2023

# Asymmetric CuH-catalyzed Reductive Coupling of Allenamides with Carbonyl Electrophiles & Development of Nanocatalysts for Heterogeneously Catalyzed Buchwald-Hartwig Amination

Raphael K. Klake

2023

# Asymmetric CuH-catalyzed Reductive Coupling of Allenamides with Carbonyl Electrophiles & Development of Nanocatalysts for Heterogeneously Catalyzed Buchwald-Hartwig Amination

Raphael K. Klake

# Asymmetric CuH-catalyzed Reductive Coupling of Allenamides with Carbonyl Electrophiles & Development of Nanocatalysts for Heterogeneously Catalyzed Buchwald-Hartwig Amination

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Doctor of Philosophy Degree at Virginia Commonwealth University

By

Raphael Kwaku Klake

Bachelor of Science, University of Ghana

Advisor and Dissertation Director: Dr. Joshua D. Sieber

Assistant Professor, Department of Chemistry

Committee: Dr. Joshua D. Sieber, Dr. Vladimir Sidorov, Dr. Soma Dhakal, Dr. Thomas D. Roper

Virginia Commonwealth University

Richmond, Virginia

May 2023

# ABSTRACT

Asymmetric CuH-catalyzed Reductive Coupling of Allenamides with

Carbonyl Electrophiles & Development of Nanocatalysts for Heterogeneously Catalyzed

Buchwald-Hartwig Amination

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Doctor of Philosophy

Degree at Virginia Commonwealth University

By Raphael Kwaku Klake

Virginia Commonwealth University, 2023

Advisor: Dr. Joshua D. Sieber, Assistant Professor, Department of Chemistry

Many drugs and natural products contain multiple stereogenic carbons bearing heteroatoms throughout their carbon framework. Therefore, methods that can efficiently install multiple heteroatoms on a molecule are valuable. Reductive coupling reactions have been extensively studied, and the allylation of carbonyls via the reductive coupling approach has been a key method for generating chiral tertiary and secondary allylic alcohols. This work utilizes inexpensive Cu for the asymmetric reductive coupling of allenamides with carbonyls to simultaneously install two heteroatoms (oxygen and nitrogen) on the product. These molecules have a polarity profile that make them difficult to make using traditional methods. Herein, we report a method for the asymmetric reductive coupling reactions. Chapter 1 describes the development of a regiodivergent

and diastereoselective CuH-catalyzed reductive coupling of *N*-based allenes and carbonyls, where stereoselectivity is controlled by a chiral auxiliary and regioselectivity is modulated by catalyst tuning through choice of ligand. This protocol provides access to novel linear and branched products. The linear products underwent standard chemical transformations to furnish (*S*)-boivinianin-A, a natural product with a γ-lactone motif. Chapter 2 details the development of the first asymmetric enantioselective aminoallylation of ketones, which features the first reported case of a reversible aminoallylation event in reductive coupling processes. This protocol provides an atom-economical approach for the synthesis of 1,2-aminoalcohols. The reaction paradigm was expanded to incorporate aldehydes as electrophiles to asymmetrically produce secondary alcohols.

The Buchwald Hartwig Amination is a powerful reaction for the synthesis of aryl amines. They are extensively used in industrial processes. Currently, homogeneous catalysts are more active and selective than heterogeneous catalysts and are therefore favored in industrial processes. Unfortunately, the use of homogeneous organic palladium complexes as catalysts incurs costs in downstream purification processes when removing palladium impurities. Heterogeneous catalysis faces no such issues because it is easily removed via filtration. These heterogeneous catalysts also have the added benefit of reusability, which makes the development of such a system valuable. Chapter 3 describes our efforts to develop a heterogeneously catalyzed Buchwald-Hartwig Amination employing nanoparticles synthesized via the Strong Electrostatic Absorption method as a catalyst. The development of this reaction, scope, and recycling studies are discussed herein.

This work is dedicated to:

*Dr. Raphael Kwaku Klake*

*Diana Klake*

*Dzidzor Maklwa Akosua Klake*

*Rita Ntobo Klake*

In loving memory of:

*Emmanuel Nambia-Klake*

*Mary Aissah Klake*

*Anastasia Alegah*

## ACKNOWLEDGEMENTS

I want to take the time to thank my advisor, Dr. Joshua D. Sieber, for going above and beyond his duties as an advisor and taking on the role of a surrogate father during my time at VCU. His patience, guidance, and encyclopedic knowledge of literature have been crucial to my growth as a chemist.

Due regard must also be given to my committee for their invaluable insights and constructive advice.

My mentors, Dr. Michael Glasgow and Dr. Christopher Kelly, for their friendship and guidance with both professional and private matters.

My fellow Sieber group members for their friendship, collaboration, and assistance in collecting data for various research projects.

My parents, Raphael and Diana Klake, for always believing in and supporting me, and for your constant love and guidance in every aspect of my life. You have instilled the value of education in me and have always pushed me to do my best in all my endeavors. I would not be here without you.

My sister, Dzidzor Klake, for forever being in my corner. Throughout my studies, you have supported me in ways that are too numerous to recount. I appreciate you and could not have asked for a better sister.

Rita, my loving wife, for being my number one fan and cheerleader. You have seen me at my best and worst, yet you are unwavering in your support of me. You are an amazing wife and will be a fantastic mother.

To all my family, each of you has supported me in some way, and I know you are there if I need you. I love you all.

To my in-laws, Dr. Leopold Zekeng, Dr. Stella Zekeng, Dr. Elsa Zekeng, Dr. Cherryl Zekeng, and Leo-Chris Zekeng, I greatly appreciate your support, friendship, and willingness to help, regardless of the situation. I am blessed and delighted to call you family.

To the Ubong family, I thank you for opening your home to me and my family. They say family is not always blood, but the people in your life who want you in theirs, the ones who accept you for who you are. You are indeed family.

Finally, thanks must go to you for whom I would be nothing without. I thank you, the righteous and eternal heavenly father, God, who so loved the world that you gave your only begotten son, Jesus Christ, that whosoever believeth in him should not perish but have everlasting life. I thank God for this wonderful gift of salvation and all the blessings bestowed upon me and my family, for which we are wholeheartedly grateful. We live and strive to glorify your name.

# TABLE OF CONTENTS

## LIST OF FIGURES

## LIST OF TABLES

## LIST OF SCHEMES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| $B_2(pin)_2$ | bis(pinacolato)diboron |
| CAN | ceric ammonium nitrate |
| Cy | cyclohexyl |
| DABCO | 1,4-diazabicyclo [2.2.2]octane |
| DBU | 1,8-Diazabicyclo(5.4.0)undec-7-ene |
| DCM | dichloromethane |
| DIBAL | diisobutylaluminium hydride |
| DMF | dimethyl formamide |
| equiv | equivalence |
| Et | ethyl |
| EtOAc | ethyl acetate |
| FG | functional group |
| Hex. | hexane |
| IPr | Isopropyl |
| Me | methyl |
| MS | molecular sieves |
| MsCl | methanesulfonyl chloride |
| MTBE | methyl tertiary-butyl ether |
| NMO | *N*-Methylmorpholine *N*-oxide |
| PBT | Polar Bond Theory |
| Ph | phenyl |
| PhCF3 | trifluorotoluene |
| PMB | *para*-methoxybenzyl |
| SEA | Strong Electrostatic Adsorption |
| t-Bu | tertiary-butyl |
| TEP | Tolman Electronic Parameter |
| THF | tetrahydrofuran |
| TPAP | tetrapropylammonium perruthenate |

# Chapter 1
# Development of Asymmetric CuH-Catalyzed Reductive Coupling of a Chiral Allenamide with Ketone Electrophiles

## I. Introduction

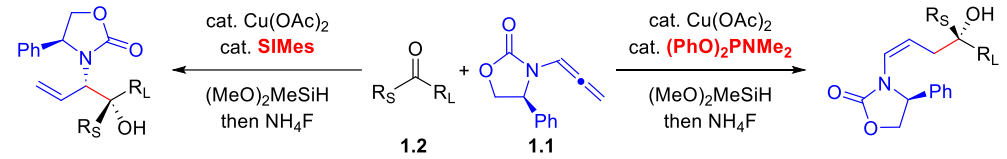
Chiral organic molecules bearing multiple heteroatom functional groups (FG) are ubiquitous in natural products and drugs.[1–10] These compounds, such as aminoalcohols,[11] diols,[12] and diamines,[13] have widespread applications in the chemical sciences. Therefore, it is necessary to develop synthetic methodologies to provide access to these valuable compounds. This is not a simple endeavor, as these synthetic methodologies need to be regio-, stereo-, and enantioselective, and have been a toilsome venture for organic chemists.

Multiple heteroatoms (*e.g.*, oxygen and nitrogen) borne by each stereogenic carbon atom have a polarizing effect on the entire carbon framework of the molecule. This polarization creates synthetic challenges when making the molecule by means of traditional chemistry.[14] In particular, challenging heteroatom substitution patterns must be created using non-traditional routes.[14–16] Arguably, the most efficient method for forming such carbon skeletons bearing two electron withdrawing heteroatoms is cross-electrophile coupling, commonly referred to as reductive coupling reactions.[9,17–21] These processes have been studied extensively and have been found to be an effective synthetic method for these non-traditional C-C bond formations.

This work advances the field of CuH catalysis for organic synthesis by inverting the inherent polarity profiles of synthons to generate dissonant molecules that would otherwise be difficult to synthesize.[22,23] This chapter discusses the development of a regiodivergent and diastereoselective CuH-catalyzed reductive coupling of a chiral *N*-substituted allene (allenamide) derived from Evans' oxazolidinone and ketone electrophiles (**Scheme 1.1**). The regioselectivity is

modulated via catalyst tuning through ligand choice to produce either linear product (**1.3**) or branched product (**1.4**).

***Scheme 1.1:*** *Method Development for CuH-Catalyzed Reductive Coupling of Allenamides and Carbonyl Electrophiles*




## II. Background

### A. Multi-Heteroatom Containing Natural Products and Drugs

Nature is the best chemist in the world, efficiently producing extremely complex and highly functionalized molecules.[3–7,21,24–26] These so-called natural products (**Figure 1.1A**, left) contain multiple heteroatoms and exhibit various types of biological activity.[27] Many drugs (**Figure 1.1B**, right) also contain multiple heteroatoms and, as such, require rigorous planning to develop viable synthetic routes.[28,29] Consequently, synthetic methodologies capable of stereoselectively installing multiple heteroatoms are important.

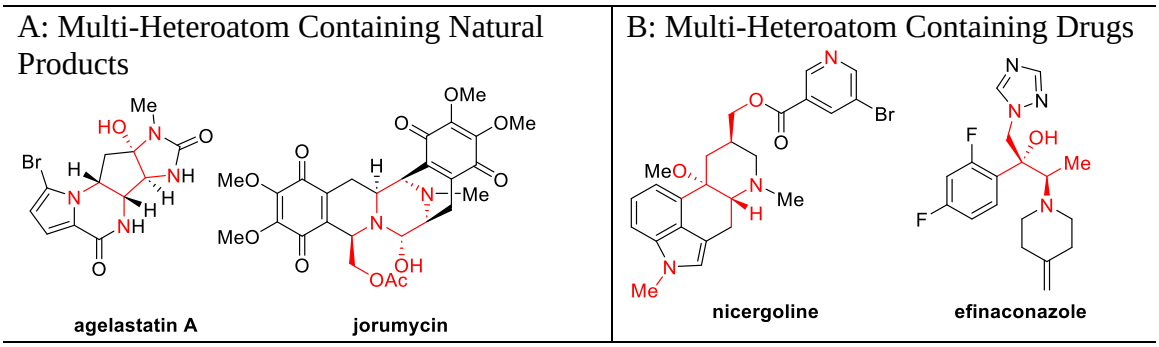



***Figure 1.1:*** *Highly Functionalized Multi-Heteroatom Containing Natural Products and Drugs*

## B. Retrosynthetic Analysis and Consonant/Dissonant Theory

Chemists must rigorously plan when attempting to synthesize highly functionalized organic molecules. Careful preparation is necessary to identify the most efficient and viable route towards the desired target molecule. To identify this route, chemists make use of E.J. Corey's retrosynthetic analysis, a concept which earned him the 1990 Nobel Prize in Chemistry.[30] Simply put, retrosynthetic analysis involves identifying key disconnections known as "strategic bonds" on the target molecule by working backwards and breaking the molecule down into simple intermediates called "synthons."[31] Using this process aids in the direct identification of possible routes that can be explored in the forward synthetic direction.

When applying retrosynthetic analysis to the synthesis of molecules with multiple functional groups, the electronic properties of the desired strategic bond must be considered. For example, a strategic bond between two functional groups positioned in such a way as to create a matched chain polarization should be easy to form using traditional two-electron chemistry. In contrast, a strategic bond between two functional groups that create a mismatched chain polarization cannot easily be formed using traditional methods. Dave Evans developed this idea in the 1970's and ascribed the terms consonant and dissonant charge affinity which has been encapsulated in his consonant/dissonant theory otherwise known as Polar Bond Theory (**Figure 1.2**).[22,23] Recently, Evans' consonant/dissonant theory was cleverly captured by Reisman.[14]

In accordance with the consonant/dissonant theory, each heteroatom on a multi-heteroatom-bearing molecule polarizes the carbon skeleton in some way. This polarization depends on the positions of the heteroatoms on the molecule. Polarization created by each heteroatom can either reinforce (consonant) or conflict (dissonant) with each other. In the case of

electron withdrawing heteroatom substituents such as oxygen and nitrogen, the situation depicted in **Figure 1.2** is the outcome.[14]

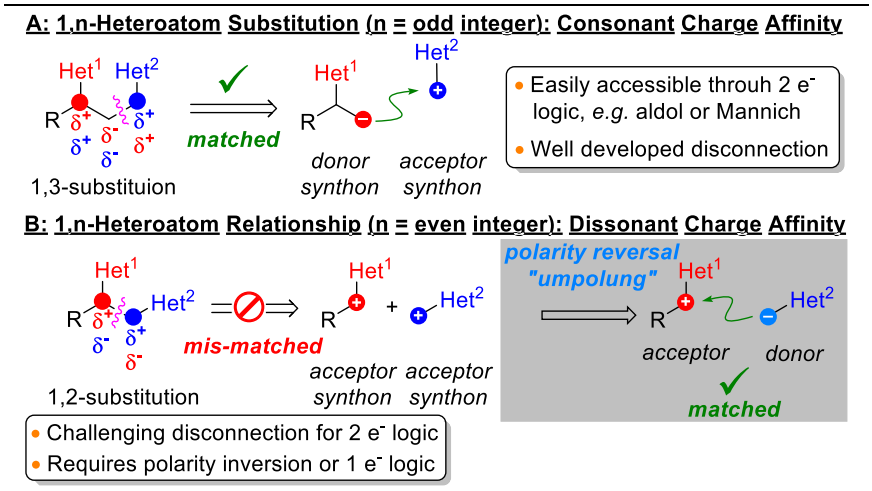



***Figure 1.2:*** *Consonant and Dissonant Theory in 1,n-substituted molecular frameworks with electron-withdrawing heteroatom groups*

When a molecule has two electron-withdrawing heteroatoms positioned in a 1,n-substitution pattern, where n is an odd integer, the result is a molecule with consonant charge affinity (**Figure 1.2A**). Retrosynthetic analysis of consonant molecules yields two synthons with matched polarities. This type of disconnection is well-developed and can be easily made using two-electron logic. Conversely, when n is an even integer, dissonant charge affinity results (**Figure 1.2B**). The polarities of the resulting synthons when applying retrosynthetic analysis to dissonant molecules are mismatched. This type of connection is difficult to construct using two-electron logic. To allow for easy of bond formation between mis-matched synthons, non-traditional methods such as umpolung (polarity reversal) can be applied.[15,16] Radical chemistry can equally be used to access dissonant molecules due to their more neutral character.[32–36]

## C. Umpolung

While Evans' polar bond theory (PBT) provides a framework for considering how functional groups may impact retrosynthetic design strategies, the challenges associated with accessing dissonant functional group patterns using traditional two-electron processes were recognized before the development of Evans' concept.[15,16,23] The need to invert the polarity of one of the reacting synthons to enable the synthesis of dissonant functional group patterns through two-electron chemistry was introduced by Seebach before Evans' PBT. Introductions of this polarity-inversion concept as a strategy to access dissonant functional group patterns was defined as umpolung chemistry by Seebach which means "polarity inversion" in German.[15,16] Using the umpolung approach results in the reversal of the inherent polarity of a functional group within a molecule, enabling nonconventional reactivity (**Figure 1.2B**). Seebach's efforts to invert the inherent polarity profile of aldehydes resulted in a strategy whereby the carbonyl is converted to a dithioacetal, which is then lithiated to generate a "masked" acyl anion. Overall, the umpolung approach represents a powerful strategy for accessing multi-heteroatom containing molecules with dissonant charge affinity. [37–41]

## D. Reductive Coupling

An efficient strategy for installing ≥ two heteroatoms within a molecule could be argued to engage two heteroatom-containing fragments in a convergent cross-coupling reaction by forming a C-C bond between the two coupling partners.[37–41] By this paradigm, if two electrophilic fragments are engaged as coupling partners, then an adequate electron density required for bond formation is not present, requiring a stoichiometric amount of a reductant to be added to supply this requisite electron density.[17,19,42–45] The reductant works in tandem with a catalyst to form the C-C bond. This process is known as reductive coupling or "cross-electrophile" coupling. Common

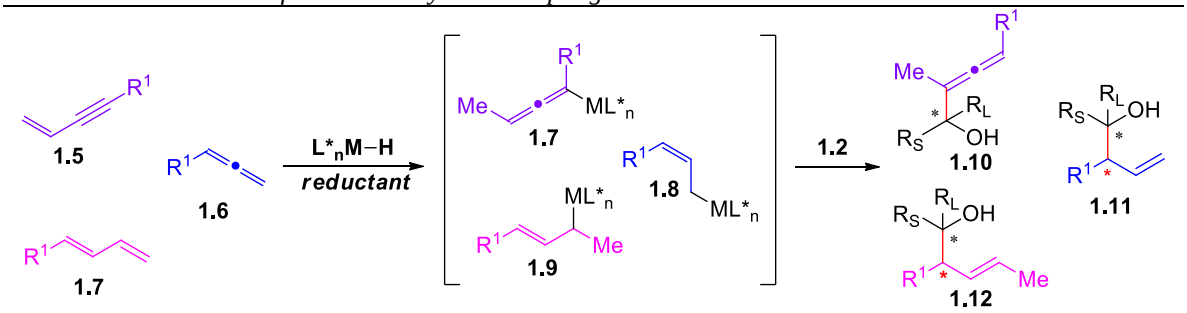
reducing agents can operate either by the addition of electrons (*e.g.* Zn, Mn)[17], or atom transfer (*e.g.* $H_2$, $BEt_3$, $B_2(pin)_2$, or $R_3SiH$).[17] This reaction paradigm utilizing atom-transfer reducing agents has been applied to carbonyl allylation to generate synthetically useful intermediates since the resulting olefin and heteroatom can undergo further functionalization.[46–49]

## E. Allylation

### *i. Pioneering Work in Allylation: H.C. Brown*

Synthetic methodologies for C-C bond formation are highly sought after because they are necessary for the synthesis of any target molecule. A powerful approach to C-C bond formation to simultaneously generate a stereogenic carbon-heteroatom bond is the allylation of carbonyl (**Scheme 1.2**).[20,50–52] Pioneering work in stereoselective allylation by H.C. Brown in the 1980's employed stoichiometric preformed chiral allylmetal nucleophiles **1.13** (**Scheme 1.3**) to stereoselectively allylate aldehydes or ketones to yield the desired homoallylic chiral alcohol.[53–55] Although useful, the active allylborane required for this reaction is highly reactive. Allylboranes are not air-stable and require cryogenic conditions when employed as allylating reagents.

***Scheme 1.2:*** *Overview of reductive allylation coupling*



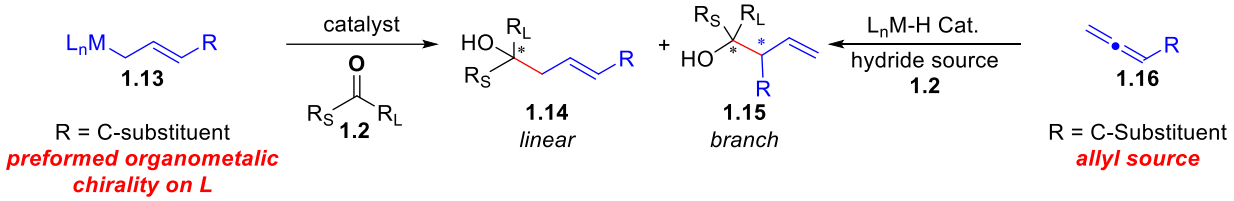

### *ii. Catalytic Methods for Allylation*

Allylation reactions employing stoichiometric amounts of allylmetal complexes have remained the standard method for allylating ketones and aldehydes for approximately 40 years.[56,57]

The most commonly used allylmetal species (**1.13**, **Scheme 1.3**) are boron[12,58–61], tin[62–65], and silicon[66,67] based. Catalytic methods have since emerged to generate allylmetal complexes *in situ* from a stable allyl source. Many of these methods take an umpolung approach in which the allylating species is nucleophilic.[37–41]

Nevertheless, reductive coupling strategies[20,50–52] for allylation in which the active allylmetal reagent is generated via hydrometallation of an unsaturated hydrocarbon represents a powerful and elegant approach for the synthesis of homoallylic alcohols **1.14** and **1.15 (Scheme 1.3)**.[50,68–74]

***Scheme 1.3**: Evolution of Reductive Allylation of Carbonyls*



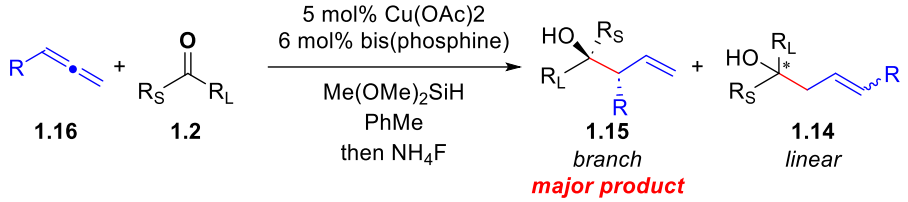

### *iii. Krische's Catalytic Reductive Allylation*

Pioneering work by Krische ushered in the development of a protocol in which an allylmetal reagent is generated *in situ* via hydrometalation of a *C*-substituted allene with catalytic Ir-[75,76] or Ru-hydride.[77] The nascent allylmetal reagent was then stereoselectively added to the carbonyl to furnish homoallylic alcohol **1.15 (Scheme 1.3)**. This protocol employs reagents that are air-stable and functionally group-tolerant. Unfortunately, Ir and Ru are precious metals worth $162.3 per gram and $16.40 per gram, respectively.[78] The astronomical cost of these precious metal catalysts necessitates the development of a more economically viable and sustainable protocol utilizing a cheaper, more readily available catalyst.

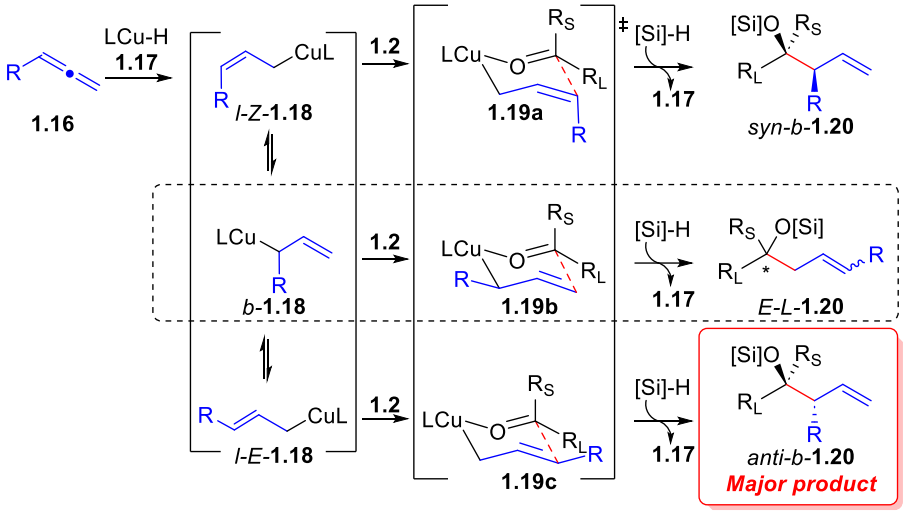
*iv. Buchwald's Catalytic CuH Allylation*

***Scheme 1.4****: Buchwald's C-substituted allene/ketone reductive coupling and working mechanistic model*

A. Buchwald's C-substituted allene/ketone reductive coupling




B. Working Proposed Mechanistic Model




Although Cu-hydrides have been studied considerably for years,[79,80] they have only recently been employed by Buchwald as a catalyst for the reductive coupling of a *C*-substituted allenes with a carbonyl to produce chiral homoallylic alcohol **1.15** in 2016 (**Scheme 1.4a**).[81] This protocol is highly cost-effective because Cu is a nonprecious metal and is worth $ 0.008 per gram.[78] This protocol has been employed to generate tertiary homoallylic alcohols **1.15** through reductive coupling reactions employing allenes[46,47,81] **1.6** or 1,3-dienes[46] **1.7** with ketone or imine electrophiles (**Scheme 1.4b**).

Buchwald's protocol uses a chiral catalyst generated from Cu and a chiral bis(phosphine) ligand working synergistically with stoichiometric silane reductant $Me(OMe)_2SiH$ to generate a chiral CuH catalyst *in-situ* (**1.17**, **Scheme 1.4B**). Subsequent hydrocupration furnishes *l*-*Z*-**1.18** which can equilibrate to *b*-**1.18** and *l*-*E*-**1.18**.[82] This equilibration is possible only because of the rate-limiting ketone addition step, which occurs through a chair-like transition structure **1.19a-c**.[48] The silane turns the cycle over to generate the O-[Si] products **1.20**. Interestingly, only *anti*-*b*-**1.20** was formed in appreciable yield and diastereoselectivity.

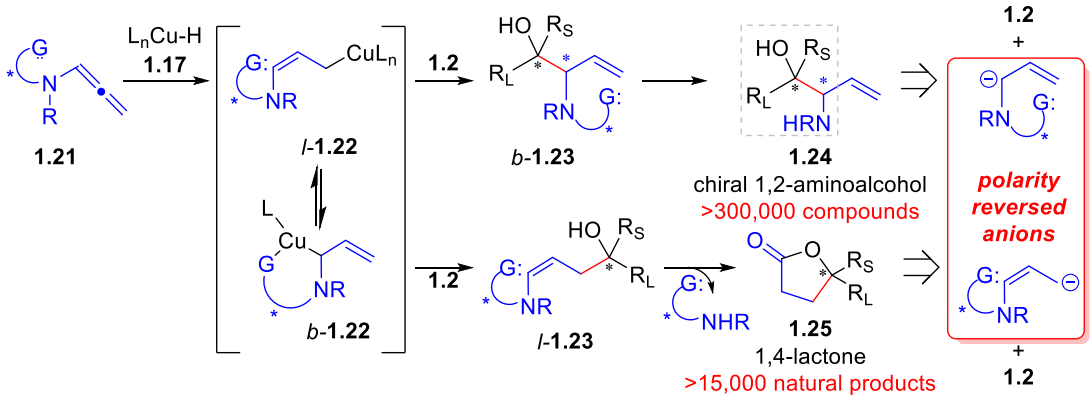
## III. Research Design

### A. Research Plan

We rationalized that the allylcopper reagents *l*-*Z*-**1.18**, *b*-**1.18**, and *l*-*E*-**1.18** exist simultaneously in solution and undergo rapid equilibration (**Scheme 1.4B**). As a result, the formation of the major observed product (*anti*-*b*-**1.20**) is proposed to occur by Curtin-Hammett kinetics, with transition structure **1.19c** being the most energetically favored. Although Buchwald has shown that both linear and branched products can be accessed when imines are employed as coupling partners with allenes by choosing the appropriate nitrogen protecting group, an analogous protocol to access both linear product *E*-*l*-**1.20** and branched product *anti*-*b*-**1.20** from coupling an allene with ketones has yet to be developed.[81] The Sieber lab therefore sought to fill this gap in the literature by developing a regiodivergent method to selectively generate the *E*-*l*-**1.20** and *anti*-*b*-**1.20** products utilizing Cu-catalysis. We theorized that the linear product *E*-*l*-**1.20** could be accessed if the transition structure *b*-**1.18** could be energetically favored; therefore, a strategy to achieve this was sought.

## B. *N*-Substituted Allene

***Scheme 1.5**: Proposed strategy for regiodivergent reductive coupling with N-substituted allenes and carbonyls*




Buchwald's Cu-catalyzed allylation reaction yields the branched *anti*-diastereomer (*anti*-*b*-**1.20**) as the major product presumably because all unfavorable steric interactions are minimized for that pathway. To develop a linear selective protocol, all steric interactions leading to *E*-*l*-**1.20** must be minimized. A viable strategy to selectively produce *E*-*l*-**1.20** would be to stabilize the branched allylcopper intermediate *b*-**1.18** by employing a directing group tethered to the allene by a heteroatom to allow for the ensuing directing group cleavage (**1.21**, **Scheme 1.5**). The tethered directing group may help stabilize *b*-**1.22** through coordination with copper. Subsequent aminoallylation of ketone **1.2** through a six-membered chair-like transition state yielded the novel dissonant linear product *l*-**1.23**, with two electron-withdrawing heteroatoms (oxygen and nitrogen). The enamine moiety of *l*-**1.23** can in theory be easily hydrolyzed[83] to furnish a 1,4-hydroxyaldehyde that sits as a 1,4-lactol, which may easily be oxidized to a 1,4-lactone.[84] The 1,4-lactone is an important motif since it is present in over 15,000 natural products.[85]

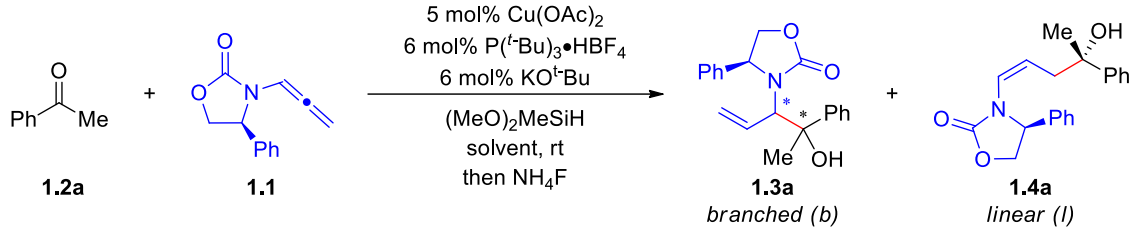
Nonetheless, branched product *b*-**1.23** should also be accessible under ligand conditions that may inhibit binding by the directing group and impede the formation of *b*-**1.22** *in situ*. We rationalized that ligands that promote a high coordination number at Cu (*e.g.,* chelating ligands)

would inhibit binding and therefore grant access to the precious dissonant 1,2-aminoalcohol **1.24**. The 1,2-aminoalcohol motif is present in over 300,000 compounds and over 80 FDA-approved drugs, making it an exceptionally important motif.[86] Synthetic methodology leading to these ubiquitous dissonant molecules with identical substitution patterns have recently intensified in the field of organic method development.

## IV. Linear-Selective Reductive Coupling Protocol Employing a Chiral Auxiliary

### A. Reaction Development

***Table 1.1:*** *Solvent Survey for Linear Selective Protocol*




**1.2a** **1.1** **1.3a** *branched (b)* **1.4a** *linear (l)*

| Entry | Solvent | *l:b*[a] | % Yield **1.4a**[c] | dr **1.4a**[a] |
|---|---|---|---|---|
| 1 | MTBE | 78:22 | 52 | 92:8 |
| 2 | Dioxane | 76:24 | 62 | 93:7 |
| 3 | $CH_2Cl_2$ | 58:42 | 33 | 91:9 |
| 4 | THF | 75:25 | 33 | 93:7 |
| 5 | toluene | 74:26 | 61 | 93:7 |
| 6[c] | toluene | 74:26 | 60 | 93:7 |

Reaction was performed with **1.2a** (0.25 mmol) and **1.1** (0.30 mmol) in 0.5 mL of toluene. See the Experimental Methods for details. [a]Determined by $^1$H-NMR spectroscopic analysis on the unpurified reaction mixture. [b]Determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture using dimethylfumarate as a standard. [c]10 mol % of P($^t$Bu)$_3$·HBF$_4$ and 10 mol % of KO$^t$Bu was used.

We initially set out to develop a linear selective protocol to generate *l*-**1.23**. We decided to begin our investigation with an allene derived from Evans chiral oxazolidinone[87] (**1.1, Table 1.1**). This auxiliary was selected because (a) it is commercially available and economically priced, and (b) allene **1.1** has been synthesized in the literature using a simple procedure.[88] We rationalized that the carbonyl of the oxazolidinone could act as a sufficient directing group for Cu, generating *b*-**1.22**, stabilizing the energy pathway when reacting with ketone **1.2a** to generate linear product

**1.4a**.[89,90] To facilitate this complexation, catalyst conditions that promote low coordination number at copper should be ideal. Consequently, non-coordinating solvents and non-chelating ligands, such as monodentate ligands, have been investigated.

We decided to probe the effects of the solvent on this reaction by investigating the impact of various solvents (**Table 1.1**). These results were obtained in collaboration with Dr. Samantha Gargaro and Dr. Joshua D. Sieber. A variety of non-coordinating aprotic solvents were examined with the aim of maintaining a low copper coordination state (entries 1, 2, 5, and 6). Interestingly, regio- and diastereoselectivity had little relation to solvent choice. Although the more polar $CH_2Cl_2$ produced both linear and branched product with minimal selectivity (entry 3), the polar coordinating solvent THF (entry 4) generated product with linear:branched selectivities identical to non-coordinating solvents like MTBE (entry 1), dioxane (entry 2), and toluene (entry 5,6)

Although the solvent choice marginally affected the regio- and diastereoselectivity, the overall reaction yield was greatly impacted. The yield of the reaction increased with decreasing polarity of the solvent (entries 4, 1, 2, and 5). The best results were obtained using toluene as solvent (entries 5 and 6). However, there was no significant difference in yield when the catalyst loading was doubled (entry 6). Therefore, toluene was selected as the ideal solvent for this reaction.

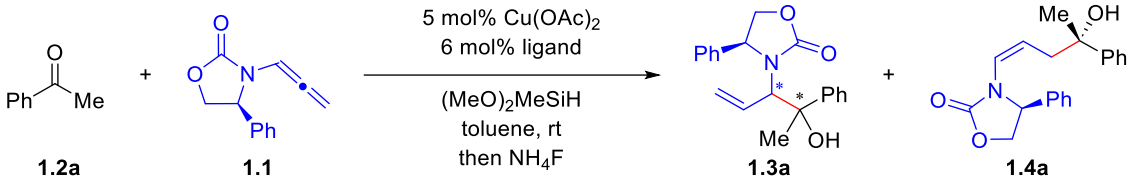
Subsequent efforts were directed towards identifying the appropriate ligand to afford linear product **1.4a** (**Table 1.2**). The results given in **Table 1.2** were obtained by Dr. Joshua Sieber, Skyler Gentry, and Sharon Elele. In accordance with our initial theory, non-chelating ligands were explored. Monodentate trialkyl phosphines favored the formation of linear products (entries 1, 3, and 4). Bidentate bis(phosphine) dcpe favored the formation of branched products (entry 2). This is consistent with the idea that the coordination of the carbonyl of the oxazolidinone to Cu is inhibited by ligands that promote high coordination numbers, thereby allowing the production of

branched product. Several sterically and electronically different monodentate phosphines were examined to determine their effects on the reaction (entries 5 – 11). It was apparent that there was a rough correlation between the ligand cone angle and diastereocontrol, where increasing the cone angle led to an increase in diastereoselectivity (entries 1, 2, 3, 4, 9,10, 13, and 14).

It was also evident that the electron-donating ability of the ligand was directly correlated with the regioselectivity of the reaction. The electron-donating or electron-withdrawing ability of a ligand is quantified by the Tolman Electronic Parameter (TEP).[91,92] The TEP of a ligand represents the νCO stretching frequency of a $LNi(CO)_3$ complex measured by Infrared Spectroscopy (IR) where L is the ligand of interest. The stretching frequency measures the strength of the CO bond, which is impacted by the metal donating electrons through its d orbitals into the empty π* antibonding orbital of CO. The degree of back bonding depends on the electron-donating ability of the ligand. A decrease in the electron-donating ability of L leads to a decrease in the back-bonding by the metal thereby strengthening the CO bond and increasing the νCO stretching frequency which increases the TEP.

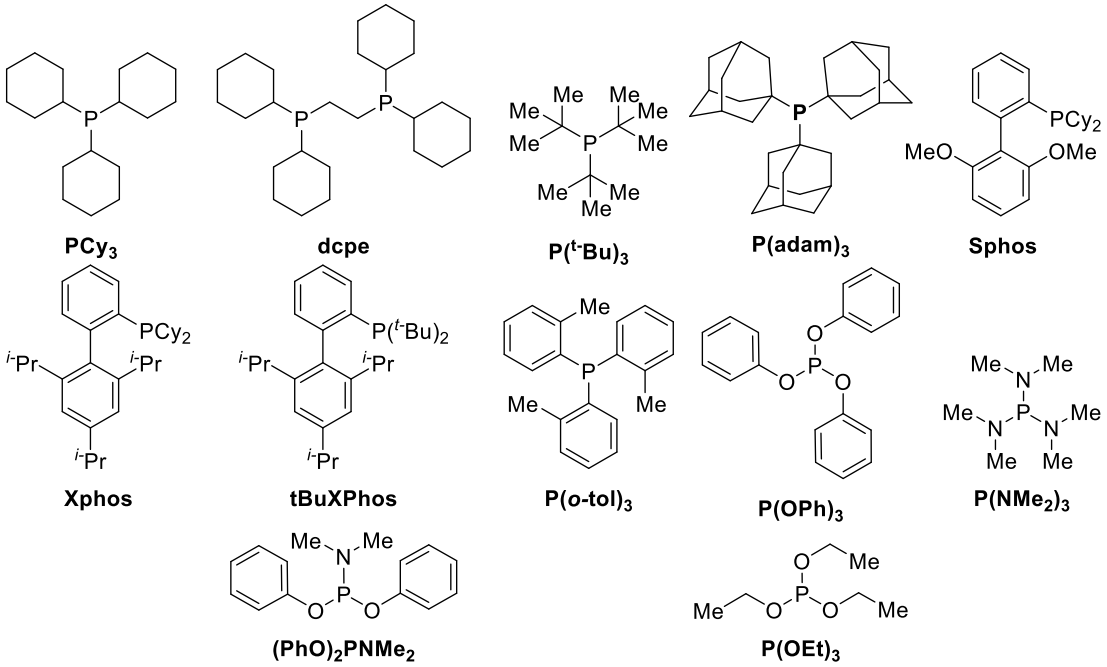
We observed an increase in linear selectivity with decreasing electron-donating ability of the ligand. This trend is consistent with oxazolidinone-Cu coordination because decreasing the electron-donating ability of the ligand increases the Lewis acidity of Cu and promotes coordination by the carbonyl of the oxazolidinone, which behaves as a Lewis base, enhancing linear selectivity. The best combination of yield, diastereoselectivity, and linear selectivity was obtained using phosphoramidite $(PhO)_2PNMe_2$ (entry 11).

***Table 1.2:*** *Ligand Survey for Linear Selective Protocol*



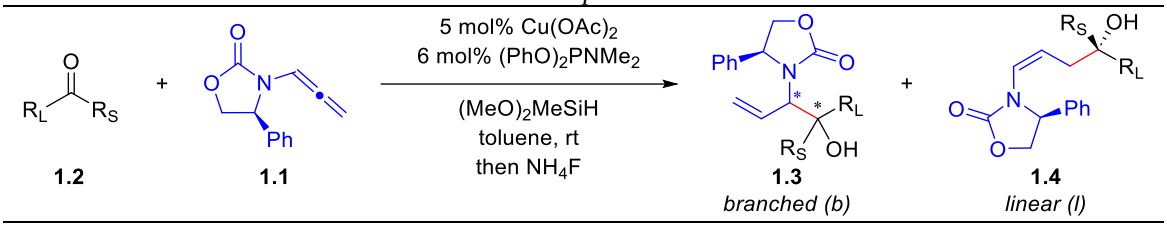

| Entry | Ligand | TEP[a] | Cone Angle[b] | *l:b*[c] | dr **1.4a**[c] | % y **1.4a**[d] |
|---|---|---|---|---|---|---|
| 1 | $PCy_3$ | 2056 | 170 | 80:20 | 84:16 | 68 |
| 2 | dcpe | - | 142 | 23:77 | 84:16 | 14 |
| 3 | $P(^tBu)_3$ | 2056 | 182 | 76:24 | 93:7 | 61 |
| 4 | $P(adam)_3$ | 2052 | - | 71:29 | 93:7 | 71 |
| 5 | Sphos | - | - | 9:91 | 68:32 | 7 |
| 6 | XPhos | - | - | 12:88 | n.d. | 5 |
| 7 | *t*BuXPhos | - | - | 26:74 | n.d. | 5 |
| 8 | $P(o\text{-tol})_3$ | 2067 | 194 | 70:30 | 81:19 | 14 |
| 9 | $P(NMe_2)_3$ | 2062 | 157 | 83:17 | 87:13 | 79 |
| 10 | $P(OEt)_3$ | 2076 | 109 | 92:8 | 83:17 | 90 |
| 11 | $(PhO)_2PNMe_2$ | - | - | 97:3 | 90:10 | 97 |
| 13 | $P(OPh)_3$ | 2085 | 128 | 99:1 | 89:11 | 76 |
| 14 | $P(C_6F_5)_3$ | 2091 | 184 | 99:1 | 85:15 | 12 |

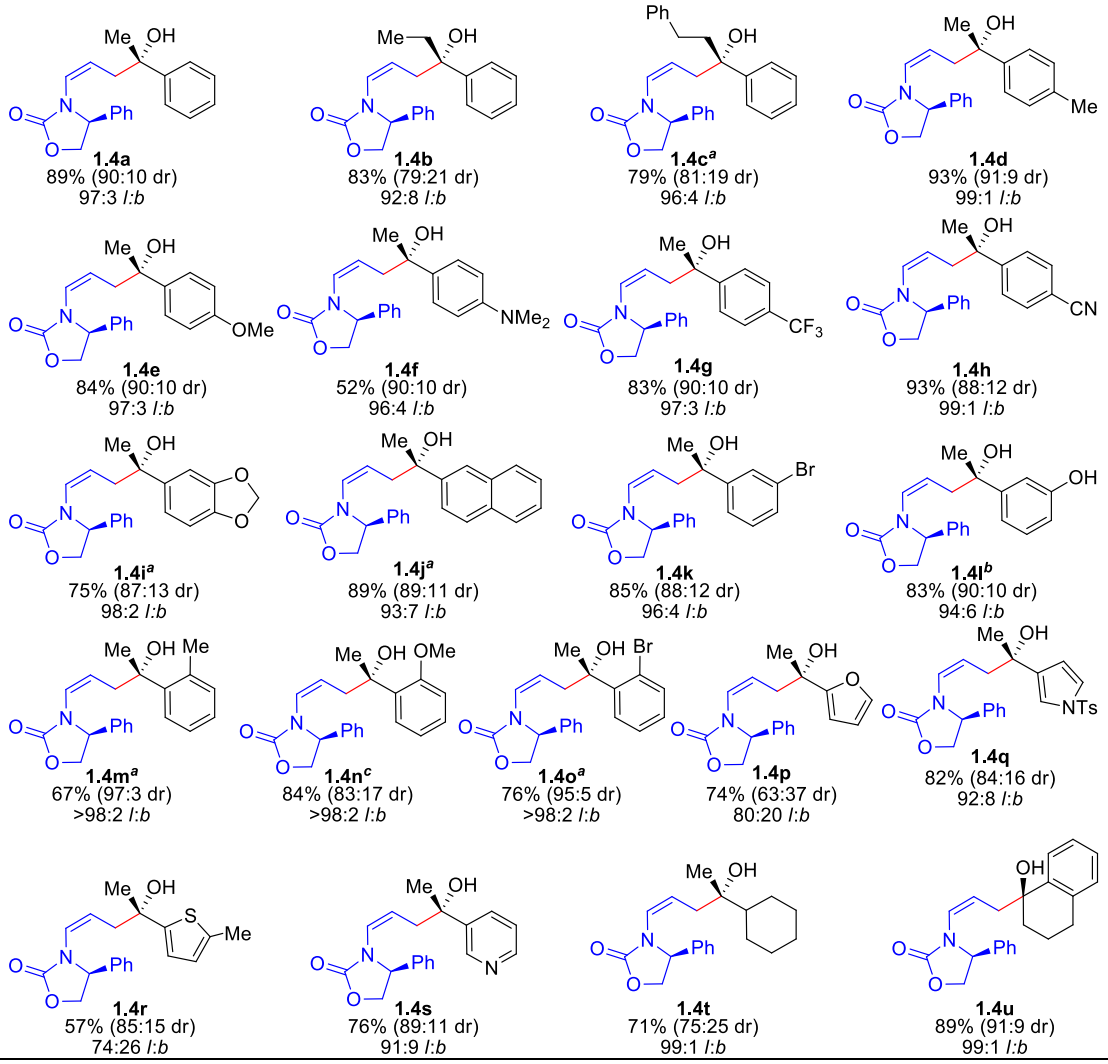
Reaction was performed with **1.2a** (0.25 mmol) and **1.1** (0.30 mmol) in 0.5 mL of toluene. See the Experimental Methods for details. [a]Tolman electronic parameter obtained from literature.[91,92] [b]Ligand cone angle obtained from literature.[91] [c]Determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture. [d]Determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture using dimethylfumarate as a standard.



## B. Substrate Scope

***Scheme 1.6**: Linear Selective Protocol Substrate Scope*




Percent yield represents isolated yield of linear product as a mixture of two diastereomers on 0.5 mmol scale of **1.2** using 1.2 equiv of **1.1**. Diastereomeric ratios (dr) and linear:branched ratios (l:b) were determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture. [a]Reaction performed at 40 °C. [b]4.0 equiv of $Me(MeO)_2SiH$ used. [c]Reaction performed at 60 °C.

With the optimal reaction conditions in hand, the scope of the reaction was investigated using a variety of sterically and electronically different ketones (**Scheme 1.6**). These results were obtained in collaboration with Dr. Samantha Gargaro, a fellow graduate student in the Sieber laboratory. Generally, the reaction is highly linearly selective and performs well for diverse groups of ketones, including electron-rich aromatic ketones (**1.4d-f, i, j, l-n**) and electron-deficient ketones (**1.4 g, h, k, o**). Interestingly, this protocol was highly functional group-tolerant, enabling coupling with ketones bearing nitrile (**1.4h**), amine (**1.4f**), and phenol (**1.4l**) to generate products in good yields. This feature of the newly developed linear selective protocol can be advantageous when planning synthetic routes that utilize these reactive functional groups for further transformations towards a target molecule.

Heteroaromatic ketones (**1.4p-s**) were also well tolerated by this system, albeit with diminished regio- and diastereoselectivities and modest yields. The low diastereoselectivity could result from the reduced steric bias between the substituents of the ketone (**1.4p-r**). This observation also holds true when comparing propiophenone (**1.4b**) and dihydrochalcone (**1.4c**) with acetophenone (**1.4a**). Conversely, increasing steric bias by employing sterically hindered ortho-substituted aromatic ketones (**1.4m-o**) generated products in excellent diastereo-selectivities even though these substrates required elevated temperatures (40 $^{o}$C) to increase conversion.

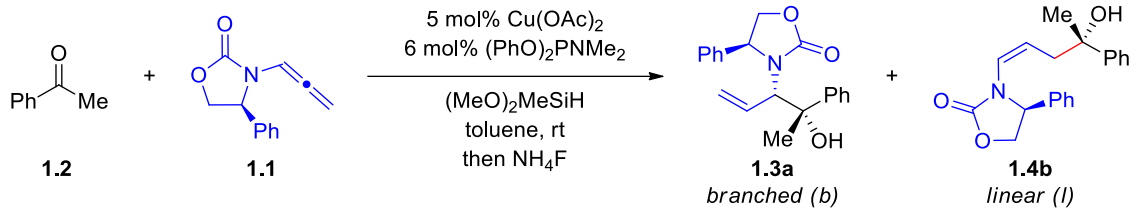
## V. Branched-Selective Reductive Coupling Protocol Employing a Chiral Auxiliary

### A. Reaction Development

We initially proposed that linear product **1.4** would be generated by turning on the oxazolidinone-Cu coordination.[93] To generate the branched product, this coordination must be turned off, possibly by using catalyst conditions that promote high coordination numbers.

Additionally, the linear selective protocol demonstrated the importance of ligand electronics to the reaction. From the results of the linear-selective protocol, oxazolidinone-Cu coordination could be inhibited by increasing the Lewis basicity of Cu by utilizing electron-rich ligands. This should furnish branched product **1.3**, which could grant access to the synthetically important 1,2-aminoalcohol (**1.24, Scheme 1.5**).

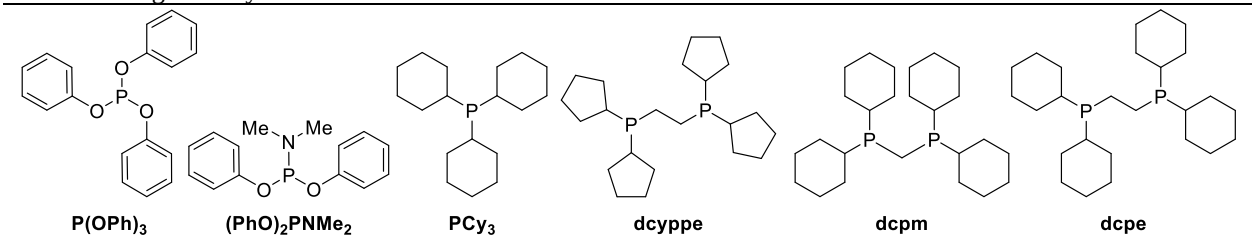
***Table 1.3:*** *Ligand Survey for Branched Selective Protocol*

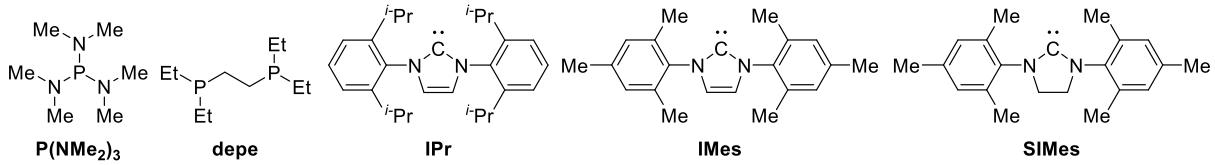



**1.2** + **1.1** → **1.3a** *branched (b)* + **1.4b** *linear (l)*

| Entry | Ligand | TEP[a] | *b:l*[b] | dr **13a**[b] | % yield **13a**[c] | Note |
|---|---|---|---|---|---|---|
| 1 | $P(OPh)_3$ | 2085 | 1:99 | - | <2 | - |
| 2 | $(PhO)_2PNMe_2$ | - | 3:97 | - | 2 | - |
| 3 | $P(NMe_2)_3$ | 2062 | 17:83 | 88:12 | 16 | - |
| 4 | $PCy_3$ | 2056 | 20:80 | 93:7 | 17 | - |
| 5 | dcpe | - | 77:23 | 53:47 | 47 | - |
| 6 | dcpe | - | 65:35 | 59:41 | 28 | DME as solvent. |
| 7 | dcpe | - | 53:47 | 60:40 | 24 | THF as solvent. |
| 8 | dcpm | - | 39:61 | 92:8 | 25 | - |
| 9 | dcyppe | - | 66:34 | 54:46 | 32 | - |
| 10 | depe | - | 50:50 | 57:43 | 27 | - |
| 11 | IPr | 2052 | 87:13 | 87:13 | 70 | - |
| 12 | SIPr | 2052 | 99:1 | 82:18 | 15 | - |
| 13 | IMes | 2051 | 93:7 | 93:7 | 76 | - |
| 14 | SIMes | 2052 | 92:8 | 92:8 | 78 | - |

Reaction was performed with **1.2a** (0.25 mmol) and **1.1** (0.30 mmol) in 0.5 mL of toluene. See the Experimental Methods for details. [a]Tolman electronic parameter obtained from literature.[91,92] [b]Determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture. [c]Determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture using dimethylfumarate as a standard.



A survey of bidentate and electron-rich ligands was conducted in collaboration with Dr. Samantha Gargaro and Dr. Joshua Sieber. (**Table 1.3**). In our previous study, monodentate phosphorous-based ligands (entries 1 – 4) selectively produced linear products. However, bis(phosphine) dcpe has already been shown to selectively generate branched products, albeit with a marginal yield and modest diastereoselectivity.

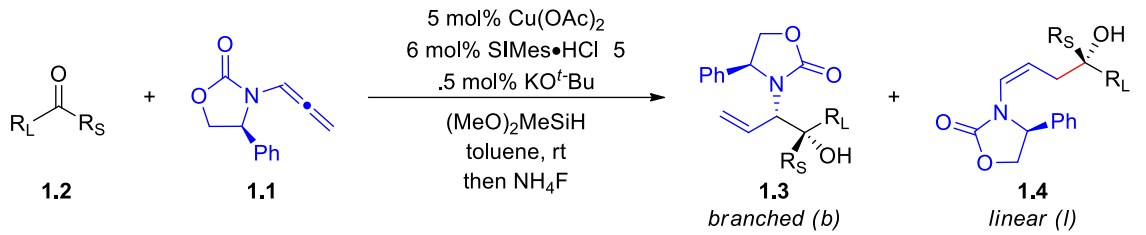
Solvent effects were briefly investigated because we predicted that the use of more coordinating solvents would inhibit oxazolidinone-Cu coordination (entries 6 and 7), generating more branched products. Interestingly, branched selectivity was reduced when THF and DME were used. However, these solvents facilitated a slight increase in diastereoselectivity of the branched product. Clearly, more factors were at play.

We then investigated the effect of the ligand bite angle on this reaction (entries 5, 8, 9, and 10). Bite angles typically affect the activity and selectivity of catalytic reactions.[94,95] They are a measure of the ligand-metal-ligand bond angle and steric effects around the metal center. For the reaction under study, the bite angle of the ligand only marginally affected dr, yield, and regioselectivity (entries 5, 8, 9, and 10).

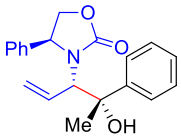
Probing ligand electronics and employing electron-rich *N*-heterocyclic carbene ligands (NHC's) facilitated the selective generation of branched products (**Table 1.3**, entries 12 – 13).[92] The sterically demanding NHC's are exceptionally electron-donating ligands[92] that sufficiently inhibit oxazolidinone-Cu coordination and generate branched product **1.3a**. The best combination of yield, regioselectivity, and diastereoselectivity of **1.3a** was obtained with IMes and SIMes. Consequently, these ligands were identified as the optimal ligands for this reaction.

## B. Substrate Scope

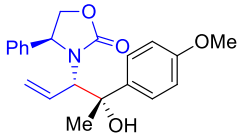
***Scheme 1.7**: Branched Selective Protocol Substrate Scope*



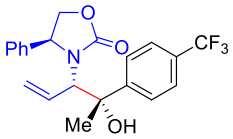

**1.2** + **1.1** → **1.3** *branched (b)* + **1.4** *linear (l)*



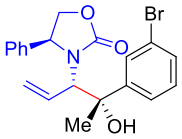
**1.3a**
81% (92:8 dr)
90:10 *b:l*



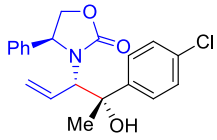
**1.3b**
66% (94:5:1 dr)
88:12 *b:l*



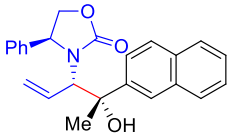
**1.3c**
73% (98:2 dr)
93:7 *b:l*



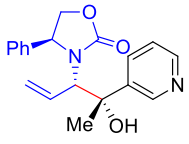
**1.3d**[a]
53% (92:6:2 dr)
81:19 *b:l*



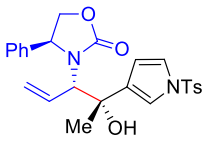
**1.3e**
81% (94:3:2 dr)
90:10 *b:l*



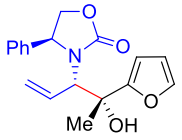
**1.3f**
55% (94:6 dr)
94:6 *b:l*



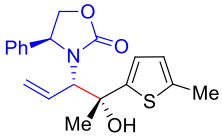
**1.3g**
64% (95:5 dr)
86:14 *b:l*



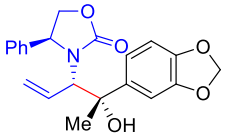
**1.3h**
90% (93:6:1 dr)
95:5 *b:l*



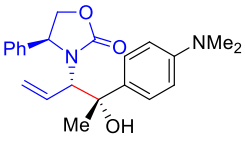
**1.3i**
85% (82:18 dr)
96:4 *b:l*



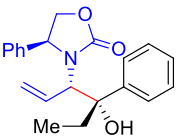
**1.3j**[a]
83% (96:4 dr)
92:8 *b:l*



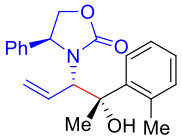
**1.3k**
66% (75:13:12 dr)
83:17 *b:l*



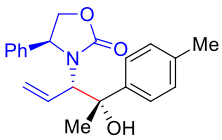
**1.3l**[b]
52% (76:21:3 dr)
81:19 *b:l*



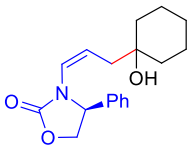
**1.3m**
70% (95:4:1 dr)
92:8 *b:l*



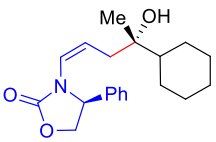
**1.3n**[b,c]
35% (76:11:13 dr)
52:48 *b:l*



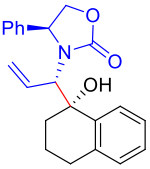
**1.3o**
62% (91:7:2 dr)
90:10 *b:l*



**1.4q**[d]
80%
11:89 *b:l*



**1.4t**[e]
69% (80:20 dr)
20:80 *b:l*



**1.3p**
55% (64:36 dr)
56:44 *b:l*

Percent yield represents isolated yield of branched product as a mixture of two diastereomers on 0.5 mmol scale of **1.2** using 1.2 equiv of **1.1**. Diastereomeric ratios (dr) and linear:branched ratios (*b:l*) were determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture. [a]IMes-HCl was used. [b]Reaction performed at 40 °C. [c]Catalyst loading was doubled. [d]Isolated yield and dr of the linear isomer. [e]Reaction performed at 60 °C.

With the optimal reaction conditions in hand, the scope of the reaction was investigated using a variety of sterically and electronically different ketones (**Scheme 1.7**). These results were obtained in collaboration with Dr. Samantha Gargaro and Kevin Burns, who were fellow graduate students in the Sieber lab.

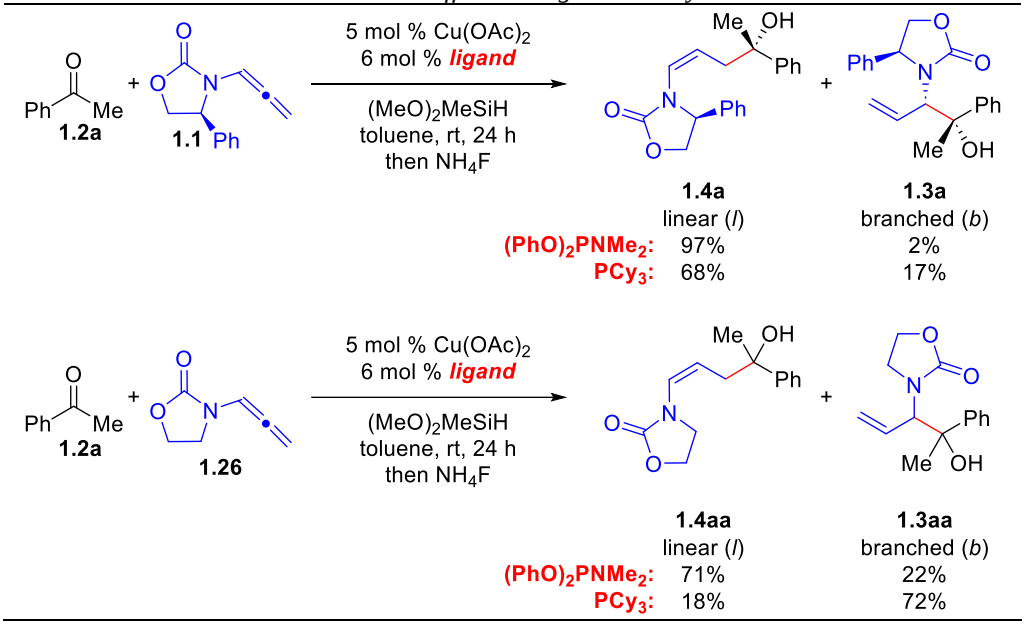
Generally, the reaction is highly branch-selective and performs well for a diverse group of ketones, including electron-rich aromatic ketones (**1.3b, k, l, o**) and electron-deficient ketones (**1.3c and e**). Heteroaromatic ketones (**1.3 g-j**) also behaved well in this system. The reaction is also highly sensitive to steric effects. Ketones containing *ortho*-substitutions were not tolerated by this reaction and generated products with poor yields and meager branched selectivity (**1.3n**). Ketones with *meta*-substitution performed better than *ortho*-substituted ketones, generating products in modest yields and with good branched selectivity (**1.3d, f, k**). Lastly, aliphatic ketones selectively generated linear products (**1.3q** and **t**).

## VI. Working Regio- and Stereochemical Model

### A. Oxazolidinone Structure Effect on Selectivity

Having developed a regiodivergent and diastereoselective reaction, where regioselectivity is defined by the ratio of branched to linear products and is modulated by catalyst tuning, we set out to develop a comprehensive model based on the empirical data collected. The chiral oxazolidinone controls the stereoselectivity of the reaction and produces products in a highly diastereoselective manner. We decided to investigate the effect of the oxazolidinone structure on the regioselectivity of the reaction by performing the reaction with allenes **1.1** and **1.26** employing phosphines with differing electron-donating strengths (**Scheme 1.8**).

***Scheme 1.8**: Oxazolidinone Structure Effect on Regioselectivity*




Performing the reaction with chiral oxazolidinone **1.1** furnished linear products selectively when using the linear selective protocol with $(PhO)_2PNMe_2$ and electron-rich $PCy_3$ as ligands. Interestingly, when switching to the smaller oxazolidinone and performing the reaction with alleneamide **1.26**, the phosphoramidite was still linear selective, but electron-rich $PCy_3$ furnished the branched product selectively. The factors that explain this switch in selectivity are discussed in the next section.

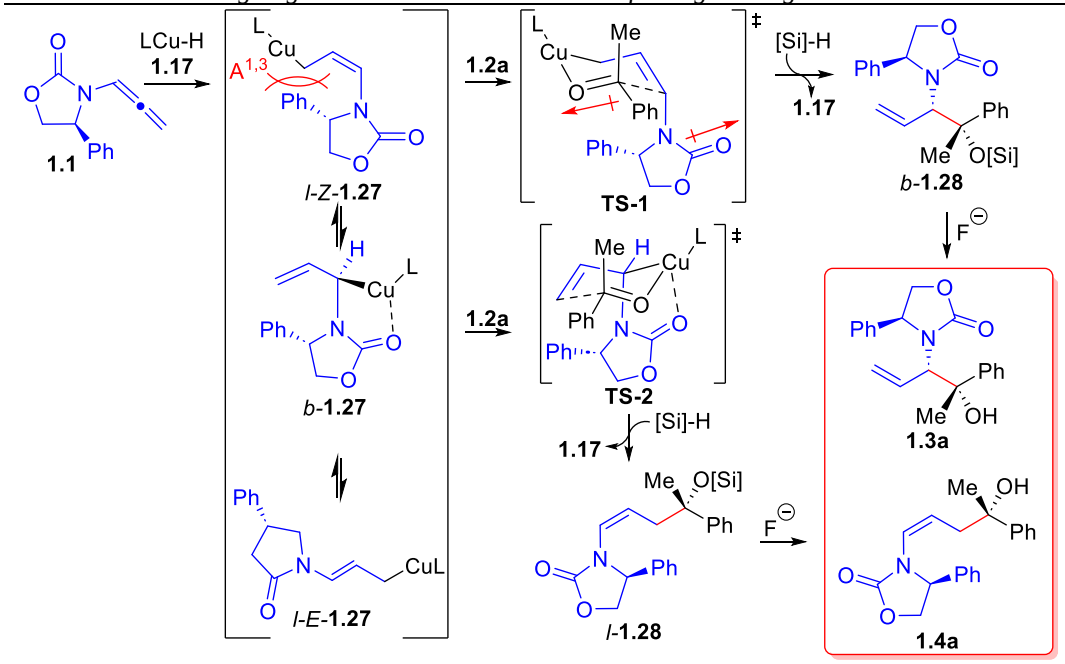
### B. Regio- and Stereochemical Model

We analyzed the empirical data and proposed a comprehensive regiochemical and stereochemical model (**Scheme 1.9**). The empirical data showed that electron-deficient ligands produce the linear product **1.4a** through aminoallylation of ketone **1.2a** by the branched allylcopper reagent *b*-**1.27**. Addition occurs at the γ-position of *b*-**1.27** through the Evans chelation-model[96] (**TS-2**), where addition occurs at the Si-face of ketone **1.2a**. Aminoallylation of ketone **1.2a** with

*l*-*Z*-**1.27** produces **1.3a** as a minor product through the Evans dipole-minimizing transition structure[96] **TS-1**.

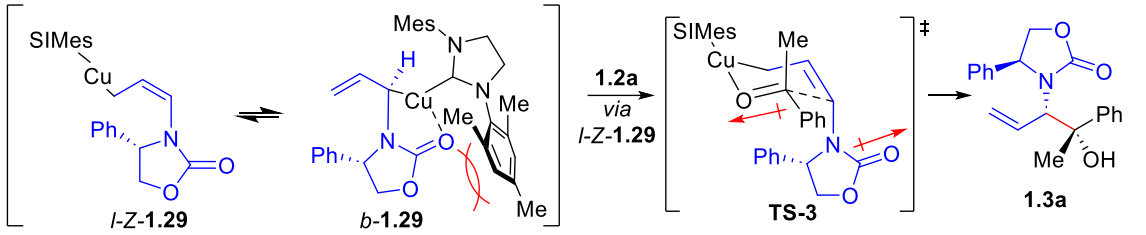
The Cu-H first hydrocuprates the least substituted olefin. This addition occurs *anti* to the oxazolidinone group, generating the σ-(allyl)Cu complex *l*-*Z*-**1.27**.[97] The catalyst turnover limiting step for reductive coupling reactions between allenes and ketones is believed to be the addition of the allylcopper complex to the ketone.[46,47,81] Consequently, the σ-(allyl)Cu complex *l*-*Z*-**1.27** can equilibrate prior to ketone addition. However, density functional theory (DFT) calculations performed by the Gutierrez group on an analogous system employing allene **1.1** shows that the energy levels for σ-(allyl)Cu complex *l*-*Z*-**1.27,** α-σ-(allyl)Cu complex *b*-**1.27**, and σ-(allyl)Cu complex *l*-*E*-**1.27** for L = $PCy_3$ are similar at -28.9, -30.5, and -28.7 kcal/mol respectively.[82] Consequently, the reaction is expected to undergo Curtin-Hammet kinetics where coordination at *b*-**1.27** stabilizes the energy pathway when reacting with ketone **1.2a**. [98]

***Scheme 1.9**: Working Regio- and Stereochemical Model for Regiodivergent Protocol*



As the electron-donating ability of the ligand decreased, the linear selectivity improved. This was due to the increased Lewis acidity of Cu, which was then bound by the Lewis basic carbonyl of the oxazolidinone group. Clearly, the observed effect of the oxazolidinone size could be due to $A^{1,3}$-interactions. The less sterically demanding oxazolidinone-derived allenamide **1.26** is expected to have reduced $A^{1,3}$-interactions, as opposed to its more sterically demanding counterpart **1.1**. In the system where $A^{1,3}$ interactions are minimal, the reaction is purely catalyst-controlled, such that more electron-deficient ligands favor linear products, whereas electron-rich ligands are selective for branched products through intermediate *l*-*Z*-**1.27.**

***Scheme 1.10**: Driving force for Branched Selective Protocol*




When strongly electron-donating ligands such as NHC's are used, initial hydrocupration occurs in a manner analogous to that of the phosphine system. From **Scheme 1.10**, it is apparent that Cu is shielded by the bulky methylene groups of the carbene ligand, inhibiting oxazolidinone-Cu coordination.[92] This shielding is supported experimentally when the more sterically demanding SIPr is employed as a ligand instead of SIMes. Bulky SIPr exclusively generated **1.3a** as its sole product (**Table 1.3**, entry 12). This is clear evidence for steric effects since SIPr and SIMes are electronically identical with a TEP of 2052.[91,92]

Impeding the oxazolidinone-Cu coordination generates the linear σ-(allyl)Cu complex *l*-*Z*-**1.29**, which can then be stereoselectively added to the ketone through the Evans dipole-minimizing transition structure **TS-3** to generate the branched product **1.3a**.[96,99,100] The sterically demanding

mesitylene groups of SIMes shield Cu in α-σ-(allyl)Cu complex *b*-**1.29**, destabilizing the energy pathway when reacting with ketone **1.2a**. Interestingly, when more sterically demanding ketones such as *ortho*-substituted and aliphatic ketones were employed, products with moderate branched selectivity were formed (**Scheme 1.7**). This reduction in branched selectivity could be the result of increased steric interactions in the transition structure **TS-3** by the more sterically demanding ketones, causing an increase in the energy of **TS-3**, leading to the branched product; thus, the transition structure leading to the linear product may be lower in energy, resulting in increased amounts of linear product formation.

Generally, there is a sensitive balance between the steric and electronic properties that determine the regio- and stereoselectivity of this reaction. This balance is governed by the electron-donating ability of the ligand, which can turn the oxazolidinone-Cu coordination on and off. Sterically demanding ligands also influence the strength of oxazolidinone-Cu coordination because they may shield Cu from coordinating with oxazolidinone. $A^{1,3}$-interactions similarly influence selectivity, as the size of the oxazolidinone group coupled with the appropriate ligand affects regioselectivity.

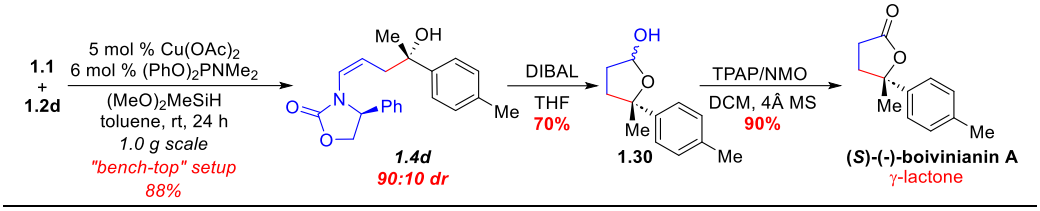
## VII. Synthetic Applications of Linear and Branched Selective Coupling Reactions

### A. Synthetic Applications of the Linear Selective Protocol

In an effort to apply this newly developed protocol for the selective synthesis of the novel linear product, The Sieber lab directed all efforts to convert the linear product to a γ-lactone (**Scheme 1.11**).[93] We were attracted to (*S*)-(-)-boivinionin-A, a natural product with the γ-lactone moiety that is obtained from the stem bark of *C. boiviniana* Baill. Synthesis of the target molecule (*S*)-(-)-boivinionin-A began by scaling up the linear selective reaction with ketone **1.2d** and allenamide **1.1** to furnish the linear product **1.4d** in 88% yield and 90:10 dr. The carbamate of **1.4d**

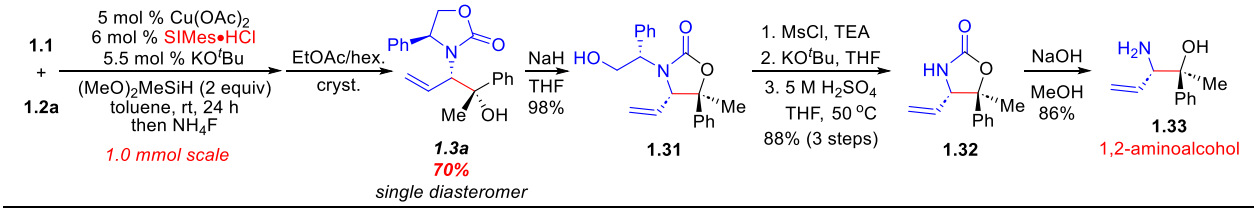
was reduced with excess DIBAL, and successive acid workup generated 1,4-lactol **1.30** in 70% yield. Subsequent oxidation of **1.30** furnished (*S*)-(-)-boivinionin-A in 90% yield.

***Scheme 1.11**: Synthesis of (S)-(-)-boivinionin-A*




## B. Synthetic Applications for the Branched Selective Protocol

***Scheme 1.12**: Amine Deprotection*




The branched selective reaction employing allenamide **1.1** and **1.2a** was successfully scaled up to a 1.0 mmol scale to generate branched product **1.3a** (**Scheme 1.12**). The crystalline nature of the branched product permitted recrystallization with hot 30% EtOAc/Hex solution to selectively crystallize the major diastereomer exclusively in 70% yield. The recrystallized branched product (**1.3a**) then underwent NaH-mediated carbamate rearrangement to furnish the primary alcohol **1.31**. The phenethanol group of **1.31** could, in theory, be cleaved by hydrogenolysis, providing that the olefin is functionalized prior to cleavage because hydrogenolysis would reduce the alkene. Therefore, we sought to develop a protocol in which the phenethanol group can be cleaved without destroying the synthetically useful olefin. This was accomplished by first mesylating the alcohol, followed by base-mediated elimination to furnish an enamide that was hydrolyzed with aqueous $H_2SO_4$ to yield carbamate **1.32** in 88% yield over three

steps. The masked aminoalcohol was then unveiled by basic hydrolysis to furnish 1,2-aminoalcohol **1.33** in 86% yield.

## VIII. Conclusion

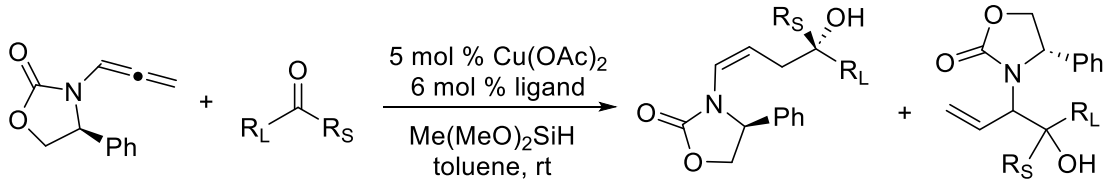
The disclosed strategy for the stereoselective reductive coupling of ketones and a chiral allenamide to selectively generate both branched and linear products is a powerful tool for accessing molecules with a dissonant charge affinity. This method employs simple starting materials and a readily available catalyst system to furnish complex chiral products efficiently. This is the first protocol of its kind to generate a novel linear product with high regio- and diastereoselectivity owing to the chiral auxiliary. Auxiliary removal grants access to unprotected 1,2-aminoalcohol and γ-lactones, which are both important motifs in organic chemistry.

## IX. Experimental Methods

**General:**

[1]**H-NMR** spectra were recorded on Bruker 600 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as an internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, br = broad, m = multiplet), and coupling constants (Hz). $^{13}C$ NMR was recorded on a Bruker 600 MHz (151 MHz) instrument with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). Liquid chromatography was performed using forced flow (flash chromatography) on silica gel purchased from Silicycle. Thin layer chromatography (TLC) was performed on glass-backed 250 μm silica gel F254 plates purchased from Silicycle. Visualization was achieved using UV light, a 10% solution of phosphomolybdic acid in EtOH, or potassium permanganate in water followed by heating. HRMS was collected using a Jeol AccuTOF-DART$^{TM}$ mass spectrometer using DART source ionization. All reactions were conducted in oven or flame dried glassware under an inert atmosphere of nitrogen or argon with magnetic stirring unless otherwise noted. Solvents were obtained from VWR as HPLC grade and transferred to septa sealed bottles, degased by Ar sparge, and analyzed by Karl-Fischer titration to ensure water content was ≤ 600 ppm. $Me(MeO)_2SiH$ was purchased from Alfa Aesar and used as received. Allenamides were prepared in one step as described in the literature.[101] $(PhO)_2PNMe_2$ was prepared from hexamethylphosphorous triamide (HMPT) and phenol according to the literature procedure, and the density was determined experimentally (1.10 g/cm$^3$).[102] Ketones were purchased from Sigma Aldrich, TCI America, Alfa Aesar, or Oakwood Chemicals and used as received. All other materials were purchased from VWR, Sigma Aldrich, Combi-Blocks, Alfa-Aesar, or Strem Chemical Company and used as received.

**General Catalyst Screen Procedure for the Linear-Selective Reductive Coupling Protocol:**




**1.1** + **1.2** → **1.4** *linear (l)* + **1.3** *branched (b)*

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 2.3 mg (0.013 mmol) of $Cu(OAc)_2$, and ligand (0.015 mmol). Toluene (0.5 mL) was then charged, and the mixture was stirred for 5 min. Allenamide **1.1** (60.4 mg, 0.300 mmol) followed by acetophenone (29.0 μL, 30.0 mg, 0.250 mmol) was then charged, and the vial was sealed with a crimp-cap septum and removed from the glove-box. The reaction was then cooled in an ice bath, and dimethoxymethylsilane (61 μL, 2 equiv) was charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)*. The mixture was then allowed

to warm to rt and stirred for 24 h. The reaction was then quenched by the addition of 95 mg of $NH_4F$ and 1.5 mL of MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 5 mL of 5% $NaHCO_3$ followed by extraction with DCM (2x4mL). The combined organics were dried with $Na_2SO_4$ and concentrated *in vacuo*. To the crude residue was charged dimethylfumarate (10 – 15 mg), and the mixture was diluted in ~0.5 mL of $CDCl_3$. Further dilution of an aliquot and analysis by NMR was used to determine the yield, dr, and b/l ratio.

**Modified procedure for the use of ligand salts (P(*t*-Bu)$_3$):** To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 0.015 mmol P(*t*-Bu)$_3$•$HBF_4$ and 1.5 mg (0.013 mmol) of KO$^t$Bu. Toluene (0.5 mL) was then charged, and the mixture stirred for 5 min. To the vial was then charged 2.3 mg (0.013 mmol) of $Cu(OAc)_2$, and the mixture was stirred an additional 5 min. The remaining reagents were then charged and the reaction performed as described above.

**General Procedure for the Linear-Selective Reductive Coupling Protocol:**

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 4.5 mg (0.025 mmol) of $Cu(OAc)_2$ and 1.0 mL of toluene. $(PhO)_2PNMe_2$ was then charged by gas-tight syringe (7.75 µL, 0.033 mmol), and the mixture was stirred for 10 min. Allene **1.1** (0.121 g, 0.600 mmol) was then added, followed by the ketone (0.500 mmol), and the vial was sealed with a crimp-cap septum and removed from the glove-box. The reaction was then cooled in an ice bath, and dimethoxymethylsilane (0.12 mL, 1.0 mmol) was charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)*. The mixture was then allowed to warm to rt and stirred for 24 h. The reaction was then quenched by the addition of 190 mg of $NH_4F$ and 2.5 mL of MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 10 mL of 5% $NaHCO_3$ followed by extraction with $CH_2Cl_2$ (2x5mL). The combined organics were dried with $Na_2SO_4$ and concentrated *in vacuo*. An aliquot of the crude mixture was analyzed by $^1$HNMR spectroscopy to determine the dr and the l/b ratio. The crude residue was then purified by flash chromatography on silica gel to afford the desired product.

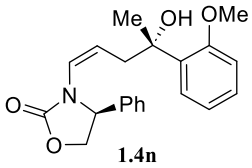
**General procedure for the branched-selective Cu(NHC) catalyzed reductive coupling:**

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 4.5 mg (0.025 mmol) of $Cu(OAc)_2$, 11.1 mg (0.0325 mmol) of SIMes•HCl, and 3.1 mg (0.028 mmol) of KO$^t$Bu. Toluene (1.0 mL) was then added, and the mixture was allowed to stir for 15 min. Allene **1.1** (0.121 g, 0.600 mmol) was then added, followed by the ketone (0.500 mmol), and the vial was sealed with a crimp-cap septum and removed from the glove-box. Dimethoxymethylsilane (0.12 mL, 1.0 mmol) was then charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)* at rt, and the mixture was then allowed to stir for 24 h. The reaction was then quenched by the addition of 190 mg of $NH_4F$ and 2.5 mL of MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 10 mL of 5% $NaHCO_3$ followed by extraction with $CH_2Cl_2$ (2x5mL). The combined organics were dried with $Na_2SO_4$ and concentrated *in vacuo*. An aliquot of the crude mixture was analyzed by $^1$HNMR spectroscopy to

determine the dr and the l/b ratio. The crude residue was then dry-loaded onto silica gel using $CH_2Cl_2$ and purified by flash chromatography on silica gel to afford the desired product.

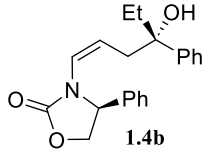
**Characterization Data:**

*i. Linear Products*



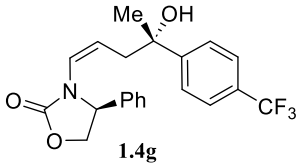
**1.4n**

**((*S*)-3-((*S,Z*)-4-hydroxy-4-(2-methoxyphenyl)pent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4n***): According to the linear-selective general procedure performed at 60 ºC for 24 h, the product was purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 151.7 mg (86%) of **1.4n** as a thick glass as an 83/17 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.33 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = + 22.0 (*c* 0.395, $CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.35 – 7.42 (m, 3H), 7.31 (dd, *J* = 7.7 Hz, *J* = 1.3 Hz, 1H), 7.24 (dd, *J* = 8.0 Hz, *J* = 1.1 Hz, 3H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 1H), 5.75 (d, *J* = 8.9 Hz, 1H), 5.04 (q, *J* = 16 Hz, *J* = 7.4 Hz, 1H), 4.93 (dd, *J* = 8.7 Hz, *J* = 6.1 Hz, 1H), 4.65 (t, *J* = 14 Hz, 1H), 4.34 (s, 1H), 4.15 (dd, *J* = 8.7 Hz, *J* = 6.0 Hz, 1H), 3.85 (s, 3H), 2.80 (ddd, *J* = 8.5 Hz, *J* = 7.1 Hz, *J* = 1.6 Hz, 1H), 2.68 (ddd, *J* = 8.6 Hz, *J* = 7.6 Hz, *J* = 1.1 Hz, 1H), 1.48 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.6, 156.5, 138.1, 134.2, 129.3, 129.0, 128.3, 127.1, 126.5, 122.4, 121.2, 120.8, 111.1, 74.0, 70.1, 61.4, 55.3, 39.4, 27.5. HRMS (DART) *m/z* calcd for $C_{21}H_{24}NO_4$ $[M + H]^+$: 354.1705; Found $[M + H]^+$: 354.1710.



**1.4b**

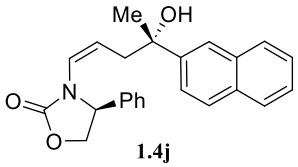
**(*S*)-3-((*S,Z*)-4-hydroxy-4-phenylhex-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4b***): According to the linear-selective general procedure performed at 40 ºC for 24 h, the product was purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 145.2 mg (86%) of **1.4b** as a thick glass as a 79/21 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.38 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = + 4.15 (*c* 0.61, $CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.34 – 7.42 (m, 6H), 7.28 – 7.33 (m, 2H), 7.24 (d, *J* = 6.0 Hz, 2H), 5.61 (d, *J* = 8.7 Hz, 1H), 4.98 – 5.05 (m, 1H), 4.94 (t, *J* = 6.9 Hz, 1H), 4.69 (t, 9.4 Hz, 1H), 4.17 (t, *J* = 7.9 Hz, 1H), 3.56 (s, 1H), 2.76 (dd, *J* = 17 Hz, *J* = 7.3 Hz, 1H), 2.53 (dd, *J* = 14 Hz, *J* = 4.4 Hz, 1H), 1.75 – 1.88 (m, 2H), 0.75 (t, *J* = 7.4 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.8, 145.7, 137.7, 129.3, 129.1, 128.0, 126.6, 126.3, 125.5, 123.4, 122.2, 75.6, 70.2, 61.9, 40.4, 36.3, 7.9. HRMS (DART) *m/z* calcd for $C_{21}H_{24}NO_3$ $[M + H]^+$: 3338.1756; Found $[M + H]^+$: 338.1755.



**1.4g**

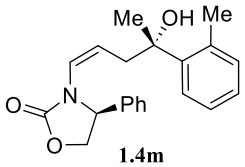
**(*S*)-3-((*S,Z*)-4-hydroxy-4-(4-(trifluoromethyl)phenyl)pent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***l*-15e**): According to the linear-selective general procedure, the product was purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 178.4 mg (82%) of **1.4g** as a thick glass as a 90/10 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.35 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = - 6.47 (*c* 0.595,

$CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.56 (s, 4H), 7.36 – 7.43 (m, 3H), 7.24 (d, *J* = 7.5 Hz, 2H), 5.62 (d, *J* = 8.8 Hz, 1H), 5.02 (td, *J* = 9.0 Hz, *J* = 6.7 Hz, 1H), 4.93 (t, *J* = 7.7 Hz, 1H), 4.71 (t, *J* = 8.9 Hz, 1H), 4.19 (dd, *J* = 8.8 Hz, *J* = 7.5 Hz, 1H), 4.10 (s, 1H), 2.76 (dd, *J* = 14 Hz, *J* = 9.4 Hz, 1H), 2.57 (dd, *J* = 14 Hz, *J* = 6.4 Hz, 1H), 1.56 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.9, 152.0, 137.5, 129.4, 129.2, 128.6 (q, $^2J_{CF}$ = 32.9 Hz), 126.6, 125.4, 125.0 (q, $^3J_{CF}$ = 3.5 Hz), 124.4 (q, $^1J_{CF}$ = 272), 123.7, 121.4, 73.0, 70.2, 61.8, 41.6, 31.0. $^{19}$F NMR (565 MHz, $CDCl_3$): – 63.3 ppm. HRMS (DART) *m/z* calcd for $C_{21}H_{21}F_3NO_3$ $[M + H]^+$: 392.1474; Found $[M + H]^+$: 392.1469.



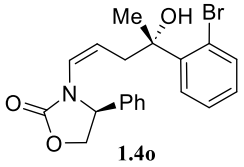
**1.4j**

**(*S*)-3-((*S,Z*)-4-hydroxy-4-(naphthalen-2-yl)pent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4j***): According to the linear-selective general procedure performed at 40 ºC for 24 h, the product was purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 166.4 mg (89%) of **1.4j** as an off white solid as a 89/11 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.33 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = + 23.48 (*c* 0.44, $CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.96 (s, 1H), 7.77 – 7.86 (m, 3H), 7.41 – 7.51 (m, 3H), 7.34 – 7.40 (m, 3H), 7.23 (dd, *J* = 7.6 Hz, *J* = 1.3 Hz, 2H), 5.65 (d, *J* = 8.8 Hz, 1H), ), 5.05 (td, *J* = 9,0 Hz, *J* = 6.4 Hz, 1H), 4.93 (dd, *J* = 8.3 Hz, *J* = 7.4 Hz, 1H), 4.68 (t, *J* = 8.8 Hz, 1H), 4.17 (dd, *J* = 8.6 Hz, 7.2 Hz, 1H), 3.78 (s, 1H), 2.81 (dd, *J* = 9.5 Hz, *J* = 15 Hz, 1H), 2.68 (dd, *J* = 15 Hz, *J* = 6.2 Hz, 1H), 1.63 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.9, 145.0, 137.7, 133.2, 132.2, 129.4, 129.1, 128.3, 127.8, 127.5, 126.5, 126.0, 125.7, 123.6, 123.5, 121.5, 73.4, 60.2, 61.7, 41.6, 31.0. HRMS (DART) *m/z* calcd for $C_{24}H_{22}NO_2$ $[M – OH]^+$: 356.1651; Found $[M – OH]^+$: 356.1659.



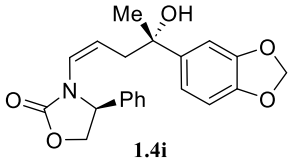
**1.4m**

**(*S*)-3-((*S,Z*)-4-hydroxy-4-(o-tolyl)pent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4m***): According to the linear-selective general procedure performed at 40 ºC for 24 h, the product was purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 126.8 mg (75%) of **1.4m** as an off white solid as a 97/3 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.34 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = + 21.9 (*c* 0.315, $CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.44 – 7.48 (m, 1H), 7.35 – 7.42 (m, 3H), 7.24 (dd, *J* = 8.0 Hz, *J* = 1.4 Hz, 2H), 7.10 – 7.16 (m, 3H), 5.72 (d, *J* = 8.8 Hz, 1H), 5.09 (td, *J* = 8.7 Hz, *J* = 6.5 Hz, 1H), 4.94 (dd, *J* = 8.7 Hz, *J* = 6.5 Hz, 1H), 4.68 (t, *J* = 8.8 Hz, 1H), 4.18 (dd, *J* = 8. 8Hz, *J* = 6.5 Hz, 1H), 3.15 (s, 1H), 2.77 (ddd, *J* = 8.4 Hz, *J* = 6.9 Hz, *J* = 1.6 Hz, 1H), 2.74 (ddd, *J* = 8.0 Hz, *J* = 6.8 Hz, *J* = 1.1 Hz, 1H), 2.50 (s, 3H), 1.58 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.7, 144.6, 137.8, 135.1, 132.6, 129.4, 129.1, 126.9, 126.5, 126.3, 125.7, 123.4, 121.4, 74.5, 70.2, 61.6, 39.8, 29.7, 22.5. HRMS (DART) *m/z* calcd for $C_{21}H_{24}NO_3$ $[M + H]^+$: 338.1756; Found $[M + H]^+$: 338.1767.



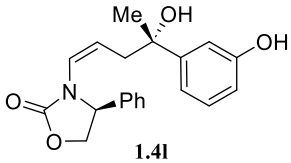
1.4o

**(*S*)-3-((*S,Z*)-4-(2-bromophenyl)-4-hydroxypent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4o***): According to the linear-selective general procedure performed at 40 ºC for 24 h, the product was purified by silica gel chromatography (eluent: 10 – 40% EtOAc in hexanes) to provide 171 mg (85%) of **1.4o** as a white solid as a 95/5 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.40 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = + 12.44 (*c* 0.46, $CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.89 (dd, *J* = 7.9 Hz, *J* = 1.2 Hz, 1H), 7.55 (dd, *J* = 7.9 Hz, *J* = 1.1 Hz, 1H), 7.36 (m, 3H), 7.30 (t, *J* = 7.6 Hz , 1H), 7.27 (dd, *J* = 7.3 Hz, *J* = 1.0 Hz, 2H), 7.08 (ddd, *J* = 8.8 Hz, *J* = 7.6 Hz, *J* = 1.3 Hz, 1H), 5.60 (d, *J* = 8.7 Hz, 1H), 5.03 (td, *J* = 8.6 Hz, *J* = 1.8 Hz, 1H), 4.94 (t, *J* = 7.5 Hz), 4.69 (t, *J* = 8.8 Hz, 1H), 4.27 (s, 1H), 4.18 (dd, *J* = 8.8 Hz, *J* = 7.4 Hz, 1H), 3.19 (dd, *J* = 15 Hz, *J* = 6.7 Hz, 1H), 2.89 (dd, *J* = 15 Hz, *J* = 8.9 Hz, 1H), 1.73 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 157.1, 145.5, 137.5, 134.8, 129.4, 129.2, 128.9, 128.5, 127.6, 126.7, 123.3, 122.4, 119.8, 74.1, 70.2, 61.88, 38.2, 28.2. HRMS (DART) *m/z* calcd for $C_{20}H_{21}BrNO_3$ $[M + H]^+$: 402.0705; Found $[M + H]^+$: 402.0716.



1.4i

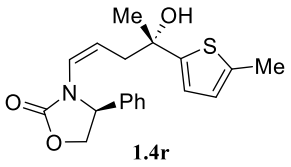
**(*S*)-3-((*S,Z*)-4-(benzo[d][1,3]dioxol-5-yl)-4-hydroxypent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4i***): According to the linear-selective general procedure performed at 40 ºC for 24 h, the product was purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 153.4 mg (83%) of **1.4i** as a thick glass as a 88/11 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.26 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = +4.99 (*c* 0.515, $CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.35 – 7.44 (m, 3H), 7.24 (dd, *J* = 8.3 Hz, *J* = 1.3 Hz, 2H), 6.94 (d, *J* = 1.6 Hz, 1H), 6.88 (dd, *J* =8.2 Hz, *J* = 1.7 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 5.93 (s, 2H), 5.69 (d, *J* =8.8 Hz, 1H), 5.06 (td, *J* = 8.9 Hz, *J* = 6.7 Hz, 1H), 4.97 (dd, *J* = 8.7 Hz, *J* = 7.0 Hz, 1H), 4.69 (t, *J* = 8.8 Hz, 1H), 4.17 (dd, *J* = 8.8 Hz, *J* = 6.9 Hz, 1H), 3.52 (s, 1H), 2.66 (dd, *J* = 15 Hz, *J* = 9.0 Hz, 1H), 2.51 (ddd, *J* = 7.8 Hz, *J* = 6.5 Hz, *J* = 1.4 Hz, 1H), 1.49, (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.6, 156.5, 138.1, 134.2, 129.3, 129.0, 128.3, 127.1, 126.5, 122.4, 121.2, 120.8, 111.1, 74.0, 70.1, 61.4, 55.3, 39.4, 27.5. HRMS (DART) *m/z* calcd for $C_{21}H_{20}NO_4$ $[M - OH]^+$: 350.1392; Found $[M - OH]^+$: 350.1417.



1.4l

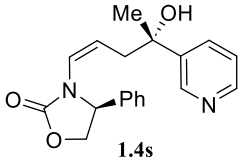
**(*S*)-3-((*S,Z*)-4-hydroxy-4-(3-hydroxyphenyl)pent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4l***): According to the linear-selective general procedure using 4.0 equiv of $(MeO)_2MeSiH$, the product was purified by silica gel chromatography (eluent: 10 – 60% EtOAc in hexanes) to provide 141.1 mg (83%) of **1.4l** as a foam as a 90/10 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.18 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = + 9.12 (*c* 0.49, $CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.35 – 7.44 (m, 3H), 7.24 (dd, *J* = 8.2 Hz, *J* = 1.9 Hz, 2H), 7.18 (t, *J* = 7.9 Hz, 1H), 6.95 – 7.01 (m, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 6.69 (dd, *J* = 7.4 Hz, 1.9 Hz, 1H), 5.65 (d, *J* = 8.6 Hz, 1H), 5.07 (td, *J* = 9.0 Hz, *J* = 6.6 Hz, 1H), 4.93 (dd, *J* = 8.6 Hz, *J* = 7.1 Hz, 1H), 4.70 (t, *J* = 18 Hz, 1H), 4.18 (dd, *J* = 8.8 Hz, *J* = 7.1 Hz, 1H), 3.80 (s, 1H), 2.69 (dd, *J* = 15 Hz, *J* = 9.2 Hz, 1H), 2.56 (dd, *J* = 15 Hz, *J* = 6.4 Hz, 1H), 1.52 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 157.3, 156.4, 149.1, 137.6, 129.35,

129.30, 129.1, 126.6, 123.1, 121.7, 116.5, 113.8, 112.4, 73.9, 70.4, 61.6, 41.6, 30.1. HRMS (DART) *m/z* calcd for $C_{20}H_{22}NO_4$ $[M + H]^+$: 340.1549; Found $[M - OH]^+$: 340.1529.



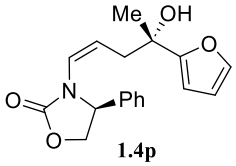
**1.4r**

**(*S*)-3-((*S,Z*)-4-hydroxy-4-(5-methylthiophen-2-yl)pent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4r***): According to the linear-selective general procedure, the product was purified by silica gel chromatography (eluent: 10 – 40% EtOAc in hexanes) to provide 94.6 (55%) of **1.4r** as a thick glass as a 85/15 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.33 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = – 114 (*c* 0.465, $CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.34 – 7.42 (m, 3H), 7.24 (dd, *J* = 7.9 Hz, *J* = 0.7 Hz, 2H), 6.63 (d, *J* = 3.4 Hz, 1H), 6.56 (dd, *J* = 3.2 Hz, *J* = 1.1 Hz, 1H), 5.79 (d, *J* = 8.9 Hz, 1H), 5.14 – 5.22 (m, 1H), 5.01 (dd, *J* = 8.7 Hz, *J* = 6.7 Hz, 1H), 4.69 (t, *J* = 8.8 Hz, *J* = 6.6 Hz, 1H), 4.17 (dd, *J* = 8.6 Hz, *J* = 6.6 Hz, 1H), 3.46 (s, 1H), 2.65 (dd, *J* = 15 Hz, *J* = 8.6 Hz, 1H), 2.59 (dd, *J* = 15 Hz, *J* = 6.9 Hz, 1H), 2.42 (s, 3H), 1.54 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.8, 150.5, 138.1, 137.9, 129.4, 129.1, 126.5, 124.7, 123.5, 122, 120.0, 72.6, 70.2, 61.4, 42.3, 31.1, 15.3. HRMS (DART) *m/z* calcd for $C_{19}H_{22}NO_3S$ $[M + H]^+$: 344.1320; Found $[M + H]^+$: 344.1347.



**1.4s**

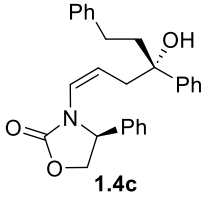
**(*S*)-3-((*S,Z*)-4-hydroxy-4-(pyridin-3-yl)pent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4s***): According to the linear-selective general procedure, the product was purified by silica gel chromatography (eluent: 0 – 100% EtOAc in $CH_2Cl_2$) to provide 123 mg (76%) of **1.4s** as a thick glass as a 88/12 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.26 (Neat EtOAc). $[\alpha]_D^{25}$ = + 10.68 (*c* 0.38, $CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 8.67 (s, 1H), 8.48 (s, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.36 – 7.44 (m, 3H), 7.23 (dd, *J* = 7.7 Hz, *J* = 0.9 Hz, 3H), 5.64 (d, *J* = 8.7 Hz, 1H), 5.04 (td, *J* = 8.8 Hz, *J* = 6.6 Hz, 1H), 4.95 (t, *J* = 7.7 Hz, 1H), 4.71 (t, *J* = 8.8 Hz, 1H), 4.19 (dd, *J* = 8.7 Hz, *J* = 7.4 Hz, 1H), 4.14 (s, 1H), 2.77 (dd, *J* = 15 Hz, *J* = 9.4 Hz, 1H), 2.57 (dd, *J* = 15 Hz, *J* = 6.5 Hz, 1H), 1.61 (s, 3H), 1.58 (s, 1H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.8, 147.6, 146.8, 143.3, 137.5, 133.0, 129.4, 129.2, 126.5, 126.5, 123.7, 120.6, 71.9, 70.2, 61.7, 41.7, 30.7. HRMS (DART) *m/z* calcd for $C_{19}H_{21}NO_3$ $[M + H]^+$: 325.1552; Found $[M + H]^+$: 325.1539.



**1.4p**

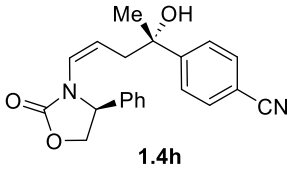
**(*S*)-3-((*S,Z*)-4-(furan-2-yl)-4-hydroxypent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4p***): According to the linear-selective general procedure, the product was purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 116.2 mg (74%) of **1.4p** as a thick glass as a 64/36 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.25 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = + 37.4 (*c* 0.305, $CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.35 – 7.42 (m, 5H), 7.30 – 7.34 (m, 1H), 6.25 (d, *J* = 2.0 Hz, 1H), 6.28 – 6.30 (m, 1H), 6.18 – 6.20 (m, 1H), 5.79 (d, *J* = 8.9 Hz, 1H), 5.08 – 5.17 (m, 1H), 5.0 – 5.05(td, *J* = 8.9 Hz, *J* = 6.8 Hz, 1H), 4.70 (t, *J* = 8.82 Hz, 1H), 4.18 (dd, *J* = 8.8 Hz, *J* = 6.3 Hz, 1H), 3.32 (s, 1H), 2.66 (dd, *J* = 15 Hz, *J* = 7.3 Hz, 1H), 2.59 (dd, *J* = 15 Hz, *J* = 8.2 Hz, 1H), 1.50 (s, 3H)

ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.2, 156.8, 141.4, 137.8, 129.4, 126.5, 123.4, 119.9, 119.2, 110.1, 104.7, 70.6, 70.2, 61.4, 39.3, 27.6. HRMS (DART) *m/z* calcd for $C_{18}H_{18}NO_3$ $[M - OH]^+$: 296.1287; Found $[M - OH]^+$: 296.1295.



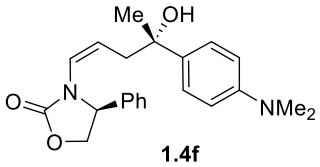
**1.4c**

**(*S*)-3-((*S*,*Z*)-4-hydroxy-4,6-diphenylhex-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4c***): According to the linear-selective general procedure, the product was purified by silica gel chromatography (eluent: 10 – 60% EtOAc in hexanes) to provide 190 mg (79%) of **1.4c** in 86 wt% purity by quantitative $^1$**H-NMR** spectroscopy using dimethylfumarate as analytical standard as a thick glass as a 81:19 mixture of diasteromers (the allene rearrangement product *N*-propenyl 4-phenyloxazolidin-2-one could not be removed by chromatography). Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.33 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = – 9.45 (*c* 0.56, $CHCl_3$); Major diastereomer: $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.44 – 7.48 (m, 2H), 7.32 – 7.40 (m, 6H), 7.2 – 7.25 (m, 4H), 7.1 – 7.16 (m, 3H), 5.60 (d, *J* = 9.06 Hz, 1H), 5.02 (td, *J* = 8.70 Hz, *J* = 6.18 Hz, 1H), 4.92 (t, *J* = 8.1 Hz, 1H), 4.69 (t, *J* = 8.64 Hz, 1H), 4.17 (t, *J* = 8.04 Hz, 1 H), 3.96 (s, 1H), 2.80 (dd, *J* = 14.64 Hz, *J* = 10.74 Hz, 1H), 2.65 – 2.76 (m, 1H), 2.54 (dd, *J* = 14.4 Hz, *J* = 5.16 Hz, 1H), 2.22 – 2.30 (m, 1H), 2.06 – 2.15 (m, 2H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.9, 145.7, 142.8, 137.6, 129.4, 129.2, 128.4, 128.3, 128.2, 126.6, 126.4, 125.6, 125.4, 123.6, 122.3, 75.3, 70.2, 61.9, 45.9, 41.2, 30.0. HRMS (DART) *m/z* calcd for $C_{27}H_{28}NO$ $[M + H]^+$: 414.2069; Found $[M + H]^+$: 414.2090.



**1.4h**

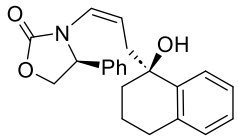
**4-((*S*,*Z*)-2-hydroxy-5-((*S*)-2-oxo-4phenyloxazolidin-3-yl)pent-4-en-2-yl)benzonitrile** (**1.4h**): According to the linear-selective general procedure, the product was purified by silica gel chromatography (eluent: 10 – 60% EtOAc in hexanes) to provide 162 mg (93%) of **1.4h** as a thick glass as a 88:12 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.13 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = – 10.22 (*c* 0.65, $CHCl_3$); Major diastereomer: $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.61 (d, *J* = 8.58 Hz, 2H), 7.57 (d, *J* = 8.52 Hz, 2H), 7.36 – 7.44 (m, 3H), 7.25 (dd, *J* = 8.16 Hz, *J* = 1.56 Hz, 2H), 5.59 (d, *J* = 8.64 Hz, 1H), 4.98 (td, *J* = 9.30 Hz, *J* = 6.42 Hz, 1H), 4.93 (dd, *J* = 8.58 Hz, 6.38 Hz, 1H), 4.72 (t, *J* = 8.88 Hz, 1H), 4.36 (s, 1H), 4.20 (dd, *J* = 8.82 Hz, *J* = 7.26 Hz, 1H), 2.77 ( dd, *J* = 14.58 Hz, *J* = 9.6 Hz, 1H), 2.55 (ddd, *J* = 7.86 Hz, *J* = 6.36 Hz, *J* = 1.55 Hz, 1H), 1.56 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.8, 153.5, 137.5, 131.9, 129.4, 129.2, 126.6, 125.9, 123.9, 121.1, 119.1, 110.17, 72.9, 70.2, 61.9, 41.5, 30.8. HRMS (DART) *m/z* calcd for $C_{21}H_{21}N_2O_3$ $[M + H]^+$: 349.1552; Found $[M + H]^+$: 349.1577.



**1.4f**

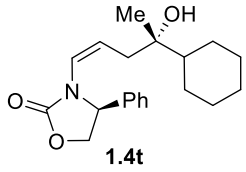
**(*S*)-3-((*S*,*Z*)-4-(4-(dimethylamino)phenyl)-4-hydroxypent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4f***): According to the linear-selective general procedure, the product was purified by silica gel chromatography (eluent: 10 – 60% EtOAc in hexanes) to provide 95 mg (52%) of **1.4f** as a thick glass as a 90:10 mixture of diasteromers.

Stereochemistry was determined by analogy to that of **1.4a**. $R_f$ = 0.11 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = + 51.27 (*c* 0.26, $CHCl_3$); Major diastereomer: $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.34 – 7.42 (m, 4H), 7.26 – 7.28 ( m, 2H), 7.23 (dd, *J* = 8.32 Hz, 1.48 Hz, 2H), 6.69 (d, *J* = 8.82Hz, 2H) 5.75 (d, 8.94 Hz, 1H), 5.07 (td, 8.64 Hz, 6.90 Hz, 1H), 4.97 ( dd, 8.58 Hz, 6.36 Hz, 1H), 4.67 (t, *J* = 8.76 Hz, 1H), 4.16 (dd, *J* = 8.64 Hz, *J* = 6.30 Hz, 1H), 2.93 (s, 6H), 2.62 (ddd, *J* = 9.66 Hz, *J* = 8.52 Hz, *J* = 1.02 Hz, J =, 1H), 2.54 (ddd, *J* = 8.34 Hz, *J* = 6.84 Hz, *J* = 1.68 Hz, 1H), 1.48 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.7, 149.3, 138.0, 135.6, 129.3, 129.0, 126.4, 125.7, 123.1, 120.9, 112.3, 73.1, 70.14, 61.4, 41.8, 40.7, 30.6. HRMS (DART) *m/z* calcd for $C_{21}H_{25}N_2O_2$ $[M - OH]^+$: 349.1916; Found $[M - OH]^+$: 349.1922.



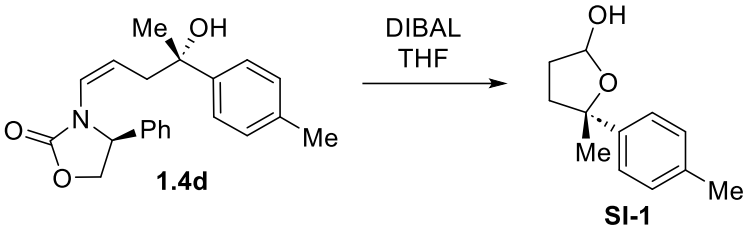
1.4u

**(*S*)-3-((*Z*)-3-((*Z*)-1-hydroxy-1,2,3,4-tetrahydronapthalen-1-yl)prop-1-en-1-yl)-4-phenyloxazolidin-2-one** (**1.4u**): According to the linear-selective general procedure, the product was purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 155 mg (89%) of **1.4u** as a thick glass as a 91:9 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.20 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = + 32.90 (*c* 0.525, $CHCl_3$); Major diastereomer: $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.45 – 7.48 (dd, *J* = 8.87 Hz, *J* = 1.17 Hz, 1H), 7.34 – 7.42 (m, 3H), 7.24 (dd, *J* = 8.38 Hz, *J* = 1.42 Hz, 2H), 7.13 – 7.20 (m, 2H), 7.06 (d, *J* = 7.32 Hz, 1H), 5.93 ( d, *J* = 9.06 Hz, 1H), 5.09 (td, *J* = 8.82 Hz, *J* = 6.78 Hz, 1H), 5.03 (dd, *J* = 8.7 Hz, *J* = 5.34 Hz, 1H), 4.67 (t, *J* = 8.70 Hz, 1H), 4.18 (dd, *J* = 8.7 Hz, *J* = 5.28 Hz, 1H), 2.83 (s, 1H), 2.75 – 2.82 (m, 1H), 2.69 (dt, *J* = 16.80 Hz, 5.88 Hz, 1H), 2.62 (ddd, *J* = 9.78 Hz, *J* = 8.64 Hz, *J* = 1.02 Hz, 1H), 2.50 (ddd, *J* = 8.1 Hz, *J* = 6.72 Hz, *J* = 1.44 Hz, 1H), 1.90 – 1.96 (m, 1H), 1.8 – 1.88 (m, 2H), 1.64 – 1.74 (m, 1H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.7, 141.9, 138.3, 136.7, 129.4, 128.9, 128.8, 127.1, 126.5, 126.3, 126.2, 123.1, 117.9, 71.9, 70.2, 60.9, 40.0, 36.4, 29.6, 19.7. HRMS (DART) *m/z* calcd for $C_{22}H_{21}NO_2$ $[M - H_2O]^+$: 331.1572; Found $[M - H_2O]^+$: 331.1579.

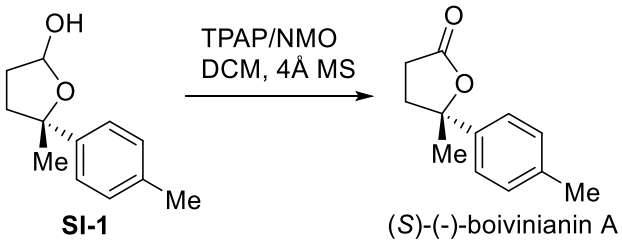


1.4t

**(*S*)-3-((*S*,*Z*)-4-cyclohexyl-4-hydroxypent-1-en-1-yl)-4-phenyloxazolidin-2-one** (***1.4t***): According to the linear-selective general procedure, the product was purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 117 mg (71%) of **1.4t** as a thick glass as a 75:25 mixture of diasteromers. Stereochemistry was determined by analogy to that of ***1.4a***. $R_f$ = 0.22 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = + 40.59 (*c* 0.305, $CHCl_3$); Major diastereomer: $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.34 – 7.44 (m, 4H), 7.25 (d, *J* = 7.72 Hz, 1H), 5.91 (d, *J* = 8.82 Hz, 1H), 5.26 (q, *J* = 7.86 Hz, 1H), 5.07 (dd, *J* = 8.76 Hz, *J* = 6.96 Hz, 1H), 4.69 (t, *J* = 8.70 Hz, 1H), 4.18 (dd, *J* = 7.98 Hz, *J* = 6.30 Hz, 1H), 2.28 (dd, *J* = 14.16 Hz, *J* = 8.40Hz, 1H), 2.21 (s, 1H), 2.10 (dd, *J* = 15.0 Hz, *J* = 7.32 Hz, 1H), 1.73 – 1.88 (m, 3H), 1.67 (t, *J* = 13,44 Hz, 2H), 1.28 – 1.36 (m, 1H), 1.14 – 1.24 (m, 2H), 1.07 – 1.14 (m, 1H), 1.03 (s, 3H), 0.87 – 0.98 (m, 2H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.7, 138.2, 129.3, 128.9, 126.3, 122.9, 119.1, 73.6, 70.1, 61.1, 48.1, 36.8, 27.6, 27.0, 26.7, 26.5, 23.8. HRMS (DART) *m/z* calcd for $C_{20}H_{26}NO_2$ $[M - OH]^+$: 312.1964; Found $[M - OH]^+$: 312.1969.



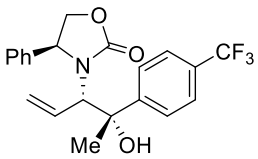

To a solution of 250.0 mg (0.741 mmol) of *l*-**15r** (95:5 dr) in 3.0 mL of THF at 0 ºC was added 3.0 mL (3.0 mmol) of a 1.0 M solution of DIBAL in hexanes (note: gas evolution!). The mixture was then warmed to rt and allowed to stir for 45 min. To the reaction was then charged 10 mL of 10% Rochelle's salt solution and 10 mL of $CH_2Cl_2$, and the mixture was agitated for 1 h to obtain two clear phases. The layers were separated, and the aqueous was extracted with $CH_2Cl_2$ (2x10mL). The combined organics were dried with $Na_2SO_4$, and concentrated *in vacuo*. The residue was then dissolved in 5 mL of $CH_2Cl_2$ and silica gel (2.0 g) was added, and the mixture was agitated for 30 min. Volatiles were removed *in vacuo*, and the dry-loaded silica gel was transferred to a silica gel column and purified by flash chromatography (gradient, hexanes to 25% EtOAc in hexanes). After combination of fractions and removal of volatile materials *in vacuo*, the obtained residue was dissolved in 10 mL of MTBE and washed with 10 mL of 1 M HCl, 10 mL of water, dried with $Na_2SO_4$, and concentrated *in vacuo* to afford 99.5 mg (70%) of **SI-1** as a colorless oil as a 60/40 mixture of hemiacetal epimers. $R_f$ = 0.27 (30% EtOAc/hexanes). $^1$HNMR ($CDCl_3$, 600 MHz, major isomer) δ: 7.26 (d, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 7.2Hz, 2H), 5.65 (m, 1H), 2.60 (d, *J* = 2.1 Hz, 1H), 2.32 (s, 3H), 1.84 – 2.37 (m, 4H), 1.67 (s, 3H) ppm. $^1$HNMR ($CDCl_3$, 600 MHz, minor isomer) δ: 7.37 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.65 (m, 1H), 2.40 (d, *J* = 4.3 Hz, 1H), 2.32 (s, 3H) 1.84 – 2.37 (m, 4H), 1.47 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 145.7, 144.7, 136.0, 128.7, 124.8, 124.4, 98.99, 98.75, 86.2, 85.95, 37.7, 37.3, 33.7, 33.2, 31.3, 29.9, 20.94, 20.91. HRMS (DART) *m/z* calcd for $C_{13}H_{15}O$ [M – OH]$^+$: 175.1123; Found [M – OH]$^+$: 175.1124.




To 78.5 mg (0.408 mmol) of lactol **SI-1** (60/40 epimeric mixture) was charged 125 mg of flame-dried 4A molecular sieves followed by 1.4 mL of $CH_2Cl_2$, under $N_2$. NMO (95.7 mg, 0.817 mmol) and 7.2 mg (0.020 mmol) of TPAP was then added sequentially, and the mixture was stirred at rt and monitored by TLC (5% EtOAc/$CH_2Cl_2$). After 15 min, the mixture was filtered through celite and concentrated *in vacuo*. The crude residue was purified by flash chromatography (gradient, $CH_2Cl_2$ to 3% EtOAc in $CH_2Cl_2$) to afford 69.9 mg (90%) of (*S*)-(-)-boivinianin A as a colorless oil. $R_f$ = 0.36 ($CH_2Cl_2$). $[\alpha]_D^{25}$ = – 34.1 (*c* 0.61, $CHCl_3$); Lit.[103]: $[\alpha]_D^{20}$ = – 38.0 (*c* 0.25, $CHCl_3$). Spectral data was consistent with that reported in the literature.[5]

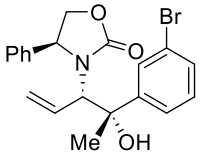
All other compounds prepared were synthesized by other group members.[93]

*ii. Branched Products*



**1.3c**

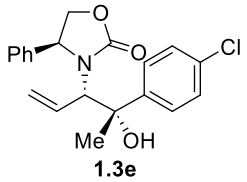
**(*S*)-3-((3*S*,4*S*-4-hydroxy-4-(4-(trifluoromethyl)phenyl)pent-1-en-3-yl)-4-phenyloxazolidin-2-one** (**1.3c**): According to the branched-selective general procedure, the product was purified by silica gel chromatography (eluent: 0 – 20% EtOAc in hexanes) to provide 162 mg (73%) of **1.3c** in 88 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a 97:3 mixture of diasteromers (allene rearrangement products *N*-allyl and *N*-propenyl 4-phenyloxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 5% EtOAc in hexanes followed by cooling to rt in 50% recovery of the major diastereomer. The stereochemistry was assigned by analogy to that of **1.3a**. m.p. 133.9 – 138.1ºC. $R_f$ = 0.23 (25% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 7.46 (d, *J* = 8.2 Hz, 2H), 7.35-7.43 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.19 (d, *J* = 7.7 Hz, 2H), 6.87 (br s, 1H), 6.78 (d, *J* = 7.5 Hz, 2H), 6.26 (dt, *J* = 17 Hz, *J* = 9.7 Hz, 1H), 5.55 (dd, *J* = 10 Hz, *J* = 1.0 Hz, 1H), 5.22 (dd, *J* = 17 Hz, *J* = 1.2 Hz, 1H), 4.64 (t, *J* = 9.2 Hz, 1H), 4.45 (t, *J* = 9.1 Hz, 1H), 3.96 (dd, *J* = 9.6 Hz, *J* = 8.9 Hz, 1H), 3.36 (d, *J* = 9.5 Hz, 1H), 1.35 (d, *J* = 0.9 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 160.1, 150.1, 135.1, 130.1, 129.6, 129.2, 128.7 (q, $^{2}J_{CF}$ = 32 Hz), 128.4, 125.5, 124.9 (q, $^{3}J_{CF}$ = 3.7 Hz), 124.3 (q, $^{1}J_{CF}$ = 272 Hz), 121.6, 75.4, 70.8, 68.1, 61.7, 29.0. $^{19}$F NMR (565 MHz, $CDCl_3$): – 63.2 ppm. HRMS (DART) *m/z* calcd for $C_{21}H_{21}F_3NO_3$ [M + H]$^+$: 392.1474; Found [M + H]$^+$: 392.1473.



**1.3d**

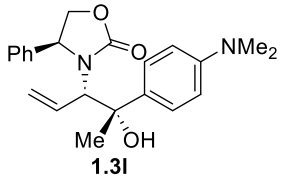
**(*S*)-3-((3*S*,4*S*-4-hydroxy-4-(3-bromophenyl)pent-1-en-3-yl)-4-phenyloxazolidin-2-one** (**1.3d**): According to the branched-selective general procedure employing IMes•HCl as ligand, the product was purified by silica gel chromatography (eluent: 0 – 30% EtOAc in hexanes) to provide 126.6 mg (53%) of **1.3d** in 85 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a 94:4:2 mixture of diasteromers (allene rearrangement products *N*-allyl and *N*-propenyl 4-phenyloxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 10% EtOAc in hexanes followed by cooling to rt in 42% recovery of the major diastereomer. The recrystallized product had a melting point of 131.9 – 135.0ºC. The stereochemistry was assigned by analogy to that of **1.3a**. $R_f$ = 0.11 (20% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 7.38 – 7.44 (m, 4H), 7.20 – 7.24 (m, 1H), 7.14 – 7.18 (m, 2H), 6.87 (d, *J* = 7.1 Hz, 2H), 6.78 (br s, 1H), 6.21 (dt, *J* = 17 Hz, *J* = 9.8 Hz, 1H), 5.53 (dd, *J* = 10 Hz, *J* = 1.0 Hz, 1H), 5.21 (d, *J* = 17 Hz, 1H), 4.69 (t, *J* = 9.7 Hz, 1H), 4.48 (t, *J* = 8.9 Hz, 1H), 3.00 (dd, *J* = 10 Hz, *J* = 9.0 Hz, 1H), 3.32 (d, *J* = 9.7 Hz, 1H), 1.31 (d, *J* = 1.0 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 160.1, 148.6, 134.7, 130.3, 129.9, 129.8, 129.7, 129.5, 128.5,

128.3 124.2, 122.3, 121.8, 75.3, 70.9, 67.9, 62.0, 29.3. HRMS (DART) *m/z* calcd for $C_{20}H_{21}BrNO_3$ $[M + H]^+$: 402.0705; Found $[M + H]^+$: 402.0716.



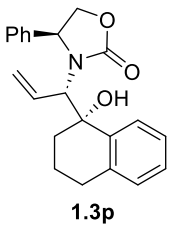
**1.3e**

**(*S*)-3-((3*S*,4*S*-4-hydroxy-4-(4-chlorophenyl)pent-1-en-3-yl)-4-phenyloxazolidin-2-one** (**1.3e**): According to the branched-selective general procedure, the product was purified by silica gel chromatography (eluent: 0 – 30% EtOAc in hexanes) to provide 156 mg (81%) of **1.3e** in 93 wt% purity by quantitative $^1$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a 95:4:1 mixture of diasteromers (allene rearrangement products *N*-allyl and *N*-propenyl 4-phenyloxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 10% EtOAc in hexanes followed by cooling to rt in 40% recovery of the major diastereomer. The stereochemistry was assigned by analogy to that of **1.3a**. m.p. 110.2 – 113.4 ºC . $R_f$ = 0.31 (25% EtOAc/hexanes). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.40 – 7.44 (m, 1H), 7.32-7.36 (m, 2H), 7.19 (d, *J* = 8.7Hz, 2H), 7.02 (d, *J* = 8.2Hz, 2H), 6.85 (d, *J* = 7.3 Hz, 2H), 6.71 (s, 1H), 6.22 (dt, *J* = 17 Hz, *J* = 9.8 Hz, 1H), 5.52 (dd, *J* = 10.1 Hz, *J* = 1.1 Hz, 1H), 5.25 (dd, *J* = 17.04 Hz, 1H), 4.65 (t, *J* = 9.2 Hz, 1H), 4.50 (t, *J* = 9 Hz, 1H), 4.04 (t, *J* = 9.24 Hz, 1H), 3.34 (d, *J* = 9.5 Hz, 1H), 1.62 (s, 1H), 1.32 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 160.0, 144.6, 135.2, 132.1, 130.4, 129.6, 129.2, 128.5, 128.0, 126.7, 121.4, 75.2, 70.8, 68.0, 61.7, 29.1. HRMS (DART) *m/z* calcd for $C_{20}H_{21}ClNO_3$ $[M + H]^+$: 358.1210; Found $[M + H]^+$: 358.1237.



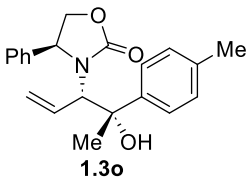
**1.3l**

**(*S*)-3-((3*S*,4*S*-4-hydroxy-4-(4-(dimethylamino)phenyl)pent-1-en-3-yl)-4-phenyloxazolidin-2-one** (**1.3l**): According to the branched-selective general procedure, the product was purified by silica gel chromatography (eluent: 0 – 30% EtOAc in hexanes) to provide 123.6 mg (52%) of **1.3l** in 75 wt% purity by quantitative $^1$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a 82:15:3 mixture of diasteromers (allene rearrangement products *N*-allyl and *N*-propenyl 4-phenyloxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 10% EtOAc in hexanes followed by cooling to rt in 53% recovery of the major diastereomer. The stereochemistry was assigned by analogy to that of **1.3a**. m.p. 133.9 – 138.1 ºC. $R_f$ = 0.25 (25% EtOAc/hexanes). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.35-7.40 (m, 1H), 7.26-7.32 (m, 2H), 7.0 (d, *J* = 8.52Hz, 2H), 6.87 (d, *J* = 7.32Hz, 2H), 6.65 (d, *J* = 8.6 Hz, 2H), 6.33 (s, 1H), 6.19 (dt, *J* = 17 Hz, *J* = 9.7 Hz, 1H), 5.45 (dd, *J* = 10 Hz, *J* = 1.4 Hz, 1H), 5.18 (d, *J* = 17 Hz, 1H), 4.69 (t, *J* = 9.2 Hz, 1H), 4.43 (t, *J* = 8.9 Hz, 1H), 3.96 (td, *J* = 9.2 Hz, 1H), 3.36 (d, *J* = 9.6 Hz, 1H), 2.99 (s, 6H), 1.32 (d, *J* = 0.9 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.9, 149.4, 135.7, 134.0, 131.2, 129.3, 129.0, 128.6, 125.9, 120.7, 112.3, 75.2, 70.8, 68.2, 61.6, 40.8, 29.2. HRMS (DART) *m/z* calcd for $C_{22}H_{26}N_2O_3$ $[M + H]^+$: 367.2022; Found $[M + H]^+$: 367.2046.



1.3p

**(S)-3-((S)-1-((S)-1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)allyl)-4-phenyloxazolidin-2-one** (**1.3p**): According to the branched-selective general procedure, the product was purified by silica gel chromatography (eluent: 0 – 30% EtOAc in hexanes) to provide 134.0 mg (55%) of **1.3p** in 72 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a thick glass as a 62/38 mixture of diasteromers (allene rearrangement products *N*-allyl and *N*-propenyl 4-phenyloxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 10% EtOAc in hexanes followed by cooling to rt in 32% recovery of the major diastereomer. The stereochemistry was assigned by analogy to that of **1.3a**. m.p. 164.6 – 170.8ºC. $R_f$ = 0.34 (25% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 7.64 (d, *J* = 8.39 Hz, 1H), 7.25-7.30 (m, 3H), 7.07 (t, *J* = 7.79 Hz, 2H), 6.94 (d, *J* = 7.43 Hz, 1H), 6.83 (s, 1H), 6.39 (d, *J* = 7.19 Hz, 2H), 6.34 (dt, *J* = 17.01 Hz, *J* = 10.06 Hz, 1H), 5.43 (dd, *J* = 10.28 Hz, *J* = 1 Hz, 1H), 5.14 (d, *J* = 17.17 Hz, 1H), 4.66 (dd, *J* = 10.62 Hz, *J* = 8.38 Hz, 1H), 4.52 (t, *J* = 8.73 Hz, 1H), 3.96 (dd, *J* = 10.69 Hz, *J* = 8.88 Hz, 1H), 3.31 (d, *J* = 9.65 Hz, 1H), 2.53 – 2.61 (m, 1H), 1.92 – 2.00 (m, 2H), 1,62 – 1.72 (m, 2H), 1.55 (s, 1H), 1.18 -1.30 (m, 1H) ppm. $^{13}$C NMR (141.3, 135.9, 134.8, 130.2, 129.1, 129.0, 128.9, 127.7, 126.9, 126.4, 125.5, 120.6, 74, 71.1, 64.0, 62.6, 33.1, 26.6, 17.9. HRMS (DART) *m/z* calcd for $C_{22}H_{24}NO_3$ $[M + H]^+$: 350.1756; Found $[M + H]^+$: 350.1735.



1.3o

**(*S*)-3-((3*S*,4*S*-4-hydroxy-4-(4-methylphenyl)pent-1-en-3-yl)-4-phenyloxazolidin-2-one** (**1.3o**): According to the branched-selective general procedure, the product was purified by silica gel chromatography (eluent: 0 – 30% EtOAc in hexanes) to provide 134.8 mg (62%) of **1.3o** in 78 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a 91:7:2 mixture of diasteromers (allene rearrangement products *N*-allyl and *N*-propenyl 4-phenyloxazolidin-2-one could not be removed by chromatography). Analytically pure material could be obtained by slurrying the material in 10 vol. of hot 10% EtOAc in hexanes followed by cooling to rt in 20% recovery of the major diastereomer. The stereochemistry was assigned by analogy to that of **1.3a**. m.p. 115.3 – 116.6°C $R_f$ = 0.28 (25% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 7.39 (d, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.84 (d, *J* = 7.6 Hz, 2H), 6.48 (br s, 1H), 6.20 (dt, *J* = 17 Hz, *J* = 9.8 Hz, 1H), 5.48 (dd, *J* = 10 Hz, *J* = 1.4 Hz, 1H), 5.20 (dd, *J* = 17 Hz, *J* = 1.4 Hz, 1H), 4.68 (t, *J* = 9.2 Hz, 1H), 4.44 (t, *J* = 8.9 Hz, 1H), 3.97 (dd, *J* = 9.4 Hz, *J* = 8.9 Hz, 1H), 3.38 (d, *J* = 9.6 Hz, 1H), 2.39 (s, 3H), 1.33 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 160.1, 143.1, 136.1, 135.6, 131.0, 129.5, 129.2, 128.8, 128.7, 125.3, 121.2, 75.5, 70.9, 68.2, 61.8, 29.4, 21.2. HRMS (DART) *m/z* calcd for $C_{21}H_{24}NO_3$ $[M + H]^+$: 338.1756; Found $[M + H]^+$: 338.1738.

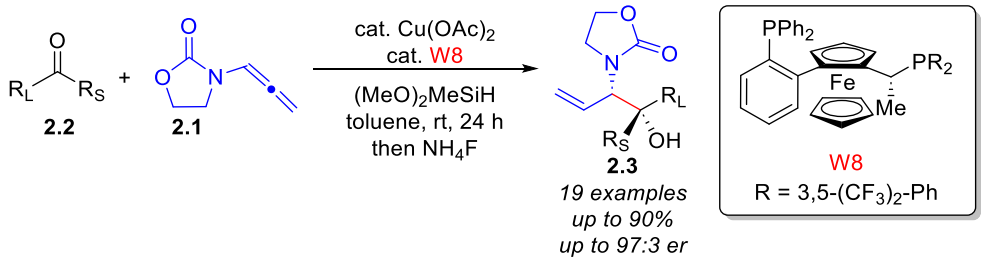
All other compounds prepared were synthesized by other group members.[104]

# Chapter 2
# Development of Enantioselective CuH-Catalyzed Reductive Coupling of an Achiral Allenamide with Ketone and Aldehyde Electrophiles

## I. Introduction

Stereo- and regiodivergent protocols to selectively generate branched and linear products from the reductive coupling of chiral allenamide **1.1** and ketones **1.2** is a powerful tool for the synthesis of aminoalcohols with dissonant charge affinities (See Chapter 1, **Scheme 1.1**).[82,93,104,105] While this method is practical because of the low cost of the Evans auxiliary,[106] we appreciate the fact that absolute stereochemical control by a chiral Cu catalyst with an achiral allenamide may increase atom efficiency.[107] Towards this end, we developed an orthogonal enantioselective branched-selective reaction using a chiral catalyst to afford 1,2-aminalcohol synthon **2.3** (**Scheme 2.1**).[108] This endeavor is not trivial because the enantioselective metal-catalyzed aminoallylation of ketones is unknown and can be more challenging than aldehydes because of the decreased reactivity and steric differentiation of ketones versus aldehydes. Our efforts towards the enantioselective aminoallylation of ketone electrophiles are discussed herein.

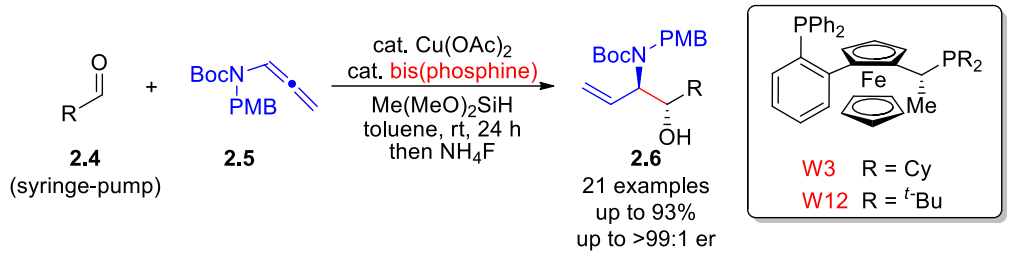
***Scheme 2.1:*** *Enantioselective CuH-Catalyzed Reductive Coupling of Achiral Allenamides and Ketones*




We then also investigated the application of aldehydes in enantioselective Cu-catalyzed aminoallylation reactions with allenamides. While the formal aminoallylation of aldehydes via

hydrogen auto-transfer has already been described by Krische using precious Ru-[73] and Ir-catalysts,[109] non-precious metal-catalyzed alternatives have not been reported and offer a more sustainable alternative to access important chiral 1,2-aminoalcohol motifs.[110] Here, we capitalize on our experience employing non-precious Cu as a catalyst[93,105,110–113] to develop a protocol for the branched-selective aminoallylation of aldehydes **2.4** employing allenamide **2.5** with ubiquitous amine protecting groups (**Scheme 2.2**). This strategy required the slow addition of **2.4** to inhibit the aldehyde reduction by Cu-H.[110]

***Scheme 2.2:*** *Enantioselective CuH-Catalyzed Reductive Coupling of Achiral Allenamides and Aldehyde*




## II. Background

### A. Chiral Auxiliary

Chiral auxiliaries are enantiomerically pure units that are temporarily incorporated into organic compounds to control the stereochemical outcomes of subsequent reactions.[106,114,115] This asymmetric synthesis approach is generally reliable and has been used for the total synthesis of many complex target molecules.[116–122] Even when poor selectivities are observed, chiral auxiliaries allow for the enrichment of diastereoselectivity by taking advantage of standard separation techniques, and hence, enhance enantioselectivity after auxiliary removal.[114] The advantages of the chiral auxiliary approach are curtailed by the cost of installing and removing the auxiliary, which increases the number of synthetic steps and reduces atom economy.[107,114]

### B. Asymmetric Catalysis

Asymmetric catalysis is a type of catalytic reaction in which a chiral catalyst directs the formation of a chiral compound such that a particular stereoisomer is favorably formed.[123,124] In this scenario, the chiral catalyst controls stereoselectivity using only catalytic amounts of chiral information. This process is more atom-economical than asymmetric reactions that employ stoichiometric amounts of chiral auxiliaries for stereocontrol.[114] However, a competing uncatalyzed background reaction or inadequate selectivity of the catalyst may result in the formation of an undesired enantiomer.[123] Consequently, asymmetric catalytic systems require extensive reaction optimization to control both the yield and enantioselectivity, and at times, the diastereoselectivity when necessary.[114,123] The benefits of asymmetric catalysis with regard to improving the "greenness" of the reaction can outweigh the laborious reaction optimization if chiral ligand costs and/or the catalyst loadings are low.

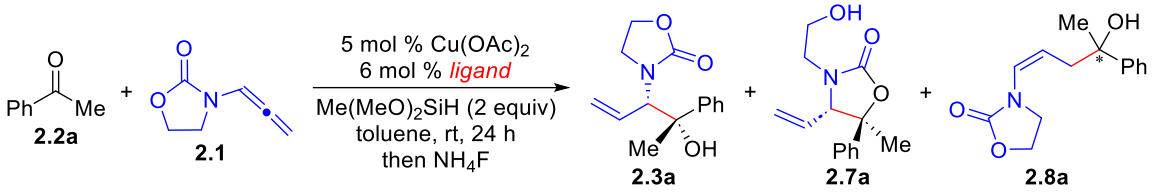
## III. Development of the Asymmetric Reductive Coupling of Allenamides and Ketones

### A. Ligand Survey

To develop the first asymmetric enantioselective aminoallylation of ketones, we employed ketone **2.2a** and achiral allenamide **2.1** as model substrates. Allenamide **2.1** was selected because it has previously displayed branched selectivity with $PCy_3$ as the ligand (See Chapter 1, **Scheme 1.8**). Initial Investigations began by identifying an appropriate chiral ligand scaffold to generate **2.3a** with high diastereo- and enantioselectivity (**Table 2.1,** entries 1 – 29). These results were obtained in collaboration with Mytia Edwards, an undergraduate student in the Sieber group that I mentored. In all cases, variable amounts of the carbamate migration product **2.8a** were observed. Phosphoramidites generated amino alcohol **2.3a** with poor enantioselectivity as a single

diastereomer (entries 1 – 3). Bis(phosphine) ligands mostly generated the desired products with higher enantiopurities than phosphoramidites (entries 4 – 29 *vs.* 1 – 3). Phenyl- and ethyl-BPE generated **2.3a** with modest enantioselectivities in 64% and 67% yields, respectively, despite their widespread use in Cu-catalyzed reductive coupling reactions.[13,46–48,81,125] The BINAP and SEGPHOS family of ligands supplied **2.3a** in varying but generally poor yields (entries 10 – 15), except for (*R*)-BINAP, which performed similarly to (*R*)-DuanPhos, furnishing **2.3a** in 82% yield and 82:13 er (entries 10 and 9, respectively). Although the Josiphos and Walphos ligand families were more enantioselective than the Mandyphos ligands (entries 16 – 19 *vs.* 23 – 29 *vs.* 20 – 23, respectively), **W8** was identified as the optimal ligand for this reaction because it generated branched aminoalcohol **2.3a** with the best combination of yield and enantioselectivity, furnishing the desired product in 77% yield and 93:7 er.

***Table 2.1:*** *Ligand Survey for the Reductive Coupling of Achiral Allenamide* ***2.1*** *and Acetophenone*




| Entry | Ligand[a] | % y **2.3a**[b] | dr **2.3a**[c] | er **2.3a**[d] | **2.3a**:**2.7a**[e] | *b:l*[c,e] |
|---|---|---|---|---|---|---|
| 1 | **L1** | 20.2 | >99:1 | 46:53 | >99 | >99:1 |
| 2 | **L2** | 54.6 | >99:1 | 51:42 | 87:13 | >99:1 |
| 3 | **L3** | 69.3 | >99:1 | 24:76 | >99 | 90:10 |
| 4 | **Feringa D1** | 38.2 | >99:1 | 57:43 | >99 | 76:24 |
| 5 | (*R*)-**Phenyl-BPE** | 64.2 | >99:1 | 20:80 | 89:11 | >99:1 |
| 6 | (*R*)-**Ethyl-BPE** | 67.3 | >99:1 | 25:75 | 90:10 | 87:11 |
| 7 | (*R*)-**QuinoxP** | 63.2 | >99:1 | 82:18 | 81:19 | 93:7 |
| 8 | (*R*)-**DuPhos** | 80.5 | >99:1 | 81:19 | 89:11 | >99:1 |
| 9 | (*R*)-**DuanPhos** | 82.0 | >99:1 | 18:82 | 84:16 | >99:1 |
| 10 | (*R*)-**BINAP** | 82.0 | >99:1 | 18:82 | 83:17 | >99:1 |
| 11 | (*R*)-**Tol-BINAP** | 57.2 | >99:1 | 77:23 | >99 | 81:19 |
| 12 | (*R*)-**DM-BINAP** | 45.4 | >99:1 | 69:31 | >99:1 | >99:1 |
| 13 | (*R*)-**SEGPHOS** | 51.4 | >99:1 | 30:70 | 86:14 | >99:1 |
| 14 | (*R*)-**DTBM-SEGPHOS** | 25.9 | >99:1 | 68:32 | 82:18 | >99:1 |
| 15 | (*R*)-**DM-SEGPHOS** | 50.3 | >99:1 | 69:31 | 86:14 | >99:1 |
| 16 | **J6** | 57.8 | >99:1 | 15.85 | 91:9 | >99:1 |
| 17 | **J7** | 70.1 | >99:1 | 18:82 | >99 | >99:1 |
| 18 | **J9** | 50.5 | >99:1 | 39:61 | 81:19 | >99:1 |
| 19 | **J11** | 59.5 | >99:1 | 28:72 | 78:22 | >99:1 |
| 20 | **M1** | 62.4 | >99:1 | 58:42 | >99:1 | >99:1 |
| 21 | **M2** | 68.0 | >99:1 | 37:63 | 87:13 | >99:1 |
| 22 | **M9** | 54.8 | >99:1 | 60:40 | >99:1 | >99:1 |
| 23 | **W1** | 12.9 | >99:1 | 70:30 | 86:14 | >99:1 |
| 24 | **W2** | 60.6 | >99:1 | 67:33 | 73:24 | >99:1 |
| 25 | **W3** | 64.3 | >99:1 | 57:43 | 90:10 | >99:1 |
| 26 | **W5** | 15.3 | >99:1 | 75:25 | 25:75 | >99:1 |
| 27 | **W6** | 59.4 | >99:1 | 60:40 | 84:16 | >99:1 |
| 28 | **W8** | 77 | >99:1 | 93:7 | 81:19 | >99:1 |
| 29 | **W9** | 52 | >99:1 | 62:38 | 55:45 | >99:1 |

Reaction performed according to the general procedure employing 0.250 mmol of **2.2a**, 0.375 mmol of **2.1**, 0.50 mmol of $Me(OMe)_2SiH$ in 0.5 mL of toluene at rt for 24 h. See Experimental Methods for details. [a]See **Figure 2.1** for Ligand structures. [b]Yield of **2.3a** determined by quantitative $^1$H-NMR spectroscopy on the unpurified reaction mixture using dimethyl fumarate as the analytical standard. [c]The ratio was determined by $^1$H-NMR spectroscopic analysis on the unpurified reaction mixture. [d]Enantiomeric ratios were determined by chiral HPLC analysis. [e]*b:l* refers to the ratio of branched to linear isomers as defined by: (**2.3a** + **2.7a**) : **2.8a**.

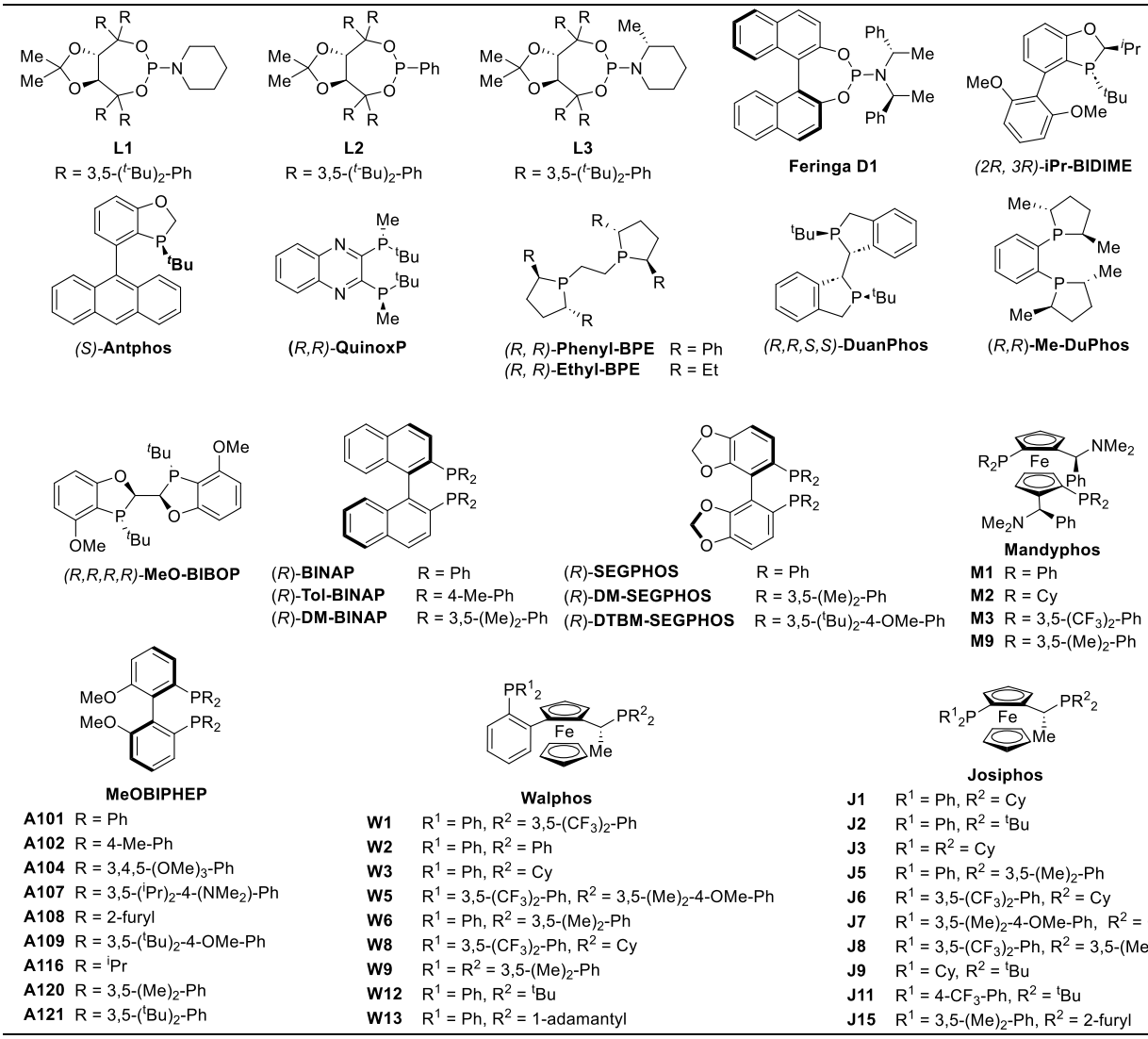


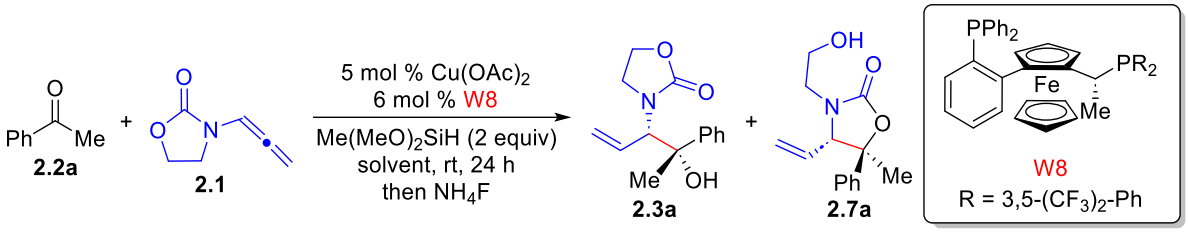

***Figure 2.1:*** *Ligand Structures*

## B. Solvent Survey

After identifying **W8** as the optimal ligand for this reaction, we next decided to probe the effects of solvent on the reaction (**Table 2.2**). Nonpolar solvents generally performed better than polar solvents (entries 1 – 3 *vs*. 4 – 6). Using toluene as the reaction solvent generated **2.3a** in 77% yield with 92:8 er and 81:19 mixture of **2.3a**:**2.7a**. Employing $PhCF_3$ as a solvent positively influenced the enantioselectivity, but negatively affected the yield and **2.3a**:**2.7a** ratio (entry 1 *vs*. 2). The more polar $CH_2Cl_2$ inhibited carbamate rearrangement to the detriment of product yield

and enantioselectivity (entry 4). Interestingly, DMF completely inhibited the carbamate rearrangement, generating **2.2a** in 77% yield, albeit with diminished enantioselectivity (entry 6).

***Table 2.2:*** *Solvent Survey for the Reductive Coupling of Achiral Allenamide* ***2.1*** *and Acetophenone*




| Entry | Solvent | % y **2.3a**[b] | dr **2.3a**[c] | er **2.3a**[d] | **2.3a**:**2.7a**[c] | *b:l*[c,e] |
|---|---|---|---|---|---|---|
| 1 | Toluene | 77 | >99:1 | 92:8 | 81:19 | >99:1 |
| 2 | $PhCF_3$ | 62 | >99:1 | 96:4 | 71/29 | >99:1 |
| 3 | MTBE | 45 | >99:1 | 90:10 | 64/36 | 90:10 |
| 4 | $CH_2Cl_2$ | 35 | >99:1 | 60:40 | >99:1 | 96:5 |
| 5 | THF | 60 | >99:1 | 89:11 | 79/21 | 96:4 |
| 6 | DMF | 77 | >99:1 | 70:30 | >99:1 | 98:2 |
| 7 | 1:1 DMF:Tol. | 73 | >99:1 | 85:15 | 86:13 | >99:1 |
| 8 | 3:7 DMF:Tol. | 33 | >99:1 | 80:20 | 90:10 | >99:1 |
| 9 | 3:7 DMF:$PhCF_3$ | 63 | >99:1 | 86:14 | 90:10 | >99:1 |
| 10 | 3:7 NMP:$PhCF_3$ | 59 | >99:1 | 86:14 | 94:6 | >99:1 |
| 11 | 3:7 DMAc:$PhCF_3$ | 68 | >99:1 | 84:16 | 98:2 | >99:1 |
| 12 | 3:7 tetramethylurea:$PhCF_3$ | 35 | >99:1 | 93:7 | 58:42 | >99:1 |
| 13 | 3:7 *N,N*-diisopropylformamide:$PhCF_3$ | 44 | >99:1 | 87:16 | 84:16 | >99:1 |
| 14 | 3:7 *N*-formylpiperidine:$PhCF_3$ | 0 | - | - | - | - |
| 15 | 3:7 DMPU:$PhCF_3$ | 74 | >99:1 | 86:14 | 88:11 | >99:1 |
| 16 | 3:7 propylene carbonate:$PhCF_3$ | 32 | >99:1 | 81:19 | >99:1 | >99:1 |

[a]Reaction performed according to the general procedure employing 0.250 mmol of **2.2a**, 0.375 mmol of **2.1**, 0.50 mmol of $Me(OMe)_2SiH$ in 0.5 mL of solvent at rt for 24 h. See Experimental Methods for details. [b]Yield of **2.3a** determined by quantitative $^1$H-NMR spectroscopy on the unpurified reaction mixture using dimethyl fumarate as the analytical standard. [c]The ratio was determined by $^1$H-NMR spectroscopic analysis on the unpurified reaction mixture. [d]Enantiomeric ratios were determined by chiral HPLC analysis. [e]*b:l* refers to the ratio of branched to linear isomers as defined by: (**2.3a** + **2.7a**) : **2.8a**.

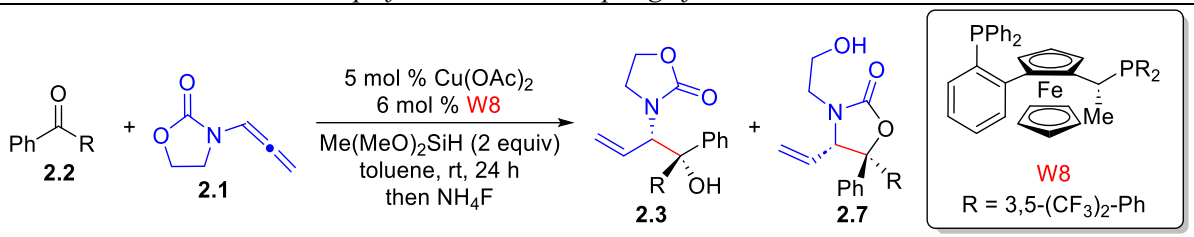
We hoped that performing the reaction with various mixtures of DMF:toluene or DMF:$PhCF_3$ would inhibit the rearrangement without negatively impacting the enantioselectivity (entries 7 – 8). Although these mixtures somewhat curtailed carbamate migration, the enantioselectivities were negatively affected. Various mixtures of amides, carbamates, and carbonates with $PhCF_3$ were also investigated; however, none of these mixtures positively affected

the reaction (entries 10 – 16). Toluene was identified as the optimal reaction solvent because it afforded **2.3a** in high yield and enantioselectivity.

## C. Reaction Mechanism

### *i. Initial Substrate Scope Studies*

***Table 2.3:*** *Initial Substrate Scope for Reductive Coupling of Achiral Allenamides and Ketones*



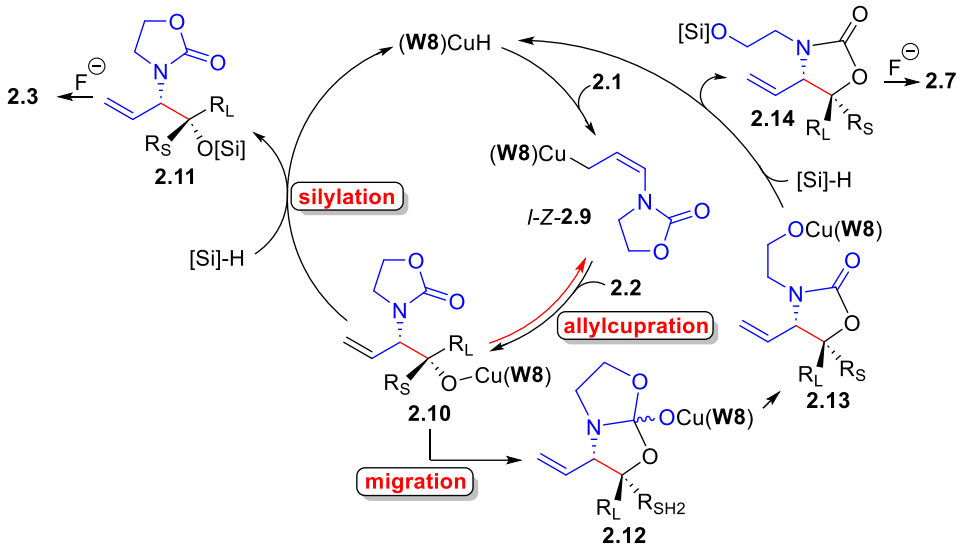

| Entry | R | % y **2.3**[a] | er **2.3**[b] | % y **2.7**[a] | er **2.7**[b] |
|---|---|---|---|---|---|
| 1 | Me | 77 | 92:8 | 13 | 50:50 |
| 2 | Et | 45 | 89:20 | 42 | 60:40 |
| 3 | $CH_2CH_2Ph$ | 0 | - | 90 | 95:5 |

Reaction performed according to the general procedure employing 0.250 mmol of **1.2**, 0.375 mmol of **1.26**, 0.50 mmol of $Me(OMe)_2SiH$ in 0.5 mL of toluene at rt for 24 h. [a]Yield determined by quantitative $^1$H-NMR spectroscopy on the unpurified reaction mixture using dimethyl fumarate as the analytical standard. [b]Enantiomeric ratios were determined by chiral HPLC analysis.

The initial extension of the substrate scope to ketones with higher substitution than methyl (*i.e.* propiophenone and dihydrochalcone) generated products with variable amounts of carbamate rearrangement (entries 2 and 3, **Table 2.3**). Notably, as the steric bulk of the R-group increased, more rearranged products (**2.7**) were generated as a single diastereomer (entry 1 *vs.* 2 *vs.* 3). Importantly, the enantioselectivity of the branched product (**2.3**) differed from that of the rearranged product (**2.7**). This observation suggested that an on-cycle carbamate migration event was occurring and that the allylcupration of the ketone was reversible **(Scheme 2.3**).[126] This result is notable since reversible allylcupration has not been previously reported for this type of metal-catalyzed allylation reaction, especially under ambient conditions.[82]

*ii. Proposed Reaction Mechanism*

***Scheme 2.3:*** *Proposed Reaction Mechanism for Reductive Coupling of Achiral Allenamide* ***2.1*** *and Ketones*

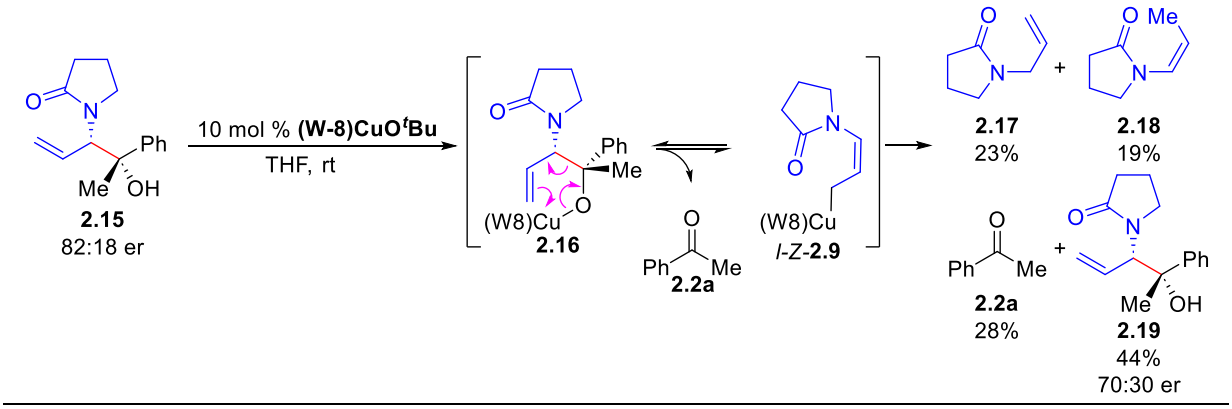



According to the proposed reaction mechanism (**Scheme 2.3**), the reaction is expected to begin via hydrometalation of **2.1** by a **W8**CuH catalyst, which would afford the allylic Cu reagent *l*-*Z*-**2.9**. Allylcupration of ketone **2.2** through a closed chair-like transition state would afford branched intermediate **2.10**.[13,46–48,81,82,93,104,105,125] This allylcupration step (*l*-*Z*-**2.9** + **2.2** → **2.10**) is likely to be stereodetermining.[82] If this step is irreversible, branched product **2.3** and migration product **2.7** must have identical enantiopurities, which was not the case. Therefore, the addition of *l*-*Z*-**2.9** to the ketone was likely reversible. Reversible allylation[126] in metal-catalyzed reductive coupling reactions had not been identified prior to our work, and this issue has significant ramifications for catalyst stereocontrol. For instance, the subsequent silylation or migration steps of **2.10** for catalytic turnover affording products **2.11** and **2.14**, respectively, may enhance or erode the initial stereoselectivity set in the addition step because silylation or carbonate migration of the initially formed diastereomeric mixture of **2.10** proceeds at different rates through diastereomeric

transition states. Under this scenario, the addition step could be highly stereoselective, providing **2.10** at a high diastereoselectivity, but if the minor diastereomer underwent migration faster than the major diastereomer, an overall poor enantioselectivity of **2.3** would be obtained, as was observed. This effect is exacerbated when using more sterically demanding ketones (entries 2 and 3, **Table 2.3**), whereby the carbamate migration rate is expected to increase owing to the enhanced Thorpe-Ingold effect,[127,128] while the silylation rate may decrease because of the increased steric demand.

### *iii. Evidence for reversibility*

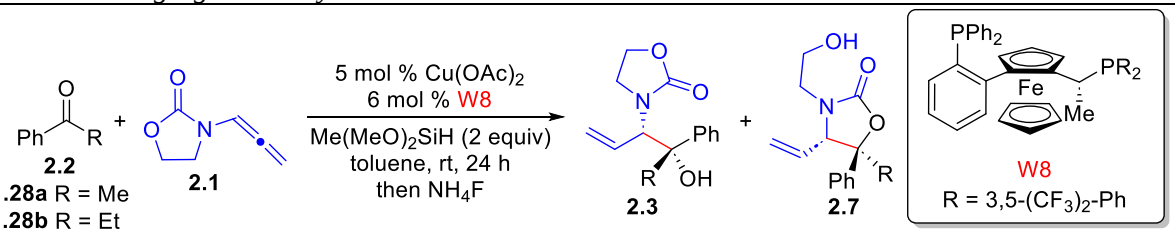
***Scheme 2.4:*** *Evidence for Reversible Ketone Addition*




To obtain experimental evidence for the reversibility of the ketone allylcupration step, we attempted to regenerate an analogous intermediate to that of **2.10 (Scheme 2.3)** from **2.15** by treatment with LCuO$^t$Bu catalyst (**Scheme 2.4**). Amide **2.15** was employed instead of carbamate **2.3a** to prevent the rearrangement that occurred when **2.3a** was treated with LCuO$^t$Bu. Gratifyingly, after treating **2.15** with (**W8)**CuO$^t$Bu, ketone **2.2a** was recovered in addition to the *N*-allyl and *N*-propenyl compounds **2.17** and **2.18**, respectively. Furthermore, **2.19** was recovered with a reduced enantiopurity. These results provide strong evidence in support of reversible ketone allylcupration event in Cu-catalyzed reductive coupling reactions of allenamides.

*iv. Efforts to Inhibit Rearrangement*

***Table 2.4:*** *Reducing Agent Survey*




| Entry | Silane | **1.2**/additive | % y **2.3**[a] | **2.3**:**2.7**[b] | dr **2.3**[b] | er **2.3**[c] |
|---|---|---|---|---|---|---|
| 1 | $Me(MeO)_2SiH$ | **1.2a**/none | 77 | 81:19 | >99:1 | 92:8 |
| 2 | $PhSiH_3$ | **1.2a**/none | 55 | >99 | >99:1 | 86/14 |
| 3 | PMHS | **1.2a**/none | 0 | - | - | - |
| 4 | $Ph_2SiH_2$ | **1.2a**/none | 66 | 94/6 | >99:1 | 80/20 |
| 5 | $(EtO)_3SiH$ | **1.2a**/none | 28 | 77/23 | >99:1 | 84/16 |
| 6 | $PhMe_2SiH$ | **1.2a**/none | 0 | - | - | - |
| 7 | (pin)BH | **1.2a**/none | 16 | >99:1 | >99:1 | 70:30 |
| 8[d] | $Me(MeO)_2SiH$ | **1.2a**/none | 71 | 87:14 | 80:20 | 87:13 |
| 9[d] | $Me(MeO)_2SiH$ | **1.2a**/TMSOAc | 57 | 74:26 | 67:33 | 86:14 |
| 10 | $Me(MeO)_2SiH$ | **1.2a**/$^t$-BuOH | 58 | >99:1 | >99:1 | 88/12 |
| 11[e] | $Me(MeO)_2SiH$ | **1.2a**/$^t$-BuOH | 61 | 90:10 | >99:1 | 91:9 |
| 12 | $Me(MeO)_2SiH$ | **1.2b**/$^t$-BuOH | 50 | >99:1 | >99:1 | 97:3 |
| 13[f] | $Me(MeO)_2SiH$ | **1.2b**/$^t$-BuOH | 77 | >99:1 | >99:1 | 96:4 |

Reaction performed according to the general procedure employing 0.250 mmol of **2.2a**, 0.375 mmol of **2.1**, 0.50 mmol of $Me(OMe)_2SiH$ in 0.5 mL of solvent at rt for 24 h. See Experimental Methods for details. [a]Determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture using dimethylfumarate as standard. [b]Determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture. [c]Value for the major diastereomer of **2.3** determined by chiral HPLC analysis. [d]Using 10 equiv of silane. [e]$PhCF_3$ used as solvent.

To improve the enantioselectivity, thereby providing a more general reaction with respect to the ketone, we reasoned that the enantioselectivity would increase if the rate of trapping of **2.10** (**Scheme 2.3**) could be increased. This may be achieved either by increasing the rate of silylation of **2.10** or by introducing an additive that can trap **2.10** by other means (**Table 2.4**). In this regard, we examined alternative silane reducing agents that, unfortunately, eroded the enantioselectivity of the reaction, as well as the yield of **2.3a** (entry 1 *vs*. entries 2 – 7). Employing 10 equivalences of silane (entry 8) or the addition of an exogenous silylating agent (TMSOAc, entry 9) led to a reduction in diastereoselectivity without inhibiting carbamate migration. Finally, the addition of $^t$-

BuOH to turnover the catalyst through protonation of **2.10** afforded the best results (entries 10 – 13).[82] With this additive, competitive quenching of *l*-*Z*-**2.9** by $^{t}$-BuOH versus aminoallylation of ketone **2.2** reduced the overall yield of the reaction. However, the replacement of toluene with $PhCF_3$ as the solvent mitigated this effect, affording improved yields of **2.3b** with propiophenone as ketone (entry 13). Therefore, the reaction conditions in entries 1 and 13 were identified as the optimal conditions for this reaction.

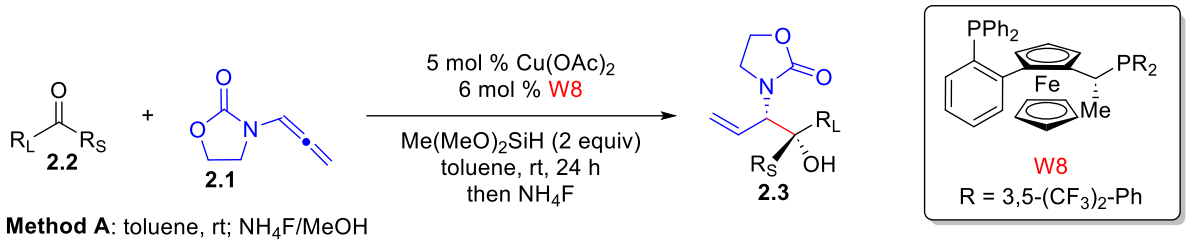
### D. Substrate Scope

With the optimal reaction conditions in hand, the scope of the ketone coupling partner in the newly developed asymmetric reductive coupling reaction was examined (**Scheme 2.5**). Notably, by employing $^{t}$-BuOH as a protic additive, ketones with increased substitution at the methyl position generated products with high enantioselectivities (**2.3b–c**), which is challenging because of the decreased steric bias of the ketone substituents. Additionally, *para*-substituted ketones generally led to a decrease in enantioselectivity (**2.38d–j**). This trend holds for ketones with both *meta*- and *para*-substitutions (**2.3i,j**). Nonetheless, enantioselectivities were enhanced by introducing $^{t}$-BuOH as an additive (Method B). In these cases, electron-poor *para*-substituted ketones (**2.3d–e**) afforded the products in decent yields, whereas products obtained from electron-rich *para*-substituted ketones (**2.3f–i**) were generally obtained in low yields using Method B because of the competitive protonation of *l*-*Z*-**2.9** (Scheme 2.3) versus the reduced rate of addition to these less electrophilic ketones.

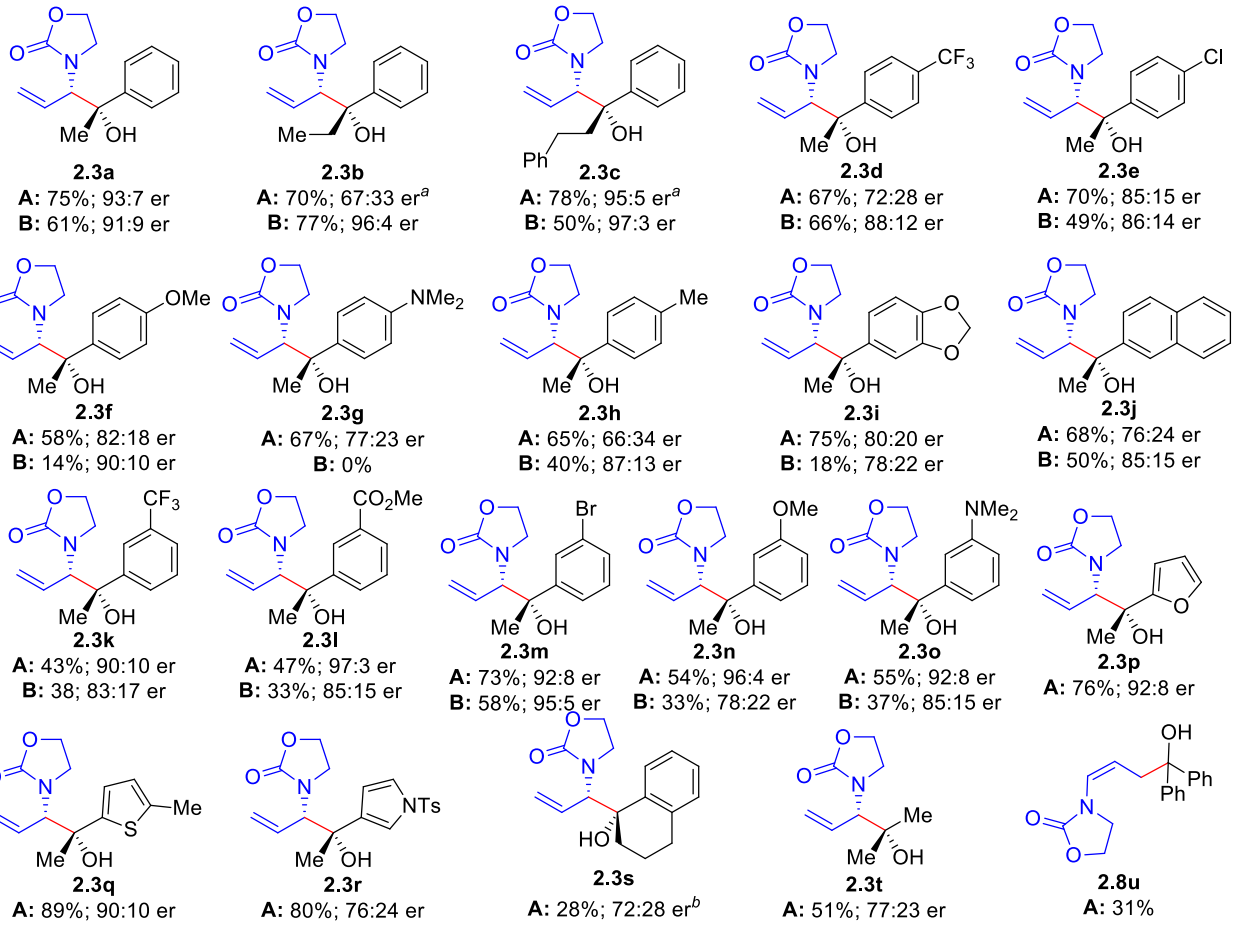
Interestingly, ketones with *meta*-substitution (**2.3k–o**) furnished products with enantiopurities identical to those of **2.3a**. Smaller heteroaromatic ketones (**2.3p–r**) generally afforded good yields and enantioselectivities, without the formation of rearranged products **2.7**. This was presumably due to the increased silylation rates of the analogous intermediate **2.10**

(**Scheme 2.3**) due to the decreased steric hindrance of the smaller tertiary Cu(alkoxide) group. Cyclic ketones afforded modest yields owing to the formation of large amounts of linear product (**2.3s**). Employing acetone as a ketone in the reaction afforded reduced enantioselectivity (**2.3u**), and the application of benzophenone afforded only linear reaction products (**2.8u**).

***Scheme 2.5:*** *Substrate Scope for Reductive Coupling of Achiral Allenamide **2.1** and Ketones*




**Method A**: toluene, rt; $NH_4F$/MeOH
**Method B**: 2 equiv *t*-BuOH, $PhCF_3$, rt; $NH_4F$/MeOH



**2.3a**
**A:** 75%; 93:7 er
**B:** 61%; 91:9 er

**2.3b**
**A:** 70%; 67:33 er[a]
**B:** 77%; 96:4 er

**2.3c**
**A:** 78%; 95:5 er[a]
**B:** 50%; 97:3 er

**2.3d**
**A:** 67%; 72:28 er
**B:** 66%; 88:12 er

**2.3e**
**A:** 70%; 85:15 er
**B:** 49%; 86:14 er

**2.3f**
**A:** 58%; 82:18 er
**B:** 14%; 90:10 er

**2.3g**
**A:** 67%; 77:23 er
**B:** 0%

**2.3h**
**A:** 65%; 66:34 er
**B:** 40%; 87:13 er

**2.3i**
**A:** 75%; 80:20 er
**B:** 18%; 78:22 er

**2.3j**
**A:** 68%; 76:24 er
**B:** 50%; 85:15 er

**2.3k**
**A:** 43%; 90:10 er
**B:** 38; 83:17 er

**2.3l**
**A:** 47%; 97:3 er
**B:** 33%; 85:15 er

**2.3m**
**A:** 73%; 92:8 er
**B:** 58%; 95:5 er

**2.3n**
**A:** 54%; 96:4 er
**B:** 33%; 78:22 er

**2.3o**
**A:** 55%; 92:8 er
**B:** 37%; 85:15 er

**2.3p**
**A:** 76%; 92:8 er

**2.3q**
**A:** 89%; 90:10 er

**2.3r**
**A:** 80%; 76:24 er

**2.3s**
**A:** 28%; 72:28 er[b]

**2.3t**
**A:** 51%; 77:23 er

**2.8u**
**A:** 31%

Reaction performed according to the general procedure employing **1a** (0.250 mmol), **11** (0.375 mmol), and 0.50 mmol $Me(MeO)_2SiH$ in 0.5 mL of toluene. See the Experimental Procedures for details. [a]Yield and er is that of **2.7**. [b]58% yield of linear isomer also isolated.

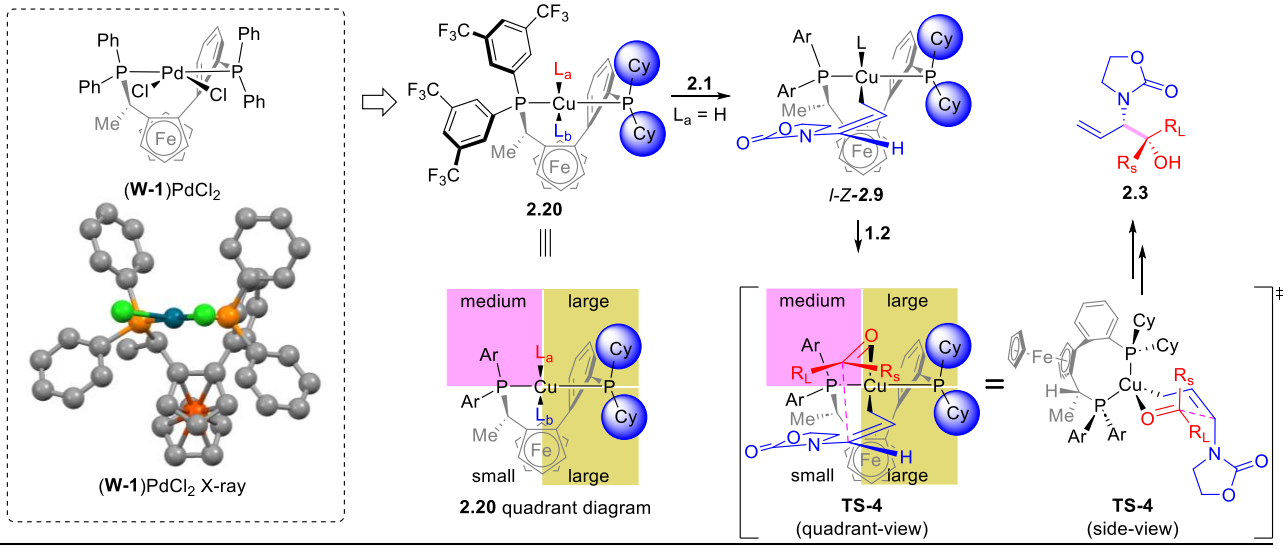
## E. Working Model for Enantiocontrol

A working mechanistic model to rationalize the observed absolute and relative stereochemical control was obtained by drawing inspiration from the previously reported X-ray structure of the (**W1**)$PdCl_2$ complex (**Scheme 2.6**).[129] The northern hemisphere of the (**W1**)$PdCl_2$ complex is more sterically demanding than the southern hemisphere because of the axial-like orientation of the two phenyl groups created by the rigidity of the Walphos chiral backbone. To apply this information to **2.20**, the Cu geometry should be tetrahedral rather than square-planar, as in the Pd(II) X-ray structure.[13,46–48,81,82,93,104,105,125] Additionally, replacing the $PPh_2$-group of **W1** with the $PCy_2$ moiety results in an increased steric bulk of the eastern hemisphere of a (**W8**)Cu-complex over the western hemisphere containing planar 3,5-bis(trifluoromethyl)phenyl substituents on phosphorous. The resulting quadrant diagram shown for **2.20** suggests the southwest quadrant is the least sterically demanding and the most "open" quadrant with the northwest quadrant being partially blocked and the north- and southeastern quadrants fully blocked by the cyclohexyl groups.

When $L_a$ is a hydride, the hydrometalation of allenamide **2.1** is expected to generate the Z-allylcopper reagent *l*-*Z*-**2.9**, because the oxazolidinone ring fits in the least sterically demanding southwestern quadrant. Subsequent complexation of the ketone electrophile (**2.2**) and nucleophilic addition to the *re*-face occur preferentially because the large substituent ($R_L$) resides in the less sterically hindered northwestern quadrant, and the small substituent ($R_S$) fits in the more sterically hindered northeast quadrant (**TS-4**, quadrant-view). The side view of **TS-4** shows a typical chair-like transition structure,[13,46–48,81,82,93,104,105,125] with the larger ketone substituent ($R_L$) at the pseudoequatorial position. Although this model correctly predicts the absolute configuration of the major enantiomer generated by this reaction, the overall enantioselectivity is a function of the

relative rates of stereoisomers in the allylcupration event and the subsequent silylation or carbonate migration steps of **2.10** (**Scheme 2.3**) for catalyst turnover, because aminoallylation is reversible.

***Scheme 2.6:*** *Model for Enantiocontrol for Reductive Coupling of Achiral Allenamide **2.1** and Ketones*



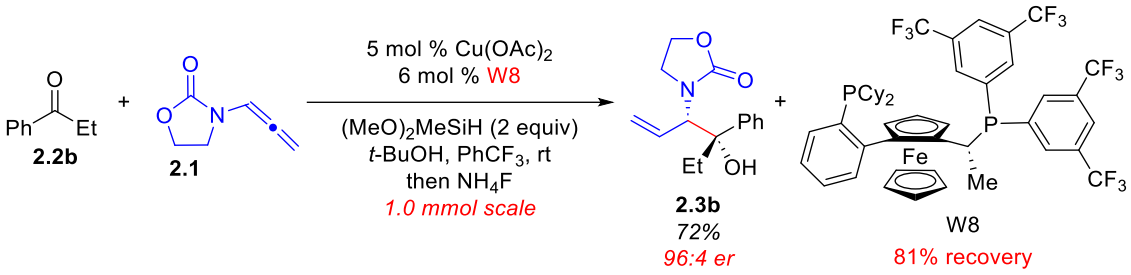

## F. Synthetic Applications

The synthetic applications of this newly developed reaction are shown in **Scheme 2.7**. The reaction was performed on a 1.0 mmol scale to afford **2.3b** in good yield with high enantiopurity as a single diastereomer (**Scheme 2.7A**). Additionally, the **W8** ligand was recovered in 80% yield and recycled to perform the same reaction, generating identical results.

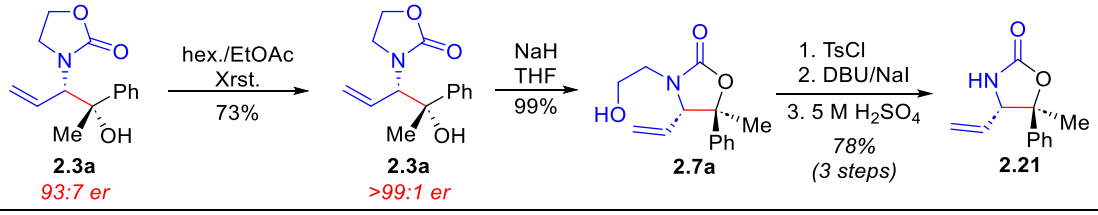
Subsequent efforts were focused on the amine deprotection of compound **2.3a**, which was first recrystallized to furnish the enantiopure material in 73% yield (**Scheme 2.7B**). Carbamate migration was achieved by treating **2.3a** with NaH to furnish the primary alcohol **2.7a**, which was then tosylated. Ensuing tosyl elimination with DBU/NaI[130] generated an enamine that was hydrolyzed to supply carbamate **2.21**.

***Scheme 2.7:*** *Synthetic Applications for Reductive Coupling of Allenamide* ***2.1*** *and Ketones*

A. Reaction Scale Up and Ligand Recovery




B. Amine Deprotection




## IV. Development of Asymmetric Reductive Coupling of Allenamides and Aldehydes

### A. Research Design

#### *i. A New Allene*

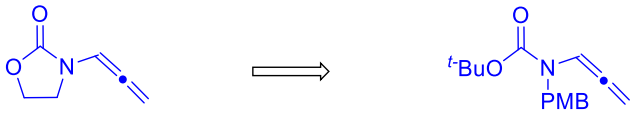



***Figure 2.2:*** *New Allenamide Design Strategy for Enantioselective Cu-Catalyzed Aminoallylation*

Allenamide **2.1** has been shown to undergo reversible ketone allylcupration when employed as an allyl source for reductive coupling reactions (*vide supra*).[108] This reversible allylcupration step allows for erosion of the enantiopurity of the resulting products, thereby limiting the substrate scope of the reaction. We hypothesized that high enantioselectivities across different carbonyls would be feasible if the carbamate migration step could be skirted.[108]

Consequently, allenamide **2.22** (**Figure 2.2**), with more ubiquitous protecting groups, was investigated in the hope that the bulky $^{t}$-Bu group would inhibit carbamate rearrangement, leading to a useful carbonyl aminoallylation reaction with an enhanced ketone scope regarding enantioselectivity.

Subsequent investigations by Stephen Collins, a graduate student in the Sieber group, engaging allenamide **2.22** as a coupling partner for ketone electrophiles, showed that the *N*-Boc group indeed inhibited rearrangement but furnished products with poor diastereoselectivity.[112] Switching from *N*-Boc to *N*-acetyl improved the diastereoselectivity, generating aminoallylation products bearing tertiary alcohols with excellent yields and enantioselectivities.[112] However, aminoallylation products containing secondary alcohols are also desirable intermediates, and therefore, synthetic methodologies leading to their synthesis are valuable. Engaging aldehydes as electrophiles in the Cu-catalyzed enantioselective reductive coupling reactions described herein could be a strategy to access these chiral compounds.

*ii. Engaging Aldehydes as Electrophiles*

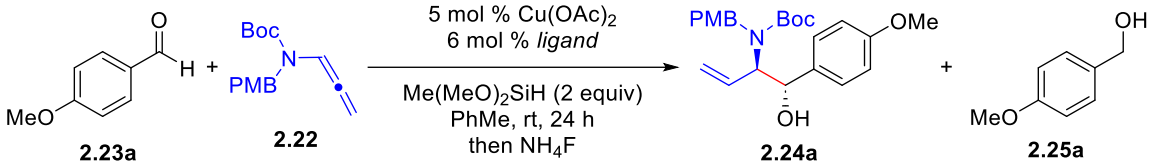
We sought to expand the reaction paradigm by using aldehydes as coupling partners for the reductive coupling of allenamide **2.22**. Only Krische has reported such a reaction with *N*-substituted allenes.[109] Unfortunately, a costly Ir catalyst was employed in his reaction and catalyst loadings were not demonstrated below 5 mol %.[109] Unfortunately, use of the cheaper and more readily available transition metal Cu as the catalyst utilizes *in-situ* generated Cu-H as the active catalyst, which has been shown to preferably reduce aldehydes to alcohols over hydrocupration of the allyl source.[49,131] This competing side reaction renders the coupling reaction null. Buchwald has recently solved this issue in Cu-catalyzed reductive coupling reactions using 1,3-dienes as an

allyl source through slow addition of the aldehyde to facilitate formation of the allylcopper reagent over aldehyde reduction to enable formation of the desired product as a secondary alcohol.[49]

### B. Ligand Survey

Investigations began by probing the effects of various sterically and electronically different ligands to identify the optimal chiral ligand scaffold for selectively generating **2.24a** with good regio-, diastereo-, and enantioselectivities from *para*-anisaldehyde (**2.23a**) and allenamide **2.22** (**Table 2.5**). Aldehyde **2.23a** was added by syringe-pump as a 0.5*M* solution in toluene over at 0.05 mL/hr to inhibit aldehyde reduction. In this reaction, allenamide **2.22** furnished product **2.24a** with excellent diastereoselectivity (entries 1 – 44). Phosphoramidite **L1** and various chiral bis(phosphines) were examined with bis(phosphines) generally outperforming **L1** (entry 1 *vs.* 2 – 44). The SEGPHOS and BINAP ligand families performed poorly, furnishing products with poor enantiopurities (entries 9 – 14). Further investigation of MeOBIPHEP, Josiphos, and Walphos ligands revealed that **W3** and **W12** were the best candidates, providing the desired branched reaction product **2.24a** with good enantioselectivity as a single diastereomer (entries 38 and 43).

***Table 2.5:*** *Ligand Survey for Reductive Coupling of Achiral Allenamides and Aldehydes*

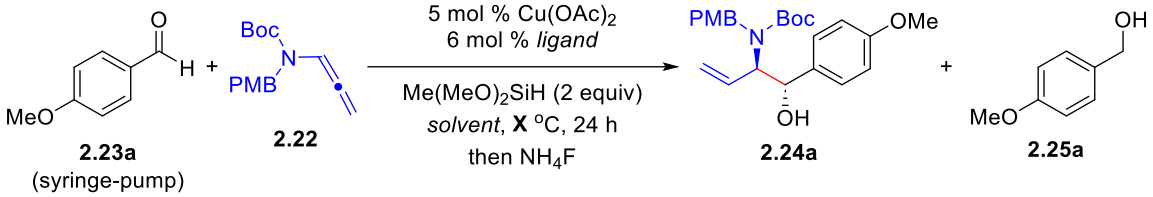



| Entry | Ligand[a] | % y **2.24a**[b] | dr **2.24a**[c] | er **2.24a**[d] | **2.24a**:**2.25a**[c] |
|---|---|---|---|---|---|
| 1 | **L1** | 15 | >99:1 | 64:36 | 15:85 |
| 2 | (*2R,3R*)-iPr-**BIDIME** | 19 | >99:1 | 25:75 | 19:81 |
| 3 | (*S*)-**Antphos** | 16 | >99:1 | 20:80 | 16:84 |
| 4 | (*R,R,R,R*)-**MeO-BIBOP** | 70 | >99:1 | 62:37 | 70:30 |
| 5 | (*R,R*)-**Ph-BPE** | 67 | >99:1 | 45:55 | 67:33 |
| 6 | (*R,R*)-**QuinoxP*** | 46 | >99:1 | 26:74 | 46:54 |
| 7 | (*R,R*)-**Me-DuPhos** | 84 | >99:1 | 54:46 | 84:16 |
| 8 | (*R,R,S,S*)-**DuanPhos** | 57 | >99:1 | 61:39 | 57:43 |
| 9 | (*R*)-**BINAP** | 71 | >99:1 | 55:45 | 71:29 |
| 10 | (*R*)-**Tol-BINAP** | 55 | >99:1 | 42:58 | 78:22 |
| 11 | (*R*)-**DM-BINAP** | 48 | >99:1 | 34:66 | 50:50 |
| 12 | (*R*)-**SEGPHOS** | 69 | >99:1 | 67:33 | 69:31 |
| 13 | (*R*)-**DTBM-SEGPHOS** | 57 | >99:1 | 60:40 | 57:43 |
| 14 | (*R*)-**DM-SEGPHOS** | 50 | >99:1 | 48:52 | 50:50 |
| 15 | **A101** | 55 | >99:1 | 53:7 | 55:45 |
| 16 | **A102** | 69 | >99:1 | 51:49 | 70:30 |
| 17 | **A104** | 48 | >99:1 | 52:48 | 48:52 |
| 18 | **A107** | 45 | >99:1 | 20:80 | 45:55 |
| 19 | **A108** | 38 | >99:1 | 33:67 | 38:62 |
| 20 | **A109** | 51 | >99:1 | 23:77 | 51:49 |
| 21 | **A116** | 38 | >99:1 | 38:62 | 38:62 |
| 22 | **A120** | 58 | >99:1 | 32:68 | 58:42 |
| 23 | **A121** | 38 | >99:1 | 44:56 | 38:62 |
| 24 | **J1** | 69 | >99:1 | 43:57 | 87:13 |
| 25 | **J2** | 78 | >99:1 | 31:70 | 81:19 |
| 26 | **J3** | 63 | >99:1 | 28:72 | 75:25 |
| 27 | **J5** | 57 | >99:1 | 52:47 | 65:35 |
| 28 | **J6** | 63 | >99:1 | 46:54 | 67:33 |
| 29[e] | **J7** | 70 | >99:1 | 18:82 | >99 |
| 30 | **J8** | 81 | >99:1 | 44:56 | 71:29 |
| 31 | **J9** | 61 | >99:1 | 22:78 | 66:34 |
| 32 | **J11** | 81 | >99:1 | 29:71 | 87:13 |
| 33 | **J15** | 60 | >99:1 | 39:61 | 79:21 |
| 34 | **M1** | 19 | >99:1 | 28:72 | 19:81 |
| 35 | **M3** | 11 | >99:1 | 23:77 | 11:89 |
| 36 | **W1** | 49 | >99:1 | 25:75 | 56:43 |
| 37 | **W2** | 79 | >99:1 | 38:62 | 78:22 |
| 38 | **W3** | 74 | >99:1 | 16:84 | 74:26 |
| 39 | **W5** | 64 | >99:1 | 20:80 | 78:22 |
| 40 | **W6** | 77 | >99:1 | 30:71 | 81:19 |
| 41 | **W8** | 47 | >99:1 | 47:53 | 50:50 |
| 42 | **W9** | 81 | >99:1 | 24:76 | 81:19 |
| 43 | **W12** | 79 | >99:1 | 10:90 | 79:21 |
| 44 | **W13** | 75 | >99:1 | 13:87 | 75:25 |

Reaction performed according to the general procedure employing 0.250 mmol of **2.23a**, 0.375 mmol of **2.22**, 0.50 mmol of $Me(OMe)_2SiH$ in 0.75 mL of toluene at rt for 24 h. See experimental procedures for more details. [a]See **Figure 2.1** for Ligand structures. [b]Yield of **2.24a** determined by quantitative $^1$H-NMR spectroscopy on the unpurified reaction mixture using dimethyl fumarate as the analytical standard. [c]The ratio was determined by $^1$H-NMR spectroscopic analysis on the unpurified reaction mixture. [d]Enantiomeric ratios were determined by chiral HPLC analysis. [e]Linear product was present at 30%.

## C. Solvent and Temperature Survey

***Table 2.6:*** *Solvent and Temperature Survey for Reductive Coupling of Achiral Allenamides and Aldehydes*




| Entry | Ligand | Solvent | X | % y **2.24** [a] | dr **2.24a** [b] | er **2.24** [c] | **2.24a**:**2.25a** [b] |
|---|---|---|---|---|---|---|---|
| 1 | **W3** | Toluene | 22 °C | 74 | >99:1 | 16:84 | 74:26 |
| 2 | **W3** | THF | 22 °C | 73 | >99:1 | 16:84 | 73:27 |
| 3 | **W3** | $PhCF_3$ | 22 °C | 70 | >99:1 | 17:83 | 70:30 |
| 4 | **W3** | MTBE | 22 °C | 61 | >99:1 | 15:85 | 61:39 |
| 5 | **W3** | 1,4-Dioxane | 22 °C | 62 | >99:1 | 14:86 | 62:38 |
| 6 | **W3** | Toluene | 0 °C | 81 | >99:1 | 12:88 | 81:19 |
| 7 | **W12** | Toluene | 0 °C | 92 | >99:1 | 8:92 | 92:8 |
| 8 | **W3** | Toluene | - 20 °C to +22 °C | 86 | >99:1 | 8:92 | 86:14 |
| 9 | **W3** | Toluene | - 40 °C to +22 °C | 92 | >99:1 | 6:94 | 92:8 |
| 10 | **W3** | Toluene | - 76 °C to +22 °C | 65 | >99:1 | 3:97 | 65:35 |
| 11 | **W3** | Xylenes | - 40 °C to +22 °C | 79 | >99:1 | 6:94 | 79:21 |
| 12 | **W3** | Anisole | - 40 °C to +22 °C | 80 | >99:1 | 7:93 | 80:20 |
| 13 | **W3** | Mesitylene | - 40 °C to +22 °C | 78 | >99:1 | 6:94 | 78:22 |
| 14 | **W12** | Toluene | - 20 °C to +22 °C | 30 | >99:1 | 8:92 | 30:70 |
| 15 | **W12** | Toluene | - 40 °C to +22 °C | 40 | >99:1 | 6:94 | 74:26 |

Reaction performed according to the general procedure employing 0.250 mmol of **2.23a**, 0.375 mmol of **2.22**, 0.50 mmol of $Me(OMe)_2SiH$ in 0.75 mL of toluene at rt for 24 h. See experimental procedures for more details. [a]Yield of **2.24** determined by quantitative $^1$HNMR spectroscopy on the unpurified reaction mixture using dimethyl fumarate as the analytical standard. [b]The ratio was determined by $^1$H-NMR spectroscopic analysis on the unpurified reaction mixture. [c]Enantiomeric ratios were determined by chiral HPLC analysis.

Investigating the solvent effects on the reductive coupling of allenamide **2.22** and *para*-anisaldehyde (**2.23a)** had little impact on enantioselectivity (entry 1 – 5, **Table 2.6**). Temperature effects were more significant (entries 6 – 15). Reducing the reaction temperature to 0 °C with toluene as the reaction solvent significantly improved both yield and enantioselectivity (entries 6 and 7). Presumably, reducing the reaction temperature decreased the rate of aldehyde reduction by Cu-H,[49,131] thereby improving the yield. Additionally, it is well known that enantioselectivity typically increases with a decrease in the reaction temperature for asymmetric reactions, accounting for the increase in enantiopurity of the resulting products when the reaction temperature

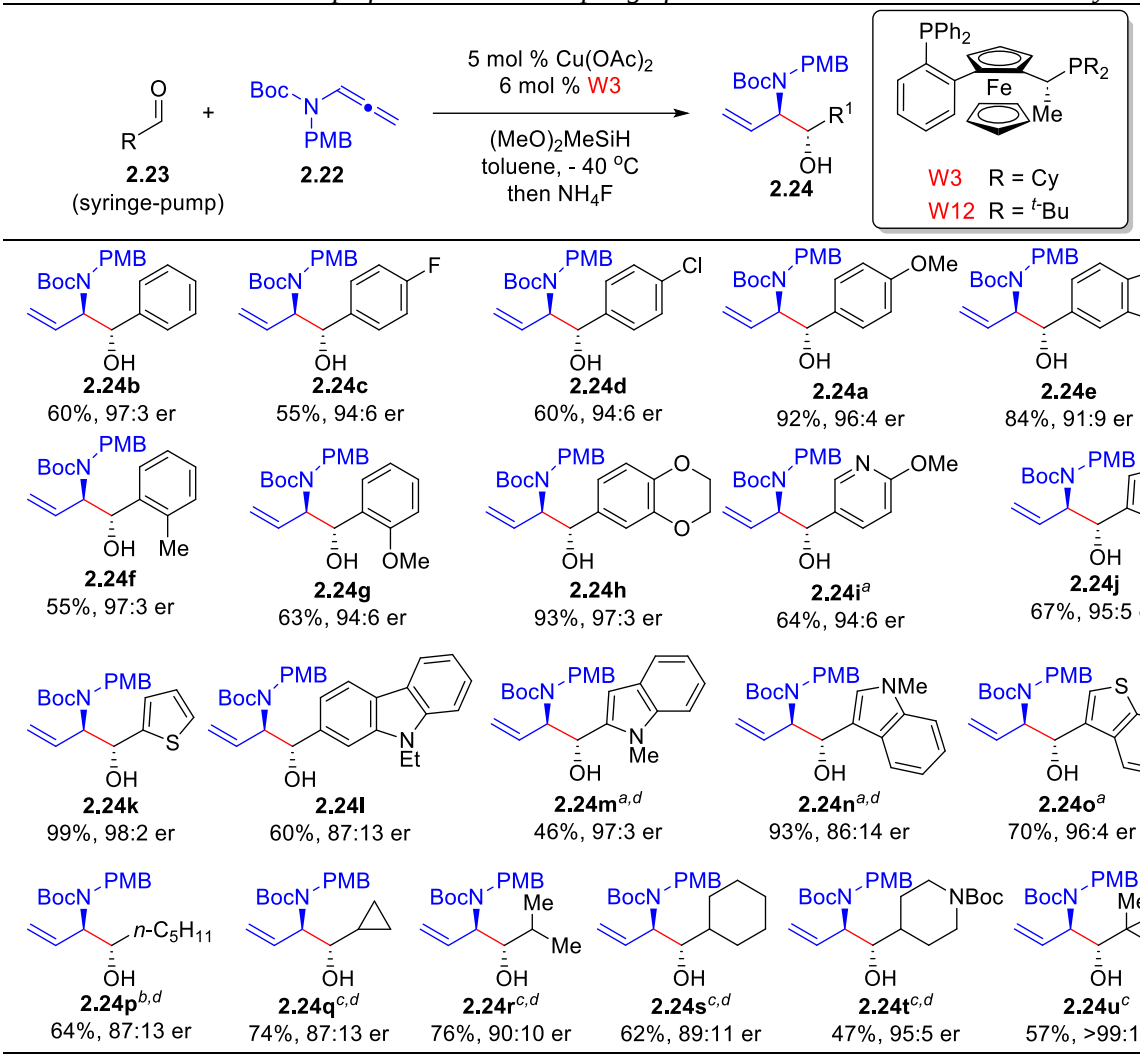
is reduced.[132] Further decreasing the reaction temperature to − 20 and then to − 40 ºC further improved the yield and enantiopurity with W3 as the ligand (entries 8 and 9). Interestingly, performing the reaction at –78 ºC led to a reduction in the overall yield of **2.24a** (entry 10). This observation could be due to the low rate of aminoallylation leading to an increased concentration of *para*-anisaldehyde in solution, which undergoes rapid reduction after increasing the reaction temperature prior to workup. Employing xylenes, anisole, and mesitylene as reaction solvents at − 40 ºC did not positively affect the reaction yield (entries 11 – 13 *vs.* 9). Interestingly, **W12** performed poorly under cryogenic conditions (entries 14 and 15 *vs.* entry 7). Based on the empirical data gathered, the optimal reaction conditions were identified as those shown in entry 9, employing **W3** as the ligand. However, because **W12** performed better than **W3** at elevated reaction temperatures (entries 7 *vs.* 6), **W12** could potentially be employed for reactions utilizing aldehydes that may require higher reaction temperatures to proceed to full conversion.

### D. Substrate Scope

The aldehyde scope of the Cu-catalyzed aminoallylation reaction was examined by performing the reaction with a variety of sterically and electronically different aldehydes which were introduced slowly by syringe-pump as a 0.5*M* solution in toluene over at 0.05 mL/hr (**Scheme 2.8**). In all cases, a single diastereomer of 1,2-aminoalcohol **2.24** was generated, with varying amounts of reduced aldehyde as the main by-product of the reaction. Electron-rich aldehydes (**2.24a,e-h**) performed well in the reaction, furnishing products in good yields and enantioselectivities. Interestingly, electron-deficient aldehydes (**2.24b-d**) typically afforded products in modest yields. This is due to the increased rate of aldehyde reduction by Cu-H due to their increased electrophilicity and, hence, reactivity. Heteroaryl aldehydes (**2.24i-o**) and *ortho*-substituted aldehydes (**2.24f,g**) were well tolerated in this reaction. Finally, aliphatic aldehydes

(**2.24p-u**) were also employed, albeit with **W12** as the ligand and at elevated temperatures (22 – 40 °C). The increased rate of aldehyde reduction at elevated temperatures necessitated a decrease in rate of aldehyde addition to 0.02 mL/hr which sufficiently inhibited production of **2.25**.

***Scheme 2.8:*** *Substrate Scope for Reductive Coupling of Achiral Allenamide* ***2.22*** *and Aldehydes*

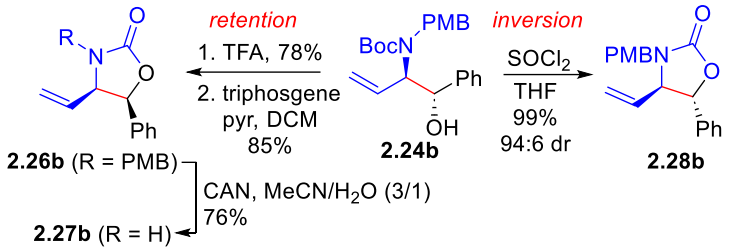



Reaction performed according to the general procedure employing 0.250 mmol of **1.43a**, 0.375 mmol of **1.42**, 0.50 mmol of Me(OMe)2SiH in 0.75 mL of toluene at rt for 24 h. See experimental procedures for more details. Only a single diastereomer observed by $^1$H-NMR spectroscopy of the unpurified reaction mixture. Reported yields are of isolated material purified by flash column chromatography on silica gel. [a]Reaction performed at 0 °C. [b]Reaction performed at 40 °C. [c]Reaction performed at 22 °C. [d]Reaction performed using **W12** as ligand.

## E. Stereochemical Determination and Synthetic Applications

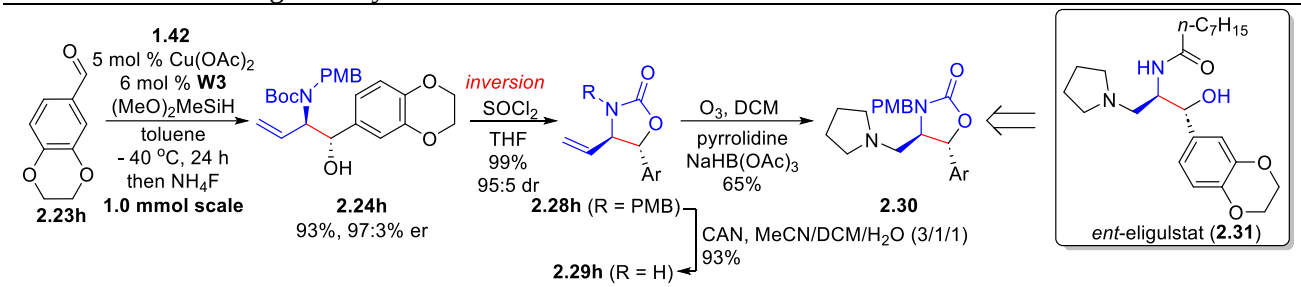
The absolute and relative stereochemistry of the aminoallylation products of this reaction were determined by converting **2.24b** to the known compound **2.27b** (**Scheme 2.9**).[133] Removal of the *N*-Boc group was achieved using TFA. The resulting 1,2-aminoalcohol was then treated with triphosgene to furnish carbamate **2.26b**. Subsequent oxidative cleavage of PMB with CAN produced **2.27b**, whose absolute rotation was compared to that of the enantioenriched literature material, confirming absolute and relative stereochemistry.[133] Additionally, the *syn*-diastereomer was intercepted via $S_N2$ type cyclocarbamation which proceeds through anchimeric assistance where the *N*-Boc group displaces the activated alcohol, inverting the carbinol stereocenter to furnish **2.28b** in quantitative yield.[134]

***Scheme 2.9:*** *Stereochemical Determination*



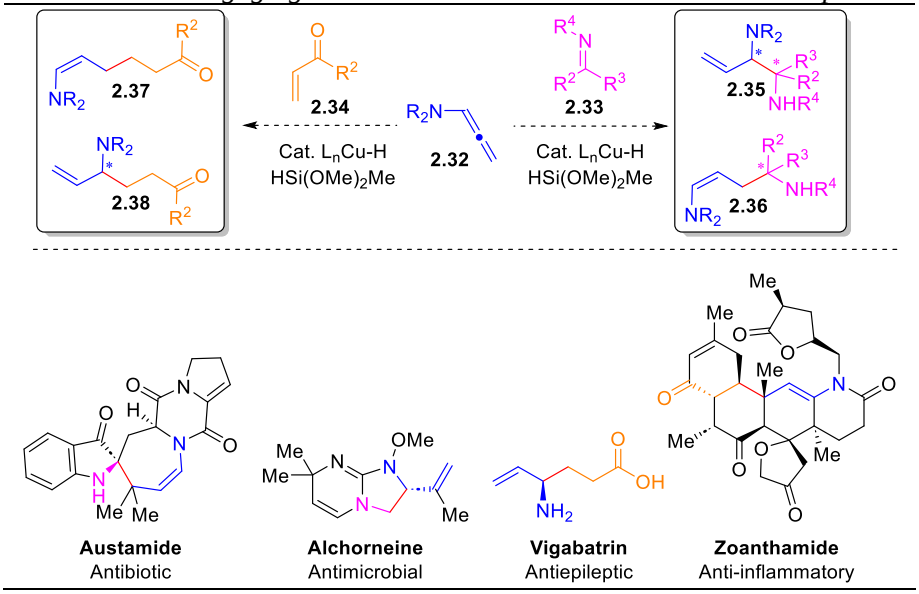

To apply the newly developed synthetic method towards a useful pharmaceutical, subsequent efforts were directed toward the asymmetric synthesis of an important drug for the treatment of Gaucher's disease, eliglustat[135] (**2.31**, **Scheme 2.10**). The aminoallylation reaction was performed on a 1.0 mmol scale to provide **2.24h** with 97:3 er in 93% yield. The subsequent inversion of the carbinol stereocenter of **2.24h** using $SOCl_2$ afforded **2.28h** in excellent yield[134] and granted access to the correct relative stereochemistry required for *ent*-eliglustat.[135] Finally, oxidative cleavage of the olefin of **2.28h** using a reductive amination workup with pyrrolidine provided **2.30** as a prospective precursor to *ent*-eligulstat.[136] Furthermore, the PMB group of **2.28h** was oxidatively cleaved with CAN to generate **2.29h**, indicating that analogous PMB deprotection of **2.30** can be carried out.

**Scheme 2.10:** *Ent*-eliglustat Synthesis




## F. Conclusions and Future Work

***Scheme 2.11:*** *Engaging Imines and Unsaturated Ketones as Electrophiles*




In conclusion, we improved the atom economy of the disclosed reductive coupling of allenamides with carbonyls (ketones and aldehydes) by employing asymmetric catalysis to stereoselectively generate 1,2-aminoalcohols in good yields with excellent diastereo- and enantioselectivities.[108,110] We hope to expand this reaction paradigm to include other electrophiles such as imines[82] (**2.33**, **Scheme 2.11**) and α,β-unsaturated ketones[137] (**2.34**) in our reductive coupling protocol with allenamides. The products of this reductive coupling of imines with allenamides could be applied to the synthesis of natural products such as austamide[138] and

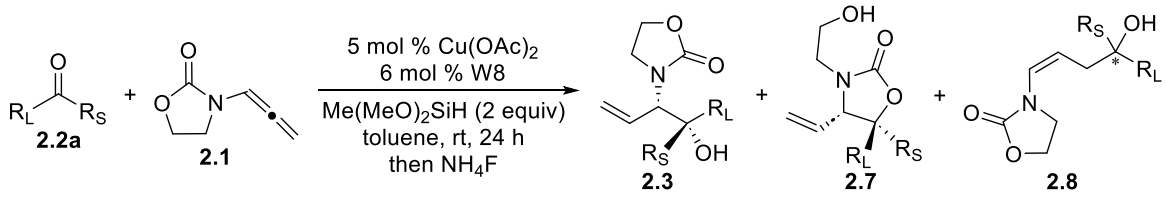
alchorneine,[139] while α,β-unsaturated ketones can be used to synthesize the antiepileptic drug vigabatrin[140] and marine alkaloid zoanthamide.[141]

## V. Experimental Methods

### General:

$^1$**H-NMR** spectra were recorded on Bruker 600 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as an internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, br = broad, m = multiplet), and coupling constants (Hz). $^{13}$C NMR was recorded on a Bruker 600 MHz (151 MHz) instrument with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). Liquid chromatography was performed using forced flow (flash chromatography) on silica gel purchased from Silicycle. Thin layer chromatography (TLC) was performed on glass-backed 250 μm silica gel F254 plates purchased from Silicycle. Visualization was achieved using UV light, a 10% solution of phosphomolybdic acid in EtOH, or potassium permanganate in water followed by heating. HRMS was collected using a Jeol AccuTOF-DART$^{TM}$ mass spectrometer using DART source ionization. All reactions were conducted in oven or flame dried glassware under an inert atmosphere of nitrogen or argon with magnetic stirring unless otherwise noted. Solvents were obtained from VWR as HPLC grade and transferred to septa sealed bottles, degased by Ar sparge, and analyzed by Karl-Fischer titration to ensure water content was $\leq$ 600 ppm. $Me(MeO)_2SiH$ was purchased from Alfa Aesar and used as received. Allenamides were prepared in one step as described in the literature. Ketones were purchased from Sigma Aldrich, TCI America, Alfa Aesar, or Oakwood Chemicals and used as received. All other materials were purchased from VWR, Sigma Aldrich, Combi-Blocks, Alfa-Aesar, or Strem Chemical Company and used as received.

**General Catalyst Screen Procedure for the branched-selective Cu(W8) catalyzed reductive coupling:**




To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 2.3 mg (0.0125 mmol) of $Cu(OAc)_2$ and ligand (0.0150 mmol). Toluene (0.5 mL) was then added, and the mixture was allowed to stir for 10 min. Alleneamide **2.1** (47.0 mg, 0.375 mmol) followed by the ketone (0.250 mmol) was then charged, and the vial was sealed with a crimp-cap septum and removed from the glove-box. The reaction was then cooled in an ice bath, and dimethoxymethylsilane (62 µL, 0.5 mmol) was then charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)* The mixture was then allowed to warm to rt and stirred for 24 h. The reaction was then quenched by the addition of 95 mg of NH4F and 1.5 mL of MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 5 mL of 5% NaHCO3 followed by extraction with $CH_2Cl_2$ (2x4mL). The combined organics were dried with $Na_2SO_4$ and concentrated *in vacuo*. An aliquot of the crude mixture was analyzed by $^1$HNMR spectroscopy to determine the dr and b/l ratio. The crude residue was then purified by flash chromatography on silica gel to afford the desired product. Enantioselectivity was determined by chiral HPLC analysis.

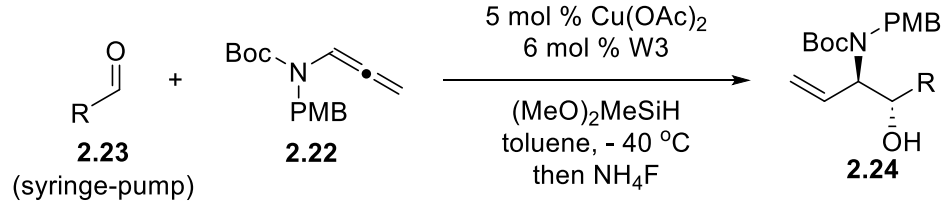
**Method A: General procedure for Cu(W8) catalyzed reductive coupling with ketones.**

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 2.3 mg (0.0125 mmol) of $Cu(OAc)_2$ and 14.0 mg (0.0150 mmol) of Walphos 8. Toluene (0.5 mL) was then added, and the mixture was allowed to stir for 10 min. Alleneamide **2.1** (47.0 mg, 0.375 mmol) followed by the ketone (0.250 mmol) was then charged, and the vial was sealed with a crimp-cap septum and removed from the glove-box. The reaction was then cooled in an ice bath, and dimethoxymethylsilane (62 µL, 0.5 mmol) was then charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)* The mixture was then allowed to warm to rt and stirred for 24 h. The reaction was then quenched by the addition of 95 mg of NH4F and 1.5 mL of MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 5 mL of 5% NaHCO3 followed by extraction with $CH_2Cl_2$ (2x4mL). The combined organics were dried with $Na_2SO_4$ and concentrated *in vacuo*. An aliquot of the crude mixture was analyzed by $^1$HNMR spectroscopy to determine the dr and b/l ratio. The crude residue was then purified by flash chromatography on silica gel to afford the desired product. Enantioselectivity was determined by chiral HPLC analysis.

**Method B: General procedure for Cu(W8) catalyzed reductive coupling with ketones.**

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 2.3 mg (0.0125 mmol) of $Cu(OAc)_2$ and 14.0 mg (0.0150 mmol) of Walphos 8. α,α,α-Trifluorotoluene (0.5 mL) was then added, and the mixture was allowed to stir for 10 min. Alleneamide **2.1** (47.0 mg, 0.375 mmol) followed by the ketone (0.250 mmol) and $^t$BuOH ( 48 µL, 0.500 mmol) was then charged. The vial was then sealed with a crimp-cap septum and removed from the glove-box. The reaction was then cooled in an ice bath, and dimethoxymethylsilane (62 µL, 0.5 mmol) was then charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)* The mixture was then allowed to warm to rt and stirred for 24 h. The reaction was then quenched by the addition of 95 mg of NH4F and 1.5 mL of MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 5 mL of 5% NaHCO3 followed by extraction with $CH_2Cl_2$ (2x4mL). The combined organics were dried with $Na_2SO_4$ and concentrated *in vacuo*. An aliquot of the crude mixture was analyzed by $^1$HNMR spectroscopy to determine the dr and b/l ratio. The crude residue was then purified by flash chromatography on silica gel to afford the desired product. Enantioselectivity was determined by chiral HPLC analysis.

**Method A: General procedure for Cu(W3) catalyzed reductive coupling with aldehydes.**



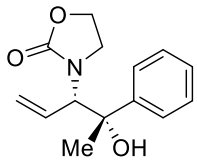

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 2.3 mg (0.0125 mmol) of $Cu(OAc)_2$ and 10.1 mg (0.0150 mmol) of **W3**. Toluene (0.25 mL) was then added, and the mixture was allowed to stir for 10 min. Alleneamide **2.22** (103 mg, 0.375 mmol) was then charged, and reaction vessel sealed with a crimp-cap septum and removed from the glove-box. The reaction was then cooled in an ice bath, and dimethoxymethylsilane (62 µL, 0.5 mmol) was then charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)* The mixture was further cooled to – 40 °C and stirred as the Aldehyde (0.250 mmol in 0.5 mL toluene) was charged to the solution at 0.05 mL/hr. After 9 h, the reaction was allowed to warm up to room temperature and stirred for an additional 15 h. The reaction was then quenched by the addition of 95 mg of $NH_4F$ and 1.5 mL of MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 5 mL of 5% $NaHCO_3$ followed by extraction with $CH_2Cl_2$ (3x4mL). The combined organics were dried with $Na_2SO_4$ and concentrated *in vacuo*. An aliquot of the crude mixture was analyzed by $^1$HNMR spectroscopy to determine the dr. The crude residue was then purified by flash chromatography on silica gel to afford the desired product. Enantioselectivity was determined by chiral HPLC analysis relative to authentic racemate prepared by the above procedure employing *rac*-BINAP as the ligand.

**Method B: General procedure for Cu(W12) catalyzed reductive coupling with aldehydes.**

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 2.3 mg (0.0125 mmol) of $Cu(OAc)_2$ and 9.3 mg (0.0150 mmol) of **W12**. Toluene (0.25 mL) was then added, and the mixture was allowed to stir for 10 min. Alleneamide **2.22** (103 mg, 0.375 mmol) was then charged, and reaction vessel sealed with a crimp-cap septum and removed from the glove-box. The reaction was then cooled in an ice bath, and dimethoxymethylsilane (62 µL, 0.5 mmol) was then charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)* The mixture was then warmed to room temperature and stirred as the aldehyde (0.250 mmol in 0.5 mL toluene) was charged to the solution at 0.02 mL/hr. After 26 h, the reaction was quenched by the addition of 95 mg of $NH_4F$ and 1.5 mL of MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 5 mL of 5% $NaHCO_3$ followed by extraction with $CH_2Cl_2$ (3x4mL). The combined organics were dried with $Na_2SO_4$ and concentrated *in vacuo*. An aliquot of the crude mixture was analyzed by $^1$HNMR spectroscopy to determine the dr. The crude residue was then purified by flash chromatography on silica gel to afford the desired product. Enantioselectivity was determined by chiral HPLC analysis relative to authentic racemate prepared by the above procedure employing *rac*-BINAP as the ligand.

**Analytical Data**

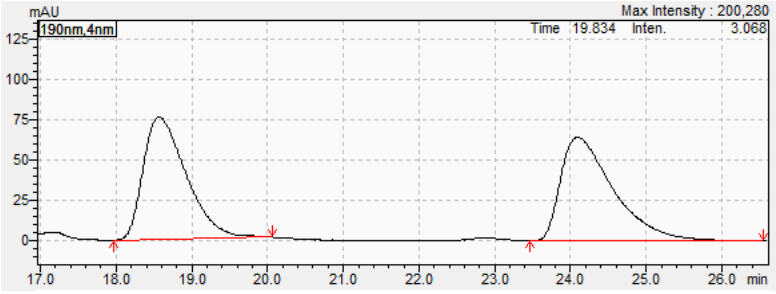
*i. Ketone coupling*



**2.3a**

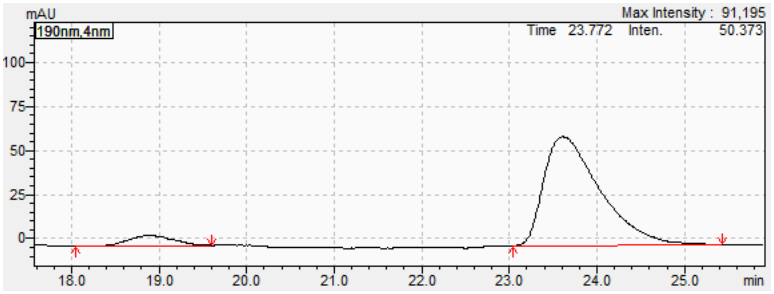
**3-((3*S*,4*S*)-4-hydroxy-4-phenylpent-1-en-3-yl)oxazolidin-2-one (2.3a)**: According to the Method A general procedure, a crude mixture of 80:20 **2.3a**/**2.7a** was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 46.3 mg (75%) of **2.3a** in 91 wt% purity by quantitative $^1$H-NMR spectroscopy using dimethylfumarate as analytical standard as an off-white solid as a single diastereomer as a 93/7 mixture of enantiomers (allene rearrangement products *N*-allyl and *N*-propenyl oxazolidin-2-one could not be removed by chromatography). Analytically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 76% recovery with >99 er. Absolute and relative stereochemistry was determined by conversion to authentic material. $R_f$ = 0.12 (30% EtOAc/hexanes). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.47 (d, *J* = 7.90 Hz, 2H), 7.34 (t, *J* = 7.30 Hz, 2H), 7.23 – 7.28 (m, 1H), 6.29 (ddd, *J* = 16.40 Hz, *J* = 9.98 Hz, 8.50 Hz, 1H), 5.43 (d, *J* = 10.6 Hz, 1H), 5.36 (dt, *J* = 17.46 Hz, *J* = 1Hz, 1H), 4.29 (br s, 1H), 4.15 (d, *J* = 8.65 Hz, 1H), 4.02 (dtd, *J* = 21.44 Hz, *J* = 8.81 Hz *J* = 7.11 Hz, 2H), 3.53 (td, *J* = 15.61 Hz, *J* = 7.11 Hz, 1H), 3.23 (td, *J* = *1*7.62 Hz, *J* = 7.01 Hz, 1H), 1.53 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.8, 145.8, 130.7, 128.1, 126.9, 124.5, 120.6, 67.0, 62.6, 45.0, 29.1 ppm. HRMS (DART) *m/z* calcd for $C_{14}H_{18}NO_3$ $[M + H]^+$: 248.1287; Found $[M + H]^+$: 248.1264.

*Chiral HPLC analysis (OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 190 nm):*
**Racemic 2.3a:**

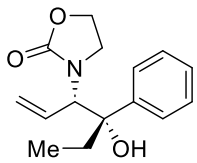



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 18.570 | 48.921 | 75785 | M | 48.921 |
| 2 | 24.093 | 51.079 | 64405 | M | 51.079 |
| Total | | 100.000 | 140191 | | 100.000 |

**2.3a from the $Cu(OAc)_2$ /W8 reaction:**



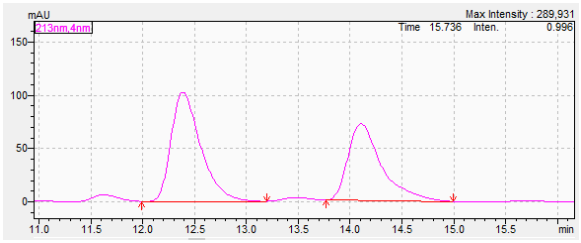

| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 18.852 | 6.965 | 5744 | M | 6.965 |
| 2 | 23.611 | 93.035 | 61653 | M | 93.035 |
| Total | | 100.000 | 67397 | | 100.000 |




**2.3b**

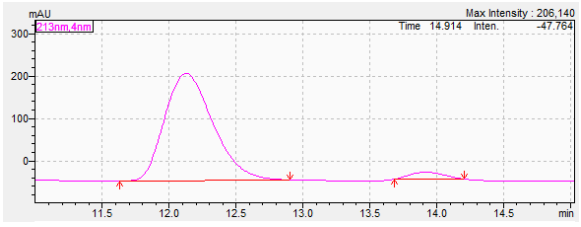
**3-((3*S*,4*S*)-4-hydroxy-4-phenylhex-1-en-3-yl)oxazolidin-2-one (2.3b)**: According to the Method B general procedure, a crude mixture of >99:1 **2.3b**/**2.7b** was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 50.3 mg (77%) of **2.3b** in 85 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as an off-white solid as a single diastereomer as a 97/3 mixture of enantiomers (allene rearrangement products *N*-allyl and *N*-propenyl oxazolidin-2-one could not be removed by chromatography). Analytically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 81% recovery with >99 er. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.18 (30% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 7.43 (d, *J* = 7.70 Hz, 2H), 7.34 (t, *J* = 7.08 Hz, 2H), 7.21-7.27 (m, 1H), 6.27 (ddd, *J* = 17.8 Hz, *J* = 10.3 Hz, *J* = 8.5 Hz, 1H), 5.41 (d, *J* = 10.3 Hz, 1H), 5.36 (d, *J* = 17.3 Hz, 1H), 4.27 (br s, 1H), 4.18 (d, *J* = 8.9 Hz, 1H), 3.98 (t, *J* = 8.6 Hz, 2H), 3.52 (q, 8.0 Hz, 1H), 3.25 (q, *J* = 8.0 Hz, 1.87 – 1.97 (m, 1H), 1.73 – 1.81 (m, 1H), 0.66 (t, *J* = 6.9 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.7, 143.2, 130.9, 128.0, 126.7, 125.2, 120.5, 79.5, 66.8, 62.6, 45.0, 33.4, 7.3 ppm. HRMS (DART) *m/z* calcd for $C_{15}H_{19}NO_3$ $[M]^+$: 261.1365; Found $[M]^+$: 261.1332.

*Chiral HPLC analysis (AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 213 nm):*
**Asymmetric 2.3b:**

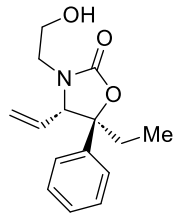



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 12.388 | 55.520 | 79465 | M | 0.000 |
| 2 | 14.103 | 44.480 | 56263 | M | 0.000 |
| Total | | 100.000 | 135727 | | 0.000 |

**2.3b from the Cu(OAc)$_2$ /W8 reaction:**



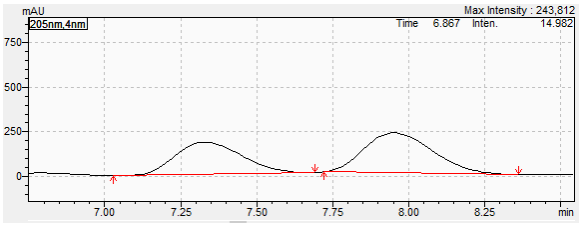

| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 12.126 | 95.743 | 253938 | M | 0.000 |
| 2 | 13.915 | 4.257 | 16458 | M | 0.000 |
| Total | | 100.000 | 270396 | | 0.000 |



**2.7b**

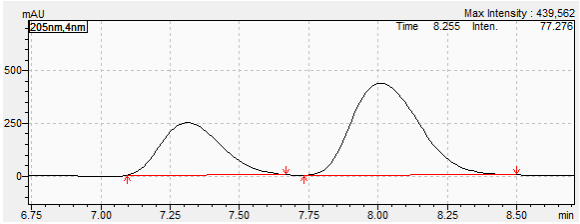
**(4*S*,5*S*)-5-ethyl-3-(2-hydroxyethyl)-5-phenyl-4-vinyloxazolidin-2-one** (**2.7b**): According to the Method A general procedure, a crude mixture of 12:88 **2.3b**:**2.7b** was obtained and purified by silica gel chromatography (eluent: 0 – 30% EtOAc in $CH_2Cl_2$) to provide 45.8 mg (70%) of **2.7b** as a thick glass as a single diastereomer as a 67:33 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.31 (30% EtOAc/ $CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.33 – 7.41 (m, 4H), 7.31 (t, *J* = 6.6 Hz, 1H), 5.95 (dt, *J* = 17.1 Hz, 9.5 Hz, 1H, 5.53 (d, *J* = 10.3 Hz, 1H), 5.44 (d, *J* = 17.2 Hz, 1H), 4.21 (d, *J* = 9.5 Hz, 1H), 3.62 – 3.74 (m, 2H), 3.47 (dt, *J* = 14.8 Hz, 4.8 Hz, 1H), 3.17 (dt, 15.1 Hz, 5.2 Hz, 1H), 2.22 (br s, 1H), 2.07 (dq, *J* = 14.4 Hz, 6.1 Hz, 1H), 1.87 (dq, 15.4 Hz, 7.0 Hz, 1H), 0.76 (t, *J* = 7.2 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.2, 142.3, 132.3, 128.7, 127.8, 124.3, 123.2, 86.3, 71.5, 61.0, 45.1, 29.5, 7.6 ppm. HRMS (DART) *m/z* calcd for $C_{15}H_{19}NO_3$ $[M]^+$: 261.1365; Found $[M]^+$: 261.1332.

*Chiral HPLC analysis (Chiralcel OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 205 nm):*
**Racemic 2.7b:**

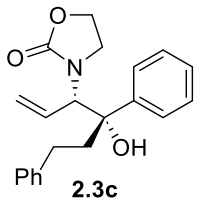



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 7.330 | 47.091 | 180354 | M | 47.091 |
| 2 | 7.952 | 52.909 | 210977 | M | 52.909 |
| Total | | 100.000 | 391331 | | 100.000 |

**2.7b from the Cu(OAc)$_2$/W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 7.312 | 32.865 | 134980 | M | 32.865 |
| 2 | 8.010 | 67.135 | 232609 | M | 67.135 |
| Total | | 100.000 | 367590 | | 100.000 |

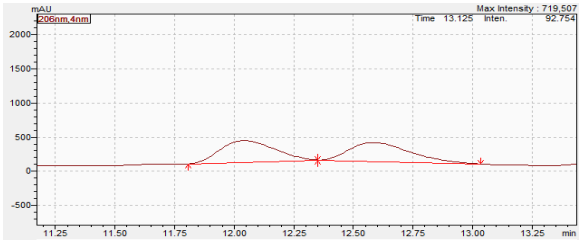


**2.3c**

**3-((3*S*,4*S*)-4-hydroxy-4,6-diphenylhex-1-en-3-yl)oxazolidin-2-one (2.3c)**: According to the Method B general procedure, a crude mixture of >99:1 **2.3c**/**2.7c** was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 42.1 mg (55%) of **2.3c** in 90 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as an off-white solid as a single diastereomer as a 93/7 mixture of enantiomers and >99 (allene rearrangement products *N*-allyl and *N*-propenyl 4-phenyloxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 76% recovery with >99 er. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.21 (30% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 7.48 (d, *J* = 7.9 Hz, 2H), 7.38 (t, *J* = 7.42 Hz, 2H), 7.27 (t, *J* = 6.7 Hz, 1H), 7.21 (t, *J* = 7.7 Hz, 2H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 7.7 Hz, 2H), 6.29 (ddd, *J* = 17.4 Hz, *J* = 10.6 Hz, *J* = 9.1 Hz, 1H), 5.39 (d, *J* = 9.31 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 4.80 (br s, 1H), 4.05 ( d, *J* = 9.3 Hz, 1H), 4.00 (q, *J* = 7.0 Hz, 1H), 3.94 (q, *J* = 8.8 Hz, 1H), 3.50 (q, J = 8.5 Hz, 1H), 3.16 (q, *J* = 6.8 Hz, 1H), 2.60 (td, *J* = 12.9 Hz, *J* = 4.9 Hz, 1H), 2.21 (td, *J* = 12.3 Hz, *J* = 5.0 Hz, 1H), 2.13 ( td, *J* = 12.7 Hz, *J* = 3.6 Hz, 1H), 1.99 (td, *J* = 12.7 Hz, *J* = 4.3 Hz, 1H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 143.5, 142.1, 130.6, 128.3, 128.2, 126.9, 125.7, 125.1, 120.8, 79.4, 67.8, 62.8, 45.6, 42.7, 29.5 ppm. HRMS (DART) *m/z* calcd for $C_{21}H_{24}NO_3$ $[M + H]^+$: 338.1756; Found $[M + H]^+$: 338.1735.

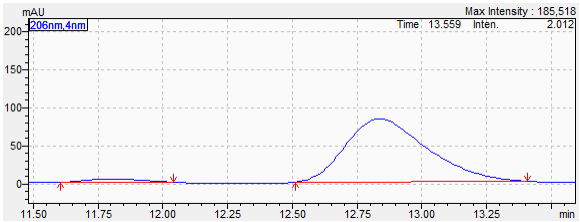
*Chiral HPLC analysis (AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 206 nm):*

**Racemic 2.3c:**

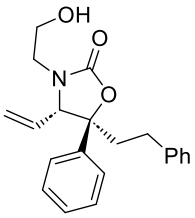



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 12.042 | 49.914 | 101377 | M | 0.000 |
| 2 | 12.582 | 50.086 | 90034 | M | 0.000 |
| Total | | 100.000 | 191411 | | 0.000 |

**2.3c from the Cu(OAc)$_2$ /W8 reaction:**



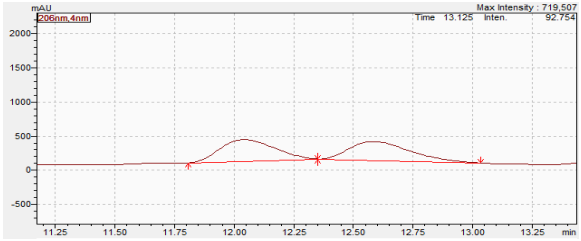

| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 11.798 | 3.306 | 3431 | M | 0.000 |
| 2 | 12.836 | 96.694 | 62430 | M | 0.000 |
| Total | | 100.000 | 65861 | | 0.000 |




**2.7c**

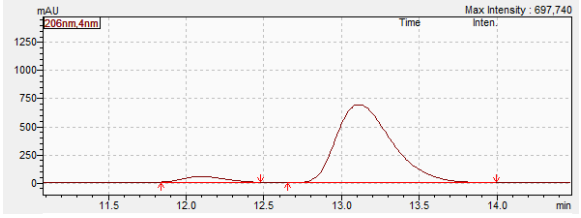
**(4*S*,5*S*)-3-(2-hydroxyethyl)-5-phenethyl-5-phenyl-4-vinyloxazolidin-2-one** (**2.7c**): According to the Method A general procedure, a crude mixture of 14:86 **2.3c**:**2.7c** was obtained and purified by silica gel chromatography (eluent: 0 – 30% EtOAc in $CH_2Cl_2$) to provide 66.7 mg (78%) of **2.7c** as a thick glass as a single diastereomer as a 95:5 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.7a**. $R_f$ = 0.35 (30% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.40 – 7.46 (m, 4H), 7.33 – 7.39 (m, 1H), 7.23 (t, *J* = 7.8 Hz, 2H), 7.16 (t, *J* = 7.30 Hz, 1H), 7.06 (d, *J* = 7.30 Hz, 2H), 5.92 (dt, *J* = 16.6 Hz, 10.3 Hz, 1H), 5.50 (d, *J* = 10.3 Hz, 1H), 5.44 (d, *J* = 17.5 Hz, 1H), 4.23 (d, *J* = 9.7 Hz, 1H), 3.63 – 3.75 (m, 2H) 3.44 (ddd, *J* = 16.9 Hz, *J* = 7.2 Hz, 4.16 Hz, 1H), 3.18 (ddd, *J* = 17.2, *J* = 7.2 Hz, 3.8 Hz, 1H), 2.7 (td, *J* = 12.8 Hz, *J* = 5.1 Hz, 1H), 2.30 (dt, *J* = 12.6 Hz, 4.6 Hz, 1H), 2.08 – 2.22 (m, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.0, 142.3, 141.5, 132.2, 128.9, 128.5, 128.3, 128.0, 126.0, 126.1, 123.4, 85.6, 71.7, 60.9, 45.1, 39.0, 29.6 ppm. HRMS (DART) *m/z* calcd for $C_{21}H_{24}NO_3$ [M + H]$^+$: 338.1756; Found [M + H]$^+$: 338.1735.

*Chiral HPLC analysis (Chiralpak AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 206 nm):*
**Racemic 2.7c:**

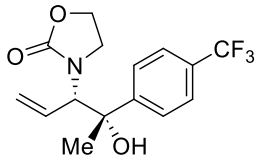



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 12.042 | 49.914 | 101377 | M | 0.000 |
| 2 | 12.582 | 50.086 | 90034 | M | 0.000 |
| Total | | 100.000 | 191411 | | 0.000 |

**2.7c from the Cu(OAc)$_2$/W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 12.096 | 5.145 | 51976 | M | 0.000 |
| 2 | 13.111 | 94.855 | 694801 | M | 0.000 |
| Total | | 100.000 | 746777 | | 0.000 |

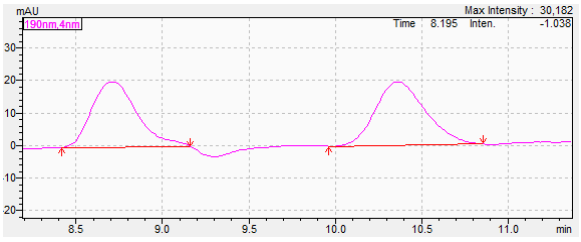


**2.3d**

**3-((3*S*,4*S*)-4-hydroxy-4-(4-(trifluoromethyl)phenyl)pent-1-en-3-yl)oxazolidin-2-one** (**2.3d**): According to the Method B general procedure, the crude mixture of >99:1 **2.3d**/**2.7d** was obtained and purified by silica gel chromatography (eluent: 0 – 20% EtOAc in $CH_2Cl_2$) to provide 52.0 mg (66%) of **2.3d** as a thick clear oil as a single diastereomer as a 86/16 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.49 (10% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.58 – 7.63 (m, 4H), 6.26 (ddd, *J* = 17.7 Hz, *J* = 9.9 Hz, *J* = 8.7 Hz, 1H), 5.46 (d, *J* = 10.2 Hz, 1H), 5. 38 (d, *J* = 17.4 Hz, 1H), 4.64 (s, 1H), 4.17 (d, *J* = 8.6 Hz, 1H), 4.0 – 4.1 (m, 2H), 3.56 (q, *J* = 8.4 Hz, 1H), 3.28 (q, *J* = 7.5 Hz, 1H), 1.51 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 150.1, 130.1, 129.3, 129.0, 125 (q, $^3J_{CF}$ = 3.5), 125.0, 121.2, 76.8, 66.9, 62.7, 40.1, 29.3 ppm. $^{19}$F NMR (565 MHz, $CDCl_3$): – 62.4 ppm. HRMS (DART) *m/z* calcd for $C_{18}H_{24}F_3NO_5Si$ $[M]^+$: 419.1376; Found $[M]^+$: 419.1376.

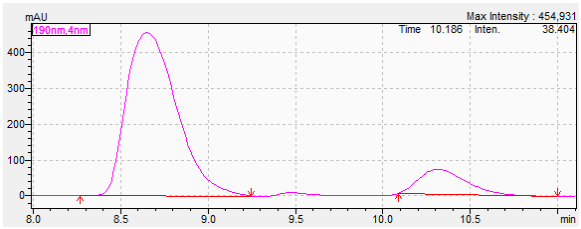
*Chiral HPLC analysis (AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 190 nm):*

**Racemic 2.3d:**

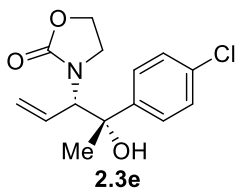



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 8.707 | 48.368 | 20117 | M | 48.368 |
| 2 | 10.364 | 51.632 | 19433 | M | 51.632 |
| Total | | 100.000 | 39550 | | 100.000 |

**2.3d from the Cu(OAc)$_2$ /W8 reaction:**



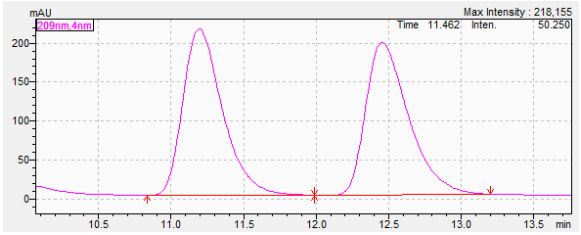

| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 8.651 | 87.737 | 454671 | M | 0.000 |
| 2 | 10.315 | 12.263 | 68870 | M | 0.000 |
| Total | | 100.000 | 523541 | | 0.000 |



**2.3e**

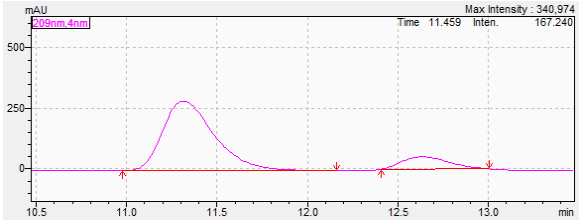
**3-((3*S*,4*S*)-4-(4-chlorophenyl)-4-hydroxypent-1-en-3-yl)oxazolidin-2-one** (**2.3e**): According to the Method A general procedure, a crude mixture of 76:24 **2.3e**/**2.7e** was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 49.2 mg (70%) of **2.3e** in 89 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a single diastereomer as a 85/15 mixture of enantiomers (allene rearrangement products *N*-allyl and *N*-propenyl oxazolidin-2-one could not be removed by chromatography). Analytically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 65% recovery with 95/5 er. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.14 (30% EtOAc/hexanes) $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 7.42 (d, *J* = 8.7 2H), 7.32 (d, *J* = 8.7 Hz, 1H), 6.25 (ddd, *J* = 18.4 Hz, *J* = 17.4 Hz, *J* = 9.0 Hz 1H), 5.44 (d, *J* = 10.4 Hz, 1H), 5.36 (d, *J* = 17.3 Hz, 1H), 4.43 (s, 1H), 4.05 - 4.15 (m, 3H), 3.55 (dt, *J* = 7.6 Hz, *J* = 8.6 Hz, 1H), 3.27 (dt, *J* = 7.9 Hz, *J* = 7.0 Hz, 1H), 1.50 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 144.5, 132.8, 130.4, 128.4, 126.1, 121.1, 76.8, 67.0, 62.8, 45.2, 29.3 ppm. HRMS (DART) *m/z* calcd for $C_{14}H_{17}ClNO_3$ $[M + H]^+$: 282.0897; Found $[M + H]^+$: 282.0883.

*Chiral HPLC analysis (OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 209 nm):*
**Racemic 2.3e:**

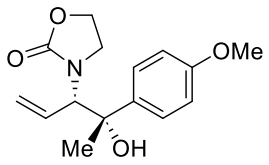



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 11.195 | 50.396 | 213816 | M | 0.000 |
| 2 | 12.457 | 49.604 | 195616 | M | 0.000 |
| Total | | 100.000 | 409433 | | 0.000 |

**2.3e from the Cu(OAc)$_2$ /W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 11.314 | 86.267 | 288084 | M | 86.267 |
| 2 | 12.633 | 13.733 | 51138 | M | 13.733 |
| Total | | 100.000 | 339222 | | 100.000 |

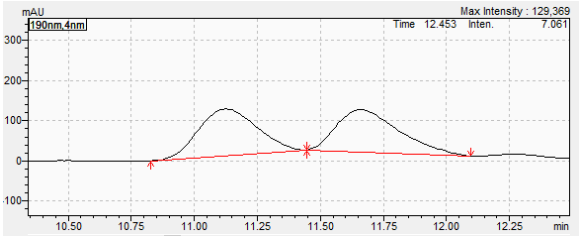


**2.3f**

**3-((3*S*,4*S*)-4-hydroxy-4-(4-methoxyphenyl)pent-1-en-3-yl)oxazolidin-2-one** (**2.3f**): According to the Method A general procedure, a crude mixture of 88:14 **2.3f**/**2.7f** was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 40.2 mg (58%) of **2.3f** in 91 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a single diastereomer as a 82/18 mixture of enantiomers (allene rearrangement products *N*-allyl and *N*-propenyl oxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 62% recovery with >99 er. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.10 (30% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 7.38 (d, *J* = 7.7 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.26 (ddd, J =. 17.5 Hz, *J* = 10.5, *J* = 8.9 Hz, 1H), 5.42 (d, *J* = 10.1 Hz, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 4.10 – 4.17 (m, 2H), 4.05 (t, *J* = 8.2 Hz, 2H), 3.52 (dt, *J* = 8.4 Hz, *J* = 7.8 Hz, 1H), 3.27 (dt, *J* = 8.2 Hz, *J* = 8.4 Hz, 1H), 1.50 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.8, 158.4, 137.9, 130.8, 125.8, 120.6, 114.5, 76.8, 67.0, 62.7, 55.2, 45.0, 29.4 ppm. HRMS (DART) *m/z* calcd for $C_{15}H_{20}NO_4$ $[M + H]^+$: 278.1392; Found $[M + H]^+$: 278.1379.

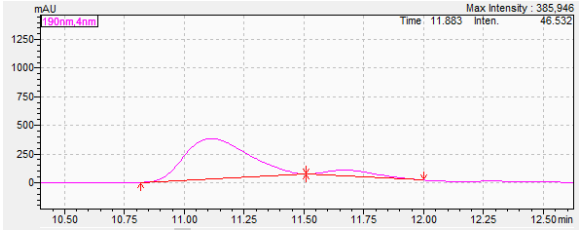
*Chiral HPLC analysis (AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 190 nm):*

**Racemic 2.3f:**

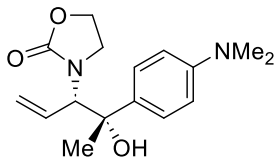



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 11.123 | 50.752 | 115905 | M | 50.752 |
| 2 | 11.659 | 49.248 | 104736 | M | 49.248 |
| Total | | 100.000 | 220641 | | 100.000 |

**2.3f from the Cu(OAc)$_2$ /W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 11.111 | 89.668 | 353191 | M | 0.000 |
| 2 | 11.669 | 10.332 | 53741 | M | 0.000 |
| Total | | 100.000 | 406932 | | 0.000 |

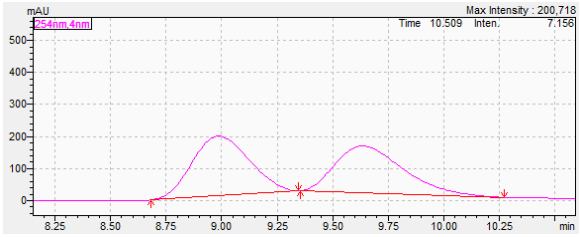


**2.3g**

**3-((3*S*,4*S*)-4-(4-(dimethylamino)phenyl)-4-hydroxypent-1-en-3-yl)oxazolidin-2-one** (**2.3g**): According to the Method A general procedure, a crude mixture of >99:1 **2.3g**/**2.7g** was obtained and purified by silica gel chromatography (eluent: 0 – 30% EtOAc in $CH_2Cl_2$) to provide 48.6 mg (67%) of **2.3g** as thick glass as a single diastereomer as a 77/23 mixture of enantiomers and >99 mixture of **2.3g**/**2.7g**. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 021 (10% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.32 (d, *J* = 8.9 Hz, 2H), 6.72 (d, *J* = 7.7, 2H), 6.26 (ddd, *J* = 17.6 Hz, *J* = 10.5 Hz, *J* = 8.4 Hz, 1H), 5.41 (d, *J* = 10.4 Hz, 1H), 5.34 (d, *J* = 17.3 Hz, 1H), 4.17 (d, *J* = 8.4 Hz, 1H), 4.05 (t, *J* = 7.7 Hz, 1H), 3.51 (dt, *J* = 8.0 Hz, *J* = 8.4 Hz, 1H), 3.28 (dt, *J* = 8.2 Hz, *J* = 8.6 Hz, 1H), 2.95 (s, 6H), 1.51 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.7, 143.2, 130.9, 128.0, 126.7, 125.2, 120.5, 79.5, 66.8, 62.6, 45.0, 33.4, 7.3 ppm. HRMS (DART) *m/z* calcd for $C_{16}H_{23}N_2O_3$ $[M + H]^+$: 291.1709; Found $[M + H]^+$: 291.1714.

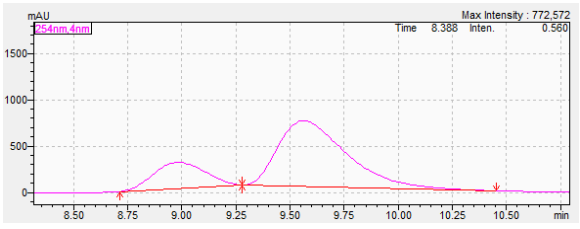
*Chiral HPLC analysis (OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 254 nm):*

**Racemic 2.3g:**

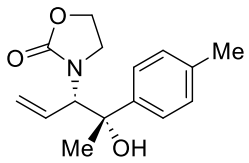



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 8.986 | 51.740 | 185880 | M | 51.740 |
| 2 | 9.634 | 48.260 | 145818 | M | 48.260 |
| Total | | 100.000 | 331699 | | 100.000 |

**2.3g from the Cu(OAc)$_2$ /W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 8.982 | 23.067 | 282239 | M | 23.067 |
| 2 | 9.562 | 76.933 | 708798 | M | 76.933 |
| Total | | 100.000 | 991036 | | 100.000 |

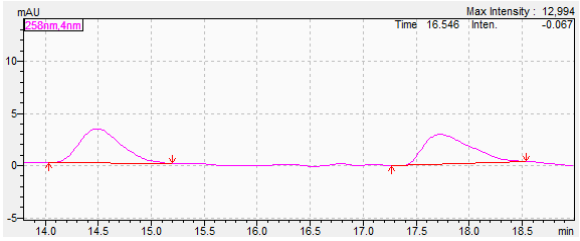


**2.3h**

**3-((3*S*,4*S*)-4-hydroxy-4-(p-tolyl)pent-1-en-3-yl)oxazolidin-2-one (2.3h)**: According to the Method B general procedure, a crude mixture of >99:1 **2.3h**/**2.7h** was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 26.1 mg (40%) of **2.3h** in 88 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a single diastereomer as a 83/17 mixture of enantiomers (allene rearrangement products *N*-allyl and *N*-propenyl oxazolidin-2-one could not be removed by chromatography). Analytically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 77% recovery with 91/9 er. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.16 (30% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 7.32 (d, *J* = 8.9 Hz, 2H), 6.72 (d, *J* = 7.7, 2H), 6.26 (ddd, *J* = 17.6 Hz, *J* = 10.5 Hz, *J* = 8.4 Hz, 1H), 5.41 (d, *J* = 10.4 Hz, 1H), 5.34 (d, *J* = 17.3 Hz, 1H), 4.17 (d, *J* = 8.4 Hz, 1H), 4.05 (t, *J* = 7.7 Hz, 1H), 3.51 (dt, *J* = 8.0 Hz, *J* = 8.4 Hz, 1H), 3.28 (dt, *J* = 8.2 Hz, *J* = 8.6 Hz, 1H), 2.95 (s, 6H), 1.51 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.7, 142.7, 136.4, 130.8, 128.8, 124.4, 120.5, 76.8, 66.8, 62.6, 44.9, 29.2, 20.9 ppm. HRMS (DART) *m/z* calcd for $C_{16}H_{23}N_2O_3$ $[M + H]^+$: 291.1709; Found $[M + H]^+$: 291.1714.

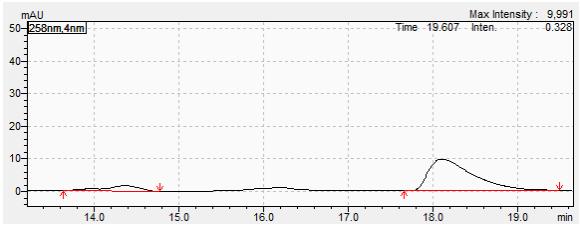
*Chiral HPLC analysis (OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 258 nm):*

**Racemic 2.3h:**

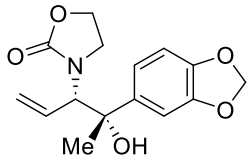



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 14.489 | 50.943 | 3306 | M | 0.000 |
| 2 | 17.727 | 49.057 | 2849 | M | 0.000 |
| Total | | 100.000 | 6155 | | 0.000 |

**2.3h from the Cu(OAc)$_2$ /W8 reaction:**



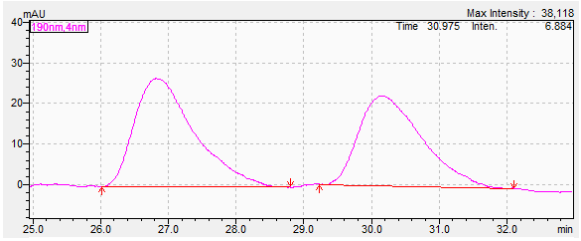

| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 14.364 | 12.610 | 1734 | M | 12.610 |
| 2 | 18.102 | 87.390 | 9733 | M | 87.390 |
| Total | | 100.000 | 11467 | | 100.000 |



**2.3i**

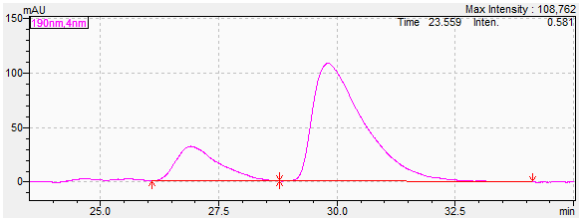
**3-((3*S*,4*S*)-4-(benzo[d][1,3]dioxol-5-yl)-4-hydroxypent-1-en-3-yl)oxazolidin-2-one** (**2.3i**): According to the Method A general procedure, a crude mixture of 88:12 **2.3i**/**2.7i** was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 54.6 mg (75%) of **2.3i** in 87 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a single diastereomer as a 80/20 mixture of enantiomers (allene rearrangement products *N*-allyl and *N*-propenyl oxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 75% recovery with 90/10 er. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.12 (30% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 6.99 (s, 1H), 6.93 (dd, *J* = 8.18 Hz, *J* = 1.1 Hz, 1H), 6.78 (d, *J* = 8.30 Hz, 1H), 6.25 (ddd, *J* = 17.3 Hz, J =. 10.8 Hz, *J* = 9.3 Hz, 1H), 5.96 (s, 2H), 5.42 (d, *J* = 10.3 Hz, 1H), 5.35 (d, *J* = 17.3 Hz, 1H), 4.21 (br, s, 1H), 4.05 - 4.14 (m, 3H), 3.6 (q, *J* = 8.4, 1H), 3.32 (q, *J* = 8.4 Hz, 3H), 1.49 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 147.6, 146.4, 140.1, 130.4, 120.8, 117.8, 107.9, 105.6, 101.1, 76.9, 67.1, 62.7, 45.1, 29.5 ppm. HRMS (DART) *m/z* calcd for $C_{15}H_{17}NO_5$ $[M + H]^+$: 291.1107; Found $[M]^+$: 291.1123.

*Chiral HPLC analysis (OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 190 nm):*
**Racemic 2.3i:**

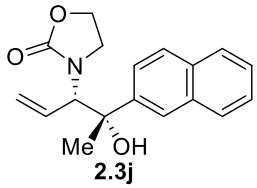



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 26.819 | 53.696 | 26762 | M | 0.000 |
| 2 | 30.140 | 46.304 | 22111 | M | 0.000 |
| Total | | 100.000 | 48873 | | 0.000 |

**2.3i from the $Cu(OAc)_2$ /W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 26.910 | 19.715 | 31608 | M | 0.000 |
| 2 | 29.821 | 80.285 | 107955 | M | 0.000 |
| Total | | 100.000 | 139563 | | 0.000 |

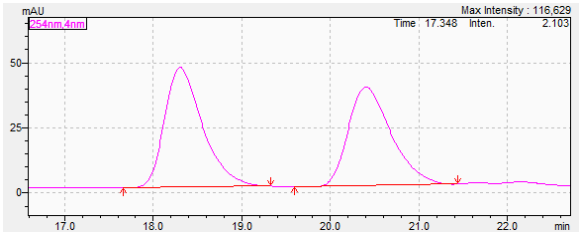


**2.3j**

**3-((3*S*,4*S*)-4-hydroxy-4-(naphthalen-2-yl)pent-1-en-3-yl)oxazolidin-2-one** (**2.3j**): According to the Method B procedure, a crude mixture of >99 **2.3j**/**2.7j** was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 37.1 mg (50%) of **2.3j** in 88 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a single diastereomer as a 85/15 mixture of enantiomers and >99 mixture of **2.3j**/**2.7j** (allene rearrangement products *N*-allyl and *N*-propenyl oxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 80% recovery with 82/17 er. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.16 (30% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 8.00 (s, 1H), 7.75 -8.86 (m, 3H), 7.4 – 7.50 (m, 3H), 6.31 (ddd, *J* = 17.4 Hz, *J* = 10.4 Hz, *J* = 9.19 Hz, 1H), 5.43 (d, *J* = 10.2 Hz, 1H), 5.37 (d, *J* = 17.27 Hz, 1H), 4.59 (s, 1H), 4.26 (d, *J* = 8.5 Hz, 1H), 3.94 (q, J= 9.0 Hz, 1H), 3.89 (q, *J* = 8.4 Hz, 1H), 3.59 (q, *J* = 8.81 Hz, 1H), 3.22 (q, *J* = 8.81 Hz, 1H) 1.56 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 143.3, 133.1, 132.3, 128.2, 127.8, 127.4, 126.1, 125.8, 123.3, 122.9, 120.7, 76.9, 66.9, 62.6, 45.1, 29.3 ppm. HRMS (DART) *m/z* calcd for $C_{18}H_{20}NO_3$ $[M + H]^+$: 298.1443; Found $[M + H]^+$: 298.1435.

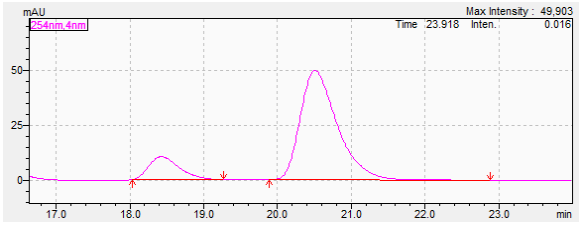
*Chiral HPLC analysis (AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 190 nm):*

**Racemic 2.3j:**

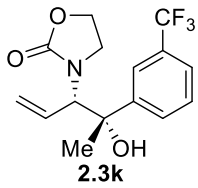



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 18.304 | 51.801 | 45920 | M | 0.000 |
| 2 | 20.402 | 48.199 | 37807 | M | 0.000 |
| Total | | 100.000 | 83727 | | 0.000 |

**2.3j from the $Cu(OAc)_2$ /W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark |
|---|---|---|---|---|
| 1 | 18.426 | 14.644 | 10430 | M |
| 2 | 20.510 | 85.356 | 49691 | M |
| Total | | 100.000 | 60121 | |

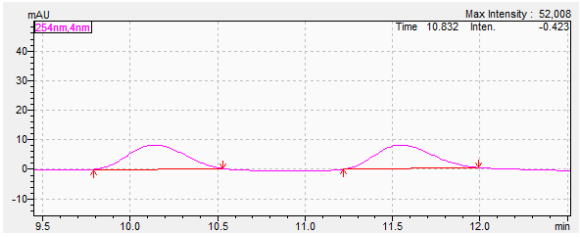


**2.3k**

**3-((3*S*,4*S*)-4-hydroxy-4-(3-(trifluoromethyl)phenyl)pent-1-en-3-yl)oxazolidin-2-one** (**2.3k**): According to the Method A general procedure, a crude mixture of 60/40 **2.3k**/**2.7k** was obtained and purified by silica gel chromatography (eluent: 0 – 20% EtOAc in $CH_2Cl_2$) to provide 33.9 mg (43%) of **2.3k** as an oil as a single diastereomer as a 89/11 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.19 (10% EtOAc/ $CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.74 (s, 1H), 7.69 (d, *J* = 8.00 Hz, 1H), 7.51 (d, *J* = 8.24 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 6.25 (ddd, *J* = 17.3 Hz, *J* = 10.8 Hz, *J* = 9.7 Hz, 1H), 5.45 (d, *J* = 9.9 Hz, 1H), 5.38 (d, *J* = 17.0 Hz, 1H), 4.55 (br s, 1H), 4.18 (d, *J* = 8.4 Hz, 1H), 4.00 – 4.07 (m, 2H), 3.60 (q, 8.4 Hz, 1H), 3.28 (q, *J* = 7.5 Hz, 1H), 1.52 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.8, 147.1, 130.3 (q, $^2J_{CF}$ = 33 Hz), 129.4 (q, $^1J_{CF}$ = 274 Hz), 128.8, 128.3, 123.7 (q, $^3J_{CF}$ = 4.2 Hz), 123.7 (q, $^3J_{CF}$ = 4.6 Hz), 121.3, 118.6, 66.7, 62.7, 61.7, 44.9, 29.1 ppm. $^{19}$F NMR (565 MHz, $CDCl_3$): – 62.5 ppm. HRMS (DART) *m/z* calcd for $C_{18}H_{24}F_3NO_5Si$ $[M]^+$: 419.1376; Found $[M]^+$: 419.1376.

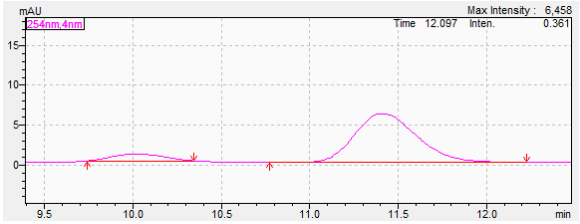
*Chiral HPLC analysis (OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 190 nm):*

**Racemic 2.3k:**

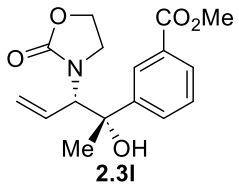



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 10.140 | 50.030 | 8151 | M | 0.000 |
| 2 | 11.549 | 49.970 | 7961 | M | 0.000 |
| Total | | 100.000 | 16112 | | 0.000 |

**2.3k from the Cu(OAc)$_2$ /W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 10.024 | 10.401 | 868 | M | 0.000 |
| 2 | 11.412 | 89.599 | 6144 | M | 0.000 |
| Total | | 100.000 | 7012 | | 0.000 |

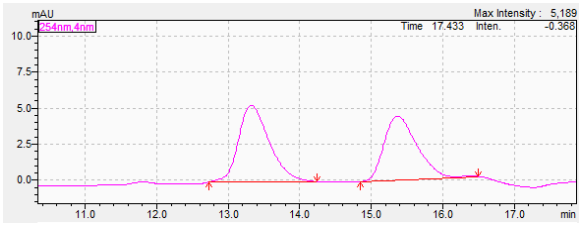


**2.3l**

**methyl 3-((2*S*,3*S*)-2-hydroxy-3-(2-oxooxazolidin-3-yl)pent-4-en-2-yl)benzoate** (**2.3l**): According to the Method A general procedure, a crude mixture of 73:27 **2.3l**/**2.7l** was obtained and purified by silica gel chromatography (eluent: 0 – 20% EtOAc in $CH_2Cl_2$) to provide 35.9 mg (47%) of **2.3l** as a thick glass as a single diastereomer as a 97/3 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.38 (10% EtOAc/ $CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 8.11 (s, 1H), 7.93 ( d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.60 Hz, 1H), 6.27 (ddd, *J* = 17.5 Hz, *J* = 9.5 Hz, *J* = 9.0 Hz, 1H), 5.45 (d, *J* = 10.0 Hz, 1H), 5.37 (d, *J* = 17.6 Hz, 1H), 4.63 (s, 1H), 4.15 (d, *J* = 9.0 Hz, 1H), 4.07 (q, *J* = 8.2, 1H), 4.01(q, *J* = 8.5 Hz, 1H), 3.92 (s, 3H), 3.58 (q, *J* = 8.5 Hz, 1H), 3.27 (q, *J* = 7.4 Hz, 1H), 1.52 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 167.1, 158.8, 146.5, 130.0, 129.9, 129.5, 128.4, 128.2, 125.5, 121.0, 76.8, 67.1, 62.7, 52.1, 45.3, 29.2 ppm. HRMS (DART) *m/z* calcd for $C_{16}H_{20}NO_5$ $[M + H]^+$: 306.1341; Found $[M]^+$: 306.1315.

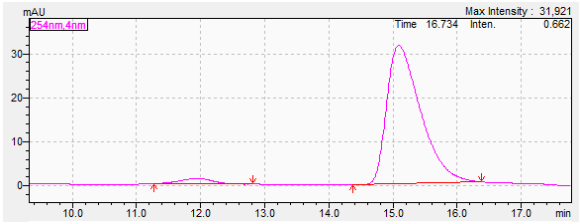
*Chiral HPLC analysis (OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 254 nm):*

**Racemic 2.3l:**

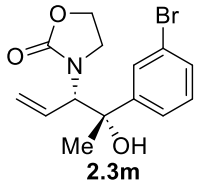



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 13.320 | 53.086 | 5302 | M | 0.000 |
| 2 | 15.368 | 46.914 | 4429 | M | 0.000 |
| Total | | 100.000 | 9731 | | 0.000 |

**2.3l from the $Cu(OAc)_2$ /W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 11.947 | 3.445 | 1254 | M | 0.000 |
| 2 | 15.090 | 96.555 | 31417 | M | 0.000 |
| Total | | 100.000 | 32671 | | 0.000 |

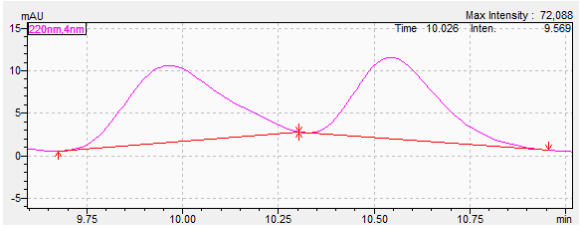


**2.3m**

**3-((3*S*,4*S*)-4-(3-bromophenyl)-4-hydroxypent-1-en-3-yl)oxazolidin-2-one** (**2.3m**): According to the Method A general procedure, a crude mixture of 74:26 **2.3m**/**2.7m** was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 67.0 mg (82%) of **2.3m** in 89 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a single diastereomer as a 92/8 mixture of enantiomers (allene rearrangement products *N*-allyl and *N*-propenyl oxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 80% recovery with 98/2 er. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.18 (30% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 7.64 (s, 1H), 7.40 (t, *J* = 8.7 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.26 (ddd, *J* = 16.91 Hz, *J* = 9.8 Hz, *J* = 8.6 Hz, 1H), 5.45 (d, *J* = 10.6 Hz, 1H), 5.37 (d, *J* = 17.6 Hz, 1H), 4.50 (br s, 1H), 4.05 – 4.15 (m, 3H), 3.57 (q, *J* = 7.6 Hz, 1H), 3.29 (q, *J* = 7.55 Hz, 1H) 1.50 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 148.5, 130.3, 130.1, 129.9, 129.8, 127.8, 123.5, 122.5, 121.2, 76.8, 67.1, 62.8, 45.3, 29.2 ppm. HRMS (DART) *m/z* calcd for $C_{14}H_{17}BrNO_3$ $[M + H]^+$: 326.0392; Found $[M + H]^+$: 326.0380.

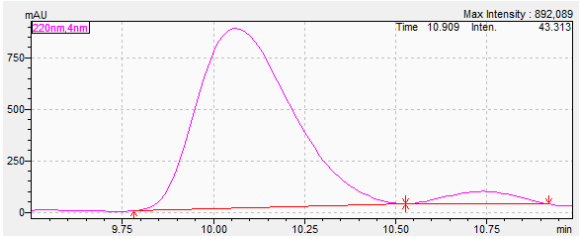
*Chiral HPLC analysis (AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 220 nm):*

**Racemic 2.3m:**

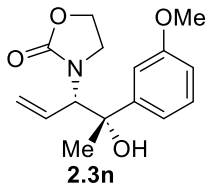



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 9.966 | 52.848 | 9083 | M | 0.000 |
| 2 | 10.543 | 47.152 | 9589 | M | 0.000 |
| Total | | 100.000 | 18672 | | 0.000 |

**2.3m from the Cu(OAc)$_2$ /W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 10.062 | 95.273 | 872763 | M | 95.273 |
| 2 | 10.741 | 4.727 | 61775 | M | 4.727 |
| Total | | 100.000 | 934538 | | 100.000 |

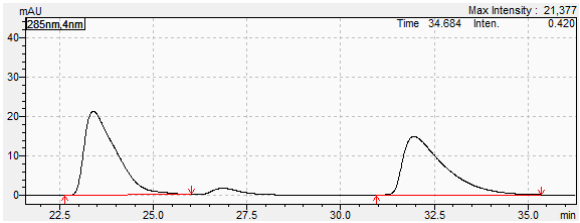


**2.3n**

**3-((3*S*,4*S*)-4-hydroxy-4-(3-methoxyphenyl)pent-1-en-3-yl)oxazolidin-2-one** (**2.3n**): According to the Method A general procedure, a crude mixture of 70:30 **2.3n**/**2.7n** was obtained and purified by silica gel chromatography (eluent: 0 – 20% EtOAc in $CH_2Cl_2$) to provide 37.4 mg (54%) of **2.3n** as a thick glass as a single diastereomer as a 96/4 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.41 (10% EtOAc/ $CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.27 (t, *J* = 8.5 Hz, 1H), 7.09 (s, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.80 (dd, *J* = 8.3 Hz, *J* = 2.1 Hz, 1H), 6.29 (ddd, *J* = 18.0 Hz, *J* = 9.8 Hz, *J* = 9.0 Hz, 1H), 5.43 (d, *J* = 10.6 Hz, 1H), 5.36 (d, *J* = 17.3 Hz, 1H), 4.43 (s, 1H), 4.17 (d, *J* = 8.4 Hz, 1H), 4.00 – 4.07 (m, 2H), 3.82 (s, 3H), 3.56 (q, *J* = 9.9 Hz, 1H), 3.28 (q, *J* = 8.5 Hz, 1H), 1.51 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.5, 158.8, 147.7, 130.7, 129.1, 120.6, 120.2, 116.9, 112.2, 111.3, 110.5, 76.9, 66.8, 62.7, 61.8, 55.2, 45.1, 44.1, 29.2 ppm. HRMS (DART) *m/z* calcd for $C_{15}H_{20}NO_4$ $[M + H]^+$: 278.1392; Found $[M + H]^+$: 278.1379.

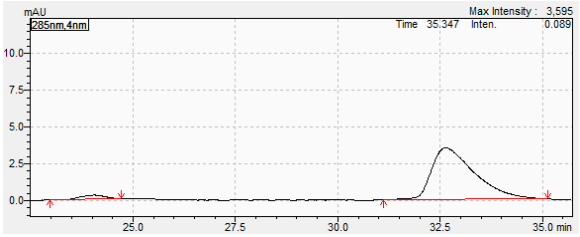
*Chiral HPLC analysis (OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 285 nm):*

**Racemic 2.3n:**

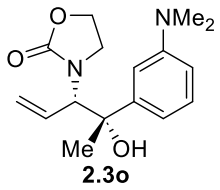



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 23.396 | 52.108 | 21289 | M | 52.108 |
| 2 | 31.954 | 47.892 | 14863 | M | 47.892 |
| Total | | 100.000 | 36152 | | 100.000 |

**2.3n from the $Cu(OAc)_2$ /W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 24.045 | 4.292 | 288 | M | 4.292 |
| 2 | 32.647 | 95.708 | 3525 | M | 95.708 |
| Total | | 100.000 | 3813 | | 100.000 |

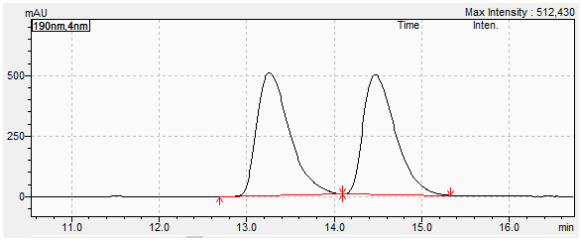


**2.3o**

**3-((3*S*,4*S*)-4-(3-(dimethylamino)phenyl)-4-hydroxypent-1-en-3-yl)oxazolidin-2-one** (**2.3o**): According to the Method A general procedure, a crude mixture of 72:28 **2.3o**/**2.7o** was obtained and purified by silica gel chromatography (eluent: 0 – 30% EtOAc in $CH_2Cl_2$) to provide 39.9 mg (55%) of **2.3o** as a thick yellow glass as a single diastereomer as a 92/8 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.19 (10% EtOAc/ $CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.19 (t, *J* = 8.2 Hz, 1H), 6.90 (br s, 1H), 6.73 (d, *J* = 9.4 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 6.29 (ddd, *J* = 17.8 Hz, *J* = 9.1 Hz, *J* = 9.3 Hz, 1H), 5.40 (d, *J* = 9.93 Hz, 1H), 5.34 (d, *J* = 16.6 Hz, 1H), 4.33 (s, 1H), 4.16 (d, *J* = 8.8 Hz, 1H), 3.98 – 4.04 (m, 2H), 3.50 (q, *J* = 7.9 Hz, 1H), 3.24 (q, *J* = 8.3 Hz, 1H), 2.94 (s, 6H), 1.50 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.8, 150.5, 146.6, 131.0, 130.8, 128.7, 120.3, 112.7, 111.0, 109.1, 66.8, 62.7, 45.1, 40.7, 29.3 ppm. HRMS (DART) *m/z* calcd for $C_{16}H_{23}N_2O_3$ $[M + H]^+$: 291.1709; Found $[M + H]^+$: 291.1714.

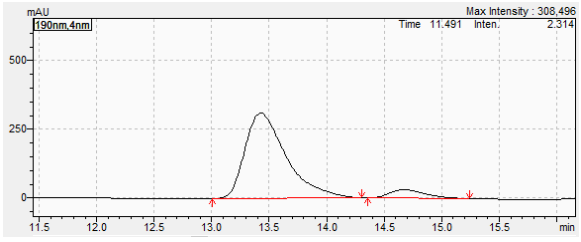
*Chiral HPLC analysis (AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 190 nm):*

**Racemic 2.3o:**

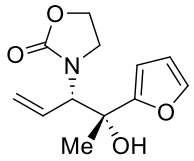



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 13.259 | 50.931 | 508325 | M | 50.931 |
| 2 | 14.469 | 49.069 | 496699 | M | 49.069 |
| Total | | 100.000 | 1005023 | | 100.000 |

**Asymmetric Reaction:**



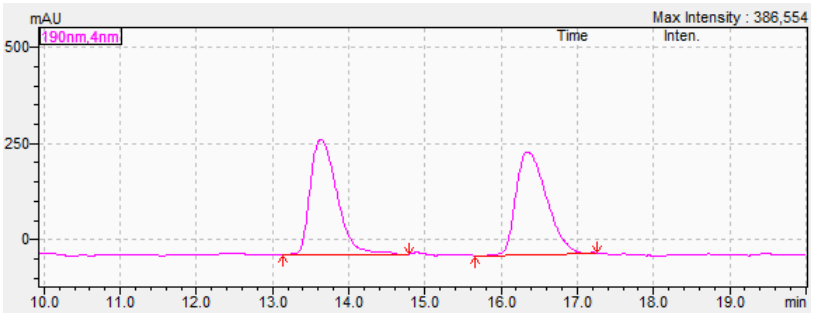

| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 13.426 | 91.997 | 309634 | M | 91.997 |
| 2 | 14.672 | 8.003 | 31327 | M | 8.003 |
| Total | | 100.000 | 340961 | | 100.000 |



**2.3p**

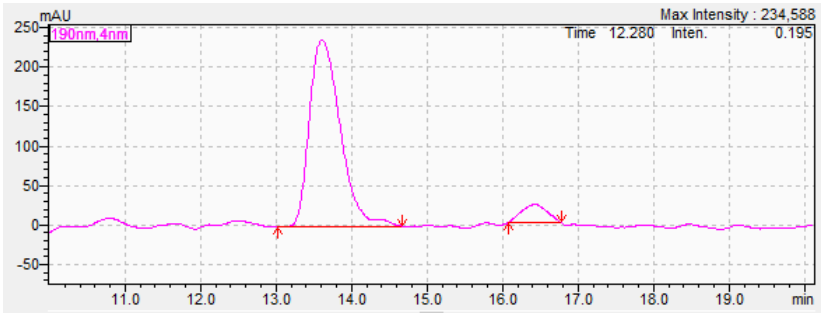
**3-((3*S*,4*R*)-4-(furan-2-yl)-4-hydroxypent-1-en-3-yl)oxazolidin-2-one (2.3p)**: According to the Method A general procedure, a crude mixture of >99:1 **2.3p**/**2.7p** was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 45.1 mg (76%) of **2.3p** in 90 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a single diastereomer as a 92/8 mixture of enantiomers (allene rearrangement products *N*-allyl and *N*-propenyl oxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 73% recovery with >99 er. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.10 (30% EtOAc/hexanes) $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 7.35 (s, 1H), 6.3 ( d, *J* = 2 Hz, 2H), 6.23 (ddd, *J* = 19.0, 17.2, 9.4, 1H), 5.42 (d, *J* = 10.2 Hz, 1H), 5.33 (d, *J* = 17.1 Hz, 1H), 4.63 (br, s, 1H), 4.21 (dd, *J* = 17.1 Hz, *J* = 8.9 Hz, 1H), 4.10 - 4.18 (m, 2H), 3.55 (dt, *J* = 8.4 Hz, *J* = 8.4, 1H), 3.34 (dt, *J* = 7.9 Hz, *J* = 8.9 Hz, 1H), 1.53 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.1, 158.3, 141.5, 130.1, 121.2, 110.6, 105.8, 74.5, 66.1, 62.9, 45.1, 25.9 ppm. HRMS (DART) *m/z* calcd for $C_{12}H_{16}NO_4$ $[M + H]^+$: 238.1079; Found $[M + H]^+$: 239.1079.

**Racemic 2.3p:**

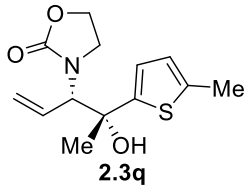



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 13.633 | 49.549 | 299112 | M | 0.000 |
| 2 | 16.347 | 50.451 | 266935 | M | 0.000 |
| Total | | 100.000 | 566047 | | 0.000 |

**2.3p from the Cu(OAc)$_2$ /W8 reaction:**




| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 13.605 | 92.354 | 236268 | M | 0.000 |
| 2 | 16.426 | 7.646 | 23189 | M | 0.000 |
| Total | | 100.000 | 259458 | | 0.000 |

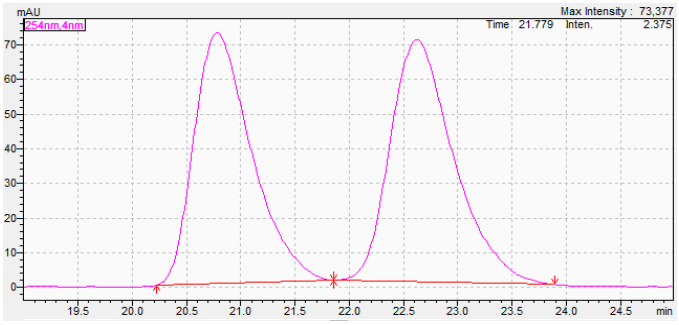


**2.3q**

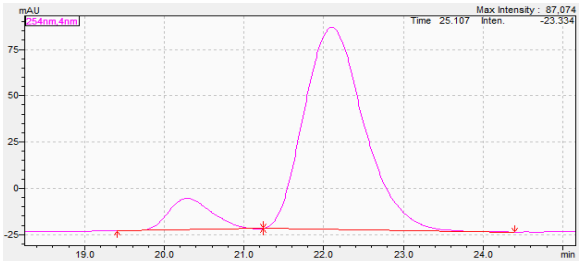
**3-((3*S*,4*R*)-4-hydroxy-4-(5-methylthiophen-2-yl)pent-1-en-3-yl)oxazolidin-2-one** (**2.3q**): According to the Method A general procedure, a crude mixture of >99:1 **2.3q**/**2.7q** was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 59.5 mg (89%) of **2.3q** in 91 wt% purity by quantitative $^{1}$H-NMR spectroscopy using dimethylfumarate as analytical standard as a yellow solid as a single diastereomer as a 90/10 mixture of enantiomers (allene rearrangement products *N*-allyl and *N*-propenyl oxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 70 recovery with 75/25 er. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.20 (30% EtOAc/hexanes). $^{1}$HNMR ($CDCl_3$, 600 MHz) δ: 6.76 (d, *J* = 3.3 Hz, 1H), 6.60 (d, *J* = 3.3 Hz, 1H), 6.22 (ddd, *J* = 17.3 Hz, *J* = 10.0 Hz, *J* = 8.6 Hz, 1H), 5.41 (d, *J* = 10.3 Hz, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 4.40 (br s, 1H), 4.14 – 4.22 (m, *2*H), 4.06 (d, *J* = 8.8 Hz, 1H), 3.65 (dt, *J* = 6.9 Hz, *J* = 8.8 Hz, 1H), 3.41 (dt, *J* = 8.2 Hz, *J* = 8.6 Hz, 1H), 2.44 (s, *3*H), 1.57 (s, *3*H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 148.0, 138.4, 130.6, 127.9, 124.9, 122.7, 121.1, 76.1, 67.5, 62.8, 44.9, 29.7, 15.2 ppm. HRMS (DART) *m/z* calcd for $C_{13}H_{18}NO_3S$ $[M + H]^+$: 268.1007; Found $[M + H]^+$: 268.0996.

*Chiral HPLC analysis (AD-3 x 254 mm, 1.0 mL/min, 95:5 heptane:IPA, 254 nm):*

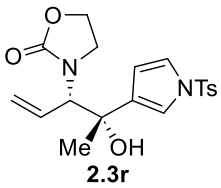
**Racemic 2.3q:**




**2.3q from the Cu(OAc)$_2$ /W8 reaction:**




| Peak# | Ret. Time | Area% | Height | Mark |
|---|---|---|---|---|
| 1 | 20.287 | 9.962 | 16965 | M |
| 2 | 22.103 | 90.038 | 109340 | M |
| Total | | 100.000 | 126305 | |

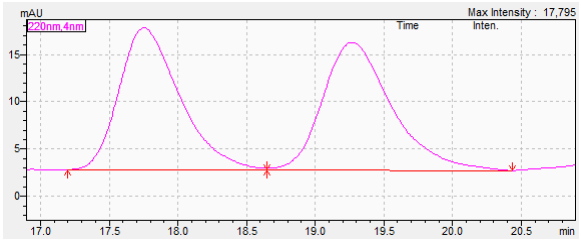


**2.3r**

**3-((3*S*,4*R*)-4-hydroxy-4-(1-tosyl-1H-pyrrol-2-yl)pent-1-en-3-yl)oxazolidin-2-one** (**2.3r**): According to the Method A general procedure, a crude mixture of >99:1 **2.3r**/**2.7r** was obtained and purified by silica gel chromatography (eluent: 20 – 70% EtOAc in hexanes) to provide 78.1 mg (80%) of **2.3r** as a thick glass as a single diastereomer as a 71/29 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.07 (30% EtOAc/hexanes). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.70 (d, *J* = 8.6 Hz, 2H), 7.9 (d, *J* = 8.6 Hz, 2H), 7.13 (t, *J* = 2.0 Hz, 1H), 7.10 – 7.12 (m, 1H), 6.22 – 6.25 (m, 1H), 6.15 (ddd, *J* = 17.2 Hz, *J* = 10.3 Hz, *J* = 8.8 Hz, 1H), 5.39 (dd, *J* = 10.1 Hz, *J* = 0.7, 1H), 5.30 (dd, *J* = 17.0 Hz, *J* = 0.8 Hz, 1H), 3.97 (dd, *J* = 9.2 Hz, *J* = 1.1 Hz, 1H), 3.92 – 3.96 (m, 1H), 3.87 (br s, 1H), 3.49 (dt, *J* = 6.6 Hz, *J* = 8.9 Hz, 1H), 3.26 (t, *J* = 7.7 Hz, *J* = 8.4 Hz, 1H), 2.40 (s, 3H), 1.44 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.7, 144.8, 135.9, 135.3, 130.3, 129.9, 126.6, 121.3, 120.9, 116.9, 111.6, 74.2, 66.1, 62.4, 44.3, 28.3, 21.5 ppm. HRMS (DART) *m/z* calcd for $C_{19}H_{23}N_2O_5S$ $[M + H]^+$: 391.1328; Found $[M + H]^+$: 391.1352.

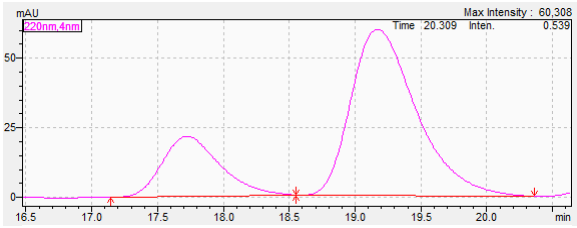
*Chiral HPLC analysis (AD-3 x 220 mm, 1.0 mL/min, 90:10 heptane:IPA, 220 nm):*

**Racemic 2.3r:**

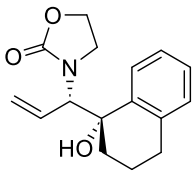



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 17.754 | 49.440 | 14981 | | 0.000 |
| 2 | 19.269 | 50.560 | 13508 | V | 0.000 |
| Total | | 100.000 | 28489 | | 0.000 |

**2.3r from the $Cu(OAc)_2$ /W8 reaction:**



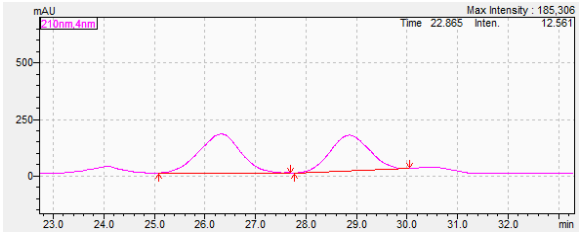

| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 17.724 | 24.010 | 21470 | M | 0.000 |
| 2 | 19.169 | 75.990 | 59608 | M | 0.000 |
| Total | | 100.000 | 81078 | | 0.000 |



2.3s

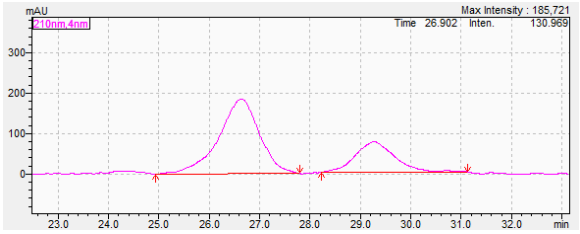
**3-((*S*)-1-((*S*)-1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)allyl)oxazolidin-2-one** (**2.3s**): According to the Method A general procedure, a crude mixture of >99:1 **2.3s**:**2.7s** and 1:2 b/l was obtained and purified by silica gel chromatography (eluent: 10 – 50% EtOAc in hexanes) to provide 29.1 mg (28%) of **2.3s** in 88 wt% purity by quantitative $^1$H-NMR spectroscopy using dimethylfumarate as analytical standard as a white solid as a single diastereomer as a 71/29 mixture of enantiomers (allene rearrangement products *N*-allyl and *N*-propenyl oxazolidin-2-one could not be removed by chromatography). Analytically and diastereomerically pure material could be obtained by slurrying the material in 10 vol. of hot 30% EtOAc in hexanes followed by cooling to rt in 66% recovery with 70/30 er. The stereochemistry was assigned by analogy to that of **2.3a**. $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.48 – 7.52 (m, 1H), 7.15 – 7.23 (m, 2H), 7.07 – 7.10 (m, 1H), 6.17 (ddd, *J* = 17.6 Hz, *J* = 10.5 Hz, *J* = 8.8 Hz, 1H), 5.35 (d, *J* = 10.0 Hz, 1H), 5.28 (d, *J* = 17.6 Hz, 1H), 4.34 (d, *J* = 8.5 Hz, 1H), 4.28 (dt, *J* = 8.8 Hz, *J* = 8.2 Hz, 1H), 4.22 (dt, *J* = 6.2 Hz, 9.1 Hz, 1H), 3.75 (dt, *J* = 6.4 Hz, *J* = 8.8 Hz, 1H), 3.40 (br, s, 1H), 3.30 (q, *J* = 8.8 Hz, 1H), 2.84 (t, *J* = 7.0 Hz, 2H), 2.14 (dt, *J* = 13.2 Hz, *J* = 5.3 Hz, 1H), 1.85 – 1.92 (m, 2H), 1.77 – 1.83 (m, 1H), 1.55 (s, 3H) ppm. $CDCl_3$: δ 159.3, 140.0, 136.6, 131.1, 129.0, 127.6, 126.2, 125.8, 120.9, 75.4, 64.6, 62.7, 44.6, 44.6, 34.5, 28.6, 19.0. HRMS (DART) *m/z* calcd for $C_{16}H_{20}NO_3$ $[M + H]^+$: 274.1444; Found $[M + H]^+$: 274.1444.

**Racemic 2.3s:**

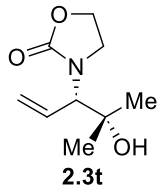



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 26.333 | 53.326 | 171682 | M | 0.000 |
| 2 | 28.864 | 46.674 | 158237 | M | 0.000 |
| Total | | 100.000 | 329919 | | 0.000 |

**2.3s from the Cu(OAc)$_2$ /W8 reaction:**



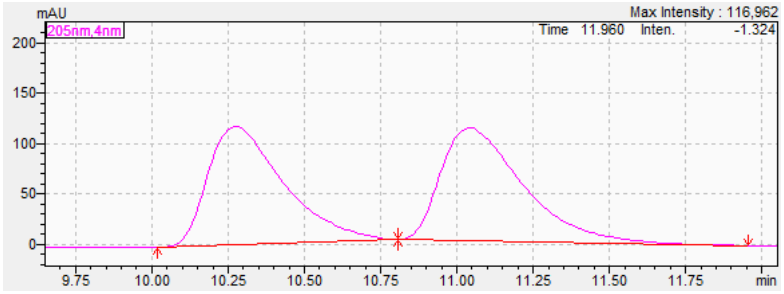

| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 26.638 | 71.600 | 185354 | M | 0.000 |
| 2 | 29.276 | 28.400 | 75477 | M | 0.000 |
| Total | | 100.000 | 260830 | | 0.000 |



**2.3t**

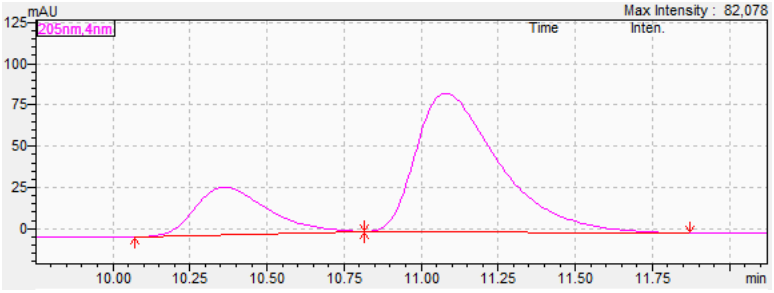
**(*S*)-3-(4-hydroxy-4-methylpent-1-en-3-yl)oxaxolidin-2-one** (**2.3t**): According to the general procedure, the product was purified by silica gel chromatography (eluent: 0 – 40% EtOAc in $CH_2Cl_2$) to provide 23.6 mg (51%) of **2.3t** as a white solid as a single diasteromer. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.24 (40% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 6.07 (ddd, *J* = 17 Hz, *J* = 10Hz, *J* = 8.8 Hz, 1H), 5.38 (d, *J* = 10 Hz, 1H), 5.32 (d, *J* = 17 Hz, 1H), 4.35 (t, *J* = 8.5 Hz, 2H), 3.94 (d, *J* = 8.8 Hz, 1H), 3.82 (dd, *J* = 16 Hz, *J* = 8.5 Hz, 1H), 3.62 (dd, *J* = 16 Hz, *J* = 8.5 Hz, 1H), 2.51 (s, 1H), 1.31 (s, 3H), 1.24 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.1, 131.1, 121.0, 72.9, 65.6, 62.6, 43.7, 27.8, 27.5. HRMS (DART) *m/z* calcd for $C_9H_{16}NO_3$ [M + H]$^+$: 186.1130; Found [M + H]$^+$: 186.1131.

**Racemic 2.3t:**

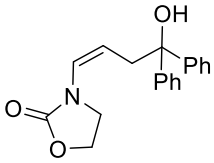



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 10.273 | 48.961 | 117290 | M | 48.961 |
| 2 | 11.042 | 51.039 | 111953 | M | 51.039 |
| Total | | 100.000 | 229243 | | 100.000 |

**2.3t from the Cu(OAc)$_2$/W8 reaction:**

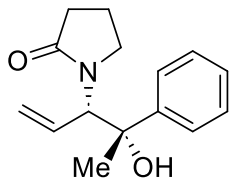



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 10.362 | 22.955 | 28738 | M | 0.000 |
| 2 | 11.080 | 77.045 | 83956 | M | 0.000 |
| Total | | 100.000 | 112694 | | 0.000 |



**2.8u**

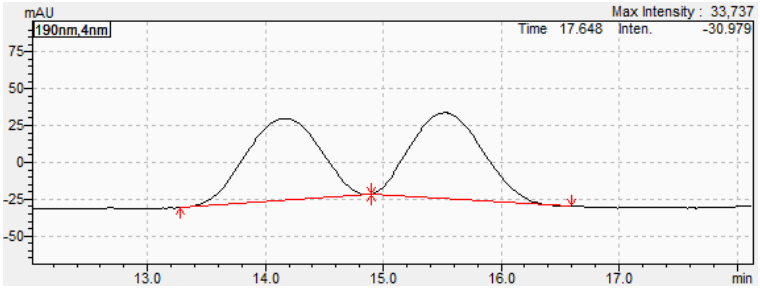
**(*Z*)-3-(4-hydroxy-4,4-diphenylbut-1-en-1-yl)oxaxolidin-2-one** (**2.8u**): According to the general procedure, the product was purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 24.2 mg (33%) of **2.8u** as a white solid. $R_f$ = 0.27 (10% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.35 (d, *J* = 8.0 Hz, 4H), 7.21 (t, *J* = 8.0 Hz, 4H), 7.12 (t, *J* = 8.0 Hz, 2H), 6.11 (d, *J* = 9.4 Hz, 1H), 4.77 (q, *J* = 9.1 Hz, 1H), 4.26 (t, *J* = 8.3 Hz, 2H), 3.79 (t, *J* = 7.8 Hz, 2H), 3.26 (s, 1H), 3.07 (d, *J* = 7.8 Hz, 2H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 156.8, 146.4, 128.2, 126.9, 125.8, 125.8, 112.1, 77.1, 62.2, 45.9, 39.2. HRMS (DART) *m/z* calcd for $C_{19}H_{20}NO_3$ $[M + H]^+$: 310.1443; Found $[M + H]^+$: 310.1435.



**2.15**

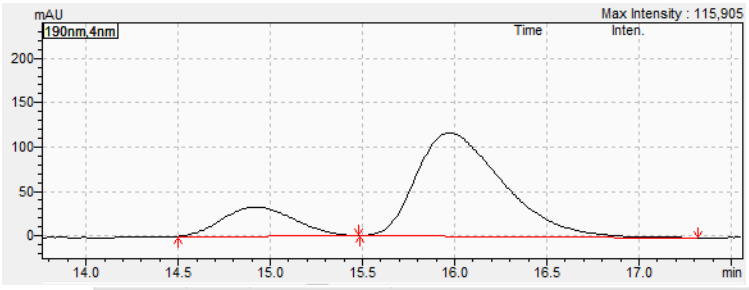
**1-((3*S*,4*S*)-4-hydroxy-4-phenylpent-1-en-3-yl)pyrrolidin-2-one** (**2.15**): According to the Method A general procedure, a crude mixture of 63:37 *b*-**2.15**:*l*-**2.15** was obtained and purified by silica gel chromatography (eluent: 0 – 30% EtOAc in $CH_2Cl_2$) to provide 40.1 mg (65%) of **2.15** as a white solid as a single diastereomer as a 82:18 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.3a**. $R_f$ = 0.40 (30% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.46 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = *8.2* Hz, 2H), 7.22 (t, *J* = *7.4* Hz , 1H), 6.37 (ddd, *J* = 18.1 Hz, *J* = 9.6 Hz, 8.50 Hz, 1H), 6.33 (s, 1H), 5.36 (d, *J* = 9.6 Hz, 1H), 5.24 (d, *J* = 17.4 Hz, 1H), 3.92 (d, *J* = *8.4* Hz, 1H), 3.32 (dt, *J* = *10.*8 Hz, 6.9 Hz, 1H), 2.88 (dt, *J* = *12.4 Hz,* 5.5 Hz, 1H), 2.17 (ddd, *J* = 17.6 Hz, *J* = *10.0* Hz, *J* = 7.8 Hz, 1H), 2.02 (ddd, *J* = *1*7.3 Hz, *J* = 10.0 Hz, *J* = 6.5 Hz, 1H), 1.72 – 1.82 (m, 1H), 1.53 – 1.61 (m, 1H), 1.50 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 176.4, 146.7, 131.3, 127.9, 126.6, 124.6, 119.4, 76.75, 70.3, 50.6, 31.6, 28.5, 18.9 ppm. HRMS (DART) *m/z* calcd for $C_{15}H_{20}NO_2$ $[M + H]^+$: 246.1494; Found $[M + H]^+$: 246.1485.

*Chiral HPLC analysis (Chiralcel OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:IPA, 190 nm):*
**Racemic 2.15:**



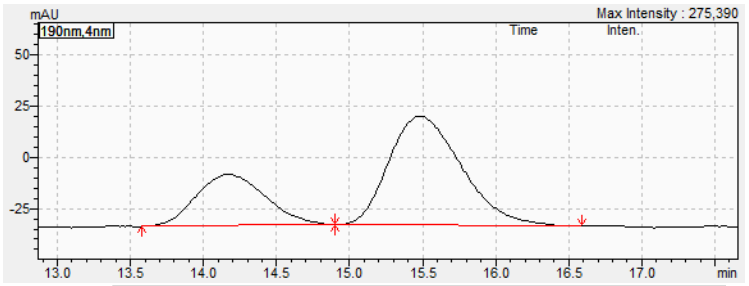

| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 14.153 | 49.760 | 55507 | M | 49.760 |
| 2 | 15.529 | 50.240 | 58213 | M | 50.240 |
| Total | | 100.000 | 113720 | | 100.000 |

**2.15 from the $Cu(OAc)_2$/W8 reaction:**

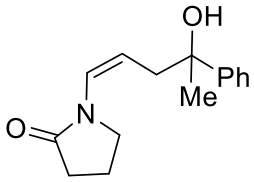



| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 14.920 | 18.336 | 49041 | M | 18.336 |
| 2 | 15.972 | 81.664 | 182395 | M | 81.664 |
| Total | | 100.000 | 231436 | | 100.000 |

**2.15 from the CuI/W8/KO$^t$Bu reaction:**



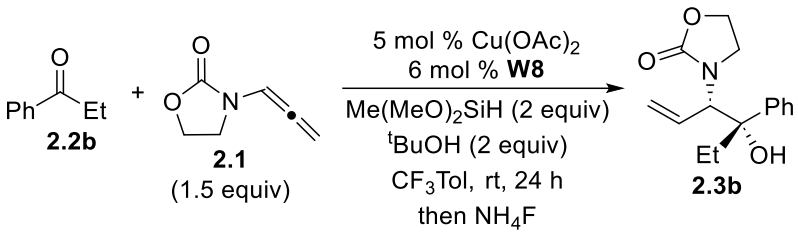

| Peak | Ret. Time | Area% | Height | Mark | Conc. |
|---|---|---|---|---|---|
| 1 | 14.158 | 30.963 | 24809 | M | 30.963 |
| 2 | 15.486 | 69.037 | 53117 | M | 69.037 |
| Total | | 100.000 | 77926 | | 100.000 |




*l*-**2.15**

**(*Z*)-1-(4-hydroxy-4-phenylpent-1-en-1-yl)pyrrolidin-2-one** (*l*-**2.15**): According to the Method A general procedure, a crude mixture of 63:37 *b*-**2.15**:*l*-**2.15** was obtained and purified by silica gel chromatography (eluent: 0 – 50% EtOAc in $CH_2Cl_2$) to provide 25.0 mg (41%) of *l*-**2.15** as a thick glass as a single diastereomer. $R_f$ = 0.21 (30% EtOAc/ $CH_2Cl_2$). $R_f$ = 0.12 (30% EtOAc/hexanes). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.47 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.23 (t, *J* = 7.6 Hz, 1H), 6.14 (d, *J* = 9.8 Hz, 1H), 4.94 (q, *J* = *8.4* Hz, 1H), 3.63 (t, *J* = 6.9 Hz, 2H), 3.57 (br s, 1H), 2.67 (p, *J* = 8.6 Hz, 2H), 2.43 (td, *J* =*8* .4 Hz, , *J* = 2.6 Hz, 2H), 2.06 (p, *J* = *7*.6 Hz, 2H), 1.58 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 174.6, 148.1, 128.2, 126.5, 125.2, 124.8, 115.4, 73.4, 49.3, 41.8, 30.8, 30.3, 18.3 ppm. HRMS (DART) *m/z* calcd for $C_{15}H_{20}NO_3$ $[M + H]^+$: 246.1494; Found $[M + H]^+$: 246.1484.

**Reaction Performed on 1.0 mmol scale:**



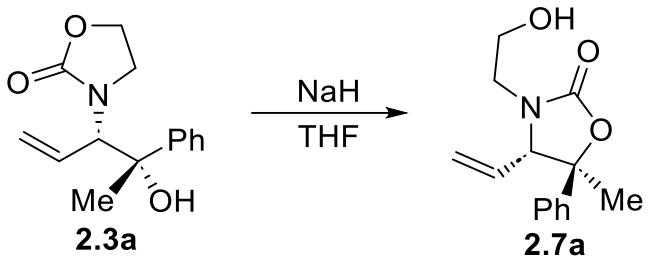

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 9.2 mg (0.05 mmol) of $Cu(OAc)_2$ and 56.0 mg (0.06 mmol) of Walphos 8. α,α,α-Trifluorotoluene (2.0 mL) was then added, and the mixture was allowed to stir for 10 min. Alleneamide **2.1** (188.0 mg, 1.5 mmol) followed by ketone **2.2b** (1.0 mmol) and $^{t}$BuOH ( 0.192 mL, 2.00 mmol) was then charged. The vial was then sealed with a crimp-cap septum and removed from the glove-box. The reaction was then cooled in an ice bath, and dimethoxymethylsilane (0.248 µL, 2.0 mmol) was then charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)* The mixture was then allowed to warm to rt and stirred for 24 h. The reaction was then quenched by the addition of 380 mg of NH4F and 6.0 mL of MeOH followed by agitation at rt for 30 min – 1 h. The crude mixture was then transferred to a separatory funnel to which 20 mL of 5% NaHCO3 was then charged and agitated. The mixture was then extracted with $CH_2Cl_2$ (2x10mL). The combined organics were dried with $Na_2SO_4$ and concentrated *in vacuo*. An aliquot of the crude mixture was analyzed by $^{1}$HNMR spectroscopy to determine the dr (>99) and b/l (>99) ratio. The crude residue was then purified by flash chromatography on silica gel (gradient, 0 – 20% EtOAc in $CH_2Cl_2$). The first spot to elute was isolated as a (**W8**)Cu complex that was then de-complexed for recovery of **W8** (see below). The product spot ($R_f$ = 0.31, 10% EtOAc in $CH_2Cl_2$) was then collected and concentrated *in vacuo* to afford 188 mg (72%) of **2.3b**. Enantioselectivity was determined by chiral HPLC analysis to be 96/4.

**Recovery of W-8:** The (**W8**)Cu complex obtained from the above reaction was further purified by flash chromatography on silica gel (gradient, 0 – 15% EtOAc in hexanes) to afford 71.0 mg of an orange solid. This material was then dissolved in 3.0 mL of 2:1 pentane:MTBE and then 1 mL of 50% $NH_4OH$ solution was added. The mixture was then agitated vigorously for 5 minutes upon which the lower blue aqueous layer was removed. The organic layer was then washed twice with 1 mL of 50% $NH_4OH$, dried with $Na_2SO_4$ and concentrated *in vacuo* to yield 45.1 mg (81% recovery) of **W8** as an orange solid. Use of this recovered ligand in the Cu-catalyzed reductive coupling with propiophenone provided identical results to that obtained with the commercially obtained **W8**.

**Large Scale recrystallization of 2.3a:**

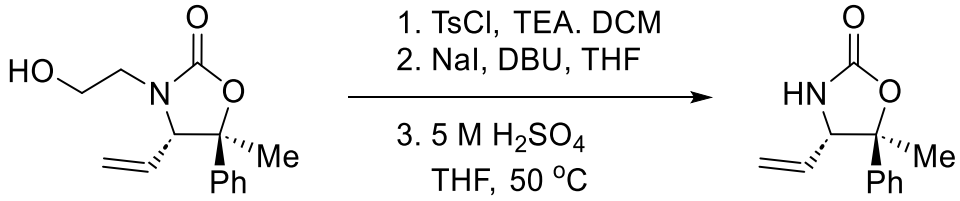
To a 20 mL crimp-cap vial with a stir-bar was charged 357.0 mg of **2.3a** of 91 wt% with 90/10 er. The vial was then added 2.0 mL of 30% EtOAc/Hexanes solution and heated to 40 °C whilst stirring vigorously. After 30 min of stirring, the mixture was allowed to stir at rt for 30 min and then filtered to yield 237.0 mg (73%) of analytically pure **2.3a** with >99:1 er.

**Protecting Group Removal:**




**2.3a** **2.7a**

To a solution of 210 mg (0.850 mmol) of 2.3a in 2.0 mL of THF at 0 °C was charged 34 mg (0.850 mmol, 60%) of NaH. The reaction was then allowed to warm to room temperature and stirred for 1 h. The reaction was then quenched by the addition of 5 mL of 1M HCl and extracted with $CH_2Cl_2$ (3 X 10 mL). The combined organics were dried with $Na_2SO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (silica gel, gradient, 20 – 50% EtOAc/hexanes) to afford 209.1 mg (99%) of **2.7a** as a thick waxy oil. $R_f$ = 0.18 (10% EtOAc/$CH_2Cl_2$). $^1$HNMR (CDCl3, 600 MHz) δ: 7.35 – 7.41 (m, 4H), 7.32 (t, *J* = 6.7 Hz, 1H), 5.91 (dt, *J* = 16.6 Hz, *J* = 10.1 Hz, 1H), 5.53 (d, *J* = 10.2 Hz, 1H), 5.43 (d, *J* = 16.2 Hz, 1H), 5.22 (d, *J* = 9.5 Hz, 1H), 3.67 – 3.75 (m, 2H), 3.45 (ddd, *J* = 14.8 Hz, *J* = 6.3 Hz, *J* = 4.2 Hz, 1H), 3.19 (ddd, *J* = 14.6 Hz, *J* = 6.9 Hz, *J* = 3.7 Hz, 1H), 1.63 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.0, 144.1, 132.3, 128.7, 127.9, 123.8, 123.1, 83.4, 70.8, 60.8, 45.0, 23.9 ppm. HRMS (DART) *m/z* calcd for $C_{14}H_{18}NO_3$ $[M + H]^+$: 248.1287; Found $[M + H]^+$: 248.1287.

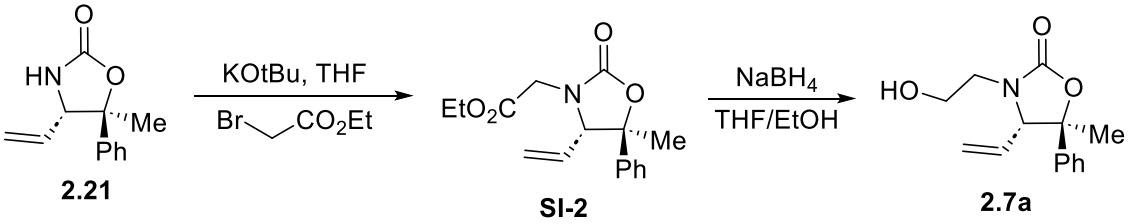



**2.7a** **2.21**

To a solution of 209.1 mg (0.846 mmol) of **2.7a** in 4.2 mL of $CH_2Cl_2$ at 0 °C was charged 141 µL (1.02 mmol) of triethylamine followed by 177 mg (0.931 mmol) of TsCl. The mixture was stirred for 30 min at 0 °C, allowed to warm to rt and stirred for 8 h. To the mixture was charged 2 mL of 10% $NH_4Cl$ followed by extraction with $CH_2Cl_2$ (3x2mL). The combined organics were dried with anhydrous $Na_2SO_4$, and volatile material was removed *in vacuo*. The crude residue was then dissolved in 8.0 mL of glyme and charged with 360 mg (2.54 mmol) of NaI and 383 µL (2.54 mmol) of DBU and refluxed for 8 h. The mixture was diluted with 30 mL of 1:1 mixture of $Et_2O$ and $H_2O$ and stirred for 10 min upon which organics were extracted with $Et_2O$ (2x10 mL). The combined organic layers were washed with brine, dried with anhydrous $Na_2SO_4$, filtered, and volatiles removed *in vacuo*. The crude residue was then dissolved in 5.0 mL of THF in a 20 mL scintillation vial. To the solution was added 1.7 mL (8.46 mmol) of 5.0 M aqueous $H_2SO_4$. The vial was purged with argon, sealed, and immersed in an oil bath at 50 °C. After 2.5 h, the reaction was cooled to rt and 10 mL of saturated aqueous $NaHCO_3$ was charged. The mixture was extracted with $CH_2Cl_2$ (3x5mL), dried with anhydrous $Na_2SO_4$, and concentrated *in vacuo*. The crude residue

was purified by flash chromatography (silica gel, gradient, hexanes to 60% EtOAc/hexanes) to afford 134.2 mg (78%) of **2.21** as a White solid. $R_f$ = 0.19 (40% EtOAc/hexanes). $^1$HNMR (CDCl3, 600 MHz) δ: 7.30 – 7.43 (m, 5H), 5.97 (ddd, *J* = 17 Hz, *J* = 10 Hz, *J* = 7.7 Hz, 1H), 5.41 (d, *J* = 10 Hz, 1H), 5.40 (d, *J* = 17 Hz, 1H), 5.27 (br s, 1H), 4.30 (d, *J* = 7.7 Hz, 1H), 1.62 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 157.8, 144.0, 132.9, 128.7, 127.9, 123.9, 120.4, 85.9, 65.8, 23.8 ppm. HRMS (DART) *m/z* calcd for $C_{2.3h14}NO_2$ $[M + H]^+$: 204.1025; Found $[M + H]^+$: 204.1025.

**Absolute and relative stereochemistry determination:**



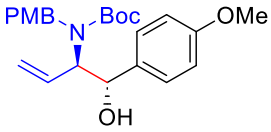

**2.21** **SI-2** **2.7a**

Diastereo- and enantiopure **23** prepared by our previous work[104] was converted to **2.7a** by the given two-step procedure[142] and then compared to **2.7a** prepared using the current $Cu(OAc)_2$/**W8** catalysts system followed by carbonate rearrangement. The major diastereomer and enantiomer formed from the $Cu(OAc)_2$/**W8** catalysts system was the same as that of authentic **2.7a** prepared by the given procedure by comparison of the authentic material by $^1$HNMR spectropscopy and chiral HPLC analysis.

**Alkylation:** To a solution of **2.21** (20.0 mg, 0.0984 mmol) in 0.25 mL of THF at 0 ºC was charged 0.11 mL of a 1.0 M (0.11 mmol) solution of KO$^t$Bu in THF. The mixture was then allowed to stir for 10 min before the addition of 12 μL (11 mg, 0.11 mmol) of ethyl bromoacetate. The mixture was warmed to rt and allowed to stir for 3 h. To the reaction was added 2 mL of 10% aqueous $NH_4Cl$, and the mixture was extracted with $CH_2Cl_2$ (3x2mL). The combined organics were dried with anhydrous $Na_2SO_4$, filtered, and concentrated *in vacuo* to afford **SI-2**. This material was used directly in the next step without further purification.

**Reduction:** To a solution of **SI-2** in 0.25 mL of 7:1 THF:EtOH was charged 11.2 mg (0.295 mmol) of $NaBH_4$, and the resultant mixture was allowed to stir at rt for 3 h. The reaction was then cooled to 0 ºC, and 2 mL of 10% aqueous $NH_4Cl$ was carefully added (gas evolution!). The mixture was then warmed to rt and extracted with EtOAc (3x2mL). The combined organics were dried with anhydrous $Na_2SO_4$, filtered, and concentrated *in vacuo* to afford 17.1 mg (70%, 2 steps) of **2.7a** as a colorless oil. $^1$HNMR spectroscopy matched that of the material prepared using the current $Cu(OAc)_2$/**W-8** catalysts system followed by carbonate rearrangement (Scheme 3). Chiral HPLC analysis of this material relative to the material prepared from the $Cu(OAc)_2$/**W8** catalysts system followed by carbonate rearrangement is given below:

*ii. Aldehyde Coupling*

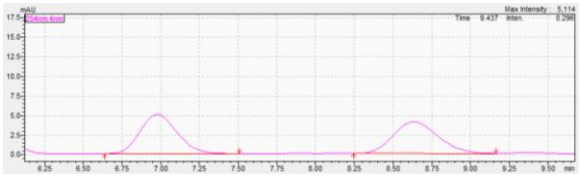



***2.24a***

***tert*-butyl ((*1S,2R*)-1-hydroxy-1-(4-methoxyphenyl)but-3-en-2-yl)(4-methoxybenzyl) carbamate (2.24a)**: According to the Method A general procedure, a crude mixture of 93/7 **2.24a**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 95.1 mg (92%) of **2.24a** as a single diastereomer as a 96:4 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b**. $R_f$ = 0.43 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR (CDCl3, 600 MHz) δ: 6.96 – 7.12 (m, 4H), 6.80 – 6.87 (m, 2H), 6.74 – 6.80 (d, *J* = 7.00 Hz, 2H), 6.15 (ddd, *J* = 16.90 Hz, 8.70 Hz, 3.40 Hz, 1H), 5.17 (d, *J* = 10.62 Hz, 1H), 4.96 (d, *J* = 4.20 Hz, 1H), 4.94 (d, *J* = 16.50 Hz, 1H), 4.20 – 4.50 (m, 2H), 4.0 (d, *J* = 10.35 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.72(br s, 1H), 1.47 (s, 2.24h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 156.2, 134.2, 131.8, 130.3, 129.0, 127.4, 80.7, 75.2, 69.2, 55.3, 55.2, 52.3, 28.5 ppm. HRMS (DART) *m/z* calcd for $C_{24}H_{32}NO_5$ $[M+H]^+$: 414.2280; Found $[M + H]^+$: 414.2277.

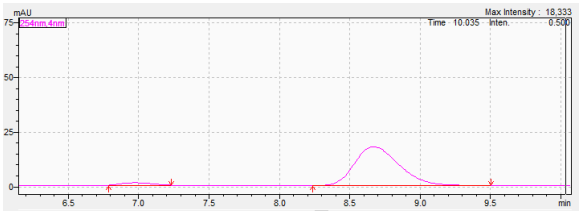
*Chiral HPLC analysis (Chiralcel OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 254 nm) $t_R$ = 7.00 min (minor), 8.7 min (major):*

**Racemic 2.24a:**

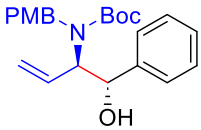


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 6.977 | 50.649 | 4964 | 0.000 |
| 8.633 | 49.351 | 4015 | 0.000 |
| | 100.000 | 8979 | 0.000 |

**2.24a from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 6.977 | 4.231 | 1153 | 0.000 |
| 8.669 | 95.769 | 17700 | 0.000 |
| | 100.000 | 18853 | 0.000 |

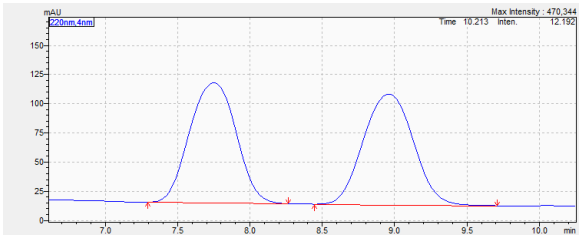



**2.24b**

***tert*-butyl ((*1S,2R*)-1-hydroxy-1-phenylbut-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24b)**: According to the Method A general procedure, a crude mixture of 63/37 **2.24b**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 57.5 mg (60%) of **2.24b** as a single diastereomer as a 93:7 mixture of enantiomers. The stereochemistry was assigned by converting **2.24b** to known compound **11** (see page S15)**.** $R_f$ = 0.45 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 ºC, 600 MHz) δ: 7.26 – 7.31(m, 1H), 7.2 – 7.25 (m, 2H), 7.12 – 7.18 (m, 1H), 7.04 – 7.11 (m, 2H), 6.80 – 6.88 (m, 2H), 6.7 – 6.80 (m, 1H), 6.14 (ddd, *J* = 17.70 Hz, *J* = 10.75 Hz, 6.60 Hz, 1H), 5.17 (d, *J* = 10.37 Hz, 1H), 5.00 ( d, *J* = 4.50 Hz, 1H), 4.91 (d, *J* = 17.31 Hz, 1H), 4.50 – 4.72 (m, 1H), 4.39 (d, *J* = 17.41 Hz, 1H), 4.01 (d, *J* = 11.97 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 1H), 3.73 – 3.77 (m, 1H), 1.48 (s, 2.24h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 133.6, 131.5, 130.2, 129.1, 128.2, 128.05, 127.3, 126.3, 113.9, 80.7, 69.2, 55.3, 55.3, 52.5, 28.5, 28.4 ppm. HRMS (DART) *m/z* calcd for $C_{23}H_{30}NO_4$ $[M+H]^+$: 384.2175; Found $[M + H]^+$: 384.2175.

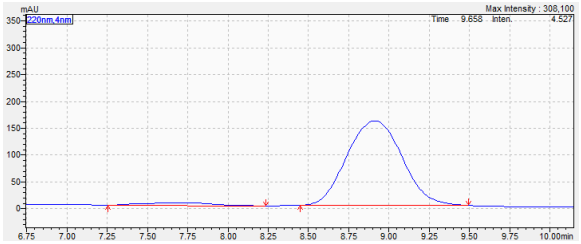
*Chiral HPLC analysis (IC-3 x 190 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ =7.7 min (minor), 8.9 min (major):*

**Racemic 2.24b:**

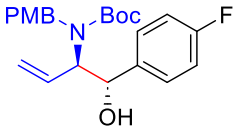



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 7.750 | 50.450 | 130351 | 50.450 |
| 8.959 | 49.550 | 120137 | 49.550 |
| | 100.000 | 250488 | 100.000 |

**2.24b from $Cu(OAc)_2$/W3 reaction:**




| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 7.682 | 4.098 | 5198 | 4.098 |
| 8.919 | 95.902 | 125729 | 95.902 |
| | 100.000 | 130927 | 100.000 |

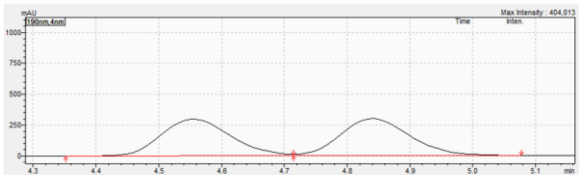



**2.24c**

***tert*-butyl ((*1S,2R*)-1-(4-fluorophenyl)-1-hydroxybut-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24c)**: According to the Method A general procedure, a crude mixture of 60/40 **2.24c**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 55.2 mg (55%) of **2.24c** as a single diastereomer as a 94/6 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.47 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.00 – 7.12 (m, 4H), 6.88 – 6.95 (m, 2H), 6.79 – 6.87 (m, 2H), 6.13 (ddd, *J* = 16.77 Hz, *J* = 11.42 Hz, *J* = 8.26 Hz, 1H), 5.19 (d, *J* = 10.21 Hz, 1H), 4.98 (d, *J* = 2.19 Hz, 1H), 4.93 (d, *J* = 16.25 Hz, 1H), 4.55 – 4.65 (m, 1H), 4.44 (d, *J* = 9.97 Hz, 1H), 3.90 – 4.00 (m, 1H), 3.81 (s, 3H), 3.75 – 3.80 (m, 1H), 3.60 – 3.70 (m, 1H), 1.49 (s, 2.24h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 162.1 (d, $^1J_{CF}$ = 244.5 Hz), 159.0, 156.3, 137.7, 133.3, 131.3, 130.1, 128.5 (d, $^2J_{CF}$ = 189.2 Hz), 118.6, 114.8(d, $^3J_{CF}$ = 22.5 Hz), 113.9, 80.9, 75.1, 69.2, 55.3, 52.4, 29.7, 28.5 ppm. $^{12.24f}$ NMR (565 MHz, $CDCl_3$): – 115.6 ppm. HRMS (DART) *m/z* calcd for $C_{23}H_{29}FNO_4$ $[M+H]^+$: 402.2081; Found $[M + H]^+$: 402.2081.

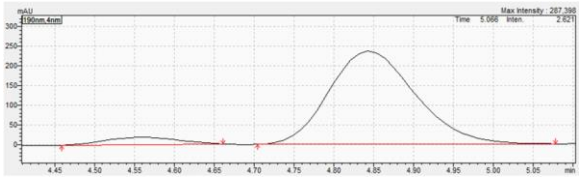
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol λ = 190 nm) $t_R$ =4.6 min (minor), 4.8 min (major):*

**Racemic 2.24c·OBz:**

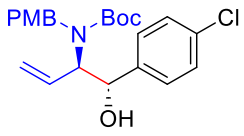


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 4.554 | 49.698 | 296546 | 49.698 |
| 4.840 | 50.302 | 298431 | 50.302 |
| | 100.000 | 594977 | 100.000 |

**2.24c·OBz from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 4.559 | 6.058 | 17917 | 6.058 |
| 4.843 | 93.942 | 236471 | 93.942 |
| | 100.000 | 254387 | 100.000 |

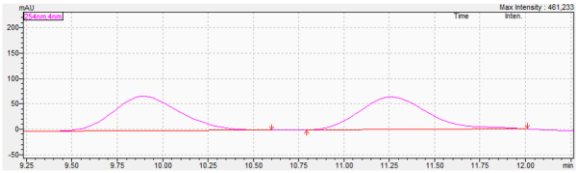



**2.24d**

***tert*-butyl ((*1S,2R*)-1-(4-chlorophenyl)-1-hydroxybut-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24d)**: According to the Method A general procedure, a crude mixture of 60/40 **2.24d**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 62.6 mg (60%) of **2.24d** as a single diastereomer as a 96/4 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.53 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.18 (d, *J* = 8.60 Hz, 2H), 6.95 – 7.10 (m, 4H), 6.77 – 6.89 (m, 2H), 6.12 (ddd, *J* = 17.65 Hz *J* = 9.45 Hz, *J* = 8.91 Hz, 1H), 5.18 ( d, *J* = 10.49 Hz, 1H), 4.97 (d, *J* = 4.30 Hz, 1H), 4.92 (d, *J* = 17.20 Hz, 1H), 4.57 – 4.71 (m, 1H), 4.50 (d, *J* = 12.30 Hz, 1H), 3.93 (d, *J* = 10.61 Hz, 1H), 3.81 (s, 3H), 3.56 – 3.66 (m, 1H), 1.49 (s, 2.24h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.0, 133.0, 131.1, 130.0, 129.2, 128.1, 127.6, 118.7, 113.9, 81.0, 75.2, 69.2, 55.3, 52.4, 29.7, 28.5 ppm. HRMS (DART) *m/z* calcd for $C_{23}H_{29}ClNO_4$ $[M+H]^+$: 418.1785; Found $[M + H]^+$: 418.1786.

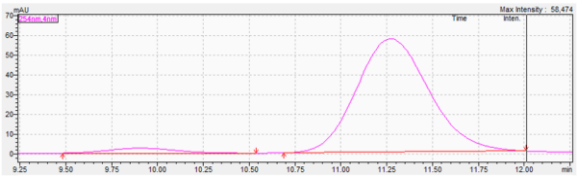
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 254 nm) $t_R$ = 9.9 min (minor), 11.3 min (major):*

**Racemic 2.24d·OBz:**

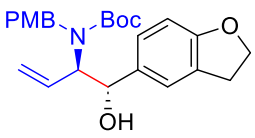


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 9.894 | 50.172 | 67541 | 0.000 |
| 11.261 | 49.828 | 64147 | 0.000 |
| | 100.000 | 131688 | 0.000 |

**2.24d·OBz from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 9.903 | 3.798 | 2499 | 0.000 |
| 11.272 | 96.202 | 57341 | 0.000 |
| | 100.000 | 59840 | 0.000 |

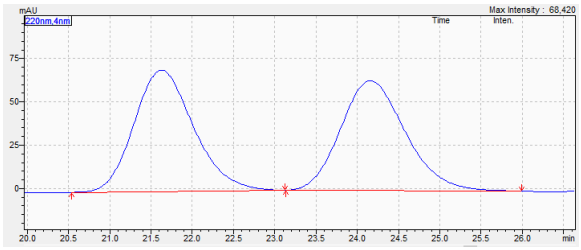



**2.24e**

***tert*-butyl ((*1S,2R*)-1-(2,3-dihydrobenzofuran-5-yl)-1-hydroxybut-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24e)**: According to the Method A general procedure, a crude mixture of 88/12 **2.24e**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 89.3 mg (84%) of **2.24e** as a single diastereomer as a 91:9 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.30 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 ºC, 600 MHz) δ: 7.07 (d, *J* = 8.46 Hz, 2H), 7.00 (s, 1H), 6.90 (d, J = 7.26 Hz, 1H), 6.81 (d, *J* = 7.71 Hz, 2H), 6.64 (d, J = 8.33 Hz, 1H), 6.17 (ddd, J = 18.61 Hz, *J* = 10.94 Hz, *J* = 8.54 Hz, 1H), 5.18 (d, *J* = 10.44 Hz, 1H), 4.95 – 5.00 (m, 2H), 4.53 (t, *J* = 9.11 Hz, 2H), 4.20 – 4.30 (m, 1H), 4.00 – 4.12 (m, 1H), 3.70 – 3.80 (m, 5H), 3.17 (t, J = 8.46 Hz, 2H), 1.45 (s, 9h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): 159.3, 158.9, 156.1, 134.2, 133.7, 132.0, 130.3, 129.1, 126.2, 122.9, 118.3, 113.7, 108.5, 80.6, 75.3, 71.3, 69.2, 55.3, 55.2, 20.7, 28.5 ppm. HRMS (DART) *m/z* calcd for $C_{25}H_{32}NO_5$ $[M+H]^+$: 426.2280; Found $[M + H]^+$: 426.2281.

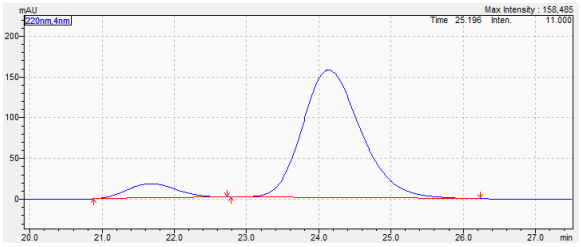
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 21.6 min (minor), 24.1 min (major):*

**Racemic 2.24e:**

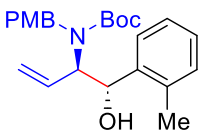



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 21.642 | 50.001 | 70052 | 50.001 |
| 24.152 | 49.999 | 63375 | 49.999 |
| | 100.000 | 133428 | 100.000 |

**2.24e from $Cu(OAc)_2$/W3 reaction:**




| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 21.621 | 9.359 | 18566 | 9.359 |
| 24.115 | 90.641 | 149391 | 90.641 |
| | 100.000 | 167957 | 100.000 |

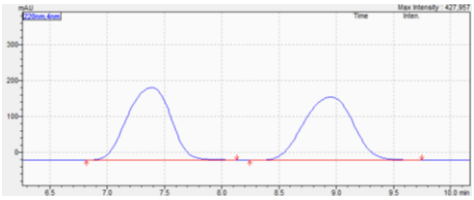



**2.24f**

***tert*-butyl ((*1S,2R*)-1-hydroxy-1-(o-tolyl)but-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24f)**: According to the Method A general procedure, a crude mixture of 60/40 **2.24f**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 61.3 mg (55%) of **2.24f** in 90 wt% purity by quantitative $^1$H NMR spectroscopy using dimethylfumarate as analytical standard as a single diastereomer as a 97:3 mixture of enantiomers (tert-butyl 4-methoxybenzylcarbamate could not be removed by chromatography). The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.40 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 °C, 600 MHz) δ: 7.24 (d, J = 7.40 Hz, 1 H), 6.97 – 7.06 (m, 2H), 6.95 (d, J = 8.19 Hz, 2H), 6.89 (d, J = 7.15 Hz, 1H), 6.67 (d, J = 8.29 Hz, 2H), 6.05 (ddd, J = 17.29 Hz, J = 11.28 Hz, J = 9.60 Hz, 1H), 5.08 (s, 1H), 5.00 ( d, J = 10.55 Hz, 1H), 4.68 (d, J = 17.33 Hz, 1H), 4.00 – 4.16 (m, 2H), 3.60 – 3.72 (m, 5H), 1.92 (s br, 3h), 1.33 (s, 9H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 140.0, 131.0, 130.3, 130.1, 129.0, 128.9, 127.1, 126.8, 125.7, 118.4, 114.0, 113.9, 113.8, 81.0, 72.4, 67.7, 55.3, 52.5, 28.5, 18.7 ppm. HRMS (DART) *m/z* calcd for $C_{24}H_{32}NO_4$ $[M+H]^+$: 398.2331; Found $[M + H]^+$: 398.2334.

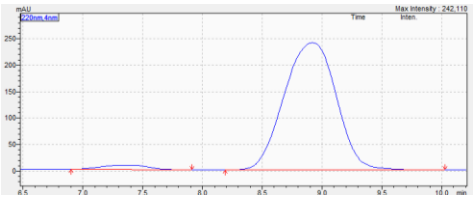
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 7.4 min (minor), 8.9 min (major):*

**Racemic 2.24f:**

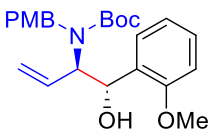


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 7.394 | 50.135 | 169798 | 50.135 |
| 8.961 | 49.865 | 149323 | 49.865 |
| | 100.000 | 319122 | 100.000 |

**2.24f from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 7.400 | 3.356 | 8054 | 3.356 |
| 8.908 | 96.644 | 197546 | 96.644 |
| | 100.000 | 205601 | 100.000 |

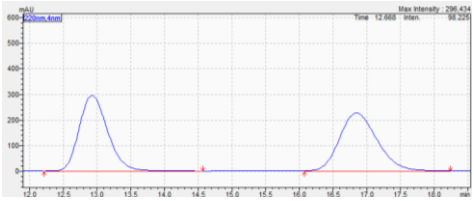



**2.24g**

***tert*-butyl ((*1S,2R*)-1-hydroxy-1-(2-methoxyphenyl)but-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24g)**: According to the Method A general procedure, a crude mixture of 65/35 **2.24g**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 65.1 mg (63%) of **2.24g** as a single diastereomer as a 94:6 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 057 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 ºC, 600 MHz) δ: 7.46 (br s, 1H), 7.21 (t, J = 8.06 Hz, 1H), 7.11 (d, J = 7.86 Hz, 2H), 6.93 (t, J = 7.54 Hz, 1H), 7.67 – 7.83 (m, 3H), 6.13 ( ddd, J = 17.16 Hz, J = 10.49 Hz, J = 7.00 Hz, 5.30 (s, 1H), 5.08 (d, J = 10.21 Hz, 1H), 4.80 (d, J = 17.25 Hz, 1H), 4.30 – 4.37 (m, 1H), 4.16 – 4.28 (m, 1H), 4.0 (s, 1H), 3.75 – 3.83 (m, 4H), 3.71 (s, 3H), 1.45 (s, 9H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.7, 156.6, 155.9, 131.9, 130.7, 129.9, 128.84, 128.1, 128.0, 120.5, 117.2, 113.6, 109.9, 80.7, 72.0, 67.4, 55.3, 55.0, 53.1, 28.5 ppm. HRMS (DART) *m/z* calcd for $C_{24}H_{32}NO_5$ $[M+H]^+$: 414.2280; Found $[M + H]^+$: 414.2276.

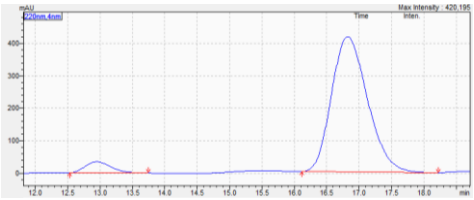
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 13.0 min (minor), 16.8 min (major):*

**Racemic 2.24g:**

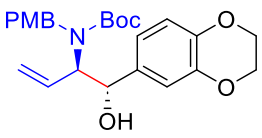


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 12.925 | 49.540 | 216455 | 49.540 |
| 16.850 | 50.460 | 168702 | 50.460 |
| | 100.000 | 385157 | 100.000 |

**2.24g from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 12.958 | 6.395 | 28158 | 6.395 |
| 16.827 | 93.605 | 289411 | 93.605 |
| | 100.000 | 317568 | 100.000 |

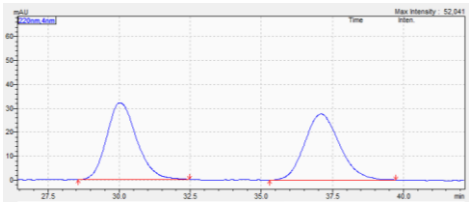



**2.24h**

***tert*-butyl ((*1S,2R*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxybut-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24h)**: According to the Method A general procedure, a crude mixture of 95/5 **2.24h**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 102.6 mg (93%) of **2.24h** as a single diastereomer as a 97:3 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.32 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 ºC, 600 MHz) δ: 7.07 (d, J = 7.40 Hz, 2H), 6.82 (d, J = 8.24 Hz, 2H), 6.70 – 6.74 (m, 2H). 6.65 (d, J = 7.85 Hz, 1H), 6.15 (ddd, J = 17.71 Hz, J = 11.23 Hz, J = 9.99 Hz, 1H), 5.16 (d, J = 10.80 Hz, 1H), 4.96 (d, J = 17.07 Hz, 1H), 4.90 – 4.93 (m, 1H), 4.20 – 4.25 (m, 6H), 3.77 – 3.81 (m, 5H), 1.45 (s, 9H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 156.3, 143.2, 133.6, 130.3, 129.1, 120.3, 119.3, 118.2, 116.7, 115.3, 113.8, 80.7, 75.1, 69.1, 64.4, 64.3, 55.3, 52.5, 29.7, 28.5, 28.4 ppm. HRMS (DART) *m/z* calcd for $C_{25}H_{32}NO_6$ $[M+H]^+$: 442.2230; Found $[M + H]^+$: 442.2229.

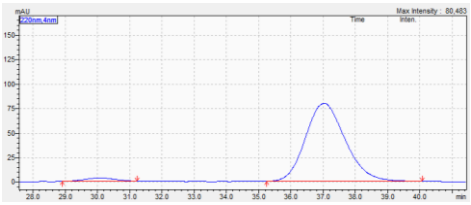
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 30.0 min (minor), 37.1 min (major):*

**Racemic 2.24h:**

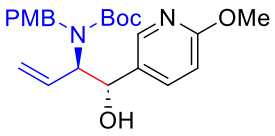


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 30.007 | 50.115 | 42456 | 50.115 |
| 37.115 | 49.885 | 37017 | 49.885 |
| | 100.000 | 79473 | 100.000 |

**2.24h from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 30.113 | 2.584 | 4557 | 2.584 |
| 37.056 | 97.416 | 100314 | 97.416 |
| | 100.000 | 104871 | 100.000 |

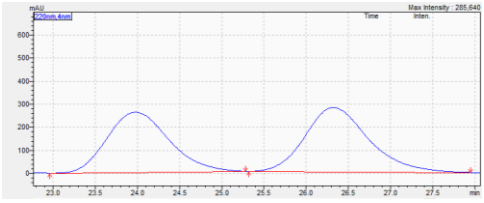



**2.24i**

***tert*-butyl ((*1S,2R*)-1-hydroxy-1-(6-methoxypyridin-3-yl)but-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24i)**: According to the Method A general procedure at 0 °C over 24 h, a crude mixture of 67/33 **2.24i**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 75.1 mg (65%) of **2.24i** in 90 wt% purity by quantitative $^1$H NMR spectroscopy using dimethylfumarate as analytical standard as a single diastereomer as a 94:6 mixture enantiomers (tert-butyl 4-methoxybenzylcarbamate could not be removed by chromatography). The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.34 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 °C, 600 MHz) δ 7.94 (s, 1H), 7.37 (d, J = 8.58 Hz, 1H), 7.06 (d, J = 7.98 Hz, 2H), 6.81 (d, J = 7.97 Hz, 2H), 6.60 (d, J = 8.56 Hz, 1H), 6.17 (ddd, J = 18.60 Hz, J = 9.94 Hz, J = 8.64 Hz, 1H), 5.20 (d, J = 9.94 Hz, 1H), 4.94 – 5.00 (m, 2H), 4.30 – 4.40 (m, 1H), 4.00 – 4.10 (m, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 3.76 – 3.79 (m, 1H), 3.70 – 3.75 (m, 1H), 1.48 (s, 9H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 163.7, 158.9, 156.3, 145.0, 137.0, 133.0, 131.2, 130.0, 129.0, 119.1, 113.9, 110.2, 81.0, 73.6, 69.1, 55.3, 55.2, 53.4, 52.3, 28.5 ppm. HRMS (DART) *m/z* calcd for $C_{23}H_{31}N_2O_5$ $[M+H]^+$: 415.2233 ; Found $[M + H]^+$: 415.2233.

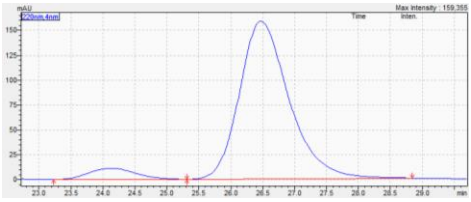
*Chiral HPLC analysis (Chiralpak AD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 24.0 min (minor), 26.3 min (major):*

**Racemic 2.24i:**

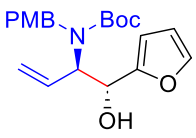


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 23.963 | 48.163 | 170890 | 48.163 |
| 26.324 | 51.837 | 181748 | 51.837 |
| | 100.000 | 352638 | 100.000 |

**2.24i from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 24.127 | 6.385 | 7856 | 6.385 |
| 26.455 | 93.615 | 106604 | 93.615 |
| | 100.000 | 114459 | 100.000 |



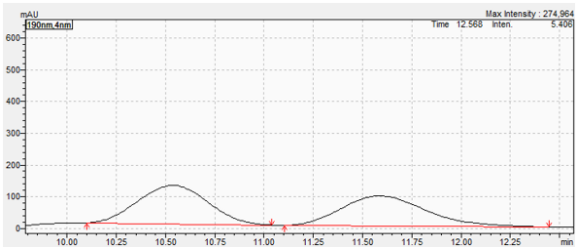

**2.24j**

***tert*-butyl ((*1R,2R*)-1-(furan-2-yl)-1-hydroxybut-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24j)**: According to the Method A general procedure, a crude mixture of 69/31 **2.24j**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 62.5 mg (67%) of **2.24j** as a single diastereomer as a 95/5 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.51 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.31 (d, *J* = 8.71 Hz, 1H), 7.11 (d, *J* = 8.25 Hz, 2H), 6.82 (d, *J* = 8.25 Hz, 2H), 6.30 (s, 1H), 6.20 – 6.28 (m, 1H), 5.90 – 6.18 (m, 1H), 5.18 (d, *J* = 10.56 Hz, 1H), 5.02 – 5.13 (m, 1H), 4.98 (d, *J* = 17.05 Hz, 1H), 4.87 – 4.93 (m, 1H), 4.17 – 4.48 (m, 2H), 3.95 – 4.10 (m, 1H), 3.79 (s, 3H), 1.45 (s, 2.24h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.8, 141.7, 133.0, 130.3, 129.1, 128.9, 117.9, 113.8, 110.3, 107.0, 81.0, 55.3, 52.4, 29.75, 28.44, 28.40 ppm. HRMS (DART) *m/z* calcd for $C_{21}H_{28}NO_5$ $[M+H]^+$: 374.1967; Found $[M + H]^+$: 374.1963.

Product **2.24j** was benzoylated using BzCl to allow for separation on HPLC.

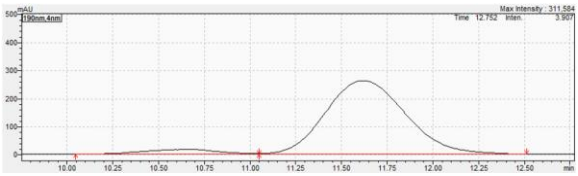
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 10.5 min (minor), 11.6 min (major):*

**Racemic 2.24j·OBz:**

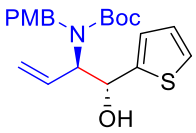


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 10.542 | 51.444 | 121288 | 51.444 |
| 11.590 | 48.556 | 94931 | 48.556 |
| | 100.000 | 216218 | 100.000 |

**2.24j·OBz from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 10.667 | 5.487 | 16689 | 5.487 |
| 11.616 | 94.513 | 261821 | 94.513 |
| | 100.000 | 278510 | 100.000 |

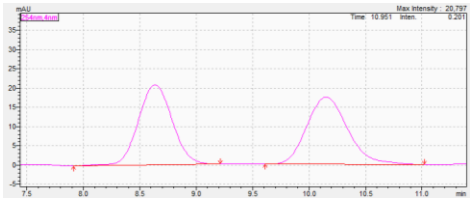



**2.24k**

***tert*-butyl ((*1R,2R*)-1-hydroxy-1-(thiophen-2-yl)but-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24k)**: According to the Method A general procedure, a crude mixture of >99/1 **2.24k**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 96.3 mg (99%) of **2.24k** as a single diastereomer as a 98:2 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.62 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.14 – 7.22 (m, 1H), 7.09 (d, *J* = 6.10 Hz, 2H), 6.88 – 6.94 (m, 1H), 6.79 – 6.86 (m, 2H), 6.68 – 6.76 (m, 1H), 6.1 – 6.2 (m, 1H), 5.27 (d, *J* = 4.27 Hz, 1H), 5.19 (d, *J* = 10.98 Hz, 1H), 4.98 (d, *J* = 17.08 Hz, 1H), 4.72 – 4.84 (m, 1H), 4.40 (d, *J* = 16.47 Hz, 1H), 4.07 (d, *J* = 12.20 Hz, 1H), 3.82 (d, *J* = 6.71 Hz, 1H), 3.79 (s, 3H), 1.49 (s, 2.24h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 158.8, 146.1, 133.3, 131.5, 130.2, 129.0, 126.5, 124.2, 123.5, 118.7, 114.0, 113.9, 80.9, 72.7, 69.4, 55.3, 55.2, 52.5, 28.5 ppm. HRMS (DART) *m/z* calcd for $C_{21}H_{28}NO_4S$ $[M+H]^+$: 390.1739; Found $[M + H]^+$: 390.1738.

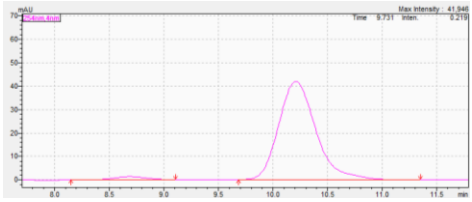
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 8.6 min (minor), 10.1 min (major):*

**Racemic 2.24k:**

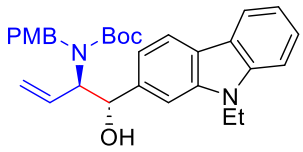


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 8.637 | 50.999 | 95503 | 50.999 |
| 10.149 | 49.001 | 79251 | 49.001 |
| | 100.000 | 174754 | 100.000 |

**2.24k from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 8.688 | 2.173 | 5197 | 2.173 |
| 10.213 | 97.827 | 176200 | 97.827 |
| | 100.000 | 181397 | 100.000 |

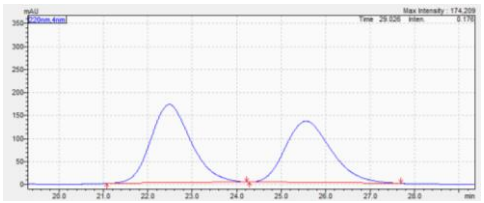



**2.24l**

***tert*-butyl ((*1S,2R*)-1-(9-ethyl-9H-carbazol-2-yl)-1-hydroxybut-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24l)**: According to the Method A general procedure, a crude mixture of 63/37 **2.24l**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 75.0 mg (60%) of **2.24l** as a single diastereomer as a 87:13 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.53 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 ºC, 600 MHz) δ: 8.02 (d, *J* = 7.25 Hz, 1H), 7.85 (s, 1H), 7.46 (t, *J* = 7.53 Hz, 1H), 7.40 (t, *J* = 8.10 Hz, 1H), 7.26 – 7.32 (m, 2H), 7.22 (t, *J* = 7.10 Hz, 1H), 7.03 – 7.10 (m, 2H), 6.75 – 6.85 (m, 2H), 6.26 (ddd, *J* = 18.04 Hz, *J* = 10.91 Hz, *J* = 9.23 Hz, 1H), 5.17 – 5.26 (m, 2H), 4.97 (d, *J* = 16.15 Hz, 1H), 4.47 – 4.56 (m, 1H), 4.38 – 4.45 (m, 1H), 4.35 (q, *J* = 6.95 Hz, 2H), 3.95 (d, J = 15.97 Hz, 1H), 3.80 -3.88 (m, 1H), 3.78 (s, 3H), 3.60 – 3.70 (m, 1H), 1.50 (s, 2.24h), 1.42 (t, *J* = 7.58 Hz, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.0, 140.2, 139.5, 132.0, 130.3, 129.3, 125.5, 124.0, 122.9, 122.6, 120.5, 118.7, 118.3, 118.1, 113.8, 108.4, 107.9, 80.6, 75.9, 69.7, 55.2, 52.4, 37.6, 28.5, 13.8 ppm. HRMS (DART) *m/z* calcd for $C_{31}H_{36}N_2O_4$ $[M]^+$: 500.2675; Found $[M + H]^+$: 500.2673.

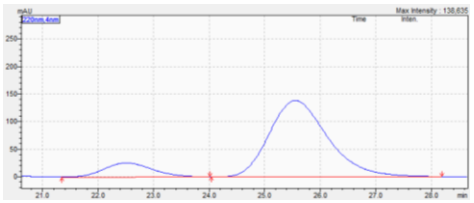
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 22.5 min (minor), 25.6 min (major):*

**Racemic 2.24l:**

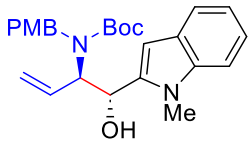


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 22.474 | 51.815 | 119171 | 51.815 |
| 25.565 | 48.185 | 95533 | 48.185 |
| | 100.000 | 214704 | 100.000 |

**2.24l from Cu(OAc)$_2$/W3 reaction:**



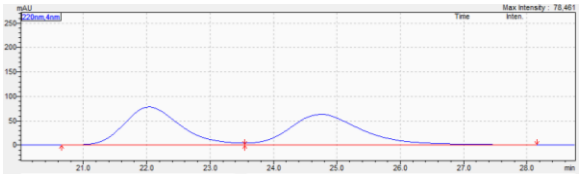
| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 22.513 | 12.995 | 33387 | 12.995 |
| 25.551 | 87.005 | 183391 | 87.005 |
| | 100.000 | 216778 | 100.000 |



**2.24m**

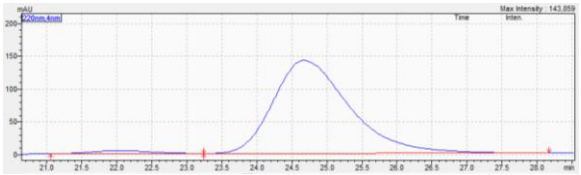
***tert*-butyl ((*1R,2R*)-1-hydroxy-1-(1-methyl-1H-indol-2-yl)but-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24m)**: According to the Method A general procedure at 0 °C over 24 h, a crude mixture of 50/50 **2.24m**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 51.3 mg (47%) of **2.24m** as a single diastereomer as a 97:3 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.53 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 °C, 600 MHz) δ: 7.54 (d, J = 7.98 Hz, 1H), 7.15 – 7.22 (m, 3H), 7.05 – 7.09 (m, 1H), 6.99 (d, J = 7.76 Hz, 2H), 6.69 (d, J = 5.76 Hz, 2H), 6.46 (s, 1H), 6.28 (ddd, J = 17.96 Hz, J = 10.64 Hz, J = 7.76 Hz, 1H), 5.28 (d, J = 10.21 Hz, 1H), 5.20 – 5.25 (m, 1H), 5.12 (d, J = 17.67 Hz, 1H), 4.12 – 4.44 (m, 3H), 3.79 (dd, J = 11.69 Hz, J = 10.45 Hz, 1H), 3.75 (s, 3H), 3.49 (s, 3H), 1.47 (s, 9H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 157.9, 156.2, 140.0, 137.8, 131.9, 130.2, 128.8, 127.4, 121.3, 120.6, 119.3, 118.6, 113.8, 109.0, 100.4, 80.9, 69.2, 65.8, 55.3, 51.7, 29.8, 28.4, 28.2 ppm. HRMS (DART) *m/z* calcd for $C_{26}H_{33}N_2O_4$ $[M+H]^+$: 437.2440; Found $[M + H]^+$: 437.2440.

**Racemic 2.24m:**

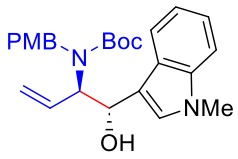


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 22.034 | 49.281 | 77881 | 0.000 |
| 24.764 | 50.719 | 62682 | 0.000 |
| | 100.000 | 140563 | 0.000 |

**2.24m from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 22.065 | 2.626 | 4856 | 0.000 |
| 24.670 | 97.374 | 141962 | 0.000 |
| | 100.000 | 146818 | 0.000 |

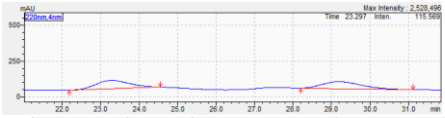



**2.24n**

***tert*-butyl ((*1S,2R*)-1-hydroxy-1-(1-methyl-1H-indol-3-yl)but-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24n)**: According to the Method B general procedure at 0 ºC with aldehyde addition rate of 0.05 mL/h for 24 h, a crude mixture of >99/1 **2.24n**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 106.9 mg (98%) of **2.24n** as a single diastereomer as a 86:14 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.45 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 ºC, 600 MHz) δ: 7.23 (s, 1H), 7.11 – 7.20 (m, 2H), 7.04 – 7.10 (m, 2H), 6.80 – 6.93 (m, 3H), 6.66 – 6.77 (m, 1H), 6.17 (ddd, *J* = 16.63 Hz, 10.76 Hz, 6.65 Hz, 1H), 5.30 – 5.40 (m, 1H), 5.22 – 5.30 (m, 1H), 5.18 (d, *J* = 10.71 Hz, 1H), 4.94 (d, *J* = 17.02 Hz, 1H), 4.68 (d, *J* = 13.24 Hz, 1H), 3.9 – 4.05 (m, 2H), 3.8 (s, 3H), 3.71 (s, 3H), 1.52 (s, 2.24h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.1, 156.7, 137.0, 131.5, 130.4, 129.2, 127.0, 125.9, 121.3, 119.0, 118.7, 117.1, 114.01, 109.1, 80.8, 70.9, 67.8, 55.3, 52.7, 32.7, 28.5 ppm. HRMS (DART) *m/z* calcd for $C_{26}H_{32}N_2O_4$ $[M]^+$: 436.2362; Found $[M]^+$: 436.2362.

*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 23.3 min (minor), 29.2 min (major):*

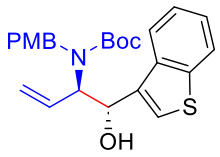
**Racemic 2.24n:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 23.309 | 50.749 | 40099 | 50.749 |
| 29.170 | 49.251 | 33716 | 49.251 |
| | 100.000 | 73815 | 100.000 |

**2.24n from $Cu(OAc)_2$/W12 reaction:**

| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 23.976 | 13.668 | 54421 | 13.668 |
| 29.792 | 86.332 | 232156 | 86.332 |
| | 100.000 | 286577 | 100.000 |

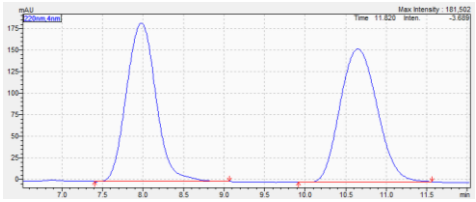



**2.24o**

***tert*-butyl ((*1S,2R*)-1-(benzo[b]thiophen-3-yl)-1-hydroxybut-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24o)**: According to the Method B general procedure at 0 °C with aldehyde addition rate of 0.05 mL/h for 24 h, a crude mixture of 74/26 **2.24o**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 76.9 mg (70%) of **2.24o** as a single diastereomer as a 96:4 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.62 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 °C, 600 MHz) δ: 7.80 (d, *J* = 7.97 Hz, 1H), 7.48 (s, 1H), 7.22 – 7.26 (m, 1H), 7.12 – 7.20 (m, 2H), 7.00 – 7.07 (m, 1H), 6.85 – 6.95 (m, 2H), 6.70 – 6.80 (m, 1H), 6.14 (ddd, *J* = 17.41 Hz, *J* = 10.88 Hz, *J* = 7.26 Hz, 1H), 5.75 – 5.85 (m, 1H), 5.24 (s, 1H), 5.19 (d, *J* = 5.18 Hz, 1H), 4.85 (d, *J* = 4.84 Hz, 1H), 4.76 (d, *J* = 13.06 Hz, 1H), 3.74 – 3.90 (m, 5H), 1.55 (s, 2.24h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.2, 156.9, 140.7, 136.8, 130.6, 130.2, 129.3, 123.9, 123.8, 123.7, 122.8, 121.5, 117.8, 114.2, 114.0, 81.3, 72.3, 67.0, 55.3, 52.8, 29.7, 28.5, 28.4 ppm. HRMS (DART) *m/z* calcd for $C_{25}H_{29}NO_4S$ $[M]^+$: 439.1817; Found $[M]^+$: 439.1818.

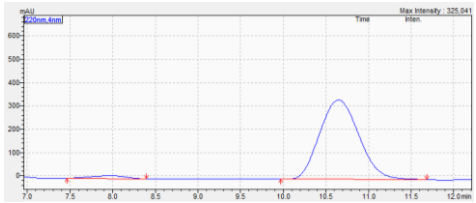
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 8.0 min (minor), 10.5 min (major):*

**Racemic 2.24o:**

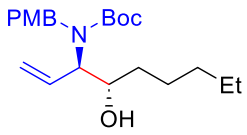


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 7.980 | 48.930 | 137796 | 48.930 |
| 10.669 | 51.070 | 115533 | 51.070 |
| | 100.000 | 253329 | 100.000 |

**2.24o from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 7.774 | 3.016 | 15618 | 3.016 |
| 10.489 | 96.984 | 329893 | 96.984 |
| | 100.000 | 345512 | 100.000 |

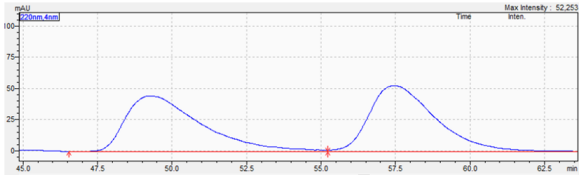


**2.24p**

***tert*-butyl ((*3R,4S*)-4-hydroxynon-1-en-3-yl)(4-methoxybenzyl)carbamate (2.24p)**: According to the Method B general procedure at 40 ºC for 26 h, a crude mixture of 65/35 **2.24p**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 60.4 mg (64%) of **2.24p** as a single diastereomer as a 87:13 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.32 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 ºC, 600 MHz) δ: 7.16 (d, *J* = 6.22 Hz, 2H), 6.84 (d, *J* = 9.33 Hz, 2H), 6.1 – 6.25 (m 1H), 5.22 (d, *J* = 10.89 Hz, 1H), 5.10 (d, *J* = 17.89 Hz, 1H), 4.54 – 4.65 (m, 1H), 4.35 – 4.53 (m, 1H), 4.00 – 4.15 (m, 1H), 3.81 (s, 1H), 3.79 (s, 3H), 3.00 – 3.10 (m, 1H), 1.46 (s, 2.24h), 1.01 – 1.39 (m, 5H), 0.70 – 1.00 (m, 3H), 0.20 – 0.37 (m, 2H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158/9, 132.4, 130.5, 128.9, 118.2, 113.8, 80.7, 78.9, 67.42, 55.3, 52.1, 32.1, 29.7, 28.47, 15.53, 14.13, 3.6, 1.8 ppm. HRMS (DART) *m/z* calcd for $C_{22}H_{35}NO_4$ $[M]^+$: 377.2566; Found $[M]^+$: 377.2562.

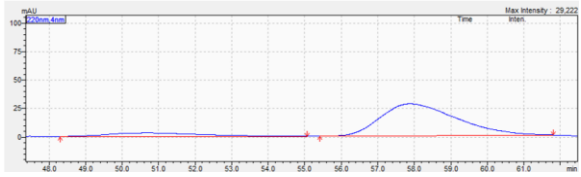
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 95:5 heptane:isopropanol, λ = 220 nm) $t_R$ = 49.2 min (minor), 57.5 min (major):*

**Racemic 2.24p:**

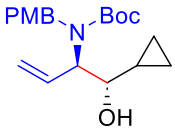


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 49.216 | 49.116 | 44362 | 0.000 |
| 57.458 | 50.884 | 52658 | 0.000 |
| | 100.000 | 97020 | 0.000 |

**2.24p from $Cu(OAc)_2$/W12 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 50.710 | 12.688 | 3299 | 0.000 |
| 57.885 | 87.312 | 27955 | 0.000 |
| | 100.000 | 31253 | 0.000 |

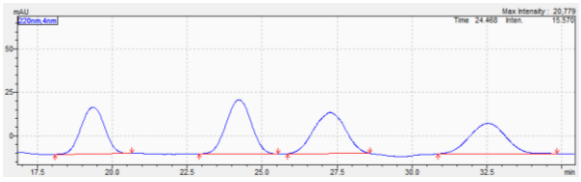



**2.24q**

***tert*-butyl ((*1S,2R*)-1-cyclopropyl-1-hydroxybut-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24q)**: According to the Method B general procedure, a crude mixture of 78/22 **2.24q**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 64.2 mg (74%) of **2.24q** as a single diastereomer as a 87:13 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.43 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 ºC, 600 MHz) δ: 7.15 (d, *J* =7.43 Hz, 2H), 6.83 (d, *J* = 8.67 Hz, 2H), 6.10 – 6.25 (m, 1H), 5.21 (d, *J* = 9.84 Hz, 1H), 5.10 (d, *J* = 17.53 Hz, 1H), 4.40 – 4.65 (m, 2H), 4.00 – 4.16 (m, 1H), 3.81 (s, 1H), 3.79 (s, 3H), 2.92 – 3.10 (m, 1H), 1.45 (s, 1H), 0.73 – 0.89 (m, 1H), 0.40 – 0.53 (m, 1H), 0.20 – 0.35 (m, 2H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 157.1, 154.6, 130.6, 128.7, 127.4, 127.2, 116.3, 111.9, 78.8, 77.1, 65.5, 53.5, 50.26, 26.6, 13.7, 13.2, 1.77, 0.01 ppm. HRMS (DART) *m/z* calcd for $C_{20}H_{30}NO_4$ $[M+H]^+$: 348.2175; Found $[M + H]^+$: 348.2177.

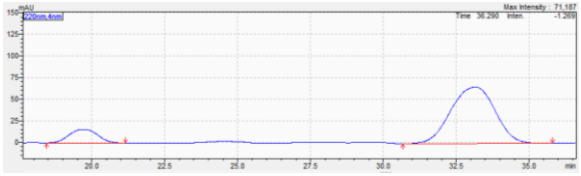
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 220 nm) $t_R$ = 19.7 min (minor), 33.1 min (major):*

**Racemic 2.24q:**

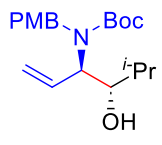


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 19.360 | 22.611 | 26737 | 22.611 |
| 24.218 | 27.719 | 31121 | 27.719 |
| 27.268 | 26.982 | 23698 | 26.982 |
| 32.544 | 22.687 | 17570 | 22.687 |
| | 100.000 | 99127 | 100.000 |

**2.24q from $Cu(OAc)_2$/W12 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 19.710 | 13.254 | 15756 | 0.000 |
| 33.145 | 86.746 | 65561 | 0.000 |
| | 100.000 | 81317 | 0.000 |

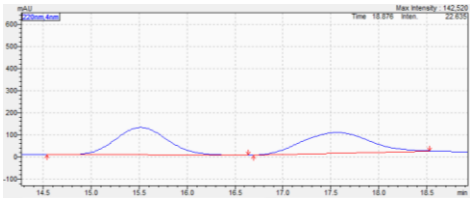


**2.24r**

***tert*-butyl ((*3R,4S*)-4-hydroxy-5-methylhex-1-en-3-yl)(4-methoxybenzyl)carbamate (2.24r)**: According to the Method B general procedure, a crude mixture of 80/20 **2.24r**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 66.4 mg (76%) of **2.24r** as a single diastereomer as a 90:10 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.42 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 ºC, 600 MHz) δ: 7.16 (d, *J* = 7.71 Hz, 2H), 6.84 (d, *J* = 8.19 Hz, 2H), 6.00 – 6.18 (m, 1H), 5.19 (d, *J* = 10.60 Hz, 1H), 5.03 (d, *J* = 17.35 Hz, 1H), 4.40 – 4.50 (m, 2H), 4.10 – 4.26 (m, 1H), 3.80 (s, 4H), 3.40 – 3.50 (m, 1H), 1.54 – 1.63 (m, 1H), 1.46 (s, 2.24h), 0.85 (s, 3H), 0.71 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.9, 124.1, 128.9, 114.0, 113.8, 80.7, 55.3, 55.2, 29.7, 28.5, 28.4, 28.0, 22.7, 19.3, 14.1 ppm. HRMS (DART) *m/z* calcd for $C_{20}H_{32}NO_4$ $[M+H]^+$: 350.2331; Found $[M+H]^+$: 350.2330.

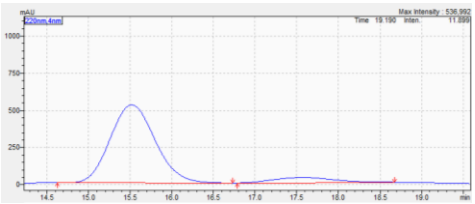
*Chiral HPLC analysis (Chiralpak AD-3 x 250 mm, 1.0 mL/min, 95:5 heptane:isopropanol, λ = 190 nm) $t_R$ = 15.6 min (minor), 17.6 min (major):*

**Racemic 2.24r:**

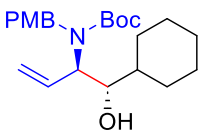


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 15.518 | 50.933 | 91286 | 50.933 |
| 17.568 | 49.067 | 69107 | 49.067 |
| | 100.000 | 160393 | 100.000 |

**2.24r from $Cu(OAc)_2$/W12 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 15.518 | 90.219 | 340043 | 90.219 |
| 17.581 | 9.781 | 28226 | 9.781 |
| | 100.000 | 368269 | 100.000 |



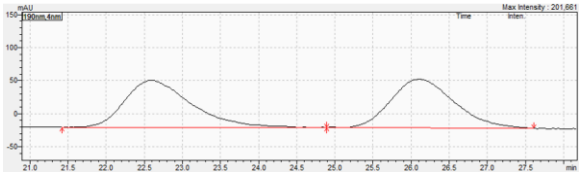

**2.24s**

***tert*-butyl ((*1S,2R*)-1-cyclohexyl-1-hydroxybut-3-en-2-yl)(4-methoxybenzyl)carbamate (2.24s)**: According to the Method B general procedure, a crude mixture of 65/35 **2.24s**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 60.3 mg (62%) of **2.24s** as a single diastereomer as a 89:11 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.53 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 ºC, 600 MHz) δ: 7.16 (d, *J* = 6.96 Hz, 2H, 6.84 (d, *J* = 8.41 Hz, 2H), 6.00 – 6.15 (m, 1H), 5.20 (d, *J* = 10.16 Hz, 1H), 5.03 (d, *J* = 17.70 Hz, 1H), 4.40 – 4.50 (m, 1H), 4.15 – 4.30 (m, 1H), 3.84 (s, 1H), 3.79 (s, 3H), 3.44 – 3.55 (m, 1H), 1.54 – 1.70 (3H), 1,46 (s, 2.24h), 1.34 – 1.41 (m, 2H), 1.20 – 1.30 (m, 2H), 1.02 – 1.17 (m, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 183.1, 158.9, 129.1, 129.0, 128.9, 114.0, 113.9, 80.7, 76.5, 55.3, 29.7, 28.5, 28.4, 26.4, 26.3, 26.0, 4.4 ppm. HRMS (DART) *m/z* calcd for $C_{23}H_{36}NO_4$ $[M+H]^+$: 390.2644; Found $[M + H]^+$: 390.2644.

Product **2.24s** was benzoylated using BzCl to allow for separation on HPLC.

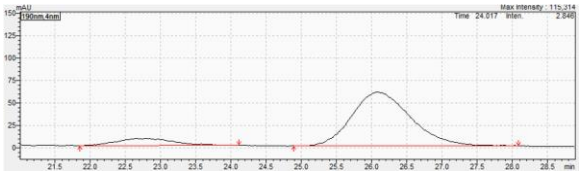
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 95:5 heptane:isopropanol, λ = 190 nm) $t_R$ = 22.6 min (minor), 26.1 min (major):*

**Racemic 2.24s·OBz:**

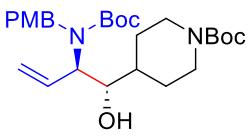


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 22.589 | 50.392 | 71045 | 50.392 |
| 26.114 | 49.608 | 73810 | 49.608 |
| | 100.000 | 144855 | 100.000 |

**2.24s·OBz from $Cu(OAc)_2$/W12 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 22.801 | 11.303 | 8013 | 11.303 |
| 26.093 | 88.697 | 59661 | 88.697 |
| | 100.000 | 67675 | 100.000 |

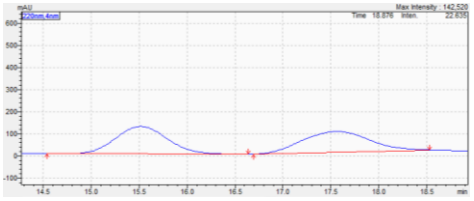



**2.24t**

***tert*-butyl 4-((*1S,2R*)-2-((tert-butoxycarbonyl)(4-methoxybenzyl)amino)-1-hydroxybut-3-en-1-yl)piperidine-1-carboxylate (2.24t)**: According to the Method B general procedure, a crude mixture of 50/50 **2.24t**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 57.6 mg (47%) of **2.24t** as a single diastereomer as a 95:5 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.51 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 ºC, 600 MHz) δ: 7.13 (d, *J* = 8.42 Hz, 2H), 6.84 (d, *J* = 8.06 Hz, 2H), 6.00 – 6.15 (m, 1H), 5.21 (d, *J* = 10.25 Hz, 1H), 5.04 (d, *J* = 16.48 Hz, 1H), 4.45 – 4.55 (m, 1H), 4.06 – 4.20 (m, 1H), 3.85 – 4.06 (m, 2H), 3.78 (s, 3H), 3.73 (s, 1H), 3.45 – 3.55 (m, 1H), 2.4 – 2.6 (m, 2H), 1/46 (s, 2.24h), 1.41 (s, 2.24h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.0, 156.7, 154.8, 132.1, 130.3, 129.1, 118.5, 113.9, 80.9, 79.2, 63.5, 60.4, 55.3, 51.8, 44.1, 43.1, 43.2, 39.1, 28.5, 14.2 ppm. HRMS (DART) *m/z* calcd for $C_{27}H_{43}N_2O_6$ $[M+H]^+$: 491.3121; Found $[M + H]^+$: 491.3122.

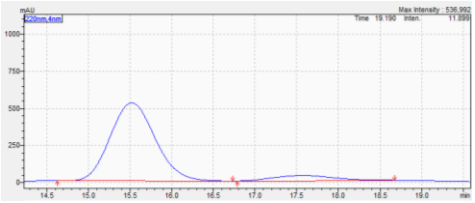
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 21.7 min (minor), 27.4 min (major):*

**Racemic 2.24t:**

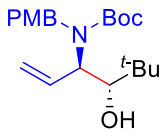


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 21.655 | 50.070 | 59452 | 50.070 |
| 27.442 | 49.930 | 43676 | 49.930 |
| | 100.000 | 103128 | 100.000 |

**2.24t from $Cu(OAc)_2$/W12 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 21.815 | 94.568 | 77610 | 94.568 |
| 27.421 | 5.432 | 4482 | 5.432 |
| | 100.000 | 82091 | 100.000 |

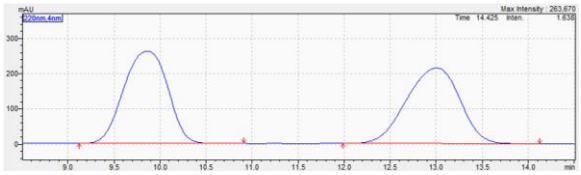


**2.24u**

***tert*-butyl ((*3R,4S*)-4-hydroxy-5,5-dimethylhex-1-en-3-yl)(4-methoxybenzyl)carbamate (2.24u)**: According to the Method A general procedure at room temperature with aldehyde addition at 0.02 mL/hr for 26 h, a crude mixture of 60/40 **2.24u**/aldehyde reduction was obtained and purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 51.8 mg (57%) of **2.24u** as a single diastereomer as a >99:1 mixture of enantiomers. The stereochemistry was assigned by analogy to that of **2.24b.** $R_f$ = 0.64 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 55 °C, 600 MHz) δ: 7.15 (d, *J* = 7.96 Hz, 2H), 6.84 (d, *J* = 8.37 Hz, 2H), 6.10 – 6.20 (m, 1H), 5.11 (d, *J* = 10.50 hz, 1H), 4.92 (d, *J* = 18.37 Hz, 1H), 4.80 – 4.90 (m, 1H), 5.58 (d, *J* = 15.75 Hz, 1H), 4.10 (d, *J* = 14.43 (d, *J* = 14.43 Hz, 1H), 3.79 (s, 3H), 3.65 – 3.75 (m, 1H), 3.42 (s, 1H), 1.47 (s, 2.24h), 0.75 (s, 2.24h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.0, 156.6, 133.7, 129.2, 116.5, 114.0, 113.9, 82.2, 80.7, 63.1, 55.3, 52.5, 34.9, 28.5, 26.4ppm. HRMS (DART) *m/z* calcd for $C_{21}H_{33}NO_4$ $[M]^+$: 363.2410; Found $[M]^+$: 363.2410.

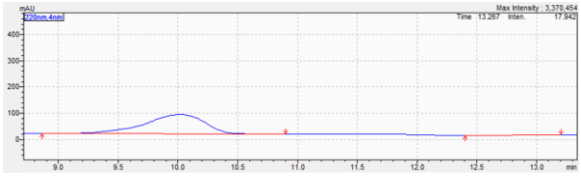
*Chiral HPLC analysis (Chiralpak IC-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 220 nm) $t_R$ = 9.9 min (minor), 13.0 min (major):*

**Racemic 2.24u:**



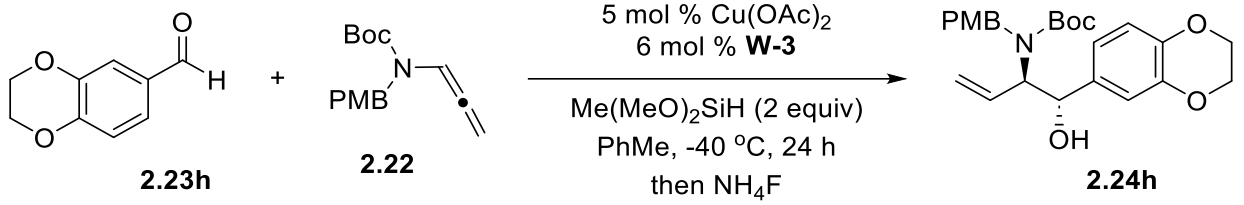
| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 9.863 | 50.193 | 260352 | 0.000 |
| 13.002 | 49.807 | 213570 | 0.000 |
| | 100.000 | 473922 | 0.000 |

**2.24u from $Cu(OAc)_2$/W3 reaction:**



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 10.018 | 99.910 | 73086 | 0.000 |
| 13.169 | 0.090 | 189 | 0.000 |
| | 100.000 | 73275 | 0.000 |

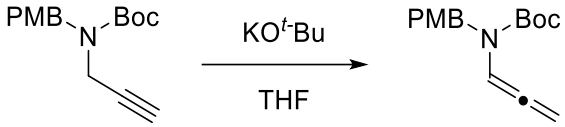
**Reaction Performed on 1.0 mmol scale:**




**2.23h** **2.22** **2.24h**

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 9.1 mg (0.05 mmol) of $Cu(OAc)_2$ and 40.2 mg (0.06 mmol) of **W3**. Toluene (1.0 mL) was then added, and the mixture was allowed to stir for 10 min. Alleneamide **2.22** (413 mg, 1.5 mmol) was then charged, sealed with a crimp-cap septum and removed from the glove-box. The reaction was then cooled in an ice bath, and dimethoxymethylsilane ( 0.25 mL, 2.0 mmol) was then charged by syringe (*caution: dimethoxymethylsilane should be handled in a well-ventilated fume hood because it is known to cause blindness. Syringes were quenched with 2M NaOH, gas evolution!, prior to disposal)* The mixture was then cooled to – 40 ºC and stirred as the Aldehyde (1.0 mmol in 2.0 mL toluene) is charged to the solution at 0.20 mL/hr. After 24 h, the reaction was quenched by the addition of 380 mg of $NH_4F$ and 4.5 mL of MeOH followed by agitation at rt for 30 min – 1 h. To the mixture was then charged 15 mL of 5% NaHCO3 followed by extraction with $CH_2Cl_2$ (3x10mL). The combined organics were dried with $Na_2SO_4$, filtered, and concentrated *in vacuo*. An aliquot of the crude mixture was analyzed by $^1$HNMR spectroscopy to determine the dr (>99) and b/l (>99) ratio. The crude residue was then purified by flash chromatography on silica gel (gradient, 0 – 10% EtOAc in $CH_2Cl_2$). The product spot ($R_f$ = 0.30, 5% EtOAc in $CH_2Cl_2$) was then collected and concentrated *in vacuo* to afford 407 mg (92%) of **2.24h**. Enantioselectivity was determined by chiral HPLC analysis to be 96:4 er.

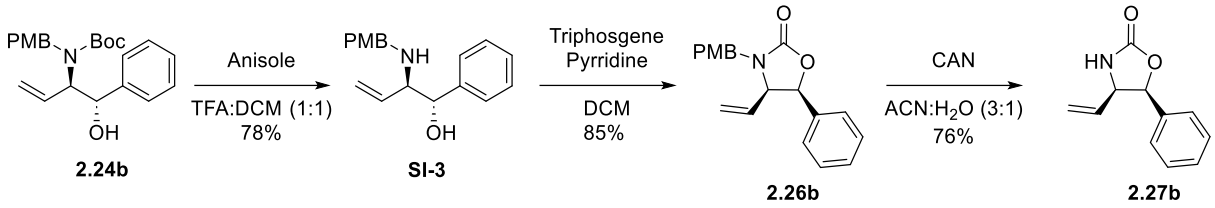
**Allene Synthesis:**




**2.22**

To a flame dried round bottom flask with 80 mL of THF was charged tert-butyl (4-methoxybenzyl)(prop-2-yn-1-yl)carbamate (8.3 g, 30.3 mmol) and then KO$^t$-Bu (340 mg, 3.03 mmol). The mixture was then stirred for 30 minutes and quenched with 20 mL of $H_2O$. The mixture was extracted with EtOAc (3 x 25 mL), dried with $MgSO_4$, decolorized with activated charcoal, filtered and concentrated *in vacuo.* The product was purified by silica gel chromatography (eluent: neat $CH_2Cl_2$) to provide 6.7 g (80%) of the desired product as a yellow oil. $R_f$ = 0.90 (Neat $CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.11 – 7.24 (m, 2H), 6.86 (d, $J$ = 8.45 Hz, 2H), 5.20 – 5.40 (m, 2H), 4.4 – 4.54 (m, 2H), 3.79 (s, 3H), 1.39 – 1.57 (m, 2.24h) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 201.9, 158.6, 152.9, 129.1, 128.6, 113.63, 100.69, 87.54, 81.22, 55.23, 47.90, 28.29. HRMS (DART) *m/z* calcd for $C_{16}H_{21}NO_3$ $[M]^+$: 275.1521; Found $[M + H]^+$: 275.1523.

**Absolute and relative stereochemistry determination for reaction products:**




Diastereo- and enantioenriched **2.24b** was prepared via the general procedure and was converted to **2.27b** by the given 3 step procedure. The absolute rotation of **2.27** matched the literature value.

To a solution of trifluoroacetic acid (0.94 mmol, 0.13 mL) in $CH_2Cl_2$ (87 µL) was charged anisole (0.31 mmol). A solution of **2.24b** (0.16 mmol) in $CH_2Cl_2$ (0.19 mL) was slowly added to the acid solution. The mixture was stirred for 1 h, taken up in $Et_2O$ (10 mL), extracted with 1 N HCl (3 × 5 mL), and basified with 30% w/v NaOH in brine. NaCl was added to make a sat. solution, which was extracted with $CH_2Cl_2$ (5 × 5 mL). The organic layer was then dried on MgSO4, filtered, and concentrated *in vacuo* to afford 35 mg (78%) of **SI-3** as a white solid. $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.25 – 7.36 (m, 5H), 7.17 (d, *J* = 8.35 Hz, 2H), 6.86 ( d, *J* = 8.35 Hz, 2H), 5.37 (ddd, *J* = 17.87 Hz, *J* = 10.77 Hz, *J* = 8.45 Hz, 1H), 5.22 (dd, *J* = 10.45 Hz, *J* = 2.06 Hz, 1H), 5.12 (d, *J* = 17.42 Hz, 1H), 4.71 (d, *J* = 4.92 Hz, 1H), 3.81 (s, 3H), 3.79 (d, *J* = 13.33 Hz, 1H), 3.62 (d, *J* = 12.20 Hz, 1H), 3.33 (dd, *J* = 8.12 Hz, 4.70 Hz, 1H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.7, 140.8, 136.6, 132.0, 129.3, 128.1, 127.5, 126.7, 118.9, 113.9, 74.3, 66.1, 55.3, 50.3 ppm. HRMS (DART) *m/z* calcd for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1651; Found $[M+H]^+$: 284.1649.

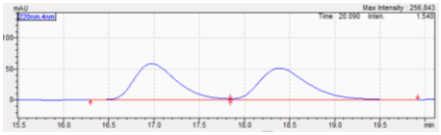
To a solution of **SI-3** (20 mg, 0.071 mmol) and Pyridine (11 mg, 0.14 mmol) in $CH_2Cl_2$ (1.0 mL) was charged a solution of triphosgene (12 µL, 0.064 mmol) in $CH_2Cl_2$ (1.0 mL) at 0 ºC. The mixture was stirred for 24 h at room temperature and quenched with brine (5 mL) and extracted with $CH_2Cl_2$ (2 x 5 mL). The combined organics were dried with $Na_2SO_4$, filtered, and concentrated *in vacuo.* The product was purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to afford 19 mg (85%) of **2.26b** as an oil in 96:4 er. $R_f$ = 0.63 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.27 – 7.37 (m, 3H), 7.16 – 7.25 (m, 4H), 6.87 (d, *J* = 8.27 Hz, 2H), 5.54 (d, *J* = 8.71 Hz, 1H), 5.00 – 5.16 (m, 3H), 4.83 (d, *J* = 15.05 Hz, 1H), 4.20 – 4.25 (m, 1H), 3.84 (d, *J* = 14.52 Hz, 1H), 3.81 (s, 3H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.3, 157.8, 135.1, 132.4, 129.9, 128.4, 127.9, 126.2, 125.7, 121.6, 114.1, 78.1, 62.3, 55.3, 45.4 ppm. HRMS (DART) *m/z* calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1443; Found $[M + H]^+$: 310.1449.

To a solution of **2.26b** (30 mg, 0.097 mmol) in 0.5 mL of 4:1 $CH_3CN$:$H_2O$ at 0 ºC was added dropwise a solution of ceric ammonium nitrate (130 mg, 0.24 mmol) in 0.3 mL of 2:1 $CH_3CN$:$H_2O$ over a period of 5 minutes. The mixture was allowed to warm up to room temperature and stirred overnight. To the reaction mixture was charged a 10% aqueous $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 x 5). The combined organics were washed with brine (5 mL) and dried with $Na_2SO_4$, filtered, and concentrated *in vacuo.* The product was purified by silica gel chromatography (eluent: 0 – 50% EtOAc in hexanes) to afford 19 mg (95%) of **2.27b** as a white solid. $R_f$ = 0.35 (40% EtOAc/hexanes). $[\alpha]_D^{25}$ = + 90.4 (c 0.94, $CHCl_3$), Lit.[133] $[\alpha]_D$ = + 100.8 (c 1.68, $CHCl_3$); $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.30 – 7.39 (m, 3H), 7.25 (d, *J* = 5.25 Hz, 2H), 5.76 (d, *J* = 7.93 Hz, 1H), 5.25 (ddd, *J* = 17.24 Hz, *J* = 10.41 Hz, *J* = 7.43 Hz, 1H), 5.18 (d, *J* = 17.34

Hz, 1H), 5.06 (d, $J$ = 10.05 Hz, 1H), 5.03 (br s, 1H), 4.57 (t, $J$ = 7.95 Hz, 1H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.94, 134.7, 133.7, 128.6, 128.5, 126.2, 118.9, 80.9, 59.6 ppm. HRMS (DART) *m/z* calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$: 189.0868; Found $[M+H]^+$: 189.0869.

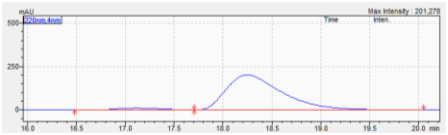
*Chiral HPLC analysis (Chiralcel OJ-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 17.0 min (minor), 18.2 min (major):*

**Racemic 2.26b:**



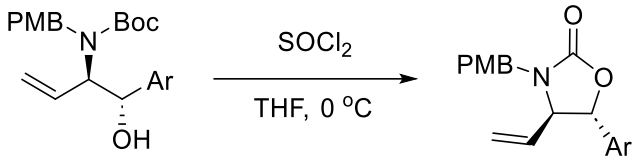
| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 16.972 | 50.271 | 64003 | 50.271 |
| 18.390 | 49.729 | 55382 | 49.729 |
| | 100.000 | 119385 | 100.000 |

**2.26b from $Cu(OAc)_2$/W3 reaction:**

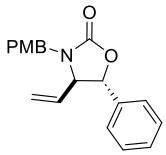


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 17.099 | 3.935 | 11730 | 3.935 |
| 18.245 | 96.065 | 215872 | 96.065 |
| | 100.000 | 227602 | 100.000 |

**General procedure for invertive cyclocarbamation:**[134]



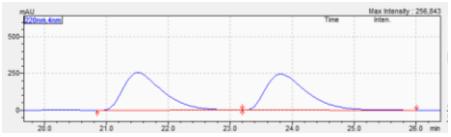

To solution of the Aminoalcohol (0.250 mmol) in 0.50 mL of THF at 0 °C in a flame dried 2-dram vial was charged $SOCl_2$ (0.18 mL, 2.50 mmol) and stirred overnight. The reaction mixture was then transferred into a ice water (5 mL) which was basified with 30% ammonia. The mixture was then extracted with $CH_2Cl_2$, washed with water, dried with $Na_2SO_4$, filtered, and concentrated *in vacuo*. The product was purified by silica gel chromatography.




**(4*R*,5*R*)-3-(4-methoxybenzyl)-5-phenyl-4-vinyloxazolidin-2-one (2.28b)**: According to the general procedure for invertive cyclocarbamation, the product was purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 76 mg (98%) of **2.8b** as an oil as a 94:6 mixture of diasteromers in 96:4 er for the major diastereomer. $R_f$ = 0.63 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.30 – 7.36 (m, 3H), 7.22 – 7.26 (m, 2H), 7.18 (d, *J* = 8.71 Hz, 2H), 6.82 (d, *J* = 9.30 Hz, 2H), 5.79 (dt, *J* = 17.12 Hz, *J* = 9.87 Hz, 1H), 5.40 ( d, *J* = 10.62 Hz, 1H), 5.18 (d, *J* = 17.42 Hz, 1H), 5.07 (d, *J* = 5.08 Hz, 1H), 4.78 (d, *J* = 15.05 Hz, 1H), 3.97 (d, *J* = 15.05 Hz, 1H), 3.81 (d, *J* = 8.50 Hz, 1H), 3.78 (s, 3H), ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.3, 157.5, 137.4, 134.2, 129.9, 128.8, 128.8, 128.7, 127.7, 125.7, 122.3, 114.1, 80.2, 66.4, 55.3, 45.5 ppm. HRMS (DART) *m/z* calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1443; Found $[M + H]^+$: 310.1449.

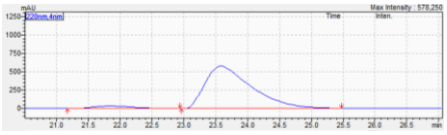
*Chiral HPLC analysis (Chiralcel OJ-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 190 nm) $t_R$ = 21.9 min (minor), 23.6 min (major):*

**Racemic 2.28b:**

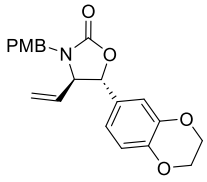


| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 21.508 | 49.895 | 267605 | 49.895 |
| 23.818 | 50.105 | 256996 | 50.105 |
| | 100.000 | 524601 | 100.000 |

**2.28b from $Cu(OAc)_2$/W3 reaction:**



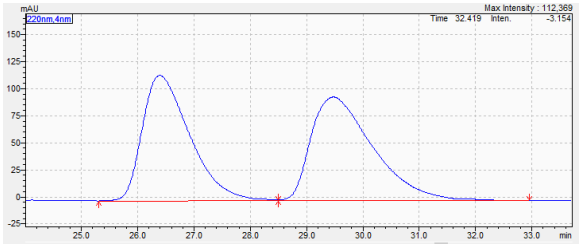
| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 21.853 | 3.729 | 32730 | 3.729 |
| 23.578 | 96.271 | 549610 | 96.271 |
| | 100.000 | 582340 | 100.000 |




***tert*-butyl ((*1S,2R*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxybut-3-en-2-yl)(4-methoxybenzyl)carbamate (2.28h)**: According to the general procedure for invertive cyclocarbamation, the product was purified by silica gel chromatography (eluent: 0 – 10% EtOAc in $CH_2Cl_2$) to provide 91 mg (98%) of **13** as a white solid as a 95:5 mixture of diastereomers in 97:3 er for the major diastereomer. $R_f$ = 0.57 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.18 (d, *J* = 8.82 Hz, 2H), 6.84 (d, *J* = 8.21 Hz, 2H), 6.80 (d, *J* = 8.21 Hz, 1H), 6.76 (s, 1H), 6.71 (dd, *J* = 8.21 Hz, *J* = 2.43 Hz, 1H), 5.73 (ddd, *J* = 17.34 Hz, *J* = 10.64 Hz, *J* = 8.52 Hz, 1H), 5.37 (d, *J* = 9.31 Hz, 1H), 5.17 (d, *J* = 17.14 Hz, 1H), 4.95 (d, *J* = 6.86 Hz, 1H), 4.77 (d, *J* = 14.69 Hz, 1H), 4.27 (s, 1H), 4.23 (s, 3H), 3.96 (d, *J* = 14.82 Hz, 1H), 3.73 – 3.82 (m, 4H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.2, 157.4, 144.0, 143.6, 134.2, 130.4, 129.9, 127.7, 122.2, 119.0, 117.6, 115.0, 114.1, 80.0, 66.4, 64.3, 55.3, 45.5 ppm. HRMS (DART) *m/z* calcd for $C_{21}H_{21}NO_5$ $[M]^+$: 368.1498; Found $[M + H]^+$: 368.1498

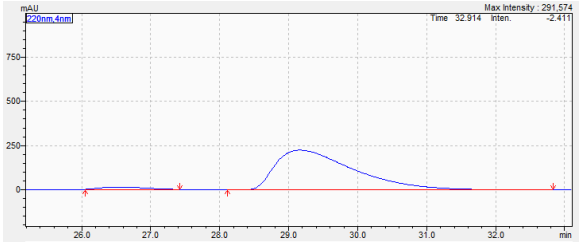
*Chiral HPLC analysis (Chiralcel OD-3 x 250 mm, 1.0 mL/min, 90:10 heptane:isopropanol, λ = 220 nm) $t_R$ = 26.4 min (minor), 29.5 min (major):*

**Racemic 2.28h:**



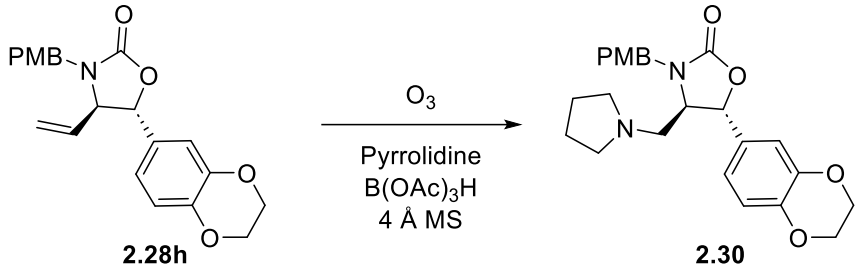

| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 26.393 | 48.245 | 115961 | 0.000 |
| 29.477 | 51.755 | 95636 | 0.000 |
| | 100.000 | 211597 | 0.000 |

**2.28h from $Cu(OAc)_2$/W3 reaction:**

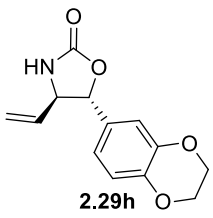



| Ret. Time | Area% | Height | Conc. |
|---|---|---|---|
| 26.543 | 3.341 | 13977 | 0.000 |
| 29.162 | 96.659 | 226158 | 0.000 |
| | 100.000 | 240135 | 0.000 |

**Ozonolysis:**




A stream of ozone from a household ozone disinfector[143] was bubbled through a long-stem glass pippette submerged in a solution of **2.28h** (40 mg, 0.11 mmol) and 1 g of 4Å molecular sieves in $CH_2Cl_2$ (25 mL) in a flame dried round bottom flask at 0 ºC. The reaction was monitored by TLC. The alkene was consumed after 25 min, and the ozone disinfector was switched off, and argon gas was bubbled through the solution for 10 min to remove the excess ozone. To the mixture was charged pyrrolidine (18 µL, 0.22 mmol) and then $Na(OAc)_3BH$ (46 mg, 0.22 mmol). The mixture was then stirred at room temperature overnight and quenched with aqueous saturated $NaHCO_3$ (5 mL). The crude mixture was filtered via vacuum filtration and the filtrate was extracted with $CH_2Cl_2$ (3 x 5 mL), dried with $MgSO_4$, and concentrated *in vacuo.* The product was purified by silica gel chromatography (eluent: 0 – 40% EtOAc in $CH_2Cl_2$) to afford 30 mg (65%) of **2.30** as a thick oil. $R_f$ = 0.10 (5% EtOAc/$CH_2Cl_2$). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 7.19 (d, *J* = 7.99 Hz, 2H), 6.83 (d, *J* = 8.50 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 1H), 6.74 (s, 1H), 6.71 (d, *J* = 8.50 Hz, 1H), 5.13 (d, *J* = 5.10 Hz, 1H), 4.80 (d, *J* = 16.26 Hz, 1H), 4.22 (s, 4H), 4.19 (d, *J* = 15.10 Hz, 1H), 3.78 (s, 3H), 3.42 (q, *J* = 4.95, 1H), 2.71 (dd, *J* = 11.87 Hz, *J* = 4.62 Hz, 1H), 2.61 (dd, *J* = 12.86 Hz, *J* = 6.93 Hz, 1H), 2.36 – 2.44 (m, 2H), 2.30 – 2.36 (m, 2H), 1.66 – 1.78 1.71 (m, 4H).ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 159.2, 157.9, 143.7, 143.6, 132.4, 129.5, 128.3, 118.9, 117.4, 114.9, 114.0, 78.7, 64.3, 64.2, 60.6, 58.0, 55.3, 54.5, 46.1, 23.6 ppm. HRMS (DART) *m/z* calcd for $C_{24}H_{28}N_2O_5$ $[M]^+$: 424.1998; Found $[M + H]^+$: 425.2076.




To a solution of **2.28h** (30 mg, 0.097 mmol) in 0.5 mL of 2:2:1 $CH_3CN$:$CH_2Cl_2$:$H_2O$ at 0 ºC was added dropwise a solution of ceric ammonium nitrate (130 mg, 0.24 mmol) in 0.3 mL of 2:1 $CH_3CN$:$H_2O$ over a period of 5 minutes. The mixture was allowed to warm up to room temperature and stirred overnight. To the reaction mixture was charged a 10% aqueous $NaHCO_3$ solution (5 mL) and extracted with EtOAc (3 x 5). The combined organics were washed with brine (5 mL) and dried with $Na_2SO_4$, filtered, and concentrated *in vacuo.* The product was purified by silica gel chromatography (eluent: 0 – 50% EtOAc in hexanes) to afford 12 mg (55%) of **2.29h** as a white solid. $R_f$ = 0.20 (40% EtOAc/hexanes). $^1$HNMR ($CDCl_3$, 600 MHz) δ: 6.85 – 6.50 (m, 2H), 6.80 – 6.85 (m, 1H), 5.87 (ddd, *J* = 18.16 Hz, *J* = 10.37 Hz, *J* = 8.43 Hz, 1H), 5.51 (s, 1H), 5.30 (d, *J* = 4.86 Hz, 1H), 5.27 (d, *J* = 12.32 Hz, 1H), 5.05 (d, *J* = 7.75 Hz, 1H), 4.26 (s, 4H), 4.18 (t, *J* = 7.46 Hz, 1H) ppm. $^{13}$C NMR (151 MHz, $CDCl_3$): δ 158.3, 144.2, 143.8, 134.9, 130.2, 119.7, 119.1, 117.7, 119.1, 117.7, 115.1, 83.2, 64.4, 64.3, 63.7 ppm.

# Chapter 3
# Development of Nanocatalysts for Heterogeneously Catalyzed Buchwald-Hartwig Amination

## I. Introduction

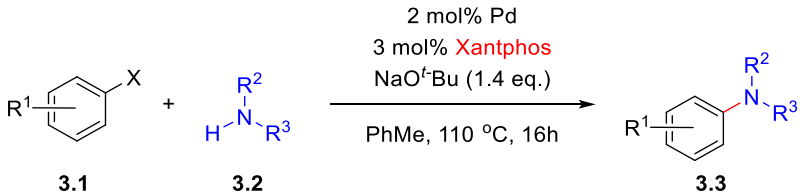
The Buchwald-Hartwig Amination is a well-established and powerful reaction used for the synthesis of aryl amines.[144–146] This Pd-catalyzed reaction couples an aryl halide with an amine to form a C($sp^2$)–N bond. This transformation has been used extensively in pharmaceutical and agrochemical industries since aromatic C($sp^2$)-N bonds are present in many compounds of interest in those industries.[146]

On average, these cross-coupling reactions are performed using homogeneous catalysis employing a soluble organic palladium complex as a catalyst.[146] These highly active homogeneous catalysts cannot be easily recycled,[147] and reactions that engage them necessitate further purification of downstream products to remove residual palladium.[148] Additional purification processes negatively impact the cost of the industrial process. Incidentally, metal nanoparticles (heterogeneous catalysts) are an excellent alternative for homogeneous systems since they are easily recovered and can therefore can potentially be reused.[147]

The El-Kaderi group at VCU employed solid-supported CuPd nanoparticles synthesized using the strong electrostatic adsorption (SEA) method to couple aryl halides with boronic acids, otherwise known as the Suzuki-Miyaura cross coupling reaction.[149] The bimetallic catalyst used in their system was shown to be highly active and recyclable. This project aims to develop a heterogeneously catalyzed Buchwald-Hartwig Amination employing nanoparticles synthesized via the SEA method.[150,151] Subsequent investigations probing all factors affecting this reaction led to a protocol that furnished aryl amines in high yields. Recycling studies have been performed and

are ongoing. The Scope of the reaction was investigated, and products were generated in modest to excellent yields.

***Scheme 3.1:*** *Heterogeneously Catalyzed Buchwald Hartwig Amination*




## II. Background

### A. Heterogeneous *vs* Homogeneous Catalysis

A catalyst is defined as a substance that increases the rate of a reaction without modifying the overall standard Gibbs free energy[152] There exist two classifications of catalysts in organic synthesis: (1) homogeneous, and (2) heterogeneous catalysts.[153] A homogeneous catalyst functions in the same phase as the chemical reactants undergoing catalysis. Conversely, a heterogenous catalyst functions in a different phase from the chemical reactants undergoing catalysis.[153]

Interest in heterogeneous catalysis has increased over the years, especially in the pharmaceutical industry, as heterogeneous catalysts can easily be recovered by simply filtering them out.[147,154–156] The recovered catalyst can then be recycled, thereby reducing the cost of industrial catalytic reactions. This is buttressed by the fact that transition metal catalysts are precious and therefore expensive.[78] Heterogeneous catalysis offers a sustainable method by which important pharmaceutical transformations can be carried out. Therefore, there is a need to develop heterogeneous catalysts for pharmaceutically relevant chemical reactions.

## Nanoparticles

Nanoparticles are synonyms to ultrafine particles and are particles of matter that are between 1 and 100 nm in diameter.[152] Nanoparticle chemistry is a relatively young branch of chemical research. Their study did not proliferate in academia until the end of the 20$^{th}$ century when modern characterization techniques such as electron microscopy became available to researchers, enabling them to analyze and characterize nanometer sized objects.[157] Scientists have since applied nanoparticles as heterogeneous catalysts to facilitate various transformations such as oxidation,[158–162] hydrogenation,[163–167] and cross coupling[168–171] reactions.

## Strong Electrostatic Adsorption (SEA)

Supported Nanoparticles are commonly prepared via impregnation, where a solid support with a high surface area is impregnated with a solution of a metal precursor.[172–176] The volatile solvents are then removed *in vacuo* or at high temperatures, and subsequent reduction of the metal produces nanoparticles. Nanoparticles prepared by impregnation exhibited non-uniform size distribution. Additionally, bimetallic nanoparticles synthesized via impregnation have inhomogeneous alloying.[177] Invented in 2008 by Regalbuto, the SEA method for nanoparticle preparation is vastly superior to the impregnation method and is known to produce ultra-small, nanoparticles with uniform size distributions.[150,151,177] The Co-SEA approach is a modification of the SEA method which furnishes bimetallic homogeneously alloyed nanoparticles.

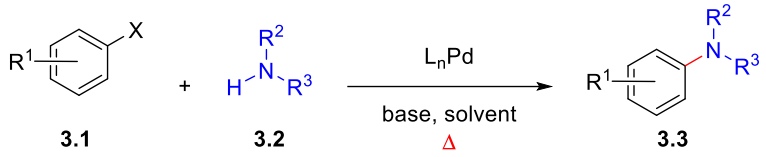
## Buchwald Hartwig Amination

### *i. History*

In 1983, Migita pioneered the use of palladium complexes as catalysts for the formation of C($sp^2$)–N bonds.[178] Migita reported the formation of aryl amines from aryl bromides and

aminostannanes employing homogeneous Palladium Phosphene complex as catalyst.[178] The use of toxic aminostannanes was subsequently skirted by Buchwald and Hartwig, who independently published a Sn-free Pd-catalyzed coupling of aryl bromides with amines in 1995.[179,180] For their efforts in developing this efficient method for C($sp^2$)–N bond formation and establishing its mechanism, the reaction was accredited to and named after Buchwald[181–189] and Hartwig.[190–197] This elegant C($sp^2$)–N bond formation reaction is now referred to as the Buchwald-Hartwig amination reaction. The typical Buchwald-Hartwig reaction employs Pd, a base, and heat to form an aryl amine from an aryl halide and an amine (**Scheme 3.2**).

***Scheme 3.2:*** *Standard Buchwald-Hartwig Amination*




ii. *Mechanism*

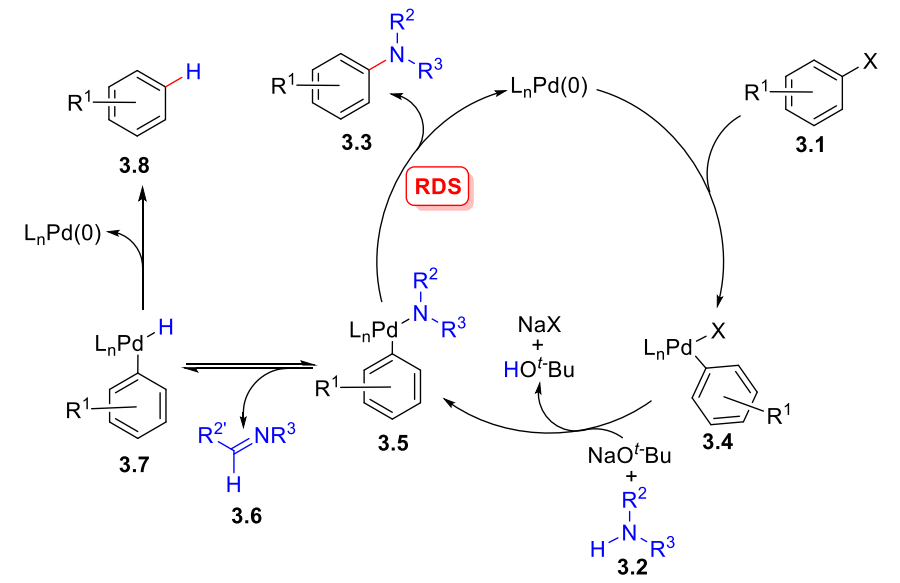



***Figure 3.1:*** *Buchwald-Hartwig Amination Mechanism*

The general mechanism for the Buchwald-Hartwig amination is depicted in **Figure 3.1** and begins with the oxidative addition of aryl halide **3.1** to a palladium(0) species to generate arylpalladium(II) complex **3.4**. This complex then reacts with amine **3.2** and a base to form the metal–nitrogen bond in complex **3.5**. Reductive elimination forges the C($sp^2$)–N bond and regenerates a palladium(0) species and the aryl amine **3.3**.[145] A competing side reaction is beta hydrogen elimination to produce an imine **3.6** and the dehalogenated arene **3.8**.[196] The reductive elimination step is turnover limiting and strongly influences the scope of the reaction.[192,193,196] Most ligands that are designed for this reaction are meant to increase the rate of reductive elimination, thereby enhancing the activity of the catalyst.[185,186,189,192–194,196]

*Factors Governing Oxidative Addition*

Oxidative addition is facilitated by electron-rich metal centers with low oxidation state.[198,199] Consequently, oxidative addition increases with decreasing C($sp^2$)–X bond strength such that the rate of oxidative addition increases in the order Cl<Br<I.[200] Lastly, the electronics of the aryl halide factors into the rate of oxidative addition.[201] Electron-rich aryl halides decrease the rate of oxidative addition whereas electron-deficient aryl halides increase the rate of oxidative addition.[201]

*Factors Governing Reductive Elimination*

The rate-determining step of the Buchwald-Hartwig amination, reductive elimination, is governed by the steric and electronic effects of the $L_nPd(0)$ complex. In general, the rate of reductive elimination increases when sterically demanding ligands are employed for the reaction because steric encumbrance at the metal center is alleviated after reductive elimination takes place. Additionally, ligands with large bite angles generally hasten reductive elimination because steric interactions can force the eliminating groups closer together, increasing the rate of C($sp^2$)–N bond

formation.[94,186,188,197] Additionally, reducing the electron density of Pd(0) by employing a sufficiently electron-withdrawing ligand dramatically accelerates the rate of reductive elimination.[197] Consequently, the choice of ligand dramatically affects the rate-limiting reductive elimination step of the Buchwald-Hartwig amination, thereby affecting the scope of the reaction. Ligands typically employed to facilitate reductive elimination are depicted in **Figure 3.2**.

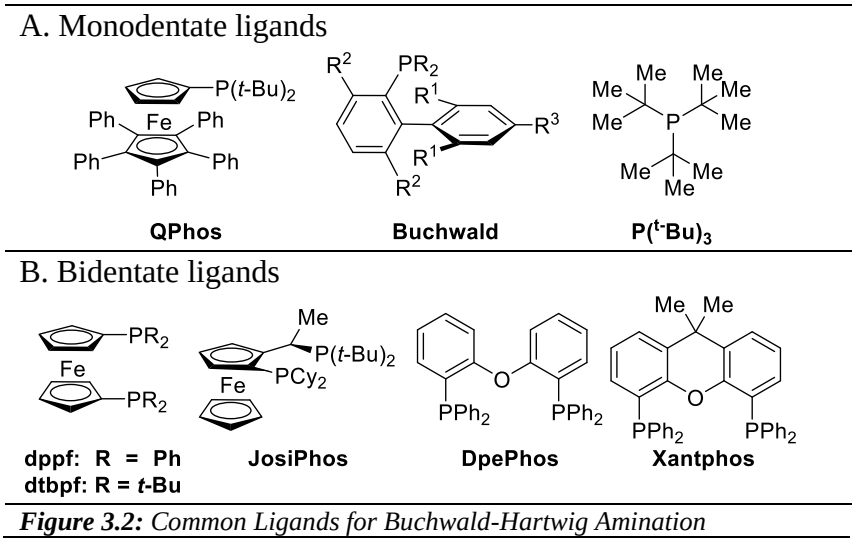



***Figure 3.2:*** *Common Ligands for Buchwald-Hartwig Amination*

## III. Reaction Development

### A. Reaction Optimization

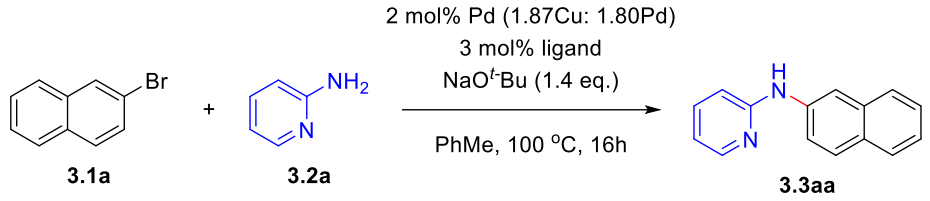
#### *i. Ligand survey for Buchwald-Hartwig Amination*

We initially set out to develop a heterogeneously catalyzed Buchwald Hartwig amination protocol employing an alloyed CuPd nanocatalyst synthesized via the Co-SEA approach. We chose the CuPd catalyst because it has been used in Suzuki-Miyaura cross coupling to enhance the rate of oxidative addition by stabilizing the Pd(0) state.[149] It has also been shown to be highly recyclable in these processes. Alexander Richard, a member of the El-Kaderi lab synthesized a CuPd nanocatalyst with equal amounts in weight of Cu (1.87 wt%) and Pd (1.80 wt%).[149]

Initial investigations began with the CuPd (1.87Cu:1.80Pd) alloyed bimetallic catalyst to perform the Buchwald-Hartwig reaction using commercially available 2-bromonaphthalene (**3.1a**) and 2-aminopyridine (**3.2a**) with NaO$^t$Bu as the base and toluene as the solvent at 100 $^o$C for 16 hours (**Table 3.1**). It was clear that the reaction did not proceed without the addition of an exogenous ligand (entry 1 *vs.* 2 – 16). Employing cBIRDP, a ligand recently used by Handa in a CuPd bimetallic micellular nanocatalytic system,[147] only generated the product in 6% yield (entry 2). Further investigation using monodentate phosphines commonly used for homogeneous Buchwald-Hartwig reactions furnished arylamine **3.3aa** in poor yields (entries 3 – 6).[145,188,189] We then employed bidentate ligands in our system, which generally produced more products than monodentate ligands (entries 2 – 6 *vs.* 7 – 15). The product yield was observed to increase with increasing ligand bite angle, which is consistent with theory (see *the factors governing reductive elimination* above). For example, dppp, with a bite angle of 91$^o$ supplied 16% of **3.3aa** whereas dppf, having a larger bite angle of 96$^o$, furnished the arylamine in 37% yield (entries 7 *vs.* 8). *Rac*-BINAP, with a slightly larger bite angle than dppf, furnished the product in 44% yield (entry 10).

A brief recycling experiment was carried out using *rac*-BINAP, which generated products in yields identical to those of the new catalyst (entry 11 *vs.* 10). Switching to xantphos ($\beta_n$ = 111$^o$, entry 14) supplied 56% of aryl amine **3.3aa**. Ligands with remarkably large bite angles, such as BISBI ($\beta_n$ = 123$^o$, entry 15) and BDFPhos ($\beta_n$ = 131$^o$, entry 16), generated product in only 3% yield, presumably because the phosphines bind *trans* instead of *cis*, rendering the catalyst inactive. At this stage, the best ligand was found to be xantphos.

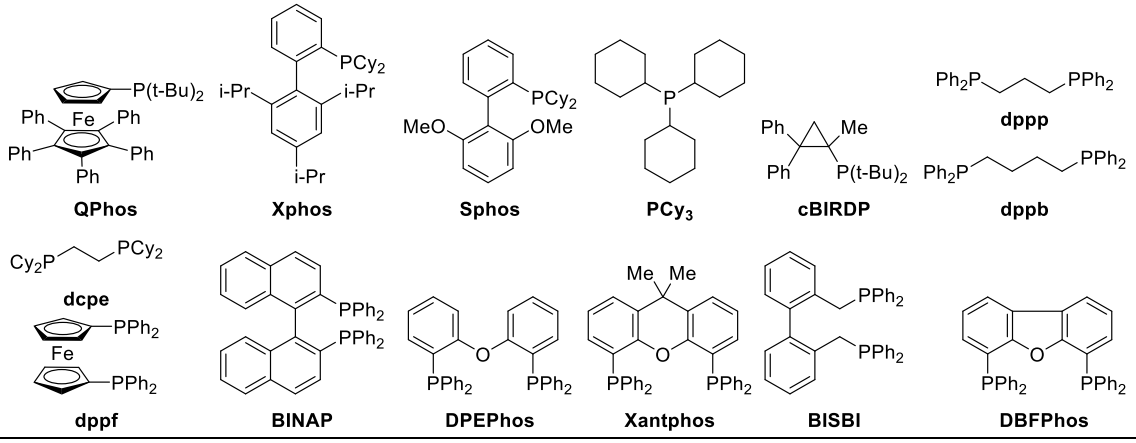
***Table 3.1:*** *Ligand Survey for Heterogeneously Catalyzed Buchwald Hartwig Amination*




**3.1a** **3.2a** **3.3aa**

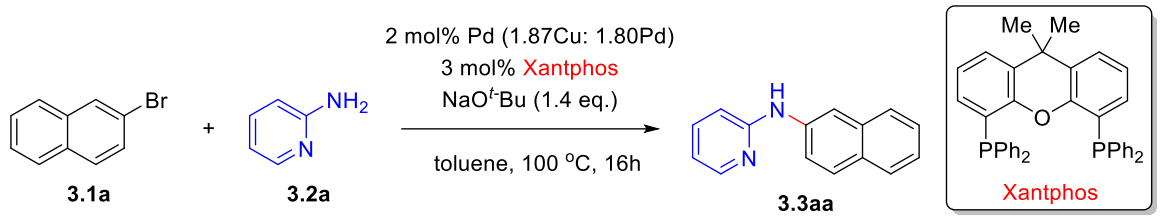
| Entry | ligand | $\beta_n$[a] | %Ar-Br[b] | %Ar-NH$_2$[b] | %Product[b] |
|---|---|---|---|---|---|
| 1 | None | - | 95 | 95 | 0 |
| 2 | cBIRDP | - | 80 | 86 | 6 |
| 3 | Sphos | - | 95 | 96 | 7 |
| 4 | Xphos | - | 95 | 94 | 3 |
| 5 | PCy3 | - | 100 | 99 | 0 |
| 6 | QPhos | - | 98 | 96 | 4 |
| 7 | dppp | 91 | 80 | 79 | 16 |
| 8 | dppf | 96 | 64 | 67 | 37 |
| 9 | dcpe | - | 99 | 99 | 2 |
| 10 | Rac-BINAP | 97 | 36 | 38 | 42 |
| 11[c] | Rac-BINAP | 97 | 48 | 55 | 44 |
| 12 | Dppb | 98 | 74 | 80 | 17 |
| 13 | DPEPhos | 103 | 82 | 90 | 10 |
| 14 | Xantphos | 111 | 49 | 44 | 56 |
| 15 | BISBI | 123 | 97 | 14 | 3 |
| 16 | DBFphos | 131 | 99 | 11 | 3 |

Reaction performed according to the general screening procedure employing **3.1a** (0.25 mmol) and **3.2a** (0.25 mmol) with NaO$^t$Bu (0.35 mmol) in 0.6 mL of toluene. See the Experimental Methods for details. [a]Ligand bite angle obtained from literature[94,95]. [b]Determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture using dimethylfumarate as standard. [c]Nanocatalyst used was recovered from entry 10.



*ii. Solvent Survey for Buchwald-Hartwig Amination*

***Table 3.2:*** *Solvent Survey for Heterogeneously Catalyzed Buchwald Hartwig Amination*




**3.1a** + **3.2a** → **3.3aa**

| Entry | Solvent | X (°C) | %Ar-Br[a] | %Ar-$NH_2$[a] | %Product[a] |
|---|---|---|---|---|---|
| 1 | toluene | 100 | 49 | 44 | 56 |
| 2 | Dioxane | 100 | 34 | 36 | 50 |
| 3 | DMF | 100 | 97 | 25 | 0 |
| 4 | THF | 70 | 99 | 98 | 2 |
| 5 | MeOH | 70 | 76 | 76 | 2 |

Reaction performed according to the general screening procedure employing **3.1a** (0.25 mmol) and **3.2a** (0.25 mmol) with NaO$^t$Bu (0.35 mmol) in 0.6 mL of toluene. See the Experimental Methods for details. [a]Determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture using dimethylfumarate as standard.

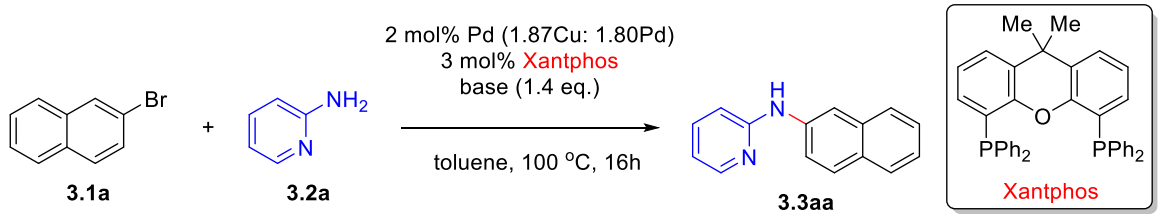
Using xantphos as ligand and Cu/Pd (1.87Cu:1.80Pd) as catalyst, the effects of solvent on this reaction was briefly probed by investigating the impact of various solvents on the reaction (**Table 3.2**). Non-coordinating solvents were well tolerated in this reaction (entries 1 and 2). Toluene generated 56% of the **3.3aa** at 100 °C whereas dioxane furnished the product in 50% yield (entry 1 *vs.* 2). Polar-coordinating solvents, such as DMF, THF, and MeOH, severely limited the reaction yield (entries 2 – 5). Consequently, toluene was identified as the optimal solvent for this reaction.

*Base Survey for Buchwald-Hartwig Amination*

To further improve the reaction yield, we investigated the impact of the base on the system by performing the reaction with xantphos as the ligand, Cu/Pd (1.87Cu:1.80Pd) as the catalyst, and toluene as the reaction solvent (**Table 3.3**). Investigations began with Group 1 metal tertiary butoxides. Interestingly, the yield of the reaction was affected by the cation associated with the

metal butoxide, with Li$O^{t}$-Bu generating 40% product, Na$O^{t}$-Bu producing 56% of **3.3aa**, and K$O^{t}$-Bu generating 72% product (entries 1 – 3). This counter-ion dependency of the base on the yield of the reaction was found to be substrate-dependent, as *N*-Boc-piperazine did not exhibit such an effect, generating product at 14% regardless of the M$O^{t}$-Bu used. The more soluble Na$O^{t}$-Amyl provided only 39% of the product (entry 4). We then employed carbonates as bases (entries 5 and 6); however, carbonates did not perform as well as alkoxide bases (entries 5 and 6 vs 1-4) with $K_2CO_3$ and $Cs_2CO_3$, generating 8 and 16% products, respectively. Tertiary amines, such as DABCO and DBU, were not suitable bases for this reaction because no product was generated when they were used as bases (entries 7 and 8). All the preceding optimization studies conducted for this reaction suggest that K$O^{t}$-Bu is the best base when a Cu/Pd (1.87Cu:1.80Pd) catalyst is employed.

***Table 3.3:*** *Base Survey for Heterogeneously Catalyzed Buchwald Hartwig Amination*



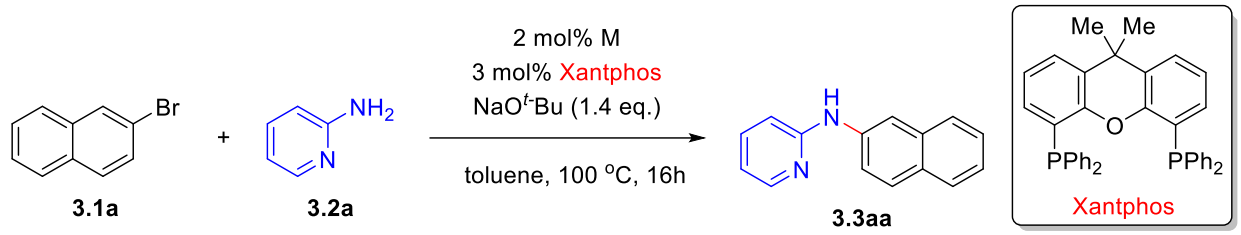

3.1a + 3.2a → 3.3aa

| Entry | Base | %Ar-Br[a] | %Ar-$NH_2$[a] | %Product[a] |
|---|---|---|---|---|
| 1 | Li$O^{t}$-Bu | 61 | 60 | 40 |
| 2 | Na$O^{t}$-Bu | 49 | 44 | 56 |
| 3 | K$O^{t}$-Bu | 30 | 30 | 72 |
| 4 | Na$O^{t}$-Amyl | 58 | 57 | 39 |
| 5 | $K_2CO_3$ | 91 | 90 | 8 |
| 6 | $Cs_2CO_3$ | 84 | 85 | 16 |
| 7 | DABCO | 98 | 97 | 0 |
| 8 | DBU | 99 | 100 | 0 |

Reaction performed according to the general screening procedure employing **3.1a** (0.25 mmol) and **3.2a** (0.25 mmol) with Base (0.35 mmol) in 0.6 mL of toluene. See the Experimental Methods for details. [a]Determined by $^{1}$H-NMR spectroscopy on the unpurified reaction mixture using dimethylfumarate as standard.

*iii. Catalyst Survey for Buchwald-Hartwig Amination*

***Table 3.4:*** *Catalyst Survey for Heterogeneously Catalyzed Buchwald Hartwig Amination*




**3.1a** + **3.2a** → **3.3aa**

| Entry | Solvent | %Ar-Br[a] | %Ar-$NH_2$[a] | %Product[a] | Note |
|---|---|---|---|---|---|
| 1 | 1.88 Cu: 1.88 Pd | 30 | 30 | 72 | KO$^t$Bu as base |
| 2 | 1.88 Cu: 1.88 Pd | 15 | 9 | 91 | KO$^t$Bu as base, 110 °C |
| 3 | 1.95 Cu: 0.480 Pd | 42 | 50 | 50 | KO$^t$Bu as base |
| 4 | Pd (1.94 Pd) | 25 | 27 | 73 | KO$^t$Bu as base |
| 5 | Pd (1.94 Pd) | 25 | 26 | 76 | - |
| 6 | Pd (1.94 Pd) | 4 | 5 | 95 | 110 °C |
| 7 | 1.35 Co: 1.16 Pd | 47 | 40 | 53 | 110 °C |
| 8 | 1.72 Co: 1.81 Pd | 20 | 18 | 78 | 110 °C |
| 9 | 0.314 Ni: 2.13 Pd | 16 | 20 | 84 | 110 °C |
| 10 | 1.71 Ni: 1.32 Pd | 15 | 17 | 85 | 110 °C |

Reaction performed according to the general screening procedure employing **3.1a** (0.25 mmol) and **3.2a** (0.25 mmol) with NaO$^t$Bu (0.35 mmol) in 0.6 mL of toluene. See the Experimental Methods for details. [a]Determined by $^1$H-NMR spectroscopy on the unpurified reaction mixture using dimethylfumarate as standard.

The catalyst composition was examined next (**Table 3.4**). Initial studies established that KO$^t$Bu was the best base when the Cu/Pd (1.80Pd:1.87Cu) catalyst was employed (entry 1). Increasing the reaction temperature to 110 °C significantly improved the yield from 72% to 91% (entry 1 *vs.* 2). Switching to a new catalyst with 1.95wt% Cu and 0.480wt% Pd to perform the reaction at 100 °C generated only 50% product (entry 3). Using a 1.94 wt% Pd catalyst without Cu at 100 °C with KO$^t$Bu produced **3.3aa** at 73% yield, whereas NaO$^t$Bu furnished 76% product (entry 4 *vs.* 5). Performing the reaction at 110 °C with the 1.94 wt% Pd catalyst and NaO$^t$Bu as base yielded 95% of the product (entry 6). Co:Pd and Ni:Pd bimetallic catalysts were also investigated but were inferior to Cu:Pd and Pd systems (entries 2 and 6 *vs.* 7-10). Although the Cu/Pd (1.80Pd:1.87Cu) catalyst performed similarly to the 1.94 wt% Pd catalyst, the introduction of Cu to the catalyst led to counter-ion dependency on the reaction, which was also substrate-

dependent. To nullify those effects, the 1.94 wt% Pd catalyst was chosen as the ideal catalyst for this reaction (entry 6).

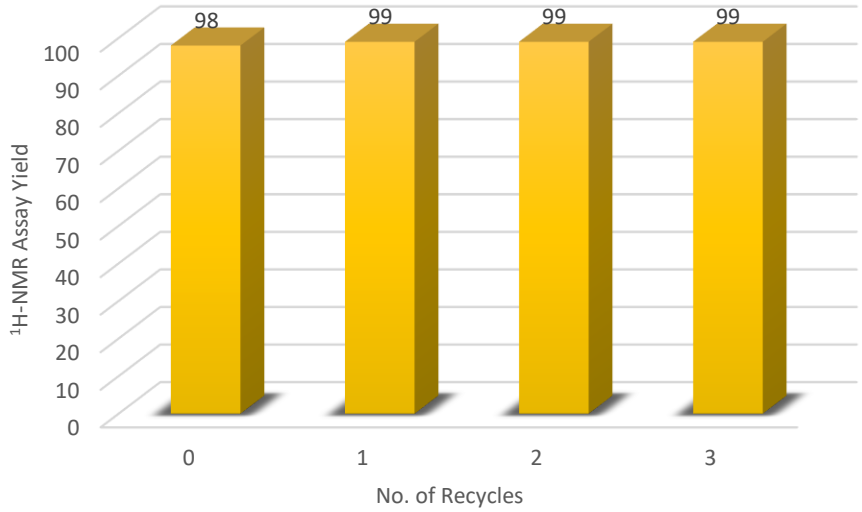
**Recycle Studies**

The major driving force behind this project was the recovery and reusability of the Pd nanocatalyst. A rudimentary recycling experiment was previously conducted using *rac*-BINAP as the ligand, which showed that the catalyst was recyclable (entries 10 and 11, **Table 3.1**). Therefore, the recyclability of the catalyst was investigated by iteratively performing the reaction under optimal conditions using the recovered catalyst (**Figure 3.3**). Initial recycling experiments at a 0.250 mmol scale with 1.94 wt% Pd showed that the catalyst remained consistently active, generating product in excellent yield over three recycles (**Figure 3.3A**). With the catalyst reserve running dry, Alexander Richard synthesized a new batch of 1.99 wt% Pd catalyst. Subsequent recycling studies were conducted on a larger scale of 2.00 mmol to test the limit of the catalyst recyclability (**Figure 3.3B**). Unfortunately, this batch of catalyst proved to be inferior to the initial batch, with a gradual decline in catalyst activity after every cycle. The crude reaction mixtures were analyzed by Alexander Richard who noted that there was negligible residual Pd in the crude reaction mixture for the initial recycle studies using 1.94 wt% Pd. However, there was an increase in residual Pd in the crude reaction mixtures for the scaled-up recycling experiment, which accounts for the shift in catalyst recyclability between the two nanocatalysts.

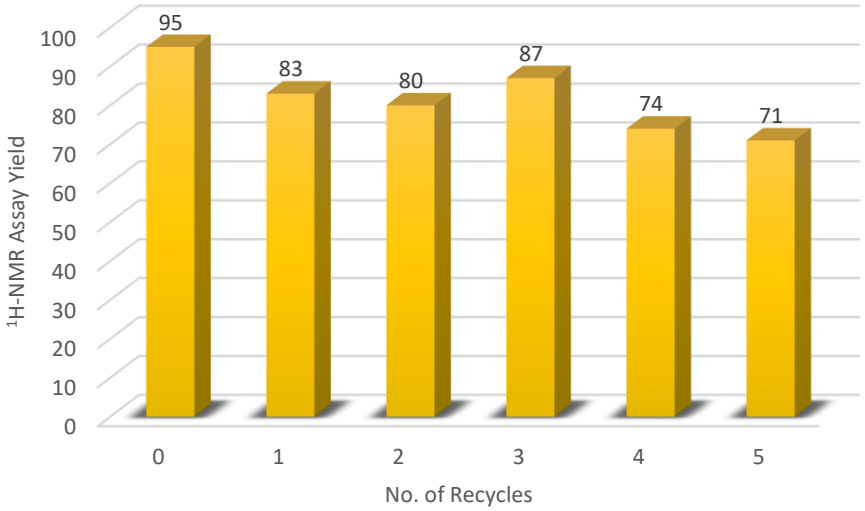
The leaching of Pd into solution prompted us to perform a homogeneous reaction with $Pd_2(dba)_2$ under optimized reaction conditions to determine whether the leached Pd is the active catalyst for the amination reaction (**Figure 3.3C**). The results of the homogeneous reaction are identical to those of the optimized heterogeneous reaction, suggesting that this reaction proceeds

via a catch and release mechanism[202] where the leached Pd performs the reaction and is adsorbed back onto the silica. However, further investigation is ongoing.

A. Recycle Study Using 1.94 wt% Pd




B. Recycle Study Using 1.99 wt% Pd




C. Homogeneous Control

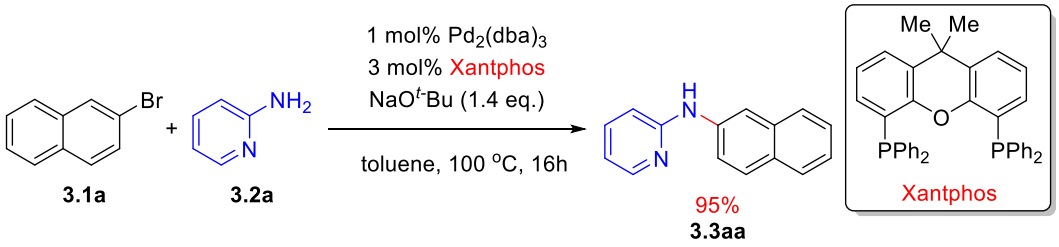
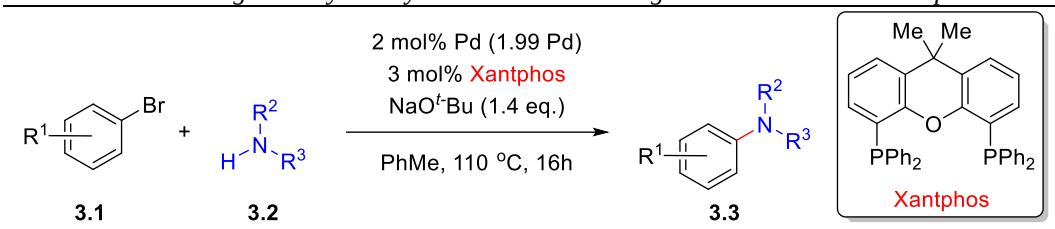


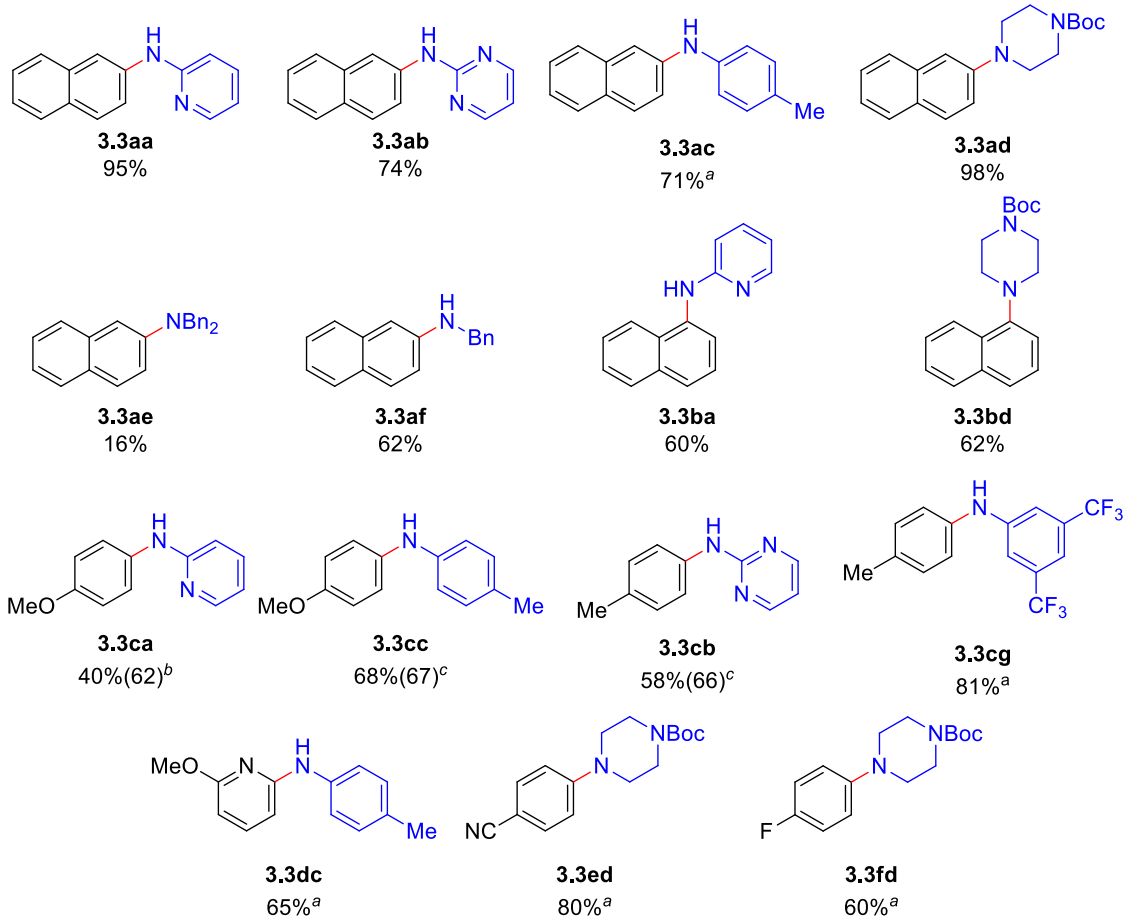

***Figure 3.3:*** *Recycle Studies Conducted Using Aryl Halide* ***3.1a*** *and Aryl Amine* ***3.3a***

## B. Substrate Scope

***Scheme 3.3:*** *Heterogeneously Catalyzed Buchwald-Hartwig Amination Substrate Scope*




**3.1** **3.2** **3.3**



**3.3aa** 95%

**3.3ab** 74%

**3.3ac** 71%[a]

**3.3ad** 98%

**3.3ae** 16%

**3.3af** 62%

**3.3ba** 60%

**3.3bd** 62%

**3.3ca** 40%(62)[b]

**3.3cc** 68%(67)[c]

**3.3cb** 58%(66)[c]

**3.3cg** 81%[a]

**3.3dc** 65%[a]

**3.3ed** 80%[a]

**3.3fd** 60%[a]

Reaction performed according to the general screening procedure employing **3.1a** (0.25 mmol) and **3.2a** (0.25 mmol) with NaO$^t$Bu (0.35 mmol) in 0.6 mL of toluene. [a]Reaction ran for 24h. [b]Reaction ran with xylene at 140 °C. [c]Aryl-iodide was used.

The scope of the reaction was investigated by employing a variety of sterically and electronically different aryl halides and amines to run the Buchwald-Hartwig Amination under the optimized reaction conditions (**Scheme 3.3**). These results were obtained in collaboration with Stephen Collins, a fellow graduate student in the Sieber laboratory. The reaction was generally

high yielding and performed well with *meta*-substituted aryl halides and electron-rich amines (**3.3aa-3.3af, 3.3dc**). However, dibenzylamine generated **3.3ae** in only 16% yield due to competing β-hydride elimination, generating 55% imine and 60% naphthalene, respectively. *ortho-substituted* aryl halides also behaved well in this system, furnishing **3.3ba,bd** in reasonable yields. Interestingly, electron-rich *para*-substituted aryl halides performed better with electron-deficient amines than with electron-rich amines (**3.3cg** vs **3.3ca**,**cc**,**cb**). The strikingly low yield of **3.3ca** prompted us to increase the reaction temperature to increase the yield, because the mass balance was the only product and starting material. Employing xylenes as a solvent permitted an increase in the reaction temperature to 140 $^{o}$C which led to a 22% increase in the yield, generating 62% of **3.3ca**. We also briefly probed the impact of the halide on the reaction to discover aryl iodides performed just as well as aryl bromides **3.3cc** and **3.3cb**.

## IV. Conclusions and Future Work

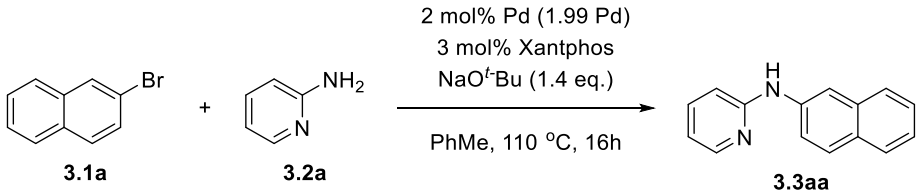
The newly developed protocol for the Buchwald-Hartwig amination employing silica-supported Pd nanoparticles synthesized via the SEA method as a catalyst was effective and generated products in good to excellent yields. The scope of this reaction requires further investigation to establish the limits of this system. Recycling studies are ongoing as new batches of catalysts are being synthesized to address the Pd leaching issue. This reaction is currently presumed to proceed through a catch-and-release mechanism;[202] however, further studies are needed to establish the mode of catalysis for this newly developed protocol.

## V. Experimental Methods

### General:

$^{1}$H-NMR spectra were recorded on Bruker 600 MHz spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as an internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, br = broad, m = multiplet), and coupling constants (Hz). $^{13}$C NMR was recorded on a Bruker 600 MHz (151 MHz) instrument with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard ($CDCl_3$: 77.0 ppm). Thin layer chromatography (TLC) was performed on glass-backed 250 μm silica gel F254 plates purchased from Silicycle. Visualization was achieved using UV light, a 10% solution of phosphomolybdic acid in EtOH, or potassium permanganate in water followed by heating. All reactions were conducted in oven or flame dried glassware under an inert atmosphere of nitrogen or argon with magnetic stirring unless otherwise noted. Solvents were obtained from VWR as HPLC grade and transferred to septa sealed bottles, degassed by Ar sparge, and analyzed by Karl-Fischer titration to ensure water content was $\leq$ 600 ppm. Amines and Aryl halides were purchased from Sigma Aldrich, TCI America, Alfa Aesar, or Oakwood Chemicals and used as received. All other materials were purchased from VWR, Sigma Aldrich, Combi-Blocks, Alfa-Aesar, or Strem Chemical Company and used as received.

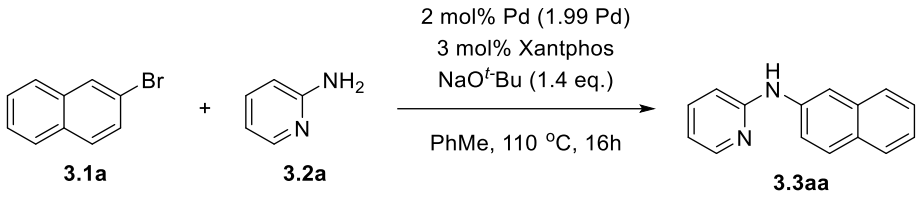
### General Screening Procedure




**3.1a** **3.2a** **3.3aa**

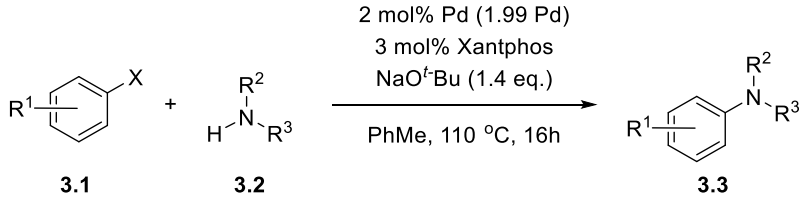
To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 51.8 mg (0.250 mmol) of 2-bromonaphthalene, 23.5 mg (0.250 mmol) of 2-aminopyradine, 33.4 mg ( 0.350 mmol) of NaO$^{t}$Bu, 27 mg (5.05 μmol) of 1.99 wt% Pd nanocatalyst, and 4.34 mg (7.50 μmol) of Xantphos. The mixture was then dissolved in Toluene (0.60 mL) and reaction vessel sealed with a crimp-cap septum and removed from the glove-box. The reaction vessel was then placed in an oil bath at 110 °C and stirred for 16h and then cooled to room temperature. To the mixture was then charged EtOAc (2.0 mL). The organics were filtered under vacuum and concentrated *in vacuo.* To the crude residue was charged dimethylfumarate (10 – 15 mg), and the mixture was diluted in ~0.5 mL of $CDCl_3$. Further dilution of an aliquot and analysis by $^{1}$H-NMR was used to determine the yield.

## Recycling Procedure



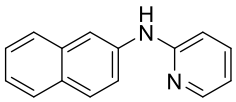

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged 414 mg (2.00 mmol) of 2-bromonaphthalene, 188 mg (2.00 mmol) of 2-aminopyradine, 269 mg ( 2.80 mmol) of NaO$^t$-Bu, 214 mg (46.0 μmol) of 1.99 wt% Pd nanocatalyst, and 34.7 mg (60.0 μmol) of xantphos. The mixture was then dissolved in toluene (4.90 mL) and reaction vessel sealed with a crimp-cap septum and removed from the glove-box. The reaction vessel was then placed in an oil bath at 110 °C and stirred for 16h and then cooled to room temperature. To the mixture was then charged EtOAc (5.0 mL). The organics were filtered under vacuum and concentrated *in vacuo.* To the crude residue was charged dimethylfumarate (10 – 15 mg), and the mixture was diluted in ~0.5 mL of $CDCl_3$. Further dilution of an aliquot and analysis by $^1$H-NMR was used to determine the yield. The nanoparticle residue on filter-paper was then washed with $H_2O$ (2 x 10 mL), then EtOH (2 x 10 mL) and then dried under vacuum for 5 minutes. The dried nanoparticle was then weighed, and the reaction was performed again adjusting reactant charges to match the recovered catalyst weight.

## General Procedure



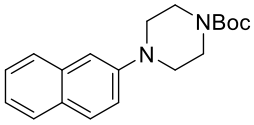

To a 20 mL crimp-cap vial with stir-bar in an Ar-filled glove-box was charged Aryl halide **3.1** (0.250 mmol), Amine **3.2** (0.250 mmol), 33.4 mg ( 0.350 mmol) of NaO$^t$-Bu, 27 mg (5.1 μmol) of 1.99 wt% Pd nanocatalyst, and 4.3 mg (7.5 μmol) of Xantphos. The mixture was then dissolved in Toluene (0.60 mL) and reaction vessel sealed with a crimp-cap septum and removed from the glove-box. The reaction vessel was then placed in an oil bath at 110 °C and stirred for 16 h and then cooled to room temperature. To the mixture was then charged EtOAc (2.0 mL). The organics were filtered under vacuum and concentrated *in vacuo*. The nanoparticle residue on filter-paper was then washed with $H_2O$ (2 x 10 mL), then EtOH (2 x 10 mL) and then dried under vacuum for 5 minutes. The dried nanoparticle was then weighed and stored under argon. The crude organic residue was then purified by flash chromatography on silica gel to afford the desired product.

**Analytical Data**



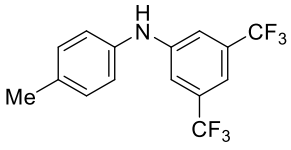
**3.3aa**

***N*-(naphthalen-2-yl)pyridin-2-amine (3.3aa)**: According to the general procedure and purified by silica gel chromatography (eluent: 0 – 30% EtOAc in Hexanes) to provide 52.1 mg (95%) of **3.3aa** as a white solid. $R_f$ = 0.3 (5% EtOAc/Hexanes). Spectral data was consistent with the literature report.[203]



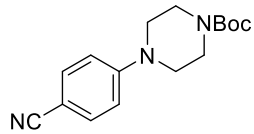
**3.3ad**

**tert-butyl 4-(naphthalen-2-yl)piperazine-1-carboxylate (3.3ad)**: According to the general procedure and purified by silica gel chromatography (eluent: 0 – 30% EtOAc in Hexanes) to provide 77.4 mg (98%) of **3.3ad** as a white solid**.** $R_f$ = 0.4 (5% EtOAc/Hexanes). Spectral data was consistent with the literature report.[204]



**3.3cg**

***N*-(p-tolyl)-3,5-bis(trifluoromethyl)aniline (3.3cg)**: According to the general procedure and purified by silica gel chromatography (eluent: 0 – 30% EtOAc in Hexanes) to provide 65.3 mg (81%) of **3.3cg** as a white solid. $R_f$ = 0.3 (10% EtOAc/Hexanes) Spectral data was consistent with the literature report.[205]

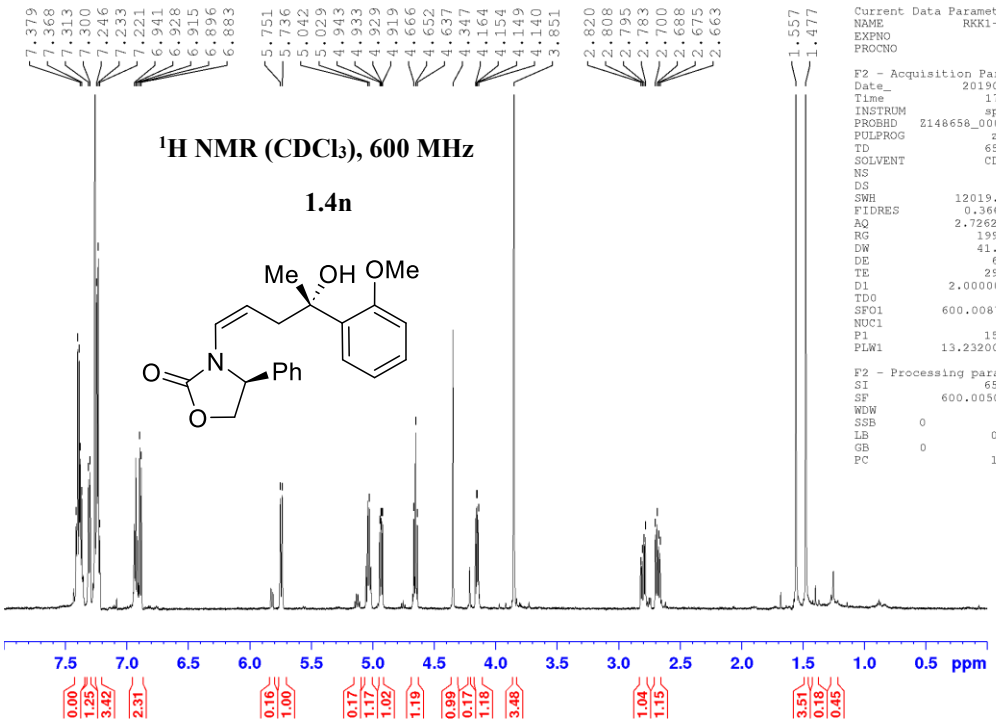


**3.3ed**

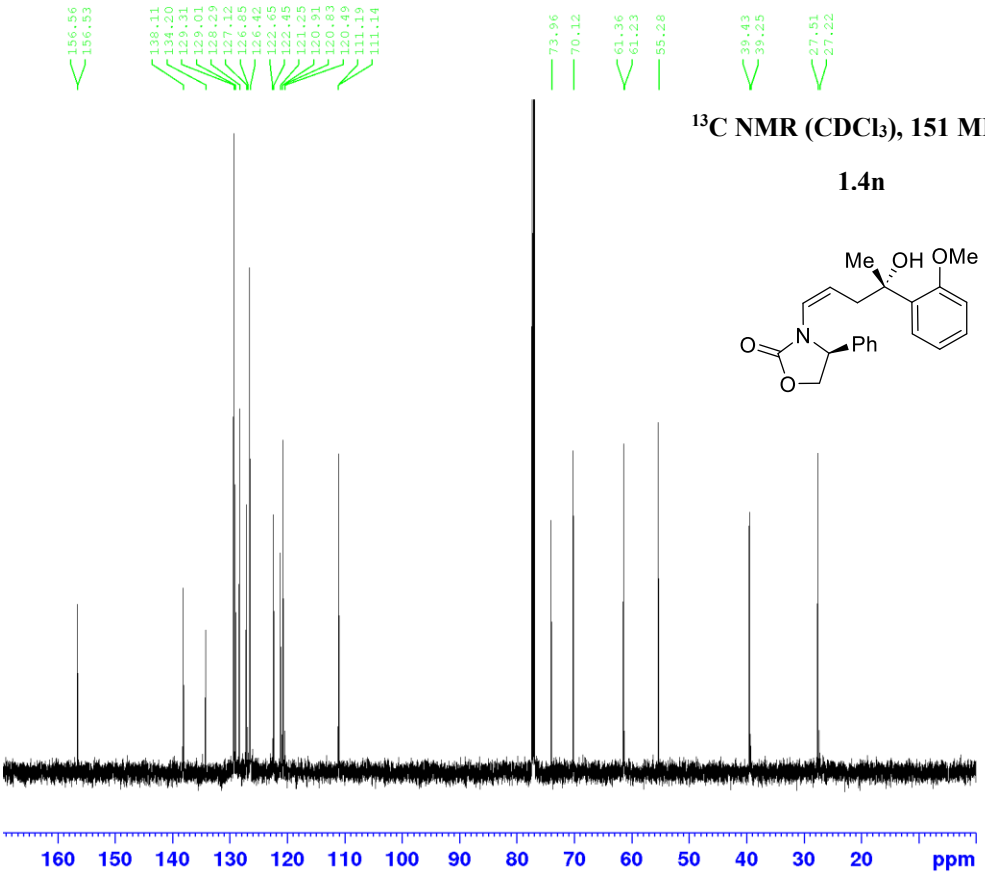
**tert-butyl 4-(4-cyanophenyl)piperazine-1-carboxylate (3.3ed)**: According to the general procedure and purified by silica gel chromatography (eluent: 0 – 30% EtOAc in Hexanes) to provide 57.2 mg (80%) of **3.3ed** as a white solid**.** $R_f$ = 0.3 (5% EtOAc/Hexanes). Spectral data was consistent with the literature report.[206]

All other compounds prepared were synthesized by other group members.

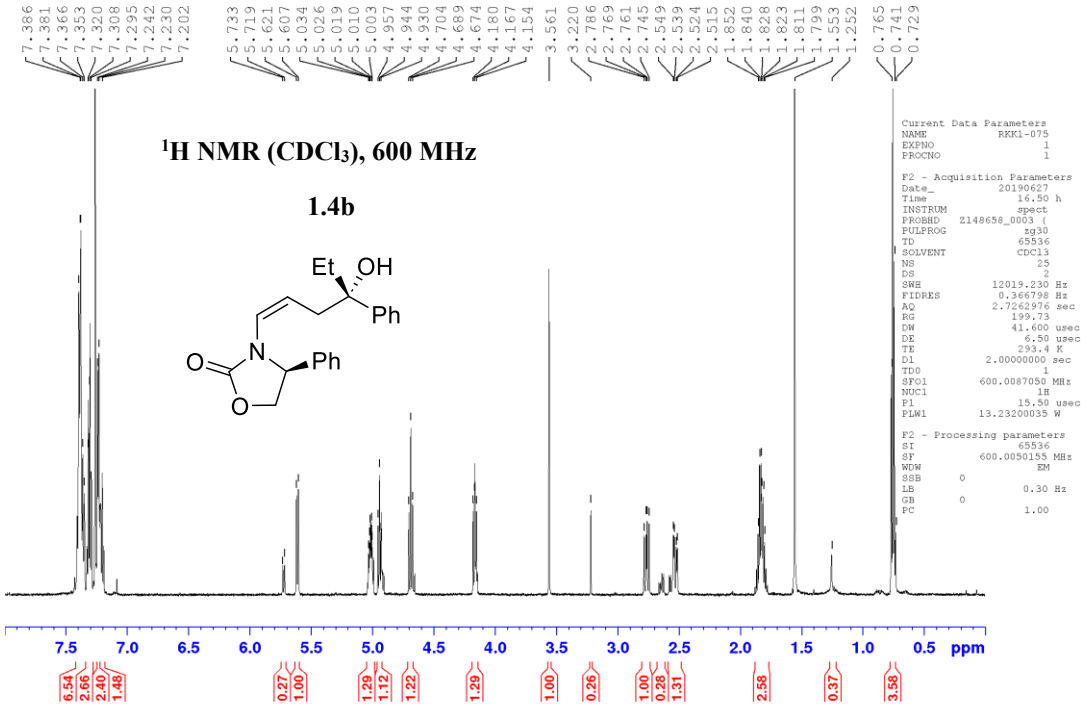
## APPENDIX A1. SELECT NMR SPECTRA FROM CHAPTER 1

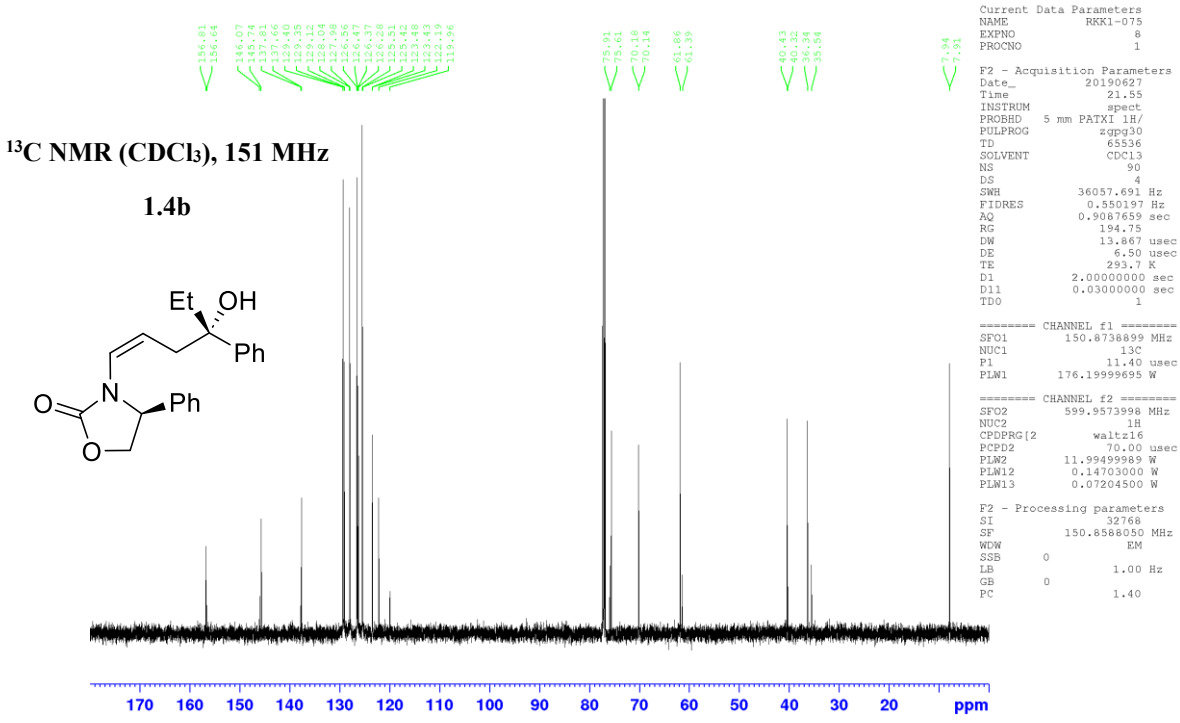


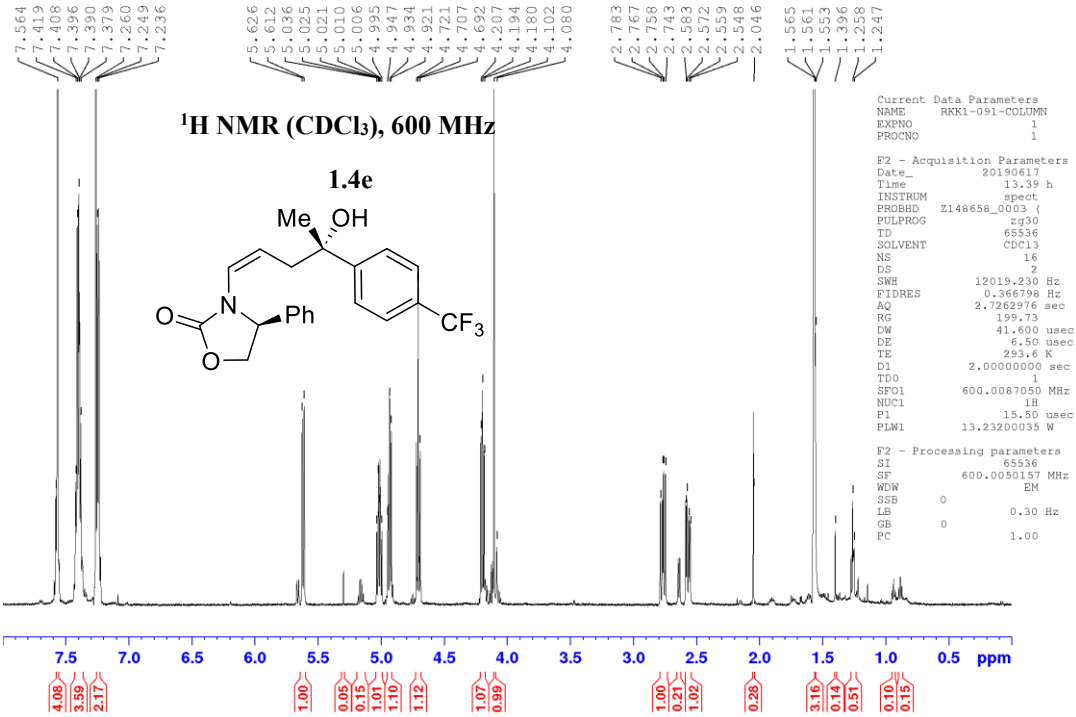

```
Current Data Parameters
NAME                  RKK1-079
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20190627
Time                   17.00 h
INSTRUM                spect
PROBHD    Z148658_0003 (
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       25
DS                        2
SWH               12019.230 Hz
FIDRES             0.366798 Hz
AQ                2.7262976 sec
RG                    199.73
DW                   41.600 usec
DE                    6.50 usec
TE                   293.4 K
D1                2.00000000 sec
TD0                          1
SFO1           600.0087050 MHz
NUC1                      1H
P1                    15.50 usec
PLW1           13.23200035 W

F2 - Processing parameters
SI                    65536
SF             600.0050155 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

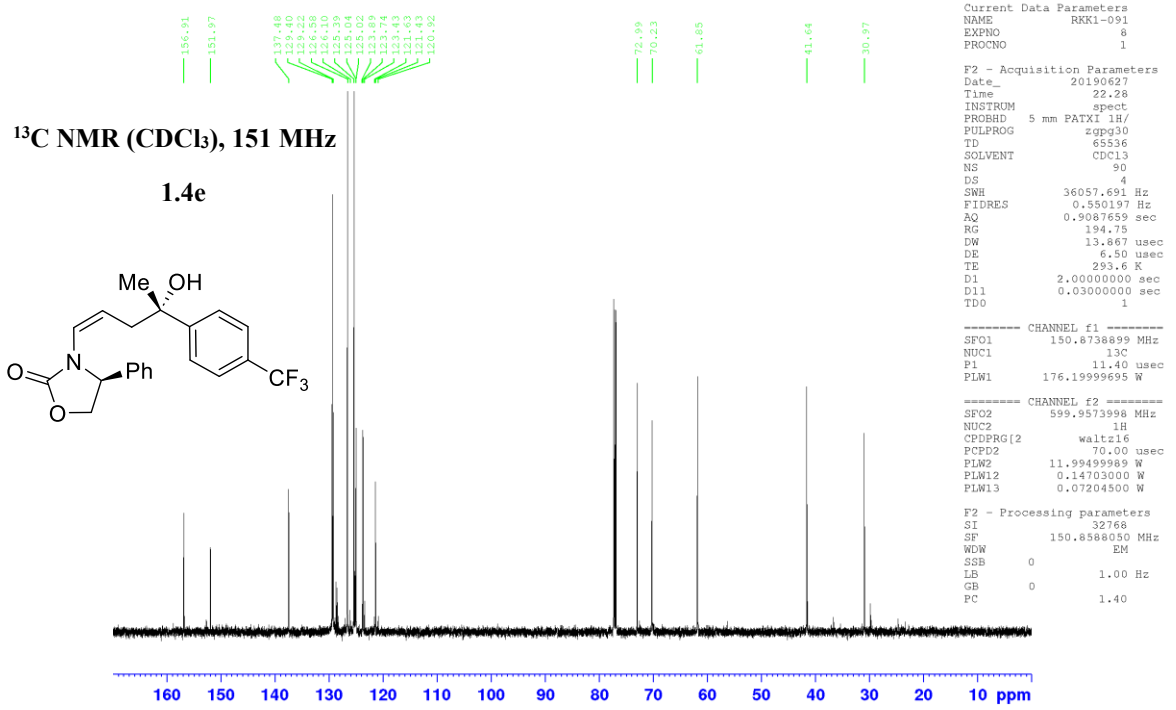


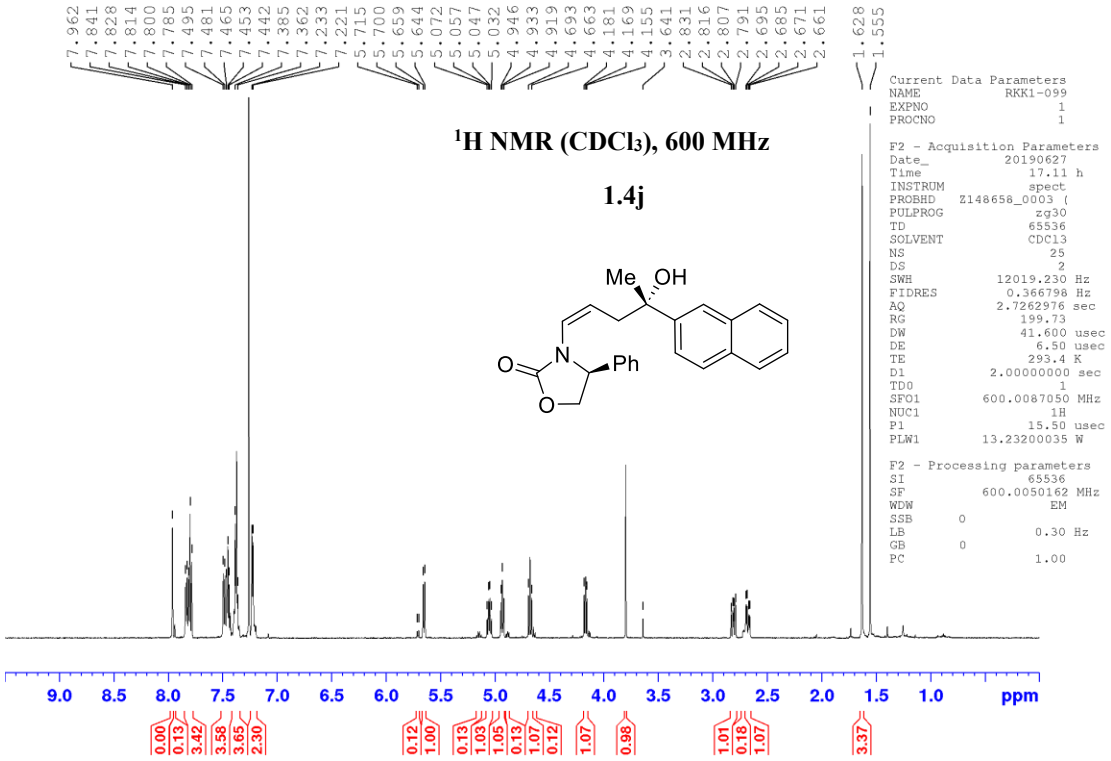

```
Current Data Parameters
NAME                  RKK1-079
EXPNO                        8
PROCNO                       1

F2 - Acquisition Parameters
Date_               20190627
Time                   22.11
INSTRUM                spect
PROBHD    5 mm PATXI 1H/
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       90
DS                        4
SWH               36057.691 Hz
FIDRES             0.550197 Hz
AQ                0.9087659 sec
RG                    194.75
DW                   13.867 usec
DE                    6.50 usec
TE                   293.7 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                          1

======== CHANNEL f1 ========
SFO1           150.8738899 MHz
NUC1                      13C
P1                   11.40 usec
PLW1         176.19999695 W

======== CHANNEL f2 ========
SFO2           599.9573998 MHz
NUC2                      1H
CPDPRG[2           waltz16
PCPD2                70.00 usec
PLW2           11.99499989 W
PLW12           0.14703000 W
PLW13           0.07204500 W

F2 - Processing parameters
SI                    32768
SF             150.8588050 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```


7.386
7.381
7.366
7.353
7.320
7.308
7.295
7.242
7.230
7.202
5.733
5.719
5.621
5.607
5.034
5.026
5.019
5.010
5.003
4.957
4.944
4.930
4.704
4.689
4.674
4.180
4.167
4.154
3.561
3.220
2.786
2.769
2.761
2.745
2.549
2.539
2.524
2.515
1.852
1.840
1.828
1.823
1.811
1.799
1.553
1.252
0.765
0.741
0.729
1H NMR (CDCl3), 600 MHz
1.4b
Et
OH
Ph
N
Ph
O
O
Current Data Parameters
NAME RKK1-075
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190627
Time 16.50 h
INSTRUM spect
PROBHD 2148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 25
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 293.4 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050155 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
6.54
2.66
2.40
1.48
0.27
1.00
1.29
1.12
1.22
1.29
1.00
0.26
1.00
0.28
1.31
2.58
0.37
3.58


156.81
156.64
146.07
145.74
137.81
137.66
129.40
129.35
129.21
128.04
127.98
126.56
126.47
126.37
126.28
125.51
125.42
123.48
123.43
122.19
122.06
119.96
75.91
75.61
70.18
70.14
61.86
61.39
40.43
40.32
36.34
35.94
7.94
7.91
13C NMR (CDCl3), 151 MHz
1.4b
Et
OH
Ph
N
Ph
O
O
Current Data Parameters
NAME RKK1-075
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190627
Time 21.55
INSTRUM spect
PROBHD 5 mm PATXI 1H/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 36057.691 Hz
FIDRES 0.550197 Hz
AQ 0.9087659 sec
RG 194.75
DW 13.867 usec
DE 6.50 usec
TE 293.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 150.8738899 MHz
NUC1 13C
P1 11.40 usec
PLW1 176.19999695 W
======== CHANNEL f2 ========
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07204500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


7.564
7.419
7.408
7.396
7.390
7.379
7.260
7.249
7.236
5.626
5.612
5.036
5.025
5.021
5.010
5.006
4.995
4.947
4.934
4.921
4.721
4.707
4.692
4.207
4.194
4.180
4.102
4.080
2.783
2.767
2.758
2.743
2.583
2.572
2.559
2.548
2.046
1.565
1.561
1.553
1.396
1.258
1.247
1H NMR (CDCl3), 600 MHz
1.4e
Me
OH
N
O
O
Ph
CF3
Current Data Parameters
NAME RKK1-091-COLUMN
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190617
Time 13.39 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 293.6 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050157 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.08
3.59
2.17
1.00
0.05
0.15
1.01
1.10
1.12
1.07
0.99
1.00
0.21
1.02
0.28
3.16
0.14
0.51
0.10
0.15

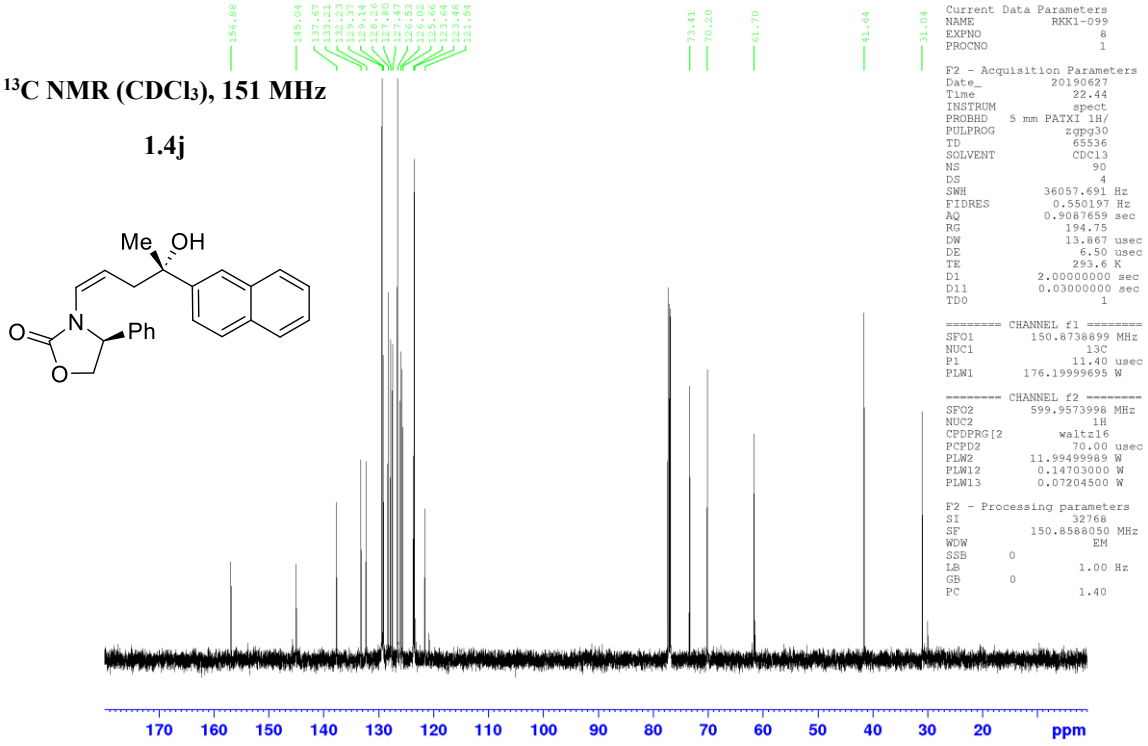

156.91
151.97
137.48
129.40
129.22
126.58
126.10
125.39
125.04
125.02
123.89
123.74
123.43
121.63
121.43
120.92
72.99
70.23
61.85
41.64
30.97
13C NMR (CDCl3), 151 MHz
1.4e
Me
OH
N
O
O
Ph
CF3
Current Data Parameters
NAME RKK1-091
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190627
Time 22.28
INSTRUM spect
PROBHD 5 mm PATXI 1H/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 36057.691 Hz
FIDRES 0.550197 Hz
AQ 0.9087659 sec
RG 194.75
DW 13.867 usec
DE 6.50 usec
TE 293.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 150.8738899 MHz
NUC1 13C
P1 11.40 usec
PLW1 176.19999695 W
======== CHANNEL f2 ========
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07204500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm




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

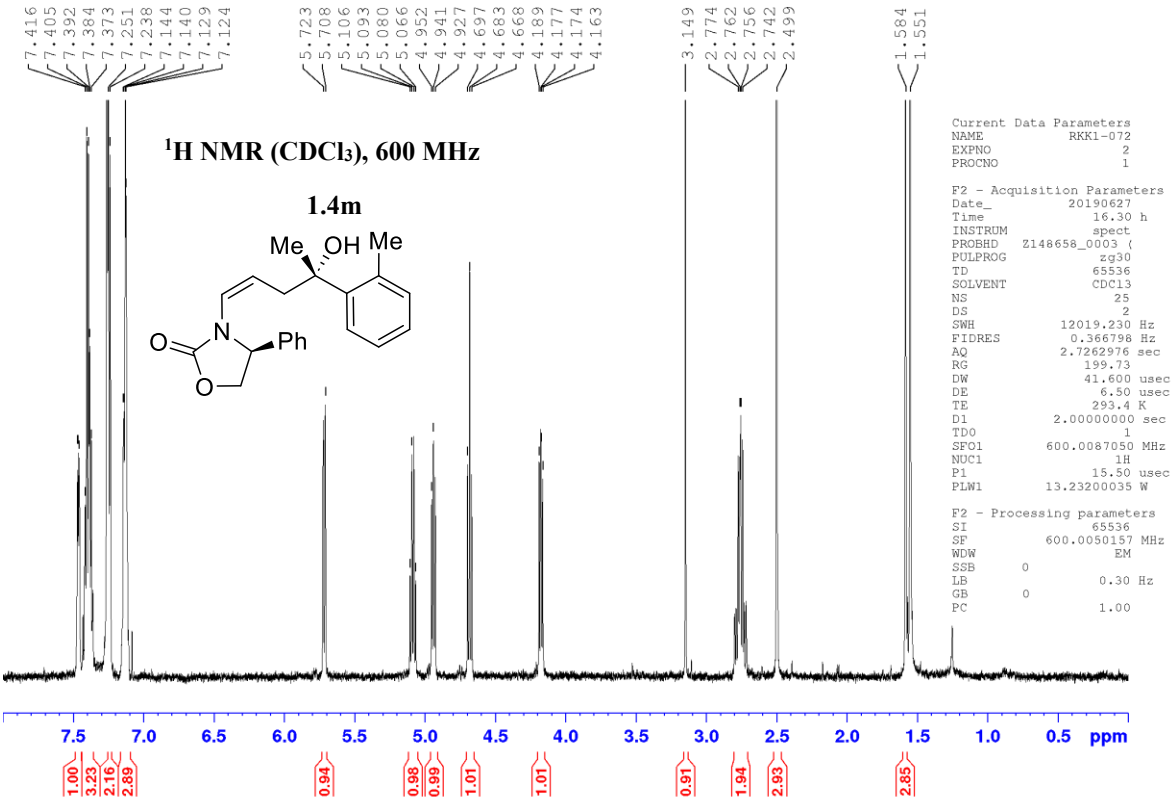
**1.4j**

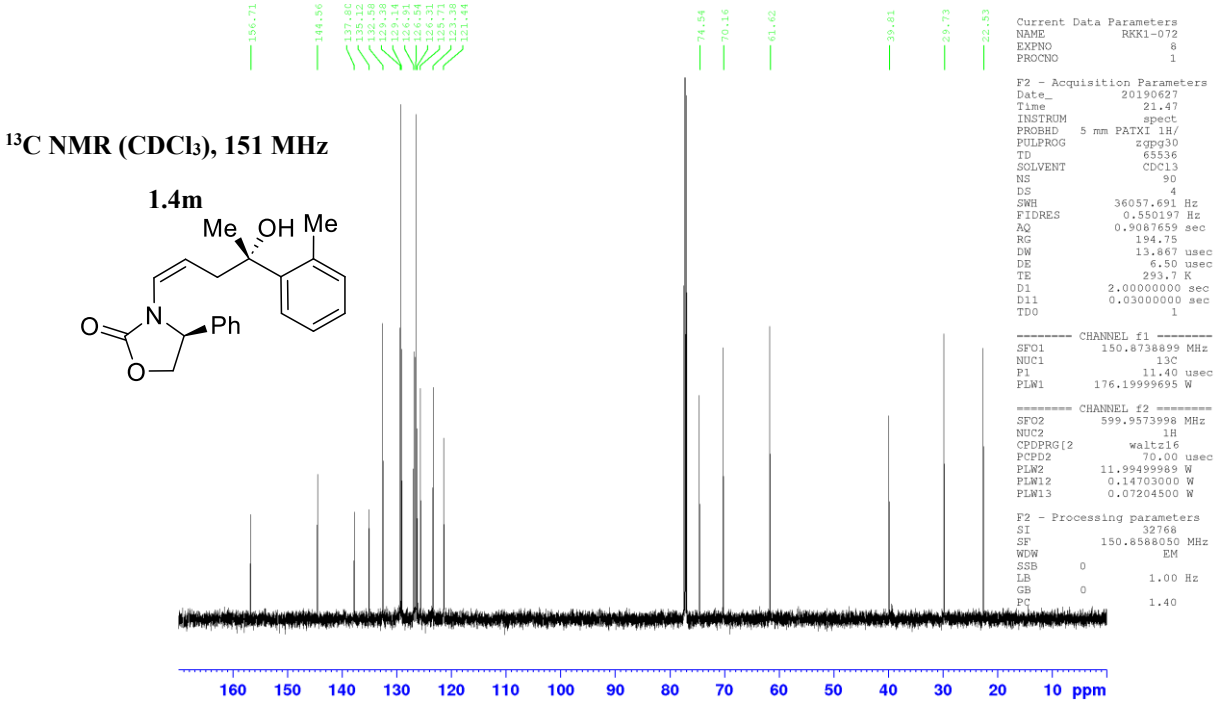



**$^{13}$C NMR ($CDCl_3$), 151 MHz**

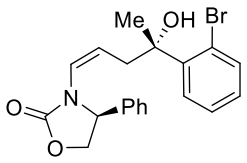
**1.4j**

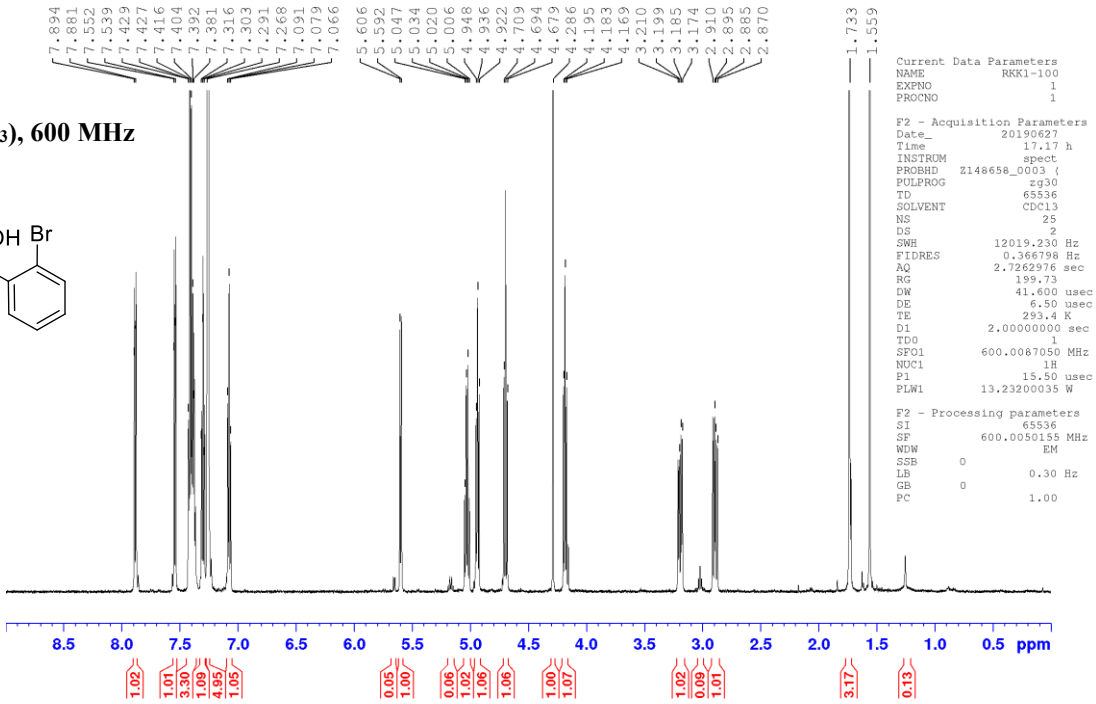

7.416
7.405
7.392
7.384
7.373
7.251
7.238
7.144
7.140
7.129
7.124
5.723
5.708
5.106
5.093
5.080
5.066
4.952
4.941
4.927
4.697
4.683
4.668
4.189
4.177
4.174
4.163
3.149
2.774
2.762
2.756
2.742
2.499
1.584
1.551
1H NMR (CDCl3), 600 MHz
1.4m
Me
OH
Me
N
Ph
O
O
Current Data Parameters
NAME RKK1-072
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190627
Time 16.30 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 25
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 293.4 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050157 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
3.23
2.16
2.89
0.94
0.98
0.99
1.01
1.01
0.91
1.94
2.93
2.85


156.71
144.56
137.86
135.12
132.88
129.38
129.14
126.91
126.54
126.31
125.73
123.38
121.44
74.54
70.16
61.62
39.81
29.73
22.53
13C NMR (CDCl3), 151 MHz
1.4m
Me
OH
Me
N
Ph
O
O
Current Data Parameters
NAME RKK1-072
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190627
Time 21.47
INSTRUM spect
PROBHD 5 mm PATXI 1H/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 36057.691 Hz
FIDRES 0.550197 Hz
AQ 0.9087659 sec
RG 194.75
DW 13.867 usec
DE 6.50 usec
TE 293.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
CHANNEL f1
SFO1 150.8738899 MHz
NUC1 13C
P1 11.40 usec
PLW1 176.19999695 W
CHANNEL f2
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07204500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

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

**1.4o**

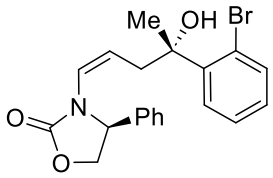



```
Current Data Parameters
NAME                  RKK1-100
EXPNO                        1
PROCNO                       1

F2 - Acquisition Parameters
Date_               20190627
Time                   17.17 h
INSTRUM                spect
PROBHD    Z148658_0003 (
PULPROG                zg30
TD                    65536
SOLVENT                CDCl3
NS                        25
DS                         2
SWH                12019.230 Hz
FIDRES             0.366798 Hz
AQ                 2.7262976 sec
RG                    199.73
DW                   41.600 usec
DE                    6.50 usec
TE                   293.4 K
D1                 2.00000000 sec
TD0                        1
SFO1              600.0087050 MHz
NUC1                      1H
P1                   15.50 usec
PLW1              13.23200035 W

F2 - Processing parameters
SI                    65536
SF                600.0050155 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

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

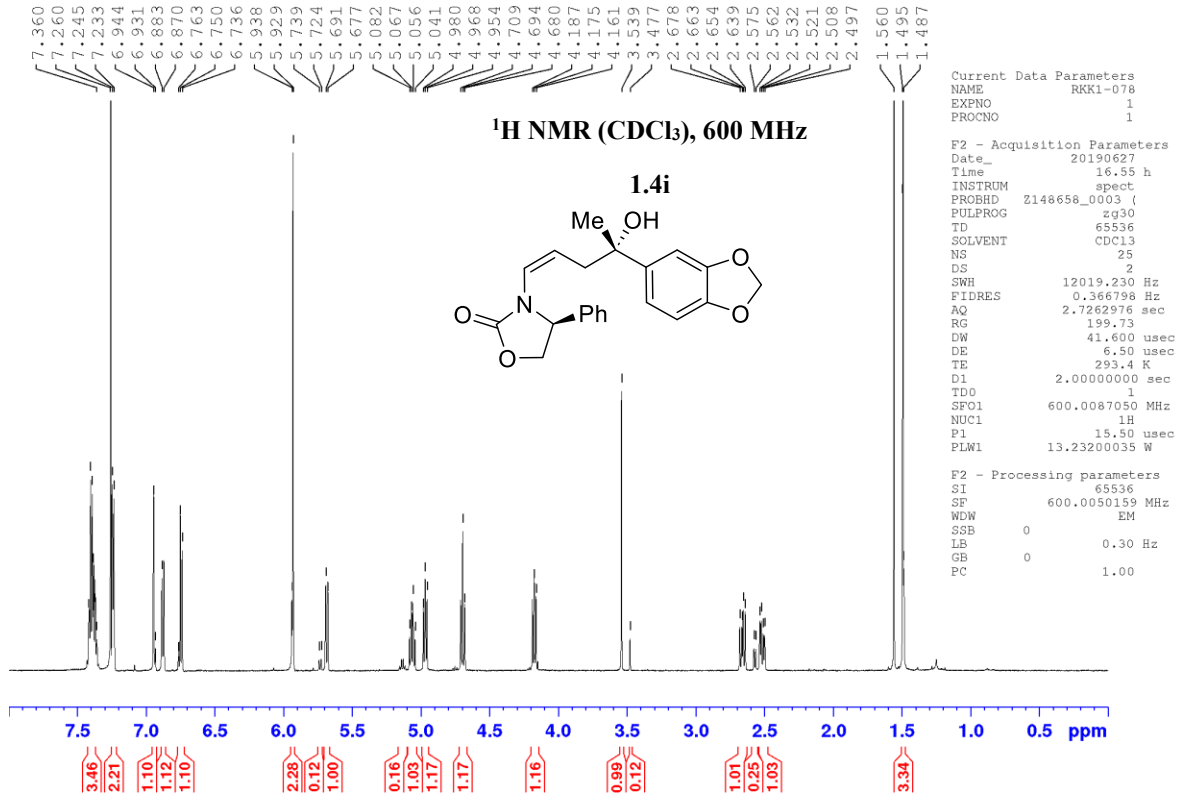
**1.4o**

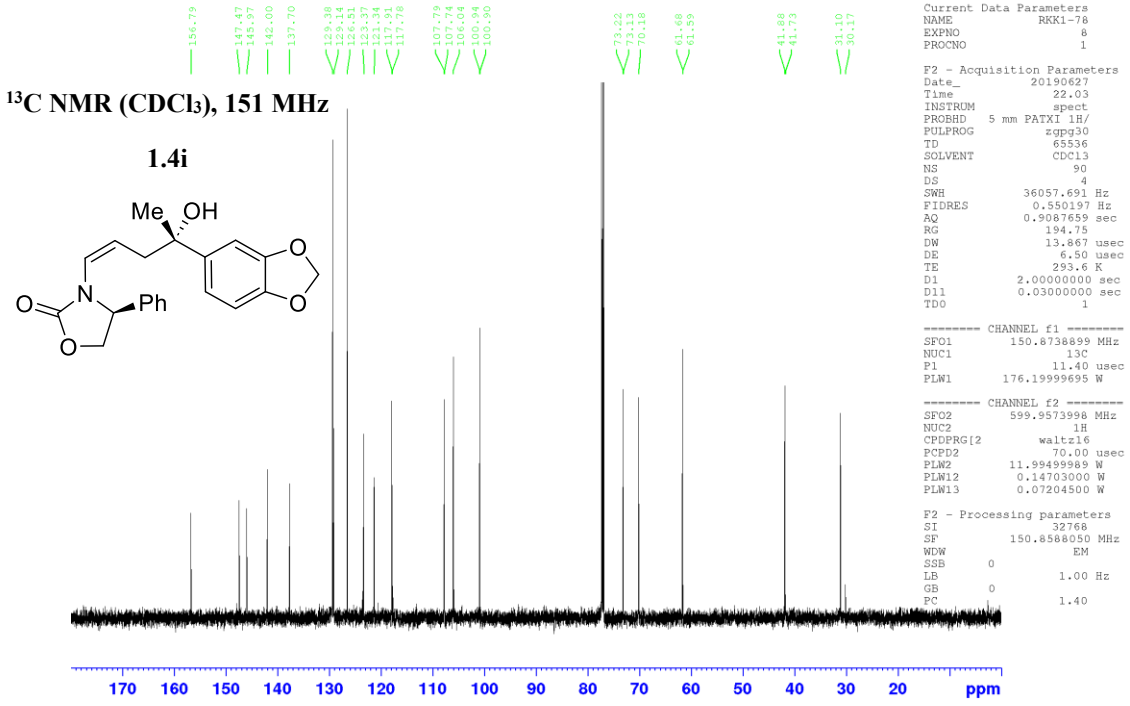


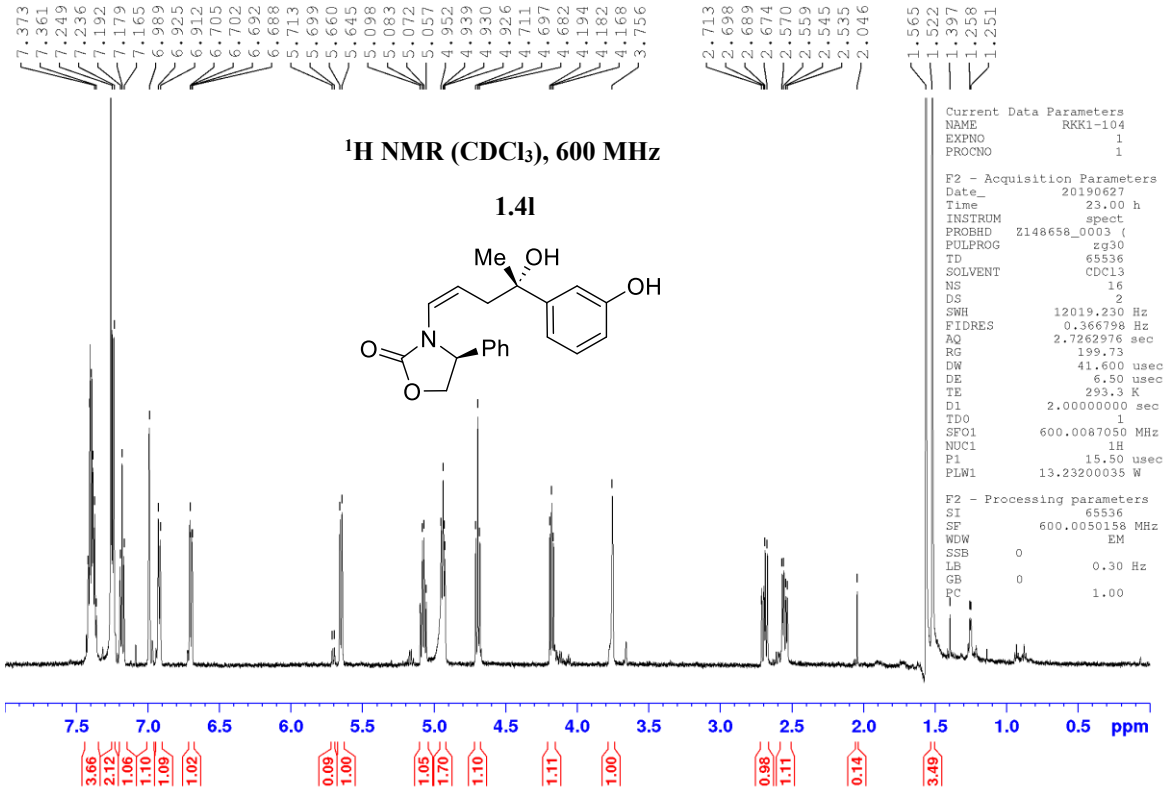




```
Current Data Parameters
NAME                  RKK1-100
EXPNO                        8
PROCNO                       1

F2 - Acquisition Parameters
Date_               20190627
Time                   22.52
INSTRUM                spect
PROBHD    5 mm PATXI 1H/
PULPROG              zgpg30
TD                    65536
SOLVENT                CDCl3
NS                        90
DS                         4
SWH                36057.691 Hz
FIDRES             0.550197 Hz
AQ                 0.9087659 sec
RG                    194.75
DW                   13.867 usec
DE                    6.50 usec
TE                   293.6 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                        1

======== CHANNEL f1 ========
SFO1              150.8738899 MHz
NUC1                      13C
P1                   11.40 usec
PLW1             176.19999695 W

======== CHANNEL f2 ========
SFO2              599.9573998 MHz
NUC2                      1H
CPDPRG[2              waltz16
PCPD2                 70.00 usec
PLW2              11.99499989 W
PLW12              0.14703000 W
PLW13              0.07204500 W

F2 - Processing parameters
SI                    32768
SF                150.8588050 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

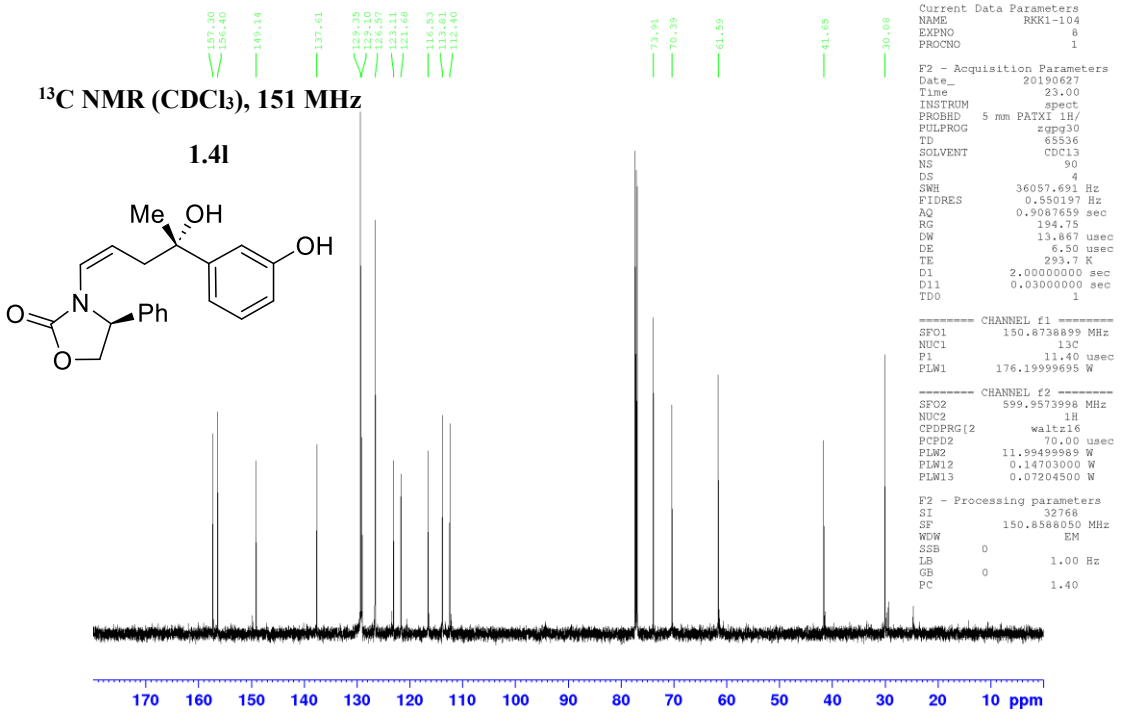

7.360
7.260
7.245
7.233
6.944
6.931
6.883
6.870
6.763
6.750
6.736
5.938
5.929
5.739
5.724
5.691
5.677
5.082
5.067
5.056
5.041
4.980
4.968
4.954
4.709
4.694
4.680
4.187
4.175
4.161
3.539
3.477
2.678
2.663
2.654
2.639
2.575
2.562
2.532
2.521
2.508
2.497
1.560
1.495
1.487
1H NMR (CDCl3), 600 MHz
1.4i
Me
OH
N
Ph
O
Current Data Parameters
NAME RKK1-078
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190627
Time 16.55 h
INSTRUM spect
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 25
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 293.4 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050159 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.46
2.21
1.10
1.12
1.10
2.28
0.12
1.00
0.16
1.03
1.17
1.17
1.16
0.99
0.12
1.01
0.25
1.03
3.34


156.79
147.47
145.97
142.00
137.70
129.38
129.14
126.51
123.37
121.34
117.91
117.76
107.79
107.74
106.04
100.94
100.90
73.22
73.13
70.18
61.68
61.59
41.88
41.73
31.10
30.17
13C NMR (CDCl3), 151 MHz
1.4i
Me
OH
N
Ph
O
Current Data Parameters
NAME RKK1-78
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190627
Time 22.03
INSTRUM spect
PROBHD 5 mm PATXI 1H/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 36057.691 Hz
FIDRES 0.550197 Hz
AQ 0.9087659 sec
RG 194.75
DW 13.867 usec
DE 6.50 usec
TE 293.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 150.8738899 MHz
NUC1 13C
P1 11.40 usec
PLW1 176.19999695 W
======== CHANNEL f2 ========
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07204500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm



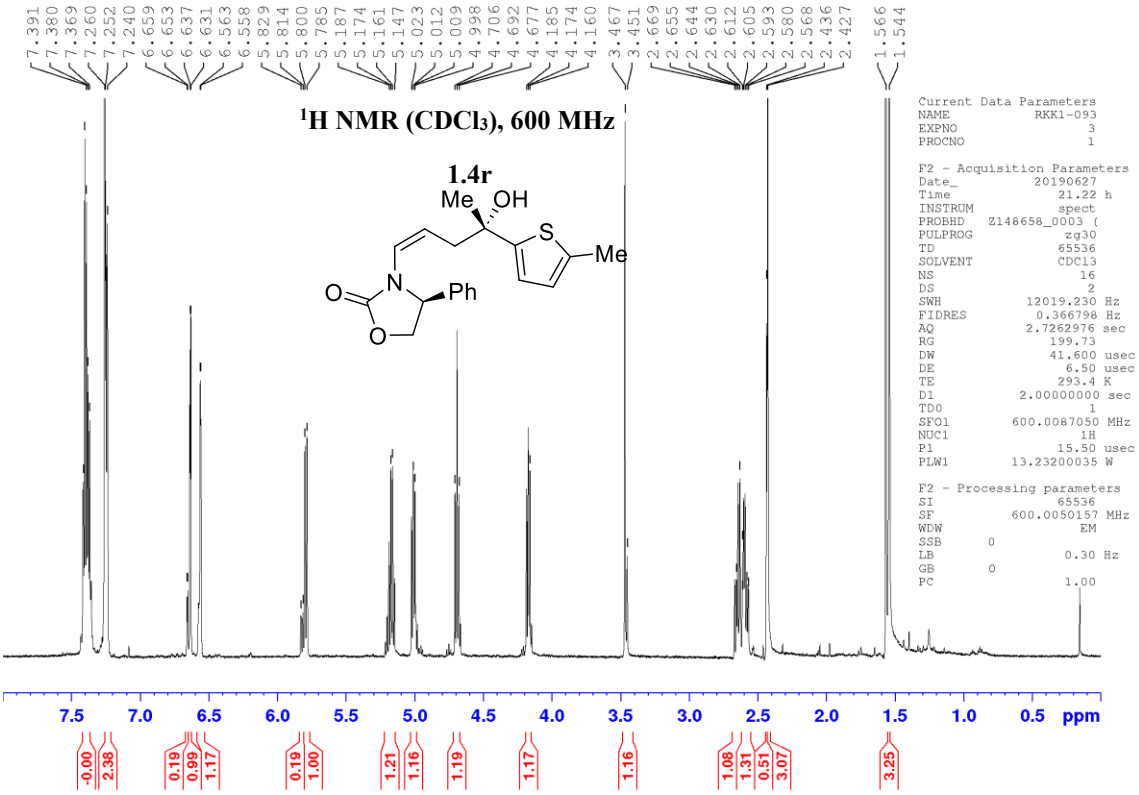

**$^{1}$H NMR ($CDCl_3$), 600 MHz**

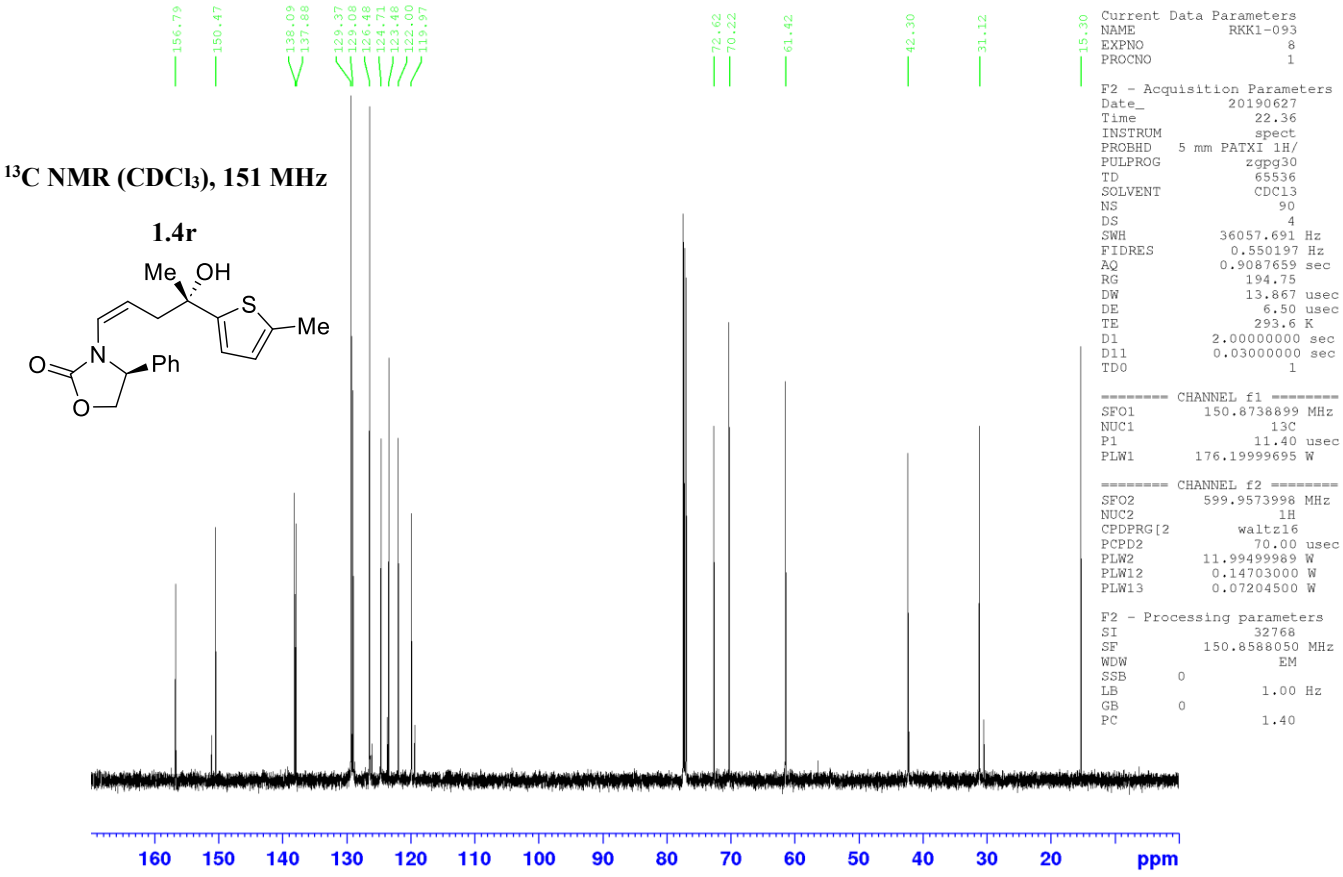
**1.4l**

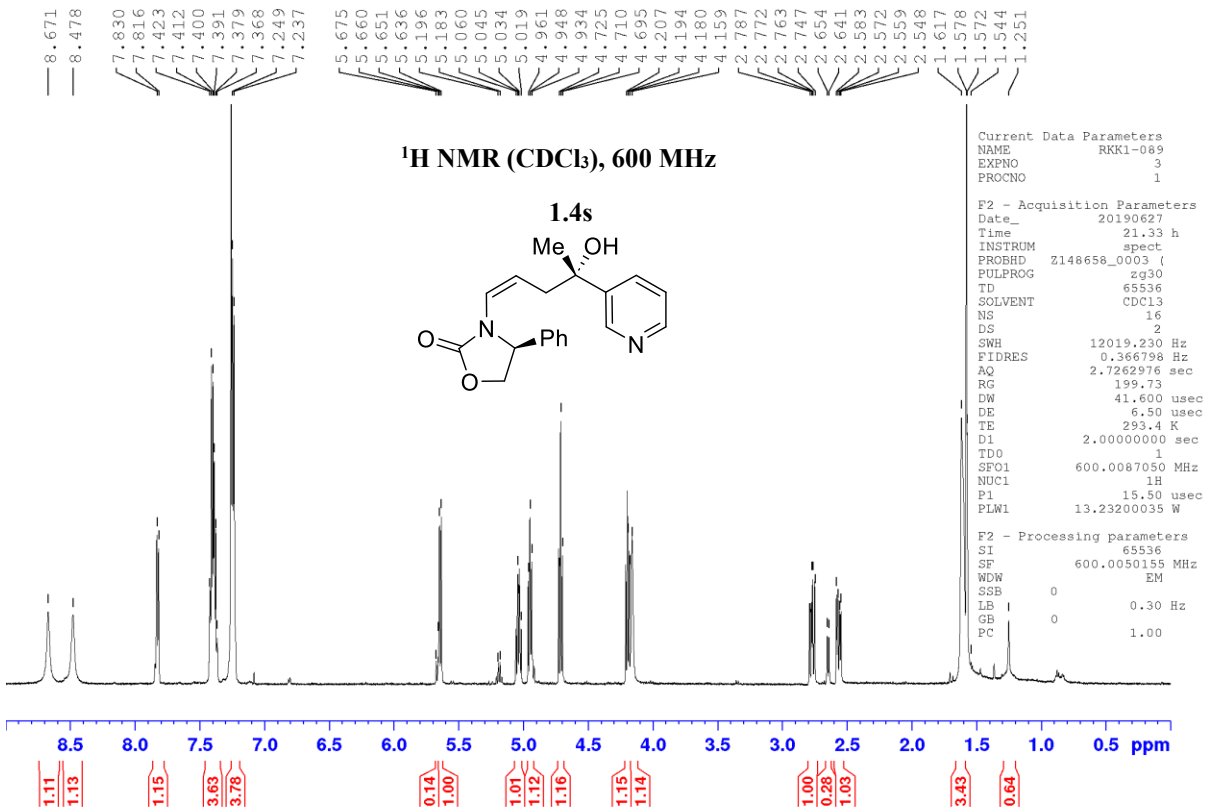


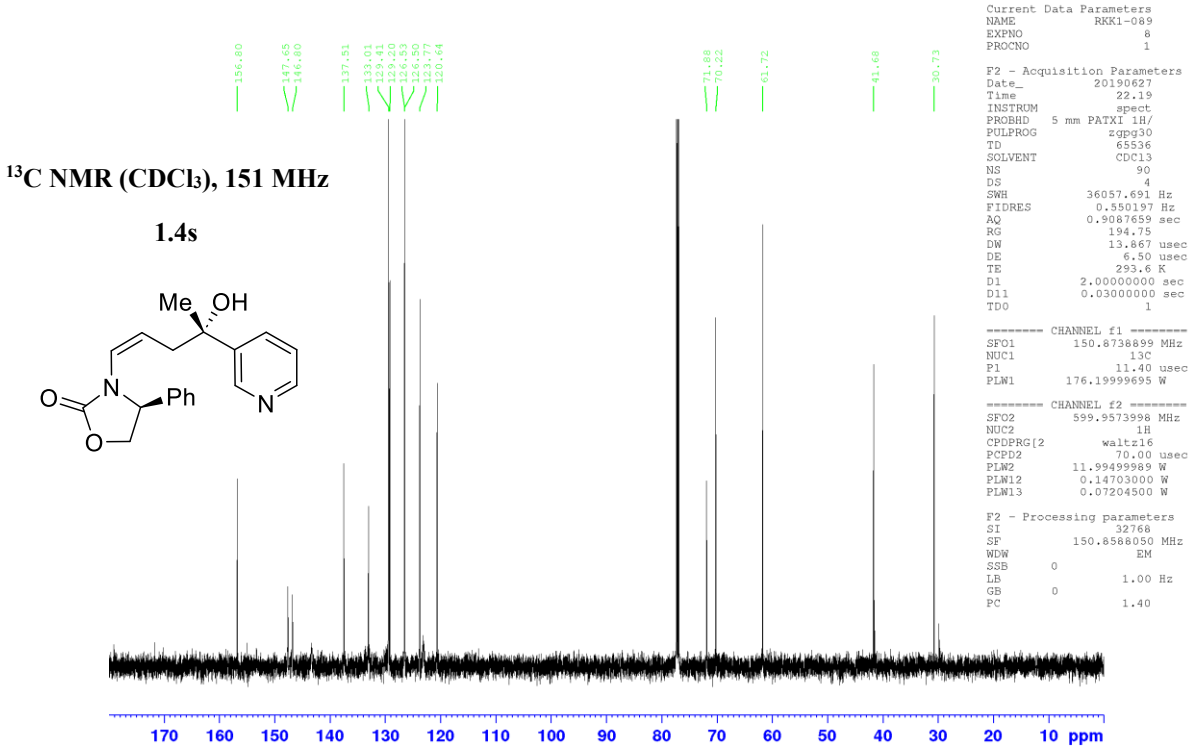

**$^{13}$C NMR ($CDCl_3$), 151 MHz**

**1.4l**


7.391 7.380 7.369 7.260 7.252 7.240 6.659 6.653 6.637 6.631 6.563 6.558 5.829 5.814 5.800 5.785 5.187 5.174 5.161 5.147 5.023 5.012 5.009 4.998 4.706 4.692 4.677 4.185 4.174 4.160 3.467 3.451 2.669 2.655 2.644 2.630 2.612 2.605 2.593 2.580 2.568 2.436 2.427 1.566 1.544
1H NMR (CDCl3), 600 MHz
1.4r
Me OH S Me N Ph O O
Current Data Parameters
NAME RKK1-093
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190627
Time 21.22 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 293.4 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050157 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
-0.00 2.38 0.19 0.99 1.17 0.19 1.00 1.21 1.16 1.19 1.17 1.16 1.08 1.31 0.51 3.07 3.25

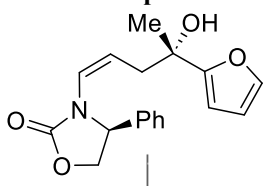

156.79 150.47 138.09 137.88 129.37 129.08 126.48 124.71 123.48 122.00 119.97 72.62 70.22 61.42 42.30 31.12 15.30
13C NMR (CDCl3), 151 MHz
1.4r
Me OH S Me N Ph O O
Current Data Parameters
NAME RKK1-093
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190627
Time 22.36
INSTRUM spect
PROBHD 5 mm PATXI 1H/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 36057.691 Hz
FIDRES 0.550197 Hz
AQ 0.9087659 sec
RG 194.75
DW 13.867 usec
DE 6.50 usec
TE 293.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 150.8738899 MHz
NUC1 13C
P1 11.40 usec
PLW1 176.19999695 W
======== CHANNEL f2 ========
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07204500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


8.671
8.478
7.830
7.816
7.423
7.412
7.400
7.391
7.379
7.368
7.249
7.237
5.675
5.660
5.651
5.636
5.196
5.183
5.060
5.045
5.034
5.019
4.961
4.948
4.934
4.725
4.710
4.695
4.207
4.194
4.180
4.159
2.787
2.772
2.763
2.747
2.654
2.641
2.583
2.572
2.559
2.548
1.617
1.578
1.572
1.544
1.251
1H NMR (CDCl3), 600 MHz
1.4s
Me
OH
N
Ph
O
O
N
Current Data Parameters
NAME RKK1-089
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190627
Time 21.33 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 293.4 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050155 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5 ppm
1.11
1.13
1.15
3.63
3.76
0.14
1.00
1.01
1.12
1.16
1.15
1.14
1.00
0.28
1.03
3.43
0.64


13C NMR (CDCl3), 151 MHz
1.4s
Me
OH
N
Ph
O
O
N
156.80
147.65
146.80
137.51
133.01
129.41
129.20
126.53
126.50
123.77
120.64
71.88
70.22
61.72
41.68
30.73
Current Data Parameters
NAME RKK1-089
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190627
Time 22.19
INSTRUM spect
PROBHD 5 mm PATXI 1H/
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 36057.691 Hz
FIDRES 0.550197 Hz
AQ 0.9087659 sec
RG 194.75
DW 13.867 usec
DE 6.50 usec
TE 293.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 150.8738899 MHz
NUC1 13C
P1 11.40 usec
PLW1 176.19999695 W
======== CHANNEL f2 ========
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07204500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm

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

**1.4p**

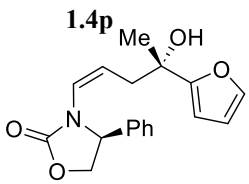


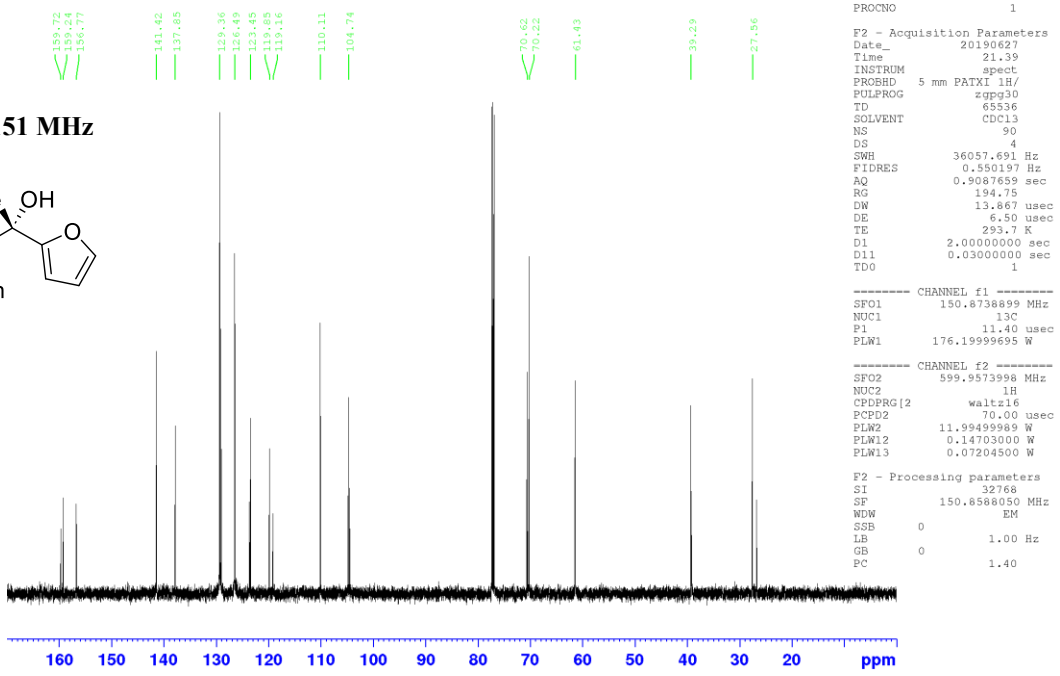


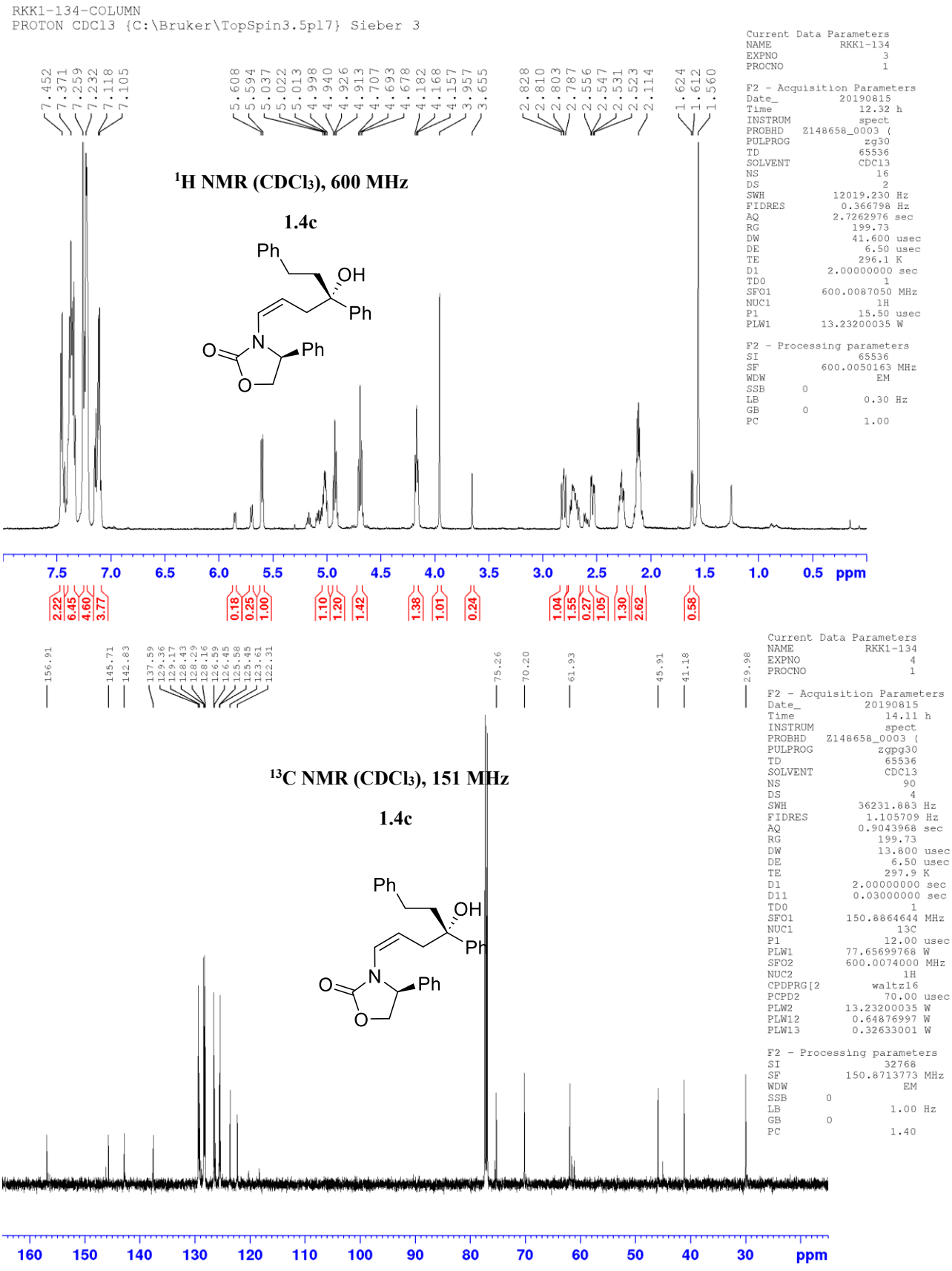


**$^{13}$C NMR ($CDCl_3$), 151 MHz**

**1.4p**

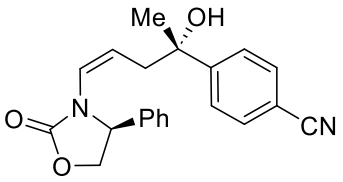


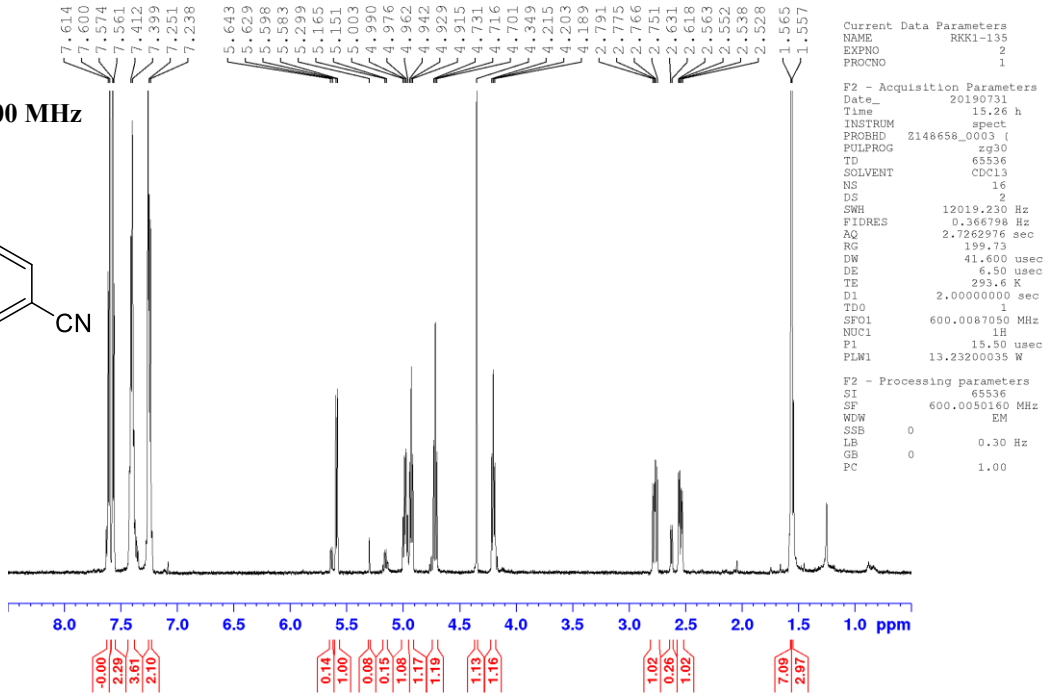




RKK1-134-COLUMN
PROTON CDCl3 {C:\Bruker\TopSpin3.5pl7} Sieber 3
Current Data Parameters
NAME RKK1-134
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190815
Time 12.32 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 296.1 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050163 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.452 7.371 7.259 7.232 7.118 7.105
5.608 5.594 5.037 5.022 5.013 4.998 4.940 4.926 4.913 4.707 4.693 4.678 4.182 4.168 4.157 3.957 3.655
2.828 2.810 2.803 2.787 2.556 2.547 2.531 2.523 2.114
1.624 1.612 1.560
1H NMR (CDCl3), 600 MHz
1.4c
Ph
OH
Ph
N
O
Ph
O
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.22 6.45 4.60 3.77 0.18 0.25 1.00 1.10 1.20 1.42 1.38 1.01 0.24 1.04 1.55 0.27 1.05 1.30 2.62 0.58
Current Data Parameters
NAME RKK1-134
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190815
Time 14.11 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 297.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
156.91 145.71 142.83 137.59 129.36 129.17 128.43 128.29 128.16 126.59 126.45 125.58 125.45 123.61 122.31
75.26 70.20 61.93 45.91 41.18 29.98
13C NMR (CDCl3), 151 MHz
1.4c
Ph
OH
Ph
N
O
Ph
O
160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

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

**1.4h**

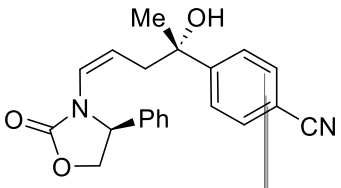



```
Current Data Parameters
NAME                  RKK1-135
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_               20190731
Time                   15.26 h
INSTRUM                spect
PROBHD     Z148658_0003 (
PULPROG                 zg30
TD                     65536
SOLVENT                CDCl3
NS                        16
DS                         2
SWH                12019.230 Hz
FIDRES             0.366798 Hz
AQ                 2.7262976 sec
RG                    199.73
DW                   41.600 usec
DE                    6.50 usec
TE                   293.6 K
D1                2.00000000 sec
TD0                        1
SFO1            600.0087050 MHz
NUC1                      1H
P1                   15.50 usec
PLW1            13.23200035 W

F2 - Processing parameters
SI                     65536
SF                600.0050160 MHz
WDW                       EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```

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

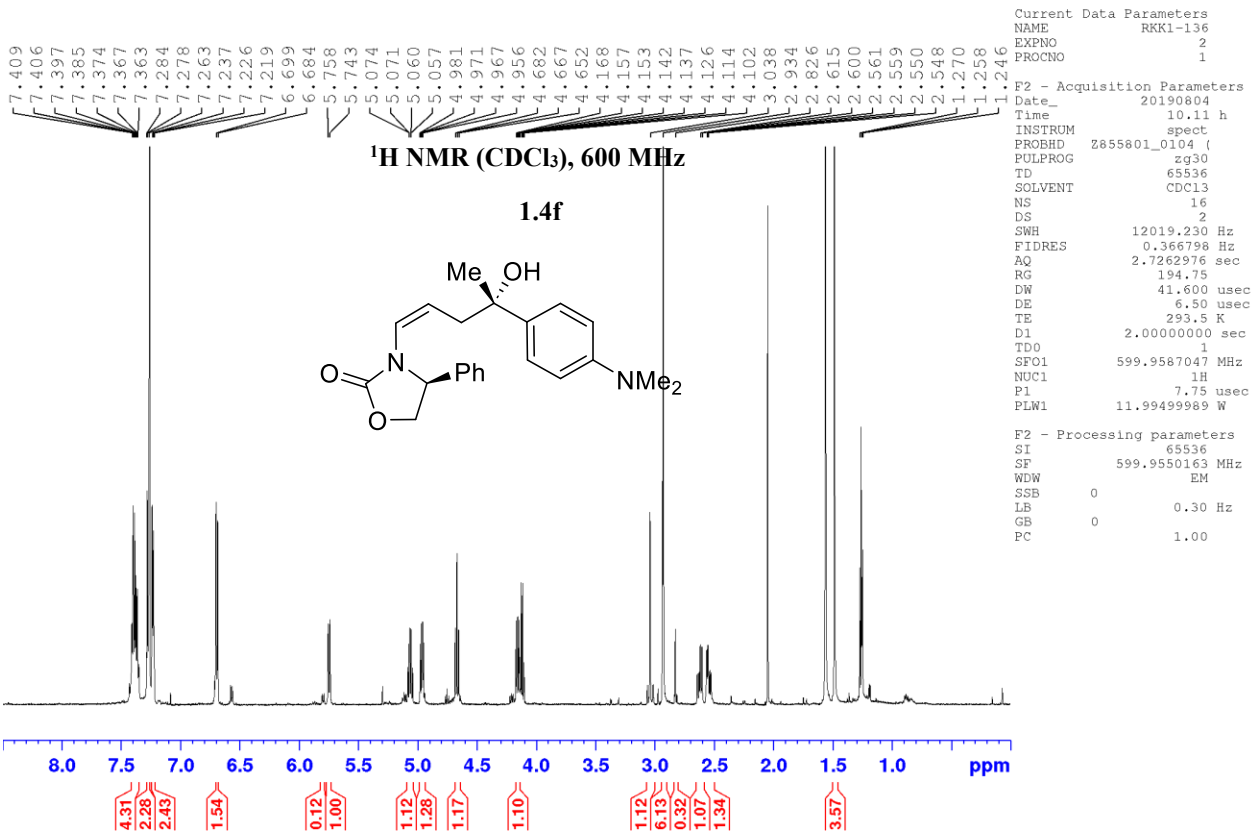
**1.4h**

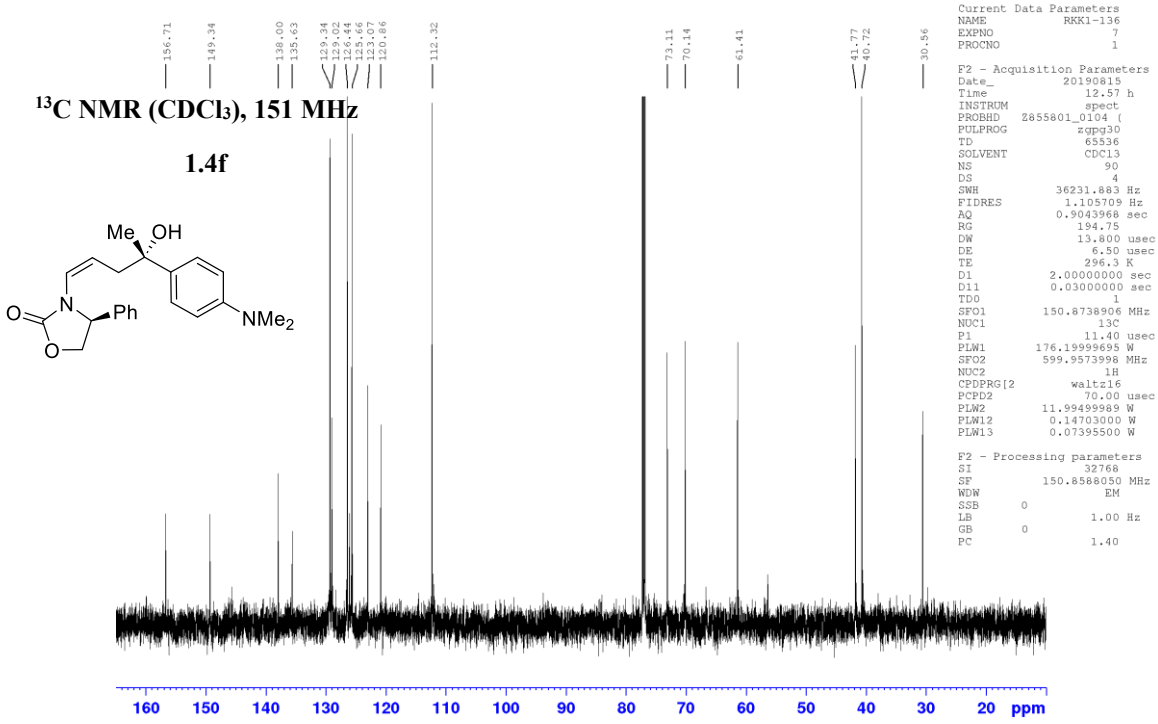


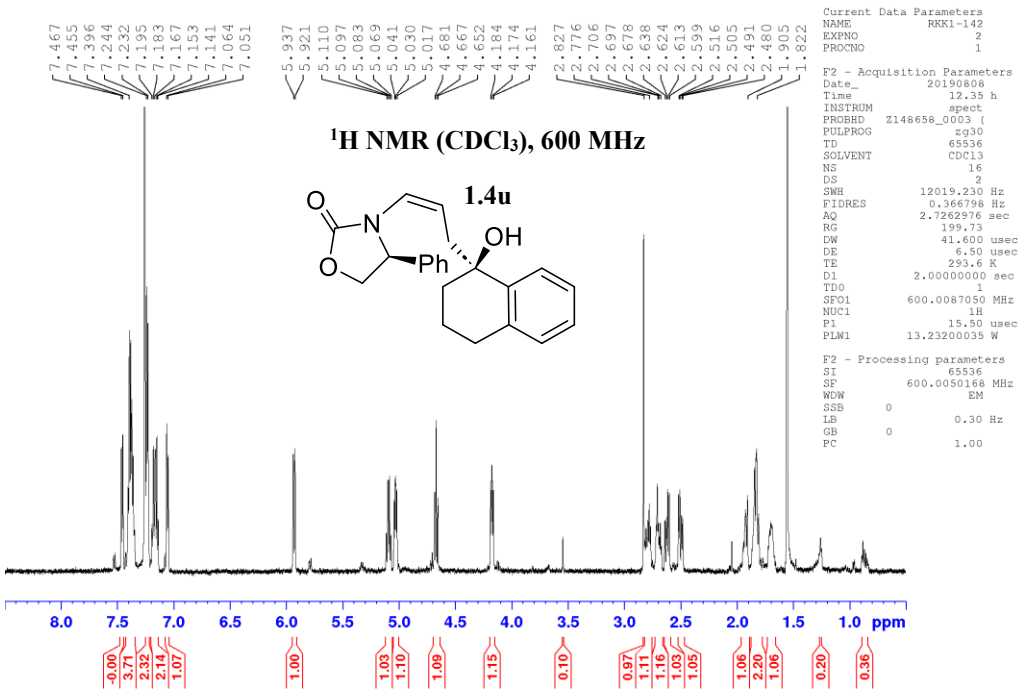


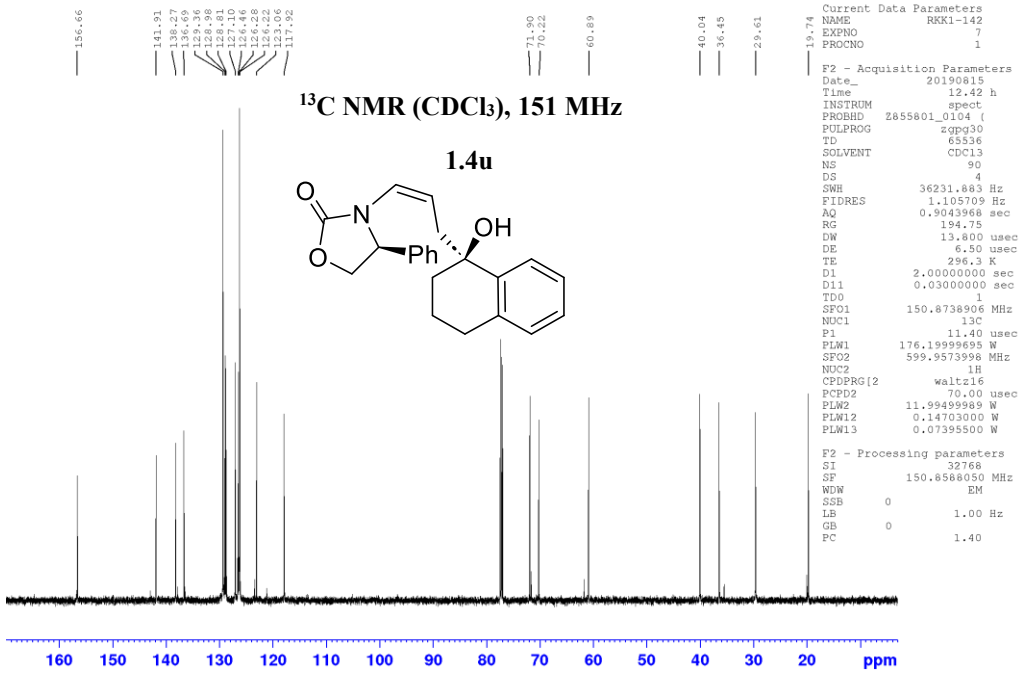


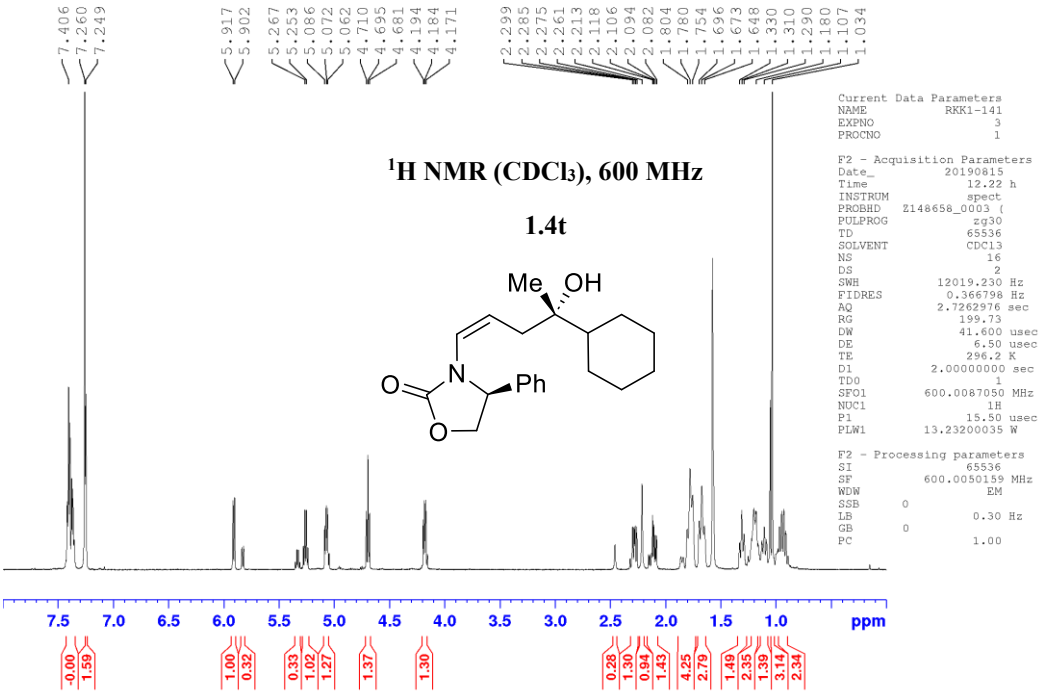
```
Current Data Parameters
NAME                  RKK1-140
EXPNO                        4
PROCNO                       1

F2 - Acquisition Parameters
Date_               20190815
Time                   13.56 h
INSTRUM                spect
PROBHD     Z148658_0003 (
PULPROG              zgpg30
TD                     65536
SOLVENT                CDCl3
NS                        90
DS                         4
SWH                36231.883 Hz
FIDRES             1.105709 Hz
AQ                 0.9043968 sec
RG                    199.73
DW                   13.800 usec
DE                    6.50 usec
TE                   297.9 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                        1
SFO1            150.8864644 MHz
NUC1                     13C
P1                   12.00 usec
PLW1            77.65699768 W
SFO2            600.0074000 MHz
NUC2                      1H
CPDPRG[2             waltz16
PCPD2                70.00 usec
PLW2            13.23200035 W
PLW12            0.64876997 W
PLW13            0.32633001 W

F2 - Processing parameters
SI                     32768
SF                150.8713773 MHz
WDW                       EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```


7.409 7.406 7.397 7.385 7.374 7.367 7.363 7.284 7.278 7.263 7.237 7.226 7.219 6.699 6.684 5.758 5.743 5.074 5.071 5.060 5.057 4.981 4.971 4.967 4.956 4.682 4.667 4.652 4.168 4.157 4.153 4.142 4.137 4.126 4.114 4.102 3.038 2.934 2.826 2.615 2.600 2.561 2.559 2.550 2.548 1.270 1.258 1.246
1H NMR (CDCl3), 600 MHz
1.4f
Me OH
O N Ph
NMe2
Current Data Parameters
NAME RKK1-136
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190804
Time 10.11 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 194.75
DW 41.600 usec
DE 6.50 usec
TE 293.5 K
D1 2.00000000 sec
TD0 1
SFO1 599.9587047 MHz
NUC1 1H
P1 7.75 usec
PLW1 11.99499989 W
F2 - Processing parameters
SI 65536
SF 599.9550163 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
4.31 2.28 2.43 1.54 0.12 1.00 1.12 1.28 1.17 1.10 1.12 6.13 0.32 1.07 1.34 3.57


156.71 149.34 138.00 135.63 129.34 129.02 126.44 125.66 123.07 120.86 112.32 73.11 70.14 61.41 41.77 40.72 30.56
13C NMR (CDCl3), 151 MHz
1.4f
Me OH
O N Ph
NMe2
Current Data Parameters
NAME RKK1-136
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190815
Time 12.57 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 194.75
DW 13.800 usec
DE 6.50 usec
TE 296.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8738906 MHz
NUC1 13C
P1 11.40 usec
PLW1 176.19999695 W
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07395500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


7.467
7.455
7.396
7.244
7.232
7.195
7.183
7.167
7.153
7.141
7.064
7.051
5.937
5.921
5.110
5.097
5.083
5.069
5.041
5.030
5.017
4.681
4.667
4.652
4.184
4.174
4.161
2.827
2.776
2.706
2.697
2.678
2.638
2.624
2.613
2.599
2.516
2.505
2.491
2.480
1.905
1.822
Current Data Parameters
NAME RKK1-142
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190808
Time 12.35 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 293.6 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050168 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
1.4u
O
N
O
Ph
OH
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.00
3.71
2.32
2.14
1.07
1.00
1.03
1.10
1.09
1.15
0.10
0.97
1.11
1.16
1.03
1.05
1.06
2.20
1.06
0.20
0.36

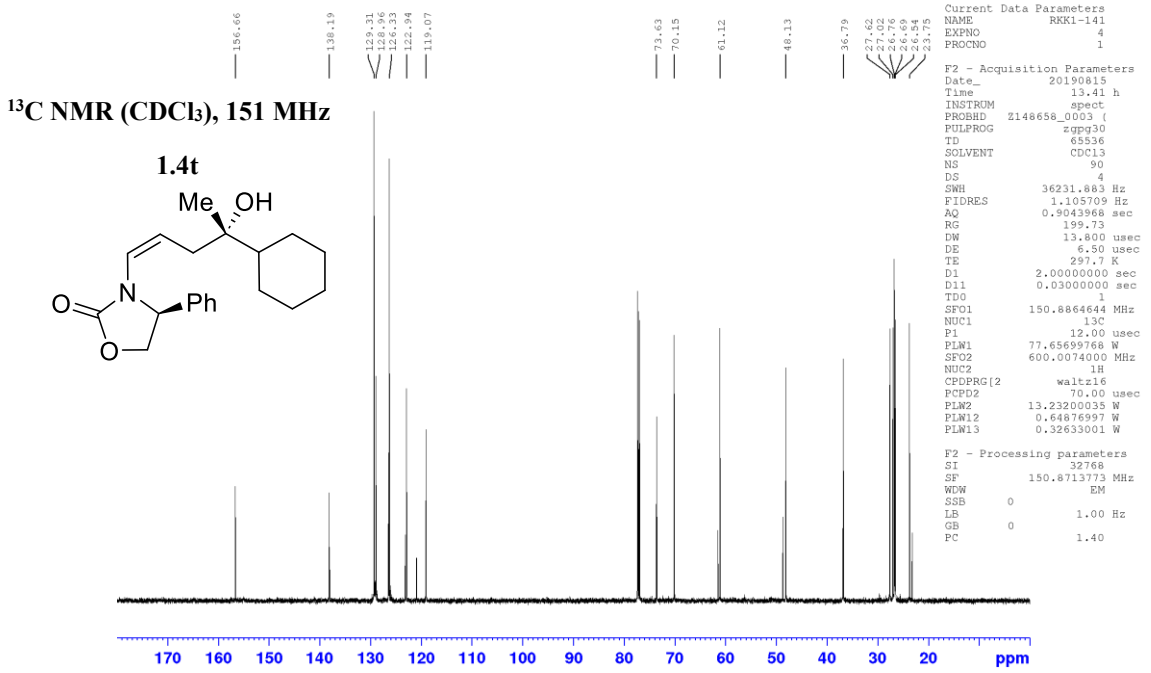

156.66
141.91
138.27
136.69
129.36
128.98
128.81
127.10
127.46
126.28
126.22
123.06
117.92
71.90
70.22
60.89
40.04
36.45
29.61
19.74
Current Data Parameters
NAME RKK1-142
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190815
Time 12.42 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 194.75
DW 13.800 usec
DE 6.50 usec
TE 296.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8738906 MHz
NUC1 13C
P1 11.40 usec
PLW1 176.19999695 W
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07395500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
1.4u
O
N
O
Ph
OH
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm




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

**1.4t**

```
Current Data Parameters
NAME                  RKK1-141
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_               20190815
Time                   12.22 h
INSTRUM                spect
PROBHD     Z148658_0003 (
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               12019.230 Hz
FIDRES                0.366798 Hz
AQ                 2.7262976 sec
RG                     199.73
DW                    41.600 usec
DE                     6.50 usec
TE                    296.2 K
D1                 2.00000000 sec
TD0                          1
SFO1              600.0087050 MHz
NUC1                        1H
P1                    15.50 usec
PLW1              13.23200035 W

F2 - Processing parameters
SI                    65536
SF                600.0050159 MHz
WDW                       EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     1.00
```



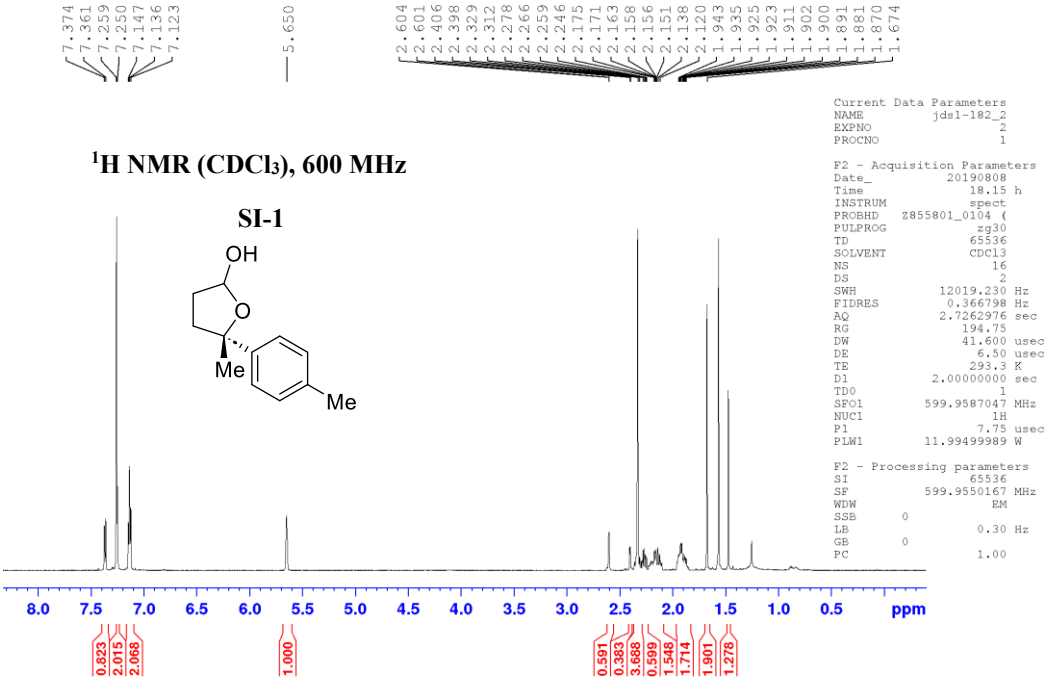

**$^{13}$C NMR ($CDCl_3$), 151 MHz**

**1.4t**

```
Current Data Parameters
NAME                  RKK1-141
EXPNO                        4
PROCNO                       1

F2 - Acquisition Parameters
Date_               20190815
Time                   13.41 h
INSTRUM                spect
PROBHD     Z148658_0003 (
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                       90
DS                        4
SWH               36231.883 Hz
FIDRES                1.105709 Hz
AQ                 0.9043968 sec
RG                     199.73
DW                    13.800 usec
DE                     6.50 usec
TE                    297.7 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                          1
SFO1              150.8864644 MHz
NUC1                        13C
P1                    12.00 usec
PLW1              77.65699768 W
SFO2              600.0074000 MHz
NUC2                        1H
CPDPRG[2             waltz16
PCPD2                 70.00 usec
PLW2              13.23200035 W
PLW12              0.64876997 W
PLW13              0.32633001 W

F2 - Processing parameters
SI                    32768
SF                150.8713773 MHz
WDW                       EM
SSB          0
LB                     1.00 Hz
GB           0
PC                     1.40
```

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

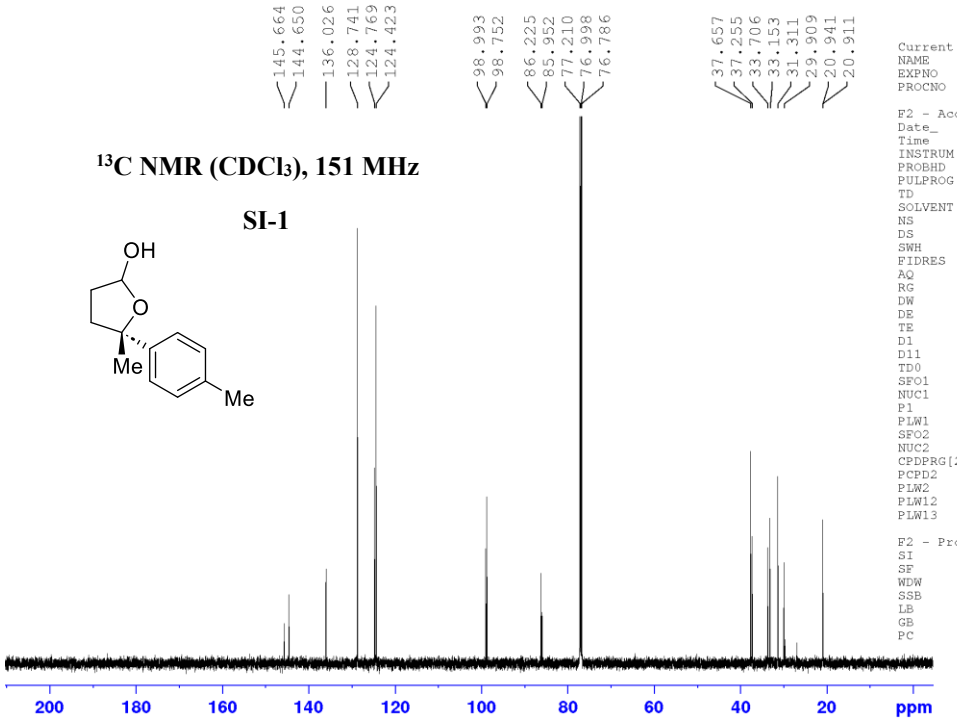
**SI-1**



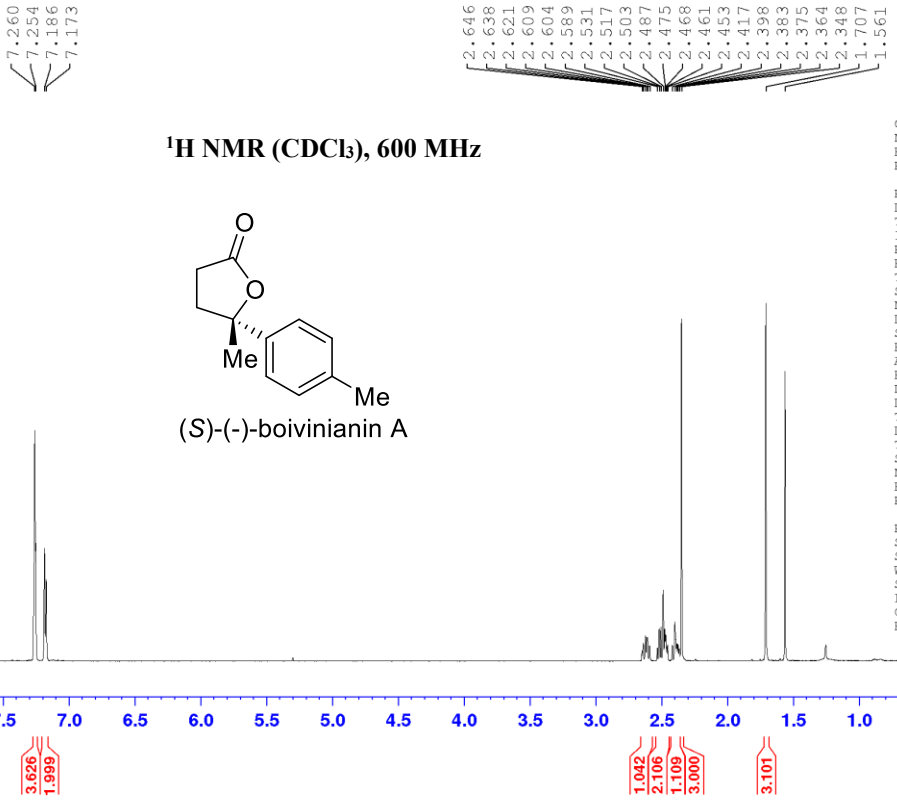

```
Current Data Parameters
NAME          jds1-182_2
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_          20190808
Time              18.15 h
INSTRUM            spect
PROBHD   Z855801_0104 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           12019.230 Hz
FIDRES        0.366798 Hz
AQ            2.7262976 sec
RG                194.75
DW                41.600 usec
DE                 6.50 usec
TE                293.3 K
D1           2.00000000 sec
TD0                    1
SFO1         599.9587047 MHz
NUC1                  1H
P1                 7.75 usec
PLW1         11.99499989 W

F2 - Processing parameters
SI                 65536
SF           599.9550167 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

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

**SI-1**



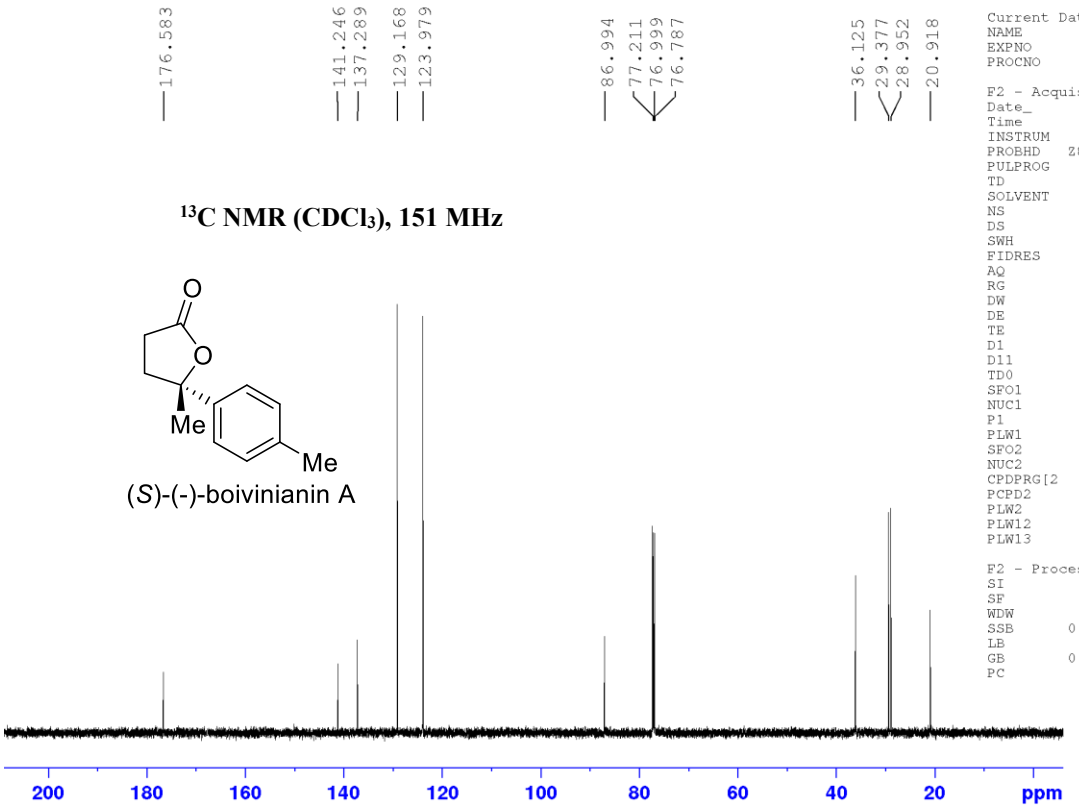

```
Current Data Parameters
NAME             jds1-182
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_          20190808
Time              20.33 h
INSTRUM            spect
PROBHD   Z148658_0003 (
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   125
DS                     4
SWH           36231.883 Hz
FIDRES        1.105709 Hz
AQ            0.9043968 sec
RG                199.73
DW                13.800 usec
DE                 6.50 usec
TE                295.2 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1
SFO1         150.8864644 MHz
NUC1                  13C
P1                12.00 usec
PLW1         77.65699768 W
SFO2         600.0074000 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2             70.00 usec
PLW2         13.23200035 W
PLW12         0.64876997 W
PLW13         0.32633001 W

F2 - Processing parameters
SI                 32768
SF           150.8713861 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```




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




(*S*)-(-)-boivinianin A

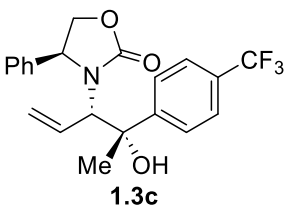



**$^{13}$C NMR ($CDCl_3$), 151 MHz**

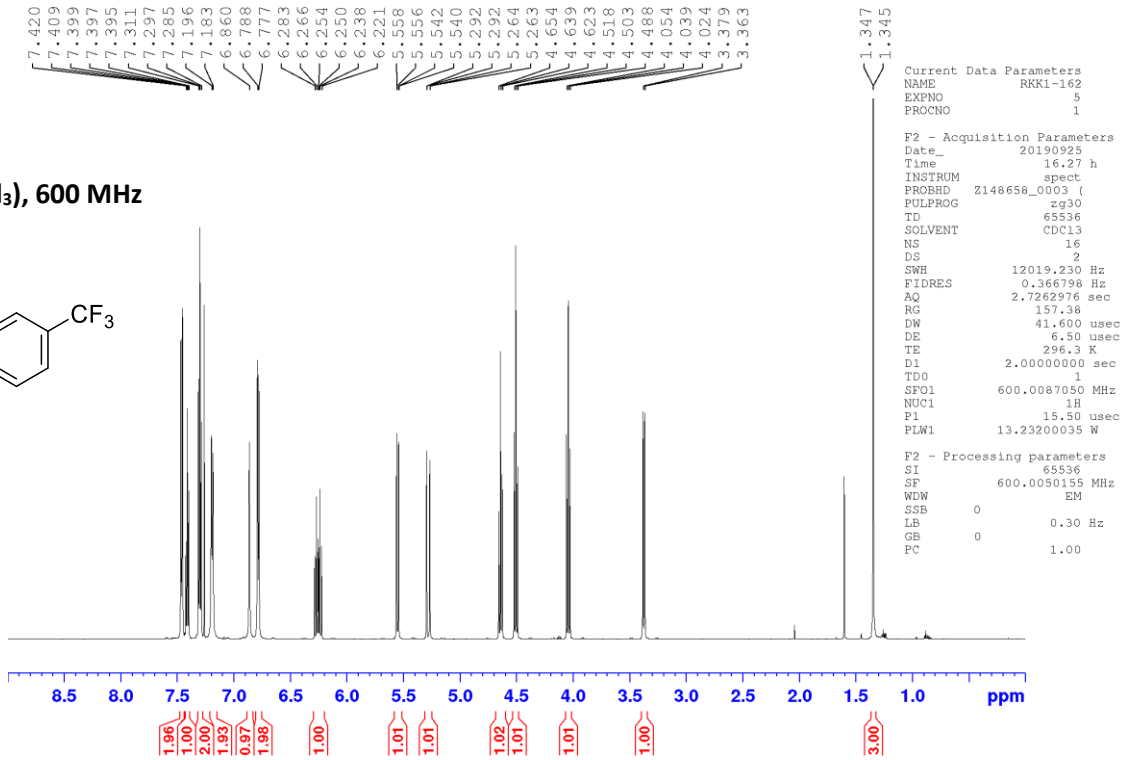



(*S*)-(-)-boivinianin A

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

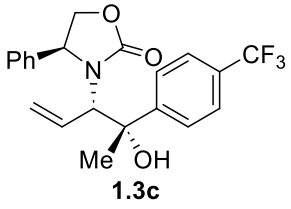



**1.3c**




```
Current Data Parameters
NAME            RKK1-162
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20190925
Time              16.27 h
INSTRUM            spect
PROBHD   Z148658_0003 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH           12019.230 Hz
FIDRES         0.366798 Hz
AQ            2.7262976 sec
RG                157.38
DW                41.600 usec
DE                 6.50 usec
TE                296.3 K
D1           2.00000000 sec
TD0                    1
SFO1        600.0087050 MHz
NUC1                1H
P1                15.50 usec
PLW1        13.23200035 W

F2 - Processing parameters
SI                 65536
SF          600.0050155 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

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

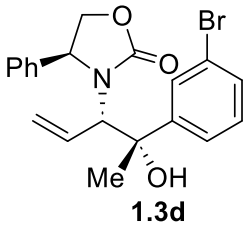



**1.3c**

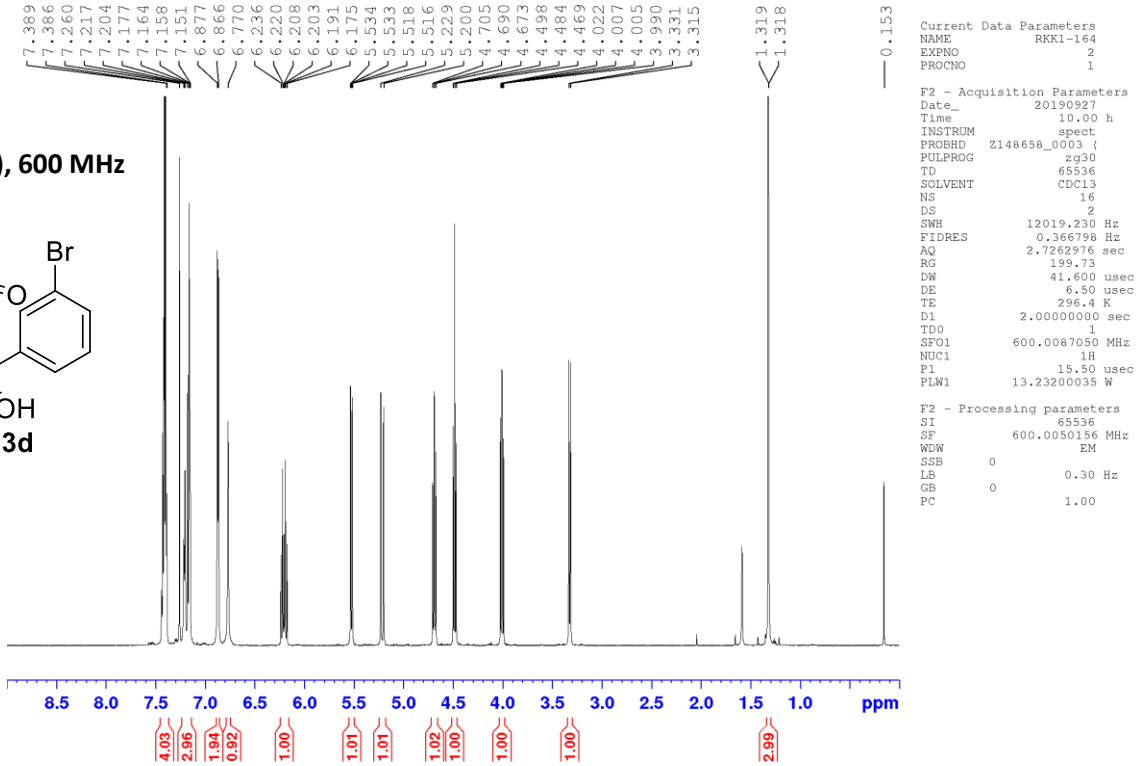



```
Current Data Parameters
NAME        RKK1-097_C13
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20190625
Time              20.33
INSTRUM            spect
PROBHD   5 mm PATXI 1H/
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   600
DS                     4
SWH           36057.691 Hz
FIDRES         0.550197 Hz
AQ            0.9087659 sec
RG                194.75
DW                13.867 usec
DE                 6.50 usec
TE                294.2 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
SFO1         150.8738899 MHz
NUC1                13C
P1                11.40 usec
PLW1       176.19999695 W

======== CHANNEL f2 ========
SFO2         599.9573998 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2             70.00 usec
PLW2         11.99499989 W
PLW12         0.14703000 W
PLW13         0.07204500 W

F2 - Processing parameters
SI                 32768
SF          150.8588134 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

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

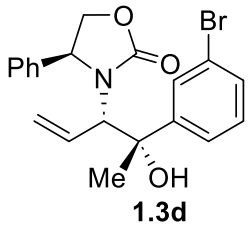



**1.3d**




```
Current Data Parameters
NAME            RKK1-164
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20190927
Time               10.00 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    16
DS                     2
SWH            12019.230 Hz
FIDRES          0.366798 Hz
AQ             2.7262976 sec
RG                199.73
DW                41.600 usec
DE                 6.50 usec
TE                296.4 K
D1             2.00000000 sec
TD0                    1
SFO1          600.0087050 MHz
NUC1                  1H
P1                 15.50 usec
PLW1          13.23200035 W

F2 - Processing parameters
SI                 65536
SF            600.0050156 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

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

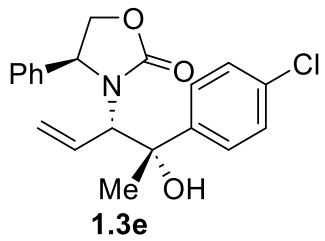



**1.3d**




```
Current Data Parameters
NAME            RKK1-164
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20190927
Time               10.06 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    90
DS                     4
SWH            36231.883 Hz
FIDRES          1.105709 Hz
AQ             0.9043968 sec
RG                199.73
DW                13.800 usec
DE                 6.50 usec
TE                297.9 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                    1
SFO1          150.8864644 MHz
NUC1                 13C
P1                12.00 usec
PLW1          77.65699768 W
SFO2          600.0074000 MHz
NUC2                  1H
CPDPRG[2          waltz16
PCPD2             70.00 usec
PLW2          13.23200035 W
PLW12          0.64876997 W
PLW13          0.32633001 W

F2 - Processing parameters
SI                 32768
SF            150.8713773 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

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

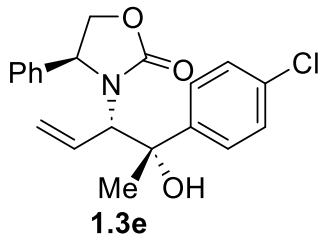



**1.3e**




```
Current Data Parameters
NAME            RKK1-167
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20191013
Time               12.45 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                    32
DS                     2
SWH            12019.230 Hz
FIDRES             0.366798 Hz
AQ              2.7262976 sec
RG                 176.24
DW                41.600 usec
DE                 6.50 usec
TE                 298.0 K
D1              2.00000000 sec
TD0                    1
SFO1           600.0087050 MHz
NUC1                  1H
P1                 15.50 usec
PLW1           13.23200035 W

F2 - Processing parameters
SI                 65536
SF            600.0050108 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

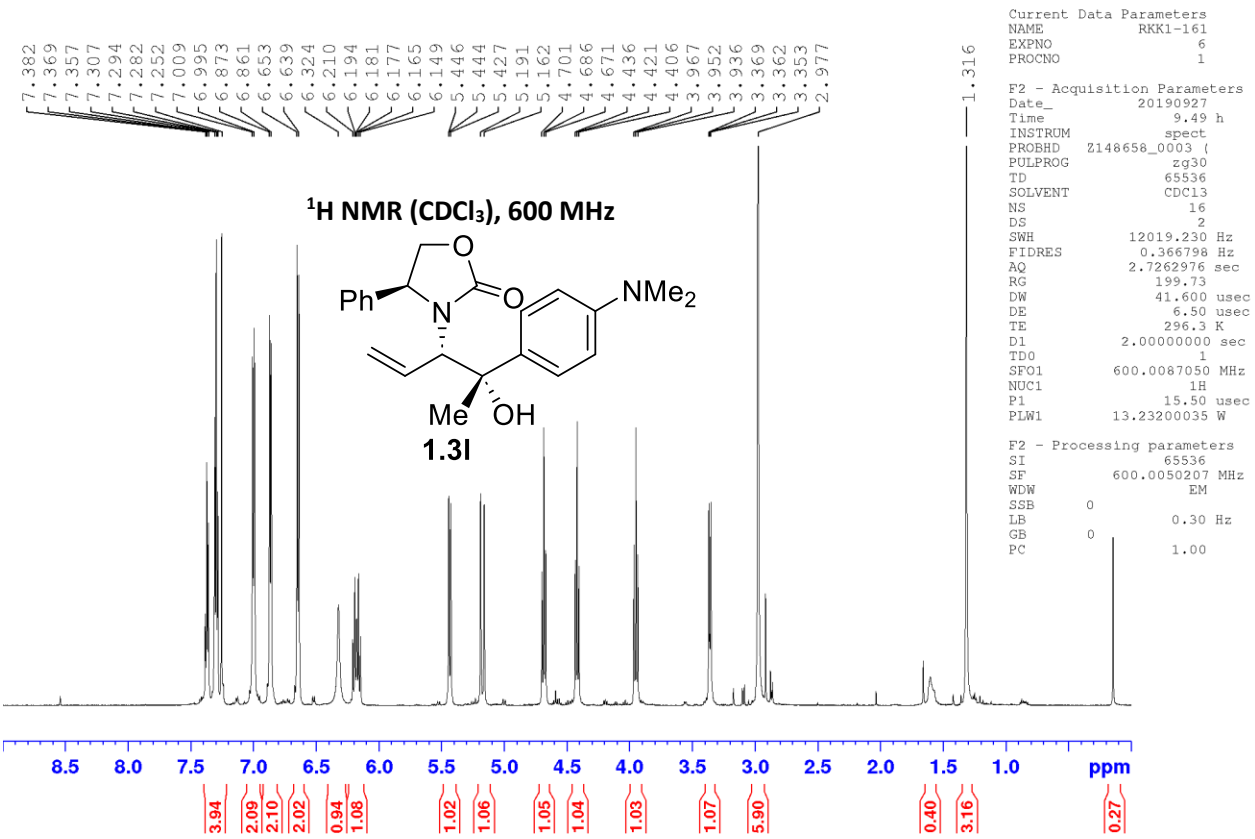
**$^{13}$C NMR ($CDCl_3$), 151 MHz**

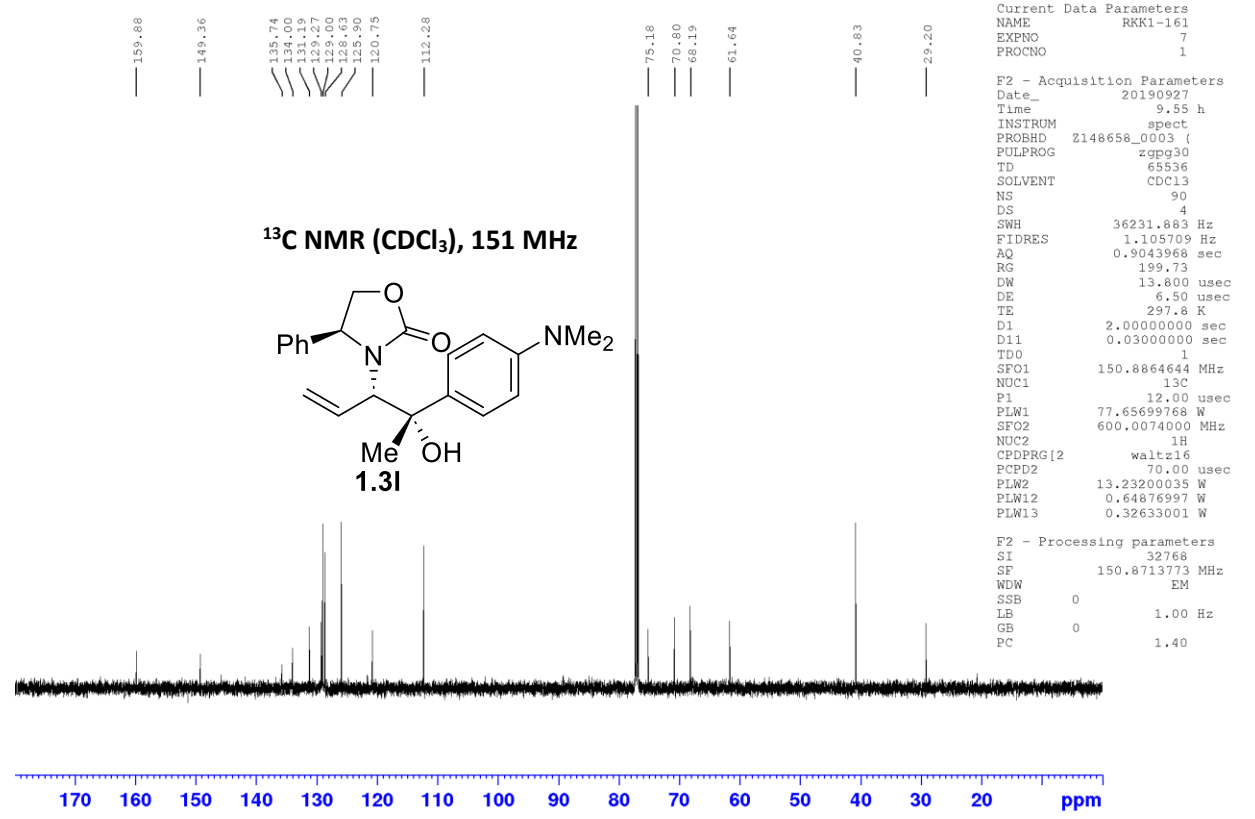


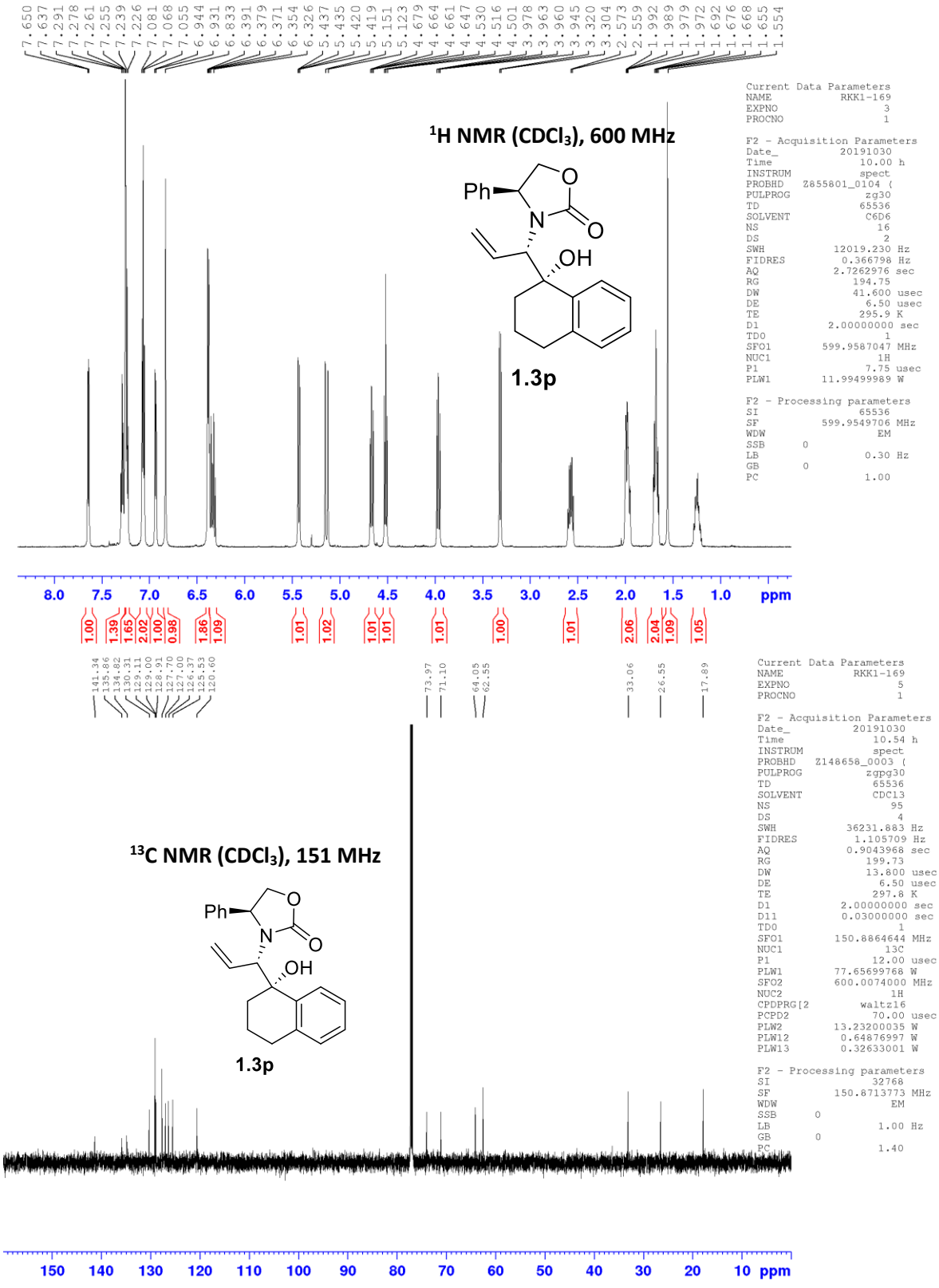

**1.3e**

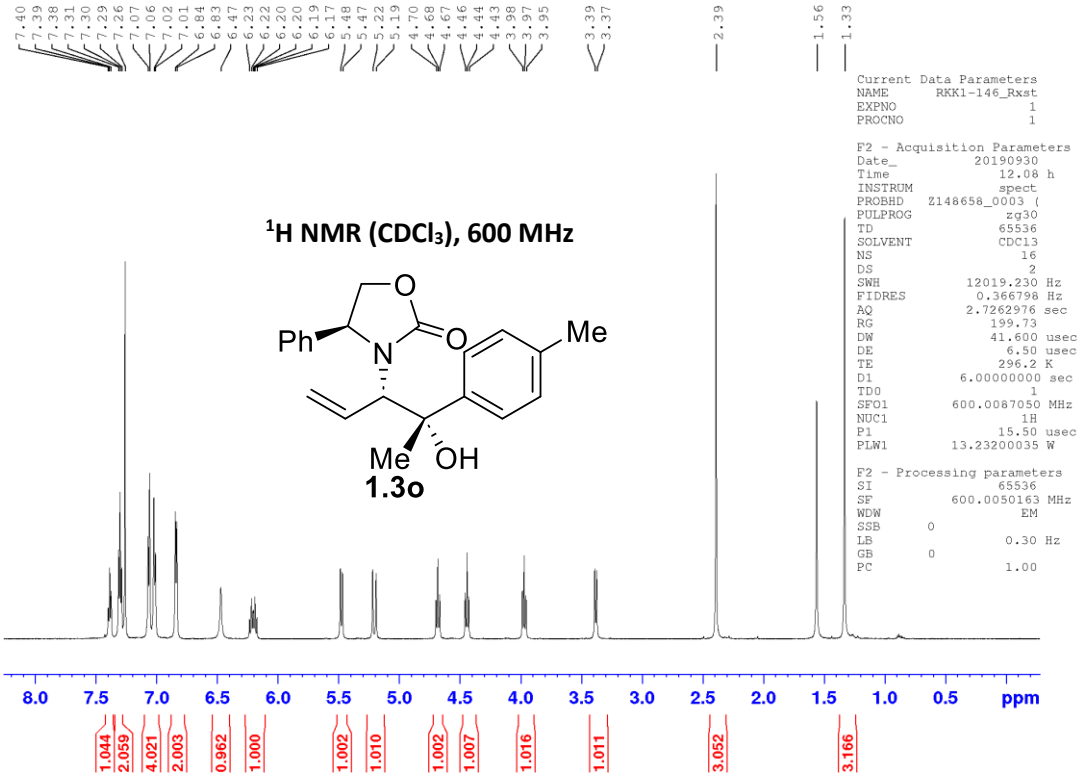


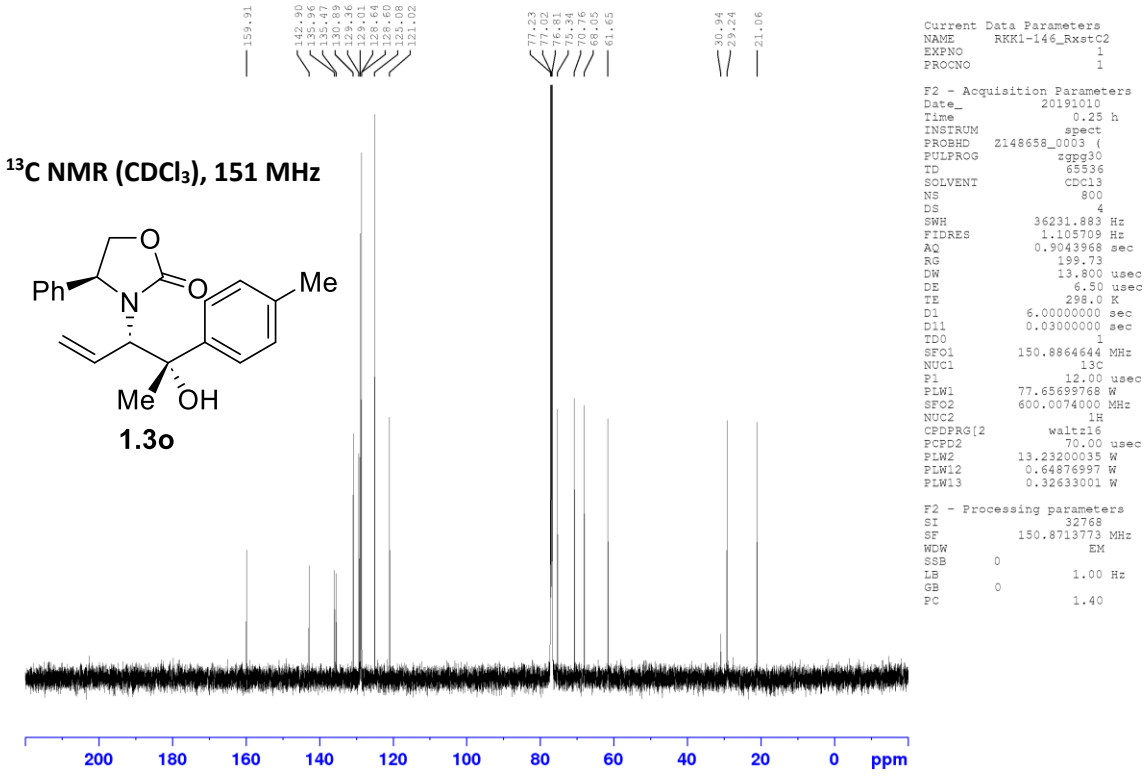

```
Current Data Parameters
NAME            RKK1-167
EXPNO                  6
PROCNO                 1

F2 - Acquisition Parameters
Date_           20191013
Time               12.50 h
INSTRUM             spect
PROBHD    Z148658_0003 (
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    90
DS                     4
SWH            36231.883 Hz
FIDRES             1.105709 Hz
AQ              0.9043968 sec
RG                 199.73
DW                13.800 usec
DE                 6.50 usec
TE                 298.2 K
D1              2.00000000 sec
D11             0.03000000 sec
TD0                    1
SFO1           150.8864644 MHz
NUC1                  13C
P1                 12.00 usec
PLW1           77.65699768 W
SFO2           600.0074000 MHz
NUC2                  1H
CPDPRG[2         waltz16
PCPD2              70.00 usec
PLW2           13.23200035 W
PLW12           0.64876997 W
PLW13           0.32633001 W

F2 - Processing parameters
SI                 32768
SF            150.8713773 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```


7.382
7.369
7.357
7.307
7.294
7.282
7.252
7.009
6.995
6.873
6.861
6.653
6.639
6.324
6.210
6.194
6.181
6.177
6.165
6.149
5.446
5.444
5.427
5.191
5.162
4.701
4.686
4.671
4.436
4.421
4.406
3.967
3.952
3.936
3.369
3.362
3.353
2.977
1.316
1H NMR (CDCl3), 600 MHz
Ph
N
O
O
NMe2
Me
OH
1.3l
Current Data Parameters
NAME RKK1-161
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190927
Time 9.49 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 296.3 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050207 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
3.94 2.09 2.10 2.02 0.94 1.08 1.02 1.06 1.05 1.04 1.03 1.07 5.90 0.40 3.16 0.27


159.88
149.36
135.74
134.00
131.19
129.27
129.00
128.63
125.90
120.75
112.28
75.18
70.80
68.19
61.64
40.83
29.20
13C NMR (CDCl3), 151 MHz
Ph
N
O
O
NMe2
Me
OH
1.3l
Current Data Parameters
NAME RKK1-161
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190927
Time 9.55 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 90
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 297.8 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

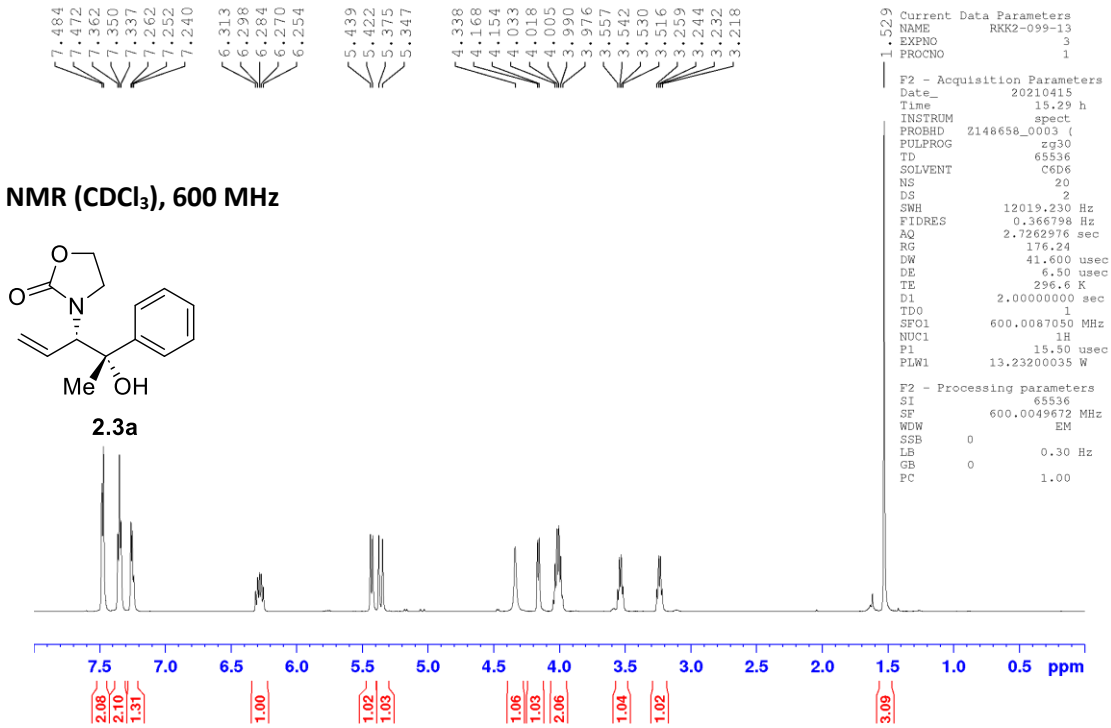

7.650
7.637
7.291
7.278
7.261
7.255
7.239
7.226
7.081
7.068
7.055
6.944
6.931
6.833
6.391
6.379
6.371
6.354
6.326
5.437
5.435
5.420
5.419
5.151
5.123
4.679
4.664
4.661
4.647
4.530
4.516
4.501
3.978
3.963
3.960
3.945
3.320
3.304
2.573
2.559
1.992
1.989
1.979
1.972
1.692
1.676
1.668
1.655
1.554
1H NMR (CDCl3), 600 MHz
Ph
O
N
O
OH
1.3p
Current Data Parameters
NAME RKK1-169
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20191030
Time 10.00 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT C6D6
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 194.75
DW 41.600 usec
DE 6.50 usec
TE 295.9 K
D1 2.00000000 sec
TD0 1
SFO1 599.9587047 MHz
NUC1 1H
P1 7.75 usec
PLW1 11.99499989 W
F2 - Processing parameters
SI 65536
SF 599.9549706 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 1.39 1.65 2.02 1.00 0.98 1.86 1.09 1.01 1.02 1.01 1.01 1.01 1.00 1.01 2.06 2.04 1.09 1.05
141.34
135.86
134.82
130.31
129.11
129.00
128.91
127.70
127.00
126.37
126.13
120.60
73.97
71.10
64.05
62.55
33.06
26.55
17.89
13C NMR (CDCl3), 151 MHz
Ph
O
N
O
OH
1.3p
Current Data Parameters
NAME RKK1-169
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20191030
Time 10.54 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT CDC13
NS 95
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 297.8 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.40
7.39
7.38
7.31
7.30
7.29
7.26
7.07
7.06
7.02
7.01
6.84
6.83
6.47
6.23
6.22
6.20
6.20
6.19
6.17
5.48
5.47
5.22
5.19
4.70
4.68
4.67
4.46
4.44
4.43
3.98
3.97
3.95
3.39
3.37
2.39
1.56
1.33
Current Data Parameters
NAME RKK1-146_Rxst
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20190930
Time 12.08 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 296.2 K
D1 6.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050163 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
Ph
N
O
O
Me
Me
OH
1.3o
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.044
2.059
4.021
2.003
0.962
1.000
1.002
1.010
1.002
1.007
1.016
1.011
3.052
3.166

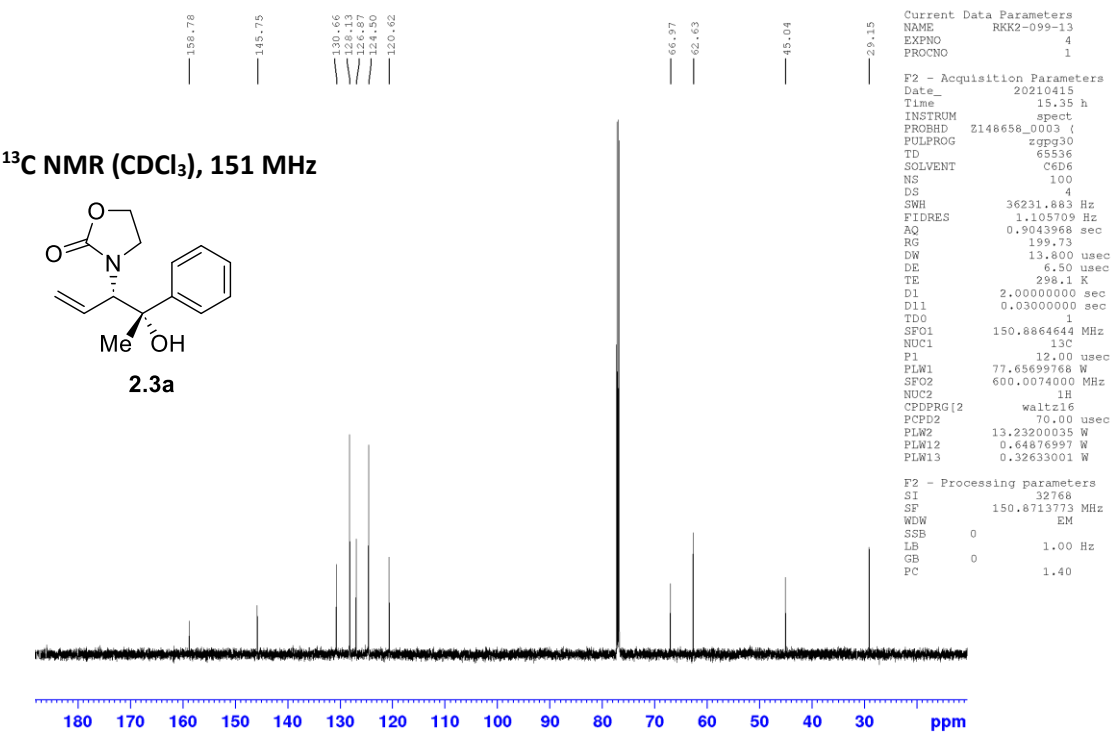

159.91
142.90
135.96
135.47
130.89
129.36
129.01
128.64
128.60
121.08
121.02
77.23
77.02
76.81
75.34
70.76
68.00
61.65
30.94
29.24
21.06
Current Data Parameters
NAME RKK1-146_RxstC2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20191010
Time 0.25 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 800
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.0 K
D1 6.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
Ph
N
O
O
Me
Me
OH
1.3o
200
180
160
140
120
100
80
60
40
20
0
ppm

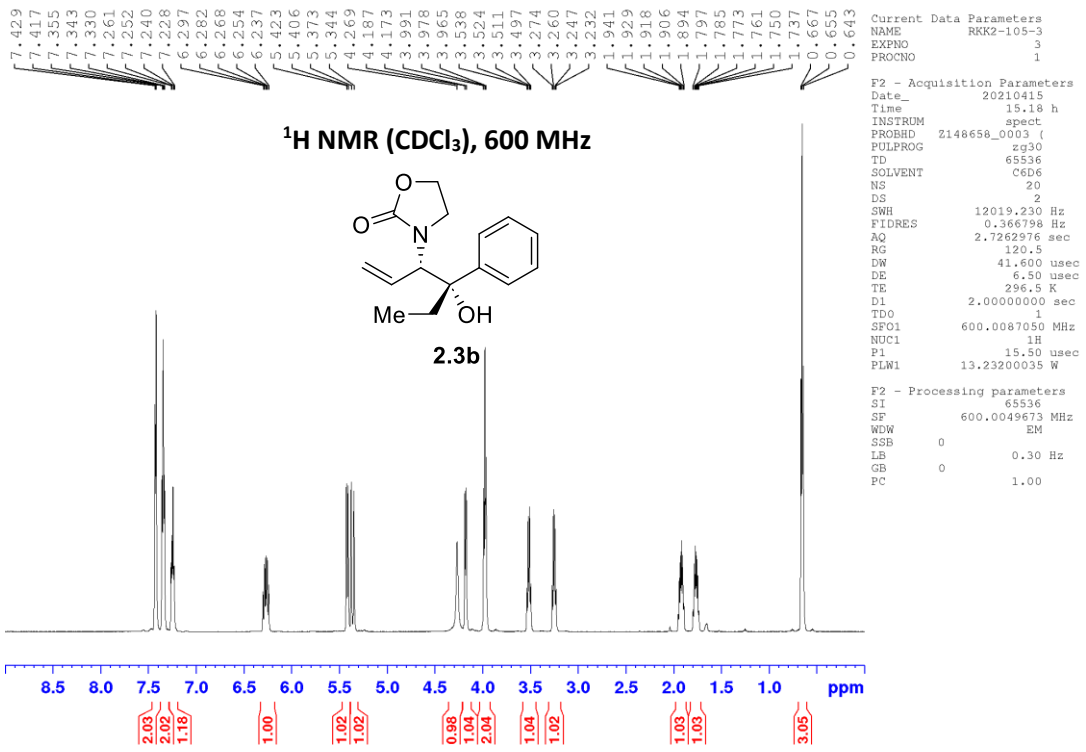
## APPENDIX A2. SELECT NMR SPECTRA FROM CHAPTER 2

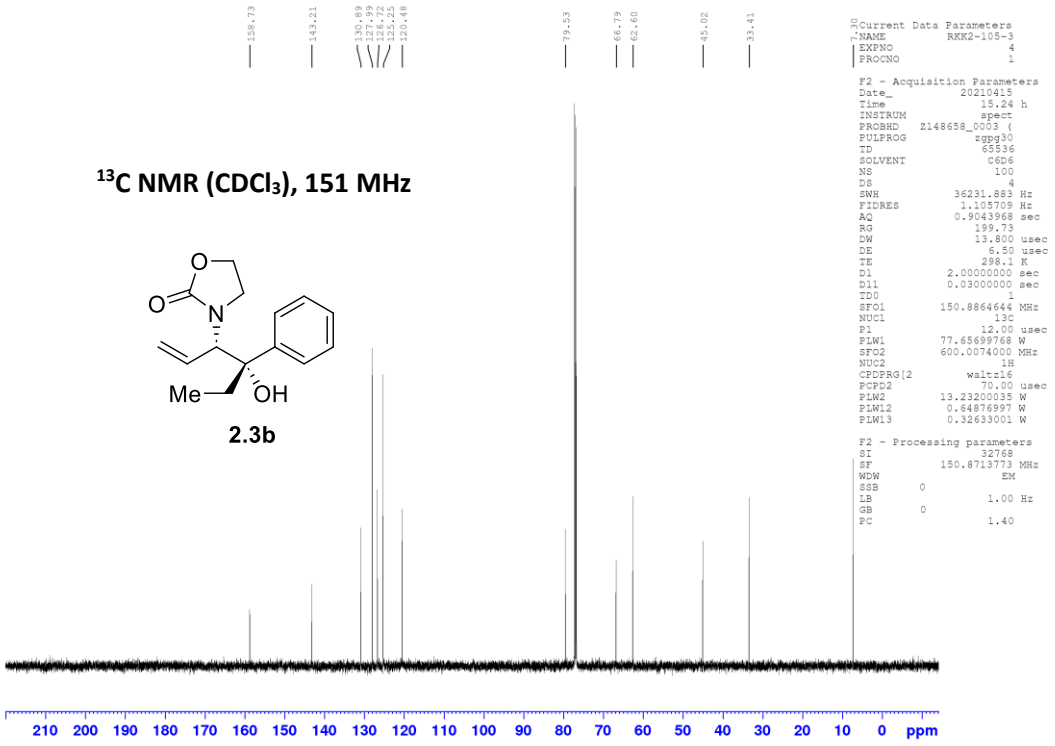
**$^{1}$H NMR ($CDCl_3$), 600 MHz**

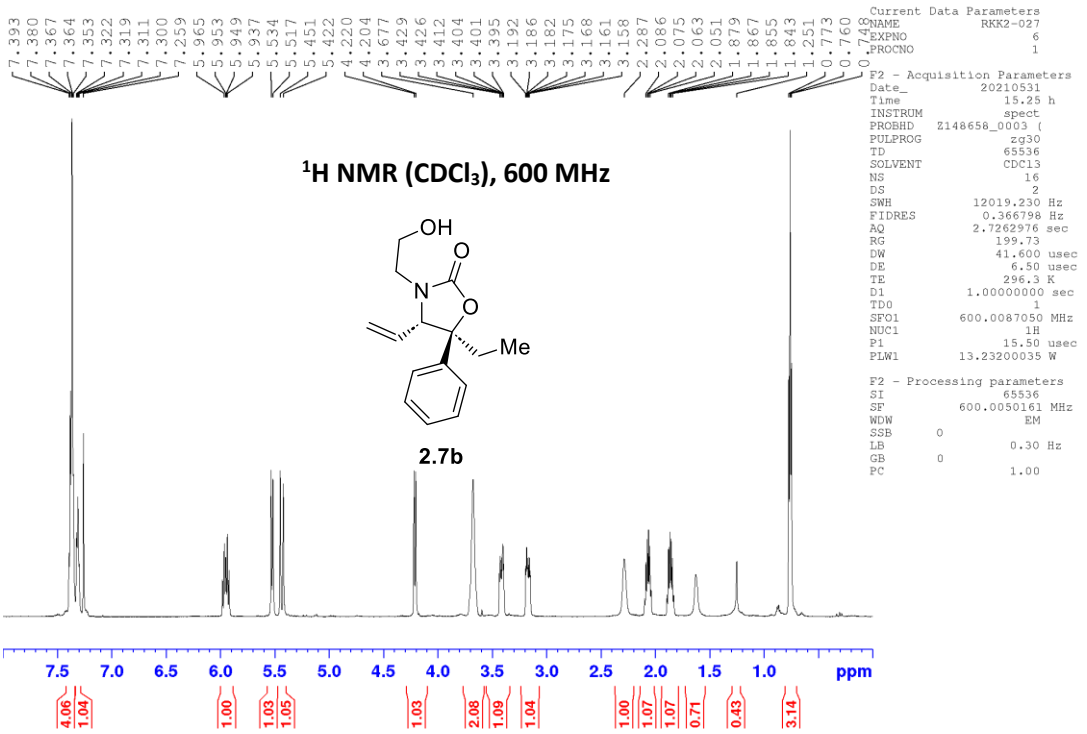


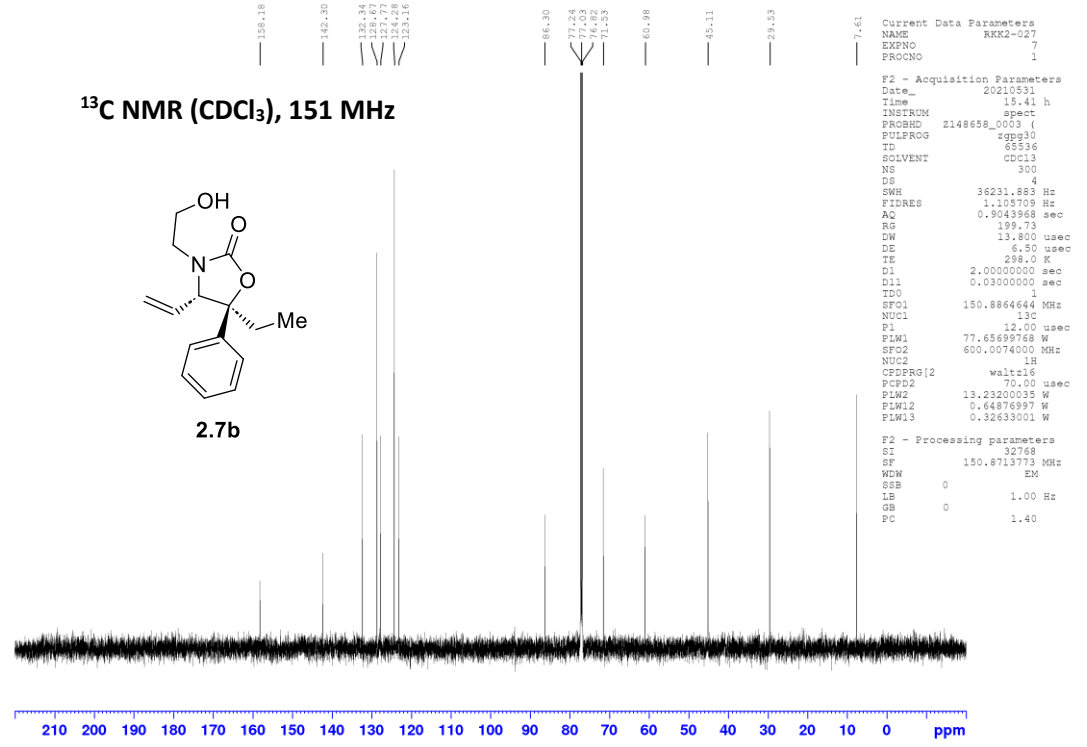

**$^{13}$C NMR ($CDCl_3$), 151 MHz**

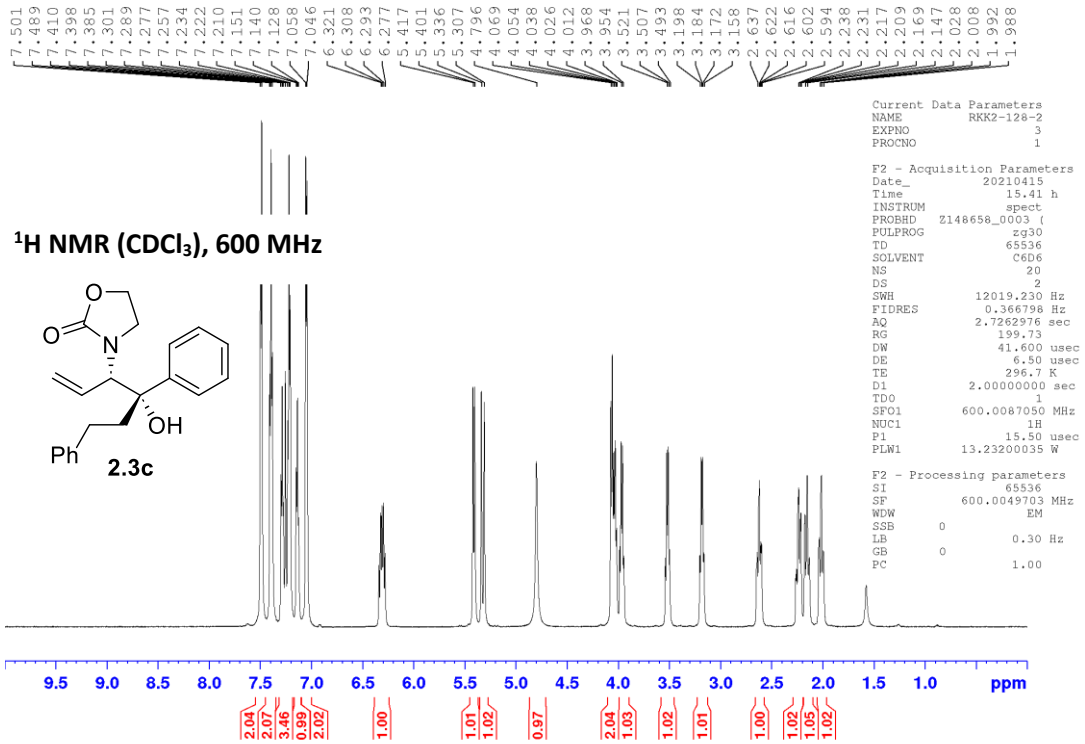



7.429
7.417
7.355
7.343
7.330
7.261
7.252
7.240
7.228
6.297
6.282
6.268
6.254
6.237
5.423
5.406
5.373
5.344
4.269
4.187
4.173
3.991
3.978
3.965
3.538
3.524
3.511
3.497
3.274
3.260
3.247
3.232
1.941
1.929
1.918
1.906
1.894
1.797
1.785
1.773
1.761
1.750
1.737
0.667
0.655
0.643
$^{1}$H NMR (CDCl$_3$), 600 MHz
O
O
N
Me
OH
2.3b
Current Data Parameters
NAME RKK2-105-3
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210415
Time 15.18 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT C6D6
NS 20
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 120.5
DW 41.600 usec
DE 6.50 usec
TE 296.5 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0049673 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.03 2.02 1.18 1.00 1.02 1.02 0.98 1.04 2.04 1.04 1.02 1.03 1.03 3.05


158.73
143.21
130.89
127.99
126.72
125.25
120.48
79.53
66.79
62.60
45.02
33.41
$^{13}$C NMR (CDCl$_3$), 151 MHz
O
O
N
Me
OH
2.3b
Current Data Parameters
NAME RKK2-105-3
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210415
Time 15.24 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 100
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


$^{1}$H NMR ($CDCl_3$), 600 MHz
OH
O
N
O
Me
2.7b
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
4.06 1.04 1.00 1.03 1.05 1.03 2.08 1.09 1.04 1.00 1.07 1.07 0.71 0.43 3.14

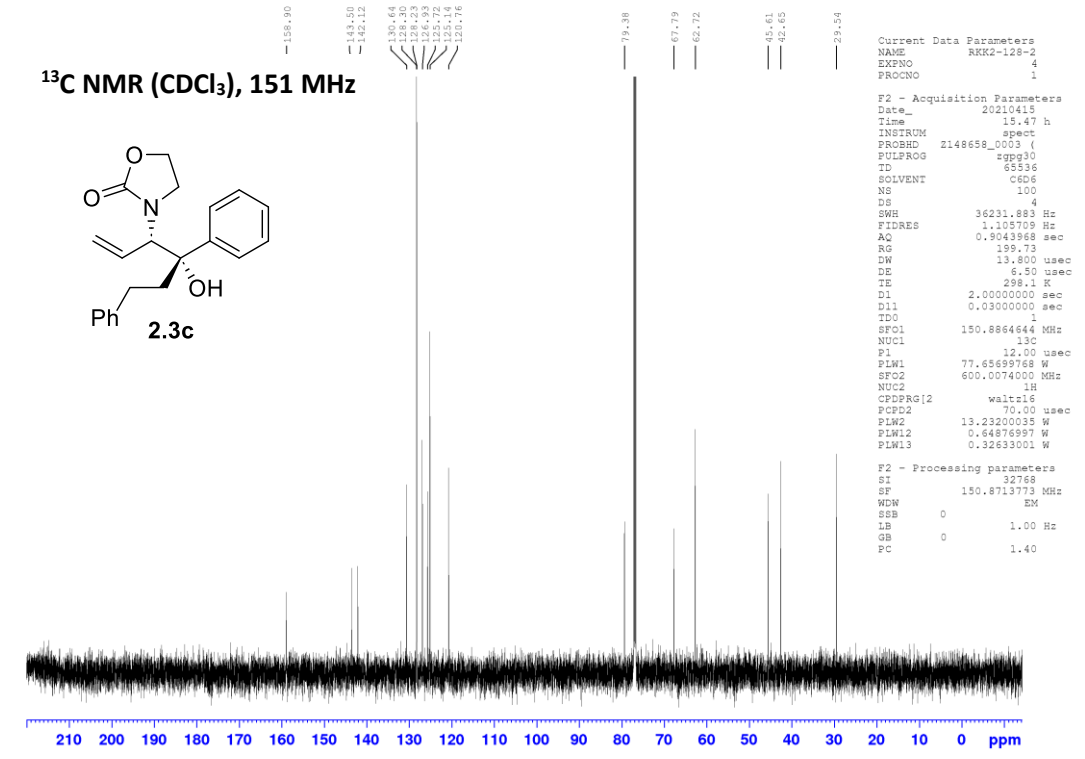

$^{13}$C NMR ($CDCl_3$), 151 MHz
OH
O
N
O
Me
2.7b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm




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



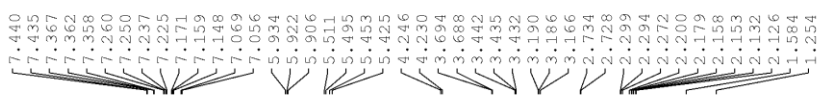

**2.3c**



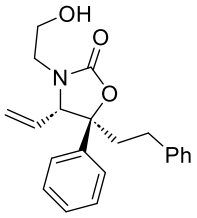

$^{13}$C NMR ($CDCl_3$), 151 MHz




**2.3c**

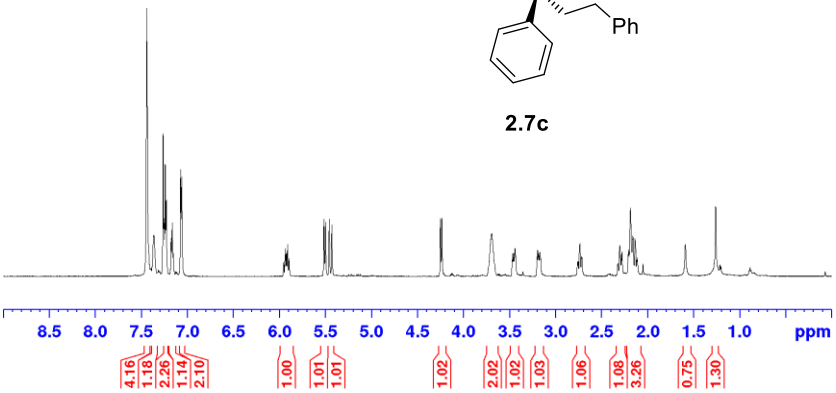



**$^{1}$H NMR ($CDCl_3$), 600 MHz**



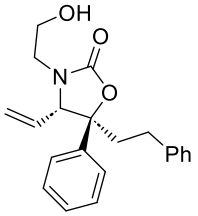

**2.7c**

```
Current Data Parameters
NAME        RKK2-104-2_2
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20210601
Time              16.05 h
INSTRUM            spect
PROBHD   Z148658_0003 (
PULPROG            zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH          12019.230 Hz
FIDRES        0.366798 Hz
AQ           2.7262976 sec
RG              199.73
DW             41.600 usec
DE              6.50 usec
TE             296.3 K
D1          1.00000000 sec
TD0                   1
SFO1        600.0087050 MHz
NUC1                1H
P1             15.50 usec
PLW1        13.23200035 W

F2 - Processing parameters
SI                65536
SF          600.0050161 MHz
WDW                  EM
SSB       0
LB              0.30 Hz
GB        0
PC              1.00
```



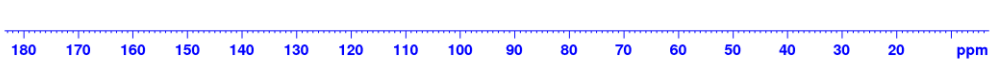


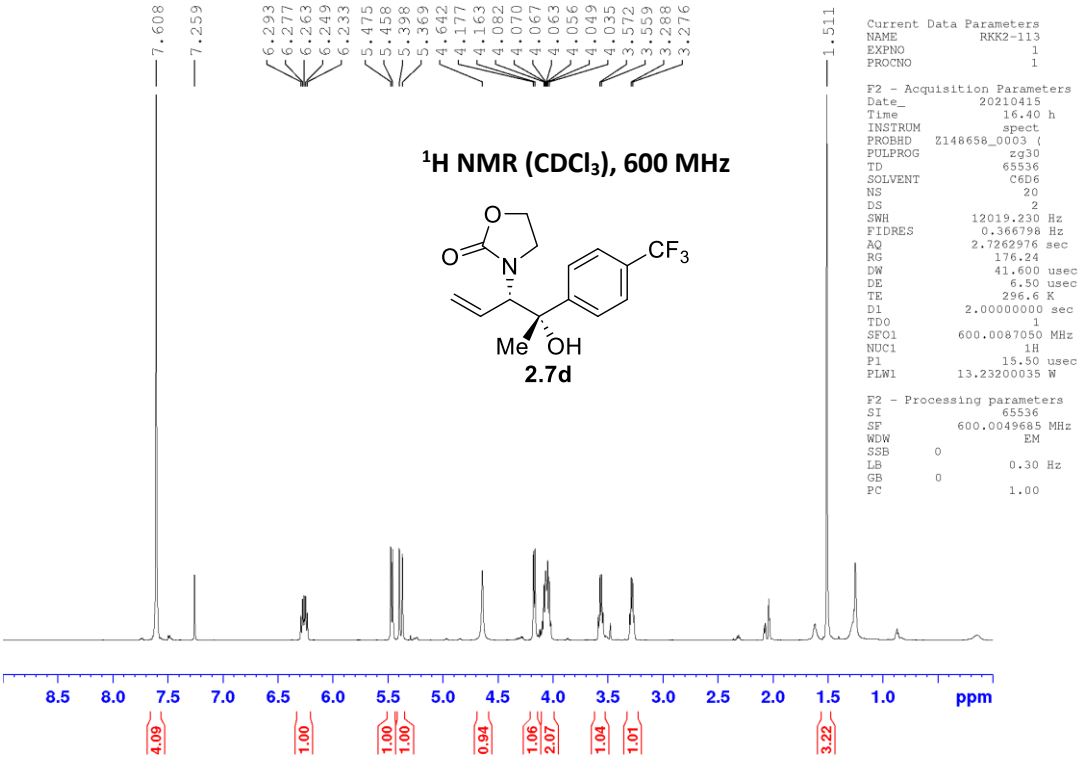

**$^{13}$C NMR ($CDCl_3$), 151 MHz**




**2.7c**

```
Current Data Parameters
NAME        RKK2-104-2_2
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20210601
Time              16.33 h
INSTRUM            spect
PROBHD   Z148658_0003 (
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                  300
DS                    4
SWH          36231.883 Hz
FIDRES        1.105709 Hz
AQ           0.9043968 sec
RG              199.73
DW             13.800 usec
DE              6.50 usec
TE             298.0 K
D1          2.00000000 sec
D11         0.03000000 sec
TD0                   1
SFO1        150.8864644 MHz
NUC1                13c
P1             12.00 usec
PLW1        77.65699768 W
SFO2        600.0074000 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2            70.00 usec
PLW2        13.23200035 W
PLW12        0.64876997 W
PLW13        0.32633001 W

F2 - Processing parameters
SI                32768
SF          150.8713773 MHz
WDW                  EM
SSB       0
LB              1.00 Hz
GB        0
PC              1.40
```

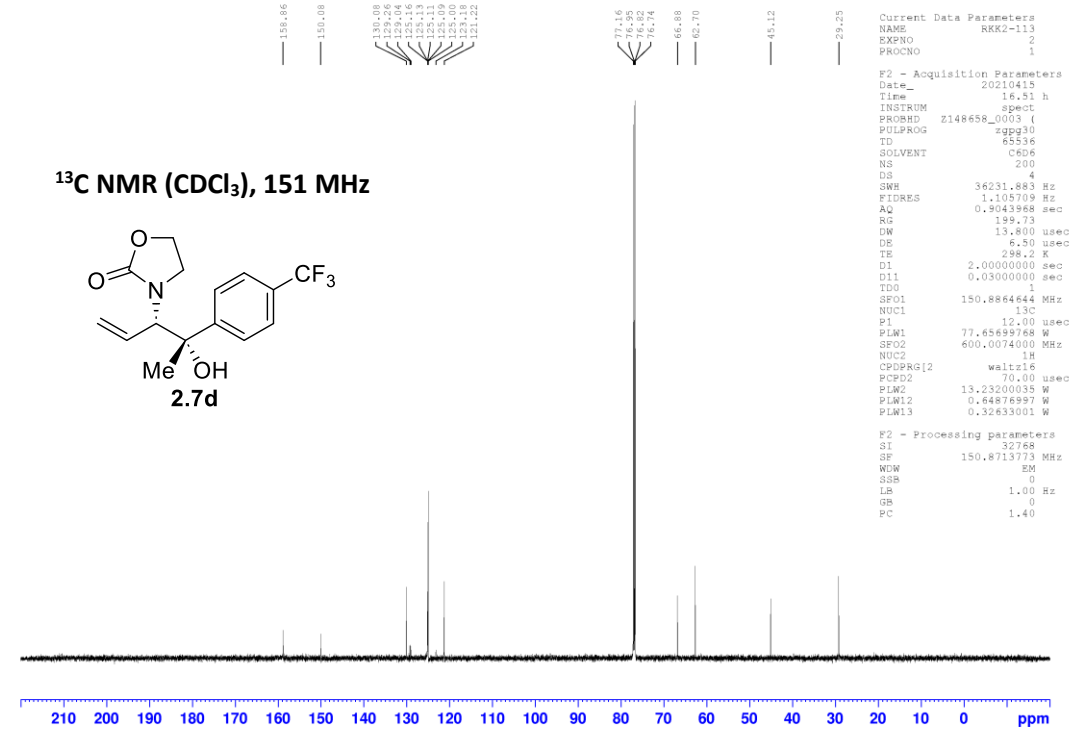





**$^{1}$H NMR ($CDCl_3$), 600 MHz**




**2.7d**

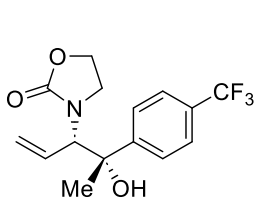



**$^{13}$C NMR ($CDCl_3$), 151 MHz**




**2.7d**

**$^{19}$F NMR ($CDCl_3$) 565 MHz**



**2.3d**




```
Current Data Parameters
NAME                  RKK2-103
EXPNO                        4
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20210415
Time                     12.11 h
INSTRUM                   spect
PROBHD    Z148658_0003 (
PULPROG          zgfhigqn.2
TD                       131072
SOLVENT                    C6D6
NS                           16
DS                            4
SWH                 133928.578 Hz
FIDRES                2.043588 Hz
AQ                    0.4893355 sec
RG                       199.73
DW                        3.733 usec
DE                        6.50 usec
TE                       297.2 K
D1                  1.00000000 sec
D11                 0.03000000 sec
D12                 0.00002000 sec
TD0                          1
SFO1                564.5123141 MHz
NUC1                        19F
P1                       15.00 usec
PLW1                26.76399994 W
SFO2                600.0074000 MHz
NUC2                        1H
CPDPRG[2                waltz16
PCPD2                    70.00 usec
PLW2                13.23200035 W
PLW12                0.64876997 W

F2 - Processing parameters
SI                           65536
SF                  564.5687710 MHz
WDW                             EM
SSB                  0
LB                        0.30 Hz
GB                   0
PC                        1.00
```

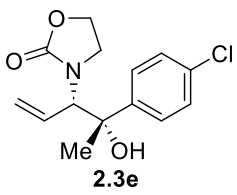
**$^{1}$H NMR ($CDCl_3$), 600 MHz**

**2.3e**




```
Current Data Parameters
NAME                  RKK2-W008
EXPNO                        12
PROCNO                        1

F2 - Acquisition Parameters
Date_                 20200904
Time                     15.29 h
INSTRUM                   spect
PROBHD    Z148658_0003 (
PULPROG                   zg30
TD                           65536
SOLVENT                   CDCl3
NS                           20
DS                            2
SWH                 12019.230 Hz
FIDRES                0.366798 Hz
AQ                    2.7262976 sec
RG                       199.73
DW                       41.600 usec
DE                        6.50 usec
TE                       296.1 K
D1                  1.00000000 sec
TD0                          1
SFO1                600.0087050 MHz
NUC1                        1H
P1                       15.50 usec
PLW1                13.23200035 W

F2 - Processing parameters
SI                           65536
SF                  600.0050158 MHz
WDW                             EM
SSB                  0
LB                        0.30 Hz
GB                   0
PC                        1.00
```

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

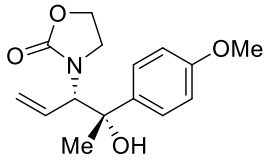



**2.3e**




```
Current Data Parameters
NAME                  RKK2-W008
EXPNO                        13
PROCNO                        1

F2 - Acquisition Parameters
Date_                 20200904
Time                     23.49 h
INSTRUM                   spect
PROBHD    Z148658_0003 (
PULPROG                zgpg30
TD                        65536
SOLVENT                   CDCl3
NS                         1024
DS                            4
SWH                   36231.883 Hz
FIDRES                1.105709 Hz
AQ                    0.9043968 sec
RG                       199.73
DW                       13.800 usec
DE                        6.50 usec
TE                       298.1 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                           1
SFO1                150.8864644 MHz
NUC1                        13C
P1                       12.00 usec
PLW1                77.65699768 W
SFO2                600.0074000 MHz
NUC2                        1H
CPDPRG[2                waltz16
PCPD2                    70.00 usec
PLW2                13.23200035 W
PLW12                0.64876997 W
PLW13                0.32633001 W

F2 - Processing parameters
SI                        32768
SF                  150.8713773 MHz
WDW                          EM
SSB                   0
LB                        1.00 Hz
GB                    0
PC                        1.40
```

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

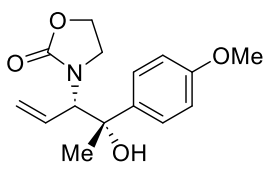



**2.3f**




```
Current Data Parameters
NAME                  RKK2-W008
EXPNO                         5
PROCNO                        1

F2 - Acquisition Parameters
Date_                 20200903
Time                     15.47 h
INSTRUM                   spect
PROBHD    Z148658_0003 (
PULPROG                   zg30
TD                        65536
SOLVENT                   CDCl3
NS                           20
DS                            2
SWH                   12019.230 Hz
FIDRES                0.366798 Hz
AQ                    2.7262976 sec
RG                       199.73
DW                       41.600 usec
DE                        6.50 usec
TE                       296.3 K
D1                    1.00000000 sec
TD0                           1
SFO1                600.0087050 MHz
NUC1                        1H
P1                       15.50 usec
PLW1                13.23200035 W

F2 - Processing parameters
SI                        65536
SF                  600.0050160 MHz
WDW                          EM
SSB                   0
LB                        0.30 Hz
GB                    0
PC                        1.00
```

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



**2.3f**

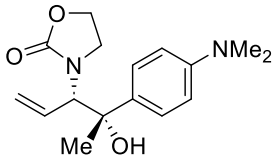



Current Data Parameters
NAME RKK2-W008
EXPNO 6
PROCNO 1

F2 - Acquisition Parameters
Date_ 20200903
Time 16.42 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 150
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 297.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W

F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

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



**2.3g**

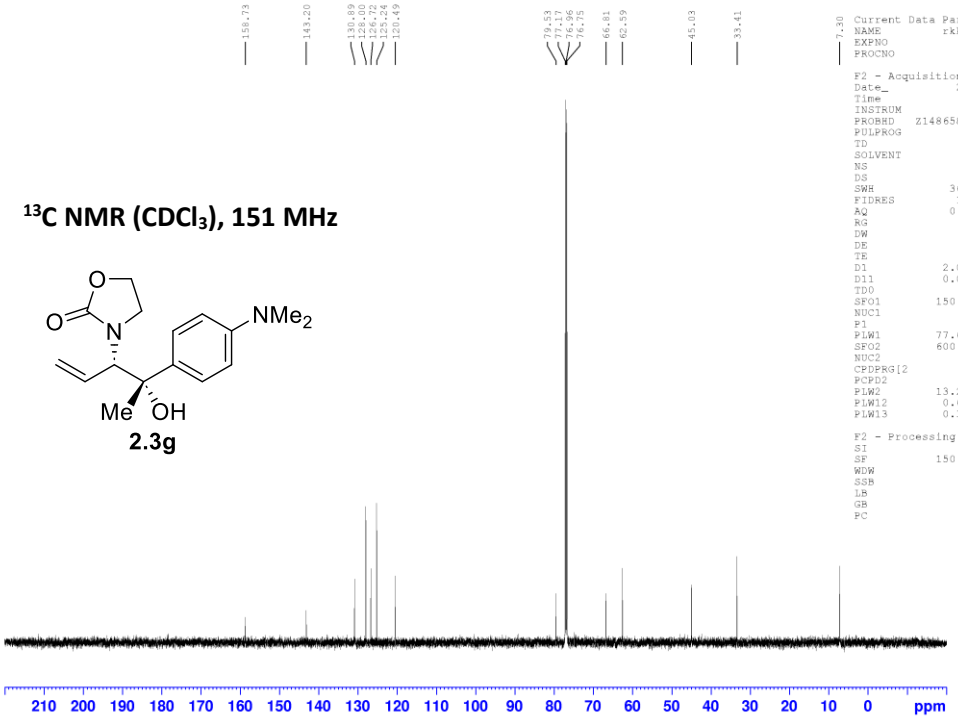



Current Data Parameters
NAME RKK2-026
EXPNO 3
PROCNO 1

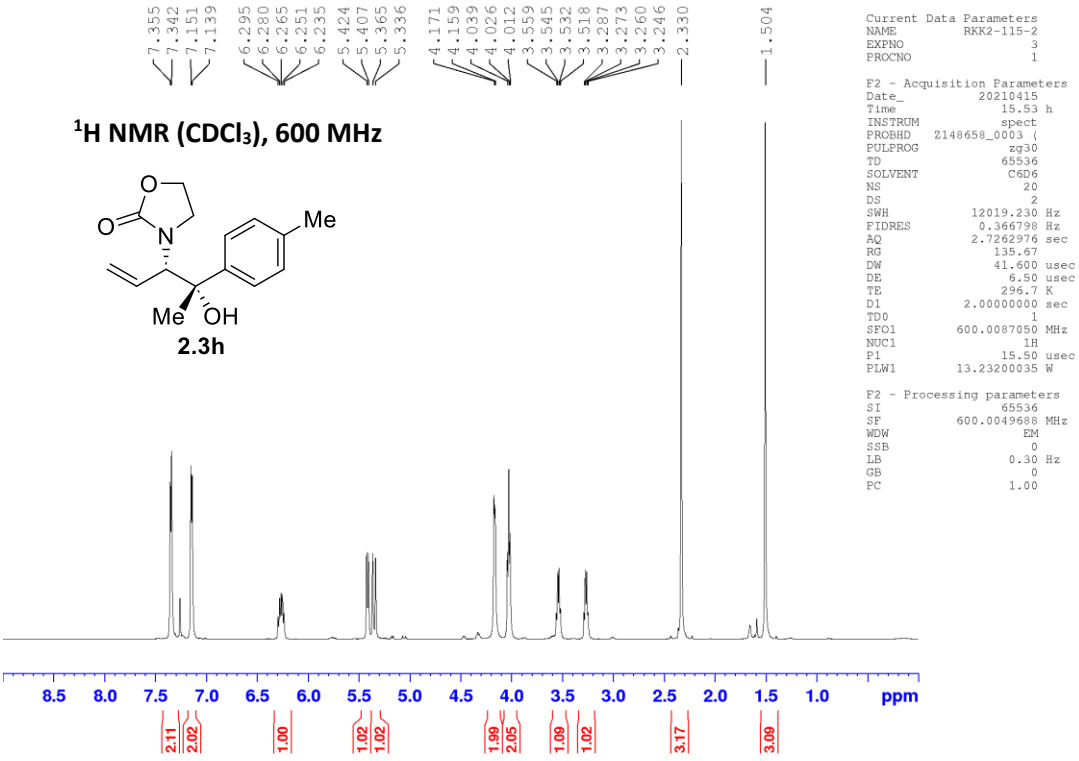
F2 - Acquisition Parameters
Date_ 20210408
Time 15.43 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 110.56
DW 41.600 usec
DE 6.50 usec
TE 296.6 K
D1 1.00000000 sec
TD0 1
SFO1 599.9587047 MHz
NUC1 1H
P1 7.75 usec
PLW1 11.99499989 W

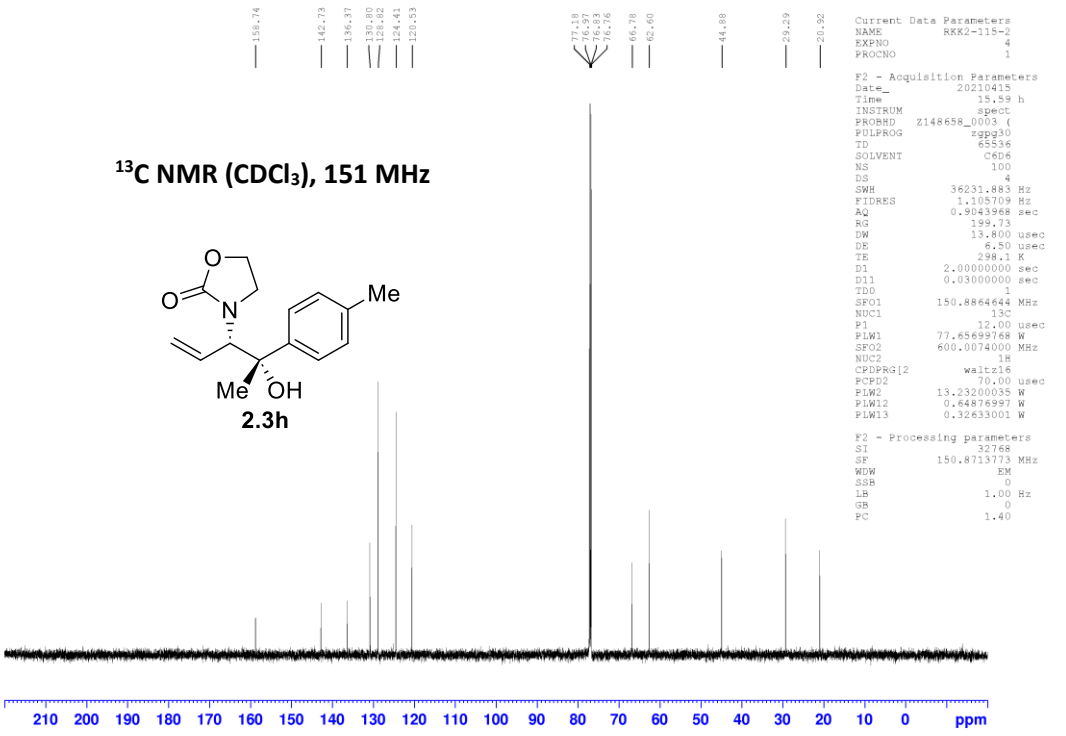
F2 - Processing parameters
SI 65536
SF 599.9550168 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

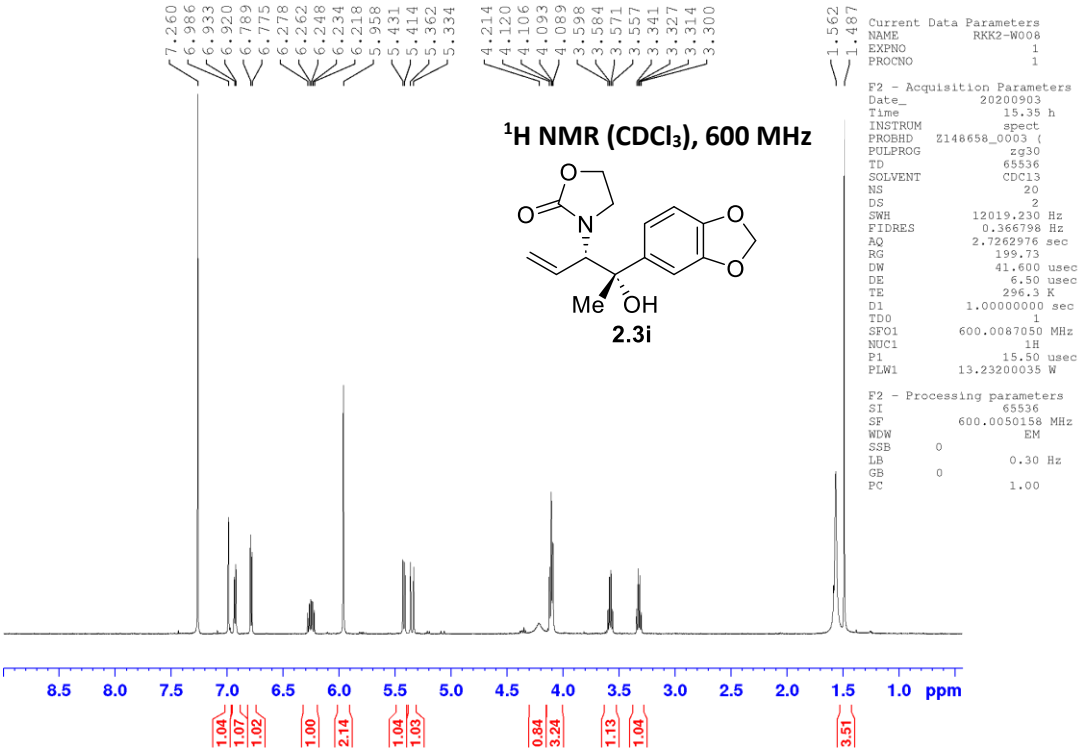
**$^{13}$C NMR ($CDCl_3$), 151 MHz**



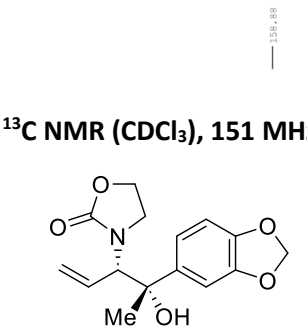

**$^{1}$H NMR ($CDCl_3$), 600 MHz**




158.74
142.73
136.37
130.80
128.82
124.41
120.53
77.18
76.97
76.63
76.16
66.78
62.60
44.88
29.29
20.92
Current Data Parameters
NAME RKK2-115-2
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210415
Time 15.59 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 100
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
O
O
N
Me
Me
OH
2.3h
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.260
6.986
6.933
6.920
6.789
6.775
6.278
6.262
6.248
6.234
6.218
5.958
5.431
5.414
5.362
5.334
4.214
4.120
4.106
4.093
4.089
3.598
3.584
3.571
3.557
3.341
3.327
3.314
3.300
1.562
1.487
Current Data Parameters
NAME RKK2-W008
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20200903
Time 15.35 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 20
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 296.3 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050158 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
O
O
N
O
O
Me
OH
2.3i
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.04
1.07
1.02
1.00
2.14
1.04
1.03
0.84
3.24
1.13
1.04
3.51

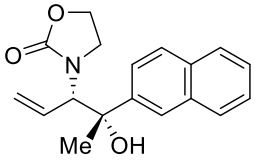
**$^{13}$C NMR ($CDCl_3$), 151 MHz**




**2.3i**

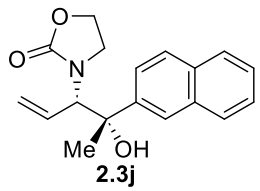



**$^{1}$H NMR ($CDCl_3$), 600 MHz**




**2.3j**

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




**2.3j**

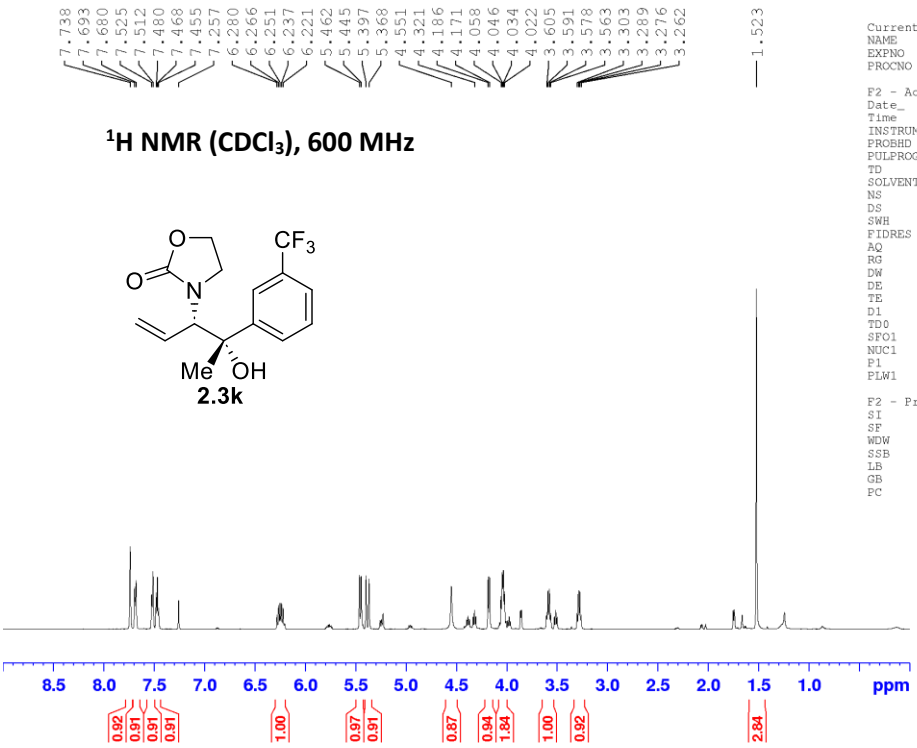



```
Current Data Parameters
NAME                  RKK1-189
EXPNO                        6
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20210416
Time                      9.38 h
INSTRUM                  spect
PROBHD     Z148658_0003 (
PULPROG                zgpg30
TD                      65536
SOLVENT                  C6D6
NS                        200
DS                          4
SWH                 36231.883 Hz
FIDRES              1.105709 Hz
AQ                  0.9043968 sec
RG                      199.73
DW                      13.800 usec
DE                       6.50 usec
TE                      298.3 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1
SFO1               150.8864644 MHz
NUC1                       13C
P1                      12.00 usec
PLW1               77.65699768 W
SFO2               600.0074000 MHz
NUC2                       1H
CPDPRG[2                waltz16
PCPD2                   70.00 usec
PLW2               13.23200035 W
PLW12               0.64876997 W
PLW13               0.32633001 W

F2 - Processing parameters
SI                        32768
SF                 150.8713773 MHz
WDW                          EM
SSB                 0
LB                      1.00 Hz
GB                  0
PC                      1.40
```

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

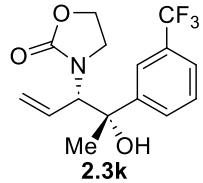



**2.3k**




```
Current Data Parameters
NAME                  rkk2-153_2
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                 20210416
Time                      7.00 h
INSTRUM                  spect
PROBHD     Z148658_0003 (
PULPROG                  zg30
TD                      65536
SOLVENT                  C6D6
NS                         20
DS                          2
SWH                 12019.230 Hz
FIDRES              0.366798 Hz
AQ                  2.7262976 sec
RG                       120.5
DW                      41.600 usec
DE                       6.50 usec
TE                      296.4 K
D1                 2.00000000 sec
TD0                         1
SFO1               600.0087050 MHz
NUC1                       1H
P1                      15.50 usec
PLW1               13.23200035 W

F2 - Processing parameters
SI                        65536
SF                 600.0049695 MHz
WDW                          EM
SSB                          0
LB                      0.30 Hz
GB                           0
PC                      1.00
```

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

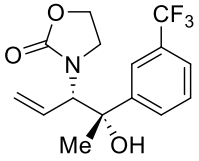



**2.3k**




```
Current Data Parameters
NAME                  rkk2-153
EXPNO                        4
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20210416
Time                      7.13 h
INSTRUM                  spect
PROBHD    Z148658_0003 (
PULPROG              zgpg30
TD                        65536
SOLVENT                   C6D6
NS                         200
DS                           4
SWH                  36231.883 Hz
FIDRES                1.105709 Hz
AQ                    0.9043968 sec
RG                       199.73
DW                       13.800 usec
DE                        6.50 usec
TE                       298.2 K
D1                    2.00000000 sec
D11                   0.03000000 sec
TD0                          1
SFO1                150.8864644 MHz
NUC1                        13c
P1                       12.00 usec
PLW1                77.65699768 W
SFO2                600.0074000 MHz
NUC2                        1H
CPDPRG[2                waltz16
PCPD2                    70.00 usec
PLW2                13.23200035 W
PLW12                0.64876997 W
PLW13                0.32633001 W

F2 - Processing parameters
SI                        32768
SF                  150.8713773 MHz
WDW                          EM
SSB                  0
LB                        1.00 Hz
GB                   0
PC                        1.40
```

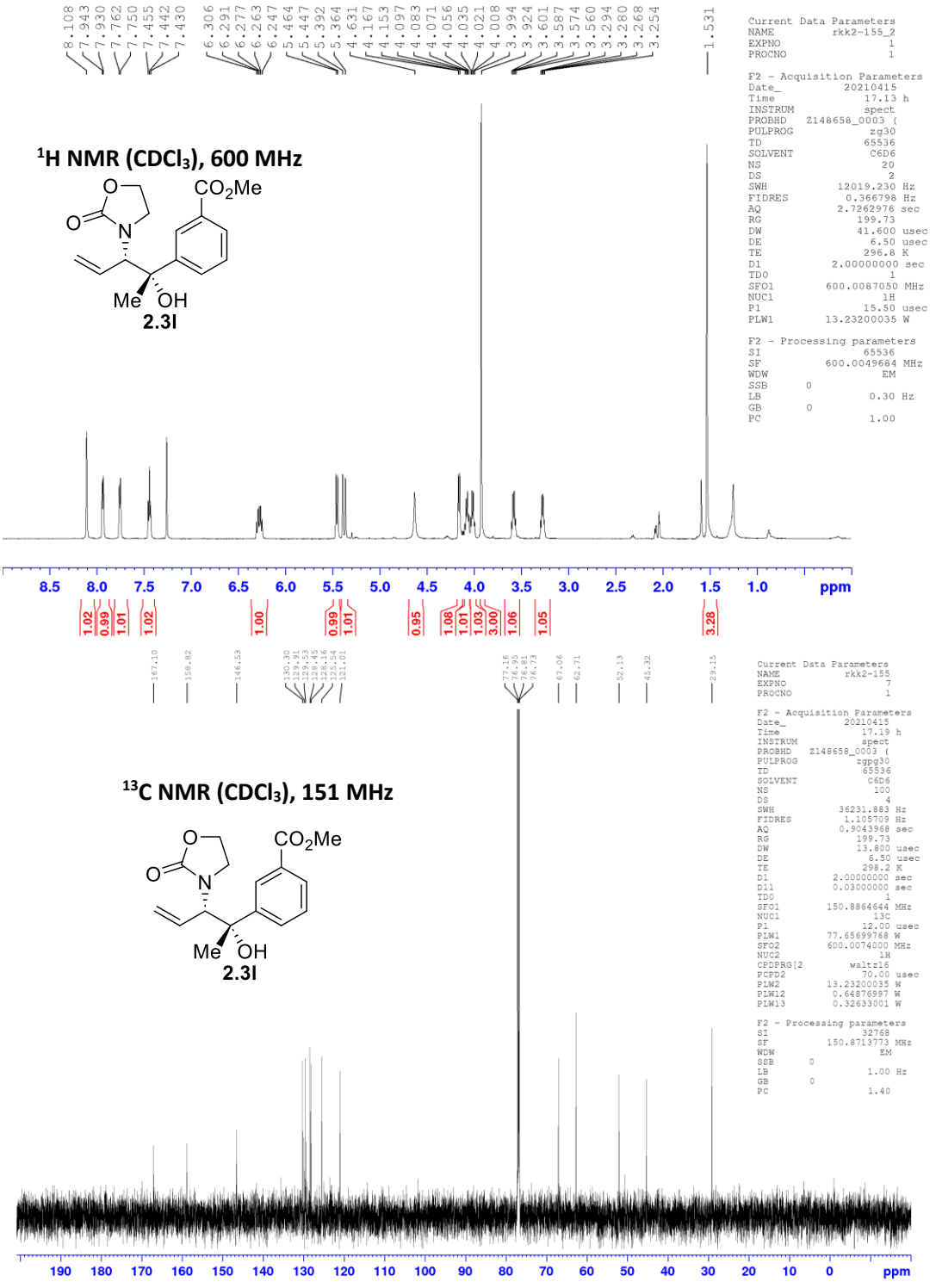
**$^{19}$F NMR ($CDCl_3$) 565 MHz**

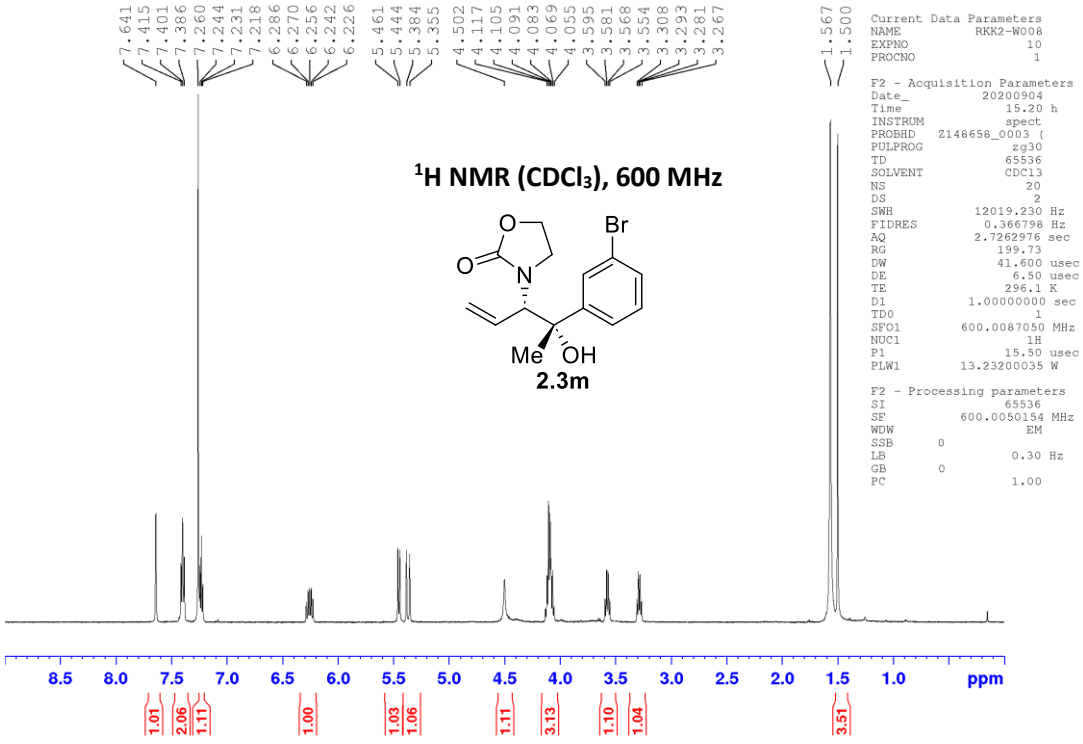


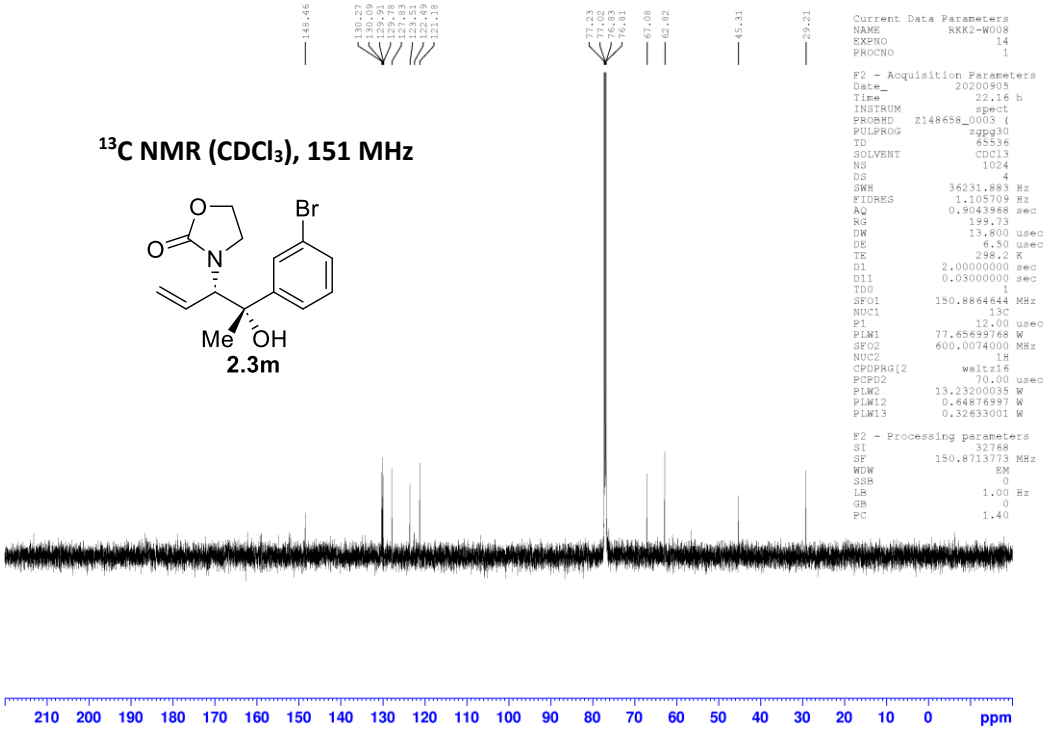

**2.3k**

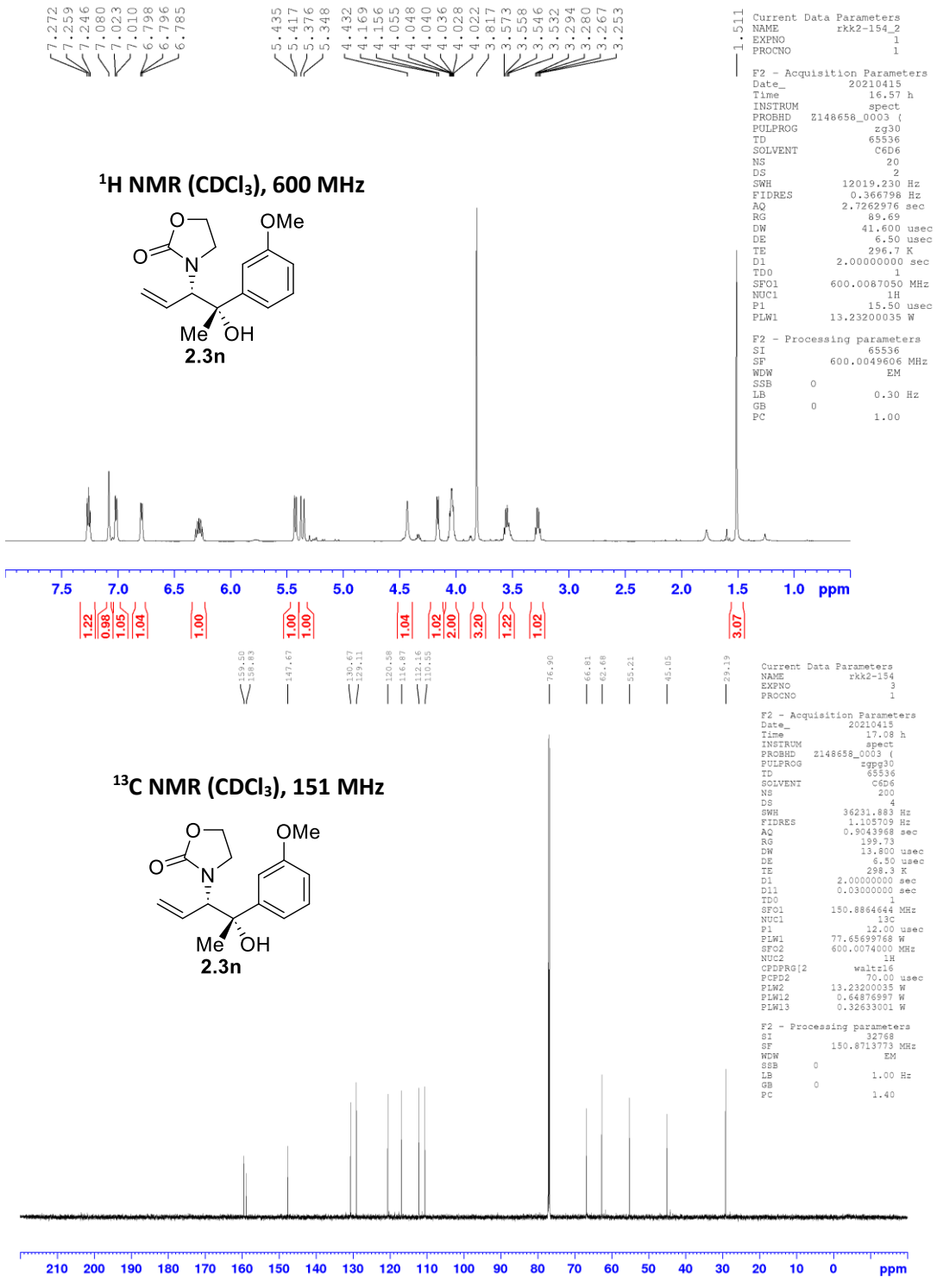


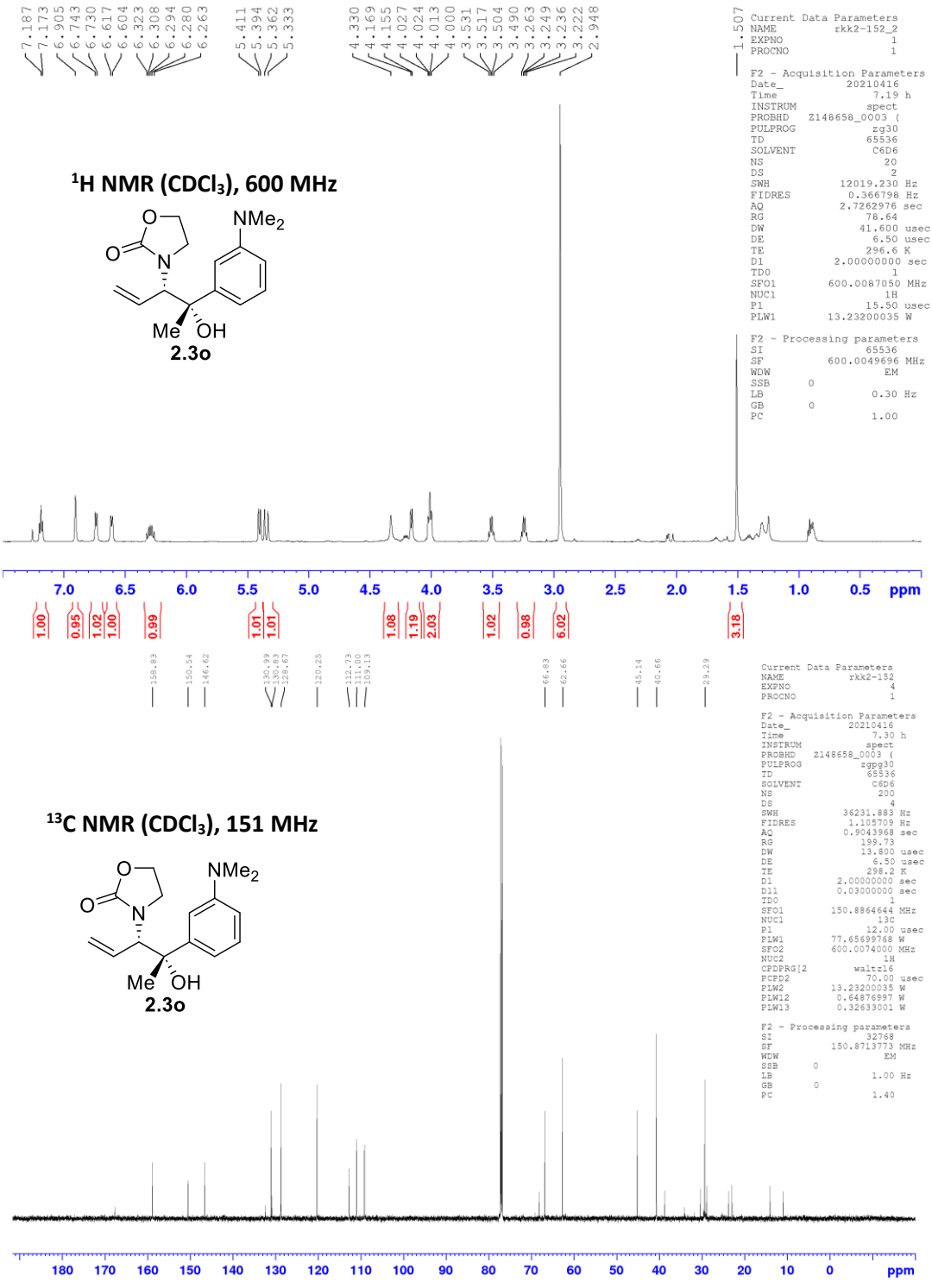

```
Current Data Parameters
NAME                  rkk2-153
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_                 20210416
Time                      7.02 h
INSTRUM                  spect
PROBHD    Z148658_0003 (
PULPROG          zgfhigqn.2
TD                       131072
SOLVENT                   C6D6
NS                          16
DS                           4
SWH                 133928.578 Hz
FIDRES                2.043588 Hz
AQ                    0.4893355 sec
RG                       199.73
DW                        3.733 usec
DE                        6.50 usec
TE                       296.8 K
D1                    1.00000000 sec
D11                   0.03000000 sec
D12                   0.00002000 sec
TD0                          1
SFO1                564.5123141 MHz
NUC1                        19F
P1                       15.00 usec
PLW1                26.76399994 W
SFO2                600.0074000 MHz
NUC2                        1H
CPDPRG[2                waltz16
PCPD2                    70.00 usec
PLW2                13.23200035 W
PLW12                0.64876997 W

F2 - Processing parameters
SI                        65536
SF                  564.5687710 MHz
WDW                          EM
SSB                  0
LB                        0.30 Hz
GB                   0
PC                        1.00
```


8.108
7.943
7.930
7.762
7.750
7.455
7.442
7.430
6.306
6.291
6.277
6.263
6.247
5.464
5.447
5.392
5.364
4.631
4.167
4.153
4.097
4.083
4.071
4.056
4.035
4.021
4.008
3.994
3.924
3.601
3.587
3.574
3.560
3.294
3.280
3.268
3.254
1.531
Current Data Parameters
NAME rkk2-155_2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210415
Time 17.13 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT C6D6
NS 20
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 296.8 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0049684 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
CO2Me
O
O
N
Me
OH
2.3l
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.02 0.99 1.01 1.02 1.00 0.99 1.01 0.95 1.08 1.01 1.03 3.00 1.06 1.05 3.28
167.10
158.82
146.53
130.30
129.31
129.53
128.45
128.16
125.64
125.41
121.71
77.16
76.95
76.73
67.06
62.71
52.13
45.32
29.15
Current Data Parameters
NAME rkk2-155
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210415
Time 17.19 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 100
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
CO2Me
O
O
N
Me
OH
2.3l
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

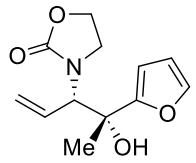

7.641
7.415
7.401
7.386
7.260
7.244
7.231
7.218
6.286
6.270
6.256
6.242
6.226
5.461
5.444
5.384
5.355
4.502
4.117
4.105
4.091
4.083
4.069
4.055
3.595
3.581
3.568
3.554
3.308
3.293
3.281
3.267
1.567
1.500
$^{1}$H NMR (CDCl$_3$), 600 MHz
Br
O
O
N
Me
OH
2.3m
Current Data Parameters
NAME RKK2-W008
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20200904
Time 15.20 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 20
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 296.1 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050154 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.01
2.06
1.11
1.00
1.03
1.06
1.11
3.13
1.10
1.04
3.51


148.46
130.27
130.09
129.91
128.78
127.83
123.51
122.49
121.18
77.23
77.02
76.83
76.81
67.08
62.82
45.31
29.21
$^{13}$C NMR (CDCl$_3$), 151 MHz
Br
O
O
N
Me
OH
2.3m
Current Data Parameters
NAME RKK2-W008
EXPNO 14
PROCNO 1
F2 - Acquisition Parameters
Date_ 20200905
Time 22.16 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.272
7.259
7.246
7.080
7.023
7.010
6.798
6.796
6.785
5.435
5.417
5.376
5.348
4.432
4.169
4.156
4.055
4.048
4.040
4.036
4.028
4.022
3.817
3.573
3.558
3.546
3.532
3.294
3.280
3.267
3.253
1.511
Current Data Parameters
NAME rkk2-154_2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210415
Time 16.57 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT C6D6
NS 20
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 89.69
DW 41.600 usec
DE 6.50 usec
TE 296.7 K
D1 2.00000000 sec
TD0 1
SFO1 600.0067050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0049606 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
O
OMe
O
N
Me
OH
2.3n
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.22
0.98
1.05
1.04
1.00
1.00
1.00
1.04
1.02
2.00
3.20
1.22
1.02
3.07
159.50
156.83
147.67
130.67
129.11
120.58
116.87
112.16
110.55
76.90
66.81
62.68
55.21
45.05
29.19
Current Data Parameters
NAME rkk2-154
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210415
Time 17.08 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 200
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
O
OMe
O
N
Me
OH
2.3n
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


7.187
7.173
6.905
6.743
6.730
6.617
6.604
6.323
6.308
6.294
6.280
6.263
5.411
5.394
5.362
5.333
4.330
4.169
4.155
4.027
4.024
4.013
4.000
3.531
3.517
3.504
3.490
3.263
3.249
3.236
3.222
2.948
1.507
Current Data Parameters
NAME rkk2-152_2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210416
Time 7.19 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT C6D6
NS 20
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 78.64
DW 41.600 usec
DE 6.50 usec
TE 296.6 K
D1 2.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0049696 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
NMe2
O
O
N
Me
OH
2.3o
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.95
1.02
1.00
0.99
1.01
1.01
1.08
1.19
2.03
1.02
0.98
6.02
3.18
158.83
150.54
146.62
130.99
130.83
128.67
120.25
112.73
111.00
109.13
66.83
62.66
45.14
40.66
29.29
Current Data Parameters
NAME rkk2-152
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210416
Time 7.30 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 200
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
NMe2
O
O
N
Me
OH
2.3o
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

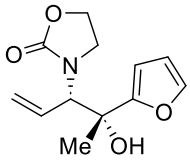
**$^{13}$C NMR ($CDCl_3$), 151 MHz**



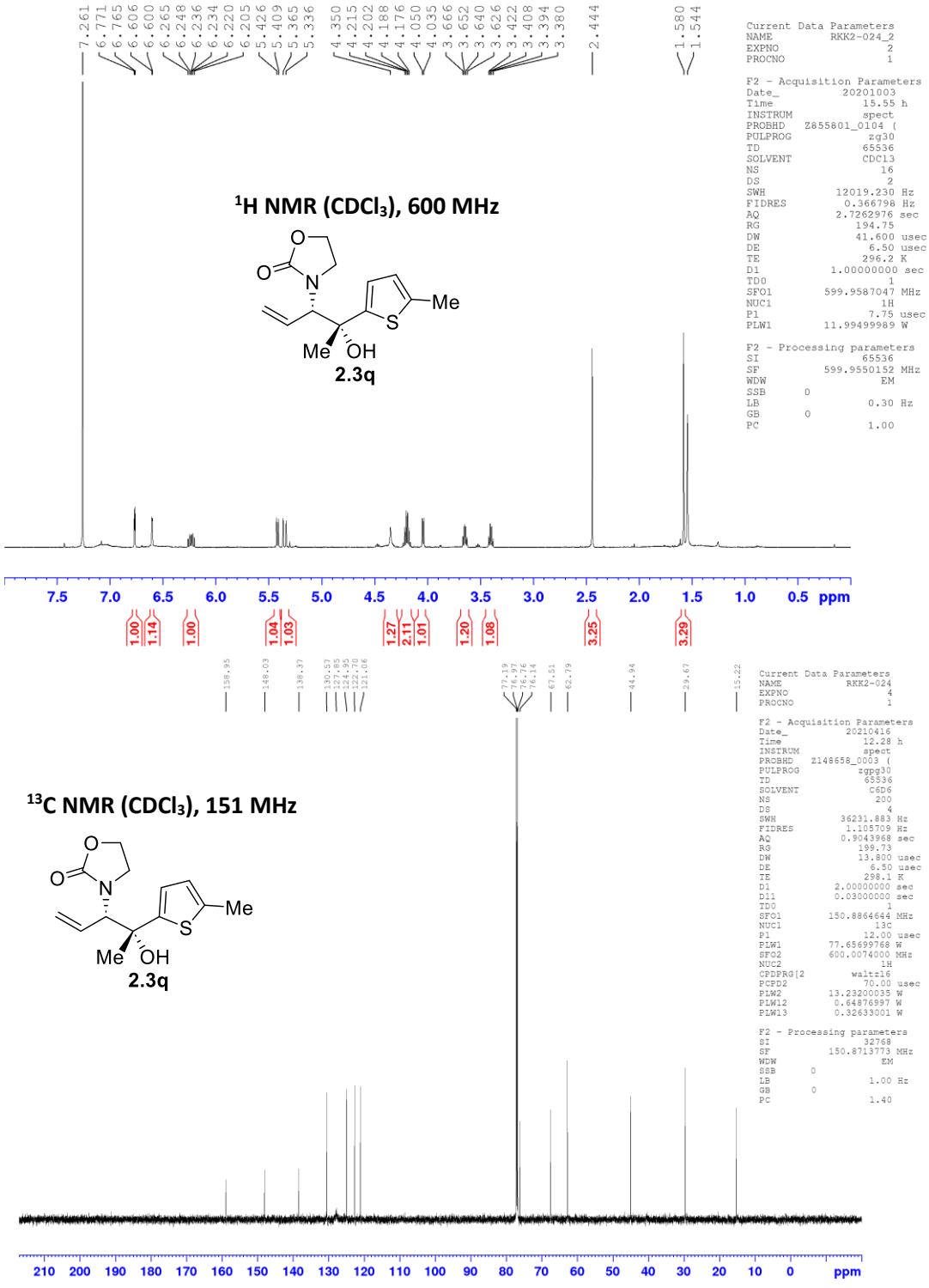

**2.3p**



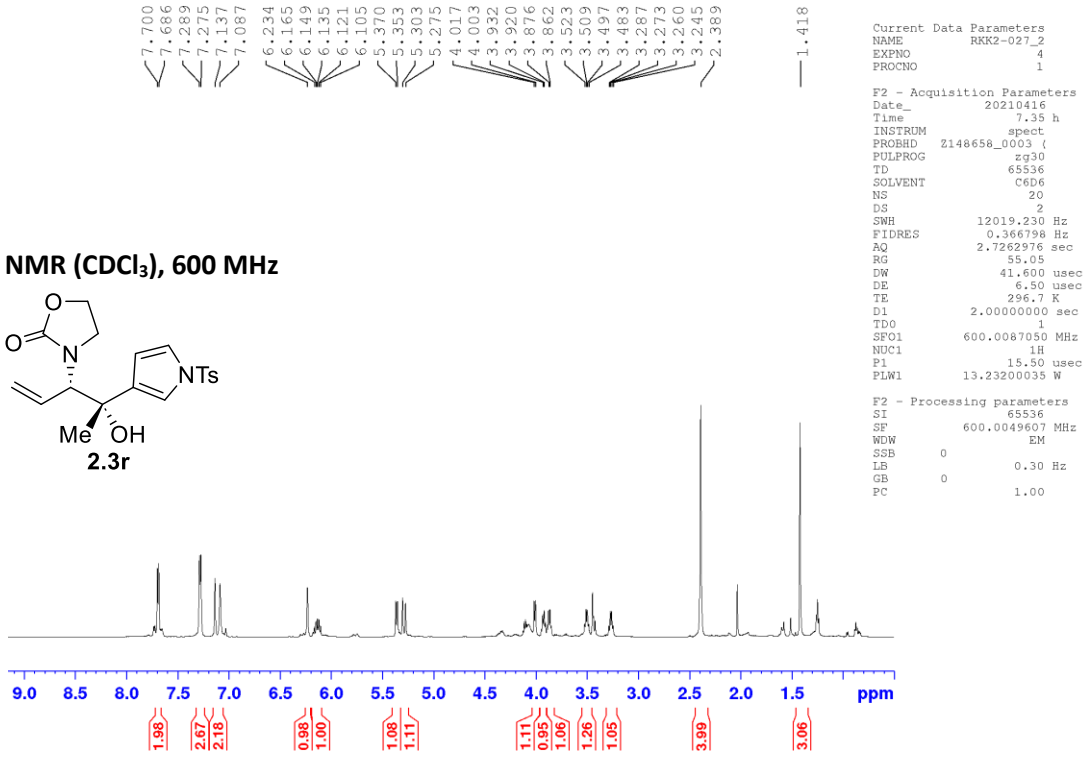

**$^{1}$H NMR ($CDCl_3$), 600 MHz**



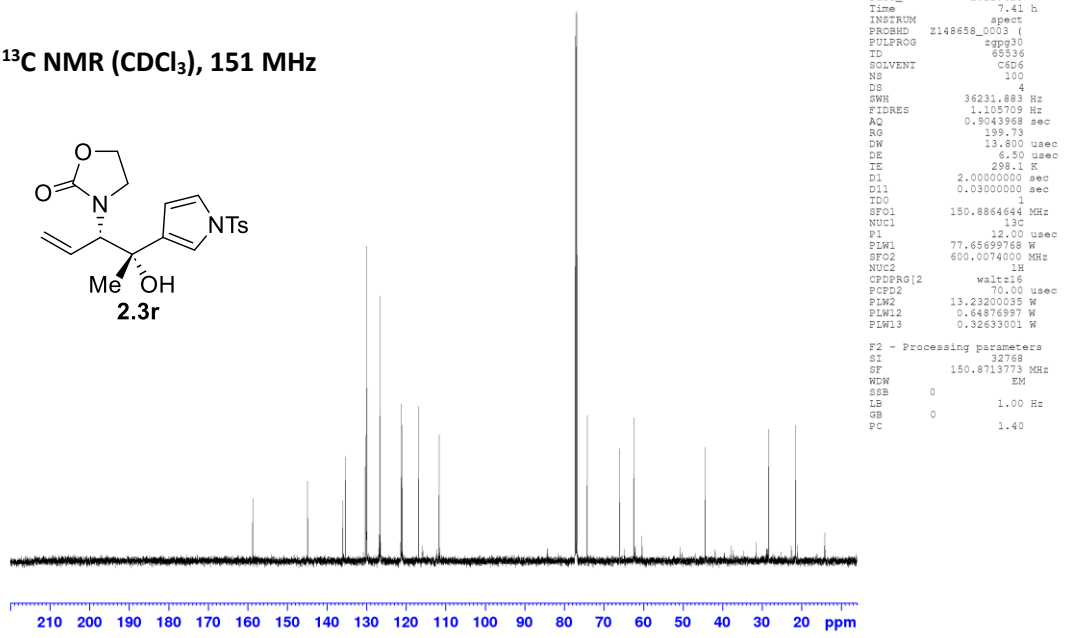

**2.3p**

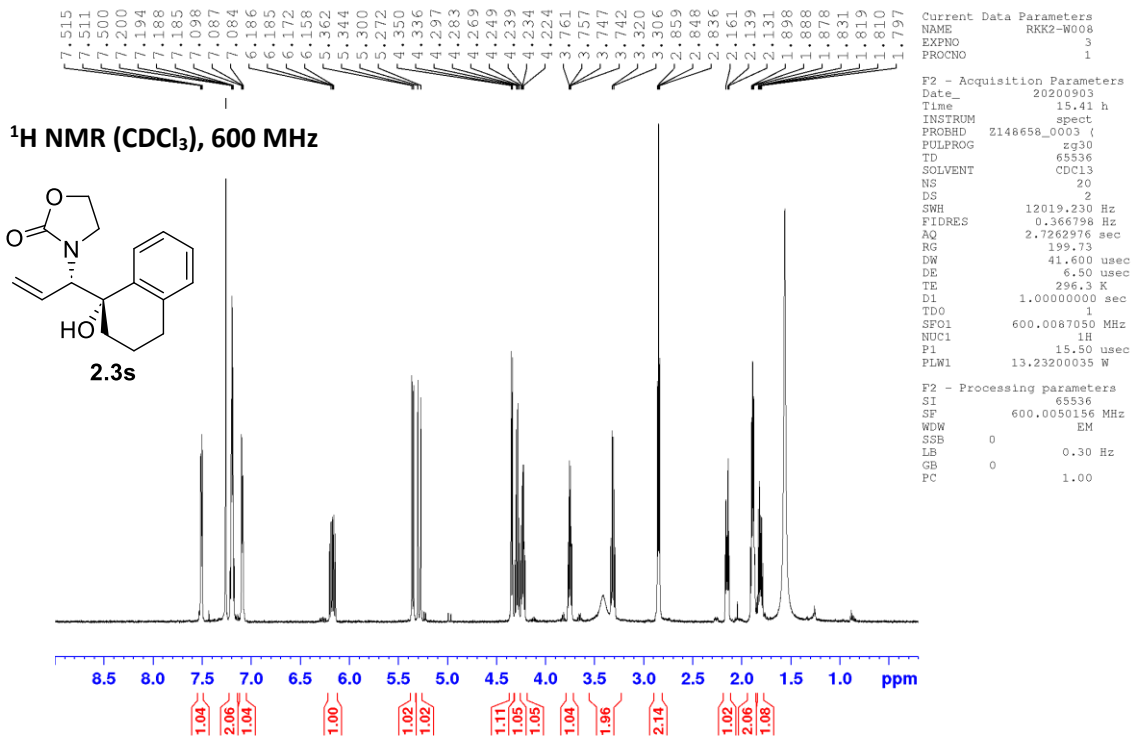

7.261
6.771
6.765
6.606
6.600
6.265
6.248
6.236
6.234
6.220
6.205
5.426
5.409
5.365
5.336
4.350
4.215
4.202
4.188
4.176
4.050
4.035
3.666
3.652
3.640
3.626
3.422
3.408
3.394
3.380
2.444
1.580
1.544
Current Data Parameters
NAME RKK2-024_2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20201003
Time 15.55 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 194.75
DW 41.600 usec
DE 6.50 usec
TE 296.2 K
D1 1.00000000 sec
TD0 1
SFO1 599.9587047 MHz
NUC1 1H
P1 7.75 usec
PLW1 11.99499989 W
F2 - Processing parameters
SI 65536
SF 599.9550152 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
Me
Me OH
2.3q
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00 1.14 1.00 1.04 1.03 1.27 2.11 1.01 1.20 1.08 3.25 3.29
158.95
148.03
138.37
130.57
127.85
124.55
122.70
121.06
77.19
76.97
76.76
76.14
67.51
62.79
44.94
29.67
15.22
Current Data Parameters
NAME RKK2-024
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210416
Time 12.28 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 200
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
Me
Me OH
2.3q
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

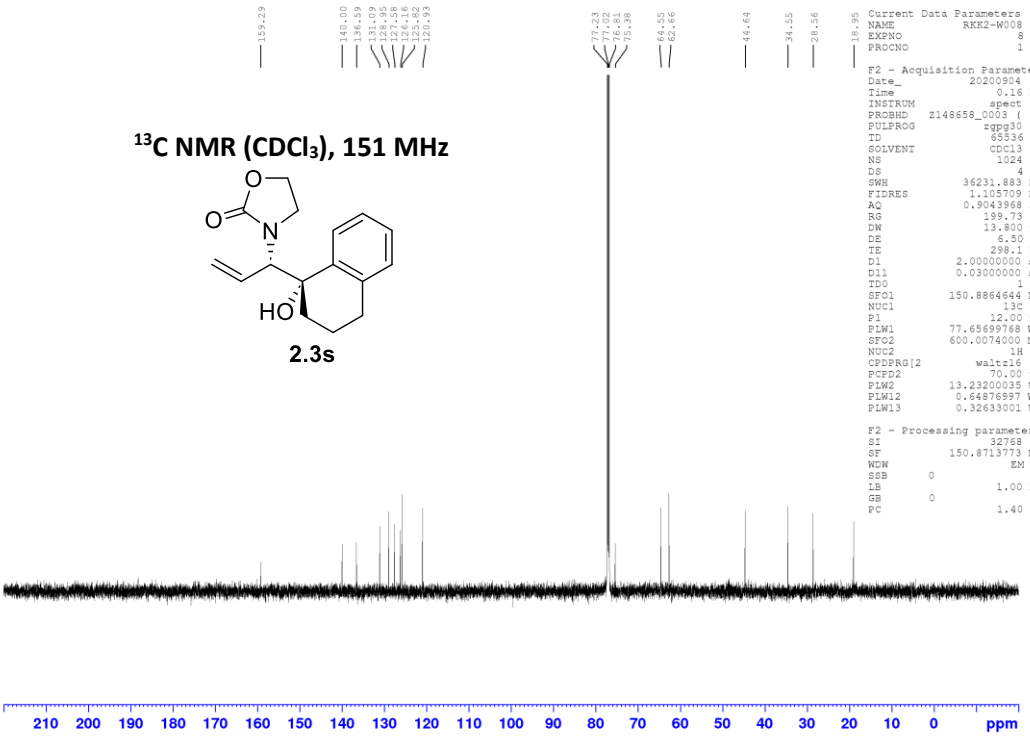
**$^{1}$H NMR ($CDCl_3$), 600 MHz**

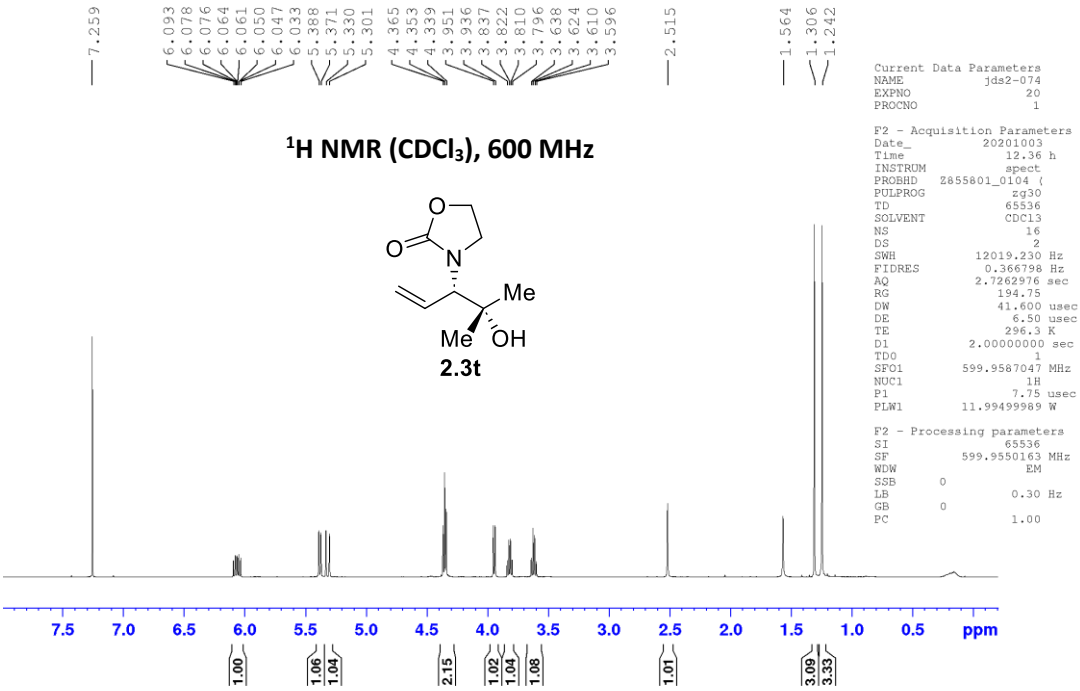



**$^{13}$C NMR ($CDCl_3$), 151 MHz**

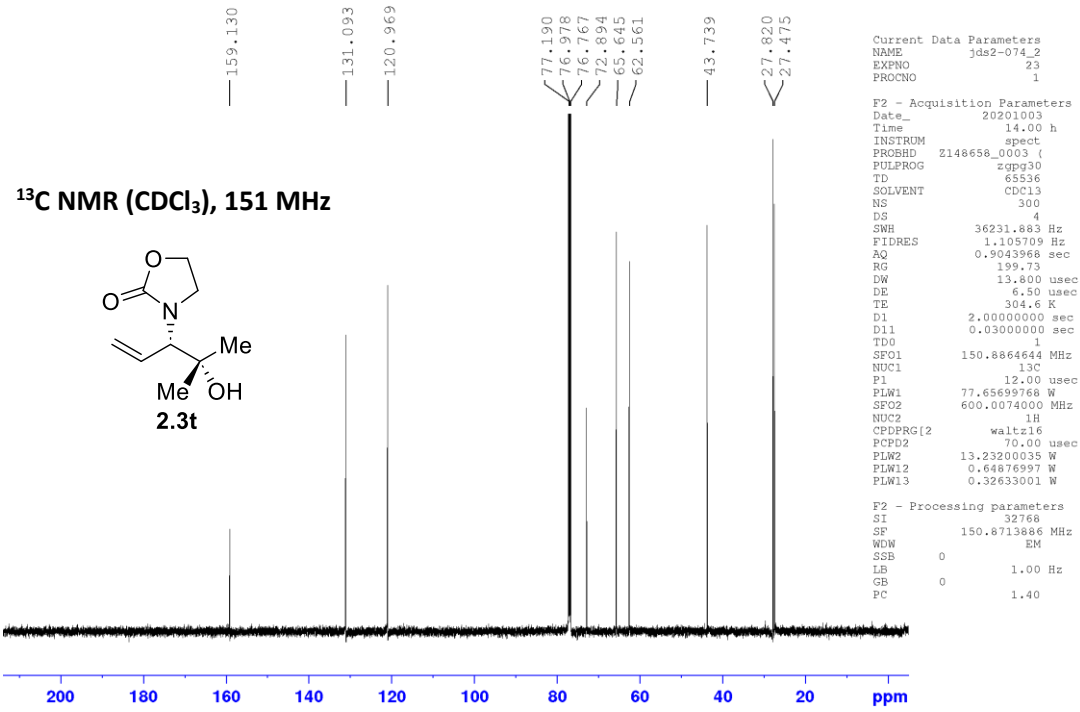



7.515
7.511
7.500
7.200
7.194
7.188
7.185
7.098
7.087
7.084
6.186
6.185
6.172
6.158
5.362
5.344
5.300
5.272
4.350
4.336
4.297
4.283
4.269
4.249
4.239
4.234
4.224
3.761
3.757
3.747
3.742
3.320
3.306
2.859
2.848
2.836
2.161
2.139
2.131
1.898
1.888
1.878
1.831
1.819
1.810
1.797
Current Data Parameters
NAME RKK2-W008
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20200903
Time 15.41 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 20
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 296.3 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050156 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
O
O
N
HO
2.3s
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.04 2.06 1.04 1.00 1.02 1.02 1.11 1.05 1.05 1.04 1.96 2.14 1.02 2.06 1.08

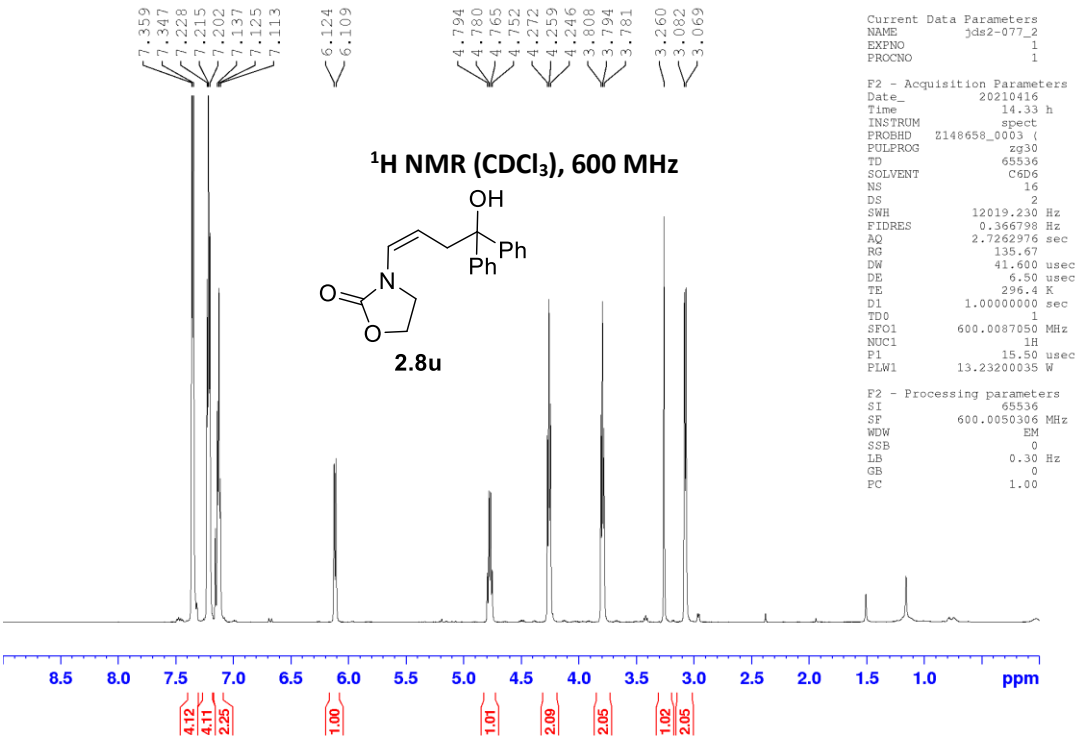

159.29
140.00
136.59
131.09
128.95
127.58
126.16
125.82
120.93
77.23
77.02
76.81
75.38
64.55
62.66
44.64
34.55
28.56
18.95
Current Data Parameters
NAME RKK2-W008
EXPNO 8
PROCNO 1
F2 - Acquisition Parameters
Date_ 20200904
Time 0.16 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
O
O
N
HO
2.3s
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

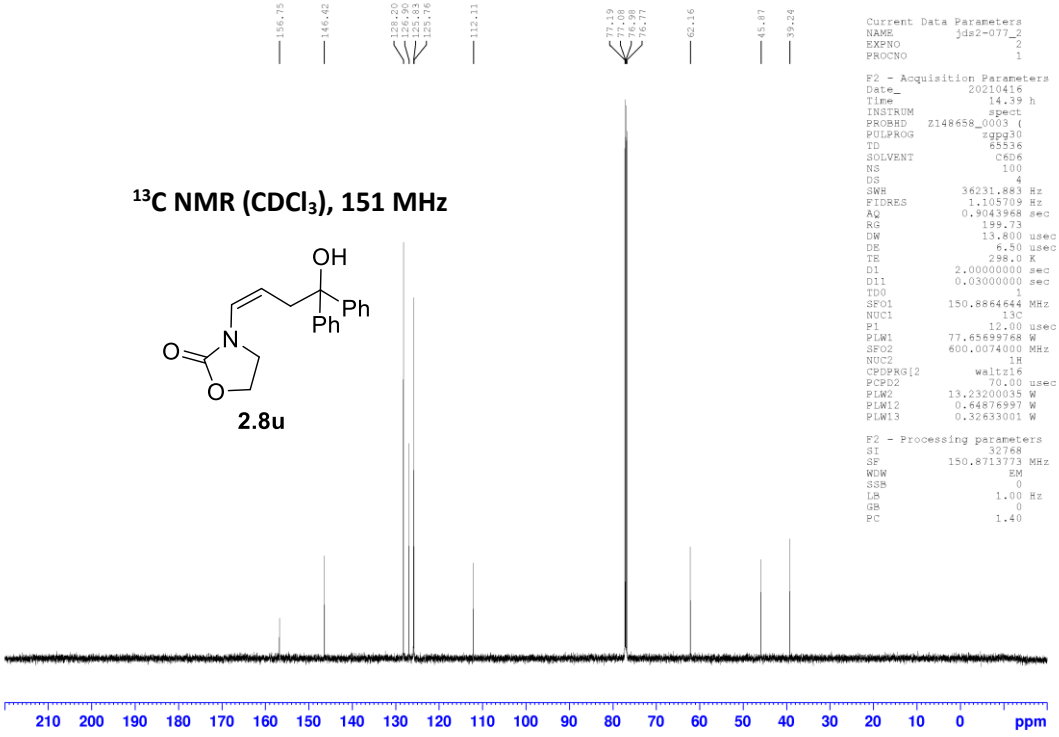


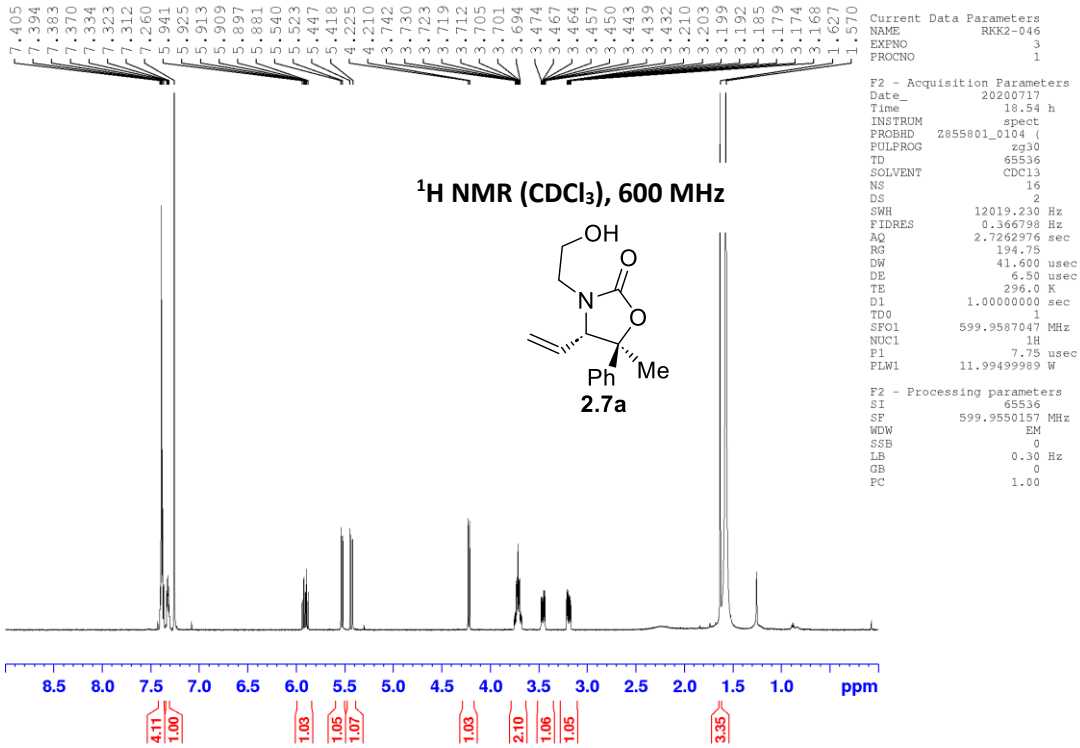

$^{1}$H NMR ($CDCl_3$), 600 MHz

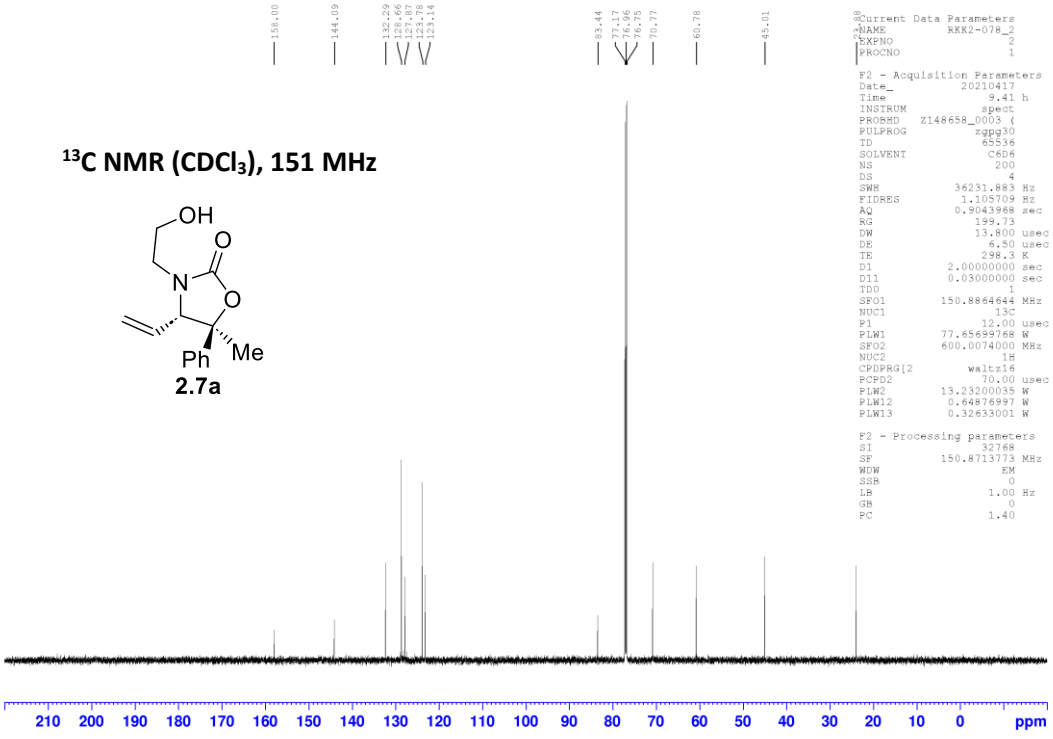


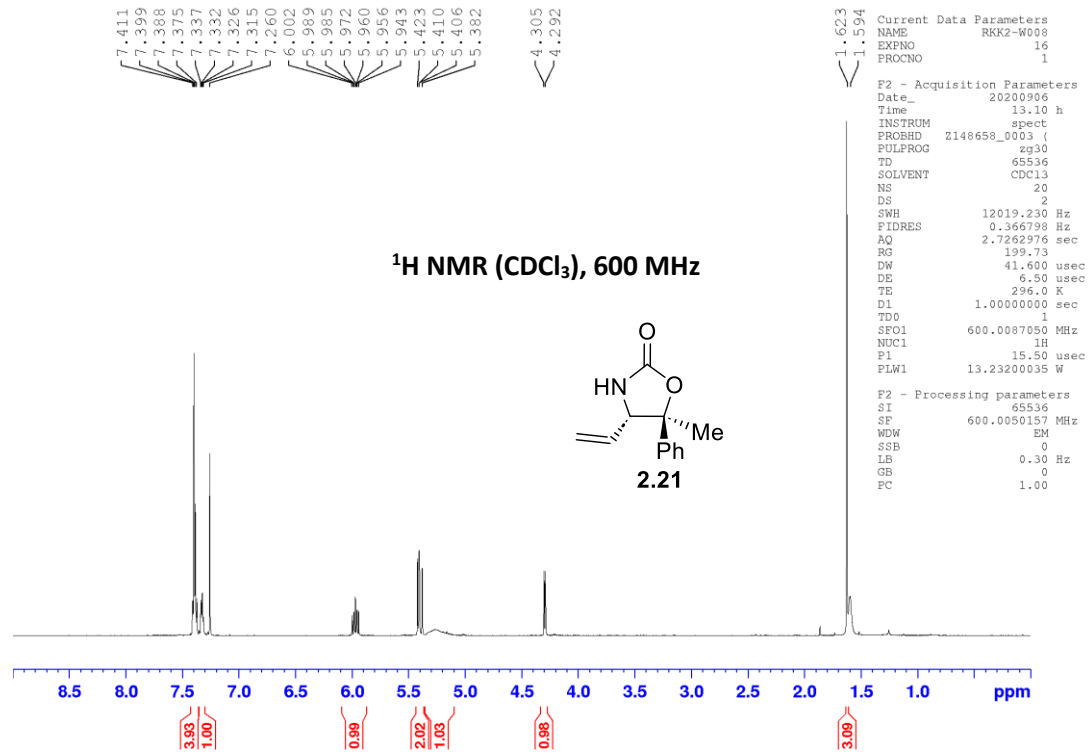

$^{13}$C NMR ($CDCl_3$), 151 MHz

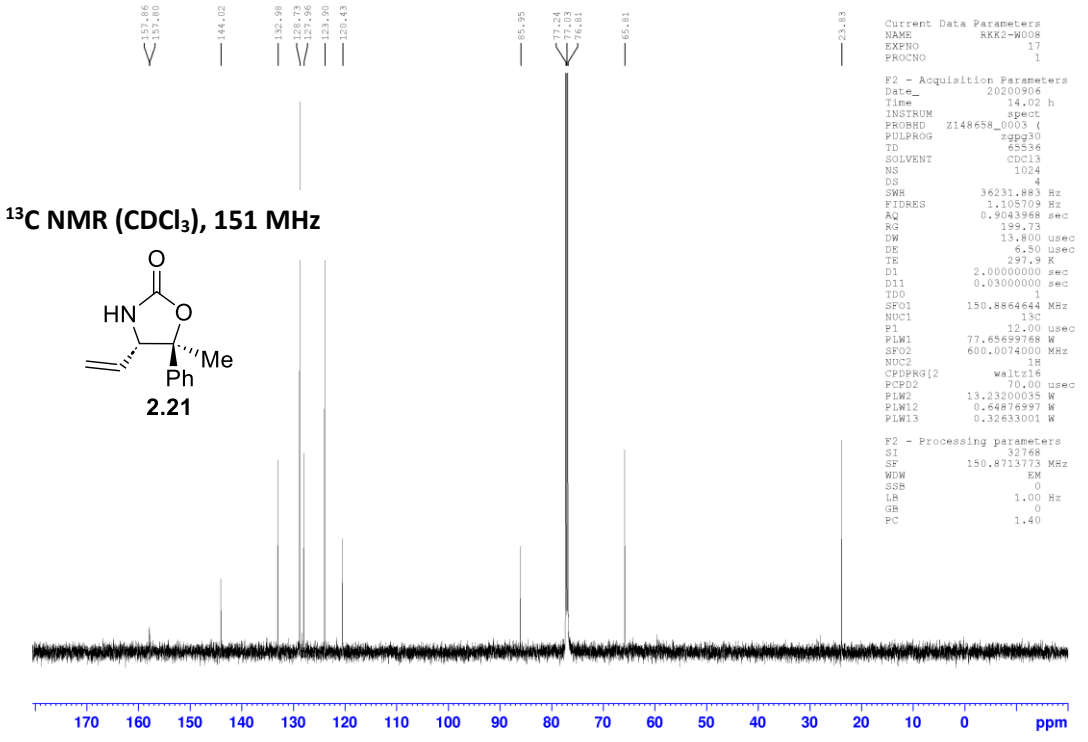

7.359
7.347
7.228
7.215
7.202
7.137
7.125
7.113
6.124
6.109
4.794
4.780
4.765
4.752
4.272
4.259
4.246
3.808
3.794
3.781
3.260
3.082
3.069
$^1$H NMR ($CDCl_3$), 600 MHz
OH
Ph
Ph
N
O
O
2.8u
Current Data Parameters
NAME jds2-077_2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210416
Time 14.33 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT C6D6
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 135.67
DW 41.600 usec
DE 6.50 usec
TE 296.4 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050306 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
4.12
4.11
2.25
1.00
1.01
2.09
2.05
1.02
2.05

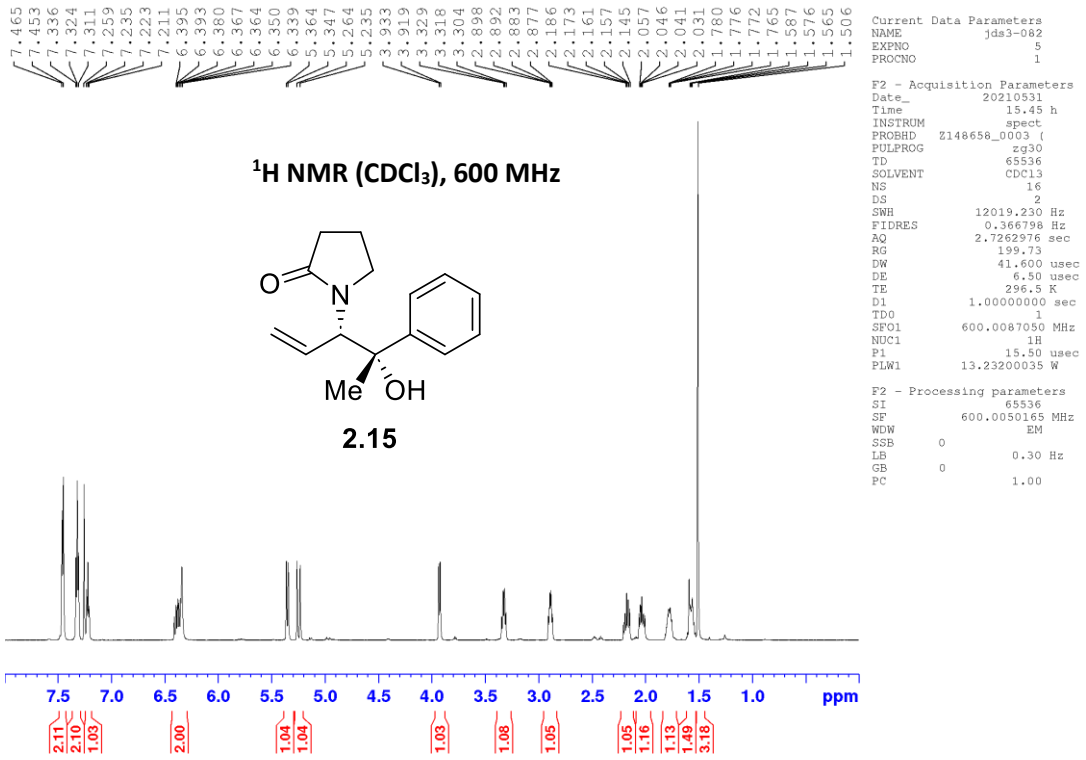

156.75
146.42
128.20
126.90
125.83
125.76
112.11
77.19
77.08
76.98
76.77
62.16
45.87
39.24
$^{13}$C NMR ($CDCl_3$), 151 MHz
OH
Ph
Ph
N
O
O
2.8u
Current Data Parameters
NAME jds2-077_2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210416
Time 14.39 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 100
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

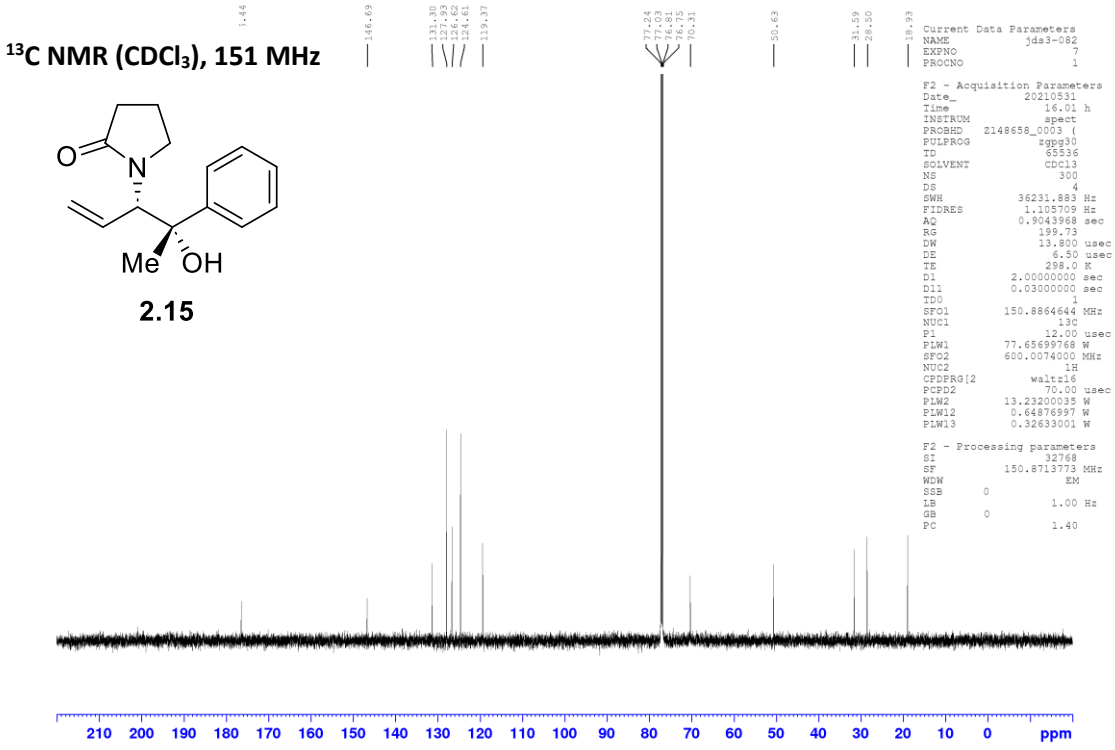

7.405
7.394
7.383
7.370
7.334
7.323
7.312
7.260
5.941
5.925
5.913
5.909
5.897
5.881
5.540
5.523
5.447
5.418
4.225
4.210
3.742
3.730
3.723
3.719
3.712
3.705
3.701
3.694
3.474
3.467
3.464
3.457
3.450
3.443
3.439
3.432
3.210
3.203
3.199
3.192
3.185
3.179
3.174
3.168
1.627
1.570
Current Data Parameters
NAME RKK2-046
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20200717
Time 18.54 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 194.75
DW 41.600 usec
DE 6.50 usec
TE 296.0 K
D1 1.00000000 sec
TD0 1
SFO1 599.9587047 MHz
NUC1 1H
P1 7.75 usec
PLW1 11.99499989 W
F2 - Processing parameters
SI 65536
SF 599.9550157 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
OH
O
N
O
Ph
Me
2.7a
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
4.11 1.00 1.03 1.05 1.07 1.03 2.10 1.06 1.05 3.35

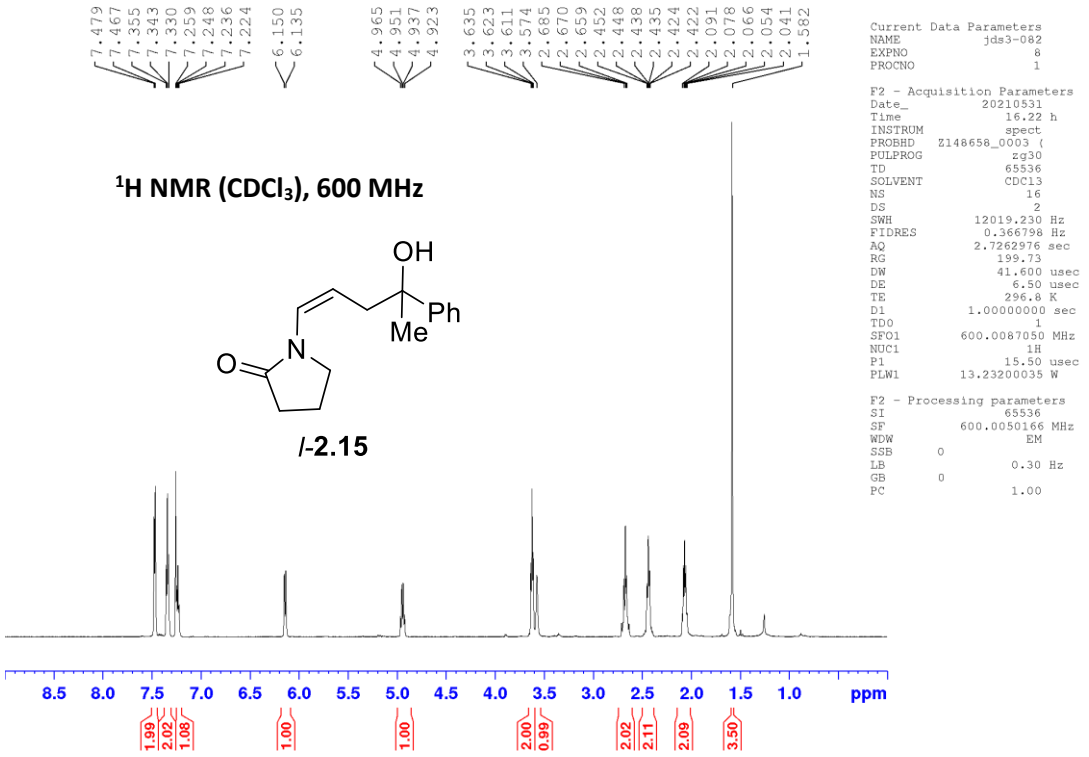

158.00
144.09
132.59
128.46
128.06
127.87
123.78
123.14
83.44
77.17
76.96
76.75
70.77
60.78
45.01
Current Data Parameters
NAME RKK2-078_2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210417
Time 9.41 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT C6D6
NS 200
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
OH
O
N
O
Ph
Me
2.7a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.411
7.399
7.388
7.375
7.337
7.332
7.326
7.315
7.260
6.002
5.989
5.985
5.972
5.960
5.956
5.943
5.423
5.410
5.406
5.382
4.305
4.292
1.623
1.594
Current Data Parameters
NAME RKK2-W008
EXPNO 16
PROCNO 1
F2 - Acquisition Parameters
Date_ 20200906
Time 13.10 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 20
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 296.0 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050157 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
O
HN
O
Me
Ph
2.21
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
3.93
1.00
0.99
2.02
1.03
0.98
3.09


157.86
157.80
144.02
132.90
128.73
127.96
123.90
120.43
85.95
77.24
77.03
76.81
65.81
23.83
Current Data Parameters
NAME RKK2-W008
EXPNO 17
PROCNO 1
F2 - Acquisition Parameters
Date_ 20200906
Time 14.02 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 297.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
O
HN
O
Me
Ph
2.21
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

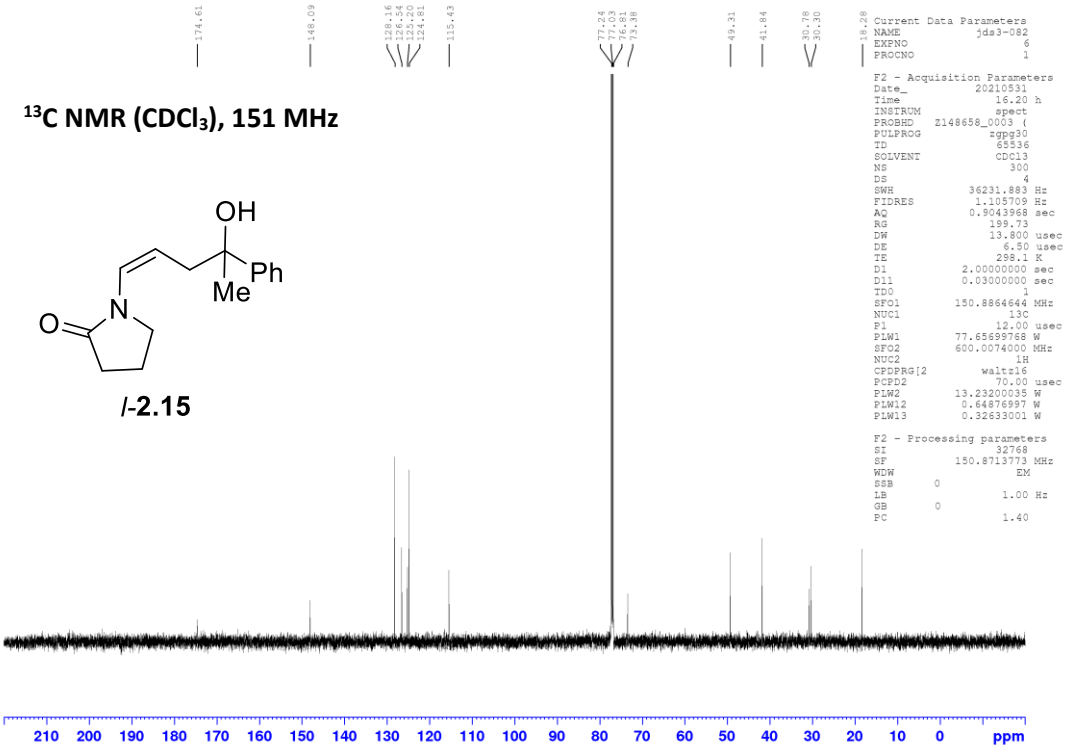

7.465 7.453 7.336 7.324 7.311 7.259 7.235 7.223 7.211 6.395 6.393 6.380 6.367 6.364 6.350 6.339 5.364 5.347 5.264 5.235 3.933 3.919 3.329 3.318 3.304 2.898 2.892 2.883 2.877 2.186 2.173 2.161 2.157 2.145 2.057 2.046 2.041 2.031 1.780 1.776 1.772 1.765 1.587 1.576 1.565 1.506
Current Data Parameters
NAME jds3-082
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210531
Time 15.45 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 6.50 usec
TE 296.5 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050165 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
O
N
Me
OH
2.15
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.11 2.10 1.03 2.00 1.04 1.04 1.03 1.08 1.05 1.05 1.16 1.13 1.49 3.18


1.44 146.69 131.30 127.93 127.62 124.61 119.37 77.24 77.03 76.81 76.75 70.31 50.63 31.59 28.50 18.93
Current Data Parameters
NAME jds3-082
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210531
Time 16.01 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 300
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 298.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P1 12.00 usec
PLW1 77.65699768 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 70.00 usec
PLW2 13.23200035 W
PLW12 0.64876997 W
PLW13 0.32633001 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
O
N
Me
OH
2.15
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



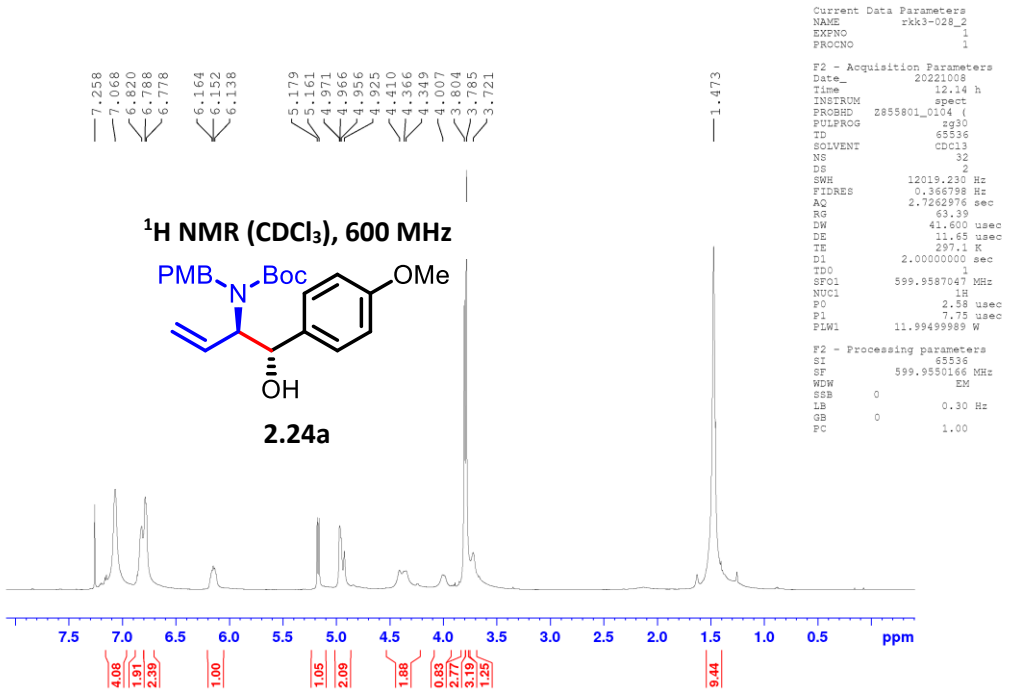

**$^{1}$H NMR ($CDCl_3$), 600 MHz**

**/-2.15**




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

**/-2.15**

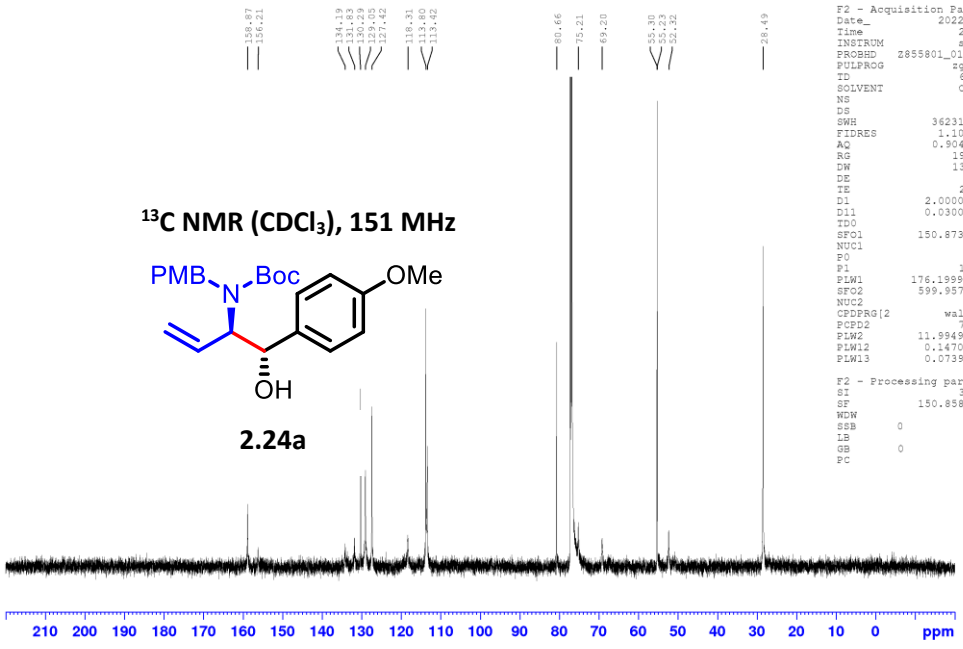



**$^{1}$H NMR ($CDCl_3$), 600 MHz**




**2.24a**

```
Current Data Parameters
NAME                 rkk3-028_2
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_               20221008
Time                    12.14 h
INSTRUM                 spect
PROBHD    Z855801_0104 (
PULPROG                 zg30
TD                     65536
SOLVENT                 CDCl3
NS                         32
DS                          2
SWH                12019.230 Hz
FIDRES              0.366798 Hz
AQ                  2.7262976 sec
RG                      63.39
DW                     41.600 usec
DE                     11.65 usec
TE                     297.1 K
D1                 2.00000000 sec
TD0                         1
SFO1            599.9587047 MHz
NUC1                       1H
P0                      2.58 usec
P1                      7.75 usec
PLW1            11.99499989 W

F2 - Processing parameters
SI                     65536
SF              599.9550166 MHz
WDW                       EM
SSB          0
LB                      0.30 Hz
GB           0
PC                      1.00
```

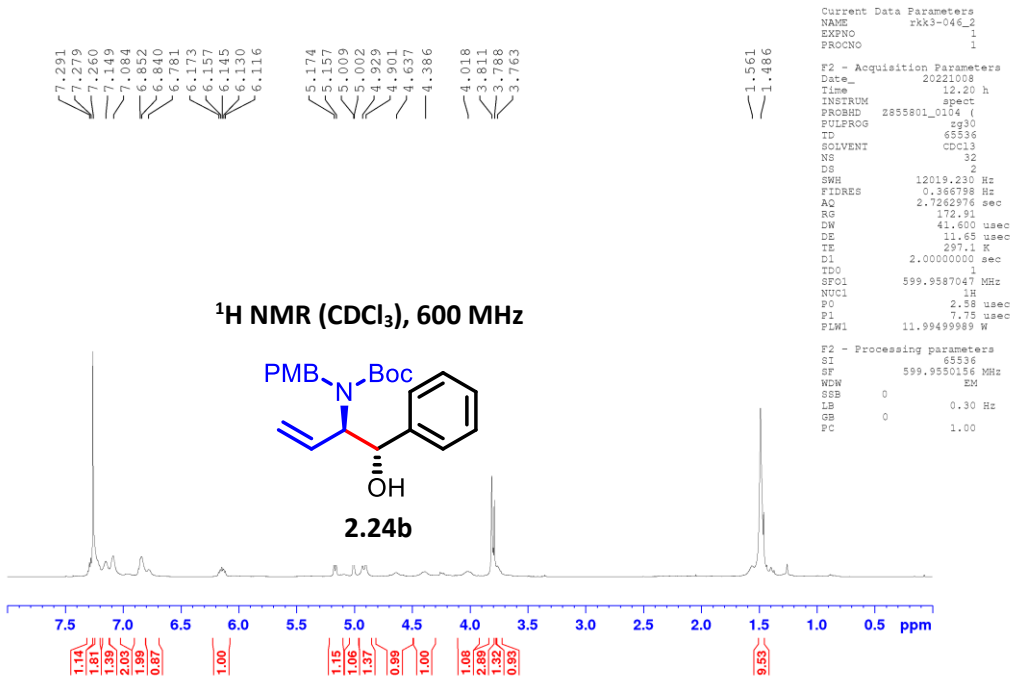



**$^{13}$C NMR ($CDCl_3$), 151 MHz**

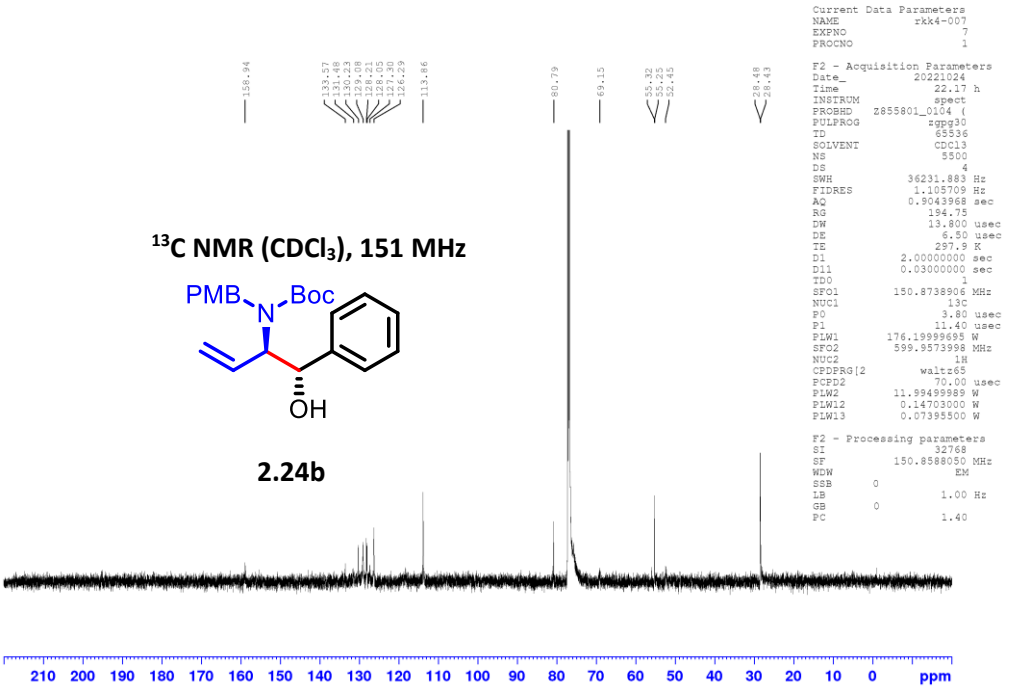



**2.24a**

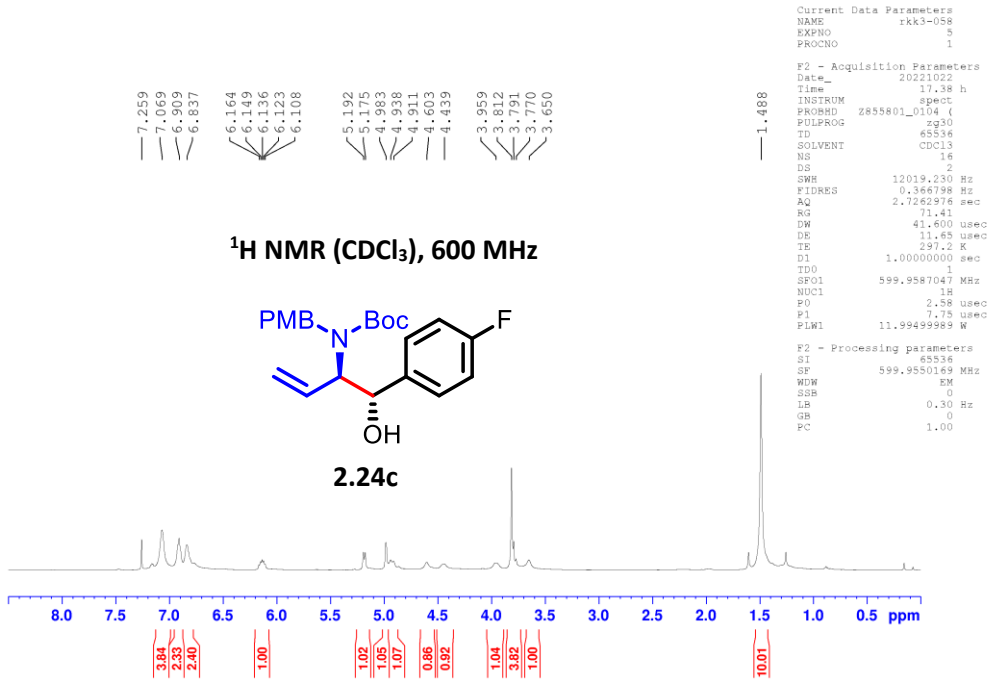
```
Current Data Parameters
NAME                 rkk3-028_2
EXPNO                         2
PROCNO                        1

F2 - Acquisition Parameters
Date_               20221009
Time                    23.28 h
INSTRUM                 spect
PROBHD    Z855801_0104 (
PULPROG                 zgpg30
TD                     65536
SOLVENT                 CDCl3
NS                       2500
DS                          4
SWH                36231.883 Hz
FIDRES              1.105709 Hz
AQ                  0.9043968 sec
RG                      194.75
DW                     13.800 usec
DE                      6.50 usec
TE                     297.6 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1
SFO1            150.8738906 MHz
NUC1                       13C
P0                      3.80 usec
P1                     11.40 usec
PLW1           176.19999695 W
SFO2            599.9573998 MHz
NUC2                       1H
CPDPRG[2              waltz65
PCPD2                  70.00 usec
PLW2            11.99499989 W
PLW12            0.14703000 W
PLW13            0.07395500 W

F2 - Processing parameters
SI                     32768
SF              150.8588050 MHz
WDW                       EM
SSB          0
LB                      1.00 Hz
GB           0
PC                      1.40
```




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

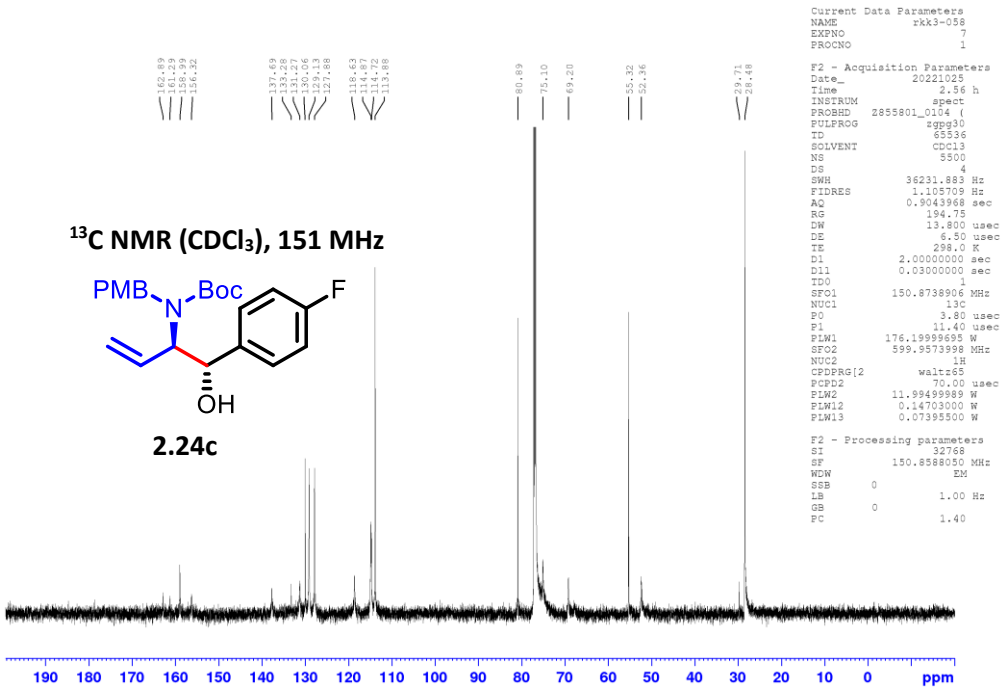



**$^{13}$C NMR ($CDCl_3$), 151 MHz**




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

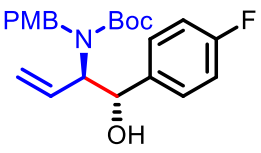
**2.24c**




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

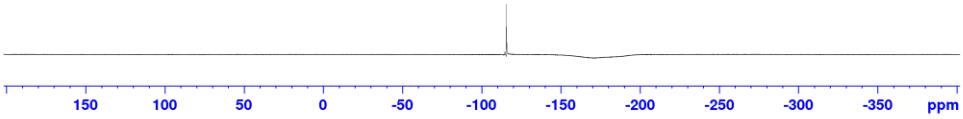
**2.24c**

**$^{19}$F NMR ($CDCl_3$) 565 MHz**



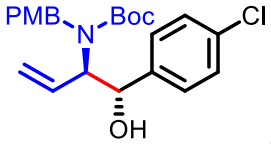

**2.24c**






```
Current Data Parameters
NAME              rkk3-058
EXPNO                   12
PROCNO                   1

F2 - Acquisition Parameters
Date_            20221114
Time                12.49 h
INSTRUM              spect
PROBHD    Z148658_0003 (
PULPROG       zgfhigqn.2
TD                  131072
SOLVENT              CDCl3
NS                      16
DS                       4
SWH             340909.094 Hz
FIDRES            5.201860 Hz
AQ                0.1922389 sec
RG                   199.73
DW                  1.467 usec
DE                  6.50 usec
TE                  296.0 K
D1             1.00000000 sec
D11            0.03000000 sec
D12            0.00002000 sec
TD0                      1
SFO1           564.5123141 MHz
NUC1                  19F
P1                  15.00 usec
PLW1           26.76399994 W
SFO2           600.0074000 MHz
NUC2                  1H
CPDPRG[2           waltz16
PCPD2               70.00 usec
PLW2           13.23200035 W
PLW12           0.64876997 W

F2 - Processing parameters
SI                    65536
SF             564.5687710 MHz
WDW                      EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

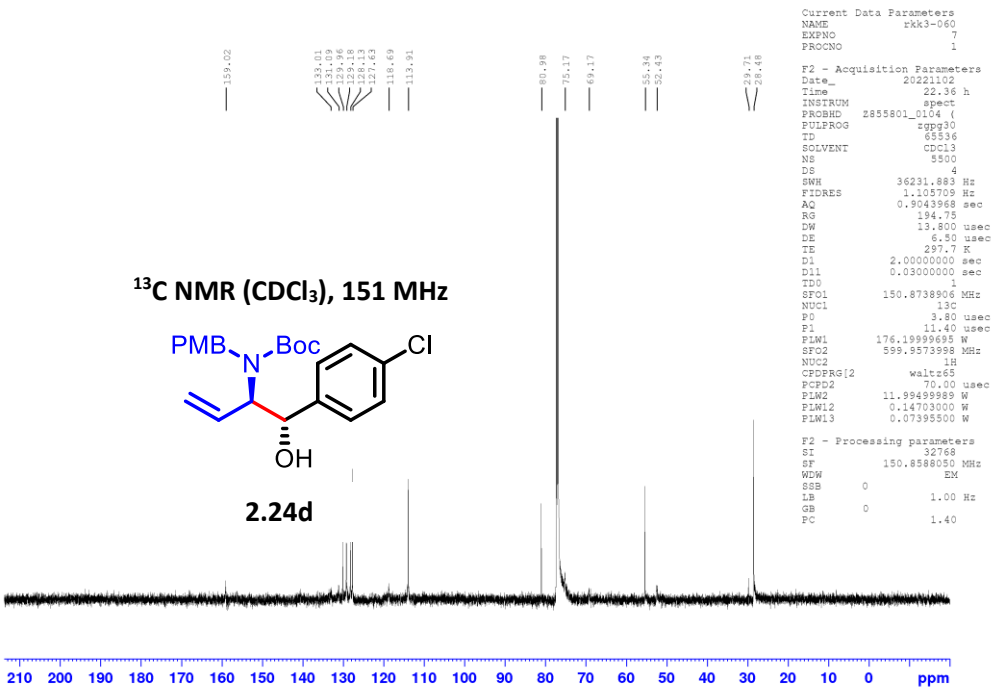
**$^{1}$H NMR ($CDCl_3$), 600 MHz**

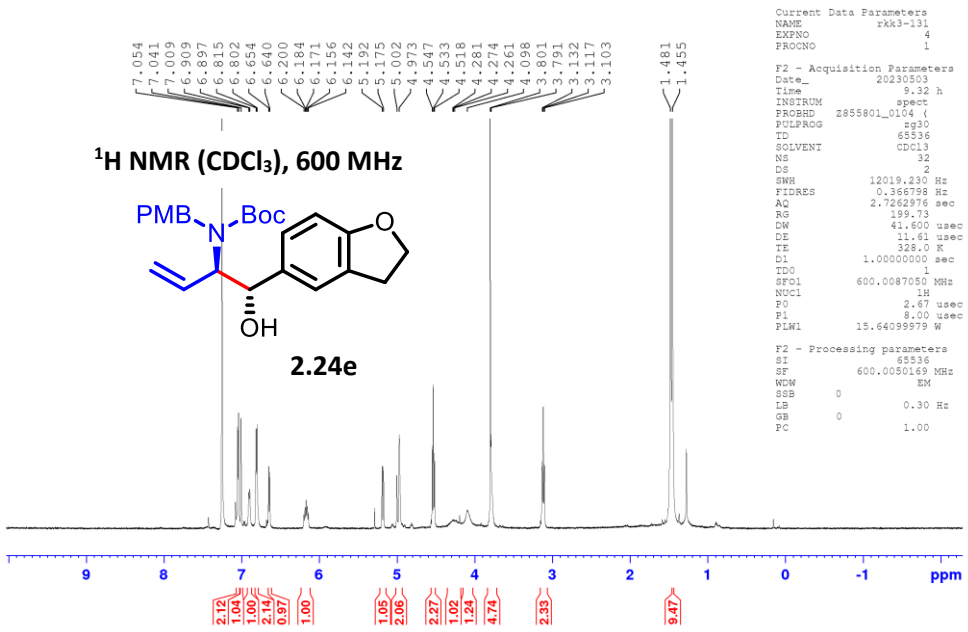


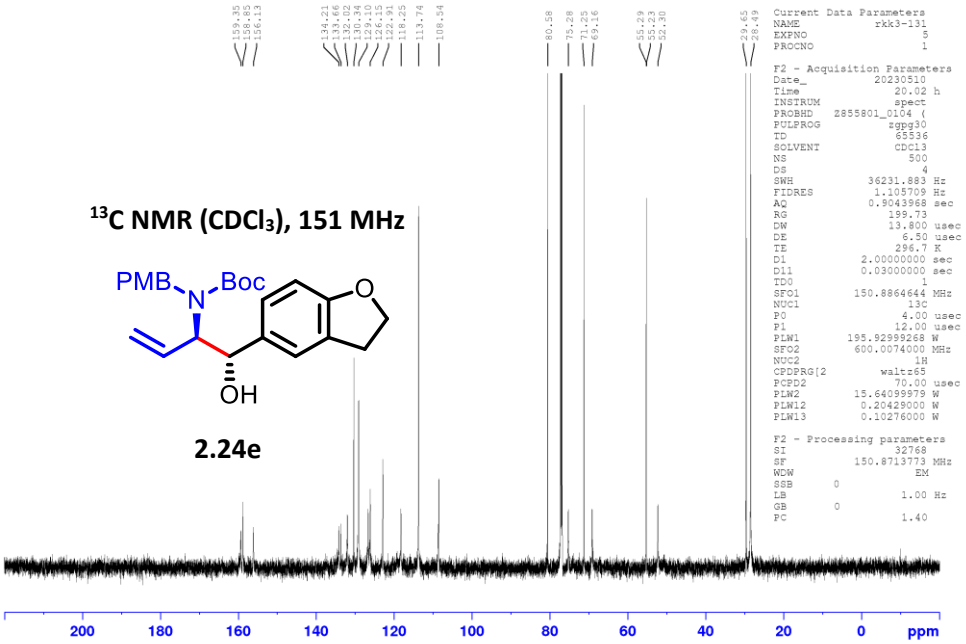

**2.24d**

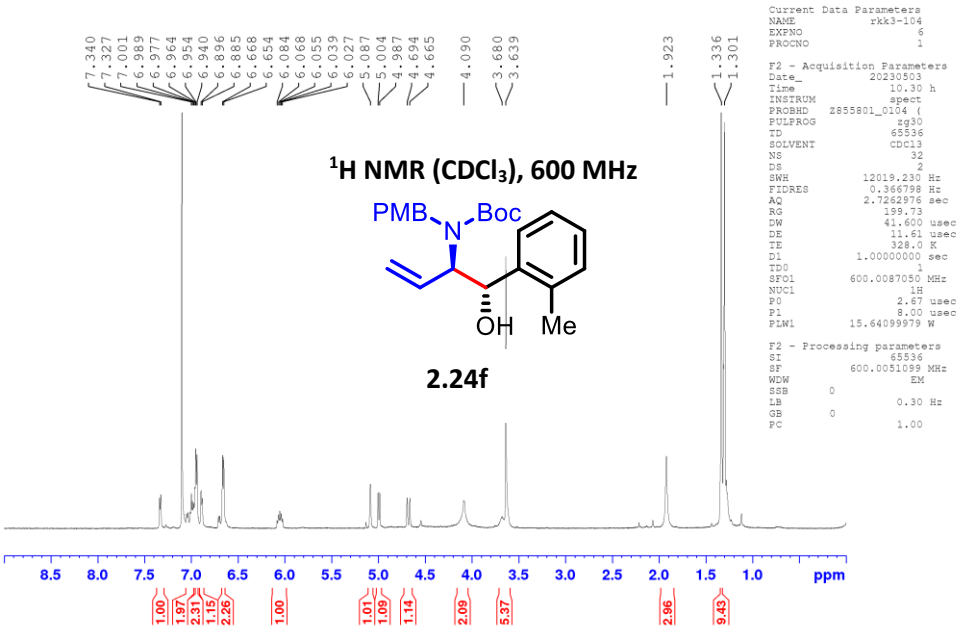


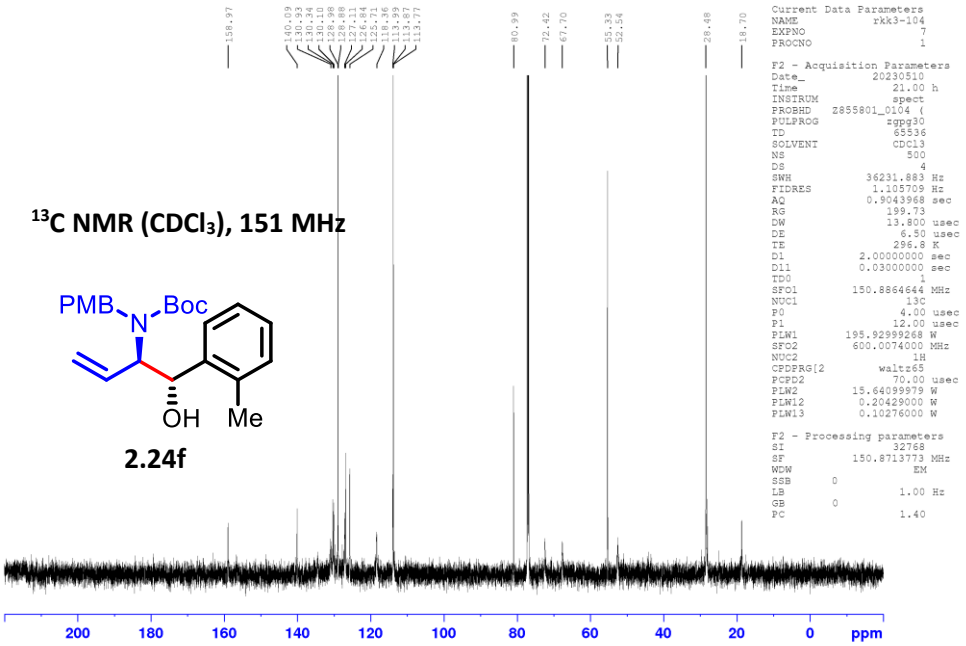

```
Current Data Parameters
NAME              rkk3-060_3
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20221008
Time                12.33 h
INSTRUM              spect
PROBHD    Z855801_0104 (
PULPROG              zg30
TD                  65536
SOLVENT              CDCl3
NS                      32
DS                       2
SWH             12019.230 Hz
FIDRES            0.366798 Hz
AQ                2.7262976 sec
RG                   140.87
DW                  41.600 usec
DE                  11.65 usec
TE                  297.0 K
D1             2.00000000 sec
TD0                      1
SFO1            599.9587047 MHz
NUC1                  1H
P0                   2.58 usec
P1                   7.75 usec
PLW1           11.99499989 W

F2 - Processing parameters
SI                    65536
SF             599.9550179 MHz
WDW                      EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

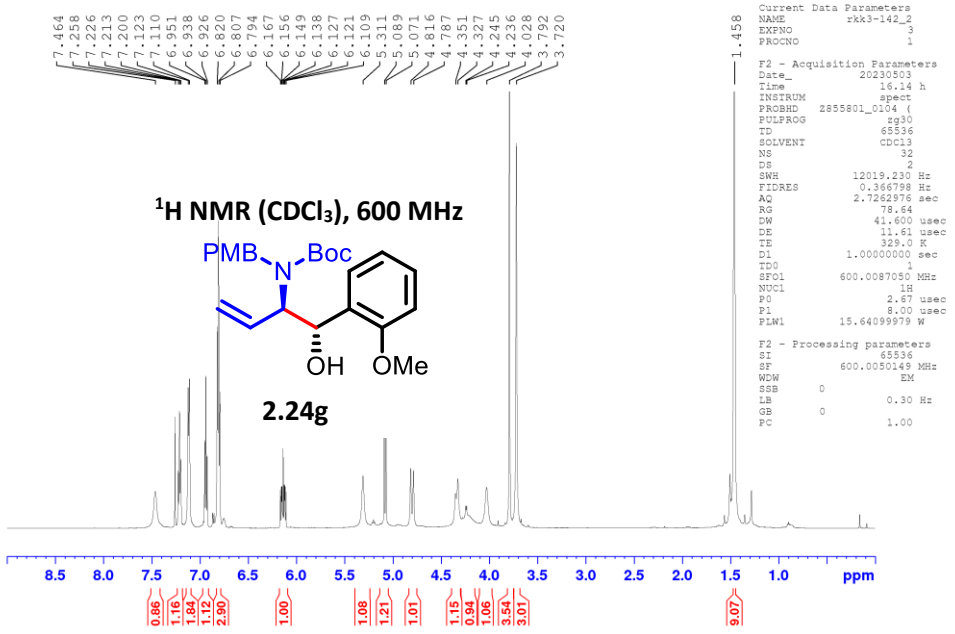

159.02
133.01
131.09
129.96
129.18
128.13
127.63
116.69
113.91
80.98
75.17
69.17
55.34
52.43
29.71
28.48
Current Data Parameters
NAME rkk3-060
EXPNO 7
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221102
Time 22.36 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 5500
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 194.75
DW 13.800 usec
DE 6.50 usec
TE 297.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8738906 MHz
NUC1 13C
P0 3.80 usec
P1 11.40 usec
PLW1 176.19999695 W
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07395500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
PMB
N
Boc
Cl
OH
2.24d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

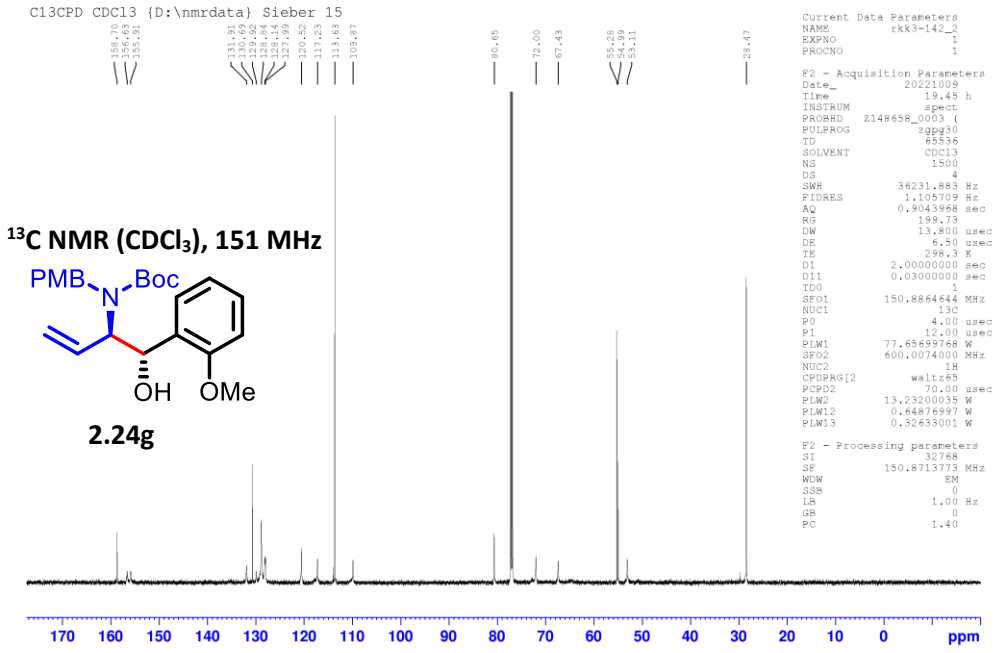

7.054
7.041
7.009
6.909
6.897
6.815
6.802
6.654
6.640
6.200
6.184
6.171
6.156
6.142
5.192
5.175
5.002
4.973
4.547
4.533
4.518
4.281
4.274
4.261
4.098
3.801
3.791
3.132
3.117
3.103
1.481
1.455
Current Data Parameters
NAME rkk3-131
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20230503
Time 9.32 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 11.61 usec
TE 328.0 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P0 2.67 usec
P1 8.00 usec
PLW1 15.64099979 W
F2 - Processing parameters
SI 65536
SF 600.0050169 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
PMB
N
Boc
O
OH
2.24e
9 8 7 6 5 4 3 2 1 0 -1 ppm
2.12
1.04
1.00
2.14
0.97
1.00
1.05
2.06
2.27
1.02
1.24
4.74
2.33
9.47


159.35
156.85
156.13
134.21
133.66
132.02
130.34
129.10
126.15
122.91
118.25
113.74
108.34
80.58
75.28
71.25
69.16
55.29
55.23
52.30
29.65
28.49
Current Data Parameters
NAME rkk3-131
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20230510
Time 20.02 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 500
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 296.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P0 4.00 usec
P1 12.00 usec
PLW1 195.92999268 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 70.00 usec
PLW2 15.64099979 W
PLW12 0.20429000 W
PLW13 0.10276000 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
PMB
N
Boc
O
OH
2.24e
200
180
160
140
120
100
80
60
40
20
0
ppm


7.340
7.327
7.001
6.989
6.977
6.964
6.954
6.940
6.896
6.885
6.668
6.654
6.084
6.068
6.055
6.039
6.027
5.087
5.004
4.987
4.694
4.665
4.090
3.680
3.639
1.923
1.336
1.301
Current Data Parameters
NAME rkk3-104
EXPNO 6
PROCNO 1
F2 - Acquisition Parameters
Date_ 20230503
Time 10.30 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 11.61 usec
TE 328.0 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P0 2.67 usec
P1 8.00 usec
PLW1 15.64099979 W
F2 - Processing parameters
SI 65536
SF 600.0051099 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
PMB
N
Boc
OH
Me
2.24f
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
1.97
2.31
1.15
2.26
1.00
1.01
1.09
1.14
2.09
5.37
2.96
9.43


$^{13}$C NMR ($CDCl_3$), 151 MHz
PMB
N
Boc
OH
Me
2.24f
200
180
160
140
120
100
80
60
40
20
0
ppm

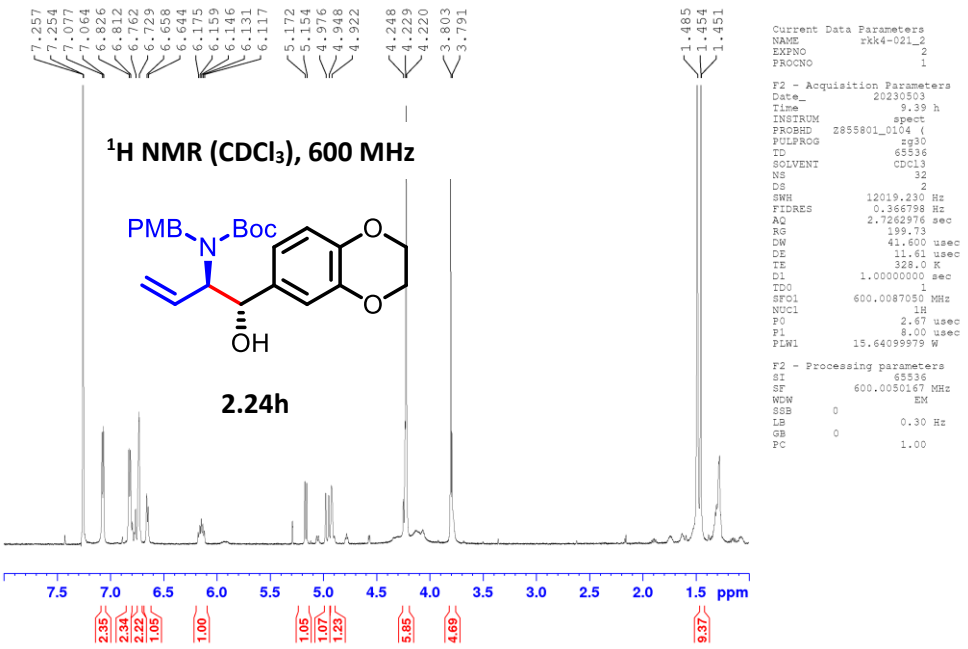

$^{1}$H NMR ($CDCl_3$), 600 MHz
PMB
N
Boc
OH
OMe
2.24g
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm




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



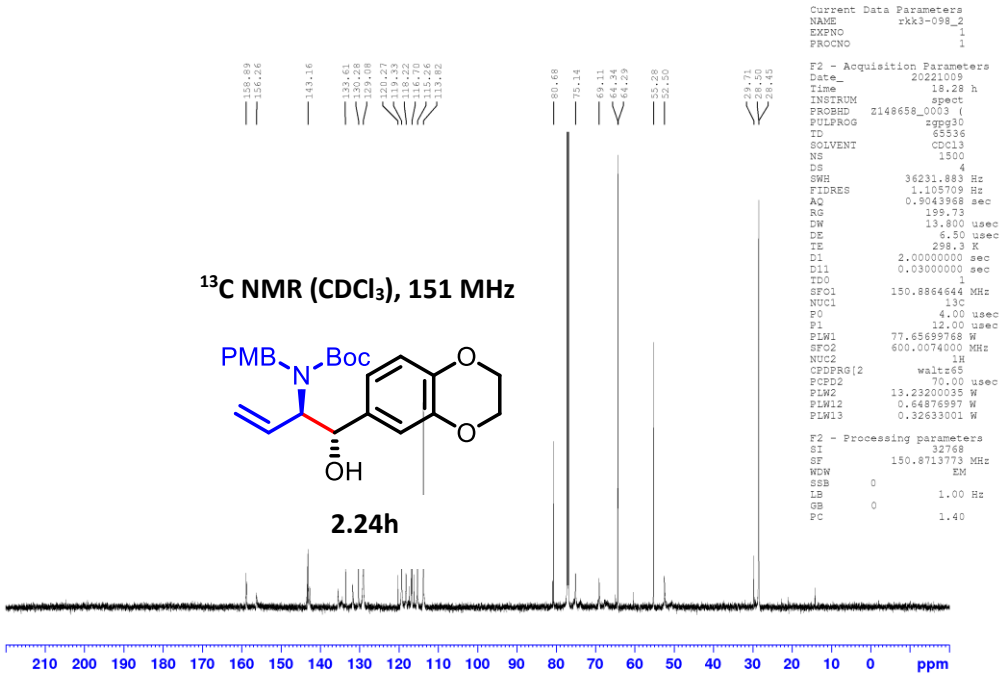

**2.24g**

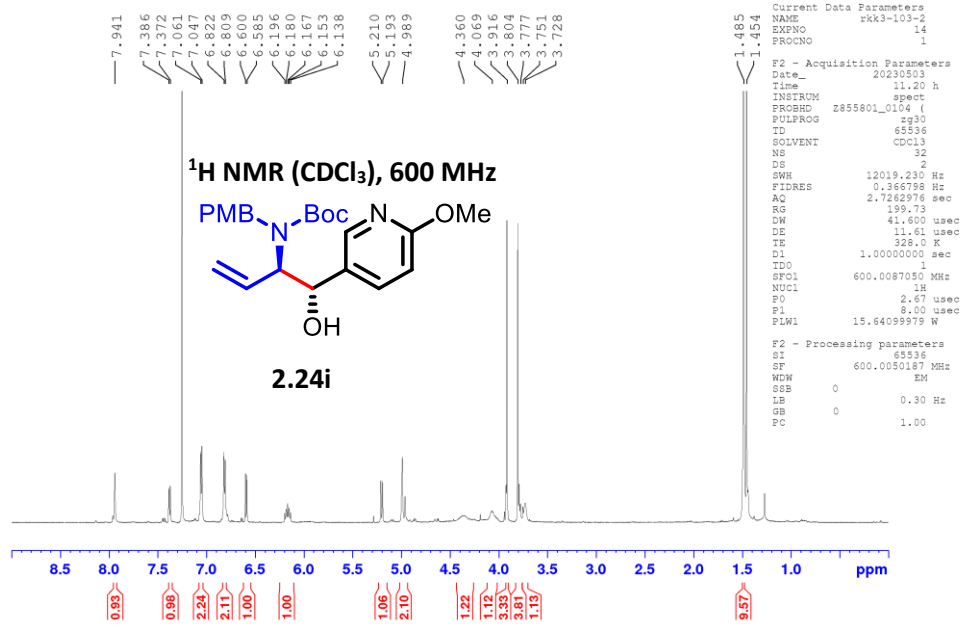


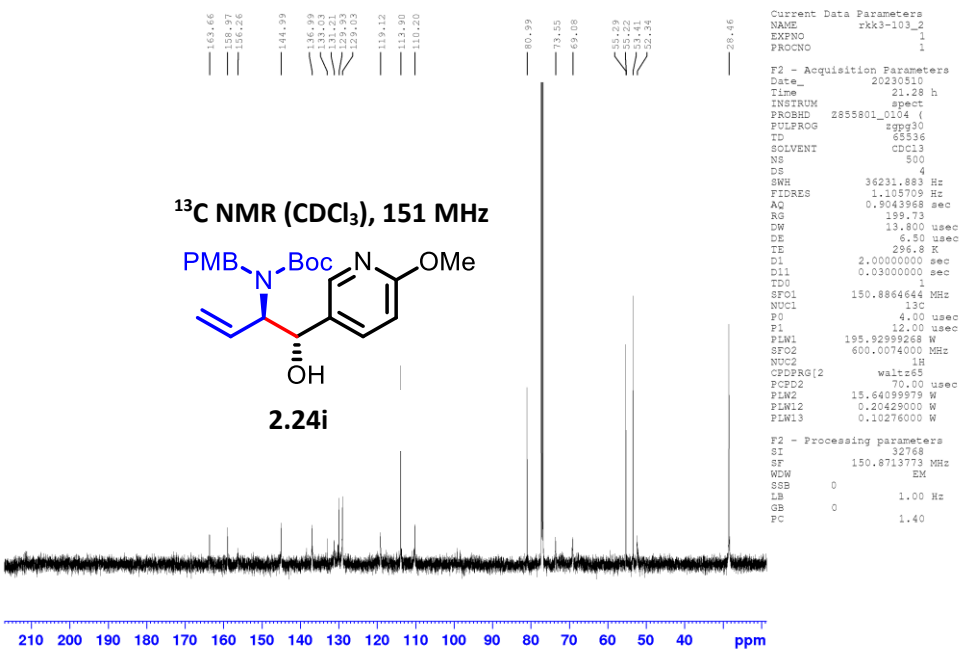

**$^{1}$H NMR ($CDCl_3$), 600 MHz**

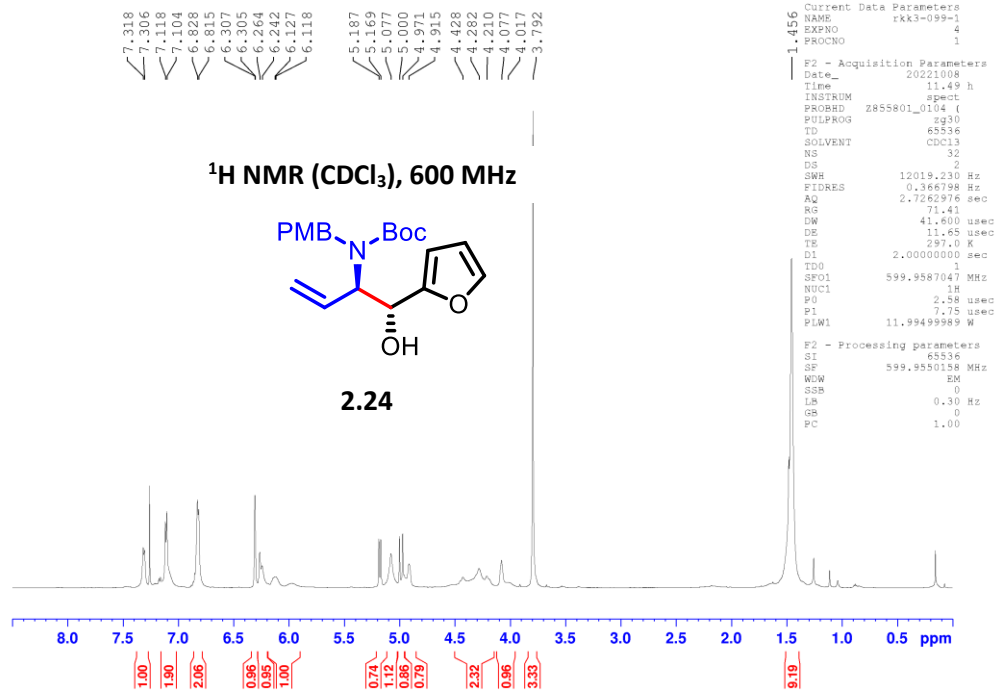


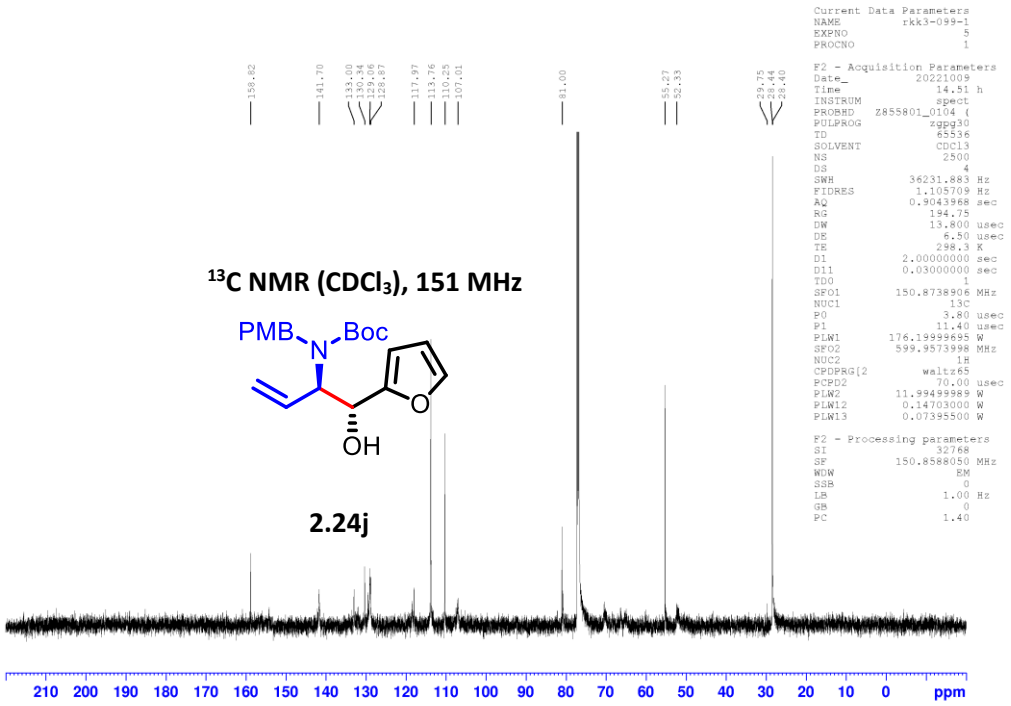

**2.24h**

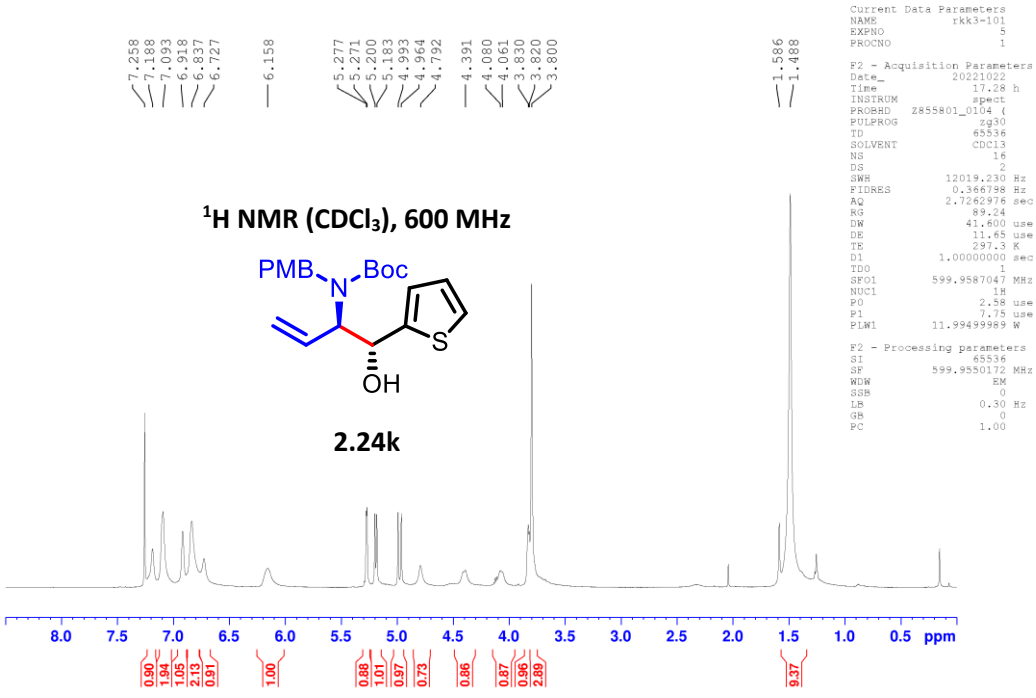

$^{13}$C NMR (CDCl$_3$), 151 MHz
PMB
N
Boc
O
O
OH
2.24h
ppm

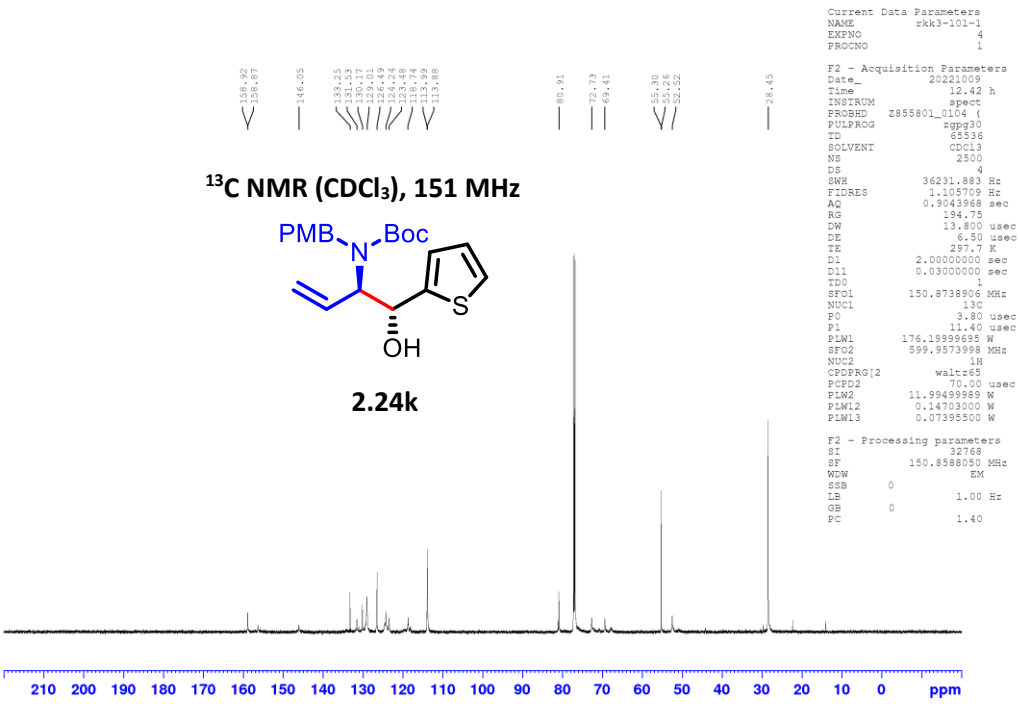

$^{1}$H NMR (CDCl$_3$), 600 MHz
PMB
N
Boc
N
OMe
OH
2.24i
ppm

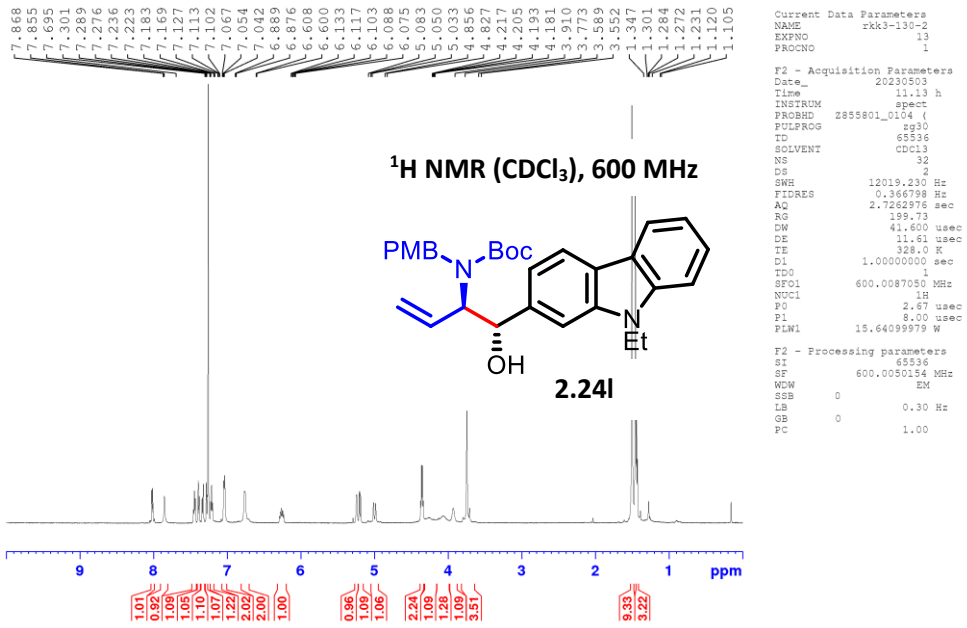

163.66
158.37
156.26
144.99
136.99
133.03
131.21
123.38
123.03
119.12
113.90
110.20
80.99
73.55
69.08
55.29
55.22
53.41
52.34
28.46
Current Data Parameters
NAME rkk3-103_2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20230510
Time 21.28 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 500
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 199.73
DW 13.800 usec
DE 6.50 usec
TE 296.8 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8864644 MHz
NUC1 13C
P0 4.00 usec
P1 12.00 usec
PLW1 195.92999268 W
SFO2 600.0074000 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 70.00 usec
PLW2 15.64099979 W
PLW12 0.20429000 W
PLW13 0.10276000 W
F2 - Processing parameters
SI 32768
SF 150.8713773 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
$^{13}$C NMR (CDCl$_3$), 151 MHz
PMB
N
Boc
N
OMe
OH
2.24i
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 ppm


7.318
7.306
7.118
7.104
6.828
6.815
6.307
6.305
6.264
6.242
6.127
6.118
5.187
5.169
5.077
5.000
4.971
4.915
4.428
4.282
4.210
4.077
4.017
3.792
1.456
Current Data Parameters
NAME rkk3-099-1
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221008
Time 11.49 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 71.41
DW 41.600 usec
DE 11.65 usec
TE 297.0 K
D1 2.00000000 sec
TD0 1
SFO1 599.9587047 MHz
NUC1 1H
P0 2.58 usec
P1 7.75 usec
PLW1 11.99499989 W
F2 - Processing parameters
SI 65536
SF 599.9550158 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
$^{1}$H NMR (CDCl$_3$), 600 MHz
PMB
N
Boc
O
OH
2.24
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.00
1.90
2.06
0.96
0.95
1.00
0.74
1.12
0.86
0.79
2.32
0.96
3.33
9.19

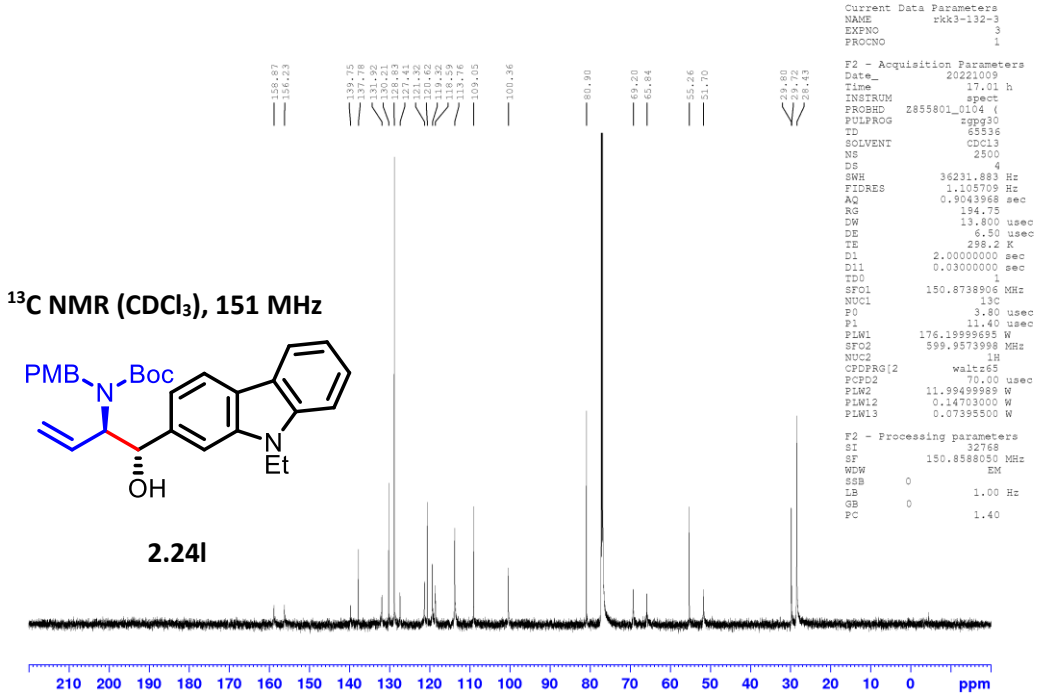

158.82
141.70
133.00
130.34
129.06
128.87
117.97
113.76
110.25
107.01
81.00
55.27
52.33
29.75
28.44
28.40
Current Data Parameters
NAME rkk3-099-1
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221009
Time 14.51 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2500
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 194.75
DW 13.800 usec
DE 6.50 usec
TE 298.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8738906 MHz
NUC1 13C
P0 3.80 usec
P1 11.40 usec
PLW1 176.19999695 W
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07395500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
PMB
N
Boc
O
OH
2.24j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.258
7.188
7.093
6.918
6.837
6.727
6.158
5.277
5.271
5.200
5.183
4.993
4.964
4.792
4.391
4.080
4.061
3.830
3.820
3.800
1.586
1.488
Current Data Parameters
NAME rkk3-101
EXPNO 5
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221022
Time 17.28 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 89.24
DW 41.600 use
DE 11.65 use
TE 297.3 K
D1 1.00000000 sec
TD0 1
SFO1 599.9587047 MHz
NUC1 1H
P0 2.58 use
P1 7.75 use
PLW1 11.99499989 W
F2 - Processing parameters
SI 65536
SF 599.9550172 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
PMB
N
Boc
S
OH
2.24k
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.90
1.94
1.05
2.13
0.91
1.00
0.88
1.01
0.97
0.73
0.86
0.87
0.96
2.89
9.37


158.92
158.87
146.05
133.25
131.53
130.17
129.01
126.49
124.24
119.78
118.74
113.99
113.88
80.91
72.73
69.41
55.30
55.26
52.52
28.45
13C NMR (CDCl3), 151 MHz
PMB
N
Boc
S
OH
2.24k
Current Data Parameters
NAME rkk3-101-1
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221009
Time 12.42 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2500
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 194.75
DW 13.800 usec
DE 6.50 usec
TE 297.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8738906 MHz
NUC1 13C
P0 3.80 usec
P1 11.40 usec
PLW1 176.19999695 W
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07395500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


7.868
7.855
7.695
7.301
7.289
7.276
7.236
7.223
7.183
7.169
7.127
7.113
7.102
7.067
7.054
7.042
6.889
6.876
6.608
6.600
6.133
6.117
6.103
6.088
6.075
5.083
5.050
5.033
4.856
4.827
4.217
4.205
4.193
4.181
3.910
3.773
3.589
3.552
1.347
1.301
1.284
1.272
1.231
1.120
1.105
1H NMR (CDCl3), 600 MHz
PMB
N
Boc
OH
N
Et
2.24l
Current Data Parameters
NAME rkk3-130-2
EXPNO 13
PROCNO 1
F2 - Acquisition Parameters
Date_ 20230503
Time 11.13 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 11.61 usec
TE 328.0 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P0 2.67 usec
P1 8.00 usec
PLW1 15.64099979 W
F2 - Processing parameters
SI 65536
SF 600.0050154 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
9 8 7 6 5 4 3 2 1 ppm
1.01
0.92
1.08
1.05
1.10
1.07
1.22
2.02
2.00
1.00
0.96
1.09
1.06
2.24
1.09
1.28
1.09
3.51
9.33
9.22

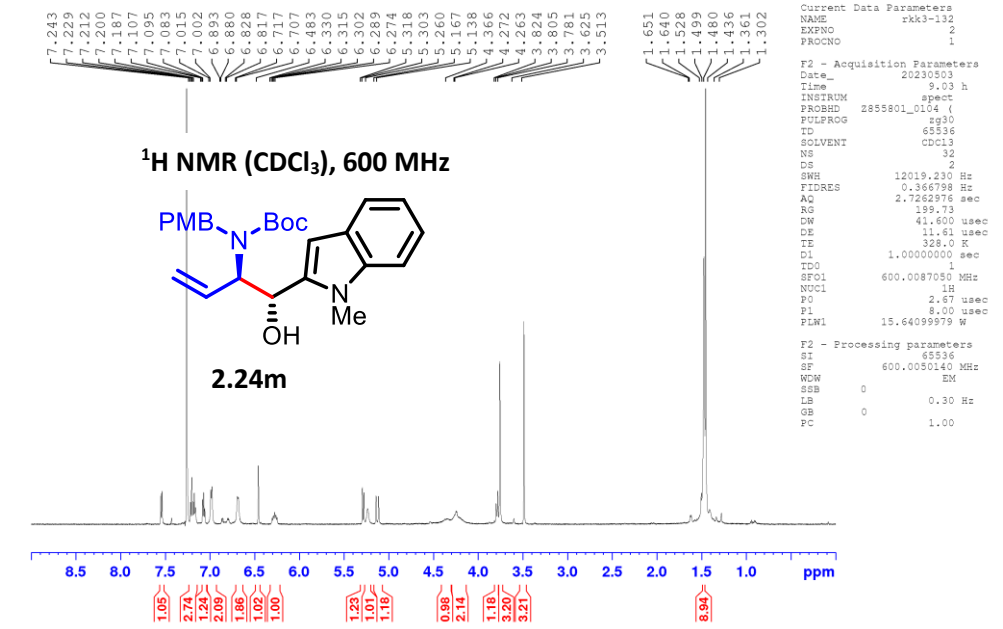
**$^{13}$C NMR ($CDCl_3$), 151 MHz**




**2.24l**

```
Current Data Parameters
NAME          rkk3-132-3
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20221009
Time              17.01 h
INSTRUM             spect
PROBHD   Z855801_0104 (
PULPROG           zgpg30
TD                65536
SOLVENT           CDCl3
NS                 2500
DS                    4
SWH           36231.883 Hz
FIDRES         1.105709 Hz
AQ             0.9043968 sec
RG                194.75
DW                13.800 usec
DE                 6.50 usec
TE                298.2 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                    1
SFO1        150.8738906 MHz
NUC1                13C
P0                 3.80 usec
P1                11.40 usec
PLW1       176.19999695 W
SFO2        599.9573998 MHz
NUC2                1H
CPDPRG[2         waltz65
PCPD2             70.00 usec
PLW2       11.99499989 W
PLW12       0.14703000 W
PLW13       0.07395500 W

F2 - Processing parameters
SI                 32768
SF          150.8588050 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 1.40
```

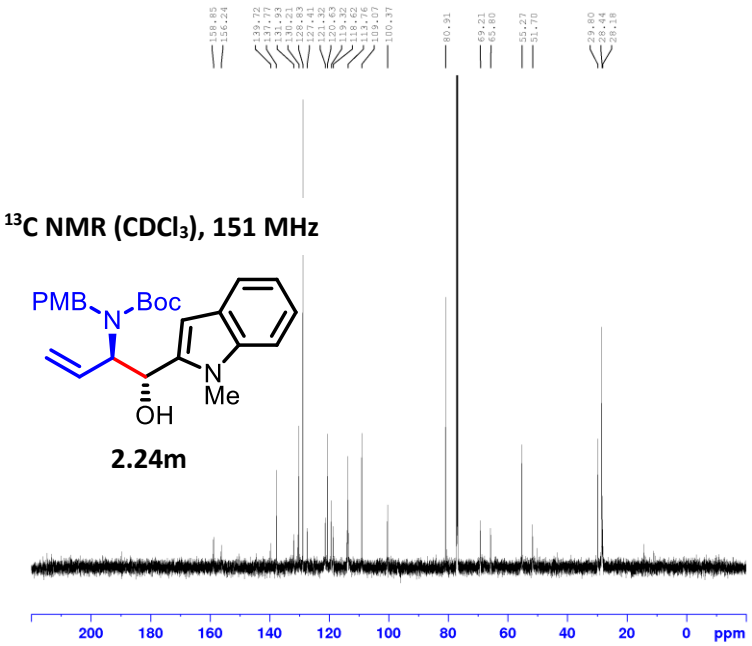
**$^{1}$H NMR ($CDCl_3$), 600 MHz**




**2.24m**

```
Current Data Parameters
NAME          rkk3-132
EXPNO                 2
PROCNO                1

F2 - Acquisition Parameters
Date_           20230503
Time              9.03 h
INSTRUM             spect
PROBHD   Z855801_0104 (
PULPROG             zg30
TD                65536
SOLVENT           CDCl3
NS                   32
DS                    2
SWH          12019.230 Hz
FIDRES         0.366798 Hz
AQ             2.7262976 sec
RG                199.73
DW                41.600 usec
DE                11.61 usec
TE                328.0 K
D1           1.00000000 sec
TD0                    1
SFO1        600.0087050 MHz
NUC1                1H
P0                 2.67 usec
P1                 8.00 usec
PLW1       15.64099979 W

F2 - Processing parameters
SI                 65536
SF          600.0050140 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 1.00
```

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



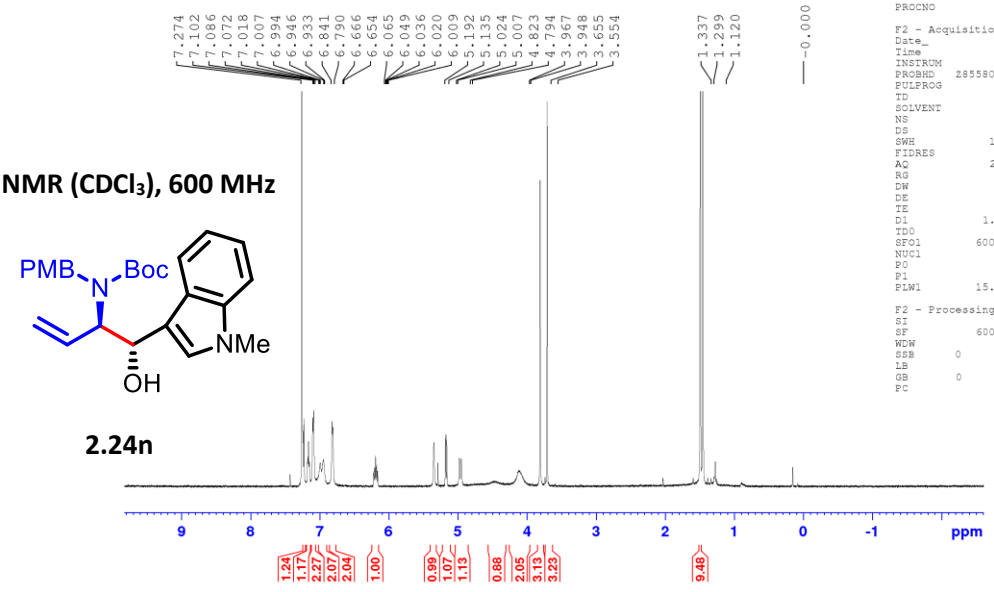




**2.24m**

```
Current Data Parameters
NAME                  rkk3-132
EXPNO                        3
PROCNO                       1

F2 - Acquisition Parameters
Date_               20230510
Time                  19.34 h
INSTRUM                 spect
PROBHD    Z855801_0104 (
PULPROG                zgpg30
TD                      65536
SOLVENT                 CDCl3
NS                        500
DS                          4
SWH                 36231.883 Hz
FIDRES              1.105709 Hz
AQ                  0.9043968 sec
RG                      199.73
DW                      13.800 usec
DE                       6.50 usec
TE                      296.7 K
D1                 2.00000000 sec
D11                0.03000000 sec
TD0                         1
SFO1               150.8864644 MHz
NUC1                       13C
P0                       4.00 usec
P1                      12.00 usec
PLW1              195.92999268 W
SFO2              600.0074000 MHz
NUC2                       1H
CPDPRG[2                waltz65
PCPD2                   70.00 usec
PLW2              15.64099979 W
PLW12              0.20429000 W
PLW13              0.10276000 W

F2 - Processing parameters
SI                      32768
SF                150.8713773 MHz
WDW                        EM
SSB                 0
LB                       1.00 Hz
GB                  0
PC                       1.40
```

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

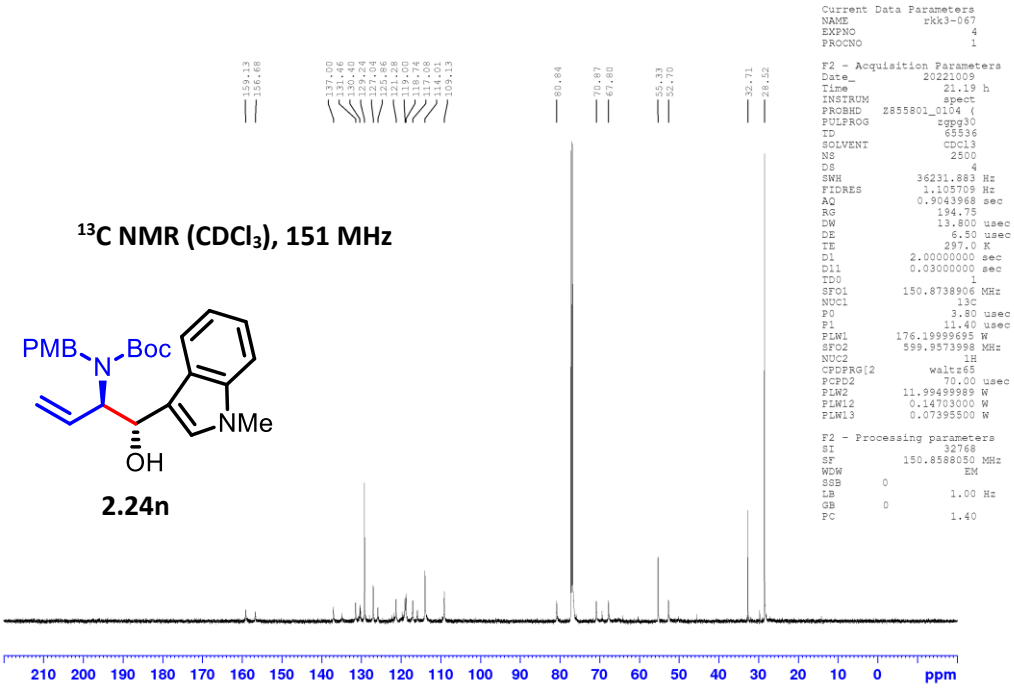




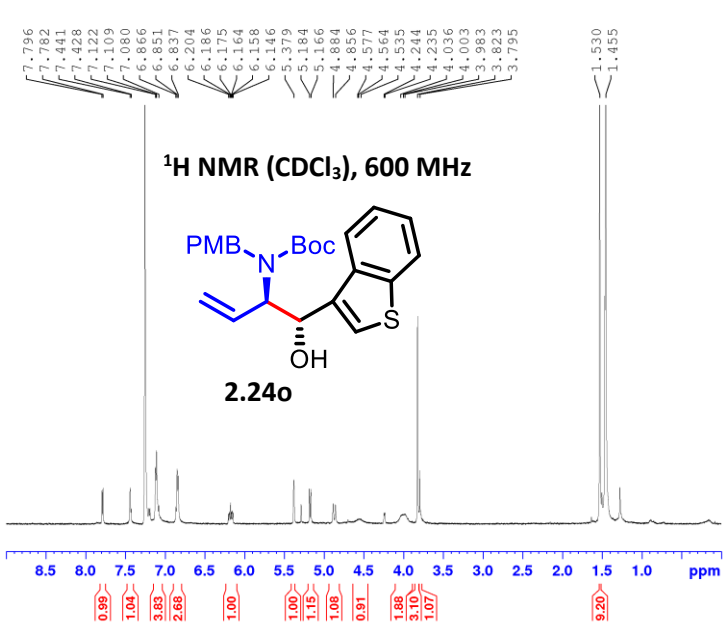


**2.24n**

```
Current Data Parameters
NAME                  RKK3-195_2
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_               20230503
Time                  10.37 h
INSTRUM                 spect
PROBHD    Z855801_0104 (
PULPROG                  zg30
TD                      65536
SOLVENT                 CDCl3
NS                         32
DS                          2
SWH                 12019.230 Hz
FIDRES              0.366798 Hz
AQ                  2.7262976 sec
RG                      199.73
DW                      41.600 usec
DE                      11.61 usec
TE                      328.0 K
D1                 1.00000000 sec
TD0                         1
SFO1               600.0087050 MHz
NUC1                       1H
P0                       2.67 usec
P1                       8.00 usec
PLW1              15.64099979 W

F2 - Processing parameters
SI                      65536
SF                600.0050155 MHz
WDW                        EM
SSB                 0
LB                       0.30 Hz
GB                  0
PC                       1.00
```

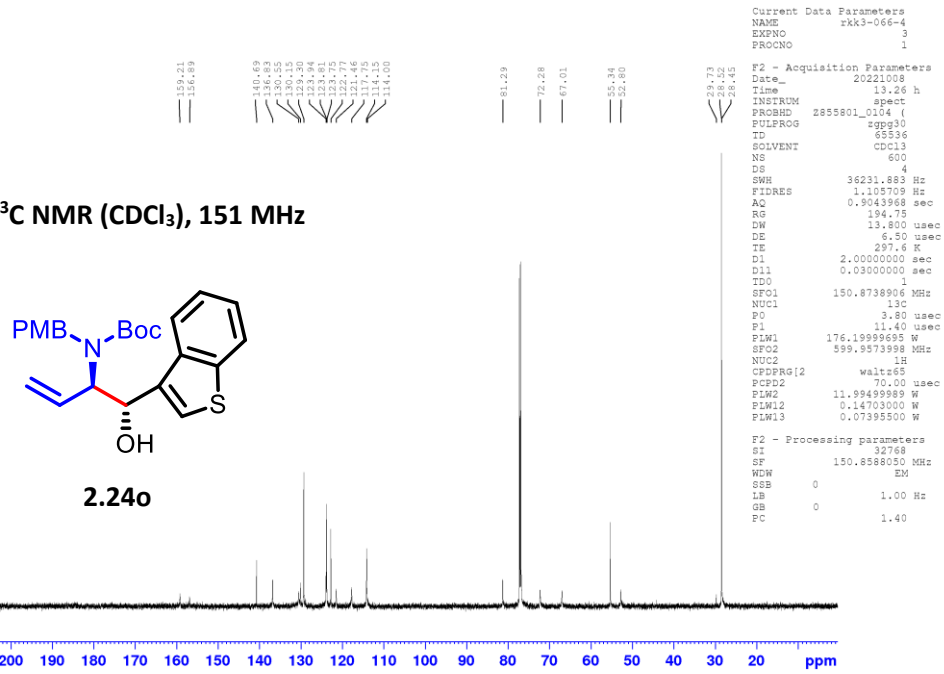



```
Current Data Parameters
NAME                  rkk3-067
EXPNO                        4
PROCNO                       1

F2 - Acquisition Parameters
Date_               20221009
Time                   21.19 h
INSTRUM                spect
PROBHD     Z855801_0104 (
PULPROG             zgpg30
TD                   65536
SOLVENT              CDCl3
NS                    2500
DS                       4
SWH              36231.883 Hz
FIDRES            1.105709 Hz
AQ                0.9043968 sec
RG                   194.75
DW                   13.800 usec
DE                    6.50 usec
TE                  297.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1
SFO1          150.8738906 MHz
NUC1                   13C
P0                    3.80 usec
P1                   11.40 usec
PLW1         176.19999695 W
SFO2          599.9573998 MHz
NUC2                   1H
CPDPRG[2           waltz65
PCPD2                70.00 usec
PLW2          11.99499989 W
PLW12          0.14703000 W
PLW13          0.07395500 W

F2 - Processing parameters
SI                   32768
SF            150.8588050 MHz
WDW                     EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```




```
Current Data Parameters
NAME              rkk3-066_3
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
Date_               20230503
Time                   11.29 h
INSTRUM                spect
PROBHD     Z855801_0104 (
PULPROG                zg30
TD                   65536
SOLVENT              CDCl3
NS                      32
DS                       2
SWH              12019.230 Hz
FIDRES            0.366798 Hz
AQ                2.7262976 sec
RG                   199.73
DW                   41.600 usec
DE                   11.61 usec
TE                  328.0 K
D1             1.00000000 sec
TD0                      1
SFO1          600.0087050 MHz
NUC1                   1H
P0                    2.67 usec
P1                    8.00 usec
PLW1         15.64099979 W

F2 - Processing parameters
SI                   65536
SF            600.0050168 MHz
WDW                     EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

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



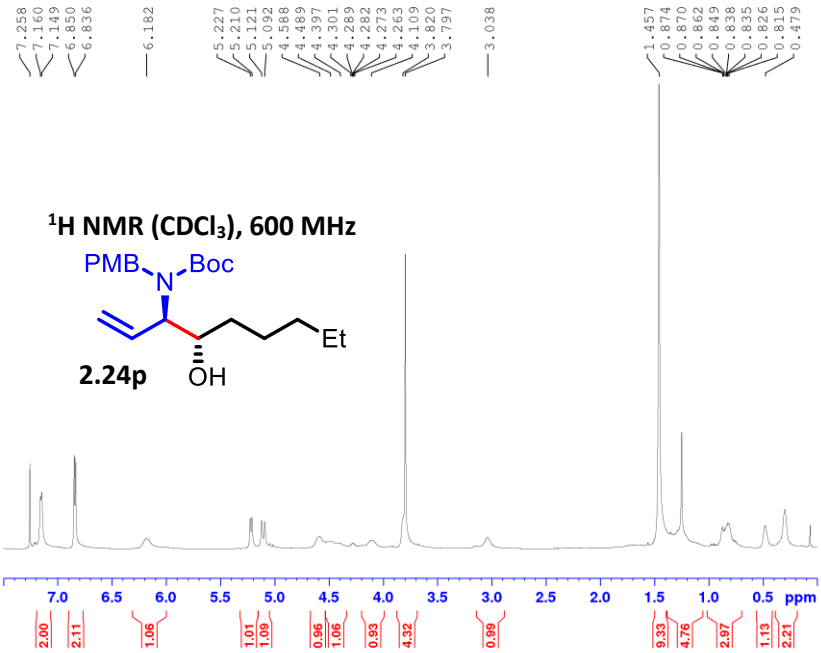

**2.24o**


Current Data Parameters
NAME rkk3-066-4
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20221008
Time 13.26 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 600
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 194.75
DW 13.800 usec
DE 6.50 usec
TE 297.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8738906 MHz
NUC1 13C
P0 3.80 usec
P1 11.40 usec
PLW1 176.19999695 W
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07395500 W

F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


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



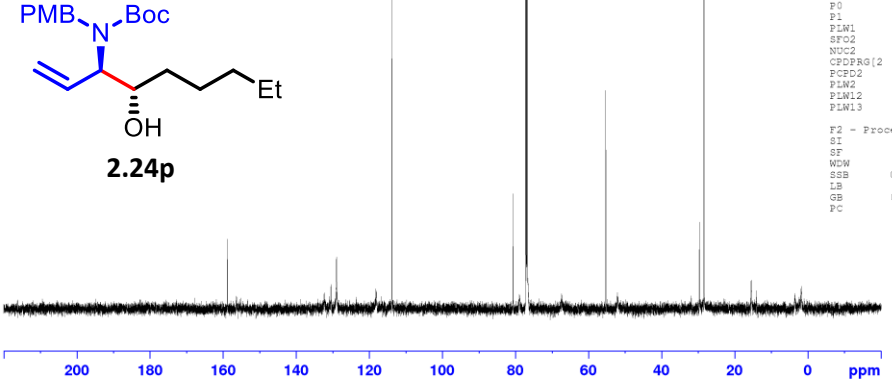

**2.24p**


Current Data Parameters
NAME rkk3-078-2_2
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20221008
Time 10.52 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 63.39
DW 41.600 usec
DE 11.65 usec
TE 296.8 K
D1 2.00000000 sec
TD0 1
SFO1 599.9587047 MHz
NUC1 1H
P0 2.58 usec
P1 7.75 usec
PLW1 11.99499989 W

F2 - Processing parameters
SI 65536
SF 599.9550170 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

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




**2.24p**



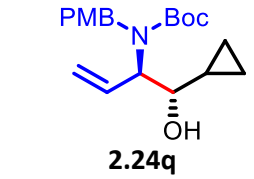


Current Data Parameters
NAME rkk3-078-2
EXPNO 2
PROCNO 1

F2 - Acquisition Parameters
Date_ 20221008
Time 15.07 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1220
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 194.75
DW 13.800 usec
DE 6.50 usec
TE 297.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8738906 MHz
NUC1 13C
P0 3.80 usec
P1 11.40 usec
PLW1 176.19999695 W
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07395500 W

F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


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




**2.24q**

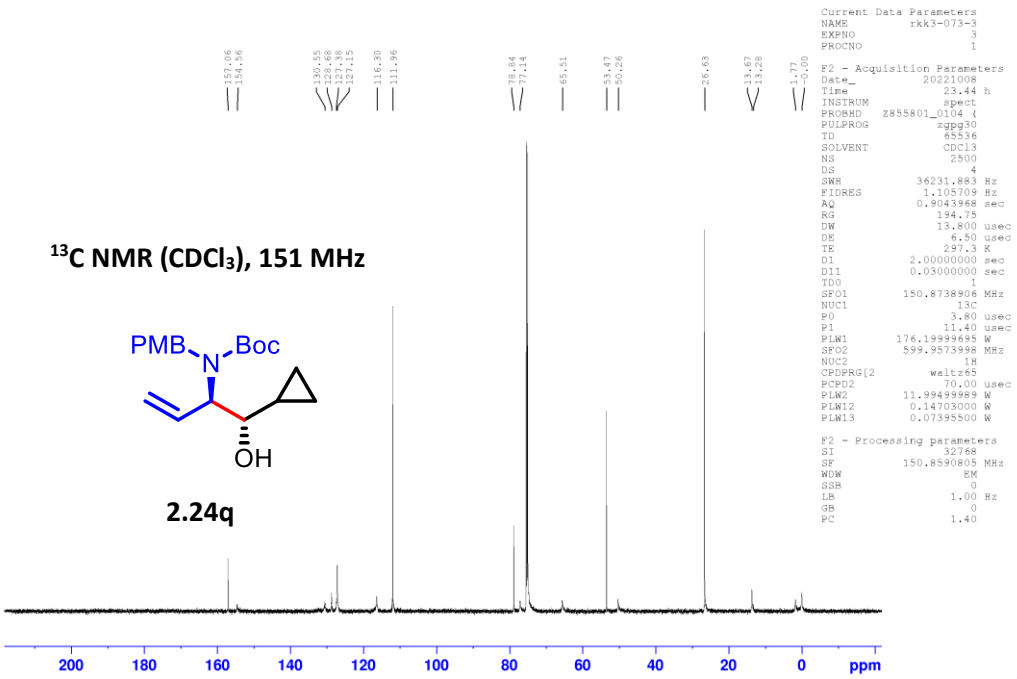


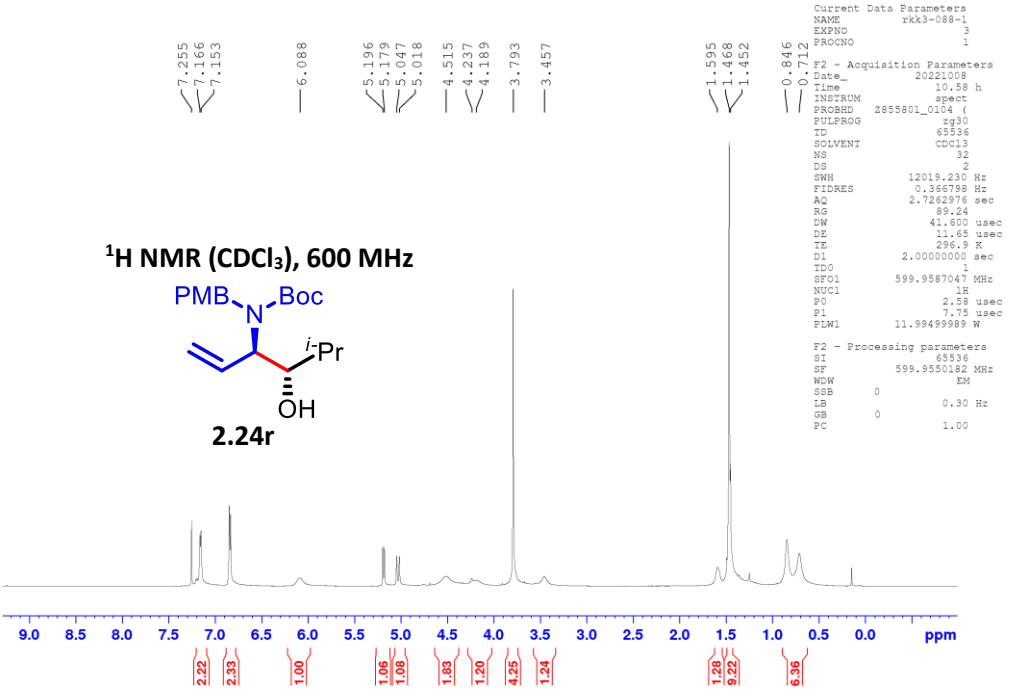


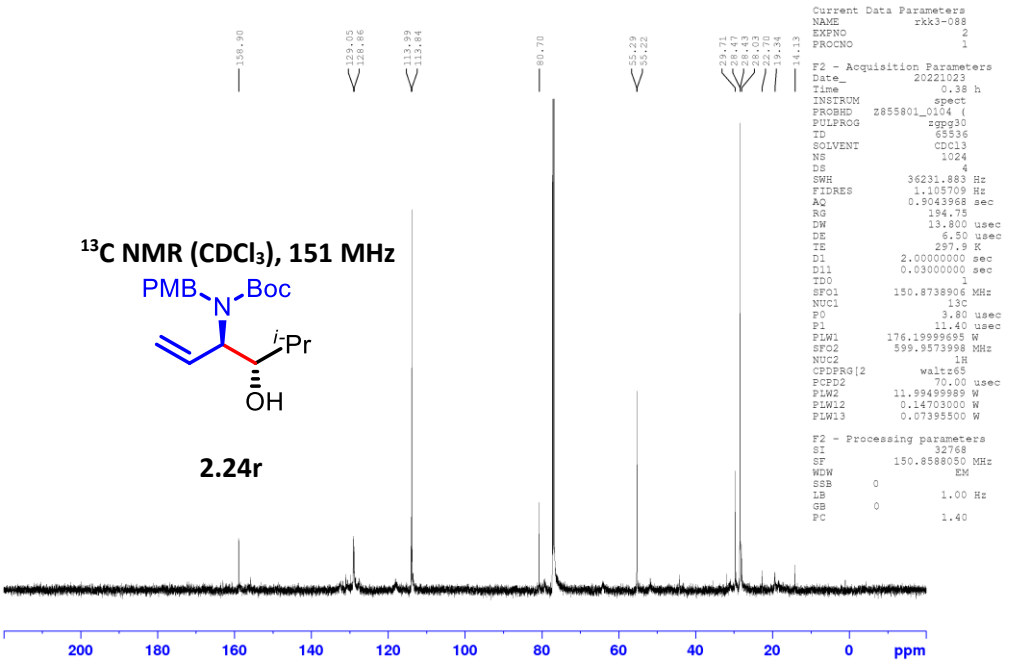
Current Data Parameters
NAME rkk3-073
EXPNO 1
PROCNO 1

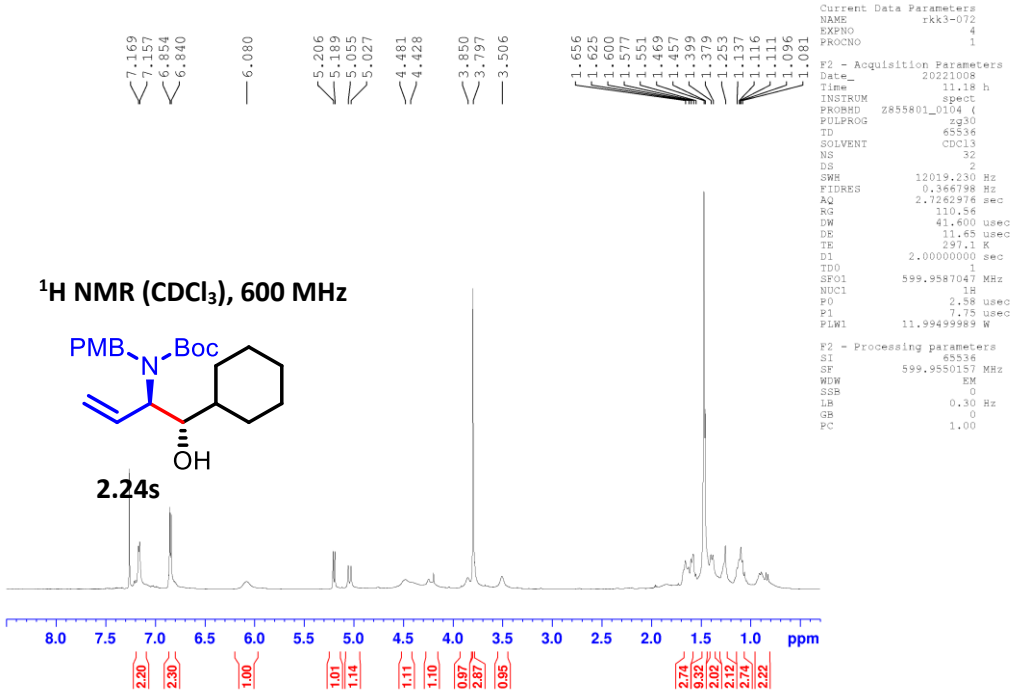
F2 - Acquisition Parameters
Date_ 20221001
Time 10.13 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 30.85
DW 41.600 usec
DE 11.65 usec
TE 296.6 K
D1 1.00000000 sec
TD0 1
SFO1 599.9587047 MHz
NUC1 1H
P0 2.58 usec
P1 7.75 usec
PLW1 11.99499989 W

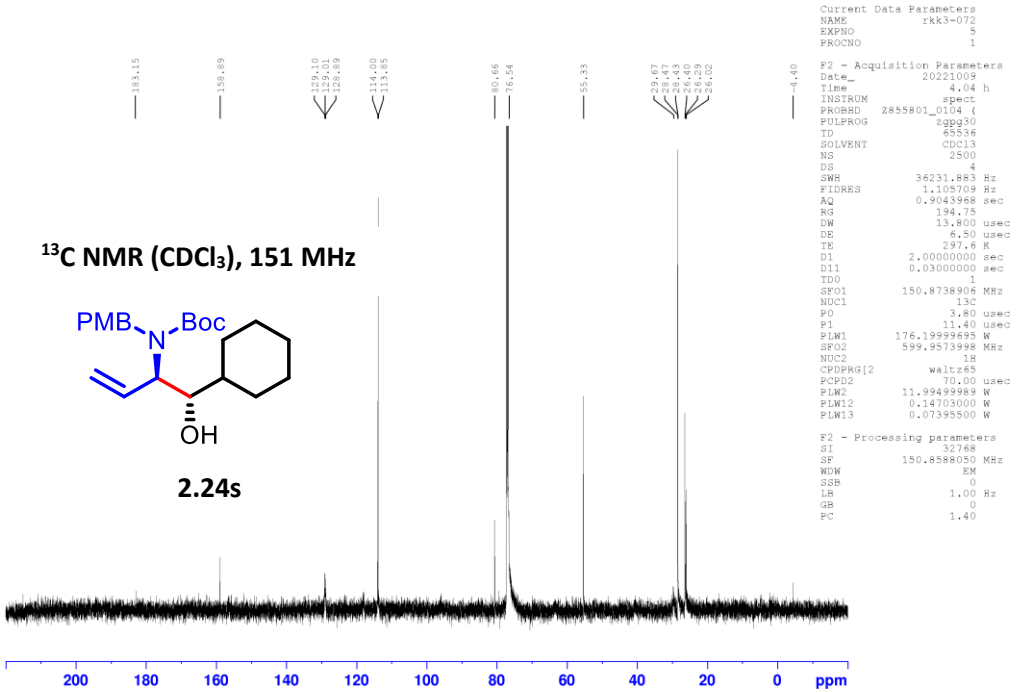
F2 - Processing parameters
SI 65536
SF 599.9550155 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

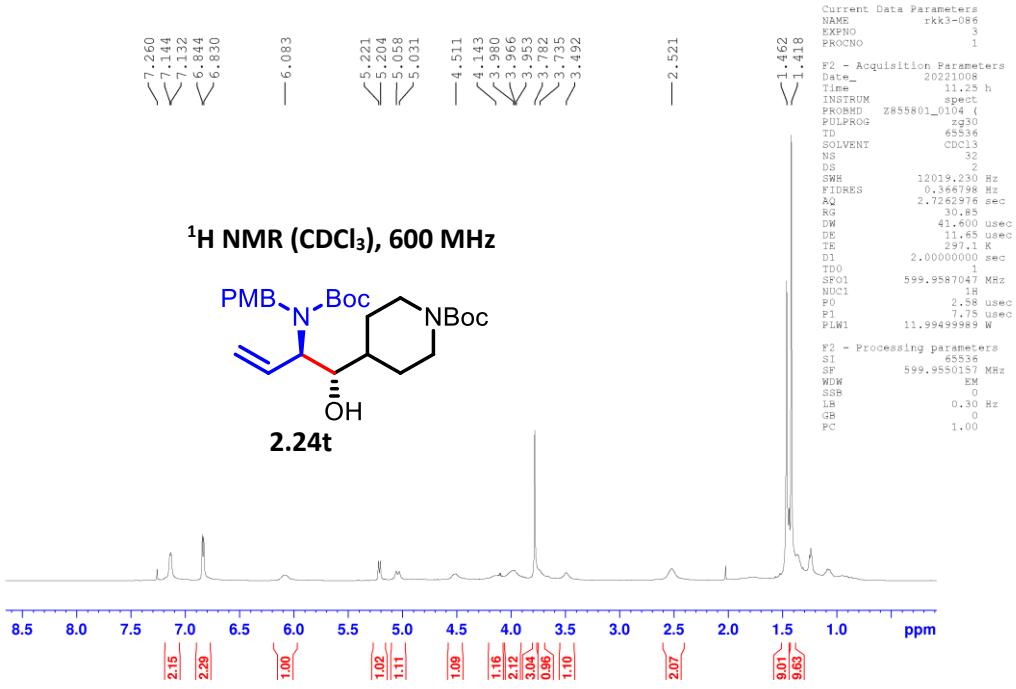

$^{13}$C NMR (CDCl$_3$), 151 MHz
PMB
N
Boc
OH
2.24q
157.06
154.56
130.55
128.68
127.38
127.15
116.30
111.96
78.84
77.14
65.51
53.47
50.26
28.63
13.67
13.28
1.77
0.00
200
180
160
140
120
100
80
60
40
20
0
ppm


$^{1}$H NMR (CDCl$_3$), 600 MHz
PMB
N
Boc
i-Pr
OH
2.24r
7.255
7.166
7.153
6.088
5.196
5.179
5.047
5.018
4.515
4.237
4.189
3.793
3.457
1.595
1.468
1.452
0.846
0.712
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.22
2.33
1.00
1.06
1.08
1.83
1.20
4.25
1.24
1.28
9.22
6.36

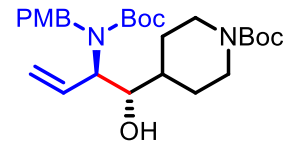

$^{13}$C NMR (CDCl$_3$), 151 MHz
PMB
N
Boc
i-Pr
OH
2.24r
158.90
129.05
128.86
113.99
113.84
80.70
55.29
55.22
29.71
28.47
28.43
28.03
27.70
19.34
14.13
Current Data Parameters
NAME rkk3-088
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221023
Time 0.38 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 194.75
DW 13.800 usec
DE 6.50 usec
TE 297.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8738906 MHz
NUC1 13C
P0 3.80 usec
P1 11.40 usec
PLW1 176.19999695 W
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07395500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200 180 160 140 120 100 80 60 40 20 0 ppm


$^{1}$H NMR (CDCl$_3$), 600 MHz
PMB
N
Boc
OH
2.24s
7.169
7.157
6.854
6.840
6.080
5.206
5.189
5.055
5.027
4.481
4.428
3.850
3.797
3.506
1.656
1.625
1.600
1.577
1.551
1.469
1.457
1.399
1.379
1.253
1.137
1.116
1.111
1.096
1.081
Current Data Parameters
NAME rkk3-072
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221008
Time 11.18 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 32
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 110.56
DW 41.600 usec
DE 11.65 usec
TE 297.1 K
D1 2.00000000 sec
TD0 1
SFO1 599.9587047 MHz
NUC1 1H
P0 2.58 usec
P1 7.75 usec
PLW1 11.99499989 W
F2 - Processing parameters
SI 65536
SF 599.9550157 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.20
2.30
1.00
1.01
1.14
1.11
1.10
0.97
2.87
0.95
2.74
9.32
2.02
2.12
2.74
2.22


$^{13}$C NMR (CDCl$_3$), 151 MHz
PMB
N
Boc
OH
2.24s
183.15
158.89
129.10
129.01
128.89
114.00
113.85
80.66
76.54
55.33
29.67
28.47
28.43
28.40
26.89
26.02
-4.40
200
180
160
140
120
100
80
60
40
20
0
ppm


$^{1}$H NMR (CDCl$_3$), 600 MHz
PMB
N
Boc
NBoc
OH
2.24t
7.260
7.144
7.132
6.844
6.830
6.083
5.221
5.204
5.058
5.031
4.511
4.143
3.980
3.966
3.953
3.782
3.735
3.492
2.521
1.462
1.418
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.15
2.29
1.00
1.02
1.11
1.09
1.16
2.12
3.04
0.96
1.10
2.07
9.01
9.63

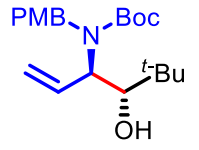
**$^{13}$C NMR ($CDCl_3$), 151 MHz**



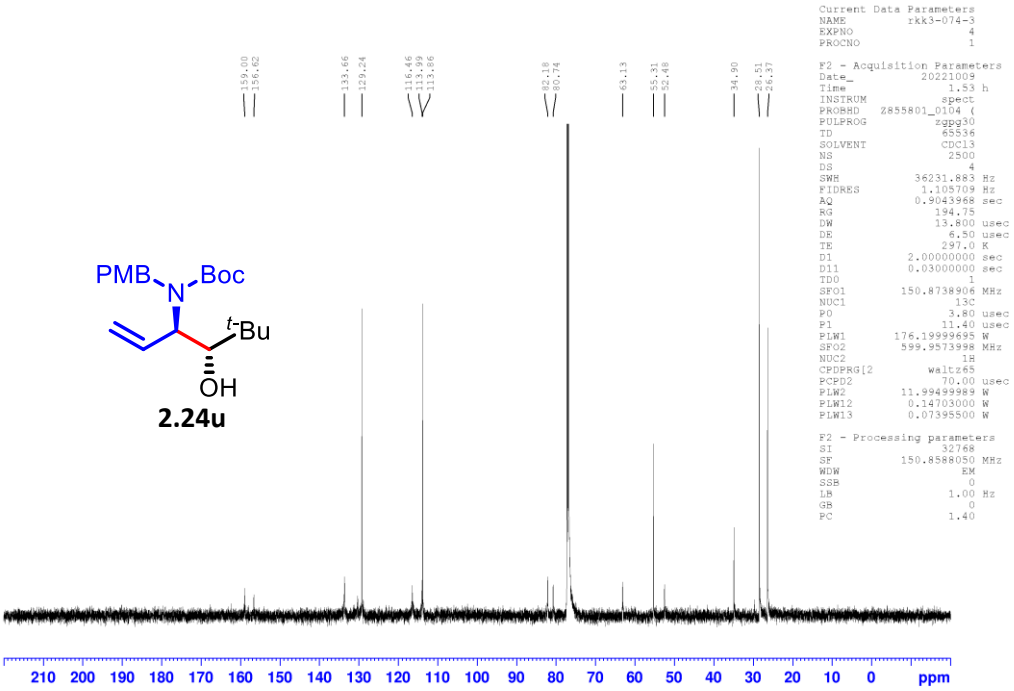

**2.24t**




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




**2.24u**

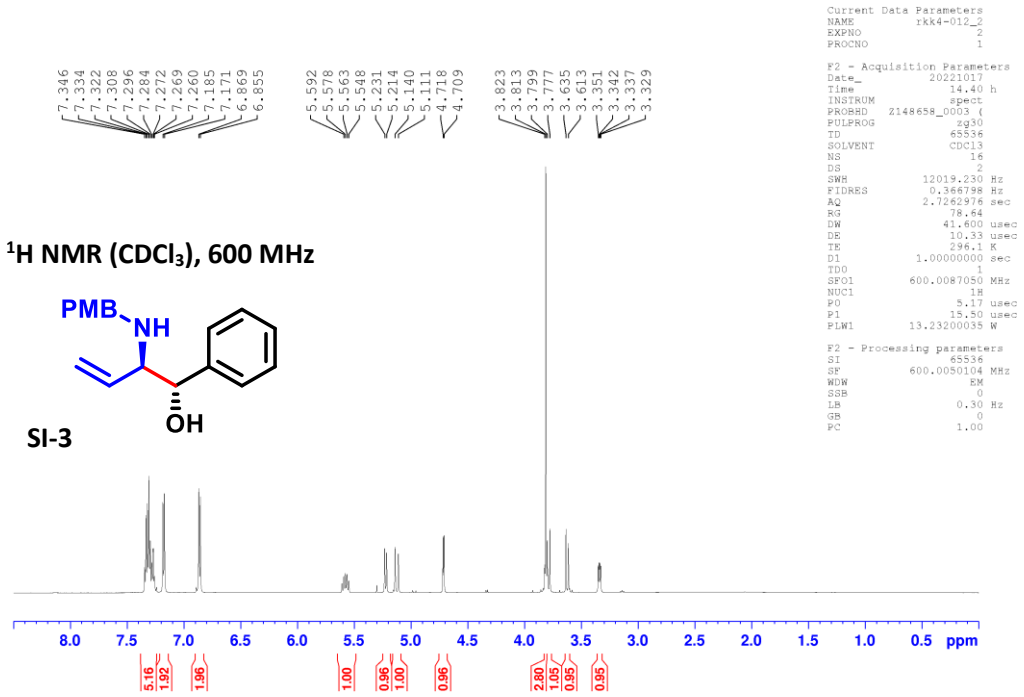




Current Data Parameters
NAME rkk3-074-3
EXPNO 4
PROCNO 1

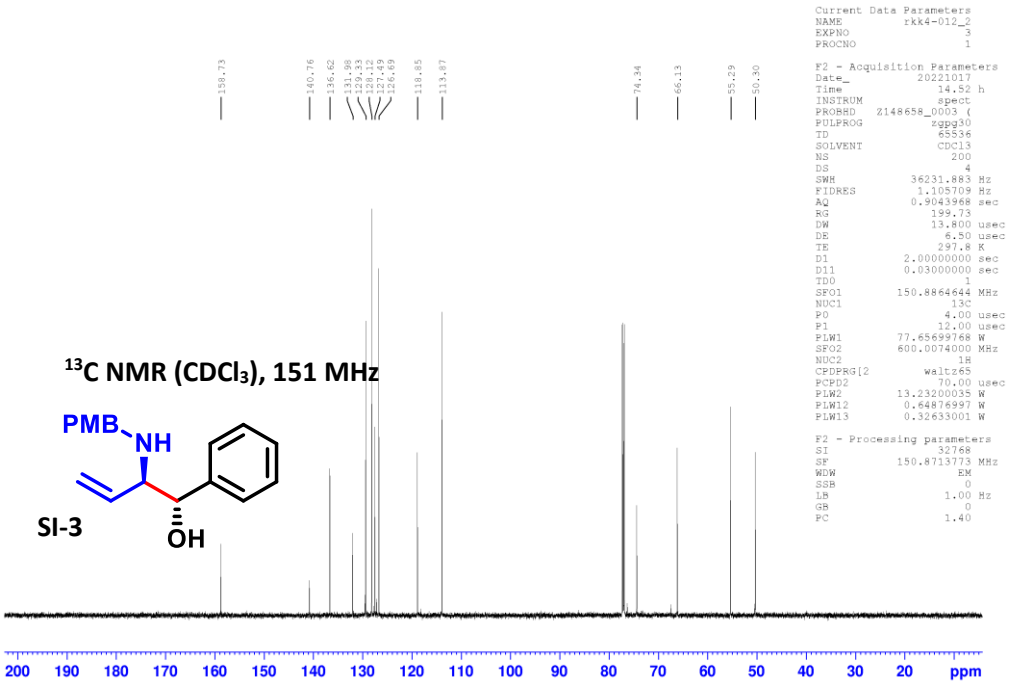
F2 - Acquisition Parameters
Date_ 20221009
Time 1.53 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 2500
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 194.75
DW 13.800 usec
DE 6.50 usec
TE 297.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8738906 MHz
NUC1 13C
P0 3.80 usec
P1 11.40 usec
PLW1 176.19999695 W
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07395500 W

F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



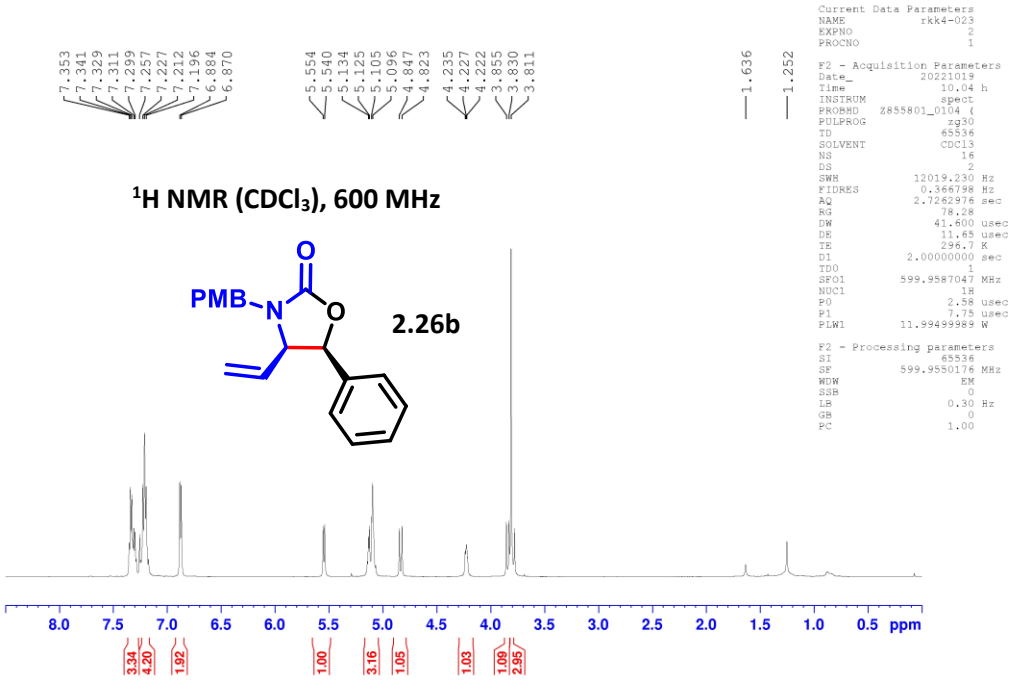

$^{1}$H NMR ($CDCl_3$), 600 MHz

SI-3

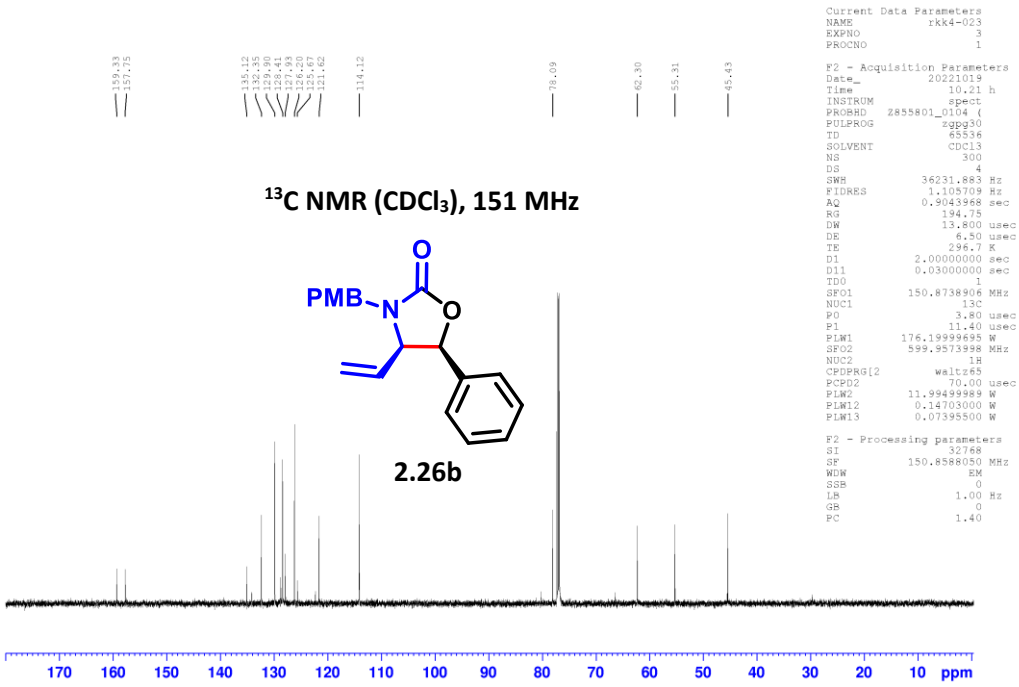



$^{13}$C NMR ($CDCl_3$), 151 MHz

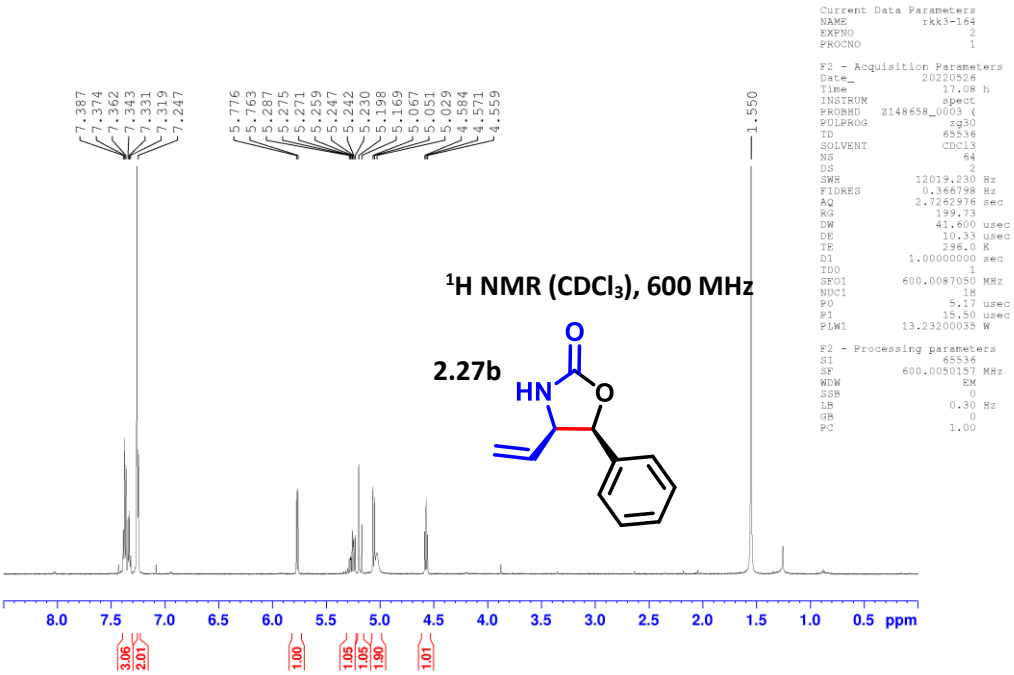
SI-3

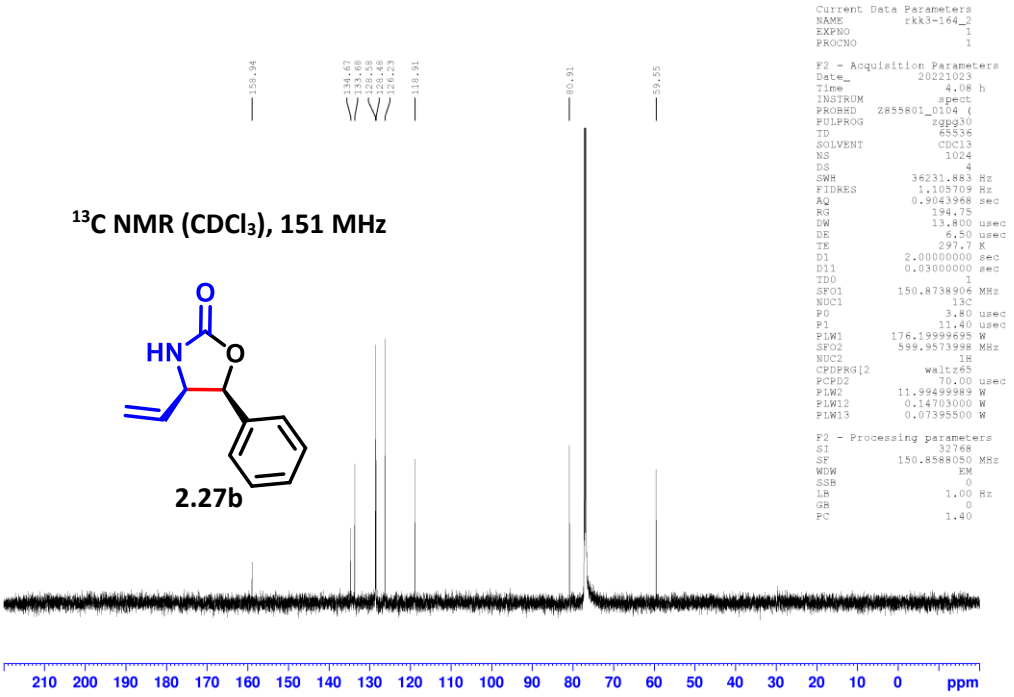


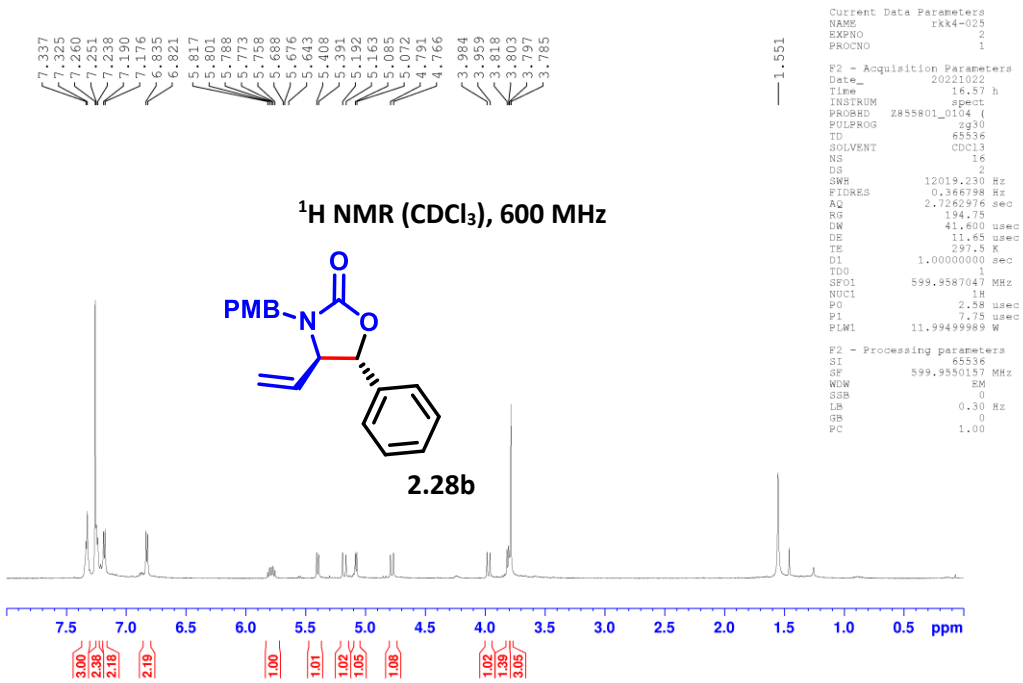

**$^{1}$H NMR ($CDCl_3$), 600 MHz**




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

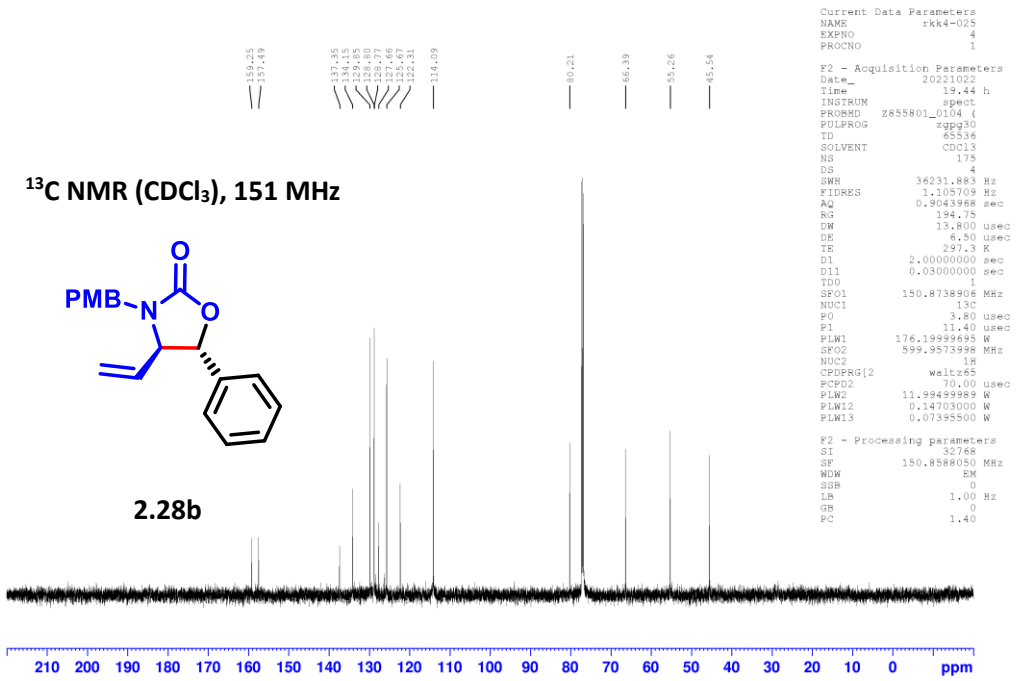

7.387
7.374
7.362
7.343
7.331
7.319
7.247
5.776
5.763
5.287
5.275
5.271
5.259
5.247
5.242
5.230
5.198
5.169
5.067
5.051
5.029
4.584
4.571
4.559
1.550
$^{1}$H NMR ($CDCl_3$), 600 MHz
2.27b
HN
O
O
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
3.06
2.01
1.00
1.05
1.05
1.90
1.01


158.94
134.67
133.68
128.58
128.48
126.23
118.91
80.91
59.55
$^{13}$C NMR ($CDCl_3$), 151 MHz
2.27b
HN
O
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm




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

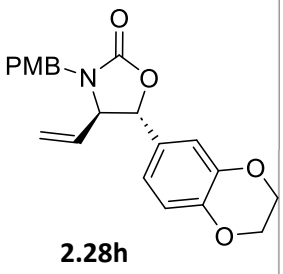
**2.28b**



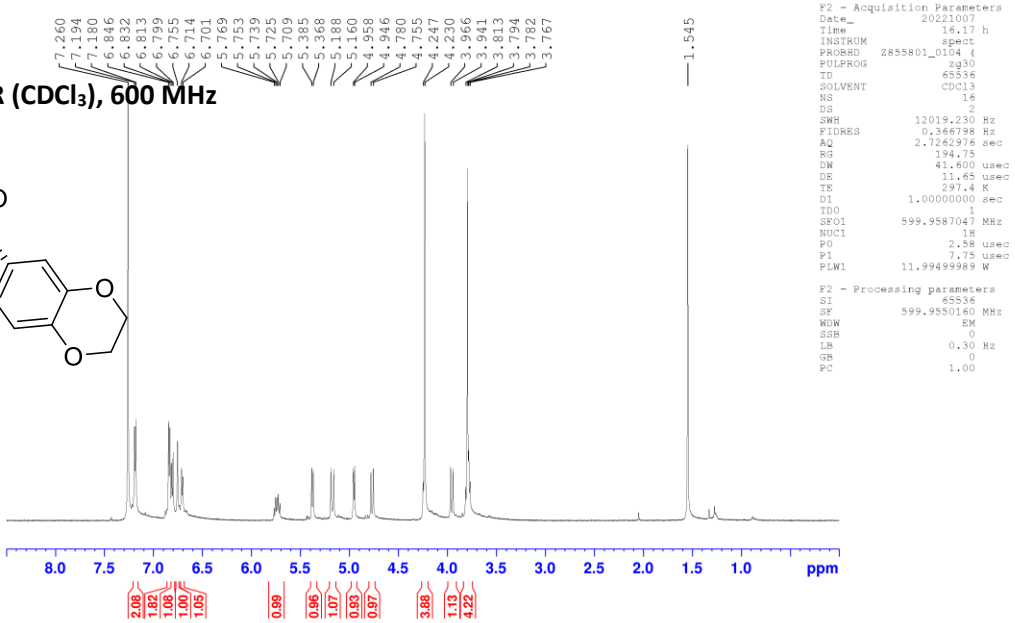

$^{13}$C NMR ($CDCl_3$), 151 MHz

**2.28b**

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

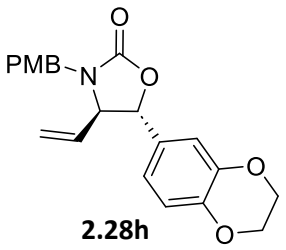



**2.28h**




```
Current Data Parameters
NAME                rkk3-188_2
EXPNO                        2
PROCNO                       1

F2 - Acquisition Parameters
Date_               20221007
Time                   16.17 h
INSTRUM                spect
PROBHD    Z855801_0104 (
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               12019.230 Hz
FIDRES                0.366798 Hz
AQ                 2.7262976 sec
RG                    194.75
DW                    41.600 usec
DE                    11.65 usec
TE                    297.4 K
D1                1.00000000 sec
TD0                          1
SFO1           599.9587047 MHz
NUC1                        1H
P0                    2.58 usec
P1                    7.75 usec
PLW1           11.99499989 W

F2 - Processing parameters
SI                       65536
SF             599.9550160 MHz
WDW                         EM
SSB                          0
LB                    0.30 Hz
GB                           0
PC                    1.00
```

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

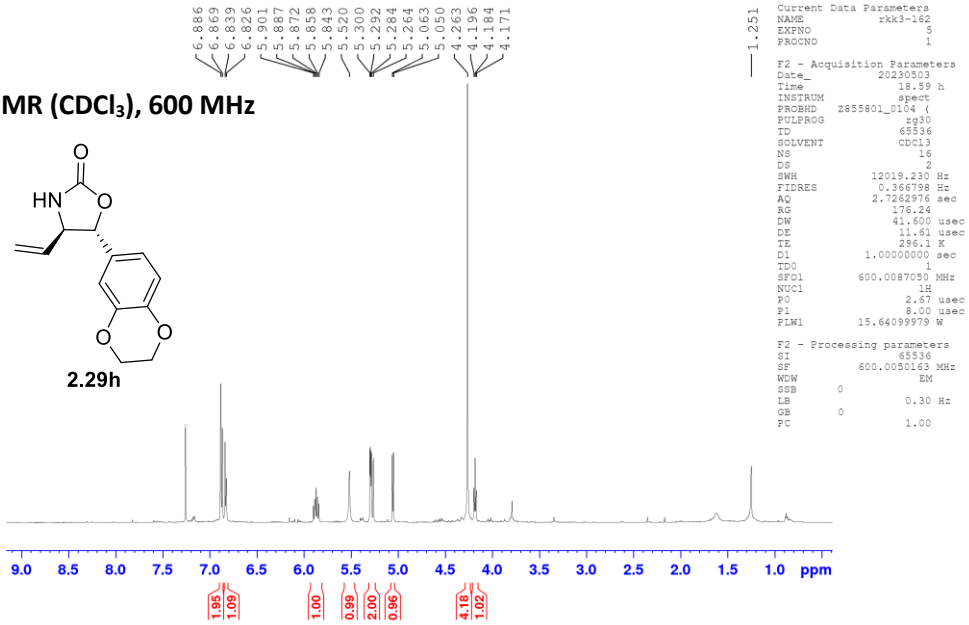



**2.28h**



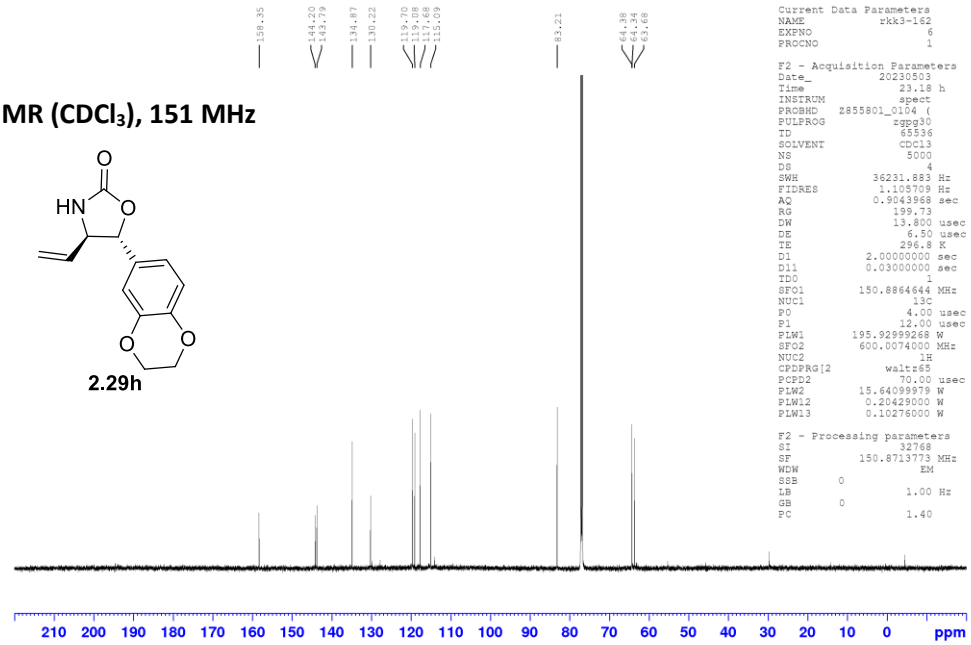

```
Current Data Parameters
NAME                rkk3-188_2
EXPNO                        4
PROCNO                       1

F2 - Acquisition Parameters
Date_               20221008
Time                    9.41 h
INSTRUM                spect
PROBHD    Z855801_0104 (
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     1024
DS                        4
SWH               36231.883 Hz
FIDRES                1.105709 Hz
AQ                 0.9043968 sec
RG                    194.75
DW                    13.800 usec
DE                     6.50 usec
TE                    297.8 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                          1
SFO1           150.8738906 MHz
NUC1                       13C
P0                    3.80 usec
P1                    11.40 usec
PLW1          176.19999695 W
SFO2           599.9573998 MHz
NUC2                        1H
CPDPRG[2             waltz65
PCPD2                 70.00 usec
PLW2           11.99499989 W
PLW12           0.14703000 W
PLW13           0.07395500 W

F2 - Processing parameters
SI                       32768
SF             150.8588050 MHz
WDW                         EM
SSB                          0
LB                    1.00 Hz
GB                           0
PC                    1.40
```

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

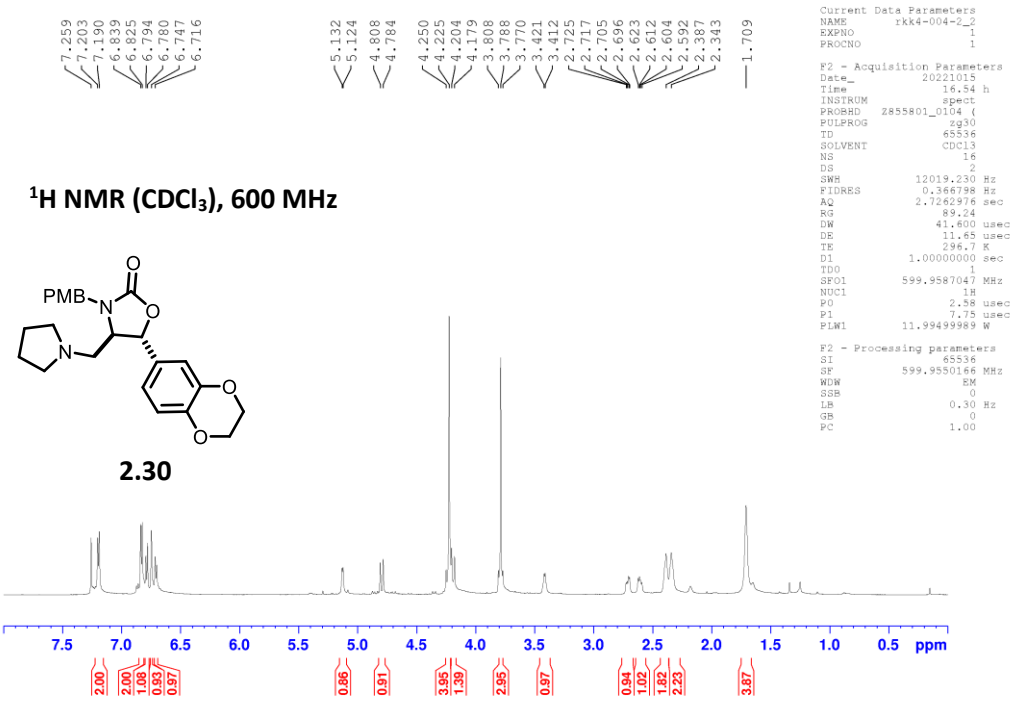



```
Current Data Parameters
NAME                  rkk3-162
EXPNO                        5
PROCNO                       1

F2 - Acquisition Parameters
Date_               20230503
Time                   18.59 h
INSTRUM                spect
PROBHD    Z855801_0104 (
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               12019.230 Hz
FIDRES             0.366798 Hz
AQ                 2.7262976 sec
RG                    176.24
DW                   41.600 usec
DE                   11.61 usec
TE                    296.1 K
D1                1.00000000 sec
TD0                       1
SFO1            600.0087050 MHz
NUC1                     1H
P0                    2.67 usec
P1                    8.00 usec
PLW1            15.64099979 W

F2 - Processing parameters
SI                    65536
SF              600.0050163 MHz
WDW                      EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

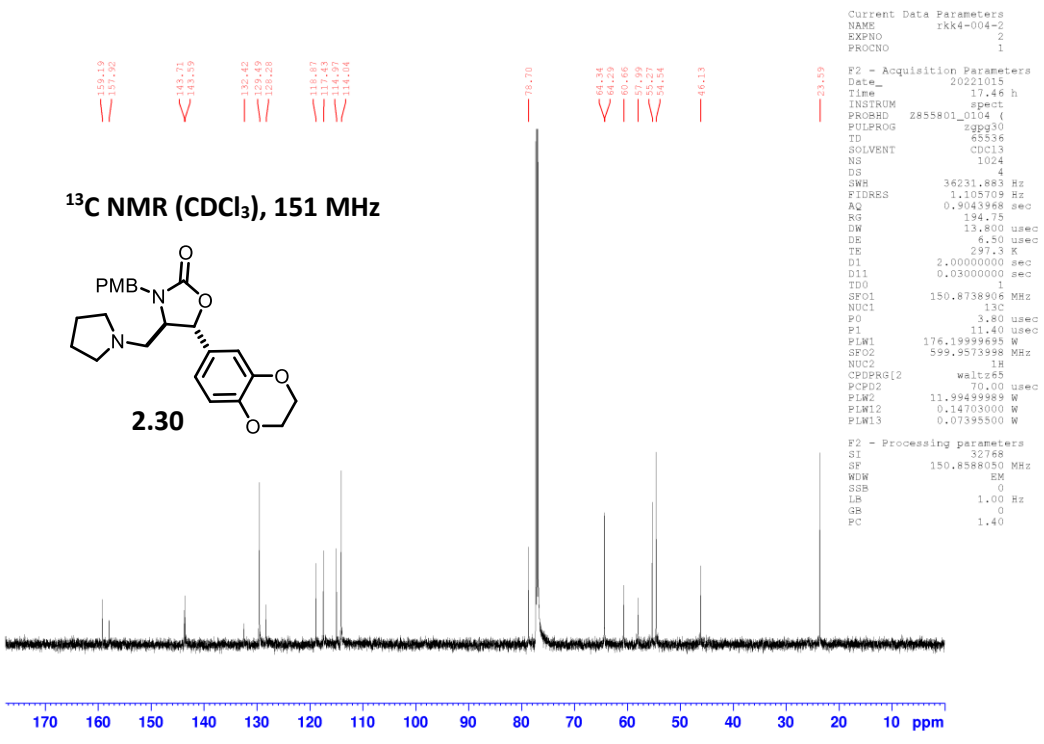
**$^{13}$C NMR ($CDCl_3$), 151 MHz**



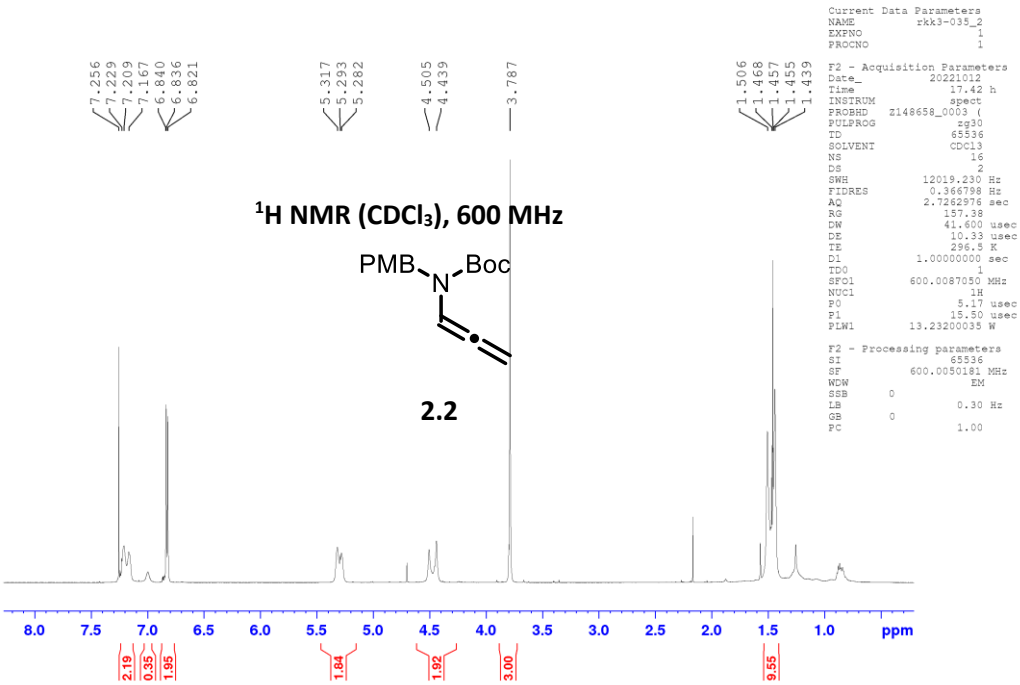

```
Current Data Parameters
NAME                  rkk3-162
EXPNO                        6
PROCNO                       1

F2 - Acquisition Parameters
Date_               20230503
Time                   23.18 h
INSTRUM                spect
PROBHD    Z855801_0104 (
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                     5000
DS                        4
SWH               36231.883 Hz
FIDRES             1.105709 Hz
AQ                 0.9043968 sec
RG                    199.73
DW                   13.800 usec
DE                    6.50 usec
TE                    296.8 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                       1
SFO1            150.8864644 MHz
NUC1                     13C
P0                    4.00 usec
P1                   12.00 usec
PLW1           195.92999268 W
SFO2            600.0074000 MHz
NUC2                     1H
CPDPRG[2             waltz65
PCPD2                70.00 usec
PLW2            15.64099979 W
PLW12            0.20429000 W
PLW13            0.10276000 W

F2 - Processing parameters
SI                    32768
SF              150.8713773 MHz
WDW                      EM
SSB          0
LB                    1.00 Hz
GB           0
PC                    1.40
```

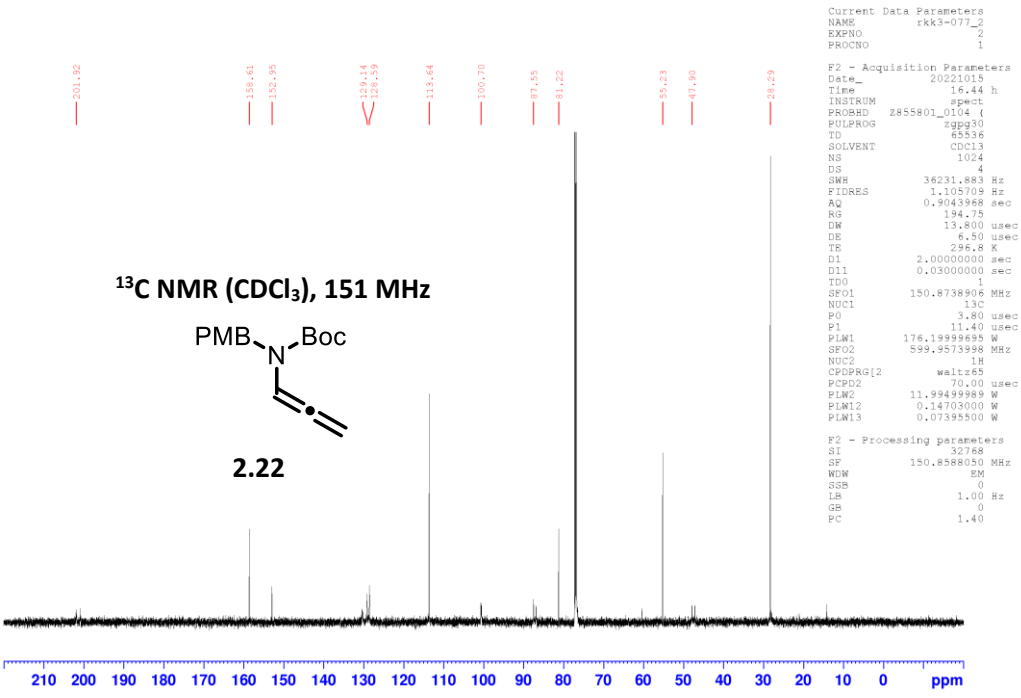



**$^{1}$H NMR ($CDCl_3$), 600 MHz**

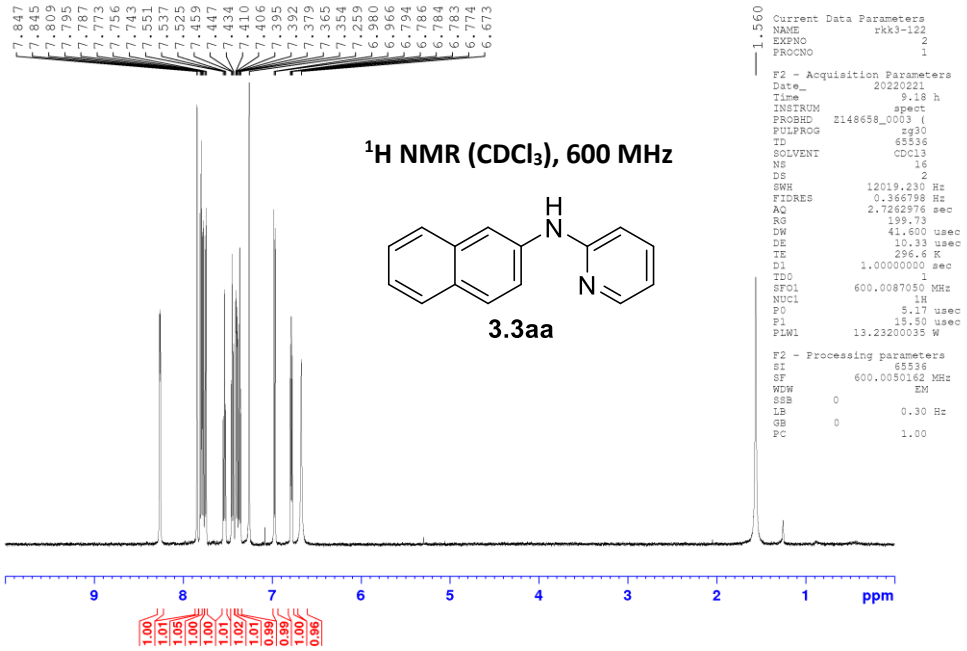


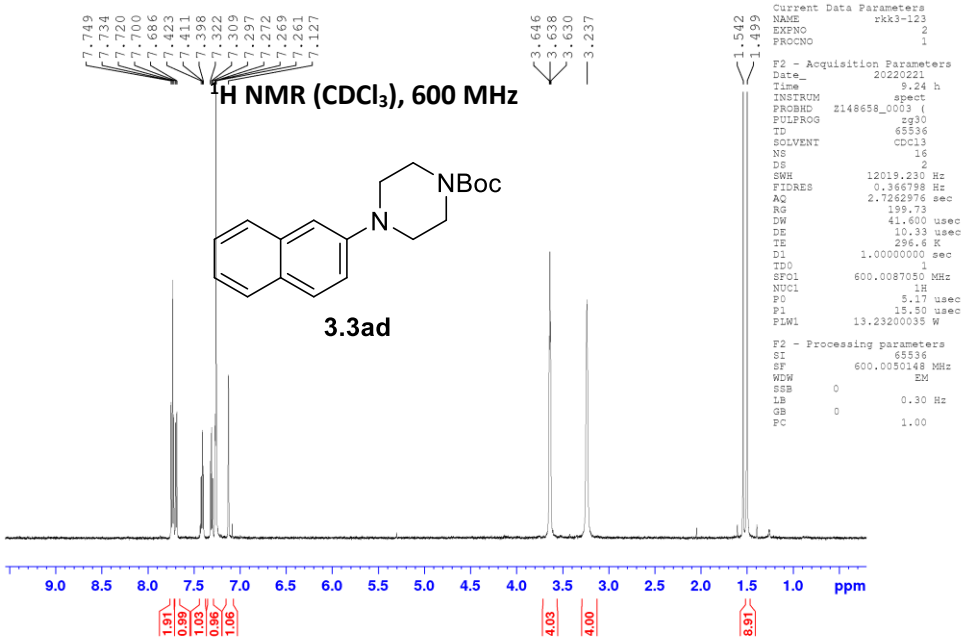

**$^{13}$C NMR ($CDCl_3$), 151 MHz**

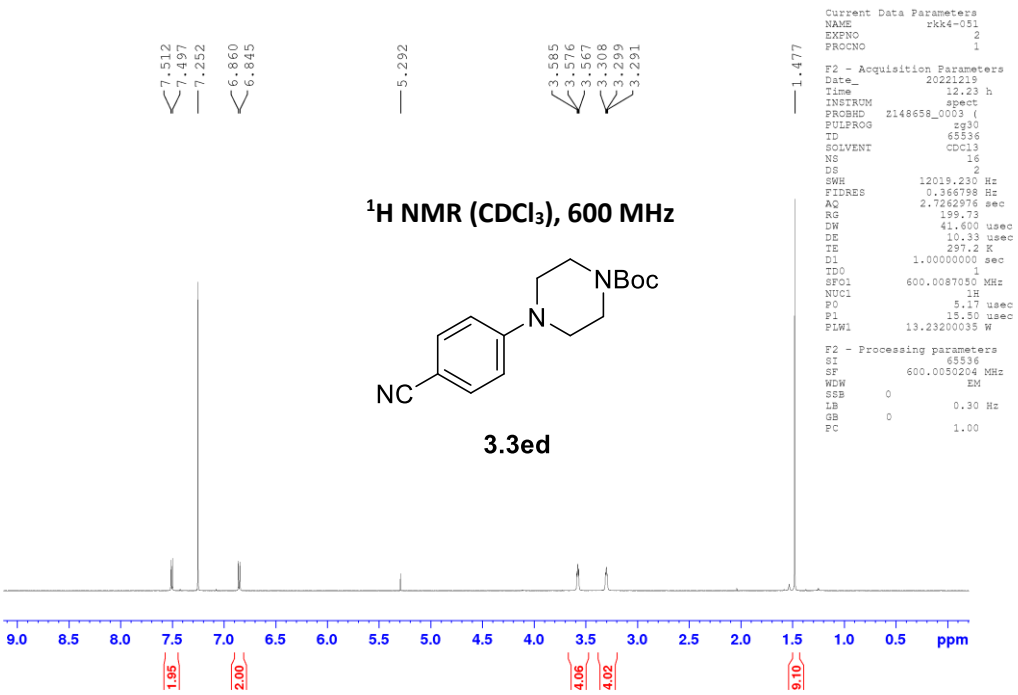

7.256
7.229
7.209
7.167
6.840
6.836
6.821
5.317
5.293
5.282
4.505
4.439
3.787
1.506
1.468
1.457
1.455
1.439
Current Data Parameters
NAME rkk3-035_2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221012
Time 17.42 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 157.38
DW 41.600 usec
DE 10.33 usec
TE 296.5 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P0 5.17 usec
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050181 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
PMB
N
Boc
2.2
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.19
0.35
1.95
1.84
1.92
3.00
9.55

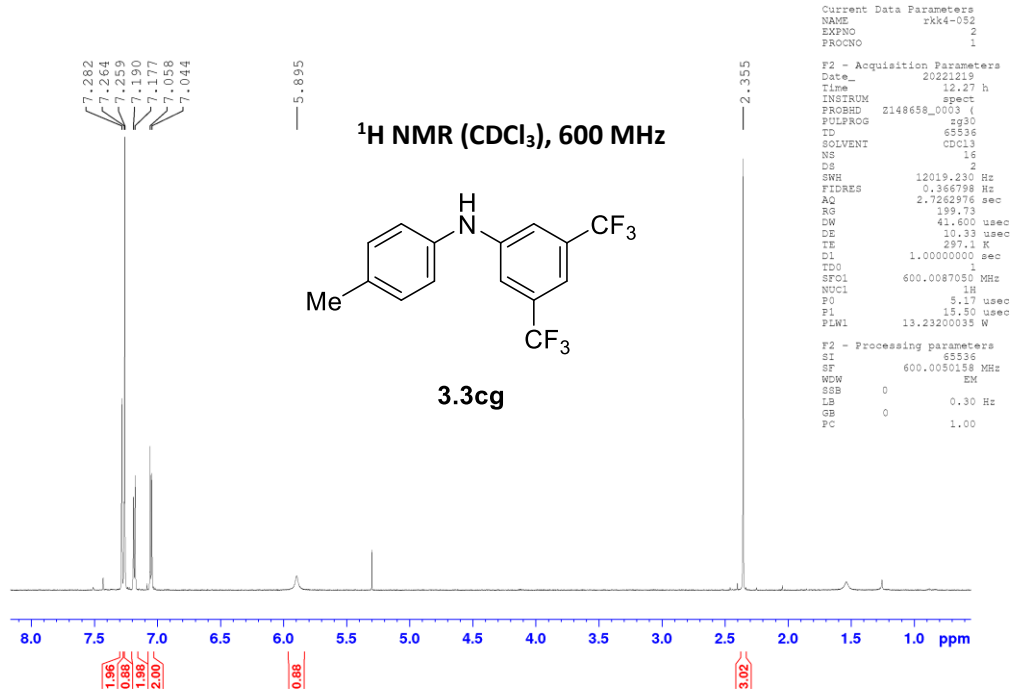

201.92
158.61
152.95
129.14
128.59
113.64
100.70
87.55
81.22
55.23
47.90
28.29
Current Data Parameters
NAME rkk3-077_2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221015
Time 16.44 h
INSTRUM spect
PROBHD Z855801_0104 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 36231.883 Hz
FIDRES 1.105709 Hz
AQ 0.9043968 sec
RG 194.75
DW 13.800 usec
DE 6.50 usec
TE 296.8 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 150.8738906 MHz
NUC1 13C
P0 3.80 usec
P1 11.40 usec
PLW1 176.19999695 W
SFO2 599.9573998 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 70.00 usec
PLW2 11.99499989 W
PLW12 0.14703000 W
PLW13 0.07395500 W
F2 - Processing parameters
SI 32768
SF 150.8588050 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
13C NMR (CDCl3), 151 MHz
PMB
N
Boc
2.22
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

## APPENDIX A3. SELECT NMR SPECTRA FROM CHAPTER 3




7.512
7.497
7.252
6.860
6.845
5.292
3.585
3.576
3.567
3.308
3.299
3.291
1.477
Current Data Parameters
NAME rkk4-051
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221219
Time 12.23 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 10.33 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P0 5.17 usec
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050204 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
NBoc
N
NC
3.3ed
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.95
2.00
4.06
4.02
9.10


7.282
7.264
7.259
7.190
7.177
7.058
7.044
5.895
2.355
Current Data Parameters
NAME rkk4-052
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221219
Time 12.27 h
INSTRUM spect
PROBHD Z148658_0003 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.366798 Hz
AQ 2.7262976 sec
RG 199.73
DW 41.600 usec
DE 10.33 usec
TE 297.1 K
D1 1.00000000 sec
TD0 1
SFO1 600.0087050 MHz
NUC1 1H
P0 5.17 usec
P1 15.50 usec
PLW1 13.23200035 W
F2 - Processing parameters
SI 65536
SF 600.0050158 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H NMR (CDCl3), 600 MHz
H
N
CF3
Me
CF3
3.3cg
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.96
0.88
1.98
2.00
0.88
3.02

## References


(1) Iwatsuki, M.; Nishihara-Tsukashima, A.; Ishiyama, A.; Namatame, M.; Watanabe, Y.; Handasah, S.; Pranamuda, H.; Marwoto, B.; Matsumoto, A.; Takahashi, Y.; Otoguro, K.; Omura, S. Jogyamycin, a New Antiprotozoal Aminocyclopentitol Antibiotic, Produced by Streptomyces Sp. a-WM-JG-16.2. *Journal of Antibiotics* **2012**, *65* (3), 169–171. https://doi.org/10.1038/ja.2011.136.

(2) Hartwig, W.; Born, L. Diastereoselective and Enantioselective Total Synthesis of the Hepatoprotective Agent Clausenamide. *J Org Chem* **1987**, *52* (19), 4353–4358.

(3) Davison, E. K.; Sperry, J. Natural Products with Heteroatom-Rich Ring Systems. *J Nat Prod* **2017**, *80* (11), 3060–3079. https://doi.org/10.1021/acs.jnatprod.7b00575.

(4) Gupta, P.; Mahajan, N. Biocatalytic Approaches towards the Stereoselective Synthesis of Vicinal Amino Alcohols. *New Journal of Chemistry* **2018**, *42* (15), 12296–12327. https://doi.org/10.1039/c8nj00485d.

(5) Wetzel, S.; Schuffenhauer, A.; Roggo, S.; Ertl, P.; Waldmann, H. Cheminformatic Analysis of Natural Products and Their Chemical Space. *Natural Products in Drug Discovery* **2007**, *61* (6), 355–360. https://doi.org/10.2533/chimia.2007.355.

(6) Sehl, T.; Maugeri, Z.; Rother, D. Multi-Step Synthesis Strategies towards 1,2-Amino Alcohols with Special Emphasis on Phenylpropanolamines. *J Mol Catal B Enzym* **2015**, *114*, 65–71. https://doi.org/10.1016/j.molcatb.2014.12.005.

(7) Mushtaq, S.; Abbasi, B. H.; Uzair, B.; Abbasi, R. Natural Products as Reservoirs of Novel Therapeutic Agents. *EXCLI Journal*. Leibniz Research Centre for Working Environment and Human Factors May 4, 2018, pp 420–451. https://doi.org/10.17179/excli2018-1174.

(8) Bergmeier, S. C. The Synthesis of Vicinal Amino Alcohols. *Tetrahedron* **2000**, *56*, 25612576.

(9) Burchak, O. N.; Py, S. Reductive Cross-Coupling Reactions (RCCR) between C=N and C=O for β-Amino Alcohol Synthesis. *Tetrahedron* **2009**, *65* (36), 7333–7356. https://doi.org/10.1016/j.tet.2009.06.003.

(10) Karjalainen, O. K.; Koskinen, A. M. P. Diastereoselective Synthesis of Vicinal Amino Alcohols. *Org Biomol Chem* **2012**, *10* (22), 4311–4326. https://doi.org/10.1039/c2ob25357g.

(11) Bamou, F. Z.; Le, T. M.; Volford, B.; Szekeres, A.; Szakonyi, Z. Synthesis and Application of 1,2-Aminoalcohols with Neoisopulegol-Based Octahydrobenzofuran Core. *Molecules 2020, Vol. 25, Page 21* **2019**, *25* (1), 21. https://doi.org/10.3390/MOLECULES25010021.

(12) Lou, S.; Moquist, P. N.; Schaus, S. E. Asymmetric Allylboration of Ketones Catalyzed by Chiral Diols. *J Am Chem Soc* **2006**, *128* (39), 12660–12661. https://doi.org/10.1021/ja0651308.

(13) Shao, X.; Li, K.; Malcolmson, S. J. Enantioselective Synthesis of Anti-1,2-Diamines by Cu-Catalyzed Reductive Couplings of Azadienes with Aldimines and Ketimines. *J Am Chem Soc* **2018**, *140* (23), 7083–7087. https://doi.org/10.1021/jacs.8b04750.

(14) Dibrell, S. E.; Tao, Y.; Reisman, S. E. Synthesis of Complex Diterpenes: Strategies Guided by Oxidation Pattern Analysis. *Acc Chem Res* **2021**, *54* (6), 1360–1373. https://doi.org/10.1021/acs.accounts.0c00858.

(15) Seebach, D. Methods of Reactivity Umpolung. *Angewandte Chemie International Edition in English* **1979**, *18*, 239–336.

(16) Seebach, D.; Kolb, M. Umpolung (Dipole Inversion) of Carbonyl Reactivity. Chem Ind 1974, 687–692. *Chem Ind* **1974**, *17*, 687–692.

(17) Agrawal, T.; Sieber, J. D. Recent Developments in C-C Bond Formation Using Catalytic Reductive Coupling Strategies. *Synthesis (Germany)* **2020**, *52* (18), 2623–2638. https://doi.org/10.1055/s-0040-1707128.

(18) Reichard, H. A.; McLaughlin, M.; Chen, M. Z.; Micalizio, G. C. Regioselective Reductive Cross-Coupling Reactions of Unsymmetrical Alkynes. *European J Org Chem* **2010**, No. 3, 391–409. https://doi.org/10.1002/ejoc.200901094.

(19) Jackson, E. P.; Malik, H. A.; Sormunen, G. J.; Baxter, R. D.; Liu, P.; Wang, H.; Shareef, A. R.; Montgomery, J. Mechanistic Basis for Regioselection and Regiodivergence in Nickel-Catalyzed Reductive Couplings. *Acc Chem Res* **2015**, *48* (6), 1736–1745. https://doi.org/10.1021/acs.accounts.5b00096.

(20) Nguyen, K. D.; Park, B. Y.; Luong, T.; Sato, H.; Garza, V. J.; Krische, M. J. Metal-Catalyzed Reductive Coupling Ofolefin-Derivednucleophiles: Reinventing Carbonyl Addition. *Science (1979)* **2016**, *354* (6310). https://doi.org/10.1126/science.aah5133.

(21) Nugent, T. C.; El-Shazly, M. Chiral Amine Synthesis - Recent Developments and Trends for Enamide Reduction, Reductive Amination, and Imine Reduction. *Adv Synth Catal* **2010**, *352* (5), 753–819. https://doi.org/10.1002/adsc.200900719.

(22) Evans, D. *An Organizational Format for the Classification of Functional Groups. Application to the Construction of Difunctional Relationships; Chemistry 206: Advanced Organic Chemistry, Handout 27A; Harvard University, 2001.*

(23) Evans, D. A.; Andrews, G. C. Allylic Sulfoxides: Useful Intermediates in Organic Synthesis. *Acc Chem Res* **1974**, *7* (5), 147–155.

(24) Kobayashi, S.; Ishitani, H. Catalytic Enantioselective Addition to Imines. *Chem Rev* **1999**, *99* (5), 1069–1094. https://doi.org/10.1021/cr980414z.

(25) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. *Chem Rev* **2020**, *120* (5), 2613–2692. https://doi.org/10.1021/acs.chemrev.9b00462.

(26) Riant, O.; Hannedouche, J. Asymmetric Catalysis for the Construction of Quaternary Carbon Centres: Nucleophilic Addition on Ketones and Ketimines. *Org Biomol Chem* **2007**, *5* (6), 873–888. https://doi.org/10.1039/b617746h.

(27) Wu, Y. C.; Zhu, J. Asymmetrie Total Syntheses of (-)-Renieramycin M and G and (-)-Jorumycin Using Aziridine as a Lynchpin. *Org Lett* **2009**, *11* (23), 5558–5561. https://doi.org/10.1021/ol9024919.

(28) Winblad, B.; Fioravanti, M.; Dolezal, T.; Logina, I.; Milanov, I. G.; Popescu, D. C.; Solomon, A. *Therapeutic Use of Nicergoline*; 2008; Vol. 28.

(29) Tatsumi, Y.; Nagashima, M.; Shibanushi, T.; Iwata, A.; Kangawa, Y.; Inui, F.; Jo Siu, W. J.; Pillai, R.; Nishiyama, Y. Mechanism of Action of Efinaconazole, a Novel Triazole Antifungal Agent. *Antimicrob Agents Chemother* **2013**, *57* (5), 2405–2409. https://doi.org/10.1128/AAC.02063-12.

(30) *The Nobel Prize in Chemistry 1990 Press Release*. https://www.nobelprize.org/prizes/chemistry/1990/press-release/ Highlight (accessed 2023-04-01).

(31) Corey, E. J.; Howe, J. W.; Orf, H. W.; Pensak, D. A.; Petersson, G. General Methods of Synthetic Analysis. Strategic Bond Disconnections for Bridged Polycyclic Structures. *J Am Chem Soc* **1975**, *97* (21), 6116–6124.

(32) Ma, J.; Harms, K.; Meggers, E. Enantioselective Rhodium/Ruthenium Photoredox Catalysis: En Route to Chiral 1,2-Aminoalcohols. *Chemical Communications* **2016**, *52* (66), 10183–10186. https://doi.org/10.1039/c6cc04397f.

(33) Yoon, U. C.; Uk, D.; Chan, K. :; Lee, W.; Choij, Y. S.; Lee, Y.-J.; A M O N , $, H. L.; Mariano, P. S. Novel and Efficient Azomethine Ylide Forming Photoreactions of N-(Silylmethy1)Phthalimides and Related Acid and Alcohol Derivatives. *J Am Chem Soc* **1995**, *117* (10), 2698–2710.

(34) Schwarz, J. L.; Kleinmans, R.; Paulisch, T. O.; Glorius, F. 1,2-Amino Alcohols via Cr/Photoredox Dual-Catalyzed Addition of α-Amino Carbanion Equivalents to Carbonyls. *J Am Chem Soc* **2020**, *142* (5), 2168–2174. https://doi.org/10.1021/jacs.9b12053.

(35) Wang, R.; Ma, M.; Gong, X.; Fan, X.; Walsh, P. J. Reductive Cross-Coupling of Aldehydes and Imines Mediated by Visible Light Photoredox Catalysis. *Org Lett* **2019**, *21* (1), 27–31. https://doi.org/10.1021/acs.orglett.8b03394.

(36) Kim, J. Y.; Lee, Y. S.; Choi, Y.; Ryu, D. H. Enantioselective 1,2-Addition of α-Aminoalkyl Radical to Aldehydes via Visible-Light Photoredox Initiated Chiral Oxazaborolidinium Ion Catalysis. *ACS Catal* **2020**, *10* (18), 10585–10591. https://doi.org/10.1021/acscatal.0c02443.

(37) Miller, J. J.; Sigman, M. S. Quantitatively Correlating the Effect of Ligand-Substituent Size in Asymmetric Catalysis Using Linear Free Energy Relationships. *Angewandte Chemie - International Edition* **2008**, *47* (4), 771–774. https://doi.org/10.1002/anie.200704257.

(38) Miller, J. J.; Sigman, M. S. Design and Synthesis of Modular Oxazoline Ligands for the Enantioselective Chromium-Catalyzed Addition of Allyl Bromide to Ketones. *J Am Chem Soc* **2007**, *129* (10), 2752–2753. https://doi.org/10.1021/ja068915m.

(39) Kim, I. S.; Ngai, M. Y.; Krische, M. J. Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level via Transfer Hydrogenative Coupling of Allyl Acetate: Departure from Chirally Modified Allyl Metal Reagents in Carbonyl Addition. *J Am Chem Soc* **2008**, *130* (44), 14891–14899. https://doi.org/10.1021/ja805722e.

(40) Chen, R. Y.; Dhondge, A. P.; Lee, G. H.; Chen, C. A Chiral Bipyridyl Alcohol for Catalytic Enantioselective Nozaki-Hiyama-Kishi Allylation of Aldehydes and Ketones. *Adv Synth Catal* **2015**, *357* (5), 961–966. https://doi.org/10.1002/adsc.201400945.

(41) In, S. K.; Ngai, M. Y.; Krische, M. J. Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level Using Allyl Acetate as an Allyl Metal Surrogate. *J Am Chem Soc* **2008**, *130* (20), 6340–6341. https://doi.org/10.1021/ja802001b.

(42) Weix, D. J. Methods and Mechanisms for Cross-Electrophile Coupling of Csp2 Halides with Alkyl Electrophiles. *Acc Chem Res* **2015**, *48* (6), 1767–1775. https://doi.org/10.1021/acs.accounts.5b00057.

(43) Wang, X.; Dai, Y.; Gong, H. Nickel-Catalyzed Reductive Couplings. *Top Curr Chem* **2016**, *374* (4). https://doi.org/10.1007/s41061-016-0042-2.

(44) Richmond, E.; Moran, J. Recent Advances in Nickel Catalysis Enabled by Stoichiometric Metallic Reducing Agents. *Synthesis (Germany)* **2018**, *50* (3), 499–513. https://doi.org/10.1055/s-0036-1591853.

(45) Standley, E. A.; Tasker, S. Z.; Jensen, K. L.; Jamison, T. F. Nickel Catalysis: Synergy between Method Development and Total Synthesis. *Acc Chem Res* **2015**, *48* (5), 1503–1514. https://doi.org/10.1021/acs.accounts.5b00064.

(46) Liu, R. Y.; Zhou, Y.; Yang, Y.; Buchwald, S. L. Enantioselective Allylation Using Allene, a Petroleum Cracking Byproduct. *J Am Chem Soc* **2019**, *141* (6), 2251–2256. https://doi.org/10.1021/jacs.8b13907.

(47) Tsai, E. Y.; Liu, R. Y.; Yang, Y.; Buchwald, S. L. A Regio- and Enantioselective CuH-Catalyzed Ketone Allylation with Terminal Allenes. *J Am Chem Soc* **2018**, *140* (6), 2007–2011. https://doi.org/10.1021/jacs.7b12271.

(48) Li, C.; Liu, R. Y.; Jesikiewicz, L. T.; Yang, Y.; Liu, P.; Buchwald, S. L. CuH-Catalyzed Enantioselective Ketone Allylation with 1,3-Dienes: Scope, Mechanism, and Applications. *J Am Chem Soc* **2019**, *141* (12), 5062–5070. https://doi.org/10.1021/jacs.9b01784.

(49) Li, C.; Shin, K.; Liu, R. Y.; Buchwald, S. L. Engaging Aldehydes in CuH-Catalyzed Reductive Coupling Reactions: Stereoselective Allylation with Unactivated 1,3-Diene Pronucleophiles. *Angewandte Chemie International Edition* **2019**, *58* (47), 17074–17080. https://doi.org/10.1002/ANIE.201911008.

(50) Holmes, M.; Schwartz, L. A.; Krische, M. J. Intermolecular Metal-Catalyzed Reductive Coupling of Dienes, Allenes, and Enynes with Carbonyl Compounds and Imines. *Chem Rev* **2018**, *118* (12), 6026–6052. https://doi.org/10.1021/acs.chemrev.8b00213.

(51) Han, S. B.; Kim, I. S.; Krische, M. J. Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol Oxidation Level via Transfer Hydrogenation: Minimizing Pre-Activation for Synthetic Efficiency. *Chemical Communications* **2009**, No. 47, 7278–7287. https://doi.org/10.1039/b917243m.

(52) Hassan, A.; Krische, M. J. Unlocking Hydrogenation for C-C Bond Formation: A Brief Overview of Enantioselective Methods. *Org Process Res Dev* **2011**, *15* (6), 1236–1242. https://doi.org/10.1021/op200195m.

(53) Brown, H. C.; Kim, K.-W.; Cole, T. E.; Singaram, B. Chiral Synthesis via Organoboranes. 8. Synthetic Utility of Boronic Esters of Essentially 100% Optical Purity. Synthesis of Primary Amines of Very High Enantiomeric Purities. *J Am Chem Soc* **1986**, *108* (21), 6761–6764.

(54) Brown, H. C.; Klender, G. J. Improved Procedures for the Synthesis of Diisopinocampheylborane of High Optical Purity. *J Am Chem Soc* **1984**, *49* (11), 2544.

(55) Brown, H. C.; Desai, M. C.; Jadhav, P. K. Hydroboration. 61. Diisopinocampheylborane of High Optical Purity. Improved Preparation and Asymmetric Hydroboration of Representative Cis-Disubstituted Alkenes. *Journal of Organic Chemistry* **1982**, *47*, 7446–7470.

(56) Yus, M.; González-Gómez, J. C.; Foubelo, F. Catalytic Enantioselective Allylation of Carbonyl Compounds and Imines. *Chem Rev* **2011**, *111* (12), 7774–7854. https://doi.org/10.1021/cr1004474.

(57) Denmark, S. E.; Fu, J. Catalytic Enantioselective Addition of Allylic Organometallic Reagents to Aldehydes and Ketones. *Chem Rev* **2003**, *103* (8), 2763–2793. https://doi.org/10.1021/cr020050h.

(58) Robbins, D. W.; Lee, K. A.; Silverio, D. L.; Volkov, A.; Torker, S.; Hoveyda, A. H. Practical and Broadly Applicable Catalytic Enantioselective Additions of Allyl-B(Pin) Compounds to Ketones and α-Ketoesters. *Angewandte Chemie - International Edition* **2016**, *55* (33), 9610–9614. https://doi.org/10.1002/anie.201603894.

(59) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. Catalytic Enantioselective Allylboration of Ketones. *J Am Chem Soc* **2004**, *126* (29), 8910–8911. https://doi.org/10.1021/ja047200l.

(60) Alam, R.; Vollgraff, T.; Eriksson, L.; Szabó, K. J. Synthesis of Adjacent Quaternary Stereocenters by Catalytic Asymmetric Allylboration. *J Am Chem Soc* **2015**, *137* (35), 11262–11265. https://doi.org/10.1021/jacs.5b07498.

(61) Shi, S. L.; Xu, L. W.; Oisaki, K.; Kanai, M.; Shibasaki, M. Identification of Modular Chiral Bisphosphines Effective for Cu(I)-Catalyzed Asymmetric Allylation and Propargylation of Ketones. *J Am Chem Soc* **2010**, *132* (19), 6638–6639. https://doi.org/10.1021/ja101948s.

(62) Wooten, A. J.; Kim, J. G.; Walsh, P. J. Highly Concentrated Catalytic Asymmetric Allylation of Ketones. *Org Lett* **2007**, *9* (3), 381–384. https://doi.org/10.1021/ol062264h.

(63) Kim, J. G.; Waltz, K. M.; Garcia, I. F.; Kwiatkowski, D.; Walsh, P. J. Catalytic Asymmetric Allylation of Ketones and a Tandem Asymmetric Allylation/Diastereoselective Epoxidation of Cyclic Enones. *J Am Chem Soc* **2004**, *126* (39), 12580–12585. https://doi.org/10.1021/ja047758t.

(64) Teo, Y. C.; Goh, J. D.; Loh, T. P. Catalytic Enantioselective Allylation of Ketones via a Chiral Indium(III) Complex. *Org Lett* **2005**, *7* (13), 2743–2745. https://doi.org/10.1021/ol051018n.

(65) Zhang, X.; Chen, D.; Liu, X.; Feng, X. Enantioselective Allylation of Ketones Catalyzed by N,N'-Dioxide and Indium(III) Complex. *Journal of Organic Chemistry* **2007**, *72* (14), 5227–5233. https://doi.org/10.1021/jo0706325.

(66) Denmark, S. E.; Fu, J. Understanding the Correlation of Structure and Selectivity in the Chiral-Phosphoramide-Catalyzed Enantioselective Allylation Reactions: Solution and Solid-State Structural Studies of Bisphosphoramide·SnCl4 Complexes. *J Am Chem Soc* **2003**, *125* (8), 2208–2216. https://doi.org/10.1021/ja021280g.

(67) Hanhan, N. V.; Tang, Y. C.; Tran, N. T.; Franz, A. K. Scandium(III)-Catalyzed Enantioselective Allylation of Isatins Using Allylsilanes. *Org Lett* **2012**, *14* (9), 2218–2221. https://doi.org/10.1021/ol300496v.

(68) Ng, S. S.; Jamison, T. F. Highly Enantioselective and Regioselective Nickel-Catalyzed Coupling of Allenes, Aldehydes, and Silanes. *J Am Chem Soc* **2005**, *127* (20), 7320–7321. https://doi.org/10.1021/ja0521831.

(69) Liang, T.; Nguyen, K. D.; Zhang, W.; Krische, M. J. Enantioselective Ruthenium-Catalyzed Carbonyl Allylation via Alkyne-Alcohol C-C Bond-Forming Transfer Hydrogenation: Allene Hydrometalation vs Oxidative Coupling. *J Am Chem Soc* **2015**, *137* (9), 3161–3164. https://doi.org/10.1021/jacs.5b00747.

(70) McInturff, E. L.; Yamaguchi, E.; Krische, M. J. Chiral-Anion-Dependent Inversion of Diastereo- and Enantioselectivity in Carbonyl Crotylation via Ruthenium-Catalyzed Butadiene Hydrohydroxyalkylation. *J Am Chem Soc* **2012**, *134* (51), 20628–20631. https://doi.org/10.1021/ja311208a.

(71) Grayson, M. N.; Krische, M. J.; Houk, K. N. Ruthenium-Catalyzed Asymmetric Hydrohydroxyalkylation of Butadiene: The Role of the Formyl Hydrogen Bond in Stereochemical Control. *J Am Chem Soc* **2015**, *137* (27), 8838–8850. https://doi.org/10.1021/jacs.5b04844.

(72) Nguyen, K. D.; Herkommer, D.; Krische, M. J. Ruthenium-BINAP Catalyzed Alcohol C-H Tert-Prenylation via 1,3-Enyne Transfer Hydrogenation: Beyond Stoichiometric Carbanions in Enantioselective Carbonyl Propargylation. *J Am Chem Soc* **2016**, *138* (16), 5238–5241. https://doi.org/10.1021/jacs.6b02279.

(73) Zhang, W.; Chen, W.; Xiao, H.; Krische, M. J. Carbonyl Anti-(α-Amino)Allylation via Ruthenium Catalyzed Hydrogen Autotransfer: Use of an Acetylenic Pyrrole as an Allylmetal Pronucleophile. *Org Lett* **2017**, *19* (18), 4876–4879. https://doi.org/10.1021/acs.orglett.7b02336.

(74) Schwartz, L. A.; Holmes, M.; Brito, G. A.; Gonçalves, T. P.; Richardson, J.; Ruble, J. C.; Huang, K. W.; Krische, M. J. Cyclometalated Iridium-PhanePhos Complexes Are Active Catalysts in Enantioselective Allene-Fluoral Reductive Coupling and Related Alcohol-Mediated Carbonyl Additions That Form Acyclic Quaternary Carbon Stereocenters. *J Am Chem Soc* **2019**, *141* (5), 2087–2096. https://doi.org/10.1021/jacs.8b11868.

(75) Skucas, E.; Bower, J. F.; Krische, M. J. Carbonyl Allylation in the Absence of Preformed Allyl Metal Reagents: Reverse Prenylation via Iridium-Catalyzed Hydrogenative Coupling of Dimethylallene. *J Am Chem Soc* **2007**, *129* (42), 12678–12679. https://doi.org/10.1021/ja075971u.

(76) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. Catalytic C-C Coupling via Transfer Hydrogenation: Reverse Prenylation, Crotylation, and Allylation from the Alcohol or Aldehyde Oxidation Level. *J Am Chem Soc* **2007**, *129* (49), 15134–15135. https://doi.org/10.1021/ja077389b.

(77) Ngai, M. Y.; Skucas, E.; Krische, M. J. Ruthenium Catalyzed C-C Bond Formation via Transfer Hydrogenation: Branch-Selective Reductive Coupling of Allenes to Paraformaldehyde and Higher Aldehydes. *Org Lett* **2008**, *10* (13), 2705–2708. https://doi.org/10.1021/ol800836v.

(78) *Metal Prices Retrieved from:* www.dailymetalprice.com (accessed 2023-04-09).

(79) Takao Yoshida, B.; Negishi, E. A Novel Copper-Containing Hydride Species and Its Application to the Reduction of Organic Substances. *J Chem Soc Chem Commun* **1974**, *2* (18), 762–763.

(80) Deutsch, C.; Krause, N.; Lipshutz, B. H. CuH-Catalyzed Reactions. *Chem Rev* **2008**, *108* (8), 2916–2927. https://doi.org/10.1021/cr0684321.

(81) Liu, R. Y.; Yang, Y.; Buchwald, S. L. Regiodivergent and Diastereoselective CuH-Catalyzed Allylation of Imines with Terminal Allenes. *Angewandte Chemie* **2016**, *128* (45), 14283–14286. https://doi.org/10.1002/ange.201608446.

(82) Agrawal, T.; Martin, R. T.; Collins, S.; Wilhelm, Z.; Edwards, M. D.; Gutierrez, O.; Sieber, J. D. Access to Chiral Diamine Derivatives through Stereoselective Cu-Catalyzed Reductive Coupling of Imines and Allenamides. *Journal of Organic Chemistry* **2021**, *86* (7), 5026–5046. https://doi.org/10.1021/acs.joc.0c02971.

(83) Maas, W.; Janssen, M. J.; Stamhuis, E. J.; Wynberg, H. Mechanism of Enamine Reactions. IV. The Hydrolysis of Tertiary Enamines in Acidic Medium. *Journal of Organic Chemistry* **1967**, *32* (4), 1111–1115. https://doi.org/10.1021/JO01279A056/ASSET/JO01279A056.FP.PNG_V03.

(84) MacAbeo, A. P. G.; Lehmann, C. W.; Reiser, O. Diastereoselective Synthesis of Enantiopure γ-Butenolide- Butyrolactones towards Pseudopterogorgia Lactone Furanocembranoid Substructures. *Synlett* **2012**, *23* (20), 2909–2912. https://doi.org/10.1055/S-0032-1317555/ID/JR000-5003.

(85) Murphy, S. K.; Dong, V. M. Enantioselective Ketone Hydroacylation Using Noyori's Transfer Hydrogenation Catalyst. *J Am Chem Soc* **2013**, *135* (15), 5553–5556. https://doi.org/10.1021/ja4021974.

(86) Spielmann, K.; Xiang, M.; Schwartz, L. A.; Krische, M. J. Direct Conversion of Primary Alcohols to 1,2-Amino Alcohols: Enantioselective Iridium-Catalyzed Carbonyl Reductive Coupling of Phthalimido-Allene via Hydrogen Auto-Transfer. *J Am Chem Soc* **2019**, *141* (36), 14136–14141. https://doi.org/10.1021/jacs.9b08715.

(87) Evans, D. A.; Bartroli, J.; Shih, T. L. Enantioselective Aldol Condensations. 2. Erythro-Selective Chiral Aldol Condensations via Boron Enolates. *J Am Chem Soc* **1981**, *103* (8), 2127–2129.

(88) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. Eficient Preparations of Novel Ynamides and Allenamides. *Tetrahedron* **2001**, *57*, 459–466.

(89) Takimoto, M.; Gholap, S. S.; Hou, Z. Alkylative Carboxylation of Ynamides and Allenamides with Functionalized Alkylzinc Halides and Carbon Dioxide by a Copper Catalyst. *Chemistry - A European Journal* **2019**, *25* (35), 8363–8370. https://doi.org/10.1002/chem.201901153.

(90) Gholap, S. S.; Takimoto, M.; Hou, Z. Regioselective Alkylative Carboxylation of Allenamides with Carbon Dioxide and Dialkylzinc Reagents Catalyzed by an N-Heterocyclic Carbene–Copper Complex. *Chemistry - A European Journal* **2016**, *22* (25), 8547–8552. https://doi.org/10.1002/chem.201601162.

(91) Tolman, C. A. Steric Effects of Phosphorus Ligands in Organometallic Chemistry and Homogeneous Catalysis. *Chem Rev* **1977**, *77* (3), 313–348.

(92) Dorta, R.; Scott, N. M.; Costabile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. Steric and Electronic Properties of N-Heterocyclic Carbenes (NHC): A Detailed Study on Their Interaction with Ni(CO)4. *J Am Chem Soc* **2005**, *127* (8), 2485–2495. https://doi.org/10.1021/ja0438821.

(93) Klake, R. K.; Gargaro, S. L.; Gentry, S. L.; Elele, S. O.; Sieber, J. D. Development of a Strategy for Linear-Selective Cu-Catalyzed Reductive Coupling of Ketones and Allenes for the Synthesis of Chiral γ-Hydroxyaldehyde Equivalents. *Org Lett* **2019**, *21* (19), 7992–7998. https://doi.org/10.1021/acs.orglett.9b02973.

(94) Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H. The Bite Angle Makes the Catalyst*. *Pure and Applied Chemistry* **1999**, *71* (8), 1443–1452.

(95) Van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. Ligand Bite Angle Effects in Metal-Catalyzed C-C Bond Formation. *Chem Rev* **2000**, *100* (8), 2741–2769. https://doi.org/10.1021/cr9902704.

(96) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. Chiral Enolate Design. *Pure & Applied Chemistry* **2009**, *53*, 1109–1127.

(97) Trost, B. M.; Xie, J.; Sieber, J. D. The Palladium Catalyzed Asymmetric Addition of Oxindoles and Allenes: An Atom-Economical Versatile Method for the Construction of Chiral Indole Alkaloids. *J Am Chem Soc* **2011**, *133* (50), 20611–20622. https://doi.org/10.1021/ja209244m.

(98) Seeman, J. I. Effect of Conformational Change on Reactivity in Organic Chemistry. Evaluations, Applications, and Extensions of Curtin-Hammet/Winstein-Holness Kinetics. *Chem Rev* **1983**, *83* (2), 83–134.

(99) Shinisha, C. B.; Sunoj, R. B. Transition State Models for Probing Stereoinduction in Evans Chiral Auxiliary-Based Asymmetric Aldol Reactions. *J Am Chem Soc* **2010**, *132* (35), 12319–12330. https://doi.org/10.1021/ja101913k.

(100) Evans, D. A.; Nelson, J. V.; Taber, T. R. Stereoselective Aldol Condensations. In *Topics in Stereochemistry*; 2007; Vol. 13, pp 1–115. https://doi.org/10.1002/9780470147221.ch1.

(101) Bousfield, T. W.; Kimber, M. C. A Simple One-Pot Preparation of N-Allenyl Amides, Ureas, Carbamates and Sulfonamides Using a DMSO/TBuOK Protocol. *Tetrahedron Lett* **2015**, *56* (2), 350–352. https://doi.org/10.1016/J.TETLET.2014.11.093.

(102) Dinev, Z.; Gannon, C. T.; Egan, C.; Watt, J. A.; McConville, M. J.; Williams, S. J. Galactose-Derived Phosphonate Analogues as Potential Inhibitors of Phosphatidylinositol Biosynthesis in Mycobacteria. *Org Biomol Chem* **2007**, *5* (6), 952–959. https://doi.org/10.1039/B616450A.

(103) Monasterolo, C.; Müller-Bunz, H.; Gilheany, D. G. Very Short Highly Enantioselective Grignard Synthesis of 2,2-Disubstituted Tetrahydrofurans and Tetrahydropyrans. *Chem Sci* **2019**, *10* (26), 6531–6538. https://doi.org/10.1039/C9SC00978G.

(104) Gargaro, S. L.; Klake, R. K.; Burns, K. L.; Elele, S. O.; Gentry, S. L.; Sieber, J. D. Access to a Catalytically Generated Umpolung Reagent through the Use of Cu-Catalyzed Reductive Coupling of Ketones and Allenes for the Synthesis of Chiral Vicinal Aminoalcohol Synthons. *Org Lett* **2019**, *21* (23), 9753–9758. https://doi.org/10.1021/ACS.ORGLETT.9B03937/ASSET/IMAGES/LARGE/OL9B03937_0005.JPEG.

(105) Ho, D. B.; Gargaro, S.; Klake, R. K.; Sieber, J. D. Development of a Modified System to Provide Improved Diastereocontrol in the Linear-Selective Cu-Catalyzed Reductive Coupling of Ketones and Allenamides. *Journal of Organic Chemistry* **2022**, *87* (4), 2142–2153. https://doi.org/10.1021/ACS.JOC.1C02062/SUPPL_FILE/JO1C02062_SI_001.PDF.

(106) Hintermann, T.; Seebach, D. A Useful Modification of the Evans Auxiliary: 4-Isopropyl-5,5-Diphenyloxazolidin-2-One. https://doi.org/10.1002/(SICI)1522-2675(19981111)81:11.

(107) Song, J. J.; Frutos, R. P.; Tampone, T.; Senanayake, C. H.; Krishnamurthy, D. 9.3 Industrial Applications of Asymmetric Synthesis: Asymmetric Synthesis as an Enabler of Green Chemistry. *Comprehensive Chirality* **2012**, *9*, 46–72. https://doi.org/10.1016/B978-0-08-095167-6.00903-4.

(108) Klake, R. K.; Edwards, M. D.; Sieber, J. D. Synthesis of 1,2-Aminoalcohols through Enantioselective Aminoallylation of Ketones by Cu-Catalyzed Reductive Coupling. *Org Lett* **2021**, *23* (16), 6444–6449. https://doi.org/10.1021/ACS.ORGLETT.1C02258/ASSET/IMAGES/LARGE/OL1C02258_0004.JPEG.

(109) Spielmann, K.; Xiang, M.; Schwartz, L. A.; Krische, M. J. Direct Conversion of Primary Alcohols to 1,2-Amino Alcohols: Enantioselective Iridium-Catalyzed Carbonyl Reductive Coupling of Phthalimido-Allene via Hydrogen Auto-Transfer. *J Am Chem Soc* **2019**, *141* (36), 14136–14141. https://doi.org/10.1021/jacs.9b08715.

(110) Klake, R. K.; Collins, S.; Sieber, J. D. A Unified Approach to the Aminoallylation of Carbonyl Compounds Through Cu-Catalyzed Enantioselective Reductive Coupling of Allenamides. **2022**. https://doi.org/10.26434/CHEMRXIV-2022-94PG8.

(111) Gargaro, S. L.; Sieber, J. D.; Gargaro, S. L.; Sieber, J. D. Asymmetric Access to Boryl-Substituted Vicinal Aminoalcohols through Cu-Catalyzed Reductive Coupling. **2022**. https://doi.org/10.26434/CHEMRXIV-2022-LMKP8.

(112) Collins, S.; Sieber, J. D. Studies Toward Improved Enantiocontrol in the Asymmetric Cu-Catalyzed Reductive Coupling of Ketones and Allenamides: 1,2-Aminoalcohol Synthesis. *Org Lett* **2023**, *25* (9), 1425–1430. https://doi.org/10.1021/ACS.ORGLETT.3C00157/ASSET/IMAGES/LARGE/OL3C00157_0004.JPEG.

(113) Agrawal, T.; Perez-Morales, K. D.; Cort, J. A.; Sieber, J. D. Asymmetric Synthesis of Propargylic α-Stereogenic Tertiary Amines by Reductive Alkynylation of Tertiary Amides Using Ir/Cu Tandem Catalysis. *Journal of Organic Chemistry* **2022**, *87* (9), 6387–6392. https://doi.org/10.1021/ACS.JOC.2C00131/SUPPL_FILE/JO2C00131_SI_001.PDF.

(114) Gnas, Y.; Glorius, F. Chiral Auxiliaries - Principles and Recent Applications. *Synthesis (Stuttg)* **2006**, No. 12, 1899–1930. https://doi.org/10.1055/S-2006-942399.

(115) Roos, G. Key Chiral Auxiliary Applications. *Key Chiral Auxiliary Applications: Second Edition* **2014**, 1–1244. https://doi.org/10.1016/C2011-1-05800-9.

(116) Heravi, M. M.; Zadsirjan, V. Oxazolidinones as Chiral Auxiliaries in Asymmetric Aldol Reactions Applied to Total Synthesis. *Tetrahedron Asymmetry* **2013**, *24* (19), 1149–1188. https://doi.org/10.1016/J.TETASY.2013.08.011.

(117) Hermann, C.; Pais, G. C. G.; Geyer, A.; Kühnert, S. M.; Maier, M. E. Total Synthesis of Hapalosin and Two Ring Expanded Analogs. *Tetrahedron* **2000**, *56* (43), 8461–8471. https://doi.org/10.1016/S0040-4020(00)00772-9.

(118) Mutou, T.; Kondo, T.; Shibata, T.; Ojika, M.; Kigoshi, H.; Yamada, K. Synthesis of Dolastatin G and Nordolastatin G, Cytotoxic 35-Membered Cyclodepsipeptides of Marine Origin. *Tetrahedron Lett* **1996**, *37* (40), 7299–7302. https://doi.org/10.1016/0040-4039(96)01653-X.

(119) Robichaud, A. J.; Berger, G. D.; Evans, D. A. The Asymmetric Syntheses of the C-1 Sidechains of Zaragozic Acid A and Zaragozic Acid C. *Tetrahedron Lett* **1993**, *34* (52), 8403–8406. https://doi.org/10.1016/S0040-4039(00)61344-8.

(120) Armstrong, A.; Barsanti, P. A.; Blench, T. J.; Ogilvie, R. Synthesis of the C1-Side Chain of Zaragozic Acid D and Progress towards a Total Synthesis. *Tetrahedron* **2003**, *59* (3), 367–375. https://doi.org/10.1016/S0040-4020(02)01514-4.

(121) Chen, C.; Crich, D. The Cyclization Route to the Calcitriol A-Ring: A Formal Synthesis of (+)-1α,25-Dihydroxyvitamin D3. *Tetrahedron* **1993**, *49* (36), 7943–7954. https://doi.org/10.1016/S0040-4020(01)88018-2.

(122) Evans, D. A.; Bender, S. L. Total Synthesis of the Ionophore Antibiotic X-206. Studies Relevant to the Stereoselective Synthesis of the C(17)–C(26) Synthon. *Tetrahedron Lett* **1986**, *27* (7), 799–802. https://doi.org/10.1016/S0040-4039(00)84104-0.

(123) Jacobsen, E.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis: Supplement 1*; Springer, 2003.

(124) Heitbaum, M.; Glorius, F.; Escher, I. Asymmetric Heterogeneous Catalysis. *Angewandte Chemie International Edition* **2006**, *45* (29), 4732–4762. https://doi.org/10.1002/ANIE.200504212.

(125) Li, K.; Shao, X.; Tseng, L.; Malcolmson, S. J. 2-Azadienes as Reagents for Preparing Chiral Amines: Synthesis of 1,2-Amino Tertiary Alcohols by Cu-Catalyzed Enantioselective Reductive Couplings with Ketones. *J Am Chem Soc* **2018**, *140* (2), 598–601. https://doi.org/10.1021/jacs.7b12213.

(126) Nogi, K.; Yorimitsu, H. Carbon-Carbon Bond Cleavage at Allylic Positions: Retro-Allylation and Deallylation. *Chem Rev* **2021**, *121* (1), 345–364. https://doi.org/10.1021/ACS.CHEMREV.0C00157/ASSET/IMAGES/MEDIUM/CR0C00157_0030.GIF.

(127) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. CXIX.—The Formation and Stability of Spiro-Compounds. Part I. Spiro-Compounds from Cyclohexane. *Journal of the Chemical Society, Transactions* **1915**, *107* (0), 1080–1106. https://doi.org/10.1039/CT9150701080.

(128) Shaw, B. L. Formation of Large Rings, Internal Metalation Reactions, and Internal Entropy Effects. *J Am Chem Soc* **1975**, *97* (13), 3856–3857. https://doi.org/10.1021/JA00846A072/ASSET/JA00846A072.FP.PNG_V03.

(129) Maddox, A. F.; Rheingold, A. L.; Golen, J. A.; Scott Kassel, W.; Nataro, C. Taniaphos and Walphos Ligands: Oxidative Electrochemistry and Complexation. Synthesis, Characterization, Oxidative Electrochemistry and X-Ray Structures of [(Taniaphos/Walphos)MCl2] (M = Pd or Pt). *Inorganica Chim Acta* **2008**, *361* (11), 3283–3293. https://doi.org/10.1016/J.ICA.2007.09.031.

(130) Phukan, P.; Bauer, M.; Maier, M. E. Facile Generation of Alkenes and Dienes from Tosylates. *Synthesis (Stuttg)* **2003**, *2003* (09), 1324–1328. https://doi.org/10.1055/S-2003-40210.

(131) Lipshutz, B. H.; Chrisman, W.; Noson, K. Hydrosilylation of Aldehydes and Ketones Catalyzed by [Ph3P(CuH)]6. *J Organomet Chem* **2001**, *624* (1–2), 367–371. https://doi.org/10.1016/S0022-328X(00)00903-7.

(132) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books, 2006.

(133) Lindström, U. M.; Somfai, P. Aminolysis of Vinyl Epoxides as an Efficient Entry to N-H Vinylaziridines. *Synthesis (Stuttg)* **1998**, *1998* (01), 109–117. https://doi.org/10.1055/S-1998-2004.

(134) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. Diastereoconversion of Threo 2-Amino Alcohols to Erythro Isomers through a New Cyclocarbamation. *Heterocycles* **1988**, *27* (5), 1241–1248. https://doi.org/10.3987/COM-88-4501.

(135) Scott, L. J. Eliglustat: A Review in Gaucher Disease Type 1. *Drugs* **2015**, *75* (14), 1669–1678. https://doi.org/10.1007/S40265-015-0468-9/TABLES/3.

(136) Yung-Son, H.; Ling, L. The Reactions of the Ozonides with Secondary Amines: An Efficient and Novel Way to Prepare Tertiary Amine from Mono- and 1,1-Di-Substituted Alkenes via Corresponding Ozonides. *Tetrahedron Lett* **1993**, *34* (33), 5309–5312. https://doi.org/10.1016/S0040-4039(00)73982-7.

(137) Li, X.; Li, L.; Tang, Y.; Zhong, L.; Cun, L.; Zhu, J.; Liao, J.; Deng, J. Chemoselective Conjugate Reduction of α,β-Unsaturated Ketones Catalyzed by Rhodium Amido Complexes in Aqueous Media. *Journal of Organic Chemistry* **2010**, *75* (9), 2981–2988. https://doi.org/10.1021/JO100256T/SUPPL_FILE/JO100256T_SI_001.PDF.

(138) Baran, P. S.; Corey, E. J. A Short Synthetic Route to (+)-Austamide, (+)-Deoxyisoaustamide, and (+)-Hydratoaustamide from a Common Precursor by a Novel Palladium-Mediated

Indole→dihydroindoloazocine Cyclization. *J Am Chem Soc* **2002**, *124* (27), 7904–7905. https://doi.org/10.1021/JA026663T/SUPPL_FILE/JA026663T_S2.CIF.

(139) Büchi, G.; Rodriguez, A. D.; Yakushijin, K. Syntheses of (±)-Alchorneine and (±)-Isoalchorneine. *Journal of Organic Chemistry* **1989**, *54* (19), 4494–4496. https://doi.org/10.1021/JO00280A009/SUPPL_FILE/JO00280A009_SI_001.PDF.

(140) James Willmore, L.; Abelson, M. B.; Ben-Menachem, E.; Pellock, J. M.; Donald Shields, W. Vigabatrin: 2008 Update. *Epilepsia* **2009**, *50* (2), 163–173. https://doi.org/10.1111/J.1528-1167.2008.01988.X.

(141) Farrokhnia, M.; Mahnam, K. Molecular Dynamics and Docking Investigations of Several Zoanthamine-Type Marine Alkaloids as Matrix Metaloproteinase-1 Inhibitors. *Iran J Pharm Res* **2017**, *16* (1), 173.

(142) Kinoshita, A.; Higashino, M.; Yoshida, K.; Aratani, Y.; Kakuuchi, A.; Hanada, K.; Takeda, H.; Naganawa, A.; Matsuya, H.; Ohmoto, K. Synthesis and Evaluation of a Potent, Well-Balanced EP2/EP3 Dual Agonist. *Bioorg Med Chem* **2018**, *26* (1), 200–214. https://doi.org/10.1016/J.BMC.2017.11.035.

(143) Buntasana, S.; Seankongsuk, P.; Vilaivan, T.; Padungros, P. Household Ozone Disinfector as An Alternative Ozone Generator for Ozonolysis of Alkenes. *Asian J Org Chem* **2021**, *10* (5), 1141–1152. https://doi.org/10.1002/AJOC.202100024.

(144) Caron, S. Honoring 25 Years of the Buchwald–Hartwig Amination. *Org Process Res Dev* **2019**, *23* (8), 1477. https://doi.org/10.1021/ACS.OPRD.9B00177.

(145) Dorel, R.; Grugel, C. P.; Haydl, A. M. The Buchwald–Hartwig Amination After 25 Years. *Angewandte Chemie International Edition* **2019**, *58* (48), 17118–17129. https://doi.org/10.1002/ANIE.201904795.

(146) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C-N Cross-Coupling Reactions. *Chem Rev* **2016**, *116* (19), 12564–12649. https://doi.org/10.1021/ACS.CHEMREV.6B00512/ASSET/IMAGES/LARGE/CR-2016-00512W_0046.JPEG.

(147) Ansari, T. N.; Taussat, A.; Clark, A. H.; Nachtegaal, M.; Plummer, S.; Gallou, F.; Handa, S. Insights on Bimetallic Micellar Nanocatalysis for Buchwald-Hartwig Aminations. *ACS Catal* **2019**, *9* (11), 10389–10397. https://doi.org/10.1021/ACSCATAL.9B02622/ASSET/IMAGES/LARGE/CS9B02622_0010.JPEG.

(148) Cole-Hamilton, D. J. Homogeneous Catalysis - New Approaches to Catalyst Separation, Recovery, and Recycling. *Science (1979)* **2003**, *299* (5613), 1702–1706. https://doi.org/10.1126/SCIENCE.1081881.

(149) Norouzi, N.; Das, M. K.; Richard, A. J.; Ibrahim, A. A.; El-Kaderi, H. M.; El-Shall, M. S. Heterogeneous Catalysis by Ultra-Small Bimetallic Nanoparticles Surpassing Homogeneous Catalysis for Carbon–Carbon Bond Forming Reactions. *Nanoscale* **2020**, *12* (37), 19191–19202. https://doi.org/10.1039/D0NR04105J.

(150) Jiao, L.; Regalbuto, J. R. The Synthesis of Highly Dispersed Noble and Base Metals on Silica via Strong Electrostatic Adsorption: I. Amorphous Silica. *J Catal* **2008**, *260* (2), 329–341. https://doi.org/10.1016/J.JCAT.2008.09.022.

(151) Jiao, L.; Regalbuto, J. R. The Synthesis of Highly Dispersed Noble and Base Metals on Silica via Strong Electrostatic Adsorption: II. Mesoporous Silica SBA-15. *J Catal* **2008**, *260* (2), 342–350. https://doi.org/10.1016/J.JCAT.2008.09.023.

(152) Vert, M.; Doi, Y.; Hellwich, K. H.; Hess, M.; Hodge, P.; Kubisa, P.; Rinaudo, M.; Schué, F. Terminology for Biorelated Polymers and Applications (IUPAC Recommendations 2012). *Pure and Applied Chemistry* **2012**, *84* (2), 377–410. https://doi.org/10.1351/PAC-REC-10-12-04/MACHINEREADABLECITATION/RIS.

(153) Farnetti, E.; Monte, R.; Kašpar, J. Encyclopedia of Life Support Systems ( EOLSS ) HOMOGENEOUS AND HETEROGENEOUS CATALYSIS.

(154) Heshmatpour, F.; Abazari, R. Formation of Dispersed Palladium–Nickel Bimetallic Nanoparticles in Microemulsions: Synthesis, Characterization, and Their Use as Efficient Heterogeneous Recyclable Catalysts for the Amination Reactions of Aryl Chlorides under Mild Conditions. *RSC Adv* **2014**, *4* (99), 55815–55826. https://doi.org/10.1039/C4RA06958G.

(155) Al-Amin, M.; Honma, T.; Hoshiya, N.; Shuto, S.; Arisawa, M. Ligand-Free Buchwald–Hartwig Aromatic Aminations of Aryl Halides Catalyzed by Low-Leaching and Highly Recyclable Sulfur-Modified Gold-Supported Palladium Material. *Adv Synth Catal* **2012**, *354* (6), 1061–1068. https://doi.org/10.1002/ADSC.201100761.

(156) Chen, Z.; Wang, S.; Lian, C.; Liu, Y.; Wang, D.; Chen, C.; Peng, Q.; Li, Y. Nano PdAu Bimetallic Alloy as an Effective Catalyst for the Buchwald–Hartwig Reaction. *Chem Asian J* **2016**, *11* (3), 351–355. https://doi.org/10.1002/ASIA.201500531.

(157) Talapin, D. V.; Shevchenko, E. V. Introduction: Nanoparticle Chemistry. *Chem Rev* **2016**, *116* (18), 10343–10345. https://doi.org/10.1021/ACS.CHEMREV.6B00566/ASSET/IMAGES/LARGE/CR-2016-00566V_0002.JPEG.

(158) Hong, H.; Hu, L.; Li, M.; Zheng, J.; Sun, X.; Lu, X.; Cao, X.; Lu, J.; Gu, H. Preparation of Pt@Fe2O3 Nanowires and Their Catalysis of Selective Oxidation of Olefins and Alcohols. *Chemistry – A European Journal* **2011**, *17* (31), 8726–8730. https://doi.org/10.1002/CHEM.201003429.

(159) Choi, J. H.; Jeong, K. J.; Dong, Y.; Han, J.; Lim, T. H.; Lee, J. S.; Sung, Y. E. Electro-Oxidation of Methanol and Formic Acid on PtRu and PtAu for Direct Liquid Fuel Cells. *J Power Sources* **2006**, *163* (1), 71–75. https://doi.org/10.1016/J.JPOWSOUR.2006.02.072.

(160) Shen, Y.; Xiao, K.; Xi, J.; Qiu, X. Comparison Study of Few-Layered Graphene Supported Platinum and Platinum Alloys for Methanol and Ethanol Electro-Oxidation. *J Power Sources* **2015**, *278*, 235–244. https://doi.org/10.1016/J.JPOWSOUR.2014.12.062.

(161) Zhou, J.; Hua, Z.; Cui, X.; Ye, Z.; Cui, F.; Shi, J. Hierarchical Mesoporous TS-1 Zeolite: A Highly Active and Extraordinarily Stable Catalyst for the Selective Oxidation of 2,3,6-Trimethylphenol. *Chemical Communications* **2010**, *46* (27), 4994–4996. https://doi.org/10.1039/C0CC00499E.

(162) Barman, B. K.; Nanda, K. K. Rapid Reduction of GO by Hydrogen Spill-over Mechanism by in Situ Generated Nanoparticles at Room Temperature and Their Catalytic Performance towards 4-Nitrophenol Reduction and Ethanol Oxidation. *Appl Catal A Gen* **2015**, *491*, 45–51. https://doi.org/10.1016/J.APCATA.2014.11.017.

(163) Li, C. H.; Yu, Z. X.; Yao, K. F.; Ji, S. F.; Liang, J. Nitrobenzene Hydrogenation with Carbon Nanotube-Supported Platinum Catalyst under Mild Conditions. *J Mol Catal A Chem* **2005**, *226* (1), 101–105. https://doi.org/10.1016/J.MOLCATA.2004.09.046.

(164) Wang, J.; Ge, D.; Cao, X.; Tang, M.; Pan, Y.; Gu, H. A Facile Synthesis of Pt@Ir Zigzag Bimetallic Nanocomplexes for Hydrogenation Reactions. *Chemical Communications* **2015**, *51* (44), 9216–9219. https://doi.org/10.1039/C5CC02905H.

(165) Han, R.; Nan, C.; Yang, L.; Fan, G.; Li, F. Direct Synthesis of Hybrid Layered Double Hydroxide–Carbon Composites Supported Pd Nanocatalysts Efficient in Selective Hydrogenation of Citral. *RSC Adv* **2015**, *5* (42), 33199–33207. https://doi.org/10.1039/C5RA03201F.

(166) Li, M.; Hu, L.; Cao, X.; Hong, H.; Lu, J.; Gu, H. Direct Hydrogenation of Nitroaromatics and One-Pot Amidation with Carboxylic Acids over Platinum Nanowires. *Chemistry – A European Journal* **2011**, *17* (9), 2763–2768. https://doi.org/10.1002/CHEM.201002801.

(167) Wang, X.; Wang, J.; Qi, F.; Hu, L.; Li, X.; Cao, X.; Gu, H. Synthesis of In-Situ Surfactant-Free Pd Nanoparticle Catalysts for the Synthesis of Aromatic Azo Compounds and for Unsaturated Bond Hydrogenation by Hydrogen Transfer. *Chinese Journal of Catalysis* **2013**, *34* (11), 2084–2088. https://doi.org/10.1016/S1872-2067(12)60665-2.

(168) Zhang, S.; Li, J.; Gao, W.; Qu, Y. Insights into the Effects of Surface Properties of Oxides on the Catalytic Activity of Pd for C–C Coupling Reactions. *Nanoscale* **2015**, *7* (7), 3016–3021. https://doi.org/10.1039/C4NR06482H.

(169) Hu, L.; Cao, X.; Ge, D.; Hong, H.; Guo, Z.; Chen, L.; Sun, X.; Tang, J.; Zheng, J.; Lu, J.; Gu, H. Ultrathin Platinum Nanowire Catalysts for Direct C-N Coupling of Carbonyls with Aromatic Nitro Compounds under 1 Bar of Hydrogen. *Chemistry – A European Journal* **2011**, *17* (50), 14283–14287. https://doi.org/10.1002/CHEM.201100818.

(170) Rout, L.; Sen, T. K.; Punniyamurthy, T. Efficient CuO-Nanoparticle-Catalyzed C-S Cross-Coupling of Thiols with Iodobenzene. *Angewandte Chemie International Edition* **2007**, *46* (29), 5583–5586. https://doi.org/10.1002/ANIE.200701282.

(171) Hun, X.; Xie, G.; Luo, X. Scaling up an Electrochemical Signal with a Catalytic Hairpin Assembly Coupling Nanocatalyst Label for DNA Detection. *Chemical Communications* **2015**, *51* (33), 7100–7103. https://doi.org/10.1039/C5CC00680E.

(172) Li, B.; Weng, W. Z.; Zhang, Q.; Wang, Z. W.; Wan, H. L. Sinter-Resistant Pd/SiO2 Nanocatalyst Prepared by Impregnation Method. *ChemCatChem* **2011**, *3* (8), 1277–1280. https://doi.org/10.1002/CCTC.201100043.

(173) Itahara, H.; Takatani, Y.; Takahashi, N.; Kosaka, S.; Nagoya, A.; Inaba, M.; Kamitaka, Y.; Morimoto, Y. Synthesis of Carbon-Supported Intermetallic Pt5Ce Compound Nanoparticles via a Water-Based

Impregnation Route. *Chemistry of Materials* **2022**, *34* (1), 422–429. https://doi.org/10.1021/ACS.CHEMMATER.1C03912/ASSET/IMAGES/LARGE/CM1C03912_0006.JPEG.

(174) Peternela, J.; Silva, M. F.; Vieira, M. F.; Bergamasco, R.; Vieira, A. M. S. Synthesis and Impregnation of Copper Oxide Nanoparticles on Activated Carbon through Green Synthesis for Water Pollutant Removal. *Materials Research* **2017**, *21* (1), e20160460. https://doi.org/10.1590/1980-5373-MR-2016-0460.

(175) Rahemi, N.; Haghighi, M.; Babaluo, A. A.; Jafari, M. F.; Estifaee, P. Synthesis and Physicochemical Characterizations of Ni/Al2O3–ZrO2 Nanocatalyst Prepared via Impregnation Method and Treated with Non-Thermal Plasma for CO2 Reforming of CH4. *Journal of Industrial and Engineering Chemistry* **2013**, *19* (5), 1566–1576. https://doi.org/10.1016/J.JIEC.2013.01.024.

(176) Sajjadi, S. M.; Haghighi, M.; Eslami, A. A.; Rahmani, F. Hydrogen Production via CO2-Reforming of Methane over Cu and Co Doped Ni/Al2O3 Nanocatalyst: Impregnation versus Sol-Gel Method and Effect of Process Conditions and Promoter. *J Solgel Sci Technol* **2013**, *67* (3), 601–617. https://doi.org/10.1007/S10971-013-3120-8/FIGURES/17.

(177) Wong, A.; Liu, Q.; Griffin, S.; Nicholls, A.; Regalbuto, J. R. Synthesis of Ultrasmall, Homogeneously Alloyed, Bimetallic Nanoparticles on Silica Supports. *Science (1979)* **2017**, *358* (6369), 1427–1430. https://doi.org/10.1126/SCIENCE.AAO6538/SUPPL_FILE/AAO6538_WONG_SM.PDF.

(178) Kosugi, M.; Kameyama, M.; Migita, T. Palladium-Catalyzed Aromatic Amination of Aryl Bromides With N,N-Di-Ethylamino-Tributyltin. *Chem Lett* **2006**, *12* (6), 927–928. https://doi.org/10.1246/CL.1983.927.

(179) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines. *Angewandte Chemie International Edition in English* **1995**, *34* (12), 1348–1350. https://doi.org/10.1002/ANIE.199513481.

(180) Louie, J.; Hartwig, J. F. Palladium-Catalyzed Synthesis of Arylamines from Aryl Halides. Mechanistic Studies Lead to Coupling in the Absence of Tin Reagents. *Tetrahedron Lett* **1995**, *36* (21), 3609–3612. https://doi.org/10.1016/0040-4039(95)00605-C.

(181) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. Palladium-Catalyzed Coupling of Optically Active Amines with Aryl Bromides. *J Am Chem Soc* **1997**, *119* (36), 8451–8458. https://doi.org/10.1021/JA971583O/ASSET/IMAGES/LARGE/JA971583OFA27F.JPEG.

(182) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. Simple, Efficient Catalyst System for the Palladium-Catalyzed Amination of Aryl Chlorides, Bromides, and Triflates. *Journal of Organic Chemistry* **2000**, *65* (4), 1158–1174. https://doi.org/10.1021/JO991699Y/SUPPL_FILE/JO991699Y_S.PDF.

(183) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. Expanding Pd-Catalyzed C-N Bond-Forming Processes: The First Amidation of Aryl Sulfonates, Aqueous Amination, and Complementarity with Cu-Catalyzed Reactions. *J Am Chem Soc* **2003**, *125* (22), 6653–6655. https://doi.org/10.1021/JA035483W/SUPPL_FILE/JA035483WSI20030428_090554.PDF.

(184) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. An Improved Catalyst System for Aromatic Carbon-Nitrogen Bond Formation: The Possible Involvement of Bis(Phosphine) Palladium Complexes as Key Intermediates. *J Am Chem Soc* **1996**, *118* (30), 7215–7216. https://doi.org/10.1021/JA9608306/SUPPL_FILE/JA7215.PDF.

(185) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. Monodentate Phosphines Provide Highly Active Catalysts for Pd-Catalyzed C-N Bond-Forming Reactions of Heteroaromatic Halides/Amines and (H)N-Heterocycles. *Angewandte Chemie International Edition* **2006**, *45* (39), 6523–6527. https://doi.org/10.1002/ANIE.200601612.

(186) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. Pd-Catalyzed Amidations of Aryl Chlorides Using Monodentate Biaryl Phosphine Ligands: A Kinetic, Computational, and Synthetic Investigation. *J Am Chem Soc* **2007**, *129* (43), 13001–13007. https://doi.org/10.1021/JA0717414/SUPPL_FILE/JA0717414SI20070312_053806.CIF.

(187) Widenhoefer, R. A.; Buchwald, S. L. Halide and Amine Influence in the Equilibrium Formation of Palladium Tris(o-Tolyl)Phosphine Mono(Amine) Complexes from Palladium Aryl Halide Dimers. *Organometallics* **1996**, *15* (12), 2755–2763. https://doi.org/10.1021/OM9509608/ASSET/IMAGES/LARGE/OM9509608F00002.JPEG.

(188) Surry, D. S.; Buchwald, S. L.; Buchwald, S. L.; Surry, D. S. Biaryl Phosphane Ligands in Palladium-Catalyzed Amination. *Angewandte Chemie International Edition* **2008**, *47* (34), 6338–6361. https://doi.org/10.1002/ANIE.200800497.

(189) Surry, D. S.; Buchwald, S. L. Dialkylbiaryl Phosphines in Pd-Catalyzed Amination: A User's Guide. *Chem Sci* **2010**, *2* (1), 27–50. https://doi.org/10.1039/C0SC00331J.

(190) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. Palladium-Catalyzed Amination of Aryl Triflates and Importance of Triflate Addition Rate. *Journal of Organic Chemistry* **1997**, *62* (5), 1268–1273. https://doi.org/10.1021/JO961930X/ASSET/IMAGES/MEDIUM/JO961930XU00002A.GIF.

(191) Louie, J.; Hartwig, J. F. Palladium-Catalyzed Synthesis of Arylamines from Aryl Halides. Mechanistic Studies Lead to Coupling in the Absence of Tin Reagents. *Tetrahedron Lett* **1995**, *36* (21), 3609–3612. https://doi.org/10.1016/0040-4039(95)00605-C.

(192) Driver, M. S.; Hartwig, J. F. A Rare, Low-Valent Alkylamido Complex, a Diphenylamido Complex, and Their Reductive Elimination of Amines by Three-Coordinate Intermediates. *J Am Chem Soc* **1995**, *117* (16), 4708–4709. https://doi.org/10.1021/JA00121A030/SUPPL_FILE/JA4708.PDF.

(193) Driver, M. S.; Hartwig, J. F. Carbon-Nitrogen-Bond-Forming Reductive Elimination of Arylamines from Palladium(II) Phosphine Complexes. *J Am Chem Soc* **1997**, *119* (35), 8232–8245. https://doi.org/10.1021/JA971057X/SUPPL_FILE/JA8232.PDF.

(194) Hamann, B. C.; Hartwig, J. F. Sterically Hindered Chelating Alkyl Phosphines Provide Large Rate Accelerations in Palladium-Catalyzed Amination of Aryl Iodides, Bromides, and Chlorides, and the First Amination of Aryl Tosylates. *J Am Chem Soc* **1998**, *120* (29), 7369–7370. https://doi.org/10.1021/JA981318I/SUPPL_FILE/JA7369.PDF.

(195) Paul, F.; Patt, J.; Hartwig, J. F. Palladium-Catalyzed Formation of Carbon-Nitrogen Bonds. Reaction Intermediates and Catalyst Improvements in the Hetero Cross-Coupling of Aryl Halides and Tin Amides. *J Am Chem Soc* **1994**, *116* (13), 5969–5970. https://doi.org/10.1021/JA00092A058/SUPPL_FILE/JA5969.PDF.

(196) Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. Influences on the Relative Rates for C-N Bond-Forming Reductive Elimination and β-Hydrogen Elimination of Amides. A Case Study on the Origins of Competing Reduction in the Palladium-Catalyzed Amination of Aryl Halides. *J Am Chem Soc* **1996**, *118* (15), 3626–3633. https://doi.org/10.1021/JA954121O/SUPPL_FILE/JA3626.PDF.

(197) Peacock, D. M.; Jiang, Q.; Hanley, P. S.; Cundari, T. R.; Hartwig, J. F. Reductive Elimination from Phosphine-Ligated Alkylpalladium(II) Amido Complexes to Form Sp3 Carbon-Nitrogen Bonds. *J Am Chem Soc* **2018**, *140* (14), 4893–4904. https://doi.org/10.1021/JACS.8B00928/SUPPL_FILE/JA8B00928_SI_004.CIF.

(198) Wang, D. Y.; Choliy, Y.; Haibach, M. C.; Hartwig, J. F.; Krogh-Jespersen, K.; Goldman, A. S. Assessment of the Electronic Factors Determining the Thermodynamics of "Oxidative Addition" of C-H and N-H Bonds to Ir(I) Complexes. *J Am Chem Soc* **2016**, *138* (1), 149–163. https://doi.org/10.1021/JACS.5B09522/SUPPL_FILE/JA5B09522_SI_002.PDF.

(199) Ozerov, O. V. Oxidative Addition of Water to Transition Metal Complexes. *Chem Soc Rev* **2008**, *38* (1), 83–88. https://doi.org/10.1039/B802420K.

(200) Rummelt, S. M.; Peterson, P. O.; Zhong, H.; Chirik, P. J. Oxidative Addition of Aryl and Alkyl Halides to a Reduced Iron Pincer Complex. *J Am Chem Soc* **2021**, *143* (15), 5928–5936. https://doi.org/10.1021/JACS.1C01486/ASSET/IMAGES/LARGE/JA1C01486_0012.JPEG.

(201) Amatore, C.; Pflüger, F. Mechanism of Oxidative Addition of Palladium(0) with Aromatic Iodides in Toluene, Monitored at Ultramicroelectrodes. *Organometallics* **1990**, *9* (8), 2276–2282. https://doi.org/10.1021/OM00158A026/ASSET/OM00158A026.FP.PNG_V03.

(202) Gruttadauria, M.; Giacalone, F.; Noto, R. "Release and Catch" Catalytic Systems. *Green Chemistry* **2013**, *15* (10), 2608–2618. https://doi.org/10.1039/C3GC41132J.

(203) Mishra, A. K.; Biswas, S. Brønsted Acid Catalyzed Functionalization of Aromatic Alcohols through Nucleophilic Substitution of Hydroxyl Group. *Journal of Organic Chemistry* **2016**, *81* (6), 2355–2363. https://doi.org/10.1021/ACS.JOC.5B02849/ASSET/IMAGES/LARGE/JO-2015-02849Q_0007.JPEG.

(204) Chen, S.; Wang, P.; Cheng, H. G.; Yang, C.; Zhou, Q. Redox-Neutral Ortho-C–H Amination of Pinacol Arylborates via Palladium(II)/Norbornene Catalysis for Aniline Synthesis. *Chem Sci* **2019**, *10* (36), 8384–8389. https://doi.org/10.1039/C9SC02759A.

(205) Zhu, C.; Kale, A. P.; Yue, H.; Rueping, M. Redox-Neutral Cross-Coupling Amination with Weak N-Nucleophiles: Arylation of Anilines, Sulfonamides, Sulfoximines, Carbamates, and Imines via Nickelaelectrocatalysis. *JACS Au* **2021**, *1* (7), 1057–1065. https://doi.org/10.1021/JACSAU.1C00148/ASSET/IMAGES/LARGE/AU1C00148_0004.JPEG.

(206) Tao, S. K.; Chen, S. Y.; Feng, M. L.; Xu, J. Q.; Yuan, M. L.; Fu, H. Y.; Li, R. X.; Chen, H.; Zheng, X. L.; Yu, X. Q. Electrochemical Cross-Dehydrogenative Aromatization Protocol for the Synthesis of Aromatic Amines. *Org Lett* **2022**, *24* (4), 1011–1016. https://doi.org/10.1021/ACS.ORGLETT.1C04129/ASSET/IMAGES/LARGE/OL1C04129_0004.JPEG.

# VITA

Raphael Kwaku Klake was born in March 1994 in Ho, Ghana. He graduated from Mawuli Senior High School in Ho, Ghana in 2013. He pursued an undergraduate degree in chemistry at the University of Ghana, where he conducted research under Prof. Augustine Donkor, focusing on characterizing greywater. Raphael was actively involved in the Ghana Students' Chemical Society and held positions as Vice President and later Electoral Commissioner.

In August 2018, Raphael joined Virginia Commonwealth University as a doctoral student in the Chemistry Department. He became one of the first graduate students of Dr. Joshua D. Sieber in the Sieber Research Group, along with Samantha Gargaro. During his time at VCU, Raphael served as Treasurer of the Chemistry Graduate Student Organization in 2021 and was later elected as President in 2022. He was awarded the Altria Fellowship for the academic year 2022-2023 and aspires to pursue a career in the pharmaceutical industry.

RAPHAEL K. KLAKE

## Education

**Ph.D. Organic Chemistry (2018 – 2023)**
**Virginia Commonwealth University – Richmond, VA**

- Advisor: Dr. Joshua D. Sieber
- Research Focus: Asymmetric Cu-Catalyzed Reductive Coupling of Allenes and Carbonyls and Heterogeneous development for the Buchwald-Hartwig Amination

**BSc. (Hons) Chemistry (2013 – 2017)**
**University of Ghana – Accra, Greater Accra Region, Ghana**

- Advisor: Dr. Augustine Donkor
- Research Focus: Assessment of Heavy Metal Content and Some Physical Parameters of Greywater

## Teaching Experience

***Teaching Assistant for the following courses at Virginia Commonwealth University***

- Organic Chemistry Laboratory I/II, Fall 2019, Spring and Fall 2020, Spring and Fall 2021, Spring 2022
- General Chem I/II Laboratory, Fall 2018, Spring 2019
- General Chem I/II, Fall 2018, Spring 2019, Fall 2021

## Work Experience

Graduate Research Assistant (Aug 2018 – May 2023); Virginia Commonwealth University – Richmond, VA
Inspections Officer (Jun 2017 – Jul 2018); National Petroleum Authority – Accra, Greater Accra Region, Ghana
Intern, Laboratory Assistant (Jun 2013 – Aug 2013); Ghana Water Company Limited – Ho, Volta Region, Ghana

## Awards

Altria Graduate Research Fellowship (2022 – 2023), Virginia Commonwealth University
Black History in the Making Award (2022), Virginia Commonwealth University
Distinguished Chemist Award (2021), Virginia Commonwealth University
Most Influential Chemistry Student Award (2017), University of Ghana

## Membership

American Chemical Society (2021 – present)
National Organization for the Professional Advancement of Black Chemists and Chemical Engineers (2021 – present)
Chemistry Graduate Students Organization (2018 – 2023), Virginia Commonwealth University
Ghana Students' Chemical Society (2013 – 2017), University of Ghana

## Leadership

President, Chemistry Graduate Student Organization, Virginia Commonwealth University (May 2022 – April 2022)
Treasurer, Chemistry Graduate Student Organization, Virginia Commonwealth University (May 2021 – April 2022)
Electoral Commissioner, Ghana Students' Chemical Society, University of Ghana (May 2016 – April 2017)
Vice President, Ghana Students' Chemical Society, University of Ghana (May 2015 – April 2016)

## Publications

**Klake, R. K.;** Collins, S.; Sieber, J. D. A Unified Approach to the Aminoallylation of Carbonyl Compounds Through Cu-Catalyzed Enantioselective Reductive Coupling of Allenamides. ChemRxiv 2022, https://doi.org/10.26434/chemrxiv-2022-94pg8

Ho, D. B.; Gargaro, S.; **Klake, R. K.;** Sieber, J. D. Development of a Modified System to Provide Improved Diastereocontrol in the Linear-Selective Cu-Catalyzed Reductive Coupling of Ketones and Allenamides. J. Org. Chem. 2021, 87 (4), 2142-2153.

**Klake, R. K.;** Edwards, M. D.; Sieber, J. D. Synthesis of 1,2-Aminoalcohols through Enantioselective Aminoallylation of Ketones by Cu-Catalyzed Reductive Coupling. Org. Lett. 2021, 23 (16), 6444–6449.

Sieber, J. D.; **Klake, R. K.;** Agrawal, T.; Ho, D. B.; Gargaro, S. L.; Collins, S.; Edwards, M. D. Cross-coupling of Allenamides and C-based Nucleophiles by Pd-catalyzed Allylic Alkylation. Isr. J. Chem. 2021, 61 (5–6), 332–339.

Gargaro, S. L.; **Klake, R. K.;** Burns, K. L.; Elele, S. O.; Gentry, S. L.; Sieber, J. D. Access to a Catalytically Generated Umpolung Reagent through the Use of Cu-Catalyzed Reductive Coupling of Ketones and Allenes for the Synthesis of Chiral Vicinal Aminoalcohol Synthons. Org. Lett. 2019, 21 (23), 9753–9758.

**Klake, R. K.;** Gargaro, S. L.; Gentry, S. L.; Elele, S. O.; Sieber, J. D. Development of a Strategy for Linear-Selective Cu-Catalyzed Reductive Coupling of Ketones and Allenes for the Synthesis of Chiral γ-Hydroxyaldehyde Equivalents. Org. Lett. 2019, 21 (19), 7992–7998.

## Public Presentations

**Klake, R. K.;** Sieber, J. D. "Synthesis of 1,2-aminoalcohols through Enantioselective aminoallylation of Carbonyls via Cu-Catalyzed Reductive Coupling" Platform Presentation, American Chemical Society Spring Meeting, 2023, Indianapolis Convention Center, Indianapolis, IN

**Klake, R. K.;** Richard, A.; Collins, S.; Reber, A.; Sieber, J. D., El-Kaderi, H. "Development of Highly Active Recyclable Heterogeneous Supported Bimetallic Nanocatalysts for Buchwald-Hartwig Amination Reactions" Platform Presentation, Center for Rational Catalyst Synthesis Fall Meeting, 2022, University of South Carolina, Columbia, SC

**Klake, R. K.;** Edwards, M. D.; Sieber, J. D. "Synthesis of 1,2-Aminoalcohols Through Enantioselective Aminoallylation of Carbonyls Via Cu-Catalyzed Reductive Coupling" Poster presentation, Chemistry Research Symposium, 2022, Virginia Commonwealth University, Richmond, VA

**Klake, R. K.;** Edwards, M. D.; Sieber, J. D. "Synthesis of 1,2-Aminoalcohols through Enantioselective Aminoallylation of Ketones and Aldehydes by Cu-Catalyzed Reductive Coupling" Poster presentation, Chemistry Research Symposium, 2021, Virginia Commonwealth University, Richmond, VA

**Klake, R. K.;** Gargaro, S. L.; Gentry, S. L.; Elele, S. O.; Sieber, J. D. "Regiodivergent Cu-Catalyzed Reductive Coupling of Ketones and Allenamides" Poster presentation, Young Researchers Conference, 2019, University of Maryland, College Park, MD

**Klake, R. K.;** Gargaro, S. L.; Gentry, S. L.; Elele, S. O.; Sieber, J. D. "Stereoselective Cu-Catalyzed Reductive Coupling of Ketones and Allenamides" Poster presentation, Chemistry Research Symposium, 2019, Virginia Commonwealth University, Richmond, VA