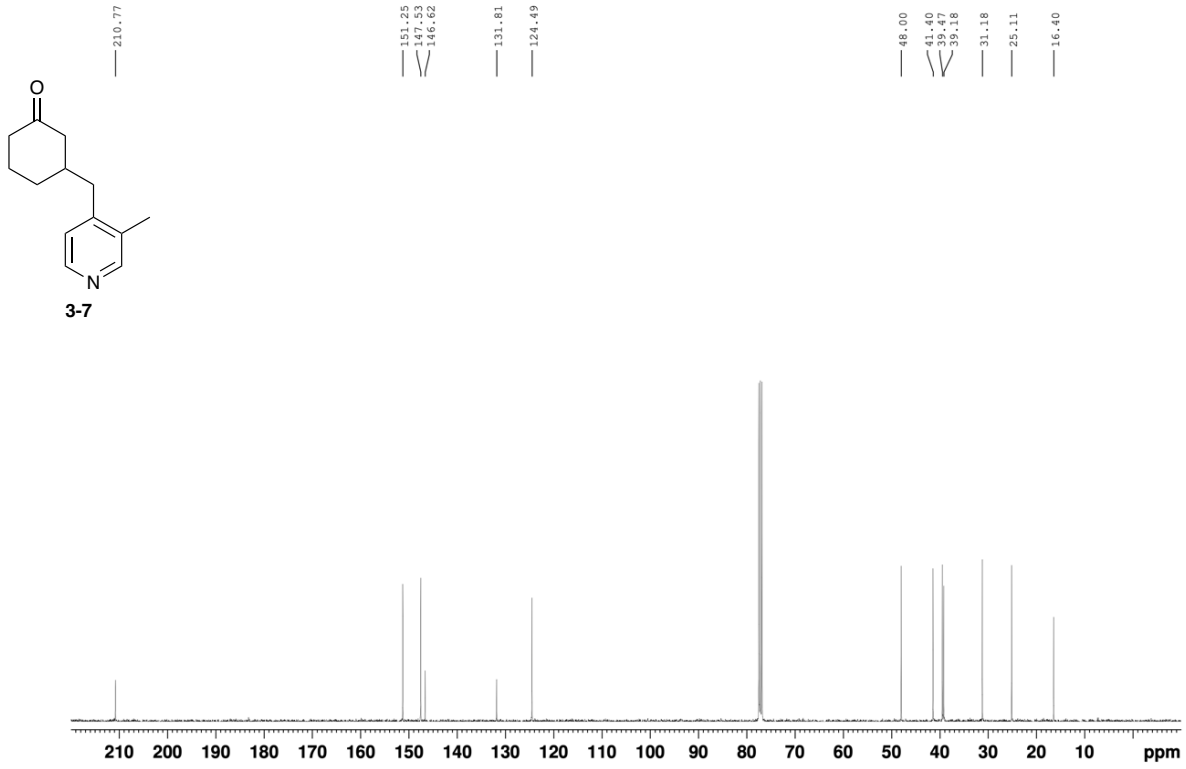
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{13}H_{18}NO$ 204.1383; Found 204.1391.

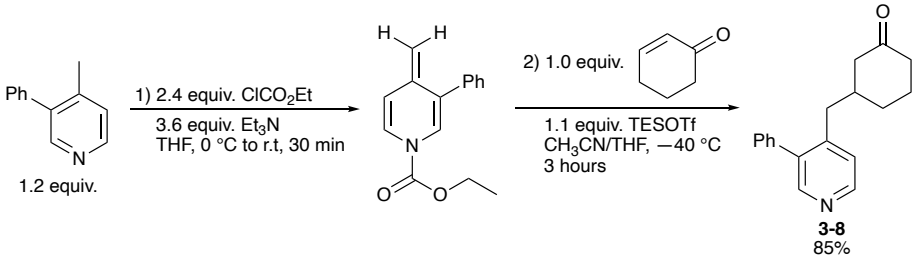
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-7**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-7**:



Synthesis of compound **3-8**:



By following the **general procedure A**, the corresponding ADHP was prepared from 3-phenyl-4-methylpyridine (203.1 mg, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.1 mL, 1.0 equiv., 1.0 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-8** as light-yellow oil (227 mg, 85% yield).

Chromatography: 60% EtOAc in Hexanes with 2% Et_3N (R_f = 0.31).

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

δ 8.48 (d, *J* = 5.2 Hz, 1H), 8.42 (s, 1H), 7.46 – 7.36 (m, 3H), 7.27 – 7.24 (m, 2H), 7.14 (d, *J* = 5.2 Hz, 1H), 2.68 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.62 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.32 – 2.23 (m, 1H), 2.22 – 2.09 (m, 2H), 1.94 – 1.79 (m, 3H), 1.71 – 1.63 (m, 1H),1.54 – 1.41 (m, 1H), 1.21 – 1.10 (m, 1H).

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

δ 210.8, 150.7, 148.7, 146.0. 138.1, 137.8, 129.5, 128.6, 127.9, 124.5, 47.8, 41.3, 39.8, 39.1, 30.9, 25.0.

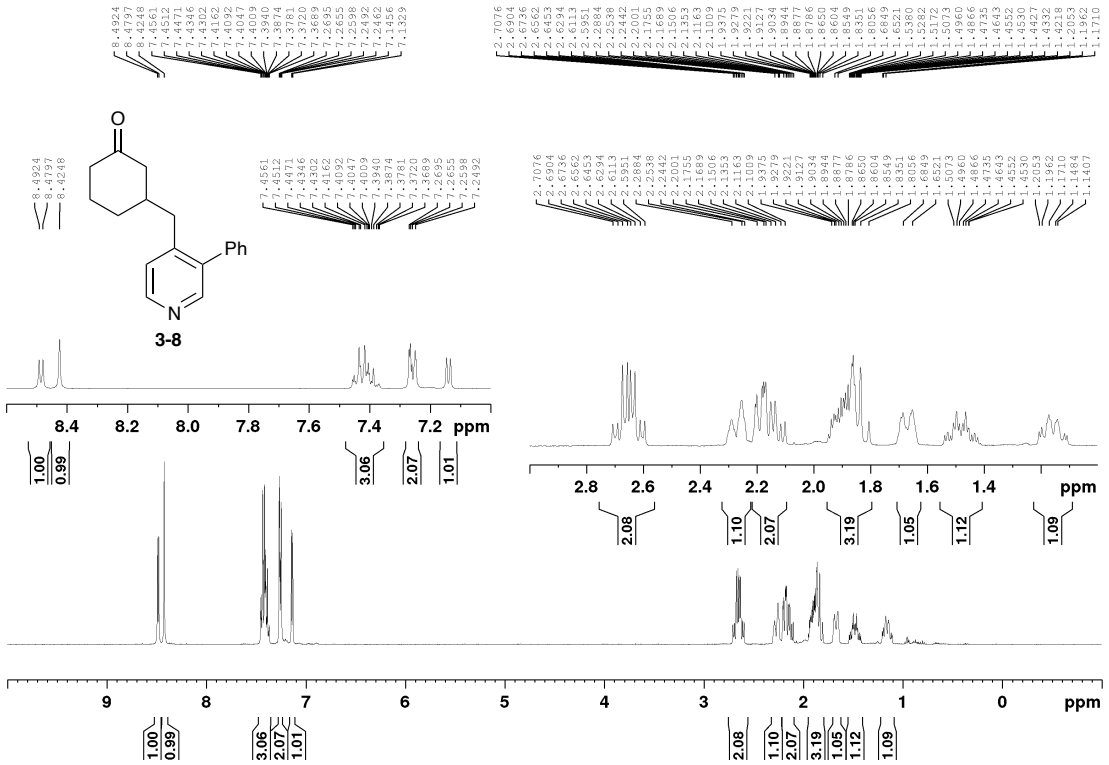
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3023, 2934, 2866, 1706, 1588, 1445 cm^{-1}.

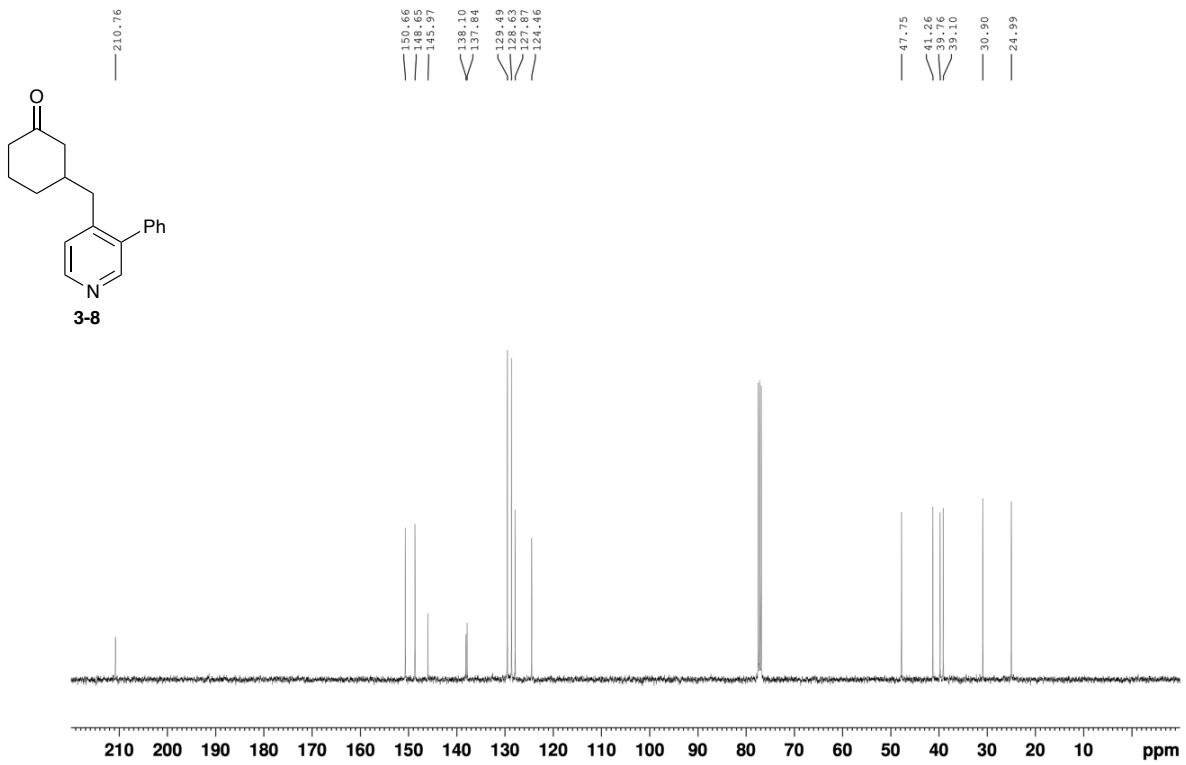
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{18}H_{20}NO$ 266.1540; Found 266.1542.

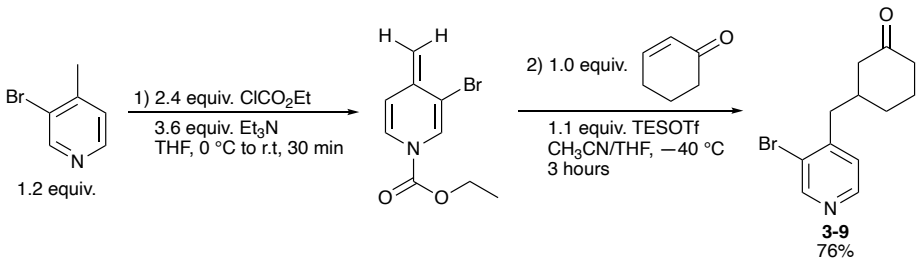
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-8**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-8**:



Synthesis of compound **3-9**:



By following the **general procedure A**, the corresponding ADHP was prepared from 3-bromo-4-methylpyridine (0.14 mL, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.1 mL, 1.0 equiv., 1.0 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford compound **3-9** as light-yellow oil (205 mg, 76% yield).

Chromatography: 70% EtOAc in Hexanes (R_f = 0.42).

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

δ 8.67 (s, 1H), 8.41 (d, *J* = 4.8 Hz, 1H), 7.09 (d, *J* = 4.8 Hz, 1H), 2.79 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.71 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.42 – 2.34 (m, 2H), 2.33 – 2.23 (m, 1H), 2.22 – 2.02 (m, 3H), 1.92 – 1.83 (m, 1H), 1.70 – 1.57 (m, 1H), 1.52 – 1.41 (m, 1H).

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

δ 210.6, 152.4, 148.2, 147.8, 126.1, 123.5, 47.6, 42.1, 41.4, 38.8, 31.0, 25.0.

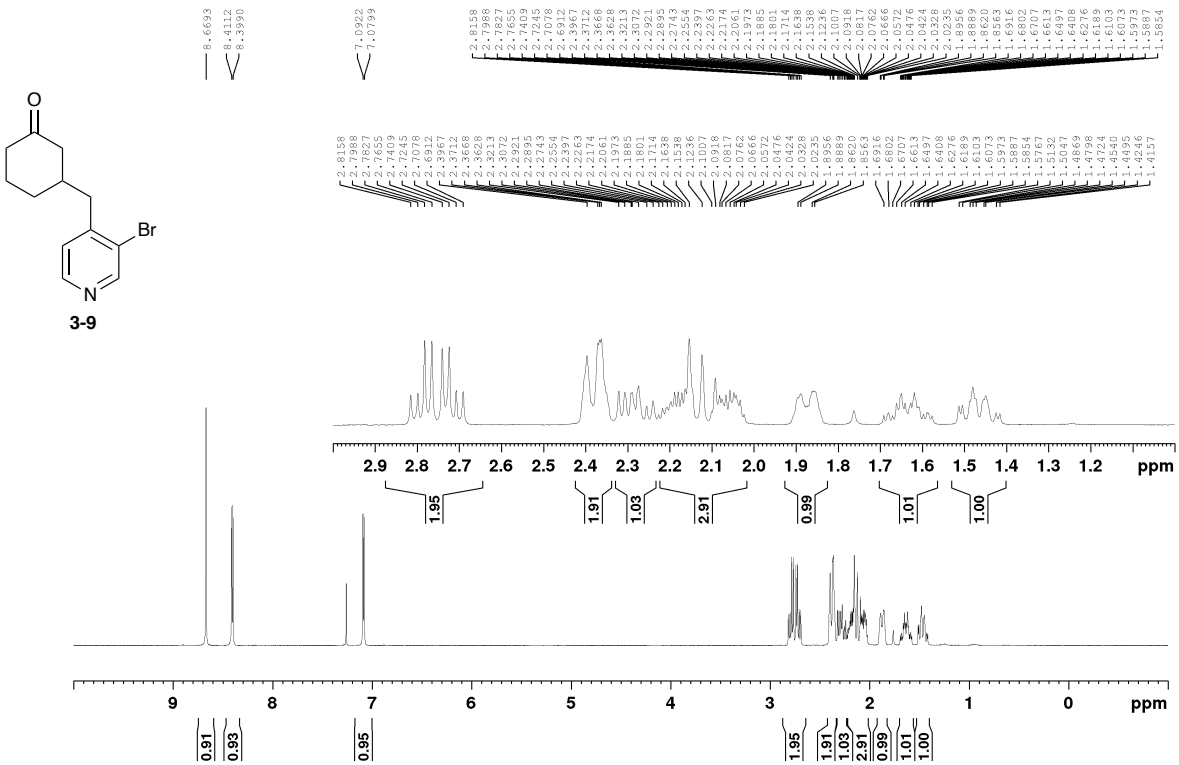
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3042, 2934, 2868, 1706, 1582, 1398, 511 cm^{-1}.

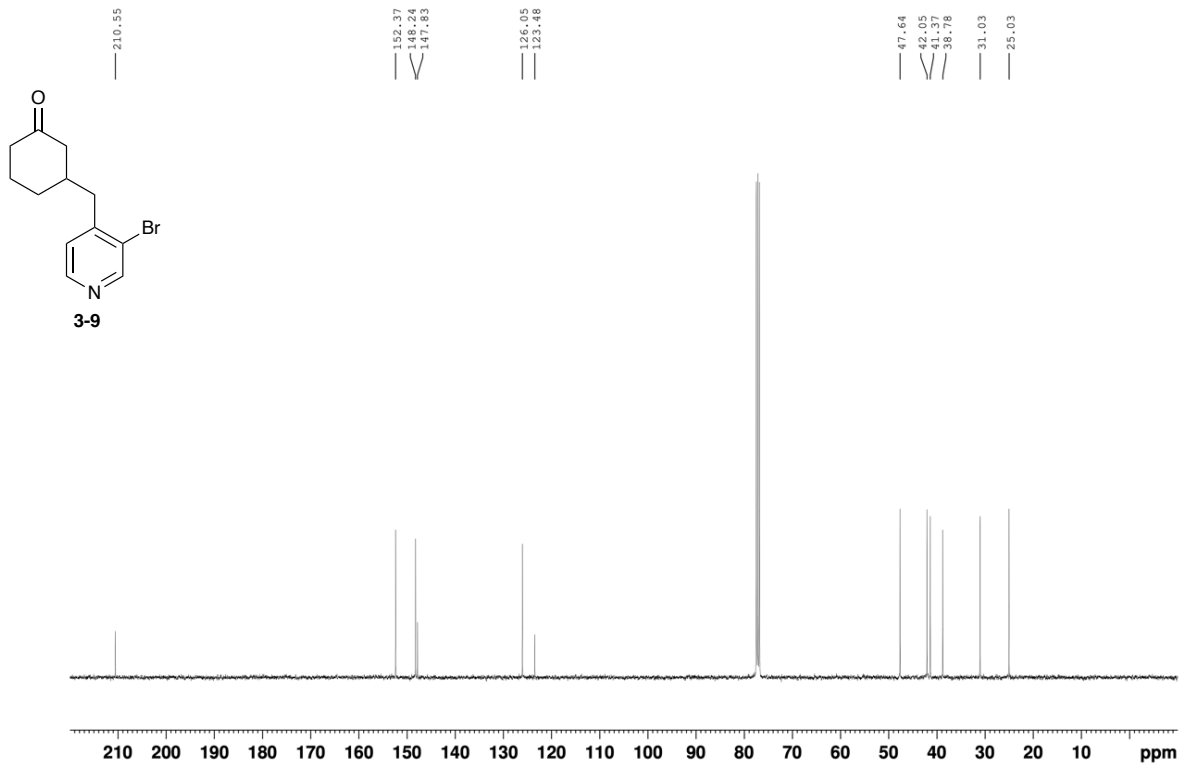
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{12}H_{15}BrNO$ 268.0332; Found 268.0347.

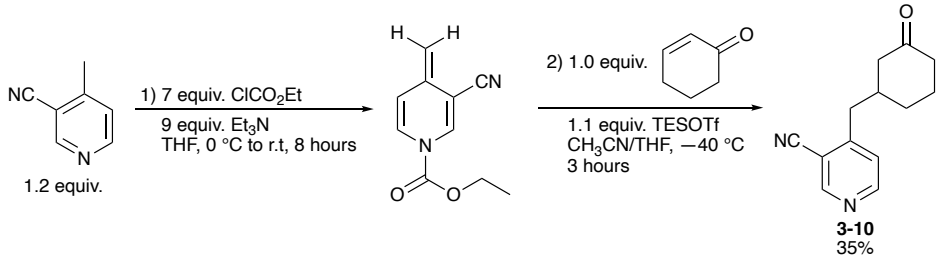
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-9**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-9**:



Synthesis of compound **3-10**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with 6 mL of anhydrous THF, 3-cyano-4-methylpyridine (71 mg, 1.2 equiv., 0.6 mmol) and triethylamine (0.75 mL, 9.0 equiv., 5.4 mmol). The resulting solution was cooled to 0 °C, and ethyl chloroformate (0.4 mL, 7.0 equiv., 4.2 mmol) was added in a dropwise manner. The resulting mixture was stirred at ambient temperature for 8 hours and concentrated using a rotary evaporator. The residue was suspended in diethyl ether for 2 – 3 minutes and filtered through a cotton plug to remove the precipitated triethylammonium chloride salt. The filtrate was concentrated using a rotary evaporator to give the corresponding ADHP as pale yellow oil, which was used in the next step without further purification.

The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.05 mL, 1.0 equiv., 0.5 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-10** as light-yellow oil (38 mg, 35% yield).

Melting point: 60.7 – 61.9 °C

Chromatography: 50% EtOAc in Hexanes with 2% Et_3N (R_f = 0.35).

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

δ 8.84 (s, 1H), 8.70 (d, *J* = 5.2 Hz, 1H), 7.23 (d, *J* = 5.2 Hz, 1H),

2.93 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.93 (dd, *J* = 13.2, 6.8 Hz, 1H),

2.43 – 2.25 (m, 3H), 2.25 – 2.06 (m, 3H), 1.95 – 1.85 (m, 1H), 1.72 – 1.60 (m, 1H), 1.57 – 1.46 (m, 1H).

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

δ 209.7, 153.2, 152.7, 152.1, 124.5, 115.9, 110.9, 47.3, 41.1, 40.7, 39.8, 30.9, 24.8.

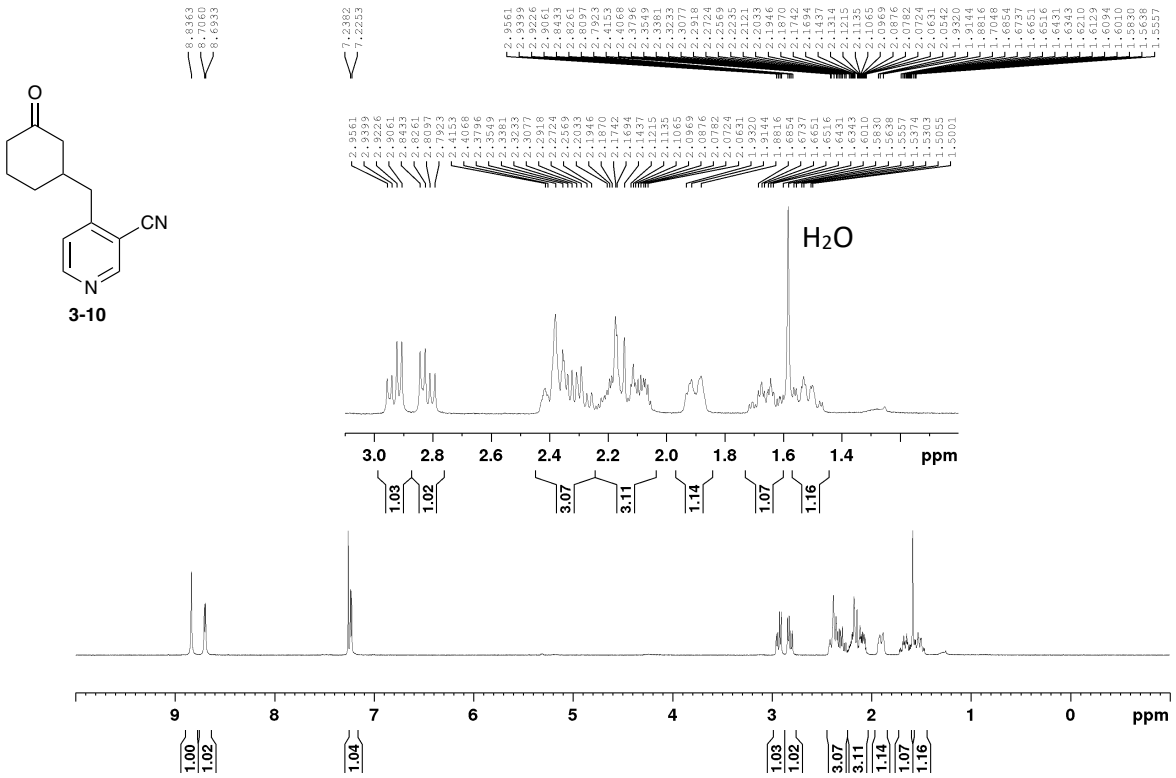
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3022, 2958, 2928, 2226, 1700, 1588, 1416 cm^{-1}.

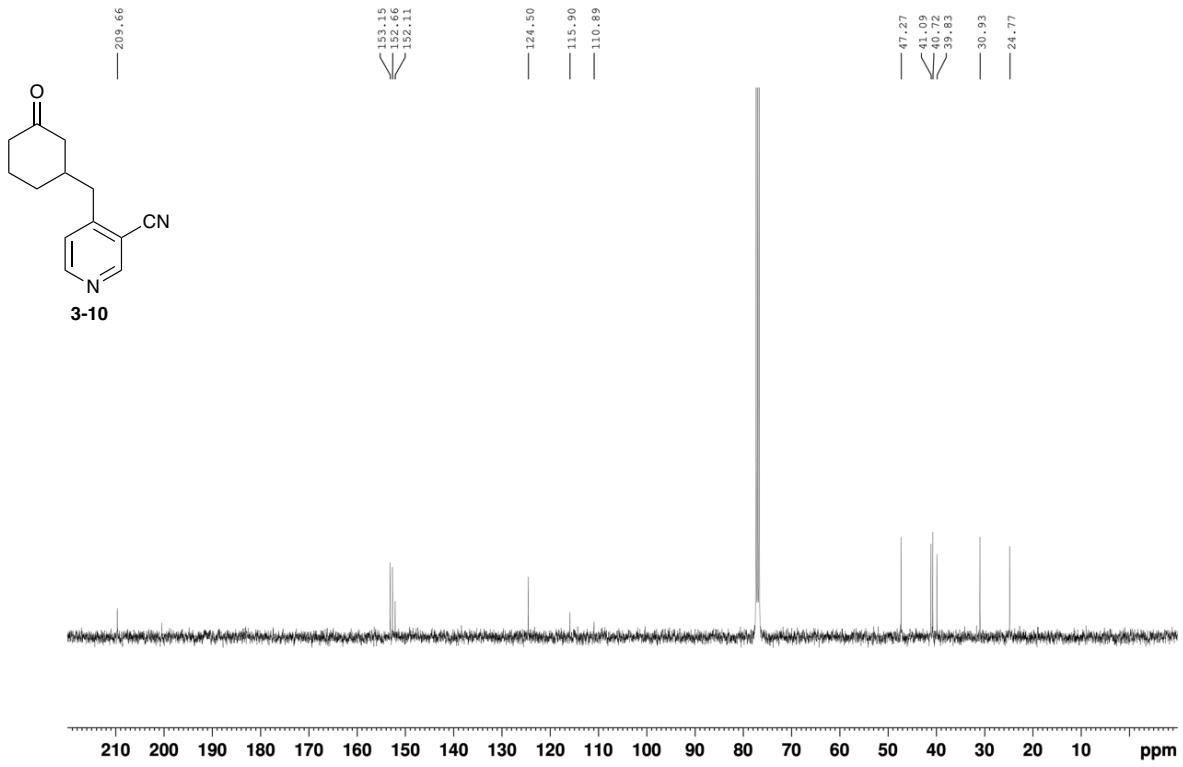
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{13}H_{15}N_2O$ 215.1179; Found 215.1186.

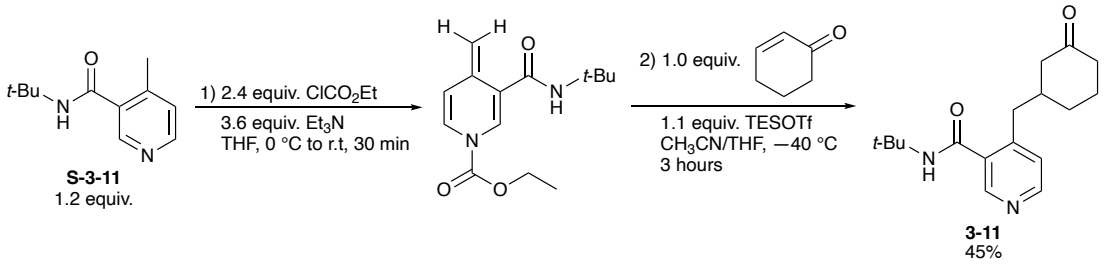
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-10**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-10**:



Synthesis of compound **3-11**:



By following the **general procedure A**, the corresponding ADHP was prepared from compound **S-3-11** (115.4 mg, 1.2 equiv., 0.6 mmol). The final product was synthesized by following the **general procedure B** but using THF (2.5 mL) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.05 mL, 1.0 equiv., 0.5 mmol) was used as an electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-11** as white solid (65.5 mg, 45% yield).

Melting point: 96.2 – 96.7 °C

Chromatography: 50% EtOAc in Hexanes with 2% Et_3N (R_f = 0.20).

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

δ 8.51 (s, 1H), 8.47 (d, *J* = 5.2 Hz, 1H), 7.08 (d, *J* = 5.2 Hz, 1H), 5.84 (s, 1H), 2.95 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.73 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.38 – 2.21 (m, 3H), 2.18 – 2.01 (m, 3H), 1.90 – 1.79 (m, 1H), 1.67 – 1.55 (m, 1H), 1.50 – 1.38 (m, 10H).

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

δ 210.9, 167.1, 150.6, 147.6, 147.4, 133.8, 52.4, 47.7, 41.4, 40.1, 39.2, 31.4, 28.9, 25.1.

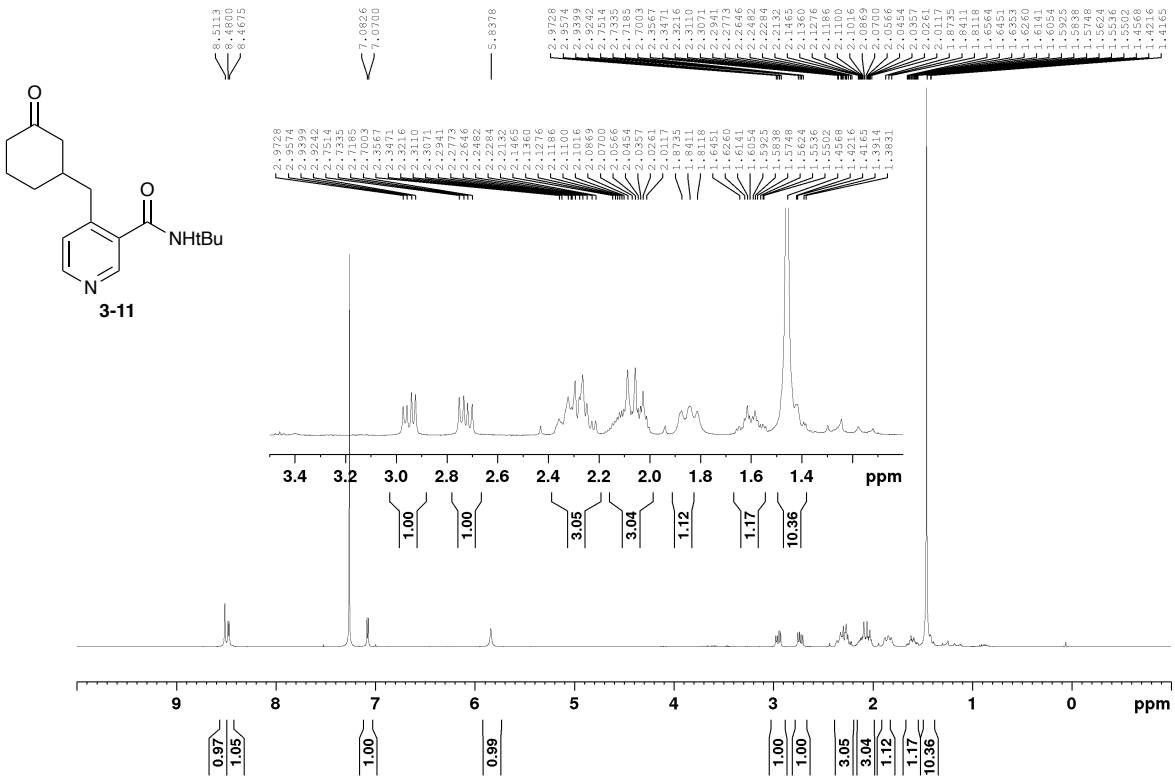
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3363, 3017, 2956, 2852, 1711, 1650, 1463 cm^{-1}.

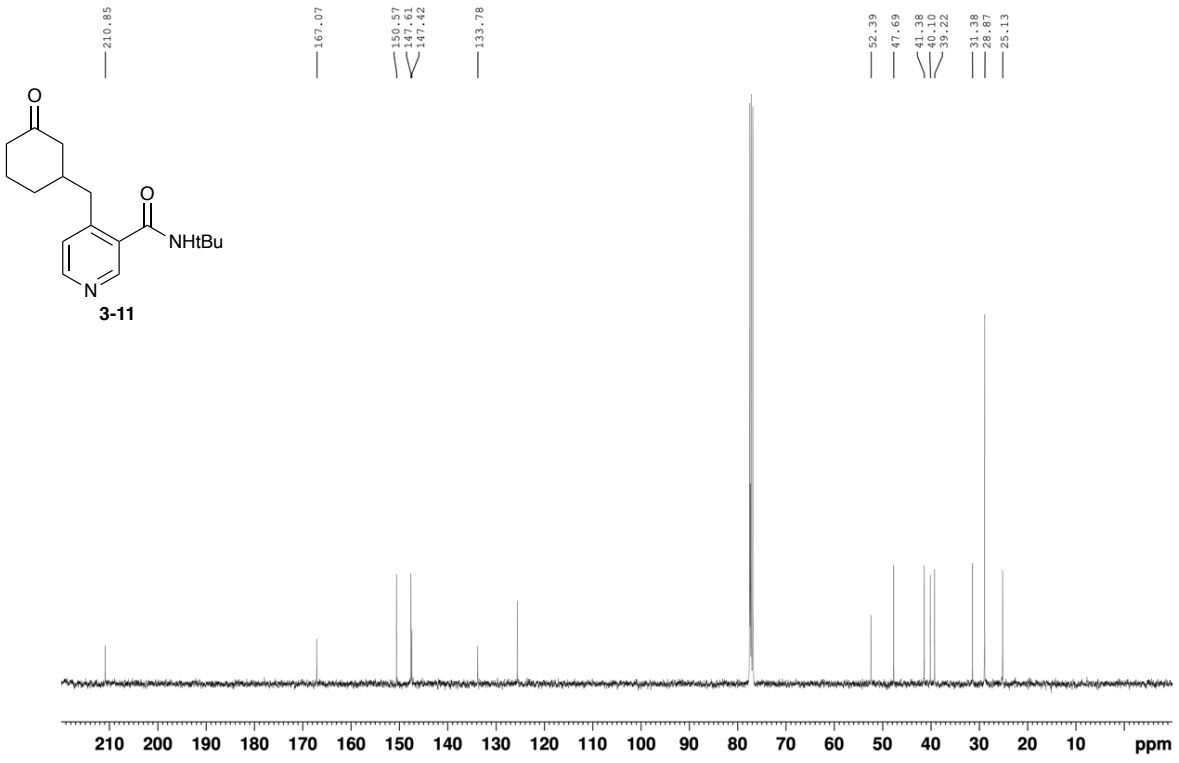
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{17}H_{25}N_2O_2$ 289.1911; Found 289.1924.

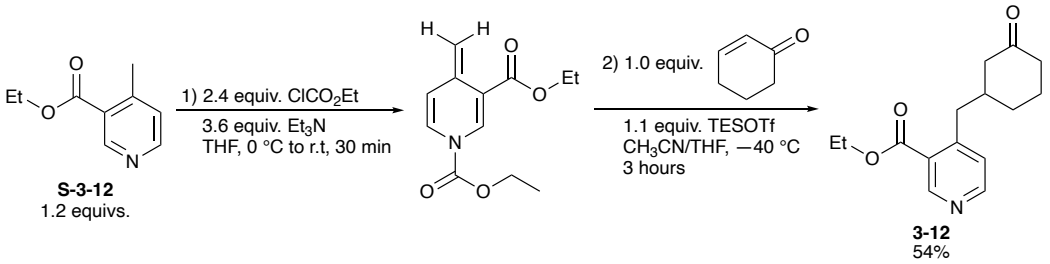
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-11**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-11**:



Synthesis of compound **3-12**:



By following the **general procedure A**, the corresponding ADHP was prepared from compound **S-3-12** (99 mg, 1.2 equiv., 0.6 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.05 mL, 1.0 equiv., 0.5 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-12** as light-yellow oil (71 mg, 54% yield).

Chromatography: 50% EtOAc in Hexanes with 2% Et_3N (R_f = 0.38).

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

δ 9.10 (s, 1H), 8.63 – 8.56 (m, 1H), 7.11 (d, *J* = 4.8 Hz, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 3.10 (dd, *J* = 12.8, 6.4 Hz, 1H), 2.97 (dd, *J* = 12.8, 6.4 Hz, 1H), 2.40 – 2.33 (m, 2H), 2.33 – 2.23 (m. 1H), 2.17 – 2.08 (m, 2H), 2.08 – 2.01 (m, 1H), 1.91 – 1.84 (m, 1H), 1.68 – 1.56 (m, 1H), 1.52 – 1.43 (m, 1H), 1.41 (t, *J* = 7.2 Hz, 3H).

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

δ 210.9, 166.1, 152.3, 152.2, 150.6, 126.4, 126.2, 61.5, 47.8, 41.5, 40.3, 40.2, 31.3, 25.1, 14.4.

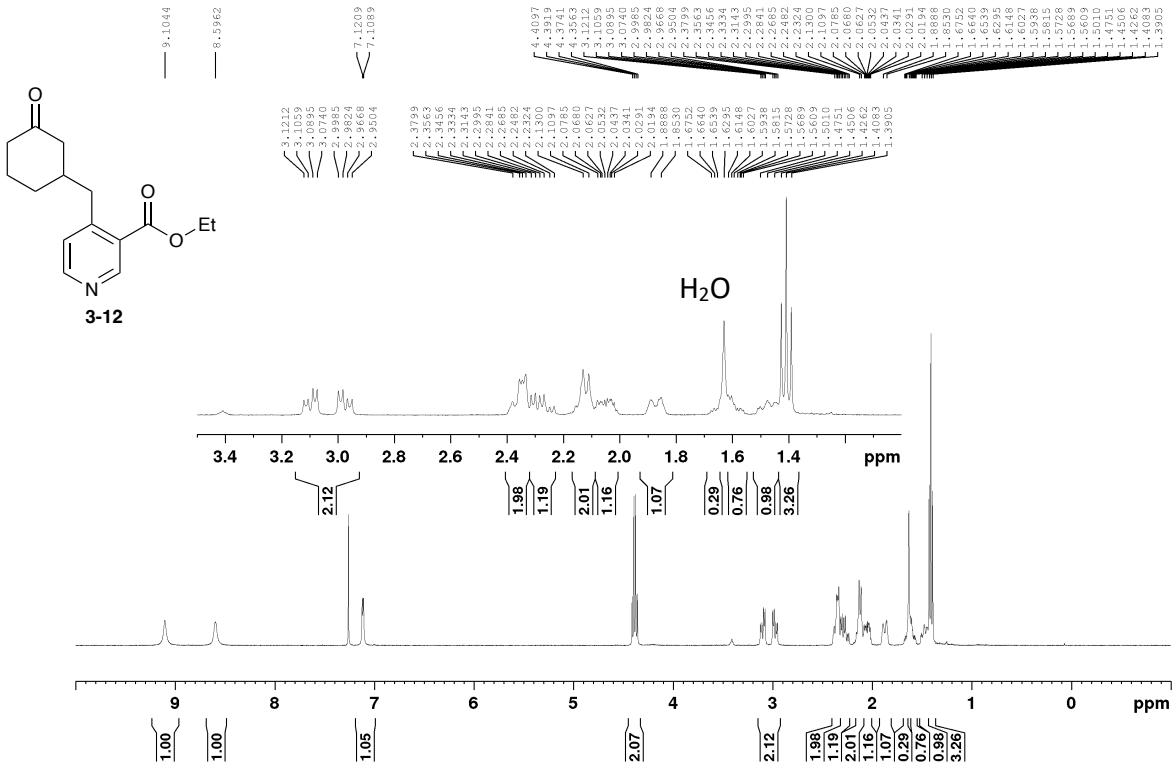
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3043, 2979, 2935, 1706, 1590, 1418, 1274cm^{-1}.

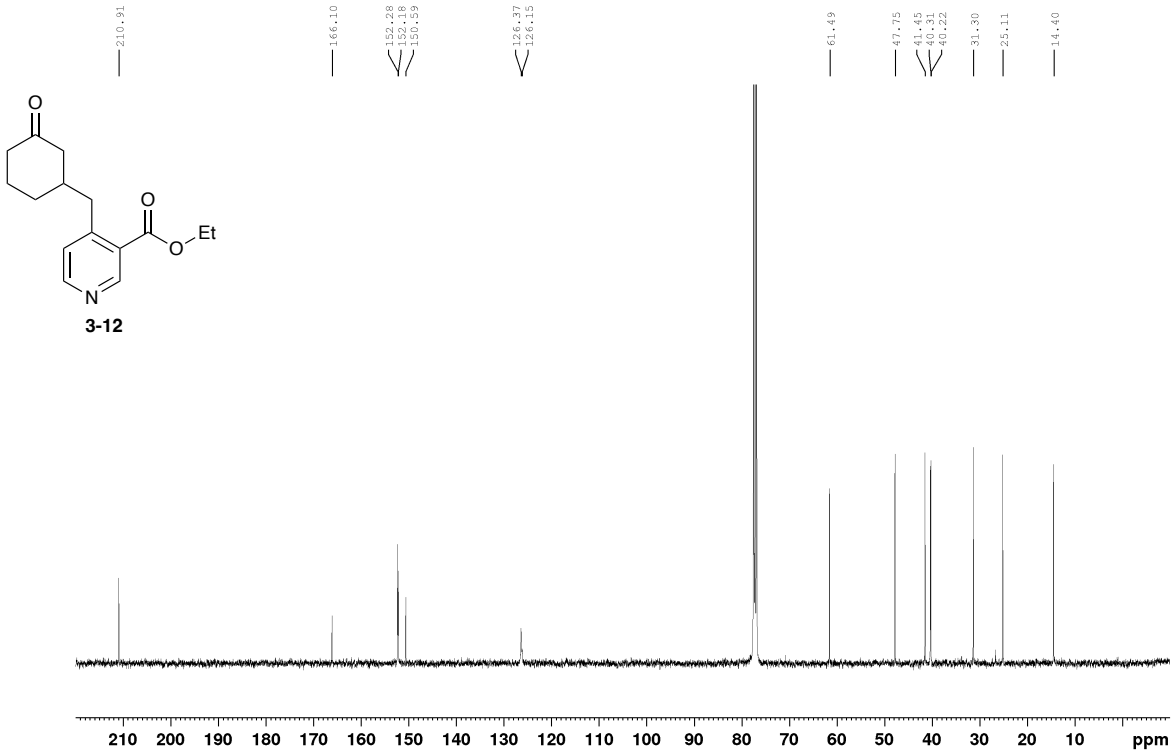
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{15}H_{20}NO_3$ 262.1438; Found 262.1453.

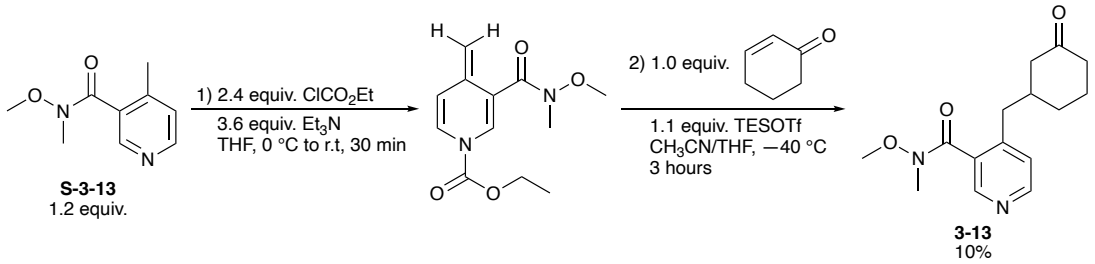
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-12**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-12**:



Synthesis of compound **3-13**:



By following the **general procedure A**, the corresponding ADHP was prepared from compound **S-3-13** (87 mg, 1.2 equiv., 0.48 mmol). The final product was synthesized by using the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.04 mL, 1.0 equiv., 0.4 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-13** as light-yellow oil (11 mg, 10% yield).

Chromatography: 40% EtOAc in Hexanes with 2% Et_3N (R_f = 0.19).

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

δ 8.60 – 8.50 (m, 2H), 7.17 (d, *J* = 5.2 Hz, 1H), 3.50 (s, 3H), 3.35 (s, 3H), 2.72 (dd, *J* = 12.8, 7.2 Hz, 1H), 2.66 (dd, *J* = 12.8, 6.8 Hz, 1H), 2.40 – 2.32 (m, 2H), 2.31 – 2.21 (m, 1H), 2.20 – 1.99 (m, 3H), 1.88 – 1.80 (m, 1H), 1.68 – 1.55 (m, 1H), 1.44 – 1.34 (m, 1H).

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

δ 210.7, 168.6, 149.9, 147.2, 147.0, 131.8, 124.9, 61.5, 47.9, 41.4, 39.6, 39.5, 33.0, 31.1, 25.1.

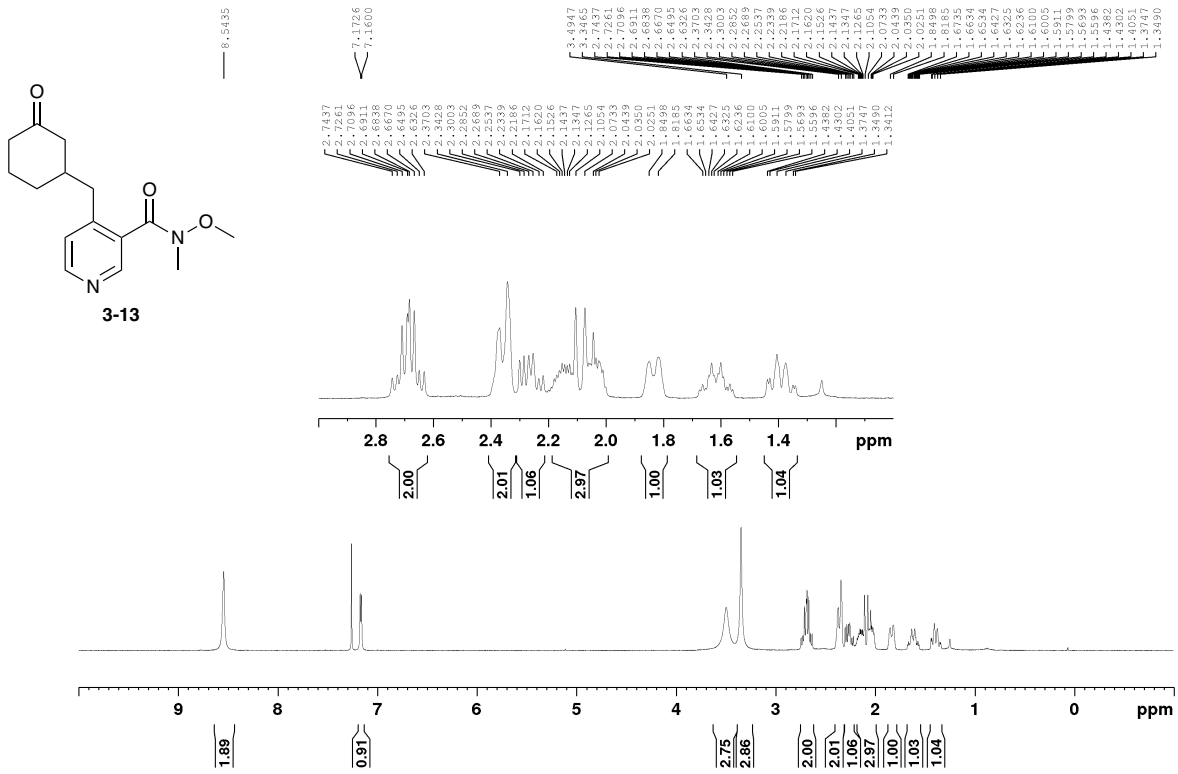
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3042, 2935, 2868, 1708, 1646, 1559, 1448, 1380, 1225 cm^{-1}.

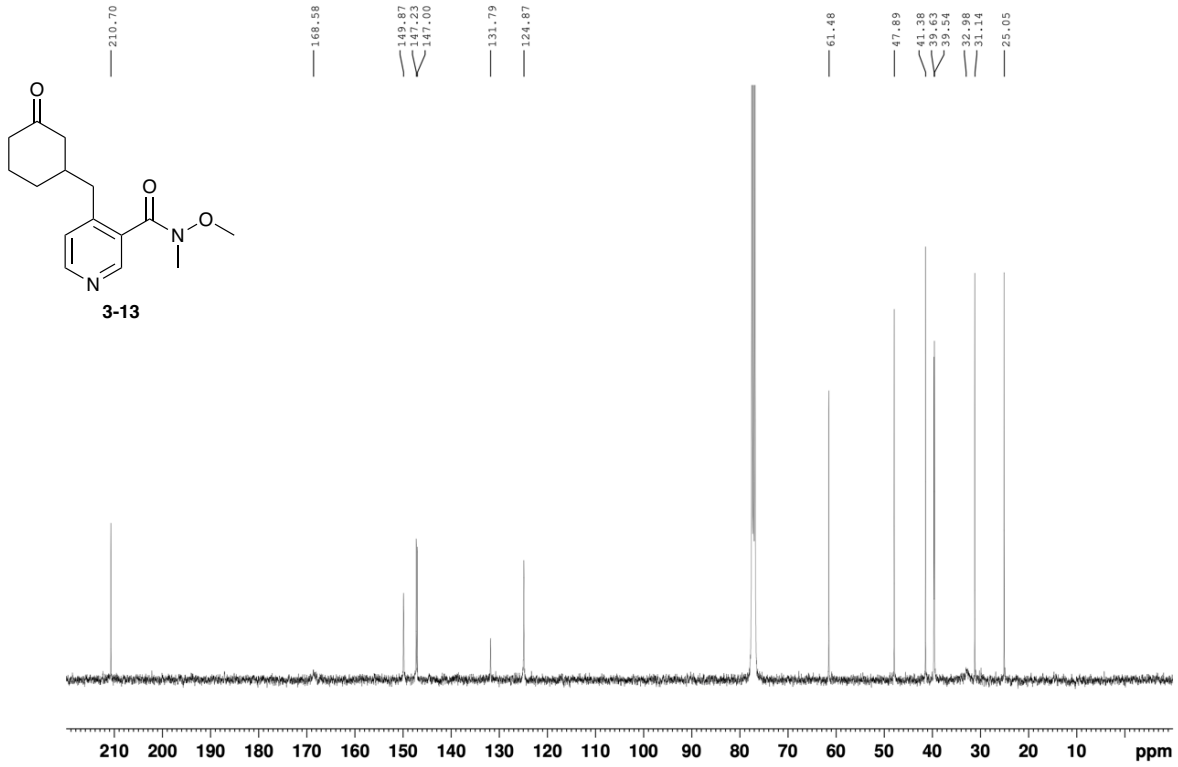
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{15}H_{21}N_2O_3$ 277.1547; Found 277.1554.

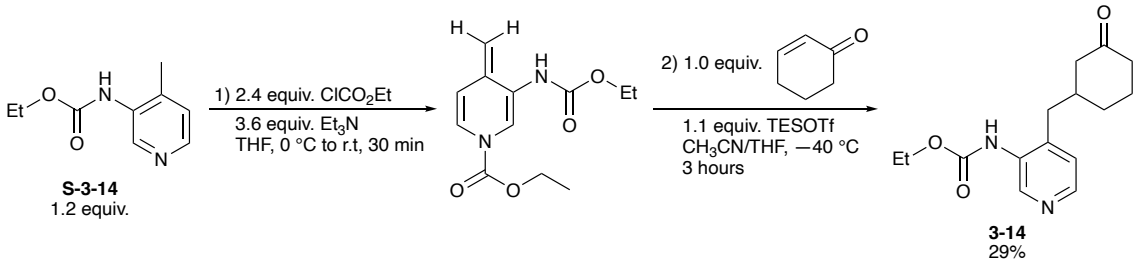
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-13**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-13**:



Synthesis of compound **3-14**:



By following the **general procedure A**, the corresponding ADHP was prepared from compound **S-3-14** (216 mg, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.1 mL, 1.0 equiv., 1.0 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-14** as light-yellow oil (81 mg, 29% yield).

Chromatography: 60% EtOAc in Hexanes with 2% Et_3N (R_f = 0.37).

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

δ 8.81 (s, 1H), 8.33 (d, *J* = 4.8 Hz, 1H), 7.06 (d, *J* = 4.8 Hz, 1H), 6.47 (s, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 2.61 (d, *J* = 6.8 Hz, 2H), 2.42 – 2.36 (m, 2H), 2.33 – 2.24 (m, 1H), 2.17 – 2.00 (m, 3H), 1.90 – 1.83 (m, 1H), 1.74 – 1.60 (m, 1H), 1.49 – 1.40 (m. 1H), 1.32 (t, *J* = 7.2 Hz, 3H).

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

δ 210.9, 154.4, 146.4(4), 146.4, 141.0, 132.7, 124.8, 62.0, 47.7, 41.4, 39.2, 37.2, 31.0, 25.0, 14.7.

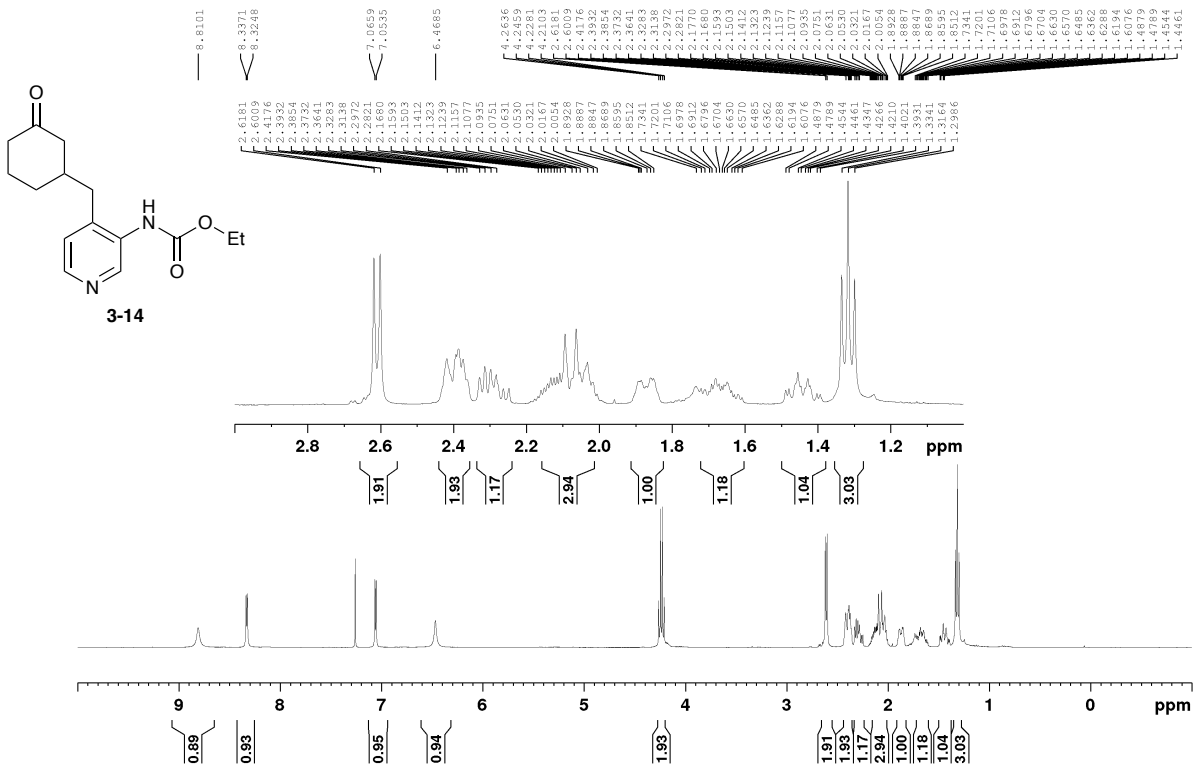
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3299, 3039, 2928, 2867, 1739, 1708, 1600, 1416 cm^{-1}.

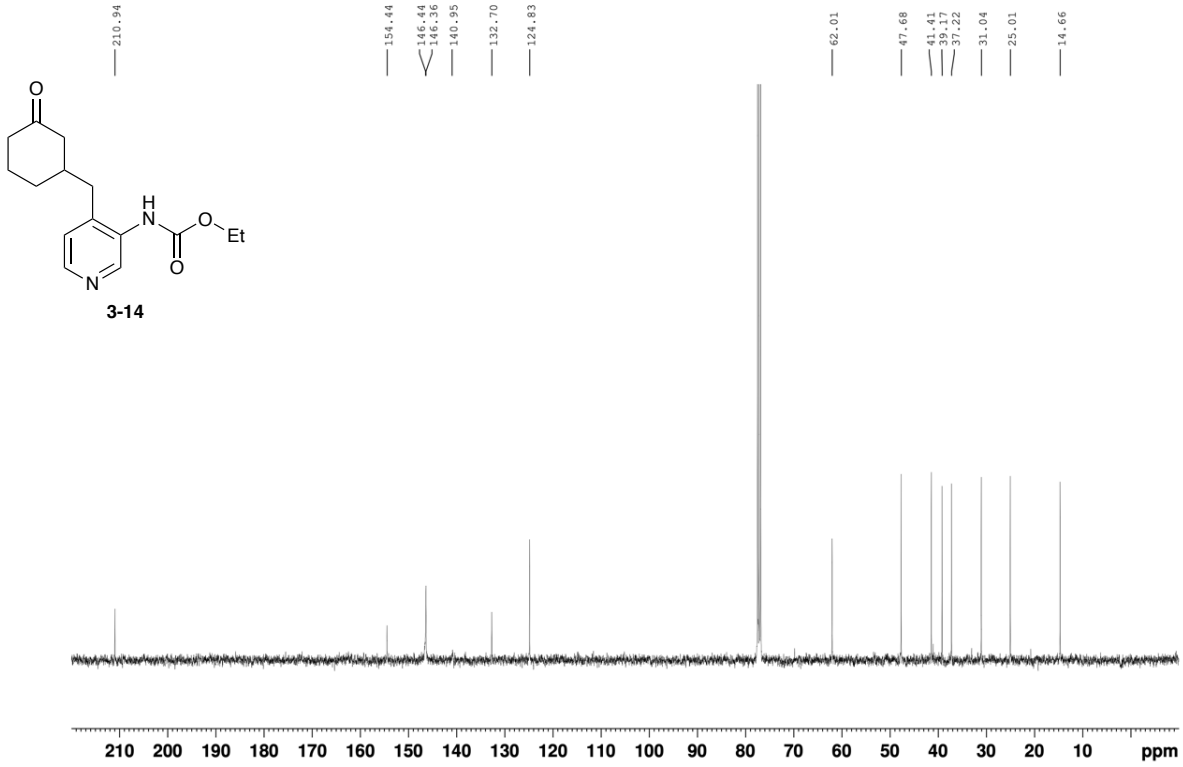
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{15}H_{21}N_2O_3$ 277.1547; Found 277.1551.

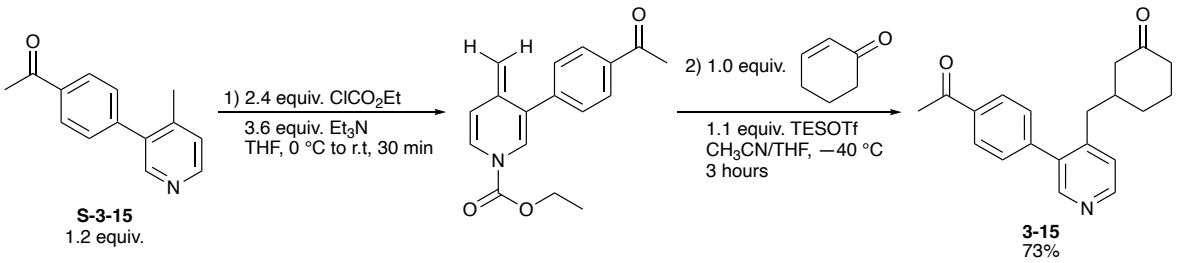
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-14**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-14**:



Synthesis of compound **3-15**:



By following the **general procedure A**, the corresponding ADHP was prepared from compound **S-3-15** (254 mg, 1.2 equiv., 1.2 mmol). The final product was prepared by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.1 mL, 1.0 equiv., 1.0 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-15** as white solid (225 mg, 73% yield).

Melting point: 65.9 – 67.0 °C

Chromatography: 70% EtOAc in Hexanes with 2% Et_3N (R_f = 0.25).

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

δ 8.51 (d, *J* = 5.2 Hz, 1H), 8.41 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 5.2 Hz, 1H), 2.71 – 2.58 (m, 5H), 2.31 – 2.23 (m, 1H), 2.20 – 2.08 (m, 2H), 1.94 – 1.78 (m, 3H), 1.70 – 1.63 (m, 1H), 1.54 – 1.41 (m, 1H), 1.21 – 1.09 (m, 1H).

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

δ 210.5, 197.6, 150.3, 149.2, 145.9, 142.8, 137.1, 136.5, 129.8, 128.7, 124.6, 47.7, 41.2, 39.8, 39.1, 30.9, 26.8, 24.9.

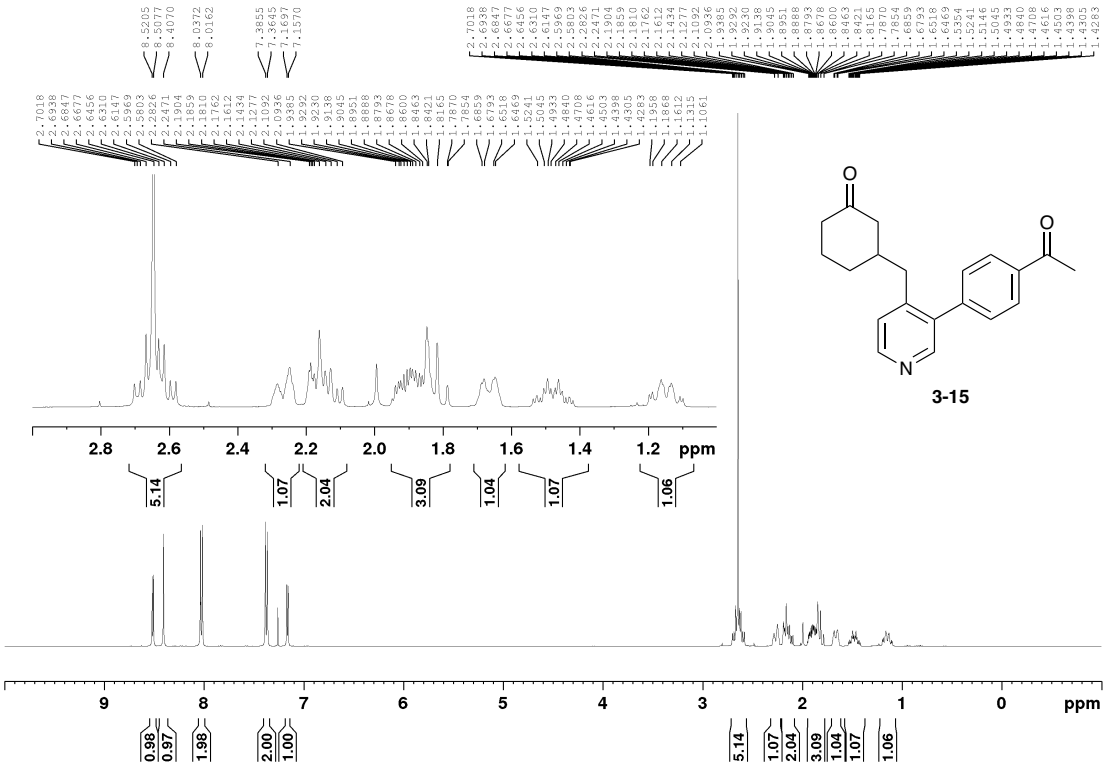
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3042, 2935, 2868, 1708, 1681, 1606, 1270 cm^{-1}.

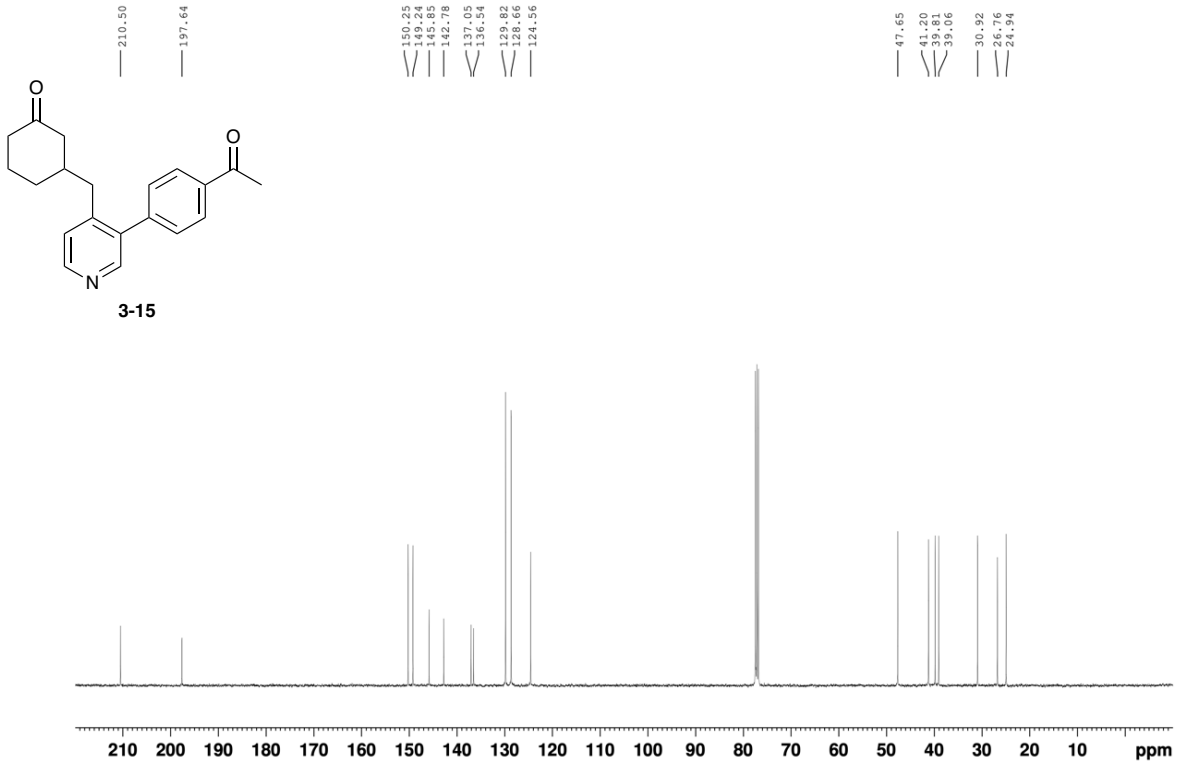
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{20}H_{22}NO_2$ 308.1645; Found 308.1647.

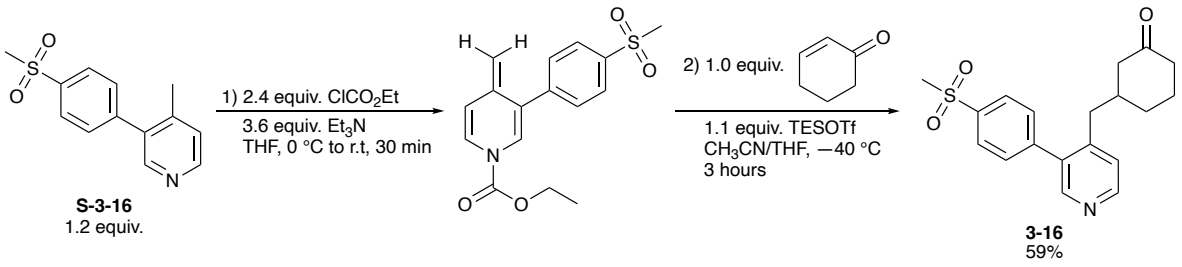
^1H NMR (400 MHz, $CDCl_3$) spectrum for **3-15**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-15**:



Synthesis of compound **3-16**:



By following the **general procedure A**, the corresponding ADHP was prepared from compound **S-3-16** (95 mg, 1.2 equiv., 0.38 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.03 mL, 1.0 equiv., 0.32 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford compound **3-16** as colorless oil (64 mg, 59 % yield).

Chromatography: 90% EtOAc in Hexanes (R_f = 0.17).

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

δ 8.57 (d, *J* = 5.2 Hz, 1H), 8.42 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 5.2 Hz, 2H), 3.14 (s, 3H), 2.68 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.59 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.35 – 2.26 (m, 1H), 2.22 – 2.13 (m, 2H), 1.99 – 1.88 (m, 2H), 1.88 – 1.81 (m, 1H), 1.74 – 1.65 (m, 1H), 1.58 – 1.46 (m, 1H), 1.23 – 1.12 (m, 1H).

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

δ 210.4, 150.2, 149.7, 145.9, 143.8, 140.3, 136.3, 130.6, 127.9, 124.6, 47.6, 44.7, 41.2, 40.0, 39.0, 31.1, 25.0.

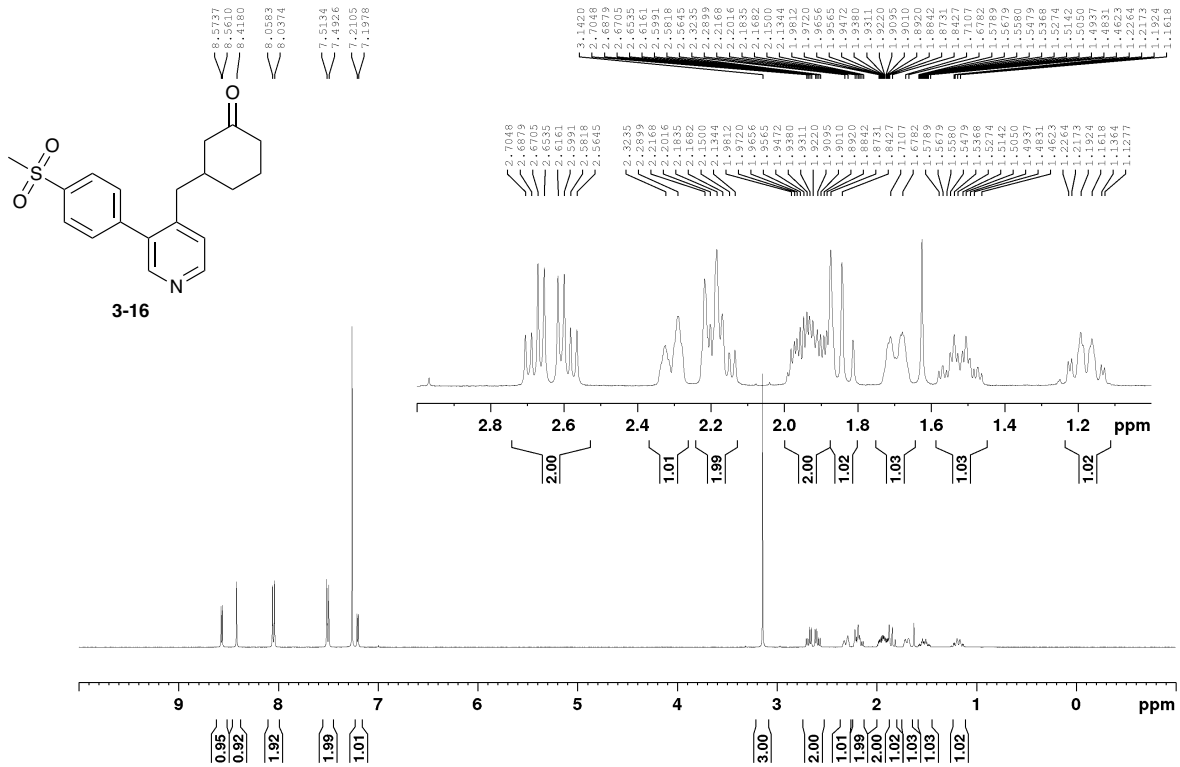
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3013, 2926, 2864, 1704, 1653, 1301, 1090 cm^{-1}.

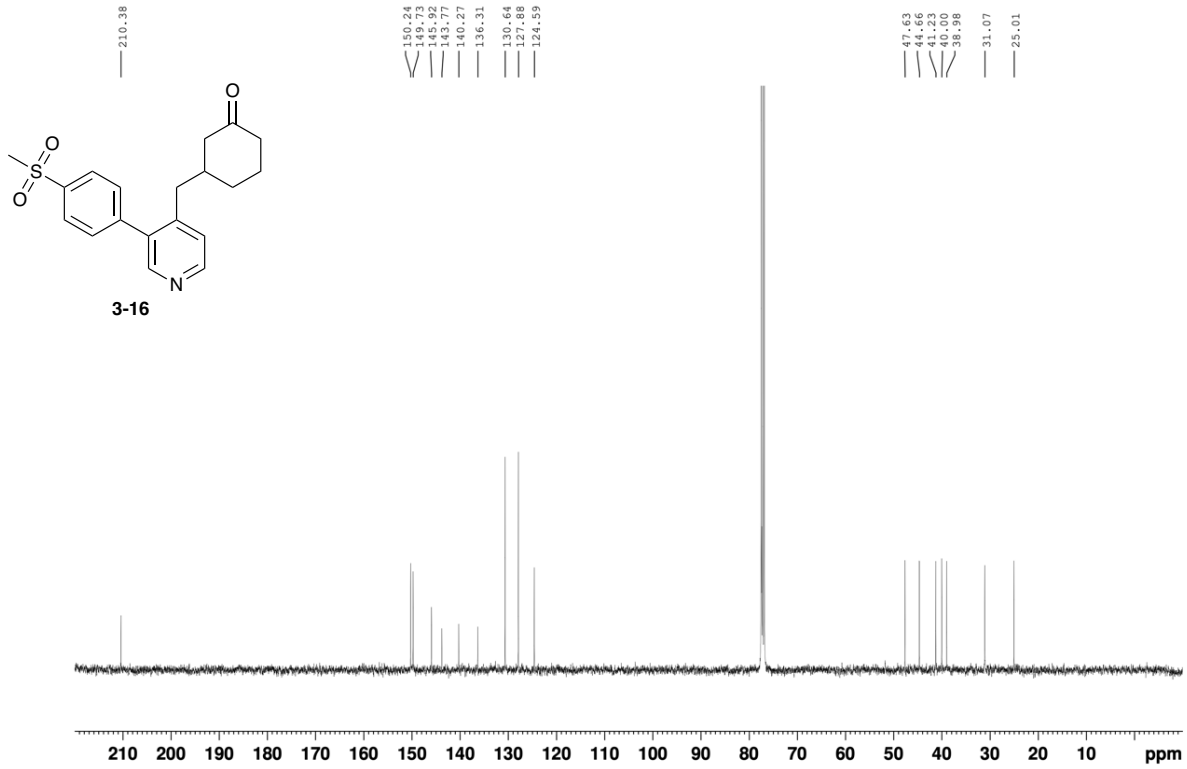
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{19}H_{22}NO_3S$ 344.1315; Found 344.1324.

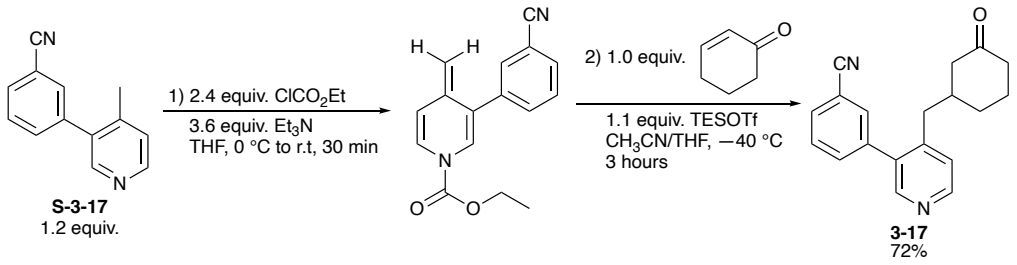
^1H NMR (400 MHz, $CDCl_3$) spectrum for **3-16**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-16**:



Synthesis of compound **3-17**:



By following the **general procedure A**, the corresponding ADHP was prepared from compound **S-3-17** (233 mg, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.1 mL, 1.0 equiv., 1.0 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-17** as white solid (209 mg, 72% yield).

Melting point: 57 – 58 °C

Chromatography: 70% EtOAc in Hexanes with 2% Et_3N (R_f = 0.28).

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

δ 8.51 (d, *J* = 5.2 Hz, 1H), 8.36 (s, 1H), 7.72 – 7.67 (m, 1H), 7.59 – 7.54 (m, 2H), 7.52 – 7.48 (m, 1H), 7.16 (d, *J* = 5.2 Hz, 1H), 2.62 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.56 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.29 – 2.22 (m, 1H), 2.18 – 2.09 (m, 2H), 1.95 – 1.78 (m, 3H), 1.69 – 1.63 (m, 1H), 1.54 – 1.42 (m, 1H), 1.22 – 1.09 (m, 1H).

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

δ 210.2, 150.2, 149.5, 145.9, 139.1, 135.8, 133.9, 132.8, 131.6, 129.6, 124.5, 118.3, 113.0, 47.5, 41.1, 39.7, 38.8, 30.8, 24.8.

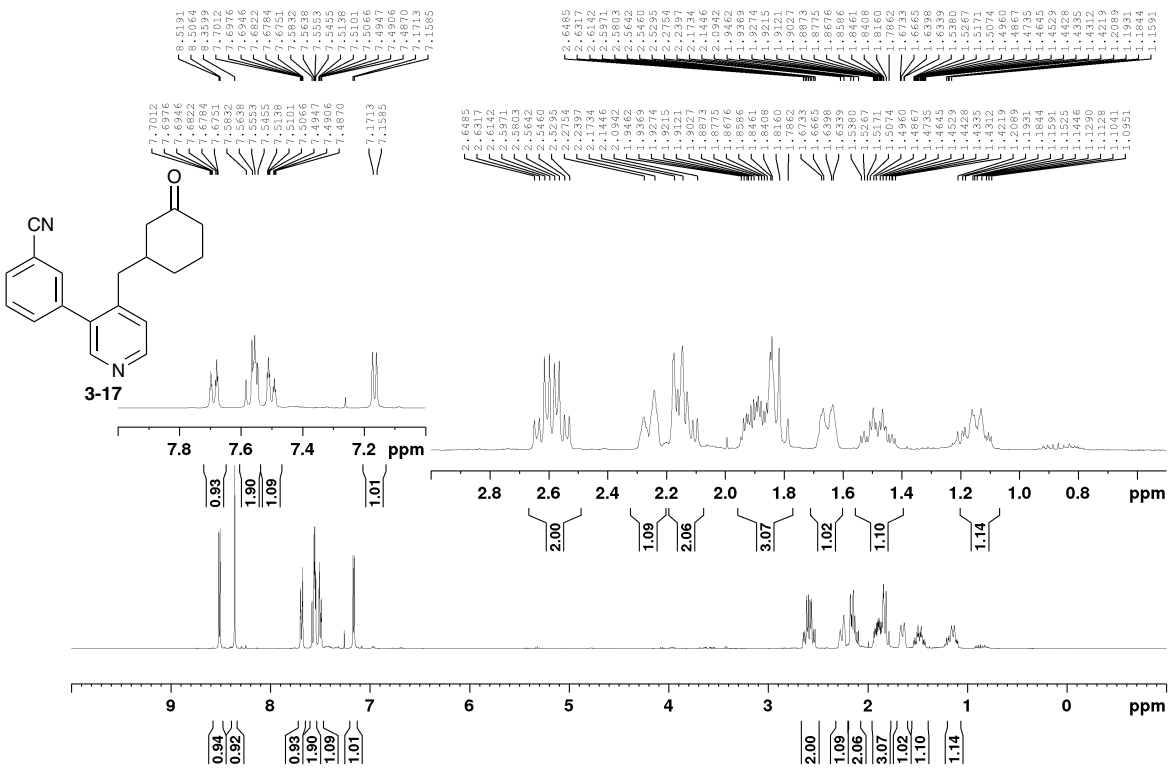
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3029, 2934, 2866, 2229, 1706, 1588, 799 cm^{-1}.

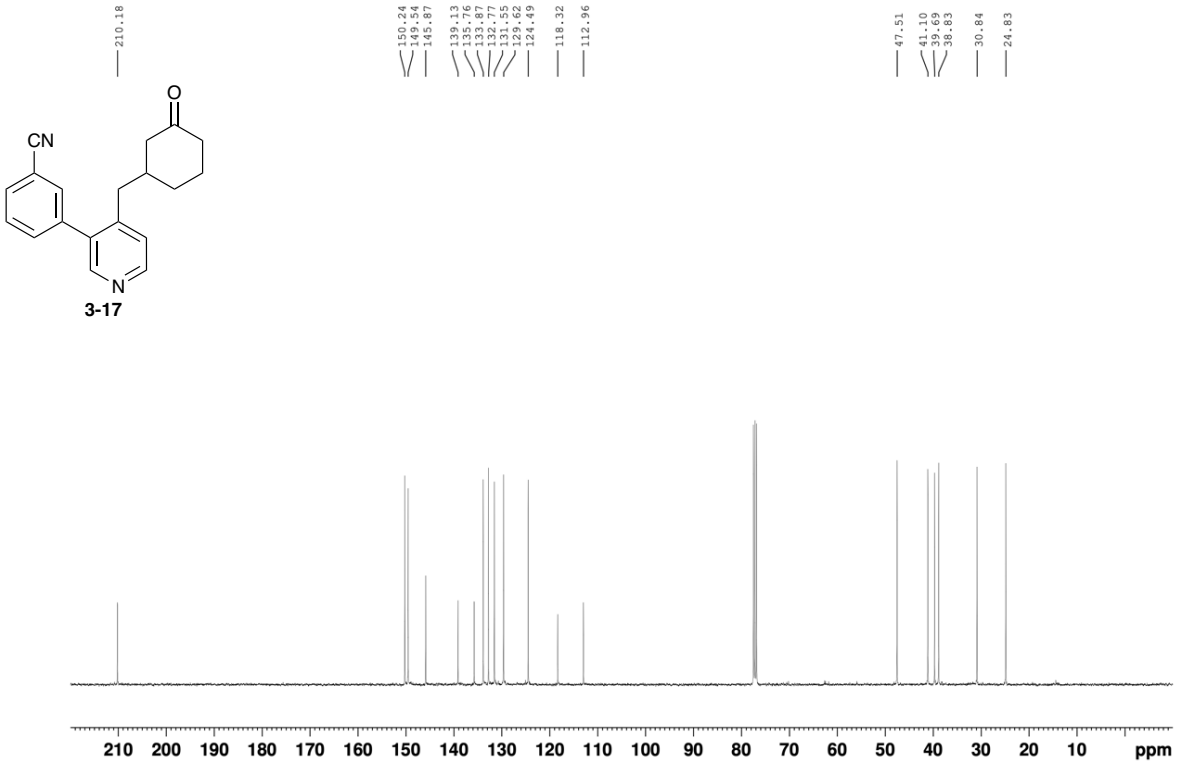
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{19}H_{19}N_2O$ 291.1492; Found 291.1497.

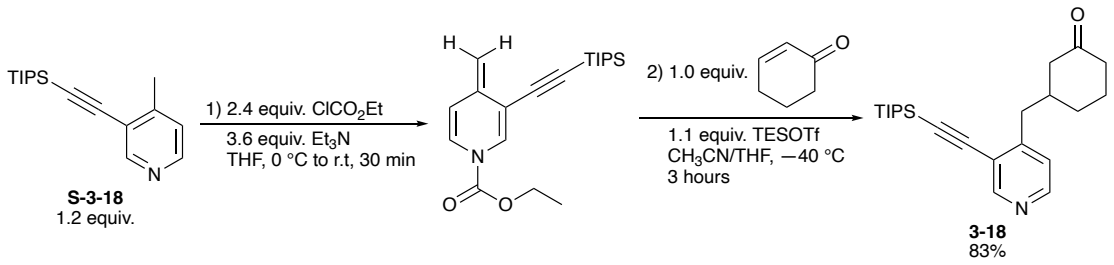
^1H NMR (400 MHz, $CDCl_3$) spectrum for **3-17**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-17**:



Synthesis of compound **3-18**:



By following the **general procedure A**, the corresponding ADHP was prepared using compound **S-3-18** (164.1 mg, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.1 mL, 1.0 equiv. 1.0 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford **3-18** as light-yellow oil (154 mg, 83% yield).

Chromatography: 30% EtOAc in Hexanes (R_f = 0.28).

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

δ 8.63 (s, 1H), 8.39 (d, *J* = 5.2 Hz, 1H), 7.03 (d, *J* = 5.2 Hz, 1H), 2.86 (dd, *J* = 12.8, 7.2 Hz, 1H), 2.73 (dd, *J* = 12.8, 7.2 Hz, 1H), 2.39 – 2.29 (m, 2H), 2.29 – 2.18 (m, 2H), 2.13 – 1.98 (m, 2H), 1.89 – 1.80 (m, 1H), 1.65 – 1.52 (m, 1H), 1.47 – 1.36 (m, 1H), 1.17 – 1.06 (m, 21H).

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

δ 210.5, 153.7, 150.1, 148.5, 124.2, 120.8, 102.2, 98.6, 47.7, 41.4, 41.0, 39.3, 31.2, 25.0, 18.8, 11.3.

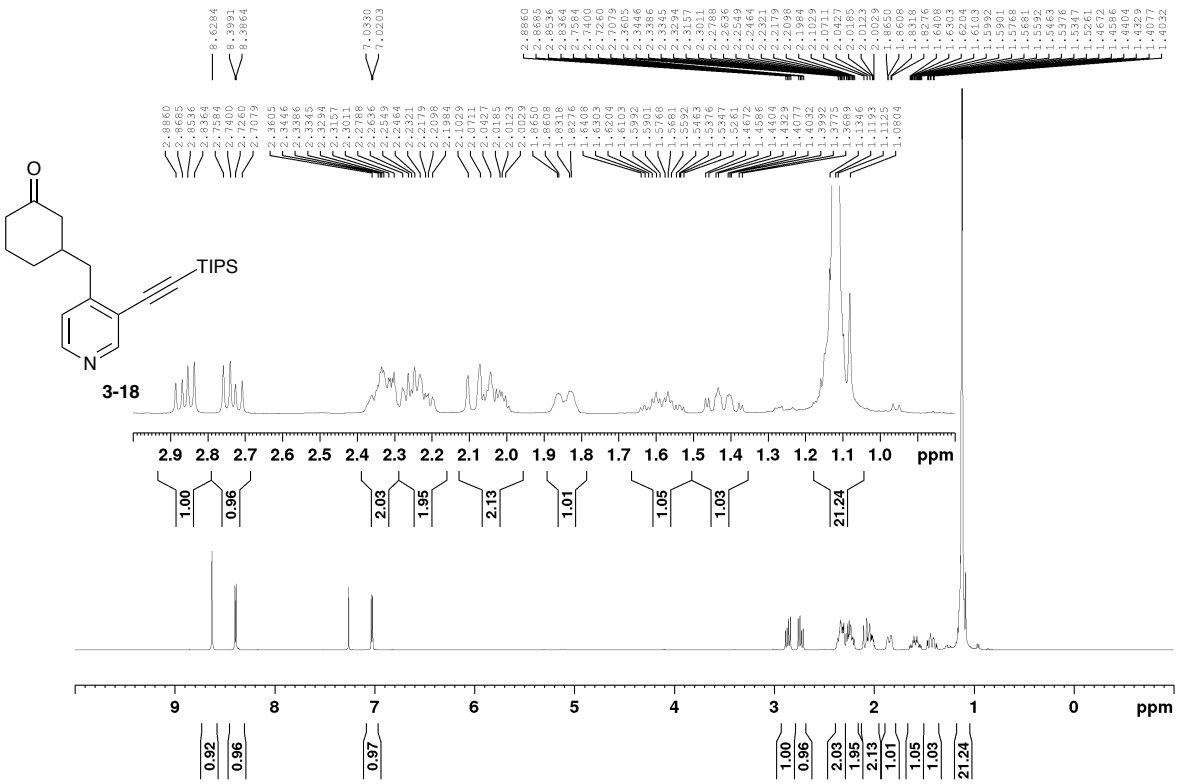
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3037, 2941, 2864, 2155, 1712, 1584, 1462, 1225 cm^{-1}.

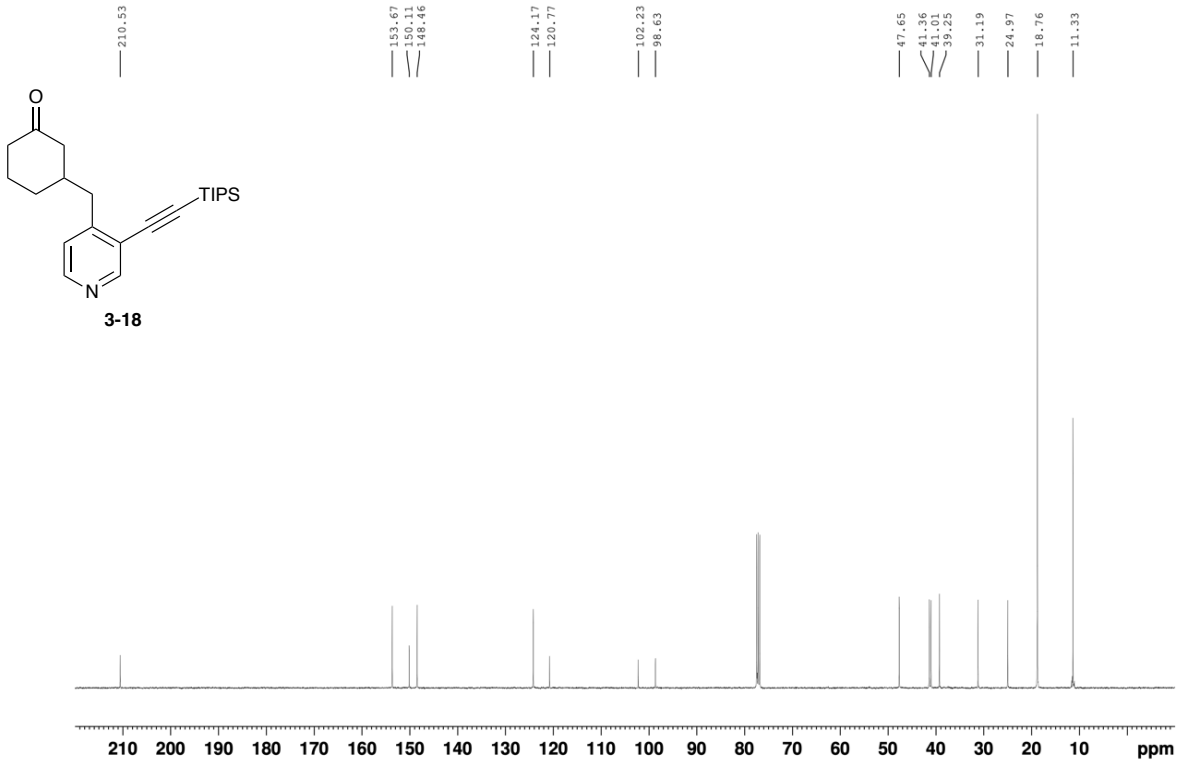
HRMS ESI-OTF

$(M+H)^+$ Calcd for $C_{23}H_{36}NOSi$ 370.2561; Found 370.2652.

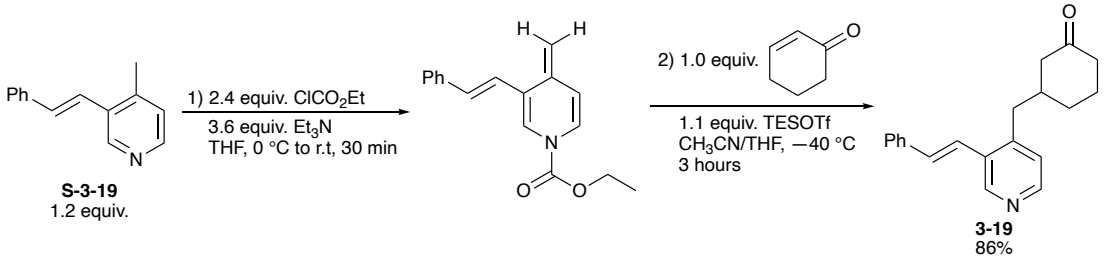
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-18**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-18**:



Synthesis of compound **3-19**:



By following the **general procedure A**, the corresponding ADHP was prepared using compound **S-3-19** (47 mg, 1.2 equiv., 0.24 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohexen-1-one (0.02 mL, 1.0 equiv. 0.2 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-19** as light-yellow oil (50 mg, 86% yield).

Chromatography: 50% EtOAc in Hexanes with 2% Et_3N (R_f = 0.29).

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

δ 8.78 (s, 1H), 8.41 (d, *J* = 4.8 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.44 – 7.37 (m, 2H), 7.34 – 7.29 (m, 1H), 7.23 – 7.17 (m, 1H), 7.07 – 7.02 (m, 2H), 2.81 – 2.69 (m, 2H), 2.44 – 2.33 (m, 2H), 2.33 – 2.22 (m, 1H), 2.17 – 2.08 (m, 2H), 2.08 – 2.00 (m, 1H), 1.91 – 1.83 (m, 1H), 1.68 – 1.55 (m, 1H), 1.48 – 1.38 (m, 1H).

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

δ 210.7, 148.4, 147.9, 145.6, 136.9, 132.8, 132.7, 129.0, 128.4, 126.9, 124.9, 122.8, 47.9, 41.4, 39.7, 39.6, 31.2, 25.0.

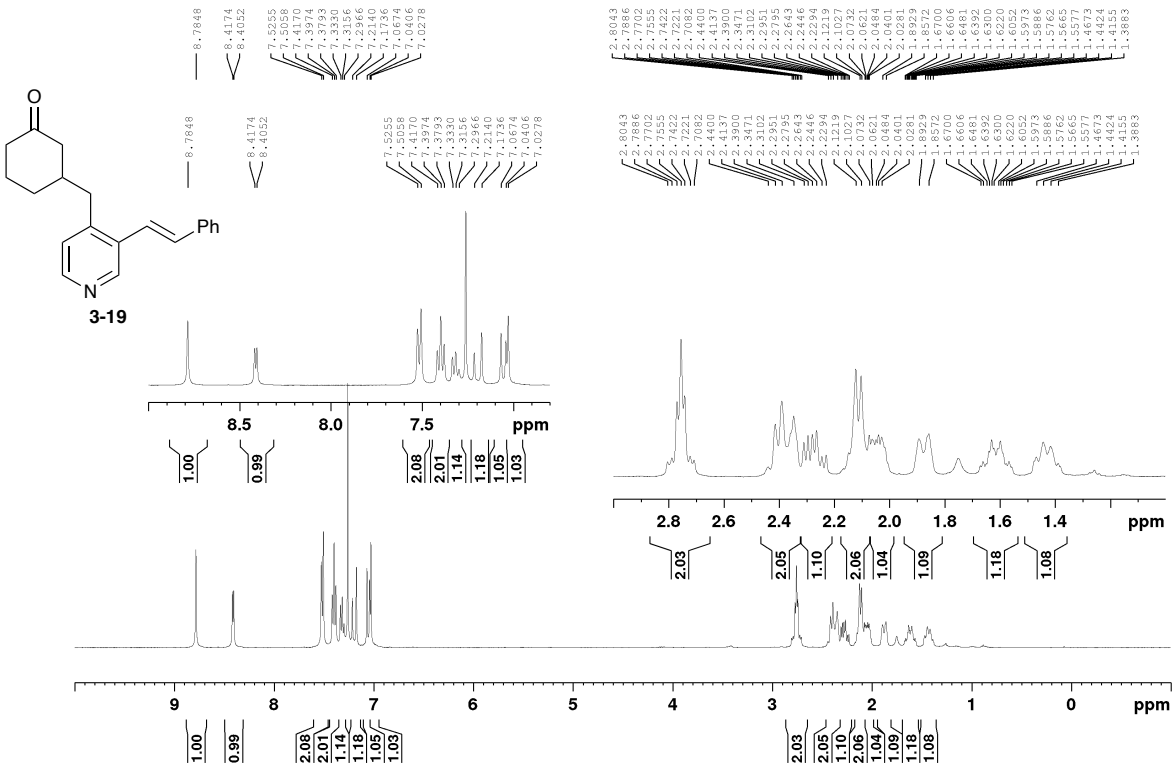
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3024, 2932, 2870, 1706, 1586, 1448, 963 cm^{-1}.

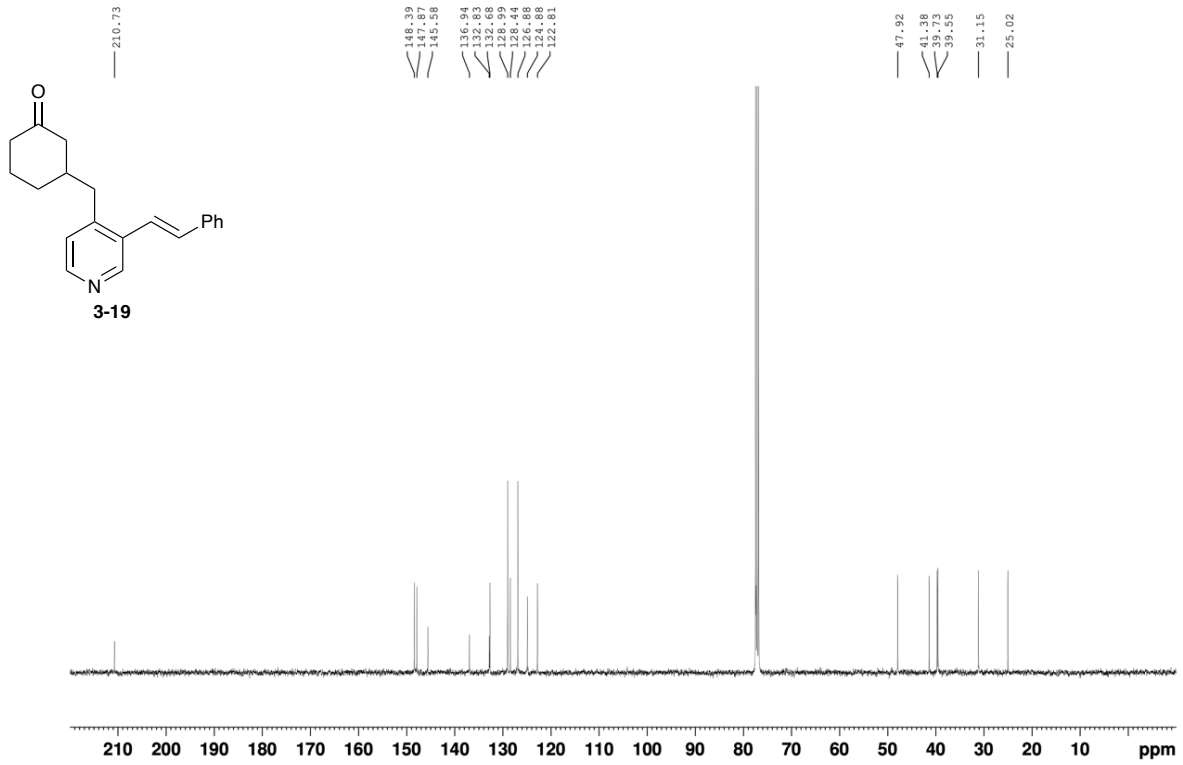
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{20}H_{22}NO$ 292.1696; Found 292.1699.

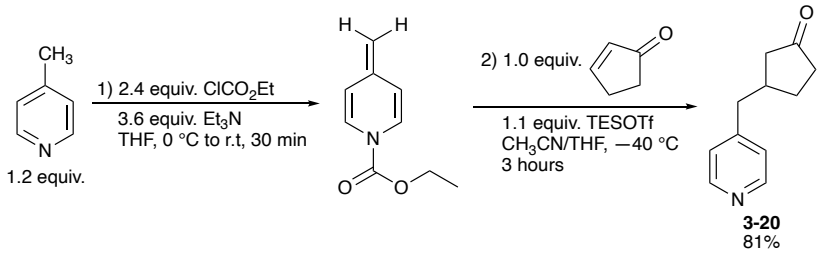
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-19**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-19**:



Synthesis of compound **3-20**:



By following the **general procedure A**, the corresponding ADHP was prepared from 4-picoline (0.12 mL, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclopenten-1-one (0.09 mL, 1.0 equiv. 1.0 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-20** as light-yellow oil (141 mg, 81% yield).

Chromatography: 50% EtOAc in Hexanes with 2% Et_3N. (R_f = 0.24).

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

δ 8.52 (d, *J* = 6.0 Hz, 2H), 7.10 (d, *J* = 6.0 Hz, 2H), 2.80 – 2.68 (m, 2H), 2.55 – 2.42 (m, 1H), 2.39 – 2.27 (m, 2H), 2.22 – 2.08 (m, 2H), 1.94 – 1.86 (m, 1H), 1.67 –1.55 (m, 1H).

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

δ 218.2, 150.0, 149.0, 124.3, 44.9, 41.0, 38.3, 38.0, 29.2.

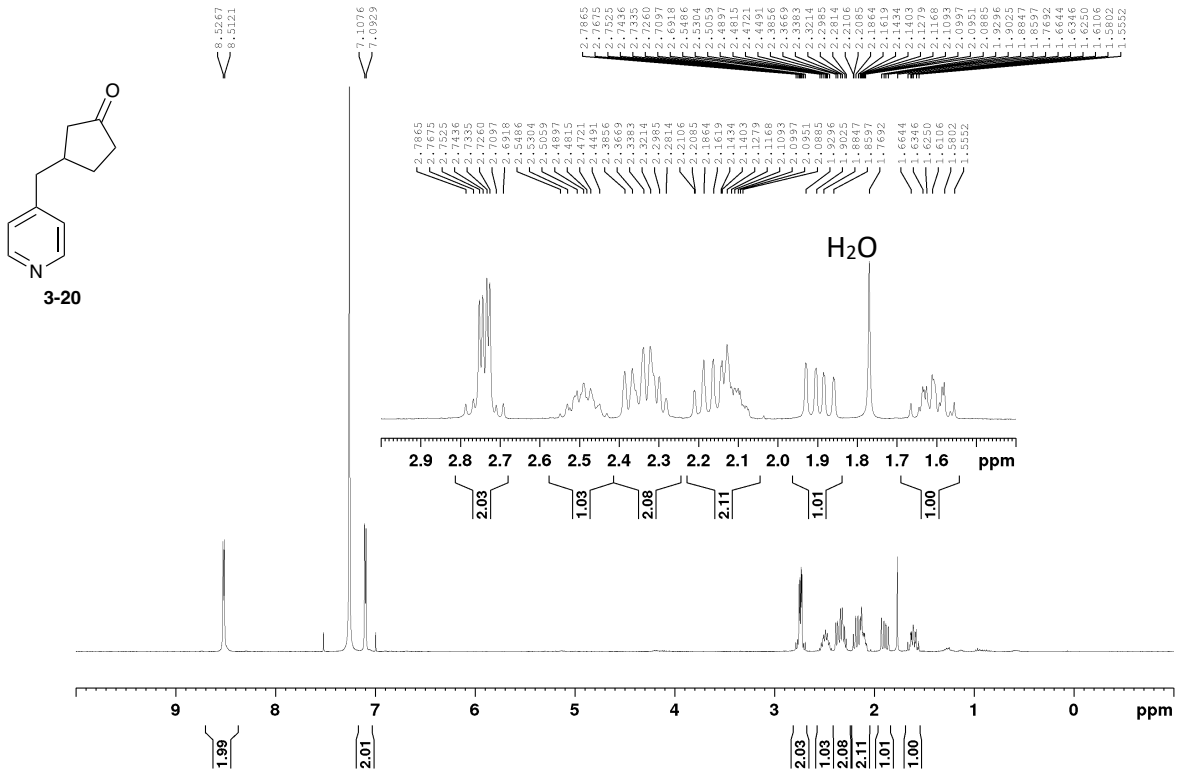
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3024, 2960, 2928, 1735, 1601, 1415 cm^{-1}.

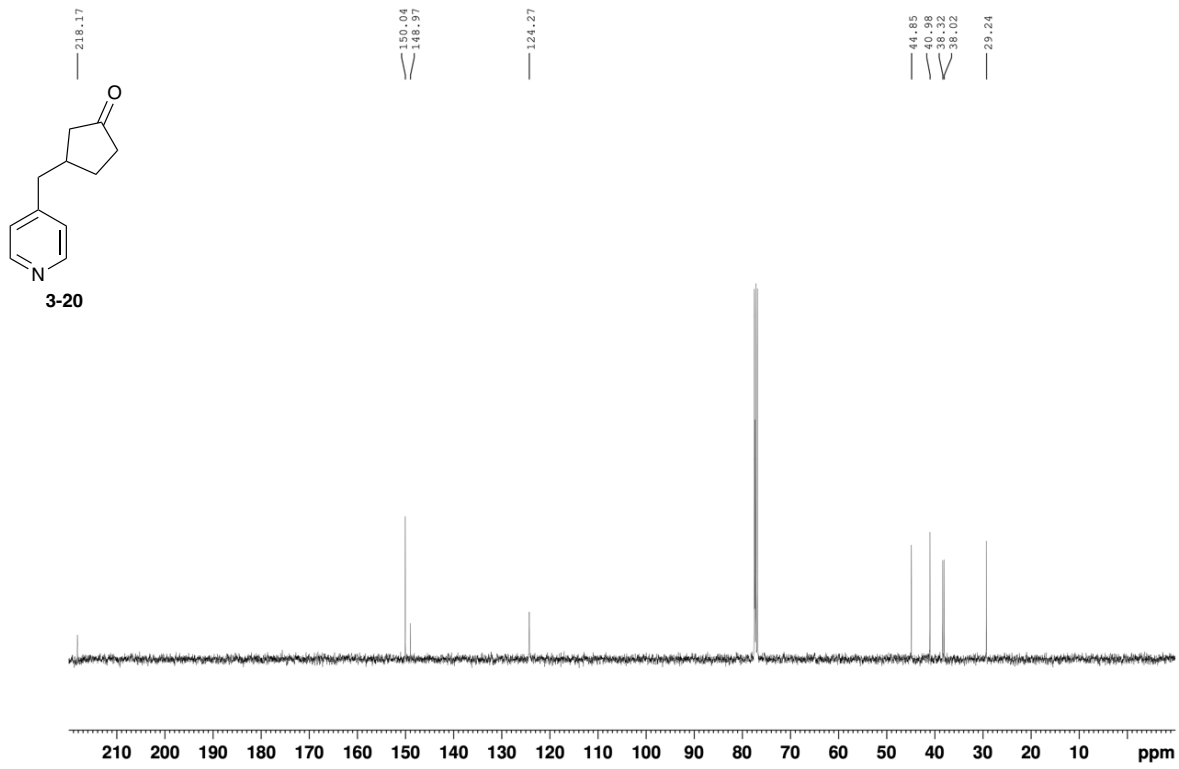
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{11}H_{14}NO$ 176.1070; Found 176.1077.

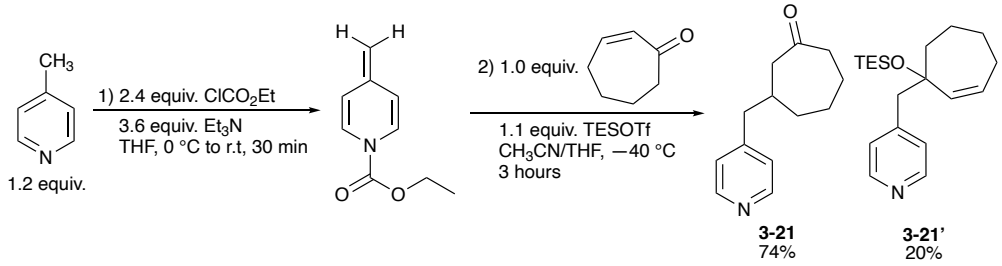
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-20**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-20**:



Synthesis of compounds **3-21** and **3-21'**:



By following the **general procedure A**, the corresponding ADHP was prepared using 4-picoline (0.23 mL, 1.2 equiv., 2.4 mmol). The final products were synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Cyclohepten-1-one (0.22 mL, 1.0 equiv. 2.0 mmol) was used as the electrophile. The resulting mixture was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-21** as light-yellow oil (304 mg, 74% yield) alongside 1,2-addition product **3-21'** as colorless oil (127 mg, 20% yield).

Data for 1,4-addition product **3-21**:

Chromatography: 50% EtOAc in Hexanes with 2% Et_3N (R_f = 0.27).

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

δ 8.45 (d, *J* = 6.0 Hz, 2H), 7.03 (d, *J* = 6.0 Hz, 2H), 2.59 – 2.48 (m, 2H), 2.48 – 2.33 (m, 4H), 2.04 – 1.92 (m, 1H), 1.89 – 1.76 (m, 3H), 1.62 – 1.50 (m, 1H), 1.38 – 1.17 (m, 2H).

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

δ 213.5, 149.9, 148.9, 124.6, 49.5, 44.0, 42.9, 37.1, 36.4, 28.4, 24.3.

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3021, 2925, 2856, 1695, 1600, 1414 cm^{-1}.

HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{13}H_{18}NO$ 204.1383; Found 204.1394.

Data for 1,2-addition product **3-21'**:

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

δ 8.44 (d, J = 5.2 Hz, 2H), 7.16 (d, J = 5.2 Hz, 2H), 5.68 – 5.60 (m, 1H),

5.45 – 5.41 (m, 1H), 2.88 (d, J = 12.8 Hz, 1H), 2.73 (d, J = 12.8 Hz, 1H),

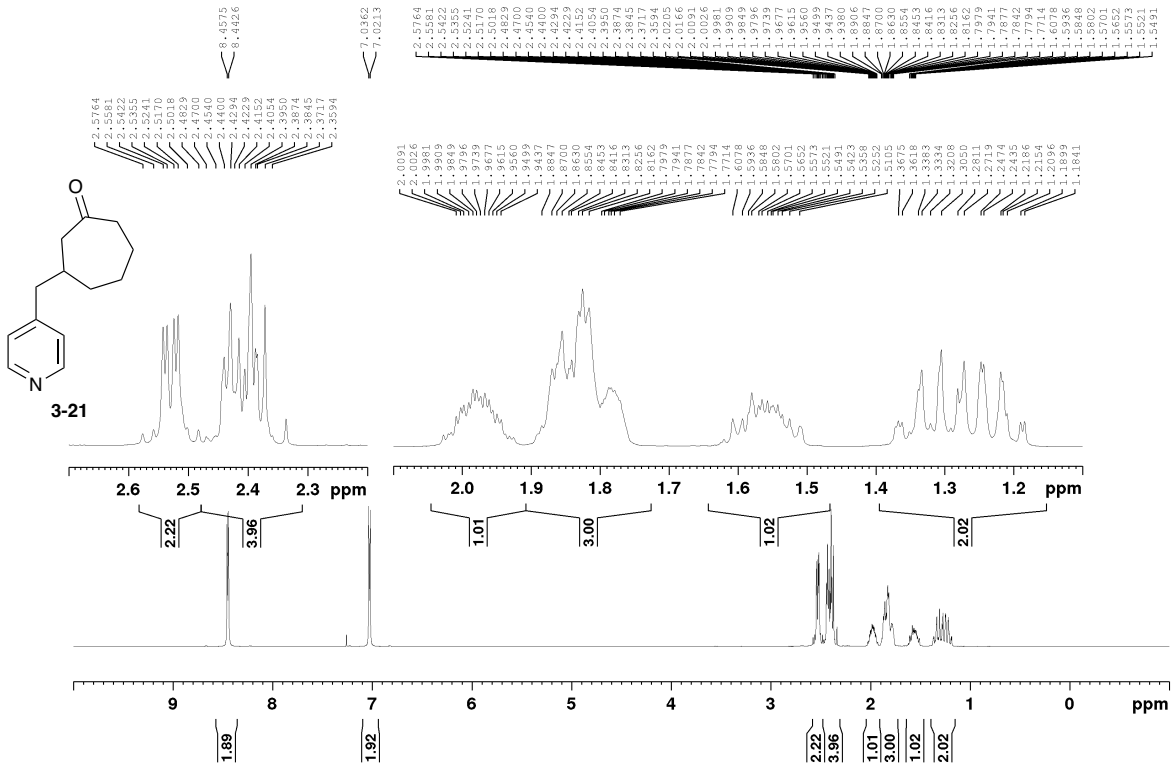
2.26 – 2.17 (m, 1H), 2.17 – 2.04 (m, 1H), 1,83 – 1.68 (m, 4H),

1.68 – 1.48 (m, 2H), 0.85 (t, J = 8.0 Hz, 9H), 0.52 (q, J = 8.0 Hz, 6H).

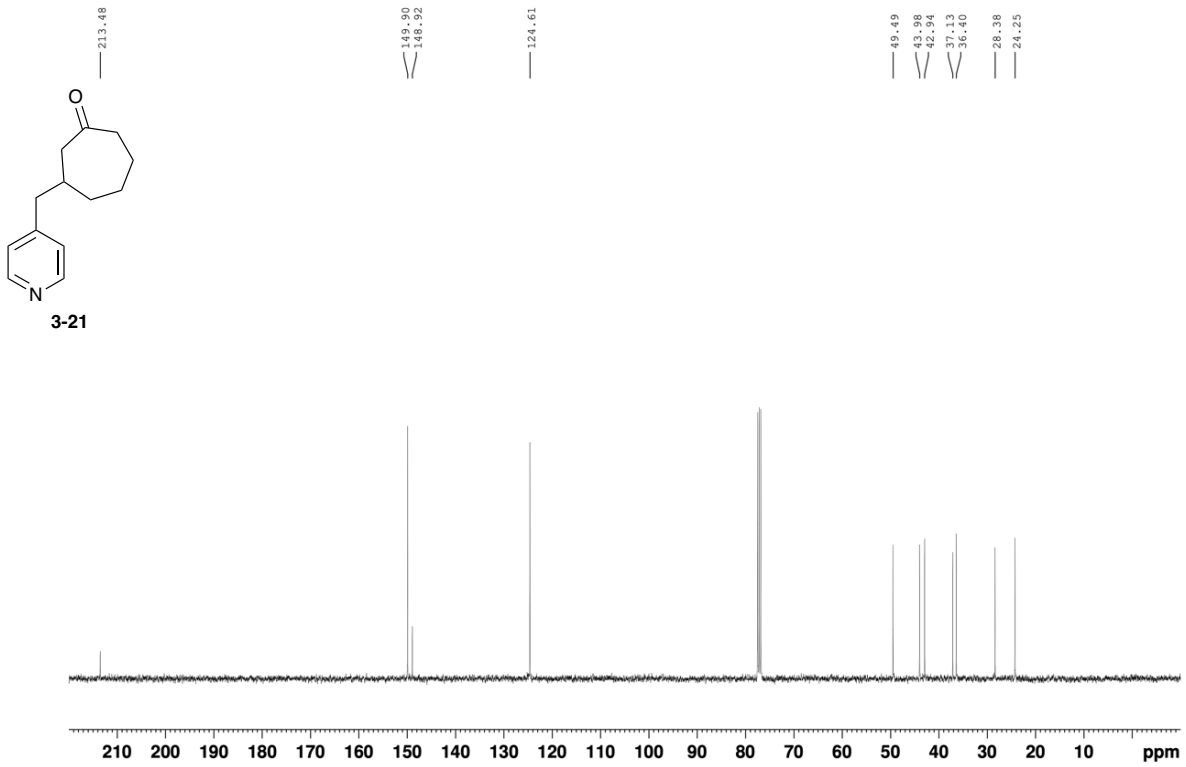
^{13}C NMR (100 MHz, $CDCl_3$)

δ 148.9, 147.3, 139.9, 128.7, 126.6, 79.2, 46.5, 39.9, 28.1, 27.6, 24.5, 7.2, 6.8.

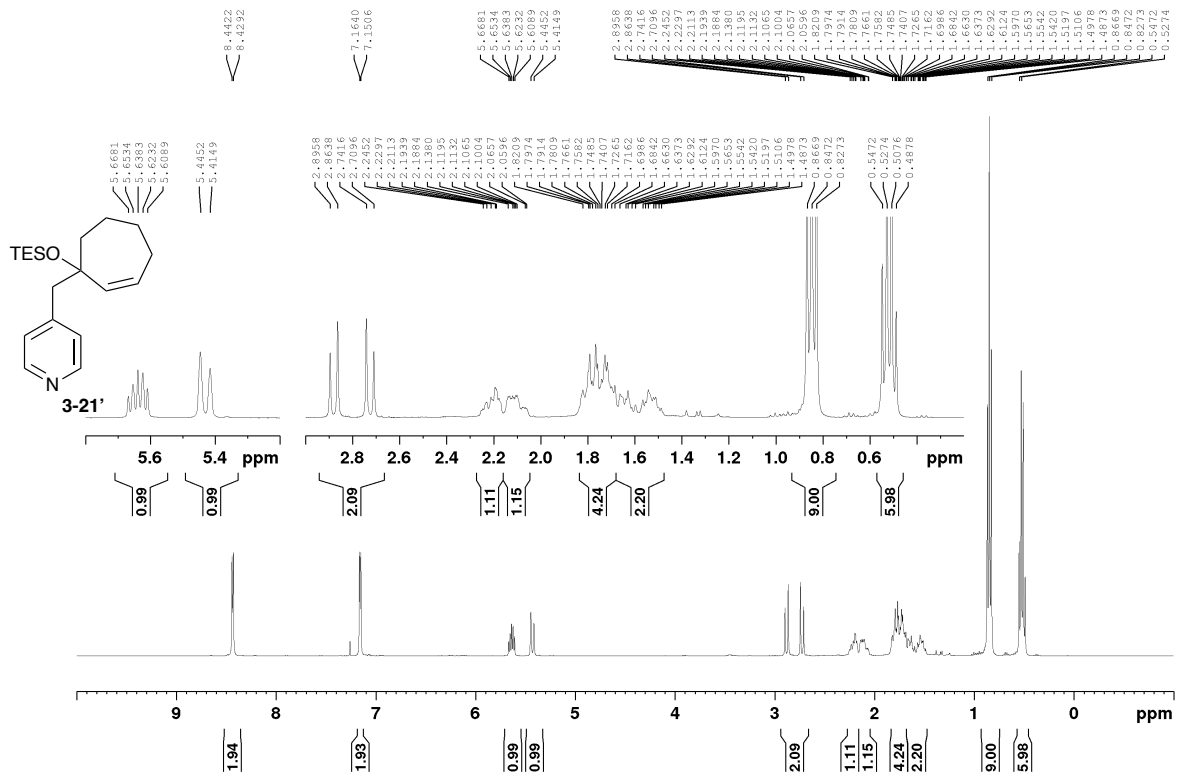
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-21**:



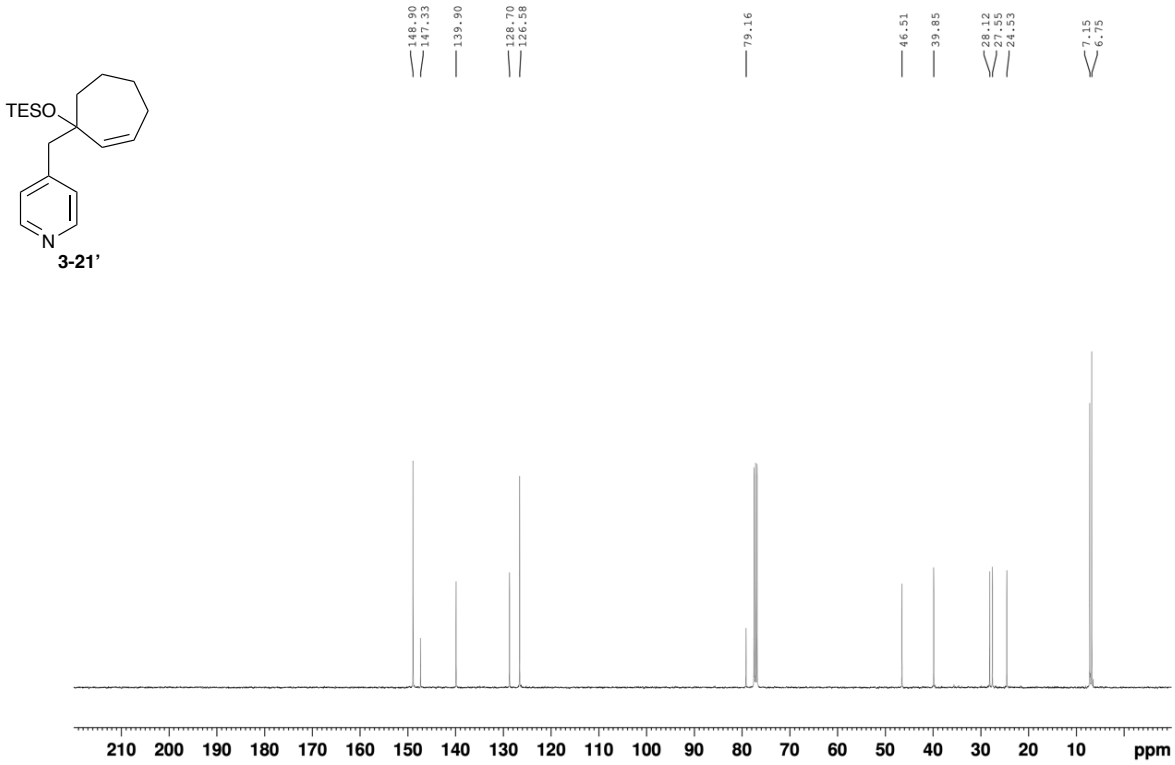
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-21**:



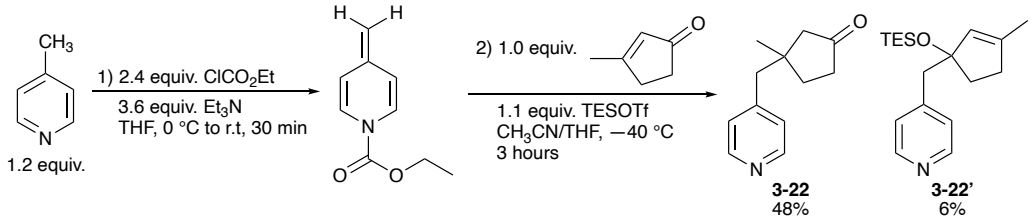
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-21'**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-21'**:



Synthesis of compounds **3-22** and **3-22'**:



By following the **general procedure A**, the corresponding ADHP was prepared using 4-picoline (0.12 mL, 1.2 equiv., 1.2 mmol). The final products were synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 3-Methyl-2-cyclopenten-1-one (0.1 mL, 1.0 equiv. 1.0 mmol) was used as the electrophile. The resulting mixture was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound **3-22** as light-yellow oil (92 mg, 48% yield) alongside 1,2-addition product **3-22'** as colorless oil (19 mg, 6% yield).

Data for 1,4-addition product **3-22**:

Chromatography: 50% EtOAc in Hexanes with 2% Et_3N (R_f = 0.24).

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

δ 8.51 (d, *J* = 6.0 Hz, 2H), 7.05 (d, *J* = 6.0 Hz, 2H), 2.73 – 2.64 (m, 2H), 2.32 – 2.27 (m, 2H), 2.21 – 2.15 (m, 1H), 2.03 – 1.96 (m, 1H), 1.95 – 1.86 (m, 1H), 1.79 – 1.71 (m, 1H), 1.02 (s, 3H).

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

δ 218.1, 149.6, 146.9, 125.4, 51.6, 46.7, 40.3, 36.4, 34.7, 25.2.

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3026, 2957, 2928, 1735, 1599, 1415 cm^{-1}.

HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{12}H_{16}NO$ 190.1227; Found 190.1238.

Data for 1,2-addition product **3-22'**:

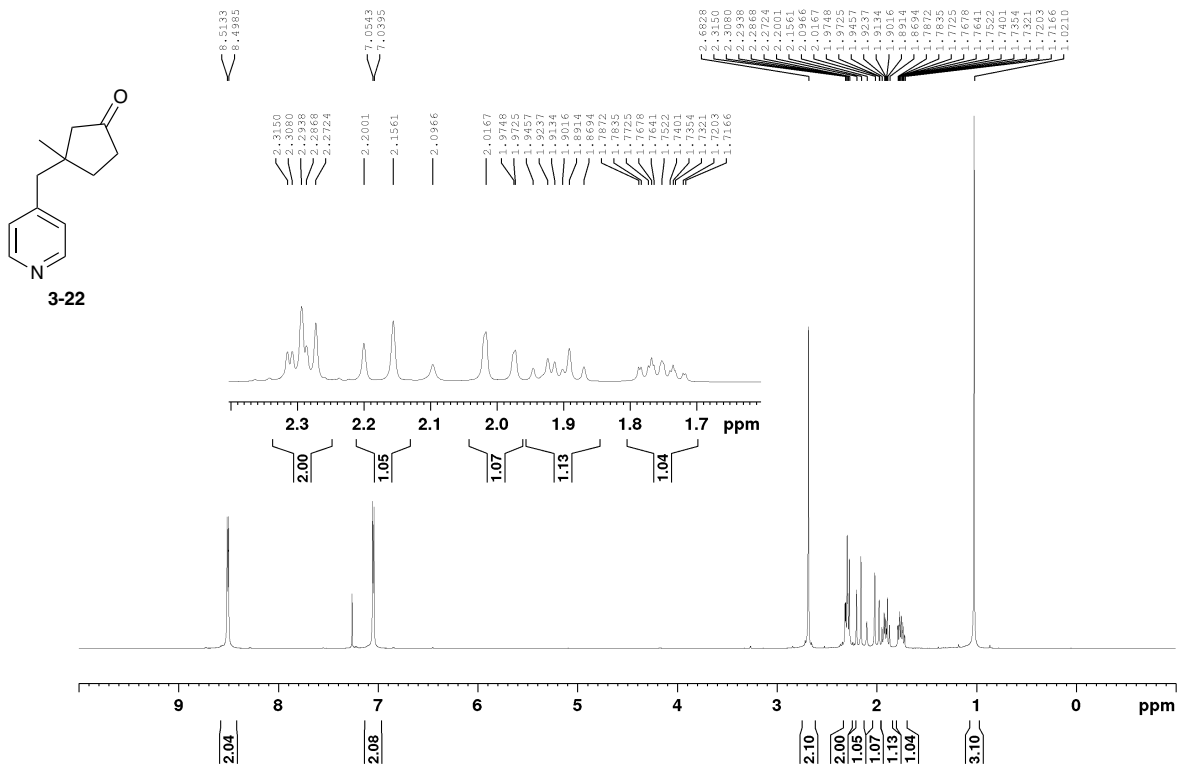
^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.45 (d, J = 6.0 Hz, 2H), 7.15 (d, J = 6.0 Hz, 2H), 5.26– 5.23 (m, 1H), 2.83 (d, J = 12.8 Hz, 1H), 2.78 (d, J = 12.8 Hz, 1H), 2.36 – 2.26 (m, 1H), 2.11 – 1.99 (m, 2H), 1.91 – 1.82 (m, 1H), 1.71 (s, 3H), 0.85 (t, J = 8.0 Hz, 9H), 0.46 (q, J = 8.0 Hz, 6H).

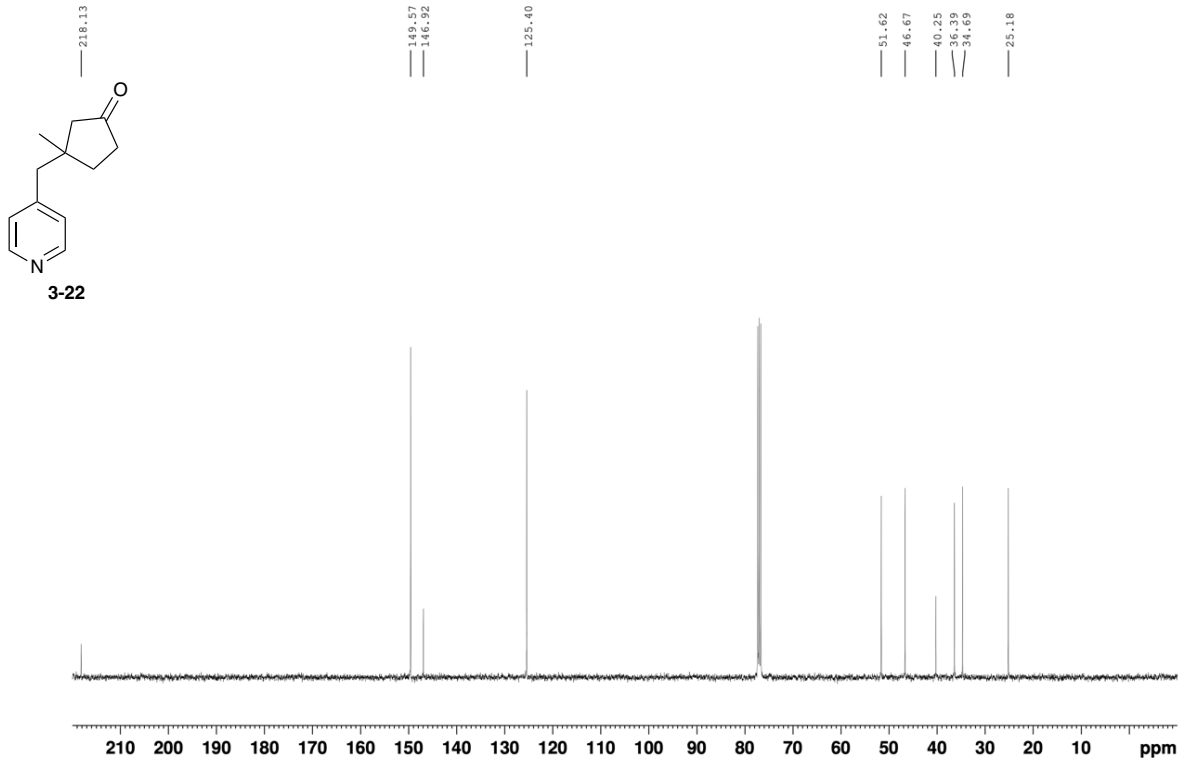
^{13}C NMR (100 MHz, $CDCl_3$)

δ 149.1, 147.9, 143.6, 130.5, 126.2, 87.8, 48.7, 39.2, 35.3, 16.9, 7.1, 6.4.

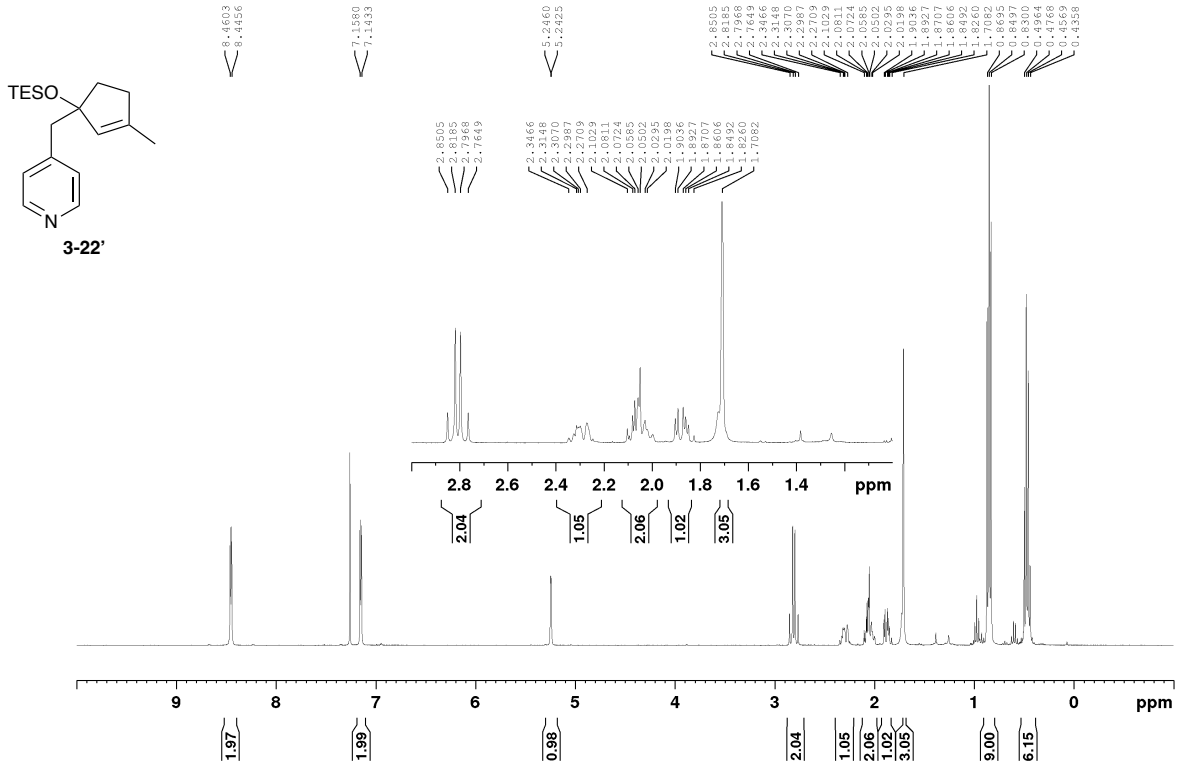
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-22**:



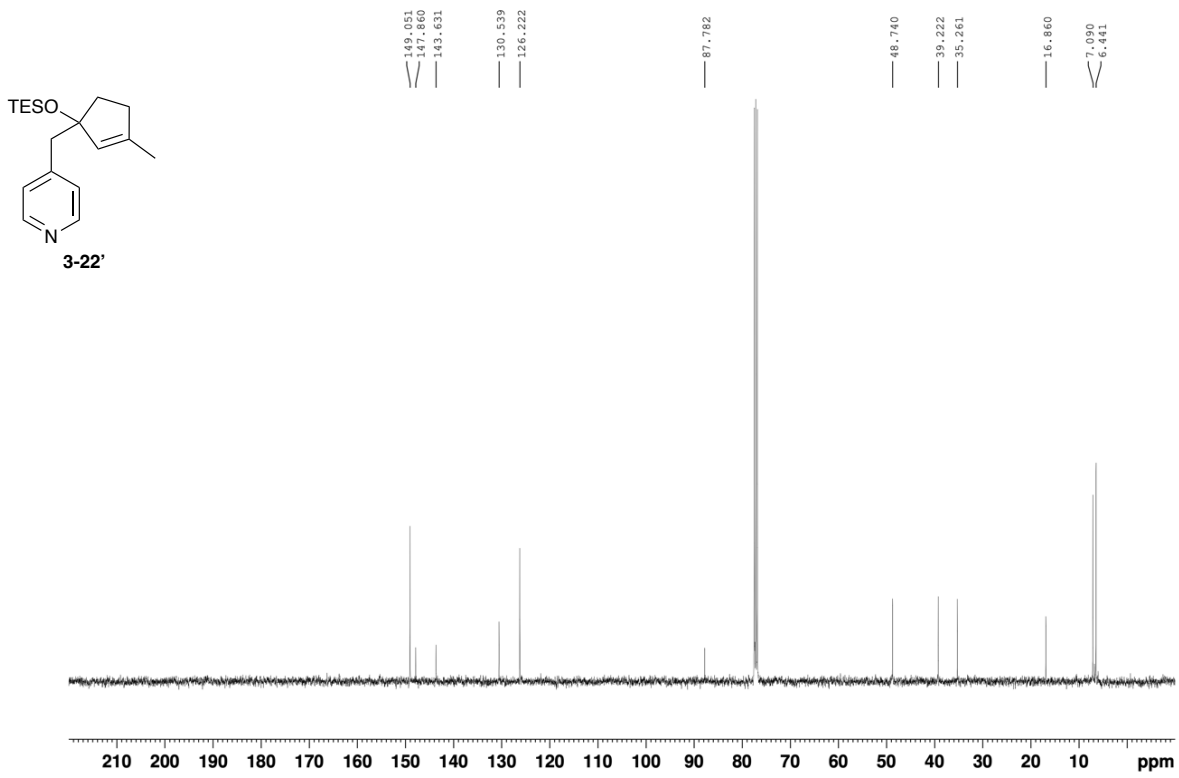
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-22**:



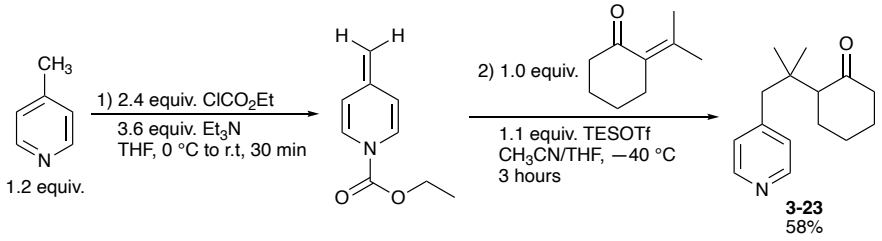
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-22'**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-22'**:



Synthesis of compound **3-23**:



By following the **general procedure A**, the corresponding ADHP was prepared using 4-picoline (0.12 mL, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. 2-Isopropylidene-cyclohexanone (0.15 mL, 1.0 equiv. 1.0 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford compound **3-23** as colorless oil (129 mg, 58% yield).

Chromatography: 70% EtOAc in Hexanes (R_f = 0.37).

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

δ 8.46 (d, *J* = 6.0 Hz, 2H), 7.02 (d, *J* = 6.0 Hz, 2H), 3.02 (d, *J* = 12.8 Hz, 1H), 2.58 (d, *J* = 12.8 Hz, 1H), 2.37 – 2.30 (m, 1H), 2.29 – 2.21 (m, 1H), 2.21 – 2.13 (m, 1H), 2.10 – 2.02 (m, 2H), 1.95 – 1.88 (m, 1H), 1.75 – 1.61 (m, 1H), 1.61 – 1.45 (m, 2H), 1.03 (s, 3H), 0.92 (s, 3H).

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

δ 213.1, 149.4, 148.5, 126.1, 58.0, 45.0, 44.5, 35.9, 29.7, 28.8, 26.1, 26.0, 24.2.

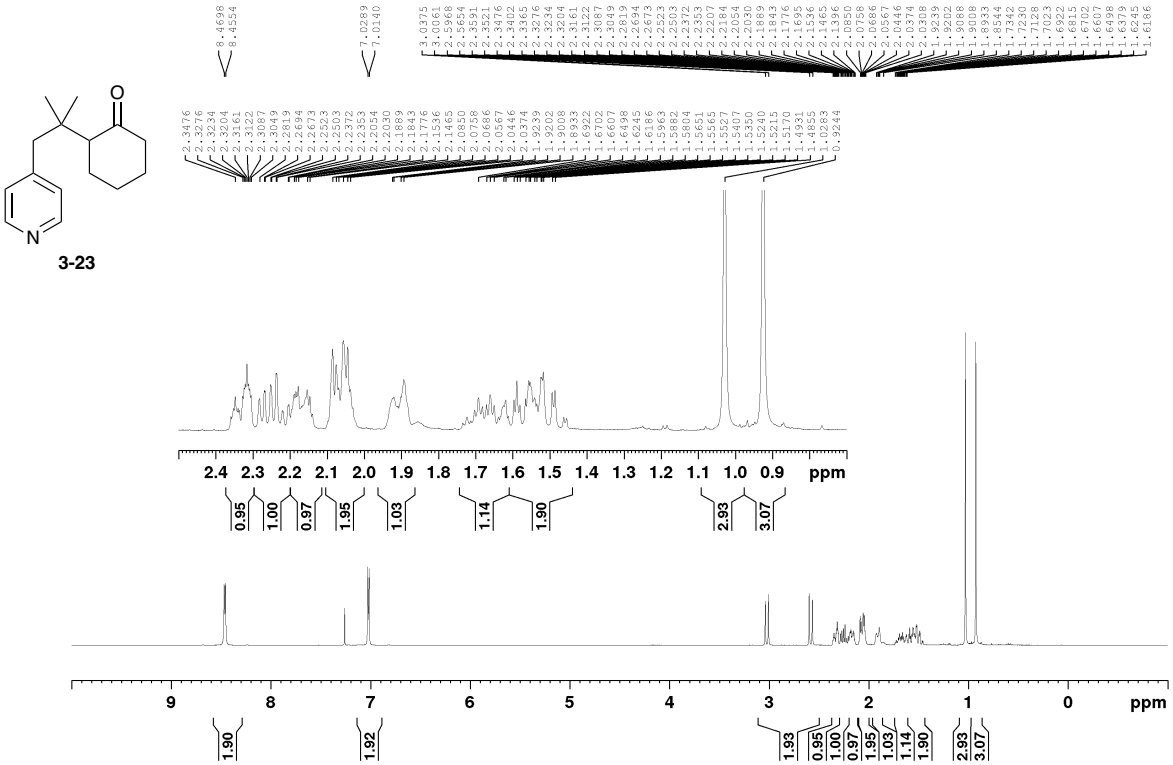
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3024, 2935, 2866, 1703, 1598, 1448 cm^{-1}.

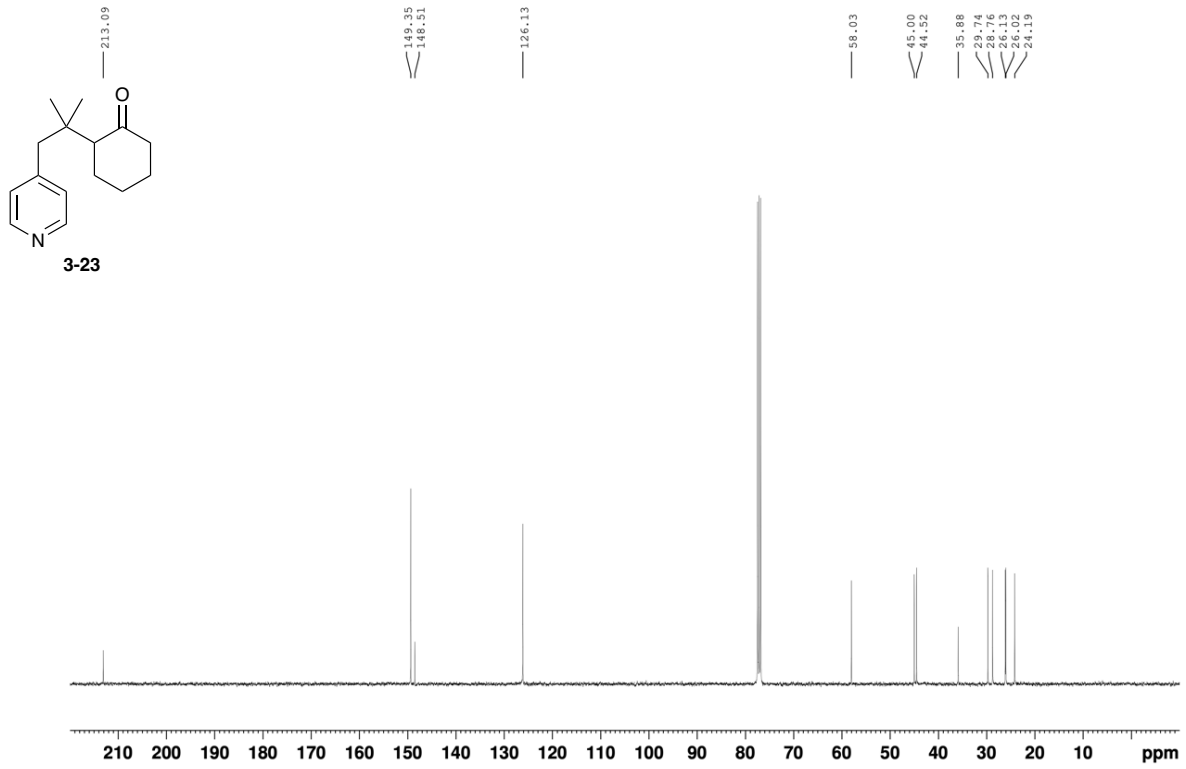
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{15}H_{22}NO$ 232.1696; Found 232.1703.

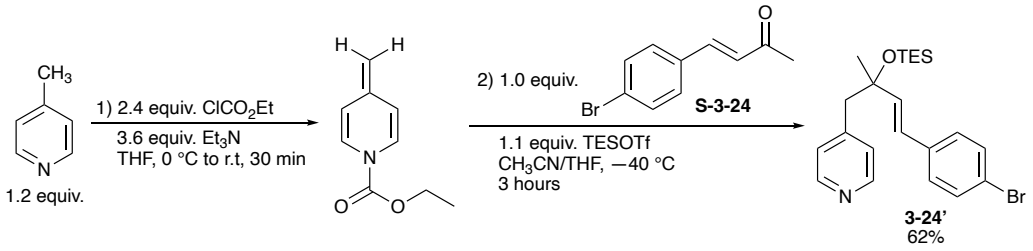
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-23**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-23**:



Synthesis of compound **3-24'**:



By following the **general procedure A**, the corresponding ADHP was prepared using 4-picoline (0.12 mL, 1.2 equiv., 1.2 mmol). The final product was synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. Compound **S-3-24** (225.1 mg, 1.0 equiv. 1.0 mmol) was used as the electrophile. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford product **3-24'** as colorless oil (270 mg, 62% yield).

Chromatography: 30% EtOAc in Hexanes (R_f = 0.36).

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

δ 8.47 (d, *J* = 6.0 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 6.0 Hz, 2H), 6.34 (d, *J* = 16.2 Hz, 1H), 6.17 (d, *J* = 16.2 Hz, 1H), 2.82 (s, 2H), 1.43 (s, 3H), 0.89 (t, *J* = 7.8 Hz, 9H), 0.55 (q, *J* = 7.8 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$)

δ 149.2, 146.7, 137.1, 135.9, 131.9, 128.0, 126.9, 126.4, 121.5, 74.9, 50.5, 27.1, 7.2, 6.8.

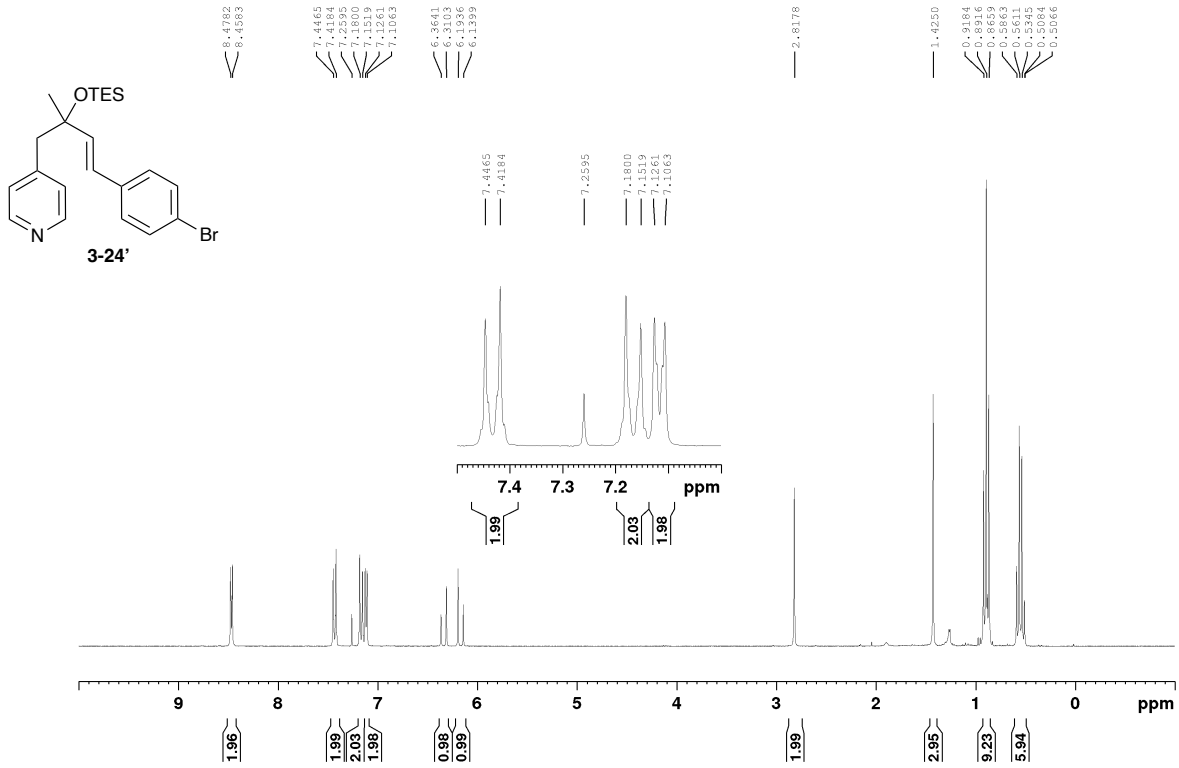
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3027, 2953, 2874, 1599, 1005, 788 cm^{-1}.

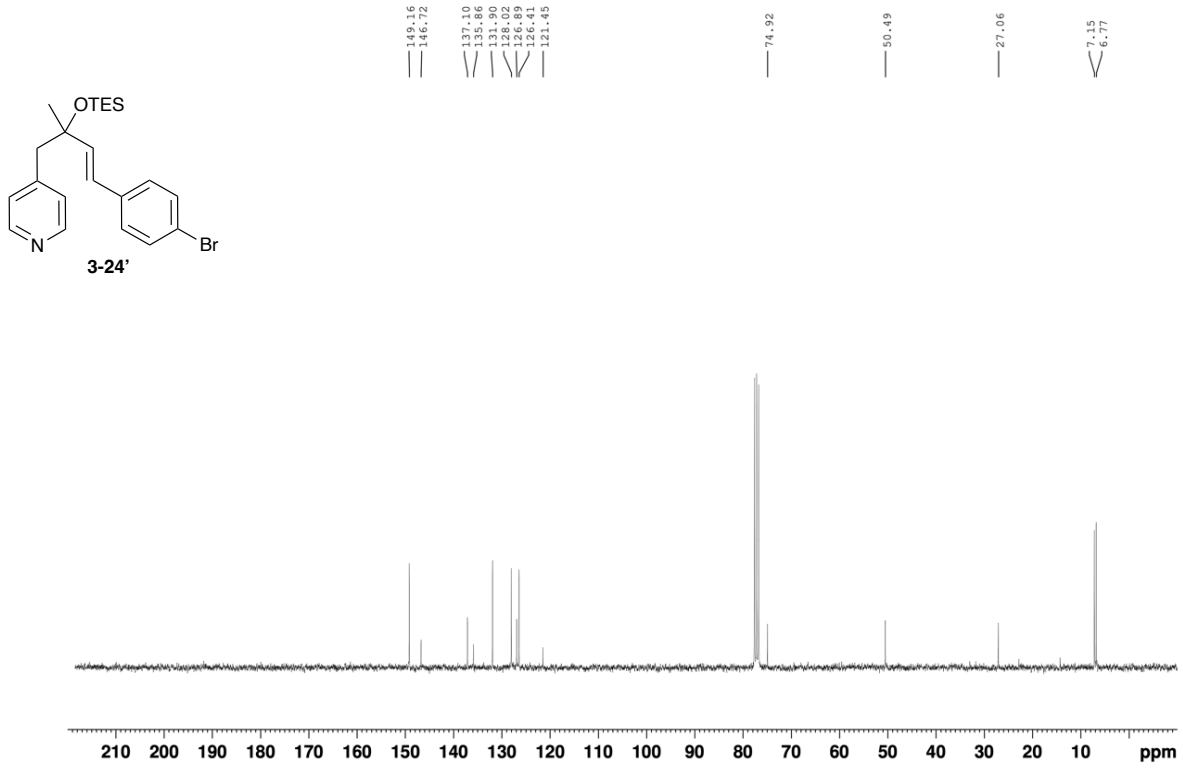
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{22}H_{31}BrNOSi$ 432.1353; Found 432.1379.

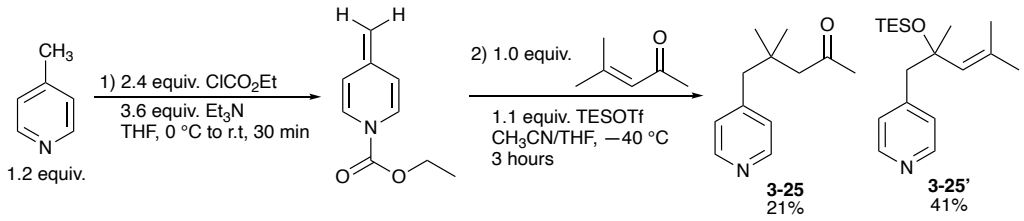
^{1}H NMR (300 MHz, $CDCl_3$) spectrum for **3-24'**:



^{13}C NMR (75 MHz, $CDCl_3$) spectrum for **3-24'**:



Synthesis of compounds **3-25** and **3-25'**:



By following the **general procedure A**, the corresponding ADHP was prepared using 4-picoline (0.12 mL, 1.2 equiv., 1.2 mmol). The final products were synthesized by following the **general procedure B** but using THF (0.2 M) to dissolve the ADHP instead of CH_3CN. Mesityl oxide (0.12 mL, 1.0 equiv. 1.0 mmol) was used as the electrophile. The resulting mixture was purified by flash column chromatography with EtOAc/Hexanes/Et_3N to afford compound 1,4-addition product **3-25** as colorless oil (41 mg, 21% yield) alongside 1,2-addition product **3-25'** as colorless oil (126 mg, 41% yield).

Data for 1,4-addition product **3-25**:

Chromatography: 50% EtOAc in Hexanes with 2% Et_3N (R_f = 0.33).

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

δ 8.47 (d, J = 5.6 Hz, 2H), 7.05 (d, J = 5.6 Hz, 2H), 2.70 (s, 2H), 2.27 (s, 2H), 2.11 (s, 3H), 1.00 (s, 6H).

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

δ 208.5, 149.5, 147.9, 126.1, 52.9, 46.6, 34.4, 32.5, 27.6.

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3069, 3024, 2960, 2929, 1709, 1600, 1416 cm^{-1}.

HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{12}H_{18}NO$ 192.1383; Found 192.1390.

Data for 1,2-addition product **3-25'**:

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

δ 8.41 (d, J = 6.0 Hz, 2H), 7.09 (d, J = 6.0 Hz, 2H), 5.16 – 5.14 (m, 1H),

2.86 (d, J = 12.8 Hz, 1H), 2.71 (d, J = 12.8 Hz, 1H), 1.68 (d, J = 1.2 Hz, 3H),

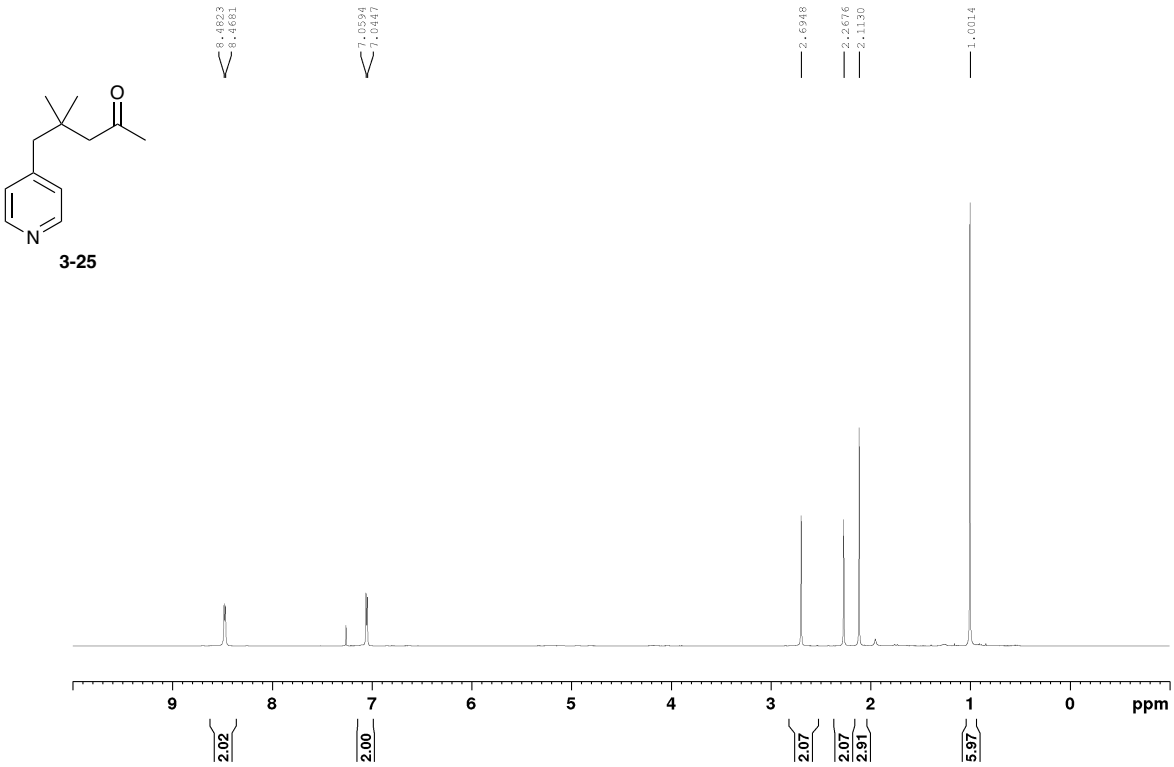
1.64 (d, J = 1.2 Hz, 3H), 1.26 (s, 3H), 0.85 (t, J = 8.0 Hz, 9H),

0.50 (q, J = 8.0 Hz, 6H).

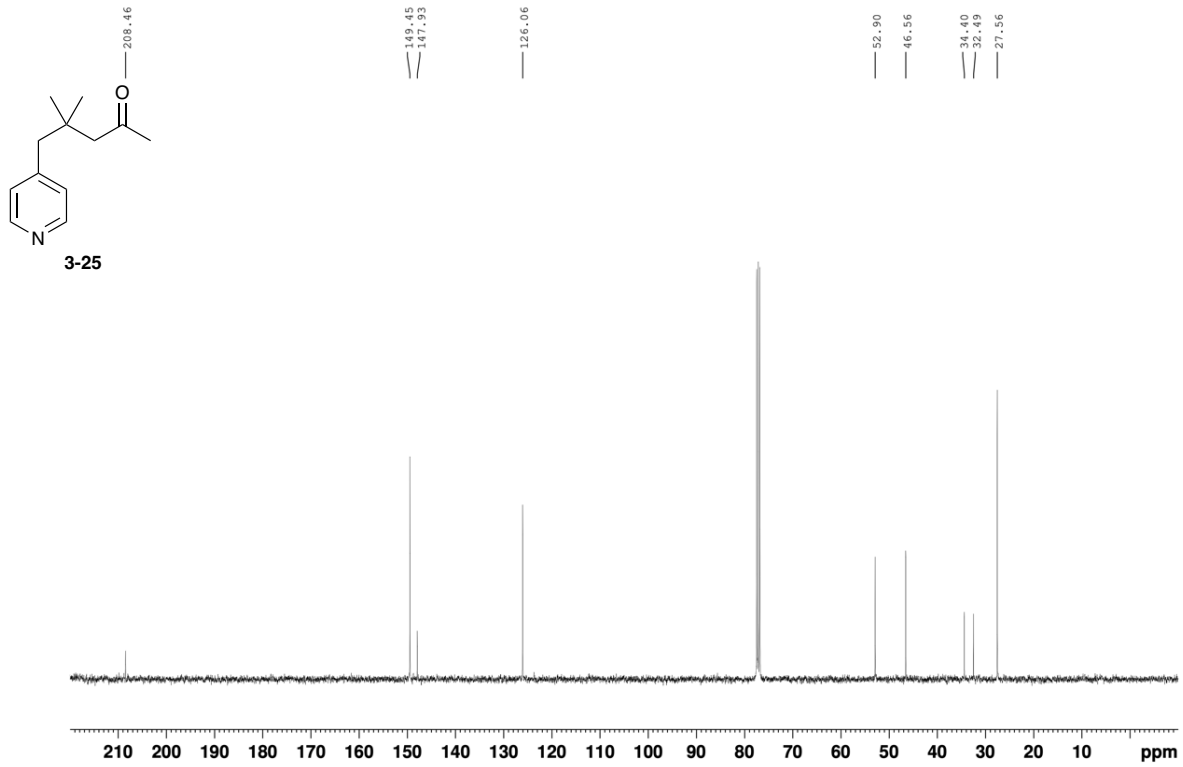
^{13}C NMR (100 MHz, $CDCl_3$)

δ 148.9, 147.5, 133.9, 131.6, 126.4, 75.0, 49.7, 29.6, 27.3, 19.0, 7.1, 6.7.

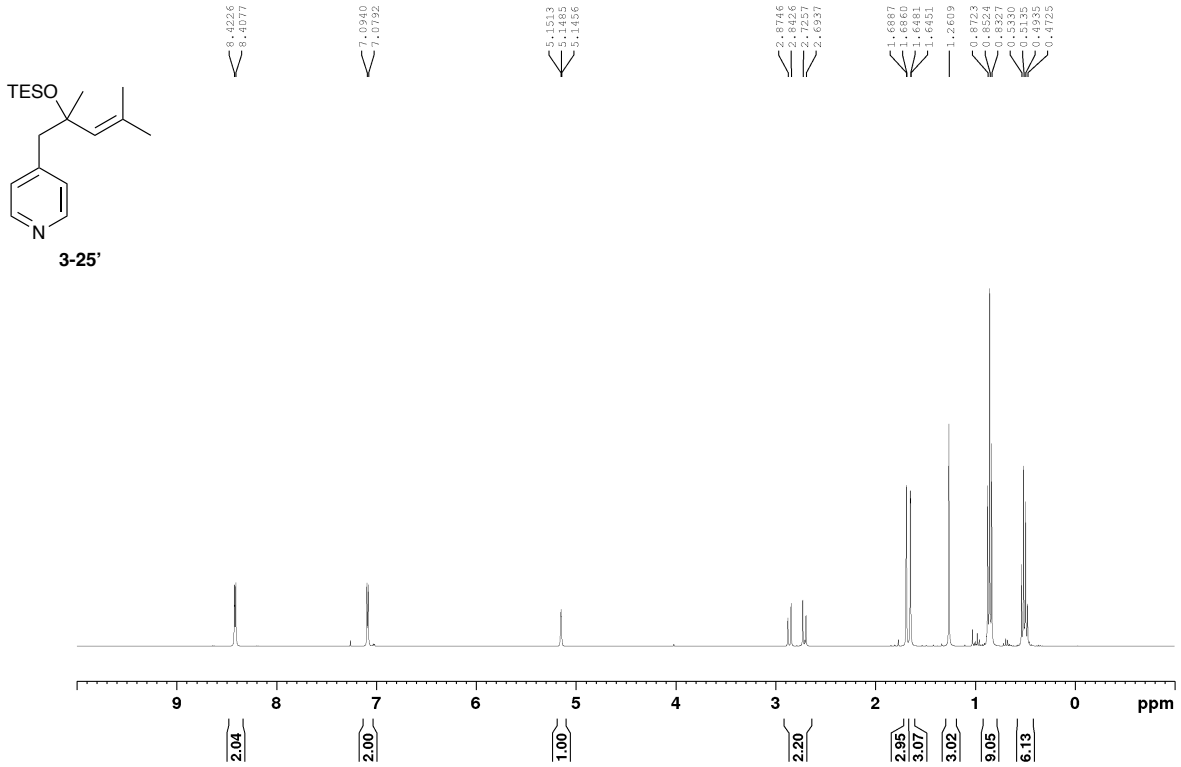
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-25**:



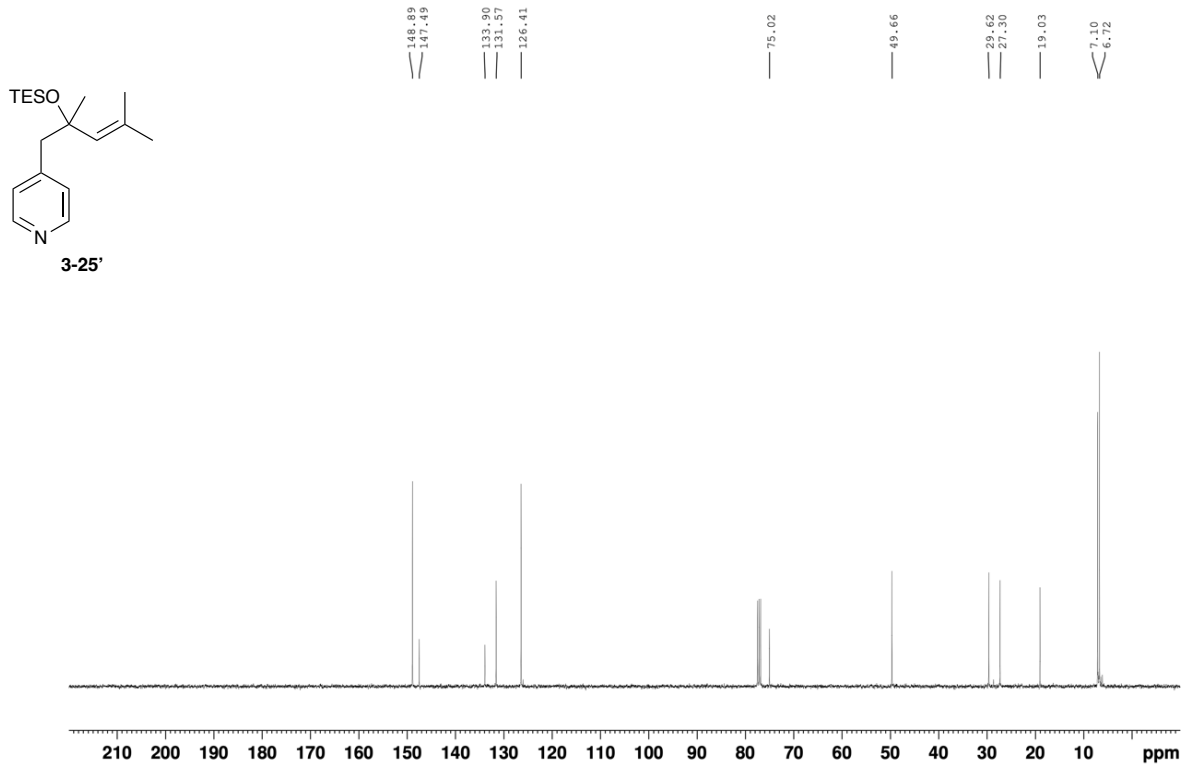
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-25**:



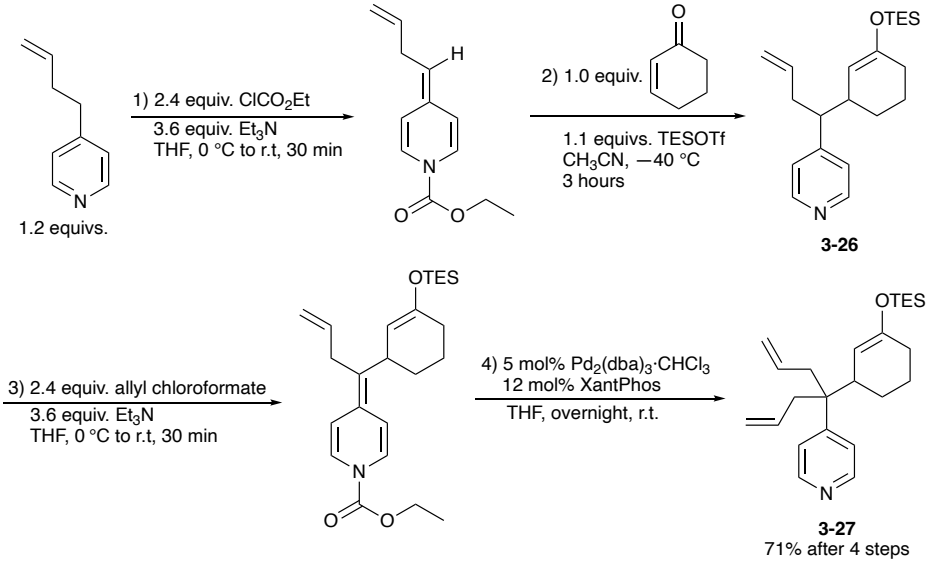
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-25'**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-25'**:



Synthesis of compound **3-27**:



By following the **general procedure A**, the corresponding ADHP was prepared from 4-(3-buten-1-yl)-pyridine (80 mg, 1.2 equiv., 0.6 mmol), and allyl chloroformate (0.13 mL, 2.4 equiv., 1.2 mmol) was used instead of ethyl chloroformate. The crude conjugate addition product **3-26** was synthesized by following **general procedure B** but with neutral aqueous work-up using a pH = 7 buffer. 2-Cyclohexen-1-one (0.05 mL, 1.0 equiv., 0.5 mmol) was used as the electrophile. The resulting residue **3-26** was obtained and used in the next step without further purification.

Compound **3-26** was converted into its corresponding ADHP by following the **general procedure A** by using allyl chloroformate (0.12 mL, 2.0 equiv., 1.0 mmol) instead of ethyl chloroformate. In another 25 mL round-bottomed flask $Pd_2(dba)_3{\cdot}CHCl_3$ (25.9 mg, 5 mol%, 0.025 mmol) and XantPhos (34.8 mg, 12 mol%, 0.06 mmol) were dissolved in 3 mL of anhydrous THF. The mixture was stirred for 30 minutes at ambient temperature. The second ADHP intermediate prepared from **3-26** was dissolved in THF (3 mL) and added to the palladium catalyst solution in a dropwise manner. The resulting mixture was stirred at ambient temperature overnight, then concentrated using a rotary evaporator. The resulting residue was purified by flash column

chromatography with EtOAc/Hexanes to afford product **3-27** as colorless oil (137 mg, 71% overall yield).

Data for **3-27**:

Chromatography: 30% EtOAc in Hexanes (R_f = 0.28).

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

δ 8.50 (d, *J* = 6.4 Hz, 2H), 7.23 (d, *J* = 6.4 Hz, 2H), 5.81 – 5.69 (m, 1H), 5.69 – 5.57 (m, 1H), 5.14 – 5.01 (m, 4H), 4.86 (s, 1H), 2.66 – 2.52 (m, 5H), 1.88 – 1.83 (m, 2H), 1.68 – 1.59 (m, 2H), 1.48 – 1.37 (m, 1H), 1.09 – 0.97 (m, 1H), 0.94 (t, *J* = 8.0 Hz, 9H), 0.60 (q, *J* = 8.0 Hz, 6H).

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

δ 154.1, 152.4, 149.4, 134.7, 134.5, 123.3, 118.2, 118.1, 104.5, 46.6, 43.3, 39.6, 38.5, 29.8, 24.1, 22.7, 6.8, 5.3.

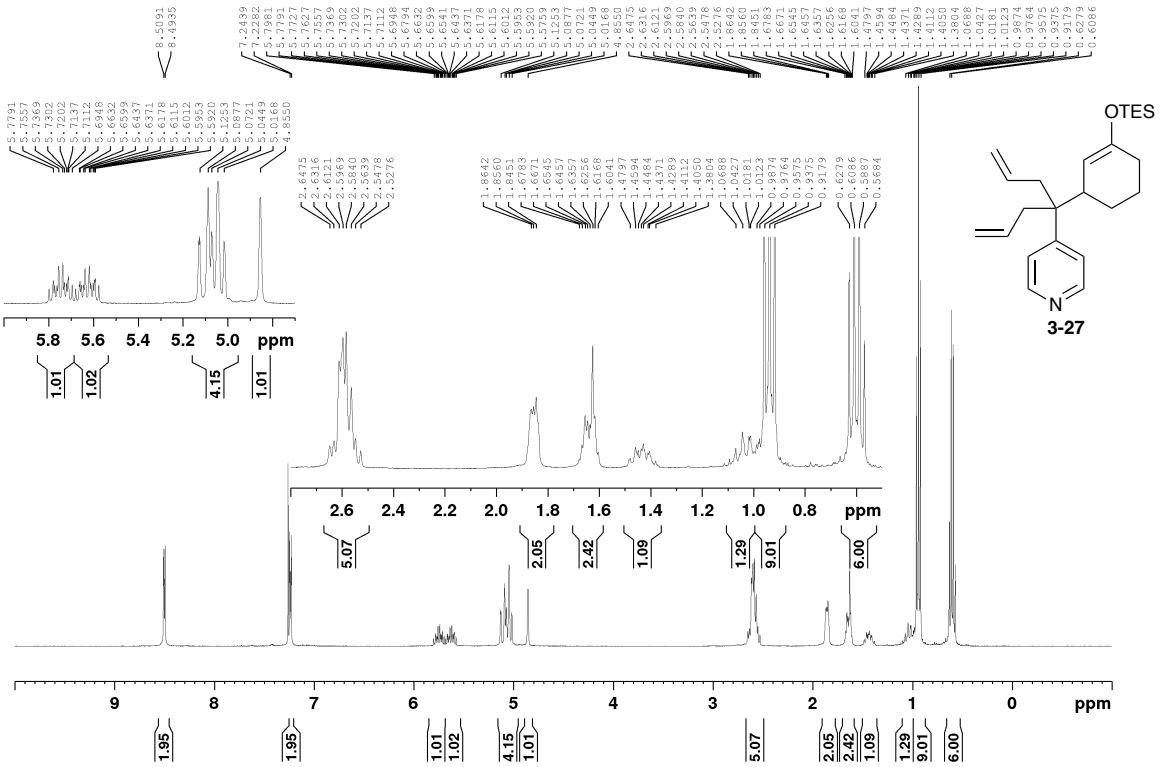
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3076, 3019, 2935, 1657, 1594, 1192 cm^{-1}.

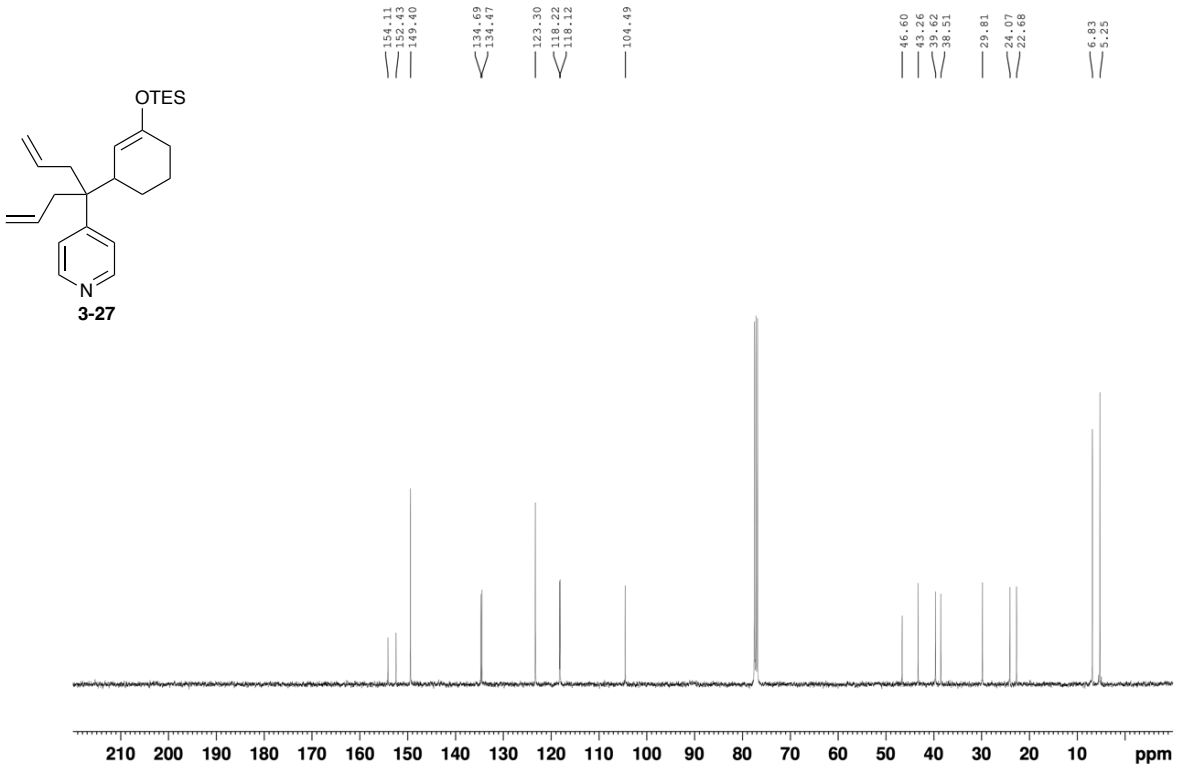
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{24}H_{38}NOSi$ 384.2717; Found 384.2721.

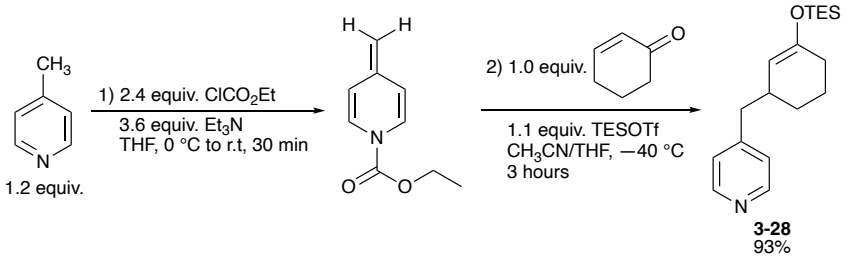
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-27**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-27**:



Synthesis of compound **3-28**:



By following the **general procedure A**, the corresponding ADHP was synthesized using 4-picoline (0.12 mL, 1.2 equiv., 1.2 mmol).

A 0.2 M solution of 2-cyclohexen-1-one (0.1 mL, 1 equiv., 1.0 mmol) in CH_3CN was prepared in an oven-dried round-bottomed flask. The solution was cooled to –40 °C and TESOTf (0.25 mL, 1.1 equiv., 1.1 mmol) was added in a dropwise manner. The resulting mixture was stirred for 15 minutes. The freshly prepared ADHP was dissolved in THF (0.2 M) and added dropwise to the above reaction mixture while maintaining the temperature at –40 °C. The mixture was stirred under –40 °C for 3 hours. The reaction mixture was placed in an ice-water bath and quenched with a pH = 7 buffer (10 mL) followed by 5 drops of triethylamine. The resulting mixture was stirred vigorously for 30 minutes and extracted with EtOAc (4 x 10 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and the filtrate was concentrated using a rotary evaporator. The resulting mixture was purified by flash column chromatography with EtOAc/Hexanes to afford product **3-28** as colorless oil (281 mg, 93% yield). Chromatography: 20% EtOAc in Hexanes (R_f = 0.33).

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

δ 8.46 (d, J = 6.0 Hz, 2H), 7.05 (d, J = 6.0 Hz, 2H), 4.68 – 4.66 (m, 1H),

2.56 – 2.49 (m, 2H), 2.48 – 2.39 (m, 1H), 2.26 – 1.91 (m, 2H),

1.79 – 1.69 (m, 1H), 1.65 – 1.56 (m, 1H), 1.56 – 1.46 (m, 1H),

1.16 – 1.05 (m, 1H), 0.92 (t, J = 8.0 Hz, 9H), 0.59 (q, J = 8.0 Hz, 6H).

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

δ 151.7, 149.9, 149.6, 124.6, 107.3, 42.8, 36.1, 29.9, 28.7, 21.5, 6.8, 5.1.

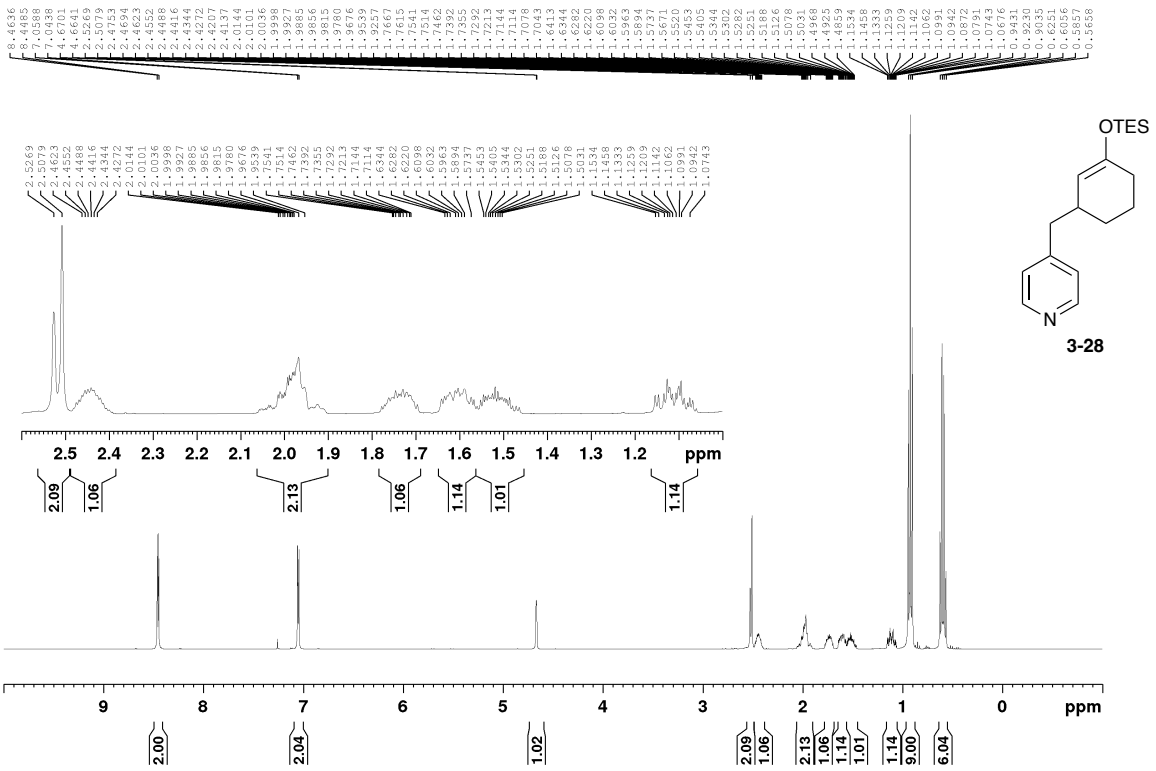
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3068, 2933, 2875, 1662, 1601, 1188 cm^{-1}.

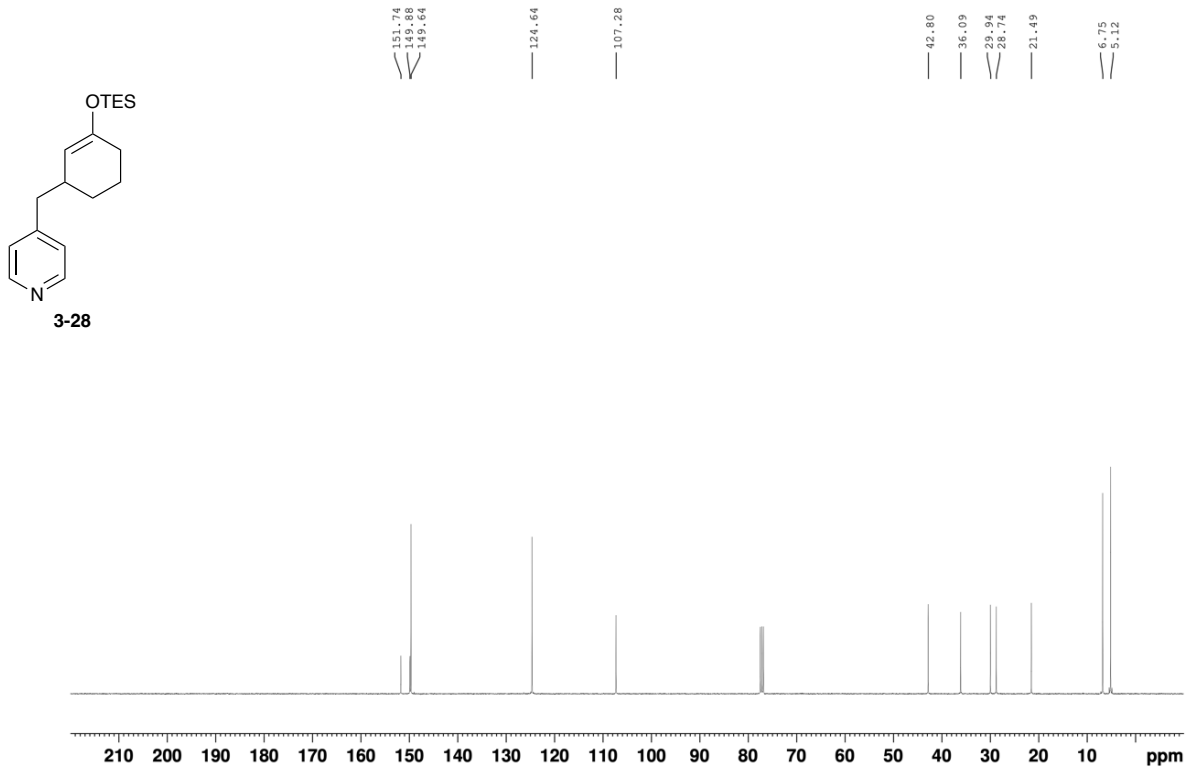
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{18}H_{30}NOSi$ 304.2091; Found 304.2092

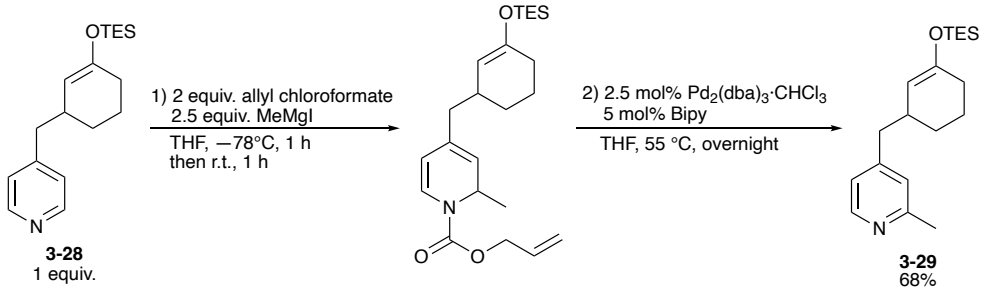
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-28**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-28**:



Synthesis of compound **3-29**:



An oven-dried round-bottomed flask equipped with a stir bar was charged with compund **3-28** (82 mg, 1.0 equiv., 0.27 mmol) and 3 mL of anhydrous THF. The mixture was cooled to –78 °C. Allyl chloroformate (0.06 mL, 2 equivs. 0.54 mmol) was added in a dropwise manner, and the resulting solution was stirred for 1 hour at –78 °C. Methylmagnesium iodide (0.68 mL, 2.5 equivs., 0.68 mmol, 1 M in diethyl ether) was added to the above mixture in a dropwise manner. The resulting mixture was stirred for 1 hour at –78 °C and an additional hour at ambient temperature. The reaction mixture was quenched with dropwise addition of water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine, dried with $MgSO_4$, filtered through a cotton plug, and concentrated using a rotary evaporator. The methylated dihydropyridine product was obtained and used without purification.

An oven-dried round-bottomed flask equipped with a stir bar was charged with 1.5 mL of anhydrous THF, $Pd_2(dba)_3{\cdot}CHCl_3$ (7 mg, 2.5 mol%, 0.00675 mmol) and 2,2'-bipyridine (2.1 mg, 5 mol%, 0.0135 mmol). The resulting mixture was stirred for 30 min. A 0.1 M solution of methylated dihydropyridine product in THF was prepared and added dropwise to the above palladium catalyst solution. The resulting mixture was placed in an oil bath, stirred, and heated to reflux overnight. The mixture was then cooled to ambient temperature and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography with EtOAc/Hexanes to afford product **3-29** as colorless oil (58 mg, 68 % yield).

Chromatography: 30% EtOAc in Hexanes (R_f = 0.25).

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

δ 8.36 (d, *J* = 5.2 Hz, 1H), 6.95 (s, 1H), 6.89 (d, *J* = 5.2 Hz, 1H), 4.69 (s, 1H), 2.51 (s, 3H), 2.51 – 2.47 (m, 2H), 2.47 – 2.42 (m, 1H), 2.09 – 1.91 (m, 2H), 1,81 – 1.72 (m, 1H), 1.68 – 1.59 (m, 1H), 1.59 – 1.48 (m, 1H), 1.18 – 1.08 (m, 1H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.62 (q, *J* = 8.0 Hz, 6H).

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

δ 158.2, 151.7, 150.2, 149.0, 124.3, 121.8, 107.5, 42.9, 36.2, 30.0, 28.9, 24.5, 21.6, 6.8, 5.2.

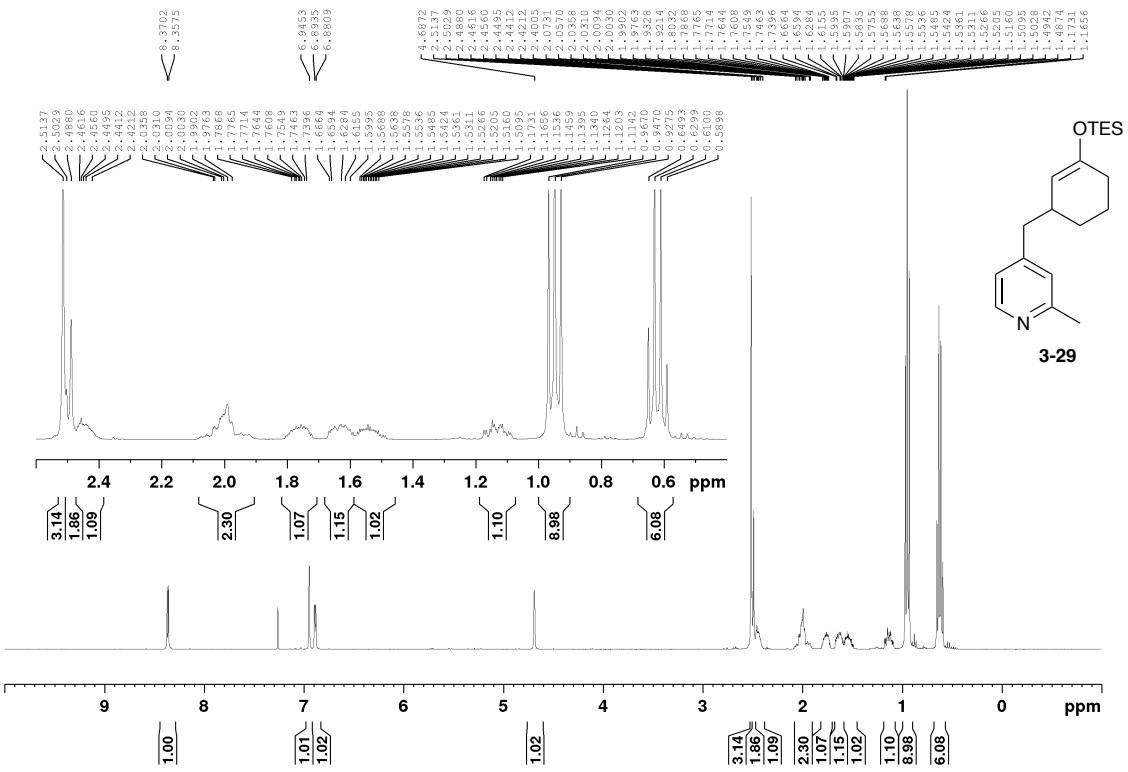
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3010. 2952. 2874, 1663, 1604, 1190 cm^{-1}.

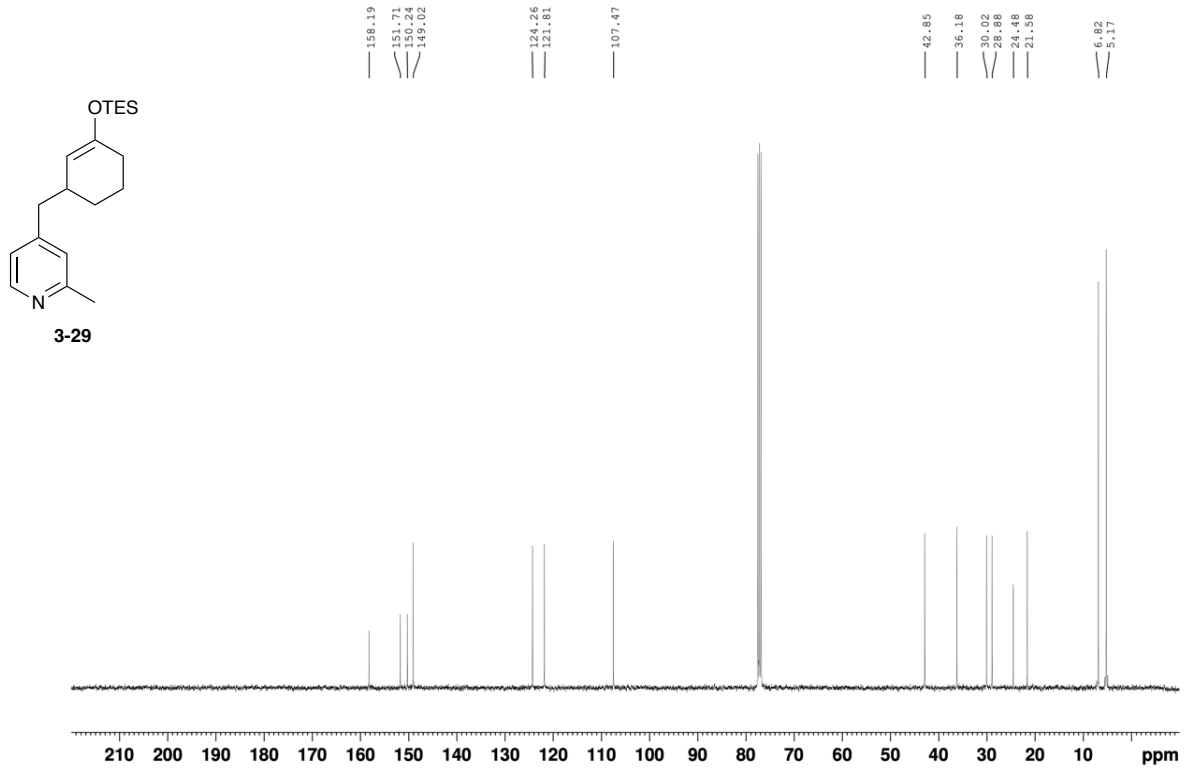
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{19}H_{32}NOSi$ 318.2248; Found 318.2247.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **3-29**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **3-29**:



6.5 Piperidine installation on 4-pyridylic carbon

6.5.1 General procedure (C) for addition of ADHP to activated pyridines

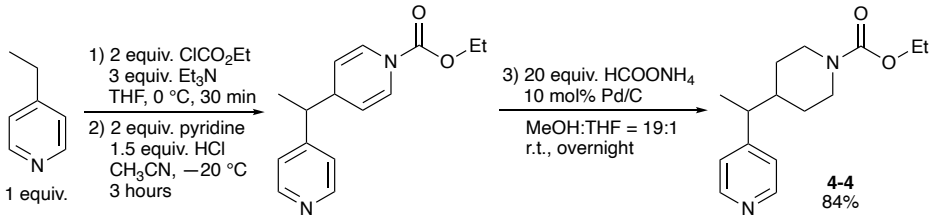
An oven-dried round-bottomed flask equipped with a stir bar was charged with a 0.4 M solution of pyridine (2.0 equiv.) in anhydrous CH_3CN. The solution was cooled to –20 °C. Hydrogen chloride (4 M in dioxane, 1.5 equiv.) was added in a dropwise manner, and the resulting mixture was stirred for 15 minutes at –20 °C. Unless otherwise stated, the ADHP was dissolved in anhydrous CH_3CN (0.2 M) and added dropwise to the reaction mixture, while maintaining the temperature at –20 °C. The reaction progress was monitored by TLC and ^{1}H-NMR. Upon consumption of the ADHP, Et_3N (4.0 equiv.) was added dropwise at –20 °C. The mixture was allowed to slowly warm to ambient temperature while stirring for at least 1 hour, and then concentrated using a rotary evaporator. The resulting residue was suspended in diethyl ether for 2 – 3 minutes and filtered through a cotton plug to remove the precipitated triethylammonium chloride salt. The filtrate was concentrated using a rotary evaporator to obtain the crude dihydropyridine (DHP), which was used in the next step without further purification.

6.5.2 General procedure (D) for reduction of dihydropyridines

A round-bottomed flask equipped with a stir bar was charged with a 1 M solution of DHP in anhydrous THF. A 1.25 M solution of ammonium formate (20 equiv.) in methanol was added slowly, followed by a slurry of Pd/C (10% w/w, 10 mol%) in methanol while stirring. Additional methanol or THF should be added to the mixture to achieve a 19:1 ratio of methanol to THF. The flask was sealed with electrical tape and the mixture was stirred overnight at ambient temperature. Upon depressurizing the flask to ambient pressure, the mixture was filtered through a pad of Celite®. The filtrate was concentrated using a rotary evaporator. Unless otherwise stated, the residue was suspended in EtOAc for 2 – 3 minutes and filtered through a cotton plug. The filtrate was concentrated using a rotary evaporator, and the resulting residue was purified using flash column chromatography to obtain the final product.

6.5.3 Synthesis and characterization of compounds

Synthesis of compound **4-4**:



The piperidine product was synthesized by following **general procedures A**, **C**, and **D** using 4-ethylpyridine (0.12 mL, 1.0 equiv., 1.0 mmol) as the starting material. Product **4-4** was obtained as colorless oil (220.3 mg, 84% yield).

Chromatography: 70% EtOAc in hexanes (R_f = 0.27).

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

δ 8.49 (d, *J* = 6.0 Hz, 2H), 7.05 (d, *J* = 6.0 Hz, 2H), 4.30 – 3.90 (m, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 12.4 Hz, 1H), 2.59 (t, *J* = 12.4 Hz, 1H), 2.45 (p, *J* = 7.2 Hz, 1H), 1.81 (d, *J* = 12.4 Hz, 1H), 1.61 – 1.49 (m, 1H), 1.33 (d, *J* = 12.4 Hz, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.19 – 1.09 (m, 1H), 1.02 (qd, *J* = 12.4, 4.0 Hz, 1H).

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

δ 155.5, 154.9, 149.9, 123.2, 61.3, 45.0, 44.1, 44.0, 42.1, 30.4, 29.6, 18.1, 14.8.

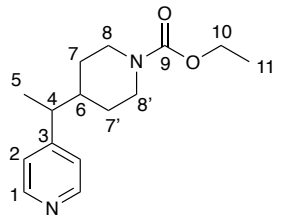
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3067, 2975, 2859, 1688, 1429, 1223 cm^{-1}.

HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{15}H_{23}N_2O_2$ 263.1754; Found 263.1742.

COSY (400 MHz, $CDCl_3$) for **4-4**:

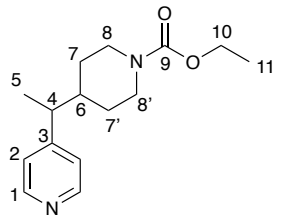


Proton No.	^{1}H δ (ppm) (multi; *J* (Hz))	COSY correlations
H-1	8.49 (d, *J* = 6.0 Hz)	H-2
H-2	7.05 (d, *J* = 6.0 Hz)	H-1
H-4	2.45 (p, *J* = 7.2 Hz)	H-5, H-6
H-5	1.24 (d, *J* = 7.2 Hz)	H-4
H-6	1.61 – 1.49 (m, 1H)	H-4
H-7a, H-7'a	1.19 – 1.09 (m) 1.02 (qd, *J* = 12.4, 4.0 Hz)	H-8a, H-8'a
H-7e, H-7'e	1.81 (d, *J* = 12.4 Hz), 1.33 (d, *J* = 12.4 Hz)	-
H-8a, H-8'a	2.69 (t, *J* = 12.4 Hz) 2.59 (t, *J* = 12.4 Hz)	H-7a, H-7'a
H-8e, H-8'e	4.30 – 3.90 (m)	-
H-10	4.09 (q, *J* = 7.2 Hz)	H-11
H-11	1.22 (t, *J* = 7.2 Hz)	H-10

Methylene carbons are designated C-X and C-X' arbitrarily. Axial methylene protons are designated H-Xa and H-X'a, and equatorial protons are designated H-Xe and H-X'e arbitrarily.

Only those correlations which could be unambiguously assigned are reported.

HMBC (400 MHz, $CDCl_3$) for **4-4**:

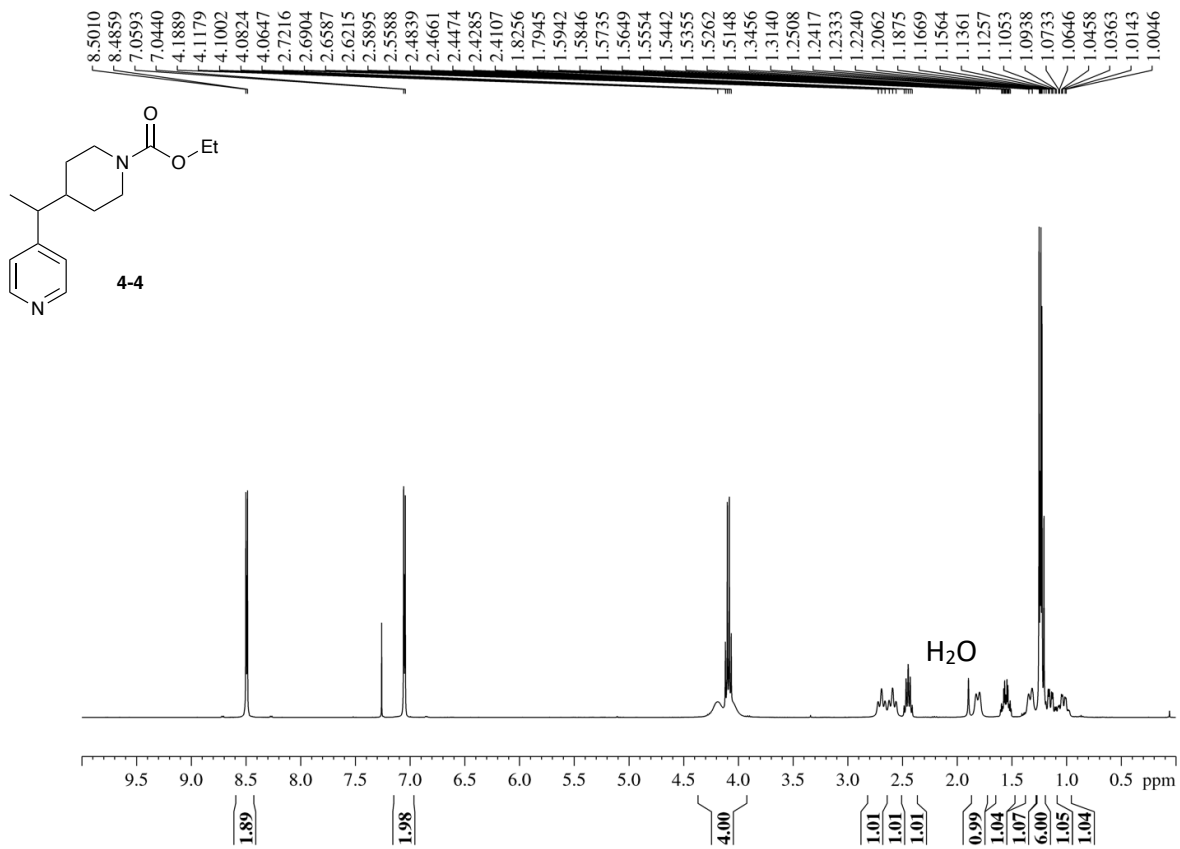


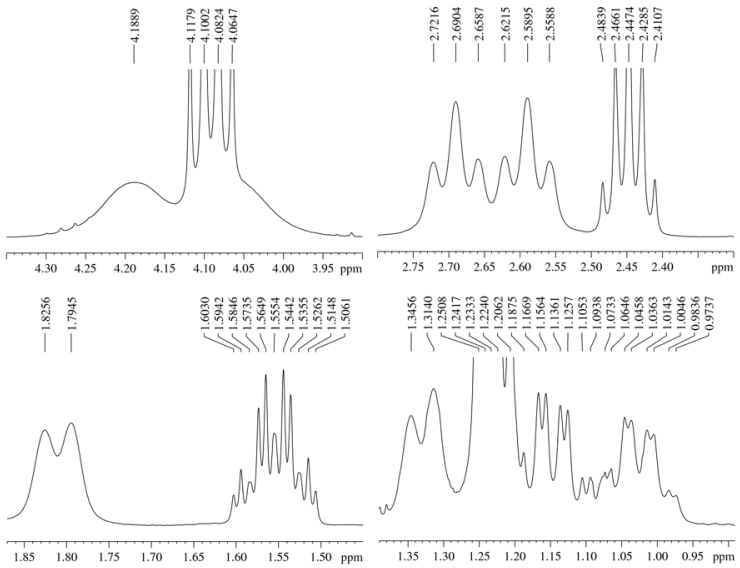
Carbon No.	^{13}C δ (ppm)	^{1}H δ (ppm) (multi; *J* (Hz))	HMBC correlations
C-1	149.9	8.49 (d, *J* = 6.0 Hz), 7.05 (d, *J* = 6.0 Hz)	H-1, H-2
C-2	123.2	8.49 (d, *J* = 6.0 Hz), 7.05 (d, *J* = 6.0 Hz), 2.45 (p, *J* = 7.2 Hz)	H-1, H-2, H-4
C-3	154.9	8.49 (d, *J* = 6.0 Hz), 2.45 (p, *J* = 7.2 Hz), 1.24 (d, *J* = 7.2 Hz), 1.61 – 1.49 (m, 1H)	H-1, H-4, H-5, H-6
C-4	45.0	8.49 (d, *J* = 6.0 Hz), 7.05 (d, *J* = 6.0 Hz), 1.24 (d, *J* = 7.2 Hz), 1.61 – 1.49 (m, 1H), 1.19 – 1.09 (m),1.02 (qd, *J* = 12.4, 4.0 Hz)	H-1, H-2, H-5, H-6, H-7a, H-7'a
C-5	18.1	1.61 – 1.49 (m, 1H)	H-6
C-6	42.1	1.24 (d, *J* = 7.2 Hz),	H-5
C-7	30.4	-	-
C-7'	29.6	-	-
C-8	44.1	-	-
C-8'	44.0	-	-
C-9	155.5	4.09 (q, *J* = 7.2 Hz)	H-10
C-10	61.3	1.22 (t, *J* = 7.2 Hz)	H-11
C-11	14.8	4.09 (q, *J* = 7.2 Hz)	H-10

Carbons are designated C-X and C-X' arbitrarily. Axial protons are designated H-Xa and H-X'a, and equatorial protons are designated H-Xe and H-X'e arbitrarily.

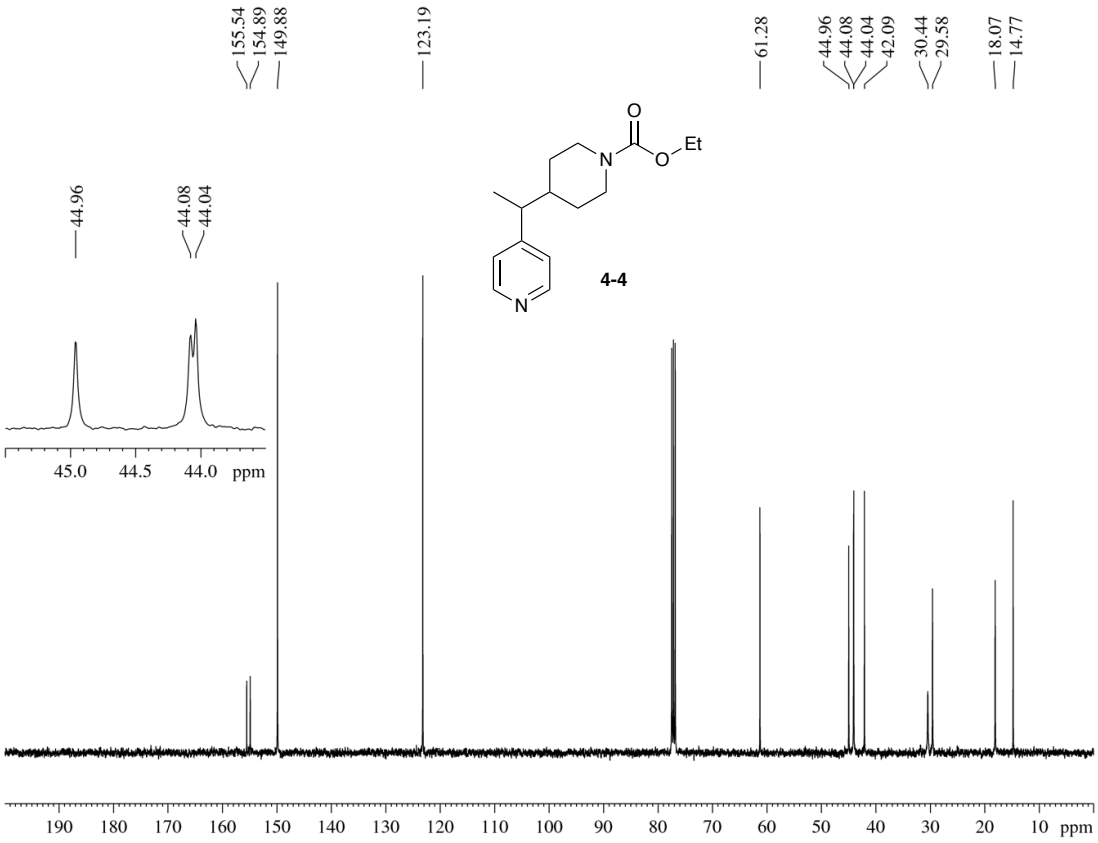
Only those correlations which could be unambiguously assigned are reported.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-4**:

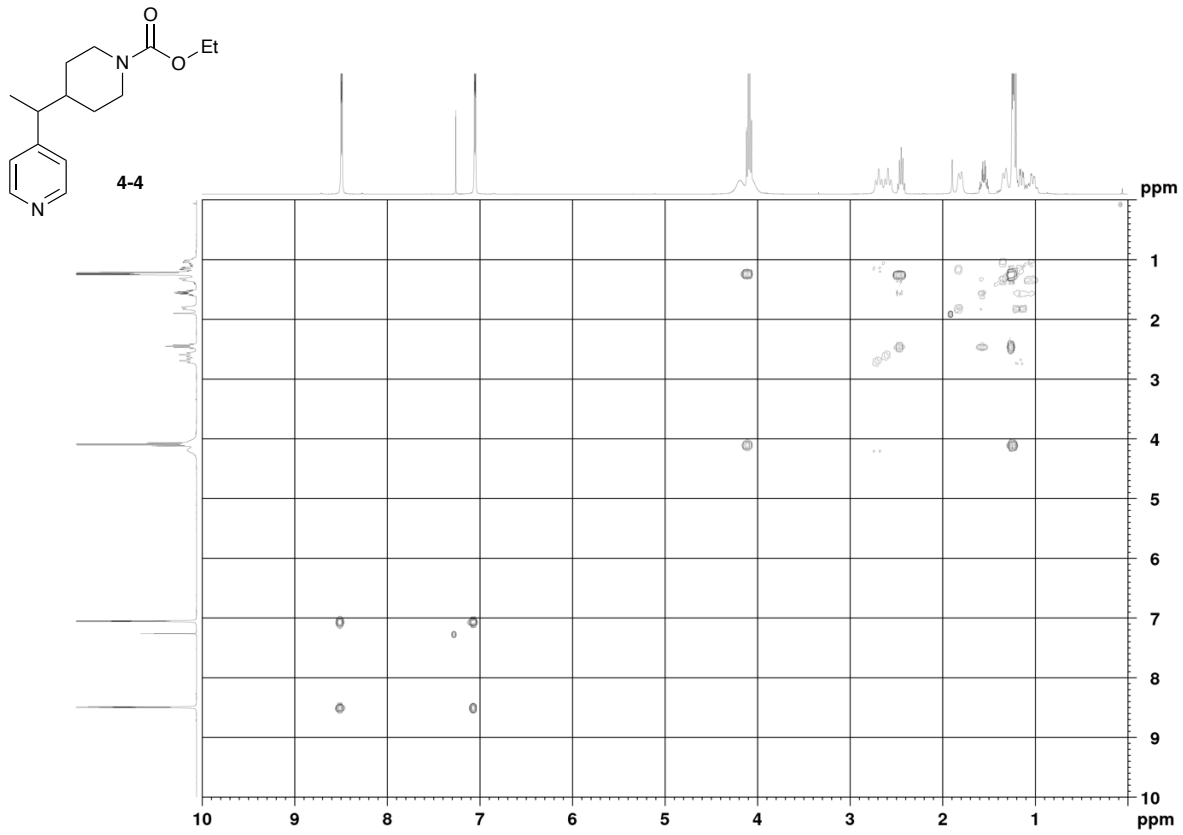




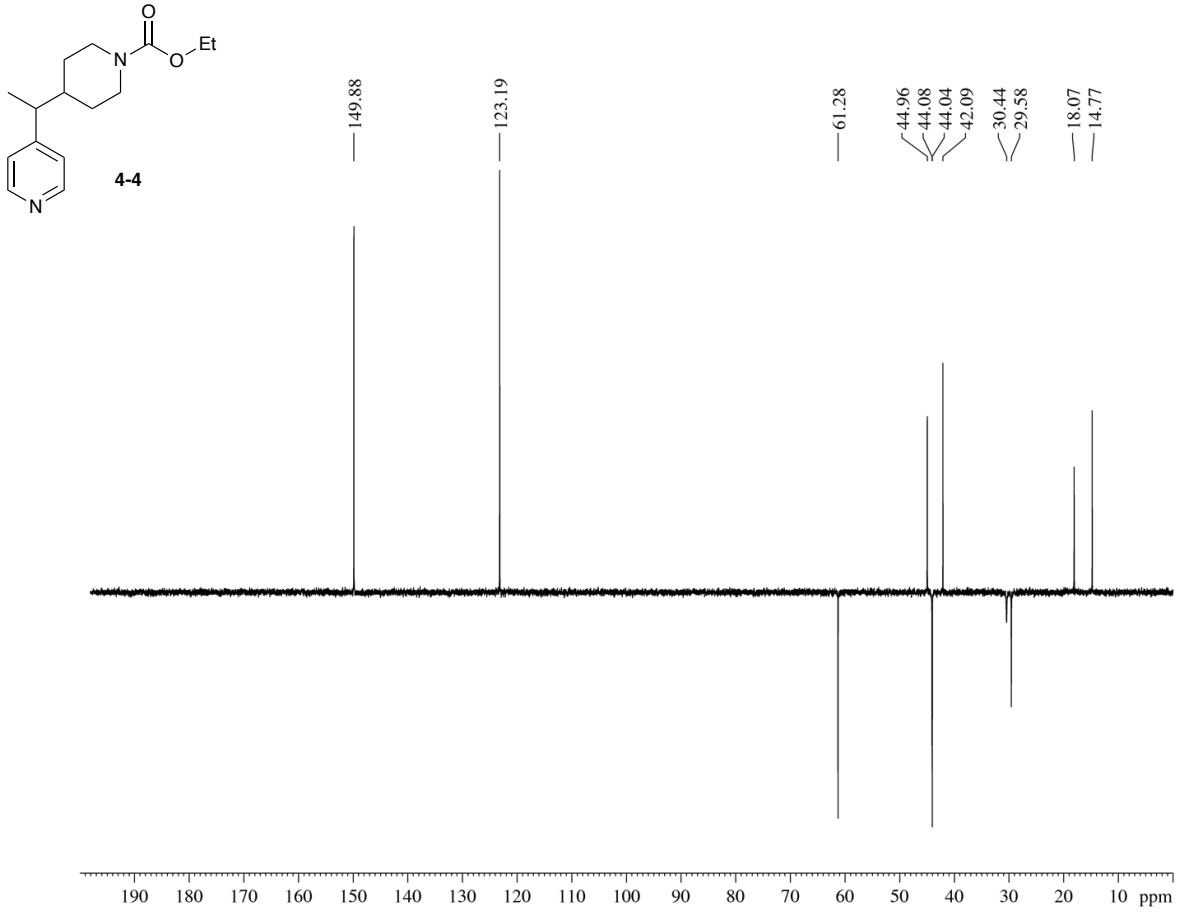
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-4**:



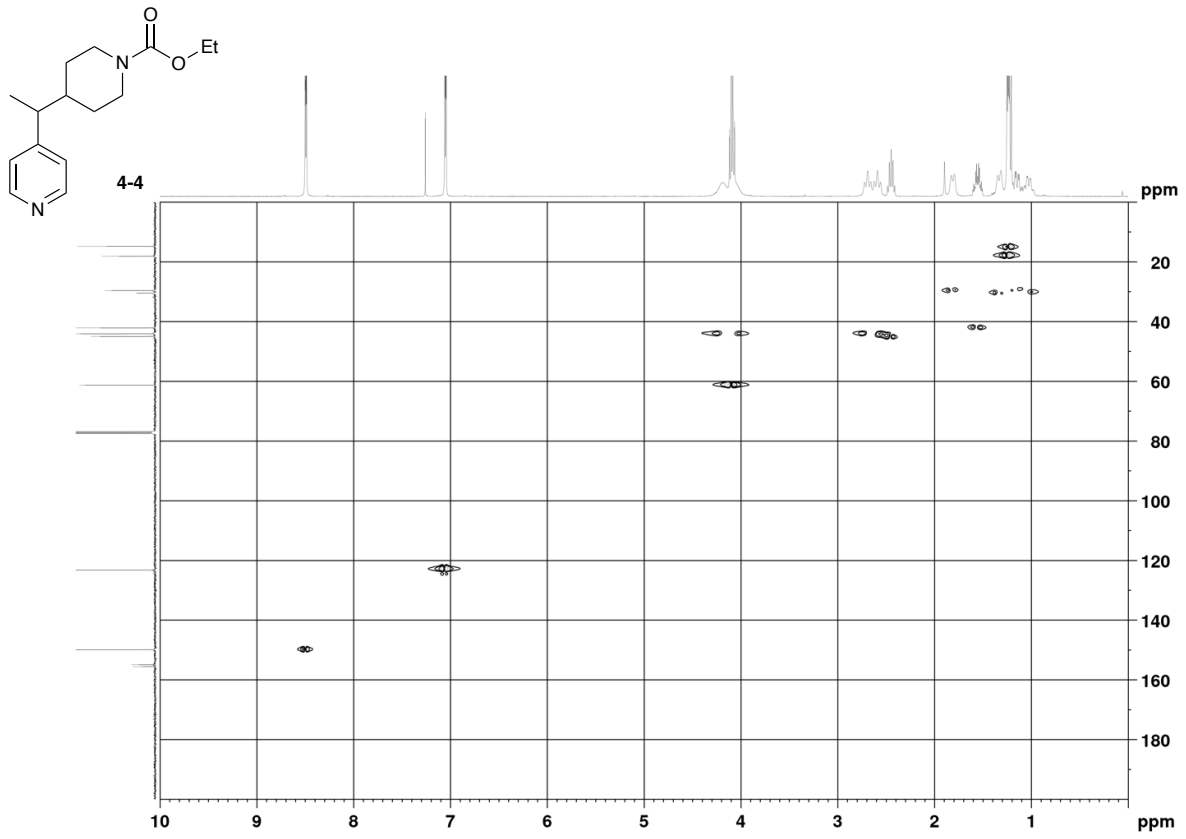
COSY (400 MHz, $CDCl_3$) Spectrum for **4-4**:



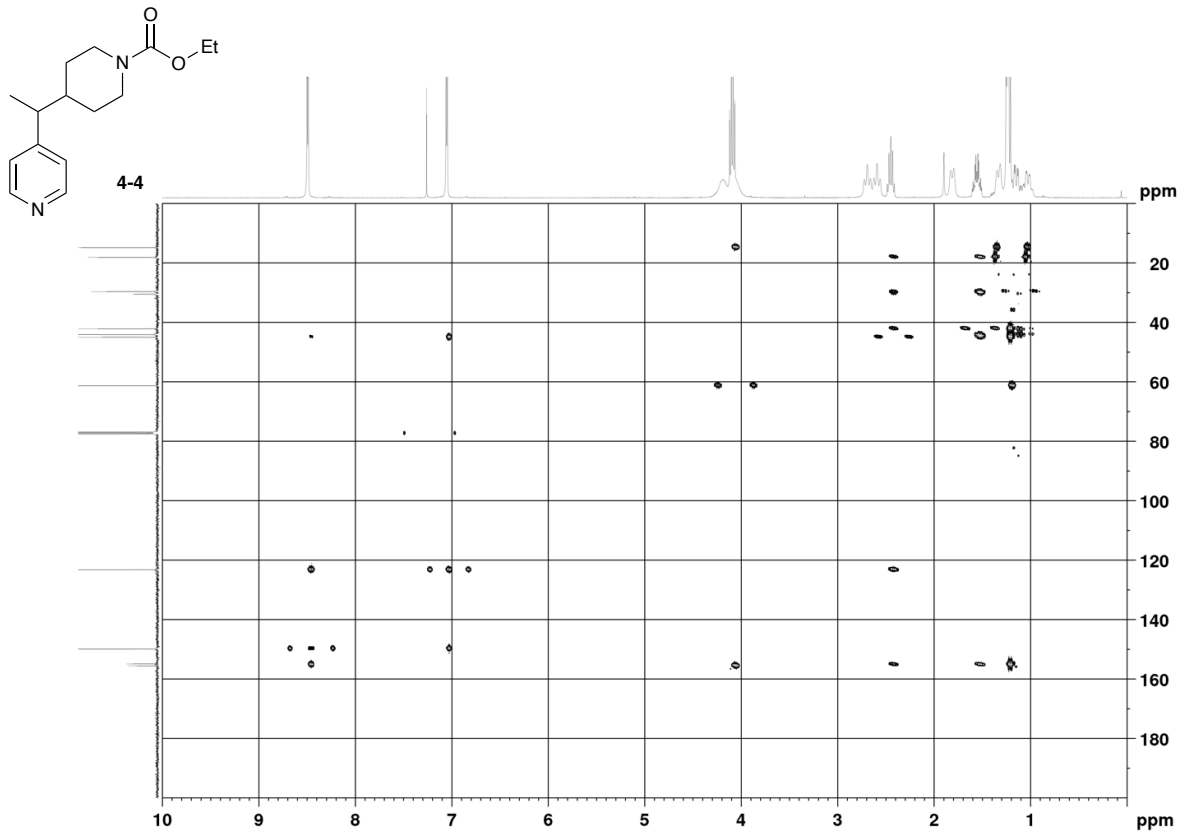
DEPT-135 (400 MHz, $CDCl_3$) Spectrum for **4-4**:



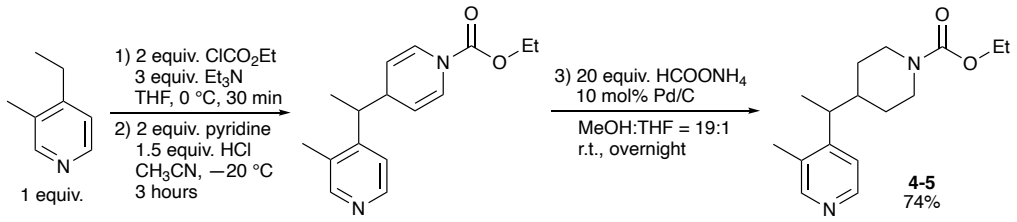
HSQC (400 MHz, $CDCl_3$) Spectrum for **4-4**:



HMBC (400 MHz, $CDCl_3$) Spectrum for **4-4**:



Synthesis of compound **4-5**:



The piperidine product was synthesized by following **general procedures A**, **C**, and **D** using 3-methyl-4-ethylpyridine[53] (122.2 mg, 1.0 equiv., 1.0 mmol) as the starting material. Product **4-5** was obtained as colorless oil (205.8 mg, 74% yield).

Chromatography: 100% EtOAc. (R_f = 0.22)

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

δ 8.36 (d, *J* = 5.2 Hz, 1H), 8.34 (s, 1H), 7.03 (d, *J* = 5.2 Hz, 1H), 4.30 – 3.95 (m, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 2.78 – 2.64 (m, 2H), 2.58 (t, *J* = 12.4 Hz, 1H), 2.25 (s, 3H), 1.87 (d, *J* = 12.4 Hz, 1H), 1.64 – 1.52 (m, 1H), 1.31 (d, *J* = 13.2 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.20 – 1.12 (m, 1H), 1.03 (qd, *J* = 12.4, 4.0 Hz, 1H).

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

δ 155.6, 153.5, 151.2, 147.9, 131.3, 120.9, 61.3, 44.1(4), 44.1(3), 41.9, 39.7, 30.5, 29.6, 18.1, 16.7, 14.8.

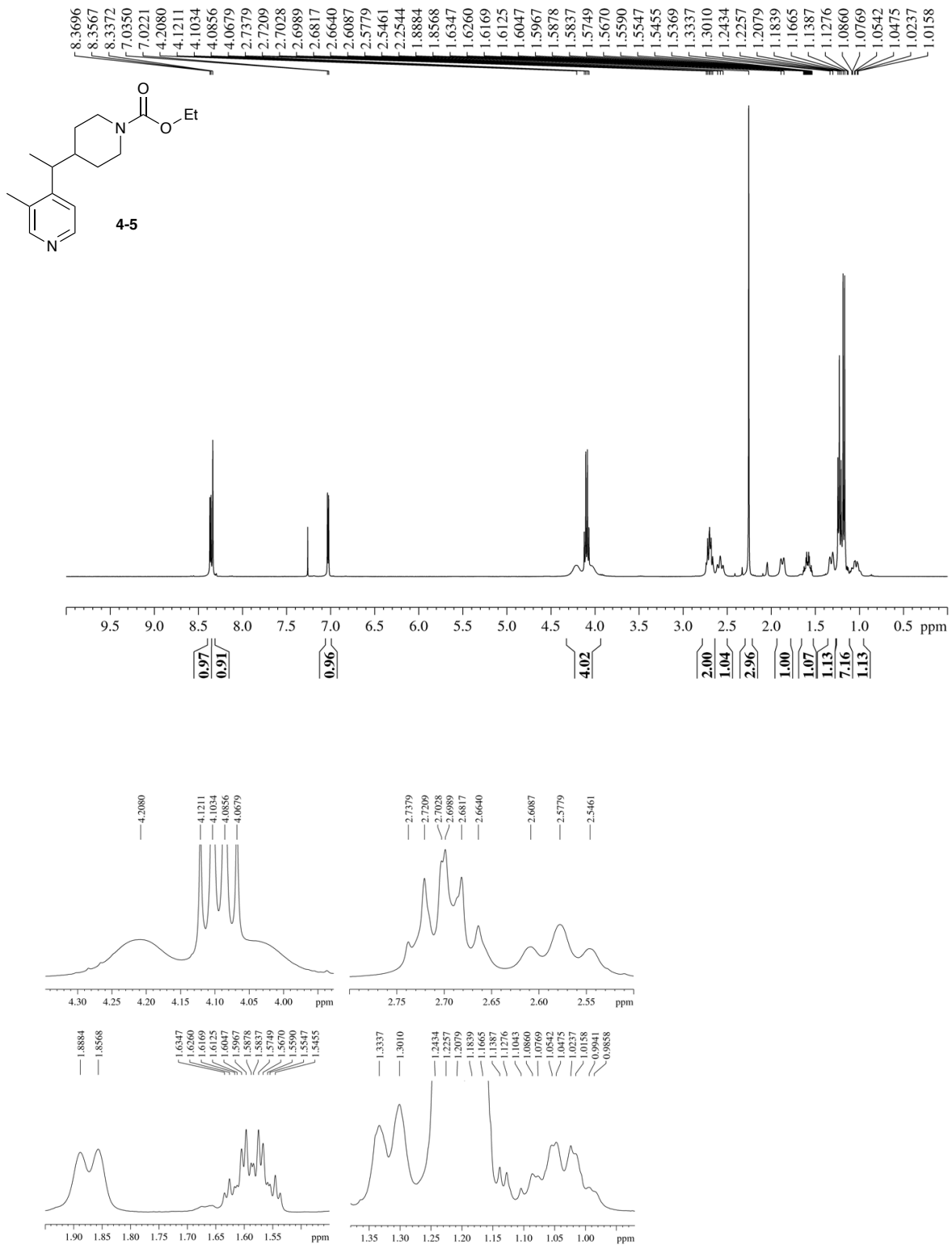
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3054, 2974, 2853, 1689, 1429, 1215 cm^{-1}.

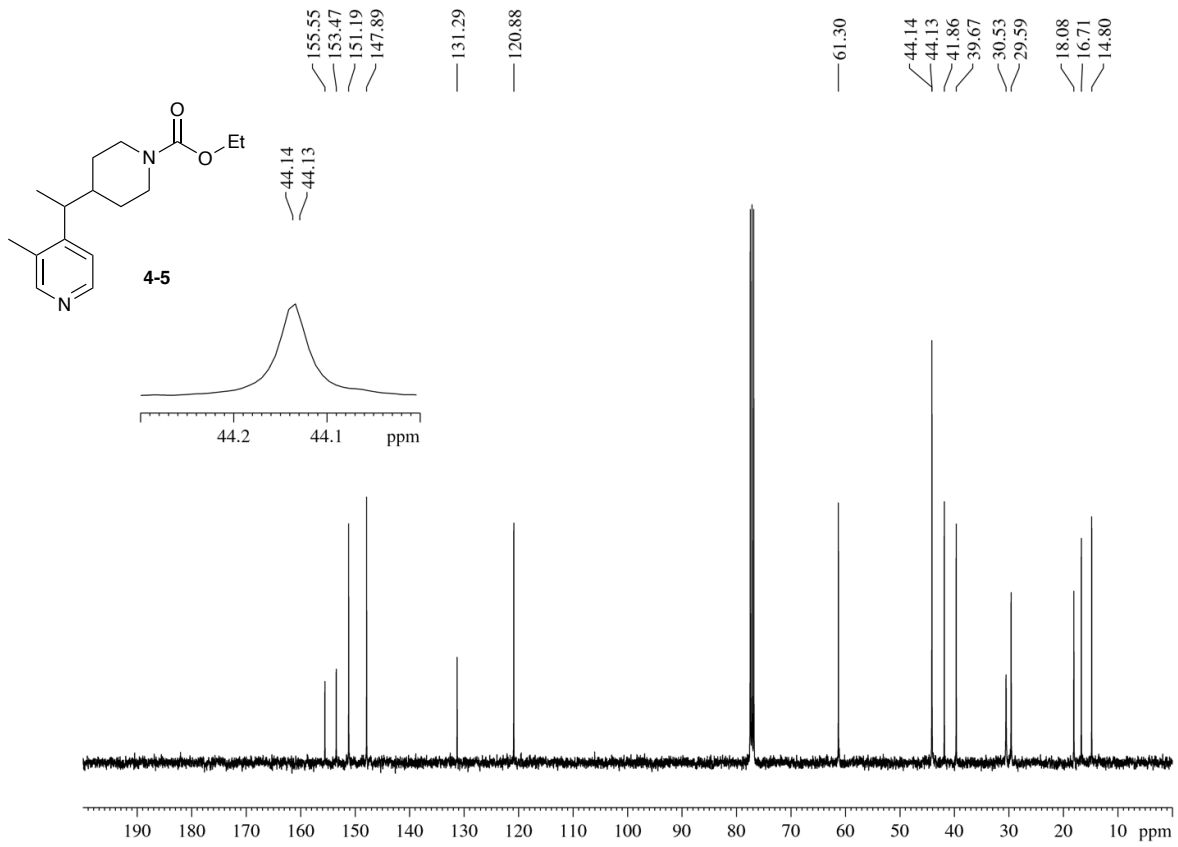
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{16}H_{25}N_2O_2$ 277.1911; Found 277.1900.

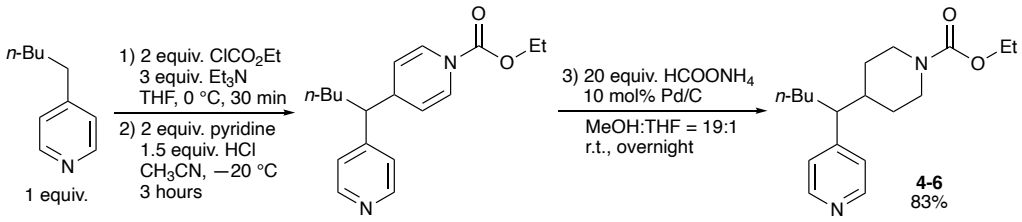
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-5**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-5**:



Synthesis of compound **4-6**:



The piperidine product was synthesized by following **general procedures A**, **C**, and **D** using 4-*n*-pentylpyridine[31] (149.2 mg, 1.0 equiv., 1.0 mmol) as the starting material. Product **4-6** was obtained as colorless oil (252.4 mg, 83% yield).

Chromatography: 70% EtOAc in hexanes (R_f = 0.32).

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

δ 8.49 (d, *J* = 6.0 Hz, 2H), 7.01 (d, *J* = 6.0 Hz, 2H), 4.30 – 3.95 (m, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 12.4 Hz, 1H), 2.58 (t, *J* = 12.4 Hz, 1H), 2.29 (ddd, *J* = 11.6, 8.4, 4.0 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.81 – 1.72 (m, 1H), 1.66 – 1.48 (m, 2H), 1.34 – 1.06 (m, 4H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.06 – 0.92 (m, 3H), 0.79 (t, *J* = 7.2 Hz, 3H).

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

δ 155.5, 153.1, 149.9, 124.1, 61.3, 51.3, 44.1(4), 44.1(1), 41.3, 31.6, 30.3, 30.2, 29.8, 22.8, 14.8, 14.0.

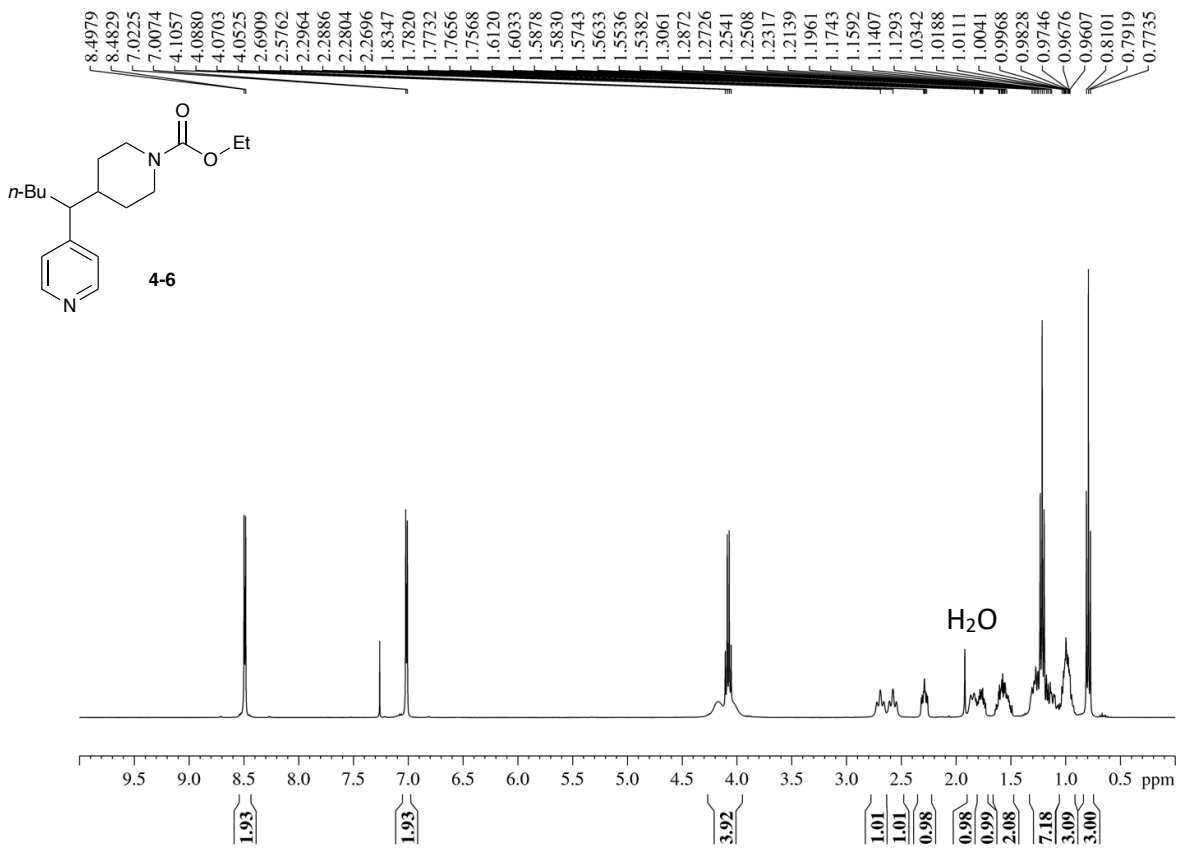
IR Alpha-Platinum ATR, Bruker, diamond crystal

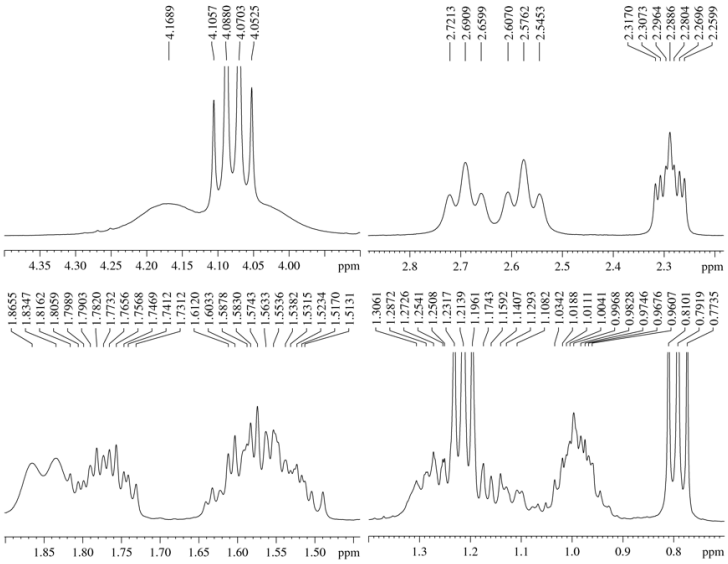
υ = 3067, 2931, 2858, 1691, 1430, 1234 cm^{-1}.

HRMS ESI-TOF

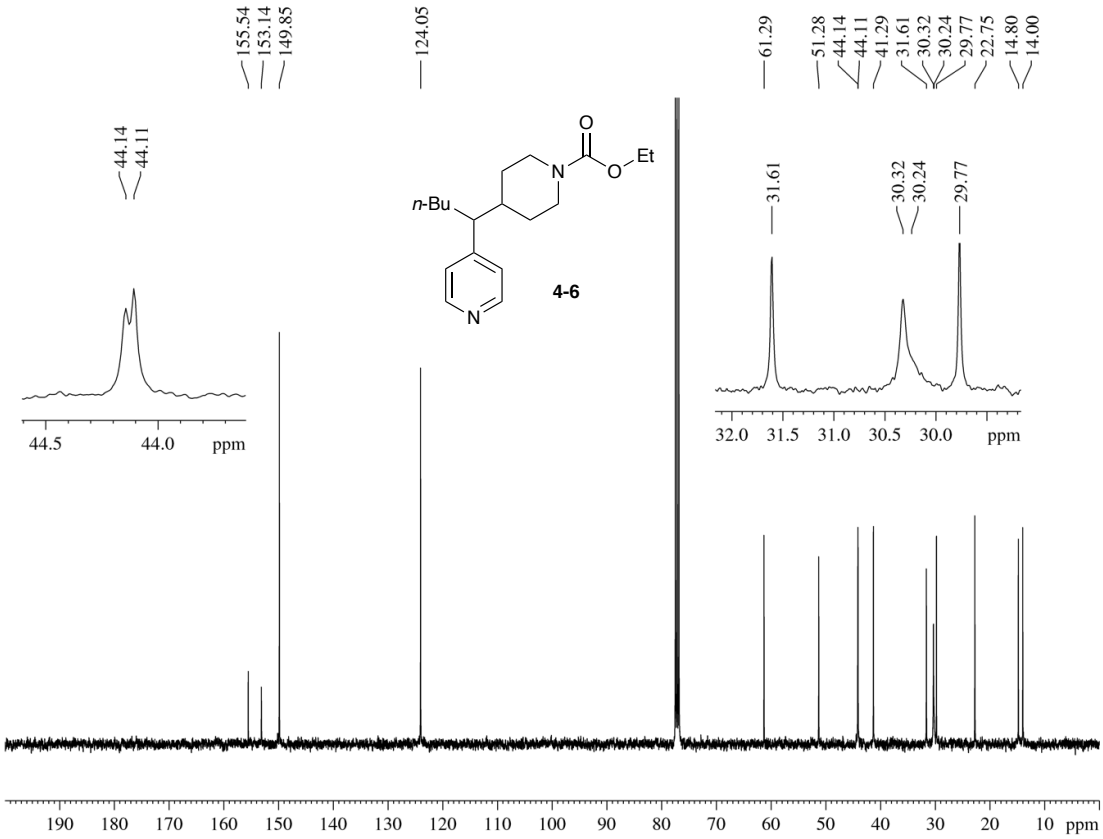
$(M+H)^+$ Calcd for $C_{18}H_{29}N_2O_2$ 305.2224; Found 305.2211.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-6**:

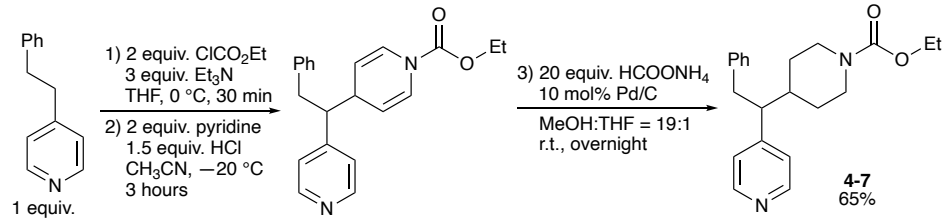




^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-6**:



Synthesis of compound **4-7**:



The piperidine product was synthesized by following **general procedures A**, **C**, and **D** using 4-phenethylpyridine[31] (183.3 mg, 1.0 equiv., 1.0 mmol) as the starting material. Final product **4-7** was obtained as colorless oil (220.1 mg, 65% yield).

Chromatography: 40% EtOAc in hexanes (R_f = 0.24).

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

δ 8.41 (d, *J* = 6.0 Hz, 2H), 7.17 – 7.06 (m, 3H), 6.95 – 6.87 (m, 4H), 4.36 – 4.00 (m, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.19 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.83 – 2.69 (m, 2H), 2.69 – 2.54 (m, 2H), 1.95 (m, 1H), 1.83 – 1.70 (m, 1H), 1.47 – 1.36 (m, 1H), 1.32 – 1.17 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.03 (qd, *J* = 12.4, 3.2 Hz, 1H).

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

δ 155.5, 151.9, 149.7, 139.6, 129.0, 128.4, 126.2, 124.2, 61.3, 53.4, 44.0(9), 44.0(5), 40.5, 38.6, 30.6, 30.0, 14.8.

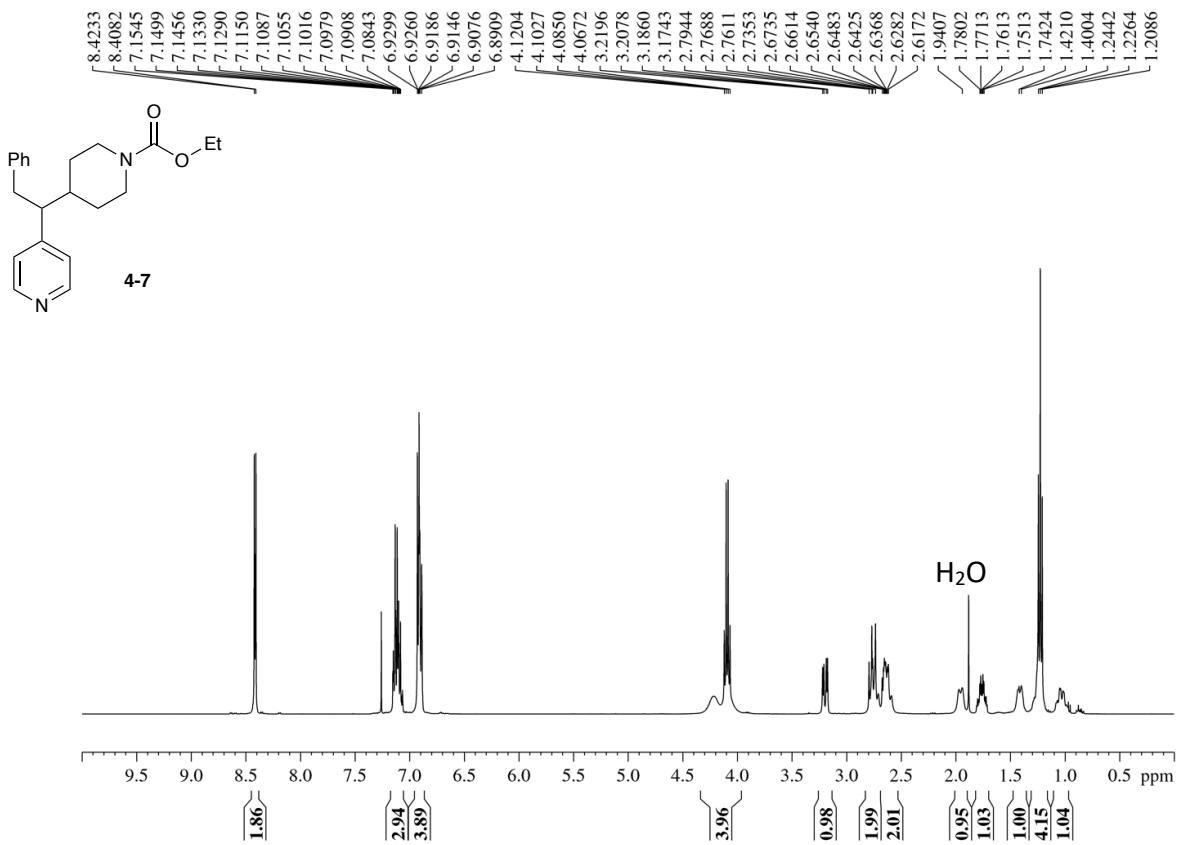
IR Alpha-Platinum ATR, Bruker, diamond crystal

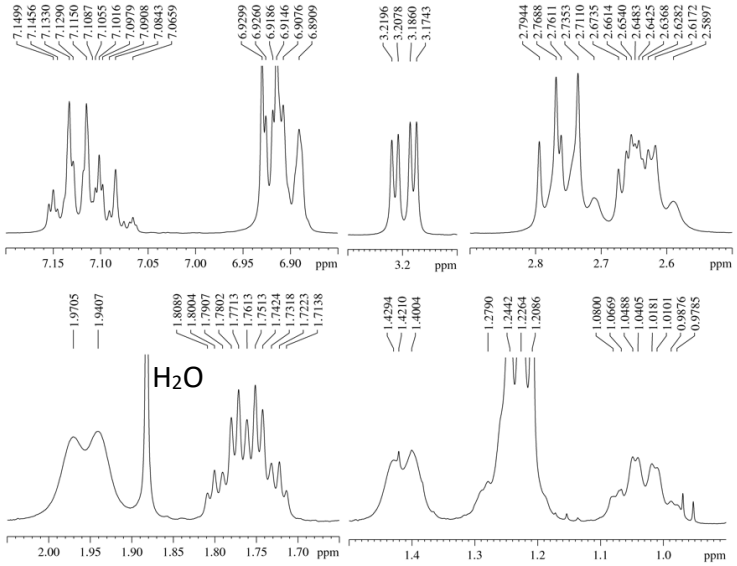
υ = 3064, 2981, 2852, 1687, 1430, 1235 cm^{-1}.

HRMS ESI-TOF

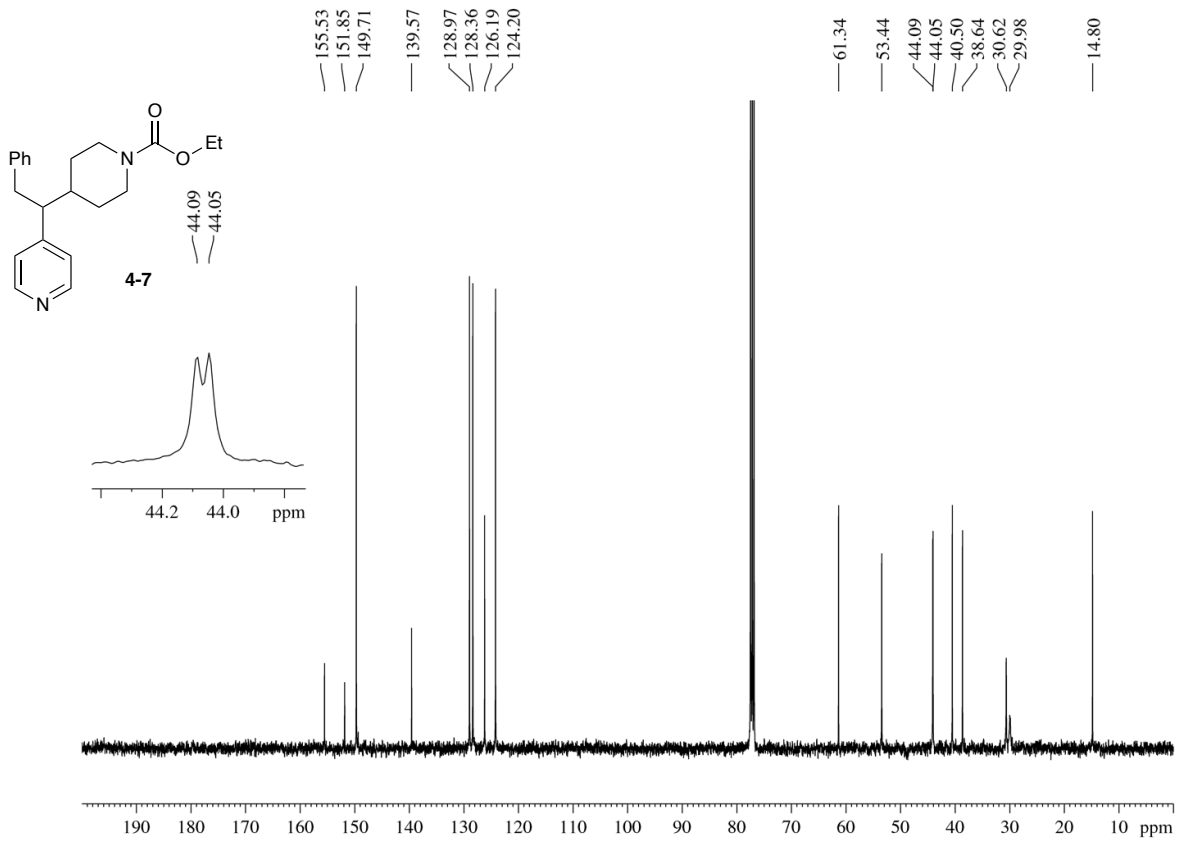
$(M+H)^+$ Calcd for $C_{21}H_{27}N_2O_2$ 339.2067; Found 339.2053.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-7**:

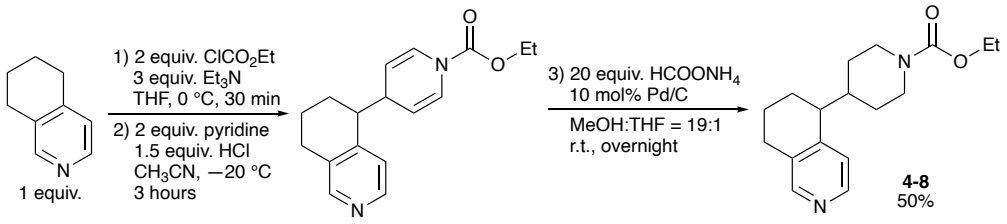




^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-7**:



Synthesis of compound **4-8**:



The ADHP was synthesized by following **general procedure A** using 5,6,7,8-tetrahydroisoquinoline (0.13 mL, 1.0 equiv., 1.0 mmol) as the starting material. This ADHP intermediate was converted to its corresponding DHP following a slightly modified version of **general procedure C**, where catalytic amount of hydrogen chloride (0.05 mL, 0.2 equiv., 0.2 mmol, 4 M in dioxane) were used. The hydrogenation of DHP was performed by following **general procedure D**, and product **4-8** was obtained as colorless oil (142.9 mg, 50% yield).

Chromatography: 30% EtOAc in hexanes (R_f = 0.16).

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

δ 8.36 – 8.28 (m, 2H), 7.05 (d, *J* = 5.2 Hz, 1H), 4.30 – 4.05 (m, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 2.76 – 2.55 (m, 5H), 2.00 – 1.85 (m, 2H), 1.83 – 1.72 (m, 1H), 1.72 – 1.60 (m, 2H), 1.60 – 1.50 (m, 1H), 1.50 – 1.39 (m, 1H), 1.39 – 1.30 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.21 – 1.11 (m, 1H).

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

δ 155.6, 150.7, 147.9, 146.7, 133.8, 122.9, 61.3, 44.5, 44.4, 41.9, 40.1, 30.6, 27.2, 26.5, 23.7, 20.7, 14.8.

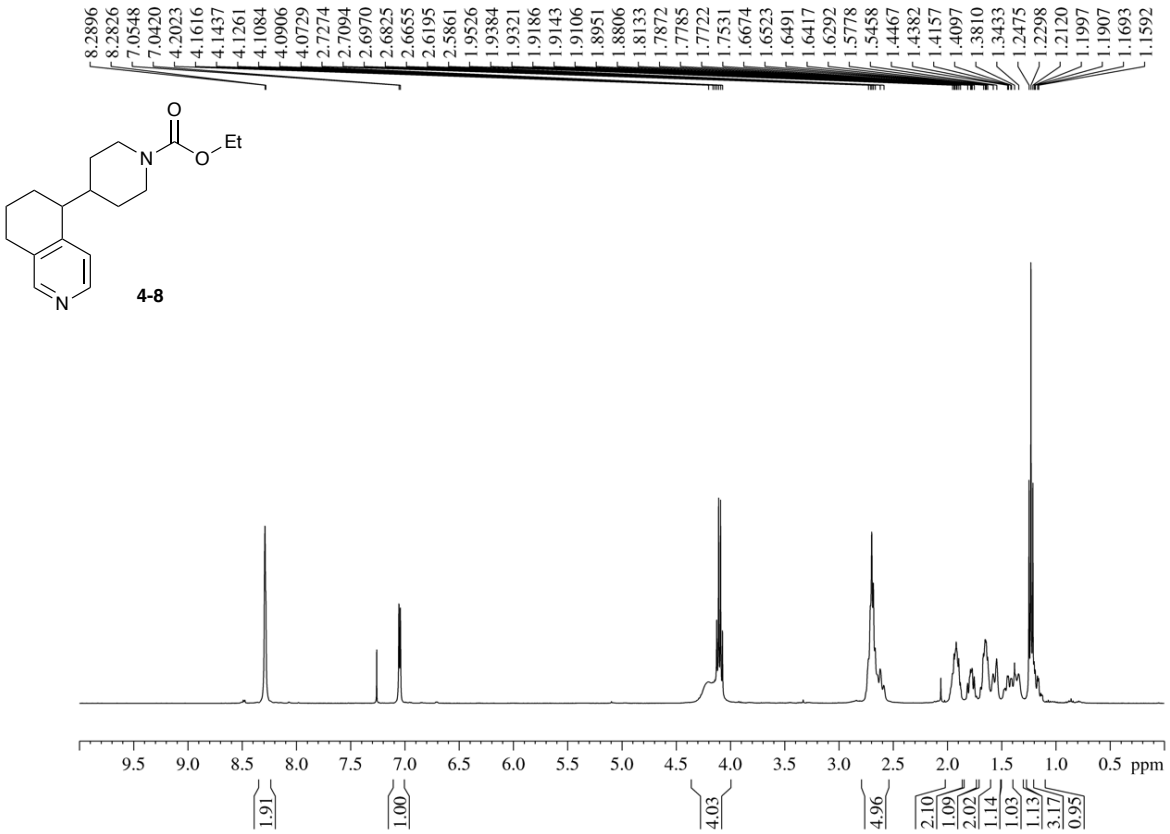
IR Alpha-Platinum ATR, Bruker, diamond crystal

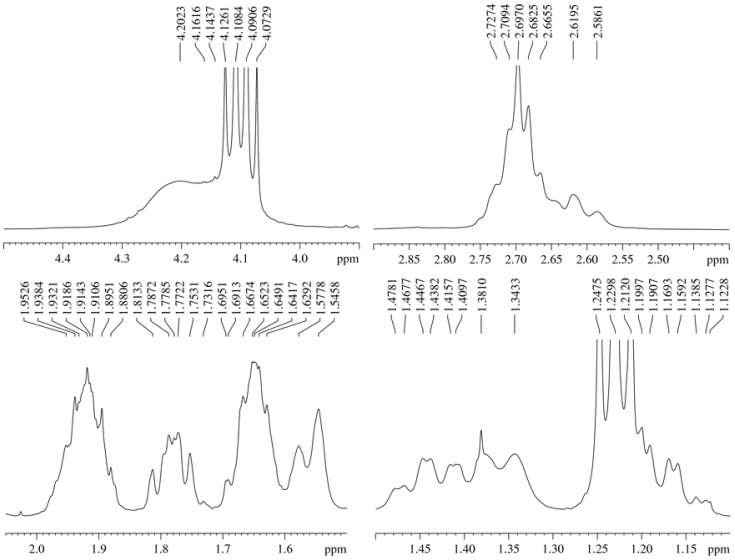
υ = 3054, 2980, 2859, 1690, 1430, 1228 cm^{-1}.

HRMS ESI-TOF

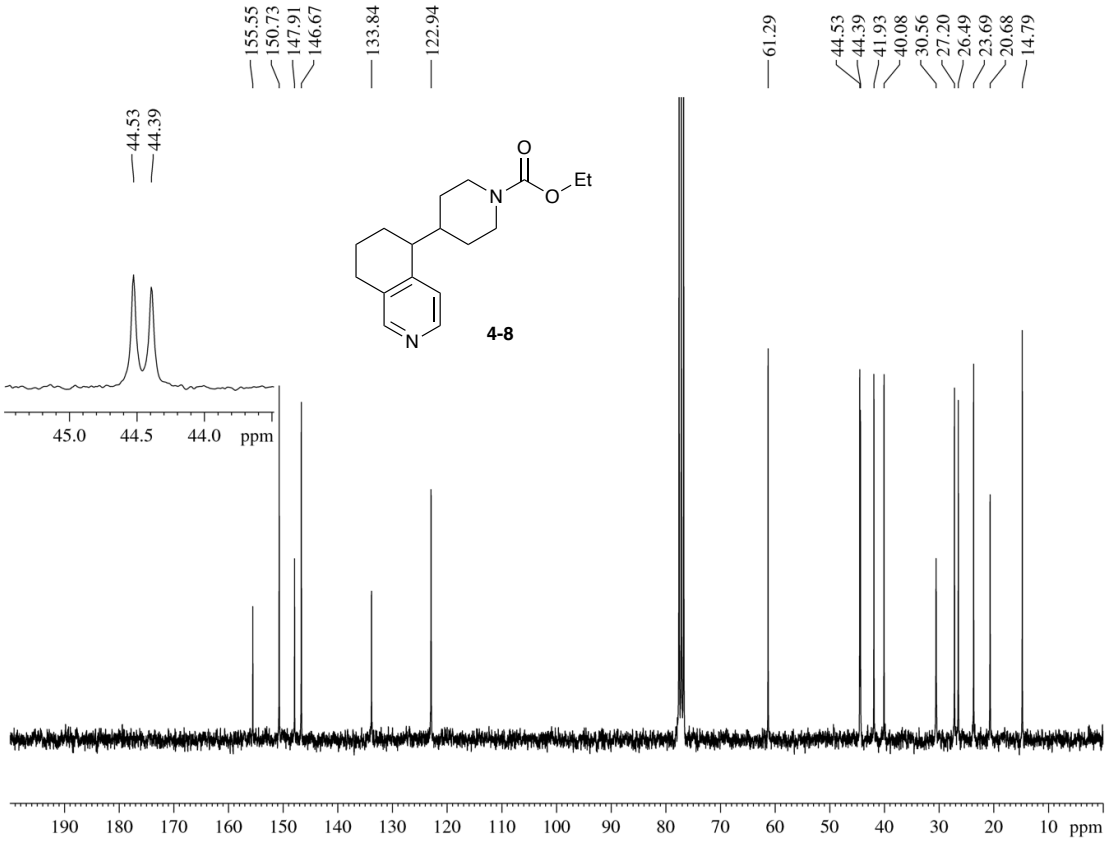
$(M+H)^+$ Calcd for $C_{17}H_{25}N_2O_2$ 289.1911; Found 289.1895.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-8**:

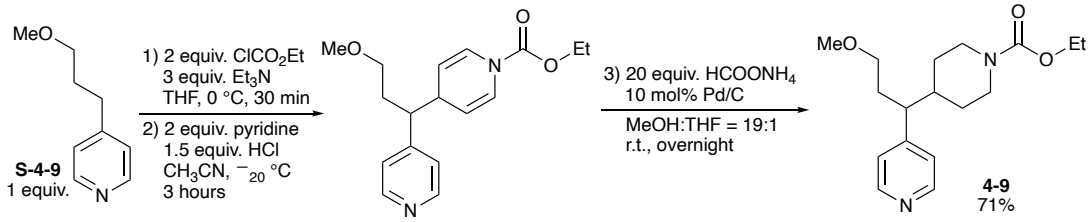




^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-8**:



Synthesis of compound **4-9**:



The piperidine product was synthesized by following **general procedures A**, **C**, and **D** using compound **S-4-9** (150.2 mg, 1.0 equiv., 1.0 mmol) as the starting material. Product **4-9** was obtained as light-yellow oil (216.7 mg, 71% yield).

Chromatography: 100% EtOAc (R_f = 0.22).

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

δ 8.50 (d, *J* = 6.0 Hz, 2H), 7.04 (d, *J* = 6.0 Hz, 2H), 4.35 – 3.97 (m, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.18 (s, 3H), 3.17 – 3.12 (m, 1H), 2.97 (dt, *J* = 8.8, 6.4 Hz, 1H), 2.77 – 2.53 (m, 2H), 2.53 – 2.45 (m, 1H), 2.19 – 2.08 (m, 1H), 1.85 (d, *J* = 12.4 Hz, 1H), 1.79 – 1.67 (m, 1H), 1.67 – 1.55 (m, 1H), 1.29 (d, *J* = 12.4 Hz, 1H), 1.21 (t, *J* = 7.2 Hz, 3H), 1.18 – 1.06 (m, 1H), 0.99 (qd, *J* = 12.4, 4.0 Hz, 1H).

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

δ 155.5, 152.3, 150.0, 124.0, 70.3, 61.3, 58.7, 47.5, 44.1, 44.0, 41.1, 32.0, 30.2(1), 30.2, 14.8.

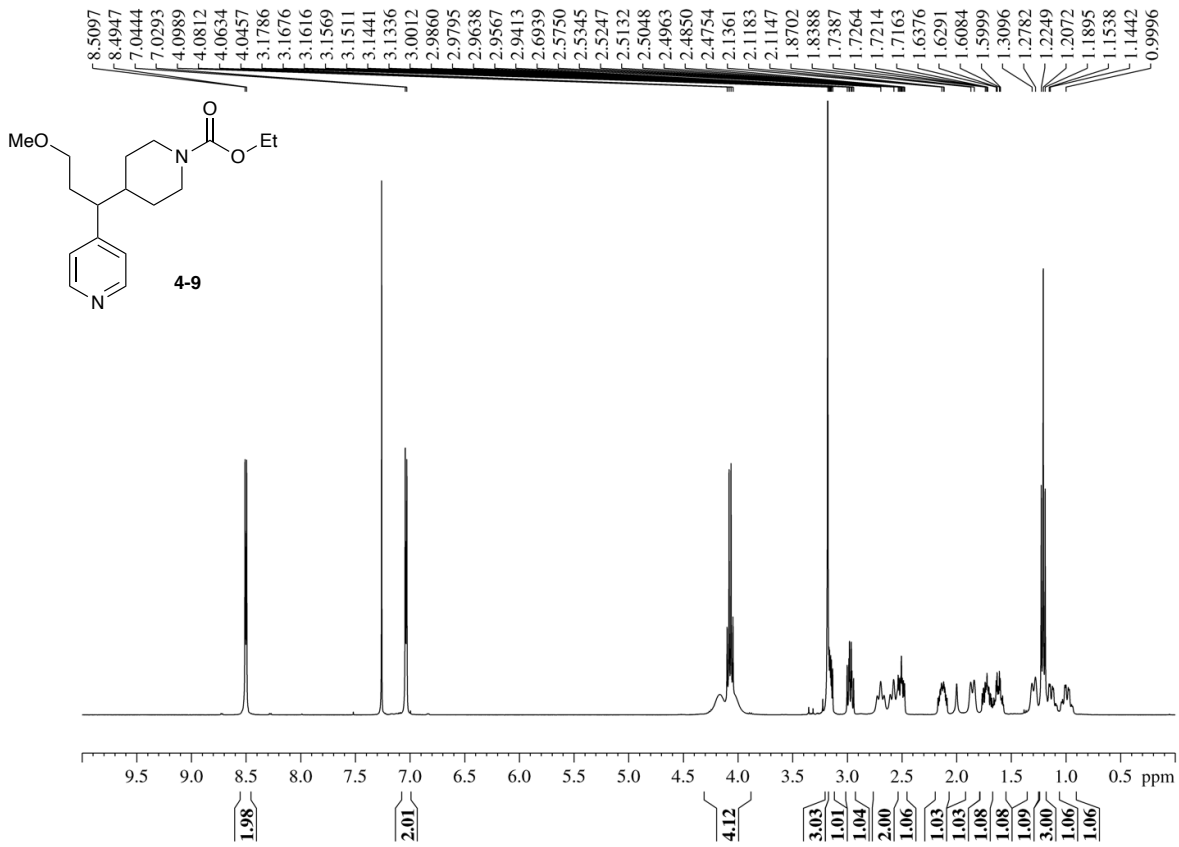
IR Alpha-Platinum ATR, Bruker, diamond crystal

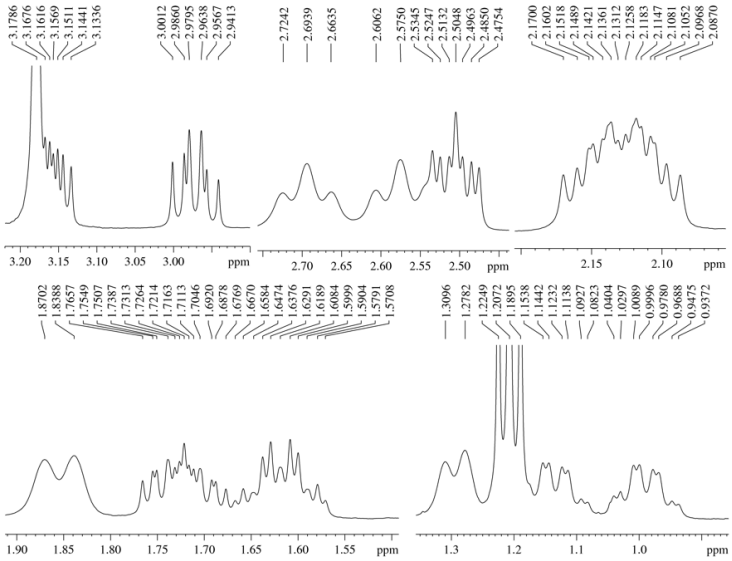
υ = 3068, 2981, 2869, 1692, 1430 cm^{-1}.

HRMS ESI-TOF

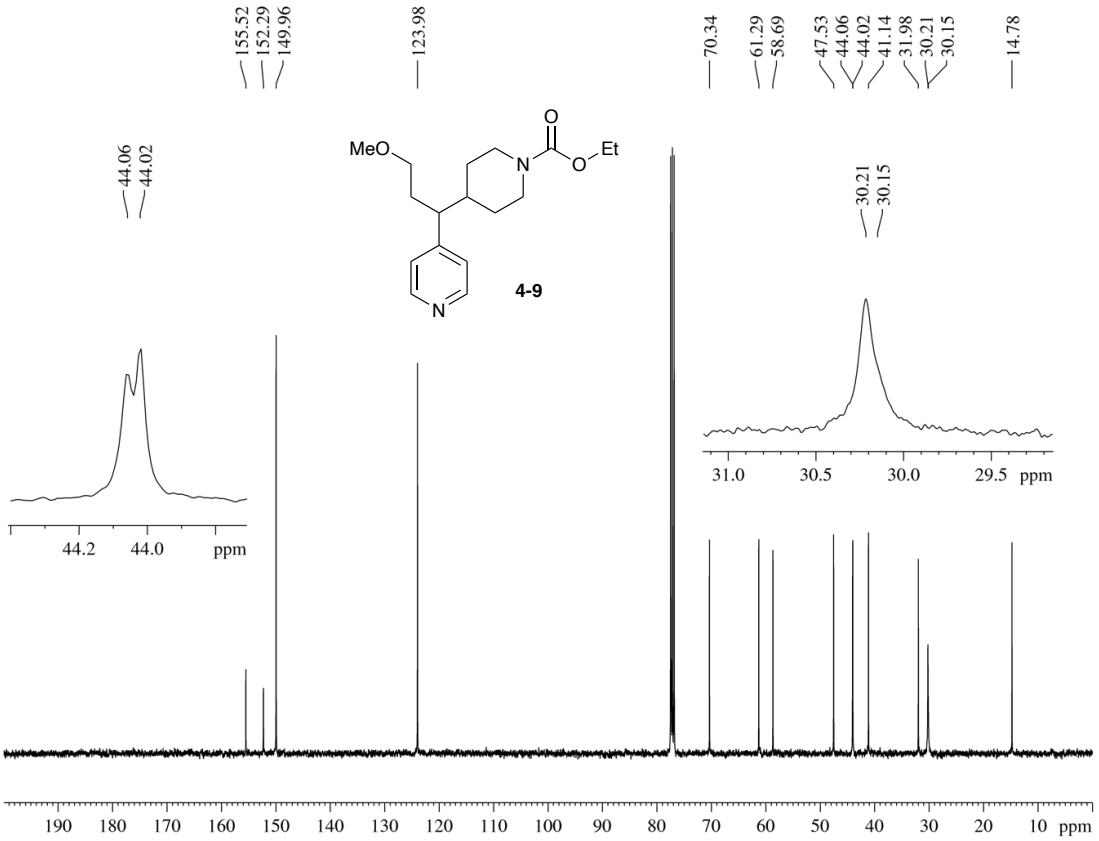
$(M+H)^+$ Calcd for $C_{17}H_{27}N_2O_3$ 307.2016; Found 307.2009.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-9**:

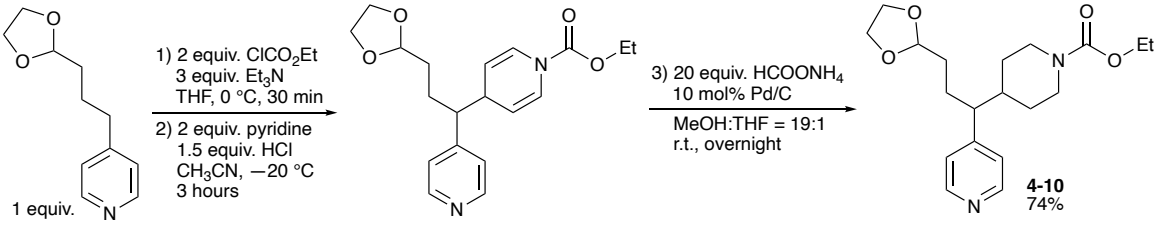




^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-9**:



Synthesis of compound **4-10**:



The piperidine product was synthesized by following **general procedures A**, **C**, and **D** using 4-(3-(1,3-dioxolan-2-yl)propyl)pyridine[31] (193.3 mg, 1.0 equiv., 1.0 mmol) as the starting material. Product **4-10** was obtained as light-yellow oil (259.1 mg, 74% yield).

Chromatography: 5% Et_3N in EtOAc (R_f = 0.29).

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

δ 8.49 (d, *J* = 6.0 Hz, 2H), 7.02 (d, *J* = 6.0 Hz, 2H), 4.76 (t, *J* = 4.4 Hz, 1H),

4.30 – 3.95 (m, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 3.95 – 3.75 (m, 4H),

2.69 (t, *J* = 12.4 Hz, 1H), 2.57 (t, *J* = 12.4 Hz, 1H),

2.34 (ddd, *J* = 11.6, 8.4, 4.0 Hz, 1H), 2.01 – 1.92 (m, 1H), 1.89 – 1.82 (m, 1H),

1.72 – 1.57 (m, 2H), 1.47 – 1.33 (m, 2H), 1.33 – 1.26 (m, 1H),

1.21 (t, *J* = 7.2 Hz, 3H), 1.18 – 1.07 (m, 1H), 0.97 (qd, *J* = 12.4, 3.2 Hz, 1H).

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

δ 155.6, 152.4, 150.0, 124.0, 104.2, 65.0(4), 65.0, 61.3, 51.1, 44.1(1), 44.1, 41.3,

31.9, 30.3, 26.0, 14.8.

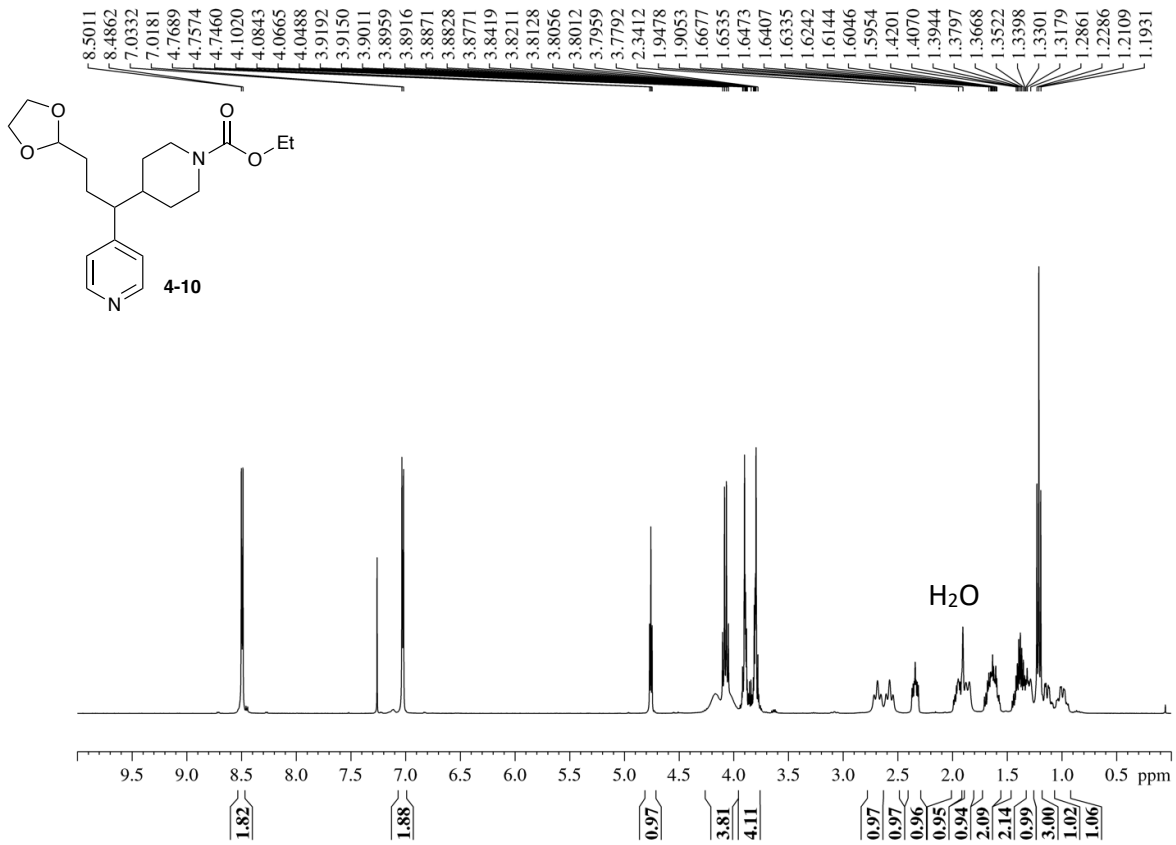
IR Alpha-Platinum ATR, Bruker, diamond crystal

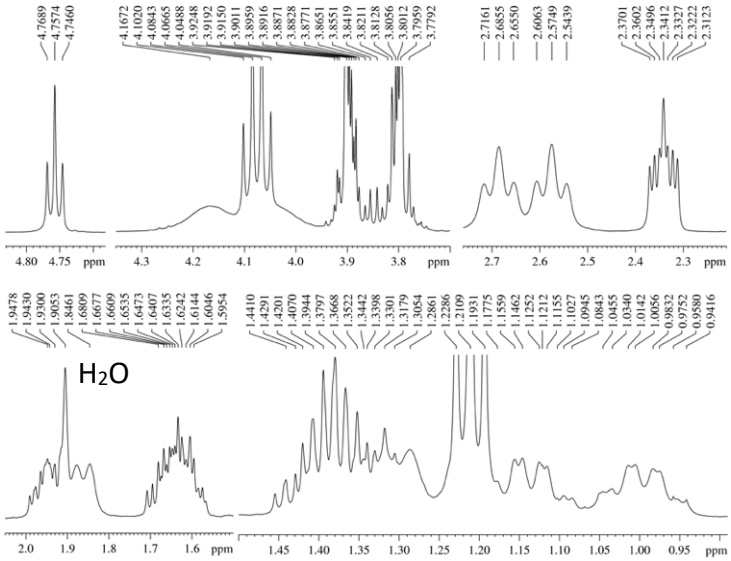
υ = 3067, 2931, 2866, 1688, 1416, 1233 cm^{-1}.

HRMS ESI-TOF

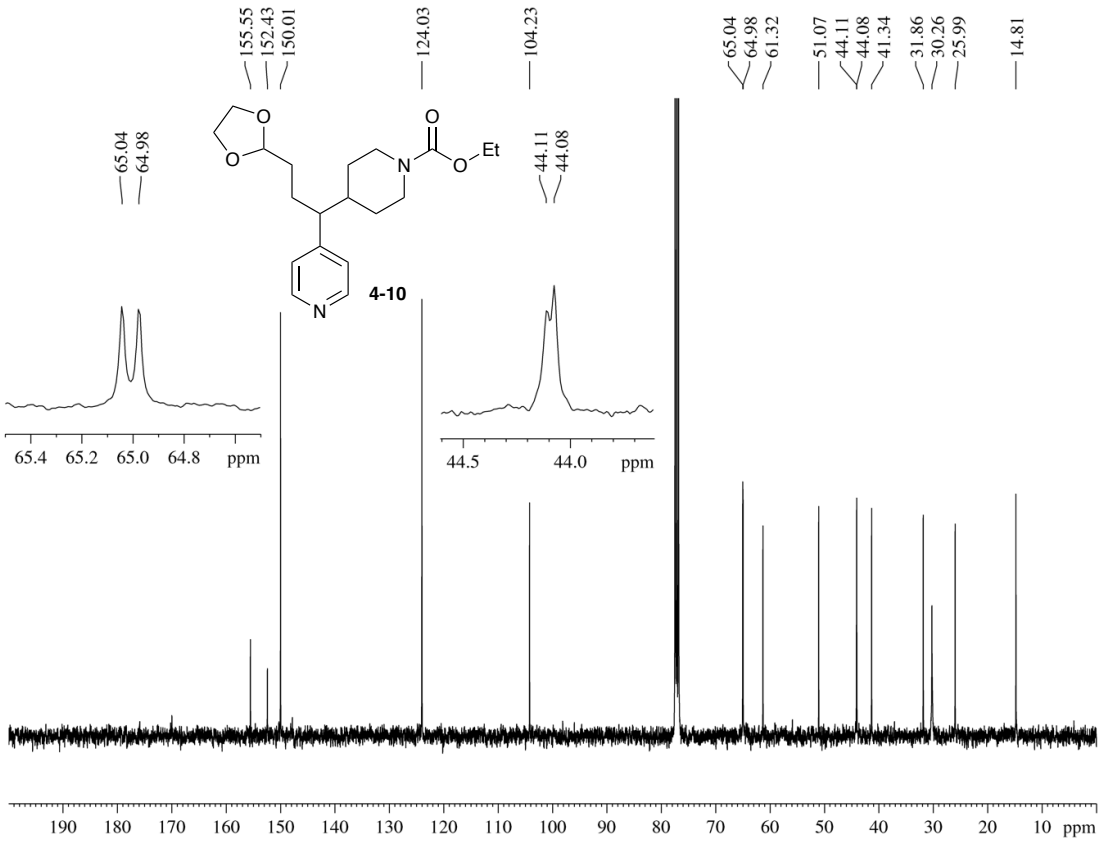
$(M+H)^+$ Calcd for $C_{19}H_{29}N_2O_4$ 349.2122; Found 349.2113.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-10**:

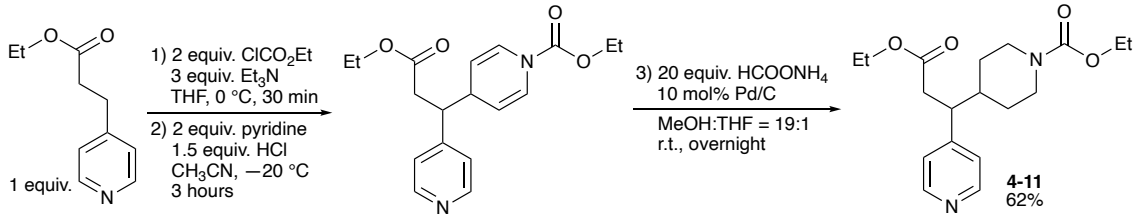




^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-10**:



Synthesis of compound **4-11**:



The piperidine product was synthesized by following **general procedures A**, **C**, and **D** using ethyl 3-(pyridin-4-yl)propanoate[31] (179.2 mg, 1.0 equiv., 1.0 mmol) as the starting material. Product **4-11** was obtained as light-yellow oil (212 mg, 62% yield).

Chromatography: 100% EtOAc (R_f = 0.26).

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

δ 8.51 (d, *J* = 6.0 Hz, 2H), 7.06 (d, *J* = 6.0 Hz, 2H), 4.31 – 4.01 (m, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.97 (qd, *J* = 12.8, 1.6 Hz, 2H), 2.98 – 2.88 (m, 1H), 2.78 (dd, *J* = 15.6, 5.2 Hz, 1H), 2.75 – 2.64 (m, 1H), 2.64 – 2.53 (m, 2H), 1.76 (d, *J* = 12.8 Hz, 1H), 1.72 – 1.60 (m, 1H), 1.41 – 1.29 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.19 – 1.11 (m, 1H), 1.08 (t, *J* = 7.2 Hz, 3H), 1.06 – 0.96 (m, 1H).

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

δ 171.8, 155.5, 151.3, 150.0, 123.7, 61.4, 60.7, 47.0, 43.9, 40.8, 37.4, 29.9, 14.8, 14.1.

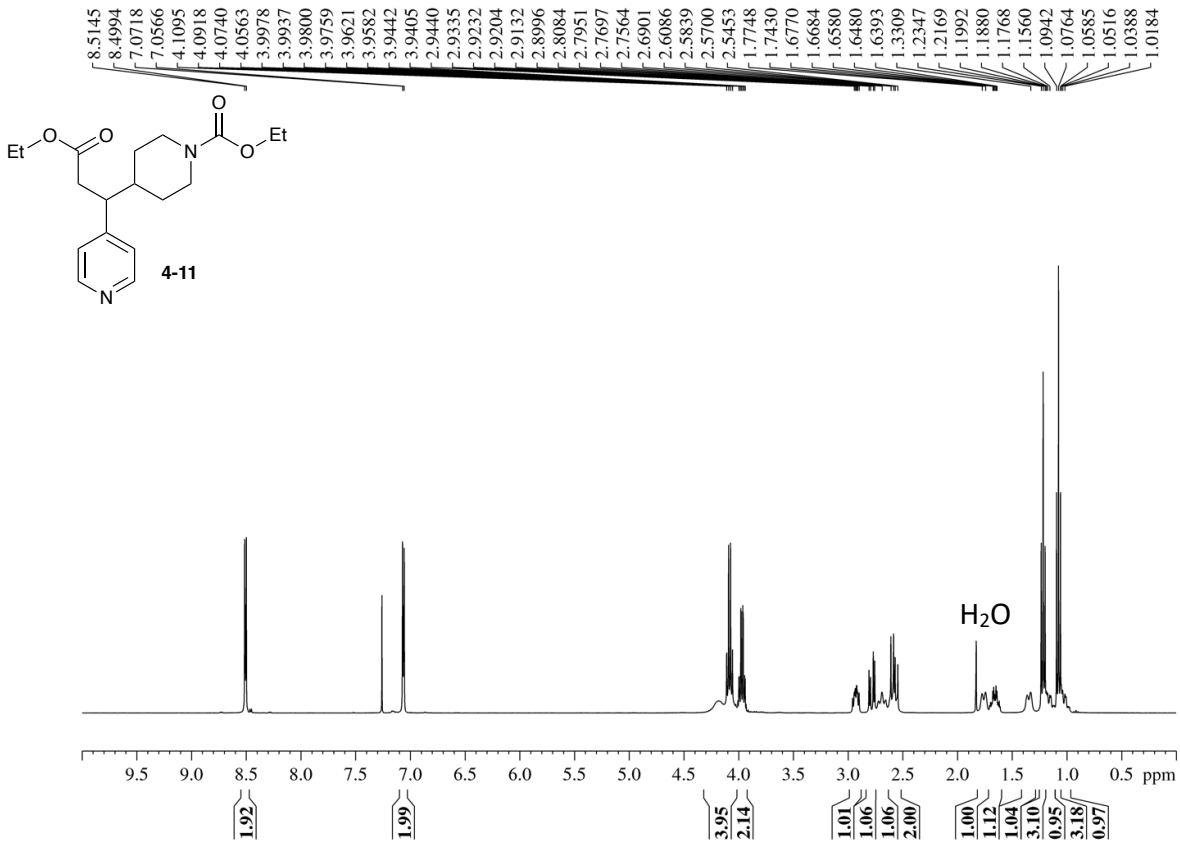
IR Alpha-Platinum ATR, Bruker, diamond crystal

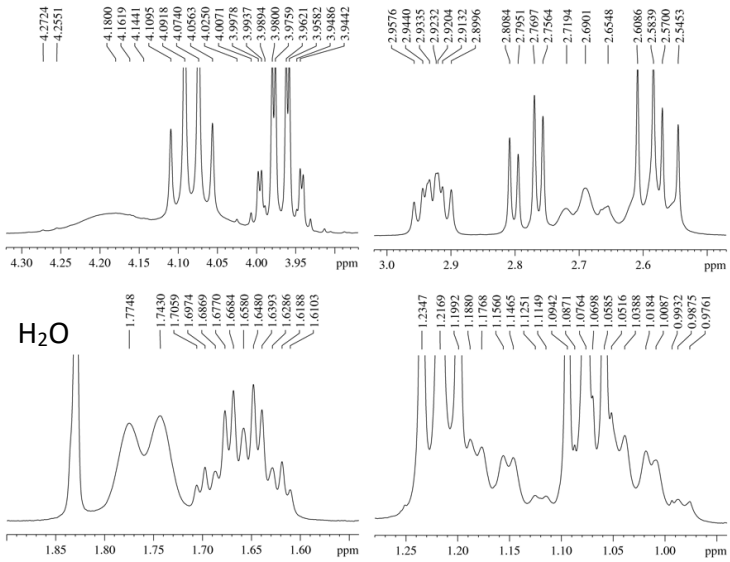
υ = 3070, 2980, 2857, 1731, 1689, 1430, 1250 cm^{-1}.

HRMS ESI-TOF

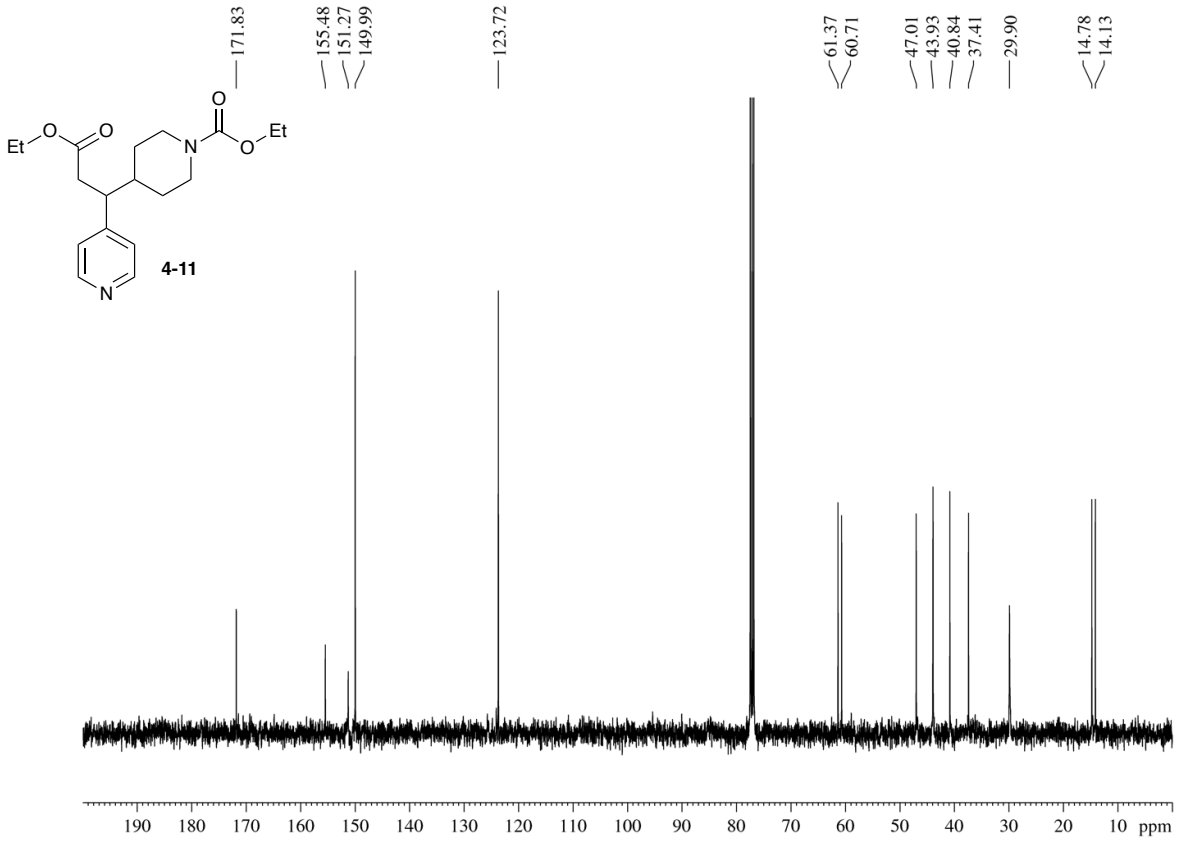
$(M+H)^+$ Calcd for $C_{18}H_{27}N_2O_4$ 335.1966; Found 335.1955.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-11**:

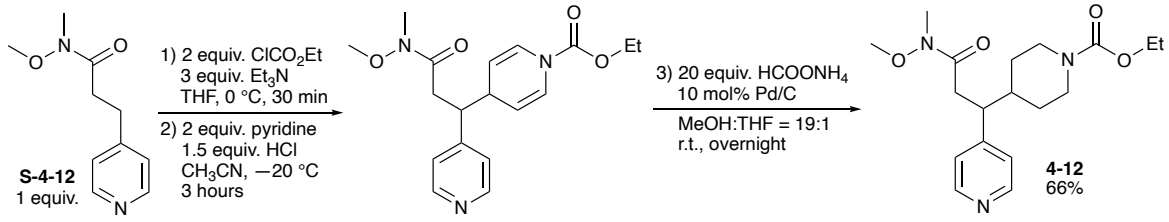




^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-11**:



Synthesis of compound **4-12**:



The piperidine product was synthesized by following **general procedures A**, **C**, and **D** using compound **S-4-12** (97.2 mg, 1.0 equiv., 0.5 mmol) as the starting material. Product **4-12** was obtained as light-yellow oil (114.5 mg, 66% yield).

Chromatography: 5% Et_3N in EtOAc (R_f = 0.26).

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

δ 8.50 (d, *J* = 6.0 Hz, 2H), 7.10 (d, *J* = 6.0 Hz, 2H), 4.30 – 3.98 (m, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.61 (s, 3H), 3.13 – 3.06 (m, 1H), 3.05 (s, 3H), 2.82 (d, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 12.4 Hz, 1H), 2.60 (t, *J* = 12.4 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.72 – 1.65 (m, 1H), 1.43 – 1.32 (m, 1H), 1.28 – 1.12 (m, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.04 (qd, *J* = 12.4, 4.0 Hz, 1H).

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

δ 172.3, 155.5, 152.1, 149.9, 123.9, 61.4, 61.3, 46.1, 44.0(1), 44.0, 40.7, 34.3, 32.2, 30.0, 29.9, 14.8.

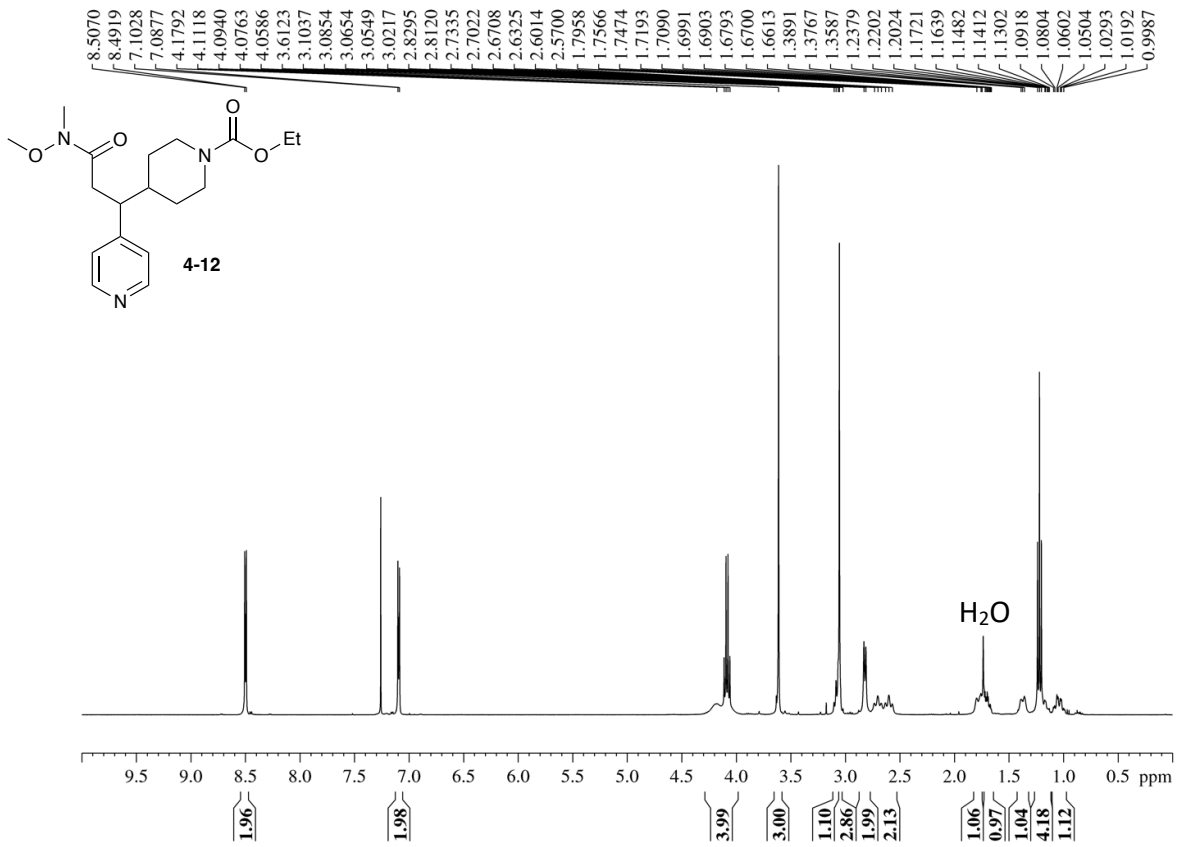
IR Alpha-Platinum ATR, Bruker, diamond crystal

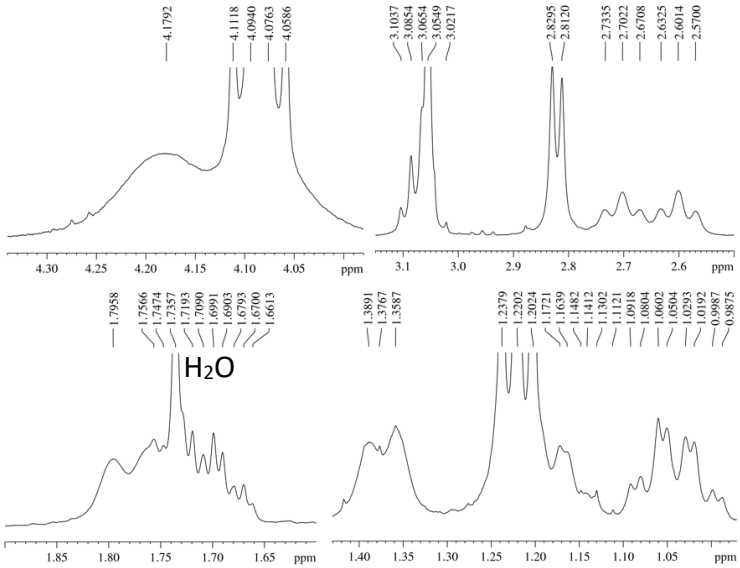
υ = 3067, 2931, 2857, 1686, 1634, 1418, 1252 cm^{-1}.

HRMS ESI-TOF

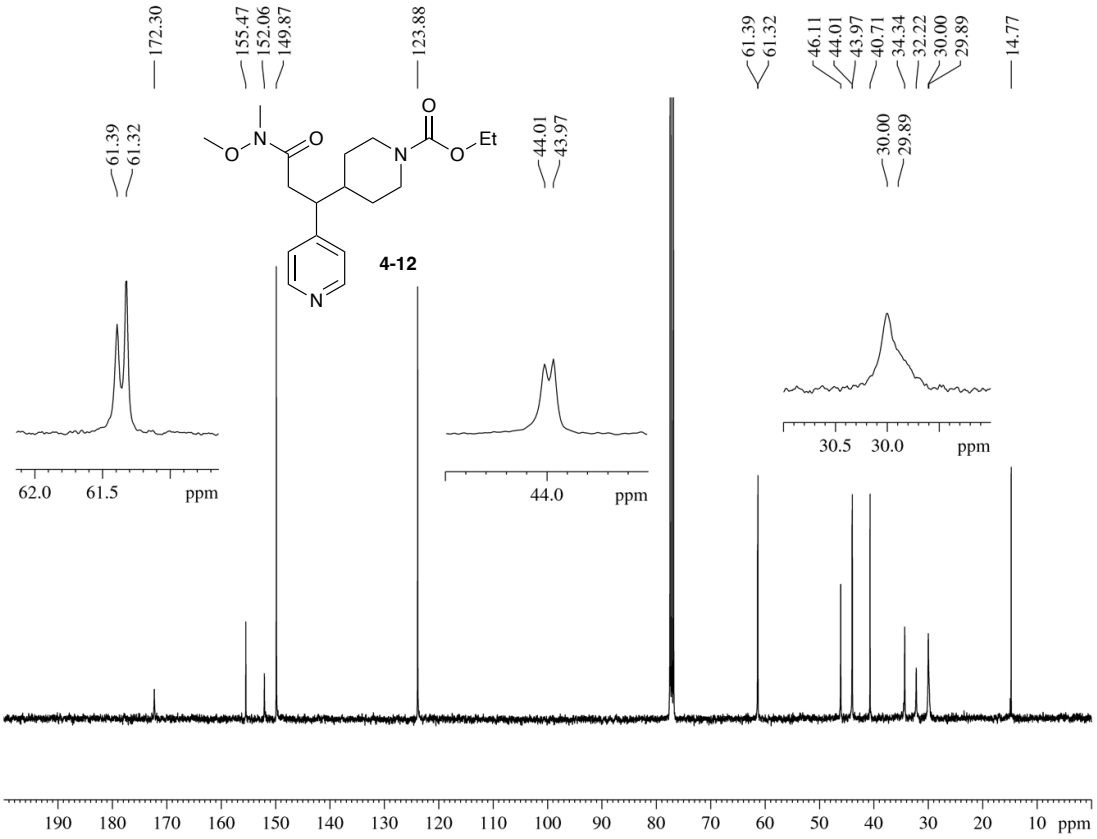
$(M+H)^+$ Calcd for $C_{18}H_{28}N_3O_4$ 350.2075; Found 350.2065.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-12**:

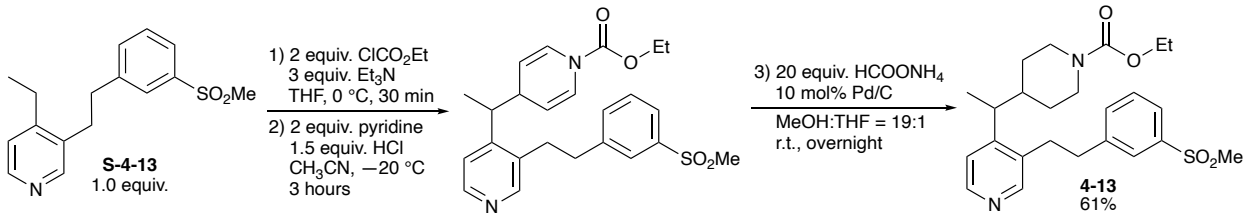




^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-12**:



Synthesis of compound **4-13**:



The piperidine product was synthesized by following **general procedures A**, **C**, and **D** using compound **S-4-13** (100 mg, 1.0 equiv., 0.34 mmol) as the starting material. Product **4-13** was obtained as colorless oil (95.1 mg, 61% yield).

Chromatography: 100% EtOAc (R_f = 0.38).

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

δ 8.40 (d, *J* = 5.2 Hz, 1H), 8.22 (s, 1H), 7.79 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.67 – 7.63 (m, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 7.6, 1.2 Hz, 1H), 7.10 (d, *J* = 5.2 Hz, 1H), 4.39 – 3.95 (m, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 3.07 – 2.98 (m, 1H), 3.02 (s, 3H), 2.98 – 2.84 (m, 3H), 2.77 – 2.63 (m, 2H), 2.57 (t, *J* = 12.4 Hz, 1H), 2.00 – 1.87 (m, 1H), 1.68 – 1.52 (m, 1H), 1.32 – 1.27 (m, 1H), 1.27 – 1.12 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.00 (qd, *J* = 12.4, 3.6 Hz,1H).

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

δ 155.5, 153.7, 150.8, 148.1, 142.5, 140.9, 134.0, 134.0, 129.8, 127.3, 125.6, 121.4, 61.4, 44.6, 44.1, 42.2, 39.5, 37.3, 31.8, 30.8, 29.9, 19.1, 14.8.

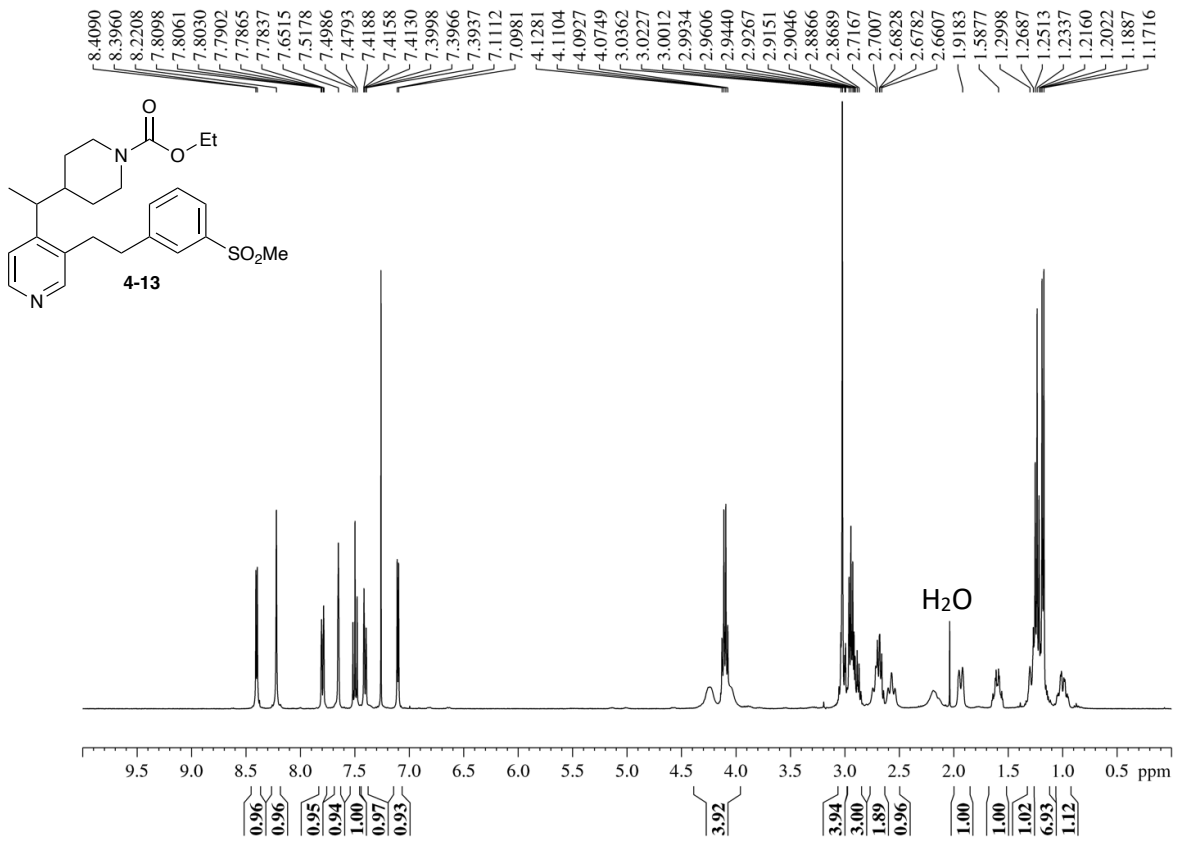
IR Alpha-Platinum ATR, Bruker, diamond crystal

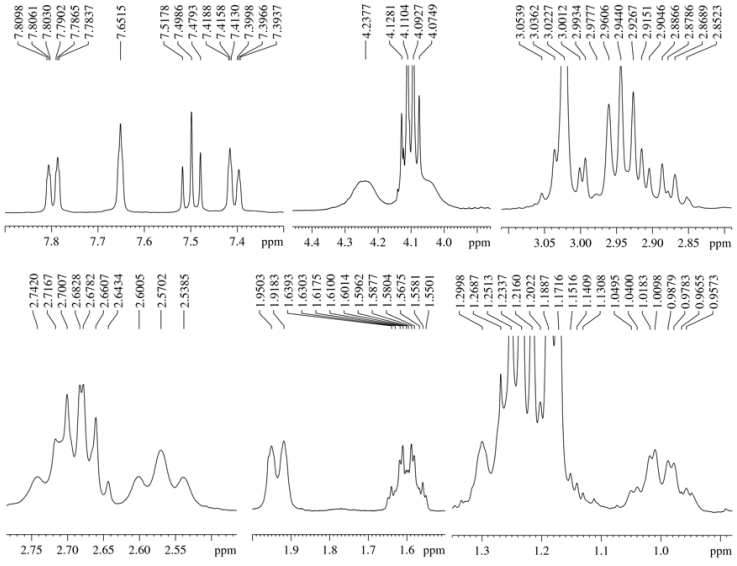
υ = 3087, 2980, 2866, 1682, 1435, 1302, 1146, 759 cm^{-1}.

HRMS ESI-TOF

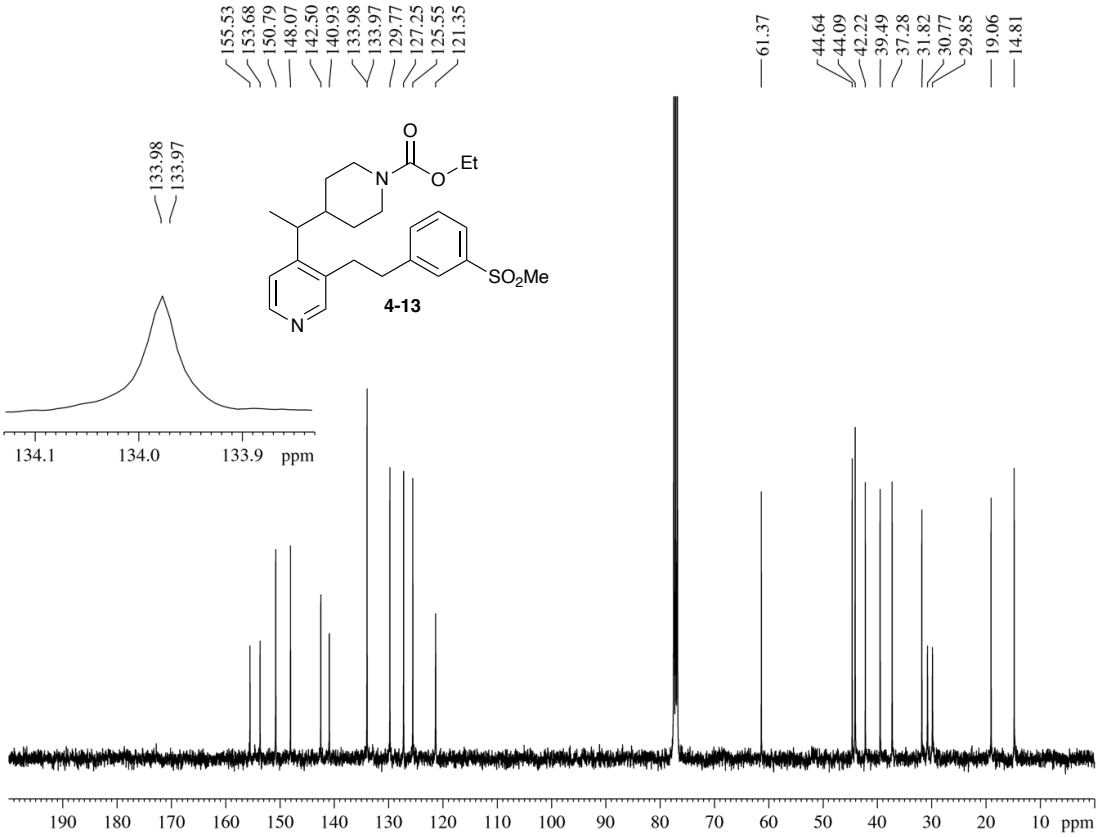
$(M+H)^+$ Calcd for $C_{24}H_{33}N_2O_4S$ 445.2156; Found 445.2150.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-13**:

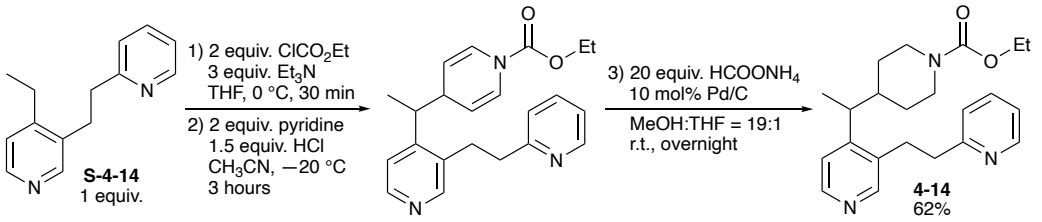




^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-13**:



Synthesis of compound **4-14**:



The piperidine product was synthesized by following **general procedures A**, **C**, and **D** using compound **S-4-14** (106.2 mg, 1.0 equiv., 0.5 mmol) as the starting material. Product **4-14** was obtained as colorless oil (113.2 mg, 62% yield).

Chromatography: 2% methanol in EtOAc (R_f = 0.27).

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

δ 8.57 (dd, *J* = 4.8, 0.8 Hz, 1H), 8.37 (d, *J* = 5.2 Hz, 1H), 8.34 (s, 1H), 7.56 (td, *J* = 7.6, 1.8 Hz, 1H), 7.17 – 7.10 (m, 1H), 7.06 (d, *J* = 5.2 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 4.37 – 4.15 (br, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 4.07 – 3.94 (br, 1H), 3.19 – 3.08 (m, 1H), 3.08 – 2.97 (m, 3H), 2.83 – 2.73 (m, 1H), 2.73 – 2.49 (m, 2H), 1.97 – 1.84 (m, 1H), 1.65 – 1.52 (m, 1H), 1.32 – 1.26 (m, 1H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.21 – 1.08 (m, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.03 (dq, *J* = 12.4, 4.0 Hz, 1H).

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

δ 160.4, 155.6, 153.4, 151.1, 149.7, 148.0, 136.6, 134.9, 123.1, 121.6, 121.1, 61.3, 44.2, 42.2, 39.9, 39.2, 30.7(2), 30.7, 30.1, 29.8, 19.0, 14.8.

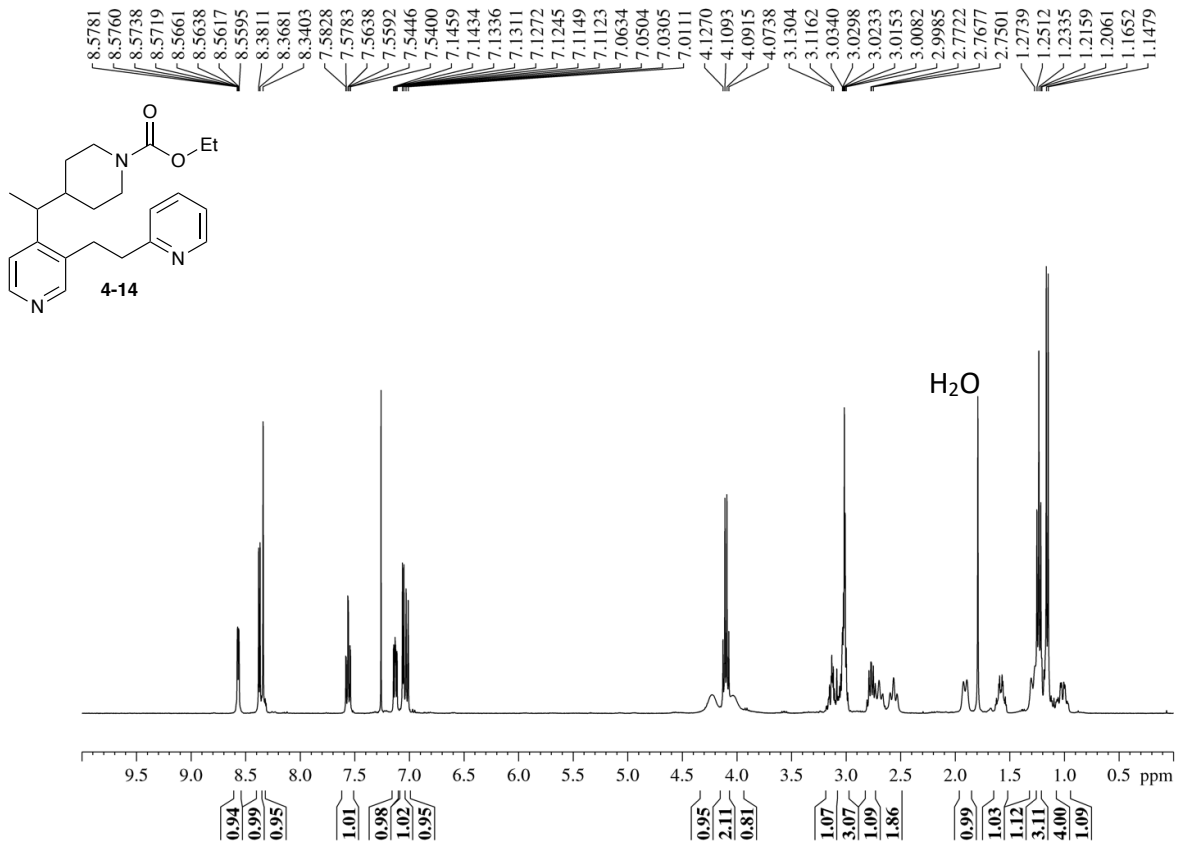
IR Alpha-Platinum ATR, Bruker, diamond crystal

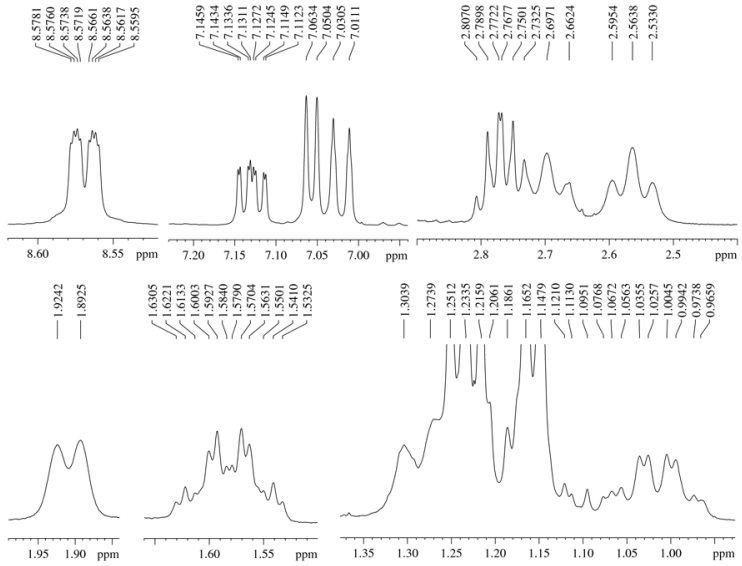
υ = 3054, 2971, 2881, 1693, 1591, 1434, 1411, 1221, 751 cm^{-1}.

HRMS ESI-TOF

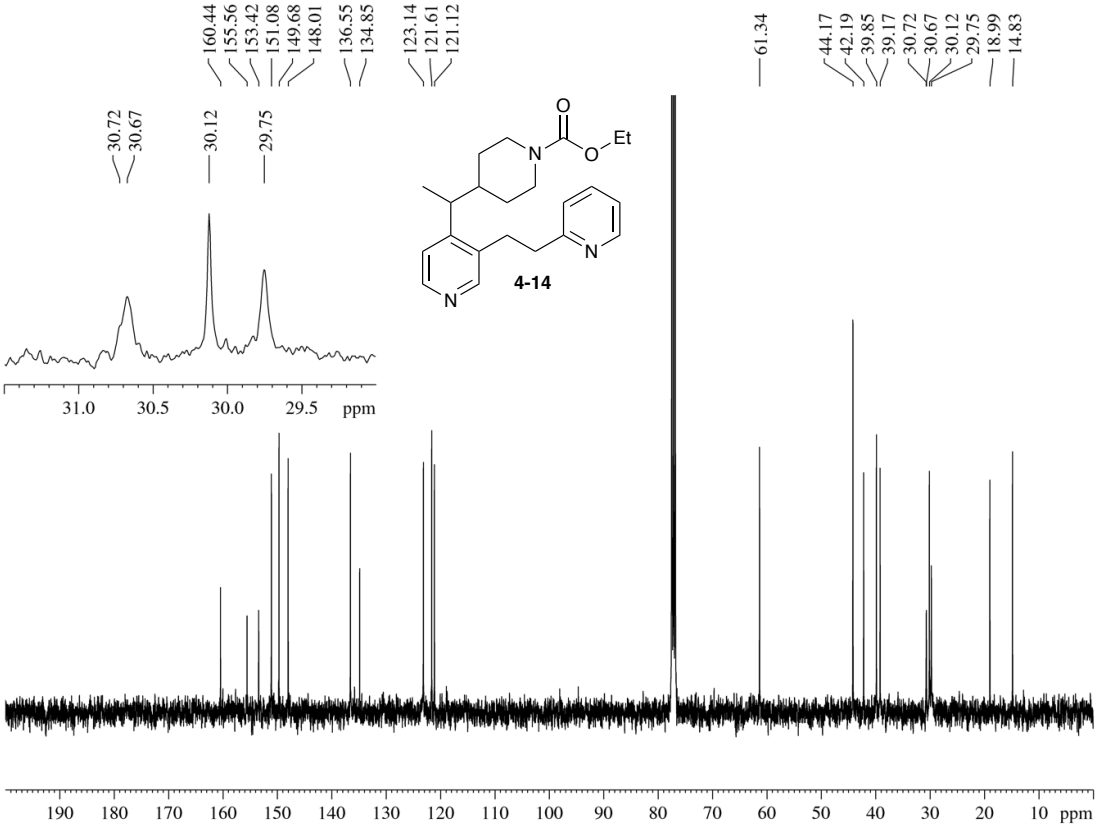
$(M+H)^+$ Calcd for $C_{22}H_{30}N_3O_2$ 368.2333; Found 368.2321.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-14**:

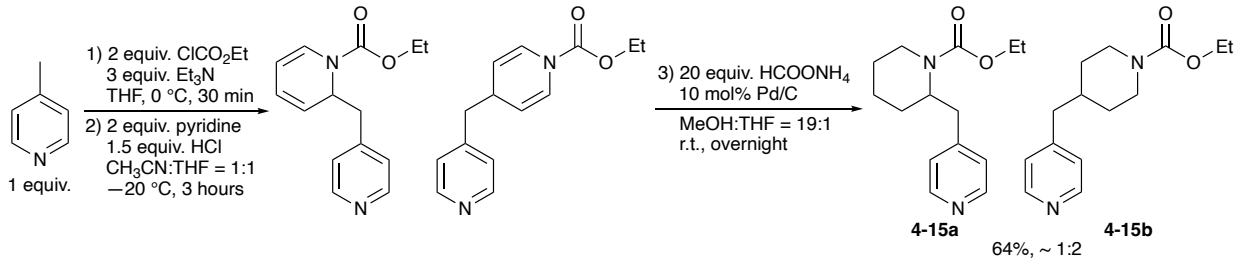




^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-14**:

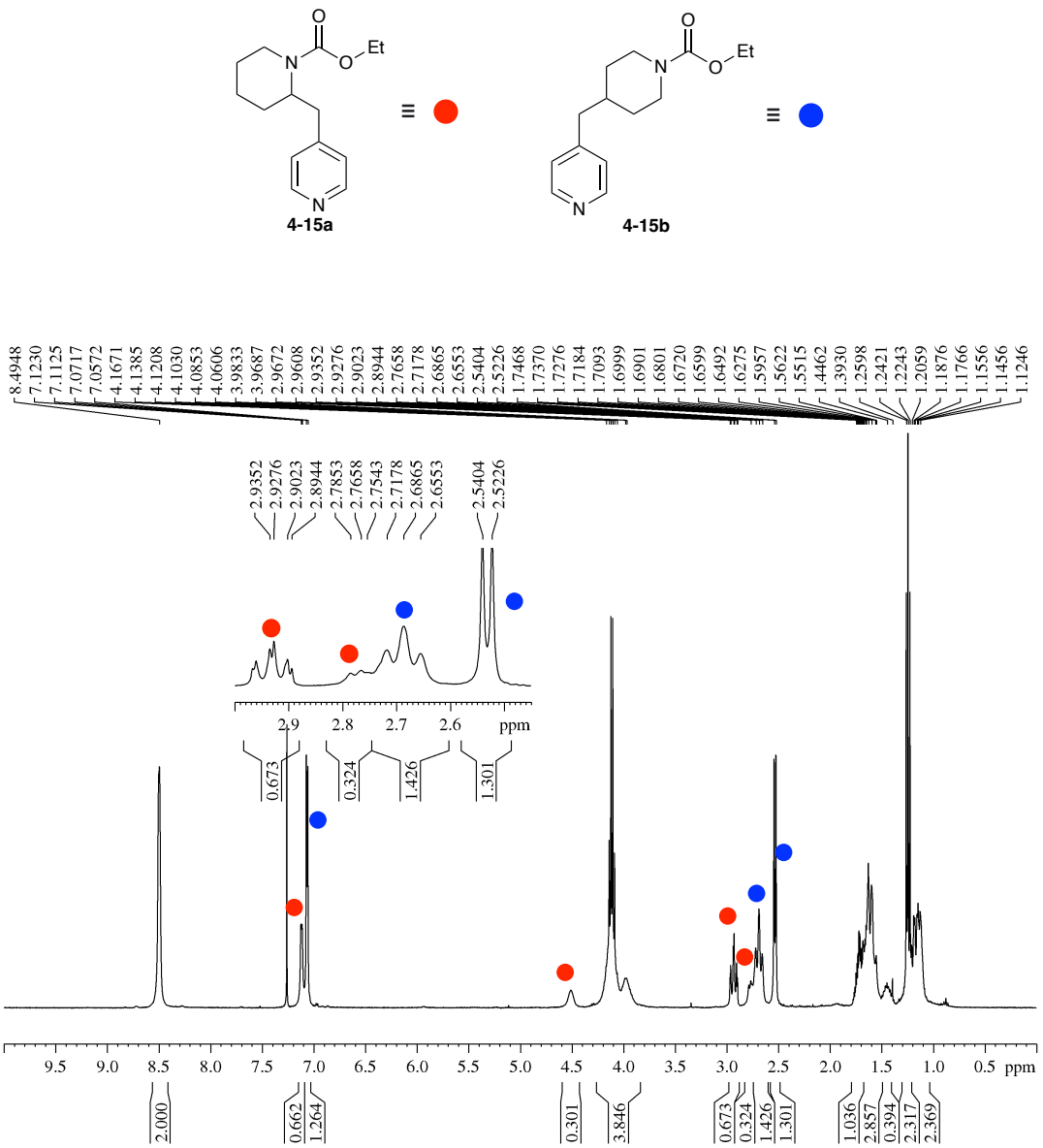


Synthesis of compounds **4-15a** and **4-15b**:

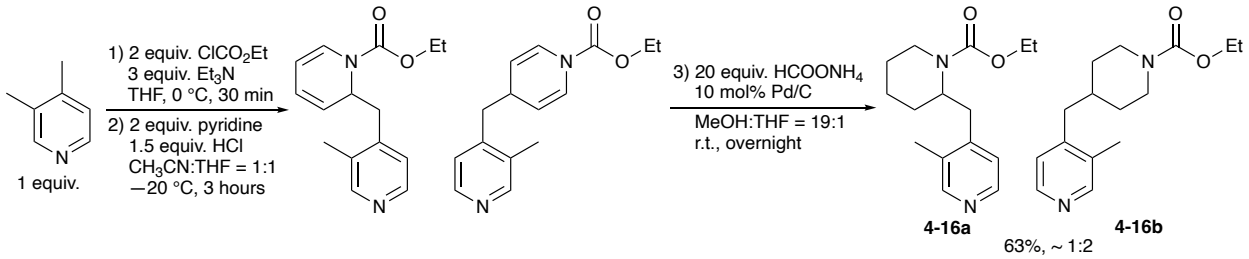


The ADHP intermediate was synthesized by following **general procedure A** using 4-picoline (93.2 mg, 1.0 equiv., 1.0 mmol) as the starting material. The DHP intermediates were synthesized by following **general procedure C** but using anhydrous THF to dissolve the ADHP instead of CH_3CN. The DHP intermediates were hydrogenated by following **general procedure D**. Product mixture of **4-15a** and **4-15b** was obtained as colorless oil (158.4 mg, ~ 1:2 ratio, 64% overall yield).

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-15a** and **4-15b**:

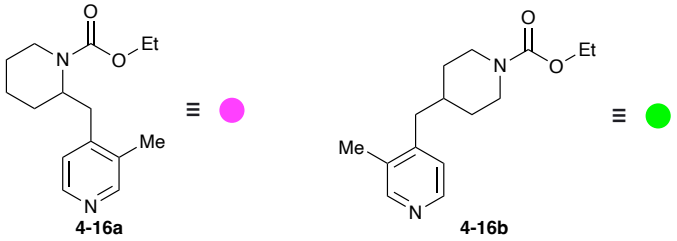


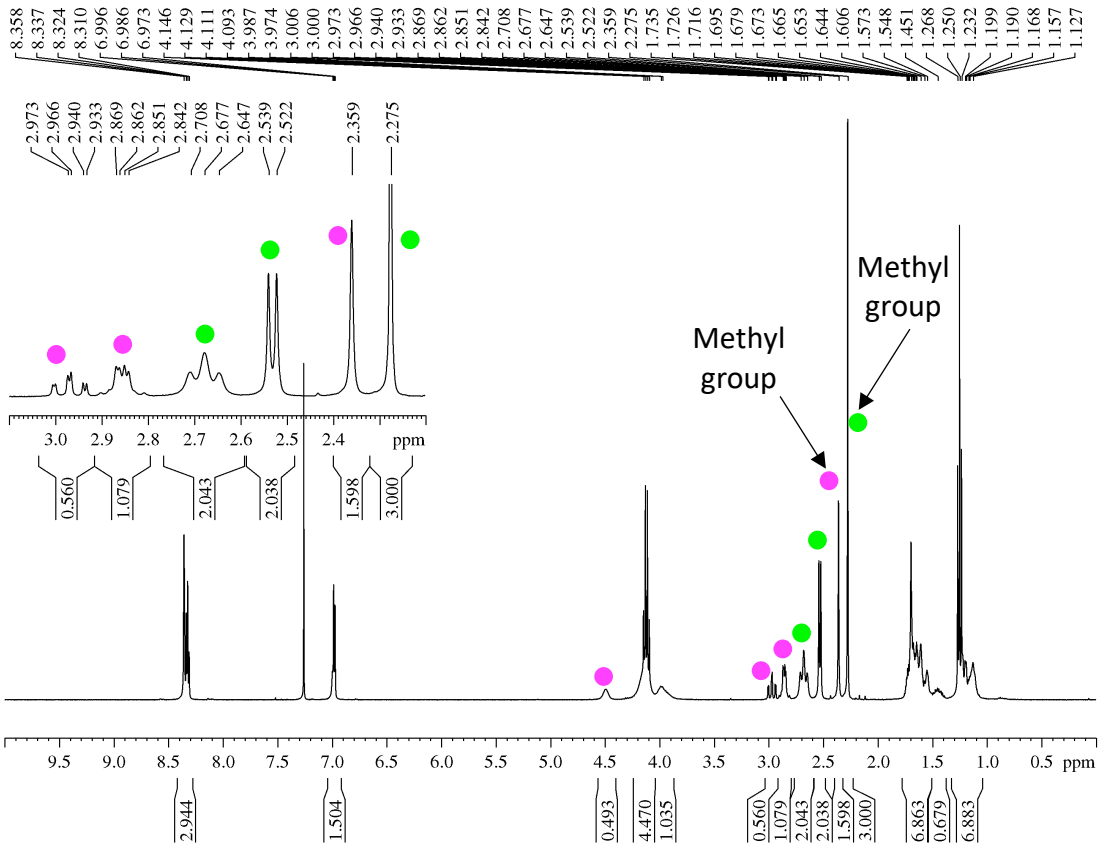
Synthesis of compounds **4-16a** and **4-16b**:



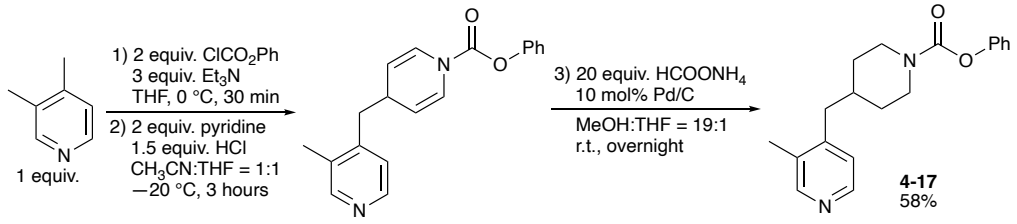
The ADHP intermediate was synthesized by following **general procedure A** using 3,4-lutidine (107.2 mg, 1.0 equiv., 1.0 mmol,) as the starting material. The DHP intermediates were synthesized by following **general procedure C** but using anhydrous THF to dissolve the ADHP instead of CH_3CN. The DHP intermediates were hydrogenated by following **general procedure D**. Product mixture of **4-16a** and **4-16b** was obtained as colorless oil (166.0 mg, ~ 1:2 ratio, 63% overall yield).

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-16a** and **4-16b**:





Synthesis of compound **4-17**:



The ADHP intermediate was synthesized by following **general procedure A** using 3,4-lutidine (107.2 mg, 1.0 equiv., 1.0 mmol), Et_3N (0.42 mL, 3.0 equiv., 3 mmol) and phenyl chloroformate (0.13 mL, 1.0 equiv., 1.0 mmol). The DHP intermediate was synthesized by following **general procedure C** but using anhydrous THF to dissolve the ADHP instead of CH_3CN. The DHP was hydrogenated by following **general procedure D**. Product **4-17** was obtained as white solid (168.6 mg, 58% yield).

Melting point: 69.2 – 70.0 °C

Chromatography: 100% EtOAc (R_f = 0.28).

^{1}H NMR (400 MHz, DCM-d_2):

δ 8.35 (s, 1H), 8.31 (d, *J* = 4.8 Hz, 1H), 7.41 – 7.33 (m, 2H),

7.20 (tt, *J* = 7.2, 0.8 Hz, 1H), 7.12 – 7.07 (m, 2H), 7.03 (d, *J* = 4.8 Hz, 1H),

4.34 – 4.13 (m, 2H), 2.97 – 2.72 (m, 2H), 2.58 (d, *J* = 7.2 Hz, 2H), 2.30 (s, 3H),

1.84 – 1.74 (m, 1H), 1.70 (d, *J* = 12.8 Hz, 2H), 1.41 – 1.26 (m, 2H).

^{13}C NMR (100 MHz, DCM-d_2):

δ 153.9, 152.1, 151.4, 147.6, 147.5, 132.3, 129.5, 125.4, 124.8, 122.2, 45.1, 44.7,

39.6, 36.7, 32.5, 32.2, 16.5.

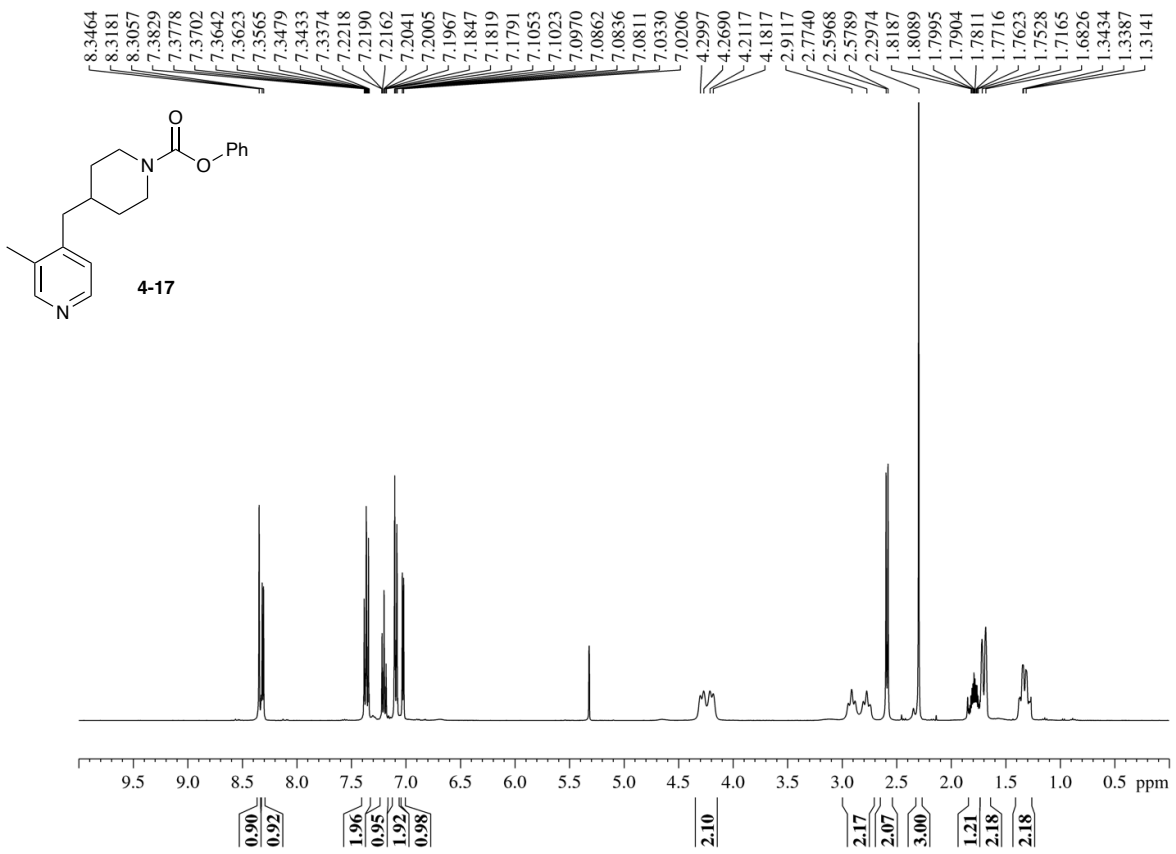
IR Alpha-Platinum ATR, Bruker, diamond crystal

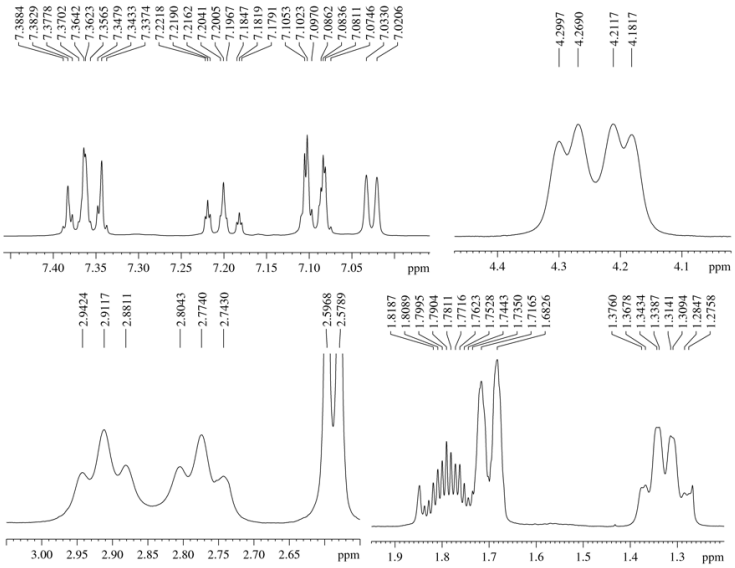
υ = 3044, 2935, 2866, 1704, 1421, 1197 cm^{-1}.

HRMS ESI-TOF

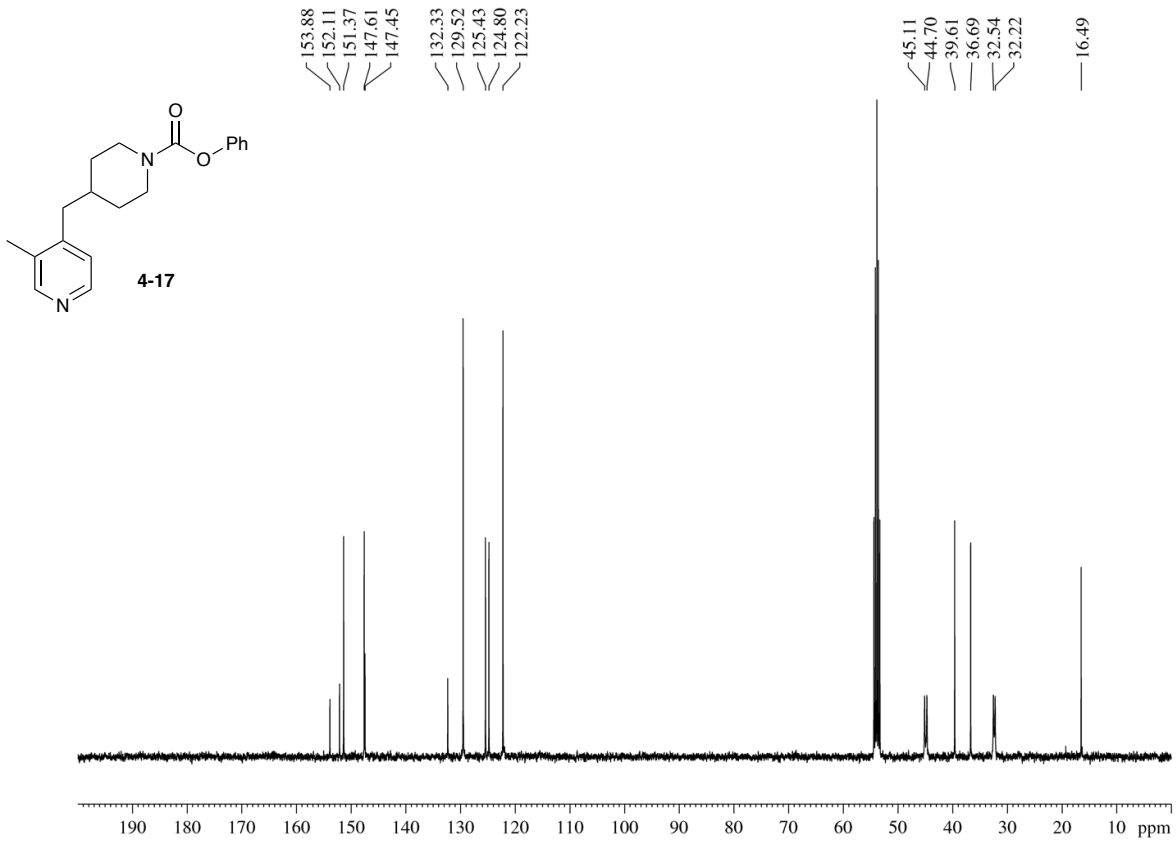
$(M+H)^+$ Calcd for $C_{19}H_{23}N_2O_2$ 311.1754; Found 311.1746.

^{1}H NMR (400 MHz, DCM-d_2) spectrum for **4-17**:

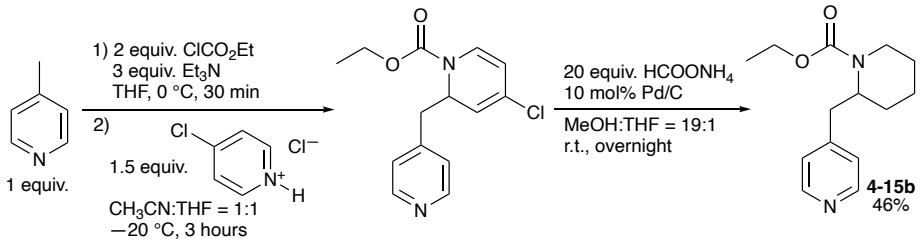




^{13}C NMR (100 MHz, DCM-d_2) spectrum for **4-17**:



Synthesis of compound **4-15b**:



The ADHP intermediate was synthesized by following **general procedure A** using 4-picoline (0.1 mL, 1.0 equiv., 1.0 mmol) as the starting material.

An oven-dried round-bottomed flask equipped with a stir bar was charged with 4-chloropyridine hydrochloride (225.1 mg, 1.5 equiv., 1.5 mmol) and 5 mL of anhydrous CH_3CN. The mixture was cooled to –20 °C. The ADHP was dissolved in 5 mL anhydrous THF and added dropwise to the reaction mixture while maintaining the temperature at –20 °C. The mixture was kept being stirred at –20 °C for 3 hours. Et_3N (0.84 mL, 4.0 equiv., 4.0 mmol) was added dropwise to the mixture at –20 °C, and the resulting mixture was allowed to warm to ambient temperature while stirring for 1 hour. The mixture was then concentrated using a rotary evaporator. The resulting residue was washed with 10 mL saturated $NaHCO_3$ solution and extracted with EtOAc (4 x 10 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, filtered through a cotton plug, and concentrated using a rotary evaporator. The DHP intermediate was collected and hydrogenated by following **general procedure D**. Product **4-15b** was obtained as colorless oil (115.3 mg, 46% yield).

Chromatography: 60% EtOAc in hexanes (R_f = 0.29).

^{1}H NMR (300 MHz, $CDCl_3$, 43 °C):

δ 8.47 (d, *J* = 5.7 Hz, 2H), 7.09 (d, *J* = 5.7 Hz, 2H), 4.62 – 4.39 (m, 1H), 4.13 – 4.02 (m, 1H), 4.02 – 3.86 (m, 2H), 2.98 – 2.84 (m, 2H), 2.81 – 2.67 (m, 1H), 1.73 – 1.51 (m, 5H), 1.51 – 1.33 (m, 1H),

1.11 (t, J = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, 43 °C):

δ 155.7, 149.9, 148.2, 124.6, 61.2, 51.8, 39.5, 35.8, 27.6, 25.5, 19.0, 14.6.

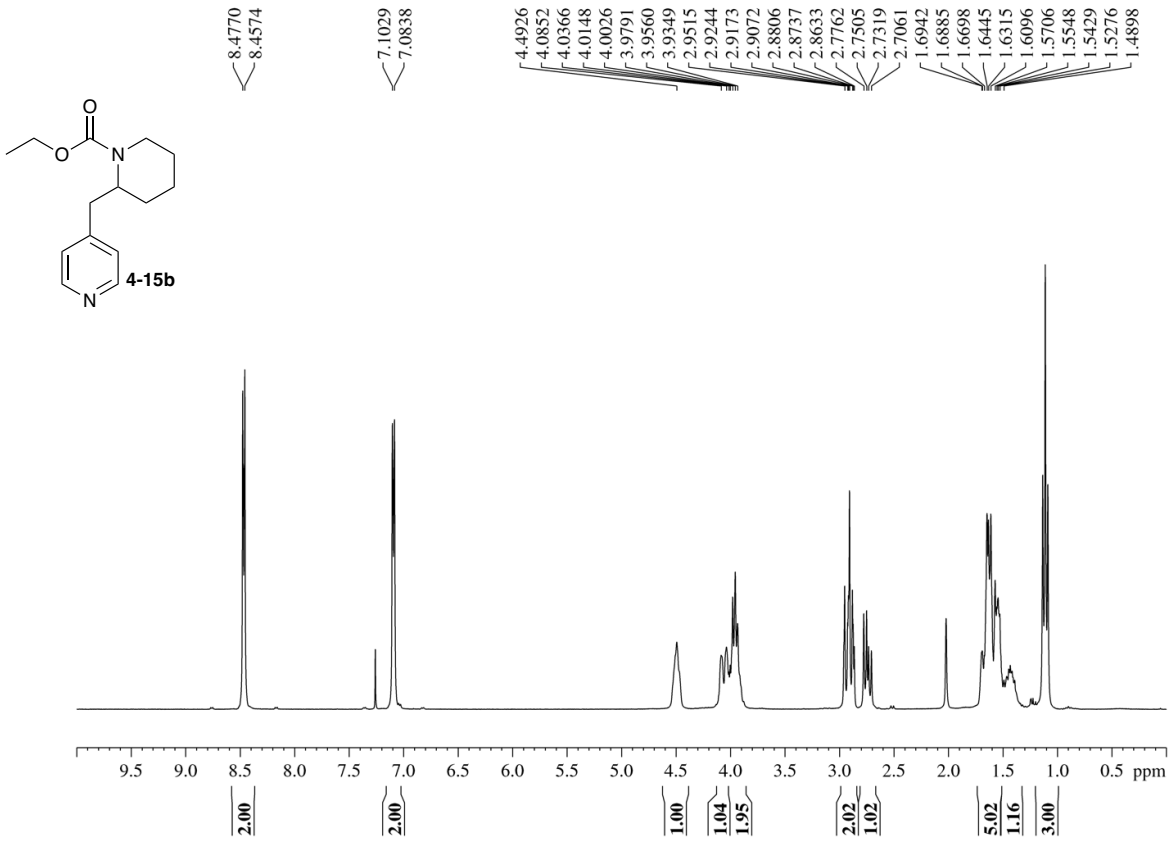
IR Alpha-Platinum ATR, Bruker, diamond crystal

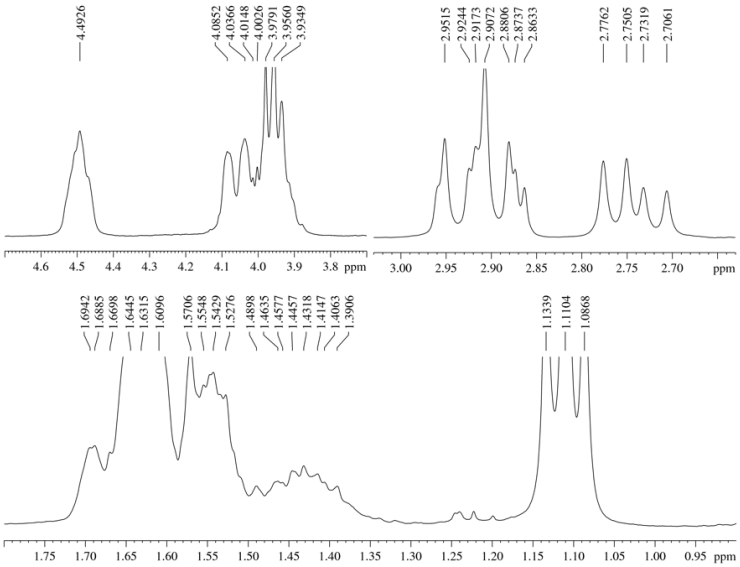
υ = 3068, 2980, 2863, 1683, 1416, 1244 cm^{-1}.

HRMS ESI-TOF

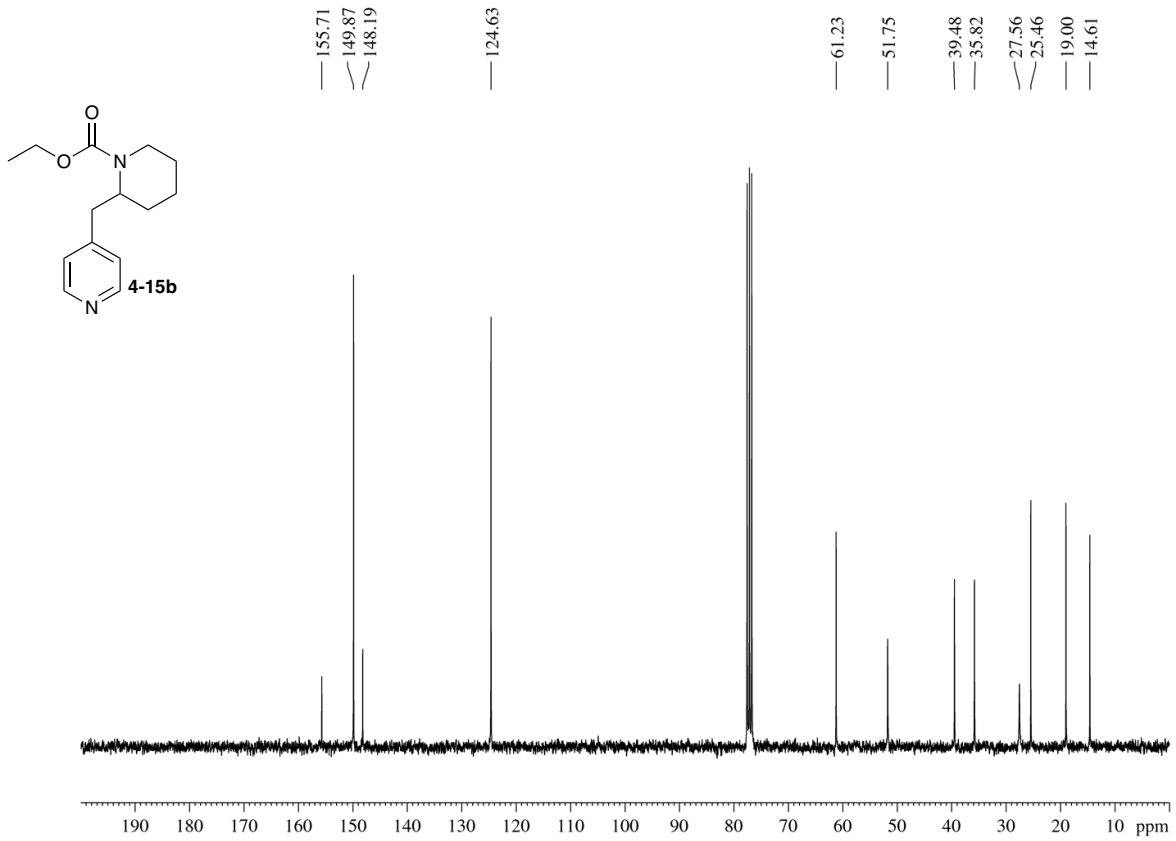
$(M+H)^+$ Calcd for $C_{14}H_{21}N_2O_2$ 249.1598; Found 249.1591.

^{1}H NMR (300 MHz, $CDCl_3$, 43 °C) spectrum for **4-15b**:

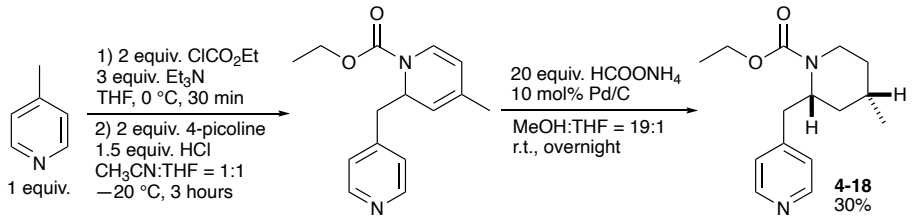




^{13}C NMR (75 MHz, $CDCl_3$, 43 °C) spectrum for **4-15b**:



Synthesis of compound **4-18**:



The ADHP intermediate was synthesized by following **general procedure A** using 4-picoline (0.1 mL, 1.0 equiv., 1.0 mmol) as the starting material.

An oven-dried round-bottomed flask equipped with a stir bar was charged with 4-picoline (0.19 mL, 2.0 equiv., 2 mmol) and 5 mL of anhydrous CH_3CN. The mixture was cooled to –20 °C. Hydrogen chloride (0.37 mL, 1.5 equiv., 1.5 mmol, 4 M in dioxane) was added in a dropwise manner, and the resulting mixture was stirred for 15 minutes at –20 °C. The ADHP was dissolved in 5 mL anhydrous THF and added dropwise to the reaction mixture while maintaining the temperature at –20 °C. The mixture was kept being stirred at –20 °C for 3 hours. Et_3N (0.84 mL, 4.0 equiv., 4.0 mmol) was added dropwise to the mixture at –20 °C, and the resulting mixture was allowed to warm to ambient temperature while stirring for 1 hour. The mixture was then concentrated using a rotary evaporator. The resulting residue was suspended in diethyl ether for 2 – 3 minutes and filtered through a cotton plug. The filtrate was concentrated using a rotary evaporator to afford crude DHP intermediate, which was then hydrogenated by following **general procedure D**. Product **4-18** was obtained as colorless oil (84.1 mg, 30% yield).

Chromatography: 100% EtOAc (R_f = 0.29).

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

δ 8.49 (d, *J* = 5.8 Hz, 2H), 7.12 (d, *J* = 5.8 Hz, 2H), 4.13 – 3.99 (m, 3H),

3.79 (ddd, *J* = 13.6, 7.2, 2.8 Hz, 1H), 3.09 – 2.95 (m, 2H), 2.78 – 2.68 (m, 1H),

1.97 – 1.83 (m, 1H), 1.71 – 1.56 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H),

1.17 – 1.07 (m, 2H), 0.97 (d, *J* = 6.8 Hz, 3H).

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

δ 156.1, 149.8, 148.1, 124.9, 61.2, 54.6, 40.2, 37.9, 34.9, 31.1, 26.3, 21.7, 14.8.

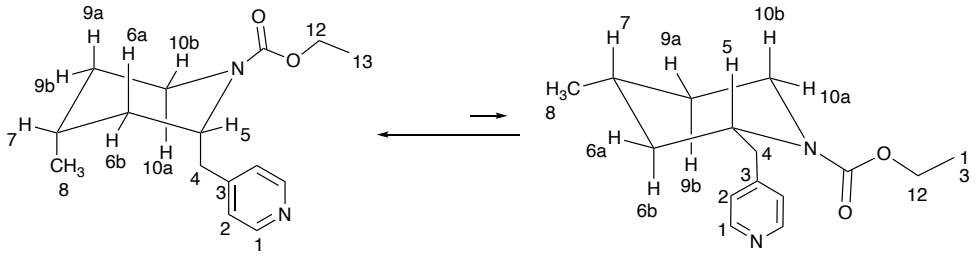
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3068, 2951, 2870, 1686, 1418, 1219 cm^{-1}.

HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{15}H_{23}N_2O_2$ 263.1754; Found 263.1746.

COSY (600 MHz, $CDCl_3$, 5 °C) for **4-18**:

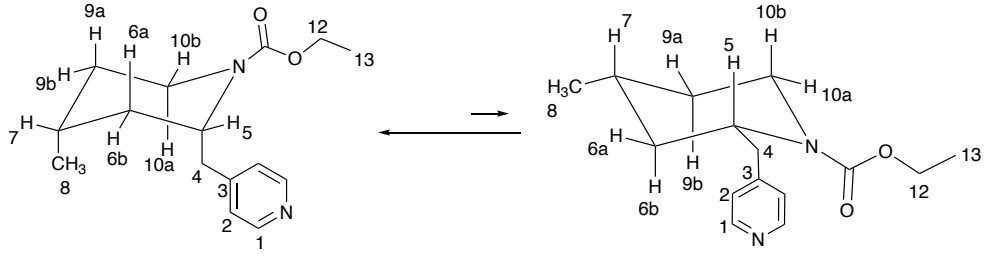


Proton No.	^{1}H δ (ppm) (multi; *J* (Hz))	COSY correlations
H-1	8.49 (d, *J* = 5.8 Hz)	H-2
H-2	7.12 (d, *J* = 5.8 Hz)	H-1
H-4	3.07 – 2.95 (m), 2.78 – 2.68 (m)	H-4, H-5
H-5	4.12 – 3.99 (m)	H-4a, H-4b, H-6a, H-6b
H-6a	1.17 – 1.07 (m)	H-5, H-6b, H-7
H-6b	1.71 – 1.56 (m)	H-5, H-6a, H-7
H-7	1.71 – 1.56 (m)	H-6a, H-6b, H-8, H-9a, H-9b
H-8	0.97 (d, *J* = 6.8 Hz)	H-7
H-9a	1.71 – 1.07(m)	H-7, H-9b, H-10a, H-10b
H-9b	1.96 – 1.83 (m)	H-7, H-9a, H-10a, H-10b
H-10a	3.07 – 2.95 (m)	H-9a, H-9b, H-10b
H-10b	3.79 (ddd, *J* = 13.6, 7.2, 2.8 Hz)	H-9a, H-9b, H-10a
H-12	4.12 – 3.99 (m)	H-13
H-13	1.19 (t, *J* = 7.2 Hz)	H-12

Methylene carbons are designated C-X and C-X' arbitrarily. Axial methylene protons are designated H-Xa and H-X'a, and equatorial protons are designated H-Xe and H-X'e arbitrarily.

Only those correlations which could be unambiguously assigned are reported.

NOSEY (600 MHz, $CDCl_3$, 5 °C) for **4-18**:

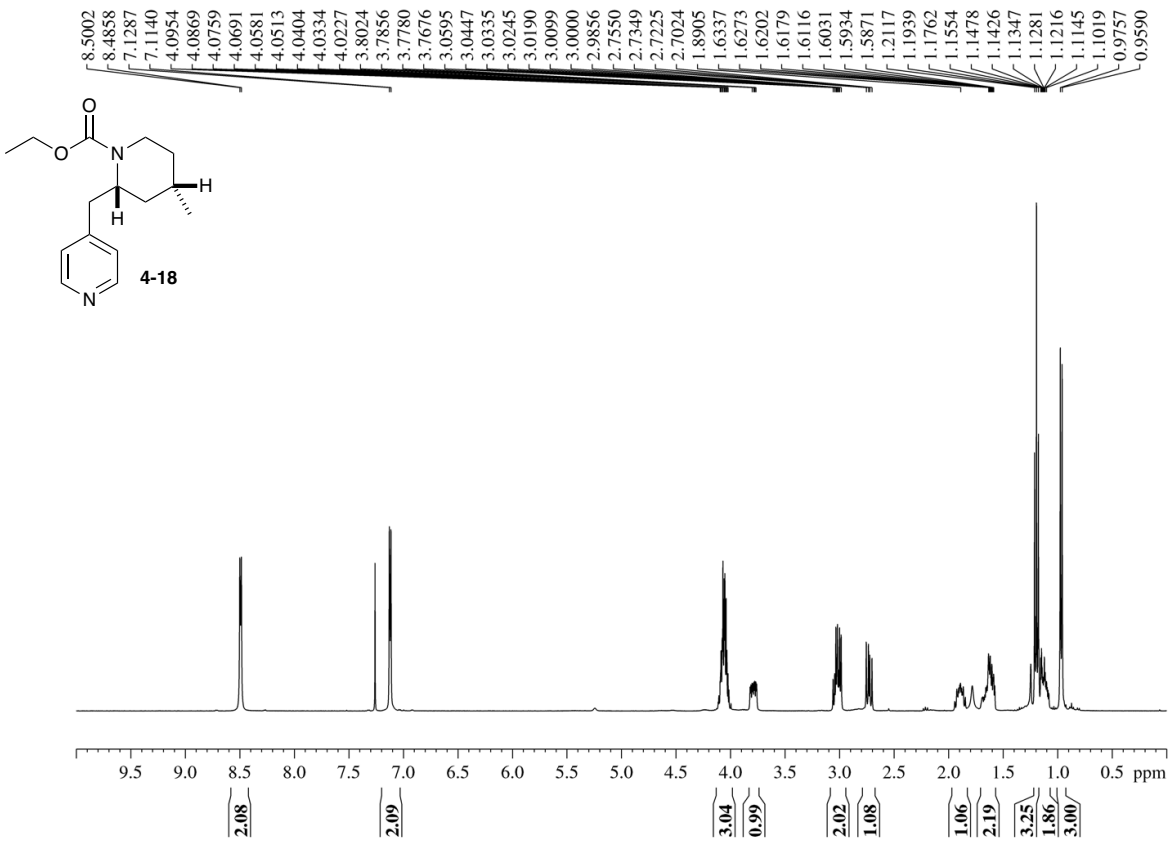


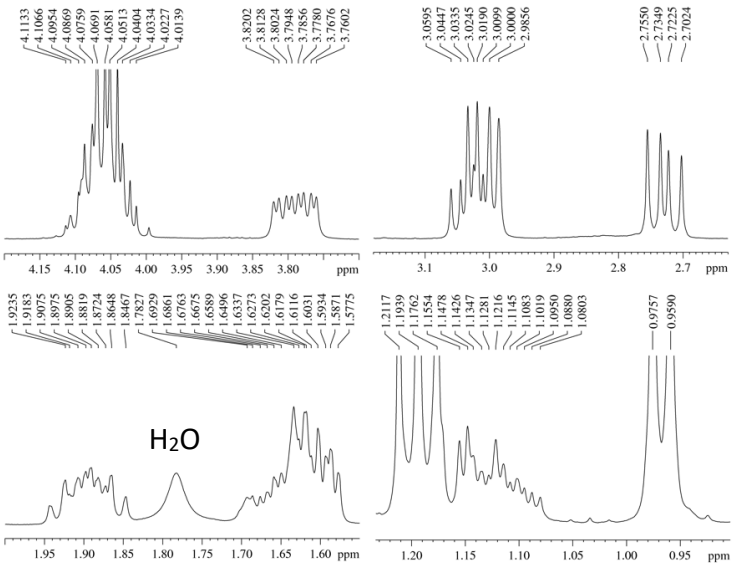
Proton No.	^{1}H δ (ppm) (multi; *J* (Hz))	NOSEY correlations
H-1	8.49 (d, *J* = 5.8 Hz)	H-2
H-2	7.12 (d, *J* = 5.8 Hz)	H-1
H-4	3.07 – 2.95 (m), 2.78 – 2.68 (m)	H-6b
H-5	4.12 – 3.99 (m)	H-7, H-10b
H-6a	1.17 – 1.07 (m)	H-9a
H-6b	1.71 – 1.56 (m)	H-4
H-7	1.71 – 1.56 (m)	H-5
H-8	0.97 (d, *J* = 6.8 Hz)	H-10a
H-9a	1.71 – 1.07(m)	-
H-9b	1.96 – 1.83 (m)	-
H-10a	3.07 – 2.95 (m)	H-8
H-10b	3.79 (ddd, *J* = 13.6, 7.2, 2.8 Hz)	H-5
H-12	4.12 – 3.99 (m)	-
H-13	1.19 (t, *J* = 7.2 Hz)	-

Methylene carbons are designated C-X and C-X' arbitrarily. Axial methylene protons are designated H-Xa and H-X'a, and equatorial protons are designated H-Xe and H-X'e arbitrarily.

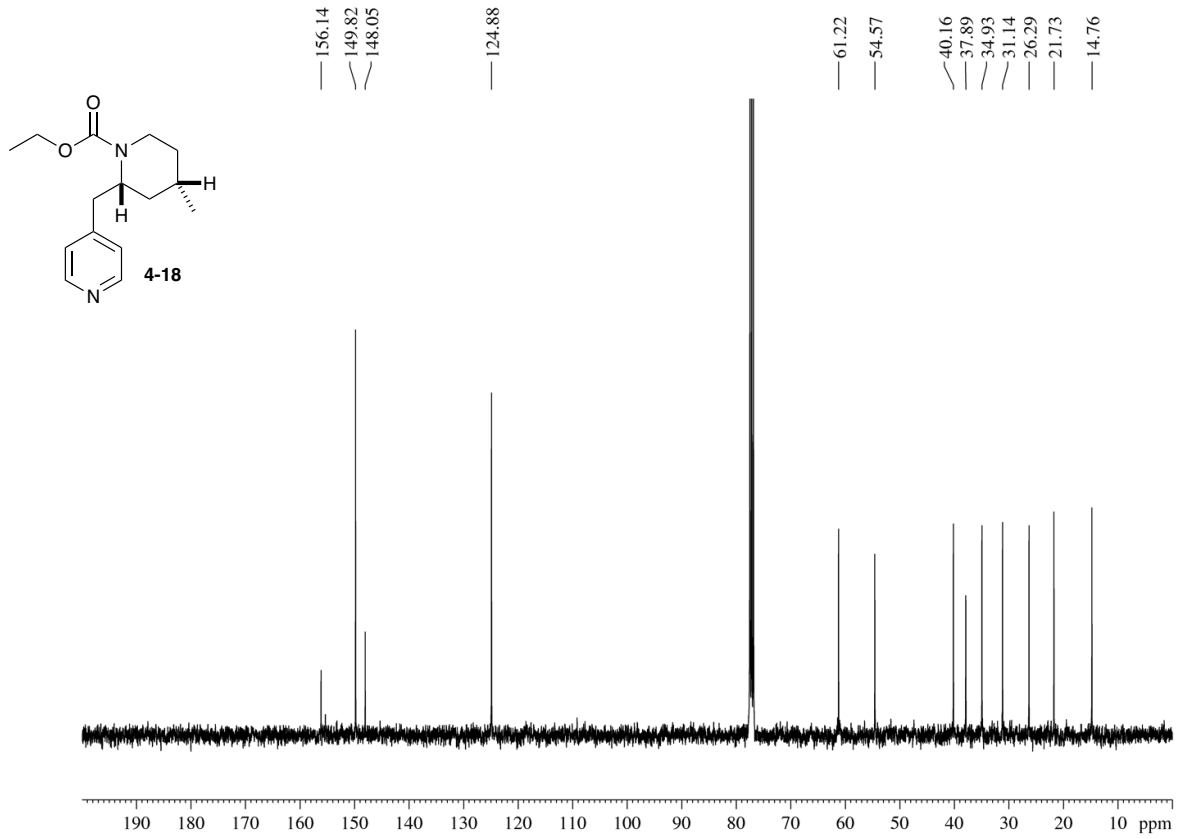
Only those correlations which could be unambiguously assigned are reported.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-18**:

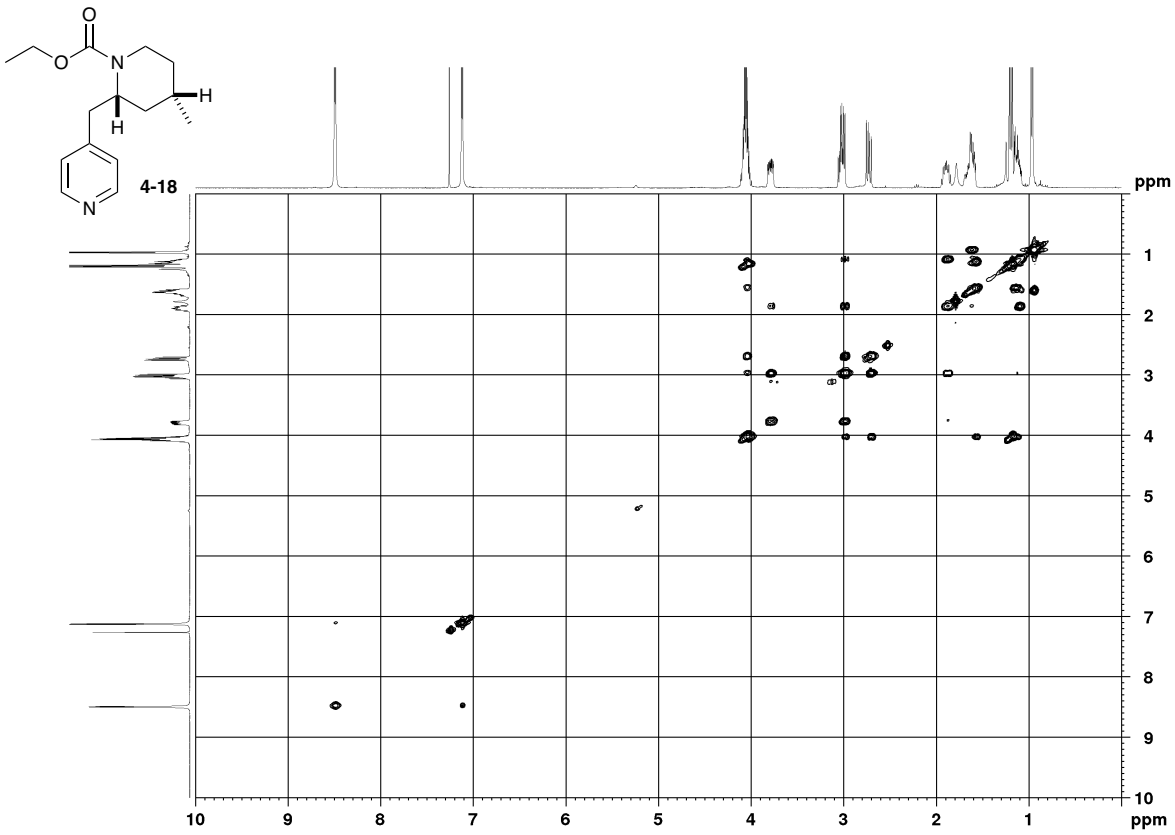




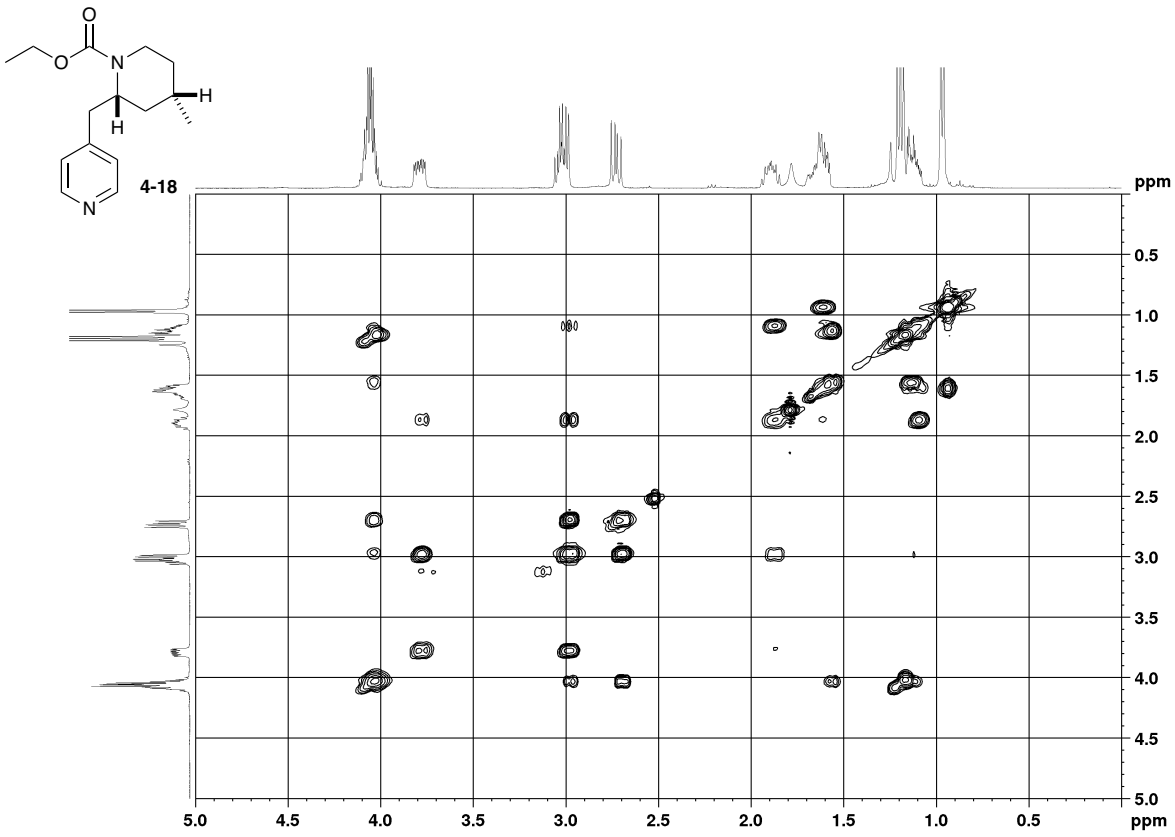
^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-18**:



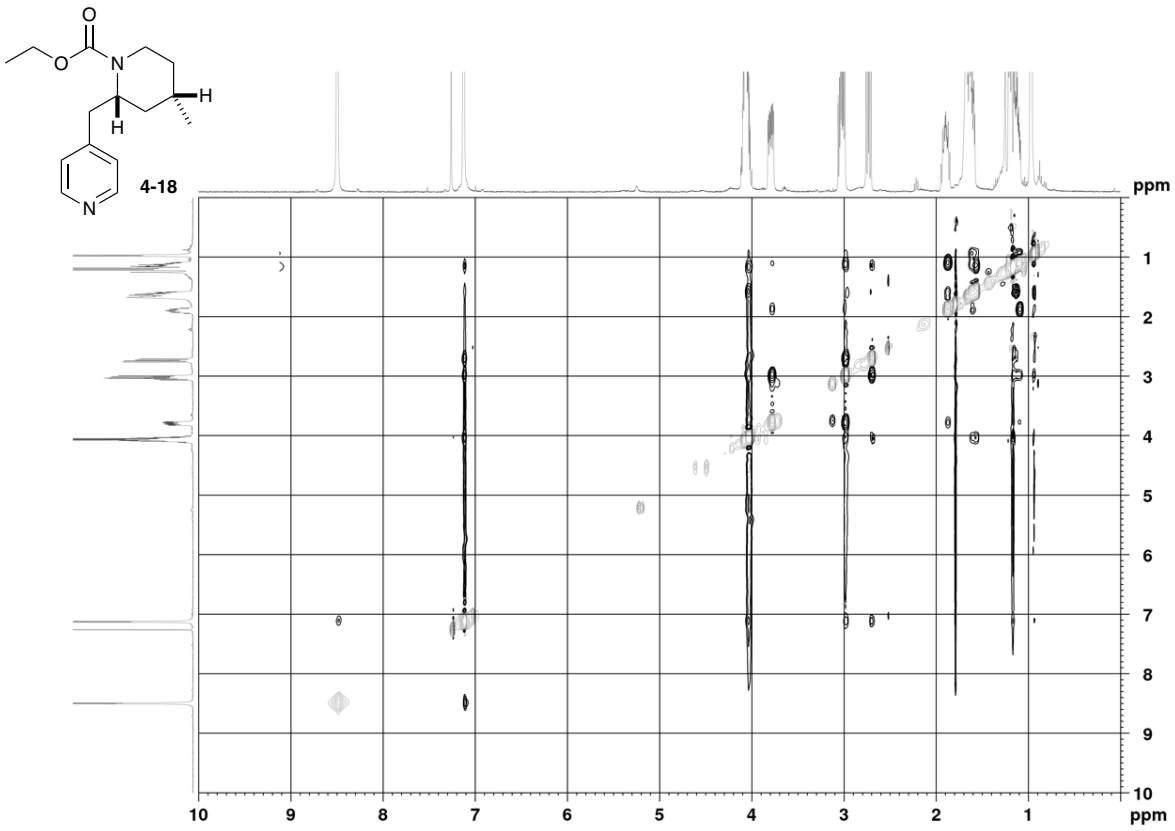
COSY (600 MHz, $CDCl_3$, 5 °C) spectrum for **4-18**:



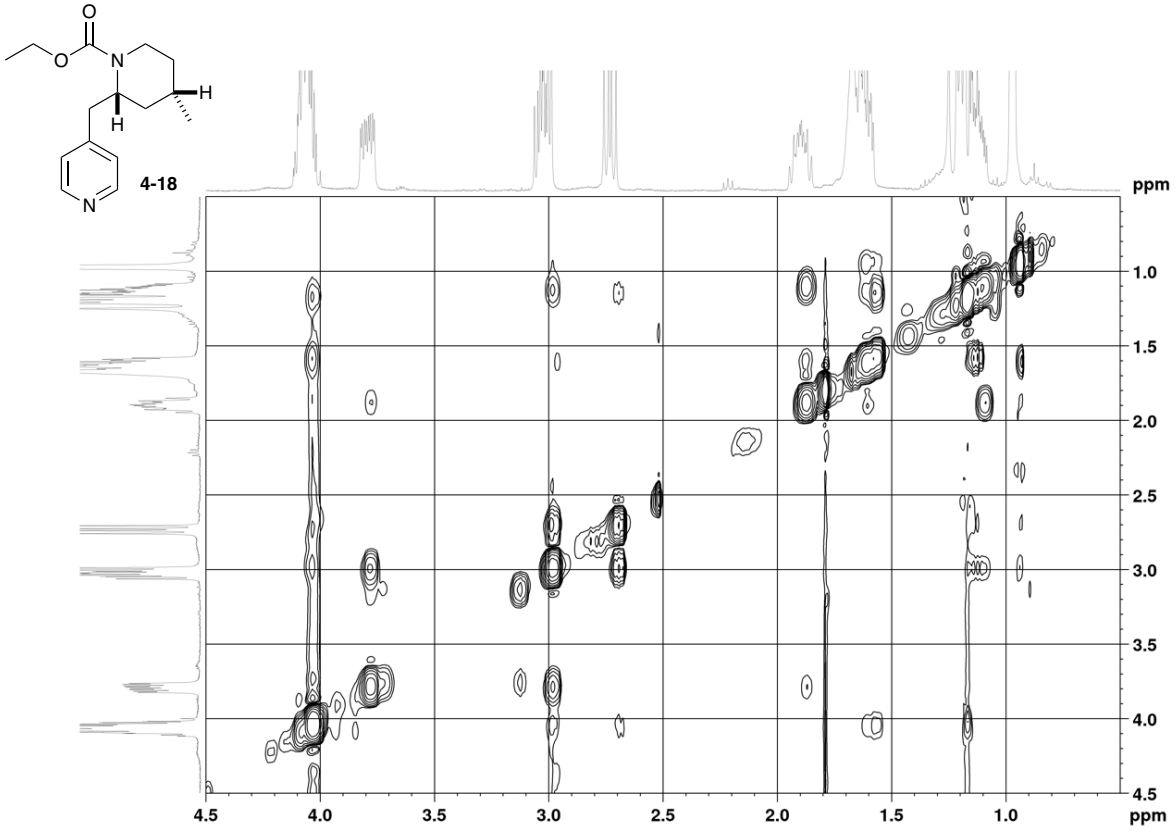
COSY (600 MHz, $CDCl_3$, 5 °C) spectrum for **4-18** (enlarged):



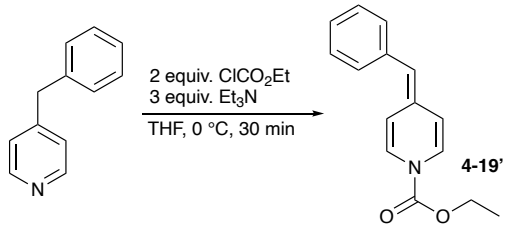
NOESY (600 MHz, $CDCl_3$, 5 °C) spectrum for **4-18**:



NOESY (600 MHz, $CDCl_3$, 5 °C) spectrum for **4-18** (enlarged):



Synthesis of compound **4-19'**:

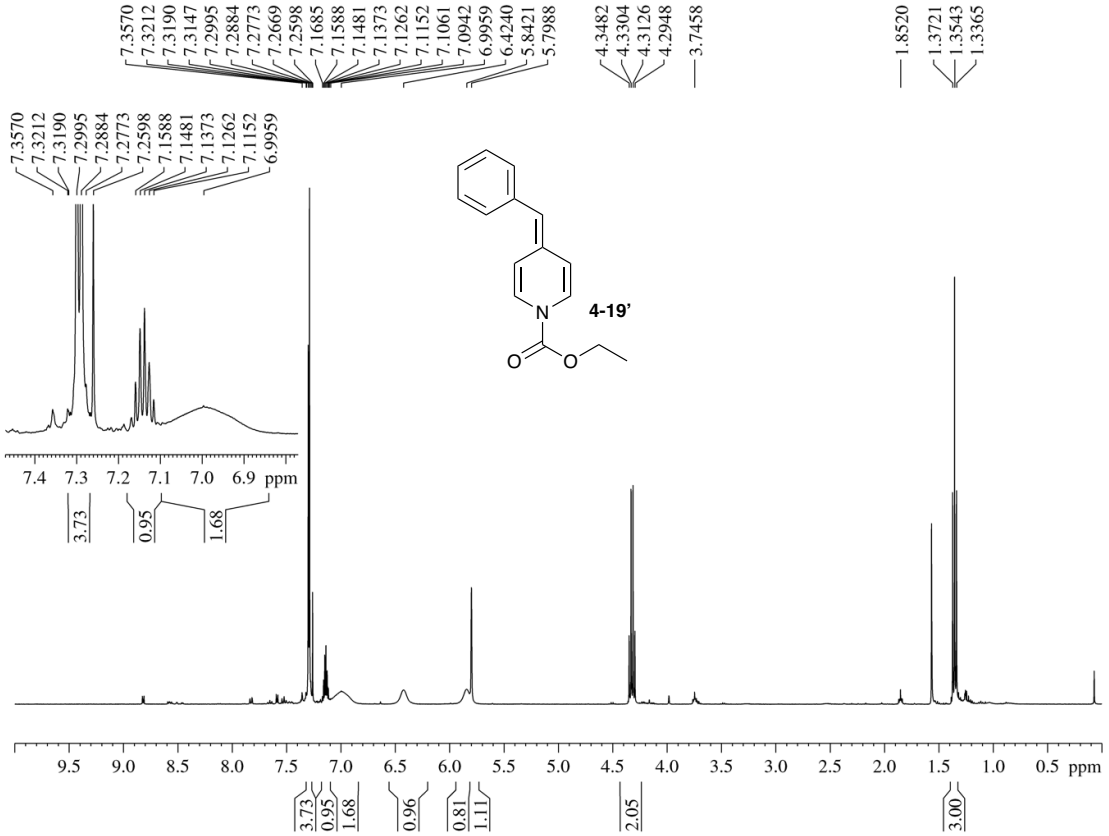


The ADHP intermediate was synthesized by following **general procedure A** using 4-benzylpyridine (0.16 mL, 1.0 equiv., 1.0 mmol) as the starting material. The resulting residue **4-19'** was characterized without further purification.

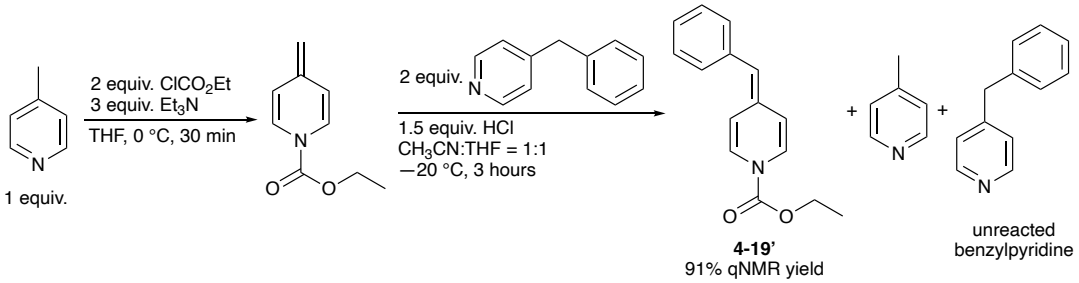
^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.36 – 7.27 (m, 4H), 7.19 – 7.09 (m, 1H), 7.09 – 6.86 (br, 2H), 6.56 – 6.22 (br, 1H), 5.94 – 5.81 (br, 1H), 5.80 (s, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H).

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-19'** (crude):



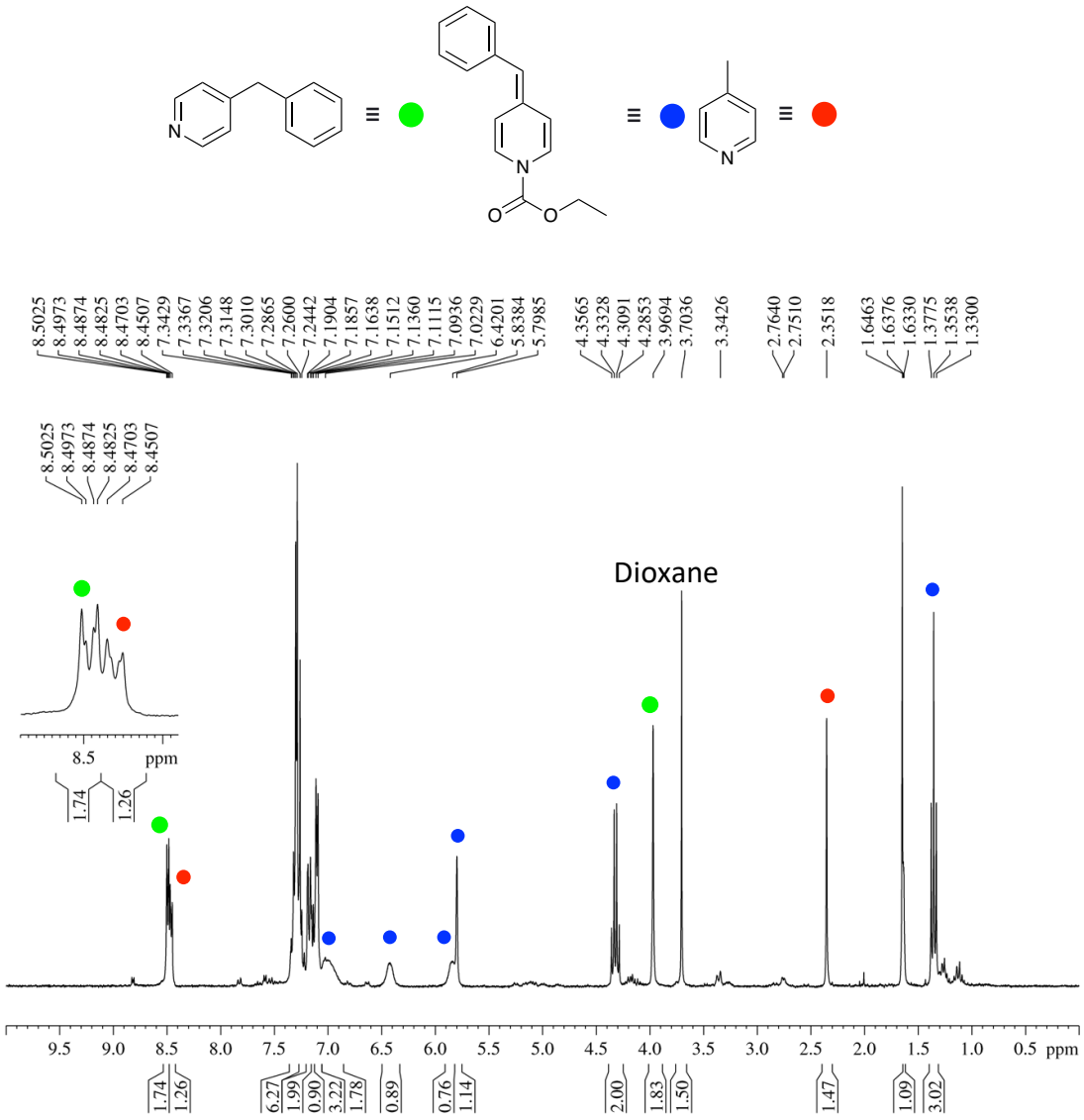
Reaction between ADHP and 4-benzylpyridine hydrochloride:



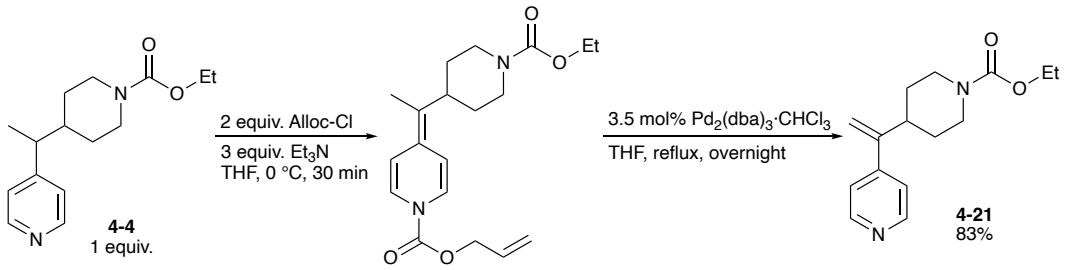
The ADHP intermediate was synthesized by following **general procedure A** using 4-picoline (0.1 mL, 1.0 equiv., 1.0 mmol) as the starting material.

An oven-dried round-bottomed flask equipped with a stir bar was charged with 4-benzylpyridine (0.32 mL, 2.0 equiv., 2 mmol) and 5 mL of anhydrous CH_3CN. The mixture was cooled to –20 °C. Hydrogen chloride (0.37 mL, 1.5 equiv., 1.5 mmol, 4 M in dioxane) was added in a dropwise manner, and the resulting mixture was stirred for 15 minutes at –20 °C. The ADHP was dissolved in 5 mL anhydrous THF and added dropwise to the reaction mixture while maintaining the temperature at –20 °C. The mixture was kept being stirred at –20 °C for 3 hours. Et_3N (0.84 mL, 4.0 equiv., 4.0 mmol) was added dropwise to the mixture at –20 °C, and the resulting mixture was allowed to warm to ambient temperature while stirring for 1 hour. The mixture was then concentrated using a rotary evaporator. The resulting residue was suspended in diethyl ether for 2 – 3 minutes and filtered through a cotton plug. The filtrate was concentrated using a rotary evaporator. The resulting residue was analyzed by quantitative ^1H NMR, and a total of 220.1 mg (91% qNMR yield) of product **4-19'** was calculated to had been formed.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for attempted addition of 4-picoline to 4-benzylpyridine:



Synthesis of compound **4-21**:



The ADHP intermediate was synthesized by following **general procedure A** using piperidine **4-4** (97 mg, 1.0 equiv., 0.37 mmol), Et_3N (112.3 mg, 3.0 equiv. 1.11 mmol) and allyl chloroformate (89.1 mg, 2.0 equiv., 0.74 mmol).

An oven-dried round-bottomed flask equipped with a stir bar was charged with $Pd_2(dba)_3{\cdot}CHCl_3$ (13.4 mg, 3.5 mol%, 0.013 mmol) and 1.5 mL of anhydrous THF. The resulting mixture was stirred for 10 min at ambient temperature. The ADHP intermediate was dissolved in 4 mL anhydrous THF and added to the palladium catalyst solution in a dropwise manner. The resulting mixture was placed in an oil bath, stirred, and heated to reflux overnight. The mixture was then cooled to ambient temperature and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography using EtOAc/hexanes to afford product **4-21** as light-yellow oil (79.8 mg, 83% yield).

Chromatography: 40% EtOAc in hexanes (R_f = 0.37).

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

δ 8.54 (d, *J* = 6.0 Hz, 2H), 7.21 (d, *J* = 6.0 Hz, 2H), 5.33 (s, 1H),

5.14 (d, *J* = 0.6 Hz, 1H), 4.36 – 4.15 (m, 2H), 4.11 (q, *J* = 7.2 Hz, 2H),

2.89 – 2.68 (m, 2H), 2.63 – 2.48 (m, 1H), 1.82 – 1.69 (m, 2H),

1.37 (qd, *J* = 12.0, 3.2 Hz, 2H), 1.24 (t, *J* = 7.2 Hz, 3H).

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

δ 155.6, 150.7, 150.1, 149.5, 121.5, 114.1, 61.4, 44.3, 40.0, 31.3, 14.8.

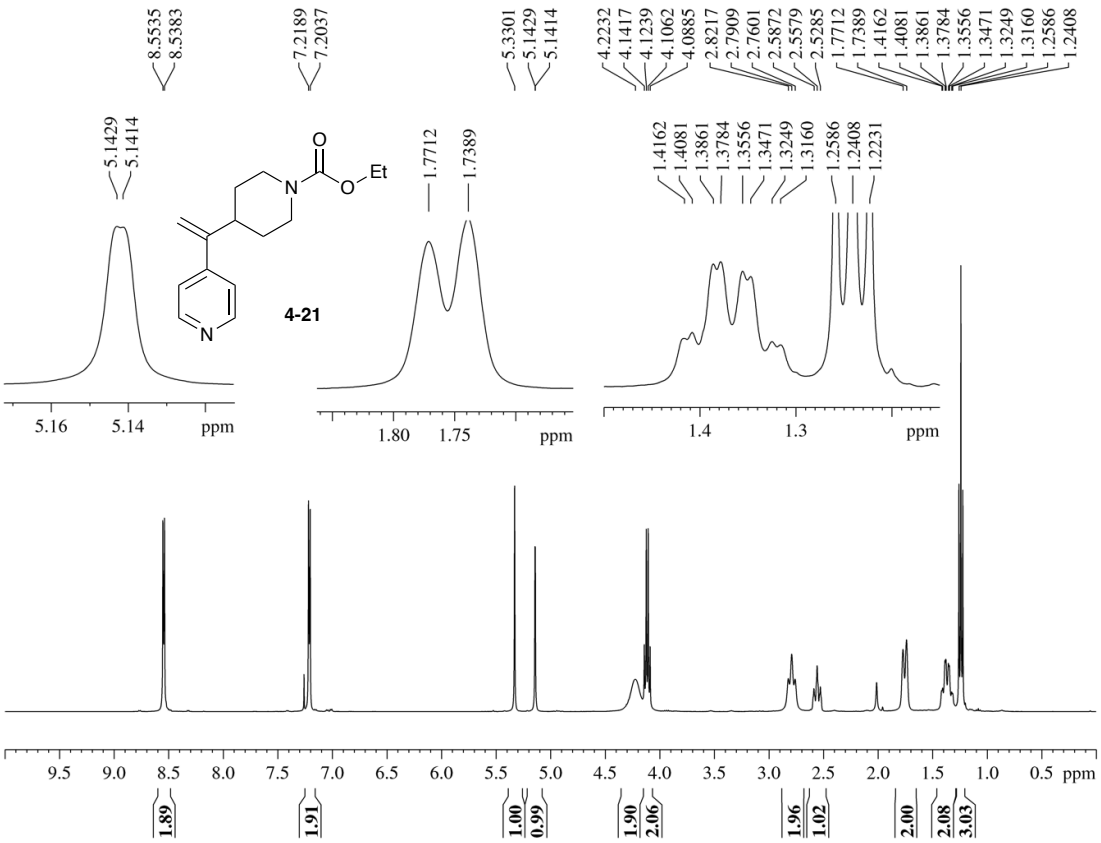
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3069, 2980, 2855, 1687, 1429, 1221 cm^{-1}.

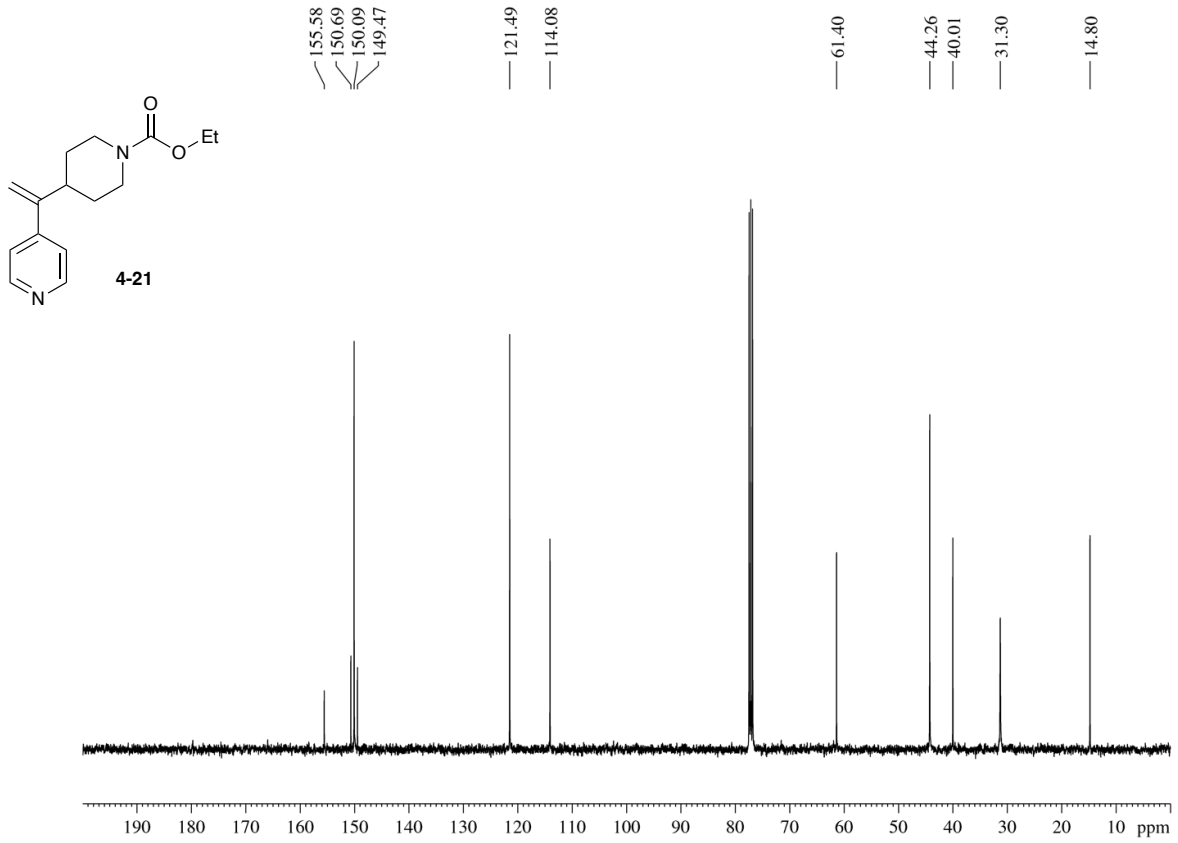
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{15}H_{21}N_2O_2$ 261.1598; Found 261.1591.

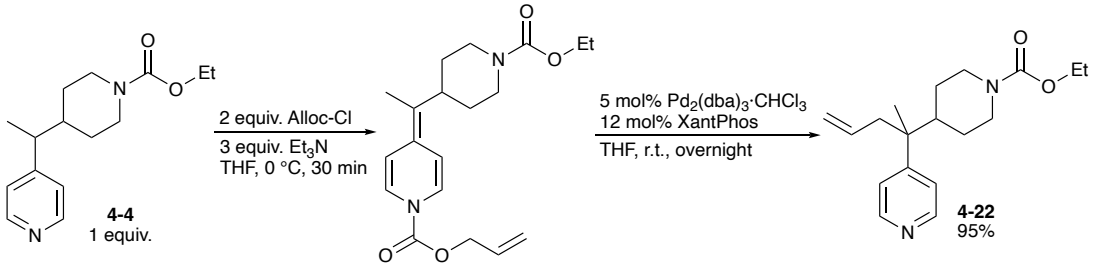
^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-21**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-21**:



Synthesis of compound **4-22**:



The ADHP intermediate was synthesized by following **general procedure A** using piperidine **4-4** (131.2 mg, 1.0 equiv., 1.0 mmol), Et_3N (0.42 mL, 3.0 equiv., 3.0 mmol) and allyl chloroformate (0.21 mL, 2.0 equiv., 1.0 mmol).

An oven-dried round-bottomed flask equipped with a stir bar was charged with $Pd_2(dba)_3{\cdot}CHCl_3$ (51.8 mg, 5 mol%, 0.05 mmol), XantPhos (69.4 mg, 12 mol%, 0.12 mmol) and 5 mL of anhydrous THF. The mixture was stirred for 30 minutes at ambient temperature. The ADHP intermediate was dissolved in 5 mL of anhydrous THF and added dropwise to the palladium catalyst solution. The resulting mixture was stirred at ambient temperature overnight. The mixture was then concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography using EtOAc/hexanes to afford product **4-22** as colorless oil (288.3 mg, 95% yield).

Chromatography: 70% EtOAc in hexanes (R_f = 0.25).

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

δ 8.48 (d, *J* = 6.0 Hz, 2H), 7.12 (d, *J* = 6.0 Hz, 2H), 5.38 – 5.22 (m, 1H), 4.97 – 4.82 (m, 2H), 4.33 – 3.90 (m, 2H), 4.04 (q, *J* = 7.2 Hz, 2H), 2.62 (t, *J* = 12.4 Hz, 1H), 2.57 – 2.43 (m, 2H), 2.37 – 2.25 (m, 1H), 1.70 (d, *J* = 12.8 Hz, 1H), 1.62 (tt, *J* = 11.6, 3.2 Hz, 1H), 1.27 – 1.12 (m, 7H), 1.12 – 0.96 (m, 2H).

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

δ 155.5, 155.3, 149.7, 134.0, 122.4, 118.1, 61.2, 46.8, 44.4, 44.3, 43.7, 43.5, 27.0, 26.7, 18.6, 14.7.

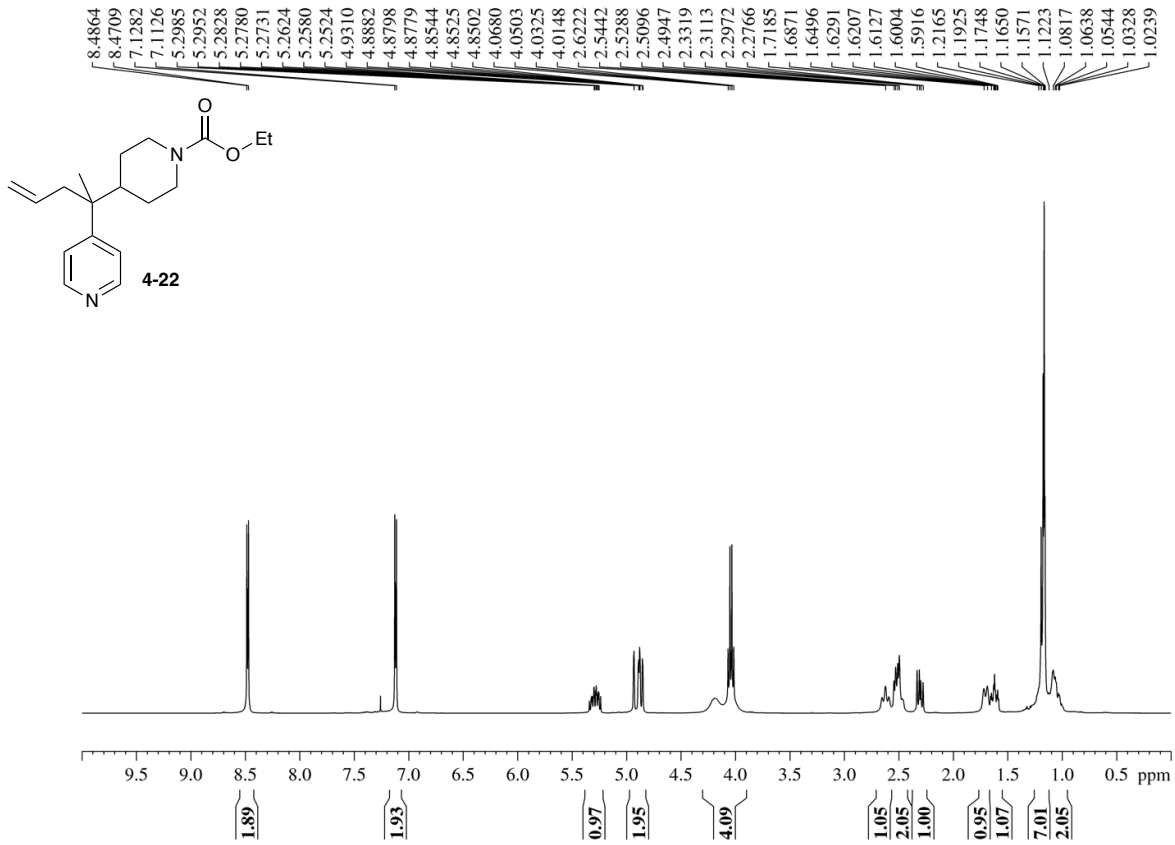
IR Alpha-Platinum ATR, Bruker, diamond crystal

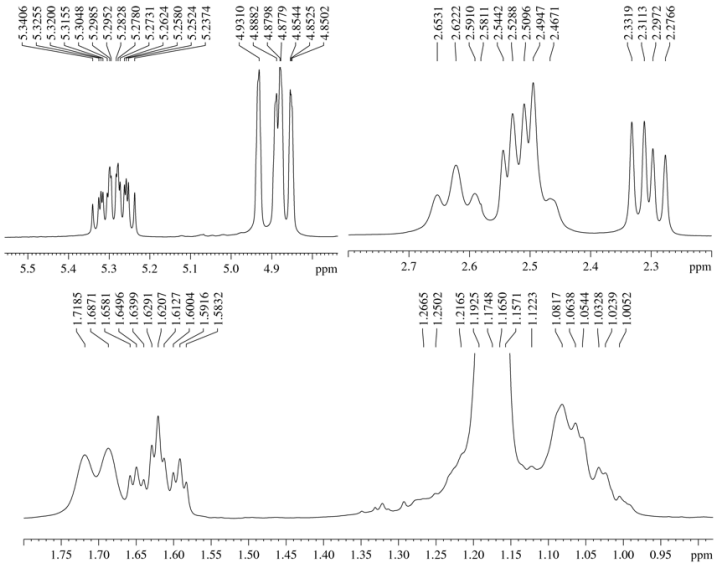
υ = 3077, 2976, 2858, 1690, 1430, 1227 cm^{-1}.

HRMS ESI-TOF

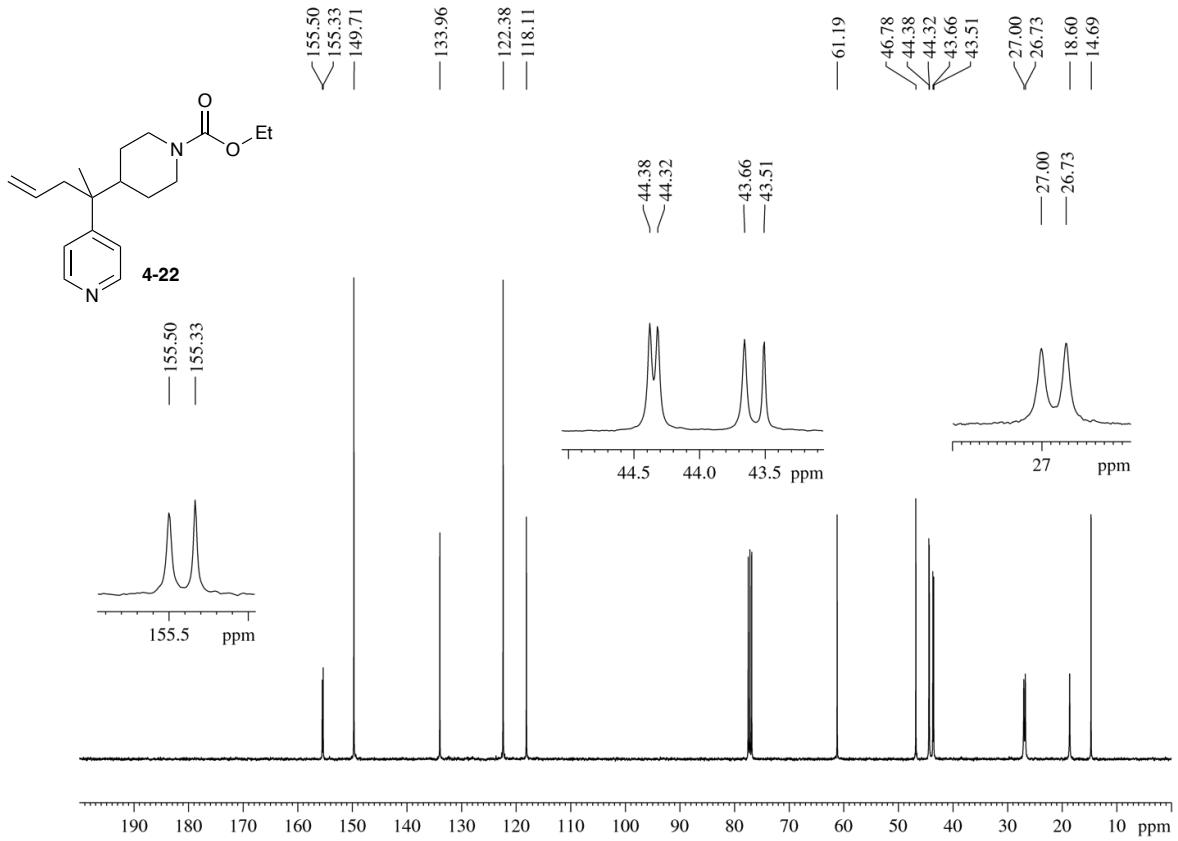
$(M+H)^+$ Calcd for $C_{18}H_{27}N_2O_2$ 303.2067; Found 303.2059.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-22**:

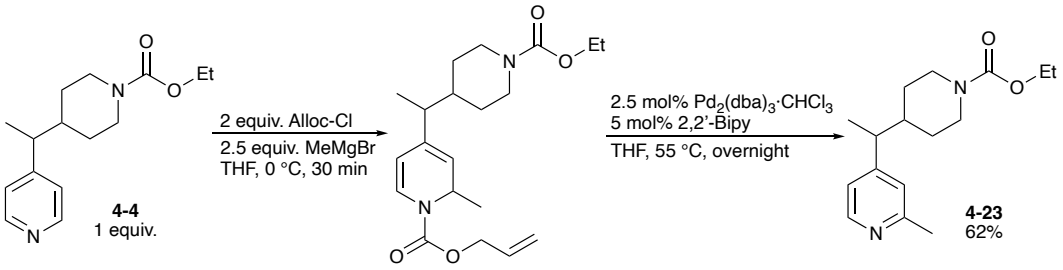




^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-22**:



Synthesis of compound **4-23**:



A dry round-bottomed flask equipped with a stir bar was charged with a 0.1 M solution of piperidine **4-4** (262.4 mg 1.0 equiv., 1.0 mmol) in anhydrous THF. The solution was cooled to –78 °C. Allyl chloroformate (0.21 mL, 2.0 equiv., 2.0 mmol) was added in a dropwise manner, and the resulting solution was stirred for 1 hour at –78 °C. Methylmagnesium bromide (0.83 mL, 2.5 equiv., 2.5 mmol, 3 M in diethyl ether) was added to the mixture in a dropwise manner. The resulting mixture was stirred for 1 hour at –78 °C. The mixture was allowed to warm to ambient temperature while stirring for 1 hour. The reaction was quenched by dropwise addition of ice-cold water (20 mL). After stirring for 15 minutes, the resulting mixture was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, filtered through a cotton plug, and concentrated using a rotary evaporator. The crude methylated dihydropyridine intermediate was obtained and used in the next step without further purification.

A dry round-bottomed flask equipped with a stir bar was charged with $Pd_2(dba)_3{\cdot}CHCl_3$ (25.9 mg, 2.5 mol%, 0.025 mmol), 2,2'-bipyridine (7.8 mg, 5 mol%, 0.05 mmol) and 5 mL of anhydrous THF. The resulting mixture was stirred for 30 minutes at ambient temperature. The methylated dihydropyridine intermediate was dissolved in 5 mL of anhydrous THF and added slowly to the palladium catalyst solution. The resulting mixture was placed in an oil bath, stirred, and heated to 55 °C overnight. The mixture was then cooled to ambient temperature and concentrated using a rotary evaporator. The resulting residue was purified by flash column

chromatography using EtOAc/hexanes to afford product **4-23** as colorless oil (170.7 mg, 62% yield).

Chromatography: 100% EtOAc (R_f = 0.36).

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

δ 8.35 (d, *J* = 5.2 Hz, 1H), 6.89 (s, 1H), 6.84 (d, *J* = 5.2 Hz, 1H), 4.38 – 3.95 (m, 2H), 4.07 (q, *J* = 7.2 Hz, 2H), 2.73 – 2.62 (m, 1H), 2.58 (t, *J* = 12.8 Hz, 1H), 2.50 (s, 3H), 2.38 (p, *J* = 7.2 Hz, 1H), 1.87 – 1.72 (m, 1H), 1.59 – 1.46 (m, 1H), 1.37 – 1.27 (m, 1H), 1.26 – 1.18 (m, 6H), 1.18 – 1.07 (m, 1H), 1.07 – 0.93 (m, 1H).

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

δ 158.4, 155.5, 155.2, 149.2, 122.7, 120.2, 61.3, 44.9, 44.0(9), 44.0(6), 42.0, 30.5, 29.6, 24.5, 18.1, 14.8.

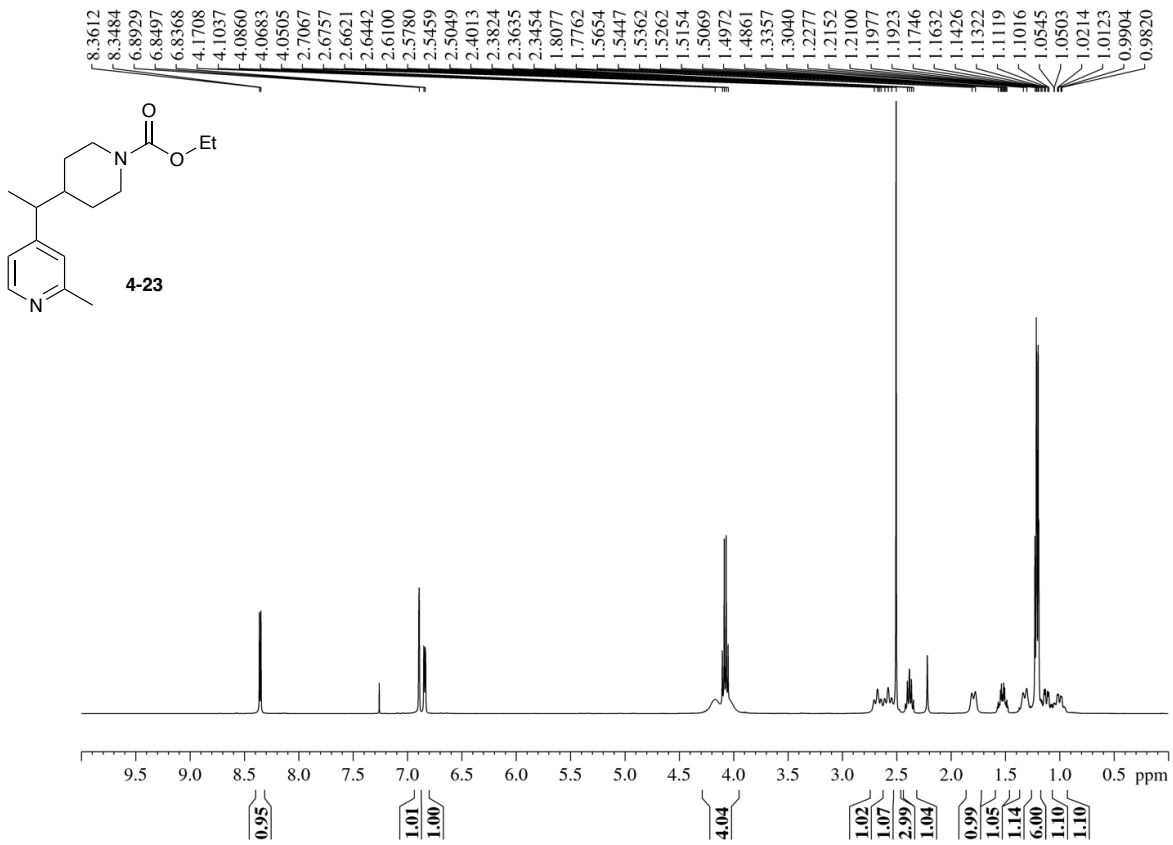
IR Alpha-Platinum ATR, Bruker, diamond crystal

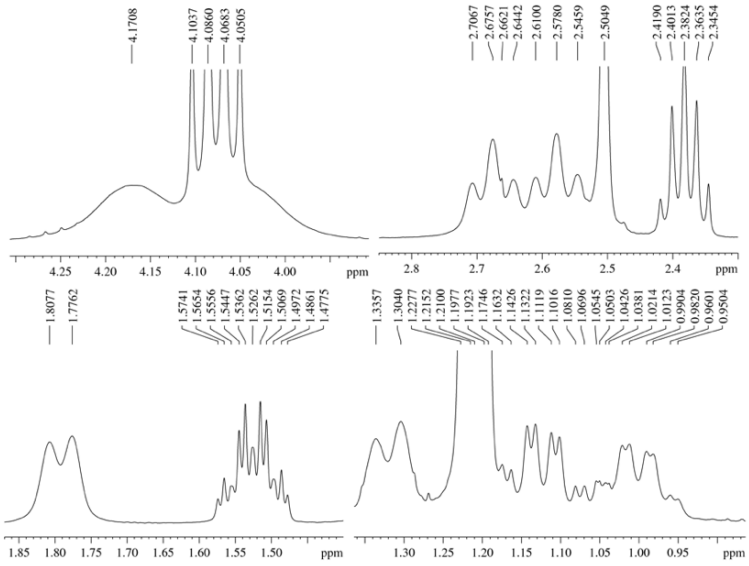
υ = 3080, 2976, 2855, 1691, 1429, 1229 cm^{-1}.

HRMS ESI-TOF

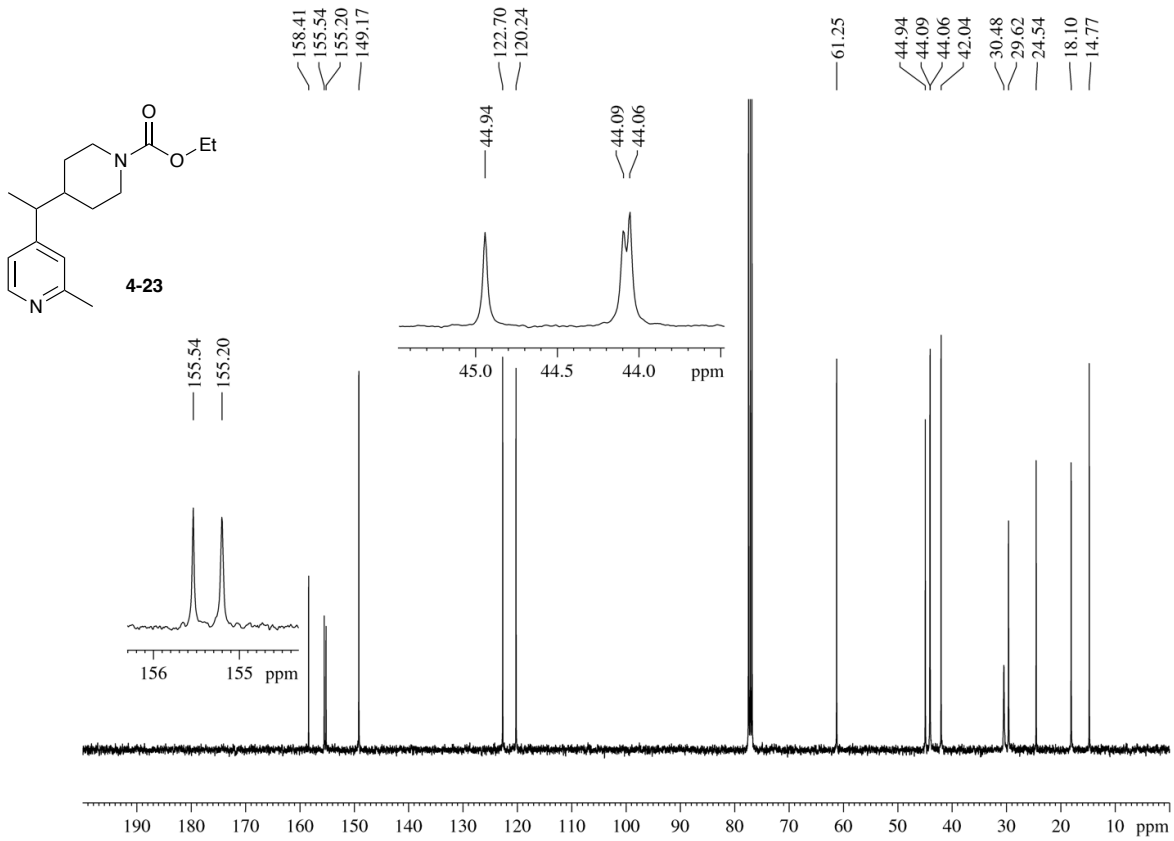
$(M+H)^+$ Calcd for $C_{16}H_{25}N_2O_2$ 277.1911; Found 277.1901.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-23**:

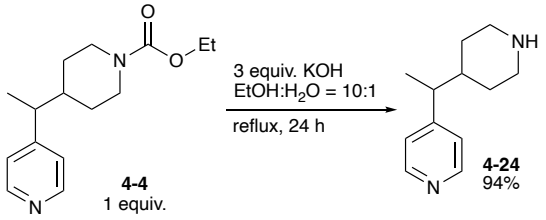




^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-23**:



Synthesis of compound **4-24**:



A round-bottomed flask was charged with a 0.05 M solution of piperidine **4-4** (78.7 mg, 1.0 equiv., 0.3 mmol) in ethanol. A 0.15 M solution of potassium hydroxide (50.5 mg, 3.0 equiv., 0.9 mmol) in water was added to the piperidine solution, and the resulting mixture was placed in an oil bath, stirred, and heated to reflux for 24 hours. The mixture was then cooled to ambient temperature and then concentrated using a rotary evaporator to remove ethanol. The resulting mixture was extracted with DCM (4 x 10 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, filtered through a cotton plug, and concentrated using a rotary evaporator. The resulting residue was purified by flash column chromatography using EtOAc/methanol/Et_3N to afford product **4-24** as colorless oil (53.7 mg, 94% yield).

Chromatography: 58% methanol, 2% Et_3N in EtOAc (R_f = 0.34).

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

δ 8.48 (d, *J* = 6.0 Hz, 2H), 7.06 (d, *J* = 6.0 Hz, 2H), 3.18 – 3.09 (m, 1H), 3.06 – 2.95 (m, 1H), 2.58 (td, *J* = 12.4, 2.8 Hz, 1H), 2.53 – 2.39 (m, 2H), 1.83 (dp, *J* = 12.4, 2.8 Hz, 1H), 1.58 – 1.45 (m, 1H), 1.38 – 1.29 (m, 1H), 1.23 (d, *J* = 7.2 Hz, 3H), 1.22 – 1.12 (m, 1H), 1.06 (qd, *J* = 12.0, 4.0 Hz, 1H).

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

δ 155.3, 149.8, 123.3, 46.7(4), 46.7, 45.5, 42.3, 31.6, 30.7, 18.0.

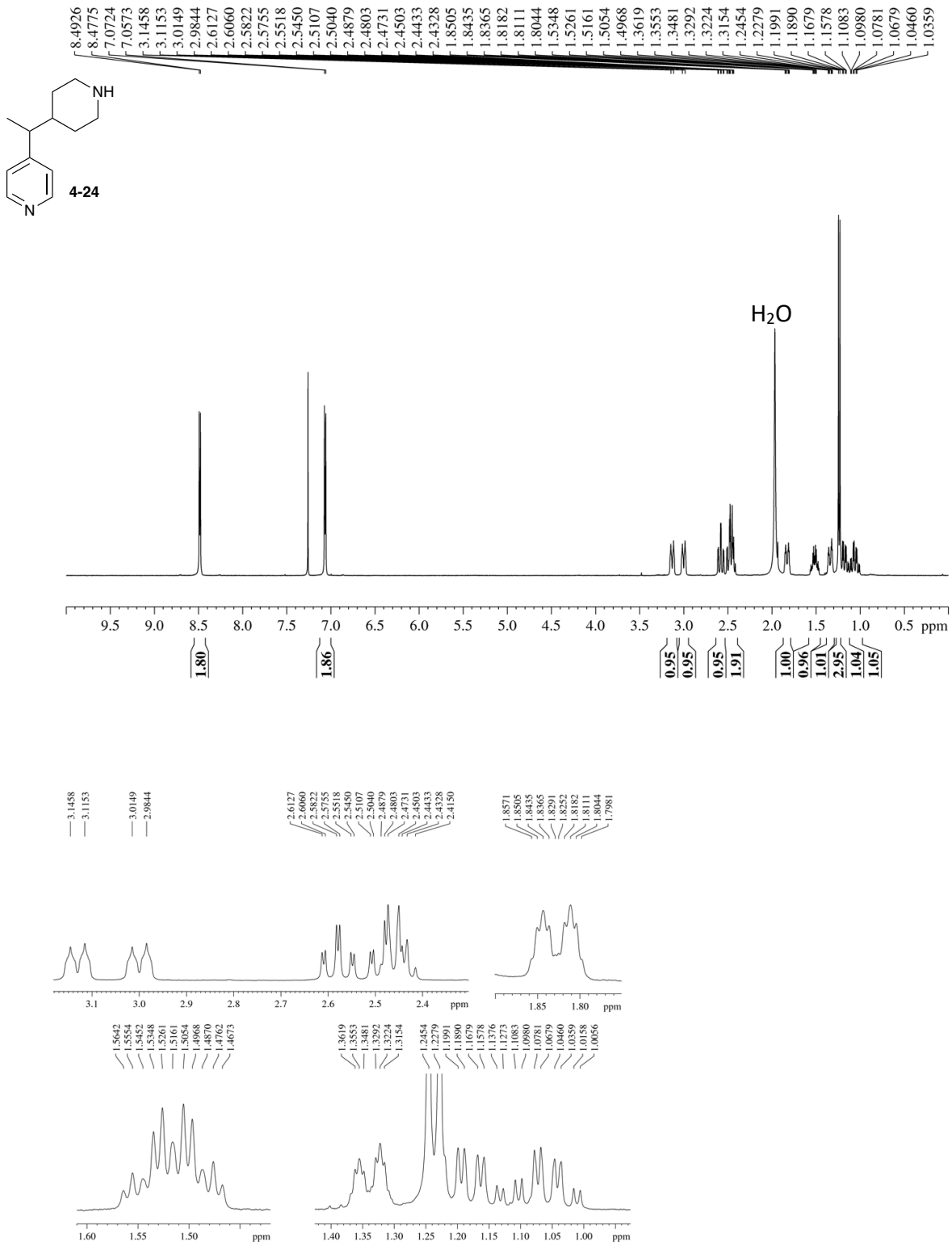
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3270, 3066, 2964, 2932, 1599, 1413 cm^{-1}.

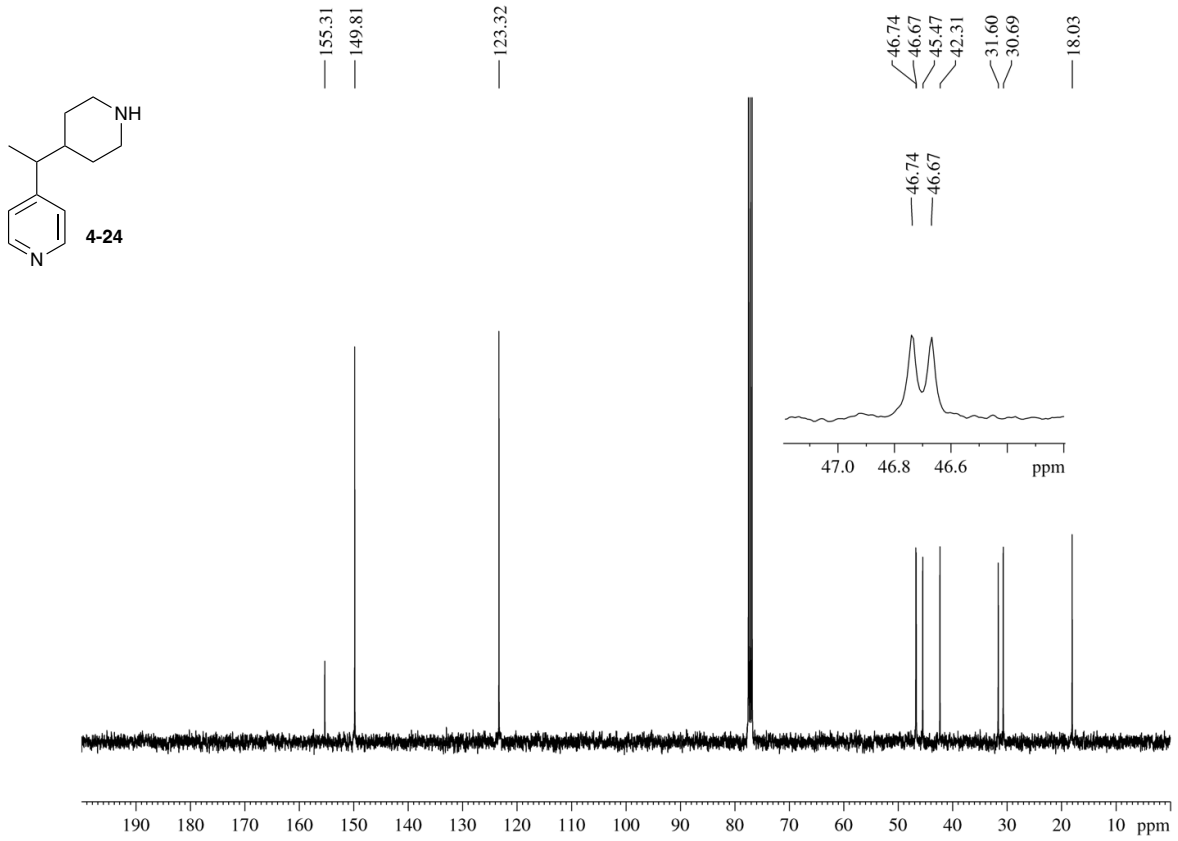
HRMS ESI-TOF

$(M+H)^+$ Calcd for $C_{12}H_{19}N_2$ 191.1543; Found 191.1536.

^{1}H NMR (400 MHz, $CDCl_3$) spectrum for **4-24**:



^{13}C NMR (100 MHz, $CDCl_3$) spectrum for **4-24**:



Reference

(1) Wentrup, C., Origins of Organic Chemistry and Organic Synthesis, *Eur. J. Org. Chem.*, **2022**, *2022* (25), e202101492. https://doi.org/10.1002/ejoc.202101492.

(2) Wöhler, F., Ueber Künstliche Bildung Des Harnstoffs, *Ann. Phys.*, **1828**, *88* (2), 253 – 256. https://doi.org/10.1002/andp.18280880206.

(3) Kolbe, H., Beiträge Zur Kenntniss Der Gepaarten Verbindungen, *Justus Liebigs Ann. Chem.*, **1845**, *54* (2), 145 – 188. https://doi.org/10.1002/jlac.18450540202..

(4) Perkin, W. H., On Mauve or Aniline-Purple, *Proc. R. Soc. Lon.*, **1864**, *13*, 170 – 176. https://doi.org/10.1098/rspl.1863.0042.

(5) Sneader, W., The Discovery of Aspirin: A Reappraisal, *BMJ*, **2000**, *321* (7276), 1591 – 1594. https://doi.org/10.1136/bmj.321.7276.1591.

(6) Nicolaou, K. C., The Emergence and Evolution of Organic Synthesis and Why It Is Important to Sustain It as an Advancing Art and Science for Its Own Sake, *Isr. J. Chem.*, **2018**, *58* (1), 104 – 113. https://doi.org/10.1002/ijch.201700121.

(7) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A., Organic Synthesis Provides Opportunities to Transform Drug Discovery, *Nat. Chem*., **2018**. *10*, 383 – 394. https://doi.org/10.1038/s41557-018-0021-z.

(8) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O., Modern Advances in Heterocyclic Chemistry in Drug Discovery, *Org. Biomol. Chem.*, **2016**, *14*, 6611 – 6637 https://doi.org/10.1039/c6ob00936k.

(9) Nadin, A.; Hattotuwagama, C.; Churcher, I., Lead-Oriented Synthesis: A New Opportunity for Synthetic Chemistry, *Angew. Chem. Int. Ed.* **2012**, *51* (5), 1114 – 1122. https://doi.org/10.1002/anie.201105840.

(10) Vitaku, E.; Smith, D. T.; Njardarson, J. T., Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals, *J. Med. Chem.*, **2014**, *57* (24), 10257 – 10274. https://doi.org/10.1021/jm501100b.

(11) Ling, Y.; Hao, Z. Y.; Liang, D.; Zhang, C. L.; Liu, Y. F.; Wang, Y., The Expanding Role of Pyridine and Dihydropyridine Scaffolds in Drug Design, *Drug Des. Develop. Ther*. **2021**, *15*, 4289 – 4338. https://doi.org/10.2147/DDDT.S329547.

(12) Hong, S.-P.; Liu, K. G.; Ma, G.; Sabio, M.; Uberti, M. A.; Bacolod, M. D.; Peterson, J.; Zou, Z. Z.; Robichaud, A. J.; Doller, D., Tricyclic Thiazolopyrazole Derivatives as Metabotropic Glutamate Receptor 4 Positive Allosteric Modulators, *J. Med. Chem.*, **2011**, *54* (14), 5070 – 5081. https://doi.org/10.1021/jm200290z.

(13) Yeung, K.-S.; Beno, B. R.; Parcella, K.; Bender, J. A.; Grant-Young, K. A.; Nickel, A.; Gunaga, P.; Anjanappa, P.; Bora, R. O.; Selvakumar, K.; Rigat, K.; Wang, Y.-K.; Liu, M.; Lemm, J.; Mosure, K.; Sheriff, S.; Wan, C.; Witmer, M.; Kish, K.; Hanumegowda, U.; Zhuo, X.; Shu, Y.-Z.; Parker, D.; Haskell, R.; Ng, A.; Gao, Q.; Colston, E.; Raybon, J.; Grasela, D. M.; Santone, K.; Gao, M.; Meanwell, N. A.; Sinz, M.; Soars, M. G.; Knipe, J. O.; Roberts, S. B.; Kadow, J. F., Discovery of a Hepatitis C Virus NS5B Replicase Palm Site Allosteric Inhibitor (BMS-929075) Advanced to Phase 1 Clinical Studies, *J. Med. Chem*., **2017**, *60* (10), 4369 – 4385. https://doi.org/10.1021/acs.jmedchem.7b00328.

(14) Hamada, Y., Role of Pyridines in Medicinal Chemistry and Design of BACE1 Inhibitors Possessing a Pyridine Scaffold, in: P.P Pandey (Ed), Pyridine, InTech, 2018. https://doi.org/10.5772/intechopen.74719.
(15) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B., Synthesis of Pyridine and Dihydropyridine Derivatives by Regio- and Stereoselective Addition to n -Activated Pyridines, *Chem. Rev.*, **2012**, *112* (5), 2642 –2713. https://doi.org/10.1021/cr200251d.
(16) Campagnuolo, C.; Fattorusso, C.; Fattorusso, E.; Ianaro, A.; Pisano, B.; Taglialatela-Scafati, O., Simplakidine A, a Unique Pyridinium Alkaloid from the Caribbean Sponge Plakortis Simplex, *Org. Lett.*, **2003**, *5* (5), 673 – 676. https://doi.org/10.1021/ol027437r.
(17) Ma, Z.; Lin, D. C. H.; Sharma, R.; Liu, J.; Zhu, L.; Li, A. R.; Kohn, T.; Wang, Y.; Liu, J.; Bartberger, M. D.; Medina, J. C.; Zhuang, R.; Li, F.; Zhang, J.; Luo, J.; Wong, S.; Tonn, G. R.; Houze, J. B., Discovery of the Imidazole-Derived GPR40 Agonist AM-3189, *Bioorg. Med. Chem. Lett.*, **2016**, *26* (1), 15 – 20. https://doi.org/10.1016/j.bmcl.2015.11.050.
(18) Alexander, R. P.; Warrellow, G. J.; Eaton, M. A. W.; Boyd, E. C.; Head, J. C.; Porter, J. R.; Brown, J. A.; Reuberson, J. T.; Hutchinson, B.; Turner, P.; Boyce, B.; Barnes, D.; Mason, B.; Cannell, A.; Taylor, R. J.; Zomaya, A.; Millican, A.; Leonard, J.; Morphy, R.; Wales, M.; Perry, M.; Allen, R. A.; Gozzard, N.; Hughes, B.; Higgs, G., CDP840. A Prototype of a Novel Class of Orally Active Anti-Inflammatory Phosphodiesterase 4 Inhibitors, *Bioorg. Med. Chem. Lett.*, **2002**, *12* (11), 1451 – 1456. https://doi.org/10.1016/S0960-894X(02)00202-0.
(19) Bordwell, F. G., Equilibrium Acidities in Dimethyl Sulfoxide Solution, *Acc. Chem. Res.*, **1988**, *21* (12), 456 – 463. https://doi.org/10.1021/ar00156a004.
(20) Taber, D. F.; Guo, P.; Pirnot, M. T., Conjugate Addition of Lithiated Methyl Pyridines to Enones, *J. Org. Chem*., **2010**, *75* (16), 5737 – 5739. https://doi.org/10.1021/jo100890s.
(21) Pinard, E.; Alberati, D.; Alvarez-Sanchez, R.; Brom, V.; Burner, S.; Fischer, H.; Hauser, N.; Kolczewski, S.; Lengyel, J.; Mory, R.; Saladin, C.; Schulz-Gasch, T.; Stalder, H., 3-Amido-3-Aryl-Piperidines: A Novel Class of Potent, Selective, and Orally Active GlyT1 Inhibitors, *ACS Med. Chem. Lett.*, **2014**, *5* (4), 428 – 433. https://doi.org/10.1021/ml500005m.
(22) Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y.-J.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Cantin, M.; Cheshire, D. R.; Kellner, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Set, L.; Vernon, P. G., Total Synthesis of Crystalline (±)-Fredericamycin A, *Stud. Nat. Prod. Chem.*, **1995**, *16*, 27 – 74. https://doi.org/10.1016/S1572-5995(06)80052-9.
(23) Abdelshaheed, M. M.; Fawzy, I. M.; El-Subbagh, H. I.; Youssef, K. M., Piperidine Nucleus in the Field of Drug Discovery, *Futur. J. Pharm. Sci.*, **2021**, *7* (1), 188. https://doi.org/10.1186/s43094-021-00335-y.
(24) Rivkin, A.; Ahearn, S. P.; Chichetti, S. M.; Hamblett, C. L.; Garcia, Y.; Martinez, M.; Hubbs, J. L.; Reutershan, M. H.; Daniels, M. H.; Siliphaivanh, P.; Otte, K. M.; Li, C.; Rosenau, A.; Surdi, L. M.; Jung, J.; Hughes, B. L.; Crispino, J. L.; Nikov, G. N.; Middleton, R. E.; Moxham, C. M.; Szewczak, A. A.; Shah, S.; Moy, L. Y.; Kenific, C. M.; Tanga, F.; Cruz, J. C.; Andrade, P.; Angagaw, M. H.; Shomer, N. H.; Miller, T.; Munoz, B.; Shearman, M. S., Purine Derivatives as Potent γ-Secretase Modulators, *Bioorg. Med. Chem. Lett*., **2010**, *20* (7), 2279 – 2282. https://doi.org/10.1016/j.bmcl.2010.02.008.

(25) Fish, P. V.; Andrews, M. D.; Jonathan Fray, M.; Stobie, A.; Wakenhut, F.; Whitlock, G. A., 4-Piperidines and 3-Pyrrolidines as Dual Serotonin and Noradrenaline Reuptake Inhibitors: Design, Synthesis and Structure-Activity Relationships, *Bioorg. Med. Chem. Lett.*, **2009**, *19* (10), 2829 – 2834. https://doi.org/10.1016/j.bmcl.2009.03.090.
(26) Zhang, X.; MacMillan, D. W. C., Direct Aldehyde C-H Arylation and Alkylation via the Combination of Nickel, Hydrogen Atom Transfer, and Photoredox Catalysis, *J. Am. Chem. Soc.*, **2017**, *139* (33), 11353 – 11356. https://doi.org/10.1021/jacs.7b07078.
(27) Meng, N.; Yu, W.; Suzuki, T.; Chen, M.; Qi, Z.; Hu, B.; Bao, J.; Debenham, J. S.; Mazzola, R.; Duffy, J. L., Mild Condition for the Deoxygenation of α-Heteroaryl-Substituted Methanol Derivatives. *J. Org. Chem.*, **2021**, *86* (8), 5560 – 5567. https://doi.org/10.1021/acs.joc.1c00067.
(28) Antoniak, D.; Barbasiewicz, M., Alkylation of Nitropyridines via Vicarious Nucleophilic Substitution, *Org. Lett.*, **2022**, *24* (2), 516 – 519. https://doi.org/10.1021/acs.orglett.1c03920.
(29) Kolthoff, I. M.; Chantooni, M. K.; Bhowmik, S., Dissociation Constants of Uncharged and Monovalent Cation Acids in Dimethyl Sulfoxide, *J. Am. Chem. Soc.*, **1968**, *90* (1), 23 – 28. https://doi.org/10.1021/ja01003a005.
(30) Parameswarappa, S. G.; Pigge, F. C., Intramolecular Cyclization Manifolds of 4-Alkylpyridines Bearing Ambiphilic Side Chains: Construction of Spirodihydropyridines or Benzylic Cyclization via Anhydrobase Intermediates, *J. Org. Chem.*, **2012**, *77* (18), 8038 – 8048. https://doi.org/10.1021/jo301247c.
(31) Wasfy, N.; Rasheed, F.; Robidas, R.; Hunter, I.; Shi, J.; Doan, B.; Legault, C. Y.; Fishlock, D.; Orellana, A., Pyridylic Anions Are Soft Nucleophiles in the Palladium-Catalyzed C(Sp3)-H Allylation of 4-Alkylpyridines, *Chem. Sci.*, **2021**, *12* (4), 1503 – 1512. https://doi.org/10.1039/d0sc03304a.
(32) Wasfy, N.; Doan, B.; Rasheed, F.; Fishlock, D.; Orellana, A., Palladium-Catalyzed, Mild Dehydrogenation of 4-Alkylpyridines, *ACS Catal.*, **2021**, *11* (6), 3251 – 3256. https://doi.org/10.1021/acscatal.0c05209.
(33) Pawar, L.; Pigge, F. C., Gold-Catalyzed Intramolecular Cyclization of Alkynones with Pyridine Anhydrobases, *Tetrahedron Lett.*, **2013**, *54* (45), 6067 – 6070. https://doi.org/10.1016/j.tetlet.2013.08.110.
(34) Lansakara, A. I.; Farrell, D. P.; Pigge, F. C., Brønsted Acid Catalyzed Intramolecular Benzylic Cyclizations of Alkylpyridines, *Org. Biomol. Chem.*, **2014**, *12* (7), 1090 – 1099. https://doi.org/10.1039/c3ob42039f.
(35) Joshi, M. S.; Pigge, F. C., Dearomatized Alkylidene Dihydropyridines as Substrates for Mizoroki-Heck Cyclizations, *ACS Catal*., **2016**, *6* (7), 4465 – 4469. https://doi.org/10.1021/acscatal.6b01151.
(36) Trost, B. M.; Van Vranken, D. L., Asymmetric Transition Metal-Catalyzed Allylic Alkylations, *Chem. Rev*., **1996**, *96* (1), 395 – 422. https://doi.org/10.1021/cr9409804.
(37) Sha, S.-C.; Zhang, J.; Carroll, P. J.; Walsh, P. J., Raising the pK_a Limit of "Soft" Nucleophiles in Palladium-Catalyzed Allylic Substitutions: Application of Diarylmethane Pronucleophiles, *J. Am. Chem. Soc.*, **2013**, *135* (46), 17602 – 17609. https://doi.org/10.1021/ja409511n.

(38) Beaulieu, E. D.; Voss, L.; Trauner, D., Conjugate Addition of Allyl Stannanes with Concomitant Triflation, *Org. Lett.*, **2008**, *10* (5), 869 – 872. https://doi.org/10.1021/ol702996t.
(39) Hosomi, A.; Sakurai, H., Conjugate Addition of Allylsilanes to α,β-Enones. A New Method of Stereoselective Introduction of the Angular Allyl Group in Fused Cyclic α,β-Enones, *J. Am. Chem. Soc*., **1977**, *99* (5), 1673 – 1675. https://doi.org/10.1021/ja00447a080.
(40) Snider, B. B.; Rodini, D. J.; van Straten, J., Lewis Acid Induced Conjugate Addition of Alkenes to α,β-Unsaturated Ketones or Aldehydes, *J. Am. Chem. Soc*., **1980**, *102* (18), 5872 – 5880. https://doi.org/10.1021/ja00538a028.
(41) Liang, G.; Xu, Y.; Seiple, I. B.; Trauner, D. Synthesis of Taiwaniaquinoids via Nazarov Triflation, *J. Am. Chem. Soc.*, **2006**, *128* (34), 11022 – 11023. https://doi.org/10.1021/ja062505g.
(42) Orellana, A.; Rovis, T., Towards the Total Synthesis of FD-838: Modular Enantioselective Assembly of the Core, *Chem. Commun.* **2008**, 730 – 732. https://doi.org/10.1039/b716445a.
(43) Pougny, J. R.; Sinaÿ, P. Reaction d'imidates de Glucopyranosyle Avec l'acetonitrile. Applications Synthetiques, *Tetrahedron Lett.*, **1976**, *17* (45), 4073 – 4076. https://doi.org/10.1016/S0040-4039(00)92578-4.
(44) Bertuzzi, G.; Bernardi, L.; Fochi, M., Nucleophilic Dearomatization of Activated Pyridines. *Catalysts*. **2018**, *8* (12), 632. https://doi.org/10.3390/catal8120632.
(45) Wang, X.; Kauppi, A. M.; Olsson, R.; Almqvist, F., Efficient Solution-Phase Parallel Synthesis of 4-Substituted *N* -Protected Piperidines, *Eur. J. Org. Chem.*, **2003**, *2003* (23), 4586 – 4592. https://doi.org/10.1002/ejoc.200300387.
(46) Corey, E. J.; Tian, Y., Selective 4-Arylation of Pyridines by a Nonmetalloorganic Process, *Org. Lett.*, **2005**, *7* (24), 5535 – 5537. https://doi.org/10.1021/ol052476z.
(47) Arnott, G.; Brice, H.; Clayden, J.; Blaney, E., Electrophile-Induced Dearomatizing Spirocyclization of *N* -Arylisonicotinamides: A Route to Spirocyclic Piperidines, *Org. Lett.*, **2008**, *10* (14), 3089 – 3092. https://doi.org/10.1021/ol801092s.
(48) Choi, J.; Laudadio, G.; Godineau, E.; Baran, P. S., Practical and Regioselective Synthesis of C-4-Alkylated Pyridines, *J. Am. Chem. Soc.*, **2021**, *143* (31), 11927 – 11933. https://doi.org/10.1021/jacs.1c05278.
(49) Still, W. C.; Kahn, M.; Mitra, A., Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution, *J. Org. Chem*., **1978**, *43* (14), 2923 – 2925. https://doi.org/10.1021/jo00408a041.
(50) Hoye, T. R.; Zhao, H., A Method for Easily Determining Coupling Constant Values: An Addendum to "A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy", *J. Org. Chem.*, **2002**, *67* (12), 4014 – 4016. https://doi.org/10.1021/jo001139v.
(51) Hoye, T. R.; Hanson, P. R.; Vyvyan, J. R., A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy, *J. Org. Chem.*, **1994**, *59* (15), 4096 – 4103. https://doi.org/10.1021/jo00094a018.
(52) Stern, T.; Rückbrod, S.; Czekelius, C.; Donner, C.; Brunner, H., A Selective and Benign Synthesis of Functionalized Benzalacetones via Mizoroki-Heck Reaction Using

Aryldiazonium Salts, *Adv. Synth. Catal.*, **2010**, *352* (11–12), 1983 – 1992. https://doi.org/10.1002/adsc.200900868.

(53) Bentley, K. W.; Dummit, K. A.; Van Humbeck, J. F., A Highly Site-Selective Radical Sp^3 C–H Amination of Azaheterocycles, *Chem. Sci.*, **2018**, *9* (30), 6440 – 6445. https://doi.org/10.1039/C8SC00590G.