EARLY TRANSITION METAL COMPLEXES OF PYRIDINE DERIVATIVES:
APPLICATIONS IN THE CATALYTIC SYNTHESIS OF AMINES AND
N-HETEROCYCLES

by

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Abstract

The work described in this thesis focuses on the development of pyridine-derived group 4 and 5 complexes for application in the catalytic synthesis of selectively substituted amines. Two different catalytic alkene hydrofunctionalization reactions were targeted: hydroamination and hydroaminoalkylation. Respectively, these transformations provide atom-economical strategies for the formation of new C–N and C–C bonds on amines, using simple alkenes as the alkylating agents.

A series of bulky mono(2-aminopyridinate)tris(dimethylamido)titanium complexes with varying steric parameters were synthesized and explored for intramolecular hydroamination reactivity using aminoalkene substrates. A titanium catalyst capable of room-temperature hydroamination reactivity was identified for the synthesis of gem-disubstituted 5- and 6-membered-ring products. This catalyst has good breadth of reactivity, including the challenging 7-membered-azepane ring formation and hydroamination with internal alkenes. A catalytically active 2-aminopyridinate-supported imido titanium complex was prepared, and reactivity investigations of this complex suggest that this reaction proceeds via an intermediate imido [2+2] cycloaddition pathway.

Various 3-substituted-2-pyridonate ligands were synthesized and examined as ancillary ligands for targeting chemoselectivity for intramolecular hydroaminoalkylation over hydroamination. Systematic ligand screening studies showed that bis(3-phenyl-2-pyridonate)bis(dimethylamido)titanium complex is selective for hydroaminoalkylation over hydroamination. This is the first catalyst that can selectively α-alkylate primary aminoalkenes to access both 5- and 6-membered-cycloalkylamines with good substrate-dependent diastereoselectivity. Mechanistic and stoichiometric experiments using this complex support the
involvement of a bimetallic imido species in the reaction. Notably, a titanium(III) species was isolated during these investigations. Reliable synthesis of this titanium(III) complex and examination of its reactivity showed that it is not active for hydroaminoalkylation.

Varying combinations of mixed 2-pyridonate/alkyl/amido/chloro tantalum complexes were targeted to expand the substrate scope for intermolecular hydroaminoalkylation. The synthesis of mono(2-pyridonate)/alkyl/chloro tantalum complex was unsuccessful. Instead, bis(2-pyridonate)tantalum alkyl complexes were formed. While these complexes showed hydroaminoalkylation reactivity for terminal alkenes, their thermal and light sensitivity presents difficulty for synthetic application. The design and synthesis of a mixed 2-pyridonate-Ta(NMe$_2$)$_3$Cl provided a sterically accessible metal center for the hydroaminoalkylation of sterically demanding disubstituted alkenes. This complex is the first effective precatalyst for the $\alpha$-alkylation of unprotected secondary amines using unactivated (E)- and (Z)-internal alkenes without C=C bond isomerization.
Preface

I, in consultation with my supervisor Dr. Laurel Schafer, designed all of the experiments disclosed in this thesis. I carried out all of these experiments except for the specific instances mentioned per chapter below. The solid-state molecular data presented herein were collected by Jacky Yim or Scott Ryken while I performed the final refinements. I wrote all of the following manuscripts entirely with suggestions and input from Dr. Laurel Schafer.

A version of chapter 2 has been published: Chong, E.; Qayyum, S.; Schafer, L. L. Organometallics 2013, 32, 1858. Vanessa Tam, an undergraduate student, synthesized some of the aminoalkene substrates under my supervision. Sadaf Qayuum from Dr. Rhett Kempe’s research group prepared the 2-aminopyridine ligands.

A portion of chapter 3 has been published: Chong, E.; Schafer, L. L. Org. Lett. 2013, 15, 6002. Dr. Brian Patrick modeled the disorders in the solid-state molecular structures of 97 and 98. Wei Xue from Dr. Pierre Kennepohl’s research group collected the EPR spectroscopic data of 95.

A portion of chapter 4 has been published: Chong, E.; Brandt, J. W.; Schafer, L. L. J. Am. Chem. Soc. 2014, 136, 10898. Jason Brandt assisted in the catalyst screening experiments (Scheme 4.18), and in the preparation of some substrates for use in intermolecular hydroaminoalkylation.
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List of Symbols and Abbreviations

Å                  angstrom (10^{-10} m)
anal.               analysis
Ap                 2-aminopyridinate
Ar                 aryl
avg                average
BARF               [B[3,5-(CF_3)_2C_6H_3]_4]^-
BINAP              2,2’-bis(diphenylphosphino)-1,1’-binaphthyl
Bn                 benzyl
br                 broad
nBu, tBu           normal butyl, tert-butyl
Bz                 benzoyl
calcd              calculated
cat.               catalyst, or catalytic
C                  Celcius
cm                 centimeter(s)
cod                1,5-cyclooctadiene
coe                cyclooctene
cond               condition
conv               conversion
Cp                 cyclopentadienyl
Cp*                pentamethycyclopentadienyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>°</td>
<td>degree</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>d</td>
<td>deuterium</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DG</td>
<td>directing group</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomer ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>EPR</td>
<td>electron paramagnetic resonance</td>
</tr>
<tr>
<td>eq</td>
<td>equation</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>η</td>
<td>hapticity</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>g</td>
<td>gram(s), or proportionality factor</td>
</tr>
<tr>
<td>GC</td>
<td>gas chromatography</td>
</tr>
<tr>
<td>gem</td>
<td>geminal</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HA</td>
<td>hydroamination</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>HAA</td>
<td>hydroaminoalkylation</td>
</tr>
<tr>
<td>Ind</td>
<td>indenyl</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>$J$</td>
<td>coupling constant</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>denticity</td>
</tr>
<tr>
<td>$K_a$</td>
<td>acid dissociation constant</td>
</tr>
<tr>
<td>L</td>
<td>ligand</td>
</tr>
<tr>
<td>LH</td>
<td>protio-ligand</td>
</tr>
<tr>
<td>M</td>
<td>metal, mol/L</td>
</tr>
<tr>
<td>$M^+$</td>
<td>molecular ion</td>
</tr>
<tr>
<td>$\mu$</td>
<td>bridging ligand, or absorption coefficient</td>
</tr>
<tr>
<td>$\mu$L</td>
<td>microliter(s)</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>$m/z$</td>
<td>mass-to-charge ratio</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>Mes</td>
<td>mesityl</td>
</tr>
<tr>
<td>mg</td>
<td>milligram(s)</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mL</td>
<td>milliliter(s)</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole(s)</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
</tbody>
</table>
mol %  mole percent
MS     mass spectrometry
HMDS   hexamethyldisilazane
NBS    N-Bromosuccinimide
n.d.   not determined
n.r.   no reaction
NMR    nuclear magnetic resonance
ORTEP Oak Ridge thermal ellipsoid plot
p      -log (as in pKₐ)
p      para
Ph     phenyl
PMP    para-methoxyphenyl
ppm    parts per million
nPr, iPr normal propyl, isopropyl
py     pyridine
q      quartet
R      organic substituent
ref.   reference
reflns reflections
rt     room temperature
s      singlet
Σ      summation
t      triplet
$t$ time

$T$ temperature

TBS tert-butyldimethylsilyl

THF tetrahydrofuran

Tf trifluoromethanesulfonyl

TMS trimethylsilyl

Ts toluenesulfonyl

X halide, or heteroatom
Acknowledgements

First and foremost, I would like to thank my supervisor, Dr. Laurel Schafer, for giving me the opportunity to be a part of her research group. Your support and mentorship have significantly contributed to my growth as a chemist. The skills that I have gained by being a member of the Schafer group are invaluable and will certainly help in my career path.

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Finally, a deep thank you to my family, and Sharon Han for their love, support, and encouragement. I could not have done this without you.
This thesis is dedicated to my parents,

Dr. Jay Chong and Mi-Ja Park,

and to my brothers,

Lee Chong and Michael Chong.
Chapter 1: Pyridine-derived chelates as supporting ligands for group 4 and 5 chemistry

1.1 Introduction

Amines and N-heterocycles are essential structural components to many biologically active compounds in the pharmaceutical and agrochemical industries.\textsuperscript{1,2} Hence, the fundamental research in the development of catalytic bond forming processes for the efficient and sustainable synthesis of selectively substituted amines is of vital significance. As a part of our research program on the catalytic synthesis of amines using atom-economic bond forming reactions,\textsuperscript{3,4} the Schafer group is investigating hydroamination\textsuperscript{5,6} and hydroaminoalkylation\textsuperscript{7} reactions (Scheme 1.1). Hydroamination is the addition of an N–H bond across a C=C bond,\textsuperscript{5,6} whereas hydroaminoalkylation is the addition of a C–H bond adjacent to nitrogen across a C=C bond.\textsuperscript{7} These transformations provide a direct catalytic route to new C–N or C–C bonds, respectively. To this end, we are interested in further developing new and improved catalysts for these synthetically valuable hydrofunctionalization reactions using earth-abundant early transition metals of low toxicity.

\textbf{Scheme 1.1} Atom-economic synthesis of amines: hydroamination and hydroaminoalkylation
The design and use of supporting ligands on early transition metals are crucial for generating effective catalyst-controlled bond formations (*vide infra*). With proper modification of the ligand environment to influence the steric and electronic properties of the resulting complex, the desired reactivity and selectivity of a targeted reaction can be achieved. While the focus of this thesis is towards applications in catalytic amine synthesis, many of the previous studies on early transition metal catalyst development, including the pyridine derivatives, which are the primary topic of this work, have been devoted to alkene polymerization.\(^8\)-\(^{20}\) Thus, polymerization catalysis will be used as an example to highlight the importance of ligand design for targeting improvements in catalytic activity and reaction selectivity. The ligand innovation in polymerization catalysis is an important aspect in organometallic chemistry that can be translated into other early transition metal catalyzed reactions.

One of the milestones in early transition metal catalysis is the discovery of Ziegler-Natta system in the 1950s, for the synthesis of carbon-containing polymers from the polymerization of ethylene and propylene (Scheme 1.2).\(^{21\text{-}27}\) This work was ground-breaking in that earth-abundant and relatively non-toxic titanium metal (TiCl\(_3\) or TiCl\(_4\)) could be used in trace amounts, in combination with an aluminum organometallic reagent (Al(C\(_2\)H\(_5\))\(_3\)), to synthesize stereo-defined linear polymers at low pressures and temperatures. For their work, Ziegler and Natta were awarded the Nobel Prize in Chemistry in 1963, and their research has had a tremendous

\[\text{Scheme 1.2} \quad \text{Early examples of polymer synthesis by Ziegler and Natta for (a) polyethylene; (b) polypropylene}\]
impact in our daily lives. The polymer industry has a global market of multi-billions of dollars and produces multi-millions of tons of polymers per year. This discovery highlights the importance and impact of early transition metal catalysts and the potential benefits that can arise from their applications in industry.

Also in the 1950s, a bis(cyclopentadienyl)iron complex was reported by Pauson that displayed remarkable air and thermal stability, including resistance to hydrochloric acid.\textsuperscript{28-33} The discovery of ferrocene was revolutionary in organometallic chemistry and, following the concomitant synthesis of the first group 4 metallocene (Cp\textsubscript{2}ZrBr\textsubscript{2}, 1) by Wilkinson,\textsuperscript{34} investigations of cyclopentadienyl (Cp) based complexes have prevailed for early transition metal complexes, especially in the field of polymerization catalysis (Figure 1.1).\textsuperscript{8-13,35} In

Figure 1.1 Selected transition metal complexes for alkene polymerization
addition, the synthetic community has benefited from the use of Cp-based reagents in organic synthesis. For example, Cp₂TiMe₂ (Petasis reagent) has been used for olefination reactions, which transform carbonyl groups to terminal alkenes.⁶⁶,³⁷

The impact of ligand design on early transition metal catalyzed reactions is tremendous. For example, among the most successful catalysts for alkene polymerization are ansa-metallocene complexes.¹⁴-¹⁶ Brintzinger and Ewen’s report on the modification of the Cp-ligands by tethering through a bridging group, forming a rigid, chelating C₂-symmetric structure (2), was a breakthrough for a precise control over the stereochemistry in the synthesis of polypropylene. Notably, the C₂-symmetric ligand feature of 2 was further utilized by Buchwald for Ti-catalyzed asymmetric hydrogenation of imines to access chiral amine products.⁴²-⁴⁵ In 1990, Bercaw reported the development of ansa-cyclopentadienyl-amido ligand set (3) for a single-component organoscandium system for alkene polymerization.⁴⁶,⁴⁷ The introduction of a monoanionic N donor into the coordination sphere of the metal, as well as the open nature of the active site from the ligand design, provided well-controlled reactivity. The titanium variant of 3 was synthesized by Okuda shortly thereafter,⁴⁸ and these constrained geometry group 4 catalysts, such as [Ti(η⁵-C₅Me₄SiMe₂NtBu)Me]⁺, have become industrially important as single-site olefin polymerization catalysts, which have been patented by Dow Chemical and Exxon Chemical.¹⁷,¹⁸

The use of a κ²-N,N-chelating acetamidinate ligand in combination with a pentamethylcyclopentadienyl (Cp*) ligand on zirconium (4), developed by Sita, has also been successful for stereoselective polymerization of 1-hexene.⁴⁹

While Cp ligand frameworks have been utilized successfully, one of its limitations is that the features of the ligand cannot be easily tuned or modified. However, the incorporation of an N donor, such as in 3 and 4, showcases robust metal-ligand interactions that arise from using a hard
donor in combination with an electrophilic metal center.\textsuperscript{50} One notable example that was discovered in the search of “post-metallocene” catalysts\textsuperscript{19,20,51} with easily modifiable and tunable ligand frameworks is the $N,N$-chelating $\alpha$-diimine ligand set (5) reported by Brookhart (Figure 1.1).\textsuperscript{52} The bulky nature and the highly electrophilic metal center generated by the electron-withdrawing $N,N$-chelating ligands were crucial in converting alkenes into high molar mass polymers, and this catalyst system has been commercialized as Versipol by Dupont.\textsuperscript{51} Other chelating ligands of hard donor atoms have also seen success, namely the $N,O$-chelating bis(phenoxylimine) ligands (6) employed on group 4 metals, developed by Fujita from Mitsui Chemicals\textsuperscript{53} and the Coates research group\textsuperscript{54,55} for highly effective stereoselective polymerization of ethylene and propylene. These early “post-metallocene” catalyst development efforts underline the importance of ligand design, with such $N,N$- and $N,O$-chelating systems, for tuning the reactivity of the metal center in the synthesis of polymers. Most importantly, the fundamental understanding derived from these early catalyst development efforts can inform the catalytic synthesis of amines.

With respect to $N,O$-chelating ligand motifs, the Schafer group investigates monoanionic $\kappa^2$-1,3-chelating ligand systems on early transition metals that form 4-membered metallacycles with tight bite angles (Figure 1.2, left). In particular, amidates,\textsuperscript{56} ureates\textsuperscript{57,58} and, more recently, 2-pyridonates\textsuperscript{59,60} have been applied as effective ligands for catalysts for the atom-economic

![Figure 1.2 N,O-Chelating ligands (left); other 2-substituted pyridine derived chelates (right)](image-url)
The synthesis of amines by hydroamination and hydroaminoalkylation (Scheme 1.1). The asymmetric binding modes offered by these N,O-chelating ligands are appealing for potential application in catalysis due to their known hemilability between the κ²-N,O-bidentate and κ¹-O-monodentate coordination modes (Figure 1.3). This fluxionality allows for an open coordination site to be readily generated at the metal center to promote reactivity. Furthermore, these N,O-chelating ligands are very modular and tunable, as they can be accessed directly or synthesized in few steps from commercially available reagents, offering flexibility in tuning the steric and electronic properties of the ligand in catalyst design. Among these three N,O-chelating ligands (Figure 1.2, left), the pyridine-derived 2-pyridonate was newly established in 2009 as a suitable ligand for use in catalytic amine synthesis.

![Figure 1.3 Hemilability of N,O-chelates on early transition metals](image)

Unlike the amidates and ureates that have R² substituents near the metal center (Figure 1.2, left), the 2-pyridonates and the related 2-substituted pyridine derivatives are particularly attractive because of the increased accessibility to the metal center provided by having the substituents tied back in a 6-membered-pyridine backbone (Figure 1.2, right). This accessibility to the metal center is especially pronounced at the N donor side of the bidentating chelate. The pyridine framework offers aromaticity that may introduce a more facile hemilability and, consequently, improved accessibility to the reactive site during the reaction. However, a survey of the literature shows that these pyridine derivatives have been mainly used in the development
of catalysts for polymer synthesis,\textsuperscript{19,20} and are relatively unexplored for their application in amine synthesis (\textit{vide infra}).\textsuperscript{59,60,65-69} Due to the potential structural variations of the pyridine chelate framework (Figure 1.2), my research has focused on the synthesis and reactivity investigations of group 4 and/or 5 metal complexes with 2-aminopyridinates (Chapter 2) and 2-pyridonates (Chapter 3 and 4). In this study, pyridine derivatives with hard donor atoms (O and N) were used. More polarizable donors (S and P) of 2-thiopyridonate or 2-pyridylphosphine ligands are known but have not been explored here.

1.2 Related pyridine derived $\kappa^2$-1,3-chelating ligands on group 4 and 5

In this section 1.2, an overview of $\kappa^2$-1,3-chelating pyridine-derived group 4 and 5 metal complexes and their synthetic applications are discussed. From the early development stages of 2-aminopyridinate and 2-pyridonate ligands to their recent emerging use in catalytic amine synthesis are presented.\textsuperscript{59,60,65-69}

1.2.1 2-Thiopyridonate and 2-pyridylphosphine ligands

Among the four pyridine derivatives shown previously in Figure 1.2, the use of 2-thiopyridinate and 2-pyridylphosphine ligands on early transition metals is rare. Few 2-thiopyridonate early transition metal complexes have been reported with few applications in polymer synthesis (Figure 1.4, 7 and 8).\textsuperscript{70-78} These existing reports are often accompanied by the synthesis of related 2-pyridonate complexes (\textit{vide infra}). The 2-pyridylphosphine derivatives have been utilized in the coordination of late transition metals.\textsuperscript{79-84} For example, a ruthenium complex 9 has been used recently as a catalyst for the \textit{anti}-Markovnikov hydration of alkynes to form aldehydes.\textsuperscript{85,86} However, to date, there has been no reported use of $\kappa^2$-$N,P$-2-pyridyl-
phosphines on early transition metals and, consequently, these systems will not be discussed further.

Figure 1.4 Selected complexes supported by 2-thiopyridonate or 2-pyridylphosphine ligands

1.2.2 2-Aminopyridinate ligands

In the search for alternatives to the aforementioned Cp ligands for early transition metals, a renaissance of amido metal (M–NR\textsuperscript{1}R\textsuperscript{2}) chemistry was witnessed near the end of the 1980s.\textsuperscript{87} One of the benefits of the amido ligand is that a greater variety in ligand design is possible, owing to the two substituents allowed at the N-donor atom. Among many possible variants, the 2-aminopyridinate (Ap) ligands have been extensively investigated in the past two decades.\textsuperscript{88-93} Three possible binding modes are known (Figure 1.5), with the strained $\kappa^2$-$N,N$-binding mode being the dominant motif for early transition metals and lanthanide chemistry.\textsuperscript{88} The bridging $\mu^2$-$N,N$ motif is more common among late transition metals for bi- and multi-metallic compounds,\textsuperscript{89} although a few exceptions do exist, such as the $\kappa^2$-$N,N$-binding mode for palladium.\textsuperscript{94,95} Cluster compounds of late transition metals with coordination to three metal centers by one Ap ligand are also known.\textsuperscript{89}
The first $\kappa^2$-$N,N$ coordination of Ap ligands was observed with (PhAp)$_2$Ru(PPh$_3$)$_2$ in a report by Cotton in 1984$^{96}$ and the first early transition metal complex, (MeAp)$_2$V(Me$_2$N(CH$_2$)$_2$NMe$_2$), was reported by Gambarotta in 1991$^{97}$. Beginning in 1996, investigations on Ap-ligated group 4 and 5 metal complexes largely focused on the synthesis, structural characterization, and catalytic applications of such complexes in polymerization studies.$^{89}$ Three different synthetic methods are known (Scheme 1.3), and early syntheses of group 4 Ap metal complexes by Kempe$^{98}$ and Polamo$^{99}$ are shown as representative examples. These synthetic strategies have also been used in the synthesis of group 5 complexes.$^{89}$ The direct synthesis involves the reaction of a metal halide with the proligand in toluene or neat conditions at elevated temperatures above 100 °C.$^{99}$ Here another equivalent of the ligand is added as a base in the synthesis of 10 as a salt.$^{99}$ The salt metathesis approach can be used to install an Ap ligand in the synthesis of 11, from the reaction of a metal halide with lithium Ap salts, and lithium chloride is generated as the byproduct.$^{98}$ The protonolysis route is usually the highest yielding and most straightforward approach of the three, as the liberated amine can be removed easily under reduced pressures.$^{98}$
Scheme 1.3 Synthetic routes to 2-aminopyridinate group 4 and 5 complexes

A selection of reported group 4 and 5 Ap metal complexes are shown in Figure 1.6. Titanium complex 12 has been reported by Kempe to have high activities for the polymerization of propene and 1-butene, while a similar zirconium variant is not as active as 12. In addition to group 4 Ap complexes, Polamo has reported several group 5 complexes of the motif 13, and the use of (PhAp(6-NHPh))2TaCl3 or (BnAp)2TaCl3 gave one of the highest activities for ethylene polymerization for a group 5 catalyst. A niobium complex 14 has been synthesized by Kempe using salt metathesis of [NbCl3(dme)(η2-PhC≡CSiMe3)] and the corresponding lithium Ap salt. Complex 14 was investigated for stoichiometric organometallic insertion chemistry and ethylene polymerization. The synthesis of a related acetylene titanium complex, [(2,6-iPr2C6H3Ap)2Ti(η2-Me2SiC≡CSiMe3)], has also been reported. Chiral Ap group 4 complexes such as 15 have been synthesized and structurally characterized by Scott, but reactivity investigations of these chiral Ap complexes have not been disclosed. More recently in 2010, two group 4 chiral examples (16 and 17) have been studied for hydroamination by Zi. Hafnium Ap complexes are also known, and the use of a mixed Cp*/Ap dimethyl hafnium complex 18 has been examined for the synthesis of alumina-terminated linear polyethylenes.
Notably, the use of an Ap-ligated early transition metal complex, \((\text{Ph}_2\text{PAp})_2\text{Ti}(\text{NEt}_2)_2\) (19), has been investigated by Eisen for hydroamination (Scheme 1.4).\(^{66,67,117}\) Ring opening of a strained alkene substrate, methylenecyclopropane, was utilized for intermolecular hydroamination with aniline derivatives.\(^{66,67}\) Additionally, 19 is also a viable catalyst for the polymerization of propylene.\(^{117}\)
Scheme 1.4 Hydroamination of methylenecyclopropane catalyzed by \((\text{Ph}_2\text{PAp})_2\text{Ti(NEt}_2\text{)}_2\)

A new class of sterically demanding Ap ligands has been explored by the Kempe research group since 2004,\textsuperscript{118-121} and these ligand sets are a main focus in recent development of early transition metal Ap complexes (Figure 1.7).\textsuperscript{122-126} In 2007, the bulky bis(Ap)zirconium complex 20 was first synthesized in a salt metathesis reaction of \(\text{ZrCl}_4\) and the corresponding potassium Ap ligand salts.\textsuperscript{122} The dimethyl complex of 20, generated from the salt metathesis of the corresponding dichloro complex and MeLi, has been reported to be an active catalyst for ethylene polymerization.\textsuperscript{122} The mono(Ap)-ligated Zr and Hf complexes 21 can be prepared, if benzyl ligands are chosen instead of methyl or chloro ligands.\textsuperscript{123} Such complexes 21 have been

\begin{align*}
\text{R}^1/\text{R}^2 & = \text{H/Me, iPr/iPr} \\
X & = \text{Cl, Me}
\end{align*}

\begin{align*}
\text{M} & = \text{Zr, Hf} \\
\text{R} & = \text{H, Me, iPr}
\end{align*}

\begin{align*}
\text{R} & = \text{H, Me, iPr}
\end{align*}

**Figure 1.7** Selected bulky 2-aminopyridinate complexes
synthesized from the protonolysis reaction of MBn₄ (M = Zr, Hf) and an Ap proligand and used for ethylene polymerization studies.¹²³ Titanium variants 22 of these bulky Ap complexes have been prepared from the protonolysis reaction of Ti(NMe₂)Cl₃ and an Ap proligand.¹²⁵ Higher activity for alkene polymerization was observed with increasing steric bulk of the ancillary ligand of 22.¹²⁵ In addition, electron-rich, group 4 Ap complexes with N-heterocyclic substituents, such as piperidines and morpholines, at the 6-position of the pyridine framework instead of aryl substituents have also been reported for polymerization studies.¹²⁴,¹²⁶ Most importantly, these bulky group 4 Ap complexes have been only directed towards the investigation of alkene polymerization and, prior to this work, they were unexplored for hydroamination.

In parallel to the work in this thesis, Doye disclosed two titanium Ap systems, in situ prepared 23 and isolated complex 24, for the intermolecular hydroaminoalkylation of styrenes with secondary amines to selectively give linear alkylated products 25a (Scheme 1.5).⁶⁸,⁶⁹ These examples represent the only other reported use of Ap ligands in the catalytic synthesis of amines, besides the aforementioned example for hydroamination. Unfortunately, a rationale for the observed regioselectivity has not been provided to date. The synthesis of 23a was previously reported by Kempe using a protonolysis reaction of Ti(NMe₂)₄ with two equivalents of N-methyl-2-aminopyridine (MeApH) (Scheme 1.6, eq 1).¹²⁷ Complex 24 has been synthesized by Doye using the same approach with the corresponding Ap proligand.⁶⁹ When a 1:1 ratio of Ti(NMe₂)₄:MeApH is used in a protonolysis reaction, an approximate 1:1:1 ratio of a three-component mixture (23b) was observed by ¹H NMR spectroscopy (Scheme 1.6, eq 2).⁶⁸ Presumably the sterically unprotected nature of the metal center, from the use of sterically less
demanding N-methyl-2-aminopyridinato, does not allow for the clean formation of a mono(Ap)titanium complex in this case.

\[
\text{catalyst: } \begin{align*}
\text{23a: } & \text{MeApH:Ti(NMe}_2\text{)}_4 = 2:1 \\
\text{or 23b: } & \text{MeApH:Ti(NMe}_2\text{)}_4 = 1:1 \\
& \text{(in situ prepared)}
\end{align*}
\]

**Scheme 1.5** Intermolecular hydroaminoalkylation with 2-aminopyridinate titanium systems

\[
\text{(1) } \begin{align*}
\text{NH} \\
\text{MeApH} \\
(2 \text{ equiv})
\end{align*}
\]

\[
\text{Ti(NMe}_2\text{)}_4 \\
25^\circ\text{C, 15 h} \\
- \text{HNMe}_2
\]

\[
23a
\]

\[
\text{(2) } \begin{align*}
\text{NH} \\
\text{N}
\end{align*}
\]

\[
\text{Ti(NMe}_2\text{)}_4 \\
25^\circ\text{C, 15 h} \\
- \text{HNMe}_2
\]

\[
23a + \text{1:1:1:1}
\]

\[
23b
\]

**Scheme 1.6** Protonolysis reactions of N-methyl-2-aminopyridine and Ti(NMe}_2\text{)}_4}
As few examples of group 4 Ap complexes have been reported for amine synthesis, an excellent opportunity exists for exploring the reactivity of these complexes. The previously studied group 4 Ap systems (16, 17, 19, 23a, 24) are all bis(Ap)-ligated, while the investigation of a mono(Ap)-ligated system have been unexplored for hydroamination. Strikingly, these previous investigations have not carried out any structural optimization of the ligand design or examined the steric accessibility to the metal center. Hence, well-defined mono(Ap)-ligated group 4 complexes with structural variability are attractive targets for examining hydroamination reactivity (Chapter 2).

1.2.3 2-Pyridonate ligands

While 2-aminopyridinate complexes have received wide attention, the investigation of the related 2-pyridonate complexes is relatively scarce for early transition metals. A variety of bonding motifs exist for 2-pyridonates (Figure 1.8), due to the fact that the oxygen atom of the ligand has an additional nonbonding pair of electrons for coordination and lacks a sterically demanding substituent in comparison to that of an amido substituent (–NR) on the pyridine framework.128,129 For a monometallic complex, three binding modes are available: κ¹-O, κ¹-N, and κ²-N,O. The κ²-N,O-binding motif has been observed for both early and late transition metals.128 When the 2-pyridonates adopt a monodentate binding mode, first-row transition metals (both early and late) have a tendency to bind through the oxygen donor.130-132 More polarizable late second- and third-row metals, such as platinum, are known to coordinate via the nitrogen.133
Early investigations of 2-pyridonate complexes have largely been dominated by bridging dimeric complexes of late transition metals with the $\mu^2\text{-}N,O$-bridging motif (Figure 1.9).\textsuperscript{128} The $D_{2d}$ isomer is the most common bridging dimeric structure, followed by the $C_{4v}$ isomer, and the investigation of such complexes have primarily focused on the use of commercially available unsubstituted- ($R = H$) or 6-substituted-2-pyridones ($R = \text{Me}, \text{halide}$).\textsuperscript{128} These 2-pyridonate ligand sets were targeted for studying the metal-metal bonding interactions that arise from these bridging motifs. For example, Cotton has investigated a series of group 6 ($M = \text{Cr}, \text{Mo}, \text{W}$) complexes of the $D_{2d}$ isomers of $[M_2(6\text{-Me\text{-}2-pyridonate})_4]$, where an increasing trend in $M\text{-}M$ bond length was observed down the group [1.879(1) Å – 2.161(1) Å].\textsuperscript{134} However, such bridging motifs have not been reported for group 4 and 5 metals to date.
The trinuclear $\mu^3$-bridging motifs shown in Figure 1.8 have been observed in polymetallic complexes of late transition metals.\textsuperscript{128,129} Such $\mu^3$-coordination modes of 2-pyridonates have not been reported in early transition metals, but the use of group 3 or lanthanide metals in combination with late transition metals is known for the synthesis of cluster complexes.\textsuperscript{128,129} For example, poly-heterometallic complexes containing the incorporation of yttrium or lanthanide 3+ ion in combination with copper, such as in $\text{Y}_2\text{Cu}_8(\mu$-2-pyridonate)\textsubscript{12}(\mu$\text{Cl})_2(\mu^4$-O)\textsubscript{2}(NO\textsubscript{3})\textsubscript{4}(H\textsubscript{2}O)\textsubscript{2}$\cdot$2H\textsubscript{2}O, have been developed for applications as high-temperature superconductors.\textsuperscript{135-139} Aside from these kinds of polymetallic arrays, the synthesis of a monometallic 2-pyridonate group 3 complex has not been disclosed.

A comprehensive compilation of reported 2-pyridonate systems of group 4 and 5 metals reveals that only a handful of complexes have been investigated, and there are very few examples of such complexes in catalysis (Figure 1.10).\textsuperscript{59,60,72,76,140-147} The syntheses of 2-pyridonate complexes also relies upon protonolysis and salt metathesis routes (\textit{vide supra}). The earliest reported 2-pyridonate early transition metal complex is the bis(Cp)titanium(III) complex 26 in 1978 by Stucky, which was synthesized by the salt metathesis of Cp\textsubscript{2}TiCl and sodium 2-
Figure 1.10 Representative 2-pyridonate/2-thiopyridonate group 4 and 5 complexes

A 2-thiopyridonate analogue of 26 has also been prepared, and both of these complexes have been examined for EPR and magnetic susceptibility studies. A structurally characterized dinuclear vanadium complex, \([\text{V}_2\text{O}_2\text{Cl}_4(6-\text{Me}-2\text{-pyridone})]\), with \(\mu^2\text{-O}\)-bridging 2-pyridones was reported by Cotton in 1983. A bridging 2-pyridonate, heterometallic Pd/Ti complex 27 has been structurally characterized by Brennan for the investigation of DNA-metal binding of the anticancer drug cisplatin. A mixed group 4 tris(pyrazol-1-yl)borato/2-pyridonate complex 28 and a mixed Cp*/tris(2-pyridonate) complex 29 have been synthesized and characterized by Otero, but no reactivity investigations were performed with
these complexes. Aside from a single report of polymerization studies with CpV(2-pyridonate)Cl$_2$,\textsuperscript{145} Cp-based complexes 30\textsuperscript{72} and 31\textsuperscript{146} are the only other disclosed 2-pyridonate group 5 complexes to date. Reactivity of these complexes (30 and 31) have not been investigated, while the solid-state structure and solution phase studies of the 2-thiopyrimidinate analogues were undertaken by Otero.\textsuperscript{72,146} In 2006, Nakayama reported the synthesis of bis(2-thiopyridonate)Ti(NMe$_2$)$_2$ complexes (32), and one example of a bis(6-Ph-2-pyridonate)Ti(NMe$_2$)$_2$, using a protonolysis reaction of Ti(NMe$_2$)$_4$ and two equivalents of proligand.\textsuperscript{76} These complexes of 32 are active catalysts for polymerization of ethylene,\textsuperscript{76} and this was one of the rare applications of 2-pyridonate early transition metal complexes in catalysis.

Beginning in 2009, the Schafer group investigated bis(2-pyridonate) group 4 complexes in catalytic transformations.\textsuperscript{59,60,64,147} The use of bis(2-pyridonate)titanium alkoxides 33 has been examined for the synthesis of random copolymers from ring-opening polymerization of lactide and caprolactone (Scheme 1.7).\textsuperscript{147} Notably, the bis(2-pyridonate)zirconium complex 34 is the only 2-pyridonate early transition metal complex that has been used in the synthesis of amines previous to this work (Scheme 1.8).\textsuperscript{59,60,64} Complex 34 is a precatalyst that is capable of both intramolecular hydroamination\textsuperscript{60} and hydroaminoalkylation\textsuperscript{59} reactions with primary aminoalkene substrates. The variation of the 2-pyridonate ligand framework has not been extensively investigated for the reaction, and the chemoselectivity between intramolecular hydroamination and hydroaminoalkylation remains challenging (\textit{vide infra}).
Scheme 1.7 Application of bis(2-pyridonate)titanium alkoxides in polymerization

Scheme 1.8 Bis(6-tBu-3-Ph-2-pyridonate)Zr(NMe₂)₂ for intramolecular hydroamination and hydroaminoalkylation

A thorough literature search of 2-pyridonate early transition metal complexes underlines the paucity in the investigation of these complexes. Bis(2-pyridonate) group 4 complexes (32–34) are the only systems that have been explored for catalytic transformations. Moreover, the synthesis and reactivity of non-Cp-based 2-pyridonate group 5 systems are unknown. The lead hydroaminoalkylation reactivity provided by 34 renders 2-pyridonates on group 4 and 5 as potential targets for further catalyst development for hydroaminoalkylation (Chapter 3 and 4).
1.3 Scope of thesis

The central theme that unifies this thesis concerns the exploitation of the steric accessibility to the metal center using the $\kappa^2$-$\eta^1,3$-chelating pyridine derived ligands for the catalytic synthesis of amines: hydroamination (Chapter 2) and hydroaminoalkylation (Chapter 3 and 4). The modular framework of these ligands holds immense potential for tailoring the metal-ligand combination for targeting reactive complexes for amine synthesis. However, early transition metal complexes supported by 2-aminopyridinate (Ap) or 2-pyridonate ligands remain largely unexplored in this area, emphasizing the importance of developing such well-characterized complexes of pyridine derivatives for exploration. Furthermore, there is a lack of modification of 2-pyridonate ligands in the literature aside from the use of commercially available 6-substituted-2-pyridonates, leaving much room for development. To this end, the unknown hydroamination reactivity of bulky Ap group 4 complexes, and unexplored hydroaminoalkylation reactivity of new 2-pyridonate complexes of group 4 and 5 have been investigated in this thesis.

Chapter 2 focuses on the synthesis, characterization and reactivity of a series of bulky mono(Ap)titanium complexes for intramolecular hydroamination. These bulky Ap complexes with varying substituents have been targeted for generating well-defined mononuclear species, and for examining the impact of steric accessibility about the metal center on the catalytic activity of these complexes. Substrate scope investigations and stoichiometric reactions have been undertaken with the mono(Ap)titanium complexes to probe the impact of bulky Ap ligands on hydroamination reactivity profile. An effective titanium catalyst for intramolecular hydroamination has been identified through these studies, revealing the importance of metal-
ligand combination and controlling steric accessibility about the metal center. A mechanism has been proposed based on the findings from these investigations.

Realizing the chemoselectivity for intramolecular hydroaminoalkylation over hydroamination with aminoalkene substrates is a challenge. Structural variation of the seminal bis(2-pyridonate)zirconium complex $34^{59}$ for targeting the chemoselectivity for hydroaminoalkylation had been previously unexplored. Chapter 3 concentrates on the synthesis, characterization and investigation of variously 3-substituted-2-pyridonates in combination with group 4 metals to address the challenge in chemoselectivity for intramolecular hydroaminoalkylation over hydroamination. Such exploratory studies lead to the development of a chemoselective catalyst, a bis(3-phenyl-2-pyridonate)titanium complex, for intramolecular hydroaminoalkylation. In an effort to gain insight into the mechanism of this reaction’s selectivity, stoichiometric synthetic experiments with this titanium complex have been performed, and mechanistic experiments have been undertaken.

The Schafer group and others have shown that electrophilic metal centers generated from the use of ancillary ligands, such as electron-withdrawing, bulky $\kappa^2$-$N,O$-chelates and chloro ligands, are crucial for improvements in the reactivity for intermolecular hydroaminoalkylation with terminal alkenes (vide infra). However, substrate scope limitations exist with internal alkene substrates. Chapter 4 describes the synthesis, characterization and reactivity of various mixed 2-pyridonate/alkyl/amido/chloro tantalum complexes for intermolecular hydroaminoalkylation. The 2-pyridonates are electron-withdrawing and a sterically less encumbered ligand framework than the amidates for targeting reactivity with sterically demanding substrates. Such substrate to catalyst combinations have been explored for expanding the reaction scope of this emerging, synthetically valuable reaction. A highly effective 2-pyridonate tantalum catalyst has been
discovered during this study for the intermolecular hydroaminoalkylation of sterically demanding internal alkenes, addressing one of the substrate scope limitations in the $\kappa^2$-N,O-chelating ligand series for group 5 intermolecular hydroaminoalkylation.

This thesis constitutes the first development of effective titanium and tantalum complexes of pyridine derivatives in the atom-economical, catalytic amine synthesis. A summary of the major findings of these research projects are presented in Chapter 5, along with future directions that can arise from the investigations provided herein. The insight into catalyst design uncovered from this work deserves further exploration for these new and promising classes of pyridine derivatives of group 4 and 5.
Chapter 2: Bulky 2-aminopyridinate titanium complexes for intramolecular hydroamination with unactivated aminoalkenes

2.1 Introduction

Nitrogen-containing molecules, including amines and N-heterocycles, are ubiquitous in biologically active compounds and natural products. Hence, efficient synthetic routes to access small molecule amine building blocks are highly desired for the agrochemical, pharmaceutical, and fine chemical industries.\textsuperscript{1,2} Catalytic reactions with transition metal complexes can be a useful method for carbon-heteroatom (such as C–N) bond formation in the synthesis of organic molecules,\textsuperscript{148,149} with a significant interest in the area of catalytic alkene functionalization.\textsuperscript{150} Furthermore, catalytic syntheses involving step\textsuperscript{151} and atom\textsuperscript{3,4} economy for sustainability are important, in light of environmental concerns and advances in green chemistry.\textsuperscript{152}

2.1.1 Alkene hydroamination

Alkene hydroamination, the addition of an N–H bond across a C=C bond, provides an atom-economical route to amines via the formation of a new C–N bond (Scheme 2.1).\textsuperscript{5,6} This reaction brings forth a direct method for the preparation of selectively substituted amines from readily available, simple amine and alkene feedstocks. The use of catalysts is essential to the success of the reaction due to the electrostatic repulsion between the nitrogen lone pair of the amine and the π-bond of the alkene. While effective catalytic systems have been realized for the hydroamination of alkynes,\textsuperscript{153–158} the hydroamination of unactivated alkenes with unprotected

amines remains a challenge and, to date, the development of a general, effective catalyst for the intermolecular reaction remains highly desired.\textsuperscript{159,160}

![Scheme 2.1 Intra- and intermolecular hydroamination of alkenes](image)

The hydroamination reaction has inspired researchers around the world, and a variety of metal complexes across the periodic table have been identified and developed for the reaction.\textsuperscript{5-6,56,149,153-157,161-184} Some of the more intensively studied catalytic systems are rare earth metals (group 3 metals and organolanthanides) and group 4 metals (Ti, Zr), which are the most active and selective systems for hydroamination with unprotected amines.\textsuperscript{183} These early transition metal complexes are highly electrophilic and typically operate via the activation of the amine. Alkali metals have been less extensively studied,\textsuperscript{162} and alkaline earth metal complexes are known to be prone to Schlenk-type ligand redistribution.\textsuperscript{175} Late transition metals (e.g. Rh, Ir, Pd, Au) are complementary to the early transition metals, as they are better known for their hydroamination catalysis of less nucleophilic, protected nitrogen atoms (e.g. sulfonamides, carbamates).\textsuperscript{182} Among these metals, earth-abundant group 4 metals are particularly attractive for the sustainable synthesis of amines because of their synthetic applicability, relatively low cost and low toxicity.
2.1.2 Group 4-catalyzed intramolecular hydroamination of alkenes

Intramolecular alkene hydroamination was first reported by Marks in 1989 using the precatalyst \((\text{Cp}_2^*\text{LaH}_2)_2\). While organolanthanide complexes are very active catalytic hydroamination systems, their use in organic synthesis is not widespread due to their air and moisture sensitivity, although the use of lanthanide triflates as Lewis acid catalysts is known. The use of group 4 metals (Ti, Zr) is advantageous as they show improved robustness and functional group tolerance over rare earth metals. They are well-established for use in organic synthesis and also industrial applications involving polymerization catalysis.

Group 4-mediated hydroamination emerged in the early 1990s, from the research groups of Bergman and Livinghouse, in their seminal work using cyclopentadienyl-based systems with alkyne and allene substrates. A breakthrough in alkene hydroamination was realized about a decade later, when it was shown that cationic Zr and Ti systems, and even neutral complexes, such as the commercially available Ti(NMe\(_2\))\(_4\), are capable of cyclizing secondary and primary aminoalkenes respectively. Significant progress has been made since then, but a persistent limitation in Ti- and Zr-catalyzed aminoalkene hydroamination (HA) is that they can undergo C–H bond functionalization adjacent to the amino group, resulting in a new C–C bond and hydroaminoalkylation (HAA) side products (Scheme 2.2). In

![Scheme 2.2](image)

**Scheme 2.2** Hydroamination reactions of challenging aminoalkene substrates with group 4 catalysts can give mixtures of hydroamination (HA) and hydroaminoalkylation (HAA) products.
particular, the 7-membered-ring cyclization with hydroamination is challenging,\textsuperscript{57} and cycloalkylamine side products resulting from the 6-membered-ring cyclization with hydroaminoalkylation are often observed (Scheme 2.2).\textsuperscript{59} Such problem does not exist in the 5-membered-ring cyclization with hydroamination, but hydroaminoalkylation side products can be formed during the 6-member-ring cyclization using group 4 systems.\textsuperscript{7,59,60,64,200,237-239} In these reactions, \textit{gem}-substituents (R), such as methyl or phenyl groups, are often used on the aminoalkene backbone to aid in the cyclization by decreasing the angle between the two reacting partners (also known as the Thorpe-Ingold effect).\textsuperscript{240} Currently, there is no report of group 4 metal catalyzed intermolecular hydroamination with alkenes in the literature.

While excellent alkyne hydroamination reactivity has been achieved with titanium complexes,\textsuperscript{153-158} including the development of a broadly applicable \textit{N,O}-chelated bis(amidate) complex 35 from the Schafer group,\textsuperscript{241,242} generally reports of titanium catalysts\textsuperscript{65,193-210} display limited substrate scope, sluggish reactivity, and unwanted side product formation during the cyclohydroamination of alkenes.\textsuperscript{59,200} Representative group 4 hydroamination catalysts that have reported reactivity with four or more aminoalkene substrates are shown in Figure 2.1.
Figure 2.1 Representative group 4 catalytic systems for alkene hydroamination

A survey of the literature and comparing the reactivity of the above complexes for 5-membered-ring hydroamination (Table 2.1), shows that zirconium metal centers with tethered, sterically open ligands are the most reactive. The larger size of zirconium over titanium and improved accessibility to metal center are generally the key features that bring forth improvements in reactivity. Noteworthy achievements include the sterically accessible, tethered N,O-chelated bis(ureate) zirconium complex 43 with expanded coordination numbers
Table 2.1 Group 4-catalyzed five-membered-ring hydroamination

![Chemical structure of the catalyst and the products](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>mol %</th>
<th>R</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>yield (%)</th>
<th>ref.</th>
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</thead>
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<td>Ph</td>
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<td>193</td>
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<td>36</td>
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<td>Ph</td>
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<td>24</td>
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<td>209</td>
</tr>
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<td>3</td>
<td>80, 93% ee</td>
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<td>11</td>
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<td>5</td>
<td>&gt;98$^a$</td>
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<td>12</td>
<td>44</td>
<td>2</td>
<td>Ph</td>
<td>100</td>
<td>3</td>
<td>&gt;95$^a$, 54% ee</td>
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<td>13</td>
<td>45</td>
<td>10</td>
<td>Ph</td>
<td>23</td>
<td>1.25</td>
<td>93, 93% ee</td>
<td>225</td>
</tr>
</tbody>
</table>

$^a$ Conversion determined by $^1$H NMR spectroscopy relative to an internal standard.

from the Schafer group (entry 10).$^{243}$ Consequently, 43 has broadly applicable reactivity in the hydroamination of unactivated alkenes and alkynes with both primary and secondary amines.$^{57,227,243}$ Most importantly, the titanium analogue of 43, which lacks the coordination of a neutral dimethylamine found in 43, showed poor catalytic activity due to its reduced availability for coordination to the metal center.$^{243}$ The Sadow group has also reported a sterically open system with the use of the tethered, zwitterionic cyclopentadienyl-bis(oxazolinyl)borato group 4 systems 45, with hydroamination reactivity at temperatures as low as -30 °C with up to 98% ee.$^{225,234}$ Meanwhile, titanium complexes 35–38 are not much better in reactivity in comparison to the commercially available Ti(NMe$_2$)$_4$ (Table 2.1, entries 1-5). The smaller ionic radius of
titanium and its established utility as a hydroaminoalkylation catalyst may rationalize the paucity of titanium hydroamination catalyst development. Thus, the development of a chemoselective catalyst for hydroamination reactivity over hydroaminoalkylation, and the development of more selective and active titanium catalyst systems is a challenge within the field. The move towards titanium catalysts over zirconium is ideal, given that titanium is more earth-abundant, and the cost of starting materials for titanium complexes are cheaper than zirconium [Ti(NMe₂)₄ ($0.07/mol) vs. Zr(NMe₂)₄ ($0.13/mol)].

2.1.3 \(N,N\)-Chelating ligands for group 4 hydroamination

In pursuit of an easily accessed, robust and effective group 4 hydroamination catalyst, ancillary ligands that incorporate hard donor atoms such as \(N,O\)-chelating (amidate, ureate, and 2-pyridonate) ligands have been shown to be very effective for hydroamination catalysis by the Schafer group and others. A survey of the complementary \(N,N\)-chelating (2-aminopyridinate (Ap), amidinate, and guanidinate) ligands for group 4 hydroamination catalysis shows that only select complexes have been investigated (Figure 2.2), and reveals reduced hydroamination reactivity profiles in comparison with \(N,O\)-chelating motifs. Among these reported complexes, only the biphenyl-tethered Ap group 4 complexes and a mixed cyclopentadienyl-guanidinate Zr complex have been tested for unactivated aminoalkene cyclohydroamination (Table 2.2). No reactivity was observed for the Ap titanium system (entry 1), and slow catalysis was observed for both of these zirconium systems (17, 46). Examination of these existing systems show that the access to metal center is impeded due to the presence of a bulky Cp* ligand or bissigation of two \(N,N\)-chelating ligands. This congestion could explain their poor reactivity and,
thus, the investigation of the effect of increased steric accessibility resulting from a mono-ligated complex was targeted.

![Image of complex structures]

**Figure 2.2** *N,N*-Chelating group 4 complexes for hydroamination

**Table 2.2** Previous reports of alkene cyclohydroamination with *N,N*-chelated group 4 systems

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>n</th>
<th>R</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>2</td>
<td>17</td>
<td>1</td>
<td>Me</td>
<td>120</td>
<td>24</td>
<td>100, 32% ee</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>17</td>
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<td>1</td>
<td>Ph</td>
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<td>48</td>
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<td>5</td>
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<td>2</td>
<td>Ph</td>
<td>130</td>
<td>48</td>
<td>0</td>
<td>217</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conversion determined by <sup>1</sup>H NMR spectroscopy relative to an internal standard.

Such *N,N*-chelating motifs remain underexplored and, considering the dramatically different reactivity reported thus far in comparison to the *N,O*-chelating motifs, such complexes are important for developing an understanding of hydroamination reactivity trends with group 4 metals. Considering the asymmetric binding mode and known hemi-lability of previously reported *N,O*-chelating amidate complexes,<sup>56</sup> the *Ap* ligands offer similar asymmetry while
affording improved opportunities for tailoring the steric bulk about the metal center (Figure 2.3).\textsuperscript{88-90,124,125} For example, there is precedent for the preparation of mono-ligated Ap titanium metal centers,\textsuperscript{124,125} while the preparation of mono(amidate)-ligated group 4 complexes that are resistant to ligand redistribution has not been successful.\textsuperscript{248} Thus, the investigation of such previously unexplored, mono-ligated Ap titanium systems for group 4-catalyzed hydroamination would provide a valuable insight towards the development of an effective and versatile titanium catalyst for alkene cyclohydroamination.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig23.png}
\caption{Binding mode of amidate (left), aminopyridinate (center), and amidinate (right)}
\end{figure}

\subsection{2.1.4 Scope of chapter}

This chapter focuses on the synthesis and reactivity of the mono-ligated 2-aminopyridinate titanium complexes, ApTi(NMe\textsubscript{2})\textsubscript{3}, with varying steric bulk about the metal center, for the hydroamination of primary aminoalkenes. A reactivity comparison of the ApTi(NMe\textsubscript{2})\textsubscript{3} complexes series with commercially available group 4 tetrakis(dimethylamido) complexes has been carried out to probe the effect of Ap ligand sets on catalytic activity. The results presented here show that controlling the steric environment at the metal center of ApTi(NMe\textsubscript{2})\textsubscript{3} is a critical determining factor for hydroamination reactivity. Factors that result in realizing selectivity for hydroamination over hydroaminoalkylation have been identified in these investigations. Substrate scope investigations reveal that ApTi(NMe\textsubscript{2})\textsubscript{3} is an effective precatalyst.
for cyclohydroamination. An Ap-supported titanium imido complex that is a hydroamination precatalyst has been prepared, and the mechanism of the reaction has been explored.

2.2 Results and discussion

2.2.1 Synthesis and characterization of ApTi(NMe$_2$)$_3$. 

The Ap proligands 49–51 (Figure 2.4) can be synthesized from 2,6-dibromopyridine in two steps according to literature procedures.$^{118-120}$ The bulky aryl substituents can be installed onto 2,6-dibromopyridine by Ni-catalyzed Kumada coupling with aryl Grignard reagents, followed by Pd-catalyzed Buchwald-Hartwig amination with aniline derivatives. The variation of methyl and/or isopropyl substituents on the Ap proligand allows for the examination of the influence of the steric environment about the metal center.$^{116,121,122,249-255}$

![Figure 2.4 Bulky 2-aminopyridine proligands](image)

The synthesis of Ap titanium complexes 52–54 can be accomplished using a protonolysis reaction between proligands 49–51 and commercially available Ti(NMe$_2$)$_4$. The resulting products can be isolated in high yields and easily purified (Scheme 2.3). For example, the complex 52 is quantitatively obtained as an analytically pure, yellow solid after the removal of the reaction solvent under vacuum, and this complex required no further purification. In the
synthesis of complexes 53 or 54, trace impurities are present upon completion of the reaction, however purification is easily accomplished by recrystallization from a solution of hexanes at -35 °C to afford yellow crystals of 53 (95%) or orange crystals of 54 (80%).

Scheme 2.3 Synthesis of mono(2-aminopyridinate)tris(dimethylamido)titanium complexes

The solid-state molecular structures of 52–54 reveal a common C1-symmetric structure with distorted trigonal bipyramidal coordination about the titanium center (Figure 2.5, Table 2.3), with N1, N3 and N4 being in the pseudo-equatorial plane (Σ of the angles in the equatorial plane are 358° (52), 355° (53) and 354° (54)). Using structure 53 as a representative example, there is a small bite angle [N1–Ti1–N2 58.84(6)°] for the Ap ligand, in agreement with similar, previously reported complexes.124,125 The binding of this N,N-chelating ligand is best described as a monoanionic amido/neutral pyridine bonding motif; the amido N1 at the equatorial site binds to Ti at a much shorter distance [Ti1–N1 2.0548(16) Å] than the pyridine N2 that occupies the axial site [Ti1–N2 2.44478(17) Å]. This Ti1–N2 bond length is unusually long compared to known Ti Ap systems (2.107–2.349 Å),90 and the presence of three dimethylamido ligands most likely promotes the loose coordination of the pyridine N2 due to the π-donation and steric bulk of the NMe2 ligands (vide infra). The sum of the angles around the dimethylamido N atoms is consistent with trigonal planar sp2-hybridization, and their short bond lengths [1.8929(16)–
Figure 2.5 ORTEP representation of the solid-state molecular structures of 52–54 plotted with 50% probability ellipsoids. All hydrogen atoms are omitted for clarity.

Table 2.3 Selected bond lengths (Å) and angles (°) for 52-54

<table>
<thead>
<tr>
<th></th>
<th>52</th>
<th>53</th>
<th>54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti1–N1</td>
<td>2.0678(17)</td>
<td>2.0548(16)</td>
<td>2.081(4)</td>
</tr>
<tr>
<td>Ti1–N2</td>
<td>2.4274(18)</td>
<td>2.4478(17)</td>
<td>2.337(4)</td>
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<tr>
<td>Ti1–N3</td>
<td>1.901(3)</td>
<td>1.9154(17)</td>
<td>1.893(4)</td>
</tr>
<tr>
<td>Ti1–N4</td>
<td>1.900(12)</td>
<td>1.8929(16)</td>
<td>1.911(4)</td>
</tr>
<tr>
<td>Ti1–N5</td>
<td>1.990(5)</td>
<td>1.9037(16)</td>
<td>1.923(4)</td>
</tr>
<tr>
<td>N1–Ti1–N2</td>
<td>59.03(6)</td>
<td>58.84(6)</td>
<td>60.50(14)</td>
</tr>
<tr>
<td>N1–Ti1–N3</td>
<td>133.65(12)</td>
<td>123.09(7)</td>
<td>131.70(16)</td>
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<td>N1–Ti1–N4</td>
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<td>122.77(7)</td>
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<tr>
<td>N3–Ti1–N4</td>
<td>107.9(3)</td>
<td>109.32(7)</td>
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</tr>
<tr>
<td>N1–Ti1–N5</td>
<td>93.52(13)</td>
<td>95.10(7)</td>
<td>98.32(16)</td>
</tr>
<tr>
<td>N2–Ti1–N5</td>
<td>152.40(12)</td>
<td>153.94(6)</td>
<td>156.05(16)</td>
</tr>
</tbody>
</table>
1.9154(17) Å] confirm the presence of Ti–N multiple bond character. The bond lengths and angles of 52 and 54 are also shown in Table 2.3 for comparison. There are no major discernible differences in Ti–N bond lengths between 52 and 53. However, the Ti1–N2 bond length of 54 is shorter than both 52 and 53, which can be attributed to the differing methyl and isopropyl substituents on opposite sides of the Ap ligand. The ApTi(NMe₂)₃ complexes are best described as 16 e⁻ species, with each of the Ap and amido ligands acting as 4 e⁻ donors to the Ti⁴⁺ metal center. Most importantly, the different methyl and isopropyl substituents of the ligands vary the steric shielding of the Ti center.

The ¹H NMR spectra of complexes 52–54 in d₆-benzene show a large and broad singlet for the dimethylamido protons in the region of δ 3.04–3.07. The dimethylamido signal integrates to eighteen protons relative to the respective proton signals of the bound Ap ligand, consistent with a mono-ligated complex. The presence of steric congestion surrounding the metal center is evident by the observation of hindered rotation of the aryl rings on the Ap ligand when isopropyl substituents are present. In complex 54, for example, two doublets (δ 1.33 and 1.21) are observed for the two isopropyl substituents at R³, whereas one singlet (δ 2.15) is observed for the two methyl substituents at R². The comparison of ¹³C NMR spectra of 52, 53 and 54 shows that these complexes are electronically similar, as the Ap C1 signals are observed at comparable chemical shifts at δ 170.2, 168.9 and 170.3, respectively. Furthermore, the dimethylamido carbon signals are present at near the same chemical shift at ca. δ 45.9. These complexes are thermally robust and show no decomposition in d₈-toluene when heated at 110 °C for one week or at 145 °C over two days.

In contrast to known bis(Ap)-ligated Ti complexes,⁶⁸,⁶⁹,¹²⁷ attempts to prepare bis-ligated systems with these bulky ligands have not been successful. The bis-ligated analogue of 52 cannot
be prepared, even when excess proligand 49 and Ti(NMe₂)₄ are heated in non-coordinating solvent at 100 °C for extended reaction times. In a similar experiment, when sterically less bulky proligand 50 and the prepared complex 53 in a 1:1 ratio are heated to 100 °C for one day, the reaction colour changes from orange to red. Inspection of the ¹H NMR spectrum of the reaction indicates the presence of unreacted 50 and trace formation of what may be a bis-ligated analogue of 53, as determined by the integration of relative peaks. However, this species could not be isolated. These observations support the resistance of these bulky Ap systems to form bis-ligated complexes and support the maintenance of a mono-ligated species in solution. With these variable mono-ligated Ap systems in hand, the effect of steric accessibility on cyclohydroamination has been examined.

2.2.2 Catalytic cyclohydroamination reactions

To investigate the catalytic activity of ApTi(NMe₂)₃ 52–54, 2,2-diphenyl-5-hexenyl-1-amine (55a) was chosen as the substrate for screening experiments (Table 2.4). This substrate is a good test substrate as it is known to give both hydroamination and hydroaminoalkylation products at 105 °C with Ti(NMe₂)₄. Thus, this substrate screen probes both the activity and chemoselectivity trends. The progress of the reaction was monitored by ¹H NMR spectroscopy in d₈-toluene by the disappearance of alkene signals of 55a centered at δ 5.68 and 4.90, and the appearance of new proton signals at δ 2.84 (dd, −CH₂N−) and 0.83 (d, −CH₃) for 55b. When the substrate and 10 mol % of 52–54 are left standing in d₈-toluene solution at room temperature (25 °C) for 24 h, surprisingly, room temperature activity for the 6-membered-ring formation of 55b was observed (entries 1–3). Room temperature activity for alkene hydroamination among group 4 systems is uncommon, and only a few neutral group 4 systems have been recently
Table 2.4 Screening of 52-54 and group 4 dimethylamido complexes for cyclohydroamination

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HA/HAA&lt;sup&gt;a,b&lt;/sup&gt;</th>
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</tr>
<tr>
<td>3</td>
<td>54</td>
<td>20</td>
<td>20:0</td>
</tr>
<tr>
<td>4</td>
<td>Ti(NMe&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>50</td>
<td>45:5</td>
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<tr>
<td>5</td>
<td>Zr(NMe&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>27:0</td>
</tr>
<tr>
<td>6</td>
<td>Hf(NMe&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>&lt;2</td>
<td>&lt;2:0</td>
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<td>7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>35</td>
<td>17</td>
<td>17:0</td>
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<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>34</td>
<td>&gt;98</td>
<td>&gt;98:0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conversion and ratio determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. <sup>b</sup> HA = hydroamination; HAA = hydroaminoalkylation. <sup>c</sup> 110 °C, 48 h (ref. 195). <sup>d</sup> 110 °C, 5 h (ref. 60).

reported for such reactivity.<sup>220,225,227,232,234</sup> The activity of the ApTi(NMe<sub>2</sub>)<sub>3</sub> system increases with a decreasing amount of steric congestion (53 > 54 > 52) present at the metal center, where the subtle difference between the methyl and isopropyl substituents in proximity to the metal is crucial. In addition, the commercially available M(NMe<sub>2</sub>)<sub>4</sub> (M = Ti, Zr and Hf) have been tested
for comparison, and some room temperature activity is observed (entries 4–6). Among the group 4 metals of M(NMe₂)₄, titanium is the most active for hydroamination, and the activity decreases down the group (Ti > Zr > Hf). However, the formation of hydroaminoalkylation side product is observed when Ti(NMe₂)₄ is utilized (entry 4), with the appearance of new proton signals at δ 3.72 (d, –CHNH₂) and 0.90 (d, –CH₃) for 55c. Here the formation of two diastereomeric products are possible, but a single unassigned diastereomer is formed. In contrast to Ti(NMe₂)₄, there is no observable formation of hydroaminoalkylation product in the reactions catalyzed by 52–54. Moreover, 53 is a much better hydroamination catalyst than Ti(NMe₂)₄ (entry 2), but the activities of 52 and 54 are significantly lower (entries 1 and 3). These results demonstrate that too much steric congestion at the metal center decreases the catalyst’s activity. Complex 53 provides a favorable amount of steric accessibility while, presumably, sufficient steric bulk is present to inhibit undesired aggregate formation and less reactive bis-ligated complexes via ligand redistribution. Most importantly, the room temperature hydroamination reactivity provided by the mono(N,N-chelate)titanium system 53 is a significant improvement over the required elevated reaction temperatures of 110 °C using the related bis(N,O-chelate) group 4 systems (35 and 34) that have been previously developed in the Schafer group (entries 7 and 8). Such difference in reactivity between the mono(Ap) versus the bis(amidate) systems highlight the importance of having a single chelate on the metal center instead of two chelates.

Previous investigations with a variety of bis-ligated systems have shown that zirconium complexes have improved reactivity over their titanium congeners, but the combination of the 2-aminopyridinate with titanium is preferred for this system. The cyclohydroamination of 55a catalyzed by the prepared complex 53 has the same reactivity as the in situ prepared titanium system [Ti(NMe₂)₄ + 50]; at 60 °C in 4 h, the reaction goes to
completion by both methods (Scheme 2.4). The in situ preparation involves stirring 10 mol % of 50 with an equimolar amounts of M(NMe₂)₄ for 5 minutes in d₈-toluene, prior to the addition of substrate. Importantly, these bulky Ap ligand sets are also capable of supporting mono(Ap)-ligated complexes on larger group 4 metals (M = Zr, Hf),¹²³ thereby allowing direct comparison in the mono(Ap)-ligated group 4 complex series. However, the combination of this ligand with Zr or Hf is not favorable, and the reactivity significantly decreases down the group. These results are in agreement with the observed trends in the group 4 tetrakis(dimethylamido) complexes in Table 2.4.

![Scheme 2.4](image)

**Scheme 2.4** Hydroamination reactivity comparison of group 4 metals with 50

### 2.2.3 Hydroamination substrate scope of 53

Encouraged by the room temperature hydroamination activity, the substrate scope of 53 has been explored using 5 mol % catalyst loading (Table 2.5). The complex 53 has a dramatically improved breadth of reactivity over Ti(NMe₂)₄ and other known titanium systems.⁶⁵,¹⁹³-²¹⁰ The hydroamination of 5- and 6-membered-rings is readily feasible in the presence of gem-disubstituents on the aminoalkene backbone at room temperature or at 60 °C (entries 1 and 2). More importantly, complex 53 can effectively cyclize known challenging aminoalkene substrates that have not seen reactivity with any other reported titanium systems.

40
Table 2.5 Catalytic hydroamination of primary aminoalkenes by complex 53

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>condition&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
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<td>Ph&lt;sub&gt;2&lt;/sub&gt;C≡CPh&lt;sub&gt;2&lt;/sub&gt;NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>56a</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;NPh&lt;sub&gt;2&lt;/sub&gt;</td>
<td>rt 12 h</td>
</tr>
<tr>
<td>2</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C≡CPh&lt;sub&gt;2&lt;/sub&gt;NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>55a</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;NPh&lt;sub&gt;2&lt;/sub&gt;</td>
<td>60 °C 4 h</td>
</tr>
<tr>
<td>3</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C≡CPh&lt;sub&gt;2&lt;/sub&gt;NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>57a</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;NPh&lt;sub&gt;2&lt;/sub&gt;</td>
<td>110 °C 80 h</td>
</tr>
<tr>
<td>4</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C≡CH&lt;sub&gt;2&lt;/sub&gt;NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>58a</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;NPh&lt;sub&gt;2&lt;/sub&gt;</td>
<td>145 °C 24 h</td>
</tr>
<tr>
<td>5</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C≡CPh&lt;sub&gt;2&lt;/sub&gt;NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>59a</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;NPh&lt;sub&gt;2&lt;/sub&gt;</td>
<td>110 °C 48 h</td>
</tr>
<tr>
<td>6</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C≡CPh&lt;sub&gt;2&lt;/sub&gt;NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>60a</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;NPh&lt;sub&gt;2&lt;/sub&gt;</td>
<td>110 °C 48 h</td>
</tr>
<tr>
<td>7</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C≡CPh&lt;sub&gt;2&lt;/sub&gt;NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>61a</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;C&lt;sub&gt;2&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;NPh&lt;sub&gt;2&lt;/sub&gt;</td>
<td>130 °C 30 h</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: substrate (1 mmol), 53 (5 mol %), d₈-toluene (1 mL).  
<sup>b</sup> Isolated yield.  
<sup>c</sup> 53 (10 mol %).  
<sup>d</sup> Isolated yield following derivitization with TsCl.  
<sup>e</sup> Isolated yield of the major isomer.  
<sup>f</sup> cis/trans ratio.

thus far (entries 3–7). The selective formation of azepane 57b without the formation of α-alkylated product is known to be difficult, especially for titanium systems that have been reported to be prone to unwanted hydroaminoalkylation side product formation (vide
Here the formation of the seven-membered-ring azepane 57b is achieved in excellent yield of 89% (entry 3). The Thorpe-Ingold effect is not required for cyclization, as 4-pentenyl-1-amine 58a undergoes hydroamination, but high temperatures and increased catalyst loading are needed (entry 4). Catalyst 53 also mediates the formation of α,α'-disubstituted piperidines 59b with excellent diastereoselectivity (entry 5, cis/trans = 18:1), with the preference of positioning methyl and the phenyl substituent equatorially to minimize the 1,3-diaxial interaction on a chair-like cyclization transition state during C–N bond formation (Scheme 2.5). Among group 4 systems, only a few zirconium catalysts (34 and 43) have been reported for hydroamination with unactivated internal alkenes, and here both the trans- and cis-aminoalkene substrates (60a and 61a) can undergo hydroamination with 53 (entries 6 and 7).

The combination of titanium with the increased accessibility of the metal center due to the mono(Ap)-ligation of 53 results in reactivity that exceeds anything previously observed for titanium systems and compares favourably with leading zirconium catalyst systems. Unfortunately, all attempts to extend the reactivity of 53 to the intermolecular hydroamination reactions involving alkylamines or anilines with alkenes or styrenes have been unsuccessful.

\[ \text{Scheme 2.5 Proposed transition state for the formation of } \alpha,\alpha'-\text{disubstituted piperidines} \]
2.2.4 Mechanism of cyclohydroamination

Three different mechanisms have been postulated for group 4-mediated alkene hydroamination: the imido [2+2] cycloaddition\cite{193,195,216,222} the amido σ-bond insertion mechanism\cite{214} and the closely related proton-assisted C–N bond formation (Scheme 2.6).\cite{225,227,230,234} Notably, the latter two mechanisms have been proposed for zirconium systems only, while imido intermediates have been consistently proposed as the catalytically active species for titanium systems.\cite{193,195} However, it is important to note that hydroamination can also be acid-catalyzed\cite{351} and Lewis acidic group 4 cationic systems can show similar reactivity trends.\cite{192}

The imido [2+2] cycloaddition mechanism was first proposed by Bergman in his seminal report involving Cp$_2$Zr(NHAr)$_2$ complexes for alkyne hydroamination.\cite{188} In a subsequent report, it has been shown that a known Cp$_2$TiMe$_2$ precatalyst for hydroamination undergoes ligand exchange in the presence of 2,6-dimethylaniline and pyridine to generate an imido complex 63, which has been characterized in the solid-state (64) following a dative ligand exchange with trimethylphosphine oxide (Scheme 2.7).\cite{257} This complex is significantly more active than Cp$_2$TiMe$_2$ for allene and alkyne hydroamination and does not show an induction period for catalysis, suggesting imido intermediates as the catalytically active species for the reaction.\cite{257} In addition, the Schafer group has shown that N,O-chelated imido zirconium complex 40 is catalytically active for alkene cyclohydroamination.\cite{195} As secondary amines with one N atom valency are unable to access such imido intermediates, the inactivity of secondary amines for the reaction has also been used to probe the imido mechanism.\cite{193,195,216,222} It is important to note that in the latter two mechanisms (Scheme 2.6 b, c), the hydroamination of both primary and secondary aminoalkenes are possible.
Scheme 2.6 Simplified hydroamination mechanisms proposed for group 4 catalysts
In an effort to probe the mechanism of hydroamination catalysis, it was noted that the Ap titanium complex 53 is unable to promote the cyclization of secondary aminoalkene substrates at room temperature or higher temperatures (Scheme 2.8). When catalytic amounts of 53 and N-methyl-aminoalkene substrate 65 are heated at 110 °C for 24 h, there is no formation of the N-methyl-pyrrolidinone product. This result is in stark contrast to that of the primary aminoalkene analogue 56a that undergoes cyclization at room temperature (Table 2.5, entry 1). This is also significantly different from several recently reported zirconium catalysts, including Zr(NMe₂)₄, that can indeed mediate cyclohydroamination of secondary aminoalkenes. The Sadow group has shown that the zirconium system 45, which is otherwise unreactive with secondary aminoalkene substrates, can undergo catalytic turnover with substoichiometric addition of a primary amine that provides a proton for a concerted C–H, C–N bond forming process (Scheme 2.6c). However, a similar experiment with the addition of n-hexylamine (10 mol %) to the reaction shown in Scheme 2.8 showed no reactivity at room temperature or higher.

**Scheme 2.7** Synthesis of a catalytically active imido titanium complex for hydroamination

**Scheme 2.8** Attempted hydroamination of secondary aminoalkenes with 53
heating at 110 °C for 24 h. Since the formation of imido species is inaccessible with secondary amines, and 53 is catalytically inactive for such substrates, this observation suggests that imido intermediates are likely involved in the catalytic cycle, as has been previously reported for Ti hydroamination catalysts.\textsuperscript{153,157} Hence, the synthesis of an imido complex has been attempted, as reported in the next section.

### 2.2.5 Synthesis and characterization of an imido Ap titanium complex

A guanidinate-supported imido titanium complex 47 has been previously isolated, structurally characterized, and used as a catalytically active complex for alkyne hydroamination.\textsuperscript{247} To investigate whether 53 is able to support such imido species, a stoichiometric reaction of 53 with 2,6-dimethylaniline (2 equiv) has been carried out in the presence of excess pyridine as a trapping agent (Scheme 2.9). Upon heating the reaction in benzene at 75 °C overnight and after the removal of the reaction solvent under vacuum, the terminal imido complex 66 is obtained. After recrystallization from benzene/pentane, 66 is obtained as an analytically pure, orange crystalline solid in 77% yield.

![Scheme 2.9 Synthesis of an imido Ap complex 66 from 53 and 2,6-dimethylaniline](image)

Scheme 2.9 Synthesis of an imido Ap complex 66 from 53 and 2,6-dimethylaniline
The relative integration of proton signals in the $^1$H NMR spectrum of 66 in $d_6$-benzene reveals a well-defined mono-ligated complex that is bound by two 2,6-dimethylaniline (imido and amido; δ 9.77 (br s, –NHAr)) and one pyridine. Well-resolved proton signals are observed with no fluxional behaviour, indicating no formation of dimers or equilibria with dimeric species. These characteristics are reminiscent of the known cyclopentadienyl-supported Ti imido complex 63 that is active in allene and alkyne hydroamination (vide supra).

An X-ray diffraction study of single crystals of 66, grown from benzene via slow diffusion of pentane, shows a $C_1$-symmetric, distorted square pyramidal structure (Figure 2.6). The imido Ti=N linkage is confirmed by its short bond length [Ti1–N3 1.7228(13) Å] and the close to linear bond angle [C24–N3–Ti1 175.64(11)°]. The second aniline is bound by an amido linkage [Ti1–N4 1.9777(13) Å], as seen by its longer bond length and its bent nature. These bond lengths are similar to the reported values for a related imido complex 64 [Ti–NAr, 1.752(8) Å,

![Figure 2.6 ORTEP representation of the solid-state molecular structure of 66 plotted with 50% probability ellipsoids, and select hydrogen atom shown. Selected bond lengths (Å) and angles (°): Ti1–N1, 2.1524(13); Ti1–N2, 2.1937(13); Ti1–N3, 1.7728(13); Ti1–N4, 1.9777(13); Ti1–N5, 2.2230(13); C24–N3–Ti1, 175.64(11); N1–Ti1–N2, 61.90(5); N1–Ti1–N5, 90.51(5); N2–Ti1–N4, 99.37(5); N3–Ti1–N4, 100.45(6); N4–Ti1–N5, 97.34(5); Ti1–N4–H1, 108.4(14).](image-url)
Ti–NHAr 1.975(9) Å.\textsuperscript{257} In contrast to 53, the Ap ligand of 66 is rather symmetrically bound to Ti [Ti1–N1, 2.1524(13) Å; Ti1–N2, 2.1937(13) Å], presumably because of the absence of the electronically saturating and sterically demanding dimethylamido ligands.

Most importantly, the isolated imido complex 66 is a competent catalyst for alkene hydroamination, as shown in Table 2.6. In 24 h at room temperature, the comparison of 53 and 66 initially shows that 66 is less active than 53 (entries 1 and 2). Upon closer examination, however, it is revealed that the presence of 2,6-dimethylaniline dramatically slows down the reaction catalyzed by 53 (entry 3), whereas the presence of added pyridine does not inhibit catalysis (entry 4). The slower catalytic activity of 53 in the presence of 2,6-dimethylaniline can be explained by competitive metal binding between the cyclizable aminoalkene substrate and the non-cyclizable 2,6-dimethylaniline.\textsuperscript{222} This explanation is confirmed by heating the reaction to 60 °C, to aid in the amido exchange processes, and here the reaction catalyzed by 66 goes to completion in 4 h (entry 5), in agreement with 53 (Table 2.5, entry 2).

**Table 2.6** Comparison of 53 and 66 for intramolecular hydroamination

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
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<th>conv (%)\textsuperscript{a}</th>
</tr>
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<tbody>
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<td>rt</td>
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<td>86</td>
</tr>
<tr>
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<td>66</td>
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</tr>
<tr>
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<td>53\textsuperscript{b}</td>
<td>rt</td>
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<td>5</td>
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<td>&gt;98</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conversion determined by \textsuperscript{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. \textsuperscript{b} 2,6-Dimethylaniline (0.20 equiv) added. \textsuperscript{c} Pyridine (0.20 equiv) added.
2.2.6 Proposed catalytic cycle of hydroamination with 53

Given that 53 is unreactive with secondary amines, even with the addition of primary amines (vide supra), the amido σ-bond insertion mechanism and the proton-assisted C–N bond formation are not likely to be operative. As complex 53 is able to readily access a catalytically active terminal imido species 66, the hydroamination catalytic cycle of 53 is postulated to proceed via the imido [2+2] cycloaddition pathway, and a plausible mechanism is proposed (Scheme 2.10). In the presence of excess primary aminoalkene substrate, dimethylamine is liberated by amido exchange reactions to generate A. A five-coordinate imido species B, analogous to 66, is then generated by α-hydrogen elimination. Here, the bulky nature of the Ap ligand presumably prevents the dimerization of B into a bridging imido species E, which has been postulated to be inactive for hydroamination, but is involved intermediate for intramolecular hydroaminoalkylation (see Chapter 3). Under catalytic conditions, a neutral amine donor is likely present in B, in place of the pyridine in 66. This neutral donor ligand would then be displaced by coordinated alkene, to promote a [2+2] cycloaddition, via a chair-like transition state C to yield azametallacyclobutane intermediate D. Finally, the protonation of D and an amido exchange with the substrate affords the cyclized product, and A is regenerated for the next catalytic cycle.
Scheme 2.10 Proposed mechanism for the catalytic cyclohydroamination using 53

2.3 Conclusion

By utilizing bulky Ap proligands 49–51 with varying substituents, a series of mono(Ap)-ligated complexes 52–54, as well as a catalytically competent Ap-supported imido titanium complex 66, have been prepared and fully characterized. Investigation of these complexes for alkene cyclohydroamination at room temperature has identified 53, which employs an Ap ligand of moderate steric bulk (50) as a supporting ligand. This complex is a very active titanium alkene
hydroamination catalyst and illustrates the catalytic potential of this inexpensive, abundant first row transition element. The investigation of these variable ligands shows the intense impact of steric bulk for such hydroamination catalysts, and points toward the importance of rapidly assembled and easily varied tunable ligand frameworks for the optimization of catalytic activity. However, the in situ screening of 50 with zirconium and hafnium has shown that these larger metals are less reactive than the smaller titanium. These results parallel the reactivity of group 4 tetrakis(dimethylamido) complexes that lack a novel ancillary ligand and highlight the importance of controlling steric accessibility at the metal center. The judicious selection of ligand steric bulk and choice of metal are crucial in the design of a reactive catalyst. Furthermore, the chemoselectivity between hydroamination over hydroaminoalkylation has been realized in the cyclization of primary aminoalkene substrates, providing insight towards the development of titanium hydroamination catalysts that could potentially rival zirconium and late transition metal systems.

2.4 Experimental

General methods. All reactions were conducted in oven dried glassware using standard Schlenk line and glovebox techniques under an atmosphere of dry dinitrogen, unless described otherwise. Benzene, hexanes and pentane were purified and dried by passage through a column of activated alumina and sparged with dinitrogen. Ti(NMe$_2$)$_4$ (Sigma-Aldrich), Zr(NMe$_2$)$_4$ (Strem), and Hf(NMe$_2$)$_4$ (Strem) were used as received. $d_6$-Benzene and $d_8$-toluene were degassed by three freeze-pump-thaw cycles and dried over activated 4 Å molecular sieves. The Ap proligands 49–51 were prepared according to literature procedure, and sublimed under heat and high vacuum before use. All amine substrates for catalytic reactions were distilled over CaH$_2$ and
degassed by three freeze-pump-thaw cycles before use. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker 400 MHz Avance spectrometer at ambient temperature and chemical shifts are given relative to the corresponding residual protio-residual solvent. Mass spectra were recorded on a Kratos MS-50 spectrometer using an electron impact (70 eV) source or a Bruker Esquire LC spectrometer using electrospray ionization source. Elemental analyses were recorded on a Carlo Erba Elemental Analyzer EA 1108. Single-crystal X-ray structure determinations were performed on a Bruker X8 APEX II diffractometer at the Department of Chemistry, University of British Columbia by Jacky C.-H. Yim.

**Synthesis of 52.** $N$-(2,6-diisopropylphenyl)-6-(2,4,6-triisopropylphenyl)-2-aminopyridine (49; 0.274 g, 0.600 mmol) in benzene (~2 mL) was treated with a solution of Ti(NMe$_2$)$_4$ (0.135 g, 0.600 mmol) in benzene (~2 mL), upon which the reaction instantly turned orange. The reaction was stirred overnight at room temperature, during which time the ligand dissolved to give an orange solution. The reaction solvent was removed under vacuum to afford analytically pure 52 as a yellow solid (>98%). Single crystals for X-ray structure determination were obtained by recrystallization from a solution of hexanes at -35 °C. $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 7.25-7.16 (m, 3H, Ar–H), 7.14 (s, 2H, Ar–H), 6.87 (dd, 1H, $J = 8.4, 7.2$ Hz, Ap–H), 6.26 (d, 1H, $J = 7.2$ Hz, Ap–H), 5.60 (d, 1H, $J = 8.4$ Hz, Ap–H), 3.55 (septet, 2H, $J = 6.9$ Hz, –CH(CH$_3$)$_2$), 3.04 (s, 18H, –N(CH$_3$)$_2$), 2.95 (septet, 2H, $J = 6.8$ Hz, –CH(CH$_3$)$_2$), 2.84 (septet, 1H, $J = 6.9$ Hz, –CH(CH$_3$)$_2$), 1.36 (d, 6H, $J = 6.8$ Hz, –CH(CH$_3$)$_2$), 1.32 (d, 6H, $J = 6.9$ Hz, –CH(CH$_3$)$_2$), 1.25 (d, 6H, $J = 6.9$ Hz, –CH(CH$_3$)$_2$), 1.20 (d, 6H, $J = 6.8$ Hz, –CH(CH$_3$)$_2$), 1.16 (d, 6H, $J = 6.8$ Hz, –CH(CH$_3$)$_2$). $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 170.2, 158.0, 149.3, 147.1,
145.1, 144.9, 138.9, 136.8, 126.0, 124.3, 120.8, 114.2, 104.6, 45.9, 35.2, 31.0, 28.9, 27.0, 25.5, 24.7, 24.3, 23.3; MS (EI): m/z = 635 (M⁺), 591 (M⁺-NMe₂), 547 (M⁺-2NMe₂), 503 (M⁺-3NMe₂).


**Synthesis of 53.** N,6-dimesityl-2-aminopyridine (50; 0.661 g, 2.00 mmol) in benzene (~3 mL) was treated with a solution of Ti(NMe₂)₄ (0.448 g, 2.00 mmol) in benzene (~3 mL), upon which the reaction instantly turned orange. The reaction was stirred at room temperature for 4 h, during which time the ligand dissolved to give an orange solution. The reaction solvent was removed under vacuum, and the resulting compound was recrystallized from a solution of hexanes at -35 °C to give 53 as yellow crystals (0.965 g, 95%). A sample from these crystals was used for X-ray structure determination. ¹H NMR (400 MHz, C₆D₆): δ 6.95 (s, 2H, Ar–H), 6.94 (dd, 1H, J = 8.4, 7.2 Hz, Ap–H), 6.83 (s, 2H, Ar–H), 6.08 (d, 1H, J = 7.2 Hz, Ap–H), 5.62 (d, 1H, J = 8.4 Hz, Ap–H), 3.07 (s, 18H, –N(C₃H₃)₂), 2.32 (s, 6H, –CH₃), 2.26 (s, 3H, –CH₃), 2.18 (s, 6H, –CH₃), 2.16 (s, 3H, –CH₃). ¹³C NMR (100 MHz, C₆D₆): δ 168.9, 158.0, 144.6, 140.3, 138.2, 137.4, 136.4, 134.0, 133.6, 129.8, 128.5, 112.2, 102.6, 46.0, 21.5, 21.4, 20.8, 19.6. MS (EI): m/z = 509 (M⁺), 465 (M⁺-NMe₂), 421 (M⁺-2NMe₂), 377 (M⁺-3NMe₂). Anal. calcd for C₂₉H₄₃N₅Ti: C, 68.36; H, 8.51; N, 13.74. Found: C, 68.55; H, 8.50; N, 13.45.

**Synthesis of 54.** N-(2,6-diisopropylphenyl)-6-(2,6-dimethylphenyl)-2-aminopyridine (51; 0.179 g, 0.500 mmol) in benzene (~2 mL) was treated with a solution of Ti(NMe₂)₄ (0.112g, 0.500 mmol) in benzene (~2 mL), upon which the reaction instantly turned orange. The reaction was stirred overnight at room temperature, during which time the ligand dissolved to give an orange solution. The
reaction solvent was removed under vacuum, and the resulting compound was recrystallized from a solution of hexanes at -35 °C to give 54 as orange crystals (0.214 g, 80%). A sample from these crystals was used for X-ray structure determination. \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): \(\delta\) 7.27-7.16 (m, 3H, Ar–H), 7.09 (t, 1H, \(J = 7.5\) Hz, Ar–H), 6.99 (d, 2H, \(J = 7.5\) Hz, Ar–H), 6.87 (dd, 1H, \(J = 8.5, 7.1\) Hz, Ap–H), 5.96 (d, 1H, \(J = 7.1\) Hz, Ap–H), 5.54 (d, 1H, \(J = 8.5\) Hz, Ap–H), 3.55 (septet, 2H, \(J = 6.9\) Hz, \(-\text{C}(\text{CH}_3)_2\)), 3.05 (s, 18H, \(-\text{N}(_3\text{CH}_3)_2\)), 2.15 (s, 6H, \(-\text{CH}_3\)), 1.33 (d, 6H, \(J = 6.9\) Hz, \(-\text{CH}(\text{CH}_3)_2\)), 1.21 (d, 6H, \(J = 6.9\) Hz, \(-\text{CH}(\text{CH}_3)_2\)). \(^{13}\)C NMR (100 MHz, C\(_6\)D\(_6\)): \(\delta\) 170.3, 157.5, 145.0, 144.7, 139.9, 136.5, 127.7, 125.9, 124.3, 111.6, 104.3, 45.9, 28.9, 25.4, 24.2, 20.8. MS (EI): \(m/z\) = 537 (M\(^+\)), 493 (M\(^+\)-NMe\(_2\)), 449 (M\(^+\)-2NMe\(_2\)), 405 (M\(^+\)-3NMe\(_2\)).

Anal. calcd for C\(_{31}\)H\(_{47}\)N\(_5\)Ti: C, 69.26; H, 8.81; N, 13.03. Found: C, 69.26; H, 8.76; N, 12.81.

**Synthesis of 66.** To 53 (0.102 g, 0.200 mmol) dissolved in benzene (~1 mL), 2,6-dimethylaniline (0.0485 g, 49.2 μL, 0.400 mmol) and pyridine (0.0633 g, 64.7 μL, 0.800 mmol) were added. The resulting red solution was heated at 75 °C for 18 h, and the reaction solvent was removed under vacuum. The residue was dissolved in benzene (~1 mL) and layered with pentane (~4 mL) and left at room temperature overnight, during which time crystals formed. The mother liquor was decanted, and volatiles were removed under vacuum to give 66 as an orange crystalline solid (0.107 g, 77%). Single crystals for X-ray structure determination were obtained by slow diffusion of pentane into a solution of 66 in benzene at room temperature. \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): \(\delta\) 9.77 (br s, 1H, \(-\text{NH}–\)); 8.53 (m, 2H, py–H\(_{\text{ortho}}\)), 7.02 (s, 1H, Ar–H), 6.99 (d, 2H, \(J = 7.4\) Hz, Ar–H), 6.94 (d, 2H, \(J = 7.4\) Hz, Ar–H), 6.91 (dd, 1H, \(J = 8.5, 7.1\) Hz, Ap–H), 6.86 (s, 1H, Ar–H), 6.74 (t, 1H, \(J = 7.4\) Hz, Ar–H), 6.69 (s,
1H, Ar–H), 6.67 (t, 1H, J = 7.4 Hz, Ar–H), 6.51 (s, 1H, Ar–H), 6.48 (m, 1H, py–H$_{\text{para}}$), 6.09 (m, 2H, py–H$_{\text{meta}}$), 5.94 (d, 1H, J = 7.1 Hz, Ap–H), 5.75 (d, 1H, J = 8.5 Hz, Ap–H), 2.74 (s, 3H, –CH$_3$), 2.54 (s, 6H, –CH$_3$), 2.40 (s, 3H, –CH$_3$), 2.29 (s, 3H, –CH$_3$), 2.20 (s, 3H, –CH$_3$), 2.10 (s, 6H, –CH$_3$), 1.84 (s, 3H, –CH$_3$), 1.75 (s, 3H, –CH$_3$). $^{13}$C NMR (100 MHz, C$_6$D$_6$): δ 167.0, 161.2, 158.7, 154.1, 150.8, 144.1, 141.1, 138.6, 137.1, 137.0, 136.9, 136.2, 135.3, 134.6, 133.4, 132.9, 130.6, 129.9, 128.8, 128.3, 128.0, 124.4, 122.7, 120.2, 118.1, 109.9, 104.3, 21.5, 21.4, 21.1, 20.8, 20.7, 20.5, 19.8, 19.6. Anal. calcd for C$_{44}$H$_{49}$N$_5$Ti: C, 75.96; H, 7.10; N, 10.07. Found: C, 76.04; H, 7.37; N, 9.94.

**General procedure for monitoring cyclohydroamination reactions.** Catalyst (0.0150 mmol, 10 mol %) and 1,3,5-trimethoxybenzene (1.25 M in $d_8$-toluene, 40.0 μL, 0.0500 mmol) were dissolved in $d_8$-toluene (460 μL) in a small vial. The substrate 2,2-diphenyl-5-hexenyl-1-amine 55a (1.50 M in $d_8$-toluene, 100 μL, 0.150 mmol) was then added and mixed with a Pasteur pipette. The resulting solution was transferred to a J. Young NMR tube and either left at room temperature or heated to 60 °C for the specified time. The reaction progress was monitored by $^1$H NMR spectroscopy.

**General procedure for catalytic hydroamination of aminoalkenes by complex 53.** Complex 53 (0.0510 g, 0.0500 mmol) and the aminoalkene (1.00 mmol) were dissolved in $d_8$-toluene (1 mL) by mixing with a Pasteur pipette in a small vial. The resulting solution was transferred to a J. Young NMR tube and heated in an oil bath at the specified temperature. Once >95% conversion was achieved as monitored by $^1$H NMR spectroscopy, the tube was opened and the contents diluted with diethyl ether. When the mixture clarified upon standing at room
temperature, it was filtered through Celite and the volatiles were removed under reduced pressure. The amines were purified by flash chromatography on silica gel.

**General considerations for amines.** Aminoalkenes 2,2-diphenyl-4-pentenyl-1-amine (56a),\(^{259}\) 2,2-diphenyl-5-hexenyl-1-amine (55a),\(^{260}\) 2,2-diphenyl-6-heptenyl-1-amine (57a),\(^{193}\) 4-pentenyl-1-amine (58a),\(^{261}\) 1-phenyl-5-hexenyl-1-amine (59a),\(^{57}\) (E)-2,2-diphenyl-4-hexenyl-1-amine (60a),\(^{260}\) 2-(cyclohex-2-enyl)-2,2-diphenylethanamine (61a),\(^{60}\) and N-methyl-2,2-diphenyl-4-pentenyl-1-amine (65)\(^{191}\) were prepared from commercially available starting materials from Aldrich as described in the literature. Column chromatography was performed using SiliaFlash F60 silica gel (230-400 mesh), using either glass columns or a Biotage Isolera One system. The following hydroamination products are known compounds, and spectral data are in agreement with literature values: 2-methyl-4,4-diphenylpyrrolidine (56b),\(^{259}\) 2-methyl-5,5-diphenylpiperidine (55b),\(^{262}\) 2-methyl-6,6-diphenylazepane (57b),\(^{59}\) 2-methyl-1-tosylpyrrolidine (58b-Ts),\(^{263}\) cis-2-methyl-6-phenylpiperidine (cis-59b),\(^{264}\) trans-2-methyl-6-phenylpiperidine (trans-59b),\(^{265}\) 2-ethyl-4,4-diphenylpyrrolidine (60b),\(^{60}\) cis-3,3-diphenyloctahydro-1H-indole (cis-61b).\(^{266}\)

\[
\text{cis-3,3-diphenyloctahydro-1H-indole (cis-61b).}^{266} \text{ Yield: 59\%. } \text{^1H NMR (400 MHz, C}_6\text{D}_6): } \delta 7.33 (d, 2H, J = 7.5 \text{ Hz, Ar–H}), 7.15-6.93 (m, 8H, Ar–H), 3.74 (d, 1H, J = 10.9 \text{ Hz, –Ph}_2\text{C–CHH–NH–}), 3.68 (d, 1H, J = 10.9 \text{ Hz, –Ph}_2\text{C–CHH–NH–}), 3.42-3.37 (m, 1H), 2.58-2.49 (m, 1H), 1.68-1.60 (m, 1H), 1.60-1.45 (m, 3H), 1.41-1.29 (m, 2H), 1.16-1.00 (m, 2H), 0.99-0.85 (m, 1H). ^1\text{H NMR (400 MHz, CDCl}_3): } \delta 7.47 (d, 2H, J = 7.5 \text{ Hz, Ar–H}), 7.32-7.17 (m, 6H, Ar–H), 7.17-7.08 (m, 2H, Ar–H), 3.93 (d, 1H, J = 11.1 \text{ Hz, –Ph}_2\text{C–CHH–NH–}), 3.88 (d, 1H, J = 11.1 \text{ Hz, –Ph}_2\text{C–CHH–NH–}), 3.56-3.48 (m, 1H), 2.86-2.75 \]
(m, 1H), 1.85 (br s, 1H, –NH–), 1.81-1.73 (m, 1H), 1.73-1.64 (m, 1H), 1.63-1.35 (m, 4H), 1.27-1.13 (m, 1H), 1.02-0.87 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.6, 145.3, 128.6, 128.3, 126.9, 126.0, 125.8, 60.1, 55.3, 54.3, 44.9, 29.3, 25.7, 25.0, 20.4. HRMS (ESI): $m/z$ calcd for C$_{20}$H$_{24}$N [M+H$^+$]: 278.1909. Found: 278.1909. Anal. calcd for C$_{20}$H$_{23}$N: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.40; H, 8.41; N, 4.85.

![trans-3,3-diphenyloctahydro-1H-indole (trans-61b). Yield: 28% $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.34-7.15 (m, 8H, Ar–H), 7.10 (d, 2H, $J = 7.1$ Hz, Ar–H), 3.94 (d, 1H, $J = 11.5$ Hz, –Ph$_2$C–CHH–NH–), 3.19 (d, 1H, $J = 11.5$ Hz, –Ph$_2$C–CHH–NH–), 2.67-2.56 (m, 1H), 2.17-2.06 (m, 2H), 2.06-1.97 (m, 1H), 1.84 (br s, 1H, –NH–), 1.78-1.68 (m, 2H), 1.46-1.22 (m, 2H), 1.16-1.00 (m, 1H), 0.64-0.48 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 148.5, 145.2, 129.3, 128.4, 127.5, 127.4, 126.2, 126.1, 61.3, 60.2, 57.5, 52.0, 33.7, 27.4, 26.1, 24.9. HRMS (ESI): $m/z$ calcd for C$_{20}$H$_{24}$N [M +H$^+$]: 278.1909. Found: 278.1908.}
Chapter 3: 2-Pyridonate titanium complexes for intramolecular hydroaminoalkylation with unactivated aminoalkenes

3.1 Introduction

Direct approaches using C–H functionalization of simple organic molecules hold immense potential for efficient synthetic methods. This nontraditional bond disconnection strategy can streamline the synthesis of a target molecule, as the pre-activation of the reactants, such as the installation of leaving groups (e.g. halides), is no longer required. However, the ability to catalytically and selectively activate specific C(sp³)–H bond among many other C–H bonds in a given molecule is a significant challenge. Notably, the direct α-C–H activation of amines has witnessed rapid development as an emerging powerful method for C–C bond formation and can be generally categorized by the involvement of four different types of reactive intermediates: α-amino anion (I), iminium cation (II), α-amino radical (III), and metallaziridine (IV) (Scheme 3.1). The generation of α-amino anion (I) requires stoichiometric use of organolithium bases. The related α-metallated intermediate can be generated catalytically with late transition metals, but they often require a directing group (e.g. R¹ = 2-pyridyl) to facilitate the C–H activation. The iminium cation (II) can be formed by thermal activation or in the presence of chemical oxidants with late transition metal catalysts. The α-amino radical (III) can be accessed by radical initiators or with photoredox chemistry involving light and late transition metal catalysts. Early transition metals have the ability to directly

functionalize unprotected amines (R^1 = H) via the metallaziridine intermediate (IV), thereby providing exciting opportunities for the development of catalytic α-C–H alkylation with unprotected amines.\(^7,59,68,69,200,210,237-239,294-310\)

Scheme 3.1 Types of reactive intermediates involved in α-C–H bond activation of amines

Hydroaminoalkylation is a catalytic alkene hydrofunctionalization reaction which results in the addition of a C–H bond adjacent to nitrogen across a C=C bond (Schemes 3.2 and 3.3).\(^7\) This emerging 100% atom economic C(sp\(^3\))–C(sp\(^3\)) bond forming strategy provides an alternative to the C–N bond forming hydroamination strategy for the catalytic synthesis of substituted amines from readily available amine and alkene feedstocks. Catalytic hydroaminoalkylation was first reported in the early 1980s, when Maspero observed the α-alkylation of dialkylamines with terminal alkenes using early transition metal (Zr, Nb, Ta) dialkylamido...
Scheme 3.3 Intramolecular hydroaminoalkylation (HAA) of alkenes

complexes. Subsequent mechanistic investigations by Nugent resulted in the proposal of a metallaziridine intermediate IV as the catalytically active species. However, the synthetic utility of catalytic hydroaminoalkylation was not further investigated until Herzon and Hartwig’s report in 2007, involving the use of N-arylamine substrates for intermolecular reactions with alkenes using Ta(NMe₂)₅ as the precatalyst. Since then, both early (Ta, Nb, Ti, Zr) and late (Ru, Ir) transition metal systems have been developed for this overall transformation, although each class of metals promotes this reaction in a mechanistically distinct fashion. The early transition metal catalysts involve a d⁰ metal center throughout this reaction, while the late transition metal systems proceed via oxidative addition/reductive elimination catalytic cycles (see p. 139, Scheme 4.6). Currently, few group 4 (Ti, Zr) complexes have been reported for intramolecular hydroaminoalkylation of primary aminoalkenes (Scheme 3.3). Moreover, only one example of a secondary aminoalkene substrate, N-(6-heptenyl)aniline (R = Ph, n = 2), exists for group 5 intramolecular hydroaminoalkylation using Ta(NMe₂)₅ as a precatalyst (Scheme 3.3). To date, there has been no report of a late transition metal-catalyzed intramolecular hydroaminoalkylation.

This chapter will focus on exploiting this unique reactivity of group 4 complexes. Therefore, the development of improved titanium complexes for intramolecular hydroaminoalkylation will be presented.
3.1.1 Titanium-catalyzed intramolecular hydroaminoalkylation

The C–H activation adjacent to nitrogen was identified early in the field of hydroamination catalysis when the racemization of α-chiral amines in the presence of titanium complexes such as Cp₂TiMe₂ was observed.³¹¹,³¹² The related alkylation adjacent to nitrogen of cyclohexylamine was observed in the stoichiometric reaction mediated by Ti(NMe₂)₄ using homoallylic alcohol as the alkylating reagent.³¹³ Catalytic intramolecular hydroaminoalkylation (HAA) was then observed as an unexpected byproduct of intramolecular hydroamination (HA) by Doye in 2008 (Scheme 3.4).²⁰⁰ During an attempt to synthesize piperidine products via hydroamination using titanium complexes, Ti(NMe₂)₄ and Ind₂TiMe₂, low yields of cyclopentylamine hydroaminoalkylation products were detected.

![Scheme 3.4 Cyclopentylamines isolated as byproducts of intramolecular hydroamination](image)

Using simple titanium complexes, Ti(NMe₂)₄ or TiBn₄, Doye also showed that the selectivity of the reaction can favor hydroaminoalkylation in a substrate-controlled reaction (Scheme 3.5).²³⁷,²³⁸ As the 7-membered-ring cyclization of hydroamination is less favored than the 6-membered-ring cyclization of hydroaminoalkylation, cyclohexylamine products can be
selectively synthesized over azepanes at elevated temperatures with long reaction times. However for 5-membered-ring cyclization with hydroaminoalkylation, piperidine heterocycle formation via hydroamination occurred preferentially.\(^{200}\) Up until this work, catalyst-controlled chemoselectivity for hydroaminoalkylation over hydroamination remained an unsolved problem.

**Scheme 3.5** Six-membered-ring hydroaminoalkylation with titanium complexes

The mechanism of Ti(NMe\(_2\))\(_4\)-catalyzed intramolecular hydroaminoalkylation of primary aminoalkenes has been investigated by Doye and a monomeric metallaziridine has been postulated as the catalytically active species (Scheme 3.6).\(^{239}\) The involvement of amido intermediates is suggested for the mechanism, as N-arylated secondary aminoalkenes do react with Ti(NMe\(_2\))\(_4\), albeit in low yields (11-26%).\(^{237}\) Based on deuterium labelling and computational studies, it has been determined that the rate-determining step is the reversible C–H activation.\(^{239}\) While this mechanistic study provides a rationale for the formation of the 6-membered-ring hydroaminoalkylation products using a simple titanium complex, it does not account for the observed hydroamination side reactivity (azepane formation) or provide insight that could address the chemoselectivity of the reaction.
Scheme 3.6 Doye’s proposed monometallic mechanism for intramolecular hydroaminoalkylation

3.1.2 Zirconium-catalyzed intramolecular hydroaminoalkylation

Alkylation and deuterium exchange at the $\alpha$-position of dimethylamine have been observed using Zr(NMe$_2$)$_4$ by Maspero$^{294}$ and Nugent.$^{295}$ The only other reported use of a zirconium system for hydroaminoalkylation is the bis(2-pyridonate)zirconium complex 34 for intramolecular hydroaminoalkylation from the Schafer group (Scheme 3.7).$^{59}$ The use of a bulky 3,6-disubstituted-2-pyridonate ligand on zirconium was shown to be important for the observed reactivity, but the impact of steric and electronic factors of the 2-pyridonate ligand were not fully investigated. Precatalyst 34 was shown to have a broad scope of reactivity for the synthesis of
cyclohexylamines and even an example of cyclopentylamine, albeit without $gem$-disubstituents which are known to promote hydroamination.\textsuperscript{59} However, the reported diastereoselectivity of the hydroaminoalkylation reaction was low, and complex 34 was also shown to be a viable hydroamination precatalyst for five- and six-carbon-chain aminoalkene substrates (Chapter 2).\textsuperscript{60} Thus, precatalyst 34 relies on substrate-control for preferential hydroaminoalkylation reactivity over hydroamination reactivity, and the development of a chemoselective catalyst for hydroaminoalkylation over hydroamination would be an attractive development.

![Scheme 3.7 Bis(6-$t$Bu-3-Ph-2-pyridonate)zirconium-catalyzed hydroaminoalkylation](image)

Based on the lack of reactivity with secondary $N$-methyl or $N$-phenyl aminoalkene substrates using 34, the involvement of imido species has been postulated for the reaction (Chapter 2). Furthermore, an increase in catalyst concentration of 34 was shown to favor the formation of hydroaminoalkylation products over hydroamination products (Scheme 3.8).\textsuperscript{59} With these preliminary mechanistic insights, as well as the isolation of a catalytically competent...
Scheme 3.8 Effect of catalyst concentration of 34 on hydroaminoalkylation selectivity

\[ \text{Scheme 3.8 Effect of catalyst concentration of 34 on hydroaminoalkylation selectivity} \]

\[ N,O\text{-chelated bridged metallaziridine 67 (Scheme 3.9),}^{314} \text{ the involvement of bimetallic imido and metallaziridine species has been postulated for the catalytic cycle for the intramolecular variant of this reaction (Scheme 3.10).}^{59} \text{ In contrast to the monometallic mechanism proposed by Doye in Scheme 3.6,}^{239} \text{ here the competing equilibria between a monomeric imido intermediate, which could promote hydroamination, and a bridging imido dimer for hydroaminoalkylation have been proposed.}^{59} \text{ This proposal would provide a rationale for mediating substrate control for hydroaminoalkylation reactivity over hydroamination reactivity using the same starting aminoalkene substrate. If this proposed mechanism is taking place in the reaction, further investigation and development of group 4 metal complexes would be fruitful for targeting catalyst-controlled chemoselectivity for hydroaminoalkylation over hydroamination, by favoring the formation of bridging dimeric intermediates. This approach would both test the previously proposed mechanism and provide a route for the development of a chemoselective catalyst for intramolecular hydroaminoalkylation.} \]
Scheme 3.9 Synthesis of a bridging metallaziridine via α-C–H activation

Scheme 3.10 Proposed bimetallic mechanism for intramolecular hydroaminoalkylation
3.1.3 Scope of chapter

This chapter involves the investigation of early transition metal-catalyzed intramolecular hydroaminoalkylation with a particular focus on titanium complexes. Given the paucity of the catalyst development for the intramolecular hydroaminoalkylation reaction, group 4 and 5 metal complexes, as well as \( N,O \)- and \( N,N \)-chelating ligands have been screened for the reaction. In particular, the impact of substituents on 2-pyridonate ligands has been investigated, and their combination with titanium has been identified to favor selectivity for hydroaminoalkylation. The synthesis and characterization of a bis(3-phenyl-2-pyridonate)Ti(NMe\(_2\))\(_2\) complex that exhibits the first example of catalyst-controlled chemoselectivity for both 5- and 6-membered-ring hydroaminoalkylation are presented. Stoichiometric experiments using this titanium complex with amines support the formation of a bimetallic bridged imido intermediate, and related complexes have been rigorously characterized. Notably, a novel 2-pyridonate-supported titanium(III) species has been isolated and characterized and has been ruled out as being catalytically relevant. Finally, deuterium labelling experiments reveal further mechanistic insight for intramolecular hydroamination catalyzed by 2-pyridonate group 4 complexes, and a mechanistic postulate based on the findings from these investigations is presented.

3.2 Results and discussion

3.2.1 Screening of known group 4 and 5 complexes for hydroaminoalkylation

Primary aminoalkene substrate \( 55a \) is a common substrate for intramolecular hydroamination that is typically resistant to intramolecular hydroaminoalkylation as piperidine hydroamination products are observed preferentially (Scheme 3.11). Thus, it is a good test substrate for examining catalyst-controlled selectivity for hydroaminoalkylation over
hydroamination. The progress of the reaction can be monitored by $^1$H NMR spectroscopy in $d_8$-toluene by observing the disappearance of alkene starting material signals of $55a$ centered at $\delta$ 5.68 and 4.90. The formation of desired cyclized products can be monitored by the appearance of new proton signals at $\delta$ 3.72 (d, $-\text{CHNH}_2$) and 0.90 (d, $-\text{CH}_3$) for hydroaminoalkylation product $55c$ and/or $\delta$ 2.84 (dd, $-\text{CHHN}$–) and 0.83 (d, $-\text{CH}_3$) for hydroamination product $55b$. Using this transformation as a simple catalyst screening reaction, a survey of known group 4 and 5 complexes shows that the formation of the hydroaminoalkylation product $55c$ over the hydroamination product $55b$ is rarely observed (Scheme 3.11). Of these screened complexes, only Ti(NMe$_2$)$_4$ shows the formation of $55c$ in modest quantities, whereas Zr(NMe$_2$)$_4$ and Hf(NMe$_2$)$_4$ give only the formation of $55b$. While Ind$_2$TiMe$_2$ is a useful catalyst for the intermolecular hydroaminoalkylation of terminal alkenes (vide infra),$^{300,308}$ it promotes hydroamination ($55b$) over hydroaminoalkylation ($55c$) with intramolecular substrate $55a$.$^{200}$ The previously reported bis(2-pyridonate)zirconium complex $34$ from the Schafer group is a good catalyst for substrate-controlled intramolecular hydroaminoalkylation,$^{59}$ but with $55a$, it also promotes hydroamination preferentially, as only the formation of $55b$ is observed.$^{60}$ Furthermore, group 5 intermolecular hydroaminoalkylation catalysts (Chapter 4), including previously reported N,O-chelated tantalum complexes $68$$^{208}$ and $69$$^{305}$ as well as TaMe$_3$Cl$_2$,$^{309}$ and Hultsch’s binaphtholate tantalum system $70a$,$^{302}$ give only the hydroamination product $55b$. Given that only titanium showed any promise for the formation of $55c$, titanium was chosen for further investigation.
Scheme 3.11 Comparison of reported group 4 and 5 precatalysts for both hydroaminoalkylation (HAA) and hydroamination (HA) reactions

3.2.2 Comparison of N,O- and N,N-chelating ligands on titanium

Initial investigations focused on exploring the reactivity of N,O- and N,N-chelated titanium complexes for reactivity with substrate 55a (Table 3.1). Related ligand sets have been employed on early transition metals for the development of intermolecular hydroaminoalkylation precatalysts. A screening of amidate complexes (entries 1 and 2) and a ureate complex (entry 3) shows that simple amidate and ureate ligand sets are not good for
intramolecular hydroaminoalkylation, as only hydroamination product 55b is observed. A bulky mono(2-aminopyridinate) complex 53 also gives 55b as the only product (entry 4). However, using 2-aminopyridinate complexes 23 generated in situ with less sterically demanding N-methyl-2-aminopyridine\(^{68}\) shows that a 1:2 mixture (23a) of Ti(NMe\(_2\))\(_4\) and the proligand is more selective for hydroaminoalkylation than a 1:1 mixture (23b, entry 5). Despite the reactivity observed with 23a, the selectivity for hydroaminoalkylation over hydroamination is poor.

To extend our investigation of group 4 bis(2-pyridonate) complexes\(^{49,60,147}\) and modify 34 for enhanced reactivity, bis(2-pyridonate)titanium complexes have been targeted (Table 3.1). Previous work in the Schafer lab has reported the synthesis and characterization of select group 4 bis(2-pyridonate) complexes (34, 71, and 72) using a protonolysis reaction of M(NMe\(_2\))\(_4\) (M = Ti, Zr) with two equivalents of 2-pyridones (Scheme 3.12).\(^{64}\) This reaction quantitatively yields analytically pure complexes upon removal of volatiles under reduced pressures.\(^{64}\) As such, the same preparation method has been used to synthesize various bis(2-pyridonate)titanium complexes. Single products can be observed by \(^1\)H NMR spectroscopy in all cases and, hence, crude products are of sufficient purity for catalytic screening without further purification. Notably, complexes 71 and 72 have not been previously tested with substrate 55a. When

\[
\text{Scheme 3.12 Synthesis of bis(2-pyridonate) group 4 complexes}
\]
Table 3.1 Screening of $N,O$- and $N,N$-ligands on titanium

<table>
<thead>
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<th>conv (%)</th>
<th>HAA/HA $^a$</th>
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<tr>
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<td><img src="image4" alt="Ligand 4" /></td>
<td>&gt;98</td>
<td>0:&gt;98</td>
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</tr>
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<td>3</td>
<td>n.d.</td>
</tr>
<tr>
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<td><img src="image8" alt="Ligand 8" /></td>
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<td>8:1</td>
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<td>4</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td><img src="image10" alt="Ligand 10" /></td>
<td>45</td>
<td>37:8</td>
</tr>
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</table>

$^a$ Conversion and ratio determined by $^1$H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. n.d. = not determined.

$^b$ LTi(NMe$_2$)$_3$, $^c$ In situ prepared complex. $^d$ Using a 1:1 mixture of Ti(NMe$_2$)$_4$ and LH.
screened for reactivity, complex 71 (titanium analogue of 34) with a bulky 3,6-disubstituted-2-pyridonate shows poor reactivity (Table 3.1, entry 6). In contrast, 72 with a simple 2-pyridonate ligand shows a preference for hydroaminoalkylation over hydroamination, but low conversion is observed with unidentified side products (entry 7). To initially probe the substituent effects at the 3- and 6-positions of 2-pyridonates, commercially available methyl-substituted 2-pyridonates have been screened for the reaction. The location of the steric bulk is shown to be critical, as 6-methyl-2-pyridonate (entry 8) is unfavorable for the reaction, while 3-methyl-2-pyridonate (entry 9) increases conversion to the desired hydroaminoalkylation products.

As the presence of substituents at the 3-position of the 2-pyridonate ligand showed promising selectivity for hydroaminoalkylation over hydroamination, various 3-substituted 2-pyridonates have been synthesized to further investigate the steric and electronic impacts of the ligand on reactivity (Scheme 3.13). Suzuki cross coupling of 3-bromo-2-pyridone and aryl

![Scheme 3.13 Synthesis of 3-aryl-2-pyridones](image-url)
boronic acids was utilized to access a series of 3-aryl-2-pyridones in low to moderate yields (21-62%). Here a general synthetic protocol was adopted, and the reaction conditions were not optimized. For the synthesis of 3-mesityl-2-pyridone 81, benzyl-protection/deprotection was required to install the bulkier mesityl substituent at the 3-position of 2-pyridone (Scheme 3.14).

With various 3-substituted-2-pyridonates in hand, bis(2-pyridonate)titanium complexes have been synthesized (vide supra) and screened as crude complexes for reactivity using substrate 55a (Table 3.2). Poor reactivity is observed when a bromine substituent is used (entry 1). A trimethylsilyl substituent, prepared from double deprotonation of 2-pyridone and subsequent reaction with TMSCl, is reactive for hydroamination but not for hydroaminoalkylation (entry 2). Gratifyingly, 3-phenyl-2-pyridonate shows a dramatic improvement in selectivity for hydroaminoalkylation over hydroamination (entry 3). This ligand, which is an analogue of 71 without a t-butyl substituent, clearly demonstrates the negative impact of having a substituent at the 6-position. The 4-methylphenyl substituent (entry 4) shows the same hydroaminoalkylation reactivity as the phenyl substituent (entry 3), while the bulkier 3,5-dimethylphenyl substituent shows reduced reactivity (entry 5). Further increase in the steric bulk at the 3-position with a mesityl substituent dramatically disfavors reactivity (entry 6). In probing the importance of electronic effects, an electron-donating 4-methoxyphenyl substituent (entry 7)
Table 3.2 Screening of 3-substituted-2-pyridonates

![Chemical structure of 55a and reaction product](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>conv (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HAA/HA&lt;sup&gt;a&lt;/sup&gt;</th>
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</tr>
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<td>38</td>
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</tbody>
</table>

<sup>a</sup> Conversion and ratio determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. n.d. = not determined.
shows negligible influence on hydroaminoalkylation reactivity over the phenyl substituent (entry 3). A 2,4-dimethoxyphenyl substituent shows reduced hydroaminoalkylation selectivity, indicating that more electron-donating character is unfavorable for the reaction (entry 8). An electron-withdrawing 3,5-difluorophenyl substituent increases the unwanted hydroamination reactivity, suggesting that a more electrophilic metal center is not advantageous for intramolecular hydroaminoalkylation (entry 9). The use of a bulky 3,5-bis(trifluoromethyl)-phenyl substituent (entry 10) is consistent with observation to date in that, presumably, the combination of its electron-withdrawing character and increased steric bulk results in poor reactivity and selectivity. The increase in hydroamination reactivity resulting from the use of more electron-withdrawing ligands such as perfluorophenyl-substituted bis(amidate)titanium complexes is known.\textsuperscript{318,319}

With the promising result of 3-phenyl-2-pyridonate for hydroaminoalkylation reactivity, 3,5-diphenyl-2-pyridone 85 was synthesized to explore whether additional benefits could be provided with an extra phenyl substituent at the 5-position of the ligand framework (Scheme 3.15). Starting from 2-(benzyloxy)-3-bromopyridine, a phenyl substituent was installed at the 3-position by using Suzuki cross coupling with phenylboronic acid to give 82. Bromination of 82 with NBS afforded 83, which was used as a substrate for another Suzuki cross coupling to synthesize 84. Benzyl deprotection of 84 by hydrogenation gave 85 for examination in hydroaminoalkylation reactivity. When 85 was tested for the cyclization of 55a with the same conditions as in Table 3.2, the reaction conversion was 83% with HAA/HA selectivity of 75:8. This result is comparable to the result obtained with the 3-phenyl-2-pyridonate (Table 3.2, entry 3), and the slight improvement in reactivity does not justify the time and cost involved in
synthesizing 85. Hence, further efforts have been directed toward the investigation of bis(3-phenyl-2-pyridonate)Ti(NMe$_2$)$_2$.

Scheme 3.15 Synthesis of 3,5-diphenyl-2-pyridone

3.2.3 Synthesis and hydroaminoalkylation reactivity of bis(3-phenyl-2-pyridonate)Ti(NMe$_2$)$_2$

With 3-phenyl-2-pyridonate chosen as the ideal ligand for intramolecular hydroaminoalkylation, the bis(2-pyridonate)titanium complex 86 can be synthesized using the protonolysis reaction of Ti(NMe$_2$)$_4$ and two equivalents of 3-phenyl-2-pyridone (Scheme 3.16). Removal of solvent and dimethylamine byproduct in vacuo quantitatively gives analytically pure complex 86 as orange-red solid. The solid-state molecular structure of 86 reveals an O-trans $C_2$-symmetric structure with a distorted octahedral coordination about the titanium center with both ligands bound in a $\kappa^2$-binding mode (Figure 3.1). Asymmetric binding of the $N,O$-chelating ligand [Ti–O$_{avg}$ 2.0268(12) Å; Ti–N$_{avg}$ 2.2567(14) Å] is observed with a ligand bite angle of 61.82(5)°. The short bond Ti–NMe$_2(avg)$ bond lengths [1.8915(14) Å] and trigonal planar sp$^3$-
Scheme 3.16 Synthesis of bis(3-phenyl-2-pyridonate)Ti(NMe₂)₂

Figure 3.1 ORTEP representation of the solid-state molecular structure of 86 plotted with 50% probability ellipsoids for non-hydrogen atoms. Benzene solvent molecule omitted for clarity. Selected average bond lengths (Å) and angles (°): Ti1–O(1,2), 2.0268(12); Ti1–N(1,2), 2.2567(14); Ti–N(3,4) 1.8915(14); N3–Ti1–N4, 100.44(6); N(1,2)–Ti1–N(4,3), 154.62(6); O1–Ti1–O2, 148.11(5); O(1,2)–Ti1–N(1,2), 61.82(5).

hybridization at the N atom support the presence of Ti–N multiple-bonding character for dimethylamido ligands. These bonding characteristics are in agreement with previously reported group 4 bis(2-pyridonate) complexes that also assume O-trans C₂-coordination geometry (34, 71, 72).⁵⁹,⁶⁴ Taking bis(2-pyridonate)Ti(NMe₂)₂ 72 as a comparison, 72 has a ligand bite angle of 61.97(5)°, a Ti–O_avg bond length of 2.010(2) Å and a Ti–N_avg bond length of 2.222(2) Å.⁶⁴ While these values are similar to those of 86, slightly tighter binding of the 2-pyridonate ligand to titanium is seen in 72 in comparison to 86 presumably due to steric effects. Aside from the
differing substituents on the ligand in the periphery of the metal center, there are no other major
discernible structural differences between 86 and 72. The solution phase structure of 86 is
consistent with its solid state structure, as a singlet that integrates to twelve protons is observed
for the dimethylamido ligands at δ 3.49, and two chemically equivalent 3-phenyl-2-pyridonate
ligands are observed in the 1H NMR spectrum. These solution phase characteristics are also
similar to 72.

Complex 86 displays catalyst controlled preferential formation of both 5- and 6-
membered cycloalkylamines from primary aminoalkene substrates, rather than N-heterocyclic
hydroamination products (Table 3.3). An overall catalyst loading of 20 mol % is added in two
batches of 10 mol % to overcome the observed slow decomposition of catalyst over the course of
the reaction (vide infra). Good reactivity of 86 at temperatures as low as 110 °C is feasible, in
comparison to Ti(NMe2)4 and TiBn4 that require temperatures in the range of 130–160 °C.238 For
the synthesis of cyclopentylamines (entries 1–3), the cis diastereomer is formed preferentially
with good selectivity (up to 10:1) (vide infra). This compares favorably with previous reports
using Ti(NMe2)4 (dr = 4:1), where the hydroaminoalkylation products are observed only as side
products of hydroamination (Scheme 3.4).200 Challenging disubstituted alkene substrates can
undergo intramolecular hydroaminoalkylation for the first time (entry 4). In contrast to the
diastereoselectivity observed with 5-membered cycloalkylamines (entries 1–3), the formation of
the trans isomer is favored in the formation of 1-aminoindane (entry 5). For the synthesis of
cyclohexylamines (entries 6–8), excellent diastereoselectivity (up to 19:1) for the trans isomer is
observed. These results are a significant enhancement over previously reported results using 34
and TiBn4 (dr < 5:1).59,238 The relative stereochemistry of the previously unknown
hydroaminoalkylation products has been assigned by X-ray crystallographic analysis of the
<table>
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<th>entry</th>
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<td>19:1</td>
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</table>

<sup>a</sup> Reaction conditions: substrate (0.60 mmol), 86 (2 x 10 mol %), toluene (2.4 mL), 110 °C, t = 48 h.  
<sup>b</sup> Isolated yield.  
<sup>c</sup> Determined by <sup>1</sup>H NMR spectroscopy prior to chromatography.  
<sup>d</sup> Yield of combined diastereomers.  
<sup>e</sup> Yield of diastereomer illustrated.  
<sup>f</sup> Derivatized prior to isolation.  
<sup>g</sup> 130 °C.  
<sup>h</sup> 145 °C.
tosylated major diastereomer, which was obtained from single crystals of the isolated product (Figures 3.2–3.4). Unfortunately, a substrate without gem-disubstituents, such as 5-hexenyl-1-amine, cannot undergo hydroaminoalkylation using 86.

Figure 3.2 ORTEP representation of the solid-state molecular structure of *cis-55c-Ts* plotted with 50% probability ellipsoids, only select hydrogens shown. Cyclohexane solvent molecule omitted for clarity.

Figure 3.3 ORTEP representation of the solid-state molecular structure of *cis-87c-Ts* plotted with 50% probability ellipsoids, only select hydrogens shown.

Figure 3.4 ORTEP representation of the solid-state molecular structure of *trans-90c-Ts* plotted with 50% probability ellipsoids, only select hydrogens shown.
To test whether 86 can also be a viable precatalyst for intermolecular hydroaminoalkylation, the typical screening reaction for intermolecular hydroaminoalkylation using N-methylaniline and 1-octene was carried out (Scheme 3.17). However, the use of 86 for intermolecular hydroaminoalkylation was rather unsuccessful and required higher temperatures of 160 °C to obtain minimal hydroaminoalkylation reactivity (9% conv). Benzylamine was also used as the amine substrate to test for intermolecular hydroaminoalkylation with 1-octene, but no reactivity was observed (vide infra). These results suggest that 86 has a unique reactivity towards intramolecular hydroaminoalkylation, but not intermolecular hydroaminoalkylation.

Scheme 3.17 Intermolecular hydroaminoalkylation of N-methylaniline and 1-octene using 86

A rationale for the observed diastereoselectivity is proposed in Figure 3.5. Based on postulated mechanisms for intramolecular hydroaminoalkylation using group 4 complexes (Schemes 3.6 and 3.10), titanaziridine is assumed as the key catalytically active species for this reaction (whether bridging or monometallic). Presumably, the relative stereochemistry is established at the C–C bond formation step involving an alkene insertion into the M–C bond of the metallaziridine intermediate. Here a chair-like conformation is postulated for the formation of 6-membered-cyclohexylamine (Figure 3.5a). Having the titanaziridine at the pseudo-equatorial position is preferred to minimize the 1,3-diaxial type interactions imposed by the bulkier NR´ substituent if at the pseudo-axial position, where R´ could be another titanium center based on the bridging bimetallic mechanism (Scheme 3.10) or H if the monometallic mechanism
Figure 3.5 Postulated rationale for observed diastereoselectivity of hydroaminoalkylation

is involved (Scheme 3.6). Consequently, the formation of trans isomer is preferred, in agreement with the observed diastereoselectivity of the cyclohexylamine products (Table 3.3, entries 6–8). A related envelope-like confirmation could be adopted for the 5-membered-ring formation (Figure 3.5b). The formation of cis isomer is preferred in this case when the titanaziridine is positioned at the pseudo-equatorial position to minimize the 1,3-diaxial-type interactions, consistent with the observed diastereoselectivity of the cyclopentylamine products (Table 3.3, entries 1–3). For the formation of 1-aminoindane product (Figure 3.5c), a boat-like conformation is likely adopted due to the rigidity of the phenyl ring and, having the titanaziridine at the pseudo-equatorial position, gives the preference for the formation of trans isomer (Table 3.3, entry 5). Generally, the observed diastereoselectivity is higher with the titanium complex 86 than the zirconium complex 34 (vide supra). Presumably, the smaller ionic radii of titanium metal.
center over the larger zirconium provides more pronounced steric effects that result in higher diastereoselectivity.

3.2.4 Mechanistic considerations

It was noted that secondary $N$-methyl or $N$-phenyl aminoalkene substrates (93 and 94) are unreactive with 86 at 110 °C or at 145 °C (Scheme 3.18). This observation suggests that titanium imido species could be involved as intermediates in the catalytic cycle, as has been proposed for the related bis(2-pyridonate)zirconium complex 34 (vide supra). Furthermore, an increase in catalyst concentration further increases the chemoselectivity for hydroaminoalkylation over hydroamination (Scheme 3.19). These observations are consistent with the previously reported formation of dimeric imido species, which are proposed to be unreactive for hydroamination, but may promote hydroaminoalkylation via bridging metallaziridine intermediates (Scheme 3.10).

Scheme 3.18 Attempted hydroaminoalkylation of secondary aminoalkenes with 86

Scheme 3.19 Effect of catalyst concentration of 86 on hydroaminoalkylation selectivity
These results are also supported by the aforementioned 2-pyridonate ligand screening (vide supra), which showed that a substituent at the 3-position (R¹) of the 2-pyridonate ligand is favorable for hydroaminoalkylation reactivity while at the 6-position (R²) is significantly disfavored for the reaction (Figure 3.6). Presumably, the presence of a substituent (e.g. Me, tBu) at the 6-position brings steric congestion to the bridging site near the metal center and disfavors the formation of μ²-bridging motif of the 2-pyridonate ligand, as illustrated in Figure 3.6. More importantly, the use of a phenyl substituent at the 3-position has shown excellent selectivity for intramolecular hydroaminoalkylation over hydroamination. This result suggests that steric bulk at the 3-position is required from the periphery of the metal center, presumably, to protect the oxygen donor site of the ligand. Due to the availability of extra lone electron pairs on the oxygen, it may be susceptible to the formation of multimetallic species (vide supra). In contrast, a bulkier mesityl substituent at the 3-position would restrict accessibility to the metal center for incoming substrates and disrupt intramolecular hydroaminoalkylation reactivity.

![Figure 3.6](image)

**Figure 3.6** Hypothetical bimetallic bridging imido 2-pyridonate intermediate with only one ligand shown for clarity.

When the catalytic reaction was monitored at different time intervals by ¹H NMR spectroscopy, both the rate of reaction conversion and hydroaminoalkylation selectivity decrease with increasing reaction times (Scheme 3.20). This observation suggests that catalyst decomposition is occurring during the reaction, and further heating of the reaction to 48 h does
not result in any further reactivity. In addition, broad signals are observed in the \(^1\)H NMR spectrum when using 86. This observation suggests that paramagnetic species might be forming during the reaction and introduces the possibility of radical intermediates in the reaction (\textit{vide infra}). As such, for reactions catalyzed by 86, the reactions had to be quenched and the \(^1\)H NMR spectrum retaken to determine the conversion and selectivity of the reaction. Most importantly, such behavior makes it difficult to carry out kinetic investigations by \(^1\)H NMR spectroscopy.

\[ \text{Scheme 3.20} \text{ Monitoring the cyclization of 55a catalyzed by 86 at different time intervals} \]

The decrease in the rate of reaction as measured by conversion, and decreased hydroaminoalkylation selectivity over time suggests that product inhibition might be occurring during the reaction. To test for product inhibition, reactions using a 1:1 ratio of the substrate 55a and various amines have been screened (Scheme 3.21). The reaction using a hydroamination product model of 55b, 2-methylpiperidine, shows that this secondary amine has a negligible influence on hydroaminoalkylation reactivity and selectivity. The use of isolated hydroaminoalkylation product \textit{cis}-55c shows a slightly reduced hydroaminoalkylation reactivity profile. Presumably, this primary amine \textit{cis}-55c may compete with the substrate 55a for ligation at the metal center, thereby resulting in a competitive inhibition. The use of cyclopentylamine
Scheme 3.21 Screening for amine inhibition on intramolecular hydroaminoalkylation

shows drastically diminished hydroaminoalkylation reactivity, suggesting that more sterically accessible primary cycloalkylamines bind preferentially at the metal center and result in inhibition of the reaction. The comparison of the conversion to products between the reactions using cis-55c and cyclopentylamine suggests that the product inhibition observed with cis-55c is not a sufficient amount to account for the reduced rates in the formation of hydroaminoalkylation product. This observation suggests that extra steric bulk from gem-disubstituents and a methyl substituent on cycloalkylamine is required to promote ligand dissociation during amido exchange in the presence of incoming substrate.

The above mechanistic investigations are most consistent with the bridging bimetallic mechanism (Scheme 3.10) being involved with 86, accompanied by unknown catalyst decomposition pathway. In order to gain further insight into the nature of intermediates involved in the catalytic cycle of intramolecular hydroaminoalkylation or off the reaction pathway, stoichiometric synthetic experiments were undertaken in the next section.
3.2.5 **Stoichiometric synthetic experiments**

As shown earlier in Scheme 3.9, previous work in the Schafer group has shown that the reaction of a bis(amidate)titanium complex with three equivalents of benzylamine leads to the formation of a catalytically competent bimetallic bridging titanaziridine 67. An amidate ligand and an imido ligand also bridge the two titanium metal centers in the structure of 67. However, efforts to extend the hydroaminoalkylation reactivity of bis(amidate)titanium systems have been unsuccessful to date (*vide supra*). While numerous late transition metal examples of bridging dimeric 2-pyridonate complexes have been reported (*vide supra*), such complexes with group 4 metals were not reported. To probe whether 2-pyridonate ligands are also capable of bridging and support the postulated bridging imido/metallaziridine intermediates, an analogous experiment was attempted using 86 and three equivalents of benzylamine (Scheme 3.22). However, broad signals with low intensity were observed in the $^1$H NMR spectrum of the crude product, suggesting the formation of paramagnetic species that could be similar to those observed in catalytic reaction studies (*vide supra*). As the identity of the products formed in this reaction is difficult to interpret in the solution phase, efforts were directed towards isolation of a solid product. After numerous attempts to grow single crystals for X-ray structure analysis, small quantities of brown crystals of 95 were obtained from recrystallization in a toluene/pentane mixture (Figure 3.7). Examination of 95 in the solid-state reveals a tris(2-pyridonate)titanium

![Scheme 3.22 Reaction of 86 and benzylamine](image-url)
Figure 3.7 ORTEP representation of the solid-state molecular structure of 95 plotted with 50% probability ellipsoids for non-hydrogen atoms. Selected bond lengths (Å) and angles (°): Ti1–O1, 1.9790(15); Ti1–O2, 2.1156(15); Ti1–O3, 2.1091(15); Ti1–N2, 2.1998(18); Ti1–N3, 2.2565(18); Ti1–N4, 2.204(2); Ti1–N5, 2.2128(19); N4–C(34), 1.481(3); N5–C(41), 1.485(3); O2–Ti1–N2, 60.98(6); O3–Ti1–N3, 60.59(6); N4–Ti1–O1, 94.11(7); N4–Ti1–N5 176.20(8); Ti1–O1–C1, 136.56(14); C34–N4–Ti1 124.10(14); C41–N5–Ti1 114.83(14).

complex with two neutrally coordinated benzylamines. Here the change in oxidation of the metal center from Ti(IV) of 86 to Ti(III) of 95 is evident by the coordination of three anionic ligands to the metal center.

Complex 95 adopts a $C_1$-symmetric pentagonal bipyramidal coordination geometry (Figure 3.7). Two 2-pyridonates bind asymmetrically in a $\kappa^2$-$N,O$-chelating motif with the oxygen atom [Ti–O$_{avg}$ 2.1124(15) Å] binding closer to the titanium center than the nitrogen atom [Ti–N$_{avg}$ 2.2282(18) Å] in the equatorial plane. The third 2-pyridonate binds in a $\kappa^1$-$O$ binding motif with much shorter Ti–O bond [1.9790(15) Å]. This solid-state molecular structure confirms the hemilabile nature of these ligands and suggests that these ligands can be fluxional
due to the different possible binding modes \((\text{vide infra})\). The bond lengths in the aromatic ring of these 2-pyridonate ligands remain consistent, and no sign of bond elongation is observed that could suggest a ligand-centered radical. The two benzylamines are neutrally coordinated at the axial position, as evidenced by their long Ti–N\(_{\text{avg}}\) bond length [2.208(2) Å]. The α-hydrogens of benzylamine remain intact, as Q peaks corresponding to the electron density of the methylene hydrogens were present from the collected X-ray diffraction data. The bond angles about the N of each benzylamine are bent [C34–N4–Ti1, 124.10(14) Å; C41–N5–Ti1, 114.83(14) Å], but consistent with anticipated bond angles for sp\(^3\)-hybridization and no evidence of distortion. These observations also indicate that there is no interaction of the α-C–H bonds of benzylamine with the titanium metal center. Furthermore, the N–C\(_{\text{avg}}\) bond length [1.483(3) Å] of benzylamines corresponds to a single N–C bond. The \(^1\)H NMR spectrum of 95 in \(d_6\)-benzene does not show any meaningful signals due to its paramagnetic character.

The paramagnetic character of 95 is further confirmed by EPR spectroscopy. The EPR spectrum of 95 mainly shows single-derivative signals (Figure 3.11), since the most abundant titanium isotope is \(^{48}\)Ti \((I = 0, 73.8\%\) abundance) which has zero nuclear spin. Two different g values \((g_\| = 1.9895\) and \(g_\perp = 1.9535\)) are observed, which is consistent with the axially elongated Ti(III) complex that is observed in the solid-state. A similar g value (1.978) has also been reported with a bis(Cp)mono(2-pyridonate)titanium(III) complex 26.\(^{140}\) Small signals of hyperfine interactions due to the naturally occurring \(^{47}\)Ti \((I = 5/2, 7.3\%\) abundance) and \(^{49}\)Ti \((I = 7/2, 5.5\%\) abundance) isotopes, which have non-zero nuclear spins, can also be seen in the spectrum. More importantly, hyperfine interactions that could arise from radical behavior in the 2-pyridonates should ligand based radical be formed are not present. This observation is
consistent with the solid-state structure of 95 and suggests localization of the unpaired electron on the titanium metal center.

![EPR spectrum](image)

**Figure 3.8** EPR spectrum (toluene, 77 K) of 95 overlaid with simulation

It was noted earlier in Scheme 3.20 that broad signals are observed by $^1$H NMR spectroscopy in hydroaminoalkylation reactions catalyzed by 86, and hydroaminoalkylation reactivity and selectivity decreases over time. When the same reaction is halted and the EPR spectrum taken of the reaction mixture at 4 h, signals corresponding to the signals of the titanium(III) complex 95 are observed (Figure 3.9). However, no paramagnetic species are present prior to heating the reaction, as no signal is observed in the EPR spectrum at $t = 0$. These observations and the isolation of tris(2-pyridonate)titanium(III) complex 95 from a bis(2-pyridonate)titanium complex 86 suggest that ligand redistribution of the complex, as well as the
reduction of the metal center from Ti(IV) to Ti(III), are likely occurring during the hydroaminoalkylation reactions. Such Ti(III) species may be the fate of catalyst decomposition.

Figure 3.9 Stacked EPR spectra (toluene, 77 K) of 95 and the hydroaminoalkylation reaction mixture using substrate 55a and precatalyst 86 showing the presence of paramagnetic species

To test this hypothesis, tris(3-phenyl-2-pyridonate)Ti(NMe₂) 96 has been separately synthesized by a protonolysis reaction of Ti(NMe₂)₄ and three equivalents of 3-phenyl-2-pyridone (Scheme 3.23). In the solid-state, 96 adopts a C₅-symmetric structure with pseudopentagonal bipyramidal coordination geometry (Figure 3.10). All three 2-pyridonates bind asymmetrically to the titanium center in a κ²-N,O-chelating motif with the oxygen atom [Ti–Oₐvg 2.0631(10) Å] binding closer to titanium center than the nitrogen atom [Ti–Nₐvg 2.2006(12) Å]. The axial N,O-chelate binds tighter to the metal center than the two equatorial 2-pyridonates,
presumably due to the availability of more coordination space, as seen by its larger bite angle [O1–Ti1–N1, 62.11(4)°] and shorter Ti1–N1 bond length [2.1864(12) Å]. Multiple bonding character is observed in the Ti–NMe2 bond, deduced from its short bond length [1.8799(12) Å] and trigonal planar sp2-hybridization at the N of the dimethylamido ligand. In the solution phase, three chemically equivalent 2-pyridonate ligands are observed in the 1H NMR spectrum (vide infra), suggesting that the ligands are rapidly exchanging on the NMR time scale.

\[
\begin{align*}
\text{Ph} & \quad \begin{array}{c}
\text{O} \\
\text{NH}
\end{array} \\
& \quad \text{Ti(NMe2)}_4 \\
& \quad \text{benzene, rt} \\
& \quad - \text{HNMe2}
\end{align*}
\]

\(\text{96 (91\%)}\)

**Scheme 3.23** Synthesis of tris(3-phenyl-2-pyridonate)Ti(NMe2)

![Scheme 3.23](image)

**Figure 3.10** ORTEP representation of the solid-state molecular structure of 96 plotted with 50% probability ellipsoids for non-hydrogen atoms. THF solvent molecule omitted for clarity. Selected bond lengths (Å) and angles (deg): Ti1–O1, 2.0889(11); Ti1–O2, 2.0572(10); Ti1–O3, 2.0432(9); Ti1–N1, 2.1864(12); Ti1–N2, 2.2101(12); Ti1–N3, 2.2053(12); Ti1–N4, 1.8799(12); O1–Ti1–N1, 62.11(4); O2–Ti1–N2, 61.58(4); O3–Ti1–N3, 61.87(4); N4–Ti1–O1, 94.54(4); N4–Ti1–N1, 156.43(4).
When the prepared 96 is reacted with three equivalents of benzylamine, 95 is isolated in high yield, reproducibly (Scheme 3.24). It can be recrystallized from a toluene/pentane mixture. An X-ray diffraction study of single crystals of the product unequivocally confirmed that the product of the reaction is 95 (vide supra). Examination of the reaction mixture in $d_6$-benzene by $^1$H NMR spectroscopy reveals broad signals with weak intensity (Figure 3.11, top), and signals corresponding to free benzylamine and 96 are absent in the spectrum. For example, the methylene C–H signals of benzylamine at δ 3.55 (Figure 3.11, middle) and dimethylamido signals of 96 at δ 3.61 (Figure 3.11, bottom) are no longer present in the reaction. Instead, a new singlet is observed at δ 4.60 in the reaction mixture (Figure 3.11, top). Further examination of the reaction mixture by gas chromatography-mass spectrometry (GC-MS) analysis shows the presence of three compounds: benzylamine, 3-phenyl-2-pyridone, and a signal with $m/z = 195$. The identity of this byproduct is $N$-benzyl-1-phenylmethanimine, which was identified by NMR spectroscopy and GC-MS analysis after independent preparation from the condensation of benzaldehyde and benzylamine. Ammonia is also released as a byproduct of the reaction, as evidenced by trapping it as NH$_4$Cl salt. Such method has been used previously in the literature to

![Scheme 3.24 Reaction of tris(3-phenyl-2-pyridone)Ti(NMe$_2$) and benzylamine](image)

Scheme 3.24 Reaction of tris(3-phenyl-2-pyridone)Ti(NMe$_2$) and benzylamine
Figure 3.11 Stacked $^1\text{H}$ NMR (400 MHz, $d_6$-benzene) spectra of the reaction of 96 and benzylamine (top), benzylamine (middle), and 96 (bottom)

detect the presence of NH$_3$.\(^{320}\) When the head space of the reaction vessel is carefully transferred over to a Schlenk tube containing a solution of HCl in dioxane, immediate formation of white NH$_4$Cl salt is observed along the inner walls of the glassware. Analysis of this precipitate by $^1\text{H}$ NMR spectroscopy in $d_6$-DMSO reveals a diagnostic triplet of $^{14}\text{NH}_4\text{Cl}$ centered at $\delta$ 7.12 with a coupling constant of 51 Hz ($^1J_{14\text{N}-1\text{H}}$), thereby confirming ammonia as one of the byproducts of this reaction.

The reproducible synthesis of titanium(III) complex 95 from a tris(2-pyridonate)titanium complex 96 and the identification of byproducts of the reaction, N-benzyl-1-phenylmethanimine and NH$_3$, show that benzylamine is reliably and cleanly reducing Ti(IV) to Ti(III). These results
are consistent with the hypothesis that the bis(2-pyridonate)titanium complex 86 is susceptible to ligand redistribution, followed by reduction of the metal center with a primary amine. Most importantly, the catalytic reaction using 95 with the aminoalkene substrate 55a does not provide any reactivity, ruling out the possibility of radical-catalyzed mechanism involving titanium(III) species. However, the catalytic reaction using 96 with 55a gives the exclusive formation of hydroamination product 55b (24% conv), suggesting that tris(2-pyridonate)titanium(IV) species, formed from ligand redistribution of 86, are responsible for the hydroamination side reactivity.

To further explore whether the 3-phenyl-2-pyridonate ligand is capable of bridging and supporting bimetallic titanium species, a primary amine without an α-C–H bond was targeted. 2,6-Dimethylaniline was used as a primary amine substrate in a 1:1 reaction with 86 (Scheme 3.25). Upon removal of volatiles in vacuo, followed by recrystallization from hot toluene, dark brown crystals of 97 were obtained in 90% yield. Single crystal X-ray analysis of the isolated product shows a bimetallic titanium complex that has a center of inversion (Figure 3.12). Complex 97 has four bridging 2-pyridonates and two terminal imido substituents. Each titanium(IV) center exhibits distorted octahedral coordination geometry. Notably, two different binding modes of the 2-pyridonate ligand are adopted in 97. The two 2-pyridonates in the equatorial plane assume a \( \mu^2-[(\kappa^2-N,O)O] \) bridging motif with the oxygen donor bridging between the two titanium centers. Here the Ti1–O1 bond length [2.3531(10) Å] involved in the \( \kappa^2-N,O \)-chelate is significantly longer than the Ti1’–O1 bond length [1.9791(10) Å] involved in the \( \mu^2-O \)-bridging mode. The other two 2-pyridonates occupy the axial position and bridge via \( \mu^2-N,O \)-bridging motif, and asymmetric binding of the 2-pyridonate ligand is observed [Ti1–O2, 1.9918(10) Å; Ti1–N2’, 2.2159(12) Å]. The imido Ti=N linkage is verified by its short
Scheme 3.25 Stoichiometric reaction of 86 with 2,6-dimethylaniline

Figure 3.12 ORTEP representation of the solid-state molecular structure of 97 plotted with 50% probability ellipsoids for non-hydrogen atoms. Toluene solvent molecule omitted for clarity. Selected average bond lengths (Å) and angles (°): Ti1–O1, 2.3531(10); Ti1–O1’, 1.9791(10); Ti1–O2, 1.9918(10); Ti1–N1, 2.1390(12); Ti1–N2’, 2.2159(12); Ti1–N3, 1.7093(12); N3–C23, 1.3797(17); Ti1–Ti1’, 3.1157(5); N2’–Ti1–O2, 156.82(4); O1–Ti1–O1’, 88.44(4); O1’–Ti1–N3, 111.23(5); N1–Ti1–N3, 101.59(5); O1–Ti1–N1, 58.65(4); C23–N3–Ti1, 173.19(11).
bond length [Ti1–N3 1.7093(12) Å] and its near linear bond angle about the imido N [C23–N3–Ti1, 173.19(11)°]. The distance between the two titanium centers is 3.1157(5) Å, and such distance gap suggests that a bonding interaction does not exist between the two metals.

Complex 97 is very poorly soluble in benzene and toluene and thus, the ¹H NMR spectrum was taken in CDCl₃. However, 97 slowly decomposes in CDCl₃ at room temperature, thereby preventing a reliable variable temperature NMR study from being undertaken. The ¹H NMR spectrum of 97 shows discrete signals corresponding to a 2:1 ratio of 2-pyridonates to imidos, consistent with the solid-state structure. Four chemically equivalent 2-pyridonate ligands are observed, suggesting rapid interconversion between the ligands on the NMR time scale. Similarly, two chemically equivalent 2,6-dimethylaniline imidos are observed with one singlet at δ 1.82 for the methyl groups. These observations suggest that 97 is highly fluxional in solution due to rapid ligand exchange. Furthermore, the catalytic reaction using 97 with the aminoalkene substrate 55a does provide selectivity for intramolecular hydroaminoalkylation (21% conversion, HAA/HA = 17:4). The low conversion is presumably due to the competitive metal binding between 2,6-dimethylaniline and cyclizable aminoalkene substrate.

In order to target a more realistic intermediate in intramolecular hydroaminoalkylation, the primary aminoalkene substrate 55a was reacted with the precatalyst 86 using a similar procedure to the synthesis of 97 (Scheme 3.26). Upon removal of dimethylamine byproduct and solvent in vacuo, followed by recrystallization from toluene at -35 °C afforded yellow-orange crystals of 98 in 64% yield. The identity of 98 has been further confirmed by elemental analysis. Single crystal X-ray structure analysis of 98 also reveals a similar bimetallic titanium structure, containing a center of inversion, with the exact same binding modes of the 2-pyridonates and imido substituents (Figure 3.13). The observed bond lengths and angles in 98 are very similar to
Scheme 3.26 Stoichiometric reaction of 86 with an aminoalkene substrate

Figure 3.13 ORTEP representation of the solid-state molecular structure of 98 (part 1) plotted with 50% probability ellipsoids for non-hydrogen atoms. Toluene solvent molecule omitted for clarity. Selected average bond lengths (Å) and angles (°): Ti1–O1, 2.3635(11); Ti1–O1’, 1.9883(12); Ti1–O2, 2.0060(13); Ti1–N1, 2.1479(14); Ti1–N2’ 2.2223(15); Ti1–N3 1.6958(13); N3–C23 1.4268(19); Ti1–Ti1’, 3.1472(6); N2’–Ti1–O2, 156.44(5); O1–Ti1–O1’, 87.77(4); O1’–Ti1–N3, 111.70(6); N1–Ti1–N3, 101.58(6); O1–Ti1–N1, 58.42(5); C23–N3–Ti1, 172.68(13).
The major difference between 98 and 97 is the amine component. In the solid-state structure of 98, methylene carbon (C23) is present, verified by the single N3–C23 bond length of 1.4268 Å. Furthermore, the bond angles about N3 of the aminoalkene [C23–N3–Ti1 172.68(13)°] confirm that C–H bond interactions to the metal center are not present in this complex.

When the analytically pure 98 is dissolved in $d_8$-toluene, complex decomposition in solution is observed by $^1$H NMR spectroscopy (Appendix B). As such, spectroscopic assignments of the signals could not be definitively assigned. Variable temperature study of 98 also does not provide any further insight on the nature of species in solution, and further decomposition of the complex is seen at elevated temperatures. When 98 is left standing at room temperature in $d_6$-benzene over a period of three days (Scheme 3.27) and examined by $^1$H NMR spectroscopy, two distinct doublet signals that could correspond to the methyl group of the cis and trans hydroaminoalkylation products 55c are observed at $\delta$ 0.46 and $\delta$ 0.32. After quenching the reaction and the $^1$H NMR spectrum retaken in CDCl$_3$, approximately 27% conversion to

![Scheme 3.27](image_url)

**Scheme 3.27** Decomposition of 98 results in the formation of hydroaminoalkylation product
hydroaminoalkylation products 55c is obtained exclusively; the key diagnostic signal for 55c is observed at δ 4.00 (d, –CHNH₂), while the diagnostic signal at δ 3.10 (d, –CHHN–) for hydroamination product 55b is absent. Further analysis by GC-MS also confirms this observation, as signals corresponding to two diastereomers of 55c, unreacted aminoalkene substrate 55a and ligand are present, but not 55b. These results suggest that 98 is a resting state that is in equilibrium with a catalytically active intermediate in the reaction.

The isolation of bimetallic titanium imido complexes 97 and 98 provides concrete evidence that the 3-phenyl-2-pyridonate is capable of bridging two metal centers. While terminal imidos are observed in the solid-state of these complexes, the solution phase of these complexes show that they are highly fluxional, as evidenced by the observation of chemically equivalent ligands in the ¹H NMR spectrum of 97. The decomposition of 98 in solution to moderate formation of hydroaminoalkylation products also suggests that rearrangement presumably occurs in solution to effect the hydroaminoalkylation reactivity. Most importantly, 98 is hydroaminoalkylation selective and moderately catalytically competent using substrate 55a (51% conversion; HAA/HA = 46:5). These results are consistent with the involvement of a bridging dimeric species in this intramolecular hydroaminoalkylation reaction.

### 3.2.6 Deuterium labelling experiments

The overall transformation of intramolecular hydroaminoalkylation involves the cleavage of the α-C–H bond of the primary aminoalkene substrate and replacement with a new C–C bond formation. Hence, the deuterium labelling experiment of the C–H bonds adjacent to N of the aminoalkene is important for gaining insight into the mechanism of intramolecular hydroaminoalkylation. The hydroaminoalkylation using an α-deuterated aminoalkene substrate
**d₂-89a** resulted in approximately 4% incorporation of deuterium onto the methyl group, and 87% of the starting deuterium remained on the α-carbon of the isolated product **d₂-89c-Ts** (Scheme 3.28).

![Scheme 3.28 Intramolecular hydroaminoalkylation of α-deuterated aminoalkene](image)

Regardless of whether a monometallic (Scheme 3.6) or a bimetallic (Scheme 3.10) intramolecular hydroaminoalkylation is taking place, some key features in the hydroaminoalkylation mechanism is uncovered from the results obtained from this deuterium labelling experiment. If the α-C–H activation step is readily reversible throughout the reaction, loss in deuterium at the α-carbon is expected due to the deuterium exchange between α-C–H bonds with the amine N–H bonds to form N–D bonds. Such an event would consequently result in the incorporation of deuterium in the methyl group of the α-alkylated product, arising from the aminolysis of the M–C bond of the 2-titanapyrrolidine intermediate with an N–D bond of the amine. However, this scenario is not readily applicable for intramolecular hydroaminoalkylation using 86 as a precatalyst. Only 13% deuterium loss at the α-carbon and 4% deuterium incorporation at the methyl group were observed in the hydroaminoalkylation product **d₂-89c-Ts** (Scheme 3.28). Furthermore, significantly lower isolated yield (16%) was obtained versus the reaction using non-deuterated substrate 89a (72%, Table 3.3, entry 4), indirectly suggesting that
C–H activation is the turnover-limiting step. These results are different from a related deuterium-labelling experiment by Doye using Ti(NMe₂)₄ as the precatalyst, which suggested a reversible turnover-limiting C–H activation step. In Doye’s experiment, 47% deuterium was incorporated at the methyl group with 69% deuterium remaining at the α-carbon. The comparison of these results from the deuterium labelling experiments between the precatalysts 86 and Ti(NMe₂)₄ suggests that the C–H activation step in the hydroaminoalkylation reaction using 86 is not as readily reversible as using Ti(NMe₂)₄. Additionally, these results also suggest that the alkene insertion step that subsequently follows the C–H activation step is much faster than the reverse of the C–H activation step.

### 3.2.7 Postulated mechanism for intramolecular hydroaminoalkylation

The catalytic reactivity investigations using substrate 55a with the isolated complexes from the synthetic stoichiometric experiments are summarized in Scheme 3.29. The use of a bridging dimeric complexes 97 and 98 result in a hydroaminoalkylation selective reaction, although these complexes are less reactive than 86 as measured by their reaction conversions. While the reduced reactivity of 97 can presumably be explained by competitive metal binding between 2,6-dimethylaniline and the substrate, the reduced reactivity of 98 is not clear at this point. The liberated dimethylamine from the precatalyst 86 could be contributing to aminolysis steps of the reaction. Most importantly, no reactivity is observed when 95 is used as a catalyst, suggesting that titanium(III) species are not active catalysts for hydroaminoalkylation, and radical reaction mechanisms are not involved in this transformation. When the tris(2-pyridonate)titanium complex 96 is used, only the formation of hydroamination product 55b is observed in low conversion, with no formation of the hydroaminoalkylation product 55c.
Taking into consideration of all the aforementioned data and observations, a plausible mechanistic pathway for intramolecular hydroaminoalkylation with precatalyst 86 is proposed (Scheme 3.30). The precatalyst 86 undergoes amido exchange in the presence of excess aminoalkene substrate to give a bimetallic bridging 2-pyridonate terminal imido intermediate A as a resting state, as evidenced by the isolation and hydroaminoalkylation reactivity of 98. Based on the highly fluxional behavior of 2-pyridonate group 4 complexes in solution as noted earlier, presumably A can rearrange to a bridging imido intermediate B, to enter the hydroaminoalkylation catalytic cycle, as previously proposed in Scheme 3.10. The \(\alpha\)-C–H activation of B would result in the bridging titanaziridine intermediate C, analogous to 67 (vide supra). Preliminary deuterium labelling study of the \(\alpha\)-C–H bonds of an aminoalkene substrate suggested that the \(\alpha\)-C–H activation step is not readily reversible and is turnover limiting. The
Scheme 3.30 Postulated simplified mechanism of intramolecular hydroaminoalkylation with 86; gem-disubstituents on aminoalkene omitted for clarity.

Subsequent alkene insertion step would form a new C–C bond and a 2-titanapyrrolidine intermediate D. The protonolysis cleavage of the M–C bond of D by reaction with an incoming equivalent of aminoalkene substrate would liberate the cycloalkylamine product and regenerate B for the next catalytic cycle. Due to the fact that A and B are surrounded in a sea of amine substrates and/or products, these intermediates are likely to be susceptible to amine coordination.
and exchange, and ligand redistribution to give a tris(2-pyridonate)titanium intermediate E at elevated temperatures. This hypothesis is supported by the isolation of the tris(2-pyridonate)titanium complex 95 from the reaction of bis(2-pyridonate)titanium complex 86 and benzylamine. Intermediate E could be responsible for the hydroamination side reactivity observed during the reaction, as the analogous tris(3-Ph-2-pyridonate)Ti(NMe$_2$)$_2$ 96 only shows hydroamination reactivity, but no hydroaminoalkylation reactivity. This would be consistent with increased rates of hydroamination occurring at later stages of the reaction, once catalyst decomposition has had a chance to occur. Finally, E is susceptible to reduction to Ti(III) species F and shutdown in catalytic activity, as evidenced by the observation of broadening of NMR signals, the reliable synthesis of 95 from 96 and benzylamine, as well as the inactivity of 95 with an aminoalkene substrate.

The detailed study on 2-pyridonate titanium complexes provided in this chapter highlight the importance of bimetallic species for targeting intramolecular hydroaminoalkylation reactivity over hydroamination reactivity. The working mechanistic postulate in Scheme 3.30 will assist in the development of new catalysts with enhanced catalytic efficiency and stereoselectivities.

3.3 Conclusion

By screening group 4 and 5 metal complexes, titanium was identified as the preferred metal for intramolecular hydroaminoalkylation. An extensive investigation of various 2-pyridonates on titanium revealed the importance of substituent effects of the ligand on this reaction. In particular, the use of a 3-phenyl-2-pyridonate was found to provide a favorable amount of steric bulk, while a substituent at the 6-position disfavors hydroaminoalkylation reactivity. Such substituent effects are consistent with the potential bridging ability of 2-
pyridonates. Using bis(3-Ph-2-pyridonate)Ti(NMe$_2$)$_2$ 86 as the precatalyst, it has been shown for the first time that intramolecular hydroaminoalkylation of primary aminoalkenes can be achieved selectively over hydroamination to access both 5- and 6-membered cycloalkylamines. Furthermore, a noticeable improvement in diastereoselectivity of up to 19:1 has been realized by utilizing the small titanium metal center in combination with 3-substituted-2-pyridonate ligands.

In an effort to gain further insight into the mechanism for the intramolecular hydroaminoalkylation using 86, a series of stoichiometric, kinetic and deuterium labelling investigations have been performed. Secondary aminoalkenes are known to be unreactive for the reaction, and increased catalyst loading results in higher selectivity for hydroaminoalkylation over hydroamination. These results are consistent with the involvement of bimetallic imido species, and such intermediates (97 and 98) have been isolated from stoichiometric reactions using 86 and amines. Unfortunately, 86 is susceptible to decomposition during the reaction, ultimately resulting in catalyst death. Paramagnetic species are present in the reaction mixture as the catalytic reaction progresses, as broad signals are observed in $^1$H NMR spectrum as well as signals in the EPR spectrum. The decomposition pathway of 86 has been identified as ligand redistribution, followed by reduction of the metal center to Ti(III) by amines. This hypothesis has been supported by the isolation of tris(2-pyridonate)titanium(III) complex 95 from the reaction of 86 and benzylamine. The reliable synthesis of 95 from the reaction of a tris(2-pyridonate)titanium(IV) complex 96 and benzylamine has been further supported by the observation that the 2-pyridonate titanium(IV) complexes are susceptible to reduction with benzylamine as the only reductant. Reactivity investigations of these complexes have ruled out titanium(III) species as being catalytically relevant, and thereby support a 2 e$^-$ mechanistic proposal over a potential radical promoted process. This work also accounts for tris(2-
pyridonate)titanium(IV) species as the source of hydroamination side reactivity. The investigations in this chapter have shed light on the mechanistic pathway of the 2-pyridonate-supported titanium-catalyzed intramolecular hydroaminoalkylation.

3.4 Experimental

General methods. All moisture/air sensitive reactions were conducted in oven-dried (160 °C) glassware using standard Schlenk line and glovebox techniques under an atmosphere of dry nitrogen. Experiments on NMR tube scale were carried out in Teflon cap sealed J. Young NMR tubes (5 mm). Benzene, toluene, and pentane were purified and dried by passage over an activated aluminum oxide column and degassed prior to use. $d_8$-Toluene and $d_6$-benzene were dried over 4 Å molecular sieves and degassed by three freeze-pump-thaw cycles. Thin layer chromatography (TLC) was performed on EMD Silica gel 60 F254 plates. Visualization was done under a 254 nm UV light source and/or by staining with iodine. SiliaFlash F60 silica gel (230-400 mesh) was purchased from Silicycle, and flash column chromatography was performed using glass columns.

Materials. Ti(NMe$_2$)$_4$ (Sigma-Aldrich), Zr(NMe$_2$)$_4$ (Strem), and Hf(NMe$_2$)$_4$ (Strem) were used as received. Aminoalkenes 2,2-diphenyl-5-hexenyl-1-amine (55a),$^{321}$ 1-(but-3-en-1-yl)cyclopentyl)methanamine (87a),$^{229}$ 2,2-dimethyl-5-hexenyl-1-amine (88a),$^{321}$ 2,2-diphenyl-6-heptenyl-1-amine (57a),$^{321}$ 1-(pent-4-en-1-yl)cyclopentyl)methanamine (91a),$^{59}$ 2,2-dimethyl-6-heptenyl-1-amine (92a),$^{59}$ and $N$-methyl-2,2-diphenyl-5-hexenyl-1-amine (93)$^{57}$ were prepared from commercially available reagents as described in the literature. The substrate (2-allylphenyl)methanamine (90a) was donated to us by Bayer CropScience. All aminoalkene
substrates were dried over CaH$_2$ or 4 Å molecular sieves and degassed prior to use. 1,3,5-
Trimethoxybenzene was purchased from Aldrich and sublimed under vacuum prior to use as an
internal standard. 3-Bromo-2-pyridone (TCI America) and aryl boronic acids (Combi-Blocks)
were used as received. 2-Pyridone, 3-methyl-2-pyridone, and 6-methyl-2-pyridone were
purchased from Alfa Aesar and sublimed under heat and vacuum before use. 1-Benzyl-3-bromo-
2-pyridone$^{322}$ 2-(benzyloxy)-3-bromopyridine,$^{323}$ and 3-(trimethylsilyl)-2-pyridone$^{317}$ were
prepared using literature procedures. Synthesized 3-aryl-2-pyridone ligands were also
sublimed or dried by heating under vacuum before use. Complexes $^{34,59}$ $^{68,298}$ $^{69,305}$ $^{71,64}$ $^{72,64}$
TaMe$_3$Cl$_2$,$^{309}$ bis(N-(2,6-diisopropylphenyl)pivalamidate)bis(dimethylamido)titanium,$^{147}$ Bis(N-
(2,6-dimethylphenyl)-benzamidate)bis(dimethylamido)titanium,$^{315}$ bis(3-(2,6-dimethylphenyl)-
1,1-diisopropylureate)-bis(dimethylamido)titanium,$^{58}$ mono(N,6-dimesityl-2-aminopyridinate)-
tris(dimethylamido)titanium (53),$^{324}$ $N$-methyl-2-aminopyridinate titanium complexes (23),$^{68}$
were synthesized as reported in literature.

**Instrumentation.** $^1$H and $^{13}$C NMR spectra were recorded on a Bruker 300 MHz or 400 MHz
Avance spectrometer at ambient temperature and chemical shifts are given relative to the
corresponding residual protio solvent. Chemical shifts $\delta$ are reported in parts per million (ppm)
and, to specify the signal multiplicity, the following abbreviations are used: $s =$ singlet, $d =$
doublet, $t =$ triplet, $q =$ quartet, $m =$ multiplet, and $br =$ broad. Mass spectra (MS) and elemental
analyses (EA) were measured by the mass spectrometry and microanalysis service at the
Department of Chemistry, University of British Columbia. Mass spectra were recorded on a
Kratos MS-50 spectrometer using an electron impact (70 eV) source or a Bruker Esquire LC
spectrometer using electrospray ionization source. Fragment signals are given in mass per charge
number (m/z). Elemental analyses were recorded on a Carlo Erba Elemental Analyzer EA 1108. The content of the specified element is expressed in percent (%). Single-crystal X-ray structure determinations were performed on a Bruker X8 APEX II or APEX DUO diffractometer at the Department of Chemistry, University of British Columbia by Jacky C.-H. Yim or Scott Ryken.

**EPR data acquisition and process.** A Bruker Elexys E500 series continuous wave EPR spectrometer [9.40 GHZ (X-band), 3 Gauss modulation amplitude and 100 KHz field modulation at 77 K] was applied. DPPH (g = 2.0036) was the standard for spectra frequency calibration (Krzystek et al. 1997). Spectrum recorded was simulated using SIMFONIA.

![3-Phenyl-2-pyridone (73)](image)

A modified literature procedure was used. In a 100 mL Schlenk tube, 3-bromo-2-pyridone (3.13 g, 18.0 mmol), phenylboronic acid (2.63 g, 21.6 mmol), Pd(PPh₃)₄ (1.04 g, 0.900 mmol), 30 mL of dimethoxyethane, and K₂CO₃ (18.0 mL of 2M solution, 36.0 mmol) were added successively. The resulting mixture was degassed and replaced with N₂ atmosphere, and stirred at 80 °C in a pre-heated oil bath for 24 h. The reaction was cooled to room temperature and filtered through Celite, and washed with CHCl₃. Water (30 mL) was added to the filtrate, and extracted with CHCl₃ (3 x 60 mL). The combined organic layer was washed with brine, dried over MgSO₄, filtered, concentrated, and the resulting crude product was triturated in hot EtOAc. Once the mixture cooled to room temperature, the product was filtered, washed with EtOAc, followed by a wash with Et₂O to give the product as a white solid (1.78 g, 58%). The ligand was sublimed under heat (~150 °C) and vacuum prior to use. ¹H NMR (400 MHz, CDCl₃): δ 12.93 (br s, 1H), 7.69 (d, J = 7.3 Hz, 2H), 7.57 (dd, J = 6.9, 2.0 Hz, 1H), 7.41 (t, J = 7.5 Hz, 2H), 7.38-7.30 (m, 2H), 6.34 (t, J = 6.7 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 164.2, 139.9, 136.8, 134.0, 131.9,
128.8, 128.5, 128.0, 107.3. HRMS (EI): \( m/z \) calcd for C\(_{11}\)H\(_9\)NO [M\(^+\)]: 171.06841. Found: 171.06847. Anal. calcd for C\(_{11}\)H\(_9\)NO: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.98; H, 5.24; N, 8.29. m.p. 209-210 °C.

General Suzuki coupling procedure for the preparation of 3-aryl-2-pyridones. In a 40 mL Schlenk tube, 3-bromo-2-pyridone (0.696 g, 4.00 mmol), arylboronic acid (4.80 mmol), Pd(PPh\(_3\))\(_4\) (0.231 g, 0.200 mmol), 12 mL of dimethoxyethane, and K\(_2\)CO\(_3\) (4.00 mL of 2M solution, 8.00 mmol) were added successively. The resulting mixture was degassed and replaced with N\(_2\) atmosphere, and stirred at 80 °C in a pre-heated oil bath for 18 h. The reaction was cooled to room temperature and filtered through Celite, and washed with CHCl\(_3\). Water (15 mL) was added to the filtrate, and extracted with CHCl\(_3\) (3 x 40 mL). The combined organic layer was washed with brine, dried over MgSO\(_4\), filtered, and concentrated. The crude residue was purified by column chromatography and/or recrystallization.

3-(p-tolyl)-2-pyridone (74). Following the general Suzuki coupling procedure, the crude residue was purified by recrystallization in a saturated solution of CH\(_2\)Cl\(_2\) at 0 °C overnight to give the product as a white needle (0.220 g, 30%). \(^1\)H NMR spectral data matches reported literature values.\(^{325}\) \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \( \delta \) 11.73 (br s, 1H), 7.64-7.58 (m, 3H), 7.35 (dd, \( J = 6.4, 2.1 \) Hz, 1H), 7.18 (d, \( J = 7.9 \) Hz, 2H), 6.27 (t, \( J = 6.7 \) Hz, 1H), 2.32 (s, 3H).
3-(3,5-dimethylphenyl)-2-pyridone (75). With a slight medication of the general Suzuki coupling procedure, the reaction was carried out on 5 mmol scale, using Na$_2$CO$_3$ as the base instead of K$_2$CO$_3$. The crude residue was purified by flash column chromatography (2% MeOH in CH$_2$Cl$_2$), and recrystallization in a saturated solution of CHCl$_3$ at 0 °C overnight afforded the product as a white crystalline solid (0.617 g, 62%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 13.45 (br s, 1H), 7.53 (dd, $J = 6.9$, 1.9 Hz, 1H), 7.36 (dd, $J = 6.4$, 1.9 Hz, 1H), 7.28 (s, 2H), 6.98 (s, 1H), 6.32 (t, $J = 6.7$ Hz, 1H), 2.36 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 164.4, 139.9, 137.9, 136.7, 134.1, 129.7, 126.6, 107.2, 21.6. HRMS (EI): $m/z$ calcd for C$_{13}$H$_{13}$NO [$M^+$]: 199.09971. Found: 199.09964. Anal. calcd for C$_{13}$H$_{13}$NO: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.13; H, 6.40; N, 7.32.

3-(4-Methoxyphenyl)-2-pyridone (76). Following the general Suzuki coupling procedure, the crude residue was purified by recrystallization in a saturated solution of EtOAc with a minimal amount of CHCl$_3$ at 0 °C overnight to give the product as a white solid (0.417 g, 52%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 12.96 (br s, 1H), 7.63 (d, $J = 8.8$ Hz, 2H), 7.54 (dd, $J = 7.0$, 2.0 Hz, 1H), 7.34 (dd, $J = 6.5$, 2.0 Hz, 1H), 6.95 (d, $J = 8.8$ Hz, 2H), 6.33 (t, $J = 6.7$ Hz, 1H), 3.83 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 164.3, 159.6, 139.0, 133.4, 131.5, 129.9, 129.2, 114.0, 107.3, 55.6. HRMS (EI): $m/z$ calcd for C$_{12}$H$_{11}$NO$_2$ [$M^+$]: 201.07898. Found: 201.07894. Anal. calcd for C$_{12}$H$_{11}$NO$_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.82; H, 5.58; N, 7.11. m.p. 194-195 °C.
**3-(2,4-dimethoxyphenyl)-2-pyridone (77).** Following the general Suzuki coupling procedure, the crude residue was triturated in EtOAc/Et₂O mixture and purified by flash column chromatography (2% to 4% MeOH in CH₂Cl₂) to give the product as a white solid (0.268 g, 29%). ¹H NMR (400 MHz, CDCl₃): δ 12.99 (br s, 1H), 7.47 (dd, J = 6.9, 2.0 Hz, 1H), 7.32-7.27 (m, 2H), 6.56-6.52 (m, 2H), 6.26 (t, J = 6.7 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 160.9, 158.3, 141.6, 133.7, 131.8, 118.6, 106.7, 104.7, 99.4, 55.9, 55.6. HRMS (EI): m/z calcd for C₁₃H₁₃NO₃ [M⁺]: 231.08954. Found: 231.08923. Anal. calcd for C₁₃H₁₃NO₃: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.13; H, 5.59; N, 5.95.

**3-(3,5-Difluorophenyl)-2-pyridone (78).** Following the general Suzuki coupling procedure, the crude residue was purified by recrystallization in a saturated solution of CH₂Cl₂ at 0 °C overnight to give the product as a white solid (0.248 g, 30%). ¹H NMR (400 MHz, CDCl₃): δ 13.37 (br s, 1H), 7.63 (dd, J = 7.1, 2.0 Hz, 1H), 7.46 (dd, J = 6.4, 2.0 Hz, 1H), 7.33-7.24 (m, 2H), 6.78 (tt, J = 8.9, 2.3 Hz, 1H), 6.42 (t, J = 6.7 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 163.6, 163.1 (dd, J = 247.2, 13.1 Hz), 140.6, 139.5 (t, J = 10.1 Hz), 135.2, 129.2 (t, J = 2.5 Hz), 111.6 (dd, J = 18.9, 7.2 Hz), 107.6, 103.4 (t, J = 25.5 Hz). ¹⁹F NMR (282 MHz, CDCl₃): δ –110.7. HRMS (EI): m/z calcd for C₁₁H₇NOF₂ [M⁺]: 207.04957. Found: 207.04944. Anal. calcd for C₁₁H₇NOF₂: C, 63.77; H, 3.41; N, 6.76. Found: C, 64.14; H, 3.55; N, 6.70. m.p. 176-177 °C.
3-(3,5-bis(trifluoromethyl)phenyl)-2-pyridone (79). Following the general Suzuki coupling procedure, the crude residue was purified by flash column chromatography (3% MeOH in CH₂Cl₂), and recrystallization in MeOH afforded the product as a white crystalline solid (0.266 g, 21%). \( ^1 \)H NMR (400 MHz, CDCl₃): \( \delta \) 13.44 (br s, 1H), 8.20 (s, 2H), 7.84 (s, 1H), 7.70 (dd, \( J = 7.0, 1.9 \) Hz, 1H), 7.47 (dd, \( J = 6.4, 1.9 \) Hz, 1H), 6.46 (t, \( J = 6.7 \) Hz, 1H). \( ^{13} \)C NMR (100 MHz, CDCl₃): \( \delta \) 163.7, 141.0, 138.6, 135.8, 131.8 (q, \( J = 33.2 \) Hz), 128.9 (d, \( J = 3.2 \) Hz), 128.6, 123.6 (d, \( J = 272.6 \) Hz), 121.7 (pentet, \( J = 3.7 \) Hz), 107.6. \( ^{19} \)F NMR (282 MHz, CDCl₃): \( \delta \) -63.1. HRMS (EI): \( m/z \) calcd for C₁₃H₇F₆NO [M⁺]: 307.04318. Found: 307.04298. Anal. calcd for C₁₃H₇F₆NO: C, 50.83; H, 2.30; N, 4.56. Found: C, 50.62; H, 2.41; N, 4.52.

1-Benzyl-3-mesityl-2-pyridone (80). A 30 mL Schlenk tube was charged with 1-benzyl-3-bromo-2-pyridone (1.32 g, 5.00 mmol), mesitylboronic acid (1.64 g, 10.0 mmol), Pd(PPh₃)₄ (0.578 g, 0.500 mmol), 5 mL of dimethoxyethane, and Cs₂CO₃ (4.89 g, 15.0 mmol). The resulting mixture was degassed and replaced with N₂ atmosphere, and stirred at 100 °C in a pre-heated oil bath for 24 hours. The reaction was cooled to room temperature, diluted with water (20 mL), and extracted with EtOAc (3 x 40 mL). The combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The crude residue was purified by flash column chromatography (3:1 EtOAc:hexanes) to give the product as a yellow solid (0.867 g, 57%). \( ^1 \)H NMR (400 MHz, CDCl₃): \( \delta \) 7.34-7.21 (m, 6H), 7.16 (dd, \( J = 6.7, 2.1 \) Hz, 1H), 6.90 (s, 2H), 6.19 (t, \( J = 6.8 \) Hz, 1H), 5.19 (s, 2H), 2.28 (s, 3H), 2.07 (s, 6H). \( ^{13} \)C NMR (100 MHz, CDCl₃): \( \delta \)
161.4, 139.4, 137.3, 137.1, 136.6, 136.5, 133.8, 133.0, 129.1, 128.43, 128.40, 128.1, 105.9, 52.6, 21.3, 20.5. HRMS (EI): m/z calcd for C_{21}H_{21}NO [M^+]: 303.16231. Found: 303.16236.

3-Mesityl-2-pyridone (81). A solution of 1-benzyl-3-mesityl-2-pyridone (0.867 g, 2.85 mmol) dissolved in ~15 mL of MeOH/EtOAc (2:1) in a 25 mL round-bottom flask was treated with 10% Pd/C (0.303 g, 10 wt%), and H₂ was bubbled into the solution while stirring for 2 days. The mixture was filtered through Celite, and thoroughly washed with CH₂Cl₂. The filtrate was concentrated and purified by flash column chromatography (3% MeOH in CH₂Cl₂) to give the product as a white solid (0.394 g, 65%). ¹H NMR (400 MHz, CDCl₃): δ 13.41 (br s, 1H), 7.35 (dd, J = 6.5, 2.1 Hz, 1H), 7.26 (dd, J = 6.8, 2.1 Hz, 1H), 6.93 (s, 2H), 6.28 (t, J = 6.7 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 164.1, 141.6, 137.6, 136.8, 134.4, 133.4, 132.1, 128.6, 106.7, 21.3, 20.5. HRMS (EI): m/z calcd for C_{14}H_{15}NO [M^+]: 213.11536. Found: 213.11549. Anal. calcd for C_{14}H_{15}NO: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.89; H, 7.08; N, 6.50. m.p. 228-229 °C.

2-(benzyloxy)-3-phenylpyridine (82). In a Schlenk tube, 2-(benzyloxy)-3-bromopyridine (2.64 g, 10.0 mmol), phenylboronic acid (1.46 g, 12.0 mmol), Pd(PPh₃)₄ (0.578 g, 0.500 mmol), 18 mL of dimethoxyethane, and K₂CO₃ (10 mL of 2M solution, 20.0 mmol) were added successively. The resulting mixture was degassed and replaced with N₂ atmosphere, and stirred at 80 °C in a pre-heated oil bath overnight. The reaction was cooled to room temperature, water (20 mL) was added, and extracted with EtOAc (3 x 60 mL). The combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. The crude residue was purified by flash column chromatography (5% Et₂O in hexanes) to give the product as a colourless oil (2.20 g, 84%). ¹H
NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 8.15 (dd, \(J = 4.9, 1.8\) Hz, 1H), 7.64 (dd, \(J = 7.3, 1.8\) Hz, 1H), 7.61-7.57 (m, 2H), 7.43-7.24 (m, 8H), 6.98 (dd, \(J = 7.2, 5\) Hz, 1H), 5.46 (s, 2H). \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 160.5, 145.9, 139.0, 137.9, 136.9, 129.5, 128.5, 128.4, 127.7, 127.6, 127.5, 125.0, 117.6, 67.8. HRMS (EI): \(m/z\) calcd for C\textsubscript{18}H\textsubscript{15}NO [M\textsuperscript{+}]: 261.11536. Found: 261.11521.

2-(benzyloxy)-5-bromo-3-phenylpyridine (83). A 25 mL round bottom flask was charged with 2-(benzyloxy)-3-phenylpyridine (0.499 g, 1.91 mmol), N-bromosuccinimide (0.340 g, 1.91 mmol), MeCN (~ 10 mL) and refluxed overnight. The resulting red solution was concentrated and purified by flash column chromatography (2% EtOAc in hexanes) to give the product as a white solid (0.430 g, 66%). \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 8.17 (d, \(J = 2.4\) Hz, 1H), 7.73 (d, \(J = 2.4\) Hz, 1H), 7.55 (d, \(J = 7.9\) Hz, 2H), 7.43-7.24 (m, 8H), 5.42 (s, 2H). \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 159.3, 146.2, 141.1, 137.4, 135.5, 129.4, 128.6, 128.5, 128.3, 127.8, 127.7, 126.7, 112.4, 68.2. HRMS (EI): \(m/z\) calcd for C\textsubscript{18}H\textsubscript{14}NOBr [M\textsuperscript{+}]: 339.02588. Found: 339.02584.

2-(benzyloxy)-3,5-diphenylpyridine (84). In a Schlenk tube, 2-(benzyloxy)-5-bromo-3-phenylpyridine (0.398 g, 1.17 mmol), phenylboronic acid (1.71 g, 1.40 mmol), Pd(PPh\textsubscript{3})\textsubscript{4} (0.0676 g, 0.0585 mmol), 5 mL of dimethoxyethane, and K\textsubscript{2}CO\textsubscript{3} (1.2 mL of 2M solution, 2.34 mmol) were added successively. The resulting mixture was degassed and replaced with N\textsubscript{2} atmosphere, and stirred at 80 °C in a pre-heated oil bath overnight. The reaction was cooled to room temperature, water (5 mL) was added, and extracted with EtOAc (3 x 15 mL). The combined organic layer was washed with brine, dried over MgSO\textsubscript{4}, filtered, and concentrated. The crude residue was purified by flash column chromatography (4% EtOAc in hexanes) to give
the product as a white solid (0.376 g, 95%). $^1$H NMR (400 MHz, CDCl$_3$): δ 8.38 (d, $J = 2.4$ Hz, 1H), 7.87 (d, $J = 2.5$ Hz, 1H), 7.67-7.63 (m, 2H), 7.60-7.55 (m, 2H), 7.48-7.25 (m, 11H), 5.52 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 159.9, 143.9, 138.03, 137.96, 137.8, 136.8, 131.0, 129.5, 129.2, 128.6, 128.4, 127.9, 127.7, 127.64, 127.56, 127.0, 124.8, 67.9. HRMS (EI): $m/z$ calcd for C$_{24}$H$_{19}$NO [M$^+$]: 337.14666. Found: 337.14685.

3,5-diphenyl-2-pyridone (85). To a solution of 2-(benzyloxy)-3,5-diphenylpyridine (0.351 g, 1.04 mmol) dissolved in ~10 mL of MeOH/EtOAc (1:1) was treated with 10% Pd/C (0.111 g, 10 wt%) in a Fischer-Porter tube. Hydrogenolysis was carried out under 30-40 psi of H$_2$ atmosphere for 2 hours. The reaction mixture was filtered through Celite, and thoroughly washed with CH$_2$Cl$_2$. The filtrate was concentrated and purified by flash column chromatography (4% MeOH in CH$_2$Cl$_2$) to give the product as a white solid (0.231 g, 90%).$^1$H NMR (400 MHz, CDCl$_3$): δ 13.19 (br s, 1H), 7.89 (d, $J = 2.6$ Hz, 1H), 7.76 (d, $J = 7.1$ Hz, 2H), 7.63 (d, $J = 2.6$ Hz, 1H), 7.48-7.26 (m, 10H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 163.6, 139.7, 136.8, 136.7, 131.7, 131.3, 129.3, 128.9, 128.6, 128.2, 127.6, 126.1, 121.5. HRMS (EI): $m/z$ calcd for C$_{17}$H$_{13}$NO [M$^+$]: 247.09971. Found: 247.09991.

Bis(3-phenyl-2-pyridonate)bis(dimethylamido)titanium (86). A Teflon capped 20 mL vial, equipped with a magnetic stir bar, was charged with 3-phenyl-2-pyridone (0.685 g, 4.00 mmol) and ~3 mL of benzene. To this vial, Ti(NMe$_2$)$_4$ (0.448 g, 2.00 mmol) dissolved in ~3 mL of benzene was quantitatively added. The mixture was stirred at room temperature for 4 hours, upon which a deep red solution was obtained. The solvent was removed in vacuo to afford the analytically pure
complex as an orange red solid (>98%). Crystals suitable for X-ray crystallography were obtained from a saturated solution of the complex in benzene layered with pentane. $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 8.04 (d, $J$ = 7.4 Hz, 4H), 7.41 (dd, $J$ = 5.1, 3.4 Hz, 2H), 7.36-7.30 (m, 6H), 7.20-7.17 (m, 2H), 6.10 (dd, $J$ = 7.5, 5.3 Hz, 2H), 3.49 (s, 12H). $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 170.2, 142.2, 139.1, 137.2, 129.2, 129.0, 127.9, 121.9, 113.6, 46.7. MS (EI): $m/z$ = 476 (M$^+$), 432 (M$^+$–NMe$_2$), 388 (M$^+$–2NMe$_2$). Anal. calcd for C$_{26}$H$_{28}$N$_4$O$_2$Ti: C, 65.55; H, 5.92; N, 11.76. Found: C, 65.80; H, 5.84; N, 11.57.

**General Procedure for Monitoring Intramolecular Hydroaminoalkylation (HAA)/Hydroamination (HA) Reactions.** For catalytic screening purposes, precatalysts were prepared by an analogous procedure to the preparation of 86 or prepared *in situ* by mixing Ti(NMe$_2$)$_4$ (1 equiv) and proligand (1 or 2 equiv) for 5 min in d$_8$-toluene. Precatalyst (0.0300 mmol, 20 mol %) and 1,3,5-trimethoxybenzene (1.25 M in d$_8$-toluene, 40.0 $\mu$L, 0.0500 mmol) were dissolved in d$_8$-toluene (460 $\mu$L) in a one dram vial. The substrate 2,2-diphenyl-5-hexenyl-1-amine (55a) (1.50 M in d$_8$-toluene, 100 $\mu$L, 0.150 mmol) was then added to the vial and mixed with a Pasteur pipet. The resulting solution was transferred to a J. Young NMR tube, closed with a Teflon cap, and $^1$H NMR spectrum was recorded. The NMR tube was placed in a preheated oil bath at 110 °C for 24 h. The progress of the reaction was monitored by the disappearance of alkene signals of 55a centered at $\delta$ 5.68 and 4.90 ppm, and the appearance of new proton signals at $\delta$ 3.72 ppm and/or 0.90 ppm for HAA and $\delta$ 2.84 and/or 0.83 ppm for HA. For those reactions that resulted in broad signals, the reaction was exposed to air, quenched with Et$_2$O. Once the mixture clarified upon sitting, filtered through Celite, concentrated and the $^1$H NMR spectrum was taken in CDCl$_3$. 

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(signals monitored for cis HAA product 55c at δ 4.00 ppm, trans HAA product 55c at δ 3.29 ppm, and HA product 55b at δ 3.10 ppm).

**General Procedure for the Substrate Scope of Intramolecular Hydroaminoalkylation.** In a nitrogen filled glovebox, the precatalyst 86 (0.0600 mmol, 10 mol %) was dissolved toluene (1.2 mL) in a one dram vial, followed by the addition of aminoalkene (0.600 mmol). The solution was quantitatively transferred to a 10 mL Schlenk tube, equipped with a Teflon screw cap and a magnetic stirring bar, with additional amount of toluene (1.2 mL). The Schlenk tube was then sealed, heated to, and maintained at the appropriate temperature for 24 h. After cooling to room temperature, the Schlenk tube was brought back into the glovebox and charged with additional precatalyst 86 (0.0600 mmol, 10 mol %) and heated for an additional 24 h. For amines that did not require derivatization for isolation, the reaction mixture was exposed to air, quenched with Et₂O, stirred until the mixture clarified, filtered through Celite, and concentrated. The crude residue was purified by flash column chromatography. For amines that were derivatized for isolation, the contents of Schlenk tube were transferred to a 25 mL round-bottom flask, and rinsed with CH₂Cl₂ (3 x 3 mL) for quantitative transfer. For tosylation, the reaction mixture was treated sequentially with 2M NaOH (0.900 mL, 1.80 mmol, 3.00 equiv) and p-toluenesulfonyl chloride (0.143 g, 0.750 mmol, 1.25 equiv). The resulting biphasic mixture was stirred vigorously at room temperature overnight. For benzylation or naphthoylation, the reaction mixture was treated with NEt₃ (250 μL, 1.80 mmol, 3.00 equiv) and, respectively, benzoyl chloride (87.1 μL, 0.750 mmol, 1.25 equiv) or 1-naphthoyl chloride (113 μL, 0.750 mmol, 1.25 equiv). The resulting mixture was stirred at room temperature overnight. Upon completion of the reaction, EtOAc (60 mL) and H₂O (20 mL) were added, and extracted. The aqueous layer was
further extracted with additional EtOAc (30 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography.

(+/-)-cis-5-methyl-2,2-diphenylcyclopentanamine$^{200}$ (cis-55c) and (+/-)-trans-5-methyl-2,2-diphenylcyclopentanamine (trans-55c). Purification by flash column chromatography (2% iPr$_2$NH in 1:1 Et$_2$O:hexanes) gave the cis isomer as a white solid (0.091 g, 60%) and the trans isomer as colourless oil (0.019 g, 13%). The relative stereochemistry was assigned based on the crystal structure of cis-55c-Ts, grown from a solution of cyclohexane cooled to 8 °C. The trans to cis ratio of 1:5 was determined from the $^1$H NMR spectrum of the crude reaction mixture.

(+/-)-cis-5-methyl-2,2-diphenylcyclopentanamine (cis-55c).$^{200}$ $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39 (d, $J = 7.4$ Hz, 2H, Ar–H), 7.33-7.19 (m, 6H, Ar–H), 7.13-7.06 (m, 2H, Ar–H), 4.00 (d, $J = 4.8$ Hz, 1H, –CHNH$_2$–), 2.66-2.52 (m, 2H, –CHCH$_3$–, –CHH–), 2.30-2.17 (m, 1H, –CHH–), 1.96-1.83 (m, 1H, –CHH–), 1.53-1.42 (m, 1H, –CHH–), 1.00 (d, $J = 7.0$ Hz, 3H, –CH$_3$), 0.96 (br s, 2H, –NH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.4 (C), 147.0 (C), 128.7 (CH), 128.5 (CH), 128.2 (CH), 126.8 (CH), 125.9 (CH), 125.8 (CH), 61.8 (CH), 61.5 (C), 35.0 (CH), 32.9 (CH$_2$), 29.2 (CH$_2$), 15.8 (CH$_3$). HRMS (ESI): $m/z$ calcd for C$_{18}$H$_{22}$N [M+H$^+$]: 252.1752. Found: 252.1748. Anal. calcd for C$_{18}$H$_{21}$N: C, 86.01; H, 8.42; N, 5.57. Found: C, 86.18; H, 8.53; N, 5.32. m.p. 78-79 °C.

(+/-)-cis-4-methyl-N-(5-methyl-2,2-diphenylcyclopentyl)benzenesulfonamide (cis-55c-Ts). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.54 (d, $J = 8.2$ Hz, 2H, Ar–H), 7.23 (d, $J = 8.2$ Hz, 2H, Ar–H), 7.18-7.14 (m, 4H, Ar–H), 7.09 (t, $J = 7.2$ Hz, 1H, Ar–H), 7.01 (s, 5H, Ar–H), 4.63 (dd, $J = 9.5$,
6.7 Hz, 1H, –CHNHTs–), 4.13 (br d, J = 9.5 Hz, 1H, –NHTs), 2.51-2.40 (m, 1H, –CHH–), 2.40 (s, 3H, Ar–CH3), 2.41-2.27 (m, 2H, –CHCH3–, –CHH–), 1.95-1.84 (m, 1H, –CHH–), 1.48-1.37 (m, 1H, –CHH–), 0.76 (d, J = 7.1 Hz, 3H, –CHH3–). 13C NMR (100 MHz, CDCl3): δ 147.4 (C), 144.2 (C), 143.1 (C), 138.8 (C), 129.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.2 (CH), 126.7 (CH), 126.3 (CH), 126.2 (CH), 63.6 (CH), 59.2 (C), 35.5 (CH), 35.4 (CH2), 29.5 (CH2), 21.7 (CH3), 17.3 (CH3). HRMS (EI): m/z calcd for C25H27NO2S [M+]: 405.17625. Found: 405.17647. m.p. 82-83 °C. (+/-)-trans-5-methyl-2,2-diphenylcyclopentanamine (trans-55c). 1H NMR (400 MHz, CDCl3): δ 7.32-7.20 (m, 6H, Ar–H), 7.16 (t, J = 7.2 Hz, 2H, Ar–H), 7.08 (d, J = 7.9 Hz, 2H, Ar–H), 3.29 (d, J = 10.3 Hz, 1H, –CHNH2–), 2.71-2.62 (m, 1H, –CHCH3–), 2.17-2.08 (m, 1H, –CHH–), 2.08-1.95 (m, 1H, –CHH–), 1.57-1.45 (m, 1H, –CHH–), 1.45-1.33 (m, 1H, –CHH–), 1.06 (d, J = 6.4 Hz, 3H, –CH3), 1.05 (br s, 2H, –NH2). 13C NMR (100 MHz, CDCl3): δ 150.3 (C), 145.0 (C), 129.8 (CH), 128.3 (CH), 127.62 (CH), 127.61 (CH), 126.2 (CH), 125.9 (CH), 64.3 (CH), 58.2 (C), 40.0 (CH), 38.0 (CH2), 29.4 (CH2), 18.4 (CH3). HRMS (ESI): m/z calcd for C18H22N [M+H+] : 252.1752. Found: 252.1748.

(+/-)-cis-4-methyl-N-(2-methylspiro[4.4]nonan-1-yl)benzenesulfonamide (cis-87c-Ts). Purification by flash column chromatography (10% EtOAc in hexanes) gave the cis product as a white crystalline solid (0.123 g, 67%). The relative stereochemistry was assigned based on the crystal structure of the product, grown from a solution of CHCl3/hexanes. The trans to cis ratio of 1:10 was determined from the 1H NMR spectrum of the crude reaction mixture.
(+/-)-cis-4-methyl-N-(2-methylspiro[4.4]nonan-1-yl)benzenesulfonamide (cis-87c-Ts). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.77 (d, $J = 8.2$ Hz, 2H, Ar–H), 7.26 (d, $J = 8.0$ Hz, 2H, Ar–H), 4.85 (br d, $J = 9.9$ Hz, 1H, –NHTs), 3.31 (dd, $J = 9.8$, 6.8 Hz, 1H, –CHNHT–), 2.40 (s, 3H, Ar–CH$_3$), 2.03 (septet, $J = 7.4$ Hz, 1H, –CHCH$_3$–), 1.81-1.70 (m, 1H, –CHH–), 1.56-1.09 (m, 11H, –CH$_2$–), 0.68 (d, $J = 7.0$ Hz, 3H, –CHC$_3$–). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 143.1 (C), 138.9 (C), 129.6 (CH), 127.2 (CH), 65.2 (CH), 39.1 (CH$_2$), 36.4 (CH$_2$), 35.6 (CH), 34.0 (CH$_2$), 30.0 (CH$_2$), 24.9 (CH$_2$), 24.5 (CH$_2$), 21.7 (CH$_3$), 16.3 (CH$_3$). HRMS (EI): $m/z$ calcd for C$_{17}$H$_{25}$NO$_2$S [M$^+$]: 307.16060. Found: 307.16034. Anal. calcd for C$_{17}$H$_{25}$NO$_2$S: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.57; H, 8.33; N, 4.45. m.p. 151-152 °C.

(+/-)-trans-4-methyl-N-(2-methylspiro[4.4]nonan-1-yl)benzenesulfonamide (trans-87c-Ts). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.78 (d, $J = 8.2$ Hz, 2H, Ar–H), 7.27 (d, $J = 8.1$ Hz, 2H, Ar–H), 4.78 (br d, $J = 9.2$ Hz, 1H, –NHTs), 2.98 (t, $J = 9.4$ Hz, 1H, –CHNHT–), 2.41 (s, 3H, Ar–CH$_3$), 1.80-1.68 (m, 1H, –CHCH$_3$–), 1.67-1.35 (m, 9H, –CH$_2$–), 1.31-1.17 (m, 2H, –CHH–), 1.15-1.03 (m, 1H, –CHH–), 0.66 (d, $J = 6.6$ Hz, 3H, –CHCH$_3$–). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 143.2 (C), 139.2 (C), 129.6 (CH), 127.3 (CH), 67.8 (CH), 52.9 (C), 40.4 (CH), 36.9 (CH$_2$), 36.8 (CH$_2$), 32.8 (CH$_2$), 29.2 (CH$_2$), 24.5 (CH$_2$), 24.3 (CH$_2$), 21.7 (CH$_3$), 18.5 (CH$_3$). HRMS (EI): $m/z$ calcd for C$_{17}$H$_{25}$NO$_2$S [M$^+$]: 307.16060. Found: 307.16077. Anal. calcd for C$_{17}$H$_{25}$NO$_2$S: C, 66.41; H, 8.20; N, 4.56. Found: C, 66.37; H, 8.00; N, 4.45. m.p. 141-142 °C.
(+/-)-cis-4-methyl-N-(2,2,5-trimethylcyclopentyl)benzenesulfonamide$^{200}$

(cis-88c-Ts). Purification by flash column chromatography (10% EtOAc in hexanes) gave the cis product as a white crystalline solid (0.089 g, 53%).

The trans to cis ratio of 1:7 was determined from the $^1$H NMR spectrum of the crude reaction mixture. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.76 (d, $J = 7.9$ Hz, 2H, Ar–H), 7.26 (d, $J = 7.7$ Hz, 2H, Ar–H), 4.71 (br d, $J = 10.2$ Hz, 1H, –NHTs), 3.22 (t, $J = 9.2$ Hz, 1H, –CHNHTs–), 2.40 (s, 3H, Ar–CH$_3$), 2.12 (septet, $J = 7.6$ Hz, 1H, –CHCH$_3$–), 1.81-1.71 (m, 1H, –CH–), 1.47-1.38 (m, 1H, –CH–), 1.35-1.14 (m, 2H, –CH$_3$–), 0.86 (s, 3H, –CH$_3$), 0.81 (s, 3H, –CH$_3$), 0.73 (d, $J = 7.1$ Hz, 3H, –CHCH$_3$–). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 143.2 (C), 138.8 (C), 129.7 (CH), 127.2 (CH), 65.7 (CH), 42.0 (C), 38.1 (CH$_2$), 35.2 (CH), 30.6 (CH$_2$), 28.9 (CH$_3$), 23.9 (CH$_3$), 21.7 (CH$_3$), 16.8 (CH$_3$). HRMS (El): m/z calcd for C$_{15}$H$_{23}$NO$_2$S [M$^+$]: 281.14495. Found: 281.14515. Anal. calcd for C$_{15}$H$_{23}$NO$_2$S: C, 64.02; H, 8.24; N, 4.98. Found: C, 64.25; H, 8.45; N, 4.85.

1-(3-Methylbut-3-en-1-yl)cyclohexane-1-carbonitrile. LDA was prepared beforehand in a 500 mL Schlenk flask by adding diisopropylamine (8.40 mL, 60.0 mmol) to a solution of nBuLi (57.2 mmol, 1.6 M in hexanes) in THF (150 mL) at -78 °C and stirring for 15 min. Cyclohexanecarbonitrile (6.49 mL, 54.6 mmol) was slowly added to the suspension of LDA, and the mixture was stirred for 30 min while warming to 0 °C. 4-Bromo-2-methyl-1-butene (8.94 g, 60.0 mmol) was added via syringe and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with sat. aq. NH$_4$Cl solution and H$_2$O, extracted with Et$_2$O two times, dried over MgSO$_4$, filtered, and concentrated. Purification by flash column chromatography (2-4% EtOAc in hexanes) gave the product as a pale yellow liquid (9.14 g, 94%). $^1$H NMR (400 MHz, CDCl$_3$): δ 4.72 (s, 1H), 4.69
(1-(3-Methylbut-3-en-1-yl)cyclohexyl)methanamine (89a). To a suspension of LiAlH₄ (2.35 g, 61.8 mmol) in Et₂O (100 mL) in a 250 mL round-bottom flask at 0 °C, 1-(3-methylbut-3-en-1-yl)cyclohexane-1-carbonitrile (9.13 g, 51.5 mmol) dissolved in Et₂O was slowly added. The reaction mixture was allowed to warm to room temperature and stirred for additional 2 h. The reaction was cooled to 0 °C, and quenched with H₂O (2.3 mL), 1M NaOH (2.3 mL) and H₂O (6.9 mL). The resulting white granules were filtered, the filtrate concentrated, and dried over CaH₂ overnight. Vacuum distillation gave the product as colourless oil (8.16 g, 87%). ¹H NMR (400 MHz, CDCl₃): δ 4.67 (s, 2H), 2.51 (s, 2H), 1.90-1.83 (m, 2H), 1.72 (s, 3H), 1.47-1.17 (m, 12H), 0.97 (br s, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 147.1, 109.5, 48.7, 36.5, 33.7, 33.2, 31.4, 26.7, 22.9, 21.7. HRMS (ESI): m/z calcd for C₁₂H₂₄N [M+H⁺]: 182.1909. Found: 182.1911. The deuterated analogue (d₂-89a) was synthesized using the same procedure using LiAlD₄ instead of LiAlH₄.

N-(2,2-dimethylspiro[4.5]decan-1-yl)-4-methylbenzenesulfonamide (89c-Ts). Purification by flash column chromatography (10% EtOAc in hexanes) gave the product as a white solid (0.145 g, 72%). ¹H NMR (400 MHz, CDCl₃): δ 7.77 (d, J = 8.2 Hz, 2H, Ar–H), 7.26 (d, J = 8.2 Hz, 2H, Ar–H), 4.66 (br d, J = 10.6 Hz, 1H, –NHTs), 2.78 (d, J = 10.6 Hz, 1H, –CHNHTs–), 2.39 (s, 3H, Ar–CH₃), 1.53-1.16 (m, 11H, –CH₂–), 1.10-1.05 (m, 2H, –CHH–), 0.95-0.82 (m, 1H, –CHH–), 0.76 (s, 3H, –CH₃), 0.68 (s, 3H, –CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 143.2 (C), 139.3 (C), 129.6

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(CH), 127.5 (CH), 72.8 (CH), 44.6 (C), 41.3 (C), 37.6 (CH₂), 37.5 (CH₂), 33.7 (CH₂), 32.2 (CH₂), 29.0 (CH₃), 25.9 (CH₂), 23.9 (CH₂), 23.1 (CH₃), 22.6 (CH₂), 21.7 (CH₃). HRMS (EI): m/z calcld for C₁₉H₂₉NO₂S [M⁺]: 335.19190. Found: 335.19203. Anal. calcld for C₁₉H₂₉NO₂S: C, 68.02; H, 8.71; N, 4.17. Found: C, 68.10; H, 8.84; N, 3.99. m.p. 142-144 °C.

(d₂-89c-Ts). Purification by flash column chromatography (10% EtOAc in hexanes) gave the product as a white solid (0.033 g, 16%). The deuterium percentage values were determined by NMR spectroscopy (see Appendix B, page 259). The relaxation time was first determined to allow proper integration of the proton signals. The α-C–H signal at δ 2.78 was integrated relative to the tosyl CH₃ signal at δ 2.39; H (13%) which corresponds to D (87%). The deuterium percentage (4%) at the methyl group was determined by relative integration to the α-C–D signal.

(+/-)-trans-4-methyl-N-(2-methyl-2,3-dihydro-1H-inden-1-yl)benzenesulfonamide  (trans-90c-Ts) and (+/-)-cis-4-methyl-N-(2-methyl-2,3-dihydro-1H-inden-1-yl)benzenesulfonamide (cis-90c-Ts). Purification by flash column chromatography (10% EtOAc in hexanes) gave the product as a mixture of trans/cis isomers (3:1) as a white solid (0.127 g, 70%). The relative stereochemistry was assigned based on the crystal structure of trans-90c-Ts, grown from a solution of EtOAc/hexanes.
(±)-trans-4-methyl-N-(2-methyl-2,3-dihydro-1H-inden-1-yl)benzenesulfonamide \((\text{trans}-90\text{c-Ts})\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.84 (d, \(J = 8.2\) Hz, 2H, Ar–H), 7.32 (d, \(J = 8.1\) Hz, 2H, Ar–H), 7.19-7.05 (m, 3H, Ar–H), 6.88 (d, \(J = 7.5\) Hz, 1H, Ar–H), 4.69 (br d, \(J = 9.1\) Hz, 1H, –NHTs), 4.35 (t, \(J = 8.5\) Hz, 1H, –CHNHTs–), 3.00 (dd, \(J = 15.7, 7.8\) Hz, 1H, –CHH–), 2.44 (s, 3H, Ar–CH\(_3\)), 2.17 (septet, \(J = 7.5\) Hz, 1H, –CHCH\(_3\)), 1.04 (d, \(J = 6.7\) Hz, 3H, –CHC\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 143.7 (C), 142.7 (C), 142.3 (C), 138.7 (C), 130.0 (CH), 128.3 (CH), 127.4 (CH), 127.1 (CH), 124.9 (CH), 124.2 (CH), 65.5 (CH), 44.5 (CH), 38.3 (CH\(_2\)), 21.8 (CH\(_3\)), 17.6 (CH\(_3\)). m.p. 148-149 °C.

(+/-)-cis-4-methyl-N-(2-methyl-2,3-dihydro-1H-inden-1-yl)benzenesulfonamide \((\text{cis}-90\text{c-Ts})\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.85 (d, \(J = 8.2\) Hz, 2H, Ar–H), 7.34 (d, \(J = 8.0\) Hz, 2H, Ar–H), 7.22-7.06 (m, 3H, Ar–H), 6.84 (d, \(J = 7.5\) Hz, 1H, Ar–H), 4.81 (dd, \(J = 9.2, 6.8\) Hz, 1H, –NHTs), 4.73 (br d, \(J = 9.5\) Hz, 1H, –CHNHTs–), 2.95 (dd, \(J = 15.2, 6.9\) Hz, 1H, –CHH–), 2.64-2.51 (m, 2H, –CHH–, –CHCH\(_3\)), 2.46 (s, 3H, Ar–CH\(_3\)), 0.93 (d, \(J = 6.8\) Hz, 3H, –CHCH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): δ 143.6 (C), 142.1 (C), 141.6 (C), 138.6 (C), 130.0 (CH), 128.4 (CH), 127.3 (CH), 127.0 (CH), 125.3 (CH), 124.4 (CH), 61.3 (CH), 38.4 (CH\(_2\)), 38.0 (CH), 21.8 (CH\(_3\)), 15.0 (CH\(_3\)). m.p. 132-133 °C.

HRMS (EI): \(m/z\) calcd for C\(_{17}\)H\(_{19}\)NO\(_2\)S (mixture of diastereomers) [M\(^{+}\)]: 301.11365. Found: 301.11351. Anal. calcd for C\(_{17}\)H\(_{19}\)NO\(_2\)S (mixture of diastereomers): C, 67.74; H, 6.35; N, 4.35. Found: C, 67.68; H, 6.28; N, 4.48.

\((\pm\)-trans-6-methyl-2,2-diphenylcyclohexanamine\(^{59}\) \((\text{trans}-57\text{c})\). Purification by flash column chromatography (2% NEt\(_3\) in 4:1 hexanes:Et\(_2\)O) gave the product as a white solid (0.126 g, 79%). The trans to cis ratio of 10:1 was determined.
from the $^1$H NMR spectrum of the crude reaction mixture.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.83 (d, $J = 7.5$ Hz, 2H, Ar–H), 7.36-7.10 (m, 8H, Ar–H), 3.04 (d, $J = 10.6$ Hz, 1H, –CHNH$_2$–), 2.47-2.41 (m, 1H, –CHH–), 2.20-2.09 (m, 2H, –CHCH$_3$–, –CHH–), 1.76-1.71 (m, 1H, –CHH–), 1.59-1.50 (m, 1H, –CHH–), 1.46-1.32 (m, 1H, –CHH–), 1.31-1.15 (m, 1H, –CHH–), 1.19 (br s, 2H, –NH$_2$), 1.02 (d, $J = 6.4$ Hz, 3H, –CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 149.4, 144.3, 131.3, 128.22, 128.19, 127.9, 126.1, 125.9, 66.5, 53.2, 40.0, 35.9, 34.3, 22.7, 20.1.

(+/-)-trans-$N$-(7-methylspiro[4.5]decan-6-yl)benzamide$^{59}$ (trans-91c-Bz).

Purification by flash column chromatography (6:1 hexanes:Et$_2$O) gave the product as a white crystalline solid (0.124 g, 76%). The trans to cis ratio of 9:1 was determined from the $^1$H NMR spectrum of the crude reaction mixture. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.74 (d, $J = 7.7$ Hz, 2H, o-Ar–H), 7.50-7.38 (m, 3H, m-, p-Ar–H), 5.84 (br d, $J = 9.6$ Hz, 1H, –NH–), 3.80 (t, $J = 10.7$ Hz, 1H, –CHNH–), 1.75-1.08 (m, 15H, –C$_2$H$_{15}$, –CHCH$_3$–), 0.91 (d, $J = 6.4$ Hz, 3H, –CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 167.8, 135.4, 131.4, 128.8, 127.0, 60.3, 47.5, 39.1, 38.6, 36.3, 34.7, 30.6, 26.6, 25.5, 22.5, 19.6.

(+/-)-trans-$N$-(2,2,6-trimethylcyclohexyl)-1-naphthamide$^{59}$ (N-1-naphthoyl)-trans-92c). Purification by flash column chromatography (10% EtOAc in hexanes) gave the product as a white crystalline solid (0.133 g, 75%). The trans to cis ratio of 19:1 was determined from the $^1$H NMR spectrum of the crude reaction mixture. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.29 (d, $J = 7.9$ Hz, 2H, Ar–H), 7.90-7.82 (m, 2H, Ar–H), 7.58-7.40 (m, 4H, Ar–H), 5.67 (br d, $J = 10.0$ Hz, 1H, –NH–), 3.76 (t, $J = 10.8$ Hz, 1H, –CH(NH(C=O)Ar–), 1.83-1.75 (m, 1H), 1.56-1.38 (m, 5H), 1.23-0.99
(m, 1H), 1.10 (s, 3H, –CH₃), 1.04 (d, J = 6.5 Hz, 3H, –CHCH₃–), 0.87 (s, 3H, –CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 169.7, 135.9, 133.9, 130.5, 130.4, 128.4, 127.3, 126.7, 125.8, 124.9, 124.3, 61.6, 40.5, 35.7, 35.1, 34.0, 30.1, 21.7, 19.8, 19.7.

2,2-Diphenyl-5-hexenal. Prepared by following literature procedure using 2,2-diphenyl-5-hexenenitrile. ¹H NMR spectral data matches reported literature values. ¹H NMR (400 MHz, CDCl₃): δ 9.79 (s, 1H), 7.38-7.16 (m, 10H), 5.83-5.71 (m, 1H), 5.00-4.89 (m, 2H), 2.39-2.33 (m, 2H), 1.82-1.74 (m, 2H).

N-Phenyl-2,2-diphenyl-5-hexenyl-1-amine (94). To a solution of 2,2-diphenyl-5-hexenal (2.50 g, 10.0 mmol) and aniline (0.931 g, 10.0 mmol) in CH₂Cl₂ in a 50 mL round-bottom flask, NaBH(OAc)₃ (4.24 g, 20.0 mmol) was added and stirred for 5 min. Then acetic acid (0.570 mL, 10.0 mmol) was added, and the reaction mixture was stirred overnight. The organic phase was poured into 1M NaOH and stirred until the evolution of gas ceased. The organic layer was separated, and the aqueous phase was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated. Crude ¹H NMR analysis showed the presence of unreacted imine and the desired product. The crude residue was added dropwise to a suspension of LiAlH₄ (0.380 g, 10.0 mmol) in Et₂O in a 100 mL round-bottom flask at 0 °C, and stirred at room temperature for an additional 30 min. The reaction was cooled to 0 °C and quenched with H₂O (0.38 mL), 1M NaOH (0.38 mL) and H₂O (1.2 mL). The resulting white granules and the organic layer was dried over MgSO₄, filtered, and concentrated. Purification by flash column chromatography (2% EtOAc in hexanes) gave the product as colourless oil (2.45 g, 84%). ¹H NMR spectral data matches reported literature values. ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.29 (m, 4H), 7.27-
7.21 (6H, m), 7.18-7.12 (2H, m), 6.69 (t, $J = 7.3$ Hz, 1H), 6.57 (d, $J = 7.7$ Hz, 2H), 5.80-5.68 (m, 1H), 4.96-4.87 (m, 2H), 3.78 (d, $J = 5.7$ Hz, 2H), 3.23 (br t, $J = 5.6$ Hz, 1H), 2.34-2.28 (m, 2H), 1.85-1.77 (m, 2H).

**Synthesis of 95.** In a small vial, complex 96 (30.1 mg, 0.0500 mmol) and benzylamine (16.4 µL, 0.105 mmol) were mixed in 1 mL of benzene. The resulting brown solution was transferred to and heated in a J. Young NMR tube at 65 °C overnight, which gave a deep brown red solution. The solution was filtered through Celite and concentrated *in vacuo*. The crude residue was recrystallized from a solution of the complex in toluene (~2 mL) at -35 °C, layered with pentane (~4 mL), overnight to give the product as a brown microcrystalline solid (36 mg, 93%). The reaction has been repeated twice using the same procedure at a larger scale, using 96 (60.3 mg, 0.100 mmol) and benzylamine (32.8 µL, 0.300 mmol), to afford 64 mg (83%) and 66 mg (85%) of product. Single crystals suitable for X-ray crystallography were obtained from slow diffusion of pentane into a solution of the complex in toluene overnight. MS (EI): $m/z = 558$ (M$^+$–2BnNH$_2$), 388 (M$^+$–2BnNH$_2$–L), where L = 3-phenyl-2-pyridonate. Anal. calcd for C$_{47}$H$_{42}$N$_5$O$_3$Ti: C, 73.05; H, 5.48; N, 9.06. Found: C, 72.70; H, 5.82; N, 9.37.

**Synthesis of 96.** A Teflon capped 20 mL vial, equipped with a magnetic stir bar, was charged with 3-phenyl-2-pyridone (0.257 g, 1.50 mmol) and ~3 mL of benzene. To this vial, Ti(NMe$_2$)$_4$ (0.112 g, 0.500 mmol) dissolved in ~2 mL of benzene was quantitatively added. The mixture was stirred at room temperature for 4 hours, forming a deep red brown solution. The solvent was removed *in vacuo*,
and the product was dissolved in hot toluene (~10 mL), and storing at -35 °C overnight afforded a tan brown microcrystalline solid (0.275 g, 91%). Single crystals suitable for X-ray crystallography were obtained from a concentrated solution of the complex in THF left standing at room temperature over a couple of days. $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 8.01 (d, $J$ = 7.2 Hz, 6H, Ph–H), 7.77 (dd, $J$ = 5.2, 1.8 Hz, 3H, Ar–H), 7.32 (dd, $J$ = 7.4, 1.8 Hz, 3H, Ar–H), 7.26 (t, $J$ = 7.7 Hz, 6H, Ph–H), 7.13 (t, $J$ = 7.5 Hz, 3H, Ph–H), 6.06 (dd, $J$ = 7.4, 5.2 Hz, 3H, Ar–H), 3.61 (s, 6H, –N(C$_3$H$_5$)$_2$). $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 171.5, 141.8, 139.4, 136.8, 129.1, 129.0, 127.9, 122.1, 113.2, 49.0. MS (EI): $m/z$ = 602 (M$^+$), 558 (M$^+$–NMe$_2$). Anal. calcd for C$_{35}$H$_{30}$N$_4$O$_3$Ti: C, 69.77; H, 5.02; N, 9.30. Found: C, 70.12; H, 5.14; N, 8.97.

**Synthesis of 97.** A Teflon capped 20 mL vial, equipped with a magnetic stir bar, was charged with bis(3-phenyl-2-pyridonato)bis(dimethylamido)titanium (95.3 mg, 0.200 mmol), 2,6-dimethylaniline (24.6 µL, 0.200 mmol) and ~3 mL of benzene. The mixture was stirred at room temperature overnight and concentrated in vacuo to give a brown solid that has a very low solubility in either benzene or toluene. The crude solid was recrystallized from hot toluene (~10 mL) which, upon sitting at room temperature overnight, dark brown crystals suitable for X-ray crystallography was obtained. The mother liquor was decanted, and the crystals were crushed and dried in vacuo to give analytically pure tan solid (91 mg, 90%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.66 (dd, $J$ = 5.6, 1.9 Hz, 4H, Ar–H), 7.66-7.61 (m, 8H, Ph–H), 7.57 (dd, $J$ = 7.2, 1.9 Hz, 4H, Ar–H), 7.05-6.99 (m, 12H, Ph–H), 6.65-6.57 (m, 8H, Ar–H, N-2,6-(CH$_3$)$_2$-C$_6$H$_5$), 6.50 (t, $J$ = 7.4 Hz, 2H, N-2,6-
(CH₃)₂C₆H₅), 1.82 (s, 12H, −CH₃). ¹³C NMR (100 MHz, CDCl₃): δ 167.6 (C), 158.6 (C), 147.4 (CH), 141.6 (CH), 136.7 (C), 133.4 (C), 129.2 (CH), 128.3 (CH), 127.9 (C), 127.4 (CH), 126.7 (CH), 120.1 (CH), 113.3 (CH), 18.7 (CH₃). MS (EI): m/z = 1014 (M⁺), 895 (M⁺−(N-2,6-(CH₃)-C₆H₅), 844 (M⁺−L), where L = 3-phenyl-2-pyridonate. Anal. calcd for C₆₀H₅₀N₆O₄Ti₂: C, 71.01; H, 4.97; N, 8.28. Found: C, 71.15; H, 5.03; N, 8.48.

**Synthesis of 98.** A Teflon capped 20 mL vial, equipped with a magnetic stir bar, was charged with bis(3-phenyl-2-pyridonate)bis(dimethylamido)titanium (71.5 mg, 0.150 mmol), aminoalkene 55a (1.50 M in d₈-toluene, 100 μL, 0.150 mmol) and ~1.5 mL of toluene. The mixture was stirred at room temperature overnight and concentrated in vacuo. The crude solid was triturated with minimal hexanes and recrystallized from a saturated toluene solution at -35°C to afford analytically pure yellow-orange microcrystalline solid (66 mg, 64%). Single crystals of suitable for X-ray crystallography, which co-crystallized with a toluene molecule, were obtained from vapor diffusion of hexanes into a solution of the complex in toluene overnight. The decomposition of complex in solution prevented NMR spectroscopic assignments. MS (EI): m/z = 1102 (M⁺−L), 930 (M⁺−2L), 853 (M⁺−L−aminoalkene), where L = 3-phenyl-2-pyridonate. Anal. calcd for C₈₀H₇₀N₆O₄Ti₂·C₇H₈: C, 76.42; H, 5.75; N, 6.15. Found: C, 76.50; H, 6.12; N, 5.66.
Chapter 4: 2-Pyridonate tantalum complexes for intermolecular hydroaminoalkylation

4.1 Introduction

Intermolecular hydroaminoalkylation provides an efficient synthetic route to industrially important selectively substituted amines (Scheme 4.1). This strategy provides the direct α-alkylation of amines, adjacent to nitrogen, using simple alkenes. Both early (Ta, Nb, Ti, Zr) and late (Ru, Ir) transition metal systems have been reported for intermolecular hydroaminoalkylation with terminal alkenes. Hydroaminoalkylation reactions using group 4 and 5 systems give the branched alkylated products selectively, except for select

![Scheme 4.1](image)

**Scheme 4.1** Intermolecular hydroaminoalkylation with terminal alkenes for (a) early and (b) late transition metals

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titanium systems (23 and 24) that give linear products preferentially using styrenes (vide supra). On the other hand, hydroaminoalkylation reactions using late transition metal catalysts involve a mechanistically different pathway and afford linear alkylated products exclusively (vide infra).

4.1.1 Early transition metal-catalyzed intermolecular hydroaminoalkylation

Intermolecular hydroaminoalkylation has seen more progress and reaction development than the intramolecular variant of this reaction within the last decade. In particular, broader substrate scope, enantioselective reactions, and room-temperature reactivity have been achieved with intermolecular hydroaminoalkylation. Contrary to the intramolecular variant, hydroamination side reactivity has not been observed during intermolecular hydroaminoalkylation. Currently there is no report of group 4 or 5 metal-catalyzed intermolecular hydroamination of unactivated alkenes with nucleophilic amines, presumably due to the high energetic barrier of intermolecular hydroamination reactions.

The proposed mechanism of intermolecular hydroaminoalkylation is shown in Scheme 4.2. The catalytically active species is the metallaziridine intermediate (A), which has been postulated to be generated from amido exchange of the precatalyst with the amine substrate followed by \( \alpha \)-C–H activation, or from the direct \( \alpha \)-C–H activation of dimethylamide of the precatalyst. A terminal alkene substrate \( (R^2 = H, R^3 \neq H) \) inserts into the M–C bond of a strained transient metallaziridine (A) with the bulky substituent pointing away from the metal center to minimize steric congestion. Hence in most cases, the formation of methyl-branched products is observed using early transition metals for this reaction. Protonation of the 5-membered-metallacycle (B) by the amine substrate and subsequent \( \alpha \)-C–H activation completes the catalytic cycle and releases the \( \alpha \)-alkylated product. Notably, the hydroaminoalkylation of
disubstituted alkenes ($R^2$ and $R^3 \neq H$) remains challenging, as reported examples have primarily been limited to the use of strained norbornene substrates.\textsuperscript{68,210,237,296,298,300,301,303-305,307}

![Scheme 4.2 Proposed mechanism for intermolecular hydroaminoalkylation](image)

**Scheme 4.2** Proposed mechanism for intermolecular hydroaminoalkylation

Representative early transition metal catalysts for intermolecular hydroaminoalkylation are shown in Figure 4.1, and the reactivity of these complexes for the $\alpha$-alkylation of $N$-methylaniline with 1-octene is shown in Table 4.1. The comparison of simple homoleptic dimethylamido complexes shows that Ta (entry 10) is more reactive than Nb (entry 9) among group 5 metals.\textsuperscript{296} For group 4 dimethylamido variants, Ti (entry 1) shows a reduced reactivity profile in comparison to group 5, and Zr (entry 8) shows almost no reactivity.\textsuperscript{238,296} Accordingly, Ta complexes have seen more application in catalyst development among early transition metals. The use of hard donor atoms of bulky $N,O$-, or $O,O$-chelating ligands that generate electrophilic
Figure 4.1 Representative group 4 and 5 complexes for intermolecular hydroaminoalkylation and sterically demanding systems have been critical for realizing effective reactivity with terminal alkenes.\textsuperscript{298,299,301-307} One exception to this approach is Ind\textsubscript{2}TiMe\textsubscript{2} (entry 3), which has been used at temperatures as low as 80 °C and has the ability to catalyze the hydroaminoalkylation of styrenes\textsuperscript{300} and dienes.\textsuperscript{308} While titanium complexes (entries 1–7) generally require higher temperatures and long reaction times, the N,N-chelating Ap systems 23 and 24 have been reported for the unique ability to synthesize linear alkylated products selectively with styrene.
substrates (*vide supra*), but not with aliphatic alkene substrates such as 1-octene (entries 5–7).

Table 4.1 Hydroaminoalkylation of *N*-methylaniline and 1-octene

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>mol %</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>yield (%)</th>
<th>104a/104b</th>
<th>ref.</th>
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<td>Ti(NMe₂)₄</td>
<td>10</td>
<td>160</td>
<td>96</td>
<td>32</td>
<td>93.7</td>
<td>238</td>
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<tr>
<td>2</td>
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<td>160</td>
<td>96</td>
<td>77</td>
<td>90.10</td>
<td>238</td>
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<tr>
<td>3</td>
<td>Ind₂TiMe₂ (36)</td>
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<td>80</td>
<td>24</td>
<td>86</td>
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<td>300</td>
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<td>99</td>
<td>5</td>
<td>120</td>
<td>48</td>
<td>77</td>
<td>97:3</td>
<td>210</td>
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<tr>
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<td>140</td>
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<td>90</td>
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<td>6ᵃ</td>
<td>23b</td>
<td>10</td>
<td>140</td>
<td>96</td>
<td>99</td>
<td>97:3</td>
<td>68</td>
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<td>140</td>
<td>96</td>
<td>59</td>
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<td>Zr(NMe₂)₄</td>
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<td>-</td>
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<td>Nb(NMe₂)₅</td>
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<td>160-165</td>
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<td>35ᶜ</td>
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<td>88</td>
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<tr>
<td>11ᵇ</td>
<td>[Cl₃Ta(NMePh)₂]₂</td>
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<td>90</td>
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<td>110</td>
<td>30</td>
<td>91ᶜ</td>
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<td>100</td>
<td>5</td>
<td>130</td>
<td>1 week</td>
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<td>5</td>
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<td>70b</td>
<td>5</td>
<td>130</td>
<td>65</td>
<td>89, 73% ee</td>
<td>1:0</td>
<td>304</td>
</tr>
<tr>
<td>19ᵉ</td>
<td>69</td>
<td>10</td>
<td>22</td>
<td>20</td>
<td>84</td>
<td>1:0</td>
<td>305</td>
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</tbody>
</table>

ᵃ Hexanes as solvent.ᵇ 1-octene (1.25 equiv).ᶜ Conversion determined by ¹H NMR spectroscopy or GC relative to an internal standard.ᵈ 1-octene (2 equiv).ᵉ 4-methoxy-*N*-methylaniline instead of *N*-methylaniline as substrate.
Notably, the Schafer group has shown that the use of $N,O$-chelated amidates on tantalum are effective for hydroaminoalkylation.\textsuperscript{299} A catalytically competent bis(amidate)-supported tantallaziridine 100 (entry 13) has been isolated and characterized in support of the proposed mechanism of the reaction.\textsuperscript{298} Furthermore, the mono(amidate) tantalum complex 68 has improved reactivity at 110 °C (entry 14) over Ta(NMe$_2$)$_3$ (entry 10),\textsuperscript{298} and has a broad amine substrate scope that includes challenging $N$-heterocycles such as piperidines and $N$-protected piperazines.\textsuperscript{307} The use of amidates has been extended to an axially chiral tantalum system 101 for the first example of enantioselective hydroaminoalkylation of up to 61% ee.\textsuperscript{298} Zi has further shown that the use of amidates in a binaphthyl-based backbone can improve enantioselectivity of up to 93% using 102, but no reactivity was observed with other group 5 analogues (V, Nb).\textsuperscript{301,303} The highest reported enantioselectivity (98% ee) to date has been observed by Hultzsch, in the hydroaminoalkylation of $N$-methylaniline with vinyltrimethylsilane, using a 3,3$'$-silylated binaphtholate niobium complex 103, which is a more active catalyst than the tantalum analogue 70b (entry 17 and 18).\textsuperscript{302,304}

Particular emphasis needs to be given to the use of alkyl and chloro ligands in the improvement of reactivity of group 5 complexes. In 2008, Herzon and Hartwig reported that the incorporation of electron-withdrawing chloro ligands on tantalum resulted in enhanced reactivity, as seen by the catalytic activity of [Cl$_3$Ta(NMePh)$_2$]$_2$ at 90 °C (Table 4.1, entry 11).\textsuperscript{297} By using a related precatalyst [Ta(NEt$_2$)$_2$Cl$_3$]$_2$, the hydroaminoalkylation of more challenging dialkylamine substrates has been realized (Scheme 4.3).\textsuperscript{297} The use of methyl ligands in place of the amido ligands in a simple organometallic complex, TaMe$_3$Cl$_2$, also results in an active precatalyst with reactivity at 110 °C (entry 12).\textsuperscript{309} In this case, CH$_4$ is released upon precatalyst activation to generate the catalytically active metallaziridine. The steric accessibility of
TaMe₃Cl₂ allowed for the first and only examples of hydroaminoalkylation of challenging disubstituted alkene substrates, such as an unactivated cyclohexene and a linear (Z)-3-hexene, using early transition metals, albeit in low yields and long reaction times (Scheme 4.4). In 2013, by installing an electron-withdrawing, bulky N,O-chelating phosphoramidate ligand onto TaMe₃Cl₂ by salt metathesis, a highly reactive phosphoramidate-TaMe₃Cl complex 69 has been shown to be capable of room temperature reactivity (entry 19). Despite the enhanced reactivity observed with these systems, the hydroaminoalkylation of disubstituted alkenes is an ongoing challenge and, previous to this work, there was no report of the direct α-alkylation of amines with (E)-alkenes without C=C bond isomerization. Given the benefits of the combination of alkyl, chloro, and N,O-chelating ligands for the reaction, it was postulated that the investigation of N,O-chelating 2-pyridonate ligand sets on tantalum may provide new complexes capable of enhanced reactivity or broadened substrate scope.

Scheme 4.3 [Ta(NEt₂)₂Cl₃]₂-catalyzed hydroaminoalkylation of dialkylamines

Scheme 4.4 TaMe₃Cl₂-catalyzed hydroaminoalkylation
4.1.2 Late transition metal-catalyzed hydroaminoalkylation

Complementary to early transition metals that predominantly give the branched alkylated products, the use of late transition metals (Ru, Ir) for the $\alpha$-alkylation of amines with terminal alkenes exclusively affords the linear alkylated products (Scheme 4.5).$^{284-293}$ Jun reported the first late transition metal example using Ru$_3$(CO)$_{12}$ in 1998 (eq 1), using a 3-methyl-2-pyridyl

\[ \text{(1)} \quad \text{Me} \quad \text{HN} \quad \text{H} \quad \text{Ph} \quad + \quad \text{Ru}_3(\text{CO})_{12} \quad (10 \text{ mol %}) \quad \text{toluene, 130 °C, 6 h} \quad \text{Jun, 1998} \]

\[ \text{(2)} \quad \text{H} \quad \text{N} \quad \text{H} \quad \text{Ph} \quad + \quad \text{Ru}_3(\text{CO})_{12} \quad (8 \text{ mol %}) \quad \text{iPrOH, 140-160 °C, 20-60 h} \quad \text{Chatani and Murai, 2001} \]

\[ \text{(3)} \quad \text{N} \quad \text{H} \quad \text{H} \quad \text{Ph} \quad + \quad [\text{Ir(cod)}_2]\text{BF}_4^- \quad + \quad (\text{S})\text{-tolBINAP} \quad (10 \text{ mol %}) \quad \text{DME, 75-95 °C, 48-72 h} \quad \text{Shibata, 2011} \]

\[ \text{(4)} \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{H} \quad \text{Ph} \quad + \quad \text{Ru}_3(\text{CO})_{12} \quad (8 \text{ mol %}) \quad \text{iPrOH, 140 °C, 1-2 h microwave, 300 W} \quad \text{Opatz, 2014} \]

\[ \text{(5)} \quad \text{O} \quad \text{N} \quad \text{NH} \quad \text{Ar} \quad + \quad \text{Ru}_3(\text{CO})_{12} \quad (3 \text{ mol %}) \quad \text{THF, 140 °C, 48 h} \quad \text{Krische, 2013} \]

Scheme 4.5 Representative hydroaminoalkylation with late transition metal complexes
directing group to assist in \( \alpha \)-C–H activation via oxidative addition (Scheme 4.6). While the precise mechanism of the reaction has not been fully determined, the formation of iminium intermediates\(^{285,290} \) and concerted metallaation-deprotonation (CMD) type mechanism\(^ {288} \) have also been proposed for \( \alpha \)-C–H activation. The regioselectivity of the reaction has been proposed to be determined at the step involving an alkene insertion into the metal-hydride intermediate.\(^ {284} \) Here the substituent (R\(^ 2 \)) of alkene points away from the metal center to minimize steric congestion at the reaction site.\(^ {284} \) Subsequent reductive elimination from the alkyl metal intermediate would generate the linear \( \alpha \)-alkylated product and regenerate the metal for further catalytic activity.

**Scheme 4.6** Generalized proposed mechanism for \( \alpha \)-alkylation using late transition metals

The reaction manifold has been extended to pyridyl-protected \( N \)-heterocycles by Chatani and Murai, however both mono- and di-alkylation were observed (Scheme 4.5, eq 2).\(^ {285} \) Recently, Ackermann has improved this methodology for the mono-alkylation of pyridyl-protected pyrrolidines using a catalytic system comprising [RuCl\(_2\)(PPh\(_3\))\(_3\)], AgOTf, and BINAP.\(^ {291} \) An
enantioselective version of the reaction has been reported by Shibata using a cationic iridium(I)-tolBINAP catalyst for the α-alkylation of 2-(alkylamino)pyridines (eq 3).\textsuperscript{287,289} The pyridyl directing group is most often used for late transition metal catalyzed α-alkylation, but the use of benzoxaol-2-yl directing group for the selective α-alkylation at the non-benzylic position of 1,2,3,4-tetrahydroisoquinolines has been reported recently by Opatz (eq 4).\textsuperscript{293} Notably, one example of directing group-free α-alkylation of hydantoins with isoprene has been reported by Krische, which has been proposed to proceed by a different mechanism comprising of hydantoin dehydrogenation followed by oxidative diene-imine coupling (eq 5).\textsuperscript{290}

Strikingly, when internal alkenes such as 2- or 3-hexene are used as substrates with late transition metal systems, C=C bond isomerization occurs to terminal alkenes prior to selective hydroaminoalkylation at the terminal position only (Scheme 4.7).\textsuperscript{284,285} Presumably, reversible metal-hydride insertion and β-hydride elimination occur to relieve steric congestion at the metal center (Scheme 4.8).\textsuperscript{284}

\begin{align*}
(1) & \quad \text{Me} \quad \text{HN} \quad \text{Ph} \quad + \quad \text{alkene} \quad (5 \text{ equiv}) \quad \xrightarrow{\text{Ru}_3(\text{CO})_{12} \, (10 \text{ mol \%})} \quad \text{Me} \quad \text{HN} \quad \text{Ph} \quad + \quad \text{alkene} \quad (10 \text{ equiv}) \quad \xrightarrow{\text{toluene, 130 °C, 6 h}} \quad \text{81%} \\
(2) & \quad \text{HN} \quad \text{Ph} \quad + \quad \text{alkene} \quad (5 \text{ equiv}) \quad \xrightarrow{\text{Ru}_3(\text{CO})_{12} \, (8 \text{ mol \%})} \quad \text{HN} \quad \text{Ph} \quad + \quad \text{alkene} \quad (10 \text{ equiv}) \quad \xrightarrow{\text{iPrOH, 140 °C, 60 h}} \quad \text{36%} \quad + \quad \text{38%}
\end{align*}

\textbf{Scheme 4.7} Intermolecular hydroaminoalkylation of internal alkenes using late transition metals
Aside from the differing regioselectivity of the α-alkylated products and the mechanism of hydroaminoalkylation between late and early transition metal systems, each system has its own advantages and disadvantages for the reaction. Late transition metal systems are able to α-alkylate tertiary amines and 2-pyridyl-protected amines, which are currently incompatible substrates for early transition metals. However, there is no report of hydroaminoalkylation of non-cyclic aliphatic amines or unprotected secondary amines using late transition metals. Early transition metal systems are able to carry out the direct α-alkylation of such substrates without using large excess of alkenes (5-10 equiv) that late transition metals require. Additionally, the installation and deprotection of the directing/protecting groups are avoided with early transition metals, stepping towards the ideal, sustainable synthesis of amines. However, the substrate scope and functional group tolerance are underdeveloped with these systems. Thus, the investigation of early transition hydroaminoalkylation catalysts holds promise for the atom-economical synthesis of amines, and further research is needed to unlock its synthetic potential.

Scheme 4.8 Plausible C=C bond isomerization of an internal alkene to a terminal alkene using late transition metals
4.1.3 Scope of chapter

This chapter explores the synthesis, characterization, and reactivity of 2-pyridonate tantalum complexes for intermolecular hydroaminoalkylation. Synthetic attempts toward alkyl-based 2-pyridonate tantalum systems will be presented. The comparison of hydroaminoalkylation reactivity of these complexes has been undertaken. As the alkyl complexes lack robustness, investigations have been extended to amido-based 2-pyridonate tantalum complexes. Most importantly, a sterically accessible precatalyst 2-pyridonate-Ta(NMe$_2$)$_3$Cl has been designed to tackle the ongoing challenge of the hydroaminoalkylation of sterically demanding disubstituted alkenes. The comparison of this complex with the 2-pyridonate-Ta(NMe$_2$)$_4$ analogue and existing tantalum precatalysts reveal the importance of the synergistic effect from the combination of 2-pyridonate and chloro ligands in bringing forth the observed reactivity. Substrate scope investigations have been carried out using 2-pyridonate-Ta(NMe$_2$)$_3$Cl, including the first examples of hydroaminoalkylation of linear (E)-alkene substrates. Diminished reactivity is seen for this complex when terminal alkenes are used, and the impact of steric congestion on hydroaminoalkylation reactivity has been explored.

4.2 Results and discussion

4.2.1 Synthesis and reactivity of alkyl-based 2-pyridonate tantalum complexes

The highly reactive nature of the previously reported $N,O$-chelated phosphoramidate-TaMe$_3$Cl (69) has been attributed to the increased electrophilicity of the metal center from the electron-withdrawing nature of the phosphoramidate and chloride ligands, as well the enhanced precatalyst activation resulting from the elimination of methane upon generation of catalytically active complexes.$^{305}$ For these reasons, the synthesis of 2-pyridonate-TaMe$_3$Cl and 2-pyridonate-
TaMe₂Cl₂ have been initially targeted. Here the synthesis of mono-\(N,O\)-chelated tantalum complexes is the preferred target, as mono-\(N,O\)-chelated complexes ⁶⁸ and ⁶⁹ are effective for hydroaminoalkylation while bis(amidate) tantalum complexes have reduced reactivity profiles.³²⁹ Based on literature pKₐ values³³⁰,³³¹ of \(N,O\)-ligands (Figure 4.2), it is reasonable to suggest that the 2-pyridonate complexes could provide similar electron-withdrawing character and reactivity profile to that of the phosphoramidate complexes.

![Figure 4.2 Comparison of pKₐ values of \(N,O\)-ligands: 2-pyridone, phosphoramidate, amide](image)

Using TaMe₃Cl₂ as a starting precursor, two different approaches can be envisioned for the synthesis of mixed 2-pyridonate/alkyl/chloro tantalum complexes (Scheme 4.9). First, the use of sodium \(N,O\)-ligand salts, generated from deprotonation of neutral amide or phosphoramidate proligands with sodium bis(trimethylsilyl)amide (NaHMDS), in salt metathesis reactions are known.⁵⁸,³⁰⁵ Secondly, the use of the direct protonolysis reactions to exchange a dimethylamido ligand for an \(N,O\)-ligand has been very effective for the synthesis of \(N,O\)-ligated group 4 and 5 complexes.⁵⁶,²⁹⁸ A similar approach can be adopted with methyl ligands for the release of methane upon protonolysis.
Scheme 4.9 Potential synthetic routes to mixed $N,O$-chelated, alkyl chloro tantalum complexes

The commercially available 6-methyl-2-pyridone was chosen as a starting point. Sodium 6-methyl-2-pyridonate can be prepared by reaction of the 2-pyridone proligand with NaHMDS in toluene at room temperature (Scheme 4.10, top). The synthetic preparation for the phosphoramidate-TaMe₃Cl (69) has been adopted. Previous reports used the dropwise addition of the sodium ligand salt in hexanes to a solution of TaMe₃Cl₂ in hexanes at -30 °C. Due to the light and heat sensitivity of these alkyl tantalum complexes, the reaction needs to be carried out without direct exposure to light and below room temperature. Here toluene was used in place of hexanes as the solvent. Despite carrying out the reaction at low temperatures (-35 °C), a mono(2-}

Scheme 4.10 Attempted synthesis of mono(6-methyl-2-pyridonate)tantalum complexes
pyridonate)TaMe₃Cl complex could not be prepared by salt metathesis. Examination of the crude products at the end of the reaction by ¹H NMR spectroscopy revealed bis(6-Me-2-pyridonate)-TaMe₃ (105) as the major product and unreacted TaMe₃Cl₂. Further attempts to synthesize mono(2-pyridonate)TaMe₃Cl by adding a cooled suspension of sodium 6-methyl-2-pyridonate in toluene onto a liquid nitrogen frozen solution of TaMe₃Cl₂ in toluene, and slowly warming to 0 °C, were also unsuccessful. When the protonolysis route (Scheme 4.10, bottom) was attempted to synthesize mono(2-pyridonate)TaMe₂Cl₂ by slow addition of the proligand in small portions to a cooled solution of TaMe₂Cl₂, the reaction cleanly resulted in the formation of bis(6-Me-2-pyridonate)TaMeCl₂ (106) and unreacted TaMe₃Cl₂. Further manipulations to synthesize mono(2-pyridonate)TaMeCl₂(NR₂) by salt metathesis of 106 with one equivalent of LiNEt₂, LiNMe₂ or NaHMDS to install an amido ligand for a chloro ligand were also unsuccessful and resulted in the formation of black sticky oil or film that could not be readily characterized.

When two equivalents of either the sodium 2-pyridonate salts or the proligand were used for the synthetic routes shown in Scheme 4.10, 105 and 106 were obtained in 73% and 83% yield respectively. It is imperative to keep these complexes away from direct light or heat due to their instability. However, they can be stored at -35°C in the freezer, in the absence of light, for months without observable decomposition as measured by ¹H NMR spectroscopy. The trimethyl complex 105 is more sensitive to light and heat exposure than the mono-methyl complex 106. When 105 is left in solution at room temperature in d₆-benzene over a couple of days, slow decomposition of the complex and the release of methane (δ 0.16, s) was observed by ¹H NMR spectroscopy. Gas evolution was also observed when crystals of 105 were dipped in oil prior to mounting the single crystal for X-ray structure analysis (vide infra).
In an effort to promote the formation of a mono(2-pyridonate) tantalum complex, a bulkier 3-mesityl-6-methyl-2-pyridone ligand 109 was synthesized (Scheme 4.11). Nucleophilic aromatic substitution of 3-bromo-2-chloro-6-methylpyridine with \textit{in situ} generated potassium benzyloxide afforded the product 107. Suzuki cross-coupling of 107 with mesitylboronic acid, followed by the benzyl deprotection of the cross-coupled product 108 by hydrogenation gave the desired proligand 109. However, the use of 109 in the synthetic routes shown in Scheme 4.10 also resulted in the same behaviour as 6-methyl-2-pyridone, and the formation of the bis-\(N,O\)-ligated complexes were observed. Presumably, the combination of 2-pyridonate ligands with methyl and chloro ligands do not provide the necessary steric bulk to maintain a mono-\(N,O\)-ligated complex. Given the propensity of these mixed 2-pyridonate/methyl/chloro tantalum systems to form \(N,O\)-ligated complexes, and that these systems have not been previously characterized or explored for hydroaminoalkylation catalysis, the trimethyl complex 110 has also been prepared using the same synthetic procedure of 105 for further investigation (Scheme 4.12).

\begin{verbatim}
\textbf{Scheme 4.11} Synthesis of 3-mesityl-6-methyl-2-pyridone
\end{verbatim}

\begin{verbatim}
\textbf{Scheme 4.12} Synthesis of trimethyl bis(3-mesityl-2-pyridonate)tantalum complex
\end{verbatim}
The $^1\text{H}$ NMR spectra of complexes, 105, 106 and 110 in $d_6$-benzene, show that the two 2-pyridonate ligands within each complex are chemically equivalent on the NMR time scale. In addition, the three methyl groups of 105 and 110 are also chemically equivalent, as seen by a singlet signal at $\delta$ 1.84 and 1.74 respectively. For complex 106, the methyl group signal is seen at $\delta$ 2.58. Based on these relative $^1\text{H}$ NMR chemical shift values of the methyl group, the dichloro methyl complex 106 has the most electrophilic metal center among the series and, among the trimethyl complexes, 105 is more electron-deficient than 110. This notion is further supplemented by comparison of the carbonyl carbon signal of the 2-pyridonate ligands in the $^{13}\text{C}$ NMR spectra, with 106 ($\delta$ 175.4) being the most downfield, followed by 105 ($\delta$ 170.3) and 110 ($\delta$ 167.9).

Considering each $N,O$-ligand as occupying one coordination site, the solid-state molecular structures of 105 and 110 reveal a severely distorted trigonal bipyramidal geometry (Figure 4.3 and 4.4). Complex 105 crystallizes in the $C_1$ point group, while complex 110 is a $C_2$-symmetric structure. A methyl group (C13 for 105, C16 for 110) and a 2-pyridonate ligand (C1) occupy the pseudo-axial positions with a $\text{H}_3\text{C}–\text{Ta1}–\text{C1}$ bond angle [105: 155.23(6)$^\circ$; 110: 167.19(18)$^\circ$] that deviates from linearity. The pseudo-equatorial positions are occupied by the other 2-pyridonate ligand and two methyl groups, with C7, C14 and C15 atoms for 105, and C1′,C17 and C18 atoms for 110 [\Sigma\text{C–Ta–C} angles are 360$^\circ$ (105) and 359$^\circ$ (110)]. Asymmetric $\kappa^2$-$N,O$-binding of the 2-pyridonates [105: Ta–O$_{\text{avg}}$ 2.0612(13) Å, Ta–N$_{\text{avg}}$ 2.3232(15) Å; 110: Ta–O$_{\text{avg}}$ 2.0905(18) Å, Ta–N$_{\text{avg}}$ 2.290(3) Å] are observed, in agreement with previously reported $N,O$-chelated tantalum complexes. The observed Ta–CH$_3$(avg) bond lengths [105: 2.1883(19) Å; 110: 2.186(6) Å] are consistent with those reported in literature for trimethyl bis(aryloxy)2-tantalum complexes (2.127–2.248 Å).
Figure 4.3 ORTEP representation of the solid-state molecular structure of 105 plotted with 50% probability ellipsoids. All hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Ta1–O1, 2.1021(12); Ta1–O2, 2.0202(13); Ta1–N1, 2.3021(15); Ta1–N2, 2.3443(15); Ta1–C13, 2.1984(19); Ta1–C14, 2.2005(19); Ta1–C15, 2.1660(19); O1–Ta1–N1, 60.00(5); O2–Ta1–N2, 60.19(5); C13–Ta1–C1, 155.23(6); C13–Ta1–C14, 77.44(7); C13–Ta1–C15, 80.56(7); C14–Ta1–C15, 119.44(8); C14–Ta1–C7, 138.97(7); C15–Ta1–C7, 101.44(7).

Figure 4.4 ORTEP representation of the solid-state molecular structure of 110 plotted with 50% probability ellipsoids. All hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Ta1–O1/O1’, 2.0905(18); Ta1–N1/N1’, 2.290(3); Ta1–C16, 2.252(6); Ta1–C17, 2.229(6); Ta1–C18, 2.078(6); O1/O1’–Ta1–N1/N1’, 60.07(8); C16–Ta1–C1, 167.19(18); C16–Ta1–C17, 79.2(2); C16–Ta1–C18, 80.7(2); C17–Ta1–C18, 115.5(2); C17–Ta1–C1’, 99.68(17); C18–Ta1–C1’, 143.92(19).
The solid-state molecular structure of 106 exhibits a pseudo-$C_{5}$-symmetric structure with a well-defined trigonal bipyramidal coordination at tantalum center. The two chloro ligands occupy the axial sites with a near linear Cl–Ta–Cl bond angle of 178.27(3)$^\circ$, while two 2-pyridonate ligands and a methyl group occupy the equatorial sites in a trigonal-planar fashion ($\Sigma$C–Ta–C angles 360$^\circ$). The Ta–CH$_3$ bond length is 2.202(3) Å, which is similar in value to those of 105 and 110.

**Figure 4.5** ORTEP representation of the solid-state molecular structure of 106 plotted with 50% probability ellipsoids. All hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles ($^\circ$): Ta1–O1, 2.064(2); Ta1–O2, 2.034(2); Ta1–N1, 2.263(2); Ta1–N2, 2.310(2); Ta1–Cl1, 2.3620(8); Ta1–Cl2, 2.3445(8); Ta1–C13, 2.202(3); O1–Ta1–N1, 60.54(8); O2–Ta1–N2, 60.36(8); Cl1–Ta1–Cl2, 178.27(3); C11–Ta1–C13, 92.42(9); C1–Ta1–C13, 108.47(10); C1–Ta1–C7, 139.14(9); C13–Ta1–C7, 112.38(10).

Despite the sensitivity of the alkyl bis(2-pyridonate)tantalum complexes, 105 and 110, are viable hydroaminoalkylation precatalysts (Scheme 4.13). Presumably, once the methyl groups are exchanged for amido groups in situ, the complexes are able to withstand heating required for catalysis. Unfortunately, these complexes are not as reactive as the phosphoramidate-TaMe$_3$Cl (69) and do not exhibit room temperature reactivity. Reactivity is seen at 90 $^\circ$C for the reaction of 4-methoxy-N-methylaniline and 1-octene for the exclusive formation of the methyl-branched alkylated product. This is an improvement in reactivity over
Scheme 4.13 Comparison of reactivity of alkyl bis(2-pyridonate)tantalum complexes

the previously reported tantalum amidate 68 that requires 130 °C. Furthermore, the comparison of 105 with TaMe₃Cl₂ shows that the use of two 2-pyridonate ligands, instead of two chlorides, offers enhanced catalytic activity. Complex 106 that has one methyl group is unreactive, even when heated to 130 °C for 24 h, suggesting that two exchangeable sites are required for the generation of the catalytically active metallaziridine intermediate. The bulky complex 110 gives a reduced reactivity profile in comparison to 105, presumably due to the negative impact of the presence of a bulky mesityl substituent and less electrophilic metal center of 110 (vide supra).

A preliminary substrate scope investigation of 105 reveals that it is a competent catalyst for the hydroaminoalkylation of styrenes, which is a challenging substrate for the tantalum amidate 68 (Scheme 4.14). However, the hydroaminoalkylation of the more challenging substrates that require higher temperatures, such as piperidines (165 °C of 68) or unactivated internal C=C bond of cyclohexene (145 °C of TaMe₃Cl₂) have not been successful. Therefore, efforts have been directed into the amido-based 2-pyridonate tantalum complexes that
could potentially offer a more robust catalytic system in addressing some of the outlined challenges in the substrate scope of hydroaminoalkylation.

![Scheme 4.14 Hydroaminoalkylation reactivity of 105](image)

**Scheme 4.14** Hydroaminoalkylation reactivity of 105

### 4.2.2 Design and synthesis of amido-based 2-pyridonate tantalum complexes

As discussed in Section 4.1.1, a survey of reported hydroaminoalkylation catalysts shows that electrophilic and sterically demanding systems are critical for realizing effective reactivity with terminal alkenes (Figure 4.1). More specifically, enhanced reactivity has been observed with electron-withdrawing chloro and $N,O$-chelating phosphoramidate ligands. However, internal alkenes could not be accommodated using such systems, presumably due to the presence of bulky aryl substituents at N of the $N,O$-chelating ligand that makes the alkene insertion more challenging (Scheme 4.15). The alkene insertion step has been proposed as a possible rate-determining step for the amidate complex $68^{329}$ and the binaphtholate complex $103^{304}$. With the observed hemilability of 3-phenyl-2-pyridonate ligand that can support both

![Scheme 4.15 Hypothetical alkene insertion step with bulky $N,O$-ligated systems](image)

**Scheme 4.15** Hypothetical alkene insertion step with bulky $N,O$-ligated systems
\(\kappa^1-O\) and \(\kappa^2-N,O\)-ligation to metal center (in Chapter 3), and the fact that N substituent is tied back in an aromatic ring for reduced steric bulk, attention was directed to the preparation of a system with reduced steric congestion at the metal center. This design was anticipated to accommodate the insertion of bulky disubstituted alkenes (\(R^2\) and \(R^3 \neq H\)) into the reactive M–C bond of the key metallaziridine intermediates. Thus, the combination of electron withdrawing 2-pyridonate and chloride ligands has been selected to provide a sterically accessible, yet tunable metal center, with variable ligands, to access reactivity with internal alkene substrates (Scheme 4.16).

![Scheme 4.16 Synthesis of amido mono(2-pyridonate)tantalum complexes](image)

The targeted 2-pyridonate tantalum complexes 111 and 112 can be synthesized by salt metathesis and protonolysis reactions respectively (Scheme 4.16). Dimethylamido ligands have been selected to provide robustness, as the alkyl tantalum complexes, bis(2-pyridonate)\(\text{TaMe}_3\) (105, 110), \(\text{TaMe}_3\text{Cl}_2\) and phosphoramidate-\(\text{TaMe}_3\text{Cl}\) (69), are both heat and light sensitive. The synthesis of 111 and 112 can be carried out at room temperature in the presence of light, providing ease in synthetic handle of these complexes. The solid-state molecular structures (Figure 4.6) of both 111 and 112 reveal a distorted trigonal bipyramidal geometry with
**Figure 4.6** ORTEP representation of one of three independent molecules of 111 (left) in the asymmetric unit and one of two independent molecules of 112 (right) in the asymmetric unit. Ellipsoids are plotted with 50% probability for non-hydrogen atoms. Hexane solvent molecule omitted for clarity for 112.

**Table 4.2** Selected bond lengths (Å) and angles (°) for 111 and 112.

<table>
<thead>
<tr>
<th></th>
<th>111</th>
<th>112</th>
</tr>
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<tbody>
<tr>
<td>Ta1–O1</td>
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</tr>
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<td>2.332(8)</td>
</tr>
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<td>-</td>
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</table>
asymmetric \( \kappa^2-N,O \)-binding of the 2-pyridonate on tantalum \[111\]: Ta–O 2.130(2) Å, Ta–N 2.289(3) Å; \[112\]: Ta–O 2.150(7) Å, Ta–N 2.332(8) Å. All of the dimethylamido N atoms in \[111\] and \[112\] exhibit multiple-bonding character to tantalum due to \( \pi \)-donation, as deduced from the trigonal planar \( sp^2 \)-hybridization at the N atom and the short Ta–NMe\(_2\) bond lengths [1.950(3) – 2.057(9) Å]. The distinguishing structural features between \[111\] and \[112\] are that the Ta–Cl bond [2.4959(8) Å] is significantly longer than Ta–NMe\(_2\)(axial) bond [1.970(3) Å] and, generally, the bonding the of Ta–N amido bond lengths are shorter in \[111\] than in \[112\]. These observations are consistent with improved metal accessibility and increased electrophilic nature of the metal center in \[111\] over \[112\].

The \(^1\)H NMR spectra of complexes \[111\] and \[112\] in \( d_6 \)-benzene show a large and broad singlet for the dimethylamido protons at \( \delta \) 3.53 (18H) and \( \delta \) 3.36 (24H) respectively. The integration of these dimethylamido signals relative to the respective well-resolved proton signals of the bound 2-pyridonate ligand indicates a mono-ligated complex, consistent with the solid-state molecular structures. The comparison of \(^{13}\)C NMR spectra of these complexes shows comparable C1 carbonyl signals at \( \delta \) 168.5 (\[111\]) and \( \delta \) 167.6 (\[112\]), as the same 3-phenyl-2-pyridonate ligand is bound to each tantalum. These relative downfield \(^1\)H and \(^{13}\)C chemical shifts observed for \[111\] in comparison to \[112\] can be attributed to \[111\] having the more electrophilic metal center than \[112\].

To date, terminal alkenes have been used for hydroaminoalkylation, and group 5 metal complexes have been largely limited to the synthesis of methylated products (\[113\], Scheme 4.17). When the more sterically accessible \[111\] is tested with the standard terminal alkene substrate, 1-octene, the reaction does not reach full conversion, even with prolonged reaction times. However, the more sterically congested complex \[112\], realizes full conversion to product \[113\] at 110 °C in
Scheme 4.17 Hydroaminoalkylation of 1-octene using amido-based tantalum N,O-chelates

24 h. This result compares favorably with the known bulky amidate complex 68. These reactivity trends suggest that steric bulk/congestion about the reactive metal center is required for hydroaminoalkylation catalytic turnover. When working with sterically less demanding terminal alkene substrates, presumably the sterically accessible nature of 111 does not provide sufficient steric bulk for product extrusion and efficient catalytic turnover, but the more sterically demanding ligand sets of 112 and 68 provide such required steric bulk. Based on these results, it was hypothesized that the combination of the more sterically accessible complex 111 with bulky disubstituted alkene substrates could be favorable for efficient catalytic turnover and, therefore, was targeted in the following section.

4.2.3 Hydroaminoalkylation of sterically demanding alkenes

Catalyst screening has been undertaken by targeting the known challenging hydroaminoalkylation of cyclohexene in collaboration with graduate student Jason Brandt (Scheme 4.18). The use of TaMe₃Cl₂ is the only early transition metal catalyzed example of this reaction. However, catalyst loadings of 10 mol % and extended reaction times (88 h) were required to achieve a modest yield of 47%. Here a standardized reaction condition of 5 mol %
catalyst loading at 145 °C has been used for comparative purposes. In this case, simple tantalum complexes, including TaMe_3Cl_2, Ta(NMe_2)_5 and [Ta(NEt_2)_2Cl_3]_2 all have minimal to no observed reactivity. Gratifyingly, 5 mol % of the sterically accessible complex 111, with the mixed 2-pyridonate/chloride ligand motif, smoothly catalyzes the hydroaminoalkylation of cyclohexene within 20 h. However, when the small, electron-withdrawing chloride ligand is replaced by a more sterically demanding dimethylamido ligand, as in complex 112, the reactivity of the precatalyst is dramatically reduced. Group 5 metals in particular are shown to be important for the reaction, as titanium complexes with either aminopyridinate 23, as previously reported by

![Scheme diagram](image)

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<th>Catalyst</th>
<th>% Conversion</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
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<td>n.r.</td>
</tr>
<tr>
<td>Ta(NMe_2)_5</td>
<td>n.r.</td>
<td>6%</td>
</tr>
<tr>
<td>[Ta(NEt_2)_2Cl_3]_2</td>
<td>n.r.</td>
<td>10%</td>
</tr>
<tr>
<td>[Ta(NMe_2)_3Cl]_2</td>
<td>n.r.</td>
<td>&gt;95% (88%)</td>
</tr>
</tbody>
</table>

*a Reaction conditions: amine (0.5 mmol), cyclohexene (0.75 mmol), catalyst (0.025 mmol), d_8-toluene (0.5 mL). Conversion determined by ^1H NMR spectroscopy. n.r. = no reaction. b Isolated yield.

**Scheme 4.18** Catalyst screening for the hydroaminoalkylation of cyclohexene
Doye, or the bis(2-pyridonate)titanium complex \(86, 335\) are unreactive for this challenging transformation. However, group 5 catalysts must possess suitable steric and electronic features as the bulky \(N,O\)-chelated tantalum systems, \(68^{298,307}\) and \(69^{305}\) are not useful for this reaction. In addition, Hultzsch has reported that the very sterically demanding binaphtholate niobium complex \(103\) is unreactive with cyclohexene as a substrate.\(^{304}\) To evaluate the role of the 2-pyridonate ligand, a comparison of amidate \(68\) with the 2-pyridonate analogue of \(112\), shows that having the substituents tied back in an aromatic backbone \((112)\), yields a slight improvement in reactivity (10% conv). Furthermore, the substitution of the 2-pyridonate ligand of \(111\) with another chloride, as in \([Ta(NMe_2)_3Cl_2]\), gives sluggish reactivity (6% conv). Presumably, the 2-pyridonate ligand plays a key role with its known hemi-lability, thereby affording variable steric congestion about the metal center throughout the catalytic reaction.

Encouraged by the excellent hydroaminoalkylation reactivity of \(111\) with cyclohexene, a variety of sterically demanding disubstituted alkenes has been further investigated (Table 4.3). Ring sizes ranging from five- to twelve-carbons undergo hydroaminoalkylation in good to excellent yields (entries 1–5). Cycloheptene is the most reactive substrate with efficient reactivity being observed at 130 °C (entry 3), whereas the small cyclopentene (entry 1) and the cis/trans-mixture of cyclododecene (entry 5), require heating at 145 °C for up to 44 h. The hydroaminoalkylation of an unactivated diene is feasible to access monoalkylated product \(115b\) (entry 2), and a higher loading of 1,4-cyclohexadiene (3 equiv) helps to minimize the formation of dialkylated product. Linear alkenes are less reactive than the cyclic alkenes, with \((E)\)-3-hexene (entry 6) being more reactive than the \((Z)\)-3-hexene (entry 7). This is the first example of hydroaminoalkylation with a linear \((E)\)-alkene without \(C=C\) bond migration.\(^{284,285}\) For unsymmetrical linear alkenes (entries 8–10), modest regioselectivities (up to 4.4:1) are seen with
Table 4.3 Hydroaminoalkylation substrate scope of disubstituted alkenes

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>product</th>
<th>cond.</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>44 h</td>
<td>73</td>
</tr>
<tr>
<td>2°</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>20 h</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>130 °C</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>20 h</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>44 h</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>44 h</td>
<td>79</td>
</tr>
<tr>
<td>7</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>44 h</td>
<td>69</td>
</tr>
<tr>
<td>8</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>44 h</td>
<td>70° (2.3:1)</td>
</tr>
<tr>
<td>9</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>24 h</td>
<td>92° (4:4:1)</td>
</tr>
<tr>
<td>10°</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>44 h</td>
<td>76° (2:1)</td>
</tr>
<tr>
<td>11</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>110 °C</td>
<td>91</td>
</tr>
<tr>
<td>12</td>
<td>![Image of alkene]</td>
<td>![Image of product]</td>
<td>54 h</td>
<td>55 (15:9:1)</td>
</tr>
</tbody>
</table>

° Reaction conditions: amine (0.5 mmol), alkene (0.75 mmol), I (0.025 mmol), d₆-toluene (0.5 mL). Isolated yield. ° Diene (1.5 mmol). ° Major isomer presented. Yields refer to combined regioisomers. ° Ratio of regioisomers determined by GC analysis. ° I (10 mol %). ° Diastereomer ratio determined by GC analysis.
the preference for C–C bond formation at the sterically less-hindered carbon (vide infra). An internal-(Z)-alkene with a silyl-protected alcohol is tolerated to access a protected amino alcohol derivative 115g (entry 8). Previously, there had been no report of hydroaminoalkylation of β-substituted styrene derivatives. Gratifyingly, here cis-β-methylstyrene and trans-anethole undergo hydroaminoalkylation with modest regioselectivity (entries 9 and 10). For 1,1-disubstituted alkenes (entries 11 and 12), alkylation occurs at the more substituted carbon to generate a quaternary-carbon center β to N in a single catalytic step. Methylene cyclohexane readily reacts at only 110 °C to give the hydroaminoalkylation product 115j in 91% yield (entry 11). Notably, (1S)-β-pinene is alkylated from the side with the less-hindered methylene bridgehead with excellent diastereoselectivity (15.9:1) (entry 12), providing the first example of hydroaminoalkylation of a naturally occurring terpene, and demonstrating tolerance of increased structural complexity.

The observed regioselectivity for non-symmetrically substituted alkenes requires further explanation. Here the C–C bond forming alkene insertion step has been assumed as the turnover limiting step, as previously proposed with other group 5 hydroaminoalkylation systems (68 and 103). In the case of 1,1-disubstituted alkenes (Table 4.3, entries 11 and 12), the observed regioselectivity is consistent to those terminal alkenes giving the methyl-branched products. In this case, the alkene inserts into the M–C bond of the metallaziridine with the non-hydrogen substituents pointed away from the metal center to minimize steric congestion (vide supra). This scenario does not apply for the internal alkene substrates with a silyl-protected alcohol (Table 4.3, entry 8). While the methylene chain (–(CH2)3OTBS) of the substrate is moderately bigger than a methyl substituent, presumably the lone pair electrons of the oxygen can coordinate to the metal center in a 6-membered-ring fashion to direct the observed regioselectivity (Figure 4.7a). In the
case of styrene substrates, metal-aryl interactions have been postulated for the intermolecular alkene hydroamination reactions for other early transition metal catalysts, including alkali,\textsuperscript{336} alkaline earth metal,\textsuperscript{337,338} and organolanthanide systems.\textsuperscript{339} A similar metal-aryl interaction could be postulated to account for the observed regioselectivity for cis-β-methylstyrene (Table 4.3, entry 9), as shown in Figure 4.7b. While the metal-arene interaction also occurs with trans-anethole (Table 4.3, entry 10), the reduced regioselectivity could be explained by the electron-donation provided by the methoxy group that would provide a favorable electrostatic alignment of the partial positive and negative charges with M–C bond of the metallaziridine intermediate (Figure 4.7c).

![Figure 4.7 Postulated transition states to account for the observed regioselectivity](image)

In hydroaminoalkylation reactions catalyzed by ruthenium systems, internal alkenes undergo isomerization to terminal alkenes prior to α-alkylation at the terminal position to give linear alkylated products (Scheme 4.7).\textsuperscript{284,285} It is worth mentioning that no C=C bond isomerization is observed using the precatalyst \textbf{111} when the reaction is monitored in the middle of the reaction, and the unreacted internal alkene substrates (as 1.5 equiv is used) remain with the original C=C bond intact. To further demonstrate that complex \textbf{111} does not catalyze C=C bond isomerization during the reaction, \textbf{111} and excess \textit{(E)}-3-hexene has been subjected to the same
reaction conditions in the absence of amine (Scheme 4.19). Examination of the reaction mixture at the end of the reaction by \(^1\)H NMR spectroscopy and GC analysis reveals decomposition of 111 and the formation of bis(\(\alpha\)-alkylated) product 116 of dimethylamide only, which has been isolated in 75% yield. No C=C bond isomerization of the remaining (\(E\))-3-hexene was observed. The formation of the bis(\(\alpha\)-alkylated) byproduct from dimethylamine and 1-octene has also been observed previously with the amidate tantalum complex 68.\(^{329}\) These observations suggest that \(\alpha\)-C–H activation can occur directly from the precatalyst, without an amido exchange with the amine substrate, to access the transient, catalytically active metallaziridine species in the proposed mechanism in Scheme 4.2.

**Scheme 4.19** Bis(\(\alpha\)-alkylated) product from the hydroaminoalkylation of dimethylamine

With these examples of hydroaminoalkylation in hand, the amine substrate scope with (\(E\))-3-hexene, a particularly challenging substrate, has been explored (Scheme 4.20). By utilizing an increased catalyst loading of 10 mol % of 111, the hydroaminoalkylation product 115f can be synthesized in excellent yield (91%) in shorter reaction times of 24 h. Substituents at the \(para\)- and \(meta\)-positions (117a) are tolerated on \(N\)-methylaniline derivatives. Substituents can even be
Scheme 4.20 Substrate scope of amines for hydroaminoalkylation of (E)-3-hexene

tolerated at the ortho-position of \( N \)-methylaniline derivatives (117b), although longer reaction times are required. Halogen substituents including fluorine (117c) and chlorine (117d) are compatible for the reaction, while bromine (117e) is tolerated with less efficiency resulting in modest product yields. Longer reaction times do not significantly improve the yield. The presence of an electron-donating methoxy group (117f) does not compromise reactivity, and the
pharmaceutically relevant trifluoromethoxy group (117g) can also be accommodated. However, the usage of the chelating catechol derivative (117h) impedes the reaction and lower yields are observed. Most importantly, this catalyst system is not limited to N-methylarylamines. For example, 1,2,3,4-tetrahydroquinoline can be used in hydroaminoalkylation to give a single diastereomeric product 117i. The relative stereochemistry of the product has been unambiguously assigned by the derivatization of isolated product 117i and X-ray structure analysis (Figure 4.8). Presumably at the C–C bond forming step, (E)-3-hexene approaches the Ta–C bond of metallaziridine intermediate with the ethyl substituent pointing in the same direction as the α-hydrogen of the N-heterocycle to minimize steric interactions (Scheme 4.21). The known challenging dialkylamine substrates$^{297}$ (117j and 117k) can also be used to give the regioselective product resulting from exclusive alkylation at the sterically less-hindered and kinetically preferred N-methyl carbon. Unfortunately, attempts to react other N-heterocycles, such as pyrrolidine, piperidine, and N-substituted piperazines, with (E)-3-hexene have been unsuccessful. In addition, a preliminary investigation into the intramolecular variant of the reaction by Jason Brandt, using the N-methyl-aminoalkene substrate 65, does not result in a promising reactivity.

![Chemical structure](image)

**Figure 4.8** ORTEP representation of $N$-(1-naphthoyl)-117i with 50% probability ellipsoids, only select hydrogens shown.
4.2.4 Modification of the catalyst design to bis(2-pyridonate)Ta(NMe$_2$)$_2$Cl

To investigate the impact of a more electrophilic metal center with increased steric bulk resulting from bis-$N,O$-ligation, an additional electron-withdrawing 2-pyridonate ligand has been installed onto 111 by the replacement of a dimethylamide via protonolysis (Scheme 4.22). From this reaction, bis(3-phenyl-2-pyridonate)Ta(NMe$_2$)$_2$Cl 118 was obtained as a bright yellow microcrystalline solid in 66% yield after recrystallization from a toluene/hexanes mixture. The solid-state molecular structures of 118 reveals a $C_1$-symmetric structure with a distorted trigonal bipyramidal geometry (Figure 4.9). A dimethylamido ligand and two 2-pyridonate ligands with asymmetric $\kappa^2-N,O$-binding [Ta–O$_{avg}$ 2.1223(18) Å, Ta–N$_{avg}$ 2.258(2) Å] occupy the pseudo-equatorial positions of 118, which makes the metal center less accessible than 111 that has one 2-pyridonate ligand bound with two dimethylamido ligands (see Figure 4.6). Analogous to 111, a chloro and a dimethylamido ligand occupy the pseudo-axial positions in 118 [Ta–Cl,

Scheme 4.22 Synthesis of bis(3-phenyl-2-pyridonate)Ta(NMe$_2$)$_2$Cl
Figure 4.9 ORTEP representation of 118 with 50% probability ellipsoids for non-hydrogen atoms. Selected bond lengths (Å) and angles (°): Ta1–O1, 2.1310(18); Ta1–O2, 2.1136(18); Ta1–N1, 2.233(2); Ta1–N2, 2.283(2); Ta1–Cl1, 2.4882(9); Ta1–N3, 1.989(2); Ta1–N4, 2.005(2); O1–Ta1–N1, 60.07(7); O2–Ta1–N2, 58.58(7); Cl1–Ta1–N3, 168.52(6); Cl1–Ta1–N4, 98.06(7); C1–Ta1–N4, 110.98(8); C1–Ta1–C12, 132.10(8); N4–Ta1–C12, 115.71(8).

2.4882(9) Å; Ta–NMe$_2$(axial), 1.989(2) Å]. These values are similar to Ta–Cl and Ta–NMe$_2$ bond lengths observed in 111 [Ta–Cl, 2.4959(8) Å; Ta–NMe$_2$(axial), 1.970(3) Å]. The solution phase structure of 118 is consistent with a bis-ligated complex with two dimethylamido ligands by the relative integration of proton signals in the $^1$H NMR spectrum. The 2-pyridonate ligands are chemically equivalent on the NMR time scale, but the dimethylamido signals exhibit broad signals, centered at $\delta$ 3.82, indicating different environments for each dimethylamide. Heating of the complex 118 in $d_8$-toluene reveals the coalescence of the broad signals into a singlet (Figure 4.10), suggesting rapid exchange of the two dimethylamides between pseudo-equatorial and axial positions on the NMR timescale.
When bis(3-phenyl-2-pyridonate)Ta(NMe$_2$)$_2$Cl$_2$ \textbf{118} was tested for the hydroaminoalkylation of a terminal alkene (1-octene) with N-methylaniline (Scheme 4.23, top), the conversion to products (76%) lied in between those values of mono(3-phenyl-2-pyridonate)Ta(NMe$_2$)$_3$Cl \textbf{111} (40%) and mono(3-phenyl-2-pyridonate)Ta(NMe$_2$)$_4$ \textbf{112} (>95%). The hydroaminoalkylation of an internal alkene, \((E)-3\)-hexene, with the same catalytic conditions as \textbf{111} revealed drastically poor reactivity of the bis-\textit{N,O}-ligated \textbf{118} (Scheme 4.23, bottom).

These results suggest that the ligand structure of the catalyst needs to be tailored to substrate combination.
Scheme 4.23 Hydroaminoalkylation of 1-octene and (E)-3-hexene with 118

4.3 Conclusion

In an effort to access a highly active catalyst for intermolecular hydroaminoalkylation, the synthesis of mixed mono(2-pyridonate)/alkyl/chloro complexes has been attempted by the modification of the known precatalyst TaMe₃Cl₂. Two synthetic routes, protonolysis and salt metathesis, have been performed to install N,O-chelating ligands and explore the impact of these ligand sets on reactivity. Presumably due to the lack of steric bulk from the combination of 2-pyridonate and methyl ligands, only the bis-N,O-ligated complexes could be formed. As such, two bis(2-pyridonate)TaMe₃ complexes (105 and 110), and a bis(2-pyridonate)TaMeCl₂ (106) have been synthesized and characterized. Hydroaminoalkylation of terminal alkenes with these complexes revealed improved reactivity over the previously established systems, TaMe₃Cl₂ and the mono(amidate)Ta(NMe₂)₄ (68). However, due to the thermal and light sensitivity of these complexes, these systems are unreactive towards the challenging N-heterocycles and internal alkene substrates. Unless room temperature stable complexes can be identified, these complexes are not synthetically useful from the stand point of difficulty in preparation and handling of these complexes.
Switching the focus to the amido-based 2-pyridonate complexes proved to be fruitful. A series of complexes have been synthesized and characterized by employing the 3-phenyl-2-pyridonate ligand: mono(3-phenyl-2-pyridonate)Ta(NMe₂)₃Cl (111), mono(3-phenyl-2-pyridonate)Ta(NMe₂)₄ (112), and bis(3-phenyl-2-pyridonate)Ta(NMe₂)₂Cl (118). Here the sterically accessible design of 111, with the combination of sterically less demanding and electron-withdrawing 2-pyridonate and chloride ligands on tantalum are preferred for accommodating such sterically encumbered substrates. Notably, complex 111 is the first broadly applicable precatalyst for the catalytic hydroaminoalkylation of unactivated, sterically demanding (E)- and (Z)-internal alkenes. In addition, 111 also exhibits good variability in the amine substrate scope in that variable steric bulk and functional group tolerance (OTBS, F, Cl, Br, OMe, OCF₃) are tolerated. Even challenging dialkylamine substrates can be used in combination with a challenging internal, unactivated alkene. Excellent diastereoselective product formation has been achieved using either substituted alkene (115k) or amine (117i) components. Most importantly, these investigations illustrate how the easily varied ligand environment of tantalum can be used to advantage in the design of mixed ligated complexes to advance the synthetic potential of α-alkylation.

4.4 Experimental

General methods. All air and moisture sensitive reactions were performed using standard inert atmosphere techniques using a Schlenk double manifold with N₂ gas and high vacuum (10⁻³ mbar), or using a MBraun LABmaster glovebox filled with a N₂ atmosphere. All pieces of glassware were dried for at least 4 hours in a 160 °C oven, or dried over a propane flame before being utilized on the Schlenk manifold, or being transferred into the glovebox. All stirring was
done with appropriately sized Teflon coated magnetic stir bars dried for at least 4 hours in a 160 °C oven. Toluene and hexanes were passed over activated alumina columns into Teflon sealed Straus flasks and stored therein until use. $d_6$-Benzene and $d_6$-toluene were dried over 4 Å molecular sieves, degassed, and stored in Teflon sealed Schlenk flasks prior to use. Experiments conducted on NMR tube scale were performed in J. Young NMR tubes (8” x 5 mm) sealed with screw-type Teflon caps. Thin layer chromatography (TLC) was performed on EMD Silica gel 60 F254 plates. Visualization was achieved under a 254 nm UV light source and/or by staining with iodine. Flash chromatography was performed using SiliaFlash F60 silica gel (230-400 mesh) (Silicycle) and glass columns, with ACS grade solvents (Sigma-Aldrich).

**Materials.** Ti(NMe$_2$)$_4$ (Sigma-Aldrich), NaHMDS (Sigma-Aldrich) and Ta(NMe$_2$)$_5$ (Strem) were used as received. All amines and alkenes were purchased from commercial sources, dried over CaH$_2$, distilled, and degassed by three freeze-pump-thaw cycles prior to use. 3-Bromo-2-chloro-6-methylpyridine was purchased from Combi-Blocks and used as received. 6-Methyl-2-pyridone was purchased from Alfa Aesar and sublimed under heat and vacuum before use. Compounds [Ta(NMe$_2$)$_3$Cl$_2$]$_2$, 340 3-Phenyl-2-pyridone, 335 TaMe$_3$Cl$_2$, 309 23, 68, 86, 335 68, 298 and 69$^{305}$ were synthesized according to literature procedures.

**Instrumentation.** $^1$H and $^{13}$C NMR spectra were recorded on a Bruker 300 MHz, 400 MHz, or 600 MHz Avance spectrometer at ambient temperature, and chemical shifts are given relative to the corresponding residual protio solvent. Chemical shifts, $\delta$, are reported in parts per million (ppm) and coupling constants $J$ are given in Hertz (Hz). The following abbreviations are used to indicate signal multiplicity: $s$ = singlet, $d$ = doublet, $t$ = triplet, $q$ = quartet, $m$ = multiplet, and $br$ = broad. Infrared (IR) spectra were recorded as neat samples using a PerkinElmer Frontier FT-IR
spectrometer fitted with an ATR sampling accessory. Mass spectra (MS) and elemental analyses (EA) were measured by the mass spectrometry and microanalysis service at the Department of Chemistry, University of British Columbia. Mass spectra were recorded on a Kratos MS-50 spectrometer using an electron impact (70 eV) source or a Bruker Esquire LC spectrometer using electrospray ionization source. Fragment signals are given in mass per charge number (m/z). Elemental analyses were recorded on a Carlo Erba Elemental Analyzer EA 1108. The content of the specified element is expressed in percent (%). GC/MS analyses were conducted on an Agilent 7890A GC equipped a 5975C inert XL CI mass detector using methane as the chemical ionization agent. Single-crystal X-ray structure determinations were performed on a Bruker X8 APEX II or APEX DUO diffractometer at the Department of Chemistry, University of British Columbia by Jacky C.-H. Yim or Scott Ryken.

**General synthesis of sodium 2-pyridonates.** A suspension of substituted 2-pyridone (1 equiv) and NaHMDS (1 equiv) was stirred in toluene, in a 20 mL vial, at ambient temperature overnight. The volatiles were removed *in vacuo*, and the resulting white salt was washed with hexanes and thoroughly dried *in vacuo* prior to use. The product was used without further purification or characterization.

**Synthesis of 105.** *Light sensitive complex, direct exposure to visible light should be avoided.* To a stirring suspension of sodium 6-methyl-2-pyridonate (78.7 mg, 0.600 mmol) in toluene (~3 mL) in a 20 mL vial at -35 °C, a cooled solution of TaMe₃Cl₂ (88.8 mg, 0.300 mmol) in toluene (~3 mL) was added. The reaction mixture was stirred for 1 h while gradually warming to 0 °C. After filtration of the reaction mixture through a plug of Celite, the solvent was removed *in vacuo*. Recrystallization of
the crude residue in hexanes at -35 °C overnight afforded 105 as an off-white microcrystalline solid (94.3 mg, 71%). Single crystals for X-ray structure analysis were obtained by recrystallization from a solution of pentane at -35 °C. $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 6.80 (t, $J$ = 7.9 Hz, 2H), 6.06 (d, $J$ = 8.3 Hz, 2H), 5.84 (d, $J$ = 7.4 Hz, 2H), 1.97 (s, 6H), 1.84 (s, 9H). $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 170.3, 153.6, 141.6, 114.9, 107.4, 84.0, 20.5. MS (EI): m/z = 427 (M$^+$–Me), 411 (M$^+$–2Me), 397 (M$^+$–3Me). Anal. calcd for C$_{15}$H$_{21}$N$_2$O$_2$Ta: C, 40.73; H, 4.79; N, 6.33. Found: C, 40.49; H, 4.69; N, 6.31.

**Synthesis of 106.** Light sensitive complex, direct exposure to visible light should be avoided. To a stirring suspension of 6-methyl-2-pyridone (65.5 mg, 0.600 mmol) in toluene (~3 mL) in a 20 mL vial at -35 °C, a cooled solution of TaMe$_3$Cl$_2$ (88.8 mg, 0.300 mmol) in toluene (~3 mL) was added. The reaction mixture was stirred for 2 h while gradually warming to room temperature. The formation of yellow orange solid was observed during this time, and the solvent was removed in vacuo. Recrystallization from a solution of toluene/hexanes afforded 106 as an orange microcrystalline solid (0.121 g, 83%). Single crystals for X-ray structure analysis were obtained from a toluene solution of the complex, layered with minimal hexanes, left at -35 °C over a week. $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 6.80 (t, $J$ = 8.0 Hz, 2H), 6.08 (d, $J$ = 8.4 Hz, 2H), 5.97 (d, $J$ = 7.5 Hz, 2H), 2.58 (s, 3H), 2.38 (s, 6H). $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 175.4, 155.1, 143.7, 116.7, 108.7, 79.8, 22.1. MS (EI): m/z = 467 (M$^+$–Me), 447 (M$^+$–Cl). Anal. calcd for C$_{13}$H$_{15}$Cl$_2$N$_2$O$_2$Ta: C, 32.32; H, 3.13; N, 5.80. Found: C, 32.72; H, 3.22; N, 6.00.
2-(benzyloxy)-3-bromo-6-methylpyridine (107). A 250 mL round-bottom flask was charged with 3-bromo-2-chloro-6-methylpyridine (4.81 g, 23.3 mmol), KOrBu (2.85 g, 25.4 mmol), and 1,4-dioxane (100 mL). Benzyl alcohol (2.41 mL, 23.3 mmol) was added to the reaction flask and refluxed for 18 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (100 mL) and water (100 mL). The organic layer was extracted, and the aqueous layer was further extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over MgSO4, filtered, and concentrated. Purification by column chromatography (hexanes – 2-4% EtOAc in hexanes) gave the product as a pale yellow oil (6.19 g, 96%). $^1$H NMR (400 MHz, CDCl3): δ 7.65 (d, $J$ = 7.7 Hz, 1H), 7.50 (d, $J$ = 7.4 Hz, 2H), 7.36 (t, $J$ = 7.4 Hz, 2H), 7.29 (t, $J$ = 7.3 Hz, 1H), 6.61 (d, $J$ = 7.7 Hz, 1H), 5.44 (s, 2H), 2.40 (s, 3H). $^{13}$C NMR (100 MHz, CDCl3): δ 158.8, 155.3, 141.9, 137.5, 128.6, 127.8, 117.5, 103.7, 68.2, 23.8. HRMS (ESI): $m/z$ calcd for C$_{13}$H$_{13}$NOBr [M+H$^+$]: 278.0181. Found: 278.0176.

2-(benzyloxy)-3-mesityl-6-methylpyridine (108). The procedure was adopted from literature.$^{341}$ A 100 mL round-bottom flask equipped with a condenser was charged with mesitylboronic acid (1.97 g, 12.0 mmol), Ba(OH)$_2$·H$_2$O (11.8 g, 37.5 mmol), Pd(PPh$_3$)$_4$ (0.578 g, 0.500 mmol). Then 1,4-dioxane/H$_2$O (v/v, 3:1, 52 mL) and 2-(benzyloxy)-3-bromo-6-methylpyridine (2.78 g, 10.0 mmol) were added, and the reaction mixture was refluxed for 24 h under N$_2$. After cooling to room temperature, the reaction mixture was diluted with CH$_2$Cl$_2$ and decanted into a separatory funnel. Water (50 mL) was added, and the organic layer was extracted with CH$_2$Cl$_2$ (3 x 80 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated. Purification by flash column chromatography (2% EtOAc in hexanes) afforded the product as a colourless oil (2.37 g,
3-mesityl-2-pyridone (109). To a solution of 2-(benzyl oxy)-3-mesityl-6-methylpyridine (1.97 g, 6.20 mmol) dissolved in ~15 mL of MeOH/EtOAc (3:1) was treated with 10% Pd/C (0.330 g, 10 wt%) in a Fischer-Porter tube. Hydrogenolysis was carried out under 30-40 psi of H₂ atmosphere for 2 h with stirring at room temperature. The reaction mixture was filtered through Celite, and thoroughly washed with CH₂Cl₂. The filtrate was concentrated and dissolved in hot methanol and minimal CHCl₃. The solution was cooled to room temperature and stored at 0 °C for couple of hours to afford the product as white crystalline solid (0.703 g, 50%). ¹H NMR (400 MHz, CDCl₃): δ 12.06 (br s, 1H), 7.14 (d, J = 6.9 Hz, 1H), 6.90 (s, 2H), 6.05 (d, J = 6.9 Hz, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 2.09 (s, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 163.9, 144.9, 141.9, 137.1, 137.0, 133.5, 128.40, 128.35, 105.7, 21.3, 20.6, 19.2. HRMS (EI): m/z calcd for C₁₅H₁₇NO [M⁺]: 227.13101. Found: 227.13087.

Synthesis of 110. Light sensitive complex, direct exposure to visible light should be avoided. To a stirring suspension of sodium 3-mesityl-6-methyl-2-pyridonate (0.184 g, 0.738 mmol) in toluene (~3 mL) in a 20 mL vial at -35 °C, a cooled solution of TaMe₃Cl₂ (0.109 mg, 0.369 mmol) in toluene (~3 mL) was added. The reaction mixture was stirred for 1 h while gradually warming to 0 °C. After filtration of the reaction mixture through a plug of Celite, the solvent was
removed in vacuo. The crude residue was triturated with hexanes (~2 mL) to precipitate out the solid product, and the product was further washed with minimal cold hexanes to give 110 as an off-white microcrystalline solid (0.186 g, 74%). Single crystals for X-ray structure analysis were obtained from a toluene solution of the complex, layered with minimal pentane, left at -35 °C overnight. \( ^1H \) NMR (400 MHz, C\(_6\)D\(_6\)): \( \delta \) 6.92 (d, \( J = 7.5 \) Hz, 2H), 6.84 (s, 4H), 6.05 (d, \( J = 7.6 \) Hz, 2H), 2.16 (s, 6H), 2.13 (s, 12H), 1.96 (s, 6H), 1.71 (s, 9H). \( ^{13}C \) NMR (100 MHz, C\(_6\)D\(_6\)): \( \delta \) 167.9, 152.5, 142.9, 137.7, 137.3, 131.9, 129.1, 120.8, 114.9, 82.8, 21.5, 21.1, 20.8. MS (EI): \( m/z \) = 663 (M\(^+\)–Me), 647 (M\(^+\)–2Me), 633 (M\(^+\)–3Me). Anal. calcd for C\(_{33}\)H\(_{41}\)N\(_2\)O\(_2\)Ta: C, 58.40; H, 6.09; N, 4.13. Found: C, 58.41; H, 6.14; N, 5.91. Reliable elementary analysis could not be obtained due to the light sensitivity of the complex.

**Synthesis of 111.** To a stirring suspension of [Ta(NMe\(_2\)\(_3\)Cl\(_2\)]\(_2\) (0.230 g, 0.300 mmol) in toluene (~3 mL) in a 20 mL vial, a suspension of sodium 3-phenyl-2-pyridonate (0.116 g, 0.600 mmol) in toluene (~3 mL) was added dropwise over 5 minutes. The mixture was stirred at ambient temperature overnight, filtered through a plug of Celite, and concentrated in vacuo. The resulting crude residue was dissolved in cold toluene (~1 mL) and carefully layered with hexanes (~4 mL). Storage at -35 °C overnight produced a yellow precipitate. The supernatant was decanted and the precipitate was dissolved in minimal hot hexanes. Upon storing at ambient temperature overnight, yellow crystals of 111 (0.218 g, 70%) were obtained. A sample from these crystals was used for single crystal X-ray structure analysis. \( ^1H \) NMR (400 MHz, C\(_6\)D\(_6\)): \( \delta \) 7.93-7.88 (m, 2H), 7.66 (dd, \( J = 5.4, 1.7 \) Hz, 1H), 7.42 (dd, \( J = 7.5, 1.7 \) Hz, 1H), 7.23 (t, \( J = 7.7 \) Hz, 2H), 7.10 (t, \( J = 7.4 \) Hz, 1H), 6.35 (dd, \( J = 7.5, 5.4 \) Hz, 1H), 3.53 (br s, 18H). \( ^{13}C \) NMR (100 MHz, C\(_6\)D\(_6\)): \( \delta \) 168.5 (C),
140.5 (CH), 139.5 (CH), 136.2 (C), 129.2 (CH), 129.0 (CH), 128.2 (CH), 125.2 (C), 113.8 (CH), 47.0 (CH). MS (EI): \( m/z = 518 \) (M\(^+\)), 474 (M\(^+\)–NMe\(_2\)). Anal. calcd for C\(_{17}\)H\(_{26}\)ClN\(_4\)OTa: C, 39.36; H, 5.05; N, 10.80. Found: C, 39.60; H, 5.09; N, 10.62.

**Synthesis of 112.** A suspension of 3-phenyl-2-pyridone (0.171 g, 1.00 mmol) and Ta(NMe\(_2\))\(_5\) (0.401 g, 1.00 mmol) was stirred in hexanes (~6 mL) in a 20 mL vial at ambient temperature for 24 h. The volatiles were removed *in vacuo*. The resulting crude residue was dissolved in minimal hexanes (~3 mL). Storage at -35 °C overnight gave golden brown crystals of 112 (0.434 g, 82%). Single crystals for X-ray structure analysis were obtained from a second recrystallization from hexanes at -35 °C. \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): \( \delta \) 8.04 (d, \( J = 7.9 \) Hz, 2H), 7.68 (dd, \( J = 5.2, 1.5 \) Hz, 1H), 7.53 (dd, \( J = 7.4, 1.5 \) Hz, 1H), 7.24 (t, \( J = 7.6 \) Hz, 2H), 7.10 (t, \( J = 7.7 \) Hz, 1H), 6.39 (dd, \( J = 7.2, 5.4 \) Hz, 1H), 3.36 (s, 24H). \(^{13}\)C NMR (100 MHz, C\(_6\)D\(_6\)): \( \delta \) 167.6, 141.7, 138.1, 137.0, 129.1, 129.0, 127.9, 124.1, 112.8, 46.5. MS (EI): \( m/z = 527 \) (M\(^+\)), 483 (M\(^+\)–NMe\(_2\)). Anal. calcd for C\(_{19}\)H\(_{32}\)N\(_5\)OTa: C, 43.27; H, 6.12; N, 13.28. Found: C, 43.40; H, 5.91; N, 13.09.

**General Procedure 1 (GP1) for Catalyst Screening.** In a glovebox, catalyst (0.0250 mmol), amine (0.500 mmol), and alkene (0.75 mmol) were dissolved in \( d_8\)-toluene (300 μL) in a one dram vial. The resulting solution was transferred to a J. Young NMR tube, and the vial rinsed with \( d_8\)-toluene (2 x 100 μL) for a total volume of 0.5 mL. The NMR tube was closed with a screw-type Teflon cap, the \(^1\)H NMR spectrum recorded, and placed in a preheated oil bath at the specified temperatures and time. For example, the progress of the reaction in Scheme 4.17 and 4.18 was monitored by the disappearance of ortho-proton signals of N-methylaniline centered at \( \delta \) 6.33, and the appearance of new ortho-proton signals of the product centered at \( \delta \) 6.41.
\begin{align*}
N\text{-}(2\text{-methyloctyl})\text{aniline (113).}^{296} & \text{Using GP1, the reaction of } N\text{-methylaniline (54.2 } \mu\text{L, 0.500 mmol), 1-octene (84 mg, 0.75 mmol), and 112 (13.2 mg, 0.0250 mmol) at 110 °C for 24 h, followed by purification by flash column chromatography (4% EtOAc in hexanes) gave the title compound as a colourless liquid (102 mg, 93%). } \\
& \text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.16 (t, J = 7.9 Hz, 2H), 6.67 (t, J = 7.3 Hz, 1H), 6.59 (d, J = 7.8 Hz, 2H), 3.66 (br s, 1H), 3.04 (dd, J = 12.2, 5.9 Hz, 1H), 2.88 (dd, J = 12.2, 7.3 Hz), 1.73 (octet, J = 6.5 Hz, 1H), 1.47-1.10 (m, 10H), 0.96 (d, J = 6.7 Hz, 3H), 0.88 (t, J = 6.7 Hz, 3H). } \\
& \text{C NMR (100 MHz, CDCl}_3\text{): } \delta 148.9, 129.4, 117.1, 112.8, 50.6, 35.0, 33.2, 32.1, 29.8, 27.2, 22.9, 18.3, 14.3.
\end{align*}

\textbf{General Procedure 2 (GP2) for the Substrate Scope of Intermolecular Hydroaminoalkylation.} Same reaction preparation as GP1, with catalyst 111 (13.0 mg, 0.0250 mmol, 5 mol % or 25.9 mg, 0.0500 mmol, 10 mol %), amine (0.500 mmol), and alkene (0.75 mmol). After heating at specified temperature and time, the reaction mixture was exposed to air and quenched with CH}_2\text{Cl}_2. Once the formation of tantalum oxide precipitate was observed, the crude residue was purified by flash column chromatography.

\begin{align*}
N\text{-}(\text{cyclohexylmethyl})\text{aniline (114).}^{309} & \text{Using GP2, the reaction of } N\text{-methylaniline (54.2 } \mu\text{L, 0.500 mmol), cyclohexene (62 mg, 0.75 mmol), and 111 (13.0 mg, 0.0250 mmol) at 145 °C for 20 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave the title compound as a colourless oil (83 mg, 88%). } \\
& \text{H NMR (400 MHz, CDCl}_3\text{): } \delta 7.18 (t, J = 7.9 Hz, 2H), 6.69 (t, J = 7.3 Hz, 1H), 6.60 (d, J = 7.9 Hz, 2H), 3.70 (br s, 1H), 2.96 (d, J = 6.7 Hz, 2H), 1.88-1.66 (m, 5H), 1.65-
1.52 (m, 1H), 1.34-1.14 (m, 3H), 1.06-0.94 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 148.8, 129.4, 117.0, 112.8, 50.8, 37.8, 31.5, 26.8, 26.2.

$N$-(cyclopentylmethyl)aniline (115a). Using GP2, the reaction of $N$-methylaniline (54.2 μL, 0.500 mmol) and cyclopentene (51 mg, 0.75 mmol), and 111 (13.0 mg, 0.0250 mmol) at 145 °C for 44 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave the title compound as a colourless liquid (64 mg, 73%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.18 (t, $J$ = 7.8 Hz, 2H), 6.69 (t, $J$ = 7.3 Hz, 1H), 6.62 (d, $J$ = 7.8 Hz, 2H), 3.65 (br s, 1H), 3.04 (d, $J$ = 7.2 Hz, 2H), 2.17 (septet, $J$ = 7.5 Hz, 1H), 1.89-1.78 (m, 2H), 1.72-1.53 (m, 4H), 1.34-1.22 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 148.8, 129.4, 117.2, 112.9, 49.7, 39.7, 30.9, 25.5.

$N$-(cyclohex-3-en-1-ylmethyl)aniline (115b). Using GP2, the reaction of $N$-methylaniline (54.2 μL, 0.500 mmol), 1,4-cyclohexadiene (120 mg, 1.50 mmol), and 111 (13.0 mg, 0.0250 mmol) at 145 °C for 20 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave the title compound as pale yellow oil (67 mg, 72%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.17 (t, $J$ = 7.5 Hz, 2H), 6.69 (t, $J$ = 7.2 Hz, 1H), 6.61 (d, $J$ = 7.9 Hz, 2H), 5.75-5.62 (m, 2H), 3.71 (br s, 1H), 3.05 (d, $J$ = 6.5 Hz, 2H), 2.25-2.00 (m, 3H), 1.98-1.72 (m, 3H), 1.42-1.25 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 148.8 (C), 129.4 (CH), 127.4 (CH), 126.1 (CH), 117.2 (CH), 112.8 (CH), 49.9 (CH$_2$), 33.7 (CH), 29.9 (CH$_2$), 27.0 (CH$_2$), 24.9 (CH$_2$). HRMS (ESI): $m/z$ calcd for C$_{13}$H$_{18}$N [M+H$^+$]: 188.1439. Found: 188.1445. IR (neat): $\tilde{\nu}$ 3417, 3051, 3021, 2911, 2836, 1601, 1504, 1471, 1432, 1321, 1251, 1179, 745, 690, 653 cm$^{-1}$.
**N-(cycloheptylmethyl)aniline (115c).**\(^{309}\) Using GP2, the reaction of N-methylaniline (54.2 μL, 0.500 mmol), cycloheptene (72 mg, 0.75 mmol), and 111 (13.0 mg, 0.0250 mmol) at 130 °C for 20 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave the title compound as a colourless oil (97 mg, 95%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.15 (t, J = 7.4 \text{ Hz}, 2H), 6.66 (t, J = 7.2 \text{ Hz}, 1H), 6.58 (d, J = 8.0 \text{ Hz}, 2H), 3.68 \text{ (br s, 1H), 2.93 (d, J = 6.3 Hz, 2H), 1.85-1.37 (m, 11H), 1.31-1.17 (m, 2H).} \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 148.9, 129.4, 117.1, 112.8, 51.0, 39.4, 32.7, 28.8, 26.6.\)

**N-(cyclooctylmethyl)aniline (115d).**\(^{309}\) Using GP2, the reaction of N-methylaniline (54.2 μL, 0.500 mmol), cyclooctene (83 mg, 0.75 mmol), and 111 (13.0 mg, 0.0250 mmol) at 145 °C for 20 h, followed by purification by flash column chromatography (2% EtOAc in hexanes) gave the title compound as a colourless oil (101 mg, 93%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.17 (t, J = 7.8 \text{ Hz}, 2H), 6.67 (t, J = 7.3 \text{ Hz}, 1H), 6.59 (d, J = 7.9 \text{ Hz}, 2H), 3.69 \text{ (br s, 1H), 2.93 (d, J = 6.8 Hz, 2H), 1.86-1.66 (m, 5H), 1.65-1.43 (m, 8H), 1.42-1.29 (m, 2H).} \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 148.8, 129.4, 117.1, 112.8, 51.3, 37.6, 30.8, 27.3, 26.5, 25.7.\)

**N-(cyclododecylmethyl)aniline (115e).** Using GP2, the reaction of N-methylaniline (54.2 μL, 0.500 mmol), a mixture of cis/trans-cyclododecene (125 mg, 0.750 mmol), and 111 (13.0 mg, 0.0250 mmol) at 145 °C for 44 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave the title compound as a viscous pale yellow oil (121 mg, 88%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.17 (dd, J = 8.3, 7.4 \text{ Hz}, 2H), 6.68 (t, J = 7.3 \text{ Hz}, 1H), 6.60 (d, J = 7.8 \text{ Hz}, 2H),\)
3.64 (br s, 1H), 2.99 (d, \( J = 6.7 \) Hz, 2H), 1.82-1.71 (m, 1H), 1.49-1.24 (m, 22H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 149.0 (C), 129.4 (CH), 117.1 (CH), 112.8 (CH), 48.8 (CH\(_2\)), 34.5 (CH), 27.7 (CH\(_2\)), 24.9 (CH\(_2\)), 24.2 (CH\(_2\)), 23.6 (CH\(_2\)), 23.5 (CH\(_2\)), 22.0 (CH\(_2\)). HRMS (ESI): \( m/z \) calcd for C\(_{19}\)H\(_{32}\)N [M+H\(^+\)]: 274.2535. Found: 274.2534. IR (neat): \( \nu \) 3422, 3056, 3018, 2927, 2860, 1602, 1505, 1469, 1319, 1259, 670, 745 cm\(^{-1}\).

\( \text{N- (2-ethylpentyl)aniline (115f)} \). Using GP2, the reaction of \( N \)-methylaniline (54.2 \( \mu \)L, 0.500 mmol), \textit{trans}-3-hexene (63 mg, 0.75 mmol), and \textbf{1} (13.0 mg, 0.0250 mmol) at 145 °C for 44 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave the title compound as a colourless oil (76 mg, 79%); for 10 mol % catalyst loading of \textbf{111} (25.9 mg, 0.0500 mmol) at 145 °C for 24 h, the yield of \textbf{115f} was 91% (87 mg). When \textit{cis}-3-hexene was used with \textbf{111} (5 mol %) at 145 °C for 44 h, the yield of \textbf{115f} was 69% (66 mg). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.17 (dd, \( J = 8.5, 7.4 \) Hz, 2H), 6.67 (t, \( J = 7.3 \) Hz, 1H), 6.60 (d, \( J = 7.6 \) Hz, 2H), 3.61 (br s, 1H), 3.02 (d, \( J = 6.2 \) Hz, 2H), 1.58 (septet, \( J = 6.1 \) Hz, 1H), 1.50-1.27 (m, 6H), 0.92 (two overlapping t, \( J = 7.3 \) Hz, 2 x 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 148.9, 129.4, 117.1, 112.8, 47.2, 39.1, 34.2, 24.7, 20.2, 14.7, 11.1.

\( \text{(Z)- tert-buty(hex-4-en-1-yloxy)dimethylsilane.} \) Silyl protection of \textit{cis}-4-hexen-1-ol was carried out by Jason Brandt using literature procedures.\(^{343}\) \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 5.49-5.30 (m, 2H), 3.59 (t, \( J = 6.5 \) Hz, 2H), 2.07 (q, \( J = 7.3 \) Hz, 2H), 1.61-1.51 (m, 5H), 0.88 (s, 9H), 0.03 (s, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 130.4 (CH), 124.4 (CH), 62.9 (CH\(_2\)), 32.9 (CH\(_2\)), 26.2 (CH\(_3\)), 23.4 (CH\(_2\)), 18.6 (C), 12.9 (CH\(_3\)), 5.1 (CH\(_3\)). HRMS
(ESI): $m/z$ calcd for C$_{12}$H$_{27}$OSi [M+H$^+$]: 215.1831. Found: 215.1835. IR (neat): $\nu$ 2954, 2930, 2858, 1472, 1463, 1388, 1361, 1254, 1098, 958, 939, 833, 773, 698, 661 cm$^{-1}$.

$N$-(6-((tert-butyldimethylsilyl)oxy)-2-methylhexylaniline$^{298}$ (115ga) and $N$-(5-((tert-butyldimethylsilyl)-oxy)-2-ethylpentylaniline (115gb). Using GP2, the reaction of N-methylaniline (54.2 μL, 0.500 mmol), (Z)-tert-butyl(hex-4-en-1-yloxy)dimethylsilane (161 mg, 0.750 mmol), and 111 (13.0 mg, 0.0250 mmol) at 145 °C for 44 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave a mixture of 115ga and 115gb as a colourless oil (113 mg, 70%). The ratio 115ga/115gb was determined to be 2.3:1 by GC analysis.

$^1$H NMR (600 MHz, CDCl$_3$): 115ga δ 7.16 (t, $J = 7.5$ Hz, 2H), 6.67 (t, $J = 7.3$ Hz, 1H), 6.59 (t, $J = 8.1$ Hz, 2H), 3.65 (br s, 1H), 3.61 (t, $J = 6.4$ Hz, 2H), 3.05 (dd, $J = 12.2$, 5.9 Hz, 1H), 2.88 (dd, $J = 12.2$, 7.3 Hz, 1H), 1.74 (m, 1H), 1.61-1.15 (m, 6H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H). 115gb δ 7.16 (t, $J = 7.5$ Hz, 2H), 6.67 (t, $J = 7.3$ Hz, 1H), 6.59 (t, $J = 8.1$ Hz, 2H), 3.65 (br s, 1H), 3.60 (t, $J = 6.3$ Hz, 2H), 3.04-3.00 (m, 2H), 1.61-1.15 (m, 7H), 0.92 (t, $J = 7.4$ Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H). $^{13}$C NMR (150 MHz, CDCl$_3$): 115ga δ 148.9 (C), 129.4 (CH), 117.1 (CH), 112.8 (CH), 63.3 (CH$_2$), 50.5 (CH$_2$), 34.7 (CH$_2$), 33.3 (CH$_2$), 33.1 (CH), 26.2 (CH$_3$), 23.4 (CH$_2$), 18.6 (C), 18.2 (CH$_3$), -5.1 (CH$_3$). 115gb δ 148.8 (C), 129.4 (CH), 117.1 (CH), 112.8 (CH), 63.6 (CH$_2$), 47.2 (CH$_2$), 39.0 (CH), 30.1 (CH$_2$), 27.8 (CH$_2$), 26.2 (CH$_3$), 24.7 (CH$_2$), 18.6 (C), 11.0 (CH$_3$), -5.1 (CH$_3$). HRMS (ESI): $m/z$ calcd for C$_{19}$H$_{36}$NOSi [M+H$^+$]: 322.2566.
Found: 322.2568. IR (neat): v 3423, 3053, 3019, 2954, 2929, 2857, 1603, 1506, 1472, 1463, 1320, 1254, 1096, 834, 774, 746, 690 cm\(^{-1}\).

\[ \text{IR (neat): } \nu = 3423, 3053, 3019, 2954, 2929, 2857, 1603, 1506, 1472, 1463, 1320, 1254, 1096, 834, 774, 746, 690 \text{ cm}^{-1}. \]

\[ \text{N-(2-methyl-3-phenylpropyl)aniline\textsuperscript{300} (115ha) and N-(2-phenylbutyl)aniline (115hb). Using} \]

\[ \text{GP2, the reaction of } N\text{-methylaniline (54.2 } \mu \text{L, 0.50 mmol), cis-} \beta\text{-methylstyrene (88.6 mg, 0.750 mmol), and 111 (13.0 mg, 0.0250 mmol) at 145 } ^{\circ} \text{C for 24 h, followed by purification by} \]

\[ \text{flash column chromatography (3\% EtOAc in hexanes) gave a mixture of 115ha and 115hb as a} \]

\[ \text{colourless oil (104 mg, 92\%). The ratio 115ha/115hb was determined to be 4.4:1 by GC} \]

\[ \text{analysis.} \]

\[ \text{H NMR (400 MHz, CDCl}_3\text{): 115ha } \delta = 7.35-7.15 \text{ (m, 7H), 6.72 (t, } J = 7.3 \text{ Hz, 1H), 6.58 (d, } J = \]

\[ \text{8.1 Hz, 2H), 3.68 (br s, 1H), 3.13 (dd, } J = 12.4, 6.0 \text{ Hz, 1H), 2.99 (dd, } J = 12.4, 7.0 \text{ Hz, 1H), 2.80} \]

\[ \text{(dd, } J = 13.5, 6.3 \text{ Hz, 1H), 2.54 (dd, } J = 13.4, 7.8 \text{ Hz, 1H), 2.12 (octet, } J = 6.7 \text{ Hz, 1H), 1.02 (d, } J} \]

\[ = 6.7 \text{ Hz, 3H). 115hb } \delta = 7.40-7.15 \text{ (m, 7H), 6.76-6.68 (m, 1H), 6.62-6.55 (m, 2H), 3.68 (br s, 1H),} \]

\[ 3.49 (dd, } J = 12.3, 5.5 \text{ Hz, 1H), 3.25 (dd, } J = 12.2, 9.0 \text{ Hz, 1H), 2.88-2.78 (m, 1H), 1.92-1.78 (m,} \]

\[ 1.78-1.62 (m, 1H), 0.89 (t, } J = 7.4 \text{ Hz, 3H). } ^{13}\text{C NMR (100 MHz, CDCl}_3\text{): 115ha } \delta = 148.6 \]

\[ (\text{C), 140.7 (C), 129.4 (CH), 129.3 (CH), 128.5 (CH), 126.2 (CH), 117.3 (CH), 112.9 (CH), 50.0} \]

\[ (\text{CH}_2), 41.6 (\text{CH}_2), 35.2 (\text{CH}), 18.3 (\text{CH}_3). 115hb } \delta = 148.4 \text{ (C), 143.2 (C), 129.4 (CH), 128.8} \]

\[ (\text{CH}), 128.1 (\text{CH}), 126.9 (\text{CH}), 117.5 (\text{CH}), 113.2 (\text{CH}), 49.6 (\text{CH}_2), 47.4 (\text{CH}), 27.4 (\text{CH}_2), 12.2} \]

\[ (\text{CH}_3). \text{HRMS (ESI): } m/z \text{ calcd for C}_{16}H_{20}N [M+H]^+: 226.1596. \text{ Found: 226.1603. IR (neat): } \nu} \]

\[ 3417, 3086, 3057, 3025, 2956, 2923, 2872, 1601, 1505, 1453, 1319, 1256, 742, 691 \text{ cm}^{-1}. \]

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Using GP2, the reaction of N-methylaniline (54.2 μL, 0.500 mmol), trans-anethole (111 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 145 °C for 44 h, followed by purification by flash column chromatography (5% EtOAc in hexanes) gave a mixture of 115ia and 115ib as a colourless oil (97 mg, 76%). The ratio 115ia/115ib was determined to be 2.0:1 by GC analysis.

\[ ^{1}H \text{ NMR (400 MHz, CDCl}_3\]: 115ia \( \delta \) 7.20-7.07 (m, 4H), 6.88-6.82 (m, 2H), 6.69 (t, \( J = 7.4 \text{ Hz, 1H} \)), 6.59-6.53 (m, 2H), 3.80 (s, 3H), 3.63 (br s, 1H), 3.10 (dd, \( J = 12.4, 6.0 \text{ Hz, 1H} \)), 2.95 (dd, \( J = 12.4, 7.0 \text{ Hz, 1H} \)), 2.71 (dd, \( J = 13.6, 6.3 \text{ Hz, 1H} \)), 2.47 (dd, \( J = 13.6, 7.7 \text{ Hz, 1H} \)), 2.04 (octet, \( J = 6.7 \text{ Hz, 1H} \)), 0.98 (d, \( J = 6.7 \text{ Hz, 3H} \)). 115ib \( \delta \) 7.20-7.07 (m, 4H), 6.92-6.87 (m, 2H), 6.69 (t, \( J = 7.4 \text{ Hz, 1H} \)), 6.59-6.53 (m, 2H), 3.81 (s, 3H), 3.63 (br s, 1H), 3.44 (dd, \( J = 12.2, 5.5 \text{ Hz, 1H} \)), 3.17 (dd, \( J = 12.1, 9.1 \text{ Hz, 1H} \)), 2.80-2.71 (m, 1H), 1.85-1.73 (m, 1H), 1.69-1.55 (m, 1H), 0.86 (t, \( J = 7.4 \text{ Hz, 3H} \)).

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3\]: 115ia \( \delta \) 158.1 (C), 148.6 (C), 132.7 (C), 130.2 (CH), 129.4 (CH), 117.2 (CH), 113.9 (CH), 112.9 (CH), 55.4 (CH\(_3\)), 49.9 (CH\(_2\)), 40.6 (CH\(_2\)), 35.3 (CH), 18.2 (CH\(_3\)). 115ib \( \delta \) 158.5 (C), 148.4 (C), 135.0 (C), 129.4 (CH), 129.0 (CH), 117.4 (CH), 114.2 (CH), 113.2 (CH), 55.4 (CH\(_3\)) 49.7 (CH\(_2\)), 46.5 (CH\(_2\)), 27.5 (CH\(_2\)), 12.2 (CH\(_3\)).

HRMS (ESI): \( m/z \) calcd for C\(_{17}\)H\(_{22}\)NO [M+H\(^{+}\)]: 256.1701. Found: 256.1703. IR (neat): \( \nu \) 3412, 3053, 3021, 2958, 2927, 2867, 2835, 1602, 1584, 1507, 1463, 1441, 1319, 1301, 1244, 1177, 1033, 831, 804,747, 691 cm\(^{-1}\).
Using GP2, the reaction of N-methylaniline (54.2 μL, 0.500 mmol), methylenecyclohexane (72 mg, 0.75 mmol), and 111 (13.0 mg, 0.0250 mmol) at 110 °C for 20 h, followed by purification by flash column chromatography (2% EtOAc in hexanes) gave the title compound as a colourless oil (93 mg, 91%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.20-7.12 (m, 2H), 6.70-6.58 (m, 3H), 3.60 (br s, 1H), 2.93 (s, 2H), 1.56-1.25 (m, 10H), 0.97 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 149.4, 129.4, 117.0, 112.9, 54.9, 36.1, 34.5, 26.6, 23.5, 22.1.

**N-(((1\text{R},2\text{S},5\text{S})\text{-2,6,6-trimethylbicyclo[3.1.1]heptan-2-yl})methyl)aniline (115k).** Using GP2, the reaction of N-methylaniline (54.2 μL, 0.500 mmol), (1\text{S})-\(\beta\)-pinene (102 mg, 0.750 mmol), and 111 (13.0 mg, 0.0250 mmol) at 145 °C for 54 h, followed by purification by flash column chromatography (2% EtOAc in hexanes) gave the title compound as a pale yellow oil (67 mg, 55%). The diastereomeric ratio of the reaction was determined to be 15.9:1 by GC analysis. The relative stereochemistry of 115k was established by NOE analysis. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.15 (t, \(J = 7.7\) Hz, 2H), 6.66 (t, \(J = 7.3\) Hz, 1H), 6.60 (d, \(J = 8.0\) Hz, 2H), 3.54 (br s, 1H), 3.05 (d, \(J = 11.7\) Hz, 1H, \(H_i\)), 2.88 (d, \(J = 11.7\) Hz, 1H, \(H_i\)), 2.21-2.14 (m, 1H, \(H_d\)), 1.97-1.78 (m, 4H, \(H_{e,f,g,h}\)), 1.65-1.50 (m, 2H, \(H_{e,f}\)), 1.30-1.25 (m, 1H, \(H_{d}\)), 1.26 (s, 3H, \(H_c\)), 1.15 (s, 3H, \(H_b\)), 1.08 (s, 3H, \(H_a\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 149.4 (C), 129.4 (CH), 117.0 (CH), 112.8 (CH), 55.7 (CH\(_2\)), 50.1 (CH), 41.1 (CH), 39.6 (C), 38.6 (C), 28.7 (CH\(_3\)), 28.4 (CH\(_2\)), 28.0 (CH\(_2\)), 26.6 (CH\(_3\)), 25.8 (CH\(_2\)), 24.5 (CH\(_3\)). HRMS (ESI): \(m/z\) calcd for C\(_{17}\)H\(_{26}\)N [M+H\(^+\)]: 244.2065. Found: 244.2065. IR (neat): \(\nu\) 3422, 3052, 2991, 2914, 2868, 1601, 1505, 1465, 1321, 1253, 1179, 744, 689 cm\(^{-1}\).
bis(2-ethylpentyl)amine (116). Using a similar procedure to GP2 without an amine, a solution of trans-3-hexene (63 mg, 0.75 mmol) and 111 (13.0 mg, 0.0250 mmol) in $d_8$-toluene (0.5 mL) were heated in a J. Young NMR tube at 145 °C for 24 h. No C=C bond isomerization of trans-3-hexene was observed, and bis(2-ethylpentyl)amine was obtained as the only product of the reaction, as monitored by $^1$H NMR spectroscopy and GC analysis. The reaction mixture was exposed to air and diluted with hexanes to precipitate out the 2-pyridonate ligand and tantalum oxides. The mixture was filtered through a plug of Celite and silica gel. The filtrate was concentrated in vacuo and dried under high vacuum to give the title compound as a pale yellow oil (12 mg, 75%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.44 (d, $J = 6.3$ Hz, 4H), 1.41 (septet, $J = 6.1$ Hz, 2H), 1.37-1.17 (m, 13H), 0.87 (t, $J = 7.0$ Hz, 6H), 0.84 (t, $J = 7.4$ Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 53.8 (CH$_2$), 39.3 (CH), 34.4 (CH$_2$), 24.7 (CH$_2$), 20.1 (CH$_2$), 14.8 (CH$_3$), 11.1 (CH$_3$). HRMS (ESI): $m/z$ calcd for C$_{14}$H$_{32}$N [M+H$^+$]: 214.2535. Found: 214.2531. IR (neat): $\nu$ 2958, 2926, 2873, 2812, 1460, 1378, 1123, 771, 735, 701 cm$^{-1}$.

$N$-(2-ethylpentyl)-3,4-dimethylaniline (117a). Using GP2, the reaction of $N$,3,4-trimethylaniline (67.6 mg, 0.500 mmol), trans-3-hexene (63 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 145 °C for 24 h, followed by purification by flash column chromatography (2% EtOAc in hexanes) gave the title compound as a colourless oil (101 mg, 92%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.92 (d, $J = 8.1$ Hz, 1H), 6.43 (d, $J = 1.4$ Hz, 1H), 6.37 (dd, $J = 8.1$, 2.1 Hz, 1H), 3.42 (br s, 1H), 2.98 (d, $J = 6.1$ Hz, 2H), 2.19 (s, 3H), 2.14 (s, 3H), 1.55 (septet, $J = 6.1$ Hz, 1H), 1.47-1.25 (m, 6H), 0.90 (two overlapping t, $J = 7.5$ Hz, 2 x 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.2 (C), 137.4
(C), 130.5 (CH), 125.1 (C), 114.7 (CH), 110.3 (CH), 47.6 (CH₂), 39.2 (CH), 34.2 (CH₂), 24.7 (CH₂), 20.3 (CH₃), 20.2 (CH₂), 18.9 (CH₃), 14.7 (CH₃), 11.1 (CH₃). HRMS (ESI): m/z calcd for C₁₅H₂₆N [M+H⁺]: 220.2065. Found: 220.2063.

IR (neat): ν 3418, 2958, 2923, 2872, 1618, 1583, 1510, 1462, 1319, 1260, 1119, 844, 799 cm⁻¹.

**N-(2-ethylpentyl)-2-methylaniline (117b).** Using GP2, the reaction of N₂-dimethylaniline (60.6 mg, 0.500 mmol), *trans*-3-hexene (63 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 145 °C for 92 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave the title compound as a pale yellow oil (72 mg, 70%). ¹H NMR (300 MHz, CDCl₃): δ 7.13 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.68-6.59 (m, 2H), 3.48 (br s, 1H), 3.07 (d, J = 6.2 Hz, 2H), 2.15 (s, 3H), 1.64 (septet, J = 6.0 Hz, 1H), 1.53-1.30 (m, 6H), 0.94 (two overlapping t, J = 7.4 Hz, 2 x 3H). ¹³C NMR (75 MHz, CDCl₃): δ 146.8 (C), 130.2 (CH), 127.4 (CH), 121.8 (C), 116.6 (CH), 109.6 (CH), 47.2 (CH₂), 39.1 (CH), 34.4 (CH₂), 24.9 (CH₂), 20.2 (CH₂), 17.6 (CH₃), 14.7 (CH₃), 11.2 (CH₃). HRMS (ESI): m/z calcd for C₁₄H₂₄N [M+H⁺]: 206.1909. Found: 206.1910. IR (neat): ν 3442, 3019, 2958, 2926, 2872, 1607, 1587, 1513, 1464, 1446, 1302, 1260, 1051, 742, 714 cm⁻¹.

**N-(2-ethylpentyl)-4-fluoroaniline (117c).** Using GP2, the reaction of 4-fluoro-N-methylaniline (62.6 mg, 0.500 mmol), *trans*-3-hexene (63 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 145 °C for 24 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave the title compound as a pale yellow oil (88 mg, 84%). ¹H NMR (300 MHz, CDCl₃): δ 6.92-6.81 (m, 2H), 6.56-6.46 (m, 2H), 3.48 (br s, 1H), 2.96 (d, J = 6.1 Hz, 2H), 1.55 (septet, J = 6.1 Hz, 1H), 1.46-1.24 (m, 6H), 0.90 (two overlapping t, J = 7.4 Hz, 2 x 3H). ¹³C NMR (75 MHz, CDCl₃): δ 155.8
(d, $J = 234$ Hz, C), 145.3 (d, $J = 1.8$ Hz, C), 115.8 (d, $J = 22.2$ Hz, CH), 113.5 (d, $J = 7.4$ Hz, CH), 47.9 (CH$_2$), 39.1 (CH), 34.2 (CH$_2$), 24.7 (CH$_2$), 20.2 (CH$_2$), 14.7 (CH$_3$), 11.1 (CH$_3$). $^{19}$F NMR (282 MHz, CDCl$_3$): $\delta$ -129.1. HRMS (ESI): m/z calcd for C$_{13}$H$_{21}$NF [M+H$^+$]: 210.1658. Found: 210.1662. IR (neat): $\nu$ 3427, 2959, 2928, 2873, 1614, 1509, 1464, 1316, 1220, 1155, 1101, 816, 776, 732 cm$^{-1}$.

4-chloro-N-(2-ethylpentyl)aniline (117d). Using GP2, the reaction of 4-chloro-N-methylaniline (70.8 mg, 0.500 mmol), trans-3-hexene (63 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 145 °C for 24 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave the title compound as a pale yellow oil (88 mg, 78%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.11-7.06 (m, 2H), 6.52-6.47 (m, 2H), 3.60 (br s, 1H), 2.98 (d, $J = 6.2$ Hz, 2H), 1.54 (septet, $J = 6.1$ Hz, 1H), 1.45-1.24 (m, 6H), 0.89 (two overlapping t, $J = 7.5$ Hz, 2 x 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.5 (C), 129.2 (CH), 121.6 (C), 113.8 (CH), 47.4 (CH$_2$), 39.1 (CH), 34.2 (CH$_2$), 24.7 (CH$_2$), 20.1 (CH$_2$), 14.7 (CH$_3$), 11.1 (CH$_3$). HRMS (ESI): m/z calcd for C$_{13}$H$_{21}$NCl [M+H$^+$]: 226.1363. Found: 226.1369. IR (neat): $\nu$ 3427, 2959, 2927, 2872, 1601, 1499, 1463, 1316, 1254, 1176, 1095, 811 cm$^{-1}$.

4-bromo-N-(2-ethylpentyl)aniline (117e). Using GP2, the reaction of 4-bromo-N-methylaniline (93.0 mg, 0.500 mmol), trans-3-hexene (63 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 145 °C for 24 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave the title compound as a pale yellow oil (32 mg, 24%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.24-7.19 (m, 2H), 6.46-6.42 (m, 2H), 3.62 (br s, 1H), 2.96 (d, $J = 6.2$ Hz, 2H), 1.54 (septet, $J = 6.1$ Hz, 1H),
1.45-1.24 (m, 6H), 0.90 (t, $J = 6.9$ Hz, 3H) 0.89 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.9 (C), 132.1 (CH), 114.3 (C), 108.5 (CH), 47.2 (CH$_2$), 39.0 (CH), 34.1 (CH$_2$), 24.7 (CH$_2$), 20.1 (CH$_2$), 14.7 (CH$_3$), 11.1 (CH$_3$). HRMS (ESI): $m/z$ calcd for C$_{13}$H$_{21}$NBr [M+H$^+$]: 270.0857. Found: 270.0859. IR (neat): v 3426, 2958, 2926, 2871, 1595, 1496, 1463, 1316, 1293, 1255, 1177, 1071, 809 cm$^{-1}$.

N-(2-ethylpentyl)-4-methoxyaniline (117f). Using GP2, the reaction of 4-methoxy-$N$-methylaniline (68.6 mg, 0.500 mmol), trans-3-hexene (63 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 145 °C for 24 h, followed by purification by flash column chromatography (6% EtOAc in hexanes) gave the title compound as a pale yellow oil (90 mg, 81%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 6.78 (d, $J = 8.8$ Hz, 2H), 6.57 (d, $J = 8.9$ Hz, 2H), 3.73 (s, 3H), 2.34 (br s, 1H), 2.96 (d, $J = 6.1$ Hz, 2H), 1.55 (septet, $J = 5.7$ Hz, 1H), 1.46-1.24 (m, 6H), 0.90 (two overlapping t, $J = 7.3$ Hz, 2 x 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 152.0 (C), 143.3 (C), 115.1 (CH), 114.1 (CH), 56.1 (CH$_3$), 48.3 (CH$_2$), 39.2 (CH), 34.2 (CH$_2$), 24.7 (CH$_2$), 20.2 (CH$_2$), 14.7 (CH$_3$), 11.1 (CH$_3$). HRMS (ESI): $m/z$ calcd for C$_{14}$H$_{24}$NO [M+H$^+$]: 222.1858. Found: 222.1859. IR (neat): v 3407, 2957, 2929, 2872, 2831, 1511, 1463, 1232, 1038, 815 cm$^{-1}$.

N-(2-ethylpentyl)-4-(trifluoromethoxy)aniline (117g). Using GP2, the reaction of $N$-methyl-4-(trifluoromethoxy)aniline (95.6 mg, 0.500 mmol), trans-3-hexene (63 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 145 °C for 24 h, followed by purification by flash column chromatography (4% EtOAc in hexanes) gave the title compound as a pale yellow oil (85 mg, 62%). $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.01 (d, $J = 8.3$ Hz, 2H), 6.56-6.49 (m, 2H), 3.66 (br s,
1H), 2.98 (d, J = 6.2 Hz, 2H), 1.56 (septet, J = 6.1 Hz, 1H), 1.48-1.24 (m, 6H), 0.91 (two overlapping t, J = 7.4 Hz, 2 x 3H). $^1$H NMR (75 MHz, CDCl$_3$): $\delta$ 147.7 (CH) 140.3 (q, J = 2.0 Hz, C), 122.6 (CH), 121.0 (q, J = 255 Hz, C), 112.9 (CH), 47.4 (CH$_2$), 39.1 (CH), 34.2 (CH$_2$), 24.7 (CH$_2$), 20.1 (CH$_2$), 14.7 (CH$_3$), 11.1 (CH$_3$). $^1$H NMR (75 MHz, CDCl$_3$): $\delta$ 58.8. HRMS (ESI): m/z calcd for C$_{14}$H$_{21}$NOF$_3$ [M+H$^+$]: 276.1575. Found: 276.1566. IR (neat): $\nu$ 3431, 2961, 2930, 2875, 1614, 1515, 1465, 1248, 1220, 1154, 1110, 916, 827, 793, 670 cm$^{-1}$.

N-(2-ethylpenty)-3,4-dimethoxylaniline (117h). Using GP2, the reaction of 3,4-dimethoxy-N-methylaniline (83.6 mg, 0.500 mmol), trans-3-hexene (63 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 145 °C for 24 h, followed by purification by flash column chromatography (15% EtOAc in hexanes) gave the title compound as a pale yellow oil (39 mg, 31%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.73 (d, J = 8.5 Hz, 1H), 6.22 (s, 1H), 6.12 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.37 (br s, 1H), 2.96 (d, J = 6.0 Hz, 2H), 1.54 (septet, J = 5.8 Hz, 1H), 1.46-1.24 (m, 6H), 0.90 (two overlapping t, J = 7.0 Hz, 2 x 3H). $^1$C NMR (100 MHz, CDCl$_3$): $\delta$ 150.3 (C), 144.0 (C), 141.5 (C), 113.7 (CH), 103.5 (CH), 98.9 (CH), 57.0 (CH$_3$), 55.9 (CH$_3$), 48.1 (CH$_2$), 39.2 (CH), 34.3 (CH$_2$), 24.8 (CH$_2$), 20.2 (CH$_2$), 14.7 (CH$_3$), 11.2 (CH$_3$). HRMS (ESI): m/z calcd for C$_{15}$H$_{26}$NO$_2$ [M+H$^+$]: 252.1964. Found: 252.1967. IR (neat): $\nu$ 3396, 2957, 2927, 2872, 1617, 1594, 1514, 1463, 1230, 1209, 1168, 1135, 1025, 818, 782, 763 cm$^{-1}$.

2-(3-hexyl)-1,2,3,4-tetrahydroquinoline (117i). Using GP2, the reaction of 1,2,3,4-tetrahydroquinoline (66.6 mg, 0.500 mmol), trans-3-hexene (63 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 145 °C for 24 h, followed by purification by flash column chromatography (3% EtOAc in hexanes) gave the title
compound as a pale yellow oil (89 mg, 82%). Single diastereomer was obtained, and the other possible diastereomer was not detected by $^1$H NMR spectroscopy and GC analysis.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.98-6.92 (m, 2H), 6.58 (t, $J = 7.3$ Hz, 1H), 6.47 (d, $J = 7.7$ Hz, 1H), 3.61 (br s, 1H), 3.35-3.27 (m, 1H), 2.88-2.68 (m, 2H), 1.88-1.80 (m, 1H), 1.74-1.62 (m, 1H), 1.59-1.47 (m, 1H), 1.44-1.23 (m, 6H), 0.94 (two overlapping t, $J = 7.2$ Hz, 2 x 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 145.5 (C), 129.4 (CH), 126.9 (CH), 121.7 (C), 116.8 (CH), 114.2 (CH), 54.0 (CH), 44.5 (CH), 32.1 (CH$_2$), 27.3 (CH$_2$), 24.6 (CH$_2$), 22.7 (CH$_2$), 21.1 (CH$_2$), 14.7 (CH$_3$), 12.4 (CH$_3$). HRMS (ESI): $m/z$ calcd for C$_{15}$H$_{24}$N [M+H$^+$]: 218.1909. Found: 218.1909. IR (neat): $\nu$ 3413, 3052, 3014, 2956, 2928, 2871, 1607, 1586, 1482, 1310, 1276, 742, 714 cm$^{-1}$.

The isolated $^{117}$i (43 mg, 0.20 mmol) was treated with 1-naphthoyl chloride (33 $\mu$L, 0.22 mmol) and NEt$_3$ (84 $\mu$L, 0.60 mmol) in CH$_2$Cl$_2$ and stirred for 1 h at room temperature. The organic layer was washed with 1M HCl solution, followed by saturated NaHCO$_3$ solution, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The relative stereochemistry of $^{117}$i was assigned based on the crystal structure of $N$-(1-naphthoyl)$^{117}$i, grown from a slow evaporation of a hexanes solution of the product. $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 8.21 (br s, 1H), 7.83 (br s, 1H), 7.71 (br s, 1H), 7.60 (br s, 1H), 7.52 (br s, 1H), 7.06 (br s, 2H), 6.86 (br s, 1H), 6.73 (br s, 1H), 6.49 (br s, 1H), 6.19 (br s, 1H), 5.13 (br s, 1H), 2.87-2.73 (m, 2H), 2.36 (br s, 1H), 1.86 (br s, 1H), 1.71 (br s, 1H), 1.51 (br s, 2H), 1.42 (br s, 2H), 1.27 (br s, 2H), 0.92 (br s, 6H).

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 169.8 (C), 138.9 (C), 135.2 (C), 133.8 (C), 133.1 (C), 131.7 (C), 129.1 (CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 126.3 (CH), 125.8 (CH), 125.7 (2 CH), 125.2 (CH), 124.6 (2 CH), 54.3 (CH), 40.6 (CH), 32.3 (CH$_2$), 26.8 (CH$_2$), 25.7 (CH$_2$), 21.8
(CH₂)$_{20}$ (CH₂), 20.0 (CH₂), 14.8 (CH₃), 11.2 (CH₃). HRMS (ESI): m/z calcd for C$_{26}$H$_{29}$NONa [M+Na$^+$]: 394.2147. Found: 394.2149. IR (neat): $\nu$ 3050, 2929, 2869, 1652, 1578, 1491, 1458, 1402, 1333, 1299, 1253, 1204, 1151, 1027, 809, 787, 755, 741, 694 cm$^{-1}$.

$N$-(2-ethylpentyl)cyclohexanamine (117j). Using GP2, the reaction of $N$-methylcyclohexylamine (56.6 mg, 0.500 mmol), trans-3-hexene (63 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 145 °C for 44 h, followed by purification by flash column chromatography (5% EtOAc/2% $i$Pr$_2$NH in hexanes) gave the title compound as a colourless oil (87 mg, 88%). $^1$H NMR (400 MHz, CDCl$_3$): δ 2.47 (d, $J = 6.1$ Hz, 2H), 2.32 (tt, $J = 10.4$, 3.7 Hz, 1H), 1.86-1.79 (m, 2H), 1.73-1.64 (m, 2H), 1.61-1.53 (m, 1H), 1.42-0.96 (m, 12H), 0.86 (t, $J = 7.0$ Hz, 3H), 0.82 (t, $J = 7.3$ Hz, 3H), 0.81 (br s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 57.4 (CH), 50.5 (CH$_2$), 39.6 (CH), 34.4 (CH$_2$), 34.0 (CH$_2$), 33.9 (CH$_2$), 26.5 (CH$_2$), 25.3 (2 CH$_2$), 24.7 (CH$_2$), 20.1 (CH$_2$), 14.7 (CH$_3$), 11.0 (CH$_3$). HRMS (ESI): m/z calcd for C$_{13}$H$_{28}$N [M+H$^+$]: 198.2222. Found: 198.2224. IR (neat): $\nu$ 2957, 2925, 2853, 1450, 1378, 1128, 888, 728 cm$^{-1}$.

$N$-butyl-2-ethylpentan-1-amine (117k). Using GP2, the reaction of $N$-butylmethylamine (43.6 mg, 0.500 mmol), trans-3-hexene (63 mg, 0.75 mmol), and 111 (25.9 mg, 0.0500 mmol) at 165 °C for 92 h, followed by purification by flash column chromatography (5% $i$Pr$_2$NH in hexanes) gave the title compound as a pale yellow oil (55 mg, 64%). $^1$H NMR (300 MHz, CDCl$_3$): δ 2.55 (t, $J = 7.2$ Hz, 2H), 2.46 (d, $J = 6.2$ Hz, 2H), 1.52-1.14 (m, 13H), 0.89 (t, $J = 7.2$ Hz, 3H), 0.87 (br s, 1H), 0.86 (t, $J = 7.0$ Hz, 3H), 0.84 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 53.6 (CH$_2$), 50.3 (CH$_2$), 39.4 (CH), 34.3 (CH$_2$), 32.5 (CH$_2$), 24.7 (CH$_2$), 20.8 (CH$_2$), 20.1 (CH$_2$), 14.7 (CH$_3$), 14.3 (CH$_3$), 11.1 (CH$_3$).
HRMS (ESI): m/z calcd for C_{11}H_{26}N [M+H^{+}]: 172.2065. Found: 172.2065. IR (neat): ν 2957, 2926, 2873, 2810, 1461, 1378, 1127, 734 cm⁻¹.

**Synthesis of 118.** To a stirring solution of (3-phenyl-2-pyridonate)Ta(NMe₂)₃Cl (0.104 g, 0.200 mmol) in toluene (~3 mL) in a 20 mL vial, 3-phenyl-2-pyridone (0.0342 g, 0.200 mmol) was added in portions. The mixture was stirred at ambient temperature for 4 h, and concentrated in vacuo. The resulting yellow solid was dissolved in hot toluene (~7 mL) and gradually cooled to room temperature. The solution was then layered with hexanes (~3 mL), and left sitting undisturbed overnight at room temperature to afford a bright yellow microcrystalline solid of 118 (0.085 g, 66%). Single crystals for X-ray structure analysis were obtained from a toluene solution of the complex, layered with minimal hexanes, left at room temperature over a couple of days. ^1H NMR (400 MHz, C₆D₆): δ 8.08 (br s, 2H), 7.89 (d, J = 7.6 Hz, 4H), 7.39 (dd, J = 7.5, 1.2 Hz, 2H), 7.30 (t, J = 7.7 Hz, 4H), 7.20-7.15 (m, 2H), 6.29 (dd, J = 7.3, 5.5 Hz, 2H), 4.15-3.50 (br m, 12H). ^13C NMR (100 MHz, C₆D₆): δ 140.3 (CH), 135.7 (C), 129.1 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 123.8 (C), 114.1 (CH), 47.0 (CH₃); due to the poor solubility of the complex, the quaternary carbonyl carbon signal of 2-pyridonate could not be observed even after an overnight experiment. MS (EI): m/z = 644 (M⁺), 600 (M⁺–NMe₂). Anal. calcd for C_{26}H_{28}ClN₄O₂Ta: C, 48.42; H, 4.38; N, 8.69. Found: C, 48.45; H, 4.46; N, 8.59.
Chapter 5: Summary and future directions

5.1 Summary

The investigations undertaken in this thesis were aimed towards the development of new catalysts for the sustainable synthesis of selectively substituted amines. Prior to this work, there was a paucity in the utilization of pyridine-derived $\kappa^2$-1,3-chelating ligands for organometallic complexes applied toward the catalytic synthesis of amines. To this end, earth-abundant early transition metal complexes bearing 2-aminopyridinate (Ap) and 2-pyridonate ligands were explored for their potential applications in the atom-economic C–N and C–C bond forming reactions, hydroamination and hydroaminoalkylation, respectively. The design, synthesis, and characterization of group 4 and 5 metal complexes supported by Ap and 2-pyridonate ligands were employed for targeting sterically accessible metal centers that would impart enhanced catalytic reactivity. From these research endeavors, a collection of efficient catalytic systems were identified for hydroamination and hydroaminoalkylation reactions with improved substrate scopes (Figure 5.1). Most importantly, the chemoselectivity challenge between intramolecular hydroaminoalkylation over hydroamination was achieved for the first time, and further mechanistic insight for intramolecular hydroaminoalkylation was uncovered.

![Figure 5.1 Selected early transition metal complexes from this work](image-url)
In Chapter 2, work on Ap ligands featuring bulky aryl substituents was discussed. Such features of the ligand were shown to be crucial for the formation of well-defined mono(Ap)-ligated titanium complexes ApTi(NMe$_2$)$_3$ (52–54). The combination of having the bulky substituents tied back in the pyridine framework and mono-ligation with this $\kappa^2$-$N,N$-chelating ligand on titanium allowed for improvements in the steric accessibility about the metal center. This resulted in significantly improved catalytic reactivity for intramolecular hydroamination. The reactivity identified in comparison to previously reported bis(Ap)$^{65}$ and the related bis($\kappa^2$-$N,O$-amidate) group 4 systems$^{195}$ was impressive, including a rare example of room temperature hydroamination with a titanium complex. The control of steric accessibility about the metal center was also shown to be important. The comparison between the series of mono(Ap)-ligated complexes 52–54 revealed that the moderate steric bulk provided by the mesityl-substituted mono(Ap)titanium complex 53 generated the most effective catalytic cyclohydroamination reactivity. Furthermore, the bulky nature of Ap ligand prevented dimer formation, thereby prohibiting hydroaminoalkylation side reactivity. The lack of reactivity with secondary aminoalkenes using 53 as a precatalyst, and the isolation of a catalytically active imido complex 66 from the stoichiometric reaction using 53 and a primary amine suggested that imido [2+2] cycloaddition is operative for the C–N bond forming step. To date, complex 53 is the most reactive titanium precatalyst for catalytic cyclohydroamination with good breadth of substrate scope.

Chapter 3 focused on the ligand synthesis and systematic screening of variously 3-substituted-2-pyridonates for use as ancillary ligands on titanium for targeting intramolecular hydroaminoalkylation reactivity. A catalyst-controlled chemoselective catalyst for intramolecular hydroaminoalkylation over hydroamination did not exist prior to this work. A previous report
with the related bis(2-pyridonate)zirconium complex had proposed a bimetallic mechanism for intramolecular hydroaminoalkylation, involving bridging imido and metallaziridine intermediates. However, a literature search revealed that there was no structural report of such 2-pyridonate-bridged group 4 bimetallic complexes, although late transition metal examples have been reported.

Through catalyst optimization studies, bis(3-phenyl-2-pyridonate)Ti(NMe$_2$)$_2$ 86 was identified as the preferred catalyst for titanium-catalyzed intramolecular hydroaminoalkylation. The observation that a phenyl substituent provides a favorable amount of steric bulk at the 3-position remote from the metal center, while the presence of a substituent at the 6-position near the metal center disfavors intramolecular hydroaminoalkylation reactivity, is consistent with the 2-pyridonate bridging postulate.

Complex 86 is the first chemoselective catalyst for intramolecular hydroaminoalkylation over hydroamination. Using 86 as a precatalyst, various 5- and 6-membered-cycloalkylamines can be synthesized from primary aminoalkene substrates, with good substrate-dependent diastereoselectivity (of up to 19:1). Notably, stoichiometric reactions using 86 and various primary amines led to the formation and structural characterization of bimetallic imido complexes (97 and 98) that are moderately catalytically competent but selective for intramolecular hydroaminoalkylation over hydroamination. Hence, this work provided the first concrete evidence for the formation of 2-pyridonate-bridged group 4 metal centers, and demonstrated their proposed role in intramolecular hydroaminoalkylation.

These terminal imido complexes were shown to be highly fluxional in solution on the NMR time scale, and presumably can rearrange to form bridging imido intermediates that can then undergo C–H activation. Regrettably, a reliable variable temperature NMR study could not
be carried out to further examine the fluxional behavior of these 2-pyridonate-bridged bimetallic complexes, due to their poor solubility and decomposition in the solution phase. Unfortunately, 86 is susceptible to ligand redistribution to yield a tris(2-pyridonate)titanium(IV) complex, which undergoes a subsequent reduction of the metal center from Ti(IV) to Ti(III) in the presence of amines. This proposal was supported by the observation of paramagnetic species from the broadening of NMR signals and the detection of EPR signals. Most importantly, the reliable synthesis, isolation and structural characterization of tris(2-pyridonate)titanium(III) complex 95 from the reaction using tris(2-pyridonate)titanium(IV) complex 96 and benzylamine as the only reductant provided confirming evidence for such proposal.

Investigation of the reactivity of these various 2-pyridonate-ligated complexes has shown that 95 is unreactive, thereby ruling out the involvement of Ti(III) species and a potential radical promoted process as a viable mechanism for intramolecular hydroaminoalkylation with these systems. Additionally, 96 exclusively promotes slow hydroamination catalysis, suggesting that the tris(2-pyridonate)titanium species can be attributed as the source of hydroamination side reactivity that grows as the reaction progresses. Preliminary deuterium labelling experiments of the α-C–H bonds of the aminoalkene substrate showed that the α-C–H activation step is not readily reversible and could be the turnover limiting step of this reaction. The mechanistic groundwork provided in Chapter 3 contributes to a better understanding of this emerging intramolecular hydroaminoalkylation reaction for future catalyst development.

Chapter 4 explored the variable combinations of mixed 2-pyridonate/alkyl/amido/chloro ligands on tantalum for targeting an expansion in substrate scope for the intermolecular hydroaminoalkylation reaction. Prior to this work, the 2-pyridonate ligand set was an unexplored member in the κ²-N,O-chelate family that included amidates298,307 and phosphoramidates305 for
catalytic intermolecular hydroaminoalkylation. Furthermore, the intermolecular α-alkylation of amines was largely limited to the use of terminal alkene substrates, such as 1-octene, and no effective catalyst existed for the hydroaminoalkylation of sterically demanding unactivated disubstituted alkenes. It was envisioned that mono(2-pyridonate)tantalum chloro complexes with exchangeable alkyl or amido ligands would provide enhanced steric accessibility about the metal center for the accommodation of sterically encumbered internal alkene substrates. However, for alkyl-based 2-pyridonate tantalum systems, only the bis(2-pyridonate)tantalum methyl complexes could be prepared. Their thermal and light sensitivity did not allow for the targeted hydroaminoalkylation with internal alkene substrates. Notably, the switch to the use of dimethylamide as supporting ancillary ligands, instead of methyl ligands, allowed for the synthesis of the targeted mono(3-phenyl-2-pyridonate)Ta(NMe₂)₃Cl 111 for hydroaminoalkylation reactivity with internal alkene substrates. Here, the combination of 2-pyridonate and chloro ligands was demonstrated to be important, as the related complexes, mono(3-phenyl-2-pyridonate)Ta(NMe₂)₄ 112 and [Ta(NMe₂)₃Cl₂]₂, that lack this exact combination could not provide efficient reactivity with internal alkene substrates.

Most importantly, complex 111 is the first broadly applicable precatalyst for the catalytic intermolecular hydroaminoalkylation of unactivated, sterically demanding (E)- and (Z)-internal alkenes without C=C bond isomerization. Interestingly, 111 was shown to be poorly reactive towards terminal alkene substrates, thereby highlighting the importance of tailoring ligand-substrate combinations for targeting the desired reactivity. The effective hydroaminoalkylation of sterically demanding alkene substrates uncovered with the development of 111, opens further catalyst development opportunities with the variation of the ligand environment about tantalum.
The variety of 2-aminopyridinate and 2-pyridonate group 4 and 5 chemistry accomplished during this work is a significant contribution to the field of atom-economical, catalytic selectively substituted amine synthesis. These modular pyridine derivatives were largely overlooked for use as supporting ancillary ligands on early transition metals for hydroamination and hydroaminoalkylation catalysis. The understanding and research advances established for these transformations in this thesis suggest further research avenues, which are discussed in the following section. Some preliminary results for alternative strategies and approaches will also be presented.

5.2 Future directions

5.2.1 Enantioselective intramolecular hydroamination

The investigation of mono(2-aminopyridinate)titanium complexes (in Chapter 2) involved the use of achiral ligands that form racemic $N$-heterocyclic products. The modular framework of pyridine allows for the possibility of exploring enantioselective versions of intramolecular hydroamination. Chiral substituents could be installed at either the 2- or 6-position of the pyridine to access chiral ligand derivatives that might be able to induce enantioselectivity during the reaction (Scheme 5.1). Based on the findings from the work reported in Chapter 2, it is critical to preserve sufficient steric bulk to maintain a mono(Ap)-ligated complex for enhanced reactivity. For example, the use of a mesityl substituent is proposed for the 6-position of the Ap ligand, which can be installed via Ni-catalyzed Kumada coupling. Nucleophilic aromatic substitution of the bromide at the 2-position with various $\alpha$-chiral amines would give access to a series of chiral Ap ligands for exploration. Given that
sufficient steric bulk is provided by these ligands, the synthesis of chiral mono(Ap)titanium complexes should provide further opportunity for hydroamination catalyst development.

Scheme 5.1 Proposed synthesis of chiral mono(2-aminopyridinate)titanium complexes

5.2.2 Cyclopentadienyl titanium amidates

Our working mechanistic postulate for the intramolecular hydroaminoalkylation of primary aminoalkenes (in Chapter 3) involves the formation of bridging dimeric imido species as intermediates in the intramolecular hydroaminoalkylation catalytic cycle. Improvements in catalyst design that promote the formation of such bridging dimeric imido species are anticipated to increase the chemoselectivity for hydroaminoalkylation over hydroamination. Bridging titanium imido complexes are known, and there is literature precedence for the related cyclopentadienyl-capped complexes. It was anticipated that the known end-capping ability of cyclopentadienyl (Cp, $\eta^5$-C$_5$H$_5$) ligands on related dimeric species might promote the bridging nature of $N,O$-ligands to access the targeted $N,O$-bridged binuclear complex (Scheme 5.2).
The synthesis of a mono(Cp)mono(amidate)bis(dimethylamido)titanium complex 119 has been carried out as a potential intramolecular hydroaminoalkylation catalyst (Scheme 5.3). Complex 119 can be synthesized in two steps, by the preparation of CpTi(NMe₂)₃ from a protonolysis reaction of Ti(NMe₂)₄ with cyclopentadiene, and a subsequent protonolysis reaction of CpTi(NMe₂)₃ with a modular N,O-ligand. Here N-(2,6-dimethylphenyl)pivalamide has been used for preliminary investigation, and complex 119 was obtained as dark red crystals in 56% yield after recrystallization from hexanes at -35 °C. In the solid-state, the complex 119 has a piano-stool tetrahedral geometry, and the amidate ligand is bound in a κ¹-binding mode through the oxygen (Figure 5.2). The chelation of the amidate ligand is presumably prevented due to the steric hindrance of the dimethylamido ligands in contrast to CpCl₂(amidate)titanium complexes that have a κ²N,O-binding motif.

![Scheme 5.2 Potential bridging ability of mixed Cp/N,O-ligand systems](image)

**Scheme 5.2** Potential bridging ability of mixed Cp/N,O-ligand systems

**Scheme 5.3** Synthetic route to mixed Cp/N,O-ligand titanium systems

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Figure 5.2 ORTEP representation one of two independent molecules of 119 plotted with 50% probability ellipsoids. All hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (°): Ti1–O1, 1.8993(8); Ti1–N2, 1.9021(11); Ti1–N3, 1.8978(11); Ti1–C14, 2.3648(12); Ti1–C15, 2.4144(13); Ti1–C16, 2.4239(14); Ti1–C17, 2.3757(14); Ti1–C18, 2.3548(14); O1–C1, 1.3230(12); C1–N1, 1.2753(14); N2–Ti1–O1, 103.35(5); N3–Ti1–O1, 107.07(5); N3–Ti1–N2, 100.44(6); Ti1–O1–C1, 153.98(7).

Preliminary catalytic screening using 119 as a precatalyst with an aminoalkene substrate shows that it is preferential for hydroamination reactivity instead of the desired hydroaminoalkylation reactivity (Scheme 5.4). In addition, the signal at δ 5.67 (s, η5-C5H5) corresponding to the Cp ligand of 119 is absent in the 1H NMR spectrum at the end of the reaction, suggesting that it might be displaced from the metal center by amines at elevated temperatures. The mixed Cp/N,O-ligand titanium systems do not seem to be promising targets for intramolecular hydroaminoalkylation reactivity. Furthermore, preliminary in situ catalytic screening using CpTi(NMe2)3 and 2-pyridone was also unsuccessful for intramolecular hydroaminoalkylation.
Scheme 5.4 Catalytic cyclization of an aminoalkene substrate using 119

5.2.3 Sterically less demanding 2-aminopyridinates

Instead of the aforementioned mixed Cp/N,O-ligand titanium systems, much room exists for further exploration of the modular N,N-chelating 2-aminopyridinate (Ap) ligand sets for intramolecular hydroaminoalkylation reactivity (Figure 5.3). Complex 23a is a known precatalyst for intermolecular hydroaminoalkylation, \(^{68}\) and preliminary catalytic screening using 23a as a precatalyst with a primary aminoalkene substrate showed some selectivity for intramolecular hydroaminoalkylation (87% conversion, HAA/HA = 52:35, Table 3.1, entry 5). Most importantly, a systematic ligand screening investigation has not been carried out for these sterically less demanding Ap ligand sets, and such ligand optimization studies could lead to an alternative intramolecular hydroaminoalkylation selective precatalyst to bis(3-phenyl-2-pyridonate)Ti(NMe\(_2\))\(_2\) 86. The differing electronic properties between Ap and 2-pyridonate

Figure 5.3 (a) Doye’s bis(N-methyl-2-aminopyridinate)Ti(NMe\(_2\))\(_2\) 23a; (b) potential sterically less demanding 2-aminopyridinate ligands for intramolecular hydroaminoalkylation
ligands might render a more robust catalytic system that could be resistant to the reduction of the metal center by amines. In particular, it would be interesting to probe whether a related bis(Ap)Ti(NMe$_2$)$_2$ complex supported by N-methyl-3-phenyl-2-aminopyridinate ligand (Figure 5.3b, left) could also benefit from steric bulk at the 3-position of the pyridine framework for bridging ability and, potentially, increased hydroaminoalkylation selectivity over hydroamination. The preparation of N-methyl-3-phenyl-2-aminopyridine from the Suzuki coupling reaction of phenylboronic acid and 3-chloro-N-methyl-2-aminopyridine is known.$^ {349}$ Alternatively, N-methyl-1-isoquinolinamine$^ {349}$ (Figure 5.3b, middle) and the commercially available 2,3-dihydro-7-azaindole (Figure 5.3b, right) could also be potential ligand targets for this reaction. Further catalyst design endeavors will lead to a more robust and efficient catalytic system with increased stereoselectivities and substrate scope for this emerging intramolecular hydroaminoalkylation reaction.

5.2.4 2-Pyridonate tantalum complexes

With the development of mono(3-phenyl-2-pyridonate)Ta(NMe$_2$)$_3$Cl 111 (in Chapter 4) for the first efficient catalytic intermolecular hydroaminoalkylation of unactivated disubstituted alkenes, mechanistic questions remain for this precatalyst. Deuterium labelling experiments, kinetic investigations, and stoichiometric synthetic experiments using 111 are therefore needed to examine the catalytic pathway of this reaction, including the elucidation of the turnover limiting step and reaction rates. For example, $\alpha$-deuterated amine substrates, such as N-(methyl-$d_3$)aniline, can be used in kinetic isotope experiments to determine whether the C–H activation is turnover limiting. The fate of the deuterium on the resulting $\alpha$-alkylated product will also provide further insight into the reaction mechanism. Such mechanistic studies will lead to better
understanding of the hydroaminoalkylation reaction and, consequently, allow for the development of improved catalytic systems.

The work presented in Chapter 4 involving 2-pyridonate tantalum complexes highlight the modularity of the ligand environment on the metal center, as well as the importance of tailoring the mixed 2-pyridonate/amido/chloro ligand combinations to access improved substrate scope. An extensive systematic ligand screening was not carried out and, hence, substituent effects on the 2-pyridonate, and various mixed ligand combinations remain to be explored for further modification of 111 to potentially target a better catalytic system (Figure 5.4). In particular, the alkyl analogue of 111, such as mono(3-phenyl-2-pyridonate)Ta(CH₂CMe₃)₃Cl, could be an interesting target for catalytic reactivity comparison to 111. Presumably the use of bulky alkyl ligands such as the neopentyl ligands could allow for the synthesis of mono(2-pyridonate)-ligated tantalum alkyl complexes from a salt metathesis reaction using Ta(CH₂CMe₃)Cl₂ and a equivalent of sodium 2-pyridonate, instead of the formation of bis(2-pyridonate)TaMe₃ complexes that was obtained from using TaMe₃Cl₂ as the tantalum precursor. The sterically bulky nature of neopentyl ligands might also provide more robustness than methyl ligands. Most importantly, the preparation of mono(3-phenyl-2-pyridonate)Ta(CH₂CMe₃)₃Cl will allow for the examination of the possible role of the bis(α-alkylated)dimethylamine

![Figure 5.4 Variable 2-pyridonate tantalum complexes](image)

**Figure 5.4** Variable 2-pyridonate tantalum complexes
byproduct that arises in the reaction as a result of precatalyst activation of 111. The preparation of such mixed 2-pyridonate/alkyl/chloro complexes will also be useful for kinetic studies, as the formation of bis(α-alkylated)dimethylamine byproduct that interferes in the rigorous kinetic analysis is avoided.

It was noted that mono(3-phenyl-2-pyridonate)Ta(NMe$_2$)$_4$ 112 can carry out the α-alkylation of N-methylaniline using 1-octene in excellent yields (93%) at 110 °C (Scheme 4.17). To date, the mono(amidate)Ta(NMe$_2$)$_4$ complex 68 is the only effective catalytic system for the intermolecular hydroaminoalkylation of various N-heterocycles, including piperidines and N-substituted piperazines, with terminal alkene substrates, but requires elevated temperatures of up to 165 °C and long reaction times.$^{298,307}$ For example, the α-alkylation of piperidine using 1-octene and 68 as a precatalyst requires 5-6 days to synthesize the hydroaminoalkylation product 120 (Scheme 5.5).$^{298}$ Preliminary substrate scope investigation with N-heterocycles and 1-octene using 112 as a precatalyst shows potential for further catalyst development (Scheme 5.5). Piperidine can be α-alkylated in significantly reduced reaction times of 48 h with a higher yield (81%) of the hydroaminoalkylation product 120. Notably, the first example of hydroaminoalkylation using a morpholine substrate was achieved to give the corresponding α-alkylated product 121, albeit in low yield of 29% using higher catalyst loading of 20 mol % and five equivalents of 1-octene. The formation of red precipitates was observed in this reaction, suggesting that catalyst decomposition occurred. Unfortunately, when N-phenyl-piperazine was used as the amine substrate, trace hydroaminoalkylation reactivity was observed. However, acetal-protected aldehyde was tolerated on the alkene coupling partner in the α-alkylation of 1,2,3,4-tetrahydroquinoline with 5,5-diethoxy-1-pentene to form 122 in moderate yield (61%).
Given these preliminary results, further catalyst optimization studies of 112 could result in the development of a more reactive catalyst with a broader substrate scope for the challenging \( \alpha \)-alkylation of \( N \)-heterocycles.

![Scheme 5.5](image)

**Scheme 5.5** Preliminary substrate scope for the hydroaminoalkylation of \( N \)-heterocycles using 112 as a precatalyst

### 5.3 Concluding statements

The findings from this work underlines the importance of ligand-controlled steric accessibility to the metal center for targeting reactive early transition metal complexes for applications in catalytic hydrofunctionalization reactions. The location and subtle changes in the steric bulk of the substituents on the pyridine ligand framework, as well as the choice of the metal, can be tailored for exploiting the desired reactivity. The 2-aminopyridinate and 2-pyridonate supporting ligands are modular and tunable, which are desirable ligand features for
catalyst optimization. The various binding modes, bridging ability, and hemilability that can be accessed by these ligands deserve more attention in the organometallic community, as they provide opportunities for synthetic applications. In particular, developing a better understanding of the complex equilibria that can arise as a result of different accessible ligand binding modes will be important. Thus, further research with these κ²,1,3-chelating pyridine-derived ligands will allow for the development of further generations of catalysts for the atom-economical, catalytic synthesis of amines. The versatility of pyridine derivatives and their potential applications as supporting ligands in organometallic chemistry are truly remarkable.

5.4 Experimental

For general methods, materials, and instrumentation, see Section 4.4.

**Synthesis of 119.** A 20 mL vial was charged with N-(2,6-dimethylphenyl)pivalamide (0.513 g, 2.50 mmol) with ~1 mL of benzene and magnetic stir bar. To this mixture, CpTi(NMe₂)₃ (0.613 g, 2.50 mmol) dissolved in ~2 mL of benzene was added, and the reaction mixture was stirred at room temperature for 4 h. The solvent was removed in vacuo, and the resulting crude product was dissolved in hexanes and filtered through Celite. Storing the filtrate at -35 °C overnight gave dark red crystals (0.571 g, 56%). A sample from these crystals was used for X-ray structure determination. ¹H NMR (300 MHz, C₆D₆): δ 7.05 (d, J = 7.4 Hz, 2 H, Ar–H), 6.91 (t, J = 7.4 Hz, 1 H, Ar–H), 5.67 (s, 5 H, η⁵-C₅H₅), 2.79 (s, 12 H, –N(CH₃)₂), 2.34 (s, 6 H, Ar(CH₃)), 1.34 (s, 9 H, –C(CH₃)₃). ¹³C NMR (100 MHz, C₆D₆): δ 169.8, 148.8, 129.0, 121.9, 117.2, 113.3, 48.8, 39.3, 29.4, 19.3. MS (EI): m/z = 405 (M⁺), 361 (M⁺–NMe₂), 317 (M⁺–
2NMe$_2$). Anal. calcd for C$_{22}$H$_{35}$N$_3$OTi: C, 65.18; H, 8.70; N, 10.37. Found: C, 65.46; H, 8.67; N, 10.06.

**2-(octan-2-yl)-1-tosylpiperidine (120-Ts).** The reaction mixture consisting of piperidine (49.4 μL, 0.500 mmol), 1-octene (84 mg, 0.75 mmol), 112 (26.4 mg, 0.0500 mmol) and $d_8$-toluene (500 μL) in a J. Young NMR tube was heated at 165 °C for 48 h. After cooling to room temperature, the crude reaction mixture was transferred to a 10 mL round-bottom flask using CH$_2$Cl$_2$ (3 x 1 mL), and treated subsequentially with 2M NaOH (0.750 mL, 1.50 mmol) and $p$-TsCl (0.124 g, 0.650 mmol). The resulting biphasic mixture was stirred vigorously at room temperature overnight. Upon completion of the reaction, EtOAc (60 mL) and H$_2$O (20 mL) were added, and extracted. The aqueous layer was further extracted with additional EtOAc (30 mL). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated. The crude residue was purified by flash column chromatography (5% EtOAc in hexanes) to afford the title compound as a colourless oil (142 mg, 81%). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.70 (d, J = 8.1 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 3.80-3.71 (m, 1H), 3.65-3.56 (m, 1H), 2.97-2.85 (m, 1H), 2.38 (s, 3H), 1.95-1.82 (m, 1H), 1.70-1.60 (m, 1H), 1.51-0.95 (m, 15H), 0.90-0.82 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 142.8, 139.6, 129.7, 127.1, 58.1, 41.2, 33.6, 32.0, 30.7, 29.8, 26.8, 24.9, 24.1, 22.8, 21.7, 18.9, 16.5, 14.3.

**3-(octan-2-yl)-4-tosylmorpholine (121-Ts).** The reaction mixture consisting of morpholine (43.7 μL, 0.500 mmol), 1-octene (281 mg, 0.750 mmol), 112 (52.7 mg, 0.100 mmol) and $d_8$-toluene (100 μL) in a J. Young NMR tube was heated at 165 °C for 46 h. After cooling to room temperature, the crude
reaction mixture was transferred to a 10 mL round-bottom flask using CH\textsubscript{2}Cl\textsubscript{2} (3 x 1 mL), and treated subsequentially with 2M NaOH (0.750 mL, 1.50 mmol) and p-TsCl (0.124 g, 0.650 mmol). The resulting biphasic mixture was stirred vigorously at room temperature overnight. Upon completion of the reaction, EtOAc (60 mL) and H\textsubscript{2}O (20 mL) were added, and extracted. The aqueous layer was further extracted with additional EtOAc (30 mL). The combined organic layer was washed with brine, dried over MgSO\textsubscript{4}, filtered, and concentrated. The crude residue was purified by flash column chromatography (10% EtOAc in hexanes) to afford the title compound as a colourless oil (52 mg, 29%). ¹H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.68 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 3.80 (d, J = 11.9 Hz, 1H), 3.62-3.52 (m, 2H), 3.36 (dd, J = 10.5, 2.4 Hz, 1H), 3.28-3.08 (m, 3H), 2.39 (s, 3H), 2.14-2.03 (m, 1H), 1.40-1.15 (m, 9H), 1.12-1.02 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl\textsubscript{3}): δ 143.4 (C), 139.1 (C), 130.0 (CH), 127.1 (CH), 66.3 (CH\textsubscript{2}), 65.7 (CH\textsubscript{2}), 58.5 (CH), 41.4 (CH\textsubscript{2}), 33.8 (CH\textsubscript{2}), 32.0 (CH\textsubscript{2}), 30.3 (CH), 29.8 (CH\textsubscript{2}), 27.0 (CH\textsubscript{2}), 22.8 (CH\textsubscript{2}), 21.7 (CH\textsubscript{3}), 16.3 (CH\textsubscript{3}), 14.3 (CH\textsubscript{3}). HRMS (ESI): m/z calcd for C\textsubscript{19}H\textsubscript{32}N\textsubscript{2}O\textsubscript{3}S [M+H\textsuperscript{+}]: 354.2103. Found: 354.2104. IR (neat): ν 2958, 2926, 2856, 1598, 1456, 1346, 1158, 1112, 979, 926, 815, 745, 677 cm\textsuperscript{-1}.

\textbf{2-(5,5-diethoxypentan-2-yl)-1,2,3,4-tetrahydroquinoline (122).}

The reaction mixture consisting of 1,2,3,4-tetrahydroquinoline (66.6 mg, 0.500 mmol), 5,5-diethoxy-1-pentene (103 mg, 0.650 mmol), \textbf{112} (26.4 mg, 0.0500 mmol) and d\textsubscript{8}-toluene (500 μL) in a J. Young NMR tube was heated at 130 °C for 48 h. After cooling to room temperature, the crude residue was purified by flash column chromatography (10% Et\textsubscript{2}O in hexanes) to afford the title compound as a colourless oil (89 mg, 61%). ¹H NMR (400 MHz, CDCl\textsubscript{3}): δ 6.98-6.92 (m, 2H), 6.58 (t, J = 7.4 Hz, 1H), 6.47
(d, J = 7.8 Hz, 1H), 4.49 (t, J = 5.5 Hz, 1H), 3.70 (br s, 1H), 3.70-3.60 (m, 2H), 3.55-3.46 (m, 2H), 3.22-3.16 (m, 1H), 2.87-2.68 (m, 2H), 1.91-1.83 (m, 1H), 1.79-1.68 (m, 2H), 1.67-1.53 (m, 3H), 1.28-1.20 (m, 1H), 1.22 (t, J = 7.1 Hz, 6H), 0.98 (d, J = 6.8 Hz, 3H). 13C NMR (100 MHz, CDCl3): δ 145.3 (C), 129.3 (CH), 126.8 (CH), 121.5 (C), 116.9 (CH), 114.2 (CH), 103.3 (CH), 61.3 (CH2), 61.0 (CH2), 56.2 (CH), 37.6 (CH), 31.8 (CH2), 27.6 (CH2), 27.1 (CH2), 24.9 (CH2), 15.5 (CH3), 15.3 (CH3). HRMS (ESI): m/z calcd for C18H30NO2 [M+H]+: 292.227. Found: 292.2276. IR (neat): ν 3388, 2968, 2928, 2875, 1606, 1487, 1373, 1309, 1275, 1121, 1056, 998, 744 cm⁻¹.
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Appendices

Appendix A  X-ray crystallographic data

Table A.1 Crystallographic parameters for 2-aminopyridinate titanium complexes (Chapter 2)

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Table A.2 Crystallographic parameters for 2-aminopyridinate titanium complexes (Chapter 2) continued

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Table A.3 Crystallographic parameters for 2-pyridonate titanium complexes (Chapter 3)

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Table A.4 Crystallographic parameters for 2-pyridonate titanium complexes (Chapter 3) continued

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<td>no. of variables</td>
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<td>638</td>
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<tr>
<td>$R_1$ ($F^2$, all data)</td>
<td>0.0607</td>
<td>0.0715</td>
</tr>
<tr>
<td>$wR_2$ ($F^2$, all data)</td>
<td>0.1180</td>
<td>0.1517</td>
</tr>
<tr>
<td>$R_1$ ($F$, $I &gt; 2\sigma(I)$)</td>
<td>0.0435</td>
<td>0.0508</td>
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<td>$wR_2$ ($F$, $I &gt; 2\sigma(I)$)</td>
<td>0.1078</td>
<td>0.1360</td>
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<tr>
<td>goodness of fit</td>
<td>1.027</td>
<td>1.049</td>
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Table A.5 Crystallographic parameters for 2-pyridonate tantalum complexes (Chapter 4)

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<th>110</th>
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<tbody>
<tr>
<td>formula</td>
<td>C₁₅H₂₁N₂O₂Ta</td>
<td>C₁₃H₁₅Cl₂N₂O₂Ta</td>
<td>C₄₀H₄₉N₂O₂Ta</td>
</tr>
<tr>
<td>F_w</td>
<td>442.29</td>
<td>483.12</td>
<td>770.76</td>
</tr>
<tr>
<td>crystal size (mm)</td>
<td>0.24 x 0.23 x 0.22</td>
<td>0.16 x 0.06 x 0.05</td>
<td>0.34 x 0.09 x 0.08</td>
</tr>
<tr>
<td>colour, habit</td>
<td>colourless, prism</td>
<td>orange, prism</td>
<td>colourless, prism</td>
</tr>
<tr>
<td>cell setting</td>
<td>monoclinic</td>
<td>monoclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td>space group</td>
<td>P 21/n</td>
<td>P 21/c</td>
<td>C 2/c</td>
</tr>
<tr>
<td>a (Å)</td>
<td>8.4111(7)</td>
<td>8.7220(13)</td>
<td>13.5454(18)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>12.1303(11)</td>
<td>10.9148(16)</td>
<td>18.842(3)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>15.5008(13)</td>
<td>15.867(2)</td>
<td>14.414(2)</td>
</tr>
<tr>
<td>α (°)</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>β (°)</td>
<td>96.066(3)</td>
<td>93.202(3)</td>
<td>102.558(3)</td>
</tr>
<tr>
<td>γ (°)</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>V (Å³)</td>
<td>1572.7(4)</td>
<td>1508.1(7)</td>
<td>3590(1)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>ρ calcld (g cm⁻³)</td>
<td>1.868</td>
<td>2.128</td>
<td>1.425</td>
</tr>
<tr>
<td>F(000)</td>
<td>856</td>
<td>920</td>
<td>1568</td>
</tr>
<tr>
<td>μ (MoKα) (mm⁻¹)</td>
<td>6.992</td>
<td>7.644</td>
<td>3.095</td>
</tr>
<tr>
<td>2θ max (°)</td>
<td>60.16</td>
<td>63.12</td>
<td>52.74</td>
</tr>
<tr>
<td>total no. of reflns</td>
<td>27939</td>
<td>25541</td>
<td>21219</td>
</tr>
<tr>
<td>no. of unique reflns</td>
<td>4607</td>
<td>5040</td>
<td>3675</td>
</tr>
<tr>
<td>no. of reflns with I &gt; 2σ(I)</td>
<td>4245</td>
<td>4200</td>
<td>3374</td>
</tr>
<tr>
<td>no. of variables</td>
<td>186</td>
<td>184</td>
<td>245</td>
</tr>
<tr>
<td>R₁ (F², all data)</td>
<td>0.0164</td>
<td>0.0355</td>
<td>0.0307</td>
</tr>
<tr>
<td>wR₂ (F², all data)</td>
<td>0.0321</td>
<td>0.0479</td>
<td>0.0525</td>
</tr>
<tr>
<td>R₁ (F, I &gt; 2σ(I))</td>
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<td>0.0250</td>
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</tr>
<tr>
<td>wR₂ (F, I &gt; 2σ(I))</td>
<td>0.0313</td>
<td>0.0450</td>
<td>0.0511</td>
</tr>
<tr>
<td>goodness of fit</td>
<td>1.065</td>
<td>1.036</td>
<td>1.091</td>
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</table>


### Table A.6 Crystallographic parameters for 2-pyridonate tantalum complexes (Chapter 4)

<table>
<thead>
<tr>
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<th>112</th>
<th>118</th>
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<tbody>
<tr>
<td><strong>formula</strong></td>
<td>3(C₁₁₀H₂₆ClNölüTa)</td>
<td>2(C₁₈₉Hₙ₂N₅OTa)</td>
<td>C₂₆H₂₈ClN₄O₂Ta</td>
</tr>
<tr>
<td><strong>F_w</strong></td>
<td>1556.45</td>
<td>1097.98</td>
<td>644.92</td>
</tr>
<tr>
<td><strong>crystal size (mm)</strong></td>
<td>0.48 x 0.44 x 0.37</td>
<td>0.32 x 0.23 x 0.22</td>
<td>0.21 x 0.19 x 0.13</td>
</tr>
<tr>
<td><strong>colour, habit</strong></td>
<td>yellow, prism</td>
<td>golden brown, prism</td>
<td>yellow, prism</td>
</tr>
<tr>
<td><strong>cell setting</strong></td>
<td>triclinic</td>
<td>triclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td><strong>space group</strong></td>
<td>P -1</td>
<td>P -1</td>
<td>P 21/n</td>
</tr>
<tr>
<td><strong>a (Å)</strong></td>
<td>10.8175(19)</td>
<td>12.3246(15)</td>
<td>16.320(6)</td>
</tr>
<tr>
<td><strong>b (Å)</strong></td>
<td>13.761(2)</td>
<td>13.0655(15)</td>
<td>9.224(4)</td>
</tr>
<tr>
<td><strong>c (Å)</strong></td>
<td>21.924(4)</td>
<td>17.410(3)</td>
<td>17.084(7)</td>
</tr>
<tr>
<td><strong>α (°)</strong></td>
<td>83.546(5)</td>
<td>68.087(5)</td>
<td>90</td>
</tr>
<tr>
<td><strong>β (°)</strong></td>
<td>76.684(5)</td>
<td>75.004(8)</td>
<td>106.717(6)</td>
</tr>
<tr>
<td><strong>γ (°)</strong></td>
<td>68.516(5)</td>
<td>64.226(5)</td>
<td>90</td>
</tr>
<tr>
<td><strong>V (Å³)</strong></td>
<td>2953.8(15)</td>
<td>2326.5(5)</td>
<td>2463(3)</td>
</tr>
<tr>
<td><strong>Z</strong></td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td><strong>ρ_calcd (g cm⁻³)</strong></td>
<td>1.750</td>
<td>1.567</td>
<td>1.739</td>
</tr>
<tr>
<td><strong>F(000)</strong></td>
<td>1524</td>
<td>1098</td>
<td>1272</td>
</tr>
<tr>
<td><strong>μ (MoKα) (mm⁻¹)</strong></td>
<td>5.73</td>
<td>4.74</td>
<td>4.602</td>
</tr>
<tr>
<td><strong>2θ_max (°)</strong></td>
<td>60.60</td>
<td>50.28</td>
<td>52.74</td>
</tr>
<tr>
<td><strong>total no. of reflns</strong></td>
<td>64307</td>
<td>29697</td>
<td>21819</td>
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<td><strong>no. of unique reflns</strong></td>
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<td>5043</td>
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<td><strong>no. of reflns with I &gt; 2σ(I)</strong></td>
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<td><strong>no. of variables</strong></td>
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<td>0.062</td>
<td>0.0208</td>
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<tr>
<td><strong>wR₂ (F², all data)</strong></td>
<td>0.0599</td>
<td>0.124</td>
<td>0.0456</td>
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<td><strong>R₁ (F, I &gt; 2σ(I))</strong></td>
<td>0.0274</td>
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<tr>
<td><strong>wR₂ (F, I &gt; 2σ(I))</strong></td>
<td>0.0573</td>
<td>0.117</td>
<td>0.0446</td>
</tr>
<tr>
<td><strong>goodness of fit</strong></td>
<td>1.074</td>
<td>1.257</td>
<td>1.104</td>
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Table A.7 Crystallographic parameters for cyclopentadienyl amidate titanium complex (Chapter 5)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>formula</td>
<td>$2\text{(C}<em>{22}\text{H}</em>{35}\text{N}_{3}\text{OTi)}$</td>
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<tr>
<td>$F_w$</td>
<td>810.82</td>
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<td>crystal size (mm)</td>
<td>0.50 x 0.40 x 0.30</td>
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<td>colour, habit</td>
<td>dark red, prism</td>
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<td>cell setting</td>
<td>triclinic</td>
</tr>
<tr>
<td>space group</td>
<td>P -1</td>
</tr>
<tr>
<td>$a$ (Å)</td>
<td>10.9951(4)</td>
</tr>
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<td>$b$ (Å)</td>
<td>13.9885(6)</td>
</tr>
<tr>
<td>$c$ (Å)</td>
<td>16.0459(6)</td>
</tr>
<tr>
<td>$\alpha$ (°)</td>
<td>71.4183(17)</td>
</tr>
<tr>
<td>$\beta$ (°)</td>
<td>79.4999(18)</td>
</tr>
<tr>
<td>$\gamma$ (°)</td>
<td>78.2135(17)</td>
</tr>
<tr>
<td>$V$ (Å$^3$)</td>
<td>2271.63(22)</td>
</tr>
<tr>
<td>$Z$</td>
<td>2</td>
</tr>
<tr>
<td>$\rho_{\text{calc}}$ (g cm$^{-3}$)</td>
<td>1.186</td>
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<tr>
<td>$F(000)$</td>
<td>872</td>
</tr>
<tr>
<td>$\mu$ (Mo$\text{K}$α) (mm$^{-1}$)</td>
<td>0.392</td>
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<td>$2\theta_{\text{max}}$ (°)</td>
<td>60.14</td>
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<td>no. of reflns</td>
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<td>with $I &gt; 2\sigma(I)$</td>
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<td>$R_1$ ($F^2$, all data)</td>
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<td>$wR_2$ ($F^2$, all data)</td>
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<td>$R_1$ ($F$, $I &gt; 2\sigma(I)$)</td>
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<tr>
<td>$wR_2$ ($F$, $I &gt; 2\sigma(I)$)</td>
<td>0.0812</td>
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<tr>
<td>goodness of fit</td>
<td>1.037</td>
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</table>
Appendix B  Selected NMR spectra

52. $^1$H NMR (400 MHz, $C_6D_6$)

52. $^{13}$C NMR (100 MHz, $C_6D_6$)
53. $^1$H NMR (400 MHz, C$_6$D$_6$)

53. $^{13}$C NMR (100 MHz, C$_6$D$_6$)
54. $^1$H NMR (400 MHz, C$_6$D$_6$)

![NMR spectrum of a compound](image)

54. $^{13}$C NMR (100 MHz, C$_6$D$_6$)

![NMR spectrum of a compound](image)
66. $^1$H NMR (400 MHz, C$_6$D$_6$)

66. $^{13}$C NMR (100 MHz, C$_6$D$_6$)
cis-61b. \(^1\)H NMR (400 MHz, CDCl\(_3\))

\[ \text{cis-61b} \]

\[ \text{C NMR (100 MHz, CDCl}_3\text{)} \]

\[ (+/-) \]

---

\[ \text{cis-61b. } ^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \]
**trans-61b, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})**

![NMR spectrum of trans-61b hydrogen nuclei](image)

**trans-61b, \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3})**

![NMR spectrum of trans-61b carbon nuclei](image)
73, $^1$H NMR (400 MHz, CDCl$_3$)

73, $^{13}$C NMR (100 MHz, CDCl$_3$)
75, $^1$H NMR (400 MHz, CDCl$_3$)

75, $^{13}$C NMR (100 MHz, CDCl$_3$)
76. $^1$H NMR (400 MHz, CDCl$_3$)

76. $^{13}$C NMR (100 MHz, CDCl$_3$)
77. $^1$H NMR (400 MHz, CDCl$_3$)

77. $^{13}$C NMR (100 MHz, CDCl$_3$)
78. $^{1}H$ NMR (400 MHz, CDCl$_3$)

78. $^{13}C$ NMR (100 MHz, CDCl$_3$)
79. $^1$H NMR (400 MHz, CDCl$_3$)

79. $^{13}$C NMR (100 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
81, $^1$H NMR (400 MHz, CDCl$_3$)

81, $^{13}$C NMR (100 MHz, CDCl$_3$)
82. $^1$H NMR (400 MHz, CDCl$_3$)

82. $^{13}$C NMR (100 MHz, CDCl$_3$)
**83. $^1$H NMR (400 MHz, CDCl$_3$)**

![1H NMR spectrum](image)

**83. $^{13}$C NMR (100 MHz, CDCl$_3$)**

![13C NMR spectrum](image)
84. $^1$H NMR (400 MHz, CDCl$_3$)

84. $^{13}$C NMR (100 MHz, CDCl$_3$)
85. $^1$H NMR (400 MHz, CDCl$_3$)

85. $^{13}$C NMR (100 MHz, CDCl$_3$)
86. $^1$H NMR (400 MHz, C$_6$D$_6$)

86. $^{13}$C NMR (100 MHz, C$_6$D$_6$)
cis-55c, $^1$H NMR (400 MHz, CDCl$_3$)

cis-55c, $^{13}$C NMR (100 MHz, CDCl$_3$)
cis-55c-Ts, $^1$H NMR (400 MHz, CDCl$_3$)

cis-55c-Ts, $^{13}$C NMR (100 MHz, CDCl$_3$)
**trans-55c**, $^1$H NMR (400 MHz, CDCl$_3$)

![NMR spectrum of trans-55c, $^1$H NMR](image)

**trans-55c**, $^{13}$C NMR (100 MHz, CDCl$_3$)

![NMR spectrum of trans-55c, $^{13}$C NMR](image)
**cis-87c-Ts, $^1$H NMR (400 MHz, CDCl$_3$)**

**cis-87c-Ts, $^{13}$C NMR (100 MHz, CDCl$_3$)**
trans-87c-Ts, $^1$H NMR (400 MHz, CDCl$_3$)

trans-87c-Ts, $^{13}$C NMR (100 MHz, CDCl$_3$)
cis-88c-Ts, $^1$H NMR (400 MHz, CDCl$_3$)

cis-88c-Ts, $^{13}$C NMR (100 MHz, CDCl$_3$)
1-(3-Methylbut-3-en-1-yl)cyclohexane-1-carbonitrile, $^1$H NMR (400 MHz, CDCl$_3$)

1-(3-Methylbut-3-en-1-yl)cyclohexane-1-carbonitrile, $^{13}$C NMR (100 MHz, CDCl$_3$)
89a, $^1$H NMR (400 MHz, CDCl$_3$)

89a, $^{13}$C NMR (100 MHz, CDCl$_3$)
$d_2$-89a, $^1$H NMR (400 MHz, CDCl$_3$)

$\text{D} \text{NH}_2$

$\text{D}$

$1.1$ $1.0$ $0.9$ $0.8$ $0.7$ $0.6$ $0.5$ $0.4$ $0.3$ $0.2$ $0.1$ $0.0$

$11.0$ $10.5$ $10.0$ $9.5$ $9.0$ $8.5$ $8.0$ $7.5$ $7.0$ $6.5$ $6.0$ $5.5$ $5.0$ $4.5$ $4.0$ $3.5$ $3.0$ $2.5$ $2.0$ $1.5$ $1.0$ $0.5$ $0.0$

$d_2$-89a, $^2$H NMR (61 MHz, CHCl$_3$)

255
89c-Ts, $^1$H NMR (400 MHz, CDCl$_3$)

89c-Ts, $^{13}$C NMR (100 MHz, CDCl$_3$)
$d_2$-89c-Ts, $^1$H NMR (400 MHz, CDCl$_3$)

$2$H NMR (61 MHz, CHCl$_3$)
trans-90c-Ts, $^1$H NMR (400 MHz, CDCl$_3$)

trans-90c-Ts, $^{13}$C NMR (61 MHz, CDCl$_3$)
cis-90c-Ts, $^1$H NMR (400 MHz, CDCl$_3$)

cis-90c-Ts, $^{13}$C NMR (100 MHz, CDCl$_3$)
trans-57c, $^1$H NMR (400 MHz, CDCl$_3$)

trans-57c, $^{13}$C NMR (100 MHz, CDCl$_3$)
trans-91c-Bz, $^1$H NMR (400 MHz, CDCl$_3$)

trans-91c-Bz, $^{13}$C NMR (100 MHz, CDCl$_3$)
N-1-naphthoyl)-trans-92c, $^1$H NMR (400 MHz, CDCl$_3$)

N-1-naphthoyl)-trans-92c, $^{13}$C NMR (100 MHz, CDCl$_3$)
96. $^1$H NMR (400 MHz, C$_6$D$_6$)

96. $^{13}$C NMR (100 MHz, C$_6$D$_6$)
97, $^1$H NMR (400 MHz, CDCl$_3$)

![H NMR spectrum]

97, $^{13}$C NMR (100 MHz, CDCl$_3$)

![C NMR spectrum]
Variable temperature study of 98, $^1$H NMR (400 MHz, $d_8$-toluene ($\delta$ 2.09))
105, $^1$H NMR (400 MHz, C$_6$D$_6$)

105, $^{13}$C NMR (100 MHz, C$_6$D$_6$)
106. $^1$H NMR (400 MHz, $C_6D_6$)

106. $^{13}$C NMR (100 MHz, $C_6D_6$)
107, $^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
108, $^1$H NMR (400 MHz, CDCl$_3$)

![NMR Spectrum]

108, $^{13}$C NMR (100 MHz, CDCl$_3$)

![NMR Spectrum]
109, $^1$H NMR (400 MHz, CDCl$_3$)

109, $^{13}$C NMR (100 MHz, CDCl$_3$)
110. $^1$H NMR (400 MHz, C$_6$D$_6$)

110. $^{13}$C NMR (100 MHz, C$_6$D$_6$)
111, $^1$H NMR (400 MHz, C$_6$D$_6$)

111, $^{13}$C NMR (100 MHz, C$_6$D$_6$)
112, $^1$H NMR (400 MHz, C$_6$D$_6$)

$^1$H NMR (400 MHz, C$_6$D$_6$)

112, $^{13}$C NMR (100 MHz, C$_6$D$_6$)

$^{13}$C NMR (100 MHz, C$_6$D$_6$)
113, $^1$H NMR (400 MHz, CDCl$_3$)

113, $^{13}$C NMR (100 MHz, CDCl$_3$)
114. $^1$H NMR (400 MHz, CDCl$_3$)

114. $^{13}$C NMR (100 MHz, CDCl$_3$)
115a, $^1$H NMR (400 MHz, CDCl$_3$)

115a, $^{13}$C NMR (100 MHz, CDCl$_3$)
115b, $^1$H NMR (400 MHz, CDCl$_3$)

![NMR Spectrogram](image)

115b, $^{13}$C NMR (100 MHz, CDCl$_3$)

![NMR Spectrogram](image)
115c, $^1$H NMR (400 MHz, CDCl$_3$)

115c, $^{13}$C NMR (100 MHz, CDCl$_3$)
115d, \(^1{}H\) NMR (400 MHz, CDCl\(_3\))

115d, \(^{13}{}C\) NMR (100 MHz, CDCl\(_3\))
115e, $^1$H NMR (400 MHz, CDCl$_3$)

![H NMR spectrum](image)

115e, $^{13}$C NMR (100 MHz, CDCl$_3$)

![C NMR spectrum](image)
115f, $^1$H NMR (400 MHz, CDCl$_3$)

115f, $^{13}$C NMR (100 MHz, CDCl$_3$)
115ga and 115gb, $^1$H NMR (600 MHz, CDCl$_3$)

115ga and 115gb, $^{13}$C NMR (150 MHz, CDCl$_3$)
115ha and 115hb, $^1$H NMR (400 MHz, CDCl$_3$)

115ha and 115hb, $^{13}$C NMR (100 MHz, CDCl$_3$)
115ia and 115ib, $^1$H NMR (400 MHz, CDCl$_3$)

115ia and 115ib, $^{13}$C NMR (100 MHz, CDCl$_3$)
115j. $^1$H NMR (400 MHz, CDCl$_3$)

115j. $^{13}$C NMR (100 MHz, CDCl$_3$)
$^{115k}$, $^1$H NMR (400 MHz, CDCl$_3$)

$^{115k}$, $^{13}$C NMR (100 MHz, CDCl$_3$)
116. $^1$H NMR (400 MHz, CDCl$_3$)

116. $^{13}$C NMR (100 MHz, CDCl$_3$)
117a, $^1$H NMR (400 MHz, CDCl$_3$)

$^1$H NMR spectrum of 117a showing resonance peaks at various ppm values.

117a, $^{13}$C NMR (100 MHz, CDCl$_3$)

$^{13}$C NMR spectrum of 117a showing resonance peaks at various ppm values.
117b, $^1$H NMR (400 MHz, CDCl$_3$)

117b, $^{13}$C NMR (100 MHz, CDCl$_3$)
117c, $^1$H NMR (300 MHz, CDCl$_3$)

117c, $^{13}$C NMR (75 MHz, CDCl$_3$)
117d, $^1$H NMR (400 MHz, CDCl$_3$)

117d, $^{13}$C NMR (100 MHz, CDCl$_3$)
$^{117e, \text{H NMR}}$ (400 MHz, CDCl$_3$)

$^{117e, \text{13C NMR}}$ (100 MHz, CDCl$_3$)
**117f, \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3})**

![NMR spectrum of 117f](image)

**117f, \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3})**

![NMR spectrum of 117f](image)
117g, $^1$H NMR (300 MHz, CDCl$_3$)

117g, $^{13}$C NMR (75 MHz, CDCl$_3$)
117h, $^1$H NMR (400 MHz, CDCl$_3$)

117h, $^{13}$C NMR (100 MHz, CDCl$_3$)
117i, $^1$H NMR (400 MHz, CDCl$_3$)

117i, $^{13}$C NMR (100 MHz, CDCl$_3$)
$N$-(1-napthoyl)-117i, $^1$H NMR (600 MHz, CDCl$_3$)

$N$-(1-napthoyl)-117i, $^{13}$C NMR (150 MHz, CDCl$_3$)
117j, $^1$H NMR (400 MHz, CDCl$_3$)

117j, $^{13}$C NMR (100 MHz, CDCl$_3$)
$^{117k}$, $^1$H NMR (400 MHz, CDCl$_3$)

$^{117k}$, $^{13}$C NMR (100 MHz, CDCl$_3$)
118. $^1$H NMR (400 MHz, C$_6$D$_6$)

118. $^{13}$C NMR (100 MHz, C$_6$D$_6$)
119, $^1$H NMR (300 MHz, C$_6$D$_6$)

119, $^{13}$C NMR (100 MHz, C$_6$D$_6$)
120-Ts, $^1$H NMR (400 MHz, CDCl$_3$)

120-Ts, $^{13}$C NMR (100 MHz, CDCl$_3$)
121-Ts, $^1$H NMR (400 MHz, CDCl$_3$)

121-Ts, $^{13}$C NMR (100 MHz, CDCl$_3$)
122, $^1$H NMR (400 MHz, CDCl$_3$)

![$^1$H NMR spectrum](image)

122, $^{13}$C NMR (100 MHz, CDCl$_3$)

![$^{13}$C NMR spectrum](image)