HYDROAMINATION AND C-H ACTIVATION REACTIVITY OF TETRAKIS(AMIDO), BIS(AMIDATE), AND BIS(2-PYRIDONATE) COMPLEXES OF TITANIUM AND ZIRCONIUM

by

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Abstract

The work reported herein focuses on expanding the reaction scope of known group four bis(amidate) and tetrakis(amido) complexes in hydroamination catalysis. The development of new titanium and zirconium complexes exhibiting improved reactivity in hydroamination catalysis and unexpected C-C bond formation are disclosed. The exceptional hydroamination activity of a bis(amidate) titanium bis(amido) precatalyst towards alkynes in the presence of aryl amine co-substrates is elucidated, and the scope of this reactivity was found to include examples of room temperature intermolecular hydroamination. The application of commercially available tetrakis(dialkylamido) titanium(IV) as a precatalyst for the cyclohydroamination of aminoalkenes to form N-heterocyclic products is a particularly attractive contribution due to the ready availability and ease of use associated with this catalyst system.

The second section involves efforts to develop more reactive and selective bis(amidate) bis(amido) hydroamination precatalysts by the rational design and implementation of new amidate ligands modified for enhanced reactivity and selectivity including attempts at enantioselective catalysis. The synthesis and characterization of a bis(amidate) titanium bis(amido) complex incorporating electron withdrawing perfluorophenyl groups for enhanced reactivity, along with the assessment of this system in terms of hydroamination is presented. The synthesis, characterization and evaluation of chiral amidate ligands for the asymmetric cyclohydroamination of aminoalkenes is also described.

In order to generate more reactive group four hydroamination precatalysts, 2-pyridone and its derivatives were investigated as a new class of amidate N,O chelating
proligand. The synthesis and characterization of the first group four bis(2-pyridonate) bis(amido) complexes is presented along with their reactivity towards aminoalkenes. These novel complexes were found to be reactive for both cyclohydroamination and catalytic intramolecular α-functionalization. The initial findings along with a substrate scope analysis, and preliminary mechanistic investigations for this unique and exciting 100% atom economic, catalytic C-C bond forming reaction is included.

The work described in this dissertation contributes to understanding of group four metal catalyzed reactions by illuminating some previously unknown reactivity associated with titanium and zirconium as well as by providing further insight into how ligand structure influences complex reactivity.
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<tbody>
<tr>
<td>2-D</td>
<td>2-Dimensional</td>
</tr>
<tr>
<td>AcOH</td>
<td>Acetic acid</td>
</tr>
<tr>
<td>APCI</td>
<td>Atmospheric pressure chemical ionization mass spectrometry</td>
</tr>
<tr>
<td>APT</td>
<td>Attached proton test</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
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<tr>
<td>Bn</td>
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<td>Gas chromatography-mass spectrometry</td>
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<td>iPr</td>
<td>iso-propyl</td>
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$J$  
Coupling constant, in NMR spectroscopy

LAH  
Lithium aluminum hydride

Ln  
Lanthanide atom

LR-MS  
Low-resolution mass spectrometry

M  
i) metal atom

ii) central atom or parent peak in MS

iii) concentration, in molarity

MS  
Mass spectrometry

m  
Multiplet, in NMR spectroscopy

Me  
Methyl

MHz  
Megahertz

mmol  
Millimole

mol  
Mole

N  
Normality

$n$Bu  
n-Butyl

NMR  
Nuclear magnetic resonance

OAc  
Acetate

ORTEP  
Oak Ridge Thermal Ellipsoid Plot

Ph  
Phenyl

PMP  
para-methoxyphenyl

ppm  
Parts per million, in NMR spectroscopy

R  
Alkyl group

RT  
Room temperature

s  
Singlet, in NMR spectroscopy

SAR  
Structure-activity relationship

sat.  
Saturated

sept  
Septet, in NMR spectroscopy

t  
Triplet, in NMR spectroscopy

T  
Temperature, °C

t  
$t$-tert

TBDMS  
t-Butyl-dimethylsilyl

$t$Bu  
t-Butyl
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</tr>
<tr>
<td>TLC</td>
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</tr>
<tr>
<td>tol</td>
<td>Toluene</td>
</tr>
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<td>Ts</td>
<td>p-toluenesulfonyl</td>
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<td>π</td>
<td>Pi, as in π-bond</td>
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<tr>
<td>σ</td>
<td>Sigma, as in σ-bond</td>
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</table>
Foreword

The work that is reported in this thesis focuses on expanding the reaction scope of known group four bis(amidate) and tetrakis(amido) complexes in hydroamination catalysis as well as the development of new titanium and zirconium complexes for improved hydroamination activity. As this is a manuscript based thesis, each chapter is meant to be a stand-alone document. Therefore, one will find that there is some repetition in the introductory information between the chapters. However, compound labeling has been maintained throughout this thesis and therefore any compound referred to in multiple chapters will have the same identifier. Each chapter is organized with an introduction, results and discussion, summary and conclusions section, and references. An appendix containing tables of crystallographic parameters, ORTEP diagrams, and representative $^1$H and $^{13}$C NMR spectra for the different classes of compounds synthesized in chapters two, three, four and five is also included at the end of this thesis. Assignment of $^1$H NMR spectra was based on chemical shift, peak shape and integration. Where confident assignment of 1D spectra was not possible, COSY, HMQC and HMBC NMR experiments were carried out to unambiguously interpret the data. Yields reported within this thesis are estimated to be accurate within +/- 5%. Instances where yields or product distributions were found to vary substantially have been highlighted.
Acknowledgements

Firstly, I would like to thank my supervisor, Dr. Laurel Schafer, for her guidance and support in all aspects of this undertaking. I would also like to thank both past and present members of the Schafer group for their help in the lab. I would like to thank the various shops and services in the chemistry department at UBC, including the mech shop, the glassblower, the NMR staff, and the analytical services staff. In particular, I would like to thank Brian Patrick, Neal Yonson and Rob Thomson for assistance with X-ray crystallography. I would like to thank UBC, the UBC chemistry department, Boehringer Ingelheim, and NSERC for funding. Finally, I would like to thank my parents for their support over the years.
Co-Authorship Statement

All of the work reported in this thesis was performed by Jason A. Bexrud. Any conclusions or experimental results referred to in the text of this thesis that were obtained by other parties have been clearly identified and cited. Laurel L. Schafer is the principle investigator for this work and assisted in design of the research program, data analysis, and manuscript preparation.
CHAPTER ONE: INTRODUCTION TO HYDROAMINATION AND THE DEVELOPMENT OF GROUP FOUR BASED HYDROAMINATION PRECATALYSTS

1.1 General introduction

Nitrogen containing compounds are ubiquitous in chemistry and are employed in a wide range of important agrochemical, pharmaceutical, and industrial roles. Therefore, the development of new methodologies that have the potential to reduce cost and simplify their production is of great importance. To this end, hydroamination (Equation 1.1) has drawn a great deal of attention in past years, primarily due to the potential for this strategy to be a much more efficient means of synthesizing these compounds than traditional methods.

\[
\text{H—NR}_2 \rightleftharpoons \text{H—NR}_2
\]  

(1.1)

As depicted in Equation 1.1, the term hydroamination describes a chemical transformation in which a new C-N bond is formed via the net addition of N-H across a carbon-carbon multiple bond (double or triple). The absence of any byproducts renders this reaction a completely atom economic process, and therefore an extremely efficient means of generating nitrogen containing molecules from readily available starting materials. From a thermodynamics standpoint, the hydroamination of alkenes is considered to be nearly thermonuetral or even slightly exothermic, while the hydroamination of alkynes has been estimated to be even more exothermic than the hydroamination of alkenes. Also, there is a high activation barrier associated with this transformation which results from electrostatic repulsion between the lone pair of the
nitrogen and the electron rich π system of the unsaturated carbon-carbon bond. In addition, a direct [2+2] cycloaddition reaction between the N-H bond and the carbon-carbon multiple bond is a symmetry forbidden process.

In order to circumvent the high activation barrier associated with this transformation, alkali metals, lanthanides and transition metal based complexes have been used to create alternative reaction pathways. This has been done using two general approaches; activation of the carbon-carbon multiple bond to nucleophilic attack, or activation of the N-H bond. Activation of an alkene or alkyne can be accomplished by their coordination to a Lewis acidic metal center, such as silver(I), gold(I), palladium(II) and platinum(II). N-H bond activation on the other hand, is achieved in four distinct ways. These include deprotonation to generate a more nucleophilic amide species (alkali metal catalyzed reactions); formation of a reactive M-N bond via protonolysis, with which a coordinated carbon-carbon multiple bond can then react through σ-bond insertion (rare earth metals, lanthanides); formation of a reactive M=N bond via protonolysis, with which a coordinated carbon-carbon multiple bond can then react in a [2+2] cycloaddition reaction (group four and five metals); and finally by oxidative addition to a low valent late transition metal such as iridium, ruthenium or rhodium to form an H-M-N species which can then subsequently react with an alkene or alkyne by a coordination/insertion/reductive elimination pathway.

As is depicted in Scheme 1.1, the hydroamination of alkynes initially produces enamines, which rapidly undergo tautomerization to the corresponding imines and aldimes (not shown). These initial products are useful synthetic intermediates that can be converted to amines, carbonyl compounds or be used for more elaborate tandem
reactions, such as the Strecker reaction\textsuperscript{15} and the Pictet-Spengler cyclization.\textsuperscript{16} The hydroamination of alkenes directly affords more highly functionalized amines, and unlike alkyne hydroamination, has the potential to generate optically active products.

\textbf{Scheme 1.1.} Hydroamination of terminal or monosubstituted alkenes and alkynes.

While the development of systems for the hydroamination of alkynes has arguably reached a level of maturity, and the methodology is beginning to be applied as a synthetic tool; a robust, reactive, selective, and functional group tolerant catalyst system capable of reacting with a broad range of unactivated alkenes substrates is still an illusive goal.\textsuperscript{1} Currently, state of the art catalyst systems developed for alkene hydroamination are only capable of the intramolecular reaction (this will be discussed in more detail in section 1.2) or are limited to activated alkenes.

Group four based organometallic complexes have played a prominent role in the field of hydroamination catalysis, primarily due to their relative low cost, low toxicity, and high reactivity.\textsuperscript{11,16,17} Recent reports highlighting the increasingly efficient and diverse capability of these catalytic systems have shown that alkynes,\textsuperscript{4, 16, 18} allenes,\textsuperscript{19}
and alkenes\textsuperscript{30} can be converted to imines, amines and N-heterocycles with a high degree of regio- and stereo-selectivity. Some of the more well recognized titanium and zirconium hydroamination catalyst systems are shown in Figure 1.1.

![Figure 1.1. Titanium and zirconium hydroamination precatalysts.](image)

The efforts of the Schafer group to further this endeavor have focused on the use of titanium and zirconium bis(amidate) bis(amido) complexes as hydroamination precatalysts.\textsuperscript{16, 19a, 20a, 21} Amidates are a group of monoanionic, N\textsubscript{2}O chelating ligands derived from amides that can be easily prepared from commercially available acid chlorides and primary amines (Equation 1.2).
The modular nature of this synthetic route allows one to systematically vary the substituents in the R¹ and R² position. This in turn permits the study of how electronic and steric properties of the ligand affect the catalytic activity in the resulting precatalyst. The bis(amide) complexes are generated from commercially available Ti(NR₂)₄ or Zr(NR₂)₄ and two equivalents of the amide proligand via protonolysis according to Equation 1.3.

\[
\begin{align*}
R^1\text{N}^+\text{M(NR}_2)_4 + \text{Et}_2\text{O} & \rightarrow \text{R}^1\text{N}^+\text{M(NR}_2)_2 \text{ (1.3)} \\
R = \text{Me, Et} & \rightarrow -2 \text{ eq. HNR}_2
\end{align*}
\]

Solid state structural information for a number the bis(amide) titanium/zirconium bis(amido) complexes indicates that a pseudo octahedral coordination geometry about the metal center is prevalent in these compounds.²² Of the five possible diastereomeric coordinational isomers shown in Figure 1.2, only the C₁, N-trans-C₂, and the O-trans-C₂ geometry, have been observed, all of which position the two amido ligands in a cis arrangement, which is desirable from a catalyst development standpoint as these represent the active sites during catalysis.²²

![Figure 1.2. Possible coordination geometries of bis(amidate) bis(amido) complexes.](image)
To date, we have found that the titanium bis(\(N\)-2,6-diisopropylphenyl(phenyl)-amidate) bis(diethylamido) complex 1.1 (\(R^1 = \text{Ph}, R^2 = 2,6\)-diisopropylphenyl) is the most effective bis(amidate) titanium bis(amido) precatalyst for the hydroamination of terminal alkynes with primary amines.\(^{16}\) With this precatalyst, secondary, tertiary, and quaternary alkyl substituted primary amines can be coupled with a range of terminal alkynes to give exclusively the anti-Markovnikov aldime products. In addition complex 1.1 was found to be tolerant of various functional groups including amides, esters, silyl protected propargylic alcohols, and imine protected propargylic amines. This particular bis(amidate) titanium bis(amido) complex adopts the N-trans-C\(_2\) geometry (Figures 1.2 and 1.3) which is favored for steric reasons due to the presence of the bulky 2,6-diisopropylphenyl substituents.

Figure 1.3. ORTEP diagram of complex 1.1 with ellipsoids set at the 50 % probability level. Hydrogen atoms have been omitted for clarity.
1.2 Intramolecular alkene hydroamination

Intramolecular alkene hydroamination, or cyclohydroamination of aminoalkenes, is simply the addition of N-H across a C=C bond in an intramolecular fashion as depicted in Equation 1.4. The products of this transformation are referred to as N-heterocycles.

\[ \text{equiv. alkene} + \text{NH}_2 \xrightarrow{\text{catalyst}} \text{N-heterocycle} \]

N-heterocyclic compounds are employed in a wide range of important agrochemical, pharmaceutical, and industrial applications. There are a multitude of alkaloid natural products containing the N-heterocyclic framework which exhibit potent biological activities and therefore serve as lead compounds for the discovery of new and more effective drug treatments of diseases plaguing modern society. Some recent examples of pyrrolidine and piperidine alkaloids having useful pharmacological properties are shown in Figure 1.4.

The pseudodistomin family of natural products are examples of piperidine alkaloids, which have been isolated from marine organisms and are known for their potent cytotoxicity and antitumor activity.\(^{23}\) Synthetic derivatives of the natural product (-)-O-acetyl-spectaline, a piperidine alkaloid isolated from a south American plant species Cassia spectabilis, have been examined as cholinesterase inhibitors for the treatment of Alzheimers disease.\(^{24}\) (-)-\(\alpha\)-Kainic acid belongs to the kainoid family of marine natural products and is an example of a pyrrolidine alkaloid.\(^{25}\) Due to the neuroexcitatory properties of this particular family of compound they have been used extensively in the
study of neurological diseases such as Alzheimers, epilepsy, and Huntingtons.\textsuperscript{26} 3,5-Disubstituted indizolidines, such as (-)-monomorine, are pyrrolidine alkaloids which are also known for their pharmacological activity.\textsuperscript{27} In particular due to their efficacy as nicotinic receptor ligands, this class of compound has drawn the attention of researchers working towards the development of treatments for Alzheimers, Parkinsons, acute and chronic pain, as well as smoking cessation.\textsuperscript{28}

![Image of pseudodistomins A-D]

\textbf{Figure 1.4}: Pyrrolidine and piperidine natural products.

Often, the actual quantities of these materials available from natural sources are severely limited, which makes their total synthesis the only available means of procuring
sufficient amounts for the study of the structure and activity of these compounds. In addition, synthetic analogues of the natural compounds designed to have different or more desirable biological properties would obviously benefit from a modular synthetic strategy. Therefore, the development of new methodologies, such as hydroamination, which have the potential to reduce cost and simplify the production of N-heterocyclic compounds is of great importance. Although the intramolecular hydroamination of aminoalkenes is a synthetically important transformation in itself, it also represents a starting point towards the ultimate goal of developing efficient methodologies for the more challenging intermolecular reaction.

Among the earliest reported alkene hydroamination catalysts are lanthanide or group three based systems which exhibited limited functional group tolerance and high moisture sensitivity, making their preparation and implementation in synthesis problematic. The postulated mechanism for lanthanide and group three catalyzed cyclohydroamination is outlined in Scheme 1.2. The key intermediate in this cycle is the catalytically active amido species A, which undergoes σ-bond insertion with the coordinated olefin to generate the new C-N bond.

Prior to this work a number of late metal based systems capable of affecting the hydroamination of alkenes had been reported. The operative mechanism for these systems is thought to involve either alkene activation, or N-H activation via oxidative addition as described in section 1.1. These systems were found to be limited to activated olefinic substrates.
Scheme 1.2. Mechanism for the lanthanide and group three intramolecular alkene hydroamination.

As was also mentioned in section 1.1, group four systems; which are attractive for their low toxicity, low cost, and high reactivity; have been widely examined as alkyne and allene hydroamination catalysts, but prior to the work described in this thesis, the only known examples of alkene hydroamination using these metals involved cationic species which are isoelectronic to group three metals and are plagued with extreme moisture sensitivity. In addition, these cationic catalysts were ineffective in carrying out the hydroamination of alkenes with primary amines. Although, the application of commercially available Ti(NMe$_2$)$_4$ for both the intra and intermolecular hydroamination of alkynes and allenes had been reported, no information was available in the literature regarding its application; or the application of any other neutral group four
metal based complex; to alkene hydroamination. This challenge is a focus of catalyst
development efforts reported in this thesis.

Another important feature of the cyclohydroamination reaction is that a stereogenic
carbon center is generated α to the nitrogen upon formation of the new C-N bond.
Therefore, the ability to affect the cyclohydroamination reaction in an enantioselective
fashion is extremely valuable, considering that all of the compounds depicted in Figure
1.4, along with a multitude of other biologically relevant compounds, possess the α-chiral
amine structural motif. The earliest reported enantioselective hydroaminations involved
the use of chiral *ansa*-lanthanocenes as catalysts for the cyclohydroamination of primary
aminoalkenes, which attained a moderate level of success with enantiomeric excesses as
high as 74%. These systems have been superseded by a number of different non-
cyclopentadienyl rare earth based complexes with enantiomeric excesses of greater than
90% being reported in some instances. As was mentioned previously, there are some
major drawbacks associated with the chemistry involving rare earth elements. Namely,
the resultant complexes developed for catalysis are difficult to prepare and handle due to
an extreme intolerance of moisture.

The first group four complex reported to affect the enantioselective
cyclohydroamination of aminoalkenes was the cationic zirconium aminophenolate
complex prepared by Scott and coworkers. The system that they developed catalyzed
the cyclization of a limited range of secondary aminoalkenes with enantioselectivities as
high as 82%. Although their work represented an important innovation in that it
demonstrated the capacity for group four based complexes to be used in this role, the fact
that the title complex was cationic somewhat detracts from its usefulness, as the reactivity
of cationic zirconium complexes are known to more closely resemble that of rare earth
based complexes and as a result they are also extremely moisture sensitive and
challenging to prepare.

Based upon the results presented in this thesis, the first published effort to exploit the
aminoalkene hydroamination activity observed with neutral group four elements and
extend the methodology to enantioselective catalysis was made by Bergman and
coworkers.\textsuperscript{20d} Their work involved the screening of various in situ prepared zirconium
catalysts that utilized readily available chiral ancillary ligands. These proligands included
sulfonamides, phosphinic amides, secondary amines, as well as alcohols, which were
either bi-, tri-, or tetradentate. Being chiral ancillary ligands, most incorporated axially
chiral biphenyl type frameworks or the chiral trans-1,2-substituted cyclohexane
backbone. The most effective in situ prepared precatalyst, which is depicted in Figure
1.5, was the bis(phosphinic amide) zirconium bis(amido) complex 1.2 that utilized a
chiral tetradentate phosphinic amide derivative of (R,R)-1,2-diaminocyclohexane as an
ancillary ligand. This compound proved to be competent in the role of enantioselective
cyclohydroamination catalysis with enantiomeric excesses as high as 80% being attained.

\begin{center}
\textbf{Figure 1.5.} Bis(amidate) zirconium bis(amido) complex 1.2 incorporating a chiral
phosphinic amide proligand prepared by Bergman and coworkers for the
asymmetric cyclohydroamination reaction.
\end{center}
The zirconium complex 1.3 depicted in Figure 1.6 was developed simultaneously in our group\textsuperscript{20a} for the enantioselective cyclohydroamination reaction. Like their most effective precatalyst, it too incorporated a chiral, tethered, tetradentate bis(amidate) ancillary ligand in which the two groups binding the metal were linked via a chiral bridge. This design feature is common to most catalysts, and it is thought to improve enantioselectivity by reducing the number of possible geometric isomers and enforcing a rigid chiral steric environment about the metal center. The Schafer precatalyst employs an axially chiral 6,6'-dimethylphenyl backbone, to which N-mesitoyl amide groups were appended in the 2 and 2' positions. The use of an axially chiral biphenyl motif as a source of chirality for asymmetric catalysis is very well preceded\textsuperscript{35} and was an obvious choice for these initial investigations.

\begin{center}
\includegraphics[width=0.2\textwidth]{figure1.6.png}
\end{center}

**Figure 1.6.** Bis(amidate) zirconium bis(amido) complex 1.3 incorporating an axially chiral ligand framework developed for enantioselective cyclohydroamination.

Complex 1.3 was found to be as effective and in some instances more effective than complex 1.2 for the enantioselective conversion of primary aminoalkene substrates to the corresponding N-heterocyclic products with enantiomeric excesses ranging from 62 – 93
The conversion of 2,2-dimethyl-4-pentenylamine to 2,4,4-trimethylpyrrolidine proceeds with the highest yet reported enantiomeric excess for this widely used test substrate (Equation 1.5). Although pyrrolidine formation proceeds for the most part with good stereoselectivity, much lower enantiomeric excesses were obtained when piperidine compounds were produced, albeit in good yield, from the requisite aminoalkene substrates. This diminished enantioselectivity in the formation of 6-membered ring products was also observed by Bergman and coworkers using complex 1.2. It is argued that this results from a larger, less organized 8-membered ring transition state through which the reaction must proceed to form the piperidine products.

\[
\begin{align*}
\text{10 mol\% precatalyst} & \\
110 \degree C, 3h & \\
\text{>98\% yield} & \\
93\% ee & \\
\end{align*}
\]

More recently the Scott group has reported that the chiral-at-metal diamide oxazoline zirconium complexes 1.4 and 1.5 depicted in Figure 1.7 are capable of affecting the enantioselective cyclization of a limited number of aminoalkenes with moderate enantiomeric excesses.\textsuperscript{36} A fundamental design aspect of this system that sets it apart from the previous two is that the chiral ancillary ligand is bidentate rather than tetradentate. One would expect this to be detrimental in terms of stereoselective catalysis as these complexes lack the configurational stability present in complexes 1.2 and 1.3, therefore more than one diastereomeric coordination isomer could then exist in solution. Interestingly, only the diastereomer depicted in Figure 1.7 was observed in solution and moderate selectivity was indeed obtained. This particular coordination geometry is likely
dictated by the bulky substituents (phenyl and t-butyl) appended to the oxazoline ring, which insure that the R group is oriented away from the pentamethylcyclopentadienyl ligand. Although the enantiomeric excesses that they observed using this system were moderate (≤ 70%) relative to the previously described chiral complexes, reaction times were notably faster.

![Complexes 1.4 and 1.5](image)

**complex 1.4**  
**complex 1.5**  

**Figure 1.7.** Chiral-at-metal diamide zirconium complexes 1.4 and 1.5 reported by Scott and coworkers.

Despite being able to obtain some impressive enantioselectivities with the systems developed thus far, these precatalysts can only be applied to a limited range of substrates which severely detract from their usefulness as tools for synthetic applications. The notable drop in enantioselectivity when they are applied to substrates that form larger piperidine compounds demonstrates a significant limitation. Clearly, a great deal of modification may be required in order to increase the reactivity of group four based complexes to a point where the intermolecular alkene hydroamination reaction becomes a possibility. To do this while maintaining stereoselectivity will be a considerable challenge.
1.3 Modifying the ligand for enhanced reactivity

Ancillary ligands play a crucial and varied role in transition metal chemistry. As we have seen in section 1.2, one of their primary functions in catalysis is to modulate the steric environment about the reactive site in order to impart a particular selectivity (regeo- or stereoselectivity) on a chemical transformation through non-bonding interactions. In the interest of achieving optimal reactivity, ancillary ligands are also often used to modify the Lewis acidity of the metal center through inductive effects. Compounds incorporating organic fragments are most commonly employed as ancillary ligands because they offer the greatest amount of flexibility in terms of structural variation, which is essential for fine tuning reactivity.

Both steric and electronic properties of the ancillary ligand can have a dramatic impact on both the activity and selectivity of group four based hydroamination precatalysts. Beller and coworkers have demonstrated that steric modification alone, can have a substantial effect on both the reactivity and selectivity of the titanium bis(aryloxide) system (Scheme 1.3). In terms of the intermolecular hydroamination of alkynes they observed that the use of less bulky aryloxide ligands resulted in catalysts that exhibited diminished reactivity and produced regioselectivities that were opposite to what was obtained when they used bulkier aryloxide ligands.
Scheme 1.3. Steric and electronic modification of the bis(phenoxide) ligand set and its impact on the hydroamination of 1-hexyne with benzylamine.

In conjunction with the work carried out by Beller and coworkers, members of our group have looked at the analogous bis(pyrimidoxide) titanium bis(amido) complexes ($X = N$, Scheme 1.3) as hydroamination precatalysts. Based on the greater relative acidity of pyrimidinols (approximate pKa value of 7), it was expected that the pyrimidoxide ancillary ligand would increase the electrophilicity at the metal center, and thus increase catalyst activity. Indeed the bis(pyrimidoxide) catalysts were found to be more reactive, yet less regioselective than the corresponding, sterically equivalent phenoxide ligands.

With respect to amide ligands, previous work done by our group indicated that varying the electronic properties of this class of ligand while maintaining consistent steric properties could dramatically modify reactivity. More specifically, it has been found that by replacing the phenyl group in the $R^1$ position of complex 1.6 (Figure 1.8) with a perfluorophenyl group (complex 1.7, Figure 1.8) the relative rate of intramolecular alkyne hydroamination could be increased by approximately 14 times (Equation 1.6).
is thought that the electron withdrawing perfluorophenyl group in this position creates a more electrophilic metal center, resulting in a complex exhibiting enhanced reactivity.

Figure 1.8: Progression in the design of the bis(amidate) ligand framework.

In addition to varying the electronic nature of the amidate ligand, former members of our group have also probed the effect of the steric environment about the reactive metal center by changing the substituent in the R² position from a t-butyl group to a more bulky 2,6-diisopropylphenyl group (complex 1.1) while leaving the phenyl group in the R¹ position unchanged. It was found that increasing the steric bulk of the ligand improves the anti-Markovnikov regioselectivity for the reaction of 1-hexyne with tert-butylamine (Equation 1.7).
As well as the enhanced regioselectivity, they also observed an increase in the relative rate of reaction when complex 1.1 was employed as the precatalyst (compared to complex 1.6). To explain the latter observation a mechanism based upon the catalytic cycles investigated by Bergman\textsuperscript{2a,8} and Doye\textsuperscript{2a} for cyclopentadienyl titanium imido catalyzed intermolecular hydroamination of alkynes (Scheme 1.4) was proposed, and therefore, the increased rate of catalysis in the presence of complex 1.1 was attributed to the added steric bulk of the N-2,6-diisopropylphenyl substituents inhibiting the formation of the inactive dimeric species B.

Scheme 1.4. Simplified proposed catalytic cycle for the group 4 catalyzed hydroamination of alkynes.
Thus both electronic and steric effects have been noted to enhance reactivity in amidate complexes of group four metals. By taking advantage of the modular ligand framework accessible here, amidate ligands allow for facile optimization of catalytic reactivity and selectivity.

1.4 Scope of thesis

Two basic strategies were employed in this thesis to further the field of group four metal catalyzed reactions involving amines. Firstly, the capabilities of existing systems were expanded upon by modifying reaction conditions or by taking advantage of unique reactivity (chapters two and five); and secondly, attempts were made to generate more reactive and selective group four catalysts by the rational design and implementation of new ancillary ligands (chapters three and four).

As was mentioned in section 1.1, the titanium bis(N-2,6-diisopropylphenyl(phenyl)amidate) bis(dimethylamido) complex 1.1 was found to be a very effective precatalyst for the hydroamination of terminal alkynes with primary aliphatic amines. Prior to this work little information with respect to the reactivity of complex 1.1 towards aryl amine substrates was available. However, there were some preliminary findings that suggested complex 1.1 might be particularly reactive in the presence of this type of amine co-substrate. In chapter two the elucidation and synthetic exploitation of the exceptional reactivity of complex 1.1 towards aryl amines is described. In addition, the reactivity of Ti(NMe$_2$)$_4$ towards aminoalkenes, along with the initial efforts made to expand the
capabilities of the bis(amide) bis(amido) system to include the intramolecular hydroamination of aminoalkenes is discussed.

In chapter three, ligand design efforts to produce bis(amide) complexes incorporating amidates modified for enhanced reactivity as well as enantioselective catalysis are described. Based on previous findings discussed in section 1.3, an improved catalyst design was devised, having a perfluorophenyl group in the \( R^1 \) position and a 2,6-diisopropylphenyl group in the \( R^2 \) position. Sections in chapter three present the synthesis and characterization of this new complex, as well as the results of alkyne and alkene hydroamination experiments carried out to assess it as a hydroamination precatalyst.

As was mentioned in section 1.2, there are significant limitations in the capabilities of current group four asymmetric cyclohydroamination catalysts which utilize tethered ligand frameworks. One of the weaknesses of the tethered ligand design is that synthesis and resolution of non-racemic derivatives, in which the actual biphenyl portion has been modified can be difficult and time consuming. These approaches impede structure activity relationship studies. Another disadvantage of this type of scaffold is that the steric environment that it creates is somewhat removed from the reactive metal center, which in turn may limit the influence that it has on selectivity. In the interest of addressing these issues we considered using non-tethered chiral amides derived from simple, readily available chiral primary amines as an alternative class of proligand. Thus, ligand design addressed in chapter three also describe the attempts made to modify the bis(amide) ligand design for enantioselective catalysis using commercially available (-)-menthone as a source of chirality.
As an alternative means of generating a more electrophilic, and hence reactive, metal center, we also considered 2-pyridone and its derivatives as a new class of N,O chelating ligands. Based loosely on relative pKa values, it was expected that the 2-pyridonate ligand framework would be more electron withdrawing than the amidate scaffold. Additionally, it was also expected that with the substituents adorning these ligands being somewhat removed from the metal center, it would be possible to create a more accessible reactive site while maintaining a sufficient level of steric bulk to mitigate the formation of catalytically inactive dimer species. Chapter four describes the synthesis and characterization of three different bis(2-pyridonate) complexes, as well as their assessment as catalysts for the cyclohydroamination of aminoalkenes.

An unexpected outcome to the application of zirconium pyridonate complexes as cyclohydroamination precatalysts is described in chapter five, where the conversion of 6-heptenylamines to aminocyclohexane derivatives via intramolecular α-functionalization is achieved. Our initial findings along with our attempts to delineate the scope, and deduce a plausible mechanistic rationale for this unique reactivity are included in this chapter.
1.5 References


(15) Lee, A.V.; Schafer, L.L. *Synlett* 2006, 18, 2973.


Senn, H. M.; Blochl, P. E.; Togni, A. J. Am. Chem. Soc. 2000, 122, 4098. (g)


CHAPTER TWO: FURTHER DELINEATING THE SYNTHETIC UTILITY OF EXISTING TETRAKIS(AMIDO) AND BIS(AMIDATE) TITANIUM BIS(AMIDO) HYDROAMINATION PRECATALYSTS

2.1 Introduction

Nitrogen containing compounds are ubiquitous in chemistry and are employed in a wide range of important agrochemical, pharmaceutical, and industrial roles. Therefore, the development of efficient methodologies, such as hydroamination, that have the potential to simplify their production is of great importance. The work carried out in the Schafer group focuses on the use of bis(amidate) bis(amido) complexes of titanium and zirconium as hydroamination precatalysts. To date, we have found that the bis(N-2,6-diisopropylphenyl(phenyl)-amidate) titanium bis(dimethylamido) complex 1.1 is the most effective bis(amidate) titanium bis(amido) precatalyst for the hydroamination of terminal alkynes with aliphatic primary amines.

During the course of initial substrate scope investigations carried out by previous members of our group, it was revealed that sterically unencumbered aryl amines, such as aniline, might be particularly reactive as hydroamination co-substrates in the presence of complex 1.1. In alkyne hydroamination reactions that were monitored by $^1$H NMR spectroscopy small amounts of product appeared to be forming prior to the application of heat. Additionally, it was apparent that some sort of side reactivity leading to the formation of unidentified byproducts was also taking place in these reactions. Sections 2.2.1 through 2.2.4 of this chapter deal with the elucidation and synthetic exploitation of the exceptional reactivity observed with aryl amines in the presence of complex 1.1.

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To fully take advantage of the possibility that this system may affect the hydroamination of alkynes under exceptionally mild conditions and in the interest of further demonstrating the synthetic utility of this methodology we also set out to investigate the possibility of using p-anisidine as the primary amine for the hydroamination of alkynes. This strategy would provide a means of preparing PMP protected primary amines from alkynes under relatively mild conditions. The PMP group is a well known protecting group for amines that can be cleaved under oxidative conditions typically using oxidizing agents such as ceric ammonium nitrate\(^1\) and more recently periodic acid.\(^2\) The net transformation is the efficient conversion of an alkyne to a primary amine (Scheme 2.1).

![Scheme 2.1](image)

**Scheme 2.1.** Hydroamination of alkynes leading to PMP-protected primary amines.

To further expand the substrate scope, we also looked at the feasibility of using TBDMS protected propargyl alcohols as alkyne substrates. The majority of catalytic systems developed for the intermolecular hydroamination of alkynes reported to date have typically employed simple non-functionalized aliphatic or aromatic alkynes as test substrates. To our knowledge only one system has been shown to affect the hydroamination of alkynes bearing protected hydroxyl functionalities directly adjacent to the carbon-carbon triple bond. Beller and coworkers\(^3\) have recently reported the
hydroamination (or more accurately the hydrohydrazination) of silyl protected propargyl alcohol derivatives with \(N\)-methyl-\(N\)-phenylhydrazines using an in situ generated bis(2,6-di-tert-butyl-4-methylphenolate)titanium bis(amido) precatalyst. These reactions required elevated reaction temperatures (100 °C) and were low yielding. In addition this system appears to be limited to applications that involve \(N\)-methyl-\(N\)-phenylhydrazine derivatives as yields of less than 5% were obtained when either aniline or isobutylamine were used as the amine substrate. The successful application of our system to the hydroamination of these types of substrates would not only demonstrate that the bis(amidate) titanium bis(amido) precatalyst is tolerant of substrates bearing proximally located protected hydroxyl functionalities but would also further demonstrate the utility of this methodology by providing entry into useful synthetic precursors to \(\beta\)-amino alcohols and \(\alpha\)-amino acids (Scheme 2.2).

![Scheme 2.2](image)

**Scheme 2.2.** Hydroamination of TBDMS protected propargyl alcohols leading to the formation of synthetically useful protected \(\beta\)-amino alcohols and \(\alpha\)-amino acids.

Section 2.2.5 describes the results of initial investigations into the neutral group four metal catalyzed intramolecular aminoalkene hydroamination reaction (Equation 1.2). As was mentioned in chapter one, prior to this work no information was available in the literature regarding the application of Ti(NMe₂)₄ to alkene hydroamination. It was
therefore important for us to examine this complex for intramolecular aminoalkene hydroamination activity in addition to our bis(amidate) complexes, as this would provide a benchmark for comparison purposes. While the majority of the work in section 2.2.5 involves the reactivity of Ti(NMe₂)₄ towards aminoalkenes, the results of experiments using complex 1.1 as the precatalyst are also included, and the reactivity of this complex relative to Ti(NMe₂)₄ is discussed.

Finally, the last section in this chapter describes experiments that were carried out to demonstrate the viability of using *in situ* generated bis(amidate) titanium bis(amide) complex 1.1 as a precatalyst for the hydroamination reaction. This is an important aspect of designing a practical catalyst system that can be conveniently utilized by synthetic chemists who do not have access to the equipment required for preparing air and moisture sensitive materials on gram scale.

2.2 Results and Discussion

2.2.1 Hydroamination of terminal alkynes with aniline and *p*-anisidine at ambient temperature

In order to elucidate the nature of the reactivity observed in the initial stages of the reaction involving complex 1.1 as the precatalyst for the hydroamination of phenylacetylene with aniline as the amine co-substrate, the original reaction conditions can be reproduced, but instead of heating the reaction, the NMR tube is simply left on a benchtop for a period of 24 hours. Isolation of the reduced amine product reveals that the
hydroamination of phenylacetylene with aniline catalyzed by complex 1.1 proceeds with good yield and almost exclusive regioselectivity for the anti-Markovnikov product (Equation 2.1). This represents one of the few examples of intermolecular hydroamination of terminal alkynes with arylamines at ambient temperature,\(^4\) consequently substrate scope was evaluated.

\[
\begin{align*}
\text{PhC} &= \text{c}+ \text{NH}_2 \rightarrow \text{PhCH} \quad 1) 5 \text{ mol\% complex 1.1} \\
& \quad \text{RT, 24h} \\
& \quad 2) \text{NaCNBH}_3 \\
& \quad 83\% \\
& \quad (>49:1 \text{ AM:M})
\end{align*}
\]

The hydroamination of various terminal alkynes with \(p\)-anisidine was then carried (Scheme 2.3). \(p\)-Anisidine was examined extensively rather than aniline because hydroamination with this co-substrate is more synthetically useful in that it leads to the formation of PMP protected primary amines, as described in the introduction to this section. These results show that the reactivity of the \(p\)-methoxy substituted analogue of aniline is comparable in the hydroamination of phenylacetylene when complex 1.1 is used as the precatalyst.
Scheme 2.3. Intermolecular alkene hydroamination reactions with complex 1.1 as the precatalyst.

The above reactions are carried out on a small preparative scale, typically on the order of 1.0 mmol of the alkyne substrate. They are set up in a nitrogen filled glove box, and involve adding the precatalyst to 1 – 2 mL of benzene followed by the amine and the alkyne. The solution is then transferred to a small Schlenk tube containing a magnetic stir bar, sealed, removed from the glove box, and left to stir at ambient temperature for 24 hours. The reduction protocol follows literature precedent for the reduction of imines with NaCNBH₃. The reported yields are based on isolated amine products following column chromatography.
With isolated yields greater than 70%, the efficiency of this method for preparing PMP protected amines from alkynes under such mild conditions is unparalleled. It should be noted that although the yield for the hydroamination of 3,3-dimethyl-1-propyne is quite moderate relative to the other reactions in this section, a higher conversion of ~70% is observed after 48 hours (vs. ~50% after 24 hours). The increased steric encumbrance coupled with the volatility of this particular substrate likely inhibits the hydroamination reaction significantly. The regioselectivities observed for most of these reactions, as determined by $^1$H NMR spectroscopy, are very high and favor the formation of the anti-Markovnikov product almost exclusively. The regioselectivity does drop off substantially when less sterically encumbered terminal alkyl substituted alkynes are employed.

2.2.3 Hydroamination of internal alkynes with $p$-anisidine

Internal alkynes had previously presented a particular challenge for our system. All previous attempts to effect the hydroamination of symmetrically substituted internal alkynes with alkyl amine co-substrates using complex 1.1 as the precatalyst had failed. It was hoped that the increased hydroamination activity of this system in the presence of aryl amines would permit the reaction to proceed even if more forcing reaction conditions were required.

Using aniline as the amine co-substrate the hydroamination of 1-phenyl-1-propyne can be carried out efficiently, although an elevated temperature of 110 °C is required (Equation 2.2). This hydroamination reaction and all other reactions described in this
section are set up and carried out in the same manner as the terminal alkyne experiments described in the last section. The one difference being that these reactions are heated for 24 hours in an oil bath rather than being left to stir for 24 hours at ambient temperature.

\[
\text{C}_6\text{D}_6, 110 ^\circ\text{C}, 24\text{h}
\]

\[
\text{NaCNBH}_3, \text{ZnCl}_2 \quad \text{MeOH}
\]

\[
> 98 \%
\]

The amine product shown in Equation 2.2 can be isolated in nearly quantitative yield as one regioisomer. By following the reaction by \(^1\text{H}\) NMR spectroscopy it is apparent that the reaction goes to completion within 1 hour at this temperature, suggesting that more moderate temperatures could be employed, in combination with longer reaction times.

As shown in Scheme 2.4 \(p\)-anisidine is as reactive as aniline, with essentially a quantitative yield of the amine product being isolated. A number of other internal alkyne substrates including diphenylacetylene, 3-hexyne, and 4,4-dimethyl-2-butyne were also utilized as the alkyne substrates. In most cases the desired amine products can be isolated in nearly quantitative yield and where regioselectivity is an issue, only the regioisomer shown can be detected by analysis of the crude \(^1\text{H}\) NMR spectra. The lower relative yield (76%) obtained for (4-methoxy-phenyl)-(1,3,3-trimethyl-butyl)-amine is due to incomplete hydroamination of 4-methyl-2-pentyne after 24 hours.
Scheme 2.4. Intermolecular hydroamination of internal alkynes with aniline and p-anisidine using complex 1.1.

2.2.4 Hydroamination of TBDMS protected propargyl alcohols with p-anisidine

Prior to this work, previous attempts to carry out the hydroamination of silyl protected propargyl alcohols with complex 1.1 had failed. At the time it was suspected that adverse side reactivity between the complex and the silyl protected hydroxyl group proximal to the alkyne was leading to catalyst decomposition under the reaction conditions employed. These initial attempts were made using alkyl primary amines and were carried out at a temperature of 65 °C. It was hoped that the more moderate reaction temperature employed in the hydroamination of alkynes with aryl primary amines would
minimize catalyst decomposition and allow the hydroamination reaction to proceed. The tert-butyl-dimethylsilyl protecting group was selected mainly for the stability of this protecting group under the conditions utilized in the reduction protocol. These reactions are set up and carried out in the same manner as the reactions described in section 2.2.1.

As shown in Equation 2.3 the hydroamination of TBDMS protected propargyl alcohol with p-anisidine proceeds with high efficiency at ambient temperature and generates the regioisomer shown almost exclusively as determined by $^1$H NMR spectroscopy. Again, the level of efficiency and selectivity for the anti-Markovnikov product under such mild conditions is without parallel.

$$\text{OTBDMS} + \begin{array}{c} \text{NH}_2 \\ \text{MeO} \end{array} \xrightarrow{\text{PhH, RT, 24h}} \text{PMPHN-OTBDMS}$$

In addition to propargyl alcohol, the TBDMS protected alcohols 3-phenyl-2-propyne-1-ol and 4-phenyl-3-butyne-2-ol were both also examined as substrates (Scheme 2.5) given that extension of this methodology to the generation of synthetically useful intermediates would require that it be applicable to the hydroamination of more challenging disubstituted alkynes. Hydroamination of TBDMS protected 3-phenyl-2-propyne-1-ol for example would generate a protected $\beta$-amino alcohol which could potentially be used as a precursor in the synthesis of the amino acid phenylalanine.
Scheme 2.5. Hydroamination of TBDMS protected 1-phenyl-2-propyne-1-ol and 4-phenyl-3-butyne-2-ol with p-anisidine using complex 1 as the precatalyst.

As one can see by the moderate yields in Scheme 2.5 these substrates clearly present more of a challenge. Catalyst decomposition/inactivation due to some adverse side reactions between the complex and substrate at the elevated reaction temperature may explain the lower conversions. Extending the reaction time at elevated temperature does not improve conversion. In order to preserve the catalytically active species, a lower reaction temperature can be employed, and as a result the hydroamination of TBDMS protected 3-phenyl-2-propyne-1-ol does indeed proceed very slowly, with approximately a 56% yield being obtained after 144 hours of heating to only 40 °C. It is noted that further optimization of the reaction conditions may result in a better yield.

When the PMP protected amines prepared via the hydroamination of 1-phenyl-1-propyne and TBDMS protected 3-phenyl-2-propyne-1-ol are subjected to the oxidative cleavage procedures recently reported by Verkade and coworkers,² the corresponding primary amines are obtained in moderate yield (Scheme 2.6). This result serves as a
proof of principle that hydroamination can be used to generate primary amines from alkynes. It should be noted that these yields are not optimized.

\[ \text{Scheme 2.6. Proof of principle: } p\text{-methoxyphenyl protected amines prepared via hydroamination are subjected to known oxidative cleavage procedures.} \]

2.2.4 Side reactivity observed during the hydroamination of phenylacetylene with aniline

When following the hydroamination of phenylacetylene with aniline by \(^1\)H NMR spectroscopy, it is apparent that compounds other than the desired hydroamination products are being formed. These side products, although being generated in comparatively minor quantities, are of interest as a better understanding of side-reactions may shed light on new reactivity profiles. In the \(^1\)H NMR spectrum of the reaction mixture, the E and Z enamine products as well as the aldimine tautomer are discernable. Additionally, there are signals at 2.39 – 2.52, 3.18 – 3.24, 3.98 – 4.01, and 4.55 – 4.58 that result from the unidentified side product(s).
When the crude hydroamination reaction mixture is directly subjected to column chromatography in order to isolate and characterize the byproduct(s), only the known tetrahydroisoquinoline\(^6\) (A, Figure 2.1) can be isolated in addition to aniline, with a yield of about 20%. The hydroamination products can not be isolated due to their propensity to decompose upon exposure to silica gel. Surprisingly the \(^1\)H NMR spectrum of the tetrahydroisoquinoline A is not consistent with any of the signals observed in the crude \(^1\)H NMR spectrum, which suggested that the formation of this species somehow occurs upon work up/isolation.

![Figure 2.1. Side-products isolated from the hydroamination of phenylacetylene with aniline.](image)

However, when the crude hydroamination reaction mixture is subjected to reducing conditions, prior to attempting to isolate the components of the mixture, the amine corresponding to the reduced anti-Markovnikov hydroamination product is obtained in 77% yield along with an alternative side product (B, Figure 2.1) which is obtained in 18% yield.

Based on the isolation of these two compounds (A and B, Figure 2.1), it is suggested that the aldime-amine depicted in Equation 2.4 is formed initially by an intermolecular reaction between the two tautomers of the hydroamination product. The conversion of
the aldimine-amine to the 1,2,3,4-tetrahydroisoquinoline is then thought to proceed via proton catalyzed intramolecular electrophilic aromatic substitution (Scheme 2.7) upon exposure of the aldimine-amine to silica gel.

![Scheme 2.7. Mechanistic rationale for the proton mediated formation of the tetrahydroisoquinoline.](image)

A similar mechanism has also been proposed for the formation of tetrahydroisoquinolines via the rhodium catalyzed oxidative amination of styrene with aniline,\textsuperscript{7} the condensation of phenylacetaldehyde with aniline hydrochloride in the presence of NaCNBH\textsubscript{3},\textsuperscript{8} and the benzotriazole promoted condensation of phenylacetaldehyde with aniline.\textsuperscript{6} Possibly, complex 1.1 may potentiate this transformation, perhaps by acting as a Lewis acid.

In light of the fact that these side products are generated in < 20% yield and that neither increased catalyst loading nor extended reaction times nor increased reaction temperature had any significant impact on the amount of the aldimine-amine being
formed (in fact yield drops off slowly over extended periods of heating), it was decided that further investigation was not warranted.

2.2.5 Intramolecular alkene hydroamination activity

2.2.5.1 Initial investigations and the gem-disubstituent effect

We began our investigation into neutral group four metal catalyzed intramolecular amino-alkene hydroamination by looking at the precursor to our bis(amidate) titanium bis(amido) complexes, Ti(NMe₂)₄. This compound is known to effect the intermolecular hydroamination of alkynes, but previous to our work no examples of alkene hydroamination using Ti(NMe₂)₄ had been reported.

2,2-Diphenyl-4-pentenylamine was our initial test substrate for the cyclohydroamination reaction with Ti(NMe₂)₄. Heating this compound in the presence of 5 mol% Ti(NMe₂)₄ affords the requisite N-heterocyclic product 1-methyl-4,4-diphenylpyrrolidine with an isolated yield of 92 % (Equation 2.5).

![Chemical structure](image)

\[
\text{PhMe, 110 °C, 24h} \quad 5 \text{ mol\% Ti(NMe}_2)_4 \quad \xrightarrow{\text{NH}_2} \quad \text{92 \%}
\]

(2.5)

Alternatively this reaction can be monitored by \(^1\text{H NMR spectroscopy. The disappearance of the two olefin signals centered at } \delta 5.44 \text{ and } 4.95 \text{ ppm and the appearance of two new signals at } \delta 2.38 \text{ and } 1.80 \text{ ppm are used to measure the progress of the reaction. In this case the reaction goes to completion within 1 hour. In addition lower reaction temperatures can be used such that within 2.5 hours at } 45 \text{ °C and } 70 \text{ °C.}
methyl-4,4-diphenylpyrrolidine forms in 38% and 70% respectively. Unfortunately, no appreciable reactivity is observed at room temperature.

By testing this system with other substrates, the importance of the gem-disubstituent or the gem-dialkyl effect for the cyclohydroamination reaction has become increasingly apparent. This effect has also been found to impact this reaction with other catalytic systems.9

It is known that intramolecular cyclization reactions can be facilitated by substrates possessing geminal substitution in a position between the two ends of the substrate bearing the functional groups undergoing reactivity. In our case the aminoalkenes are substituted in the 2-position by groups such as phenyl and methyl, and when the steric bulk of the substituents in this position is decreased (phenyl to methyl to hydrogen), or when only one substituent is present, the reaction time increases dramatically. This phenomenon, known as the gem-disubstituent effect10 results from a combination of the Thorpe – Ingold effect11 and the reactive rotamer effect (Scheme 2.8).12

Scheme 2.8. The components of the "gem-dialkyl" effect, Thorpe-Ingold theory and reactive rotamer theory.

The extent to which this phenomenon dictates the relative reactivity of these substrates is obvious with this catalytic system. Table 2.1 lists a series of results for the
cyclohydroamination of various substrates bearing progressively less sterically demanding substituents in the 2-position, i.e. diphenyl to dimethyl to monomethyl to unsubstituted. The change from phenyl to methyl results in a drop in reaction progress after 24 hours of almost two thirds. Reduction in the number of substituents in the 2-position further reduces the degree to which these reactions proceed within a given time frame. Going from 2,2-dimethyl- to 2-methyl-pentenylamine reduces reaction progress by about a quarter after 96 hours. The unsubstituted 4-pentenylamine substrate is completely unreactive with this system regardless of reaction time or temperature (up to 145 °C).

Table 2.1. The impact of the gem-disubstituent effect on cyclohydroamination using Ti(NMe$_2$)$_4$.

<table>
<thead>
<tr>
<th>aminoalkene</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Ph}_2\text{NH}_2$</td>
<td>$\text{Ph} \quad \text{Ph}$</td>
<td>92$^a$(24h)</td>
</tr>
<tr>
<td>$\text{Ph} \quad \text{NH}_2$</td>
<td>$\text{Ph}$</td>
<td>32$^b$(24h)</td>
</tr>
<tr>
<td>$\text{R}_2\text{NH}_2$</td>
<td>$\text{R}$</td>
<td>52$^b$(96h)</td>
</tr>
<tr>
<td>$\text{R} \quad \text{NH}_2$</td>
<td>$\text{R}$</td>
<td>43$^c$(120h)</td>
</tr>
<tr>
<td>$\text{NH}_2$</td>
<td>$\text{N}$</td>
<td>38$^b$(96h)</td>
</tr>
</tbody>
</table>

$^a$ Isolated yield. $^b$ Yield determined by $^1$H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. $^c$Isolated yield following derivitization with benzoyl chloride.
2.2.5.2 Diastereoselectivity

Generally, selectivity, be it regio-, diastereo- or enantioselectivity, is an important aspect of catalytic systems and chemical transformations. The cyclohydroamination of substrates possessing differential substitution in any one position can lead to the formation of at least two diastereomeric products. In the interest of investigating the diastereoselectivity associated with this system, a number of substrates differentially substituted in either the 1-position or 2-position were studied. Table 2.2 lists these substrates along with their resulting diastereomeric pyrrolidine products and reaction outcomes.

Table 2.2. Investigating diastereoselectivity when Ti(NMe₂)₄ is employed as a precatalyst.

<table>
<thead>
<tr>
<th>entry</th>
<th>aminoalkene</th>
<th>products</th>
<th>yield% (reaction time) [cis:trans]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₂PhNH₂</td>
<td>Ph₂PhNH₂ + Ph₂PhNH₂</td>
<td>90% (24h) [1 : 33]</td>
</tr>
<tr>
<td>2</td>
<td>Ph₂NH₂</td>
<td>Ph₂NH₂ + Ph₂NH₂</td>
<td>33% (96h) [1 : 2.6]</td>
</tr>
<tr>
<td>3</td>
<td>Ph₂NH₂</td>
<td>Ph₂NH₂ + Ph₂NH₂</td>
<td>52% (24h) [1.4 : 1]</td>
</tr>
<tr>
<td>4</td>
<td>Ph₂NH₂</td>
<td>Ph₂NH₂ + Ph₂NH₂</td>
<td>26% (24h) [1.4 : 1]</td>
</tr>
</tbody>
</table>

*Isolated yield. †NMR yield based on 1,3,5-trimethoxy-benzene as an internal standard.
‡Isolated yield following derivitization with benzoyl chloride.
For the most part, the diastereoselectivities are poor, and in line with what has been found with other hydroamination catalytic systems. Entry 1 in Table 2.2 does stand apart from the other entries dramatically however, with a very high selectivity for the anti-product. It should be noted that this substrate is completely novel and therefore no results from literature were available for comparison.

These diastereoselectivities can be rationalized by invoking a chair like transition state argument for the mechanism of this transformation, which has been proposed for other systems. This rationalization is illustrated in Scheme 2.9. Substituents adorning the substrate can be oriented either axially or equatorially, and it is well known that cyclohexyl derivatives favor the conformation that positions bulky substituents equatorially to avoid or minimize 1,3-diaxial steric interactions. With respect to the 2,5-substituted pyrrolidine products, the trans-diastereomer predominates due to the fact that the methyl group in the 1-position of the substrate is preferentially located in an equatorial position to minimize 1,3-diaxial interactions. The fact that the cis-product is slightly favored when substrates bearing differential substitution in the 2 position are employed is also consistent with this hypothesis.
Scheme 2.9. Rationale for the diastereoselectivity observed in the cyclohydroamination of substrates differentially substituted in either the 1-position or 2-position.

A qualitative explanation for the high diastereoselectivity observed with 1-methyl-2,2-diphenyl-4-pentenylamine (entry 1, Table 2.2) relative to what was observed with 2-methyl-4-pentenylamine (entry 2, Table 2.2) is that the bulky phenyl groups in the 2-position of the substrate more rigidly enforce a chair like geometry in the transition state of this reaction and render other possible transition state geometries which could lead to the cis product being more energetically disfavored.
2.2.5.3 Substrate scope

In the interest of determining the limitations of Ti(NMe₂)₄ as an intramolecular alkene hydroamination precatalyst, substrates of varying chain length as well as substrates bearing substituted alkenes were investigated. All of these substrates incorporate two phenyl groups in the 2-position to take full advantage of the gem-disubstituent effect. Table 2.3 presents the results of these experiments.

Table 2.3. Substrate scope investigation using Ti(NMe₂)₄.

<table>
<thead>
<tr>
<th>entry</th>
<th>aminoalkene</th>
<th>product</th>
<th>yield% (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Ph}<em>{n}\text{Ph}</em>{n}\text{NH}_{2})</td>
<td>(\text{Ph}<em>{n}\text{Ph}</em>{n}\text{NH}_{2})</td>
<td>80(24h)</td>
</tr>
<tr>
<td>2</td>
<td>(\text{Ph}<em>{n}\text{Ph}</em>{n}\text{NH}_{2})</td>
<td>(\text{Ph}<em>{n}\text{Ph}</em>{n}\text{NH}_{2})</td>
<td>N/R (^b)</td>
</tr>
<tr>
<td>3</td>
<td>(\text{Ph}<em>{n}\text{Ph}</em>{n}\text{NH}_{2})</td>
<td>(\text{Ph}<em>{n}\text{Ph}</em>{n}\text{NH}_{2})</td>
<td>67(96h)</td>
</tr>
<tr>
<td>4</td>
<td>(\text{Ph}<em>{n}\text{Ph}</em>{n}\text{NH}_{2})</td>
<td>(\text{Ph}<em>{n}\text{Ph}</em>{n}\text{NH}_{2})</td>
<td>N/R (^b)</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield. \(^b\) Determined by NMR after extended reaction times.
Both six and seven membered ring precursors (entries 1 and 2, Table 2.3) were tested, but only the six membered ring precursor undergoes cyclization. The seven membered ring precursor shows no signs of reaction even after 240 hours at 110 °C with 5 mol% catalyst loading. Heating this substrate to 145 °C in the presence of 20 mol% Ti(NMe₂)₄ however results in some unexpected side reactivity, which will be discussed in chapter five.

The internal olefin bearing substrates 2,2,5-triphenyl-pent-4-enylamine and 2,2-diphenyl-hex-4-enylamine (entries 3 and 4, table 2.3) were both tested and only the substrate bearing the activated alkene undergoes cyclization. No reaction is observed with 2,2-diphenyl-hex-4-enylamine even at 145 °C.

2.2.5.4 Mechanistic rationale

The trends observed with these reactions resulting from variation in substrate structure, namely the effect that geminal substitution had on reaction progress and the diastereoselectivities observed in the cyclization of racemic chiral substrates, are consistent with a chair like transition state which has been proposed for intramolecular hydroamination reactions. What is not apparent from these experiments is the nature of the reactive Ti-N bond in the catalytically active species (A, Scheme 2.9). Work carried out by Bergman, Doye, Mountford, as well as other members of our group has shown that for the catalytic hydroamination of alkynes, A is a titanium imido species.¹⁶
Scheme 2.9. Proposed catalytic cycle for the intramolecular hydroamination of aminoalkenes catalyzed by Ti(NMe₂)₄.

An alternative reaction pathway involving the direct insertion of the olefin into a Ti-N σ-bond is also plausible. This hypothesis, which proposes a titanium amido species as the active catalyst, has been established in the case of group three, lanthanide, and cationic group four catalyzed intramolecular alkene hydroamination¹⁴b,¹⁷ and cannot be refuted in the case of neutral group four systems based on the above mentioned observations.

In situ generation of a titanium imido type complex requires the presence of a primary amine, otherwise formation of the reactive Ti=N bond is not possible. With this requirement in mind, a secondary aminoalkene can be used as the test substrate; if cyclization does not occur then the involvement of an amido species in catalysis is unlikely and the argument for a catalytically active imido intermediate as the active catalyst is supported. On the other hand, if cyclization of this secondary aminoalkene
substrate does indeed occur, then the cyclohydroamination of primary aminoalkenes may involve either an imido or amido complex as the active catalyst.

When other members of our group attempted the cyclization of \( N \)-methyl-2,2-diphenyl-4-pentenylamine using \( \text{Ti(NMe}_2\text{)}_4 \) as the precatalyst they saw no reaction whatsoever (Equation 2.6). Even elevated reaction temperatures and extended reaction times affords no \( N \)-methyl-pyrrolidine product. This result supports the argument that the reactivity with \( \text{Ti(NMe}_2\text{)}_4 \) and primary aminoalkenes is proceeding via an \textit{in situ} generated titanium imido species, consistent with what has been established for the better understood group 4 catalyzed hydroamination of alkenes.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \quad \text{H} \\
\text{N} & \quad \text{Ti(NMe}_2\text{)}_4 \\
\text{PhMe} & \quad \text{PhMe}_2 \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

(2.6)

2.2.5.5 Tetrakis(amido) vs bis(amidate) titanium bis(amido) precatalysts

Having investigated \( \text{Ti(NMe}_2\text{)}_4 \) and determined some of the limitations associated with this system, we turned our attention back to our amidate complexes. A substrate scope investigation was carried out using complex 1.1 as the precatalyst for cyclohydroamination under the same reaction conditions employed in the \( \text{Ti(NMe}_2\text{)}_4 \) catalyzed reactions (Table 2.4).

It is apparent from these results that our most active catalyst for the hydroamination of alkenes is substantially less effective than \( \text{Ti(NMe}_2\text{)}_4 \) for the cyclohydroamination of aminoalkenes. Although reactivity is comparable for the cyclization of 2,2-diphenyl-4-pentenylamine (entry 1, Table 2.4), the dramatic effect of the \textit{gem}-disubstituent
phenomenon is even more pronounced with complex 1.1. Replacing the diphenyl substituents with dimethyl groups in the 2-position of the substrate results in a substantially slower reaction with complex 1.1. In addition, whereas Ti(NMe₂)₄ affects the cyclization of 2-amino-5-hexene to some degree, no reaction whatsoever was observed using complex 1.1 as the precatalyst even after extended periods at 110 °C. The cyclohydroamination of the six membered ring precursor (entry 3, Table 2.4) again demonstrates the stark difference in reactivity between the two precatalysts.

Table 2.4. Comparison of cyclohydroamination activity of complex 1.1 to Ti(NMe₂)₄.

<table>
<thead>
<tr>
<th>entry</th>
<th>aminoalkene</th>
<th>product</th>
<th>complex 1.1¹ Ti(NMe₂)₄.²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>⁹⁰%b (24h) ⁹²%b (24h)</td>
</tr>
<tr>
<td>2</td>
<td>NH₂</td>
<td>NH₂</td>
<td>²⁵% (120h) ⁵²% (96h)</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>NH₂</td>
<td>¹⁷% (48h) ⁸⁰% (24h)</td>
</tr>
<tr>
<td>4</td>
<td>NH₂</td>
<td>NH₂</td>
<td>NR (96h) ⁶⁷%b (96h)</td>
</tr>
<tr>
<td>5</td>
<td>NH₂</td>
<td>NH₂</td>
<td>NR (144h) ³³% (96h)</td>
</tr>
</tbody>
</table>

¹ Yield determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard, unless otherwise stated. ² Isolated yield.
The current rationalization for the decrease in reactivity seen with complex 1.1 is that the large steric bulk of the amidate ligand, though adventitious for minimizing the \textit{in situ} formation of catalytically inactive imido dimers,\textsuperscript{18} may at the same time be impeding these intramolecular aminoalkene reactions by reducing the accessibility to the reactive metal center. The fact that no reaction was observed with 2,2,5-triphenyl-4-pentenylamine or 2-amino-5-hexene (entries 4 and 5 respectively), which possess bulky substituents in close proximity to the nuclei directly involved in the bond formation processes, loosely supports this argument. In addition, while Ti(NMe\textsubscript{2})\textsubscript{4} catalyzes the cyclization of 1-methyl-2,2-diphenyl-4-pentenylamine with a yield of 90\% (entry 1, Table 2.2), complex 1.1 generates the corresponding \textit{cis} and \textit{trans} pyrrolidine with a slightly lower yield of 80\%. Interestingly, a lower diastereoselectivity (1.7:1 \textit{trans:cis}) was observed using complex 1.1 as the precatalyst with this substrate.

2.2.6 Hydroamination using \textit{in situ} prepared precatalyst

There are a number of desirable characteristics necessary for any new catalyst system to be adopted by the organic synthetic community and chemists in general. Among these characteristics are: ease of use, availability from commercial sources and cost effectiveness. In an effort to demonstrate these aspects of our system, in particular ease of use, we carried out a series of hydroamination experiments in which we utilized an \textit{in situ} generated precatalyst. This protocol would require only Ti(NMe\textsubscript{2})\textsubscript{4}; which is inexpensive, can be purchased directly from any major chemical supplier, and is easily handled using standard syringe techniques; as well as the \(N\)-(2,6-diisopropyl-phenyl)-
benzamide proligand, which can be prepared in a straightforward manner using literature procedures from benzoyl chloride and 2,6-diisopropylaniline.\textsuperscript{19}

Scheme 2.10 presents the results of a series of intermolecular alkyne hydroamination reactions carried out using \textit{in situ} generated precatalyst. These reactions are set up on a 0.5 mmol scale in a nitrogen filled glove box. The procedure involves first weighing out the appropriate amount of amide proligand into a small vial and then dispensing an accurately measured aliquot of a standardized solution of Ti(NMe\textsubscript{2})\textsubscript{4} dissolved in benzene to the same vessel. The amine, followed by the alkyne substrate is added, and the reaction mixture is then transferred to a J. Young NMR tube, or a small Schlenk tube, removed from the glovebox and stirred at the specified temperature for the specified amount of time. The reduction protocol employed in the previous hydroamination experiments is also utilized in these experiments. Overall, the yields and selectivities obtained for these examples are comparable to with the results obtained in which the precatalyst had been prepared in advance, isolated and characterized.

\textbf{Scheme 2.10.} Intermolecular alkyne hydroamination using \textit{in situ} generated precatalyst.
The intramolecular cyclohydroamination of 2,2-diphenyl-4-pentenylamine can be also carried out using \textit{in situ} generated precatalyst (Equation 2.6) with no difference in yield being observed in comparison to using the bis(amidate)titanium bis(amido) complex prepared in advance as the precatalyst. This reaction is initiated and carried out in the same manner as the intermolecular alkyne hydroamination experiments.

\begin{align*}
\text{Ph} &= 5 \text{ mol\% Ti(NMe}_2\text{)4} \\
\text{Ph}_2\text{C} &= 10 \text{ mol\% pro-ligand} \\
\text{PhMe, } 110 \degree \text{C, 24h} &> 98 \% \\
\end{align*}

(2.6)

2.3 Summary and conclusions

The work in this chapter has demonstrated some unique capabilities, as well as further delineated the limitations of complex 1.1 as a hydroamination precatalyst. It was found that in conjunction with \textit{p}-anisidine, complex 1.1 could be used to effect the hydroamination of various terminal alkynes at ambient temperature. In addition, it was found that complex 1.1 could effect the coupling of \textit{p}-anisidine to symmetrically substituted internal alkynes, which were substrates that complex 1.1 had previously been unreactive towards when alkyl amines were used as the amine co-substrate. These coupling reactions of alkynes to \textit{p}-anisidine provide a means of preparing PMP protected primary amines which can be liberated under oxidative conditions. The net transformation is the efficient conversion of an alkyne to a primary amine which was demonstrated by the preparation of DL-amphetamine. The successful application of our system to the hydroamination of TBDMS protected propargyl alcohols demonstrates that
complex 1.1 is tolerant of substrates bearing proximally located silyl-protected hydroxyl functionalities. This is important in that this methodology can then provide entry into useful synthetic precursors to compounds such as α-amino acids and their derivatives.

In addition to the work with alkynes, it was established that commercially available Ti(NMe₂)₄ can be used for the catalytic preparation of pyrrolidine and piperidine heterocyclic products from aminoalkene substrates in good yields. This reaction is particularly efficient for geminally substituted substrates and proceeds with modest, diastereoselectivity that can be rationalized by invoking a chair-like transition state for the intramolecular hydroamination reaction. The inability of this system to affect the cyclization of secondary amine bearing aminoalkene substrates suggests that the mechanism of this transformation does not involve σ-bond metathesis, and rather requires the formation of an in situ generated catalytically active titanium imido species in order to proceed through a mechanism analogous to the titanium catalyzed hydroamination of alkynes. This precatalyst was found to be effective for the intramolecular hydroamination of not only terminal alkenes, but also activated internal alkenes. These preliminary results with Ti(NMe₂)₄ have laid the groundwork for all subsequent and future development of neutral titanium catalysts for the hydroamination of alkenes.

The assessment of complex 1.1, in terms of intramolecular aminoalkene hydroamination catalysis, revealed that this system is much less active than the precursor complex, Ti(NMe₂)₄, in affecting this transformation, and illuminates a severe limitation to its synthetic utility. Clearly, substantial modification to the metal complexes will have to be made in order to increase the reactivity of this system to a level such that the
efficient intramolecular hydroamination of a broad range of aminoalkene substrates becomes feasible.

2.4 Experimental

General. \(^1\)H and \(^{13}\)C NMR spectra were recorded on either a Bruker 300 MHz or 400 MHz Avance spectrometer at ambient temperature and chemical shifts are given relative to residual solvent. The assignment of \(N\)-benzoyl-pyrrolidine stereochemistry was based on NOE difference experiments. \(\text{Cis/trans}\) ratios were determined by GCMS analysis. GCMS spectra were recorded on an Agilent series 6890 GC system with a 5973 Mass Selective Detector. MS (ESI), HRMS and elemental analyses determinations were performed at the Department of Chemistry, University of British Columbia. All reactions were carried out using standard Schlenk line and glovebox techniques under an atmosphere of nitrogen. Unless otherwise stated. \(\text{Ti(NR}_2\text{)}_4\) (\(\text{R=Me, Et}\)) was purchased from Strem and used as received. \(d_6\)-benzene, \(d_{10}\)-xylenes and \(d_8\)-toluene were degassed and dried over molecular sieves. Amino alkenes 2,2-diphenyl-4-pentenylamine,\(^{20}\) 2,2-diphenyl-5-hexenylamine,\(^{21}\) 2,2,5-triphenyl-4-pentenylamine,\(^{21,22}\) 2,2-diphenyl-4-hexenylamine,\(^{21}\) 2,2-dimethyl-4-pentenylamine,\(^{22}\) 2-methyl-4-pentenylamine,\(^{22}\) 2-phenyl-4-pentenylamine,\(^{21}\) 2-methyl-2-phenyl-4-pentenylamine,\(^{21}\) 4-pentenylamine,\(^{22}\) and 2,2-diphenyl-6-heptenylamine\(^{23}\) were prepared as described in the literature with some modification from commercially available starting materials purchased from Aldrich. Characterization data for 2,2-diphenyl-6-heptenylamine is provided below. 1-Methyl-2,2-diphenyl-4-pentenylamine was prepared from 3,3-diphenyl-hex-5-en-2-one using modified literature procedures\(^{24}\) with full characterization data reported below. 1-Chloro-
3-prop-1-ynyl-benzene,\textsuperscript{25} \textit{tert}-Butyl-dimethyl-(3-phenyl-prop-2-ynyloxy)-silane\textsuperscript{26} and \textit{tert}-butyl-dimethyl-(1-methyl-3-phenyl-prop-2-ynyloxy)-silane were prepared using modified literature procedures\textsuperscript{27} with full characterization data for \textit{tert}-butyl-dimethyl-(1-methyl-3-phenyl-prop-2-ynyloxy)-silane reported below. Prior to use, all substrates were purified either by distillation or recrystallization. In addition liquid substrates were degassed and dried over molecular sieves prior to use. Heterocyclic products 2-methyl-4,4-diphenylpyrrolidine,\textsuperscript{20} 2-methyl-5,5-diphenylpiperidine,\textsuperscript{14b} 2-methyl-4,4-dimethylpyrrolidine,\textsuperscript{22} 2-methyl-4-methylpyrrolidine,\textsuperscript{28} 2-methyl-4-phenylpyrrolidine\textsuperscript{29} are known compounds. (4-Methoxy-phenyl)-(1-methyl-2-phenyl-ethyl)-amine,\textsuperscript{30} phenethyl-phenyl-amine,\textsuperscript{31} hexyl-(4-methoxy-phenyl)-amine,\textsuperscript{32} N-benzyl-hexylamine,\textsuperscript{19} (1-Methyl-2-phenyl-ethyl)-phenyl-amine,\textsuperscript{33} and the hydrochloride salt of 1-methyl-2-phenyl-ethylamine,\textsuperscript{34} are also known compounds. The bis(N-2',6'-diisopropylphenyl(phenyl)-amidate) titanium bis(dimethylamido) complex 1 was prepared as described in the literature.\textsuperscript{19} Full characterization data for all new compounds are given below.

**General procedure for NMR-tube scale intramolecular amino alkene hydroamination.** All NMR-tube scale reactions were prepared in an N\textsubscript{2}-filled glove box. An NMR-tube equipped with a Teflon screw cap was charged with the internal standard (1,3,5-trimethoxybenzene) (0.5 mmol), the catalyst (0.025 mmol), and the amino alkene (0.5 mmol) dissolved in either \textit{d}_{6}-benzene (~1 mL), \textit{d}_{10}-xylenes (~1 mL) or \textit{c}_{8}-toluene (~1 mL). The tube was then sealed, heated to, and maintained at, the appropriate temperature for the stated duration of time. The conversion and yield were determined by
comparing the integration of the internal standard with a well resolved signal for the cyclic product.

2,2-Diphenyl-6-heptenylamine.\textsuperscript{23} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 0.86 (2H, s, CH\textsubscript{2}-NH\textsubscript{2}), 1.05-1.17 (2H, m, CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}), 1.97-2.05 (2H, m, CH\textsubscript{2}=CH-CH\textsubscript{2}), 2.07-2.14 (2H, m, CH\textsubscript{2}-CH\textsubscript{2}-CPh\textsubscript{2}), 3.31 (2H, s, Ph\textsubscript{2}C-CH\textsubscript{2}-NH\textsubscript{2}), 4.89-4.98 (2H, m, CH\textsubscript{2}=CH), 5.65-5.75 (1H, m, CH\textsubscript{2}=CH), 7.15-7.31 (10H, m, Ar-H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): \(\delta\) 23.36, 34.18, 35.87, 49.06, 51.73, 114.63, 125.89, 127.96, 128.21, 138.57, 146.53; MS (ESI): \(m/z\) 266 (M+H\textsuperscript{+}); Anal. Calcd for C\textsubscript{19}H\textsubscript{23}N: C, 85.99; H, 8.74; N, 5.28. Found: C, 85.64; H, 9.08; N, 5.24.

3,3-Diphenyl-hex-5-en-2-one.\textsuperscript{24} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 2.06 (3H, s, Ph\textsubscript{2}C-CO-CH\textsubscript{3}), 3.10 (2H, d, J = 7.0 Hz, CH\textsubscript{2}=CH-CH\textsubscript{2}-), 4.83 – 4.90 (2H, m, CH\textsubscript{2}=CH-), 5.30 – 5.60 (1H, m, CH\textsubscript{2}=CH-CH\textsubscript{2}), 7.24 – 7.37 (10H, m, Ar-H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): \(\delta\) 27.42, 42.06, 66.28, 118.15, 126.99, 128.17, 130.18, 134.17, 140.97; HRMS Calcd for C\textsubscript{18}H\textsubscript{19}O [M+H\textsuperscript{+}]: 251.1429; Found: 251.1436.
1-Methyl-2,2-diphenyl-4-pentenylamine.²⁴ ¹H NMR (CDCl₃, 300 MHz): δ 0.94 (2H, d, J = 6.5 Hz, CH-CH₃), 1.06 (2H, br s, -NH₂), 2.87 (2H, dd, J = 6.8, 13.9 Hz, CH₂=CHCH₂), 3.81 (1H, q, J = 6.5, CH₃-CH-NH₂), 4.89 – 5.00 (2H, m, CH₂=CH-), 5.30 – 5.50 (1H, m, CH₂=CH-CH₂), 7.20 – 7.33 (10H, m, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 19.11, 43.62, 49.17, 56.24, 117.39, 126.07, 126.11, 127.30, 127.60, 129.68, 129.87, 134.67, 143.32, 144.37; MS (EI): m/z 252 (M+H⁺), 210 (M- CH₂=CH-CH₂⁺); Anal. Calcd for C₁₈H₂₃N: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.98; H, 8.25; N, 5.80.

1-Chloro-3-prop-1-ynyl-benzene.²⁵ Yield 90%. NMR (CDCl₃, 400 MHz): δ 2.06 (3H, s, Ar-CC-CH₃), 7.17 – 7.49 (4H, m, ArH); ¹³C NMR (CDCl₃, 101 MHz): δ 5.2, 79.5, 88.3, 126.8, 128.8, 130.4, 130.6, 132.4, 135.0; MS (EI): m/z 150 (M⁺).

tert-Butyl-dimethyl-(3-phenyl-prop-2-ynloxy)-silane.²⁶ NMR (CDCl₃, 400 MHz): δ 0.20 (6H, s, -Si(CH₃)₂), 0.97 (9H, s, -Si-C(CH₃)₃), 4.56 (2H, s, -C-CH₂-O-), 7.30 – 7.50 (5H, m, Ar-H); ¹³C NMR (CDCl₃, 101 MHz): δ -4.9, 18.5, 26.0, 52.4, 85.0, 88.1, 123.1, 128.4, 131.74; MS (EI): m/z (M⁺) 246.
tert-Butyl-dimethyl-(1-methyl-3-phenyl-prop-2-ynyloxy)-silane.\textsuperscript{27} NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 0.17 (3H, s, -Si(CH\textsubscript{3})-CH\textsubscript{3}), 0.19 (3H, s, -Si(CH\textsubscript{3})-CH\textsubscript{3}), 0.95 (9H, s, -Si(CH\textsubscript{3})\textsubscript{2}-C(CH\textsubscript{3})\textsubscript{3}), 1.51 (3H, d, \textit{J} = 6.5 Hz, -CH-CH\textsubscript{3}), 4.76 (1H, q, \textit{J} = 6.5 Hz, -CH-CH\textsubscript{3}), 7.25 – 7.45 (5H, m, Ar-H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): \(\delta\) -4.7, -4.3, 18.4, 25.5, 26.0, 59.6, 83.4, 92.0, 123.3, 128.2, 131.7; MS (EI): \textit{m/z} (M-CH\textsubscript{3})\textsuperscript{+} 245; Anal. Calcd. for. C\textsubscript{16}H\textsubscript{24}OSi: C, 73.79; H, 9.48. N. Found: C, 73.52; H, 9.48.

General procedure for amino alkene hydroamination experiments in which the product was isolated. All reactions were prepared in an N\textsubscript{2}-filled glovebox. A small Schlenk tube equipped with a magnetic stirbar would be charged with the catalyst (0.025 mmol) and the amino alkene (0.5 mmol) dissolved in D\textsubscript{8}-toluene (~ 1 mL). The Schlenk tube would then be sealed, heated to the appropriate temperature, and stirred for the stated duration of time. Following this the solution would be concentrated under reduced pressure and the crude product would be either be converted to the N-benzoyl derivative according to literature procedures,\textsuperscript{20} or directly subjected to flash column chromatography (hexanes/ether or ether or ether/NEt\textsubscript{3}, SiO\textsubscript{2}) to afford the purified pyrrolidine or piperidine product.
2,5-Dimethyl-3,3-diphenyl-pyrrolidine. A combined yield of 90% was obtained for the mixture of diastereomers. It was possible to separate a sufficient quantity of the major diastereomer by chromatography (hexane/ether, SiO2) to provide $^1$H NMR and $^{13}$C NMR data for this compound. This in turn facilitated the identification of the $^1$H and $^{13}$C NMR data for the minor diastereomer. $^1$H NMR (major diastereomer) (CDCl$_3$, 300 MHz):

δ 0.95 (3H, d, J = 6.4 Hz, Ph$_2$C-CH-CH$_3$), 1.21 (3H, d, J = 6.5 Hz, Ph$_2$C-CH$_2$-CH-CH$_3$), 1.87 (1H, dd, J = 6.8, 13.7 Hz, Ph$_2$C-CHH-CH), 2.45 (1H, br s, NH), 3.06 (1H, dd, J = 8.26, 13.7, Ph$_2$C-CHH-CH), 3.67 – 3.72 (1H, m, CH$_2$-CH-NH-), 3.96 (1H, q, J = 6.4 Hz, Ph$_2$C-CH-NH-), 6.98 – 7.31 (10H, m, Ar-H);

$^1$H NMR (minor diastereomer) (CDCl$_3$, 300 MHz): δ 0.89 (3H, d, J = 6.7 Hz, Ph$_2$C-CH-CH$_3$), 1.39 (3H, d, J = 6.4 Hz, -CH$_2$-CH-CH$_3$), 2.36 – 2.54 (2H, m, Ph$_2$C-CH$_2$-CH), 3.11 (1H, br s, NH), 3.20 – 3.30 (1H, m, CH$_2$-CH-NH-), 4.19 (1H, q, J = 6.7 Hz, Ph$_2$C-CH-NH), 7.04 – 7.31 (10H, m, Ar-H);

$^{13}$C NMR (major diastereomer) (CDCl$_3$, 100 MHz): δ 16.89, 24.78, 51.08, 51.55, 57.91, 60.32, 125.95, 126.08, 127.62, 127.81, 128.54, 129.08, 144.56, 148.60; $^{13}$C NMR (minor diastereomer) (CDCl$_3$, 75 MHz): δ 21.15, 21.61, 46.75, 51.74, 59.69, 60.21, 125.86, 125.91, 127.53, 127.81, 128.15, 128.28, 146.60, 149.10; HRMS (mixture of diastereomers) Calcd for C$_{18}$H$_{21}$N [M$^+$]: 251.16740; Found: 251.16772.
2-Benzyl-4,4-diphenyl-pyrrolidine. Yield 67%; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 2.06 (1H, br s, NH), 2.17 (1H, dd, J = 9.0, 12.7 Hz, CHH-CH-Bn), 2.69-2.78 (2H, m, CHH-CH-Bn, Ph-CHH-CH), 2.88 (1H, dd, J = 7.0, 13.3 Hz, Ph-CHH-CH), 3.50-3.61 (2H, m, Bn-CH-NH, Ph$_2$C-CHH-NH), 3.73 (1H, d, J = 11.3 Hz, Ph$_2$C-CHH-NH), 7.17-7.29 (15H, m, Ar-H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 43.53, 44.85, 56.56, 57.64, 59.12, 125.99, 126.08, 126.40, 126.90, 127.04, 128.28, 128.34, 129.04, 129.34, 139.83, 146.77, 147.67; MS (ESI): m/z 314 (M+H$^+$), 336 (M+Na$^+$); Anal. Calcd for C$_{23}$H$_{23}$N: C, 88.13; H, 7.40; N, 4.47. Found: C, 87.80; H, 7.80; N, 4.75.

$\text{N-Benzoyl-2-methyl-4,4-dimethylpyrrolidine.}$ Yield 43%; $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 0.86 (3H, s, CH$_2$-C(CH$_3$_)$_2$-CH$_2$), 1.00 (3H, s, CH$_2$-C(CH$_3$_)$_2$-CH$_2$), 1.33-1.42 (4H, m, (CH$_3$_)CH, (CH$_3$_)$_2$C-CHH-CH(CH$_3$_)), 1.90 (1H, dd, J = 6.0, 12.0Hz, (CH$_3$_)$_2$C-CHH-CH(CH$_3$_)), 3.05 (1H, d, J = 10.0 Hz, (CH$_3$_)$_2$C-CHH-NBz), 3.25 (1H, d, J = 10.0 Hz, (CH$_3$_)$_2$C-CHH-NBz), 4.27-4.35 (1H, m, CH$_2$-CH-(CH$_3$)), 7.30-7.49 (5H, m, Ar-H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 20.15, 25.39, 25.64, 38.18, 47.49, 52.83, 62.53, 127.42, 128.08, 129.83, 137.22, 170.00; HRMS Calcd for C$_{14}$H$_{19}$N$_{0.0}$ [M$^+$]: 217.14666; Found: 217.14674.
N-Benzoyl-2-methyl-4-phenylpyrrolidine. A combined yield of 26% was obtained for the mixture of diastereomers. It was possible to separate a sufficient quantity of the major diastereomer by chromatography (hexane/ether, SiO₂) to provide ¹H NMR, ¹³C NMR, and GCMS (EI) data for this compound. This in turn facilitated the identification of the ¹H, ¹³C NMR and GCMS (EI) data for the minor diastereomer.¹H NMR (major diastereomer) (CDCl₃, 400 MHz): δ 1.50 (3H, d, J = 6.0 Hz, CH₃-CH-NBz), 1.76 – 1.87 (1H, m, PhCH-CHH-CH(CH₃)), 2.53 – 2.61 (1H, m, PhCH-CHH-CH(CH₃)), 3.15 – 3.22 (1H, m, CH₂-PhCH-CH₂), 3.50 – 3.56 (1H, m, PhCH-CHH-NBz), 3.75 – 3.79 (1H, m, PhCH-CHH-NBz), 4.36 – 4.42 (1H, m, CH₂-C(CH₃)H-NBz), 7.15 – 7.58 (10H, m, Ar-H); ¹H NMR (minor diastereomer) (CDCl₃, 400 MHz): δ 1.44 (3H, d, J = 6.3 Hz, CH₃-CH-NBz), 1.98 – 2.04 (1H, m, PhCH-CHH-CH(CH₃)), 2.22 – 2.28 (1H, m, PhCH-CHH-CH(CH₃)), 3.33 - 3.40 (1H, m, PhCH-CHH-NBz), 3.83 - 3.87 (1H, m, PhCH-CHH-NBz), 4.05 – 4.20 (1H, m, CH₂-PhCH-CH₂), 4.50 – 4.65 (1H, m, CH₂-C(CH₃)H-NBz), 7.12 – 7.47 (10H, m, Ar-H); ¹³C NMR (major diastereomer) (CDCl₃, 75 MHz): δ 20.3, 40.8, 44.1, 54.0, 57.0, 127.0, 127.1, 127.7, 128.1, 128.6, 130.2, 136.9, 139.7, 169.8; ¹³C NMR (minor diastereomer) (CDCl₃, 75 MHz): δ 20.0, 39.4, 42.5, 53.1, 56.0, 126.7, 126.8, 128.3, 128.6, 129.5, 137.5, 141.3, 169.6; MS (EI) (major diastereomer): m/z 265 (M⁺), 250 (M⁺-CH₃); MS (EI) (minor diastereomer): m/z 265 (M⁺), 250 (M⁺-CH₃); Anal.
Calcd for C_{18}H_{19}NO (mixture of diastereomers): C, 81.47; H, 7.22; N, 5.28. Found: C, 81.24; H, 7.29; N, 5.35.

_N-Benzyol-2,4-dimethyl-4-phenylpyrrolidine._ A combined yield of 52% was obtained for the mixture of diastereomers. It was possible to separate a sufficient quantity of the major diastereomer by chromatography (hexane/ether, SiO₂) to provide ¹H NMR, ¹³C NMR, and GCMS (EI) data for this compound. This in turn facilitated the identification of the ¹H, ¹³C NMR and GCMS (EI) data for the minor diastereomer. ¹H NMR (major diastereomer) (CDCl₃, 300 MHz): δ 0.86 (3H, s, PhC(CH₃)-CH₂), 1.44 (3H, d, J = 6.0 Hz, (CH₃)CH-NBz), 1.93 (1H, dd, J = 10.0, 12.1 Hz, (CH₃)CH-CHH-CPh(CH₃)), 2.41 (1H, dd, J = 7.2, 12.4 Hz, (CH₃)CH-CHH-CPh(CH₃)), 3.60 (1H, d, J = 10.4 Hz, Ph(CH₃)C-CHH-NBz), 3.72 (1H, d, J = 10.4, Ph(CH₃)C-CHH-NBz), 4.48–4.52 (1H, m, (CH₃)CH-CHH-NBz), 7.10–7.59 (10H, m, Ar-H); ¹H NMR (minor diastereomer) (CDCl₃, 300 MHz): δ 1.35 (3H, s, PhC(CH₃)-CH₂), 1.42 (3H, d, J = 5.8 Hz, (CH₃)CH-NBz), 1.74 (1H, dd, J = 9.7, 12.8 Hz, (CH₃)CH-CHH-CPh(CH₃)), 2.65 (1H, dd, J = 6.3, 13.1 Hz, (CH₃)CH-CHH-CPh(CH₃)), 3.47 (1H, d, J = 7.1 Hz, Ph(CH₃)C-CHH-NBz), 3.87 (1H, d, J = 7.1, Ph(CH₃)C-CHH-NBz), 4.0–4.1 (1H, m, (CH₃)CH-CHH-NBz), 7.10–7.59 (10H, m, Ar-H); ¹³C NMR (major diastereomer) (CDCl₃, 75 MHz): δ 20.12, 27.27, 45.34, 45.64, 52.51, 60.88, 125.55, 126.42, 127.56, 128.26, 128.49, 130.12, 136.97, 146.54, 170.29; ¹³C NMR (minor diastereomer) (CDCl₃, 75 MHz): δ 20.1, 27.3, 45.9,
47.4, 60.9, 125.3, 126.4, 127.2, 128.3, 128.5, 129.9, 137.2, 146.5, 169.8; MS (El) (major diastereomer): m/z 279 (M⁺), 264 (M⁺-CH₃); MS (El) (minor diastereomer): m/z 279 (M⁺), 264 (M⁺-CH₃); Anal. Calcd for C₁₉H₂₁N₀ (mixture of diastereomers): C, 81.68; H, 7.58; N, 5.01. Found: C, 81.32; H, 7.28; N, 5.31.

General procedure for the NMR-tube scale intermolecular alkyne hydroamination reactions. All NMR-tube scale reactions were prepared in an N₂-filled glove box. A J. Young NMR tube was charged with the internal standard (1,3,5-trimethoxy benzene) (0.17 mmol, 0.33 equiv), the precatalyst (0.025 mmol, 0.05 equiv), the alkyne (0.5 mmol, 1.0 equiv) and the primary amine (0.6 mmol, 1.2 equiv) and dissolved in either d₆-benzene (~1 mL) or d₈-toluene (~1 mL). The tube was sealed, heated to, and/or maintained at ambient temperature, 65 °C or 110 °C for the stated duration of time. The conversion and yield were determined by comparing the integration of the internal standard with a well resolved signal for the imine product.

General procedure for intermolecular alkyne hydroamination where isolated yields are given. All hydroamination reactions were prepared in an N₂-filled glovebox. A small Schlenk tube equipped with a magnetic stir bar would be charged with a solution of the precatalyst (0.05 mmol, 0.05 equiv), the alkyne (1.0 mmol, 1.0 equiv), and the primary amine (1.2 mmol, 1.2 equiv) dissolved in benzene (~2 mL) or toluene (~2 mL). The Schlenk tube would then be sealed and maintained at the stated temperature for 24 h. After allowing the reaction mixture to cool to room temperature the resultant hydroamination products were directly subjected to NaCNBH₃ as described in the
literature to afford the crude amine products. Column chromatography then afforded the purified amine products either as single compounds or as a mixture of regioisomers.

(4-Methoxy-phenyl)-phenethyl-amine. Yield 76%. $^1$H NMR (CDCl$_3$, 400 MHz): δ 2.96 (2H, t, $J = 7.0$ Hz, Ph-CH$_2$-CH$_2$-NHPMP), 3.41 (2H, t, $J = 7.0$ Hz, Ph-CH$_2$-CH$_2$-NHPMP), 3.47 (1H, br s, NH), 3.80 (3H, s, CH$_3$-O-Ph), 6.62 (2H, d, $J = 8.9$ Hz, Ar-H), 6.85 (2H, d, $J = 8.9$ Hz, Ar-H), 7.26 – 7.40 (5H, m, Ar-H); $^{13}$C NMR (CDCl$_3$, 101 MHz): δ 35.8, 46.2, 56.0, 114.5, 115.1, 126.6, 128.8, 129.0, 139.6, 142.5, 152.4; MS (EI): $m/z$ 227 (M$^+$); Anal. Calcd. for C$_{15}$H$_{17}$NO: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.06; H, 7.42; N, 6.37.

(4-Methoxy-phenyl)-(1-methyl-2-phenyl-ethyl)-amine.$^{30}$ Yield >98%. $^1$H NMR (CDCl$_3$, 400 MHz): δ 1.18 (3H, d, $J = 6.0$ Hz, PMPNH-CH-CH$_3$), 2.71 (1H, dd, $J = 7.6$ 13.2 Hz, Ph-CH/H-NHPMP), 2.97 (1H, dd, $J = 4.8$ 13.2 Hz, Ph-CH/H-NHPMP), 3.70 – 3.76 (1H, m, CH$_3$-CH(NHPMP)-CH$_2$), 3.80 (3H, s, CH$_3$-OPh), 6.65 (2H, d, $J = 10.4$ Hz, Ar-H), 6.85 (2H, d, $J = 10.4$ Hz, Ar-H), 7.20 – 7.37 (5H, m, Ar-H); $^{13}$C NMR (CDCl$_3$, 101 MHz): δ 21.3, 43.4, 51.4, 56.8, 116.1, 127.3, 129.3, 130.5, 139.8, 142.5, 153.1; MS (EI): $m/z$ 241 (M$^+$).
(2-Cyclohex-1-enyl-ethyl)-(4-methoxy-phenyl)-amine. Yield 80%. NMR (CDCl₃, 400 MHz): δ 1.5 – 1.7 (4H, m, CH-CH₂-CH₂-CH), 1.9 – 2.1 (4H, m, =CH-CH₂-CH₂-CH₂-CH₂-CH₂-C=), 2.27 (2H, t, J = 6.8 Hz, C-CH₂-CH₂-NHAr), 3.14 (2H, t, J = 6.8 Hz, C-CH₂-CH₂-NHAr), 3.4 (1H, br s, ArNH), 3.76 (3H, s, Ar-OCH₃), 5.5 (1H, m, -CH₂-CH=CH₂, 6.6 (2H, d, J = 9 Hz, Ar-H), 6.8 (2H, d, J = 9 Hz, Ar-H); ¹³C NMR (CDCl₃, 101 MHz): δ 23.4, 23.9, 26.3, 28.9, 38.8, 43.5, 56.8, 115.3, 115.9, 124.5, 136.0, 143.8, 153.0; MS (EI): m/z 231 (M⁺); Anal. Calcd. for C₁₅H₂₁NO: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.12; H, 9.11; N, 5.81.

Phenethyl-phenyl-amine.³¹ Yield 83%. NMR (CDCl₃, 400 MHz): δ 3.01 (2H, t, J = 7.0, Ph-CH₂-CH₂-NHAr), 3.51 (2H, t, J = 7.0, Ph-CH₂-CH₂-NHAr), 3.76 (1H, br s, ArNH-); ¹³C NMR (CDCl₃, 101 MHz): δ 35.8, 45.3, 113.3, 117.7, 126.7, 128.9, 129.1, 129.6, 139.6, 148.3; MS (EI): m/z 197 (M⁺).

(3,3-Dimethyl-butyl)-(4-methoxy-phenyl)-amine. Yield 80%. NMR (CDCl₃, 400 MHz): δ 1.00 (9H, s, -CH₂-C(CH₃)₃), 1.54 (2H, m, -CH₂-C(CH₃)₃), 3.10 (2H, m, ArNH-CH₂-), 3.25 (1H, br s, ArNH-), 3.77 (3H, s, -NHAr-OCH₃), 6.60 (2H, d, J = 9 Hz, -NH-ArH-OMe), 6.81 (2H, d, J = 9 Hz, -NH-ArH-OMe); ¹³C NMR (CDCl₃,
101 MHz): \( \delta \) 30.6, 31.0, 42.3, 44.7, 57.0, 115.1, 115.9, 143.9, 153.0; MS (EI): 
\( m/z \) 207 (M\(^+\)); Anal. Calcd. for \( \text{C}_{13}\text{H}_{21}\text{N} \): C, 75.32; H, 10.21; N, 6.76. Found: C, 75.38; H, 10.33; N, 6.76.

(4-Methoxy-phenyl)-(1-methyl-pentyl)-amine and hexyl-(4-methoxy-phenyl)-amine.

A combined yield of 77% was obtained for the mixture of regioisomers (2.3 : 1, AM : M), which were inseparable by chromatography. The \(^1\)H and \(^{13}\)C NMR spectra as well as the elemental analysis for the mixture have been provided. Hexyl-(4-methoxy-phenyl)-amine is a known compound.\(^{32}\) The \(^1\)H, \(^{13}\)C NMR and HRMS data for (4-methoxy-phenyl)-(1-methyl-pentyl)-amine obtained by the reductive amination of 2-hexanone with \( p \)-anisidine\(^{35}\) is reported herein. \(^1\)H NMR ((4-methoxy-phenyl)-(1-methyl-pentyl)-amine) (CDCl\(_3\), 400 MHz): \( \delta \) 0.91 (3H, t, \( J = 7.2 \) Hz, -CH\(_2\)-CH\(_3\)), 1.17 (3H, d, \( J = 6.4 \) Hz, -CH(NHAr)-CH\(_3\)), 1.30 – 1.70 (6H, m, CH\(_3\)-(CH\(_2\))\(_3\)-CH(NHAr)-CH\(_3\)), 3.15 (1H, br s, ArNH-), 3.30 – 3.50 (1H, m, -CH(NHAr)-), 3.76 (3H, s, -NH-Ar-OCH\(_3\)), 6.57 (2H, d, \( J = 9 \) Hz, -NH-ArH-OMe), 6.79 (2H, d, \( J = 9 \) Hz, -NH-ArH-OMe); \(^{13}\)C NMR ((4-methoxy-phenyl)-(1-methyl-pentyl)-amine) (CDCl\(_3\), 101 MHz): \( \delta \) 14.2, 21.0, 28.5, 37.1, 49.6, 56.0, 114.8, 115.1, 142.1, 151.9; HRMS Calcd for ((4-methoxy-phenyl)-(1-methyl-pentyl)-amine) \( \text{C}_{13}\text{H}_{21}\text{NO} \) [M\(^+\)]: 207.1623; Found: 207.16242; Anal. Calcd. for (mixture of regioisomers) \( \text{C}_{13}\text{H}_{21}\text{NO} \): C, 75.32; H, 10.21; N, 6.76. Found: C, 75.44; H, 10.09; N, 6.61.
$N$-Benzyl-hexylamine.$^{19}$ Yield 79%. NMR (CDCl$_3$, 400 MHz): $\delta$ 3.21 (3H, t, $J = 6.8$ Hz, -CH$_2$-CH$_3$), 1.22 – 1.39 (7H, m, BnNH-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 1.50 – 1.57 (2H, m, BnNH-CH$_2$-CH$_2$-CH$_2$-CH$_2$-), 2.65 (2H, t, $J = 7.2$ Hz, BnNH-CH$_2$-CH$_2$-), 3.81 (2H, s, Ph-CH$_2$-NH-), 7.24 – 7.37 (5H, m, ArH); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 15.1, 21.4, 23.7, 24.2, 28.1, 31.2, 32.8, 50.6, 55.2, 127.8, 129.1, 129.4, 141.7; MS (EI): $m/z$ 191 (M$^+$.)

2,2-Dimethyl-propionic acid 5-(4-methoxy-phenylamino)-pentyl ester and 2,2-dimethyl-propionic acid 4-(4-methoxy-phenylamino)-pentyl ester. A combined yield of 77% was obtained for the mixture of regioisomers (>2 : 1, AM : M). It was possible to separate a sufficient quantity of the major diastereomer by chromatography (hexane/ether, SiO$_2$) to provide $^1$H NMR and $^{13}$C NMR data for this compound. Due to weak intensity and extensive overlap of peaks, it was not possible to definitively assign the $^1$H NMR or $^{13}$C NMR signals for the minor diastereomer. Yield 77% (mixture of regioisomers). $^1$H NMR (major regioisomer) (CDCl$_3$, 400 MHz): $\delta$ 1.21 (9H, s, O=C-C-(CH$_3$)$_3$), 1.45 – 1.50 (2H, m, ArNH-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-), 1.61 – 1.71 (4H, m, ArNH-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_2$-O$_2$CtBu), 3.09 (2H, t, $J = 7.1$ Hz, ArNH-CH$_2$-CH$_2$-CH$_2$-), 3.76 (1H, br s, Ar-NH-CH$_2$-), 3.76 (3H, s, -NH-Ar-OCH$_3$), 4.08 (2H, t, $J = 6.5$ Hz, CH$_2$-CH$_2$-).
O₂C-tBu), 6.58 (2H, d, J = 9 Hz, Ar-H), 6.77 (2H, d, J = 9 Hz, Ar-H); ¹³C NMR (major regioisomer) (CDCl₃, 101 MHz): δ 23.7, 27.3, 28.6, 29.4, 38.9, 45.0, 56.0, 64.3, 114.1, 115.1, 142.8, 152.2, 178.7; MS (EI) (mixture of regiosomers): m/z (M⁺) 293; Anal. Calcd. for C₁₇H₂₇N₀₃ (mixture of regioisomers): C, 69.59; H, 9.28; N, 4.77. Found: C, 69.71; H, 9.01; N, 5.15.

![Chemical structure 1](image1)

(1-Methyl-2-phenyl-ethyl)-phenyl-amine.³⁴ Yield >98%. NMR (CDCl₃, 400 MHz): δ 1.23 (3H, d, J = 6.4 Hz, Ph-CH₂-CH(NHAr)-CH₃), 2.77 (1H, dd, J = 7.2, 13.2 Hz, Ph-CHH-CH(NHAr)-CH₃), 3.02 (1H, dd, J = 4.8, 13.2 Hz, Ph-CHH-CH(NHAr)-CH₃), 3.6 (1H, br s, ArNH), 3.83 – 3.88 (1H, m, Ph-CH₂-CH(NHAr)-CH₃), 6.71 (2H, d, J = 8 Hz, -NHArH), 6.79 (1H, t, J = 7.6 Hz, -NHArH), 7.25 – 7.40 (7H, m, ArH); ¹³C NMR (CDCl₃, 101 MHz): δ 21.3, 43.4, 50.4, 114.4, 118.3, 127.4, 129.4, 130.4, 130.6, 139.6, 148.3; MS (EI): m/z 211 (M⁺).

![Chemical structure 2](image2)

(1,2-Diphenyl-ethyl)-(4-methoxy-phenyl)-amine. Yield >98%. NMR (CDCl₃, 400 MHz): δ 3.06 (1H, dd, J = 8.2, 13.9 Hz, Ph-CHH-CH(NHAr)-Ph), 3.18 (1H, dd, J = 5.6, 13.8 Hz, Ph-CHH-CH(NHAr)-Ph), 3.72 (3H, s, -NH-Ar-OCH₃), 3.90 (1H, br s, ArNH-), 4.56 – 4.60 (1H, m, Ph-CHH-CH(NHAr)-Ph), 5.50 (2H, d, J = 9 Hz, MeO-Ar-H), 6.71 (2H, d, J = 9 Hz, MeO-Ar-H), 7.17 – 7.39 (10H, m, Ar-H); ¹³C NMR (CDCl₃, 101 MHz): δ 45.4, 55.9, 60.3, 114.9, 115.1, 126.7, 126.9, 127.2, 128.7, 128.7,
(1-Ethyl-butyl)-(4-methoxy-phenyl)-amine. Yield >98%. NMR (CDCl₃, 400 MHz): δ 0.94 (6H, t, J = 7.2 Hz, H₃C-CH₂-CH₂-CH(NHAr)-CH₂-CH₃), 1.40 – 1.62 (6H, m, H₃C-CH₂-CH₂-CH(NHAr)-CH₂-CH₃), 3.15 (1H, br s, ArNH), 3.19 – 3.24 (1H, m, -CH₂-CH(NHAr)-CH₂-), 3.76 (3H, s, -NH-Ar-OCH₃), 6.56 (2H, d, J = 9 Hz, Ar-H), 6.77 (2H, d, J = 9 Hz, Ar-H); ¹³C NMR (CDCl₃, 101 MHz): δ 11.0, 15.3, 20.2, 28.2, 37.7, 55.9, 56.9, 115.3, 116.0, 143.6, 152.6; MS (El): m/z 207 (M⁺); Anal. Calcd. for. C₁₃H₂₁NO: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.26; H, 10.10; N, 7.16.

(4-Methoxy-phenyl)-(1,3,3-trimethyl-butyl)-amine. Yield 76%. NMR (CDCl₃, 400 MHz): δ 0.93 (3H, d, J = 6.6 Hz, (H₃C)-CH-CH₂-), 0.96 (3H, d, J = 6.6 Hz, (H₃C)-CH-CH₂-), 1.15 (3H, d, J = 6.2 Hz, CH₂-CH(NHAr)-CH₃), 1.20 – 1.31 (1H, m, (H₃C)₂CH-CHH-CH-NHAr), 1.44 – 1.54 (1H, m, (H₃C)₂CH-CHH-CH-NHAr), 1.71 – 1.85 (1H, m, (H₃C)₂CH-CHH-CH-NHAr), 3.03 (1H, br s, ArNH), 3.41 – 3.52 (1H, m, -CH₂-ArNH-CH-CH₃), 3.76 (3H, s, -NH-OCH₃), 6.57 (2H, d, J = 9 Hz, Ar-H), 6.79 (2H, d, J = 9 Hz, Ar-H); ¹³C NMR (CDCl₃, 101 MHz): δ 21.2, 22.7, 23.2, 25.2, 47.1, 47.7, 56.0, 114.7, 115.1, 142.1, 1551.9; MS (El): m/z 207 (M⁺); Anal. Calcd. for. C₁₃H₂₁NO: C, 75.32; H, 10.12; N, 6.76. Found: C, 75.38; H, 10.18; N, 6.51.
[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-(4-methoxy-phenyl)-amine. Yield 75%.

NMR (CDCl₃, 400 MHz): δ 0.10 (6H, s, -CH₂-Si(CH₃)₂-C(CH₃)₃), 0.95 (9H, s, -CH₂-Si(CH₃)₂-C(CH₃)₃), 1.80 – 1.88 (2H, m, ArNH-CH₂-CH₂-CH₂-OTBDMS), 3.21 (2H, t, J = 6.5 Hz, ArNH-CH₂-CH₂-), 3.77 (3H, s, -NHArOCH₃), 3.78 (2H, t, J = 5.7, -CH₂-CH₂-OTBDMS), 6.59 (2H, d, J = 9 Hz, Ar-H), 6.80 (2H, d, J = 9 Hz, Ar-H);

¹³C NMR (CDCl₃, 101 MHz): δ -5.2, 26.1, 32.3, 43.0, 56.0, 57.9, 62.1, 114.1, 115.1, 143.1, 152.1; MS (EI): m/z 295 (M⁺); Anal. Calcd. for. C₁₆H₂₉N₀: C, 65.03; H, 9.89; N, 4.74. Found: C, 65.24; H, 9.77; N, 5.06.

[1-Benzyl-2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-(4-methoxy-phenyl)-amine.

Yield 80%. NMR (CDCl₃, 400 MHz): δ 0.08 (3H, s, -Si(CH₃)(tBu)-CH₃), 0.10 (3H, s, -Si(CH₃)(tBu)-CH₃), 1.00 (9H, s, -Si-C(CH₃)₃), 2.90 – 2.95 (2H, m, Ar-CH₂-CH(NHAr)-CH₂-OTBDMS), 3.56 – 3.62 (2H, m, -CH₂-CH(NHAr)-CH₂-OTBDMS), 3.60 (1H, s, ArNH), 3.71 – 3.73 (1H, m, -CH₂-CH(NHAr)-CH₂-), 3.79 (3H, s, Ar-O-CH₃), 6.65 (2H, d, J = 9Hz, -NH-ArH-OMe), 6.82 (2H, d, J = 9Hz, -NH-ArH-OMe), 7.22 – 7.36 (5H, m, Ar-H); ¹³C NMR (CDCl₃, 101 MHz): δ -5.2, 18.5, 26.1, 37.0, 55.9, 56.9, 62.6, 115.1, 115.5, 126.3, 128.5, 129.6, 139.2, 141.5, 152.4; MS
[(+/-)-1-(R)-Benzyl-2-(S)-((tert-butyl-dimethyl-silanyloxy)-propyl)-(4-methoxy-phenyl)-amine and [(+/-)-1-(S)-Benzyl-2-(R)-((tert-butyl-dimethyl-silanyloxy)-propyl)-(4-methoxy-phenyl)-amine]. A combined yield of 30% was obtained for the mixture of diastereomers, which were subsequently separated for characterization purposes. Relative stereochemistry was assigned by comparing the $^1$H NMR spectra of the deprotected compounds to the known (+/-)-(2R,3S)-3-amino-4-phenyl-2-butanol and (+/-)-(2S,3R)-3-amino-4-phenyl-2-butanol.36

$^1$H NMR (syn product) (CDCl$_3$, 400 MHz): δ 0.12 (3H, s, -Si(CH$_3$)(tBu)-CH$_3$), 0.15 (3H, s, -Si(CH$_3$)(tBu)-CH$_3$), 1.00 (9H, s, -Si(CH$_3$)$_2$(C(CH$_3$)$_3$)), 1.16 (3H, d, J = 6.2 Hz, -CH(OTBDMS)-CH$_3$), 2.78 – 2.85 (2H, m, Ar-CH$_2$-CH(NHAr)-), 3.36 – 3.41 (1H, m, -CH$_2$-CH(NHAr)-CH$_2$-), 3.75 (3H, s, -NH-Ar-OCH$_3$), 3.98 – 4.01 (1H, m, -CH(NHAr)-CH(OTBDMS)-CH$_3$), 6.56 (2H, d, J = 9 Hz, -NH-ArH-OMe), 6.77 (2H, d, J = 9 Hz, -NH-ArH-OMe), 7.19 – 7.33 (5H, m, -CH$_2$-ArH); $^{13}$C NMR (syn product) (CDCl$_3$, 101 MHz): δ -4.5, 18.3, 21.1, 26.1, 37.6, 56.0, 61.4, 68.2, 115.4, 115.2, 126.2, 128.5, 129.3, 140.0, 142.4, 151.8; MS (syn product) (EI): m/z 385 (M$^+$); $^1$H NMR (anti product) (CDCl$_3$, 400 MHz): δ 0.01 (3H, s, -Si(CH$_3$)(tBu)-CH$_3$), 0.03 (3H, s, -Si(CH$_3$)(tBu)-CH$_3$), 0.93 (9H, s, -Si(CH$_3$)$_2$(C(CH$_3$)$_3$)), 1.22 (3H, d, J = 6.4 Hz, -CH(OTBDMS)-CH$_3$), 2.74 (1H, dd, J =
8.4, 14.4 Hz, Ar-CHH-CH(NHar-), 2.98 (1H, dd, J = 4.4, 14.4 Hz, Ar-CCH-
CH(NHar-), 3.42 – 3.48 (1H, m, -CH2-CH(NHar)-CH2-), 3.50 (1H, br s, ArNH-),
3.73 (3H, s, -NH-Ar-OCH3), 3.96 – 4.04 (1H, m, -CH(NHar)-CH(OTBDMS)-CH3),
6.47 (2H, d, J = 9 Hz, -NH-ArH-OMe), 6.72 (2H, d, J = 9 Hz, -NH-ArH-OMe), 7.14
– 7.30 (5H, m, -CH2-ArH); 13C NMR (anti product) (CDCl3, 101 MHz): δ -4.6, -4.1,
18.2, 20.7, 26.0, 35.8, 38.9, 55.9, 61.6, 69.5, 114.4, 115.1, 126.1, 128.4, 129.3,
140.0, 142.1, 152.0; MS (anti product) (EI): m/z 385 (M+); Anal. Calcd.
for C23H35NO2Si (mixture of syn/anti products): C, 71.64; H, 9.15; N, 3.63. Found: C,
72.00; H, 9.24; N, 3.89.

**Hydrochloride salt of 1-methyl-2-phenyl-ethylamine.** Yield 63%. Although the 1H
NMR spectrum of the HCl salt displayed extensive peak broadening, the chemical shift
and integration of each peak were consistent with the known compound. In addition, the
13C-APT spectrum is consistent with the literature spectrum. NMR (CDCl3, 400 MHz):
δ 1.27 (3H, br), 2.80 (1H, br), 3.27 (1H, br), 3.62 (1H, br), 7.2 (5H, br), 7.8 (2H, br);
13C-APT NMR (CDCl3, 101 MHz): δ 18.9 (CH3), 41.9 (CH2), 51.1 (CH), 128.2
(CH), 129.9 (CH), 130.3 (CH), 136.8 (C); HRMS Calcd for C9H14N [M+]: 136.1131;
Found: 136.1126.
2-Amino-3-phenyl-propan-1-ol. Yield 57%. NMR (CDCl₃, 400 MHz): δ 2.54 (1H, dd, J = 8.6, 13.5 Hz, Ph-CHH-CH-), 2.80 (1H, dd, J = 5.3, 13.5 Hz, Ph-CHH-CH-), 3.1 – 3.3 (1H, m, -CH₂-CH₃-CH₂-), 3.40 (1H, dd, J = 7.2, 10.7 Hz, HO-CHH-CH-), 3.65 (1H, dd, J = 3.8, 10.7 Hz, HO-CHH-CH-), 7.17 – 7.33 (5H, m, Ar-H); ¹³C NMR (CDCl₃, 101 MHz): δ 40.8, 54.3, 66.2, 126.6, 128.7, 129.3, 183.7; HRMS Calcd for C₉H₁₃NO [M+Na⁺]: 174.0895; Found: 174.0891.

[2-(3-Chloro-phenyl)-1-methyl-ethyl]-phenyl-amine.³⁴ Yield 93%. NMR (CDCl₃, 400 MHz): δ 1.17 (3H, d, J = 6.4 Hz, Ph-CH₂-CH(NHAr)-CH₃), 2.70 (1H, dd, 7.2, 13 Hz, Ph-CHH-CH(NHAr)-CH₃), 2.93 (1H, dd, J = 4.8, 13 Hz, Ph-CHH-CH(NHAr)-CH₃), 3.52 (1H, br s, ArNH-), 3.74 – 3.84 (1H, m, Ph-CHH-CH(NHAr)-CH₃), 6.64 (2H, d, J = 8 Hz, -NHArH), 6.76 (1H, t, J = 7.2 Hz, -NHArH), 7.08 – 7.27 (6H, m, ArH); ¹³C NMR (CDCl₃, 101 MHz): δ 20.33, 42.0, 49.3, 113.5, 117.5, 126.6, 127.8, 129.6, 129.7, 134.2, 140.8, 147.1; MS (EI): m/z 245 (M⁺); Anal. Calcd. for C₁₅H₁₆ClN: C, 73.31; H, 6.56; N, 5.70. Found: C, 73.62; H, 6.79; N, 5.79.
(2-Benzyl-3-phenyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine.\(^6\) Yield 20\%.\(^1\) H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.48 (1H, dd, \(J = 10.7, 13.6\) Hz, Ph-CH\(_2\)-CH-NH), 2.78 (1H, dd, \(J = 2.4, 13.6\), Ph-CH\(_2\)-CH-NH), 3.14 (1H, t, \(J = 9.7\) Hz, NH-CH-CH(Ph)-CH), 3.87 – 3.93 (1H, m, NH-CH(Ph\(_2\))-CHPh), 3.93 (2H, br s, NH, NH), 4.80 (1H, d, \(J = 9.8\) Hz, PhNH-CH-CH(Ph)), 6.35 – 6.45 (3H, m, Ar-H), 6.60-6.70 (2H, m, Ar-H), 7.05 – 7.15 (3H, Ar-H), 7.2 – 7.5 (11H, m, Ar-H); \(^13\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 41.2, 51.0, 57.5, 57.7, 113.7, 114.2, 114.6, 117.4, 117.9, 124.2, 125.9, 127.3, 128.2, 128.5, 129.0, 129.2, 129.3, 129.6, 138.4, 141.2, 143.8, 148.0; MS (E1): \(m/z\) 390 (M\(^+\)).

2,4-N\(_1\),N\(_3\)-Tetrapheny-butane-1,3-diamine. Yield 17 %. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.48 (1H, dd, \(J = 7.2\) 14.0 Hz, Ph-CH\(_2\)-CH-NH), 2.47 (1H, dd, \(J = 4.4\) 14.0 Hz, Ph-CH\(_2\)-CH-NH), 3.08 – 3.14 (1H, m, NH-CH\(_2\)-CHPh-CH), 3.39 (1H, dd, \(J = 8.8\) 12.0 Hz, PhNH-CH-CHPh), 3.6 (2H, br s, NH, NH), 3.74 (1H, dd, \(J = 4.8\) 12.4 Hz, PhNH-CH-CHPh), 4.10 – 4.16 (1H, m, (Ph)CH\(_2\)-CH-NPh), 6.50 (2H, d, \(J = 8.4\) Hz, PhNH-CH-CHPh), 6.80 (2H, d, \(J = 8.4\) Hz, PhNH-CH-CHPh).
Ar-H), 6.61 (2H, d, J = 8.0 Hz, Ar-H), 6.65 - 6.73 (2H, m, Ar-H), 7.00 - 7.50 (14H, m, Ar-H); \(^{13}\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 38.6, 47.9, 50.1, 57.7, 114.2, 114.6, 118.5, 118.6, 127.3, 128.3, 129.2, 129.9, 129.9, 130.2, 130.5, 130.5, 139.0, 141.3, 148.5, 149.0; HRMS Calcd for C\(_{28}\)H\(_{28}\)N\(_2\)Na [M+Na\(^+\)]: 415.2150; Found: 415.2146.
2.5 References


(18) Bexrud, J.A.; Li, C.; Schafer, L.L. *Organometallics* 2007, 26, 6366.


(33) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D.


CHAPTER THREE: CATALYST DEVELOPMENT OF GROUP FOUR BASED SYSTEMS INCORPORATING AMIDATES AS N,O CHELATING ANCILLIARY LIGANDS

3.1 Introduction

Amidate ligands offer a great deal of versatility in terms of structural modifications that can be made to alter the electronic and steric properties of the resultant complexes. The relative proximity of $R^1$, which largely impacts electronic properties, and $R^2$, which effects steric properties, makes it easier to control the two effects independently. The work described in this chapter takes advantage of the modular nature of the amidate scaffold with the intent of generating more reactive and selective hydroamination catalysts (Figure 3.1).

![Figure 3.1. Amidate proligands designed for improved reactivity (3.1) and stereoselectivity (3.2).](image)

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In section 3.2.1 the efforts to improve the reactivity of complex 1.1 by varying the substituent in the R\(^1\) position is presented. In particular, the phenyl group employed in complex 1.1 is replaced by an electron withdrawing pentafluorophenyl group (ligand 3.1, Figure 3.1) with the intent of generating a more electrophilic, and hence reactive metal center. The synthesis, structural elucidation, and assessment of this new system as a hydroamination precatalyst is discussed.

In section 3.2.2 an optically active menthyl group is incorporated in the R\(^2\) position (ligand 3.2, Figure 3.1) in order to impose a chiral steric environment about the metal active site for asymmetric catalysis. For the reasons described in section 1.4, this was done to ascertain whether or not a bis(amidate) complex utilizing a chiral non-tethered amidate ligand could affect the enantioselective cyclohydroamination of aminoalkenes. Ligand synthesis and characterization along with the results of enantioselectivity determinations are presented.

3.2 Results and discussion

3.2.1 Altering the electronics of the amidate ligand for improved reactivity

As was discussed in section 1.3, both electron withdrawing substituents (e.g. complex 1.7)\(^1\) and enhanced steric bulk (e.g. complex 1.1)\(^2\) have been shown to contribute to increased catalytic activity. Thus an improved catalyst design was devised, complex 3.1 (Scheme 3.1), having a perfluorophenyl group in the R\(^1\) position and a 2,6-diisopropylphenyl group in the R\(^2\) position. It was expected that this complex which
takes advantage of both reactivity enhancing steric and electronic effects, would be an even more active precatalyst, capable of affecting the hydroamination of a wide range of alkyne and alkene substrates with optimized reactivity and selectivity. This section presents the synthesis and structural characterization of complex 3.1, as well as the results of experiments assessing its performance as a hydroamination precatalyst. In addition, the unexpected susceptibility to decomposition of this complex, under hydroamination reaction conditions, is also discussed.

Scheme 3.1. Evolution of the bis(amidate) system.

3.2.1.1 Complex synthesis and characterization

Synthesis of proligand 3.1 is carried out according to literature procedures by reacting pentafluorobenzoyl chloride with 2,6-diisopropylaniline. This compound can be easily isolated in analytically pure form following aqueous workup, washing with hexanes (or pentanes), and then recrystallizing the crude material from CH$_2$Cl$_2$. Prior to use, the
proligand is dried via sublimation. Characterization data for this compound is consistent with the assigned structure, however the signals in the $^{13}$C NMR spectrum for the carbons of the aromatic ring bearing the fluorine atoms were obscured due to extensive coupling to fluorine.

Complex 3.1 is prepared by the reaction of two equivalents of $N$-2,6-diisopropylphenylperfluorophenylamide with one equivalent of Ti(NEt$_2$)$_4$ in anhydrous ether, followed by filtration through Celite and removal of all volatiles to give a red microcrystalline solid. Crystals suitable for X-ray crystallographic analysis are obtained by recrystallization from benzene, and the solid-state molecular structure is shown in Figure 3.2. (Selected bond lengths and angles are given in Table 3.1.) It should be noted that either the crude microcrystalline or the recrystallized product can be used for subsequent hydroamination experiments without any notable difference in activity.

**Figure 3.2.** Diagram of bis(amidate) titanium bis(amido) complex 3.1 with thermal ellipsoids set at the 50% probability level.
Table 3.1. Selected Bond Distances (Å) and Angles (deg) for bis(N-2,6-diisopropylphenyl-perfluorophenylamidate)titanium-bis(diethylamide) complex 3.1.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length Å</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti – N(2)</td>
<td>1.903(1)</td>
<td></td>
</tr>
<tr>
<td>Ti – O(1)</td>
<td>2.170(1)</td>
<td></td>
</tr>
<tr>
<td>Ti – N(1)</td>
<td>2.201(1)</td>
<td></td>
</tr>
<tr>
<td>C(1) – O(1)</td>
<td>1.281(2)</td>
<td></td>
</tr>
<tr>
<td>C(1) – N(1)</td>
<td>1.315(2)</td>
<td></td>
</tr>
<tr>
<td>O(1) – C(1) – N(1)</td>
<td>117.4(1)</td>
<td></td>
</tr>
<tr>
<td>C(21) – N(2) – C(23)</td>
<td>113.5(2)</td>
<td></td>
</tr>
<tr>
<td>O(1) – Ti – O(1)</td>
<td>80.53(5)</td>
<td></td>
</tr>
<tr>
<td>N(1) – Ti – N(1)</td>
<td>139.06(6)</td>
<td></td>
</tr>
<tr>
<td>N(1) – Ti – N(2)</td>
<td>104.82(4)</td>
<td></td>
</tr>
<tr>
<td>N(1) – Ti – N(2)</td>
<td>100.16(4)</td>
<td></td>
</tr>
<tr>
<td>O(1) – Ti – N(1)</td>
<td>87.22(4)</td>
<td></td>
</tr>
<tr>
<td>O(1) – Ti – N(2)</td>
<td>159.23(4)</td>
<td></td>
</tr>
<tr>
<td>O(1) – Ti – N(1)</td>
<td>60.98(4)</td>
<td></td>
</tr>
</tbody>
</table>

As previously reported for the structurally similar and non-fluorinated complex 1.1,2,3 the bis(amido) titanium complex 3.1 is rigorously C2-symmetric, with N atoms of the amidate ligand being trans to each other, while the amido ligands are in a cis orientation. This N-trans geometry is favored for steric reasons due to the bulky 2,6-diisopropylphenyl substituents. Another notable feature of 3.1 is that like complex 1.1 the binding of the oxygen and nitrogen donors of the amidate ligand to the metal center is nearly symmetric, with the Ti-O bond being the shorter (Ti – N(1) = 2.201(1) Å and Ti – O(1) = 2.170(1) Å for complex 3.1 and Ti – N(1) = 2.156(1) Å and Ti – O(1) = 2.146(1) Å for complex 1.1).2 In addition, one will notice that the Ti-N and Ti-O bond lengths found in complex 3.1 are both longer than the analogous bonds found in complex 1.1. This is suggestive of an enhanced ionic ligand-metal interaction in complex 3.1 versus
complex 1.1. The nearly symmetric Ti-N and Ti-O bonding found in complexes 1.1 and 3.1 is in contrast to complex 1.7 which was reported to have substantially different Ti-O and Ti-N bond lengths (Ti – N = 2.356(7) Å vs Ti – O = 2.044(6) Å)\(^1\) and is best characterized as an alkoxide, neutral imine donor. Also, as with all of our previously reported bis(amidate) titanium-bis(amido) complexes, the sum of the bond angles about the amido N atoms in complex 3.1 indicates \(sp^2\) hybridization and formal donation of four electrons to the metal center, resulting in a sixteen electron complex.

3.2.1.2 Reactivity towards alkynes

To probe the scope, activity, and regioselectivity of complex 3.1 in terms of the intermolecular hydroamination of alkynes, a selection of alkynes and primary amines with differing steric bulk and electronic properties were screened. The most notable results clearly demonstrate the much higher reactivity of complex 3.1 over complex 1.1 in terms of alkyne hydroamination. These results can be obtained with the internal alkyne phenyl-1-propyne and 2,6-dimethylaniline as substrates, as depicted in Scheme 3.2.

\[\text{Scheme 3.2. Hydroamination of 1-phenyl-1-propyne with 2,6-dimethylaniline.}\]
In this case, an elevated reaction temperature of 110 °C is required for the reaction to proceed to completion within 24 h. The imine product is subsequently reduced to the corresponding amine. Using complex 3.1 this reaction is nearly quantitative, and exhibits extremely high regioselectivity with the anti-Markovnikov product being formed exclusively. Complex 1.1 also affords the anti-Markovnikov compound with high selectivity, but with a substantially lower isolated yield. The symmetrically substituted internal alkynes 3-hexyne and diphenylacetylene can also be screened on an NMR tube scale under the same hydroamination reaction conditions and are found to be modestly reactive in the presence of complex 3.1 and completely unreactive in the presence of complex 1.1. With complex 3.1 conversions of up to 12% and 16% are observed for these two substrates respectively following 24 h at 110 °C, while no reaction is observed at all in the presence of complex 1.1 under the same conditions. Interestingly, this limited catalytic activity towards symmetrically substituted internal alkynes is in contrast to a number of other group 4 based systems, including Ti(NR₂)₄, which have been found to be effective precatalysts for these transformations.⁴

As substrates, we also screened a number of terminal alkynes such as phenylacetylene, 4-methoxy-phenylacetylene, and 1-hexyne with the primary amines 2,6-dimethylaniline, t-butylamine, and benzylamine. In an earlier report² it was demonstrated that for some of these substrates, under the same reaction conditions employed here, these transformations proceed with excellent yield and selectivity with complex 1.1. Results for both complex 1.1 and complex 3.1 are listed in Table 3.2, thereby permitting a direct comparison of activity and regioselectivity.
Table 3.2. Hydroamination reactions with terminal alkynes and primary amines using complexes 1.1 and 3.1

\[
\begin{align*}
H \equiv \equiv \equiv R^1 + H_2N-R^2 & \xrightarrow{\text{C}_8D_8, 65^\circC, 24\text{h}} C_8D_8 \xrightarrow{\text{LiAlH}_4, \text{Et}_2\text{O}, \text{RT, 24h}} \text{NHR}^2 + \text{NHR}^2 \\
\text{1) precatalyst (5 mol%)} & \\
\text{2) } \text{NHR}^2 \text{H} + \text{R}^1 & \\
\text{anti-Markovnikov} & \text{Markovnikov} \\
\text{(anti-M)} & \text{(M)}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>complex 1.1 Yield(^a)(anti-M:M)(^b)</th>
<th>complex 3.1 Yield(^a)(anti-M:M)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>2,6-dimethylphenyl</td>
<td>62%((&gt;49:1))</td>
<td>69%((3:1))</td>
</tr>
<tr>
<td>2</td>
<td>p-MeOPh</td>
<td>2,6-dimethylphenyl</td>
<td>57%((&gt;49:1))</td>
<td>65%((1.2:1))</td>
</tr>
<tr>
<td>3</td>
<td>( nBu )</td>
<td>2,6-dimethylphenyl</td>
<td>72%(&lt;1:49)</td>
<td>84%(&lt;1:49)</td>
</tr>
<tr>
<td>4</td>
<td>( nBu )</td>
<td>( t )-butyl</td>
<td>82%((&gt;49:1)^2)</td>
<td>&gt;90%((&gt;49:1)^2)</td>
</tr>
<tr>
<td>5</td>
<td>( nBu )</td>
<td>benzyl</td>
<td>88%((&gt;49:1)^2)</td>
<td>45%((2:1))</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields unless otherwise stated. \(^b\) Ratio determined by NMR. \(^c\) Yield and ratio of the imine hydroamination product determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

These reactions are carried out on small scale with benzene as a solvent. The resulting imine mixture is diluted with ether and reduced with LiAlH\(_4\) to give the corresponding amine products. It should be emphasized that the times and temperatures that are employed do not reflect optimized reaction conditions and are chosen for consistency. While monitoring by \(^1\)\(HNMR\) spectroscopy it is found that in the case of entries 3 and 4, when using complex 3.1, the reactions both go to completion within 4 h at 65 °C, again consistent with the enhanced activity of this precatalyst.

In general, with respect to entries 1 through 4 the yields that are obtained using complex 3.1 are comparable to, if not marginally better than those obtained using complex 1.1 as the precatalyst. However, the regioselectivity observed when using precatalyst 3.1 is found in some cases to be lower than when 1.1 is used as the
precatalyst. It should be noted that the comparable regioselectivities observed for entry 4 can be attributed to the significant steric bulk of the reactive t-butyl substituted titanium-imido intermediate (A, of Scheme 1.5) which has been previously reported to favor the formation of the anti-Markovnikov product. The enhanced steric accessibility to the reactive metal centre in complex 3.1, due to the increased ionic character of the metal-ligand bonding interaction, may promote the observed enhanced rates of reaction and the reduced regioselectivity with less bulky substrate combinations.

Although entries 1 through 4 suggest that the reactivity of complex 3.1 towards alkynes is similar to the analogous non-fluorinated complex 1.1, an important difference can be observed when 3.1 is used for the hydroamination of 1-hexyne with benzylamine (entry 5). Not only is the regioselectivity found to be diminished using 3.1 (only the anti-Markovnikov product is detected when 1.1 is used as the precatalyst), but the yield obtained using this precatalyst (45%) is substantially lower than when 1.1 is used (88%). Interestingly, it has been previously shown that commercially available Ti(NR₂)₄ shows the reverse regioselectivity, with the Markovnikov product formation being favored over the anti-Markovnikov product. Thus in the cases where bulkier amines are used as substrates, the yields obtained using complex 3.1 are slightly better than those obtained using complex 1.1 as the precatalyst. However, the dramatic change in reactivity when benzylamine is used as the substrate can be attributed to undesirable side reactions between benzylamine and the pentafluorophenyl bearing ligand (vide infra). Furthermore, the significant differences in observed reactivity and regioselectivity between the bis(amidate) bis(amido) titanium complexes 1.1, 1.7 and 3.1 and Ti(NR₂)₄ (which could be formed in situ if conproportionation is occurring) suggest that the
modified reactivity reported here can be attributed to the unique reaction environment afforded by the N,O chelating ligands.

3.2.1.3 Reactivity towards aminoalkenes

As a further challenge to the competency of precatalysts 1.1, 1.7 and 3.1, they were also tested for intramolecular alkene hydroamination activity using 2,2-diphenylpentenylamine as a substrate (Table 3.3). Alkene hydroamination reactivity remains a significant challenge and provides a useful example for contrasting catalytic activity. This particular substrate, geminally disubstituted in the 2 position, is chosen to take advantage of the gem-disubstituent effect, which has been observed to have a significant effect on the rate of reaction using these and similar precatalysts.7, 8

Table 3.3. Comparing intramolecular aminoalkene hydroamination using precatalysts 1.1, 1.7, and 3.1.

<table>
<thead>
<tr>
<th>Precatalyst</th>
<th>Yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>90%</td>
</tr>
<tr>
<td>1.7</td>
<td>4%b</td>
</tr>
<tr>
<td>3.1</td>
<td>30%</td>
</tr>
</tbody>
</table>

aIsolated yields. bYield determined by NMR spectroscopy using 1,3,5-trimethoxy benzene as an internal standard.
A temperature of 110 °C is required for this transformation to occur in the presence of complex 1.1, and for consistency the reactions where complexes 1.7 and 3.1 are used as precatalysts are also carried out at 110 °C. Where isolated yields are given, the reaction mixtures are quenched by the addition of CH₂Cl₂, and all volatiles are removed in vacuo to give an oily brown solid that could then be purified by column chromatography to yield the pyrrolidine product.

Unfortunately, the results listed in Table 3.3 show that precatalysts 1.7 and 3.1 are substantially less effective than complex 1.1 in effecting this transformation. In fact only complex 1.1 exhibited reactivity similar to that of the precursor to these complexes, Ti(NEt₂)₄, which has been previously reported⁷e to catalyze this reaction with an isolated yield of 92% using the same reaction conditions. This indicates that the perfluorophenyl group has a significant detrimental effect on the application of these complexes for intramolecular alkene hydroamination.

In the reactions in which complexes 1.7 and 3.1 were used as precatalysts, extended reaction times at 110 °C did not significantly improve conversion. However, when the same reaction using complex 3.1 as the precatalyst was carried out with a higher catalyst loading (20 mol%) and at a lower reaction temperature (65 °C) over a longer period of time (168 h) a higher conversion (56%) was observed. It should be noted that complex 1.1 does not promote intramolecular alkene hydroamination at this temperature. The improved low temperature reactivity of 3.1 suggests that at elevated temperatures this complex decomposes or converts to some catalytically inactive species. Again the substantial difference in catalytic activity between the fluorinated and non-fluorinated
precatalysts can be attributed to undesirable side reactions of the pentafluorophenyl bearing ligand.

3.2.1.4 Side reactivity of the N-2,6-diisopropylphenylperfluorophenyl-amidate ligand

To investigate catalyst decomposition/inactivation as a possible explanation for the differences in reactivity between the fluorinated and non-fluorinated precatalysts, the reaction conditions employed in the hydroamination experiments with complex 3.1 can be used for reaction with 2,2-diphenylpentylamine. This modified substrate does not contain an alkene, thereby eliminating hydroamination as a possible reaction pathway. The mixture of products obtained from this initial experiment result from nucleophilic displacement of fluorine on the perfluorinated aromatic ring of the ligand by 2,2-diphenylpentylamine and also by the diethylamido ligand of the precatalyst.\(^9\) Simply heating complex 3.1 to 110 °C in toluene for several days results in significant complex decomposition caused by the addition of the amido ligand to the amidate ligand. In addition to these findings, while studying the hydroamination of 1-hexyne with benzylamine using complex 3.1 as the precatalyst, it is possible to isolate a byproduct that is consistent with the addition of benzylamine to the amidate ligand via nucleophilic aromatic substitution. The characterization of these decomposition products 3.4 and 3.5 can be confirmed by their independent syntheses in the absence of metal, as shown in Scheme 3.3.
Scheme 3.3. Reaction of N-2,6-diisopropylphenylperflourophenylamide with 2,2-
diphenylpentylamine and benzylamine.

All these observations are consistent with the fact that perfluorinated aromatic
compounds can undergo nucleophilic aromatic substitution reactions due to their highly
electron deficient ring systems and availability of leaving groups (F). In the
aforementioned decomposition reactions, the concomitant formation of HF would cause
immediate catalyst decomposition via the formation of unidentified Ti-F species. This
unexpected catalyst decomposition is consistent with the poor yields observed when less
bulky amine substrates are used for hydroamination.

3.2.2.6 Summary and conclusions for modifying the electronic properties of the
amidate ligand

A bis(N-2,6-diisopropyl(phenyl)perfluorophenylamide)titanium-bis(diethylamido)
complex incorporating electron withdrawing perfluorophenyl groups in the ligand
backbone was prepared, characterized and examined as a hydroamination precatalyst. The
solid state structure of this compound indicated that it is rigorously $C_2$-symmetric, with N
atoms of the amidate ligand being *trans* to each other, while the amido ligands are in a *cis* orientation.

The inclusion of the electron withdrawing perfluorophenyl group was expected to improve catalyst activity relative to previous non-perfluorophenyl bearing variants. However, hydroamination screening experiments revealed that this complex is susceptible to decomposition under the conditions employed for catalysis. Catalyst decomposition was attributed to the addition of amine substrate to the perfluorinated aromatic ring of the amidate ligand via nucleophilic aromatic substitution. The work described in this section highlights the need for the judicious selection of reactivity modifying substituents when designing catalyst systems, and indicates that perfluoroaromatic substituents may not be suitable as electron withdrawing groups for complexes employed as hydroamination catalysts.

3.2.2. Modifying the structure of the amidate ligand for asymmetric cyclohydroamination

Modifications can, and have been made to the axially chiral biphenyl ligand of complex 1.3 (Figure 3.3) resulting in some significant changes to reactivity. However, as was mentioned previously, one of the weaknesses of this ligand design is that synthesis and resolution of non-racemic derivatives can be difficult and time consuming, which impedes structure activity relationship studies for asymmetric catalysis. In addition, the steric environment imposed by this tethered amidate ligand is somewhat removed from the reactive metal center, which in turn limits the influence that it has on selectivity.
Figure 3.3. Bis(amidate) zirconium bis(amido) complex 1.3 incorporating an axially chiral ligand framework developed for enantioselective cyclohydroamination.

In the interest of addressing these issues we considered using non-tethered chiral amides derived from simple, readily available chiral primary amines as an alternative class of proligand. The use of non-tethered amides would allow for a greater degree of structural variation and potentially accelerate structure activity relationship studies by virtue of the modular and simple synthetic route to these proligands. The use of non-racemic, commercially available primary amines or amine precursors circumvents the need for chiral resolution of enantiomers. It may also be easier to address the issue of limited steric influence because, as will be discussed, these complexes are expected to adopt an $N$-trans $C_2$ geometry, and this geometry allows for a greater amount of steric bulk to be positioned closer the reactive site of the catalyst.

As mentioned in the introduction to this thesis (-)-menthone was selected for these initial investigations as an inexpensive commercially available source of asymmetry (Scheme 3.3). The non-racemic ketone could easily be converted to the corresponding amine via reductive amination and then derivitized with benzoyl chloride to yield the
requisite amide. This synthetic protocol was expected to afford a mixture of diastereomers which could then be separated, before preparing the new chiral bis((N-menthyl)phenylamidate) zirconium bis(amido) complexes (Scheme 3.4).

**Scheme 3.4.** Using commercially available (–)-menthone as a source of asymmetry for the synthesis of chiral zirconium precatalysts (hypothetical geometry shown).

Without a rigid, and configurationally defining tetradeutate ligand framework, there are a number of possible coordination isomers that these bis((N-menthyl)phenylamidate) zirconium complexes could potentially adopt. It is however possible, to propose a preferred geometry based on structural information gathered from a range of known group four bis(amidate) bis(amido) complexes. The solid state structures of these compounds have indicated that the strongly donating amido ligands occupy adjacent coordination sites cis to one another. Furthermore, when the amidate ligands bear bulky N-substituents, such as 2,6-diisopropylphenyl, it has been found that of the five possible diastereomeric coordination isomers, they preferentially adopt an N-trans C2 geometry (Figure 1.2) in order to minimize the steric strain imposed by these bulky groups. Although structural assignment is based primarily on solid state X-ray crystallographic
data, the solution phase $^1$H NMR spectra collected for a number of zirconium and titanium complexes bearing the bulky N-2,6-diisopropylphenyl substituent indicate the presence of only one highly organized, C$_2$ symmetric geometry that is consistent with the solid state structures. Considering these findings it is proposed that the ((N-menthyl)phenylamidate) zirconium complexes would also adopt the N-\textit{trans} C$_2$ geometry due to the steric bulk provided by the N-menthyl substituent (Scheme 3.5).

**Scheme 3.5.** Hypothesized preferred coordination geometries for the bis((N-menthyl)benzamidate) zirconium bis(amido) complex.

In the \textit{N-\textit{trans}} C$_2$ coordination geometry, either of the two diastereomers shown in Scheme 3.5 are possible. Assigning a preferred diastereomer at this point is only
speculative, but in light of the observations made by Scott and coworkers that complexes 1.6 and 1.7 exist as a single diastereomers,\textsuperscript{12} it is not unreasonable to suggest that differential steric interactions could potentially cause one diastereomer to be favored over the other.

The primary objective of these investigations is to achieve enantioselective catalysis. Therefore, the geometries of some of the key intermediates and transition states implicated in the catalytic cycle deserve consideration, as these species will dictate the stereochemical outcome of the transformation. For the group four catalyzed cyclohydroamination of aminoalkenes, the chair-like transition state represents the point along the reaction pathway in which the stereochemistry of the newly created stereogenic carbon atom is set (for the proposed mechanism of the cyclohydroamination reaction see Scheme 2.9 in section 2.2.5.4 of this thesis).\textsuperscript{7a} The intermediate immediately preceding this transition state is the actual catalyst for the transformation; an \textit{in situ} generated zirconium-imido complex. It is the chiral steric environment created by the ancillary amidate ligands about the reactive zirconium imido bond that will ultimately determine the most energetically favorable geometric configuration for the chair-like transition state.

The only well characterized bis(amidate) supported zirconium imido complex is the TPPO stabilized complex depicted in Scheme 3.6.\textsuperscript{11} The structure of this compound was found to be a distorted-pentagonal-pyrimidal geometry in which the amidate ligands occupy the four coordination sites at the base of the pyramid, and are oriented in such a way that the bulky 2,6-diisopropylphenyl groups are again as far removed from one another as possible. This complex is chiral at metal and therefore is also comprised of
enantiomers. Exchanging the achiral 2,6-diisopropylphenyl group for a chiral $R$-group such as menthyl, would render these enantiomers optically active diastereomers. Again, as was suggested for the bis(amidate) bis(amido) diastereomers depicted in Scheme 3.4, possibly differential steric interactions will cause one isomer to be favored over the other, and therefore, enantioselective catalysis may be achieved using this conformationally flexible system.

![TPPO stabilized bis(amidate) supported Zr imido complex](image)

**Scheme 3.6.** Proposed geometry of the catalytically active zirconium imido species.

### 3.2.2.1 Synthesis and characterization of the proligand

The proposed synthetic route to the (-)-menthone derived bis(\(N\)-menthyl)phenyl-amidate) zirconium bis(amido) complexes is outlined in Scheme 3.7. It was expected that the protocol employed to generate the benzamide proligand(s) would produce a mixture of two diastereomers differing only in the stereochemistry associated with the
carbon atom located α to the nitrogen. The plan was to then separate these diastereomers via column chromatography and/or recrystallization, and react each of the purified amides with Zr(NMe₂)₄ using known methods. The resulting bis(amidate) zirconium bis(dimethylamido) complexes were to be characterized and then screened using a standard test substrate for enantioselective cyclohydroamination.

Scheme 3.7. Overall synthetic route to the (-)-menthone derived bis((N-menthyl)phenylamidate) zirconium bis(amide) complexes.

Instead of the expected (1R,2R,5R)-3.2 and (1S,2R,5R)-3.6 N-benzoyl derivatives of menthylamine, the reagents and conditions outlined in Scheme 3.8 unexpectedly afford a mixture of (1R,2S,5R)-3.7 and (1R,2R,5R)-3.2 (Scheme 3.8). It is apparent that these compounds share the same stereochemistry at the 1-position of the cyclohexyl ring, α to the nitrogen atom, but the stereochemistry at the carbon in the 2-position bearing the iso-propyl group has undergone epimerization. It is suspected that the oxime initially formed
in the first step may be in equilibrium with the equivalent of an enamine tautomer, which upon protonation to reform the oxime can undergo epimerization at the 2-position.

Scheme 3.8. (-)-Menthone derived proligand synthesis.

Compounds 3.7 and 3.2 are obtained as a mixture following column chromatography in low yield (<40%) in a ratio of about three to one in favor of the 1R,2R,5R-isomer. Recrystallization of this mixture from diethyl ether affords analytically pure 3.7, while repeated recrystallization of the residue recovered from the mother liquor from hexanes/CH₂Cl₂ (4:1) eventually gives 3.2 as a pure compound. It should be noted that these reactions were only carried out to generate chiral amide compounds in quantities sufficient for study as proligands, and therefore, the reaction conditions and purification protocols employed have not been optimized.

The relative stereochemistries of 3.7 and 3.2 are assigned based on their solid state molecular structures determined by X-ray crystallography. Figures 3.4 and 3.5 depict the ORTEP diagrams for each diastereomer. Interestingly, the unit cell for 3.7 contains both of the possible chair conformations that this compound can adopt, while the ¹H NMR data is consistent with there being only one conformer present in solution.
3.2.2.2 Complex synthesis and characterization

It has been found by other members of our group that with a number of chiral bis(amidate) complexes, there is little variation in enantioselectivity between using recrystallized, crude, or in situ generated precatalysts. For the purposes of this investigation, complete structural elucidation of the complexes used for catalysis was not
thought to be crucial, as the primary concern was whether it was even possible to affect enantioselective catalysis using the non-tethered ligand framework. Therefore, the following described crude complexes were used in the subsequent enantioselective catalysis investigations without further purification or analysis. In addition, due to our inability to obtain an adequate amount of proligand 3.2 for complex synthesis we opted to test this proligand for enantioselective cyclohydroamination using in situ generated catalyst screening experiments.

With sufficient quantities of \( N-((1R,2S,5R)-2\text{-isopropyl-5-methylcyclohexyl})\text{-benzamide} \) 3.7 in hand however, it was decided to proceed with complex synthesis using this proligand (Equation 3.1). Complex 3.2 can be prepared simply by adding one equivalent of \( \text{Zr(NMe}_2)_4 \), which is dissolved in a small amount of benzene, to a vial containing a stir bar and two equivalents of proligand suspended in a small amount of benzene. The resulting solution is capped and then stirred for approximately 24h at ambient temperature. Removal of the solvents under reduced pressure affords an amorphous material having elemental analysis data consistent with the target complex.

\[
\begin{align*}
\text{O.5eq \text{M(NMe}_2)_4} & \quad \text{PhH, RT 24h} \\
\text{M=Zr, complex 3.2} & \quad \text{M=Ti, complex 3.3}
\end{align*}
\]

The \( ^1\text{H} \) and \( ^{13}\text{C} \) NMR spectra for this compound are quite convoluted, possibly due to the presence of multiple rotational atropisomers in solution, and are not useful for
definitive structural characterization purposes. It is important to point out, however, that
the $^1$H NMR spectrum is devoid of any significant peaks within the range of 5 – 7 ppm, which is where one would expect to find the NH resonance corresponding to free proligand, if there was in fact free proligand remaining in solution. This is a strong indicator that the protonolysis reaction has gone to completion and the amide is now coordinated to the metal. Mass spectral data (electron impact) provided no additional useful information. Attempts to recrystallize the crude material for solid state structural determinations may have been complicated by the presence of multiple isomers, and were not successful.

The analogous bis(N-((1R,2S,5R)-2-isopropyl-5-methylcyclo-hexyl)benzamidate) titanium bis(diethylamido) complex 3.3 can also prepared using the synthetic protocol described for the synthesis of complex 3.2 using Ti(NEt$_2$)$_4$ in place of Zr(NMe$_2$)$_4$. The resulting crude titanium compound is a red oil. The $^1$H and $^{13}$C NMR spectra for this compound are also quite convoluted and not useful for characterization purposes. The $^1$H NMR spectrum is again devoid of any significant peaks within the range of 5 – 7 ppm, suggesting that there is no free ligand remaining in the crude mixture. Although no molecular ion was discernable in the MS (EI) of the crude material, the fragments corresponding to (M - 2NEt$_2$)$^+$ and (M – amidate ligand)$^+$ were observed and are consistent with other characterized bis(amidate) titanium bis(amido) type complexes. Attempts to recrystallize the crude material for solid state structural determinations may have been complicated by the presence of multiple isomers, and were not successful.
3.2.2.3 Enantioselectivity determinations

Both the zirconium and titanium bis(N-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)benzamidate) complexes 3.2 and 3.3 were tested for enantioselective cyclohydroamination using the standard test substrate 2,2-diphenyl-4-pentenylamine. In addition, the in situ generated zirconium catalyst using proligand 3.2 was also screened. The results of these experiments are listed in Table 3.4.

Table 3.4. Enantioselective hydroamination studies using bis(amidate) titanium bis(amido) precatalysts derived from (-)-menthone.

<table>
<thead>
<tr>
<th>metal</th>
<th>ligand</th>
<th>loading (mole %)</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti</td>
<td>3.7</td>
<td>5</td>
<td>110</td>
<td>24</td>
<td>85</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Zr</td>
<td>3.7</td>
<td>10</td>
<td>110</td>
<td>5</td>
<td>&gt;98c</td>
<td>26</td>
</tr>
<tr>
<td>Zr</td>
<td>3.7</td>
<td>10</td>
<td>65</td>
<td>48</td>
<td>91d</td>
<td>23</td>
</tr>
<tr>
<td>Zr</td>
<td>3.2</td>
<td>10</td>
<td>65</td>
<td>48</td>
<td>94f</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

| a Complex 3.3. | b Complex 3.2. | c Conversion, 54% conversion after 1 hour. | d 62% conversion after 24h at 65 °C. | e Prepared in situ. | f 67% conversion after 24h at 65 °C. |

These cyclohydroamination reactions are prepared and carried on an NMR tube scale and are monitored by \(^1\)H NMR spectroscopy. Enantiomeric excesses are based on \(^1\)H NMR spectroscopy of the product following derivatization with (+)-(S)-α-methoxy-α-trifluoromethylphenylacetyl chloride as previously described in the literature.\(^{7a}\)
The most efficient and selective precatalyst of this group was the zirconium complex 3.2, with the cyclohydroamination reaction going to completion within 5 hours at 110 °C and an enantiomeric excess of 26%. Lowering the reaction temperature to 65 °C did not significantly impact the observed enantioselectivity with this precatalyst, but as one might expect the reaction time increased dramatically. The analogous titanium complex, complex 3.3, exhibited reasonably good reactivity with the cyclization going to completion (>98% conversion) within 24 hours, but no stereoselectivity was observed. The in situ prepared zirconium precatalyst that utilized proligand 3.2 was found to be about as reactive as complex 3.2, with comparable conversions after 24 hours at 65 °C, however, no appreciable enantioselectivity was observed using this system. As a benchmark example from the literature for comparison purposes, complex 1.3 catalyzes the complete conversion of 2,2-diphenyl-4-pentenylamine to the corresponding N-heterocycle within 1.25 hours at 110 °C, and it does so with an enantiomeric excess of 74%. \(^7\)

3.2.2.4 Summary of incorporating (-)-menthone as a source of chirality for the asymmetric hydroamination of aminoalkenes

In this section, the synthesis and characterization of two chiral amides derived from (-)-menthone has been described. The synthetic protocol that was employed unexpectedly afforded \(N\)-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide as the major product along with a small amount of the (1R,2R,5R)-isomer. An attempt was made to prepare chiral titanium and zirconium bis(amidate) bis(amido) complexes using the (1R,2S,5R)-amide as a proligand. It was not possible to purify or definitively
characterize the resulting products. The data that was obtained; in the form of NMR, elemental analysis, and mass spectral (EI) data; was consistent with complexation of the metal by the amide proligand. No attempt was made to prepare the corresponding complexes using the (1R,2R,5R)-isomer due to the insufficient quantities of this compound. This proligand was instead used in the enantioselectivity investigations by generating the precatalyst in situ.

The zirconium complex incorporating \( N-((1R,2S,5R)-2\text{-isopropyl}-5\text{-methylcyclohexyl})\text{-benzamide} \) as proligand proved to be the most effective enantioselective catalyst of those examined in this section, with an enantiomeric excess of 26\% being observed for the cyclization of 2,2-diphenyl-4-pentenylamine. Although this selectivity is quite moderate in relation to what has been reported for other chiral neutral group four systems, the fact that any enantioselectivity at all was observed using the non-tethered ligand framework is impressive considering the less rigidly defined coordination environment and greater potential for the existence of multiple isomeric species in solution.

To summarize, these investigations using bis((\(N\)-menthyl)phenylamidate) zirconium bis(amido) complexes were devised as a proof of principle, that chiral non-tethered amidate ligands can be used to generate bis(amidate) zirconium bis(amido) precatalysts capable of affecting the enantioselective cyclohydroamination of aminoalkenes. The chiral non-tethered amidate ligand framework is advantageous due to the modular and simple way in which the amide proligands can be produced. In most cases these amides can be made chiral by drawing from a wealth of commercially available, naturally occurring non-racemic chiral starting materials, which obviates the need for chiral
resolution and speeds up structure activity relationship studies. In order to obtain good enantioselectivities using metal based catalysts a readily accessible coordination geometry that imposes a sufficient degree of chiral steric influence on the reactive site is required. Although it is recognized that a major drawback to using the non-tethered ligand framework is the greater number of potential geometric isomers; it has been argued, based on previous work, that one could predominate over the others, and this may make enantioselective catalysis using these systems possible. Although the bis(N-((1R,2S,5R)-2-isopropyl-5-methylcyclo-hexyl)benzamidate) system is itself not worth pursuing any further, this work does demonstrate that the non-tethered chiral amidate ligand motif can be used to generate chiral zirconium complexes capable of effecting enantioselective catalysis and may provide an alternative to the tethered bis(amide) ligand framework.

3.3 Overall summary and conclusions

The incorporation of an electron withdrawing substituent in the R¹ position of the amidate ligand framework resulted in increased reactivity. However, the particular substituent used (perfluorophenyl) was found to suffer from adverse side reactivity with the amine substrate which results in catalyst inactivation. Therefore alternative electron withdrawing groups should be used in the design of hydroamination precatalysts.

An optically active amidate ligand incorporating a menthyl derivative in the R² position was easily prepared from commercially available (-)-menthone. When the resultant bis(amidate) complex was used as a catalyst for the asymmetric
cyclohydroamination of 2,2-diphenyl-4-pentenylamine an enantiomeric excess of 26% was achieved. This enantioselectivity is quite modest relative to other contemporary group four based asymmetric cyclohydroamination precatalysts which incorporate configurationally rigid tethered ligand frameworks, and highlights the importance of this aspect to ligand design.

These investigations have demonstrated the versatility that amidate ligands provide in terms of structural modifications that can be made to alter the electronic and steric properties of the resultant complexes. In particular, the work described in this chapter has further contributed to our understanding of how the modular nature of the amidate scaffold can be used to generate more reactive and selective hydroamination catalysts.

3.4 Experimental

**General.** $^1$H and $^{13}$C NMR spectra were recorded on either a Bruker 300 MHz or 400 MHz Avance spectrometer at ambient temperature and chemical shifts are given relative to residual solvent. GCMS spectra were recorded on an Agilent series 6890 GC system with a 5973 Mass Selective Detector. Single crystal X-ray structure determinations, MS (ESI) and elemental analyses determinations were performed at the Department of Chemistry, University of British Columbia. All reactions were carried out using standard Schlenk line and glovebox techniques under an atmosphere of nitrogen, unless described otherwise. Ti(NR$_2$)$_4$ and Zr(NR$_2$)$_4$ (R = Et, Me) were purchased from Strem and used as received. $d_6$-benzene and $d_8$-toluene were degassed and dried over molecular sieves. Acid chlorides were purchased from Aldrich and used as received. Amines were distilled
from CaH₂ under nitrogen. Alkynes were purchased from Aldrich and purified by distillation prior to use. 2,2-Diphenyl-4-pentenylamine, was prepared as described in the literature with some modification from commercially available starting materials purchased from Aldrich. 2,2-Diphenylpentylamine was prepared using modified literature procedures, with full characterization data presented here. The amide proligands were prepared from the appropriate amines and acid chlorides according to literature procedures. Complexes 1.1 and 1.7 were prepared as previously reported in the literature.

\[
\begin{align*}
\text{N-2,6-diisopropyl(phenyl)perflourophenylamide proligand 3.1.}^{14} & \text{ Prepared using modified literature procedures.}^{21} \\
\text{One should note that the signals in the } ^{13}\text{C NMR spectrum for the carbons of the aromatic ring bearing the fluorine atoms were obscured due to extensive coupling to fluorine. Yield: 51%.} \\
\text{H NMR (CDCl}_3, 300 MHz): & \delta 1.22 (12H, d, J = 6.9 Hz, CH-(CH}_3)_2, 3.12 - 3.21 (2H, septet, J = 6.9 Hz, CH-(CH}_3)_2), 7.06 - 7.40 (3H, m, Ar-H); \\
\text{C NMR (CDCl}_3, 75 MHz): & \delta 23.5, 28.8, 123.6, 129.2, 129.3, 146.2, 157.0; \\
\text{F NMR (CDCl}_3, 282 MHz): & \delta -63.6 (2F), -73.9 (1F), -83.0 (2F); MS (EI): m/z 371 (M^+), 356 (M^+CH}_3), 328 (M^+CH(CH}_3)_2), 195 (M^+NHCH}_3CH(CH}_3)_2); \\
\text{Anal. Calcd for C}_{19}H_{18}F_{3}NO: } & \text{C, 61.45; H, 4.89; N, 3.77. Found: C, 61.71; H, 4.50; N, 3.78.}
\end{align*}
\]
Bis(N-2,6-diisopropyl(phenyl)perfluorophenylamidate)titanium-bis(diethylamido) complex 3.1. Prepared using modified literature procedures. Yield: 65%. The NMR spectra of this compound are very complicated and not helpful for characterization due to the presence of multiple isomers in solution. Suitable crystals for X-ray crystallography were grown from benzene at ambient temperature; MS (EI): \( m/z \) 860 (M-NEt₂), 788 (M-NEt₂ X 2); Anal. Calcd. for C₄₆H₅₆F₁₀N₄O₂Ti: C, 59.10; H, 6.04; N, 5.99. Found: C, 59.15; H, 5.99; N, 6.20.

General procedure for intermolecular alkyne hydroamination. All hydroamination reactions were prepared in an N₂-filled glovebox. A small Schlenk tube equipped with a magnetic stir bar was charged with a solution of the precatalyst (0.05 mmol, 0.05 equiv), the alkyne (1.0 mmol, 1.0 equiv), and the primary amine (1.2 mmol, 1.2 equiv) dissolved in benzene (~2 mL) or toluene (~2 mL). The Schlenk tube was then sealed and heated to either 65 °C or 110 °C for 24 h. The reaction mixture was then allowed to cool to room temperature and transferred to a small round bottom flask containing a stirring slurry of LiAlH₄ (1.5 mmol, 1.5 equiv) in diethylether (5 - 10 mL). This mixture was stirred at room temperature overnight under N₂(g). The reaction would then be quenched by the slow addition of water (0.06 mL), then 1 M NaOH (0.06 mL), and a further aliquot of water (0.18 mL). Following suction filtration and removal of the solvents under reduced
pressure, column chromatography (hexane: ether, SiO$_2$) afforded the purified amine products either as single compounds or as a mixture of regioisomers. $N$-(2,6-Dimethylphenyl)-2-phenylethylamine,$^{15}$ $N$-(2,6-dimethylphenyl)phenylethylamine,$^{16}$ $N$-(2,6-dimethylphenyl)-1-(4-methoxyphenyl)ethylamine,$^{16}$ $N$-(2,6-dimethylphenyl)-1,2-methylphenylethylamine,$^{15}$ $N$-benzylhexylamine,$^2$ and $N$-benzyl-1-methylpentylamine$^{17}$ are known compounds. Full characterization data for $N$-(2,6-dimethylphenyl)-2-(4-methoxyphenyl)ethylamine and $N$-(2,6-dimethylphenyl)-1-methylpentylamine is provided below.

$$N$-(2,6-Dimethylphenyl)-2-(4-methoxyphenyl)ethylamine. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 2.25 (6H, s, Ar-CH$_3$), 2.92 (2H, $t$, $J = 6.9$ Hz, pMeOPh-CH$_2$), 3.16 (1H, br s, CH$_2$-NH-Ar), 3.33 (2H, $J = 6.9$ Hz, ArNH-CH$_2$), 3.88 (3H, s, Ar-O-CH$_3$), 6.88 – 7.26 (7H, m, Ar-H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 18.7, 36.3, 49.8, 55.5, 56.4, 114.2, 121.9, 129.0, 129.3, 130.0, 131.7, 132.8, 146.2, 158.5; HRMS Calcd for C$_{17}$H$_{21}$NO [M$^+$]: 255.16231; Found: 255.16226.

$$N$-(2,6-Dimethylphenyl)-1-methylpentylamine. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 0.91 (3H, $t$, $J = 6.9$ Hz, CH$_2$-CH$_2$-CH$_3$), 1.05 (3H, $d$, $J = 6.3$ Hz, ArNH-CH-CH$_3$), 1.29 – 1.57 (6H, m, ArNH-CH-(CH$_2$)$_3$-CH$_3$), 2.26 (6H, s, Ar-CH$_3$); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 15.5, 20.5, 22.8, 24.3, 30.1, 39.6, 53.9, 122.5, 130.2, 130.3, 146.7; HRMS Calcd for C$_{14}$H$_{23}$N [M$^+$]: 205.18305; Found: 205.18315.
General procedure for the NMR-tube scale intermolecular alkyne hydroamination reactions. All NMR-tube scale reactions were prepared in an N₂-filled glove box. A J. Young NMR tube was charged with the internal standard (1,3,5-trimethoxybenzene) (0.17 mmol, 0.33 equiv), the precatalyst (0.025 mmol, 0.05 equiv), the alkyne (0.5 mmol, 1.0 equiv) and the primary amine (0.6 mmol, 1.2 equiv) and dissolved in either d₆-benzene (~1 mL) or d₈-toluene (~1 mL). The tube was sealed, heated to, and maintained at 65 °C or 110 °C for the stated duration of time. The conversion and yield were determined by comparing the integration of the internal standard with a well resolved signal for the imine product.

Procedure for the NMR-tube scale intramolecular hydroamination of 2,2-diphenyl-4-pentenylamine. All NMR-tube scale reactions were prepared in an N₂-filled glove box. A J. Young NMR tube was charged with the precatalyst (0.025 mmol), and 2,2-diphenyl-4-pentenylamine (0.5 mmol) dissolved in d₈-toluene (~1 mL). Where yields were determined 1,3,5-trimethoxybenzene (0.5 mmol) was also added as an internal standard. The tube was then sealed, heated to, and maintained at, the appropriate temperature for the stated duration of time. Yields were determined by comparing the integration of the internal standard with a well resolved signal for the heterocyclic product. Conversions were determined by comparing well resolved signals for the substrate and product.⁷e

Procedure for the intramolecular hydroamination of 2,2-diphenyl-4-pentenylamine and isolation of 2-methyl-4,4-diphenylpyrrolidine. All reactions were prepared in an N₂-filled glovebox. A small Schlenk tube equipped with a magnetic stir bar was charged
with the catalyst (0.025 mmol) and 2,2-diphenyl-4-pentenylamine (0.5 mmol) dissolved in toluene (~ 1 mL). The Schlenk tube was then sealed, heated to the appropriate temperature, and stirred for the stated duration of time. After cooling to room temperature, “wet” CH₂Cl₂ (~1 mL) would be added and the solution was stirred for ~10 min. Then, following concentration under reduced pressure, the crude product was directly subjected to flash column chromatography (ether, SiO₂) to afford 2-methyl-4,4-diphenylpyrrolidine as a colorless oil.

\[ \text{2,2-Diphenylpentylamine compound 3.3.} \]

Prepared using modified literature procedures, with full characterization data presented here. ¹H NMR (CDCl₃, 300 MHz): 0.85 – 0.90 (5H, m, CH₂-CH₃, CH₂-NH₂), 1.02 – 1.04 (2H, m, CH₂-CH₂-CH₃), 2.05 – 2.10 (2H, m, Ph₂C-CH₂-CH₂), 3.32 (2H, s, Ph₂C-CH₂-NH₂), 7.15 – 7.30 (10H, m, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 14.75, 17.39, 38.94, 49.11, 51.89, 125.85, 127.94, 128.24, 146.71; MS (El): m/z 209 (M⁺-CH₂NH₂); Anal. Calcd. for C₁₇H₂₁N: C, 85.30; H, 8.84; N, 5.85. Found: C, 85.08; H, 8.93; N, 6.05.

\[ \text{N-(2,6-Diisopropylphenyl)-2-(N-2,2-diphenylpentylamino)-3,4,5,6-tetrafluoro-} \]

benzamide compound 3.4. To a round bottom flask equipped with a magnetic stir bar
was added toluene (~10 mL), 2,2-diphenylpentylamine (0.125 g, 0.52 mmol, 1.0 equiv.), N-2,6-diisopropyl(phenyl)perflourophenylamide (0.187 g, 0.50 mmol, 1.0 equiv.), and triethylamine (0.22 mL, 1.6 mmol, 3.0 equiv.). The reaction mixture was heated to reflux for 16 h and then allowed to cool to room temperature. The crude reaction mixture was diluted with ether (250 mL), washed with 1 M NaOH, water, and brine. Following drying of the organic phase over Na₂SO₄ and removal of solvents under reduced pressure, the crude material was subjected to column chromatography (36:1 hexanes: ether, SiO₂) to provide 3.4 as a colorless foam. One should note that the signals in the ¹³C NMR spectrum for the carbons of the aromatic ring bearing the fluorine atoms were obscured due to extensive coupling to fluorine. Yield: 68%. ¹H NMR (CDCl₃, 400 MHz): δ 0.87 (3H, t, J = 7.2 Hz, CH₃-CH₂), 1.01 – 1.09 (2H, m, CH₃-CH₂-CH₂), 1.24 (12H, d, J = 6.8 Hz, CH-(CH₃)₂), 2.18 – 2.23 (2H, m, Ph₂C-CH₂-CH₂), 3.08 – 3.15 (2H, m, CH-(CH₃)₂), 4.23 (2H, d, J = 2.8 Hz, Ph₂C-CH₂-NH), 7.13 – 7.60 (13H, m, Ar-H), 7.75 (1H, br s, NH); ¹³C NMR (CDCl₃, 75 MHz): δ 14.57, 17.33, 23.62, 28.79, 38.77, 50.51, 50.53, 52.33, 52.46, 101.49, 123.48, 126.06, 127.90, 127.95, 128.65, 130.43, 137.67, 146.09, 146.197, 163.60; ¹⁹F NMR (CDCl₃, 400 MHz): δ -140.8 (1F), -152.3 (1F), -155.3 (1F), -175.0 (1F); MS (ESI): m/z 589 (M⁻H); Anal. Calcd. for. C₃₆H₃₈F₄N₂O: C, 73.20; H, 6.48; N, 4.74. Found: C, 73.40; H, 6.38; N, 4.70.
**N-(2,6-Diisopropylphenyl)-2-(N-benzylamino)-3,4,5,6-tetrafluorobenzamide**

**compound 3.5.** To a round bottomed flask equipped with a magnetic stir bar was added toluene (~10 mL), benzylamine (0.070 mL, 0.64 mmol, 1.2 equiv.), N-2,6-diisopropyl(phenyl)perfluorophenylamide (0.200 g, 0.50 mmol, 1.0 equiv.), and triethylamine (0.30 mL, 2.2 mmol, 4.0 equiv.). The reaction mixture was heated to reflux for 24 h and then allowed to cool to room temperature. The crude reaction mixture was diluted with CH$_2$Cl$_2$ (150 mL), washed with 1 M NaOH, water, and brine. Following drying of the organic phase over Na$_2$SO$_4$ and removal of solvents under reduced pressure, the crude material was subjected to column chromatography (16:1 hexanes: ether, SiO$_2$) to provide 3.5 as a white amorphous solid. One should note that the signals in the $^{13}$C NMR spectrum for the carbons of the aromatic ring bearing the fluorine atoms were obscured due to extensive coupling to fluorine. Yield: 94%.

**$^1$H NMR (CDCl$_3$, 300 MHz):** δ 1.25 (12H, d, $J = 6.9$ Hz, CH-(CH$_3$)$_2$), 3.10 – 3.17 (2H, septet, $J = 6.9$ Hz CH-(CH$_3$)$_2$), 4.58 (2H, d, $J = 3.6$ Hz, Ph-CH$_2$-NH), 7.25 – 7.37 (8H, m, Ar-H), 7.6 (2H, br s, ArNHC=O, ArNHCH$_2$Ar); $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 23.75, 29.09, 49.97, 50.13, 123.89, 127.58, 127.67, 128.79, 129.20, 130.24, 139.30, 146.35, 164.12; $^{19}$F NMR (CDCl$_3$, 282 MHz): δ -140.8 (1F), -151.8 (1F), -155.7 (1F), -173.1 (1F); MS (El): m/z 458 (M$^-$-H); Anal. Calcd. for C$_{26}$H$_{26}$F$_4$N$_2$O: C, 68.11; H, 5.72; N, 6.11. Found: C, 67.95; H, 5.92; N, 6.21.
N-((1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl)-benzamide proligand 3.7 and N-((1R,2R,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide proligand 3.2. To a small round bottomed flask containing a magnetic stir bar was added: EtOH (30mL), NH₂OH·HCl (2.11g, 30.4 mmol), pyridine (2.50mL, 30.9 mmol), and (-)-menthone (3.50mL, 20.3 mmol). A reflux condenser was affixed and the mixture was heated to reflux for ~40h, then allowed to cool to ambient temperature. Following removal of the EtOH under reduced pressure, the crude reaction mixture was dissolved in Et₂O (300mL), washed with water (3X50 mL) followed by sat. aqueous NaCl (1X50 mL), dried over Na₂SO₄, gravity filtered, and then subjected to rotary evaporation to remove the Et₂O. The crude oxime mixture was then dissolved in THF (100 mL), transferred to a round bottomed flask containing a stir bar and cooled to ~0°C using an ice-water bath. LiAlH₄ (1.3 g, 34.3 mmol) was carefully added to the solution portion wise as it was stirred and maintained at ~0°C. A reflux condenser was affixed, and the slurry was heated to reflux for ~40h and then cooled to ~0°C using an ice-water bath. The reaction was then quenched by the slow, careful addition of water (1.5 mL), aqueous 1M NaOH (1.5 mL), Et₂O (100 mL), and then another aliquot of water (4.5 mL). After allowing the resulting suspension to stir for a further 0.5h at ambient temperature, it was subjected to vacuum filtration and the filtrate was dried over MgSO₄. (Although not carried out here, it is recommended for future reference that this reaction be worked up by extracting the HCl salts of the amine products with water followed by neutralization and back extraction with ether) Following
removal of the solvents under reduced pressure, the crude reaction mixture was transferred to an oven dried, septum sealed, round bottomed flask containing a stir bar which was maintained under N\textsubscript{2} (g). Dry CH\textsubscript{2}Cl\textsubscript{2} (60 mL) was then added and the flask was cooled to ~0 °C using an icewater bath. After the addition of NEt\textsubscript{3} (8.0 mL, 57 mmol), and BzCl (2.60 mL, 22.6 mmol) the reaction was stirred at ambient temperature for ~20 h and then worked up by diluting with CH\textsubscript{2}Cl\textsubscript{2} (240 mL), washing with 1M HCl (3X50 mL), 1M NaOH (3X50 mL), water (1X50 mL), and finally sat. aqueous NaCl (1X50 mL). The organic phase was then dried over MgSO\textsubscript{4}, and the solvents were removed under reduced pressure. Column chromatography (18:1:1 hexanes:CH\textsubscript{2}Cl\textsubscript{2}:MeOH, SiO\textsubscript{2}) afforded ~2 g of a mixture of N-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide and N-((1R,2R,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide (along with a small amount of unidentified impurities) in a ratio of approximately 3:1 in favor of the (1R,2S,5R)-isomer. Repeated recrystallization from Et\textsubscript{2}O afforded N-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide as a pure compound. Crystalls of the 1R,2S,5R-isomer suitable for x-ray chystallography were obtained from Et\textsubscript{2}O. Repeated recrystallization from hexanes/CH\textsubscript{2}Cl\textsubscript{2} (~4:1) afforded N-((1R,2R,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide as a pure compound. Crystalls of the 1R,2R,5R-isomer suitable for x-ray chystallography were obtained from hexanes/CH\textsubscript{2}Cl\textsubscript{2} (~4:1). H NMR (N-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide) (CDCl\textsubscript{3}, 400 MHz): 7 0.8 – 1.1 (9H, m), 1.2 – 1.4 (1H, m), 1.4 – 1.7 (7H, m), 1.7 – 1.9 (1H, m), 4.3 – 4.4 (1H, m, -CH(NHBz)-), 6.1 – 6.2 (1H, br d, -NHBz), 7.35 – 7.50 (3H, m, Ar-H), 7.70 – 7.80 (2H, m, Ar-H); C NMR (N-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide) (CDCl\textsubscript{3}, 101 MHz): 7 21.65, 21.75, 22.28,
24.02, 27.60, 29.28, 30.44, 36.60, 44.35, 49.73, 126.67, 128.63, 131.22, 135.25, 166.34; MS (N-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide) (El): m/z 259 (M⁺); Anal. Calcd for C₁₉H₂₅N0 (N-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide): C, 78.72; H, 9.71; N, 5.40. Found: C, 79.10; H, 9.76; N, 5.42. ⁱH NMR (N-((1R,2R,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide) (CDCl₃, 400 MHz): δ 0.8 – 0.9 (9H, m), 1.1 – 1.2 (2H, m), 1.4 – 1.6 (1H, m), 1.6 – 1.8 (2H, m), 1.9 – 2.0 (1H, m), 2.0 – 2.1 (1H, m), 3.9 – 4.1 (1H, m, -CH(NHBz)-), 5.75 – 5.85 (1H, br d, -NHBz), 7.35 – 7.50 (3H, m, Ar-H), 7.70 – 7.80 (2H, m, Ar-H); ¹³C NMR (N-((1R,2R,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide) (CDCl₃, 101 MHz): δ 16.30, 21.22, 22.16, 23.95, 27.06, 31.93, 34.58, 43.20, 48.43, 50.42, 126.83, 128.53, 131.23, 135.17, 166.69; MS (N-((1R,2R,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide) (El): m/z 259 (M⁺); Anal. Calcd for C₁₉H₂₅N0 (N-((1R,2R,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide): C, 78.72; H, 9.71; N, 5.40. Found: C, 78.64; H, 10.00; N, 5.62.

Bis(N-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)benzamidate) zirconium bis(dimethylamido) complex 3.2. All metal complex synthesis reactions were carried out in nitrogen filled glovebox. To a small screw capped vial containing a magnetic stir bar was added N-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide (0.471 g, 1.8 mmol), benzene (2 mL), and tetrakis(dimethylamido)zirconium (0.243 g, 0.9 mmol.
dissolved in 1 mL of benzene). The mixture was then stirred at room temperature for ~24 h. The solvents were then removed under reduced pressure to afford 0.610 g (97%) of the analytically pure bis(N-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)benzamidate) zirconium bis(dimethylamido) complex as a pale yellow foam. The NMR spectra of this compound have been provided, but are very complicated and have not been assigned due to the possible presence of multiple isomers in solution. Attempts to recrystallize this compound were not successful. It was not possible to obtain useful information from MS (EI) spectral data. Elemental analysis was consistent with the desired compound. Anal. Calcd for C_{38}H_{60}N_{4}O_{2}Zr: C, 65.56; H, 8.69; N, 8.05. Found: C, 65.90; H, 8.77; N, 7.73.

\[
\text{Ti(NEt}_2\text{)}_2 \text{Bis(N-((1R,2S,5R)-2-isopropyl-5-methylcyclo-hexyl)benzamidate)} \quad 
\text{titanium bis(dimethylamido) complex 3.3.}
\]

All metal complex synthesis reactions were carried out in nitrogen filled glovebox. To a small screw capped vial containing a magnetic stir bar was added N-((1R,2R,5R)-2-isopropyl-5-methylcyclohexyl)-benzamide (0.204g, 0.8 mmol), benzene (3 mL), and tetrakis(diethylamido)titanium (0.132 g, 0.4 mmol). The mixture was then stirred at room temperature for ~24 h. The solvents were then removed under reduced pressure to afford 0.280 g (>98%) of the crude bis(N-((1R,2S,5R)-2-isopropyl-5-methylcyclo-hexyl)benzamidate) titanium bis(diethylamido) complex as a red oil. The $^1$H and $^{13}$C-APT NMR spectra of this compound have been provided. Two
of the aromatic C-H peaks could not be assigned in the $^{13}$C-NMR spectrum as they were obscured by the C$_6$D$_6$ solvent signal. Attempts to recrystallize this compound were not successful. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.8 – 2.4 (26H, m), 3.5 – 4.0 (8H, m, L$_3$Zr-(-N-(CH$_2$-CH$_3$)$_2$)$_2$), 4.6 – 4.7 (~1H, m, -CH(NHBz)-), 7.2 – 7.4 (4H, m, Ar-H), 8.3 – 8.5 (2H, m, Ar-H); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 16.30, 21.22, 22.16, 23.95, 27.06, 31.93, 34.58, 43.20, 48.43, 50.42, 126.83, 128.53, 131.23, 135.17, 166.69; MS (EI): m/z 635(M-HNEt$_2$), 564 (M-2 X NEt$_2$), 450 (M-1 X amide ligand).

Procedure for the NMR-tube scale enantioselective intramolecular hydroamination of 2,2-diphenyl-4-pentenylamine and enantiomeric excess determinations. All NMR-tube scale reactions were prepared in an N$_2$-filled glove box. A small vial would be charged with the precatalyst (0.05 mmol), and 2,2-diphenyl-4-pentenylamine (0.5 mmol) dissolved in $d_8$-toluene (~1 mL). The reaction mixture would then be transferred to a J. Young NMR tube which would be sealed, heated to, and maintained at, the appropriate temperature for the stated duration of time. Where isolated yields have been given, the crude reaction mixture would be concentrated under reduced pressure, and then directly subjected to column chromatography (10:1 CH$_2$Cl$_2$:MeOH, SiO$_2$) to afford the known 2-methyl-4,4-diphenylpyrrolidine as a colorless oil. Conversions were determined by comparing well resolved signals for the substrate and product. Enantiomeric excesses are based on $^1$H NMR spectroscopy of the product following derivatization with (+)-(S)-\alpha-
methoxy-α-trifluoromethylphenylacetyl chloride as previously described in the literature.\textsuperscript{7a}
3.5 References


CHAPTER FOUR: GROUP FOUR BASED HYDROAMINATION CATALYSTS INCORPORATING 2-PYRIDONATES AS N,O CHELATING ANCILLIARY LIGANDS

4.1 Introduction

To date, the work carried out in the Schafer group has focused on the use of bis(amidate) bis(amido) complexes of titanium and zirconium as hydroamination precatalysts. In the interest of expanding our N-O chelating ancillary ligand set beyond amidates, 2-pyridone and its derivatives were considered as a basis for further discovery. As proligands, these compounds offer some of the same desirable characteristics that make amides attractive as proligands, such as a modular structure and the availability of numerous derivatives which can be obtained commercially, or synthesized through various routes. In addition to this, there are unique electronic and steric properties associated with 2-pyridones that set them apart from amides and may result in the formation of complexes exhibiting a level of reactivity not seen with the bis(amidate) based systems. It was anticipated that the synthesis of these complexes could be achieved efficiently following the same protocol to the one used for the preparation of the bis (amidate) complexes (Scheme 4.1).

Scheme 4.1. Proposed synthetic route to the bis(2-pyridonate) complexes.

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As was mentioned in chapter one, 2-pyridonates were selected as a new class of N,O chelating ligand, primarily as an alternative means of increasing the Lewis acidity of the metal center for enhanced hydroamination catalysis. It was anticipated that these ligands would be more electron withdrawing than their amidate counterparts based on the respective pKa values for the neutral proligands (δ-lactam pKa = 26.6 (in DMSO), N-phenylbenzamide pKa = 18.8, 2-pyridone pKa = 17.0 (in DMSO)).

Investigations into the intramolecular hydroamination of aminoalkenes have shown that the bis(amidate) systems developed to affect this transformation so far, exhibit only moderate reactivity, resulting in inordinately long reaction times and requiring somewhat extreme reaction temperatures. In addition, these catalysts have been found to suffer from a severely limited substrate scope. One possible explanation for this is that the large steric bulk associated with the amidate ligands, though advantageous for minimizing the in situ formation of catalytically inactive imido dimers, may be impeding these intramolecular aminoalkene reactions by reducing accessibility to the reactive metal center.

It was hoped that the 2-pyridonate ligand framework would address this issue by making it possible to increase accessibility to the reactive site while maintaining a sufficient level of steric bulk to mitigate the formation of catalytically inactive dimer species. This supposition is based on the fact that substituents located in the \( R^6 \) position of 2-pyridonates are more removed from the metal center than the \( N \)-substituents of amidates (Scheme 4.2). Therefore, the desirable steric properties of 2-pyridonates provide additional imputes for the study of titanium and zirconium hydroamination catalysts which incorporate them as ancillary ligands.
Scheme 4.2. Improved accessibility to the metal center using 3,6-substituted 2-pyridones as proligands.

There are also some fundamental coordination chemistry questions that this ligand set addresses. Firstly, although there are numerous examples of late transition metal complexes employing this type of ligand, only a few 2-pyridone complexes based on metals from groups three, four, or five have been reported. Among those reported are the dinuclear vanadium complex \([V_2O_2Cl_4(Hmhp)_3]\), where Hmhp = 6-methyl-2-pyridone, the monopentamethylcyclopentadienyl zirconium (IV) complex \([[(\eta^5-C_5Me_5)Zr(\eta^2-O,N-ONC_7H_8)_3]]\), and the monopentamethylcyclopentadienyl titanium (IV) complex \([[\eta^5-C_5Me_5]TiMe(\eta^1-O-OC_8H_7N_2)]\). Therefore, group four complexes incorporating 2-pyridone derivatives as ligands are rare and it was not known whether stable, isolable bis(2-pyridonate) titanium/zirconium bis(amido) complexes could actually be prepared and characterized as outlined above.

Additionally, although there are many examples in the literature where 2-pyridones have been used to bridge two metals, comparatively few complexes have been reported where this type of ligand has been used as a chelate for one metal center. Therefore, the question of whether a group four metal based bis(2-pyridonate) bis(amido) complex would exist as discrete monomeric or polymeric species was of primary interest to us as this may impact resultant reactivity trends.

Another feature of the 2-pyridone based ligand set derives from the fact 2-pyridone itself can exist in two tautomeric forms (Scheme 4.3), either the lactam (2-pyridone) or
the lactim (2-hydroxypyridine). This phenomenon has been well studied over the past decades.\textsuperscript{1b,8} In solution it has been found that the relative abundance of each tautomer depends on conditions such as concentration, temperature, and the polarity of the solvent. Polar solvents strongly favor the 2-pyridone form, while in solutions employing non-polar solvents both the 2-pyridone and 2-hydroxypyridine tautomers can exist in an equilibrium favoring the 2-hydroxypyridine form.\textsuperscript{9,10} Additionally, intermolecular hydrogen bonding between the monomeric species can lead to the formation of dimers.\textsuperscript{8} In the solid state and the gas phase, 2-pyridone is thought to be the prevailing tautomer.\textsuperscript{11,12} It is also known that substituents can also affect this equilibrium, with compounds having electron withdrawing substituents in the 6-position (adjacent to the nitrogen), favoring the pyridinol form.\textsuperscript{1b} This tautomerization leads to the basic question of how varied 2-pyridonate ligands will bind the metal center in the bis(2-pyridonate) bis(amido) Ti/Zr complexes.

Scheme 4.3. The tautomeric equilibrium between 2-pyridone and 2-hydroxypyridine.

Scheme 4.4 depicts the three distinct binding modes that the 2-pyridonate ligand could adopt in a monometallic complex.\textsuperscript{1b} At one extreme, ligation could occur exclusively through the oxygen as a phenoxide like ligand, and at the other extreme the 2-pyridone could bond to the metal solely through the nitrogen in an N bound mode. A number of complexes have been structurally characterized and reported in the literature.
to date incorporating the anionic form of these ligands that adopt the N binding motif.\textsuperscript{5g,h,13} Ligation of 2-pyridonates through the oxygen in as a phenoxide appears to be quite rare, with the only example being the previously mentioned [(η\textsuperscript{5}-C\textsubscript{5}Me\textsubscript{5})TiMe(η\textsuperscript{1}-O-OC\textsubscript{8}H\textsubscript{7}N\textsubscript{2})\textsubscript{2}]\textsuperscript{6a} complex. The other possibility lies intermediate between these two extremes, where like the group 4 bis(amidate) complexes we have characterized so far,\textsuperscript{14} a bidentate κ\textsuperscript{2} N,O 2-pyridonate binding mode could predominate. Again, this type of ligand interaction in monometallic species is relatively rare, with the reported examples that we could find being the mer-(PM\textsubscript{3})\textsubscript{2}Os(H)(η\textsuperscript{2}-O,N-ONC\textsubscript{7}H\textsubscript{8}) complex,\textsuperscript{5h} the Ru(ρ-cymene)(η\textsuperscript{2}-O,N-ONC\textsubscript{7}H\textsubscript{8})Cl complex,\textsuperscript{15} the [(η\textsuperscript{5}-C\textsubscript{5}Me\textsubscript{5})Zr(η\textsuperscript{2}-O,N-ONC\textsubscript{7}H\textsubscript{8})\textsubscript{3}] complex,\textsuperscript{6b} [C\textsubscript{p}\textsubscript{2}Mo(η\textsuperscript{2}-O,N-ONC\textsubscript{7}H\textsubscript{8})][PF\textsubscript{6}],\textsuperscript{16} and the Ir(COD)(η\textsuperscript{2}-O,N-ONC\textsubscript{7}H\textsubscript{8})Cl\textsubscript{2} complex.\textsuperscript{7d}

\[
\begin{align*}
\text{Scheme 4.4. Possible binding modes adopted by the 2-pyridonate ligand.}
\end{align*}
\]

Information with respect to the charge localization on the deprotonated anionic form of 2-pyridone may provide additional information helpful in predicting the binding mode that the bis(2-pyridone) titanium/zirconium bis(amido) complexes might adopt. It has been suggested by Spinner and White,\textsuperscript{17} based on the analysis of the sodium salt of 2-pyridone using infrared, ultraviolet and Raman spectroscopies, that the anion of 2-pyridone exists as a pyridoxide type structure with the negative charge located mainly on the oxygen atom. This result seems to support either the O bound or κ\textsuperscript{2} N,O binding
modes, with the latter being comprised of largely an aryloxide covalent O – M type bonding in combination with a dative N – M type interaction.

Structural information for the two known group 4 complexes bearing these types of ligands suggests that either $\kappa^2$ N,O or O coordination could be expected in the bis(2-pyridonato) bis(amido) complexes. The monocyclopentadienyl zirconium (IV) complex $[(\eta^5-C_5Me_5)Zr(\eta^2-O,N-ONC_7H_8)_3]$ (Figure 4.1) was assigned the $\kappa^2$ N,O binding motif with dynamic processes occurring in solution. This assignment was based on NMR spectroscopic data and the crystal structure for a related compound $[(\eta^5-C_5Me_5)Zr(\eta^2-O,N-ON_2C_7H_8)_3]$.

![Figure 4.1. Coordination geometries of the $[(\eta^5-C_5Me_5)Zr(\eta^2-O,N-ONC_7H_8)_3]$ complex and the $[(\eta^5-C_5Me_5)TiMe(\eta^1-O-OC_8H_7N_2)_2]$ complex..](image)

An O coordination mode was proposed for the monocyclopentadienyl titanium (IV) complex $[(\eta^5-C_5Me_5)TiMe(\eta^1-O-OC_8H_7N_2)_2]$ (Figure 4.1) which was based on NMR spectroscopic data. Notably, these complexes incorporate a bulky cyclopentadienyl type ligand which imposes a substantially different coordination environment than a dialkylamido ligand both sterically and electronically, therefore the nature of the ligand metal interaction occurring in the bis(2-pyridonato) bis(amido) complexes may differ.

The basic question of coordination geometry is also of primary concern because from a catalyst development perspective, the amido ligands are ideally situated in adjacent
coordination sites, as these represent the active sites during catalysis.\textsuperscript{18} Assuming that the bis(2-pyridonate) bis(amido) complexes are indeed monomeric, and that the 2-pyridonate ligands bind in a bidentate $\kappa^2$ N,O fashion, then there are 5 possible diasteromeric coordination geometries that these complexes could adopt (Figure 1.2, chapter 1). It has been found that group four bis(amidate) bis(amido) complexes preferentially adopt the N-trans $C_2$ geometry, which positions the two amido ligands in the desired cis arrangement.\textsuperscript{14} In order to be useful as precatalysts the bis(2-pyridonate) bis(amido) complexes, in addition to being monomeric, would also have to adopt this or a similar type of geometry in which the amido ligands are cis to one another.

Knowing that substituents can influence the tautomeric equilibrium exhibited by 2-pyridone derivatives, one would also expect the coordination chemistry of these ligands as well as any reactivity that the resulting complexes might have to be influenced by substituents on the 2-pyridone ring. To the best of our knowledge, there have been no investigations into this matter. We are therefore very interested in how the effect of substituents in the 3- and 6-position of the 2-pyridone will impact the structure and reactivity of these complexes in hydroamination catalysis.
4.2 Results and discussion

4.2.1 Synthesis and characterization of titanium and zirconium complexes incorporating 2-pyridone and 6-tert-butyl-3-phenyl-2-pyridone as proligands

2-Pyridone itself was employed as a proligand in order to provide a benchmark for comparison with substituted proligands. The 3- and 6-positions of 2-pyridone were then chosen for derivitization because any steric or electronic influences imposed by substituents in these positions would likely have the greatest impact on complex structure and activity due to their proximal location with respect to the atoms involved in chelation. 6-tert-Butyl-3-phenyl-2-pyridone was selected for these initial investigations primarily because this compound is analogous to N-tert-butyl-benzamide which was used as a proligand in the earliest bis(amidate) bis(amido) complexes,\textsuperscript{3b,14,18} and therefore it represents a useful starting point for comparative purposes.

While the 2-pyridone proligand is commercially available, the 6-tert-butyl-3-phenyl-derivative must be prepared. The preparation of 3,6-disubstituted 2-pyridones can be achieved utilizing a modular procedure for the thermal rearrangement of pyrrolidine psuedoureas developed by Overman et al. (Scheme 4.5).\textsuperscript{1e} The pyrrolidine pseudoureas (which are subsequently converted to the 3,6-disubstituted-2-pyridones) are generated from a propargylic alcohol and 1-cyanopyrrolidine. The propargylic alcohol can easily be made from a terminal alkyne and derivatives of acetaldehyde. The substituents located at the 3 and 6 positions of the 2-pyridone ring are then determined by which acetaldehyde derivative and terminal acetylene (respectively) are used in the initial formation of the
propargylic alcohol. This method affords 6-tert-butyl-3-phenyl-2-pyridone as an amorphous solid with yields as high as 63%. The proligand is recrystallized and then dried by heating to 80 °C under vacuum for at least 3-days prior to use.

Scheme 4.5. Modular synthetic route to the 3,6-disubstituted 2-pyridones.

The bis(2-pyridonate) titanium bis(dimethylamido) complex 4.1, as well as the bis(6-tert-butyl-3-phenyl-2-pyridonate) titanium bis(dimethylamido) complex 4.2, and the bis(6-tert-butyl-3-phenyl-2-pyridonate) zirconium bis(dimethylamido) complex 4.3 can be prepared in a very simple and high yielding one step procedure according to Scheme 4.6. These reactions are carried out on a small (< 1g) scale in a nitrogen filled glove box, and involve simply weighing out the proligand into a small vial equipped with a stir bar, and then adding benzene. A concentrated solution of the tetrakis(dimethylamido) titanium or zirconium complex in benzene is then added and the mixture is stirred at ambient temperature for ~24 hours. Solvent removal en vacuo affords the analytically pure products as either red (titanium) or pale yellow (zirconium) amorphous solids in nearly quantitative yields. Crystals suitable for X-ray crystallography can obtained from saturated solutions of each complex in benzene layered with either pentane or hexane.
Scheme 4.6. Synthesis of the bis(2-pyridonate) titanium and zirconium bis(amido) complexes 4.1 – 4.3.

The zirconium analogue of complex 4.1 cannot be prepared using this protocol. Instead, when 2-pyridone is allowed to react with Zr(NMe₂)₄ in this fashion, an amorphous yellow solid consisting of a mixture of oligomers is obtained, as was determined by NMR spectroscopy and X-ray crystallography (Figure 4.3).

In the solid state, complexes 4.1, 4.2 and 4.3 exhibit similar structural characteristics (Figures 4.2, 4.4, and 4.5). X-ray analysis of these compounds indicate that they are monomeric, and possess a distorted octahedral geometry about the metal center with the 2-pyridonate ligands adopting a bidentate binding motif. Importantly, these complexes assume an O-trans C₂ coordination geometry with the dimethylamido ligands positioned cis to one another. Table 4.1 lists some pertinent bond lengths and angles for these three compounds. The sum of the metallacyclic bond angles in complexes 4.1, 4.2, and 4.3 is 359.9°, 360.0°, and 360.0° respectively, confirming that the ligand, bound in an κ² fashion, is planar. The binding of the 2-pyridonate oxygen and nitrogen donors to the metal center is asymmetric however, as can be seen by the substantially different Ti-O/Ti-N bond lengths. This result verifies that the 2-pyridonate binding motif is best described as κ² N,O and is comprised of an aryloxide O – M bonding in combination
with a dative $N - M$ interaction. The most pronounced asymmetry is present in the bis(6-tert-butyl-3-phenyl-2-pyridonate) complexes, which is presumably due to steric repulsion between the bulky tert-butyl group of the 2-pyridonato ligand and the remainder of the metal complex.

**Figure 4.2.** Diagram of the bis(2-pyridonate) titanium bis(dimethylamido) complex 4.1 with thermal ellipsoids set at the 50% probability level. Hydrogen atoms have been omitted for clarity.

**Figure 4.3.** ORTEP depiction of a dimer obtained by the reaction of $Zr(NMe_2)_4$ with 2-pyridone. Elipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.
Figure 4.4. Diagram of the bis(6-tert-butyl-3-phenyl-2-pyridonate) titanium bis(dimethylamido) complex 4.2 with thermal ellipsoids set at the 50% probability level. Hydrogen atoms have been omitted for clarity.

Figure 4.5. Diagram of the bis(6-tert-butyl-3-phenyl-2-pyridonate) zirconium bis(dimethylamido) complex 4.3 with thermal ellipsoids set at the 50% probability level. Hydrogen atoms have been omitted for clarity.
Table 4.1. Selected Bond lengths and angles for complexes 4.1, 4.2, and 4.3.

<table>
<thead>
<tr>
<th>Bond Length (Angstroms)</th>
<th>Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.1</td>
</tr>
<tr>
<td>M-N (amido)</td>
<td>1.880(2)</td>
</tr>
<tr>
<td>M-N (2-pyridonato)</td>
<td>2.222(2)</td>
</tr>
<tr>
<td>M-O</td>
<td>2.010(2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond Angle (degrees)</th>
<th>Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.1</td>
</tr>
<tr>
<td>N(amido)-M-N(2-pyridonato)</td>
<td>155.69(7)</td>
</tr>
<tr>
<td>O-M-O</td>
<td>145.90(6)</td>
</tr>
<tr>
<td>O-M-N(2-pyridonato)</td>
<td>61.97(5)</td>
</tr>
</tbody>
</table>

The $^1$H and $^{13}$C-NMR spectra for compounds 4.1, 4.2, and 4.3 are consistent with their respective solid state structures. Results of NOE spectroscopic investigations, along with variable temperature NMR experiments suggest that these complexes have a discrete geometry, with the 2-pyridonato ligands being bound in an $\eta^2$ fashion and no observable fluctional behavior. Complex 4.1 exhibits a strong NOE contact between the methyl groups of the dimethylamido ligand and the proton in the 6-position of the pyridonato ligand (Scheme 4.7), while little to no enhancement is observed with the protons in the other three positions of the 2-pyridonate ligand. This supports either the $\kappa^2$ bonding motif or the N-bound species, as a phenoxide type complex would not display an NOE signal corresponding to the H adjacent to N. Similar experiments carried out with complexes 4.2 and 4.3 show that the methyl groups of the amido ligand and the tert-butyl group of the 6-tert-butyl-3-phenyl-2-pyridonato ligand are located in close proximity to one another, as they would be in an $\kappa^2$ bound or N-bound arrangement (Scheme 4.7). In addition, an NOE contact was also found between the tert-butyl group...
and the phenyl group of the two adjacent 6-tert-butyl-3-phenyl-2-pyridonato ligands (Scheme 4.7), which are positioned approximately side by side, but in opposing orientations to one another (see Figures 4.4 and 4.5). Again, the close proximity of these groups on adjacent ligands supports the assignment of a highly organized \( \kappa^2 \) N,O, geometry. Also, the addition of strong neutral donors, such as trimethylphosphine oxide and triethylamine, to a solution of complex 4.1 do not appear to influence the binding modes of the 2-pyridone ligand as observed by NMR spectroscopy.

\[
\text{complex 4.1}
\]

\[
\text{complex 4.2}
\]

\[
\text{M = Ti: complex 4.2}
\]

\[
\text{M = Zr: complex 4.3}
\]

Scheme 4.7. NOE contacts observed for complexes 4.1, 4.2, and 4.3.
4.2.2 Intramolecular alkene hydroamination activity: substrate scope investigation

Complexes 4.1, 4.2, and 4.3 were tested for aminoalkene hydroamination activity using the standard test substrate 2,2-diphenyl-4-pentenylamine (Scheme 4.8). This aminoalkene, geminally disubstituted in the 2 position, is typically chosen as a primary screening substrate to take advantage of the gem-disubstituent effect, which has been observed to have a significant effect on the rate of reaction using these and similar precatalysts. The titanium complexes 4.1 and 4.2 are completely unreactive towards this substrate under these conditions. The zirconium complex 4.3 however, is capable of efficiently catalyzing this transformation, with the aminoalkene undergoing complete conversion to the N-heterocyclic product 2-methyl-4,4-diphenylpyrrolidine within five hours. The amorphous solid consisting of a mixture of oligomers that was obtained from the reaction of Z(NMe₂)₄ with two equivalents of 2-pyridone also affects this transformation with a yield of about 15 % after 24 hours at 110 °C. The disparity in catalytic activity between titanium complex 4.2 and zirconium complex 4.3 is consistent with what has been observed previously with bis(amidate) and bis(pyrimidinoxide) systems when comparing aminoalkene hydroamination activity of analogous titanium and zirconium complexes.
Scheme 4.8. Intramolecular hydroamination of 2,2-diphenyl-4-pentenylamine.

Results of a cyclohydroamination substrate scope investigation using complex 4.3 as the precatalyst are listed in Table 4.2. Yields obtained using the bis(N-2,6-diisopropylphenyl-(phenyl)-amidate) zirconium bis(dimethylamido) complex, which is one of the most effective bis(amidate) cyclohydroamination precatalysts reported to date, have also been included for comparison.

Overall, complex 4.3 exhibits an acceptable level of reactivity that is comparable to the zirconium bis(amidate) complex. Entry 6 however, illuminates an important difference. While no cyclization of 2,2-diphenyl-4-hexenylamine is observed using the bis(amidate) complex; this substrate, bearing an unactivated internal C=C bond, does indeed undergo cyclohydroamination in the presence of complex 4.3. This is an important result because the difference in reactivity between these two complexes towards this substrate may be a direct consequence of the more accessible metal center afforded by the 2-pyridone ligand being more accommodating to alkenes bearing non-activating alkyl substituents.
Table 4.2. Substrate scope using complex 4.3 and the bis(N-2,6-diisopropylphenyl-(phenyl)-amidate) zirconium bis(dimethylamido) complex.

<table>
<thead>
<tr>
<th>entry</th>
<th>aminoalkene</th>
<th>time (h)</th>
<th>temp (°C)</th>
<th>complex 4.3&lt;sup&gt;a&lt;/sup&gt;</th>
<th>bis(amidate) zirconium complex&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph Ph NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>5</td>
<td>110</td>
<td>&gt;98%</td>
<td>&gt;98%</td>
</tr>
<tr>
<td>2</td>
<td>Ph Ph NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>96</td>
<td>110</td>
<td>87%</td>
<td>87%</td>
</tr>
<tr>
<td>3</td>
<td>Ph Ph NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>5</td>
<td>110</td>
<td>&gt;98%</td>
<td>&gt;98%</td>
</tr>
<tr>
<td>4</td>
<td>Ph-)&lt;NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>96</td>
<td>110</td>
<td>43%</td>
<td>48%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>96</td>
<td>110</td>
<td>35%</td>
<td>72%</td>
</tr>
<tr>
<td>6</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>168</td>
<td>145</td>
<td>59%</td>
<td>NR</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yield determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. <sup>b</sup> After 192 hours at 110 °C.

Entry 5 shows that substrates with substitution α to the nitrogen (in this case a methyl group) are amenable to cyclization. The product of this reaction can generate two possible diastereomers of 2,5-dimethylpyrrolidine, where one isomer has the two methyl groups oriented cis relative to each other, and the other isomer has the two methyl groups in an trans arrangement. A diastereoselectivity of greater than 10:1 in favor of the trans product is obtained using complex 4.3. This selectivity for the trans product is consistent with a preference for the α-methyl group to be in an equatorial position in the proposed chair like transition state through which this reaction is thought to proceed. <sup>4b,20c</sup>
Taking advantage of the reactivity of complex 4.3 towards unactivated internal alkene bearing aminoalkene substrates, the cyclization of 2-cyclohex-2-enyl-2,2-diphenyl-ethylamine can be carried with moderate yield and very high selectivity for the cis-fused octahydroindole (Equation 4.4). This reaction demonstrates the potential of this methodology for the generation of more complex, biologically relevant polycyclic structural motifs.

\[
\begin{array}{c}
\text{Ph} \quad \text{Ph} \\
\text{NH}_2
\end{array} \xrightarrow{1) \; 20 \text{ mol} \% \text{ complex 3}}
\begin{array}{c}
\text{Ph} \quad \text{Ph} \\
\text{N}
\end{array}
\text{d}_8-\text{tol, } 145^\circC, \text{168h}
\xrightarrow{2) \; \text{TsCl, NEt}_3, \text{CH}_2\text{Cl}_2}
\begin{array}{c}
\text{Ph} \quad \text{Ph} \\
\text{Ts}
\end{array}
\text{(+/-)}
\text{52\% isolated yield}
\]

4.3 Summary and conclusions

The work in this chapter involved the synthesis and characterization of the first titanium and zirconium bis(2-pyridonate) bis(amide) complexes. Attempts were made to prepare complexes using either 2-pyridone or 6-tert-butyl-3-phenyl-2-pyridone as proligands. It was found that the bis(2-pyridone) titanium bis(dimethylamido) complex 4.1, along with the bis(6-tert-butyl-3-phenyl-2-pyridone) titanium bis(dimethylamido) complex 4.2 and the bis(6-tert-butyl-3-phenyl-2-pyridone) zirconium bis(dimethylamido) complex 4.3 can all be prepared in very high yield using the simple protocol described in section 4.2.1. The X-ray structures of complexes 4.1, 4.2, and 4.3 reveal that they are all monomeric, and possess a distorted octahedral geometry about the metal center with the 2-pyridonate ligands adopting a bidentate binding motif.
Importantly, these complexes assume an O-trans $C_2$ like coordination geometry with the dimethylamido ligands positioned cis to one another. NMR spectroscopic data for these compounds is consistent with their solid state structures. The bis(2-pyridonate) zirconium bis(dimethylamido) complex could not be prepared as a discrete monomeric compound using this method, and clearly demonstrates that there is a minimum level of steric bulk that these ligands must possess in order to form monomeric complexes.

The activity of these complexes towards aminoalkenes was investigated and both titanium complexes 4.1 and 4.2 were found to be completely unreactive, while the zirconium complex 4.3 was found to be an efficient catalyst for the cyclohydroamination reaction. Further substrate screening experiments demonstrated that complex 4.3 can effect the cyclization of more challenging aminoalkenes bearing unactivated internal C=C bonds; substrates which had previously been inert towards intramolecular hydroamination using the most active bis(amidate) zirconium bis(amido) complex. This result is consistent with the greater accessibility to the metal center afforded by the 6-tert-butyl-3-phenyl-2-pyridonate ligand being more accommodating to substituents on the olefin.

4.4 Experimental

General. $^1$H and $^{13}$C NMR spectra were recorded on either a Bruker 300 MHz or 400 MHz Avance spectrometer at ambient temperature and chemical shifts are given relative to residual solvent. GCMS spectra were recorded on an Agilent series 6890 GC system with a 5973 Mass Selective Detector. Single crystal X-ray structure determinations, MS,
and elemental analyses determinations were performed at the Department of Chemistry, University of British Columbia. All reactions were carried out using standard Schlenk line and glovebox techniques under an atmosphere of nitrogen, unless described otherwise. Ti(NMe2)4 and Zr(NMe2)4 were purchased from Strem and used as received. 

d8-Toluene was degassed and dried over molecular sieves. Amino alkenes 2,2-diphenyl-4-pentenylamine,22 2,2-diphenyl-5-hexenylamine,23 2,2,5-triphenyl-4-pentenylamine,23,24 2,2-diphenyl-4-hexenylamine,23 2,2-dimethyl-4-pentenylamine,24 and 1-methyl-4-pentenylamine25 were prepared as described in the literature with some modification from commercially available starting materials purchased from Aldrich. Amino alkene substrates were dried over CaH or 4Å molecular sieves and degassed prior to use. Heterocyclic products 2-methyl-4,4-diphenylpyrrolidine,22 2-methyl-5,5-diphenylpiperidine,26 2-methyl-4,4-dimethylpyrrolidine,24 2-benzyl-4,4-diphenylpyrrolidine,20c 2,5-dimethylpyrrolidine27 and (+/-)-(S,S)-3, 3-diphenyl-1-(p-toluenesulfonyl)-octahydro-indole28 are known compounds. The 6-tert-butyl-3-phenyl-2-pyridone proligand was prepared as described in the literature16 and was heated to 80 °C under vacuum for at least three days prior to use. 2-Pyridone was purchased from Aldrich and sublimed prior to use. 2-Cyclohex-2-enyl-2,2-diphenyl-ethylamine was prepared using modified literature procedures29 from commercially available starting materials with full characterization data provided below. 1,3,5-Trimethoxybenzene purchased from Aldrich, was used as an internal standard and was sublimed under vacuum prior to use. The (N-2',6'-diisopropylphenyl(phenyl)-amidate) zirconium bis(dimethylamido) complex was prepared as described in the literature.4b,18
6-tert-Butyl-3-phenyl-2-pyridone.\textsuperscript{16} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 1.38 (9H, s, -(CH\textsubscript{3})\textsubscript{3}), 6.19 (1H, d, \(J = 7.4\) Hz, C5-H), 7.24 – 7.41 (3H, m, Ar-H), 7.55 (1H, d, \(J = 7.4\) Hz, C4-H), 7.78 – 7.81 (2H, m, Ar-H), 12.00 (1H, br s, NH); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): \(\delta\) 28.9, 34.8, 101.8, 127.2, 127.7, 127.9, 128.3, 136.6, 139.1, 156.2, 163.5; MS (EI): \(m/z\) 227 (M\textsuperscript{+}).

\[
\begin{array}{c}
\text{O} \\
\text{Ti(NMe\textsubscript{2})\textsubscript{2}}
\end{array}
\]

Bis(2-pyridonate) titanium bis(dimethylamido) complex 4.1. All metal complex synthesis reactions were carried out in a glovebox unless otherwise stated. To a small screw capped vial containing a magnetic stir bar was added 2-hydroxypyridine (0.8203 g, 8.44 mmol), benzene (3 mL), and tetrakis(dimethylamido)titanium (0.946 g, 4.22 mmol in 3 mL of benzene). The mixture was then stirred at room temperature for 20 hours. The solvents were then removed under reduced pressure to afford the analytically pure bis(2-pyridonato)titanium-bis(dimethylamido) complex 4.1 as a deep red microcrystalline solid. Yield: > 98%. Crystals suitable for X-ray crystallography were obtained from a saturated solution of the complex in benzene. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 3.60 (12H, s, Ti-(N(CH\textsubscript{3})\textsubscript{2})\textsubscript{2}), 6.08 (2H, m, Ar-H), 6.51 (2H, m, Ar-H), 7.03 (2H, m, Ar-H), 7.60 (2H, m, Ar-H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 46.2, 109.7, 112.2, 140.3, 143.0, 172.2; MS (EI): \(m/z\) 324 (M\textsuperscript{+}), 280 (M-NMe\textsubscript{2}), 236 (M-2NMe\textsubscript{2}); Anal. Calcd
Bis(2-pyridonate) zirconium bis(dimethylamido) complex. All metal complex synthesis reactions were carried out in a glovebox unless otherwise stated. To a small screw capped vial containing a magnetic stir bar was added 2-hydroxypyridine (0.8576 g, 9.0 mmol), benzene (3 mL), and tetrakis(dimethylamido)zirconium (0.946 g, 4.5 mmol in 3 mL of benzene). Vigorous evolution of gas was observed upon addition of the tetrakis(dimethylamido)zirconium solution to the undissolved 2-hydroxypyridine proligand. The mixture was then stirred at room temperature for 20 hours. The solvents were then removed under reduced pressure to afford the analytically pure bis(2-pyridonato)zirconium-bis(dimethylamido) complex 2 as a bright yellow microcrystalline solid. Yield: > 98%. Crystals suitable for X-ray crystallography were obtained from a saturated solution of the complex in benzene. The $^1$H and $^{13}$C NMR spectra along with solid state X-ray crystallographic information for the material obtained from this reaction indicate that the product consists of a mixture of oligomers. Anal. Calcd for C$_{14}$H$_{20}$N$_4$O$_2$Zr: C, 45.75; H, 5.48; N, 15.24. Found: C, 45.55; H, 5.43; N, 14.90.
Bis(6-tert-butyl-3-phenyl-2-pyridonate) titanium bis(dimethylamido) complex 4.2.

All metal complex synthesis reactions were carried out in a glovebox unless otherwise stated. To a Schlenk tube containing a magnetic stir bar was added tetrakis(dimethylamido)titanium (0.740 g, 3.3 mmol), benzene (30 mL), and 6-tert-butyl-3-phenyl-2-pyridone (1.50 g, 6.6 mmol). The mixture was then stirred at room temperature for 5 hours. The solvents were then removed under reduced pressure to afford the analytically pure bis(6-tert-butyl-3-phenyl-2-pyridonato)titanium-bis(dimethylamido) complex 4.2 as a red microcrystalline solid. Yield: > 98%. Crystals suitable for X-ray crystallography were obtained from a saturated solution of the complex in benzene. \(^{1}\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.24 (18H, s, \(-C(CH_3)_3\)), 3.44 (12H, s, Ti-(N(CH_3)_2)), 6.59 (2H, d, J=8.0 Hz, Ar-H), 7.24 (2H, m, Ar-H), 7.43 (4H, m, Ar-H), 7.55 (2H, d, J=8.0 Hz, Ar-H), 8.12 (4H, m, Ar-H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 29.7, 36.5, 47.1, 110.4, 119.4, 127.1, 128.4, 128.9, 137.5, 139.7, 165.6, 168.8; MS (EI): \(m/z\) 588 (M\(^+\)), 544 (M-NMe\(_2\)), 500 (M-2NMe\(_2\)); Anal. Calcd for C\(_{34}\)H\(_{44}\)N\(_4\)O\(_2\)Ti: C, 69.38; H, 7.53; N, 9.52. Found: C, 69.00; H, 7.59; N, 9.55.

Bis(6-tert-butyl-3-phenyl-2-pyridonate) zirconium bis(dimethylamido) complex 4.3.

All metal complex synthesis reactions were carried out in a glovebox unless otherwise stated. To a small screw capped vial containing a magnetic stir bar was added 6-tert-
butyl-3-phenyl-2-pyridone (0.850 g, 3.7 mmol), benzene (3 mL), and tetrakis(dimethylamido)zirconium (0.500 g, 1.9 mmol in 2 mL of benzene). The mixture was then stirred at room temperature for 20 h. The solvents were then removed under reduced pressure to afford the analytically pure bis(6-tert-butyl-3-phenyl-2-pyridonato)zirconium-bis(dimethylamido) complex 4.3 as a pale yellow microcrystalline solid. Yield: > 98%. Crystals suitable for X-ray crystallography were obtained from a saturated solution of the complex in benzene/pentanes. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.26 (18H, s, -C(CH$_3$)$_3$), 3.26 (12H, s, Zr-(N(CH$_3$)$_2$)$_2$), 6.57 (2H, d, $J$=7.9 Hz, Ar-H), 7.25 (2H, m, Ar-H), 7.44 (4H, m, Ar-H), 7.55 (2H, d, $J$=7.8 Hz, Ar-H), 8.07 (4H, m, Ar-H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 29.7, 36.3, 42.6, 110.1, 121.1, 128.4, 128.9, 137.2, 140.4, 165.3; MS (El): $m/z$ 631 (M$^+$), 587 (M-NMe$_2$), 543 (M-2NMe$_2$); Anal. Calcd for C$_{34}$H$_{44}$N$_4$O$_2$Zr: C, 64.62; H, 7.02; N, 8.87. Found: C, 64.71; H, 7.18; N, 9.07.

2-Cyclohex-2-enyl-2,2-diphenyl-ethylamine. $^{29}$ $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.77 (2H, br s, -NH$_2$), 0.9 – 1.1 (1H, m, -CH$_2$-CHH-CH=CH-), 1.5 – 1.6 (2H, m, -CH$_2$-CH$_2$-CH$_2$-), 1.6 – 1.8 (1H, m, -CH=CH-CHH-CH$_2$-), 1.8 – 2.0 (2H, m, -CH=CH-CHH-CH$_2$-), 1.9 – 2.5 (1H, m, -CH$_2$-CHH-CH-CH=CH-), 2.3 – 3.4 (2H, m, -CH=CH-CH-, -Ph$_2$C-CHH-NH$_2$), 3.45 (1H, d, $J$ = 13.2 Hz, -Ph$_2$C-CHH-NH$_2$), 5.5 – 5.7 (1H, m, -CH=CH-), 5.8 – 5.9 (1H, m, -CH=CH-), 7.1 – 7.4 (10H, m, ArH); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 22.59, 24.97, 25.18, 39.77, 49.65, 56.74, 126.15, 126.20, 127.50, ...
127.92, 129.07, 129.38, 129.76, 129.90, 142.80, 144.80; MS (EI): m/z 276 (M-H\(^+\)). Anal. Calcd for C\(_{20}\)H\(_{23}\)N: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.39; H, 8.39; N, 5.04.

**General procedure for NMR-tube scale intramolecular amino alkene hydroamination.** All NMR-tube scale reactions were prepared in an N\(_2\)-filled glove box. A J. Young NMR-tube equipped with a Teflon screw cap would be charged with the internal standard (1,3,5-trimethoxybenzene) (0.5 mmol), the catalyst (0.025 mmol), and the amino alkene (0.5 mmol) dissolved in either d\(_6\)-benzene (~1 mL), d\(_{10}\)-xylene (~1 mL) or d\(_8\)-toluene (~1 mL). The tube would then be sealed, heated to, and maintained at, the appropriate temperature for the stated duration of time. The conversion and yield were determined by comparing the integration of the internal standard with a well resolved signal for the cyclic product.

![Diagram](image)

**2-Ethyl-4,4-diphenyl-pyrrolidine.** \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 0.97 (3H, t, \(J = 7.4\) Hz, -CH\(_2\)-CH\(_3\)), 1.49 – 1.70 (2H, m, -CH-CH\(_2\)-CH\(_3\)), 2.10 (1H, dd, \(J = 9.6, 12.7\) Hz, Ph\(_2\)-C-CHH-CH(Et)-NH-), 2.77 (1H, dd, \(J = 9.6, 12.6\) Hz, Ph\(_2\)-C-CHH-CH(Et)-NH-), 3.15 – 3.24 (1H, m, -CH\(_2\)-CH(Et)-NH-), 3.34 (1H, br s, -NH-), 3.47 (1H, d, \(J = 11.5\) Hz, Ph\(_2\)-C-CHH-NH-), 3.80 (1H, d, \(J = 11.5\) Hz, Ph\(_2\)-C-CHH-NH-), 7.15 – 7.40 (10H, m, Ar\(H\)); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta\) 12.6, 30.5, 45.7, 57.4, 58.0, 60.7,
(+/-)-(S,S)-3,3-Diphenyl-1-(p-toluenesulfonyl)-octahydro-indole. The hydroamination reaction was prepared in an N$_2$-filled glovebox. A J. Young NMR-tube equipped with a Teflon screw cap was charged with a solution of the precatalyst (0.032 g, 0.05 mmol) and 2-cyclohex-2-enyl-2,2-diphenyl-ethylamine (0.069 g, 0.25 mmol) dissolved in $d_8$-toluene (~ 1 mL). The NMR-tube was then sealed and heated to 145 °C for 168 hours. Following this the solution was concentrated under reduced pressure and the crude hydroamination mixture was transferred to a small round bottomed flask containing TsCl (1.3 eq) and NEt$_3$ (3.3 eq), dissolved in CH$_2$Cl$_2$ (2-3 mL). This mixture was then stirred overnight at room temperature. Following aqueous workup, purification by column chromatography (36:1 hexanes/EtOAc, SiO$_2$) afforded 0.056 g (52%) of the analytically pure (+/-)-(S,S)-3, 3-diphenyl-1-(p-toluenesulfonyl)-octahydro-indole as a colorless foam. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.10 - 1.30 (2H, m), 1.40 - 1.65 (5H, m), 2.32 (3H, s), 2.40 - 2.60 (1H, m), 2.90 - 3.0 (1H, m), 3.70 - 3.80 (1H, m), 4.25 (1H, d, J = 11 Hz), 4.48 (1H, d, J = 11 Hz), 6.90 - 7.44 (10H, m, ArH); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 21.1, 22.4, 25.4, 26.4, 29.7, 45.2, 56.4, 59.1, 60.0, 126.6, 127.0, 127.6, 128.0, 128.5, 129.3, 129.5, 130.2, 135.3, 143.7, 144.8, 146.1; MS
(ESI):  m/z 454 (M + Na\(^+\)). Anal. Calcd for C\(_{27}\)H\(_{29}\)NO\(_2\)S: C, 75.14; H, 6.77; N, 3.25. Found: C, 75.04; H, 6.84; N, 3.20.
4.5 References


(2) Values obtained from the Bordwell pKa table.


(6) (a) Fandos, R.; Hernandez, C.; Otero, A.; Rodríguez, A.M.; Ruiz, M.J.; Terreros, P.
Corrochano, A.E.; Fandos, R.; Fernandez-Baeza, J.; Rodríguez, A.M.; Ruiz, M.J.;
Otero, A. Organometallics 1999, 18, 5219. (c) Cotton F.A.; Lewis, G.E.; Mott,

(7) (a) Fandos, R.; Hernandez, C.; Otero, A.; Rodríguez, A.M.; Ruiz, M.J.; Terreros, P.
Corrochano, A.E.; Fandos, R.; Fernandez-Baeza, J.; Rodríguez, A.M.; Ruiz, M.J.;
Otero, A. Organometallics 1999, 18, 5219. (c) Cotton F.A.; Lewis, G.E.; Mott,


1982, 14, 45.


(13) (a) Schreiber, A.; Krizanivic, O.; Fusch, E.C.; Lippert, B; Lianza, F.;
1994, 33, 477.

(14) Thomson, R.K.; Zahariev, F.E.; Zhang, Z.; Patrick, B.O.; Wang, Y.A.;


CHAPTER FIVE: α-FUNCTIONALIZATION OF PRIMARY AMINES VIA sp³ HYBRIDIZED C-H BOND ACTIVATION

5.1 Introduction

The direct, selective, catalytic activation of C-H bonds by transition metals and subsequent C-C bond formation represents an important avenue of research for synthetic chemists owing to the fact that C-H bonds are among the most abundant that can be found in organic molecules.¹ Over the past couple of decades much of the work in this field has been devoted to the activation of sp and sp² hybridized C-H bonds, while the activation of sp³ hybridized C-H bonds has received comparatively little attention due to the relatively inert nature of this bond.¹

One particular area of research concerning sp³ C-H bond activation that has drawn notable interest is the selective activation / functionalization of sp³ C-H bonds located α to a heteroatom such as nitrogen.² Methodologies developed for the direct catalytic α-functionalization of amines have enormous potential as tools for the synthesis of a broad range of amine containing natural products, pharmaceuticals, and other fine chemicals. Although numerous transition metal based systems have already been applied to the catalytic α C-H activation/functionalization of tertiary amines,²⁾, only recently have secondary amines been successfully implemented as substrates. Hartwig and coworkers reported that secondary aryl-alkyl amines undergo coupling with olefins via a tantalum catalyzed C-H activation and subsequent C-C bond forming reaction (Equation 5.1).⁴

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A version of this chapter has been submitted for publication. Bexrud, J.A.; Eisenberger, P.; Payne, P.R.; Schafer, L.L. Zirconium 2-Pyridonates for Catalytic, Intramolecular α-Functionalization of Primary Amines. September 2008.
To date, there have not yet been any systems designed specifically to effect the catalytic \( \alpha \)-functionalization of primary amines reported in the literature. However, in a recent paper by Doye and coworkers, which described a series of group four metal based catalysts for the cyclohydroamination of aminoalkenes, it was noted that these types of substrates can also undergo undesirable side reactivity involving \( \alpha \)-C-H bond activation and ensuing C-C bond formation to afford amino-cyclopentane derivatives in low yield (Equation 5.2).

Additionally, titanium and zirconium imido complexes (the catalytically active species for the cyclohydroamination reaction) are known to be capable of activating sp, sp\(^2\) and sp\(^3\) hybridized C-H bonds. In particular, Doye has observed the racemization of \( \alpha \)-chiral primary amines in the presence of catalytic quantities of various titanium complexes during alkyne hydroamination experiments. To date, no attempt has been made to take advantage of this reactivity for the \( \alpha \)-functionalization of primary amines.

Prior to the work by Doye and coworkers, we had also encountered this side reaction when studying the aminoalkene hydroamination activity of the 2-pyridone derived zirconium complexes. Recognizing the potential usefulness of this
transformation, we decided to undertake further investigations. This chapter describes our initial findings along with our attempts to delineate the scope of this unique reactivity, and deduce a plausible mechanistic rationale.

5.2 Results and discussion

5.2.1 Preliminary findings and catalyst screening

During our substrate scope investigations to determine the limits of the bis(6-tert-butyl-3-phenyl-2-pyridonate) zirconium system (complex 4.3) in terms of catalyzing the cyclohydroamination reaction, we had observed side reactivity attributable to α C-H activation. Heating a J. Young NMR tube containing a solution of 2,2-diphenyl-6-heptenylamine, 20 mol% complex 4.3, and 1,3,5-trimethoxybenzene to 145 °C for 96 hours, produces a mixture of the cis and trans diastereomers of 2,2-diphenyl-6-methylcyclohexylamine; the product formed presumably via α C-H activation/alkene insertion; along with the intended 2-methyl-6,6-diphenylazepane hydroamination product in yields of 56% and 28% respectively as is determined by 1H NMR spectroscopy (Equation 5.3). The products of this reaction are all fully characterized, and relative stereochemistry is assigned based on the solid state structural data for the N-Ts derivative of the trans-product. Although this reaction has been previously viewed as undesirable side reactivity, we adopt the alternative mindset that this reactivity illuminates a starting point for the development of a new efficient, atom economical methodology for the synthesis of α-chiral amines.
Screening of two other zirconium complexes; Z(NMe₂)₄ as well as the bis(N-2,6-diisopropylphenyl-(phenyl)-amidate) zirconium bis(dimethylamido) complex (entries 1, 2, and 5, Table 5.1); reveals that only the bis(6-tert-butyl-3-phenyl-2-pyridonate) zirconium bis(dimethylamido) complex 4.3 catalyzes the formation of the α C-H activation product preferentially. The bis(N-2,6-dimethylphenyl-(tert-butyl)-amidate) zirconium bis(dimethylamido) complex has also recently been screened for this reactivity by other members of our group and only the hydroamination product is observed in nearly quantitative yield. Interestingly, of the analogous titanium complexes, only Ti(NMe₂)₄ is capable of potentiating any reaction whatsoever, with the α C-H activation product forming preferentially with a yield of 70%. It should be noted that Ti(NMe₂)₄ does not effect the cyclization of this substrate at 110 °C with 5 mol% catalyst loading, which is in agreement with what has been observed by Doye and coworkers."
Table 5.1. Catalyst screening for the α-activation/functionalization reaction.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>precatalyst</th>
<th>loading</th>
<th>time</th>
<th>NMR yield A</th>
<th>NMR yield B</th>
<th>A (trans:cis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zr(NMe₂)₄</td>
<td>20 mol%</td>
<td>24h</td>
<td>23%</td>
<td>57%</td>
<td>(&gt;1.5:1)</td>
</tr>
<tr>
<td>2</td>
<td>Zr(NMe₂)₄</td>
<td>40 mol%</td>
<td>24h</td>
<td>19%</td>
<td>62%</td>
<td>(&gt;1.5:1)</td>
</tr>
<tr>
<td>3</td>
<td>4.3</td>
<td>20 mol%</td>
<td>96h</td>
<td>56%</td>
<td>28%</td>
<td>(1.5 : 1)</td>
</tr>
<tr>
<td>4</td>
<td>4.3</td>
<td>40 mol%</td>
<td>48h</td>
<td>62%</td>
<td>21%</td>
<td>(1.7 : 1)</td>
</tr>
<tr>
<td>5</td>
<td>L₂Zr(NMe₂)₂</td>
<td>20 mol%</td>
<td>96h</td>
<td>0%</td>
<td>28%</td>
<td>N/A</td>
</tr>
<tr>
<td>6</td>
<td>Ti(NMe₂)₄</td>
<td>20 mol%</td>
<td>24h</td>
<td>70%</td>
<td>8%</td>
<td>(1 : 1.5)</td>
</tr>
<tr>
<td>7</td>
<td>4.2</td>
<td>40 mol%</td>
<td>24h</td>
<td>N/R</td>
<td>N/R</td>
<td>N/A</td>
</tr>
<tr>
<td>8</td>
<td>1.1</td>
<td>20 mol%</td>
<td>48h</td>
<td>N/R</td>
<td>N/R</td>
<td>N/A</td>
</tr>
</tbody>
</table>

a. 1,3,5-Trimethoxybenzene as an internal standard. b. Determined by NMR. c. Average of five runs. d. L = N-2,6-diisopropyl-phenyl-(phenyl)-amidate

These reactions are carried out with either a 20 mol% catalyst loading or a 40 mol% catalyst loading since preliminary findings suggest (vide infra) that catalyst loading can impact product distribution. It should also be noted that this particular substrate appears to give somewhat inconsistent product ratios, which may be due to the presence of undetectable trace impurities in the substrate or the precatalyst. Therefore, the reported yield using complex 4.3 at 20 mol% is based on the average of five runs. To give an indication of variability, combined overall yields using complex 4.3 range from 77% to 88%, and the product ratios vary between 0.9 : 1 and 3 : 1 (A : B).
Entries 6 and 1 of Table 4.3 show that Ti(NMe₂)₄ dramatically favors formation of the smaller six membered ring α C-H functionalization product, while Zr(NMe₂)₄ favors the formation of the larger seven membered ring hydroamination product, which might suggest that the product distribution is influenced by the relative sizes of the metal involved in catalysis. The complete inactivity of complex 4.2 and the bis(amidate) titanium complex (entries 7 and 8) towards this substrate, may be due to the decreased size of titanium in combination with the added steric bulk imposed by the chelating ligands, rendering the metal center too sterically inaccessible for either α C-H activation/functionalization or hydroamination catalysis to proceed. The differences in activity among the zirconium complexes towards this substrate are intriguing, and somewhat more difficult to rationalize. The hydroamination activity of each complex, in combination with their propensity to form dimers in situ may play a role in determining product distribution. It is thought that the relatively open coordination environment afforded by the 6-tert-butyl-3-phenyl-2-pyridonate ligand; as compared to the very bulky N-2,6-diisopropylphenyl-(phenyl)-amidate ligand may increase the susceptibility of complex 4.3 to form a dimer in situ and therefore shift the product distribution in favor of compound A. This may then explain the different product distributions observed with complex 4.3 and the bis(amidate) zirconium complex, but it does not obviously account for why complex 4.3 favors α C-H activation/functionalization while Zr(NMe₂)₄ favors hydroamination. In order to rationalize the latter dissimilarity, one must also consider that the product distributions in Table 4.3 result from a competition between α C-H activation/functionalization and cyclohydroamination. Considering the product distributions listed for entries 1 and 6, in addition to the fact that Zr(NMe₂)₄ is an efficient
catalyst for the cyclohydroamination of aminoalkenes, it is clear that the rate of formation of product B exceeds the rate of formation of product A. Therefore, the presence of either the 6-tert-butyl-3-phenyl-2-pyridonate or the N-2,6-diisopropylphenyl-(phenyl)-amidate ligands actually inhibits the hydroamination reaction, which is slightly favored with zirconium, but the relatively open coordination environment afforded by the 6-tert-butyl-3-phenyl-2-pyridonate ligand also permits the formation of dimeric species which may be responsible for the α C-H activation reactivity. Therefore, Zr(NMe₂)₄ rapidly yields predominantly the hydroamination product; the bis(amidate) zirconium complex slowly gives only the hydroamination product; and complex 4.3 slowly produces a mixture containing mainly the α C-H functionalization product. It is obvious that the most effective catalyst for the α C-H functionalization reaction in Table 4.3 is Ti(NMe₂)₄. However, future efforts to realize enantiocontrol in this reaction are dependant upon the design of the coordination environment of the catalytically active metal complex. Thus, complex 4.3 is used for the following substrate scope investigations as chiral, modular pyridonate ligands could be targeted in future work.
5.2.2 Substrate scope investigation

The α C-H activation/intramolecular C-C bond forming reaction observed in the cyclization of 2,2-diphenyl-6-heptenylamine is not an isolated case. A number of other aminoalkene substrates also undergo cyclization via α C-H activation/functionalization in the presence of catalytic quantities of complex 4.3. Table 4.4 lists a series of substrates and the resulting cyclohexylamine derivatives which are generated as products of this transformation.

All of these reactions give predominantly the α C-H functionalization products with only small amounts (<15 %) of what could be the hydroamination product being detected upon analysis of the crude reaction mixture using ¹H NMR spectroscopy. 2-(3-Butene)benzylamine (entry 1) should be particularly susceptible to α C-H functionalization because the C-H bonds undergoing activation are situated in a benzylic position; and in fact this reaction goes to completion within 24 hours. The N-tosyl derivative of the initially formed 1-amino-2-methyl-tetralin can then be isolated, following derivatization, in excellent yield and with modest diastereoselectivity. Entries 2 and 3 demonstrate that the intramolecular α C-H activation/functionalization reaction can be potentiated by the gem-disubstituent effect in analogy to the cyclohydroamination reaction. Importantly, entry 4 reveals that substituents are, however, not required for this reaction to proceed. It should be noted that the low yields for entries 2 and 4 result in part from product volatility as well as difficulties that are encountered during purification.
Table 5.2. Synthesis of cyclohexylamine derivatives via catalytic α-functionalization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aminoalkene</th>
<th>Product</th>
<th>Time</th>
<th>Yield ( \text{trans:} \text{cis} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{C} = \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{N} )</td>
<td>( \text{C} = \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{N} )</td>
<td>24h(^a)</td>
<td>90(^b)(3:1)(^c)</td>
</tr>
<tr>
<td>2</td>
<td>( \text{C} = \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{N} )</td>
<td>( \text{C} = \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{N} )</td>
<td>24h(^a)</td>
<td>50(^b)(3:1)(^c)</td>
</tr>
<tr>
<td>3(^f)</td>
<td>( \text{C} = \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{N} )</td>
<td>( \text{C} = \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{N} )</td>
<td>22h(^a)</td>
<td>91(^b)(2:1)(^c)</td>
</tr>
<tr>
<td>4</td>
<td>( \text{C} = \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{N} )</td>
<td>( \text{C} = \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{N} )</td>
<td>72h(^b)</td>
<td>43(^b)(2:1)(^c)</td>
</tr>
<tr>
<td>5</td>
<td>( \text{C} = \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{N} )</td>
<td>( \text{C} = \text{C} - \text{C} - \text{C} - \text{C} - \text{C} - \text{N} )</td>
<td>120h(^d)</td>
<td>51(^e)(1:19)(^c)</td>
</tr>
</tbody>
</table>

\(^a\) 20 mol% catalyst at 145\(^\circ\)C. \(^b\) Isolated yield of derivatized C-H activation products. \(^c\) Ratio from \(^1\)H-NMR spectroscopy. \(^d\) 40 mol% catalyst at 155\(^\circ\)C. \(^e\) NMR yield using 1,3,5-trimethoxybenzene as internal standard.

\(^f\) This experiment was carried out by another member of our group.

Characterization data for the substrate and product can be found in reference 9.

The most notable of all these experiments is the cyclization of 1-phenyl-6-heptenylamine (entry 5) which demonstrates that sterically congested pseudo-quaternary, stereogenic carbon centers located \( \alpha \) to a nitrogen atom can be generated by taking advantage of this unique reactivity. The product of this cyclization, \((+/-)-(1S,2R)-2-\)
methyl-1-phenylcyclohexylamine, is a known precursor to biologically active PCP derivatives.\textsuperscript{11} It is interesting, and worth highlighting that the relatively high diasteroselectivity observed in this reaction is in stark contrast to what was found for entries 1 – 4.

5.2.3 Mechanistic considerations

When Doye and coworkers\textsuperscript{5} described a possible mechanism for the formation of the aminocyclopentane side products as $\alpha$ C-H activation and subsequent alkene insertion into a Ti-C bond, they had drawn analogy to the hydroaminoalkylation process that had recently been reported by Hartwig and coworkers.\textsuperscript{4} The mechanism proposed by Hartwig for the tantalum catalyzed hydroaminoalkylation of unactivated alkenes with N-alkyl aryl amines is shown in Scheme 5.1. It involves amine elimination to form a group five $\eta^2$ imine complex followed by alkene insertion into the resulting M-C bond.

\begin{center}
\textbf{Scheme 5.1.} Mechanism proposed by Hartwig and coworkers for the tantalum catalyzed hydroaminoalkylation reaction.
\end{center}

A mechanism such as this is plausible considering that zirconium $\eta^2$-imine complexes, or zirconaaziridines, are known to undergo stoichiometric reactions with alkenes and alkynes to form $\alpha$ functionalized products (Scheme 5.2).\textsuperscript{12} However, none of
these catalytic or stoichiometric systems involve primary amines as substrates. Therefore the $N$-methyl and $N$-phenyl secondary amine derivatives of 2,2-diphenyl-6-heptenylamine were prepared and tested as substrates using the same conditions employed in the original experiment. The $N$-phenyl derivative was included because it has been shown that zirconocene $\eta^2$-imine complexes are formed faster starting from $N$-alkyl arylamido complexes than from their dialkylamido analogues.$^{13}$

![Scheme 5.2. Reactivity of zirconium $\eta^2$-imine complexes towards alkenes and alkynes.](image)

Surprisingly, complex 4.3 does not catalyze the cyclization of either the $N$-methyl or the $N$-phenyl derivative of 2,2-diphenyl-6-heptenylamine (Equation 5.4). The $N$-phenyl substrate remains completely unreacted after 144 hours at 145 °C. This lack of reactivity with secondary amines suggests that the mechanism for group four catalyzed $\alpha$ C-H functionalization is fundamentally different from the one proposed by Hartwig for the tantalum catalyzed hydroaminoalkylation reaction. Namely, it is conceivable that the catalytically active species may be some form of group four metal imido complex, as both titanium and zirconium imido complexes are known to be capable of activating C-H bonds.$^6$
In addition to these findings, catalyst loading experiments carried out by other members of our group demonstrate that higher catalyst concentrations shift the product distribution towards the $\alpha$ C-H functionalized product. This suggests that a dimeric or higher order multi-metallic species is involved in catalyzing this transformation. Group four imido complexes are known to form dimers, and 2-pyridones have been used in the preparation of numerous bimetallic complexes.

Based on all of the above information, the mechanism outlined in Scheme 5.3 is proposed for the group four catalyzed intramolecular $\alpha$ C-H functionalization of aminoalkenes. Initially the substrate reacts with the precatalyst to form an imido complex, which can then undergo dimerization to form a bridging imido species. $\beta$-hydrogen abstraction/amine elimination leads to the bridging zirconium $\eta^2$ imine intermediate. Alkene insertion then ensues, followed by protonolysis of the resulting Zr-C bond. Displacement of the product by another equivalent of substrate via protonolysis liberates the $\alpha$ functionalized amine and regenerates the bridging imido dimer.
Scheme 5.3. Postulated mechanism for the zirconium catalyzed a C-H activation/C-C bond forming reaction.

This mechanism is only meant to serve as a working hypothesis that is consistent with the information gathered so far. Efforts to characterize intermediates of this catalytic cycle have not been successful. The stoichiometric reaction of complex 4.3 with 2,2-diphenyl-6-heptenylamine yields an oil which consist of a complex mixture of compounds that has resisted characterization by solid state analysis or $^1$H NMR spectroscopy.

Experiments involving 1,1-dideuterium labeled 2,2-diphenyl-6-heptenylamine show approximately 10% incorporation of deuterium onto the methyl group, and approximately 30% loss of deuterium $\alpha$-to the nitrogen in the $\alpha$-C-H functionalized product (Scheme 5.4). These observations are consistent with the proposed mechanism outlined in scheme
5.3, and suggest that the β-hydrogen abstraction/amine elimination step is reversible. Deuterium labeling experiments utilizing 1,1-dideutero-2,2-diphenyl-butylamine as a substrate also support the latter presumption, as exchange of deuterium for hydrogen is observed when this compound is heated to 145 °C in the presence of 20 mol% complex 4.3.

Scheme 5.4. Experiment involving 1,1-dideutero labeled 2,2-diphenyl-6-heptenylamine.

With the mechanism of this transformation being postulated to involve a zirconium $\eta^2$-imine complex, rationalization of the observed diastereoselectivities can be accomplished by recognizing that the appended olefin can approach and insert into the Zr-C bond in a conformation that resembles a chairlike geometry (Scheme 5.5). Therefore, two chairlike conformations are possible; one having the nitrogen in a pseudoequatorial position and the R group (R = H entries 1-4 Table 5.2; or R = Ph entry 5 Table 5.2) in a pseudoaxial position; and in the other conformation these relative orientations are reversed. When R = H it is argued that the conformation that positions the nitrogen in a pseudoequatorial orientation is favored over the conformation in which it is axial to minimize 1,3-diaxial interactions; and this results in the observed product distribution slightly favoring the NH$_2$/CH$_3$-trans diastereomer. When R = Ph on the other hand (entry 5, Table 5.2), the product distribution shifts dramatically in favor of the
NH$_2$/CH$_3$-cis diastereomer. This is consistent with the comparatively bulky phenyl group adopting the pseudoequatorial orientation to minimize 1,3-diaxial interactions, thus forcing the nitrogen into a pseudooaxial position resulting in the NH$_2$/CH$_3$-cis diastereomer now being the favored product.

![Scheme 5.5. Rationalization of the diastereoselectivities observed in the intramolecular α-functionalization reaction.](image)

5.3 Summary and conclusions

While attempting to expand the substrate scope of this system by employing higher reaction temperatures and higher catalyst loadings, side reactivity attributable to α C-H activation and subsequent intramolecular C-C bond formation was observed. Heating 2,2-diphenyl-6-heptenylamine in the presence of 20 mol% complex 4.3 to 145 °C for 96 hours, produced a mixture of the cis and trans diastereomers of 2,2-diphenyl-6-methylcyclohexylamine, the product formed presumably via α C-H activation/alkene insertion, along with the intended 2-methyl-6,6-diphenylazepane hydroamination product in yields of 56% and 28% respectively. Similar side reactions have also been observed by Doye and coworkers.
Recognizing the potential value of this $\alpha$ functionalization reactivity to the synthetic community, further investigations were carried out. Catalyst screening experiments in which 2,2-diphenyl-6-heptenylamine was employed as the substrate revealed that of the catalysts tested, complex 4.3 is the most effective zirconium catalyst and $\text{Ti(NMe}_2)_4$ is the most effective overall, for the $\alpha$ C-H functionalization reaction. Substrate screening experiments using complex 4.3 as the catalyst demonstrated that this reactivity is not an isolated case. In fact the $\alpha$ C-H activation products tend to be favored over the hydroamination products to a greater extent when aminoalkenes other than 2,2-diphenyl-6-heptenylamine were employed as substrates. Importantly, the $N$-methyl and $N$-phenyl derivatives of 2,2-diphenyl-6-heptenylamine were found to be completely unreactive as substrates for the $\alpha$ C-H functionalization reaction and the cyclohydroamination reaction in the presence of complex 4.3.

Based on known stoichiometric and catalytic early transition metal chemistry involving the $\alpha$ functionalization of amines, along with our own observations that secondary aminoalkenes do not undergo $\alpha$ functionalization, and that increased catalyst loading favors the $\alpha$ functionalized products the mechanism of this reaction is thought to involve a bridging imido dimer and a group four bridging $\eta^2$-imine complex as key intermediates. The mechanism proposed in section 5.2.3 is a working hypothesis that is consistent with previous work and our own observations. The exact nature of the intermediates, and the specific processes involved require further elucidation and is the focus of investigations for another doctoral student.
5.4 Experimental

General. $^1$H and $^{13}$C NMR spectra were recorded on either a Bruker 300 MHz or 400 MHz Avance spectrometer at ambient temperature and chemical shifts are given relative to residual solvent. GCMS spectra were recorded on an Agilent series 6890 GC system with a 5973 Mass Selective Detector. Single crystal X-ray structure determinations, MS, and elemental analyses determinations were performed at the Department of Chemistry, University of British Columbia. All reactions were carried out using standard Schlenk line and glovebox techniques under an atmosphere of nitrogen, unless described otherwise. Ti(NMe$_2$)$_4$ and Zr(NMe$_2$)$_4$ were purchased from Strem and used as received. $d_6$-Toluene was degassed and dried over molecular sieves. 2,2-Diphenyl-6-heptenylamine$^{14}$ was prepared as described in the literature with some modification from commercially available starting materials purchased from Aldrich. Amino alkene substrates were dried over CaH or 4Å molecular sieves and degassed prior to use. The 6-tert-butyl-3-phenyl-2-pyridone proligand was prepared as described in the literature$^{15}$ and was heated to 80 °C under vacuum for at least three days prior to use. 1,1-Dideutero-2,2-diphenylbutylamine was prepared using modified literature procedures$^{14}$ from commercially available starting materials with full characterization for this compound provided below. 2-(3-Butene)benzylamine was prepared from 2-(3-butenyl)benzaldehyde$^{16}$ via oxime formation$^{17}$ followed directly by reduction$^{18}$ with full characterization data provided below. 2,2-Dimethyl-6-heptenylamine was prepared from commercially available starting materials using modified literature procedures$^{14}$ with full characterization data provided below. 6-Heptenylamine was prepared using literature
procedures\textsuperscript{19} from 6-heptenenitrile with full characterization data provided below. 1-Phenyl-hept-6-enylamine was prepared from 1-phenyl-hept-6-en-1-one\textsuperscript{20} by reductive amination using NH\textsubscript{4}OAc / NaCNBH\textsubscript{3}.\textsuperscript{21} 2,2-Diphenyl-hept-6-enal was prepared using modified literature procedures.\textsuperscript{22} with full characterization data provided below. 2,2-Diphenyl-hept-6-enyl-phenyl-amine was prepared from 2,2-diphenyl-hept-6-enal and aniline using modified literature procedures with full characterization data provided below.\textsuperscript{22} (2,2-Diphenyl-hept-6-enyl)-methyl-amine was prepared from 2,2-diphenyl-6-heptenylamine using modified literature procedures with full characterization data provided below.\textsuperscript{23} 1,3,5-Trimethoxybenzene purchased from Aldrich, was used as an internal standard and was sublimed under vacuum prior to use. The bis(N-2,6-diisopropylphenyl(phenyl)-amidate) titanium bis(dimethylamido) and (N-2,6-diisopropylphenyl(phenyl)-amidate) zirconium bis(dimethylamido) complexes were prepared as described in the literature.\textsuperscript{24}

\[
\text{1,1-Dideutero-2,2-diphenyl-butylamine.}\textsuperscript{14} ^1\text{H NMR (CDCl}_3, 400 MHz): } \delta \text{ 0.71 (3H, t, J = 7.2 Hz, } -\text{CH}_3), 2.19 (2H, q, J = 7.2 Hz, } -\text{CH}_2-), 7.10 - 7.40 (10H, m, ArH); ^13\text{C NMR (CDCl}_3, 101 MHz): } \delta \text{ 8.8, 28.9, 47.7, 52.1, 126.0, 128.2, 128.5, 146.7; HRMS Calcd for C}_{16}H_{18}D_2N [M+H\textsuperscript{+}]: 228.1721; \text{ Found: 228.1721.}
2-(3-butenyl)benzylamine.\textsuperscript{16,17,18} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 1.39 (2H, br s, \(-\text{NH}_2\)), 2.34 – 2.41 (2H, m, Ar-CH\textsubscript{2}-CH\textsubscript{2}-CH=CH\textsubscript{2}), 2.75 – 2.80 (2H, m, Ar-CH\textsubscript{2}-CH\textsubscript{2}-CH=CH\textsubscript{2}), 3.91 (2H, s, Ar-CH\textsubscript{2}-NH\textsubscript{2}), 5.00 – 5.11 (2H, m, -CH=CH\textsubscript{2}), 5.80 – 6.00 (1H, m, -CH=CH\textsubscript{2}), 7.19 – 7.36 (4H, m, Ar); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): \(\delta\) 31.8, 35.4, 43.7, 115.2, 126.5, 127.0, 127.8, 129.4, 138.2, 139.4, 140.9; MS (El): \(m/z\) 160 (M-H\textsuperscript{+}). Anal. Calcd for C\textsubscript{11}H\textsubscript{15}N: C, 81.94; H, 9.38; N, 8.69. Found: C, 81.92; H, 9.62; N, 8.94.

\[
\text{\begin{tikzpicture}
\node at (0,0) {\text{2-(3-butenyl)benzylamine.}};
\end{tikzpicture}}
\]

2,2-Dimethyl-hept-6-enylamine.\textsuperscript{14} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): \(\delta\) 0.83 (6H, s, -CH\textsubscript{2}-(CH\textsubscript{3})\textsubscript{2}C-CH\textsubscript{2}-NH\textsubscript{2}), 0.98 – 1.06 (2H, m, -CH\textsubscript{2}-CH\textsubscript{2}-(CH\textsubscript{3})\textsubscript{2}C-CH\textsubscript{2}-NH\textsubscript{2}), 1.17 – 1.21 (2H, m, -CH\textsubscript{2}-CH\textsubscript{2}CH\textsubscript{2}-(CH\textsubscript{3})\textsubscript{2}C-), 2.00 – 2.05 (2H, m, CH\textsubscript{2}=CH-CH\textsubscript{2}CH\textsubscript{2}-), 2.43 (2H, s, -CH\textsubscript{2}-(CH\textsubscript{3})\textsubscript{2}C-CH\textsubscript{2}-NH\textsubscript{2}), 4.93 – 5.02 (2H, m, CH\textsubscript{2}=CH-CH\textsubscript{2}-), 5.76 – 5.86 (1H, m, CH\textsubscript{2}=CH-CH\textsubscript{2}-); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): \(\delta\) 24.3, 25.7, 35.4, 35.6, 39.9, 53.9, 115.4, 140.0; HRMS Calcd for C\textsubscript{9}H\textsubscript{19}N [M\textsuperscript{+}]: 141.15175; Found: 141.15164.

\[
\text{\begin{tikzpicture}
\node at (0,0) {\text{2,2-Dimethyl-hept-6-enylamine.}};
\end{tikzpicture}}
\]

6-Heptenylamine.\textsuperscript{10} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): \(\delta\) 1.01 (2H, br s, -NH\textsubscript{2}), 1.23 – 1.40 (6H, m), 1.95 – 2.02 (2H, m), 2.62 (2H, t, \(J = 6.6\) Hz, -CH\textsubscript{2}-CH\textsubscript{2}-NH\textsubscript{2}), 4.85 – 4.96 (2H, m, H\textsubscript{2}C=CH-CH\textsubscript{2}-), 5.67 – 5.79 (1H, m, H\textsubscript{2}C=CH-CH\textsubscript{2}-); \textsuperscript{13}C NMR (CDCl\textsubscript{3},
101 MHz): δ 26.5, 28.9, 33.8, 33.8, 42.2, 114.4, 139.0; HRMS Calcd for C7H16N [M⁺]: 114.1283; Found: 114.1282.

1-Phenyl-hept-6-enylamine. ¹H NMR (CDCl₃, 400 MHz): δ 1.23 – 1.26 (1H, m), 1.30 – 1.45 (3H, m), 1.50 (2H, br s, -NH₂), 1.65 – 1.71 (2H, m), 1.98 – 2.06 (2H, m), 3.88 (1H, t, J = 6.8, Ph-CH(NH₂)-CH₂-), 4.91 – 5.06 (2H, m, -CH=CH₂), 5.73 – 5.84 (1H, m, -CH₂=CH₂), 7.22 – 7.28 (5H, m, Ar-H); ¹³C NMR (CDCl₃, 101 MHz): δ 26.2, 29.0, 33.8, 39.7, 56.4, 114.5, 126.7, 127.0, 128.9, 139.0, 147.0; MS (El): m/z (M+H⁺) 190; Anal. Calcd for C13H19N: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.24; H, 10.05; N, 7.30.

2,2-Diphenyl-hept-6-enal. ¹H NMR (CDCl₃, 400 MHz): δ 1.16 – 1.22 (2H, m, -CH₂=CH₂-CH₂-), 2.04 – 2.10 (2H, m, H₂C=CH-CH₂-CH₂-), 2.28 – 2.33 (2H, m, -CH₂=CH₂-CPh₂-), 4.93 – 5.01 (2H, m, H₂C=CH-), 5.69 – 5.80 (1H, m, H₂C=CH-CH₂-), 7.19 – 7.40 (10H, m, ArH), 9.82 (1H, s, -Ph₂C-CH=O); ¹³C NMR (CDCl₃, 101 MHz): δ 25.0, 34.5, 35.1, 64.7, 115.8, 128.3, 129.7, 130.1, 139.3, 141.2, 199.6; HRMS Calcd for C₁₈H₁₉ [M-HCO⁺]: 235.14868; Found: 235.14846.
2,2-Diphenyl-hept-6-enyl-phenyl-amine.\textsuperscript{22} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz): $\delta$ 1.18 – 1.26 (2H, m, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-), 1.97 – 2.03 (2H, m, H\textsubscript{2}C=CH-CH\textsubscript{2}-CH\textsubscript{2}-), 2.21 – 2.26 (2H, m, -CH\textsubscript{2}-CH\textsubscript{2}-CPh\textsubscript{2}-), 3.25 (1H, br t, J = 5.6 Hz, -NH-), 3.77 (2H, d, J = 5.6 Hz, -Ph\textsubscript{2}C-CH\textsubscript{2}-NH-), 4.89 – 4.97 (2H, m, H\textsubscript{2}C=CH-), 5.64 – 5.74 (1H, m, H\textsubscript{2}C=CH-CH\textsubscript{2}-), 6.57 – 6.59 (2H, m, -NHArH), 6.68 – 6.72 (1H, m, -NHArH), 7.14 – 7.22 (12H, m, ArH); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): $\delta$ 24.6, 35.1, 38.1, 51.2, 51.4, 114.0, 115.6, 118.4, 127.3, 129.0, 129.2, 130.2, 139.5, 147.2, 149.5; MS (ESI): m/z 342 (M+H\textsuperscript{+}). Anal. Calcd for C\textsubscript{25}H\textsubscript{27}N: C, 87.93; H, 7.97; N, 4.10. Found: C, 87.92; H, 7.96; N, 4.13.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{structure1.png}
\end{figure}

(2,2-Diphenyl-hept-6-enyl)-methyl-amine.\textsuperscript{23} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz): $\delta$ 0.4 (1H, br s, -CH\textsubscript{2}-NH-CH\textsubscript{3}), 1.10 – 1.18 (2H, m, -CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-), 2.00 – 2.08 (2H, m, H\textsubscript{2}C=CH-CH\textsubscript{2}-CH\textsubscript{2}-), 2.21 – 2.26 (2H, m, Ph\textsubscript{2}C-CH\textsubscript{2}-CH\textsubscript{2}-), 2.39 (3H, s, -NH-CH\textsubscript{3}), 3.21 (2H, s, -Ph\textsubscript{2}C-CH\textsubscript{2}-NH-), 4.90 – 5.00 (2H, m, H\textsubscript{2}C=CH-), 5.6- 5.8 (1H, m, H\textsubscript{2}C=CH-CH\textsubscript{2}-), 7.18 – 7.32 (10H, m, ArH); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 101 MHz): $\delta$ 23.71, 34.40, 37.07, 37.55, 50.50, 59.36, 114.55, 126.04, 128.12, 128.21, 138.98, 147.35;
MS (EI): m/z (M+). Anal. Calcd for C_{20}H_{25}N: C, 85.97; H, 9.02; N, 5.01. Found: C, 85.74; H, 9.07; N, 5.01.

**General procedure for catalytic α-functionalization reactions.** All α-functionalization reactions were carried out in a J. Young NMR-tube equipped with a Teflon screw cap and were prepared in an N\textsubscript{2}-filled glove box. A small vial would be charged with the internal standard (1,3,5-trimethoxybenzene) (0.08 mmol), the precatalyst (0.05 or 0.1 mmol), d\textsubscript{8}-toluene (1.0 g) followed by the aminoalkene (0.25 mmol). The solution would then be transferred to a J. Young NMR tube which would be sealed, heated to, and maintained at, the appropriate temperature for the stated duration of time. Unless otherwise stated, the crude amines would then be directly converted to either the N-benzoyl, N-tosyl, or N-napthoyl derivative by transferring the crude hydroamination reaction mixture to a small round bottomed flask containing a solution of the acid chloride (0.38 mmol) and NEt\textsubscript{3} (1.25 mmol) dissolved in CH\textsubscript{2}Cl\textsubscript{2} (2-3 mL). This mixture would then be stirred overnight. Following aqueous work up, the crude mixture would be subjected to column chromatography (SiO\textsubscript{2}) to afford the analytically pure products as mixtures of diastereomers which could then be separated by further column chromatography (SiO\textsubscript{2}) or recrystallization.
2-Methyl-6,6-diphenyl-azepane, (+/-)-(1S,6R)-2,2-diphenyl-6-methylcyclohexylamine, and (+/-)-(1S,6S)-2,2-diphenyl-6-methylcyclohexylamine. A yield of 83% was obtained for the mixture of compounds (1.1:1 [1.3:1], hydroamination:CH activation product [anti:syn]) isolated via column chromatography (4:1 Hexanes:Et2O with 2 % NEt3, SiO2), which were subsequently separated via chromatography (4:1 Hexanes:Et2O with 2 % NEt3, SiO2) for characterization purposes. Relative stereochemistry was assigned based on the crystal structure of the NTs derivative of (+/-)-(1S,6R)-2,2-diphenyl-6-methylcyclohexylamine.

$^1$H NMR (2-methyl-6,6-diphenyl-azepane) (CDCl$_3$, 400 MHz): $\delta$ 1.10 (3H, d, J = 6.4 Hz, -CH-CH$_3$), 1.26 – 1.38 (1H, m, -CH$_2$-CHH-CH(CH$_3$)-NH-), 1.60 (1H, br s, -NH-), 1.65 – 1.77 (1H, m, -CH$_2$-CHH-CH$_2$-CH(CH$_3$)-NH-), 1.78 – 1.92 (2H, m, -CH$_2$-CHH-CH$_2$-CH(CH$_3$)-NH-, -CH$_2$-CHH-CH(CH$_3$)-NH-), 2.13 (1H, dd, J = 10, 14.8 Hz, -Ph$_2$C-CHH-CH$_2$-), 2.59 (1H, dd, J = 8.4, 14.8 Hz, -Ph$_2$C-CHH-CH$_2$-), 2.80 – 2.86 (1H, m, -CH$_2$-CH(CH$_3$)-NH-), 7.14 – 7.26 (10H, m, ArH); $^{13}$C NMR (2-methyl-6,6-diphenyl-azepane) (CDCl$_3$, 101 MHz): $\delta$ 23.97, 24.43, 41.06, 41.12, 53.31, 57.66, 58.46, 126.59, 126.77, 128.39, 128.54, 129.15, 129.19, 149.26, 151.16; HRMS (2-methyl-6,6-diphenyl-azepane) Calcd for C$_{19}$H$_{23}$N [M$^+$]: 265.18305; Found: 265.18365.

$^1$H NMR ((+/-)-(1S,6R)-2,2-diphenyl-6-methylcyclohexylamine) (CDCl$_3$, 400 MHz): $\delta$ 1.02 (3H, d, J = 6.4 Hz, -CH$_2$-CH(CH$_3$)-CH(NH$_2$)-), 1.19 – 1.30 (1H, m, -CH$_2$-CHH-
CH₂), 1.33 - 1.45 (3H, m, -CH₂-CHH-CH(CH₃)-, -CH(NH₂)-CH₂-), 1.52 - 1.57 (1H, m, -CH₂-CHH-CH(CH₃)-), 1.71 - 1.77 (1H, m, -CH₂-CHH-CH₂-), 2.10 - 2.19 (2H, m, -CH(CH₃)-, Ph₂C-CHH-CH₂-), 2.42 - 2.47 (1H, m, Ph₂C-CHH-CH₂-), 3.04 (1H, d, J = 10.4 Hz, -CH(ND₂)-), 7.10 - 7.36 (8H, m, ArH), 7.83 (2H, d, J = 7.2 Hz, ArH); ¹³C NMR ((+/-)-(1S,6R)-2,2-diphenyl-6-methylcyclohexylamine) (CDCl₃, 101 MHz): δ 20.93, 23.46, 35.08, 36.64, 40.85, 54.04, 67.30, 126.73, 126.95, 128.69, 129.01, 129.05, 132.04, 145.08, 150.21; HRMS ((+/-)-(1S,6R)-2,2-diphenyl-6-methylcyclohexylamine) Calcd for C₁₉H₂₃N [M⁺]: 265.18305; Found: 265.18372.

¹H NMR ((+/-)-(1S,6S)-2,2-diphenyl-6-methylcyclohexylamine) (CDCl₃, 400 MHz): δ 1.03 (3H, d, J = 6.8 Hz, -CH(CH₃)-), 1.11 (2H, br s, -NH₂), 1.27 - 1.42 (3H, m, -CH₂-CH₂-CH(CH₃)-, -CH₂-CHH-CH₂-CH(CH₃)-), 1.65 - 1.70 (1H, m, -CH₂-CHH-CH₂-CH(CH₃)-), 2.19 - 2.26 (1H, m, CH₂-CH(CH₃)-CH(NH₂)-), 2.34 - 2.41 (1H, m, -Ph₂C-CHH-CH₂-), 2.49 - 2.57 (1H, m, -Ph₂C-CHH-CH₂-), 3.94 - 3.95 (1H, m, -CH(CH₃)-CH(NH₂)-CPh₂-), 7.06 - 7.41 (10H, m, ArH); ¹³C NMR ((+/-)-(1S,6S)-2,2-diphenyl-6-methylcyclohexylamine) (CDCl₃, 101 MHz): δ 20.62, 23.12, 28.46, 28.52, 32.36, 52.03, 57.64, 126.43, 126.57, 127.60, 128.32, 129.43, 146.88, 149.32; HRMS ((+/-)-(1S,6S)-2,2-diphenyl-6-methylcyclohexylamine) Calcd for C₁₉H₂₃N [M⁺]: 265.18305; Found: 265.18367.

Anal. Calcd for C₁₉H₂₃N (mixture of all three compounds): C, 85.99; H, 8.74; N, 5.28. Found: C, 85.72; H, 8.73; N, 5.22.
(+/-)-(1S,6S)-N-Tosyl-2,2-diphenyl-6-methylcyclohexylamine. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.03 (3H, d, \(J = 6.8\) Hz), 1.05 – 1.15 (1H, m), 1.20 – 1.40 (1H, m), 1.41 – 1.50 (1H, m), 1.60 – 1.72 (1H, m), 1.90 – 2.05 (1H, m), 2.25 – 2.35 (1H, m), 2.34 (3H, s), 2.60 – 2.70 (1H, m), 4.30 (1H, d, \(J = 9\) Hz), 4.82 (1H, d, \(J = 9\) Hz), 6.80 – 7.35 (14H, m); \(^13\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 20.51, 22.35, 22.42, 32.93, 51.85, 62.60, 126.54, 126.79, 127.39, 127.78, 128.01, 129.04, 129.61, 130.07, 140.04, 142.89, 145.93, 147.78; HRMS Calcd for C\(_{26}\)H\(_{29}\)N\(_2\)O\(_2\)S: 419.19190; Found: 419.19243.

(+/-)-(1S,6R)-N-Tosyl-2,2-diphenyl-6-methylcyclohexylamine. See Figure A4.2 for an ORTEP diagram of this compound. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.02 (3H, d, \(J = 6.7\) Hz), 1.20 – 1.50 (2H, m), 1.55 – 1.65 (1H, m), 1.8 – 1.9 (1H, m), 2.10 – 2.20 (1H, m), 2.23 – 2.45 (2H, m), 2.4 (3H, s), 3.95 (1H, dd, \(J = 8.6, 10.4\) Hz), 4.90 (1H, d, \(J = 8.5\) Hz), 6.97 – 7.32 (14H, m); \(^13\)C NMR (CDCl\(_3\), 101 MHz): \(\delta\) 20.8, 21.5, 22.1, 35.4, 35.9, 40.6, 54.3, 67.6, 126.2, 126.4, 126.6, 127.9, 128.3, 128.4, 129.3, 130.1, 139.1, 142.3, 143.5, 147.9; MS (EI): \(m/z\) 419 (M\(^+\)). Anal. Calcd for C\(_{26}\)H\(_{29}\)N\(_2\)O\(_2\)S: C, 74.43; H, 6.97; N, 3.34. Found: C, 74.39; H, 7.13; N, 3.53.
(+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine and (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1R)-methylnaphthalenamine. Relative stereochemistry was assigned based on the crystal structure of (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine.

\[ \text{(+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine} \]

\[ \text{(+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1R)-methylnaphthalenamine}. \]

\[ \text{Relative stereochemistry was assigned based on the crystal structure of (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine.} \]

\[ \text{\textsuperscript{1}H NMR ((+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine) (CDCl\textsubscript{3}, 400 MHz):} \]

\[ \text{\textsuperscript{1}H NMR ((+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine) (CDCl\textsubscript{3}, 400 MHz):} \]

\[ \delta 0.87 (3H, d, J = 6.8 Hz, -CH-CH\textsubscript{3}), 1.52 – 1.61 (1H, m, Ar-CH\textsubscript{2}-CHH-CH(CH\textsubscript{3})-), 1.92 – 2.04 (2H, m, Ar-CH\textsubscript{2}-CHH-CH(CH\textsubscript{3})-, Ar-CH\textsubscript{2}-CHH-CH(CH\textsubscript{3})-), 2.47 (3H, s, Ar-CH\textsubscript{3}), 2.74 (2H, m, Ar-CH\textsubscript{2}-CH\textsubscript{2}-CH(CH\textsubscript{3})-), 4.10 – 4.14 (1H, m, ArCH(NHT\textsubscript{s})-CH(CH\textsubscript{3})-), 4.58 (1H, d, J = 7.6 Hz, -NH-Ts), 6.89 (1H, d, ArH), 7.04 (2H, d, ArH), 7.14 (1H, t, ArH), 7.34 (2H, d, ArH), 7.81 (2H, d, ArH); \textsuperscript{13}C NMR ((+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine) (CDCl\textsubscript{3}, 101 MHz):} \]

\[ \delta 17.54, 21.70, 26.02, 26.20, 34.58, 45.30, 58.48, 126.48, 127.27, 127.64, 129.12, 129.56, 129.84, 135.27, 137.13, 138.52, 143.46. \]

\[ \text{\textsuperscript{1}H NMR ((+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1R)-methylnaphthalenamine) (CDCl\textsubscript{3}, 400 MHz):} \]

\[ \delta 0.94 (3H, d, J = 6.8 Hz, -CH-CH\textsubscript{3}), 1.53 – 1.60 (1H, m, -CH\textsubscript{2}-CHH-CH(CH\textsubscript{3})-), 1.72 – 1.76 (1H, m, -CH\textsubscript{2}-CHH-CH(CH\textsubscript{3})-), 1.94 – 2.00 (1H, m, -CH-CH(CH\textsubscript{3})-CH\textsubscript{2}-), 2.46 (3H, s, Ar-CH\textsubscript{3}), 2.69 – 2.85 (2H, m, Ar-CH\textsubscript{2}-CH\textsubscript{2}-), 4.47-4.49 (2H, m, TsNH-CH\textsubscript{2}, TsNH\textsubscript{-}), 6.80 – 7.36 (6H, m, ArH), 7.80 (2H, d, J = 8.2 Hz, ArH); \textsuperscript{13}C NMR ((+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1R)-methylnaphthalenamine) \]
MS (mixture of diastereomers) (ESI): m/z (M-H) 314.2.

**Anal. Calcd for C\textsubscript{18}H\textsubscript{21}N\textsubscript{2}O\textsubscript{2}S (mixture of diastereomers):** C, 68.54; H, 6.71; N, 4.44.

**Found:** C, 68.44; H, 6.75; N, 4.44.

(+/-)-N-Napthoyl-(1S,6R)-2,2,6-trimethylcyclohexylamine and (+/-)-N-Napthoyl-(1S,6S)-2,2,6-trimethylcyclohexylamine. Relative stereochemistry was assigned based on the crystal structure of (+/-)-N-Napthoyl-(1S,6R)-2,2,6-trimethylcyclohexylamine.

\[^1\text{H}~\text{NMR}\ (+(/-)-N-Napthoyl-(1S,6R)-2,2,6-trimethylcyclohexylamine)\ (CDCl\textsubscript{3}, 400 MHz):\ \delta~0.91\ (3\text{H}, \text{s}, CH\textsubscript{3}-(CH\textsubscript{3})C-), \ 1.07\ (3\text{H}, \text{d}, J = 6.4 \text{Hz}, -CH-CH\textsubscript{3}), \ 1.03-1.24\ (1\text{H}, \text{m}), \ 1.13\ (3\text{H}, \text{s}, \text{CH}_3-(\text{CH}_3)\text{C}-), \ 1.43-1.57\ (5\text{H}, \text{m}), \ 1.77-1.86\ (1\text{H}, \text{m}), \ 3.75-3.82\ (1\text{H}, \text{m}, -(\text{CH}_3)_2\text{C-CH(NHTs)-CH(CH}_3)-), \ 5.67\ (1\text{H}, \text{d}, J = 10\text{Hz}, -\text{NH}-), \ 7.44-7.61\ (4\text{H}, \text{m}, \text{Ar}-\text{H}), \ 7.85-7.93\ (2\text{H}, \text{m}, \text{Ar}-\text{H}), \ 8.30-8.33\ (1\text{H}, \text{m}, \text{Ar}-\text{H}); \ ]^{13}\text{C} \ NMR (+(/-)-N-Napthoyl-(1S,6R)-2,2,6-trimethylcyclohexylamine) (CDCl\textsubscript{3}, 101 MHz): \delta~19.7, 19.8, 21.6, 30.1, 33.9, 35.1, 35.6, 40.4, 61.5, 124.2, 124.8, 125.7, 126.6, 127.2, 128.3, 130.3, 130.4, 133.8, 135.8, 169.7. \ MS (+(/-)-N-Napthoyl-(1S,6R)-2,2,6-trimethylcyclohexylamine) (EI): m/z 295 (M\textsuperscript{+});
\(^1\)H NMR ((\(+/–\))-N-Napthoyl-(1S,6S)-2,2,6-trimethylcyclohexylamine) (CDCl\(_3\), 400 MHz): \(\delta\) 1.05 (3H, d, J = 6.4 Hz, -CH-CH\(_3\)), 1.10 (3H, s, CH\(_3\)-(CH\(_3\))C-), 1.11 – 1.21 (1H, m), 1.15 (3H, s, CH\(_3\)-(CH\(_3\))C-), 1.28 – 1.38 (1H, m), 1.50 – 1.61 (4H, m), 2.18 – 2.21 (1H, m, -CH\(_2\)-CH(CH\(_3\))-CH-), 4.10 – 4.16 (1H, m, -CH\(_2\)-CH(NH-Napthoyl)- C(CH\(_3\))-), 5.80 – 6.00 (1H, m, -NH-Napthoyl), 7.45 – 7.63 (4H, m, Ar-H), 7.85 – 7.95 (2H, m, Ar-H), 8.26 – 8.33 (1H, m, Ar-H); \(^{13}\)C NMR ((\(+/–\))-N-Napthoyl-(1S,6S)-2,2,6-trimethylcyclohexylamine) (CDCl\(_3\), 101 MHz): \(\delta\) 19.3, 21.6, 25.5, 29.0, 29.1, 30.6, 34.1, 34.9, 57.6, 124.2, 124.9, 125.8, 126.6, 127.3, 128.3, 130.4, 130.4, 133.9, 136.0, 169.7; MS ((\(+/–\))-N-Napthoyl-(1S,6S)-2,2,6-trimethylcyclohexylamine) (EI): m/z 295 (M\(^+\)); Anal. Calcd for C\(_{20}\)H\(_{25}\)N0 (mixture of diastereomers): C, 81.31; H, 8.53; N, 4.74. Found: C, 80.93; H, 8.51; N, 4.74.

![](image)

(\(+/–\))-N-benzoyl-(1R,2R)-methylcyclohexylamine and (\(+/–\))-N-benzoyl-(1R,2S)-methylcyclohexylamine. Both (\(+/–\))-N-benzoyl-(1R,2R)-methylcyclohexylamine\(^{25}\) and (\(+/–\))-N-benzoyl-(1R,2S)-methyl cyclohexylamine\(^{26}\) are known compounds. The ratio of 2:1 anti to cis was determined from the \(^1\)H NMR of the reaction mixture following removal of the internal standard via column chromatography. The trans and cis products were isolated with a ratio of 8:1 respectively due to our inability to cleanly isolate the cis isomer along with the trans isomer. In light of this, it should be noted that the C-H activation reaction
proceeds to 75% conversion, and the lower isolated yield for the derivized products is likely also due to our inability to cleanly isolate the cis isomer. Only the peaks for the major diastereomer and the key diagnostic peaks for the minor diastereomer have been assigned in the $^1$H NMR spectrum. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.95 (d, J = 6.8 Hz, -CH$_3$ minor diast.), 1.00 (3H, d, J = 6.4 Hz, -CH$_3$ major diast.), 1.10 – 1.44 (4H, m), 1.65 – 1.84 (4H, m), 2.02 – 2.12 (1H, m), 3.66 – 3.76 (1H, m, -CH(NHBz)-), 4.24 – 4.32 (m, -(CH(NHBz)- minor diast.), 5.90 (1H, br d, -NHBz), 7.40 – 7.53 (3H, m, ArH), 7.74 – 7.79 (2H, m, ArH); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 19.3, 25.6, 25.9, 33.9, 34.5, 38.9, 54.6, 126.9 128.7, 131.4, 135.3, 167.1. HRMS Calcd for C$_{14}$H$_{19}$NO (mixture of diastereomers) [M$^+$]: 217.14666; Found: 217.14661. Anal. Calcd for C$_{14}$H$_{19}$NO: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.19; H, 8.82; N, 6.17.

(+/-)-(1S,2R)-2-Methyl-1-phenylcyclohexylamine.$^{11}$ The reported yield of 52 % for this compound is an NMR yield based on comparison of a well resolved doublet resulting from the methyl group of (+/-)-(1S,2R)-2-methyl-1-phenylcyclohexylamine to a well resolved signal generated by the internal standard 1,3,5-trimethoxybenzene. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.57 (3H, d, J = 6.8 Hz, -CH$_3$), 1.35 – 1.52 (4H, m), 1.55 – 1.68 (4H, m), 1.72 – 1.82 (2H, m), 1.95 – 2.06 (1H, m), 7.17 – 7.23 (1H, m, ArH), 7.30 – 7.36 (2H, m, ArH), 7.50 – 7.54 (2H, m, ArH); $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 16.0, 22.4, 26.5, 30.6, 40.0, 42.4, 57.4, 126.1, 126.7, 128.9, 150.0; MS (ESI): $m/z$ (M+H$^+$); HRMS Calcd for C$_{13}$H$_{19}$N [M$^+$]: 189.15175; Found: 189.15192.
5.5 References


CHAPTER SIX: CONCLUSIONS AND FUTURE WORK

6.1 Summary, conclusions and suggested future work

Two basic strategies were employed in this dissertation to further the field of group four metal catalyzed reactions involving amines. Firstly, the capabilities of existing catalyst systems were expanded upon by modifying reaction conditions or by taking advantage of their unique reactivity (chapters two and five); and secondly, attempts were made to generate more reactive and selective group four catalysts by the rational design and implementation of new N,O-chelating ancillary ligands (chapters three and four).

The exceptional reactivity of the titanium bis(N-2,6-diisopropylphenyl(phenyl)amidate) bis(dimethylamido) complex 1.1 towards alkynes in the presence of arylamines was elucidated and then expanded upon in the work described in chapter two. It was found that in conjunction with aniline and p-anisidine, this complex could be used to effect the hydroamination of various terminal alkynes, including TBDMS protected propargyl alcohol, at ambient temperature. Internal alkynes, and most importantly symmetrically substituted internal alkynes, could also be used as substrates. However, heating was required for these reactions to proceed within a reasonable amount of time. Hydroamination reactions involving the coupling of alkynes with p-anisidine provide a means of preparing PMP protected primary amines using relatively mild conditions, and the hydroamination of protected propargyl alcohols is particularly advantageous, as this methodology can then provide entry into useful synthetic precursors to compounds such as β-amino alcohols.
Preliminary investigations into the intramolecular hydroamination of aminoalkenes using commercially available Ti(NMe₂)₄ as the precatalyst showed that this system is capable of cyclizing primary aminoalkene substrates to form pyrrolidine and piperidine heterocyclic products with moderate to good yield. Based on the observation that Ti(NMe₂)₄ does not effect the cyclization of secondary amine bearing aminoalkene substrates, it is argued that this system requires the formation of an in situ generated catalytically active titanium imido species in order to proceed through a mechanism analogous to the titanium catalyzed hydroamination of alkynes. Although the substrate scope using Ti(NMe₂)₄ was found to be quite limited, this first reported example of neutral group four metal catalyzed alkene hydroamination laid the groundwork for all subsequent developments involving neutral group four catalysts for this transformation. Indeed the area has received a substantial amount of attention from a number of research groups since this breakthrough was reported in 2005.

The assessment of complex 1.1, in terms of intramolecular aminoalkene hydroamination catalysis revealed that this system is much less active than the precursor complex, Ti(NMe₂)₄. Based on these results it became apparent that substantial modification to the bis(amidate) precatalysts would have to be made in order to increase their reactivity to a level such that the efficient intramolecular hydroamination of a broad range of aminoalkene substrates could become feasible.

In chapter three a titanium compound, which was analogous to complex 1.1 but incorporated amidate ligands bearing electron withdrawing perfluorophenyl groups was synthesized and evaluated as a hydroamination precatalyst. The inclusion of electron withdrawing perfluorophenyl groups was expected to improve catalyst activity relative to
complex 1.1 by generating a more Lewis acidic metal center. Hydroamination screening experiments revealed that the perfluorophenyl variant of complex 1.1 is indeed more reactive; however, it was also found to be susceptible to decomposition under the conditions employed for catalysis. This was attributed to the addition of amine substrate to the perfluorinated aromatic ring of the amidate ligand via nucleophilic aromatic substitution. Based on these findings, it is evident that pefluoro-aromatic substituents are not suitable as electron withdrawing groups for complexes employed as hydroamination catalysts. The use of alternative electron withdrawing groups, such as trifluoromethyl, may achieve the desired effect while avoiding the aforementioned side reactivity.

The investigations using amide proligands derived from (-)-menthone were intended to explore whether chiral non-tethered amidate ligands could be used to generate group four bis(amidate) bis(amido) precatalysts capable of affecting the enantioselective cyclohydroamination of aminoalkenes. The chiral non-tethered amidate ligand framework attracted our attention due to the modular and simple way in which they can be produced, though a major drawback to this approach is the potential for more than one coordination isomer. For reasons described in chapter three, it was argued that one coordination isomer could predominate over the others, and this may make enantioselective catalysis using these systems possible. Indeed, enantioselectivity was achieved for the cyclohydroamination reaction, albeit with low enantiomeric excess. While the particular ligands described in chapter three are not worth pursuing, this work demonstrates that the non-tethered chiral amidate ligand motif can be used to generate chiral zirconium complexes capable of effecting enantioselective catalysis and may provide an alternative to the axially chiral tethered bis(amidate) ligand framework.
Future work to improve the performance of this system could include an investigation of how the steric and electronic properties of the substituent in the $R^1$ position influence reactivity and stereoselectivity (Figure 6.1).

![Figure 6.1. Potential modifications to the bis($N$-((1$R$,2$S$,5$R$)-2-isopropyl-5-Methyl-cyclohexyl)benzamidate) zirconium bis(dimethylamido) precatalyst.](Image)

This thesis also included the synthesis and characterization of the first titanium and zirconium bis(2-pyridonate) bis(amido) complexes which utilized either 2-pyridone or 6-\textit{tert}-butyl-3-phenyl-2-pyridone as proligands. For the reasons discussed in chapter four, this ligand set was devised as an alternative to the amidate ligand set in order to generate more reactive hydroamination catalysts. X-ray analysis indicated that the bis(2-pyridonate) titanium bis(dimethylamido) complex 4.1, the bis(6-\textit{tert}-butyl-3-phenyl-2-pyridonate) titanium bis(dimethylamido) complex 4.2, and the bis(6-\textit{tert}-butyl-3-phenyl-2-pyridonate) zirconium bis(dimethylamido) complex 4.3 are all monometallic and adopt a pseudoctahedral $O$-trans $C_2$ coordination geometry. The bis(2-pyridonate) zirconium bis(dimethylamido) complex could not be prepared as a discrete monomeric compound, and clearly demonstrates that there is a minimum level of steric bulk that these ligands must possess in order to form monomeric zirconium complexes.
Of the four compounds studied, zirconium complex 4.3 was the only one found to be an efficient catalyst for the cyclohydroamination reaction, and this complex exhibited reactivity comparable to the most active zirconium bis(amidate) bis(amido) complexes. Further substrate screening experiments demonstrated that complex 4.3 can affect the cyclization of more challenging aminoalkenes bearing unactivated internal C=C bonds; substrates which had previously been inert towards intramolecular hydroamination using the bis(amidate) system. This result is consistent with the greater accessibility to the metal center afforded by the 6-tert-butyl-3-phenyl-2-pyridonate ligand being more accommodating to substituents on the olefin.

Future work involving the 2-pyridone derived ligand set may include further investigation into how the steric and electronic properties of the substituents in the R³ and R⁶ positions of the pyridone ring influence catalysis (Figure 6.2). Based on reactivity trends recently observed with the amidate ligand set,⁵ a zirconium 2-pyridonate complex incorporating proligand 6.1 could be included in future structure/activity studies of these complexes. In addition, the incorporation of an electron withdrawing substituent in either the R⁴ or the R⁵ position may be of interest.

**Figure 6.2.** Bis(2-pyridonate) titanium and zirconium bis(amido) complexes.
The discovery that titanium(IV) and zirconium(IV) complexes catalyze the α C-H bond activation/intramolecular aminoalkylation of 6-heptenylamines has shed light on a unique transformation that has the potential to be developed into an efficient, atom economical new methodology which could ultimately be applied to the synthesis of α-chiral amines. Among the complexes tested for α functionalization reactivity, Ti(NMe₂)₄ proved to be the most effective catalyst over all; while the zirconium 2-pyridonate complex 4.3 was found to be the next most effective, and most effective of the zirconium complexes. It should be noted that an important advantage associated with the 2-pyridonate system is that the ancillary ligands provide a handle for modifying reactivity and selectivity. None of the bis(amidate) complexes tested were found to catalyze the α functionalization reaction. Through a brief substrate scope analysis it was shown that this reactivity is not exclusive to the substrate initially tested, and in fact other substrates undergo cyclization to form the respective cyclohexylamine derivatives more readily. More detailed mechanistic investigation, including kinetic studies as well as the characterization of reaction intermediates is required for a better understanding of this transformation. Additional catalyst structure / activity studies coupled with a more comprehensive substrate scope analysis should provide valuable insight into this intriguing reaction.

The most significant work described in this dissertation contributes to the understanding of group four metal catalyzed reactions by illuminating some previously unknown reactivity associated with titanium and zirconium. Namely, it was established that neutral titanium(IV) complexes can be used as catalysts for the intramolecular hydroamination of aminoalkenes; and also that both titanium and zirconium complexes
can potentiate the conversion of 6-heptenylamines to aminocyclohexane derivatives through an α C-H bond activation/alkene insertion type process. If catalyst systems capable of efficiently and selectively promoting these transformations with a wide range of substrates in an intermolecular fashion could be developed, they would serve as powerful methodologies which could ultimately be applied to the synthesis of a multitude of highly sought after nitrogen containing fine chemicals. The work in this thesis involving catalyst development has further demonstrated the dramatic influence that ligand structure can have on reactivity as well as provided some alternative avenues for future research.
6.2 References


APPENDIX

Tables of crystallographic parameters, ORTEP diagrams, selected $^1$H and $^{13}$C NMR spectra:

Representative $^1$H and $^{13}$C NMR spectra for the different classes of compounds synthesized in chapters two, three, four and five can be found in the following pages.
Table A1: Crystallographic parameters for complex 3.1, 4.1, 4.2, and 4.3.

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**Figure A1.** ORTEP depiction of (+/-)-(1S,6R)-N-Tosyl-2,2-diphenyl-6-methylcyclohexylamine. Elipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.

**Figure A2.** ORTEP depiction of (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine. Elipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.
Figure A3. ORTEP depiction of N-Napthoyl-(1S,6R)-2,2,6-trimethyl-cyclohexylamine. Elipsoids are drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.
Figure A4. $^1$H NMR spectrum of (4-methoxy-phenyl)-phenethyl-amine.

Figure A5. $^{13}$C APT NMR spectrum of (4-methoxy-phenyl)-phenethyl-amine.
Figure A6. $^1$H NMR spectrum of (3,3-dimethyl-butyl)-(4-methoxy-phenyl)-amine.

Figure A7. $^{13}$C APT NMR spectrum of (3,3-dimethyl-butyl)-(4-methoxy-phenyl)-amine.
Figure A8. $^1$H NMR spectrum of (1,2-diphenyl-ethyl)-(4-methoxy-phenyl)-amine.

Figure A9. $^{13}$C APT NMR spectrum of (1,2-diphenyl-ethyl)-(4-methoxy-phenyl)-amine.
Figure A10. $^1$H NMR spectrum of (4-methoxy-phenyl)-(1,3,3-trimethyl-butyl)-amine.

Figure A11. $^{13}$C APT NMR spectrum of (4-methoxy-phenyl)-(1,3,3-trimethyl-butyl)-amine.
Figure A12. $^1$H NMR spectrum of [3-(tert-butyl-dimethyl-silanyloxy)-propyl]-(4-methoxy-phenyl)-amine.

Figure A13. $^{13}$C APT NMR spectrum of [3-(tert-butyl-dimethyl-silanyloxy)-propyl]-(4-methoxy-phenyl)-amine.
Figure A14. $^1$H NMR spectrum of [1-benzyl-2-(tert-butyl-dimethyl-silyloxy)-ethyl]-(4-methoxy-phenyl)-amine.

Figure A15. $^{13}$C APT NMR spectrum of [1-benzyl-2-(tert-butyl-dimethyl-silyloxy)-ethyl]-(4-methoxy-phenyl)-amine.
Figure A16. $^1$H NMR spectrum of 2-amino-3-phenyl-propan-1-ol.

Figure A17. $^{13}$C APT NMR spectrum of 2-amino-3-phenyl-propan-1-ol.
Figure A18. $^1$H NMR spectrum of the hydrochloride salt of 1-methyl-2-phenyl-ethylamine.

Figure A19. $^{13}$C APT NMR spectrum of the hydrochloride salt of 1-methyl-2-phenyl-ethylamine.
Figure A20. $^1$H NMR spectrum of 2,4-$N_1,N_3$-tetraphenyl-butane-1,3-diamine.

Figure A21. $^{13}$C APT NMR spectrum of 2,4-$N_1,N_3$-tetraphenyl-butane-1,3-diamine.
Figure A22. $^1$H NMR spectrum of (2-benzyl-3-phenyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine.
Figure A23. $^{13}$C APT NMR spectrum of (2-benzyl-3-phenyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine.
Figure A24. $^1$H NMR spectrum of 2-methyl-4,4-diphenylpyrrolidine.

Figure A25. $^{13}$C APT NMR spectrum of 2-methyl-4,4-diphenylpyrrolidine.
Figure A26. $^1$H NMR spectrum of 2-methyl-4,4-diphenylpiperidine.

Figure A27. $^{13}$C NMR spectrum of 2-methyl-4,4-diphenylpiperidine.
Figure A28. $^1$H NMR spectrum of N-benzoyl-2-methyl-4,4-dimethylpyrrolidine.

Figure A29. $^{13}$C APT NMR spectrum of N-benzoyl-2-methyl-4,4-dimethylpyrrolidine.
Figure A30. $^1$H NMR spectrum of 2-benzyl-4,4-diphenyl-pyrrolidine.

Figure A31. $^{13}$C APT NMR spectrum of 2-benzyl-4,4-diphenyl-pyrrolidine.
Figure A32. $^1$H NMR spectrum of 2,2-diphenyl-6-heptenylamine.

Figure A33. $^{13}$C APT NMR spectrum of 2,2-diphenyl-6-heptenylamine.
Figure A34. $^1$H NMR spectrum of 2,5-dimethyl-3,3-diphenyl-pyrrolidine (mixture of diastereomers).
Figure A.35. 13C APT NMR spectrum of 2,5-dimethyl-3,3-diphenyl-pyrrolidine (mixture of diastereomers).

II-117-JB (3) CDC13 C1+C2
II-113-JB (2) C1 CDC13

Figure A36. 1H NMR spectrum of trans-2,5-dimethyl-3,3-diphenyl-pyrrolidine.
Figure A37. $^{13}$C APT NMR spectrum of trans-2,5-dimethyl-3,3-diphenylpyrrolidine.
1H observe $P_1$=13.50us at 0db ref. to CDC13 at 7.27 ppm.

Current Data Parameters
NAME J3313
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Data 20050922
Time 7.56
INSTRUM av300
PROBHD 5 mm GNP 1H/13
POLPROG zg30
T0 15384
SOLVENT CDC13
NS 26
DS 2
SN 3742.5 Hz
FORES 0.228425 Hz
AG 2.189524 sec
RG 143.7
DW 133.600 usec
DE 5.00 usec
TE 100.0 K
DI 10000000 sec

--- CHANNEL f1 ---
H2C 1H
P1 13.50 usec
PL1 0.00 dB
SF01 300.131000000 MHz

F2 - Processing parameters
SI 32768
SF 300.130000000 MHz
WON 0
SSB 0
LB 0.10 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 20.00 cm
CY 8.00 cm
F1P 10000 ppm
F1 3001.30 Hz
F2P -0.500 ppm
F2 -150.07 Hz
PRMC 0.5250 ppm
H2H 157.5685 Hz
Figure A39. $^1$H NMR spectrum of $N$-(2,6-dimethylphenyl)-1,2-methyl-phenylethylamine

Figure A40. $^{13}$C NMR spectrum of $N$-(2,6-dimethylphenyl)-1,2-methyl-phenyl ethylamine.
Figure A41. $^1$H NMR spectrum of $N$-(2,6-dimethylphenyl)-1-methylpentylamine.

Figure A42. $^{13}$C NMR spectrum of $N$-(2,6-dimethylphenyl)-1-methylpentylamine.
Figure A43. $^1$H NMR spectrum of a (2:1) mixture of $N$-benzylhexylamine, and $N$-benzyl-1-methylpentyamine.
Figure 4.4. 13C NMR spectrum of a (2:1) mixture of N-benzylhexylamine, and N-benzyl-1-methylpentylamine.
Figure A45. $^1$H NMR spectrum of $N$-(2,6-diisopropylphenyl)-2-($N$-2,2-diphenylpentylamino)-3,4,5,6-tetrafluoro-benzamide compound 3.4.
Figure A46. $^{13}$C NMR spectrum of $N$-(2,6-diisopropylphenyl)-2-($N$-2,2-diphenylpentylamino)-3,4,5,6-tetrafluoro-benzamide compound 3.4.
Figure A47. $^1$H NMR spectrum of Y-(2,6-diphenylphenyl)-2-(N2,2,6-
diphenylbenzamide)-3,4,5,6-tetrafluorophenylaminio)-3,4,5,6-tetrafluoro-
benzamide compound 34.
Figure A48. $^1$H NMR spectrum of 6-tert-butyl-3-phenyl-2-pyridone.

Figure A49. $^{13}$C APT NMR spectrum of 6-tert-butyl-3-phenyl-2-pyridone.
Figure A50. $^1$H NMR spectrum of bis(2-pyridonate) titanium bis(dimethylamido) complex 4.1.

Figure A51. $^{13}$C APT NMR spectrum of bis(2-pyridonate) titanium bis(dimethylamido) complex 4.1.
Figure A52. $^1$H NMR spectrum of bis(6-tert-butyl-3-phenyl-2-pyridonate) titanium bis(dimethylamido) complex 4.2.
Figure A53. $^{13}$C APT NMR spectrum of bis(6-tert-butyl-3-phenyl-2-pyridonate) titanium bis(dimethylamido) complex 4.2.
\textbf{Figure A54.} \textsuperscript{1}H NMR spectrum of bis(6-tert-butyl-3-phenyl-2-pyridonate) zirconium bis(dimethylamido) complex 4.3.

\textbf{Figure A55.} \textsuperscript{13}C APT NMR spectrum of the bis(6-tert-butyl-3-phenyl-2-pyridonate) zirconium bis(dimethylamido) complex 4.3.
Figure A56. $^1\text{H}$ NMR spectrum of 2-cyclohex-2-enyl-2,2-diphenyl-ethylamine in $d_6$-benzene.

Figure A57. $^{13}\text{C}$ NMR spectrum of 2-cyclohex-2-enyl-2,2-diphenyl-ethylamine in $d_6$-benzene.
Figure A58. $^1$H NMR spectrum of (+/−)-(S,S)-3, 3-diphenyl-1-(p-toluenesulfonyl)-octahydro-indole.

Figure A59. $^{13}$C APT NMR spectrum of (+/−)-(S,S)-3, 3-diphenyl-1-(p-toluenesulfonyl)-octahydro-indole.
Figure A60. $^1$H NMR spectrum of 2-ethyl-4,4-diphenyl-pyrrolidine.

Figure A61. $^{13}$C APT NMR spectrum of 2-ethyl-4,4-diphenyl-pyrrolidine.
Figure A62. $^1$H NMR spectrum of 1,1-dideutero-2,2-diphenyl-butylamine.

Figure A63. $^{13}$C APT NMR spectrum of 1,1-dideutero-2,2-diphenyl-butylamine.
Figure A64. $^1$H NMR spectrum of 2-(3-butene)benzylamine.

Figure A65. $^{13}$C APT NMR spectrum 2-(3-butene)benzylamine.
Figure A66. $^1$H NMR spectrum of (+/-)-$N$-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine.

Figure A67. $^{13}$C APT NMR spectrum of (+/-)-$N$-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine.
Figure A69. $^1$H NMR spectrum of (+/-)-$N$-Tosyl-1,2,3,4-tetrahydro-(2R,1R)-methylnaphthalenamine.

Figure A69. $^{13}$C APT NMR spectrum of (+/-)-$N$-Tosyl-1,2,3,4-tetrahydro-(2R,1R)-methylnaphthalenamine.
Figure A70. $^1$H NMR spectrum of 1-phenyl-hept-6-enylamine.

Figure A71. $^{13}$C APT NMR spectrum of 1-phenyl-hept-6-enylamine.
Figure A72. $^1$H NMR spectrum of (+/-)-(1S,2R)-2-methyl-1-phenylcyclohexylamine.

Figure A73. $^{13}$C APT NMR spectrum of (+/-)-(1S,2R)-2-methyl-1-phenylcyclohexylamine.
Figure A74. $^1$H NMR spectrum of (+/-)-(1S,6R)-2,2-diphenyl-6-methylcyclohexyl-amine.

Figure A75. $^{13}$C APT NMR spectrum of (+/-)-(1S,6R)-2,2-diphenyl-6-methylcyclohexyl-amine.
Figure A76. $^1$H NMR spectrum of (+/-)-(1S,6S)-2,2-diphenyl-6-methylcyclohexylamine.

Figure A77. $^{13}$C APT NMR spectrum of (+/-)-(1S,6S)-2,2-diphenyl-6-methylcyclohexylamine.
Figure A78. $^1$H NMR spectrum of 2-methyl-6,6-diphenyl-azepane.

Figure A79. $^{13}$C APT NMR spectrum of 2-methyl-6,6-diphenyl-azepane.
Figure A80. $^1$H NMR spectrum of (+/-)-(1S,6S)-N-tosyl-2,2-diphenyl-6-methylcyclohexylamine.

Figure A81. $^{13}$C APT NMR spectrum of (+/-)-(1S,6S)-N-tosyl-2,2-diphenyl-6-methylcyclohexylamine.
Figure A82. $^1$H NMR spectrum of $(+/-)-(1S,6R)$-N-tosyl-2,2-diphenyl-6-methylcyclohexylamine.

Figure A83. $^{13}$C APT NMR spectrum of $(+/-)-(1S,6R)$-N-tosyl 2,2-diphenyl-6-methylcyclohexylamine.
Figure A84. $^1$H NMR spectrum of 2,2-dimethyl-hept-6-enylamine.

Figure A85. $^{13}$C APT NMR spectrum of 2,2-dimethyl-hept-6-enylamine.
Figure A86. $^1$H NMR spectrum of (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine and (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1R)-methylnaphthalenamine.

Figure A87. $^{13}$C NMR spectrum of (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine and (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1R)-methylnaphthalenamine.
Figure A88. $^1$H NMR spectrum of (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine.

Figure A89. $^{13}$C APT NMR spectrum of (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1S)-methylnaphthalenamine.
Figure A90. $^1$H NMR spectrum of (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1R)-methylnaphthalenamine.

Figure A91. $^{13}$C NMR spectrum of (+/-)-N-tosyl-1,2,3,4-tetrahydro-(2R,1R)-methylnaphthalenamine.
Figure A92. $^1$H NMR spectrum of 6-heptenylamine.

Figure A93. $^{13}$C APT NMR spectrum of 6-heptenylamine.
Figure A94. $^1$H NMR spectrum of complex 1.1.

Figure A95. $^{13}$C NMR spectrum of complex 1.1.