CATALYTIC HYDROGENATION USING TITANIUM COMPLEXES

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Abstract:
A catalyst system for the asymmetric hydrogenation of imines has been developed using the chiral titanocene complex, ethylene-1,2-bis(h5-4,5,6,7-tetrahydro-1-indenyl)titanium 1,1'-binaphth-2,2'-diolate. For reduction of acyclic imines the enantiomeric excesses obtained are moderate to good and depend on several reaction parameters. The most dramatic effect is that of lowering the hydrogen pressure. As the pressure is lowered the ee for the acyclic substrates is diminished. For cyclic imines this catalyst system gives excellent ee's (95-99 %) in all cases investigated. The enantiomeric excesses are virtually independent of most variables including hydrogen pressure. A rational model was developed to explain the asymmetry transfer from catalyst to substrate.

The scope of the reaction has also been determined by preparing and hydrogenating several imines containing other functional groups. It has been shown that imines can be hydrogenated in the presence of trisubstituted olefins, alcohols, acetals and some other functional groups. Substrates such as hydrazines and oximes destroyed the active catalyst.

A mechanistic study of the reaction was also undertaken. Kinetic analysis of the reaction revealed that it is first order in both hydrogen and catalyst concentration and zero order in imine concentration. This is consistent with hydrogenolysis of the intermediate titanium amide being rate determining. Studies for the hydrogenation of acyclic imines indicate that the syn and anti isomers are converted to opposite enantiomers of product. The syn isomer was also found to react faster than the anti isomer. This serves to explain the pressure dependence of ee. As the pressure is lowered more of the substrate can react via the syn (minor) isomer.

Two novel chiral methylene bridged titanocene complexes were also synthesized. One contained a tetrahydroindenyl ligand and the other contained
the indenyl ligand. Although resolution of the racemic mixtures was hampered by decomposition, the complexes were effective imine hydrogenation catalysts. A faster rate of reaction was observed for the catalyst which contained the more electron donating tetrahydroindenyl ligand. The results of this study suggest that a more electron rich complex should have higher activity toward imine hydrogenation.

Some novel titanium complexes bearing o-phosphinophenol ligands were prepared and examined. The feature of this ligand system is that its electronic and steric properties can be independently tuned. The complexes were found to be fluxional by \(^1\)H NMR analysis at low temperature. An X-Ray structural analysis showed that in the solid state the molecule is chiral at the metal center. These complexes were effective olefin hydrogenation and imine hydrosilylation catalysts.

Thesis Supervisor: Stephen L. Buchwald
Title: Professor of Chemistry
Acknowledgments

Over the past five years at MIT many people have added greatly to my experience. First, my advisor, Steve Buchwald has taught me a great deal about being an experimental scientist and has allowed me to develop as a researcher. Additionally I thank him for his support in helping me make the next step in my career.

Of the Buchwald group members three people stand out as being key to my scientific development. The first two are Dr. Krissy Kreutzer and Dr. Alberto Guterriez. Their enthusiasm, intellect and interest in my research was invaluable in the early stages of my graduate work. The other is Dr. Benjamin "Buck" Warner. His insightful discussions have helped repeatedly to overcome the stumbling blocks that chemistry places in one's path. In addition I have been fortunate to develop close friendships with each of these people. Krissy deserves special thanks for keeping the "metal edge".

One other person who I have become good friends with over the years is Ron Duff. Not only have I enjoyed our many hacking adventures, he has taught me the ins and outs of car maintainence. His help has saved me many dollars in repair.

As for my past there two Instructors that have helped me along the way. The first is Mr. J. Faye Jacobson. Who could have guessed that taking his A. P. Chemistry course would lead to this? I thank him for being an excellent teacher. Second is Dr. Fred West. I thank Fred for allowing me to get into the lab as an undergraduate and get my hands dirty. This is where I really developed an interest in chemistry research.

I thank my parents. Their love, support and confidence in me will always be appreciated. They have been a constant source of encouragement.

Finally I thank my wife, Miki. She has given me perspective on life and has shown me what's really important. Her patience and understanding through graduate school will not go unrewarded.
Preface

Much of this thesis has been adapted from articles co-written by the author:


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### Chapter 3 Part 2: Synthesis and Reactivity of a novel class of Titanium Complexes Bearing Electronically and Sterically Flexible o-Phosphinophenol Ligands

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INTRODUCTION

AN OVERVIEW OF THE CATALYTIC ASYMMETRIC REDUCTION OF IMINES
The synthesis of chiral organic compounds where nitrogen is bonded to a stereogenic carbon is an important area of research. The reason for this stems from the fact that many bioactive molecules possess an amino group bound to an asymmetric center. Additionally it is often the case that only one of the enantiomers has the desired biological activity. The other enantiomer is usually inactive or may possess other undesirable characteristics. Thus the necessity for enantiomerically pure amine containing compounds has resulted in the development of many methods for their preparation. Among these, the asymmetric reduction of the C=N bond is one of the most widely studied. A review of this process has recently been published\(^1\) and therefore only transition metal catalyzed methods will be described here.

The reaction scheme for transition metal catalyzed reduction of imines is illustrated in Scheme 0.1 where \(L_n^*M-H\) represents a transition metal complex bearing chiral ligands. The metal hydride can add to the imine to give two diastereomeric metal amide complexes which can then be converted with hydrogen to the amine. Addition to the si\(^{\dagger}\) face of the imine leads

**Scheme 0.1 Metal Catalyzed Hydrogenation of Imines**

\[ R_L^+ R_S^- N^R \rightarrow \text{Si addition} \rightarrow \text{H}_2 \rightarrow \text{Re addition} \rightarrow \]

\[ \text{ (R) amine} \]

\[ \text{ (S) amine} \]

to the (R) amine while addition to the re face gives the (S) amine. Catalytic hydrogenation offers two major advantages over other methods. First, only a small amount of a chiral material is required to produce a large quantity of
product. Secondly the chiral ligands can be systematically modified to maximize the enantioselectivity and/or reactivity of the complex.

The first example of asymmetric imine reduction was reported by Kagan in 1975. A rhodium complex with the chiral DIOP ligand was employed in the hydrosilylation of several imines (Scheme 0.2). Reactions were conducted with 1 mol% rhodium catalyst and diphenylsilane as the stoichiometric reducing agent. The reduction of N-(1-methyl)benzylidene benzylamine gave the best results. The product was isolated with an ee of 65%.

**Scheme 0.2** Rhodium Catalyzed Hydrosilylation of Imines

Since this initial report several groups have investigated the rhodium and iridium catalyzed reduction of imines. Table 0.1 shows some of the best results from these studies. The imine derived from 4-methoxy acetophenone and benzylamine was hydrogenated by Becalski and co-workers using 0.5 mol% of the rhodium chiraphos catalyst to give the product with a 91% ee. Bakos et al. have used a rhodium catalyst bearing sulfonated chiral phosphine ligands to convert this imine to the product with an ee of 95%. The sulfonated ligands allow the reaction to be carried out in water/ethylacetate mixtures. Becker and co-workers have employed the rhodium DIOP catalyst in the hydrosilylation of 2-phenylpyrrroline. This cyclic amine was converted to the product with 64% ee. Chiral iridium complexes have also been employed in the hydrogenation of imines. For example iridium(DPPP) has been studied by Chan and Osborn.
The cyclic imine 2,3,3-trimethylindolenine was converted with 0.1 mol % catalyst to the amine with an ee of 80%. With this system acyclic imines were reduced

Table 0.1 Imine Reduction Using Late Metal Catalysts

<table>
<thead>
<tr>
<th>Imine</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Reductant</th>
<th>ee</th>
<th>Ref</th>
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<tr>
<td><img src="image1" alt="Imine Structure 1" /></td>
<td>0.5 % rhodium</td>
<td><img src="image2" alt="Ligand Structure 1" /></td>
<td>H$_2$, 1500 psi</td>
<td>91%</td>
<td>3</td>
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<tr>
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<td>1 % rhodium</td>
<td><img src="image4" alt="Ligand Structure 2" /></td>
<td>H$_2$, 1000 psi</td>
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<tr>
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<td><img src="image6" alt="Ligand Structure 3" /></td>
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<td>H$_2$, 580 psi</td>
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<td><img src="image10" alt="Ligand Structure 5" /></td>
<td>H$_2$, 20 bar</td>
<td>84%</td>
<td>7</td>
</tr>
</tbody>
</table>

Ar = ![Ar Structure](image11)

with lower selectivity. Spindler, Pugin and Blaser have investigated the iridium catalyzed hydrogenation of some imines which are important intermediates in the synthesis of herbicides. In the best case the imine was reduced to the desired product with an ee of 84%.

One of the most recent advances in the enantioselective reduction of the C=N bond was reported in 1992 by Burk and Feaster. The strategy they developed is based on the reduction of N-acylhydrazones (scheme 0.3). The N-acyl hydrazones are conviently prepared by condensation of the hydrazine with
the desired ketone. The hydrazones are then reduced to N-acylhydrazines using 0.1 mol % of a rhodium complex bearing novel diphospholane ligands.

**Scheme 0.3** Hydrogenation of N-Acylhydrazones

\[
\begin{align*}
\text{HN} & \quad \text{HN} \\
\text{Ar} & \quad \text{Ar} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{O} & \quad \text{O}
\end{align*}
\]

\begin{align*}
0.1 \% \text{Rh (Et-DuPHOS)} & \quad 1 \text{ atm H}_2 \\
\text{Sml}_2 & \quad \text{R}_1 \text{NH}_2 \\
72-97 \% \text{ ee} & \quad \text{Et-DuPHOS} = \text{Et-DuPHOS}
\end{align*}

Subsequent cleavage of the N-N bond was effected with Sml₂ to give the amines in good to excellent enantioselectivity. The best results were observed when one of the substituents on the imine carbon is aromatic. The key feature of this chemistry is the nature of the phospholane ligands. X-ray data show that the ethyl substituents on the 5 membered rings are in close proximity to the metal center. This results in efficient transfer of asymmetry from the ligand to the substrate.

The catalytic asymmetric reduction of imines is a powerful method for the construction of chiral amines. Much research effort has been devoted to the development of this reaction. To date all of the catalysts have been late metal systems with chiral phosphine ligands. Enantioselectivities observed with these catalysts range from moderate to excellent. However much can be learned from
further development of new catalysts for this process. The study of the first early transition metal catalyst system is the subject of this thesis.
REFERENCES

CHAPTER 1

CATALYTIC ASYMMETRIC HYDROGENATION OF IMINES WITH A CHIRAL TITANOCENE COMPLEX: SCOPE AND LIMITATIONS
INTRODUCTION

The development of methods for the construction of optically pure molecules represents an ever increasing challenge to the synthetic organic chemist. An efficient approach to this challenge is the transfer of asymmetry to a prochiral substrate with a catalytic amount of a chiral reagent. Due to the high specificity with which enzymes recognize certain substrates, enzymes have been commonly employed to catalyze many asymmetric reactions. In most cases products with very high enantiomeric excesses can be isolated in this manner. An alternative approach is to use a transition metal catalyst possessing chiral ligands. Since the chiral ligands can be tailored to meet the needs of a reaction, metal-catalyzed processes are potentially more general than enzymatic methods. To this end, development of catalysts for the hydrogenation of achiral substrates to form enantiomerically enriched products represents a major area of research.\textsuperscript{1} Levels of selectivity that rival those of enzymatic systems have been achieved for the asymmetric hydrogenation of olefins\textsuperscript{2} and ketones.\textsuperscript{3} With the growing importance of enantiomerically pure nitrogen containing compounds in the pharmaceutical and agrochemical industries, the asymmetric hydrogenation of imines to enantiomerically enriched amines has received much recent attention.\textsuperscript{4} Virtually all of the systems employed for this reaction are derived from late transition metals and in general the substrates must possess an additional coordinating ligand, such as a carbonyl group, for high levels of reactivity and selectivity to be realized.

This chapter describes the successful development of a novel early transition metal catalyst for asymmetric hydrogenation. The present catalyst is particularly successful for the hydrogenation of cyclic imines for which ee's of 95-99 % were obtained. The system also exhibits a good degree of functional group
tolerance thus making it applicable to the synthesis of complex molecules. Furthermore, the catalyst does not require that the substrate possess an additional coordinating ligand to achieve high selectivity; the enantiofacial preference is determined solely by steric interactions between the rigid ligand environment and the substrate.

BACKGROUND

The work described in this chapter evolved from a reaction discovered by Dr. Kristina Kreutzer in 1990. While working on a project directed at the synthesis of novel group 4 silyl hydride complexes, Kreutzer observed that reaction of $\text{Cp}_2\text{Ti}(\text{PMe}_3)_2$ with dimethyl(ethoxy)silane afforded not the expected titanocene silyl hydride complex but instead gave two new silanes, dimethylsilane and diethoxysilane (Scheme 1.1, equation 1). Furthermore, the initial titanium complex, $\text{Cp}_2\text{Ti}(\text{PMe}_3)_2$, was also observed in the product mixture, suggesting that the process was catalytic in titanium. Kreutzer rationalized these results with the catalytic cycle shown in Scheme 1.1. A titanium hydride complex is formed (most likely a titanocene(III) hydride, see chapter 2) and reacts with dimethyl(ethoxy)silane via a $\sigma$-bond metathesis process to give a titanocene alkoxide and dimethylsilane. The titanocene alkoxide then reacts with another equivalent of dimethyl(ethoxy)silane to produce diethoxy(dimethyl)silane and regenerate the titanium hydride.

The mechanistic features of this reaction suggested its potential application to organic chemistry. Kreutzer reasoned that if the titanium alkoxide could be formed from the titanium hydride via an alternate pathway, such as the 1,2-insertion of a carbonyl compound, a catalytic process for the hydrosilylation of organic carbonyls could be developed (Scheme 1.2). The discovery that an active catalyst could be formed from titanocene dichloride and 2 equivalents of
butyllithium further enhanced the synthetic potential of this reaction since this circumvented the need for preparation and manipulation of the air sensitive $\text{Cp}_2\text{Ti}(\text{PMe}_3)_2$. This methodology has subsequently applied to the catalytic reduction of esters$^6$ and amides$^5$ as well as the asymmetric reduction of ketones.$^7$

The focus of this chapter is the application of the above reaction to the catalytic asymmetric reduction of imines. By replacing the carbonyl oxygen (Scheme 1.2) with a nitrogen, we reasoned that a process for the reduction of imines could be developed. Furthermore by using a suitable chiral titanocene complex, we expected that the amines could be produced in an enantioselective manner. While there are many known chiral titanocene complexes, we chose to
Scheme 1.2  Titanocene-Catalyzed Reduction of Organic Carbonyls

\[
\begin{align*}
\text{Cp}_2\text{TiCl}_2 & \quad \xrightarrow{2 \text{ equiv. } n-\text{BuLi}} \\
\text{R'}_3\text{SiH} & \quad \xrightarrow{\text{Cp}_2\text{Ti}-\text{H}} \\
\text{R'}_3\text{SiH} & \quad \xrightarrow{\text{Cp}_2\text{Ti}-\text{H}} \\
\end{align*}
\]

use Brintzinger's \textit{ansa} titanocene complex, \((R,R,R)-1\) (Figure 1.1). This complex was chosen on the basis of the following criteria; 1) The synthesis and resolution of the complex is relatively short and simple. 2) The ethylene bridged

\[
\text{(R,R,R)-1}
\]

Figure 1.1  Brintzinger's Chiral Titanocene Complex
tetrahydroindenyl ligand system provides a rigid C₂ symmetric chiral environment. 3) Previous work in our labs by Dr. Robert Grossman had shown that, using the analogous zirconium complex, allylic amines with high levels of enantiomeric excesses could be synthesized by the coupling of alkynes with zirconocene imine complexes.⁹

RESULTS and DISCUSSION

We began our investigation of the titanocene catalyzed hydrosilylation of imines by studying the reduction of the aryl methyl imines shown in Scheme 1.3. Initial experiments were carried out with 10 mol % titanium and indicated that phenylsilane was the optimum stoichiometric reductant. While the reduction of an N-methyl derivative proceeded at room temperature (25 °C) in 16 h with excellent enantioselectivity, the corresponding N-benzyl derivative was reduced much more slowly. After heating the mixture at 80 °C for 63 h the reaction had proceeded to ca. 75 % conversion (Scheme 1.3). Assuming normal Arrhenius behavior this is a rate decrease of ca. 250. We also observed that qualitative

Scheme 1.3  Hydrosilylation of Aryl Methyl Imines

reaction rates were dependent on the silane used and therefore concluded that silane was involved in the rate limiting step. We rationalized these results as shown in Scheme 1.4.
In the second step of the catalytic cycle, a titanium amide is cleaved by the silane (in analogy to the mechanism for hydrosilylation of organic carboxyls in Scheme 1.2). More bulky substituents on nitrogen would result in more steric hindrance as the silane approaches the metal complex and a slower reaction would be expected. It became apparent that by using a smaller silane we could circumvent this problem; however low molecular weight silanes such as silane itself are extremely pyrophoric and difficult to use. Thus we turned our attention to the use of hydrogen as an alternative. As indicated in Scheme 1.4, the small hydrogen molecule should be only slightly affected by steric interactions.

**Scheme 1.4 Rationale for Rate Dependence Nitrogen Substituents**

\[
\begin{align*}
\text{Cp'}_2 \text{Ti} & \quad \text{N} \quad \text{R} \\
\text{H} & \quad \text{SiR}_3 \\
\text{R}_2 & \quad \text{R}_3 \\
\text{Cp'}_2 \text{Ti} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{R}_2 & \quad \text{R}_3 \\
\text{R}_3 \text{Si} & \quad \text{N} \quad \text{R}_1 \\
\end{align*}
\]

\[
\text{Cp'}_2 = \text{bis(tetrahydroindenyl)ethane}
\]

Additionally, the use of hydrogen results in a more attractive process since no silane by-products are generated during work up. While the hydrogenolysis of a titanium amide bond had not been reported, the cleavage of titanium carbon bonds with hydrogen is a facile reaction\(^{10}\) and there are many examples of titanocene-catalyzed olefin hydrogenations.\(^{11,12}\)

The optimized protocol for the imine hydrogenation is shown in scheme 1.5. Treatment of a THF solution of \(\langle R,R,R\rangle\)-1 with 2 equivalents of \(n\)-butyllithium
followed by 3 equivalents of phenylsilane$^{13}$ results in the formation of an active hydrogenation catalyst, presumed to be a titanium(III) hydride.$^{14}$ Under a hydrogen atmosphere (80-2000 psig H$_2$), this species effects the catalytic hydrogenation of imines to the corresponding amines.

The proposed catalytic cycle for this reaction is presented in Scheme 1.6. The first step is reaction of the titanium hydride with an imine, via a 1,2-insertion reaction, to form two diastereomeric titanium amide complexes.$^{15}$ The second

**Scheme 1.5** Titanocene Catalyzed Imine Hydrogenation

![Scheme 1.5](image)

step is hydrogenolysis of the intermediate amide complexes, via a σ-bond metathesis reaction,$^{16}$ to regenerate the titanium hydride and form the two enantiomeric amines.

During the course of our investigations differences in the behavior of cyclic imines and acyclic imines emerged. Therefore, these two classes of substrates will be discussed separately.

**Hydrogenation of Acyclic Imines:** Our results for the hydrogenation of several acyclic imines are shown in Table 1.1. A characteristic of these substrates is that they exist as mixtures of anti and syn isomers.$^{17}$ This property is important when considering the stereochemical outcome of the reaction. We
chose to focus on the hydrogenation of  

$N$-benzyl imines since, in general, the benzyl group can be subsequently removed to afford the primary amines.$^{18}$

Scheme 1.6 Proposed Catalytic Cycle for Imine Hydrogenation

\[ \text{Cp}_2'Ti\cdot N\overset{R}{\rightarrow}R_L \]

\[ \text{H}_2 \]

$(R) -$ amine

$(S) -$ amine

\[ \text{Cp}_2'Ti\cdot N\overset{R}{\rightarrow}R_L \]

\[ \text{H}_2 \]

As can be seen in Table 1.1, the reaction proceeds to afford the amines with moderate to good enantiomeric excesses. When $(R,R,R)$-1 is used as the catalyst precursor, imines are generally converted to the $(R)$ enantiomers of the amines. For example, at a hydrogen pressure of 2000 psig, $N$-(1-phenyl)-ethylidene benzylamine (entry 10) is converted to $N$-benzyl $(R)-\alpha$-methylbenzyl amine with an average ee of 77%. Likewise, $N$-(1-cyclohexyl)-ethylidene benzylamine (entry 4) was hydrogenated, at 2000 psig, to the corresponding $(R)$ amine with an ee of 76%. For entries 7 and 9 the isolated amines also had an
(R) configuration. The absolute configurations were established by comparison of the optical rotation with known values.

In order to develop a model to rationalize these results an understanding of the orbital interactions between the metal and the substrate is necessary. Hoffmann and Lauher have calculated the valence orbitals for bent metallocene complexes at the extended Hückel level. They discuss the orbital interactions for insertion of an olefin into a metallocene hydride. The molecular orbital diagram for this process is shown in Scheme 1.7. An important feature of the intermediate olefin-hydride complex is emphasized by this diagram. One end of the olefin is much closer to the cyclopentadienyl ligands. Therefore
<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>(anti / syn)</th>
<th>Amine</th>
<th>Pressure (psig)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<td>(3.3:1)</td>
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<td>77ᵈ</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CH₃-CH=CH-N⁺⁺Ph</td>
<td>2000</td>
<td>93</td>
<td>85ᵉ</td>
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<td>(10:1)</td>
<td>CH₃-CH=CH-N⁺⁺Ph</td>
<td>2000</td>
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<td>53</td>
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<tr>
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<td>CH₃-CH=CH-N⁺⁺Ph</td>
<td>(44:1)</td>
<td>CH₃-CH=CH-N⁺⁺Ph</td>
<td>2000</td>
<td>82</td>
<td>70</td>
</tr>
</tbody>
</table>

ᵃReactions were run using 5 mol % 1 as the (R, R, R) diastereomer unless otherwise noted. All new compounds were characterized by ¹H NMR, ¹³C NMR and IR spectroscopy. Elemental composition was determined by elemental analysis or high resolution mass spectrometry. Enantiomeric excesses were determined by HPLC analysis using a Chiralcel OD HPLC column. Absolute configurations in entries 4, 7, 9, and 10 were determined by optical rotation. bWith 10 mol % 1. cThe absolute configuration of the product is opposite to that observed at 2000 psig. dThe ee of product ranged from 65-87% for several experiments. eWith 2 mol % 1.
the substituents on the closer end (the carbon that becomes bound to the metal) will have a much stronger influence on the selectivity of insertion. For a niobocene olefin hydride complex, this geometry has been confirmed by an X-ray crystallographic study.\textsuperscript{20}

Since imines and olefins are isolobal, the reaction of an imine with the titanium hydride will be analogous. Orbital analysis of the titanocene catalyzed imine hydrogenation leads to the model shown in scheme 1.8. For proper overlap of the titanocene orbitals and the imine $\pi$ orbitals the plane defined by the nitrogen atom, the imine carbon and the imine substituents ($R_S$ and $R_L$), must be orthogonal to the plane containing the titanium, the nitrogen atom and hydride ligand. Interaction of an $anti$ imine with the $(R,R)$ titanium complex leads to two possible intermediates, A and B. In A, the nitrogen substituent points down away from the cyclohexyl part of the tetrahydroindenyl ligand while in B the nitrogen substituent is up and interacts unfavorably with the ligand. Thus reaction via A should require less energy than via B, and for an $anti$ imine the $(R,R)$ titanium complex is expected to give the $(R)$-amine. Since the nitrogen substituent, $R_N$, is much closer to the ligand during the insertion step its effects on the stereochemistry of the reaction are magnified relative to the effects of the substituents on the imine carbon ($R_L$ and $R_S$).

For a $syn$ imine two intermediates C and D are also possible. In C an unfavorable interaction exists between the nitrogen substituent, $R_N$ and the tetrahydroindenyl ligand. In D, $R_N$ points down, away from the ligand and there is no interaction. Therefore reaction via D is expected to be a lower energy pathway than via C. Again the carbon substituents, $R_S$ and $R_L$ are more remote from the ligand so the effect of these groups are small relative to that of $R_N$. Thus with the $(R,R)$ complex, the $syn$ imine is expected to afford the $(S)$-amine.
Importantly the two predictions of this model are: (1) The stereochemistry is determined predominately by the orientation of the nitrogen substituent; (2) Syn and anti imines react to give the amine with opposite absolute configuration. Experimental evidence to support this prediction has been observed (*vide infra*).

**Scheme 1.8** Stereochemical Model for the Hydrogenation of Imines

The ethyene bridge is omitted for clarity

The enantiomeric excesses of the products correlate roughly with the anti / syn ratios of the imines. For example *N*-\((1\text{-methyl})\text{p}-\text{pentylidene benzylamine (entry 1, anti/syn }=3.3:1\text{)} and *N*-\((1,5\text{-dimethyl})\text{hex-5-enylidene benzylamine (entry 2, anti/syn }=3:1\text{)} are reduced, at 2000 psig and 65 °C, to the corresponding amines with ee's of 58 % and 62 % respectively. The reduction of the olefin in
entry 2 suggested that we may be able to hydrogenate trisubstituted olefins with this catalyst. This was successfully demonstrated by Dr. Rick Broene.\textsuperscript{21}

$N$-(1,2-dimethyl)propyldiene benzylamine (entry 3, \textit{anti/syn} =13:1) and $N$-(1-cyclohexyl)ethylidene benzylamine (entry 4, \textit{anti/syn} =11:1) are both reduced to the corresponding amines, at 2000 psig, with 76 \% ee. As illustrated by entries 4 and 6 the ee changed very little when the nitrogen substituent was changed from a benzyl to a propyl group. However, when the nitrogen substituent was a methyl group (entry 7, \textit{anti/syn} =11:1) the ee was significantly higher, 92 \% vs 76 \%, than when it was a benzyl group (entry 4). In addition, when the nitrogen substituent was a methyl group the reaction occurred at 80 psig of hydrogen with no effect on the enantiomeric excess (an explanation for this is offered below).

In order to increase the utility of this reaction for the synthesis of enantiomerically enriched amines we examined the reaction at lower hydrogen pressures. We found, however, that for the hydrogenation of acyclic imines high hydrogen pressures are required to achieve the maximum ee's. For example, when $N$-(1-cyclohexyl)ethylidene benzylamine (entry 4) was hydrogenated at 2000 psig the ee of the isolated amine was 76 \%. When the hydrogen pressure was reduced to 500 psig the ee decreased to 43 \%. Similarly $N$-(1-cyclohexyl)ethylidene (4-methoxy)benzylamine (entry 5) was hydrogenated at 2000 psig to the corresponding amine with an ee of 78 \%. When the reaction was run at 500 psig the ee of the amine was 62 \%. We also observed this behavior for non-benzylc imines as demonstrated by the hydrogenation of $N$-(1-cyclohexyl)ethylidene propylamine (entry 6). At 2000 psig this imine was hydrogenated to the corresponding amine with an ee of 79 \%. When the reaction was conducted at 80 psig the amine was isolated with only a 4 \% ee.
Interestingly the amine formed at 80 psig was of the opposite absolute configuration to that observed at 2000 psig. A pressure dependence was also observed for the imines in entries 2 and 10, and appears to be general for most acyclic imines.

Experimental evidence suggests that this pressure dependence can be explained on the basis of the interconversion of the anti and syn isomers of the imine. We observed that for the hydrogenation of N-(1-cyclohexyl)ethylidene benzylamine (entry 4) that the syn isomer reacts faster than the anti isomer. However, the syn isomer does not completely disappear over the course of the reaction, suggesting that it is being replaced by isomerization of the anti isomer\textsuperscript{22} (see chapter 2). Since our transition state model for the reaction (Scheme 1.8) predicts that the anti and syn isomers react to form opposite enantiomers of the amine, as the pressure is lowered, more of the imine can react via the syn isomer and the observed ee of the product will be lower.

One exception to the pressure dependence for acyclic imines is the hydrogenation of N-(1-cyclohexyl)ethylidene methylamine (entry 7, anti/syn =11:1). This imine was converted to the corresponding amine either at 500 psig or at 80 psig with 92 % ee. The insensitivity of ee to changes in pressure for this imine is presumably due to the faster rate of hydrogenolysis relative to the rate of interconversion of syn and anti isomers. The N-methyl imine (entry 7) reacts ca. 16 times faster than the N-propyl imine (entry 6) which shows a dramatic pressure dependence, while the interconversion rate of anti and syn isomers should be similar for both substrates.\textsuperscript{17,22} Furthermore, the ee for this substrate does not correlate very well to the anti / syn ratio. The reason for this is probably because the methyl group on the nitrogen is small. When this is the case RS and RL become more important in determining selectivity. For the anti isomer,
intermediate A (Scheme 1.8) is still energetically favored relative to B since in B there is an interaction between $R_L$ and the tetrahydroindenyl ligand. Thus the selectivity for the anti isomer will not be significantly effected. However the energy difference between C and D will be lessened since the interaction between $R_L$ and the tetrahydroindenyl ligand in D raises its energy relative to C. Therefore the selectivity for hydrogenation of the syn isomer will be lower. This would result in a higher ee for the product since reaction through C gives the same enantiomer as reaction through A.

**Hydrogenation of Cyclic Imines:** Based on the stereochemical model presented in Scheme 1.8 we expected that an isomerically pure imine (either anti or syn) could be hydrogenated with high selectivity. In addition, heterocyclic compounds, in which a nitrogen is bound to a stereogenic carbon, make up a large body of naturally occurring and medicinally important compounds. We therefore investigated the asymmetric hydrogenation of cyclic imines as a possible synthetic route to highly enantiomerically enriched cyclic amines. For many late transition metal catalysts asymmetric hydrogenation of cyclic imines has been less successful. Therefore, it was of particular interest to us to define the functional group compatibility of this catalyst system. The results are presented in Table 1.2.

The hydrogenation of cyclic imines to cyclic amines was found to occur with excellent levels of enantiomeric excesses in all cases investigated. Furthermore, in almost all cases, the reactions could be conducted at much lower hydrogen pressure than for acyclic imines. This greatly increases the practical utility of the reaction because the reactions can be conducted in a standard Fisher-Porter bottle rather than a high pressure autoclave. A notable difference between the hydrogenation of cyclic imines and that of acyclic imines is that the
enantiomeric excesses for cyclic imines are virtually insensitive to changes in hydrogen pressure. For example 2-phenyl-1-pyrroline (entry 1) was hydrogenated at 2000 psig, with (R,R,R)-1, to afford (R)-2-phenylpyrrolidine with an ee of >98%. This corresponds to a $\Delta \Delta G^\ddagger$ of >3 kcal / mol. That the product has an (R) absolute configuration is consistent with the model shown in Scheme 1.8, since the imine has anti geometry. At 500 psig and at 80 psig the ee of the

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Amine</th>
<th>Pressure (psig)</th>
<th>T (°C)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>![Imine 1]</td>
<td>![Amine 1]</td>
<td>2000</td>
<td>65</td>
<td>77</td>
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<td>65</td>
<td>78</td>
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<td>![Amine 7]</td>
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<td>50</td>
<td>73</td>
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<td>8</td>
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<td>![Amine 8]</td>
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<td>9</td>
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<td>45</td>
<td>72</td>
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<td>10</td>
<td>![Imine 10]</td>
<td>![Amine 10]</td>
<td>2000</td>
<td>65</td>
<td>81</td>
<td>98</td>
</tr>
</tbody>
</table>
Table 1.2 (Con't) Asymmetric Hydrogenation of Cyclic Imines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Amine</th>
<th>Pressure (psig)</th>
<th>T (°C)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
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<tbody>
<tr>
<td>11</td>
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<td>TBDMSO</td>
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<td>12</td>
<td></td>
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<td>65</td>
<td>82</td>
<td>99</td>
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<tr>
<td>13</td>
<td></td>
<td></td>
<td>80</td>
<td>65</td>
<td>84</td>
<td>99</td>
</tr>
</tbody>
</table>

a Reactions were run using 5 mol % 1 as the (R, R, R) diastereomer unless otherwise noted. All new compounds were characterized by 1H NMR, 13C NMR, IR and HRMS. Enantiomeric excesses were determined by HPLC analysis using a Chiralcel OD HPLC column. The absolute configurations in entries 1, 2, 4 and 5 were determined by optical rotation. Yields refer to isolated yields of products of >95% purity unless otherwise noted. b With 1 mol % catalyst. c This yield includes 5-8% of the saturated compound and <1% of the Z isomer; the ee was determined on the product mixture. d This yield includes 14-18 % of the E isomer and 13-19 % of the saturated compound; the ee was determined by hydrogenating the mixture to the saturated compound (H2, Pd/C) and measuring the ee of the product. e With 1.1 eq phenylalanine / imine.

amine was 99 %. Likewise, when the imine is part of a six or a seven membered ring as in entries 2 and 3, the ee was also found to be independent of hydrogen pressure. In both cases the amines were isolated with ee's ranging from 97-98 %. Note that the anti imine (entry 2) also is converted to the (R)-amine. For the hydrogenation of 6,7-dimethoxy-3,4-dihydro-1-methyl isoquinoline (entry 4) a small effect of lowering the hydrogen pressure was observed. At 2000 psig the average ee of the amine was 98 %, while at 80 psig the ee was 95 %.

Significantly this substrate, which has syn geometry, was hydrogenated by (R,R,R)-1 to the (S)-amine. This result supports the prediction that a syn imine reacts to give the (S) product (Scheme 1.8).

We next examined the functional group compatibility of our catalyst system by preparing and hydrogenating a number of 2-substituted pyrrolines with various organic groups. A substrate with a benzyl protected pyrrolyl substituent (entry 5) was of particular interest to Professor Masamune as a ligand for use in
catalytic asymmetric Michael reactions.\textsuperscript{23} We found that this imine could be cleanly hydrogenated to the corresponding amine with excellent enantioselectivity. However the free pyrrole, \textit{4a}, (Table 1.3) caused destruction of the catalyst. The lithio derivative, \textit{4b}, did not react at all, but the catalyst remained active.\textsuperscript{24} This can be ascribed to chelation of the substrate to titanium through the pyrrolyl nitrogen and the imine lone pair. When the substrate is coordinated in this fashion, proper orbital overlap necessary for 1,2-Insertion cannot occur. The trimethylsilyl derivative, \textit{4c}, also failed to react under standard conditions, presumably for steric reasons. An imine containing a pyridine substituent, 3-pyridyl-2-pyrrole \textit{6}, also failed to react under normal conditions. The reason for this is not clear at present. At 80 psig and 65 \textdegree{}C, 2-furyl-2-pyrrole, \textit{7}, reacted to \textit{ca}. 80 \% conversion after 60 h. Even at elevated hydrogen pressures (1000 psig, 65 \textdegree{}C, 48 h) the reaction could not be forced to completion. This behavior may be due to product inhibition by binding of the amine to the metal in a bidentate fashion. Presumably as the concentration of amine increases the concentration of free catalyst decreases and the reaction slows down.\textsuperscript{25}

Since early transition metal complexes are conventionally perceived to have limited functional group tolerance, we examined the selectivity of cyclic imines containing various organic functional groups (Table 1.2). As can be seen by entry 6, a trisubstituted olefin is completely tolerated under standard conditions. The amino olefin was isolated in good yield and with an excellent enantiomeric excess of 99 \%. No reduction of the olefin was observed. When the olefin is a bulky disubstituted one, as in an (\textit{E})-trimethylsilyl substituted olefin (entry 7), a small amount of reduction (\textit{ca}. 5-8 \%) and isomerization to the (\textit{Z}) isomer (\textit{ca}. 1 \%) was observed. The product was isolated in good yield with an
ee of 99%. Dialkyl substituted olefins (i.e. entry 8) were hydrogenated and isomerized concomitantly with imine reduction. In this case ca. 13-18 % reduction and ca. 14-18 % isomerization to the (E) isomer was observed. However the ee of the products was 99 %. This was determined by hydrogenating the product mixture (H₂, Pd/C) and measuring the ee of the saturated amine. The hydrogenation of a substrate containing a terminal olefin (entry 9) illustrates that terminal olefins are reduced faster than imines at 80 psig and 45 °C with this catalyst. The ee of the product was again excellent, 99 %.

Substrates containing certain oxygenated functional groups were also found to be compatible with this methodology. For example, a substrate containing a tert-butyldimethylsilyl ether (entry 11) was hydrogenated to the corresponding amine with an ee of 99 %. Interestingly a substrate containing a hydroxyl group (entry 13) was converted to the corresponding amino-alcohol with an excellent ee, 99 %. For this reaction it was necessary to add 1.1 equivalents of phenylsilane. Presumably, silylation of the alcohol takes place prior to reduction of the imine.\textsuperscript{5,26} A substrate containing an acetal (entry 12) was also hydrogenated to the corresponding amine in good yield with an ee of 99 %. This result is interesting in view of the oxophilic nature of titanium. When a competition experiment between 2-phenylpyrroline and acetophenone was conducted, no reaction of the imine was observed unless 1 equivalent of phenylsilane was added. Under these conditions, the acetophenone was hydrosilylated before any imine was reduced. The 1-phenylethanol obtained from this reaction had an ee of 33 %\textsuperscript{7} while the ee of the isolated (R)-2-phenylpyrroldidine was 98 %. This result shows that while this catalyst is more reactive toward a carbonyl group than an imine, the presence of a ketone does not significantly affect the course of imine reduction.
Several other substrates were investigated with this system (Table 1.3). For example, imines containing a tert-butyl group, either on the nitrogen as in 3 or on the imine carbon as in 2 were found not to react, even under forcing conditions (2000 psig H₂, 65° C). Presumably the bulkiness of the t-butyl group makes the insertion step (see Scheme 1.6) unfavorable. An imine containing an aromatic bromide, 5, was found to deactivate the catalyst. In this reaction ca. 5 % of the debrominated imine was observed (GC/MS). Similar reactivity has been reported for reduced titanocene species and is evidence that titanium is in the +3 oxidation state during the reaction. Imine 8 which contains a trifluoromethyl group, also destroyed the catalyst. In this case we were unable to determine the nature of the decomposition products.

Substrates such as oximes and hydrazones would be particularly interesting because they can be isolated in isomerically pure form. Based on the
model in Scheme 1.8 these substrates were expected to be reduced with high enantioselectivity. Unfortunately for these substrates deactivation of the catalyst was also observed. In the case of hydrazone 9, the major species in the reaction was starting material. However, a trace of 1-cyclohexylethylamine was detected by GC/MS. For the reaction of oxime 10a and its derivatives 10b (R=CH₃) and 10c (R=TBDMS), traces (ca 2-4 %) of 1-phenylethylamine were detected along with starting material. The presence of 1-phenylethylamine indicates that N-O bond cleavage occurred under the reaction conditions and that the C=N double bond was reduced prior to N-O bond cleavage. The N-O bond cleavage of hydroxyl amines with TiCl₃ has been previously observed.²⁸

**Kinetic Resolution of Acyclic Imines:** We also briefly examined the kinetic resolution²⁹ of imines possessing an asymmetric center with this catalyst system. The results are shown in Table 1.4. As indicated, the kinetic resolution of acyclic imines proceeds with only modest selectivity. The best results were obtained with the imine derived from tetralin (entry 3). In this case a $k_{rel}$ of 4.5 is found which corresponds to a $\Delta\Delta G^\ddagger$ of 1.0 kcal/mol.

Although the enantiomeric excesses of the products are not high enough to be useful some interesting results are observed. First, when using (R,R,R)-1 as the catalyst precursor the (S)-amine is produced as the major enantiomer (entries 1 and 2). This is opposite to what is observed in the ketimine hydrogenation (table 1.1, entry 10). Second, when the hydrogenation of $N$-benzylidine(1-phenylethyl)amine (entry 1) is run to completion (at 2000 psig) racemic product is isolated. Since hydrogenation of the corresponding ketimine proceeds with 77 % ee we can conclude that little or no isomerization to the ketimine occurs during the reaction. Third, for the kinetic resolution of $N$-benzylidine(1-phenylethyl)amine the $k_{rel}$ values at 2000 psig and 150 psig are
approximately the same (2.1 and 2.5 respectively). This indicates that the resolution occurs at the 1,2-insertion step and not the hydrogenolysis step of the process (Scheme 1.6).

Table 1.4. Kinetic Resolution of Acyclic Imines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Pressure (psig)</th>
<th>% conversion</th>
<th>ee (config) of amine (%)</th>
<th>( k_{rel} )</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td></td>
<td>2000</td>
<td>100</td>
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<td></td>
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<td>2000</td>
<td>25</td>
<td>31 (S)</td>
<td>2.1</td>
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<tr>
<td></td>
<td></td>
<td>150</td>
<td>70</td>
<td>23 (S)</td>
<td>2.5</td>
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<tr>
<td>2</td>
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<td>2000</td>
<td>29</td>
<td>16 (S)</td>
<td>1.5</td>
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<tr>
<td>3</td>
<td></td>
<td>2000</td>
<td>44</td>
<td>51</td>
<td>4.5</td>
</tr>
</tbody>
</table>

*Reactions were run using 5 mol % 1 as the \((R, R, R)\) diastereomer unless otherwise noted. All new compounds were characterized by \(^1\text{H}\) NMR, \(^{13}\text{C}\) NMR and IR spectroscopy. Elemental composition was determined by elemental analysis or high resolution mass spectrometry. Enantiomeric excesses were determined by HPLC analysis using a Chiralcel OD HPLC column. Absolute configurations in entries 1 and 2 were determined by optical rotation. \(^b\) These values were calculated using the method in reference 24.*

Given the excellent enantiomeric excess observed for the hydrogenation of cyclic imines it seemed reasonable to expect that the kinetic resolution of cyclic imines would be successful with this system. This was demonstrated by Dr. Alma Viso and Dr. Nancy Lee.\(^{30}\) For 2,5 disubstituted pyrroline, when the reduction is stopped at 50 % conversion both the imine and the amine were isolated with 95-99 % ee.

**CONCLUSIONS**

We have successfully developed a procedure for the asymmetric hydrogenation of imines using a chiral titanocene catalyst. The reaction has been shown to produce amines with good to excellent levels of enantioselectivity and in good isolated yield. For acyclic imines (with the exception of \(N\)-methyl imines) the enantiomeric excesses are still below the level of practical utility.
However, the catalyst system is particularly useful for the hydrogenation of cyclic imines. For these imines the titanocene catalyst system affords the amines with 95-99 % enantiomeric excess. Other catalysts for the asymmetric reduction of cyclic imines have been less successful.4c-f

Our system exhibits tolerance to several common organic functional groups, including trisubstituted olefins, acetics and alcohols. Additionally our system does not require coordinating ligand in the substrate for high selectivity to be observed. The catalyst discriminates purely on the basis of the "shape" of the substrate. In fact, in some cases an additional ligand in the substrate appears to have a negative effect on the reaction. This is in contrast to the late metal systems in which a coordinating group is often required for good enantioselectivity to be observed.4

The catalyst system also affects the kinetic resolution of racemic chiral imines. The data indicate that the resolution occurs in the first step (the 1,2-insertion step) of the catalytic cycle. Although for the acyclic substrates the resolution was not particularly good (the highest relative rate constant observed was 4.5) this work provided the basis for development of an efficient kinetic resolution of cyclic imines.30

In addition, it has been shown that under the proper reaction conditions olefins are also reduced by this catalyst (compare table 1.1 entry 2 and table 1.2 entry 6). Accordingly this system has also been applied to the asymmetric hydrogenation of olefins21 and enamines.31
EXPERIMENTAL SECTION

**General Considerations:** All reactions were conducted under an atmosphere of argon, nitrogen or hydrogen using standard Schlenk and glove box techniques. Hydrogenation reactions were conducted in a Fisher-Porter Bottle (purchased from Aerosol Lab Equipment, Walton, NY) or in a Parr model 4751 high pressure autoclave (Parr Instrument Co, Moline, IL). Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Unity-300, Varian XL-300 or Bruker AC-250 Fourier transform spectrometer. Infrared (IR) spectra were recorded on a Mattson Cygnus Starlab 100 or Perkin Elmer 1600 series Fourier transform spectrometer. High resolution mass spectra (HRMS) were recorded on a Finnigan system 8200 mass spectrometer. Elemental analyses were performed by Desert Analytics (Tucson, AZ). Gas chromatographic (GC) analyses were performed on a Hewlett-Packard model 5890 gas chromatograph with a flame ionization detector and a model 3392A integrator using a 25 meter capillary column with cross linked HP-1 or HP-17 as a stationary phase. High performance liquid chromatography (HPLC) was conducted using a Hewlett-Packard model 1050 pumping system with a Hewlett-Packard model 1040A ultraviolet detector and a Chiralcel OD chiral stationary phase (Daicel Chemical Industries, Ltd.). Optical rotations were measured with a Perkin Elmer model 241 polarimeter. Melting points were determined with a Haake Buchler melting point apparatus and are uncorrected.

Tetrahydrofuran (THF) and diethyl ether were dried and deoxygenated by refluxing and distilling from sodium / benzophenone ketyl under an argon atmosphere. For large scale preparations of complex 1, THF was purchased from Aldrich Chemical Co. in Sure Seal bottles and used as received. Hexane and benzene were dried and deoxygenated by refluxing and distilling from
sodium / benzophenone ketyl under a nitrogen atmosphere. Toluene was dried by refluxing and distilling from sodium metal under a nitrogen atmosphere. Diisopropylamine and methylene chloride were dried by refluxing and distilling from CaH₂ under a nitrogen atmosphere. Preparative flash chromatography was performed on silica (E. M. Science Kieselgel 60, 230-400 mesh) or neutral alumina (ICN Alumina N, Akt. I). Deactivated silica was prepared by washing silica with acetone and drying in the oven. All reagents, unless otherwise stated, are commercially available and were used as received.

Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated by capillary GC and/or ¹H NMR spectrometry. All new compounds were characterized by ¹H NMR, ¹³C NMR and IR spectrometry, and by high resolution mass spectrometry or elemental analysis.

**Preparation materials:**

**rac- and meso-Ethylene-1,2-bis(η⁵-3-indenyl)titanium dichloride:** This complex was prepared by a modification of the original procedure. In a 1 l. Schlenk flask under an argon atmosphere 1,2-bis(3-indenyl)ethane-dependently (12.92 g, 50 mmol) was dissolved in 500 mL dry THF. The solution was cooled to 0 °C and a solution of n-butyllithium (2.5 M in hexanes, 40 mL, 100 mmol) was added. This mixture was allowed to warm to room temperature and stir for 30 min. It was then transferred dropwise, via cannula, under argon to a suspension of TiCl₃ (7.71 g, 50 mmol, purchased from Aldrich) in 500 mL dry THF, over a period of 2 h. The resulting green-brown solution was allowed to stir for an additional 4 h. CHCl₃ (50 mL, 600 mmol) was then added to the mixture and it was allowed to stir overnight. The resulting dark green solution was concentrated in vacuo to yield a brown air stable solid. The solid was washed with Et₂O (300 mL), water
(50 mL), and aqueous HCl (4 M, 20 mL). The solid was again washed with water (20 mL) followed by ethanol (50 mL) and dried in vacuo. A brown solid (10.04 g, 53 % yield) was recovered as a 1:1 to 1 mixture of meso- to rac- isomers (¹H NMR). ¹H NMR (300 MHz, CDCl₃, TMS): δ 7.6-7.1 (m, 16H), 6.9 (dd, 2H), 6.7 (dd, 2H), 6.5 (d, 2H), 6.0 (d, 2H), 4.8-3.7 (m, 8H); ¹³C NMR (75 MHz, CDCl₃): δ 128.6, 128.5, 128.4, 128.3, 126.1, 122.7, 122.2, 122.0, 119.7, 116.6, 115.5, 30.4, 29.6.

**rac-Ethylene-1,2-bis(η₅-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride:**
Prepared from rac- and meso-Ethylene-1,2-bis(η₅-3-indenyl)titanium dichloride as described⁸ Yield: 75 % based on amount of rac- isomer present in the initial mixture ¹H NMR (300 MHz, CDCl₃, TMS): δ 6.6 (d, 2H), 5.56 (d, 2H), 3.3-3.0 (m, 6H), 2.7-2.5 (m, 4H), 2.5-2.3 (m, 2H), 2.3 .8 (m, 4H), 1.45-1.6 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ 137.79, 134.69, 128.94, 126.32, 111.55, 27.87, 24.50, 24.17, 21.77, 21.75.

**[(R,R)-Ethylene-1,2-bis(η₅-4,5,6,7 tetrahydro-1-indenyl)titanium (R)-1,1'-binaphth-2,2'-diol]**: Prepared as described³,³³ with a modification of the workup. A dry 1 L Schlenk flask under an argon atmosphere was charged with 5.0 g of sodium (50% dispersion in paraffin, 109 mmol). The solid sodium was washed, by cannula filtration, with dry hexanes (3 x 25 mL). Dry toluene (400 mL) was added and the mixture was stirred at 80 °C for 1 h. Solid rac-ethylene-1,2-bis(η₅-4,5,6,7-tetrahydro-1-indenyl)-titanium dichloride (5.0 g, 13 mmol) and solid (R)-1,1'-binaphth-2,2'-diol (1.87 g, 6.5 mmol, purchased from Aldrich) were then added to the solution. The mixture was stirred at 80 °C for 45 min (reaction times vary from 45 min to 4 h) at which point TLC analysis of an aliquot (1:1
methylene chloride : hexanes) showed no remaining \((R)-1,1'-\text{binaphth}-2,2'-\text{diol}\). The warm solution was filtered through celite and concentrated to give 7.06 g of a red air-stable solid. The desired \((R,R)-\text{ethylene}-1,2\text{-bis}(\eta^5-4,5,6,7\ \text{tetrahydro}-1\text{-indenyl})\text{titanium} \ (R)-1,1'-\text{binaphth}-2,2'-\text{diolate}\) was separated by flash chromatography under nitrogen on alumina using 1:1 methylene chloride : hexanes. A red solid (3.5 g) was obtained which was recrystallized by dissolving it in methylene chloride and adding hexanes until crystals began to form. The mixture was allowed to stand until no further crystallization was apparent. Removal of the solvent yielded 2.83 g (73% yield based on one enantiomer) of product as dark red air-stable crystals. \(^1\text{H NMR} \ (300 \text{ MHz, CDCl}_3, \text{TMS}): \delta 7.78 \ (d, 2H), 7.75 \ (d, 2H), 7.16 \ (t, 2H), 7.10 \ (d, 2H), 7.01 \ (t, 2H), 6.88 \ (d, 2H), 5.56 \ (m, 4H), 3.33 \ (m, 2H), 3.09 \ (m, 2H), 2.55 \ (m, 4H), 1.71 \ (m, 6H), 1.49 \ (m, 4H), 1.20 \ (m, 2H); \(^{13}\text{C NMR} \ (75 \text{ MHz, CDCl}_3): \delta 165.6, 137.13, 134.72, 132.88, 128.61, 128.30, 127.61, 126.94, 125.43, 125.09, 121.79, 121.42, 117.75, 116.20, 106.42, 27.44, 23.91, 23.17, 22.09, 21.81. \left[\alpha\right]_{578} = -3690^\circ \pm 44^\circ \ (c = 0.45 \text{ mg/mL in CHCl}_3); \text{lit.value}^8 \left[\alpha\right]_{578} = +3100^\circ \ ((S,S,S) \text{ diastereomer, } c = 0.040 \text{ mg/mL in CHCl}_3); \text{lit.value}^{33} \left[\alpha\right]_{578} = +4085^\circ \ ((S,S,S) \text{ diastereomer, } c = 0.045 \text{ mg/mL in CHCl}_3).

**General procedure the preparation of acyclic imines:**\(^{34}\) The ketone (1 equiv) and the appropriate amine (1 equiv) were dissolved in dry toluene (50-100 mL) in a round bottom flask under nitrogen. The flask was equipped with a reflux condenser and a Dean-Stark trap and the mixture was heated to reflux for 2-5 days after which the solvent was removed \textit{in vacuo}. The imine products were purified by distillation or recrystallization. The ratio of geometric isomers was determined by \(^1\text{H NMR} \text{ spectrometry}.)
N-(α-Methylbenzylidene)benzylamine: The general procedure was followed using benzylamine (10.9 mL, 100 mmol) and acetophenone (11.7 mL, 100 mmol). The compound was purified by distillation (132 °C, 0.08 mm Hg) to afford 10.4 g (50 % yield) of the desired product, which solidified on standing, as a 17:1 mixture of geometric isomers. 1H NMR (300 MHz, CDCl₃, TMS): major isomer δ 7.85 (m, 2H), 7.45-7.15 (m, 8H), 4.75 (s, 2H), 2.35 (s, 3H); minor isomer δ 4.42 (s, 2H), 2.39 (m 3H); aromatic resonances are obscured by those of the major isomer; 13C NMR (75 MHz, CDCl₃): both isomers, δ 156.41, 141.62, 141.13, 130.13, 129.15, 128.92, 128.88, 128.81, 128.75, 128.24, 127.30, 127.25, 127.12, 127.08, 126.57, 57.79, 56.24, 18.33, some resonances of the minor isomer are obscured; IR (neat): 3083, 3023, 2857, 1631, 1602, 1576, 1493, 1447, 1376, 1349, 1301, 1283, 1268, 1044, 1025, 759, 730, 695, 689; mp 41.0-42.7 °C.

N-(1-cyclopropylethylidene)benzylamine: The general procedure was followed using benzylamine (2.73 mL, 25 mmol) and acetyl/cyclopropane (2.48 mL, 25 mmol). The compound was purified by distillation (73 °C, 0.1 mm Hg) to afford 2.61 g (60 % yield) of the desired product as a 7.5:1 mixture of geometric isomers. 1H NMR (300 MHz, CDCl₃, TMS): major isomer δ 7.34-7.19, (m, 5H), 4.47, (s, 2H), 1.79, (s, 3H), 1.8-1.65, (m, 1H), 0.88-0.71, (m, 4H), minor isomer δ 4.69, (s, 2H), 1.9-1.8, (m, 1H), all other resonances are obscured; 13C NMR (75 MHz, CDCl₃): both isomers δ 170.9, 140.6, 128.2, 128.1, 127.6, 127.4, 126.3, 54.6, 54.3, 22.0, 20.5, 15.8, 12.7, 6.5, 5.7, IR (neat): 3085, 3062, 3025, 3003, 2863, 1494, 1451, 1385, 1369, 1345, 1300, 1264, 1210, 1176, 1116, 1026, 956, 892, 818, 731, 696; HRMS: calc. for C₁₂H₁₅N; 173.1204, found 173.1205.
**N-\([\alpha\text{-Methyl}(4\text{-methoxy})\text{benzylidene}]\)benzylamine:** The general procedure was followed using benzylamine (5.5 mL, 50 mmol) and 4-methoxyacetophenone (7.5 g, 50 mmol). The compound was purified by recrystallization from pentane to afford 2.51 g (18% yield) of the desired product as a 17:1 mixture of geometric isomers. \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS): major isomer \(\delta\) 7.75 (d, 2H), 7.45, (d, 2H), 7.36-7.25 (m, 3H), 6.92, (d, 2H), 4.73 (s, 2H), 3.84, (s, 3H), 2.30 (s, 3H); minor isomer \(\delta\) 7.15, (d, 2H), 4.50 (s, 2H), 2.39 (m 3H); some resonances are obscured by those of the major isomer; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): major \(\delta\) 164.8, 160.8, 140.7, 133.7, 128.2, 128.1, 127.6, 113.3, 55.4, 55.1, 15.3, minor \(\delta\) 146.8, 131.8, 113.9, 29.5, 12.3, some resonances of the minor isomer are obscured; IR (CDCl\(_3\)): 3064, 3029, 2959, 2935, 2090, 2838, 2053, 1948, 1863, 1605, 1576, 1509, 1453, 1415, 1368, 1347, 1306, 1252, 1174, 1114, 1074, 1031, 928, 920, 910, 906, 893, 834, 804, 747, 734; mp 61.4-63.3 °C.

**N-(1-(2-Furyl)ethylidene)benzylamine:** The general procedure was followed using benzylamine (5.5 mL, 50 mmol) and 2-acetylfuran (5.5 mL, 50 mmol). The compound was purified by distillation (106 °C, 0.22 mm Hg) to afford 4.8 g (48% yield) of the desired product, which solidified on cooling (-10 °C), as a 10:1 mixture of geometric isomers. \(^1\)H NMR (250 MHz, CDCl\(_3\), TMS): major isomer \(\delta\) 7.50 (d, 1H), 7.4-7.2 (m, 5H), 6.82 (d, 1H), 6.45 (dd, 1H), 4.75 (s, 2H), 2.25 (s, 3H); minor isomer \(\delta\) 7.55 (d, 1H), 6.8 (d, 1H), 6.52 (dd, 1H), 4.85 (s, 2H), 2.48 (m, 3H); all aromatic resonances are obscured by those of the major isomer; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): both isomers, \(\delta\) 157.76, 154.71, 144.49, 140.50, 128.94, 128.89, 128.23, 128.26, 127.10, 111.89, 111.83, 111.67, 55.82, 15.43, some resonances of the minor isomer are obscured; IR (neat): 3150, 3030, 2876, 2866, 1635, 1627, 1623, 1616, 1602, 1581, 1495, 1493, 1490, 1488, 1450, 1402, 1394.
1351, 1294, 1171, 1046, 1022, 765, 743, 734, 698; HRMS: calc. for C_{13}H_{13}NO; 199.0997, found 199.0995.

\textit{N-(1-Methylpentyldiene)benzylamine:} The general procedure was followed using benzylamine (3.25 mL, 30 mmol) and 2-hexanone (3.7 mL, 30 mmol). The product was purified by distillation (67 °C, 0.05 mm Hg) to afford 3.64 g (64 % yield) of a clear oil as a 3.3:1 mixture of geometric isomers. \textit{\textit{1}}H NMR (300 MHz, CDCl₃, TMS): major isomer δ 7.31 (s, 2H), 7.30 (s, 2H), 7.25-7.21 (m, 1H), 4.47 (s, 2H), 2.32 (t, 2H), 1.89 (s, 3H), 1.60-1.54 (m, 2H), 1.39-1.31 (m, 2H), 0.92 (t, 3H), minor isomer δ 4.50 (s, 2H), 2.31 (t, 2H), 2.07 (m, 3H), 0.93 (t, 3H); all other resonances are obscured by those of the major isomer; \textit{\textit{13}}C NMR (75 MHz, CDCl₃): both isomers, δ 171.33, 140.56, 128.34, 128.29, 127.74, 127.63, 126.46, 126.37, 55.06, 54.63, 42.61, 32.24, 28.74, 28.46, 22.92, 22.55, 17.48, 13.94, 13.83, some resonances of the minor isomer are obscured; IR (neat): 3063, 3027, 3000, 2956, 2930, 2871, 2861, 1660, 1495, 1466, 1452, 1434, 1420, 1376, 1367, 1347, 730, 696.

\textit{N-(1-Cyclohexylethylidene)benzylamine:} The general procedure was followed using benzylamine (2.18 mL, 20 mmol) and acetylcylohexane (2.76 mL, 20 mmol). The reaction mixture was filtered through celite and concentrated to recover 3.7g (85 % yield) of a slightly yellow oil as a 11:1 mixture of geometric isomers. \textit{\textit{1}}H NMR (300 MHz, CDCl₃, TMS), major isomer δ 7.33 (s, 2H), 7.31 (s, 2H), 7.26-7.20 (m, 1H), 4.50 (s, 2H), 2.35-2.0 (m, 1H), 1.86 (s, 3H), 1.86-1.77 (m, 5H), 1.44-1.22 (m, 5H), minor isomer δ 4.57 (s, 2H), 2.01 (m, 3H), all other resonances are obscured by those of the major isomer; \textit{\textit{13}}C NMR (75 MHz, CDCl₃): both isomers, δ 174.65, 140.72, 128.32, 128.23, 127.69, 127.47, 126.40,
126.26, 54.64, 50.55, 30.20, 29.65, 26.16, 25.98, 15.70, 6.76, some resonances of the minor isomer are obscured; IR (neat): 3062, 3027, 2927-2851, 1657, 1494, 1450, 730, 696; HRMS: calc. for C_{18}H_{21}N; 215.1674, found 215.1675.

\textit{N-(1-Cyclohexylethylidene)(4-methoxybenzyl)amine:} The general procedure was followed using 4-methoxybenzylamine (2.61 mL, 20 mmol) and acetylcylohexane (2.76 mL, 20 mmol). The reaction mixture concentrated to recover 5.64 g of a slightly yellow oil. The material was purified by vacuum distillation (142 C, 0.011 mm Hg) to afford 3.12 g 64 % yield) of desired product as a 14:1 mixture of geometric isomers. \textit{1H NMR (300 MHz, CDCl\textsubscript{3}, TMS), major isomer} δ 7.22 (d, 2H, J=8.4 Hz), 6.86 (d, 2H, J=8.4 Hz), 4.42 (s, 2H), 3.79, (s, 3H), 2.30-2.18 (m, 1H), 1.84 (s, 3H), 1.86-1.62 (m, 5H), 1.45-1.15 (m, 5H), minor isomer δ 4.5 (s, 2H), 2.75 (m, 1H), 1.99 (m, 3H), all other resonances are obscured by those of the major isomer; \textit{13C NMR (75 MHz, CDCl\textsubscript{3}):} both isomers, δ 174.1, 158.0, 132.7, 128.3, 113.6, 113.5, 54.9, 53.9, 51.4, 50.3, 40.3, 30.0, 29.5, 26.0, 25.8, 21.7, 15.4, some resonances of the minor isomer are obscured; IR (neat): 2944, 2925, 2849, 2666, 2062, 1872, 1654, 1611, 1584, 1511, 1461, 1447, 1365, 1345, 1299, 1245, 1170, 1105, 1037, 910, 888, 815, 778, 752, 725, 702, 684, 668, 625; HRMS: calc. for C\textsubscript{16}H\textsubscript{23}NO; 245.17795, found 215.1780.

\textit{N-(1-Cyclohexylethylidene)propylamine:} A steel autoclave was charged with propylamine (12.5 mL, 150 mmol) and acetylcylohexane (4.13 mL, 30 mmol). Ether (100 mL) was added along with 10 g of 3 A molecular sieves. The vessel was sealed and heated to 100 °C for 48 h. The vessel was opened and the reaction mixture was filtered through celite and concentrated to recover 5.4 g of a
slightly yellow oil. Fractional vacuum distillation (134 °C, 20 mm Hg, using base washed glassware) afforded 2.61 g (52 % yield) of desired product as a 9:1 mixture of geometric isomers. 1H NMR (300 MHz, CDCl3, TMS), major isomer δ 3.2-3.15 (t, 2H), 2.21-2.10, (m, 1H), 1.78-1.54, (m, 7H), 1.74, (s, 3H), 1.48-1.17, (m, 5H), 0.94-0.89, (t, 3H), minor isomer δ 3.29-3.21, (t, 2H), 2.69-2.59, (m, 1H), 1.94, (s, 3H), all other resonances are obscured by those of the major isomer; 13C NMR (75 MHz, CDCl3): both isomers, δ 172.9, 52.9, 51.7, 50.6, 40.2, 30.2, 29.8, 26.2, 24.2, 24.0, 23.6, 14.8, 12.0, some resonances of the minor isomer are obscured; IR (neat): 2927, 2852, 1659, 1449, 1374, 1306, 1243, 1198, 1065, 889. HRMS: calc. for C11H21N; 167.1674, found 167.1675.

N-(1-Cyclohexylethylidene)methylamine: A steel autoclave was charged with methylamine (3.9 g, 127 mmol, condensed into a tarred flask cooled with dry ice / acetone) and acetylcyclohexane (3.5 mL, 25 mmol). Ether (75 mL) was added along with 10 g of 3 A molecular sieves. The vessel was sealed and heated to 110 °C for 24 h. The vessel was opened and the reaction mixture was filtered through celite and concentrated to recover a yellow oil. Fractional vacuum distillation (106 °C, 20 mm Hg, using base washed glassware) afforded 2.01 g (59 % yield) of desired product as a 11:1 mixture of geometric isomers. 1H NMR (300 MHz, CDCl3, TMS), major isomer δ 3.07, (s, 3H), 2.12, (m, 1H) 1.85-1.6, (m, 8H), 1.40-1.10, (m, 5H), minor isomer 3.15 (s, 3H), 1.9, (s, 1H), all other resonances are obscured by those of the major isomer; 13C NMR (75 MHz, CDCl3): both isomers, δ 175.3, 50.3, 38.4, 30.4, 29.3, 28.3, 26.2, 26.1, 25.9, 15.1, some resonances of the minor isomer are obscured; IR (neat): 2924, 2850, 2665, 1709, 1660, 1447, 1395, 1359, 1305, 1292, 1205, 1143, 1115, 1095, 955,
888, 855, 765, 745, 635, 619, 605; HRMS: calc. for C₉H₁₇N; 139.1361, found 139.1362.

\( \text{N-(1,2 Dimethypropyldene)benzylamine:}^{38} \) Benzyamine (2.18 mL, 20 mmol) and 3-methyl-2-butanol (2.1 mL, 20 mmol) were dissolved in benzene under nitrogen containing 10 g of 3 A molecular sieves. The mixture was heated to reflux for 12 h. The solvent was removed in vacuo. The product was purified by distillation (73 °C, 0.26 mm Hg) to afford 2.39 g (68 % yield) of a clear oil as a 13:1 mixture of geometric isomers. ¹H NMR (300 MHz, CDCl₃, TMS): major isomer δ 7.32 (s, 2H), 7.31 (s, 2H), 7.23-7.21 (m, 1H), 4.48 (s, 2H), 2.57 (m 1H), 1.84 (s, 3H), 1.12 (d, 6H); minor isomer δ 4.57 (s, 2H), 3.10 (m, 1H), 2.0 (m, 3H), 1.8 (d, 6H); all other resonances are obscured by those of the major isomer; ¹³C NMR (75 MHz, CDCl₃): both isomers, δ 175.25, 140.72, 128.39, 128.30, 127.73, 127.51, 126.35, 54.66, 40.21, 19.88, 14.98, some resonances of the minor isomer are obscured; IR (neat): 3027, 2965, 2870, 1661, 1495, 1464, 1452, 1365, 730, 696.

\( \text{N-(1-(2-Naphthyl)ethylidene)benzylamine:} \) The general procedure was followed using benzyamine (10.9 mL, 100 mmol) and 2-acetonaphthone (11.7 mL, 100 mmol). The compound was purified by recrystallization from toluene/hexanes to afford 3.74 g (71 % yield) of the desired product as a 44:1 mixture of geometric isomers. ¹H NMR (300 MHz, CDCl₃, TMS): major isomer δ 8.2 (s, 1H), 8.15 (dd, 1H), 7.89 (m, 1H), 7.82 (m, 2H), 7.5-7.4 (m, 4H), 4.8 (s, 2H), 2.4 (s 3H); minor isomer δ 4.49 (s, 2H), 2.73 (s, 3H); all other resonances are obscured by those of the major isomer; ¹³C NMR (75 MHz, CDCl₃): (minor isomer not detected) δ 166.19, 141.08, 138.82, 134.56, 133.49, 129.24, 128.92, 49
128.30, 128.23, 128.09, 127.16, 127.09, 127.06, 126.63, 124.85, 56.33, 16.22; IR (CHCl₃): 3062, 3024, 3013, 2965, 1627, 1495, 1452, 1433, 1372, 1349, 1289, 1228, 1194, 1130, 1028, 892, 860, 824, 742, 732, 725, 698, 674, 665; HRMS: calc. for C₁₅H₁₇N; 259.1361, found 259.1360; mp 107.5-109.8 °C.

*N-(1,5-Dimethylhex-5-enylidene)benzylamine*: The general procedure was followed using benzylamine (2.18 mL, 20 mmol) and 6-methyl-5-heptene-2-one (2.95 mL, 20 mmol). The product was purified by distillation (107 °C, 0.25 mm Hg) to afford 2.66 g (62 % yield) of a yellow oil as a 3:1 mixture of geometric isomers. ¹H NMR (300 MHz, CDCl₃, TMS): major isomer δ 7.31 (s, 2H), 7.30 (s, 2H), 7.25-7.21 (m, 1H), 5.14 (m, 1H), 4.48 (s, 2H), 2.40-2.25 (m, 4H), 1.89 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H); minor isomer δ 4.51 (s, 2H), 2.25-2.18 (m, 2H), 2.08 (m, 3H); all other resonances are obscured by those of the major isomer; ¹³C NMR (75 MHz, CDCl₃): both isomers, δ 170.80, 140.52, 131.01, 128.34, 128.27, 127.75, 127.82, 126.46, 126.35, 123.68, 55.05, 42.68, 25.87, 25.17, 17.64, some resonances of the minor isomer are obscured; IR (neat): 3085, 3062, 3027, 2966, 2856, 1659, 1495, 1452, 1437, 1419, 1375, 1368, 1347, 1028, 730, 696; HRMS: calc. for C₁₅H₂₁N; 215.1674, found 215.1672.

*N-Benzyllidene(1-phenylethyl)amine*: A solution of 1-phenylethylamine (2.58 mL, 20 mmol) and benzaldehyde (2.04 mL, 20 mmol) in diethyl ether was stirred over magnesium sulfate (4 g) under an argon atmosphere for 2 h. The mixture was filtered and concentrated to give 4.14 g (98 % yield) of a colorless oil. ¹H NMR (300 MHz, CDCl₃, TMS): 8.36 (s, 1H), 7.77 (m, 2H), 7.44-7.3 (m, 7H), 7.25-7.20 (m, 1H), 4.54 (q, 1H), 1.59 (d, 3H).
N-Benzylidne(1-cyclohexylethyl)amine: A solution of benzaldehyde (3.76 mL, 37 mmol) and 1-(cyclohexyl)ethyl amine (5.0 g, 37 mmol) in 120 mL of ether was stirred over magnesium sulfate (6.0 g) for 12 h. The resulting mixture was filtered and concentrated. Vacuum distillation (99 °C, 0.01 mm Hg), afforded 6.27 g (79 % yield) of desired 6 as a colorless liquid. $^1$H NMR (300 MHz, CDCl$_3$, TMS): 8.21 (s, 1H), 7.8-7.71 (m, 2H), 7.47-7.40 (m, 3H), 3.00 (pentet, 1H), 1.86-1.5 (m, 5H), 1.52-1.40 (m, 1H), 1.3-1.15 (m, 3H), 1.22 (d, 3H), 1.0-0.8 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): 158.5, 136.6, 128.4, 128.0, 71.9, 43.8, 29.9, 29.8, 26.6, 26.4, 26.2, 19.9; IR (neat): 3082, 3061, 3025, 2965, 2928, 2851, 2662, 1953, 1881, 1705, 1645, 1601, 1580, 1491, 1449, 1380, 1330, 1307, 1289, 1263, 1217, 1189, 1169, 1155, 1127, 1100, 1090, 1071, 1041, 1024, 1000, 987, 938, 903, 891, 873, 850, 789.

N-Benzylidne(1-tetralinyl)amine: A solution of 1-aminotetralin (4.0 g, 27 mmol) (prepared by the method of Borch$^{39}$, yield: 79 %, $^1$H NMR (250 MHz, CDCl$_3$, TMS): 7.41-7.35 (dd, 1H), 7.2-7.05 (m, 3H), 4.0 (t, 1H), 2.9-2.65 (m, 2H), 2.1-1.6 (m, 4H), 1.5 (bs, 2H, NH)) and benzaldehyde (2.75 mL, 27 mmol) in diethylether was stirred over magnesium sulfate (5 g) under an argon atmosphere for 5 h. The mixture was filtered and concentrated and the crude residue was purified by Kugelrohr distillation to give 5.24 g (82 % yield) of a colorless oil which solidified on standing. $^1$H NMR (300 MHz, CDCl$_3$, TMS): 8.4 (s, 1H), 7.82-7.75 (m, 2H), 7.45-7.38 (m, 3H), 7.2-7.1 (m, 3H), 7.05 (d, 1H), 4.52 (t, 1H), 3.00-2.8 (m, 2H), 2.27-2.0 (m, 3H), 1.19-1.80 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): 160.5, 137.3, 137.1, 136.4, 130.6, 129.2, 128.6, 128.5, 126.9, 125.8, 68.6, 31.6, 29.5, 20.2; IR (neat) 3266, 3156, 3059, 3022, 2927, 2859, 2666, 2619, 2360, 2328, 1955, 1901, 1814, 1640, 1602, 1579, 1536, 1490, 1450, 1377,
1323, 1312, 1301, 1289, 1236, 1217, 1201, 1169, 1157, 1116, 1067, 1037, 1024, 1000, 968, 947, 936, 922, 905, 894, 879, 870, 853, 802, 770, 739, 695; \textit{HRMS}: calc for C$_{17}$H$_{17}$H; 235.1361, found 235.1359; mp 34.9-35.8 C.

\textbf{2-Phenyl-1-pyrroline}: Was prepared by the method of Sorgi\textsuperscript{40} from \textit{N-vinylpyrrrolidinone (26.7 mL, 250 mmol) and methyl benzoate (31.1 mL, 250 mmol). Distillation (0.5 mm Hg, 95 °C) afforded 12.51 g (34 % yield) of the desired 2-Phenyl-1-pyrroline which solidified on standing. $^1$H NMR (300 MHz, CDCl$_3$, TMS), $\delta$ 7.85-7.81 (m, 2H), 7.42-7.37 (m, 3H), 4.09-4.03 (tt, 2H), 2.97-2.90 (tt, 2H), 2.07-1.97 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): 173.16, 134.65, 130.32, 128.33, 127.53, 61.53, 34.88, 22.67; IR (neat): 3058, 3029, 2961-2859, 1615, 1574, 1495, 1446, 1340, 1046, 1026, 761, 693.

\textbf{2-Phenyl-3,4,5,6-tetrahydropyridine}: The procedure of Gallulo\textsuperscript{41} was followed using 5-chlorovaleronitrile (3.38 mL, 30 mmol) and phenyllithium (18.3 mL, 33 mmol, 1.8 M in 7:3 cyclohexane : diethyl ether) The crude product was purified by distillation (109 °C, 0.8 mm Hg) to afford 1.79 g (37 % yield) of the desired material. $^1$H NMR (300 MHz, CDCl$_3$, TMS), $\delta$ 7.76-7.70 (m, 2H), 7.36-7.31 (m, 3H), 3.84-3.77 (m, 2H), 2.62-2.54 (m, 2H), 1.83-1.74 (m, 2H), 1.74-1.60 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): 165.26, 140.11, 129.25, 127.99, 125.69, 49.77, 26.81, 21.74, 19.62; IR (neat): 3082, 3056, 3034, 3024, 2933, 2844, 1635, 1577, 1446, 1358, 1352, 1330, 1237, 1062, 763, 743, 693.

\textbf{2-Phenyl-4,5,6,7-tetrahydro-3H-azepine}:\textsuperscript{42} The method of Bielawski\textsuperscript{43} was used to prepare 2-Methyl-4,5,6,7-tetrahydro-3H-azepine from \textit{N-(E-2-phenylethenyl)-hexahydroazepin-2-one}\textsuperscript{44} (10.3 g, 47 mmol) and phenyllithium
(36 mL, 57 mmol, 1.0 M in 7:3 cyclohexane : ether). The crude product (7.75 g) was obtained as a mixture of the cyclic imine and the amino ketone as reported. The material was placed in a round bottom flask containing 10 mg p-toluenesulfonic acid and 100 mL toluene. The flask was fitted with a reflux condenser and a Dean-Stark trap and the system was purged with nitrogen. The mixture was refluxed for 15 h at which point an $^1$H NMR spectrum showed that the product mixture contained mainly the desired imine. After removal of the solvent, fractional distillation (6 mm Hg, 135 °C) afforded 2.90 g (37 % yield) of the desired product. $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ 7.8-7.65 (m, 2H), 7.4-7.3 (m, 3H), 3.86-3.8 (m, 2H), 2.9-2.82 (m, 2H), 1.9-1.82 (m, 2H), 1.69-1.58 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 174.1, 141.3, 129.0, 128.0, 126.3, 52.3, 31.3, 30.7, 25.9, 23.5; IR (neat): 3080, 3054, 3030, 2921, 2848, 2682, 1953, 1890, 1809, 1631, 1576, 1492, 1469, 1445, 1362, 1343, 1334, 1281, 1257, 1218, 1195, 1177, 1146, 1097, 1078, 1053, 1026, 1000, 977, 917, 882, 855, 839, 766, 720, 694.

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline: Was prepared by the method of Brossi.$^{45}$ Yield : 72 %. $^1$H NMR (CDCl$_3$ 300 MHz TMS): δ 6.98 (s, 1H), 6.68 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.65-3.60 (m, 2H), 2.65-2.60 (m, 2H), 2.36-2.35 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): 163.49, 150.86, 147.48, 131.13, 122.53, 110.30, 109.19, 56.25, 55.93, 47.03, 25.75, 23.17; IR (CHCl$_3$): 3026, 3020, 3011, 2940, 2837, 1628, 1605, 1573, 1513, 1464, 1376, 1352, 1323, 1287, 1267, 1234, 1156, 1062, 861, 808, 779, 762, 742, 740, 737. mp 102.3-104.0 °C.

2-[2-(N-benzyl)pyrrolyl]-1-pyrroline: Was provided by Professor Satoru Masamune and Dr. Yaping Hong.
5-Hexyl-1-pyrroline: In a 250 mL Schlenk flask under argon magnesium turnings (2.4 g, 100 mmol) and I₂ (10 mg) were placed in 25 mL diethyl ether. A solution of 1-iodohexane (7.4 mL, 50 mmol), in 25 mL of diethyl ether was added dropwise via cannula and the mixture was allowed to stir at room temperature for 1 h. The resulting solution was the transferred via cannula (with filtering) to a 2 neck round bottom flask fitted with a reflux condenser. A solution of 4-chlorobutyronitrile (4.5 mL, 50 mmol) in 50 mL ether was added dropwise via cannula and the reaction mixture was heated to reflux for 1.5 h. The flask was then fitted with a dropping funnel and distillation apparatus. While distilling off the ether, toluene was added through the dropping funnel to keep the volume in the reaction flask constant. When the temperature at the distillation head reached 110 °C the mixture was cooled to room temperature washed with water (50 mL). The aqueous layer was extracted with ether, the ether and toluene layers were combined and extracted with 1 M HCl (3 x 50 mL). The acid layers were neutralized with KOH and extracted with ether (4 x 75 mL). The ether layers were dried over magnesium sulfate and concentrated. The crude product was purified by Kugelrohr distillation to yield 2.3 g (30%) of the desired product. ¹H NMR (300 MHz, CDCl₃, TMS): δ 3.82-3.75 (tt, 2H), 2.47-2.41 (tt, 2H), 2.34-2.29 (t, 2H), 1.89-1.79 (m, 2H), 1.62-1.52 (m, 2H), 1.35-1.26 (m, 6H), 0.91-0.85 (m, 3H); ¹³C NMR (75 MHz, CDCl₃): 177.10, 59.68, 36.05, 32.72, 30.58, 28.15, 25.30, 21.51, 21.48, 12.94; IR (neat): 2955-2860, 1643, 1465, 1456, 1436, 1430, 1419, 1378, 1325, 1301, 1013, 957.

2-[1-(4-Methylpent-4-enyl)]-1-pyrroline: A dry flask under an argon atmosphere was charged with a magnetic stir bar, 100 mL of THF and
diisopropylamine (3.0 mL, 21 mmol). The solution was cooled to -5 °C and a solution of N-butyllithium (8.1 mL, 2.7 M in hexanes, 22 mmol) was added via syringe. The mixture was allowed to stir for 30 min and was cooled to -78 °C. 2-Methyl-1-pyrrole (1.89 mL, 20 mmol) was added and the resulting yellow mixture was stirred for 30 min. 1-Bromo-3-methylbut-2-ene (2.76 mL, 24 mmol) was added dropwise via syringe. The solution was kept at -78 °C for 1 h then warmed to room temperature and diluted with 100 mL of ether. The organic solution was extracted with three 25 mL portions of 1 M HCl. The combined aqueous layers were cooled to 0 °C, made basic with solid NaOH and extracted with four 50 mL portions of methylene chloride. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (silica, 95:5 hexane : triethylamine) afforded 2.13 g (71 % yield) of the desired 2-[1-(4-methylpent-4-enyl)]-1-pyrrole as a yellow oil. ¹H NMR (300 MHz, CDCl₃, TMS): δ 5.16-5.1 (m, 1H), 3.83-3.76 (m, 2H), 2.50-2.40 (m, 2H), 2.37-2.23 (m, 4H), 1.9-1.8 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 177.8, 131.9, 123.3, 60.6, 37.1, 33.7, 25.4, 24.8, 22.4, 17.4; IR (neat): 3268, 2918, 2864, 2729, 1644, 1449, 1431, 1326, 1339, 1303, 1223, 1130, 1104, 1056, 1014, 984, 949, 832; HRMS: calc. for C₁₀H₁₇N; 151.1361, found 151.1360.

E-2-[1-[6-(Trimethylsilyl)hex-5-enyl]]-1-pyrrole: A dry flask under an argon atmosphere was charged with a magnetic stir bar, 100 mL of THF and diisopropylamine (2.2 mL 15.6 mmol). The solution was cooled to -5 °C and a solution of N-butyllithium (10 mL, 1.56 M in hexanes, 15.6 mmol) was added via syringe. The mixture was allowed to stir for 30 min and was cooled to -78 °C. 2-Methyl-1-pyrrole (1.36 mL, 14.4 mmol) was added and the resulting yellow mixture was stirred for 30 min. E-5-Iodo-1-(trimethylsilyl)-1-pentene⁴⁶ (3.37 g, 90
% pure, 12 mmol) was added dropwise via syringe. The solution was kept at -78 °C for 30 min then warmed to room temperature and diluted with 50 mL of ether / 20 mL of water. The layers were separated and the aqueous layer was extracted with two 50 mL portions of methylene chloride. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to provide 2.85 g of a yellow oil. Flash chromatography (silica, 97:3 hexane : triethylamine) afforded 2.22 g (83 % yield) of the desired E-2-[1-[6-(trimethylsilyl)hex-5-eny]]-1-pyrroline as a yellow oil. ¹H NMR (300 MHz, CDCl₃, TMS): δ 6.1-5.95 (dt J₁=18 Hz, J₂=12 Hz, 1H), 5.67-5.58 (d, J=18 Hz, 1H), 3.83-3.76 (m, 2H), 2.47-2.41 (m, 2H), 2.35-2.3 (t, J=6 Hz, 2H), 2.16-2.09 (m, 1H), 1.90-1.80 (m, 2H), 1.63-1.55 (m, 2H), 1.45-1.38 (m, 2H), 0.03 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ 177.9, 146.5, 129.6, 60.7, 37.1, 36.4, 33.7, 28.6, 25.9, 22.6, -1.1; IR (neat): 2952, 2863, 1644, 1616, 1461, 1431, 1301. 1246, 987, 864, 837, 767, 730, 703, 613; HRMS: calc. for C₁₃H₂₅NSi; 223.1756, found 223.1757.

2-(1-Hex-5-eny)]-1-pyrroline: A dry flask under an argon atmosphere was charged with a magnetic stir bar, 100 mL of THF and diisopropylamine (3.1 mL, 22 mmol). The solution was cooled to -5 °C and a solution of N-butyllithium (13.3 mL, 1.7 M in hexanes, 22 mmol) was added via syringe. The mixture was allowed to stir for 30 min and then cooled to -78 °C. 2-Methyl-1-pyrroline (1.99 mL, 20 mmol) was added and the resulting yellow mixture was stirred for 30 min. 1-Iodo-5-pentene⁴⁷ (4.31 g, 22 mmol) was added dropwise via syringe and the mixture was stirred at -78 °C for 1 h. The solution was warmed to room temperature, quenched with 20 mL of sat. aq. NH₄Cl and diluted with 100 mL of ether. The layers were separated and the aqueous layer was extracted with 100 mL of ether. The combined organic layers were dried over Na₂SO₄ and
concentrated in vacuo. Flash chromatography (silica, 97:3 pentane:diethylamine) afforded 2.15 g (71 % yield) of the desired 2-{1-hex-5-enyl}-1-pyrrolidine as a yellow oil. ^1H NMR (250 MHz, CDCl₃, TMS): δ 5.9-5.72 (m, 1H), 5.08-4.92 (m, 2H), 3.85-3.75 (m, 2H), 2.5-2.4 (t, J=7.8 Hz, 2H), 2.39-2.3 (t, J=7.2 Hz, 2H), 2.15-2.04 (m, 2H), 1.95-1.81 (m, 2H), 1.69-1.57 (m, 2H), 1.5-1.38 (m, 2H); ^13C NMR (75 MHz, CDCl₃): δ 177.2, 137.9, 113.8, 60.3, 36.7, 33.1, 33.0, 28.3, 25.4, 22.1; IR (neat): 3075, 2928, 2862, 1821, 1641, 1461, 1449, 1430, 1301, 1213, 1147, 992, 968, 909; HRMS: calc. for [M-H]^+: C_{10}H_{16}N; 150.1283, found 150.1282.

2-{1-(4-tert-Butyldimethylsiloxy)butyl}-1-pyrrolidine: A dry flask under nitrogen was charged with 50 mL of DMF, tert-butyldimethylchlorosilane (6.0 g, 40 mmol), and imidazole (3.3 g, 48 mmol). 3-Bromopropanol (3.6 mL, 40 mmol) was added via syringe and the mixture was allowed to stir overnight. The solution was diluted with 100 mL of ether, washed with three 50 mL portions of water, dried over MgSO₄ and concentrated in vacuo. The residue was dissolved in 150 mL of acetone and NaI (30 g, 200 mmol) was added. The mixture was heated to reflux under a nitrogen atmosphere for 48 h. The acetone was removed by rotary evaporation, the residue was diluted with 100 mL of ether, washed with two 50 mL of portions water and dried over MgSO₄. Removal of solvent afforded 10.2 g crude tert-butyldimethylsiloxy-3-iodopropane⁴⁸ (86 % pure, 70 % crude yield). ^1H NMR (300 MHz, CDCl₃, TMS): δ 3.66 (t, 2H), 3.27 (t, 2H), 1.99 (m, 2H), 0.89 (s, 9H), 0.07 (s, 6H).

A dry flask under an argon atmosphere was charged with a magnetic stir bar, 100 mL of THF and diisopropylamine (2.9 mL, 21 mmol). The solution was cooled to -5 °C and a solution of N-butyllithium (7.4 mL, 2.7 M in hexanes, 20
mmol) was added via syringe. The mixture was allowed to stir for 30 min and was cooled to -78 °C. 2-Methyl-1-pyrroline (1.80 mL, 19 mmol) was added and the resulting yellow solution was stirred for 30 min. tert-Butyldimethylsiloxy-3-iodopropane (6.9 g, 23 mmol) was added dropwise via syringe. After 1 h the mixture was quenched with 20 mL of sat. aq. NH₄Cl and diluted with 100 mL of ether. The layers were separated and the aqueous layer was extracted with 50 mL of ether. The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (silica, 95:5 hexane : triethylamine) afforded 2.53 g (55 % yield) of the desired 2-[1-(4-tert-
butyldimethylsiloxyl)butyl]-1-pyrroline as a yellow oil. ¹H NMR (300 MHz, CDCl₃, TMS): δ 3.81-3.73 (m, 2H), 3.62-3.58 (t, J=6.1 Hz, 2H), 2.48-2.39 (t, J=7.8 Hz, 2H), 2.38-2.3 (t, J=7.2 Hz, 2H), 1.89-1.78 (m, 2H), 1.68-1.49 (m, 4H), 0.86 (s, 9H), 0.02 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 178.1, 62.8, 60.7, 36.9, 33.5, 32.6, 25.9, 22.7, 22.5, 18.3, -5.3; IR (neat): 2954, 2857, 2737, 2709, 1643, 1471, 1462, 1431, 1387, 1360, 1343, 1301, 1255, 1188, 1102, 1040, 1006, 956, 939, 909, 894, 812, 775, 715, 662; HRMS: calc. for C₁₄H₂₉NO₂Si; 255.2018, found 255.2017.

2-[4-(1,3-Dioxolan-2-y1)butyl]-1-pyrroline: A dry round bottom flask under a nitrogen atmosphere was charged with a magnetic stir bar, 80 mL of acetone, NaI (24 g, 100 mmol), and CaCO₃ (20 g, 200 mmol). The mixture was stirred for 30 min and 2-(2-bromoethyl)-1,3-dioxolane (4.7 mL, 40 mmol) was added via syringe. The flask was fitted with a reflux condenser and the mixture was refluxed for 14 h. The acetone was removed by rotary evaporation and the residue was diluted with 200 mL of ether / 100 mL of water. The layers were separated and the aqueous solution was extracted with 100 mL of ether. The
combined organic portions were washed with 25 mL of sat. aq. Na$_2$SO$_3$, and 25 mL of sat. brine, then dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash chromatography (deactivated silica, see general considerations for preparation, 35:65 methylene chloride : pentane) afforded 6.52 g (71 % yield) of the desired 2-(2-iodoethyl)-1,3-dioxolane$^{49}$ as a clear oil. $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ 4.75 (t, 1H), 4.0-3.82 (m, 4H), 3.21 (t, 2H), 2.25-2.19 (m, 2H).

A dry flask under an argon atmosphere was charged with a magnetic stir bar, 50 mL of THF and diisopropylamine (3.1 mL, 22 mmol). The solution was cooled to -5 °C and a solution of N-butyllithium (13.3 mL, 1.7 M in hexanes, 22 mmol) was added via syringe. The mixture was allowed to stir for 30 min and was cooled to -78 °C. 2-Methyl-1-pyrroline (1.89 mL, 20 mmol) was added and the resulting yellow mixture was stirred for 30 min. 2-(2-Iodoethyl)-1,3-dioxolane (4.31 g, 22 mmol) was added dropwise via syringe and the mixture was stirred at -78 °C for 1 h. The mixture was warmed to room temperature and washed with 50 mL of sat brine. The aqueous layer was extracted with five 75 mL portions of ether (the product is somewhat soluble in aqueous media). The combined organic portions were dried over Na$_2$SO$_4$ and concentrated in vacuo. Flash chromatography (deactivated silica, see general considerations for preparation, first eluting with 1:1 methylene chloride : hexane then eluting with 5:47:48 triethylamine : methylene chloride : hexane) afforded 2.0 g (55 % yield) of the desired 2-[4-(1,3-dioxolan-2-yl)butyl]-1-pyrroline as a clear oil. $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ 4.88-4.84 (t, J=4.8 Hz, 1H), 3.99-3.89 (m, 2H), 3.86-3.74 (m, 4H), 2.48-2.42 (t, J=7.8 Hz, 4H), 2.42-2.36 (t, J=7.2 Hz, 2H), 1.90-1.8 (m, 2H), 1.8-1.65 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 177.6, 104.2, 64.9, 60.9, 37.2, 33.68, 33.5, 22.7, 20.9; IR (neat): 2952, 2868, 1642, 1459, 1431, 1410,
1301, 1213, 1139, 1028, 974, 942, 812; HRMS: calc. for [M-H]⁺: C₁₀H₂₆NO₂: 
182.1181, found 182.1178.

2-[1-(7-hydroxy)heptyl]-1-pyrrolone: A dry flask under nitrogen was charged 
with 50 mL of DMF, tert-butyldimethylchlorosilane (6.0 g, 40 mmol), and 
imidazole (3.3 g, 48 mmol). 6-Chlorohexanol (3.75 mL, 40 mmol) was added via 
syringe and the mixture was allowed to stir for 40 h. The solution was diluted 
with 200 mL of ether and washed with three 75 mL portions of water. The 
aqueous layer was extracted with 100 mL of ether and the combined organic 
layers were dried over MgSO₄ and concentrated in vacuo. The residue was 
dissolved in 150 mL of acetone and NaI (30 g, 200 mmol) was added. The 
mixture was heated to reflux under a nitrogen atmosphere for 15 h. The acetone 
was removed by rotary evaporation and the residue was diluted with 200 mL of 
ether / 100 mL of water. The layers were separated and the organic layer was 
washed with 50 mL of sat. Na₂SO₃ and 50 mL of sat. brine. The organic portion 
was dried over MgSO₄ and concentrated in vacuo to afford 10.1 g crude product. 
Kugelrohr distillation afforded 8.82 g (73 % yield) of tert-butyldimethylsiloxy-6-
iodohexane.⁵⁰ ¹H NMR (300 MHz, CDCl₃, TMS): δ 3.62-3.57 (t, 2H), 3.21-3.16 
(t, 2H), 1.85-1.78 (m, 2H), 1.57-1.47 (m, 2H), 1.45-1.32 (m, 4H), 0.89 (s, 9H), 
0.07 (s, 6H).

A dry flask under an argon atmosphere was charged with a magnetic stir 
bar, 50 mL of THF and diisopropylamine (4.3 mL, 31 mmol). The solution was 
cooled to -5 °C and a solution of N-butyllithium (12.3 mL, 2.7 M in hexanes, 31 
mmol) was added via syringe. The mixture was allowed to stir for 30 min and 
was cooled to -78 °C. 2-Methyl-1-pyrroline (2.43 mL, 25.7 mmol) was added and 
the resulting yellow solution was stirred for 30 min. tert-Butyldimethylsiloxy-6-
iodohexane (8.82 g, 25.7 mmol) was added dropwise via syringe. After 30 min the mixture was warmed to room temperature and diluted with 100 mL of ether / 50 mL of water. The layers were separated and the aqueous layer was extracted with 50 mL of ether. The combined organic layers were washed with 30 mL of sat. brine, dried over Na₂SO₄ and concentrated to afford 8.23 g of crude 2-[1-(7-tert-butyldimethylsiloxy)heptyl]-1-pyrrole. The material was dissolved in 100 mL of methanol and 2 mL conc. HCl was added. The mixture was stirred for 20 min and made basic (to pH 9) with 30% NaOH. The methanol was removed by rotary evaporation, the residue was diluted with 100 mL of ether and washed with 30 mL of 1 M NaOH / sat NaCl. The aqueous layer was extracted with three 50 mL portions of ether and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. Distillation (130 °C, 0.1 mm Hg) afforded 2.40 g (51% yield) of the desired 2-[1-(7-hydroxy)heptyl]-1-pyrrole as a clear oil. ¹H NMR (300 MHz, CDCl₃, TMS): δ 3.8-3.76 (m, 2H), 3.65-3.60 (t, J=6.6 Hz, 2H), 2.48-2.40 (t, J=7.5 Hz, 2H), 2.36-2.28 (t, J=7.8 Hz, 2H), 1.91-1.8 (m, 2H), 1.8-1.65 (bs, 1H), 1.63-1.48 (m, 4H), 1.39-1.3 (m, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 178.6, 62.1, 60.45, 37.0, 33.5, 32.6, 29.3, 29.0, 26.2, 22.6, 22.3; IR (neat): 3274, 2927, 2856, 1643, 1463, 1429, 1330, 1303, 1214, 1134, 1060, 1016, 960, 724; HRMS: calc. for [M-H]⁺, C₁₁H₂₀NO; 182.1545, found 182.1549.

**Z-2-(1-Non-6-enyl)-1-pyrrole:** A dry round bottom flask was charged with 100 mL of THF, triethylamine (5 mL, 39 mmol) and Z-5-octen-1-ol (3.85 g, 30 mmol). The flask was purged with argon and cooled to 0 °C. freshly distilled methanesulfonyl chloride (2.8 mL, 36 mmol) was added via syringe and the mixture was stirred for 2 h. The mixture was diluted with 100 mL of ether and filtered through celite. The solvent was removed in vacuo to afford 5.27 g of the
crude mesylate. The compound was dissolved in 100 mL of acetone under a nitrogen atmosphere and NaI (20 g, 50 mmol) was added. Diisopropylethylamine (0.5 mL) was added and the mixture was stirred at room temperature for 36 h. The solvent was removed \textit{in vacuo} and residue was diluted with 200 mL of ether / 100 mL of water. The layers were separated and the organic layer was washed with sat. brine. The solvent was removed \textit{in vacuo} and Kugelrohr distillation afforded 4.70 g (66 % yield) of Z-1-iodooct-5-ene. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta$ 5.41-5.22 (m, 2H), 3.21-3.16 (t, 2H), 2.1-1.93 (m, 4H), 1.86-1.78 (m, 2H), 1.51-1.4 (m, 2H), 0.98-0.93 (t, 3H).

A dry flask under an argon atmosphere was charged with a magnetic stir bar, 100 mL of THF and diisopropylamine (3.2 mL, 23.7 mmol). The solution was cooled to -5 °C and a solution of $N$-butyllithium (13.9 mL, 1.7 M in hexanes, 23.7 mmol) was added \textit{via} syringe. The mixture was allowed to stir for 30 min and then cooled to -78 °C. 2-Methyl-1-pyrroline (1.87 mL, 19.7 mmol) was added and the resulting yellow mixture was stirred for 40 min. Z-1-iodooct-5-ene (4.7 g, 19.7 mmol) was added dropwise \textit{via} syringe and the mixture was stirred at -78 °C for 1 h. The solution was warmed to room temperature and diluted with 100 mL of ether. The mixture was washed with 50 mL of water then 50 mL of sat. brine. The layers were separated and the aqueous layer was extracted with 100 mL of ether. The combined organic layers were dried over Na$_2$SO$_4$ and concentrated \textit{in vacuo}. Kugelrohr distillation afforded 3.34 g (88 % yield) of the desired Z-2-(1-non-6-enyl)-1-pyrroline as a yellow oil. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta$ 5.9-5.72 (m, 1H), 5.35-5.22 (m, 2H), 3.8-3.72 (m, 2H), 2.46-2.39 (t, J=7.8 Hz, 2H), 2.31-2.27 (t, J=7.2 Hz, 2H), 2.08-1.95 (m, 4H), 1.88-1.76 (m, 2H), 1.38-1.28 (m, 4H), 0.95-0.89 (t, J=7.5 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 172.0, 131.4, 128.8, 60.7, 37.1, 33.2, 29.5, 29.1, 26.9, 26.2, 22.5, 20.5, 14.3; IR (neat): 3003,
2930, 2858, 1643, 1461, 1301, 1011, 967; HRMS: calc. for [M-H]+, C_{13}H_{22}N; 192.1752, found 192.1752.

**Asymmetric Hydrogenation reactions:**

**General procedure A (for reactions run at 80 psig):** A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve and a pressure release valve (see appendix) was charged with \((R,R)\)-ethylene-1,2-bis(\(\eta^5\)-4,5,6,7 tetrahydro-1-indenyl)titanium \((R)\)-1,1′-binaphth-2,2′-diolate and a magnetic stir bar. The system was evacuated and filled with hydrogen (5-10 psig). THF (10 mL) was added via high pressure syringe. After the complex had dissolved, a solution of N-butyllithium (1.6 M in hexanes, 2 equiv) was added and the mixture was stirred for 2-3 min at which point it was a green color. Phenylsilane (2.5-3 equiv) was added and no color change was observed. A solution of the imine (20 equiv, in 1-2 mL THF) was added via syringe and the vessel was placed in an oil bath at the indicated temperature. The pressure was then adjusted to the specified value (Caution: an appropriate safety shield should be used) and the mixture was allowed to stir for the indicated time. When the reaction had reached completion (GC\(^51\)), the mixture was cooled and carefully vented. The amine was isolated as described below.

**General procedure B (for reactions run at >80 psig):** In a dry Schlenk flask under an argon atmosphere, \((R,R)\)-ethylene-1,2-bis(\(\eta^5\)-4,5,6,7 tetrahydro-1-indenyl)titanium \((R)\)-1,1′-binaphth-2,2′-diolate was dissolved in THF (10 mL). A solution of N-butyllithium (1.6 M in hexanes, 2 equiv) was added and the mixture was allowed to stir for 5 min at which point it was a brown-green color.
Phenylsilane (2.5-3.0 equiv) was added and mixture immediately turned dark brown. The resulting solution was moved into a dry box and transferred into a Parr high pressure autoclave containing a magnetic stir bar. The imine (20 eq based on Ti) was added. The vessel was sealed and moved to a fume hood where it was charged with hydrogen (specified below) and placed in an oil bath at the indicated temperature. The reaction mixture was allowed to stir for the specified time under hydrogen pressure. The vessel was cooled to room temperature, carefully vented and opened to air. The solvent was removed *in vacuo*. The amine was isolated as described below.

**Determination of enantiomeric excesses:** The enantiomeric excesses of the amines were determined by HPLC analysis of the amines or the corresponding amide derivatives (see below) using a Chiralcel OD column. HPLC chromatograms were compared with those of the racemic compounds. In some cases ee's were determined by GC analysis of the α-methoxy-α-(trifluoromethyl)-phenylacetamides amides using a Cyclodex B column (J & W Scientific).

**General procedure for the preparation of amides:** The amine (10-20 mg) was dissolved in CDCl$_3$ and triethylamine (1.5 equiv) was added. The appropriate acid halide or acid anhydride (1 equiv) was added and the reaction was monitored by $^1$H NMR. Upon completion the mixture was filtered through a plug of silica and the amide was recovered by removal of solvent.

**General procedure for the preparation of (S)-α-methoxy-α-(trifluoromethyl)-phenylacetamides** The amine (0.08 mmol) was dissolved in CDCl$_3$ (700 μL) in an NMR tube. Triethylamine (15 μL, 0.12 mmol) was added followed by (S)-α-
methoxy-α-(trifluoromethyl)phenylacetyl chloride\(^{52}\) (17.2 µL, 0.089 mmol). The mixture was shaken briefly, then allowed to stand for 30 min (or until the reaction was complete by \(^1\)H NMR). Aqueous NaOH (5 M, 10 µL) was added and the mixture was sonicated for 5 min. The mixture was then filtered through a plug of magnesium sulfate and concentrated to yield the \((S)\)-α-methoxy-α-(trifluoromethyl)phenylacetamide.

**Preparation of racemic amines.** The racemic amines were prepared from the imines by sodium borohydride or lithium aluminum hydride reduction. Alternatively imines were reduced to racemic amines following general procedure A or B and using titanocene dichloride rather than ((\(R\),\(R\))-ethylene-1,2-bis(\(\eta^5\)-4,5,6,7 tetrahydroindenyl) titanium \((R)\)-1,1'-binaphth-2,2'-diolate.

The following are representative experimental procedures for each example listed. Some reactions were initially carried out using 10 mol % catalyst and the products of these reactions were fully characterized. Subsequent experimentation showed that 5 mol % catalyst could be used in most cases. The products of these reactions were characterized by \(^1\)H NMR and GC. Enantiomeric excesses were determined the same way, and were comparable to, those obtained using 10 mol % catalyst. In the following procedures "titanium complex" refers to ((\(R\),\(R\))-ethylene-1,2-bis(\(\eta^5\)-4,5,6,7 tetrahydroindenyl) titanium \((R)\)-1,1'-binaphth-2,2'-diolate.

\((R)\)\:-\((+)\)-\textit{N}-Benzyl-1-phenylethylamine\(^{53}\) (at 2000 psig)

\(N\)-(α-Methylbenzylidene)benzyl amine (175 mg, 0.84 mmol) was reduced by according to general procedure B with 10 mol % catalyst (titanium complex: 50
mg, 0.084 mmol; \(N\)-butyllithium: 130 \(\mu\)L, 1.29 M in hexanes, 0.168 mmol; phenylsilane: 26 \(\mu\)L, 0.21 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 48 h in an oil bath at 65 °C. The THF was removed \textit{in vacuo} and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 30 mL). The ether layers were combined, dried over anhydrous sodium sulfate and concentrated. The amine was purified by flash chromatography on silica (5:2:93 diethyl ether : triethylamine : hexanes) to afford 142 mg (80 % yield) of product. HPLC analysis indicated 79 % ee. \(^1\)H NMR (300 MHz, \(\text{C}_6\text{D}_6\), TMS): \(\delta\) 7.3-7.08 (m, 10H), 3.59 (q, 1H, \(J=6.4\) Hz), 3.50 (dd, 2H, \(J_1=13.1\), \(J_2=39\) Hz), 1.18 (d, 3H, \(J=6.8\) Hz), 1.4-0.5 (bs, N-H); \(^{13}\)C NMR (75 MHz, \(\text{C}_6\text{D}_6\)): \(\delta\) 146.32, 141.43, 128.7, 128.49, 128.35 (obscured by solvent), 127.71, 127.13, 126.99, 57.88, 51.94, 24.90; IR (neat): 3370, 3250, 3083, 3062, 3026, 2962, 2924, 2902, 2862, 2833, 2812, 2805, 1492, 1452, 1125, 909,761, 733, 699; [\(\alpha\)]\(^{22}\) = + 44.3° ± 1.7° (c=5.87 mg/mL in cyclopentane); lit. value\(^5\) ((S) enantiomer) [\(\alpha\)]\(^{25}\) = - 49.2° (c=6.04 mg/mL in cyclopentane).

(\(R\))-\((\pm)\)-\(N\)-BenzyI-1-phenylethylamine (at 2000 psig)
\(N\)-(\(\alpha\)-Methylbenzylidene)benzyl amine (1.05 g, 5.0 mmol) was reduced following general procedure B with 2 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; \(N\)-butyllithium: 117 \(\mu\)L, 1.71 M in hexanes, 0.20 mmol; phenylsilane: 31 \(\mu\)L, 0.25 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 23 h in an oil bath at 65 °C. The THF was removed \textit{in vacuo} and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with solid KOH
and extracted with diethyl ether (4 x 50 mL). The ether layers were combined, dried over anhydrous sodium sulfate and concentrated to afford the pure amine (982 mg, 93\% yield). HPLC analysis indicated 85\% ee.

\((+)-N\text{-}Benzyl\text{-}1\text{-}(<\text{4}\text{-}methoxyphenyl)>\text{ethylamine: \text{54 (at 2000 psig)}}\)

\(\text{N-(α-Methyl(4-methoxy)benzylidene)benzyl amine (479 mg, 2.0 mmol) was reduced by according to general procedure B with 5 mol }\%\text{ catalyst (titanium complex: 59 mg, 0.1 mmol; }\text{N-butyllithium: 129 }\mu\text{L, 1.55 M in hexanes, 0.2 mmol; phenylsilane: 37 }\mu\text{L, 0.3 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 18 h in an oil bath at 65°C. The THF was removed in vacuo and the residue was taken up in ethyl acetate. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with solid KOH and extracted with chloroform (4 x 30 mL). The organic were combined, dried over anhydrous sodium sulfate and concentrated to afford 416 mg (86\% yield) of product. HPLC analysis indicated 86\% ee.} \text{\textit{1H NMR (300 MHz, CDCl}_3, TMS): }\delta7.32-7.18 \text{ (m, 7H), 6.88, (d, 2H, J=6 Hz), 3.81, (s, 3H), 3.76, (q, 1H, J=6.6 Hz), 3.61, (dd, J}_1=12.9 \text{ Hz, J}_2=9.3 \text{ Hz), 1.52, (bs, 1H), 1.34, (d, 3H, J=6.6 Hz); \text{\textit{13C NMR (75 MHz, CDCl}_3): }\delta158.6, 140.7, 137.7, 128.3, 128.1, 127.7, 126.7, 112.3, 56.8, 55.2, 51.6, 24.5; \text{IR (neat): }3650, 3328, 3069, 3026, 2998, 2958, 2927, 2883, 2054, 1998, 1883, 1610, 1584, 1511, 1494, 1453, 1441, 1368, 1344, 1301, 1284, 1245, 1201, 1176, 1115, 1036, 909, 832, 808, 736, 694, 637; [\alpha]^{22\circ}=+40.3° \pm 1.3° \text{ (c=7.7 mg/mL in methylene chloride).}"

\((+)-N\text{-}Benzyl\text{-}1\text{-}(2-furyl)>\text{ethylamine: \text{at 2000 psig)}}\)
N-(1-(2-Furyl)ethylidene)benzylamine (167 mg, 0.84 mmol) was reduced according to general procedure B with 10 mol % catalyst (titanium complex: 50 mg, 0.084 mmol; N-butyllithium: 130 μL, 1.29 M in hexanes, 0.166 mmol; phenylsilane: 26 μL, 0.21 mmol). The vessel was charged to 2000 psig and mixture was stirred for 48 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 30 mL). The ether layers were combined, dried over anhydrous sodium sulfate and concentrated. The amine was purified flash chromatography on silica (1:2:97 diethyl ether : triethylamine : hexanes) to afford 101 mg (60 % yield) product. HPLC analysis indicated 62 % ee. 1H NMR (300 MHz, CDCl₃, TMS): δ 7.76 (m, 1H), 7.35-7.2 (m, 5H), 6.3 (m, 1H), 6.15 (d, 1H, J=2.7 Hz), 3.85 (q, 1H, J=6.6 Hz), 3.7 (dd, 2H, J₁=13.8 Hz J₂=27 Hz), 1.65 (bs, N-H), 1.4 (d, 3H, J=6.8 Hz); 13C NMR (75 MHz, CDCl₃): δ 157.84, 141.36, 140.33, 128.35, 128.15, 126.89, 109.85, 105.39, 51.13, 50.52, 20.45; IR (neat): 3410, 3280, 3112, 3086, 3063, 3028, 2972, 2849, 1504, 1495, 1463, 1453, 1150, 1120, 1009, 910, 805, 735, 730, 698; Anal: calc. for C₁₃H₁₅NO; C, 77.58; H, 7.51; found C, 77.86, H, 7.37; [α]²² = + 50.0° ± 2.0° (c=5.20 mg/mL in methylene chloride).

(+)-N-Benzyl-1-(2-furyl)ethylamine: (at 2000 psig)

N-(1-(2-Furyl)ethylidene)benzylamine (598 mg, 3.0 mmol) was reduced according to general procedure B with 5 mol % catalyst (titanium complex: 89 mg, 0.15 mmol, N-butyllithium, 175 μL, 1.71 M in hexanes: 0.30 mmol; phenylsilane: 56 μL, 0.45 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 45 h in an oil bath at 65°C. The THF was removed in
vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 40 mL). The ether layers were combined, dried over anhydrous sodium sulfate and concentrated. The amine was purified by flash chromatography on silica (1:2:97 diethyl ether : triethylamine : hexanes) to afford 420 mg (70 % yield) product. HPLC analysis indicated 53 % ee.

(+)-N-BenzyL-1-(1-naphthyl)ethylamine: (at 2000 psig)

N-(1-(1-naphthyl)ethyldiene)benzyl amine (519 mg, 2.0 mmol) was reduced by following general procedure B with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; N-butyllithium: 117 µL, 1.71 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 12 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with NaOH and extracted with methylene chloride (4 x 30 mL). The organic layers were combined, dried over anhydrous sodium sulfate and concentrated. The amine was purified by flash chromatography on silica (1:2:97 diethyl ether : triethylamine : hexanes) to afford 492 mg (90 % yield) of product. HPLC analysis indicated 69 % e.e. $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ 7.85-7.8 (m, 3H), 7.78 (d, 1H, J=1 Hz), 7.54-7.43 (m, 5H), 3.98 (q, 1H, J=6.6 Hz), 3.65 (dd, 2H, J$_1$=13.2 Hz, J$_2$=21 Hz), 1.64 (bs, N-H), 1.44 (d, 3H, J=6.6 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 142.97, 140.62, 133.46, 132.18, 128.31, 128.22, 128.07, 127.68, 127.6, 126.79, 125.87, 125.39, 125.32, 124.89, 57.57, 51.68, 24.44; IR (neat): 3322, 3083, 3055, 3025, 2962, 2923, 2868, 2822, 1679, 1632, 1600, 1584, 1506,
1494, 1452, 1369, 1314, 1175, 1130, 1118, 897, 856, 819, 746, 698; Anal: calc. for C₁₉H₁₉N; C, 87.31; H, 7.33, found; C, 87.17; H, 6.95; [α]²²° = + 31.0° ± 1.7° (c=2.9 mg/mL in methylene chloride).

(-)-N-Benzyl-2-aminohexane:⁵⁵ (at 2000 psig)
N-(1-Methylpentyldiene)benzylamine (159 mg, 0.84 mmol) was reduced according to general procedure B with 10 mol % catalyst (titanium complex: 50 mg, 0.084 mmol; N-butyllithium: 130 µL, 1.29 M in hexanes, 0.168 mmol; phenylsilane: 26 µL, 0.21 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 48 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 10 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 20 mL). The amine was purified flash chromatography on silica (1:2:97 diethyl ether : triethylamine : hexanes) to afford 105 mg (65 % yield) product. HPLC analysis indicated 59 % ee. ¹H NMR (300 MHz, C₆D₆, TMS), δ 7.40 (m, 2H), 7.33 (m, 2H), 7.11 (m, 1H), 3.65 (dd, 2H, J₁=13.2 Hz, J₂=30 Hz), 2.53 (m, 1H), 1.25-1.19 (m, 6H), 0.95 (d, 3H, J=6.6 Hz), 0.87 (t, 3H, J=5.5 Hz), 0.70 (bs, N-H);
¹³C NMR (75 MHz, C₆D₆): δ 141.98, 128.45, 128.36, 126.90, 52.79, 51.68, 37.36, 28.44, 23.34, 20.63, 14.35; IR (neat): 3300, 3090, 3020, 2957, 2857, 1464, 1456, 1453, 731, 697; [α]²²° = - 7.5° ± 0.9° (c=5.32 mg/mL in methylene chloride).

(-)-N-Benzyl-1-(cyclohexyl)ethylamine:⁵⁶ (at 2000 psig)
N-(1-Cyclohexylethyldiene)benzyl-amine (108 mg, 0.50 mmol) was reduced according to general procedure B with 10 mol % catalyst (titanium complex: 30
mg, 0.050 mmol; N-butyllithium: 78 μL, 1.29 M in hexanes, 0.10 mmol; phenylsilane: 15 μL, 0.125 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 48 h in an oil bath at 65 ºC. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 10 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 20 mL) to afford the pure amine (88 mg, 81 % yield). HPLC analysis indicated 84 % ee. 1H NMR (300 MHz, CDCl₃, TMS): δ 7.34-7.22 (m, 5H), 3.77 (dd, 2H, J₁=13.2 Hz, J₂=40.8 Hz), 2.49 (m, 1H), 1.76-1.64 (m, 5H), 1.36-0.97 (m, 7H), 1.02 (d, 3H, J=6.6 Hz); 13C NMR (75 MHz, CDCl₃): δ 128.25, 128.075, 128.036, 126.66, 57.05, 51.54, 42.97, 29.82, 28.07, 26.77, 26.64, 26.51, 16.73; IR (neat): 3320, 3062, 3026, 2923, 2851, 1495, 1471, 1464, 1455, 731, 697; [α]₂²° = -22.4° ± 1.6° (c=3.12 mg/mL in methylene chloride).

(−)-N-Benzyl-1-(cyclohexyl)ethylamine: (at 2000 psig)

N-(1-Cyclohexylethylidene)benzyl-amine (430 mg, 2.0 mmol) was reduced according to general procedure B with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; N-butyllithium: 120 μL, 1.66 M in hexanes, 0.20 mmol; phenylsilane: 37 μL, 0.30 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 9 h in an oil bath at 65 ºC. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 30 mL) to afford the pure amine (400 mg, 93 % yield). HPLC analysis indicated 76 % ee.
(-)-N-Benzyl-1-(cyclohexyl)ethylamine: (at 500 psig)

N-(1-Cyclohexylethylidene)benzyl-amine (430 mg, 2.0 mmol) was reduced according to general procedure B with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; N-butyllithium: 120 μL, 1.66 M in hexanes, 0.20 mmol; phenylsilane: 37 μL, 0.30 mmol). The vessel was charged to 500 psig and the mixture was stirred for 72 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 30 mL) to afford the pure amine (366 mg, 85 % yield). HPLC analysis indicated 43 % ee.

(-)-N-Benzyl-3-methyl-2-aminobutane:57 (at 2000 psig)

N-(1,2 Dimethylpropylidene)benzyl-amine (147 mg, 0.84 mmol) was reduced according to general procedure B with 10 mol % catalyst (titanium complex: 50 mg, 0.084 mmol; N-butyllithium: 130 μL, 1.29 M in hexanes, 0.168 mmol; phenylsilane: 26 μL, 0.21 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 48 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 10 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 20 mL) to afford the pure amine (115 mg, 77 % yield). HPLC analysis indicated 80 % ee. 1H NMR (300 MHz, CDCl3, TMS), δ 7.35-7.30 (m, 4H), 7.2-7.3 (m, 1H), 3.77 (dd, 2H, J1=17.4 Hz, J2= 34.8 Hz), 2.51 (m, 1H), 1.75 (m, 1H), 1.2 (bs, N-H), 0.99 (d, 3H, J=6.6 Hz), 0.89 (d, 3H, J=6.3 Hz), 0.87 (d, 3H, J=6.6 Hz). 13C NMR (CDCl3 75 MHz TMS), δ 141.09, 128.34, 128.27, 128.05, 126.69, 57.53, 51.53,
32.21, 19.28, 17.25, 15.96; IR (neat): 3350, 3260, 3085, 3063, 3026, 2959, 2872, 2826, 2813, 2807, 1494, 1463, 1453, 1384, 1371, 1153, 1139, 1122, 1097, 1083, 1028, 733, 697. \[ \alpha \]22° = - 25.0° ± 1.1° (c=8.40 mg/mL in methylene chloride).

\((-\text{-})-N\text{-Benzy1-6-methyl-2-aminooheptane}:^{58}\) (at 2000 psig)

\(N\text{-[(1,5-Dimethylhex-5-enylidene)-benzylamine (215 mg, 1.0 mmol)} \) was reduced according to general procedure B with 10 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; \(N\text{-butyllithium: 155 } \mu\text{L, 1.29 M in hexanes, 0.20 mmol; phenylsilane: 31 } \mu\text{L, 0.25 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 48 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 30 mL). The amine was purified by flash chromatography on silica (1:2:97 diethyl ether : triethylamine : hexanes) to yield 145 mg (66 % yield) of product. HPLC analysis indicated 60 % ee. \(^1\text{H NMR (300 MHz, CDCl_3, TMS): } \delta \text{ 7.32-7.22 (m, 5H), 3.77 (dd, 2H, J_1=12.9 Hz, J_2=29.1 Hz), 2.88 (m, 1H), 1.54-1.31 (m, 2H), 1.31-1.26 (m, 4H), 1.26-1.13 (m, 2H), 1.07 (d, 3H, J=6.0 Hz), 0.86 (d, 6H, J=6.3 Hz); } \text{^13C NMR (75 MHz, CDCl_3): } \delta \text{ 140.92, 128.27, 128.02, 126.68, 52.45, 51.39, 39.12, 37.32, 27.88, 23.65, 22.59, 222.53, 20.32; IR (neat): 3300, 3260, 3063, 3027, 2954, 2868, 1494, 1466, 1453, 1383, 1372, 1366, 1156, 1028, 731, 697; } \alpha \]22° = - 18.2° ± 2.0° (c=5.02 mg/mL in methylene chloride).

\((-\text{-})-N\text{-}(4\text{-Methoxybenzyl)1-(cyclohexyl)ethylamine:}\) (at 500 psig)

\(N\text{-[(1-Cyclohexylethylidene)(4-methoxybenzyl)amine (491 mg, 2.0 mmol)} \) was reduced according to general procedure B with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; \(N\text{-butyllithium: 155 } \mu\text{L, 1.29 M in hexanes, 0.20 mmol; phenylsilane: 31 } \mu\text{L, 0.25 mmol). The vessel was charged to 500 psig and the mixture was stirred for 48 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 30 mL). The amine was purified by flash chromatography on silica (1:2:97 diethyl ether : triethylamine : hexanes) to yield 145 mg (66 % yield) of product. HPLC analysis indicated 60 % ee. \(^1\text{H NMR (300 MHz, CDCl_3, TMS): } \delta \text{ 7.32-7.22 (m, 5H), 3.77 (dd, 2H, J_1=12.9 Hz, J_2=29.1 Hz), 2.88 (m, 1H), 1.54-1.31 (m, 2H), 1.31-1.26 (m, 4H), 1.26-1.13 (m, 2H), 1.07 (d, 3H, J=6.0 Hz), 0.86 (d, 6H, J=6.3 Hz); } \text{^13C NMR (75 MHz, CDCl_3): } \delta \text{ 140.92, 128.27, 128.02, 126.68, 52.45, 51.39, 39.12, 37.32, 27.88, 23.65, 22.59, 222.53, 20.32; IR (neat): 3300, 3260, 3063, 3027, 2954, 2868, 1494, 1466, 1453, 1383, 1372, 1366, 1156, 1028, 731, 697; } \alpha \]22° = - 18.2° ± 2.0° (c=5.02 mg/mL in methylene chloride).}
complex: 59 mg, 0.1 mmol; N-butyllithium: 113 μL, 1.75 M in hexanes, 0.20 mmol; phenylsilane: 37 μL, 0.3 mmol). The vessel was charged to 500 psig and the mixture was stirred for 68 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 15 mL). The aqueous layers were combined and made basic with solid KOH and extracted with methylene chloride (4 x 20 mL) to afford the pure amine (400 mg, 81 % yield). To determine the ee, the amine was debenzylated with 10 % Pd/C and formic acid (30 min rt). HPLC analysis of the 1-naphthamide indicated 62 % ee. 1H NMR (300 MHz, CDCl₃, TMS): δ 7.26-7.21, (d, 2H, J=8.6 Hz), 6.88-6.83, (d, 2H, J=8.7 Hz), 3.79, (s, 3H), 3.8-3.6, (dd, 2H, J₁=12.9 Hz, J₂=28.8 Hz), 2.5-2.46, (m, 1H), 1.8-1.6, (m, 5H), 1.4-0.94, (m 7H), 1.01, (d, 3H, J=6 Hz); 13C NMR (75 MHz, CDCl₃): δ 158.4, 133.2, 129.2, 113.7, 56.9, 55.2, 50.9, 42.9, 29.8, 26.8, 26.6, 26.5, 16.7; IR (neat): 3300, 2923, 2849, 2350, 1898, 1810, 1584, 1511, 1448, 1371, 1321, 1299, 1248, 1172, 1105, 1030, 906, 891, 824, 734, 700; HRMS: calc. for C₁₆H₂₅NO: 247.1936, found 247.1934; [α]²²° = -16.4° ± 1.6° (c=3.12 mg/mL in methylene chloride).

(-)-N-(4-Methoxybenzyl)-1-(cyclohexyl)ethylamine: (at 2000 psig)
N-(1-Cyclohexylethylidene)(4-methoxybenzyl)amine (491 mg, 2.0 mmol) was reduced according to general procedure B with 5 mol % catalyst (titanium complex: 59 mg, 0.1 mmol; N-butyllithium: 115 μL, 1.74 M in hexanes, 0.20 mmol; phenylsilane: 37 μL, 0.3 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 15 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (4 x 10 mL). The aqueous layers were
combined and made basic with solid KOH and extracted with methylene chloride (4 x 20 mL) to afford the pure amine (453 mg, 92 % yield). To determine the ee, the amine was debenzylated with 10 % Pd/C and formic acid (30 min rt). HPLC analysis of the 1-naphthamide indicated 78 % ee.

\((-\text{N-(Methyl)-1-(cyclohexyl)ethylamine})^{59}\) (at 500 psig)

\(N\)-(1-Cyclohexylethylidene)methylamine (279 mg, 2.0 mmol) was reduced according to general procedure B with 5 mol % catalyst (titanium complex: 59 mg, 0.1 mmol; \(N\)-butyllithium: 118 \(\mu\)L, 1.69 M in hexanes, 0.20 mmol; phenylsilane: 37 \(\mu\)L, 0.3 mmol). The vessel was charged to 500 psig and the mixture was stirred for 45 h at room temperature. The THF was removed \textit{in vacuo} and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 10 mL). The aqueous layers were combined and made basic with solid NaOH and extracted with methylene chloride (4 x 20 mL) to afford the pure amine (241 mg, 85 % yield). HPLC analysis of the 1-naphthamide indicated 92 % ee. \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\), TMS): \(\delta\) 2.4, (s, 3H), 2.5-2.32, (pentet, 1H, J=6.3 Hz), 1.80-1.60, (m, 5H), 1.51, (bs, 1H), 1.4-0.95, (m, 6H), 0.99, (d, 3H, J=6.3 Hz); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)): \(\delta\) 59.6, 42.6, 34.2, 29.8, 27.9, 26.7, 26.6, 26.5, 16.0; IR (neat): 3676, 3300, 2920, 2850, 2784, 2700, 2662, 2602, 2361, 1593, 1476, 1448, 1371, 1337, 1294, 1263, 1239, 1191, 1155, 1134, 1093, 1052, 986, 927, 891, 837, 778, 735; \(\lbrack\alpha\rbrack_{\text{D}}^{22} = -13.7^\circ \pm 1.6^\circ\) (c=2.19 mg/mL in methylene chloride).

\((-\text{N-(Methyl)-1-(cyclohexyl)ethylamine})\) (at 80 psig)

\(N\)-(1-Cyclohexylethylidene)methylamine (418 mg, 3.0 mmol) was reduced according to general procedure A with 5 mol % catalyst (titanium complex: 89
mg, 0.15 mmol; N-butyllithium: 176 µL, 1.70 M in hexanes, 0.3 mmol; phenylsilane: 56 µL, 0.45 mmol). The vessel was charged to 80 psig and the mixture was stirred for 5 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 15 mL). The aqueous layers were combined and made basic with solid KOH and extracted with methylene chloride (4 x 20 mL) to afford the pure amine (263 mg, 62 % yield). HPLC analysis of the 1-naphthamide indicated 92 % ee.

(-)-N-(Propyl)-1-(cyclohexyl)ethylamine: (at 2000 psig)
N-(1-Cyclohexylethylidene)propylamine (251 mg, 1.5 mmol) was reduced according to general procedure B with 5 mol % catalyst (titanium complex: 45 mg, 0.075 mmol; n-butyllithium: 80 µL, 1.87 M in hexanes, 0.15 mmol; phenylsilane: 28 µL, 0.23 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 24 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 10 mL). The aqueous layers were combined and made basic with solid NaOH and extracted with methylene chloride (4 x 20 mL). The combined organic layers were dried over Na2SO4 and concentrated Flash chromatography (silica, 1:99 triethylamine : hexanes) afforded the pure amine (175 mg, 70 % yield). HPLC analysis of the 1-naphthamide indicated 79 % ee. 1H NMR (300 MHz, CDCl3, TMS): δ 2.62-2.4, (m, 3H), 1.77-1.64, (m, 5H), 1.53-1.43, (sextet, 2H, J=6.9 Hz), 1.35-1.13, (m, 3H), 0.96, (d, 3H, J=6.6 Hz), 0.91, (t, 3H, J=7.2 Hz), 1.04-0.8, (m, 4H); 13C NMR (75 MHz, CDCl3): δ 57.8, 49.6, 30.0, 27.9, 26.8, 26.7, 26.6, 23.6, 16.9, 11.9; IR (neat): 3347, 2926, 2851, 1443, 1370, 1336, 1293, 1262, 1237, 1190, 1154.
1124, 800, 711; HRMS: calc. for C_{11}H_{23}N: 169.1831, found 169.1830; [α]^{22\circ} = -17.3\circ \pm 1.6\circ \text{ (c=29.5 mg/mL in methylene chloride).}

\textit{N-(Propyl)-1-(cyclohexyl)ethylamine:} (at 80 psig)

\textit{N-(1-Cyclohexylethylidene)propylamine} (334 mg, 2.0 mmol) was reduced according to general procedure A with 5 mol \% catalyst (titanium complex: 59 mg, 0.1 mmol; \textit{n}-butyllithium: 121 μL, 1.65 M in hexanes, 0.2 mmol; phenylsilane: 37 μL, 0.3 mmol). The vessel was charged to 80 psig and the mixture was stirred for 81 h in an oil bath at 65 \textdegree C. The THF was removed \textit{in vacuo} and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 10 mL). The aqueous layers were combined and made basic with solid NaOH and extracted with methylene chloride (4 x 20 mL). The combined organic layers were dried over Na_{2}SO_{4} and concentrated to afford the pure amine (220 mg, 65 \% yield). HPLC analysis of the 1-naphthamide indicated 4 \% ee, the opposite enantiomer as above was formed.

\textit{(−)-N-(Benzyl)-1-(cyclopropyl)ethylamine:} (at 2000 psig)

\textit{N-(1-Cyclopropylethylidene)benzylamine} (347 mg, 2.0 mmol) was reduced according to general procedure B with 5 mol \% catalyst (titanium complex: 59 mg, 0.1 mmol; \textit{n}-butyllithium: 120 μL, 1.66 M in hexanes, 0.2 mmol; phenylsilane: 37 μL, 0.3 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 14 h in an oil bath at 65 \textdegree C. The THF was removed \textit{in vacuo} and Kugelrohr distillation afforded the pure amine (321 mg, 91 \% yield). HPLC analysis indicated 61 \% ee. ¹H NMR (500 MHz, CDCl₃, TMS): δ 7.33-7.22, (m, 5H), 3.87-3.81, (dd, 2H, J₁=7.8 Hz, J₂=4 Hz), 1.91-1.88, (m, 1H), 1.5, (bs, 1H), 1.19-1.17, (d, 3H, J=7 Hz), 0.79-0.75, (m, 1H), 0.51-0.41, (m, 2H), 0.17-0.13, (m,
1H), 0.09-0.03, (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 140.8, 128.2, 127.9, 126.6, 58.2, 51.6, 20.4, 17.9, 4.3, 1.7; IR (neat): 3317, 3075, 3025, 2999, 2965, 2925, 2869, 2814, 1945, 1806, 1602, 1494, 1453, 1370, 1325, 1299, 1184, 1132, 1057, 1027, 1018, 979, 938, 914, 821, 734, 697; HRMS: calc. for C$_{12}$H$_{17}$N; 175.1365, found 175.1361; $[\alpha]^{22\circ} = -30.2\,^{\circ}\pm 0.2\,^{\circ}$ (c=57.2 mg/mL in methylene chloride).

(R)-(+)2-Phenylpyrrolidine$^{60}$ (at 2000 psig)

2-Phenylpyrrolidine (122 mg, 0.84 mmol) was reduced according to general procedure B with 10 mol % catalyst (titanium complex: 50 mg, 0.084 mmol; n-butyllithium: 130 µL, 1.29 M in hexanes, 0.168 mmol; phenylsilane: 26 µL, 0.21 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 48 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 10 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 20 mL) to afford the pure amine (92 mg, 74 % yield). GC analysis of the (S)-$\alpha$-methoxy-$\alpha$-(trifluoromethyl)phenyl-acetamide indicated >98 % ee. $^1$H NMR (300 MHz, CDCl$_3$, TMS): 7.38-7.31 (m, 4H), 7.29-7.20 (m, 1H), 4.11 (t, 1H, J=7.5 Hz), 3.25-3.17 (m, 1H), 3.05-2.97 (m, 1H), 2.21-2.13 (m, 1H), 2.01-1.70 (m, 2H), 2.01 (bs, N-H), 1.73 -1.61 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$), $\delta$ 144.92, 128.28, 126.67, 126.44, 62.57, 47.01, 34.34, 25.60; IR (neat): 3338, 3318, 3276, 3081, 3026, 2961, 2870, 1602, 1490, 1453, 1419, 1101, 1068, 1027, 754, 699; $[\alpha]^{22\circ} = +64.0^\circ\pm 2.7^\circ$ (c=3.75 mg/mL in methylene chloride); $[\alpha]^{22\circ} = +35.0^\circ\pm 3.0^\circ$ (c=3.42 mg/mL in methanol) lit. value$^{60}$ ((S) enantiomer); $[\alpha]^{22\circ} = -22.0^\circ$ (c=2.0 in methanol).
(R)-(+)\text{-}2\text{-}Phenylpyrrolidine: (at 80 psig)

General procedure A was used to reduce 2-phenyl-1-pyrrole (290 mg, 2.0 mmol) with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; n-butyllithium: 117 µL, 1.70 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol) at 80 psig of H₂ and 65 °C. The mixture was stirred for 7 h. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (3 x 10 mL). The aqueous portion was made basic with NaOH and extracted with methylene chloride (3 x 20 mL). The combined organic portions were dried over Na₂SO₄ and concentrated \textit{in vacuo} to afford 247 mg (84 % yield) of the desired (R)-(+)\text{-}2\text{-}phenylpyrrolidine. HPLC analysis of the 1-naphthamide (85:15 hexane : isopropanol) indicated 99 % ee. [α]^{22}_D = +65.3° ± 1.1° (c=11.3 mg/mL in methylene chloride).

(R)-(+)\text{-}2\text{-}Phenylpyrrolidine: (at 500 psig)

General procedure B was used to reduce 2-phenyl-1-pyrrole (218 mg, 1.5 mmol) with 5 mol % catalyst (titanium complex: 45 mg, 0.075 mmol; n-butyllithium: 85 µL, 1.76 M in hexanes, 0.15 mmol; phenylsilane: 28 µL, 0.22 mmol) at 500 psig of H₂ and 21 °C. The mixture was stirred for 24 h. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (4 x 8 mL). The aqueous layers were made basic with NaOH and extracted with methylene chloride (3 x 15 mL). The combined organic portions were dried over Na₂SO₄ and concentrated to afford 190 mg (86 % yield) of the desired (R)-(+)\text{-}2\text{-}phenylpyrrolidine with no further purification necessary. HPLC analysis of the 1-naphthamide (85:15 hexane : isopropanol) indicated 99 % ee.

(R)-(+)\text{-}2\text{-}Phenylpyrrolidline: (at 80 psig)
General procedure A was used to reduce 2-phenyl-1-pyrroline (1.45 g, 10.0 mmol) with 1 mol % catalyst (titanium complex: 59 mg, 0.10 mmol, n-butyllithium: 122 µL, 1.64 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol) at 80 psig of H₂ and 65 ºC. The mixture was stirred for 42 h. The solvent was removed in vacuo and Kugelrohr distillation afforded 1.21 g (83 % yield) of the desired (R)-(+)2-phenylpyrrolidine. HPLC analysis of the 1-naphthamide (85:15 hexane : isopropanol) indicated 99 % ee.

(R)-(+)2-Phenylpyrrolidine: (at 80 psig)

General procedure A was used to reduce 2-phenyl-1-pyrroline (290 mg, 2.0 mmol) with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; n-butyllithium: 122 µL, 1.64 M in hexanes, 0.20 mmol; no phenylsilane used) at 80 psig of H₂ and 65 ºC. The mixture was stirred for 8 h. The solvent was removed in vacuo and Kugelrohr distillation afforded 235 mg (80 % yield) of the desired (R)-(+)2-phenylpyrrolidine. HPLC analysis of the 1-naphthamide (85:15 hexane : isopropanol) indicated >99 % ee.

(R)-(+)2-Phenylpiperdine:⁶¹ (at 2000 psig)

2-Pheny-3,4,5,6-tetrahydropyridine (80 mg, 0.5 mmol) was reduced according to general procedure B with 10 mol % catalyst (titanium complex: 30 mg, 0.050 mmol; n-butyllithium: 78 µL, 1.29 M in hexanes, 0.10 mmol; phenylsilane: 16 µL, 0.125 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 48 h in an oil bath at 65 ºC. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 10 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 20 mL) to afford the pure amine (65
mg, 81 % yield). HPLC analysis indicated 95% ee. $^1$H NMR (300 MHz, CDCl$_3$, TMS): 7.37-7.21 (m, 5H), 3.59 (m, 1H), 3.18 (m, 1H), 2.79 (m, 1H), 1.90 (m, 1H), 1.81-1.77 (m, 1H), 1.69-1.64 (m, 2H including N-H), 1.58-1.47 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 145.58, 128.29, 126.92, 126.57, 62.33, 47.81, 34.99, 25.93, 25.43; IR (neat): 3322, 3270, 326, 3082, 3061, 3026, 2932, 2873, 2851, 2816, 2786, 2719, 2697, 1452, 1440, 1432, 1325, 1307, 1122, 1109, 1020, 753, 699; [$\alpha$]$^{22}$$^\circ$ = + 49.5$^\circ$ ± 2.5$^\circ$ (c=2.02 mg/mL in methylene chloride).

**(R)-(+-)2-Phenylpiperidine:** (at 2000 psig)

2-Phenyl-3,4,5,6-tetrahydropyridine (318 mg, 2.0 mmol) was reduced according to general procedure B with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; $n$-butyllithium: 120 $\mu$L, 1.66 M in hexanes, 0.20 mmol; phenylsilane: 37 $\mu$L, 0.30 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 11 h in a oil bath at 65 °C. The pure amine (225 mg, 70%) was obtained after chromatography (silica, 2:2:96 triethylamine : diethyl ether : hexanes). HPLC analysis indicated 97% ee.

**(R)(+-)2-Phenylpiperidine:** (at 500 psig)

General procedure B was used to reduce 2-phenyl-3,4,5,6-tetrahydropyridine (318 mg, 2.0 mmol) with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol, $n$-butyllithium: 122 $\mu$L, 1.63 M in hexanes, 0.20 mmol; phenylsilane: 37 $\mu$L, 0.30 mmol) at 500 psig of H$_2$ and 65 °C. The mixture was stirred for 24 h. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (4 x 10 mL). The aqueous portions were made basic with NaOH and extracted with methylene chloride (3 x 20 mL). The combined organic portions were dried over Na$_2$SO$_4$ and concentrated. Flash chromatography (silica, 43:1:1 hexane : ether :
diethylamine) afforded 248 mg (77 % yield) of the desired \((R)-(+)-2\)-phenylpiperidine. HPLC analysis of the trifluoroacetamide (98:2 hexane : isopropanol) indicated 98 % ee. \([\alpha]^{22}_D = +48.4^\circ \pm 3.2^\circ\) (c=3.1 mg/mL in methylene chloride).

\textbf{(+)-2-Phenylhexahydroazepine:} (at 80 psig)

General procedure A was used to reduce 2-phenyl-4,5,6,7-tetrahydro-3H-azepine (347 mg, 2.0 mmol) with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol, \(n\)-butyllithium: 122 \(\mu\)L, 1.63 M in hexanes, 0.20 mmol; phenylsilane: 37 \(\mu\)L, 0.30 mmol) at 80 psig of \(H_2\) and 65 °C. The mixture was stirred for 30 h. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (4 x 8 mL). The aqueous portion was made basic with NaOH and extracted with methylene chloride (3 x 20 mL). The combined organic portions were dried over \(Na_2SO_4\) and concentrated. Flash chromatography (silica, 49:49:2 hexane : ether : diethylamine) afforded 278 mg (74 % yield) of the desired \((+)-2\)-phenylhexahydroazepine. HPLC analysis of the 1-naphthamide (93:7 hexane : isopropanol) indicated 97 % ee. \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS): \(\delta\) 7.39-7.17 (m, 5H) 3.76-3.72 (dd, \(J_1=3.6\) Hz, \(J_2=9.9\) Hz, 1H), 3.17-3.10 (dt, \(J_1=13.5\) Hz, \(J_2=4.2\) Hz, 1H), 2.89-2.80 (m, 1H), 2.01-1.91 (m, 1H), 1.90-1.57 (m, 8H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 146.9, 128.1, 126.4, 126.1, 64.7, 48.0, 38.9, 30.8, 26.7, 25.9; IR (neat): 3650, 3335, 3082, 3060, 3025, 2924, 2851, 1940, 1874, 1806, 1757, 1633, 1601, 1584, 1492, 1449, 1355, 1337, 1270, 1249, 1210, 1143, 1072, 1027, 999, 951, 915, 904, 840, 753, 699; HRMS: calc. for C\(_{12}\)H\(_{17}\)N; 175.1361, found 175.1360; \([\alpha]^{23}_D = +62.0^\circ \pm 2^\circ\) (c=47.7 mg/mL in methylene chloride).

\textbf{(+)-2-Phenylhexahydroazepine:} (at 80 psig)
General procedure B was used to reduce 2-phenyl-4,5,6,7-tetrahydro-3H-azepine (347 mg, 2.0 mmol) with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol, n-butyllithium: 122 µL, 1.63 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol) at 500 psig of H₂ and 45 °C. The mixture was stirred for 24 h. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (4 x 10 mL). The aqueous layers were made basic with NaOH and extracted with methylene chloride (3 x 20 mL). The combined organic portions were dried over Na₂SO₄ and concentrated. Flash chromatography (silica, 49:49:2 hexane : ether : diethylamine) afforded 249 mg (71 % yield) of the desired (+)-2-phenylhexahydroazepine. HPLC analysis of the 1-naphthamide (93:7 hexane : isopropanol) indicated 98 % ee.

(S)-(--)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydrossoquinoline:⁷² (at 2000 psig)

6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (172 mg, 0.84 mmol) was reduced according to general procedure B with 10 mol% catalyst (titanium complex: 50 mg, 0.084 mmol; n-butyllithium: 128 µL, 1.3 M in hexanes, 0.168 mmol; phenylsilane: 26 µL, 0.21 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 48 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 30 mL) to afford the pure amine (151 mg, 87 % yield). HPLC analysis indicated 94 % ee. ¹H NMR (300 MHz, CDCl₃, TMS): δ 6.63 (s, 1H), 6.57 (s, 1H), 4.04 (q, 1H, 6.6 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 3.30-3.21 (dt, 1H, J₁=12.9 Hz, J₂=7.5 Hz), 3.05-2.95 (m, 1H), 2.83-2.74 (m, 1H), 2.65-2.60 (m, 1H), 1.65 (bs, N-H), 1.44 (d,
3H, J=6.6 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 147.30, 147.22, 132.55, 126.85, 111.84, 109.15, 55.98, 55.81, 51.21, 41.85, 29.58, 22.84; IR (KBr): 3327, 2956, 2972, 2849, 2831, 2793, 1609, 1513, 1463, 1452, 1371, 1353, 1324, 1307, 1282, 1266, 1256, 1222, 1126, 1117, 1098, 1029, 997, 857, 788; [α]$_{21}^{	ext{D}}$ = -55.0° ± 2.0° (c=4.90 mg/mL in ethanol); lit value$^{[56a]}$ [α]$_{22}^{	ext{D}}$ = -41.5° (c=1.71 in ethanol, 70% ee); lit value$^{[56b]}$ [α]$_{22}^{	ext{D}}$ = -59.5° (c=4.39 in ethanol).

(S)-(−)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline: (at 2000 psig)
6,7-Dimethoxy-1-methyl-3,4-dihydroisoquinoline (410 mg, 2.0 mmol) was reduced according to general procedure B with 5 mol% catalyst (titanium complex: 59 mg, 0.10 mmol; n-butyllithium: 120 µL, 1.66 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 11 h in an oil bath at 65 °C. The amine was purified by flash chromatography on silica (3:5:92 triethylamine : methanol : ethyl acetate) to yield 370 mg (90 % yield) product. HPLC analysis indicated 99 % ee.

(S)-(−)-6,7-Dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline: (at 80 psig)
General procedure A was used to reduce 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (410 mg, 2.0 mmol) with 5 mol% catalyst (titanium complex: 59 mg, 0.10 mmol, n-butyllithium: 121 µL, 1.65 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol) at 80 psig of H$_2$ and 65 °C. The mixture was stirred for 50 h. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (3 x 10 mL). The aqueous layers were made basic with KOH and extracted with methylene chloride (3 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated. Flash chromatography (silica, 92:5:3 ethyl acetate : methanol : triethylamine) afforded 339 mg (82 % yield) of (S)-(−)-6,7-Dimethoxy-
1-methyl-1,2,3,4-tetrahydroisoquinoline. HPLC analysis of the amine (5:1 hexane : isopropanol) indicated 95 % ee. \([\alpha]^{21}_D = -54.3^\circ \pm 2.0^\circ \) (c=5.7 mg/mL in ethanol).

\((R)-(\cdot)-2-[2-(N-benzylpyrrolyl)]pyrroldine: \text{ (at 80 psig)}\)

General procedure A was used to reduce 2-[2-(N-benzylpyrrolyl)]-1-pyrrole (449 mg, 2.0 mmol) with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol, n-butyllithium: 122 \(\mu\)L, 1.63 M in hexanes, 0.20 mmol; phenylsilane: 37 \(\mu\)L, 0.30 mmol) at 80 psig of \(H_2\) and 65 °C. The mixture was stirred for 6 h. The crude mixture was washed with 1 M NaOH (10 mL), dried over Na\(\_2\)SO\(_4\) and concentrated in vacuo. Flash chromatography (silica, 97:3 ethyl acetate : triethylamine) afforded 327 mg (72 % yield) of \((R)-(\cdot)-2-[2-(N-benzylpyrrolyl)]pyrroldine. \) HPLC analysis of the acetamide (5:1 hexane : isopropanol) indicated >99 % ee. \(^1\)H NMR (250 MHz, CDCl\(_3\), TMS): \(\delta \) 7.24-7.15 (m, 3H), 7.03-6.97 (m, 2H), 6.65-6.62 (m, 1H), 6.15-6.1 (m, 2H), 5.38-5.1 (dd, \(J=17\) Hz, 2H), 3.96-3.91 (t, \(J=7\) Hz, 1H), 3.14-3.07 (m, 1H), 2.89-2.79 (m, 1H), 2.03-1.72 (m, 4H), 1.52 (bs, N-H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta \) 138.6, 134.8, 128.5, 127.1, 126.2, 121.9, 106.9, 105.0, 54.9, 50.2, 46.7, 31.6, 25.4; IR (neat): 3285, 3098, 3086, 3062, 3028, 2961, 2871, 1949, 1863, 1808, 1735, 1696, 1604, 1585, 1495, 1482, 1453, 1431, 1413, 1356, 1331, 1295, 1241, 1208, 1189, 1134, 1071, 1029, 1001, 951, 910, 844, 798, 776, 707, 622, 614; HRMS: calc. for C\(_{15}\)H\(_{18}\)N\(_2\): 226.1470, found 226.1469; \([\alpha]^{22}_D = -27.1^\circ \pm 1^\circ \) (c=7.5 mg/mL in methylene chloride). The absolute configuration was determined by optical rotation of the Cbz derivative\(^63\) (prepared and measured by Dr. Yaping Hong).

\((R)-(\cdot)-2-[2-(N-benzylpyrrolyl)]pyrroldine: \text{ (at 500 psig)}\)
General procedure B was used to reduce 2-{2-(N-benzyl)pyrrolyl}-1-pyrroline (225 mg, 1.0 mmol) with 5 mol % catalyst (titanium complex: 30 mg, 0.05 mmol, n-butyllithium: 61 μL, 1.63 M in hexanes, 0.10 mmol; phenylsilane: 19 μL, 0.15 mmol) at 500 psig of H₂ and 23 °C. The mixture was stirred for 24 h. The crude mixture was washed with 1 M NaOH (10 mL), dried over Na₂SO₄ and concentrated. Flash chromatography (silica, 97:3 ethyl acetate : triethylamine) afforded 189 mg (83 % yield) of (R)-(-)-2-{2-(N-benzylpyrrolyl)pyrrolidine. HPLC analysis of the acetamide (5:1 hexane : isopropanol) indicated >99 % ee.

(+)-2-[1-(4-Methylpent-4-ethyl)]pyrrolidine: (at 80 psig)

General procedure A was used to reduce 2-{1-(4-methylpent-4-ethyl)}-1-pyrroline (454 mg, 3.0 mmol) with 5 mol % catalyst (titanium complex: 90 mg, 0.15 mmol, n-butyllithium: 184 μL, 1.65 M in hexanes, 0.30 mmol; phenylsilane: 56 μL, 0.45 mmol) at 80 psig of H₂ and 50 °C. The mixture was stirred for 23 h. The solvent was removed in vacuo and the crude material was isolated by Kugelrohr distillation. Flash chromatography (silica, 97:3 methylene chloride : diethylamine) afforded 350 mg (76 % yield) of (+)-2-{1-(4-methylpent-4-ethyl)}pyrrolidine. HPLC analysis of the 1-naphthamide (91:9 hexane : isopropanol) indicated 99 % ee. 

^1H NMR (300 MHz, CDCl₃, TMS): δ 5.14-5.06, (m, 1H), 3.15-2.89 (m, 2H), 2.86-2.77 (m, 1H), 2.08-1.99 (m, 2H), 1.9-1.8 (m, 2H) 1.78-1.65 (m, 2H), 1.66 (s, 3H), 1.60 (s, 3H), 1.59-1.39 (m, 2H), 1.3-1.18 (m, 1H); ^13C NMR (75 MHz, CDCl₃): δ 131.47, 124.3, 58.9, 46.5, 36.5, 31.8, 26.0, 25.7, 25.3, 17.6; IR (neat): 3350, 2961, 2921, 2856, 1616, 1539, 1400, 1107, 811, 614; HRMS: calc. for C₁₀H₁₉N: 153.1517, found 153.1516; [α]₂⁴° = + 17.0° ± 0.8° (c=12.8 mg/mL in methylene chloride).
(+)-E-2-[1-(6-Trimethylsilyl)hex-5-enyl]pyrrolidine: (at 80 psig)

General procedure A was used to reduce E-2-[1-(6-Trimethylsilyl)hex-5-enyl]-1-pyrroline (223 mg, 1.0 mmol) with 5 mol % catalyst (titanium complex: 30 mg, 0.05 mmol, n-butyllithium: 60 μL, 1.66 M in hexanes, 0.10 mmol; phenylisilane: 19 μL, 0.15 mmol) at 80 psig of H₂ and 50 °C. The mixture was stirred for 27 h at which time GC showed >94 : <1 : 5 E isomer : Z isomer : saturated compound. Flash chromatography (silica, 96:4 methylene chloride : triethylamine) afforded 158 mg (70 % yield) of a mixture of (+)-E-2-[1-(6-Trimethylsilyl)hex-5-enyl]pyrrolidine (>94%), Z-2-[1-(6-Trimethylsilyl)hex-5-enyl]pyrrolidine (<1%) and 2-[1-(6-Trimethylsilyl)hexyl]-pyrrolidine (5%) as a yellow oil. HPLC analysis of the 1-naphthamide (91:9 hexane : isopropanol) indicated 99 % ee for the mixture of compounds. ¹H NMR (300 MHz, CDCl₃, TMS): (+)-E-2-[1-(6-Trimethylsilyl)hex-5-enyl]pyrrolidine; δ 6.05-5.95 (dt, J₁=18 Hz, J₂=6 Hz, 1H), 5.64-5.56 (d, J=18 Hz, 1H), 3.03-2.75 (m, 3H), 2.12-2.06 (q, J=6 Hz, 2H), 1.94 (bs, 1H). 1.84-1.65 (m, 3H), 1.5-1.13 (m, 7H), 0.25 (s, 9H); 2-[1-(6-Trimethylsilyl)hexyl]pyrrolidine: δ 0.5-0.4 (m, 2H), -0.49 (s, 9H) all other resonances are obscured; ¹³C NMR (75 MHz, CDCl₃): (+)-E-2-[1-(6-Trimethylsilyl)hex-5-enyl]pyrrolidine: δ 146.7, 129.4, 59.2, 46.4, 36.6, 36.2, 31.8, 28.8, 27.0, 25.3, -1.1; 2-[1-(6-Trimethylsilyl)hexyl]pyrrolidine: δ 36.4, 33.5, 29.5, 27.5, 23.8, 16.7, -1.6 all other resonances are obscured; IR (neat, mixture): 3285, 2925, 2854, 1616, 1458, 1420, 1246, 1106, 987, 863, 837, 763, 730, 691; HRMS: (+)-E-2-[1-(6-Trimethylsilyl)hex-5-enyl]pyrrolidine; calc. for C₁₉H₂₇NSi; 225.1912, found 225.1911; [α]²²° (mixture) = +12.3° ± 0.5° (c=19.5 mg/mL in methylene chloride).

(+)-2-Hexy1pyrrolidine: (at 2000 psig)
2-hexylpyrrolidine (460 mg, 3.0 mmol) was reduced according to general procedure B with 5 mol % catalyst (titanium complex: 89 mg, 0.15 mmol; n-butyllithium: 175 μL, 1.7 i M in hexanes, 0.30 mmol; phenylsilane: 56 μL, 0.45 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 8 h in an oil bath at 65 °C. The THF was removed in vacuo and the residue was taken up in diethyl ether. The ether layer was extracted with aqueous 1 M HCl (3 x 20 mL). The aqueous layers were combined and made basic with solid KOH and extracted with diethyl ether (4 x 30 mL) to afford the pure amine (375 mg, 80 % yield). GC analysis of the (S)-α-methoxy-α-(trifluoromethyl)-phenylacetamide indicated >97 % ee. ¹H NMR (300 MHz, CDCl₃, TMS): 3.05-2.95 (m, 1H), 2.90 (t, 1H, J=6.8 Hz), 2.85-2.75 (m, 1H), 1.93-1.80 (m, 1H), 1.78-1.65 (m, 2H), 1.57 (bs, N-H), 1.5-1.18 (m, 11H), 0.80 (t, 3H, J=6.6Hz); ¹³C NMR (75 MHz, CDCl₃): δ 59.23, 46.42, 36.42, 31.75, 31.69, 29.35, 27.35, 25.25, 22.46, 13.88; IR (neat): 3312, 3300, 3296, 2956, 2924, 2871, 2855, 1466, 1459, 1434, 1430, 1420, 1402, 1378, 1364, 1342, 1302, 1282, 1260, 1097, 811, 752; HRMS: calc. for C₁₀H₂₁N; 155.1674, found 155.1672; [α]²⁴ = + 14.2° ± 0.8° (c=12.0 mg/mL in methylene chloride).

(+)-2-Hexylpyrrolidine: (at 80 psig)

General procedure A was used to reduce 2-(1-hex-5-enyl)-1-pyrrole (302 mg, 2.0 mmol) with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; n-butyllithium: 121 μL, 1.65 M in hexanes, 0.20 mmol; phenylsilane: 37 μL, 0.30 mmol) at 80 psig of H₂ and 45 °C. The mixture was stirred for 23 h (monitoring of the reaction by GC/MS showed that the olefin was reduced much faster than the imine). The solvent was removed in vacuo and Kugelrohr distillation afforded 223 mg (72 % yield) of (+)-2-Hexylpyrrolidine. HPLC analysis of the 1-
naphthamide (91:9 hexane : isopropanol) indicated 99 % ee. $[\alpha]^{24\circ} = + 15.1\circ \pm 0.7\circ$ (c=15.2 mg/mL in methylene chloride).

(+)-2-[1-(4-tert-Butyldimethylsiloxy)butyl]pyrrolidine: (at 80 psig)
General procedure A was used to reduce 2-[1-(4-tert-butyldimethylsiloxy)butyl]-1-pyrroline (510 mg, 2.0 mmol) with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol, n-butyllithium: 121 $\mu$L, 1.65 M in hexanes, 0.20 mmol; phenylsilane: 37 $\mu$L, 0.30 mmol) at 80 psig of H$_2$ and 65 $^\circ$C. The mixture was stirred for 10 h. The solvent was removed in vacuo and Kugelrohr distillation afforded 440 mg (85 % yield) of (+)-2-[1-(4-tert-butyldimethylsiloxy)butyl]pyrrolidine. HPLC analysis of the 1-naphthamide (91:9 hexane : isopropanol) indicated 99 % ee. $^1$H NMR (300 MHz, CDCl$_3$, TMS): $\delta$ 3.6-3.58 (t, J=6.6 Hz, 2H), 3.02-2.82 (m, 2H), 2.81-2.77 (m, 1H), 1.91-1.80 (m, 1H), 1.79-1.30 (m, 9H), 1.28-1.18 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 63.1, 59.3, 46.5, 36.8, 32.9, 31.8, 25.9, 25.4, 23.7, 18.3, -5.3; IR (neat): 3298, 2930, 2857, 2737, 1617, 1540, 1471, 1461, 1402, 1360, 1255, 1190, 1099, 1005, 938, 915, 836, 812, 774, 712, 66; HRMS: calc. for C$_{14}$H$_{31}$NOSi: 257.2175, found 257.2173; $[\alpha]^{24\circ} = + 9.2\circ \pm 0.7\circ$ (c=14.1 mg/mL in methylene chloride).

(+)-2-[4-(1,3-Dioxolan-2-y1)butyl]pyrrolidine: (at 80 psig)
General procedure A was used to reduce 2-[4-(1,3-dioxolan-2-y1)butyl]-1-pyrroline (366 mg, 2 mmol) with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol, n-butyllithium: 121 $\mu$L, 1.65 M in hexanes, 0.20 mmol; phenylsilane: 37 $\mu$L, 0.30 mmol) at 80 psig of H$_2$ and 65 $^\circ$C. The mixture was stirred for 16 h. The solvent was removed in vacuo and Kugelrohr distillation afforded 314 mg (85 % yield) (+)-2-[4-(1,3-dioxolan-2-y1)butyl]pyrrolidine. HPLC analysis of the *
naphthamide (85:15 hexane : isopropanol) indicated 99 % ee. \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS): \(\delta\) 4.86-4.82 (t, \(J=4.8\) Hz, 1H), 3.98-3.81 (m, 4H), 3.01-2.76 (m, 3H), 1.92-1.8 (m, 1H), 1.79-1.6 (m, 4H), 1.58-1.39 (m, 5H), 1.3-1.17 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 104.4, 64.8, 59.2, 46.6, 36.4, 34.0, 31.8, 25.4, 22.0; IR (neat): 3285, 2947, 2868, 1458, 1434, 1410, 1361, 1211, 1141, 1032, 942, 890, 708; HRMS: calc. for [M-H]\(^+\), C\(_{10}\)H\(_{18}\)NO\(_2\): 184.1338, found 184.1337; \([\alpha]^{24}_D = +10.6^\circ \pm 0.4^\circ\) (c=25.5 mg/mL in methylene chloride).

(+)\(2\)-[1-(7-Hydroxy)heptyl]pyrrolidine: (at 80 psig)
General procedure A was used to reduce \(2\)-[1-(7-hydroxy)heptyl]-1-pyrroline (336 mg, 2.0 mmol) with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol, n-butyllithium: 121 \(\mu\)L, 1.65 M in hexanes, 0.20 mmol; phenylsilane: 271 \(\mu\)L, 2.2 mmol) at 80 psig of H\(_2\) and 65 °C. The mixture was stirred for 8 h. The mixture was transferred to a round bottom flask and 2 mL 30 % NaOH was added. After stirring for 4 h, the THF was removed in vacuo and the residue was diluted with 20 mL of chloroform / 5 mL of sat NaCl. The layers were separated and the aqueous layer was extracted with chloroform (2 x 20 mL). The chloroform layers were dried over Na\(_2\)SO\(_4\) and concentrated. Flash chromatography (silica, 3:15:82 triethylamine : methanol : chloroform) afforded 319 mg (86 % yield) (+)-2-[1-(7-Hydroxy)heptyl]pyrrolidine as a white solid. HPLC analysis of the 1-naphthamide (80:20 hexane : isopropanol) indicated 99 % ee. \(^1\)H NMR (300 MHz, CDCl\(_3\), TMS): \(\delta\) 3.65-3.6 (t, \(J=6.6\) Hz, 2H), 3.02-2.7 (m, 3H), 1.9-1.6 (m, 5H) 1.6-1.14 (m, 13H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 62.4, 59.3, 46.4, 36.3, 32.9, 31.9, 29.8, 29.4, 27.4, 25.8, 25.4; IR (neat): 3230, 3100, 2920, 2850, 1460, 1373, 1344, 1138, 1082, 1051, 1013, 993, 947, 890, 772, 719; HRMS: calc. for [M-H]\(^+\),
C\textsubscript{11}H\textsubscript{22}NO; 184.1701, found 184.1703; [\alpha]\textsuperscript{23}_D = + 12.2^\circ \pm 1.1^\circ (c=9.0 \text{ mg/mL in methylene chloride}); mp: 62-64.5 ^\circ \text{C}.

(+)-\textit{E}-2-(1-Non-6-enyl)pyrrolidine: (at 80 psig)

General procedure A was used to reduce \textit{Z}-2-(1-non-6-enyl)-1-pyrrole (290 mg, 1.5 mmol) with 5 mol % catalyst (titanium complex: 45 mg, 0.075 mmol, \textit{n}-butyllithium: 90 \mu L, 1.66 M in hexanes, 0.15 mmol; phenylsilane: 28 \mu L, 0.23 mmol) at 80 psig of H\textsubscript{2} and 50 ^\circ \text{C}. The mixture was stirred for 25 h. The mixture was concentrated and flash chromatography (silica, 97:3 methylene chloride : triethylamine) afforded 201 mg (69% yield) of a mixture of \textit{E}-2-(1-non-6-enyl)pyrrolidine (68%), \textit{Z}-2-(1-non-6-enyl)pyrrolidine (14%, prepared independently by sodium borohydride reduction of \textit{Z}-2-(1-non-6-enyl)-1-pyrrole, spectral data below) and 2-(1-nonyl)pyrrolidine (18%, prepared independently by Pd/C hydrogenation of \textit{Z}-2-(1-non-6-enyl)-1-pyrrole, spectral data below). These compounds were identified by GC/MS, and \textsuperscript{1}H NMR as the major components; in the \textsuperscript{13}C NMR some extra peaks were present indicating the presence of small amounts of other olefin isomers. The position of the olefin in the major products was determined by selective homonuclear decoupling experiments; irradiation of the resonances at 1.98 ppm (allylic methylene) caused the two overlapping triplet resonances at 0.98-0.92 ppm (methyl groups for the \textit{E} and \textit{Z} isomers) to collapse to singlets; irradiation of the resonances at 1.33 (methylenes) caused the triplet resonance at 0.91-0.83 (methyl group for the saturated compound) to collapse to a singlet. The ee was determined by reducing the product mixture with 10% Pd/C under 500 psig H\textsubscript{2} to 2-(1-nonyl)pyrrolidine. The crude 2-(1-nonyl)pyrrolidine was converted to the 1-naphthamide and HPLC analysis (91:9 isopropanol : hexane) indicated 99% ee.
Spectral data for product mixture: $^1$H NMR (300 MHz, CDCl$_3$, TMS): E and Z isomer; δ 5.5-5.3 (m, 2H), 3.07-2.77 (m, 3H), 2.11-2.08 (bs-1H), 2.08-1.61 (m, 7H), 1.57-1.18 (m, 10H), 0.98-0.92 (t, J=7.5 Hz, 3H); The only resolved resonance for the saturated isomer was 0.9-0.83 (t, J=7.5 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): E isomer only: δ 131.7, 129.0, 59.3, 46.4, 36.3, 32.4, 31.8, 29.5, 29.3, 27.3, 25.5, 25.3, 14.0; IR (neat): 3283, 2959, 2924, 2853, 1459, 1374, 1298, 1080, 966, 724; HRMS: for major product (E isomer) calc. for C$_{13}$H$_{25}$N; 195.1987, found 195.1985; $[\alpha]^{23}_{D}$ (mixture) = +12.4° ± 0.5° (c=18.6 mg/mL in methylene chloride).

Spectral data for 2-(1-nonyl)pyrrolidine (independently prepared by Pd/C hydrogenation): $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ 3.08-2.79 (m, 3H), 1.94-1.67 (m, 4H), 1.5-1.17 (m, 17H), 0.91-0.84 (t, 3H, J=7.5 Hz) $^{13}$C NMR (75 MHz, CDCl$_3$): δ 59.4, 46.5, 36.5, 31.9, 29.8, 29.6, 29.5, 29.3, 27.5, 25.4, 22.6, 14.0; IR (neat): 3283, 2924, 2853, 1465, 1458, 753, 733; HRMS: calc. for C$_{13}$H$_{27}$N; 197.2143, found 197.2144.

Spectral data for Z-2-(1-non-6-eryl)pyrrolidine (independently prepared by sodium borohydride reduction): $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ 5.45-5.25 (m, 2H), 3.08-2.77, (m, 3H), 2.12-1.55, (m, 8H), 1.55-1.15 (m, 10H), 0.99-0.9 (t, 3H, J=7.5 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 131.4, 129.1, 59.4, 46.6, 36.5, 31.9, 29.8, 29.5, 27.5, 27.1, 25.5, 20.6, 14.5.

**Kinetic resolution of N-Benzylidene(1-phenylethyl)amine:** (at 150 psig) N-Benzylidene(1-phenylethyl)amine (418 mg, 2.0 mmol) was reduced according to general procedure B with 5 mol % catalyst (titanium complex: 59 mg, 0.1 mmol; n-butyllithium: 112 μL, 1.78 M in hexanes, 0.2 mmol; phenylsilane: 37 μL, 0.3 mmol). The vessel was charged to 150 psig and the mixture was stirred for 36 h.
in an oil bath at 65 °C. The vessel was carefully vented and opened to air. GC analysis showed 70 % amine, 25 % aldimine (starting material), and 3 % ketimine. After standard acid / base workup the product was purified by chromatography (94:3:3 hexane:ether:triethylamine) to give 266 mg of a light yellow oil (63 %) HPLC analysis showed 23 % ee ((S) enantiomer).

**Kinetic resolution of N-Benzylidine(1-phenylethyl)amine:** (at 2000 psig) N-Benzylidine(1-phenylethyl)amine (418 mg, 2.0 mmol) was reduced according to general procedure B with 5 mol % catalyst (titanium complex: 59 mg, 0.1 mmol; n-butyllithium: 112 μL, 1.78 M in hexanes, 0.2 mmol; phenylsilane: 37 μL, 0.3 mmol). The vessel was charged to 2000 psig and the mixture was stirred for 4 h in an oil bath at 65 °C. The vessel was carefully vented and opened to air. GC analysis showed 45 % amine, 52 % aldimine (starting material), only a trace of ketimine was observed. A portion of the mixture was transferred to a flask containing 5 mL THF and 5 mL 1 M HCl and stirred overnight. The layers were separated, the aqueous layer was made basic with NaOH and extracted with ether (3 x 20 mL). The organic portions were dried with Na₂SO₄ and concentrated. HPLC analysis of the product showed 31 % ee ((S) enantiomer).

**Kinetic resolution of N-Benzylidine(1-cyclohexylethyl)amine:** (at 2000 psig) Benzylidine(1-cyclohexyl-ethyl)amine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; n-butyllithium: 114 μL, 1.75 M in hexanes, 0.20 mmol; phenylsilane: 37 μL, 0.30 mmol). The reaction vessel was charged to 2000 psig and the reaction mixture was stirred for 4 h. At this point GC showed 71 % remaining aldimine (starting material) and 29 % amine (only a trace of the ketimine was observed).
The mixture was transferred to a flask containing 5 mL 1 M HCl and stirred overnight. The layers were separated, the aqueous layer was made basic with NaOH and extracted with ether (3 x 20 mL). The organic portions were dried with Na₂SO₄ and concentrated. Column chromatography (silica, 2 % triethylamine : hexane) afforded 88 mg (20 % yield) of product. HPLC analysis indicated 16 % ee ((S) enantiomer).

**Kinetic resolution of \( ^\beta \)-Benzyldiene(1-tetralinyl)amine:** (at 2000 psig)
Benzyldiene(1-tetralinyl)amine (471 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst (titanium complex: 59 mg, 0.10 mmol; \(n\)-butyllithium: 119 µL, 1.68 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol). The reaction vessel was charged to 2000 psig and the reaction mixture was stirred for 4 h. At this point GC showed 56 % remaining aldimine (starting material) and 44 % amine (no ketimine was observed). The mixture was transferred to a flask containing 10 mL THF and 6 mL 1 M HCl and stirred overnight. The layers were separated, the aqueous layer was made basic with NaOH and extracted with ether (3 x 20 mL). The organic portions were dried with Na₂SO₄ and concentrated. HPLC analysis indicated 51 % ee.
REFERENCES


13. When the catalyst is generated under a hydrogen atmosphere no silane is required thus we believe that the silane serves to stabilize the active species during preparation and manipulation.


24. The activity of the catalyst was checked by adding a small amount of 2-phenylpyrrole after several hours. The added 2-phenylpyrrole was hydrogenated to 2-phenylpyrrolidine.

25. We have observed rate deceleration as product accumulates for other substrates containing coordinating groups such as an olefin or furan.


51. By GC a trace of the imine is sometimes present. It may be formed from the amine on the GC injector (260 °C) as has been observed for similar compounds. See Fales, H. M.; Comstock, W.; Jones, T. H. *Analytical Chem.* 1980, 52, 980.

52. Prepared by treatment of the acid (Aldrich) with oxalyl chloride.


Schematic of Fisher-Porter Bottle Assembly

- Septum
- Female tube connector
- Ball valve
- Needle valve
- Pressure relief valve
- Street Tee
- Female cross
- Barbed connector
- Male hex nipple
- Bottle assembly
- Gage
CHAPTER 2

CATALYTIC ASYMMETRIC HYDROGENATION OF IMINES WITH A CHIRAL TITANOCENE COMPLEX: MECHANISTIC INVESTIGATIONS
INTRODUCTION

An understanding of reaction mechanisms is essential to the development of a working knowledge of chemistry. Familiarity with the mechanisms by which many reactions occur can reveal similarities between seemingly unrelated transformations. The information obtained by mechanistic studies is often crucial to improving existing procedures and developing new methods. One of the most useful transformations in organic chemistry is the catalytic hydrogenation of unsaturated molecules. The variety of metal complexes which catalyze these reactions provide the practicing organic chemist great flexibility for solving many synthetic challenges. Accordingly, several homogeneous hydrogenation catalysts have been studied in detail for both asymmetric\(^1\) and non-asymmetric reactions.\(^2\) These studies have provided insight into the mechanism and origin of selectivity for these systems. With an understanding of these reaction mechanisms, chemists are better prepared to accurately predict which catalyst will be most suitable for a particular synthetic application.

The catalyst system discussed in this thesis is based on a titanium hydride complex. As shown in chapter 1 the catalyst system was found to hydrogenate imines with moderate to excellent enantioselectivity depending on the nature of the substrate. For cyclic imines ee's were generally very high and independent of reaction conditions. However, acyclic imines gave variable results depending on the conditions used, the most significant effect being that of hydrogen pressure. This chapter presents a detailed mechanistic study of the titanocene catalyzed asymmetric hydrogenation of a cyclic and an acyclic imine. The investigation described herein provides insight into the differences between the two classes of imines under consideration. An understanding of these mechanistic issues should allow one to predict with reasonable accuracy what synthetic applications the present chemistry will be amenable to. In addition it is hoped that these
studies will aid in the development of an improved system for the asymmetric reduction of organic compounds.

**BACKGROUND**

Titanium hydrides have been implicated in a variety of organic reactions including the hydrogenation,\(^3\) hydromagnesiation,\(^4\) hydroalumination,\(^5\) and hydroboration\(^6\) of olefins and acetylenes, the reduction of organic carbonyls,\(^7\) and aromatic bromides,\(^8\) the dehydrocoupling of organosilanes\(^9\) and the cyclization of dienes.\(^10\) As such many titanium hydride complexes have been isolated\(^11\) and several have been structurally characterized.\(^12\) A detailed discussion of the chemistry of all of these complexes will not be presented here. The following few paragraphs cover the work most relevant to this thesis and are meant to give a general overview of the reactivity of titanium hydride complexes and their role in hydrogenation reactions.

The first examples of olefin hydrogenation catalyzed by titanocene complexes appeared in the 1960's by two research groups. Shikata and coworkers reported that the combination of titanocene dichloride with 2-5 equivalents of an alkyl lithium or alkyl Grignard reagent resulted in the formation of an olefin hydrogenation catalyst (Scheme 2.1, equation 1).\(^{3a}\) The active catalyst was proposed to be a titanium(III) hydride. A year later Hagihara et. al. showed that under hydrogen atmosphere dicarbonyltitanocene could also effect olefin and alkyne hydrogenation (Scheme 2.1, equation 2).\(^{3b}\)

In a related paper Jellinek and Martin showed that reaction of titanocene dichloride with 2 equivalents of isopropylmagnesium bromide followed by a diene lead to the formation of the titanocene(III) allyl complexes (equation 3).\(^{13}\) The mechanism that they proposed for this reaction is shown in Scheme 2.2. By monitoring the reaction using UV spectroscopy, in was shown that the first equivalent of the Grignard reagent reduced titanocene dichloride to titanocene
Scheme 2.1 Titanocene Catalyzed Hydrogenation of Olefins and Acetylenes

\[ \text{R} = \text{R}' + \text{H}_2 \xrightarrow{\text{Cp}_2\text{TiCl}_2 / 2 \text{n-BuLi}} \text{eq. 1} \]

\[ \text{R} = \text{R}' + \text{H}_2 \xrightarrow{\text{Cp}_2\text{TiCl}_2 / 2 \text{EtMgX}} \]

\[ \text{R} = \text{R}' \]

monochloride. The second equivalent of the magnesium reagent reacted with \( \text{Cp}_2\text{TiCl} \) to form a titanium(III) alkyl species. This complex underwent \( \beta \)-hydride elimination to give a titanium(III) hydride, which then reacted with the diene to afford the allyl complex. However, the intermediate titanium hydride was not observed. It was also shown that when methyllithium was used dimethyl-titanocene was formed rather than the desired allyl complexes. Since a methyl group has no \( \beta \)-hydrogens formation of a titanium hydride is not possible. This observation lends support to the proposed mechanism.
About the same time Brintzinger and Bercaw reported on the study of the titanocene system in more detail.\textsuperscript{11a,b,14a} They found that reaction of solid dimethyltitanocene with hydrogen resulted in the formation of a dimeric titanocene(III) hydride complex (Scheme 2.3).\textsuperscript{11a} This complex was characterized by IR spectroscopy and by its reactivity. The complex was found to react with HCl to give titanocene dichloride. Reaction of the dimer with CO

**Scheme 2.3** Synthesis and Reactions of a Titanium(III) Hydride

![Scheme 2.3](image)

resulted in the formation of the known dicarbonyltitanocene. When triphenylphosphine was added to the dimeric hydride complex the monomeric titanocene(hydrido)phoshine complex was observed by EPR spectroscopy. Reaction with borane resulted in the formation of the previously reported titanocene borohydride complex.\textsuperscript{11g} While all of this evidence strongly supports the proposed structure, an X-ray structure determination was not possible due to the instability of this highly reactive species. Upon warming the dimeric hydride complex decomposed to another dimeric complex known as titanocene.\textsuperscript{14}
deactivation of catalysts in olefin hydrogenation has been attributed to formation of this complex.\textsuperscript{3e}

Very recently Harrod and coworkers have reported the preparation of a titanium(III) hydride complex\textsuperscript{12b} that has particular relevance to this work. Treatment of Brintrzinger's \textit{ansa} titanocene dichloride complex\textsuperscript{15} with methyllithium followed by phenylmethylsilane resulted in the formation of the dimeric titanium(III) hydride complex which was isolated in 90 \% yield as dark green crystals (equation 4). An X-ray structure determination indicated that the complex was a homochiral dihydride bridged dimer, 1-D as shown in Scheme 2.4 (\((R,R)-(R,R)\) dimer shown).

\textbf{Scheme 2.4 Synthesis of a Chiral Titanium(III) Hydride}

\begin{equation}
\text{Cl}^*\text{Ti}^\text{III} \text{Cl} \xrightarrow{1. \text{MeLi}} \xrightarrow{2. \text{PhMeSiH}_2} \text{1-D}
\end{equation}

Given the similarity of the reaction conditions used for the preparation of this complex and those used to generate the catalyst for our asymmetric hydrogenation reactions (see chapter 1), Harrod's result supports the notion that the active catalyst in these studies is complex 1-D (most likely the monomer).

\textbf{RESULTS}

\textbf{Catalyst Studies:} Based on the known chemistry of titanocene we had good reason to suspect that the active catalyst was a titanium(III) complex. In support of this hypothesis \textsuperscript{1H} NMR spectra of solutions of the active catalyst show only broad signals, indicative of a paramagnetic species. Additionally EPR spectra (room temperature) show signals in the expected range for a paramagnetic organometallic complex. To gain further insight into this possibility
we conducted a study of the catalytic activity of several titanium complexes as shown in Table 2.1. The complexes were employed in the hydrogenation of 2-phenylpyrroline, 2, as 80 psig of hydrogen and 65 °C (equation 5). Starting with enantiomerically

\[
\begin{array}{c}
\text{2} \xrightarrow{80 \text{ psig } H_2} \text{3} \\
\text{5 mol % cat. (see table 2.1)}
\end{array}
\]

pure 1a as the catalyst precursor we found that 2 was reduced to 3 with identical enantiomeric excess and similar isolated yield either in the presence or in the absence of phenylsilane. Furthermore the relative rates were the same with experimental error. When phenylsilane was not used, however, the activation with n-butyllithium had to be conducted under a hydrogen atmosphere. The

<table>
<thead>
<tr>
<th>Catalyst Precursor</th>
<th>Activation</th>
<th>Rxn time</th>
<th>Yield</th>
<th>ee</th>
<th>k_{rel}</th>
</tr>
</thead>
<tbody>
<tr>
<td>((R,R,R))-1a</td>
<td>2 eq n-BuLi PhSiH₃</td>
<td>7 h</td>
<td>84</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>((R,R,R))-1a</td>
<td>2 eq n-BuLi H₂</td>
<td>8 h</td>
<td>80</td>
<td>99</td>
<td>0.9</td>
</tr>
<tr>
<td>rac C₃₂Ti(CH₃)₂ 1c</td>
<td>H₂</td>
<td>12 h</td>
<td>82</td>
<td>0.6 b</td>
<td></td>
</tr>
<tr>
<td>rac C₃₂TiCl 1d</td>
<td>1 eq n-BuLi PhSiH₃</td>
<td>6 h</td>
<td>69</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>rac C₃₂TiN(CH₃)₂ 1e</td>
<td>H₂</td>
<td>8 h</td>
<td>70</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)All reactions were conducted at 80 psig of hydrogen and 65 °C with 5 mol % catalyst precursor. Approximate catalyst concentrations were 0.02 M. C₃₂ = ethylene-(bis)tetrahydroindenyl. \(^b\)Benzene was used as the solvent.

dimethyl derivative, 1c, catalyzed the hydrogenation reaction to afford the amine in good yield. In this case no reaction was observed unless hydrogen was added prior to the addition of 2. By analogy to the reaction of dimethyltitanocene with hydrogen (Scheme 2.3), 1c should be converted to the titanium(III) hydride complex upon reaction with hydrogen. This is required before catalysis can be observed. We also prepared two titanium(III) complexes 1d and 1e\(^{16}\) and
studied their catalytic activity. Of note is that magnetic susceptibility measurements on 1d and 1e using the Evans method\textsuperscript{17} indicate that they are both monomeric in benzene solution.\textsuperscript{18} Complex 1d, when treated with 1 equivalent of n-butyllithium followed by phenylsilane, was found to catalyze the hydrogenation of 2 to 3 with a rate similar to that observed when 1a was used. Most significantly, however is that complex 1e which is an analog to the proposed intermediate in the catalytic cycle (see Scheme 2.6), was found to catalyze the hydrogenation of 2 with no activation necessary. Again the rate was in good agreement with that observed using 1a.

**Hydrogenation of Cyclic Imines:** We examined the kinetics of the hydrogenation of 2-phenylpyrroline, 2 with the catalyst system described above (equation 6). The reactions were conducted in a Parr model 4565 autoclave at constant catalyst concentration and constant hydrogen pressure. Formation of amine was monitored, versus an internal standard, by capillary GC analysis of aliquots taken from the reaction vessel. During the course of the reaction only 2, 3 and phenylsilane were observed by GC.

\[
\text{eq. 6}
\]

The effects of varying reaction parameters on the reaction rate are shown by the data in Table 2.2. When (R,R,R)-1a was employed as the catalyst precursor (R)-2-phenylpyrrolidine 3, was produced. Significantly, the observed enantiomeric excess of the isolated amine are virtually independent of the reaction conditions (Table 2.2). This behavior distinguishes cyclic imines from acyclic ones as the latter show a dependence of ee on hydrogen pressure (\textit{vide infra}) with this catalyst system.
Figure 2.1 shows a plot of amine concentration versus time at various hydrogen pressures. The data fall on a straight lines for at least 3 half lives,

<table>
<thead>
<tr>
<th>[Ti]₀ (mmol / L)</th>
<th>[imine]₀ (mmol / L)</th>
<th>T (K)</th>
<th>H₂ pressure (psi)</th>
<th>reaction rate (mmol / L * min)</th>
<th>ee of amine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.75</td>
<td>150</td>
<td>318</td>
<td>815</td>
<td>1.16 (± 0.07)</td>
<td>---</td>
</tr>
<tr>
<td>3.75</td>
<td>75</td>
<td>318</td>
<td>815</td>
<td>1.20 (± 0.07)</td>
<td>99</td>
</tr>
<tr>
<td>3.75</td>
<td>75</td>
<td>318</td>
<td>615</td>
<td>0.94 (± 0.05)</td>
<td>99</td>
</tr>
<tr>
<td>3.75</td>
<td>75</td>
<td>318</td>
<td>415</td>
<td>0.61 (± 0.03)</td>
<td>99</td>
</tr>
<tr>
<td>3.75</td>
<td>75</td>
<td>318</td>
<td>215</td>
<td>0.32 (± 0.02)</td>
<td>99</td>
</tr>
<tr>
<td>3.75</td>
<td>75</td>
<td>318</td>
<td>215 a</td>
<td>0.21 (± 0.03)</td>
<td>98</td>
</tr>
<tr>
<td>7.50</td>
<td>75</td>
<td>318</td>
<td>415</td>
<td>1.33 (± 0.05)</td>
<td>99</td>
</tr>
<tr>
<td>5.63</td>
<td>75</td>
<td>318</td>
<td>415</td>
<td>0.94 (± 0.05)</td>
<td>---</td>
</tr>
<tr>
<td>1.88</td>
<td>75</td>
<td>318</td>
<td>415</td>
<td>0.28 (± 0.05)</td>
<td>98</td>
</tr>
<tr>
<td>3.75</td>
<td>75</td>
<td>308</td>
<td>415</td>
<td>0.27 (± 0.02)</td>
<td>---</td>
</tr>
<tr>
<td>3.75</td>
<td>75</td>
<td>328</td>
<td>415</td>
<td>1.12 (± 0.05)</td>
<td>---</td>
</tr>
<tr>
<td>3.75</td>
<td>75</td>
<td>338</td>
<td>415</td>
<td>2.11 (± 0.07)</td>
<td>---</td>
</tr>
</tbody>
</table>

aData with D₂ indicating that the reaction rate is independent of imine concentration (this conclusion was verified by doubling the initial imine concentration and observing

![Graph showing amine concentration vs time for the hydrogenation of 2](image)

**Figure 2.1** Plot of Amine Concentration vs Time for the Hydrogenation of 2
no change in rate). A first order plot of rate versus hydrogen pressure gave a

![Graph showing rate vs H2 pressure](image)

**Figure 2.2** Plot of Rate vs Pressure for the Hydrogenation of 2 straight line (Figure 2.2), demonstrating that the reaction is first order in hydrogen. Plotting the rate vs catalyst concentration also gave a straight

![Graph showing rate vs [Ti] concentration](image)

**Figure 2.3** Plot of Rate vs Catalyst Concentration for the Hydrogenation of 2
line indicating that the reaction is first order in catalyst. Varying the concentration of phenylsilane had a negligible effect on rate (10% over 10 fold excess), suggesting that this parameter is not involved in the rate law. From the above data we obtain the experimental rate expression given in equation 7.

\[ \text{rate} = k_{\text{obs}} [\text{Ti}] [\text{H}_2] \quad \text{eq. 7} \]

Use of deuterium (215 psi) rather than hydrogen resulted in a rate decrease from 0.32 mmol/L·min to 0.21 mmol/L·min. From this data, a kinetic isotope effect of 1.5 (±0.2) was calculated. As expected, when the reduction of 2 was conducted under 80 psig of deuterium at 65 °C complete deuterium incorporation was observed at the stereogenic carbon (Figure 2.4). Quite unexpectedly, however, about 0.8 mol deuterium per mol of amine was observed in the ortho position of the phenyl group,\textsuperscript{19} as determined by \textsuperscript{1}H and \textsuperscript{2}H NMR. Four to five percent deuterium incorporation was observed at the other carbon α to the nitrogen. By \textsuperscript{1}H and \textsuperscript{2}H NMR the product was a single diastereomer, the relative stereochemistry of the deuteria was tentatively assigned as \textit{cis} based on the known addition of hydrogen \textit{trans} to the 5-substituent in 2,5 disubstituted pyrrolines.\textsuperscript{20} At 50% conversion imine 2 contained ca. 0.5 mol deuterium per mol imine in the ortho position. When the unlabeled amine (\textit{R})-3 was subjected to the same reaction conditions (80 psig D\textsubscript{2}, 65 °C), no deuterium incorporation

![Figure 2.4 Isotope Incorporation for the Deuteration of 2](image)

111
was observed. This indicates that the process of deuterium incorporation into the phenyl group is independent of the reactions leading to amine since it occurs only with the starting material.

An Eyring plot for the hydrogenation of 2 is shown in figure 2.5. The plot is linear with a slope of -6742. Using the Eyring equation the enthalpy of activation, $\Delta H^\ddagger$ was determined to be 13.4 kcal / mol. Unfortunately solubility data for hydrogen in THF is not available so the concentration of dissolved hydrogen can not be accurately determined. Therefore the entropy of activation, $\Delta S^\ddagger$ can not be calculated since it depends on hydrogen concentration. However, by assuming that the solubility of hydrogen in THF falls within the range of hydrogen solubility in other solvents (2.5 - 10.0 x 10^{-3} M at 1 atm)\textsuperscript{21} we can approximate the entropy of activation at 65 °C to be -39.7 < $\Delta S^\ddagger$ < -37.8 eu. From this data the free energy of activation is estimated to be 26.2 < $\Delta G^\ddagger$ < 26.8 kcal / mol at 65 °C.

![Figure 2.5 Eyring Plot for the Hydrogenation of 2.](image-url)
Hydrogenation of Acyclic Imines: As previously mentioned, the behavior of acyclic imines differs dramatically from that of cyclic imines. Typical differences are demonstrated by the reaction of \( N'(1\text{-cyclohexylethylidene})\text{benzylamine}, \) \( 4 \) (equation 8). We note here that an important difference between acyclic imines and cyclic imines is that acyclic imines exist as mixtures of slowly interconverting geometric isomers.\(^{22}\) The ratio of isomers in \( 4 \) is ca. 11 / 1 (\(^1\text{H NMR}\)).

\[
\text{CH}_3
\begin{align*}
\text{R} & \quad \text{N} \\
\text{anti} / \text{syn} & = 11 / 1
\end{align*}
\]

\[
\text{CH}_3
\begin{align*}
\text{N} & \quad \text{R} \\
\text{eq. 8}
\end{align*}
\]

Table 2.3 shows the effects of various reaction parameters on the observed enantiomeric excess of the amine for the hydrogenation of \( 4 \). As in the hydrogenation of \( 2 \), above, when the \((R)\) enantiomer of the catalyst precursors are used, the \((R)\) enantiomer of the amine is formed. However, in contrast to the cyclic imines, the ee of \((R)-5\) depends on many factors. First, and most significant, is the effect of hydrogen pressure (Table 2.3, entries 1-6). At 2500 psig the reaction proceeded to afford \( 5 \) with an ee of 81%. As the pressure was decreased, the ee also decreased; at 150 psig the ee of \( 5 \) was only 12%. A plot of ee vs hydrogen pressure is shown in Figure 2.7. When the reaction is conducted with a stoichiometric amount of catalyst, \((R)-5\) is isolated with an ee of 83%. This corresponds to an \((R) / (S)\) ratio of 11 / 1; identical to the ratio of \textit{anti} and \textit{syn} isomers in \( 4 \) (11 / 1). It is important to note that when \((R)-5\), with an ee of 93%, was combined with the active catalyst at 80 psig and 65 °C no other organic species and no racemization was observed after 30 h.
A second major factor is the amount of n-butyllithium used. As indicated in Table 2.3, using less than two equivalents (relative to 1a) resulted in no significant change in ee (77 %, entry 12; vs 76 %, entry 2). However, when more than two equivalents were used the ee sharply dropped from 76 % with 2.0 equiv (entry 2) to 39 % with 2.5 equiv (entry 13). Complex 1c (entry 10) catalyzed the hydrogenation of 4 to 5 with an ee of 84 %. With 1a (entry 2), the observed ee of 5 is 76 %. This difference between 1a and 1c was also observed at 500 psig (entry 5 vs entry 11). When the dichloride precursor 1b was used in place of 1a, the reaction proceed to afford 5 with an identical ee (entry 9).

We also observed a small solvent effect. With 1a, in benzene, 4 was reduced to 5 with an ee of 81 % when the reaction is carried out at 2000 psig (entry 7). In THF, under otherwise identical conditions the ee is 76 % (entry 2). Similarly, at 500 psig, in benzene, 4 was reduced to 5 with an ee of 52 % (entry 8). In THF, under the same conditions 5 was isolated with an ee of 43 % (entry 5). As previously pointed out none of these effects were observed for the hydrogenation of cyclic imine 2.

Table 2.3  Dependence of ee on Various Reaction Parameters for the Hydrogenation of 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>H₂ pressure (psl)</th>
<th>Solvent</th>
<th>Catalyst Precursor</th>
<th>n-BuLi / Catalyst</th>
<th>ee of amine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2500</td>
<td>THF</td>
<td>1a</td>
<td>2.0</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>2000</td>
<td>THF</td>
<td>1a</td>
<td>2.0</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>1500</td>
<td>THF</td>
<td>1a</td>
<td>2.0</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>1000</td>
<td>THF</td>
<td>1a</td>
<td>2.0</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>500</td>
<td>THF</td>
<td>1a</td>
<td>2.0</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>150</td>
<td>THF</td>
<td>1a</td>
<td>2.0</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>2000</td>
<td>benzene</td>
<td>1a</td>
<td>2.0</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>500</td>
<td>benzene</td>
<td>1a</td>
<td>2.0</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>2000</td>
<td>THF</td>
<td>1b</td>
<td>2.0</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>2000</td>
<td>THF</td>
<td>1c</td>
<td>----</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>500</td>
<td>THF</td>
<td>1c</td>
<td>----</td>
<td>61</td>
</tr>
<tr>
<td>12</td>
<td>2000</td>
<td>THF</td>
<td>1a</td>
<td>1.5</td>
<td>77</td>
</tr>
<tr>
<td>13</td>
<td>2000</td>
<td>THF</td>
<td>1a</td>
<td>2.5</td>
<td>39</td>
</tr>
</tbody>
</table>

*All reactions were conducted at 65 °C using (R,R,R) catalyst precursors
Figure 2.6 Plot of ee vs Hydrogen Pressure for the Hydrogenation of 4

Another difference between acyclic and cyclic imines is that for acyclic imines formation of another organic compound is observed during the reaction. This compound was identified as the corresponding aldimine. The reduction of 4 typical as illustrated in Figure 2.7. At 2000 psig of hydrogen and 65 °C the formation of aldimine 6 was observed. The amount of 6 increased to about 7 % of the organic products after ca. 2.5 h under these conditions. Only after ketimine 4 had reacted completely did 6 begin to disappear. At lower hydrogen pressure more 6 is observed. At 500 psig of hydrogen, after 64 % conversion, 12 % (R)-6 (75 % ee) and 52 % (R)-5 (41 % ee) were present when (R,R,R)-1a was used.

In order to probe the role of 6 in the reaction, we prepared 6, in both racemic and enantiomerically enriched form, and tested its reactivity under several sets of reaction conditions. This data is shown in Table 2.4.

When racemic 6 was hydrogenated with (R,R,R)-1a a kinetic resolution20 was observed. After 30 % conversion, the ee of isolated 5 was 16 %. From this
Figure 2.7 Plot of Concentration vs Time for the Hydrogenation of 4

value a \( k_{rel} \) of 1.5 (± 0.2) was calculated. Interestingly (S)-5 is observed as the major enantiomer. This is in contrast to the hydrogenation of 4 where using (R,R,R)-1a as the catalyst precursor results in formation of (R)-5. Thus (S)-6 and (R,R,R)-1a constitute a matched pair while (R)-6 and (R,R,R)-1a are a mismatched pair. When enantiomerically enriched (R)-6 was used (94-95 % ee), only slight racemization was observed with either (R,R,R)-1a (mismatched) or (S,S,S)-1a (matched) when the reaction was run at either 500 or at 2000 psig of hydrogen.

Table 2.4 Hydrogenation\(^a\) of Aldimine 6

<table>
<thead>
<tr>
<th>H(_2) pressure (psig)</th>
<th>Catalyst Precursor</th>
<th>ee (config) of starting imine</th>
<th>ee (config) of amine</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>(R,R,R)-1a</td>
<td>0 % (rac)</td>
<td>16 % (S)(^b)</td>
</tr>
<tr>
<td>2000</td>
<td>(R,R,R)-1a</td>
<td>95 % (R)</td>
<td>91 % (R)</td>
</tr>
<tr>
<td>2000</td>
<td>(S,S,S)-1a</td>
<td>95 % (R)</td>
<td>93 % (R)</td>
</tr>
<tr>
<td>500</td>
<td>(R,R,R)-1a</td>
<td>94 % (R)</td>
<td>89 % (R)</td>
</tr>
<tr>
<td>500</td>
<td>(S,S,S)-1a</td>
<td>94 % (R)</td>
<td>91 % (R)</td>
</tr>
</tbody>
</table>

\(^a\)All reactions were conducted at 85 °C in THF. \(^b\)After 30 % conversion.
We briefly examined the kinetics for the hydrogenation of 4 and 6 to provide further insight into the pressure dependence of ee for the acyclic imines. This data is shown in Table 2.5.

**Table 2.5 Rate Data for the Hydrogenation\(^a\) of imines 4 and 6\(^b\)**

<table>
<thead>
<tr>
<th>H(_2) Pressure (psi)</th>
<th>Catalyst Precursor</th>
<th>([\text{Ti}]_0) (mmol/L)</th>
<th>Imine</th>
<th>Rate (mmol/L·min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>((R,R,R)-1a)</td>
<td>3.75</td>
<td>4</td>
<td>0.31 (+0.02)</td>
</tr>
<tr>
<td>2015</td>
<td>((R,R,R)-1a)</td>
<td>1.88</td>
<td>4</td>
<td>0.13 (+0.02)</td>
</tr>
<tr>
<td>1015</td>
<td>((R,R,R)-1a)</td>
<td>3.75</td>
<td>4</td>
<td>0.14 (+0.02)</td>
</tr>
<tr>
<td>2015</td>
<td>((R,R,R)-1a)</td>
<td>3.75</td>
<td>((R)-6)</td>
<td>0.14 (+0.03)</td>
</tr>
<tr>
<td>1015</td>
<td>((R,R,R)-1a)</td>
<td>3.75</td>
<td>((R)-6)</td>
<td>0.09 (+0.02)</td>
</tr>
<tr>
<td>515</td>
<td>((R,R,R)-1a)</td>
<td>3.75</td>
<td>((R)-6)</td>
<td>0.06 (+0.01)</td>
</tr>
<tr>
<td>2015</td>
<td>((S,S,S)-1a)</td>
<td>3.75</td>
<td>((R)-6)</td>
<td>0.12 (+0.03)</td>
</tr>
<tr>
<td>515</td>
<td>((S,S,S)-1a)</td>
<td>3.75</td>
<td>((R)-6)</td>
<td>0.06 (+0.01)</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were conducted at 65 ±1 °C in THF. Initial imine concentrations were 56.3 mmol/L and the hydrogen pressure was held constant. \(^b\) For this imine, initial rates (ca. 25 % conversion) were used. In this region, plots of concentration vs time were linear.

For the reduction of imine 6, the reaction is non-first order in hydrogen. The order of the reaction in hydrogen was about 0.6, for both the matched or mismatched pairs ((\(R\))-6 with \((S,S,S)-1a\) and \((R\))-6 with \((R,R,R)-1a\) respectively). We also observed formation of a small amount of 4 for both pairs (matched; ca. 2 % at 25 % conversion, mismatched; ca. 6 % at 25 % conversion, both at 500 psig). Interestingly, in view of the kinetic resolution of racemic 6, the rates for the hydrogenation of \((R\))-6, both at 500 psig and at 2000 psig were virtually identical when either \((R,R,R)-1a\) (mismatched) or \((S,S,S)-1a\) (matched) was used as the catalyst precursor. This apparent discrepancy will be explained in the discussion section.

The reaction of 4 showed first order behavior in hydrogen and catalyst, similar to what was observed for the cyclic imine 2. Additionally we found that the ratio of *anti* and *syn* isomers of 4 did not remain constant over the course of the reaction. We monitored the changes in the *anti*/*syn* ratio, under two
different sets of conditions, by 500 MHz $^1$H NMR analysis of aliquots taken from the reaction vessel. As shown in Table 2.6, when the reaction was conducted at 2000 psig and at 65 °C, the anti / syn ratio changed from an initial ratio of 11 / 1 to a ratio of 18 / 1 after mixing 4 with the catalyst. The ratio had increased to 30 / 1 at 22 % conversion and remained constant over the rest of the reaction. At 1500 psig and 75 °C, a similar phenomenon was observed. After mixing 4 and the catalyst the ratio had changed from 11 / 1 to 15 / 1. As the reaction proceeded, the ratio leveled off at 17 / 1 after 33 % conversion, and at 60 % conversion the ratio was 16 / 1.$^{24}$

<table>
<thead>
<tr>
<th></th>
<th>2000 psi, 65°C</th>
<th>1500 psi, 75°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>initial ratio</td>
<td>11 / 1</td>
<td>initial ratio</td>
</tr>
<tr>
<td>after adding 1a</td>
<td>18 / 1</td>
<td>after adding 1a</td>
</tr>
<tr>
<td>after 22 % conversion</td>
<td>30 / 1</td>
<td>after 33 % conversion</td>
</tr>
<tr>
<td>after 43 % conversion</td>
<td>30 / 1</td>
<td>after 60 % conversion</td>
</tr>
</tbody>
</table>

$^a$Reactions were conducted in THF with 6.7 mol % catalyst. $^b$These are the same within experimental error.

DISCUSSION

As outlined in chapter 1 the catalyst employed in our studies is generated by reaction of Brintzinger's ansa titanocene complex, 1a,$^{15}$ with 2 equivalents of n-butyllithium followed by phenylsilane. Based on the discussion of titanium chemistry in the introduction, the proposed mechanism for catalyst activation outlined in Scheme 2.5. The titanium(IV) species, either as the binaphtholate (1a) or the dichloride (1b), is first reduced with 1 equivalent of n-butyllithium to the titanium(III) complex, 1d. The second equivalent of n-butyllithium affords the titanium(III) alkyl$^{25}$ which can either react with phenylsilane or undergo β-H elimination to give the titanium(III) hydride, 1h. In THF solution the hydride complex is presumed to be monomeric$^{26}$ (see Scheme 2.3).
The titanium(III) hydride can then react with an imine via a 1,2-insertion reaction to give two diastereomeric titanium(III) amide complexes (Scheme 2.5).

Scheme 2.5  Mechanism of Catalyst Formation

\[ (R,R,R)-1a \quad X = \text{OCH}_3 \]
\[ (R,R,R)-1b \quad X = \text{Cl} \]

For the reaction of an anti imine with the \((R,R)\) titanium hydride the \((R,R,R)\) intermediate is formed while the reaction of a syn imine with the \((R,R)\) titanium hydride gives the \((R,R,S)\) intermediate (see chapter 1, Scheme 1.6). These intermediates then react with hydrogen via a \(\sigma\)-bond metathesis reaction to give the two enantiomeric amines and regenerate the titanium(III) hydride.

Evidence for the active catalyst being titanium(III) is demonstrated by catalyst studies conducted (Table 2.1). In direct analogy to the titanocene system (Scheme 2.3), the reaction of 1c with hydrogen should give the titanium(III) hydride complex. That this results in an active hydrogenation catalyst implies that titanium(III) is the active catalytic species. Additionally the observation that complex 1d and 1 equivalent of \(n\)-butyllithium form an active catalyst is consistent with titanium being in the +3 oxidation state during the reaction. Finally the activity of complex 1e, with no additional reagents necessary, further supports this hypothesis.

For cyclic imines we found that an anti imine was converted, with the \((R,R)\) catalyst to the \((R)\)-amine while a syn imine was hydrogenated with the same
catalyst to the (S)-amine. In both cases high enantioselectivity was observed (see chapter 1). Additionally when imine 4 was reacted with the (R,R)-catalyst in

**Scheme 2.6 Catalytic Cycle for Imine Hydrogenation**

The ethylene bridge is omitted for clarity

a stoichiometric ratio, (R)-5 was isolated with an ee of 83%. This ee corresponds to an (R)/(S) ratio of 11 / 1 which is in excellent agreement with the 11 / 1 ratio of anti and syn isomers in 4. These results indicate the anti and syn imines are converted, both with high selectivity, to opposite enantiomers of the amine. Thus the orientation of the nitrogen substituent has the dominant effect on the stereochemical outcome of the reaction. For the 1,2-insertion of olefins
into cationic zirconium $\eta^2$-pyrid-2yl complexes containing the ethylene(bis)-tetrahydroindenyl ligand, the facial selectivity was found to be controlled by the substituents on the carbon that becomes bound to the metal.\textsuperscript{28}

**Hydrogenation of Cyclic Imines:** The proposed reaction mechanism for the titanocene catalyzed hydrogenation of 2 is shown in Scheme 2.7. Because of the high chemo and enantioselectivity observed for this substrate the pathways leading to the minor enantiomer do not contribute significantly to the mechanism. Therefore, only the major stereochemical manifold of the reaction need be considered. The steady state rate expression for this mechanism is given in equation 9 (the derivation is given in the appendix), where [2] is the imine concentration and [Ti] is the total concentration of titanium.

**Scheme 2.7** Mechanism for the Hydrogenation of 2

\[
\begin{align*}
\text{Cp'}_2\text{TiH} & \quad \xrightarrow{k_1} \quad \text{Cp'}_2\text{TiN}(\text{Ph}) \quad (R,R,R)-1f \\
\text{H}_2 & \quad \xrightarrow{k_2} \quad \text{Cp'}_2\text{TiH} \quad (R,R)-1h \\
\text{Ph} & \quad \xrightarrow{k_1} \quad \text{Ph} \\
\text{Ph} & \quad \xrightarrow{k_2} \quad \text{Ph} \\
\end{align*}
\]

where $\text{Cp'}_2 = \text{ethylene(bis)tetrahydroindenyl}$

\[
\text{rate} = \frac{k_2 [\text{Ti}] [\text{H}_2] [2]}{k_1 + k_2 [\text{H}_2]} + [2] \quad \text{eq. 9}
\]

From the kinetic data for the hydrogenation of 2, we obtained the experimental rate expression given in equation 7. If we assume that insertion is fast relative to hydrogenolysis ($k_1 \gg k_2[H_2]$) and fast relative to $\beta$-H elimination
(k₁ >> k₋₁) then the left hand term in the denominator of equation 9 goes to zero. Under these conditions equation 9 simplifies to equation 10. Equation 10 is

\[
\text{rate} = k_2 [\text{Ti}] [\text{H₂}] \quad \text{eq. 10}
\]

identical to equation 7, where k_{obs} = k₂. Thus, the kinetic data are consistent with a mechanism that involves: (1) fast 1,2-insertion of 2 into the titanium hydride, 1h, to form the titanium amide intermediate, 1f; (2) slow β-H elimination of imine from 1f to form 2; and (3) slow hydrogenolysis of 1f to form amine 3 and regenerate 1h.

A relatively large kinetic isotope effect of 1.5 ± 0.2 was observed for this reaction. This value is greater than that observed by Bercaw for the insertion of an olefin into a niobium hydride bond (k_H / k_D = 1.1).²⁹ The isotope effect for the titanocene system is also larger than typical kinetic isotope effects observed for the oxidative addition of hydrogen to late transition metals,³⁰ which are generally about 1.2. This implies that there is a significant amount of H-H bond breaking in the rate limiting step, consistent with hydrogenolysis being the slow step.

Since it is difficult to measure the rate of β-H elimination from 1f to form 2, (without isolating 1f and measuring the rate) we can use the amount of isotope incorporation in the other carbon α to the nitrogen to estimate this rate. For a related niobocene hydride-olefin system it has been shown that the favorable electronic effect of the phenyl group is offset by the unfavorable steric demands required for elimination from a tertiary carbon.²⁹,³¹ By analogy to the niobocene system and to a first approximation, the rate of β-H elimination of 1f to form 2 should be similar to the rate of formation of the isomeric imine. In this study 4-5% incorporation of deuterium at the carbon α to nitrogen was observed (Figure 2.4). Since the rate of isomeric imine formation is reflected by the amount of isotope incorporation we can estimate that \( k_2[H₂] \sim 20 \text{k}^{-1} \), and this is consistent with the proposed mechanism. If β-H elimination were fast relative to
hydrogenolysis ($k_1 >> k_2[H_2]$), the ee would probably be dependent on hydrogen pressure since it would be determined by the relative concentrations and relative rates of hydrogenolysis of the two diastereomeric amide intermediates ($R,R,R$)-1f and ($R,R,S$)-1f. That this is not observed (see chapter 1) further supports the proposed mechanism for the hydrogenation of 2.

While only approximate, the activation parameters for the reaction provide additional insight into the nature of the transition state. The relatively small value obtained for $\Delta H^\ddagger$ of 13.4 kcal / mol suggests that the hydrogenolysis step is concerted. The large negative entropy of $-39.7 < \Delta S^\ddagger < -37.8$ eu indicates that there is a significant amount of organization relative to starting materials (1g and H$_2$) in the transition state. This is consistent with a bimolecular process.

**Hydrogenation of Acyclic Imines:** The reaction scheme for the hydrogenation of 4 is presented in Scheme 2.8. Since the formation of 6 occurs after the selectivity determining step (the 1,2-insertion of 4), the presence or absence of 6 during the reaction has no effect on the ee of 5, provided that the reaction is run to completion. Furthermore, because the ee for the hydrogenation of 4 is not close to 100 % both stereochemical manifolds of the reaction must be operative.

The kinetic data for the hydrogenation of 4 (Table 2.5) imply that the reaction is first order in titanium and first order in hydrogen. Also, the data in Figure 2.7. indicate that the rate is independent of imine concentration. Together, these data suggest a mechanism for the reaction of 4 that is similar to that for 2. Namely, fast insertion of the imine to form the intermediate titanium amides and slow hydrogenolysis to form 5. As with the hydrogenation of 2, $\beta$-H elimination of both of the diastereomeric intermediates, ($R,R,R$)-1g and ($R,R,S$)-1g, either to the ketimine, 4 or aldimine, 6 is slow relative to hydrogenolysis. This can be seen by examining Figure 2.7. If the 1,2-insertion / $\beta$-H elimination
sequence was fast in both directions a thermodynamic ratio of 4 and 6 would be observed throughout the course of the reaction.

From the stoichiometric reaction of 4 (anti / syn = 11 / 1) with (R,R)-1h, amine 5 was obtained with an ee of 83 % as the (R) enantiomer ((R) / (S) = 11 / 1). However, when the reduction of 4 is conducted catalytically, the ee is dependent on hydrogen pressure (Table 2.3), and never reaches or exceeds 83 %. In fact the ee appears to approach this value asymptotically (see Figure 2.6). At 2500 psig (the maximum pressure explored) the observed ee was 81 %.

**Scheme 2.8 Mechanism for Hydrogenation of Imine 4**

Given the mechanism shown in Scheme 2.8 there are three explanations that can account for ee being dependent on hydrogen pressure: (1) (R,R,R)-1g
and \((R,R,S)-1g\) are interconverting via \(\beta\)-H elimination to 4 and the rate of \(\beta\)-H elimination is faster for \((R,R,R)-1g\) than for \((R,R,S)-1g\); This phenomenon has been termed isoinversion.\(^{32}\) As the hydrogen pressure is lowered this process becomes competitive and results in more of the product being formed via the minor intermediate, \((R,R,S)-1g\); (2) \((R,R,R)-1g\) and \((R,R,S)-1g\) are interconverting via \(\beta\)-H elimination to 4 and hydrogenolysis of \((R,R,S)-1g\), to form \((S)-5\), is faster than that for \((R,R,R)-1g\) to form \((R)-5\) This effect has been observed by Halpern in the asymmetric hydrogenation of acrylamides by a chiral rhodium complex.\(^{\text{0,1b}}\) In this case as the pressure is lowered, the relative rates of formation of the enantiomeric products changes to favor formation of \((S)-5\) at lower pressure; (3) \textit{Anti}-4 and \textit{syn}-4 are interconverting at a rate that is independent of hydrogen pressure and \textit{syn}-4 reacts to form \((R,R,S)-1g\) faster than \textit{anti}-4 reacts to from \((R,R,R)-1g\). As in case 1 when the pressure is lowered the imine isomerization becomes competitive and more imine reacts via the \textit{syn} isomer (minor pathway). This is conceptually identical to a kinetic resolution.

By using enantiomerically enriched aldimine \(6\) as a convenient way to obtain \textit{in situ}, nearly enantiomerically pure \((R,R,R)-1g\) or \((S,S,R)-1g\) we were able to separately study the two diastereomeric pathways. The results obtained provide some insight into why the ee's for acyclic imines depend on hydrogen pressure.

First, when the reduction of \((R)-6\) was conducted at 500 psig formation of 4 was observed for both the matched and the mismatched pairs \((S,S,R)-1g\) and \((R,R,R)-1g\) respectively). For the matched pair, after 25 \% conversion, 4 made up ca. 2 \% of the mixture. For the mismatched pair, 4 was ca. 6 \% of the mixture at 25 \% conversion. This indicates that \(\beta\)-H elimination for the matched pair is slower than that for the mismatched pair. However the difference is not significant. Secondly, by examining the data in Table 2.4, we find that very little
racemization occurs during the hydrogenation of (R)-6 with either (R,R,R)-1a or (S,S,S)-1a at 2000 or at 500 psig, furthermore, the amount of racemization is very similar for both diastereomeric pairs. Although, as expected, it is slightly higher for the mismatched pair. Thus even though a small amount of β-H elimination is occurring for both the matched and the mismatched pairs, the difference is not enough, in itself, to account for observed pressure dependence.

We also observed a kinetic resolution of racemic 6 with (R,R,R)-1a. However, when we measured the rates of hydrogenation of (R)-6 with both (R,R,R)-1a and (S,S,S)-1a, we found that they were almost identical at both 2000 psig and 500 psig (Table 2.5). It is important to note that the measured rate is the overall reaction rate and not necessarily the rates of the individual steps of the reaction. The fact that the observed rates are similar for the matched and mismatched pairs means that the kinetic resolution must happen in a fast step that is not part of the rate expression. Computer simulation of the kinetics indicate that if k₁ (rate of 1,2-insertion) ~ 5 k₂ (rate of hydrogenolysis) the reaction would be 0.6 th order in hydrogen. Under these conditions and using a k rel of 1.5 for the insertion step the observed reaction rates for matched and mismatched pairs are predicted to be within experimental error of each other.

If, as in the case of imine 2, hydrogenolysis were the rate limiting step we could conclude that the rates of hydrogenolysis of (S,S,R)-1g and (R,R,R)-1g were the same. However, the reaction is about 0.6 th order in hydrogen, suggesting hydrogenolysis is not entirely rate limiting in this case. Therefore the observed reaction rate does not accurately reflect the rate of the hydrogenolysis step and it is difficult to conclude whether (S,S,R)-1g and reacts with hydrogen faster than (R,R,R)-1g.

The ee data for cyclic imines and the stoichiometric reaction of 4 with the active catalyst suggest that syn and anti imines are converted to opposite
enantiomers of the product. With this in mind the competitive interconversion of the syn and anti imine isomers appears to be an attractive explanation for the pressure dependence. However, for this hypothesis to hold the syn isomer must react faster than the anti isomer, either by faster 1,2-insertion or by faster hydrogenolysis of the intermediate. The data in Table 2.6 indicate that this is in fact the case. At 65 °C and 2000 psig the initial 11 / 1 isomer ratio a 4 changes to 18 / 1 upon mixing with the active catalyst, suggesting that indeed syn-4 reacts faster than anti-4. As the reaction proceeds, the ratio levels off at 30 / 1, implying that syn-4 is being formed as fast as it reacts.

If the rate of imine isomerization is increased relative to the rate of conversion to amine then the concentration of syn imine should be higher. By increasing the temperature of the reaction the rate of interconversion and the rate of reaction to 5 will both be increased. Lowering the pressure will decrease the rate conversion to 5. Thus increasing the temperature and lowering the pressure will result in an increased rate of anti - syn isomerization relative to hydrogenation. Under these conditions the anti / syn ratio should be smaller when steady state is obtained. We find that this is the case. When the reaction is conducted at 75 °C and 1500 psig, the isomer ratio (11 / 1 initially) levels off at ca. 16 / 1. That the observed steady state concentrations of anti and syn-4 are different under these two different sets of reaction conditions supports the hypothesis that syn-4 reacts with 1f faster than anti-4 and that syn-4 and anti-4 are slowly interconverting.

The rationale for the enantiomeric excess being dependent on hydrogen pressure for the hydrogenation of 4 is outlined in Scheme 2.9. We know from the kinetics for the hydrogenation of 6 that $k_2$ and $k_2'$ are similar. We have also seen that $k_1'$ is faster than $k_1$ and that the isomeric imines are interconverting. Additionally we have observed that syn and anti imines are hydrogenated to
opposite enantiomers of the amine. Thus when the rate of hydrogenation ($k_2$ and $k_2'$) is slowed by lowering the pressure, more of the imine can be formed by hydrogenation of the syn isomer. In other words a dynamic kinetic resolution of the imine is occurring.

The effect of excess n-butyllithium on the ee for the hydrogenation of 4 is also consistent with this explanation. Smith et. al.\textsuperscript{22b} have shown that the rate of interconversion of syn and anti imine isomers is enhanced by the presence of a small amount of an azaallylithium species (the anion formed from the reaction of an imine with lithium diisopropyl amide). In light of this observation, it is

**Scheme 2.9 Rationale for ee being Dependent on Hydrogen pressure**

reasonable to conclude that any n-butyllithium present in the reaction mixture could increase the rate of interconversion of syn-4 and anti-4 relative to hydrogenation. Since syn-4 reacts faster than anti-4, we would expect the ee of 5 to decrease when the rate of interconversion is increased, which is exactly what is observed. That the ee of 3 is not affected by the presence of excess n-
butyllithium for the hydrogenation of 2 implies that excess n-butyllithium does not adversely affect the active catalyst.

CONCLUSIONS

A mechanistic study of the titanocene catalyzed imine hydrogenation has revealed several interesting features of the reaction. Our kinetic data for imines 2 and 4 are consistent with a mechanism involving fast insertion of the imine into a titanium hydride, slow β-H elimination of the resulting titanium amide intermediate(s) and slow hydrogenolysis of the titanium amide(s) to form the amine and regenerate the titanium hydride. The activation parameters for the hydrogenation of 2 suggest that the hydrogenolysis step is a concerted bimolecular process. For imine 6, the reaction deviates from first order behavior in hydrogen. This implies that the rate of the insertion step for imine 6 is similar to the rate of the hydrogenolysis step. The observed slower rate of insertion for imine 6 serves to demonstrate sensitivity of this catalyst system to changes in the steric of the substrate.

We have proposed a rational stereoechemical model that accounts for the observed selectivity of the system and can be used as a guide to predict the absolute configuration of the products of this reaction. A characteristic of this model is that it predicts that syn and anti imines react to give opposite enantiomers of the amine, and this has been verified experimentally.

We have also provided evidence that the syn isomer of imine 4 reacts faster than the anti isomer and that syn -4 and anti -4 are interconverting under the reaction conditions. This provides a reasonable explanation for the observed pressure dependence of ee that we observed for the hydrogenation of acyclic imine 4.
EXPERIMENTAL SECTION

General Considerations: The experiments in this chapter were conducted with the same general considerations as outlined in chapter 1 with the following additional notes: Electron paramagnetic resonance (EPR) spectra were recorded with a Bruker ESP 300 spectrometer. Elemental analyses were performed by Onieda Research Services (Whitesboro, NY) or by Desert Analytics (Tucson, AZ).

Tetrahydrofuran (THF), ether, benzene and pentane were dried and deoxygenated by refluxing and distilling from sodium / benzophenone ketyl under an argon atmosphere. Phenylsilane and pentadecane used in kinetics experiments were dried by refluxing and distilling from CaH₂ under a nitrogen atmosphere.

Preparation of materials: 2-Phenylpyrroline, 2, was prepared by the method of Sorgi et. al.³³ and was further purified, for use in kinetics experiments, by recrystallization from hexanes. 1-(Cyclohexyl)ethyldine-N-benzylamine, 4, was prepared as described in chapter 1 as an 11:1 ratio of isomers.

Benzyldine(1-cyclohexylethyl)amine, 6: This material was prepared as described in chapter 1. Enantiomerically enriched (R)-6 (94-95 % ee) was prepared in an analogous manner from (R)-1-(cyclohexyl)ethyl amine (Aldrich). The enantiomeric excess of this material was determined by HPLC analysis.

Ethylene-1,2-bis(η⁵-4,5,6,7-tetrahydro-1-indenyl)titanium-1,1'-binaphth-2,2'-dilolate, (R,R,R)-1a and (S,S,S)-1a were prepared as previously described in chapter 1. Ethylene-1,2-bis(η⁵-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride, (R,R)-1b, and ethylene-1,2-bis(η⁵-4,5,6,7-tetrahydro-1-indenyl)dimethyltitanium, 1c, were prepared by the method of Brintzinger et al.¹⁵
rac Ethylene-1,2-bis(η⁶-4,5,6,7-tetrahydro-1-indenyl)titanium chloride, 1d: In a glove box, a mixture of racemic ethylene-1,2-bis(η⁶-4,5,6,7-tetrahydro-1-indenyl)titanium dichloride, 1b, (1.50 g, 3.9 mmol), and 3 g Na / Hg (22 mol % Na, 4.2 mmol) were stirred for 4 h in 50 mL of THF. The purple solution was filtered through celite and concentrated in vacuo. The residue was recrystallized from a saturated diethyl ether solution, at -40 °C, to afford 0.91 g (70 % yield) green-brown crystals. Anal: calc. for C₂₀H₂₄TiCl; C, 69.08; H, 6.96. found C, 68.90; H, 7.11; IR (KBr): 2928, 2852, 1489, 1440, 1377, 1320, 1241, 1116, 1029, 905, 768; EPR (THF, rt): g = 1.9687. μₑₑₑ = 1.76 μB, calc; 1.73 for 1 unpaired electron. Treatment of a small amount of this material with PbCl₂ gave 34 afforded 1b.

racemic Ethylene-1,2-bis(η⁶-4,5,6,7-tetrahydro-1-indenyl)(dimethylamido)titanium, 1e: In a glove box, a mixture of 1d (0.694 g, 2.0 mmol) and LiN(CH₃)₂ (0.102 g, 2.0 mmol) were stirred in 20 mL of ether for 12 h, affording an orange-brown solution. The solvent was removed in vacuo and the residue was extracted with pentane. The pentane solution was concentrated to ca. 10 mL and cooled to -40 °C to afford 0.11 g (15 % yield) of desired 1e as brown needles. Anal: calc. for C₂₂H₃₀NTi; C, 74.14; H, 8.48; N, 3.93. found C, 74.38; H, 8.45; N, 3.57; IR (KBr): 3077, 2922, 2843, 2788, 2749, 1437, 1223, 1036, 946, 765, 723, 645; EPR (THF, rt): g = 1.9787. μₑₑₑ = 1.78 μB, calc; 1.73 for 1 unpaired electron. Treatment of a small amount of this material with PbCl₂ gave a product with an ¹H NMR spectrum consistent with the chloro amide.

Kinetics Experiments:
All kinetics reactions were conducted in a Parr model 4565 autoclave complete with a magnetically driven stirrer, a thermocouple and a sampling tube.
The reactions were maintained at constant temperature (± 1°C) with a Parr model 4842 temperature controller and stirred at constant speed (300 rpm). Samples were withdrawn from the reaction and analyzed by capillary GC (isothermal runs). Formation of amine was monitored versus n-pentadecane as an internal standard. Plots of amine concentration versus time were constructed and reaction rates were calculated from the slope of the linear portion of the data (85 % conversion for 2 and 4, 25 % conversion for 6). Errors were derived from the standard deviation of the data. Anti / syn isomer ratios of 4 during the reaction were determined by integration of the benzylic resonances in the 500 MHz 1H NMR spectra of withdrawn aliquots.

**Typical procedure for the hydrogenation of 2:** To a dry Schlenk flask under argon was added \((R,R,R)-1\text{a}\) (0.090 g, 0.15 mmol) and 36 mL THF. A solution of \(n\)-butyllithium (176 μL, 0.30 mmol, 1.7 M in hexanes) was added and after 2-3 min the color of the solution was green-brown. Phenylsilane (55 μL, 0.45 mmol), was added and the color turned dark brown. Imine 2 (4 mL of a 0.75 M stock solution in THF containing 10 mol % n-pentadecane) was added via syringe. The mixture was moved to a glove box and transferred to a Parr® model 4565 reactor. The vessel was sealed and moved to a bench. A hydrogen tank was connected and the line was evacuated. The temperature was set to 45 ºC. When the temperature had reached equilibrium, hydrogen was added (815 psi) initiating the reaction. Liquid samples were withdrawn at 2-5 min intervals and analyzed by capillary GC. The pressure was kept constant by adding hydrogen after each aliquot was taken. The ee of the amine was determined to be > 99 % by HPLC analysis of the 1-naphthamide.
Typical procedure for the hydrogenation of (R)-6: To a dry Schlenk flask under argon was added \((R, R, R)-1a\) (0.090 g, 0.15 mmol) and 34 mL THF. A solution of \(n\)-butyllithium (176 \(\mu\)L, 0.30 mmol, 1.7 M in hexanes) was added and after 2-3 min the color of the solution was green-brown. Phenylsilane (55 \(\mu\)L, 0.45 mmol), was added and the color turned dark brown. Imine 6 (6 mL of a 0.375 M stock solution in THF containing 20 mol % \(n\)-pentadecane) was added via syringe. The mixture was moved to a glove box and transferred to a Parr® model 4565 reactor. The vessel was sealed and moved to a bench. A hydrogen tank was connected and the line was evacuated. The temperature was set to 65 °C. When the temperature had reached equilibrium, hydrogen was added (2000 psig) initiating the reaction. Liquid samples were withdrawn at 15-20 min intervals and analyzed by capillary GC. The pressure was kept constant by adding hydrogen after each aliquot was taken.

Typical procedure for the hydrogenation of 4: To a dry Schlenk flask under argon was added \((R, R, R)-1a\) (0.090 g, 0.15 mmol) and 40 mL THF. A solution of \(n\)-butyllithium (173 \(\mu\)L, 0.30 mmol, 1.73 M in hexanes) was added and after 2-3 min the color of the solution was green-brown. Phenylsilane (55 \(\mu\)L, 0.45 mmol), was added and the color turned dark brown. The mixture was moved to a glove box and transferred to a Parr® model 4565 reactor. Imine 4 (0.484 g, 2.25 mmol) and \(n\)-pentadecane (88 mg, 0.41 mmol) was added. The vessel was sealed and moved to a bench. A hydrogen tank was connected and the line was evacuated. The temperature was set to 65 °C. When the temperature had reached equilibrium, hydrogen was added (2000 psig) initiating the reaction. Liquid samples were withdrawn at 15-20 min intervals and analyzed by capillary GC. The pressure was kept constant by adding hydrogen after each aliquot was taken.
Synthetic Experiments:

Hydrogenation of 2 with \((R,R,R)-1\)\textsubscript{a}: A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve and a pressure release valve was charged with \((R,R,R)-1\)\textsubscript{a} (59 mg, 0.10 mmol) and a magnetic stir bar. The vessel was evacuated and filled with hydrogen (5-10 psig). THF (10 mL) was added via high pressure syringe. After the complex had dissolved, a solution of \(n\)-butyllithium (117 \(\mu\)L, 1.70 M in hexanes, 0.20 mmol) was added and the mixture was stirred for 2-3 min at which point it was a green color. Phenylsilane (37 \(\mu\)L, 0.30 mmol) was added and no color change was observed. A solution of 2 (290 mg, 2.0 mmol, in 2mL THF) was added via syringe and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (Caution: an appropriate safety shield should be used) and the mixture was allowed to stir for 7 h. The vessel was cooled and carefully vented. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (3 x 10 mL). The aqueous portion was made basic with NaOH and extracted with methylene chloride (3 x 20 mL). The combined organic portions were dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo} to afford 247 mg (84 % yield) of the desired \((R)-(+)\)-2-phenylpyrrolidine, \((R)-3\).\textsuperscript{35} HPLC analysis of the 1-naphthamide (85:15 hexane : isopropanol) indicated 99 % ee.

Deuteration of 2 with \((R,R,R)-1\)\textsubscript{a}: A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve and a pressure release valve was charged with \((R,R,R)-1\)\textsubscript{a} (30 mg, 0.05 mmol) and a magnetic stir bar. The vessel was evacuated and filled with deuterium (5-10 psig). THF (5 mL) was added via high pressure syringe. After the complex had dissolved, a solution of \(n\)-butyllithium (59 \(\mu\)L, 1.70 M in hexanes, 0.10 mmol) was added and the mixture was stirred for 2-3 min at which point it was a green
color. Phenylsilane (19 μL, 0.15 mmol) was added and no color change was observed. A solution of 2 (145 mg, 1.0 mmol, in 1 mL of THF) was added via syringe and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (Caution: an appropriate safety shield should be used) and the mixture was allowed to stir for 23 h. The solvent was removed in vacuo and Kugelrohr distillation afforded 120 mg (81 % yield) of the desired (R)-(+)\text{-}2-phenylpyrroolidine, (R)\text{-}3. \textsuperscript{1}H NMR analysis (300 MHz, CDCl\textsubscript{3}, TMS) showed absence of the triplet resonance at 4.1 ppm for the benzylic hydrogen. \textsuperscript{2}H NMR analysis (46 MHz, CDCl\textsubscript{3}, TMS) showed a resonance for the benzylic deuterium (δ = 4.08, 1 D), resonances for the ortho phenyl deuterium (δ = 7.4, 0.8 D) and a resonance for the deuterium α to the nitrogen (non-benzylic, δ = 3.18, 0.04 D). The stereochemistry of this deuterium, relative to the phenyl group, was assigned based on the known addition of hydrogen trans to substituents in the 5 position for the hydrogenation of 5 substituted pyrrolines with this catalyst system.\textsuperscript{20}

Reaction of (R)\text{-}3 with (R,R,R)\text{-}1a under deuterium: A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve and a pressure release valve was charged with (R,R,R)\text{-}1a (30 mg, 0.05 mmol) and a magnetic stir bar. The vessel was evacuated and filled with deuterium (5-10 psig). THF (5 mL) was added via high pressure syringe. After the complex had dissolved, a solution of n-butyllithium (59 μL, 1.70 M in hexanes, 0.10 mmol) was added and the mixture was stirred for 2-3 min at which point it was a green color. Phenylsilane (19 μL, 0.15 mmol) was added and no color change was observed. A solution of (R)-3 (147 mg, 1.0 mmol, in 1 mL of THF) was added via syringe and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (Caution: an
appropriate safety shield should be used) and the mixture was allowed to stir for 8 h. The solvent was removed in vacuo and Kugelrohr distillation afforded 101 mg (69 % yield) of the desired \((R)-(+)\)-2-phenylpyrrolidine, \((R)\)-3. \(^2\text{H}\) NMR analysis (46 MHz, CDCl\(_3\), TMS) showed no resonances. GC / MS showed no peaks for deuterated 3.

**Hydrogenation of 2 with \((R,R,R)\)-1a (without phenylsilane):** A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve and a pressure release valve was charged with \((\{R,R,R\}\)-1a (59 mg, 0.10 mmol) and a magnetic stir bar. The vessel was evacuated and filled with hydrogen (5-10 psig). THF (10 mL) was added via high pressure syringe. After the complex had dissolved, a solution of \(n\)-butyllithium (117 \(\mu\)L, 1.70 M in hexanes, 0.20 mmol) was added and the mixture was stirred for 2-3 min at which point it was a green color. A solution of 2 (290 mg, 2.0 mmol, in 1 mL of THF) was added via syringe and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (Caution: an appropriate safety shield should be used) and the mixture was allowed to stir for 8 h. The vessel was cooled and carefully vented. The solvent was removed in vacuo and Kugelrohr distillation afforded 235 mg (80 % yield) of the desired \((R)-(+)\)-2-phenylpyrrolidine, \((R)\)-3. HPLC analysis of the 1-naphthamide (85:15 hexane : isopropanol) indicated >99 % ee.

**Hydrogenation of 2 with 1c:** A dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve and a pressure release valve was charged with \((\text{rac})\)-1c (26 mg, 0.075 mmol) and a magnetic stir bar. The vessel was evacuated and filled with hydrogen (5-10 psig) resulting in an immediate color change to green. Benzene (4 mL) was
added via high pressure syringe. A solution of 2 (218 mg, 1.5 mmol, in 1 mL benzene) was added via syringe and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (Caution: an appropriate safety shield should be used) and the mixture was allowed to stir for 12 h. The vessel was cooled and carefully vented. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (3 x 10 mL). The aqueous portion was made basic with NaOH and extracted with methylene chloride (3 x 20 mL). The combined organic portions were dried over Na₂SO₄ and concentrated in vacuo to afford 182 mg (82 % yield) of the desired 2-phenylpyrrolidine, 3.

**Hydrogenation of 2 with 1d:** In a glove box, a dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve and a pressure release valve was charged with (rac)-1d (26 mg, 0.075 mmol) and a magnetic stir bar. The vessel was moved to a vacuum line, evacuated and filled with hydrogen (5-10 psig). THF 6 mL) was added via syringe. After the complex had dissolved, a solution of n-butyllithium (42 μL, 1.78 M in hexanes, 0.075 mmol) was added and the mixture was stirred for 2-3 min at which point it was a green color. Phenylsilane (28 μL, 0.23 mmol) was added and no color change was observed. A solution of 2 (218 mg, 1.5 mmol, in 1.5 mL of THF) was added via syringe and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (Caution: an appropriate safety shield should be used) and the mixture was allowed to stir for 6 h. The vessel was cooled and carefully vented. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (3 x 10 mL). The aqueous portion was made basic with NaOH and extracted with methylene chloride (3 x 20 mL). The combined organic portions were dried over Na₂SO₄ and concentrated in vacuo to afford 151 mg (69 % yield) of the desired 2-phenylpyrrolidine, 3.
Hydrogenation of 2 with 1e: In a glove box, a dry Fisher-Porter bottle properly fitted with a pressure coupling closure complete with a gas inlet, pressure gauge, inlet valve and a pressure release valve was charged with \((rac)-1e\) (27 mg, 0.075 mmol), 2 (218 mg, 1.5 mmol) and a magnetic stir bar. The vessel was moved to a vacuum line, evacuated and filled with hydrogen (5-10 psig). THF (10 mL) was added via high pressure syringe and the vessel was placed in an oil bath at 65 °C. The pressure was then adjusted to 80 psig (Caution: an appropriate safety shield should be used) and the mixture was allowed to stir for 8 h. The vessel was cooled and carefully vented. The crude mixture was diluted with ether (10 mL) and extracted with 1 M HCl (3 x 10 mL). The aqueous portion was made basic with NaOH and extracted with methylene chloride (3 x 20 mL). The combined organic portions were dried over Na$_2$SO$_4$ and concentrated in vacuo to afford 153 mg (70 % yield) of the desired 2-phenylpyrrolidine, 3.

General procedure for the hydrogenation of imines 4 and 6 at high pressure: In a dry Schlenk flask under an argon atmosphere, \((R,R,R)-1a\) was dissolved in THF (10 mL). A solution of n-butyllithium (1.6 M in hexanes, 2 equiv) was added and the mixture was allowed to stir for 5 min, at which point it was a brown-green color. Phenylsilane (2.5-3.0 equiv) was added and mixture immediately turned dark brown. The resulting solution was moved into a dry box and transferred to a Parr high pressure autoclave containing a magnetic stir bar. The imine (20 eq based on Ti) was added. The vessel was sealed and moved to a fume hood where it was charged with hydrogen (specified below) and placed in an oil bath at 65 °C. The reaction mixture was allowed to stir (time specified below) under hydrogen pressure. The vessel was cooled to room temperature, carefully vented and opened to air. The solvent was removed in vacuo.
amine extracted with 1 M HCl (3 x 10 mL). The aqueous layers were combined and made basic with solid NaOH (0°C), then extracted with ether (3 x 20 mL). The combined organic fractions were dried over Na₂SO₄ and concentrated to afford 5.

**Hydrogenation of 4 at 2500 psig:** N-(1-Cyclohexylethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst ((R,R,R)-1a: 59 mg, 0.10 mmol; n-butyllithium: 129 µL, 1.55 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol). The reaction vessel was charged to 2500 psig and the reaction mixture was stirred for 10 h. The pure amine⁵ (404 mg, 94% yield) was obtained after extraction. HPLC analysis indicated 81% ee ((R) enantiomer). The absolute configuration was determined by independent synthesis.

**Hydrogenation of 4 at 2000 psig:** N-(1-Cyclohexylethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst ((R,R,R)-1a: 59 mg, 0.10 mmol; n-butyllithium: 120 µL, 1.66 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol). The reaction vessel was charged to 2000 psig and the reaction mixture was stirred for 9 h. The pure amine (400 mg, 93% yield) was obtained after extraction. HPLC analysis indicated 76% ee ((R) enantiomer).

**Hydrogenation of 4 at 1500 psig:** N-(1-Cyclohexylethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst ((R,R,R)-1a: 59 mg, 0.10 mmol; n-butyllithium: 114 µL, 1.75 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol). The reaction vessel was charged to 1500 psig and the reaction mixture was stirred for 24 h. The pure
amine (386 mg, 89 % yield) was obtained after extraction. HPLC analysis indicated 74 % ee ((R) enantiomer).

**Hydrogenation of 4 at 1000 psig:** $N$-(1-Cyclohexylethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst ((R,R,R)-1a: 59 mg, 0.10 mmol; n-butyllithium: 114 µL, 1.75 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol). The reaction vessel was charged to 1000 psig and the reaction mixture was stirred for 48 h. The pure amine (341 mg, 79 % yield) was obtained after extraction. HPLC analysis indicated 65 % ee ((R) enantiomer).

**Hydrogenation of 4 at 500 psig:** $N$-(1-Cyclohexylethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst ((R,R,R)-1a: 59 mg, 0.10 mmol; n-butyllithium: 114 µL, 1.75 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol). The reaction vessel was charged to 500 psig and the reaction mixture was stirred for 72 h. The pure amine (367 mg, 85 % yield) was obtained after extraction. HPLC analysis indicated 43 % ee ((R) enantiomer).

**Hydrogenation of 4 at 150 psig:** $N$-(1-Cyclohexylethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst ((R,R,R)-1a: 59 mg, 0.10 mmol; n-butyllithium: 114 µL, 1.75 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol). The reaction vessel was charged to 150 psig and the reaction mixture was stirred for 102 h. The pure amine (372 mg, 86 % yield) was obtained after extraction. HPLC analysis indicated 12 % ee ((R) enantiomer).
Hydrogenation of 4 at 2000 psig in benzene: N-(1-Cyclohexylethylidene)-benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure, using benzene in place of THF, with 5 mol % catalyst ((R,R,R)-1a: 59 mg, 0.10 mmol; n-butyllithium: 129 µL, 1.55 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol). The reaction vessel was charged to 2000 psig and the reaction mixture was stirred for 14 h. The pure amine (390 mg, 89 % yield) was obtained after extraction. HPLC analysis indicated 81 % ee ((R) enantiomer).

Hydrogenation of 4 at 500 psig in benzene: N-(1-Cyclohexylethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure, using benzene in place of THF, with 5 mol % catalyst ((R,R,R)-1a: 59 mg, 0.10 mmol; n-butyllithium: 122 µL, 1.63 M in hexanes, 0.20 mmol; phenylsilane: 37 µL, 0.30 mmol). The reaction vessel was charged to 500 psig and the reaction mixture was stirred for 72 h. The pure amine (390 mg, 89 % yield) was obtained after extraction. HPLC analysis indicated 52 % ee ((R) enantiomer).

Hydrogenation of 4 at 2000 psig with (R,R)-1b: N-(1-Cyclohexylethylidene)-benzylamine (101 mg, 0.47 mmol) was reduced according to the general procedure, using (R,R)-1b in place of (R,R,R)-1a, with 10 mol % catalyst ((R,R)-1b: 18 mg, 0.047 mmol; n-butyllithium: 68 µL, 1.39 M in hexanes, 0.094 mmol; phenylsilane: 15 µL, 0.12 mmol). The reaction vessel was charged to 1950 psig and the reaction mixture was stirred for 3 h. The amine (83 mg, 94 % pure by GC, 82 % yield) was obtained after extraction. HPLC analysis indicated 76 % ee ((R) enantiomer).
Hydrogenation of 4 at 2000 psig with (R,R)-1c: In a glove box, a Parr model 4751 high pressure autoclave containing a magnetic stir bar, was charged with (R,R)-1c (35 mg, 0.10 mmol) and 10 mL THF. Phenylsilane (31 mL, 0.25 mmol) was added and the mixture was stirred for 10 min. Imine, 4, (215 mg, 1.0 mmol) was added and the vessel sealed, moved to a fume hood and charged with hydrogen (1950 psig). The mixture was heated in an oil bath at 65 °C for 22 h. The solvent was removed in vacuo and the amine (150 mg, 69 % yield) was isolated by extraction. HPLC analysis indicated 84 % ee ((R) enantiomer).

Hydrogenation of 4 at 500 psig with (R,R)-1c: In a glove box, a Parr model 4751 high pressure autoclave containing a magnetic stir bar, was charged with (R,R)-1c (35 mg, 0.10 mmol) and 10 mL THF. Phenylsilane (37 mL, 0.30 mmol) was added. Imine, 4, (430 mg, 2.0 mmol) was added and the vessel sealed, moved to a fume hood and charged with hydrogen (500 psig). The mixture was heated in an oil bath at 65 °C for 72 h. The solvent was removed in vacuo and the amine (337 mg, 78 % yield) was isolated by extraction. HPLC analysis indicated 61 % ee ((R) enantiomer).

Hydrogenation of 4 at 2000 psig with excess n-butyllithium: N-(1-Cyclohexyl- ethylidene)benzylamine (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst ((R,R,R)-1a: 59 mg, 0.10 mmol; n-butyllithium: 149 µL, 1.68 M in hexanes, 0.25 mmol; phenylsilane: 37 µL, 0.30 mmol). The reaction vessel was charged to 2000 psig and the reaction mixture was stirred for 12 h. The pure amine (332 mg, 76 % yield) was obtained after extraction. HPLC analysis indicated 39 % ee ((R) enantiomer).
Hydrogenation of 4 at 2000 psig with a deficiency of n-butyllithium: \( N-(1\text{-}Cyclohexylethylidene)\text{benzylamine} \) (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst \((R,R,R)-1\text{a}: 59 \text{ mg, 0.10 mmol; } n\text{-butyllithium: 89 } \mu\text{L, 1.68 M in hexanes, 0.15 mmol; phenylsilane: 37 } \mu\text{L, 0.30 mmol})\). The reaction vessel was charged to 2000 psig and the reaction mixture was stirred for 12 h. The pure amine (400 mg, 92 % yield) was obtained after extraction. HPLC analysis indicated 77 % ee \((R)\) enantiomer.

Kinetic resolution of racemic 6 at 2000 psig: Benzyldiene\(1\text{-cyclohexyl-ethylamine} \) (430 mg, 2.0 mmol) was reduced according to the general procedure with 5 mol % catalyst \((R,R,R)-1\text{a}: 59 \text{ mg, 0.10 mmol; } n\text{-butyllithium: 114 } \mu\text{L, 1.75 M in hexanes, 0.20 mmol; phenylsilane: 37 } \mu\text{L, 0.30 mmol})\). The reaction vessel was charged to 2000 psig and the reaction mixture was stirred for 4 h. At this point GC showed 71 % remaining 6 and 29 % 5 (only a trace of 4 was observed). The mixture was transferred to a flask containing 5 mL 1 M HCl and stirred overnight. The layers were separated, the aqueous layer was made basic with NaOH and extracted with ether (3 x 20 mL). The organic portions were dried with \(Na_2SO_4\) and concentrated. Column chromatography (silica, 2 % triethylamine : hexane) afforded 88 mg (20 % yield) of amine 5. HPLC analysis indicated 16 % ee \((S)\) enantiomer.

Hydrogenation of \((R)-6\) at 2000 psig with \((R,R,R)-1\text{a}:\) Benzyldiene\(1\text{-cyclohexyl-ethylamine} \) (6 mL of a 0.375 M stock solution in THF, 2.25 mmol, 95 % ee) was reduced according to the general procedure with 6.7 mol % catalyst \((R,R,R)-1\text{a}: 90 \text{ mg, 0.30 mmol; } n\text{-butyllithium: 176 } \mu\text{L, 1.70 M in hexanes, 0.10 mmol; phenylsilane: 55 } \mu\text{L, 0.45 mmol})\). The reaction vessel was charged to
2000 psig and the reaction mixture was stirred for 10 h. HPLC analysis of amine (R)-5 (not purified) indicated 91 % ee.

**Hydrogenation of (R)-6 at 2000 psig with (S,S,S)-1a:** Benzylidine(1-cyclohexyl-ethyl)amine (6 mL of a 0.375 M stock solution in THF, 2.25 mmol, 95 % ee) was reduced according to the general procedure, using (S,S,S)-1a in place of (R,R,R)-1a, with 6.7 mol % catalyst (titanium complex: 90 mg, 0.15 mmol; n-butyllithium: 176 µL, 0.30 mmol, 1.70 M in hexanes; phenylsilane: 55 µL, 0.45 mmol). The reaction vessel was charged to 2000 psig and the reaction mixture was stirred for 10 h. HPLC analysis of amine (R)-5 (not purified) indicated 93 % ee.

**Hydrogenation of (R)-6 at 500 psig with (R,R,R)-1a:** Benzylidine(1-cyclohexyl-ethyl)amine (215 mg, 1.0 mmol, 94 % ee) was reduced according to the general procedure with 5 mol % catalyst (titanium complex: 30 mg, 0.05 mmol; n-butyllithium: 59 µL, 1.70 M in hexanes, 0.10 mmol; phenylsilane: 19 µL, 0.15 mmol). The reaction vessel was charged to 500 psig and the reaction mixture was stirred for 40 h. The pure amine (R)-5 (199 mg, 92 % yield) was obtained after Kugelrohr distillation. HPLC analysis indicated 89 % ee.

**Hydrogenation of (R)-6 at 500 psig with (S,S,S)-1a:** Benzylidine(1-cyclohexyl-ethyl)amine (215 mg, 1.0 mmol, 94 % ee) was reduced according to the general procedure, using (S,S,S)-1a in place of (R,R,R)-1a, with 5 mol % catalyst (titanium complex: 30 mg, 0.05 mmol; n-butyllithium: 59 µL, 1.70 M in hexanes, 0.10 mmol; phenylsilane: 19 µL, 0.15 mmol). The reaction vessel was charged to 500 psig and the reaction mixture was stirred for 40 h. Pure amine (R)-5 (201
mg. 93 % yield) was obtained after Kugelrohr distillation. HPLC analysis indicated 91 % ee.

**Stoichiometric reaction of 4 with \((R,R,R)\)-1a:** A dry Schlenk flask, under an argon atmosphere, was charged with \((R,R,R)\)-1a (120 mg, 0.2 mmol) and 10 mL THF. A solution of \(n\)-butyllithium (235 µL, 0.4 mmol, 1.70 M in hexanes) was added via syringe. After 2-3 min the solution was brown in color. Phenylsilane (65 µL, 0.6 mmol) was added and the solution turned dark brown. Imine 4 was added and the color lightened slightly. The mixture was stirred for 30 min and quenched with 1 M NaOH (2 mL). The solvent was removed in vacuo and the residue passed down a column of silica using 2 % triethylamine : hexane (to remove the metal complex). HPLC analysis of the crude residue indicated 83 % ee for amine 5 ((\(R\)) enantiomer).
REFERENCES


18. Titanium(III) complexes that have dimeric structures with bridging ligands usually exhibit spin-spin coupling of the unpaired electrons. This results in a lower observed magnetic moment for the complex (for an example of this cf. reference 14c). Magnetic moments for 1d and 1e are \( \mu_{\text{eff}} = 1.76 \, \mu_{\text{B}} \) and \( \mu_{\text{eff}} = 1.78 \, \mu_{\text{B}} \), respectively, in good agreement with that expected value of 1.73 \( \mu_{\text{B}} \) for 1.
unpaired electron / metal center. In contrast the magnetic moment for Cp₂TiCl
was determined under the same conditions to be 1.4 μB.

19. This type of reactivity has been observed for Ti(III) alkyls. cf. Teuben, J. H.
In *Fundamental and Technological aspects of Organo-f-Element Chemistry*,
Marks, T. J.; Fragala, I. L. Eds.; Reidel, D.; Dordrecht, Holland, 1985: p 195 and
references cited therein.

20. The kinetic resolution of 2,5-disubstituted pyrrolines has recently been
investigated with this catalyst system. Viso, A.; Lee, N. E.; Buchwald, S. L.

1, **1958**; pp.1087-1093.

22. a) K. Harada in S. Patai; *Chemistry of the Carbon-Nitrogen Double Bond*,


24. 15 / 1, 17 / 1, and 16 / 1 are statistically same number under the
conditions of our measurements.

25. For a study of the reactivity of Ti(III) alkyls cf. Luinstra, G. A.; ten Cate, L.


APPENDIX

Derivation of Rate Expression for Hydrogenation of 2

\[
\begin{align*}
\text{Cp}^*_{2}\text{Ti-H} + \ \text{2} & \quad \underset{k_{-1}}{\xrightarrow{k_{1}}} \quad \text{Cp}^*_{2}\text{Ti-N} \quad \text{(R,R,R)-1f} \\
\text{H}_2 + \ \text{Cp}^*_{2}\text{Ti-N} & \quad \underset{k_{2}}{\xrightarrow{k_{2}}} \quad \text{3} + \ \text{Cp}^*_{2}\text{Ti-H} \quad \text{(R,R)-1h}
\end{align*}
\]

\( \text{Cp}^*_{2} = \text{ethylene(bis)tetrahydorindenyl} \)

The reaction rate is defined as:

\[
\text{rate} = \frac{d [3]}{dt} = k_2 [1f] [H_2] \quad (1)
\]

Applying the steady state approximation to 1f gives:

\[
\frac{d [1f]}{dt} = 0
\]

Therefore

\[
k_1 [1h] [2] = k_{-1} [1f] + k_2 [1f] [H_2]
\]

Which can be solved for [1f] to give:

\[
[1f] = \left( \frac{k_1}{(k_{-1} + k_2 [H_2])} \right) [1h] [2] \quad (2)
\]

The total titanium concentration, [Ti] is:

\[
[\text{Ti}] = [1h] + [1f]
\]

Solving for the hydride concentration yields:

\[
[1h] = [\text{Ti}] - [1f] \quad (3)
\]
Substituting (3) into (2) gives:

$$[1f] = \left( \frac{k_1}{(k_1 + k_2 [H_2])} \right) ([Ti] - [1f]) [2]$$

Which simplifies to:

$$[1f] = \frac{[Ti] [2]}{k_1 + k_2 [H_2]} + [2]$$

Substituting into (1) gives the rate law:

$$\text{rate} = \frac{k_2 [Ti] [H_2] [2]}{k_1 + k_2 [H_2]} + [2]$$

eq. 9
CHAPTER 3  Part 1

PREPARATION, X-RAY STRUCTURE AND REACTIVITY OF A NOVEL BRIDGED TITANOCENE COMPLEX: ELECTRONIC EFFECTS IN THE CATALYTIC HYDROGENATION OF IMINES
INTRODUCTION

Chapters 1 and 2 discussed the development and study of a novel titanocene catalyst system for the asymmetric hydrogenation of imines. The catalyst was particularly successful for the hydrogenation of cyclic imines in which ee's of 95-99 % were obtained. For acyclic imines lower ee's were observed. In addition the ee's were found to be dependent on hydrogen pressure. This was attributed to the fact that syn and anti imines are converted to opposite enantiomers of the products and that the two imine isomers are interconverting under the reaction conditions. The stereochemical model for imine hydrogenation presented in chapter 1 reveals that the orientation of nitrogen substituent controls the stereochemical outcome of the reaction. It is this feature that gives rise to the fact that syn and anti imines are converted to opposite enantiomers of the amine. If the steric interaction between the metal complex and the nitrogen substituent were removed, the interactions between the carbon substituents and the ligand would become important. As illustrated in Scheme 3.1.1 this would result in both the syn and the anti imine being converted to the same enantiomer of the product.

For the anti imine two pathways leading to product are possible.¹ In both A and B the interactions between the nitrogen substituent, R_N and the ligand are equivalent. Therefore the interactions that determine the facial selectivity are between the carbon substituents and the ligand. In B a steric interaction between R_L and the ligand is present and makes reaction via B less favorable than via A. For the syn imine two pathways are also possible.¹ Again the nitrogen substituent should not influence the reaction since its interactions with the ligand are the equivalent in both C and D. Thus the interaction that should control the facial selectivity is between R_L and the ligand. On this basis D is expected to be higher in energy than C. Since reaction via A and C both give the
same enantiomer of the amine a complex with this ligand environment should give the same enantiomer for both the \textit{syn} and \textit{anti} imines.

\textbf{Scheme 3.1.1}  Design of a Catalyst that Converts Both Imine Isomers to The Same Enantiomer of the Amine

\begin{align*}
\text{(A)} & \quad \text{(B)} \\
\text{(C)} & \quad \text{(D)}
\end{align*}

The bridge is omitted for clarity

Thus a complex that possesses both a cyclopentadienyl and a tetrahydroindenyl ligand would have the desired ligand environment. A suitable tether between the two ligands would provide the complex with the necessary stereochemical rigidity. The preparation and reactivity of such a complex is the subject of this chapter.
The synthesis of group 4 metallocenes has been the subject of much study. This derives from their activity as catalysts for the Ziegler-Natta polymerization of olefins. As such there are many methods available for the preparation of these complexes. Our goal was to devise a short, flexible sequence in which we could prepare a number of titanocene complexes. We then wished to study the catalytic activity of these complexes in the hydrogenation of imines.

RESULTS and DISCUSSION

The syntheses of the cyclopentadienyl-indenyl complex 2a and its saturated derivative 2b are outlined in Scheme 3.1.2. Addition of indenyllithium to pentamethylene fulvene afforded the monolithium salt of desired ligand framework, 1-Li. Ligand 1-Li was converted without isolation, to the dianion, by deprotonation with 1 equivalent of n-butyllithium. Treatment of titanium trichloride with the dilithium salt of 1, followed by oxidation with lead (II) chloride afforded the desired titanocene complex 2a in 18% overall yield (from indene) after recrystallization from toluene. Catalytic hydrogenation of 2a with PtO₂ at 80 psig

**Scheme 3.1.2 Synthesis of Complexes 2a and 2b**

![Chemical diagram showing the synthesis of complexes 2a and 2b]
of hydrogen afforded the saturated analog 2b. Pure 2b was obtained in 82% yield by recrystallization from hot toluene. Importantly, when the hydrogenation of 2a was conducted at higher pressures of hydrogen significant decomposition of the complex was observed.

In order to determine if the complexes possessed the anticipated steric environment an X-ray crystallographic study of complex 2b was conducted. The ORTEP diagram is shown in Figure 3.1.1 and selected bond distances and bond angles are listed in Table 3.1.1.

Figure 3.1.1 ORTEP Diagram of Complex 2b
Table 3.1.1 Selected Bond Distances and Angles for Complex 2b

<table>
<thead>
<tr>
<th>Bond Distance, Å</th>
<th>Bond Distance, Å</th>
<th>Angle, deg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti-Cl(1)</td>
<td>2.346(2)</td>
<td>Cl(1)-Ti-Cl(2) 97.6(1)</td>
</tr>
<tr>
<td>Ti-Cl(2)</td>
<td>2.338(2)</td>
<td>Cp-Ti-Cp' 121.8(1)</td>
</tr>
<tr>
<td>Ti-C(1)</td>
<td>2.307(6)</td>
<td>C(2)-C(15)-C(6) 96.3(4)</td>
</tr>
<tr>
<td>Ti-C(2)</td>
<td>2.335(6)</td>
<td></td>
</tr>
<tr>
<td>Ti-C(3)</td>
<td>2.427(6)</td>
<td></td>
</tr>
<tr>
<td>Ti-C(4)</td>
<td>2.508(6)</td>
<td></td>
</tr>
<tr>
<td>Ti-C(5)</td>
<td>2.429(6)</td>
<td></td>
</tr>
</tbody>
</table>

The complex crystallizes in the space group Pbca with one molecule in the orthorhombic unit cell. The bridging cyclohexyl moiety adopts a normal chair conformation with the larger tetrahydroindenyl substituent in the equatorial position. Overall the structure closely resembles that of the methylene bridged bis(cyclopentadienyl) titanium dichloride complex, $\text{CH}_2(\text{C}_5\text{H}_4)_2\text{TiCl}_2$. Significant distortion of the geometry relative to that of titanocene dichloride is observed in complex 2b. The C(6)-C(15)-C(2) angle is 96.3(4)°, about 13° smaller than that expected for a tetrahedral carbon. The Cp-Ti-Cp' angle of 121.8° (Cp=cyclopentadienyl, Cp' = tetrahydroindenyl) is about 7° less than that of titanocene dichloride indicating an opening of the wedge formed by the two cyclopentadienyl ligands. This is accompanied by a larger Cl(1)-Ti-Cl(2) angle of 97.6(1)°. The Cl-Ti-Cl angle in Cp$_2$TiCl$_2$ is 94.4°. The Ti-Cp and Ti-Cp' distances are 2.07(1) and 2.08(1) Å respectively. However the metal to ring carbon distances are not equal. The Ti-C distances at the front [C(8) and C(4)] of the complex are longer than those at the bridge [C(6) and C(2)] position by 0.11 Å (for Ti-Cp) and 0.17 Å (for Ti-Cp'). This indicates the strain imposed by the single atom bridge. The Ti-Cl distances of 2.338(2) and 2.346(2) are in good agreement with that found for CH$_2$(C$_5$H$_4$)$_2$TiCl$_2$. The single atom bridge constrains the two cyclopentadienyl rings in a near eclipsed conformation which causes the C(14) and C(13) atoms of the tetrahydroindenyl ring to project toward
the front of the complex. Thus the cyclohexyl portion of the tetrahydroindenyl ligand is positioned to interact with substrates as they approach the metal center.

For our imine hydrogenation studies we required enantiomerically pure 2b. To this end we attempted a resolution of racemic 2b into its enantiomers using the methods developed by Brintzinger for the ethylene bridged bis(tetrahydroindenyl) titanium complex (Scheme 3.1.3). Unfortunately all attempts met with limited success. Reaction of complex 2b with 0.5 equivalents of (R)-BINOL in the presence of sodium resulted in formation of only one complex as indicated by $^1$H NMR. However we were unable to obtain a pure

**Scheme 3.1.3 Attempted resolution of complex 2b**

![Diagram](image)

product from this reaction as decomposition was observed. We also investigated the use of chiral carboxylic acids as resolving agents for complex 2b. In this case the two diastereomeric titanium complexes were formed as determined by $^1$H NMR analysis but no tractable products could be isolated. The instability of these products reflects the increased strain that is imposed by shortening the bridge from two to one carbon atoms.

We examined the catalytic activity of complexes 2a and 2b for the hydrogenation of 2-phenylpyrrole (Scheme 3.1.4). As can be seen, both

159
complexes catalyzed the hydrogenation with lower reaction rates than our standard catalyst system. When complex 2a was used a $k_{rel}$ of 0.11 was obtained, while that for complex 2b was 0.57. These results are consistent with those reported by Brintzinger for the hydrogenation of olefins using bridged titanocene complexes.9 Namely, when the number of atoms in the bridge is decreased from two to one lower catalytic activity is observed.

It is informative to compare the reaction rates for complexes 2a and 2b. Complex 2b catalyzed the hydrogenation reaction at a rate of about 5 times that observed for complex 2a. While there are subtle steric differences between the two complexes,10 this effect is presumed to be largely electronic. Complex 2a, which possesses the indenyl ligand, is more electron deficient than complex 2b which has the more electron donating tetrahydroindenyl ligand. Thus a more electron rich metal center results in an increased reaction rate. We have shown that with the ethylene(bis)tetrahydroindenyl catalyst system the rate limiting step in the imine hydrogenation reaction is hydrogenolysis of the titanium amide intermediate (see chapter 2). These results are consistent with activation of dihydrogen via a polar mechanism11 in the rate limiting transition state (Scheme

\[ \text{Scheme 3.1.4} \quad \text{Hydrogenation of 2-Phenylpyrroline with Various Titanium Complexes} \]

\[
\begin{array}{ccc}
\text{Ti Complex} & \text{turnovers / h} & k_{rel} \\
EBTHITiCl}_2 & 2.8 & 1.00 \\
2a & 0.3 & 0.11 \\
2b & 1.6 & 0.57 \\
\end{array}
\]

EBTHI = ethylene(bis)tetrahydroindenyl
3.1.5). A more electron rich metal center is expected to lower $\Delta G^\ddagger$ in two ways: 1) stabilization of the developing positive charge at the metal center will serve to lower the transition state energy and; 2) a more electron rich metal center will increase the ground state energy of the titanium amide complex. These two effects work in a cooperative fashion to lower the barrier of activation.

**Scheme 3.1.5 Hydrogenolysis of a Titanium Amide Complex**

\[
\begin{align*}
\text{Ti} & \quad \text{N} \\
\text{H} & \quad \text{H} \\
\text{Ti} & \quad \mathbf{H} \quad + \quad 
\text{N} \quad \text{H} \\
\text{Ti} & \quad \mathbf{H} \quad + \quad 
\end{align*}
\]

The ligands on titanium and the substituents on nitrogen are omitted for clarity

**CONCLUSIONS**

Two novel titanocene complexes have been synthesized via a short synthetic sequence. An X-ray structural analysis of complex 2b indicates that there is significant strain in the molecule. The structural data show that the orientation of the tetrahydroindenyl ligand is such that substrate-ligand interactions can occur to influence reactions at the metal center. While the ultimate goal of this project was unsuccessful since the complexes could not be resolved, imine hydrogenation studies using complexes 2a and 2b revealed some interesting features. Catalytic hydrogenation of 2-phenylpyrrolidine using the indenyl complex 2a and the tetrahydroindenyl complex 2b indicate that the reaction rates are affected by changing the electronic nature of the complex.
Namely a more electron rich metal appears to be a more active catalyst. The results of these studies should aid in the further development of titanium catalysts for the hydrogenation of organic substrates.
EXPERIMENTAL SECTION (Part 1)

General Considerations: The experiments in this chapter were conducted using standard inert atmosphere techniques as outlined in chapters 1 and 2. Catalytic imine hydrogenations using complexes 2a and 2b were conducted as described in chapter 1.

Preparation of 2a: A dry Schlenk flask was charged with indene (3.5 mL, 30 mmol) in 60 mL of THF. The solution was cooled to 0 °C and n-butyllithium (13.2 mL, 36 mmol, 2.72 M in hexanes) was added dropwise via syringe. The orange solution was warmed to room temperature and stirred for 30 min then cooled to -78 °C. A solution of pentamethylene fulvene^4 (4.4 g, 30 mmol) in 30 mL THF was added dropwise via cannula and the resulting mixture was warmed to room temperature and stirred overnight. At this point a small aliquot was removed, quenched with sat. aqueous NH₄Cl and analyzed by capillary GC/MS. Several isomers of the product (mw = 262) were observed totaling 90% of the mixture. The solution was cooled to -78 °C and n-butyllithium (13.2 mL, 36 mmol, 2.72 M in hexanes) was added. The mixture was warmed to room temperature and transferred via cannula to an ice cold suspension of TiCl₃ (4.63 g, 30 mmol) in 300 mL THF. After stirring at room temperature for 4 h the solution was added via cannula to a suspension of PbCl₂ (4.2 g, 15 mmol) in 50 mL THF. The dark green mixture was stirred for 2 h, then opened to air and concentrated. The residue was diluted with 400 mL toluene and filtered through celite. The solution was concentrated to ca. 200 mL and cooled to -20 °C to afford dark green crystals. The supernatant liquid was decanted and the crystals were dried in vacuo to give 2.04 g (18% yield) of complex 2a. ¹H NMR (300 MHz, CDCl₃, TMS): δ 7.66-7.62 (d, 1H, J=8.6 Hz), 7.52-7.45 (m, 2H), 7.22-7.21, (d, 1H, J=3.4 Hz), 7.06-7.0 (m, 1H), 6.77-6.74 (m, 1H), 6.71-6.68 (m, 1H), 5.82-5.80 (d, 1H,
J=3.5 Hz), 5.6-5.54 (m, 2H), 2.91-2.84 (m, 1H), 2.62-2.43 (m, 2H), 2.35-2.25 (m, 1H), 1.95-1.85 (m, 4H), 1.79-1.70, (m, 2H); $^{13}$C NMR (75 MHz, CDCl₃): δ 136.1, 128.8, 128.7, 127.9, 126.9, 125.5, 124.4, 120.1, 115.8, 111.2, 110.7, 109.3, 98.1, 44.5, 34.2, 33.5, 25.9, 22.3, 21.7; IR (KBr): 3085, 2918, 1443, 1411, 1283, 1220, 1158, 1044, 803, 767, 751, 705, 466; Anal calc for C$_{20}$H$_{20}$TiCl$_{2}$: C; 63.35, H; 5.32, found: C; 63.35, H; 5.36.

**Preparation of 2b:** A dry Fisher-Porter bottle was charged with complex 2a (1.11 g, 2.9 mmol), PtO$_2$, (27 mg, 0.12 mmol) and 50 mL methylene chloride. The vessel was purged with hydrogen (3 x) and pressurized to 80 psig. The resulting solution was stirred at room temperature for 3 h at which time the color had changed from dark green to brown-red. The vessel was vented and opened to air and the mixture was filtered through celite. The crude solid was recrystallized from ca. 30 mL hot toluene. Removal of the supernatant liquid followed by drying *in vacuo* afforded 0.92 g (82 % yield) of complex 2b as black crystals. $^1$H NMR (300 MHz, CDCl$_3$, TMS): δ 7.09-7.05 (m, 1H), 6.9-6.86 (m, 1H), 6.55-6.54 (d, 1H, J=3.5 Hz), 5.64-5.61 (m, 1H), 5.53-5.52 (d, 1H, J=3.0 Hz), 5.41-5.38 (m, 1H), 3.14-3.09 (m, 1H), 2.8-2.57 (m, 2H), 2.53-2.43 (m, 5H), 1.57-1.40 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 142.8, 129.7, 129.3, 128.2, 126.0, 113.8, 113.3, 109.9, 109.3, 108.6, 44.3, 33.8, 32.8, 27.5, 25.9, 25.4, 22.6, 21.9, 21.7, 20.9; IR (KBr): 3081, 2925, 2857, 1637, 1449, 1417, 1346, 1253, 1146, 1079, 1040, 959, 872, 816, 768, 724, 476; Anal calc for C$_{20}$H$_{24}$TiCl$_{2}$: C; 63.28, H; 6.47, found: C; 62.74, H; 6.19.

**X-Ray Structure of 2b:** X-Ray structure determination of complex 2b was conducted using a Rigaku-AFC6R diffractometer at 195 K. A total of 4451 reflections were collected. The crystals are orthorhombic, space group Pbca;
a=15.059, b=17.470, c= 13.188, α=90.0°, β=90.0°. An empirical absorption correction, using the DIFABS$^{12}$ program was applied. Anisotropic refinement was conducted using a combination of the Patterson method and direct methods$^{13}$. The final cycle was based on 1709 reflections and converged with an agreement factor of $R = 0.046$. 
CHAPTER 3   Part 2

SYNTHESIS AND REACTIVITY OF A NOVEL CLASS OF TITANIUM
COMPLEXES BEARING ELECTRONICALLY AND STERICALLY FLEXIBLE
o-PHOSPHINOPHENOL LIGANDS
INTRODUCTION

The cyclopentadienyl ligand is one of the most widely used ligands in organometallic chemistry. The application of biscyclopentadienyl complexes of the group 4 transition metals to organic synthesis has been extensively studied.\textsuperscript{14} Previous parts of this thesis discuss the development of a biscyclopentadienyl titanium complex that functions as a catalyst for the hydrogenation of imines. For many reactions of transition metal complexes ligand electronic effects can dramatically change the reactivity and/or selectivity.\textsuperscript{15} One of the limitations of the cyclopentadienyl ligand is that its electronic properties are not easily modified without significantly changing the steric environment. We therefore sought to develop an electronically flexible ligand system in order to probe the electronic effects in the titanium catalyzed reduction of organic substrates.

To accomplish this goal we required a ligand that has the same basic properties as a cyclopentadienyl ligand but allows a systematic variation of its electron donating ability. The $\alpha$-phosphinophenol\textsuperscript{16} ligands appear to posses the desired criteria. Figure 3.2.1 compares the cyclopentadienyl ligand to the $\alpha$-phosphinophenol ligand. Both ligands are mono anionic; the cyclopentadienyl ligand acts as a 6 electron donor. The $\alpha$-phosphinophenol ligand can also serve as a 6 electron donor if a metal-oxygen $\pi$ bond is present. Titanium oxygen bonds are known to posses double bond character and thus,\textsuperscript{17} when bound to titanium, the phosphinophenol ligand should act as a six electron, mono anionic ligand. An additional feature of the $\alpha$-phosphinophenol ligand is that by changing the substituents on phosphorous the electronic properties can be easily tuned without affecting steric properties of the metal complex. In addition the steric environment imposed by these ligands can also be modified. For example by placing two different substituents on phosphorous the potential for a chiral ligand
array exists. The preparation and properties of some novel titanium complexes bearing α-phosphinophenol ligands is the focus of the second part of this chapter.

**Figure 3.2.1** Comparison of Cyclopentadienyl and α-Phosphinophenol Ligands

Synthetic routes to α-phosphinophenols are rare. Only two compounds of this type have appeared in the literature, α-(diphenylphosphino)phenol and α-(di-tert-butyl)phosphinophenol. These compounds were prepared by metatation of protected phenol followed by reaction of the aryllithium with the corresponding disubstituted chlorophosphine (Scheme 3.2.1). Deprotection of the hydroxy group with strong acid afforded the desired compounds in modest yields.

**Scheme 3.2.1** Published Route to α-Phosphinophenols

![Scheme 3.2.1](image)

While the existing method for the preparation of the desired ligands is relatively simple it suffers from some drawbacks. First, the use of the hazardous methylchloromethyl ether is undesirable. The second drawback is that strong acid is required in the deprotection step, when R = Me refluxing 50 % aqueous HI was necessary to give the product. Additionally, for our studies a bulky substituent in the 6 position (ortho to the hydroxy) is required to prevent dimerization of the metal complexes through a bridging oxygen. The formation of
oxygen bridged oligomers is well known for titanium complexes. We therefore set out to devise an alternate route to the desired ligands.

RESULTS and DISCUSSION

Synthesis: The synthesis of the desired o-phosphinophenol ligands is shown in Scheme 3.2.2. Bromination of the commercially available 2-substituted phenols\textsuperscript{19} afforded the corresponding 2-bromo-6-alkylphenols. We found that this reaction worked well for R = Me, i-Pr and t-Bu. Exclusive bromination in the 2 position was observed and the products could be easily purified by either distillation or chromatography. We chose to focus on the more bulky t-Bu derivatives in order to inhibit oligomerization of the metal complexes.

Deprophenol with sodium hydride in ether followed by metal halogen exchange with n-butyllithium at 0 °C resulted in formation corresponding aryllithium species. Addition of the requisite diarylchlorophosphine gave the desired ligands after aqueous workup and chromatography in 26-78 % yields. These compounds are air and stable and can be stored for several months at room temperature. The \textsuperscript{31}P NMR shows a single broad resonance (3a, \textit{\delta} = -31.1 ppm; 3b, \textit{\delta} = -32.7 ppm). In the \textsuperscript{1}H NMR spectra the phenolic proton appears as a doublet with \textit{J}_{\text{HP}} = 11.2 \text{ Hz} indicating hydrogen bonding to the phosphorous atom. This may serve to stabilize the compounds toward oxidation of the phosphorous. The corresponding sodium salts are oxidized in air over a period of several hours at room temperature.

\textbf{Scheme 3.2.2} Synthesis of o-Phosphinophenol Ligands

\[
\begin{align*}
R & \quad \text{Br}_2 / \text{t-BuNH}_2 \quad \text{CH}_2\text{Cl}_2 \quad \rightarrow \quad R & \quad \text{Br} \\
& \quad \text{1. NaH} \quad \text{2. n-BuLi} \quad \text{3. Ar}_2\text{PCl} \\
3a; R = \text{t-Bu}, & \quad \text{Ar} = \text{C}_6\text{H}_5 \\
3b; R = \text{t-Bu}, & \quad \text{Ar} = \text{p-C}_6\text{H}_4\text{Me}
\end{align*}
\]
In order to study some titanium complexes of the $\alpha$-phosphinophenol ligands the monocyclopentadienyl dichloro titanium complexes of these ligands were prepared.\textsuperscript{20,21} Reaction of the $\alpha$-phosphinophenols with $n$-butyllithium in THF followed by slow addition of the anion to a THF solution of CpTiCl$_3$ (Scheme 3.2.3) afforded the desired titanium complexes in 45-63% isolated yields after recrystallization from toluene or toluene / hexane.

**Scheme 3.2.3 Synthesis of CpTi(Cl)$_2$$\alpha$-PPO Complexes**

![Scheme 3.2.3 Synthesis of CpTi(Cl)$_2$$\alpha$-PPO Complexes](image)

$3a-b$  

$1.$ n-BuLi  

$2.$ CpTiCl$_3$

$4a; \quad Ar = C_6H_5, \quad 63\%$

$4b; \quad Ar = p-C_6H_4Me, \quad 45\%$

The complexes are orange, moisture-sensitive crystalline solids. They are very soluble in halogenated solvents such as methylene chloride and slightly soluble in ethereal solvents. The compounds exhibit limited solubility in toluene or benzene. The $^1$H NMR spectra of $4$ (C$_6$D$_6$, rt) display a doublet for the Cp hydrogens ($4a$, $\delta$ 6.18 ppm, $J_{HP}$=2.7 Hz; $4b$, $\delta$ 6.21 ppm, $J_{HP}$=2.4 Hz) which indicates that the phosphorous is bound to titanium. Additionally the chemical shifts in the $^{31}$P NMR spectra ($4a$, $\delta$ 28.4 ppm; $4b$, $\delta$ 27.6 ppm) are consistent with a triaryl phosphine coordinated to a metal center. By $^1$H NMR the two aryl groups bound to phosphorous are equivalent at room temperature. The protons ortho to phosphorous (in complex $4a$) appear as a multiplet at 7.66 ppm integrating for 4 hydrogens. For complex $4b$ the para methyl groups appear as a singlet at $\delta$ 1.91 ppm. Similarly the $^{13}$C NMR spectra indicate equivalence of the two aromatic groups. The signals for the ortho and meta carbons of the two equivalent aryl groups are split into doublets by coupling to phosphorous.
Since the solid state structure indicates inequivalence of the two aromatic groups (\textit{vide infra}) the molecule must be fluxional at room temperature. In order to support this hypothesis a solution of 4a in toluene-d$_8$ was examined by variable temperature NMR spectroscopy. When the spectrum was acquired at temperatures above -30 °C a triplet resonance at 7.60 ppm integrating for 4 hydrogens is observed. These hydrogens are the ones ortho to the phosphorous on the two phenyl groups. Upon cooling to -35 °C this signal begins to broaden and at -40 °C is observed as a broad singlet. At -50 °C the signal begins to sharpen into two triplets. When the sample is cooled to -60 °C complete resolution is observed; the two triplets appear at 7.61 and 7.54 ppm, each signal integrates to two hydrogens.

\textbf{Cyclic Voltammetry:} Titanium compounds generally exhibit reversible redox behavior between the +3 and +4 oxidation states. For titanocene dichloride electrochemical measurements have shown that there is a reversible redox wave that appears at -0.800 V (vs SCE).\textsuperscript{22} With this in mind the reduction potential of complexes 4 serve as a useful probe of the electron

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
Complex & $E_{\text{red vs SCE}}$ \\
\hline
\includegraphics[width=0.1\textwidth]{CpTiCl2-O-tBu-tBu} & -0.69 (±0.02) V \\
\hline
Cp$_2$TiCl$_2$ & -0.800 V \textsuperscript{22} \\
\hline
4a & -0.79 (±0.02) V \\
\hline
4b & -0.78 (±0.02) V \\
\hline
\end{tabular}
\caption{Reduction Potentials of Various Titanium Complexes}
\end{table}

donating capabilities of the o-phosphinophenol ligands. Thus cyclic voltammetry studies were conducted on complexes 4 and some other related titanium complexes. The results are shown in Table 3.2.1. Complexes 4a and 4b
exhibited reversible redox waves at potentials of -0.79 (±0.02) V and -0.78 (±0.02) V (vs SCE). In comparison the CpTiCl$_2$O-(2,6-diBuC$_6$H$_3$) complex has a reduction potential of -0.69 (±0.02) V. These results show that as expected 4a and 4b are more electron rich than the related CpTiCl$_2$OAr complex. The potentials of 4a and 4b are comparable to that of Cp$_2$TiCl$_2$ at -0.800 V indicating that these ligands are electronically similar to the cyclopentadienyl ligand. However under the conditions of these experiments the reduction potential is not sensitive enough to determine the subtle electronic differences between 4a and 4b.

**X-ray structure:** Crystals of 4a suitable for single crystal X-ray analysis were isolated by slow cooling of a saturated hot toluene solution. The ORTEP diagram is shown in Figure 3.2.2 and selected bond distances and angles are listed in Table 3.2.2. The crystals are triclinic in the P1 space group. In the solid state the molecule adopts a distorted square based pyramidal coordination geometry. The cyclopentadienyl ligand occupies the apical position with the two chlorines, the oxygen and the phosphorous atoms making up the base of the pyramid. In this geometry the molecule is chiral with the two phenyl groups on the phosphorous being diastereotopic. Both of the Ti-Cl bond lengths of 2.333(3) and 2.340(2) are in good agreement with those of Cp$_2$TiCl$_2$. The Cl(1)-Ti-Cl(2) angle of 89.14(9) °, however, is smaller than that for Cp$_2$TiCl$_2$ which is 94.4 °. The Ti-O bond length is 1.860(5) Å which is consistent with a π bond being present. The Ti-O bond in [CpTiCl$_2$]O is 1.74 Å while that in Cp$_2$Ti(Cl)OEt is 1.855(2) Å. The Ti-O-C(1) angle is 134.9(4) and also indicates a π bond between titanium and oxygen. The Ti-P distance of 2.624(3) Å is in good agreement with known Ti-P distances. The Ti-P-C(6) angle is 97.2(2) Å. Some strain in the ligand framework is evident from the O-C(1)-C(6) and the P-C(6)-
C(1) angles (116.6(6)° and 111.8(5)° respectively) as these angles are significantly smaller than the expected value of 120 degrees.

**Figure 3.2.2 ORTEP Diagram of Complex 4a**
Table 3.2.2 Selected Bond Distances and Angles for Complex 4a

<table>
<thead>
<tr>
<th>Bond Distance, ( \text{Å} )</th>
<th>Bond Angle, ( \text{deg} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti-Cl(1) 2.333(3)</td>
<td>Cl(1)-Ti-Cl(2) 89.14(9)</td>
</tr>
<tr>
<td>Ti-Cl(2) 2.340(2)</td>
<td>Cl(1)-Ti-P 142.09(9)</td>
</tr>
<tr>
<td>Ti-P 2.624(3)</td>
<td>Cl(1)-Ti-O 89.2(2)</td>
</tr>
<tr>
<td>Ti-O 1.860(5)</td>
<td>Cl(2)-Ti-P 78.77(8)</td>
</tr>
<tr>
<td>P-C(6) 1.794(7)</td>
<td>Cl(2)-Ti-O 129.7(2)</td>
</tr>
<tr>
<td>O-C(1) 1.367(8)</td>
<td>P-Ti-O 72.4(2)</td>
</tr>
<tr>
<td>Cp-Ti 2.13(2)</td>
<td>Ti-P-C(6) 97.2(2)</td>
</tr>
<tr>
<td></td>
<td>Ti-O-C(1) 134.9(4)</td>
</tr>
<tr>
<td></td>
<td>O-C(1)-C(6) 116.6(6)</td>
</tr>
<tr>
<td></td>
<td>P-C(6)-C(1) 111.85</td>
</tr>
</tbody>
</table>

Catalytic Studies: An investigation of the catalytic activity of complex 4a was also conducted. The results are shown in Scheme 3.2.4. Treatment of complex 4a with n-butyllithium under a hydrogen atmosphere resulted in the formation of an active olefin hydrogenation catalyst. Hydrogenation of 1-octene proceeded under mild conditions (r.t., 20 psig \( \text{H}_2 \)) to give a mixture of octane and an unidentified octene isomer (most likely 2-octene) in a 90:5 ratio respectively. Hydrogenation of an imine was not successful with this complex. At 80 psig and

Scheme 3.2.4 Catalytic activity of complex 4a

\[
\begin{align*}
\text{Catalyst} & \quad 5 \text{ mol} \% \ 4a \\
& \quad 10 \text{ mol} \% \ n-\text{BuLi} \\
\text{5 h, ether} & \quad 20 \text{ psig} \ \text{H}_2, \text{ rt} \\
\end{align*}
\]

100% conversion
90/5 octane / octene isomer

65 °C no reduction of \( N \)-benzylidenemethylamine was observed. However, hydrosilylation of \( N \)-benzylidenemethylamine was affected. Treatment of complex 4a with \( n \)-butyllithium in THF followed by addition of phenylsilane afforded an active hydrosilylation catalyst with converted the starting imine.
completely to product in 54 h at 65 °C. No side products were observed in this reaction.

CONCLUSIONS

An alternate route to the o-phosphinophenol ligand system has been worked out. Using these ligands, two novel titanium complexes have been prepared and studied. Cyclic voltammetry measurements indicate that the ligands are similar to the cyclopentadienyl ligand in their electron donating properties. By changing the substituents on phosphorous the o-phosphinophenol ligands can be tailored both electronically and sterically making the o-phosphinophenol ligands well suited for detailed reaction studies. Catalytic studies have shown that the complexes are effective in the hydrogenation of an olefin and the hydrosilylation of an imine. However, the reaction chemistry of these new titanium complexes remains largely unexplored. These complexes should provide an expanded repertoire for the study of catalytic and stoichiometric transformations.
EXPERIMENTAL SECTION (Part 2)

General Considerations: The experiments in this chapter were conducted using standard inert atmosphere techniques as outlined in chapters 1 and 2. Variable temperature NMR experiments were conducted using a Varian VXR-500 spectrometer.

2-Bromo-6-<i>tert</i>-butylphenol: The method of Pearson<sup>19</sup> was used to prepare 2-bromo-6-<i>tert</i>-butylphenol from 2-<i>tert</i>-butylphenol. The product was purified by column chromatography (silica, hexane) to give a colorless oil (61% yield). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, TMS): δ 7.34-7.31 (m, 1H), 7.22-7.19 (d, 1H, J=7.8 Hz), 6.75-6.70 (t, 1H, J=7.7 Hz), 5.79 (s, 1H), 1.39 (s, 9H).

2-Diphenylphosphinino-6-<i>tert</i>-butylphenol, 3a: A dry Schlenk flask under argon was charged with NaH (0.4 g, 16.5 mmol) and 60 mL of ether. The suspension was cooled to 0 °C and 2-bromoc-6-<i>tert</i>-butylphenol (3.4 g, 15 mmol) was added dropwise via syringe. The mixture was allowed to stir for 3 h and n-butyllithium (9.5 mL, 1.74 M in hexanes, 16.5 mmol) was added. After stirring the mixture for 1 h, Ph<sub>2</sub>PCl was added. The reaction mixture was warmed to room temperature and stirred for 16 h. Ether (100 mL) and sat. NH<sub>4</sub>Cl (100 mL) were added and the layers were separated. The organic portion was dried over MgSO<sub>4</sub> and concentrated to give the crude product. Column chromatography (silica, 100:1 Hexane:EtOAc) afforded 3.92 g (78% yield) of the product as a viscous oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, TMS): δ 7.35-7.32 (m, 11H, 6.98-6.95 (d, 1H, J<sub>HP</sub>=11.3 Hz), 6.87-6.80 (m, 2H), 1.40 (s, 9H); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>, 85% H<sub>3</sub>PO<sub>4</sub>): δ -31.3; HRMS: calc. 334.1486, found 334.1488.
2-Bis(4-methylphenyl)phosphino-6-tert-butylphenol, 3b: Prepared as above from 2-bromo-6-tert-butylphenol and bis(4-methylphenyl)chlorophosphine.\textsuperscript{15b} Yield, 26%: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}, TMS): \(\delta\) 7.31-7.28 (d, 1H, \textit{J}=7.8 Hz), 7.24-7.17 (m, 8H), 6.97-6.91 (d, 1H, \textit{J}_\text{HP}=11.2 Hz), 6.90-6.78 (m, 2H), 2.36 (s, 6H), 1.40 (s, 9H); \textsuperscript{31}P NMR (121 MHz, CDCl\textsubscript{3}, 85% H\textsubscript{3}PO\textsubscript{4}): \(\delta\) -32.7; HRMS: calc. 362.1799, found 362.1801.

**Preparation of Cyclopentadienyl titanium complexes, 4a:** A dry Schlenk flask under an argon atmosphere was charged with 3a (1.33 g, 4 mmol) and 20 mL THF. A solution of \textit{n}-butyllithium (2.4 mL, 1.74 M in hexanes, 4.2 mmol) was added and the mixture was allowed to stir for 1 h. The resulting solution was then added via cannula to a solution of CpTiCl\textsubscript{3} (0.877 g, 4 mmol) in 20 mL THF over a period of 10 min. The deep red solution was stirred overnight (12 h) and the solvent was removed \textit{in vacuo} to give an orange solid. Toluene (40 mL) was added and the mixture was heated to 100 °C then filtered via cannula. Slow cooling to -20 °C afforded orange crystals which were isolated by decanting and washed with hexane. Removal of the residual solvents afforded 1.3 grams (63% yield of the desired complex. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}, TMS): \(\delta\) 7.72-7.62 (m, 4H), 7.2-7.18 (d, 1H, \textit{J}=7.5 Hz), 7.0-6.9 (m, 7H), 6.67-6.60 (t, 1H, \textit{J}=7.5 Hz), 6.18-6.17 (d, \textit{J}_\text{HP}=2.7 Hz), 1.55 (s, 9H); \textsuperscript{31}P NMR (121 MHz, C\textsubscript{6}D\textsubscript{6}, 85% H\textsubscript{3}PO\textsubscript{4}): \(\delta\) 28.4; \textsuperscript{13}C NMR (75 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \(\delta\) 171.3 (d, \textit{J}_{CP}=27.5 Hz), 138.6 (d, \textit{J}_{CP}=3.8 Hz), 132.6 (d, \textit{J}_{CP}=9.8 Hz), 131.4, 131.1 (d, \textit{J}_{CP}=11.3 Hz), 129.5 (d, \textit{J}_{CP}=9 Hz), 129.3, 128.5, 125.6, 122.4 (d, \textit{J}_{CP}=6 Hz), 121.5, 35.4, 29.7; Anal. calc. for C\textsubscript{27}H\textsubscript{27}Cl\textsubscript{2}OPTi; C, 62.69, H, 5.26; found C, 62.94, H, 5.37.

4b: A dry Schlenk flask under an argon atmosphere was charged with 3b (1.4 g, 3.8 mmol) and 20 mL THF. A solution of \textit{n}-butyllithium (2.5 mL, 1.60 M in
hexanes, 4.1 mmol) was added and the mixture was allowed to stir for 1h. The resulting solution was then added via cannula to a solution of CpTiCl₃ (0.847g, 3.8 mmol) in 20 mL THF over a period of 10 min. The deep red solution was stirred overnight (12 h) and the solvent was removed in vacuo to give an orange solid. Toluene (25 mL) and Hexane (20 mL) were added and the mixture was heated to 80 °C and filtered via cannula. The solution was slowly cooled to -20 °C to give orange crystals. The crystals were washed with hexane and dried in vacuo to afford 0.54 g of product. The supernatant liquid was concentrated and resulting solid recrystallized in a similar manner to give an additional 0.4 g of product. Yield: 0.94 g (45 %). ¹H NMR (300 MHz, CDCl₃, TMS): δ 7.68-7.62 (m, 4H), 7.22-7.20 (d, 1H, J=7.8 Hz), 7.12-7.09 (m, 1H), 6.81-6.78 (m, 4H), 6.68-6.63 (t, 1H, J=7.8 Hz), 6.21-6.20 (d, Jₕp=2.4 Hz), 1.91 (s, 6H), 1.55 (s, 9H); ³¹P NMR (121 MHz, C₆D₆, 85 % H₃PO₄): δ 27.6; ¹³C NMR (75 MHz, CD₂Cl₂) δ 171.1(d, JₕCp=27.2 Hz), 142.0, 138.5 (d, JₕCp=4.5 Hz), 132.5 (d, JₕCp=9.5 Hz), 130.9 (d, JₕCp=14 Hz), 130.2 (d, JₕCp=9.9 Hz), 129.3, 128.5, 125.8, 122.3 (d, JₕCp=5.3 Hz), 121.5, 35.3, 29.7, 21.6; Anal. calc. for C₂₇H₂₇Cl₂OPTi; C, 63.87, H, 5.73; found C, 63.92, H, 5.96.

X-Ray Structure of 4a: X-Ray structure determination of complex 4a was conducted using a Rigaku-AFC6R diffractometer at 195 K. A total of 4016 reflections were collected. The crystals are triclinic, space group P1; a=10.009, b=14.590, c= 9.889, α=92.95°, β=98.56°, γ=77.72°. An empirical absorption correction, using the DIFABS¹² program was applied. Anisotropic refinement was conducted using direct methods.¹³ The final cycle was based on 2117 reflections and converged with an agreement factor of R = 0.052.
Cyclic Voltammetry: In a glove box the titanium complex, Bu₄NPF₆ and ferrocene were dissolved in THF (5 mL). The measurements were conducted using a Pine RDE 4 potentiostat with a glassy carbon working electrode, a Pt counter electrode and a Ag reference electrode. The potential was scanned at a rate of 100 mV/s and the voltammograms were recorded using a Kipp & Zonen B690 xy Recorder. The potentials were corrected vs the Cp₂Fe/Cp₂Fe⁺ couple (+0.51 V vs SCE). Cp₂TiCl₂N(TMS)₂: -0.77 (+0.02) V; Cp₂TiCl₂O(2,6-iBuC₆H₃): -0.69 (+0.02) V; 4a: -0.79 (+0.02) V; 4b: -0.78 (+0.02) V.

Hydrogenation of 1-octene with 4a: A dry Fisher-Porter bottle under nitrogen was charged 4a (52 mg, 0.1 mmol) and the vessel was evacuated and filled with hydrogen (3x). Ether (10 mL) and 1-octene (314 μL, 2 mmol) were added. A solution of n-butyllithium (123 μL, 1.63 M in hexanes, 0.2 mmol) was added and the mixture turned dark brown. The vessel was charged to 20 pislg and the mixture was stirred at room temperature for 5 h. At this point GC/MS analysis showed no 1-octene. Two new products were present in a 90/5 ratio. The major product was octane (mw = 114) and the minor product was an octene isomer (mw = 112).

Hydrosilylation of N-benzyldinemethylamine with 4a: A dry Schlenk flask under argon was charged with 4a (52 mg, 0.1 mmol) and 5 mL THF. The solution was cooled to 0 °C and a solution of n-butyllithium (123 μL, 1.63 M in hexanes, 0.2 mmol) was added. After 1 min phenylsilane (271 μL, 2.2 mmol) was added followed by N-benzyldinemethylamine (250 μL, 2.0 mmol). The mixture was heated in an oil bath at 65 °C for 54 h. At this point GC analysis showed no imine and 100 % N-methylbenzylamine.
REFERENCES

1. A complex of this type no longer possesses C₂ symmetry. Therefore there are actually four possible pathways for both the syn and anti imines. The two not shown are expected to be very unfavorable due to interactions between the R₇ and the ligand.


10. Molecular Mechanics calculations at the MM2 level indicate that the ligand in complex 2b is actually slightly more bulky than that in 2a. Thus on a steric basis complex 2a should be more reactive. Since it this in not the case we believe the effect is due to electronic differences.


Report, 1984 / 1 Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegen, Netherlands.

18. While this work was in progress a report on the related 2-hydroxyethylphosphine complexes of titanium appeared. cf. van Doorn, J. A.; van der Heijden, H.; Oprean, A. G. Organometallics 1994, 13, 4271.