O-Vinyl Oximes for Formation of Carbon–Carbon and Carbon–Nitrogen Bonds, Pyridines from N-Vinyl Nitrones

BY

Daniel Stephen Mueller

BSc., Southern Illinois University Edwardsville, 2009

THESIS

Submitted as partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry in the Graduate College of the University of Illinois at Chicago, 2015

Chicago, Illinois

Defense Committee:

Laura L. Anderson, Advisor and Chair, Chemistry
Tom G. Driver, Chemistry
Duncan J. Wardrop, Chemistry
Justin T. Mohr, Chemistry
Chad Eichman, Loyola University Chicago
ACKNOWLEDGEMENTS

I would first like to thank my advisor, Dr. Laura L. Anderson for all the guidance provided throughout my time as a graduate student. This thesis and all the work associated with it would not be possible without her input. I am very thankful to have been a member of her lab. Her mentoring and guidance were always extremely helpful. Additionally, the overall open environment to discuss science, research and chemistry was an amazing experience to ensure I was always learning something new. Lastly, I am extremely grateful for all the experiences and opportunities she provided. These were invaluable in my training to become a chemist and grow as a professional.

Additionally, I would like to thank Dr. Tom G. Driver. His input, support and guidance have helped to provide great insight and shape my views as a chemist and scientist. I would like to thank Dr. Duncan J. Wardrop as well for his input and insightful discussions. Next, I would like to thank Dr. Justin T. Mohr and Dr. Chad Eichman for sitting on my defense committee and providing their time.

I owe Dr. Dan McElheny deep gratitude for his support during my three years as an NMR technician and teaching assistant. My time in this position provided a great amount of valuable knowledge in the area of NMR spectroscopy. Without this opportunity I would not be able accomplish as much as I have.

My fellow graduate students cannot go unmentioned. First I would like to thank Dr. Heng-Yen Wang. She was a great person to work with and the frank discussions we had about chemistry and science led to many of the great ideas in our research. Next, Dr. Ashley Pumphrey for being a great chemist and friend during our years as
graduate students. The support she provided in and out of the lab has been valuable then and now. The current and former members of the Anderson Group, including: Dr. Dong-Liang Mo, Dr. Aditi Patil, Dr. Dimitra Kontokosta, Wikky Pace, Jongwoo Son, Michelle Kroc, Hannah Londino and Amy Burnstine. The time spent working with them was a great experience and I am glad to have worked with all of these great people. I must thank the members of the Driver group, especially for their assistance in my early years.

Finally, I would like to thank my family and friends. My parents for all the support they have provided throughout my life and especially during my time as a graduate student. They have always pushed me and taught me to keep working hard. All this hard work has paid off and I have them to thank. In addition, I owe my brothers, Kenny and Johnny, great respect for their words of encouragement. Last but not least, one of my best friends, Dr. Marcela Smid, for being a great inspiration to push myself further everyday and go outside of my comfort zone.

Without all of these people in both my academic and personal life I could not be where I am today. I will always remember them and pass on what I have learned.

DSM
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>CHAPTER</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O-Vinyl Oximes for the Synthesis of Di- and Trisubstituted Pyrroles</td>
</tr>
<tr>
<td>1.1</td>
<td>Introduction</td>
</tr>
<tr>
<td>1.1.1</td>
<td>Importance of Pyrroles</td>
</tr>
<tr>
<td>1.1.2</td>
<td>Synthetic Methods to Access Pyrroles</td>
</tr>
<tr>
<td>1.1.3</td>
<td>Paal-Knorr Cyclization</td>
</tr>
<tr>
<td>1.1.4</td>
<td>Examples of Cycloaddition Reactions to Access Pyrroles</td>
</tr>
<tr>
<td>1.2</td>
<td>Discovery of Iridium Isomerization and Expansion of Method</td>
</tr>
<tr>
<td>1.3</td>
<td>Mechanistic Studies</td>
</tr>
<tr>
<td>1.4</td>
<td>Conclusion</td>
</tr>
<tr>
<td>1.5</td>
<td>Supporting Information</td>
</tr>
<tr>
<td>1.5.1</td>
<td>General Experimental Information</td>
</tr>
<tr>
<td>1.5.2</td>
<td>Synthesis of O-Allyl Oxime Ethers</td>
</tr>
<tr>
<td>1.5.3</td>
<td>Synthesis of O-Vinyl Oxime Ethers</td>
</tr>
<tr>
<td>1.5.4</td>
<td>Synthesis of Pyrroles</td>
</tr>
<tr>
<td>1.5.5</td>
<td>Synthesis of Deoxybenzoin Derivatives</td>
</tr>
<tr>
<td>1.5.6</td>
<td>Mechanistic Studies</td>
</tr>
<tr>
<td>2</td>
<td>Synthesis of α-Amino Aldehydes by [1,3]-Rearrangement of O-Vinyl Oximes</td>
</tr>
<tr>
<td>2.1</td>
<td>Introduction</td>
</tr>
<tr>
<td>2.1.1</td>
<td>Use of α-Amino Aldehydes in Total Synthesis</td>
</tr>
<tr>
<td>2.1.2</td>
<td>Known Methods for Synthesis of α-Amino Aldehydes</td>
</tr>
<tr>
<td>2.2</td>
<td>Discovery of [1,3]-Rearrangement of O-Vinyl Oximes</td>
</tr>
<tr>
<td>2.2.1</td>
<td>Camphor Oxime as Chiral Auxiliary</td>
</tr>
<tr>
<td>2.3</td>
<td>Benzophenone Oxime as a Coupling Fragment</td>
</tr>
<tr>
<td>2.4</td>
<td>Mechanistic Experiments</td>
</tr>
<tr>
<td>2.5</td>
<td>Conclusion</td>
</tr>
<tr>
<td>2.6</td>
<td>Supporting Information</td>
</tr>
<tr>
<td>2.6.1</td>
<td>General Experimental Information</td>
</tr>
<tr>
<td>2.6.2</td>
<td>Preparation of O-Vinyl Oximes</td>
</tr>
<tr>
<td>2.6.3</td>
<td>[1,3]-Rearrangement of O-Vinyl Oximes</td>
</tr>
<tr>
<td>2.6.4</td>
<td>Rearrangement and Olefination of O-Vinyl Oximes</td>
</tr>
<tr>
<td>2.6.5</td>
<td>Preparation of Vinylboronic Acids</td>
</tr>
<tr>
<td>2.6.6</td>
<td>Preparation of O-Allyl Camphor Oxime</td>
</tr>
<tr>
<td>3</td>
<td>Synthesis of Pyridines From N-Vinyl Nitrones</td>
</tr>
<tr>
<td>3.1</td>
<td>Introduction</td>
</tr>
<tr>
<td>3.1.1</td>
<td>Modern Methods for Synthesis of Multisubstituted Pyridines</td>
</tr>
<tr>
<td>3.2</td>
<td>Discovery of N-Vinyl Nitrone Coupling</td>
</tr>
<tr>
<td>3.3</td>
<td>N-Vinyl Nitrones and Synthesis of Pyridines</td>
</tr>
<tr>
<td>3.4</td>
<td>Mechanistic Experiments</td>
</tr>
<tr>
<td>3.5</td>
<td>Conclusion</td>
</tr>
<tr>
<td>CHAPTER</td>
<td>PAGE</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>3.6 Supporting Information</td>
<td>152</td>
</tr>
<tr>
<td>3.6.1 General Experimental Information</td>
<td>152</td>
</tr>
<tr>
<td>3.6.2 Preparation of Nitrones</td>
<td>153</td>
</tr>
<tr>
<td>3.6.3 Preparation of Pyridines</td>
<td>163</td>
</tr>
<tr>
<td>Cited Literature</td>
<td>176</td>
</tr>
<tr>
<td>Appendices</td>
<td>181</td>
</tr>
<tr>
<td>VITA</td>
<td>298</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1.1 Scope of 3-Cyano Pyrroles</td>
<td>7</td>
</tr>
<tr>
<td>Table 1.2 Scope of 3-Cyano Pyrroles Continued</td>
<td>9</td>
</tr>
<tr>
<td>Table 1.3 Scope of deoxybenzoin derivatives.</td>
<td>14</td>
</tr>
<tr>
<td>Table 1.4 Scope of deoxybenzoin derived O-allyl oximes</td>
<td>16</td>
</tr>
<tr>
<td>Table 1.5 Scope of 3-arylpyrroles</td>
<td>17</td>
</tr>
<tr>
<td>Table 2.1 Optimization of Counterion and Hydride Source</td>
<td>73</td>
</tr>
<tr>
<td>Table 2.2 Optimization of hydride sources</td>
<td>74</td>
</tr>
<tr>
<td>Table 2.3 Optimization of Copper-Promoted Etherification</td>
<td>80</td>
</tr>
<tr>
<td>Table 2.4 Etherification Products</td>
<td>82</td>
</tr>
<tr>
<td>Table 2.5 Optimization of [1,3]-Rearrangement</td>
<td>84</td>
</tr>
<tr>
<td>Table 2.6 Scope of [1,3]-Rearrangement</td>
<td>86</td>
</tr>
<tr>
<td>Table 2.7 Scope of HWE Olefination</td>
<td>88</td>
</tr>
<tr>
<td>Table 3.1 Optimization of N-Vinyl Nitrone Formation</td>
<td>143</td>
</tr>
<tr>
<td>Table 3.2 Scope of Copper-Catalyzed Coupling</td>
<td>144</td>
</tr>
<tr>
<td>Table 3.3 Scope of Copper-Promoted Coupling</td>
<td>146</td>
</tr>
<tr>
<td>Table 3.4 Scope of Pyridine Synthesis</td>
<td>148</td>
</tr>
<tr>
<td>SCHEME</td>
<td>PAGE</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>Scheme 1.1 Synthesis of 1,4-diketone and Paal-Knorr Cyclization</td>
<td>2</td>
</tr>
<tr>
<td>Scheme 1.2 Rhodium-Catalyzed synthesis of 1,4-diketone and Paal-Knorr Cyclization</td>
<td>3</td>
</tr>
<tr>
<td>Scheme 1.3 Pyrroles from 1,3–dipolar cycloaddition</td>
<td>4</td>
</tr>
<tr>
<td>Scheme 1.4 Regioselective pyrrole synthesis by [3+2] cycloaddition</td>
<td>5</td>
</tr>
<tr>
<td>Scheme 1.5 Trofimov Reaction For The Synthesis of Pyrroles</td>
<td>6</td>
</tr>
<tr>
<td>Scheme 1.6 Synthesis of 3-cyano-4-methylpyrrole by one-pot method</td>
<td>6</td>
</tr>
<tr>
<td>Scheme 1.7 Controlling regioselectivity of α-ester pyrrole formation</td>
<td>10</td>
</tr>
<tr>
<td>Scheme 1.8 Regioselective control with α-ester by addition of DBU</td>
<td>11</td>
</tr>
<tr>
<td>Scheme 1.9 Regioselective control in the synthesis of 3-aryl pyrrole</td>
<td>12</td>
</tr>
<tr>
<td>Scheme 1.10 Deoxybenzoin derivatives by palladium-catalyzed cross coupling</td>
<td>13</td>
</tr>
<tr>
<td>Scheme 1.11 Synthesis of 3-aryl pyrrole by two-step method</td>
<td>17</td>
</tr>
<tr>
<td>Scheme 1.12 Regiocontrol of 2-tert-butyl-3-cyano pyrrole formation</td>
<td>18</td>
</tr>
<tr>
<td>Scheme 1.13 Confirmation of α-imino aldehyde intermediate</td>
<td>19</td>
</tr>
<tr>
<td>Scheme 1.14 Proposed mechanism for the formation of 3-cyano-4-methyl-pyrrole</td>
<td>20</td>
</tr>
<tr>
<td>Scheme 1.15 Mechanistic pathways for the formation of pyrrole regioisomers</td>
<td>22</td>
</tr>
<tr>
<td>Scheme 2.1 Natural products synthesized with a-amino aldehydes</td>
<td>66</td>
</tr>
<tr>
<td>Scheme 2.2 Retrosynthesis of Lactacystin</td>
<td>67</td>
</tr>
<tr>
<td>Scheme 2.3 Retrosynthetic strategy for (−)-Saframycin</td>
<td>67</td>
</tr>
<tr>
<td>Scheme 2.4 Retrosynthesis of Syringolin A</td>
<td>68</td>
</tr>
<tr>
<td>Scheme 2.5 Forward synthesis of intermediates for Syringolin A</td>
<td>68</td>
</tr>
</tbody>
</table>
### LIST OF SCHEMES

<table>
<thead>
<tr>
<th>SCHEME</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme 2.6 Synthesis of N-TIPS-α-amino aldehydes from amino acids</td>
<td>70</td>
</tr>
<tr>
<td>Scheme 2.7 Organocatalytic α-amination of aldehydes</td>
<td>71</td>
</tr>
<tr>
<td>Scheme 2.8 Isomerization and 1,3-Rearrangement of O-Vinyl Oxime Ether</td>
<td>72</td>
</tr>
<tr>
<td>Scheme 2.9 Isomerization and 1,3-Rearrangement of O-Vinyl Camphor Oxime Ether</td>
<td>72</td>
</tr>
<tr>
<td>Scheme 2.10 Optimal Conditions for α-Imino Aldehyde Formation</td>
<td>74</td>
</tr>
<tr>
<td>Scheme 2.11 Reduction and Wittig Olefination of α-Imino Aldehyde</td>
<td>76</td>
</tr>
<tr>
<td>Scheme 2.12 Formation of a-Imino Ketone and Addition of Grignard</td>
<td>76</td>
</tr>
<tr>
<td>Scheme 2.13 Copper-Promoted Coupling of Oximes with Aryl Boronic Acids</td>
<td>77</td>
</tr>
<tr>
<td>Scheme 2.14 Coupling of Camphor Oxime with Hexenyl Boronic Acid</td>
<td>78</td>
</tr>
<tr>
<td>Scheme 2.15 Thermally Induced Isomerization of O-Vinyl Camphor Oxime</td>
<td>78</td>
</tr>
<tr>
<td>Scheme 2.16 Wittig Olefination of α-Imino Aldehyde</td>
<td>87</td>
</tr>
<tr>
<td>Scheme 2.17 Radical Trap Experiments</td>
<td>90</td>
</tr>
<tr>
<td>Scheme 2.18 Experimental test for stereochemical induction in [1,3]-rearrangement</td>
<td>91</td>
</tr>
<tr>
<td>Scheme 2.19 Crossover During 1,3-Rearrangement</td>
<td>91</td>
</tr>
<tr>
<td>Scheme 3.1 Bohlman-Ratz Pyridine Synthesis</td>
<td>139</td>
</tr>
<tr>
<td>Scheme 3.2 Pyridines from Oximes and Alkynes</td>
<td>139</td>
</tr>
<tr>
<td>Scheme 3.3 Regioselective Pyridine Synthesis by Fragment Coupling</td>
<td>140</td>
</tr>
<tr>
<td>Scheme 3.4 Ketonitrone Synthesis by Coupling with Boronic Acids</td>
<td>141</td>
</tr>
<tr>
<td>Scheme 3.5 Monitoring Pyridine Formation</td>
<td>149</td>
</tr>
<tr>
<td>Scheme 3.6 Competition Experiment for the Formation of Pyridines</td>
<td>150</td>
</tr>
</tbody>
</table>
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>Angstom</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl (MeCO)</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetone</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>ATR</td>
<td>attenuated total reflection</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoylecyl</td>
</tr>
<tr>
<td>CAM</td>
<td>ceric ammonium molybdate</td>
</tr>
<tr>
<td>cod</td>
<td>cyclooctadiene</td>
</tr>
<tr>
<td>coe</td>
<td>cyclooctene</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>Cu</td>
<td>copper</td>
</tr>
<tr>
<td>CuTC</td>
<td>copper(I) thiophenecarboxylate</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarization transfer</td>
</tr>
<tr>
<td>DHP</td>
<td>3,4-dihydro-2H-pyran</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>dt</td>
<td>doublet of triplets</td>
</tr>
<tr>
<td>equiv</td>
<td>molar equivalent</td>
</tr>
<tr>
<td>E</td>
<td>entgegen (opposite, trans)</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier transform</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>Hex</td>
<td>hexyl (C₆H₁₃)</td>
</tr>
<tr>
<td>HRMS</td>
<td>high-resolution mass spectrometry</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner-Wadsworth-Emmons</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>i-</td>
<td>iso</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
</tbody>
</table>
s   singlet

 t   triplet

 t-   tertiary

 TBAF  tetra-n-butyl-ammonium fluoride

 TBS   tert-butyl dimethylsilyl (also TBDMS)

 td   triplet of doublets

 TEA   triethylamine

 TEMPO  (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl

 Tf    triflate (F₃CSO₂)

 THF   tetrahydrofuran

 TLC   thin-layer chromatography

 TMEDA  N,N,N',N'-Tetramethylethylenediamine

 Tol   tolyl

 tt   triplet of triplets

 UV    ultraviolet

 wt    weight

 Z     zussamen (together, cis)
SUMMARY

In this thesis I show how a variety of oximes can be used as a starting point for three very different products. Starting with Chapter 1, I outline my initial work using O-allyl oximes, which could selectively be transformed into pyrroles by formation of a carbon–carbon bond from a [3,3]-sigmatropic rearrangement. Additionally, I found that some O-allyl oximes would undergo a [1,3]-rearrangement forming a new carbon-nitrogen bond intermediate. This transformation gave pyrroles with different regioselectivity. In Chapter 2, I describe how we exploited and controlled the newly discovered [1,3]-rearrangement of O-vinyl oximes to give α-imino aldehydes. These investigations allowed access to new derivatives of α-imino aldehydes as well. Finally, in Chapter 3 I show how using a different oxime and a copper promoted coupling with vinylboronic acids allowed for access to N-vinyl ketonitrones, which allowed for quick formation of multisubstituted pyridines.
Chapter 1

Chapter 1. O-Vinyl Oximes for the Synthesis of Di- and Trisubstituted Pyrroles

1.1 Introduction

1.1.1 Importance of Pyrroles

The pyrrole is a privileged heterocycle present in many pharmaceuticals and natural products.\(^1\)\(^-\)\(^6\) Many methods have been developed to access this motif in a selective manner. One of the oldest methods is the Paal-Knorr cyclization, which relies on creative strategies to synthesize 1,4-diketones.\(^7\)\(^-\)\(^8\) Other approaches involve some variations on cycloaddition reactions. These include some well-planned strategies with 1,3-dipolar and [3+2] cycloadditions.\(^9\)\(^-\)\(^{17}\) Lastly there is the Trofimov reaction, which allows for quick access to the pyrrole motif from a multicomponent reaction.\(^{18}\)\(^-\)\(^{19}\)

1.1.2 Synthetic Methods to Access Pyrroles.

1.1.2.1 Paal-Knorr Cyclization

One of the ways to synthesize pyrroles is the Paal-Knorr cyclization. The important starting material for this reaction is the 1,4-diketone. In the Paal-Knorr synthesis, the amine condenses with one of the ketones, tautomerizes to the enamine and eventually attacks the other ketone giving a hemiaminal. Finally dehydration of the hemiaminal intermediate gives the pyrrole.\(^7\)\(^-\)\(^8\) This reaction has been utilized to quickly construct various types of pyrroles. Additionally since all substituents are in place before the cyclization event regioselectivity is not an issue unless migration can occur.

There are many examples where the diketone and ammonia readily give the pyrrole. A simple example reported by Lubell relies on acid promoted conditions with
ammonia and a 1,4-diketone (Scheme 1.1). The pyrrole was obtained in high yield under fairly mild reaction conditions. Synthesis of the 1,4-diketone was described in detail within this report as well. Lubell describes a simple method for synthesizing the ketones with a cascade reaction from the ester (Scheme 1.1) with a vinyl Grignard and copper cyanide to catalyze the 1,4-addition. The homoallylic ketone (Scheme 1.1) is then oxidized under Wacker oxidation conditions to provide the 1,4-dione. These examples were isolated and used without purification so yields are not available for their method. These were immediately carried on to the pyrrole. The example by Lubell shows that while the Paal-Knorr cyclization can be efficient. Other methods to access the 1,4-diketone include the Stetter reaction\textsuperscript{16-21} and oxidative enolate coupling.\textsuperscript{22-25}

**Scheme 1.1** Synthesis of 1,4-diketone and Paal-Knorr Cyclization.

The 1,4-diketones can require multiple steps to obtain and others have tried to develop methods to circumvent this issue when synthesizing pyrroles by the Paal-Knorr method. Some work has been done to simplify these reactions into a one-pot synthesis and avoiding purifications between intermediates. A two-step, one-pot reaction was
described by Castanet where α,β-enones and aryl boronic acids are used in a rhodium-catalyzed carbonylative Heck reaction to generate the 1,4-diketone. After evaporation of the volatiles and a solvent switch to THF, iodine and aniline are added. This completes the two-step process to give the pyrrole. In a specific example they describe using methyl vinyl ketone (Scheme 1.2) aryl boronic acid, in methanol with 0.5 mol percent of [RhH(CO)(PPh₃)₃]. A pressurized reaction vessel was used under 20 bar of carbon monoxide. The mixture was heated at 80 °C for 18 hours upon which time the volatiles were removed and solvent switched. After heating with aniline and iodine in THF the pyrrole was obtained in good yield (Scheme 1.2). Other variations of the Paal-Knoor synthesis exist but center around creative ways of generating the 1,4-diketone.

![Scheme 1.2 Rhodium-Catalyzed synthesis of 1,4-diketone and Paal-Knoor Cyclization](image)

**1.1.2.2 Examples of Cycloaddition Reactions to Access Pyrroles**

Another method to access the pyrrole motif is by cycloaddition. One of these types of cycloaddition is the 1,3-dipolar varieties which has been used to construct various heterocycles. An example by Padwa generates the azomethine ylide from a
silyl iminium in the presence of cesium fluoride, which can then be trapped by a dipolarophile. Starting from the iminium (Scheme 1.3), treatment with cesium fluoride gives the silicate intermediate and loss of trimethylsilyl fluoride leads to the azomethine ylide. To complete the cycloaddition methyl propiolate was used as a dipolarophile. After elimination of methyl sulfide pyrroles were obtained in good yield (Scheme 1.3). As for regioisomers, an equimolar but separable mixture of was observed. While the regioisomers could be separated the lack of regioselectivity in the reaction does make the process less efficient overall if one isomer is desired. The main issue with this reaction is the lack of regioselectivity for the 1,3-dipolar cycloaddition.

Scheme 1.3 Pyrroles from 1,3–dipolar cycloaddition.

Later Katrizky found that use of benzotriazole (Bt) could be utilized in a [3 + 2] cycloaddition reaction as a good leaving group. In this case it is believed the reaction proceeds through a Michael addition pathway to give rise to the [3+2] cycloaddition adduct. In one of the examples a thioamide (Scheme 1.4) was treated with butyl lithium and methyl iodide to give the thioimidate. Combining thioimidate with the crotononitrile, followed by deprotonation of the methylene carbon with sodium hydride the cycloaddition could proceed smoothly. The proposed pyrrolidine intermediate would then undergo
elimination of benzotriazole (Bt) and methy mercaptate (MeS–) to give the pyrrole in good yield and as one regiosiomer. The single regioisomer is important because in previously reported cycloadditions by Padwa mixtures were observed. While this method had an advantage over the others in regards to regioselectivity. It does require strong base to generate the thioimidate intermediate and promote the cycloaddition, which could cause complications with sensitive functionalities.

Scheme 1.4 Regioselective pyrrole synthesis by [3+2] cycloaddition.

The previous examples were meant to highlight the known methods for pyrrole formation. The method we developed had different beginnings and inspiration. One report is that by Trofimov where pyrroles were synthesized using an oxime and ethylene under strongly basic conditions. In the report acetone oxime (Scheme 1.5) was treated with an atmosphere of ethylene, which gave rise to the O-vinyl oxime, pyrrole and N-vinyl pyrrole. It is believed the O-vinyl oxime is an intermediate in the pyrrole formation. While this reaction is interesting because in one step with simple starting materials the pyrrole motif can be obtained. The issue lies in the mixture of products which overall leads to a decrease in efficiency and difficulty with large-scale
applications. Additionally, only acetylene can be used at high pressures which makes this procedure less attractive as a synthetic method.

\[
\begin{align*}
\text{N} & \text{OH} \\
\text{Me} & \text{Me} \\
\rightarrow & \\
\text{N} & \text{O} \\
\text{Me} & \text{Me} \\
\text{DMSO, 90 °C, 6 h} & \\
\text{KOH 2 equiv} & \\
\end{align*}
\]

**Scheme 1.5** Trofimov Reaction For The Synthesis of Pyrroles.

1.2 Discovery of Iridium Isomerization and Expansion of Method

During the course of our studies Dr. Heng-Yen Wang discovered that O-allyloxime ether 13a (**Scheme 1.6**) would proceed directly—in an impressive yield of 83%—to 4-methylpyrrole (14a). We were excited with this result because we could obtain the pyrrole with the iridium-catalyzed conditions in one step at room temperature. Considering the interesting reactivity of the α-cyano oximes it was decided to explore the reactivity of by varying substitution on the aryl group.

\[
\begin{align*}
\text{Ph} & \text{CN} \\
\text{CN} & \text{CN} \\
\rightarrow & \\
\text{Ph} & \text{N} \\
\text{HN} & \text{Me} \\
\end{align*}
\]

**Scheme 1.6** Synthesis of 3-cyano-4-methylpyrrole by one-pot method.

I explored the functional group tolerance of this transformation. It was found that electron-donating groups lead to reduced yield of the pyrrole (**entries 2-3, table 1.1**). Aryl bromide 3e (**table 1.1**) lead to a slightly reduced yield as well with the bromide
intact to allow the possibility of further functionalization. Examples with electron-withdrawing groups gave a reduced yield as well. For example methyl ester 14f (entry 6, table 1.1) gave a significantly reduced yield. The example bearing a trifluoromethyl 14g was slightly less efficient than phenyl (entry 7, table 1.1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="14a" /></td>
<td>83%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="14b" /></td>
<td>73%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="14c" /></td>
<td>74%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="14d" /></td>
<td>79%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="14e" /></td>
<td>76%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="14f" /></td>
<td>30%</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="14g" /></td>
<td>60%</td>
</tr>
</tbody>
</table>
Table 1.1 Scope of 3-Cyano Pyrroles.

Through testing the α-cyano O-ally oxime ethers I found that full-conversion was the problem and helped to explain the reduced yield. This was most apparent with the examples bearing the electron-withdrawing substituents on the aryl group. Some impurities were detected in the crude reaction mixtures that were most likely a result of unreacted O-vinyl oxime ether. We believed that the O-vinyl intermediate could not undergo [3,3]-sigmatropic rearrangement at ambient temperature. So a plan was devised to allow these less reactive substrates to react at ambient temperature for 24 hours. The mixture was then heated at 50 °C for an additional 24 hours. This two-step method increased the yield considerably. We now had a method to access less reactive examples with electron-withdrawing groups. The two-step method led to a significant increase for the yield of p-methylester 14f (table 1.2). Additionally the method overcame the limitations with para-fluoro 14h substitution as well. Also this allowed access to an aryl chloride 14i (table 1.2), which could be useful in cross-coupling reactions later. Lastly a unique furanyl substituted pyrrole 14j (table 1.2) could now be accessed that we believed might had suffered coordination issues at ambient temperatures. The elevated temperature appeared to overcome this unfavorable coordination to give the pyrrole in reasonable yield. With a wide variety of the 3-cyano pyrroles obtained other variations were explored.
Table 1.2 Scope of 3-Cyano Pyrroles Continued.

The working hypothesis was that the strong electron-withdrawing nature of the nitrile group made tautomerization to the enamine more facile. Other electron withdrawing groups could produce a similar situation and give the desired pyrrole in good yield. We knew that β-ketoesters were readily available and might provide the system we desired. We had discovered that oxime 13k could be converted to 5-methylpyrrole 14ka, which meant that the O-vinyl oxime ether intermediate had undergone a [1,3]-rearrangement before forming the pyrrole (Scheme 1.7). It was decided to find a way to shift the regioselectivity of the pyrrole by using a base to
promote tautomerization of the imine to the enamine. Dr. Heng-Yen Wang found that by isolating the intermediate \( O \)-vinyl oxime ether \( 15k \) and then heating with triethylamine gave a regioisomeric mixture of 4-methylpyrrole \( 14k \) and 5-methylpyrrole \( 14ka \) (Scheme 1.7).

![Scheme 1.7 Controlling regioselectivity of α-ester pyrrole formation.](image)

Later it was identified that adding DBU to the isomerization conditions that one regioisomer could be obtained. These conditions gave 4-methylpyrrole \( 14k \) in 86\% yield as one regioisomer (Scheme 1.8). This result was great because we could overcome the regioselectivity and access two different substitution patterns from the same substrate. In addition, the yield more than doubled from the original result, suggesting that the \([3,3]\)-rearrangement which gives rise to the 4-methylpyrrole \( 14k \) is the more efficient pathway (Scheme 1.8).
Considering that regioselectivity could be controlled with the α-ester pyroles it was hypothesized that the addition of an amine base could control the formation of similar products. Previously we found that deoxybenzoin derived oximes gave the 5-methylpyrrole and therefore proceeded through the [1,3]-rearrangement. We decided to test the hypothesis and see if the different pathways could be controlled. Also this would further solve the regioselectivity issues. The O-vinyl oxime ether 15l, which was isolated from the isomerization reaction, was combined with DBU in a solution of THF and heated at 75 °C for 25 hours (Scheme 1.9). The result was an 80:20 mixture of 5-methyl 3l and 4-methylpyrrole 14la in a reasonable yield of 59% (Scheme 1.9). While there was room for improvement the regioselectivity was now in a more reasonable ratio and could be feasible to separate these mixtures. To further test DBU as an additive, DBU was added with the isomerization reaction mixture. The isomerization was allowed to proceed at ambient temperature before being heated to 75 °C. After heating the regioselectivity ratio for pyroles 14l and 14la were observed to be 63:37, which was reduced from the previous method (Scheme 1.9). Additionally the two-step method gave 40% yield, diminished from the two-step method. Since additives could not fully
control the regioselectivity for formation of 3-arylpyrrole 14l another approach would be explored to favor the [3,3]-rearrangement pathway (Scheme 1.9).

![Scheme 1.9](image)

**Scheme 1.9** Regioselective control in the synthesis of 3-aryl pyrrole.

To favor the formation of the 3-aryl-4-methylpyrrole, substrate control would be utilized to favor the [3,3]-sigmatropic pathway. The hypothesis was that electron withdrawing substituents on the aryl group would increase tautomerization of the imine to the enamine. The ketones required to access these examples were not readily available so a method was devised to synthesize these examples. Hartwig had reported a palladium-catalyzed method to synthesize deoxybenzoin derivatives from acetophenone and aryl iodides. The palladium-catalyzed method could be used to synthesize the ketones needed to test substrate control for the formation of 3-arylpyrrole.
Using the same palladium precatalyst, ligand and base as described by Hartwig as a starting point we used different aryl iodides to construct para-substituted deoxybenzoins. The ketones were easily obtained in about two hours and the yields were good to moderate. I was able to synthesize para-trifluoromethyl 18m, ethyl ester 18n and cyano 18o substituted deoxybenzoins (table 1.3). These products could easily be carried on to the condensation stage with O-allyl hydroxylamine using previously reported methods.\textsuperscript{22-23}
Table 1.3 Scope of deoxybenzoin derivatives.

The O-allyl oximes were usually synthesized by simple condensation with O-allyl hydroxylamine in methanol. We used the same approach for the deoxybenzoin derivatives due to the ease of use and shorter overall reaction time. Condensation proceeded smoothly with all of the examples. Mild heating was required for full conversion of the ketone to the O-allyl oxime. Each was isolated as an inseparable E:Z mixture. The trifluoromethyl-substituted oxime 13m saw a reduced yield (entry 1, table
1.4). The ethyl ester $13n$ and cyano $13o$ were isolated in good yield and easily purified (entries 2-3, table 1.4). From here the best pathway to the 3-aryl-4-methylpyrrole could be tested.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$13m$</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$(E:Z) = 3:1$</td>
</tr>
<tr>
<td>2</td>
<td>$13n$</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$(E:Z) = 3:1$</td>
</tr>
<tr>
<td>3</td>
<td>$13o$</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$(E:Z) = 3:1$</td>
</tr>
</tbody>
</table>

Table 1.4: Scope of deoxybenzoin derived O-allyl oximes.

With the starting materials in hand two different pathways to the 3-aryl-4-methylpyrrole would be tested. I decided to test the one-step method with DBU as an additive. This method was operationally simple and allowed me to quickly test our
hypothesis about these examples. The trifluoromethyl example 14m (entry 1, table 1.5) was obtained in a decent yield and most importantly I observed only one regioisomer of the 3-aryl-4-methylpyrrole from the reaction. For the ethyl ester substrate 14n the highest yield of this group was observed (entry 2, table 1.5). Additionally, the desired 3-aryl-4-methylpyrrole was obtained without any signs of the other regiosiomer. Lastly, the cyano example 14o proceeded smoothly to the 3-aryl-4-methylpyrrole (entry 3, table 1.5). While this was a less than optimal yield we could still control the formation of the regioisomers for the 3-arylpyrroles.

![Reactions](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>43%</td>
</tr>
<tr>
<td>2</td>
<td>14m</td>
<td>56%</td>
</tr>
<tr>
<td>3</td>
<td>14n</td>
<td>46%</td>
</tr>
</tbody>
</table>

Table 1.5 Scope of 3-arylpyrroles.
To further understand the effect of the substituted aryl I performed a two-step method to obtain the 3-aryl-4-methylpyrrole. Starting from O-allyl oxime 13m our established iridium-catalyzed isomerization conditions were used to obtain the O-vinyl oxime. The O-vinyl oxime 15m was obtained in good yield and easily purified (Scheme 1.11). With O-vinyl oxime in hand I could test the thermal induced conditions with DBU as an additive to induce more facile tautomerization of the imine to enamine. After heating O-vinyl oxime for 25 hours at 75 °C the 3-aryl-4-methylpyrrole 14m was obtained in good yield (Scheme 1.11). Since I could obtain the same product over two steps this helped to support our hypothesis that favoring tautomerization would help to favor the [3,3]-rearrangement over the [1,3]-rearrangement. Additionally this showed that the isomerization step in this reaction is likely the least efficient step and could explain the reduced yield observed in the one-pot reaction.

Scheme 1.11 Synthesis of 3-aryl pyrrole by two-step method.
Considering the power of regiocontrol that the base additive brought to the reaction I wanted to see if this could be applied to another difficult example. Previously I found that tert-butyl α-cyano oxime 13p gave a two to three regioisomeric mixture of the 4-methylpyrrole 14p and 5-methylpyrrole 14pa in 49% yield (Scheme 1.12). The initial result was surprising because all the α-cyano oximes gave the 4-methylpyrrole exclusively. The lack of an aryl group adjacent to the oxime must raise the pKₐ of the α-protons and lower the favorability towards tautomerization to the enamine.³⁴ Additionally attempts to isolate the O-vinyl oxime at ambient temperature were unsuccessful. The hope was to isolate the analogous O-vinyl oxime and exploit the use of DBU to favor the formation of 4-methylpyrrole 14p (Scheme 1.12). Since this was not an option I decided to use the one pot method with DBU added to the isomerization conditions. I was happy to find that DBU increased the yield to 59% and the shifted the ratio of 4-methylpyrrole 14p and 5-methylpyrrole 14pa regioisomers to four to one. While this didn’t achieve full regioselectivity of 4-methylpyrrole 14p it was still pleasing to see that by adding a mild amine base a shift toward one product could be observed.

![Scheme 1.12 Regiocontrol of 2-tert-butyl-3-cyano pyrrole formation.](image)

---

³⁴ The value of pKₐ for tert-butyl α-cyano group is approximately 10, which is higher than that of methyl group (≈ 4-5), thus making the formation of 5-methylpyrrole 14pa less favorable.
1.3 Mechanistic Studies

After all the studies of substrate and reaction condition manipulation we wanted to understand how two different products were being formed. Isolation of intermediates seemed to be the most straightforward approach to confirm the mechanistic pathways. We knew that an aldehyde intermediate could be observed by $^1$H and $^{13}$C NMR studies and this could be used as a starting point to isolate one of the intermediates. Since the α-imino aldehyde was presumed to be unstable to normal isolation and purification methods, trapping the intermediate by reduction was proposed to give a more stable product that could more easily be isolated. The O-vinyl oxime 15q was heated in dioxane for about 2 hours upon which time the solution was transferred to a cooled suspension of LiAlH$_4$ in THF (Scheme 1.13). After the reduction had consumed all of the aldehyde the 1,2-amino alcohol 20q was obtained in good yield over two steps. This derivative we believe confirms the presence of the α-imino aldehyde 19q intermediate in the reaction. More importantly this experiment helps to confirm that the reaction must proceed through a [1,3]-rearrangement of the O-vinyl oxime. This experiment helps to support the pathway for the formation the 5-methyl pyrrole.

**Scheme 1.13** Confirmation of α-imino aldehyde intermediate.
With the [1,3]-pathway confirmed a general scheme could be imagined for the regioselective synthesis of tetrasubstituted pyrroles. The [1,3]-rearrangement has been studied by Saito, Padwa, Rovis, Grieco and Nelson. The report by Saito involved the cleavage of an N–O bond followed by [1,3]-rearrangement. The accounts of Padwa observed a similar N–O bond cleave followed by [1,3]-rearrangement. Rovis, Grieco and Nelson have studied [1,3]-rearrangements with allyl vinyl ethers and these examples provided some additional mechanistic insight to our reaction. When the α-cyano substrate 13a was used we saw exclusive formation of the 3-cyano-4-methyl-pyrrole (14a, Scheme 1.6). From these observations we can conclude that pyrrole formation proceeds through a mechanism where upon alkene isomerization to the O-vinyl oxime 15, tautomerization immediately occurs to give the enamine (Scheme 1.14). Following enamine formation the next proposed step is a [3,3]-sigmatropic rearrangement, which would give rise to the imino aldehyde intermediate (22, Scheme 1.14). Considering previous reports by Amarnath the imine should undergo tautomerization before a Paal-Knorr-type attack of the aldehyde. The Paal-Knorr cyclization step would be subsequently followed by dehydration giving the 3-cyano-4-methyl-pyrrole product (14, Scheme 1.14). While the α-cyano substrates exclusively gave the 4-methyl pyrrole others we had studied yielded mixtures that could be controlled.

Scheme 1.14 Proposed mechanism for the formation of 3-cyano-4-methyl-pyrrole.
If the α-group on the O-vinyl oxime changed to other less electron-withdrawing groups different regioselectivity was observed. If an aryl or ethyl ester was in the α-location of the O-vinyl oxime and the reaction was performed in the presence of DBU then we observed 4-methyl pyrrole 14 as the major product (Scheme 1.15). If the α-substituent was either hydrogen, methyl or another alkyl group the 5-methyl pyrrole 3ra was the major product obtained. Considering the mechanism to 3-cyano-methyl-pyrrole 13, it was believed the α-aryl and α-ester O-vinyl oximes proceeds through a similar pathway once the base DBU was added. We believe that DBU promotes tautomerization to the enamine 21 and favors the [3,3]-rearrangement (Scheme 1.15). The result of [3,3]-rearrangement is the imino aldehyde (8r, Scheme 1.15). Upon formation of imino aldehyde 8r another tautomerization step would allow for enamine formation and the system would be primed for the Paal-Knorr cyclization. After cyclization dehydration would give the 4-methyl pyrrole 14. If the electron-withdrawing nature of the α-substituent was changed then a separate pathway will predominate. The proposed mechanism for the transformation with α-methyl O-vinyl oxime starts with the irreversible [1,3]-rearrangement to give the α-imino aldehyde (19, Scheme 1.15). We had isolated this intermediate previously to confirm this intermediate. From the α-imino aldehyde 19 tautomeration of the imine to the enamine would allow for nucleophilic attack of the aldehyde moiety, generating 4-hydroxy-dihydropyrrole (23, Scheme 1.15). Once the cyclization has occurred dehydration completes the formation of 5-methyl pyrrole (14’, Scheme 1.15).
1.4 Conclusion

In conclusion, I have outlined my contributions to the regioselective synthesis of pyrroles and how these related to other research done in the Anderson research group. Overall our method helps to solve some issues present in current synthetic methods for generating pyrroles. By expanding the scope of the 3-cyano-4-methyl pyrroles we were able to access a wide variety of these unique pyrroles. Additionally, through use of a base additive I was able to find a regioselective synthesis of 3-aryl-4-methyl pyrroles. This also allowed us to see that the isomerization step of the synthesis was the less efficient process for the 3-aryl-4-methyl pyrroles. Lastly the base additive was utilized to shift the regioselectivity of difficult substrates that gave mixtures of regioisomers. Finally, by isolating and observing intermediates the two pathways of either [3,3] or [1,3]-rearrangement could be explained. These advances give access to a variety of di-
and trisubstituted pyrroles. Further research of the [1,3]-rearrangement continued after these studies.

1.5 Supporting Information
1.5.1 General Experimental Information.

$^1$H NMR and $^{13}$C NMR spectra were recorded at ambient temperature using 500 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the $\delta$ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. High-resolution mass spectra were acquired on an LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Flash chromatography was performed to force flow the indicated solvent system down columns packed with 60Å (40 – 60 μm) mesh silica gel (SiO$_2$). Unless otherwise noted, all reagents were obtained from commercial sources and, where appropriate, purified prior to use. THF was dried by filtration through alumina according to the procedure of Grubbs.$^{42}$ Dioxane was distilled over CaH$_2$ and stored under N$_2$ prior to use. Dioxane-$d_8$ was dried over activated 4Å molecular sieves, degassed and stored in an inert atmosphere glovebox prior to use.

1.5.2 Synthesis of O-Allyl Oxime Ethers

**General Procedure A: Preparation of O-Allyl Oximes:** A 100 mL rbf was charged with 1 equiv of allylhydroxylamine hydrochloride salt, 1 equiv of NaOAc, and ~ 40 mL of MeOH. The resulting slurry was allowed to stir at 25 oC for 30 min. At this time, 1 equiv of the corresponding ketone was added to the slurry over a 5 min time period.
Regardless of their physical state, ketones were weighed into scintillation vials, mixed with 15 mL of MeOH, and added as solutions with a syringe. The reaction mixtures were then allowed to stir at 25 °C for 12-24 h or heated to 60 °C for 24 h. At this time, 30 mL of water were added to the flask and a white precipitate appeared. The mixture was then transferred to a separatory funnel and mixed with an additional 20 mL of water and 40 mL of MTBE or CH₂Cl₂. The water layer was extracted with 3 × 15 mL of MTBE or CH₂Cl₂ and the organic layer was extracted with 2 × 20 mL of water and 1 × 20 mL of brine. The organic layers were then combined and dried over MgSO₄, and filtered. Solvent was separated from the product under vacuum on a rotary evaporator. Allyl oxime 1 was then transferred to a scintillation vial and all remaining volatiles were removed on a high vacuum line. No further purification of the products was required in most cases. For condensation reactions that did not go to completion, the remaining starting material was separated by flash chromatography using a solvent gradient of 2% TEA/hexanes – 10% EtOAc/2% TEA/hexanes. The isomeric ratios of E:Z-oximes present in the product mixtures were determined by comparison of the integration of the allylic methylene resonances in the ¹H NMR spectrum.

[Chemical structure image]

**Allyl Oxime Ether 13a:** Allyl oxime ether 13a was synthesized according to general procedure A. Allyl hydroxylamine hydrochloride (601 mg, 5.49 mmol) was treated with
NaOAc (675 mg, 8.23 mmol) and benzoylacetonitrile (716 mg, 4.93 mmol) and allowed to stir at 60 °C for 12 h. After workup and column chromatography 13a was isolated as a clear, colorless oil (810 mg, 82%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.67-7.65 (m, 2H), 7.39-7.36 (m, 3H), 6.09-7.06 (m, 1H), 5.38 (dd, $J = 17.0$ Hz, $J = 1.0$ Hz, 1H), 5.29 (dd, $J = 10.5$ Hz, $J = 1.0$ Hz, 1H), 4.79 (d, $J = 5.5$ Hz, 2H), 3.81 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 146.5, 133.5, 133.3, 130.2, 128.9, 126.2, 118.4, 115.0, 76.0, 15.3; IR (thin film) 2926, 2252, 1604, 1445, 1415, 1341, 1020, 930, 759, 691, 532 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{12}$H$_{13}$N$_2$O (M+H)$^+$ 201.1028, found 201.1027. The $^1$H NMR spectrum showed that <10% of the product mixture was the Z-oxime isomer.

![13b]

**O-Allyl Oxime 13b:** O-Allyl oxime 13b was synthesized according to general procedure A. Allylhydroxylamine hydrochloride (0.76 g, 6.9 mmol) was treated with NaOAc (0.57 g, 6.9 mmol) and 4-toluylacetonitrile (1.0 g, 6.3 mmol). The reaction mixture was allowed to stir for 24 h. After workup, 13b was isolated as a clear, colorless oil (1.2 g, 89%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.55-7.53 (m, 2H) 7.23-7.22 (m, 2H), 6.09-6.03 (m, 1H), 5.38 (d, $J = 18.0$ Hz, 1H), 5.27 (d, $J = 12.0$ Hz, 1H), 4.78 (d, $J = 6.0$ Hz, 2H), 3.79 (s, 2H), 2.38 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 146.5, 140.5, 133.6, 130.4, 129.6, 126.1, 118.3, 115.2, 75.9, 21.4, 15.2; IR (thin film) 3090, 2986, 2924, 2870, 2254, 1617, 1514, 1251, 1024, 927, 715 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{13}$H$_{15}$N$_2$O (M+H)$^+$ 215.1184, found 215.1188. The $^1$H NMR spectrum showed that <10% of the product mixture was
the Z-oxime isomer.

![1c]

**O- Allyl Oxime 13c:** O-Allyl oxime 13c was synthesized according to general procedure A. Allylhydroxylamine hydrochloride (0.606 g, 5.53 mmol) was treated with NaOAc (0.454 g, 5.53 mmol) and 4-methoxybenzoylacetonitrile (0.876 g, 5.01 mmol). The reaction mixture was allowed to stir for 24 h. After workup, 13c was isolated as a clear, colorless oil (0.997 g, 87%). ¹H NMR (500 MHz, CDCl₃) δ 7.60-7.58 (m, 2H), 6.94-6.92 (m, 2H), 6.06-6.02 (m, 1H), 6.04 (d, J = 18.0 Hz, 1H), 5.37 (d, J = 12.0 Hz, 1H), 4.76 (d, J = 8.0 Hz, 2H), 3.83 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 161.2, 146.1, 133.6, 127.6, 125.7, 118.3, 115.3, 114.2, 75.8, 55.4, 15.2; IR (thin film) 3084, 2958, 2930, 2255, 1609, 1515, 1251, 1178, 1019, 930, 727 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₃H₁₅N₂O₂ (M+H)⁺ 231.1134, found 231.1127. The ¹H NMR spectrum showed that <5% of the product mixture was the Z-oxime isomer.
**Allyl Oxime Ether 13d**: Allyl oxime ether 13d was synthesized according to general procedure A. Allyl hydroxylamine hydrochloride (663 mg, 6.06 mmol) was treated with NaOAc (745 mg, 9.08 mmol) and (5,6,7,8-Tetrahydro-2-napthoyl)acetonitrile (1.09 g, 5.45 mmol) and allowed to stir at 60 °C for 12 h. After workup and column chromatography 13d was isolated as a clear, colorless oil (1.17 g, 84%). 1H NMR (500 MHz, CDCl₃) δ 7.36-7.32 (m, 2H), 7.11-7.10 (m, 1H), 6.09-6.03 (m, 1H), 5.37 (dd, J = 17.5 Hz, J = 1.5 Hz, 1H), 5.27 (d, J = 10.5 Hz, 1H), 4.77 (d, J = 5.5 Hz, 2H), 3.78 (s, 2H), 2.80-2.78 (m, 4H), 1.81-1.80 (m, 4H); 13C NMR (125 MHz, CDCl₃) δ 146.7, 139.8, 137.8, 133.6, 130.4, 129.6, 126.8, 123.2, 118.2, 115.2, 75.9, 29.5, 29.3, 23.0, 22.9, 15.3; IR (thin film) 2926, 2859, 2250, 1650, 1424, 1330, 1021, 927, 852, 703 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₆H₁₉N₂O (M+H)⁺ 255.1497, found 255.1496. The ¹H NMR spectrum showed that <10% of the product mixture was the Z-oxime isomer.

![structure](image)

**O-Allyl Oxime 13e**: O-Allyl oxime 13e was synthesized according to general procedure A. Allylhydroxylamine hydrochloride (0.606 g, 5.53 mmol) was treated with NaOAc (0.454 g, 5.53 mmol) and (4-bromobenzoyl)acetonitrile (1.12 g, 5.00 mmol). The reaction mixture was allowed to stir for 24 h. After workup, 13e was isolated as a clear, colorless oil (1.24 g, 89%). ¹H NMR (500 MHz, CDCl₃) δ 7.54-7.56 (m, 2H), 7.51-7.53 (m, 2H), 6.01-6.07 (m, 1H), 5.37 (d, J = 18.0 Hz, 1H), 5.28 (d, J = 12.0 Hz, 1H), 4.78 (d,
\[ J = 6.0 \text{ Hz, } 2\text{H}, \] 3.78 (s, 2H); \[^{13}\text{C} \text{ NMR (125 MHz, CDCl}_3\] \( \delta \) 145.6, 133.3, 132.1 (2C), 127.7, 124.7, 118.6, 114.9, 76.2, 15.0; IR (thin film) 3088, 2983, 2926, 2873, 2255, 1589, 1490, 1259, 1019, 930, 714 cm\(^{-1}\); HRMS (ESI) \( m/z \) calcd. for C\(_{12}\)H\(_{12}\)N\(_2\)OBr (M+H\(^+\)) 279.0133, found 279.0142. The \(^1\text{H} \text{ NMR spectrum showed that <10\% of the product mixture was the Z-oxime isomer.} \]

**O-Allyl Oxime 1f3:** O-Allyl oxime 1f3 was synthesized according to general procedure A. Allylhydroxylamine hydrochloride (0.606 g, 5.53 mmol) was treated with NaOAc (0.454 g, 5.53 mmol) and methyl 4-(cyanoacetyl)benzoate (1.01 g, 5.0 mmol). The reaction mixture was allowed to stir for 24 h. After workup, 1f3 was isolated as a white solid (0.963 mg, 75%). \(^1\text{H} \text{ NMR (500 MHz, CDCl}_3\] \( \delta \) 8.09-8.07 (m, 2H), 7.74-7.72 (m, 2H), 6.06-6.02 (m, 1H), 5.38 (d, \( J = 18.0 \text{ Hz, } 1\text{H} \)), 5.29 (d, \( J = 12.0 \text{ Hz, } 1\text{H} \)), 4.81 (d, \( J = 6.0 \text{ Hz, } 2\text{H} \)), 3.94 (s, 3H), 3.83 (s, 2H); \[^{13}\text{C} \text{ NMR (125 MHz, CDCl}_3\] \( \delta \) 166.4, 145.7, 137.2, 133.2, 131.5, 130.0, 126.1, 118.7, 114.7, 76.4, 52.4, 15.1; IR (thin film) 3084, 3007, 2958, 2884, 2251, 1723, 1609, 1556, 1279, 1189, 1002, 950, 767 cm\(^{-1}\); HRMS (ESI) \( m/z \) calcd. for C\(_{14}\)H\(_{15}\)N\(_2\)O\(_3\) (M+H\(^+\)) 259.1083, found 259.1086.; mp 63-65 °C. The \(^1\text{H} \text{ NMR spectrum showed that <10\% of the product mixture was the Z-oxime isomer.} \]
Allyl Oxime Ether 13g: Allyl oxime ether 13g was synthesized according to general procedure A. Allyl hydroxylamine hydrochloride (539 mg, 4.92 mmol) was treated with NaOAc (443 mg, 5.40 mmol) and 3-(Trifluoromethyl)benzoylacetonitrile (868 mg, 4.07 mmol) and allowed to stir at 60 ºC for 12 h. After workup and column chromatography 13g was isolated as a clear, colorless oil (1.02 g, 93%). \( ^1H \text{NMR} (500 \text{ MHz, CDCl}_3) \) d 7.73 (s, 1H), 7.82 (d, \( J = 7.5 \text{ Hz, } 1\text{H} \)), 7.69 (d, \( J = 7.5 \text{ Hz, } 1\text{H} \)), 7.56 (m, 1H), 6.08-6.02 (m, 1H), 5.39 (dd, \( J = 19.0 \text{ Hz, } J = 1.5 \text{ Hz, } 1\text{H} \)), 5.30 (dd, \( J = 10.5 \text{ Hz, } J = 1.0 \text{ Hz, } 1\text{H} \)), 4.82 (d, \( J = 6.0 \text{ Hz, } 2\text{H} \)), 3.84 (s, 2H); \( ^{13}C \text{NMR} (125 \text{ MHz, CDCl}_3) \) d 145.4, 134.2, 133.3, 131.8, 131.6 (d, \( J_{C-F} = 32.5 \text{ Hz} \)), 129.6, 129.5, 126.9, 123.9 (q, \( J_{C-F} = 270 \text{ Hz} \)), 123.2, 119.0, 114.7, 76.6, 15.3; IR (thin film) 2900, 2251, 1616, 1424, 1304, 1278, 1125, 1021, 930, 800 cm\(^{-1}\); HRMS (ESI) \( m/z \) calcd. for \( C_{13}H_{12}F_3N_2O \) (M+H\(^+\)) 269.0902, found 269.0904. The \( ^1H \) NMR spectrum showed that <10% of the product mixture was the Z-oxime isomer.

Allyl Oxime Ether 13h: Allyl oxime ether 13h was synthesized according to general procedure A. Allyl hydroxylamine hydrochloride (682 mg, 6.22 mmol) was treated with NaOAc (562 mg, 6.85 mmol) and 4-fluorobenzoyl-acetonitrile (1.02 g, 6.25 mmol) and allowed to stir at 60 ºC for 36 h. After workup and column chromatography 13h was
isolated as a clear, colorless oil (1.06 g, 78%). $^1$H NMR of $E$-imine isomer (500 MHz, CDCl$_3$) d 7.66-7.63 (m, 2H), 7.13-7.09 (m, 2H), 6.07-6.02 (m, 1H), 5.37 (dd, J = 17.0 Hz, J = 1.0 Hz, 1H), 5.27 (dd, J = 10.5 Hz, J = 1.0 Hz, 1H), 4.77 (d, J = 5.5 Hz, 2H), 3.80 (s, 2H); $^{13}$C NMR of $E$-imine isomer (125 MHz, CDCl$_3$) d 163.9 (d, $J_{C-F}$ = 248.8 Hz), 145.5, 133.4, 129.4, 128.2, 118.5, 116.1, 114.9, 76.1, 15.2; $^{13}$C NMR of $Z$-imine isomer (125 MHz, CDCl$_3$) d 163.9 (d, $J_{C-F}$ = 248.8 Hz), 145, 133.4, 129.4, 128.1, 118.5, 115.9, 114.9, 76.1, 15.2; IR (thin film) 2930, 2257, 1602, 1511, 1417, 1233, 1161, 1022, 931, 835 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{12}$H$_{12}$FNO$_2$ (M+H)$^+$ 219.0934, found 219.0933. The $^1$H NMR spectrum showed that <10% of the product mixture was the $Z$-oxime isomer.

![Chemical Structure](image)

**Allyl Oxime Ether 13i:** Allyl oxime ether 1i was synthesized according to general procedure A. Allyl hydroxylamine hydrochloride (500 mg, 5.57 mmol) was treated with NaOAc (412 mg, 5.02 mmol) and 4-Chlorobenzoyl-acetonitrile (818 mg, 4.56 mmol) and allowed to stir at 60 °C for 36 h. After workup and column chromatography 13i was isolated as a clear, colorless oil (843 mg, 79%). $^1$H NMR (500 MHz, CDCl$_3$) d 7.60-7.59 (m, 2H), 7.40-7.38 (m, 2H), 6.07-6.01 (m, 1H), 5.36 (dd, J = 20.0 Hz, J = 1 Hz, 1H), 5.29 (dd, J = 10.5 Hz, J = 1.0 Hz, 1H), 4.78 (d, J = 6.0 Hz, 2H), 3.79 (s, 2H); $^{13}$C NMR of $E$-oxime isomer (125 MHz, CDCl$_3$) d 163.9, 145.5, 133.3, 131.6, 129.1, 127.4, 118.6, 114.8, 76.2, 15.1; $^{13}$C NMR of $Z$-oxime isomer (125 MHz, CDCl$_3$) d 163.9, 145.5, 136.3, 133.3, 129.1, 127.4, 118.6, 114.8, 76.2, 15.1; IR (thin film) 2950, 2250, 1600, 1490, 1300 cm$^{-1}$. 
1412, 1327, 1092, 1009, 930, 829 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for C\(_{12}\)H\(_{12}\)ClN\(_2\)O (M+H\(^+\)) 235.0638, found 235.0640. The \(^1\)H NMR spectrum showed that <10% of the product mixture was the Z-oxime isomer.

\[
\text{E:Z} = 3:1
\]

**Allyl Oxime Ether 13j**: Allyl oxime ether 13j was synthesized according to general procedure A. Allyl hydroxylamine hydrochloride (405 mg, 3.70 mmol) was treated with NaOAc (334 mg, 4.07 mmol) and 2-Furoylacetonitrile (500 mg, 3.70 mmol) and allowed to stir at 60 °C for 12 h. After workup and column chromatography 13j was isolated as a clear, colorless oil (530 mg, 75%). \(^1\)H NMR of E-imine isomer (500 MHz, CDCl\(_3\)) \(d\) 7.55-7.54 (m, 1H), 6.84-6.83 (m, 1H), 6.53-6.52 (m, 1H), 6.10-6.04 (m, 1H), 5.40 (dd, \(J = 17.5\) Hz, \(J = 1.5\) Hz, 1H), 5.30 (dd, \(J = 10.5\) Hz, \(J = 1.5\) Hz, 1H), 3.76 (s, 2H); \(^{13}\)C NMR of E-imine isomer (125 MHz, CDCl\(_3\)) \(d\) 147.2, 144.6, 139.2, 133.2, 118.6, 114.7, 112.0, 111.1, 76.3, 14.6; \(^1\)H NMR of Z-imine isomer (500 MHz, CDCl\(_3\)) \(d\) 7.54-7.53 (m, 1H), 7.42-7.41 (m, 1H), 6.59-6.58 (m, 1H), 6.10-6.04 (m, 1H), 5.38 (dd, \(J = 17.5\) Hz, \(J = 1.5\) Hz, 1H), 5.30 (dd, \(J = 10.5\) Hz, \(J = 1.5\) Hz, 1H), 3.73 (s, 2H); \(^{13}\)C NMR of Z-imine isomer (125 MHz, CDCl\(_3\)) \(d\) 143.8, 143.4, 137.3, 133.5, 119.0, 118.4, 115.8, 112.7, 76.5, 20.9; IR (thin film) 2932, 2255, 1602, 1482, 1411, 1161, 999, 935, 896, 750 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for C\(_{10}\)H\(_{11}\)N\(_2\)O\(_2\) (M+H\(^+\)) 191.0822, found 191.0821.
**O-allyl oxime 13k**: O-allyl oxime 13k was synthesized according to general procedure A. Allylhydroxylamine hydrochloride (0.606 g, 5.53 mmol) was treated with NaOAc (0.454 g, 5.53 mmol) and ethyl benzoylacetate (0.961 g, 4.90 mmol). The reaction mixture was allowed to stir for 24 h. After workup, 13k was isolated as a clear colorless liquid (1.19 g, 98%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.66-7.64 (m, 2H), 7.37-7.36 (m, 3H), 6.06-5.99 (m, 1H), 5.34 (d, \(J = 18.0\) Hz, 1H), 5.22 (d, \(J = 12.0\) Hz, 1H), 4.73 (d, \(J = 8.5\) Hz, 2H), 4.14 (q, \(J = 7.0\) Hz, 2H), 3.78 (s, 2H), 1.21 (t, \(J = 7.0\) Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 168.8, 151.6, 135.5, 134.1, 129.4, 128.5, 128.1, 117.3, 75.3, 61.1, 33.4, 14.1; IR (thin film) 3079, 2983, 2930, 2906, 2870, 1732, 1648, 1495, 1250, 1158, 1021, 920, 763 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for C\(_{14}\)H\(_{18}\)NO\(_3\) (M+H)\(^+\) 248.1287, found 248.1278. The \(^1\)H NMR spectrum showed that <10% of the product mixture was the Z-oxime isomer.

**O-allyl oxime 13l**: O-allyl oxime 13l was synthesized according to general procedure
A. Allylhydroxylamine hydrochloride (0.513 g, 4.69 mmol) was treated with NaOAc (0.385 g, 4.69 mmol) and 2-phenylacetophenone (0.834 g, 4.26 mmol). The reaction mixture was allowed to stir for 12 h. After workup, 13I was isolated as a clear, colorless oil (0.830 g, 78%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.68-7.65 (m, 2H), 7.34-7.32 (m, 3H), 7.29-7.24 (m, 4H), 7.30-7.18 (m, 1H), 6.11-6.04 (m, 1H), 5.34 (d, $J = 19.0$ Hz, 1H), 5.23 (d, $J = 12.0$ Hz, 1H), 4.70 (d, $J = 8.5$ Hz, 2H), 4.20 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 156.3, 136.8, 135.8, 134.4, 129.1, 128.6, 128.5, 128.4, 126.6, 126.3, 117.4, 75.2, 32.8; IR (thin film) 3060, 3027, 2920, 2862, 1596, 1492, 1030, 914, 754, 680 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{17}$H$_{18}$NO (M+H)$^+$ 252.1388, found 252.1381. Only the E-oxime isomer was observed in the $^1$H NMR spectrum.

\[ E:Z = 3:1 \]

**O-Allyl Oxime 13m:** O-Allyl oxime ether 13m was synthesized according to general procedure A. Allyl hydroxylamine hydrochloride (0.082 g, 0.75 mmol) was treated with NaOAc (0.92 mg, 1.1 mmol) and ketone 18m (0.198 g, 0.750 mmol). The reaction flask was then attached to a reflux condenser and allowed to stir at 60 °C for 24 h. After workup and flash chromatography (2% TEA/hexanes – 2% EtOAc/2%TEA/hexanes),
13m was isolated as a clear, colorless oil (0.163 g, 68%). $^1$H NMR of E-imine isomer (500 MHz, CDCl$_3$) $d$ 7.98-7.94 (m, 2H), 7.66-7.64 (m, 2H), 7.35-7.28 (m, 5H), 6.08-6.00 (m, 1H), 5.32 (d, $J = 18.0$ Hz, 1H), 5.24 (d, $J = 10.5$ Hz, 1H), 4.76 (d, $J = 5.5$ Hz, 2H), 4.22 (s, 2H); $^{13}$C NMR of E-imine isomer (125 MHz, CDCl$_3$) $d$ 155.4, 141.0, 135.3, 134.4, 134.2, 129.6, 128.9, 128.8, 128.2, 126.4, 117.8, 75.4, 32.9 (the CF$_3$ resonance was not observed due to $^{19}$F splitting); $^1$H NMR of Z-imine isomer (500 MHz, CDCl$_3$) $d$ 7.98-7.94 (m, 2H), 7.66-7.64 (m, 2H), 7.35-7.28 (m, 5H), 6.08-6.00 (m, 1H), 5.32 (d, $J = 18.0$ Hz, 1H), 5.24 (d, $J = 10.5$ Hz, 1H), 4.63 (d, $J = 5.5$ Hz, 2H), 3.91 (s, 2H); $^{13}$C NMR of Z-imine isomer (125 MHz, CDCl$_3$) $d$ 155.4, 141.0, 135.3, 134.4, 134.2, 129.6, 128.9, 128.8, 128.2, 125.4, 117.2, 75.0, 41.5 (the CF$_3$ resonance was not observed due to $^{19}$F splitting); IR (thin film) 3067, 2920, 1681, 1616, 1321, 1109, 1066, 1017, 923, 692 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{18}$H$_{16}$F$_3$NO (M+H)$^+$ 320.1262, found 320.1255.

\[
\begin{align*}
\text{E:Z} &= 3:1 \\
13o
\end{align*}
\]

**O- Allyl Oxime Ether 13o**: Allyl oxime ether 13o was synthesized according to general procedure A. Allyl hydroxylamine hydrochloride (0.61 g, 0.57 mmol) was treated with NaOAc (0.62 g, 0.76 mmol) and ketone 18o (0.11 g, 0.50 mmol). The reaction flask was then attached to a reflux condenser and allowed to stir at 60 °C for 24 h. After workup and flash chromatography (2% TEA/hexanes – 5% EtOAc/2%TEA/hexanes), 13o was
isolated as a clear, colorless oil (0.11 g, 79%). $^1$H NMR of $E$-imine isomer (500 MHz, CDCl$_3$) d 7.62-7.60 (m, 2H), 7.55-7.52 (m, 2H), 7.35-7.28 (m, 5H), 6.05-5.99 (m, 1H), 5.30 (dd, $J = 16.0$ Hz, $J = 1.0$ Hz, 1H), 5.23 (dd, $J = 11.5$ Hz, $J = 1.0$ Hz, 1H), 4.74 (d, $J = 6.0$ Hz, $J = 1.0$ Hz, 2H), 4.21 (s, 2H); $^{13}$C NMR of $E$-imine isomer (125 MHz, CDCl$_3$) d 154.9, 142.5, 135.1, 134.1, 132.4, 129.3, 128.6, 128.1, 126.4, 118.9, 117.8, 110.3, 75.4, 32.9; $^1$H NMR of $Z$-imine isomer (500 MHz, CDCl$_3$) d 7.62-7.60 (m, 2H), 7.55-7.52 (m, 2H), 7.35-7.28 (m, 5H), 6.05-5.99 (m, 1H), 5.30 (dd, $J = 16.0$ Hz, $J = 1.0$ Hz, 1H), 5.21 (dd, $J = 10.5$ Hz, $J = 1.0$ Hz, 1H), 4.13 (d, $J = 5.5$ Hz, $J = 1.0$ Hz, 2H), 3.91 (s, 2H); $^{13}$C NMR of $Z$-imine isomer (125 MHz, CDCl$_3$) d 154.9, 142.5, 135.1, 134.3, 132.3, 129.7, 129.5, 129.1, 128.2, 118.9, 117.3, 110.3, 75.1, 41.8; IR (thin film) 3060, 2923, 2865, 2227, 1607, 1502, 1444, 1020, 922, 694 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{18}$H$_{16}$N$_2$O (M+H)$^+$ 277.1341, found 277.1345.

**O-Allyl Oxime Ether 13n**: Allyl oxime ether 13n was synthesized according to general procedure A. Allyl hydroxylamine hydrochloride (0.128 g, 1.17 mmol) was treated with NaOAc (0.131 g, 1.60 mmol) and ketone 18n (0.285 g, 1.06 mmol). The reaction flask was then attached to a reflux condenser and allowed to stir at 60 °C for 24 h. After workup and flash chromatography (2% TEA/hexanes – 5% EtOAc/2%TEA/hexanes),
**13n** was isolated as a clear, colorless oil (0.271 g, 79%). $^1$H NMR of E-imine isomer (500 MHz, CDCl$_3$) d 7.98-7.94 (m, 2H), 7.66-7.64 (m, 1H), 7.35-7.27 (m, 6H), 6.10-6.04 (m, 1H), 5.34 (dd, $J = 17.5$ Hz, $J = 1.5$ Hz, 1H), 5.25 (dd, $J = 10.5$ Hz, $J = 1.0$ Hz, 1H), 4.78 (dd, $J = 6.0$ Hz, $J = 1.5$ Hz, 2H), 4.36 (q, $J = 7.0$ Hz, 2H), 4.24 (s, 2H), 1.38 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR of E-imine isomer (125 MHz, CDCl$_3$) d 166.5, 155.6, 142.2, 134.5, 134.3, 129.9, 129.3, 128.9, 128.5, 128.0, 126.5 117.6, 75.3, 60.8, 32.9, 14.4; $^1$H NMR of Z-imine isomer (500 MHz, CDCl$_3$) d 7.98-7.94 (m, 2H), 7.66-7.64 (m, 1H), 7.35-7.28 (m, 6H), 6.09-6.02 (m, 1H), 5.30 (dd, $J = 17.0$ Hz, $J = 1.5$ Hz, 1H), 5.23 (dd, $J = 8.0$ Hz, $J = 1.5$ Hz, 1H), 4.65 (dd, $J = 5.5$ Hz, $J = 1.5$ Hz, 2H), 4.36 (q, $J = 7.0$ Hz, 2H), 3.92 (s, 2H), 1.38 (t, $J = 7.0$ Hz, 3H); $^{13}$C NMR of Z-imine isomer (125 MHz, CDCl$_3$) d 166.5, 155.6, 142.2, 135.4, 134.3, 129.8, 129.0, 128.9, 128.7, 128.1, 126.6, 117.2, 75.0, 60.9, 41.8, 14.4; IR (thin film) 2980, 2919, 1714, 1611, 1415, 1272, 1102, 1020, 918, 693 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{20}$H$_{21}$NO$_3$ (M+H)$^+$ 324.1600, found 324.1599.

\[\text{13p}\]

**Allyl Oxime Ether 13p**: Allyl oxime ether 1p was synthesized according to general procedure A. Allyl hydroxylamine hydrochloride (241 mg, 2.20 mmol) was treated with NaOAc (246 mg, 3.00 mmol) and 4,4-Dimethyl-3-oxopentanenitrile (257 mg, 2.05 mmol) and allowed to stir at 60 $^\circ$C for 12 h. After workup and column chromatography 13p was isolated as a clear, colorless oil (305 mg, 83%). $^1$H NMR (500 MHz, CDCl$_3$) d 6.00-5.94 (m, 1H), 5.29 (dd, $J = 17.0$ Hz, $J = 1.5$ Hz, 1H), 5.18 (dd, $J = 10.5$ Hz, $J = 1.0$ Hz, 1H),
4.60 (d, J = 6 Hz, 2H), 3.25 (s, 2H), 1.15 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 154.6, 133.8, 117.6, 115.5, 75.1, 37.3, 27.3, 13.4; IR (thin film) 2969, 2871, 2251, 1720, 1480, 1366, 1122, 1021, 924, 849 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{10}$H$_{11}$N$_2$O$_2$ (M+H)$^+$ 181.1341, found 181.1340.

![Structural formula of 13q](image)

**O- Allyl Oxime 13q:** O-Allyl oxime 13q was synthesized according to general procedure A. Allylhydroxylamine hydrochloride (0.548 g, 5.00 mmol) was treated with NaOAc (0.410 g, 5.00 mmol) and 4'-methoxypropiophenone (0.820 g, 5.00 mmol). The reaction mixture was allowed to stir for 24 h. After workup, 13q was isolated as a clear, colorless oil (0.858 g, 78%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.60-7.58 (m, 2H), 6.90-6.88 (m, 2H), 6.07-6.04 (m, 1H), 5.34 (d, J = 19.0 Hz, 1H), 5.22 (d, J = 12.0 Hz, 1H), 4.68 (d, J = 8.0 Hz, 2H), 2.76 (q, J = 7.5 Hz, 2H), 3.82 (s, 3H), 1.14 (t, J = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 160.3, 159.5, 134.7, 128.2, 127.6, 117.0, 113.8, 74.8, 55.3, 20.1, 11.2; IR (thin film) 3080, 2972, 2913, 2835, 1609, 1511, 1248, 1177, 1030, 919, 760 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{13}$H$_{18}$NO$_2$ (M+H)$^+$ 220.1338, found 220.1328. Only the E-oxime isomer was observed in the $^1$H NMR spectrum.

**1.5.3 Synthesis of O-Vinyl Oxime Ethers**

**General Procedure B: Preparation of O-Vinyl Oximes 15k, 15m, 15q:** In an inert atmosphere drybox, a 20 mL scintillation vial was charged with 0.5 equiv of [(cod)IrCl]$_2$,
1 equiv AgOTf, 1 equiv NaBH₄ or 1 equiv LiAlH₄, and 3 mL of THF. This mixture was then allowed to stir at 25 °C for 20 min. O-Allyl oxime 1 (10 equiv) was mixed with 2 mL of THF in a small vial. The oxime solution was then transferred to the scintillation vial containing the 10 mol % iridium mixture. The reaction mixture was then allowed to stir at 25 °C for 18-36 h. After stirring, an aliquot of the crude reaction mixture was removed from the scintillation vial and removed from the glovebox. The solvent was removed from the aliquot under vacuum on a high vacuum line and then the crude mixture was checked by ¹H NMR spectroscopy to determine if the reaction had gone to completion and to determine the E:Z ratio of the vinyl group of the O-vinyl oxime product by comparison of the integrations of the terminal vinyl protons of the E- and Z-isomers. This ¹H NMR spectrum was used to determined the E:Z vinyl oxime ratio before purification by chromatography. Once ¹H NMR spectroscopy had been used to verify that the isomerization reaction had gone to completion, the reaction mixture was removed from the glovebox and dry-loaded onto ~3 mL of silica. The crude product was purified by flash chromatography using a gradient eluent of 2% TEA/hexanes – 2/% TEA/ 2% EtOAc/ hexanes. The fractions containing 2 were combined, the solvent was removed under vacuum using a rotary evaporator, and then the product was transferred to a scintillation vial and all remaining volatiles were removed under high vacuum for a minimum of 10 min.
**15k**

**O-Vinyl Oxime 15k:** O-Vinyl oxime 15k was synthesized according to general procedure B. The catalyst mixture was prepared by mixing [(cod)IrCl]₂ (23.0 mg, 0.0342 mmol), AgOTf (17.6 mg, 0.0685 mmol), and NaBH₄ (2.6 mg, 0.070 mmol) in THF for 15 min. Allyl oxime ether 13k (132 mg, 0.534 mmol) was then added to the catalyst mixture and the complete reaction mixture was allowed to stir for 18 h. A ¹H NMR spectrum of an aliquot of the reaction mixture showed that the isomerization had gone to completion and that the E:Z vinyl oxime ratio was 1:2.9. After column chromatography, 15k was isolated as a clear colorless oil (76.8 mg, 58%). ¹H NMR of E-isomer (500 MHz, CDCl₃) δ 7.68-7.65 (m, 2H), 7.42-7.36 (m, 3H), 6.91-6.85 (m, 1H), 5.28-5.20 (m, 1H), 4.20-4.14 (m, 2H), 3.81 (s, 2H), 1.62 (d, J = 7.0 Hz, 3H), 1.24-1.20 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 168.5, 153.3, 147.1, 134.8, 129.8, 128.6, 128.5, 101.6, 61.3, 34.1, 14.1, 12.2; ¹H NMR of Z-isomer (500 MHz, CDCl₃) δ 7.68-7.65 (m, 2H), 7.42-7.36 (m, 3H), 6.91-6.85 (m, 1H), 4.56-4.53 (m, 1H), 4.20-4.14 (m, 2H), 3.81 (s, 2H), 1.62 (d, J = 7.0 Hz, 3H), 1.24-1.20 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 168.5, 153.3, 146.6, 134.8, 129.8, 128.6, 128.5, 100.3, 61.3, 34.1, 14.1, 9.4; IR (thin film) 3057, 2980, 2927, 2860, 1734, 1699, 1670, 1653, 1558, 1511, 1456, 1354, 1248, 1165, 1038 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₄H₁₈NO₃ (M+H)⁺ 248.1287, found 248.1282. The ¹H NMR spectrum of 15k indicated that <5% of the corresponding reduction product was present in the product mixture.
O-Vinyl Oxime 15I: O-Vinyl oxime 15I was synthesized according to general procedure B. The catalyst mixture was prepared by mixing [(cod)IrCl]₂ (23.0 mg, 0.0342 mmol), AgOTf (17.6 mg, 0.0685 mmol), and LiAlH₄ (2.6 mg, 0.070 mmol) in THF for 15 min. Allyl oxime ether 13I (171 mg, 0.673 mmol) was then added to the catalyst mixture and the complete reaction mixture was allowed to stir for 18 h. A ¹H NMR spectrum of an aliquot of the reaction mixture showed that the isomerization had gone to completion and that the E:Z vinyl oxime ratio was 1:2.3. After column chromatography, 15I was isolated as a clear colorless oil (134 mg, 79%). ¹H NMR of E-isomer (500 MHz, CDCl₃) δ 7.70-7.68 (m, 2H), 7.37-7.32 (m, 3H), 7.30-7.19 (m, 5H), 6.97-6.92 (m, 1H), 5.26-5.22 (m, 1H), 4.21 (s, 2H), 1.66-1.63 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 158.0, 147.4, 146.8, 136.4, 135.0, 129.6, 128.7, 128.5, 126.8, 126.5, 101.2, 33.4, 12.3; ¹H NMR of Z-isomer (500 MHz, CDCl₃) δ 7.70-7.68 (m, 2H), 7.37-7.32 (m, 3H), 7.30-7.19 (m, 5H), 6.97-6.92 (m, 1H), 4.57-4.54 (m, 1H), 4.21 (s, 2H), 1.66-1.63 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 158.0, 147.4, 146.8, 136.3, 135.0, 129.6, 128.7, 128.5, 126.8, 126.5, 100.0, 33.2, 9.6; IR (thin film) 3060, 3027, 2919, 2858, 1670, 1600, 1494, 1444, 1388, 1361, 1236, 1130, 1033, 933 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₇H₁₈NO (M+H)⁺ 252.1388, found 252.1384. The ¹H NMR spectrum of 15I did not contain any resonances associated with the corresponding reduction product.
O-Vinyl Oxime 13m: O-Vinyl Oxime 13m was synthesized according to general procedure B. The catalyst mixture was synthesized by mixing [(cod)IrCl$_2$ (16.4 mg, 0.0244 mmol), AgOTf (11.0 mg, 0.0428 mmol), and NaBH$_4$ (1.8 mg, 0.047 mmol) in THF for 15 min. Allyl oxime ether 13m (165.9 mg, 0.5196 mmol) was then added to the catalyst mixture and the reaction mixture was allowed to stir for 12 h. After workup and column chromatography, 15m was isolated as an light yellow oil (109.3 mg, 65 %). $^1$H NMR of E-imine, E-vinyl isomer (500 MHz, CDCl$_3$) $d$ 7.70-7.68 (m, 1H), 7.56-7.53 (m, 2H), 7.39-7.34 (m, 6H), 6.98 (dq, $J$ = 6.5 Hz, $J$ = 1.5 Hz, 1H), 4.58 (q, $J$ = 7 Hz, 1H), 4.30 (s, 2H), 1.62 (dd, $J$ = 7.0 Hz, $J$ = 1.5 Hz, 3H); $^{13}$C NMR of E-imine, E-vinyl isomer (125 MHz, CDCl$_3$) $d$ 157.1, 146.8, 140.5, 134.6, 129.9, 128.8, 128.7, 128.6, 128.2, 126.7, 125.6, 100.3, 33.2, 9.55; $^1$H NM of E-imine, Z-vinyl isomer (500 MHz, CDCl$_3$) $d$ 7.70-7.68 (m, 1H), 7.56-7.53 (m, 2H), 7.39-7.34 (m, 6H), 6.94 (dd, $J$ = 12.5 Hz, $J$ = 1.5 Hz, 1H), 5.28 (q, $J$ = 5.5 Hz, 1H), 4.26 (s, 2H), 1.67 (dd, $J$ = 6.5 Hz, $J$ = 1.5 Hz, 3H); $^{13}$C
Chapter 1

NMR of E-imine, Z-vinyl isomer (125 MHz, CDCl₃) δ 157.1, 147.3, 140.5, 134.6, 129.9, 128.8, 128.7, 128.6, 128.2, 126.7, 125.6, 99.7, 33.0, 12.3; ¹H NMR of Z-imine, E-vinyl isomer (500 MHz, CDCl₃) δ 7.70-7.68 (m, 1H), 7.56-7.53 (m, 2H), 7.39-7.34 (m, 6H), 6.86 (dd, $J = 6.5$ Hz, $J = 2.0$ Hz, 1H), 4.48 (q, $J = 6.5$ Hz, 1H), 3.96 (s, 2H), 1.50 (dd, $J = 7.0$ Hz, $J = 1.5$ Hz, 3H); ¹³C NMR of E-imine, Z-vinyl isomer (125 MHz, CDCl₃) δ 156.9, 147.3, 140.5, 134.6, 129.9, 128.8, 128.7, 128.6, 128.2, 126.7, 125.6, 101.5, 41.2, 12.3. The Z-imine, Z-vinyl isomer was less than 10% of the mixture and most resonances were not fully detected.

![15q]

**O-Vinyl Oxime 15q:** O-Vinyl oxime 15q was synthesized according to general procedure B. The catalyst mixture was prepared by mixing [(cod)IrCl]₂ (23.0 mg, 0.0342 mmol), AgOTf (17.6 mg, 0.0685 mmol), and LiAlH₄ (2.6 mg, 0.070 mmol) in THF for 15 min. Allyl oxime ether 13q (146 mg, 0.673 mmol) was then added to the catalyst mixture and the complete reaction mixture was allowed to stir for 18 h. A ¹H NMR spectrum of an aliquot of the reaction mixture showed that the isomerization had gone to completion and that the $E:Z$ vinyl oxime ratio was 1:2.9. After column chromatography, 15q was isolated as a clear colorless oil (117 mg, 79%). ¹H NMR of $E$-isomer (500 MHz, CDCl₃) δ 7.63-7.60 (m, 2H), 6.92-6.87 (m, 3H), 5.19-5.23 (m, 1H), 3.83 (s, 3H), 2.84-2.77 (q, $J = 7.5$ Hz, 2H), 1.62 (d, $J = 8.5$ Hz, 3H), 1.15 (t, $J = 7.5$ Hz, 3H); ¹³C NMR (125 MHz,
CDCl$_3$ $\delta$ 161.1, 160.7, 147.6, 127.9, 127.3, 113.9, 100.3, 55.3, 20.5, 12.3, 11.2; $^1$H NMR of Z-isomer (500 MHz, CDCl$_3$) $\delta$ 7.63-7.60 (m, 2H), 6.92-6.87 (m, 3H), 4.51-4.48 (m, 1H), 3.83 (s, 3H), 2.84-2.77 (q, $J$ = 7.5 Hz, 2H), 1.68 (d, $J$ = 8.5 Hz, 3H), 1.20 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 161.1, 160.7, 147.1, 127.9, 127.3, 113.9, 99.1, 55.3, 20.7, 11.2, 9.5; IR (thin film) 3058, 2969, 2937, 2836, 1670, 1610, 1513, 1463, 1351, 1305, 1253, 1178, 1097, 1037, 960 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{13}$H$_{18}$NO$_2$ (M+H)$^+$ 220.1338, found 220.1328.

1.5.4 Synthesis of Pyrroles

**General Procedure C: Preparation of Pyrroles 14a-14j, 14p:14pa:** In an inert atmosphere drybox, a 20 mL scintillation vial was charged with 0.5 equiv of [(cod)IrCl]$_2$, 1 equiv AgOTf, 1 equiv NaBH$_4$, and 3 mL of THF. This mixture was then allowed to stir at 25 °C for 20 min. $O$-Allyl oxime 1 (10 equiv) was mixed with 2 mL of THF in a small vial. The oxime solution was then transferred to the scintillation vial containing the 10 mol % iridium mixture. The reaction mixture was then allowed to stir at 25 °C for 24-48 h. After the indicated reaction time, an aliquot was removed from the reaction mixture and checked by $^1$H NMR spectroscopy to determine if the transformation had gone to completion. The reaction mixture was then dry-loaded on to silica gel and 3 was purified by flash chromatography (2% TEA/hexanes – 40% EtOAc/2% TEA/hexanes).

**General procedure E: Preparation of Pyrroles 14:** In an inert atmosphere drybox, a 20 mL scintillation vial was charged with 0.5 equiv of [(cod)IrCl]$_2$, 1 equiv AgOTf, 1 equiv...
NaBH₄, and 3 mL of THF. This mixture was then allowed to stir at 25 °C for 20 min. O-
Allyl oxime 1 (10 equiv) was mixed with 2 mL of THF in a small vial. The oxime solution
was then transferred to the scintillation vial containing the 10 mol % iridium mixture and
DBU (10 equiv) was added after the substrate. The reaction mixture was then
transferred to a Teflon-sealed, conical vial and allowed to stir at 25 °C for 1 h. The vial
was then removed from the glovebox and heated to 75 °C for 24 h in an aluminum block.
At this time, an aliquot was removed from the reaction mixture and checked by ¹H NMR
spectroscopy to determine if the transformation had gone to completion. The reaction
mixture was then dry-loaded on to silica gel and 3 was purified by flash chromatography
(2% TEA/hexanes – 40% EtOAc/ 2% TEA/hexanes).

14a

**Pyrrole 14a:** Pyrrole 14a was synthesized according to general procedure C. The
catalyst mixture was prepared by mixing [((cod)IrCl]₂ (0.023 g, 0.034 mmol), AgOTf
(0.017 g, 0.066 mmol), and NaBH₄ (0.0023 g, 0.066 mmol) in THF for 15 min. Allyl
oxime ether 13a (122 mg, 0.610 mmol) was then added to the catalyst mixture and the
reaction mixture was allowed to stir for 36 h. After workup and column chromatography,
14a was isolated as a light yellow solid (92 mg, 83%). ¹H NMR (500 MHz, CDCl₃) d
8.70 (vbs, 1H), 7.69-7.67 (m, 2H), 7.45-7.41 (m, 2H), 7.37-7.33 (m, 1H), 6.60 (m, 1H),
2.23 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) d 138.5, 130.1, 129.2, 128.5, 125.5, 124.2,
117.4, 116.8, 91.6, 10.7; IR (thin film) 3214, 3042, 2920, 2218, 1584, 1468, 1098, 763, 694, 623 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₂H₁₁N₂ (M+H)⁺ 183.0922, found 183.0920; mp 120-122 °C.

Pyrrole 14b: Pyrrole 14b was synthesized according to general procedure C. The catalyst mixture was prepared by mixing [(cod)IrCl]₂ (0.0230 g, 0.0342 mmol), AgOTf (0.0176 g, 0.0685 mmol), and NaBH₄ (0.0026 g, 0.070 mmol) in THF for 15 min. Allyl oxime ether 1b (0.1260 g, 0.587 mmol) was then added to the catalyst mixture and the complete reaction mixture was allowed to stir for 24 h. After column chromatography, 14b was isolated as light yellow solid (84.7 mg, 74%). ¹H NMR (500 MHz, CDCl₃) δ 8.75 (vbs, 1H), 7.58-7.56 (m, 2H), 7.23-7.21 (m, 2H), 6.57 (s, 1H), 2.37 (s, 3H), 2.21 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.8, 138.6, 129.9, 127.3, 125.4, 124.0, 117.7, 116.5, 91.0, 21.3, 10.7; IR (thin film) 3429, 3295, 3027, 2941, 2917, 2857, 2206, 1641, 1536, 820, 771 cm⁻¹; HRMS (ESI) m/z calcd. For C₁₃H₁₃N₂ (M+H)⁺ 197.1079, found 197.1076.; mp 135-137 °C.

Pyrrole 14c: Pyrrole 14c was synthesized according to general procedure C. The
catalyst mixture was prepared by mixing \([(\text{cod})\text{IrCl}]_2\) (0.0230 g, 0.0342 mmol), AgOTf (0.0176 g, 0.0685 mmol), and NaBH$_4$ (0.0026 g, 0.070 mmol) in THF for 15 min. Allyl oxime ether 13c (147 mg, 0.636 mmol) was then added to the catalyst mixture and the complete reaction mixture was allowed to stir for 24 h. After column chromatography, 3c was isolated as light yellow solid (101 mg, 75%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.83 (vbs, 1H), 7.61-7.59 (m, 2H), 6.93-6.91 (m, 2H), 6.54 (s, 1H), 3.82 (s, 3H), 2.19 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 159.8, 138.9, 127.0, 123.7, 122.9, 117.9, 116.2, 114.6, 90.4, 55.4, 10.7; IR (thin film) 3288, 3133, 3108, 2917, 2840, 2206, 1613, 1536, 1251, 820, 727 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. For C$_{13}$H$_{13}$N$_2$O (M+H)$^+$ 213.1028, found 213.1026.; mp 114-116 °C.

![14d](image1.png)

**Pyrrole 14d:** Pyrrole 14d was synthesized according to general procedure C. The catalyst mixture was synthesized by mixing \([(\text{cod})\text{IrCl}]_2\) (0.0230 g, 0.0342 mmol), AgOTf (0.0176 g, 0.0685 mmol), and NaBH$_4$ (0.0026 g, 0.070 mmol) in THF for 15 min. Allyl oxime ether 13d (122 mg, 0.481 mmol) was then added to the catalyst mixture and the reaction mixture was allowed to stir for 36 h. After workup and column chromatography, 14d was isolated as a light yellow solid (89.5 mg, 79%). $^1$H NMR (500 MHz, CDCl$_3$) 8.37 (vbs, 1H), 7.40-7.38 (m, 1H), 7.35 (s, 1H), 7.14-7.12 (m, 1H), 6.56 (s, 1H), 2.80-
2.79 (m, 4H), 2.22 (s, 3H), 1.83-1.80 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 138.9, 138.1, 138.0, 127.3, 126.1, 124.1, 122.7, 117.3, 116.1, 91.3, 29.4, 29.3, 23.0, 10.7; IR (thin film) 3268, 2917, 2852, 2217, 1736, 1580, 1467, 1106, 826, 713 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{16}$H$_{19}$N$_2$O (M+H)$^+$ 237.1392, found 237.1391; mp 174-176 ºC

14e

**Pyrrole 14e**: Pyrrole 14e was synthesized according to general procedure C. The catalyst mixture was prepared by mixing [(cod)IrCl]$_2$ (0.0230 g, 0.0342 mmol), AgOTf (0.0176 g, 0.0685 mmol), and NaBH$_4$ (0.0026 g, 0.070 mmol) in THF for 15 min. Allyl oxime ether 13e (168 mg, 0.602 mmol) was then added to the catalyst mixture and the complete reaction mixture was allowed to stir for 24 h. After column chromatography, 14e was isolated as light yellow solid (120 mg, 76%). $^1$H NMR (500 MHz, CD$_3$OD) δ 7.64-7.62 (m, 2H), 7.60-7.58 (m, 2H), 6.68 (s, 1H), 2.18 (s, 3H) the NH peak did not appear in the $^1$H NMR spectrum; $^{13}$C NMR (125 MHz, CD$_3$OD) δ 136.9, 131.8, 129.6, 126.8, 123.5, 121.5, 117.8, 117.1, 90.3, 9.2; IR (thin film) 3284, 3133, 2921, 2860, 2218, 1523, 824, 771, 706 cm$^{-1}$; HRMS (ESI) m/z calcd. For C$_{12}$H$_{10}$N$_2$Br (M+H)$^+$ 261.0027, found 261.0023.; mp 212-215 ºC.
14f

**Pyrrole 14f**: Pyrrole 14f was synthesized according to general procedure C. The catalyst mixture was prepared by mixing [(cod)IrCl]$_2$ (0.0230 g, 0.0342 mmol), AgOTf (0.0176 g, 0.0685 mmol), and NaBH$_4$ (0.0026 g, 0.070 mmol) in THF for 15 min. Allyl oxime ether 13f (328 mg, 1.27 mmol) was then added to the catalyst mixture and the complete reaction mixture was allowed to stir for 24 h. After column chromatography, 14f was isolated as light yellow solid (91.6 mg, 30%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.98 (vbs, 1H), 8.07-8.05 (m, 2H), 7.76-7.74 (m, 2H), 6.67 (s, 1H), 3.93 (s, 3H), 2.23 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.6, 136.8, 134.1, 130.5, 129.6, 125.1, 125.0, 117.9, 117.0, 92.9, 52.3, 10.7; IR (thin film) 3251, 3035, 2954, 2926, 2214, 1714, 1613, 1580, 1271, 857, 727 cm$^{-1}$; HRMS (ESI) m/z calcd. For C$_{14}$H$_{13}$N$_2$O$_2$ (M+H)$^+$ 241.0977, found 241.0969; mp 198-200 °C.

14g

**Pyrrole 14g**: Pyrrole 14g was synthesized according to general procedure C. The catalyst mixture was synthesized by mixing [(cod)IrCl]$_2$ (0.0230 g, 0.0342 mmol), AgOTf (0.0176 g, 0.0685 mmol), and NaBH$_4$ (0.0026 g, 0.070 mmol) in THF for 15 min. Allyl oxime ether 13g (0.180 g, 0.671 mmol) was then added to the catalyst mixture and the reaction mixture was allowed to stir for 36 h. After workup and column chromatography, 14g was isolated as an light yellow solid (0.101 g, 60%). $^1$H NMR (500 MHz, CDCl$_3$) δ
8.59 (vbs, 1H), 7.96-7.94 (m, 1H), 7.81 (s, 1H), 7.63-7.57 (m, 2H), 6.67 (s, 1H), 2.25 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 136.5, 130.8, 130.0, 129.0, 125.1, 124.8, 121.9, 117.5, 116.6, 93.0, 10.7; IR (thin film) 3265, 2930, 2222, 1587, 1522, 1469, 1314, 1168, 1109, 803 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{13}$H$_{10}$N$_2$F$_3$ (M+H)$^+$ 251.0796, found 251.0797; mp 178-180 ºC

![Image](image_url)

**Pyrrole 14h**: Pyrrole 14h was synthesized according to general procedure C. The catalyst mixture was prepared by mixing [(cod)IrCl)$_2$ (0.0225 g, 0.0335 mmol), AgOTf (0.0168 g, 0.0654 mmol), and NaBH$_4$ (0.0025 g, 0.066 mmol) in THF for 15 min. Allyl oxime ether 13h (0.153 g, 0.701 mmol) was then added to the catalyst mixture and the reaction mixture was allowed to stir for 24 h. After workup and column chromatography, 14h was isolated as a light yellow solid (0.103 g, 74%). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.70 (vbs, 1H), 7.65-7.62 (m, 2H), 7.16-7.12 (m, 2H), 6.60 (m, 1H), 2.22 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 162.7 (d, $J_{C,F} = 247.5$ Hz), 154.8, 136.7, 134.5, 129, 128.4, 126.1, 117.3, 75.1, 12.8; IR (thin film) 3262, 2929, 2850, 2208, 1606, 1528, 1495, 1229, 1092, 822, cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{12}$H$_{10}$FN$_2$ (M+H)$^+$ 201.0828, found 201.0831; mp 124-126 ºC
Pyrrole 14i: Pyrrole 14i was synthesized according to general procedure C. The catalyst mixture was synthesized by mixing \([\text{(cod)IrCl}]_2\) (27 mg, 0.040 mmol), AgOTf (20.7 mg, 0.0805 mmol), and NaBH₄ (3.1 mg, 0.081 mmol) in THF for 15 min. Allyl oxime ether 13i (182.3 mg, 0.777 mmol) was then added to the catalyst mixture and the reaction mixture was allowed to stir for 24 h and then heated at 50°C for 24 h. After workup and column chromatography, 14i was isolated as an light yellow solid (136.1 mg, 81%). ¹H NMR (500 MHz, CDCl₃) δ 8.45 (vbs, 1H), 7.62-7.58 (m, 2H), 7.42-7.40 (m, 2H), 2.23 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 137.2, 134.5, 129.5, 128.5, 126.7, 124.5, 117.0, 92.2, 10.7; IR (thin film) 3252, 2917, 2852, 2215, 1646, 1457, 1083, 948, 820, 709 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₂H₉ClN₂ (M+H)+ 217.0533, found 217.0534; mp 177-179 °C

Pyrrole 14j: Pyrrole 14j was synthesized according to general procedure C. The catalyst mixture was synthesized by mixing \([\text{(cod)IrCl}]_2\) (23 mg, 0.034 mmol), AgOTf (17 mg, 0.066 mmol), and NaBH₄ (2.2 mg, 0.058 mmol) in THF for 15 min. Allyl oxime ether 13j (129.8 mg, 0.683 mmol) was then added to the catalyst mixture and the reaction
mixture was allowed to stir at 25 °C for 24 h then at 50 °C for 24 h. After workup and column chromatography, 14j was isolated as a light-yellow solid (74.2 mg, 54 %). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.76 (vbs, 1H), 7.40 (s, 1H), 6.91-6.90 (m, 1H), 6.54 (s, 1H), 6.50-6.49 (m, 1H), 2.20 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) 144.8, 141.7, 130.2, 123.5, 116.5, 116.2, 112.1, 107.0, 90.0, 10.6; IR (thin film) 3265, 2925, 2214, 1614, 1561, 1441, 1092, 1017, 887, 733 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{10}$H$_9$N$_2$O (M+H)$^+$ 173.0715, found 173.0715; mp 102-104 °C.

**Pyrrole 14k.** Pyrrole 14k was synthesized using general procedure E [(cod)IrCl]$_2$ (0.0225 g, 0.0335 mmol), AgOTf (0.0168 g, 0.0654 mmol), and NaBH$_4$ (0.0025 g, 0.066 mmol) in THF for 15 min. Allyl oxime 13k (0.165 g, 0.667 mmol) was then added to the catalyst mixture, followed by DBU (0.145 g, 0.952 mmol). The reaction mixture was allowed to stir for 1h at 25 °C and then heated to 75 °C for 24h. After flash chromatography (2% TEA/hexanes 40% EtOAc/2% TEA/hexanes), 14k was isolated as light yellow solid (0.132 g, 86%): $^1$H NMR (500 MHz, CDCl$_3$) δ 8.46 (br s, 1H), 7.43!7.40 (m, 2H), 7.04!7.01 (m, 2H), 6.50 (s, 1H), 4.14 (q, J = 7.0 Hz, 2H), 2.30 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 166.0, 137.6, 133.1, 129.1, 128.9, 127.9, 122.5, 116.8, 111.3, 59.4, 14.1, 12.6; IR (thin film) 3301, 2981, 2925, 2857, 1670, 1432, 1284, 1137, 1081, 759 cm$^{-1}$; HRMS (ESI) $m/z$ calcd for C$_{14}$H$_{16}$NO$_2$ (M+H)$^+$ 230.1181,
found 230.1183; mp 90-92 °C.

**Pyrrole 14ka:** The catalyst mixture was prepared by mixing [(cod)IrCl]$_2$ (0.0225 g, 0.0335 mmol), AgOTf (0.0168 g, 0.0654 mmol), and NaBH$_4$ (0.0025 g, 0.066 mmol) in THF for 15 min. Allyl oxime 13k (0.128 mg, 0.518 mmol) was then added to the catalyst mixture, and the complete reaction mixture was allowed to stir for 24 h and then transferred to a Teflon-sealed reaction flask and heated to 75 °C for 15 h. After flash chromatography (2% TEA/hexanes - 40% EtOAc/2% TEA/hexanes), 14ka was isolated as light yellow oil (0.0478 g, 40%): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.41 (br s, 1H), 7.56-7.54 (m, 2H), 7.37-7.30 (m, 3H), 6.38 (s, 1H), 4.16 (q, J = 7.0 Hz, 2H), 2.24 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 165.3, 136.1, 132.3, 128.9, 128.0, 127.9, 127.8, 112.0, 109.5, 59.6, 14.3, 12.7; IR (thin film) 3292, 3028, 2980, 2925, 1666, 1593, 1528, 1222, 814, 762 cm$^{-1}$; HRMS (ESI) m/z calcd for C$_{14}$H$_{16}$NO$_2$ (M+H)$^+$ 230.1181, found 230.1179.

**14l:14la**
Pyrrole mixture 14l:14la (4:1): Pyrrole mixture 14l:14la (4:1) was initially synthesized from O-vinyl oxime 13l. O-Vinyl oxime 14l (0.0904 g, 0.360 mmol) was dissolved in 3 mL of THF and mixed with DBU (0.0822 g, 0.540 mmol). The reaction mixture was then transferred to a teflon-sealed reaction flask at allowed to heat at 75 °C for 24 h. After column chromatography, pyrrole mixture 14l:14la was isolated as a light yellow oil (0.0493 g, 59%). The ratio of 14l:14la was 4:1 and the ratio was determined by the relative $^1$H integrations of the pyrrole methine resonances. $^1$H NMR of 14l (500 MHz, CDCl$_3$) δ 8.07 (br s, 1H), 7.40-7.17 (m, 10H), 6.73 (s, 1H), 2.13 (s, 3H); $^{13}$C NMR of 14l (125 MHz, CDCl$_3$) δ 136.4, 133.4, 130.5, 128.6, 128.4, 128.3, 127.4, 126.9, 126.5, 126.3, 126.0, 116.4, 11.1; $^1$H NMR of 14l (500 MHz, CDCl$_3$) δ 7.94 (br s, 1H), 7.40-7.17 (m, 10H), 6.14 (s, 1H), 2.37 (s, 3H); $^{13}$C NMR of 14la (125 MHz, CDCl$_3$) δ 137.0, 133.7, 128.7, 128.6, 128.3, 128.2, 127.4, 126.9, 126.3, 125.7, 122.3, 109.1, 13.1.

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \quad \text{Ph} \\
\text{Ph} & \quad \text{N} \\
\text{Me} & \quad \text{Ph}
\end{align*}
\]

14l:14la

Pyrrole mixture 14l:14la (5:3): Pyrrole mixture 14l:14la (5:3) was synthesized according to general procedure E. The catalyst mixture was prepared by mixing [(cod)IrCl]$_2$ (0.0225 g, 0.0335 mmol), AgOTf (0.0168 g, 0.0654 mmol), and NaBH$_4$ (0.0025 g, 0.066 mmol) in THF for 15 min. Allyl oxime ether 1r (0.168 g, 0.668 mmol) was then added to the catalyst mixture, followed by DBU (0.145 g, 0.952 mmol). The reaction mixture was allowed to stir for 1 h at 25 °C and then heated to 75 °C for 24 h.
After flash chromatography (2% TEA/hexanes – 40% EtOAc/2% TEA/hexanes), a mixture 14l:14la was isolated as light orange oil (0.062 g, 40%). The ratio of 14l:14la was 5:3 and the ratio was determined by the relative $^1$H integrations of the pyrrole methine resonances. $^1$H NMR of 14l (500 MHz, CDCl$_3$) δ 8.07 (br s, 1H), 7.40-7.17 (m, 10H), 6.73 (s, 1H), 2.13 (s, 3H); $^{13}$C NMR of 14l (125 MHz, CDCl$_3$) δ 136.4, 133.4, 130.5, 128.6, 128.4, 128.3, 127.4, 126.9, 126.5, 126.3, 126.0, 116.4, 11.1; $^1$H NMR of 14la (500 MHz, CDCl$_3$) δ 7.94 (br s, 1H), 7.40-7.17 (m, 10H), 6.14 (s, 1H), 2.37 (s, 3H); $^{13}$C NMR of 14la (125 MHz, CDCl$_3$) δ 137.0, 133.7, 128.7, 128.6, 128.3, 128.2, 127.4, 126.9, 126.3, 125.7, 122.3, 109.1, 13.1; IR (thin film) 3414, 3056, 3020, 2916, 2897, 1596, 1499, 1076, 803, 744 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{17}$H$_{16}$N (M+H)$^+$ 234.1283, found 234.1278.

![14m](image)

**Pyrrole 14m:** Pyrrole 14m was synthesized according to general procedure E. The catalyst mixture was prepared by mixing [(cod)IrCl]$_2$ (0.0225 g, 0.0335 mmol), AgOTf (0.0168 g, 0.0654 mmol), and NaBH$_4$ (0.0025 g, 0.066 mmol) in THF for 15 min. Allyl oxime ether 13m (0.213 g, 0.667 mmol) was then added to the catalyst mixture. DBU (0.132 g, 0.873 mmol) was added to the complete reaction mixture and the complete
reaction mixture was allowed to stir at 25 °C for 1h and then heated to 75 °C for 24 h. After flash chromatography (2% TEA/hexanes – 40% EtOAc/2% TEA/hexanes), 14m was isolated as light yellow solid (0.0858 g, 43%). 1H NMR (500 MHz, CDCl3) δ 8.14 (br s, 1H), 7.60-7.58 (m, 2H), 7.40-7.39 (m, 2H), 7.29-7.27 (m, 2H), 7.25-7.20 (m, 3H), 6.74 (s, 1H), 2.14 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 140.2, 132.9, 130.5, 129.5, 128.7, 127.8, 127.1, 126.7, 125.1, 124.6 (q, JCF = 270Hz), 120.8, 119.5, 116.7, 11.0; IR (thin film) 3401, 2949, 2926, 2864, 1698, 1616, 1322, 1164, 1066, 694 cm⁻¹; HRMS (ESI) m/z calcd. for C18H15NF3 (M+H)⁺ 302.1157, found 302.1159; mp 72-75 °C.

**Pyrrole 14mm**: Pyrrole 14m was also synthesized according to general procedure D. O-Vinyl oxime 2m (0.109, 0.342 mmol) was treated with DBU (0.078mg, 0.51 mmol), and the reaction mixture was allowed to stir for 18 h at 75 °C. After workup and column chromatography, 14m was isolated as a yellow solid (0.0847 g, 82%).

![14n](image)

**Pyrrole 14n**: Pyrrole 14n was synthesized according to general procedure E. The catalyst mixture was prepared by mixing [(cod)IrCl]₂ (0.0135 g, 0.0201 mmol), AgOTf (0.0101 g, 0.0398 mmol), and NaBH₄ (0.0015 g, 0.040 mmol) in THF for 15 min. Allyl oxime ether 13n (0.127 g, 0.390 mmol) was then added to the catalyst mixture. DBU (0.079 g, 0.524 mmol) was added to the complete reaction mixture and the complete
reaction mixture was allowed to stir for 1 h at 25 °C and then heated to 75 °C for 24 h. After flash chromatography (2% TEA/hexanes – 40% EtOAc/2% TEA/hexanes), 14n was isolated as light orange oil (0.0684 g, 56%). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.23 (br s, 1H), 8.01-7.99 (m, 2H), 7.35-7.33 (m, 2H), 7.26-7.23 (m, 2H), 7.20-7.19 (m, 3H), 6.73 (s, 1H), 4.38 (q, \(J\) = 7.0 Hz, 2H), 2.12 (s, 3H), 1.40 (t, \(J\) = 7.0 Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 170.0, 141.4, 133.0, 130.2, 129.5, 129.4, 128.7, 127.8, 127.1, 126.6, 121.2, 119.5, 116.7, 60.8, 11.4, 11.1; IR (thin film) 3336, 2983, 2915, 2877, 2848, 1737, 1607, 1372, 1044, 847 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for C\(_{20}\)H\(_{20}\)NO\(_2\) (M+H)\(^+\) 306.1494, found 306.1492.

\[
\text{14o}
\]

**Pyrrole 14o:** Pyrrole 14o was synthesized according to general procedure E. The catalyst mixture was prepared by mixing [(cod)IrCl\(_2\) (0.0135 g, 0.0201 mmol), AgOTf (0.0101 g, 0.0393 mmol), and NaBH\(_4\) (0.0015 g, 0.040 mmol) in THF for 15 min. Allyloxime ether 13o (0.110 g, 0.398 mmol) was then added to the catalyst mixture. DBU (0.079 g, 0.524 mmol) was added to the complete reaction mixture and the complete reaction mixture was allowed to stir at 25 °C for 1 h and then heated to 75 °C for 24 h. After flash chromatography (2% TEA/hexanes – 40% EtOAc/2% TEA/hexanes), 14o
was isolated as light yellow solid (0.0465 g, 46\%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.16 (br s, 1H), 7.58-7.57 (m, 2H), 7.35-7.34 (m, 2H), 7.29-7.26 (m, 2H), 7.24-7.18 (m, 3H), 6.74 (s, 1H), 2.11 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 141.6, 132.6, 132.0, 130.8, 129.9, 128.8, 127.3, 127.0, 120.3, 119.5, 119.3, 117.0, 109.2, 11.1; IR (thin film) 3332, 2973, 2929, 2893, 2861, 2227, 1603, 1174, 1002, 841 cm$^{-1}$; HRMS (ESI) m/z calcd. For C$_{18}$H$_{15}$N$_2$ (M+H)$^+$ 259.1235, found 259.1230; mp 185-188 °C.

$^{14}$p:14pa = 3:2

**Pyrrole mixture of 14p:14pa:** Pyrrole mixture 14p:14pa was synthesized according to general procedure D. The catalyst mixture was synthesized by mixing [(cod)IrCl]$_2$ (0.0204 g, 0.0304 mmol), AgOTf (0.013 g, 0.051 mmol), and NaBH$_4$ (0.0021 g, 0.0550 mmol) in THF for 15 min. Allyl oxime 13p (0.147 g, 0.816 mmol) was then added to the catalyst mixture and the reaction mixture was allowed to stir at 25 °C for 18 h then at 50 °C for 24 h. After flash chromatography (2% TEA/hexanes – 40% EtOAc/2% TEA/hexanes), 14p:14pa was isolated as a light-yellow oil (0.0639 g, 48%). $^1$H NMR of 14p (500 MHz, CDCl$_3$) $\delta$ 8.38 (vbs, 1H), 6.35 (s, 1H), 2.13 (s, 3H), 1.41 (s, 9H); $^{13}$C NMR of 14p (125 MHz, CDCl$_3$) $\delta$ 149.0, 123.1, 117.9, 113.5, 89.3, 32.8, 29.6, 10.6; $^1$H NMR of 14pa (500 MHz, CDCl$_3$) $\delta$ 8.38 (vbs, 1H), 6.01 (s, 1H), 2.21 (s, 3H), 1.41 (s, 9H); $^{13}$C NMR of 14pa (125 MHz, CDCl$_3$) $\delta$ 148.3, 126.1, 118.7, 109.8, 87.2, 32.8, 29.9,
12.5; IR (thin film) 3275, 2968, 2868, 2210, 1594, 1444, 1367, 1267, 804, 756 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for \(\text{C}_{10}\text{H}_{15}\text{N}_{2} (\text{M+H})^+\) 163.1235, found 163.1234.

![14p:14pa diagram]

**Pyrrole mixture of 14p:14pa**: Pyrrole mixture **14p:14pa** was synthesized according to general procedure E. The catalyst mixture was synthesized by mixing \([(\text{cod})\text{IrCl}]_2\) (0.0230 g, 0.0343 mmol), \(\text{AgOTf}\) (0.013 g, 0.051 mmol), and \(\text{NaBH}_4\) (0.0025 g, 0.065 mmol) in THF for 15 min. Allyl oxime **13p** (0.142 g, 0.787 mmol) was then added to the catalyst mixture followed by DBU (0.179 g, 1.18 mmol). The reaction mixture was allowed to stir for 1 h at 25 °C and then heated to 50 °C for 18 h. After flash chromatography (2% TEA/hexanes – 40% EtOAc/2% TEA/hexanes), **14p:14pa** was isolated as a light-yellow oil (0.0744 g, 58%). \(^1\text{H}\) NMR of **14p** (500 MHz, CDCl\(_3\)) \(\delta\) 8.38 (vbs, 1H), 6.35 (s, 1H), 2.13 (s, 3H), 1.41 (s, 9H); \(^{13}\text{C}\) NMR of **14p** (125 MHz, CDCl\(_3\)) \(\delta\) 149.0, 123.1, 117.9, 113.5, 89.3, 32.8, 29.6, 10.6; \(^1\text{H}\) NMR of **14pa** (500 MHz, CDCl\(_3\)) \(\delta\) 8.38 (vbs, 1H), 6.01 (s, 1H), 2.21 (s, 3H), 1.41 (s, 9H); \(^{13}\text{C}\) NMR of **14pa** (125 MHz, CDCl\(_3\)) \(\delta\) 148.3, 126.1, 118.7, 109.8, 87.2, 32.8, 29.9, 12.5; IR (thin film) 3275, 2968, 2868, 2210, 1594, 1444, 1367, 1267, 804, 756 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for \(\text{C}_{10}\text{H}_{15}\text{N}_{2} (\text{M+H})^+\) 163.1235, found 163.1234.

**1.5.5 Synthesis of Deoxybenzoin Derivatives**
Ketone 18m: Ketone 18m was prepared via a cross coupling reaction between acetophenone and 4-trifluoromethyl iodobenzene. In an inert atmosphere glovebox, a 25 mL round-bottom flask was charged with Pd(dba)$_2$ (0.045 g, 0.078 mmol) and dppf (0.052 g, 0.094 mmol). To the flask, 6 mL of THF were added and allowed to stir for 5 minutes before the addition of NaOt-Bu (0.211 g, 2.20 mmol). The remaining solids were washed from the sides of the flask with 4 mL of THF. The flask was then removed from the glovebox and placed under an atmosphere of N$_2$ with a needle. While stirring, 4-iodobenzotrifluoride (0.271 g, 1.00 mmol) was added to the catalyst mixture, followed by acetophenone (0.120 g, 1.00 mmol). The reaction flask was then attached to a reflux condenser and the reaction mixture was heated to 75 °C for 2.5 h. The crude product was dry loaded on to silica and purified by flash chromatography (2% TEA/ hexanes – 10% EtOAc/ 2% TEA/hexanes) to afford 18m as a white solid (0.229 g, 76%). $^1$H NMR (500 MHz, CDCl$_3$) d 8.03-8.01 (m, 2H), 7.61-7.58(m, 3H), 7.51-7.48 (m, 2H), 7.40-7.38 (m, 2H), 4.36 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 196.7, 138.5, 136.4, 133.5, 130.0, 129.4, 129.2, 128.8, 128.5, 125.6, 45.1 (the CF$_3$ resonance was not observed due to $^{19}$F splitting); IR (thin film) 3057, 2912, 1675, 1594, 1327, 1112, 994, 870, 754, 687 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{15}$H$_{11}$OF$_3$ (M+H)$^+$ 265.0840, found 265.0843; mp 130-132 °C.
Ketone 18n: Ketone 18n was prepared via a cross coupling reaction between acetophenone and 4-cyano iodobenzene. In an inert atmosphere glovebox, a 25 mL round-bottom flask was charged with Pd(dba)$_2$ (0.087 g, 0.150 mmol) and dppf (0.099 g, 0.18 mmol). To the flask, 6 mL of THF were added and allowed to stir for 5 minutes before the addition of NaOt-Bu (0.211 g, 2.20 mmol). The remaining solids were washed from the sides of the flask with 4 mL of THF. The flask was then removed from the glovebox and placed under an atmosphere of N$_2$ with a needle. While stirring, 4-iodobenzonitrile (0.462 g, 2.02 mmol) was added to the catalyst mixture, followed by acetophenone (0.240 g, 2.0 mmol). The reaction flask was then attached to a reflux condenser and the reaction mixture was heated to 75 ºC for 2.5 h. The crude product was dry loaded on to silica and purified by flash chromatography (2% TEA/ hexanes – 10% EtOAc/ 2% TEA/hexanes) to afford 18n as a white solid (0.238 g, 53%). $^1$H NMR (500 MHz, CDCl$_3$) $d$ 8.01-7.99 (m, 2H), 7.63-7.59 (m, 3H), 7.51-7.48 (m, 2H), 7.38-7.36 (m, 2H), 4.36 (s, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $d$ 196.2, 140.0, 136.2, 133.7, 132.3, 130.6, 128.9, 128.5, 118.8, 111.0, 45.2; IR (thin film) 3063, 2897, 2223, 1686, 1605, 1447, 1338, 1219, 999, 683cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{15}$H$_{11}$NO (M+H)$^+$ 222.0919, found 222.0919; mp 101-103 ºC.
Ketone 18n: Ketone 18n was prepared via a cross coupling reaction between acetophenone and 4-(ethyl ester) iodobenzene. In an inert atmosphere glovebox, a 25 mL round-bottom flask was charged with Pd(dba)$_2$ (0.0863 g, 0.150 mmol) and dppf (0.0998 g, 0.179 mmol). To the flask, 6 mL of THF were added and allowed to stir for 5 minutes before the addition of NaOt-Bu (0.288 g, 3.00 mmol). The remaining solids were washed from the sides of the flask with 4 mL of THF. The flask was then removed from the glovebox and placed under an atmosphere of N$_2$ with a needle. While stirring, ethyl 4-iodobenzoate (0.553 g, 2.00 mmol) was added to the catalyst mixture, followed by acetophenone (0.240 g, 2.0 mmol). The reaction flask was then attached to a reflux condenser and the reaction mixture was heated to 75 ºC for 2.5 h. The crude product was dry loaded on to silica and purified by flash chromatography (2% TEA/ hexanes – 10% EtOAc/ 2% TEA/hexanes) to afford 18n as a white solid (0.285 g, 53%). $^1$H NMR (500 MHz, CDCl$_3$) d 8.02-7.99 (m, 4H), 7.59-7.56 (m, 1H), 7.50-7.44 (m, 2H), 7.35-7.33 (m, 2H), 4.36 (q, J = 7.0 Hz, 2H), 4.35 (s, 2H), 1.38 (t, J = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 196.8, 166.4, 139.7, 139.7, 136.4, 133.4, 129.9, 129.6, 129.2, 128.8, 128.6, 60.3, 45.4, 14.4; IR (thin film) 3053, 2982, 2884, 1707, 1683, 1610, 1449, 1104, 997, 755 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{17}$H$_{16}$O$_3$ (M+H)$^+$ 269.1178, found 269.1178; mp 88-90 ºC.
1.5.6 Mechanistic Studies

In an inert atmosphere glovebox, a 10 mL Teflon-sealed flask was charged with 15q (0.1081 g, 0.493 mmol) and 4 mL of dioxane. The flask was then stoppered, removed from the glovebox, and heated to 75 °C for 2.5 h. At this time, an aliquot was removed from the flask and checked by $^1$H NMR spectroscopy which showed that 15q had been completely converted into aldehyde 19q: $^1$H NMR (500 MHz, CDCl$_3$) δ 9.78 (s, 1H), 7.79 (d, $J$ = 9.0 Hz, 2H), 6.91 (d, $J$ = 9.0 Hz, 2H), 2.71 (q, $J$ = 7.5 Hz, 2H), 2.62 (q, $J$ = 7.5 Hz, 1H), 1.39 (d, $J$ = 7.0 Hz, 3H), 1.12 (t, $J$ = 7.5 Hz, 3H). Compound 19q was not isolated or purified. The crude solution of 19q was transferred to a 25 mL round bottom flask containing a slurry of LiAlH$_4$ (0.039 g, 1.03 mmol) in 10 mL THF. The reaction mixture was then allowed to stir for 4 h. At this time, the reaction mixture was diluted with 20 mL of MTBE and slowly quenched with water. The reaction mixture was then extracted with 3 x 20 mL of 1M HCl, neutralized with 1M NaOH, extracted with 3 x 15 mL of MTBE, and volatiles were removed under reduced pressure to give 20q as a light yellow oil (0.0728 g, 66%). $^1$H NMR of major diastereomer (500 MHz, CDCl$_3$) δ 7.19-7.17 (m, 2H), 6.87-6.86 (m, 2H), 3.79 (s, 3H), 3.60 (dd, $J$ = 8.0 Hz, $J$ = 6.0 Hz, 1H), 3.37 (dd, $J$ = 10.5 Hz, $J$ = 4.5 Hz, 1H), 3.13 (dd, $J$ = 10.5 Hz, $J$ = 8.0 Hz, 1H), 2.56-2.53 (m, 1H), 1.69-1.60 (m, 2H), 0.99 (d, $J$ = 6.0 Hz, 3H), 0.79 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR of major diastereomer (125 MHz, CDCl$_3$) δ 158.7, 135.9, 128.3, 113.8, 66.6, 61.2, 55.2, 51.3, 31.9, 16.8, 10.9;
\(^1\)H NMR of minor diastereomer (500 MHz, CDCl\(_3\)) \(\delta\) 7.16-7.14 (m, 2H), 6.87-6.86 (m, 2H), 3.80 (s, 3H), 3.57 (dd, \(J = 10.5\) Hz, \(J = 4.0\) Hz, 1H), 3.48 (dd, \(J = 7.5\) Hz, \(J = 6.5\) Hz, 1H), 3.16 (dd, \(J = 10.5\) Hz, \(J = 5.5\) Hz, 1H), 3.17-3.14 (m, 1H), 1.77-1.72 (m, 1H), 1.59-1.53 (m, 1H), 0.94 (d, \(J = 6.5\) Hz, 3H), 0.80 (t, \(J = 7.5\) Hz, 3H); \(^{13}\)C NMR of minor diastereomer (125 MHz, CDCl\(_3\)) \(\delta\) 158.6, 136.7, 127.9, 113.8, 64.6, 61.6, 55.3, 51.4, 30.9, 18.6, 10.9; IR (thin film) 3294, 3191, 2959, 2929, 2871, 2834, 1610, 1510, 1245, 1035, 828 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for C\(_{13}\)H\(_{23}\)N\(_2\)O (M+H\(^+\)) 223.1810, found 223.1814.
Chapter 2. Synthesis of α-Amino Aldehydes by [1,3]-Rearrangement of O-Vinyl Oximes

2.1 Introduction

In this chapter I hope to highlight how α-amino aldehydes are commonly synthesized and why they are important products. Additionally this will show how the method developed by my coworkers and me provide a new and alternative route that is vastly different than the accepted methods. Usually α-amino aldehydes are generated by two methods. Either of these is accessed by derivatization of a α-amino acid or electrophilic amination of an aldehyde. Derivatization, while a direct method to α-amino aldehydes does require multiple steps and usually is constrained by the amino acids available. Amination of aldehydes is a powerful method but is limited by the electrophilic nitrogen sources that comply with the reaction. Our method allows for formation of α-amino aldehydes by an initial fragment coupling with an oxime and vinylboronic acid to give the O-vinyl oxime. The resulting O-vinyl oxime can then be subjected to a thermally induced [1,3]-rearrangement, which yields the α-amino aldehyde. Herein I will describe the new method and the synthetic utility of the products. Additionally mechanistic experiments will be discussed to probe the mechanistic pathway of the [1,3]-rearrangement.

2.1.1 Use of α-Amino Aldehydes in Total Synthesis

The synthetic utility of α-amino aldehydes is apparent in the synthesis of many natural products. They are useful since aldehydes can undergo various transformations and form new C–C and C–N bonds. Some examples of these syntheses are Lactacystin,
(−)-Saframycin and Syringolin A (Scheme 2.1). These natural products have been targeted due to their unique properties. Lactacystin has been found to induce differentiation of neuroblastoma cell lines, which could prove useful for nerve cell growth. In the case of (−)-Saframycin, it was identified as a strong anti-tumor agent. Lastly, Syringolin A targets neuroblastoma and ovarian cancer cell lines. In addition, Syringolin A has been shown to be a promising multiple myeloma treatment.

Scheme 2.1 Natural products synthesized with α-amino aldehydes.

Work in the Corey group to synthesize Lactacystin began with a plan to start from α-amino ester. They believed could be used to generate an α-amino aldehyde, which would be useful in construction of the core of Lactacystin. In this plan reduction of the methyl ester and oxidation of the alcohol would be required to produce the required α-amino aldehyde (Scheme 2.2).

Scheme 2.2 Retrosynthesis of Lactacystin
The Myers group has used α-amino aldehydes in the synthesis some natural products. One example is (-)-Saframycin, which, they planned to synthesize from α-amino aldehyde. The retrosynthetic strategy relied on forming the core of by dimerization of two α-amino aldehydes (Scheme 2.3). This unique strategy avoided making two separate fragments of the (-)-Saframycin. In order to synthesize a three-step process would be needed involving alkylation, reduction and oxidation starting with the amino acid glycine.

Scheme 2.3 Retrosynthetic strategy for (-)-Saframycin.

Stephenson devised a retrosynthetic strategy where the macrocycle of Syringolin A would be constructed from a Boc-protected α-amino aldehyde (Scheme 2.4). The α-amino aldehyde would be derived from protection and reduction of L-valine. Since valine is commercially available in large quantities this was a great starting point for Syringolin A.

Scheme 2.4 Retrosynthesis of Syringolin A.
With L-valine as the starting point the amine was protected with Boc₂O and the carboxylic acid converted to the Weinreb amide (Scheme 2.5). This gave in good yield and the amide could then be reduced to the aldehyde by treatment with lithium aluminum hydride. The aldehyde was immediately carried on to the Horner-Wadsworth-Emmons (HWE) olefination giving the γ-amino-α, β-unsaturated methyl ester in high yield over two steps. The fragment was then used in later steps to construct the diamide macrocycle of Syringolin A.

![Scheme 2.5 Forward synthesis of intermediates for Syringolin A.](image)

These examples of total syntheses highlight the common way to synthesize α-amino aldehydes. Also they show how useful these can be in forming important structures in natural products. Lastly, accessing natural products like these are important due their interesting biological relevance.

### 2.1.2 Known Methods for Synthesis of α-Amino Aldehydes

Other methods exist for synthesizing α-amino aldehydes. These mostly rely on a variation of the methods described in the total synthesis section. Usually involving a protection and manipulation of a α-amino acid. ⁵⁰⁻⁵¹
The work of Soderquist utilizes readily available amino acids to produce α-amino aldehydes while retaining the stereochemistry. The method is unique due to its mild borane-dimethyl sulfide reducing conditions and the less common N-silyl protecting group. The example in Scheme 2.6 starts with enantiomerically pure L-phenylalanine and under basic conditions protects the amine and carboxylic acid with triisopropylsilyl groups. The resulting N,O-disilyl protected amino acid was obtained in high yield and without any evidence of epimerization. Using borane-dimethyl sulfide as the reducing agent, the reduced intermediate could be generated and observed by NMR. Addition of water to the reaction mixture led to hydrolysis of the borane and produced the mixed acetal, which eliminates triisopropylsilanol to give the α-amino aldehyde in moderate yield. The most interesting part about this method is that due to the N-silyl protection the aldehyde is stable for extended periods of time. They claim these N-silyl-α-amino aldehydes can be stored for weeks at −20 °C under nitrogen without noticeable decomposition. As shown in previous examples the α-amino aldehydes are usually derivatized immediately to a more stable product. While Soderquist demonstrates derivatization of aldehyde, this is a significant step in the synthesis of α-amino aldehydes.
Scheme 2.6 Synthesis of N-TIPS-α-amino aldehydes from amino acids.

So far most of the methods have focused on ways of generating the aldehyde from amino acids and their derivatives. Formation of the carbon–nitrogen bond is another approach to generate α-amino aldehydes. In a report by Sudalai electrophilic amination was used to install the amine functional group. Using simple aldehydes, L-proline as a catalyst and a diazodicarboxylate as the amine source the α-amino aldehyde was generated. In Scheme 2.7 valeraldehyde was subjected to the organocatalytic conditions to give the amination intermediate, which was subjected to mild HWE olefination. The γ-amino-α,β-unsaturated ethyl ester was obtained in good yield and high enantiomeric excess. Electrophilic amination is still being developed further and this is an example where amination has been used to solve the synthetic problem of α-amino aldehydes.

Scheme 2.7 Organocatalytic α-amination of aldehydes.
These examples show that most routes to $\alpha$-amino aldehydes involve manipulation of existing $\alpha$-amino carbonyl compounds or $\alpha$-amination of aldehydes. While these are reliable methods the starting materials are a limitation. Here I will describe how our method was developed and to add a new route in the synthesis of $\alpha$-amino aldehydes.

2.2 Discovery of [1,3]-Rearrangement of $O$-Vinyl Oximes.

During our studies with iridium-catalyzed alkene isomerization of $O$-allyl oximes to $O$-vinyl oximes we discovered a subsequent [1,3]-rearrangement to give $\alpha$-imino aldehydes. To divert from pyrrole formation we changed the identity of the oxime to one that cannot tautomerize readily. Initial choices were benzophenone oxime and camphor oxime since the phenyl groups of benzophenone oxime cannot tautomerize to the enamine. Camphor oxime has the possibility to tautomerize but we hypothesized that [1,3]-rearrangement would proceed faster than tautomerization.

Initial work by Dr. Heng-Yen Wang with $O$-allyl benzophenone oxime ether 41a, [Ir(cod)Cl]$_2$, NaBH$_4$ and AgOTf showed that the alkene isomerization did proceed in good yield to give $O$-vinyl benzophenone oxime ether 42a (Scheme 2.8). When 42a was heated in dioxane $\alpha$-imino aldehyde 43a was obtained. Dr. Heng-Yen Wang explored this method further while I discovered that a different substrate would undergo a similar transformation.
Scheme 2.8 Isomerization and 1,3-Rearrangement of O-Vinyl Benzophenone Oxime Ether.

2.2.1 Camphor Oxime as Chiral Auxiliary

The camphor derived O-allyl oxime ether 44a was used because it was hypothesized that it could act as a chiral auxiliary and provide stereochemical control of the 1,3-rearrangement (Scheme 2.9). The screening process began with O-allyl oxime ether 44a, [Ir(cod)Cl]₂, NaBH₄ and AgOTf, which gave 15% NMR yield of 46a. We believed that the reaction proceeded through the O-vinyl oxime (45a) intermediate and then immediately proceeded to α-imino aldehyde 46a through a 1,3-rearrangement. Attempts to observe or isolate intermediate 45a were unsuccessful.

Scheme 2.9 Isomerization and 1,3-Rearrangement of O-Vinyl Camphor Oxime Ether.

Later a cationic iridium precatalyst [Ir(cod)₂]BF₄ (table 2.1, entry 1) was used with hydrogen gas as the hydride source but this was not a competent system with 44a. Changing the counterion did not improve the formation of 46a. Eventually DIBAL-H with [Ir(cod)₂]BF₄ (table 2.1, entry 5) and gave an NMR yield of 30%.
Table 2.1 Optimization of Counterion and Hydride Source.

While triethylsilane (table 2.2, entry 5) showed a slightly higher yield, DIBAL-H (entry 6) was used for further studies due to the solution being easier to handle and allowed for more precise control of amount. Excess hydride would lead to decreased yield or reduction of 44a.
Table 2.2 Optimization of hydride sources.

<table>
<thead>
<tr>
<th>entry</th>
<th>hydride source</th>
<th>NMR yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9-BBN</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>LiHBEt$_3$</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>HB(cat)</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>HB(pin)</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>HSiEt$_3$</td>
<td>32</td>
</tr>
<tr>
<td>6</td>
<td>DIBAL-H</td>
<td>30</td>
</tr>
</tbody>
</table>

(a) Percent yield determined by $^1$H NMR spectroscopy using CH$_2$Br$_2$ as a reference.

Allowing the isomerization and 1,3-rearrangement to proceed at ambient temperature for 40 hours gave the highest observed NMR yield of 55% (Scheme 2.10). With these conditions two-step reactions were devised to exploit the synthetic utility of the $\alpha$-imino aldehyde and allow more facile isolation and purification. Reduction and Wittig olefination are some of the most common reactions with aldehydes and so these were tested with the product.

Scheme 2.10 Optimal Conditions for $\alpha$-Imino Aldehyde Formation.
The first attempt at derivatizing the α-imino aldehyde product was through a simple reduction process. The reduction of aldehyde 46a to 1,2-imino alcohol 47a was accomplished with NaBH₄ in methanol in 60% yield over two steps (Scheme 2.11). This result was pleasing since the reduction product could be isolated and purified with silica gel chromatography. The diastereomeric ratio of 47a could be determined by ¹H NMR and was found to be an equimolar ratio. Epimerization of α-imino aldehyde 46a could explain the lack of observed diastereoselectivity. It was hypothesized that methanol being a polar protic solvent could be assisting in the epimerization process. Reduction of aldehydes with NaBH₄ in THF had been previously reported. Switching to THF gave the same results but a slight increase in yield to 64% of 47a was observed. Wittig olefination was tried as well. In order to avoid overly basic conditions an excess of the benzyl phosphonium was used. This would avoid any side reactions that could result from an excess of n-butyl lithium. Olefination of aldehyde 46a was accomplished by adding the filtered reaction mixture to a pre-mixed solution of phosphonium and n-butyl lithium. The resulting allylic amine 48a was obtained in 44% yield over two steps and was easily purified. Analysis showed an equimolar diastereomeric ratio though.
Scheme 2.11 Reduction and Wittig Olefination of α-Imino Aldehyde.

To reduce the possibility of epimerization O-allyl oxime ether (44b) was prepared since this would give α-imino ketone (46b). The product would be more stable and less prone to epimerization (Scheme 2.12). A new set of isomerization conditions were explored and [Ru(PPh₃)₃(H)₂(CO)] was identified to give α-imino ketone (46b). Analysis by ¹H NMR appeared to show one diastereomer. Derivatization with methylmagnesium bromide to give the tertiary alcohol (47b) showed an equal mixture of diastereomers.

Scheme 2.12 Formation of α-Imino Ketone and Addition of Grignard.
At this point it was believed that the iridium or ruthenium complexes could be acting as Lewis acids and assisting with epimerization of the α-imino carbonyl products. Since the O-vinyl oxime ether (45a, Scheme 2.9) could not be isolated prior to 1,3-rearrangement a different approach was needed to avoid exposure to a Lewis acid.

A more modular approach was devised utilizing a copper-promoted etherification with vinylboronic acids.\textsuperscript{54-62} This was inspired by many reports of Chan-Lam-Evans type coupling reactions with alcohols and both aryl and vinylboronic acids.\textsuperscript{54-62} A report by Huang and coworkers showed that benzophenone oxime (49a) and acetophenone oxime are competent nucleophiles under copper-promoted conditions with phenylboronic acid to give the O-aryl oxime ethers (Scheme 2.13).\textsuperscript{62} These conditions provided a starting point for developing a new etherification method to obtain O-vinyl oxime ethers.

![Scheme 2.13 Copper-Promoted Coupling of Oximes with Aryl Boronic Acids.](image)

Beginning with camphor oxime (49b), 1-hexenylboronic acid (51b), stoichiometric copper (II) acetate, pyridine as the amine base, desiccant 4Å molecular sieves and 1,2-dichloroethane (DCE) for solvent (Scheme 2.14). The etherification product (45ba) was obtained in a low yield under stoichiometric copper conditions. Eventually, it was found that decreasing the amount of Cu(OAc)\textsubscript{2} to 10 mol % and adding a second portion of vinylboronic acid (51b) after 6 hours lead to a dramatic increase in yield to 74%.
Scheme 2.14 Coupling of Camphor Oxime with Hexenyl Boronic Acid.

With O-vinyl oxime ether (45ba) in hand we decided to try the thermal conditions to induce the [1,3]-rearrangement. The reaction was prepared in a glovebox with dried and degassed dioxane-\(d_8\). Only alkene isomerization was observed when the temperature was increased to 150 °C (Scheme 2.13). The desired α-imino aldehyde (46ba) was not observed.

Scheme 2.15 Thermally Induced Isomerization of O-Vinyl Camphor Oxime

2.3 Benzophenone Oxime as a Coupling Fragment

During the same time my co-worker Dr. Dimitra Kontokosta had discovered copper-promoted etherication conditions with benzophenone oxime (49a) and vinylboronic acid (51a) to give the O-vinyl oxime ether (45ba, table 2.3, entry 1). Initial
results showed low yields and suffered from hydrolysis of benzophenone oxime (11). Changing the copper salt to copper (I) thiophenecarboxylate (CuTC) and base to DABCO (entry 7) provided a combination that gave the product 42a in moderate yield and avoided hydrolysis due to short reaction time. The addition of silver salts were found to increase the yield of C–O bond formation. Most likely the silver salts are controlling the oxidation state of copper in solution. Ultimately AgClO₄ was identified as the best silver salt (entry 11). Addition of a second portion of vinylboronic acid (51) after 1.5 hours resulted in a significant increase in yield. We decided these were the optimal conditions for the coupling and explored the scope of the etherification.
Table 2.3 Optimization of Copper-Promoted Etherification.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>Cu Salt</th>
<th>base</th>
<th>Additive</th>
<th>$2.35^b$ (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Cu(OAc)$_2$</td>
<td>Py</td>
<td>none</td>
<td>42a (18)</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Cu(OAc)$_2$</td>
<td>NEt$_3$</td>
<td>none</td>
<td>42a (12)</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Cu(OAc)$_2$</td>
<td>DMAP</td>
<td>none</td>
<td>42a (28)</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Cu(OAc)$_2$</td>
<td>DABCO</td>
<td>none</td>
<td>42a (32)</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>CuCl</td>
<td>DABCO</td>
<td>none</td>
<td>42a (29)</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Cu(acac)$_2$</td>
<td>DABCO</td>
<td>none</td>
<td>42a (nr)</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>CuTC</td>
<td>DABCO</td>
<td>none</td>
<td>42a (51)</td>
</tr>
<tr>
<td>8</td>
<td>$n$-Bu</td>
<td>CuTC</td>
<td>DABCO</td>
<td>AgBF$_4$</td>
<td>42b (62)</td>
</tr>
<tr>
<td>9</td>
<td>$n$-Bu</td>
<td>CuTC</td>
<td>DABCO</td>
<td>AgOTf</td>
<td>42b (58)</td>
</tr>
<tr>
<td>10</td>
<td>$n$-Bu</td>
<td>CuOTf$^c$</td>
<td>DABCO</td>
<td>None</td>
<td>42b (7)</td>
</tr>
<tr>
<td>11</td>
<td>$n$-Bu</td>
<td>CuTC</td>
<td>DABCO</td>
<td>AgClO$_4$</td>
<td>42b (70)</td>
</tr>
<tr>
<td>12</td>
<td>$n$-Bu</td>
<td>CuTC</td>
<td>DABCO</td>
<td>AgClO$_4$</td>
<td>42b (39)</td>
</tr>
<tr>
<td>13</td>
<td>$n$-Bu</td>
<td>CuTC</td>
<td>DABCO</td>
<td>AgClO$_4$</td>
<td>42b (90)</td>
</tr>
</tbody>
</table>

(a) Reaction mixtures were prepared as 1:2:1:3:4:0.5 of 49a/51/[Cu]/Na$_2$SO$_4$/additive in DCE (0.1 M). (b) Percent yield determined by 1H NMR spectroscopy using CH$_2$Br$_2$ as a reference. (c) [CuOTf]$_2$-Tol. (d) 0.2 equiv of AgClO$_4$ was used. (e) A second portion of 51 was added after 1.5 h. (f) Optimization performed by Dr. Dimitra Kontokosta.
For the etherification, the coupling was general for mono-substituted vinylboronic acids. Alkyl chains were some of the best performing substrates (table 2.4, entries 1-3). Bulkier alkyl groups were tolerated as well but in reduced yield (entries 4-6). Benzylic substitution performed well also (entry 7). While phenyl substitution resulted in homo-coupling of the boronic acid as the major product. The aryl ethyl substituted vinylboronic acid (entry 8) etherification proceeded in good yield, which was pleasing to see a different substitution pattern. Benzyl and silyl ethers (entries 10-11) gave the coupling product in good yields. Chloro- and ester performed moderately (entries 12-13). Lastly the cyano substituted vinylboronic acid (entry 14) gave product 42n in the highest yield of 96%. We could now access a wide variety of O-vinyl oxime ethers with different functional groups to test the [1,3]-rearrangement.
With the O-vinyl oxime ether product easily obtained the conditions of the [1,3]-rearrangement were explored. Previously work in our group showed that dioxane was the best solvent for the rearrangement of O-vinyl oximes. To quickly explore the reactivity of 42 we performed these reactions in a J-Young tube in deuterated solvent.
and determined yield by $^1$H NMR spectroscopy. In addition, this avoided complications with isolating the unstable product. With the previous condition of 75 °C in dioxane-$d_8$ the [1,3]-rearrangement was complete in 3 hours (table 2.5, entry 1). Changing to more and less polar solvents resulted in decreased yield (entries 2-4). It appears that dioxane-$d_8$ is polar enough to stabilize the intermediate of the [1,3]-rearrangement and form the new C–N bond of the α-imino aldehyde 43b. Also a lower temperature and longer time resulted in low conversion and yield of 43b (entry 5). Ultimately we found that a higher temperature (100 °C) and short reaction time (30 minutes) lead to the optimal yield (entry 6). After determining the optimal conditions for the [1,3]-rearrangement the scope and functional group tolerance could be explored with the new etherification products.
Using the optimal conditions for the [1,3]-rearrangement the scope was explored. The alkyl-substituted examples were the best performing with \( n\text{-Bu} \) (43b) and cyclohexyl (43e) (Table 2.6, entries 2-5) being the highest yields. We were happy to see that bulky \( t\text{-Bu} \) (43f, entry 6) was well tolerated with the reaction. While the allylic \( O\text{-silyl ether} \) was not tolerated in the reaction (entry 10) the homoallylic \( O\text{-benzyl ether} \) (entry 11) was well tolerated. Other functional groups that were tolerated in the reaction included chloro, methyl ester and cyano (entries 12-14). These examples could be useful as synthetic handles in later syntheses. Another notable example was 43h (entry 8) since after rearrangement a 1:1 diastereomeric mixture was observed. This suggests that the rearrangement cannot be controlled by a substituent adjacent to the alkene. Lastly the

---

(a) 0.1 M solutions.  (b) Percent yield determined by 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

**Table 2.5** Optimization of [1,3]-Rearrangement.
cyclopropyl of 43i did not show any evidence of ring-opening, which suggests that the rearrangement does occur through a radical. Now that all of these α-imino aldehydes could be observed in situ a plan was devised to utilize and isolate these valuable products.
Chapter 2

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>72(^b)</td>
<td>9</td>
<td>22(^c)</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>10</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>11</td>
<td>56(^b)</td>
</tr>
<tr>
<td>5</td>
<td>72(^b)</td>
<td>12</td>
<td>63(^b)</td>
</tr>
<tr>
<td>6</td>
<td>64(^b)</td>
<td>13</td>
<td>56</td>
</tr>
<tr>
<td>7</td>
<td>66(^b)</td>
<td>14</td>
<td>58(^b)</td>
</tr>
</tbody>
</table>

(a) Percent yield determined by \(^1\)H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. (b) Compounds prepared by Dr. Dimitra Kontokosta. (c) No evidence of ring-opening was observed.

Table 2.6 Scope of [1,3]-Rearrangement.
Drawing from previous reports olefination was considered and we explored both Wittig and Horner-Wadsworth-Emmons (HWE) methods. Initial attempts with Wittig olefination showed greatly reduced yields from what we had observed by NMR. With a two-step method O-vinyl oxime ether (43c) was subjected to thermal conditions and the solution of 43c was added to a solution of the preformed ylide (Scheme 2.16). Allylic amine 52c’ was isolated after the two-step method. The highest yield observed for α-imino aldehyde (43c) was 62% and it was hypothesized that the Wittig conditions were too harsh. We found that phosphonates with a milder base were more suitable for our products. With these conditions we could quickly derivatize our previously observed α-imino aldehydes.

Scheme 2.16 Wittig Olefination of α-Imino Aldehyde

The HWE olefination was amicable to the majority of the α-imino aldehydes. The alkyl-substituted examples gave the γ-amino-α,β-unsaturated ester 52 in good to moderates yields. The best of which was cyclohexyl (52f) with 70% (table 2.7, entry 5). Sterically demanding t-Bu produced 52f in a moderate yield as well (entry 6) which was pleasing to see the bulky substituent well tolerated. Additionally, O-benzyl ether, chloro, methyl ester and cyano were easily converted to the γ-amino-α,β-unsaturated ester (entries 9-12) in moderate yields. These are important since the functional groups provide a valuable synthetic handle for further derivatization. Lastly, example 52h
(entry 7) was found to give an equal mixture of diastereomers, which further supports, an inability to have substrate control of diastereoselectivity.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>7</td>
<td>63 (^a)</td>
</tr>
<tr>
<td>2</td>
<td>69 (^b)</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>(52a)</td>
<td></td>
<td>(52g)</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>9</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>(52b)</td>
<td></td>
<td>(52h)</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>10</td>
<td>52 (^b)</td>
</tr>
<tr>
<td></td>
<td>(52c)</td>
<td></td>
<td>(52k)</td>
</tr>
<tr>
<td>5</td>
<td>70 (^e)</td>
<td>11</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>(52d)</td>
<td></td>
<td>(52l)</td>
</tr>
<tr>
<td>6</td>
<td>64 (^f)</td>
<td>12</td>
<td>55 (^b)</td>
</tr>
<tr>
<td></td>
<td>(52e)</td>
<td></td>
<td>(52m)</td>
</tr>
<tr>
<td></td>
<td>(52f)</td>
<td></td>
<td>(52n)</td>
</tr>
</tbody>
</table>

(a) Percent isolated yields. (b) compounds prepared by Dr. Dimitra Kontokosta.

**Table 2.7** Scope of HWE Olefination
2.4 Mechanistic Experiments

Since this reaction had not been reported before we wanted to probe the possible mechanistic pathways. It was hypothesized that there were three possible pathways for the transformation. First was a radical pathway where the N–O bond homolysis would lead to a carbon centered radical. Followed by radical recombination to form the new C–N bond. A radical pathway could be tested by the presence of a intra- or intermolecular radical trap. Another pathway would be a concerted reaction where C–N bond formation would occur simultaneously with N–O cleavage. If this was the case, stereochemical induction could result with an enantioenriched substrate leading to diastereoselectivity. Lastly, a ionic pathway might lead to an electrophilic imine intermediate that would be resonance stabilized by the adjacent phenyl groups. Preparing a reaction mixture with two different substrates and checking for crossover would test for this pathway.

A vinyl cyclopropane can act as radical clocks by trapping radical and the cyclopropane readily opens when a radical is adjacent. Various reports of substituted cyclopropyl groups have been shown by Newcomb to act as radical traps. The O-vinyl oxime ether $42i$ was easily prepared with the optimized coupling conditions. Under the thermal conditions there was no evidence of ring-opening and α-imino aldehyde $43i$ was the only product observed (Scheme 2.17). This satisfied testing of a intramolecular radical trap for the [1,3]-rearrangement. Testing for a radical intermediate with an intermolecular trap is common as well. For our case TEMPO was chosen since we believed it could form an α-oxygenated aldehyde as a result of radical recombination.
Upon heating 42b with TEMPO, the product 53b was observed in a lower NMR yield than previously observed. A radical crossover product was not observed though. The intra- and intermolecular radical traps suggest that most likely, for these examples the [1,3]-rearrangement is not going through a radical pathway.

![Scheme 2.17 Radical Trap Experiments](image)

In addition to the radical probe I had prepared chiral O-vinyl oxime ether 42h (table 2.4, entry 8) to test for diastereoselectivity in the [1,3]-rearrangement. When α-imino aldehyde 43h was observed in situ a 1:1 mixture of diastereomers were apparent (Scheme 2.18). Additionally when the two-step rearrangement and olefination was performed a 1:1 mixture of diastereomers for 52h were isolated. These experiments suggest that O-vinyl oxime ether 42h cannot control the intermediate in the [1,3]-rearrangement. Also this provides some evidence that a concerted mechanism might not be the pathway for the [1,3]-rearrangement.
Scheme 2.18 Experimental test for stereochemical induction in [1,3]-rearrangement.

In order to test for crossover a slightly different oxime had to be prepared to trace both halves of the O-vinyl oxime ether. For the crossover 42fa was synthesized and combined in a 3:1 ratio with 42a in dioxane-d$_8$ (Scheme 2.19). With help of Dr. Heng-Yen Wang we were able to observe crossover for the [1,3]-rearrangement. The α-imino aldehydes 43f and 43aa showed that the O-vinyl fragment from 42fa and 42a were able to crossover to the different imine fragments during the course of the reaction. This experiment highly suggests to us that the [1,3]-rearrangement proceeds through a solvent separated ionic dissociation pathway.

Scheme 2.19 Crossover During 1,3-Rearrangement

Considering all the mechanistic studies a proposed pathway could be an ion pair pathway seems the most likely. Initially, the enantioenriched substrate did not show
diastereocontrol during rearrangement which rules out a concerted path way and opens up the possibility of either an ion pair or radical pathway for 1,3-rearrangement. The crossover experiment supports an ion pair pathway since the experiment gave a mixture of products that could only occur if a solvent separated intermediate was formed. Since we observed crossover of differing fragments this follows other reports where crossover has been observed in reactions with ion pair pathways. Additionally the radical trap experiments suggest that a radical intermediate is not present during the rearrangement since ring opening was not observed nor was radical crossover with TEMPO. From these results we believe that an ion pair pathway is the most likely but a radical pathway could a second competing mechanism for the reaction.

2.5 Conclusion

In closing, we believe that the [1,3]-rearrangement of O-vinyl oxime ethers provide an advantageous alternative route to yielding a-amino aldehydes. Our modular coupling method allows for a variety of mono-substituted vinylboronic acids to quickly be coupled to benzophenone oxime to make the O-vinyl oxime ether starting material. With these the O-vinyl oxime ether simple thermal conditions in dioxane can provide the α-imino aldehydes in good yield and these products can then be used in the synthesis of other important molecules. Lastly the mechanistic studies help to support that a cationic pathway is present during the [1,3]-rearrangement.
2.6.1 General Experimental Information.

$^1$H NMR and $^{13}$C NMR spectra were recorded at ambient temperature using 500 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the $\delta$ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. High-resolution mass spectra were acquired on an LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Medium pressure liquid chromatography was performed to force flow the indicated solvent system down columns packed with 60Å (40 – 60 μm) mesh silica gel (SiO$_2$). Unless otherwise noted, all reagents were obtained from commercial sources and, where appropriate, purified prior to use. THF was dried by filtration through alumina according to the procedure of Grubbs.$^{42}$ Dioxane was distilled over CaH$_2$ and stored under N$_2$ prior to use. Dioxane-$d_8$ was dried over activated 4Å molecular sieves, degassed and stored in an inert atmosphere glovebox prior to use. Anhydrous dichloroethane (DCE) was used as received. Copper (I) thiophenecarboxylate was prepared according to the procedure of Maleczka.$^{66}$ Benzophenone oxime $49a$ and 4,4'-dimethylbenzophenone oxime $49aa$ were prepared according to Park.$^{67}$ Camphor oxime $49b$ was prepared according to Paquette.$^{62}$ O-Allyl camphor oxime $44a$ was prepared according to Gladiali.$^{73}$ Vinylboronic acids $51e$ and $51g$ were commercially available from Aldrich and used as received. The following alkenyl boronic acids were prepared via hydroboration by literature procedures: $51a$$^{68}$,
The following alkenyl boronic acid pinacol esters were prepared via hydroboration by literature procedures: S-1f, S-1j, S-1k, S-1l, and S-1n. Alkyne S-7h was prepared according to Fu.

2.6.2 Preparation of O-Vinyl Oximes

General Procedure F. A scintillation vial was charged with benzophenone oxime 49a (1 equiv), alkenyl boronic acid 51 (2 equiv), copper (I) thiophenecarboxylate (1 equiv), DABCO (3 equiv), AgClO₄ (0.5 equiv), and anhydrous Na₂SO₄ (4 equiv). These solids were then diluted with 1,2-dichloroethane (DCE) to form a 0.1 M solution of benzophenone oxime. The scintillation vial was then capped with a septum pierced with a ventilation needle and the reaction mixture was stirred at 25 °C for 1.5 h. At this time, the septum was removed and a second portion of alkenyl boronic acid (2 equiv) was added to the reaction mixture and the sides of the vial were washed with 1 mL of DCE. The reaction was once again capped with a septum pierced with a ventilation needle and the reaction mixture was allowed to stir for an additional 1.5 h (Note: The second addition of alkenyl boronic acid is not required; however, the yield of the C–O bond coupling will decrease by 26-48% depending on the identity of the substrate). The reaction mixture was then filtered through 5 mL of silica on a course glass fritted filter and washed with CH₂Cl₂ or EtOAc. Volatile materials were then removed from the filtrate under vacuum and the crude product mixture was purified by medium pressure
chromatography (100% hexanes – 1:10; ethyl acetate:hexanes) to give 14 as a yellow oil or solid.

![Image of 42a]

**O-Alkenylbenzophenone oxime 42a:** General procedure F was applied using the following reagents: benzophenone oxime 49a (0.030 g, 0.15 mmol), prop-1-enylboronic acid 51a (first addition, 0.026 g, 0.30 mmol), prop-1-enylboronic acid 51a (second addition, 0.026 g, 0.30 mmol), CuTC (0.029, 0.15 mmol), DABCO (0.051 g, 0.45 mmol), AgClO₄ (0.016 g, 0.075 mmol), and Na₂SO₄ (0.25 g, 1.8 mmol). This procedure afforded 42a as a colorless liquid (0.032 g, 90%) after purification using medium pressure chromatography (100% hexanes). "H NMR (500 MHz, CDCl₃): δ 7.52-7.50 (m, 2H), 7.46-7.43 (m, 3H), 7.41-7.33 (m, 5H), 6.87 (d, J = 12.5 Hz, 1H), 5.18 (dq, J = 12.5, 6.9 Hz, 1H), 1.62 (d, J = 6.9 Hz, 3H); "C NMR (125 MHz, CDCl₃): δ 158.6, 147.5, 135.9, 132.9, 129.7, 129.2, 129.1, 128.3, 128.2, 128.1, 101.1, 12.3; IR (thin film) 3056, 2921, 1671, 1494, 1444, 1326, 1304, 1265, 1126, 1098, 1032 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₆H₁₆NO (M+H)+ 238.1232, found 238.1236.

![Image of 42b]

**O-Alkenylbenzophenone oxime 42b:** General procedure F was applied using the following reagents: benzophenone oxime 49a (0.050 g, 0.25 mmol), hex-1-enylboronic acid 51b (first addition, 0.065 g, 0.51 mmol), hex-1-enylboronic acid 51b (second...
addition, 0.065 g, 0.51 mmol), CuTC (0.048 g, 0.25 mmol), DABCO (0.084 g, 0.75 mmol), AgClO₄ (0.026 g, 0.012 mmol), and Na₂SO₄ (0.25 g, 1.8 mmol). This procedure afforded 42b as a colorless liquid (0.062 g, 89%) after purification using medium pressure chromatography (100% hexanes). ¹H NMR (500 MHz, CDCl₃): δ 7.54-7.52 (m, 2H), 7.46-7.44 (m, 3H), 7.40-7.35 (m, 5H), 6.89 (d, J = 12.8 Hz, 1H), 5.19 (dt, J = 12.8, 7.3 Hz, 1H), 2.02-1.97 (m, 2H), 1.40-1.33 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.5, 147.0, 135.9, 132.9, 129.7, 129.3, 129.1, 128.3, 128.2, 128.1, 106.5, 32.4, 27.1, 22.1, 13.9; IR (thin film) 3057, 2925, 2871, 1669, 1465, 1444, 1326, 1169, 1142, 1115, 1032 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₉H₂₂NO (M+H)⁺ 280.1701, found 280.1707.

**42c**

**O-Alkenylbenzophenone oxime 42c:** General procedure F was applied using the following reagents: benzophenone oxime 49a (0.0400 g, 0.203 mmol), octenylboronic acid 51c (first addition, 0.0643 g, 0.412 mmol), second addition, 0.0750 g, 0.481 mmol), CuTC (0.0420 g, 0.221 mmol), DABCO (0.072 g, 0.64 mmol), AgClO₄ (0.023, 0.11 mmol), and Na₂SO₄ (0.26 g, 1.9 mmol). This procedure afforded 43c as a yellow oil (0.060 g, 96%) after purification using medium pressure chromatography (100% hexanes). ¹H NMR (500 MHz; CDCl₃): δ 7.54-7.52 (m, 2H), 7.46-7.44 (m, 3H), 7.40-7.35 (m, 5H), 6.89 (d, J = 12.6 Hz, 1H), 5.13 (dt, J = 12.6, 7.5 Hz, 1H), 2.01-1.97 (m, 2H), 1.42-1.36 (m, 2H), 1.35-1.28 (m, 6H), 0.91 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.5, 147.1, 136.0, 133.0, 129.7, 129.3, 129.1, 128.3, 128.2, 128.1, 106.5,
31.8, 30.3, 28.8, 27.5, 22.7, 14.2; IR (thin film) 3057, 2955, 2853, 1668, 1444, 1325, 1115, 977, 922, 771, 692 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{21}$H$_{26}$NO (M+H)$^+$ 308.2014, found 308.2019.

![Image of 42d](image)

**O-Alkenylbenzophenone oxime 42d:** General procedure F was applied using the following reagents: benzophenone oxime 49a (0.050 g, 0.25 mmol), 3-methylbut-1-enylboronic acid 51d (first addition, 0.058 g, 0.51 mmol), 3-methylbut-1-enylboronic acid 51d (second addition, 0.058 g, 0.51 mmol), CuTC (0.048 g, 0.25 mmol), DABCO (0.084 g, 0.75 mmol), AgClO$_4$ (0.026 g, 0.012 mmol), and Na$_2$SO$_4$ (0.25 g, 1.8 mmol). This procedure afforded 43d as a colorless liquid (0.055 g, 83%) after purification using medium pressure chromatography (100% hexanes). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.53-7.50 (m, 2H), 7.46-7.43 (m, 3H), 7.40-7.33 (m, 5H), 6.87 (d, $J = 12.7$ Hz, 1H), 5.17 (dd, $J = 12.7$, 6.8 Hz, 1H), 2.35-2.28 (m, 1H), 1.03 (d, $J = 6.8$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 158.5, 145.7, 135.9, 132.9, 129.7, 129.3, 129.1, 128.3, 128.2, 128.1, 113.7, 27.2, 23.3; IR (thin film) 3059, 2958, 2870, 1717, 1651, 1623, 1597, 1465, 1275, 1176, 1041 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{18}$H$_{20}$NO (M+H)$^+$ 266.1545, found 266.1544.

![Image of 42e](image)
**O-Alkenylbenzophenone oxime 42e:** General procedure F was applied using the following reagents: benzophenone oxime 49a (0.030 g, 0.15 mmol), 2-cyclohexylvinylboronic acid 51e (first addition, 0.047 g, 0.30 mmol), 2-cyclohexylvinylboronic acid 51e (second addition, 0.047 g, 0.30 mmol), CuTC (0.029 g, 0.15 mmol), DABCO (0.051 g, 0.45 mmol), AgClO$_4$ (0.016 g, 0.075 mmol), and Na$_2$SO$_4$ (0.25 g, 1.8 mmol). This procedure afforded 42e as a colorless liquid (0.038 g, 84%) after purification using medium pressure chromatography (100% hexanes). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.53-7.50 (m, 2H), 7.46-7.43 (m, 3H), 7.40-7.33 (m, 5H), 6.88 (d, J = 12.7 Hz, 1H), 5.16 (dd, J = 12.7, 7.6 Hz, 1H), 2.00-1.91 (m, 1H), 1.77-1.69 (m, 4H), 1.68-1.62 (m, 1H), 1.33-1.23 (m, 2H), 1.21-1.06 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 158.4, 146.0, 136.0, 132.9, 129.7, 129.3, 129.1, 128.3, 128.2, 128.1, 112.6, 36.7, 33.9, 26.0, 26.1; IR (thin film) 3058, 2921, 2849, 1666, 1493, 1444, 1325, 1169, 1124, 1091, 1075 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{21}$H$_{24}$NO (M+H)$^+$ 306.1858, found 306.1865.

![42f](image)

**O-Alkenylbenzophenone oxime 42f:** General procedure F was applied using the following reagents: benzophenone oxime 49a (0.040 g, 0.20 mmol), 3,3-dimethylbut-1-enylboronic acid 51f (first addition, 0.053 g, 0.41 mmol), 3,3-dimethylbut-1-enylboronic acid 51f (second addition, 0.053 g, 0.41 mmol), CuTC (0.038 g, 0.20 mmol), DABCO (0.067 g, 0.60 mmol), AgClO$_4$ (0.021 g, 0.10 mmol), and Na$_2$SO$_4$ (0.25 g, 1.8 mmol). This procedure afforded 51f as a colorless liquid (0.034 g, 61%) after purification using medium pressure chromatography (100% hexanes). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.54-
7.50 (m, 2H), 7.47-7.43 (m, 3H), 7.40-7.33 (m, 5H), 6.88 (d, \( J = 12.8 \) Hz, 1H), 5.24 (d, \( J = 12.8 \) Hz, 1H), 1.07 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 158.4, 145.1, 136.0, 132.9, 129.7, 129.3, 129.1, 128.3, 128.2, 128.1, 117.8, 30.9, 30.3; IR (thin film) 3061, 2959, 2903, 2866, 1662, 1474, 1462, 1444, 1362, 1201, 1113 cm\(^{-1}\); HRMS (ESI) \( m/z \) calcd. for C\(_{19}\)H\(_{22}\)NO (M+H\(^+\)) 280.1701, found 280.1697.

\[ \text{42g} \]

**O-Alkenylbenzophenone oxime 42g:** General procedure F was applied using the following reagents: benzophenone oxime 11 (0.040 g, 0.20 mmol), 3-phenylprop-1-enylboronic acid 51g (first addition, 0.066 g, 0.41 mmol), 3-phenylprop-1-enylboronic acid 51g (second addition, 0.066 g, 0.41 mmol), CuTC (0.038 g, 0.20 mmol), DABCO (0.067 g, 0.60 mmol), AgClO\(_4\) (0.021 g, 0.10 mmol), and Na\(_2\)SO\(_4\) (0.25 g, 1.8 mmol). This procedure afforded 42g as a colorless liquid (0.049 g, 78%) after purification using medium pressure chromatography (100% hexanes). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.55-7.50 (m, 2H), 7.49-7.41 (m, 3H), 7.41-7.31 (m, 5H), 7.31-7.29 (m, 2H), 7.29-7.19 (m, 3H), 6.96 (d, \( J = 12.5 \) Hz, 1H), 5.38 (dt, \( J = 12.5, 7.5 \) Hz, 1H), 3.33 (d, \( J = 7.5 \) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 158.9, 148.0, 141.0, 135.8, 132.8, 129.8, 129.3, 129.1, 128.5, 128.4, 128.3, 128.2, 128.1, 126.0, 105.1, 33.8; IR (thin film) 3059, 3026, 1668, 1494, 1444, 1326, 1168, 1125, 1031 cm\(^{-1}\); HRMS (ESI) \( m/z \) calcd. for C\(_{22}\)H\(_{20}\)NO (M+H\(^+\)) 314.1545, found 314.1540.
**O-Alkenylbenzophenone oxime 42h:** General procedure F was applied using the following reagents: benzophenone oxime 49a (0.0384 g, 0.194 mmol), 3-(4'-tert-butylphenyl)pentenylboronic acid 51h (first addition, 0.114 g, 0.429 mmol, second addition, 0.109 g, 0.416 mmol), CuTC (0.0395 g, 0.208 mmol), DABCO (0.0744 g, 0.664 mmol), AgClO₄ (0.0211, 0.101 mmol), and Na₂SO₄ (0.311 g, 2.22 mmol). This procedure afforded 42h as an amorphous solid (0.054 g, 69%) after purification using medium pressure chromatography (100% hexanes). ¹H NMR (500 MHz; CDCl₃): δ 7.52-7.50 (m, 2H), 7.44-7.43 (m, 3H), 7.39 (d, J = 7.24 Hz, 1H), 7.37-7.31 (m, 6H), 7.16 (d, J = 7.2 Hz, 2H), 6.92 (d, J = 12.6 Hz, 1H), 5.33 (dd, J = 12.6, 8.8 Hz, 1H), 3.12-3.07 (m, 1H), 1.79-1.68 (m, 2H), 1.32 (s, 9H), 0.91 (t, J = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 158.6, 148.7, 147.2, 142.3, 135.9, 132.9, 129.8, 129.3, 129.1, 128.3, 128.2, 128.1, 127.1, 125.3, 110.2, 45.8, 34.4, 31.5, 29.4, 12.4; IR (thin film) 3054, 2961, 2928, 2870, 1664, 1505, 1444, 1270, 1126, 995 cm⁻¹; HRMS (ESI) m/z calcd. for C₂₈H₃₂NO (M+H)⁺ 398.2484, found 398.2481.

**O-Alkenylbenzophenone oxime 42i:** General procedure F was applied using the following reagents: benzophenone oxime 49a (0.0402 g, 0.204 mmol), 2-
(cyclopropyl)ethenylboronic acid 51i (first addition, 0.0488 g, 0.381 mmol, second addition, 0.0427 g, 0.381 mmol), CuTC (0.0362 g, 0.191 mmol), DABCO (0.079 g, 0.71 mmol), AgClO₄ (0.0282, 0.136 mmol), and Na₂SO₄ (0.281 g, 2.01 mmol). This procedure afforded 42i as a yellow oil (0.0303 g, 56%) after purification using medium pressure chromatography (100% hexanes). ¹H NMR (500 MHz; CDCl₃): δ 7.52-7.50 (m, 2H), 7.44-7.43 (m, 3H), 7.40-7.33 (m, 5H), 6.96 (d, J = 12.5 Hz, 1H), 4.93 (dd, J = 12.5, 8.0 Hz, 1H), 1.32-1.27 (m, 1H), 0.67-0.64 (m, 2H), 0.33-0.29 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 158.7, 146.5, 135.9, 132.9, 129.8, 129.3, 129.1, 128.3, 128.2, 128.1, 110.1, 9.0, 5.9; IR (thin film) 3061, 3007, 2921, 1660, 1492, 1446, 1318, 1276, 1176, 1028 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₈H₁₈NO (M+H)⁺ 264.1388, found 264.1385.

![Image](image-url)

42j

O-Alkenylbenzophenone oxime 42j: General procedure F was applied using the following reagents: benzophenone oxime 49a (0.045 g, 0.23 mmol), 3-(tert-butylidimethylsiloxy)prop-1-enylboronic acid 51j (first addition, 0.090 g, 0.42 mmol, second addition, 0.13 g, 0.58 mmol), CuTC (0.038 g, 0.20 mmol), DABCO (0.076 g, 0.68 mmol), AgClO₄ (0.022, 0.11 mmol), and Na₂SO₄ (0.29 g, 2.1 mmol). This procedure afforded 42j as a yellow oil (0.059 g, 71%) after purification using medium pressure chromatography (100% hexanes). ¹H NMR (500 MHz; CDCl₃): δ 7.55-7.53 (m, 2H), 7.47-7.45 (m, 3H), 7.41 (d, J = 7.0 Hz, 1H), 7.38-7.35 (m, 4H), 7.07 (d, J = 12.5 Hz, 1H), 5.38 (dd, J = 12.5, 6.5 Hz, 1H), 4.19 (dd, J = 6.5, 1.0 Hz, 2H), 0.94 (s, 9H),
0.12 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 159.4, 149.1, 135.7, 129.9, 129.3, 129.2, 129.1, 128.3, 128.2, 128.1, 105.0, 60.8, 26.1, 18.5, -5.0; IR (thin film) 3064, 2953, 2928, 1666, 1470, 1445, 1123, 1053, 833, 809 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{22}$H$_{29}$NO$_2$Si (M+H)$^+$ 368.2042, found 368.2046.

42k

**O-Alkenylbenzophenone oxime 42k:** General procedure F was applied using the following reagents: benzophenone oxime 49a (0.040 g, 0.20 mmol), 4-(benzyloxy)but-1-enylboronic acid 51k (first addition, 0.085 g, 0.41 mmol), 4-(benzyloxy)but-1-enylboronic acid 51k (second addition, 0.085 g, 0.41 mmol), CuTC (0.038 g, 0.20 mmol), DABCO (0.067 g, 0.60 mmol), AgClO$_4$ (0.021 g, 0.10 mmol), and Na$_2$SO$_4$ (0.25 g, 1.8 mmol). This procedure afforded 42k as a colorless liquid (0.058 g, 82%) after purification using medium pressure chromatography (1:10, EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.54-7.50 (m, 2H), 7.47-7.43 (m, 3H), 7.41-7.38 (m, 1H), 7.38-7.33 (m, 8H), 7.31-7.27 (m, 1H), 6.94 (d, $J = 12.6$ Hz, 1H), 5.20 (dt, $J = 12.6$, 7.5 Hz, 1H), 4.53 (s, 2H), 3.50 (t, $J = 7.69$ Hz, 2H), 2.35-2.29 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 158.9, 148.4, 138.5, 135.8, 132.8, 129.8, 129.2, 129.1, 128.4, 128.3, 128.2, 128.1, 127.7, 127.5, 102.2, 72.9, 70.7, 28.1; IR (thin film) 3059, 2854, 1669, 1494, 1444, 1362, 1326, 1265, 1207, 1169, 1098; HRMS (ESI) $m/z$ calcd. for C$_{24}$H$_{24}$NO$_2$ (M+H)$^+$ 358.1807, found 358.1807.

42I
O-Alkenylbenzophenone oxime 42l: General procedure F was applied using the following reagents: benzophenone oxime 49a (0.0415 g, 0.211 mmol), 6-chlorohexenylboronic acid 51l (first addition, 0.0687 g, 0.423 mmol), (second addition, 0.086 g, 0.53 mmol), CuTC (0.0424g, 0.223 mmol), DABCO (0.0758 g, 0.677 mmol), AgClO₄ (0.0295, 0.143 mmol), and Na₂SO₄ (0.31 g, 2.2 mmol). This procedure afforded 42l as an amorphous solid (0.0481 g, 73%) after purification using medium pressure chromatography (0:1, EtOAc:hexanes). ¹H NMR (500 MHz; CDCl₃): δ 7.54-7.52 (m, 2H), 7.47-7.45 (m, 3H), 7.41-7.34 (m, 5H), 6.90 (d, J = 12.6 Hz, 1H), 5.17 (dt, J = 12.6, 7.5 Hz, 1H), 3.55 (t, J = 6.7 Hz, 2H), 2.05-2.00 (m, 2H), 1.84-1.78 (m, 2H), 1.57-1.53 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 158.8, 147.6, 135.9, 133.0, 129.9, 129.3, 129.2, 128.4, 128.3, 128.2, 105.5, 45.0, 32.0, 27.4, 26.8; IR (thin film) 3070, 2921, 1668, 1443, 1324, 1169, 1119, 977, 772, 693 cm⁻¹; HRMS (ESI) m/z calcd. for C₁₉H₂₁ClNO (M+H)⁺ 314.1312, found 314.1305.

![Chemical Structure](image)

O-Alkenylbenzophenone oxime 42m: General procedure F was applied using the following reagents: benzophenone oxime 49a (0.0399 g, 0.203 mmol), methyl 5-hexenoateboronic acid 51m (first addition, 0.0714 g, 0.415 mmol, second addition, 0.0725 g, 0.422 mmol), CuTC (0.0388 g, 0.204 mmol), DABCO (0.0704 g, 0.629 mmol), AgClO₄ (0.0294, 0.142 mmol), and Na₂SO₄ (0.301 g, 2.15 mmol). This procedure afforded 42m as a yellow oil (0.042 g, 64%) after purification using medium pressure chromatography (5:95, EtOAc:hexanes). ¹H NMR (500 MHz; CDCl₃): δ 7.52-7.50 (m,
2H), 7.45-7.44 (m, 3H), 7.40-7.33 (m, 5H), 6.88 (d, \( J = 12.6 \) Hz, 1H), 5.13 (dt, \( J = 12.6, 7.5 \) Hz, 1H), 3.66 (s, 3H), 2.34, (t, \( J = 7.5 \) Hz, 2H), 2.05-2.00 (m, 2H), 1.75-1.69 (m, 2H);

\( ^{13}C \) NMR (125 MHz, CDCl\(_3\)): \( \delta \) 174.1, 158.8, 147.8, 135.8, 132.8, 129.8, 129.3, 129.2, 128.3, 128.2, 128.1, 104.9, 51.5, 33.3, 26.9, 25.4; IR (thin film) 3057, 2917, 2848, 1735, 1667, 1443, 1324, 1167, 1123, 978 cm\(^{-1}\); HRMS (ESI) \( m/z \) calcd. for C\(_{20}\)H\(_{22}\)NO\(_3\) (M+H)\(^+\) 324.1600, found 324.1596.

\[
\begin{align*}
\text{42n} \\
\text{O-Alkenylbenzophenone oxime 42n:} \text{ General procedure F was applied using the following reagents: benzophenone oxime 49a (0.040 g, 0.20 mmol), 5-cyanopent-1-enylboronic acid 51n (first addition, 0.061 g, 0.40 mmol), 5-cyanopent-1-enylboronic acid 51n (second addition, 0.061 g, 0.4mmol), CuTC (0.038 g, 0.20 mmol), DABCO (0.067 g, 0.60 mmol), AgClO}_4 (0.021 g, 0.10 mmol), and Na\(_2\)SO\(_4\) (0.25 g, 1.8 mmol). This procedure afforded 42n as a colorless liquid (0.056 g, 96%) after purification using medium pressure chromatography (1:10, EtOAc:hexanes).} \\
\text{\( ^1H \) NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.53-7.49 (m, 2H), 7.47-7.43 (m, 3H), 7.41-7.39 (m, 1H), 7.37-7.32 (m, 4H), 6.92 (d, \( J = 12.54 \) Hz, 1H), 5.09 (dt, \( J = 12.54, 7.62 \) Hz, 1H), 2.36 (t, \( J = 7.16 \) Hz, 2H), 2.18-2.12 (m, 2H), 1.78-1.70 (m, 2H); \( ^{13}C \) NMR (125 MHz, CDCl\(_3\)): \( \delta \) 159.2, 148.5, 135.7, 132.8, 130.0, 129.2, 128.4, 128.3, 128.2, 128.1, 119.6, 103.1, 26.3, 25.8, 16.2; IR (thin film) 3058, 2933, 2245, 1668, 1494, 1443, 1325, 1305, 1179, 1127cm\(^{-1}\); HRMS (ESI) \( m/z \) calcd. for C\(_{19}\)H\(_{19}\)N\(_2\)O (M+H)\(^+\) 291.1497, found 291.1505.}
\end{align*}
\]
**O-Alkenyl-4,4’-dimethyl benzophenone oxime 42fa:** General procedure F was applied using the following reagents: 4,4’-dimethyl benzophenone oxime 49aa (0.11 g, 0.51 mmol), 3,3-dimethylbut-1-enylboronic acid 51f (first addition, 0.14 g, 1.1 mmol, second addition, 0.11 g, 0.87 mmol), CuTC (0.11 g, 0.58 mmol), DABCO (0.20 g, 1.7 mmol), AgClO₄ (0.052, 0.25 mmol), and Na₂SO₄ (0.62 g, 4.5 mmol). This procedure afforded 42fa as a yellow oil (0.064 g, 41%) after purification using medium pressure chromatography (0:100, EtOAc:hexanes).¹H NMR (500 MHz, CDCl₃): δ 7.40 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 13.0 Hz, 1H), 5.23 (d, J = 13.0 Hz, 1H), 2.42 (s, 3H), 2.37 (s, 3H), 1.06 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 158.5, 145.1, 139.8, 139.0, 133.4, 130.1, 129.4, 129.0, 128.7, 128.3, 117.6, 30.9, 30.4, 21.5, 21.4.

**2.6.3 [1,3] Rearrangement of O-Vinyl Oximes**

![Diagram](image)

**General Procedure G.** In an inert atmosphere glovebox, a J-Young tube was charged with O-alkenyl benzophenone oxime 14 (1 equiv), 1,3,5-trimethoxybenzene (0.3 equiv), and diluted to make a 0.1 M solution of 14 in dioxane-d₆. The tube was then removed
from the glovebox and heated to 100 ºC in an oil bath for 30 min. ¹H NMR spectroscopy was then used to determine the yield of the aldehyde 15 with respect to the trimethoxybenzene internal standard. Additional spectroscopic characterization was collected using the same solution.

α-Iminoaldehyde 43a: General procedure G was applied using the following reagents: O-alkenylbenzophenone oxime 42a (0.028 g, 0.12 mmol) and 1,3,5-trimethoxybenzene (0.0091 g, 0.054 mmol). ¹H NMR analysis of the reaction mixture indicated that the yield of the in situ generated α-iminoaldehyde 43a was 56%. ¹H NMR (500 MHz; dioxane-d₈): δ 9.63 (d, J = 1.4 Hz, 1H), 7.52-7.44 (m, 4H), 7.44-7.37 (m, 3H), 7.36-7.31 (m, 3H), 3.89-3.82 (m, 1H), 1.28 (d, J = 6.82 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 200.8, 169.7, 136.5, 130.3, 128.6, 128.5, 128.4, 127.9, 127.7, 127.6, 66.6, 16.1.

α-Iminoaldehyde 43b: General procedure G was applied using the following reagents: O-alkenylbenzophenone oxime 42b (0.029 g, 0.10 mmol) and 1,3,5-trimethoxybenzene (0.010 g, 0.059 mmol). ¹H NMR analysis of the reaction mixture indicated that the yield of the in situ generated α-iminoaldehyde 43b was 72%. ¹H NMR (500 MHz; dioxane-d₈): δ 9.59 (d, J = 1.7 Hz, 1H), 7.50-7.44 (m, 3H), 7.44-7.37 (m, 4H), 7.36-7.31 (m, 3H),
3.81-3.76 (m, 1H), 1.84-1.78 (m, 2H), 1.35-1.12 (m, 4H), 0.86 (t, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 200.3, 170.1, 139.4, 136.7, 130.2, 128.6, 128.5, 128.4, 127.9, 127.8, 71.6, 31.0, 27.7, 22.3, 13.3.

\(\text{43c}\)

\(\alpha\)-Iminoaldehyde 43c: General procedure G was applied using the following reagents: \(O\)-alkenylbenzophenone oxime \(42c\) (0.0315 g, 0.103 mmol) and 1,3,5-trimethoxybenzene (0.0069 g, 0.041 mmol). \(^1\)H NMR analysis of the reaction mixture indicated that the yield of the in situ generated \(\alpha\)-iminoaldehyde 43c was 62%. \(^1\)H NMR (500 MHz; dioxane-\(d_8\)): \(\delta\) 9.58 (d, \(J = 1.8\) Hz, 1H), 7.49-7.38 (m, 7H), 7.35-7.32 (m, 3H), 3.80-3.77 (m, 1H), 1.83-1.79 (m, 2H), 1.34-1.29 (m, 2H), 1.25-1.22 (m, 6H) 0.86 (t, \(J = 6.7\) Hz, 3H); \(^{13}\)C NMR (125 MHz, dioxane-\(d_8\)): \(\delta\) 200.3, 170.1, 139.4, 136.6, 130.2, 128.6, 128.5, 128.4, 127.9, 127.8, 71.5, 31.5, 31.3, 28.9, 25.5, 22.4, 13.5.

\(\text{43d}\)

\(\alpha\)-Iminoaldehyde 42d: General procedure G was applied using the following reagents: \(O\)-alkenylbenzophenonem oxime \(42d\) (0.022 g, 0.083 mmol) and 1,3,5-trimethoxybenzene (0.0092 g, 0.055 mmol). \(^1\)H NMR analysis of the reaction mixture indicated that the yield of the in situ generated \(\alpha\)-iminoaldehyde 43d was 63%. \(^1\)H NMR (500 MHz; dioxane-\(d_8\)): \(\delta\) 9.61 (d, \(J = 2.1\) Hz, 1H), 7.49-7.37 (m, 7H), 7.36-7.31 (m, 3H),
3.59-3.55 (m, 1H), 2.36-2.27 (m, 1H), 1.00 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.7 Hz, 3H);

$^{13}$C NMR (125 MHz, dioxane-$d_8$): $\delta$ 200.4, 170.4, 139.6, 136.6, 130.2, 128.5, 128.5, 128.4, 128.0, 127.9, 77.1, 30.8, 18.8, 17.9.

![Diagram](image)

**$\alpha$-Iminoaldehyde 43e:** General procedure G was applied using the following reagents: $O$-alkenylbenzophenone oxime 42e (0.027 g, 0.088 mmol) and 1,3,5-trimethoxybenzene (0.0088 g, 0.052 mmol). $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated $\alpha$-iminoaldehyde 43e was 72%. $^1$H NMR (500 MHz; dioxane-$d_8$): $\delta$ 9.60 (d, $J = 2.29$ Hz, 1H), 7.49-7.36 (m, 7H), 7.35-7.30 (m, 3H), 3.60-3.56 (m, 1H), 2.10-2.00 (m, 1H), 1.76-1.66 (m, 6H), 1.31-1.17 (m, 4H); $^{13}$C NMR (125 MHz, dioxane-$d_8$): $\delta$ 200.3, 170.1, 139.6, 136.6, 130.2, 128.5, 128.4, 128.3, 128.0, 127.9, 76.9, 40.4, 29.6, 28.7, 26.1.

![Diagram](image)

**$\alpha$-Iminoaldehyde 43f:** General procedure G was applied using the following reagents: $O$-alkenylbenzophenone oxime 42f (0.024 g, 0.086 mmol) and 1,3,5-trimethoxybenzene (0.014 g, 0.081 mmol). $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated $\alpha$-iminoaldehyde 43f was 64%. $^1$H NMR (500 MHz; dioxane-$d_8$): $\delta$ 9.71 (d, $J = 2.8$ Hz, 1H), 7.47-7.41 (m, 5H), 7.41-7.37 (m, 2H), 7.36-7.31 (m, 3H), 3.43
(d, \( J = 2.8 \) Hz, 1H), 1.02 (s, 9H); \(^{13}\)C NMR (125 MHz, dioxane-\(d_8\)): \( \delta \) 200.7, 170.1, 139.7, 136.5, 130.2, 129.2, 128.5, 128.5, 128.0, 127.9, 79.8, 36.0, 26.3.

\[ \text{43g} \]

**α-Iminoaldehyde 43g:** General procedure G was applied using the following reagents: O-alkenylbenzophenone oxime 42g (0.027 g, 0.086 mmol) and 1,3,5-trimethoxybenzene (0.012 g, 0.071 mmol). \(^1\)H NMR analysis of the reaction mixture indicated that the yield of the in situ generated α-iminoaldehyde 43g was 66%. \(^1\)H NMR (500 MHz; dioxane-\(d_8\)): \( \delta \) 9.66 (d, \( J = 2.3 \) Hz, 1H), 7.50-7.35 (m, 4H), 7.34-7.26 (m, 7H), 7.21-7.13 (m, 4H), 4.02-3.96 (m, 1H), 3.18-3.06 (m, 2H); \(^{13}\)C NMR (125 MHz, dioxane-\(d_8\)): \( \delta \) 199.6, 170.7, 139.3, 137.9, 136.3, 130.3, 129.8, 128.5, 128.3, 128.2, 128.1, 127.9, 127.5, 126.1, 73.4, 37.3.

\[ \text{43h} \]

**α-Iminoaldehyde 43h:** General procedure G was applied using the following reagents: O-alkenylbenzophenone oxime 42h (0.0379 g, 0.0953 mmol) and 1,3,5-trimethoxybenzene (0.0044 g, 0.026 mmol). \(^1\)H NMR analysis of the reaction mixture indicated that the yield of the in situ generated α-iminoaldehyde 43h was 39%, 1:1.3 d.r. \(^1\)H NMR (major diastereomer) (500 MHz; dioxane-\(d_8\)): \( \delta \) 9.55 (d, \( J = 1.4 \) Hz, 1H), 7.55-
7.53 (m, 2H), 7.45-7.38 (m, 3H), 7.36-7.27 (m, 7H), 6.71-6.70 (m, 2H), 3.90-3.89 (m, 1H), 3.31-3.27 (m, 1H), 1.93-1.87 (m, 1H), 1.69-1.62 (m, 1H), 1.30 (s, 9H), 0.76 (t, J = 7.3 Hz, 3H); $^{13}$C NMR (125 MHz, dioxane-$d_8$): $\delta$ 199.6, 170.7, 149.3, 139.5, 138.2, 126.3, 128.9, 128.6, 128.3, 128.0, 127.9, 127.6, 125.1, 124.8, 76.3, 49.4, 34.2, 30.9, 23.5, 11.8. $^1$H NMR (minor diastereomer) (500 MHz; dioxane-$d_8$): $\delta$ 9.54 (d, J = 2.6 Hz, 1H) 7.45-7.38 (m, 3H), 7.36-7.27 (m, 7H), 7.01-7.00 (m, 2H), 6.83-6.82 (m, 2H), 3.97-3.95 (m, 1H), 3.19-3.15 (m, 1H), 1.93-1.87 (m, 1H), 1.69-1.62 (m, 1H), 1.29 (s, 9H), 0.72 (t, J = 7.3 Hz, 3H); $^{13}$C NMR (125 MHz, dioxane-$d_8$): $\delta$ 199.8, 170.2, 149.1, 139.7, 138.2, 126.3, 128.9, 128.6, 128.3, 128.0, 127.9, 127.6, 125.1, 124.8, 77.0, 49.6, 34.2, 30.9, 24.8, 11.6.

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{O} \\
\text{Ph} \\
\end{array}
\]

\textbf{43i}

\textbf{α-Iminoaldehyde 43i:} General procedure G was applied using the following reagents: O-alkenylbenzophenone oxime 42i (0.0303 g, 0.115 mmol) and 1,3,5-trimethoxybenzene (0.0078 g, 0.046 mmol). $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated α-iminoaldehyde 43i was 22%. $^1$H NMR (500 MHz; dioxane-$d_8$): $\delta$ 9.67 (d, J = 2.0 Hz, 1H), 7.49-7.37 (m, 7H), 7.35-7.32 (m, 3H), 3.35-3.33 (m, 1H), 2.19-1.12 (m, 1H), 0.50-0.49 (m, 2H), 0.29-0.28 (m, 2H); $^{13}$C NMR (125 MHz, dioxane-$d_8$): $\delta$ 199.1, 161.6, 136.5, 130.2, 129.2, 129.0, 128.5, 128.1, 127.9, 127.7, 74.2, 12.4, 0.7.
**α-Iminoaldehyde 43k:** General procedure G was applied using the following reagents:

\[ \text{O-alkenylbenzophenone oxime 43k (0.026 g, 0.072 mmol) and 1,3,5-trimethoxybenzene (0.0096 g, 0.057 mmol).} \]

\[ 1^H \text{ NMR analysis of the reaction mixture indicated that the yield of the in situ generated α-iminoaldehyde 43k was 56% (ratio of 43k:43k'} = 1:0.4). \]

\[ {1^H \text{NMR (500 MHz; dioxane-d}_8): \delta 9.55 (d, } J = 1.3 \text{ Hz, 1H), 7.44-7.22 (m, 15H), 4.05-4.03 (m, 1H), 4.41 (s, 2H), 3.48-3.44 (m, 2H), 2.15-2.11 (m, 2H); diagnostic resonance for minor isomer: } {1^H \text{NMR (500 MHz; dioxane-d}_8): \delta 9.63 (d, } J = 1.5 \text{ Hz); } ^{13}C \text{ NMR (125 MHz, dioxane-d}_8): \delta 199.4, 170.7, 139.4, 138.8, 136.7, 130.2, 128.6, 128.5, 128.4, 128.0, 127.9, 127.7, 127.3, 110.0, 72.3, 68.8, 64.5, 31.6.} \]

**α-Iminoaldehyde 43l:** General procedure G was applied using the following reagents:

\[ \text{O-alkenylbenzophenone oxime 42l (0.0329 g, 0.105 mmol) and 1,3,5-trimethoxybenzene (0.0073, 0.043 mmol).} \]

\[ 1^H \text{ NMR analysis of the reaction mixture indicated that the yield of the in situ generated α-iminoaldehyde 43l was 63%.} \]

\[ {1^H \text{NMR (500 MHz; dioxane-d}_8): \delta 9.58 (d, } J = 1.6 \text{ Hz, 1H), 7.50-7.44 (m, 4H), 7.43-7.38 (m, 3H), 7.35-7.32 (m, 3H), 3.83-3.80 (m, 1H), 3.51 (t, } J = 6.8 \text{ Hz, 2H), 1.86-1.82 (m, 2H), 1.71-} \]

110
1.64 (m, 2H), 1.46-1.40 (m, 1H), 1.39-1.34 (m, 1H); $^{13}$C NMR (125 MHz, dioxane-$d_8$): δ 200.1, 170.6, 139.3, 136.6, 130.4, 128.7, 128.6, 128.5, 128.0, 127.8, 71.3, 44.3, 32.3, 30.5, 23.0.

\[ \text{43m} \]

**α-Iminoaldehyde 43m:** General procedure G was applied using the following reagents: O-alkenylbenzophenoneoxime 42m (0.0374 g, 0.116 mmol) and 1,3,5-trimethoxybenzene (0.0094, 0.056 mmol). $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated α-iminoaldehyde 43m was 56%. $^1$H NMR (500 MHz; dioxane-$d_8$): δ 9.57 (d, $J = 1.5$ Hz, 1H), 7.50-7.44 (m, 4H), 7.42-7.38 (m, 3H), 7.35-7.32 (m, 3H), 3.83-3.79 (m, 1H), 3.58 (s, 3H), 2.24-2.19 (m, 2H), 1.86-1.81 (m, 2H), 1.60-1.57 (m, 1H), 1.53-1.49 (m, 1H); $^{13}$C NMR (125 MHz, dioxane-$d_8$): δ 200.1, 172.8, 170.6, 161.7, 139.3, 136.6, 130.34, 128.6, 128.5, 128.0, 127.8, 71.3, 50.6, 33.1.

\[ \text{43n} \]

**α-Iminoaldehyde 43n:** General procedure G was applied using the following reagents: O-alkenylbenzophenoneoxime 42n (0.028 g, 0.096 mmol) and 1,3,5-trimethoxybenzene (0.0098 g, 0.058 mmol). $^1$H NMR analysis of the reaction mixture indicated that the yield of the in situ generated α-iminoaldehyde 43n was 58%. $^1$H NMR (500 MHz; dioxane-$d_8$): δ 9.57 (d, $J = 1.25$ Hz, 1H), 7.53-7.39 (m, 7H), 7.38-7.33 (m, 3H), 3.87-3.82
(m, 1H), 2.37-2.24 (m, 2H), 1.95-1.89 (m, 2H), 1.71-1.52 (m, 2H); \(^{13}\)C NMR (125 MHz, dioxane-\(d_8\)): \(\delta\) 199.8, 171.2, 139.1, 136.4, 130.5, 128.7, 128.6, 128.5, 128.1, 127.7, 119.3, 70.7, 30.3, 21.9, 16.2.

\[
\text{43fa}
\]

**\(\alpha\)-Iminoaldehyde 43fa:** \(^1\)H NMR (500 MHz; dioxane-\(d_8\)): \(\delta\) 9.70 (d, \(J = 3.0\) Hz, 1H), 7.54 (d, \(J = 8.0\) Hz, 2H), 7.25 (d, \(J = 8.0\) Hz, 2H), 7.13 (d, \(J = 8.0\) Hz, 2H), 6.96 (d, \(J = 8.0\) Hz, 2H), 3.42 (d, \(J = 3.0\) Hz, 1H), 2.38 (s, 3H), 2.34 (s, 3H), 1.00 (s, 9H); \(^{13}\)C NMR (125 MHz, dioxane-\(d_8\)): \(\delta\) 201.0, 170.1, 140.3, 138.1, 137.4, 133.7, 129.0, 128.6, 128.5, 127.8, 79.7, 36.0, 26.3, 20.4, 20.3.

### 2.6.4 Rearrangement and Olefination of O-Vinyl Oximes

**General Procedure H.** In an inert atmosphere glovebox, a Teflon-sealed reaction flask was charged with a 0.1 M solution of \(O\)-alkenylbenzophenone oxime 42 (1 equiv) in dioxane. The flask was then removed from the glovebox and heated to 100 °C for 30 minutes in an oil bath. While heating the solution of 42, an oven-dried 25 mL round bottom flask was equipped with a magnetic stir bar, capped with a septum, flushed with \(N_2\), and charged with a 0.1 M solution of triethylphosphonoacetate (2 equiv) in THF.
The triethylphosphonoacetate solution was then cooled to -78 °C in a dry ice/acetone bath, a 1.0 M solution of KOt-Bu in THF (1.5 equiv) was added via syringe, and the reaction mixture was allowed to stir at -78 °C for approximately 15 min. At this time, the cooled dioxane solution was added dropwise via syringe to the HWE reagent. The olefination reaction mixture was then allowed to warm to 25 °C and stir for 12 h. The reaction mixture was quenched with saturated NH₄Cl (0.5 mL) and extracted with ethyl acetate (3 x 10 mL). The organic layer was dried with MgSO₄ and concentrated under vacuum. The crude product mixture was purified by medium pressure chromatography (100% hexanes – 1:10; EtOAc: hexanes) to give 52 as a light yellow oil.

![Structure of 52a](image)

**γ-Iminoacrylate 52a:** General procedure H was applied using the following reagents: O-alkenylbenzophenone oxime 42a (0.028 g, 0.12 mmol), triethylphosphonoacetate (0.053 g, 0.23 mmol) and KOtBu (0.14 mL, 0.14 mmol). This procedure afforded 52a as a colorless oil (0.020 g, 52%) after purification using medium pressure chromatography (5:95; EtOAc:hexanes). ¹H NMR (500 MHz, CDCl₃): δ 7.64 (d, J = 7.3 Hz, 2H), 7.48-7.43 (m, 3H), 7.39-7.37 (m, 1H), 7.36-7.31 (m, 2H), 7.14 (d, J = 7.4 Hz, 2H), 7.04 (dd, J = 15.7, 5.1 Hz, 1H), 5.88 (d, J = 15.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.16-4.10 (m, 1H), 1.34-1.26 (m, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 167.8, 166.8, 151.4, 139.6,
136.5, 130.2, 128.6, 128.5, 128.2, 128.1, 127.4, 119.8, 60.3, 58.4, 21.8, 14.3; IR (thin film) 3057, 2979, 1708, 1652, 1622, 1443, 1369, 1265, 1177, 1031 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{20}$H$_{22}$NO$_2$ (M+H)$^+$ 308.1651, found 308.1656.

**γ-Iminoacrylate 52b**: General procedure H was applied using the following reagents: O-alkenylbenzophenone oxime 42b (0.030 g, 0.11 mmol), triethylphosphonoacetate (0.048 g, 0.21 mmol) and KOTBu (0.13 mL, 0.13 mmol). This procedure afforded 52b as a colorless oil (0.026 g, 69%) after purification using medium pressure chromatography (5:95; EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.64 (d, $J = 7.4$ Hz, 2H), 7.47-7.40 (m, 3H), 7.40-7.37 (m, 1H), 7.36-7.30 (m, 2H), 7.11 (d, $J = 6.9$ Hz, 2H), 7.05 (dd, $J = 15.7, 5.5$ Hz, 1H), 5.81 (d, $J = 15.7$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.99-3.94 (m, 1H), 1.79-1.70 (m, 1H), 1.70-1.62 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.26-1.11 (m, 4H), 0.84 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 168.2, 166.8, 150.6, 139.6, 136.7, 130.1, 128.6, 128.5, 128.4, 128.1, 127.5, 120.2, 63.3, 60.3, 36.0, 28.4, 22.6, 14.3, 14.0; IR (thin film) 2956, 2931, 2858, 1718, 1652, 1623, 1446, 1367, 1269, 1174,1042 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{23}$H$_{28}$NO$_2$ (M+H)$^+$ 350.2120, found 350.2122.
**γ-Iminoacrylate 52c**: General procedure H was applied using the following reagents: O-alkenylbenzophenone oxime 42c (0.0705 g, 0.229 mmol), triethylphosphonoacetate (0.103 g, 0.459 mmol) and KOt-Bu (0.34 mL, 0.34 mmol). This procedure afforded 52c as a yellow oil (0.057 g, 66%) after purification using medium pressure chromatography (100% hexanes). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta 7.65-7.64 (m, 2H), 7.45-7.42 (m, 3H), 7.39 (d, J = 7.3 Hz, 1H), 7.34 (t, J = 7.3 Hz, 2H), 7.12-7.11 (m, 2H), 7.06 (dd, J = 15.7, 5.5 Hz, 1H), 5.81 (d, J = 15.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.99-3.95 (m, 1H), 1.75-1.70 (m, 1H), 1.67-1.62 (m, 1H), 1.30-1.27 (m, 4H), 1.24-1.19 (m, 7H), 0.85 (t, J = 6.9 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 168.3, 166.8, 150.6, 136.7, 132.4, 130.2, 128.6, 128.5, 128.3, 128.1, 127.6, 120.2, 63.3, 60.3, 36.3, 31.8, 29.2, 26.2, 22.6, 14.3, 14.1; IR (thin film) 3054, 2927, 2855, 1717, 1653, 1622, 1445, 1272, 1172, 1038 cm\(^{-1}\); HRMS (ESI) m/z calcd. For C\(_{25}\)H\(_{32}\)NO\(_2\) (M+H)^+ 378.2433, found 378.2430.

![52d](image)

**γ-Iminoacrylate 52d**: General procedure H was applied using the following reagents: O-alkenylbenzophenone oxime 42d (0.028 g, 0.11 mmol), triethylphosphonoacetate (0.047 g, 0.21 mmol) and KOtBu (0.13 mL, 0.13 mmol). This procedure afforded 52d as a colorless oil (0.019 g, 54%) after purification using medium pressure chromatography (5:95; EtOAc:hexanes). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.65 (d, J = 7.2 Hz, 2H), 7.46-7.41 (m, 3H), 7.40-7.37 (m, 1H), 7.36-7.31 (m, 2H), 7.12-7.06 (m, 3H), 5.77 (d, J = 15.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.76-3.71 (m, 1H), 2.01-1.94 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H).
Hz, 3H), 0.95 (d, $J = 6.7$ Hz, 3H), 0.88 (d, $J = 6.7$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): 
$\delta$ 168.2, 166.7, 149.6, 139.8, 136.7, 130.1, 128.6, 128.4, 128.1, 128.0, 127.6, 121.2, 69.2, 60.3, 34.1, 19.5, 18.9, 14.3; IR (thin film) 3058, 2957, 2867, 1667, 1494, 1465, 1444, 1325, 1144, 1103 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{22}$H$_{26}$NO$_2$ (M+H)$^+$ 336.1964, found 336.1964.

\begin{center}
\includegraphics[width=0.2\textwidth]{52e.png}
\end{center}

**γ-Iminoacrylate 52e:** General procedure H was applied using the following reagents: O-alkenylbenzophenone oxime 42e (0.032 g, 0.10 mmol), triethylphosphonoacetate (0.047 g, 0.21 mmol) and KOrBu (0.12 mL, 0.12 mmol). This procedure afforded 52e as a colorless oil (0.026 g, 70%) after purification using medium pressure chromatography (5:95; EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.64 (d, $J = 7.4$ Hz, 2H), 7.45-7.41 (m, 3H), 7.39-7.36 (m, 1H), 7.36-7.31 (m, 2H), 7.12-7.05 (m, 3H), 5.74 (d, $J = 16.1$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.76-3.71 (m, 1H), 1.79-1.60 (m, 6H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.24-1.16 (m, 2H), 1.14-0.98 (m, 2H), 0.97-0.87 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 168.1, 166.7, 149.7, 139.8, 136.7, 130.1, 128.6, 128.4, 128.3, 128.1, 127.6, 121.0, 68.8, 60.3, 43.7, 30.0, 29.4, 26.3, 14.3; IR (thin film) 2926, 2855, 1717, 1649, 1620, 1443, 1369, 1268, 1171, 1040 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{25}$H$_{30}$NO$_2$ (M+H)$^+$ 376.2277, found 376.2277.

\begin{center}
\includegraphics[width=0.2\textwidth]{52e.png}
\end{center}
γ-Iminoacrylate 52f: General procedure H was applied using the following reagents: O-alkenylbenzophenone oxime 42f (0.026 g, 0.093 mmol), triethylphosphonoacetate (0.042 g, 0.19 mmol) and KOTBu (0.11 mL, 0.11 mmol). This procedure afforded 52f as a colorless oil (0.021 g, 64%) after purification using medium pressure chromatography (5:95; EtOAc:hexanes). ¹H NMR (500 MHz, CDCl₃): δ 7.66 (d, J = 7.2 Hz, 2H), 7.45-7.40 (m, 3H), 7.40-7.37 (m, 1H), 7.36-7.31 (m, 2H), 7.15 (dd, J = 15.7, 6.1 Hz, 1H), 7.08 (d, J = 6.2 Hz, 2H), 5.74 (d, J = 15.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.63 (d, J = 6.1 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 0.94 (s, 9H); ¹³C NMR (125 MHz, CDCl₃): δ 167.8, 166.7, 148.4, 139.8, 136.6, 130.1, 128.6, 128.4, 128.3, 128.0, 127.6, 121.8, 72.3, 60.3, 36.4, 26.9, 14.3; IR (thin film) 2961, 1711, 1649, 1625, 1446, 1392, 1366, 1265, 1177, 1039 cm⁻¹; HRMS (ESI) m/z calcd. for C₂₃H₂₈NO₂ (M+H)⁺ 350.2120, found 350.2129.

γ-Iminoacrylate 52g: General procedure H was applied using the following reagents: O-alkenylbenzophenone oxime 42g (0.030 g, 0.096 mmol), triethylphosphonoacetate (0.043 g, 0.19 mmol) and KOTBu (0.12 mL, 0.12 mmol). This procedure afforded 52g as a colorless oil (0.023 g, 63%) after purification using medium pressure chromatography (5:95; EtOAc:hexanes). ¹H NMR (500 MHz, CDCl₃): δ 7.59 (d, J = 7.3 Hz, 2H), 7.41-7.35 (m, 1H), 7.35-7.31 (m, 3H), 7.31-7.25 (m, 3H), 7.22-7.16 (m, 4H), 7.13 (dd, J = 15.7, 5.2 Hz, 1H), 7.02 (d, J = 7.4 Hz, 2H), 5.88 (d, J = 15.7 Hz, 1H), 4.20 (q, J = 7.2 Hz,
2H), 4.17-4.10 (m, 1H), 3.04 (dd, J = 13.1, 9.0 Hz, 1H), 2.96 (dd, J = 13.1, 4.4 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 168.8, 166.7, 149.6, 139.4, 138.3, 136.4, 130.1, 129.8, 129.6, 128.5, 128.3, 128.2, 128.0, 127.2, 126.2, 120.7, 65.2, 60.3, 42.7, 14.2; IR (thin film) 3066, 2988, 1710, 1649, 1620, 1447, 1307, 1262, 1177, 1041 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for C\(_{26}\)H\(_{26}\)NO\(_2\) (M+H)\(^+\) 384.1964, found 384.1955.

\(\text{52h}\)

\(\gamma\)-Iminoacrylate 52h: General procedure H was applied using the following reagents: \(O\)-alkenylbenzophenone oxime 42h (0.0786 g, 0.198 mmol), triethylphosphonoacetate (0.0887 g, 0.395 mmol) and KO\(_t\)-Bu (0.30 mL, 0.30 mmol). This procedure afforded 52h as a yellow oil (0.0251 g, 26%, \(dr = 1:1\)) after purification using medium pressure chromatography (5:95; EtOAc:hexanes). \(^1\)H NMR (major diastereomer) (500 MHz; CDCl\(_3\)): \(\delta\) 7.67-7.66 (m, 2H), 7.37-7.33 (m, 4H), 7.30-7.27 (m, 2H), 7.24-7.21 (m, 2H), 7.15 (dd, \(J = 16, 7\) Hz, 1H), 6.99-6.96 (m, 2H), 6.74-6.73 (m, 2H), 5.80 (dd, \(J = 16, 1\) Hz, 1H), 4.15 (q, \(J = 7\) Hz, 2H), 4.09-4.05 (m, 1H), 2.88-2.83 (m, 1H), 1.84-1.78 (m, 1H), 1.59-1.52 (m, 1H), 1.29 (s, 9H), 0.89 (t, \(J = 7\) Hz, 3H), 0.73 (t, \(J = 7\) Hz, 3H); \(^{13}\)C NMR (major diastereomer) (125 MHz, CDCl\(_3\)): \(\delta\) 168.7, 168.1, 149.2, 140.0, 138.4, 136.4, 130.1, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.2, 125.0, 121.4, 69.3, 60.2, 53.3, 34.4, 31.4, 24.3, 14.3, 12.4; \(^1\)H NMR (minor diastereomer) (500 MHz; CDCl\(_3\)): \(\delta\) 7.45-
7.43 (m, 2H), 7.41-7.40 (m, 2H), 7.37-7.33 (m, 4H), 7.30-7.27 (m, 2H), 7.24-7.21 (m, 2H), 6.95-6.93 (m, 2H), 6.69-6.68 (m, 2H), 5.72 (dd, J = 16, 2 Hz, 1H), 4.20 (q, J = 7 Hz, 2H), 4.09-4.05 (m, 1H), 2.88-2.83 (m, 1H), 1.94-1.89 (m, 1H), 1.75-1.70 (m, 1H), 1.30 (s, 9H); 13C NMR (minor diastereomer) (125 MHz, CDCl₃): δ 168.1, 166.7, 150.0, 139.6, 138.7, 136.5, 130.2, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 127.2, 124.8, 120.8, 68.7, 60.3, 53.2, 34.4, 31.4, 24.3, 14.2, 12.4; IR (thin film) 3054, 2960, 2874, 1717, 1650, 1623, 1445, 1270, 1170, 1050 cm⁻¹; HRMS (ESI) m/z calcd. For C₃₂H₃₆NO₂ (M+H)⁺ 468.2903, found 468.2904.

y-Iminoacrylate 52k: General procedure H was applied using the following reagents: O-alkenylbenzophenone oxime 42k (0.026 g, 0.072 mmol), triethylphosphonoacetate (0.032 g, 0.14 mmol) and KOTBu (0.086 mL, 0.086 mmol). This procedure afforded 52k as a colorless oil (0.016 g, 51%) after purification using medium pressure chromatography (10:90; EtOAc:hexanes). ¹H NMR (500 MHz, CDCl₃): δ 7.64 (d, J = 7.5 Hz, 2H), 7.43-7.32 (m, 6H), 7.31-7.27 (m, 3H), 7.20 (d, J = 6.9 Hz, 2H), 7.10 (d, J = 7.7 Hz, 2H), 7.04 (dd, J = 15.7, 5.4 Hz, 1H), 5.79 (d, J = 15.7 Hz, 1H), 4.44-4.36 (m, 2H), 4.27-4.22 (m, 1H), 4.18 (q, J = 7.0 Hz, 2H), 3.56-3.50 (m, 1H), 3.50-3.44 (m, 1H), 2.10-1.97 (m, 2H), 1.28 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 169.1, 166.7, 150.0, 139.6, 138.3, 136.3, 130.2, 128.6, 128.5, 128.4, 128.2, 128.1, 127.5, 127.4,
127.3, 120.5, 72.8, 67.1, 60.3, 60.2, 36.1, 14.2; IR (thin film) 2986, 2857, 1715, 1652, 1622, 1446, 1367, 1266, 1174, 1097, 1029 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for \(\text{C}_{28}\text{H}_{30}\text{NO}_3\) (M+H\(^+\)) 428.2226, found 428.2224.

\[
\begin{align*}
\text{52I}
\end{align*}
\]

\textbf{γ-Iminoacylate 52I:} General procedure H was applied using the following reagents: \(O\)-alkenylbenzophenone oxime \(42I\) (0.0949 g, 0.302 mmol), triethylphosphonoacetate (0.135 g, 0.605 mmol) and LiHMDS (0.45 mL, 0.45 mmol). This procedure afforded \(52I\) as a yellow oil (0.066 g, 52\%) after purification using medium pressure chromatography (5:95; EtOAc:hexanes). \(^1\text{H NMR}\) (500 MHz; CDCl\(_3\)): \(\delta\) 7.65 (d, \(J = 8.0\) Hz, 2H), 7.44 (d, \(J = 6.2\) Hz, 3H), 7.40-7.38 (m, 1H), 7.34 (t, \(J = 7.4\) Hz, 2H), 7.13-7.11 (m, 2H), 7.04 (dd, \(J = 15.7, 5.4\) Hz, 1H), 5.82 (d, \(J = 15.7\) Hz, 1H), 4.19 (q, \(J = 7.1\) Hz, 2H), 4.01-3.97 (m, 1H), 3.48 (t, \(J = 6.6\) Hz, 2H), 1.78-1.75 (m, 1H), 1.71-1.67 (m, 3H), 1.46-1.41 (m, 1H), 1.40-1.34 (m, 1H), 1.29 (t, \(J = 7.1\) Hz, 3H); \(125\) MHz, CDCl\(_3\)): \(\delta\) 168.7, 166.7, 150.1, 139.5, 136.6, 130.3, 128.7, 128.6, 128.5, 128.1, 127.5, 120.6, 63.0, 60.4, 44.8, 35.5, 32.4, 23.6, 14.3; IR (thin film) 2937, 1714, 1651, 1445, 1269, 1175, 981, 780, 694 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. For \(\text{C}_{23}\text{H}_{27}\text{ClNO}_2\) (M+H\(^+\)) 384.1730, found 384.1739.

\[
\begin{align*}
\text{52m}
\end{align*}
\]
**γ-Iminoacrylate 52m:** General procedure H was applied using the following reagents: O-alkenylbenzophenone oxime 42m (0.0659 g, 0.204 mmol), triethylphosphonoacetate (0.0913 g, 0.407 mmol) and KOt-Bu (0.30 mL, 0.30 mmol). This procedure afforded 52m as a yellow oil (0.042 g, 52%) after purification using medium pressure chromatography (5:95; EtOAc:hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.65-7.63 (m, 2H), 7.44-7.43 (m, 3H), 7.39-7.38 (m, 1H), 7.33 (t, $J = 7.3$ Hz, 2H), 7.12-7.10 (m, 2H), 7.02 (dd, $J = 15.7$, 5.5 Hz, 1H), 5.81, (d, $J =15.7$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 4.01-3.97 (m, 1H), 3.64 (m, 3H), 2.24 (t, $J = 7.1$ Hz, 2H), 1.78-1.74 (m, 1H), 1.70-1.61 (m, 2H), 1.58-1.51 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 3H); (125 MHz, CDCl$_3$): δ 173.8, 168.8, 166.6, 150.0, 139.4, 136.5, 130.3, 128.7, 128.6, 128.5, 128.1, 127.5, 120.6, 62.9, 60.4, 51.5, 35.6, 33.9, 21.7, 14.3; IR (thin film) 3064, 2921, 2849, 1736, 1660, 1445, 1318, 1276, 1176 cm$^{-1}$; HRMS (ESI) m/z calcd. For C$_{24}$H$_{28}$NO$_4$ (M+H)$^+$ 394.2018, found 394.2019.

![52n](image)

**γ-Iminoacrylate 52n:** General procedure H was applied using the following reagents: O-alkenylbenzophenone oxime 42n (0.017 g, 0.059 mmol), triethylphosphonoacetate (0.026 g, 0.12 mmol) and LiHMDS (0.071 mL, 0.071 mmol). This procedure afforded 52n as a colorless oil (0.012 g, 55%) after purification using medium pressure chromatography (10:90; EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): δ 7.64 (d, $J = 7.28$ Hz, 2H), 7.48-7.44 (m, 3H), 7.43-7.39 (m, 1H), 7.38-7.32 (m, 2H), 7.10 (d, $J = 6.9$ Hz, 2H), 6.99 (s, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 1.99-1.93 (m, 2H), 1.73-1.66 (m, 1H), 1.20-1.10 (m, 3H); (125 MHz, CDCl$_3$): δ 173.8, 168.8, 166.6, 150.0, 139.4, 136.5, 130.3, 128.7, 128.6, 128.5, 128.1, 127.5, 120.6, 62.9, 60.4, 51.5, 35.6, 33.9, 21.7, 14.3; IR (thin film) 3064, 2921, 2849, 1736, 1660, 1445, 1318, 1276, 1176 cm$^{-1}$; HRMS (ESI) m/z calcd. For C$_{24}$H$_{28}$NO$_4$ (M+H)$^+$ 394.2018, found 394.2019.
Hz, 2H), 7.00 (dd, \( J = 15.7 \), 5.3 Hz, 1H), 5.84 (d, \( J = 15.7 \) Hz, 1H), 4.19 (q, \( J = 7.1 \) Hz, 2H), 4.06-3.99 (m, 1H), 2.32-2.26 (m, 2H), 1.93-1.84 (m, 1H), 1.82-1.74 (m, 1H), 1.72-1.61 (m, 2H), 1.29 (t, \( J = 7.1 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 169.2, 166.4, 149.1, 139.1, 136.2, 130.5, 128.8, 128.7, 128.6, 128.2, 127.3, 121.2, 119.4, 62.2, 60.5, 34.9, 22.1, 17.1, 14.2; IR (thin film) 2982, 2925, 2362, 1714, 1651, 1616, 1445, 1363, 1280, 1180 cm\(^{-1}\); HRMS (ESI) \( m/z \) calcd. for \( \text{C}_{23}\text{H}_{25}\text{N}_{2}\text{O}_{2} \) (M+H)\(^+\) 361.1918, found 361.1916.

2.6.5 Preparation of Vinylboronic Acids

Methyl 5-hexenoateboronic acid 13m. A round bottom flask was flame-dried under N\(_2\), charged with methyl 5-hexynoate (1.302 g, 10.32 mmol) and cooled to 0 °C with an ice-water bath. The alkyne was then diluted with a 1M solution of HBBr\(_2\)·SMe\(_2\) in CH\(_2\)Cl\(_2\) (12 mL, 12 mmol) and allowed to stir for 3 h. The reaction mixture was then treated with 30 mL of a 10:1 mixture of diethyl ether and water and allowed to stir for 15 minutes. The reaction mixture was then diluted with additional diethyl ether (50 mL) and extracted with water (3 x 10 mL). The organic layer was then dried with brine and MgSO\(_4\) and concentrated under vacuum to give a crude sample of alkenyl boronic acid 51m (0.899 g, 51%) as brown oil. This crude sample was then used for the copper-promoted oxime etherification without further purification. Any impurities that were carried on to general procedure F were not observed to affect the efficiency of the process when compared to the use of a pure sample of boronic acid. \(^{1}\)H NMR (500 MHz; CDCl\(_3\)): \( \delta \) 6.90 (dt, \( J = 17.6 \), 6.5 Hz, 1H), 5.54 (d, \( J = 17.6 \) Hz, 1H), 3.67 (s, 3H),
2.45 (t, $J = 7.4$ Hz, 2H), 2.25-2.24 (m, 2H), 2.20-2.16 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 174.1, 156.1, 69.1, 51.6, 34.8, 33.4, C-B was too broad to be observed.

**General Procedure I.** A scintillation vial was charged with alkenyl boronic acid pinacol ester S-1 (1 equiv), NaIO$_4$ (2 equiv), and NH$_4$OAc (2 equiv). These reagents were then diluted with a mixture of acetone and water in a 1:1 ratio to form a 0.1 M solution of the alkenyl boronic acid pinacol ester. The resulting slurry was allowed to stir vigorously for 16-48 h. The slurry was then diluted with ethyl acetate or diethyl ether (30 mL) and extracted with water (2 x 10 mL). The organic layer was then dried with brine and MgSO$_4$ and concentrated under reduced pressure to give a crude sample of the alkenyl boronic acid 13. This crude sample was then used for the copper-promoted oxime etherification without further purification. Any impurities that were carried on to general procedure F were not observed to affect the efficiency of the process when compared to the use of a pure sample of boronic acid.

3-methyl-butenylboronic acid 51d: General procedure I was applied using the following reagents: 3-methylbutenylboronic acid pinacol ester S-1d (0.652 g, 3.33 mmol), NaIO$_4$ (1.30 g, 6.09 mmol), and NH$_4$OAc (0.437 g, 5.67 mmol). This procedure gave 51d (0.206 g, 54%) as an amorphous solid after extraction. $^1$H NMR (500 MHz;
CDCl$_3$: $\delta$ 6.95 (dd, $J = 17.8$, 6.2 Hz, 1H), 5.49 (dd, $J = 17.8$, 1.6 Hz, 1H), 2.43-2.38 (m, 1H), 1.05 (d, $J = 6.9$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 163.9, 33.5, 21.4, C-B was too broad to be observed.


$\text{(HO)}_2B\equiv\text{t-Bu}$

**51f**

3,3-dimethylbutenylboronic acid 51f: General procedure I was applied using the following reagents: 3,3-dimethylmethylbutenylboronic acid pinacol ester S-1f (0.468 g, 2.23 mmol), NaIO$_4$ (0.815 g, 3.81 mmol), and NH$_4$OAc (0.502 g, 6.44 mmol). This procedure gave 51f (0.262 g, 92%) as an amorphous solid after extraction. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 6.97 (d, $J = 18.0$ Hz, 1H), 5.47 (d, $J = 18.0$ Hz, 1H), 1.07 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.4, 35.1, 28.8, C-B was too broad to be observed.

$\text{(HO)}_2B\equiv\text{t-Bu}$

**51h**

3-(4'-tert-butylphenyl)pentenylboronic acid 51h: General procedure I was applied using the following reagents: 3-(4'-tert-butylphenyl)pentenylboronic acid pinacol ester S-1h (1.25 g, 3.80 mmol), NaIO$_4$ (1.79 g, 8.37 mmol), and NH$_4$OAc (0.626 g, 8.02 mmol). This procedure gave 51h (0.929 g, 99%) as yellow oil after extraction. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.34-7.31 (m, 2H), 7.13-7.11 (m, 2H), 6.99 (dd, $J = 17.2$, 7.5 Hz, 1H),
5.53 (d, $J = 17.2$ Hz, 1H), 3.27-3.23 (m, 1H), 1.84-1.72 (m, 2H), 1.32 (s, 9H), 0.89 (t, $J = 6.8$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 160.2, 149.1, 140.2, 127.5, 125.4, 53.0, 34.4, 27.7, 17.9, C-B was too broad to be observed.

\[ (\text{HO})_2\text{B} = \text{C} \]

51i

2-(cyclopropyl)ethenylboronic acid 51i: General procedure I was applied using the following reagents: 2-cyclopropylethenylboronic acid pinacol ester $S$-1i (0.691 g, 3.56 mmol), NaIO$_4$ (1.43 g, 6.70 mmol), and NH$_4$OAc (0.503 g, 6.54 mmol). This procedure gave 13i (0.321 g, 80%) as an amorphous solid after extraction. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 6.38 (dd, $J = 17.5$, 9.4 Hz, 1H), 5.56 (d, $J = 17.5$ Hz, 1H), 1.61-1.55 (m, 1H), 0.89-0.85 (m, 2H), 0.61-0.58 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 161.6, 17.0, 8.4, C-B was too broad to be observed.

\[ (\text{HO})_2\text{B} \text{-OTBS} \]

51j

3-(tert-butylidimethylsiloxy)prop-1-enylboronic acid 51j: General procedure I was applied using the following reagents: 3-(tert-butylidimethylsiloxy)prop-1-enylboronic acid pinacol ester $S$-1j (0.707 g, 2.38 mmol), NaIO$_4$ (0.959 g, 4.48 mmol), and NH$_4$OAc (0.43 g, 5.6 mmol). This procedure gave 13j (0.47 g, 71%) as a light yellow oil after extraction. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 6.99 (dd, $J = 17.5$, 2.6 Hz, 1H), 5.83 (d, $J =$
17.5 Hz, 1H), 4.34-4.31 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 152.2, 60.5, 26.0, 18.5, -5.3, C-B was too broad to be observed.

51k

4-(benzyloxy)but-1-enylboronic acid 51k: General procedure I was applied using the following reagents: 4-(benzyloxy)but-1-enylboronic acid pinacol ester S-1k (0.185 g, 0.644 mmol), NaIO$_4$ (0.279 g, 1.30 mmol), and NH$_4$OAc (0.141 g, 1.83 mmol). This procedure gave 51k (0.094 g, 71%) as a light yellow oil after extraction. $^1$H NMR (500 MHz; CDCl$_3$): δ 7.34 (d, $J = 4.3$ Hz, 5H), 6.97 (dt, $J = 17.7$, 6.4 Hz, 1H), 5.63 (d, $J = 17.7$ Hz, 1H), 4.54 (s, 2H), 3.62-3.59 (m, 2H), 2.55 (t, $J = 6.4$ Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 153.7, 138.3, 128.4, 127.7, 127.6, 72.9, 68.8, 36.0, C-B was too broad to be observed.

51l

6-Chlorohexenylboronic acid 51l: General procedure I was applied using the following reagents: 6-chlorohexenylboronic acid pinacol ester S-1l (0.885 g, 3.62 mmol), NaIO$_4$ (1.66 g, 7.78 mmol), and NH$_4$OAc (0.631 g, 8.19 mmol). This procedure gave 51l (0.583 g, 98%) as an amorphous solid after extraction. $^1$H NMR (500 MHz; CDCl$_3$): δ 6.94 (dt, $J = 17.7$, 6.4 Hz, 1H), 5.55 (d, $J = 17.7$ Hz, 1H), 3.55 (t, $J = 6.5$ Hz, 2H), 2.28-
2.24 (m, 2H), 1.82-1.77 (m, 2H), 1.62 (t, \( J = 7.5 \) Hz, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 156.7, 44.9, 34.7, 32.0, 25.4, C-B was too broad to be observed.

\[\text{HO}_2B\text{-C} = \text{CN}\]

\(51\text{n}\)

5-cyanopentenylboronic acid 51n: General procedure I was applied using the following reagents: 5-cyanopentenylboronic acid pinacol ester S-1n (0.315 g, 1.42 mmol), NaIO\(_4\) (0.290 g, 1.36 mmol), and NH\(_4\)OAc (0.100 g, 1.36 mmol). This procedure gave 51n (0.165 g, 76%) as an amorphous solid after extraction. \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 6.88 (dt, \( J = 17.6, 6.5 \) Hz, 1H), 5.62 (d, \( J = 17.6 \) Hz, 1H), 2.36 (dt, \( J = 14.7, 7.1 \) Hz, 2H), 1.84-1.81 (m, 4H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 154.31, 119.3, 34.03, 23.90, 16.52 C-B was too broad to be observed.
**General Procedure J.** In the glovebox, a Teflon-sealed reaction flask equipped with a stir bar was charged with Cp₂ZrHCl (10 mol %). The flask was then capped, removed from the glovebox, and flushed onto a Schlenk line. The alkyne (1 equiv), HB(pin) (1.05 equiv), and triethylamine (10 mol %) were added to the reaction flask through a septa under a high flow of N₂. The septa was then removed, the flask was sealed, and heated to 60 °C for 16 h. Volatiles were then removed under vacuum and the crude product mixture was directly purified by medium pressure chromatography (100% hexanes-5:95 EtOAc:hexanes).

**S-1d**

3-methyl butenylboronic acid pinacol ester S-1d: General procedure J was applied using the following reagents: 3-methylbutyne (1.33 g, 19.6 mmol), Cp₂ZrHCl (0.253 g, 0.980 mmol), HB(pin) (2.63 g, 20.5 mmol) and triethylamine (0.197 g, 1.96 mmol). This procedure gave S-1d (3.16 g, 82%) as a yellow oil. ¹H NMR (500 MHz; CDCl₃): δ 6.61 (dd, J = 18.1, 6.0 Hz, 1H), 5.37 (d, J = 18.1 Hz, 1H), 2.37-2.30 (m, 1H), 1.26 (s, 12H), 0.99 (d, J = 6.8 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃): δ 161.0, 83.0, 33.6, 24.8, 21.4, C-B was too broad to be observed. Matches spectral data reported by Murakami.²

**S-1i**

2-cyclopropylethenylboronic acid pinacol ester S-1i: General procedure J was applied using the following reagents: cyclopropylacetylene (1.32 g, 20.0 mmol), Cp₂ZrHCl (0.245 g, 0.950 mmol), HB(pin) (2.69 g, 21.0 mmol) and triethylamine (0.20 g, 0.20 mmol). This procedure gave S-1i (3.52 g, 91%) as a clear oil. ¹H NMR (500 MHz; CDCl₃): δ 6.05 (dd, J = 17.8, 9.3 Hz, 1H), 5.47 (d, J = 17.8 Hz, 1H), 1.52-1.47 (m, 1H), 1.23 (s, 12H), 0.80-0.76 (m, 2H) 0.53-0.50 (m, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 158.5, 82.9, 24.8, 17.0, 7.9, C-B was too broad to be observed.

**S-1h**

3-(4'-tert-butylphenyl)pentenylboronic acid pinacol ester S-1h: General procedure J was applied using the following reagents: 3-(4'-tert-butylphenyl)pentyne S-2h (1.43 g, 7.14 mmol), Cp₂ZrHCl (0.203 g, 0.789 mmol), HB(pin) (0.96 g, 7.5 mmol) and triethylamine (0.071 g, 0.71 mmol). This procedure gave S-1h (1.25 g, 53%) as a yellow oil. ¹H NMR (500 MHz; CDCl₃): δ 7.30 (d, J = 8.3, 2H), 7.10 (d, J = 8.3 Hz, 2H), 6.71 (dd, J = 17.9, 7.4 Hz, 1H), 5.40 (d, J = 17.9 Hz, 1H), 3.17 (q, J = 7.4 Hz, 1H), 1.81-1.69 (m, 1H), 1.30 (s, 9H), 1.25 (s, 12H), 0.86 (t, J = 7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 157.2, 148.9, 140.4, 127.5, 125.3, 83.1, 53.3, 31.4, 28.0, 24.8, 17.7, 12.4, C-
B was too broad to be observed. HRMS (ESI) m/z calcd. For C_{21}H_{33}BO_{2} (M+H)^{+} 329.2652, found 329.2655.

\[ \text{S-2h} \]

3-(4'-\text{tert-butylphenyl})pentyne S-2h: A 50 mL round bottom flask equipped with a magnetic stir bar was charged with (3-(4'-\text{tert-butylphenyl})pentylnyl)triisopropylsilane (2.55 g, 7.14 mmol) flushed with N\textsubscript{2} and diluted with 15 mL of dry THF. A 1.0 M solution of tetrabutylammonium fluoride in THF (14.0 mL, 14.0 mmol) was added dropwise. After 2 h solvent was evaporated and the crude oil was loaded onto 50 mL of silica and eluted with hexanes to give S-2h (1.43 g, 98%) as light yellow oil. ¹H NMR (500 MHz; CDCl\textsubscript{3}): δ 7.35 (d, J = 8.3, 2H), 7.29 (d, J = 8.3 Hz, 2H), 3.57-3.54 (m, 1H), 2.26 (s, 1H), 1.81- 1.77 (m, 2H), 1.32 (s, 9H), 1.02 (t, J = 7.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl\textsubscript{3}): δ 149.6, 138.4, 127.1, 125.4, 86.2, 70.7, 38.7, 34.5, 31.5, 31.4, 11.8.

2.6.6 Preparation of Camphor Derivatives

\[ \text{18} \rightarrow \text{19b} \]
O-but-3-en-2-yl Camphor Oxime 19b: To a 100 mL round-bottom flask camphor oxime 18 (0.337 g, 2.02 mmol) was added along with dry THF to form a 0.2 M solution. To this solution t-BuOK (0.336 g, 3.00 mmol), NaBr (0.204 g, 2.00 mmol) and Bu₄NCl (0.11 g, 0.40 mmol) were added and the mixture was allowed to stir. Finally 3-chlorobutene (0.199 g, 2.20 mmol) was added dropwise and the mixture was allowed to stir over night. The mixture was diluted with water and extracted with EtOAc (3 x 30 mL) and dried with MgSO₄. The crude product was isolated by flash chromatography (0:100, EtOAc:Hexanes) to yield 19b (0.278 g, 62%) as a light yellow oil. ¹H NMR (500 MHz; CDCl₃): δ 5.96-5.85 (m, 1H), 5.18 (t, J = 17.7 Hz, 1H), 5.08 (dd, J = 15.8, 10.6 Hz, 1H), 4.62 (t, J = 6.2 Hz, 1H), 2.00 (dd, J = 17.8, 2.4 Hz, 1H), 1.86-1.78 (m, 2H), 1.71-1.65 (m, 1H), 1.45 (td, J = 8.5, 4.2 Hz, 1H), 1.28 (dd, J = 11.9, 6.5 Hz, 3H), 1.24-1.19 (m, 1H), 0.99 (d, J = 5.3 Hz, 3H), 0.90 (s, 3H), 0.77 (d, J = 6.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 164.0, 140.0, 114.0, 114.4, 78.5, 48.0, 43.8, 33.9, 32.9, 32.8, 27.3, 19.9, 19.8, 19.5, 18.6, 11.2.

O-hexenyl camphor oxime 20b: In a 100 mL round bottom flask camphor oxime 18 (0.170 g, 1.02 mmol), 1-hexenyl boronic acid 13b (0.270 g, 2.11 mmol), Cu(OAc)₂ (0.042 g, 0.23 mmol) and 4Å molecular sieves (0.250 g) were combined and diluted to 0.1 M of oxime with DCE. After 6 hours an additional portion of 1-hexenyl boronic acid
13b (0.230 g, 1.80 mmol) was added and the mixture stirred overnight. After filtration through a 10 mL silica plug the product was purified by medium pressure chromatography (0:100 EtOAC:Hexanes) to give O-hexenyl camphor oxime 20b as a light yellow oil (0.186 g, 74%). \(1^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 6.64 (dt, \(J = 13, 1\) Hz, 1H), 5.89 (dt, \(J = 13, 7\) Hz, 1H), 2.44-2.36 (m, 1H), 2.10-2.07 (m, 2H), 1.94 (dd, \(J = 11, 7\) Hz, 2H), 1.87-1.81 (m, 7H), 1.20 (dt, \(J = 8, 4\) Hz, 1H), 1.00 (s, 3H), 0.90-0.84 (m, 9H), 0.75 (s, 3H). \(13^1\)C NMR (500 MHz, CDCl₃) \(\delta\) 181.8, 136.3, 129.5, 53.8, 47.3, 43.8, 36.1, 32.3, 31.9, 30.1, 27.4, 22.3, 19.7, 19.0, 13.9, 11.3.

**α-Imino ketone 21b:** In a glovebox O-3-butenyl camphor oxime 19b (0.144 g, 0.654 mmol) and [(PPh₃)₃Ru(H)₂(CO)] (0.048 g, 0.052 mmol) were combined in v-vial equipped with a stir bar and diluted to 0.1 M solution with dry DCE. The mixture was sealed with a screw cap and then heated to 80 °C for 48 hours. The mixture was then filtered through 5 mL of silica gel and washed with EtOAc (2 x 5 mL). The crude product was purified by medium-pressure chromatography (20:80 EtOAc:hexanes) to give 21b (0.050 g, 35%) as a clear oil. \(1^1\)H NMR (500 MHz; CDCl₃): \(\delta\) 3.84 (dd, \(J = 11.9, 6.8\) Hz, 1H), 2.30 (d, \(J = 3.0\) Hz, 1H), 2.14 (d, \(J = 5.5\) Hz, 3H), 1.93 (d, \(J = 3.9\) Hz, 1H), 1.84-
1.76 (m, 2H), 1.66 (s, 1H), 1.30 (s, 1H), 1.23 (dd, $J = 6.7, 4.2$ Hz, 3H), 0.96 (s, 3H), 0.91 (s, 3H), 0.73 (s, 4H). $^{13}$C NMR (501 MHz; CDCl$_3$): $\delta$ 211.0, 183.1, 67.2, 66.8, 43.8, 35.3, 35.2, 32.1, 32.0, 27.5, 26.3, 19.6, 19.4, 19.0, 18.9, 18.0, 11.5, 11.3.

**Allylic amine 22:** In a glovebox [(cod)$_2$(Ir)]BF$_4$ (0.011 g, 0.021 mmol) and DIBAL-H (0.02 mL, 0.02 mmol) were combined in a v-vial with 2 mL of dry THF. After 10 minutes O-allyl camphor oxime 19a (0.083 g, 0.021 mmol) was added dropwise. The vial was sealed with a screw cap and heated to 75°C for 20 hours. After heating the crude mixture was filtered through celite (5 mL) and washed with Et$_2$O (2 x 5 mL). The washings were concentrated and 21a reserved. Meanwhile in a flame-dried 25 mL round-bottom flask (4-methoxy)methylene triphenylphosphonium bromide (0.247 g, 0.589 mmol) was added with 4 mL dry THF. The slurry was cooled to -78 °C and 2.5 M BuLi (0.18 mL, 0.44 mmol) was added dropwise. The resulting mixture stirred for 15 minutes and then a THF solution of 21a was added dropwise at -78 °C. The reaction was allowed to come to room temperature and stir overnight. The reaction was
quenched with water and extracted with EtOAc (3 x 15 mL) and dried with MgSO₄. The product was purified by medium-pressure chromatography giving allylic amine 22 (0.056 g, 44%) as a light yellow oil. ¹H NMR (500 MHz; CDCl₃): δ 7.27 (d, J = 10.4 Hz, 1H), 7.15 (dd, J = 8.5, 3.4 Hz, 2H), 6.84 (td, J = 8.8, 5.4 Hz, 3H), 6.35 (t, J = 12.4 Hz, 1H), 5.69 (dt, J = 22.2, 10.9 Hz, 1H), 4.32 (dd, J = 13.9, 6.2 Hz, 1H), 3.81 (s, 3H), 2.13 (s, 1H), 2.00 (s, 1H), 1.92 (s, 1H), 1.80 (dt, J = 10.4, 4.7 Hz, 2H), 1.28 (dd, J = 13.5, 6.4 Hz, 5H), 1.01 (s, 1H), 0.97 (s, 3H), 0.88 (d, J = 4.6 Hz, 3H), 0.71 (s, 2H), 0.69 (s, 2H). 181.0, 158.4, 135.1, 130.2, 127.4, 127.0, 113.9, 113.5, 58.7, 55.3, 54.3, 53.4, 47.0, 43.9, 35.6, 32.2, 27.6, 22.3, 19.6, 19.1, 19.0, 18.0, 11.6.

In a glovebox [(cod)₂(Ir)]BF₄ (0.028 g, 0.056 mmol) and DIBAL-H (0.054 mL, 0.054 mmol) were combined in a v-vial with 2 mL of dry THF. After 10 minutes O-allyl camphor oxime 19a (0.117 g, 0.565 mmol) was added dropwise. The vial was sealed with a screw cap and heated to 75°C for 20 hours. After heating the crude mixture was filtered through celite (5 mL) and washed with Et₂O (2 x 5 mL). The washings were concentrated and 21a reserved. 1H-NMR (501 MHz; CDCl₃): δ 3.54 (s, 2H), 3.42 (s, 1H), 2.44-2.40 (m, 1H), 2.31 (s, 1H), 1.96 (d, J = 16.9 Hz, 1H), 1.92 (d, J = 4.1 Hz, 1H), 1.80 (d, J = 16.9 Hz, 2H), 1.68-1.63 (m, 1H), 1.30 (s, 1H), 1.20 (s, 1H), 1.00

Imino alcohol 24: In a glovebox [(cod)₂(Ir)]BF₄ (0.028 g, 0.056 mmol) and DIBAL-H (0.054 mL, 0.054 mmol) were combined in a v-vial with 2 mL of dry THF. After 10 minutes O-allyl camphor oxime 19a (0.117 g, 0.565 mmol) was added dropwise. The vial was sealed with a screw cap and heated to 75°C for 20 hours. After heating the crude mixture was filtered through celite (5 mL) and washed with Et₂O (2 x 5 mL). The washings were concentrated and 21a reserved. 1H-NMR (501 MHz; CDCl₃): δ 3.54 (s, 2H), 3.42 (s, 1H), 2.44-2.40 (m, 1H), 2.31 (s, 1H), 1.96 (d, J = 16.9 Hz, 1H), 1.92 (d, J = 4.1 Hz, 1H), 1.80 (d, J = 16.9 Hz, 2H), 1.68-1.63 (m, 1H), 1.30 (s, 1H), 1.20 (s, 1H), 1.00
(dd, $J = 6.4$, 1.1 Hz, 3H), 0.94 (s, 3H), 0.91 (d, $J = 1.9$ Hz, 3H), 0.74 (d, $J = 1.3$ Hz, 3H).

$^{13}$C NMR (501 MHz; CDCl$_3$): $\delta$ 181.9, 67.6, 57.5, 57.1, 53.8, 47.1, 46.5, 43.9, 43.8, 35.5, 35.4, 32.6, 32.1, 27.5, 19.6, 19.5, 19.1, 18.9, 16.9, 16.8, 11.6, 11.5.

25

**a-Imino alcohol 25**: In an oven-dried 25 mL round-bottom flask equipped with a stir bar a 0.1 M solution of ketone 21b (0.050 g, 0.23 mmol) and dry THF was added. The flask was cooled to -78 °C and a 3.0 M solution of MeMgBr (0.07 mL, 0.22 mmol) was added dropwise. The resulting mixture was allowed to come to room temperature and stir overnight. After quenching with water the mixture was extracted with EtOAc (3 x 15 mL) and dried with MgSO$_4$. The crude product was purified by medium-pressure chromatography (20:80 EtOAc:hexanes) to give imino alcohol 25 (0.038 g, 70%) as a clear oil. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 3.07 (dd, $J = 33.9$, 6.5 Hz, 1H), 2.36-2.26 (m, 1H), 1.92 (d, $J = 4.3$ Hz, 1H), 1.73 (d, $J = 16.8$ Hz, 1H), 1.17 (s, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.97 (dd, $J = 6.5$, 0.8 Hz, 3H), 0.92 (dd, $J = 6.1$, 3.0 Hz, 6H), 0.73 (d, $J = 1.3$ Hz, 3H). $^{13}$C NMR (501 MHz; CDCl$_3$): $\delta$ 180.6, 71.6, 63.9, 53.7, 47.1, 43.9, 35.2, 32.4, 28.2, 28.0, 27.6, 27.5, 19.6, 19.0, 15.3, 11.5. $^{13}$C NMR (125 MHz; CDCl$_3$): $\delta$ 181.0, 158.3, 135.1, 130.2, 127.4, 127.0, 113.9, 113.5, 58.7, 55.3, 54.3, 53.4, 47.0, 43.9, 35.6, 32.2, 27.6, 27.5, 22.3, 19.6, 19.1, 18.0, 11.6.
Chapter 3. Synthesis of Pyridines From N-Vinyl Nitrones

Pyridines are common in many natural products and pharmaceuticals. This important heterocycle has long been difficult to functionalize and many techniques have been developed to access functionalized pyridines. These methods have included the Hantzsh pyridine synthesis, which constructs the pyridine by joining fragments together. Other methods have tried to develop a direct functionalization of the pyridine core, which requires a prefunctionalization step to activate the pyridine before the functionalization step.

3.1 Introduction

3.1.1 Modern Methods for Synthesis of Multisubstituted Pyridines

Other methods have attempted to construct pyridines from different fragments to access different substitution patterns. Additionally building a pyridine core with varying fragments can allow for libraries of compounds to be built up quickly. Many of these methods have been further developed in recent years.

The Bohlman-Ratz synthesis of pyridines was first reported in the last century and has been utilized to synthesize unsymmetrical pyridines. Recently others have used modifications of the reaction to obtain pyridines. Bagely reported a synthesis to synthesize pyridine (Scheme 3.1) as a fragment for a more complex target molecule. In their synthesis they found that a catalytic amount of Lewis acid, zinc bromide increased the reaction considerably. In previous attempts the yield was 25% without the addition of Lewis acid. So by starting with enamine and alkynoate they could obtain the desired pyridine in a reasonable yield and as just one regiosiomer. This method allows
for quick construction but can be limited by the enamine and alkynoates that can be obtained or synthesized. While this method uses a Lewis acid to catalyze the reaction others have turned to other methods to facilitate cyclization.

[Chemical Reaction]

Scheme 3.1 Bohlman-Ratz Pyridine Synthesis

Other methods developed rely on transition-metal catalyzed processes to induce cyclization and form the pyridine core. One of these methods utilizes α,β-unsaturated oximes as one of the fragments. In the reaction oxime and 1-hexyne are subjected to rhodium(I) catalyzed conditions (Scheme 3.2). The C–H bond functionalization is believed to be followed by an electrocyclization step. The final step then is dehydration giving the pyridine as a regioisomeric mixture. Since alkynes are readily available this reaction can allow for a variety of different substituents to be added to the molecules. Other variations of this reaction have been reported by Ellman, which allow for different substituents and disubstituted alkynes as coupling partners.
Rhodium has been quite popular for these kinds of transformations and Rovis has developed some methods that exploit oxime derivatives to build multisubstituted pyridines.\textsuperscript{82-83} Starting with a O-pivaloyl oxime and acrylic acid they were able to use rhodium(I) to catalyze the formation of pyridine (Scheme 3.3). The pyridine is obtained as one regioisomer in the reaction and no side products are observed. It was hypothesized that the acrylic acid fragment directs the formation of the new carbon–carbon in the reaction and then the carboxylate portion is lost by decarboxylation at the end of the catalytic cycle. This would explain why only one regioisomer was obtained in the reaction. Additionally it gives products where the ester isn’t incorporated into the final product.

\begin{equation}
\begin{array}{c}
\text{Me}_3\text{CNOPiv} + \text{Hex} = \text{CO}_2\text{H} \\
\xrightarrow{[\text{RhCp}^\text{CF}_3\text{C}_2\text{Cl}]_2 (2.5 \text{ mol } \%), \text{AgOTs} (0.9 \text{ equiv}), \text{K}_2\text{S}_2\text{O}_8 (1.05 \text{ equiv})} \text{HFIP, 58 °C} \\
\text{Me}_3\text{C}N \quad \text{79%}
\end{array}
\end{equation}

**Scheme 3.3** Regioselective Pyridine Synthesis by Fragment Coupling

These examples highlight how regioselectivity can be an issue for the synthesis of multisubstituted pyridines from fragment coupling methods. Many of the transition-metal catalyzed methods are incrementally being improved to overcome these regioselectivity issues. Until a general and regioselective method can be devised other methods will need to be developed to access specific substitution patterns.
3.2 Discovery of N-Vinyl Nitrone Coupling

Our interest in pyridine synthesis came from a discovery in our lab by Dr. Dong-Liang Mo. He discovered that certain oximes under copper-promoted conditions with vinyl boronic acids would give ketonitrones. The initial report was with fluorenone oxime and cyclohexenyl boronic acid (51o) to give ketonitrone in good yield (Scheme 3.4). The initial discovery was exciting because only one other report of N-vinyl nitrones exists in the literature. This was reported by Denmark and required multiple steps and harsh conditions.

![Scheme 3.4 Ketonitrone Synthesis by Coupling with Boronic Acids](image)

While Dr. Mo found that these nitrones could undergo an interesting reaction to form spiroisoxazolines further work was done to see what other ketonitrones could be obtained. Eventually he found that chalcone oximes would form ketonitrones as well.

3.3 N-Vinyl Nitrones and Synthesis of Pyridines

The newly discovered copper-promoted coupling reaction with arylboronic acids and α,β-unsaturated oximes gave N-aryl ketonitrones in good yields. It was decided to explore the coupling reaction with vinylboronic acids to obtain new products with different synthetic handles. Cyclohexenylboronic acid (51o) was used for the initial
screening of conditions. Previously two equivalents of Cu(OAc)$_2$ were used to promote $N$-aryl ketonitrone formation but initially we found that only one equivalent of Cu(OAc)$_2$ was required to promote formation of the $N$-vinyl nitrones (table 3.1). Different copper (I and II) salts did not improve the reaction. Decreasing the amount of Cu(OAc)$_2$ to 10 mol % did produce similar results to the stoichiometric reaction conditions. Addition of alkenes and akynes had been shown to increase the yield of copper-promoted Chan-Lam-Evans-like coupling reactions by Merlic.$^{59}$ Alkenes showed the most significant increase with cyclooctadiene (COD) being the best and giving a yield of 72 % (table 3.1, entry 14). Conditions are reported using fluoride sources to activate the vinylboronic acid to the borate and therefore create a more efficient transmetalation reagent in situ. Fluoride sources, CsF and tetrabutylammonium fluoride (TBAF) (table 3.1, entries 17-18) did not improve the efficiency of the coupling and actually hindered the formation of nitrone 62a. Decreasing the amount of boronic acid 13o further decreased yield of nitrone 62a. Lastly gently heating the reaction to 50 °C lead to decomposition of oxime 62a and boronic acid 62o. We determined that 10 mol % of Cu(OAc)$_2$ with 1.1 equiv of COD produced the best results with oxime 62a and boronic acid 51o.
Table 3.1 Optimization of N-Vinyl Nitrone Formation

From here we decided to explore the tolerance of the copper-catalyzed coupling with different oximes. It was quickly discovered that electron-withdrawing groups on the adjacent aryl lead to an increased yield (table 3.2) for \( p \)-fluoro and \( p \)-trifluoromethyl, nitrones 62b and 62c. The presence of a \( p \)-methoxy on oxime resulted in a decreased yield of nitrone 62d. Some linear boronic acids were amicable to the copper-catalyzed
conditions with chalcone oxime. We were surprised that bulky tert-butyl was tolerated and gave the product in good yield. Additionally cyclopropyl was surprising since the ring remained intact after the coupling (entry 6). Lastly the TBS ether was a nice addition since it could be synthetically useful later (entry 8). I wanted to explore the scope of this reaction more but found that some vinyl boronic acids gave low yields under the catalytic conditions.

![Reaction scheme]

Table 3.2 Scope of Copper-Catalyzed Coupling.

<table>
<thead>
<tr>
<th>entry</th>
<th>yield</th>
<th>entry</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>74&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>80&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>63&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

(a) Compounds prepared by Dr. Dimitra Kontokosta.
In the process of exploring the substrate scope of the coupling reaction I discovered that some vinyl boronic acids gave higher yields with stoichiometric copper (II) acetate. The dibenzylideneacetone oximes with acyclic boronic acids required the copper-promoted conditions. These gave interesting products in good yields under these conditions (table 3.3, 29i-k). Additionally other linear vinyl boronic acids could be accessed as well (entries 4-6). The 2-butenylboronic acid gave one of the lowest yields observed (entry Also under these conditions cinnamaldehyde oxime would undergo coupling to give N-vinyl nitrones (29p-r). These were examples that could be accessed before and could give interesting products later. Additionally these could not be synthesized under the normal condensation methods usually employed for the synthesis of aldehyde nitrones.
With these products in hand we decided to determine their reactivity. The first thought was that these could undergo a cyclization to form pyridines. Dr. Mo and Dr. Kontokosta found that DMSO was the best solvent for this process with early examples of the nitrones (Table 3.4, entries 1-4). I contributed to these results by testing the newly obtained examples with the same conditions. I quickly found that the linear $N$-
vinyl nitrones were not as efficient at forming the pyridine as previous examples. The cyclopropyl substituted \(^N\)-vinyl nitrone gave a small amount of pyridine (table 3.4, entry 5) but none of the ring-opened product was observed. The dibenzylideneacetone nitrones (table 3.4, entries 6-7) gave much better yields and the styrene substituent could prove useful for later functionalization and give different synthetic options. The other styrenyl substituted pyridine \(63k\) gave a similar yield and then provided a different substitution pattern compared to pyridine \(63j\). The last example (entry 10) gave the pyridine in a reasonable yield. Overall the trend appears to be that disubstituted vinyl substituents on the \(^N\)-vinyl nitrone.
3.4 Mechanistic Experiments

While we knew some of the trends of the reaction we wanted to solve some of the mechanistic questions we had about this reaction. The first was how is the reaction

Table 3.4 Scope of Pyridine Synthesis.

<table>
<thead>
<tr>
<th>entry</th>
<th>yield</th>
<th>entry</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>6</td>
<td>36&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>68&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>7</td>
<td>34&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>45&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>8</td>
<td>38&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>64&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>9</td>
<td>18&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>17&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10</td>
<td>50&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

(a) Condition A. (b) Condition B. (c) Compounds prepared by Dr. Dimitra Kontokosta.
proceeding to the pyridine. The other was if an electron donating or withdrawing could influence the reactivity of the nitrones over others for the formation of the pyridine. The mechanism we thought could be determined by observing formation of the pyridine by NMR spectroscopy. To answer the electronic effect an intramolecular competition experiment was devised.

To observe the formation of pyridine by NMR nitrone 62I was used since previously we found that it slowly proceed to the pyridine so the hope was that the intermediates could be observed during this process (Scheme 3.5). After heating in DMSO-<i>d</i><sub>6</sub> for 4 hours a mixture of products could be observed. I believe these were 64 and 65 from the NMR spectra observed (Scheme 3.5). After heating for an additional 12 hours only the pyridine was observed. This rules out a pathway where electrocyclization followed by loss of water in the reaction. We believe that after formation of 65 the styrenyl enamine fragment can attack the ketone and then by dehydration give the pyridine (63I).

![Scheme 3.5 Monitoring Pyridine Formation.](image)

The competition experiment required a substrate where two sides could be differentiated. The idea was that if the oxygen transfer required to form the pyridine was
selective for one side then this could be determined by the product ratio. Also this would suggest if electron donating or withdrawing groups would influence the oxygen transfer step. The nitrone was synthesize and an equimolar ratio of $E:Z$ isomers were obtained from the coupling reaction (Scheme 3.6). Upon subjecting the nitrone (63pa:63pb) to the thermal conditions to form the pyridine two regioisomers were observed. From the $^1$H NMR it was determined that the mixture of isomers was equal as well. Since no selectivity was observed from this reaction it is hard to conclude if the oxygen transfer step favors a more electron deficient or rich alkene. Also since the nitrone was obtained in a one to one mixture as well it can not be ruled out if that had more influence on the selectivity of the reaction. Probably other examples could be prepared with differing $E:Z$ ratios and observe the result of pyridine formation.

![Scheme 3.6 Competition Experiment for the Formation of Pyridines](image.jpg)

3.5 Conclusion

In conclusion, the method of $N$-vinyl nitrone formation was further explored and expanded for linear and disubstituted vinyl boronic acids. These we found to be good coupling partners in the reaction with $\alpha,\beta$-unsaturated oximes. Additionally it was discovered that cinnamaldehyde oxime was an efficient coupling partner in the $N$-vinylation reaction but these were not suitable substrates in the formation of pyridines.
Lastly the mechanism of the reaction was probed and NMR spectroscopy suggests that oxygen transfer to the alkene moiety occurs first followed by cyclization and dehydration. Further mechanistic studies could prove useful in understanding this reaction and developing a broader substrate scope. Lastly, mechanistic experiments could suggest strategies for improving the yield and possibly a lower temperature condition for the formation of pyridines from N-vinyl nitrones.

3.6 General Experimental Information.

$^1$H NMR and $^{13}$C NMR spectra were recorded at ambient temperature using 500 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the $\delta$ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. High-resolution mass spectra were acquired on an LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Medium pressure liquid chromatography was performed to force flow the indicated solvent system down columns packed with 60Å (40 – 60 μm) mesh silica gel (SiO$_2$). Unless otherwise noted, all reagents were obtained from commercial sources and, where appropriate, purified prior to use. THF was dried by filtration through alumina according to the procedure of Grubbs.$^{32}$ Dioxane was distilled over CaH$_2$ and stored under N$_2$ prior to use. Dioxane-$d_8$ was dried over activated 4Å molecular sieves, degassed and stored in an inert atmosphere glovebox prior to use.
Anhydrous dichloroethane (DCE) was used as received. Copper (I) thiophenecarboxylate was prepared according to the procedure of Maleczka.  

3.6.1 Preparation of Nitrones

**General Procedure A:** A scintillation vial was charged with oxime 61 (1.0 equiv), vinylboronic acid 13 (2 equiv), Cu(OAc)$_2$ (10 mol %) and anhydrous Na$_2$SO$_4$ (8-9 equiv). These solids were diluted with 1,2-dichloroethane to form a 0.1 M solution of oxime. Pyridine (5 equiv) was added to the resulting slurry via syringe, followed by cyclooctadiene (1.2 equiv). The scintillation vial was then capped with a septum pierced with a ventilation needle and the reaction mixture was stirred at 25 °C for 4-6 h. 1,2-Dichloroethane and pyridine were removed under reduced pressure and the crude reaction mixture was purified by medium pressure chromatography (2:1; ethyl acetate:hexanes) to give 62 as a yellow oil or solid.
General Procedure B: A scintillation vial was charged with oxime 61 (1.0 equiv), vinylboronic acid 51 (2 equiv), Cu(OAc)$_2$ (1 equiv) and anhydrous Na$_2$SO$_4$ (8-9 equiv). These solids were diluted with 1,2-dichloroethane to form a 0.1 M solution of oxime. Pyridine (5 equiv) was added to the resulting slurry via syringe. The scintillation vial was then capped with a septum pierced with a ventilation needle and the reaction mixture was stirred at 25 °C for 4-6 h. 1,2-Dichloroethane and pyridine were removed under reduced pressure and the crude reaction mixture was purified by medium pressure chromatography (2:1; ethyl acetate:hexanes) to give 29 as a yellow oil or solid.

Nitrone 62a: General procedure A was applied using the following reagents: chalcone oxime 29a (0.030 g, 0.13 mmol), cyclohex-1-enylboronic acid 51o (0.033 g, 0.26 mmol), Cu(OAc)$_2$ (0.0024 g, 0.013 mmol), pyridine (0.052 mL, 0.65 mmol), COD (0.021 mL, 0.16 mmol), and Na$_2$SO$_4$ (0.11 g, 0.77 mmol). This procedure afforded 62a as a yellow solid (0.028 g, 72%) after purification using medium pressure chromatography (2:1, EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.00 (d, $J$ = 16.4 Hz, 1H), 7.48-7.34 (m, 5H), 7.29-7.19 (m, 5H), 6.54 (d, $J$ = 16.4 Hz, 1H), 5.56-5.53 (m, 1H), 2.31-2.23 (m, 2H), 2.17-2.10 (m, 2H).
1.82-1.80 (m, 2H), 1.57-1.49 (m, 2H), 1.35- 1.32 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$
148.5, 144.2, 140.3, 136.3, 133.3, 129.8, 129.1, 129.0, 128.6, 128.3, 127.5, 125.8,
121.6, 26.9, 23.9, 21.9, 21.0; HRMS (ESI) m/z calcd. for C$_{21}$H$_{22}$NO (M+H)$^+$ 304.1701,
found 304.1700.

Nitrone 62b: General procedure A was applied using the following reagents: chalcone oxime 28d (0.030 g, 0.10 mmol), cyclohex-1-enylboronic acid 13o (0.026 g, 0.21 mmol),
Cu(OAc)$_2$ (0.0018 g, 0.010 mmol), pyridine (0.042 mL, 0.51 mmol), COD (0.015 mL,
0.12 mmol), and Na$_2$SO$_4$ (0.10 g, 0.70 mmol). This procedure afforded 29b as a yellow solid (0.015 g, 41%) after purification using medium pressure chromatography (2:1,
EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.00 (d, $J = 16.5$ Hz, 1H), 7.70 (d, $J =
8.0$ Hz, 2H), 7.52-7.45 (m, 2H), 7.42-7.40 (m, 2H), 7.37-7.27 (m, 3H), 6.50 (d, $J = 16.5$
Hz, 1H), 5.57-5.55 (m, 1H), 2.39-2.26 (m, 2H), 1.96- 1.78 (m, 2H), 1.65-1.54 (m, 2H),
1.48-1.31 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 146.8, 144.3, 140.0, 137.2, 136.1,
130.5, 130.3, 129.3 (d, J$_{C-F}$ = 225.0 Hz), 128.9, 128.8, 127.5, 126.4, 125.5, 125.4, 27.0,
23.9, 21.9, 21.0; IR (thin film) 3056, 2936, 1617, 1468, 1322, 1269, 1230, 1165, 1123,
1067 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{22}$H$_{21}$NOF (M+H)$^+$ 372.1575, found 372.1585.
**Nitrone 62c:** General procedure A was applied using the following reagents: chalcone oxime 28e (0.040 g, 0.17 mmol), cyclohex-1-enylboronic acid 13o (0.042 g, 0.33 mmol), Cu(OAc)$_2$ (0.0031 g, 0.017 mmol), pyridine (0.069 mL, 0.85 mmol), COD (0.025 mL, 0.20 mmol), and Na$_2$SO$_4$ (0.11 g, 0.77 mmol). This procedure afforded 29c as a yellow solid (0.032 g, 60%) after purification using medium pressure chromatography (2:1, EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.01 (d, $J = 16.3$ Hz, 1H), 7.46 (d, $J = 7.2$ Hz, 2H), 7.33-7.21 (m, 5H), 7.15-7.09 (m, 2H), 6.52 (d, $J = 16.3$ Hz, 1H), 5.58-5.56 (m, 1H), 2.41-2.17 (m, 2H), 2.00-1.82 (m, 2H), 1.66-1.50 (m, 2H), 1.49-1.32 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 163.8 (d, $J_{C-F} = 290.0$ Hz), 147.1, 144.4, 140.0, 136.2, 131.8, 131.7, 129.2, 128.7, 127.5, 125.9, 121.7, 115.7, 27.0, 23.9, 22.0, 21.1; IR (thin film) 3055, 2930, 2859, 1602, 1514, 1447, 1362, 1118, 1094, 1075 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{21}$H$_{21}$NOF (M+H)$^+$ 322.1607, found 322.1606.
Nitrone 62d: General procedure B was applied using the following reagents: chalcone oxime 28f (0.040 g, 0.16 mmol), cyclohex-1-enylboronic acid 13o (0.040 g, 0.32 mmol), Cu(OAc)$_2$ (0.0029 g, 0.016 mmol), pyridine (0.065 mL, 0.80 mmol), COD (0.024 mL, 0.19 mmol), and Na$_2$SO$_4$ (0.11 g, 0.77 mmol). This procedure afforded 29d as a yellow solid (0.033 g, 63%) after purification using medium pressure chromatography (2:1, EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.05 (d, J = 16.4 Hz, 1H), 7.51 (d, J = 7.5 Hz, 2H), 7.37-7.29 (m, 3H), 7.21 (d, J = 8.3 Hz, 2H), 6.97 (d, J = 8.3 Hz, 2H), 6.61 (d, J = 16.4 Hz, 1H), 5.66-5.64 (m, 1H), 2.40-2.20 (m, 2H), 1.95-1.92 (m, 2H), 1.74-1.54 (m, 2H), 1.52-1.38 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 159.9, 148.0, 144.6, 140.1, 136.4, 131.2, 129.0, 128.7, 127.5, 125.6, 125.4, 122.1, 113.8, 55.3, 27.1, 24.0, 22.1, 21.1; IR (thin film) 3039, 2933, 2836, 1606, 1573, 1517, 1447, 1289, 1247, 1223, 1174 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{22}$H$_{24}$NO$_2$ (M+H)$^+$ 334.1807, found 334.1800.

N-Alkenylchalcone nitron e 62e: General procedure A was applied using the following reagents: chalcone oxime 28a (0.2466 g, 1.105 mmol), 3,3-dimethylbut-1-enylboronic acid 13f (0.3937 g, 3.076 mmol), Cu(OAc)$_2$ (0.0313 g, 0.172 mmol), pyridine (0.45 mL,
5.0 mmol), cyclooctadiene (160 μL, 1.3 mmol), Na₂SO₄ (0.xxx g, xxx mmol). This procedure afforded 29e as an amorphous yellow solid (0.230 g, 68%) after medium pressure chromatography (20:80 EtOAc:hexanes). ¹H NMR (500 MHz; CDCl₃): δ 8.18 (d, J = 16.4, 1H), 7.53-7.51 (m, 3H), 7.49-7.47 (m, 2H), 7.34-7.30 (m, 4H), 7.29-7.28 (m, 1H), 6.90 (d, J = 13.2, 1H), 6.55 (d, J = 13.2, 1H), 6.51 (d, J = 16.4, 1H), 0.98 (s, 9H); ¹³C NMR (125 MHz): δ 140.7, 140.5, 136.5, 132.2, 130.3, 129.7, 129.4, 129.2, 128.9, 128.8, 128.5, 127.6, 122.6, 32.4, 19.2; IR (thin film) 3061, 2961, 2866, 1663, 1604, 1574, 1449, 1334, 1213, 1016 cm⁻¹; HRMS (ESI) m/z calcd. for C₂₁H₂₄NO (M+H)⁺ 306.1853, found 306.1858.

N-Alkenylchalcone nitrone 62f: General procedure A was applied using the following reagents: chalcone oxime 28a (0.2457 g, 1.101 mmol), cyclopropylvinylboronic acid 13i (0.3569 g, 3.189 mmol), Cu(OAc)₂ (0.0351 g, 0.193 mmol), pyridine (0.45 mL, 5.0 mmol), cyclooctadiene (160 μL, 1.3 mmol), Na₂SO₄ (0.7186 g, 5.061 mmol). This procedure afforded 29f as an orange oil (0.179 g, 56%) after medium pressure chromatography (1:4 EtOAc:hexanes). ¹H NMR (500 MHz; CDCl₃) δ 8.18 (d, J = 16.4 Hz, 1H), 7.53-7.51 (m, 3H), 7.46 (d, J = 7.2 Hz, 2H), 7.33-7.31 (m, 2H), 7.30-7.28 (m, 2H), 7.27-7.26 (m, 1H), 6.74 (d, J = 12.8 Hz, 1H), 6.45 (d, J = 16.4 Hz, 1H) 6.37 (dd, J = 12.8, 10.4 Hz, 1H) 1.37-1.32 (m, 1H), 0.84-0.80 (m, 2H), 0.58-0.54 (m, 2H); ¹³C NMR (125 MHz) δ 146.7, 140.4, 136.6, 135.4, 132.2, 130.4, 130.2, 129.7, 129.2, 129.0,
128.8, 127.6, 122.6, 12.1, 8.2; IR (thin film) 3061, 3029, 1661, 1604, 1448, 1333, 1015, 977, 944, 745 cm⁻¹; HRMS (ESI) m/z calcd. for C₂₀H₂₀NO (M+H)⁺ 290.1545, found 290.1548.

\[
\text{62g}
\]

**N-Alkenylchalcone nitrone 62g**: General procedure A was applied using the following reagents: chalcone oxime 28a (0.2603 g, 1.166 mmol), enylboronic acid 13g (0.5812 g, 3.588 mmol), Cu(OAc)₂ (0.0307 g, 0.169 mmol), pyridine (0.45 mL, 5.0 mmol), cyclooctadiene (160 μL, 1.3 mmol), Na₂SO₄ (0.774 g, 5.45 mmol). This procedure afforded 29g as an amorphous yellow solid (0.182 g, 46%) after medium pressure chromatography (2:3 EtOAc:hexanes). ¹H NMR (500 MHz; CDCl₃) δ 8.19 (d, J = 16.4 Hz, 1H), 7.51-7.47 (m, 5H), 7.33-7.28 (m, 5H), 7.26-7.23 (m, 2H), 7.11 (d, J = 7.0 Hz, 2H), 7.04 (dt, J = 13.0, 7.4 Hz, 1H), 6.63 (dd, J = 13.0, 1.3 Hz, 1H), 6.52 (d, J = 16.4 Hz, 1H), 3.41 (d, J = 7.4 Hz, 2H); ¹³C NMR (125 MHz) δ 148.3, 144.9, 141.1, 138.4, 136.5, 133.3, 130.3, 129.8, 129.4, 129.0, 128.9, 128.8, 128.7, 128.5, 127.7, 126.5, 122.4, 35.5; HRMS (ESI) m/z calcd. for C₂₄H₂₂NO (M+H)⁺ 340.1700, found 340.1701.

\[
\text{62h}
\]

**N-Alkenylchalcone nitrone 62h**: General procedure A was applied using the following reagents: chalcone oxime 29a (0.0453 g, 0.203 mmol), vinylboronic acid 13j (0.128 g, 0.595 mmol), Cu(OAc)₂ (0.013 g, 0.074 mmol), pyridine (0.065 mL, 0.80 mmol), COD
(0.024 mL, 0.19 mmol), and Na₂SO₄ (0.11 g, 0.77 mmol). This procedure afforded 29h as an amorphous yellow solid (0.034 g, 42%) after medium pressure chromatography (2:3 EtOAc:hexanes). ¹H NMR (500 MHz; CDCl₃) δ 8.20 (d, \( J = 16.4 \) Hz, 1H), 7.50-7.47 (m, 5H), 7.32-7.27 (m, 5H), 6.92-6.91 (m, 2H), 6.51 (d, \( J = 16.4 \) Hz, 1H), 4.31 (s, 2H), 0.70 (s, 9H), -0.083 (s, 6H); ¹³C NMR (125 MHz) δ 148.6, 141.1, 136.5, 132.1, 131.8, 130.2, 129.7, 129.3, 129.0, 128.8, 127.7, 122.4, 60.8, 25.7, 18.0, -5.6.

![Diagram](62i)

**N-Alkenyldibenzylideneacetone nitrone 62i:** General procedure B was applied using the following reagents: dibenzylideneacetone oxime 28c (0.260 g, 1.04 mmol), 2-butenyloboronic acid 13q (0.346 g, 3.46 mmol), Cu(OAc)₂ (0.212 g, 1.17 mmol), pyridine (0.80 mL, 10.0 mmol), Na₂SO₄ (1.24 g, 8.74 mmol). This procedure afforded 29i as an amorphous yellow solid (0.22 g, 68%) after medium pressure chromatography (60:40 EtOAc:hexanes). ¹H NMR (500 MHz; CDCl₃) δ 7.59-7.57 (m, 2H), 7.53-7.50 (m, 2H), 7.45-7.44 (m, 2H), 7.37 (q, \( J = 7.3 \) Hz, 4H), 6.95 (s, 2H), 5.72-5.68 (m, 1H), 2.12 (s, 3H), 1.79 (d, \( J = 6.8 \) Hz, 3H); ¹³C NMR (125 MHz) δ 144.6, 141.9, 139.2, 136.7, 136.4, 134.0, 129.0, 128.9, 128.8, 128.7, 127.4, 126.8, 123.2, 120.4, 119.1, 14.6, 12.8; IR (thin film) 3055, 3025, 2925, 1694, 1597, 1447, 1216, 1191, 963, 753 cm⁻¹; HRMS (ESI) m/z calcd. for C₂₁H₂₁NO (M+H)⁺ 304.1701, found 304.1702.
**N-Alkenyldibenzylideneacetone nitrone 62j:** General procedure B was applied using the following reagents: dibenzylideneacetone oxime 28c (0.251 g, 1.01 mmol), 13p (0.726 g, 4.13 mmol), Cu(OAc)$_2$ (0.197 g, 1.09 mmol), pyridine (0.8 mL, 10 mmol), Na$_2$SO$_4$ (1.2 g, 8.7 mmol). This procedure afforded 29j as a yellow solid (0.248 g, 65%) after medium pressure chromatography (60:40 EtOAc:hexanes). $^1$H NMR (500 MHz; CDCl$_3$) δ 7.66-7.60 (m, 4H), 7.57-7.54 (m, 2H), 7.43-7.32 (m, 11H), 7.12 (d, $J$=16 Hz, 1H), 6.95 (d, $J$ = 16 Hz, 1H), 6.04 (t, $J$ = 8 Hz, 1H), 2.40 (qint, $J$ = 8 Hz, 2H), 1.31 (t, $J$ = 8 Hz, 3H); $^{13}$C NMR (125 MHz) δ 146.1, 144.1, 139.7, 136.6, 134.7, 133.2, 132.4, 129.2, 129.0, 128.9, 128.8, 128.7, 128.4, 127.5, 126.8, 120.4, 118.9, 21.6, 14.0; IR (thin film) 3058, 2970, 2935, 1707, 1610, 1496, 1444, 1259, 1175, 960 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{27}$H$_{26}$NO (M+H)$^+$ 380.2014, found 380.2016.

**N-Alkenyldibenzylideneacetone nitrone 62k:** General procedure B was applied using the following reagents: dibenzylideneacetone oxime 28d (0.093 g, 0.38 mmol), 13p (0.356 g, 2.02 mmol), Cu(OAc)$_2$ (0.086 g, 0.47 mmol), pyridine (0.5 mL, 6.2 mmol), Na$_2$SO$_4$ (0.61 g, 4.3 mmol). This procedure afforded 29k as a yellow solid (0.063 g, 44%) after medium pressure chromatography (60:40 EtOAc:hexanes). $^1$H NMR (500 MHz; CDCl$_3$) δ 7.66-7.60 (m, 4H), 7.57-7.54 (m, 2H), 7.43-7.32 (m, 11H), 7.12 (d, $J$=16 Hz, 1H), 6.95 (d, $J$ = 16 Hz, 1H), 6.04 (t, $J$ = 8 Hz, 1H), 2.40 (qint, $J$ = 8 Hz, 2H), 1.31 (t, $J$ = 8 Hz, 3H); $^{13}$C NMR (125 MHz) δ 146.1, 144.1, 139.7, 136.6, 134.7, 133.2, 132.4, 129.2, 129.0, 128.9, 128.8, 128.7, 128.4, 127.5, 126.8, 120.4, 118.9, 21.6, 14.0; IR (thin film) 3058, 2970, 2935, 1707, 1610, 1496, 1444, 1259, 1175, 960 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{27}$H$_{26}$NO (M+H)$^+$ 380.2014, found 380.2016.
MHZ; CDCl$_3$ δ 7.58 (d, $J = 15$ Hz, 1H), 7.40-7.36 (m, 3H), 7.33-7.21 (m, 10H), 7.11-7.09 (m, 2H), 7.05-6.99 (m, 3H) 6.56 (d, $J = 15$ Hz, 1H), 6.38 (dd, $J = 15$, 11 Hz, 1H), 5.96 (t, $J = 8$ Hz, 1H), 2.07-2.01 (m, 2H), 0.85 (t, $J = 8$ Hz, 3H); $^{13}$C NMR (125 MHz) δ 149.4, 145.1, 140.5, 137.2, 136.6, 133.8, 132.9, 132.8, 130.3, 128.9, 128.8, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 126.8, 125.6, 21.2, 13.4; IR (thin film) 3058, 3029, 2964, 2931, 1673, 1598, 1446, 1232, 992, 758 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{27}$H$_{26}$NO (M+H)$^+$ 380.2014, found 380.2010.

\[ \text{62l} \]

**N-Alkenylchalcone nitrone 62l:** General procedure A was applied using the following reagents: chalcone oxime 28a (0.116 g, 0.520 mmol), trans-(4-fluorophenyl)vinylboronic acid 13r (0.252 g, 1.52 mmol), Cu(OAc)$_2$ (0.012 g, 0.066 mmol), pyridine (0.23 mL, 2.5 mmol), cyclooctadiene (80 μL, 0.65 mmol), Na$_2$SO$_4$ (0.614 g, 4.35 mmol). This procedure afforded 28l as a yellow oil (0.018 g, 10%) after medium pressure chromatography (40:60 EtOAc:hexanes). General procedure B was applied using the following reagents: chalcone oxime 28a (0.227 g, 1.02 mmol), trans-(4-fluorophenyl)vinylboronic acid 13r (0.507 g, 3.05 mmol), Cu(OAc)$_2$ (0.197 g, 1.09 mmol), pyridine (0.80 mL, 10.0 mmol), Na$_2$SO$_4$ (1.23 g, 8.64 mmol). This procedure afforded 29l as a yellow oil (0.16 g, 46%) after medium pressure chromatography (40:80 EtOAc:hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 8.27 (d, $J = 16.5$ Hz, 1H), 7.72 (d, $J = 13.0$ Hz, 1H), 7.57-7.55 (m, 3H), 7.51-7.49 (m, 2H), 7.40-7.38 (m, 2H), 7.32-7.31 (m,
3H), 7.26-7.21 (m, 3H), 6.97 (t, J = 8.0 Hz, 2H), 6.58 (d, J = 16.5 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 164.1 (d, J$_{C:F}$ = 248.0 Hz), 149.5, 141.6, 136.4, 131.9, 130.8, 130.5, 130.1, 129.5, 129.3, 129.1, 128.8, 128.6, 127.8, 126.9, 122.5, 116.0; HRMS (ESI) m/z calcd. for C$_{23}$H$_{19}$NOF (M+H)$^+$ 344.1451, found 344.1449.

$^62m$

**N-Alkenylchalcone nitrone 62m:** General procedure A was applied using the following reagents: chalcone oxime 28a (0.113 g, 0.505 mmol), trans-(2-cyclohexylvinyl)boronic acid 13e (0.205 g, mmol), Cu(OAc)$_2$ (0.012 g, 0.066 mmol), pyridine (0.23 mL, 2.5 mmol), cyclooctadiene (80 μL, 0.65 mmol), Na$_2$SO$_4$ (0.614 g, 4.32 mmol). This procedure afforded 29m as a yellow oil (0.037 g, 22%) after medium pressure chromatography (40:80 EtOAc:hexanes). General procedure B was applied using the following reagents: chalcone oxime 28a (0.123 g, 0.551 mmol), trans-(2-cyclohexylvinyl)boronic acid 13e (0.255 g, 1.65 mmol), Cu(OAc)$_2$ (0.0948 g, 0.522 mmol), pyridine (0.45 mL, 5.0 mmol), Na$_2$SO$_4$ (0.623 g, 4.39 mmol). This procedure afforded 29m as a yellow oil (0.158 g, 87%) after medium pressure chromatography (40:80 EtOAc:hexanes). $^1$H NMR (500 MHz; CDCl$_3$) δ 8.18 (d, J = 16.4, 1H), 7.51 (t, J = 3.1 Hz, 3H), 7.46 (t, J = 7.2, 2H), 7.31-7.24 (m, 5H), 6.82 (dd, J = 13.1, 7.9 Hz, 1H), 6.59 (d, J = 13.1 Hz, 1H), 6.48 (d, J = 16.4, 1H), 2.04-1.98 (m, 1H), 1.69-1.59 (m, 5H), 1.24-1.03 (m, 5H); $^{13}$C NMR (125 MHz) δ 147.8, 140.5, 136.5, 135.9, 132.2, 130.7, 130.3, 129.7, 129.2, 129.0, 127.6, 122.6, 38.3, 32.5, 25.9, 25.7; IR (thin film) 3055,
Chapter 3

2924, 2847, 1664, 1604, 1448, 1334, 1213, 1015, 971 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for \(C_{23}H_{26}NO\) (M+H)\(^+\) 332.2014, found 332.2010.

\[ \text{Nitrone 62n: General procedure B was applied using the following reagents: chalcone oxime 28a (0.066 g, 0.30 mmol), hexenylboronic acid 13b (0.10 g, 0.78 mmol), Cu(OAc)\(_2\) (0.11 g, 0.59 mmol), pyridine (0.24 mL, 3.0 mmol), and Na\(_2\)SO\(_4\) (0.36 g, 2.53 mmol). This procedure afforded 28a as a yellow liquid (0.068 g, 75%) after purification using medium pressure chromatography (2:1, EtOAc:hexanes).} \]

\[ ^1\text{H NMR (500 MHz; CDCl}_3\text{): } \delta \text{ 8.19 (d, } J = 16.5 \text{ Hz, 1H), 7.52-7.40 (m, 5H), 7.30-7.26 (m, 5H), 6.89-6.83 (m, 1H), 6.61 (d, } J = 13.0 \text{ Hz, 1H), 6.50 (d, } J = 16.5 \text{ Hz, 1H), 2.06-2.01 (m, 2H), 1.36-1.33 (m, 2H), 1.29-1.25 (m, 2H), 0.85 (t, } J = 7.0 \text{ Hz, 3H);} \]

\[ ^1\text{H NMR (125 MHz, CDCl}_3\text{): } \delta \text{ 147.9, 140.9, 136.4, 132.0, 130.9, 130.3, 129.7, 129.3, 129.0, 128.8, 128.7, 127.6, 122.5, 30.8, 29.0, 22.1, 13.7; IR (thin film) 3052, 2929, 1712, 1604, 1575, 1448, 1364, 1335, 1264, 1216 cm}^{-1}; \text{ HRMS (ESI) } m/z \text{ calcd. for } C_{21}H_{24}NO\text{ (M+H)}^+ \text{ 306.1858, found 306.1860.} \]

\[ N\text{-Alkenylchalcone nitron 62o: General procedure B was applied using the following reagents: chalcone oxime 28a (0.230 g, 1.03 mmol), 2-butenylboronic acid 13q (0.311} \]
g, 3.12 mmol), Cu(OAc)$_2$ (0.219 g, 1.20 mmol), pyridine (0.90 mL, 10.0 mmol), Na$_2$SO$_4$ (1.35 g, 9.52 mmol). This procedure afforded 29o as a light yellow amorphous solid (0.042 g, 15%) after medium pressure chromatography (80:20 EtOAc:hexanes). $^1$H NMR (500 MHz; CDCl$_3$) $\delta$ 8.03 (d, $J = 15$ Hz, 1H), 7.47-7.46 (m, 2H), 7.43-7.40 (m, 3H), 7.32-7.27 (m, 3H), 7.24-7.23 (m, 2H), 5.44-5.40 (m, 1H), 1.91 (s, 3H), 1.41 (d, $J = 7$ Hz, 3H); $^{13}$C NMR (125 MHz) $\delta$ 148.2, 142.0, 140.3, 136.3, 133.4, 129.8, 129.1, 129.0, 128.7, 128.5, 127.5, 123.7, 121.8, 15.2, 12.4; IR (thin film) 3055, 2925, 2854, 1663, 1604, 1449, 1335, 1214, 1015, 747 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{19}$H$_{20}$NO (M+H)$^+$ 278.1545, found 278.1542.

62q

$N$-Alkenylcinnamaldehyde nitrone 62q: General procedure B was applied using the following reagents: cinnamaldehyde oxime 28b (0.1656 g, 1.125 mmol), boronic acid 13e (0.4204 g, 2.730 mmol), Cu(OAc)$_2$ (0.2424 g, 1.335 mmol), pyridine (0.80 mL, 10.0 mmol), Na$_2$SO$_4$ (0.595 g, 4.19 mmol). This procedure afforded 29q as a yellow solid (0.189 g, 66%) after medium pressure chromatography (2:3 EtOAc:hexanes). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.58 (dd, $J = 16.3$, 9.7, Hz, 1H), 7.47-7.45 (m, 2H), 7.29-7.22 (m, 4H), 7.01 (d, $J = 16.3$ Hz, 1H), 6.75 (dd, $J = 13.1$, 7.4 Hz, 1H), 6.60 (d, $J = 13.1$ Hz, 1H), 2.14-2.08 (m, 1H), 1.73-1.68 (m, 4H), 1.62 (d, $J = 12.7$, 1H), 1.25-1.19 (m, 2H), 1.16-1.09 (m, 3H); $^{13}$C NMR (125 MHz) $\delta$ 139.4, 137.6, 136.2, 135.0, 133.4, 129.4, 128.9, 127.5 118.8, 37.9, 32.5, 25.9, 25.8; IR (thin film) 3058, 2922, 2848, 1678, 1447, 1408,
1145, 962, 748, 688 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for C\(_{17}H_{22}NO\) (M+H\(^+\)) 256.1701, found 256.1695.

\[
\text{62q}
\]

\textit{N-Alkenylcinnamaldehyde nitrone 62q:} General procedure X was applied using the following reagents: cinnamaldehyde oxime \textbf{28b} (0.1666 g, 1.132 mmol), boronic acid \textbf{13q} (0.287 g, 2.88 mmol), Cu(OAc)\(_2\) (0.231 g, 1.27 mmol), pyridine (0.80 mL, 10.0 mmol), Na\(_2\)SO\(_4\) (0.616 g, 4.34 mmol). This procedure afforded \textbf{29q} as an amorphous yellow solid (0.0678 g, 30%) after medium pressure chromatography (4:1 EtOAc:hexanes). \(^1\)H NMR (500 MHz; CDCl\(_3\)): \(\delta\) 7.56 (dd, \(J = 16.2, 9.6\) Hz, 1H), 7.50-7.45 (m, 3H), 7.33-7.29 (m, 2H), 7.28-7.25 (m, 1H), 7.05 (d, \(J = 16.2\) Hz, 1H), 6.25-6.21 (m, 1H), 2.06 (s, 3H), 1.74 (d, \(J = 7.2\) Hz, 3H); \(^13\)C NMR (125 MHz) \(\delta\) 143.3, 139.2, 136.3, 135.1, 129.2, 128.9, 127.4, 120.4, 119.1, 13.2, 12.9; IR (thin film) 3055, 2925, 1678, 1522, 1444, 1362, 1191, 1111, 1066, 970 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for C\(_{13}H_{16}NO\) (M+H\(^+\)) 202.1232, found 202.1231.

\[
\text{62r}
\]

\textit{N-Alkenylcinnamaldehyde nitrone 62o:} General procedure X was applied using the following reagents: cinnamaldehyde oxime \textbf{28b} (0.309 g, 2.10 mmol), cyclohexenylboronic acid \textbf{13o} (0.668 g, 5.30 mmol), Cu(OAc)\(_2\) (0.396 g, 2.18 mmol),
pyridine (1.70 mL, 21.0 mmol), Na$_2$SO$_4$ (1.20 g, 8.44 mmol). This procedure afforded

29r as an amorphous yellow solid (0.345 g, 72%) after medium pressure chromatography (2:3 EtOAc:hexanes). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.63 (dd, $J = 16.2$, 9.6 Hz, 1H), 7.54 (d, $J = 7.5$ Hz, 2H), 7.37-7.34 (m, 1H), 7.32-7.29 (m, 1H) 7.05 (d, $J = 16.2$ Hz, 1H) 6.60-6.59 (m, 1H) 2.50-2.47 (m, 2H), 2.27-2.24 (m, 2H), 1.83-1.78 (m, 2H), 1.67-1.62 (m, 2H); $^{13}$C NMR (125 MHz) $\delta$ 144.3, 139.2, 136.3, 134.2, 129.3, 128.9, 127.4, 123.2, 25.1, 24.4, 22.4, 21.5; IR (thin film) 2935, 2863, 1711, 1674, 1448, 1311, 1169, 1120, 973, 758 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{15}$H$_{18}$NO (M+H)$^+$ 228.1388, found 228.1387.

\[
\begin{align*}
\text{N-Alkenyldibenzylideneacetone nitrone 29sa:29sb:} & \text{ General procedure A was applied using the following reagents: dibenzylideneacetone oxime 28X (0.119 g, 0.427 mmol), cyclohexenylboronic acid 13o (0.181 g, 1.43 mmol), Cu(OAc)$_2$ (0.0080 g, 0.044 mmol), pyridine (0.17 mL, 2.1 mmol), cyclooctadiene (64 $\mu$L, 0.47 mmol), Na$_2$SO$_4$ (0.589 g, 4.15 mmol). This procedure afforded 29sa:29sb as an amorphous yellow oil (0.12 g, 76%) after medium pressure chromatography (60:40 EtOAc:hexanes). E-isomer$^1$H NMR (500 MHz; CDCl$_3$) $\delta$ 7.57 (d, $J = 10$ Hz, 1H), 7.52 (d, $J = 10$ Hz, 1H), 7.49-7.43 (m, 3H), 7.40-7.35 (m, 4H), 7.33-7.31 (m, 1H), 6.95 (m, 1H), 6.92-6.85 (m, 3H), 5.91-5.89 (m, 1H), 3.83 (s, 3H), 2.49-2.47 (m, 2H), 2.24-2.21 (m, 2H), 1.85-1.81 \end{align*}
\]
(m, 2H), 1.71-1.68 (m, 2H); $^{13}$C NMR of E-isomer (125 MHz) $\delta$ 160.5, 145.3, 139.3, 136.7, 134.1, 129.4, 129.0, 128.9, 128.8, 128.2, 127.4, 125.4, 120.4, 119.3, 114.5, 55.4, 26.3, 24.2, 22.3, 21.5; $^{13}$C NMR of Z-isomer (125 MHz) $\delta$ 160.3, 144.3, 139.1, 136.4, 133.9, 129.1, 129.0, 128.8, 128.2, 127.4, 126.8, 125.3, 118.2, 116.9, 114.3, 55.3, 26.2, 24.2, 22.3, 21.5; IR (thin film) 3022, 2938, 2860, 1701, 1601, 1510, 1249, 1172, 1104, 1030 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{24}$H$_{26}$NO$_2$ (M+H)$^+$ 360.1964, found 360.1964.

### 3.6.2 Preparation of Pyridines

![Pyridine Preparation Diagram](image)

**General Procedure C:** A sealed-tube was charged with nitrone 29, 4 Å molecular sieves (3 beads) and DMSO (0.1 M) and solution was heated at 140 °C for 8-12 h. The solution was then diluted with EtOAc (10 mL), and extracted with water. The aqueous layer was extracted twice with EtOAc (2 x 10 mL), and the combined organic extracts were washed with brine (1 x 10 mL). The organic layer was dried with MgSO$_4$ and concentrated under vacuum. The crude product mixture was purified by medium pressure chromatography (15:85, EtOAc: hexanes) to give 18 as a light yellow oil.

![Pyridine Preparation Diagram](image)

**General Procedure D:** A sealed-tube was charged with nitrone 29, 4 Å molecular sieves (3 beads) and DMSO (0.1 M) and solution was heated at 120 °C for 8-12 h. The
solution was then diluted with EtOAc (10 mL), and extracted with water. The aqueous
layer was extracted twice with EtOAc (2 x 10 mL), and the combined organic extracts
were washed with brine (1 x 10 mL). The organic layer was dried with MgSO₄ and
concentrated under vacuum. The crude product mixture was purified by medium
pressure chromatography (15:85, EtOAc: hexanes) to give 18 as a light yellow oil.

Pyridine 63a: General procedure C was applied using nitrone 29a (0.031 g, 0.10 mmol).
This procedure afforded 30a as a yellow oil (0.020 g, 71%) after purification using
medium pressure chromatography (15:85, EtOAc:hexanes). ¹H NMR (500 MHz, CDCl₃):
δ 7.99-7.96 (m, 2H), 7.49-7.42 (m, 5H), 7.39-7.35 (m, 2H), 7.37-7.33 (m, 2H), 3.10 (t, J
= 6.5 Hz, 2H), 2.66 (t, J = 6.3 Hz, 2H), 2.02-1.90 (m, 2H), 1.84-1.68 (m, 2H) ; ¹³C NMR
(125 MHz, CDCl₃) δ 157.6, 154.3, 150.3, 139.7, 128.9, 128.6, 128.5, 128.4, 128.3,
128.0, 127.7, 126.9, 119.1, 33.3, 27.3, 23.1, 23.0; IR (thin film) 3057, 2932, 2859, 1587,
1542, 1495, 1439, 1419, 1381, 1264, 1073 cm⁻¹; HRMS (ESI) m/z calcd. for C₂₁H₂₀N
(M+H)⁺ 286.1596, found 286.1599.

Pyridine 63b: General procedure C was applied using nitrone 29b (0.027 g, 0.074
mmol). This procedure afforded 30b as a yellow solid (0.018 g, 68%) after purification using medium pressure chromatography (15:85, EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.11 (d, $J = 8.1$ Hz, 2H), 7.69 (d, $J = 8.1$ Hz, 2H), 7.49-7.41 (m, 4H), 7.36-7.33 (m, 2H), 3.11 (t, $J = 6.6$ Hz, 2H), 2.68 (t, $J = 6.3$ Hz, 2H), 2.06-1.88 (m, 2H), 1.84-1.71 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 158.1, 152.5, 139.3, 130.9, 129.6, 129.0, 128.8, 128.7, 128.5, 128.4, 127.9, 127.1, 125.6 (d, $J_{C-F} = 204.0$ Hz), 119.4, 33.2, 27.3, 23.0, 22.9; IR (thin film) 2937, 1714, 1587, 1541, 1496, 1449, 1322, 1264, 1164, 1108, 1067 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{22}$H$_{19}$NF$_3$ (M+H)$^+$ 354.1470, found 354.1463.

Pyridine 63d: General procedure C was applied using nitrone 29d (0.015 g, 0.047 mmol). This procedure afforded 30d as a yellow oil (0.010 g, 64%) after purification using medium pressure chromatography (15:85, EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.93 (d, $J = 8.7$ Hz, 2H), 7.48-7.43 (m, 2H), 7.43-7.39 (m, 1H), 7.36-7.32 (m, 3H), 6.97 (d, $J = 8.7$ Hz, 2H), 3.85 (s, 3H), 3.08 (t, $J = 6.6$ Hz, 2H), 2.64 (t, $J = 6.3$ Hz, 2H), 2.01-1.86 (m, 2H), 1.82-1.68 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 160.1, 157.3, 141.1, 140.1, 139.8, 128.5, 128.3, 128.1, 127.7, 127.5, 127.2, 118.5, 114.0, 55.3, 33.29, 29.72, 27.25, 23.12; IR (thin film) 2931, 2856, 1606, 1587, 1513, 1494, 1449, 1414, 1379, 1249, 1171 cm$^{-1}$. 
Pyridine 63f: General procedure D was applied using nitrone 29f (0.101 g, 0.350 mmol). This procedure afforded 30f as a yellow oil (0.016 g, 17%) after purification using medium pressure chromatography (5:95, EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.35 (s, 1H), 8.00-7.99 (m, 2H), 7.61 (s, 1H), 7.52-7.38 (m, 8H), 1.93-1.88 (m, 1H), 0.94-0.91 (m, 2H), 0.82-0.79 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.6, 150.6, 146.9, 139.4, 139.3, 134.4, 134.0, 129.0, 128.9, 128.8, 128.7, 128.6, 128.4, 127.4, 126.7, 125.8, 120.8, 11.6, 9.1; IR (thin film) 3058, 3022, 2935, 1688, 1590, 1480, 1373, 1224, 1081, 746 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{20}$H$_{18}$N (M+H)$^+$ 272.1439, found 272.1438.

Pyridine 63i: General procedure C was applied using nitrone 29i (0.0642 g, 0.212 mmol). This procedure afforded 30i as a yellow oil (0.0217 g, 36%) after purification using medium pressure chromatography (5:95, EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.58-7.55 (m, 3H), 7.48-7.45 (m, 2H), 7.43-7.32 (m, 5H), 7.29-7.27 (m, 1H), 7.20-7.17 (m, 2H), 2.63 (s, 3H), 2.20 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 157.7, 152.0, 150.0, 140.1, 137.0, 131.6, 128.8, 128.7, 128.4, 128.3, 128.0, 127.7, 127.6, 127.0, 120.5, 23.7, 16.2; IR (thin film) 3058, 2967, 1721, 1575, 1495, 1416, 1257, 1087, 964, 761 cm$^{-1}$; HRMS (ESI) $m/z$ calcd. for C$_{21}$H$_{20}$N (M+H)$^+$ 286.1596, found 286.1592.
Pyridine 63j: General procedure C was applied using nitrone 29j (0.0655 g, 0.173 mmol). This procedure afforded 30j as a yellow oil (0.0212 g, 34%) after purification using medium pressure chromatography (5:95, EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.06-8.08 (m, 3H), 7.91 (s, 1H), 7.60 (d, $J$ = 7.4 Hz, 3H), 7.57-7.55 (m, 4H), 7.49-7.40 (m, 16H), 7.31 (dd, $J$ = 31.1, 14.7 Hz, 7H), 2.82 (d, $J$ = 7.5 Hz, 2H), 1.18 (t, $J$ = 7.5 Hz, 3H); IR (thin film) 3061, 2967, 2928, 1724, 1574, 1415, 1412, 1256, 1091, 967 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{27}$H$_{23}$N (M+H)$^+$ 362.1909, found 362.1919.

Pyridine 63k: General procedure C was applied using nitrone 29k (0.081 g, 0.213 mmol). This procedure afforded 30k as a yellow oil (0.029 g, 38%) after purification using medium pressure chromatography (5:95, EtOAc:hexanes). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.56 (t, $J$ = 6.3 Hz, 6H), 7.48 (t, $J$ = 7.3 Hz, 6H), 7.45-7.39 (m, 7H), 7.35 (dd, $J$ = 15.4, 7.7 Hz, 6H), 7.29-7.26 (m, 4H), 2.65 (d, $J$ = 7.5 Hz, 2H), 0.75 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 159.8, 152.4, 150.9, 141.6, 140.2, 136.9, 133.8, 133.6, 132.3, 129.2, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.3, 127.0, 126.4, 125.4, 121.5, 22.3, 14.9; IR (thin film) 3055, 3025, 2970, 2928, 1580, 1553, 1492, 1447, 1383, 1074 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{27}$H$_{23}$N (M+H)$^+$ 362.1909, found 362.1908.
**Pyridine 63m**: General procedure D was applied using nitrone 29m (0.072 g, 0.218 mmol). This procedure afforded 30m as a yellow oil (0.013 g, 18%) after purification using medium pressure chromatography (5:95, EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.35 (s, 1H), 8.00 (d, $J$ = 7.6 Hz, 3H), 7.60 (s, 1H), 7.52-7.38 (m, 12H), 1.93-1.89 (m, 1H), 0.93 (q, $J$ = 6.9 Hz, 2H), 0.81 (q, $J$ = 5.2 Hz, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 154.6, 150.5, 146.9, 139.4, 139.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 127.9, 126.7, 120.7, 59.4, 11.6, 9.1; IR (thin film) 3048, 2928, 2854, 1662, 1600, 1493, 1477, 1448, 1214, 756 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{23}$H$_{24}$N (M+H)$^+$ 314.1909, found 314.1909.

**Pyridine 63n**: General procedure D was applied using nitrone 29n (0.059 g, 0.20 mmol). This procedure afforded 30n as a yellow oil (0.038 g, 71%) after purification using medium pressure chromatography (15:85, EtOAc:hexanes). $^1$H NMR (500 MHz, CDCl$_3$): δ 8.59 (s, 1H), 8.01 (d, $J$ = 8.0 Hz, 2H), 7.57 (s, 1H), 7.47-7.39 (m, 6H), 7.36-7.35 (m, 2H), 2.61 (t, $J$ = 7.5 Hz, 2H), 1.48-1.45 (m, 2H), 1.27-1.24 (m, 2H), 0.82 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 154.8, 150.7, 150.0, 139.5, 139.2, 134.1, 129.0, 128.7, 128.5, 128.4, 127.9, 126.7, 121.3, 33.2, 29.7, 22.3, 13.7; IR (thin film) 3057, 2958, 2860, 2361, 1592, 1576, 1474, 1446, 1375, 1265, 1216 cm$^{-1}$; HRMS (ESI) m/z
calcd. for C_{21}H_{22}N (M+H)^{+} 288.1752, found 288.1750.

**Pyridine 63o:** General procedure C was applied using nitrone 29o (0.0421 g, 0.152 mmol). This procedure afforded 30o as a yellow oil (0.0198 g, 50%) after purification using medium pressure chromatography (5:95, EtOAc:hexanes). \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 7.58-7.55 (m, 3H), 7.48-7.45 (m, 1H), 7.43-7.41 (m, 1H), 7.37-7.32 (m, 3H), 7.28-7.26 (m, 1H), 7.20-7.17 (m, 2H), 2.63 (s, 3H), 2.20 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 157.7, 151.9, 149.9, 140.1, 137.0, 131.5, 128.7, 128.6, 128.3, 128.0, 127.7, 126.9, 120.4, 23.6, 16.2; IR (thin film) 3055, 3022, 2922, 1580, 1545, 1495, 1448, 1388, 966, 779 cm\(^{-1}\); HRMS (ESI) \(m/z\) calcd. for C\(_{19}\)H\(_{18}\)N (M+H)^{+} 260.1439, found 260.1437.

**Pyridine 63sa:63sb:** General procedure C was applied using nitrone 29sa:29sb (0.0895 g, 0.249 mmol). This procedure afforded 30sa:30sb as a yellow oil (0.0272 g, 32%) after purification using medium pressure chromatography (40:60, EtOAc:hexanes). \(^1\)H NMR of pyridine 30sa (500 MHz, CDCl\textsubscript{3}): \(\delta\) 7.56 (d, \(J = 5\) Hz, 1H), 7.52-7.39 (m, 3H), 7.38-7.32 (m, 2H), 7.28-7.27 (m, 1H), 7.21-7.15 (m, 2H), 7.09-7.05 (m, 1H), 6.98 (d, \(J = 5\) Hz, 1H), 6.89 (d, \(J = 5\) Hz, 1H), 3.87 (s, 3H), 3.05-3.02 (m, 2H), 2.67-2.61 (m, 2H), 1.94-1.91 (m, 2H); \(^1\)H NMR of pyridine 30sb (500 MHz, CDCl\textsubscript{3}): \(\delta\)
3.82 (s, 3H); $^{13}$C NMR of pyridine $30sa$ (125 MHz, CDCl$_3$) δ 159.6, 157.5, 150.0, 139.7, 131.6, 129.8, 128.7, 128.5, 128.3, 128.2, 128.0, 127.0, 126.5, 120.0, 114.1, 55.4, 33.3, 27.6, 27.4, 23.1; $^{13}$C NMR of pyridine $30sb$ (125 MHz, CDCl$_3$) δ 159.3, 157.4, 149.7, 137.0, 131.3, 129.8, 128.7, 128.5, 128.3, 128.2, 127.7, 127.0, 126.5, 119.5, 113.8, 55.4, 33.3, 27.4, 23.0; IR (thin film) 3061, 2930, 2857, 1607, 1510, 1450, 1246, 1174, 1033, 830 cm$^{-1}$; HRMS (ESI) m/z calcd. for C$_{24}$H$_{24}$NO (M+H)$^+$ 342.1858, found 342.1863.
Cited Literature


61. Winternheimer, D. J.; Shade, R. E.; Merlic, C. A. Synthesis 2010, 2497.


APPENDIX A1: $^1$H and $^{13}$C-NMR spectra of 1a (500/125 MHz, CDCl$_3$)
APPENDIX A2: $^1$H and $^{13}$C-NMR spectra of 1b (500/125 MHz, CDCl$_3$)
APPENDIX A3: $^1$H and $^{13}$C-NMR spectra of 1c (500/125 MHz, CDCl$_3$)
APPENDIX A4: $^1$H and $^{13}$C-NMR spectra of 1d (500/125 MHz, CDCl$_3$)
APPENDIX A5: $^1$H and $^{13}$C-NMR spectra of 1e (500/125 MHz, CDCl$_3$)
APPENDIX A6: $^1$H and $^{13}$C-NMR spectra of 1f (500/125 MHz, CDCl$_3$)
APPENDIX A7: $^1$H and $^{13}$C-NMR spectra of 1g (500/125 MHz, CDCl$_3$)
APPENDIX A8: $^1$H and $^{13}$C-NMR spectra of 1h (500/125 MHz, CDCl$_3$)
APPENDIX A9: $^1$H and $^{13}$C-NMR spectra of **1i** (500/125 MHz, CDCl$_3$)
APPENDIX A10: $^1\text{H}$ and $^{13}\text{C}$-NMR spectra of 1j (500/125 MHz, CDCl$_3$)
APPENDIX A11: $^1$H and $^{13}$C-NMR spectra of 1k (500/125 MHz, CDCl$_3$)
APPENDIX A12: $^1$H and $^{13}$C-NMR spectra of 1I (500/125 MHz, CDCl$_3$)
APPENDIX A13: $^1$H and $^{13}$C-NMR spectra of 1m (500/125 MHz, CDCl$_3$)
APPENDIX A14: $^1$H and $^{13}$C-NMR spectra of 1n (500/125 MHz, CDCl$_3$)
APPENDIX A15: $^1$H and $^{13}$C-NMR spectra of 1o (500/125 MHz, CDCl\textsubscript{3})
APPENDIX A16: $^1$H and $^{13}$C-NMR spectra of 1p (500/125 MHz, CDCl$_3$)

$^1$H-NMR spectrum of 1p (500 MHz, CDCl$_3$)

$^{13}$C-NMR spectrum of 1p (125 MHz, CDCl$_3$)

---

SI DSM-2-107 tBu-CN Allyl

---

CI3 DSM-2-107 tBu-CN Allyl
APPENDIX A17: $^1$H and $^{13}$C-NMR spectra of 1q (500/125 MHz, CDCl$_3$)
APPENDIX A18: $^1$H and $^{13}$C-NMR spectra of 2k (500/125 MHz, CDCl$_3$)
APPENDIX A19: $^1$H and $^{13}$C-NMR spectra of 2I (500/125 MHz, CDCl$_3$)
APPENDIX A20: $^1$H and $^{13}$C-NMR spectra of 2m (500/125 MHz, CDCl$_3$)
APPENDIX A21: $^1$H and $^{13}$C-NMR spectra of 2q (500/125 MHz, CDCl$_3$)
APPENDIX A22: $^1$H and $^{13}$C-NMR spectra of 3a (500/125 MHz, CDCl$_3$)
APPENDIX A23: $^1$H and $^{13}$C-NMR spectra of 3b (500/125 MHz, CDCl$_3$)
APPENDIX A24: $^1$H and $^{13}$C-NMR spectra of 3c (500/125 MHz, CDCl$_3$).
APPENDIX A25: $^1$H and $^{13}$C-NMR spectra of 3d (500/125 MHz, CDCl$_3$)
APPENDIX A26: $^1$H and $^{13}$C-NMR spectra of 3e (500/125 MHz, CDCl$_3$)
APPENDIX A27: $^1$H and $^{13}$C-NMR spectra of 3f (500/125 MHz, CDCl$_3$)
APPENDIX A28: \(^1\)H and \(^{13}\)C-NMR spectra of 3g (500/125 MHz, CDCl\(_3\))
APPENDIX A29: $^1$H and $^{13}$C-NMR spectra of 3h (500/125 MHz, CDCl$_3$)
APPENDIX A30: $^1$H and $^{13}$C-NMR spectra of 3i (500/125 MHz, CDCl$_3$)
APPENDIX A31: $^1$H and $^{13}$C-NMR spectra of 3j (500/125 MHz, CDCl$_3$)
APPENDIX A32: $^1$H and $^{13}$C-NMR spectra of $3k$ (500/125 MHz, CDCl$_3$)
APPENDIX A33: $^1$H and $^{13}$C-NMR spectra of 3l:3la (500/125 MHz, CDCl$_3$)
APPENDIX A34: $^1$H and $^{13}$C-NMR spectra of 3m (500/125 MHz, CDCl$_3$)
APPENDIX A35: $^1$H and $^{13}$C-NMR spectra of 3n (500/125 MHz, CDCl$_3$)
APPENDIX A36: $^1$H and $^{13}$C-NMR spectra of 3n (500/125 MHz, CDCl$_3$)
APPENDIX A37: $^1$H and $^{13}$C-NMR spectra of 3p:3pa (500/125 MHz, CDCl$_3$)
APPENDIX A38: $^1$H and $^{13}$C-NMR spectra of 3p:3pa (500/125 MHz, CDCl$_3$)
APPENDIX A39: $^1$H and $^{13}$C-NMR spectra of 4m (500/125 MHz, CDCl₃)
APPENDIX A40: $^1$H and $^{13}$C-NMR spectra of 4n (500/125 MHz, CDCl$_3$)
APPENDIX A41: $^1$H and $^{13}$C-NMR spectra of 4o (500/125 MHz, CDCl$_3$)
APPENDIX A42: $^1$H and $^{13}$C-NMR spectra of 6q (500/125 MHz, CDCl$_3$)
APPENDIX A43: $^1$H and $^{13}$C-NMR spectra of 14a (500/125 MHz, CDCl$_3$)
APPENDIX A44: $^1$H and $^{13}$C-NMR spectra of 14b (500/125 MHz, CDCl$_3$)
APPENDIX A45: $^1$H and $^{13}$C-NMR spectra of 14c (500/125 MHz, CDCl$_3$)
APPENDIX A46: $^1$H and $^{13}$C-NMR spectra of 14d (500/125 MHz, CDCl$_3$)
APPENDIX A47: $^1$H and $^{13}$C-NMR spectra of 14e (500/125 MHz, CDCl$_3$)
APPENDIX A48: $^1$H and $^{13}$C-NMR spectra of 14f (500/125 MHz, CDCl$_3$)
APPENDIX A49: $^1$H and $^{13}$C-NMR spectra of 14g (500/125 MHz, CDCl$_3$)
APPENDIX A50: $^1$H and $^{13}$C-NMR spectra of 14h (500/125 MHz, CDCl$_3$)
APPENDIX A51: $^1$H and $^{13}$C-NMR spectra of 14i (500/125 MHz, CDCl$_3$)
APPENDIX A52: $^1$H and $^{13}$C-NMR spectra of 14j (500/125 MHz, CDCl$_3$)
APPENDIX A53: $^1$H and $^{13}$C-NMR spectra of 14k (500/125 MHz, CDCl$_3$)
APPENDIX A54: $^1$H and $^{13}$C-NMR spectra of 14I (500/125 MHz, CDCl$_3$)
APPENDIX A55: $^1$H and $^{13}$C-NMR spectra of 14m (500/125 MHz, CDCl$_3$)
APPENDIX A56: $^1$H and $^{13}$C-NMR spectra of 14n (500/125 MHz, CDCl$_3$)
APPENDIX A57: $^1$H and $^{13}$C-NMR spectra of 26f (500/125 MHz, CDCl$_3$)
APPENDIX A58: $^1$H and $^{13}$C-NMR spectra of 15a (500/125 MHz, CDCl$_3$)
APPENDIX A59: $^1$H and $^{13}$C-NMR spectra of 15b (500/125 MHz, CDCl$_3$)
APPENDIX A60: $^1$H and $^{13}$C-NMR spectra of 15c (500/125 MHz, CDCl$_3$)
APPENDIX A61: $^1$H and $^{13}$C-NMR spectra of 15d (500/125 MHz, CDCl$_3$)
APPENDIX A62: $^1$H and $^{13}$C-NMR spectra of 15e (500/125 MHz, CDCl$_3$)
APPENDIX A63: $^1$H and $^{13}$C-NMR spectra of 15f (500/125 MHz, CDCl$_3$)
APPENDIX A64: $^1$H and $^{13}$C-NMR spectra of 15g (500/125 MHz, CDCl₃)
APPENDIX A65: $^1$H and $^{13}$C-NMR spectra of 15h (500/125 MHz, CDCl$_3$)
APPENDIX A66: $^1$H and $^{13}$C-NMR spectra of 15i (500/125 MHz, CDCl$_3$)
APPENDIX A67: $^1$H and $^{13}$C-NMR spectra of 15k (500/125 MHz, CDCl$_3$)
APPENDIX A68: $^1$H and $^{13}$C-NMR spectra of 15I (500/125 MHz, CDCl$_3$)
APPENDIX A69: $^1$H and $^{13}$C-NMR spectra of 15m (500/125 MHz, CDCl$_3$)
APPENDIX A70: $^1$H and $^{13}$C-NMR spectra of 15n (500/125 MHz, CDCl$_3$)
APPENDIX A71: $^1$H and $^{13}$C-NMR spectra of 27f (500/125 MHz, CDCl$_3$)
APPENDIX A72: $^1$H and $^{13}$C-NMR spectra of 16a (500/125 MHz, CDCl$_3$)
APPENDIX A73: $^1$H and $^{13}$C-NMR spectra of 16b (500/125 MHz, CDCl$_3$)
APPENDIX A74: $^1$H and $^{13}$C-NMR spectra of 16c (500/125 MHz, CDCl$_3$)
APPENDIX A75: $^1$H and $^{13}$C-NMR spectra of 16d (500/125 MHz, CDCl$_3$)
APPENDIX A76: $^1$H and $^{13}$C-NMR spectra of 16e (500/125 MHz, CDCl$_3$)
APPENDIX A77: $^1$H and $^{13}$C-NMR spectra of 16f (500/125 MHz, CDCl$_3$)
APPENDIX A78: $^1$H and $^{13}$C-NMR spectra of 16g (500/125 MHz, CDCl$_3$)
APPENDIX A79: $^1$H and $^{13}$C-NMR spectra of 16h (500/125 MHz, CDCl$_3$)
APPENDIX A80: $^1$H and $^{13}$C-NMR spectra of 16k (500/125 MHz, CDCl$_3$)
APPENDIX A81: $^1$H and $^{13}$C-NMR spectra of 16l (500/125 MHz, CDCl$_3$)
APPENDIX A82: $^1$H and $^{13}$C-NMR spectra of 16m (500/125 MHz, CDCl$_3$)
APPENDIX A83: $^1$H and $^{13}$C-NMR spectra of 16n (500/125 MHz, CDCl₃)
APPENDIX A84: $^1$H and $^{13}$C-NMR spectra of 19b (500/125 MHz, CDCl$_3$)
APPENDIX A85: $^1$H and $^{13}$C-NMR spectra of 21b (500/125 MHz, CDCl$_3$)
APPENDIX A86: $^1$H and $^{13}$C-NMR spectra of 24 (500/125 MHz, CDCl$_3$)
APPENDIX A87: $^1$H and $^{13}$C-NMR spectra of 21b (500/125 MHz, CDCl$_3$)
APPENDIX A88: $^1$H and $^{13}$C-NMR spectra of 25 (500/125 MHz, CDCl$_3$)
APPENDIX A89: $^1$H and $^{13}$C-NMR spectra of 20b (500/125 MHz, CDCl$_3$)
APPENDIX A90: $^1$H and $^{13}$C-NMR spectra of 29a (500/125 MHz, CDCl$_3$)
APPENDIX A91: $^1$H and $^{13}$C-NMR spectra of 29b (500/125 MHz, CDCl$_3$)
APPENDIX A92: $^1$H and $^{13}$C-NMR spectra of 29c (500/125 MHz, CDCl$_3$)
APPENDIX A93: $^1$H and $^{13}$C-NMR spectra of 29d (500/125 MHz, CDCl$_3$)
APPENDIX A94: $^1$H and $^{13}$C-NMR spectra of 29e (500/125 MHz, CDCl$_3$)
APPENDIX A95: $^1$H and $^{13}$C-NMR spectra of 29f (500/125 MHz, CDCl$_3$)
APPENDIX A96: $^1$H and $^{13}$C-NMR spectra of 29g (500/125 MHz, CDCl$_3$)
APPENDIX A97: $^1$H and $^{13}$C-NMR spectra of 29h (500/125 MHz, CDCl$_3$)
APPENDIX A98: $^1$H and $^{13}$C-NMR spectra of 29i (500/125 MHz, CDCl$_3$)
APPENDIX A99: $^1$H and $^{13}$C-NMR spectra of 29j (500/125 MHz, CDCl$_3$)
APPENDIX A100: $^1$H and $^{13}$C-NMR spectra of 29k (500/125 MHz, CDCl$_3$)
APPENDIX A102: $^1$H and $^{13}$C-NMR spectra of 29m (500/125 MHz, CDCl$_3$)
APPENDIX A103: $^1$H and $^{13}$C-NMR spectra of 29o (500/125 MHz, CDCl$_3$)
APPENDIX A104: $^1$H and $^{13}$C-NMR spectra of 29p (500/125 MHz, CDCl$_3$)
APPENDIX A105: $^1$H and $^{13}$C-NMR spectra of 29q (500/125 MHz, CDCl$_3$)
APPENDIX A106: $^1$H and $^{13}$C-NMR spectra of 29r (500/125 MHz, CDCl$_3$)
APPENDIX A107: $^1$H and $^{13}$C-NMR spectra of 29sa:29sb (500/125 MHz, CDCl$_3$)
APPENDIX A108: $^1$H and $^{13}$C-NMR spectra of 30a (500/125 MHz, CDCl$_3$)
APPENDIX A109: $^1$H and $^{13}$C-NMR spectra of 30b (500/125 MHz, CDCl$_3$)
APPENDIX A110: $^1$H and $^{13}$C-NMR spectra of 30d (500/125 MHz, CDCl$_3$)
APPENDIX A111: $^1$H and $^{13}$C-NMR spectra of 30f (500/125 MHz, CDCl$_3$)
APPENDIX A112: $^1$H and $^{13}$C-NMR spectra of 30i (500/125 MHz, CDCl$_3$)
APPENDIX A113: $^1$H NMR spectra of 30j (500/125 MHz, CDCl₃)
APPENDIX A114: $^1$H and $^{13}$C-NMR spectra of 30k (500/125 MHz, CDCl$_3$)
APPENDIX A115: $^1$H and $^{13}$C-NMR spectra of 30m (500/125 MHz, CDCl$_3$)
APPENDIX A116: $^1$H and $^{13}$C-NMR spectra of 30o (500/125 MHz, CDCl$_3$)
APPENDIX A117: $^1$H and $^{13}$C-NMR spectra of 30sa:30sb (500/125 MHz, CDCl$_3$)
VITA

Daniel S. Mueller
University of Illinois at Chicago 541 W. Oakdale Ave Apt. 410
845 W. Taylor St, 4500 SES Chicago, IL 60657
Chicago, IL 60607 314.753.5345
dmuell6@uic.edu danielsmueller@icloud.com

Education

University of Illinois at Chicago, Chicago, IL 2014
Ph.D., Organic Chemistry

Southern Illinois University Edwardsville,
Edwardsville, IL 2009
ACS-Certified Bachelor of Science, Chemistry

Work Experience

Analytical Internship
Improved gas chromatography methods for qualitative and quantitative analysis.
Tested and validated a new analytical method for analysis of Stepan products.

Research Experience

Graduate Student Researcher
University of Illinois at Chicago, Chicago, IL 5/2009-8/2014
Developed a new organic method for the synthesis of α-amino aldehydes.
Experienced with multi-step synthesis of organic compounds.
Routinely used air- and moisture-sensitive synthetic technique.
Possess extensive knowledge with analytical instrumentation techniques.
Implemented a new system for safety procedures and documentation.

Undergraduate Student Researcher
Devised new methods for the synthesis of sialic acid glycoconjugates.
Trained and advised the junior undergraduate students.

Teaching Experience

NMR Technician and Teaching Assistant 1/2011-8/2014
University of Illinois at Chicago
Assisted undergraduate students with NMR spectrometers for instrumental and physical chemistry lab experiments.
Implemented new undergraduate lab experiments utilizing NMR instruments.
Trained graduate students on NMR spectrometers.
Performed regular instrument maintenance.
Graduate Student Teaching Assistant
University of Illinois at Chicago
9/2009-5/2010
Led undergraduate organic discussion sections and proctored weekly quizzes.
Supervised a weekly organic chemistry lab sections for about 20 students.

Undergraduate Student Teaching Assistant
Southern Illinois University Edwardsville
8/2008-12/2008
Supervised a weekly general chemistry lab class for a group of 20 students.

Publications


Book Chapters


Presentations

“Oximes in the Synthesis of N-Heterocycles and α-Amino Aldehydes” Southern Illinois University Edwardsville, June 2014

Presentations (continued)


Affiliations

Member, American Chemical Society 2013-present
Representative, University of Illinois at Chicago Graduate Student Council 2013-2014

Awards

UIC College of Liberal Arts and Sciences Ph.D. Travel Award Spring 2014
UIC Graduate Student Council Travel Award Spring 2014