BIS(AMIDATE) AND BIS(UREATE) COMPLEXES OF ZIRCONIUM AND TANTALUM: SYNTHESIS AND CATALYTIC APPLICATION IN C-N AND C-C BOND FORMATION

by

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ABSTRACT

This is a study of early metal organometallic complexes for catalytic C-N and C-C bond formation using amines. The use of zirconium complexes as hydroamination catalysts is explored first. New axially-chiral bis(amide) and bis(urea) proligands are designed. Synthetic methods used to generate these compounds are described and X-ray crystallographic analysis of a bis(sulfonamide) establishes the absolute configuration of the chiral proligands. Installation of the new bis(amide) and bis(urea) ligands onto zirconium is undertaken and the structure of these complexes is examined in solution and, where possible, in the solid state. Where well-defined zirconium complexes can be obtained, those complexes are tested for their efficacy in enantioselective catalytic hydroamination. In the absence of well-defined zirconium complexes, an in situ catalyst generation protocol is employed. Catalysts featuring a bis(amide) ligand derived from 2,2'-diamino-6,6'-dimethylbiphenyl achieve modest hydroamination activity with a primary aminoalkene at 110 °C, with enantiomeric excesses (ee’s) of up to 25%. Catalysts featuring a bis(amide) ligand derived from 3,3',5,5'-tetrabromo-2,2'-diamino-6,6'-dimethylbiphenyl display impressive reactivity with a primary aminoalkene, including room temperature hydroamination, with ee’s ranging from 52-55%. Catalysts featuring a bis(urea) ligand derived from 2,2'-diamino-6,6'-dimethylbiphenyl are shown to be capable of cyclizing secondary aminoalkenes with ee’s up to 63%. Capillary electrophoresis is developed as a method to determine the ee of tertiary amine products. A kinetic study of a catalyst featuring a bis(amide) ligand derived from 2,2'-diamino-6,6'-dimethylbiphenyl supports established mechanistic proposals for neutral group 4
hydroamination catalysts. Solid state molecular structures, combined with existing knowledge of bonding and catalytic reaction pathways, are used to propose models for how enantioselectivity is achieved through the use of different ligand frameworks.

The use of known ligands in the formation of tantalum complexes for hydroaminoalkylation catalysis is then explored. Installation of such axially-chiral bis(amidate) ligands onto tantalum centres is undertaken and the structure of these complexes is examined in solution and, where possible, in the solid state. Catalytic testing reveals general competence of these catalysts for the hydroaminoalkylation reaction.
PREFACE

This dissertation is original, unpublished work by the author, Neal Yonson. The experiments described herein were designed in consultation with my supervisor, Professor Laurel Schafer, and performed independently with her support and guidance. I synthesized all of the new compounds featured in Chapters 2-5, and carried out all of the catalytic testing experiments. I collected all of the capillary electrophoresis and X-ray crystallographic data. The vast majority of nuclear magnetic resonance data was collected by me, with some high field NMR spectra (\(^1\)H NMR of compounds **90-92**; \(^{13}\)C NMR of **25-27, 29, 30, 90-92**) collected by Dr. Philippa Payne of the Schafer Group. Mass spectrometry and elemental analysis data was collected by technicians in the UBC Chemistry department, from samples I provided. Aminoalkene substrates utilized for catalytic testing were synthesized by a variety of Schafer group members, including Dr. David Leitch, Dr. Rashidat Ayinla, Dr. Philippa Payne, Dr. Jason Bexrud, Jacky Yim, Eugene Chong, and myself.

Portions of Chapter 1 are in press as a book chapter. I am a co-author of this book chapter. Portions of Chapter 2 have been assembled in a manuscript for submission for publication. I am the sole experimental author of this manuscript.
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rt  Room temperature
s  Singlet
t  Triplet
t  Time
T  Temperature
iBu  tert-Butyl
Tf  Triflate
THF  Tetrahydrofuran
1,2,3,4-THIQ  1,2,3,4-Tetrahydroisoquinoline
TMS  Trimethylsilyl
TOF  Tunover frequency
Ts  Toluenesulfonyl (tosyl)
UV  Ultraviolet
UV/Vis  Ultraviolet-Visible
[α]D  Specific Rotation
α  alpha
β  beta
γ  gamma
δ  delta, Chemical shift
κ  kappa, Denticity
η  eta, Hapticity
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Chapter 1: Early Transition Metal Catalysts for Hydroamination and Hydroaminoalkylation

1.1 Introduction to Hydroamination

Hydroamination is the formal addition of an N-H bond across the C-C multiple bond of alkene, allene, or alkyne substrates (Scheme 1.1). It is an atom-economical and direct route to access a variety of amine functionalities, including α-chiral amines. Hydroamination is a sought after transformation because it has the potential to achieve the direct synthesis of amines or amine derivatives from simple petrochemical feedstocks.

Scheme 1.1: A general metal-catalyzed hydroamination reaction with an alkyne substrate.

Indeed, atom-economical N-centred chemistry has been identified as one of the “10 most sought after chemical transformations,”\(^{[1]}\) sparking intense interest in developing new routes to achieve such transformations. Since 1990 there has been an intense growth in the development of the hydroamination reaction (Figure 1.1), yet the goal of realizing a generally applicable catalytic system for this transformation over a broad range of substrates remains elusive.
Figure 1.1: Number of publications on the topic of hydroamination over the two decade period from 1990-2010.

In practice, hydroamination is often a challenging reaction to carry out. Thermodynamically, simple bond enthalpy calculations would indicate that the transformation should be slightly favourable, but the reaction is disfavoured entropically. Kinetically, there is a substantial activation barrier as a result of both the amine and the C-C π-bond being electron-rich moieties. The latter limitation on reactivity necessitates the development of efficient catalytic routes to reach the desired products. Efforts to identify suitable catalyst systems have so far spanned across the periodic table.\textsuperscript{[2]}

Hydroamination can be catalyzed by virtually every group in the periodic table with inspiring contributions involving noble metals in the 70’s\textsuperscript{[3–8]} and later pioneering reactivity investigations featuring lanthanide metals\textsuperscript{[9–11]} and group 4 metals\textsuperscript{[12]} in the late 80’s and early 90’s. In the early 2000’s most every region of the periodic table was being
investigated for this desirable transformation and in 2008, a comprehensive review was assembled that presented catalytic systems including alkali and alkaline earth metals, groups 3, 4, 5, 8, 9, 10, 11 and 12 in the d-block as well as lanthanide and actinide metal catalysts.\textsuperscript{[2]} More recently, group 13 main-group metals have also been exploited for this transformation.\textsuperscript{[13]}

1.2 Mechanistic Aspects of Hydroamination

The first widely reported and mechanistically explored hydroamination catalysts were based on metals from groups 3, 4 and 5.\textsuperscript{[11,12,14,15]} In particular, group 3 or rare-earth (Sc, Y, La) catalysts were initially investigated by Marks and co-workers for their application in the cyclohydroamination of primary and secondary aminoalkenes and aminoalkynes.\textsuperscript{[9,16]}

These reactions have been rigorously investigated using reaction kinetics and deuterium labeling experiments in addition to a thorough evaluation of substrate scope.\textsuperscript{[11]} The reaction has been proposed to proceed through a catalytic cycle involving the formation of a metal-amido species (A, Scheme 1.2), followed by σ-bond insertion to give a metal-alkyl species (B, Scheme 1.2), then protonolysis to yield the cyclized product (D, Scheme 1.2) and re-form the metal-amido species A. Early work focused on the generation of 5- and 6-membered N-heterocycles and set the precedent for preferred substrates that are commonly used in the field to benchmark catalytic activity (Table 1.1).\textsuperscript{[9,11,16–21]}
Scheme 1.2: General cyclohydroamination reaction scheme using an Yttrium catalyst (top) and illustration of the general catalytic cycle (bottom).
Table 1.1: Benchmark reactivity for common substrates and products of hydroamination using group 3 and rare-earth catalysts.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>T (°C)</th>
<th>TOF (h⁻¹)ᵃ</th>
<th>Metal</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂N−C≡C−Ph</td>
<td>![Product Image]</td>
<td>21</td>
<td>1210</td>
<td>U</td>
<td>[17]</td>
</tr>
<tr>
<td>H₂N−C≡C−Ph</td>
<td>![Product Image]</td>
<td>21</td>
<td>2830</td>
<td>Sm</td>
<td>[16]</td>
</tr>
<tr>
<td>H₂N−C≡C−Ph</td>
<td>![Product Image]</td>
<td>60</td>
<td>140</td>
<td>La</td>
<td>[9]</td>
</tr>
<tr>
<td>H₂N−C≡C−Ph</td>
<td>![Product Image]</td>
<td>25</td>
<td>1460</td>
<td>Th</td>
<td>[17]</td>
</tr>
</tbody>
</table>

ᵃ reaction progress monitored using ¹H NMR spectroscopy
Scheme 1.3: General alkyne hydroamination reaction using a Zr catalyst (top) and illustration of the general catalytic cycle (bottom).
Hydroamination catalysts featuring group 4 metals started with the pioneering work of Bergman and coworkers in the early 1990s.\textsuperscript{[12,22,23]} While much of the early work with group 3 and rare-earth catalysts used aminoalkene substrates for cyclohydroamination, work with group 4 catalysts focused on intermolecular hydroamination using alkyne and primary amine substrates to provide more ideal thermodynamic conditions (Scheme 1.3). Initial stoichiometric experiments coupled with kinetic investigations resulted in the mechanistic proposal for neutral group 4 metals shown in Scheme 1.3,\textsuperscript{[12]} whereby a zirconium bis(amido) species twice undergoes protonolysis by a primary amine starting material to yield a Zr=N imido complex (A, Scheme 1.3). After coordination of the C-C multiply bonded species, a formal [2+2]-type cycloaddition occurs, resulting in a metallacyclic intermediate (C, Scheme 1.3). A new amine substrate protonates the metallacycle twice to free the product (E, Scheme 1.3) and regenerate the Zr=N imido complex A, completing the catalytic cycle.

Due to the importance of the zirconium-imido species in the putative reaction pathway, it was initially believed that neutral group 4 catalysts would only be capable of utilizing primary amine substrates for hydroamination reactions. More recently however, some neutral group 4 catalysts have been reported for hydroamination using secondary amine substrates.\textsuperscript{[21,24–28]} To achieve this, an alternative mechanistic profile must be operational, perhaps similar to the σ-bond insertion observed for previously intensely investigated rare-earth hydroamination catalyst systems.\textsuperscript{[11]} The first neutral group 4 catalyst capable of hydroamination with a variety of secondary amine substrates was a zirconium complex developed in the Schafer group featuring a tethered bis(ureate) ligand (2, Scheme 1.4).\textsuperscript{[24]}
Scheme 1.4: Proposed catalytic cycle for a bis(urate) bis(amido) zirconium catalyst capable of cyclizing secondary aminoalkene substrates.
In order to realize the observed hydroamination of secondary amines with 2, an alternate mechanism to the well-established [2+2] cycloaddition pathway must be operating in this process. Mechanistic investigations of 2 resulted in a proposed catalytic cycle in which there is concerted C-N and C-H bond formation with the bond formation event being “proton assisted” by a second uncyclized substrate molecule (Scheme 1.4). The cycle begins with the formation of a seven-coordinate species which incorporates a coordinated neutral amine donor (A, Scheme 1.4). A highly-ordered transition state (B, Scheme 1.4) forms in which the proton of the neutral amine donor is transferred to the terminal position of the alkene, while the internal position of the alkene undergoes C-N bond formation through a nucleophilic attack by nitrogen. Once the new C-N and C-H bonds are formed, the cyclized product is neutrally bound to the zirconium centre (C, Scheme 1.4). Dissociation of the product (D, Scheme 1.4) will result in a six-coordinate species (E, Scheme 1.4) which can then bind another molecule of substrate to re-form the seven-coordinate species A.

The mechanistic investigation of bis(ureate) zirconium catalyst 2 resulted in an observed primary kinetic isotope effect ($k_H/k_D = 5.2\pm0.4$). Attempts to kinetically observe product inhibition clearly showed that product inhibition is not a challenge with this Zr system and suggested that the N-D bond cleavage step is indeed involved in the turnover limiting step of the catalytic cycle. Stoichiometric experiments also helped to clarify the preferred 7-coordinate environment of this sterically accessible precatalyst. This mechanistic proposal has been further investigated computationally and important insights into this cooperative mechanistic profile have been obtained independently by Tobisch.
A similar mechanistic proposal was independently developed by Sadow and co-workers for an impressively reactive zwitterionic zirconium catalyst (3, Scheme 1.5). Careful deuterium labeling experiments illustrated that H (or D) transfer is required to assist with a proton-assisted turnover limiting ring-closure step.\textsuperscript{[28,31]} This overall neutral complex 3 is capable of achieving alkene hydroamination at room temperature, much like rare-earth catalysts, while elevated reaction temperatures are required for most other neutral group 4 alkene hydroamination reactions. This enhanced reactivity may be attributable to the formally cationic metal centre in this zwitterionic species, making it isoelectronic with rare-earth elements.

Despite this alternative mechanistic profile, compound 3 is unexpectedly limited to primary amine substrates. This limitation of the zwitterionic species 3 when compared to bis(ureate) system 2 may be attributed to the fact that the proton transfer is believed to occur from an anionically bound aminoalkene in the former, compared to a neutrally-bound aminoalkene in the latter. This substrate scope also differs from previously reported cationic Zr species, which were limited to secondary amine substrates because it was presumed that Zr-imido complexes, which are catalytically incompetent with cationic Zr species, were formed when primary amines substrates were used.\textsuperscript{[15,32]}

Interestingly, zwitterionic catalyst 3 could cyclize a secondary aminoalkene substrate in the presence of 10–30 mol\% of primary amine additive n-propylamine. This further supports that an anionic amido ligand participates in the proton-assisted bond formation, rather than a neutrally bound amino donor.
Scheme 1.5: Proposed catalytic cycle for a zwitterionic zirconium catalyst capable of room temperature alkene hydroamination.
1.3 Recent Developments in Hydroamination with Group 4 Catalysts

1.3.1 Recent Developments in Alkyne Hydroamination with Group 4 Catalysts

Intramolecular alkyne hydroamination reactions, while being some of the most common hydroamination investigations early on in reaction development,[33] are now rarely investigated. This is in part due to the observation that many metal systems, and indeed even strong acid, can catalyze this transformation.[2] Thus, such reactions are rarely useful probes for identifying unique and promising reactivity trends. Some recent examples for reference include catalyst 4, which has been shown to be particularly useful for 5, 6 and even 7-membered ring formation (Scheme 1.6).[34]

![Scheme 1.6](image)

**Scheme 1.6**: Formation of 5, 6, and 7-membered rings using a bis(thiophosphinimamide) zirconium catalyst.
**Table 1.2:** Alkyne hydroamination with secondary amines using a bis(ureate) zirconium catalyst.

![Chemical reaction equation]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>R³</th>
<th>R⁴</th>
<th>Yield (%) A</th>
<th>Yield (%) B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methylbenzylamine</td>
<td>Ph</td>
<td>H</td>
<td>93</td>
<td>&lt;2</td>
</tr>
<tr>
<td>2</td>
<td>Piperidine</td>
<td>Ph</td>
<td>H</td>
<td>80</td>
<td>&lt;2</td>
</tr>
<tr>
<td>3</td>
<td>1,2,3,4-THIQ&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Ph</td>
<td>H</td>
<td>92</td>
<td>&lt;2</td>
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<tr>
<td>4</td>
<td>Morpholine</td>
<td>Ph</td>
<td>H</td>
<td>97</td>
<td>&lt;2</td>
</tr>
<tr>
<td>5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Morpholine</td>
<td>Ph</td>
<td>Me</td>
<td>57</td>
<td>&lt;2</td>
</tr>
<tr>
<td>6&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Morpholine</td>
<td>Ph</td>
<td>Ph</td>
<td>44</td>
<td>n/a</td>
</tr>
<tr>
<td>7</td>
<td>Morpholine</td>
<td>C₈H₁₇</td>
<td>H</td>
<td>37</td>
<td>44</td>
</tr>
<tr>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2,6-Dimethylaniline</td>
<td>C₈H₁₇</td>
<td>H</td>
<td>29</td>
<td>54</td>
</tr>
</tbody>
</table>

- **a)** Reaction temperature 145 °C. **b)** Reaction temperature 110 °C. **c)** 1,2,3,4-THIQ = 1,2,3,4-tetrahydroisoquinoline.
Intermolecular hydroamination of alkynes has been extensively investigated by many research groups with the recent focus being on expansion of substrate scope and improvement of regioselectivity in the hydroamination of both terminal and internal alkynes. The most significant recent advance has been with the use of bis(ureate) zirconium catalyst 2, due to its ability to catalyze intermolecular alkyne hydroamination with secondary amines, summarized in Table 1.2.\textsuperscript{[24]} Enamine products that can be characterized \textit{in situ} were synthesized from piperidine (Table 1.2, Entry 2), 1,2,3,4-tetrahydroisoquinoline (Table 1.2, Entry 3) and morpholine (Table 1.2, Entries 4-7) starting materials.

\textbf{1.3.2 Recent Developments in Allene Hydroamination with Group 4 Catalysts}

Allene hydroamination is less commonly explored than either alkyne or alkene hydroamination. Compound 5 has been shown to be useful for allene hydroamination catalysis in an intermolecular fashion, even with less reactive, sterically less demanding alkyl amine substrates (Table 1.3).\textsuperscript{[35]} These results show good selectivity for the branched product and recent results show that even heteroatom substituted allenes can be tolerated with this precatalyst.
**Table 1.3**: Intermolecular allene hydroamination with bis(amidate) zirconium catalyst 5.

![Image of the reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>t (h)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>24</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>Bn</td>
<td>7</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>OCH₃</td>
<td>2</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>O(2,6-(CH₃)₂C₆H₃)</td>
<td>24</td>
<td>68</td>
</tr>
</tbody>
</table>

**1.3.3 Recent Developments in Alkene Hydroamination with Group 4 Catalysts**

While a broad range of early transition metal catalysts have been developed in recent years for intramolecular alkene hydroamination, few of them have succeeded in improving reactivity or expanding substrate scope. Many group 4 complexes, including simple and commercially available Ti(NMe₂)₄\textsuperscript{[36]} and Zr(NMe₂)₄\textsuperscript{[27]} can mediate intramolecular alkene hydroamination (Scheme 1.7). The benchmark reaction
temperatures and reaction times of 110 °C and 24 h respectively, are readily achievable reaction conditions with a broad range of catalysts, as previously reviewed.[2] Furthermore, the incorporation of such gem-disubstituted substrates is commonly used, due the combined contributions of the Thorpe-Ingold Effect[37] and the Reactive Rotamer Effect[38] to promote facile ring closure. More recent efforts have continued the search for more reactive catalyst systems that can accommodate a broader substrate scope in order to render this important transformation more useful to the organic synthetic community.

Figure 1.2: Neutral group 4 catalysts for intramolecular hydroamination of challenging primary aminoalkene substrates.
Scheme 1.7: Baseline reaction times for 2,2-diphenyl-4-pentenamine using homoleptic Ti and Zr amides.

Recent expansions of substrate scope have been realized with ligands that promote the formation of sterically accessible, electrophilic reactive metal centres (Table 1.4). For example, a dipyrrolylmethane complex from Odom, 6 (Figure 1.2), takes advantage of the known fluxional binding modes ($\eta^5$ and $\eta^1$) of the pyrrollyl moiety.\(^{[27]}\) Notably, the previously reported Ti version of this precatalyst is known to be a highly effective catalyst for intermolecular alkyne hydroamination,\(^{[39]}\) although for intramolecular alkene hydroamination the Zr version shows much improved reactivity.

Similarly, a Zr pyridonate complex from the Schafer group, 7 (Figure 1.2), can also be used for a broad range of substrates, even including an example of 7-membered ring formation via cyclohydroamination, although elevated temperatures and prolonged reaction temperatures are required.\(^{[40]}\) Such pyridonate ligands, while being isolated in the solid phase as $\kappa^2$-complexes, may adopt a mono-dentate binding mode to enhance accessibility to the reactive metal centre during catalysis.

Another N,O-ligated complex featuring imidazolonate ligands was reported by Ong and co-workers, 8 (Figure 1.2). It adopts a dimeric structure in which each imidazolonate ligand acts as a bridging N,C,O moiety between the two zirconium centres.\(^{[25]}\) This complex features a cyclic ureate mono-anionic ligand that is not reported to chelate a
single metal centre. Even with such dimeric species, hydroamination reactivity with typical substituted substrates occurs readily and secondary amines can be used as substrates using prolonged reaction times at elevated temperatures. Notably, work pursued using this complex has not yet been reported to have undergone rigorous mechanistic analysis and no direct comments are made as to the catalytically active species. Whether it remains dimeric under catalytic conditions and if it can access multiple reaction manifolds including [2+2] cycloaddition and σ-bond insertion remain outstanding questions.

Zirconium complex 2, bearing a tethered dianionic bis(ureate) ligand shown remarkable substrate scope such that 5, 6, and 7-membered rings can be readily formed via cyclohydroamination (Table 1.4) and most importantly, this complex is an efficient catalyst for hydroamination with secondary amines (Table 1.5).[^24] Indeed, the reaction times are somewhat shorter using secondary amines, suggesting that the catalytic mechanism is not the [2+2] cycloaddition route most typically observed for group 4 hydroamination catalysts. Indeed, this and related systems have been extensively explored in mechanistic investigations in order to gain important insights into an alternative mechanistic profile (Scheme 1.4, *vide supra*).[^29]
Table 1.4: Group 4 hydroamination utilizing an expanded scope of aminoalkene substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>cat.</th>
<th>mol %</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[^27]</td>
<td>( \text{Zr(NMe}_2)_4 )</td>
<td>6</td>
<td>10</td>
<td>100</td>
<td>1</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>2[^27]</td>
<td>( \text{Ph}_2\text{PhNH}_2 )</td>
<td>6</td>
<td>5</td>
<td>100</td>
<td>1</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>3[^25]</td>
<td>( \text{Ph}_3\text{PhNH}_2 )</td>
<td>8</td>
<td>5</td>
<td>130</td>
<td>0.25</td>
<td>&gt;95</td>
<td></td>
</tr>
<tr>
<td>4[^27]</td>
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<td>6</td>
<td>5</td>
<td>100</td>
<td>3</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>5[^25]</td>
<td></td>
<td>8</td>
<td>5</td>
<td>130</td>
<td>1.5</td>
<td>&gt;95</td>
<td></td>
</tr>
<tr>
<td>6[^27]</td>
<td></td>
<td>6</td>
<td>5</td>
<td>100</td>
<td>3</td>
<td>100 (dr 1:1)</td>
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<td>7[^25]</td>
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<td>8</td>
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<td>130</td>
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<td>&gt;95 (dr 3:2)</td>
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<td>8[^27]</td>
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<td>6</td>
<td>5</td>
<td>110</td>
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<tr>
<td>9[^40]</td>
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<td>10</td>
<td>110</td>
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<td>10[^27]</td>
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<td>6</td>
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<td>150</td>
<td>96</td>
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<td>6</td>
<td>5</td>
<td>150</td>
<td>120</td>
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<td>12[^25]</td>
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<td>10</td>
<td>130</td>
<td>4</td>
<td>82 (dr 7:3)</td>
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</tr>
</tbody>
</table>
Table 1.4 (con’t): Group 4 hydroamination utilizing an expanded scope of aminoalkene substrates.

<table>
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<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>cat.</th>
<th>mol %</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>conv. (%)</th>
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\end{array}
\] | \[
\begin{array}{c}
\text{N}
\end{array}
\] | 2 | 10 | 145 | 16 | 86 |
| 14\[^{[24]}\] | \[
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\] | \[
\begin{array}{c}
\text{NPh}
\end{array}
\] | 2 | 10 | 145 | 2 | 90 \((\text{dr 5:1})\) |
| 15\[^{[40]}\] | \[
\begin{array}{c}
\text{CH}_2=\text{CHCH}_2\text{NH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{N}
\end{array}
\] | 7 | 10 | 110 | 96 | 35 \((\text{dr >10:1})\) |
| 16\[^{[24]}\] | \[
\begin{array}{c}
\text{CH}_2=\text{CHCH}_2\text{NH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{NPh}
\end{array}
\] | 2 | 10 | 145 | 20 | 90 |
| 17\[^{[24]}\] | \[
\begin{array}{c}
\text{C}_6\text{H}_4\text{NH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{N}
\end{array}
\] | 2 | 10 | 145 | 18 | 76 |
| 18\[^{[24]}\] | \[
\begin{array}{c}
\text{C}_6\text{H}_4\text{NH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{N}
\end{array}
\] | 2 | 10 | 145 | 48 | 84 |
| 19\[^{[40]}\] | \[
\begin{array}{c}
\text{CH}_2=\text{CHCH}_2\text{NH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{NPh}
\end{array}
\] | 7 | 10 | 145 | 168 | 59 |
| 20\[^{[24]}\] | \[
\begin{array}{c}
\text{C}_6\text{H}_4\text{NH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{NPh}
\end{array}
\] | 2 | 10 | 145 | 55 | 64 \((\text{dr >20:1})\) |
| 21\[^{[40]}\] | \[
\begin{array}{c}
\text{C}_6\text{H}_4\text{NH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{N}
\end{array}
\] | 7 | 10 | 145 | 168 | 52 |
Table 1.5: Zirconium-catalyzed hydroamination of secondary aminoalkenes.

<table>
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<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>cat.</th>
<th>mol %</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>conv. (%)</th>
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<td>150</td>
<td>12</td>
<td>100</td>
</tr>
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<td>5[^25]</td>
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<td><img src="image10" alt="Product" /></td>
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<td>10</td>
<td>145</td>
<td>15</td>
<td>91</td>
</tr>
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<td>7[^24]</td>
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<td>10</td>
<td>100</td>
<td>4</td>
<td>86</td>
</tr>
<tr>
<td>8[^24]</td>
<td><img src="image15" alt="Substrate" /></td>
<td><img src="image16" alt="Product" /></td>
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<td>10</td>
<td>100</td>
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<td>87</td>
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<td>9[^24]</td>
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<td><img src="image18" alt="Product" /></td>
<td>2</td>
<td>10</td>
<td>100</td>
<td>28</td>
<td>89</td>
</tr>
</tbody>
</table>
The most significant recent development in group 4 hydroamination has been the expansion of substrate scope to include secondary amines, with results summarized in Table 1.5. While some group 4 catalysts can indeed promote reactivity with secondary substrates, it is worth noting that even the Zr(NMe$_2$)$_4$ precatalyst can be used at similar high temperatures to achieve ring-closure with the most reactive secondary amine substrates (Table 1.5, Entry 4).$^{[27]}$ Thus, discerning between the reactivity of ligated systems and some Zr(NMe$_2$)$_4$ formed in situ due to ligand redistribution remains a challenge when monitoring catalytic reactions. Notably the tethered bis(ureate) compound 2 also shows tolerance for acetals or protected amines (Table 1.5, Entries 7-9), suggesting that these group 4 complexes, which are often overlooked for applications in organic synthesis due to their moisture sensitivity and oxophilicity, may be suitable catalysts for organic synthesis, much like the more commonly applied late-transition metal catalysts.

1.3.4 Recent Developments in Asymmetric Alkene Hydroamination with Group 4 Catalysts

Beyond the chemo- and regioselective challenges of allene and alkyne hydroamination, alkene hydroamination can create a stereocentre α to the nitrogen atom, resulting in enantioselectivity and possibly diastereoselectivity challenges. Asymmetric alkene hydroamination remains a long-standing goal in the field and to date there are only a handful of catalysts from across the periodic table that can achieve this reaction with enantioselectivities in excess of 90%.$^{[41–46]}$
In 2007, the Schafer group reported bis(amidate) bis(amido) zirconium precatalyst 9 based on an axially-chiral biphenyl backbone (Figure 1.3).[^41] Intramolecular hydroamination of aminoalkene substrates using 9 resulted in pyrrolidine formation with ee's up to 93%, one of the highest enantioselectivities reported to date. This result was subsequently duplicated and confirmed by Scott and co-workers, who independently developed the identical precatalyst.[^47]

Many other enantioselective group 4 catalysts have recently been generated in the Hultzsch,[^48] Schafer,[^49,50] and Zi[^51–58] groups. Over 100 new ligands have been screened by the Zi group, all based on axially-chiral biphenyl or binaphthyl backbones, and bound to the group 4 metal centre through N, O, or S. Most of these recent complexes result in competent product formation over a range of common aminoalkene substrates, with modest to good ee's (40-85% ee). However, none of these alternative ligands have been demonstrated to advance the state of the art for group 4 enantioselective hydroamination.
Table 1.6: Enantioselective room temperature hydroamination catalyzed by a zwitterionic zirconium catalyst.

![Zirconium catalyst 10](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>$t$ (h)</th>
<th>conv. (%)</th>
<th>ee (%)</th>
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<td>&gt;95</td>
<td>93</td>
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<td>2$^a$</td>
<td><img src="image" alt="Substrate 2" /></td>
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<td>120</td>
<td>&gt;95</td>
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<td>&gt;95</td>
<td>90</td>
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<tr>
<td>4$^b$</td>
<td><img src="image" alt="Substrate 4" /></td>
<td>[D$_8$]THF</td>
<td>11</td>
<td>93</td>
<td>94</td>
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<tr>
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<td><img src="image" alt="Substrate 5" /></td>
<td>C$_6$D$_6$</td>
<td>4</td>
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</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Substrate 7" /></td>
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<td>&gt;95</td>
<td>92,93 (dr 1.1:1)</td>
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<td>46</td>
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<tr>
<td>9</td>
<td><img src="image" alt="Substrate 9" /></td>
<td>C$_6$D$_6$</td>
<td>40</td>
<td>48</td>
<td>31</td>
</tr>
</tbody>
</table>

$^a$ Reaction temperature $-30 ^\circ C$; $^b$ Reaction temperature $0 ^\circ C$. 

---

24
The most significant recent contribution in enantioselective alkene hydroamination is from Sadow and co-workers, a chiral zwitterionic Zr complex 10 which can achieve ee’s up to 99%, the highest reported to date (Table 1.6).\textsuperscript{[28,31]} Furthermore, ee’s of at least 88% were achieved for five different aminoalkene substrates. Impressively, these results are attained in a timely fashion (<8 h) at room temperature giving excellent yields. Unfortunately ee’s drop substantially when piperidines are formed, with a maximum of 46% ee achieved (Table 1.6, Entries 8 and 9).

It is clear that important advances in group 4 catalyzed hydroamination have been realized recently. The expansion of substrate scope to include secondary amine substrates opens a whole new avenue for future catalyst development. Achievement of reactivity at room temperature will encourage the use of milder reaction conditions. Perhaps most impressively, exploration into the substrate scope of group 4 hydroamination catalysts also indirectly led to the discovery of another application for those catalysts: the hydroamination reaction.

1.4 Recent Developments in Hydroaminoalkylation

While testing the substrate scope of bis(pyridonate) Zr precatalyst 7 for hydroamination,\textsuperscript{[40]} it was discovered that this complex produced an unexpected direct $\alpha$-alkylation product when a 7-membered aminoalkene substrate was used (Scheme 1.8).\textsuperscript{[59]}
Scheme 1.8: Unexpected C-C bond formation during hydroamination of 2,2-diphenyl-1-amino-6-heptene.

This reaction, named hydroaminoalkylation, is formally described as the addition of a C-H bond alpha to nitrogen across a C-C unsaturation. It was subsequently found by Doye to be an accessible reaction using simple titanium complexes Ti(NMe$_2$)$_4$, Ti(CH$_2$Ph)$_4$, and Ind$_2$TiMe$_2$ at elevated temperatures (Scheme 1.9).[60,61]

Scheme 1.9: Hydroaminoalkylation with a 7-membered aminoalkene substrate.

While these examples of hydroaminoalkylation with group 4 catalysts were informative, more progress has recently been achieved with group 5 metals, specifically tantalum. The first examples of tantalum-catalyzed hydroaminoalkylation were published in the 1980s,[62] requiring elevated temperatures and with limited substrate scope. No subsequent hydroaminoalkylation literature was published until 2007 when Herzon and Hartwig demonstrated reactivity with Ta(NMe$_2$)$_5$,[63] using arylamines and terminal
alkenes as substrates at high temperatures (150-160 °C). Herzon and Hartwig followed this up with a report using [TaCl₅(NEt₂)₂]₂ which expanded the substrate scope to dialkylamines and proceeded at lower temperatures for arylamines.[64]

Figure 1.4: Monoamidate tantalum hydroaminoalkylation catalyst.

The Schafer group then reported a monoamidate tantalum complex 11 (Figure 1.4), which further extended substrate scope to include unactivated internal alkenes, silyl protected enols, dienes and N-containing heterocycles such as piperidine.[65]

The proposed catalytic cycle for group 5 hydroaminoalkylation catalysis involves the formation of a tantalaziridine species (A, Scheme 1.10), followed by insertion of the alkene to form a 5-membered metallacycle (B, Scheme 1.10). Protonolysis with a new molecule of amine causes the metallacycle to open (C, Scheme 1.10), and a subsequent β-hydrogen abstraction regenerates the tantalaziridine A and completes the catalytic cycle. Two mechanistic investigations of both a group 4[66] and group 5[67] catalytic systems support the metallaziridine-based mechanism.
Scheme 1.10: Proposed mechanism of tantalum-catalyzed hydroaminoalkylation.

As with alkene hydroamination, hydroaminoalkylation with alkenes results in a stereogenic centre making enantioselectivity a potential challenge in catalyst development. So far, three catalysts for asymmetric hydroaminoalkylation have been published by Schafer,\textsuperscript{[65]} Zi,\textsuperscript{[68,69]} and Hultzsch,\textsuperscript{[70]} all based on axially-chiral ligands (Figure 1.5). In particular, silylated binaphtholate tris(amido) complex 14 from Hultzsch has been shown to enantioselectively catalyze hydroaminoalkylation with a good range of
substrates and ee’s up to 98%. Furthermore, the niobium version of 14 is more catalytically active than the tantalum versions. While the contributions to hydroaminoalkylation catalyst development up to this point have greatly enhanced understanding of this relatively obscure reaction, the field remains open to much further research.

**Figure 1.5:** Chiral group 5 hydroaminoalkylation catalysts.

### 1.5 Scope of This Thesis

Much of the work of the Schafer group to date has focused on group 4 complexes bearing amidate ligands for hydroamination catalysis. While the first example of an amidate group ligated to a group 4 metal was published in 2001 by Arnold and coworkers for the purpose of olefin polymerization,[71] the Schafer group has led the field by extensively examining these types of complexes in catalytic amine synthesis.[35,40,41,49,50,59,72–83]

Group 4 metals are particularly attractive for catalysis because they are inexpensive and non-toxic compared to their late metal and rare-earth counterparts. Amide proligands are
easy to synthesize from a wide variety of amine and acid chloride or acid anhydride precursors, making them tunable on both the amine and carbonyl moieties. Formation of amidate-ligated group 4 complexes can be accomplished in a straightforward manner via protonolysis reactions with commercially-available metal starting materials.

The work on [N,O]-ligated group 4 complexes in the Schafer group has attempted to (1) elucidate the fundamental chemistry of these compounds, and (2) demonstrate their applicability towards metal-mediated organic transformations. Consistent with these overarching research goals, this thesis will outline the development and synthesis of [N,O]-ligated complexes of certain early metals, and the catalytic applicability of these complexes towards hydroamination and hydroaminoalkylation.

Chapter 2 outlines the design and synthesis of new bis(amide) proligands derived from the 2,2′-diamino-6,6′-dimethylbiphenyl tether, a class of proligand which had been previously investigated in the group. It was hypothesized that targeted ligand modifications to either change the steric or electronic environment around the metal centre would result in advantageous effects on catalysts reactivity and enantioselectivity. Such modifications to both the carbonyl and amine sides of the amide bond are explored. The newly-developed proligands are used to create new bis(amidate) bis(amido) zirconium complexes, and the efficiency of these complexes for enantioselective alkene hydroamination is determined. The use of in situ catalyst generation is explored as a simplified catalyst preparation method. In addition, the structural and mechanistic aspects of the zirconium complexes are probed.
In Chapter 3, development of new tethered bis(urea) proligands is undertaken to further explore hydroamination with secondary amine substrates. New chiral bis(ureate) zirconium catalysts were expected to facilitate the enantioselective production of \( N \)-heterocycles containing tertiary amines, derived from secondary aminoalkene substrates. The structure and bonding of bis(ureate) bis(amido) zirconium complexes is presented. A chiral bis(ureate) zirconium hydroamination catalyst is synthesized and the cyclization of secondary aminoalkenes is undertaken. The use of capillary electrophoresis for ee determination of the tertiary amine products is developed.

In Chapter 4, the synthesis bis(amidate) tris(amido) tantalum complexes will be demonstrated, using tethered ligand architectures, similar to those used in the development of zirconium catalysts for hydroamination. Exploring bis(amidate) ligand binding to tantalum was expected to give insight into further catalyst development and reactivity trends. Accessible coordination modes of potentially tetradentate ligands will be discussed, along with initial applications towards catalyzing hydroaminoalkylation reactions.

In Chapter 5, highlights of the work presented in this thesis will be summarized. Possible future research directions arising from the studies undertaken as part of this thesis will be proposed and discussed.
Chapter 2: Development of New Bis(amidate) Bis(amido) Zirconium Catalysts for Enantioselective Alkene Hydroamination

2.1 Introduction

One of the most challenging transformations in hydroamination catalyst development is intramolecular asymmetric reactions with alkene substrates. While many catalysts have successfully dealt with issues of chemo- and regioselectivity, relatively few have attempted to address enantioselectivity.\cite{84} While the pioneering work on enantioselective hydroamination catalysts was undertaken by Marks in the early 1990s using lanthanide complexes,\cite{85} the development of enantioselective group 4 catalysts is more recent, starting with contributions from Scott\cite{32} and Bergman\cite{86} in the mid-2000s.

In 2007, the Schafer group reported an axially chiral bis(amidate) bis(amido) zirconium catalyst, 9, which can carry out intramolecular alkene hydroamination with enantioselectivities of up to 93% ee (Scheme 2.1).\cite{41} This was the highest reported enantioselectivity achieved with a group 4 system at the time. Catalyst 9 was also independently synthesized by Scott and co-workers and was confirmed to have the same reactivity and selectivity as the version generated in the Schafer group.\cite{47}

In addition to catalyst 9, a number of other bis(amidate) bis(amido) zirconium complexes bearing ligands derived from a 2,2’-diamino-6,6’-dimethylbiphenyl backbone were previously prepared in the Schafer group, primarily by Mark Wood. These variations were based on installing different functional groups connected to the carbonyl (in catalyst 9, \( R = \text{mesityl} = 2,4,6\text{-trimethylphenyl} \)). Some of these variants (\( R = \text{naphthyl}, \)

32
adamantyl) were included in the original report of catalyst 9,[41] while others (R= CF₃, 4-CF₃C₆H₄, 3,5-(CF₃)₂C₆H₃) were published as part of a master’s thesis by Mark Wood.[87]

While the exploration of a variety of R-groups attached to a common diamine tether did identify 9 as a very good catalyst, the ability to construct proligands in a modular fashion via amide bond synthesis allowed for the further investigation of new ligand motifs.

**Scheme 2.1:** Enantioselective hydroamination using an axially chiral bis(amide) bis(amido) zirconium catalyst developed in the Schafer group.

This chapter details efforts to create new bis(amide) proligands derived from an axially-chiral 2,2'-diamino-6,6'-dimethylbiphenyl tether, to synthesize bis(amide) bis(amido) zirconium complexes using those proligands, and to carry out enantioselective alkene hydroamination using the resulting zirconium complexes. The first part summarizes modifications made to the carbonyl substituent of the amide bond, while the latter part features strategies for modifying the biphenyl tether on the amine side of the amide bond.
2.2 Modifications to the Aryl Carbonyl Substituent of Bis(amide) Proligands

Derived from 2,2’-Diamino-6,6’-dimethylbiphenyl

2.2.1 Assignment of Absolute Stereochemistry to 2,2’-Diamino-6,6’-
dimethylbiphenyl and Revised Selectivity Proposal

While developing these new axially chiral proligand sets, we were alerted to an error in
the original published report from the Schafer group featuring bis(amide) zirconium
complexes. The original manuscript\cite{41} included a solid state molecular structure of
catalyst 9 where the ligand was shown to adopt an (S) absolute configuration. It was
noted in the text that the proligand had been synthesized from enantiopure 2,2’-
diamino-6,6’-dimethylbiphenyl with a measured optical rotation of \([\alpha]_D = -35^\circ\) in 10% HCl. We
were alerted that a negative optical rotation measurement in 10% HCl should instead
have corresponded to an (R) absolute configuration of the biphenyldiamine.

Upon re-examination of the data, the sample used for X-ray crystallography had in fact
been racemic, with space group P(−1). Both (R) and (S) configurations were present in
the crystal, but the representation selected for the paper illustrated the (S) configuration of
the biphenyldiamine backbone rather than the (R) configuration.

This erroneous solid state molecular structure had been used to develop a selectivity
model outlining how the (S) enantiomer of catalyst 9 resulted in preferential formation of
one enantiomer of the cyclized pyrrolidine product. In order to verify the accuracy of the
selectivity model, it became necessary to review and verify the absolute stereochemistry
of the biphenyl backbone.
The first assignment of the absolute stereochemistry of 2,2'-diamino-6,6'-dimethylbiphenyl was reported in 1958 by Mislow and co-workers, who measured the optical rotation of (R)-2,2'-diamino-6,6'-dimethylbiphenyl in 12 different solvents.\textsuperscript{[88]} The sign of the optical rotation was found to depend on the nature of the solvent. In organic solvents such as ethanol, acetone, or acetonitrile, the optical rotation had a positive sign. In acidic solvents, such as sulfuric acid, aqueous HCl, or acetic acid, the optical rotation had a negative sign. Mislow defined the sign for the (R)-enantiomer in reference to its rotation in ethanol ([\(\alpha\)]\textsubscript{D} = +49° in EtOH), noted as (R)-(+)2,2'-diamino-6,6'-dimethylbiphenyl. A subsequent study using (S)-(−)-2,2'-diamino-6,6'-dimethylbiphenyl determined the absolute stereochemistry of the molecule using X-ray crystallography. Its optical rotation measurement of [\(\alpha\)]\textsubscript{D}= −51.7 ± 2.4° in EtOH was in agreement with previous results.\textsuperscript{[89]}

In order to further ensure accurate identification of the absolute configuration of our compounds, an enantiopure sample of (+)-2,2'-diamino-6,6'-dimethylbiphenyl was obtained through a tartaric acid resolution. The optical rotation of the sample was measured to be [\(\alpha\)]\textsubscript{D} = −34.5° in 10% HCl and [\(\alpha\)]\textsubscript{D} = +107° in pyridine, which corresponds well to Mislow’s reported values of −36° and +111°, respectively.\textsuperscript{[88]} The enantiopure biphenyl diamine was combined with 2.1 equivalents of an enantiopure reagent, (1S)-(+)10-camphorsulfonyl chloride, and 2.1 equivalents of triethylamine in dichloromethane (Scheme 2.2). The resulting bis(sulfonamide) product 15 was isolated and purified. The product was recrystallized from a hexanes/acetone mixture and the colourless prisms obtained were analyzed using X-ray crystallography. Examination of the solid state molecular structure (Figure 2.1) revealed that only one diastereomer was
present, with the (+)-biphenyldiamine indeed corresponding to an absolute (R) orientation of the biphenyldiamine backbone as expected (Figure 2.2). Unfortunately, because the (+)-configuration of the biphenyl had been erroneously represented in an ORTEP illustration in the original communication as the (S) absolute orientation, a corrigendum was issued reflecting this new information and a revised model for enantioselectivity was generated (Figure 2.3).[90]

In this work, the naming convention of (R)-(+) 2,2′-diamino-6,6′-dimethylbiphenyl and (S)-(−) 2,2′-diamino-6,6′-dimethylbiphenyl will be continued. Enantioenriched proligands bearing a (+) or (−) notation denote which enantiomer of 2,2′-diamino-6,6′-dimethylbiphenyl the proligand was synthesized from, not the optical rotation of the proligand itself.

Scheme 2.2: Synthesis of a diastereomerically pure bis(sulfonamide) derivative of (+)-2,2′-diamino-6,6′-dimethylbiphenyl.
Figure 2.1: ORTEP representation of the solid-state molecular structure of 15 (ellipsoids plotted at 50% probability). All H-atoms omitted for clarity.

Figure 2.2: Assignment of (R) configuration to biphenyl backbone of compound 15.
In the revised model developed to rationalize the stereochemical outcome, the aminoalkene substrate is bound as a terminal imido in an axial position, consistent with previous findings for group 4 hydroamination catalysts (Figure 2.3). While undergoing the [2+2] cycloaddition step in which the orientation of the stereocentre is established, the substrate is postulated to adopt a chair-like conformation. In one of the two possible chair-like conformations, the mesityl group of the ligand is postulated to have a steric interaction with the allylic carbon of the substrate, accounting for the observed enantioselectivity. In particular, the methyl group at the ortho-position of the mesityl is the moiety causing steric interaction with the substrate.
Scheme 2.3: Synthesis of new bis(amide) proligands.

Based on the importance of the ortho-position on the aryl ring in Figure 2.3, three new proligand targets were developed, containing different groups at the ortho-positions of a phenyl ring. The first variant incorporated 2,4,6-triisopropylphenyl substituents. Because an isopropyl group is larger than a methyl group, it was hoped that this ligand might exert additional steric influence on the substrate, resulting in better enantioselectivity. The second variant incorporated 2,4,6-tribromophenyl substituents. A bromine substituent is approximately the same size as a methyl group (van der Waals radius of 1.95 and 2.0 Å, respectively),\textsuperscript{[91]} but has a different electronic profile. Previous work in the Schafer group has shown that electron-withdrawing groups enhance the reactivity of group 4 bis(amidate) catalyst systems.\textsuperscript{[79]} It was hoped that a mesityl analogue containing bromine substituents in place of methyl groups would have a similar steric profile as the mesityl ligand, while also resulting in enhanced reactivity due to electronic effects. In addition, a
proligand incorporating unsubstituted phenyl groups was synthesized as an analogue with no ortho-substituents. 2,2’-Diamino-6,6’-dimethylbiphenyl was synthesized using previously published methods.\cite{92} The racemate was resolved using successive tartaric acid recrystallizations and verified to have an ee of greater than 98\% using polarimetry.\cite{41}

Proligand 17 was synthesized by combining 2,2’-diamino-6,6’-dimethylbiphenyl with 2 equivalents of benzoyl chloride along with excess pyridine in 1,2-dichloroethane, then heating to reflux for 1 hour (Scheme 2.3). After purification and crystallization, colourless crystals of 17 were obtained in 55\% yield, and characterized using $^1$H and $^{13}$C NMR spectroscopy, mass spectrometry and elemental analysis. For the synthesis of proligand 18, the addition of 2 equivalents of 2,4,6-triisopropylbenzoyl chloride to the diamine tether did not result in full conversion to product. Unreacted 2,2’-diamino-6,6’-dimethylbiphenyl as well as the product of monoamidation were present in the reaction mixture despite heating to reflux in 1,2-dichloroethane for an extended period of time. The minimum amount of 2,4,6-triisopropylbenzoyl chloride required to remove all traces of unreacted diamine or monoamidation product from the reaction mixture was determined to be 6 equivalents. This required the removal of large quantities of the major byproduct of the reaction, 2,4,6-triisopropylbenzoic acid, which was non-trivial as the acid byproduct was not soluble in basic aqueous solutions. Furthermore, thin layer chromatography, using mixtures of hexanes, diethyl ether, and ethyl acetate as eluents resulted in very close spotting of 2,4,6-triisopropylbenzoic acid and 18. Gradient-elution silica gel chromatography using mixtures of hexanes and ethyl acetate as eluent was required to isolate 18 in small quantities, with yields up to 36\%. Characterization data
obtained from $^1$H NMR spectroscopy indicated a symmetrical molecule with two inequivalent isopropyl groups in a 2:1 ratio, corresponding to the isopropyl groups at the 2,6 and 4 positions of the phenyl ring, respectively. The methine protons of the two isopropyl groups also resulted in separate signals due to their different chemical environments. Mass spectrometry and elemental analysis also provided support for the identification of 18.

Scheme 2.4: Synthesis of proligand 19.

While benzoyl chloride and 2,4,6-trisopropylbenzoyl chloride are affordably available from commercial sources, the 2,4,6-tribromobenzoyl chloride required for the synthesis of 19 had to be prepared from 1,3,5-tribromobenzene (Scheme 2.4). Using a modified literature procedure,$^{[93]}$ 1,3,5-tribromobenzene was dissolved in THF and cooled to $-78$ °C, and treated with freshly-prepared LDA. CO$_2$ was passed through a drying tube and bubbled through the reaction mixture for a period of 45 minutes. A 3M aqueous HCl solution was used to quench the reaction and acidify the reaction mixture. After successive extractions with dichloromethane, 2,4,6-tribromobenzoic acid (20, Scheme 2.4) was dried and isolated in 56% yield. The crude acid product was then dissolved in dry dichloromethane and treated with excess oxalyl chloride in the presence of catalytic amounts of N,N-dimethylformamide to form 2,4,6-tribromobenzyol chloride. All
volatiles, including excess oxalyl chloride were removed under reduced pressure. Under a nitrogen atmosphere, dry 1,2-dichloroethane was added to dissolve the crude acid chloride, followed by 1 equivalent of pyridine and 0.33 equivalents of 2,2’-diamino-6,6’-dimethylbiphenyl. The mixture was heated to reflux for 3 hours. After aqueous work-up, proligand 19 was isolated using silica gel chromatography in a 13% yield. The $^1$H NMR spectrum of the product contained a strong singlet at $\delta$ 1.98 ppm, as well as two doublets and a doublet of doubles in the aromatic region, consistent with signals arising from the biphenyl backbone. In addition, a broad singlet was observed in the aromatic region at $\delta$ 7.60 ppm, corresponding to the aromatic protons on the 2,4,6-tribromophenyl group. Mass spectrometry of the product resulted in the expected isotope pattern for a multiply brominated species, and elemental analysis was consistent with expected results.

Proligands 17-19 were crushed into powders then placed into small vials. The vials were heated to 70 °C in vacuo for at least 12 hours to dry the proligands before being brought into a nitrogen-filled glovebox.

### 2.2.3 Synthesis of Zirconium Complexes

Zirconium complexes were formed by mixing an equimolar mixture of proligand and Zr(NMe$_2$)$_4$ in solution in a nitrogen-filled glovebox. The solvent was then removed under reduced pressure, leaving behind a yellow solid product. Discrete monomeric complexes were difficult to obtain, despite attempts to use solvents that were both coordinating (THF) and non-coordinating (benzene, toluene, hexanes). As a result, characterization of these complexes was a challenge. In studies of similar bis(amidate) zirconium complexes, Scott and co-workers reported fluxional solution-phase behaviour for related bis(amidate)
group 4 complexes, finding that only compound 9 adopted a discrete, monomeric complex in solution.\textsuperscript{47} The remainder were believed to adopt “poorly defined” dimeric or oligomeric structures in solution. \textsuperscript{1}H NMR spectroscopy of the zirconium complexes in this study also indicated multiple species in solution, displaying multiple adjacent signals. For example, a mixture of Zr(NMe\textsubscript{2})\textsubscript{4} and proligand 18 contained more than 15 doublets between $\delta$ 1.0 and 1.8 ppm, some isolated, some overlapping, and all likely corresponding to isopropyl methyl groups of the ligand in various conformations. Likewise, the aromatic region of the spectrum contained far more signals than would be expected for a single product in solution. The ligand must adopt multiple distinct coordination environments to result is such a large quantity of distinct signals.

Attempts to recrystallize zirconium complexes from benzene, hexanes, toluene, or mixtures of those solvents prior to catalytic use were unsuccessful despite repeated attempts. As a result, zirconium complexes were obtained as yellow solids but could not be isolated as discrete, defined compounds prior to evaluating their potential application in catalysis. While not ideal this was determined to be satisfactory as no evidence of unreacted proligand or Zr(NMe\textsubscript{2})\textsubscript{4} could be detected in solution.

\textbf{2.2.4 Hydroamination Reactivity and Enantioselectivity}

Cyclohydroamination of aminoalkenes reactions were set up in a nitrogen-filled glovebox. 2,2-Diphenyl-4-pentenamine was used as a preferred test substrate, and was synthesized according to literature procedures.\textsuperscript{36} The zirconium complex was weighed out into a vial, then dissolved in 0.5 grams of dry deuterated benzene. The aminoalkene substrate was weighed out separately into a second vial. The contents of the two vials
were mixed thoroughly using a glass pipette and then the reaction mixture was loaded into a Teflon-sealed J. Young NMR tube. The tube was sealed, removed from the glovebox and placed in an oil bath heated to 110 °C and the reaction was monitored periodically by $^1$H NMR spectroscopy. Once complete, the reaction was quenched with dichloromethane, and products were isolated using silica gel chromatography. To determine the enantiomeric excess of the hydroamination products, the amine was mixed with Mosher’s acid chloride and triethylamine in dichloromethane. Determination of the ee of the product was performed using $^1$H and $^{19}$F NMR spectroscopy of the Mosher’s amide product according to established literature procedures.[94]

Table 2.1: Screening of new bis(amidate) zirconium complexes for hydroamination of 2,2-diphenyl-4-pentenamine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Proligand used</th>
<th>t (h)</th>
<th>conv. (%)</th>
<th>ee (%)</th>
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<td>1.25</td>
<td>&gt;98</td>
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<tr>
<td>2</td>
<td>(+)-17</td>
<td>72</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>(+)-18</td>
<td>22</td>
<td>&gt;98</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>(+)-19</td>
<td>53</td>
<td>25</td>
<td>17</td>
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</tbody>
</table>
The zirconium complexes synthesized from the newly-developed proligands were inferior to complex (+)-9 in terms of both reactivity and enantioselectivity. The most active, derived from proligand (+)-18, took 22 hours to achieve full conversion, while those derived from proligands (+)-17 and (+)-19 only achieved 38% and 25% conversion, respectively, even after extended reaction times. No ee greater than 25% was observed for any of the new Zr complexes. The low reactivity and enantioselectivity of these new zirconium complexes may be related to the difficulty in obtaining discrete monomeric complexes, meaning that some coordination isomers may not be catalytically active.

Subsequent to the catalytic testing undertaken in this work, a report about similar bis(amidate) bis(amido) zirconium hydroamination catalysts was published by Scott and co-workers.\textsuperscript{[47]} The article indicated the Scott group also synthesized proligand 18 but that “initial experiments suggest that substituting mesityl for 2,4,6-triisopropylphenyl greatly reduces reactivity.” No data or further information about proligand 18 was provided in that report.

The results with these new proligands and other variants based on the 2,2’-diamino-6,6’-dimethylbiphenyl backbone clearly established catalyst 9 as the best-performing chiral tethered bis(amidate) zirconium catalyst for a number of metrics: substrate scope, reactivity and enantioselectivity. Consequently, a mechanistic investigation of 9 was undertaken in an attempt to better understand its mode of action.
2.2.5 Kinetic Study of Catalyst 9

In order to better understand mechanistic aspects of catalytic hydroamination using compound 9 a series of kinetic experiments were performed. Kinetic tests of compound 9 were carried out using 2,2-dimethyl-4-pentenamine (21) as a hydroamination substrate in $d_6$-benzene, at catalyst concentrations of 7.5, 10, and 12.5%. Reaction mixtures were heated to 90 °C in a 400MHz $^1$H NMR spectrometer, and new spectra acquired every 2-3 minutes. 1,3,5-Trimethoxybenzene was included as an internal standard to monitor the progress of the reaction over time.

![Figure 2.4: Plot of substrate concentration vs. time at catalyst loadings of 7.5, 10, and 12.5%.]
The data in Figure 2.4 reveal a logarithmic decay in the substrate concentration with time. From this a plot of ln[substrate] vs. time was generated, shown in Figure 2.5, to obtain the respective observed rate constant. The linear plots observed for the three catalyst concentrations tested are consistent with a reaction that is first order in substrate.

Figure 2.5: Plot of ln[substrate] vs. time a catalyst loadings of 7.5, 10, 12.5%.

Figure 2.6, showing a plot of \( k_{\text{obs}} \) vs. catalyst concentration, suggests that this reaction is also first order in catalyst. This results in an empirical rate law of rate = k[cat][substrate].
The proposed catalytic cycle for hydroamination for neutral group 4 complexes was first proposed by Bergman, as a result of kinetic mechanistic studies (Scheme 1.3, *vide supra*).\textsuperscript{[12,22,23,95,96]} Computational analysis has also lent support to the imido pathway as the operative catalytic mechanism.\textsuperscript{[97–99]} Previous work with bis(amidate) zirconium complexes generated in the Schafer group has shown that terminal imido species can act as reactive intermediates to generate hydroamination products.\textsuperscript{[78]} In addition, a secondary amine substrate unable to form a terminal imido species, \textit{N}-methyl-2,2-diphenyl-4-pentenamine, was tested for hydroamination with 9 but resulted in no reactivity.\textsuperscript{[87]}

\textbf{Figure 2.6}: Plot of \(k_{\text{obs}}\) vs catalyst loading.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.6.png}
\caption{Plot of \(k_{\text{obs}}\) vs catalyst loading.}
\end{figure}
The kinetic data collected, which indicated a rate-determining step that is first-order in catalyst and first-order in substrate, is consistent with protonolysis being rate-determining for the imido pathway mechanism by which hydroamination with catalyst 9 proceeds. This suggests that the ligand design needs to incorporate sufficient steric bulk to result in the formation of monomeric species, which enables imido formation and creates a well-defined steric environment for enantioselectivity, while also ensuring the coordination sphere around the metal centre remains accessible to a second equivalent of the substrate needed for the turnover-limiting step.

2.3 Bis(amide) Proligand Modification via Bromination

Unfortunately, modifications to the ortho-position of an aryl ring attached to the carbonyl end of a bis(amide) proligand did not achieve the hoped-for increases in reactivity and selectivity and in fact resulted in much poorer catalytic performance. A new strategy for proligand modification was sought. Examining the selectivity model once again, it was proposed that rather than varying the carbonyl side of the amide, modifications to the biphenyldiamine backbone might be effective at creating a slightly more restricted steric environment around the metal centre. In particular, substituents in the 3,3’-positions of the backbone seemed most likely to affect substrate-ligand interactions.

One possibility is that the 3,3’-substituents may themselves interact with the substrate, resulting in enantioselective product formation. The other possibility is that the 3,3’-substituents might interact with the aryl ring of the carbonyl substituent causing the aryl ring to adopt a slightly different position. In the current selectivity model (Figure 2.7, left), the aryl ring of the mesityl is rotated about 45° in relation to the plane defined by
the ligand’s N-C-O chelates. Adding substituents on the proximal side of the backbone may cause the aryl ring to adopt an orientation nearing perpendicular to the zirconium-amidate plane (Figure 2.7, right). In that scenario, the aryl ring would then be in closer contact with hydroamination substrate, contributing to improved enantioselectivity.

![Diagram showing the effect of addition of substituents to 3,3’ positions of a biphenyldiamine backbone.]

**Figure 2.7:** Proposed effect of addition of substituents to 3,3’ positions of a biphenyldiamine backbone.

In determining what substituent to use at the 3,3’-position of the biphenyldiamine backbone, consideration was given to the size of the substituent and the ease of installing that substituent on an aryl ring. Bromine was identified as the initial candidate because of its moderate size (similar to a methyl group),[91] and the fact that procedures for the addition of halides to aryl rings are very well established. Furthermore, bromine may also present an opportunity to enhance reactivity, as previous work has demonstrated that electron-withdrawing substituents enhance reactivity in group 4 hydroamination catalysts.[79]
2.3.1 Synthesis of Brominated Bis(amide) Proligands

Scheme 2.5: Synthesis of new brominated bis(amide) proligands.

Treatment of 2,2'-diamino-6,6'-dimethylbiphenyl with excess bromine in glacial acetic acid according to literature procedures\textsuperscript{[100]} resulted in clean tetrabromination at the 3,3',5,5'-positions and the brominated biphenyl could be obtained in quantitative yields. Enantiopure 2,2'-diamino-6,6'-dimethylbiphenyl could be used to produce enantiopure 2,2'-diamino-3,3',5,5'-tetrabromo-6,6'-dimethylbiphenyl. The synthesis of a set of novel bis(amide) proligands based on this tetrabrominated tether was accomplished by reacting diamine 23 with a variety of acid chlorides along with pyridine in 1,2-dichloroethane heated to reflux (Scheme 2.5).

Generally, using the brominated biphenyl backbone 23 required more than 2 equivalents of acid chloride to drive the reaction to completion. This is likely due to the steric bulk of the diamine, as similar proligands have been synthesized from the non-brominated biphenyl and did not require more than 2 equivalents of acid chloride (such as proligand
18; vide supra) to achieve complete conversion to the bis(amide) product.\textsuperscript{[87]} Removal of excess acid chloride or acid byproducts was easily accomplished by aqueous workup, washing with cold hexanes, or silica gel chromatography.

Proligands 24 and 25 generated very simple $^1$H NMR spectra due to their symmetry, resulting in simple characterization. The use of additional $^{19}$F NMR spectroscopy allowed for easy identification of 26 and 27. Further confirmation of identity for all compounds was obtained using low-resolution and high-resolution mass spectrometry, and elemental analysis. Proligands were dried thoroughly by heating them to 70 °C in vacuo before bringing them into a glovebox.

Attempts to synthesize a mesityl derivative of 23 (the 3,3′,5,5′-tetrabrominated analogue of the ligand in complex 9) were unsuccessful, even with large excesses of 2,4,6-trimethylbenzoyl chloride, high temperatures, and long reaction times. Only the formation of a monoamide-monoamine mixed product could be detected in the reaction mixture, likely due to excessive steric bulk. Subjecting the unbrominated proligand in 9 to the bromination procedure (mixing with Br$_2$ in glacial AcOH) resulted in an inseparable mixture of products.

In summary, the generation of brominated bis(amide) proligands could be effectively carried out with yields of 66-84%. The steric bulk of 2,2′-diamino-3,3′,5,5′-tetrabromo-6,6′-dimethylbiphenyl made synthesis more challenging, and precluded formation of a bis(2,4,6-trimethylbenzoyl) derivative. Proligands 24-27 have been rigorously characterized and could be thoroughly dried to be suitable for installation on the metal centre.
2.3.2 Synthesis of Zirconium Complexes Bearing Brominated Bis(amidate) Ligands

Metal complexes were formed in a glovebox by mixing an equimolar ratio of proligand and Zr(NMe₂)₄ in dry benzene. The products of these reactions as observed by ¹H NMR spectroscopy resulted in very poorly-defined spectra, suggesting the presence of multiple species in solution. However, whereas the zirconium complexes in section 2.2.3 gave rise to a large number of well-defined signals in their ¹H NMR spectra, the NMR spectra of zirconium complexes synthesized with proligands 24-27 contain broader signals with less definition. This suggests the complexes are fluxional in solution on the NMR time scale. The appearance of broad NMR signals was further supported by the use of ¹⁹F NMR spectroscopy on reaction mixtures starting from proligands 26 and 27. Multiple poorly defined ¹⁹F signals were observed (Figure 2.8) suggesting not only different binding modes, but possible formation of dimers or oligomers and frequent changes in configuration and binding. Dimer and oligomer formation with similar tethered bis(amidate) zirconium complexes has been reported by the Schafer⁴⁹ and Scott⁴⁷ groups; so far, 9 is the only bis(amidate) zirconium complex based on a biphenyl tether which adopts a stable monomeric coordination mode.

To further characterize some of the zirconium species being formed, a zirconium complex synthesized from proligand 25 was successfully crystallized from a mixture of hexanes and benzene. In the solid state, it was found to adopt a dimeric structure (Figure 2.9) with 7-coordinate zirconium centres. The bis(amidate) ligand adopts a κ⁴-coordination mode with oxygen atoms acting as a bridge between the two zirconium atoms, along with two dimethlyamido ligands attached to each metal centre.
Figure 2.8: $^{19}$F NMR spectrum (C$_6$D$_6$, 282 MHz, 25 °C) of [26+Zr(NMe)$_2$)$_4$].

The amidate moiety not involved in bridging (N2, C15, O2) is more tightly bound to the zirconium metal centre than the bridging amidate (N1, C22, O1), as evidenced by shorter Zr-N bonds [Zr1-N2, 2.423(3) Å; Zr1-N1, 2.454(3) Å] and shorter Zr-O bonds [Zr1-O2, 2.225(2) Å; Zr1-O1, 2.292(2) Å]. Interestingly, the bridging O1 atom lies almost equidistant from both zirconium atoms [Zr1-O1, 2.292(2) Å; Zr2-O1 2.293(2) Å]. The dihedral angle between the two phenyl groups in the biphenyl tether, 64.8°, is significantly smaller than in the solid state structure of complex 9, which had a dihedral angle of 74.9°.[$^{41}$]
**Figure 2.9:** ORTEP representation of the solid-state molecular structure of dimeric Zr complex generated from proligand 25 (ellipsoids plotted at 50% probability). All H-atoms omitted for clarity.

While the dimeric structure provides insight into possible ligand coordination modes, the broad signals in the NMR spectra suggest that other coordination modes must be accessible in the solution phase. Additionally, a large amount of amine is present during hydroamination reactions, which can coordinate with zirconium and potentially disrupt the tight ligand binding seen in the dimeric structure. In an attempt to isolate a complex in the presence of exogenous donor, an excess of pyridine was added to an equimolar mixture of proligand 25 and Zr(NMe₂)₄. Upon recrystallization from a mixture of hexanes and benzene, the solid state structure of the resulting zirconium complex (Figure
2.10) showed a different ligand binding mode than in the previous dimeric structure (Figure 2.9). In the presence of an excess of neutral amine, the ligand adopts a $\kappa^2$-coordination mode, bound through only the oxygen atoms of the amidate moieties. Two dimethylamido ligands and two neutrally-bound pyridine rings form a 6-coordinate structure.

**Figure 2.10:** ORTEP representation of the solid-state molecular structure of a monomeric Zr complex formed with proligand 25 in the presence of excess donor pyridine (ellipsoids plotted at 50% probability). All H-atoms, and pyridine rings bound at N3 and N4 omitted for clarity.
The carbon-nitrogen bonds in the ligand [N5-C7, 1.309(8) Å; N6-C22, 1.313(9) Å] are close to what would be expected for a C=N double bond. Bonds between the ligand and the metal centre in the κ² complex [Zr1-O2, 2.086(5) Å; Zr1-O1, 2.121(5) Å] are slightly shorter than the Zr-O bonds in the dimeric structure.

The dihedral angle between the two phenyl groups of the biphenyl tether in the κ²-bound ligand is 109.7°. This is far higher than the same dihedral angle in the solid state molecular structure of the dimer, 64.8°. Assuming the zirconium complexes are fluxional in solution, with both κ² and κ⁴-bound species accessible, the ligand must undergo a large conformational change to switch between the two, possibly proceeding through a κ³ arrangement. The dimeric structure also suggests that other species where the amidate moieties of the ligand are bound to two different metal centres are a realistic possibility. Thus, the identification of two dramatically different solid state molecular structures makes it easy to envision that the ligand can adopt many different conformations under catalytic reaction conditions.

2.3.3 Catalytic Testing of Zirconium Complexes Bearing Brominated Bis(amidate) Ligands for Enantioselective Alkene Hydroamination

2.3.3.1 In situ Catalyst Generation

Due to the challenges of obtaining discrete metal species in solution, reactivity with in situ generated zirconium complexes was investigated. In situ catalyst generation has been used successfully for group 4 hydroamination in a number of other instances and has proven itself to be a viable method for catalyst screening. Hydroamination
reactions were carried out using isolated zirconium species and compared to hydroamination reactions carried out using *in situ* generated zirconium species.

**Table 2.2:** Reactivity comparison between isolated catalysts and *in situ* generated catalysts.

![Chemical structure](image)

<table>
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<tr>
<th>Entry</th>
<th>Proligand</th>
<th>t (h)</th>
<th>Conv. (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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Reactions performed using sealed NMR tube using 0.55 g C<sub>6</sub>D<sub>6</sub>.<sup>a</sup>Determined relative to 1,3,5-trimethoxybenzene internal standard. <sup>b</sup>Determined using <sup>19</sup>F NMR of Mosher's amide derivative.  
<sup>c</sup>Using isolated Zr catalyst  
<sup>d</sup>Catalyst generated *in situ*

In reactions using an isolated zirconium species, an equimolar mixture of proligand and Zr(NMe<sub>2</sub>)<sub>4</sub> were combined in a glovebox and dissolved in benzene. The mixture was stirred for 30 minutes at room temperature, then the solvent was removed under reduced pressure to yield a solid yellow product. The resulting solid was then weighed out into a
vial, combined with the aminoalkene substrate, and dissolved in deuterated benzene and loaded into a Teflon-sealed J. Young NMR tube.

In reactions using an in situ generated zirconium catalyst, the hydroamination substrate was weighed into a vial in the glovebox. In the same vial 10 mol% of Zr(NMe₂)₄ was weighed out, followed by 11 mol% of proligand. A slight excess of proligand was used to ensure that all of the zirconium was complexed; Zr(NMe₂)₄ is known to be a competent hydroamination catalyst. The entire mixture was then dissolved in deuterated benzene and placed in a Teflon-sealed J. Young NMR tube.

In both cases the NMR tube was sealed, removed from the glovebox, and placed in an oil bath heated to 110 °C. The reaction was monitored periodically by ¹H NMR spectroscopy. Once complete, the reaction was quenched with dichloromethane, and products were isolated using short silica gel plugs. To determine the enantiomeric excess of the hydroamination products, the amine was mixed with Mosher’s acid chloride with triethylamine in dichloromethane. Determination of ee was performed using ¹H and ¹⁹F NMR spectroscopy of the Mosher’s amide product.

The results of in situ catalyst generation are shown in Table 2.2, and demonstrate identical reaction times and yields. The difference between an isolated catalyst and an a catalyst generated in situ is at most 2%, which is within the experimental error of the NMR technique used to quantify ee’s. Isolation of catalytic material is not required as in situ generated catalysts yielded nearly identical results and the remainder of the catalytic testing was undertaken using in situ generated catalyst.
2.3.3.2 Reactivity of in situ Generated Zirconium Complexes for Alkene Hydroamination

*In situ* catalyst screening using other proligands was performed at 110 °C (Table 2.3) using 2,2-diphenyl-4-pentenamine as a test substrate. The brominated proligand set showed accelerated reactivity over analogous non-brominated proligands. In particular, reactions with proligand 27 were extremely fast, completing the hydroamination reaction as quickly as 15 minutes.

**Table 2.3:** Reactivity and enantioselectivity of *in situ* generated Zr complexes bearing brominated bis(amidate) ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Proligand</th>
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<td>(+)-27</td>
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Reactions performed using sealed NMR tube using 0.55 g C<sub>6</sub>D<sub>6</sub>.<sup>a</sup> Determined relative to 1,3,5-trimethoxybenzene internal standard. <sup>b</sup> Determined using<sup>19</sup>F NMR of Mosher's amide derivative. <sup>c</sup> Using isolated Zr catalyst.
The swift reactivity observed using proligands 26 and 27 spurred us to continue testing these proligands at lower temperatures. Table 2.4 summarizes results of the cyclization of 2,2-diphenyl-4-pentenamine (21) at 65 °C, 40 °C, and at room temperature. Surprisingly, reactions performed at room temperature also showed product formation, although they did not go to completion; the reaction was quenched after 1 week without full conversion. Proligands 24 and 25 were tested for room temperature hydroamination activity but no product formation was observed. It is suspected that long reaction times result in complex deactivation, possibly via dimerization. While a slight upward trend in ee values can be observed as the reaction temperature decreases, the variation is small, and attempting to achieve further increases in ee by lowering the reaction temperature is not viable.

Table 2.4: Hydroamination reactivity at 65 °C, 40 °C, and room temperature.

<table>
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<tr>
<th>Entry</th>
<th>Proligand</th>
<th>T (°C)</th>
<th>t (h)</th>
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</table>
Room temperature intramolecular hydroamination of olefins is well-established for rare-earth, late metal, and alkali metal catalysts.\textsuperscript{2} In contrast, there have only been only a few such reports for group 4 systems, from Sadow\textsuperscript{28,31,104} and Schafer.\textsuperscript{29,103} It is important to note that the work of Sadow and co-workers is based upon a zwitterionic complex in which the zirconium centre carries a formal positive charge. The postulated mechanism of this zwitterionic complex is through a proton-assisted C-N bond formation, which more closely resembles the postulated mechanisms for rare-earth and alkali metal systems.

In contrast, the vast majority of neutral, non-zwitterionic group 4 systems are postulated to proceed through a [2+2] cycloaddition mechanism to form a metallacyclic intermediate. Three titanium complexes bearing bulky 2-aminopyridinate ligands have recently been reported for the cyclization of 2,2-diphenyl-5-hexenamine at room temperature.\textsuperscript{103} Conversion to a piperidine product is found in amounts from 5-86% after 24 hours. In addition, homoleptic complexes Ti(NMe\textsubscript{2})\textsubscript{4} and Zr(NMe\textsubscript{2})\textsubscript{4} were also capable of cyclizing 2,2-diphenyl-5-hexenamine at room temperature, in yields of 50% and 27%, respectively, after 24 hours. While not unique, the ability to catalyze hydroamination at room temperature using a neutral group 4 complex remains rare.

In previous studies with complex \textbf{9}, the highest ee values were obtained for 2,2-dimethyl-4-pentenamine. Unfortunately, attempts to cyclize this aminoalkene substrate resulted in limited product formation with all of the brominated proligands in this study, a surprising finding considering the increased reactivity with the diphenyl-substituted aminoalkene. However, due to the fact that the enantioselectivities obtained with 2,2-diphenyl-4-
pentenamine were not outstanding, exploring further possible proligand modifications was prioritized over extensive substrate scope investigations.

2.3.3.3 Enantioselectivity of Brominated Bis(amidate) Zirconium Complexes for Alkene Hydroamination

For previous biphenyl-tethered bis(amidate) zirconium catalysts developed in the Schafer group, the model generated to rationalize the observed enantioselectivity (Figure 2.3) has postulated that the observed asymmetry in the product is caused by a steric interaction between the substrate and the carbonyl substituent of the amidate ligand. Many different proligands derived from 2,2ʹ-diamino-6,6ʹ-dimethylbiphenyl (16) have been synthesized, varying only in the substituent attached to the carbonyl of the amides. In catalyst screening experiments, the observed ee varied widely depending on the size and substitution pattern of the carbonyl substituent.

In contrast, the four zirconium complexes generated using brominated bis(amide) proligands in this study showed very little variation in ee during catalyst screening experiments (Table 2.3). All four proligands yielded products with ee’s from 52-55%. Given the ±2% accuracy of NMR integration the enantioselectivity of the ligands can be deemed to fall within experimental error and are independent of the substituent on the carbonyl.

The two solid state structures obtained (Figures 2.9 and 2.10) can be examined for more insight into possible ligand conformations. In both the dimeric structure with a κ⁴-bound ligand and the monomeric structure with a κ²-bound ligand, the phenyl groups attached to the carbonyls adopt a position which is fairly distant from the metal centre, making an
interaction with the substrate unlikely. In contrast, the 3,3’-bromine substituents of the biphenyl backbone are directed near the metal centre in both the dimeric and monomeric structures and an interaction between those bromine substituents and an axially-bound substrate molecule\textsuperscript{[78]} is the most likely cause of the observed enantiomeric selectivity.

To further explore this hypothesis, 2,2’-diamino-5,5’- dibromo-6,6’-dimethylbiphenyl (28) was synthesized by reaction of 2,2’-diamino-6,6’-dimethylbiphenyl with 2 equivalents of \( N \)-bromosuccinimide (Scheme 2.6). This new backbone was subsequently reacted with 2 equivalents of 3,5-bis(trifluoromethyl)benzoyl chloride to make 29, an analogue of proligand 27. 2,2’-Diamino-5,5’- dibromo-6,6’-dimethylbiphenyl was also reacted with 2 equivalents of 2,4,6-trimethylbenzoyl chloride to make 30, an analogue of the ligand in complex 9.

\[
\begin{align*}
\text{(+)-enantiomer} & \quad \text{NBS} \quad \text{THF} \quad \text{RCOCI (2 equiv.)} \quad \text{pyridine} \quad 1,2\text{-dichloroethane} \quad 110 \degree C \\
\text{(+)-28} & \quad \text{Br} \quad \text{NH}_2 \quad \text{Br} \quad \text{Br} \\
\text{(+)-29} & \quad \text{Br} \quad \text{NH}_2 \quad \text{Br} \quad \text{Br} \quad \text{RCO}_2 \quad \text{R} = 3,5\text{-(CF}_3\text{)}_2\text{C}_6\text{H}_3 \quad \text{(68\%)} \\
\text{(+)-30} & \quad \text{Br} \quad \text{NH}_2 \quad \text{Br} \quad \text{Br} \quad \text{RCO}_2 \quad \text{R} = 2,4,6\text{-(CH}_3\text{)}_3\text{C}_6\text{H}_2 \quad \text{(38\%)}
\end{align*}
\]

**Scheme 2.6:** Synthesis of 5,5’- dibrominated bis(amide) proligands.

Attempts to synthesize zirconium complexes with proligand 30 were unsuccessful; an equimolar mixture of 30 and \( \text{Zr(NMe}_2\text{)}_4 \) in benzene contained undissolved solid and the \textsuperscript{1}H NMR spectra of the mixture indicated the presence of unreacted proligand. However, \textit{in situ} reactivity with proligand 29 was possible (Scheme 2.7). The results demonstrated reasonable reactivity, though much slower than with proligand 27. The ee of the product
(10%) was also much lower than with proligand 27, or with any of the proligands with bromine substituents in the 3,3'-positions of the biphenyl tether. This result provides strong support for the important effect of the bromine substituents in the 3,3'-positions of the biphenyl tether for both the reactivity and enantioselectivity observed with the brominated bis(amide) proligands 24-27. It is proposed that a steric interaction between the substrate and the bromines in the 3,3'-positions results in asymmetric product formation (Figure 2.11).

Scheme 2.7: Hydroamination, under in situ catalyst formation, with proligand (+)-29.

Figure 2.11: Model for selectivity with ligands containing bromines in the 3,3'-positions of a biphenyldiamine tether.
2.4 Further Modification of Bis(amide) Proligands Derived from 2,2'-Diamino-6,6'-dimethylbiphenyl

While bromine substitution at the 3,3'-positions of the biphenyldiamine backbone did result in increased reactivity, it also suffered drawbacks such as lack of substrate scope and a fixed enantioselectivity range. The installation of alternate substituents at the 3,3'-positions may help to address these issues by creating different steric and electronic environments.

2.4.1 Pd-catalyzed Arylation at the 3,3'-Positions of 2,2'-Diamino-6,6'-dimethylbiphenyl

A Pd-catalyzed protocol developed by Stahl and co-workers offered an alternate method of modifying the 3,3'-positions of the biphenyl backbone. Their method involves using the amide functionality as a directing group to preferentially functionalize the C-H bond ortho to the amide. Using this approach, a bis(pivaloyl) derivative of 2,2'-diamino-6,6'-dimethylbiphenyl (31) was functionalized with phenyl groups in the 3,3'-positions (Scheme 2.8) to form 32. This proligand was characterized by $^1$H NMR spectroscopy and mass spectrometry. This represents a new synthetic strategy for modification of bis(amide) proligands. Previously, proligand modifications were made to amines or acids (as precursors to acid chlorides), before the formation of the amide bond. Stahl’s use of the amide as a directing group allows for proligand modification after the amide bond is already formed.
Scheme 2.8: Pd-catalyzed ortho-functionalization of a bis(amide) proligand.

Figure 2.12: ORTEP representation of the solid-state molecular structure of 33 (ellipsoids plotted at 50% probability). All H-atoms omitted for clarity.
Proligand \( \text{32} \) was thoroughly dried at 70 °C \textit{in vacuo} for 16 hours and brought into a glovebox. Formation of a zirconium complex \textit{via} protonolysis by mixing an equimolar mixture of \( \text{32} \) and Zr(NMe\(_2\))\(_4\) in benzene resulted in a discrete, monomeric complex \( \text{33} \) adopting a previously postulated κ\(^3\) coordination mode with one amidate bound through both N and O, and the other O-bound only (Figure 2.12). This tridentate coordination is likely due to the greatly increased steric bulk on the biphenyl backbone. The presence of two inequivalent singlets for the tBu groups, as well as two inequivalent methyl singlets attached to the biphenyl backbone in the \(^1\)H NMR spectra supports the ligand’s asymmetric binding in the solution phase as well.

The geometry around the metal centre is best approximated as pseudo-tetrahedral, if the N,O chelate is considered as a single point of coordination. In the solid state, the bond length between the ligand and the metal centre was 2.0116(14) Å for the O-bound Zr-O2 and 2.1705(16) Å and 2.2828(17) Å for the chelated Zr-O1 and Zr-N1, respectively.

The dihedral angle between the planes of the two phenyl rings of the biphenyl tether is 92.4°, which falls between the values for the observed for the κ\(^2\) (64.8°) and κ\(^4\) (109.7°) structures derived from proligand \( \text{25} \) and also greater than the value for complex \( \text{9} \) (74.9°).\(^{[41]} \) The tridentate ligand does create an asymmetric environment around the metal centre, making it possible to carry out asymmetric reactions. Hydroamination using catalyst (+)-\( \text{33} \) was undertaken at 110 °C, resulting in reactivity that was uniformly slow, with reaction times exceeding 48 hours to cyclize 2,2-diphenyl-4-pentenamine (\( \text{21} \)). Despite the low reactivity, the ee of the isolated pyrrolidine product was 65%. Reactivity
with other substrates was even slower, limiting the substrate scope and further investigations of this catalyst.

**2.5 Summary**

A variety of bis(amidate) zirconium complexes based on an axially chiral biphenyl backbone were tested for enantioselective intramolecular alkene hydromination. Building upon an established biphenyl-based catalyst 9, modifications were made to the carbonyl moiety, and to the biphenyl backbone itself. The absolute stereochemistry of 2,2’-diamino-6,6’-dimethylbiphenyl was confirmed by X-ray crystallography and an updated model for enantioselectivity was generated.

Three new bis(amide) proligands derived from 2,2’-diamino-6,6’-dimethylbiphenyl containing alternate phenyl-based groups at the carbonyl moiety were synthesized and used to make zirconium complexes. The resulting metal compounds were not discrete monomeric species; it is likely that multiple species and coordination modes were present in the solution phase. These zirconium complexes were screened for enantioselective alkene hydroamination but exhibited poor reactivity and selectivity. With 9 established as the most effective catalyst, kinetic data was collected which indicated that the rate-determining step of the catalytic cycle is first-order in substrate and first-order in catalyst, consistent with established mechanistic proposals for hydroamination with neutral group 4 complexes.

Bromination of 2,2’-diamino-6,6’-dimethylbiphenyl resulted in a new compound, 2,2’-diamino-3,3’,5,5’-tetrabromo-6,6’-dimethylbiphenyl (23). Four new bis(amide) proligands were synthesized from this brominated biphenyl tether. When the proligands
were combined with Zr(NMe$_2$)$_4$, the resulting zirconium complexes displayed a high degree of fluxionality in solution. Despite this, two separate solid state molecular structures of a zirconium complex bearing the same bis(amidate) ligand were generated. One was a dimeric structure featuring the ligand adopting a $\kappa^4$-binding mode with one of the oxygen atoms acting as a bridge between metal centres. The other was a monomeric structure featuring the ligand adopting a $\kappa^2$-binding mode bound only through the oxygen atoms of the amidates and incorporating two equivalents of a neutral pyridine donor. The distinctly different coordination modes obtained using the same ligand provides support for multiple interchangeable conformations present in the solution phase.

Proligand screening for enantioselective hydroamination was undertaken. Generation of the zirconium catalyst species in situ was evaluated and found to be viable. In situ hydroamination reactions revealed promising low-temperature reactivity, including hydroamination activity in some cases at room temperature, though the substrate scope was very limited. Observed enantioselectivities were modest, but consistent, suggesting that the enantioselectivity is transferred from catalyst to substrate through the 3,3′-bromine substituents. A ligand derived from a 5,5′-dibrominated biphenyl tether was synthesized and tested for catalytic hydroamination. In the absence of bromines in the 3,3′-positions, the reaction time quadrupled and the enantioselectivity decreased significantly, indicating that those bromine substituents play a large role in both the reactivity and enantioselectivity of the tetrabrominated proligand set.
An example of a modified backbone with phenyl groups resulted in a stable \( \kappa^3 \) coordination of the ligand, which demonstrated good enantioselectivity, but limited substrate scope.

### 2.6 Conclusions

The original goal in the development of new proligands and zirconium complexes was to build off of the success achieved by catalyst 9 through subtle, but targeted alterations to the steric and electronic environment around the metal centre. Although the steric modifications made in the design of proligands 17-19 were small (substitution of CH\(_3\) groups with CH(CH\(_3\))\(_2\), Br, or H), those changes resulted in a significant detrimental effect on the formation of well-defined zirconium complexes. This, in turn, resulted in poor catalytic competence and enantioselectivity during intramolecular alkene hydroamination trials. Seemingly minor adjustments of the proligand’s steric profile caused considerable detriment to overall catalyst stability and competence. Since the kinetic results collected for catalyst 9 indicated a first-order rate dependence on catalyst concentration, these results underline both the difficulty and importance of achieving a stable, well-defined zirconium complex to realize optimal performance for hydroamination catalysis.

Likewise, the addition of electron-withdrawing bromine substituents to the 3,3’-positions of a 2,2’-diamino-6,6’-dimethylbiphenyl tether had unintended consequences for zirconium complex formation. While the addition of electron-withdrawing groups did result in accelerated hydroamination reactivity as hoped, it also resulted in far less robust binding of the ligand to the zirconium centre, leading to fluxional complexes in solution.
and lowered enantioselectivity. Meanwhile, the substitution of phenyl in the 3,3′-positions resulted in a stable, monomeric complex that exhibited improved enantioselectivity over its bromine-substituted counterparts, but much lower reactivity. Electronic modification of these bis(amide) proligand systems may involve inevitable trade-offs between enantioselectivity and reactivity such that attempting to augment both simultaneously through electronic proligand modifications may require a more rigid tether to ensure a stable bonding environment around the metal centre.
2.7 Experimental

General Experimental Procedures

Except where noted, syntheses of proligands were carried out in ambient atmosphere. All other reactions were carried out using oven-dried glassware under an atmosphere of dry N₂ using Schlenk or glovebox techniques. Benzene was sparged with nitrogen and purified using a column of activated alumina. d₆-Benzene was degassed by several freeze-pump-thaw cycles and dried over 4Å molecular sieves before use. All common, commercially-available reagents were purchased from Sigma Aldrich. Tetrakis(dimethylamido)zirconium was purchased from Strem and used as received. Synthesis and resolution of 2,2'-diamino-6,6'-dimethylbiphenyl (16) was performed according to literature procedures.¹⁴¹ Substrate 2,2'-diphenyl-4-pentenylamine (21) and cyclized product 2-methyl-4,4'-diphenylpyrrolidine (22) are previously reported.³⁶¹ ¹H, ¹³C and ¹⁹F NMR spectra were recorded using Bruker Avance 300 MHz, 400 MHz, or 600 MHz spectrometers, with chemical shifts given relative to the residual solvent peak. Mass spectra were recorded on either a Kratos MS-50 spectrometer using a 70 eV electron impact source or a Bruker Esquire~LC using an electrospray ionization source. Elemental analysis was recorded on a Carlo Erba Elemental Analyzer EA 1108. Single crystal X-ray structure determinations were obtained using a Bruker APEX II.

Synthesis of 15

To a solution of (−)-2,2’-Diamino-6,6’-dimethylbiphenyl (0.100 g, 0.47 mmol) in dichloromethane (5 mL) was added triethylamine (0.119 g, 1.1 mmol), followed by (1S)-(+)-camphor-10-sulfonyle chloride (0.248 g, 0.99 mmol). The reaction mixture was stirred
at room temperature for 6 hours. An additional portion of dichloromethane (5 mL) was added, then the reaction mixture was washed with 1M HCl (1 x 10 mL), 1M NaOH (1 x 10 mL), and brine (1 x 10 mL). The organic portion was dried over MgSO₄, filtered through a Büchner funnel, and the solvent removed using rotary evaporation. The crude product was recrystallized from a mixture of acetone and hexanes to produce colourless crystals which were used for X-ray diffraction analysis.

**Synthesis of 17**

To a solution of (±)-2,2'-diamino-6,6'-dimethylbiphenyl (0.250 g, 1.18 mmol) in 1,2-dichloroethane (10 mL) was added pyridine (0.200 g, 2.52 mmol), followed by gradual addition of benzoyl chloride (0.350 g, 2.49 mmol) over 10 minutes. The mixture was heated to reflux, with stirring, for 1 hour. Volatiles were removed using rotary evaporation and the remaining solid was dissolved in diethyl ether (150 mL), and then washed with 1M NaOH (2 x 50 mL), 1M HCl (2 x 50 mL), and brine (1 x 50 mL). The organic portion was dried over MgSO₄, filtered through a Büchner funnel, and the solvent removed using rotary evaporation. The crude product was recrystallized from hexanes and ethyl acetate, resulting in colourless crystals.

Yield: 0.290 g (55%). ¹H NMR (CDCl₃, 300 MHz) δ 2.05 (6H, s, Ar-CH₃), 7.23 (2H, d, Ar-H), 7.33 (4H, m, Ar-H), 7.40-7.49 (8H, m, Ar-H), 7.70 (2H, s, N-H), 8.43 (2H, d, Ar-H); ¹³C NMR (CDCl₃, 75 MHz) δ 19.3, 119.5, 126.1, 126.8, 128.9, 129.8, 129.8, 132.0, 134.5, 136.2, 137.6. MS(EI) m/z 420 (M+); Elemental Analysis Calcd for C₂₉H₂₄N₂O₂: C, 79.98; H, 5.75; N, 6.66. Found: C, 79.67; H, 5.71; N, 6.60.
Synthesis of 18

To a solution of (±)-2,2'-diamino-6,6'-dimethylbiphenyl (0.100 g, 0.47 mmol) in 1,2-dichloroethane (10 mL) was added pyridine (0.400 g, 5.1 mmol), followed by 2,4,6-triisopropylbenzoyl chloride (0.750 g, 2.83 mmol). The mixture was heated to reflux, with stirring, for 6 hours. Volatiles were removed using rotary evaporation and the remaining solid was dissolved in dichloromethane (100 mL), then washed with 1M HCl (3 x 75 mL), 1M NaOH (3 x 75 mL), and brine (1 x 75 mL). The organic portion was dried over MgSO₄, filtered through a Büchner funnel, and the solvent removed using rotary evaporation. The crude product was purified using gradient-elution column chromatography (10:1 → 8:1 → 4:1 hexanes/ethyl acetate).

Yield: 0.115 g (36%). ¹H NMR (CDCl₃, 400 MHz) δ 1.15 (12H, d, CH(CH₃)₂), 1.24 (24H, d, CH(CH₃)₂), 1.98 (6H, s, Ar-CH₃), 2.68 (2H, br s, CH(CH₃)₂), 2.87 (4H, m, CH(CH₃)₂), 6.95 (4H, s, Ar-H), 7.21 (2H, d, Ar-H), 7.38 (2H, dd, Ar-H), 7.43 (2H, s, NH), 7.86 (2H, d, Ar-H); ¹³C NMR (CDCl₃, 100 MHz) δ 20.0, 23.9, 34.4, 120.9, 122.6, 127.9, 128.8, 130.8, 133.1, 135.8, 137.3, 149.66, 169.8. MS(EI) m/z 672 (M⁺−1); Elemental Analysis Calcd for C₄₆H₆₀N₂O₂: C, 82.10; H, 8.99; N, 4.16. Found: C, 81.96; H, 9.06; N, 4.29.

Synthesis of 19

Synthesis of 2,4,6-tribromobenzoic acid (20)

Under an atmosphere of N₂, a solution of 1,3,5-tribromobenzene (5.0 g, 15.9 mmol) in dry THF (50 mL) was cooled to −78 °C. A freshly prepared solution of LDA (15.9
mmol) in dry THF was added gradually over a period of 30 minutes. The mixture was stirred for 1 hour at –78 °C. CO₂ was passed through a drying tube and bubbled through the reaction mixture for 45 minutes while allowing the reaction mixture to warm to room temperature. The reaction was quenched with 6M HCl (20 mL) and the organic portion was isolated, and washed with additional portions of 3M HCl (2 x 50 mL). The organic phase was extracted with 3M NaOH (3 x 50 mL). The aqueous phase was isolated and concentrated HCl was added until the solution was strongly acidic. The aqueous solution was extracted with dichloromethane (3 x 50 mL). The organic portion was dried over MgSO₄, filtered through a Büchner funnel, and the solvent removed using rotary evaporation. The crude orange product was used without further purification.

Yield: 3.18 g (56%). ¹H NMR (CDCl₃, 300 MHz) δ 7.75 (2H, s, Ar-H); MS(EI) m/z 358 (M⁺).

**Synthesis of 19**

Under an atmosphere of N₂, a solution of 2,4,6-tribromobenzoic acid (1.0 g, 2.78 mmol) in dry dichloromethane (30 mL) was cooled to 0 °C. Oxalyl chloride (2.12 g, 16.72 mmol) followed by a catalytic amount of N,N-dimethylformamide (5 drops) were added gradually over a period of 10 minutes. The reaction was allowed to warm to room temperature, with stirring, for 30 minutes. Volatiles were removed *in vacuo*. An additional portion of dry dichloromethane (5 mL) was added, and volatiles were once again removed *in vacuo* leaving an orange residue. A solution of (±)-2,2’-diamino-6,6’-dimethylbiphenyl (0.160 g, 0.76 mmol) and pyridine (0.220 g, 2.79 mmol) in dry 1,2-dichloroethane (15 mL) was added to the residue. The mixture was refluxed for 3 hours.
The reaction mixture was filtered through a small portion of silica gel using excess dichloromethane. The organic layer was washed with 1M NaOH (1 x 50 mL), 3M NaOH (3 x 50 mL), 1M NaOH (1 x 50 mL) and brine (1 x 50 mL). The organic portion was dried over MgSO$_4$, filtered through a Büchner funnel, and the solvent removed using rotary evaporation. The crude product was purified using column chromatography (4:1 hexanes/ethyl acetate).

Yield: 0.090 g (13%). $^1$H NMR (CDCl$_3$, 400 MHz) δ 1.98 (6H, s, Ar-CH$_3$), 7.22 (2H, d, Ar-H), 7.37 (2H, d, Ar-H), 7.44 (2H, s, N-H), 7.60 (4H, s, Ar-H), 7.87 (2H, d, Ar-H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 21.2, 121.8, 123.7, 124.9, 129.5, 130.1, 131.5, 135.3, 135.8, 139.0, 139.2, 165.7. MS(EI) $m/z$ 894 (M$^+$); Elemental Analysis Calcd for C$_{28}$H$_{18}$Br$_6$N$_2$O$_2$: C, 37.62; H, 2.03; N, 3.13. Found: C, 37.99; H, 2.18; N, 3.05.

General procedure for NMR-scale intramolecular hydroamination and determination of ee

In a nitrogen-filled glovebox, approximately 0.03 mmol zirconium catalyst was weighed out into a vial and dissolved in 0.5 g C$_6$D$_6$. In a separate vial, 0.3 mmol of the aminoalkene substrate was weighed out. The contents of the two vials were thoroughly mixed, placed in a Teflon-sealed J. Young NMR tube, sealed and removed from the glovebox. The NMR tube was placed in an oil bath heated to the indicated temperature. The reaction was periodically monitored for conversion by $^1$H NMR spectroscopy and when complete, was quenched by opening the seal of the J. Young tube and adding 1 mL of CH$_2$Cl$_2$. The reaction mixture was filtered through a small bed of silica gel, first using 20 mL of a 4:1 hexanes:ethyl acetate eluent to remove the proligand, followed by 20 mL.
of CH₂Cl₂ containing 10% MeOH and 1% NEt₃, which caused the amine product to elute. The product was isolated from the CH₂Cl₂ portion by using rotary evaporation to remove volatiles.

Determination of ee values follows previously published procedures.⁹⁴ Approximately 0.02 mmol of amine product was combined with 0.02 mmol of (S)-(+)−α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride [(S)-Mosher’s acid chloride] and 1 drop of NEt₃ in 1 mL of CH₂Cl₂. The mixture was agitated for 1 minute, then volatiles were removed using rotary evaporation. The Mosher’s amide product was analyzed by ¹H NMR spectroscopy at room temperature, and ¹⁹F NMR spectroscopy at room temperature and at 60 °C.

Synthesis of 23

To a solution of (±)-2,2'-diamino-6,6'-dimethylbiphenyl (1.56 g, 7.3 mmol) in glacial acetic acid (100 mL) was added bromine (10.0 g, 125 mmol). The mixture was stirred at room temperature for 12 hours. The mixture was flushed with N₂ for 2 minutes and then quenched with excess sodium bisulphite until the product fully precipitated from solution. The crude product was isolated using vacuum filtration, dissolved in dichloromethane (50 mL), and washed with 1M NaOH (50 mL) and brine (50 mL). The organic portion was dried over MgSO₄, filtered through a Büchner funnel, and the solvent removed using rotary evaporation. The crude product was obtained as a light orange solid in quantitative yield and used without further purification.
$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.99 (6H, s, Ar-CH$_3$), 3.91 (4H, s, N-H), 7.69 (2H, s, Ar-H).

**Synthesis of 24**

To a solution of (±)-2,2′-diamino-3,3′,5,5′-tetrabromo-6,6′-dimethylbiphenyl (0.75 g, 1.42 mmol) in 1,2-dichloroethane (30 mL) was added pyridine (0.370 g, 4.69 mmol), followed by isobutyryl chloride (0.5 g, 4.69 mmol). The reaction was heated to reflux for 4 hours. The mixture was washed with 1M NaOH (2 x 50 mL), 1M HCl (2 x 50 mL), H$_2$O (1 x 50 mL) and brine (1 x 50 mL), then dried over MgSO$_4$, filtered through a Büchner funnel, and the solvent was removed using rotary evaporation. The crude product was washed repeatedly with cold hexanes until a purified white solid product was obtained.

Yield: 0.801 g (84%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 0.94 (6H, d, CH(CH$_3$)$_2$), 1.00 (6H, d, CH(CH$_3$)$_2$), 2.00 (6H, s, Ar-CH$_3$), 2.33 (2H, sept, CH(CH$_3$)$_2$), 7.93 (2H, s, Ar-H); MS(EI) $m/z$ 668 (M+); Elemental Analysis Calcd for C$_{22}$H$_{24}$Br$_4$N$_2$O$_2$: C, 39.55; H, 3.62; N, 4.19. Found: C, 39.79; H, 4.20; N, 4.20.

**Synthesis of 25**

To a solution of (±)-2,2′-diamino-3,3′,5,5′-tetrabromo-6,6′-dimethylbiphenyl (0.350 g, 0.66 mmol) in 1,2-dichloroethane (20 mL) was added pyridine (0.315 g, 3.98 mmol) followed by a gradual addition over a period of 10 minutes of benzoyl chloride (0.280 g, 1.989 mmol). The reaction was heated to reflux, with stirring, for 5 hours. The solvent was removed by rotary evaporation and the remaining solid was dissolved in
dichloromethane (20 mL) and filtered through a small bed of silica gel. The crude product was washed repeatedly with cold hexanes until a purified product was obtained.

Yield: 0.320 g (66%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.04 (6H, s, Ar CH$_3$), 7.43 (4H, m, Ar-H), 7.53 (2H, m, Ar-H), 7.75 (4H, d, $J$ = 7.31 Hz, Ar-H), 7.91 (2H, s, Ar-H); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 20.1, 121.4, 126.9, 128.3, 131.6, 132.9, 135.6; MS(EI) $m/z$ 736 (M$^+$); HRMS (EI) Calcd for C$_{28}$H$_{20}$Br$_4$N$_2$O$_2$: 731.82582; Found: 731.82503.

**Synthesis of 26**

To a solution of (±)-2,2ʹ-diamino-3,3ʹ,5,5ʹ-tetabromo-6,6ʹ-dimethylbiphenyl (1.0 g, 1.89 mmol) in 1,2-dichloroethane (20 mL) was added pyridine (0.370 g, 7.6 mmol) followed by 4-trifluoromethylbenzoyl chloride (1.6 g, 7.6 mmol). The reaction was heated to reflux, with stirring, for 3 hours. The solvent was removed using rotary evaporation and the remaining solid was dissolved in dichloromethane (20 mL) and filtered through a small bed of silica gel. The crude product was washed repeatedly with cold hexanes until a purified product was obtained.

Yield: 1.327 g (81%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 2.06 (6H, s, Ar-CH$_3$), 7.72 (4H, d, Ar-H), 7.85 (4H, d, Ar-H), 7.95 (2H, s, Ar-H); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 20.8, 121.9, 122.8, 124.6, 126.1, 128.0, 136.5; $^{19}$F NMR (CDCl$_3$, 282 MHz) $\delta$ -63.45; MS(EI) $m/z$ 872 (M$^+$); HRMS (ESI) Calcd for C$_{30}$H$_{19}$N$_2$O$_2$F$_6^{79}$Br$_3^{81}$Br ([M+H]$^+$): 870.8064; Found: 870.8075.

**Synthesis of 27**
To a solution of (±)-2,2'-diamino-3,3',5,5'-tetrabromo-6,6'-dimethylbiphenyl (0.865 g, 1.63 mmol) in 1,2-dichloroethane (20 mL) was added pyridine (0.625 g, 7.9 mmol) followed by 3,5-bis(trifluoromethyl)benzoyl chloride (2.18 g, 7.9 mmol). The reaction was heated to reflux, with stirring, for 4 hours. The solvent was removed using rotary evaporation and the remaining solid was dissolved in dichloromethane (20 mL) and filtered through a small bed of silica gel. The crude product was washed repeatedly with cold hexanes until a purified product was obtained.

Yield: 1.1 g (67%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.08 (6H, s, Ar-CH$_3$), 7.99 (2H, s, Ar-H), 8.05 (2H, s, Ar-H), 8.12 (4H, s, Ar-H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 20.6, 39.9, 117.5, 120.0, 121.8, 123.6, 124.7, 125.4, 127.6, 129.2, 132.4, 132.6, 136.5, 143.4, 176.8; $^{19}$F NMR (CDCl$_3$, 282 MHz) δ −63.37; MS(EI) m/z 1008 (M+); Elemental Analysis Calcd for C$_{32}$H$_{16}$Br$_4$F$_{12}$N$_2$O$_2$: C, 38.13; H, 1.60; N, 2.78. Found: C, 38.49; H, 1.88; N, 2.78.

**General procedure for NMR-scale, in situ, intramolecular hydroamination and determination of ee**

In a nitrogen-filled glovebox, approximately 0.033 mmol of proligand and 0.03 mmol of Zr(NMe$_2$)$_4$ were weighed out into a vial and mixed in 0.5 g C$_6$D$_6$ for 5 minutes, or until the solution was clear. In a separate vial, 0.3 mmol of the aminoalkene substrate was weighed out. The contents of the two vials were thoroughtly mixed, placed in a J. Young NMR tube, sealed and removed from the glovebox. The NMR tube was placed in an oil bath heated to the indicated temperature. The reaction was periodically monitored for conversion by $^1$H NMR spectroscopy and when complete, was quenched by opening the
seal of the J. Young tube and adding 1 mL of CH₂Cl₂. The reaction mixture was filtered through a small bed of silica gel, first using 20 mL of a 4:1 hexanes:ethyl acetate eluent to remove the proligand, followed by 20 mL of CH₂Cl₂ containing 10% MeOH and 1% NEt₃, which caused the amine product to elute. The product was isolated from the CH₂Cl₂ portion by using rotary evaporation to remove volatiles.

Determination of ee values follows previously published procedures.⁹⁴ Approximately 0.02 mmol of amine product was combined with 0.02 mmol of (S)-(+)⁻α-Methoxy⁻α-(trifluoromethyl)phenylacetyl chloride [(S)-Mosher’s acid chloride] and 1 drop of NEt₃ in 1 mL of CH₂Cl₂. The mixture was agitated for 1 minute, then volatiles were removed using rotary evaporation. The Mosher’s amide product was analyzed by ¹H NMR spectroscopy at room temperature, and ¹⁹F NMR spectroscopy at room temperature and at 60 °C.

**Synthesis of 28**

To a solution of (±)-2,2'-diamino-6,6'-dimethylbiphenyl (1.0 g, 4.7 mmol) in THF (10 mL), cooled to 0 °C, was added N-bromosuccinimide (1.68 g, 9.4 mmol). The mixture was stirred vigorously for 2 minutes. A saturated aqueous solution of NaS₂O₃ (10 mL) was added followed by a saturated aqueous NaHCO₃ solution (10 mL). The mixture was stirred for 15 minutes and allowed to warm to room temperature. The reaction mixture was extracted with EtOAc (3 x 50 mL). The organic fractions were combined and washed with brine (1 x 50 mL), then dried over MgSO₄, filtered through a Büchner funnel, and the solvent was removed using rotary evaporation. The solid product obtained was used without further purification.
Yield: 1.65 g (95%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.04 (6H, s, Ar-CH$_3$), 3.47 (4H, s, N-H), 6.57 (2H, d, Ar-H), 7.37 (2H, d, Ar-H).

**Synthesis of 29**

To a solution of (±)-2,2'-diamino-5,5'-dibromo-6,6'-dimethylbiphenyl (0.335 g, 0.9 mmol) in 1,2-dichloroethane (20 mL) was added pyridine (0.143 g, 1.8 mmol) followed by 3,5-bis(trifluoromethyl)benzoyl chloride (0.5 g, 1.8 mmol). The mixture was heated to reflux, with stirring, for 2 hours. The reaction mixture was filtered through a small portion of silica gel using excess dichloromethane. The solid product was washed repeatedly with cold hexanes until a purified product was obtained.

Yield: 0.520 g (68%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.11 (6H, s, Ar-CH$_3$), 7.73 (4H, m, Ar-H), 7.94 (4H, s, Ar-H), 7.97 (2H, s, Ar-H), 8.22 (2H, s, Ar-H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 20.5, 121.3, 123.4, 123.5, 124.0, 125.7, 127.2, 131.0, 132.4, 134.0, 134.2, 137.4, 163.3; $^{19}$F NMR (CDCl$_3$, 282 MHz) δ −63.4. MS(EI) m/z 850 (M+); HRMS (ESI) Calcd for C$_{32}$H$_{19}$N$_2$O$_2$F$_{12}$Br$_2$ ([M+H]$^+$): 848.9622; Found: 848.9609.

**Synthesis of 30**

To a solution of (±)-2,2'-diamino-5,5'-dibromo-6,6'-dimethylbiphenyl (0.5 g, 1.35 mmol) in 1,2-dichloroethane (25 mL) was added pyridine (0.320 g, 4.05 mmol) followed by 2,4,6-trimethylbenzoyl chloride (0.738 g, 4.05 mmol). The mixture was heated to reflux, with stirring for 6 hours. The mixture was cooled and filtered through a small portion of silica gel using excess dichloromethane. The solvent was removed using rotary
evaporation and the crude product was purified using column chromatography (4:1 hexanes/ethyl acetate) followed by a dichloromethane/hexanes layered recrystallization.

Yield: 0.335 g (38%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.06 (6H, s, Ar-CH$_3$), 2.09 (12H, s, Ar-CH$_3$), 2.24 (6H, s, Ar-CH$_3$), 6.78 (4H, s, Ar-H), 7.18 (2H, s, Ar-H), 7.67 (2H, d, Ar-H, J=8.7Hz), 7.78 (2H, d, Ar-H, J=8.7Hz). $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 18.8, 20.5, 21.0, 122.9, 124.4, 128.4, 132.3, 133.4, 134.0, 134.1, 134.8, 137.1, 139.0, 169.7; MS(EI) $m/z$ 662 (M+).

**Synthesis of 32**

To a solution of the bis(pivaloyl) derivative of 2,2'-diamino-6,6'-dimethylbiphenyl (0.380 g, 1 mmol) in trifluoroacetic acid (3 mL) was added Pd(OAc)$_2$ (34 mg, 0.15 mmol), iodobenzene (1.02 g, 5 mmol), and AgOAc (384 mg, 2.3 mmol). The reaction was heated to reflux, with stirring, for 4 hours. The mixture was cooled to room temperature and toluene (10 mL) was added. The mixture was filtered through Celite and volatiles removed *in vacuo*. The crude product was purified using gradient-elution column chromatography (8:1 → 4:1 → 2:1 hexanes/ethyl acetate).

Yield: 0.300 g (56%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 0.81 (18H, s, C(CH$_3$)$_3$), 2.00 (6H, s, Ar-CH$_3$), 7.28-7.45 (14H, m, Ar-H); MS(EI) $m/z$ 532 (M+); HRMS (EI) Calcd for C$_{36}$H$_{40}$O$_2$N$_2$ (M+): 532.30898; Found: 532.30884.
Chapter 3: Development of New Bis(ureate) Bis(amido) Zirconium Catalysts for Secondary Amine Hydroamination

3.1 Introduction

Although work on group 4 hydroamination catalysts has been underway for some time, one specific area where group 4 catalysts fall short of their late metal or rare earth counterparts is in amine substrate scope: group 4 catalysts have largely been limited only to primary amine substrates. This fact is not surprising when viewed in the context of the catalytic cycle for neutral group 4 complexes, which is postulated to proceed through a metal-imido intermediate, followed by a [2+2] cycloaddition of the metal-imido and the C-C multiple bond. Because secondary amines cannot form the M=N imido species necessary for the reaction to proceed, these substrates were long believed to be catalytically inert with neutral group 4 systems.

Figure 3.1: Cationic zirconium complexes for secondary amine hydroamination.

35a: \( R = H, \ X^- = \text{MeB}(C_6F_5)_3^- \)
35b: \( R = H, \ X^- = B(C_6F_5)_4^- \)
35c: \( R = \text{Me}, \ X^- = \text{MeB}(C_6F_5)_3^- \)
35d: \( R = \text{Me}, \ X^- = B(C_6F_5)_4^- \)
Table 3.1: Enantioselective secondary amine hydroamination with a cationic zirconium catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>$t$ (h)</th>
<th>ee (%)$^b$</th>
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</thead>
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<td><img src="image2" alt="Product 1" /></td>
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<td>64</td>
</tr>
<tr>
<td>2$^a$</td>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
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<td><img src="image7" alt="Substrate 4" /></td>
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<td>nd</td>
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<tr>
<td>5</td>
<td><img src="image9" alt="Substrate 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>3</td>
<td>20</td>
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</tbody>
</table>

$^a$ 5 mol% catalyst, 70 °C. 30% alkene isomerisation product.  
$^b$ NMR analysis of (R)-(+)‐Mosher’s acid salt.

A small number of cationic zirconium complexes capable of cyclizing secondary amine substrates have been reported thus far (Figure 3.1). Complex 34, developed by Scott and co-workers, cyclized five secondary aminoalkene substrates, at temperatures
from 70-100 °C with reaction times from 3-192 h (Table 3.1). Owing to the fact that the bis(aminophenol) ligand in 34 was derived from 2,2'-diamino-6,6'-dimethylbiphenyl, an axially-chiral molecule, the zirconium complexes were also formed as chiral compounds, achieving ee’s up to 82%.

A series of achiral cationic zirconium metallocenes (35a-d) were developed by Hultzsch and co-workers. Four secondary aminoalkene substrates containing either N-methyl or N-benzyl groups were cyclized with as little as 1 mol% catalyst at temperatures from 80-100 °C. The catalysts containing Cp groups (35a,b) were far more active than their Cp*-containing counterparts (35c,d). A cationic titanocene catalyst was also tested but displayed poor reactivity. Cationic zirconium catalyst 36 with a tridentate O,N,S ligand was reported in 2011 by Tang et al. and was successful in cyclizing eight secondary aminoalkene substrates with consistently high yields (82-98%). This catalyst was used as a racemate and thus enantioselective hydroamination was not explored.

However, because 34-36 are cationic complexes, they may not mediate hydroamination through the same mechanism as a neutral zirconium catalyst. Instead, they have been proposed to proceed through a σ-bond insertion pathway, a mechanism originally proposed for lanthanide hydroamination catalysts rather than the [2+2] cycloaddition pathway proposed for neutral group 4 systems. In fact, no catalytic activity was observed with 34 or 35a-d in the presence of primary aminoalkene substrates. This was attributed to the formation of a zirconium imido species, which is catalytically inactive in the σ-bond insertion pathway. Complex 36 was catalytically active towards primary amine substrates and attempts to generate a zirconium imido species resulted only in the
formation of bis(amido) species. It was concluded that catalysis likely proceeds through a zirconium-amido species for both primary and secondary amine substrates.\textsuperscript{[106]} For neutral group 4 catalysts, formation of a zirconium imido species is an integral part of the catalytic cycle, a necessary precursor to the [2+2] cycloaddition step which forms the new C-N bond. Although 34-36 are zirconium complexes capable of secondary amine hydroamination, direct comparisons should not be made between cationic group 4 complexes and neutral group 4 complexes.

Recently, a limited number of neutral group 4 systems capable of cyclizing secondary aminoalkenes have also been reported (Figure 3.2).\textsuperscript{[21,24–28,31]} Hydroamination results for these catalysts with a common aminoalkene substrate are summarized in Table 3.2. Of particular note is that Zr(NMe\textsubscript{2})\textsubscript{4} is a competent catalyst for the cyclization of N-methyl-2,2-diphenyl-4-pentenamine,\textsuperscript{[27]} though Ti(NMe\textsubscript{2})\textsubscript{4} is not.\textsuperscript{[36]} Catalyst 10 has an overall neutral charge, but is more accurately viewed as a zwitterionic compound with a formal positive charge on the metal centre and a formal negative charge on the boron atom. Complex 10 is also a chiral catalyst, capable of producing enantiomerically enriched hydroamination products.\textsuperscript{[28,31]} However, the ee of the pyrrolidine product resulting from the cyclization of N-methyl-2,2-diphenyl-4-pentenamine was not determined. While a dipyrrrolylmethane complex 6 from the Odom group,\textsuperscript{[27]} imidazolonate dimer 8 from Ong and co-workers,\textsuperscript{[25]} half-sandwich complexes 37 from Marks,\textsuperscript{[21]} and metallocene complex 38 from Doye\textsuperscript{[26]} (Figure 3.2) have all been used for secondary amine hydroamination, none of the reports included more than 2 examples of secondary amine substrates that could be cyclized. For the most part, the catalysts in Figure 3.2 were
limited to one or two substrates and did not show general competence for secondary amine hydroamination.

In contrast, a neutral bis(ureate) zirconium complex developed in the Schafer group, 2, was shown to be much more broadly effective for hydroamination with a variety of challenging primary and secondary aminoalkene substrates in good yields (Tables 1.4 and 1.5, *vide supra*). It can also perform intermolecular hydroamination of alkynes with secondary amines such as piperidine and morpholine.

**Figure 3.2:** Neutral group 4 catalysts capable of hydroamination with secondary amine substrates.
Table 3.2: Hydroamination of \(N\)-methyl-2,2-diphenyl-4-pentenamine with neutral group 4 catalysts.

![Chemical structure](image_url)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>mol%</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>(t) (h)</th>
<th>conv. (%)</th>
<th>TOF (h(^{-1}))</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{Zr(NMe}_2\text{)}_4)</td>
<td>5</td>
<td>(\text{C}_7\text{D}_8)</td>
<td>150</td>
<td>12</td>
<td>&gt;98</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>10(^a)</td>
<td>(\text{C}_6\text{D}_6)</td>
<td>rt</td>
<td>1</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>5</td>
<td>(\text{C}_7\text{D}_8)</td>
<td>150</td>
<td>120</td>
<td>35(^b)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>5</td>
<td>(\text{C}_7\text{D}_8)</td>
<td>130</td>
<td>19</td>
<td>88</td>
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<td>24</td>
<td>13</td>
<td>-</td>
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<tr>
<td>8</td>
<td>2</td>
<td>10</td>
<td>(\text{C}_6\text{D}_6)</td>
<td>100</td>
<td>4</td>
<td>&gt;98</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) Required the use of 10-30 mol% of \(n\text{PrNH}_2\) as additive. \(^b\) 34% of a dehydrogenated \(N\)-heterocyclic side product was also formed in the reaction mixture.
3.2 New Bis(ureate) Zirconium Complexes for Secondary Amine Hydroamination

While catalyst 2 has been studied in depth,[24,29,30] the majority of group 4 catalysts remain unable to promote hydroamination with secondary aminoalkene substrates. Development of related catalysts with similar expanded substrate scope was identified as a priority, as was the development of an enantioselective variant to take advantage of the availability of a new class of substrates. These new compounds were synthesized to further probe the possibilities of bis(ureate) catalyst systems for challenging primary and secondary amine substrates. Notably, related bis(amidate) catalysts developed in the Schafer group cannot mediate cyclohydroamination of secondary amine substrates.

3.2.1 Synthesis of New Bis(urea) Proligands

Three new tethered bis(urea) proligands were designed and synthesized (Figure 3.3). Two of the new proligands (41 and 42) are based on an axially-chiral 2,2’-diamino-6,6’-dimethylbiphenyl backbone, allowing for the possibility of enantioselective hydroamination of secondary amine substrates. This biphenyl tether has been used to construct the bis(aminophenol) ligand in cationic zirconium complex 34, which has been used successfully for enantioselective hydroamination of secondary aminoalkenes.[32] Proligand 43 utilizes the 2,2-dimethyl-1,3-propanediamine tether used in the bis(ureate) ligand of compound 2, but replaces the diisopropylamino substituents with a more rigid cis-2,6-dimethylpiperidinyl substituent. Although this proligand is not chiral, synthesis of this proligand was desired in order to see what effect using a cyclic amine in place of diisopropylamine would have on the bonding, structure, and reactivity of the resulting zirconium complex. Proligand 44 (Figure 3.3) is a bis(amide) proligand that has previously been installed on zirconium for the catalytic hydroamination of primary
amines. A zirconium complex 9 synthesized from proligand 44 had been tested once previously for hydroamination with N-methyl-2,2-diphenyl-4-pentenamine,[87] and was found to be unreactive. However, the recent advances in secondary amine hydroamination and ready availability of secondary aminoalkene substrates in the Schafer group warranted further probing of this compound’s substrate scope.

![Chemical structures](image)

**Figure 3.3**: New bis(urea) proligands.

The synthesis and full characterization of proligand 41 has been reported in a PhD thesis by Dr. David Leitch of the Schafer group.[108] In that work, 41 was primarily used to generate zirconium alkyl complexes for ethylene polymerization. The related bis(ureate) bis(amido) zirconium complex was screened for hydroamination but in depth applicability towards secondary amine hydroamination was not pursued. Proligand 41 was synthesized using a two-step procedure illustrated in Scheme 3.1. First, 2,2′-diamino-6,6′-dimethylbiphenyl was dissolved in dry dichloromethane, then treated with two equivalents of phenyl chloroformate in the presence of triethylamine, forming a bis(phenylcarbamate) intermediate containing phenol leaving groups. Isolation of the
crude, oily intermediate and subsequent treatment with excess diisopropylamine in DMSO resulted in the formation of the bis(urea). The crude product was purified by filtration through a small bed of silica gel, then recrystallization from a minimum amount of ethyl acetate. The colourless crystals formed were analyzed by $^1$H NMR spectroscopy and mass spectrometry and were shown to match existing characterization data.\textsuperscript{[108]}

**Scheme 3.1:** Two-step synthesis of bis(urea) proligand 41.

Proligand 42 was synthesized from 2,2′-diamino-6-6′-dimethylbiphenyl using the same two step procedure as proligand 41, replacing isopropylamine with cis-2,6-dimethylpiperidine in the second step. The crude product was purified by filtration through a small bed of silica gel and characterized using $^1$H and $^{13}$C NMR spectroscopies, mass spectrometry, and elemental analysis to confirm its identity. The $^1$H NMR spectra contained two inequivalent doublets corresponding to the methyl groups on the piperidine substituent indicating two distinct chemical environments for the methyl groups. The methine protons of the piperidine rings also appeared as overlapping multiplets, another indication of different chemical environments. A broad multiplet from 1.35-1.70 integrating to 12 protons resulted from the methylene protons of the piperidine ring. An
N-H signal was observed at δ 6.22 ppm, and the aromatic region contained two well-defined doublets and a doublet of doublets, an expected pattern resulting from the protons of the biphenyl tether.

Proligand 43 was synthesized from 2,2-dimethyl-1,3-propanediamine using the same two step procedure as proligand 41, replacing diisopropylamine with cis-2,6-dimethylpiperidine in the second step. The crude product was purified by filtration through a small bed of silica gel and fully characterized. Unlike 42, the 1H NMR spectra of 43 contained only one doublet corresponding to the methyl groups on the piperidine substituent. The N-H signal is shifted upfield to δ 5.70 ppm compared to the proligands based upon the biphenyl tether. Finally, bis(amide) proligand 44 was synthesized from 2,2′-diamino-6-6′-dimethylbiphenyl using literature procedures.[41]

3.2.2 Synthesis and Structure of Bis(ureate) Zirconium Complexes

Purified proligands were dried in vacuo by heating them to 70 °C overnight and brought into a nitrogen-filled glovebox, then mixed in an equimolar ratio with Zr(NMe₂)₄ in hexanes and/or benzene. Volatiles were removed under reduced pressure to leave a white solid. Recrystallization, where successful, was carried out from hexanes. Structures of the zirconium complexes generated, as determined using X-ray crystallography, are summarized in Figure 3.4.
Complex 45 was analyzed by $^1$H NMR spectroscopy and was found to match existing characterization data.$^{[108]}$ In the solid state, complex 45 adopts a 7-coordinate pentagonal bipyramidal structure (Figure 3.5). The atoms in the equatorial plane of 45 show very little distortion in their bonding; the sum of the angles around the zirconium centre is 359.81°. This binding mode is similar to the structure of complex 2 – there are only subtle differences in bonding between the two. In both complexes, the two ureate moieties and one dimethylamido ligand occupy the equatorial plane while a dimethylamido ligand and a neutrally-bound dimethylamine occupy the axial sites. The Zr-O bonds in 45 (2.2334(19) Å and 2.2417(19) Å) are within experimental error to those of 2 (2.2338(12) Å and 2.2402(12) Å), while the Zr-N bonds to the ureate ligand are longer in 45 (2.291(2) Å and 2.316(2) Å) than in 2 (2.2792(13) Å and 2.2796(14) Å). For compound 45, The Zr-N5 bond to the axial dimethylamido substituent (2.132(2) Å) is longer than the Zr-N6 bond to the equatorial dimethylamido (2.089(2) Å). This is the reverse of compound 2, in which the equatorial Zr-N bond (2.1348(15) Å) is longer than the axial Zr-N bond (2.0924(16) Å). This difference may arise from the variation in how
tightly the bis(ureate) ligand is bound in each compound. The tighter ligand binding in 2 causes a lengthening of the equatorial Zr-NMe₂ bond, while the shortening of the equatorial Zr-NMe₂ bond in 45 is to compensate for the less effective donation from this geometrically-constrained ligand binding environment seen in that compound.

It was found that complex 45 is prone to ligand redistribution, yielding crystals of the 8-coordinate homoleptic complex bearing two tetradeionate bis(urea) ligands. If each N,O chelate is considered as a single substituent, the arrangement in this compound is pseudo-tetrahedral around the metal centre. Ligand disproportionation has been observed in other zirconium hydroamination catalysts with tethered, tetradeionate ligands. This disproportionation can occur thermally, resulting from heating a zirconium complex in solution for a period of time, and produces Zr(NMe₂)₄ along with the homoleptic zirconium complex. All homoleptic complexes have been observed to be catalytically inactive for hydroamination. Notably, homoleptic zirconium species with 2 are not readily formed (Scheme 3.2). Using 2:1 stoichiometry of the bis(urea) proligand used to synthesize compound 2 to the Zr(NMe₂)₄ starting material resulted in a full equivalent of unreacted ligand present in the ¹H NMR spectra of the reaction mixture. Recrystallization of the crude material obtained from the reaction resulted in the crystallization of the uncoordinated bis(urea) proligand. Heating 2 in d₈-toluene to 145 °C resulted in decomposition of the zirconium complex, but no formation of Zr(NMe₂)₄ was observed, precluding ligand disproportionation as the major decomposition pathway.
Figure 3.5: ORTEP representation of the solid-state molecular structure of 45 (top) and homoleptic complex (bottom) (ellipsoids plotted at 50% probability). All H-atoms omitted for clarity.
Scheme 3.2: Previous attempts to synthesize a homoleptic tetra(ureate) zirconium complex.

The $^1$H NMR spectrum of complex 46, like that of proligand 42, contains two inequivalent doublets assigned to the methyl groups of the cis-2,6-dimethylpiperidine substituents, indicating two distinct chemical environments. While the protons of the dimethylamido groups appear as a single broad peak at $\delta$ 3.32 ppm, the aromatic protons of the biphenyl tether are well defined as two doublets at $\delta$ 6.86 and 6.91 ppm, and a doublet of doublets at $\delta$ 7.12 ppm.

In the solid state, 46 was also found to adopt a 7-coordinate, pentagonal bipyramidal configuration in the solid state (Figure 3.6) like compounds 2 and 45. Both ureate moieties of the ligand lie in the equatorial plane along with one of the dimethylamido groups, while another dimethylamido ligand and a neutrally-bound dimethylamine occupy the axial positions. The equatorial plane around zirconium has very little
Figure 3.6: ORTEP representation of the solid-state molecular structure of 46 (top) with a view along the equatorial plane (bottom) (ellipsoids plotted at 50% probability). All H-atoms omitted for clarity.
distortion; the sum of the angles around the equatorial plane is 360.43°. While the two Zr-N bond lengths are identical at 2.297(2) Å for Zr-N1 and 2.298(2) Å for Zr-N2, the Zr-O2 bond length is slightly elongated at 2.2275(18) Å compared to the Zr-O1 bond length of 2.2004(18) Å. The angle between the two axial groups is 175.99(10)°, close to ideal. Similar to the solid state structure of 45, the Zr-N5 bond to the axial dimethylamido substituent (2.341(3) Å) in 46 is longer than its Zr-N6 bond to the equatorial dimethylamido (2.085 (2) Å).

The C2-symmetric arrangement of the ligand, and especially of the cis-2,6-dimethylpiperidine groups, is illustrated in the bottom image of Figure 3.6. Interestingly, in order for the methyl groups to lie perpendicular to the plane of the ligand-zirconium chelate, they must occupy the axial positions of the chair-like structure adopted by the piperidine ring resulting in an unfavourable 1,3-diaxial interaction between the methyl groups. It would be reasonable to expect those groups to prefer to sit in equatorial positions in order to minimize that steric strain. However, the electronic profile of ureate ligands allows a monoanionic species to access a number of contributing resonance structures, outlined in Figure 3.7. For such resonance, both the central carbon and the distal nitrogen would adopt a co-planar geometry consistent with $sp^2$-hybridization.

The sum of the angles around the central carbon of the ureate in 46 is 359.9° and the sum of the angles around the piperidine nitrogen is 358.4°, indicating $sp^2$-like hybridization. The C1-N3 bond length is 1.351(3) Å, indicating a high degree of double bond character. Thus, the ureate ligand in 46 adopts a conformation similar to resonance form C in Figure 3.7.
Figure 3.7: Resonance forms of ureate ligands.

While 1,3-diaxial interactions are present in molecules such as piperidine that adopt chair-like conformations, the presence of a double bond also results in allylic strain. Figure 3.8 outlines the possible sources of steric interaction with a delocalized ureate-zirconium structure containing a pseudo-double bond between the central carbon of the ureate and the amine of the piperidine. In conformation A, the methyl groups lie in the equatorial positions of the piperidine ring. While this minimizes 1,3-diaxial interactions, it creates a significant amount of allylic strain between the methyl group and the N,O groups attached to the zirconium centre. In conformation B, the methyl groups lie in the axial positions of the piperidine ring. While it does create a 1,3-diaxial interaction, the allylic strain is minimized.

Figure 3.8: Possible orientations of the piperidine ring in a delocalized ureate structure.
The results showing the methyl groups of cis-2,6-dimethylpiperidine in axial positions are consistent with previous studies that have been carried out on the conformation of cyclic amides with 2,6-substituents. These reports also show that the substituents prefer the axial positions both in solution, and in the solid state.\textsuperscript{109,110}

Interestingly, complex 47 crystallized as a dimeric species with bridging dimethylamido groups (Figure 3.9). In solution, the \textsuperscript{1}H NMR spectrum of complex 47 contains two inequivalent doublets, each integrating to 6 protons, corresponding to the methyl groups of the cis-2,6-dimethylpiperidine substituents. This is different from the \textsuperscript{1}H NMR spectra of its proligand 43, in which only one doublet integrating to 12 protons is present. Inequivalent signals are also present for the methyl groups of the propyl tether, further indicating that binding of the ligand to zirconium results in a fixed orientation. In general, the alkyl peaks of the propyl tether and the piperidine ring appear as poorly-defined multiplets. The dimeric structure gives rise to two separate dimethylamido singlets at $\delta$ 3.06 ppm and $\delta$ 3.31 ppm, each integrating to 6 protons.

In the solid state, each zirconium centre in 47 is 7-coordinate, with ligands arranged in a pentagonal bipyramidal fashion. In this orientation, the non-bridging dimethylamido group is in an axial position, while the bridging dimethylamido groups occupy both the axial and equatorial positions. The Zr-O bonds of 47 (2.2004(18) Å and 2.2275(18) Å) are slightly shorter than in compound 2, while the Zr-N bonds to the ligand in 47 (2.297(2) Å and 2.298(2) Å) are slightly longer.
The C1-N3 bond length of 1.359(11) Å indicates significant double bond character between the piperidinyl nitrogen and the central carbon of the ureate. The sum of the angles around N3 is 359.3°, expected for $sp^2$-hybridization of the atom. As in 46, the piperidinyl moiety and the ureate’s N-C-O framework are co-planar, and the methyl groups on the cis-2,6-dimethylpiperidine substituents sit in axial positions of the chair-like ring structure in order to avoid allylic strain. Unlike the C$_2$-symmetry of the ligand in 46, the ligand in 46 exhibits C$_s$-symmetry.
Table 3.3: Comparison of bond lengths of bis(ureate) bis(amido) zirconium solid state molecular structures (bond lengths in Å).

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<tr>
<th>Bond</th>
<th>2\textsuperscript{[24]}</th>
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<th>46</th>
<th>47</th>
<th>9\textsuperscript{[41]}</th>
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<td>2.2334(19)</td>
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<td>2.280(3)</td>
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<td>Zr-O</td>
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<td>2.2417(19)</td>
<td>2.2275(18)</td>
<td>2.229(6)</td>
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<td>2.297(2)</td>
<td>2.221(8)</td>
<td>2.313(4)</td>
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<td>Zr-N (chelate)</td>
<td>2.2796(14)</td>
<td>2.291(2)</td>
<td>2.298(2)</td>
<td>2.231(7)</td>
<td>2.347(4)</td>
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<td>Zr-N (NMe\textsubscript{2}, axial)</td>
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<td>2.132(2)</td>
<td>2.341(3)</td>
<td>2.094(8)</td>
<td>2.065(4)</td>
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<td>Zr-N (HNMe\textsubscript{2}, axial)</td>
<td>2.5030(16)</td>
<td>2.441(3)</td>
<td>2.220(3)</td>
<td>2.360(8)\textsuperscript{a}</td>
<td>2.536(4)</td>
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<tr>
<td>Zr-N (NMe\textsubscript{2}, equatorial)</td>
<td>2.1348(15)</td>
<td>2.089(2)</td>
<td>2.085(2)</td>
<td>2.341(7)\textsuperscript{a}</td>
<td>2.069(4)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Bridging dimethylamido group

Complex 9 has been previously published and also crystallizes as a 7-coordinate complex with a distorted pentagonal bipyramidal structure.\textsuperscript{[41]} Two dimethylamido substituents occupy axial and equatorial positions, and a neutrally-bound dimethylamine molecule occupies the other axial position. On average, the ligand is bound more loosely to zirconium than any of the ureate ligands, with longer Zr-O and Zr-N bond lengths (Table 3.3). Different from the ureate ligands, the mesityl group is not co-planar with the N-C-O framework attached to zirconium. While the phenyl ring of the mesityl does contain π-
electrons which could potentially participate in π-bonding with the amidate, this conformation would result in severe allylic strain.

3.2.3 Catalytic Testing of Bis(ureate) Zirconium Complexes for Hydroamination

For initial hydroamination tests, racemic versions of catalysts 9 and 45-47 were screened using three secondary amine substrates (48-50), and one primary aminoalkene containing an internal alkene (51) as shown in Table 3.4. Compound 45 catalyzed the cyclization of all four substrates in excellent yield. Catalysts 46 and 47 were also generally effective hydroamination catalysts, but in most cases required longer reaction times or resulted in lower yields than catalyst 45. Bis(amidate) catalyst 9 was initially expected to be inert towards secondary amine substrates as it had previously been tested with N-methyl-2,2-diphenyl-4-pentenamine and no cyclization was observed.[87] Remarkably, 9 did manage to cyclize N-benzyl and N-piperonyl substrates 48 and 49 (Table 3.4, Entries 13 and 14). However, this achievement required long reaction times and high reaction temperatures to produce low product yields of only 20-25%. While the three bis(ureate) catalysts tested all yielded moderate to good yields of hydroamination product, catalyst 45 showed consistently high yields with low reaction times and warranted further study.
Table 3.4: Secondary amine hydroamination using bis(ureate) zirconium catalysts.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Substrate</th>
<th>( t ) (h)</th>
<th>( T ) (°C)</th>
<th>Conv.</th>
</tr>
</thead>
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<td>110</td>
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<td>45</td>
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<td>N/A</td>
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<td>9</td>
<td>51</td>
<td>16</td>
<td>110</td>
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</table>
A variety of primary and secondary aminoalkene substrates were tested with catalyst 45 (Table 3.5). Substrate selection was often based on quantity and availability of pure aminoalkene molecules, but substrates for which catalysis data exists with 2 were prioritized. Unchallenging 5- and 6-membered primary aminoalkene substrates (Table 3.5, Entries 1 and 2) were cyclized easily in 6 and 4 hours, respectively. Full conversion was achieved when testing $N$-methylated substrates (Table 3.5, Entries 3 and 4), although the secondary aminoalkene substrates required longer reaction times than their primary aminoalkene counterparts. This is in contrast to 2, which cyclized the six-membered $N$-methylated substrates at a 5-fold faster rate than its primary amine analogue.[29]

Cyclization of 6-membered rings was more efficient than cyclization of 5-membered rings for both primary and secondary amine substrates, a finding consistent with the behaviour of 2. A challenging 6-membered substrate without gem-disubstituents (Table 3.5, Entry 3) required 48 hours of heating but did achieve full conversion. However, no reaction was observed when using an even more challenging primary amine substrate, containing an internal alkene with no gem-disubstituents (Table 3.5, Entry 6). No reaction was observed using secondary aminoalkene substrates without gem-disubstituents (Table 3.5, Entries 8 and 9), nor with a substrate bearing an $N$-allyl substituent (Table 3.5, Entry 10), despite heating to elevated temperatures. In general, catalyst 45 was slightly less efficient than catalyst 2, consistently exhibiting longer reaction times to drive the reaction to completion. However, 45 is still a viable catalyst for hydroamination of a wide variety of secondary aminoalkene substrates, but has the added advantage of being a chiral molecule with potential for carrying out hydroamination enantioselectively.
Table 3.5: Substrate scope testing of bis(ureate) zirconium catalyst 45.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>t (h)</th>
<th>T (°C)</th>
<th>Conv. (%)</th>
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</thead>
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<tr>
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<td>4</td>
<td><img src="image" alt="Substrate 54" /></td>
<td><img src="image" alt="Product 55" /></td>
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<td>110</td>
<td>&gt;98</td>
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<tr>
<td>5</td>
<td><img src="image" alt="Substrate 56" /></td>
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<td><img src="image" alt="Substrate 58" /></td>
<td><img src="image" alt="Product 59" /></td>
<td>96</td>
<td>110</td>
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</tr>
</tbody>
</table>
Table 3.5 (con’t): Substrate scope testing of bis(ureate) zirconium catalyst 45.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>t (h)</th>
<th>T (°C)</th>
<th>Conv. (%)</th>
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<td><img src="67.png" alt="Image" /></td>
<td>5</td>
<td>145</td>
<td>0</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.25 mmol substrate, 0.025mmol 45, dissolved in 0.5 g $d_8$-toluene.
Reaction progress monitored via $^1$H NMR spectroscopy.

3.3 Development of an Asymmetric Bis(ureate) Zirconium Catalyst for Secondary Amine Hydroamination

Alkene cyclohydroamination yields a product with a chiral centre in a position α to nitrogen. While many enantioselective hydroamination catalysts have been developed,
reliable enantioselective control over a broad range of substrates is still an outstanding challenge of the field. In particular, since there is a dearth of group 4 catalysts capable of secondary amine hydroamination, only two enantioselective examples have been reported. Compound 34, from the Scott group, cyclized five secondary substrates achieving ee’s ranging from 14-82% (Table 3.1).[32] While compound 10 is a known enantioselective hydroamination catalyst, the ee of the product resulting from cyclization of a secondary aminoalkene substrate was not determined.[28]

Catalyst 45, capable of hydroamination with a range of secondary aminoalkene substrates, is based on an axially-chiral 2,2’-diamino-6,6’-dimethylbiphenyl tether and can thus be deployed as an enantioselective catalyst. An enantioenriched proligand (+)-41 was synthesized from (+)-2,2’-diamino-6-6’-dimethylbiphenyl and then used to create an enantioenriched version of zirconium complex (+)-45.

However, a challenge in the development of a chiral catalyst for secondary amine hydroamination soon became apparent: the necessity of a reliable method of measuring the enantiomeric excess of the hydroamination products. The most common practice for measuring the enantiomeric excess of hydroamination products catalyzed by group 4 complexes has been the use of chiral resolving agents.[28,41,47,51–57,94,111,112] The predominant method involves using enantiomerically-pure Mosher’s acid (α-methoxy-α-trifluoromethylphenylacetic acid)[113] or its acid chloride derivative to form an amide product with the N-heterocyclic hydroamination product. The diastereomeric amide products that are formed can be identified and quantified using 1H and 19F NMR spectroscopy, allowing the enantiomeric excess of a particular reaction to be determined.
However, amide bond formation is limited to primary and secondary amines. Tertiary amines, which are the products of hydroamination using secondary amine substrates, cannot be derivatized in this manner to measure enantioselectivity. A method to separate enantiomers of amine products without derivatization was needed.

Previous examples of enantioselective hydroamination of secondary aminoalkenes using late metal catalysts has determined the ee’s of the resulting compounds using chiral HPLC\cite{114-121} or chiral GC\cite{114,115,122}. The substrates and products of these reactions, for the most part, incorporate protecting groups (Cbz, Ts, Tf, etc.) on the nitrogen centre and are best described as dialkyl-substituted sulfonamides or carbamates.

In contrast, secondary aminoalkene substrates used for hydroamination with lanthanide and cationic group 4 catalysts do not use protected nitrogen centres. Instead, the nitrogen centres bear alkyl groups, resulting in trialkyl-substituted tertiary amine centres which are less amenable to chromatographic separation. Previous enantioselective hydroamination work producing cyclic trialkyl-substituted amines has determined the ee’s of the resulting compounds though salt formation with chiral resolving agents $(R)$-$(−)$-$O$-acetylmandelic acid,\cite{123} or Mosher’s acid.\cite{32,94} While this has been shown to be a viable method of ee determination for select products, it is not generally applicable. For example, $(R)$-$(−)$-$O$-acetylmandelic acid has only been utilized with a single compound.\cite{123} As well, one of the substrates cyclized by Scott in Table 3.1 listed its ee as “not determined” (entry 4) because salt formation Mosher’s acid proved unsuccessful.\cite{32} Chiral HPLC was also attempted for this product and deemed unsuccessful. Development of a more general
method to determine ee’s of cyclic trialkyl tertiary amines would be a useful contribution to the development of enantioselective catalysts for secondary aminoalkenes.

3.3.1 Capillary Electrophoresis

Capillary electrophoresis (CE) is an analytical technique which uses applied voltage to separate charged species within a conducting liquid. A schematic of a generic capillary electrophoresis instrument is presented in Figure 3.10. There are two reservoirs containing solutions of a background electrolyte, often an aqueous buffer. The reservoirs are connected by a glass capillary tube, as well as electrodes connected to a high voltage source. A sample is injected into one end of the capillary and then an electric field is applied to the system using the electrodes. The charge differential between the two reservoirs causes the solution to move through the capillary tube via electroosmotic flow. A detector, usually utilizing UV absorbance, is used to monitor the solution and detect analytes. The separation of analytes is based on their size to charge ratios, but will also depend on factors such as the length and internal diameter of the capillary, and the pH and contents of the background electrolyte solution.

Capillary electrophoresis was identified as a potentially useful method for analyzing the tertiary amine products resulting from secondary amine hydroamination due to the fact that the only product derivitization required would be the formation of an amine salt, which is easily accomplished by treatment with any strong acid. It should also be noted that CE is therefore not limited to tertiary amines; salts of primary and secondary amines can also be analyzed using this technique. This would avoid the installation of costly chiral derivatizing agents.
While CE can be used to separate mixtures of different compounds, it can also be used for enantiomeric separations through the use of chiral selectors. These selectors are usually dissolved in the solution of the background electrolyte, and as the analyte moves through the capillary, the differential affinities of the enantiomers with the chiral selector will cause a staggered elution time. This is akin to the interaction with a chiral stationary phase in chiral HPLC, although there is no “stationary” phase in CE. The chiral additive

**Figure 3.10:** Schematic of a capillary electrophoresis.
moves through solution along with the sample, and the inside walls of the capillary tube are plain glass, though special treatments can be applied if desired.\textsuperscript{[124]}

Chiral separations using CE are well-known.\textsuperscript{[124-131]} Some recent examples of enantioselective separations of compounds containing cyclic amines are featured in Figure 3.11.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure311.png}
\caption{Recent examples of enantiomeric compounds containing cyclic amines separated by capillary electrophoresis.}
\end{figure}

Enantiomers of nicotine and 4 related compounds were separated by Kodama \textit{et al.} using a capillary coated with amino groups on the interior surface.\textsuperscript{[132]} The nicotine content of cigarettes and cigarette smoke was established using sulfated $\beta$-cyclodextrin as the chiral selector in an aqueous acetate buffer. Saad \textit{et al.} used CE to perform simultaneous separations of the enantiomers of ofloxacin and ornidazole.\textsuperscript{[133]} These two pharmaceuticals are sometimes combined into a single tablet for treatment of gastrointestinal infections, and \textit{(S)}-(-)-ofloxacin and \textit{(R)}-(+)-ornidazole are more
pharmacologically active than their corresponding enantiomers. The use of sulfated β-cyclodextrin as chiral selector allowed for the enantiomeric separation and quantification of both compounds in a commercially-available preparation.\textsuperscript{[133]} Németh et al. studied the application of CE for enantiomeric separations of 5 anti-malarial drugs, including mefloquine.\textsuperscript{[134]} A variety of cyclodextrin derivatives were tested for each compound to achieve optimal separation. Cetirizine, an antihistamine found in over-the-counter allergy medications, was separated by Chen et al. employing sulfated β-cyclodextrin.\textsuperscript{[135]} The $R$-enantiomer, levocetirizine exhibits significantly higher pharmacological activity than dextrocetirizine ($S$-enantiomer), and CE analysis allowed the quantification of levocetirizine in commercial pharmaceuticals. Bonato et al. has demonstrated the efficacy of CE for the enantiomeric separation of mirtazapine, an anti-depressant, and its metabolites.\textsuperscript{[136]} The enantiomers of mirtazapine undergo differential primary metabolic pathways and the quantities of mirtazapine and its metabolites in a urine sample were determined using cyclodextrin derivatives as chiral selectors. Notably, to the best of my knowledge, there are no examples of the application of CE in asymmetric catalysis involving amines.

\textbf{3.3.2 Capillary Electrophoresis for the Separation of Tertiary Amines}

Capillary electrophoresis has a number of parameters influencing the separation of compounds. Optimization of these various parameters is necessary to achieve a successful enantiomeric separation.
Capillary tube

A capillary length of 57 cm (50 cm effective length) was selected and internal diameters of 50 μm and 75 μm were tested. While the smaller 50 μm diameter capillary resulted in slightly longer elution times, it also resulted in better separations than the 75 μm diameter tube. A 50cm x 50 μm i.d. capillary was used for further method development.

Cyclodextrins

In this work, the additives used to help separate enantiomers are cyclodextrin derivatives. Cyclodextrins are cyclic glucose oligosaccharides which come in three main varieties, denoted α-, β-, and γ-cyclodextrin (often shortened as α-CD, β-CD, or γ-CD), and which are composed of 6, 7, and 8 glucose molecules, respectively. Since glucose naturally occurs in an enantiomerically pure form as D-glucose, cyclodextrins derived from pure D-glucose are also enantiomerically pure. This allows them to interact with enantiomers of a compound in different ways, allowing those enantiomers to be differentiated over the course of a electrophoretic separation. Due to their cyclic nature, they adopt a conical bowl shape, with a hydrophobic interior and a hydrophilic exterior. The cyclodextrin derivatives used in this study have been sulfated, transforming many of the –OH groups of the glucose residues into –OSO₂OH residues, which would typically exist as –OSO₃⁻ in buffer solutions at a range of pH values (Figure 3.12).

The effectiveness of enantiomer separations will depend in part on the relative sizes of the pyrrolidine hydroamination products and the cyclodextrin additives. Since the three common cyclodextrin varieties each consist of a different number of glucose residues, the
size of their internal cavities vary. The diameter of the internal cavity of highly sulfated α-cyclodextrin (HS-α-CD) is 4.7-5.2 Å, 6.0-6.4 Å for HS-β-CD, and 7.5-8.3 Å for HS-γ-CD.[137] Initial testing carried out in collaboration with the Chen laboratory at the UBC Chemistry Department identified HS-β-CD as the best choice for the pyrrolidine derivatives produced during hydroamination. Experiments with HS-α-CD and HS-γ-CD were performed and found to result in less distinct separation of peaks. Since all of the products being studied are similar, based on a diphenylpyrrolidine framework, HS-β-CD was used exclusively.

![Molecular structure of HS-β-CD](image)

**Figure 3.12**: Molecular structure of HS-β-CD.

The concentration of cyclodextrins in the buffer medium can also be varied and a range of solutions from 1% to 6% w/v HS-β-CD in phosphate buffer were tested. While separation was sometimes observed using lower concentrations of cyclodextrin, the best
results were consistently obtained with the most concentrated solution. Thus, 6% w/v HS-β-CD in phosphate buffer was used.

**Voltage**

The amount of voltage applied to the system will affect the flow rate of the solution through the capillary and will subsequently affect the elution times and separation within the capillary. Initial testing identified 30 kV as the optimal potential difference. Separations at 15 kV were tested but peak separation was not as defined as separations at higher voltages, so 30 kV was maintained as the ideal potential difference.

**Background Electrolyte**

A phosphate buffer solution (pH 7.2) was used for all CE runs. No other buffer solutions were tested in this study.

**Detection**

UV detection was carried out at a 214 nm wavelength. No other wavelengths were tested in this study.

**3.3.3 Enantioselective Secondary Amine Hydroamination**

An enantioenriched version of proligand 41 was synthesized from (+)-2,2’-diamino-6-6’-dimethylbiphenyl and then used to create an enantioenriched version of zirconium complex 45. Reactions were carried out at 110 °C using 10 mol% of catalyst in deuterated benzene and monitored periodically using $^1$H NMR spectroscopy.
Hydroamination products were isolated using silica gel chromatography. Approximately 5 mg of the product was dissolved in acetone in a small vial and one drop of concentrated hydrochloric acid was added. Volatiles were removed under reduced pressure leaving behind the amine salt. The salt was prepared into an aqueous solution by adding approximately 100 μL deionized H₂O, 20 μL phosphate buffer solution (pH 7.2), and 15 μL HPLC-grade methanol. The mixture was agitated and filtered if necessary to yield a clear solution with no visible particulate matter, and transferred to a sample vial and placed into the CE apparatus.

A Beckman Coulter capillary electrophoresis equipped with a UV detector was used in reverse mode with a 50 μm internal diameter capillary tube, 50 cm in length. All aqueous solutions were prepared using deionized water, and only HPLC-grade methanol was used. The capillary was cleaned with MeOH, 0.1N HCl, 0.1N NaOH and phosphate buffer solution. A sample injection at 0.5 psi for 5 seconds was followed by a 20 minute separation at 30 kV using 6% w/v HS- β-CD in phosphate buffer. Results are listed in Table 3.6.

A six-membered, N-methylated substrate (Table 3.6, Entry 4) was cyclized efficiently but resulted in very low observed enantioselectivity, with only 9% ee. However, the 5-membered substrates resulted in better observed enantioselectivity. A moderate ee of 32% was found for an N-benzyl substrate (Table 3.6, Entry 1), and 49% ee was observed with an N-cyclohexyl version (Table 3.6, Entry 3). The best results were seen with an N-piperonyl substituent (Table 3.6, Entry 2), with an ee of 63%. Not only is secondary
amine hydroamination possible with a variety of substrates, it is also possible to carry it out enantioselectively with moderate ee’s.

Table 3.6: Enantioselective secondary amine hydroamination using a chiral bis(ureate) zirconium catalyst.

\[
\text{secondary aminoalkene} \xrightarrow{(+)-45 \text{ (10 mol\%)}} \text{C}_6\text{D}_6 \quad 110 \, ^\circ\text{C} \rightarrow \text{N-heterocyclic product}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>( t ) (h)</th>
<th>conv. (%)</th>
<th>ee (%)</th>
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<td>9</td>
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</tbody>
</table>
The mechanism by which enantioselectivity is imparted from the catalyst to the substrate is not clear at this time. The rate-determining step is hypothesized to involve a highly-ordered transition state in which an axially-bound amine transfers a proton to the terminal position of the alkene during which the orientation of the stereogenic centre of the \(N\)-heterocyclic product is established. In this transition state, the aminoalkene substrate and proton-donating amine ligand are expected to adopt a conformation resembling \textit{trans}-decalin (Scheme 1.4, \textit{vide supra}).

![Figure 3.13: Model of the transition state conformation leading to each enantiomer of a piperidine product.](image)

The stereochemistry of the product is determined by the orientation of the bicyclic transition state and the two orientations are not interchangeable through chair flipping (Figure 3.13). While the ligand in complex \textbf{45} is asymmetric, the solid state molecular structure of \textbf{45} (Figure 3.5) demonstrates that binding of the N-C-O chelates are co-planar and thus the ligand’s diisopropylamine substituents are arranged symmetrically. The catalyst’s asymmetry is manifested instead in the biphenyl backbone of the ligand. However, that portion of the ligand is distant enough from the metal centre that it is
unlikely to have any sort of interaction with the amine donor or aminoalkene substrate during the turnover-limiting step, in which the orientation of the stereocentre is established. Based on the information available, a model to demonstrate how the observed enantioselectivity is induced cannot be put forward at this time.

3.4 Summary

After the unprecedented success of bis(ureate) bis(amido) zirconium catalyst 2 for secondary amine hydroamination, three new tethered bis(urea) proligands were designed and synthesized. The proligands were then used to synthesize bis(ureate) bis(amido) zirconium complexes which were screened for hydroamination activity with challenging aminoalkene substrates. Catalyst screening identified 45 as the most promising new compound and was shown to effectively cyclize a variety of secondary aminoalkene substrates in good yield.

Capillary electrophoresis was developed as a method to effectively separate enantiomers of tertiary amine products without the need for derivatization with chiral resolving agents. An enantioselective version of catalyst 45 was used to carry out enantioselective hydroamination of four secondary aminoalkene substrates, achieving ee’s up to 63%.

3.5 Conclusions

A series of new tethered bis(ureate) zirconium catalysts demonstrates that the general viability of the bis(ureate) ligand framework for the hydroamination of secondary amine substrates, and its superiority to the bis(amidate) ligand frameworks previously tested. However, the fact that a bis(amidate) catalyst also demonstrated basic competence for
secondary amine hydroamination was fortunate. These results suggesting that this bis(amidate) zirconium catalyst is capable of accessing the 7-coordinate, proton-assisted mechanistic pathway believed to be operative in the case of bis(ureate) catalysts.

The successful generation of chiral tertiary amine products lays the groundwork for the possibility of developing further enantioselective group 4 catalysts capable of secondary amine hydroamination. Use of capillary electrophoresis as a straightforward method for the analysis of tertiary amine products will greatly expedite future catalyst development efforts.
3.6 Experimental

*General Experimental Procedures*

Except where noted, syntheses of proligands were carried out in ambient atmosphere. All other reactions were carried out using oven-dried glassware under an atmosphere of dry N$_2$ using Schlenk or glovebox techniques. Benzene and hexanes were sparged with nitrogen and purified using a column of activated alumina. $d_6$-Benzene and $d_8$-toluene were degassed by several freeze-pump-thaw cycles and dried over 4Å molecular sieves before use. All common, commercially-available reagents were purchased from Sigma Aldrich. Tetrakis(dimethylamido)zirconium was purchased from Strem and used as received. Synthesis and resolution of 2,2′-diamino-6,6′-dimethylbiphenyl (16), as well as compounds 41 and 45 were performed according to literature procedures. Known substrates include benzyl(2,2-diphenyl-4-pentenyl)amine (48),$^{[138]}$ N-piperonyl-2,2-diphenyl-1-amino-4-pentene (49),$^{[138]}$ N-cyclohexyl-2,2-diphenyl-1-amino-4-pentene (50),$^{[24]}$ 2,2-Diphenyl-1-amino-4-hexene (51),$^{[139]}$ 2,2-diphenyl-4-pentenamine (21),$^{[36]}$ 2,2-diphenyl-5-hexeneamine (52),$^{[139]}$ N-methyl-2,2-diphenyl-1-amino-4-pentene (39),$^{[18]}$ N-methyl-2,2-diphenyl-1-amino-5-hexene (54),$^{[24]}$ hex-5-en-1-amine (56),$^{[140]}$ N-(hex-5-ethyl)aniline (62),$^{[141]}$ Cyclized hydroamination products have also been characterized, including N-benzyl-2-methyl-4,4-diphenylpyrroolidine (68),$^{[138]}$ N-piperonyl-2-methyl-4,4-diphenylpyrroolidine (69),$^{[18]}$ N-cyclohexyl-2-methyl-4,4-diphenylpyrroolidine (70),$^{[24]}$ 2-ethyl-4,4-diphenylpyrroolidine,$^{[142]}$ 2-methyl-4,4-diphenylpyrroolidine (22),$^{[36]}$ 2-methyl-5,5-diphenylpiperidine (53),$^{[143]}$ 1,2-dimethyl-4,4-diphenylpyrroolidine (40),$^{[27]}$ and 1,2-dimethyl-5,5-diphenylpiperidine (55).$^{[24]}$ $^1$H and $^{13}$C and NMR spectra were recorded using Bruker Avance 300 MHz, 400 MHz, or 600 MHz.
spectrometers, with chemical shifts given relative to the residual solvent peak. Mass
spectra were recorded on either a Kratos MS-50 spectrometer using a 70 eV electron
impact source or a Bruker Esquire-LC using an electrospray ionization source. Elemental
analysis was recorded on a Carlo Erba Elemental Analyzer EA 1108. Single crystal X-ray
structure determinations were obtained using a Bruker APEX II.

Synthesis of 41
A solution of (+)-2,2′-diamino-6,6′-dimethylbiphenyl (0.72 g, 3.39) in dichloromethane
(30 mL) was cooled to 0 °C in a dry Schlenk tube under an atmosphere of N₂. Pyridine
(0.67 g, 8.5 mmol) was added followed by gradual addition of phenyl chloroformate
(1.11 g, 7.2 mmol) over a period of 15 minutes. The mixture was allowed to warm to
room temperature with stirring for 1 hour. The reaction mixture was washed with 1M
HCl (2 x 30 mL), brine (1 x 25 mL), then dried over MgSO₄, filtered through a Büchner
funnel, and the solvent was removed using rotary evaporation to give a thick oil. DMSO
(10 mL) was added to dissolve the crude product and to this solution was added
diisopropylamine (0.82 g, 8.2 mmol). The mixture was stirred at room temperature for 3
hours. Dichloromethane (10 mL) was added to the mixture, which was then filtered
through a small bed of silica gel, and the solvent removed by rotary evaporation. The
crude product was recrystallized from ethyl acetate to yield colourless crystals.

Yield: 0.95g (60%). ¹H NMR (CDCl₃, 300 MHz) δ 0.98 (24H, m, CH(CH₃)₂), 1.99 (6H,
s, Ar-CH₃), 3.80 (4, sept, CH(CH₃)₂), 6.06 (2H, s, N-H), 7.01 (2H, d, Ar-H), 7.30 (2H,
dd, Ar-H), 8.27 (2H, d, Ar-H).
Synthesis of 42

A solution of (±)-2,2′-diamino-6,6′-dimethylbiphenyl (2.0 g, 9.4 mmol) in dry dichloromethane (50 mL) was cooled to 0 °C in a dry Schlenk tube under an atmosphere of N₂. Pyridine (1.96 g, 24.8 mmol) was added, followed by gradual addition of phenyl chloroformate (3.25 g, 20.7 mmol) over a period of 15 minutes. The mixture was allowed to warm to room temperature with stirring for 16 hours. The reaction mixture was washed with 1M HCl (2 x 50 mL), brine (1 x 75 mL), then dried over MgSO₄, filtered through a Büchner funnel, and the solvent was removed using rotary evaporation to give a thick yellow oil. This oil was dissolved in DMSO (10 mL) and to this solution was added cis-2,6-dimethylpiperidine (2.27 g, 20.1 mmol). The mixture was stirred at room temperature for 3 hours, becoming very cloudy. Dichloromethane (30 mL) was added to clarify the mixture, which was then washed with H₂O (30 mL), 1M HCl (25 mL), 1M NaOH (25 mL), H₂O (25 mL), and brine (25 mL). The organic portion was dried over MgSO₄, filtered through a Büchner funnel, and the solvent removed using rotary evaporation to give a white solid. The solid was dissolved in dichloromethane (15 mL) and filtered through a small bed of silica gel, and the solvent removed using rotary evaporation to yield a white solid product.

Yield: 1.3 g (28%). ¹H NMR (CDCl₃, 300 MHz) δ 0.89 (6H, d, piperidine-CH₃), 0.92 (6H, d, piperidine-CH₃), 1.35-1.70 (12H, m, alkyl H), 1.99 (6H, s, Ar-CH₃), 3.90 (4H, m, alkyl H), 6.22 (2H, m, N-H), 7.02 (2H, d, Ar-H), 7.30 (2H, dd, Ar-H), 8.13 (2H, d, Ar-H); ¹³C NMR (CDCl₃, 75 MHz) δ 13.7, 19.9, 20.5, 30.3, 45.5, 118.6, 124.5, 125.1, 129.2,
137.2, 138.0, 154.7. MS (EI) m/z 490 (M+). Anal. Calcd for C_{30}H_{42}N_{4}O_{2}: C, 73.43; H, 8.63; N, 11.42. Found: C, 73.35; H, 8.37; N, 10.67.

**Synthesis of 43**

A solution of 2,2-dimethyl-1,3-propanediamine (2.0 g, 19.5 mmol) in dry dichloromethane (50 mL) was cooled to 0 °C in a dry Schlenk tube under an atmosphere of N\textsubscript{2}. Pyridine (3.4 g, 43 mmol) was added, followed by gradual addition of phenyl chloroformate (6.43 g, 41 mmol) over a period of 15 minutes. The mixture was allowed to warm to room temperature with stirring for 16 hours. The reaction mixture was washed with 1M HCl (2 x 50 mL), brine (1 x 75 mL), then dried over MgSO\textsubscript{4}, filtered through a Büchner funnel, and the solvent was removed using rotary evaporation to give a thick yellow oil. This oil was dissolved in DMSO (30 mL), and to this solution was added cis-2,6-dimethylpiperidine (4.5 g, 39.8 mmol). The mixture was stirred at room temperature for 3 hours, becoming very cloudy. Dichloromethane (60 mL) was added to clarify the mixture, which was then washed with H\textsubscript{2}O (40 mL), 1M HCl (25 mL), 1M NaOH (25 mL), H\textsubscript{2}O (25 mL), and brine (25 mL). The organic portion was dried over MgSO\textsubscript{4}, filtered through a Büchner funnel, and the solvent was removed using rotary evaporation to give a white solid. The solid was dissolved in dichloromethane (15 mL) and filtered through a small bed of silica gel, and the solvent removed using rotary evaporation to yield a white solid product.

Yield: 2.3 g (31%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ 0.83 (6H, s, C(CH\textsubscript{3})\textsubscript{2}), 1.18 (12H, d, piperidine-CH\textsubscript{3}), 1.40-1.80 (12H, m, alkyl H), 3.02 (4H, d, alkyl H) 4.22 (4H, m, alkyl H), 5.70 (2H, m, N-H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) δ 14.0, 20.8, 23.8, 30.5, 36.8, 45.3,
46.8, 158.2. MS (EI) m/z 380 (M⁺). Anal. Calcd for C₂₁H₄₀N₄O₂: C, 66.28; H, 10.59; N, 14.72. Found: C, 66.12; H, 10.48; N, 14.77.

**Synthesis of 45**

¹H NMR (CD₆, 400 MHz) δ 0.83 (12H, d, CH(CH₃)₂), 1.51 (12H, d, CH(CH₃)₂), 2.02 (4H, br s, CH(CH₃)₂), 2.07 (6H, s, Ar-CH₃), 3.27 (9H, br s, N-CH₃), 6.70 (2H, d, Ar-H), 6.83 (2H, d, Ar-H) 7.05 (2H, t, Ar-H); ¹³C NMR (CD₆, 100 MHz) δ18.8, 20.5, 21.5, 21.7, 39.2, 45.0, 45.6, 48.7, 118.3, 122.8, 127.1, 132.4, 127.6, 149.0, 168.85. MS (EI) m/z 1170, 1018 (homoleptic complex), 642 (M−HNMe₂)⁺. Anal Calcd. for C₃₄H₆₁N₇O₂Zr: C, 59.09; H, 8.90; N, 14.19. Found: C, 59.66; H, 8.68; N, 14.18.

**Synthesis of 46**

In a nitrogen-filled glovebox, proligand 42 (0.200 g, 0.41 mmol) and tetratakis(dimethylamido)zirconium (0.109 g, 0.41 mmol) were weighed out into a vial. Hexanes (2 mL) was added, followed by benzene (1 mL) to help achieve complete dissolution. The mixture was stirred at room temperature overnight and then the volatiles removed in vacuo to yield a white solid. Recrystallization from hot hexanes produced colourless crystals.

¹H NMR (CD₆, 300 MHz) δ 0.99 (6H, d, piperidine CH₃), 1.08 (4H, m, alkyl-H), 1.24 (6H, d, piperidine CH₃), 1.46 (4H, m, alkyl-H), 2.03 (4H, br s, alkyl-H), 2.07 (6H, s, Ar-CH₃), 3.32 (10H, br s, N-CH₃), 4.45 (4H, br, alkyl-H), 6.86 (2H, d, Ar-H), 6.91 (2H, d, Ar-H), 7.12 (2H, m, Ar-H).
Synthesis of 47

In a nitrogen-filled glovebox, proligand 43 (0.150 g, 0.39 mmol) and tetratakis(dimethylamido)zirconium (0.105 g 0.39 mmol) were weighed out into a vial. Hexanes (2 mL) was added, followed by benzene (1 mL) to help achieve complete dissolution. The mixture was stirred at room temperature for 16 hours and then the volatiles were removed in vacuo to yield a white solid. Recrystallization from hot benzene produced colourless crystals.

$^1$H NMR ($C_6D_6$, 300 MHz) δ 0.94 (3H, s, C(CH$_3$)$_2$), 1.23 (3H, s, C(CH$_3$)$_2$), 1.25-1.35 (6H, m, alkyl-H), 1.30 (6H, d, piperidine CH$_3$), 1.34 (6H, d, piperidine CH$_3$), 1.44 (2H, m, alkyl-H), 1.66 (4H, m, alkyl-H), 3.06 (6H, s, N-CH$_3$), 3.21 (2H, d, piperidine CH), 3.31 (6H, s, N-CH$_3$), 3.48 (2H, d, piperidine CH), 4.42 (2H, m, alkyl-H), 4.82 (2H, m, alkyl-H).

General procedure for NMR-scale intramolecular hydroamination

In a nitrogen-filled glovebox, approximately 0.03 mmol zirconium catalyst was weighed out into a vial and dissolved in 0.5 g $C_6D_6$. In a separate vial, 0.3 mmol of the aminoalkene substrate was weighed out. The contents of the two vials were thorroughly mixed, placed in a Teflon-sealed J. Young NMR tube, sealed and removed from the glovebox. The NMR tube was placed in an oil bath heated to the indicated temperature. The reaction was periodically monitored by $^1$H NMR spectroscopy until complete.

General procedure for measuring enantioselectivity using capillary electrophoresis

Hydroamination reactions were quenched by adding a small amount of dichloromethane into the reaction mixture and the product was isolated using flash chromatography. A
small amount (~5 mg) of the product was placed in a CE-compatible vial and dissolved in 0.5 mL acetone. One drop of concentrated HCl was added and the mixture agitated. Volatiles were removed using rotary evaporation until the solid salt product remained. The amine salt was dissolved in HPLC-grade MeOH (15μL), pH 7.2 phosphate buffer (20μL), and deionized H₂O (1 mL). If necessary, in order to ensure no particulate matter remained, additional MeOH was added, or the mixture was filtered through a small bed of Celite.

Prior to sample injection, the capillary was rinsed with 0.1N NaOH (20 psi, 20 min), deionized H₂O (20 psi, 20 min), and pH 7.2 phosphate buffer solution (20 psi, 20 min). The sample was injected (0.5 psi, 5.0 seconds) and the separation protocol initiated (30 kV, 25 min, reverse polarity). Between samples, the capillary was rinsed with 0.1N NaOH (20 psi, 3 min), HPLC-grade MeOH (20 psi, 3 min), deionized H₂O (20 psi, 3 min), and pH 7.2 buffer solution (20 psi, 3 min). After all samples were tested, the capillary was washed with 0.1N HCl (20 psi, 2 min) and deionized H₂O (20 psi, 3 min).
Chapter 4: Synthesis of New Bis(amidate) Tantalum Complexes for Catalytic Hydroaminoalkylation

4.1 Introduction

The hydroaminoalkylation reaction (Scheme 4.1) has been the subject of renewed interest in catalysis after modern reports were published by Hartwig and Herzon starting in 2007.\cite{63,64} Using Ta(NMe$_2$)$_5$ and [TaCl$_3$(NMe$_2$)$_2$)$_2$ as catalysts, the substrate scope of hydroaminoalkylation, previously limited to a select few examples,\cite{62,144} was expanded to encompass a variety of amine and alkene substrates. A number of catalysts for the $\alpha$-alkylation of amines has since been developed utilizing primarily group 5\cite{65,67,68,70,145} and group 4\cite{26,59–61,66,146,147} elements. In addition, mechanistic investigations have generated a proposed catalytic cycle for hydroaminoalkylation for Group 5 catalyst systems, which proceeds through a $\beta$-hydrogen abstraction to form a metallaziridine intermediate, followed by alkene insertion (Scheme 1.10, vide supra).\cite{144}

$$\begin{align*}
R^1\text{R}^2 + R^3\text{N}^\text{H}^\text{N}^\text{R}^4 &\xrightarrow{[\text{M} \text{catalyst}]} R^3\text{H}^\text{N}^\text{R}^4 R^1\text{R}^2
\end{align*}$$

Scheme 4.1: Hydroaminoalkylation reaction to yield an $\alpha$-alkylated amine product.

In 2009, the Schafer group published the first example of enantioselective hydroaminoalkylation, using tantalum complex 12 (Scheme 4.2).\cite{65} The bis(amidate) ligand in 12, although bound to the tantalum in a $\kappa^2$ fashion through its oxygen atoms, is
similar to the bis(amidate) ligands featured in Chapter 2, with the main structural differences being found in the orientation of the amide bond. In 12, the carbonyl portion of the amide is directly adjacent to the biphenyl backbone, while in the ligands featured earlier, the amine portion of the amide is directly adjacent to the biphenyl backbone. Five examples of enantioselective hydroaminoalkylation using 12 were reported, with yields of 50-92%, and ee’s ranging from 43-61%.

Scheme 4.2: Enantioselective hydroaminoalkylation example using axially-chiral tantalum complex 12.

Two subsequent reports of enantioselective hydroaminoalkylation have been published by Zi\footnote{68,69} and Hultzsch.\footnote{70} Zi employed 3 structurally similar binaphthyl- and biphenyl-based bis(amidate) tantalum complexes (Figure 4.1) for hydroaminoalkylation of a limited number of substrates, observing ee’s up to 93%. Nb versions of 13a,b and 71 were synthesized but were found to have no competency for hydroaminoalkylation.\footnote{68,69}
Hultzsch screened a series of bulky binaphtholate tantalum and niobium complexes, identifying 14 as the optimal catalyst for hydroaminoalkylation (Figure 4.2). Unlike Zi, Hultzsch found niobium complexes to have superior reactivity than analogous tantalum complexes, while exhibiting equal or better enantioselectivities in all but one case. Using 5 mol% of catalyst at 140 °C resulted in yields of 59-93% and enantioselectivities of up to 80%.

Since a variety of successful axially-chiral O- and N- bonded ligands had been shown to be successful for hydroaminoalkylation, previously generated ligands also containing these motifs, such as those featured in Chapter 2, were identified as being possible candidates for the generation of new hydroaminoalkylation catalysts.
4.2 Synthesis of Bis(amide) Proligands

Synthesis of proligands 24-27 and 72 (Scheme 4.3) was carried out as described in Chapter 2. 2,2’-Diamino-3,3’,5,5’-tetrabromo-6,6’-dimethylbiphenyl (23) was combined with 2-6 equivalents of various acid chlorides and pyridine in refluxing 1,2-dichloroethane to yield bis(amide) products in moderate to good yields. Proligand 44 was also synthesized as described in Chapter 2, from 2,2’-diamino-6,6’-dimethylbiphenyl (16) and 2,4,6-trimethylbenzoyl chloride.

![Scheme 4.3: Synthesis of bis(amide) proligands for use in hydroaminoalkylation catalysis.](image)

**Scheme 4.3**: Synthesis of bis(amide) proligands for use in hydroaminoalkylation catalysis.

4.3 Synthesis and Characterization of Tantalum Complexes

Proligands 24-27, 44, and 72 were thoroughly dried and brought into a nitrogen-filled glovebox, then mixed in an equimolar ratio with Ta(NMe$_2$)$_5$ in a minimum volume of benzene or hexanes. The mixture was heated with agitation to ensure thorough mixing.
and then allowed to cool and sit for at least 1 hour. In some instances, orange-red crystals formed at the bottom of the reaction vessel. Where crystals did not form, solvent was removed under reduced pressure to yield an orange-red solid in good yield. Figure 4.3 outlines the new tantalum precatalysts reported, with structural aspects of each individual complex discussed below.

**Figure 4.3:** Bis(amidate) tantalum catalysts developed for hydroaminoalkylation.

In the solid state, complex 73 adopts a $C_1$-symmetric $\kappa^3$-$O,O,N$-bonding mode (Figure 4.4). The arrangement around the metal centre is a distorted trigonal bipyramidal structure with the arm of one amidate – bound through both N and O – in the pseudo-equatorial plane, and the O-bound amidate occupying a pseudo-axial position. In the $\kappa^1$-
bound arm, the C19-N2 bond length of 1.284(6) Å and the C19-O2 bond length of 1.321(5) Å are within the range expected for a carbon-nitrogen double bond and carbon-oxygen single bond, respectively. In comparison, the C1-N1 bond length of the κ²-bound arm is slightly longer at 1.303(6) Å and the C1-O1 bond length of 1.304(5) Å is slightly shorter than its κ¹-bound counterpart, indicative of more delocalization in the N-C-O framework. Also reflecting the differential binding, the Ta-O2 bond of the oxo-bound arm measures 2.047(3) Å while the Ta-O1 bond to the chelate is a slightly longer at 2.117(3) Å.

Figure 4.4: ORTEP representation of the solid-state molecular structure of 73 (ellipsoids plotted at 50% probability). All H-atoms omitted for clarity.
In solution, the $^1$H NMR spectrum of 73 is also consistent with a $C_1$-symmetric tridentate binding mode. Two singlets of equal integration at $\delta$ 7.88 and $\delta$ 7.78 are present, representing the two aromatic protons, as well as singlets at $\delta$ 2.09 and $\delta$ 1.70 for the two methyl groups attached to the biphenyl. The presence of four separate doublets, corresponding to the isopropyl methyl groups, demonstrate that not only are the two isopropyl groups in distinct chemical environments due to the $\kappa^3$ binding, there is also restricted rotation on the NMR time scale.

A crystalline sample of 74 could not be obtained for solid-state analysis, but it is also postulated to adopt a tridentate binding mode. The $^1$H NMR spectrum of 74 contains two singlets at $\delta$ 7.82 and $\delta$ 7.86 corresponding to aromatic protons on the brominated biphenyl backbone, indicating a $C_1$-symmetric binding mode, assigned to be due to the $\kappa^3$-$O,O,N$-arrangement analogous to that in compound 73.

The solid state structure of 75 also exhibits a $C_1$-symmetric $\kappa^3$-$O,O,N$-bonding mode (Figure 4.5). The arrangement around the tantalum centre is distorted trigonal bipyramidal like in 73 and the bond lengths and angles near the metal centre of those two compounds are very similar.

In solution, peaks in the aromatic region of the $^1$H NMR spectrum indicate the presence of inequivalent aromatic proton signals, consistent with the tridentate ligand bonding. Two singlets, representing the distinct methyl groups attached to the biphenyl backbone appear quite far apart in the spectrum, at $\delta$ 2.07 and $\delta$ 0.64. Additionally the $^{19}$F NMR spectrum contains two distinct singlets corresponding to chemically inequivalent trifluoromethyl groups.
Figure 4.5: ORTEP representation of the solid-state molecular structure of 75 (ellipsoids plotted at 50% probability). All H-atoms omitted for clarity.

A crystalline sample of 76 could not be obtained to examine its solid-state structure, but as with complexes 73-75, the $^1$H NMR spectrum of 76 also indicates a tridentate $N,O,O$ bonding mode of the ligand with distinct singlets for all of the aromatic protons. As well, the methyl groups on the brominated biphenyl backbone generate very distinct signals at $\delta$ 1.95 and $\delta$ 0.78, as would be expected for a complex with $C_1$-symmetry.
Figure 4.6: ORTEP representation of the solid-state molecular structure of 77 (ellipsoids plotted at 50% probability). All H-atoms omitted for clarity.

Unlike the other tantalum complexes described in this section, complex 77 adopts a $\kappa^2$-$O,O$-bonding mode both in solution and in the solid state. In the solid state, complex 77 is $C_1$-symmetric, with a distorted trigonal bipyramidal structure (Figure 4.6). In this arrangement, one oxygen occupies a pseudo-axial position and another occupies a pseudo-equatorial position. The pseudo-axial Ta-O1 bond is 1.9336(15) Å, while the pseudo-equatorial Ta-O2 bond is elongated at 2.0375(16) Å. In solution, all peaks appearing in the the $^1$H NMR spectrum contains are singlets, corresponding to the methyl groups on the brominated biphenyl backbone, the aromatic protons on the brominated
backbone, the tert-butyl groups, and the dimethylamido ligands. Only 4 total signals are observed, indicating that the ligand is bound symmetrically and that the dimethylamido groups are equivalent on the NMR timescale.

The $\kappa_2$-binding arrangement seen only in this instance is likely due to the steric bulk of the $\tau$Bu groups. Previous work by Rashidat Ayinla of the Schafer group using the biphenyl tether present in compound 12 has shown that there is an equilibrium of the $\kappa_2$- and $\kappa_3$-bound species.\[101\] It was found that the larger the functional group on the amidate ligand, the more the equilibrium favoured the $\kappa_2$ arrangement over its $\kappa_3$ analogue. A similar phenomenon is likely responsible for the bidentate binding in 77, resulting from the large steric bulk of the $\tau$Bu groups.

Figure 4.7: ORTEP representation of the solid-state molecular structure of 71 (ellipsoids plotted at 50% probability). All H-atoms omitted for clarity.
A crystalline sample of complex $71$ was obtained and found to adopt a $\kappa^3$-$O,O,N$-binding mode (Figure 4.7). An identical tantalum complex was reported by Zi in 2010, which also exhibited a tridentate binding mode.\footnote{The oxo-bound Ta-O2 bond measures 2.051(3) Å while the chelate-bound Ta-O1 bond is 2.163(3) Å (identical Ta-O bond lengths of 2.051(2) Å and 2.164(2), respectively, were reported by Zi.)}

With the notable exception of $77$, all bis(amidate) tantalum complexes in this study adopted a tridentate binding mode through $O$, $O$, and $N$. This is interesting, though unsurprising: using very similar tethered bis(amidate) ligands, Zi saw exclusively tridentate $O,O,N$ binding to tantalum.\footnote{Tetradentate bis(amidate) tantalum complexes have been reported for non-tethered ligands, but only one such tethered example has been reported by Rashidat Ayinla of the Schafer group (Scheme 4.4). Even in this instance, the tetradentate arrangement $78$ was found to be the minor product, in a 1:5 ratio with the major product, tridentate species $79$.}

Tetradentate bis(amidate) tantalum complexes have been reported for non-tethered ligands, but only one such tethered example has been reported by Rashidat Ayinla of the Schafer group (Scheme 4.4). Even in this instance, the tetradentate arrangement $78$ was found to be the minor product, in a 1:5 ratio with the major product, tridentate species $79$.

**Scheme 4.4**: Only known example of tetradentate bis(amidate) ligand binding to tantalum.
The reasons for the lack of tetradeutate tethered bis(amidate) tantalum complexes has not been conclusively identified, but possible reasons could include the slightly smaller size of Ta (atomic radius 1.49 Å) compared to Zr (atomic radius 1.6 Å). In addition, the extra dimethylamide ligand found in Ta(V) complexes (in comparison to Zr(IV) complexes) may cause additional steric crowding around the metal centre, preventing tight tetradeutate binding from bulky tethered ligands. Additionally, a κ\(^4\)-bound bis(amidate) tris(amido) tantalum species would formally be a 20\(\text{e}^-\) species. Tris(amidate) tantalum species with κ\(^3\)- (18\(\text{e}^-\)) or κ\(^2\)-bound (16\(\text{e}^-\)) species are likely to be preferred electronically.

Unlike with hydroamination, it is not clear that tetradeutate ligand binding would be desirable for promoting hydroaminoalkylation. Work in the Schafer group has shown that monoamidate tantalum complexes are more competent catalysts than bis(amidate) tantalum complexes and therefore additional ligand binding may hinder, rather than help catalyst performance.

### 4.4 Testing Bis(amidate) Tantalum Complexes for Catalytic Hydroaminoalkylation

With the success of other amidate-ligated tantalum complexes for hydroamination, preliminary screening of complexes \(\text{71, 73-77}\) was undertaken using \(N\)-methylaniline and 1-octene. This combination of substrates was chosen because it has previously been used by Hartwig and Herzon,\(^{[63,64]}\) Schafer,\(^{[65]}\) Zi,\(^{[68,69]}\) and Hultzsch\(^{[67,70]}\) for intermolecular hydroaminoalkylation catalyst screening.

The catalyst (10 mol%) and substrates were combined in a nitrogen-filled glovebox with \(d_8\)-toluene then placed in a Teflon-sealed NMR tube and heated in an oil bath outside the
glovebox. Reactions were monitored via $^1$H NMR spectroscopy with results summarized in Table 4.1.

In each case, the reactions demonstrated excellent regioselectivity for the branched isomer, consistent with all other reported group 5 systems, and product formation was observed with every catalyst except 77 (Table 4.1, Entry 7). Unfortunately, reactivity of the complexes was uniformly low, with a maximum of 39% yield after 24 h of heating (Table 4.1, Entry 8). Catalyst 71 was also screened for this reaction by Zi and co-workers. They managed to achieve 76% conversion after 120 hours of heating at 130 °C with a 5 mol% catalyst loading.$^{[68]}$ In this work, longer reaction times with catalyst 71 resulted in only minor increases in conversion, up to 46% after 72 hours of heating.

Often, extreme temperatures are used to help promote hydroaminoalkylation. However, in these preliminary tests, heating to 160 °C (Table 4.1, Entries 4 and 6) inexplicably resulted in lower yields than reactions using the same catalyst and substrates carried out at 130 °C (Table 4.1, Entries 3 and 5). It is possible that catalyst decomposition is hastened at high temperatures.
Table 4.1: Screening of new bis(amidate) tantalum complexes for hydroaminoalkylation using \( N \)-methylaniline and 1-octene.

![Chemical Reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>T (°C)</th>
<th>( t ) (h)</th>
<th>Conv. (%)</th>
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<td>130</td>
<td>88</td>
<td>13</td>
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<tr>
<td>7</td>
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<tr>
<td>8</td>
<td>71</td>
<td>135</td>
<td>24</td>
<td>39</td>
</tr>
</tbody>
</table>

Further preliminary catalytic testing was carried out using 10 mol% \([\text{Ta}]\) catalyst, 1 equivalent \( N \)-methylaniline again as the amine substrate, with 2 equivalents of norbornene as alkene substrate. The results are summarized in Table 4.2.
Table 4.2: Screening of new bis(amidate) tantalum complexes for hydroaminoalkylation using N-methylaniline and norbornene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>Conv. (%)</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>73</td>
<td>130</td>
<td>88</td>
<td>5</td>
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</tr>
<tr>
<td>4</td>
<td>77</td>
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<tr>
<td>5</td>
<td>71</td>
<td>135</td>
<td>48</td>
<td>47</td>
</tr>
</tbody>
</table>

Once again, no hydroaminoalkylation activity was seen with 77 (Table 4.2, Entry 4). The product of the hydroaminoalkylation reaction was seen in the $^1$H NMR spectra of reactions with catalysts 73, 75, and 76 (Table 4.2, Entries 1-3), but yields were again quite low. Catalyst 71 achieved a moderate yield of 47% after 48 h of heating at 135 °C (Table 4.2, Entry 5), which was less effective than that reported by Zi and co-workers using the same catalyst: 71% conversion after 120 hours of heating at 130 °C, using a 5 mol% catalyst loading.\textsuperscript{[68]}
Due to the low hydroaminoalkylation reactivity demonstrated by all catalysts in this study except 71, no further testing on an expanded substrate scope was undertaken. While enantiopure versions of all the proligands used in this work can be synthesized using methods described in Chapter 2, the decision was made not to pursue the chiral versions in light of low reactivity observed. It is unclear why catalyst 77 exhibits no competence for hydroaminoalkylation. Its $\kappa^2$-O,O binding, while unique amongst the complexes featured here, is present in other successful hydroaminoalkylation catalysts such as compounds 12 and 14. In the work of Rashidat Ayinla, who studied catalyst 12 and similar compounds, many of the complexes were found to exist in solution as an equilibrium of their $\kappa^2$-O,O and $\kappa^3$-O,O,N species.\(^{[101]}\) Her results indicated that complexes that favoured a $\kappa^2$ binding mode were the most effective catalysts while those that favoured a $\kappa^3$ binding mode were the least effective. Thus, it is surprising that catalyst 77 demonstrated no hydroaminoalkylation activity whatsoever.

While 71 did show promise in these preliminary hydroaminoalkylation results, during these tests, Zi and coworkers published reports outlining their hydroaminoalkylation results with an identical catalyst to 71;\(^{[68,69]}\) pursuit of further results with this particular complex was unlikely to be fruitful.

### 4.5 Bis(ureate) Tantalum Complex

Given the surprising activity of bis(ureate) zirconium complexes for hydroamination, an attempt to utilize a bis(urea) proligand to synthesize tantalum complexes was undertaken as well (Scheme 4.5). 3-(Aminomethyl)benzylamine was mixed first with 2.1 equivalents phenyl chloroformate and 2.1 equivalents of triethylamine in dichloromethane, followed
by treatment with diisopropylamine to produce a bis(urea) proligand 85. The proligand was thoroughly purified and dried and brought into a nitrogen-filled glovebox. The proligand was mixed in equimolar ratio with Ta(NMe₂)₅ in hexanes with heating and agitation. Upon cooling to room temperature, the volatiles were removed to yield a yellow solid, 86.

![Scheme 4.5: Synthesis of a bis(ureate) tantalum complex.](image)

The ¹H NMR spectrum of 86 shows 4 separate doublets for the methyl groups on the isopropyl moieties, however they overlap to such a great degree that integration of individual signals was not possible. Due to the fact that each methyl signal is inequivalent, it is believed that the ligand adopts a κ³-O,O,N-attachment to the tantalum centre, although a crystalline sample could not be obtained to confirm this via X-ray crystallography.

A hydroaminoalkylation test was undertaken by mixing 1 equivalent of N-methylamine with 2 equivalents of 1-octene with 10 mol% of 86, in d₈-toluene. The mixture was placed into a J. Young NMR tube and heated to 135 °C. Despite heating for 67 hours the subsequent ¹H NMR spectra of the reaction mixture did not show even trace amount of the expected hydroaminoalkylation product.
4.6 Conclusion

Six new tantalum complexes bearing bis(amidate) ligands were synthesize, characterized, and tested for efficacy in hydroaminoalkylation reactions using N-methylaniline. While all but one complex catalyzed the hydroamination reaction, product yields were generally poor in comparison to other established catalysts for this reaction. Elevated temperatures unexpectedly resulted in lower yields.

One new tantalum complex bearing a bis(urea) proligand was synthesized and tested for hydroaminoalkylation. Despite an elevated reaction temperature and long reaction time, no hydroaminoalkylation product was observed.
4.7 Experimental

General Experimental Procedures

All common reagents including solvents, amines, alkenes, and acid chlorides were purchased from Sigma Aldrich and used as received. Pentakis(dimethylamido)tantalum was purchased from Strem and used as received. Syntheses of proligands were carried out in ambient atmosphere. All other reactions were carried out using oven-dried glassware under an atmosphere of dry N₂ using Schlenk or glovebox techniques. Hexanes, benzene, and toluene were sparged with nitrogen and purified using a column of activated alumina. d₈-Toluene was degassed by several freeze-pump-thaw cycles and dried over 4Å molecular sieves before use.

The syntheses of 2,2’-diamino-6,6’-dimethylbiphenyl, 2,2’-diamino-3,3’,5,5’-tetrabromo-6,6’-dimethylbiphenyl, proligands 24-27 and 44 have been previously reported (vide supra) as has the characterization of the products of hydroaminoalkylation reactions. All characterization was carried out using services available from the Department of Chemistry at the University of British Columbia. ¹H, ¹³C and ¹⁹F NMR spectra were recorded using Bruker Avance 300 MHz, 400 MHz, or 600 MHz spectrometers, with chemical shifts given relative to the residual solvent peak. Mass spectra were recorded on either a Kratos MS-50 spectrometer using a 70 eV electron impact source or a Bruker Esquire~LC using an electrospray ionization source. Elemental analysis was recorded on a Carlo Erba Elemental Analyzer EA 1108. Single crystal X-ray structure determinations were obtained using a Bruker APEX II.
Synthesis of 72

To a solution of (±)-2,2’-diamino-3,3’,5,5’-tetra-6,6’-dimethylbiphenyl (1.0 g, 1.89 mmol) in 1,2-dichloroethane (50 mL) was added pyridine (0.90 g, 11.4 mmol), followed by trimethylacetyl chloride (1.37 g, 11.4 mmol). The reaction was heated to reflux, with stirring for 4 hours. The reaction mixture was filtered through a small bed of silica gel using dichloromethane then volatiles were removed using rotary evaporation. The crude product was washed repeatedly with cold hexanes until a purified white solid product remained. Yield: 0.86 g (65%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.03 (18H, s, C(CH$_3$)$_3$), 2.01 (6H, s, Ar- CH$_3$), 7.92 (2H, s, Ar-H); HRMS (EI) m/z (M$^+$) Calcd for C$_{24}$H$_{28}$N$_2$O$_2$Br$_4$ 691.88842; Found 691.88879.

Synthesis of 85

A solution of 3-(aminomethyl)benzylamine (1.28 g, 9.39 mmol) in dry dichloromethane (30 mL) was cooled to 0 °C in a dry Schlenk tube under an atmosphere of N$_2$. Pyridine (2.0 mL, 24 mmol) was added, followed by gradual addition of phenyl chloroformate (2.6 mL, 20.7 mmol) over a period of 15 minutes. The mixture was allowed to warm to room temperature with stirring for 1 hour. The reaction mixture was washed with 1M HCl (2 x 50 mL), brine (1 x 50 mL) then dried over MgSO$_4$, filtered through a Büchner funnel, and the solvent was removed using rotary evaporation. The resulting white solid was dissolved in DMSO (20 mL) and to this solution was added diisopropylamine (1.9 g, 19 mmol). The reaction mixture was stirred at room temperature for 3 hours, then washed with H$_2$O (2 x 30 mL), 1M HCl (2 x 30 mL), 1M NaOH (2 x 30 mL) and brine (1 x 30 mL). The solution was dried over MgSO$_4$, filtered through a Büchner funnel, and the
solvent was removed using rotary evaporation. The crude product purified using column chromatography (4:1 hexanes/ethyl acetate). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 1.21 (24H, d, CH(CH$_3$)$_2$), 3.84 (4H, m, CH(CH$_3$)$_2$), 4.39 (4H, d, Ar-CH$_2$-), 4.51 (2H, br s, N-H), 7.17 (3H, m, Ar-H), 7.24 (1H, d, Ar-H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 21.4, 44.6, 45.1, 126.2, 126.7, 128.7, 140.1, 157.0; MS (El) m/z 390 (M+); Anal. Calcd for C$_{22}$H$_{38}$N$_4$O$_2$: C, 67.66; H, 9.81; N, 14.35. Found: C, 67.34; H, 9.76; N, 14.14.

**Synthesis of 73**

In a nitrogen-filled glovebox, proligand 24 (0.150 g, 0.22 mmol) and pentakis(dimethylamido) tantalum (0.090 g, 0.22 mmol) were weighed out into a small vial. Benzene (1 mL) was added to the mixture and the vial was capped and agitated with heating for 3 minutes. The reaction was allowed to cool, and the volatiles were removed in vacuo, leaving behind a foamy red solid. Recrystallization from a minimum amount of hexanes produced red-yellow prisms. $^1$H NMR (C$_6$D$_6$, 300 MHz) $\delta$ 0.60 (3H, d, CH(CH$_3$) CH$_3$), 1.00 (3H, d, CH(CH$_3$) CH$_3$), 1.23 (3H, d, CH(CH$_3$) CH$_3$), 1.42 (3H, d, CH(CH$_3$) CH$_3$), 1.70 (3H, s, Ar- CH$_3$), 1.76 (1H, t, CH(CH$_3$)$_2$), 2.09 (3H, s, Ar- CH$_3$), 2.12 (1H, t, CH(CH$_3$)$_2$), 3.35 (18H, s, N-(CH$_3$)$_2$), 7.78 (1H, s, Ar-H), 7.88 (1H, s, Ar-H).

**Synthesis of 74**

In a nitrogen-filled glovebox, proligand 25 (0.250 g, 0.34 mmol) and pentakis(dimethylamido)tantalum (0.136 g, 0.34 mmol) were weighed out into a small vial. Hexanes (3 mL) was added to the mixture and the vial was capped and agitated with heating for 3 minutes. Benzene (1 mL) was added to help solubilize the proligand. The
vial was capped and agitated with heating for a further 3 minutes. The reaction was allowed to cool, and the volatiles were removed in vacuo, leaving behind a foamy red solid. $^1$H NMR (C$_6$D$_6$, 300 MHz) δ 0.77 (3H, s, Ar-CH$_3$), 2.12 (3H, s, Ar-CH$_3$), 6.98 (4H, m, Ar-H), 7.08 (2H, m, Ar-H), 7.29 (2H, m, Ar-H), 7.82 (1H, s, Ar-H), 7.86 (1H, s, Ar-H), 8.03 (2H, m, Ar-H).

**Synthesis of 75**

In a nitrogen-filled glovebox, proligand 26 (0.250 g, 0.29 mmol) and pentakis(dimethylamido)tantalum (0.115 g, 0.29 mmol) were weighed out into a small vial. Hexanes (3 mL) was added to the mixture and the vial was capped and agitated with heating for 3 minutes. Benzene (1 mL) was added to help solubilize the proligand. The vial was capped and agitated with heating for a further 3 minutes. The reaction was allowed to cool, and the volatiles were removed in vacuo, leaving behind a foamy red solid. $^1$H NMR (C$_6$D$_6$, 300 MHz) δ 0.64 (3H, s, Ar-CH$_3$), 2.07 (3H, s, Ar-CH$_3$), 7.14 (4H, s, Ar-H), 7.26 (2H, d, Ar-H), 7.80 (1H, s, Ar-H), 7.88 (1H, s, Ar-H), 7.91 (2H, d, Ar-H). $^{19}$F NMR (C$_6$D$_6$, 282 MHz) δ −62.73, −63.54.

**Synthesis of 76**

In a nitrogen-filled glovebox, proligand 27 (0.250 g, 0.25 mmol) and pentakis(dimethylamido)tantalum (0.100 g, 0.25 mmol) were weighed out into a small vial. Hexanes (3 mL) was added to the mixture and the vial was capped and agitated with heating for 3 minutes. Benzene (1 mL) was added to help solubilize the proligand. The vial was capped and agitated with heating for a further 3 minutes. The reaction was
allowed to cool, and the volatiles were removed in vacuo, leaving behind a foamy red solid. Recrystallization from a minimal amount of benzene yielded orange-red prisms. $^1$H NMR (C$_6$D$_6$, 300 MHz) δ 0.78 (3H, s, Ar-CH$_3$), 1.95 (3H, s, Ar-CH$_3$), 3.0-3.5 (18H, br s, N-(CH$_3$)$_2$), 7.75 (1H, s, Ar-H), 7.78 (2H, s, Ar-H), 7.80 (1H, s, Ar-H), 7.89 (2H, s, Ar-H), 8.57 (2H, s, Ar-H). $^{19}$F NMR (C$_6$D$_6$, 282 MHz) δ –62.98.

Synthesis of 77

In a nitrogen-filled glovebox, proligand 72 (0.350 g, 0.50 mmol) and pentakis(dimethylamido)tantalum (0.200 g, 0.50 mmol) were weighed out into a small vial. Hexanes (3 mL) was added to the mixture and the vial was capped and agitated with heating for 3 minutes. The reaction was allowed to cool, and the volatiles were removed in vacuo, leaving behind a foamy red solid. Recrystallization from a minimal amount of hexanes yielded yellow-red prisms. $^1$H NMR (C$_6$D$_6$, 300 MHz) δ 1.07 (18H, s, C(CH$_3$)$_3$), 2.29 (6H, s, Ar-CH$_3$), 3.09 (18H, s, N-(CH$_3$)$_2$), 7.80 (2H, s, Ar-H).

Synthesis of 71

In a nitrogen-filled glovebox, proligand 44 (0.203 g, 0.41 mmol) and pentakis(dimethylamido)tantalum (0.161 g, 0.50 mmol) were weighed out into a small vial. Hexanes (3 mL) was added to the mixture and the vial was capped and stirred at room temperature for 12 hours. The volatiles were removed in vacuo, leaving behind a foamy brown solid. Recrystallization from a minimal amount of hexanes yielded red-brown prisms. $^1$H NMR (C$_6$D$_6$, 300 MHz) δ 1.92-1.98 (9H, m, ArCH$_3$), 2.03 (3H, s, Ar-
CH₃), 2.05 (3H, s, Ar-CH₃), 2.13-2.25 (9H, m, Ar-CH₃), 3.56-3.64 (18H, m, N-(CH₃)₂), 6.37-7.13 (10H, m, Ar-H).

**Synthesis of 86**

In a nitrogen-filled glovebox, proligand 85 (0.100 g, 0.25 mmol) and pentakis(dimethylamido)tantalum (0.102 mg, 0.25 mmol) were weighed out into a small vial. Hexanes (2 mL) was added and the mixture stirred at room temperature for 16 h. Volatiles were removed *in vacuo* to leave a yellow solid. The ¹H NMR spectrum of the product contained two isomers of the metal complex which could not easily be distinguished.

**Representative Hydroaminoalkylation Procedure**

In a nitrogen-filled glovebox, a small vial was charged with N-methylaniline (80) (39 µL, 0.038 g, 0.36 mmol), 1-octene (81) (113 µL, 0.080 g, 0.72 mmol) and 76 (0.0475 g, 0.036 mmol). d₈-Toluene (0.55 g) was added and the mixture agitated until a uniform solution was achieved. The mixture was transferred to a Teflon-sealed J. Young NMR tube, sealed and removed from the glovebox. The NMR tube was placed into an oil bath heated to the temperature indicated and the reaction monitored periodically by ¹H NMR spectroscopy.
Chapter 5: Summary and Future Directions

5.1 Summary

This thesis focuses on zirconium and tantalum complexes bearing bis(amidate) and bis(ureate) ligands for use in C-N and C-C bond forming reactions. The synthesis, characterization, and catalytic efficacy of these complexes were studied to further understand and explore potential applications of early transition metal catalysts for atom-economic amine synthesis. Chapters 2 and 3 looked at applications in hydroamination, attempts to improve enantioselectivity, reduce reaction temperatures, and broaden substrate scope. Chapter 4 explored new catalysts for applications in hydroaminoalkylation, as well as the bonding and coordination of multidentate ligands to tantalum.

In Chapter 2, work on proligands featuring an axially-chiral biphenyldiamine tether was discussed. The absolute configuration of the chiral proligands was verified using X-ray crystallography, and used to devise an updated model for stereoselective control during hydroamination. Kinetic studies of a previously developed bis(amidate) bis(amido) zirconium catalyst 9 revealed a first order rate dependence on both the substrate and the catalyst concentration, consistent with established mechanistic proposals which proceed through [2+2] cycloaddition during the C-N bond-forming step and turnover-limiting protonolysis step.\[^{12}\]

New biphenyldiamine-based proligands, 17-19, were used to create bis(amidate) bis(amido) zirconium complexes, which were tested for enantioselective alkene hydroamination. The modest hydroamination results highlighted the difficulty in
achieving conformationally and coordinatively stable zirconium complexes with tetradeutate ligands. Furthermore, its importance to achieving predictable, efficient reactivity was reinforced.

A second strategy involving direct modification of the biphenyldiamine tether was undertaken, resulting in a new set of brominated proligands, 24-27. Experiments using \textit{in situ} catalyst preparation yielded promising low-temperature reactivity, including hydroamination activity observed at room temperature, which is rare for group 4 catalysts. Enantioselectivities observed under uniform reaction conditions were all between 52-55\% regardless of the proligand used, suggesting that selectivity is derived from the brominated tether rather than from the substituent of the amidate, a departure from the mechanistic rationale developed for the non-brominated systems. A proligand featuring phenyl substituents in the 3,3′-positions (32) was also explored. Its steric bulk resulted in $\kappa^3$ coordination to the metal centre. However, reactivity in hydroamination trials was limited, posing substrate scope challenges.

The expansion of hydroamination substrate scope was the focus of Chapter 3. New bis(ureate)bis(amido)zirconium complexes capable of cyclizing secondary aminoalkenes were screened, identifying 45 as the most promising candidate for broad reactivity over a range of substrates. Reactivity with secondary aminoalkene substrates is on par with previously-developed bis(ureate) zirconium catalyst 2.

An enantioenriched version of 45 was synthesized and used to carry out asymmetric hydroamination of secondary aminoalkenes. A capillary electrophoretic method to measure enantiomeric excesses of cyclic tertiary amines was developed, in which
enantiomeric amine products needed no chemical derivitization in order to be separated and quantified. Hydroamination using enantioenriched version of catalyst 45 was found to achieve ee’s up to 63%. While this is a modest display of selectivity compared to tertiary amine products resulting from rare earth hydroamination catalysts, it represents a promising starting point for neutral group 4 catalysts.

Five new bis(amidate)tris(amido)tantalum compounds, 73-77, were featured in Chapter 4 for hydroaminoalkylation catalysis. In comparison to their zirconium congeners, the tantalum complexes formed discrete organometallic species, but most preferred to adopt a κ³ arrangement of the ligand. Catalytic testing for hydroaminoalkylation was undertaken with all but one compound successfully carrying out the reaction. However, the moderate product yields observed did not warrant wider investigation of these compounds. Significant steric bulk on ligands does not appear to be a positive trait for the development of new hydroaminoalkylation catalysts.

The work reported as part of this thesis represents a tangible contribution to the further development of amidate- and ureate-ligated complexes of early transition metals. The importance of achieving a stable coordination environment in order to realize predictable reactivity and selectivity results was highlighted in studies of bis(amidate) zirconium complexes. The development of chiral bis(urea) proligands demonstrated that neutral group 4 compounds can be utilized for enantioselective synthesis of tertiary amines, and the continued refinement of capillary electrophoretic methods will allow for more efficient analysis of a wide variety of amine products. The development of new bis(amidate) tantalum species provided new information about the coordination patterns of tetradequate ligands and its effect on hydroaminoalkylation reactivity. In this manner,
this study contributes to the foundation of knowledge, better informing all future development of early metal catalysts for hydroamination and hydroaminoalkylation.

5.2 Future Research Directions

5.2.1 Modification of 6,6′-Positions of 2,2′-Diaminobiphenyl

In Chapter 2, modifications to the existing bis(amide) proligand framework were contemplated at the carbonyl moiety of the amide, and at the 3,3′-positions of the biphenyldiamine backbone. However, further modifications to this framework are also possible, such as modifications of the 6,6′-positions of the biphenyldiamine. Two modifications are proposed: replacement of methyl groups with electron-withdrawing trifluoromethyl groups, and joining the methyl groups to result in a tethered 4,5-dihydrophenanthrene backbone structure.

5.2.1.1 Proligands with Electron-withdrawing Character derived from 2,2′-Diamino-6,6′-bis(trifluoromethyl)biphenyl

Because it is known that electron-withdrawing groups enhance the reactivity of group 4 hydroamination systems,[79] a structure was proposed in which the methyl groups at the 6,6′-positions of the biphenyl backbone are replaced with trifluoromethyl groups. Since the trifluoromethyl group is distal from the binding area, it was hoped that the ligand binding would not be significantly affected but that the electron-withdrawing character of the trifluoromethyl groups would result in increased reactivity.

To investigate this possibility in a preliminary manner, 2,2′-diamino-6,6′-bis(trifluoromethyl)biphenyl, 89, was synthesized in 3 steps from commercially available
2-amino-3-nitrobenzotrifluoride (Scheme 5.1). The first step utilized the Sandmeyer reaction to form 2-iodo-3-nitrobenzotrifluoride, 87, which was then used in an Ullmann coupling to form 2,2'-dinitro-6,6'-bis(trifluoromethyl)biphenyl, 88. The nitro groups were hydrogenated using Pd/C to form 2,2'-diamino-6,6'-bis(trifluoromethyl)biphenyl, 89. All of the steps can be performed on 100 mmol scale in good yields.

Scheme 5.1: Synthesis of 2,2'-diamino-6,6'-bis(trifluoromethyl)biphenyl.

Scheme 5.2: Synthesis of bis(amide) proligands featuring a trifluoromethylated biphenyl backbone.

The racemic trifluoromethylated diamine was then combined with acid chlorides and pyridine in refluxing 1,2-dichloroethane to create new bis(amide) proligands 90-92.
Three such proligands have been successfully prepared in moderate to good yield. All of the compounds were purified using silica gel chromatography and analyzed using $^1$H, $^{13}$C, and $^{19}$F NMR, low-resolution and high-resolution mass spectrometry with characterization data matching expected values. The proligands were thoroughly dried by heating them to 70 °C in vacuo for at least 12 hours, then brought into a nitrogen-filled glovebox. However, reactions with Zr(NMe$_2$)$_4$ did not result in the formation of new organometallic species. The $^{19}$F NMR spectra of the reaction mixtures contained no signals at all, indicating a complete absence of free proligand or coordinated ligand in solution. Use of a variety of solvents, extended reaction times, and heating of the reaction mixture also did not yield new products. Due to the fact that bis(amidate) Zr complexes could not be formed, no catalytic testing could be undertaken. Exploration of other possible methods for zirconium complex synthesis, such as salt metathesis, may prove more successful, allowing for this class of bis(amidate)bis(amido)zirconium complexes to be evaluated for catalytic hydroamination.

5.2.1.2 Proposed Synthesis of Tethered Biphenyl Backbone

The work presented in Chapter 2 identified the reliable formation of discrete, monomeric species as both a desirable property, and a major challenge of bis(amidate)bis(amido)zirconium complexes. The ability of bis(amidate) ligands to adopt multiple coordination modes in solution, and the potential for the formation of dimeric, trimeric, or oligomeric species can often make it difficult to identify a defined zirconium complex with reliable catalytic activity and enantioselectivity for hydroamination reactions. In Chapter 2, the zirconium complex derived from proligand 25 exhibited dihedral angles between the two phenyl groups of the biphenyl tether measured at 64.8°.
(for a κ²-binding mode) and 109.7° (for a κ⁴-binding mode), indicating a high degree of rotational flexibility within the ligand’s biphenyldiamine tether. Introducing more rigidity into the structure of the biphenyldiamine tether may help limit the formation of multiple species in solution. This additional rigidity could be introduced by connecting the two methyl groups in the 6,6′-positions of 2,2′-diamino-6,6′-dimethylbiphenyl to result in 4,5-diamino-9,10-dihydrophenanthrene, \( \text{95} \) (Scheme 5.3).

Synthesis of this compound can be achieved starting from 2,2′-dinitro-6,6′-dimethylbiphenyl. Mislow and co-workers reported that treatment of this compound with NBS yields 2,2′-dinitro-6,6′-bis-(bromomethyl)-biphenyl, \( \text{93} \).\(^{[148]} \) A subsequent report from Dannenberg and Blackwood suggested that \( \text{Ni(cod)}_2 \) can be used to join the two bromomethyl moieties to give 4,5-dinitro-9,10-dihydrophenanthrene, \( \text{94} \).\(^{[149]} \) Hydrogenation using Pd/C should yield the biphenyldiamine containing an additional alkyl tether at the 6,6′-positions.

![Scheme 5.3: Proposed synthesis of 4,5-diamino-9,10-dihydrophenanthrene.](image)

4,5-Diamino-9,10-dihydrophenanthrene could then be used to synthesize a new class of more rigid bis(amide) proligands which could subsequently be used for the synthesis of new bis(amidate)bis(amido)zirconium complexes. As 4,5-diamino-9,10-
dihydrophenanthrene is axially-chiral, the potential for carrying out enantioselective catalytic hydroamination will be retained.

**5.2.2 Use of Chiral Amine Additives for Enantioselective Hydroamination of Secondary Amines**

Bis(ureate)bis(amido)zirconium hydroamination catalysts such as those featured in Chapter 3 are believed to proceed through a proton-assisted mechanistic pathway in which a neutrally-bound amine ligand transfers a proton to the alkene of the aminoalkene substrate undergoing cyclization. The role of the neutrally-bound amine must be fulfilled by either a second molecule of the aminoalkene substrate, or by the N-heterocyclic product resulting from a previous catalytic turnover. Experiments with catalyst 2 in which 2-methylpiperidine was added to reaction as a mimic of the hydroamination product showed no rate dependence as a function of the concentration of the amine additive. It was concluded that amine additives, and hydroamination products, are not competitive inhibitors. Rather, it suggests that 2-methylpiperidine is capable of participating in the proton-assisted bond formation that is the turnover-limiting step in the catalytic cycle of 2. If amine additives are likely participants in hydroamination, it may be possible to promote enantioselective secondary amine hydroamination with achiral catalysts combined with the use of chiral amine additives.
Table 5.1: Secondary amine hydroamination with neutral amine additives.

![Chemical structure](image)

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<td>130</td>
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<tr>
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<td>45</td>
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<td>15</td>
<td>130</td>
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<tr>
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Initial tests were carried out, and a 5-membered aminoalkene substrate featuring an N-cyclohexyl substituent was chosen as a standard test substrate. Reactions were carried out using 10 mol% of achiral zirconium catalyst 2 or a racemic version of catalyst 45. Entries 1 and 2 of Table 5.1 outline catalyst performance with no amine additives. When (R)-(α)-
methylbenzylamine was used as an additive (Table 5.1, Entries 3-8) all hydroamination was inhibited, and no product formation was observed. It was suspected this may be due to the fact that it is a primary amine. Previous experiments in which 2 was mixed with 2,6-diisopropylaniline showed the formation of dimeric and imido species, both of which are catalytically inactive.\textsuperscript{[29]} A similar process is likely underway with (R)-(α)-methylbenzylamine resulting in deactivation of the catalyst, accounting for the lack of reactivity.

When \textit{cis}-2,6-dimethylpiperidine was used as an additive (Table 5.1, Entries 9-12), catalytic hydroamination was able to proceed at rates similar to reactions carried out without additives, as expected. However, since \textit{cis}-2,6-dimethylpiperidine is a meso compound, the effect of amine additives on enantioselectivity remains unknown.

Screening a series of chiral secondary amines additives to determine if they can effect enantioselective hydroamination with achiral zirconium catalysts would be a worthwhile undertaking. Some basic chiral secondary amines such as \textit{N}-methyl-1-phenylethanamine (both enantiomers), \textsuperscript{96} 2-methylpyrrolidine (both enantiomers), \textsuperscript{97} and 2-methylpiperidine (\textit{S}-enantiomer only), \textsuperscript{98} are commercially available. Results of such investigations may also provide more valuable insight into mechanistic aspects of bis(ureate)bis(amido)zirconium catalyst systems and greatly inform strategies for achieving asymmetric products.
While this work has highlighted many challenges involved in modern catalyst development efforts, the groundwork for new research directions to overcome those challenges has also been established. Enantioselective hydroamination of secondary aminoalkenes with group 4 catalysts and enantioselective hydroaminoalkylation with group 5 catalysts remain largely unexplored. The versatility of amidate and ureate ligands will continue to allow for a wealth of potential catalyst development pathways to be pursued with these systems, work that is ongoing in the Schafer group.

**Figure 5.1**: Commercially-available chiral secondary amines.
5.3 Experimental

Synthesis of 2-iodo-3-nitrobenzotrifluoride (87)

To a 50 mL round-bottom flask charged with H$_2$SO$_4$ (5 mL) at 0 °C was slowly added, with stirring, NaNO$_2$ (1.0 g, 14.36 mmol). The mixture was heated until it turned clear (approximately 75 °C) and stirred for 5 minutes. The mixture was allowed to cool to room temperature and solidify.

In a separate flask, to a solution of 2-amino-3-nitrobenzotrifluoride (2.0 g, 9.57 mmol) in glacial acetic acid (10 mL) at 0 °C was slowly added the H$_2$SO$_4$/NaNO$_2$ mixture with stirring. The reaction was allowed to warm to room temperature and stirred for 30 minutes.

Excess urea (1.0 g, 16.7 mmol) dissolved in a minimal amount of H$_2$O was added very slowly, causing bubbling. Sodium iodide (2.39 g, 14.36 mmol) dissolved in a minimal amount of H$_2$O was then added turning the solution dark purple. Excess sodium bisulphite was added until the product was fully precipitated from solution. 2-Iodo-3-nitrobenzotrifluoride was isolated as an orange solid and used in its crude form.

Yield: 2.7 g (89%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.05 (1H, dd, Ar-$H$), 8.28 (1H, d, Ar-$H$), 8.49 (1H, d, Ar-$H$); $^{19}$F NMR (CDCl$_3$, 282 MHz): δ –63.84; MS(EI) m/z 317 (M+).

Synthesis of 2,2'-dinitro-6,6'-bis(trifluoromethyl)biphenyl (88)

To a solution of 2-ido-3-nitrobenzotrifluoride (2.5 g, 7.89 mmol) in N,N-dimethylformamide (20 mL) was added copper powder (2.0 g) and the reaction was heated to reflux, with stirring, for 4 hours. The mixture was filtered through a small bed
of Celite and the solvent was removed under reduced pressure. The crude solid was
dissolved in diethyl ether (50 mL) and washed with 3M HCl (2 x 50 mL), then dried over
MgSO₄, filtered through a Büchner funnel, and the solvent was removed using rotary
evaporation to give a brown solid which was used without further purification.

¹H NMR (CDCl₃, 300 MHz) δ 7.56 (1H, d, Ar-H), 8.50 (1H, dd, Ar-H), 8.70 (1H, d, Ar-
H); ¹⁹F NMR (CDCl₃, 282 MHz): δ −58.89; MS(EI) m/z 380 (M+).

Synthesis of 2,2′-amino-6,6’-bis(trifluoromethyl)biphenyl (89)

In a large round-bottom with side-arm, to a solution of 2,2′-dinitro-6,6’-
bis(trifluoromethyl)biphenyl (36 g, 0.11 mol) in ethyl acetate (500 mL) was added 10%
Pd/C (750 mg). The reaction vessel was sealed and put under an H₂ atmosphere for 6
hours. The mixture was filtered through a small bed of Celite and the solvent was
removed using rotary evaporation. Crude 2,2′-diamino-6,6’-bis(trifluoromethyl)biphenyl
was obtained as a brown solid in quantitative yield and used in its crude form.

Yield: 35 g (100%). ¹H NMR (CDCl₃, 300 MHz) δ 7.55 (1H, d, Ar-H), 8.50 (1H, dd, Ar-
H), 8.69 (1H, d, Ar-H); ¹⁹F NMR (CDCl₃, 282 MHz): δ −58.90; MS(EI) m/z 320 (M+).

Compounds 90-92 were synthesized using similar methods, representative procedure for
synthesis of 90:

To a solution of 2,2′-diamino-6,6’-bis(trifluoromethyl)biphenyl (0.5 g, 1.56 mmol) in
dichloromethane (100 mL) was added triethylamine (0.475 g, 4.7 mmol), followed by
gradual addition of trimethylacetyl chloride (0.56 g, 4.7 mmol) over a period of 10
minutes. The mixture was stirred at room temperature for 16 hours, until significant
quantities of a white precipitate appeared. To the reaction, 1M NaOH (30 mL) was added and the mixture stirred for 30 minutes. Additional dichloromethane (50 mL) was added, followed by addition of acetone until the precipitate dissolved and the solution became clear. The organic layer was isolated then washed with 1M NaOH (3 x 50 mL), 1M HCl (3 x 50 mL), and brine (1 x 75 mL). The organic layer was dried using MgSO₄, filtered through a Büchner funnel, and the solvent was removed using rotary evaporation. Dichloromethane (20 mL) and hexanes (120 mL) were added to the crude product to make a suspension which was filtered to isolate the precipitate. Purification of the isolated crude solid using flash chromatography (hexanes/acetone) gave a fine white powder.

Yield: 0.560 g (74%). ¹H NMR ((CD₃)₂CO, 600 MHz) δ 1.33 (18H, s, C(CH₃)₃), 7.28 (2H, d, Ar-H), 8.00 (2H, m, Ar-H), 8.25 (2H, m, Ar-H), 9.01 (2H, br s, N-H); ¹³C NMR ((CD₃)₂CO, 150 MHz) δ 27.7, 40.5, 40.5, 117.9, 122.7, 122.8, 124.2, 132.6, 133.4, 140.7, 140.8, 177.8, 177.9; ¹⁹F NMR (CDCl₃, 282 MHz): δ −58.76. MS(EI) m/z 488 (M+); HRMS (EI) Calcd For C₂₄H₂₆O₂N₂F₆ (M+): 488.18940; Found: 488.18950.

Yield: 0.550 g (67%). ¹H NMR ((CD₃)₂CO, 600 MHz) δ 7.41 (2H, d, Ar-H), 7.55 (4H, dd, Ar-H), 7.62 (2H, dd, Ar-H), 8.07 (4H, d, Ar-H), 8.18 (2H, m, Ar-H), 8.44 (2H, m, Ar-H), 9.93 (2H, br s, N-H); ¹³C NMR ((CD₃)₂CO, 150 MHz) δ 118.2, 123.1, 128.6, 129.5, 132.8, 133.6, 135.8, 140.7, 166.9; ¹⁹F NMR (CDCl₃, 282 MHz): δ −58.67. MS(EI) m/z 528 (M+); HRMS (EI) Calcd For C₂₈H₁₈O₂N₂F₆ (M+): 528.12759; Found: 528.12759.
Yield: 0.500 g (52%). \(^1\)H NMR ((CD\(_3\))\(_2\)CO, 600 MHz) \(\delta\) 2.29 (6H, s, Ar-CH\(_3\)), 2.32 (12H, s, Ar-CH\(_3\)), 6.92 (4H, s, Ar-H), 7.43 (2H, d, Ar-H) 8.10 (2H, m, Ar-H), 8.45 (2H, m, Ar-H), 9.73 (2H, br s, N-H); \(^{13}\)C NMR ((CD\(_3\))\(_2\)CO, 150 MHz) \(\delta\) 19.5, 21.3, 117.6, 122.5, 122.6, 126.1, 129.1, 133.1, 133.9, 135.2, 136.5, 139.6, 140.7, 170.0; \(^{19}\)F NMR (CDCl\(_3\), 282 MHz): \(\delta\) −58.66. MS(EI) \(m/z\) 612 (M+); HRMS (EI) Calcd For C\(_{34}\)H\(_{30}\)O\(_2\)N\(_2\)F\(_6\) (M+): 612.22115; Found: 612.22110.
References


[87] M. C. Wood, Synthesis of Chiral Bis(amidate)bis(amido) Titanium and Zirconium Complexes for Catalyzed Asymmetric Alkene Hydroamination, University of British Columbia, **2006**.


### Appendix A: TABULATED X-RAY CRYSTALLOGRAPHIC DATA

**Table A.1**: X-ray Crystallographic Data for 15, 25+Zr(NMe₂)₄ (dimer), and [25+Zr(NMe₂)₄]•(py)₂

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Table A.2: X-ray Crystallographic Data for 33, 45, and 45 (homoleptic).

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<td>1398.3(4)</td>
<td>1855.56(22)</td>
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<td>2</td>
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<td>ρ_{calcd} (g cm⁻¹)</td>
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<td>1.205</td>
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<td>Mo Kα (λ = 0.71073 Å)</td>
<td>Mo Kα (λ = 0.71073 Å)</td>
<td>Mo Kα (λ = 0.71073 Å)</td>
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<tr>
<td>temp (K)</td>
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<td>173(2)</td>
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<td>832</td>
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<td>1.98-27.63</td>
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<td>30090</td>
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<td>no. of unique reflns</td>
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<td>6450</td>
<td>8434</td>
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<td>I = 2σ(I) no. of variables</td>
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<td>447</td>
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<td>wR2 (all data)</td>
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<td>R1 (I &gt; 2σ(I))</td>
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<td>0.1272</td>
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<tr>
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<td>goodness of fit</td>
<td>1.029</td>
<td>1.128</td>
<td>1.097</td>
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Table A.4: X-ray Crystallographic Data for 73, 75, and 77.

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<td>ls286</td>
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<td>F_w</td>
<td>979.24</td>
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<td>1007.29</td>
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<td>crystal size (mm)</td>
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<td>0.4 x 0.2 x 0.2</td>
<td>0.5 x 0.4 x 0.2</td>
</tr>
<tr>
<td>colour, habit</td>
<td>colourless, prism</td>
<td>yellow, prism</td>
<td>yellow, prism</td>
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<tr>
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<td>P21/c</td>
<td>P-1</td>
<td>P-1</td>
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<td>triclinic</td>
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<td>a (Å)</td>
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<td>10.3903(4)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>11.2070(4)</td>
<td>13.470(2)</td>
<td>19.1891(7)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>20.1299(7)</td>
<td>13.938(2)</td>
<td>19.4293(7)</td>
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<tr>
<td>α (°)</td>
<td>90</td>
<td>65.441(7)</td>
<td>108.792(1)</td>
</tr>
<tr>
<td>β (°)</td>
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<td>78.846(7)</td>
<td>97.869(1)</td>
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<tr>
<td>γ (°)</td>
<td>90</td>
<td>79.979(8)</td>
<td>92.653(2)</td>
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<td>V (Å³)</td>
<td>3592.29(32)</td>
<td>1910.9(6)</td>
<td>3615.88(34)</td>
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<td>Z</td>
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<td>ρ_{calc} (g cm^{-1})</td>
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<td>radiation</td>
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<td>Mo Kα (λ = 0.71073 Å)</td>
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<tr>
<td>temp (K)</td>
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<td>100(2)</td>
<td>100(2)</td>
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<td>F(000)</td>
<td>1888</td>
<td>1136</td>
<td>1952</td>
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<td>μ (Mo Kα) (mm^{-1})</td>
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<tr>
<td>total no. of reflns</td>
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<td>62012</td>
<td>59558</td>
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<td>no. of unique reflns I = 2σ(I)</td>
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<td>8615</td>
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<tr>
<td>no. of variables</td>
<td>373</td>
<td>495</td>
<td>785</td>
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<td>R1 (all data)</td>
<td>0.0468</td>
<td>0.0266</td>
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<td>wR2 (all data)</td>
<td>0.1075</td>
<td>0.0439</td>
<td>0.0436</td>
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<tr>
<td>R1 (I &gt; 2σ(I))</td>
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<td>0.0198</td>
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<tr>
<td>wR2 (I &gt; 2σ(I))</td>
<td>0.1021</td>
<td>0.0414</td>
<td>0.0422</td>
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<tr>
<td>goodness of fit</td>
<td>1.099</td>
<td>1.060</td>
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</table>
Appendix B: NMR SPECTRA OF SELECTED COMPOUNDS

Unless otherwise indicated, spectra were obtained at ambient temperature.

17 (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

17 (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))
18 (¹H NMR, 400 MHz, CDCl₃)

18 (¹³C NMR, 100 MHz, CDCl₃)
27 (¹H NMR, 300 MHz, CDCl₃)

27 (¹³C NMR, 150 MHz, CDCl₃)
**29 (¹H NMR, 300 MHz, CDCl₃)**

![¹H NMR Spectrum](image)

**29 (¹³C NMR, 100 MHz, CDCl₃)**

![¹³C NMR Spectrum](image)

Ar = 3,5-(CF₃)₂C₆H₃

29
42 (\(^1\)H NMR, 300 MHz, CDCl\(_3\))

42 (\(^{13}\)C NMR, 75 MHz, CDCl\(_3\))
43 (\(^1\)H NMR, 400 MHz, CDCl\(_3\))

43 (\(^{13}\)C NMR, 100 MHz, CDCl\(_3\))
**85 (1H NMR, 400 MHz, CDCl₃)**

![1H NMR spectrum](image)

**85 (13C NMR, 100 MHz, CDCl₃)**

![13C NMR spectrum](image)
Mosher’s Amide derivative of **22**, from a reaction catalyzed by *in situ* generated [**26** (11 mol%) + Zr(NMe₂)₄ (10 mol%)] (**¹⁹F NMR, 282 MHz, CDCl₃, 25 °C*)

---

Mosher’s Amide derivative of **22**, from a reaction catalyzed by *in situ* generated [**26** (11 mol%) + Zr(NMe₂)₄ (10 mol%)] (**¹⁹F NMR, 282 MHz, CDCl₃, 60 °C*)

---

1.00–0.24
1.00 + 0.24
= 61% ee
Mosher’s Amide derivative of 22, from a reaction catalyzed by in situ generated [27 (11 mol%) + Zr(NMe₂)₄ (10 mol%)] (¹⁹F NMR, 282 MHz, CDCl₃, 25 °C)

=60% ee
Capillary electrophoretic analysis of the product of cyclization of aminoalkene substrate 21 by catalyst Zr(NMe₂)₄ (10 mol%).

**Area % Report**

![Capillary electrophoretic analysis graph](image1)

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<td><strong>Totals</strong></td>
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Capillary electrophoretic analysis of the product of cyclization of aminoalkene substrate 21 by catalyst (+)-46 (10 mol%).

**Area % Report**

![Capillary electrophoretic analysis graph](image2)

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<td>7.967</td>
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Capillary electrophoretic analysis of the product of cyclization of aminoalkene substrate 48 by catalyst (+)-45 (10 mol%).

Area % Report

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Capillary electrophoretic analysis of the product of cyclization of aminoalkene substrate 50 by catalyst (+)-45 (10 mol%).

Area % Report

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