INTRAMOLECULAR HYDROAMINATION OF ALKYNES CATALYZED BY SILVER–PHENANTHROLINE COMPLEXES

A Dissertation

Submitted to the Graduate School
of the University of Notre Dame
in Partial Fulfillment of the Requirements
for the Degree of

Doctor of Philosophy

by

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April 2009
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Abstract
by
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The intramolecular hydroamination reaction is among the more versatile means of forming nitrogen-containing heterocycles, compounds of interest in a variety of chemical disciplines. While the reaction has been intensely studied, concerns still exist over its amenability to organic synthesis. This thesis details the implementation of a readily-recyclable silver-1,10-phenanthroline catalyst which has demonstrated high efficiency for the hydroamination of a variety of aminoalkynes. As a means for developing a protocol for enantioselective synthesis, the desymmetrization of a prochiral diyne was accomplished using the silver-1,10-phenanthroline catalyst. This desymmetrization creates chiral compounds, an occurrence not often observed in the alkyne hydroamination.

A separate project involved in the development of improved immunotherapies led us to develop and complete a synthesis of β–hydroxy-methionine. The third attempt via vinyl glycine eventually allowed for the completion of this molecule. It is planned for this amino acid derivative to be included in an antigenic peptide.
To my wife Tiffany
FIGURES

Figure 1.1 Early Chiral 1,10-Phenanthroline Ligands ........................................................ 4
Figure 1.2 Gladiali’s Doebner-Miller-type Phenanthroline Construction ......................... 5
Figure 1.3 Gladiali’s Demonstration of the Utility of Proximal Chirality ......................... 5
Figure 1.4 Early, Chiral $C_2$-Symmetric 2,2’-Bipyridine Ligands ..................................... 6
Figure 1.5 Bolm’s Synthesis of Chiral Bipyridine 8.......................................................... 7
Figure 1.6 Asymmetric Addition of Diethylzinc to Benzaldehyde ...................................... 8
Figure 1.7 Chiral 2,2’-Bipyridines in Copper-Catalyzed Cyclopropanation ....................... 8
Figure 1.8 Asymmetric Cyclopropanation and Allylic Oxidation .................................... 10
Figure 1.9 Desymmetrization of a meso-Epoxide............................................................. 11
Figure 1.10 General Reaction Sequence for the Hydroamination of Alkynes ................. 15
Figure 1.11 Mechanism of the Early Transition Metal-Catalyzed Hydroamination .......... 16
Figure 1.12 Mechanism of the Rare Earth Metal-Catalyzed Hydroamination ............... 16
Figure 1.13 Hydroamination with an Imidozirconocene Complex .................................. 17
Figure 1.14 Catalytic Hydroamination with a Bis-amidozirconocene Complex ............. 18
Figure 1.15 Catalytic Intramolecular Hydroamination with Ti and Zr.......................... 18
Figure 1.16 Application of Titanium-Catalyzed Hydroamination to Monomorine Synthesis ........................................................................................................ 19
Figure 1.17 Rate-Enhancement of TMS-Substituted Aminoalkynes ......................... 20
Figure 1.18 Samarium-Catalyzed Tandem C-N/C-C Bond Forming Reaction .............. 21
Figure 1.19 Yttrium-Catalyzed Intramolecular Hydroamination of an Aminoalkyne ..... 21
Figure 1.20 Mechanism of the Late Transition Metal-Catalyzed Hydroamination ....23
Figure 1.21 Mercury-Catalyzed Intermolecular Hydroamination of 1-Heptyne .......... 24
Figure 1.22 Mercury-Catalyzed Intermolecular Hydroamination of 1-Octyne .......... 25
Figure 1.23 Silver-Catalyzed Intramolecular Hydroamidation of β-Lactam .......... 27
Figure 1.24 Base and Silver-Catalyzed Cyclization of β-Alkynylpropanamides ... 27
Figure 1.25 Synthesis of Proline-Derived Nitrogen Heterocycles ......................... 28
Figure 1.26 End Game in the Total Synthesis of Pseudodistomin D ....................... 29
Figure 1.27 Potential Tandem Alkyne Hydroamination/Conjugate Addition ............. 29
Figure 1.28 Desymmetrization of a Prochiral Diyne ............................................. 30
Figure 1.29 Palladium/Triphenylphosphine-Catalyzed Alkyne Hydroamination .... 31
Figure 1.30 End Game in the Total Synthesis of Indolizidine (−)-209D ................. 32
Figure 1.31 Iridium-Catalyzed Enantioselective Hydroamination of Norbornene .... 34
Figure 1.32 Palladium-Catalyzed Enantioselective Hydroamination of Styrenes .... 35
Figure 1.33 Evans’ Enantioselective Aldol for the Synthesis of Threonine ............ 38
Figure 1.34 Corey’s Asymmetric Aldol Reaction under Phase Transfer Catalysis ... 39
Figure 1.35 Asymmetric Aminohydroxylation in Unnatural Amino Acid Synthesis .... 40
Figure 1.36 Unnatural Amino Acids from Vinylglycine Derivatives ...................... 40
Figure 1.37 Roemmele and Rapoport Synthesis of β-Hydroxy Methionine ......................... 42

Figure 2.1 Helquist Use of Chiral Phenanthroline in Pd-Catalyzed Allylic Alkylation... 45

Figure 2.2 Samarium-Promoted Coupling of Ketones and 1,10-Phenanthroline .......... 46

Figure 2.3 SmI₂-Promoted Couplings of Aldehydes and Epoxides.............................. 47

Figure 2.4 Comparison of Novel Chiral Bipyridine with Known Ligands..................... 48

Figure 2.5 Initial Formation of Silver-Phenanthroline Complex.................................... 53

Figure 2.6 Formation of Ag–Phenanthroline and Ag–Neocuproine Complexes........... 55

Figure 2.7 Formation of Phenanthroline Complexes of Palladium and Gold.............. 56

Figure 3.1 General Scheme for the Intramolecular Hydroamination of Alkynes .......... 59

Figure 3.2 Initial Helquist Silver–Phenanthroline-Catalyzed Hydroamination ............ 61

Figure 3.3 Synthesis of Phenyl-Substituted Aminoalkynes........................................... 62

Figure 3.4 Synthesis of Terminal Aminoalkynes .......................................................... 63

Figure 3.5 The Use of Trifluoroacetamide as an Alternative Protecting Group.......... 64

Figure 3.6 Synthesis of Methyl-Substituted Aminoalkynes........................................... 65

Figure 3.7 Initial Qualitative Screening of Metals for the Hydroamination............... 66

Figure 3.8 Isolation of the Volatile 2-Methyl-Pyrroline.............................................. 72

Figure 3.9 Synthesis of Proline-Derived Nitrogen Heterocycles................................. 74

Figure 3.10 Hydroamination and Facile Benzylic Oxidation....................................... 74

Figure 3.11 Synthesis of Alkynylsulfonamides......................................................... 76

Figure 3.12 Attempts at the Hydroamination of Sulfonamide Derivatives............... 77
Figure 3.13 Synthesis of Substrate for C–N/C–C Tandem Reaction................................. 78
Figure 3.14 Attempted Ag-Catalyzed Tandem Hydroamination/Conjugate Addition..... 78
Figure 3.15 Beginning of the Synthesis of Prochiral 1,6-Diyne\textsuperscript{24} ...................... 79
Figure 3.16 Synthesis of Prochiral Alcoholic Diynes......................................................... 80
Figure 3.17 End Game for the Synthesis of Prochiral Aminodiynes............................. 81
Figure 3.18 Desymmetrization of Terminal Aminodiyne................................................. 83
Figure 3.19 Further Elaboration of Aminodiyne ............................................................. 84
Figure 3.20 Partial Synthesis of a (3-Aminopropyl)-1,4-Diyne ........................................... 85
Figure 3.21 Partial Synthesis of a (2-Aminoethyl)-1,4-Diyne............................................ 86
Figure 3.22 Partial Synthesis of a 5-Amino-1,8-diyne ....................................................... 88
Figure 3.23 Computationally Predicted Enantiomeric Excesses Employing Ag\textsuperscript{103} \textsuperscript{24} ..... 90
Figure 4.1 Crystal Structure of HLA-A2 ........................................................................ 93
Figure 4.2 Crystal Structure of Antigenic Peptide within Heavy Chain Binding Surface 94
Figure 4.3 Crystallographic Superimposition of the Native and Modified Peptides ...... 95
Figure 4.4 Retrosynthetic Analysis of 3-Hydroxy Methionine via an Aldol Route ............ 96
Figure 4.5 Synthesis of Cinchona-Derived Phase Transfer Catalyst............................... 97
Figure 4.6 Formation of Silyl Ketene Acetal for Enantioselective Aldol Reaction .......... 98
Figure 4.7 Retrosynthetic Analysis for the Asymmetric Dihydroxylation Route ............ 99
Figure 4.8 Preparation of Z-Olefins for Unnatural Amino Acid Targets .................... 100
Figure 4.9 Retrosynthetic Analysis for the Asymmetric Aminohydroxylation Route ... 101
Figure 4.10 Preparation of E-Olefins for Unnatural Amino Acid Targets ..................... 102

Figure 4.11 Alternative Synthesis of an Unsaturated Ester for the Route to Methionine ............................................................................................................................. 103

Figure 4.12 Shortened Synthesis to the Methyl Ester for the Route to Methionine ...... 104

Figure 4.13 Aminohydroxylation to Form Benzyl Carbamate-Protected Amino Acids 105

Figure 4.14 Employment of Chloramine-T in the Aminohydroxylation Reaction........ 106

Figure 4.15 Retrosynthetic Analysis via Protected Vinyl Glycine ................................. 107

Figure 4.16 Final Synthesis of 3-Hydroxy-Methionine .................................................. 108

Figure 5.1 Core Structure of a Pyrrolizidine Alkaloid....................................................... 112

Figure 5.2 Silver-Catalyzed Hydroamination Toward the Pyrrolizidine Alkaloid Core 113

Figure 5.3 Potential Silver-Catalyzed Tandem Reaction with Chirality Transfer......... 113

Figure 5.4 Use of the Trifluoroacetamide as a Novel Protecting Group in the Alkene Hydroamination .................................................................................................................. 114

Figure 5.5 Comparison of Three Bidentate Nitrogen Ligand Classes ............................ 115
TABLES

Table 2.1 Samarium-Promoted Epoxide Coupling with 2,2’-Bipyridine...........48
Table 2.2 Development of Samarium-Catalyzed Epoxide Coupling.............51
Table 3.1 Screening of Metal Phenanthroline Complexes.......................66
Table 3.2 Silver-Catalyzed Hydroamination of Aminoalkynes.....................69
Table 3.3 Desymmetrization of Prochiral Diyne 138b............................80
ACKNOWLEDGEMENTS

There are many people that I owe a great deal of gratitude to for their help over my graduate career. First and foremost, I would like to thank God for blessing me with all He has throughout my life. Among these, the most prominent being my wife, without whom I would not have been able to accomplish what I have. Her support has helped me to get through the trials that are associated with research. I also want to thank my family, Dad, Mom, and Jonathan for their support; and I apologize for not being able to spend more time with you over the past five years.

I also would like to thank my advisor Paul Helquist, who spent painstaking hours mentoring me and reading this document. His guidance and the joy he continues to get from teaching have directly influenced my career choice, and it is my goal to continue to care for my students as long as he has. His mentorship in this research was a great balance of keeping me on task while also allowing me to explore those results I found interesting. I’d also like to give my thanks to my committee for their helpful discussions and guidance throughout my years of study.

Finally, I owe a great many thanks to my fellow Helquistadors past and present. Past group members to whom I owe thanks include Dr. Jeremy Weitgenant, Dr. Dirk Schweitzer, Dr. Douglas Schauer, Jeremy A. Bates, Jamie Zigterman, Dr. Jacob Plummer, and Christine Lewis. I owe a great deal of gratitude to the current members of the group, who spent countless hours proofreading this document including John
Markiewicz, Casey Cosner, Aaron Forbes, and Pauline Bourbon. I’d also like to thank the undergraduates who I was privileged to work with, including Stephen Canham, Ed Ruane, Marinus “Goose” Bigi, Chris Mariani, and Anthony Cipolla.

I owe special thanks to Dr. Bill Boggess and Dr. Michelle Joyce for their assistance in the mass spectroscopy analysis of Ag(phen)$_2$OTf (112) and (2S,3S)-N-(fluorenylmethyloxycarbonyl)-2-amino-3-hydroxy-4-(methylthio)-butanoic acid (193).
ABBREVIATIONS

° ........................................................................................................... degree
°C ......................................................................................................... degrees Celsius
Å ....................................................................................................... angstrom
Ac ................................................................................................. acetyl
aq ................................................................................................. aqueous
AQN .............................................................................................. anthraquinone
Ar ................................................................................................. aromatic
atm ................................................................................................. atmosphere
bipy ............................................................................................... 2,2′-bipyridine
br ................................................................................................. broad
Bn ................................................................................................. benzyl
Bu ................................................................................................. butyl
calcd .............................................................................................. calculated
Cbz .............................................................................................. benzyloxy carbonyl
cod ............................................................................................... 1,5-cyclooctadiene
concd ............................................................................................ concentrated
d .................................................................................................... doublet
DBU ............................................................................................. 1,8-diazabicycloundec-7-ene
DHQ .............................................................................................. dihydroquinine
DHQD......................................................................................dihydroquinidine
DMAP.......................................................................................dimethylaminopyridine
DMF.............................................................................................N,N-dimethylformamide
dmp..........................................................................................2,9-dimethyl-1,10-phenanthroline
DMSO............................................................................................dimethylsulfoxide
dr.................................................................................................diastereomeric excess
ee.................................................................................................enantiomeric excess
equiv..............................................................................................equivalents
Et.........................................................................................................ethyl
EtOAc..............................................................................................ethyl acetate
FT IR.............................................................................................Fourier transform IR
g.........................................................................................................gram
h.........................................................................................................hour
HMDS............................................................................................hexamethyldisilazane
Hz...................................................................................................hertz
IR.......................................................................................................infrared
J........................................................................................................NMR coupling constant
kcal.............................................................................................kilocalorie
LDA..........................................................................................lithium diisopropylamide
lit..................................................................................................literature
M.................................................................................................molar
m.................................................................................................multiplet
M^+ ...............................................................................................molecular ion
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
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<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
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<td>milliliter</td>
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<td>millimole</td>
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<tr>
<td>MM</td>
<td>molecular mechanics</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonate</td>
</tr>
<tr>
<td>N</td>
<td>normal (concentration)</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>OTf</td>
<td>trifluoromethanesulfonate</td>
</tr>
<tr>
<td>p-TSA</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>phen</td>
<td>1,10-phenanthroline</td>
</tr>
<tr>
<td>Phthal</td>
<td>phthalimide</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>QM</td>
<td>quantum mechanics</td>
</tr>
<tr>
<td>t</td>
<td>tertiary</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
</tbody>
</table>
TFA……………………………………………………………………………trifluoroacetic acid
Ts……………………………………………………………………………p-toluenesulfonyl
CHAPTER 1

INTRODUCTION

1.1 Enantioselective Synthesis

When in the course of human events it becomes necessary to synthesize an organic molecule, a consideration of stereochemistry is often required. Whether this compound is to be used as a potential treatment against disease, prove chemical identity or to probe for a better understanding of chemical reactivity, the ability to access this molecule with specific stereochemistry is vital. The chirality of a molecule acts as both a blessing and an obstacle in organic synthesis. While one specific enantiomer can often demonstrate greater biological activity, difficulty arises from the identical properties of these enantiomers, which includes their identical heats of formation. When no chiral information is present in a reaction that forms a chiral center, each enantiomer is made in an equal amount.

There are three common methods for the installation of chirality into an organic molecule: use of the chiral pool, use of a chiral auxiliary, and enantioselective catalysis. All of these methods rely on the same principle; a differentiation of transition states in a chemical transformation that lowers the energy in favor of the formation of one stereoisomer over another. The differences in these methods arise from the means by which this energy difference is accessed. While each of these methods offers advantages
worth mentioning, this dissertation will focus on enantioselective catalysis and chiral pool synthesis.

Use of the chiral pool provides easily accessed, enantiopure compounds via reaction of an existing enantiopure starting material typically obtained from natural sources. This method is often limited to employing a chiral amino acid or natural product and is effective when the desired target molecule is structurally similar to an available chiral source. This process is therefore limited to the synthesis of structures that are fundamentally similar to readily available chiral compounds.

Chiral auxiliaries provide another means for the stereoselective synthesis of compounds. A chiral auxiliary is a chemical structure incorporated into a starting material through a chemical reaction in order to bias the formation of one enantiomer over another in a subsequent reaction. The auxiliary is then removed in a separate chemical transformation and can potentially be recycled. While the use of chiral auxiliaries has provided substantial value for the formation of chiral centers, it is limited in that it requires two or more extra reaction steps, to install and remove the auxiliary. Both chiral pool synthesis and the use of chiral auxiliaries utilize a chiral educt in the reaction, such that making any new chiral center results in diastereomers, thus avoiding the formation of enantiomers. These methods therefore require an entire molar equivalent of chiral moiety. It is in these limitations of chiral pool synthesis and the use of chiral auxiliaries that a better understanding of enantioselective catalysis becomes necessary.
1.2 Enantioselective Catalysis

Organic synthesis has been given a strong tool over the course of the past half century in the form of enantioselective or asymmetric catalysis. As the syntheses of more complex molecules become necessary, development and knowledge of chirality becomes increasingly important. Enantioselective catalysis allows for the generation of chiral products from nonchiral starting materials. Another advantage of enantioselective catalysis over other methods of asymmetric synthesis lies in its potential efficiency. Sub-stoichiometric amounts of the acting chiral components, which can often be expensive, are typically utilized.

One of the most common methods for the induction of asymmetry into a reaction is through the use of chiral ligands within a transition-metal catalyzed reaction. By coordinating a metal center with chiral ligands, the stereochemical outcome of a reaction can often be influenced. The use of chiral ligands has become increasingly more common since their introduction in the 1960’s by Nozaki, Knowles, and Horner. While many researchers have provided a variety of potential chiral ligands in the forty years since their introduction, only a select few have demonstrated efficacy in a variety of transformations. This provides an opportunity for the discovery of new chiral ligand classes for the induction of asymmetry in various transition metal-catalyzed reactions.

1.2.1 1,10-Phenanthroline and 2,2’-Bipyridine

Due to the variety of metal ions used in catalysis, the search for a suitable ligand class for application to the breadth of organometallic transformations should begin with a scaffold known to form complexes with a broad range of metals. The related compounds, 1,10-phenanthroline and 2,2’-bipyridine, are known to bind a variety of metal ions to
form stable complexes in a bidentate mode. For these reasons, phenanthroline and bipyridine have been used as ligands in a variety of catalytic reactions. While research into the manipulation of these ligands with various metal catalysts has been frequent, their use in enantioselective catalysis has not been as extensively explored. A rational explanation for this is that phenanthroline and bipyridine contain no innate chirality, and therefore are not easily employed in the synthesis of chiral compounds.

**Figure 1.1 Early Chiral 1,10-Phenanthroline Ligands**

Though achiral, phenanthroline and bipyridine contain the desired properties of a promising ligand class. Structural similarities to bis(oxazoline) ligands, can be seen in their bidentate binding of sp² nitrogen atoms to the metal center. Bis(oxazoline) ligands are members of the “privileged” class of chiral ligands, so named due to a demonstration of high enantioselectivity across a variety of transformations. Therefore synthetic efforts have been undertaken to yield chiral derivatives of phenanthroline ligands in hopes to demonstrate similar selectivity in asymmetric reactions (Figure 1.1). The research group of Serafino Gladiali first reported chiral phenanthroline derivatives in 1986. These ligands were synthesized via a Doebner-Miller-type reaction of 8-aminoquinoline (4) and α,β-unsaturated aldehydes such as 5 (Figure 1.2). In a rhodium-catalyzed transfer hydrogenation reaction of acetophenone (6), these 1,10-phenanthroline derivatives provided the desired product in up to 31% ee and this research served as the groundwork for the production of other chiral phenanthrolines.
Gladiali and coworkers furthered their development of this ligand class by introducing chiral substituents at the 2 position of 1,10-phenanthroline, which served to increase the observed enantioselectivity of the hydrosilylation of acetophenone (6) relative to other phenanthroline derivatives (Figure 1.3). Relocation of a pinenyl group from the 3 position to the 2 position altered the observed enantiomeric excess from 5.9% to 75.6% in the rhodium-catalyzed hydrosilylation reaction. This result demonstrated the importance of proximity of the existing chiral center to the forming center in order to optimize asymmetric induction.
These displays of asymmetric induction using chiral phenanthroline ligands have led to further synthetic approaches by other researchers.\textsuperscript{9,10} In another notable application, Chelucci et al. synthesized chiral phenanthroline ligands for use in a palladium-catalyzed allylic substitution.\textsuperscript{11-13} Construction of a variety of ligands via a Friedländer condensation of 8-aminoquinoline-7-carbaldehyde with naturally occurring ketones and aldehydes, allowed for the testing of catalyst complexes that placed chirality near the metal center. Steroidal derivatives of 1,10-phenanthroline gave products in the palladium-catalyzed allylic substitution that ranged from 4 to 96\% ee.\textsuperscript{11} Similar steroidal-phenanthroline ligands have also been employed by the Chelucci group in transition metal-catalyzed cyclopropanation and hydrosilylation reactions, with the highest observed enantiomeric excesses of 68\% and 33\% respectively.\textsuperscript{14}

Chiral 2,2'-bipyridines have also demonstrated efficacy in asymmetric induction and actually preceded chiral phenanthrolines in the literature.\textsuperscript{15} Bipyridine offers a less rigid ligand scaffold for metal complexes, but maintains a stable bidentate binding mode. This rotational ability present in bipyridine, but absent in phenanthroline, allows for a complementary set of ligand systems whose comparison could provide insight into the necessary flexibility of the chiral complex.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{bipyridines.png}
\caption{Early, Chiral $C_2$-Symmetric 2,2'-Bipyridine Ligands}
\end{figure}
While chiral 2,2'-bipyridines were first reported in 1984, the first $C_2$–symmetric chiral 2,2'-bipyridine (8) was reported by Bolm in 1990 (Figure 1.4). The advantage of employing ligands that contain $C_2$-symmetry in enantioselective reactions comes from the simplification of potential products of the reaction, because $C_2$-symmetric ligands reduce the number of potential transition states. Bolm’s chiral bipyridine was synthesized via a three-step process from 2,6-dibromopyridine (11) (Figure 1.5). Synthesis of ketone (12) began by nucleophilic substitution of methyl pivalate by a lithiated bromopyridine. After a chiral reduction of the 12 to the chiral alcohol, two molecules of 13 were coupled using a nickel-promoted transformation. This chiral ligand and its methyl ether derivative were initially used to promote stereocontrolled addition of diethyl zinc to various aldehydes (Figure 1.6). In the case of the diethyl zinc addition to benzaldehyde, Bolm reported cases with 94% yield and ee’s as high as 97%. This served to demonstrate the ability of chiral bipyridines to guide asymmetric induction and opened the avenue for further exploration by other research groups.

![Figure 1.5 Bolm’s Synthesis of Chiral Bipyridine 8](image)

**Figure 1.5 Bolm’s Synthesis of Chiral Bipyridine 8**

Conditions: (a) $n$-BuLi, $t$-BuCO$_2$CH$_3$, THF, –78 °C to 25 °C, 3.5 h (80%); (b) i. (–)-$B$-chlorodiisopinocampheylborane (1.2 equiv) neat, 25 °C, 2 d, ii. iminodiethanol (3.6 equiv), ether, 3 h (59%); (c) NiCl$_2$·6 H$_2$O (1.2 equiv), Zn (1.3 equiv), PPh$_3$ (4.8 equiv), DMF, 72 °C, 3.5 h (55%).
Figure 1.6 Asymmetric Addition of Diethylzinc to Benzaldehyde
Conditions: (a) Et₂Zn, 8 (5 mol %), −25 °C, 48 h (94% yield, 97% ee).

The Katsuki group employed a chiral 2,2′-bipyridine (9), derived from the
dimerization of tetrahydroquinoline derivatives, in a copper-catalyzed cyclopropanation
of styrene (Figure 1.7). It was found that ligand 9, among others, provided excellent
yields of 18 with enantioselectivity ranging from 24-99% ee. These ligands, a second-
generation of ligands developed by this group, were equal to and, in some cases, better
than the commonly used bis(oxazoline) ligands for this transformation. It was discovered
that replacement of the methyl groups in the first generation of catalysts with
trimethylsilyl groups, served to increase enantioselectivity of the cyclopropanation
significantly.

Figure 1.7 Chiral 2,2′-Bipyridines in Copper-Catalyzed Cyclopropanation
Conditions: (a) CuOTf·C₆H₆ (1.3 mol %), 9 (1.3 mol %), CH₂Cl₂, 25 °C,
2 h (75% yield, trans:cis = 86:14, trans = 92% ee, cis = 98% ee).
Chiral bipyridine derivative 10 was employed in the reaction of benzaldehyde with diethylzinc. This ligand was synthesized in an analogous manner to Bolm’s initial $C_2$-symmetric bipyridine (8), as it was formed via a nickel-promoted coupling of two molecules of a chiral bromopyridine derivative. The chiral substituents were incorporated onto the pyridine rings via nucleophilic addition onto commercially available, optically active ketones. Ligand 10 was the best ligand reported in this study; and while it offered similar enantiomeric excesses to the asymmetric addition of diethylzinc to benzaldehyde promoted by ligand 8 in previous work (vida supra), it produced the desired alcohol in lower yields. Despite this deficiency in yield, this study demonstrated improved syntheses of these bipyridine ligands by offering a direct route to chirality, through the incorporation of readily available chiral ketones.

Recently, Malkov et al. have reported a variety of chiral bipyridine derivatives synthesized from naturally occurring terpenes. After the synthesis of a small library of ligands, researchers tested their enantioselectivity in the copper-catalyzed cyclopropanation and allylic oxidation reactions (Figure 1.8). Among the most selective ligands for the two transformations, was a ligand (21) derived from carene, given the name CANDY. In the allylic oxidation (Figure 1.8b), CANDY provided yields that ranged from 33-98%, and ee’s that ranged from 43-82%, while its employment in the cyclopropanation reaction provided a yield of 96% and an ee of only 59%. This study further expanded the number of reactions in which chiral bipyridine ligands proved to be efficient sources of chiral induction.
Figure 1.8 Asymmetric Cyclopropanation and Allylic Oxidation

Conditions: (i) Cu(OTf)$_2$ (2 mol %), PhNHNH$_2$, 21 (2 mol %), CH$_2$Cl$_2$, 20 °C, 4 h (96% yield, trans:cis = 86:14, trans = 59% ee); (ii) Cu(OTf)$_2$ (5 mol %), PhNHNH$_2$, 21 (5 mol %), PhCO$_2$t-Bu, acetone, 20 °C, 0.5 h (35% yield, 82% ee).

Another key point in this study was the use of molecular modeling to rationally design superior ligands for these reactions. In an initial study conducted by this research group three years earlier, chiral bipyridine ligands were found to give modest enantioselectivity in the allylic oxidation of cycloheptene.$^{22}$ However, molecular modeling revealed that those ligands might not provide the optimum asymmetric induction, and this led the researchers to develop a synthesis of CANDY (21). For the allylic oxidation, this rational ligand design ultimately increased the observed enantiomeric excess by 15% to the optimized value of 82% (Figure 1.8b).

Ligand 8 has also been employed in enantioselective additions of alcohols and amines to meso-epoxides (Figure 1.9).$^{23}$ Multiple epoxides (i.e. 22 and 24) were treated with Lewis acidic Sc(OTf)$_3$ in the presence of a chiral ligand and various oxygen and nitrogen nucleophiles to lead to the ring-opened products. Multiple ligands were initially screened, and chiral bipyridine 8 was ultimately selected. This scandium-bipyridine catalytic complex was capable of opening a variety of aromatic epoxides with high
stereoselectively, however ee’s dropped slightly in the cases where aliphatic epoxides were used. In addition, aliphatic amine nucleophiles were not compatible, perhaps due to a strong Lewis acid/Lewis base interaction with the scandium triflate. However, this methodology was further enhanced by the demonstration that compounds such as 23, could be deprotected to reveal chiral 1,2-diols or oxidized to yield ketones with a chiral $\alpha$-hydroxyl moiety. This study furthered the enantioselective reaction scope of the chiral $C_2$-symmetric bipyridine ligands to include ring-opening reactions as a complement to the extensive studies already completed on ring-forming reactions.

![Figure 1.9 Desymmetrization of a meso-Epoxide](image)

**Figure 1.9 Desymmetrization of a meso-Epoxide**

Conditions: (a) Sc(OTf)$_3$ (10 mol %), 8 (10 mol%), MeOH (2 equiv), CH$_2$Cl$_2$, 25 °C, 12 h (83% yield, 93% ee); (b) Sc(OTf)$_3$ (10 mol %), 8 (10 mol %), PhNHCH$_3$ (2 equiv), CH$_2$Cl$_2$, 25 °C, 12 h (85% yield, 97% ee).

In summary, the literature contains many examples of chiral 1,10-phenanthroline and 2,2′-bipyridine ligands in the enantioselective synthesis of chiral molecules. In most cases, these ligands have demonstrated the ability to adequately yield chiral compounds by acting as scaffolds on a reactive metal center. The promise of these ligands as chiral agents in other metal-catalyzed transformations is vast, but there are some hindrances to wide acceptance. In order for these ligands to compete in laboratory use with some of the
more commonly used chiral complexes, i.e. bis(oxazolines), BINOL, BINAP, DIOP, salen complexes or *cinchona* alkaloids, their availability would need to increase. The 1,10-phenanthroline and bipyridine derivatives described were constructed in multi-step processes that were often poor-yielding. Based on the success that has already been reported with these ligands, should access to these compounds become more straightforward, further use in other metal-catalyzed reactions would certainly be warranted.

1.2.2 *Computational Ligand Design and Screening*

Finding the proper chiral ligand to use for any given reaction is not a simple assignment. The number of ligands that exist or could exist is limited only by the chemist’s imagination. Choosing a specific chiral ligand for a given reaction is often done simply by experimentation, through trial and error. This is one of the overarching drawbacks of the development of chiral ligands. Varying both the scaffold and chiral appendages of the ligand offers a plethora of potential candidates and testing them all in a reaction is not feasible.

The concept of computational ligand design and virtual screening of these ligands offers the opportunity to greatly reduce the overall number of ligands that would be used in actual experimentation. This could streamline the process of choosing viable ligand classes and save countless hours of experimentation in the laboratory, as well as the cost of synthetic materials. In order to make use of computational methods, a fair comparison of the two reaction pathways, *pro-R* and *pro-S*, needs to be realized when a given chiral ligand is applied. Use of the quantum mechanical guided molecular mechanics (Q2MM) approach, developed by Per-Ola Norrbyp, provides a convenient
method for comparison of the relative energies of the transition states of the two
diastereomeric pathways.\textsuperscript{26}

Past transition state modeling methods have suffered from several drawbacks.\textsuperscript{24}Molecular mechanics (MM) has been widely used however these force fields are often inadequate for describing the complex abilities of transition metals during a reaction. Methods based around quantum mechanics (QM) are capable of detailing the nature of transition metals, but would suffer from unreasonably long computational times. The Q2MM method improved upon known computational methods by combining the speed of molecular mechanical (MM) with the overall operational flexibility of quantum mechanical (QM) computations, while still maintaining a reasonable computational timeline.

A virtual ligand screening, done concomitantly with experimental verification, could provide a means for the improvement of enantioselectivity for an asymmetric reaction. Once the transition state is modeled and parameters are set for the reaction in question using Q2MM, an iterative process could be maintained, whereby a modeling study identifies ligands as potential candidates and those ligands are then tested. Experimental results, in the form of enantiomeric excesses, can be used to better ascertain improvements to the computational method to allow for better chiral ligand selection in future generations of those reactions. In the case of developing a Q2MM method, even a poor result, i.e. when a ligand predicted to give high enantioselectivity in silico, gives only modest or poor ee in vitro, provides a better understanding of the entire process. This virtual screening of potential ligands would greatly improve the overall ligand
selection process, as well as determine what other ligands could possibly be designed to best induce asymmetry in a reaction.

### 1.3 Hydroamination of Alkynes

A hydroamination reaction is the addition of nitrogen and hydrogen across an olefin or an alkyne.\(^{27}\) Due to its efficiency and the lack of byproduct formation, the reaction is an attractive means for creating amine derivatives. This ability to directly incorporate nitrogen across a carbon-carbon multiple bond allows for diverse functionalization of chemical compounds in one step. The result of the hydroamination of alkynes leaves one remaining degree of unsaturation in the product, which ultimately gives access to enamines or imines (Figure 1.10). The catalysis of this reaction has been extensively studied and has been shown to proceed well in the presence of a variety of metals,\(^{28}\) acids,\(^{29,30}\) and even bases.\(^{31,32}\) A synthetic advantage of the hydroamination of alkynes over alkenes is that the alkyne hydroamination is exothermic by ~35 kcal/mol, whereas alkene hydroaminations are essentially thermoneutral.\(^{33}\) Though this process is exothermic, it also has a large barrier of activation, as the transition state brings two electron-rich components into close proximity. For this reason, acid or metal catalysis is necessary to make this reaction synthetically useful. Base-catalyzed hydroaminations often require specialized substrates, or high temperatures and pressures in order to overcome this large activation barrier.\(^{32}\) Nitrogen heterocycles are a class of compounds that serve as important synthetic targets in terms of natural product total synthesis and drug discovery.\(^{34}\) While it is pertinent to discuss initial work in the intermolecular
hydroamination of alkynes, the focus of this discussion will center on intramolecular 
hydroaminations, which allow for access to nitrogen heterocycles.

\[
\text{R}_2\text{N} - \text{H} \quad \text{catalyst} \quad \text{R}_2\text{N} \equiv \text{H} \quad \text{R} = \text{H} \quad \text{RN} \\
\text{R}^\prime \equiv \equiv \text{R}^\prime
\]

**Figure 1.10 General Reaction Sequence for the Hydroamination of Alkynes**

1.3.1 Early Transition and Rare Earth Metal-Catalyzed Hydroamination of Alkynes

There exists two means for a catalyst to activate the substrates in the 
hydroamination reaction. Either the metal-activator can interact with the triple bond and 
make it electrophilic, or the metal-activator can activate the N-H bond to increase the 
likelihood of nucleophilic attack by the nitrogen moiety. Early transition metals and 
rare earth metals tend to favor activation of the nitrogen to produce a highly nucleophilic 
nitrogen species for direct attack onto the alkyne. The proposed mechanisms for the 
early transition metal-catalyzed hydroamination and lanthanide-catalyzed hydroamination 
are found below, in Figure 1.11 and Figure 1.12 respectively. The two mechanisms differ 
in one aspect, that is the ability of early transition metals to be oxidized to form an imido 
complex (M=N) after initial imino (M-N) complexation. Therefore, the early transition 
metal reaction of an amine and an alkyne acts more as a [2 + 2] cycloaddition. In rare 
earth metal-catalyzed reactions, the metal forms a σ-bond with the amine and reacts via 
an insertion pathway. In both cases, the resulting alkenyl-metal species undergoes 
protonolysis to give either enamine or imine products and regenerate the reactive metal 
catalyst.
Figure 1.11 Mechanism of the Early Transition Metal-Catalyzed Hydroamination

Figure 1.12 Mechanism of the Rare Earth Metal-Catalyzed Hydroamination
Of the early transition metals, titanium and zirconium have received the most interest in the field of hydroaminations.\textsuperscript{36} One of the first examples of an early transition metal-initiated hydroamination of an alkyne was reported in 1988 by Walsh et al., in which an imidozirconocene complex was formed and trapped by various internal alkynes (Figure 1.13).\textsuperscript{37} In a representative example of this initial work, imidozirconocene complex 27 was trapped with 1-phenyl-1-propyne. The resulting enamine product (29) was not isolated, but immediately hydrolyzed with water in the presence of silica gel to yield phenylacetone (30), representative of anti-Markovnikov regioselectivity. This process was made catalytic in 1992 with the use of a bis-amidozirconocene (31) as a precatalyst for the formation of the active imidozirconocene (Figure 1.14). The reaction of 2,6-dimethylaniline (32) and diphenylacetylene with 3 mol % of complex 31 gave enamine 33 in 60% yield, albeit after 13 days and at temperature ranges between 95-120 °C.\textsuperscript{38}

Figure 1.13 Hydroamination with an Imidozirconocene Complex

Conditions: (a) 4-\textit{tert}-butylaniline, PhH, 85 °C, 3 d (70% yield); (b) 1-phenyl-1-propyne; (c) H\textsubscript{2}O, silica gel; (d) H\textsubscript{2}O.
Figure 1.14 Catalytic Hydroamination with a Bis-amidozirconocene Complex

Conditions: (a) 31 (3 mol %), diphenylacetylene, PhCH$_3$, 110 °C, 13 d (60% yield).

As a contemporary discovery of these imidozirconocene complexes, McGrane et al., reported the use of a titanium catalyst for the hydroamination of alkynes as the first example of an intramolecular [2 + 2] cycloaddition of similar metal-imido compounds (Figure 1.15). As expected, the conditions for the intramolecular hydroamination were significantly milder than those for intermolecular hydroaminations. Reaction temperatures of 25 °C, reaction times of 1 h, and yields over 90% represented notable improvements on previous hydroaminations. Cyclization to form 5-membered cyclic imines proceeded in higher yields than cyclizations of their 6-membered analogues.

Figure 1.15 Catalytic Intramolecular Hydroamination with Ti and Zr

Conditions: (a) CpTi(CH$_3$)$_2$Cl (20 mol %), THF, 25 °C, 1 h; (b) CpZr(CH$_3$)$_2$Cl (20 mol %), THF, 25 °C, 10 m; (c) 5% methanolic NaOH.
These conditions were applied by McGrane et al. as the key step in a concurrent communication detailing the racemic total synthesis of the naturally-occurring indolizidine alkaloid \((\pm)-\text{monomorine}\) \((39)\). Cyclization of aminoalkyne \(37\) with a titanium catalyst resulted in imine \(38\) in high yields. Monomorine could then be synthesized by reduction of the imine moiety, removal of the ketal protecting group, and an intramolecular reductive amination (Figure 1.16).

![Figure 1.16 Application of Titanium-Catalyzed Hydroamination to Monomorine Synthesis](image)

**Figure 1.16 Application of Titanium-Catalyzed Hydroamination to Monomorine Synthesis**

Conditions: (a) i. \(\text{Et}_3\text{N}\) (40 mol %), \(\text{Cp}_2\text{TiCl}_3\) (20 mol %), THF, 25 °C, 1 h, ii. 5% methanolic NaOH (93% yield); (b) DIBAL-H (4 equiv), THF, –78 °C (95 %); (c) i. aq HCl, ii. \(\text{K}_2\text{CO}_3\), iii . THF, \(\text{NaBH}_3\text{CN/MeOH}\), 5% aq HCl (75%).

The research group of Tobin Marks has played a preeminent role in the development of lanthanide and actinide catalysts in the hydroamination of all sorts of carbon-carbon unsaturated substrates. Though they first developed lanthanide catalysts for the intramolecular hydroamination of alkenes, Marks’ research group was also the first to extend these complexes to the hydroamination of alkynes. Among the examples of the primary aminoalkynes that underwent hydroamination in this early study were phenyl-substituted, alkyl-substituted, and silyl-substituted alkynes. Cyclizations to form 5, 6, and 7-membered rings were also reported. There was a marked rate enhancement for TMS-substituted alkynes, which also allowed for the resulting imine to be formed in
the highest yield. This effect was presumed to be a factor of favorable polarization of the transition state (41) (Figure 1.17). These samarium-based catalysts were efficient in the hydroamination of aminoalkynes at loadings as low as 2 mol %, however rigorously anhydrous conditions and extended reaction times were required.

![Figure 1.17 Rate-Enhancement of TMS-Substituted Aminoalkynes](image)

**Figure 1.17 Rate-Enhancement of TMS-Substituted Aminoalkynes**

Conditions: (a) \((\eta^5\text{-Me}_5\text{C}_5)_2\text{SmCH(TMS)}_2\) (2 mol %), 25 °C, 2 d, C\(_6\)D\(_6\) (92% yield).

In a subsequent study published by the Marks group, a variety of lanthanide catalysts were employed in the aminoalkyne hydroamination.\(^{42}\) It was discovered that a decrease in ionic radius of the metal center led to higher turnover frequencies for the catalysts. Lutetium (0.977 Å) demonstrated the highest catalytic activity, followed by samarium (1.079 Å), neodymium (1.109 Å), and lanthanum (1.160 Å), which gave the lowest turnover frequencies. This discovery was contrary to what was found in the case of the hydroamination of aminoalkenes and allowed for a better understanding of this catalytic process.\(^ {43}\)

In an intriguing demonstration of a catalytic tandem reaction process, the Marks group once again employed a Sm-based catalyst for a C-N/C-C bond forming bicyclization.\(^ {44}\) Following hydroamination, Li and Marks made use of the resulting metalated intermediate, by trapping with a pendant alkyne (Figure 1.18). This represented an efficient transformation to form alkaloid-like bicyclic compounds (44) in one catalytic step, from a relatively simple secondary amine substrate.
Figure 1.18 Samarium-Catalyzed Tandem C-N/C-C Bond Forming Reaction

Conditions:  (a) \((\eta^5\text{-Me}_5\text{C}_5)_2\text{SmCH(TMS)}_2\) (2 mol %), 21 °C, C\(_6\)D\(_6\) (95\% yield).

In 2003, Gribkov et al. reported the use of biphenolate and binaphtholate yttrium complexes for the intramolecular hydroamination of alkynes (Figure 1.19) as part of a study on chiral ligands in the enantioselective hydroamination of alkenes (vide infra).\(^{45}\)

A racemic mixture of catalyst 45 was employed in the intramolecular cyclization of 5-phenyl-4-pentyn-1-amine (34a). The reaction proceeded with complete consumption of starting aminoalkyne and though it required temperatures above 25 °C, it represented an example of significantly reduced reaction times, when compared to previous examples in this class of metal catalysts.

Figure 1.19 Yttrium-Catalyzed Intramolecular Hydroamination of an Aminoalkyne

Conditions:  (a) 45 (4 mol %), 60 °C, C\(_6\)D\(_6\), 19 h (>99% conversion).
The reports of the intramolecular hydroamination of aminoalkynes with early transition and rare-earth metal complexes demonstrate highly-active catalysts (loadings <5 mol %). However, limitations exist in the requirement for strictly anhydrous conditions and longer reaction times. It has been determined that in the case of lanthanide catalysts, the metals with smaller atomic radii provide the best yields, and a variety of ancillary ligands have been employed efficiently, including bidentate alkoxides and \( \eta^5 \)-cyclopentadienyl ligands. These catalytic systems have also been employed in the total synthesis of some natural products and in the syntheses of biologically interesting nitrogen heterocycles.

1.3.2 Late Transition Metal-Catalyzed Hydroamination of Alkynes

Amine additions to alkynes promoted by late transition metals have been known for nearly seventy years. A potential reason for the earlier study of these metals, when compared to early transition metals and rare-earth metals, is that some late transition metals form stable salts and are widely abundant in nature. This relative stability allowed for their use in reactions prior to modern structural determination methods. The robust nature of late transition metal catalysts is an asset in the hydroamination reaction, due to the ease of their handling, as well as the potential for the employment of relatively inexpensive materials, such as nickel, copper, and silver catalysts.\(^{46} \) Being less oxophilic, late transition metals are more tolerant of polar functional groups than early transition metals or lanthanides. This offers the potential for developments in hydroamination methodology to be applied to more complex substrates, and consequently, provide avenues to more complex products.
The mechanism for late transition metal-catalyzed hydroamination is different from that of the catalysts previously discussed. Late transition metals tend to coordinate to the alkyne and activate it for nucleophilic attack by the amine moiety.\textsuperscript{27} A typical mechanistic scheme is presented in Figure 1.20. Though coordination of the metal to the amine has been shown to represent the resting state of the catalytic cycle, nucleophilic nitrogen attack becomes possible upon metal coordination to the $\pi$ system.\textsuperscript{47} Activation of the $\pi$ system followed by rapid attack of the amine leads to an alkenyl-metal intermediate. This intermediate then loses a proton and undergoes protonolysis at the alkenyl-metal site, to yield enamine products directly. In cases where the starting amine was primary, more stable imine products result after tautomerization from the enamine.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure120.png}
\caption{Mechanism of the Late Transition Metal-Catalyzed Hydroamination}
\end{figure}

The first selective formation of products via metal-catalyzed hydroamination of alkynes was reported in 1939 by Loritsch and Vogt at the University of Notre Dame (Figure 1.21).\textsuperscript{48} The addition of aniline (47) to 1-heptyne (46) in the presence of catalytic mercuric oxide and BF$_3$·OEt$_2$, resulted in the formation of imine 48. This methodology was extended to internal alkynes, such as 3-octyne, and also to secondary aryl amines, like $N$-ethylaniline. In the examples where secondary amines were used as nitrogen
sources, enamines were the resulting product. This study was limited to aryl amines, but represented an excellent method for the hydroamination by demonstrating low catalyst loadings, relatively short reaction times, and high regioselectivity, as the major product arose from Markovnikov addition.

\[
\begin{align*}
\text{C}_5\text{H}_{11} & \equiv \text{H} + \text{C}_5\text{H}_{11} \text{CH}_3\text{NPh} \\
\text{46} & \xrightarrow{a} \text{N} - \text{Ph} \\
\text{47} & \xrightarrow{} \text{48}
\end{align*}
\]

**Figure 1.21 Mercury-Catalyzed Intermolecular Hydroamination of 1-Heptyne**

Conditions: (a) HgO (4 mol %), BF\textsubscript{3}·OEt\textsubscript{2} (2.8 mol %), neat, 60 °C, 1 h (34% yield).

This seminal contribution has gone relatively unnoticed in the literature, and when it has been cited, other authors have mistakenly stated that it was stoichiometric rather than catalytic.\textsuperscript{49} The effect of this oversight was a greater than forty-year gap in the development of mercury-catalyzed hydroaminations. Barluenga employed mercury(II) salts in 1980 seemingly unaware of the work presented by Loritsch and Vogt.\textsuperscript{50} In their work, Barluenga et al. effected hydroamination of aniline and aniline derivatives with the direct addition of mercury salts, such as mercuric chloride or mercuric acetate. Barluenga and coworkers were able to demonstrate selective formation of enamine and imine products by reaction of various amines with acetylenic compounds. In a reaction similar to that of Loritsch and Vogt, aniline (47) was reacted with 1-octyne (49) in the presence of 5 mol % mercuric acetate to produce imine 50 in 69% yield (Figure 1.22). This work thoroughly characterized potential side reactions within the mercury-catalyzed hydroamination, and also introduced the use of aryl alkynes, which served to demonstrate the possibility of new substrates in the hydroamination.
Since the use of mercury in the intermolecular hydroamination of alkynes, a variety of other metals have been employed in this reaction, as well as the intramolecular complement.\textsuperscript{51,52} Rhodium and nickel have also been reported in the alkyne hydroamination, although researchers were unsuccessful in turning this rhodium-promoted process into a catalytic hydroamination.\textsuperscript{53} The nickel-catalyzed process proceeded at temperatures of 125 °C, with 20 h reaction times and yields of 40%. It has also recently been shown that $N,N$-bidentate ligands are proficient ligands in the iridium and rhodium-catalyzed hydroamination.\textsuperscript{54} These catalyst complexes were active at 1.4-1.6 mol % loadings, and yields reached $>90\%$ for both metal catalysts.

The understanding of the intramolecular hydroamination was greatly expanded with an article published in 2000 by Müller and coworkers.\textsuperscript{47} A study of the various effects of metal catalysts, conditions, and counter-ions was accomplished. The hydroamination of alkynes was reported, with varying success, for palladium, zinc, copper, silver, nickel, rhenium, mercury, cadmium, gold and rhodium. It was reported that late transition metals were capable of competing with Marks’ lanthanide catalysts in regards to turnover frequency, which was once thought to be a distinct advantage for rare earth metal catalysts. Müller also reported a profound effect of the anion in the reaction. Catalysts containing sulfonate-derived anions were discovered to be more active, due to their large size and lower nucleophilicity. The catalytic activity of all discussed catalysts,
except nickel(0) complexes, were unaffected by catalyst poisons, such as water. This further demonstrated the robust nature of late transition metal complexes. Efficient catalysts for the intramolecular hydroamination were found in complexes with a d⁸ and d¹⁰ electron configuration, with copper(I), zinc(II), and palladium(II) reported as the most active.

1.3.3 Silver-Catalyzed Hydroamination and Hydroamidation of Alkynes

Though not often employed in hydroamination reactions, silver has found recent success as a catalyst in the synthesis of substituted pyrroles,⁵⁵-⁵⁸ an intermolecular hydroamination of phenylacetylene,⁵⁹ a syn-selective intermolecular hydroamination of siloxy alkynes,⁶⁰ and as a heterogeneous catalyst in a solvent-free intermolecular hydroamination.⁶¹ Despite the fact that the intramolecular hydroamination of alkynes has gained much attention in recent years, this promising metal catalyst has received considerably less attention.⁶²,⁶³ Despite the relatively low cost of silver compared to other precious metals, silver-catalyzed hydroaminations have not been extensively studied. The first report of a silver-catalyzed hydroamidation of an alkyne was made in 1988 by Prasad and Liebeskind (Figure 1.23).⁶⁴ This early attempt to cyclize a β-lactam (51) onto a tethered alkyne was accomplished with limited success. Only internal alkynes were reactive, reactions sometimes required a full equivalent of silver, and reaction yields were less than 50% after multiple days. This cyclization demonstrated the initial use of silver in hydroaminations and provided yields that allowed for further development of cyclizations on substrates that did not contain such restrictive bicyclic structures.
Figure 1.23 Silver-Catalyzed Intramolecular Hydroamidation of β-Lactam

Conditions: (a) AgNO$_3$ (50–100 mol %), CaCO$_3$, H$_2$O/acetone, 25 °C.

Koseki et al. reported the use of silver and strong bases in a catalytic cyclization of β-alkynylpropanamides (53) to γ-lactams (54) in 1998 (Figure 1.24).\textsuperscript{65} This methodology improved upon established procedures for the use of silver in catalytic hydroaminations. These reactions required strong bases, such as lithium hexamethyldisilazane or n-butyllithium. Varying the amount of base and silver triflate showed that two equivalents of base were needed, relative to silver, in order for the reaction to proceed at all. It was also noted that any extension of this methodology to γ-alkynylbutanamides in order to form δ-valerolactams was unsuccessful.

Figure 1.24 Base and Silver-Catalyzed Cyclization of β-Alkynylpropanamides

Conditions: (a) LHMDS (30 mol %), AgOTf (15 mol %), PhCH$_3$, 60-70 °C, 3-4 h.
Silver was also employed in the formation of proline derivatives by van Esseveldt et al. in 2005.\textsuperscript{66} This study utilized the cyclization of primary amines, instead of amides, and resulted in pyrroline and tetrahydropyridine derivatives (Figure 1.25). The yields of the reaction were modest, however silver reigned as the most efficient metal for this study, out-competing gold, zinc, tin, scandium, copper and aluminum. The utility of this study is exemplified by providing access to derivatives of the natural amino acid proline.

![Figure 1.25 Synthesis of Proline-Derived Nitrogen Heterocycles](image)

**Figure 1.25 Synthesis of Proline-Derived Nitrogen Heterocycles**

Conditions: (a) i. HCl, EtOAc, 25 °C, 3 h, ii. aq NH\textsubscript{3}, dioxane/H\textsubscript{2}O (1:1 v/v), 25 °C, 15 m; (b) AgOTf (10 mol%), MeCN, reflux, 1 h.

In a recent publication, Trost utilized a silver-catalyzed intramolecular hydroamination in the penultimate step of the total synthesis of (+)-pseudodistomin D (59) (Figure 1.26).\textsuperscript{67} Cyclization of unprotected diamine (57) by AgOTs, followed by imine reduction, and finally silyl ether deprotection, furnished (+)-pseudodistomin (59) in a concise and original total synthesis. This work by Trost provided an interesting use of the silver-catalyzed alkyne hydroamination to form the necessary diamino heterocycle. It is important to note, however, that the chiral center present at C-2 of piperidine 58 was not put in place by the hydroamination, but by a diastereoselective reduction of the resulting imine. The mechanism of the alkyne hydroamination, as shown in Figure 1.20, would not allow for the direct formation of a chiral center.
Figure 1.26 End Game in the Total Synthesis of Pseudodistomin D

Conditions: (a) AgOTs (10 mol %), MeCN, 40 °C, 2 h; (b) MeOH, H₂O, AcOH, THF, NaBH₃CN, 25 °C, 18 h (52% yield for two steps); (c) TBAF, THF, 25 °C, 20 h (100% yield).

1.3.4 Asymmetric Hydroamination of Alkynes

As mentioned in the previous sections, alkyne hydroamination does not typically lead to chiral products, a result of the formation of achiral enamines or imines. There are three major pathways by which this limitation can be circumvented. The first involves the exploitation of the intermediate alkenyl-metal species. This species typically undergoes protonolysis; however, if this intermediate were to be quenched in a subsequent reaction with an electrophile that allowed for a chiral center to be formed, it can be envisioned that this process could be made enantioselective. If chiral ligands were used on the metal catalyst, they could influence the forming chiral center (Figure 1.27). This method could be used as an extension of the analogous work done by Marks, in the Sm-catalyzed, tandem C-N/C-C bond forming reaction discussed in Figure 1.18.

Figure 1.27 Potential Tandem Alkyne Hydroamination/Conjugate Addition
A second means for forming a chiral center in the alkyne hydroamination would be the use of a prochiral substrate. Desymmetrization of a prochiral diyne would form a chiral center in the resulting cyclic imine (Figure 1.28). This method has been achieved in the hydroamination of alkenes by both Lebeuf et al., in a base-catalyzed cyclization,\textsuperscript{68} and the research group of Marks, in a thorium- or uranium-catalyzed desymmetrization of a prochiral diene.\textsuperscript{69} An extension of this to the hydroamination of alkynes would allow for the formation of a chiral center where it was otherwise not possible.

![Desymmetrization of a Prochiral Diyne](image)

**Figure 1.28 Desymmetrization of a Prochiral Diyne**

The final means for obtaining chiral products in the alkyne hydroamination has been thoroughly explored by Yamamoto. This research group proposes a change in mechanism for the palladium-catalyzed alkyne hydroamination when additives such as benzoic acid\textsuperscript{70} or triphenylphosphine\textsuperscript{71} were added. Through this mechanistic manifold, allylic amines were obtained instead of the typical imines or enamines allowing for the formation of a chiral center (Figure 1.29).
Yamamoto exploited this mechanistic switch in the first reported asymmetric alkyne hydroamination.\textsuperscript{72} This methodology was then extended to the total synthesis of indolizidine \((-\)-209D (62) (Figure 1.30).\textsuperscript{73} The palladium-catalyzed alkyne hydroamination was used to cyclize pyrrolidine 60 and install the chiral center of 61, and hydrogenation was used to reduce the resulting alkene. This differs significantly from previous reports of the alkyne hydroamination in the total synthesis of chiral compounds, because the chiral center actually results from the hydroamination, and not a subsequent step.
Figure 1.30 End Game in the Total Synthesis of Indolizidine (−)-209D

Conditions: (a) Pd(PPh₃)₄ (5 mol %), PhCO₂H (10 mol %), Et₃N (2 equiv), 1,4-dioxane, 100 °C, 12 h (74% yield); (b) H₂, 10% Pd/C, MeOH, 24 h (85% yield).

Making use of any of these three methods: tandem reactions, desymmetrization of prochiral diynes, or a Pd/benzoic acid catalytic system, would allow for the development of alkyne hydroaminations in a direction not normally accessed. Further experimentation in this field is certainly worth considering, as the use of alkynes in the hydroamination has been shown to be an efficient method for incorporating nitrogen and nitrogen heterocycles into organic molecules. Progress in formation of chiral materials from alkynes in this manner would open new avenues for discovery.

1.4 Hydroamination of Alkenes

1.4.1 Late Transition Metal-Catalyzed Enantioselective Alkene Hydroamination

The hydroamination of alkenes is an analogous process to that of alkynes (vide supra). A key difference is that the hydroamination of alkenes leads to amine derivatives, and pyrrolidine derivatives in the examples of intramolecular hydroamination." This allows for more straightforward formation of chiral compounds, which has enticed
researchers to explore this reaction in more depth than the corresponding alkyne hydroamination. Since the overall transformation of alkene hydroaminations is not as exothermic as the alkyne hydroaminations, often more forceful conditions are necessary. Typically, activated olefins are required, and in intramolecular variants, the use of geminal disubstitution along the substrate backbone is common. This practice is widespread in cyclization reactions because a steric interaction of the geminal substituents tends to bring the reacting centers into closer proximity. This effect is known as the Thorpe-Ingold effect. While rare earth metal catalysts, early transition metal catalysts, acids, and bases have all been used in the alkene hydroamination, the use of late transition metals offers the distinct advantage of being insensitive to air and moisture as well as more tolerant of polar functional groups. Despite these intrinsic advantages, late transition metals have been relatively unexplored.

The first report of an enantioselective late transition metal-catalyzed hydroamination was made in 1997 by the research group of Antonio Togni. Iridium catalysts were tested with a variety of chiral ligands in the addition of aniline (47) to norbornene (63) (Figure 1.31). The highest enantioselectivities came from reactions in which BINAP-based catalytic systems were used. After 72 h and a catalyst loading of 1 mol %, the corresponding (2R)-(phenylamino)norbornane (64) was synthesized in only 22% yield, despite racemic reactions of the same sort giving 64 in 100% yield.
Figure 1.31 Iridium-Catalyzed Enantioselective Hydroamination of Norbornene

Conditions: (a) 65 (1 mol %), {N[P(NMe$_2$)$_3$]}$^+\text{F}^-$, neat, 75 °C, 72 h (22% yield, 95% ee).

A premier researcher in the arena of late transition metal hydroaminations is Prof. John Hartwig, who explored the enantioselective hydroamination of styrene and derivatives of styrene using palladium catalysis. Hartwig observed Markovnikov addition of aniline (47) to $p$-trifluoromethylstyrene (66) and vinlynaphthalene (68) in excellent yields and good enantioselectivity when a BINAP-based palladium catalyst was employed (Figure 1.32). This helped to further extend the scope of the late transition metal-catalyzed hydroamination, as well as provided an excellent example of high yielding and mild conditions in the intermolecular hydroamination reaction.
Figure 1.32 Palladium-Catalyzed Enantioselective Hydroamination of Styrenes

Conditions: (a) [(R)-BINAP]Pd(OTf)$_2$ (10 mol %), PhCH$_3$, 25 °C, 72 h (81% yield, 81% ee); (b) [(R)-BINAP]Pd(OTf)$_2$ (5 mol %), PhCH$_3$, 45 °C, 36 h (99% yield, 64% ee).

Gold catalysts have recently been used in the hydroamination of alkenes by other researchers. The intramolecular gold-catalyzed cyclization of secondary, Cbz-protected amines onto olefins was an extension of research where platinum was found to be a competent catalyst. This methodology demonstrated an efficient hydroamination of unactivated olefins, an uncommon substrate class for this reaction. Use of the geminal disubstitution allowed the reactions to proceed at lower temperatures, led to decreased reaction times, and also increased the reaction yields. However, these conditions have yet to be reported as proceeding in an enantioselective manner.

Hartwig has also recently developed rhodium-catalyzed methodology for the alkene hydroamination. This study introduced a metal catalyst system that was active for secondary and primary amines, as well as terminal and non-terminal olefins. The substrates in this study did not require the geminal disubstitution typically employed to bias substrates for cyclization, via the Thorpe-Ingold effect. While Hartwig succeeded in
discovering a very active catalyst, this methodology has not yet been demonstrated in an enantioselective fashion, though that was the immediate desire of the authors.

The chemical community has seen a number of catalysts developed for the asymmetric hydroamination of alkenes, but most of the discoveries have dealt with rare earth metal-based complexes. The area of hydroaminations is heading in the direction of the more hearty late transition metals. At this time however, much work remains before the alkene hydroamination can be universally employed in the synthesis of chiral nitrogen heterocycles. The precious metals seem to hold the future for this reaction, as palladium, platinum, gold, and rhodium have all been recently successful in catalyzing hydroaminations.

1.5 Unnatural Amino Acid Synthesis

In addition to nitrogen heterocycles, unnatural amino acid derivatives are also an important class of synthetically useful molecules. Construction of these amino acid mimics would allow researchers to experiment with biological function, to gain a better understanding of the innate chemistry of a specific system. Of course, most naturally occurring amino acids appear in enantiopure forms; therefore it is desirable for enantioselective syntheses of these compounds to be developed. Asymmetric catalysis, chiral auxiliaries, and the natural chiral pool have all been employed in the syntheses of unnatural amino acids.
1.5.1 Syntheses of β-Hydroxy α-Amino Acids

An important and often studied unnatural amino acid class is the β-hydroxy α-amino acid class. These amino acids, derivatives of serine and threonine, have received considerable interest in synthetic methodology. Synthetic strategies towards these targets have centered on aldol reactions, aminohydroxylation reactions, and elaboration of chiral amino acid derivatives.

Early work in the development of synthetic methodology towards β-hydroxy α-amino acids was done by Evans via the enantioselective aldol reaction. Evans was able to demonstrate both syn and anti selectivity for this process (Figure 1.33). Using chiral oxazolidinones as an auxiliary, Evans provided a complementary set of reactions to synthesize both L-allo-threonine and L-threonine selectively. Reaction of oxazolidinone (70) with acetaldehyde and dibutylboryl triflate provided excellent yields and diastereoselectivity in the formation of adduct 71. Substitution of the aldol adduct (71) with sodium azide, followed by removal of the oxazolidinone and reduction of the azide, furnished 72 in a stereoselective manner. The syn-selective synthesis of L-threonine was accomplished via the aldol reaction of acetaldehyde with isothiocyanate 73. Following the diastereoselective aldol reaction, the product was isolated as the cyclized derivative (74), which could be hydrolyzed to give threonine (75).
Another common method for the synthesis of β-hydroxy α-amino acids is the aldol reaction promoted by a phase transfer catalyst. This method often employs a cinchona-derived quaternary ammonium species. Corey et al. helped to develop this methodology by first applying phase transfer catalysis to the enantioselective alkylation of glycine derivatives. This work was extended to the asymmetric aldol reaction to give β-hydroxy α-amino acids (Figure 1.34). A TMS-protected enolate of a benzophenone imine derivative of glycine (76) acted as the nucleophile which reacted with various aldehydes as the electrophile. Under phase transfer conditions, Corey and coworkers were able to synthesize a variety of amino acid derivatives with modest syn-selectivity and great ee for both the syn and anti adducts (77).
Figure 1.34 Corey’s Asymmetric Aldol Reaction under Phase Transfer Catalysis

Conditions: (a) i. isobutyraldehyde, 78 (10 mol %), hexanes:CH₂Cl₂ (3:1), –78 °C, 7 h, ii. 0.5 M citric acid, THF, 25 °C, 15 h (70% yield over two steps; syn:anti = 6:1; syn-77 = 95% ee, anti-77 = 83% ee).

The asymmetric aminohydroxylation reaction, developed by Sharpless, offers a controlled addition of both nitrogen and oxygen functionality across an olefin. This method has also been applied to the synthesis of β-hydroxy α-amino acid derivatives. Utilizing cinchona ligands, Sharpless has demonstrated ligand-dependent regioselectivity for the aminohydroxylation. This reaction has best been employed on cinnamates (79), leading to β-hydroxy phenylalanine derivatives (80) (Figure 1.35). It has been found that the bis-cinchona-appendages control the enantiomer that is formed during the reaction, while the anthraquinone or phthalazine scaffold, on which those appendages are bound, provides the diastereoselectivity. Other α,β-unsaturated esters have been used as substrates in the asymmetric aminohydroxylation, however not to the extent or with the success of aromatic derivatives.
Another common method for the synthesis of β-hydroxy α-amino acids is based on the functionalization of preexisting amino acid derivatives. Shaw et al. first reported the use of the intermediate vinylglycine as a starting material for the construction of β-hydroxy α-amino acids (Figure 1.36). This method provides a versatile chiral scaffold for the incorporation of nucleophiles. Obtaining vinylglycine (81) from D-methionine, Shaw formed the epoxide (82), and demonstrated the epoxide-opening with nitrogen and sulfur nucleophiles to give unnatural amino acids (83). This research provided yet another efficient method for the construction of unnatural amino acids. One limitation is that the desired unnatural amino acid must have a side chain that is highly nucleophilic and has relatively low basicity. This study found that a base-induced rearrangement could take place and limit the formation of the desired product.
1.5.2 Synthesis of β-Hydroxy Methionine

Unnatural amino acids that combine properties of two or more natural amino acids are desirable targets for synthesis. Inclusion of this kind of synthetic amino acid into a peptide could provide a better understanding of the mechanisms of certain biological functions. The structure of β-hydroxy methionine combines the hydrophobic side chain of methionine with the hydrogen-bonding capabilities of threonine or serine. A more complete discussion of the potential benefits of β-hydroxy methionine can be found in Chapter 4.

There has been one previous synthesis of β-hydroxy methionine, which was reported by Roemmele and Rapoport in 1989. This synthesis was published as a paper detailing the syntheses of a variety of β-hydroxy amino acids, all starting from the natural amino acid serine. The overall synthesis was eight steps and provided (2R,3R)-3-hydroxymethionine, the opposite configuration of natural methionine, in a reported 30% overall yield (Figure 1.37). Protection of the natural serine derivative as the phenylsulfonamide (85) installed a robust nitrogen protecting group tolerant of a range of functional group transformations. Aminoacylation of the lithium carboxylate of 85 provided ketone 86 with limited formation of the tertiary alcohol. Diastereoselective reduction to the diol (87) was affected with L-selectride and ketal formation with dimethoxypropane in the presence of p-toluenesulfonic acid provided 88 in good yield. Protection of the sulfide with a benzyl group proceeded well to form 89, where ketal deprotection was presumably due to trace amounts of triflic acid present during the reaction. Platinum oxidation to the hydroxy acid (90) was followed by hydrogenolysis of the benzyl group to provide the N-protected hydroxy amino acid (91). Diol 87 was a
major byproduct of this reaction; however that material could be reused in the synthesis.

The final \((2R,3R)-3\)-hydroxymethionine (92) was obtained by electrolysis of the phenylsulfone in good yield.

![Chemical structures](image)

**Figure 1.37 Roemmele and Rapoport Synthesis of \(\beta\)-Hydroxy Methionine**

Conditions:  
(a) \(\text{PhSO}_2\text{Cl}, \text{K}_2\text{CO}_3, \text{H}_2\text{O}, 4\) h; (b) i. \(n\)-\(\text{BuLi}\) (3 equiv), THF, \(-78^\circ\text{C}, 0.5\) h, ii. (methylthio)methylithium, \(25^\circ\text{C}, 18\) h (80% yield); (c) \(L\)-selectride (3 equiv), THF, \(-78^\circ\text{C}, 2\) h (95% yield, \(\text{syn:anti}=9:1\)); (d) 2,2-dimethoxypropane, PTSA, THF, \(25^\circ\text{C}, 3\) h (87%); (e) \(\text{Tf}_2\text{O}, \text{benzyl alcohol, } i-\text{Pr}_2\text{NEt, CH}_2\text{Cl}_2, 0.5\) h (85%); (f) 50 wt % \(\text{PtO}_2, \text{O}_2, \text{H}_2\text{O, } i-\text{PrOH, 60}\) °C, 18 h (80%); (g) 10% \(\text{Pd/C, H}_2, \text{MeOH, 25}\) °C, 0.5 h (49%); (h) electrolytic cleavage, Pt foil (anode), Hg pool (cathode), \(\text{Me}_4\text{N}^+\text{F}^-, 18-20\) mA current (73%).

Overall, the synthesis of \((2R,3R)-3\)-hydroxymethionine (92) was an efficient and relatively high yielding example of the use of the chiral pool in enantioselective synthesis. However, if the natural stereoisomer of methionine was desired as a backbone for unnatural amino acid targets, this method would be unnecessarily lengthy. This method employed by Roemmele and Rapoport changed the acid functionality of the natural source into the side chain in the target, and manipulated the side chain of the
natural source into the acid moiety of the target. A synthesis of \((2S,3S)-3\)-hydroxymethionine would be better undertaken utilizing one of the methods discussed in the previous section.
CHAPTER 2

PHENANTHROLINE AND BIPYRIDINE

2.1 Previous Work in the Helquist Laboratory

The use of unsubstituted 1,10-phenanthroline and 2,2′-bipyridine as ligands in transition metal catalyzed reactions has been thoroughly explored. The diverse binding abilities of these ligand classes has helped to promote their use, however a lack of chirality had until recently, hindered their introduction into asymmetric transformations. The known syntheses of chiral 1,10-phenanthroline and 2,2′-bipyridine derivatives are often lengthy and low-yielding. This limitation inspired the Helquist laboratory to discover new reactions that allow for easy access to these chiral ligand classes from commercial materials.

The Helquist group began work in the area of chiral phenanthroline derivatives in a study of enantioselective palladium-catalyzed allylic alkylations in 1996.\textsuperscript{93} The syntheses and screening of a variety of chiral phenanthroline derivatives were performed for use in this reaction (Figure 2.1). Molecular mechanics was used to predict the enantioselectivities of phenanthroline-based ligands in the Pd-catalyzed alkylation reaction, and those predictions were then compared to experimental results. The reaction of dimethyl malonate (94) with racemic allylic acetate 93 in the presence of
phenanthroline ligand 96 and a palladium catalyst, gave the alkylated product 95 in up to 80% yield with ee’s that ranged from 80-92%. In this reaction, molecular mechanics had predicted ligand 96 would give high ee, and those predictions were then verified by experimentation, thus providing evidence for computational chemistry assisting the rational design of ligands.

![Figure 2.1 Helquist Use of Chiral Phenanthroline in Pd-Catalyzed Allylic Alkylation](image)

**Figure 2.1 Helquist Use of Chiral Phenanthroline in Pd-Catalyzed Allylic Alkylation**

Conditions: (a) 96 (20 mol %), (η₃-1,3-dimethylallyl)palladium trifluoroacetate (10 mol %), KOAc, O,N-bis(trimethylsilyl)acetamide, THF, 0 → 25 °C, 14 h (up to 80% yield, predicted high ee, 80-92% ee).

In the previous example, Peña-Cabrera and coworkers constructed ligand 96 via a one-step process by reaction of a commercially available hydrazone and phenanthroline. Though this represented an efficient means to access chiral ligands, the other phenanthroline-based ligands employed in the study were synthesized through multi-step routes. The successful use of phenanthroline derivatives led the Helquist laboratory to explore new methods for accessing these ligands. In 1999, O’Neill and Helquist reported a samarium-promoted coupling of ketones to the phenanthroline scaffold, an effective reaction for the introduction of substituents at the 2-position (Figure 2.2). Reaction of 1,10-phenanthroline (phen) (97) and cyclohexanone (98) in the presence of 2.2 equivalents of samarium diiodide resulted in adduct 99 in 88% yield. This discovery offered a new method to derivatize phenanthroline, and when applied to commercially
available chiral ketones, provided access to chiral phenanthroline derivatives. The reaction of (−)-thujone (100) and 1,10-phenanthroline (97) in the presence of 2.2 equivalents of SmI$_2$ provided chiral derivative 101 in 45% yield. The application of this coupling reaction to commercially available, chiral ketones allowed for easy access to this promising class of chiral ligands, with chiral substituents present at optimal locations for the induction of asymmetry in chemical transformations as demonstrated by Gladiali (Figure 1.3)$^8$.

![Diagram of Samarium-Promoted Coupling of Ketones and 1,10-Phenanthroline](image)

Figure 2.2 Samarium-Promoted Coupling of Ketones and 1,10-Phenanthroline

Conditions: (a) SmI$_2$ (0.1 M in THF, 2.2 equiv), THF, 25 °C, 12 h (99, 88% yield; 101, 45% yield).

Since the introduction of this reaction, the Helquist group has extended this methodology to include coupling of aldehydes (Figure 2.3a)$^{95}$ and epoxides (Figure 2.3b)$^{96}$ with phenanthroline, as well as the coupling of aldehydes onto a bipyridine scaffold (Figure 2.3c)$^{97}$ Subsequent reactions of coupled products like 102 have included methylation, acylation, and deoxygenation of the resulting alcohol moiety.$^{95}$ Acylated products have also been shown to undergo further coupling reaction with carbonyls in the presence of SmI$_2$ to provide substituents with varying chain lengths.$^{97}$ Reactions of phenanthroline (97) with epoxides resulted in products of dual addition.
Ligands such as 103 provide remarkably similar binding potential to the privileged salen ligands. By adding the ability to couple aldehydes and epoxides, the Helquist group has significantly expanded the number of potential ligands available via this coupling reaction.

**Figure 2.3 SmI$_2$-Promoted Couplings of Aldehydes and Epoxides**

Conditions: (i) propanal (2 equiv), SmI$_2$ (0.1 M in THF, 2.2 equiv), THF, 25 °C, 1 h (94% yield); (ii) (R)-(−)-1,2-epoxybutane (4 equiv), SmI$_2$ (0.1 M in THF, 5 equiv), THF, 23 °C, 3.5 d (103, up to 42% yield; 104, up to 13%); (iii) isobutyraldehyde (2 equiv), SmI$_2$ (0.1 M in THF, 2.5 equiv), THF, 25 °C, 1 h (43% yield).

### 2.2 Synthesis of Novel 2,2′-Bipyridine Ligands

In order to further develop the library of ligands available via the SmI$_2$-promoted coupling reaction, this methodology was extended to the reaction of chiral epoxides with 2,2′-bipyridine. It was envisioned that extension of the epoxide-coupling methodology to the bipyridine ligand scaffold would provide ligands such as 107, a one-carbon homologue of the chiral bipyridine 8 reported by Bolm in 1990 (Figure 2.4). These
ligands would also possess structural similarities to the salen ligands (108) employed by Jacobsen in asymmetric epoxidations of alkenes. The development of a synthesis of 107 would also allow for simple access to $C_2$-symmetric ligands. The structural similarities of ligand 107 to ligands that have been demonstrated to effectively induce asymmetry in transition metal catalyzed reactions, along with the extension of this methodology into the underdeveloped bipyridine ligand class made this an attractive synthetic pursuit.

![Figure 2.4 Comparison of Novel Chiral Bipyridine with Known Ligands](image)

Figure 2.4 Comparison of Novel Chiral Bipyridine with Known Ligands

Beginning with the known protocol for the coupling of aldehydes, ketones, and epoxides to phenanthroline and of carbonyl compounds to bipyridine, the synthesis $C_2$-symmetric ligand 107 commenced. It was thought that 4 equivalents of SmI$_2$ would be necessary to form the desired 107, as the reaction required 2 equivalents of samarium(II) for products of single addition in all previous syntheses. In order to reduce the number of potential stereoisomeric products in this initial screening, enantiomerically pure ($R$)-(+)-1,2-epoxybutane (109) was employed. It was found that reactions of epoxides were not as pliant as those for ketones or aldehydes, such that 4 equivalents of epoxide were typically necessary to detect even minimal amounts of products of single addition (Table 2.1). Initially, only bipyridine derivative 110, a result of single addition of epoxide to the bipyridine scaffold, was observed. The increase of temperature, by refluxing the reaction
mixture in THF, allowed for the reduction of reaction time from 48 to 16 hours, but did not effectively enhance the yield of either 107 or 110 (Entry 2). Longer reaction times, refluxing temperatures, and an extra equivalent of SmI₂, allowed for the isolation of 110 in 22% yield (Entry 3). The first observation of the formation of ligand 107 came under these conditions, albeit in only 3% yield.

**TABLE 2.1**

**SAMARIUM-PROMOTED EPOXIDE COUPLING WITH 2,2'-BIPYRIDINE**

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>equiv of SmI₂</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield of 107</th>
<th>Yield of 110</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>25</td>
<td>48</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>67</td>
<td>16</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>67</td>
<td>48</td>
<td>3</td>
<td>22</td>
</tr>
</tbody>
</table>

Conditions: (a) SmI₂, 109 (4 equiv), THF.
2.2.1 Attempts to Develop Samarium-Catalyzed Coupling Reaction

It was apparent that the amount of samarium required for this reaction was not optimal and that this required excess might become a hindrance to the broad use of this methodology by the chemical community. For this reason, attempts were made to develop a coupling reaction that was catalytic in samarium. A common technique for employing catalytic samarium diiodide includes the addition of an excess of Mischmetall, an alloy of various lanthanides.\(^9\) At the end of our coupling reaction, and other reactions employing SmI\(_2\), the active Sm(II) has been oxidized to the inactive Sm(III). By providing Mischmetall as a stoichiometric co-reductant, it has been shown that reactions can become catalytic in samarium.\(^1\) This would offer the benefit of using fewer molar equivalents of the expensive SmI\(_2\), while utilizing the cheaper Mischmetall alloy in the molar amounts necessary for the transformation.

A detailed description of the process used in these reactions is appropriate, due to metalworking being an uncommon procedure employed in organic synthesis. The preparation of Mischmetall for a coupling reaction of bipyridine (105) and epoxide (109) in the presence of SmI\(_2\) was carried out in a fume hood. The brown oxide layer was removed from the Mischmetall ingot with a commercial rasp. Once the shiny, metallic surface of the Mischmetall was exposed, the ingot was suspended with a clamp above a tared, flame-dried Schlenk flask under a flow of argon gas, meant to maintain an inert atmosphere for the freshly rasped metal filings. A funnel in the Schlenk flask assisted in the collection of the small filings that resulted from grinding the ingot with the rasp. Care was necessary, as the rasping process produced sparks due to the pyrophoricity of
the Mischmetall ingot. The Schlenk flask could then be stoppered and massed to determine the amount of Mischmetall filings collected. The vigor required to rasp the metal ingot precluded the use of a glove box, and previous reports of the use of Mischmetall describe similar manipulations in the successful employment of this alloy.

A summary of reactions in the presence of Mischmetall are summarized in Table 2.2. Initial experiments to examine the effect of the presence of Mischmetall had on the coupling resulted in the formation of both 110 and 107 in yields slightly higher than in previous reactions (Table 2.1). Increasing the molar equivalents of Mischmetall did not increase the yields of the desired ligands, but instead, neither 107 nor 110 was observed (Entry 2). Attempts to reduce the equivalents of SmI\(_2\) in the reaction, while maintaining the necessary equivalents of Mischmetall, also did not result in the formation of the desired ligands (Entry 3). Therefore, it was determined that 5 equivalents of SmI\(_2\) and 0.6 equivalents of Mischmetall, at a temperature of 50 °C and a reaction time of 48 h were optimal for formation of the desired coupling products (Entry 1). It appeared that the major product of this reaction was the result of the coupling of two molecules of epoxide. Alterations to the stoichiometry and the order of addition, in an attempt to prevent the likelihood of this homo-coupling did not have a profound effect on the outcome of the reaction.
TABLE 2.2

DEVELOPMENT OF SAMARIUM-CATALYZED EPOXIDE COUPLING

\[
\begin{align*}
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

Entry | Equiv of SmI\(_2\) | Equiv of Mischmetall | Temp (°C) | Time (h) | Yield of 107 | Yield of 110 |
--- | --- | --- | --- | --- | --- | --- |
1 | 5 | 0.6 | 50 | 48 | 10 | 20 |
2\(^b\) | 5 | 3 | 50 | 48 | n/a | n/a |
3\(^b\) | 2 | 3 | 50 | 48 | n/a | n/a |

Conditions and Notes: (a) SmI\(_2\), 109 (4 equiv), THF; equiv of Mischmetall calculated from an average g/mol of metals contained within the alloy; (b) No product peaks were present in the crude \(^1\)H NMR, homo-coupled epoxide was the likely product.

While the presence of Mischmetall did not allow for the use of SmI\(_2\) in catalytic quantities, it did provide slightly better access to the disubstituted ligand 107, which had only been formed in minimal amounts in all previous attempts. This result could be due to the reactions containing Mischmetall allowing for the regeneration of a small amount of samarium(II) in the reaction mixture, effectively increasing the number of equivalents available for the transformation, though not going quite far enough to make the reaction catalytic in samarium diiodide. Ultimately, both the mono- and disubstituted ligands could be produced by employing a SmI\(_2\)/Mischmetall system, albeit in low yields.
2.3 Synthesis of Metal Complexes of 1,10-Phenanthroline

The ultimate goal in the development of new ligand systems for transition metal-catalyzed reactions within the Helquist group is the employment of those ligands in an enantioselective transformation. For that reason, a reaction needed to be found that lent itself to the eventual incorporation of a chiral ligand system. The metal-catalyzed hydroamination with the use of phenanthroline ligands has not been previously reported. While the goal will eventually lead to enantioselective catalysis, the groundwork needed to be established with the simple 1,10-phenanthroline scaffold as a ligand in this hydroamination reaction. In order to accomplish this goal, metal complexes of these ligands were synthesized.

To this end, Jonathan Mortison, an undergraduate researcher in the Helquist group, was the first to synthesize a silver-phenanthroline complex for the purpose of catalyzing an intramolecular hydroamination of 5-phenyl-4-pentyn-1-amine (34a). This synthesis involved the reaction of phenanthroline (97) and silver nitrate to form catalyst complex 111 (Figure 2.5) for which an X-ray crystal structure was obtained. This early reaction served as the basis for the formation of other silver-phenanthroline metal complexes, as well as the complexes of other metals, all for the purposes of employment in the intramolecular hydroamination.

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

\[
\begin{align*}
\text{a} \\
\text{N} \quad \text{N} \\
\text{N} \quad \text{N} \\
\text{N} \quad \text{N}
\end{align*}
\]

\[
\begin{align*}
\text{Ag}^{+} \\
\text{NO}_{3}^{-}
\end{align*}
\]

**Figure 2.5 Initial Formation of Silver-Phenanthroline Complex**
Conditions: (a) AgNO$_3$ (1 equiv), MeOH/H$_2$O (1:1), 5 min.
A variety of silver-phenanthroline complexes were synthesized for eventual
testing in the hydroamination of alkynes. With the information presented in the report of
Müller,\textsuperscript{47} the first alteration attempted in this study was the use of silver(I)
trifluoromethanesulfonate (triflate) as the initial silver salt (Figure 2.6a). Müller had
discovered that the triflate counter ion generally provided a more active catalyst than the
nitrate anion in the hydroamination of alkynes. This complex also had other benefits to
the nitrate analogue, in that it was more easily handled. The general procedure for this
complexation was to combine a solution of 1,10-phenanthroline in methanol and a
solution of silver (I) salt in water. Immediately upon addition of the two solutions, the
metal complex precipitated and could be isolated by filtration. The complexes of
Ag(phen)NO\textsubscript{3} (\textbf{111}) formed hard, solid masses that were difficult to collect, while
complexes of Ag(phen)\textsubscript{2}OTf (\textbf{112}) formed moist pastes that could be transferred more
easily. Both complexes were dried under vacuum over P\textsubscript{2}O\textsubscript{5} prior to use. Electrospray
ionization analysis carried out with the cooperation of the Center for Environmental
Science and Technology (CEST) at the University of Notre Dame allowed for further
characterization of complex \textbf{112}. This technique unambiguously determined that the
major complex was the one with the structure shown below, in which two phenanthroline
ligands were coordinated to the metal center. This result came in spite of the initial 1:1
molar ratio of silver triflate to ligand.

In addition to the formation of these Ag(phen)\textsubscript{2}OTf complexes, the formation of a
neocuproine complex (\textbf{114}) was also accomplished (Figure 2.6b) using the procedure
above. The use of neocuproine or 2,9-dimethyl-1,10-phenanthroline (dmp) (\textbf{113}) as a
ligand allowed for access to metal complex systems that would probe for the tolerance of
the hydroamination reaction for substitution on the phenanthroline scaffold at the 2 and 9 positions. The Ag(dmp)OTf complex 114 was more soluble in the methanol/water mixture, and therefore collection by filtration provided lower yields. However, of the silver complexes, 114 was the most easily handled, as it formed a white powder. Initial mass spectrometry studies on this complex show strong peaks that correspond to instances of both a single coordinating ligand and dual coordination. More sensitive techniques, like those employed for the structural determination of 112 described above, would be particularly interesting for this and other ligands with 2 and 9 substituents.

\[
\begin{align*}
\text{(a) } & \quad \text{97} & \quad \text{i} & \quad \text{112} \\
\text{(b) } & \quad \text{113} & \quad \text{i} & \quad \text{114}
\end{align*}
\]

**Figure 2.6 Formation of Ag–Phenanthroline and Ag–Neocuproine Complexes**

Conditions: (i) AgOTf (1 equiv), MeOH/H\(_2\)O (1/1) 5 min (112, 87%; 114, 23%).

For the purposes of screening other metal catalysts, palladium and gold were also complexed with phenanthroline (Figure 2.7) using adaptations of routes previously reported. Reaction of Pd(acac)\(_2\) with 1,10-phenanthroline was completed by stirring the two reactants in CH\(_2\)Cl\(_2\) at room temperature over 3 h.\(^{101}\) The complex (115) could be isolated by removal of the solvent under reduced pressure. The complex of gold(III) phenanthroline (116) was initially formed by the addition of sodium tetrachloroaurate
dihydrate to a solution of 1,10-phenanthroline in EtOH. After stirring for 4 h at 100 °C, the complex 116 was then dissolved in water and recrystallized by the addition of concentrated nitric acid. Both 115 and 116 were dried under vacuum prior to use and stored under argon atmosphere at 25 °C.

![Figure 2.7 Formation of Phenanthroline Complexes of Palladium and Gold](image)

**Figure 2.7 Formation of Phenanthroline Complexes of Palladium and Gold**

Conditions: (i) Palladium(II) acetylacetonate (1 equiv), CH₂Cl₂, 25 °C, 3 h (99% yield); (ii) NaAuCl₄·2H₂O (0.5 equiv), EtOH, 100 °C, 4 h, then concd HNO₃ (98% yield).

### 2.4 Future Work

The synthesis of novel ligands 107 and 110 has opened the avenue within the Helquist group for the synthesis of a variety of chiral bipyridine derivatives. While both phenanthroline derivatives and bipyridine derivatives have been studied in asymmetric reactions, the prior focus of synthetic efforts within the Helquist group has been on 1,10-phenanthroline derivatives. Having access to both ligand analogues will allow for future comparison of their ability to induce asymmetry in a broad range of reactions.

In the initial reports of samarium-promoted coupling reactions of 1,10-phenanthroline and 2,2′-bipyridine to aldehydes, overall yields were dramatically
different (compare Figure 2.3a vs. 2.3c). It seems there is an inherent difficulty to the coupling of ketones, aldehydes, and epoxides to the 2,2′-bipyridine system, but the reason for this is still unknown. A possible extension of this project is the study of 3,3′-disubstituted-2,2′-bipyridines, which would provide another data set for comparison in this Sm-promoted coupling. These compounds have been shown to act as metal chelators for a variety of transition metals, and are therefore potentially useful as ligands for transition metal-catalyzed reactions. Such ligands would present structures intermediate to those of phenanthroline and bipyridine, which could help to further the understanding of the limits of the SmI$_2$-promoted coupling reaction, and allow for access to another interesting set of ligands with slightly different structural characteristics.

The development of a Sm-catalyzed coupling of epoxides and bipyridine scaffolds has been attempted through the employment of stoichiometric quantities of Mischmetall. While these reactions have not yet produced a samarium-catalyzed protocol, future reactions could make use of other cheap, stoichiometric co-reductants. One possibility is the use of magnesium metal, which has recently been demonstrated to act as an efficient co-reductant in the SmI$_2$-catalyzed intramolecular pinacol coupling. Due to the higher yields when ketones and aldehydes are coupled with 1,10-phenanthroline, further studies on a catalytic system should begin with these amiable reactions. A reduction in the amount of samarium necessary in this transformation would further enhance an already efficient means to access chiral ligands directly from commercially available products.

Future synthetic efforts in the metal complexes of phenanthroline and bipyridine derivatives could explore the complexation of different metal salts and test these complexes for activity in transition metal-catalyzed reactions. Not much is known about
the binding capabilities of bipyridine ligands 107 and 110. Metal complexes of both of these ligands could be explored to gain a better understanding for the selection of chiral substituents for transition metal catalysis.
CHAPTER 3

INTRAMOLECULAR HYDROAMINATION OF ALKYNES

3.1 Introduction and Previous Work

The desire to further develop transition metal catalyzed reactions through the employment of such ligands as 1,10-phenanthroline and its derivatives, led the Helquist laboratory to begin studying the intramolecular hydroamination (Figure 3.1). This reaction was of particular interest because of the ability to access nitrogen heterocycles, which are important due to their common appearance in biologically relevant compounds.\(^{34}\)

![Figure 3.1 General Scheme for the Intramolecular Hydroamination of Alkynes](image)

Figure 3.1 General Scheme for the Intramolecular Hydroamination of Alkynes
A variety of metals have been shown to catalyze the intramolecular hydroamination (Sections 1.3 and 1.4). However, many problems persist with current protocols, in that catalysts often suffer from one or more of several common drawbacks. While the lanthanide and actinide metals have been thoroughly explored as catalysts for the hydroamination,\textsuperscript{35} it is known that these metals and their complexes are highly sensitive to air and moisture. Early transition metals are also known to be sensitive, and often require strictly anhydrous conditions.\textsuperscript{36} For these reasons, late transition metals seem to have an advantage of stability over other metals known to catalyze this reaction.\textsuperscript{27} However, late transition metals known to catalyze hydroamination reactions also happen to be some of the more precious metals, including rhodium, platinum, palladium, and gold. Despite the relatively low cost of silver compared to more precious metals, silver-catalyzed hydroaminations have not been as extensively studied.\textsuperscript{55-61,64-67}

The Helquist laboratory commenced the development of a metal catalyst for the hydroamination that would quell some of the common shortcomings seen in other metal complexes, while at the same time developing a further extension for the 1,10-phenanthroline ligands.\textsuperscript{108} While several metals would ultimately be studied, the desire to develop a protocol through the use of a less expensive metal led to initial work using silver. Through the work of an undergraduate researcher in this laboratory, William Wuest, silver–phenanthroline complexes were found to catalyze the hydroamination of primary amine 34a (Figure 3.2).
Figure 3.2 Initial Helquist Silver–Phenanthroline-Catalyzed Hydroamination

Conditions: (a) 111 (10 mol %), CH₃CN, 70 °C, 16 h.

3.2 Substrate Synthesis

With a proof of concept established, further exploration into the intramolecular hydroamination of aminoalkynes required the synthesis of a variety of aminoalkyne substrates. In addition to studying alternatives to the synthetic methods used by William Wuest, substrates of varying chain lengths and substitution were necessary. The desired aminoalkynes for this study have been reported previously,⁴² and synthetic efforts towards these targets were accomplished as adaptations of the known literature.

By employing 1-bromo-3-chloropropane (117a) in place of 1,3-dibromopropane, the starting material used previously, the chloroalkyne 118a was synthesized in good yields and excellent chemoselectivity, as there was no evidence of dual nucleophilic addition (Figure 3.3). The requisite nitrogen moiety was installed via the use of potassium phthalimide, as part of the Gabriel synthesis. Though the yields of the phthalimide substitution were fairly low, the reaction was amenable to large scale, and purification by trituration allowed for simple access to phthalimide derivative 119a. Cleavage of the imide was accomplished with hydrazine and HCl to give the amine derivative 34a. Because hydrazine is a highly toxic substance, an alternative route (conditions d) employing NaOH was also successfully manipulated to access 34a from
the corresponding phthalimide derivative 119a in excellent yield.\textsuperscript{109} The aminohexyne derivative 34b was also synthesized via this Gabriel pathway. By first employing 1-bromo-4-chlorobutane (117b) in the reaction with lithium phenylacetylide, chloroalkyne 118b was synthesized in good yields. Subsequent reaction with phthalimide and cleavage of derivative 119b with hydrazine provided the primary amine 34b in excellent yield.

With the phenyl-substituted substrates in hand, work continued on the synthesis of terminal aminoalkynes (Figure 3.4). Commercially available 5-chloro-1-hexyne (120a) was reacted with potassium phthalimide to give the N-substituted phthalimide derivative 121a in excellent yields. Through the use of the initial hydrazine conditions for the cleavage of the phthalimide protecting group, amine 34e was produced in only 12% yield. It was believed that the volatility of the substrate led to the observed poor yields. Collection of the sensitive amine compound 34e as its hydrochloride salt, followed by a
separate treatment of this salt with 1 N NaOH and evaporation of organic solvents, allowed for the isolation of 34e in 35% yield. When this route was applied to the synthesis of 34f, the commercially available 6-chloro-1-hexyne (120b) was reacted with phthalimide to give 121b in good yield. This phthalimide could be cleaved, and the volatile amine 34f was obtained via the hydrochloride salt in 83% yield.

![Figure 3.4 Synthesis of Terminal Aminoalkynes](image)

**Figure 3.4 Synthesis of Terminal Aminoalkynes**

Conditions: (a) NaI (10 mol %), potassium phthalimide, DMF, 100 °C, 48 h (121a, 55% yield; 121b, 90%); (b) N₂H₄·H₂O, concd HCl, MeOH, reflux, 12 h (34e, 12% yield; 34f, 53%); (c) i. N₂H₄·H₂O, concd HCl, MeOH, reflux, 12 h, ii. 1 N NaOH, Et₂O, 10 min, (34e, 35% yield over two steps; 34f, 83%).

An alternative approach to these volatile amines was also pursued in order to provide higher yields and avoid the need for purification of the aminoalkynes following phthalimide cleavage (Figure 3.5). By using a modification of a known alternative to the phthalimide protecting group in the Gabriel synthesis, trfluoroacetamide derivative 122a could be prepared in yields comparable to that of the phthalimide derivative 121a. Mild cleavage of this protecting group allowed for pure aminoalkyne derivative 34e to be isolated. Careful atmospheric distillation to simply remove the reaction solvent after workup allowed for the isolation of the amine as the residual liquid in pure form and in vastly improved yields without the need for chromatography.
Figure 3.5 The Use of Trifluoroacetamide as an Alternative Protecting Group

Conditions:  (a) NaH (60% dispersion in oil), CF$_3$C(O)NH$_2$, DMF, 60 °C, 16 h (41% yield); (b) 1 N NaOH, MeOH, 25 °C, 16 h (97% yield).

To expand the library of aminoalkynes for the study of the intramolecular hydroamination, methyl-substituted alkynes were synthesized via similar synthetic steps (Figure 3.6). The reaction of 120a with $n$-BuLi and quenching with CH$_3$I as the electrophile, provided the methyl-substituted chloroalkyne 123a along with an equimolar amount of the methyl-substituted iodoalkyne 124a, presumably formed via a Finkelstein reaction. The mixture of alkynyl halides could be employed in the phthalimide substitution to provide N-substituted phthalimide derivative 125a in 69% yield. Phthalimide cleavage with hydrazine monohydrate afforded aminoalkyne 34g in 66% yield. Via the same synthetic steps, the one-carbon homologue 34h was synthesized from 6-chloro-1-hexyne (120b). Once more, both the chloroalkyne 123b and iodoalkyne 124b were observed following reaction with $n$-BuLi and CH$_3$I. Substitution with potassium phthalimide and then subsequent cleavage of the phthalimide group provided the aminoalkyne derivative 34h in good yield.
Figure 3.6 Synthesis of Methyl-Substituted Aminoalkynes

Conditions: (a) i. n-BuLi (1 equiv), THF, −78 °C, 1 h, ii. CH$_3$I (1 equiv), reflux, 3 h (quantitative yield, 123a:124a (1:1); 123b:124b (1:1)); (b) potassium phthalimide, DMF, 100 °C, 48 h (125a, 69% yield; 125b, 84%); (c) N$_2$H$_4$:H$_2$O, concd HCl, MeOH, reflux, 12 h (34g, 66% yield; 34h, 59%).

3.3 Optimization Studies in the Hydroamination of Primary Amines

While it had been established that silver–phenanthroline catalysts were effective in the intramolecular hydroamination of aminoalkynes, it was necessary to extend this study to a wider range of metal–phenanthroline complexes. Therefore, complexes of the parent 1,10-phenanthroline with a variety of metals were explored in the hydroamination of 5-phenyl-4-pentyn-1-amine (34a). This brief qualitative screening was carried out in conjunction with the Spring 2004 class of CHEM 248L Organic Chemistry Laboratory at the University of Notre Dame. Among the metal catalysts chosen were Ni, Yb, Sm, Ti, Cu, Au, and Ag. These preliminary experiments found that there was a metal dependence of whether the imine 36a or the isomeric enamine 126 was obtained as the major product. This initial screening found that both Ag and Pd favored formation of 36a, whereas Yb, Sm, and Ni preferentially gave tautomeric enamine 126 (Figure 3.7).
For the purposes of our study, we chose to focus on the use of those metals that lead to selective formation of the cyclic imines.

Figure 3.7 Initial Qualitative Screening of Metals for the Hydroamination

Conditions: (a) AgNO$_3$ (10 mol %) or Pd(OAc)$_2$ (10 mol %) and 1,10-phenanthroline (10 mol %); (b) Yb(OTf)$_3$ (10 mol %) or Sm(OTf)$_3$ (10 mol %) or NiCl$_2$ (10 mol %) and 1,10-phenanthroline (10 mol %).

Early preparative work for optimization of the intramolecular hydroamination was marred by the sensitivity of imine 36a (vide infra). Therefore, NMR scale reactions were utilized to determine conditions in this initial metal screening, with preparative scale and purification techniques to follow once the optimal conditions had been discovered. The metals chosen for this more quantitative screening were palladium, gold, and silver (Table 3.1). The preformed metal complexes were prepared as described in Section 2.3.
### TABLE 3.1

**SCREENING OF METAL PHENANTHROLINE COMPLEXES**

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Mol %</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOTf</td>
<td>10</td>
<td>4</td>
<td>70</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>Ag(phen)$_2$OTf (112)</td>
<td>10</td>
<td>4</td>
<td>70</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>112</td>
<td>4</td>
<td>4</td>
<td>70</td>
<td>82</td>
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<tr>
<td>4</td>
<td>112</td>
<td>4</td>
<td>4</td>
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<td>84</td>
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<tr>
<td>5</td>
<td>112</td>
<td>1</td>
<td>4</td>
<td>70</td>
<td>71</td>
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<tr>
<td>6</td>
<td>Pd(acac)$_2$</td>
<td>10</td>
<td>24</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Pd(phen)(acac)$_2$ (115)</td>
<td>10</td>
<td>6</td>
<td>100</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>NaAuCl$_4$</td>
<td>10</td>
<td>4</td>
<td>25</td>
<td>46</td>
</tr>
<tr>
<td>9</td>
<td>Au(phen)Cl$_2$NO$_3$ (116)</td>
<td>10</td>
<td>4</td>
<td>25</td>
<td>59</td>
</tr>
</tbody>
</table>

Conditions and Comments:  
(a) Reactions were performed in CD$_3$CN, unless otherwise indicated; (b) Yields were calculated from $^1$H NMR spectra using mesitylene as an internal standard; (c) Result from catalyst that was collected by filtration after reaction in entry 3, washed with CH$_2$Cl$_2$, and reused; (d) Reactions run in $d_6$-dimethylsulfoxide; (e) In the absence of supporting ligand, Pd(acac)$_2$ formed Pd black which did not catalyze the cyclization.

A clear advantage of silver–phenanthroline complexes over the naked silver salt was established with the increase in yield of imine 36a (Entry 1 vs. Entry 2, Table 3.1). In palladium-catalyzed reactions, the benefit of phenanthroline was seen in its ability to stabilize the metal in the reaction mixture (Entry 6 vs. Entry 7, Table 3.1). The Pd(acac)$_2$ salt without a supporting ligand formed palladium black upon introduction into the reaction mixture. Heating of the substrate 34a in the presence of the palladium black for 24 h showed no conversion to the desired imine product 36a, while employment of Pd(phen)(acac)$_2$ (115) provided the desired imine in 69% yield in only 6 h (Entry 7, Table 3.1).
Table 3.1). Both the NaAuCl₄ salt and Au(phen)Cl₂NO₃ (116) provided excellent reactivity in the intramolecular hydroamination (reactions proceeded instantaneously at 25 °C), but the observed yields of 36a were lower than for the other two metals studied (Entries 8 and 9). Enamine 126 was not observed in any of the reactions in Table 3.1.

Overall, silver complex (112) provided 36a in higher yields than either palladium-based (115) or gold-based (116) catalysts. There were also other benefits to the Ag(phen)₂OTf catalyst that led us to choose 112 for further studies. The reactions run in acetonitrile using phenanthroline complexes were heterogeneous at 25 °C but became homogeneous at temperatures above 35 °C. After the reaction mixture was cooled, the phenanthroline complex (112) could be recovered by filtration, whereas AgOTf could not be recycled as readily because of its solubility at 25 °C. The filtered catalyst (112) was washed with CH₂Cl₂ and dried under reduced pressure before being employed in the hydroamination a second time. No loss of activity was observed in the subsequent run (Entry 4, Table 3.1). It was also determined that Ag(phen)₂OTf (112) was active using a catalyst loading as low as one mole percent (Entry 5, Table 3.1), but the rate was too slow for the reaction to go to completion under the standard conditions. In addition to its recyclability, the silver–phenanthroline complex (112) was air- and moisture-stable for at least 6 months after preparation, a benefit over other catalysts for which strict anhydrous and anaerobic conditions are necessary. It was also not necessary to take special care in storage of the catalyst (112), as it was stored at 25 °C in the dark with no precautions to avoid exposure to air.

With silver–phenanthroline complex 112 established as the premium catalyst for the hydroamination of 34a, studies shifted to the exploration of the hydroamination of the
other primary aminoalkynes (Section 3.2). Complexes of silver with both 1,10-phenanthroline and 2,9-dimethyl-1,10-phenanthroline (neocuproine, dmp) were synthesized (Chapter 2) to examine these cyclizations further. The inclusion of substituents at the 2 and 9 positions of the ligand scaffold would probe for future tolerance of chiral substituents in those positions. Because most of the substrates employed in the reaction were either sensitive or volatile, the study was primarily conducted on an NMR-scale to best understand the true conversion provided by the catalyst in this hydroamination reaction. The imine products could also be isolated on a preparative scale for the purposes of characterization, but a decrease in yield was typically observed. A summary of the silver-catalyzed hydroamination of primary aminoalkynes is provided in Table 3.2.
## TABLE 3.2

SILVER-CATALYZED HYDROAMINATION OF AMINOALKYNES\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Product</th>
<th>% Yield\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{NH}_2)(\equiv\text{Ph}) 34a</td>
<td>Ag(phen)(_2)OTf</td>
<td>4</td>
<td>(\text{Ph})(\equiv\text{N}) 36a</td>
<td>95 (87)</td>
</tr>
<tr>
<td>2</td>
<td>(\text{NH}_2)(\equiv\text{Ph}) 34a</td>
<td>Ag(dmp)OTf</td>
<td>6</td>
<td>(\text{Ph})(\equiv\text{N}) 36a</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>(\text{NH}_2)(\equiv\text{Ph}) 34b</td>
<td>Ag(phen)(_2)OTf</td>
<td>6</td>
<td>(\text{Ph})(\equiv\text{N}) 36b</td>
<td>77 (70)</td>
</tr>
<tr>
<td>4</td>
<td>(\text{NH}_2)(\equiv\text{H}) 34e</td>
<td>Ag(dmp)OTf</td>
<td>4</td>
<td>(\text{H}_3\text{C})(\equiv\text{N}) 36e</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>(\text{NH}_2)(\equiv\text{H}) 34f</td>
<td>Ag(dmp)OTf</td>
<td>5</td>
<td>(\text{H}_3\text{C})(\equiv\text{N}) 36f</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>(\text{NH}_2)(\equiv\text{CH}_3) 34g</td>
<td>Ag(dmp)OTf</td>
<td>10</td>
<td>(\text{H}_3\text{C})(\equiv\text{N}) 36g</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>(\text{NH}_2)(\equiv\text{CH}_3) 34h</td>
<td>Ag(phen)NO(_3)</td>
<td>72</td>
<td>(\text{H}_3\text{C})(\equiv\text{N}) 36h</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>(\text{NH}_2)(\equiv\text{CH}_3) 34h</td>
<td>Ag(phen)(_2)OTf</td>
<td>48</td>
<td>(\text{H}_3\text{C})(\equiv\text{N}) 36h</td>
<td>N/A\textsuperscript{c}</td>
</tr>
<tr>
<td>9</td>
<td>(\text{NH}_2)(\equiv\text{CH}_3) 34h</td>
<td>Ag(dmp)OTf</td>
<td>24</td>
<td>(\text{H}_3\text{C})(\equiv\text{N}) 36h</td>
<td>40</td>
</tr>
</tbody>
</table>

Conditions and Comments: 
(a) catalyst (10 mol %), CD\(_3\)CN (0.75 mL), 70 °C; (b) Yields were calculated from \(^1\text{H}\) NMR spectra using mesitylene as an internal standard. Isolated yields shown in parentheses where applicable; (c) Yield undetermined, but the reaction mixture consisted of a 3:1 mixture of starting material and product as measured by crude \(^1\text{H}\) NMR.
The reactions shown in Table 3.2 were carefully monitored in order to minimize reaction times. A catalyst loading of 10 mol % was standardized, despite the demonstration of the potential for lower loadings, because this loading allowed for the complete conversion of starting material within a reasonable reaction time. All reactions were run in $d_3$-acetonitrile, at a temperature of 70 °C. Replacement of phenanthroline with neocuproine showed no effect on activity, which demonstrated a tolerance for substitution at those positions of the phenanthroline scaffold.

In general, 4-pentyn-1-amine derivatives cyclized more efficiently than their 5-hexyn-1-amine counterparts (compare Entries 1 vs. 3, 4 vs. 5, and 6 vs. 9; Table 3.2). The 5-hexyn-1-amine derivatives typically proceeded with lower yields over longer reaction times. This observed reactivity could result from the need of the approaching amine to be anti to the dissociating metal. The 4-pentyn-1-amine derivatives are more capable of providing this necessary angle of attack. The angle of attack also explains the exclusive formation of 5-membered rings when the 4-pentyn-1-amine derivatives are employed.

The catalysts were effective in the cyclization of terminal and disubstituted alkynes, including an unactivated methyl-substituted alkyne (Entry 6). The aminoalkyne $34h$ was the least active substrate with reaction times exceeding 24 hours. This reduced reactivity is potentially due to an unactivated methyl-substituted alkyne combined with the less favorable factor of forming the 6-membered ring in $36h$. A comparison of silver triflate and silver nitrate (Entries 7 vs. 9) revealed a much shorter reaction time when the former is used as a precatalyst.
Isolation of the resulting imines was problematic because of the sensitivity of imine 36a and the volatility of 36e-h. Preparative scale reactions could be run in CH$_3$CN, with monitoring by TLC to determine the completion of the reaction. 2-Benzylpyrroline (36a) and the 2-benzyl-3,4,5,6-tetrahydropyridine (36b) were isolated through the removal of the reaction solvent under reduced pressure in the absence of heat, followed by purification with alumina chromatography. Because of its volatility, 2-methyl-1-pyrroline (36e) was isolated as its N-methyl-pyrrolinium derivative 127 by reaction with iodomethane in acetonitrile. This solid could be precipitated and recrystallized to yield the previously reported derivative, albeit in low yield (Figure 3.8). Low yield in this ordinarily efficient reaction could be the result of the loss of the volatile, tautomeric enamine. The isolation techniques for the other volatile imines 36f-h did not require such extreme measures. Once these reactions were determined to be complete by TLC, Kugelrohr distillation of the reaction mixtures provided the resulting imines 36f-h.

Figure 3.8 Isolation of the Volatile 2-Methyl-Pyrroline

Conditions: (a) Ag(phen)$_2$OTf (10 mol %), CH$_3$CN, 70 °C, 4 h; (b) CH$_3$I (2 equiv), CH$_3$CN, 25 °C, 2 h (28% yield).
With the silver-catalyzed cyclization of a variety of aminoalkynes completed, one overarching question that remained in this study was the origin of the sensitivity of imine 36a. It became our desire to discover the identity and origin of any other products of this reaction. Further work was required in order to achieve this knowledge.

3.4 Facile Aerobic Oxidation of Cyclic Imine 36a

Throughout the literature, 5-phenyl-4-pentyn-1-amine (34a) has been employed in the intramolecular hydroamination of alkynes. Reactions of 34a are often excellent; however, the resulting imine product, 2-benzyl-1-pyrroline (36a), and derivatives that share the benzyl and pyrroline moieties, are often referred to as sensitive. It was not intuitive, however, why this compound was troublesome, and any rationalization for its sensitivity had yet to be published. During the course of this research, it was also noted that reactions to form 36a would often result in the appearance of spurious peaks within the 1H NMR and, on occasion, would result in the complete formation of a second product of unknown identity.

In 2005, van Esseveldt and coworkers reported a silver-catalyzed hydroamination of a similar substrate to yield the substituted 2-benzyl-1-pyrroline 56a (Figure 3.9).66 In this report, it was mentioned that the pyrroline product was sensitive; however there was no mention as to the source of this sensitivity or whether 56a underwent conversion to another compound. Richmond and coworkers reported that in a palladium-catalyzed hydroamination of 34a, a byproduct was observed, which comprised 15% of the reaction
mixture. The structure of this byproduct was thought to be the nitroso derivative PhCC(\(\text{CH}_2\))\(_3\)NO, on the basis of \(^1\text{H} \text{NMR}\) and GCMS, though more complete characterization was not provided.\(^{112}\)

![Figure 3.9 Synthesis of Proline-Derived Nitrogen Heterocycles](image)

**Figure 3.9 Synthesis of Proline-Derived Nitrogen Heterocycles**

Conditions: (a) i. HCl, EtOAc, 25 °C, 3 h, ii. aq NH\(_3\), dioxane/H\(_2\)O (1:1 v/v), 25 °C, 15 m; (b) AgOTf (10 mol %), MeCN, reflux, 1 h.

Determined to discover the identity of our byproduct, we sought to establish the optimal conditions for its formation and to isolate the compound for complete characterization (Figure 3.10). The result of this characterization study was the elucidation of 2-benzoyl-1-pyrroline (128), which could be formed under slightly modified hydroamination conditions in 60% yield. This compound has an identical molecular weight to the byproduct reported by Richmond and coworkers in 2002.\(^{112}\) Further characterization and observations corroborate a different structure for our byproduct. We hypothesize that it is a facile aerobic oxidation of the benzylic position in 36a that could be the cause of this compound’s reputed sensitivity.

![Figure 3.10 Hydroamination and Facile Benzylic Oxidation](image)

**Figure 3.10 Hydroamination and Facile Benzylic Oxidation**

Conditions: (a) Ag(phen)\(_2\)OTf (112) (10 mol %), CH\(_3\)CN, 70 °C, 16 h; (b) air oxidation, (60% yield over two steps).
A similar oxidation has been previously reported for analogous compounds as taking place simply by reaction with air. The rationalization for our observance of this transformation, in spite of the reactions initially being set up under argon atmosphere, could be that no further precautions were taken to prevent exposure to air during the long reaction times. While monitoring this transformation by $^1$H NMR, it was determined that peaks corresponding to imine 36a would decrease, while those for α-ketoimine 128 would increase during the course of the reaction, further corroborating the belief that 128 is formed via imine 36a.

This facile oxidation can be controlled, allowing for either the pyrrole 36a or ketoimine 128 to be isolated as the major product. Therefore, this transformation represents an interesting two-step reaction sequence. This useful functionalization of an alkyne to an α-ketoimine allows for the formation of products related to the amino acid proline, which could be made possible through a selective reduction of the imine moiety. The isolation and characterization of 128 has answered the question of the cause of the apparent sensitivity of pyrrole 36a.

3.5 Synthesis and Attempted Hydroamidation Reaction of Secondary Amide and Sulfonamide Derivatives

Ultimately, the use of chiral phenanthrolines as ligands in the metal-catalyzed hydroamination would be a desirable development, providing another example of the utility of this diverse ligand class. The reactions of alkynes in the hydroamination, however, do not typically allow for chiral centers to be formed (Section 1.3.4). Two of the potential methods for accessing chiral compounds through alkyne hydroamination
involve the use of secondary amides and sulfonamides. Therefore, exploration beyond the hydroamination of primary aminoalkynes has also been attempted. A few examples of amide derivatives, known to participate in metal-catalyzed hydroaminations, were synthesized for this study. Yamamoto and coworkers reported a palladium-catalyzed intramolecular hydroamidation of an alkyne to generate chiral allylic sulfonamides (Figure 1.29). The substrates employed in this study were alkynylsulfonamides, derived from tosyl protection of primary amines. For the purposes of attempting similar hydroamination reactions with our catalysts, alkynylsulfonamides 129a and 129b were synthesized from their corresponding primary amines by reaction with p-TsCl (Figure 3.11).

With the desired alkynylsulfonamides (129) in hand, attempts at the hydroamination commenced (Figure 3.12). Unfortunately, reactions with our catalysts did not result in reaction of the starting material. Employing Ag(dmp)OTf (114) at a catalyst loading of 10 mol %, in DMSO at 110 °C, did not result in the observation of any reaction of sulfonamide 129b after 65 h. Using a catalytic system of palladium(0) and benzoic acid also did not result in the observance of any of the desired products. Neither Pd2(dba)3CHCl3 nor Pd(PPh3)4 were effective catalysts in a variety of reaction conditions. In many reaction mixtures, the formation of palladium black was observed;
therefore, complexes of palladium with neocuproine were also employed in this reaction, but to no avail. Even an attempt to repeat Yamamoto’s original work, by running the reaction with Pd(PPh\textsubscript{3})\textsubscript{4} and PhCO\textsubscript{2}H in dioxane did not result in the formation of the desired product.\textsuperscript{70} The lack of success in the formation of discernible products in this pathway, led us to pursue other means towards the potential formation of chiral derivatives in the alkyne hydroamination.

Another means to access a product containing a chiral center through the alkyne hydroamination is to add a pendant reactive site capable of undergoing a second reaction to form the desired chiral center. This new center could potentially be formed in an enantioselective fashion if a chiral ligand is involved in this second bond-forming reaction. A single substrate associated with the concept of extending the intramolecular hydroamination reaction to a tandem C–N/C–C bond forming reaction was therefore synthesized (Figure 3.13). Reaction of primary amine 34b with crotonyl chloride in the presence of triethylamine provided \(\alpha,\beta\)-unsaturated amide 131 in low yield. Amide 131 would provide an opportunity to trap the alkenyl-metal intermediate, formed during the

Figure 3.12 Attempts at the Hydroamination of Sulfonamide Derivatives

Conditions: (a) 114 (10 mol %), \(d_6\)-DMSO, 110 °C, 65 h; (b) Pd\textsubscript{2}(dba)\textsubscript{3}CHCl\textsubscript{3} (10 mol %), PhCO\textsubscript{2}H (40 mol %), \(d_6\)-DMSO, 100 °C, 65 h; (c) Pd(dmp)(dba) (20 mol%), PhCO\textsubscript{2}H (40 mol %), \(d_6\)-DMSO, 120 °C, 60 h; (d) Pd(PPh\textsubscript{3})\textsubscript{4} (10 mol %), PhCO\textsubscript{2}H (10 mol %), 1,4-dioxane, 100 °C, 70 h.
hydroamidation, via a conjugate addition onto the pendant unsaturated amide (Figure 3.14).

![Figure 3.13 Synthesis of Substrate for C–N/C–C Tandem Reaction](image)

**Figure 3.13 Synthesis of Substrate for C–N/C–C Tandem Reaction**

Conditions: (a) Crotonyl chloride (1.5 equiv), Et₃N (2 equiv), CH₂Cl₂, 25 °C, 20 h (36% yield).

Silver complexes Ag(phen)₂OTf (112) and Ag(dmp)OTf (114) were employed in the attempted tandem reaction of amide 131 (Figure 3.14), using the optimized conditions from the primary aminoalkynes described above. Unfortunately, the use of these catalysts did not result in formation of the desired product, but instead a complex mixture. Therefore, it was decided that the most efficient means to access chiral products from the alkyne hydroamination would be through the employment of prochiral diynes (Figure 1.28).

![Figure 3.14 Attempted Ag-Catalyzed Tandem Hydroamination/Conjugate Addition](image)

**Figure 3.14 Attempted Ag-Catalyzed Tandem Hydroamination/Conjugate Addition**

Conditions: (a) 112 (30 mol %), CD₃CN, 70 °C, 48 h; (b) 114 (30 mol %), CH₃CN, 70 °C, 20 h.
3.6 Synthesis of Prochiral Diynes

The third method to arrive at chiral compounds from the alkyne hydroamination was explored through the synthesis of a prochiral diyne. Our synthesis was begun by Dr. Patrick Donoghue in collaboration with the laboratory of Dr. Olaf Wiest (Figure 3.15). Since we had developed the silver–catalyzed hydroamination of 5-phenyl-4-pentyn-1-amine (34a), and aminopentyne derivatives tended to give higher yields than the corresponding aminohexyne compounds, we sought to explore a synthesis of a prochiral variant of 34a. Beginning with methyl malonate (133), double alkylation with propargyl bromide provided diester 134 in excellent yield. The diester could be reacted via a Krapcho decarboxylation using LiCl to yield the monoester diyne 135, which also proceeded in very good yield. This synthesis could be carried out on a large scale and provided a substantial amount of 135 for continuation in the synthesis of the necessary aminodiynes.24

![Figure 3.15: Beginning of the Synthesis of Prochiral 1,6-Diyne](image)

Figure 3.15 Beginning of the Synthesis of Prochiral 1,6-Diyne

Conditions: (a) NaH (60% dispersion), propargyl bromide (2 equiv), THF, –10 → 25 °C, 20 h (84% yield); (b) LiCl (3 equiv), H2O (2 equiv), DMSO, reflux, 1 h (90% yield).
The synthesis continued by reduction of 135 with LiAlH₄, which resulted in alcohol 136a (Figure 3.16). This alcohol was the key intermediate in the synthesis, as it could be used to access both the phenyl-substituted and terminal prochiral aminodiynes. The alkynes of 136a could be functionalized via a Sonogashira coupling with iodobenzene, giving the phenyl-substituted alcohol 136b, an overall addition of two aromatic groups, in 95% yield.

Figure 3.16 Synthesis of Prochiral Alcoholic Diynes

Conditions:  (a) LiAlH₄ (1.5 equiv), THF, 25 °C, 12 h (78% yield); (b) Pd(PPh₃)₄ (1 mol %), CuCl (2 mol %), Et₃N, PhI (2 equiv), 50 °C, 1.5 h (95% yield).

The conversion of the alcohols 136 to the corresponding amines proved to be problematic. Initially, the conversion of the alcohols to a good leaving group (i.e. –OMs or –OTs) was sought to provide a means to incorporate the necessary nitrogen moiety as a phthalimide derivative, which could be cleaved using the conditions described above. However, it was found that the cleavage conditions employing hydrazine were not amenable to the diyne substrate. An alternative procedure, in which the mesylate or tosylate was displaced with an azide, was also explored. However, initial results showed poor yields for this substitution reaction, and it was known that reduction of the azide with LiAlH₄ would not tolerate the phenyl-substituted alkynes had the azide been formed efficiently. It was hypothesized that the acidic conditions necessary during the hydrazine cleavage of phthalimide were the cause of the poor yields in earlier reactions. For this reason, a base-labile nitrogen source was sought for our synthetic route.
Trifluoroacetamide has been employed in a modified Gabriel synthesis,\textsuperscript{110} and had been utilized effectively in the synthesis of 4-pentyn-1-amine (34e). By conversion of the alcohols 136a,b to the corresponding trifluoroacetamides 137a,b, the prochiral aminodiynes 138a,b could finally be synthesized (Figure 3.17). The yields for the substitution of the –OMs were very poor; however, the removal of the trifluoroacetamide group to reveal the primary amine resulted in the desired compounds 138a,b in high yields without the need for purification. Incorporation of the trifluoroacetamide often led to isolation of the alcohols 136a,b, presumably via $O$-alkylation of the acetamide nucleophile followed by hydrolysis.

![Figure 3.17 End Game for the Synthesis of Prochiral Aminodiynes](image)

**Figure 3.17 End Game for the Synthesis of Prochiral Aminodiynes**

Conditions: (a) i. MsCl (1.2 equiv), Et$_3$N (1.5 equiv), CH$_2$Cl$_2$, 0 °C, 2 h, ii. NaH (60% dispersion in oil, 1.5 equiv), CF$_3$C(O)NH$_2$ (1.5 equiv), DMF, 70 °C, 24 h (20% yield); (b) 1 N NaOH (2 equiv), 25 °C, 16 h (95% yield).

### 3.7 Hydroamination Studies of Prochiral Aminodiynes

With the synthesis of the requisite prochiral aminodiynes completed, focus moved to the optimization of the hydroamination with these diynes. While the ultimate goal was the formation of products enantioselectively, we initially sought optimization of cyclization conditions using an achiral catalyst, with future plans for the use of enantioselective catalysis. Under the conditions optimized for the simple aminoalkynes, 138b was cyclized to form the racemic but desymmetrized cyclic imine 139b (Table 3.3).
TABLE 3.3

DESYMMETRIZATION OF PROCHIRAL DIYNE 138B

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysta</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>% Yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ag(phen)$_2$OTf (112)</td>
<td>CD$_3$CN</td>
<td>4</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>112</td>
<td>CD$_3$CN</td>
<td>24</td>
<td>70</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>112</td>
<td>CD$_3$CN</td>
<td>48</td>
<td>70</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>112</td>
<td>CD$_3$CN</td>
<td>2</td>
<td>35</td>
<td>67 (48)</td>
</tr>
<tr>
<td>5</td>
<td>Ag(dmp)OTf (114)</td>
<td>CD$_3$CN</td>
<td>4</td>
<td>35</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>114</td>
<td>(CD$_3$)$_2$SO</td>
<td>2</td>
<td>35</td>
<td>67</td>
</tr>
</tbody>
</table>

Conditions and Comments: (a) catalyst (10 mol %); (b) Yields were calculated from $^1$H NMR spectra using mesitylene as an internal standard. Isolated yields are shown in parentheses where applicable.
Interestingly, it was found that the prochiral diyne underwent cyclization under much milder conditions than the previous aminoalkynes (Section 3.3). When Ag(phen)OTf (112) and Ag(dmp)OTf (114) complexes were used to catalyze this reaction, a temperature of 35 °C was found to be adequate for formation of imine 139b. Reactions using 114 in d₆-DMSO allowed for shorter reaction times when compared to those run in d₃-acetonitrile.

The terminal aminodiyne 138a was also employed using similar conditions (Figure 3.18). In order to obtain an idea as to the activity of the catalyst, regardless of the volatility or sensitivity of the product, the yields were first measured via ¹H NMR using mesitylene as an internal standard. It was found that 2 h was the optimal reaction time for the formation of imine 139a, which was the sole product formed in 97% yield. Attempts at isolating 139a have not provided spectroscopically pure compound for complete characterization at this time.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{H} \\
\begin{array}{c}
\text{H}_2\text{N} \\
\text{H}
\end{array} & \quad \begin{array}{c}
\text{H}
\end{array} \\
\text{C} & \quad \text{H}
\end{align*}
\]

Figure 3.18 Desymmetrization of Terminal Aminodiyne

Conditions: (a) 112 (10 mol %), CD₃CN, 35 °C, 2 h (97% yield).

A consequence of the initial formation of cyclic imine 139b is the differentiation of the identical alkynes of 138b. Now distinguishable, these moieties can undergo fundamentally distinct reactions, demonstrating the utility of a racemic desymmetrization reaction. As was the case with pyrroline 36a, pyrroline 139b also underwent facile oxidation at the benzylic position to give α-ketoimine 140 (Figure 3.19). This reaction exemplifies the separate chemical reactivity of the once similar alkynes. It was our desire
to further demonstrate this differentiation; therefore the remaining alkyne was employed in a reaction typical of this functional group. Lindlar hydrogenation of α-ketoimine 140 gave cis-alkene 141 in good yield after a reaction time of only 15 min.

![Chemical structures](image)

**Figure 3.19 Further Elaboration of Aminodiyne**

Conditions: (a) 112 (10 mol %), CD$_3$CN, 70 °C, 48 h; (b) air oxidation (50% yield over two steps); (c) quinoline (15 mol %), Pd/CaCO$_3$, Pb (5 mol %), H$_2$ (1 atm), EtOH, 25 °C, 15 min (75% yield).

The racemic desymmetrization of prochiral aminodiynes has been demonstrated using silver-phenanthroline catalysts. Both the terminal and phenyl-substituted 1,6-diynes underwent hydroamination in good to excellent yields, with catalyst loadings of 10 mol %. The product of the hydroamination of 138b was employed in further reactions to fully demonstrate the differentiation of the once identical alkynes. This facile hydroamination will allow us to proceed with this strategy for the enantioselective hydroamination of aminoalkynes.

### 3.8 Partial Syntheses of Other Prochiral Diynes

As part of the continuing exploration of the opportunity to employ prochiral diynes in the silver-catalyzed hydroamination reaction, synthetic efforts for other diynes
having various branching points have commenced. It is of value to explore the effect that
the proximity of the prochiral center to the metal catalyst will have on the observed
enantioselectivity. The synthesis of 1,4-diynes provides substrates in which the prochiral
center exists at the propargylic position, the closest that the metal can get to the forming
chiral center. The synthesis of such substrates has begun (Figure 3.20 and 3.21).

Figure 3.20 Partial Synthesis of a (3-Aminopropyl)-1,4-Diyne
Conditions: (a) n-BuLi (1.0 equiv), HCO₂Et (0.4 equiv), THF, –78 °C, 3 h
(57% yield); (b) acetyl chloride (1.25 equiv), py (2 equiv), CH₂Cl₂, 0 °C, 1 h
(97% yield); (c) allyltrimethylsilane (1.5 equiv), B(C₆F₅)₃ (5 mol %),
CH₂Cl₂, 25 °C, 2 h (93% yield); (d) 9-BBN, H₂O₂, NaOH, 50 °C, 2 h; (e) MsCl (1.2 equiv), Et₃N (1.5 equiv), CH₂Cl₂, 0 °C, 2 h, ii. NaH (60%
dispersion in oil, 1.5 equiv), CF₃C(O)NH₂ (1.5 equiv), DMF, 70 °C, 24 h;
(f) 1 N NaOH (2 equiv), 25 °C, 16 h.
The reaction of two equivalents of phenylacetylene (144) with ethyl formate provided alcohol 145 in moderate yield (Figure 3.20). The alcohol 145 was converted to the acetate 146 by reaction with acetyl chloride in the presence of Et₃N. The Lewis acid B(C₆F₅)₃ has been used to substitute allyl groups for propargylic acetates. Conversion of acetate 146 to enediyne 147 was accomplished in 93% yield using boron-catalyzed conditions based upon those reported by Schwier and coworkers.¹¹⁴ Enediyne 147 could be employed in a chemoselective hydroboration using 9-BBN to provide alcohol 148.¹¹⁵ The synthesis could then continue through the methods used to prepare the amino-1,6-diyynes reported above by converting the alcohol to the mesylate, followed by substitution with trifluoroacetamide, to give the amide 149. This group could then be easily cleaved under mildly basic conditions to provide the amino-1,4-diyne 150.

![Chemical Reaction Diagram]

**Figure 3.21 Partial Synthesis of a (2-Aminoethyl)-1,4-Diyne**

Conditions: (a) triflic acid, CH₂Cl₂, 25 °C, 1 h; (b) acetaldehyde (1.5 equiv), Et₃N (1.5 equiv), CH₂Cl₂, 25 °C, 2 h (41% yield); (c) 146, B(C₆F₅)₃ (5 mol %), CH₂Cl₂, 25 °C, 2 h; (d) H₂NN(CH₃)₂; (e) Na₂S₂O₄.
The synthesis of the corresponding (2-aminoethyl)-1,5-diphenyl-1,4-pentadiyne (156) has also begun (Figure 3.21). The reaction pathway was started by formation of the supersilyl triflate (152) from tris(trimethylsilyl)silane (151) and triflic acid through a previously published process. The stable supersilylenol ether 153 was formed by reaction with acetaldehyde, through the employment of Yamamoto’s conditions. The reaction of this silyl enol ether and bispropargylic acetate 146 under B(C₆F₅)₃–catalyzed conditions could provide aldehyde 154 and serve as a new application of this recently reported propargylic substitution. These conditions were previously employed for the related reaction of allyltrimethylsilane as the nucleophile with 146. Conversion of the aldehyde to the amine by reductive amination via the reaction with N,N-dimethylhydrazine and reduction by Na₂S₂O₄ could provide the other 1,4-diyne substrate 156 for study in the hydroamination.

5-Amino-1,9-diphenyl-1,8-nonadiyne (164) would also be a valuable prochiral diyne for employment in the hydroamination. The prochiral center in this substrate is far removed from the metal coordination site in the transition state. Once again this could provide a deeper insight into the effect of the proximity of the ligand’s chiral substituents to the forming chiral center. The synthesis of this diyne has also been started (Figure 3.22).
Figure 3.22 Partial Synthesis of a 5-Amino-1,8-diyne

Conditions: (a) \( n\)-BuLi, paraformaldehyde, THF, –78 °C, 3 h (57% yield); (b) PBr\(_3\), CH\(_2\)Cl\(_2\), 0 °C, 30 min (66% yield); (c) NaH (60% dispersion in oil), \( n\)-BuLi, 158, THF, –78 °C, 3 h (45% yield); (d) NaH (60% dispersion in oil), 158, THF, –78 °C, 3 h; (e) LiCl (3 equiv), H\(_2\)O (2 equiv), DMSO, reflux, 1 h; (f) H\(_2\)NN(CH\(_3\))\(_2\); (g) Na\(_2\)S\(_2\)O\(_4\).

The reaction of phenylacetylene (144) and \( n\)-BuLi with paraformaldehyde to provide alcohol 157, and conversion of the alcohol to the bromide 158 with PBr\(_3\) are known reactions, and both occurred smoothly to give 158 in good yield. Alkylation of methyl acetoacetate via the dianion provided \( \beta \)-keto ester 160 through an adaptation of a known method.\(^{118}\) However, early exploration of this reaction has only provided moderate yields of 160 thus far. Continuing the synthesis, another alkylation reaction would yield diyne 161. This diyne could be decarboxylated to give the ketone (162), which can undergo reductive amination to yield the requisite aminodiyne (164).
3.9 Conclusions and Future Work

Comparison of silver complexes to those of palladium and gold demonstrated the need to develop a methodology based around this relatively inexpensive metal. The employment of silver–1,10-phenanthroline in the hydroamination of primary aminoalkynes was successfully demonstrated on a variety of alkynyl substrates. The yields were typically high and, in all but one case, the complete conversion of starting material was observed. The advantage of this catalyst is featured in its air- and moisture-stability, a change from what is often reported for metal catalysts in hydroaminations.

The development of 1,10-phenanthroline as a scaffold for the intramolecular hydroamination was pursued in order to further explore opportunities for the implementation of chiral 1,10-phenanthroline derivatives in transition metal-catalyzed reactions. This remains the immediate goal of the project. As part of our continued collaboration with the research group of Prof. Olaf Wiest, a virtual screening of chiral ligands was accomplished for the silver-catalyzed desymmetrization of amino-1,6-diynes 138a and 138b. These computational studies focused on ligands that could be accessed from a scaffold of 1,10-phenanthroline by reactions using SmI₂ (Chapter 2). The interesting result of this initial screening was a vast difference in the predicted enantioselectivity for the hydroamination of 138a versus 138b when chiral complex Ag·103 was employed (Figure 3.23).
Establishing a standard protocol for the silver–1,10-phenanthroline-catalyzed hydroamination reaction has provided the basis for a variety of other projects. The immediate continuation of this work should focus on the exploration of other chiral ligands for the enantioselective desymmetrization of the synthesized amino-1,6-diynes (138a,b). Through the continued collaboration with the laboratories of Prof. Wiest, virtual screening will provide more ligands for use in the hydroamination. Employing those ligands that are predicted to give poor enantioselectivity in silico would also be desirable, in order to afford experimental verification of these computational methods.

Continuing syntheses of the family of prochiral diynes and employing those diynes in the enantioselective hydroamination would assist to further the determination of the optimal chiral ligands. By varying the branching positions in the diyne substrates, the effect of proximal chirality can be monitored. Efforts in the synthesis of these prochiral diynes could also provide interesting examples of new synthetic methodologies.

Only the surface has been scratched in the exploration of tandem reactions involving the alkyne hydroamination. A thorough study of the employment of various
metals in this reaction could result in the accomplishment of the desired hydroamination/conjugate addition tandem sequence. Other reactions could also be utilized to form a chiral center, such as attaching a pendant alkene, allene, or other potential reactive sites for the intermediate alkenyl metal species. Further development of tandem processes would expand the range of chiral products available from alkyne hydroaminations.

Finally, the natural conclusion of this project will incorporate the exploration of other forms of unsaturated C–C bonds besides alkynes in the hydroamination. Instead of searching for routes to circumvent the limitation of the standard alkyne hydroamination, employing alkenes, allenes, and dienes would provide chiral compounds directly without the need for desymmetrization of more elaborate polyfunctional substrates. Silver has no precedence for the alkene hydroamination, but many late transition metals, known to complex with 1,10-phenanthroline ligands, have been used efficiently in the alkene hydroamination (Section 1.4). The use of carbamates and sulfonamides is also a common practice in this field and may be required for initial examination of developing this methodology with late transition metals. The majority of nitrogen protecting groups employed in this area are removed under acidic conditions. Therefore, the development of an alkene hydroamination based around the base-labile trifluoroacetamide protecting group would present an interesting alternative. A variety of potential projects emanate from the foundation established in the Ag-catalyzed hydroamination of aminoalkynes.
CHAPTER 4

SYNTHESIS OF UNNATURAL AMINO ACID DERIVATIVES

4.1 Utility of Unnatural Amino Acids and Previous Work by Collaborators

The syntheses of natural and unnatural amino acids have been the focus of many scientific studies, because of their importance as the building blocks of life.\textsuperscript{119} \(\beta\)-Hydroxy-\(\alpha\)-amino acids are an important class of compounds, because they are present in nature, in both the common amino acids (such as serine and threonine), as well as some natural products.\textsuperscript{120-122} Our synthesis of \(\beta\)-hydroxy-\(L\)-methionine was originally undertaken to create a chirospecific amino acid for inclusion in a specific peptide.

Human Leukocyte Antigen-A2 (HLA-A2) is an antigen-presenting protein present in most cells. HLA-A2 is a class I major histone compatible (MHC) complex that is composed of three components consisting of a heavy chain, \(\beta\)-2 microglobulin, and a variable antigenic peptide (Figure 4.1). The heavy chain forms a binding interface that surrounds the antigenic peptide with two \(\alpha\)-helices and a \(\beta\)-sheet floor (Figure 4.2). The immunogenic potency of the antigen is determined largely by its binding within the heavy chain.\textsuperscript{123} Studies of HLA-A2 in the area of cancer research have shown that one of the specific antigenic peptides known as gp100\textsuperscript{209-217}, has a relatively fast dissociation from the HLA-A2 protein.\textsuperscript{124} A more efficient binding of this antigen to the cell through
stronger interactions with HLA-A2 could allow for easier recognition of the antigen by cytotoxic t-cell receptors (cTCR), assisting in the termination of the tumor cell.

Parkhurst et al. have shown that slower dissociation was possible by changing the amino acid at position 2 of the peptide, considered to be the anchor due to the close association of this residue of the antigenic peptide to the eponymous P2 pocket of the heavy chain.\textsuperscript{124} The wild-type peptide contains threonine at position 2, but when position 2 was modified to a methionine residue, there was an enhanced stability as well as immunogenicity.

\textbf{Figure 4.1 Crystal Structure of HLA-A2}

The crystal structure of the HLA-A2 complex, with the heavy chain shown in orange, \(\beta\)-2 microglobulin in blue, and the antigenic peptide, represented by gp100\textsubscript{209-217}, in ball and stick notation.
Figure 4.2 Crystal Structure of Antigenic Peptide within Heavy Chain Binding Surface

A top on view of the crystal structure of gp100\textsubscript{209-217}, bound in the heavy chain of HLA-A2 (orange), showing the two α-helices and the β-sheet floor. β-2 Microglobulin and the α3 domain of the heavy chain have been omitted for clarity.

Crystal structures of both the HLA-A2 protein bound to the wild-type gp100\textsubscript{209-217} and HLA-A2 protein bound to the modified peptide (T2M) were solved by Baker and coworkers at the University of Notre Dame (Figure 4.3). Superimposition of the two crystal structures around the P2 pocket of the heavy chain, as well as thermodynamic characterization allowed for further information as to the mechanism of enhanced stability. Our collaborators have shown that while the modified peptide demonstrated a more entropically unfavorable dissociation, the loss of hydrogen bonding capabilities decreased its enthalpic stability. It has been hypothesized that the increased hydrophobicity of the modified peptide, due to the sulfide-containing side chain, allowed for this enhanced effect.
Figure 4.3 Crystallographic Superimposition of the Native and Modified Peptides

Image of the P2 pocket appears as a cross-eye stereoview, with the peptide backbone in yellow, the carbon constituents of threonine in gray, the oxygen of threonine in red, the side chain of methionine in blue, the Glu 63 residue of the MHC complex in red, and the rest of the MHC complex in gray.

The current hypothesis is that an anchor residue that contains both a hydrophobic side chain and hydrogen bonding capabilities would provide a more stably bound antigen for immunotherapy. It is hypothesized that the optimum amino acid to fit this description would be β-hydroxy-methionine. This unnatural amino acid would provide a synergistic effect by incorporating properties of both threonine and methionine. Therefore, synthesis of β-hydroxy-methionine was undertaken to allow for the continued exploration of the effect that the amino acid at position 2 had on the binding abilities of the peptide. The β-hydroxy derivatives of leucine and norleucine were also targeted for this hypothesis, because both of these unnatural amino acids have similar hydrogen bonding capabilities, but offer varying degrees of hydrophobicity.

4.2 First Helquist Strategy – Aldol Chemistry

Although 3-hydroxy-methionine has been prepared in the past, the specific stereoisomer we sought had not been reported. The work of Roemmele and Rapoport
manipulated chemical transformations to form the three isomer of a D-methionine backbone. However we needed to access the other enantiomer of this unnatural amino acid derivative for our studies. Based upon the precedence for mildly syn-selective aldol reactions under phase transfer catalysis by Corey and coworkers, our retrosynthetic analysis began with the disconnection shown in Figure 4.4. The greatest benefit of this disconnection was the overall convergency. With the amino acid side chain coming from the aldehyde in the aldol reaction, three desired amino acids could be formed simply from the reaction of three different aldehydes. The drawback to this route was the need to synthesize the catalyst itself (78).

$\text{ent-92} \quad \text{165} \quad \text{166}$

Figure 4.4 Retrosynthetic Analysis of 3-Hydroxy Methionine via an Aldol Route

It was not known what effect the employment of (methylthio)acetaldehyde (165) would have on the system. For that reason, along with the ultimate desire to synthesize unnatural amino acids for comparative purposes, initial work aimed at the use of butyraldehyde and 2-methylpropanal in this aldol reaction, as a means to synthesize 3-hydroxy-norleucine and 3-hydroxy-leucine respectively. The synthetic route began with the synthesis of the necessary phase transfer catalyst 78 (Figure 4.5).
Figure 4.5 Synthesis of Cinchona-Derived Phase Transfer Catalyst

Conditions: (a) 9-(chloromethyl)anthracene, PhCH$_3$, reflux, 2 h (99% yield); (b) BnBr, aq KOH/CH$_2$Cl$_2$ (1/1), 25 °C, 4 h (41% yield); (c) Amberlyst A-26(OH) ion exchange resin, MeOH, 1 N HF (91% yield).

Reaction of commercially available (–)-cinchonidine (167) with 9-(chloromethyl)anthracene gave the quaternary ammonium salt 168 in good yield. The alcohol of 168 was benzyl protected by reaction with benzyl bromide to give the quaternary ammonium bromide 169, albeit in poor yields. This bromide was converted to the hydrogen difluoride salt 78 by passage of the material through an ion exchange resin, with elution by 1 N HF solution.

With the catalyst complete, synthetic efforts turned towards the required substrates. The nucleophile necessary for the aldol reaction was a silyl ketene acetal derived from the tert-butyl glycinate hydrochloride (170) (Figure 4.6).$^{82}$ Transimination of 170 with benzophenone imine formed the desired glycyl imine 166. However,
formation of silyl ketene acetal 171 by deprotonation of imine 166 with lithium diisopropylamide and trapping with a chlorosilane was never observed. Initially, trimethylchlorosilane was used as the trapping electrophile; however, due to concerns of instability; the more robust tert-butyldimethylchlorosilane was employed. Neither electrophile allowed for the isolation of silyl ketene acetal 171. Only starting material was isolated using a variety of deprotonation conditions. While there is little doubt that the deprotonation occurred, it is likely that protonation of the enolate occurred sometime either during the addition of the electrophile or during work up and isolation techniques. Attempts to trap the enolate using methyl iodide as an electrophile were also inconclusive. The previous report of the preparation of 171 by this method notwithstanding, we can only conclude that some unknown cause of hydrolysis prevented us from obtaining the desired ketene acetal. This inability to isolate the necessary silyl ketene acetal, along with the necessity of synthesizing the cinchona-derived catalyst in this route, led us to pursue a different means to form the desired amino acid derivatives.

**Figure 4.6 Formation of Silyl Ketene Acetal for Enantioselective Aldol Reaction**

Conditions: (a) benzophenone imine, CH₂Cl₂, 25 °C, 24 h (96% yield); (b) i. LDA, THF, 0 °C, 1 h, ii. TMSCl or TBSCl, 25 °C, 3 h.
4.3 Second Helquist Strategy – Asymmetric Dihydroxylation and Aminohydroxylation

The use of asymmetric aminohydroxylation and its predecessor, the asymmetric dihydroxylation, have both been demonstrated as a concise way of synthesizing unnatural amino acid derivatives.\textsuperscript{126} We envisioned the desired unnatural amino acids for this study could also be synthesized the asymmetric dihydroxylation (Figure 4.7).

Retrosynthetically, the reduction of an azide would yield the requisite amino group. The azide could be accessed through a nucleophilic ring opening of a cyclic sulfonate, which in turn was formed from the diol. A \textit{syn}-dial would result from the dihydroxylation reaction, therefore in order to arrive at the necessary \textit{syn}-amino acid, a \textit{Z}-olefin is needed. This olefin could be formed from a \textit{Z}-selective Horner-Wadsworth-Emmons (HWE) reaction starting with an aldehyde that contains the appropriate \( R \) group for incorporation as the side chain of the amino acid.

Figure 4.7 Retrosynthetic Analysis for the Asymmetric Dihydroxylation Route
The necessary Z-olefins, 173 and 175, were synthesized for possible inclusion in the dihydroxylation route (Figure 4.8). The synthesis of olefin Z-173 began with the commercially available butyraldehyde (172). A Z-selective Horner-Wadsworth-Emmons reaction was performed using standard conditions to provide Z-173 in 68% yield and in a 4:1 (Z:E) ratio, as measured by 1H NMR of the crude reaction mixture.

(Methylthio)acetaldehyde was not commercially available; therefore the synthesis of Z-175 began with the (methylthio)acetaldehyde dimethyl acetal (174). The best conditions for the conversion of the dimethyl acetal into the aldehyde were found to be reaction with p-TsOH at room temperature for 8 h. Separation of the aldehyde from the acetal starting material, however, was problematic, resulting in poor yields. The employment of methylthioacetaldehyde in the HWE reaction provided α,β-unsaturated ester Z-175 in low yield and with low 2:1 (Z:E) selectivity.

![Chemical structures](image)

**Figure 4.8 Preparation of Z-Olefins for Unnatural Amino Acid Targets**

Conditions: (a) (CF₃CH₂O)₂P(O)CH₂CO₂CH₃, NaHMDS (2.0 M in THF), THF, −78 °C, 3 h (68% yield, Z:E = 4:1); (b) p-toluenesulfonic acid (2 equiv), 25 °C, 8 h (46% yield); (c) (CF₃CH₂O)₂P(O)CH₂CO₂CH₃, NaHMDS (2.0 M in THF), THF, −78 °C, 3 h, (13% yield, Z:E = 2:1).
Although we obtained the substrates required for the desired dihydroxylation, we did not pursue their use further. Instead, the route to our desired amino acids could be accomplished more concisely via the asymmetric aminohydroxylation (Figure 4.9). The aminohydroxylation could insert both the needed amino and hydroxy functionality in one step with the proper stereochemistry. Conditions have been reported to access the β-hydroxy-α-amino acids as well as the regioisomeric α-hydroxy-β-amino acids. For this synthesis, the E-olefin would be necessary for the L-threo isomers of the target amino acids, once again due to the syn-addition inherent in this osmium-catalyzed transformation. While this presented a vastly shorter synthesis of the amino acids, there were also a few drawbacks. Both the aminohydroxylation and the dihydroxylation incorporate the amino acid side chains in the olefination step, eliminating any possible convergency for the synthesis of the three potential targets. There also was little precedent for the aminohydroxylation of aliphatic α,β-unsaturated esters, let alone esters that contained a sulfide. Despite these potential hindrances, this route was considered an attractive alternative to the previously studied aldol reaction.

\[
\begin{align*}
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&\text{OH} \\
&\text{O} \\
&\text{NH}_2 \\
\end{align*}
\begin{align*}
\iff &\text{R} \quad \text{OR'} \\
&\text{OH} \\
&\text{O} \\
&\text{NHPG} \\
\end{align*}
\begin{align*}
\iff &\text{R'} \quad \text{OH} \\
&\text{O} \\
&\text{KH} \\
\end{align*}
\]

\textbf{Figure 4.9 Retrosynthetic Analysis for the Asymmetric Aminohydroxylation Route}
In order to pursue the asymmetric aminohydroxylation and to obtain amino acids of the proper configuration, the $E$-olefins of the necessary $\alpha,\beta$-unsaturated esters needed to be prepared (Figure 4.10). (Methylthio)acetaldehyde (165) was prepared as demonstrated above (Figure 4.8). Under standard conditions for an $E$-selective HWE reaction, ethyl 2-hexenoate (177) and ethyl 3-methyl-2-pentenoate (178) were formed in 95 and 97% yield respectively. In both cases, the $E$-isomer was the only isomer formed as determined by $^1$H NMR of the crude reaction mixture. The aldehyde 165 did not seem to tolerate the standard conditions for the HWE reaction, as only a small amount of product was observed in the crude $^1$H NMR. Mild, zinc-promoted HWE reaction conditions, developed by Dr. Douglas Schauer of the Helquist laboratory, were also used in attempts to form 179; however, product formation remained minimal. In order to further the development of an aminohydroxylation reaction to synthesize 3-hydroxy-methionine, an alternative route to $\alpha,\beta$-unsaturated ester 179 was sought (Figure 4.11).

![Figure 4.10 Preparation of $E$-Olefins for Unnatural Amino Acid Targets](image)

**Figure 4.10 Preparation of $E$-Olefins for Unnatural Amino Acid Targets**

Conditions: (a) $((\text{CH}_3)_2\text{CHO})_2\text{P(O})\text{CH}_2\text{CO}_2\text{CH}_3$, NaHMDS (2.0 M in THF), THF, –78 °C, 5 h (90-95% yield, $E:Z = >95:5$); (b) $((\text{CH}_3)_2\text{CHO})_2\text{P(O})\text{CH}_2\text{CO}_2\text{CH}_3$, Zn(OTf)$_2$ (2.2 equiv), DBU (4 equiv), TMEDA (1.2 equiv), THF, 25 °C, 16 h.
Instead of the olefination reaction as the route to unsaturated ester 179, an approach in which the methylthio group was added via a substitution of the bromine atom in ethyl 4-bromo-2-butenoate (180) was attempted (Figure 4.11). Reaction of bromocrotonate 180 with dimethyl sulfide provided sulfonium bromide 181 in 75% yield. Further reaction of sulfonium bromide 181 with dimethyl sulfide at elevated temperatures and in a sealed tube provided the desired ethyl (2E)-4-(methylthio)butenoate (179) in 62% yield.

![Chemical Reaction](image)

**Figure 4.11 Alternative Synthesis of an Unsaturated Ester for the Route to Methionine**

Conditions: (a) dimethyl sulfide (2.5 equiv), acetone, 25 °C, 48 h (75% yield); (b) dimethyl sulfide (5 equiv), DMSO, 60 °C, sealed tube, 48 h (62% yield).

Now that a method for the formation for 179 had been successfully developed, attempts to improve the synthesis were made (Figure 4.12). The ester moiety would eventually need to be removed, and milder cleavage conditions are known for methyl esters when compared to ethyl esters. For that reason we elected to synthesize the corresponding methyl ester of 179. Owing to the similar reaction conditions to form sulfonium bromide 181 and the desired neutral ester, the synthesis shown above was shortened to provide the desired unsaturated ester E-175 in one step. Beginning with methyl 4-bromo-2-butenoate (182), this more direct route provided the desired ester E-175 in 95% yield directly from commercial products.
Figure 4.12 Shortened Synthesis to the Methyl Ester for the Route to Methionine

Conditions: (a) dimethyl sulfide (6 equiv), DMSO, 60 °C, sealed tube, 48 h (95% yield).

With the desired α,β-unsaturated esters in hand, attempts at the aminohydroxylation reaction commenced. Initial reactions were run on the aliphatic unsaturated esters 177 and 178 (Figure 4.13). Conditions for the desired configurations were reported by Tao et al. in 1998.\textsuperscript{90} Though these conditions were primarily optimized for cinnamate derivatives, it was reported that aliphatic derivatives also led to the desired 2S,3R enantiomer selectively. These conditions called for the use of tert-butyl hypochlorite to generate a reactive intermediate from benzyl carbamate in situ. The tert-butyl hypochlorite was prepared from commercial bleach, 2-methyl-2-propanol, and acetic acid. Reaction of t-butyl hypochlorite with benzyl carbamate formed the N-chloro amide sodium salt, a nitrene equivalent. This nitrene could then bind to the osmium metal center for reaction with the olefin. Common side products do arise from this reaction, including the corresponding dihydroxylation products, as well as the 3-amino-2-hydroxy regioisomers. These side products, along with an excess of unreacted benzyl carbamate, made purification of these protected amino acids problematic. Ethyl N-(benzyloxycarbonyl)-3-hydroxy-norleucine (183) was synthesized in 24% yield using these conditions; however attempts to remove the Cbz protecting group via hydrogenation were unsuccessful. Ethyl 3-hydroxy-leucine hydrochloride (186) was
isolated in 24% yield by running an acidic deprotection on the crude reaction mixture of the aminohydroxylation reaction of 178.

Figure 4.13 Aminohydroxylation to Form Benzyl Carbamate-Protected Amino Acids

Conditions: (a) benzyl carbamate (3 equiv), t-BuOCl (3 equiv), 0.67 N NaOH/n-PrOH, (1/3), (DHQD)$_2$AQN (4 mol %), K$_2$[OsO$_2$(OH)$_4$] (4 mol %), 25 °C, 1.5 h (24% yield of 183); (b) 5% Pd/C, H$_2$, EtOH, 25 °C, 16 h; (c) 3 N HCl, EtOH, 25 °C, 3 h (24% yield of 186 over two steps).

To test whether the formation of nitrene from benzyl carbamate was causing low yields, commercially available nitrene equivalent chloramine-T was employed in the aminohydroxylation (Figure 4.14). In a reaction of chloramine-T with pentenoate 178, the protected amino acid 187 was synthesized in 82% yield. However, the tosyl protecting group proved too difficult to remove. Standard reductive conditions had been reported to not be tolerant of proximal hydroxyl groups, and a mixture of HBr in CH$_3$CO$_2$H was also unsuccessful. While reaction with chloramine-T provided a reasonable method for access to the protected forms of the desired amino acid 187, deprotection was necessary in order to accommodate the ultimate goal of using this peptide in immunological testing.
Figure 4.14 Employment of Chloramine-T in the Aminohydroxylation Reaction

Conditions: (a) chloramine-T monohydrate (1.5 equiv), CH₃CN/H₂O, (1/1), (DHQD)₂AQN (4 mol %), K₂[OsO₂(OH)₄] (4 mol %), 25 °C, 16 h (82% yield); (b) phenol (30 equiv), 30% HBr in CH₃CO₂H, EtOAc, 25 °C, 16 h.

Any attempts at employing the sulfide-containing unsaturated ester $E-175$ or its precursors in the aminohydroxylation resulted in complex mixtures with no evidence of the desired products. It was thought that the sulfide moiety would not be tolerated in the oxidizing conditions of the aminohydroxylation or the dihydroxylation. For this reason, the aminohydroxylation was attempted on methyl 4-bromo-2-butenoate (182). However this also did not provide the desired amino ester. Though the aminohydroxylation reaction had provided small quantities of the aliphatic amino acid derivatives, its lack of amenability in the synthesis of the keystone of this study, β-hydroxy methionine, ultimately necessitated the search for another route.

4.4 Final Helquist Strategy – Via Vinylglycine

Due to past failures, the new route attempted was inspired solely by the desire to synthesize β-hydroxy methionine. Where the sulfide moiety had been viewed as a hindrance in past, it would now be fully exploited for our purpose. This route would make use of chiral pool synthesis, in lieu of the enantioselective catalysis discussed in Sections 4.2 and 4.3. The retrosynthetic analysis of the final route to (2S,3S)-3-
hydroxymethionine is shown in Figure 4.15. Vinyl glycine,\textsuperscript{130} an intermediate used in previous reports of 3-hydroxy amino acid syntheses, would serve as the lynchpin of this new route. Making use of the nucleophilicity of sulfur through an epoxide-opening reaction would provide the necessary side chain for our target amino acid. The stereochemistry of the unnatural amino acid could be determined through the influence, in a diastereoselective manner, of the chiral starting material on the epoxidation of vinyl glycine. Large scale synthesis of vinyl glycine has been reported from the elimination of a $\gamma$-sulfoxide. The starting material could therefore be L-methionine, as our target bears the configuration of the natural methionine compound.

The methionine methyl ester hydrochloride (189) is available commercially and provided one of the necessary protecting groups for the synthetic pathway (Figure 4.16). Protection of the amino group with benzyl chloroformate provided the carbamate 190 in excellent yields by crystallization from hexanes. Oxidation of the sulfide to sulfoxide 191 proceeded in high yields, and there was no observed over-oxidation to the sulfone. The sulfoxide 191 was then heated to reflux as a suspension in mesitylene to induce the elimination. Chromatography afforded 52\% of the protected vinyl glycine \textit{ent}-81, a $\beta,\gamma$-unsaturated ester. The \textit{E} and \textit{Z} isomers of the $\alpha,\beta$-unsaturated methyl \textit{N}-
(benzyloxycarbonyl)-2-amino-2-butenoate were the major side products of this reaction. Oxidation of \textit{ent}-81 with \textit{meta}-chloroperoxybenzoic acid provided the desired isomer of \textit{ent}-82 in 60\% yield and a 4:1 (\textit{syn}:\textit{anti}) ratio. The \textit{syn} and \textit{anti} isomers of these previously reported compounds were assigned by comparison of the $^1$H NMR of the crude mixture with the literature data.\textsuperscript{91} This selectivity could be due to the Henbest effect, where the carbamate serves to guide the facial selectivity of the oxidation.

![Chemical Structures]

\textbf{Figure 4.16 Final Synthesis of 3-Hydroxy-Methionine}

Conditions: (a) benzyl chloroformate, NaHCO$_3$ (5 equiv), EtOAc/H$_2$O (1/1), 25 °C, 3 h (96\% yield); (b) NaIO$_4$, MeOH/H$_2$O (1/1), 0 °C, 4 h (98\% yield); (c) mesitylene, 120 °C, 24 h (52\% yield); (d) \textit{m}-CPBA (7 equiv), CH$_2$Cl$_2$, 0 to 25 °C, 48 h (67\% yield, \textit{syn}:\textit{anti} = 4:1); (e) NaSCH$_3$ (2.2 equiv), NH$_4$Cl (1.8 equiv), MeOH, 0 °C, 2 h (68\% yield); (f) 6 N HCl, 100 °C, 2 h; (g) Fmoc-OSu, NaHCO$_3$ (8 equiv), THF/H$_2$O (1/1), 25 °C, 24 h (40\% yield).
The epoxide (ent-82) and its enantiomer have been synthesized previously for the purpose of arriving at unnatural amino acids. Work has been done with nitrogen nucleophiles and sulfur nucleophiles; however sulfur anions have been restricted to thiophenoxide. The use of a thioalkoxide has not been previously reported. Epoxide-opening with sodium thiomethoxide would provide the necessary side chain for a methionine derivative. Epoxide ent-82 was treated with NaSCH₃ in methanol; however initial reactions only provided yields of protected methionine derivative 192 in less than 30%. In previous work, it was noted that a major side product would form as a result of a base-induced cyclization, which could be limited by the addition of ammonium chloride to the reaction mixture. We also sought to limit the base-induced cyclization, and when ammonium chloride was added to our reaction, yields of 192 improved from less than 30% to 68%.

Protected methionine derivative 192 was only a few deprotection steps away from the chosen amino acid substrate. It was desirable to have this unnatural amino acid (ent-92) ready-made for inclusion into a peptide. Typical synthetic procedures for peptides make use of base-labile protecting group on the nitrogen. For this reason, as well as its prominence in peptide chemistry, the 9-fluorenylmethyloxycarbonyl (Fmoc) group was selected. The methyl ester and the carbamate of methionine derivative 192 were both deprotected in one step by heating in 6 N HCl to give amino acid ent-92. Reprotection as the Fmoc-derivative through the use of Fmoc-OSu, was done on the crude ent-92 without the need for purification. This protection step gave the preferred amino acid derivative 193 in 40% yield and ready for use in a form compatible with standard peptide synthesis conditions.
4.5 Future Work

The immediate direction of this project will be to incorporate the synthetic amino acid into an antigenic peptide and to determine the effect it may have on antigen binding to the HLA-A2 protein. Should more data return from that study, further alterations to peptide structure could be possible through the synthesis of other unnatural amino acids. While it is thought that 3-hydroxy methionine would be the optimal amino acid anchor residue, other modifications may be necessary to better enable peptide binding.

While the desired (2S,3S)-3-hydroxymethionine was formed, the ultimately successful route is only amenable to amino acid derivatives that contain nucleophilic side chains. This route also makes use of a less efficient means for incorporation of chirality, as it would be more desirable to develop a method that only uses a catalytic amount of chirality to form any new chiral centers. In order to synthesize the β-hydroxynorleucine and β-hydroxyleucine amino acids, an adaptation of one of the previous discussed routes would need to be explored. Asymmetric aminohydroxylation reactions are not as reliable as their counterparts the asymmetric dihydroxylation reactions. To provide good yields and predictable selectivity in the formation of the other desired amino acid derivatives, the route shown in Figure 4.5, employing the Z-olefins such as 173, would perhaps be the most efficient. This route would limit the formation of side products in the key dihydroxylation steps, and all other steps in this route are known to proceed with high yields. It would also be beneficial to revisit the aldol approach, the most highly convergent and researched of all of the routes discussed. Ultimately, following this pathway could allow access to the desired β-hydroxy-α-amino acids in the highest efficiency.
CHAPTER 5

CONCLUSIONS

5.1 Summary

The work in this thesis has established a protocol for the silver–1,10-phenanthroline-catalyzed intramolecular alkyne hydroamination. This protocol has been successfully extended to the desymmetrization of prochiral aminodiynes, providing access to products that contain chiral centers. Discovery and optimization of a facile aerobic oxidation of 2-benzyl pyrroline derivatives has also provided a novel two-step process for the synthesis of complex molecules. In the case of the desymmetrized imine products, further elaboration demonstrated the complete differentiation of once identical alkyne moieties.

This thesis also demonstrated the continuation of SmI$_2$-promoted coupling reactions developed by the Helquist laboratories, to encompass the reaction of 2,2’-bipyridine and epoxides. Initial attempts to develop SmI$_2$-catalyzed protocol through the use of Mischmetall as a coreductant have not been successful; however access to a new class of ligands could prove valuable in future enantioselective transformations.

The synthesis of β-hydroxy-methionine experienced many difficulties from the beginning. The route that was ultimately successful, involved the use of vinyl glycine as
the key intermediate. This allowed for the exploitation of the nucleophilicity of the methylthio side chain to reach the desired structure. The successful synthesis has provided the desired amino acid residue as the Fmoc-protected derivative, ready-made for inclusion into the mutant antigenic peptide.

5.2 Future Directions

The establishment of the methodology for the silver–1,10-phenanthroline-catalyzed hydroamination could open up a variety of avenues for future research. Because of the robust nature of the catalysts, and the relative tolerance of late transition metals to a wide array of functional groups, silver catalysis in the realm of hydroamination could easily be expanded to more complex substrates. While many other catalysts have been demonstrated as active catalysts in the hydroamination of a variety of olefins, silver maintains a high selectivity for alkynes. The pyrrolizidine alkaloids (Figure 5.1) would be ideal targets for these silver-catalyzed conditions. This class of alkaloids often contains a variety of oxygen-containing functionality surrounding a bicyclic nitrogen core. The synthesis of similar compounds could begin with substrates not much more complex than those studied in this account (Figure 5.2).

![Figure 5.1 Core Structure of a Pyrrolizidine Alkaloid](image-url)
In addition to the hydroamination of alkynes leading to achiral products, the strategies discussed in this research to access chiral products from alkyne hydroamination are also worthy of further pursuit. Tandem reactions perhaps represent the most intriguing of these possibilities. The alkenyl-metal intermediate formed in the hydroamination reaction could be further exploited by reaction with an electrophile. A variety of possibilities are opened up for both chiral and achiral variants, as many reactions of alkenyl-metal species are known. If a prochiral electrophile were used, the opportunity to develop enantioselective reactions becomes available. The ability to employ aldehydes, ketones, and even epoxides as electrophiles, allows the chance to explore many potential reactions (Figure 5.3).

Figure 5.2 Silver-Catalyzed Hydroamination Toward the Pyrrolizidine Alkaloid Core
Potential conditions: (a) Ag(phen)$_2$OTf (10 mol %), CH$_3$CN, 70 °C.

Figure 5.3 Potential Silver-Catalyzed Tandem Reaction with Chirality Transfer
Potential conditions: (a) Ag(phen)$_2$OTf (10 mol %), CH$_3$CN, 70 °C.
The optimization of alkene hydroaminations has been an ongoing process for many research groups (Section 1.4). While silver catalysis may not be an option for olefin hydroaminations, one potentially new development in this arena could stem from the use of a novel protecting group. One drawback of late transition metal-catalyzed alkene hydroaminations is that a protecting group (i.e. carbamate or sulfonamide) is often necessary in order for the desired transformation to occur. A potential application of the trifluoroacetamide derivative used throughout Chapter 3 would be as both a protecting group and an activating group in the alkene hydroamination. This base-labile group would offer a complement to the current methods employed for this reaction.

![Figure 5.4 Use of the Trifluoroacetamide as a Novel Protecting Group in the Alkene Hydroamination](image)

**Figure 5.4 Use of the Trifluoroacetamide as a Novel Protecting Group in the Alkene Hydroamination**

Potential conditions: (a) Au(phen)Cl₂NO₃ (10 mol %), CH₃CN, 70 °C; (b) 1 N NaOH, MeOH, 25 °C, 16 h.

Finally, the development of more efficient means to access chiral ligands has been a focus of this thesis. The SmI₂-promoted coupling of aldehydes, ketones, and epoxides to 1,10-phenanthroline and 2,2′-bipyridine has been well developed by the Helquist laboratory. However, the aspiration remains for this reaction to be converted into one that is catalytic in SmI₂. While Mischmetall has not yet provided this outcome, the use of other stoichiometric reductants has been published for related reactions. The use of magnesium metal has been discovered to allow for a catalytic turnover of SmI₂ in a recent report of a pinacol coupling.¹⁰⁷ This coreductant should also be explored as it relates to the synthesis of 1,10-phenanthroline and 2,2′-bipyridine ligands. The
development of another core ligand scaffold, the 3,3′-disubstituted-2,2′-bipyridine ligands, could also be explored for ligand design and enantioselective reactions (Figure 5.5). While it is yet unknown whether the rigid structure of phenanthroline, or the flexible structure of bipyridine allow for the optimal enantioselection, the structures related to the scaffolds of 3,3′-disubstituted-2,2′-bipyridine ligands could offer benefits of both scaffolds. The use of this ligand class could also be explored in the SmI$_2$-promoted coupling reactions as a further test to discover the reasons for the higher yields observed when phenanthroline is used in this reaction as compared to 2,2′-bipyridine.

![Figure 5.5 Comparison of Three Bidentate Nitrogen Ligand Classes](image)

The research performed in this document has provided access to many future directions of research. The further investigation of hydroaminations certainly warrants attention, as does the development of improved reactions conditions for the synthesis of chiral ligands. All of these developments could assist the chemical community with increased access to enantioselective catalysis.

The immediate future of the synthetic endeavors into β-hydroxy-methionine is the incorporation of this amino acid into the antigenic peptide of HLA-A2. Once this peptide is synthesized, the effect this residue has on its stability and immunogenicity can be measured. From this new information, alterations to this amino acid or synthesis of
others may become necessary in order to establish the optimal residue for the anchor position of the antigenic peptide.
CHAPTER 6

EXPERIMENTAL SECTION

6.1 General Methods

All reactions were carried out under an atmosphere of argon with magnetic stirring at room temperature unless otherwise noted. Final product solutions were dried over sodium sulfate, decanted, and removed under reduced pressure with a rotary evaporator. When necessary, reactions were heated above 25 ºC with an oil bath or heating mantle. All organic starting materials, reagents, and solvents were purchased from Aldrich Chemical Co. or Acros Organics and were used without further purification unless otherwise noted. All metallic salts were purchased from Strem Chemicals Inc. and used without further purification. Acetonitrile-\(d_3\) and dimethylsulfoxide-\(d_6\) were purchased from Cambridge Isotope Laboratories (99.8+ atom % D). THF was purified by passage through a solvent purification system (Innovative Technology). Methylene chloride was purified by distillation from calcium hydride. Flash chromatography was performed using silica 60Å (230-400 mesh) or basic Al\(_2\)O\(_3\) (70-230 mesh). Medium pressure liquid chromatography (MPLC) was carried out using Biotage prepacked silica cartridges. Triethylamine was distilled prior to use from KOH and stored over KOH. Iodobenzene was washed with Na\(_2\)S\(_2\)O\(_3\), and distilled from CaCl\(_2\). All \(^1\)H NMR spectra
were obtained on a Varian instrument at 500 MHz or at 300 MHz. $^{13}$C NMR spectra were measured at 125 MHz on a Varian instrument. Chemical shifts ($\delta$) for $^1$H and $^{13}$C are referenced to internal solvent resonances and reported relative to Me$_4$Si. Yields of hydroamination reactions run on NMR-scale were determined by NMR integration using 1,3,5-trimethylbenzene (mesitylene) as an internal standard via comparison of the most downfield methylene proton signal in the cyclized products vs. the aromatic mesitylene signal. Extended relaxation times were required in order to obtain accurate results. IR spectra were measured on a Perkin Elmer Paragon 1000 FT-IR spectrometer. HRMS data were recorded on a JEOL JMS-AX505HA double sector mass spectrometer using the FAB technique.

\[
\begin{align*}
\text{N} & \text{N} \\
\text{HO} & \text{HO} \\
\text{107} & \text{110}
\end{align*}
\]

6,6′-Bis((R)-2-hydroxybutyl)-2,2′-bipyridine (107) and 6-((R)-2-hydroxybutyl)-2,2′-bipyridine (110). To a solution of dry 2,2′-bipyridine (0.312 g, 2.0 mmol), Mischmetall (0.177 g, 1.26 mmol), and (R)-(+)1,2-epoxybutane (0.576 g, 8.0 mmol) in dry THF (5 ml), a solution of samarium(II) diiodide (0.1 M in THF, 100 mL, 10 mmol) was added via syringe. The reaction mixture was stirred and heated to 50 °C for 48 h. The reaction mixture was brought to 25 °C and acidified with the slow addition of 1 N HCl (25 mL). The solution was neutralized by the addition of sat. NaHCO$_3$ solution (100 mL), and then extracted with dichloromethane (3 × 75 mL). The organic layer was washed with brine (150 mL) and dried over magnesium sulfate. Solvent was removed
under reduced pressure and ligand 110 was then isolated by column chromatography (20% EtOAc:Hexanes) on Biotage KP-NH column as yellow oil (0.09 g, 0.39 mmol, 20% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.68 ppm (dd, $J = 4.79$, 0.80 Hz, 1 H, Py(6′)), 8.29 (d, $J = 7.78$ Hz, 2 H, Py(3, 3′)), 7.71 - 7.85 (m, 2 H, Py(4, 4′)), 7.28 - 7.35 (m, 1 H, Py(5′)), 7.18 (d, $J = 7.38$ Hz, 1 H, Py(5)), 5.44 - 5.58 (m, 1 H, -OH), 4.02 - 4.09 (m, 1 H, O-CH), 2.99 (dd, $J = 15$, 2.5 Hz, 1 H, Py-CHH), 2.90 (dd, $J = 15.5$, 9.5 Hz, 1 H, Py-CHH), 1.54 - 1.72 (m, 2 H, CH$_2$Me), 1.05 (t, $J = 7.48$ Hz, 3 H, -CH$_3$); $^{13}$C NMR (125 Hz, CDCl$_3$) δ 159.8 (C6, C6′), 149.3 (C2, C2′), 137.9 (C3), 137.1 (C3′), 123.9 (C4), 123.8 (C4′), 120.9 (C5), 119.1 (C5′), 72.4 (C-OH), 42.6 (C-Py), 30.0 (CH$_2$Me), 10.1 (CH$_3$); High resolution mass spectrum, calcd for C$_{14}$H$_{16}$N$_2$O(M$^+$) 229.1341, found 229.1368.

Isolation of ligand 107 was accomplished by column chromatography (40% EtOAc:Hexanes) on Biotage KP-NH columns as a yellow oil (0.060 g, 0.2 mmol, 10% yield, with approximately 5% impurity due to 110). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.15 ppm (d, $J = 7.78$ Hz, 2 H, Py(3, 3′)), 7.74 (t, $J = 7.78$ Hz, 2 H, Py(C4, C4′)), 7.16 (d, $J = 7.58$ Hz, 2 H, Py(5, 5′)), 4.00 - 4.07 (m, 2 H, O-CH), 3.01 (dd, $J = 14.5$, 2 Hz, 2 H, Py-CHH), 2.92 (dd, $J = 14.5$, 8.5 Hz, 2 H, Py-CHH), 1.52 - 1.69 (m, 4 H, -CH$_2$Me), 1.03 (t, $J = 7.48$ Hz, 6 H, -CH$_3$); $^{13}$C NMR (125 Hz, CDCl$_3$) δ 159.9 (C6, C6′), 154.6 (C2, C2′), 138.0 (C4, C4′), 124.0 (C3, C3′), 118.9 (C5, C5′), 72.4 (2 × C-OH), 42.6 (2 × C-Py), 30.0 (2 × HOCC), 10-1 (2 × CH$_3$); high resolution mass spectrum, calcd for C$_{18}$H$_{24}$N$_2$O$_2$(M$^+$) 301.1916, found 301.1898.
To a solution of 1,10-phenanthroline monohydrate (0.76 g, 3.8 mmol) in MeOH (10 mL) was added a solution of silver nitrate (0.65 g, 3.8 mmol) in H₂O (10 mL). The reaction mixture was stirred for 15 min. The reaction mixture was filtered, and the precipitate was collected and recrystallized from hot 20% nitric acid. The mixture was filtered again, and solids were dried under reduced pressure, resulting in 1.704 g of a wet yellow solid. The solid was dried over P₂O₅ for 24 h. Characterization of this compound had been completed by previous researchers and was not pursued in this report due to the better activity and easier handling provided by the Ag(phen)$_2$OTf (112) complex.
Ag(1,10-phenanthroline)$_2$OTf (112). To a solution of 1,10-phenanthroline monohydrate (0.200 g, 1.11 mmol) in MeOH (7 mL) was added a solution of silver triflate (0.285 g, 1.11 mmol) in H$_2$O (7 mL). The reaction mixture was stirred for 15 min. The reaction mixture was filtered and washed with MeOH. The solid was collected and dried over P$_2$O$_5$ for 24 h, to give the title complex (0.422 g, 0.903 mmol, 81% yield). ESI mass spectrum revealed parent peaks at 467 and 469 corresponding to the title compound with the two main isotopes of Ag (107 (52%) and 109 (48%)). MS/MS analysis revealed daughter peaks that corresponded to the complex with a single phen ligand (287 and 289 m/z); (lit.$^{133}$ MS).
**Ag(2,9-dimethyl-1,10-phenanthroline)OTf (114).** To a solution of 2,9-dimethyl-1,10-phenanthroline (neocuproine) (0.220 g, 1.06 mmol) in MeOH (7 mL) was added a solution of silver triflate (0.272 g, 1.06 mmol) in H₂O (7 mL). The reaction mixture was stirred for 15 min. The reaction mixture was filtered and washed with MeOH. The solid was collected and dried over P₂O₅ for 24 h, to give the title complex (0.115 g, 0.247 mmol, 23% yield); mass spectrum (FAB+) calcd for C₁₄H₁₂N₂Ag (M⁺) 315, found peaks at both 315 (monochelate) and 523 (bischelate). (lit.¹³³ MS).

**Pd(1,10-phenanthroline)(acac)₂ (116).** To a solution of dry 1,10-phenanthroline (0.083 g, 0.461 mmol) in dry CH₂Cl₂ (6 mL) was added palladium (II) acetylacetonate (0.127 g, 0.417 mmol). The color of the solution changed from yellow to red after 15 min. The reaction mixture was stirred at 25 °C for 2h. The solvent was removed to give a red solid (0.200 g, 0.413 mmol, 99% yield); mass spectrum (FAB+) calcd for C₁₂H₈N₂Pd (M⁺) 286.42 and found peak at 286. (lit.¹⁰¹ MS).
**Au(1,10-phenanthroline)Cl$_2$NO$_3$.** To a solution of 1,10-phenanthroline (0.200 g, 1.11 mmol) in EtOH (5 mL) was added a solution of sodium tetrachloroauroate dihydrate (0.170 g, 0.43 mmol) in EtOH (5 mL). The reaction mixture was heated to 100 °C for 4 h, during which the color of the mixture turned from yellow to deep orange. The reaction mixture was cooled to 25 °C, and the solvent was removed. The resulting solid was dissolved in H$_2$O (35 mL), and to this solution was added concd HNO$_3$ (10 drops), resulting in the formation of a yellow precipitate. The yellow solid was collected by filtration and dried over P$_2$O$_5$ for 20 h to give the title compound (0.215 g, 0.424 mmol, 98% yield). High resolution mass spectrum, calcd for C$_{12}$H$_8$AuN$_2$$^{3+}$(M$^+$ -Cl$_2$ - NO$_3$) 377.0353, found 377.0364; (lit.$^{102}$ HRMS).

**5-Chloro-1-phenyl-1-pentyne (118a).** To a solution of 1-bromo-3-chloropropane (2.93 g, 18.6 mmol) in dry THF (12 mL) was added lithium phenylacetylide (1.0 M in THF, 18.6 mL, 18.6 mmol) dropwise over 20 min while stirring at 0 °C. The reaction mixture was then warmed to 25 °C and refluxed for 12 h. After reflux, the reaction mixture was cooled to 25 °C and poured into H$_2$O (10 mL), and the layers were separated. The aq layer was extracted (3 × 10 mL) with diethyl ether. Combined organic phases were washed with brine (20 mL), dried over Na$_2$SO$_4$, and decanted. All residual
solvents were removed under reduced pressure by rotary evaporation. Vacuum distillation resulted in 3.233 g of a brown oil (97% yield): \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35 – 7.44 (m, 2H, Ph), 7.23 – 7.35 (m, 3H, Ph), 3.72 (t, \(J = 6.3\) Hz, 2H, CH\(_2\)Cl), 2.62 (t, \(J = 6.9\) Hz, 2H, CH\(_2\)C≡C), 1.98 – 2.18 (m, 2H, CH\(_2\)); (lit.\(^{42}\) \(^{1}\)H NMR).

\[
\begin{align*}
\text{Ph} & \quad \equiv \quad \text{Cl} \\
118b
\end{align*}
\]

6-chloro-1-phenyl-1-hexyne (118b).\(^{42}\) To a solution of 1-bromo-4-chlorobutane (14.8 g, 86.3 mmol) in dry THF (50 mL) was added lithium phenylacetylide (1.0 M in THF, 86.3 mL, 86.3 mmol) was added dropwise over 45 min while stirring at 0 °C. The reaction mixture was then warmed to 25 °C and refluxed for 12 h. After reflux, the reaction mixture was cooled to 25 °C and poured into H\(_2\)O (100 mL), and the layers were separated. The aq layer was extracted with diethyl ether (2 \times 75 mL). Combined organic phases were washed with of H\(_2\)O (100 mL), brine (100 mL), dried, and decanted. All residual solvents were removed under reduced pressure. Vacuum distillation resulted in a brown oil as the residual liquid (16.3 g, 82.0 mmol, 95% yield, with an approximate 10% impurity due to 1-bromo-4-chlorobutane). \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.35 – 7.44 (m, 2H, Ph), 7.23 – 7.35 (m, 3H, Ph), 3.61 (t, \(J = 6.6\) Hz, 2H, CH\(_2\)Cl), 2.47 (t, \(J = 7.2\) Hz, 2H, CH\(_2\)C≡C), 1.90 – 2.05 (m, 2H, CH\(_2\)), 1.65 – 1.85 (m, 2H, CH\(_2\)); (lit.\(^{42}\) \(^{1}\)H NMR).
*N-(5-Phenyl-4-pentynyl)phthalimide (119a).* To a solution of 5-chloro-1-phenyl-1-pentyne (118a) (0.939 g, 5.26 mmol) in *N,N*-dimethylformamide (DMF) (15 mL) was added NaI (0.079 g, 10 mol %) was charged, and the reaction mixture was stirred for 10 min. Solid potassium phthalimide (0.978 g, 5.26 mmol) was charged to the reaction flask in one portion. The reaction mixture was heated at 100 °C for 2 h. Mixture was cooled to 25 °C and partitioned between dichloromethane (25 mL) and water (25 mL), and the layers were separated. Aq layer was extracted (3 × 15 mL) with dichloromethane. Combined organics were washed with 1 N KOH (20 mL), H₂O (20 mL) and brine (20 mL) and dried. Solvent was removed under reduced pressure, resulting in a light brown solid. The solid was triturated with diethyl ether (3 × 20 mL), and a white solid (0.751 g, 2.60 mmol, 49% yield) was collected after filtration. ¹H NMR (300 MHz, CDCl₃) δ 7.84 (dd, *J* = 5.7, 3 Hz, 2H, Phthal), 7.7 (dd, *J* = 5.5, 3.3 Hz, 2H, Phthal), 7.25 – 7.31 (m, 2H, Ph), 7.18 – 7.25 (m, 3H, Ph), 3.79 (t, *J* = 7 Hz, 2H, CH₂N), 2.55 (t, *J* = 6.9 Hz, 2H, CH₂C≡C), 2.05 (quint, *J* = 6.9 Hz, 2H, CH₂); (lit.¹² ¹H NMR).
$N$-(6-Phenyl-5-hexynyl)phthalimide (119b). To a solution of 6-chloro-1-phenyl-1-hexyne (118b) (19.0 g, 98.7 mmol) in DMF (250 mL), solid potassium phthalimide (27 g, 145 mmol) was charged. The reaction mixture was heated at 100 °C and stirred overnight. The reaction mixture was cooled to 25 °C and partitioned between diethyl ether (100 mL) and H$_2$O (100 mL), and the layers were separated. Aq layer was extracted with diethyl ether (3 × 75 mL). Combined organics were washed with 1 N NaOH (75 mL) and brine (75 mL) and then dried. Solvent was removed under reduced pressure, resulting in a light brown solid. Aq layer extracted again with dichloromethane (2 × 150 mL) and organics washed with H$_2$O (6 × 75 mL), 1 N NaOH (75 mL), brine (75 mL) and dried. Solvent was removed under reduced pressure resulting in a dark brown solid. Both crops of solids were triturated with diethyl ether (2 × 80 mL), which resulted in a light brown solid (18.0 g, 62.2 mmol, 63% yield) that was collected after filtration. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.95 (dd, $J = 5.7$, 3 Hz, 2H, Phthal), 7.85 (dd, $J = 5.4$, 3 Hz, 2H, Phthal), 7.35 – 7.45 (m, 2H, Ph), 7.25 – 7.35 (m, 3H, Ph), 3.8 (t, $J = 7.2$ Hz, 2H, CH$_2$N), 2.5 (t, $J = 7.2$ Hz, 2H, CH$_2$C≡C), 1.9 (quint, $J = 7.5$ Hz, 2H, CH$_2$), 1.7 (quint, $J = 6.6$ Hz, 2H, CH$_2$); (lit.$^{42}$ $^1$H NMR).
5-Phenyl-4-pentyn-1-amine (34a).\textsuperscript{42} To a solution of $N$-(5-phenyl-4-pentynyl)phthalimide (119a) (1.22 g, 4.22 mmol) dissolved in MeOH (12 mL), a solution of hydrazine monohydrate (98% in H\textsubscript{2}O, 0.32 mL, 6.47 mmol) was added dropwise. The reaction mixture was refluxed for 12 h. The reaction mixture was cooled to 0 °C and by the addition of 4 N HCl was made acidic. The reaction stirred at reflux for 16 h. The reaction mixture was cooled to 0 °C and filtered, and the removed solid was washed with MeOH (3 × 10 mL). Organics were partitioned between H\textsubscript{2}O and diethyl ether, and 1 N NaOH (15 mL) was added to the ether solution. The layers were separated, and the aq layer was extracted with diethyl ether (2 × 15 mL) and dichloromethane (1 × 15 mL). Organics were combined and washed with H\textsubscript{2}O (30 mL) and brine (30 mL), and dried. Solvent was removed under reduced pressure, resulting in a yellow oil. Silica gel column chromatography was run with 60/1 NH\textsubscript{3} saturated CH\textsubscript{2}Cl\textsubscript{2}/MeOH resulted in a pale yellow oil (0.651 g, 4.1 mmol, 97% yield); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}, $\delta$) 7.35-7.43 (m, 2 H, Ph), 7.23-7.32 (m, 3 H, Ph), 2.87 (t, $J$ = 6.94 Hz, 2 H, CH\textsubscript{2}-N), 2.49 (t, $J$ = 6.94 Hz, 2 H, CH\textsubscript{2}C≡C), 1.67-1.82 (m, 2 H, C-CH\textsubscript{2}-C), 1.28 (br s, 2 H, NH\textsubscript{2}); (lit.\textsuperscript{39} \textsuperscript{1}H NMR).
6-Phenyl-5-hexyn-1-amine (34b). To a solution of \(N\)-(6-phenyl-5-hexynyl)phthalimide (119b) (1.00 g, 3.3 mmol) dissolved in MeOH (10 mL), a solution of hydrazine monohydrate (98% in H\(_2\)O) (0.249 mL, 5.03 mmol) was added dropwise. The reaction mixture was cooled to 0 °C, and by the addition of 4 N HCl was made acidic. The reaction stirred at reflux for 16 h. The reaction mixture was cooled to 0 °C and filtered, and the filtered solid was washed with MeOH (3 × 10 mL). Organics were partitioned between H\(_2\)O and diethyl ether, and 1 N NaOH (10 mL) was added to the ether solution. The layers were separated, and the aq layer was extracted with diethyl ether (2 × 15 mL). Organic layers were combined and washed with H\(_2\)O (15 mL) and brine (15 mL) and dried. Solvent was removed under reduced pressure, resulting in a yellow oil (0.554 g, 3.2 mmol, 97% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.40\) (m, 2H, Ph), \(7.28\) (m, 3H, Ph), \(2.76\) (t, \(J = 6.3\) Hz, 2H, CH\(_2\)N), \(2.45\) (t, \(J = 6.6\) Hz, 2H, \(\text{CH}_2\text{C≡C}\)), \(1.79\) (m, 4H, 2 × CH\(_2\)), \(1.25\) (br s, 2H, NH\(_2\)); (lit.\(^2\) \(^1\)H NMR).
**N-(4-Pentynyl)-phthalimide (121a).**

To a flask of 5-chloro-1-pentyne (0.500 g, 4.87 mmol) in DMF (10 mL), 10 mol % of solid sodium iodide (0.74 g, 0.49 mmol) was added, and the reaction mixture was stirred for 15 min. Solid potassium phthalimide (0.906 g, 4.87 mmol) was added, and the reaction mixture was stirred at 100 °C for 48 h. The reaction mixture was allowed to cool to 25 °C, then it was partitioned between diethyl ether (50 mL) and water (50 mL), and the layers were separated. The aq layer was extracted with diethyl ether (3 × 30 mL). The organic layers were combined, washed with 1 N NaOH (50 mL) and brine (50 mL), dried, and evaporated. A white solid resulted (0.570 g, 2.70 mmol, 55 % yield). \(^1\)H NMR (300 MHz, CDCl$_3$) δ 7.81 - 7.88 (m, 2H, Phth), 7.67 - 7.75 (m, 2H, Phthal), 3.8 (t, J = 7.5 Hz, 2H, CH$_2$NPhthal), 2.25 (dt, J = 7.2, 2.4 Hz, 2H, CH$_2$C=C), 1.85 - 2.0 (m, 3H, HC=C + CH$_2$); (lit.\(^1\)H NMR).
To a flask of solid potassium phthalimide (7.98 g, 42.9 mmol) in DMF (100 mL), 6-chloro-1-hexyne (5.0 g, 42.9 mmol) was added via syringe. The reaction mixture was heated at 100 °C for 48 h. The reaction mixture was cooled to 25 °C and partitioned between water (100 mL) and diethyl ether (100 mL), and the layers were separated. The aq layer was extracted with diethyl ether (3 × 50 mL), and the organic layers were combined, washed with 1 N NaOH (75 mL) and brine (75 mL), dried, and evaporated, resulting in a white crystalline solid. The solid was triturated with diethyl ether and collected by filtration, resulting in a white solid (8.781 g, 38.6 mmol, 90% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.84 (dd, $J = 5.4$, 3 Hz, 2H, Phthal), 7.69 (dd, $J = 5.7$, 3 Hz, 2H, Phthal), 3.7 (t, $J = 6.9$ Hz, 2H, CH$_2$N), 2.25 (dt, $J = 6.9$, 2.7 Hz, 2H, CH$_2$C≡C), 1.95 (t, $J = 3$ Hz, 1H, HC≡C), 1.75 – 1.90 (m, 2H, CH$_2$), 1.5 – 1.65 (m, 2H, CH$_2$); (lit.$^{134}$H NMR).
4-Pentyn-1-amine (34e). To a flask of N-(4-pentynyl)-phthalimide (121a) (0.683 g, 3.2 mmol) in MeOH (12 mL), hydrazine (35 % in water, 0.58 mL, 6.4 mmol) was added dropwise via syringe. The reaction mixture was heated at reflux for 16 h. Conc. HCl (2 mL) was added, resulting in the formation of a white precipitate. The reaction mixture was heated at reflux for 3 h. The reaction mixture was cooled to 0 °C and then filtered, and the resulting solid was washed with MeOH (3 × 10 mL). Solvent from the filtrate was removed under reduced pressure, resulting in an off-white residue. The residue was partitioned between 1 N NaOH (50 mL) and diethyl ether (50 mL), and the layers were separated. The aq layer was extracted with diethyl ether (3 × 10 mL), and the organic layers were combined, washed with brine (75 mL), dried, and then evaporated, which resulted in a yellow oil (0.033 g, 0.40 mmol, 12 % yield). ¹H NMR (300 MHz, CDCl₃) δ 2.81 (t, J = 6.94 Hz, 2 H, CH₂N), 2.20-2.32 (dt, J = 6.9, 2.7 Hz, 2 H, CH₂C≡C), 1.95 (t, J = 2.75 Hz, 1 H, HC≡C), 1.65 (quint, J = 6.9 Hz, 2 H, CH₂), 1.39 (br s, 2 H, NH₂); (lit.⁴² ¹H NMR).
**5-Hexyn-1-amine (34f).** To a flask of N-(5-hexynyl)-phthalimide (121b) (1.00 g, 4.41 mmol) in MeOH (15 mL), hydrazine (35 % in water, 0.80 mL, 8.82 mmol) was added dropwise via syringe. The reaction mixture was heated at reflux for 16 h. Concdd HCl (8 mL) was added, and a white precipitate resulted. The reaction mixture was heated at reflux for 3 h, then cooled to 25 °C, and filtered. The solvent was removed, resulting in an off-white residue. The residue was taken into diethyl ether (50 mL) and 1 M NaOH (50 mL), and the layers were separated. The aq layer was extracted with diethyl ether (3 × 25 mL). The organic layers were combined, washed with brine (50 mL), dried, and then evaporated, resulting in a yellow oil (0.226 g, 2.32 mmol, 53% yield). \(^1^H\) NMR (300 MHz, CDCl\(_3\)) δ 2.75 (t, \(J = 6.48 \text{ Hz}, 2 \text{ H CH}_2\)), 2.20-2.29 (m, 2 H, CH\(_2\)C≡C), 1.98 (t, \(J = 2.69 \text{ Hz}, 1 \text{ H, HC}≡\text{C}\)), 1.54-1.66 (m, 4 H, 2 × CH\(_2\)), 1.25 (br s, 2 H, NH\(_2\)); (lit. \(^1^H\) NMR).

**N-(4-Pentynyl)-2,2,2-trifluoroacetamide (122a).** To a suspension of sodium hydride (60% wt in mineral oil, 1.64 g, 41 mmol) in anhyd N,N-dimethylformamide (20 mL) was added trifluoroacetamide (4.96 g, 44 mmol). The reaction mixture was stirred until H\(_2\) evolution ceased. To this solution was added a solution of the 5-chloro-1-pentyne (3.00 g, 29.3 mmol) in N,N-dimethylformamide (10.0 mL). The reaction mixture was heated to 70 °C for 24 h. The reaction mixture was diluted with diethyl ether (50
mL) and washed with H$_2$O (3 × 50 mL). The organic layer was washed with brine (100 mL), dried over MgSO$_4$, filtered, and evaporated to give a crude oil. Purification of the crude oil by silica gel column chromatography (hexanes/ethyl acetate, 4/1) gave the title compound as a light brown solid (2.14 g, 12 mmol, 41% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 6.65 (br s, 1H, NH), 3.52 (app. q, 2H, CH$_2$N), 2.31 (dt, $J$ = 6.9, 2.7 Hz, 2H, CH$_2$C≡C), 2.05 (t, $J$ = 2.7 Hz, 1H, HC≡C), 1.83 (quint, $J$ = 6.6 Hz, 2H, CH$_2$); (lit.$^{135}$ $^1$H NMR).

1-Chloro-4-hexyne (123a) and 1-iodo-4-hexyne (124a). To a flask of dry THF (45 mL), 5-chloro-1-pentyne (2.25 g, 21.7 mmol) was added via syringe. The reaction mixture was cooled to –78 °C, and n-butyllithium (2.17 M in hexanes, 10 mL, 21.7 mmol) was charged dropwise via syringe. The reaction mixture was stirred at –78 °C for 1 h. Methyl iodide (3.08 g, 21.7 mmol) was added dropwise via syringe, and the reaction mixture was heated at reflux for 3 h. The reaction mixture was cooled to 25 °C, partitioned between diethyl ether (30 mL) and water (30 mL), and then the layers were separated. The aq layer was extracted with diethyl ether (3 × 15 mL). The organics were combined, washed with brine (50 mL), dried, and then evaporated, resulting in a yellow oil (2.50 g, quantitative yield, 123a:124a (1:1)). $^1$H NMR (300 MHz, CDCl$_3$) δ 3.65 (t, $J$ = 6 Hz, 2H, CH$_2$Cl), 3.31 (t, $J$ = 6.9 Hz, 2H, CH$_2$I), 2.25 – 2.40 (m, 4H, 2 × CH$_2$C≡C), 1.95 - 2.05 (m, 4H, 2 × CH$_2$), 1.79 (t, $J$ = 2.4 Hz, 6H, 2 × CH$_3$); 123a (lit.$^{136}$ $^1$H NMR), 124a (lit.$^{137}$ $^1$H NMR).
1-Chloro-5-heptyne (123b) and 1-iodo-5-heptyne (124b). To a flask of dry THF (20 mL), 6-chloro-1-hexyne (2.0 g, 17.2 mmol) was added via syringe. The reaction mixture was cooled to −78 °C, and n-butyllithium (7.9 mL, 17.2 mmol, 2.17 M in hexanes) was added via syringe. The reaction mixture was stirred at −78 °C for 1 h. Methyl iodide (2.44 g, 17.2 mmol) was added via syringe, and the reaction mixture was warmed to 25 °C. The reaction mixture was heated at reflux for 3 h. The reaction mixture was cooled and partitioned between diethyl ether and water. The layers were separated, and the aq. layer was extracted with diethyl ether (3 × 15 mL). Organic layers were combined, washed with brine, and then dried. The solvent was removed under reduced pressure resulting in an oil. (2.226 g, quantitative yield, 123b:124b (1:1.4)). $^1$H NMR (300 MHz, CDCl$_3$) δ 3.6 (t, $J = 6.6$ Hz, 2H, CH$_2$Cl), 3.22 (t, $J = 7.2$ Hz, 2H, CH$_2$I), 2.10 - 2.22 (m, 4H, 2 × C≡CCH$_2$), 1.83 – 2.00 (m, 4H, 2 × CH$_2$CX), 1.8 (t, $J = 2.4$ Hz, 6H, C≡CCH$_3$), 1.50 – 1.70 (m, 2H, 2 × C≡CCCH$_2$); (lit.$^{138}$ $^1$H NMR).
To a flask of 123a/123b (0.500 g, 4.29 mmol) in DMF (8 mL), solid potassium phthalimide (0.798 g, 4.29 mmol) was added. The reaction mixture was stirred at 100 °C for 48 h. The reaction mixture was then cooled to 25 °C and partitioned between diethyl ether and water. The layers were separated, and the aq layer was extracted with diethyl ether (3 × 15 mL). Organic layers were combined, washed with 1 N NaOH (20 mL), brine (20 mL), and then dried. The solvent was removed under reduced pressure, and an off-white solid resulted. The solid was triturated with diethyl ether and filtered to collect a white solid (0.678 g, 2.99 mmol, 69 % yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.85 (dd, \(J = 5, 2.7\ \text{Hz}, 2\text{H, Phthal})\), 7.70 (dd, \(J = 5.7, 3.3\ \text{Hz}, 2\text{H, Phthal})\), 3.8 (t, \(J = 6.6\ \text{Hz}, 2\text{H, CH}_2\text{N})\), 2.2 (m, 2H, C≡CCH\(_2\)), 1.9 (quint, \(J = 7.2\ \text{Hz}, 2\text{H, CH}_2)\), 1.6 (t, \(J = 2.7\ \text{Hz}, 3\text{H, C≡CCH}_3)\); (lit.\(^4\) \(^1\)H NMR).

To a flask of 123b/124b (1.175 g, 8.99 mmol) dissolved in DMF (15 mL), solid potassium phthalimide (1.7 g, 8.99 mmol) was charged. The reaction mixture was heated at 100 °C for 48 h. The reaction mixture was cooled and partitioned between diethyl ether and water, and then the layers were separated. The aq layer was extracted with diethyl ether (3 × 15 mL), and the organic layers were combined, washed with 1 M NaOH and brine, and then dried. The solvent
was removed under reduced pressure, resulting in a light yellow crystalline solid. The solid was triturated with diethyl ether, resulting in the desired product (1.831 g, 7.9 mmol, 84% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.85 (dd, \(J = 5.4, 3\) Hz, 2H, Phthal), 7.70 (dd, \(J = 5.7, 3.3\) Hz, 2H, Phthal), 3.7 (t, \(J = 6.9\) Hz, 2H, CH\(_2\)N), 2.12 - 2.24 (m, 2H, C≡CCH\(_2\)), 1.7-1.85 (m, 5H, CH\(_2\), C≡CCH\(_3\)), 1.45 – 1.60 (m, 2H, CH\(_2\)); (lit.\(^{139}\) \(1\)H NMR).

\[
\text{4-Hexynyl-1-amine (34g).}^{42}
\]

To a flask of 125a (1.00 g, 4.39 mmol) in MeOH (25 mL), hydrazine (0.793 mL, 8.77 mmol, 35 % in water) was added dropwise via syringe. The reaction mixture was heated at reflux for 16 h. Concd HCl was added to the reaction mixture, resulting in the formation of a white precipitate. The reaction mixture was then stirred at reflux for 4 h, cooled to 25 °C, and filtered to remove solid. The solvent of the filtrate was removed under reduced pressure, and the resulting white residue was taken into 1 N NaOH and diethyl ether. The layers were separated, and the aq layer was extracted with diethyl ether. Organic layers were combined, washed with brine, and dried over Na\(_2\)SO\(_4\). Solvent was removed under reduced pressure resulting in a yellow oil (0.281 g, 2.9 mmol, 66 % yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.78 (t, \(J = 6.94\) Hz, 2 H, CH\(_2\)N), 2.12-2.26 (m, 2 H, C≡CCH\(_2\)), 1.76 (t, \(J = 2.63\) Hz, 3 H, CH\(_3\)), 1.60 (quint, \(J = 7.2\) Hz, 2 H, C-CH\(_2\)-C), 1.27 (br s, 2 H, NH\(_2\)); (lit.\(^{42}\) \(1\)H NMR).
5-Heptyn-1-amine (34h). To a flask of 125b (0.500 g, 2.07 mmol) in MeOH (15 mL), hydrazine (0.417 g, 4.56 mmol, 35 % in water), was added via syringe. The reaction mixture was heated at reflux overnight. Concd HCl (2 mL) was added to the reaction mixture, and a white precipitate resulted. The reaction mixture was heated at reflux for 16 h. The reaction mixture was cooled and filtered to remove solid. The filtrate was removed under reduced pressure resulting in a white residue which was taken into 1 N NaOH and diethyl ether. The layers were separated, and the aq layer was extracted with diethyl ether. The organics were combined, washed with brine, and then dried. The solvent was removed under reduced pressure, resulting in a yellow oil (0.136 g, 1.2 mmol, 59 % yield). $^1$H NMR (300 MHz, CDCl$_3$) $\Delta$ 2.7 (t, $J$ = 6.5 Hz, 2H, CH$_2$N), 2.12 – 2.20 (m, 2H, C≡CCH$_2$), 1.8 (t, $J$ = 3 Hz, 3H, -C≡C-CH$_3$), 1.45 - 1.57 (m, 4H, CH$_2$), 1.47 (br s, 2H, NH$_2$); (lit.$^{138}$ $^1$H NMR).

**General Hydroamination Procedures:**

**Typical NMR-scale catalytic hydroamination reaction.** To a solution of 5-phenyl-4-pentyn-1-amine (36a) (6.0 mg, 37.7 μmol) and mesitylene (6.0 mg, 50 μmol) in $d_3$-acetonitrile (0.75 mL) in an NMR tube was added Ag(phen)$_2$OTf (1.6 mg, 2.60 μmol). The reaction vessel was capped and heated with an oil bath to 70 °C, in the absence of light. The reaction was monitored by $^1$H NMR, and the yields were determined (see General Methods). The NMR-scale reaction of aminoalkyne 34a provided cyclic imine 36a in 97% yield.
Typical preparative-scale catalytic hydroamination Method A (non-volatile products). To a solution of 5-phenyl-4-pentyn-1-amine (34a) (0.100 g, 0.629 mmol) in CH₃CN (4 mL) under an atmosphere of Ar was added Ag(phen)₂OTf (0.022 g, 0.036 mmol). The reaction was heated to 70 °C by use of an oil bath for 4 h in the absence of light. The reaction mixture was cooled to 25 °C, passed through a column of basic alumina with CH₂Cl₂. Solvent evaporation gave 36a as a clear oil (0.087 g, 0.547 mmol, 87% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.06-7.52 (m, 5 H, Ph), 3.77-3.93 (m, 2 H, C=N-CH₂), 3.70 (s, 2 H, PhCH₂), 2.34-2.53 (m, 2 H, N=C-CH₂), 1.78-1.97 (m, 2 H, C-CH₂-C); High resolution mass spectrum, calcd for C₁₁H₁₃N(M⁺) 160.1139, found 160.1126; (lit. ³⁹¹H NMR, MS).

Preparative-scale catalytic hydroamination Method B (volatile products). To a solution of 4-hexyn-1-amine (34g) (0.150 g, 1.55 mmol) in CH₃CN (3 mL) under an atmosphere of Ar was added Ag(phen)₂OTf (0.068 g, 0.110 mmol). The reaction was heated to 70 °C in an oil bath for 10 h in the absence of light. The reaction mixture was cooled to 25 °C, and the title compound was isolated by distillation with a Kugelrohr apparatus to give 2-ethyl-1-pyrroline (36g) a clear oil (0.070 g, 0.72 mmol, 47% yield; low yields due to product volatility). ¹H NMR (300 MHz, CDCl₃) δ 3.80 (t, J = 7.2 Hz, 2 H, C=N-CH₂), 2.45 (t, J = 8.1 Hz, 2 H, N=C-CH₂-CH₂), 2.34 (q, J = 7.41 Hz, 2 H,
2-Benzyl-3,4,5,6-tetrahydropyridine (36b). The reaction of Ag(phen)$_2$OTf with 34b in the NMR-scale procedure described above gave the title compound in 77% yield, as determined with an internal standard of mesitylene (as described above). The title imine was isolated on a preparative scale using Method A. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.28-7.33 (m, 2 H, Ph), 7.19-7.25 (m, 3 H, Ph), 3.58-3.66 (m, 2 H, C=N-CH$_2$), 3.48 (s, 2 H, PhCH$_2$), 2.04-2.10 (m, 2 H, N=C-CH$_2$-CH$_2$), 1.58-1.64 (m, 2 H, -CH$_2$-CH$_2$), 1.51-1.57 (m, 2 H, -CH$_2$-CH$_2$); (lit.$^{141}$ $^1$H NMR).

2-Methyl-1-pyrroline (36e) and 1,2-dimethyl-1-pyrrolinium iodide (127). The reaction of Ag(dmp)OTf with 34e in the NMR-scale procedure described above, gave the title pyrroline in 95% yield, as determined with an internal standard of mesitylene. Due to its particular volatility, imine 36e was isolated as a derivative. Following reaction on a preparative-scale using method B, a solution of 36e (0.140 g, 1.69 mmol) in CH$_3$CN (10 mL) was obtained. To this solution, iodomethane (0.242 g, 1.71 mmol) was added dropwise at 25 ºC. The reaction mixture was stirred for 1 h, and then solvent was removed under reduced pressure. The resulting residue was recrystallized from EtOH, and 1,2-dimethyl-1-pyrrolinium iodide (127) was collected as needle-like crystals (0.090
g, 0.4 mmol, 24% yield). 1H NMR (500 MHz, CDCl3) \( \delta \) 4.27-4.37 (m, 2 H, C=N\(^+\)-CH\(_2\)), 3.56 (s, 3 H, N\(^+\)-CH\(_3\)), 3.39-3.49 (m, 2 H, N=C-CH\(_2\)-CH\(_2\)), 2.63 (s, 3 H, CH\(_3\)-C=N), 2.33 (quint, \( J = 8.5 \) Hz, 2 H, N=C-CH\(_2\)-CH\(_2\)); mp = 231 °C (decomp). High resolution mass spectrum, calcd for C\(_6\)H\(_{12}\)N(M\(^+\)) 98.0970, found 98.0978; (lit.\(^{111}\) 1H NMR, mp).

2-Methyl-3,4,5,6-tetrahydropyridine (36f). The reaction of Ag(dmp)OTf with 34f in the NMR-scale procedure described above gave pyridine derivative 36f in 78% yield, as determined with an internal standard of mesitylene. The title imine was also isolated on a preparative scale using method B described above. 1H NMR (300 MHz, CDCl3) \( \delta \) 3.51-3.60 (m, 2 H, C=N-CH\(_2\)), 2.10-2.18 (m, 2 H, N=C-CH\(_2\)-CH\(_2\)), 1.93 (t, \( J = 1.69 \) Hz, 3 H, CH\(_3\)-C=N), 1.64-1.74 (m, 2 H, -CH\(_2\)-CH\(_2\)-), 1.52-1.62 (m, 2 H, -CH\(_2\)-CH\(_2\)); (lit.\(^{39}\) 1H NMR).

2-Ethyl-1-pyrroline (36g). The reaction of Ag(dmp)OTf and 34g in the NMR-scale procedure described above gave 36g in 90% yield, as determined with an internal standard of mesitylene. 1H NMR reported above.
2-Ethyl-3,4,5,6-tetrahydropyridine (36h). The reaction of Ag(dmp)OTf with 34h in the NMR-scale procedure described above, gave pyridine derivative 36h in 40% yield, as determined with an internal standard of mesitylene. The title imine was also isolated on a preparative scale using method B described above. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.56 (tt, $J$ = 6, 2 Hz, 2H, CH$_2$N), 2.17 (qt, $J$ = 7.5, 1.5 Hz, 2H, MeCH$_2$), 2.12 (tt, $J$ = 6.5, 2 Hz, 2H, N=CCH$_2$), 1.63 – 1.70 (m, 2H, NCCH$_2$), 1.54 – 1.59 (m, 2H, N=CCCH$_2$), 1.07 (t, $J$ = 7.5 Hz, 3H, CH$_3$); (lit. $^1$H NMR).

2-Benzoyl-1-pyrroline (128). To a solution of 34a (0.120 g, 0.755 mmol) in CH$_3$CN (5 mL) was added Ag(phen)$_2$OTf (0.033 g, 0.054 mmol). The reaction mixture was heated to 70 °C for 16 h and monitored by TLC. The reaction mixture was cooled to 25 °C and purified by silica gel column chromatography (hexanes/ethyl acetate, 4/1) to give 128 as an oil (0.078 g, 0.453 mmol, 60% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.2 (d, $J$ = 7.5 Hz, 2H, o-Ph), 7.6 (t, $J$ = 7.5 Hz, 1H, p-Ph), 7.42 (t, $J$ = 8 Hz, 2H, m-Ph), 4.24 (tt, $J$ = 8, 7.5 Hz, 2H, C=N-CH$_2$), 2.99 (tt, $J$ = 8, 8 Hz, 2H, N=C-CH$_2$-CH$_2$), 2.0 (quintet, $J$ = 8 Hz, 2H, N=C-CH$_2$-CH$_2$). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 191.3 (C=O), 174.4 (C=N), 135.9 (Ph), 133.7 (Ph), 130.7 (Ph), 128.6 (Ph), 63.5 (C-N), 35.9 (=C-C), and 22.0 (C-C-C). IR (film) (cm$^{-1}$) 3050, 2925, 1656, 1600, 1450, 1350, 1263, 975, and 719.
High resolution mass spectrum, calcd for C\textsubscript{11}H\textsubscript{11}NO(M\textsuperscript{+}) 174.0919, found 174.0912. (lit.\textsuperscript{143} \textsuperscript{1}H NMR, MS).

\[ \text{H}_3\text{C} \quad \text{N} \quad \text{H} \]

\textbf{139a}

2-Methyl-4-(2-propynyl)-1-pyrroline (139a). The reaction of Ag(phen)\textsubscript{2}OTf with 138a in the NMR-scale procedure described above gave the title compound in 97% yield, as calculated with an internal standard of mesitylene (as described above). The title imine was not isolated in pure enough form for full characterization when the reaction was done on a preparative scale. Crude \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta 9.14 (dd, \(J = 4.5, 1.8\) Hz, 0.17 H, phen), 8.20 (dd, \(J = 7.8, 1.5\) Hz, 0.17 H, phen), 7.75 (s, 0.17H, phen), 7.59 (dd, \(J = 8.1, 4.2\) Hz, 0.17 H, phen), 3.87 (ddq, \(J = 15.6, 7.8, 2.1\) Hz, 1H, \(-\text{N-CH}_2\text{H}\)), 3.48 – 3.58 (m, 1H, \(-\text{N-CH}\)), 2.54 – 2.66 (m, 1H, N=C-CHH), 2.42 – 2.54 (m, 1H, CH), 2.25 – 2.35 (m, 1H, N=C-CHH), 2.12 – 2.19 (m, 2H, CH\textsubscript{2}CC), 1.94 – 1.98 (m, 3H, CH\textsubscript{3}), 1.88 (t, \(J = 2.7\) Hz, 1H, CCH).

\[ \text{Ph} \quad \text{N} \quad \text{Ph} \quad \text{=H} \]

\textbf{139b}

2-Benzyl-4-(3-phenyl-2-propynyl)-1-pyrroline (139b). To a solution of 138b (0.050 g, 0.183 mmol) in CH\textsubscript{3}CN (3 mL) was added Ag(phen)\textsubscript{2}OTf (0.008 g, 0.0130 mmol). The reaction mixture was kept at 35 °C away from light and was monitored by TLC. After 2 h the reaction mixture was cooled to 25 °C, and solvent was removed under reduced pressure at \(\leq 25\) °C. The resulting residue was purified by silica gel chromatography (hexanes/ethyl acetate, 1/1 → 100% EtOAc) to give the title compound.
as a yellow oil (0.024 g, 0.088 mmol, 48% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.20-7.41 (m, 10 H, 2 × Ph), 4.03-4.11 (dd, $J = 18, 8$ Hz, 1 H, N-CH$_2$H), 3.73-3.79 (m, 1 H, N-CH$_2$H), 3.72 (s, 2 H, PhCH$_2$), 2.71-2.79 (m, 1 H, N=C-CH$_2$H-CH$_2$), 2.63-2.71 (m, 1 H, CH), 2.48-2.51 (m, 1 H, N=C-CH$_2$H-CH$_2$), 2.46 (dd, $J = 7.78, 6.38$ Hz, 2 H, CC-CH$_2$); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 176.3 (C=N), 137.0 (Ph), 131.9 (Ph), 129.3 (Ph), 128.9 (Ph), 128.5 (Ph), 128.0 (Ph), 126.9 (Ph), 123.8 (Ph), 88.2 (C≡C), 81.7 (C≡C), 66.3 (=N-C), 42.6 (PhCH$_2$), 41.2 (=C-CH$_2$), 36.4 (CH$_2$-C≡C), and 24.7 (CH). IR (film) (cm$^{-1}$) 3061, 2916, 1654, 1597, 1446, 1270, 1156, and 1026. High resolution mass spectrum, calcd for C$_{20}$H$_{19}$N(M$^+$) 274.1596, found 274.1578.

![structure](image)

**2-Benzoyl-4-(3-phenyl-2-propynyl)-1-pyrroline (140).** To a solution of 138b (0.111 g, 0.407 mmol) in CH$_3$CN (3 mL) was added Ag(phen)$_2$OTf (0.018 g, 0.029 mmol). The reaction mixture was heated to 70 °C for 40 h. The reaction mixture was cooled to 25 °C, and the solvent was removed under reduced pressure. Purification of the resulting residue by silica gel column chromatography (hexanes/ethyl acetate, 6/1) gave the title compound as a clear oil (0.058 g, 0.202 mmol, 50% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.17 (d, $J = 6.7$ Hz, 2 H, Ph), 7.60 (t, $J = 7.41$ Hz, 1 H, Ph), 7.34 – 7.45 (m, 4 H, Ph), 7.24-7.31 (m, 3 H, Ph), 4.40 (ddt, $J = 17.4, 7.8, 2.4$ Hz, 1 H, N-CH$_2$H-CH), 4.17 (ddt, $J = 17.4, 1.8, 1.8$ Hz, 1 H, N-CHH-CH), 3.22 (ddt, $J = 18.3, 9, 2.4$ Hz, 1 H, N=C-CHH-CH), 2.93 (ddt, $J = 18.3, 1.8, 1.8$ Hz, 1 H, N=C-CHH-CH), 2.67-2.83 (m, 1 H,
CH), 2.55 (d, \( J = 6.46 \) Hz, 2 H, CH\(_2\)C≡C); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \( \delta \) 191.1 (C=O), 173.6 (C=N), 135.7 (Ph), 133.7 (Ph), 131.9 (Ph), 130.8 (Ph), 128.6 (Ph), 128.5 (Ph), 128.1 (Ph), 123.6 (Ph), 87.5 (C≡C), 82.2 (C≡C), 68.3 (N-C), 41.6 (=C=CH\(_2\)), 35.1 (CH\(_2\)C=), and 24.8 (CH). IR (film) (cm\(^{-1}\)) 3060, 2941, 2920, 2362, 1660, 1617, 1596, 1488, and 1247. High resolution mass spectrum, calcd for C\(_{20}\)H\(_{17}\)NO(M\(^+\)) 288.1388, found 288.1369.

![129a](image)

**N-(6-Phenyl-5-hexynyl)-p-toluensulfonylamide (129a).** To a stirring solution of 34b (0.100 g, 0.578 mmol) in CH\(_2\)Cl\(_2\) (8 mL), p-toluensulfonyl chloride (0.164 g, 0.867 mmol) and K\(_2\)CO\(_3\) (0.096 g, 0.693 mmol) were charged. The reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was diluted with CH\(_2\)Cl\(_2\) and filtered to remove K\(_2\)CO\(_3\). The filtrate was washed with sat. Na\(_2\)CO\(_3\) solution (3 × 15 mL), water, and brine, and then it was dried. Solvent was removed under reduced pressure, and a brown solid resulted. Solid triturated with diethyl ether (2 x 20 mL), resulting in a light brown solid (0.122 g, 0.378 mmol, 65%). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.75 (d, \( J = 8.7 \) Hz, 2H, Ts), 7.34 – 7.42 (m, 2H, Ph), 7.24 - 7.34 (m, 5H, Ph, Ts), 4.30 – 4.40 (m, 1H, NH), 2.97 – 3.08 (CH\(_2\)N), 2.35 – 2.45 (m, 2H, CH\(_2\)-C≡C), 2.40 (s, 3H, C\(_6\)H\(_4\)-CH\(_3\)), 1.54 – 1.73 (m, 4H, -CH\(_2\)-CH\(_2\)). Full characterization of this compound has not been previously reported, and its use was not pursued further for this thesis.
**N-(5-Hexynyl)-p-toluensulfonylamide (129b).** To a flask containing p-toluensulfonyl chloride (0.690 g, 3.63 mmol) and K₂CO₃ (0.550 g, 3.96 mmol) was added a solution of 5-hexyn-1-amine (34f) (0.320 g, 3.30 mmol) in CH₂Cl₂ (50 mL). The reaction was stirred at 25 °C for 16 h. The reaction mixture was filtered and washed with CH₂Cl₂. The filtrate was washed with sat. Na₂CO₃ solution (3 × 30 mL), water (50 mL), and brine (50 mL). The organic layer was dried, and the solvent was removed under reduced pressure, resulting in an off-white solid. The crude product was purified via flash chromatography (silica, EtOAc/hexanes, 1/9) to give a white solid (0.547 g, 2.18 mmol, 66% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.76 (d, J = 8.1 Hz, 2H, Tos), 7.32 (d, J = 7.8 Hz, 2H, Tos), 4.41 (br s, 1H, NH), 2.98 (app. q, 2H, N-CH₂), 2.44 (s, 3H, C₆H₄-C₃H₃), 2.17 (td, J = 6.9, 3 Hz, 2H, C≡C-CH₂), 1.93 (t, J = 2.4 Hz, 1H, C≡C-H), 1.45 – 1.67 (m, 4H, 2 × CH₂). Full characterization of this compound has not been previously reported, and its use was not pursued further for this thesis.

**(E)-N-(6-Phenylhex-5-ynyl)but-2-enamide (131).** To a solution of 6-phenyl-5-hexyn-1-amine (34b) (0.190 g, 1.09 mmol) in CH₂Cl₂ (15 mL) was added triethylamine (0.220 g, 2.18 mmol) via syringe. Crotonyl chloride (0.170 g, 1.64 mmol) was added via syringe, and the reaction mixture was stirred at 25 °C for 16 h. The reaction mixture was poured into sat. NaHCO₃ solution, and the aq layer was extracted with CH₂Cl₂ (2 × 50 mL). The organic layers were combined, washed with 1 N HCl, and then dried over
MgSO₄. The solvent was removed under reduced pressure to give a solid, which was purified by trituration with diethyl ether, to give the title compound as a pure solid (0.94 g, 0.392 mmol, 36% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.38 – 7.42 (m, 2 H, Ph), 7.26 – 7.33 (m, 3H, Ph), 6.83 (dq, J = 12.5, 7 Hz, 1H, H-C=C-C(O)NR), 5.80 (dq, J = 15, 2 Hz, 1H, C=CH-C(O)NR), 5.70 (br s, 1H, NH), 3.40 (q, J = 7 Hz, 2H, CH₂N), 2.46 (t, J = 6.5 Hz, 2H, CC-CH₂), 1.86 (dd, J = 7, 1.5 Hz, 3H, C=C-CH₃), 1.62 – 1.77 (m, 4H, 2 × CH₂); ¹³C NMR (175 MHz, CDCl₃) δ 166.3 (C=O), 140.0 (C=C), 131.8 (C=C), 128.5 (Ph), 127.9 (Ph), 125.3 (Ph), 124.0 (Ph), 89.9 (C≡C), 81.3 (C≡C), 39.2 (N-C), 29.2 (CC≡C), 26.3 (CH₂CH₂), 19.4 (CH₂CH₂), and 18.0 (CH₃). IR (film) (cm⁻¹) 3242, 2946, 2854, 2353, 1666, and 1610. High resolution mass spectrum, calcd for C₁₆H₁₉NO(M⁺) 242.1545, found 242.1552.

4-(Hydroxymethyl)-1,6-heptadiyne (136a). To a suspension of lithium aluminum hydride (1.25 g, 33.0 mmol) in dry THF (40 mL) stirring at −10 °C was added a solution of methyl 2-(2-propynyl)-4-pentynoate (135)²⁴ (3.06 g, 20.4 mmol) in dry THF (10 mL). The reaction mixture was allowed to warm to 25 °C and stirred for 12 h. The reaction mixture was then quenched through the dropwise addition of H₂O (1.25 mL), an aq 10% NaOH solution (1.25 mL), and then additional H₂O (3.75 mL). The reaction mixture was then stirred for 30 min until the suspended solids turned white. The mixture was then filtered, and the solids were washed with diethyl ether (100 mL). The resulting solution was concentrated on a rotary evaporator yielding a pale yellow oil. The crude oil was purified by flash chromatography on a silica gel column using 10% EtOAc in
hexanes as the eluent, resulting in 1.95 g of a clear oil (78% yield); ¹H NMR (500 MHz, CDCl₃) δ 3.73 (d, J = 5.7 Hz, 2H, CH₂O), 2.40 (dd, J = 6.3, 2.4 Hz, 4H, 2 × CCCH₂), 1.95 – 2.07 (m, 3H, 2 × CCH, CH), 1.70 (s, 1H, OH). (lit.¹⁴⁴ ¹H NMR).

1,7-Diphenyl-4-(hydroxymethyl)-1,6-heptadiyne (136b). To a solution of 4-(hydroxymethyl)-1,6-heptadiyne (136a) (0.100 g, 0.820 mmol), Pd(PPh₃)₄ (0.009 g, 8.2 μmol), and CuCl (0.0016 g, 16.4 μmol) in freshly distilled Et₃N (6 mL) in a Schlenk flask was added freshly distilled iodobenzene (0.200 mL, 1.72 mmol). The reaction mixture was heated to 50 °C for 1.5 h. The reaction mixture was cooled to 25 °C, filtered, and concentrated, resulting in an oil. Purification of the crude oil by silica gel flash chromatography (hexanes/ethyl acetate, 4/1) gave the title alcohol as a clear oil (0.214 g, 0.78 mmol, 95% yield). ¹H NMR (500 MHz, CDCl₃) δ 7.42 (dd, J = 6.58, 2.99 Hz, 4 H, Ph), 7.27-7.34 (m, 6 H, Ph), 3.88 (d, J = 5.78 Hz, 2 H, CH₂-O), 2.69 (dd, J = 17.5, 6.5 Hz, 2H, 2 × CHHC≡C), 2.65 (dd, J = 16.5, 6.5 Hz, 2H, 2 × CHHC≡C), 2.12-2.22 (m, 1 H, CH), 1.82 (br s, 1 H, OH); ¹³C NMR (175 MHz, CDCl₃) δ 131.9 (Ph), 128.5 (Ph), 128.1 (Ph), 123.8 (Ph), 87.7 (C≡C), 82.6 (C≡C), 64.9 (CH₂-O), 40.2 (CH₂C≡C), and 21.3 (CH). IR (film) (cm⁻¹) 3390, 3050, 2950, 2250, 1600, 1500, 1450, and 1050. High resolution mass spectrum, calcd for C₂₀H₁₈O(M⁺) 274.1358, found 274.1348.
To a solution of 1,7-diphenyl-4-(hydroxymethyl)-1,6-heptadiyne (136b) (0.184 g, 0.672 mmol) and Et$_3$N (0.14 mL, 1.0 mmol) in dry dichloromethane (6 mL) stirring at 0 °C was added methanesulfonyl chloride (0.092 g, 0.806 mmol) via syringe. The reaction mixture was stirred at 0 °C for 2 h. The mixture was poured into a separatory funnel containing ice-cold 1 N HCl (30 mL) and extracted with CH$_2$Cl$_2$ (3 × 50 mL). The organic layers were combined, washed with a satd aq NaHCO$_3$ (50 mL), dried over MgSO$_4$, filtered, and evaporated to give a yellow oil. The crude mesylate was used in the next step without purification. To a suspension of sodium hydride (60% wt in mineral oil, 0.037 g, 0.941 mmol) in anhyd N,N-dimethylformamide (2.0 mL) was added trifluoroacetamide (0.113 g, 1.01 mmol). The reaction mixture was stirred until H$_2$ evolution ceased. To this solution was added a solution of the crude mesylate in N,N-dimethylformamide (1.0 mL). The reaction mixture was heated to 70 °C for 24 h. The reaction mixture was diluted with diethyl ether (30 mL) and washed with H$_2$O (3 × 50 mL). The organic layer was washed with brine (30 mL), dried over MgSO$_4$, filtered, and concentrated to give a crude oil. Purification of the crude oil by silica gel column chromatography (hexanes/ethyl acetate, 4/1) gave the title compound as a light brown solid (0.050 g, 0.136 mmol, 20% yield). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.37-7.45 (m, 4 H, Ph), 7.27-7.34 (m, 6 H, Ph), 6.85 (br s, 1 H, NH), 3.66 (app. t, $J = 6.22$ Hz, 2 H, CH$_2$-N), 2.69 (dd, $J = 17$, 6 Hz, 2H, 2
× CHHC≡C), 2.65 (dd, J = 17, 6 Hz, 2H, 2 × CHHC≡C), 2.22-2.38 (m, 1 H, CH); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 157.5 (C=O), 131.9 (Ph), 128.6 (Ph), 128.4 (Ph), 123.2 (Ph), 86.3 (C≡C), 83.6 (C≡C), 43.6 (C-N), 37.2 (CH\(_2\)C≡C), and 22.7 (CH). IR (film) (cm\(^{-1}\)) 3300, 1705, 1555, 1487, 1441, 1207, and 1166. High resolution mass spectrum, calcd for C\(_{22}\)H\(_{18}\)F\(_3\)NO(M\(^{+}\)) 369.1340, found 369.1321.

\[\text{H}_2\text{N}\]
\[\equiv\]
\[\equiv\]
\[\text{138a}\]

4-(Aminomethyl)-1,6-heptadiyne (138a). To a solution of 4-(hydroxymethyl)-1,6-heptadiyne (136a) (0.410 g, 3.36 mmol) and Et\(_3\)N (0.509 mL, 5.00 mmol) in dry dichloromethane (6 mL) stirring at 0 °C was added methanesulfonyl chloride (0.462 g, 4.00 mmol) via syringe. The reaction mixture was stirred at 0 °C for 2 h. The mixture was poured into a separatory funnel containing ice-cold 1 N HCl (30 mL) and extracted with CH\(_2\)Cl\(_2\) (3 × 50 mL). The organic layers were combined, washed with a satd aq NaHCO\(_3\) (50 mL), dried over MgSO\(_4\), filtered, and evaporated to give a yellow oil. The crude mesylate was used in the next step without purification. To a suspension of sodium hydride (60% wt in mineral oil, 0.252 g, 6.29 mmol) in anhyd N,N-dimethylformamide (2.0 mL) was added trifluoroacetamide (0.753 g, 6.66 mmol). The reaction mixture was stirred until H\(_2\) evolution ceased. To this solution was added a solution of the crude mesylate in N,N-dimethylformamide (1.0 mL). The reaction mixture was heated to 70 °C for 24 h. The reaction mixture was diluted with diethyl ether (30 mL) and washed with H\(_2\)O (3 × 50 mL). The organic layer was washed with brine (30 mL), dried over MgSO\(_4\), filtered, and concentrated to give a crude oil. Purification of the crude oil by silica gel column chromatography (hexanes/ethyl acetate, 4/1) gave the \(N\)-(trifluoroacetyl)-4-
(aminomethyl)-1,6-heptadiyne (137a) compound as a light brown solid (0.209 g, 0.963 mmol, 26% yield). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.21 (br s, 1H, NH), 3.51 (dd, $J = 6$ Hz, 2H, CH$_2$N), 2.38 (dd, $J = 7$, 3 Hz, 4H, 2 $\times$ CCCH$_2$), 2.10 – 2.18 (m, 1H, CH), 2.09 (t, $J = 2.5$ Hz, 2H, 2 $\times$ CCH); $^{13}$C NMR (175 MHz, CDCl$_3$, data showed a significant impurity) $\delta$ 157.7, 80.9, 71.3, 43.2, 36.3, and 21.2; IR (film) (cm$^{-1}$) 3295, 3117, 2918, 1704, 1568, 1449, 1182, and 1156. To a solution of N-(trifluoroacetyl)-4-(aminomethyl)-1,6-heptadiyne (137a) (0.049 g, 0.226 mmol) in EtOH (10 mL) was added 1 N NaOH (0.452 mL, 0.452 mmol) via syringe. The reaction mixture was stirred for 20 h. Solvent was removed, and the resulting residue was partitioned between CH$_2$Cl$_2$ (15 mL) and H$_2$O (15 mL). The aq layer was extracted with CH$_2$Cl$_2$ (3 $\times$ 20 mL). The organic layers were combined, dried, and concentrated to give the title compound as a clear oil (0.025 g, 0.205 mmol, 91% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 2.84 (d, $J = 6.6$ Hz, 2H, CH$_2$N), 2.38 (dd, $J = 6.3$, 2.7 Hz, 4H, 2 $\times$ C=CCH$_2$), 1.98 (t, $J = 2.7$ Hz, 2H, 2 $\times$ C=CH), 1.80 (quint, $J = 6.3$ Hz, 1H, CH), 1.57 (br s, 2H, NH$_2$); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 82.1 (C=C), 70.2 (H=C=C), 44.5 (C=N), 39.9 (C=CCH$_2$), and 20.7 (CH). IR (film) (cm$^{-1}$) 3293, 2925, 2118, 1579, and 1482. High resolution mass spectrum, calcd for C$_8$H$_{11}$N(M$^+$) 122.0970, found 122.0961.
4-(Aminomethyl)-1,7-diphenyl-1,6-heptadiyne (138b). To a solution of N-(trifluoroacetyl)-4-(aminomethyl)-1,7-diphenyl-1,6-heptadiyne (137b) (0.050 g, 0.136 mmol) in EtOH (10 mL) was added 1 N NaOH (0.271 mL, 0.271 mmol) via syringe. The reaction mixture was stirred for 20 h. Solvent was removed, and the resulting residue was partitioned between CH$_2$Cl$_2$ (15 mL) and H$_2$O (15 mL). The aq layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The organic layers were combined, dried, and concentrated to give the title compound as a clear oil (0.035 g, 0.128 mmol, 95% yield). $^1$H NMR (300 MHz, CDCl$_3$, actual measured peak areas reported for this sensitive amine) δ 7.36-7.48 (m, 3 H, Ph), 7.23-7.35 (m, 4 H, Ph), 2.96 (d, $J$ = 6.22 Hz, 2 H, CH$_2$-N), 2.65 (d, $J$ = 6.70 Hz, 4 H, 2 × C≡CCH$_2$), 1.92-2.08 (m, 1 H, CH), 1.38 (br s, 2 H, NH$_2$); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 131.9 (Ph), 128.5 (Ph), 128.0 (Ph), 123.8 (Ph), 87.4 (C≡C), 82.8 (C≡C), 44.4 (C-N), 39.8 (C≡CCH$_2$), and 22.0 (CH). IR (film) (cm$^{-1}$) 3373, 3051, 2916, 2220, 1669, 1487, 756, and 689. High resolution mass spectrum, calcd for C$_{20}$H$_{19}$N(M$^+$) 274.1596, found 274.1583.
2-Benzoyl-4-((2Z)-3-phenyl-2-propenyl)-1-pyrroline (141). A stirring solution of 140 (0.035 g, 0.122 mmol) and quinoline (0.002 g, 0.018 mmol) in EtOH (3 mL) was degassed (× 3) and placed under Ar. To the stirring solution, palladium on calcium carbonate poisoned with lead (5% Pd, 0.013 g, 6 μmol, Acros Organics) was added, and the flask was evacuated and refilled (× 3) with H₂ (1 atm). After stirring at 25 °C for 15 min, the reaction mixture was evacuated, refilled with Ar, and filtered. The solvent was removed under reduced pressure, and the resulting oil was purified by silica gel column chromatography (hexanes/ethyl acetate, 6/1) to give the title compound as a clear oil (0.027 g, 0.093 mmol, 76% yield). ¹H NMR (300 MHz, CDCl₃) δ 8.14 (d, J = 7.18 Hz, 2 H, Ph-C=O), 7.61 (t, J = 7.41 Hz, 1 H, Ph-C=O), 7.45 (t, J = 7.2 Hz, 2 H, Ph-C=O), 7.29-7.38 (m, 2 H, Ph), 7.16-7.28 (m, 3 H, Ph), 6.55 (d, J = 11.48 Hz, 1 H, Ph-CH=), 5.65 (dt, J = 11.7, 6.9 Hz, 1 H, Ph-C=CH), 4.34 (ddt, J = 17.1, 7.2, 2.4 Hz, 1 H, N-CH₃-CH), 3.95 (ddt, J = 17.4, 2.7, 2.7 Hz, 1 H, N-CHH-CH), 3.14 (ddt, J = 18, 8.7, 2.4 Hz, 1 H, N=C-CHH-CH), 2.69 (ddt, J = 18, 2.4, 2.4 Hz, 1 H, N=CH-CH), 2.38-2.63 (m, 3 H, CH, CH₂C=C); ¹³C NMR (175 MHz, CDCl₃) δ 191.1 (C=O), 174.0 (C=N), 137.5 (C=C), 135.7 (Ph), 133.7 (Ph), 131.1 (Ph), 130.7 (Ph), 129.9 (C=C), 129.1 (Ph), 128.6 (Ph), 128.5 (Ph), 127.1 (Ph), 68.5 (C-N), 41.7 (N=C=C), 36.5 (CH), and 33.6 (C-C=C). IR (film) (cm⁻¹) 3061, 3007, 2932, 2847, 1659, 1616, 1600, 1573, 1493, and 1247. High resolution mass spectrum, calcd for C₂₀H₁₉NO(M⁺) 290.1545, found 290.1550.
1,5-Diphenyl-3-hydroxy-1,4-pentadiyne (145). To a solution of freshly distilled phenylacetylene (0.965 g, 9.45 mmol) in THF (30 mL) at −78 °C was added \( n \)-BuLi (1.6 M in THF, 5.9 mL, 9.45 mmol) dropwise. The reaction mixture was allowed to stir for 10 min, at the end of which time, ethyl formate (0.280 g, 3.78 mmol) was added via syringe. The reaction mixture was stirred for 3 h at −78 °C and then allowed to warm to 25 °C over the course of 1 h. The reaction mixture was partitioned between water (100 mL) and \( \text{CH}_2\text{Cl}_2 \) (100 mL), at which time 1 N HCl (50 mL) was added. The layers separated, and the aqueous layer was extracted with \( \text{CH}_2\text{Cl}_2 \) (3 × 75 mL). The organic layers were combined, washed with water (75 mL) and brine (75 mL), and then dried. The solvent was removed under reduced pressure to yield an oil, that was purified by flash chromatography (silica, EtOAc/hexanes, 1/20) to give a clear oil (0.500 g, 2.16 mmol, 57% yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.45 – 7.54 (m, 4H, Ph), 7.29 – 7.40 (m, 6H, Ph), 5.60 (d, \( J = 7.5 \) Hz, 1H, CH), 2.41 (d, \( J = 7.5 \) Hz, 1H, OH); (lit.\(^{145}\) \(^1\)H NMR).
**O-Acetyl-1,5-diphenyl-3-hydroxy-1,4-pentadiyne (146).** To a solution of 145 (0.250 g, 1.16 mmol) in CH$_2$Cl$_2$ (5 mL) at 25 °C was added pyridine (0.183 g, 2.32 mmol). The reaction mixture was cooled to 0 °C, and acetyl chloride (0.114 g, 1.45 mmol) was added via syringe. The heterogeneous reaction mixture was allowed to warm to 25 °C, and it was stirred for 1 h. 1 N HCl (5 mL) was added to the reaction vessel, and the acidified reaction mixture was extracted with diethyl ether (3 × 50 mL). The organic layers were combined, washed with sat. NaHCO$_3$ (75 mL), and brine (75 mL), and then dried over MgSO$_4$. The solvent was removed under reduced pressure to give an amorphous solid (0.290 g, 1.13 mmol, 97% yield); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.47 – 7.55 (m, 4H, Ph), 7.28 – 7.40 (m, 6H, Ph), 6.53 (s, 1H, CH), 2.19 (s, 3H, Ac); (lit.$^{146}$ $^1$H NMR).

**3- Allyl-1,5-diphenyl-1,4-pentadiyne (147).** To a solution of 146 (0.951 g, 3.68 mmol) and allyltrimethylsilane (0.632 g, 5.53 mmol) in CH$_2$Cl$_2$ (5 mL) was added a solution of B(C$_6$F$_5$)$_3$ (0.105 g, 0.184 mmol) in CH$_2$Cl$_2$ (5 mL). The reaction mixture was stirred at 25 °C for 2 h. The crude product was poured onto a column of basic alumina and eluted with hexanes, which resulted in a yellow oil (0.895 g, 3.5 mmol, 93% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.44 – 7.53 (m, 4H, Ph), 7.28 – 7.40 (m, 6H, Ph), 6.53 (s, 1H, CH), 2.19 (s, 3H, Ac); (lit.$^{146}$ $^1$H NMR).
(ddt, $J = 17.1$ 10.2, 6.9 Hz, 1H, C-CH=), 5.30 (d, $J = 17.1$ Hz, 1H, C=CHH), 5.25 (d, $J = 10.2$ Hz, 1H, C=CHH), 3.89 (t, $J = 6.6$ Hz, 1H, C=C-CH-C=C), 2.67 (t, $J = 6.9$ Hz, 2H, CH$_2$-C=); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 134.4 (C=C), 131.8 (Ph), 128.2 (Ph), 128.1 (Ph), 123.1 (Ph), 118.0 (C=C), 87.2 (C≡C), 81.8 (C≡C), 40.2 (CH), and 24.9 (CH$_2$). IR (film) (cm$^{-1}$) 3064, 2919, 2198, 1954, 1882, 1599, 1490, and 1443.8. High resolution mass spectrum, calcd for C$_{20}$H$_{16}$(M$^+$) 255.1174, found 255.1175.

O-Tris(trimethylsilyl)silyl-1-hydroxy-ethene (153). To a solution of triflic acid (0.600 g, 4 mmol) in CH$_2$Cl$_2$ (18 mL) was added tris(trimethylsilyl)silane (1.00 g, 4 mmol), and the reaction mixture was stirred at 25 °C for 1 h. After 1 h, a solution of acetaldehyde (0.176 g, 4 mmol) and triethylamine (0.607 g, 6 mmol) in CH$_2$Cl$_2$ (6 mL) was added dropwise via syringe. The reaction mixture was stirred for 2 h, and the solvent was removed under reduced pressure resulting in an oil. The oil was purified by flash chromatography (silica, hexanes) to give a viscous oil (0.476 g, 1.64 mmol), 41% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.32 (dd, $J = 13.5$, 5.7 Hz, 1H, =C(OR)H), 4.34 (d, $J = 13.2$ Hz, 1H, HH=C), 4.03 (d, $J = 6.6$ Hz, 1H, HHC=), 0.213 (s, 27H, Si(TMS)$_3$); (lit.$^{116}$ $^1$H NMR).
3-Phenyl-2-propyn-1-ol (157). To a solution of phenylacetylene (1.50 g, 14.7 mmol) in THF (15 mL) at −78 °C was added n-BuLi (1.6 M in THF, 11 mL, 17.6 mmol). The reaction mixture was stirred at −78 °C for 30 min. Paraformaldehyde (0.540 g, 17.6 mmol) was added in one portion, and the reaction mixture was allowed to warm to 25 °C, and it was stirred for 3 additional hours. The reaction was quenched with the addition of sat. NH₄Cl solution (15 mL), and the mixture was extracted with EtOAc (5 × 50 mL). The organic layers were combined, washed with brine (100 mL), and then dried over MgSO₄. The solvent was removed under reduced pressure to yield a clear oil (1.1 g, 8.33 mmol, 57% yield) that could be used without further purification. ¹H NMR (300 MHz, CDCl₃) δ 7.40 – 7.48 (m, 2H, Ph), 7.28 – 7.36 (m, 3H, Ph), 4.50 (d, J = 6.3 Hz, 2H, CH₂O), 1.70 (t, J = 6 Hz, 1H, OH); (lit.¹⁴ ¹H NMR).

3-Phenyl-2-propynyl bromide (158). To a solution of 157 (1.10 g, 8.33 mmol) in minimal CH₂Cl₂ (2 mL) was added phosphorous tribromide (1.0 M in CH₂Cl₂, 12.5 mL, 12.5 mmol) dropwise via syringe at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, and it was then poured into ice water (30 mL). The solution was neutralized with the addition of NaHCO₃, and it was extracted with CH₂Cl₂ (3 × 20 mL). The organic layers were combined, washed with brine (75 mL), and then dried over MgSO₄. The solvent was removed under reduced pressure to yield an oil, which was purified via flash chromatography (silica, hexanes) to yield a clear oil (1.08 g, 5.54 mmol, 66%
yield); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.41 – 7.48 (m, 2H, Ph), 7.28 – 7.36 (m, 3H, Ph), 4.17 (s, 2H, CH\textsubscript{2}Br); (lit.\textsuperscript{147} \textsuperscript{1}H NMR).

\begin{center}
\includegraphics[width=0.5\textwidth]{160.png}
\end{center}

**Methyl 3-oxo-7-phenyl-6-heptynoate (160).** Solid sodium hydride (60% dispersion in oil, 0.036 g, 0.899 mmol) was suspended in THF (5 mL). To this suspension, freshly distilled methyl acetoacetate (0.094 g, 0.817 mmol) was added via syringe at 0 °C. The reaction mixture was stirred for 10 min. To this mixture was added \(n\)-BuLi (1.6 M in hexanes, 0.536 mL, 0.858 mmol) at 0 °C, and the reaction mixture was allowed to stir for 15 min. A solution of 158 (0.200 g, 1.03 mmol) in THF (2 mL) kept over mol. sieves was added dropwise at 0 °C, and the reaction stirred for an additional 30 min. The reaction was quenched with the addition of 1 N HCl, and the reaction mixture was extracted with diethyl ether (3 \(\times\) 15 mL). The organic layers were combined, washed with brine (50 mL), and then dried over MgSO\textsubscript{4}. The solvent was removed under reduced pressure, and the resulting crude oil was purified by flash chromatography (silica, EtOAc/hexanes, 1/9) to give the title compound (0.084g, 0.365 mmol, 45% yield).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 7.34 – 7.41 (m, 2H, Ph), 7.24 – 7.31 (m, 2H, Ph), 3.75 (s, 3H, CO\textsubscript{2}CH\textsubscript{3}), 3.52 (s, 2H, C(O)CH\textsubscript{2}CO\textsubscript{2}Me), 2.90 (t, \(J = 7.5\) Hz, 2H, C≡CH\textsubscript{2}), 2.70 (t, \(J = 7.2\) Hz, 2H, CH\textsubscript{2}C(O)); \textsuperscript{13}C NMR (175 MHz, CDCl\textsubscript{3}) \(\delta\) 201 (C=O), 167.7 (O-C=O), 131.8 (Ph), 128.5 (Ph), 128.1 (Ph), 123.7 (Ph), 88.2 (C≡C), 81.5 (C≡C), 52.7 (O-C), 49.3 (CH), 42.2 (O=CCH\textsubscript{2}), and 14.5 (C≡CCH\textsubscript{2}). IR (film) (cm\textsuperscript{-1}) 2956, 2915, 2864, 1747,
1717, 1257. High resolution mass spectrum, calcd for $\text{C}_{14}\text{H}_{14}\text{O}_3(M^+)$ 231.1021, found 231.1024.

![Structure of Z-173](image)

**Methyl (Z)-2-hexenoate (173).** To a solution of bis(2,2,2-trifluoroethyl)-methoxycarbonylmethane phosphonate (1.105 g, 3.50 mmol) in dry THF (8 mL), a 2.0 M solution of sodium hexamethyldisilazane in toluene (1.75 mL, 3.50 mmol) was added dropwise via syringe at –80 °C. The reaction mixture was stirred for 1 h. A solution of freshly distilled butyraldehyde (172) (0.250 g, 3.50 mmol) in THF stored over activated molecular sieves was added dropwise via syringe at –80 °C. The reaction mixture was stirred for 15 min at –80 °C and then for 3 h at 0 °C. The reaction mixture was then warmed to 25 °C and poured into sat. NH$_4$Cl solution. The aq layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL). All organics were combined, washed with brine, and then dried. The solvent was removed under reduced pressure, and a yellow oil resulted (0.380 g, 2.97 mmol, 85% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.98 (dt, $J = 15.3, 7.2$ Hz, 0.25H, minor olefin isomer), 6.25 (dt, $J = 11.5, 7.5$ Hz, 1H, HC=CH-CO$_2$Me), 5.75 (dt, $J = 12, 1.5$ Hz, C=CH-CO$_2$Me), 3.74 (s, 0.25H, minor olefin isomer), 3.72 (s, 3H, CO$_2$Me), 2.65 (dt, $J = 7.5, 1.8$ Hz, 2H, =C-CH$_2$), 1.40 – 1.54 (m, 2H, CH$_2$-Me), 0.97 (t, $J = 7.8$ Hz, 3H, -CH$_3$); (lit.$^{148}$ $^1$H NMR).
**Methyl (Z)-4-(methylthio)-but-2-enoate (Z-175).** To a solution of bis(2,2,2-trifluoroethyl)-methoxycarbonylmethane phosphonate (1.958 g, 6.16 mmol) in dry THF, a 0.6 M solution of sodium hexamethyldisilazane in toluene (10.26 mL, 6.16 mmol) was added dropwise via syringe at –80 °C. The reaction mixture was stirred for 30 min. A solution of methylthioacetaldehyde (165) (0.554 g, 6.16 mmol) in THF stored over activated molecular sieves was added dropwise via syringe at –80 °C. The reaction mixture was stirred for 15 min at –80 °C and then for 3 h at 0 °C. The reaction mixture was then warmed to 25 °C and poured into a sat. NH₄Cl solution. The aq layer was extracted with CH₂Cl₂ (3 × 20 mL). All organics were combined, washed with brine, and then dried over sodium sulfate. The solvent was removed under reduced pressure and a yellow oil resulted (1.153 g crude). After column chromatography (silica, EtOAc/hexanes gradient) the desired olefin was isolated as the major product (0.130 g, 0.890 mmol, 14% yield). §H NMR (300 MHz, CDCl₃) δ 6.23 (dt, J = 11.1, 8.1 Hz, 1H, CH₂-HC=C), 5.89 (d, J = 11.4 Hz, 1H, C=CH), 3.68 – 3.78 (m, 2H, SCH₂), 3.7 (s, 3H, OCH₃), 2.05 (s, 3H, SCH₃), (lit. 149 §H NMR).
Methyl (E)-4-(methylthio)-2-butenoate (175). To a solution of methyl-4-bromocrotonate (0.913 g, 4.34 mmol) in DMSO (1.5 mL) in a sealed tube was added dimethyl sulfide (1.91 g, 30.8 mmol) via syringe. The reaction vessel was sealed, and the reaction was heated to 60 °C for 48 h. The reaction was allowed to cool to 25 °C, at which it was filtered and washed with diethyl ether and acetone. The solvents were removed under reduced pressure, the resulting residue was partitioned between CH$_2$Cl$_2$ (15 mL) and water (15 mL), and the layers were separated. The organic layer was washed with water (25 mL) and brine (25 mL) and then dried. The solvent was removed under reduced pressure to give an oil. The yellow oil was purified by flash chromatography (silica, EtOAc/hexanes, 1/9) to give a clear oil (0.600 g, 4.12 mmol, 95% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 6.88 (dt, $J$ = 15.3, 7.8 Hz, 1H, HC=C-CO$_2$Me), 5.87 (d, $J$ = 15.9 Hz, 1H, =CH-CO$_2$Me), 3.76 (s, 3H, OCH$_3$), 3.20 (d, $J$ = 7.8 Hz, 2H, S-CH$_2$), 2.03 (s, 3H, SCH$_3$). (lit.$^{149}$ $^1$H NMR).

Ethyl (E)-2-hexenoate (177). To a solution of diisopropyl(ethoxycarbonylmethyl)phosphonate (5.045 g, 0.020 mol) in THF (25 mL) was added sodium bis(trimethylsilyl) amide (2.0 M in THF) (10 mL, 0.020 mol) via syringe at −78 °C. The reaction mixture was stirred at −78 °C for 45 min, and freshly distilled butyraldehyde (1.44 g, 0.020 mol) was added dropwise via syringe. The reaction mixture was brought to 0 °C and was stirred for 1 h, at which time an immobile gel formed. The reaction
mixture was partitioned between CH₂Cl₂ (45 mL) and aq NH₄Cl solution (45 mL). The layers were separated, and the aq layer was extracted with CH₂Cl₂ (3 × 40 mL). The organic layers were combined, washed with brine (50 mL), and then dried over sodium sulfate. Solvent was removed under reduced pressure yielding a light yellow liquid (2.704 g, 0.019 mol, 95% yield). ¹H NMR (300 MHz, CDCl₃) δ 6.97 (dt, J = 15.9, 7.2 Hz, 1H, H-C=C-CO₂Et), 5.82 (d, J = 15.79, 1H, C=CH-CO₂Et), 4.19 (q, J = 7.18, 2H, -CO₂CH₂), 2.10-2.26 (m, 2H, CH₃CH₂-CH₂-C=), 1.41-1.59 (m, 2H, CH₃CH₂-CH₂-C=), 1.29 (t, J = 7.2 Hz, 3H, -CO₂CH₂CH₃), 0.95 (t, J = 7.2 Hz, 3H, CH₃CH₂-CH₂-C=); ¹³C NMR (175 MHz, CDCl₃) δ 166.62 (=C-CO₂Et), 149.04 (C=CH-CO₂Et), 121.34 (C=CH-CO₂Et), 60.00 (C=CH-CO₂C), 34.913 (CH₃CH₂-CH), 21.22 (CH₃CH₂-CH), 14.19 (CO₂CC), 13.57 (-CH₃). (lit.¹⁵⁰¹H NMR).

**Ethyl (E)-4-methyl-2-pentenoate (178).** To a solution of diisopropyl(ethoxycarbonylmethyl)phosphonate (5.045 g, 0.020 mol) in THF (25 mL) was added sodium bis(trimethylsilyl) amide (2.0 M in THF, 10 mL, 0.020 mol) via syringe at -78 °C. The reaction mixture was stirred at -78 °C for 45 min and freshly distilled isobutyraldehyde (1.44 g, 0.020 mol) was added dropwise via syringe. The reaction mixture was brought to 0 °C and was stirred for 0.5 h at which time an immobile gel formed. The reaction mixture was partitioned between CH₂Cl₂ (45 mL) and aq NH₄Cl solution (45 mL). The layers were separated and aq layer was extracted with CH₂Cl₂ (3 × 40 mL). The organic layers were combined and washed with brine (50 mL) and dried over sodium sulfate. Solvent was removed under reduced pressure, yielding a
light yellow liquid (2.524 g, 0.018 mol, 90% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.95 (dd, $J$= 15.79, 6.70, 1H, H-C=C-CO$_2$Et), 5.79 (d, $J$ = 15.9 Hz, 1H, C=CH-CO$_2$Et), 4.19 (q, $J$= 7.18, 2H, -CO$_2$CH$_2$), 2.38-2.55 (m, 1H, (CH$_3$)$_2$-CH=C=), 1.30 (t, $J$ = 7.18, 3H, CO$_2$C-CH$_3$), 1.07 (d, $J$= 6.70, 6H, -C(CH$_3$)$_2$). $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 166.97 (=C-CO$_2$Et), 155.34 (C=C-CO$_2$Et), 118.66 (C=C-CO$_2$Et), 60.11 (C=C-CO$_2$C), 30.95 ((CH$_3$)$_2$-CH), 21.22 ((CH$_3$)$_2$-CH), 14.26 (CO$_2$CC). (lit.$^{151}$ $^1$H NMR).

![Image](https://via.placeholder.com/150)

**Ethyl (E)-4-(methylthio)crotonate (179).** To a solution of dimethyl sulfide (0.387 g, 6.24 mmol) in acetone (6 mL), ethyl-4-bromocrotonate (0.631 g, 2.45 mmol) was added via syringe. The reaction mixture was placed in 25 °C water bath and stirred for 64 h, and the product precipitated over time. The reaction mixture was filtered, and the resulting solid was washed with acetone. A white solid (0.467 g, 1.84 mmol, 75% yield) was collected and characterized without further purification. $^1$H NMR (300 MHz, CD$_3$OD) $\delta$ 6.89 (d, $J$ = 15.31, 1H, H-C=C-CO$_2$Et), 6.38 (d, $J$ = 15.79, 1H, C=CH-CO$_2$Et), 4.24 (q, $J$ = 6.86, 2H, -CO$_2$CH$_2$), 2.95 (m, 8H, 2 × S-CH$_3$, SCH$_2$), 1.31 (t, $J$ = 7.18, 3H, -CO$_2$CCH$_3$). To a solution of (3-ethoxycarbonyl-prop-2-enyl)dimethylsulfonium bromide (181) (0.150 g, 0.857 mmol) in dimethylsulfoxide (2 mL), dimethyl sulfide (0.182 g, 2.94 mmol) was added via syringe. The reaction mixture was heated to 60 °C in a sealed tube for 48 h. Sulfonium bromide salts precipitated upon the addition of ether. The reaction mixture was filtered, and the filtrate was washed with water (5 × 25 mL) to remove excess dimethylsulfoxide. The organic layer was dried over sodium sulfate, and solvent was removed under reduced pressure to yield a clear liquid (0.053 g, 0.331 mmol, 39%
yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.87 (dt, $J =$ 15.6, 7.2 Hz, 1H, H-C=C-CO$_2$Et), 5.86 (d, $J =$ 7.18, 1H, C=CH-CO$_2$Et), 4.22 (q, $J =$ 7.18, 2H, -CO$_2$CH$_2$), 3.20 (d, $J =$ 7.18, 2H, S-CH$_2$-C=), 2.04 (s, 3H, S-CH$_3$), 1.31 (t, $J =$ 7.18, 3H, -CO$_2$CCH$_3$). (lit.$^{152}$ $^1$H NMR).

![Ethyl (2S,3R)-2-(benzyloxycarbonylamino)-3-hydroxyl-hexanoate (183).](image)

Ethyl (2S,3R)-2-(benzyloxycarbonylamino)-3-hydroxyl-hexanoate (183). To a solution of benzyl carbamate (0.330 g, 2.18 mmol) in $n$-propanol (10 mL) and sodium hydroxide solution (0.67 M, 3.2 mL), $t$-BuOCl (0.232 g, 2.148 mmol) was added via syringe. After 15 min of stirring, a solution of (DHQD)$_2$AQN (11.67 mM, 2.57 mL, 0.030 mmol) in $n$-propanol, ethyl (E)-2-hexenoate (177) (0.100 g, 0.704 mmol), and a solution of K$_2$[OsO$_2$(OH)$_4$] (0.05 M, 0.56 mL, 0.28 mmol) in water were all added via syringe. The reaction mixture was stirred at 25 °C for 1.5 h. The reaction mixture was quenched by the addition of sodium bisulfite (~500 mg) and partitioned between ethyl acetate (25 mL) and water (25 mL). The layers were separated, and the aq layer was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, washed with brine (75 mL), and dried over magnesium sulfate. Solvent was removed under reduced pressure, yielding a yellow oil. Purification of the oil by column chromatography (silica, 20/1, hexanes/ethyl acetate) yielded the title compound (0.130 g, 0.333 mmol, 47% yield). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.30 – 7.41 (m, 5H, Ph), 5.07 (s, 2H, CH$_2$Ph), 4.07 – 4.27 (m, 4H, OCH$_2$, N-CH, O-CH), 1.53 – 1.66 (m, 2H, O-C-CH$_2$), 1.36 – 1.50 (m, 2H, O-C-C-CH$_2$), 1.26 (t, $J =$ 7.2 Hz, 3H, CO$_2$CH$_2$CH$_3$), 0.96 (t, $J =$ 7.2
Hz, 3H, CH₂CH₃). Full characterization of this compound has not been previously reported, and its use was not pursued further for this thesis.

![Chemical Structure](image)

**Ethyl (2S,3R)-2-amino-3-hydroxy-4-methylpentanoate hydrochloride (186).**

To a solution of benzyl carbamate (0.348 g, 2.30 mmol) in n-propanol (10 mL) and sodium hydroxide solution (0.67 M, 3.2 mL), t-BuOCl (0.232 g, 2.148 mmol) was added via syringe. After 15 min of stirring, a solution of (DHQD)$_2$AQN (11.67 mM, 2.4 mL, 0.028 mmol) in n-propanol, ethyl 3-methyl-2-pentenoate (0.100 g, 0.704 mmol), and a solution of K$_2$[OsO$_2$(OH)$_4$] (0.05 M, 0.56 mL, 0.28 mmol) in water were all added via syringe. The reaction mixture was stirred at 25 °C for 1.5 h. The reaction mixture was quenched by the addition of sodium bisulfite (~500 mg) and partitioned between ethyl acetate (25 mL) and water (25 mL). The layers were separated, and the aq layer was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, washed with brine (75 mL), and dried over magnesium sulfate. Solvent was removed under reduced pressure, yielding a yellow oil. Flash chromatography was performed (silica, 6/4/1, hexanes/dichloromethane/methanol) however the mixture still contained benzyl carbamate. This mixture was employed in the subsequent reaction to remove the benzyl carbamate protecting group and any excess benzyl carbamate. The protected compound (185) was dissolved in EtOH (5 mL), and 3 N HCl (5 mL) was added. The reaction mixture was stirred at 25 °C for 3 h. The reaction solvent was removed under reduced pressure, and a solid resulted (0.35 g, 0.20 mmol, 28% yield). $^1$H NMR (300 MHz,
CD$_3$OD) δ 4.31 (q, $J = 7.2$ Hz, 2H, CO$_2$CH$_2$CH$_3$), 4.11 (d, $J = 3.3$ Hz, 1H, N-CH), 3.71 (dd, $J = 8.7$, 3.6 Hz, 1H, O-CH), 1.66 – 1.80 (m, 1H, CH(CH$_3$)$_2$), 1.33 (t, $J = 7.2$ Hz, 3H, CO$_2$CH$_2$CH$_3$), 1.05 (d, $J = 6.6$ Hz, 3H, CH(CH$_3$)(CH$_3$)), 0.98 (d, $J = 6.6$ Hz, 3H, CH(CH$_3$)(CH$_3$)). Full characterization of this compound has not been previously reported, and its use was not pursued further for this thesis.

Ethyl (2S,3R)-3-hydroxy-4-methyl-2-(tosylamino)pentanoate (187). To a solution of (DHQD)$_2$AQN (11.67 mM, 2.4 mL, 0.028 mmol) in $n$-propanol was added acetonitrile (10 mL) and water (10 mL). Ethyl (E)-3-methyl-2-pentenoate (0.100 g, 0.704 mmol) and a solution of K$_2$[OsO$_2$(OH)$_4$] (0.05 M, 0.56 mL, 0.28 mmol) in water were added via syringe, and solid chloramine-T monohydrate (0.240 g, 1.05 mmol) was added through a solid addition funnel. The reaction mixture was stirred at 25 °C for 1.5 h. The reaction mixture was quenched by the addition of sodium bisulfite (~500 mg) and partitioned between ethyl acetate (25 mL) and water (25 mL). The layers were separated, and the aq layer was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, washed with brine (75 mL), and then dried over magnesium sulfate. Solvent was removed under reduced pressure, yielding a black oil. Purification by column chromatography (silica, 6/4/1, hexanes/dichloromethane/methanol) yielded the title compound (0.191 g, 0.581 mmol, 82% yield). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.83 (d, $J = 8.7$ Hz, 2H, Tos), 7.33 (d, $J = 8.1$ Hz, 2H, Tos), 4.74 (br s, 2H, NH, OH), 4.30 (q, $J = 7.2$ Hz, 2H, CO$_2$CH$_2$CH$_3$), 4.26 – 4.31 (m, 1H, N-CH), 3.51 (br d, $J = 9.3$ Hz, 1H, O-CH),
2.45 (s, 3H, C₆H₄-CH₃), 1.81 – 1.97 (m, 1H, CH(CH₃)₂), 1.34 (t, J = 7.2 Hz, 3H, CO₂CH₂CH₃), 1.07 (d, J = 6.6 Hz, 3H, CH(CH₃)(CH₃)), 1.00 (d, J = 6.6 Hz, 3H, CH(CH₃)(CH₃)). Full characterization of this compound has not been previously reported, and its use was not pursued further for this thesis.

\[
\begin{align*}
\text{S} & \quad \text{OCH}_3 \\
\text{NHCbz} &
\end{align*}
\]

\textbf{N-(Benzyloxycarbonyl)-L-methionine methyl ester (190).} To a stirring solution of sodium bicarbonate (6.20 g, 75.0 mmol), and L-methionine methyl ester (3.0 g, 15.0 mmol) in ethyl acetate (60 mL) and water (40 mL) at 0 °C was added benzyl chloroformate (2.87 g, 16.8 mmol) over the course of 30 sec. The reaction mixture was allowed to stir for 4 h, at which time the mixture was decanted and washed with 1 N HCl (2 × 60 mL), and water (2 × 75 mL). The organic layer was dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give a colorless oil. Hexanes were added and crystallization occurs after mixing and cooling at 0 °C for several hours. The precipitate was collected by filtration to give a white solid (4.28 g, 14.4 mmol, 96% yield). \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.37 (s, 5 H, Ph), 5.40 (d, 1 H, NH), 5.13 (s, 2 H, OCH₂Ph), 4.45 - 4.58 (m, 1 H, CH), 3.77 (s, 3 H, CO₂CH₃), 2.54 (t, J = 7.28 Hz, 2 H, SCH₂), 2.13 - 2.26 (m, 1 H, CHH), 2.10 (s, 3 H, SCH₃), 1.92 - 2.05 (m, 1 H, CHH). (lit.\(^ {130}\) \(^1\)H NMR).
Methyl (S)-2-((benzyloxycarbonyl)amino)-4-(methylsulfinyl) butenoate (191).

To a stirring solution of N-(benzyloxycarbonyl)-L-methionine methyl ester (190) (0.508 g, 1.75 mmol) in methanol (7 mL) at 0 °C was added sodium periodate (0.388 g, 1.81 mmol) in water (7 mL). The reaction was stirred at 0 °C for 4.5 h. The reaction was allowed to warm and was filtered. The salts were washed with methanol and the filtrate solvent was removed under reduced pressure. The resulting solid was taken into chloroform (25 mL) and water (25 mL) and the layers were separated. The aq layer was extracted with chloroform (3 × 20 mL) and the combined organics were washed with water (2 × 50 mL). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure, resulting in a colorless oil (0.530 g, 1.7 mmol, 98% yield). ¹H NMR (300 MHz, CDCl₃) δ 7.36 (s, 5 H, Ph), 5.66 (d, 1 H, NH), 5.12 (s, 2 H, OCH₂Ph), 4.42 - 4.58 (m, 1 H, CH), 3.77 (s, 3 H, CO₂CH₃), 2.63 - 2.85 (m, 2H, S(O)CH₂), 2.56 (s, 3 H, S(O)CH₃), 2.35 (m, 1 H, CH/H), 2.15 (m, 1 H, CH/H). (lit.¹²⁰¹H NMR).

Methyl N-(benzyloxycarbonyl)-2-amino-3-butenoate (ent-81). A suspension of 191 (17.79 g, 56.8 mmol) in mesitylene (200 mL) was heated to 160 °C for 24 h. The reaction mixture was poured onto a silica gel column, and eluted with hexanes (1 L) then...
15% EtOAc/Hexanes to give the title compound as an oil (7.040 g, 28.3 mmol, 52% yield); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.35 (s, 5H, Ph), 5.92 (ddd, $J$ = 16.5, 10.2, 5.4 Hz, 1H, CH$_2$=CH), 5.45 (br d, 1H, NH), 5.32 (d, $J$ = 17.1 Hz, 1H, CHH=), 5.28 (d, $J$ = 10.5 Hz, 1H, CHH=), 5.14 (s, 2H, CH$_2$Ph), 4.95 (m, 1H, N-CH), 3.76 (s, 3H, CO$_2$CH$_3$). (lit.$^{130}$ $^1$H NMR).

![Methyl (2S,3S)-N-(benzyloxycarbonyl)-2-amino-3,4-epoxy-butanoate (ent-82)](image)

**Methyl (2S,3S)-N-(benzyloxycarbonyl)-2-amino-3,4-epoxy-butanoate (ent-82).** To a solution of ent-81 (2.5 g, 10 mmol) in CH$_2$Cl$_2$ (125 mL) at 0 °C, was added m-chlorobenzoic acid (12.1 g, 70 mmol). The reaction mixture was warmed to 25 °C and stirred for 72 h. The reaction mixture was filtered and the filtrate was then washed with 10% Na$_2$SO$_3$ (50 mL) and the layers were separated. The organic layer was filtered, washed with 10% Na$_2$SO$_3$ (50 mL), sat. NaHCO$_3$ (75 mL) and then dried. Solvent was removed under reduced pressure to yield an oil. Silica gel chromatography (EtOAc/Hexanes, 1/4) provided the two diastereomers of ent-82 (1.5 g, 5.7 mmol, 57% yield, syn:anti (4:1)). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.36 (s, 5H, Ph), 5.27 (br d, $J$ = 7.5 Hz, 1H, NH), 5.12 (s, 2H, CH$_2$Ph), 4.73 (d, $J$ = 8.7 Hz, 1H, N-CH), 3.82 (s, 3H, CO$_2$CH$_3$), 3.46 (m, 1H, O-CH), 3.23 (m, 0.25H, O-CH, minor diastereomer), 2.80 (m, 1H, O-CH/H), 2.69 (m, 1H, O-CH/H). (lit.$^{84}$ $^1$H NMR).
Methyl (2S,3S)-N-(benzyloxycarbonyl)-2-amino-3-hydroxy-4-(methylthio)-butanoate (192). To a solution of ent-82 (1.20 g, 4.5 mmol) in MeOH (30 mL) at 0 °C was added NH₄Cl (0.436 g, 8.2 mmol) and NaSCH₃ (0.693 g, 9.9 mmol). The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was warmed to 25 °C, then the solvent was removed under reduced pressure. The resulting residue was taken into CH₂Cl₂/H₂O (1/1, 100 mL) and the layers were separated. The aq layer was extracted with CH₂Cl₂ (3 × 50 mL), and the organic layers were combined, washed with brine (100 mL) and dried. Flash chromatography (silica gel, EtOAc/Hexanes (1/3)) gave the title compound (0.904 g, 2.89 mmol, 68% yield); ¹H NMR (300 MHz, CDCl₃) δ 7.35 (s, 5H, Ph), 5.75 (br m, 0.33 H, N-H, minor diastereomer), 5.55 (br d, 1H, NH), 5.13 (s, 2H, CH₂Ph), 4.46 (m, 1H, N-CH), 4.22 (m, 1H, O-CH), 3.78 (s, 3H, CO₂CH₃), 3.28 (br m, 0.33 H, O-CH, minor diastereomer), 2.81 (s, 1H, OH), 2.70 (m, 1H, SCHH), 2.57 (dd, J = 14, 10 Hz, 1H, SCHH); ¹³C NMR (125 MHz, CDCl₃) δ 171.4 (O-C=O), 157.0 (O-C(O)-N), 136.3 (Ph), 128.8 (Ph), 128.4 (Ph), 128.3 (Ph), 69.1 (C2), 67.5 (C3), 57.3 (OCH₃), 53.0 (CH₂Ph), 38.5 (SCH₂), 15.6 (SCH₃); IR (film) (cm⁻¹) 3395, 3027, 2946, 2915, 1727, 1712, 1518, 1436, 1216 and 1058; High resolution mass spectrum, calcd for C₁₄H₁₉NO₅S (M⁺) 314.1062, found 314.1059.
(2S,3S)-N-(Fluorenylmethyloxycarbonyl)-2-amino-3-hydroxy-4-(methylthio)-butanoic acid (193). A solution of 192 (0.504 g, 1.61 mmol) in 6 N HCl (15 mL) was heated to reflux for 2 h. The solvent was removed under reduced pressure, and the resulting residue was partitioned between THF (20 mL) and H₂O (20 mL). To this stirring solution was added sodium bicarbonate (1.72 g, 12.9 mmol) and Fmoc-OSu (0.651 g, 1.92 mmol). The reaction mixture was stirred at 25 °C for 16 h. At the end of the reaction, the solution was made acidic with the addition of 6 N HCl, and the mixture was poured into EtOAc (50 mL). The layers were separated, and the aq layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), and dried over Na₂SO₄. Solvents were removed under reduced pressure, and the resulting solid was purified by flash column chromatography (silica gel, EtOAc/acetic acid, 198/1) to give a white solid (0.250 g, 0.65 mmol, 40% yield); **¹H NMR (500 MHz, CD₃OD) δ 7.79 (d, J = 7.5 Hz, 2H, Fmoc), 7.67 (t, J = 7.5 Hz, 2H, Fmoc), 7.38 (t, J = 7.5 Hz, 2H, Fmoc), 7.30 (t, J = 8.5 Hz, 2H, Fmoc), 4.42 (dd, J = 10.5, 7 Hz, 1H, O-CHH-Fmoc), 4.33 (dd, J = 10.5, 7 Hz, 1H, O-CHH-Fmoc), 4.29 (br d, J = 2.5 Hz, 1H, N-CH), 4.22 (app. t, 2H, O-CH, CHFmoc), 2.59 (dd, J = 14, 6 Hz, 1H, SCHH), 2.52 (dd, J = 14, 8 Hz, 1H, SCHH), 2.11 (s, 3H, SCH₃). **¹³C NMR (75 MHz, CDCl₃) δ 173.1 (O-C=O), 158.9 (O-C(O)-N), 145.6 (Ph), 142.7 (Ph), 128.9 (Ph), 128.3 (Ph), 126.4 (Ph), 121.1 (Ph), 72.7 (C2), 68.0 (C3), 60.2 (NC(O)OCH₂), 39.1 (CHFmoc), 170
32.9 (SCH$_2$), 16.2 (SCH$_3$); IR (film) (cm$^{-1}$) 3376, 3057, 2955, 2913, 1701, 1686, 1588, 1450, 1419; MS (ESI (negative ion)) calcd for C$_{20}$H$_{20}$NO$_5$S (M$^+$-H) 386.11, found C$_{20}$H$_{20}$NO$_5$S (M$^+$-H) 386.2.
04-262 in 2:1 methanol:methylene chloride

Scan ES+
5.02e6
04-262 in 2:1 methanol:methylene chloride

collision energy = 20 eV
6,6'-Bis((R)-2-hydroxybutyl)-2,2'-bipyridine (107)
6,6'-Bis((R)-2-hydroxybutyl)-2,2'-bipyridine (107)
6-((R)-2-Hydroxybutyl)-2,2'-bipyridine (110)
6-((R)-2-Hydroxybutyl)-2,2'-bipyridine (110)
N-(5-Phenyl-4-pentynyl)phthalimide (119a)
N-(6-Phenyl-5-hexynyl)phthalimide (119b)
5-phenyl-4-pentyn-1-amine (34a)
6-phenyl-5-hexyn-1-amine (34b)
5-Hexyn-1-amine (34f)
1-Chloro-4-hexyne (123a) and 1-iodo-4-hexyne (124a)
1-Chloro-5-heptyne (123b) and 1-iodo-5-heptyne (124b)
N-(4-Hexylyl)phthalimide (125a)
N-(5-Heptynyl)phthalimide (125b)
4-Hexynyl-1-amine (34g)
5-Heptyl-1-amine (34h)
2-Benzyl-3,4,5,6-tetrahydropyridine (36b)
1,2-Dimethyl-1-pyrroline iodide (127)
2-Methyl-3,4,5,6-tetrahydropyridine (36f)
2-Ethyl-1-pyrroline (36g)
2-Ethyl-3,4,5,6-tetrahydropyridine (36h)

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\begin{align*}
\text{H}_3\text{C} &\quad \text{N} \\
\end{align*}
\]
2-Benzoyl-1-Pyrroline (128)
2-Benzoyl-1-Pyrroline (128)
2-Methyl-4-(2-propynyl)-1-pyrroline (139a)
2-Benzyl-4-(3-phenyl-2-propynyl)-1-pyrroline (139b)
2-Benzoyl-4-(3-phenyl-2-propynyl)-1-pyrroline (140)
N-(6-Phenyl-5-hexynyl)-p-toluensulfonyleamide (129a)
N-(5-Hexynyl)-p-toluensulfonamide (129b)
(E)-N-(6-Phenylhex-5-ynyl)but-2-ynamide (131)
(E)-N-(6-Phenylhex-5-ynyl)but-2-enamide (131)
4-(Hydroxymethyl)-1,6-heptadiyne (136a)
1,7-Diphenyl-4-(hydroxymethyl)-1,6-heptadiyne (136b)
N-(Trifluoroacetyl)-4-(aminomethyl)-1,6-heptadiyne (137a)
N-(Trifluoroacetyl)-4-(aminomethyl)-1,7-diphenyl-1,6-heptadiyne (137b)
N-(Trifluoroacetyl)-4-(aminomethyl)-1,7-diphenyl-1,6-heptadiyne (137b)
4-(Aminomethyl)-1,6-heptadiyne (138a)
4-(Aminomethyl)-1,6-heptadiyne (138a)
4-(Aminomethyl)-1,7-diphenyl-1,6-heptadiyne (138b)
2-Benzoyl-4-((2Z)-3-phenyl-2-propenyl)-1-pyrroline (141)
2-Benzoyl-4-((2Z)-3-phenyl-2-propenyl)-1-pyrroline (141)
1,5-Diphenyl-3-hydroxy-1,4-pentadiyne (145)
O-Acetyl-1,5-diphenyl-3-hydroxy-1,4-pentadiyne (146)
3-Allyl-1,5-diphenyl-1,4-pentadiyne (147)
3-Allyl-1,5-diphenyl-1,4-pentadiyne (147)
O-Tris(trimethylsilyl)silyl-1-hydroxy-ethene (153)
3-Phenyl-2-propyn-1-ol (157)
3-Phenyl-2-propynyl bromide (158)
Methyl 3-oxo-7-phenyl-6-heptynoate (160)
Methyl (Z)-2-hexenoate (173)
Methyl (Z)-4-(methylthio)-2-butenoate (Z175)
Methyl (E)-4-(methylthio)-2-butoenoate (E175)
Ethyl (E)-4-methyl-2-pentenoate (178)
Ethyl (E)-4-methyl-2-pentenoate (178)
Ethyl (E)-4-(methylthio)-butanoate (179)
Ethyl (2S,3R)-2-(benzyloxycarbonylamino)-3-hydroxy-hexanoate (183)
Ethyl (2S,3R)-2-amino-3-hydroxy-4-methyl-pentanoate hydrochloride (186)
Ethyl (2S,3R)-3-hydroxy-4-methyl-2-(tosylamino)pentanoate (187)
N-(Benzoyloxycarbonyl)-L-methionine methyl ester (190)
Methyl (S)-2-(benzyloxycarbonylamo)-4-(methylsulfinyl) butanoate (191)
Methyl (S)-2-(benzyloxycarbonylamino)-3-butenoate (ent-81)
Methyl (2S,3S)-2-(benzyloxycarbonylamino)-3,4-epoxy-butanoate (ent-82)
Methyl (2S,3S)-N-(benzyloxycarbonyl)-2-amino-3-hydroxy-4-(methylthio)-butanoate (192)
Methyl (2S,3S)-2-(benzyloxycarbonylamino)-3-hydroxy-4-(methylthio)-butanoate (192)
(2S,3S)-2-(9-Fluorenylmethylcarbonylamino)-3-hydroxy-4-(methylthio)-butanoic acid (193)
(2S,3S)-2-(9-Fluorenlymethylcarbonylamino)-3-hydroxy-4-(methylthio)-butanoic acid (193)
(2S,3S)-2-(Fluorenlymethylxycarbonylamino)-3-hydroxy-4-(methylthio)-butanoic acid (193)
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