



Intramolecular alkene hydroaminations mediated by simple group 3 metal complexes: the development of non-lanthanocene-based catalysts  
by Young Kwan Kim

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry  
Montana State University  
© Copyright by Young Kwan Kim (2003)

Abstract:

Metallocene-based Group 3 metal complexes; lanthanocenes, have intrinsic problems for use as a universal catalysis. For example, preparations of most complexes are complicated, and most lanthanocenes are extremely sensitive to air and water and have structural limitation on variation.

The first application of non-metallocene-based Group 3 metal catalysts to intramolecular aminoalkene cyclizations has been achieved. Simple amido lanthanide complexes of the type  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  ( $\text{Ln} = \text{Y}, \text{Nd}$ ) have been found to be competent catalysts for this reaction, which have similar or superior activity in cyclization including diastereoselectivity to the lanthanocenes. Modification of the metal center in  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  ( $\text{Ln} = \text{Y}, \text{Nd}, \text{La}$ ) has been readily achieved by amine elimination in the presence of hindered chelating diamines, bis(thiophosphinic) amines, or bis(thioenamides) in situ, to provide new Group 3 amido chelates. These complexes have shown remarkably improved catalytic activities and stereoselectivities [e.g., 33:1 (trans/cis) in the cyclization of 2-aminohept-5-ene. An X-ray crystallographic structure of one of the bis(thiophosphinic amide)-based Group 3 metal complexes has been defined. Chiral lanthanide complexes have been implemented for enantioselective hydroamination reactions. The  $C_2$  symmetric catalysts exhibit good enantioselectivity in the cyclization of 1-amino-2,2-dimethylpent-5-ene, as high as 66% enantiomeric excess at 10 °C.

These non-metallocene-based Group 3 metal complexes have shown superiority in terms of preparation, thermal stability, and catalytic activity over lanthanocenes in the hydroamination of aminoalkenes. In addition, the amido complexes should allow for a variety of ligand derivatives.

INTRAMOLECULAR ALKENE HYDROAMINATIONS MEDIATED BY SIMPLE  
GROUP 3 METAL COMPLEXES: THE DEVELOPMENT OF NON-  
LANTHANOCENE-BASED CATALYSTS

by

Young Kwan Kim

A dissertation submitted in partial fulfillment  
of the requirements for the degree

of

Doctor of Philosophy

in

Chemistry

MONTANA STATE UNIVERSITY  
Bozeman, Montana

April 2003

© COPYRIGHT

by

Young Kwan Kim

2003

All Right Reserved

D378  
K56137

APPROVAL

of a dissertation submitted by

Young Kwan Kim

This dissertation has been read by each member of the dissertation committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

Tom Livinghouse, Ph.D. Tom Livinghouse 4/18/03  
(Signature) Date

Approved for the Department of Chemistry and Biochemistry

Paul Grieco, Ph.D. Paul Grieco 4-18-03  
(Signature) Date

Approved for the College of Graduate Studies

Bruce R. McLeod, Ph.D. Bruce R. McLeod 4-21-03  
(Signature) Date

## STATEMENT OF PERMISSION TO USE

In presenting this dissertation in partial fulfillment of the requirements for a doctoral degree at Montana State University, I agree that the Library shall make it available to borrowers under the rules of the Library. I further agree that copying of this dissertation is allowable only for scholarly purpose, consistent with "fair use" as prescribed in the U.S. Copyright Law. Requests for extensive copying or reproduction of this dissertation should be referred to Bell & Howell Information and Learning, 300 North Zeeb Road, Ann Arbor, Michigan 48106, to whom I have granted "the exclusive right to reproduce and distribute my dissertation in and from microform along with the non-exclusive right to reproduce and distribute my abstract in any format in whole or in part."

Signature Kim Young Kwon

Date 4-18-03

To my father

To all of my family

## ACKNOWLEDGEMENTS

I would like to express my deepest appreciation for Professor Tom Livinghouse for his patience, advice, assistance, and encouragement. His deep insight, creative thinking and great enthusiasm to chemistry has made an indelible impression on me that will serve to inspire me through my own career in chemistry.

I would like to thank Professor Paul Grieco for his sincere advice. I also thank Professor Edwin Abbott, Professor Mary Cloninger and Professor Trevor Douglas for their generous advice, discussions and encouragement.

I am indebted to all my talented colleagues for their fruitful discussions and continuous help. Special thanks go to Mr. Todd Meyer, Mrs. Tamara Thompson, Mr. Heath Freyer, and Dr. Yoshikazu Horino. I wish to thank Dr. Joe Sears for his generous help with mass spectra and Dr. Scott Busse for his assistance with NMR. I owe special thanks to Mr. Larry Henling at Caltech for contributing his crystallography expertise.

I also give grateful acknowledgements to Dr. Chang Yong Hong, Dr. Cheol Hae Lee and to LG Research Institute in Korea for their invaluable assistance and encouragement.

The support of all my family in Korea and the sacrifice and encouragement with endless love of my sweet daughter Yeri and my wonderful wife Suh Jung will be forever appreciated.

Praise be to the God and Father of our Lord Jesus Christ who always guides me.

## TABLE OF CONTENTS

1. INTRODUCTION .....	1
2. BACKGROUND .....	5
3. RESULT AND DISCUSSION	
INTRAMOLECULAR ALKENE HYDROAMINATIONS CATALYZED BY SIMPLE AMIDO DERIVATIVES OF THE GROUP 3 METALS.....	17
Introduction.....	17
Synthesis of Substrates.....	19
Intramolecular Alkene Hydroamination Catalyzed by $L_n(N(TMS)_2)_3$ .....	22
Summary .....	27
DRAMATIC RATE ENHANCEMENTS AND IMPROVED DIASTEROSELECTIVITIES VIA CHELATING DIAMIDE COORDINATION .....	29
Introduction.....	29
Synthesis of Proligands.....	32
Synthesis of Substrates.....	35
Generation of Group 3 Amido Complexes In Situ.....	38
The Intramolecular Hydroamination of Aminoalkenes by Group 3 Metal Amido Complexes Generated in Situ.....	40
Summary .....	49
TETRADENTATE LIGAND-BASED GROUP 3 METAL COMPLEXES: CHELATING (THIO, SELENO, TELLURO)PHOSPHORAMIDE LIGANDS .....	50
Introduction.....	50
Synthesis of Proligands .....	52
Generation of Tetradentate Ligand-Based Group 3 Metal Complexes In Situ .....	53
X-ray Crystallographic Studies .....	55
The Intramolecular Hydroamination of Aminoalkenes by Tetradentate Ligand-Based Group 3 Metal Complexes in Situ .....	60
Summary .....	73
ENANTIOSELECTIVE CATALYTIC HYDROAMINATION REACTION BY GROUP 3 METAL COMPLEXES.....	74
Introduction.....	74
Synthesis of Asymmetric Proligands .....	77
Enantioselective Intramolecular Hydroamination: Asymmetric Catalysis with Group 3 Metal Amido Complexes.....	80
4. CONCLUSION .....	86



## TABLE OF CONTENTS –CONTINUED

5. EXPERIMENTAL.....	88
REFERENCES CITED.....	174
APPENDICES.....	183
APPENDIX A: CRYSTALLOGRAPHIC ANALYSIS FOR <b>63</b> .....	184
APPENDIX B: $^1\text{H}$ , $^{13}\text{C}$ AND $^{31}\text{P}$ SPECTRA FOR SUBSTRATES, CYCLIZED PRODUCTS AND PROLIGANDS .....	197

## LIST OF TABLES

Table	Page
1. Substrates Utilized for Hydroamination .....	12
2. Substates Utilized for Bicyclization.....	13
3. Ln[N(TMS) <sub>2</sub> ] <sub>3</sub> ( <b>1</b> ) Catalyzed Cyclization of Aminoalkenes <b>15a, b</b> .....	22
4. Ln[N(TMS) <sub>2</sub> ] <sub>3</sub> ( <b>1</b> ) Catalyzed Cyclization of Aminoalkenes <b>15c, d, e</b> .....	24
5. Generation of Group 3 Amido Complexes in Situ.....	39
6. Catalyzed Cyclization of 2-Aminohex-5-ene ( <b>15e</b> ).....	41
7. Catalyzed Cyclization of 2-Aminohex-5-ene ( <b>15e</b> ).....	43
8. Catalyzed Cyclization of 2-Methylaminohex-4-ene ( <b>15c</b> )... ..	45
9. Catalyzed Cyclization of 3-Methylaminohex-4-ene ( <b>44</b> ) .....	46
10. Catalyzed Cyclization of 2,2-Dimethylaminohex-4-ene ( <b>41</b> ).....	47
11. Catalyzed Cyclization of 2-Aminohept-6-ene ( <b>50</b> ).....	48
12. Generation of Tetradentate Ligand-Based Group 3 Complexes.....	54
13. Selected Bond Lengths [Å] and Angles [°] for <b>63</b> .....	58
14. Catalyzed Cyclization of 2-Aminohex-5-ene ( <b>15e</b> ).....	61
15. Catalyzed Cyclization of 2-Aminohex-5-ene ( <b>15e</b> ).....	64
16. Catalyzed Cyclization of 2-Aminohex-5-ene ( <b>15e</b> ).....	66
17. Catalyzed Cyclization of 2-Aminohex-5-ene ( <b>15e</b> ).....	68
18. Catalyzed Cyclization of 2,2-Dimethylaminohex-4-ene ( <b>47</b> ).....	69
19. Catalyzed Cyclization of 2-Aminohept-6-ene ( <b>50</b> ).....	70

## TABLE OF CONTENTS – CONTINUED

Table	Page
20. Thermal Stability of Complex <b>70b</b> .....	73
21. Catalyzed Asymmetric Hydroamination of Aminoalkene <b>15e</b> .....	81

## LIST OF FIGURES

Figure	Page
1. Catalysts Developed for Hydroamination.....	6
2. Asymmetric Catalysts for Hydroamination .....	9
3. Another Type of Lanthanocene.....	10
4. The First Non-metallocene-Based Early-Metal Catalysts for Hydroamination .....	10
5. Natural Products Synthesized via Hydroamination .....	14
6. The First Three-Coordinated Lanthanide Complexes.....	18
7. Aminoalkenes <b>15a-f</b> .....	19
8. Rationalization of Diastereoselectivity .....	25
9. Bidentate Proligands <b>22</b> , <b>23</b> , <b>24</b> and <b>25</b> .....	29
10. Coordinatively and Electronically Less Saturated Complexes.....	30
11. Aminoalkenes <b>44</b> , <b>47</b> and <b>50</b> .....	35
12. Tetradentate Proligands .....	50
13. View from Perpendicular Angle to Square Plane (S1-N1-N2-S2) of <b>63</b> .....	55
14. (A) View from an Acute Angle to Square Plane (S1-N1-N2-S2) of <b>63</b> (B) Simplified Structure of <b>A</b> .....	56
15. Structure of <b>63</b> .....	56
16. Electron Donation from the Filled <i>p</i> -Orbital of N to the Empty <i>d</i> -Orbital of Y .....	57
17. Complexes ( <b>65a</b> , <b>65b</b> and <b>65c</b> ) .....	67

## LIST OF FIGURES-CONTINUED

Figure	Page
18. Proligand <b>69a</b> and <b>69b</b> .....	71
19. Asymmetric Proligands <b>71,72,73a-c</b> .....	75

## LIST OF SCHEMES

Scheme	Page
1. Preparation of Lanthanocenes (7).....	8
2. Relative Catalytic Activities toward Hydroamination .....	8
3. Proposed Mechanism for Hydroamination of Aminoalkenes .....	14
4. Rationalization of Diastereoselectivity in the Cyclization.....	16
5. Group 4 Metal Alkyl Mediated Aminoalkyne Cyclizations .....	17
6. Synthesis of Aminoalkenes <b>15a,b,c</b> .....	19
7. Synthesis of Aminoalkene <b>15d</b> .....	20
8. Synthesis of Aminoalkenes <b>15e,f</b> .....	21
9. Comparison of the Catalytic Activities .....	23
10. Comparison of Catalytic Activities.....	26
11. Catalytic Activity of $Y[N(TMS)_2]_3$ in Bicyclization.....	27
12. Proposed Mechanism for Ligand Exchange Reaction .....	31
13. Synthesis of Proligand <b>22</b> .....	32
14. Synthesis of Proligand <b>23</b> and <b>25b</b> .....	32
15. Synthesis of Proligand <b>24</b> .....	33
16. Synthesis of Proligand <b>25</b> .....	34
17. Synthesis of Proligand <b>24</b> .....	34
18. Synthesis of Aminoalkene <b>44</b> .....	35
19. Synthesis of Aminoalkene <b>47</b> .....	36

## LIST OF SCHEMES - CONTINUED

Scheme	Page
20. Synthesis of Aminoalkene <b>50</b> .....	37
21. Catalysts <b>27b-d</b> , <b>27h-j</b> .....	42
22. Hydroamination by Catalyst <b>28b</b> , <b>27h</b> or <b>29b</b> .....	44
23. Catalyzed Cyclization of 2-Aminohex-5-ene ( <b>15e</b> ) .....	44
24. Lanthanocene Catalyzed Cyclization of <b>41</b> .....	48
25. Synthesis of Proligand <b>59e</b> .....	52
26. Cyclization of <b>15e</b> Catalyzed by <b>64a</b> , <b>67</b> or <b>68</b> .....	60
27. Cyclization of <b>15e</b> Catalyzed by <b>65a</b> or <b>66a</b> .....	62
28. Cyclization of <b>15e</b> Catalyzed by <b>63</b> or <b>66d</b> .....	63
29. Cyclization of <b>15e</b> Catalyzed by <b>66e</b> or <b>66f</b> .....	67
30. Catalyzed Hydroamination of aminoalkene <b>15e</b> .....	72
31. Synthesis of Proligand <b>71a</b> .....	77
32. Synthesis of Proligand <b>71b</b> .....	77
33. Synthesis of Proligand <b>72</b> .....	78
34. Synthesis of Proligands <b>73a</b> , <b>73b</b> .....	79
35. Synthesis of Intermediate <b>76c</b> for Proligand <b>73c</b> .....	79
36. Substituent Effect on Enantioselective Hydroamination .....	82
37. Comparison of Catalytic Asymmetric Aminoalkene Hydroaminations .....	83

## LIST OF SCHEMES – CONTINUED

Scheme	Page
38. Pseudo-Chair Seven Membered Transition States in the Cyclization of 2,2-Dimethylaminopen-4-ene by <b>80</b> .....	84
39. Rationalization of the Enantioselectivity in the Cyclization of 2,2-Dimethylaminopen-4-ene by <b>80</b> .....	84



## ABBREVIATIONS

<i>n</i> -BuLi	<i>n</i> -butyllithium
bp	boiling point
CaH <sub>2</sub>	calcium hydride
CH <sub>2</sub> Cl <sub>2</sub>	methylene chloride
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
DMF	dimethyl formamide
Et <sub>3</sub> N	triethylamine
EtOH	ethanol
Et <sub>2</sub> O	diethyl ether
HCl	hydrochloric acid
LiAlH <sub>4</sub>	lithium aluminum hydride
MgSO <sub>4</sub>	magnesium sulfate
mp	melting point
Ms	methanesulfonate
NaHCO <sub>3</sub>	sodium bicarbonate
NaBH <sub>4</sub>	sodium borohydride
NaOH	sodium hydroxide
NH <sub>4</sub> Cl	ammonium chloride
NH <sub>2</sub> OH·HCl	hydroxylamine hydrochloride
Ph	phenyl
THF	tetrahydrofuran
TsCl	<i>p</i> -toluenesulfonyl chloride
Ts	<i>p</i> -toluenesulfonate

## ABSTRACT

Metallocene-based Group 3 metal complexes; lanthanocenes, have intrinsic problems for use as a universal catalysis. For example, preparations of most complexes are complicated, and most lanthanocenes are extremely sensitive to air and water and have structural limitation on variation.

The first application of non-metallocene-based Group 3 metal catalysts to intramolecular aminoalkene cyclizations has been achieved. Simple amido lanthanide complexes of the type  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  ( $\text{Ln} = \text{Y}, \text{Nd}$ ) have been found to be competent catalysts for this reaction, which have similar or superior activity in cyclization including diastereoselectivity to the lanthanocenes. Modification of the metal center in  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  ( $\text{Ln} = \text{Y}, \text{Nd}, \text{La}$ ) has been readily achieved by amine elimination in the presence of hindered chelating diamines, bis(thiophosphinic) amines, or bis(thioenamides) in situ, to provide new Group 3 amido chelates. These complexes have shown remarkably improved catalytic activities and stereoselectivities [e.g., 33:1 (*trans/cis*)] in the cyclization of 2-aminohept-5-ene. An X-ray crystallographic structure of one of the bis(thiophosphinic amide)-based Group 3 metal complexes has been defined. Chiral lanthanide complexes have been implemented for enantioselective hydroamination reactions. The  $C_2$  symmetric catalysts exhibit good enantioselectivity in the cyclization of 1-amino-2,2-dimethylpent-5-ene, as high as 66% enantiomeric excess at 10 °C.

These non-metallocene-based Group 3 metal complexes have shown superiority in terms of preparation, thermal stability, and catalytic activity over lanthanocenes in the hydroamination of aminoalkenes. In addition, the amido complexes should allow for a variety of ligand derivatives.

## CHAPTER 1

## INTRODUCTION

Among bond-forming processes, metal-catalyzed reactions are considered to be one of the most useful methods due to their unique efficiency and selectivity in molecular construction. Metal-catalyzed chemistry for the formation of carbon-carbon or carbon-hydrogen bonds has been well established by numerous studies.<sup>1</sup>

Many physiologically active substances contain carbon-oxygen or carbon-nitrogen bonds. The metal-catalyzed intramolecular hydroamination of carbon-carbon multiple bonds has come to be recognized as one of the most powerful methods for the synthesis of azacyclic intermediates.<sup>2</sup> However, organometallic-catalyzed formations of carbon-heteroatoms, particularly carbon-nitrogen bonds, are still rare.<sup>2</sup> In particular the efficient hydroamination of aliphatic alkenes remains among the most important challenges for catalysis research.

To date, various synthetic methods for the amination of C-C multiple bonds have been developed in two basic synthetic approaches, activation of nucleophilic amines and activation of electrophilic alkenes. Hydroamination via addition of nucleophilic amines to alkenes activated by groups such as keto, ester, nitrile, sulfoxide, and nitro<sup>3</sup> are generally useful for the synthesis of nitrogenous compounds. On the other hand, nonactivated alkenes are mostly promoted by late-transition metal complexes. An electrophilic transition metal complex such as Fe(II), Pd(II), Pt(II), Hg(II), Mo(II), or W(II) promotes

the electrophilicity of alkenes toward the nucleophilic attack of amines. In this case, however, a stoichiometric amount of metal complex is often required: because of the high affinity of amines to transition metals, they have tendency toward displacement of coordinated alkenes rather than nucleophilic attack.<sup>4</sup>

The activation of amines can be accomplished by an alkali metal such as Li or Na, but the hydroamination frequently incurs a side reaction, especially polymerization.<sup>2</sup> Early- and late-transition metals also competently activate amines toward catalytic hydroamination reactions. Whereas early-transition metal activate amines via the formation of amido complex, late-transition metal activate amines via oxidative addition of the amine to the metal center, followed by insertion of the alkyne or alkene into the M-N bond.<sup>5d</sup> However, nucleophilic addition of the amine to alkyne or alkene activated by metal coordination, is also a possible pathway proposed for late-transition metal catalysis.<sup>6</sup> Recently, catalytic hydroamination using titanium,<sup>7</sup> rhodium,<sup>5</sup> palladium<sup>5c, 6</sup> and nickel,<sup>8</sup> have been reported. However, most of the reactions catalyzed by transition metals utilize 1,3-dienes, styrenes, aminoalkynes, aminoallenes or deactivated nucleophiles such as anilines or sulfonamides to reduce the coordination strength of amine to metal cation.<sup>9, 10</sup> From a thermodynamic point of view, insertion of alkenes into the metal-nitrogen bond is more difficult due to approximately 29 kcal/mol and >35 kcal/mol less exothermic than that of allenes and alkynes, respectively.<sup>11,12,13</sup> In general, alkynes are more reactive than alkenes in metal catalyzed amination reactions because of

the sterically less hindered cylindrical  $\pi$ -system as well as more nucleophilic *sp*-hybridized C-atoms to be better  $\pi$ -donors.<sup>14</sup>

Of the variety of metal-based catalysts, complexes of lanthanide appear very well suited for effecting chemoselective, diastereoselective and enantioselective alkene hydroaminations under mild reaction conditions.<sup>11,15</sup> However, the development of lanthanide chemistry for hydroamination has progressed slowly and is in its initial stages today. Most of the complexes developed to date are metallocene-based and have various problems to overcome such as preparation of catalysts and stability with respect to thermal conditions and air. Overall, lanthanocenes have been quite limited in variety.

This dissertation describes the first non-metallocene-based Group 3 metal catalysts developed for hydroamination. In a historical context, the X-ray crystallographic structure of tetradentate ligand based complex **63** and the preliminary results that established its catalytic activity in aminoalkene hydroamination originally preceded the discovery of  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  activity. These results were obtained by Professor Tom Livinghouse at Caltech. Since the detailed experiments on the simple amides were performed first, these results will be described prior to the discussion of the NPA series. Thus, the first part of this dissertation will discuss the catalytic activity of simple amido complexes for intramolecular alkene hydroaminations. The second section will describe dramatically improved catalytic activities as well as the diastereocontrol of Group 3 metals by coordination with non-metallocene bidentate ligands. Another type of non-metallocene-based Group 3 metal complex and its catalytic activities will be described in

the third section. In the last part, the catalyzed enantioselective hydroamination reaction will be discussed briefly.

## BACKGROUND

All *f*-block element ions, from  $_{57}\text{La}$  to  $_{71}\text{Lu}$ , have the trivalent oxidation state as their the most stable state. In the strict sense, scandium and yttrium are *d*-block elements, but these are generally classified with the lanthanides because of their chemical similarities, as is lanthanum that does not have a *4f* electron.<sup>16</sup> Lanthanides and transition metals have quite different chemical properties. While transition metals, which characteristically have full *d*-type (*n*-1) orbitals, often result in a coordinate covalent bonding with a ligand, organolanthanide complexes have a mainly ionic character and behave as typical hard acids. Due to the lanthanide contraction of the *4f* orbitals and the well-shielded environment by the *5s* and *5p* orbitals, the *f* orbitals have little interaction with ligand orbital resulting minimized ligand field stabilization effects (LFSE). The poor overlap with the ligand orbitals contributes to the predominantly ionic character, which causes the strong oxophilicity of the lanthanide cation. Furthermore, lanthanides have noticeably larger ionic radii and a greater flexibility in geometry and coordination numbers than transition metals, so their coordination numbers are usually eight, ten, or twelve.

Since three coordinate organolanthanides  $[\text{Ln}\{\text{N}(\text{TMS})_2\}_3]$  ( $\text{Ln} = \text{La}, \text{Ce}, \text{Pr}, \text{Nd}, \text{Sm}, \text{Eu}, \text{Gd}, \text{Ho}, \text{Y}, \text{Yb}, \text{Lu}$ ) (**1**), which are coordinatively highly unsaturated complexes, were synthesized by Bradley and co-workers in 1973,<sup>17</sup> many Group 3 complexes have been developed and their catalytic activity investigated for chemical reactions.<sup>2, 18</sup>

Organolanthanides are known to be among the most suitable catalysts for Ziegler-Natta-type polymerization.<sup>19</sup> In addition, organolanthanides exhibit unique characteristics as catalysts in hydrogenation,<sup>19f,20</sup> oligomerization,<sup>21</sup> hydroamination,<sup>15c,22</sup> hydrosilylation,<sup>23</sup> hydroboration,<sup>24</sup> and hydrophosphination.<sup>25</sup>

Although the first organolanthanide-catalyzed hydroamination reactions were described by Marks and co-workers in 1989,<sup>22j</sup> only nine types of catalysts have been reported to date. In the initial study, they used  $[\text{Cp}_2^*\text{LnR}]$  (**2**),  $[\text{Me}_2\text{SiCp}^*_2\text{LnR}]$  (**3**) and  $[\text{Et}_2\text{SiCp}^*\text{CpLnR}]$  (**4**) complexes, which have also proven their catalytic activity for polymerization, hydrogenation, and oligomerization.<sup>19,20,21</sup> Complexes **3** and **4** are sterically more open structures due to the silyl linkage and therefore have much higher

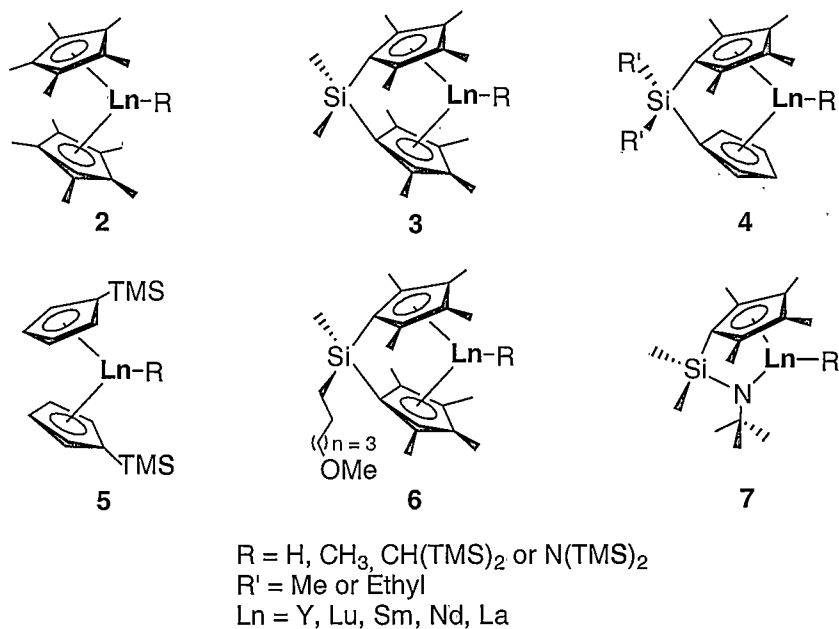


Figure 1. Catalysts Developed for Hydroamination

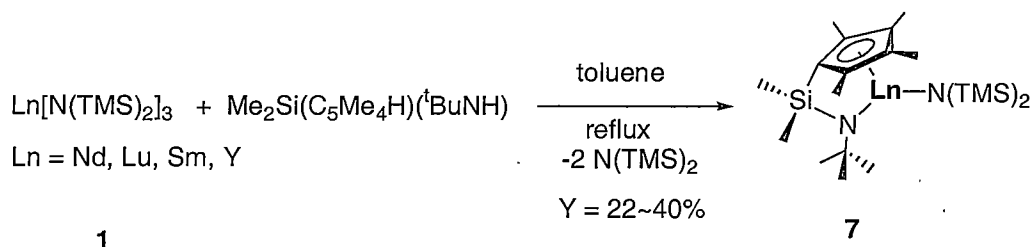


catalytic activity towards aminoalkene hydroaminations than  $[\text{Cp}_2^*\text{LnR}]$  (**2**). Among this series of complexes (**2**, **3** and **4**),  $[\text{Et}_2\text{SiCp}^*\text{CpLnR}]$  (**4**) exhibits the highest activity.<sup>22i</sup>

The sterically bulky trimethylsilyl group has been introduced onto the cyclopentadienyl units to open the reactive metal center for interaction with olefins. The  $[\text{Cp}^{\text{TMS}}_2\text{LnMe}]_2$  ( $\text{Ln} = \text{Y}, \text{Sm}, \text{Nd}$ ) (**5**) complexes have shown excellent catalytic activity for 1,1-disubstituted aminoalkenes. However, the  $\text{Cp}^{\text{TMS}}$ -based complexes still have lower activity in the cyclization than the  $\text{Me}_2\text{SiCpCp}^*$ -based complexes.<sup>15c</sup> Recently, a new series of constrained-geometry organolanthanide  $[\text{Me}_2\text{SiCp}^*(\text{t-BuN})\text{LnR}]$  (**7**) catalysts has been developed.<sup>15b</sup> These complexes afford significantly enhanced catalytic activity, with an increase in turnover numbers per hour of up to 30-fold over the  $\text{Cp}^*$  ligand arrays. The silyl-linked amido cyclopentadienyl ligand  $[\text{Me}_2\text{SiCp}^*(\text{t-BuN})]^{2-}$ , which was originally developed for Sc,<sup>26</sup> makes a 12-electron  $[\text{R} = \text{CH}(\text{TMS})_2]$  or 14-electron  $[\text{R} = \text{N}(\text{TMS})_2]$  system complex by donating 8 electrons to the Group 3 metal. Accordingly, it makes electronically more unsaturated complexes than typical  $\text{Cp}^*_2\text{LnR}$  complexes which make a 14-electron  $[\text{R} = \text{CH}(\text{TMS})_2]$  or 16-electron  $[\text{R} = \text{N}(\text{TMS})_2]$  system. In addition, it has a sterically more favored structure for coordination of aminoalkenes.<sup>22a</sup>

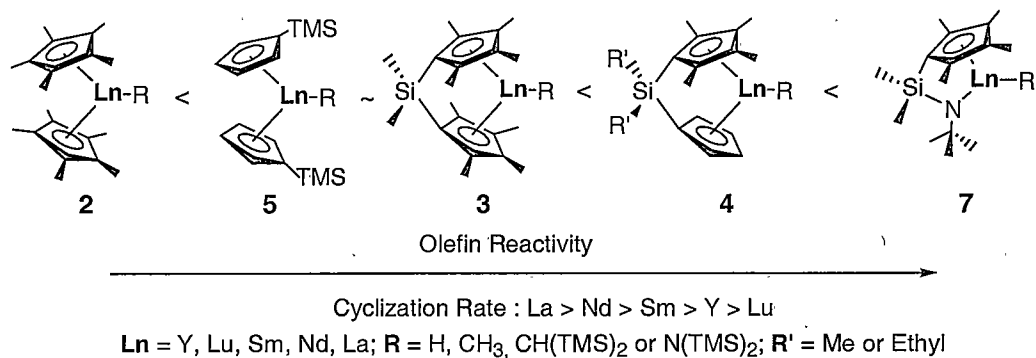
As with other lanthanocenes, however, the preparation of these complexes is very complicated and the synthetic yields are low (22-49%). Examples include Nd (24%), Lu (32%), Sm (22%) and Y (40%). As shown in Scheme 1, complex **7** is prepared using  $\text{LnR}_3$   $[\text{R} = \text{N}(\text{TMS})_2]$  and  $\text{Cp}^*\text{HSiNHt-C}_4\text{H}_9$  at 110°C in toluene. However, to complete

the reaction, periodic removal of  $\text{HN}(\text{TMS})_2$  from the system, by evacuating the vessel to dryness, reintroducing solvent, and continuing heating, was required.



Scheme 1. Preparation of Lanthanocenes (7)

A methoxy group was introduced into  $[\text{MeO}(\text{CH}_2)_5(\text{Me})\text{SiCp}^*_2]\text{YCH}(\text{SiMe}_3)_2$  (6) to investigate the effect of a Lewis base.<sup>20a</sup> However, the methoxy group decreased the catalytic activity of the complex in both diastereocontrol and the rate of cyclization. For sterically less hindered simple aminoalkenes, the order of catalytic activity of the



Scheme 2. Relative Catalytic Activities Toward Hydroamination

lanthanocenes is  $2 < 5 \sim 3 < 4 < 7$  <sup>15c,22a,h,i</sup> (Scheme 2). However, for sterically more hindered aminoalkenes, such as 1,1-disubstituted and 1,2-disubstituted aminoalkenes, the lanthanocenes have different orders of activity dependent upon substrate. As summarized in Scheme 2, the rate of cyclization increases when the Cp\* ligands are changed to the Me<sub>2</sub>SiCp\*<sub>2</sub> system or when a lanthanide metal with a larger ionic radius is employed. <sup>22h,i</sup>

In addition to C<sub>2</sub> (**2,3** and **5**) and C<sub>s</sub>-symmetric lanthanocenes (**7**), two types of chiral C<sub>1</sub>-symmetric catalysts (**8, 9**) have been utilized for the asymmetric aminoalkene hydroamination reaction (Figure 2). In both cases, a chiral auxiliary is introduced onto the cyclopentadienyl unit. Complex **8** (Ln = Sm) afforded up to 74% enantioselectivity at 30 °C (the turnover number, N<sub>t</sub> (h<sup>-1</sup>), is not available) in the cyclization of 1-amino-2,2-dimethylpen-5-ene. <sup>22g</sup> Chiral C<sub>1</sub>-symmetric catalyst of the type [Me<sub>2</sub>Si(η<sup>5</sup>-OHF)(η<sup>5</sup>-C<sub>5</sub>H<sub>3</sub>R\*)YN(SiMe<sub>3</sub>)<sub>2</sub>] (**9**) [OHF = octahydrofluorenyl; R\* = (-)-menthyl] exhibits 67%

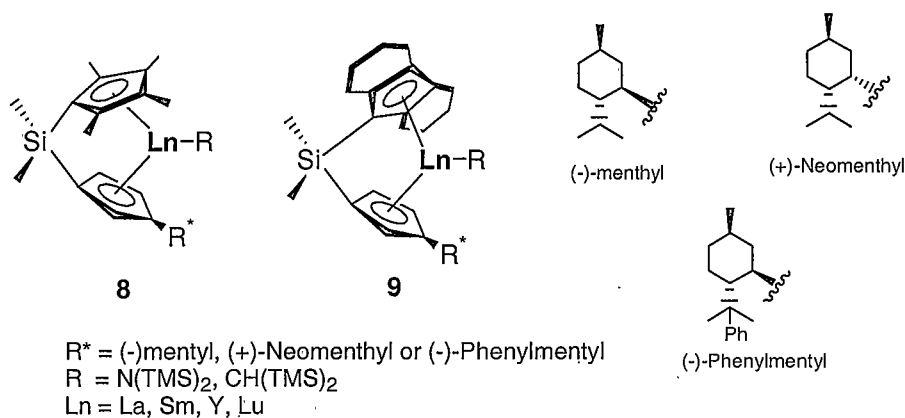


Figure 2. Asymmetric Catalysts for Hydroamination

(+) enantioselection at 25 °C [ $N_t$  ( $h^{-1}$ ) = 2.1] in the cyclization of 1-amino-2,2-dimethylhex-5-ene to provide (+)-2,5,5-trimethylpiperidine.<sup>27</sup>

On the other hand, Broene and co-workers have explored a new ligand system other than the Cp\* class in the intramolecular aminoalkene hydroamination reaction. Even though 1,2-bis (indenyl) ethane-derived lanthanocene **10** has moderate catalytic activity, it is more difficult to synthesize than the Cp\* systems. In addition, it has no particular merits in the cyclization reactions.<sup>28</sup>

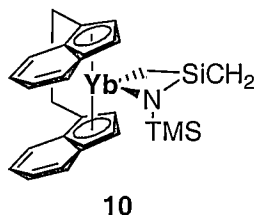


Figure 3. Another Type of Lanthanocene

Lately, as a substitution for the cyclopentadienyl unit, aminotroponimines ([ATI]-), which are known to stabilize coordinatively unsaturated main group metal

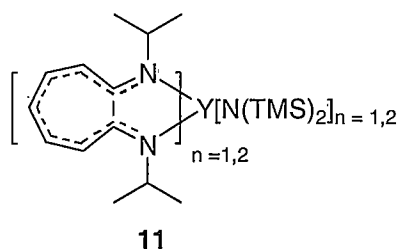


Figure 4. The First Non-metallocene-Based Early-Metal Catalysts for Hydroamination

complexes,<sup>29</sup> have been introduced for group 3<sup>3a</sup> and group 4 metals.<sup>30</sup> Roesky and co-workers have explored these complexes as the first non-metallocene-based Group 3 metal catalysts for intramolecular aminoalkyne hydroamination.<sup>31</sup> Unfortunately, the complexes have no catalytic activity for the aminoalkene cyclization reaction. These complexes have shown very little activity towards the hydroamination of aminoalkynes.

Various aminoalkene substrates have been examined for the generality and scope of the reaction catalyzed by organolanthanocenes. In this dissertation, the hydroamination reactions for aminoalkynes and aminoallenes are not reviewed. Using lanthanocene catalysts, the intramolecular alkene hydroamination reactions have created five-, six-, and seven-membered nitrogenous rings. The rates of cyclization of aminoalkenes are dependent on the ring size, in the order  $5 > 6 \gg 7$ . Even 1,1- (Table 1, Entries 5-7) and 1,2-disubstituted aminoalkenes (Table 1, Entries 8-10 and 12) lead to cyclization reactions. Among these substrates, 1,2-disubstituted aminoalkenes are the least reactive toward cyclization. Meanwhile, 2,2-dimethyl substituent on the aminoalkenes accelerates cyclization, through the Thorpe-Ingold effect,<sup>32</sup> when compared to unsubstituted substrates under similar conditions. On the other hand, organolanthanocene catalysts have shown 1000 times lower activity in the intermolecular hydroamination reaction than in the intramolecular version.<sup>18,33</sup> The scope of hydroamination reactions has been successfully expanded to bicyclic and bridged bicyclic amines. In some cases, however, the cyclization reactions require a larger catalyst loading, higher temperatures and longer

reaction times. For example, the preparation of 1-aza-2,2,5-trimethylbicyclo [3.3.0] octane was found to proceed with 41 mol% of  $[\text{Cp}^{\text{TMS}}_2\text{NdMe}]_2$  (**5**) at 120 °C for seven days (yield 53%) [Table 2, Entry 3].<sup>15c</sup>

Table 1. Substrates Utilized for Hydroamination

Entry <sup>ref.</sup>	Substrate	Product	Entry <sup>ref.</sup>	Substrate	Product
1 <sup>15d</sup>			8 <sup>15q</sup>		
2 <sup>15d</sup>			9 <sup>5q</sup>		
3 <sup>15d</sup>			10 <sup>5q</sup>		
4 <sup>15d</sup>			11 <sup>22i</sup>		
5 <sup>15c</sup>			12 <sup>15a</sup>		
6 <sup>15c</sup>			13 <sup>15d</sup>		
7 <sup>15c</sup>			14 <sup>22i</sup>		

Organolanthanide catalysis allows exquisite construction of nitrogenous natural products with high selectivity and efficiency. To date, two natural products have been

synthesized via organolanthanide-catalyzed intramolecular hydroamination by Molander and co-workers. A total synthesis of the alkaloid (-)-Pininol was performed in 10 steps with 19% overall yield to an enantiomeric purity in excess of 99.9+% using  $\text{Cp}^*_2\text{NdCH}(\text{TMS})_2$  (**2**).<sup>34</sup> This brief and efficient synthetic strategy has also been applied to the synthesis of MK-801. The potent anticonvulsant and neuroprotective agent MK-801<sup>35</sup> was synthesized with a 38% overall yield using the lanthanocene  $[\text{Cp}^{\text{TMS}}\text{NdMe}]_2$  (**5**) for the hydroamination reaction.<sup>36</sup>

Table 2. Substates Utilized for Bicyclization

Entry <sup>ref</sup>	Substrate	Product	Entry <sup>ref</sup>	Substrate	Product
1 <sup>22c</sup>			5 <sup>15c</sup>		
2 <sup>22c</sup>			6 <sup>15c</sup>		
3 <sup>15c</sup>			7 <sup>15c</sup>		
4 <sup>15c</sup>			8 <sup>15c</sup>		

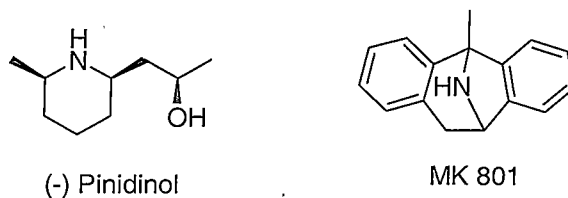
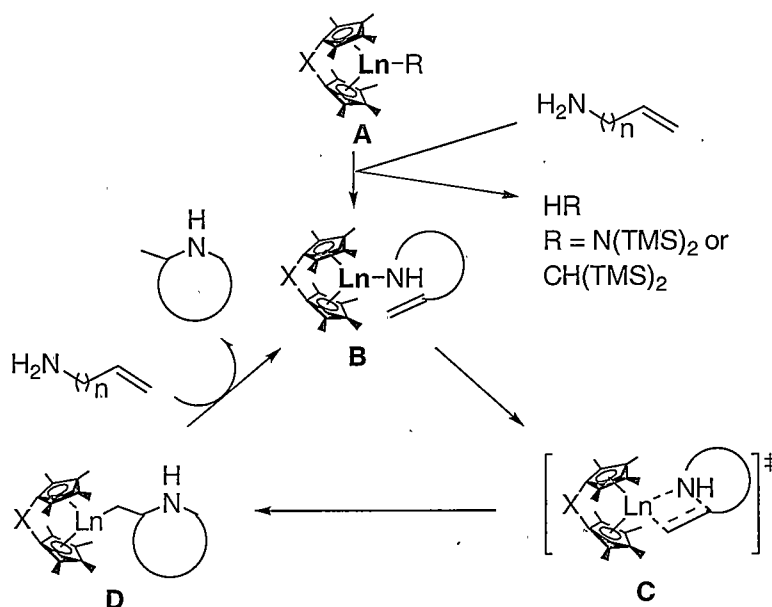


Figure 5. Natural Products Synthesized via Hydroamination

A characteristic feature of many lanthanide catalyzed reactions is the absence of accessible metal oxidation states for oxidative addition and reductive elimination processes. This implies that an addition is favorable for the reaction of alkenes/alkynes with the metal-nitrogen bond in catalytic hydroaminations. The proposed mechanism (Scheme 3),<sup>2,22e,g,h</sup> which is a similar process to the other catalytic cycles, has been

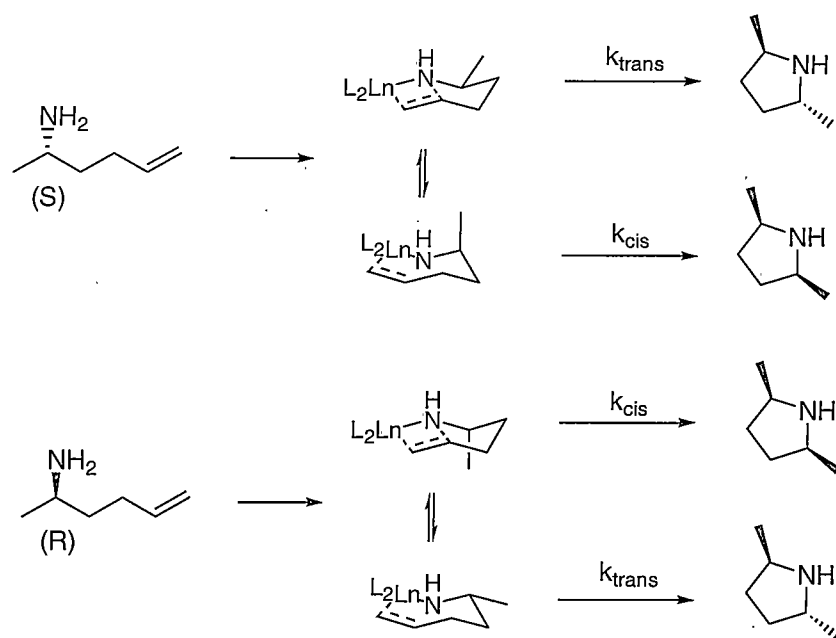
Scheme 3. Proposed Mechanism for Hydroamination of Aminoalkenes





established based on extensive kinetics studies.<sup>22h</sup> The precatalysts undergo rapid M-R bond metathesis by the amine. This protonolysis generates quantitative amido complexes or mixed amino-amide adducts as the resting state of the catalytic cycle (**B**).<sup>22e,g</sup> In the rate-determining step (**C**), the intramolecular olefin inserts into the M-N bond via a four-centered transition state has been proposed.<sup>2,22h</sup> This sterically demanding transition state creates a more sterically open lanthanide complex with a large-sized metal than with a small one. Accordingly, it will make a favorable olefin insertion into M-N bond and increase the reaction rate. Rapid protonolysis of the resulting M-C bond (**D**) by another amine regenerates the catalytically active Group 3 amido complex with liberation of the cyclic amine product. Kinetic analysis of the cyclization of aminoalkenes shows that the rate dependence is first-order in catalyst concentration and zero-order in substrate over at least three half-lives:  $v = k[\text{catalyst}]^1[\text{substrate}]^0$ .<sup>2,2h</sup>

The diastereoselectivity of products was rationalized based on the presumed catalyst-substrate steric interactions in the transition state (Scheme 4). In the case of 2-aminohex-5-ene (Table 1, Entry 3), the sterically more demanding axial methyl conformation may raise nonbonded interactions with the metal coordination sphere. So, a pseudo-chair seven-membered transition state favors an equatorial methyl conformation to afford the *trans* product. In comparison, 2-methylaminopent-4-ene (Table 1, Entry 4) is sterically less sensitive concerning diastereoselection by making a pseudo-chair seven-membered transition state, in which the methyl substituent is one more position distant from the sterically demanding metal center.



Scheme 4. Rationalization of Diastereoselectivity in the Cyclization

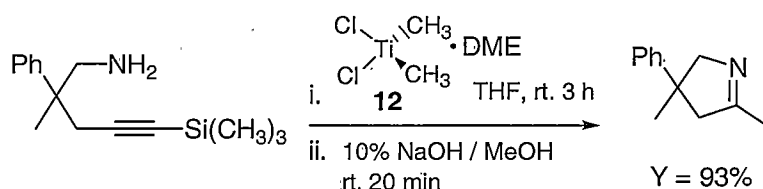
Even though organolanthanide-catalyzed intramolecular hydroamination reactions were initially explored using lanthanocenes, the complexes have several disadvantages to overcome. For example, preparation of precatalysts is complicated and the synthetic yields are generally low. In addition, most lanthanocenes are extremely sensitive to air and unstable with respect to temperature. Overall, lanthanocenes have structural limitations on variation for the further development of lanthanide chemistry

## CHAPTER 2

## INTRAMOLECULAR ALKENE HYDROAMINATIONS CATALYZED BY SIMPLE AMIDO DERIVATIVES OF THE GROUP 3 METALS

## INTRODUCTION

Recently, the Livinghouse group has found that simple, non-metallocene-based Group 4 metal alkyls (**12**) have excellent activity towards aminoalkyne cyclizations (Scheme 5).<sup>38</sup>



Scheme 5. Aminoalkyne Cyclizations Mediated by Group 4 Metal Alkyl

Based on these results, preliminary studies toward the development of non-metallocene-based Group 3 metal catalysts were conducted by Professor Livinghouse that demonstrated catalytic activity for NPS-type Group 3 metal complexes and  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  in aminoalkene hydroaminations. Subsequently, we decided to first perform the detailed investigation with readily available  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  complexes for the efficient development of non-metallocene Group 3 catalysts.

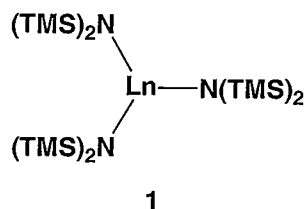
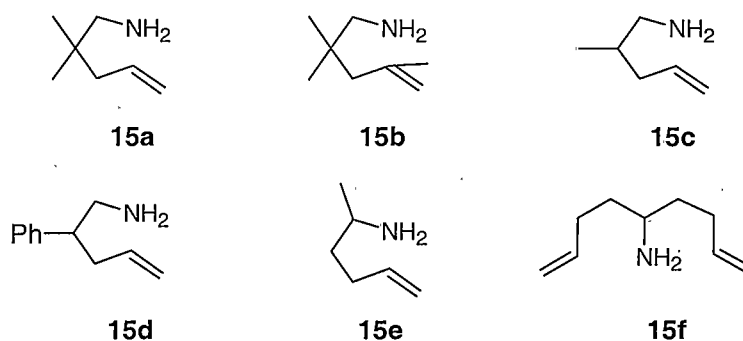


Figure 6. The First Three-Coordinated Lanthanide Complexes

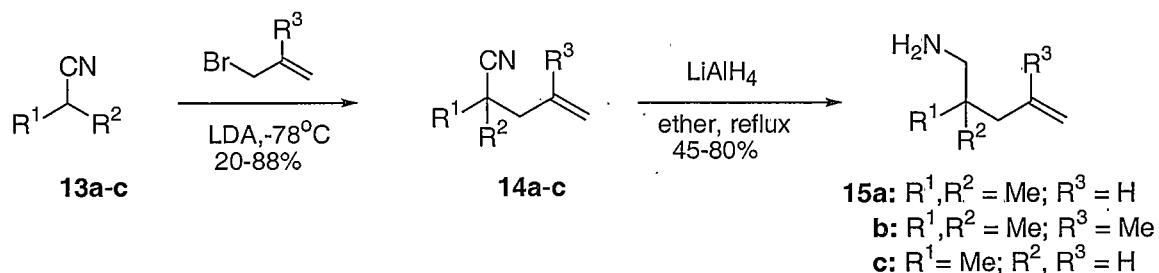
The  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  (1) species were the first three-coordinate lanthanide complexes and were prepared by Bradley and co-workers in 1973.<sup>17</sup> These complexes have an electronically unsaturated 12-electron system. As previously mentioned, over the last decade  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  complexes were utilized only as starting materials for the preparation of organolanthanocenes via a tedious procedure, and the latter are more sensitive to air and thermally unstable than the  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  complexes. Interestingly, the simple amido complexes  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  were never investigated as catalysts for the intramolecular hydroamination reaction.

## SYNTHESIS OF SUBSTRATES

Initially, six representative aminoalkenes (**15a-f**) were prepared according to literature procedures as shown in Schemes 6, 7, and 8.<sup>15c,39</sup> Among them, aminoalkenes **15c,d,e** and **f** were specifically assessed in diastereoselectivity studies.

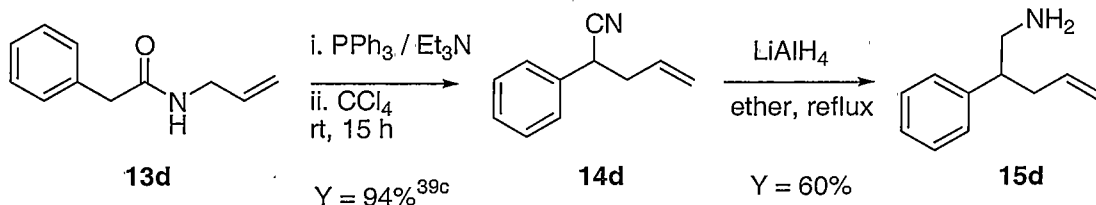
Figure 7. Aminoalkenes **15a-f**

Aminoalkenes **15a-c** were prepared by the method described in Scheme 6. Various alkenyl halides were alkylated with lithiated nitriles generated by the reaction

Scheme 6. Synthesis of Aminoalkenes **15a,b,c**

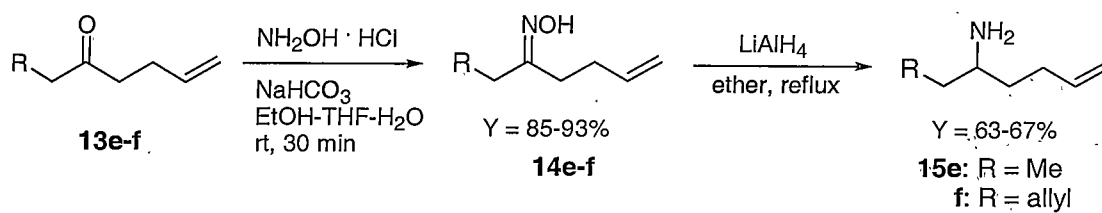
with lithium diisopropylamine (LDA) at  $-78^{\circ}\text{C}$  in 20-88% yield. The resulting nitriles **14a-c** were reduced with lithium aluminum hydride in ethyl ether followed by heating at reflux to provide the corresponding aminoalkenes **15a-c** in 45-80% yield.

As shown in Scheme 7, **14d** was prepared according to literature procedure<sup>39c</sup> from **13d** via a 3-Aza-Cope rearrangement. The nitrile **14d** was reduced by lithium aluminum hydride to provide the aminoalkene **15d** in 60% yield.



Scheme 7. Synthesis of Aminoalkene **15d**

2-Amino-hex-5-ene **15e** and 1-but-3-enyl-pent-4-enylamine (**15f**) were prepared by the method described in Scheme 8. Treatment of **13e** or **13f** with two equivalents of hydroxylamine hydrochloride in ethanol/tetrahydrofuran/water (4:2:1), followed by addition of sodium bicarbonate, afforded oxime **14e** or **14f** in 85% and 93% yield, respectively. Then, further conversion to aminoalkene **15e** or aminodiene **15f** was provided by the reduction with lithium aluminum hydride.

Scheme 8. Synthesis of Aminoalkenes **15e,f**

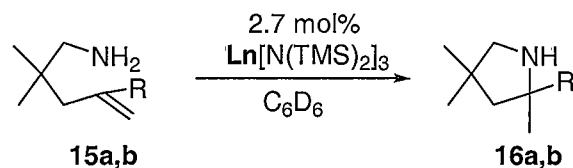
Each of these aminoalkenes was distilled from  $\text{CaH}_2$  under an atmosphere of argon and stored in a dry box prior to hydroamination reactions.

INTRAMOLECULAR ALKENE HYDROAMINATIONS CATALYZED BY  
Ln[N(TMS)<sub>2</sub>]<sub>3</sub>

Our preliminary survey focused on the evaluation of Y[N(TMS)<sub>2</sub>]<sub>3</sub> (**1a**) and Nd[N(TMS)<sub>2</sub>]<sub>3</sub> (**1b**).<sup>40</sup> Among Group 3 metals, yttrium and neodymium were selected as representative smaller- and larger-sized lanthanides, respectively. The ionic radii of Y(III) and Nd(III) are 1.040 Å and 1.123 Å, respectively, in 6-coordinate complexes.<sup>41</sup>

As revealed in Table 3 and Table 4, Ln[N(TMS)<sub>2</sub>]<sub>3</sub> (**1**) complexes were shown to have excellent catalytic activity in intramolecular alkene hydroamination reactions. Aminoalkene **15a** cyclized smoothly to **16a** with 2.7 mol% of Nd[N(TMS)<sub>2</sub>]<sub>3</sub> in C<sub>6</sub>D<sub>6</sub> at 24°C in 4 h (>95 % yield), and with Y[N(TMS)<sub>2</sub>]<sub>3</sub> at 24°C in 6 h. The size of the metal

Table 3. Ln[N(TMS)<sub>2</sub>]<sub>3</sub> (**1**) Catalyzed Cyclization of Aminoalkenes **15a,b**



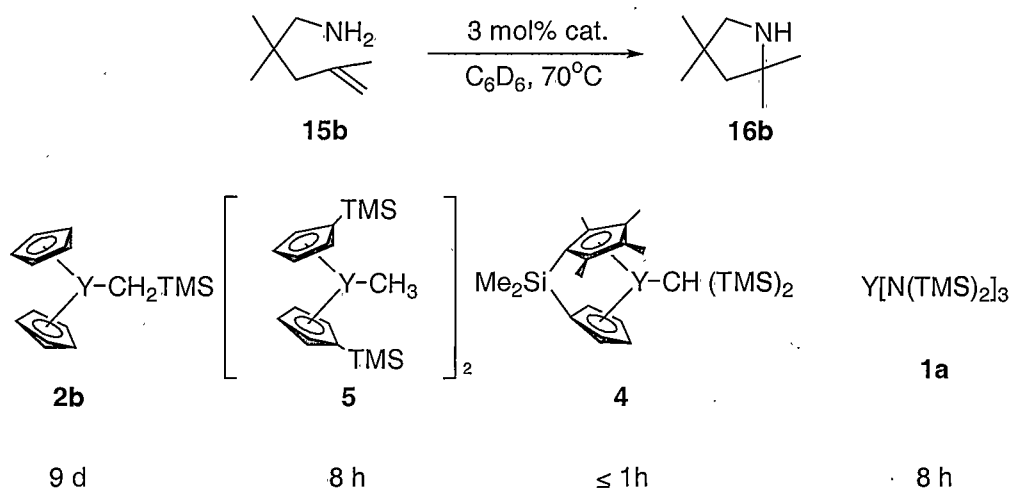
	R	Ln	Temp (°C)	t <sub>React.</sub> <sup>a</sup>	Conv. [%] <sup>b</sup>
<b>15a</b>	H	Y	24	6 h	>95%
	H	Nd	24	4 h	>95%
<b>15b</b>	Me	Y	45	45 h	93 (80) <sup>c</sup> %
	Me	Y	70	8 h	94% <sup>d</sup>

<sup>a</sup> All reactions were conducted in C<sub>6</sub>D<sub>6</sub>. <sup>b</sup> Based on <sup>1</sup>H NMR integration. <sup>c</sup> Isolated yield as a *p*-toluenesulfonamide. <sup>d</sup> 3 mol% of catalyst was utilized.



did have an effect.<sup>22h</sup> The larger-metal neodymium complex furnished the cyclized product with a faster reaction rate than the smaller yttrium complex, which is in accord with the observations of the organolanthanocene-catalyzed cyclization.<sup>22h</sup>

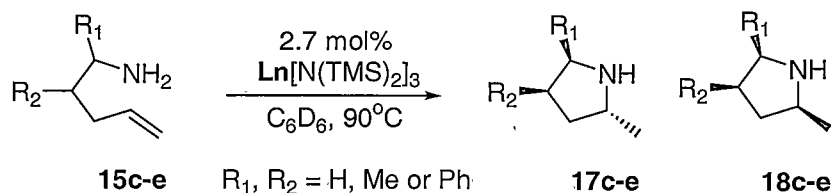
The simple amido Group 3 metal complexes exhibited excellent catalytic activities even with more hindered aminoalkenes such as **15b**. Aminoalkene **15b**, which has a protertiary center, was subjected to 3.0 mol% of  $Y[N(TMS)_2]_3$  complex to afford 2,2-disubstituted pyrrolidine **16b** at 70°C in 8 h in 94% yield. On the other hand, cyclization using organolanthanocenes,  $Cp_2YCH_2TMS$  (**2b**),  $[Cp^{TMS}_2YMe]_2$  (**5**) or  $Me_2SiCpCp^*YCH(TMS)_2$  **4**, requires 9 d, 8 h, or  $\leq 1$  h, respectively,<sup>15c</sup> under the same reaction conditions (Scheme 9).



Scheme 9. Comparison of Catalytic Activities

The diastereocontrol of these  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  complexes was investigated using aminoalkenes **15c,d,e** [Table 4]. In the case of **15e**, a highly diastereoselective cyclization was realized with  $\text{Y}[\text{N}(\text{TMS})_2]_3$  **1a** at  $90^\circ\text{C}$  to provide >95% yield in a ratio of 7:1 (*trans/cis*) in 6 d, whereas a 4:1 ratio of diastereoselectivity was obtained with  $\text{Nd}[\text{N}(\text{TMS})_2]_3$  **1b** at  $90^\circ\text{C}$  in 2 d. However, the cyclizations of C2-substituted aminoalkenes **15c** and **15d** proceeded with relatively low diastereoselectivity (1:1.7~2.2 = *trans/cis*). Moreover, the cyclization of aminoalkene **15c** and **15d** were insensitive to

Table 4.  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  (**1**) Catalyzed Cyclization of Aminoalkenes **15c, d, e**



Substrate	Ln	$t_{\text{React.}}^a$	Product	dr ( <i>trans/cis</i> ) <sup>b</sup>	Conv. (%) <sup>b</sup>
<b>15c</b>	<b>Y</b>	10 d	+ <i>cis</i>	1 : 2	>95
	<b>Nd</b>	7 d		1 : 2	>95
<b>15d</b>	<b>Y</b>	1.5 h	+ <i>cis</i>	1 : 1.7	95 (94) <sup>c</sup>
	<b>Nd</b>	1.5 h		1 : 2.2	>95
<b>15e</b>	<b>Y</b>	6 d	+ <i>cis</i>	7 : 1	94
	<b>Nd</b>	2 d		4 : 1	>95

<sup>a</sup> All reactions were conducted at  $90^\circ\text{C}$ . <sup>b</sup> Based on integration of the  $^1\text{H}$  NMR spectrum; **17c** / **18c** : 0.81 (d) / 0.90 (d) ppm; **17d** / **18d** : 1.02 (d) / 1.08 (d) ppm; **17e** / **18e** : 3.14 (septet) / 2.93 (m) ppm. <sup>c</sup> Isolated yield as a *p*-toluenesulfonamide.

the size of the metal in terms of cyclization rate and diastereoselectivity. Presumably, in sterically demanding transition states as shown in Figure 8 (C,D), the methyl or phenyl group of the aminoalkenes (**15c,d**) would be located far away from the metal center. Hence, the sterically hindered surrounding of the complex might less affect the diastereoselective cyclization of aminoalkenes (**15c,d**) than in the case of aminoalkene **15e** also shown in Figure 8 (A,B). Generally, the reaction rate was dependent on the metal size of the complex.

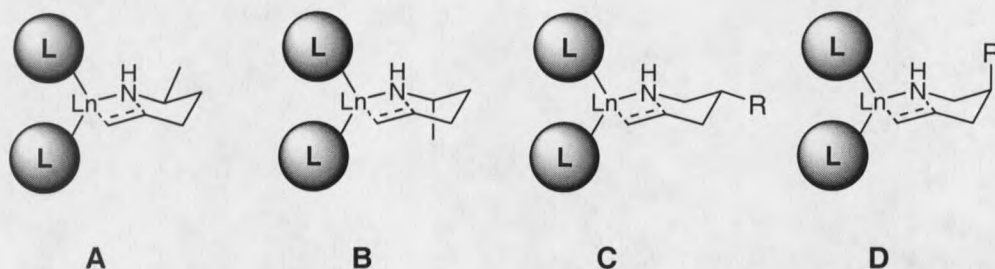


Figure 8. Rationalization of the Diastereoselectivity in the Cyclization of Aminoalkenes

The cyclization of **15d** proceeded notably faster than that of either **15c** or **15e**. The ancillary phenyl substituent in **15d** presumably accelerates the cyclization in a manner related to the Thorpe-Ingold effect.<sup>32</sup> In contrast, the sterically less hindered aminoalkene **15c** was cyclized very slowly. According to experimental observations, the aminoalkene formed a viscous solution with catalysts as soon as the substrate was added to the complex. The cyclization proceeded slowly only after it dissolved at 90°C.



















































































































































































































































































































































































































































































































































































































































































































