

PART 1: STUDY TOWARD THE TOTAL SYNTHESIS OF ACUTUMINE  
PART 2: ASYMMETRIC INTRAMOLECULAR HYDROAMINATION  
CATALYZED BY GROUP 3 METAL COMPLEXES

by

Khoi Quang Huynh

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of

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## ABBREVIATIONS

$\mu\text{l}$	Microliter
$^{\circ}\text{C}$	Degrees Celsius
Ac	Acetyl
Aq	Aqueous
BP	Boiling point
$\text{CaH}_2$	Calcium Hydride
Cat.	Catalyst
$\text{CH}_2\text{Cl}_2$	Methylene Chloride
DBU	1,8-diazabicyclo [5.4.0]undec-7-ene
DCM	Dichloromethane
DMAP	4-dimethylaminopyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	Dimethylsulfoxide
Et	Ethyl
$\text{Et}_2\text{O}$	Diethyl ether
$\text{Et}_3\text{N}$	Triethylamine
EtOH	Ethanol
g	Gram
h	Hour
HCl	Hydrochloride
HMPA	Hexamethylphosphoric triamide
Hz	Hertz
IR	Infrared
J	Coupling constant in Hertz
LDA	Lithium diisopropylamine
$\text{LiAlH}_4$	Lithium aluminum hydride

## ABBREVIATIONS – CONTINUED

M	Molarity
Me	Methyl
mg	Milligram
MgSO <sub>4</sub>	Magnesium sulfate
min	Minutes
mmol	Millimole
mp	Melting point
MS	Mass spectrometry
Ms	Methanesulfonate
NaBH <sub>4</sub>	Sodium borohydride
NaHCO <sub>3</sub>	Sodium bicarbonate
NaOH	Sodium hydroxide
<i>n</i> -BuLi	<i>n</i> -Butylithium
NCS	<i>N</i> -Chromosuccinimide
NH <sub>2</sub> OH-HCl	Hydroxylamine hydrochloride
NH <sub>4</sub> Cl	Ammonium chloride
NMR	Nuclear magnetic resonance
Ph	Phenyl
ppm	Parts per million
p-TsOH	<i>P</i> -Toluenesulfonic acid
RT	Room temperature
TBAF	Tetrabutylammonium fluoride
TBS	<i>t</i> -Butyldimethylsilyl
t-Bu	Tertiary butyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine

## ABBREVIATIONS – CONTINUED

TMS	Trimethylsilyl
Ts	<i>p</i> -Toluenesulfonate
TsCl	<i>p</i> -Toluenesulfonyl Chloride

## ABSTRACT

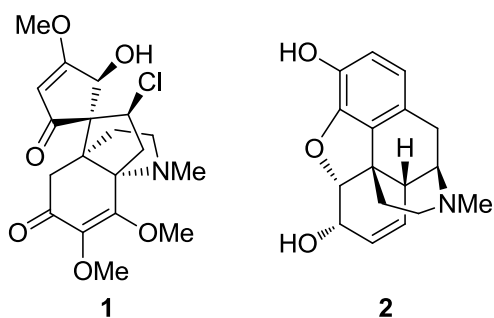
Acutumine **1** is a tetracyclic alkaloid isolated from *Menispermum dauricum*, which exhibits selective T-Cell cytotoxicity. It is potentially useful for specific therapy T-Cell related Leukemia and lymphoma. Acutumine is a highly functionalized tetracyclic natural product, containing a [4.3.3]-propellane core and a 5,5-spirocycle. The synthesis of the 5,5-spirocycle is prepared via enantioselective Pd<sup>II/IV</sup> catalyzed chloro-induced semi pinacol rearrangement. However, studies showed Pd catalyst functioned as Lewis acid to oxidant, PhI(OAc)<sub>2</sub> rather than forming a  $\pi$ -complex with the substrate as proposed. Fortunately, the preparation of the spirocycle can be accomplished from an asymmetric Pd<sup>II</sup>/Brønsted acid cocatalyzed semi pinacol rearrangement via direct allylic C–H activation. [4.3.3] propellane core was concisely synthesized in eight step sequences featuring a phosphoric Brønsted acid catalyzed aldol condensation and radical N-cyclization as the key transformations.

Hydroamination, the addition of an amine N–H bond across an unsaturated carbon–carbon linkage, allows a highly atom economical access to industrial and pharmaceutical important alkaloids. The hydroamination of alkene by early transition metal has seen significant process. Herein, we reported the substrate structural effect in Yttrium(III)-catalyzed intramolecular hydroaminations. Aminoalkenes possessing a terminal 2- (5-trimethylsilyl)thienyl group exhibited substantially enhanced reactivity. Cyclization efficiency for a representative aminoalkene possessing a *Z*-configured 2-(phenyl)ethenyl group is considerably higher than that observed for the corresponding *E*-isomer. Enantioselective hydroamination/cyclization of representative aminoalkenes catalyzed by chelating diamide complexes of La(III) and Y(III) are described. The La(III) complex derived from the sterically demanding (*R*)-*N,N'*-dibenzosuberyl-1,1'-binaphthyl-2,2'-diamine proligand provides enantioselectivities that are in many cases significantly higher than those obtained with the corresponding Y(III) analog.

## CHAPTER 1 – INTRODUCTION ON ACUTUMINE

Background

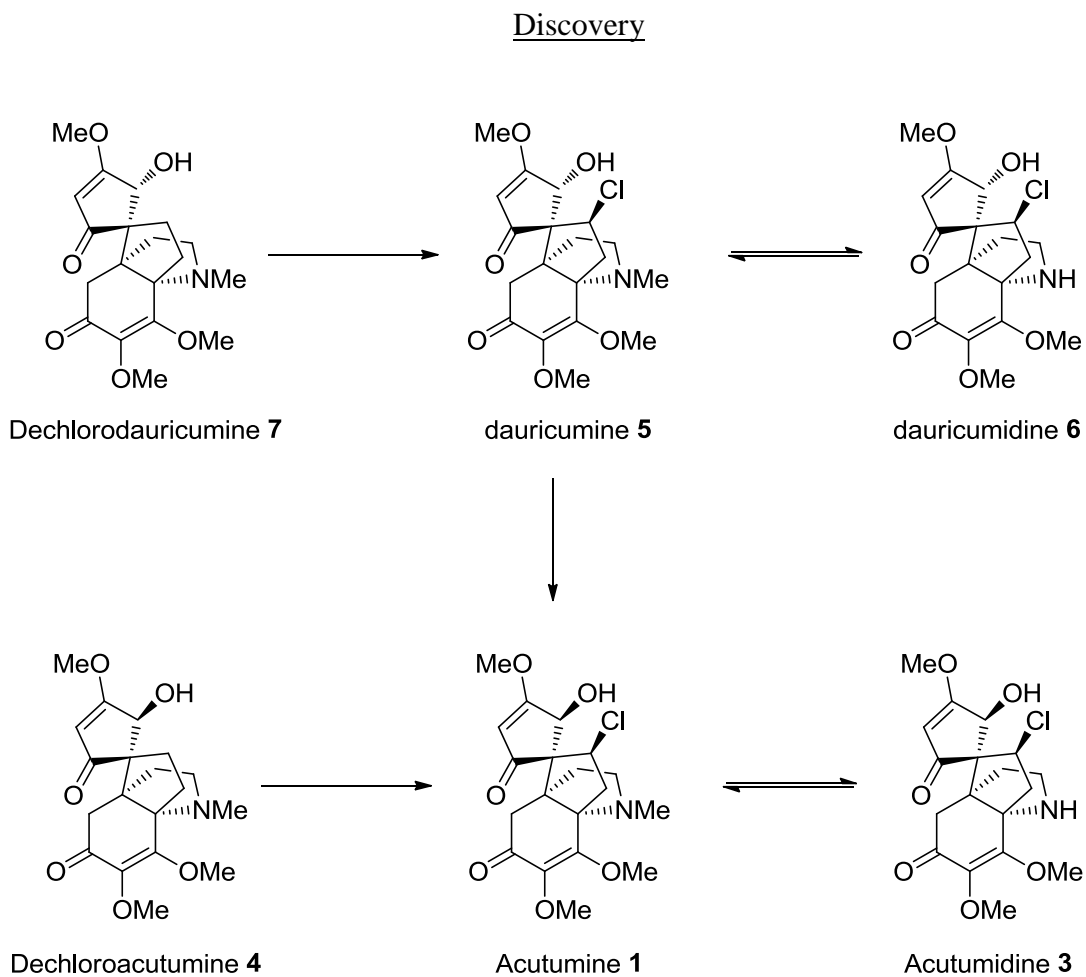
Alkaloids are among the most interesting and important natural products in bio-organic chemistry. Alkaloids are a group of natural chemical compounds that contain at least one basic nitrogen atom. Most of them are extracted from plants and have strong biological significances.<sup>1</sup> Alkaloids often have pharmacological effects and are used as recreational drugs.<sup>2</sup> The first isolated alkaloid, morphine **2** was isolated in 1804 by Friedrich Sertürner (Scheme 1). Due to their significant bioactivity and intriguing structures, alkaloid syntheses have been an intensive research focus in organic synthesis.



Scheme 1: Structure of Acutumine (1) and Morphine (2)

In the Rainey group, we are interested in the synthesis of Acutumine **1** (Scheme 1). It's a tetracyclic alkaloid with intriguing structure. Acutumine **1** is characterized by a propellane-type system, a spirocycle, and a neopentyl secondary chloride. The chloride resides in the cyclopentane ring along with three contiguous quaternary stereocenters, two of which are all-carbon quaternary centers.<sup>3</sup> Forming quaternary stereocenters would

prove to be a significant challenge due to the extreme steric hindrance. Thus, it is our goal to synthesize Acutumine **1**.



Scheme 2: Proposed biosynthesis among Acutumine alkaloids

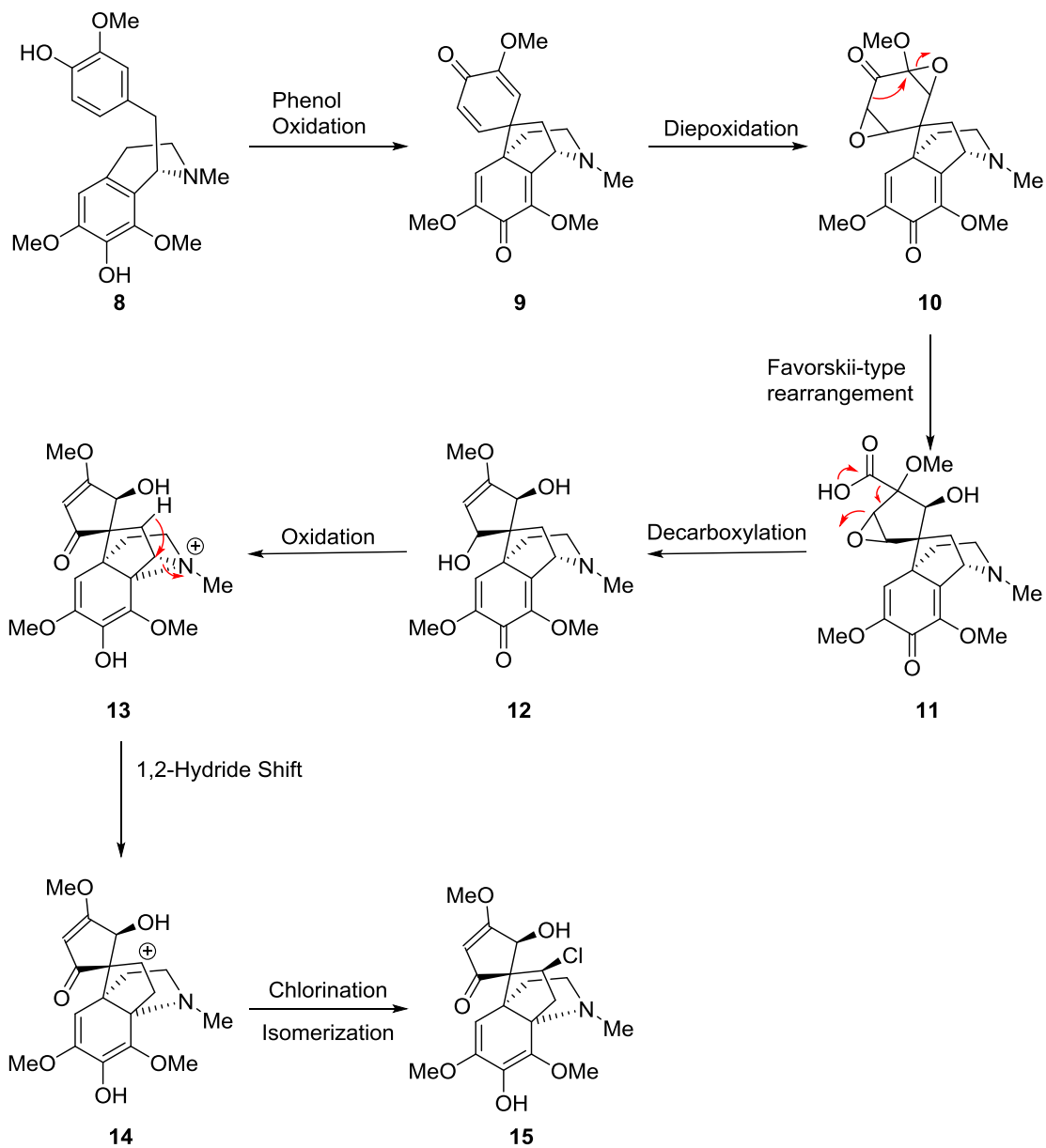
Acutumine **1** was isolated by K. Goto and H. Sudzuki in 1929.<sup>4</sup> The structure and the stereochemistry were determined by Tomita and coworkers through X-ray crystallographic studies in 1967.<sup>5</sup> Acutumine **1** consists of a propellane-like [4.3.3.0] fused tricyclic backbone, a spirocyclic cyclopentenone moiety, and a neopentyl secondary chloride. Since the original structural extraction of **1** in 1960s, a total of 12 related

alkaloids have been identified including epimeric alcohol dauricumine **5** and dauricumidine **6**,<sup>6</sup> the *N*-demethylated acutumidine **3**,<sup>7</sup> dechloroacutumine **4**, dechlorodauricumine **7**,<sup>8</sup> and hypserpanine (Scheme 2).<sup>9</sup>

Sugimoto et al. proposed a biosynthetic relationship among those similar alkaloids. Dechlorodauricumine **7** is the original precursor (Scheme 2). The regioselective and stereoselective chlorination of **7** with the help of enzyme(s) provide dauricumidine **6**, which would then epimerize to form Acutumine **1**. Similarly, Acutumine **1** would also be formed by enzyme(s) catalyzed chlorination of dechloroacutumine **4**.

#### Biological Activity of Acutumine

Acutumine **1** is a tetracyclic alkaloid isolated from the Asian vine *Menispermum dauricum*,<sup>10</sup> *Sinomenium acutum*,<sup>11</sup> and *Menispermum canadense*.<sup>12</sup> The stems of *rhizomes Menispermaceae* are well known as a rich source of various alkaloids. Studies had demonstrated that the alkaloids reduced the production of several inflammatory mediators such as prostaglandin E<sub>2</sub>, leukotriene C<sub>4</sub>, and nitric oxide from activated macrophages.<sup>13</sup> Acutumine possesses anti-amnesic properties<sup>14</sup> and selective T-Cell cytotoxicity.<sup>15</sup> Hence, Acutumine can play an important role in the development of selective T-Cell cytotoxic agents which can be potentially used for specific T-cell related leukemia and lymphoma therapy.

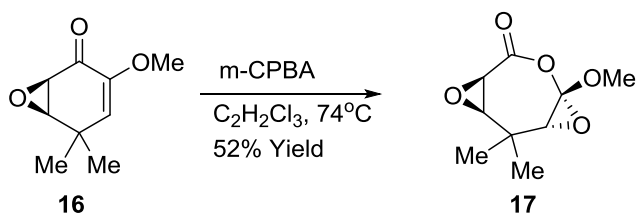
Biosynthesis

Scheme 3: Baron's proposed biosynthesis of the Acutumine 1

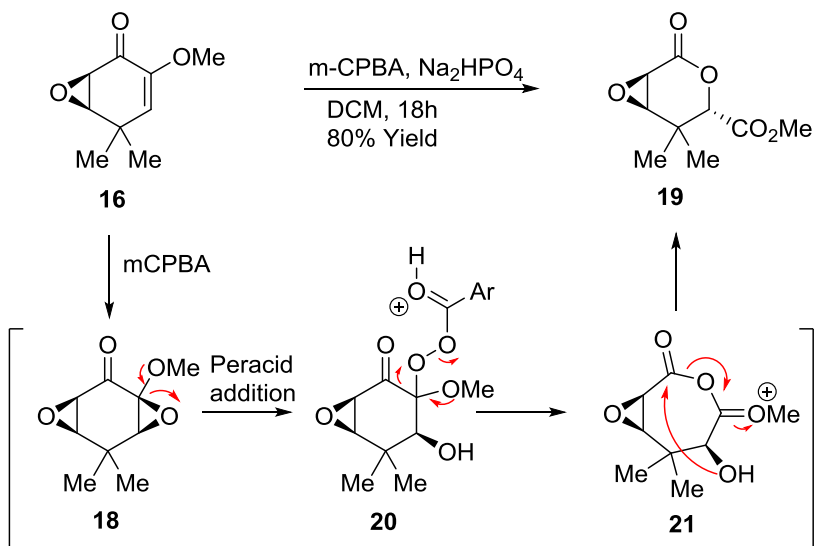
In 1968, during the biosynthetic studies of several morphine alkaloids, Barton and coworkers proposed a biosynthetic pathway for acutumine **1**.<sup>16</sup> The isoquinoline **8**

undergoes intramolecular phenol oxidative coupling to form spirocycle **9** (Scheme 3). Epoxidation of **9** provides diepoxide **10** which undergoes a Favorskii-type rearrangement to establish the core structural ring of acutumine forming carboxylic acid **11**. Decarboxylation followed by oxidation of acid **11** results in the formation of cyclopentenone **12**. The formation of propellane core is established by nucleophilic attack of the isoquinoline nitrogen forming aziridinium ion **13**, which then undergoes 1, 2-hydride shift affording carbocation **14**. Chloride installation and isomerization of **14** would yield the natural product acutumine **1**.

I. Matoba and coworkers, 1984

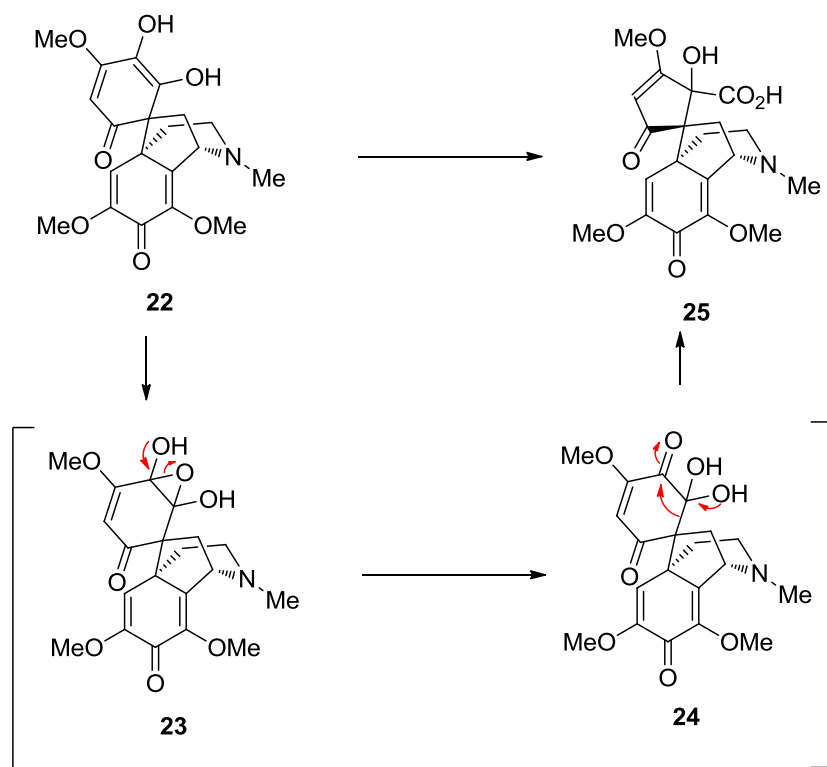


II. Wipf and coworkers, 2007



Scheme 4: Examine Favorskii-type cyclopentenone formation through epoxidation study

On investigating the Favorskii-type cyclopentone formation with a simple model substrate, Matoba and coworkers reported that treating epoxide **16** with *m*-CPBA in refluxing 1,1,1-trichloroethane lead to the formation of lactone **17** via Bayer-Villiger rearrangement (Scheme 4).<sup>17</sup> Wipf and coworkers recently further confirmed and proposed an oxidative rearrangement of alkyl enol ether to lactone and spiroketal ester.<sup>18</sup> Initially, biepoide **18** was formed from treating **16** with *m*CPBA. However, rapid epoxide ring opening of **18** generated an oxocarbenium ion, and peracid addition afforded the intermediate **20**. Baeyer-Villiger ring expansion and translactonization of **20** provided the lactone **19**.



Scheme 5: Wipf's alternative proposal for the biosynthesis of Acutumine

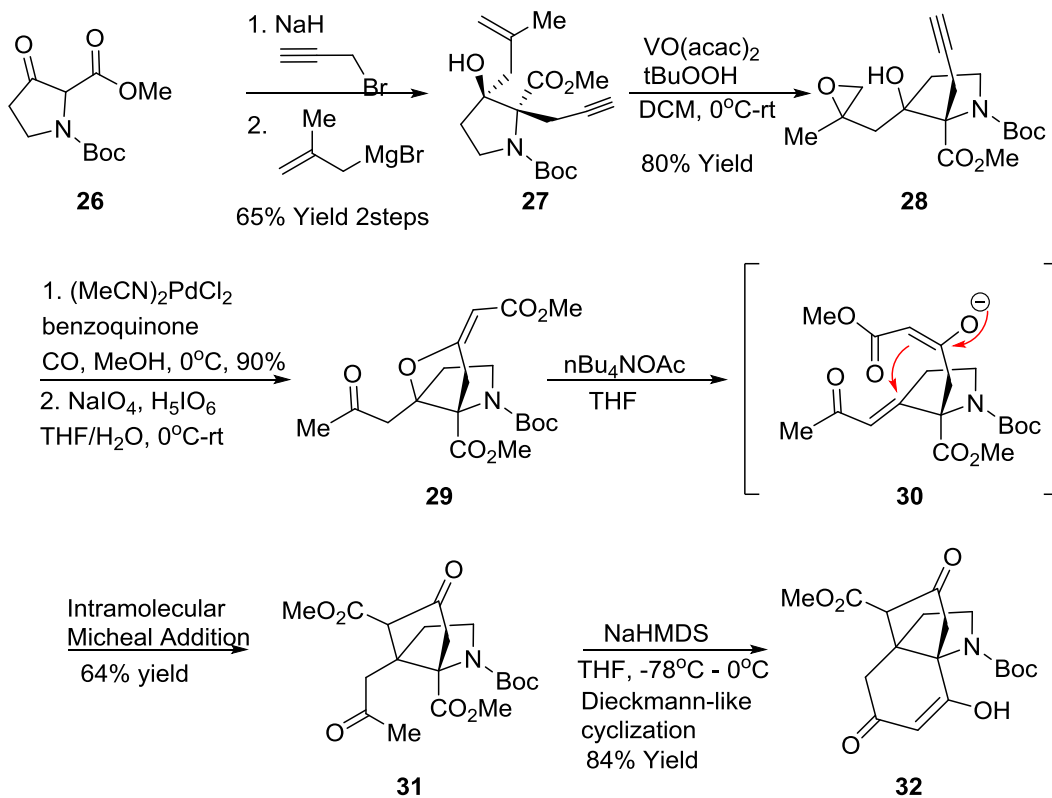
Based on the observation in scheme **4**, Wipf and coworkers proposed an alternative proposal for the biosynthesis of acutumine **1** (Scheme 5). The epoxidation of dienol **22** gives epoxide diol **23**; which undergoes epoxide opening forming ketone hydrate **24**. And semi pinacol type rearrangement of ketone **24** yields carboxylic acid **25**.

### Previous Total Syntheses

Eighty years has passed since the elucidation of acutumine, but only two complete total syntheses of acutumine have been reported to date; Castle (2009) and Herzon (2013). The strategies and the key transformations of each synthesis are discussed below.

#### Sorensen's Strategy

In 2007, Sorensen and Moreau reported their synthetic strategy toward constructing the propellane [4.3.3.0] fused tricyclic core of acutumine.<sup>19</sup> Alkyne **27** was generated through an enolate alkylation and Grignard addition of readily available pyrrolidine **26** (Scheme 6). Sharpless vanadium-based epoxidation of disubstituted alkene **27** yielded a directed diastereoselective epoxide **28**. Pd<sup>II</sup>-catalyzed carbonylative cyclization of **28** provided the vinylogous carbonate, followed by periodate-mediated oxidation to afford methyl ketone **29**.  $\beta$ -Elimination or intramolecular Michael cyclization of ketone **29** with a mild base formed enolate **30**, which immediately underwent nucleophilic attack with  $\alpha,\beta$ -unsaturated ketone to yield  $\beta$ -ketoether **31**. Dieckmann cyclization of **31** generated propellane **32** in 84% yield. However, the synthesis of acutumine has proven unsuccessful from the intermediate **32**.<sup>20</sup>

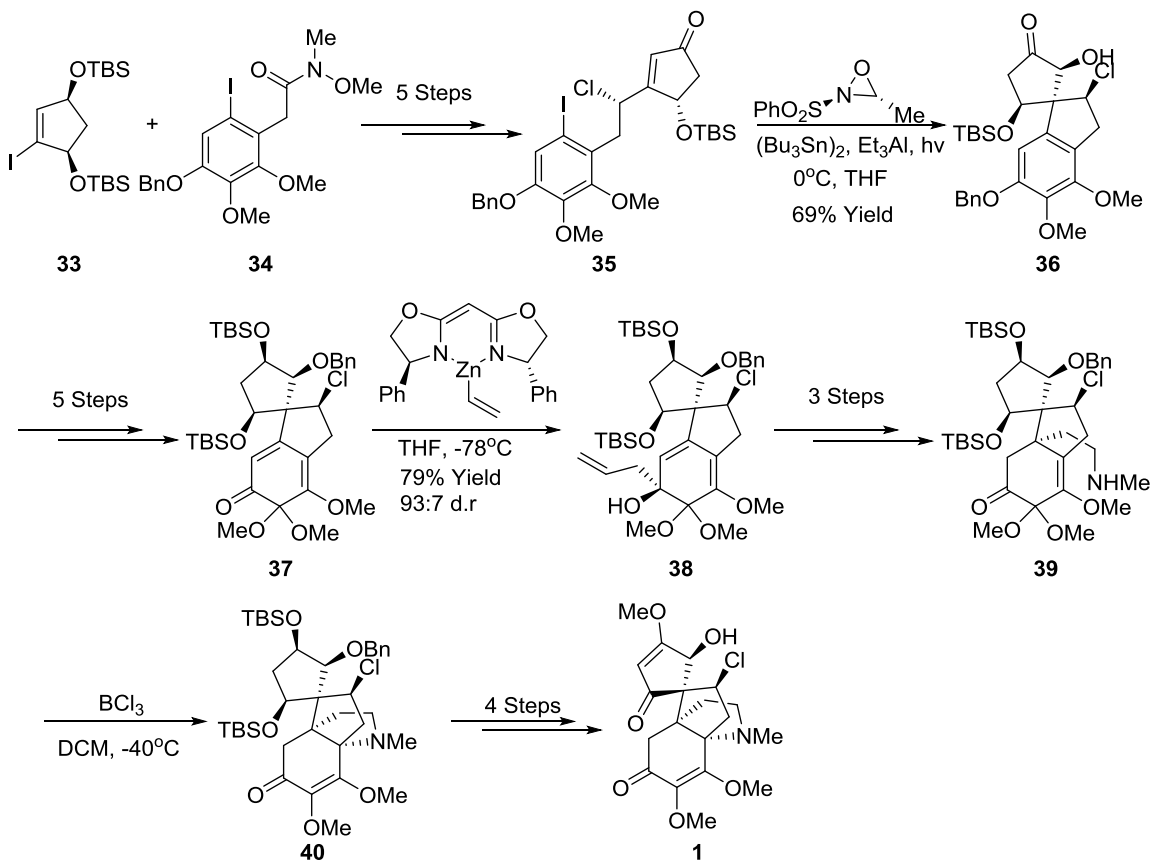


Scheme 6: Sorensen's synthesis of tricyclic core structure of Acutumine

### Castle's Total Synthesis

The first total synthesis of acutumine was reported by Castle and Coworkers in 2009.<sup>21</sup> Initially, Weinreb amide **34** underwent nucleophilic attack with Grignard coupling of vinyl iodide **33** (Scheme 7),<sup>22</sup> and followed by five-step sequences; including 1,2 selective reduction, Corey-Bakshi-Shibata reaction and inverted chlorination, the allyl ketone **35** was generated. In the next key step, irradiation of ketone **35** in presence of (Bu<sub>3</sub>Sn)<sub>2</sub>/EtAl and oxaziridine yielded 5,5-spirocyclic **36** in 66% yield. O-quinone monoketal **37** was formed via five step sequences from **36**. Allylation of **37** with Nakamura's chiral allyl zinc reagent<sup>23</sup> provided alcohol **38** in good yield and diastereoselectivity (79%, and dr: 93:7). The pendant methylamine **39** was generated in

addition of three-step sequences: Oxy-cope rearrangement, ozonolysis and reductive amination of **38**. Finally, cyclization of **39** in presence Lewis acid,  $\text{BCl}_3$  provided pyrrolidine **40** which contains the entire tetracyclic core of acutumine. The synthesis of acutumine was completed in 29 steps

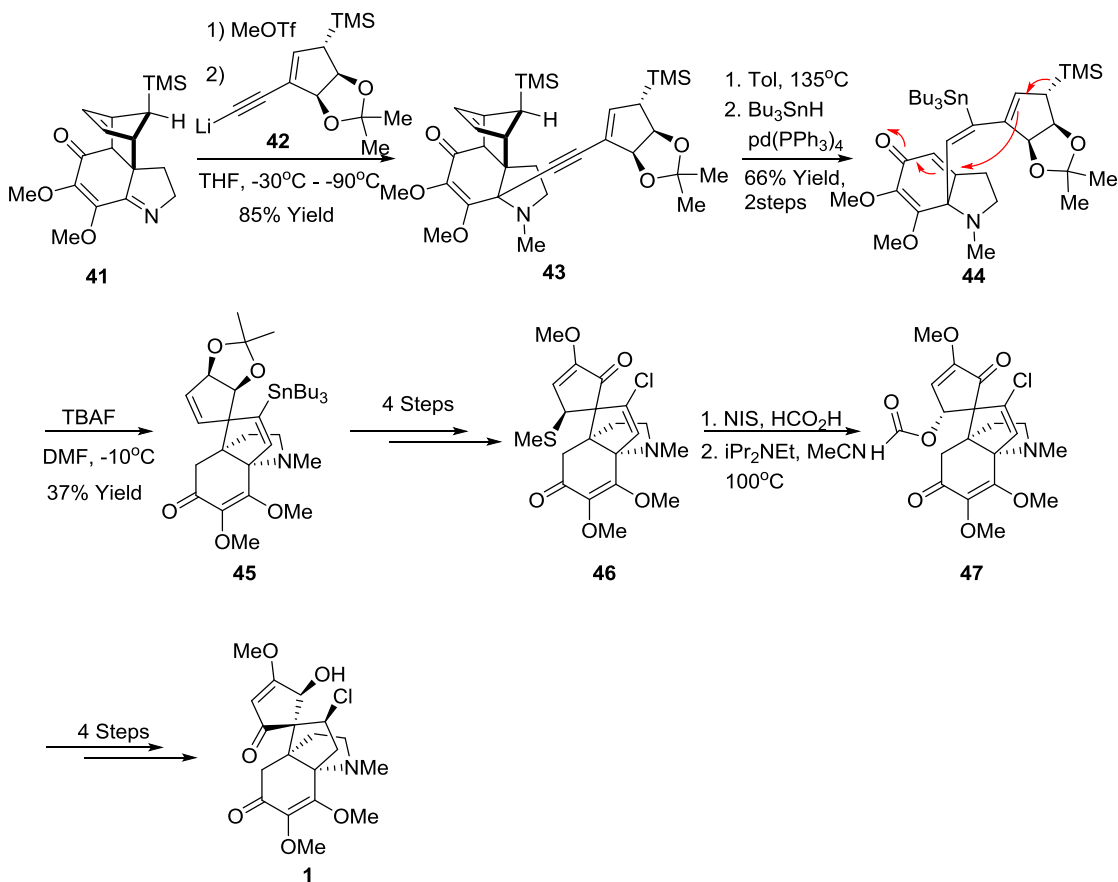


Scheme 7: Castle's total synthesis of Acutumine

### Herzon's Total Synthesis

Recently, the Herzon group reported a couple syntheses of various hasubanan alkaloids.<sup>24</sup> From those synthetic routes they disclosed both the synthesis of acutumine **1** and dechloroacutumine **4** (Scheme 8).<sup>25</sup> N-methylation of imine **41** at  $-60^\circ\text{C}$  provided the thermal unstable N-methyliminium ion, which undergoes stereo-selective and site-

selective addition of organolithium acetylide **42** affording 1, 2-addition product **43** as a single diastereomer with 85% yield. Thermal extrusion of trimethylsilylcyclopentadiene followed by Pd-catalyzed regio- and stereo-selective hydrostannylation of **43** produced vinyl stannane **44**. As a key transformation, activation of allylic silane functional group of **44** with TBAF in DMF induced a Hosomi–Sakurai allylation to yield the tetracycle **45** as a single detectable diastereomer with 37% yield. With the key step, Herzon was able to install both all-carbon quaternary stereocenters.

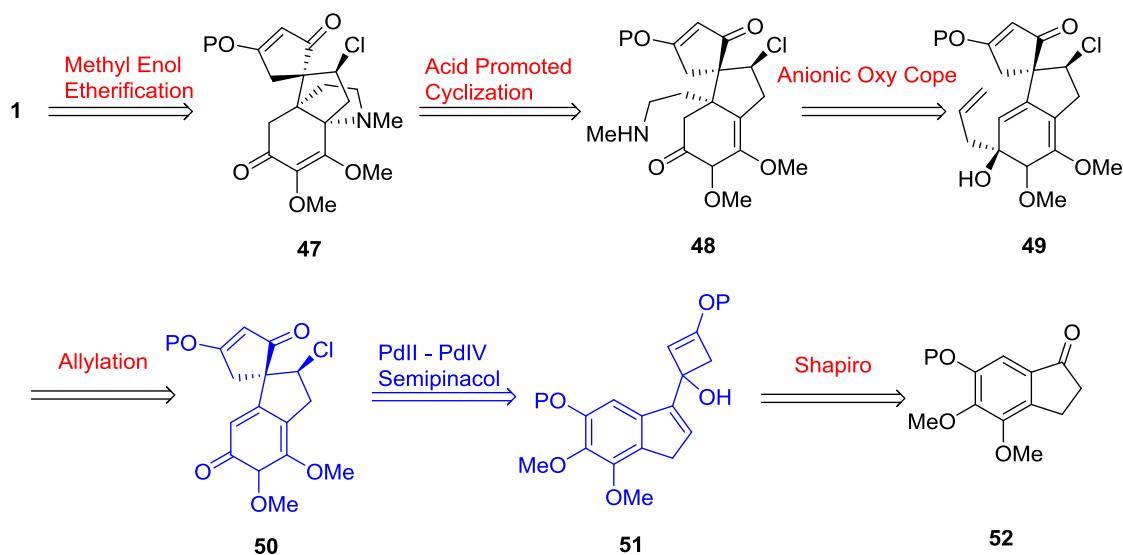


Scheme 8: Herzon's total synthesis of Acutumine

Vinyl stannane tetracycle **45** was converted to vinyl chloro methoxyenone **46** in four step sequences including chlorodestannylation and acid-mediated acetonide cleavage, diol oxidation, and thiomethoxide 1,4 addition. Sulfide activation of **46** with N-iodosuccinimide in formic acid resulted in oxidative elimination of the methanethiol substituent to form an oxocarbenium ion, which then underwent 1,2 addition to furnish ketal **47**. Thermolysis of **47** promoted thermal [3,3] sigmatropic rearrangement to generate formate ester **48**. In four additional steps, Acutumine **1** and dechloroacutumine **4** were synthesized.

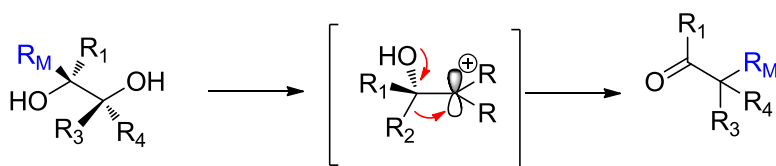
CHAPTER 2 – STUDY OF ETHYL ACETATE INDUCED Pd<sup>II/IV</sup>- CATALYZED  
SEMI-PINACOL REACTION FOR SPIROCYCLIC  
CORE OF ACUTUMINE

Introduction

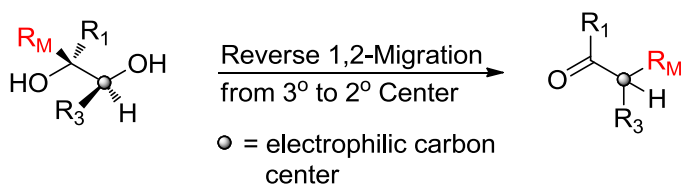


Scheme 9: Retrosynthesis of Acutumine and Pd<sup>II/IV</sup> Semi-Pinacol rearrangement methodology

The retrosynthesis analysis of **1** is shown in Scheme 9. The sequence of reactions including methyl enol etherification would transform tetracycle **47** into the natural product, acutumine **1**. The pyrrolidine ring of **47** would form from  $\alpha,\beta$  unsaturated ketal **48** via acid promoted cyclization. **48** is envisioned to form via anionic oxy-Cope rearrangement of homoallylic alcohol **49**, which possibly be constructed by an allylation of ketone **50**. Ketone **50** can be constructed via ring expansion of cyclobutanol indene **51** from Pd<sup>II/IV</sup> semipinacol reaction. Shapiro reaction of indenone **52** would give **51**.

Background: Precedence of Semi-Pinacol ReactionSemi-Pinacol Rearrangement

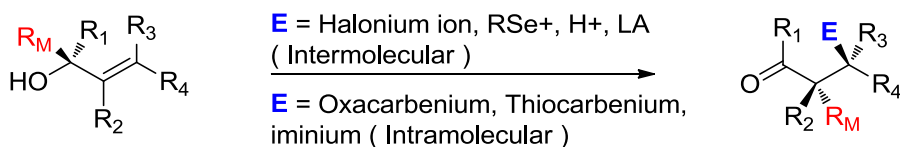
Scheme 10: Pinacol rearrangement



Scheme 11: Semi-Pinacol rearrangement

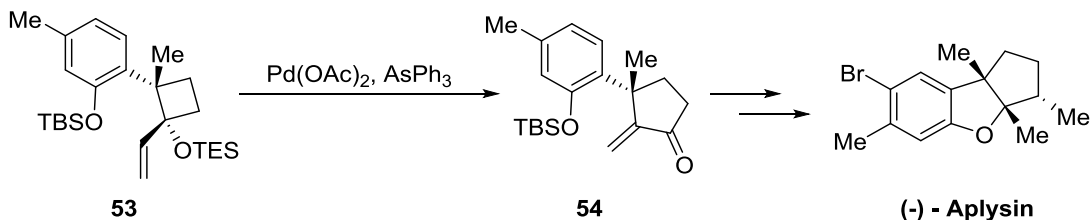
The Pinacol rearrangement<sup>26</sup> is an acid-catalyzed transformation of 1,2-diols to ketones or aldehydes by 1,2-migration of a C-C or C-H bond toward the vicinal carbocation (Scheme 10). For the past decade, this type of rearrangement has been an active area of research for chemist-addressing its limits and disadvantages: regio- and diastereo-selectivity.<sup>27</sup> The semipinacol rearrangement is a type of pinacol rearrangement in which the tertiary 1, 2-diol undergoes alkyl 1, 2-migration toward the secondary carbon center, rather than the tertiary one (Scheme 11).<sup>28</sup> Several variations of this rearrangement existed, which mechanistically shared a common relative species; electrophilic carbon center is vicinal to an oxygen-containing carbon and alkyl 1, 2-migration generates a carbonyl group.

Based on the type of electrophilic carbon center, the classification of the semipinacol rearrangement has been established. Reactions are categorized into the following four types: the rearrangement of 2-heterosubstituted alcohols (type I), and rearrangements of allylic alcohols (type II) (Scheme 12), rearrangements of epoxides (type III), and rearrangements of tertiary  $\alpha$ -hydroxyl ketones and imines (type IV).<sup>28</sup> Type II rearrangement of allylic alcohols closely resembles our model study of the Pd<sup>II/IV</sup> semipinacol reaction.



Scheme 12: Depict Type II Semi-Pinacol rearrangement

Rearrangement of Allylic Alcohol. In the type II rearrangement of allylic alcohols, an electrophilic carbon center is generated from the addition of an electrophile to an alkene. Generally, electrophiles such as haloniums, selenium cations, and Brønsted and Lewis acids initiate intermolecular rearrangements.<sup>28</sup> In contrast, oxocarbeniums, thiocarbeniums, and iminiums mainly undergo intramolecular rearrangement. The latter case is also known as the Prins-pinacol rearrangement by Overman's group.<sup>29</sup>



Scheme 13: Pd-Catalyzed Semi-Pinacol rearrangement and total synthesis of (-)-Aplysin

Induced by Lewis Acid. Lewis acid such as  $\text{BF}_3 \cdot \text{OEt}_2$ ,<sup>30</sup>  $\text{Hg}(\text{OCOCF}_3)_2$ ,<sup>31</sup> and  $\text{Pd}^{\text{II}}$  catalysts have been used to induce the semipinacol rearrangement of allylic alcohols by activating the C=C bond. Relevantly to our methodology study, Nemoto, Fukumoto, and co-workers developed the Pd(II)-catalyzed semipinacol rearrangement of various chiral vinylcyclobutanols to generate cyclopentanones containing a chiral quaternary carbon center.<sup>32</sup> By utilizing the ring expansion strategy towards forming chiral cyclobutanones, Nemoto and Fukumoto have synthesized several terpenes including the total synthesis of (-)-Aplysin (Scheme 13)

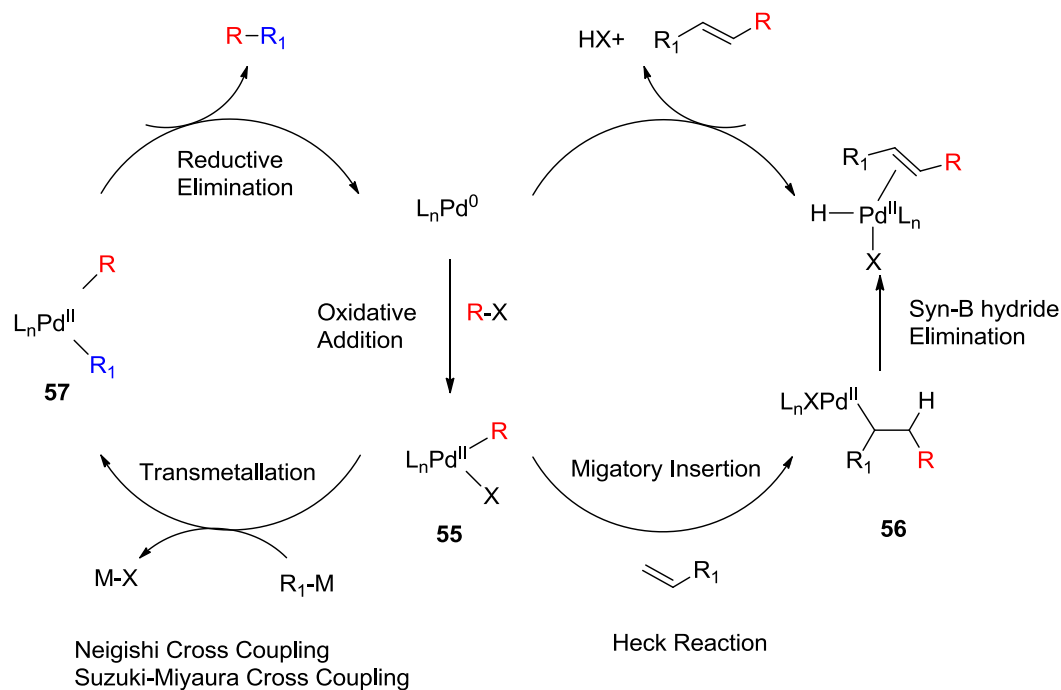
### Palladium<sup>II/IV</sup> Catalysis

Homogeneous Pd-catalyzed reactions are widely used for the construction of important organic molecules, pharmaceuticals<sup>33</sup>, and polymers.<sup>34</sup> Since the development of cross coupling reactions, Pd catalysis has been used extensively in the construction of carbon-carbon, carbon-heteroatom bonds,  $\alpha$ -arylation, decarboxylative coupling, and direct arylation by C-H activation. Improvement and advancement in Pd-catalyzed processes have led to a wide range of robust, synthetically valuable synthetic methods.<sup>35</sup> In our study, we were interested in OAc and Cl induced Pd-catalyzed semipinacol rearrangement forming spirocyclic ring of acutumine **1**.

### General Mechanistic Pd Catalytic Cycle of Cross Coupling Reactions

The general mechanisms of the Pd catalytic cycle of cross coupling reactions are depicted in Scheme **14**. The oxidative addition of aryl halide to the  $\text{Pd}^0$  species generates

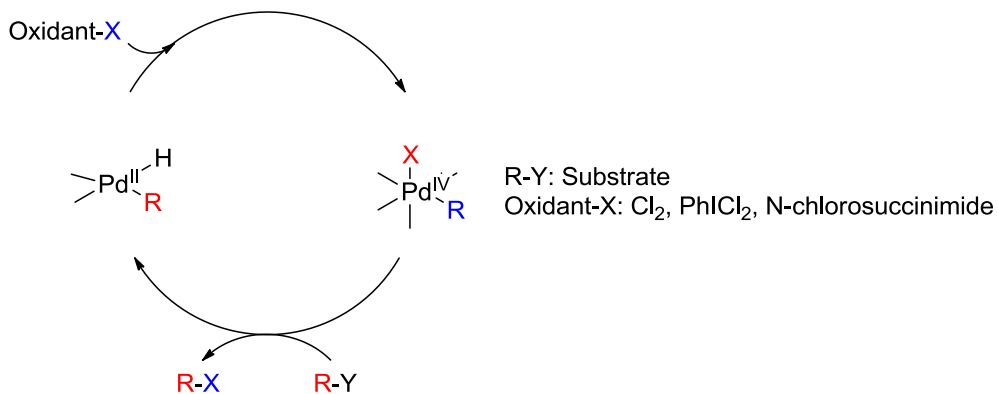
an active  $\text{Pd}^{\text{II}}$  species **55**. In the Heck reaction, the  $\text{Pd}^{\text{II}}$  species **55** coordinate to the alkene via syn migratory insertion forming organopalladium species **56**, which would undergo syn- $\beta$  hydride elimination to afford alkene product and regenerate the  $\text{Pd}^0$  species.



Scheme 14: Pd catalytic cycles for Heck, Neigishi, Suzuki reactions

For both Neigishi and Suzuki reactions, the transmetalation of the oxidative  $\text{Pd}^{\text{II}}$  species **55** generates organopalladium intermediate **57** which consists of two cross coupling partners (Scheme 14). Reductive elimination of **57** results in the formation of carbon-carbon bond and regeneration of  $\text{Pd}^0$  species. According to the Heck cross coupling reaction mechanism, we rationalized that in order to induce the OAc or Cl group to form the neopentyl OAc or Cl in the Pd-catalyzed semipinacol reaction, the  $\beta$  hydride elimination process would have to be disfavored and reductive elimination favored.

Therefore, the use of high-valent palladium complexes in catalysis may prevent the  $\beta$  hydride elimination while promoting reductive elimination of OAc or Cl.

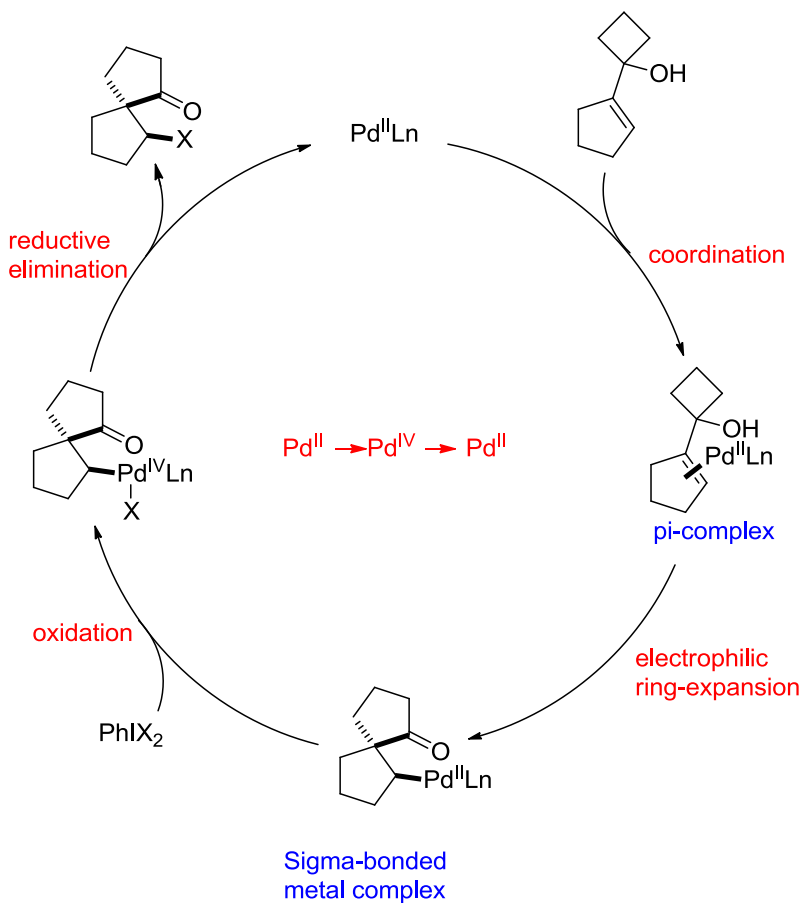


Scheme 15: High-Valent Palladium formation in catalytic cycle

High-Valent Organometallic Palladium ( $Pd^{II} \rightarrow Pd^{IV}$ ) Catalysis. High valent palladium complexes are in the +3 or +4 oxidation state.<sup>37</sup> Usually palladium metal is oxidized to form a high-valent organometallic intermediate during the catalytic cycle (Scheme 15). Studies showed high-valent organometallic palladium halide complexes can be generated through the stoichiometric oxidation of  $Pd^{II}$  with electrophilic halogenating reagents such as  $Cl_2$ ,  $PhICl_2$ , N-chlorosuccinimide, and  $XeF_2$ .<sup>36</sup> Also, early literature has demonstrated that electron-donating, rigid, multidentate ligands stabilize high-valent Pd intermediates.<sup>37</sup> Over the past decade, numerous  $Pd^{II/IV}$  catalysis methods have been reported. A wide range of carbon-heteroatom bond formations via reductive elimination reactions were achieved from these high-valent palladium species. These results have established the feasibility and synthetic utility of high-oxidation state palladium catalysis in organic synthesis.

The Proposed Pd<sup>II/IV</sup> Semi-Pinacol Reaction

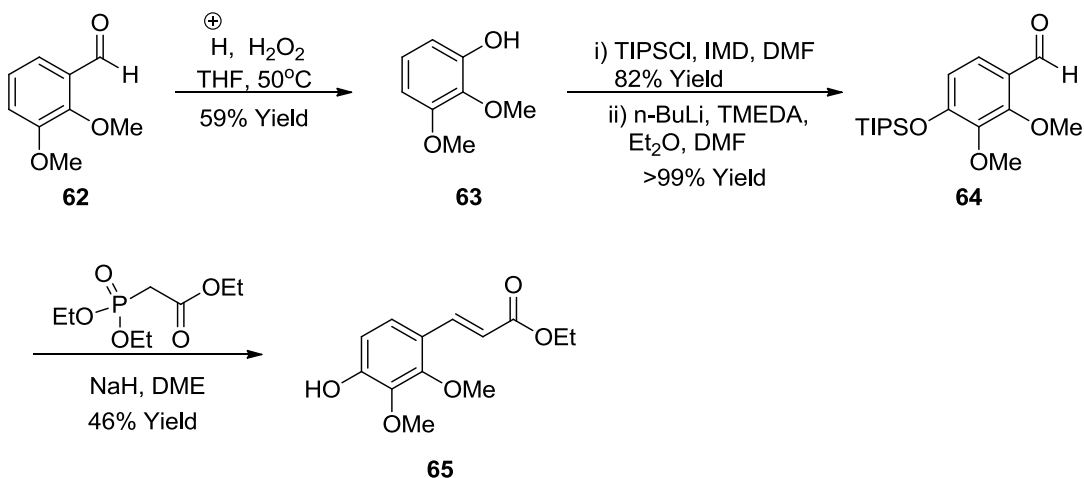
The Sanford group<sup>38</sup> and others<sup>39</sup> have recently reported numerous catalytic reactions that involve Pd<sup>IV</sup> complexes as key intermediates. The transformations are attractive because they can provide access to novel organic products that are highly complementary to those in conventional Pd<sup>0/II</sup>-catalyzed processes. For examples, Pd<sup>IV</sup> complexes undergo reductive elimination to form C-F, C-I, C-OAc, and C-OCH<sub>2</sub>CF<sub>3</sub> bonds. In addition, Pd<sup>IV</sup> complexes are often resistant to β-hydride elimination processes and allowing diverse functionalization of Pd<sup>IV</sup> σ-alkyl intermediates.



Scheme 16: Proposed Pd<sup>II</sup> → Pd<sup>IV</sup> Semi-Pinacol reaction

Due to the significant advantages of Pd<sup>II/IV</sup> catalysis, asymmetric semipinacol reaction with Pd<sup>II/IV</sup> catalysis was explored. The proposed Pd<sup>II/IV</sup> semipinacol reaction is depicted in Scheme 16. Pd<sup>II</sup> coordinates the cyclopentenyl cyclobutanol forming a  $\pi$  complex. Such  $\pi$  complex promotes the electrophilic ring expansion providing the  $\sigma$ -bonded metal complex. Upon oxidant addition, PhIX<sub>2</sub>, the  $\sigma$ -bonded metal complex oxidizes to generate a Pd<sup>IV</sup> complex. Reductive elimination affords the spirocycle product and recycled Pd<sup>II</sup>Complex.

### Synthesis of Dimethoxy-Indenyl Cyclobutanol

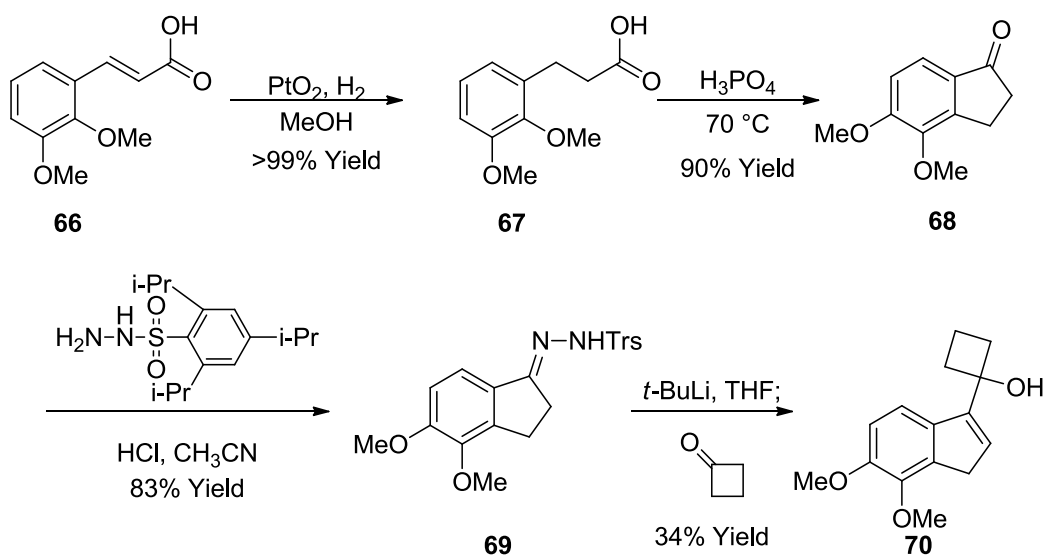


Scheme 17: Synthesis of dimethoxyphenyl acrylate

The synthesis of dimethoxy-indenyl cyclobutanol is outlined in Scheme 17. Dakin oxidation of dimethoxy benzaldehyde **62** afforded benzyl alcohol **63**. TIPS protection and formylation of **63** provided the triisopropylsilyloxy benzaldehyde **64**. The aldehyde **64** was coupled triethyl phosphonoacetate via a Horner-Wadsworth-Emmons olefination

gave **65**. With the TIPS removal, alcohol **65** can be protected with any protecting groups late in the synthesis.

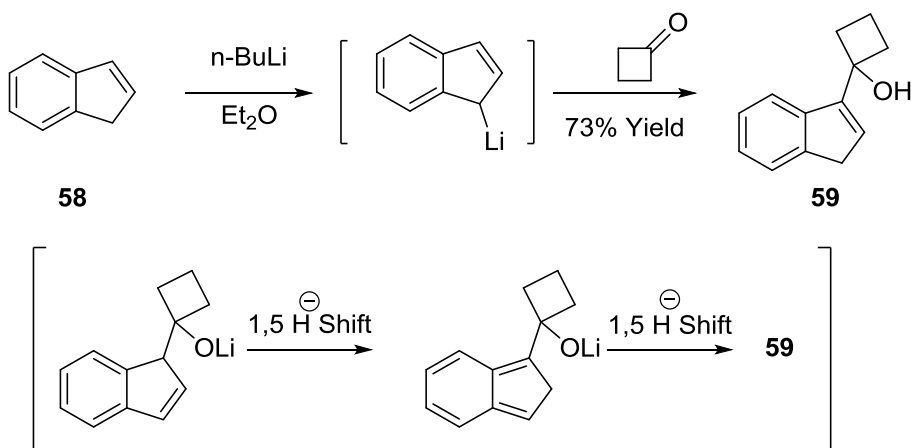
As a large amount of precursor was necessary for the key transformation; Pd<sup>II/IV</sup> semipinacol reaction, commercial available **66** was used and treated with Adam's catalyst to give hydrogenated product, propanoate **67** (Scheme 18). Phosphoric acid promoted cyclization of **67** provided dimethoxy indenone **68**. Sulfonylhydrazide **69** was formed via olefination of indenone **68**. Shapiro reaction of sulfonylhydrazide **69** with cyclobutanone afforded cyclobutanol **70**. With the successful preparation of **70**, cyclobutanol indene **51**, the precursor of the Pd<sup>II/IV</sup> semipinacol reaction in the synthesis of acutumine, can be synthesized utilizing the similar reaction sequences.



Scheme 18: Synthesis of dimethoxy indenyl cyclobutanol

### Synthesis of Indenyl Cyclobutanol

A much simpler precursor for the Pd<sup>II/IV</sup> methodology study was easily made in large quantities in one step, shown in Scheme 19. The 1H-indene **58** was lithiated and reacted with cyclobutanone to provide indenyl cyclobutanol **59** in 73% yield.<sup>80a</sup>



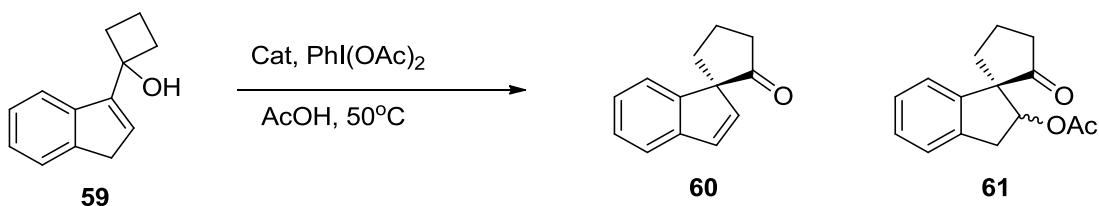
Scheme 19: Synthesis of indenyl cyclobutanol

### Ethyl Acetate Induced Semi-Pinacol Reaction

The methodology study was started with standard conditions developed by Sanford and others.<sup>40</sup> The control and Pd catalytic reaction results are shown in Table 1. In entry 1, with the absence of Pd catalyst, both **60** and **61** were observed. The oxidant,  $\text{PhI}(\text{OAc})_2$  coordinated to the  $\pi$  orbital and promoted the ring expansion to afford both **60** and **61**. Proposed mechanisms are shown in Scheme 20a and 20b. Both **60** and **61** were not formed in the presence of  $\text{Pd}(\text{OAc})_2$  without  $\text{PhI}(\text{OAc})_2$ , thus it's mechanistically suggested that  $\text{Pd}(\text{OAc})_2$  did not react to the alkene. However, the reaction with both  $\text{PhI}(\text{OAc})_2$  and  $\text{Pd}(\text{OAc})_2$ , gave only **61** (entry 3). Therefore,  $\text{Pd}(\text{OAc})_2$  possibly acted as

a Lewis acid to  $\text{PhI}(\text{OAc})_2$ , shown in Scheme 20c. The same reaction conditions were repeated with  $\text{Pd}(\text{TFA})_2$ . However,  $\text{Pd}(\text{TFA})_2$  in the absence of oxidant,  $\text{PhI}(\text{OAc})_2$  gave **60**, this suggests  $\text{Pd}(\text{TFA})_2$  reacted with the  $\pi$  orbital of the alkene. In entry 5, using  $\text{PhI}(\text{OAc})_2$  and a catalytic amount of  $\text{Pd}(\text{TFA})_2$ , only **61** was obtained. This result suggested two possible mechanisms, either  $\text{Pd}(\text{TFA})_2$  acted as Lewis acid to the oxidant (Scheme 20c), or  $\text{Pd}^{\text{II}}(\text{TFA})_2$  reacted to the alkene and promoted the ring expansion forming  $\sigma$ -bonded metal complex, which then oxidized with  $\text{PhI}(\text{OAc})_2$  to generate  $\text{Pd}^{\text{IV}}$  complex. Reductive elimination of  $\text{Pd}^{\text{IV}}$  complex gave **61**, shown in Scheme 20d.

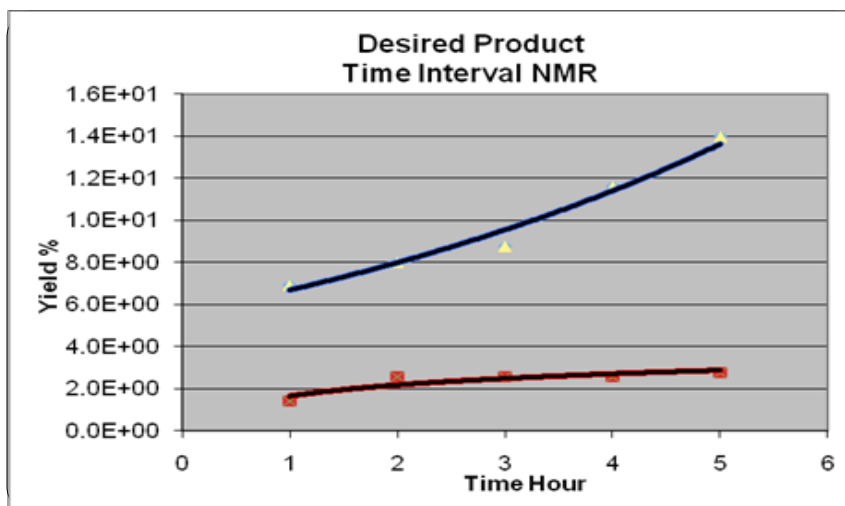
Table 1: Control and catalytic reactions



Entry	Catalyst	Oxidant	% Yield ( <b>60:61</b> )
1	N/A	$\text{PhI}(\text{OAc})_2$	11 : 57
2	$\text{Pd}(\text{OAc})_2$ (1eq)	N/A	0 : 0
3	$\text{Pd}(\text{OAc})_2$ (0.2 eq)	$\text{PhI}(\text{OAc})_2$	0 : 77
4	$\text{Pd}(\text{OTFA})_2$ (1eq)	N/A	> 95 : 0
5	$\text{Pd}(\text{OTFA})_2$ (0.2 eq)	$\text{PhI}(\text{OAc})_2$	0 : 42

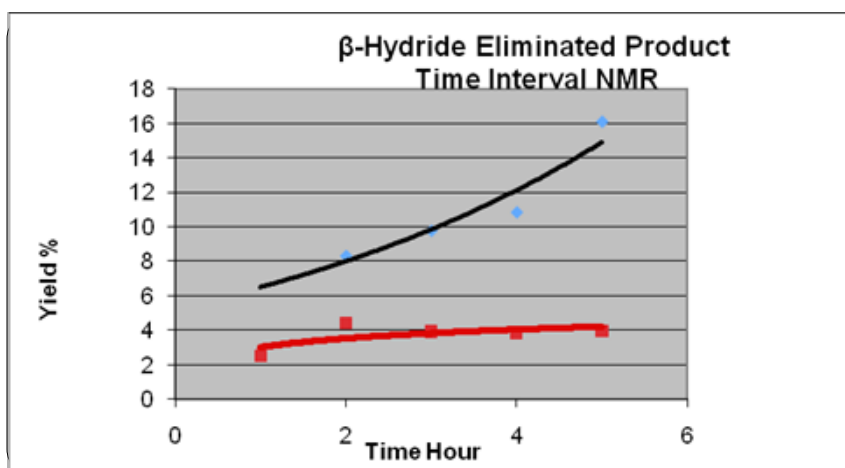
With oxidant,  $\text{PhI}(\text{OAc})_2$  enabled the ring expansion without the aid of Pd catalyst in entry 1, the effect of  $\text{Pd}(\text{TFA})_2$  on the ring expansion was studied. The NMR time intervals between entry 1 and entry 5 of Table 1 were performed and shown in Figure 1. In Figure 1, the indene acetate **61** rate of formation with  $\text{Pd}(\text{TFA})_2$  presence, (blue) was faster than the control (red), and with higher percent yield.

Graph 1: NMR time intervals for desired product, 61



Desired product, **61** formed with catalytic amount of Pd(OTFA)<sub>2</sub> (blue), **61** formed without Pd(OTFA)<sub>2</sub>, red

Graph 2: NMR time intervals for  $\beta$  hydride eliminated product, **60**

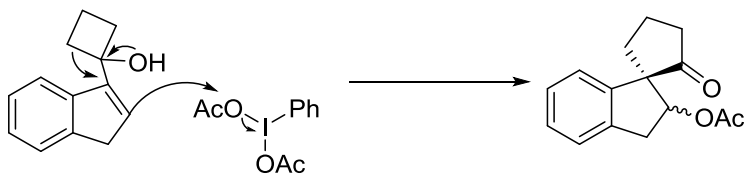


$\beta$  Hydride eliminated product, **60** formed with catalytic amount of Pd(OTFA)<sub>2</sub>, black. **60** formed without Pd(TFA)<sub>2</sub>, red

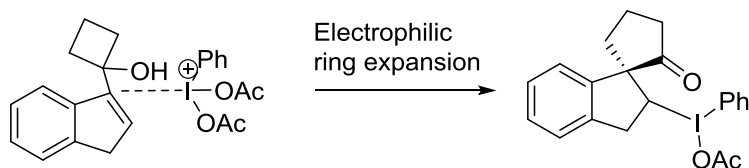
Also, Graph 2 showed that the  $\beta$ -hydride eliminated product **60** was formed faster with higher yield. With this result, Pd(TFA)<sub>2</sub> is confirmed playing an important role in catalyzing the semi pinacol reaction. However, it's rather not known whether Pd(TFA)<sub>2</sub> reacted as a Lewis acid to PhI(OAc)<sub>2</sub> (Scheme 20c) or reacted to  $\pi$ -orbital of the alkene

and oxidized by the oxidant  $\text{PhI}(\text{OAc})_2$  to form  $\text{Pd}^{\text{IV}}(\text{TFA})_2$  (Scheme 20d). From the result in entry 2,  $\text{Pd}(\text{OAc})_2$  was confirmed that it did not react to  $\pi$ -orbital of the alkene. Hence, the NMR time interval between entry 1 and entry 3 may help confirming the role of the Pd catalyst in this ring expansion reaction.

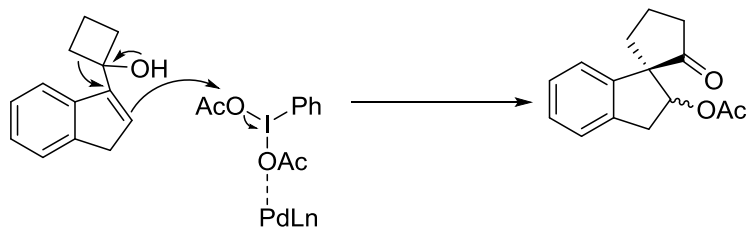
a) Ring expansion and substitution



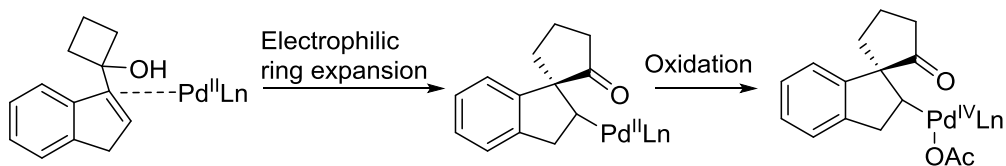
b) Oxidant reacts to alkene promote ring expansion



c)  $\text{PdLn}$  as Lewis acid catalyzed  $\text{PhI}(\text{OAc})_2$



d)  $\text{Pd}^{\text{III/IV}}$  Catalyzed Reaction

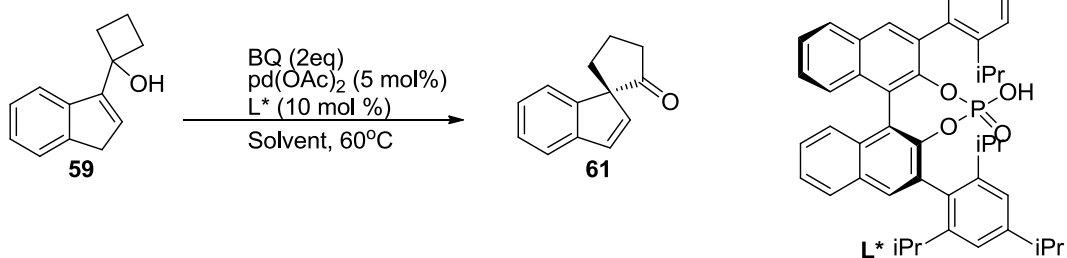


Scheme 20: Proposed four possible mechanistic pathways

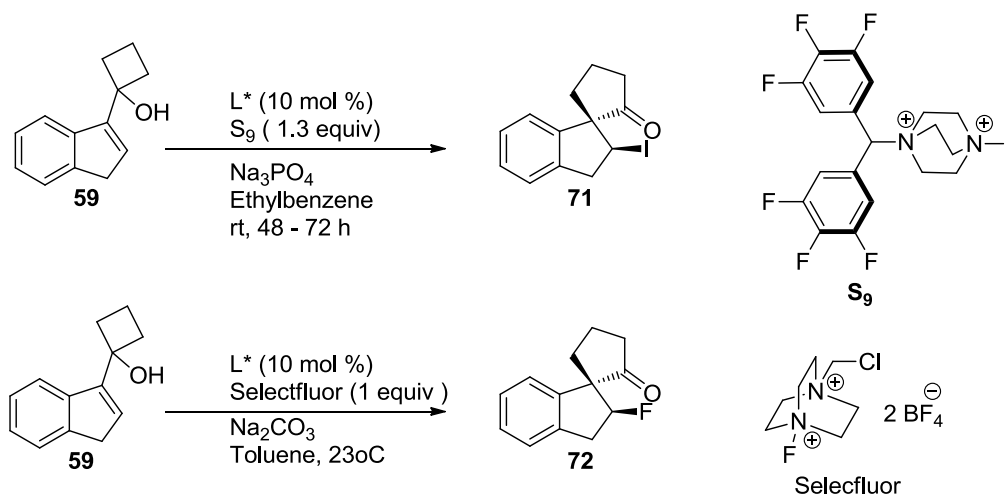
Recent Developed Semi-Pinacol Reactions  
Induced by Bronsted Acid and Lewis Acid

Unfortunately, the recent total of synthesis of Acutumine published by Steven Castle in 2009 was similar to ours; from the anionic Oxy Cope rearrangement to the acid promoted N-cyclization. Thus the new approach of synthesizing Acutumine was proposed. Due to recent publications on the asymmetric semi pinacol reaction in the Rainey group<sup>41</sup> and Alexakis group<sup>42</sup> (Scheme 21), we confidently rationalized that semi pinacol could be used as a last step of the acutumine synthesis. In the next approach, our intent was to focus on synthesizing the tetracyclic core of acutumine.

a) Rainey and Chai (2012)



b) Alexakis and Michailidis (2013)

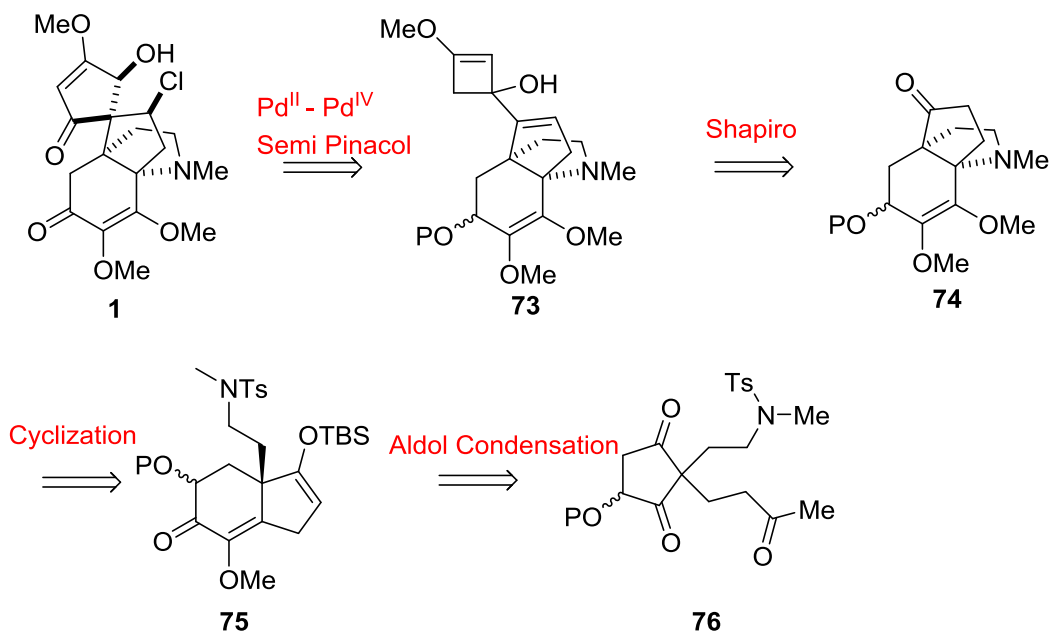


Scheme 21: Reported Semi-Pinacol reactions

CHAPTER 3 - PROGRESS TOWARD THE CONSTRUCTION OF THE TRICYCLIC  
CORE IN THE TOTAL SYNTHESIS OF ACUTUMINE

Retrosynthesis

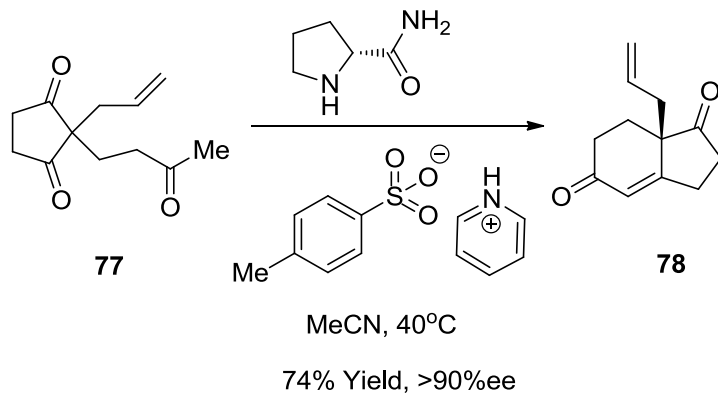
As described from previous retrosynthetic analysis, acutumine **1** can be synthesized from tricycle **74** via Shapiro reaction, followed by the semi pinacol reaction. The propellane core **74** is generated from the N-cyclization of tosyl methyl amine **75** (Scheme 22). Organocatalyzed asymmetric aldol condensation of diketone **76** affords the bicyclic allyl ketone **75**.



Scheme 22: Retrosynthetic strategy

Key Steps and Precedence:  
Asymmetric Aldol Condensation

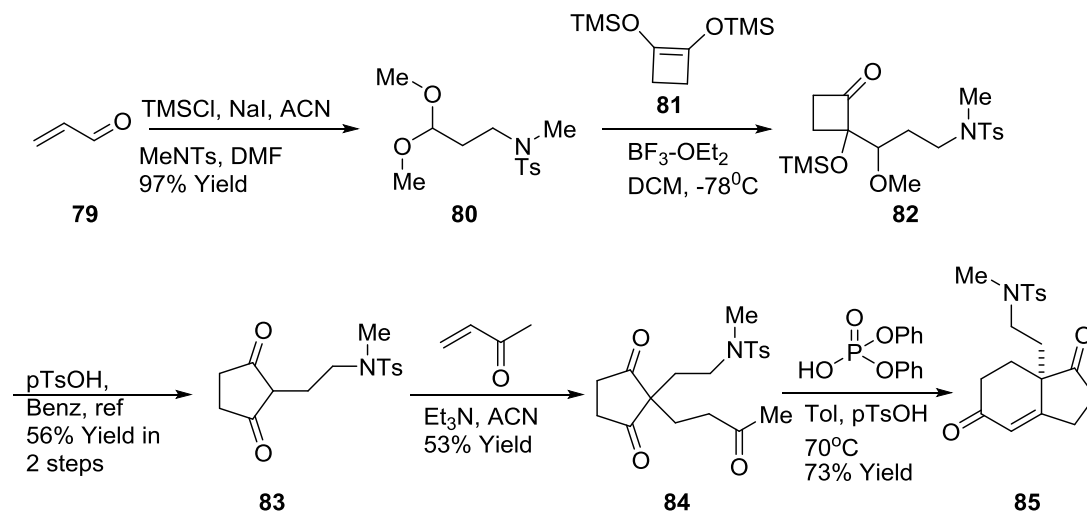
In 2007, Landais and coworkers reported a highly reactive organocatalyst for asymmetric aldol condensation (Scheme 23).<sup>44</sup> In the total synthesis of (-)-Jiadifenolide,<sup>45</sup> the Theodorakis group demonstrated the preparation of enantiomerically enriched diketone **78** in large scale via a D-prolinamide/PPTS-catalyzed<sup>46</sup> and optimized asymmetric aldol condensation of **77**. With the establishment of the optimized asymmetric aldol condensation condition, we envisioned the bicyclic allyl ketone **75** (Scheme 22) can be prepared using the same condition. From this approach, stereochemistry is established at the beginning of the synthetic approach, and steric hindrance of tosyl methyl amine can dictate and direct the formation of other desired stereocenters of the acutumine **1**.



Scheme 23: Asymmetric Aldol condensation

### Synthesis of Model Substrate Indene Dione

The treatment of acrolein with TMSCl and NaI in acetonitrile generated iodo dimethyl acetal<sup>47</sup> which immediately reacted with N-methyl-tosyl amide in DMF to afford the corresponding dimethyl acetal amide **80** in 97% yield (Scheme 24). The aldol condensation reaction between dimethyl acetal **80** and cyclobutene **81** catalyzed by  $\text{BF}_3\text{Et}_2\text{O}$  yielded cyclobutanone **82**, which was converted to the diketone **83** via acid catalyzed ring expansion.<sup>48</sup> Michael addition of **83** with methyl vinyl ketone provided the symmetrical dione **84**. Brønsted phosphoric acid catalyzed Robinson annulation of **84** formed the desired bicyclic ketone **85**.



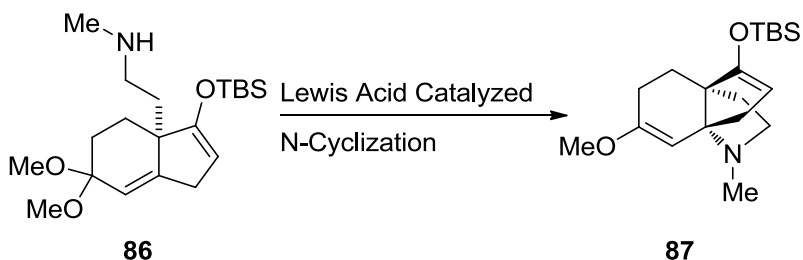
Scheme 24: Synthesis of indene dione

### Strategy for Tricyclic Ring Formation

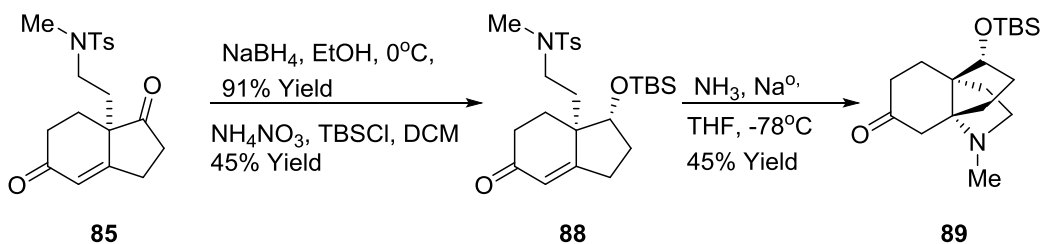
With the preparation of indenone **85**, we envisioned the formation of tricyclic core **87** can be derived from the dimethyl acetal **86** via a Lewis acid catalyzed N-

cyclization (Scheme 25).  $\text{BCl}_3$  proved to effectively catalyze N-cyclization in Castle's acutumine synthesis. Initially, ketone **85** was treated with LDA to form the enolate which was immediately trapped with TBSCl affording the enol silyl ether **86**, but the reaction was unsuccessful. Also, the protection of the ketone via ketal formation was also unfruitful.

Indenone **85** was selectively reduced with  $\text{NaBH}_4$  in EtOH giving a syn-alcohol,<sup>80c</sup> which was readily protected with TBSCl and a mild acid,  $\text{NH}_4\text{NO}_3$  to form silyl ether **88** (Scheme 26). The deprotection of the tosyl group in the presence of  $\text{NH}_3$  and sodium metal, to our delight, produced the cyclized product **89**.



Scheme 25: Proposed strategy for the formation of tricyclic core

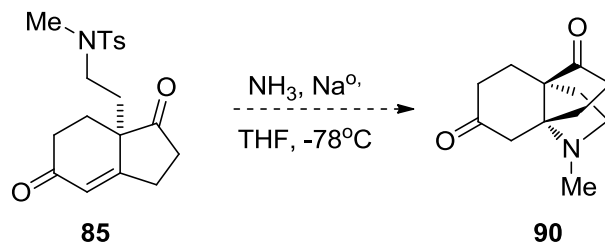


Scheme 26: Prepared tricyclic core via radical amino cyclization

### Conclusion

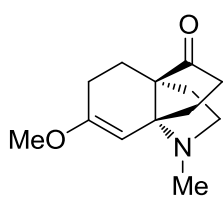
In summary, the tricyclic core **89** was concisely synthesized in eight steps. The strategy could be further optimized through a radical amino cyclization of **85** to produce **90** (Scheme 27). With this reaction we aimed to reduce up to four excessive step sequences: carbonyl reduction, TBS protection, TBS deprotection, and oxidation. Comparing the desired tricyclic ring **74** with model substrate **91**, the actual substrate **74** consists of a carbonyl group at C4 and a methoxy group at C2 (Figure 1). The presence of the vinyl methoxy group at C2 may result in reduced reactivity of radical amino cyclization due to its electron donating resonance.

As shown in scheme 28, the desired tricyclic ring, **74** could be synthesized utilizing analogous sequences of **91** synthesis. Michael addition of **83b** with 1-methoxybut-3-en-2-one will provide 2-methoxy ketone **84b**. Asymmetric aldol condensation of **84b** with chiral Brønsted phosphoric acid would afford desired bicyclic ring **85b**, which will provide the vinyl methoxy group at C2 and a carbonyl group at C4 in the tricyclic acutumine intermediate **74**.

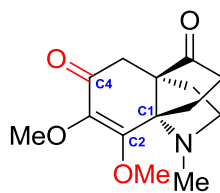


Scheme 27: Radical N-cyclization of indenone

31

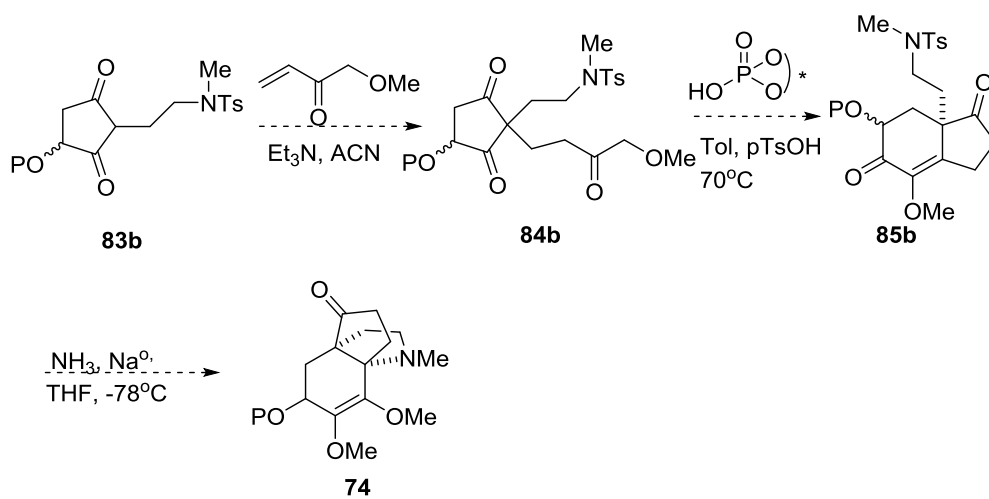


91



74

Figure 1: Comparison of the model tricyclic ring 103 and the actual core 74



Scheme 28: Proposed strategy toward the preparation of desired tricyclic core 74

## CHAPTER 4 - HYDROAMINATION INTRODUCTION

General Background

Hydroamination is the addition reaction of an amine N-H bond across an unsaturated C-C bond, which allows a facile and highly atom-economic transformation for the generation of nitrogen-containing fine chemicals and pharmaceuticals, as well as alkaloid skeletons.<sup>49</sup> In general, high activation energy is required for the direct addition of amines across C-C bonds due to the electrostatic repulsion between the electron lone pair at the nitrogen and the electron rich  $\pi$  bond of the alkenes.<sup>49,50</sup> The high energy difference between the orbitals  $\pi(\text{C}=\text{C})/\sigma^*(\text{N}-\text{H})$  or  $\sigma(\text{N}-\text{H})/\pi^*(\text{C}=\text{C})$  renders the cyclization process is unfavorable.<sup>50</sup> For the last two decades, research activity has been focused on development of catalytic systems for hydroamination/cyclization reaction. There are two main types of catalytic system: Lanthanide-, and Alkali-metalamide (late transition metals Pd, Ir, or Rd) catalytic systems.

Among the development of hydroamination catalysts, organo rare earth transition metal complexes are arguably the most versatile and most reactive catalysts for the hydroamination of non-activated alkenes, alkynes, allenes and dienes to form amines, imines, and enamines.<sup>51</sup> In our group, we focus on the development of catalysts for intramolecular hydroamination of alkenes; using early transition metals specifically group 3 metals.

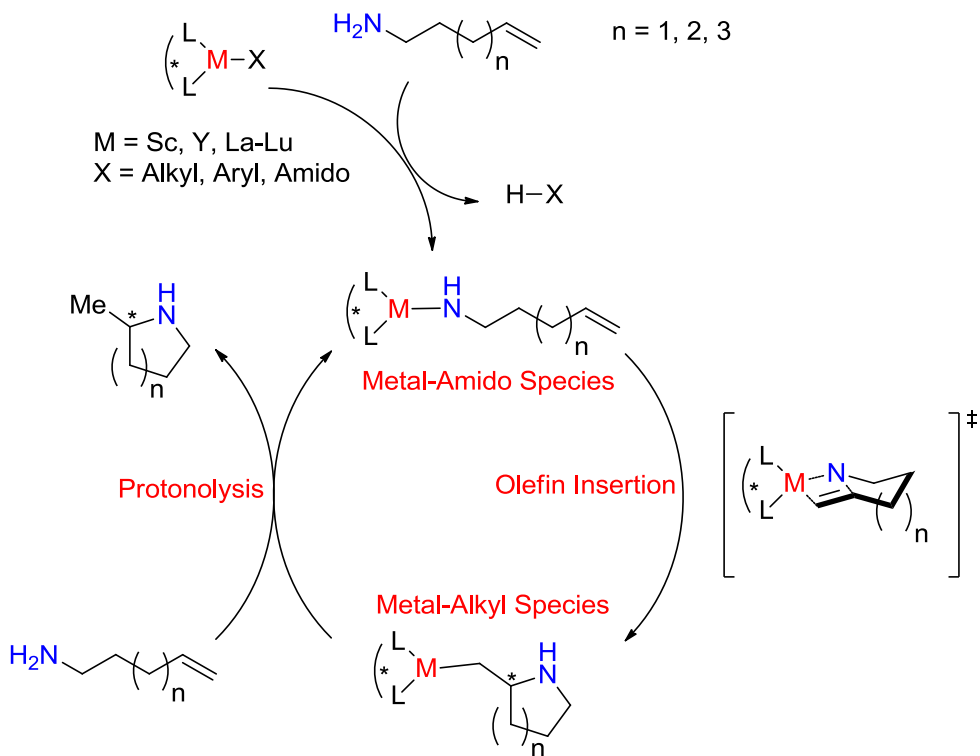
### Group 3 Metals: Lanthanides

F-block element ions,  $_{57}\text{La}$ - $_{71}\text{Lu}$ , have the trivalent oxidation level as the most stable state. Lanthanides and transition metals have different chemical properties. While transition metals have full d-type orbitals and often covalently bonded to ligand, organolanthanide complexes generally have substantial ionic character and behave as typical “hard” acids.<sup>52</sup> Furthermore, lanthanides have larger ionic radii and greater flexibility in geometry and coordination sites than transition metals (eight, ten, and twelve coordination complexes).<sup>52</sup> Common for all early transition metal complexes in hydroamination, group 3 metals are highly electrophilic and “hard” binding partners operating via activation of the amine rather than via activation of the alkene due to their lack of d-electrons for effective  $\pi$ -bond interaction. Metal-carbon  $\sigma$ -bonds of the lanthanides are typically very reactive and short-lived.<sup>52</sup> Importantly, due to the high electrophilicity of the complexes, the lanthanide complexes are generally air and moisture sensitive which require the use anaerobic techniques, and dry solvents.

### Mechanism of Intramolecular Hydroamination of Alkenes

In group 3 complex catalyzed hydroamination, the metals involved are formally in the  $d^0$  state, and involve neither oxidative addition nor reductive elimination.<sup>53</sup> The reaction mechanism involves insertion, cycloaddition, and ligand redistribution via  $\sigma$  metathesis; hence the oxidation state of the metal is unchanged. The catalytic cycle initially proceeds through metal-amide species which is formed upon protonolysis of the metal complex and aminoalkene substrate (Scheme 29). Insertion of the unsaturated C-C

bond with the metal-amide bond with a seven member chair-like transition state ( $n=1$ ) resulting the metal-alkyl species. This sterically demanding transition state creates a more sterically open lanthanide complex with a large-sized metal than with a smaller one. The insertion step is considered to be rate determining.<sup>53</sup> The metal-alkyl species undergoes fast protonolysis with a second aminoalkene substrate regenerating the metal-amino species and producing the heterocyclic product.



Scheme 29: Proposed mechanism for hydroamination/cyclization of aminoalkenes

### The First Group 3 Catalyzed Hydroamination

In 1989, Marks and coworkers reported the first organolanthanide-catalyzed hydroamination reactions.<sup>54</sup> In this study, Marks and coworkers developed  $[Cp_2^*LnR]$  (**92**),  $[Me_2SiCp_2LnR]$  (**93**), and  $[Et_2SiCp_2LnR]$  (**94**) complexes (Figure 2). Complexes **93**

and **94** are sterically more open structures due to silyl linkage, and thus they have much higher catalytic activity than complex **92**. For less hindered and more simple aminoalkenes, the order of catalytic activity of the lanthocenes is **92** < **95** < **93** < **94** < **96** (Scheme 30).<sup>55</sup> In summary, the rate of cyclization increases when Cp ligands are changed to TMSCp, and the larger ionic radius of lanthanide metal also increases the reaction rate of hydroamination.

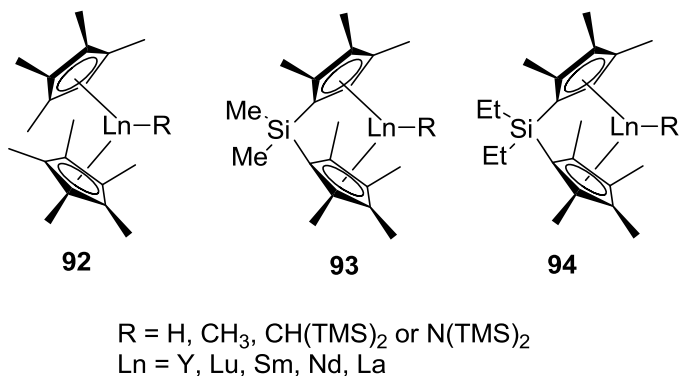
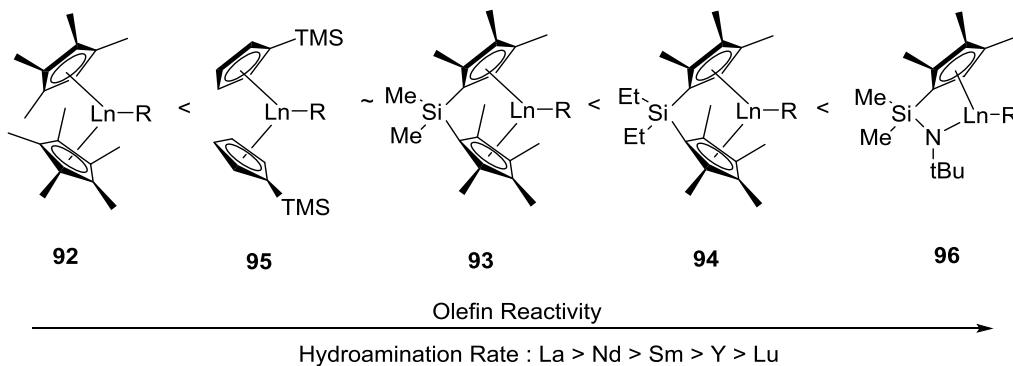
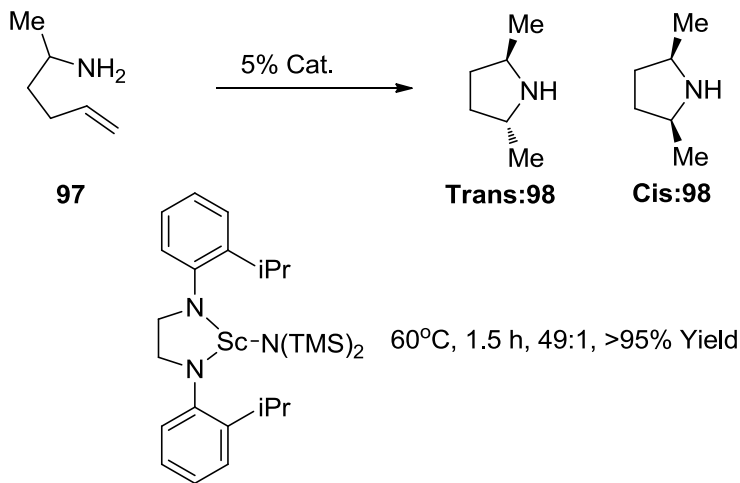


Figure 2: Developed catalysts for hydroamination

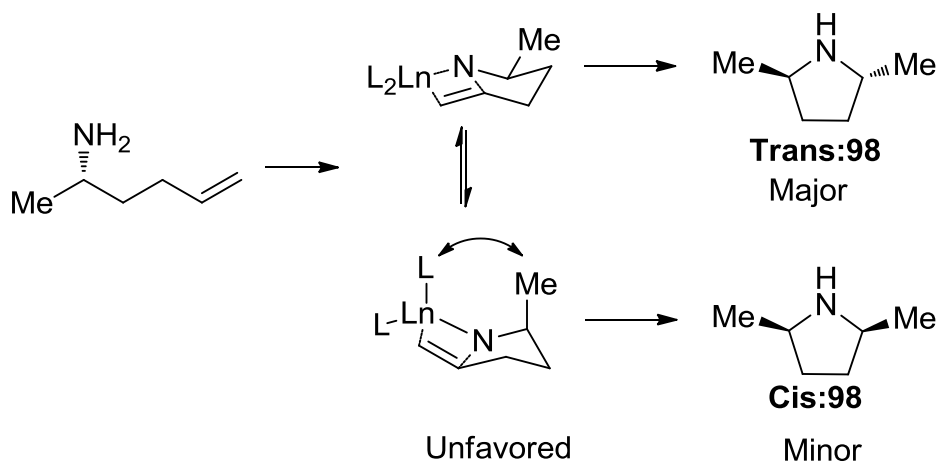


Scheme 30: Relative catalytic activities of Lanthanide complexes for hydroamination



Scheme 31: Diastereoselective cyclization of **97**

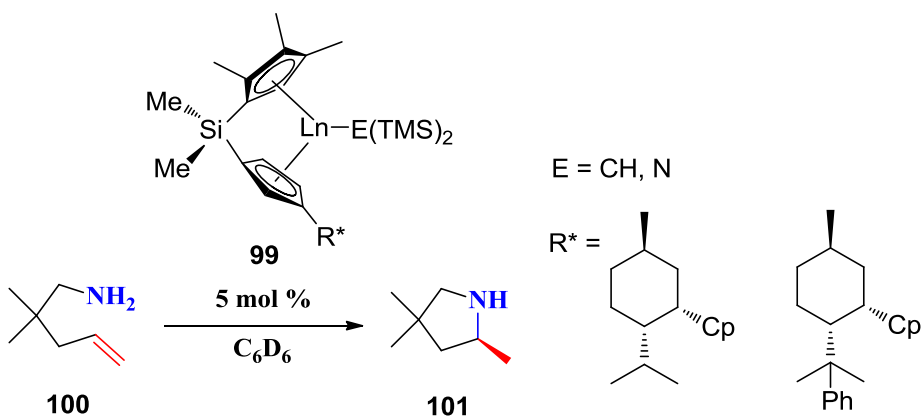
Since then, many more lanthanide-based catalysts had been developed for aminoalkene hydroamination, ranging from simple tris(amides)  $\text{Ln}[\text{N}(\text{TMS})_2]_3$ <sup>56</sup> to more elaborate frameworks: chelating diamides,<sup>57</sup> diamido amine,<sup>58</sup> tridentate triamine.<sup>59</sup> Most noticeably, Kim and Livinghouse developed catalytic systems that generated in situ from rare earth metal tris(amides)  $\text{Ln}[\text{N}(\text{TMS})_2]_3$  and various chelating diamines had shown exceptional rate enhancement and improved diastereoselectivities in intramolecular hydroamination (Scheme 31).<sup>57</sup> The challenging cyclization of aminoalkene **97** was accomplished with high *trans*-diastereoselectivity (49:1 dr). The preferred formation of *trans*-**98** is favorable due to its minimal 1,3-diaxial interaction between methyl substituent and the steric metal ligand in the chair-like cyclization transition state (Scheme 32). Also, we further investigated the hydroamination reactivity and diastereoselectivity based on substrate dependence. The results of this study are discussed in chapter 5.



Scheme 32: Rationalization of diastereoselectivity

### Asymmetric Hydroamination

#### The First Lanthanide - Catalyzed Asymmetric Hydroamination



Scheme 33: Marks' Lanthoanocene-catalyzed asymmetric hydroamination

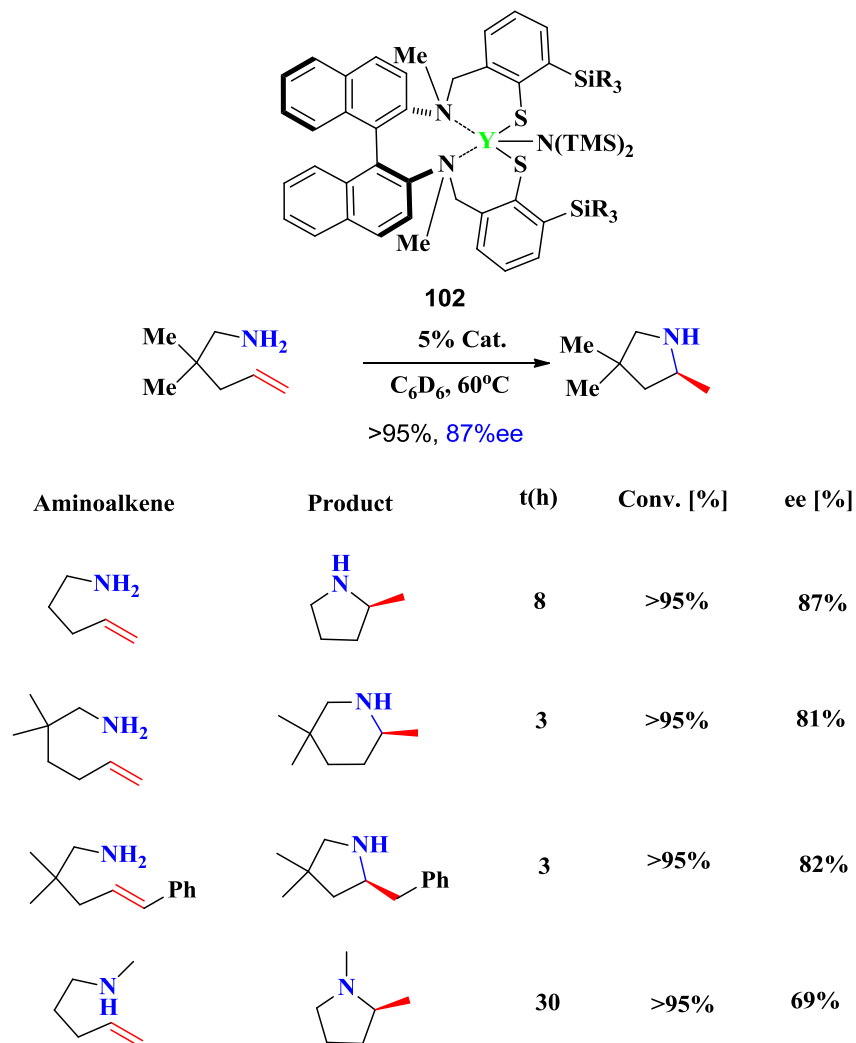
As a result of the large size and geometrical flexibility of organolanthanides, precise control of the metal coordination can be difficult. However, the first catalytic enantioselective intramolecular hydroamination was reported by Mark and coworkers in

1992.<sup>60</sup> The use of chiral *ansa*-metallocenes, **99** complex afforded chiral pyrrolidine **101** in 74% ee (Scheme 33). The cyclization of aminoalkene substrates showed the increase in enantiomer excess with decreasing temperature, and the enantiomer excess increases with decreasing lanthanide ionic radius. However, the application of these C<sub>1</sub>-symmetric chiral *ansa*-lanthanocenes **99** was limited due to facile epimerization process via reversible protolytic cleavage of the metal cyclopentadienyl bond under the reaction conditions of catalytic hydroamination.

#### Livinghouse's Asymmetric Hydroamination from Bis-(thiolate) Complexes

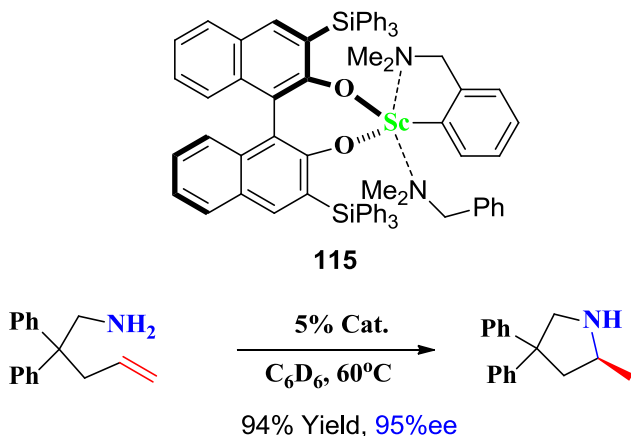
A number of group III and lanthanide catalysts had been discovered for enantioselective hydroamination. Kim and Livinghouse reported that Yttrium (III) bistiophenoate complex **102**, prepared in situ from homoleptic yttrium amide and a bistiolate ligand, has shown to be an excellent catalyst for enantioselective hydroamination (Table 2).<sup>61</sup> Variations of the sterically demanding silyl substituents on the thiophenolate moiety allows facile fine-tuning of the enantiomeric excess resulting in increasing selectivity with increase steric hindrance. The aminothiophenolate catalyst system **102** provided good to high enantioselectivities for a wide range of aminoalkene substrates; including secondary amine, and disubstituted alkene.

Table 2: Livinghouse's Yttrium asymmetric hydroamination



### Hultzsche's Asymmetric Hydroamination

Hultzsche and others also reported significantly high catalytic reactivity when scandium 3,3'-tris(phenylsilyl)binaphtholate complex **103** was used (Scheme 34). The sterically demanding tris(aryl)silyl substituents at the 3 and 3' position show excellent catalytic activity and provide up to 95% ee for pyrrolidines.<sup>62</sup>



Scheme 34: Hultzschi's Scandium asymmetric hydroamination

Marks' chiral lanthocenes underwent facile epimerization via reversible protolytic cleavage of the metal cyclopentadienyl bond.<sup>63</sup> Thus, the enantioselectivity is limited by the catalyst epimeric ratio. For both Livinghouse and Hultzschi, although the yttrium and scandium complexes provided a good enantioselectivities, the chelated ligands were difficultly accessible via multistep synthesis. In our study, we decided to develop a much simple catalyst system based on commercially available 1,1'-binaphthyl diamine. The chiral ligand precursor is commercially available; therefore it can be readily modified with different sterically demanding substituents for fine-tuning enantioselectivity and catalytic reactivity.

#### Development of New Hydroamination Catalyst Systems

Initial study with (+)-**104a** with both yttrium and samarium showed promising results, and up to 75 and 72 % ee were achieved respectively (Table 3). Fine-tuning the enantioselectivity of both (+)-**104b** and (+)-**104c** ligands, which have the methyl

substituents on the aryl moieties to increase the steric hindrance, decreased stereoselectivity and reactivity for both yttrium and samarium complexes. Fortunately, the use of samarium *N,N'*-dibenzosuberyl-1,1'-binaphthyl-2,2'-diamine **104d** provided the chiral pyrrolidine **106** in 90% ee. From this initial data, we observed that the percent ee increases with increasing lanthanide ionic radius, which is opposite with what Marks observed with the *ansa*-metallocenes, **99**. The detailed results of this study are discussed in chapter 6.

Table 3: Optimization of ligand substituents for asymmetric hydroamination



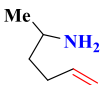
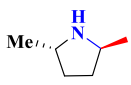
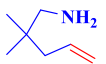

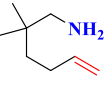



**105**  $\xrightarrow[\text{C}_6\text{D}_6]{\text{5 mol \% 104}}$  **106**

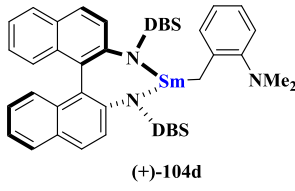
Precatalyst	Metal	t	C <sup>a</sup>	ee[%] <sup>b</sup> (config.)	
(+)- <b>104a</b>	Y	7 d	>95%	75	a: R =
(+)- <b>104a</b>	Sm	5 h	>95%	72	
(+)- <b>104b</b>	Y	2 d <sup>c</sup>	>95%	14	b: R =
(+)- <b>104b</b>	Sm	14 d	>95%	56	
(+)- <b>104c</b>	Y	2 d <sup>c</sup>	>95%	20	c: R =
(+)- <b>104c</b>	Sm	3 d	>95%	52	
(+)- <b>104d</b>	Y	4.5 d	>95%	76	d: R =
(+)- <b>104d</b>	Sm	4 h	>95%	90	

### Substrate Scope Investigation

The use of complex (+)-**104a** for hydroamination of aminoalkene **107** and **109** proved to be unsuccessful (Table 4, entry 1 and 2). However, the cyclization of gem-dimethyl aminoalkene **105** with (+)-**104a** provided up to 90% ee (entry 3). Unfortunately, the gem-dimethyl aminoalkene **111** which forms chiral 6-member ring pyrrolidine **112** provided a very low enantioselectivity (entry 4). The same result was observed with phenyl methanamine **113** with only 20% ee of quinolone **114** being obtained (entry 5). The samarium binaphthyl diamine (+)-**104a** catalyst system proved to be limited in term of substrate scope. Only gem-dimethyl aminoalkenes that form 5-membered ring pyrrolidine provided a good enantioselectivity. Thus the gem-dimethyl substituent not only provided the Thorpe-Ingold effect increasing the reactivity, but also played a significant role in stereoselectivity.

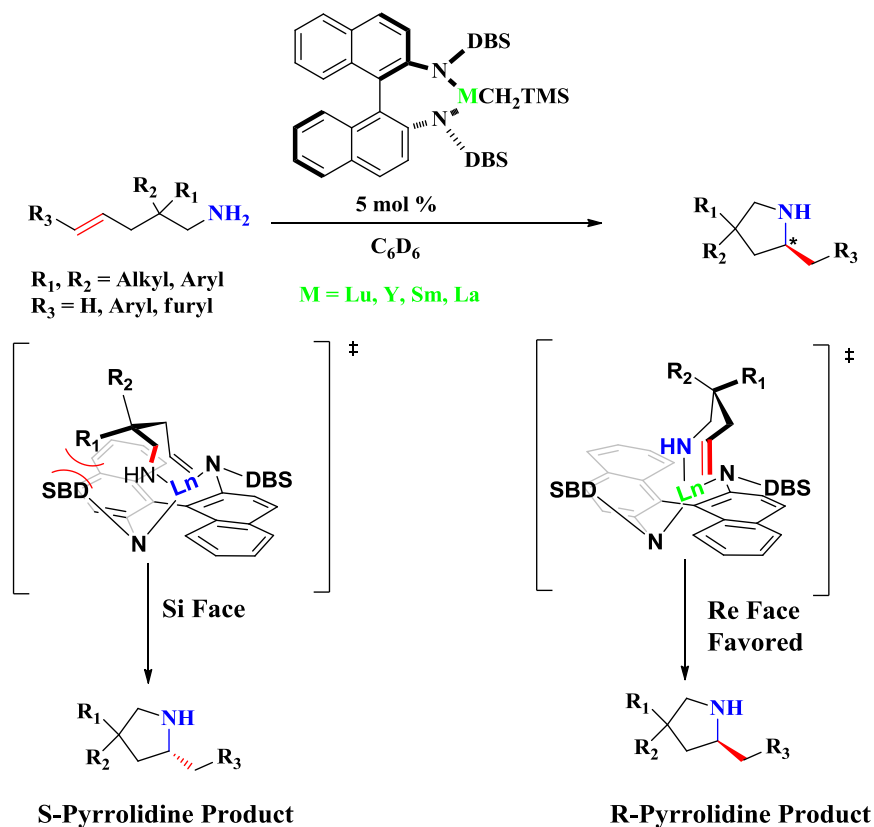
Table 4: Substrate scope

Entry	Precatalyst	Aminoalkene	Product	t(h)	Yield [%]	ee [%]
1	(+)-104d	 <b>107</b>	 <b>108</b>	58 d	>95%	0
2	(+)-104d	 <b>109</b>	 <b>110</b>	24 h	>95%	0
3	(+)-104d	 <b>105</b>	 <b>106</b>	4 h	>95%	96
4	(+)-104d	 <b>111</b>	 <b>112</b>	20 h 45 °C	>95	17
5	(+)-104d	 <b>113</b>	 <b>114</b>	90 °C 14 d	95%	20

  
 (+)-104d

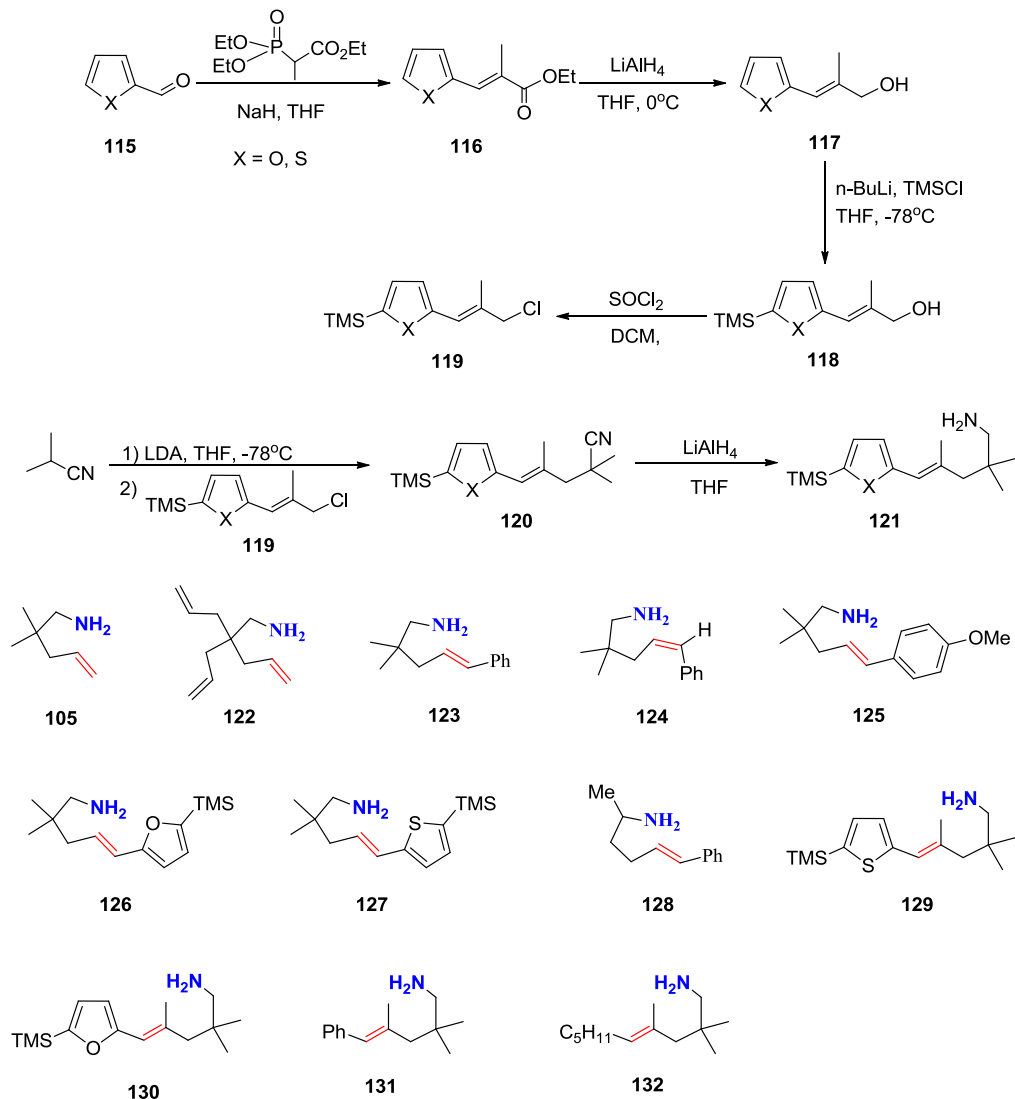
### Proposed Stereo-Chemical Model

According to the results in table 4, the reactivity and stereoselectivity were determined at the olefin insertion step (scheme 29). The chair-like transition state for an approach of Ln-N to the *si* face of the olefin, forming the (*S*)-pyrrolidine product, is blocked by sterically unfavorable interactions of the gem-dimethyl substituent with one of the alkyl groups of the catalyst complex (Scheme 35). Whereas, the approach on the *re* face, leading to the formation of (*R*)-pyrrolidine, is favored.<sup>64</sup>



Scheme 35: Proposed stereochemical model for asymmetric hydroamination

### Synthesis of Aminoalkene Substrates



Scheme 36: Synthesis of aminoalkenes

The preparation of aminoalkenes commenced with the Horner-Wadsworth-Emmons reaction of the aldehyde **115** and ethyl phosphonate producing ethyl acrylate **116**, which undergoes reduction ( $\text{LiAlH}_4$ ) yielding allyl alcohol **117** (Scheme 36). Treatment of **117** with *n*-BuLi, followed by the addition of TMSCl provided the alkyl

trimethylsilylated alcohol **118**. The alcohol **118** was converted to the chloride **119** in presence of thionyl chloride. Alkylation of allyl chloride **119** and isobutyronitrile in presence of LDA afforded the nitrile **120**, which was reduced to give the corresponding aminoalkene **121**.

CHAPTER 5 - SUBSTRATE STRUCTURAL EFFECT IN Y(III)-CATALYZED  
HYDROAMINATION/CYCLIZATION OF 1,2-DISUBSTITUTED AND  
1,1,2-TRISUBSTITUTED AMINOALKENES TERMINATED  
BY 2-(2-HETEROARENYL) GROUPS

Contribution of Authors and Co-Authors

Manuscript in Chapter 5.

Author: Dr. Tao Jiang

Contributions: Examined catalytic hydroamination and mechanistic studies involving aminoalkenes terminated by the 2-(Phenyl)ethenyl group (49-50). Initiated the study: Hydroamination/cyclization of 1,1,2-trisubstituted aminoalkenes and diastereoselectivity studies (51-52). Repeated and confirmed the study of catalytic hydroamination involving 1,2-disubstituted and 1,1,2-trisubstituted aminoalkenes terminated by 2-(2-heteroarenyl) groups (53-54). Prepared and analyzed aminoalkene substrates and tosyl pyrrolidine products.

Author: Khoi Huynh

Contributions: Repeated and confirmed hydroamination/cyclization of 1,1,2-trisubstituted aminoalkenes and diastereoselectivity studies (51-52). Examined the study of catalytic hydroamination involving 1,2-disubstituted and 1,1,2-trisubstituted aminoalkenes terminated by 2-(2-heteroarenyl) groups (53-54). Prepared and analyzed aminoalkene substrates.

Author: Prof. Tom Livinghouse

Contributions: Advised and supervised the project.

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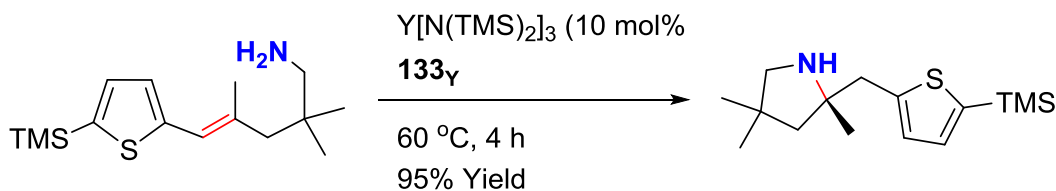
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Abstract

A series of 2-phenyl- and 2-(2-heteroarenyl)-bearing amines possessing 1,2-disubstituted and 1,1,2-trisubstituted alkenes have been evaluated in intramolecular hydroaminations catalyzed by Y[N(TMS)<sub>2</sub>]<sub>3</sub> (**133<sub>γ</sub>**). Aminoalkenes possessing a terminal 2-(5-trimethylsilyl)thienyl group exhibited substantially enhanced reactivity compared to their 2-(phenyl)-containing counterparts. Cyclization efficiencies imparted by the 2-[(5-trimethylsilyl)furanyl] substituent were comparable or only slightly better than those obtained with the simple the 2-(phenyl) group.

Introduction

The catalytic hydroamination/cyclization of alkenes constitutes one of the most efficient synthetic routes to nitrogen containing heterocycles. Whereas main-group metal complexes have recently been used as catalysts for alkene hydroamination,<sup>65a,b</sup> the most general cases for the synthesis of amines and their derivatives by this important reaction involve transition-metal catalysis using complexes of rhodium,<sup>65c-e</sup> ruthenium,<sup>65f-g</sup> nickel,<sup>65h-j</sup> palladium,<sup>65k-q</sup> gold<sup>65r-t</sup> as well as the group 3<sup>66a-o</sup> and group 4<sup>66p-z</sup> metals. In contrast to catalysis by many complexes of the late transition metals, hydroaminations involving complexes of the group 3 metals are believed to proceed via insertion of the

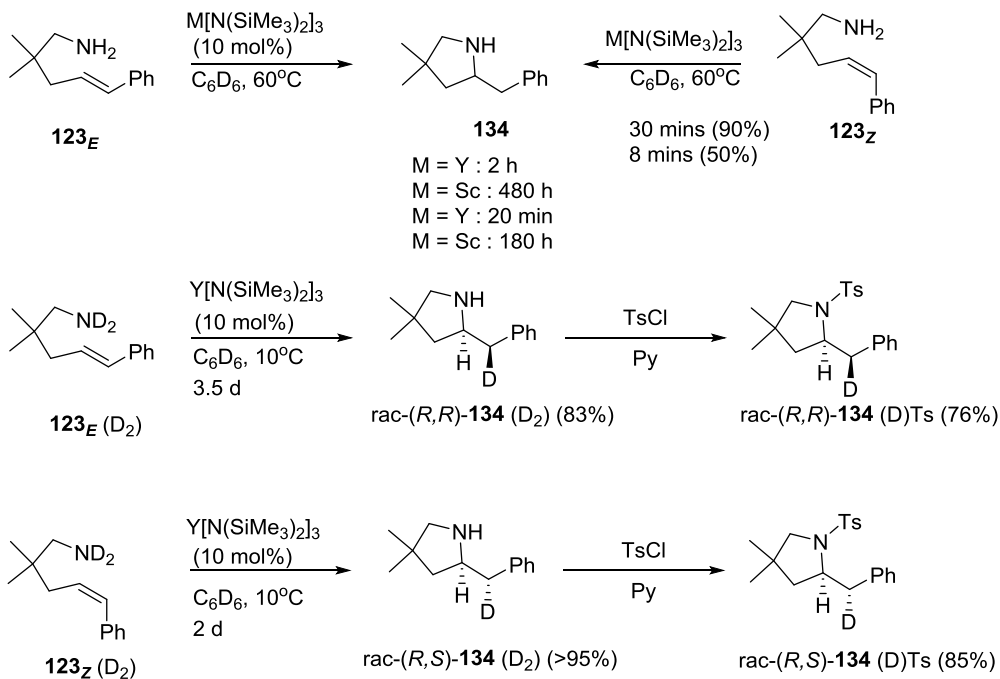
C=C double bond into the metal-amido (M–N) bond with overall *syn*-addition.<sup>66a,b</sup> It is also noteworthy that the relative rates associated with intramolecular hydroaminations by group 3 metals are correlated with both the covalent radius of the metal (i.e., Y > Sc) and its ligand environment.<sup>66a,c</sup>

Herein, we document hydroamination/cyclizations involving 1,1,2-trisubstituted alkenes and describe substantial rate enhancements that are obtained when 2-[(5-trimethylsilyl)thienyl] groups are employed as addends. In addition, we provide direct experimental evidence for *syn*-metalloamination<sup>67</sup> as well as the geometrical dependence of cyclization efficiency. The amino-alkenes **123-132** employed in this study were prepared by the alkylation of the requisite allylic chlorides with lithioiso-butyronitrile followed by reduction (LiAlH<sub>4</sub>). Amino-alkene **128** was prepared by alkylation of the lithio derivative of 2-propanone-*N,N*-dimethylhydrazone with (*E*)-1-chloro-3-phenyl-2-propene followed by hydrolysis (H<sub>3</sub>O<sup>+</sup>) and reductive amination (NH<sub>4</sub>OAc, NaBH<sub>3</sub>CN).

Catalytic Hydroamination and Mechanistic  
Studies Involving Aminoalkenes Terminated  
by the 2-(Phenyl)ethenyl Group

Dr. Jiang and Prof. Livinghouse commenced this investigation by examining the hydroamination/cyclization of **123<sub>E</sub>** catalyzed by simple group 3 tris(amide) compounds Y[N(TMS)<sub>2</sub>]<sub>3</sub> (**133<sub>Y</sub>**) and Sc[N(TMS)<sub>2</sub>]<sub>3</sub> (**133<sub>Sc</sub>**). Exposure of **123<sub>E</sub>** to **134<sub>Y</sub>** (10 mol %) in C<sub>6</sub>D<sub>6</sub> at 60 °C resulted in efficient cyclization over 2 h to provide the corresponding pyrrolidine **134** (ca. 90%, NMR; Scheme 37),<sup>68</sup> which was isolated as the corresponding 4-methylbenzenesulfonamide **134<sub>TS</sub>** in 83% yield. As expected, the cyclization of **123<sub>E</sub>**

catalyzed by **133<sub>Sc</sub>** was considerably more lethargic, giving **134** (90%, NMR) after fully 480 h at 60 °C.<sup>66c</sup> It is of interest that the rates of hydroamination/cyclization were typically not linear throughout the course of the reaction, but instead decreased as the reaction progressed. Accordingly, cyclization of **123<sub>E</sub>** in the presence of **133<sub>Y</sub>** (10 mol%) required only 20 min at 60 °C, whereas **133<sub>Sc</sub>** (10 mol%) catalyzed 50% cyclization in 180 h under these conditions. In light of the above results, all subsequent studies focused on intramolecular hydroaminations catalyzed by **133<sub>Y</sub>**. The effect of alkene geometry on the rate of cyclization was probed by subjecting **123<sub>Z</sub>** to **133<sub>Y</sub>** (10 mol%, C<sub>6</sub>D<sub>6</sub>, 60 °C). In this instance, a pronounced rate enhancement was observed because conversion into **134** required only 30 min (90%, NMR) furnishing **134<sub>Ts</sub>** in 82% isolated yield. For this substrate, 50% cyclization was achieved in only 8 min under identical conditions (Scheme 37).

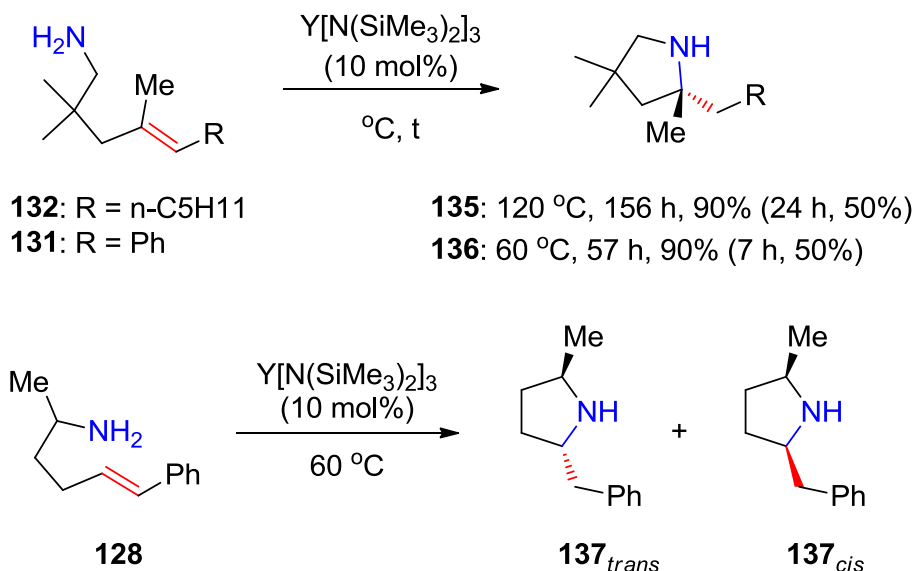


Scheme 37: Hydroamination/cyclization of aminostyrenes

It is generally accepted that alkene hydroamination catalyzed by complexes of the group 3 metals proceeds via *syn*-addition of the metal-amido (M–N) bond to the C=C double bond.<sup>66a,b,4</sup> To probe this experimentally, amino-alkenes **123<sub>E</sub>(D<sub>2</sub>)** and **123<sub>Z</sub>(D<sub>2</sub>)** were prepared by H–D exchange and subjected to cyclization catalyzed by **133<sub>Y</sub>** (C<sub>6</sub>D<sub>6</sub>, 10 °C). Under these conditions, **123<sub>E</sub>(D<sub>2</sub>)** provided *rac*-(*R,R*)-**134(D<sub>2</sub>)** in 3.5 days (83% NMR) and **123<sub>Z</sub>(D<sub>2</sub>)** gave *rac*-(*R,S*)-**134(D<sub>2</sub>)** in 2 days (>95% NMR). Subsequent conversion of *rac*-(*R,R*)-**134(D<sub>2</sub>)** and *rac*-(*R,S*)-**134(D<sub>2</sub>)** into the corresponding 4-methylbenzenesulfon-amides afforded *rac*-(*R,R*)-**134(D)**<sub>Ts</sub> and *rac*-(*R,S*)-**134(D)**<sub>Ts</sub> in 76 and 85% yield, respectively. Experimental validation for the structural assignments of these diastereomers was based on <sup>1</sup>H NMR H–H coupling constants conferred by hindered rotation arising from the *N*-tosyl substituent. For *rac*-(*R,R*)-**134(D)**<sub>Ts</sub>, the vicinal *J* value observed for the benzylic proton was 9.5 Hz, which is consistent with that expected for a pseudo-*anti* orientation. In contrast, for *rac*-(*R,S*)-**134(D)**<sub>Ts</sub>, the corresponding *J* value was 3.6 Hz, as would be expected for a pseudo-*syn* disposition. In addition, the <sup>2</sup>H NMR chemical shifts for *rac*-(*R,R*)-**134(D)**<sub>Ts</sub> and *rac*-(*R,S*)-**134(D)**<sub>Ts</sub> were unique, appearing as singlets at δ = 3.47 and 2.65 ppm, respectively (Scheme 37).

We have previously demonstrated that simple, nonconjugated 1,2-disubstituted alkenes are among the least reactive carbon–carbon double bonds toward intramolecular hydroamination catalyzed by group 3 amide complexes.<sup>66b,d</sup> It is therefore of interest that nonconjugated 1,1,2- trisubstituted alkenes have experienced limited evaluation in the context of hydroamination/cyclization using these catalysts.<sup>69</sup> The latter objective was approached by subjecting **132** in toluene-*d*<sub>8</sub> to **133<sub>Y</sub>** (10 mol%) at 120 °C. Under these

admittedly forcing conditions, **132** was indeed converted into **135** (90%, NMR), albeit after 156 hours, with 50% conversion being achieved in 24 hours. In sharp contrast, the conjugated 1,1,2-trisubstituted aminoalkene **131** underwent relatively facile ring closure in the presence of **133<sub>Y</sub>** (10 mol%, C<sub>6</sub>D<sub>6</sub>) at 60 °C in 57 hours to provide **136** (90%, NMR). In this case, 50% conversion occurred in only 7 hours. As would be expected, lower catalyst loadings resulted in diminished rates of product formation. For **131**, hydroamination/cyclization using **133<sub>Y</sub>** (5 mol%) required 5 days (50% conversion, NMR). In an experiment designed to reveal the diastereoselectivity associated with hydroamination/cyclization involving a simple 2-(phenyl)ethenyl substituent, **128** was treated with **133<sub>Y</sub>** (10 mol%, C<sub>6</sub>D<sub>6</sub>) at 60 °C to provide **137<sub>trans</sub>** and **137<sub>cis</sub>** (*t/c* = 6:1, 90%, NMR). Under identical conditions, 50% conversion was observed in 3 days. The results of this study are summarized in Scheme 38. (The study as discussed above was initiated by Dr. Jiang. The result was later repeated and confirmed by me).



Scheme 38: Hydroamination/cyclization of 1,1,2-trisubstituted aminoalkenes and diastereoselectivity Studies

Catalytic Hydroamination Involving 1,2-Disubstituted  
and 1,1,2-Trisubstituted Aminoalkenes  
Terminated by 2-(2-Heteroarenyl) Groups

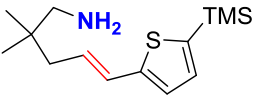
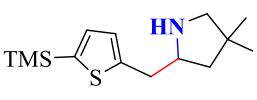
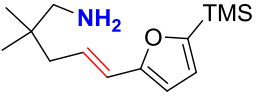
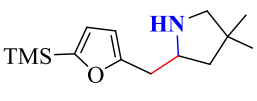
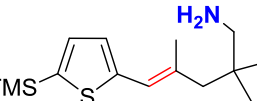
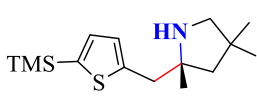
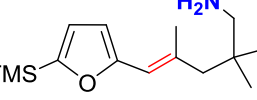
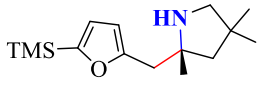
We have previously shown that the incorporation of a 2-(2-thienyl) moiety leads to a marked acceleration of Sc(III)-catalyzed bicyclization of an aminodiene enroute to the pheromone xenovine.<sup>66b</sup> The synthetic utility of 2-heteroarenyl substituents is significant in that the thienyl nucleus is readily convertible into the corresponding alkane by reductive desulfurization,<sup>66b</sup> and because the furanyl group can serve as a synthon for a 1,4-dione through acid-catalyzed hydrolysis.<sup>70</sup>

In a set of studies to determine the efficacy of alternatives to the simple 2-phenyl group as conjugative adjuvants in simple hydroaminative ring closures, Dr. Jiang and I under Prof. Livinghouse's supervision investigated the utility of 2-[(5-trimethylsilyl)thienyl] and 2-[(5-trimethyl-silyl)furanyl] substituents as potential aromatic facilitators for Y(III)-catalyzed hydroamination/cyclization. To this end, aminothiophenes **127** and **129**, and aminofurans **126** and **130** were subjected to the standard protocol (**133<sub>Y</sub>**, 10 mol%, C<sub>6</sub>D<sub>6</sub>, 60 °C). In all cases the 2-[(5-trimethylsilyl)thienyl] subunit proved to be superior to the corresponding 2-[(5-trimethylsilyl)furanyl] group as assistants in efficient ring closures to furnish pyrrolidines **138,140** and **139,147**, respectively.<sup>71a,b</sup> As with previous cases, rates of cyclization diminished over the course of the reaction, with 50% conversion being attained in 0.16, 1.0, and 8.0 h for **126**, **129**, and **130**, respectively (Table 5).

As expected, cyclization of **129** in the presence of **133<sub>Y</sub>** (5 mol%) required fully 2 hours (50% conversion) and 12 hours (90% conversion, NMR). It is of considerable

interest that although the 2-[(5-trimethylsilyl)thienyl] group imparts a markedly enhanced predisposition toward hydroamination/cyclization than its simple 2-(phenyl) counterpart, the 2-[(5-trimethylsilyl)furyl] substituent is roughly comparable in reactivity to the latter.

Table 5: Hydroamination/cyclization of amines tethered to 2-(2-heteroarenyl)ethenyl groups

Aminoalkene	Pyrrolidine	Time (h) <sup>a,b</sup>	Time (h) <sup>a</sup>	NMR Yield (%) <sup>c</sup>	Isolated Yield (%) <sup>d</sup>
 <b>127</b>	 <b>138</b>	-	0.5	95%	87
 <b>126</b>	 <b>139</b>	0.16	1.5	95%	92
 <b>129</b>	 <b>140</b>	1	4	95%	76
 <b>130</b>	 <b>141</b>	8	57	83%	68

a: All reactions were conducted at 60 °C.

b: Time required for 50% conversion.

c: Integration relative to p-xylene as an internal standard.

d: Isolated as the p-toluenesulfonamide.

We have shown that structurally diverse 1,1,2-trisubstituted alkenes can serve as effective participants in intramolecular hydroaminations catalyzed by  $Y[N(TMS)_2]_3$  (**133<sub>Y</sub>**), particularly when used in conjugation with a 2-(trimethyl-silyl)thienyl substituent. Cyclization efficiency for a representative aminoalkene possessing a *Z*-configured 2-(phenyl)ethenyl group is considerably higher than that observed for the corresponding *E*-isomer. In addition, deuterium labeling studies have provided the first *direct* experimental evidence for *syn*-metalloamination of the C=C bond during the course of Hydroamination/Cyclization.

CHAPTER 6 - *N,N'*-DIBENZOSUBERYL-1,1'-BINAPHTHYL-2,2'-DIAMINE. A  
HIGHLY EFFECTIVE SUPPORTING LIGAND FOR THE ENANTIO-  
SELECTIVE CYCLIZATION OF AMINOALKENES  
CATALYZED BY CHELATING DIAMIDE  
COMPLEXES OF La(III) AND Y(III)

Contribution of Authors and Co-Authors

Manuscript in Chapter 6.

Author: Dr. Helena Lovick

Contributions: Examined the optimization of ligand substituents for asymmetric hydroamination.

Author: Khoi Huynh

Contributions: Prepared catalyst complexes. Studied enantioselective hydroamination catalyzed by group 3 metal complexes.

Author: Prof. Tom Livinghouse

Contributions: Advised and supervised the project.

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Authors: Khoi Huynh, Tom Livinghouse, Helena Lovick  
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### Abstract

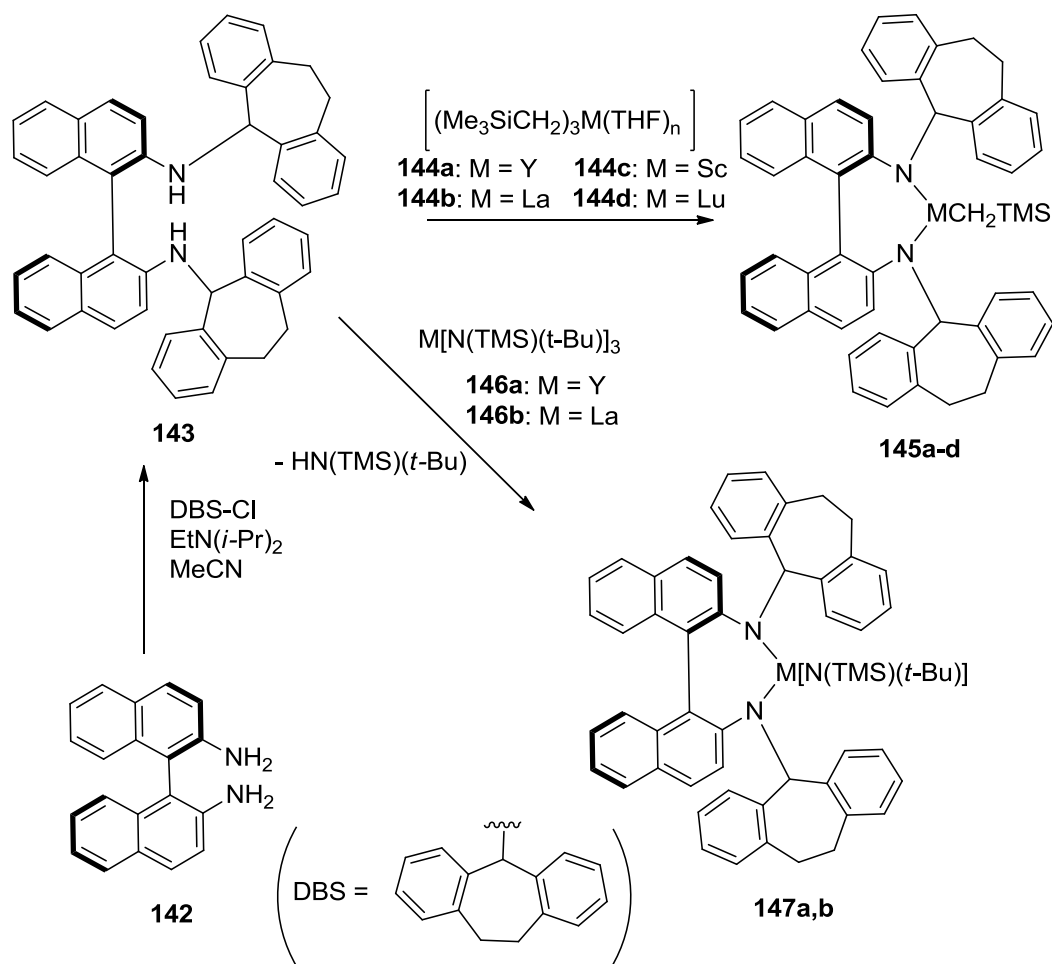
Enantioselective hydroamination/cyclization of representative aminoalkenes catalyzed by chelating diamide complexes of La(III) and Y(III) are described. It is noteworthy that the La(III) complex derived from the sterically demanding (*R*)-*N,N'*-dibenzosuberyl-1,1'-Binaphthyl-2,2'-diamine proligand provides enantioselectivities that are in many cases significantly higher than those obtained with the corresponding Y(III) analog. In addition, the presence of LiCl was typically found to suppress both the rates and enantioselectivities obtained with the Y(III) complex when compared to its La(III) counterpart, in addition to completely suppressing the bicyclization of **148b**. The amide complexes employed in the latter study were prepared by “amine elimination” using the new, highly active bases La[N(TMS)(*t*-Bu)]<sub>3</sub> and Y[N(TMS)(*t*-Bu)]<sub>3</sub>.

### Introduction

The elucidation of highly enantioselective reactions for the construction of carbon-nitrogen bonds remains a central goal of chemical synthesis. Catalytic hydroamination/cyclization of aminoalkenes constitutes such a synthetic method and is, by definition, a highly atom economical route to heterocycles. Although main-group metal complexes have recently been used as catalysts for alkene hydroamination,<sup>72a</sup> the most general cases for the synthesis of amines and their derivatives involve transition metal catalysis using complexes of rhodium,<sup>72b-d</sup> ruthenium,<sup>72e-f</sup> nickel,<sup>72g-l</sup> palladium,<sup>72j-p</sup> and gold<sup>72q-s</sup> as well as the group 3<sup>73a-o</sup> and group 4<sup>73p-y</sup> metals. We recently disclosed that chelating diamide complexes of selected group 3 metals derived from simple *N,N'*-

di(aryl)methyl-1,1'-binaphthyl-2,2'-diamine motifs are effective catalysts for enantioselective hydroamination/cyclization.<sup>73e</sup> In this communication we show that (*R*)-*N,N'*-Dibenzosuberyl-1,1'-binaphthyl-2,2'-diamine (**143**) is a vastly superior proligand for this process and, importantly, that the derived chelating diamide complexes of La(III), the largest lanthanide, provide generally higher enantioselectivities than the more sterically congested Y(III) congeners.

### Catalyst Preparation

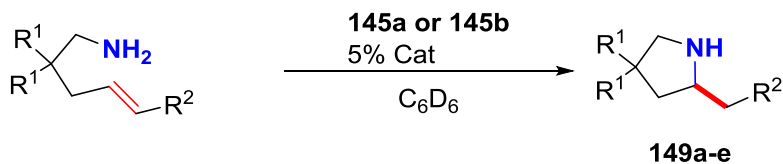


Scheme 39: Synthesis of proligand **143** and complexes **145a-d**, and **147a,b**

(*R*)-*N,N'*-Dibenzosuberyl-1,1'-binaphthyl-2,2'-diamine (**143**) was expeditiously prepared in 81% yield by the reaction of the commercially available reagents (*R*)-1,1'-binaphthyl-2,2'-diamine (**142**) and 5-chlorodibenzosuberane (2.1 equiv) in the presence of ethyldiisopropylamine (2.3 equiv) in MeCN. The catalytic complexes **145a-145d** utilized in this study were prepared in situ as follows. Sequential treatment of ScCl<sub>3</sub>(THF)<sub>3</sub>, LuCl<sub>3</sub>(THF)<sub>3</sub>, LaCl<sub>3</sub>(THF)<sub>1.5</sub> or YCl<sub>3</sub>(THF)<sub>3.5</sub> (1 equiv each) with Me<sub>3</sub>SiCH<sub>2</sub>Li (3.05 equiv) in C<sub>6</sub>D<sub>6</sub> generated solutions of the corresponding homoleptic alkyls (Me<sub>3</sub>SiCH<sub>2</sub>)<sub>3</sub>M(THF)<sub>n</sub> **144a**, **c-d**(*n* = 2) and **144b** (*n* = 1.5)<sup>74</sup> respectively. Immediate addition of **2** (1 equiv, 20 h, rt) then delivered solutions of **145a-d**, to which the aminoalkenes **148a-e** were added (Scheme 39).<sup>75</sup>

### Enantioselective Hydroamination Studies

Our initial investigations focused on the enantioselective cyclization of aminoalkene **148a** catalyzed by **145c** and **145d** that contain group 3 metals possessing the smallest covalent radii. Hydroamination/cyclization of **148a** in the presence of the Sc(III) complex **145c** proceeded comparatively slowly (60 °C, 90 h, 95% conversion) and provided pyrrolidine **149a** in 47% e.e.<sup>76</sup> The corresponding Lu(III) complex also proceeded lethargically, but with an improved (81%) e.e.<sup>77</sup> As expected, the use of the Y(III) and La(III) complexes **145a** and **145b** led to faster cyclization rates,<sup>73a,d,j</sup> but also with surprisingly high enantiomeric excesses (85% and 88% respectively).



**148a:** R<sup>1</sup> = Me, R<sup>2</sup> = H

**148b:** R<sup>1</sup> = allyl, R<sup>2</sup> = H

**148c:** R<sup>1</sup> = Me, R<sup>2</sup> = C<sub>6</sub>H<sub>6</sub>

**148d:** R<sup>1</sup> = Me, R<sup>2</sup> = 4-(MeO)C<sub>6</sub>H<sub>4</sub>

**148e:** R<sup>1</sup> = Me, R<sup>2</sup> = 5-(TM)-2-furanyl

Scheme 40: Enantioselective cyclization of aminodienes 148

Table 6: Enantioselective conversions to pyrrolidines 149

Entry	Substrate	Metal	t <sup>a</sup>	ee% <sup>b</sup>
1	<b>148a</b>	Y	5.6 d <sup>c</sup>	85
2	<b>148a</b>	La	5 h <sup>c</sup>	88
3	<b>148b</b>	Y	18 h <sup>c</sup>	74
4	<b>148b</b>	La	15 min <sup>c</sup>	82
5	<b>148c</b>	Y	6 d <sup>d</sup>	59
6	<b>148c</b>	La	10 h <sup>d</sup>	77
7	<b>148d</b>	Y	12.1 d <sup>e</sup>	61
8	<b>148d</b>	La	9.1 d <sup>f</sup>	87
9	<b>148e</b>	Y	29 h <sup>d</sup>	58
10	<b>148e</b>	La	9 h <sup>g</sup>	87

[a] >95 % conversion as determined by <sup>1</sup>H NMR spectroscopy with p-xylene as the internal standard. [b] Enantiomeric excess.

[c] T = 23 °C. [d] T = 60 °C. [e] T = 90 °C. [f] T = 45 °C. [g] T = 35 °C.

In light of these unexpectedly favorable results, all subsequent experiments were conducted with Y(III) and La(III)-based catalysts. Accordingly, exposure of the

aminoalkenes **148b-e** to the preformed complexes **145a** and **145b** (5 mol %, C<sub>6</sub>D<sub>6</sub>) were performed under the indicated reaction conditions. The results obtained in this study are presented in Table 6. As would be expected, faster conversion rates were always observed when the lanthanum based complex **144b** was employed compared to its yttrium based congener **144a**. This is in accord with the observation that the relative rates of hydroamination/cyclization is coupled to the ionic radius of the group 3 metal within otherwise identical complexes, with the fastest rates being associated with the largest metal centers.<sup>73a,d,j</sup> In contrast, it was not intuitively obvious at the outset of this study that the sterically “less encumbered” complex **144b** would consistently provide higher enantioselectivities (and sometimes substantially so) than **144a**. That this is the case is likely attributable to the unusually congested binding pocket of proligand **143**, compared to its more conventional *N,N*-di(aryl)methyl 15 counterparts.<sup>73e</sup> The steric factor in the present case is doubtless markedly enhanced by conformational immobilization of the aryl rings of the dibenzosuberyl substituents imposed by the ethylene bridge, resulting in the envelopment of smaller metals (i.e., Y < La).

The magnitude of enantioselectivity was also found, in some cases, to be temperature dependent. Accordingly, hydroamination/cyclization of aminoalkene **148d** furnished pyrrolidine **149d** in 87% ee after 9.1 d at 45 °C (Table 6, entry 8). When this reaction was instead conducted at 90 °C (for a direct comparison to the Y complex **144a**, entry 7) the reaction time was reduced to 21 h, but with suppression of the observed ee to 61%.<sup>76</sup> Trifonov and Hannedouche have shown that the presence of LiCl can enhance both the rates and enantioselectivities of representative hydroamination/cyclizations

catalyzed by a Y(III) complex derived from the *N,N*-di(cyclopentyl)-1,1'-binaphthyl-2,2'-diamine proligand. In contrast, LiCl was found to suppress the cyclization rate observed with a Y(III) complex derived from the more sterically hindered *N,N*-di(*t*-butyldimethylsilyl)-1,1'-binaphthyl-2,2'-diamine proligand.<sup>73k</sup> We therefore embarked on an investigation of the activity of LiCl free amide complexes of both Y(III) and La(III) generated by “amine elimination.” Unfortunately, the conventional amide precursors  $M[N(TMS)_2]_3$  and  $M[N(SiHMe_2)_2]_3(THF)_2$  proved insufficiently reactive to metallate **143**. We therefore synthesized the new tris(amide)s  $Y[N(TMS)(t-Bu)]_3$  (**148a**) and  $La[N(TMS)(t-Bu)]_3$  (**148b**) with the expectation that the more strongly basic amide ligand would rapidly take part in the required deprotonation event.<sup>78</sup> This indeed proved to be the case as treatment of **143** with **148a** or **148b** ( $C_6D_6$ , 90 °C) led to rapid ligand exchange with concomitant generation of the corresponding amide complexes **149a** and **149b** in 8 h and 21 h respectively (Scheme 39).

Asymmetric hydroamination/cyclization of the aminoalkenes **148a** and **148c-d** were then conducted in the 60 usual manner ( $C_6D_6$ ) leading to the results presented in Table 6. It is of special interest that the intramolecular hydroamination of **148b** catalyzed by **147a** or **147b** proceeded rapidly to a subsequent bicyclization event leading to the formation of **150**. That the Y(III) catalyst proved more reactive than its La(III) counterpart is consistent with our earlier observation in a related series of bicyclizations where a Sc(III) amide catalyst was more efficient than its Y(III) congener (Scheme 41).

As is evident from the results presented in Tables 6 and 7, The presence of LiCl generally results in rate suppression for the Y(III) complex of **143**, this, in consonance

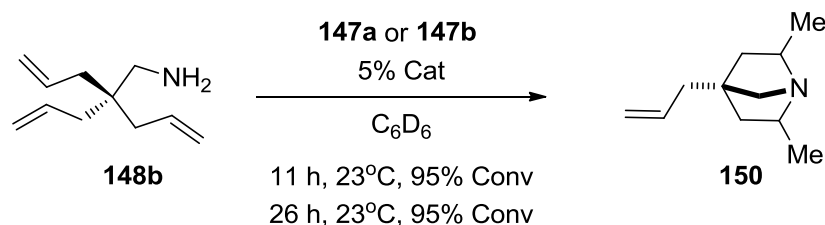
with the more hindered *t*-butyldimethylsilyl-bearing complex reported previously.<sup>73k</sup> The LiCl effect on reaction rates for La and enantioselectivities for *both* metals is less clear. It is noteworthy, however, that the presence of LiCl substantially restricts bicyclization in the case of **148b** for both La and Y under comparable temperature regimes.

Table 7: Enantioselective conversions to 149 catalyzed by 147a and 147b

Entry	Substrate	Metal	t <sup>a</sup>	ee% <sup>b</sup>
1	<b>148a</b>	Y	2.2 d <sup>c</sup>	68
2	<b>148a</b>	La	3 h <sup>c</sup>	87
3	<b>148c</b>	Y	5.5 d <sup>d</sup>	48
4	<b>148c</b>	La	89 h <sup>c</sup>	82
5	<b>148d</b>	Y	4.0 d <sup>g</sup>	70
6	<b>148d</b>	La	3.9 d <sup>f</sup>	84
7	<b>148e</b>	Y	9 h <sup>d</sup>	78
8	<b>148e</b>	La	12 h <sup>f</sup>	84

[a] >95 % conversion as determined by <sup>1</sup>H NMR spectroscopy with *p*-xylene as the internal standard. [b] Enantiomeric excess.

[c] T = 23 °C. [d] T = 60 °C. [f] T = 35 °C. [g] T = 90 °C.



Scheme 41: Catalytic bicyclization of aminodiene 148b

### Conclusion

In conclusion, we have shown that the readily available La(III) chelating diamide complexes **144b** and **146b** are unusually enantioselective precatalysts for asymmetric aminoalkene hydroamination/cyclizations leading to substituted pyrrolidines. Significantly, **144b** possesses significantly higher catalytic reactivity than the corresponding Y(III) complex **144a** and has provided some of the highest enantioselectivities for intramolecular alkene hydroamination reported to date over a range of substrates.

CHAPTER 7 – HIGHLY ENANTIOSELECTIVE INTRAMOLECULAR  
HYDROAMINATION/CYCLIZATION OF AMINOALKENES BY  
TETRAAMIDE ANIONIC COMPLEXES OF La(III) AND Y(III)

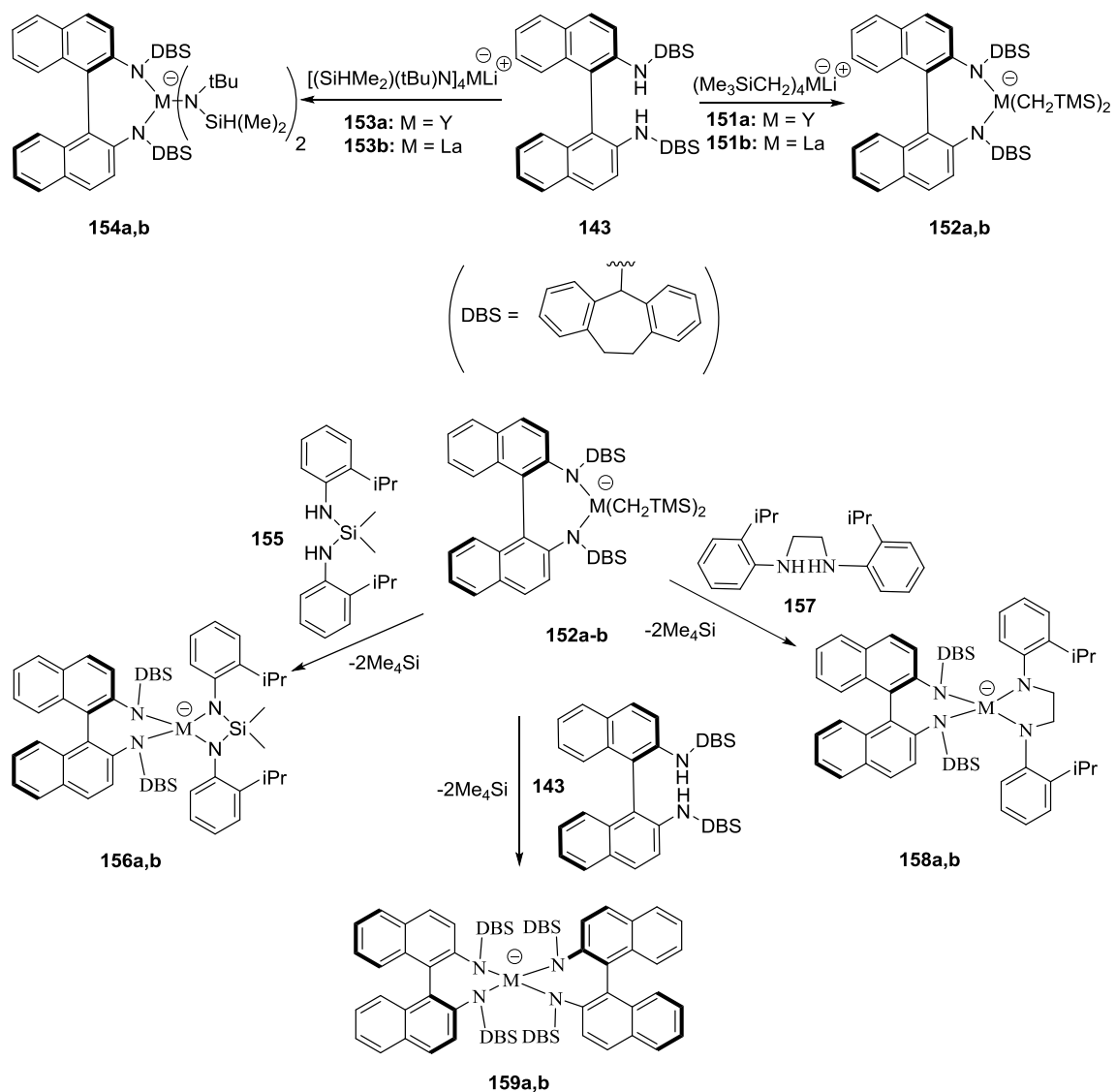
Introduction

We recently disclosed that chelating diamide complexes of selected group 3 metals derived from simple *N* – alkyl substituted diamide motifs are effective catalysts for enantioselective hydroamination/cyclization.<sup>73e</sup> Furthermore, as discussed in Chapter 6, we demonstrated that (*R*)-*N,N'*-Dibenzosuberyl-1,1'-binaphthyl-2,2'-diamine (**143**) is a vastly superior proligand for this process and the chelating diamide complexes derived from La(III), the largest lanthanide metal, provide higher enantioselectivities than the more sterically congested Y(III) congeners. In this chapter, we show the reactivity and enantioselectivity for intramolecular hydroamination catalyzed by the new family of lanthanide *ate*-complexes,<sup>82</sup> derived from chiral disubstituted (*R*)-binaphthylamide ligand and achiral diamide ligand motifs.

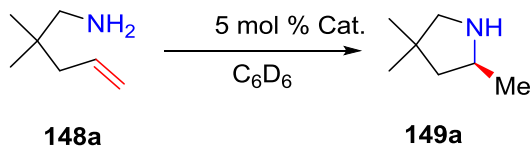
Catalyst Generation

The catalytic complexes, **154**, **156**, **158**, **159** utilized in this study were prepared in situ as follows. Sequential treatment of YCl<sub>3</sub>(THF)<sub>3.5</sub> or LaCl<sub>3</sub>(THF)<sub>1.5</sub> (1 equiv each) with Me<sub>3</sub>SiCH<sub>2</sub>Li (4 equiv) in THF generated solutions of the corresponding anionic hemoleptic alkyl (Me<sub>3</sub>SiCH<sub>2</sub>)<sub>4</sub>M<sup>⊖</sup>Li<sup>⊕</sup> complexes **151a,b**. Immediate addition of **143** (1 equiv, 20 min, 23 °C) delivered the preformed solutions of **152a,b**. Addition of either

supporting ligand motifs, **155**, **157**, or **143** (1 equiv each) afforded the solution of anionic complexes **156**, **158**, or **159**. After the complex formation was complete, THF was removed in vacuo and replaced by C<sub>6</sub>D<sub>6</sub> prior to the addition of the aminoalkenes (Scheme 42).



Scheme 42: Synthesis of anionic group 3 metal complexes (152, 154, 155, 156, 157)

Enantioselective Hydroamination StudiesTable 8: Enantioselective conversion of aminoalkene **148a** to pyrrolidine **149a**

Entry	Precatalyst	t <sup>a</sup>	Temp (°C)	ee[%] <sup>b</sup>
1	Y- <b>152</b>	21 h	60	80
2	La- <b>152</b>	8 d	23	84
3	Y- <b>154</b>	25 h	60	66
4	La- <b>154</b>	5 h	23	84
5	Y- <b>156</b>	20 h	60	25
6	La- <b>156</b>	9 h	23	83
7	Y- <b>158</b>	40 h	60	65
8	La- <b>158</b>	<b>3 h</b>	<b>23</b>	<b>87</b>
9	Y- <b>159</b>	16 h	60	80
10	La- <b>159</b>	<b>3 h</b>	<b>23</b>	<b>86</b>

[a] >95 % conversion as determined by <sup>1</sup>H NMR spectroscopy with p-xylene as the internal standard.

[b] Enantiomeric excess, calculated by <sup>19</sup>F from Mosher salts

Initially, our investigation focuses on the enantioselective hydroamination of terminal aminoalkenes **148a** catalyzed by anionic *ate*-complexes **152a** and **152b**. Cyclization of **148a** in the presence of the Y(III) complex **152a** proceeded comparatively slowly (60 °C, 24 h) and provided pyrrolidine **149a** in a modest 80% ee (Table 8, entry 1). The corresponding La(III) complex also proceeded very slowly, but with improved enantioselectivity (23 °C, 8 d, 84% ee) (entry 2). From this result, the anionic complexes

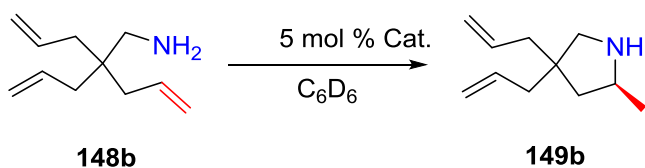
**152a, b** generally possessed much lower catalytic activity and stereoselectivity than the neutral complexes **145c, d** (as discussed in chapter 6, Table 6). The lower reactivity is likely attributable to the unusually congested binding pockets of the *ate*-complexes.

In light of these unexpected results, we turned our efforts toward the preparation of more active catalysts. The Y(III) anionic complex **154a**, coordinated by tert-butyl silyl amide, showed no significant reactivity and enantioselectivity improvements (Table 8, entry 3). However, the amide *ate* complex **154b** is more catalytically active than the analogous complex **152b** (23 °C, 5 h), and the enantioselectivity is practically unchanged 84% ee (entry 4). Modifying the steric perturbation, both four-membered chelate derived from the sterically hindered diamine **155** and five-membered chelate using diamine **157** led to clearly inferior results in cyclization activity and as well as enantioselectivity in Y(III) complexes **156a, 158a** (25% and 65% respectively) (entry 5 and 8). This transformation further emphasizes the enantioselective sensitivity of Y(III) complexes to increase steric perturbation within the ligand domain. Surprisingly, the use of Y(III) and La(III) anionic complexes **159**, coordinated by *N*-substituted dibenzosuberyl binaphthylamines **143**, led to faster cyclization rates, and also with significantly high enantioselective excess (80% and 86% respectively) (entry 9 and 10).

Furthermore, the compilation of reaction times and enantioselectivities observed for the hydroamination of aminoalkene **148b** catalyzed by anionic complexes **152, 154, 156, 158, 159** (5 mol%, C<sub>6</sub>D<sub>6</sub>) are presented in Table 9. As would be expected, faster conversion rates were always observed when anionic La(III) complexes were employed compared to their Y(III) anionic analogs. Thus, the relative rates of the cyclization is

coupled to the ionic radius of the group 3 metal within identical ligand spheres, with the fastest rates being associated with the largest metal centers.<sup>73a,d,j</sup> Out of the five employed anionic complexes, the ate complex **159** proved to be the most reactive and enantioselective in the cyclization of aminoalkenes **148a,b** (Table 8 and 9, entry 10).

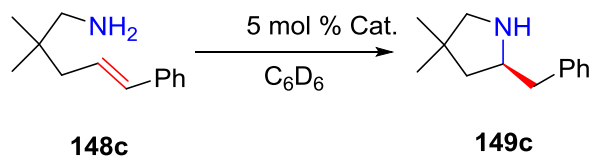
Table 9: Enantioselective conversion of aminoalkene 148b to pyrrolidine 149b



Entry	Precatalyst	t <sup>a</sup>	Temp (°C)	ee[%] <sup>b</sup>
1	Y-152	15 h	23	61
2	La-152	1 h	23	62
3	Y-154	5 h	23	50
4	La-154	5 h	23	77
5	Y-156	5 h	23	22
6	La-156	2 h	23	72
7	Y-158	4 h	23	30
8	La-158	<b>15 min</b>	<b>23</b>	<b>74</b>
9	Y-159	4 h	23	64
10	La-159	<b>30 min</b>	<b>23</b>	<b>81</b>

[a] >95 % conversion as determined by <sup>1</sup>H NMR spectroscopy with p-xylene as the internal standard.

[b] Enantiomeric excess, calculated by <sup>19</sup>F from Mosher salts

Table 10: Asymmetric hydroamination of disubstituted aminoalkene **148c**

Entry	Precatalyst	t <sup>a</sup>	Temp (°C)	ee[%] <sup>b</sup>
1	Y-152	9 d	60	42
2	La-152	24 h	45	74
3	Y-154	4.6 d	60	38
4	La-154	4.5 d	23	74
5	Y-156	4.6 d	60	25
6	La-156	5.6 d	23	73
7	Y-158	6.1 d	60	30
8	La-158	<b>69 h</b>	<b>23</b>	<b>80</b>
9	Y-159	6.8 d	60	48
10	La-159	62 h	45	74

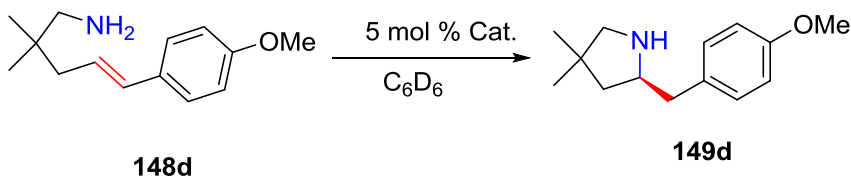
[a] >95 % conversion as determined by <sup>1</sup>H NMR spectroscopy with p-xylene as the internal standard.

[b] Enantiomeric excess, calculated by <sup>19</sup>F from Mosher salts

1, 2 disubstituted alkenes are known to be less reactive toward asymmetric intramolecular hydroamination as shown in chapter 6. To estimate the substrate control of enantioselectivity as well as reactivity during the formation of substituted pyrrolidines, the aminoalkenes were subjected to cyclization in the presence of 5 mol% of the anionic complexes (Table 10). The aminoalkene **148c** was efficiently converted into pyrrolidine **149c** catalyzed by the anionic *ate*- Y(III) and La(III) complexes. As expected, faster conversion rates were always observed with the *ate*- La(III) complexes compared to its

*ate*- Y(III) congeners (entries 1-10). As observed with terminal alkenes **148a,b**, the anionic complex **158b** was a superior catalyst for the cyclization of **148c** (23 °C, 69 h, 80% ee) (Table 10, entry 8) compared to other anionic complexes **152**, **154**, **156** and **159**. Most importantly, the anionic La (III) complex **158b** significantly enhanced the hydroamination reactivity of **148c** compared to neutral La(III) complex (35 °C, 9 h) (Table 6, entry 10).

Table 11: Enantioselective conversion of electron donating aminoalkene **148d**



Entry	Precatalyst	t <sup>a</sup>	Temp (°C)	ee[%] <sup>b</sup>
1	La- <b>152</b>	8 d	45	83
2	La- <b>154</b>	4.6 d	45	85
3	La- <b>156</b>	14.5 d	45	68
4	La- <b>158</b>	<b>4.3 d</b>	<b>45</b>	<b>81</b>
5	La- <b>159</b>	<b>4.3 d</b>	<b>45</b>	<b>84</b>

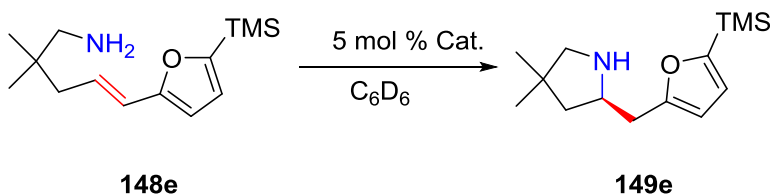
[a] >95 % conversion as determined by <sup>1</sup>H NMR spectroscopy with *p*-xylene as the internal standard.

[b] Enantiomeric excess, calculated by <sup>19</sup>F from Mosher salts

The catalytic activity of the anionic complexes was subsequently examined in the cyclization of the electron donating *P*-methoxy aminoalkene **148d**. Most of the anionic complexes **152b**, **154b**, **158b**, and **159b** provided similar enantioselectivities (81% - 85% ee) (Table 11, entries 1 - 5). In comparison to the cyclization of **148c** to the pyrrolidine

**149c** with anionic complex **158b** proceeded at 23 °C in 69 h (Table 10, entry 8), the cyclization of electron donating methoxyaminoalkene **148d** was 85% complete at 45 °C in 4.3 d (Table 11, entry 4). Related catalytic activity employing the chelated anionic tetraamido complexes was diminished, catalyzing the intramolecular hydroamination of electron donating aminoalkene

Table 12: Enantioselective conversion of induction induced aminoalkene 148e



Entry	Precatalyst	t <sup>a</sup>	Temp (°C)	ee[%] <sup>b</sup>
1	La-152	2 h	23	82
2	La-154	16 h	45	83
3	La-156	24 h	23	78
4	La-158	5 h	23	78
5	La-159	14 h	23	83

[a] >95 % conversion as determined by <sup>1</sup>H NMR spectroscopy with p-xylene as the internal standard.

[b] Enantiomeric excess, calculated by <sup>19</sup>F from Mosher salts

In addition, the inductive effect of hydroamination/cyclization catalyzed by the anionic *ate* complexes was investigated (Table 12). As expected, hydroamination/cyclization of 5-(TMS)-2-furanyl aminoalkene **148e** in the presence of the anionic complexes provided pyrrolidine **149e** in comparatively similar % ee with **149c, d** (Table 10 and 11). Significantly, the cyclization of **148e** proceeded faster (23 °C,

5 h) (Table 12, entry 4) compared to phenylaminoalkene **148c** (23 °C, 69 h) (table 10, entry 8) and the electron donating aminoalkene **148d** (45 °C, 4.3 d) (Table 11, entry 4). Accordingly, the magnitude of catalytic activity of the intramolecular hydroamination/cyclization was shown to be substrate dependent, induction induced substitution enhances cyclization, while electron donating substituents decreased catalytic activity.

In conclusion, we have shown that anionic La(III) tetraamido complexes are highly enantioselective and have significantly higher catalytic activity than the corresponding anionic Y(III) complexes. In general, the La(III) anionic complexes **159** and **158** proceeded faster cyclization rates, and high enantioselective excess. Hydroamination/cyclization catalyzed by anionic La(III) complexes is greatly diminished with electron donating substituted aminoalkene **148d**, and significantly enhanced with induction induced furanyl substituted aminoalkene **149e**.

## CONCLUSIONS

We reported the synthesis of dimethoxy indenyl cyclobutanol. The key feature included Dakin oxidation, Horner-Wadsworth-Emmons olefination, and the Shapiro reaction. Furthermore, the study of Pd<sup>II/IV</sup> catalyzed semi-pinacol reaction towards the total synthesis of Acutumine had shown promising preliminary results. But mechanistically, the Pd catalyst functioned as a Lewis acid to the oxidant PhI(OAc)<sub>2</sub> rather than forming the  $\pi$ -complex as proposed (scheme 16). Fortunately, the success of asymmetric semi-pinacol reaction in Rainey's group and Alexakis's group had indeed confirmed that 5, 5 spirocycles can be prepared via halogen-induced Wagner-Meerwein rearrangement. The synthesis of Acutumine's propellane tricyclic ring was concisely synthesized in eight steps featuring phosphoric Brønsted acid catalyzed aldol condensation and radical N-cyclization as the key transformations.

We have shown that structurally diverse 1, 1, 2-trisubstituted alkenes can serve as effective participants in intramolecular hydroaminations catalyzed by Y[N(TMS)<sub>2</sub>]<sub>3</sub> (**133<sub>Y</sub>**). We document substantial rate enhancements that are obtained when 2-[(5-trimethylsilyl)thienyl] groups are employed as addends. Cyclization efficiency for a representative aminoalkene possessing a *Z*-configured 2-(phenyl)ethenyl group is considerably higher than that observed for the corresponding *E*-isomer. Deuterium labeling studies have provided the first *direct* experimental evidence for *syn*-metalloamination of the C=C bond during the course of hydroamination/cyclization.

In addition, we have reported enantioselective hydroamination/cyclization of representative aminoalkenes catalyzed by chelating diamide complexes of La(III) and

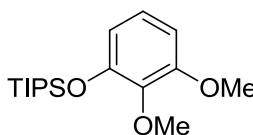
Y(III). The La(III) complex derived from the sterically demanding (*R*)-*N,N'*-dibenzosuberyl-1,1'-Binaphthyl-2,2'-diamine proligand provides enantioselectivities that are in many cases significantly higher than those obtained with the corresponding Y(III) analog. Also, the presence of LiCl was typically found to suppress both the rates and enantioselectivities obtained with the Y(III) complex when compared to its La(III) counterpart, in addition to completely suppressing the bicyclization of **148b**. We have shown that La(III) anionic complexes **159** and **158** led to faster cyclization rates, and also with significantly high enantioselective excess. Hydroamination/cyclization catalyzed by anionic La(III) complexes is greatly diminished with electron donating substituted aminoalkene **148d**, and significantly enhanced with induction induced furanyl substituted aminoalkene **149e**.

## EXPERIMENTAL SUPPORTING INFORMATION

Materials and Methods

Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. THF and diethyl ether were distilled from sodium/benzophenone under nitrogen. CH<sub>2</sub>Cl<sub>2</sub> was distilled from CaH<sub>2</sub> under nitrogen. All other materials were used as received from commercial sources and all reactions were carried out under nitrogen unless otherwise noted. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator. Flash chromatographic columns were packed with Merck silica gel 60 as a slurry in the initial elution solvent. Nuclear magnetic resonance (NMR) data were obtained from Bruker DPX-300 (300 MHz) and Bruker DPX-500 (500 MHz). Infrared spectra (IR) were obtained from JASCO FTIR-4100. High-resolution mass spectra (HRMS) were obtained from Bruker MicroTOF with an Agilent 1100 HPLC.

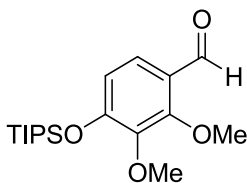
(2,3-Dimethoxyphenoxy)  
Triisopropylsilane (63)



Dimethoxy-benzyl-alcohol (**62**) (17.6 mmol) and DMF (10 ml) was added to a round bottom flask. Imidazol (17.6 mmol) and TIPSCl (17.6 mmol) were then added subsequently. The solution was stirred for 4 h at 25 °C under argon. The solution was

quenched with H<sub>2</sub>O (25 ml) and extracted with DCM (3 x 12 ml). The organic extracts were brined, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude was purified with 5% EtOAc:Hexane gave 90% Yield of **63** as colorless oil (8.5 mmol, 2.65 g). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.83 (t, *J* = 8.3 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 2H), 3.86 – 3.71 (m, 6H), 1.24 (h, *J* = 7.6 Hz, 3H), 1.06 (d, *J* = 7.6 Hz, 19H). <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δ 123.14, 113.55, 105.04, 60.49, 55.91, 17.88, 12.78. IR (thin film) 2986, 1590, 1476, 1255, 1095 cm<sup>-1</sup>. HRMS (MH)<sup>+</sup> requires *m/z* 311.2037, found *m/z* 311.2036.

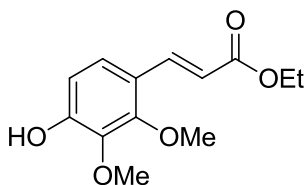
2,3-Dimethoxy-4-(Triisopropylsilyloxy) Benzaldehyde (**64**)



Triisopropylsilane (**63**) (14.43mmol), TMEDA (21.6 mmol), and Et<sub>2</sub>O (22.2ml) were added to round bottom flask. 8.7ml <sup>n</sup>BuLi in 2.5M hexane was added over 8min at 0°C. After addition was completed, the mixture was stirred at room temperature for 1hr. DMF (43.34 mmol) was added drop wise over 7mins at -78°C. The reaction mixture was then allowed to warm to room temperature and stirred for 14 h. The solution was quenched with aq. Sat. NH<sub>4</sub>Cl (15dml) and further diluted with addition of 50 ml of sat.NH<sub>4</sub>Cl, and extracted with EtOAc (2x 25 ml). The combined extracts were washed with (2x 25 ml) H<sub>2</sub>O, brine, dried (MgSO<sub>4</sub>), filtered and concentrated. The crude was purified with 10% EtOAc:Hexane gave 48% Yield of **64** (1.6 mmol, 0.549 g). <sup>1</sup>H NMR

(500 MHz, CDCl<sub>3</sub>)  $\delta$  10.19 (s, 1H), 7.45 (d,  $J$  = 8.5 Hz, 1H), 6.65 (d,  $J$  = 8.5 Hz, 1H), 3.97 (s, 3H), 3.82 (s, 3H), 1.28 (p,  $J$  = 7.6 Hz, 3H), 1.08 (d,  $J$  = 7.6 Hz, 20H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  188.86, 123.51, 116.13, 62.31, 60.67, 17.81, 12.83. IR (thin film) 2942, 2870, 1688, 1586, 1490, 1460, 1308 cm<sup>-1</sup>. HRMS (MH)<sup>+</sup> requires  $m/z$  339.1986, found  $m/z$  339.2036.

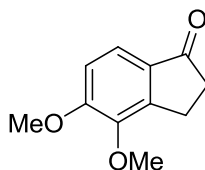
(E)-Ethyl 3-(4-Hydroxy-2,3-Dimethoxyphenyl) Acrylate (65)



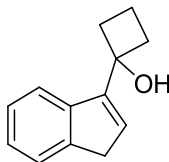
Freshly Distilled DMF (9.3 ml) was transferred into flask, contained NaH (4.65 mmol) under argon. The mixture was stirred for 10 min. triethylphosphonoacetate (4.65 mmol) was added dropwise at 21 °C. and stirred for 1 h until gas evolution ceased. The dimethoxybenzaldehy (**64**) (4.65 mmol) in DMF (2ml) was added dropwise at 0 °C. The solution was stirred overnight at 21 °C. The reaction was diluted with excess water and extracted with EtOAc ( 2x 20 ml). The combined organic extracts was washed with Saturated NaCl and dried over MgSO<sub>4</sub>, filtered and concentrated. The crude was purified with 25% EtOAc:Hexane gave 56% Yield of **65** as light yellow oil (0.91mmol, 0.2286 g). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.84 (d,  $J$  = 16.1 Hz, 1H), 7.20 (d,  $J$  = 8.4 Hz, 1H), 6.71 (d,  $J$  = 8.4 Hz, 1H), 6.37 (d,  $J$  = 16.3 Hz, 1H), 5.96 (s, 1H), 4.23 (q,  $J$  = 7.2 Hz, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 1.30 (d,  $J$  = 7.2 Hz, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  167.50, 152.17, 151.58, 139.87, 139.21, 123.54, 121.02,

116.94, 111.07, 61.00, 60.87, 60.27, 14.35. IR (thin film) 3365, 2935, 2981, 1692, 1590, 1494, 1460, 1267  $\text{cm}^{-1}$ . HRMS (MH)<sup>+</sup> requires  $m/z$  253.1090, found  $m/z$  253.1071.

4,5-Dimethoxy-2,3-Dihydro  
-1H-Inden-1-one (**68**)<sup>80b</sup>



Phosphorous acid (0.6 mol) was stirred at 100 °C for 10 mins, then cool to 70°C. Propanoate, **67** (30 mmol) was added in one portion. The mixture was stirred at 70°C for 45 min then small portion of phosphorous acid was added and stirred for 30 min. the reaction mixture was cool to rt then transferred to ice water and extracted with Et<sub>2</sub>O. The organic was washed with (3x 100 ml) NaHCO<sub>3</sub>, brine, dried (MgSO<sub>4</sub>), filtered and concentrated. Purification gave 65% yield of colorless oil, **68** (3.774 g). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.51 (d, *J* = 8.4 Hz, 1H, Ar-**H**), 6.95 (d, *J* = 8.4 Hz, 1H, Ar-**H**), 3.93 (s, 3H, OCH<sub>3</sub>), 3.89 (s, 3H, OCH<sub>3</sub>), 3.08 (d, *J* = 6.0 Hz, 2H, CH<sub>2</sub>-CH<sub>2</sub>), 2.68 – 2.63 (m, 2H, CH<sub>2</sub>-CH<sub>2</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 205.53 (s), 168.58 (s), 157.64 (s), 145.56 (s), 131.62 – 131.15 (m), 120.30 (s), 112.38 (s), 60.44 (s), 56.32 (s), 36.51 (s), 22.57 (s). IR (thin film) 2932, 2835, 1704, 1597, 1490, 1275  $\text{cm}^{-1}$ . HRMS (MH)<sup>+</sup> requires  $m/z$  193.09, found  $m/z$  193.08.

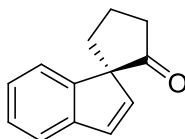
1-(1H-Inden-3-yl) Cyclobutanol (59)<sup>80</sup>

<sup>n</sup>BuLi (43 mmol) was added drop wise into 1H-indene (43 mmol) in Et<sub>2</sub>O at -78 °C. The reaction was maintained at -78 °C for 20 min. it was subsequently allowed to warm to room temperature and stirred for a further 4 h. cyclobutanone was added drop wise at -78 °C. The resulting solution stirred at -78 °C and slowly warm to room temperature over 2 h periods. The solution was stirred at room temperature for further 12 h. the solution was cooled to -78 °C and quenched with AcOH (25 ml), warmed to room temperature and partitioned between water (500 ml) and EtOAc (250 ml). The separated and aqueous phase was extracted with EtOAc (3x 200 ml). The combined extracts were dried (MgSO<sub>4</sub>), filtered, and concentrated. The crude product was yellow oil which solidified upon standing. The solid was recrystallization with EtOAc and hexane provide 68% yield, white powder cyclobutanol **59** (5.34g). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.57 (d, *J* = 7.5 Hz, 1H, Ar-**H**), 7.47 (d, *J* = 7.3 Hz, 1H, Ar-**H**), 7.28 (t, *J* = 7.5 Hz, 1H, Ar-**H**), 7.21 (t, *J* = 7.4 Hz, 1H, Ar-**H**), 6.45 (s, 1H, **CH=C**), 3.39 (s, 2H, **CH<sub>2</sub>-CH**), 2.61 – 2.52 (m, 2H, **CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>**), 2.42 – 2.33 (m, 2H, **CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>**), 1.88 (dd, *J* = 20.1, 10.0 Hz, 2H, **CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>**), 1.65 – 1.52 (m, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 128.37 (s), 126.22 (s), 125.03 (s), 124.23 (s), 121.75 (s), 37.81 (s), 35.75 (s), 13.44 (s). IR (thin film) 3276, 3203, 1971, 2938 cm<sup>-1</sup>.

General Procedure for Pd Catalyst:

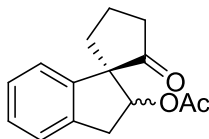
Indene-cyclobutanol, **59** (0.134 mmol) in DCM (4M) was added Pd catalyst. The oxidant, PhI(OAc)<sub>2</sub> (0.268 mmol), was then added to the reaction mixture. The reaction solution filtered through Si<sub>2</sub>O column with EtOAc. The filtrate was washed with H<sub>2</sub>O (2x), NaHCO<sub>3</sub> (2x), brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. The crude was purified through column chromatography with 10% EtOAc: Hex gave spiro cyclopentane indenone (**60**) and Oxo indene acetate (**61**).

Spiro[cyclopentane-1,  
1'-Inden]-2-one (**60**)<sup>80</sup>



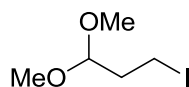
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.39 – 7.31 (m, 1H, Ar-**H**), 7.25 (dd, *J* = 15.7, 7.0 Hz, 3H, Ar-**H**), 6.87 (d, *J* = 5.5 Hz, 1H, **CH=CH**), 6.36 (d, *J* = 5.5 Hz, 1H, **CH=CH**), 2.57 (dd, *J* = 11.4, 7.1 Hz, 2H, **CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>**), 2.48 – 2.39 (m, 1H, **CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>**), 2.35 (dt, *J* = 15.2, 5.5 Hz, 2H, **CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>**), 2.29 – 2.18 (m, 1H, **CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>**). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 204.40 (s), 137.26 (s), 133.16 (s), 130.54 (s), 127.76 (s), 126.01 (s), 122.18 (s), 121.99 (s), 47.08 (s), 39.14 (s), 33.33 (s), 20.61 (s). IR (thin film) 2975, 2927, 2850, 1733, 1658, 1245, 1227 cm<sup>-1</sup>.

2-Oxo-2',3'-Dihydrospiro[Cyclopentane-1,1'-Indene]-2'-yl Acetate (**61**)



$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 (d,  $J = 7.6$  Hz, 1H), 7.63 (t,  $J = 7.6$  Hz, 1H), 7.55 – 7.48 (m, 1H), 7.46 – 7.41 (m, 1H), 7.39 – 7.35 (m, 2H), 5.41 (dd,  $J = 8.0, 4.9$  Hz, 1H), 3.65 (dd,  $J = 16.9, 8.0$  Hz, 1H), 3.59 (t,  $J = 2.9$  Hz, 1H), 3.03 (dd,  $J = 16.9, 4.8$  Hz, 1H), 2.80 (td,  $J = 6.2, 3.0$  Hz, 1H), 2.58 – 2.52 (m, 1H), 2.21 (dd,  $J = 12.9, 6.2$  Hz, 1H), 2.17 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  136.11, 129.01, 128.36, 126.85, 124.71, 121.93, 74.26, 38.40, 35.19, 33.66, 23.81, 23.17, 21.02. IR (thin film) 2928, 1656, 1608, 1398, 1372, 1228  $\text{cm}^{-1}$ . HRMS (MH) $^+$  requires  $m/z$  245.1172, found  $m/z$  245.1172.

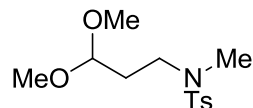
3-Iodo-1,1-Dimethoxy Propane (**79b**)



NaI (13.46 g, 89.9 mmol) was added into a round bottom flask. MeCN (185 ml, 0.4M) and acrolein (5 ml, 74 mmol) were added into flask subsequently. The mixture solution was cooled to 0 °C. TMSCl was added slowly over 1min. The solution was stirred for 5min. Dry MeOH (5.75 ml, 179 mmol) was added in one portion. The reaction solution was stirred for 20 min. The solution was quenched with 5% sat.  $\text{NaHCO}_3$ , and the solution was extracted with pentane (2x, 150 ml). The combined organic extracts

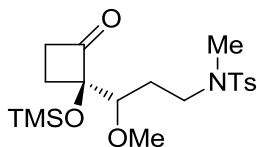
were washed with 5% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and sat. NaCl, dried over MgSO<sub>4</sub>, filtered and concentrated under vacuo. The crude was immediately used in the next step.

*N*-(3,3-Dimethoxypropyl)-*N*,4-Dimethyl Benzenesulfonamide (**80**)



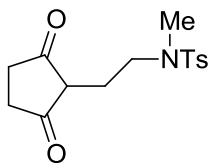
MeNTs (6.1 g, 31.8 mmol) and NaH (1.41 g, 34.7 mmol) in round bottom flask was added DMF (28 ml, 1M). The reaction solution was stirred for 10 min at 21 °C. 3-iodo-1,1-dimethoxypropane **79b** (6.6532 g, 29 mmol) in DMF (28 ml, 1M) was added and the solution mixture was stirred at 21 °C for 3h. The solution was quenched with water (100 ml) and extracted with Et<sub>2</sub>O (2 x 10 ml). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated under vacuo. The crude was recrystallized with 20% EtOAc : hexane gave brown solid **80** (8.047 g, 97% yield). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.43 (t, *J* = 5.7 Hz, 1H), 3.32 (s, 6H), 3.03 (t, *J* = 7.3 Hz, 2H), 2.70 (s, 3H), 2.40 (s, 3H), 1.86 – 1.74 (m, 2H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 143.29, 129.64, 127.40, 102.52, 53.46, 46.26, 35.12, 31.38, 21.46. IR (thin film) 2935, 1339, 1161cm<sup>-1</sup>. HRMS (MH)<sup>+</sup> requires *m/z* 288.1264, found *m/z* 288.1269.

*N*-((*R*)-3-Methoxy-3-((*R*)-2-Oxo-1-((Trimethylsilyl)oxy)Cyclobutyl)propyl)-*N*,4-Dimethyl Benzenesulfonamide (**82**)



*N*-(3,3-dimethoxypropyl)-*N*,4-dimethylbenzenesulfonamide **81** (3.84 g, 13.3 mmol) in DCM (13 ml, 1M) was cooled to -78 °C and BF<sub>3</sub>OEt (13.3 mmol) was added. The reaction mixture was stirred for 5 mins, then 1,2-bis((trimethylsilyl)oxy)cyclobut-1-ene (3.43 ml, 13.3 mmol) was added at -78 °C and stirred for 4 h. The solution was quenched with H<sub>2</sub>O (50 ml) and extracted with DCM (2 x 50 ml). The combined organic extracts were dried over NaSO<sub>4</sub>, filtered and concentrated under vacuo. The crude was readily used in next step.

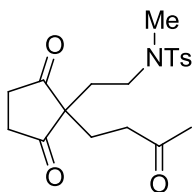
*N*-(2-(2,5-Dioxocyclopentyl)Ethyl)-*N*,4-Dimethyl Benzenesulfonamide (**83**)



*N*-((*R*)-3-methoxy-3-((*R*)-2-oxo-1-((trimethylsilyl)oxy)cyclobutyl)propyl)-*N*,4-dimethylbenzenesulfonamide **82** (13.3 mmol) in distilled benzene (13 ml, 1M) was added pTsOH (13.3 mmol) at 21 °C. The reactant mixture was held at 80 °C for 5 days. The solution was diluted with DCM (100 ml) and washed with H<sub>2</sub>O (2 x 50ml). The product

was precipitated out in DCM and flown above the solution. Hexane was added and the precipitated was sunk to the bottom. The solid was filtered and the filtrate was concentrated via vacuo. The crude was recrystallized with 20% EtOAc : Hexane. The *N*-(2-(2,5-dioxocyclopentyl)ethyl)-*N*,4-dimethylbenzenesulfonamide, **83** was obtained as white solid (2.2123 g, 54% yield over 2 steps).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 (d,  $J = 8.0$  Hz, 2H), 7.29 (d,  $J = 8.0$  Hz, 2H), 3.01 (t,  $J = 6.7$  Hz, 2H), 2.78 (s, 4H), 2.71 (s, 3H), 2.44 (t,  $J = 6.7$  Hz, 2H), 2.40 (s, 3H), 2.37 (s, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  143.74, 133.65, 129.80, 129.13, 127.41, 125.96, 115.08, 48.41, 35.80, 30.45, 21.48, 19.99. IR (thin film) 2924, 1579, 1386, 1342, 1164  $\text{cm}^{-1}$ . HRMS (MH) $^+$  requires  $m/z$  310.1104, found  $m/z$  310.1108.

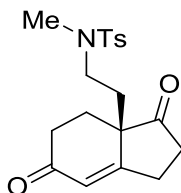
*N*-(2-(2,5-Dioxo-1-(3-Oxobutyl)  
Cyclopentyl)Ethyl)-*N*,4-Dimethyl  
Benzenesulfonamide (**84**)



*N*-(2-(2,5-dioxocyclopentyl)ethyl)-*N*,4-dimethylbenzenesulfonamide **84** (0.9974 g, 3.2 mmol) in MeCN (10 ml, 0.5M) was subsequently added  $\text{Et}_3\text{N}$  (3.84 mmol), and methyl vinyl ketone (3.84 mmol) at 21  $^\circ\text{C}$  under  $\text{N}_2$ . The reaction was stirred overnight. The reactant mixture was quenched with  $\text{H}_2\text{O}$  (50 ml) and extracted with EtOAc (2 x 100 ml). The combined organic extracts were washed with sat. NaCl, and dried over  $\text{MgSO}_4$ . The mixture was filtered and concentrated via vacuo. The crude was recrystallized with

20% EtOAc : Hexane giving yellow solid, **84** (0.8686 g, 71% yield). 110 °C M.P.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 (d,  $J = 8.0$  Hz, 2H), 7.24 (d,  $J = 8.0$  Hz, 2H), 3.06 – 2.97 (m, 2H), 2.81 – 2.71 (m, 4H), 2.41 (t,  $J = 7.4$  Hz, 2H), 2.38 (s, 3H), 2.36 (s, 3H), 2.06 (s, 3H), 1.89 (t,  $J = 6.0$  Hz, 2H), 1.75 (t,  $J = 7.4$  Hz, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  216.12, 206.46, 143.74, 132.82, 129.67, 127.55, 77.29, 77.24, 77.04, 76.78, 56.72, 46.60, 36.95, 35.32, 34.13, 29.99, 29.43, 21.44. IR (thin film) 3464, 2928, 1719, 1593, 1453, 1339, 1161  $\text{cm}^{-1}$ . HRMS (MH) $^+$  requires  $m/z$  380.1526, found  $m/z$  380.1526.

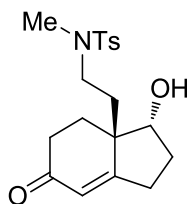
*N*-(2-(3,6-Dioxo-2,3,3a,4,5,6-Hexahydro-1H-Inden-3a-yl)Ethyl)-*N*,4-Dimethyl Benzenesulfonamide (**85**)



*N*-(2-(2,5-dioxo-1-(3-oxobutyl)cyclopentyl)ethyl)-*N*,4-dimethylbenzenesulfonamide **84** (0.2043 g, 0.5 mmol) in Hexane: Toluene (1:5) (5.5 ml, 0.1M) was added diphenyl phosphate (13.5 mg, 0.38 mmol) and pTsOH (9.3 mg, 0.05 mmol). The reactant mixture was stirred at 80 °C for 2 d and concentrated under vacuo. The crude was purified with 75% EtOAc: Hexane giving the product as colorless oil **85** (58.9 mg, 73% yield). 125 °C M.P.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 (d,  $J = 8.0$  Hz, 2H), 7.33 (d,  $J = 8.0$  Hz, 2H), 6.03 (d,  $J = 2.4$  Hz, 1H), 3.21 – 3.11 (m, 3H), 2.95 – 2.78 (m, 4H), 2.66 (s, 3H), 2.44 (d,  $J = 6.9$  Hz, 7H), 2.16 (d,  $J = 13.0$  Hz, 1H), 2.06 (dt,  $J = 15.6, 7.8$  Hz, 1H), 2.01 – 1.92 (m, 1H), 1.76 (td,  $J = 13.0, 7.0$  Hz, 1H).  $^{13}\text{C}$  NMR (126

MHz, CDCl<sub>3</sub>)  $\delta$  215.77, 197.44, 168.74, 143.74, 133.71, 129.78, 127.49, 124.71, 77.23, 76.97, 76.72, 50.65, 46.37, 36.13, 35.41, 32.55, 31.74, 27.23, 26.97, 21.49. IR (thin film) 2924, 1738, 1664, 1339, 1161 cm<sup>-1</sup>. HRMS (ESI): Calcd for C<sub>19</sub>H<sub>23</sub>NO<sub>4</sub>S [M+H]<sup>+</sup>: 362.1421, found: 362.1382

*N*-(2-((3*S*,3*aR*)-3-Hydroxy-6-Oxo-2,3,3*a*,4,5,6-Hexahydro-1*H*-Inden-3*a*-yl) Ethyl)-*N*,4-Dimethyl Benzenesulfonamide (**85b**)

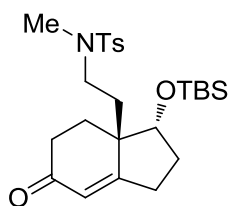


*N*-(2-(2,5-dioxo-1-(3-oxobutyl)cyclopentyl)ethyl)-*N*,4-dimethylbenzenesulfonamide **85** (0.2626 g, 0.726 mmol) in EtOH:THF (1:1) (1.5 ml, 0.5M) was added NaBH<sub>4</sub> (6.9 mg, 0.18 mmol) at 21 °C. The reactant solution was stirred for 1 h. The solution was diluted with EtOAc (20 ml) and washed with H<sub>2</sub>O (2 x 10 ml). The solution was washed with sat. NaCl, dried over MgSO<sub>4</sub>, and filtered. The solution was concentrated under vacuo. The crude was purified with 80% EtOAc : Hexane gave colorless oil, **85b** (0.2388 g, 0.657 mmol) with 91% yield. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.65 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.80 (d, *J* = 2.0 Hz, 1H), 3.92 (dd, *J* = 10.1, 7.6 Hz, 1H), 3.51 (ddd, *J* = 13.9, 11.2, 4.6 Hz, 1H), 3.10 (ddd, *J* = 13.9, 10.6, 6.0 Hz, 1H), 2.77 (s, 3H), 2.76 – 2.65 (m, 2H), 2.43 (s, 3H), 2.40 – 2.31 (m, 3H), 2.17 (ddd, *J* = 12.5, 7.8, 2.4 Hz, 2H), 2.03 – 1.97 (m, 1H), 1.97 – 1.86 (m, 2H), 1.81 (ddd, *J* = 14.3, 11.2, 6.0 Hz, 1H), 1.72 (td, *J* = 12.5, 7.8 Hz, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  198.40 ,

173.82 , 143.48 , 134.76 , 129.73 , 127.27 , 123.89 , 82.01 , 47.62 , 46.87 , 35.35 , 33.34 ,  
31.22 , 29.83 , 29.73 , 26.85 , 21.47. IR (thin film) 3394, 2924, 1652, 1331, 1158  $\text{cm}^{-1}$ .

HRMS (MH)<sup>+</sup> requires  $m/z$  364.1577, found  $m/z$  364.1594

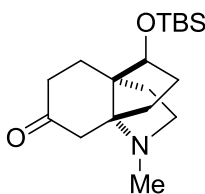
*N*-(2-((3*S*,3*aR*)-3-((Tert-Butyl dimethylsilyl)Oxy)-6-oxo-2,3,3*a*,4,5,6-Hexahydro-1*H*-Inden-3*a*-yl)Ethyl)-*N*,4-Dimethyl Benzenesulfonamide (**88**)



*N*-(2-((3*S*,3*aR*)-3-hydroxy-6-oxo-2,3,3*a*,4,5,6-hexahydro-1*H*-inden-3*a*-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **87b** (0.2328 g, .0641 mmol) in DMF (6 ml, 0.5M) was added  $\text{NH}_4\text{NO}_3$  (0.16 g, 1.9 mmol) and TBSCl (0.19 g, 1.3 mmol) subsequently at 21 °C. The reactant mixture was stirred for 2 h. The solution was diluted with  $\text{Et}_2\text{O}$  (30 ml) and washed with  $\text{H}_2\text{O}$  (15 ml, 2x). The diluted solution was washed with sat. NaCl, and dried over  $\text{MgSO}_4$  and filtered. The solution was concentrated under vacuo. The crude was purified with 80% EtOAc: Hex gave colorless oil, **88** (0.1374 g, 0.0288 mmol, 45% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.60 (d,  $J = 8.0$  Hz, 2H), 7.26 (d,  $J = 8.0$  Hz, 2H), 5.75 (s, 1H), 3.78 – 3.67 (m, 1H), 3.31 (dd,  $J = 12.4, 5.4$  Hz, 1H), 3.18 (td,  $J = 13.1, 12.4, 4.5$  Hz, 1H), 2.71 (s, 3H), 2.69 – 2.58 (m, 1H), 2.38 (s, 3H), 2.34 (dd,  $J = 12.1, 7.6$  Hz, 2H), 2.22 (dd,  $J = 15.0, 3.0$  Hz, 1H), 2.03 – 1.85 (m, 2H), 1.84 – 1.73 (m, 2H), 1.70 – 1.56 (m, 2H), 0.81 (s, 7H), 0.01 (s, 3H), -0.01 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  198.52, 173.17,

143.26, 134.98, 129.65, 127.22, 123.97, 82.23, 47.52, 47.20, 34.90, 33.26, 31.65, 29.86, 29.40, 26.74, 25.76, 21.45, 17.95, -4.64, -4.91. IR (thin film) 2954, 2854, 1664, 1342, 1158, 1113  $\text{cm}^{-1}$ . HRMS (MH)<sup>+</sup> requires  $m/z$  478.2442, found  $m/z$  478.2438.

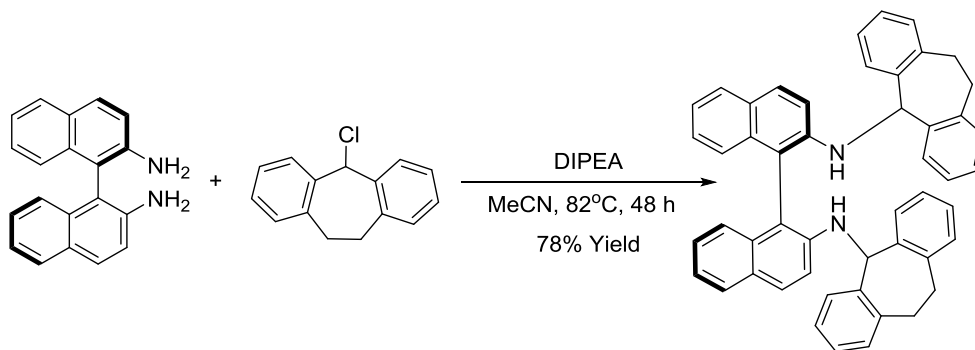
(1*S*,3*aR*,7*aS*)-1-((Tert-Butyldimethylsilyl)Oxy)-10-MethylTetrahydro-1*H*-3*a*,7*a*-(Epiminoethano) Inden-5(4*H*)-one (**89**)



$\text{NH}_3$  was condensed in the 3-neck round bottom flask at  $-78\text{ }^\circ\text{C}$ .  $\text{Na}^0$  metal was slowly added portion-wise. The reactant mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 10 mins. *N*-(2-((3*S*,3*aR*)-3-((tert-butyldimethylsilyl)oxy)-6-oxo-2,3,3*a*,4,5,6-hexahydro-1*H*-inden-3*a*-yl)ethyl)-*N*,4-dimethylbenzenesulfonamide **88** (84.3 mg, 0.177 mmol) in THF (2 ml, 0.1M) was transferred to the  $\text{NH}_3$  and  $\text{Na}^0$  solution via cannula at  $-78\text{ }^\circ\text{C}$ . The reactant mixture was stirred for 2 h. The red solution was turned to deep blue and green, then light yellow. The solution was quenched with sat.  $\text{NH}_4\text{Cl}$  slowly until white precipitate formed. The mixture was extracted with EtOAc (2 x 20 ml). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated via vacuo. The crude was purified with 80% EtOAc : Hexane giving yellow oil **89** (24.1 mg, 0.0744 mmol, 45% yield).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  3.80 (dd,  $J = 7.6, 5.3$  Hz, 1H), 2.70 (t,  $J = 9.6$  Hz, 1H), 2.61 – 2.43 (m, 3H), 2.37 (ddd,  $J = 19.3, 10.5, 5.3$  Hz, 2H), 2.24 – 2.20 (m, 2H), 2.17 (s, 3H), 1.91 – 1.78 (m, 2H), 1.76 – 1.66 (m, 2H), 1.60 – 1.51 (m, 1H), 1.38 (dt,  $J =$

13.7, 7.6 Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  212.94, 79.43, 77.23, 77.18, 76.98, 76.92, 76.72, 71.77, 54.65, 53.42, 45.99, 34.04, 33.97, 33.79, 32.87, 31.04, 30.15, 29.67, 27.48, 25.75, 17.99, -4.42, -4.95. IR (thin film) 2935, 2857, 1716, 1461, 1251, 1120, 1047  $\text{cm}^{-1}$ . HRMS (MH)<sup>+</sup> requires  $m/z$  324.2353, found  $m/z$  324.2387.

Synthesis and Characterization  
of **143**, and Anionic Complexes

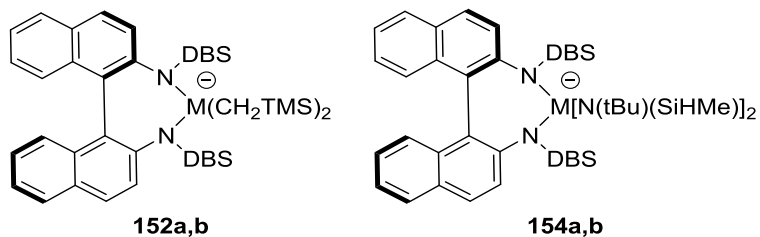


*N,N'*-Bis(10,11-Dihydro-5H  
-Dibenzo[*a,d*][7] Annulen  
-5-yl)-[1,1'-Binaphthalene]  
-2,2'-Diamine (**143**)<sup>83a</sup>

$^1\text{H}$ -NMR (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.83 (dd,  $J = 23.1, 8.2$  Hz, 4H, 4Ar-**H**), 7.22 (d,  $J = 24.3$  Hz, 6H, 6Ar-**H**), 7.08 (dd,  $J = 24.3, 6.8$  Hz, 7H, 7Ar-**H**), 6.96 (d,  $J = 7.5$  Hz, 8H, 8Ar-**H**), 6.91 (d,  $J = 6.9$  Hz, 2H, 2Ar-**H**), 6.85 (d,  $J = 7.0$  Hz, 2H, 2Ar-**H**), 5.98 (s, 2H, 2CH), 4.75 (dt,  $J = 2.6, 1.2$  Hz, 2H, 2NH), 3.12 (dt,  $J = 19.4, 10.1$  Hz, 4H, 2CH<sub>2</sub>), 2.98 (t,  $J = 9.2$  Hz, 4H, 2CH<sub>2</sub>).  $^{13}\text{C}$  NMR (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  144.0, 140.6, 138.3, 134.3, 130.6, 130.1, 128.4, 127.5, 127.2, 126.57, 126.42, 126.01, 125.92, 124.7, 122.6, 115.5,

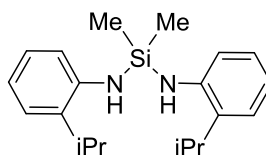
113.6, 59.7, 32.54, 32.37; IR (film) 3416, 3053, 2931, 1616, 1594, 1509, 1481, 1425, 910, 732  $\text{cm}^{-1}$ ; HRMS (ESI): Calcd for  $\text{C}_{50}\text{H}_{40}\text{N}_2$   $[\text{M}+\text{H}]^+$ : 669.3264, found: 669.3242.

Formation of Complexes in THF (152a, b and 154a, b)



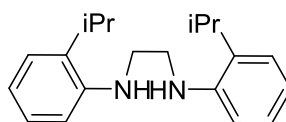
In an argon-filled glove box,  $\text{YCl}_3(\text{THF})_3$  (4.08 mg, 0.01 mmol), or  $\text{LaCl}_3(\text{THF})_{1.5}$  (3.52 mg, 0.01 mmol) and THF (0.5 mL) were added into a J. Young NMR tube equipped with teflon screw cap. (Trimethylsilyl)methyl lithium (3.72 mg, 0.04 mmol) or *N*-tert-butyl-1,1-dimethylsilanamine<sup>85</sup> (2.62 mg, 0.04 mmol) was added and the reactant mixture was kept at 21°C for 30 min. *N,N'*-Bis(10,11-dihydro-5H-dibenzo[*a,d*][7]annulen-5-yl)-[1,1'-binaphthalene]-2,2'-diamine (**143**) (6.68 mg, 0.01 mmol) was added and The complex formation was monitored by NMR (no-D). The solution was maintained at 21°C overnight. Removal of THF in vacuo was then followed by addition of  $\text{C}_6\text{D}_6$  (0.4 mL) in the glovebox.

*N,N'*-Bis(2-Isopropylphenyl)-1,1-Dimethylsilanediimine (**155**)<sup>83b</sup>



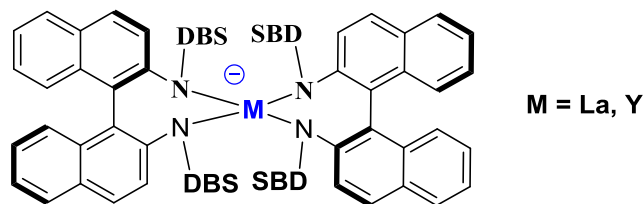
$^1\text{H-NMR}$  (500 MHz;  $\text{C}_6\text{D}_6$ ):  $\delta$  7.33 (d,  $J = 8.0$  Hz, 2H), 7.27 (d,  $J = 5.6$  Hz, 2H), 7.18 (t,  $J = 7.5$  Hz, 2H), 6.97 (t,  $J = 7.5$  Hz, 2H), 3.81 (s, 2H), 2.87 (dt,  $J = 13.5, 6.8$  Hz, 2H), 1.23 (d,  $J = 6.8$  Hz, 12H), 0.46 (s, 5H), 0.41 (s, 3H).

*N,N'*-Bis(2-Isopropylphenyl)  
Ethane-1,2-Diamine (**157**)<sup>83b</sup>



$^1\text{H-NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.18 (dd,  $J = 16.8, 8.1$  Hz, 4H, 4Ar-H), 6.81 (t,  $J = 7.0$  Hz, 2H, 2Ar-H), 6.76 (d,  $J = 8.0$  Hz, 2H, 2Ar-H), 3.96 (s, 2H, 2NH), 3.53 (s, 4H, 2CH<sub>2</sub>), 2.87 (dt,  $J = 13.5, 6.8$  Hz, 2H, 2Ar-CH), 1.26 (d,  $J = 6.8$  Hz, 13H, 4CH-CH<sub>3</sub>).

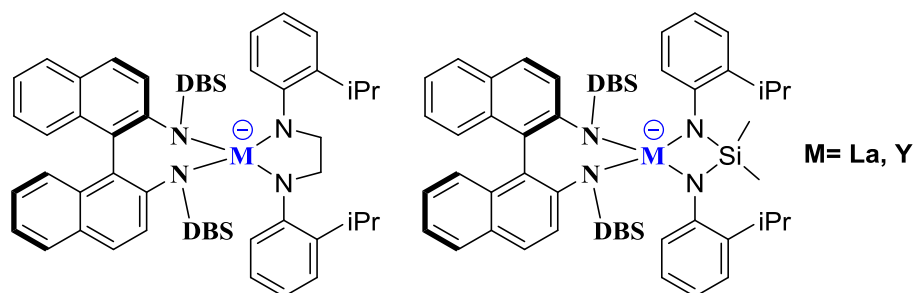
Formation of Complexes (**159a, b**)<sup>73n</sup>



In an argon-filled glove box,  $\text{YCl}_3(\text{THF})_3$  (4.08 mg, 0.01 mmol) or  $\text{LaCl}_3(\text{THF})_{1.5}$  (3.52 mg, 0.01 mmol) and THF (0.5 mL) were added into a J. Young NMR tube equipped with teflon screw cap. (Trimethylsilyl)methyl lithium (3.76 mg, 0.04 mmol) was added and the reactant mixture was kept at 21°C for 30 min. *N,N'*-Bis(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-yl)-[1,1'-binaphthalene]-2,2'-diamine (**143**) (13.36

mg, 0.02 mmol) was added and the complex formation was monitored by NMR (no-D). The solution was maintained at 21°C for 18 h. Removal of THF in vacuo was then followed by addition of C<sub>6</sub>D<sub>6</sub> (0.4 mL) in glovebox.

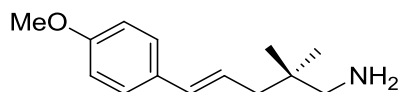
Formation of Complexes  
(156a, b and 158a, b)



In an argon-filled glove box, YCl<sub>3</sub>(THF)<sub>3</sub> (4.08 mg, 0.01 mmol) or LaCl<sub>3</sub>(THF)<sub>1.5</sub> (3.52 mg, 0.01 mmol) and THF (0.5 mL) were added into a J. Young NMR tube equipped with teflon screw cap. (Trimethylsilyl)methyl lithium (3.76 mg, 0.04 mmol) was added and the reactant mixture was kept at 21°C for 30 min. *N,N'*-bis(2-isopropylphenyl)ethane-1,2-diamine (**157**) (2.96 g, 0.01 mmol), or *N,N'*-bis(2-isopropylphenyl)-1,1-dimethylsilanedi-amine (**155**) (3.26 g, 0.01 mmol) was added. The first ligand exchange was held at 21°C for 20 min. *N,N'*-Bis(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-yl)-[1,1'-binaphthalene]-2,2'-diamine (**143**) (13.36 mg, 0.02 mmol) was then added and the complex formation was monitored by NMR (no-D). The solution was maintained at 21°C for 18 h. Removal of THF in vacuo was then followed by addition of C<sub>6</sub>D<sub>6</sub> (0.4 mL) in glovebox.

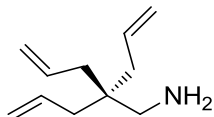
General LiAlH<sub>4</sub> Reduction Procedure

(E)-5-(4-Methoxyphenyl)-2,2-Dimethylpent-4-en-1-Amine (148d)<sup>83a</sup>

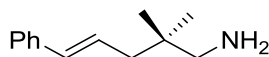


To a mixture of LiAlH<sub>4</sub> (0.294 g, 7.75 mmol) and anhydrous Et<sub>2</sub>O (30 mL) was added a solution of (E)-5-(4-methoxyphenyl)-2,2-dimethylpent-4-enenitrile (0.83 g, 3.87 mmol) in Et<sub>2</sub>O (10 mL) at 0 °C. The reaction mixture was stirred at 21 °C overnight and was then re-cooled to 0 °C. Water was slowly added dropwise until hydrogen evolution ceased. The resulting suspension was diluted with diethyl ether (50 mL) and subsequently was dried with Na<sub>2</sub>SO<sub>4</sub>. The white solid was removed by vacuum filtration.

Concentration in vacuo followed by bulb to bulb distillation from CaH<sub>2</sub> afforded (E)-5-(4-methoxyphenyl)-2,2-dimethylpent-4-en-1-amine (**5d**) (0.76 g, 3.5 mmol, 92%) as a colorless oil. <sup>1</sup>H-NMR (500 MHz; CDCl<sub>3</sub>): δ 7.30 (t, *J* = 6.4 Hz, 2H, 2Ar-H), 6.86 (d, *J* = 8.7 Hz, 2H, 2Ar-H), 6.35 (d, *J* = 15.7 Hz, 1H, Ar-CH=C), 6.11 (dt, *J* = 15.6, 7.7 Hz, 1H, Ar-C=CH), 3.81 (s, 3H, OCH<sub>3</sub>), 2.51 (s, 2H, CH<sub>2</sub>NH<sub>2</sub>), 2.12 (d, *J* = 7.6 Hz, 2H, C=C-CH<sub>2</sub>), 1.04 (s, 2H, NH<sub>2</sub>), 0.92 (s, 6H, 2CH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 159.2, 131.0, 127.5, 125.4, 114.3, 55.7, 53.2, 43.5, 36.0, 25.1; ; IR (film) 3375, 2957, 1609, 1513, 1465 1296, 1245, 1175, 1032, 970 cm<sup>-1</sup>;

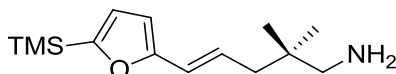
2,2-Diallylpent-4-en-1-Amine (148b)<sup>73r</sup>

The title compound 2,2-diallylpent-4-en-1-amine (**148b**) (1.35 g, 8.2 mmol, 88%) was obtained as a colorless oil from 2,2-diallylpent-4-enenitrile ( 1.50 g, 9.32 mmol) by the general LiAlH<sub>4</sub> reduction procedure. <sup>1</sup>H-NMR (500 MHz; CDCl<sub>3</sub>): δ 5.88-5.79 (m, 3H, 3CH<sub>2</sub>-CH=C), 5.10-5.06 (m, 6H, 3CH<sub>2</sub>-CH=CH<sub>2</sub>), 2.03 (dd, *J* = 7.5, 0.8 Hz, 6H, 3CH<sub>2</sub>-CH=C), 0.99 (s, 2H, NH<sub>2</sub>). <sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 134.9, 117.9, 47.8, 41.0, 39.5

(E)-2,2-Dimethyl-5-Phenyl Pent-4-en-1-Amine (148b)<sup>73h</sup>

The title (*E*)-2,2-dimethyl-5-phenylpent-4-en-1-amine (**148b**) (1.31 g, 6.92 mmol, 85%) was obtained as a colorless oil from (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile ( 1.51 g, 8.15 mmol) by the general LiAlH<sub>4</sub> reduction procedure. <sup>1</sup>H-NMR (500 MHz; CDCl<sub>3</sub>): δ 7.38 (d, *J* = 7.4 Hz, 2H, 2Ar-H), 7.33 (t, *J* = 7.6 Hz, 2H, 2Ar-H), 7.23 (t, *J* = 7.3 Hz, 1H, Ar-H), 6.42 (d, *J* = 15.7 Hz, 1H, Ar-CH=C), 6.27 (dt, *J* = 15.6, 7.7 Hz, 1H, Ar-C=CH), 2.53 (s, 2H, CH<sub>2</sub>NH<sub>2</sub>), 2.16 (d, *J* = 7.4 Hz, 2H, C=C-CH<sub>2</sub>), 1.14 (s, 2H, NH<sub>2</sub>), 0.94 (s, 6H, 2CH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 138.1, 132.6, 128.9, 127.7, 127.3, 126.4, 53.2, 43.5, 36.0, 25.2

(E)-2,2-Dimethyl-5-(5-(Trimethylsilyl)Furan-2-yl) Pent-4-en-1-Amine (**148e**)<sup>73j</sup>



The title compound (*E*)-2,2-dimethyl-5-(5-trimethylsilyl-furan-2-yl)-pent-4-enylamine (**148e**) (0.48 g, 1.9 mmol, 95%) was obtained as colorless oil from (*E*)-2,2-dimethyl-5-(5-trimethylsilyl-furan-2-yl)-pent-4-enitrile (0.52 g, 2.1 mmol) by the general  $\text{LiAlH}_4$  reduction procedure.  $^1\text{H-NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.59 (d,  $J = 3.1$  Hz, 1H, Ar-**H**), 6.29-6.16 (m, 4H, 2Ar-C=CH and 2Ar-**H**), 2.53 (s, 2H, CH<sub>2</sub>-NH<sub>2</sub>), 2.13 (d,  $J = 7.2$  Hz, 2H, C=C-CH<sub>2</sub>), 1.37 (s, 2H, NH<sub>2</sub>), 0.94 (s, 6H, 2CH<sub>3</sub>), 0.29 (s, 9H, 3SiCH<sub>3</sub>).  $^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  159.7, 157.4, 126.9, 121.54, 121.46, 106.8, 53.1, 43.5, 36.0, 25.1, -1.1

General Hydroamination Procedure

The catalytic complexes **152**, **154**, **156**, **158** or **159** was prepared in-situ according to the generation of complexes (**156a, b** or **158a, b**) procedure. The aminoalkenes (0.2 mmol) were added to the preformed complex and the reactant mixture was subsequently held at indicated temperature until the cyclization of aminoalkenes was judged complete ( $\geq 95\%$  conversion by  $^1\text{H NMR}$  integration).

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<sup>68</sup> All <sup>1</sup>H NMR yields are based on integration relative to *p*-xylene as the internal standard.

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<sup>71</sup> (a) **General Cyclization/Hydroamination Procedure:** In an argon-filled glove box, Y[N(TMS)<sub>2</sub>]<sub>3</sub> (5.70 mg, 0.010 mmol) and benzene-*d*<sub>6</sub> (0.5 mL) were added into a J. Young NMR tube equipped with a Teflon screw cap. (*E*)-2,2,4-Trimethyl-5-[5-(trimethylsilyl)-2-thienyl]pent-4-enylamine (**130**; 28 mg, 0.10 mmol) and *p*-xylene (10 μL) were then added and the reactant mixture was subsequently held at 60 °C in an oil bath for 4 h until cyclization/hydroamination was judged complete (≥95% by <sup>1</sup>H NMR integration).

(b) **Synthesis of *p*-Toluenesulfonamide; 2,4,4-Trimethyl- 1-(toluene-4-sulfonyl)-2-[5-(trimethylsilyl)thiophene-2-ylmethyl]tetrahydropyrrole (**141**<sub>Ts</sub>):** Tetrahydropyrrole **141** was prepared from (*E*)-2,2,4-trimethyl-5-[5-(trimethylsilyl)-2-thienyl]pent-4-enylamine (**130**; 28 mg, 0.10 mmol) by the general hydroamination procedure. The Teflon screw cap was then removed and the crude product was diluted with anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3 mL). TsCl (22 mg, 0.12 mmol) and pyridine (9.70 μL, 0.12 mmol) were added in succession. The reactant mixture was stirred at room temperature for 12 h, then the reactant mixture was diluted with Et<sub>2</sub>O (10 mL), washed with saturated NaHCO<sub>3</sub> (3 mL) and brine (3 mL), and the organic phase was subsequently dried with Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo followed by flash chromatography on silica gel (hexane–EtOAc, 15:1) afforded 2,4,4-trimethyl-1-(toluene-4-sulfonyl)-2-[5-(trimethylsilyl)thiophene-2-ylmethyl]tetrahydropyrrole (**141**<sub>Ts</sub>; 33.2 mg, 76%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.75 (d, *J* = 8.0 Hz, 2 H, 2Ar-H), 7.26 (d, *J* = 8.0 Hz, 2 H, 2Ar-H), 7.07 (d, *J* = 3.0 Hz, 1 H, Ar-H), 6.98 (d, *J* = 3.0 Hz, 1 H, Ar-H), 3.57 (d, *J* = 14.0 Hz, 1 H, CH), 3.29 (d, *J* = 14.0 Hz, 1 H, CH), 3.06 (d, *J* = 9.5 Hz, 1 H, CH), 2.98 (d, *J* = 10.0 Hz, 1 H, CH), 2.40 (s, 3 H, ArCH<sub>3</sub>), 2.15 (d, *J* = 13.0 Hz, 1 H, CH), 1.51 (s, 3 H, CH<sub>3</sub>), 1.42 (d, *J* = 13.5 Hz, 1 H, CH), 0.97 (s, 3 H, CH<sub>3</sub>), 0.90 (s, 3 H, CH<sub>3</sub>), 0.27 (s, 9 H, 3 SiCH<sub>3</sub>); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>): δ = 145.2, 142.8, 138.4, 133.9, 129.4, 129.3, 127.3, 68.7, 61.8, 52.6, 42.3, 36.2, 27.6, 27.2, 27.1, 21.5, –0.02; IR (film): 2957, 1439, 1342, 1251, 1209, 1154, 1092, 1055, 984, 840, 814, 759, 714, 659, 592, 548 cm<sup>–1</sup>; HRMS (ESI): *m/z* [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>33</sub>NO<sub>2</sub>S<sub>2</sub>Si: 436.1816; found: 436.1897. NH<sub>2</sub> NH S SiMe<sub>3</sub> S SiMe<sub>3</sub> Y[N(TMS)<sub>2</sub>]<sub>3</sub> (10 mol%) 60 °C, 4 h 95% graphical

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<sup>74</sup> The complex  $(\text{Me}_3\text{SiCH}_2)_3\text{La}(\text{THF})_{1.5}$  (**144b**) undergoes slow decomposition at 23 °C and must be used immediately upon its generation.

<sup>75</sup> Alternatively, the complexes **145a-b** could be prepared in THF. In these cases the THF was removed in vacuo and replaced with  $\text{C}_6\text{D}_6$  prior to the addition of the aminoalkene.

<sup>76</sup> Enantiomeric excesses were determined by conversion of the pyrrolidine products to the corresponding Mosher's amides followed by  $^{19}\text{F}$  NMR spectroscopic evaluation, and comparison to authentic racemates.

<sup>77</sup> We have previously observed a related suppression of activity when a Lu(III) complex derived from similar proligand type was used for hydroamination/cyclization.

<sup>78</sup> Tris(amide)s **146a** and **146b** were readily prepared from preformed  $\text{LiN}(\text{TMS})(t\text{-Bu})$  and  $\text{YCl}_3$  or  $\text{LaCl}_3(\text{THF})_{1.5}$  in  $\text{Et}_2\text{O}$  or THF respectively, followed by removal of the solvent and sublimation.

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APPENDICES

APPENDIX A

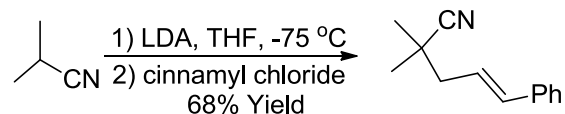
SUBSTRATE STRUCTURAL EFFECT IN YTTRIUM(III)-CATALYZED  
HYDROAMINATION/CYCLIZATION OF 1,2-DISUBSTITUTED AND  
1,1,2-TRISUBSTITUTED AMINOALKENES TERMINATED  
BY 2-(2-HETEROARENYL) GROUPS

### Materials and Methods

Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. THF and diethyl ether were distilled from sodium/benzophenone under nitrogen. CH<sub>2</sub>Cl<sub>2</sub> was distilled from CaH<sub>2</sub> under nitrogen. All other materials were used as received from commercial sources and all reactions were carried out under nitrogen unless otherwise noted. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator. Flash chromatographic columns were packed with Merck silica gel 60 as a slurry in the initial elution solvent. Nuclear magnetic resonance (NMR) data were obtained from Bruker DRX-300 (300 MHz) and Bruker DRX-500 (500 MHz). Infrared spectra (IR) were obtained from JASCO FTIR-4100. High-resolution mass spectra (HRMS) were obtained from Bruker MicroTOF with an Agilent 1100 HPLC.

### General Nitrile Preparation Procedure

#### (E)-2,2-Dimethyl-5-Phenylpent-4-Enenitrile

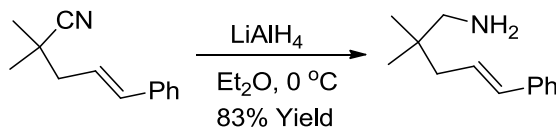


A 200-mL, round-bottomed flask equipped with a magnetic stirring bar and a N<sub>2</sub> inlet was charged with anhydrous diisopropylamine (5.6 mL, 39.6 mmol) and anhydrous THF (100 mL) was subsequently added. The resulting solution was cooled to 0 °C with an ice-water bath and *n*-BuLi (10 M, 4.0 mL, 40.0 mmol) was slowly added drop wise.

The reactant mixture was stirred for 30 min at 0 °C, and then cooled to -78 °C with a Dry Ice-acetone bath. Isobutyronitrile (3.6 mL, 39.6 mmol) was added and the reactant mixture was stirred for 2 h at -78 °C. Cinnamyl chloride (2.73 mL, 19.8 mmol) in anhydrous THF (5 mL) was then slowly added. The reactant mixture was warmed to room temperature and stirred for 2 h when judged complete by TLC. The reactant mixture was diluted with diethyl ether (100 mL), washed with saturated NaHCO<sub>3</sub> (30 mL), brine (30 mL). The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo followed by flash chromatography on silica gel (20:1 hexane/EtOAc for elution) afforded (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (2.5 g, 13.5 mmol, 68%) as a light yellow oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.37 (d, *J*=7.5 Hz, 2H, 2Ar-**H**), 7.31 (t, *J*=7.0 Hz, 2H, 2Ar-**H**), 7.23 (t, *J*=8.0 Hz, 1H, Ar-**H**), 6.50 (d, *J*=15.5 Hz, 1H, Ar-**CH**=C), 6.25 (ddd, apparent dt, *J*=15.0, 7.5 Hz, 1H, Ar-C=**CH**), 2.43 (d, *J*=7.0 Hz, 2H, **CH**<sub>2</sub>), 1.37 (s, 6H, 2**CH**<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 136.7, 134.8, 128.6, 127.7, 126.4, 124.8, 123.6, 44.3, 32.6, 26.3; IR (film) 2979, 2233, 1450, 969, 744, 696 cm<sup>-1</sup>.

#### General LiAlH<sub>4</sub> Reduction Procedure

##### (*E*)-2,2-Dimethyl-5-Phenyl Pent-4-Enylamine (**123<sub>E</sub>**)



A 50-mL, round-bottomed flask equipped with a magnetic stirring bar and a N<sub>2</sub> inlet was charged with LiAlH<sub>4</sub> (81 mg, 2.12 mmol) and anhydrous diethyl ether (8 mL)

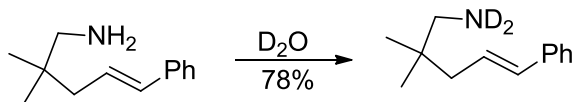
was subsequently added. The resulting mixture was cooled to 0 °C with an ice-water bath. (*E*)-2,2-Dimethyl-5-phenylpent-4-enitrile (0.26 g, 1.42 mmol) in anhydrous diethyl ether (2 mL) was then added at 0 °C. The reactant mixture was stirred for 10 h when judged complete by TLC. Water was slowly added drop wise until no hydrogen was evolved. The reactant mixture was diluted with diethyl ether (10 mL) and subsequently was dried with Na<sub>2</sub>SO<sub>4</sub>. The white solid was removed by vacuum filtration.

Concentration in vacuo followed by bulb to bulb distillation from CaH<sub>2</sub> afforded (*E*)-2,2-dimethyl-5-phenylpent-4-enylamine (**123<sub>E</sub>**) (0.22 g, 1.18 mmol, 83%) as a colorless oil.

<sup>1</sup>H NMR (500 MHz, toluene-D<sub>8</sub>) δ 7.22 (d, *J* = 7.1 Hz, 2H, 2Ar-H), 7.12 (t, *J* = 7.6 Hz, 2H, 2Ar-H), 7.05 – 7.01 (m, 1H, Ar-H), 6.29 (d, *J* = 15.7 Hz, 1H, Ar-CH=C), 6.15 (dt, *J* = 15.5, 7.5 Hz, 1H, Ar-C=CH), 2.26 (s, 2H, CH<sub>2</sub>NH<sub>2</sub>), 1.99 (dd, *J* = 7.6, 1.3 Hz, 2H, C=C-CH<sub>2</sub>), 0.78 (s, 6H, 2CH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, toluene-D<sub>8</sub>) δ 137.08, 132.18, 128.33, 127.76, 126.72, 126.02, 52.20, 42.93, 35.38, 24.48; IR (film) 2957, 1576, 1472, 1364, 1309, 969, 751, 692 cm<sup>-1</sup>.

#### General H/D Exchange Procedure

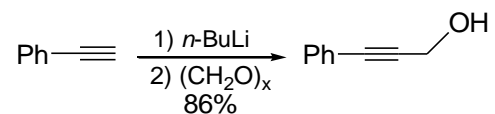
(*E*)-2,2-Dimethyl-5-Phenylpent-4-  
-Enylamine-*N,N*-D<sub>2</sub> [**123<sub>E</sub>** (**D<sub>2</sub>**)]



A 15-mL, round-bottomed flask equipped with a magnetic stirring bar and a N<sub>2</sub> inlet was charged with (*E*)-2,2-dimethyl-5-phenylpent-4-enylamine (**123<sub>E</sub>**) (0.88 g, 4.67

mmol) and anhydrous benzene (2.5 mL) was subsequently added. D<sub>2</sub>O (1.88 g, 93.0 mmol) was subsequently added. The reactant mixture was stirred for 12 h. The lower D<sub>2</sub>O layer was removed by syringe and the H/D exchange was repeated three times. Concentration in vacuo followed by bulb to bulb distillation afforded (*E*)-2,2-dimethyl-5-phenylpent-4-enylamine-*N,N*-D<sub>2</sub> [**123<sub>E</sub>** (**D<sub>2</sub>**)] (0.69 g, 3.61 mmol, 78%) as a colorless oil. <sup>1</sup>H NMR (500 MHz, toluene-D<sub>8</sub>) δ 7.22 (d, *J* = 7.5 Hz, 2H, 2Ar-**H**), 7.14 – 7.10 (m, 2H, 2Ar-**H**), 7.05 – 7.01 (m, 1H, Ar-**H**), 6.29 (d, *J* = 15.7 Hz, 1H, Ar-**CH=C**), 6.15 (dt, *J* = 15.5, 7.6 Hz, 1H, Ar-**C=CH**), 2.27 (s, 2H, **CH<sub>2</sub>ND<sub>2</sub>**), 1.99 (dd, *J* = 7.6, 1.3 Hz, 2H, **C=C-CH<sub>2</sub>**), 0.78 (s, 6H, 2**CH<sub>3</sub>**); <sup>13</sup>C NMR (126 MHz, toluene-D<sub>8</sub>) δ 137.89, 137.07, 132.19, 128.66, 128.47, 128.33, 126.72, 126.02, 52.40, 42.91, 35.40, 24.46; IR (film) 2954, 1598, 1469, 1364, 1309, 966, 751, 692 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>13</sub>H<sub>17</sub>D<sub>2</sub>ND [M+D]<sup>+</sup> 193.1779, found 193.1779.

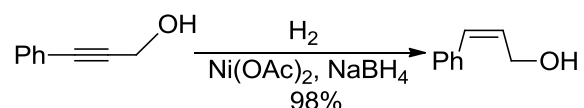
### 3-Phenyl-Prop-2-yn-1-ol



A 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a N<sub>2</sub> inlet was charged with phenylethyne (20 mL, 179 mmol) and anhydrous THF (180 mL) was subsequently added. The resulting solution was cooled to -78 °C with a Dry Ice-acetone bath, *n*-BuLi (2.6M, 82.4 mL, 214 mmol) was slowly added drop wise, and the reactant mixture was stirred at -78 °C for 40 min. Paraformaldehyde (6.43 g, 217 mmol) was added and the reactant mixture was warmed to room temperature and stirred for 10 h.

The reactant mixture was diluted with diethyl ether (200 mL), washed with saturated  $\text{NH}_4\text{Cl}$  (50 mL), brine (50 mL), and the organic phase was subsequently dried with  $\text{Na}_2\text{SO}_4$ . Concentration in vacuo followed by flash chromatography on silica gel (3:1 hexane/EtOAc for elution) afforded 3-phenyl-prop-2-yn-1-ol (20.2 g, 153 mmol, 86%) as a light yellow oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.43-7.24 (m, 5H, 5Ar-**H**), 4.49 (d,  $J=6.0$  Hz, 2H, **CH**<sub>2</sub>), 1.69 (dd, apparent triplet,  $J=5.5$  Hz, 1H, **OH**);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  131.7, 128.5, 128.3, 85.7, 51.7; IR (film) 3324, 1491, 1033, 755, 692  $\text{cm}^{-1}$ .

(Z)-3-Phenyl-Prop-2-en-1-ol

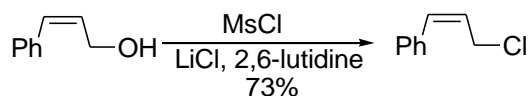


A 100-mL, round-bottomed flask equipped with a magnetic stirring bar and a  $\text{N}_2$  inlet was charged with anhydrous ethanol (30 mL),  $\text{Ni(OAc)}_2 \cdot 4\text{H}_2\text{O}$  (0.83 g, 3.32 mmol) and  $\text{NaBH}_4$  (0.13 g, 3.32 mmol) were added in succession. The reactant mixture was purged by hydrogen gas three times. Ethylenediamine (0.45 mL, 6.63 mmol) and 3-phenyl-prop-2-yn-1-ol (2.19 g, 16.6 mmol) in absolute ethanol (5 mL) were added in succession. The reactant mixture was stirred under hydrogen at room temp for 10 h. Filtration of the reactant mixture through silica gel followed by concentration in vacuo afforded (Z)-3-phenyl-prop-2-en-1-ol (2.16 g, 16.1 mmol, 98%) as a colorless oil, which is used without further purification.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35-7.18 (m, 5H, 5Ar-**H**), 6.56 (d,  $J=12.0$  Hz, 1H, Ar-**CH=C**), 5.86 (ddd, apparent dt,  $J=13.0, 6.5$  Hz, 1H, Ar-**C=CH**), 4.43 (d,  $J=6.0$  Hz, 2H, **CH**<sub>2</sub>), 1.56 (s, 1H, **OH**);  $^{13}\text{C}$  NMR (126 MHz,

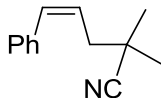
CDCl<sub>3</sub>):  $\delta$  131.1, 131.0, 128.8, 128.3, 127.3, 59.7; IR (film) 3328, 1498, 1013, 769, 700 cm<sup>-1</sup>.

General Allylic Chloride  
Preparation Procedure

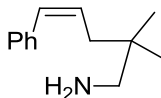
[(Z)-3-Chloro-Propenyl]-Benzene<sup>84</sup>



A 50-mL, round-bottomed flask equipped with a magnetic stirring bar and a N<sub>2</sub> inlet was charged with LiCl (780 mg, 18.4 mmol) and anhydrous DMF (30 mL) was subsequently added. The resulting mixture was stirred at 0 °C for 10 min until the LiCl had dissolved. (Z)-3-Phenyl-prop-2-en-1-ol (2.1 g, 15.3 mmol) and anhydrous 2,6-lutidine (2.1 mL, 18.4 mmol) were added in succession. MsCl (1.42 mL, 18.4 mmol) was then slowly added. The reactant mixture was stirred for 3 h when judged complete by TLC. The reactant mixture was diluted with diethyl ether (20 mL), washed with water (5 mL), and the ether layer was subsequently dried with Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo followed by flash chromatography on silica gel (10:1 hexane/EtOAc for elution) afforded [(Z)-3-chloro-propenyl]-benzene (1.82 g, 11.9 mmol, 73%) as a light yellow oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  7.38-7.18 (m, 5H, 5Ar-H), 6.65 (d, *J*=11.5 Hz, 1H, Ar-CH=C), 5.89 (m, 1H, Ar-C=CH), 4.25 (d, *J*=8.0 Hz, 2H, CH<sub>2</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  135.6, 133.4, 128.7, 128.5, 127.7, 126.9, 40.8; IR (film) 3028, 1495, 1446, 1257, 811, 773, 700 cm<sup>-1</sup>.

(Z)-2,2-Dimethyl-5-Phenylpent-4-Enenitrile

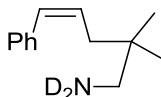
The title compound (Z)-2,2-dimethyl-5-phenylpent-4-enenitrile (0.85 g, 4.62 mmol, 52%) was obtained as a light yellow oil from [(Z)-3-chloro-propenyl]-benzene (1.35 g, 8.85 mmol) by the general nitrile preparation procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35-7.21 (m, 5H, 5Ar-H), 6.68 (d,  $J=11.5$  Hz, 1H, Ar-CH=C), 5.78 (dt,  $J=12.0, 7.0$  Hz, 1H, Ar-C=CH), 2.54 (d,  $J=7.0$  Hz, 2H,  $\text{CH}_2$ ), 1.32 (s, 6H, 2 $\text{CH}_3$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  136.8, 132.8, 128.7, 128.3, 127.0, 125.9, 124.8, 39.1, 32.5, 26.4; IR (film) 2979, 2233, 1495, 1446, 1368, 807, 773, 703  $\text{cm}^{-1}$ ; HRMS (ESI): Calcd for  $\text{C}_{13}\text{H}_{16}\text{N}$  [ $\text{M}+\text{H}$ ] $^+$ : 186.12773, found: 186.12706; Calcd for  $\text{C}_{13}\text{H}_{16}\text{NO}$  [ $\text{M}+\text{OH}$ ] $^+$ : 202.12264, found: 202.12331;  $\text{C}_{13}\text{H}_{15}\text{NONa}$  [ $\text{M}+\text{Na}$ ] $^+$ : 208.10967, found: 208.10906.

(Z)-2,2-Dimethyl-5-Phenyl Pent-4-Enylamine (**123<sub>Z</sub>**)

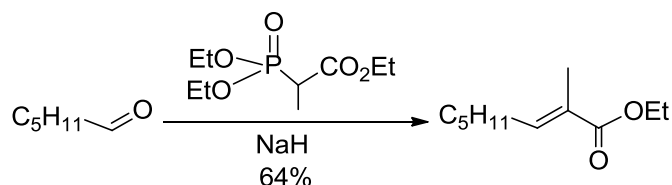
The title compound (Z)-2,2-dimethyl-5-phenylpent-4-enylamine (**137<sub>Z</sub>**) (0.53 g, 2.78 mmol, 79%) was obtained as a colorless oil from (Z)-2,2-dimethyl-5-phenylpent-4-enenitrile (0.65 g, 3.51 mmol) by the general  $\text{LiAlH}_4$  reduction procedure.  $^1\text{H}$  NMR (500 MHz, toluene- $\text{D}_8$ )  $\delta$  7.31 (d,  $J = 7.5$  Hz, 2H, 2Ar-H), 7.21 (t,  $J = 7.5$  Hz, 2H, 2Ar-H), 7.11 – 7.06 (m, 1H, Ar-H), 6.53 (d,  $J = 11.8$  Hz, 1H, Ar-CH=C), 5.70 (dt,  $J = 11.8, 7.5$  Hz,

1H, CH<sub>2</sub>NH<sub>2</sub>), 2.29 (s, 2H, C=C-CH<sub>2</sub>), 2.27 (dd, *J* = 7.5, 1.9 Hz, 2H, 2CH<sub>3</sub>), 0.80 (s, 6H), 0.46 (s, 2H, NH<sub>2</sub>); <sup>13</sup>C NMR (126 MHz, toluene-D<sub>8</sub>) δ 137.07, 130.33, 129.12, 128.84, 127.98, 126.35, 52.19, 37.24, 35.15, 24.36.; IR (film) 2954, 1602, 1469, 1364, 807, 773, 696 cm<sup>-1</sup>.

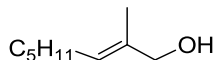
(*Z*)-2,2-Dimethyl-5-Phenylpent-4-Enylamine-*N,N*-D<sub>2</sub> [**123<sub>Z</sub>**(D<sub>2</sub>)]



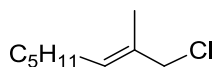
The title compound (*Z*)-2,2-dimethyl-5-phenylpent-4-enylamine-*N,N*-D<sub>2</sub> [**137<sub>Z</sub>**(D<sub>2</sub>)] (0.65 g, 3.4 mmol, 67%) was obtained as a colorless oil from (*Z*)-2,2-dimethyl-5-phenylpent-4-enylamine (**123<sub>Z</sub>**) (0.96 g, 5.1 mmol) by the general H/D exchange procedure. <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>) δ 7.37 (d, *J* = 7.5 Hz, 2H, 2Ar-**H**), 7.24 (t, *J* = 7.5 Hz, 2H, 2Ar-**H**), 7.14 – 7.09 (m, 1H, 2Ar-**H**), 6.58 (d, *J* = 11.8 Hz, 1H, Ar-**CH=C**), 5.74 (dt, *J* = 11.8, 7.5 Hz, 1H, Ar-C=**CH**), 2.31 (dd, *J* = 7.5, 2.0 Hz, 2H, C=C-**CH<sub>2</sub>**), 2.30 (s, 2H, **CH<sub>2</sub>ND<sub>2</sub>**), 0.82 (s, 6H, 2**CH<sub>3</sub>**); <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ 137.99, 130.44, 129.36, 128.99, 128.32, 128.20, 126.56, 52.11, 37.40, 35.24, 24.54; IR (film) 2954, 1364, 1450, 1495, 1469, 803, 769, 700 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>13</sub>H<sub>17</sub>D<sub>2</sub>ND [M+D]<sup>+</sup> 193.1779, found 193.1767.

General Horner-Wadsworth-Emmons Procedure(E)-2-Methyl-Oct-2-enoic Acid Ethyl Ester<sup>86</sup>

A 250-mL, round-bottomed flask equipped with a magnetic stirring bar and a N<sub>2</sub> inlet was charged with NaH (60% in oil, 1.96 g, 49.1 mmol) and anhydrous THF (100 mL) was added. After cooling to 0 °C, triethyl 2-phosphonopropionate (10.7 mL, 49.1 mmol) was slowly added. The reactant mixture was stirred at 0 °C for 30 min. Hexanal (5 mL, 40.9 mmol) was then slowly added and the reactant mixture was stirred for 30 min. The reactant mixture was diluted with diethyl ether (200 mL), washed with saturated NaHCO<sub>3</sub> (50 mL), brine (50 mL), and the ether layer was subsequently dried with Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo followed distillation afforded (*E*)-2-methyl-oct-2-enoic acid ethyl ester (4.79 g, 26.0 mmol, *E/Z*: 5.4/1, 64%) as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): (*E*) isomer δ 6.72 (t, *J*=7.5 Hz, 1H, CH=C), 4.15 (ddd, apparent quartet, *J*=7.0 Hz, 2H, OCH<sub>2</sub>), 2.12 (ddd, apparent quartet, *J*=7.5 Hz, 2H, C=C-CH<sub>2</sub>), 1.79 (s, 3H, C=C-CH<sub>3</sub>), 1.32-1.21 (m, 9H, 3CH<sub>2</sub> and CH<sub>3</sub>), 0.85 (dd, apparent triplet, *J*=6.5 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): (*E*) and (*Z*) mixture δ 168.3, 143.1, 142.4, 127.6, 60.3, 60.0, 31.5, 29.5, 29.1, 28.6, 28.2, 22.5, 20.6, 14.3, 14.0, 12.3; IR (film): (*E*) and (*Z*) mixture 2957, 2932, 2862, 1712, 1650, 1461, 1368, 1254, 1195, 1143, 1098, 1029, 741 cm<sup>-1</sup>.

(E)-2-Methyl-Oct-2-en-1-ol<sup>86</sup>

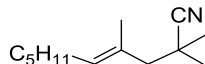
The title compound (*E*)-2-methyl-oct-2-en-1-ol (3.85 g, 25.0 mmol, *E/Z*: 4/1, 98%) was obtained as a colorless oil from (*E*)-2-methyl-oct-2-enoic acid ethyl ester (4.70 g, 25.5 mmol) by the general LiAlH<sub>4</sub> reduction procedure. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): (*E*) isomer δ 5.38 (t, *J*=7.0 Hz, 1H, CH=C), 3.97 (s, 2H, OCH<sub>2</sub>), 1.99 (ddd, apparent quartet, *J*=6.5 Hz, 2H, C=C-CH<sub>2</sub>), 1.63 (s, 3H, C=C-CH<sub>3</sub>), 1.40-1.21 (m, 6H, 3CH<sub>2</sub>), 0.86 (dd, apparent triplet, *J*=7.0 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): (*E*) and (*Z*) mixture δ 134.5, 128.9, 126.7, 69.0, 61.6, 31.5, 31.4, 30.3, 29.7, 29.2, 27.5, 22.6, 21.2, 14.1, 13.6; IR (film): (*E*) and (*Z*) mixture 3309, 2925, 2858, 1460, 1380, 1013 cm<sup>-1</sup>.

(E)-1-Chloro-2-Methyl-Oct-2-ene

The title compound (*E*)-1-chloro-2-methyl-oct-2-ene (2.49 g, 15.5 mmol, *E/Z*: 3.5/1, 63%) was obtained as a colorless oil from (*E*)-2-methyl-oct-2-en-1-ol (3.50 g, 24.7 mmol) by the general allylic chloride preparation procedure. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): (*E*) isomer δ 5.51 (t, *J*=7.0 Hz, 1H, CH=C), 4.00 (s, 2H, Cl-CH<sub>2</sub>), 2.00 (ddd, apparent quartet, *J*=5.5 Hz, 2H, C=C-CH<sub>2</sub>), 1.71 (s, 3H, C=C-CH<sub>3</sub>), 1.40-1.21 (m, 6H, 3CH<sub>2</sub>), 0.86 (dd, *J*=6.5 Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): (*E*) and (*Z*) mixture

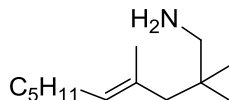
$\delta$  131.6, 131.4, 131.3, 52.7, 43.8, 31.5, 29.3, 28.8, 28.0, 27.8, 22.5, 21.5, 14.0; IR (film): (E) and (Z) mixture 2957, 2928, 2854, 1461, 1380, 1261, 685  $\text{cm}^{-1}$ .

(E)-2,2,4-Trimethyl-Dec-4-Enenitrile



The title compound (*E*)-2,2,4-trimethyl-dec-4-enenitrile (1.12 g, 5.79 mmol, *E/Z*: 3.5/1, 93%) was obtained as a colorless oil from (*E*)-1-chloro-2-methyl-oct-2-ene (1.0 g, 6.23 mmol) by the general nitrile preparation procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ) (*E*) isomer  $\delta$  5.28 – 5.21 (m, 1H,  $\text{CH}=\text{C}$ ), 2.18 (s, 2H,  $\text{CH}=\text{C}$ ), 2.04 – 1.91 (m, 3H,  $\text{C}=\text{C}-\text{CH}_2$ ), 1.79 – 1.71 (m, 3H,  $\text{C}=\text{C}-\text{CH}_3$ ), 1.36 – 1.31 (m, 4H,  $2\text{CH}_2$ ), 1.29 (s, 6H,  $2\text{CH}_3$ ), 1.28-1.22 (m, 4H,  $2\text{CH}_2$ ) 0.86 (t,  $J = 6.9$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ): (*E*) and (*Z*) mixture  $\delta$  131.42, 131.09, 129.89, 125.69, 50.49, 42.32, 31.71, 31.56, 31.52, 29.45, 29.18, 28.54, 28.04, 27.28, 27.00, 24.92, 22.57, 22.54, 17.48, 14.08.; IR (film): (*E*) and (*Z*) mixture 2957, 2932, 2858, 2233, 1469, 1390, 1368, 1280, 1195, 1140, 914, 877, 729, 692  $\text{cm}^{-1}$ .

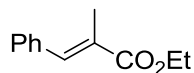
(E)-2,2,4-Trimethyl-Dec-4-Enylamine (132)



The title compound (*E*)-2,2,4-trimethyl-dec-4-enylamine (**132**) (1.04 g, 5.27 mmol, *E/Z*: 3.7/1, 92%) was obtained as a colorless oil from (*E*)-2,2,4-trimethyl-dec-4-

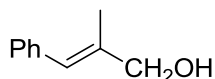
enenitrile (1.10 , 5.70 mmol) by the general LiAlH<sub>4</sub> reduction procedure. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.15 – 5.02 (m, 1H, CH=C), 2.41 (s, 2H, C=C-CH<sub>2</sub>), 1.99 – 1.92 (m, 2H, C=C-CH<sub>2</sub>), 1.87 (s, 2H, N-CH<sub>2</sub>), 1.64 – 1.60 (m, 3H, C=C-CH<sub>3</sub>), 1.34 – 1.19 (m, 6H, 3CH<sub>2</sub>), 1.04 (s, 2H, NH<sub>2</sub>), 0.81 (s, 6H, 2CH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 132.24, 129.15, 129.09, 54.09, 53.30, 49.16, 41.31, 31.58, 29.42, 28.15, 25.51, 25.26, 22.58, 18.91, 14.11; IR (film): (*E*) and (*Z*) mixture 2961, 2925, 2858, 1579, 1465, 1380, 1062, 807, 725 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>13</sub>H<sub>27</sub>N [M+H]<sup>+</sup>: 198.2216, found: 198.2250.

Ethyl (*E*)-2-Methyl-3-Phenyl-2-Propenoate



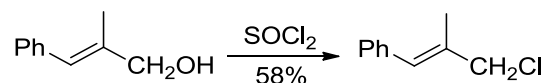
The title compound ethyl (*E*)-2-methyl-3-phenyl-2-propenoate (3.78 g, 19.9 mmol, 97%) was obtained as colorless oil from benzaldehyde (2.1 mL, 20.6 mmol) by the general Horner-Wadsworth-Emmons procedure. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.68 (s, 1H, Ar-CH=C), 7.39-7.23 (m, 5H, 5Ar-H), 4.26 (ddd, apparent quartet, *J*=7.0 Hz, 2H, CH<sub>2</sub>), 2.10 (s, 3H, CH<sub>3</sub>), 1.33 (dd, apparent triplet, *J*=7.0 Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 138.6, 135.9, 129.6, 128.3, 128.2, 60.9, 14.3, 14.1; IR (film) 2983, 1705, 1634, 1446, 1364, 1254, 1202, 1110, 1033, 763, 700 cm<sup>-1</sup>.

(*E*)-2-Methyl-3-Phenylprop-2-en-1-ol



The title compound (*E*)-2-methyl-3-phenylprop-2-en-1-ol (2.8 g, 18.9 mmol, 96%) was obtained as a colorless oil from ethyl (*E*)-2-methyl-3-phenyl-2-propenoate (3.78 g, 19.9 mmol) by the general LiAlH<sub>4</sub> reduction procedure. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.35-7.21 (m, 5H, 5Ar-H), 6.52 (s, 1H, Ar-CH=C), 4.18 (s, 2H, CH<sub>2</sub>), 1.89 (s, 3H, CH<sub>3</sub>), 1.71 (s, 1H, OH); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 137.7, 137.5, 128.9, 128.2, 126.4, 125.0, 69.0, 15.3; IR (film) 3324, 2913, 2858, 1602, 1491, 1439, 1372, 1069, 1007, 918, 844, 741, 696 cm<sup>-1</sup>.

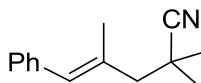
[(*E*)-3-Chloro-2-Methylpropenyl]-Benzene



A 250-mL, round-bottomed flask equipped with a magnetic stirring bar and a N<sub>2</sub> inlet was charged with (*E*)-2-methyl-3-phenylprop-2-en-1-ol (2.8 g, 18.9 mmol) and anhydrous diethyl ether (100 mL) was subsequently added. After cooling to 0 °C, freshly distilled SOCl<sub>2</sub> (1.33 mL, 18.9 mmol) was slowly added. The reactant mixture was stirred for 30 min when judged complete by TLC. The reactant mixture was diluted with diethyl ether (100 mL), washed with saturated NaHCO<sub>3</sub> (50 mL), brine (50 mL), and the organic layer was subsequently dried with Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo followed by flash chromatography on silica gel (hexane for elution) afforded [(*E*)-3-chloro-2-methylpropenyl]-benzene (1.83 g, 11.0 mmol, 58%) as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.35-7.23 (m, 5H, 5Ar-H), 6.58 (s, 1H, Ar-CH=C), 4.18 (s, 2H, CH<sub>2</sub>), 1.98 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 136.8, 134.1, 129.7, 129.0, 128.5,

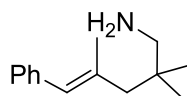
128.2, 127.1, 52.9, 15.9; IR (film) 3024, 2951, 1491, 1439, 1261, 1013, 922, 855, 747, 696, 515  $\text{cm}^{-1}$ .

(E)-2,2,4-Trimethyl-5-Phenylpent-4-Enenitrile



The title compound (*E*)-2,2,4-trimethyl-5-phenylpent-4-enenitrile (0.5 g, 2.56 mmol, 85%) was obtained as a light yellow oil from [(*E*)-3-chloro-2-methylpropenyl]-benzene (0.5 g, 3.0 mmol) by the general nitrile preparation procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35-7.19 (m, 5H, 5Ar-H), 6.36 (s, 1H, Ar-CH=C), 2.40 (s, 2H,  $\text{CH}_2$ ), 2.03 (s, 3H,  $\text{CH}_3$ ), 1.40 (s, 6H, 2 $\text{CH}_3$ );  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  130.6, 128.9, 128.1, 126.5, 51.5, 27.1, 19.5; IR (film) 2979, 2935, 2233, 1598, 1491, 1469, 1446, 1390, 1368, 1364, 1273, 1187, 1021, 918, 744, 696, 515  $\text{cm}^{-1}$ .

(E)-2,2,4-Trimethyl-5-Phenylpent-4-Enylamine (**131**)

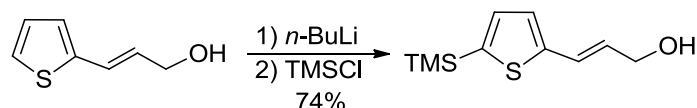


The title compound (*E*)-2,2,4-trimethyl-5-phenylpent-4-enylamine (**131**) (0.38 g, 1.87 mmol, 93%) was obtained as a colorless oil from (*E*)-2,2,4-trimethyl-5-phenylpent-4-enenitrile (0.4 g, 2.0 mmol) by the general  $\text{LiAlH}_4$  reduction procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.30 (t,  $J = 7.5$  Hz, 2H, 2Ar-H), 7.22 (s, 2H, 2Ar-H), 7.17 (t,  $J = 7.5$  Hz,

1H, Ar-**H**), 6.23 (s, 1H, Ar-**CH=C**), 2.51 (s, 2H, N-**CH<sub>2</sub>**), 2.10 (s, 2H, C=C-**CH<sub>2</sub>**), 1.92 (d,  $J = 1.4$  Hz, 3H, **CH<sub>3</sub>**), 1.29 (s, 2H, **NH<sub>2</sub>**), 0.92 (s, 6H, 2**CH<sub>3</sub>**);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  138.42, 136.62, 128.87, 128.77, 128.01, 125.93, 53.37, 50.43, 36.37, 25.31, 21.09.; IR (film) 2957, 1572, 1469, 1372, 1309, 751, 700  $\text{cm}^{-1}$ ; HRMS (ESI): Calcd for  $\text{C}_{14}\text{H}_{21}\text{N}$   $[\text{M}+\text{H}]^+$ : 204.175, found: 2104.170.

### General Silylation Procedure

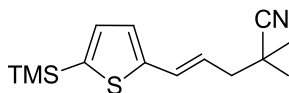
#### (E)-3-(5-Trimethylsilylanyl-Thio Phen-2-yl)-Prop-2-en-1-ol



A 100-mL, round-bottomed flask equipped with a magnetic stirring bar and a  $\text{N}_2$  inlet was charged with (*E*)-3-thiophen-2-yl-prop-2-en-1-ol (1.0 g, 7.14 mmol) and anhydrous THF (40 mL) was subsequently added. The resulting solution was cooled to  $-78$  °C with a dry ice-acetone bath and *n*-BuLi (2.5 M, 7.15 mL, 17.9 mmol) was slowly added drop wise. The reactant mixture was warmed up to  $-15$  °C and stirred for 20 min, and then re-cooled back to  $-78$  °C. The freshly distilled TMSCl (2.3 mL, 17.9 mmol) was slowly added and the reactant mixture was stirred for another 30 min at  $-78$  °C. The reactant mixture was diluted with diethyl ether (100 mL), washed with aqueous 10% HCl (10 mL), brine (30 mL), and the ether layer was subsequently dried with  $\text{Na}_2\text{SO}_4$ . Concentration in vacuo followed by flash chromatography on silica gel (4:1 hexane/EtOAc for elution) afforded (*E*)-3-(5-trimethylsilylanyl-thiophen-2-yl)-prop-2-en-

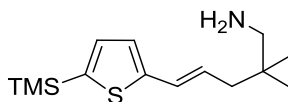
1-ol (1.12 g, 5.28 mmol, 74%) as a colorless oil.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.07 (d,  $J=3.0$  Hz, 1H, Ar-**H**), 6.99 (d,  $J=3.0$  Hz, 1H, Ar-**H**), 6.74 (d,  $J=16.0$  Hz, 1H, Ar-**CH=C**), 6.20 (ddd, apparent dt,  $J=16.0$ , 6.0 Hz, 1H, Ar-**C=CH**), 4.27 (dd, apparent triplet,  $J=6.0$  Hz, 2H, C=C-**CH<sub>2</sub>**), 1.38 (dd, apparent triplet,  $J=5.5$  Hz, 1H, **OH**), 0.28 (s, 9H, 3Si**CH<sub>3</sub>**);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  134.3, 128.5, 127.1, 124.2, 63.5, -0.16; IR (film) 3305, 2954, 1251, 984, 840  $\text{cm}^{-1}$ .

(E)-2,2-Dimethyl-5-(5-Trimethylsilylthiophen-2-yl)-Pent-4-Enenitrile



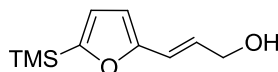
The title compound (*E*)-2,2-dimethyl-5-(5-trimethylsilylthiophen-2-yl)-pent-4-enenitrile (0.31 g, 1.18 mmol, 37 %) was obtained as a colorless oil from (*E*)-3-(5-trimethylsilylthiophen-2-yl)-prop-2-en-1-ol (0.68 g, 3.20 mmol) by the general nitrile preparation procedure in which the highly unstable intermediate (*E*)-3-(5-trimethylsilylthiophen-2-yl)-prop-2-en-1-chloride was prepared by treating (*E*)-3-(5-trimethylsilylthiophen-2-yl)-prop-2-en-1-ol with 1 eq  $\text{SOCl}_2$  in THF at 0 °C and the crude product was used directly without work up.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.08 (d,  $J = 3.4$  Hz, 1H, Ar-**H**), 6.99 (d,  $J = 3.4$  Hz, 1H, Ar-**H**), 6.64 (d,  $J = 15.5$  Hz, 1H, Ar-**CH=C**), 6.09 (dt,  $J = 15.5$ , 7.6 Hz, 1H, Ar-**C=CH**), 2.39 (dd,  $J = 7.6$ , 1.3 Hz, 2H, C=C-**CH<sub>2</sub>**), 1.36 (s, 6H, 2**CH<sub>3</sub>**), 0.30 (s, 9H, 3Si**CH<sub>3</sub>**);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  146.74, 139.68, 134.32, 127.67, 126.91, 124.72, 123.53, 44.21, 32.62, 26.26, -0.14; IR (film) 2957, 2233, 1469, 1435, 1251, 1202, 1065, 988, 958, 848, 755, 700, 626, 523  $\text{cm}^{-1}$ .

(E)-2,2-Dimethyl-5-(5-Trimethylsilyl-  
Thiophen-2-yl)-Pent-4-Enylamine (127)



The title compound (*E*)-2,2-dimethyl-5-(5-trimethylsilylthiophen-2-yl)-pent-4-enylamine (**127**) (0.22 g, 0.80 mmol, 87 %) was obtained as a light yellow oil from (*E*)-2,2-dimethyl-5-(5-trimethylsilylthiophen-2-yl)-pent-4-enitrile (0.24 g, 0.93 mmol) by the general  $\text{LiAlH}_4$  reduction procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.05 (d,  $J$  = 3.4 Hz, 1H, Ar-**H**), 6.90 (d,  $J$  = 3.4 Hz, 1H, Ar-**H**), 6.51 (d,  $J$  = 15.5 Hz, 1H, Ar-**CH=C**), 6.07 (dt,  $J$  = 15.5, 7.7 Hz, 1H, Ar-**C=CH**), 2.47 (s, 2H, N-**CH**<sub>2</sub>), 2.07 (dd,  $J$  = 1.3, 2H, C=C-**CH**<sub>2</sub>), 1.21 (s, 2H, **NH**<sub>2</sub>), 0.88 (s, 6H, 2**CH**<sub>3</sub>), 0.28 (s, 9H, 3Si**CH**<sub>3</sub>);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  148.03, 134.30, 127.81, 125.74, 125.16, 52.70, 43.03, 35.68, 24.69, -0.13; IR (film) 2954, 1472, 1435, 1247, 1199, 1065, 984, 955, 840, 795, 755  $\text{cm}^{-1}$ ; HRMS (ESI): Calcd for  $\text{C}_{14}\text{H}_{25}\text{NSSi}$  [ $\text{M}+\text{H}$ ]<sup>+</sup>: 268.155, found: 268.161.

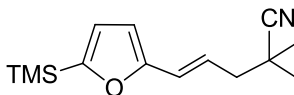
(E)-3-(5-Trimethylsilyl-  
Furan-2-yl)-Prop-2-en-1-ol



The title compound (*E*)-3-(5-trimethylsilylfuran-2-yl)-prop-2-en-1-ol (2.70 g, 13.8 mmol, 74%) was obtained as a colorless oil from (*E*)-3-furan-2-yl-prop-2-en-1-ol (2.32 g, 18.7 mmol) by the general silylation procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.56 (d,  $J$ =3.0 Hz, 1H, Ar-**H**), 6.46 (d,  $J$ =16.0 Hz, 1H, Ar-**CH=C**), 6.33 (ddd, apparent dt,

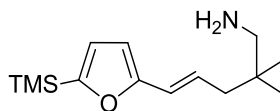
$J=15.5$ , 5.5 Hz, 1H, Ar-C=CH), 6.21 (d,  $J=3.0$  Hz, 1H, Ar-H), 4.29 (m, 1H, CH<sub>2</sub>), 1.60 (s, 1H, OH), 0.25 (s, 9H, 3SiCH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 156.1, 127.4, 121.1, 119.5, 108.2, 63.4, -1.57; IR (film) 3324, 2957, 1251, 1092, 1013, 962, 929, 844, 759, 630 cm<sup>-1</sup>.

(E)-2,2-Dimethyl-5-(5-Trimethylsilyl-furan-2-yl)-Pent-4-Enenitrile



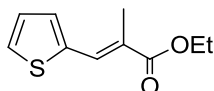
The title compound (*E*)-2,2-dimethyl-5-(5-trimethylsilyl-furan-2-yl)-pent-4-enenitrile was obtained (0.15 g, 0.61 mmol, 33%) as a colorless oil from (*E*)-3-(5-trimethylsilyl-furan-2-yl)-prop-2-en-1-ol (0.36 g, 1.84 mmol) by the general nitrile preparation procedure. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.57 (d,  $J = 3.2$  Hz, 1H, Ar-H), 6.35 (d,  $J = 15.7$  Hz, 1H, Ar-H), 6.22 – 6.15 (m, 2H, Ar-CH=CH), 2.39 (dd,  $J = 7.6$ , 1.3 Hz, 2H, CH=C-CH<sub>2</sub>), 1.36 (s, 6H, 2CH<sub>3</sub>), 0.26 (s, 9H, 3SiCH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 160.20, 156.02, 124.79, 123.38, 122.29, 121.15, 107.98, 44.26, 32.65, 26.29, -1.50; IR (film) 2957, 2233, 1469, 1254, 1180, 1114, 1013, 962, 929, 844, 785, 759, 700, 634 cm<sup>-1</sup>.

(E)-2,2-Dimethyl-5-(5-Trimethylsilyl-furan-2-yl)-Pent-4-Enylamine (126)



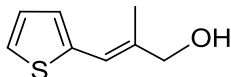
The title compound (*E*)-2,2-dimethyl-5-(5-trimethylsilyl-furan-2-yl)-pent-4-enylamine (**126**) (0.16 g, 95%) was obtained as colorless oil from (*E*)-2,2-dimethyl-5-(5-trimethylsilyl-furan-2-yl)-pent-4-enitrile (0.17 g, 0.68 mmol) by the general LiAlH<sub>4</sub> reduction procedure. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.54 (d, *J* = 3.0 Hz, 1H, Ar-**H**), 6.29 – 6.07 (m, 3H, Ar-**H**, and Ar-**CH=CH**), 2.47 (s, 2H, **CH**<sub>2</sub>-NH<sub>2</sub>), 2.07 (d, *J* = 7.2 Hz, 2H, C=C-**CH**<sub>2</sub>), 1.05 (s, 2H, **NH**<sub>2</sub>), 0.88 (d, *J* = 2.7 Hz, 6H, 2**CH**<sub>3</sub>), 0.24 (s, 9H, 3Si**CH**<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 159.3, 157.0, 126.6, 121.1, 106.4, 52.7, 43.1, 35.7, 29.7, 24.7, -1.50; IR (film) 2961, 1475, 1251, 910, 840, 737 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>14</sub>H<sub>26</sub>NOSi [M+H]<sup>+</sup>: 252.17782, found: 252.17721.

(*E*)-2-Methyl-3-Thiophen-2-yl-Acrylic Acid Ethyl Ester



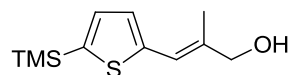
The title compound (*E*)-2-methyl-3-thiophen-2-yl-acrylic acid ethyl ester (4.1 g, 20.0 mmol, 98%) was obtained as a colorless oil from 2-thiophenecarboxaldehyde (1.96 mL, 20.6 mmol) by the general Horner-Wadsworth-Emmons procedure. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.83 (s, 1H, Ar-**CH=C**), 7.46 (d, *J*=5.0 Hz, 1H, Ar-**H**), 7.25 (d, *J*=3.5 Hz, 1H, Ar-**H**), 7.09 (t, *J*=3.5 Hz, 1H, Ar-**H**), 4.24 (ddd, apparent quartet, *J*=7.0 Hz, 2H, O**CH**<sub>2</sub>), 2.19 (s, 3H, C=C-**CH**<sub>3</sub>), 1.32 (dd, apparent triplet, *J*=7.5 Hz, 3H, **CH**<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 168.5, 139.3, 131.6, 131.4, 129.1, 127.3, 124.9, 60.9, 14.4, 14.3; IR (film) 2979, 1701, 1624, 1364, 1269, 1206, 1106, 700 cm<sup>-1</sup>.

(E)-2-Methyl-3-Thiophen-2-yl-Prop-2-en-1-ol



The title compound (*E*)-2-methyl-3-thiophen-2-yl-prop-2-en-1-ol (3.0 g, 19.7 mmol, 94%) was obtained as a colorless oil from (*E*)-2-methyl-3-thiophen-2-yl-acrylic acid ethyl ester (4.1 g, 20.0 mmol) by the general  $\text{LiAlH}_4$  reduction procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.24 (s, 1H, Ar-**CH**=C), 7.01 (t,  $J=3.5$  Hz, 1H, Ar-**H**), 7.00 (d,  $J=4.5$  Hz, 1H, Ar-**H**), 6.66 (m, 1H, Ar-**H**), 4.18 (d, 2H,  $J=5.5$  Hz, C=C-**CH**<sub>2</sub>), 1.99 (s, 3H, C=C-**CH**<sub>3</sub>), 1.48 (dd, apparent triplet,  $J=6.0$  Hz, 3H, **OH**);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  127.0, 126.8, 124.9, 118.4, 68.9, 16.0; IR (film) 3213, 2913, 1439, 1243, 1033, 874, 855, 703  $\text{cm}^{-1}$

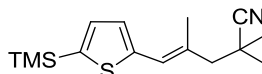
(E)-2-Methyl-3-(5-Trimethylsilylanyl Thiophen-2-yl)-Prop-2-en-1-ol



The title compound (*E*)-2-methyl-3-(5-trimethylsilylanyl-thiophen-2-yl)-prop-2-en-1-ol (3.62 g, 16.0 mmol, 54%) was obtained as a colorless oil from (*E*)-2-methyl-3-thiophen-2-yl-prop-2-en-1-ol (4.57 g, 30.0 mmol) by the general silylation procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.13 (d,  $J=3.0$  Hz, 1H, Ar-**H**), 7.03 (d,  $J=3.0$  Hz, 1H, Ar-**H**), 6.68 (s, 1H, Ar-**CH**=C), 4.11 (s, 2H, **CH**<sub>2</sub>), 2.02 (s, 3H, C=C-**CH**<sub>3</sub>), 1.70 (s, 1H, **OH**),

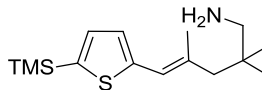
0.30 (s, 9H, 3SiCH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 145.9, 140.0, 136.2, 133.8, 128.4, 118.3, 68.9, 16.1, -0.07; IR (film) 3294, 2957, 1431, 1247, 988, 840, 747, 626 cm<sup>-1</sup>.

(E)-2,2,4-Trimethyl-5-(5-Trimethylsilanyl-Thiophen-2-yl)-Pent-4-Enenitrile



The title compound (*E*)-2,2,4-trimethyl-5-(5-trimethylsilylthiophen-2-yl)-pent-4-enenitrile (1.0 g, 3.61 mmol, 37%) was obtained as a light yellow solid from (*E*)-2-methyl-3-(5-trimethylsilylthiophen-2-yl)-prop-2-en-1-ol (2.2 g, 9.73 mmol) by the general nitrile preparation procedure. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.14 (d, *J* = 3.5 Hz, 1H, Ar-**H**), 7.03 (d, *J* = 3.5 Hz, 1H, Ar-**H**), 6.52 (s, 1H, Ar-**CH=C**), 2.41 (s, 2H, C=C-**CH**<sub>2</sub>), 2.16 (s, 3H, C=C-**CH**<sub>3</sub>), 1.36 (s, 6H, 2**CH**<sub>3</sub>), 0.30 (s, 9H, 3Si**CH**<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 133.8, 132.1, 128.5, 125.3, 123.7, 51.8, 32.1, 27.0, 20.4, -0.10; IR (film) 2957, 1446, 1251, 1209, 1073, 1069, 988, 840, 755, 696, 630, 533 cm<sup>-1</sup>.

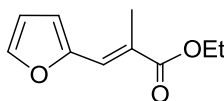
(E)-2,2,4-Trimethyl-5-(5-Trimethylsilyl-Thiophen-2-yl)-Pent-4-Enylamine (**129**)



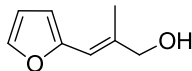
The title compound (*E*)-2,2,4-trimethyl-5-(5-trimethylsilylthiophen-2-yl)-pent-4-enylamine (**129**) (0.37 g, 1.32 mmol, 91%) was obtained as a colorless oil from (*E*)-2,2,4-trimethyl-5-(5-trimethylsilylthiophen-2-yl)-pent-4-enenitrile (0.4 g, 1.44 mmol)

by the general  $\text{LiAlH}_4$  reduction procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.12 (d,  $J = 3.6$  Hz, 1H, Ar-H), 6.97 (d,  $J = 3.6$  Hz, 1H, Ar-H), 6.41 (s, 1H, Ar-CH=C), 2.48 (s, 2H,  $\text{NCH}_2$ ), 2.11 (s, 2H, C=C-CH<sub>2</sub>), 2.04 (s, 3H, C=C-CH<sub>3</sub>), 1.08 (s, 2H,  $\text{NH}_2$ ), 0.88 (s, 6H, 2CH<sub>3</sub>), 0.29 (s, 9H, 3SiCH<sub>3</sub>);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  146.9, 139.0, 135.8, 133.8, 127.5, 121.9, 53.3, 50.7, 36.6, 25.1, 21.9, -0.06; IR (film) 2954, 1431, 1251, 1073, 988, 836, 795, 751  $\text{cm}^{-1}$ ; HRMS (ESI): Calcd for  $\text{C}_{15}\text{H}_{27}\text{NSSi}$   $[\text{M}+\text{H}]^+$ : 282.171, found: 282.164.

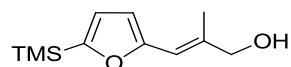
(E)-3-Furan-2-yl-2-Methyl  
-Acrylic Acid Ethyl Ester



The title compound (*E*)-3-furan-2-yl-2-methyl-acrylic acid ethyl ester (3.66 g, 20.3 mmol, 98%) was obtained as a colorless oil from 2-furaldehyde (1.8 mL, 20.6 mmol) by the general Horner-Wadsworth-Emmons procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.50 (m, 1H, Ar-H), 7.42 (s, 1H, Ar-CH=C), 6.58 (d,  $J=3.0$  Hz, 1H, Ar-H), 6.46 (m, 1H, Ar-H), 4.22 (ddd, apparent quartet,  $J=7.0$  Hz, 2H, CH<sub>2</sub>), 2.19 (s, 3H, C=C-CH<sub>3</sub>), 1.31 (dd, apparent triplet,  $J=7.0$  Hz, 3H, CH<sub>2</sub>CH<sub>3</sub>);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.5, 152.0, 143.9, 125.6, 125.1, 114.6, 112.0, 60.8, 14.3, 14.1; IR (film) 2979, 1705, 1634, 1475, 1372, 1269, 1209, 1176, 1114, 1021, 740  $\text{cm}^{-1}$ .

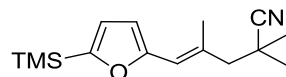
(E)-3-Furan-2-yl-2-Methyl-Prop-2-en-1-ol

The title compound (*E*)-3-furan-2-yl-2-methyl-prop-2-en-1-ol (2.70 g, 19.6 mmol, 98%) was obtained as a colorless oil from (*E*)-3-furan-2-yl-2-methyl-acrylic acid ethyl ester (3.60 g, 20.0 mmol) by the general  $\text{LiAlH}_4$  reduction procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36 (s, 1H, Ar-**CH**=C), 6.38 (m, 1H, Ar-**H**), 6.31 (m, 1H, Ar-**H**), 6.24 (d,  $J=3.0$  Hz, 1H, Ar-**H**), 4.12 (s, 2H, **CH**<sub>2</sub>), 2.04 (s, 1H, **OH**), 1.97 (s, 3H, C=C-**CH**<sub>3</sub>);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  153.1, 141.2, 136.3, 113.6, 111.1, 108.7, 68.5, 15.8; IR (film) 3324, 2917, 2858, 1495, 1446, 1380, 1069, 1021, 737, 592  $\text{cm}^{-1}$ .

(E)-2-Methyl-3-(5-Trimethylsilylanyl-Furan-2-yl)-Prop-2-en-1-ol

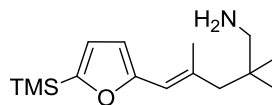
The title compound (*E*)-2-methyl-3-(5-trimethylsilylanyl-furan-2-yl)-prop-2-en-1-ol (2.52 g, 12.0 mmol, 61%) was obtained as a colorless oil from (*E*)-3-furan-2-yl-2-methyl-prop-2-en-1-ol (2.70 g, 19.6 mmol) by the general silylation procedure.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.60 (d,  $J=3.0$  Hz, 1H, Ar-**H**), 6.37 (s, 1H, Ar-**CH**=C), 6.24 (d,  $J=3.0$  Hz, 1H, Ar-**H**), 4.15 (d,  $J=3.0$  Hz, 2H, **CH**<sub>2</sub>), 2.02 (s, 3H, C=C-**CH**<sub>3</sub>), 1.47 (t,  $J=6.0$  Hz, 1H, **OH**), 0.29 (s, 9H, 3**CH**<sub>3</sub>);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  120.9, 114.0, 108.9, 68.7, 15.9, -1.66; IR (film) 3320, 2957, 1254, 1013, 932, 840, 781, 751, 630  $\text{cm}^{-1}$ .

(E)-2,2,4-Trimethyl-5-(5-Trimethylsilanyl-Furan-2-yl)-Pent-4-Enenitrile



The title compound (*E*)-2,2,4-trimethyl-5-(5-trimethylsilanyl-furan-2-yl)-pent-4-enenitrile (0.99 g, 3.81 mmol, 32%) was obtained as a colorless oil from (*E*)-2-methyl-3-(5-trimethylsilanyl-furan-2-yl)-prop-2-en-1-ol (2.5 g, 11.9 mmol) by the general nitrile preparation procedure. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.61 (d, *J*=3.3 Hz, 1H, Ar-**H**), 6.24 (d, *J*=3.3 Hz, 1H, Ar-**H**), 6.20 (s, 1H, Ar-**CH=C**), 2.38 (s, 2H, **CH**<sub>2</sub>), 2.16 (s, 3H, C=C-**CH**<sub>3</sub>), 1.37 (s, 6H, 2**CH**<sub>3</sub>), 0.25 (s, 9H, 3**CH**<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 125.3, 121.0, 119.6, 109.2, 51.7, 32.0, 27.0, 20.3, -1.65; IR (film) 2961, 1469, 1251, 1199, 1128, 1021, 932, 840, 789, 755, 634 cm<sup>-1</sup>.

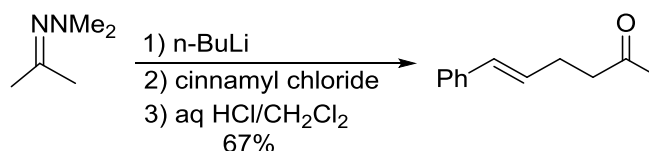
(E)-2,2,4-Trimethyl-5-(5-Trimethylsilanyl-Furan-2-yl)-Pent-4-Enylamine (**130**)



The title compound (*E*)-2,2,4-trimethyl-5-(5-trimethylsilanyl-furan-2-yl)-pent-4-enylamine (**130**) (0.39 g, 1.45 mmol, 95%) was obtained as a colorless oil from (*E*)-2,2,4-trimethyl-5-(5-trimethylsilanyl-furan-2-yl)-pent-4-enenitrile (0.4 g, 1.53 mmol) by the general LiAlH<sub>4</sub> reduction procedure. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.59 (d, *J* = 3.2 Hz, 1H, Ar-**H**), 6.16 (d, *J* = 3.2 Hz, 1H, Ar-**H**), 6.10 (s, 1H, Ar-**CH=C**), 2.47 (s, 2H, N-**CH**<sub>2</sub>),

2.08 (s, 2H, C=C-CH<sub>2</sub>), 2.01 (s, 3H, C=C-CH<sub>3</sub>), 1.19 – 1.02 (m, 2H, NH<sub>2</sub>), 0.88 (d, *J* = 3.2 Hz, 7H, 2CH<sub>3</sub>), 0.24 (d, *J* = 3.2 Hz, 9H, 3SiCH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 158.2, 157.5, 136.1, 121.0, 117.9, 107.9, 53.3, 50.5, 36.6, 25.1, 21.9, -1.62; IR (film) 2954, 1475, 1247, 1021, 936, 840, 781, 755, 630 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>15</sub>H<sub>27</sub>NOSi [M+H]<sup>+</sup>: 266.193, found: 266.200.

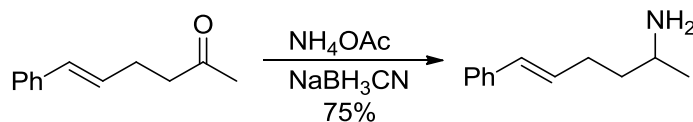
(E)-6-Phenyl-Hex-5-en-2-one



A 100-mL, round-bottomed flask equipped with a magnetic stirring bar and a N<sub>2</sub> inlet was charged with acetone dimethylhydrazone (3.0 g, 30.0 mmol) and anhydrous THF (50 mL) was subsequently added. The resulting solution was cooled to -78 °C with a Dry Ice-acetone bath and *n*-BuLi (5.2 M, 5.77 mL, 30 mmol) was slowly added drop wise. The reactant mixture was warmed to 0 °C and stirred for 2 h, and then cooled back to -78 °C. Cinnamyl chloride (2.76 mL, 20.0 mmol) in THF (6 mL) was slowly added and the reactant mixture was warmed to 0 °C and stirred for 6 h. The reactant mixture was diluted with diethyl ether (60 mL), washed with saturated NaHCO<sub>3</sub> (10 mL), brine (10 mL) and concentrated in vacuo. CH<sub>2</sub>Cl<sub>2</sub> (30 mL) and diluted aqueous HCl (6.0 M, 30 mL, 180 mmol) were added in succession and the reactant mixture was stirred for 10 h at room temperature. The organic phase was separated, washed with saturated NaHCO<sub>3</sub> (10 mL), brine (10 mL) and subsequently dried with Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo

followed by flash chromatography on silica gel (15:1 hexane/EtOAc for elution) afforded (*E*)-6-phenyl-hex-5-en-2-one (2.36 g, 13.6 mmol, 68%) as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.33-7.17 (m, 5H, 5Ar-**H**), 6.39 (d, *J*=15.5 Hz, 1H, Ph-**CH=C**), 6.19 (ddd, apparent dt, *J*=15.5, 6.5 Hz, 1H, Ph-**C=CH**), 2.60 (m, 2H, **CH**<sub>2</sub>), 2.47 (m, 2H, **CH**<sub>2</sub>), 2.15 (s, 3H, **CH**<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 208.1, 137.4, 130.7, 128.8, 128.5, 127.1, 126.0, 43.2, 30.1, 27.1; IR (film): 3028, 2917, 1712, 1362, 1158, 966, 744, 692 cm<sup>-1</sup>.

(*E*)-1-Methyl-5-Phenyl  
Pent-4-Enylamine (**128**)



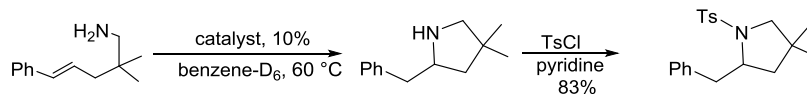
A 15-mL, round-bottomed flask equipped with a magnetic stirring bar and a N<sub>2</sub> inlet was charged with (*E*)-6-phenyl-hex-5-en-2-one (0.2 g, 1.15 mmol) and anhydrous methanol (5 mL) was subsequently added. NH<sub>4</sub>OAc (1.33 g, 17.2 mmol) and NaBH<sub>3</sub>CN (0.11 g, 1.72 mmol) were added in succession. The reactant mixture was stirred at room temperature for 24 h until judged complete by TLC. Aqueous 10% NaOH was slowly added until pH was raised to 10. The reactant mixture was extracted with diethyl ether (10 mL), and the organic phase was dried with Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo followed by bulb-to-bulb distillation from CaH<sub>2</sub> afforded (*E*)-1-methyl-5-phenylpent-4-enylamine (**128**) (0.15 g, 0.86 mmol, 75%) as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.32 (d, *J* = 7.4 Hz, 2H, 2Ar-**H**), 7.27 (t, *J* = 7.4 Hz, 2H, 2Ar-**H**), 7.17 (t, *J* = 7.4 Hz, 1H, Ar-**H**),

6.38 (d,  $J = 15.9$  Hz, 1H, Ph-CH=C), 6.20 (dt,  $J = 15.9, 6.7$  Hz, 1H, Ph-C=CH), 2.93 (q,  $J = 6.3$  Hz, 1H, CH<sub>2</sub>), 2.25 (m,  $J = 6.7$  Hz, 2H, CH<sub>2</sub>), 1.55 – 1.44 (m, 2H, CH<sub>2</sub>), 1.26 (s, 2H, NH<sub>2</sub>), 1.08 (d,  $J = 6.3$  Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 130.5, 129.9, 128.5, 126.9, 125.9, 46.5, 39.6, 30.0, 24.0; IR (film): 2932, 2356, 1576, 1446, 1372, 966, 741, 692 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>12</sub>H<sub>17</sub>N [M+H]<sup>+</sup>: 176.1434, found: 176.1476.

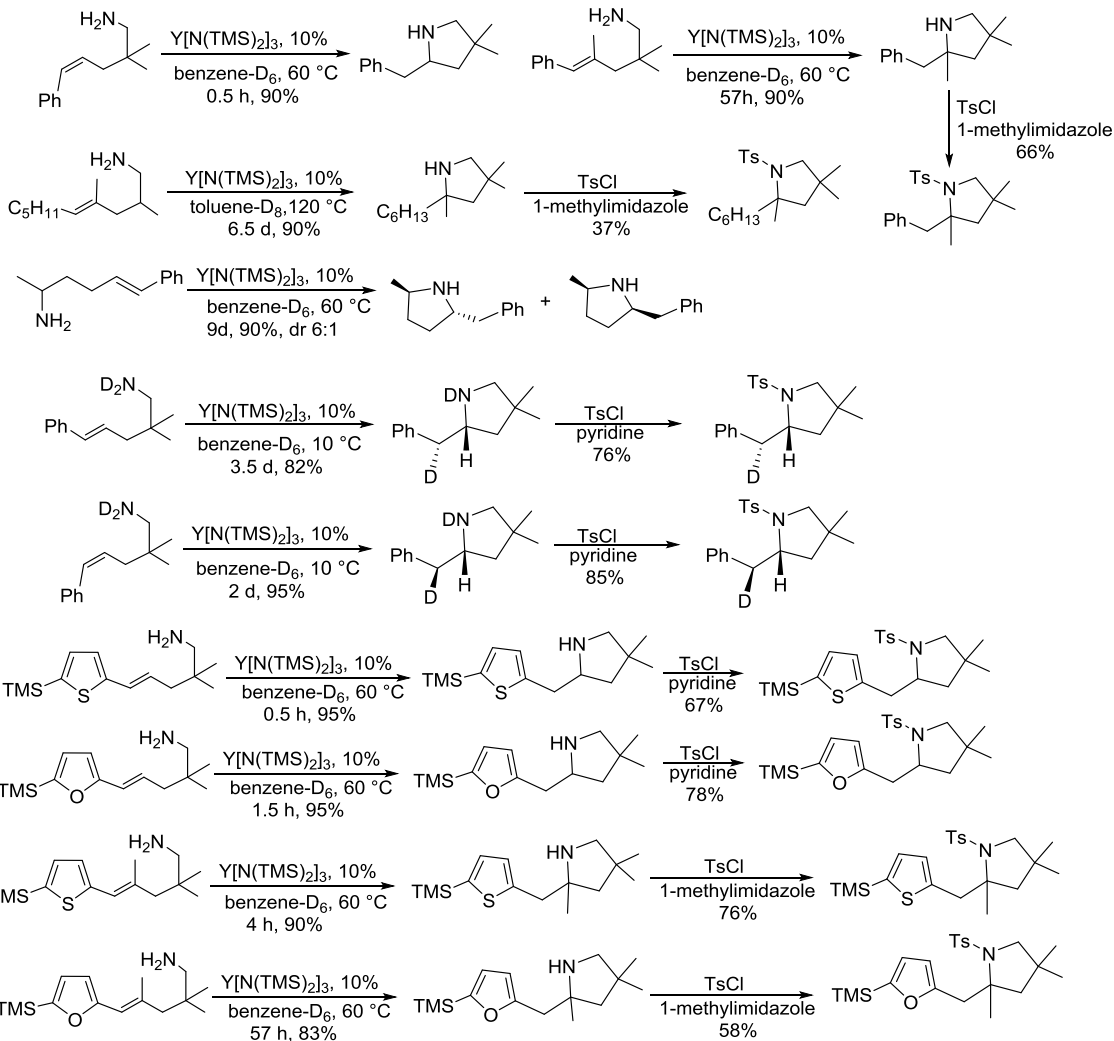
#### General Hydroamination Procedure

In an argon-filled glove box, Y[N(TMS)<sub>2</sub>]<sub>3</sub> (5.70 mg, 0.01 mmol) and benzene-D<sub>6</sub> (0.5 mL) were added into a J. Young NMR tube equipped with teflon screw cap. Then (*E*)-2,2-dimethyl-5-phenylpent-4-enylamine (**123<sub>E</sub>**) (19 mg, 0.1 mmol) and *p*-xylene (10 μL) were added and the reactant mixture was subsequently held at 60 °C in an oil bath for 2 h until ring closure was judged complete (≥90% by <sup>1</sup>H NMR integration).

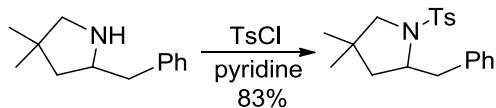
## Hydroamination Results



(1) Sc[N(TMS)<sub>2</sub>]<sub>3</sub>, 20 d, 90%, (2) Y[N(TMS)<sub>2</sub>]<sub>3</sub>, 2 h, 90%

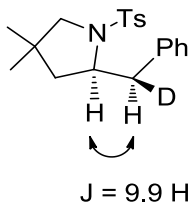


### 2-Benzyl-4,4-Dimethyl-1-(4-Methyl Benzenesulfonyl) Pyrrolidine (**134<sub>Ts</sub>**)



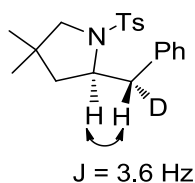
The tetrahydropyrrole was prepared from (*E*)-2,2-dimethyl-5-phenylpent-4-enylamine (**124<sub>E</sub>**) (19 mg, 0.10 mmol) by the general hydroamination procedure. The teflon screw cap was then removed and crude product was diluted with anhydrous CH<sub>2</sub>Cl<sub>2</sub> (3 mL). TsCl (22 mg, 0.12 mmol) and pyridine (9.70 μL, 0.12 mmol) were added in succession. The reactant mixture was stirred at room temperature for 12 h. The reactant mixture was diluted with diethyl ether (10 mL), washed with saturated NaHCO<sub>3</sub> (3 mL) and brine (3 mL). The organic phase was subsequently dried with Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo followed by flash chromatography on silica gel (15:1 hexane/EtOAc for elution) afforded 2-benzyl-4,4-dimethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (**134<sub>Ts</sub>**) (32 mg, 0.09 mmol, 83%) as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.77 (d, *J*=8.1 Hz, 2H, 2Ar-H), 7.25 (m, 7H, 7Ar-H), 3.77 (m, 1H, CH-N), 3.56 (dd, *J*=13.2, 3.3 Hz, 1H, Ph-CH), 3.10 (s, 2H, CH<sub>2</sub>NTs), 2.75 (dd, *J*=13.2, 9.9 Hz, 1H, Ph-CH), 2.41 (s, 3H, ArCH<sub>3</sub>), 1.45 (m, 2H, CH<sub>2</sub>-CH), 0.96 (s, 3H, CH<sub>3</sub>), 0.43 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 143.3, 138.5, 129.6, 129.5, 128.4, 127.6, 126.4, 61.7, 61.6, 45.8, 42.9, 37.3, 26.5, 25.8, 21.6; IR (film) 2957, 1346, 1158, 1092, 662, 589, 548 cm<sup>-1</sup>.

2-[2'-(<sup>2</sup>H)(Phenyl)Methyl]-4,4-Dimethyl-1-(4-Methylbenzenesulfonyl)  
2αH,2'αH-Pyrrolidine [(*R,R*)-**134(D)**<sub>Ts</sub>]



The title compound 2-[2'-(<sup>2</sup>H)(phenyl)methyl]-4,4-dimethyl-1-(4-methylbenzenesulfonyl)-2 $\alpha$ H,2' $\alpha$ H-pyrrolidine [(*R,R*)-**134(D)**<sub>Ts</sub>] (57 mg, 0.17 mmol, 76%) was obtained as a white solid from (*E*)-2,2-dimethyl-5-phenylpent-4-enylamine-*N,N*-D<sub>2</sub> (**123<sub>E</sub>**) (41.0 mg, 0.22 mmol) by the general hydroamination and *p*-toluenesulfonamide procedures <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.77 (d, *J* = 8.2 Hz, 2H, 2Ar-H), 7.33 – 7.17 (m, 7H, 7Ar-H), 3.75 (dt, *J* = 9.9, 7.8 Hz, 1H, CH-NTs), 3.11 (s, 2H, NCH<sub>2</sub>), 2.73 (d, *J* = 9.9 Hz, 1H, Ph-CH), 2.41 (s, 3H, ArCH<sub>3</sub>), 1.54-1.38 (m, 2H, CH<sub>2</sub>), 0.97 (s, 3H, CH<sub>3</sub>), 0.42 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  143.3, 138.5, 135.1, 129.6, 129.5, 128.4, 127.5, 126.3, 61.6, 61.5, 45.7, 42.9, 42.6 (triplet,  $\Delta J$  = 0.16), 37.2, 26.5, 25.8, 21.6; <sup>2</sup>D NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  3.47; IR (film) 2961, 1342, 1158, 1095, 700, 658, 589, 545 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>20</sub>H<sub>24</sub>NDO<sub>2</sub>S [M+H]<sup>+</sup>: 345.1742, found: 345.1757.

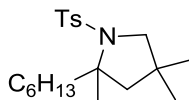
2-[2'-(<sup>2</sup>H)(Phenyl)Methyl]-4,4-Dimethyl-1-(4-Methylbenzenesulfonyl)-2 $\alpha$ H,2' $\beta$ H-Pyrrolidine [(*R,S*)-**134(D)**<sub>Ts</sub>]



The title compound 2-[2'-(<sup>2</sup>H)(phenyl)methyl]-4,4-dimethyl-1-(4-methylbenzenesulfonyl)-2 $\alpha$ H,2' $\beta$ H-pyrrolidine [(*S,R*)-**134(D)**<sub>Ts</sub>] (70 mg, 0.20 mmol, 85%) was obtained as a white solid from (*Z*)-2,2-dimethyl-5-phenylpent-4-enylamine-*N,N*-D<sub>2</sub> (**123<sub>Z</sub>**) (45 mg, 0.24 mmol) by the general hydroamination and *p*-

toluenesulfonamide procedures.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.77 (d,  $J = 8.2$  Hz, 2H, 2Ar-H), 7.33 – 7.25 (m, 4H, 4Ar-H), 7.25 – 7.17 (m, 3H, 3Ar-H), 3.76 (td,  $J = 7.8, 3.6$  Hz, 1H, N-CH), 3.54 (d,  $J = 3.6$  Hz, 1H, Ph-CH), 3.11 (s, 2H, NCH<sub>2</sub>), 2.41 (s, 3H, ArCH<sub>3</sub>), 1.52 – 1.40 (m, 2H, CH-CH<sub>2</sub>), 0.96 (s, 3H, CH<sub>3</sub>), 0.42 (s, 3H, CH<sub>3</sub>);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  143.4, 138.4, 135.1, 129.6, 129.5, 128.4, 127.5, 126.3, 61.6, 61.5, 45.7, 45.63, 42.88 (triplet,  $\Delta J = 0.16$ ), 37.20, 26.44, 25.76, 21.57;  $^2\text{D}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  2.65; IR (film) 2961, 1346, 1158, 1092, 1039, 814, 737, 703, 662, 589, 548  $\text{cm}^{-1}$ ; HRMS (ESI): Calcd for  $\text{C}_{20}\text{H}_{24}\text{NDO}_2\text{S}$   $[\text{M}+\text{H}]^+$ : 345.1742, found: 345.1745.

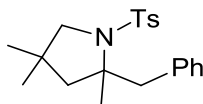
2-Hexyl-2,4,4-Trimethyl-1-(Toluene  
-4-Sulfonyl)-Pyrrolidine (**135<sub>Ts</sub>**)



The title compound 2-hexyl-2,4,4-trimethyl-1-(toluene-4-sulfonyl)pyrrolidine (**135<sub>Ts</sub>**) (26 mg, 0.07 mmol, 37%) was obtained as a colorless oil from (*E*)-2,2,4-trimethyl-dec-4-enylamine (**132**) (40 mg, 0.2 mmol) by the general hydroamination and *p*-toluenesulfonamide preparation procedures.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J = 7.4$  Hz, 2H, 2Ar-H), 7.36 – 7.18 (m, 2H, 2Ar-H), 3.15 – 2.95 (m, 2H, N-CH<sub>2</sub>), 2.38 (d,  $J = 5.5$  Hz, 3H, ArCH<sub>3</sub>), 1.91 (d,  $J = 10.0$  Hz, 1H, CH), 1.83 (d,  $J = 12.9$  Hz, 1H, CH), 1.71 (d,  $J = 11.9$  Hz, 1H, CH), 1.46 (s, 3H, CH<sub>3</sub>), 1.32 – 1.14 (m, 9H, 4CH<sub>2</sub>), 0.99 (s, 6H, CH<sub>3</sub>), 0.95 (s, 6H, CH<sub>3</sub>), 0.86 (s, 3H, CH<sub>3</sub>);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  142.5, 129.2, 127.2, 69.2, 61.5, 53.1, 42.4, 36.1, 31.8, 29.7, 27.6, 27.5, 27.43, 25.1, 22.7, 21.5, 14.1; IR (film): 2957, 2932, 2869, 1469, 1339, 1154, 1092, 969, 814, 711, 659, 592, 552

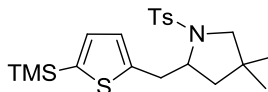
cm<sup>-1</sup>; HRMS (ESI): Calcd for [M+H]<sup>+</sup>: C<sub>20</sub>H<sub>33</sub>NO<sub>2</sub>S [M+H]<sup>+</sup>: 352.2305, found: 352.2306.

2-Benzyl-2,4,4-Trimethyl-1-(4-Methyl  
Benzenesulfonyl) Pyrrolidine (**136<sub>Ts</sub>**)



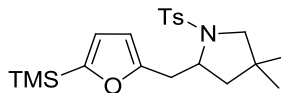
The title compound 2-benzyl-2,4,4-trimethyl-1-(4-methylbenzenesulfonyl)pyrrolidine (**136<sub>Ts</sub>**) (26.1 mg, 0.07 mmol, 66%) was obtained as a colorless oil from (*E*)-2,2,4-trimethyl-5-phenylpent-4-enylamine (**131**) (23 mg, 0.11 mmol) by the general hydroamination and *p*-toluenesulfonamide procedures in which 1.2 eq 1-methylimidazole was used instead of pyridine because of the hindered substrate. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.77 (d, *J* = 8.3 Hz, 2H, 2Ar-H), 7.32 – 7.19 (m, 7H, 7Ar-H), 3.27 (d, *J* = 13.1 Hz, 1H, CH), 3.12 (d, *J* = 13.1 Hz, 1H, CH), 3.03 (d, *J* = 9.6 Hz, 1H, CH), 2.88 (d, *J* = 9.6 Hz, 1H, CH), 2.40 (s, 3H, ArCH<sub>3</sub>), 2.07 (d, *J* = 13.1 Hz, 1H, CH), 1.49 (s, 3H, CH<sub>3</sub>), 1.27 (d, *J* = 13.1 Hz, 1H, CH), 0.90 (s, 3H, CH<sub>3</sub>), 0.85 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 142.7, 138.0, 131.1, 129.3, 128.0, 127.3, 126.4, 69.1, 61.7, 51.6, 47.8, 36.1, 27.6, 27.5, 27.2, 21.5; IR (film) 2957, 2869, 1602, 1495, 1450, 1339, 1154, 1058, 966, 814, 755, 711, 656, 592, 548 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>21</sub>H<sub>27</sub>NO<sub>2</sub>S [M+H]<sup>+</sup>: 358.1835, found: 358.1840.

4,4-Dimethyl-1-(Toluene-4-Sulfonyl)  
-2-(5-TrimethylSilanyl-Thiophen-2-  
-yl Methyl)-Pyrrolidine (**138**<sub>Ts</sub>)



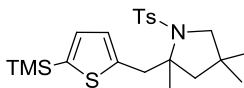
The title compound 4,4-dimethyl-1-(toluene-4-sulfonyl)-2-(5-trimethylsilyl-thiophen-2-ylmethyl)-pyrrolidine (**138**<sub>Ts</sub>) (28 mg, 0.07 mmol, 67%) was obtained as a colorless oil from (*E*)-2,2-dimethyl-5-(5-trimethylsilyl-thiophen-2-yl)-pent-4-enylamine (**127**) (27 mg, 0.1 mmol) by the general hydroamination and *p*-toluenesulfonamide preparation procedures. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.75 (d, *J* = 8.0 Hz, 2H, 2Ar-**H**), 7.31 (d, *J* = 8.0 Hz, 2H, 2Ar-**H**), 7.05 (d, *J* = 3.5 Hz, 1H, Ar-**H**), 6.89 (d, *J* = 3.5 Hz, 1H, 2Ar-**H**), 3.81 – 3.73 (m, 1H, **CH**<sub>2</sub>), 3.70 (d, *J* = 14.3, 3.5 Hz, 1H, **CH**<sub>2</sub>), 3.10 (td, *J* = 16.0, 14.3, 9.8 Hz, 3H, **CH**<sub>2</sub>-**CH**), 2.41 (d, *J* = 4.0 Hz, 3H, Ar**CH**<sub>3</sub>), 1.60 (d, *J* = 4.0 Hz, 1H, **CH**<sub>2</sub>), 1.57 – 1.50 (m, 1H, **CH**<sub>2</sub>), 0.98 (s, 3H, **CH**<sub>3</sub>), 0.45 (s, 3H, **CH**<sub>3</sub>), 0.27 (s, 9H, 3Si**CH**<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 145.8, 143.4, 139.1, 135.0, 133.9, 129.6, 127.6, 127.5, 61.7, 61.1, 45.9, 37.3, 36.9, 26.4, 25.8, 21.6, -0.01; IR (film) 2957, 1346, 1247, 1158, 1092, 1047, 981, 840, 814, 759, 662, 592, 548 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>21</sub>H<sub>31</sub>NO<sub>2</sub>S<sub>2</sub>Si [M+H]<sup>+</sup>: 422.164, found: 422.165.

4,4-Dimethyl-1-(Toluene-4-Sulfonyl)  
-2-(5-TrimethylSilanyl-Furan-2-yl  
Methyl) Pyrrolidine (**139**<sub>Ts</sub>)



The title compound 4,4-dimethyl-1-(toluene-4-sulfonyl)-2-(5-trimethylsilyl-furan-2-yl)methylpyrrolidine (**139<sub>Ts</sub>**) (32 mg, 0.08 mmol, 78 %) was obtained as a colorless oil from (*E*)-2,2-dimethyl-5-(5-trimethylsilyl-furan-2-yl)-pent-4-enylamine (**126**) (25 mg, 0.1 mmol) by the general hydroamination and *p*-toluenesulfonamide procedures. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.74 (d, *J* = 8.2 Hz, 2H, 2Ar-H), 7.29 (d, *J* = 8.0 Hz, 2H, 2Ar-H), 6.50 (d, *J* = 3.1 Hz, 1H, 1Ar-H), 6.04 (d, *J* = 3.1 Hz, 1H, 2Ar-H), 3.84 – 3.74 (m, 1H, N-CH), 3.51 (dd, *J* = 14.6, 3.4 Hz, 1H, Ar-CH), 3.11, 3.04 (ABq, *J* = 7.3 Hz, 2H, N-CH<sub>2</sub>), 2.92 (dd, *J* = 14.6, 9.4 Hz, 1H, Ar-CH), 2.41 (s, 3H, ArCH<sub>3</sub>), 1.60 (d, *J* = 7.8 Hz, 2H, CH<sub>2</sub>-CH-N), 0.98 (s, 3H, CH<sub>3</sub>), 0.46 (s, 3H, CH<sub>3</sub>), 0.22 (s, 9H, 3SiCH<sub>3</sub>).; <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 159.91, 156.9, 143.3, 135.129.6, 127.5, 120.4, 107.1, 61.5, 59.3, 46.0, 37.3, 35.2, 26.4, 25.8, 21.6, -1.58; IR (film) 2961, 1350, 1247, 1158, 1095, 844, 662, 589, 548 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>21</sub>H<sub>32</sub>NO<sub>3</sub>SSi [M+H]<sup>+</sup>: 406.18667, found: 405.18537; Calcd for C<sub>21</sub>H<sub>31</sub>NNaO<sub>3</sub>SSi [M+Na]<sup>+</sup>: 428.16817, found: 428.16861.

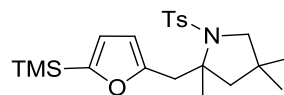
2,4,4-Trimethyl-1-(Toluene-4-Sulfonyl)-2-(5-Trimethylsilyl-Thiophen-2-yl Methyl)-Pyrrolidine (**140<sub>Ts</sub>**)



The title compound 2,4,4-trimethyl-1-(toluene-4-sulfonyl)-2-(5-trimethylsilyl-thiophen-2-yl)methyl-pyrrolidine (**140<sub>Ts</sub>**) (36.2 mg, 0.08 mmol, 76%) was obtained as a colorless oil from (*E*)-2,2,4-trimethyl-5-(5-trimethylsilyl-thiophen-2-yl)-pent-4-

enylamine (**129**) (31 mg, 0.11 mmol) by the general hydroamination and *p*-toluenesulfonamide preparation procedures.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J$  = 8.1 Hz, 2H, 2Ar-**H**), 7.26 (d,  $J$  = 8.1 Hz, 2H, 2Ar-**H**), 7.07 (d,  $J$  = 3.4 Hz, 1H, Ar-**H**), 6.98 (d,  $J$  = 3.4 Hz, 1H, 1Ar-**H**), 3.58 (d,  $J$  = 14.2 Hz, 1H, **CH**), 3.29 (d,  $J$  = 14.2 Hz, 1H, **CH**), 3.06 (d,  $J$  = 9.5 Hz, 1H, **CH**), 2.98 (d,  $J$  = 9.5 Hz, 1H, **CH**), 2.40 (s, 3H, Ar**CH**<sub>3</sub>), 2.15 (d,  $J$  = 13.2 Hz, 1H, **CH**), 1.51 (s, 3H, **CH**<sub>3</sub>), 1.42 (d,  $J$  = 13.2 Hz, 1H, **CH**), 0.97 (s, 3H, **CH**<sub>3</sub>), 0.90 (s, 3H, **CH**<sub>3</sub>), 0.27 (s, 9H, 3Si**CH**<sub>3</sub>);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  145.2, 142.8, 138.4, 133.9, 129.4, 129.3, 127.3, 68.7, 61.8, 52.6, 42.3, 36.2, 27.6, 27.2, 27.1, 21.5, -0.02; IR (film) 2957, 1439, 1342, 1251, 1209, 1154, 1092, 1055, 984, 840, 814, 759, 714, 659, 592, 548  $\text{cm}^{-1}$ ; HRMS (ESI): Calcd for  $\text{C}_{22}\text{H}_{33}\text{NO}_2\text{S}_2\text{Si}$  [ $\text{M}+\text{H}$ ] $^+$ : 436.1816, found: 436.1897.

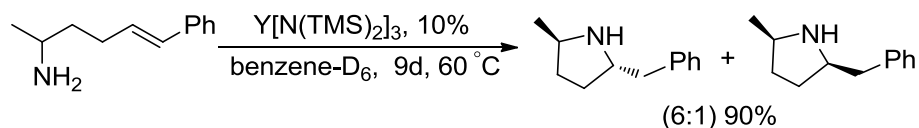
2,4,4-Trimethyl-1-(Toluene-4-Sulfonyl)-2-(5-TrimethylSilanyl-Furan-2-yl Methyl)-Pyrrolidine (**141**<sub>Ts</sub>)



The title compound 2,4,4-trimethyl-1-(toluene-4-sulfonyl)-2-(5-trimethylsilyl-furan-2-ylmethyl)-pyrrolidine (**141**<sub>Ts</sub>) (26.5 mg, 0.06 mmol, 58%) was obtained as a colorless oil from (*E*)-2,2,4-trimethyl-5-(5-trimethylsilyl-furan-2-yl)-pent-4-enylamine (**130**) (29 mg, 0.11 mmol) by the general hydroamination and *p*-toluenesulfonamide preparation procedures.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 – 7.70 (m, 2H, 2Ar-**H**), 7.26 (d,  $J$  = 8.6 Hz, 2H, 2Ar-**H**), 6.52 (d,  $J$  = 3.2 Hz, 1H, 2Ar-**H**), 6.15 (d,  $J$  = 3.2 Hz, 1H,

2Ar-**H**), 3.33 (d,  $J = 14.4$  Hz, 1H, **CH**), 3.17 (d,  $J = 14.4$  Hz, 1H, **CH**), 3.02 (d,  $J = 9.5$  Hz, 1H, **CH**), 2.93 (d,  $J = 9.5$  Hz, 1H, **CH**), 2.40 (s, 3H, Ar**CH**<sub>3</sub>), 2.16 (d,  $J = 13.3$  Hz, 1H, **CH**), 1.47 (s, 3H, **CH**<sub>3</sub>), 1.41 (d,  $J = 13.3$  Hz, 1H, **CH**), 0.93 (s, 3H, **CH**<sub>3</sub>), 0.89 (s, 3H, **CH**<sub>3</sub>), 0.21 (s, 9H, 3Si**CH**<sub>3</sub>); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ 156.9, 142.7, 129.3, 127.3, 120.5, 108.7, 68.4, 61.5, 52.8, 40.7, 36.0, 27.6, 27.4, 27.1, 21.5, -1.58; IR (film) 2957, 1339, 1251, 1154, 1095, 1011, 840, 755, 711, 662, 585, 545 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>22</sub>H<sub>33</sub>NO<sub>3</sub>SSi [M+H]<sup>+</sup>: 420.202, found: 420.205.

2-Benzyl-5-Methyl-2αH,  
5βH-Pyrrolidine (**137**)



In an argon-filled glove box, Y[N(TMS)<sub>2</sub>]<sub>3</sub> (6.5 mg, 0.01 mmol) and benzene-D<sub>6</sub> (0.5 mL) were introduced into a J. Young NMR tube equipped with teflon screw cap. *p*-xylene (10 μL) and (*E*)-1-methyl-5-phenylpent-4-enylamine (**128**) (20 mg, 0.11 mmol) were subsequently added. The reactant mixture was maintained at 60 °C in an oil bath for 9 days until ring closure was complete (90%, dr 6:1) as indicated by <sup>1</sup>H NMR spectrum. Removal of the solvent followed by bulb to bulb distillation from CaH<sub>2</sub> afforded 2-benzyl-5-methyl-2αH,5βH-pyrrolidine (**137**) (16.5 mg, 0.09 mmol, 83%) as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.28 – 7.13 (m, 5H, 5Ar-**H**), 3.39 (h,  $J = 6.5$  Hz, 1H, **CH**), 3.23 (p,  $J = 6.5$  Hz, 1H, **CH**), 2.68 (dd,  $J = 13.2, 7.3$  Hz, 1H, **CH**), 2.58 (dd,  $J = 13.2, 6.2$  Hz, 1H, **CH**), 1.86 – 1.74 (m, 2H, **CH**<sub>2</sub>), 1.67 (s, 1H, **CH**), 1.33 (dt,  $J = 12.5, 7.9$

Hz, 1H, **CH**), 1.11 (dd,  $J = 15.2, 6.5$  Hz, 1H, **CH**), 1.05 (s, 1H, **NH**), 1.00 (d,  $J = 6.5$  Hz, 3H, **CH<sub>3</sub>**);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  129.3, 128.0, 127.8, 127.6, 125.9, 59.3, 52.9, 43.6, 34.3, 32.4, 22.2; IR (film) 2957, 1495, 1453, 1402, 744, 700  $\text{cm}^{-1}$ ; HRMS (ESI): Calcd for  $\text{C}_{12}\text{H}_{17}\text{N}$   $[\text{M}+\text{H}]^+$ : 176.1434, found: 176.1473.

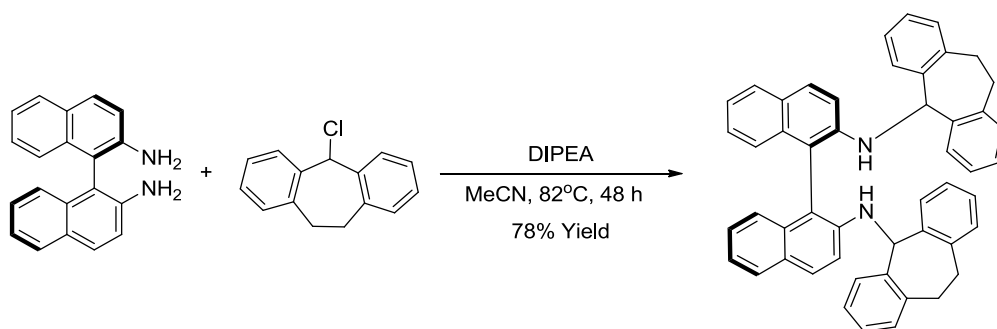
APPENDIX B

*N,N'*-DIBENZOSUBERYL-1,1'-BINAPHTHYL-2,2'-DIAMINE. A HIGHLY  
EFFECTIVE SUPPORTING LIGAND FOR THE ENANTIO-  
SELECTIVE CYCLIZATION OF AMINOALKENES  
CATALYZED BY CHELATING DIAMIDE  
COMPLEXES OF La(III) AND Y(III)

### Materials and Methods

Reactions employed oven- or flame-dried glassware under nitrogen unless otherwise noted. THF and diethyl ether were distilled from sodium/benzophenone under nitrogen.  $\text{CH}_2\text{Cl}_2$  was distilled from  $\text{CaH}_2$  under nitrogen. All other materials were used as received from commercial sources and all reactions were carried out under nitrogen unless otherwise noted. Thin-layer chromatography (TLC) employed 0.25 mm glass silica gel plates with UV indicator. Flash chromatographic columns were packed with Merck silica gel 60 as a slurry in the initial elution solvent. Nuclear magnetic resonance (NMR) data were obtained from Bruker DRX-300 (300 MHz) and Bruker DRX-500 (500 MHz). Infrared spectra (IR) were obtained from JASCO FTIR-4100. High-resolution mass spectra (HRMS) were obtained from Bruker MicroTOF with an Agilent 1100 HPLC.

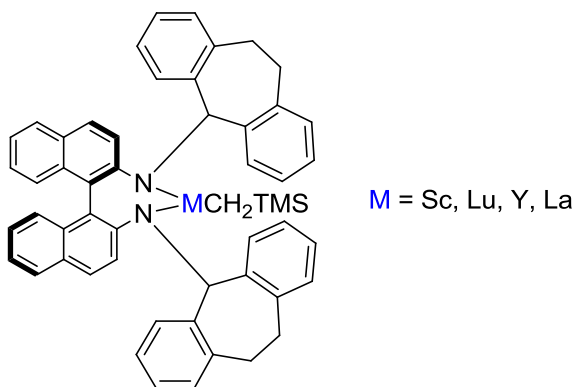
#### Synthesis and Characterization of **143**, and **144a** and **144b** Complexes



*N,N'*-Bis(10,11-Dihydro-5H-Di  
benzo[a,d][7]Annulen-5-yl)-[1,1'  
-Binaphthalene]-2,2'-Diamine (**143**)

A 10-mL round-bottomed flask equipped with a magnetic stirring bar and a N<sub>2</sub> inlet was charged with (*R*)-(+)-1,1'-Binaphthyl-2,2'-diamine (**142**) (0.62 g, 2.2 mmol) followed by 5-chlorodibenzosuberane (1.14 g, 4.8 mmol), and anhydrous MeCN (5 mL) was subsequently added. To the resultant solution was added *N,N*-Diisopropylethylamine (1 mL, 5.5 mmol) at 21°C. The reactant mixture was heated at reflux until the reaction was judged complete by TLC analysis (48 h). The solution was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL), washed with H<sub>2</sub>O (2 x 10 mL), dried over MgSO<sub>4</sub>. The suspension was then filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (5% EtOAc/hexanes) to afford *N,N'*-Bis(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-yl)-[1,1'-binaphthalene]-2,2'-diamine (**143**) (1.14 g, 78%) as a white solid. <sup>1</sup>H-NMR (500 MHz; CDCl<sub>3</sub>): δ 7.83 (dd, *J* = 23.2, 8.2 Hz, 4H, 4Ar-**H**), 7.22-7.12 (m, 7H, 6Ar-**H**), 7.06 (d, *J* = 8.4 Hz, 2H, 2Ar-**H**), 7.01 (q, *J* = 7.5 Hz, 5H, 5Ar-**H**), 6.98-6.89 (m, 9H, 9Ar-**H**), 6.86 (t, *J* = 7.5 Hz, 3H, 3Ar-**H**), 5.93 (s, 2H, 2CH), 4.70 (s, 2H, 2NH), 3.13-3.01 (m, 4H, 2CH<sub>2</sub>), 2.98-2.85 (m, 4H, 2CH<sub>2</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 143.58, 140.19, 137.89, 137.85, 133.91, 130.19, 130.13, 129.71, 128.02, 127.87, 127.10, 126.73, 126.15, 125.99, 125.59, 125.47, 124.26, 122.22, 115.04, 113.16, 59.27, 32.14, 31.96.; IR (film) 3416, 3053, 2931, 1616, 1594, 1509, 1481, 1425, 910, 732 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>50</sub>H<sub>40</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 669.3264, found: 669.3242

Formation of Complexes  
in THF (**144a** and **144b**)



In an argon-filled glove box,  $\text{ScCl}_3(\text{THF})_3$  (3.64 mg, 0.01 mmol) and  $\text{LuCl}_3(\text{THF})_3$  (4.08 mg, 0.01 mmol), or  $\text{YCl}_3(\text{THF})_3$  (4.08 mg, 0.01 mmol), or  $\text{LaCl}_3(\text{THF})_{1.5}$  (3.52 mg, 0.01 mmol) and THF (0.5 mL) were added into a J. Young NMR tube equipped with teflon screw cap. (Trimethylsilyl)methyl lithium (2.87 mg, 0.03 mmol) was added and the reactant mixture was kept at 21°C for 30 min. *N,N'*-Bis(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-yl)-[1,1'-binaphthalene]-2,2'-diamine (**143**) (6.68 mg, 0.01 mmol) was added and the complex formation was monitored by NMR (no-D). The solution was maintained at 21°C overnight. Removal of THF in vacuo was then followed by addition of  $\text{C}_6\text{D}_6$  (0.4 mL) in the glovebox.

Formation of Complexes  
in  $\text{C}_6\text{D}_6$  (**145a** and **145b**)

In an argon-filled glove box,  $\text{LuCl}_3(\text{THF})_3$  (4.08 mg, 0.01 mmol), or  $\text{YCl}_3(\text{THF})_3$  (4.08 mg, 0.01 mmol), or  $\text{LaCl}_3(\text{THF})_{1.5}$  (3.52 mg, 0.01 mmol) and  $\text{C}_6\text{D}_6$  (0.4 mL) were added into a J. Young NMR tube equipped with teflon screw cap.

(Trimethylsilyl)methylolithium (2.87 mg, 0.03 mmol) was added and the reactant mixture was kept at 21°C for 30 min. *N,N'*-Bis(10,11-dihydro-5H-dibenzo[*a,d*][7]annulen-5-yl)-[1,1'-binaphthalene]-2,2'-diamine (**143**) (6.68 mg, 0.01 mmol) was added and the complex formation was monitored by <sup>1</sup>H NMR.

**(143)YCH<sub>2</sub>TMS (145a).**

<sup>1</sup>H-NMR (500 MHz; C<sub>6</sub>D<sub>6</sub>): δ 7.77-7.75 (m, 5H, 5Ar-**H**), 7.66-7.62 (m, 2H, 2Ar-**H**), 7.46-7.37 (m, 3H, 3Ar-**H**), 7.23-7.17 (m, 5H, 5Ar-**H**), 7.14-7.10 (m, 4H, 4Ar-**H**), 7.04-6.90 (m, 9H, 9Ar-**H**), 6.87-6.84 (m, 2H, 2Ar-**H**), 6.00 (d, *J* = 5.8 Hz, 1H, **CH**), 5.15 (d, *J* = 5.8 Hz, 1H, **CH**), 2.91-2.79 (m, 6H, 4**CH**<sub>2</sub>), 0.41 (s, 9H, 3Si-**CH**<sub>3</sub>), 0.24 (s, 5H, Free **CH**<sub>2</sub>-TMS), 0.12 (s, 18H, Free 2Si-**CH**<sub>3</sub>), -0.77 (s, 2H, **CH**<sub>2</sub>-TMS). <sup>13</sup>C NMR (126 MHz; C<sub>6</sub>D<sub>6</sub>): δ 144.3, 140.9, 138.4, 130.80, 130.67, 130.43, 130.34, 129.8, 128.7, 127.56, 127.46, 127.37, 126.71, 126.57, 126.39, 126.24, 124.9, 122.9, 115.7, 60.7, 41.9, 32.6, 32.4, 25.6, 4.9, 4.5, 0.1

**(143)LaCH<sub>2</sub>TMS (145b)**

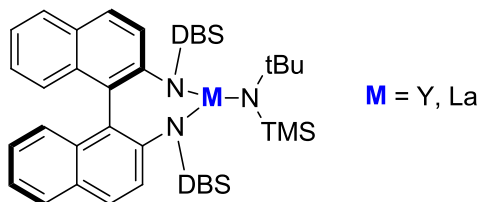
<sup>1</sup>H-NMR (500 MHz; C<sub>6</sub>D<sub>6</sub>): δ 7.77-7.75 (m, 3H, 3Ar-**H**), 7.66 (d, *J* = 0.4 Hz, 1H, 1Ar-**H**), 7.54 (d, *J* = 9.7 Hz, 1H, 1Ar-**H**), 7.45-7.39 (m, 3H, 3Ar-**H**), 7.19 (dd, *J* = 7.6, 7.1 Hz, 3H, 3Ar-**H**), 7.13 (d, *J* = 7.3 Hz, 2H, 2Ar-**H**), 7.03-6.92 (m, 6H, 6Ar-**H**), 6.86 (t, *J* = 0.8 Hz, 2H, 2Ar-**H**), 6.01 (d, *J* = 6.1 Hz, 1H, **CH**), 5.16-5.15 (m, 1H, **CH**), 2.85-2.82 (m, 6H, 4**CH**<sub>2</sub>), 1.04 (s, 2H, **CH**<sub>2</sub>-TMS), 0.12 (s, 14H, 2Si-**CH**<sub>3</sub>). <sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 138.4, 130.81, 130.67, 130.3, 129.8, 128.7, 128.5, 127.56, 127.47, 126.72, 126.58, 126.40, 126.25, 124.9, 122.9, 115.7, 63.5, 60.7, 34.4, 32.6, 32.4, 0.1

Lanthanum Tris[*(t*-butyl)  
(Trimethylsilyl)] Amide (**145b**)

A 25-mL Schlenk flask equipped with a magnetic stirring bar, an argon inlet and a septum was charged with THF (15 mL) and *t*-butyl(trimethylsilyl)amine (2.13 g, 2.8 mL, 14.7 mmol). The stirred solution was cooled in an ice-salt bath and *n*-butyllithium (10 M, 1.4 mL, 14 mmol) was added dropwise by syringe. After stirring for 5 min, the stirring was stopped and  $\text{LaCl}_3(\text{THF})_{1.5}$  (1.65 g, 4.66 mmol) was added in one portion. The reactant mixture was subsequently stirred at 23 °C for 16 h. The solvents were removed in vacuo and the residue was subjected to vacuum sublimation at 110 °C (0.0005 torr) to provide 2.23 g (84 %) of  $\text{La}[\text{N}(\textit{t}\text{-Bu})(\text{TMS})]_3$  as a white solid.  $^1\text{H-NMR}$  (500 MHz;  $\text{C}_6\text{D}_6$ ):  $\delta$  1.50 (s, 9H), 0.45 (s, 9H).  $^{13}\text{C NMR}$  (126 MHz;  $\text{C}_6\text{D}_6$ ):  $\delta$  35.1, 4.3

Yttrium Tris[*(t*-butyl)(Tri  
methylsilyl)] Amide (**145a**)

A 50-mL Schlenk flask equipped with a magnetic stirring bar, an argon inlet and a septum was charged with  $\text{Et}_2\text{O}$  (25 mL) and *t*-butyl(trimethylsilyl)amine (1.67 g, 2.19 mL, 11.5 mmol). The stirred solution was cooled in an ice-salt bath and *n*-butyllithium (10 M, 1.10 mL, 11 mmol) was added dropwise by syringe. After stirring for 5 min, the stirring was stopped and  $\text{YCl}_3$  (0.73 g, 3.76 mmol) was added in one portion. The reactant mixture was subsequently stirred at 23 °C for 20 h. The resulting suspension was filtered to remove the LiCl and the solvents were removed from the filtrate in vacuo. The residue was subjected to vacuum sublimation at 110 °C (0.0005 torr) to provide 1.50 g (79 %) of  $\text{Y}[\text{N}(\textit{t}\text{-Bu})(\text{TMS})]_3$  as a white solid.  $^1\text{H-NMR}$  (500 MHz;  $\text{C}_6\text{D}_6$ ):  $\delta$  1.55 (s, 9H), 0.46 (s, 9H).  $^{13}\text{C NMR}$  (126 MHz;  $\text{C}_6\text{D}_6$ ):  $\delta$  35.8, 4.6.

Formation of Complexes (**147a** and **147b**)

In an argon-filled glove box,  $Y[N(t\text{-Bu})(\text{TMS})]_3$  (5.21 mg, 0.01 mmol) (**146a**) or  $La[N(t\text{-Bu})(\text{TMS})]_3$  (5.71 mg, 0.01 mmol) (**146b**) and  $C_6D_6$  (0.5 mL) were added into a J. Young NMR tube equipped with teflon screw cap. *N,N'*-Bis(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-yl)-[1,1'-binaphthalene]-2,2'-diamine (**143**) (6.68 mg, 0.01 mmol) was added and the mixture was held at 90°C. The complex formation was monitored by  $^1H$  NMR. The ligand exchange was complete when the ratio was 1:2 Metal-coordinated (TMS)N(*t*-Bu): Free (TMS)NH(*t*-Bu).

(**143**)Y[N(TMS)(*t*-Bu)] (**147a**)

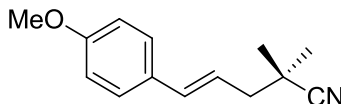
$^1H$ -NMR (500 MHz;  $C_6D_6$ ):  $\delta$  7.77-7.75 (m, 2H, 2Ar-H), 7.41 (dd,  $J = 21.1, 8.7$  Hz, 3H, 3Ar-H), 7.20 (dd,  $J = 14.9, 7.3$  Hz, 3H, 3Ar-H), 7.12 (t,  $J = 7.5$  Hz, 2H, 2Ar-H), 7.00 (dt,  $J = 21.5, 7.2$  Hz, 4H, 4Ar-H), 6.92 (t,  $J = 7.5$  Hz, 3H, 3Ar-H), 6.85 (t,  $J = 5.5$  Hz, 2H, 2Ar-H), 6.00 (d,  $J = 6.1$  Hz, 1H, CH), 5.15 (d,  $J = 6.1$  Hz, 1H, CH), 2.95-2.80 (m, 5H, 4CH<sub>2</sub>), 1.56 (s, 8H, tBu), 1.22 (s, 14H, Free 2 *t*-BuNHTMS), 0.46 (s, 9H, TMSN), 0.25 (s, 15H, Free 2 *t*-BuNHTMS).  $^{13}C$  NMR (126 MHz;  $C_6D_6$ ):  $\delta$  144.3, 140.90, 140.80, 138.49, 138.39, 134.7, 130.80, 130.67, 130.3, 128.7, 128.5, 127.6, 126.71, 126.58, 126.40, 126.26, 124.9, 122.9, 115.7, 114.1, 60.7, 35.8, 34.0, 32.6, 32.4, 4.6, 2.9

(143)La[N(TMS)(*t*-Bu)] (147b)

<sup>1</sup>H-NMR (500 MHz; C<sub>6</sub>D<sub>6</sub>): δ 7.77-7.75 (m, 3H, 3Ar-H), 7.67 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.44 (d, *J* = 8.3 Hz, 2H, 2Ar-H), 7.39 (d, *J* = 8.9 Hz, 2H, 2Ar-H), 7.20 (dd, *J* = 15.2, 7.4 Hz, 6H, 6Ar-H), 7.13 (dd, *J* = 13.6, 6.9 Hz, 4H, 2Ar-H), 2.95-2.80 (m, 6H, 4CH<sub>2</sub>), 1.56 (s, 9H, *t*-BuN), 1.22 (s, 26H), 0.46 (s, 11H), 0.25 (s, 25H). <sup>13</sup>C NMR (126 MHz; C<sub>6</sub>D<sub>6</sub>): δ 144.3, 140.90, 140.80, 138.48, 138.39, 134.7, 130.80, 130.67, 130.3, 128.7, 128.5, 127.59, 127.56, 127.46, 126.71, 126.57, 126.40, 126.26, 124.9, 122.9, 115.7, 60.7, 35.1, 34.5, 34.0, 32.6, 32.4, 5.1, 4.3, 2.9

Synthesis of Aminoalkene Substrate  
and Hydroamination Products

(*E*)-5-(4-Methoxyphenyl)-2,2-Dimethylpent-4-Enenitrile

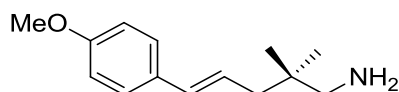


A 100-mL round-bottomed flask equipped with a magnetic stirring bar and a N<sub>2</sub> inlet was charged with anhydrous THF (25 mL) and anhydrous diisopropylamine (0.67 mL, 4.7 mmol) was subsequently added. The resulting solution was cooled to 0 °C with an ice bath and *n*-BuLi (2.0 M, 2.3 mL, 4.7 mmol) was slowly added dropwise. The reactant mixture was stirred for 30 min at 0 °C, then cooled to -78 °C with a dry ice-acetone bath. Isobutyronitrile (0.43 mL, 4.7 mmol) was added and the reactant mixture was stirred for 2 h at -78 °C. (*E*)-1-(3-chloroprop-1-en-1-yl)-4-methoxybenzene (0.79 g, 4.3 mmol) in anhydrous THF (5 mL) was then slowly added. The reactant mixture was warmed to

21°C and stirred for 4 h until judged complete by TLC. The reactant mixture was diluted with diethyl ether (100 mL), washed with saturated NaHCO<sub>3</sub> (30 mL), brine (30 mL), and the organic phase was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuo followed by flash chromatography on silica gel (20:1 hexane/EtOAc for elution) afforded (*E*)-5-(4-methoxyphenyl)-2,2-dimethylpent-4-enenitrile (0.83 g, 3.88 mmol, 90%) as a colorless oil. <sup>1</sup>H-NMR (500 MHz; CDCl<sub>3</sub>): δ 7.35 (d, *J* = 8.8 Hz, 2H, 2Ar-**H**), 6.84 (d, *J* = 8.8 Hz, 2H, 2Ar-**H**), 6.43 (d, *J* = 15.6 Hz, 1H, , Ar-**CH=C**), 6.09 (dd, *J* = 15.4, 7.5 Hz, 1H, Ar-**C=CH**), 3.80 (s, 3H, O**CH**<sub>3</sub>), 2.40 (d, *J* = 7.5 Hz, 2H, **CH**<sub>2</sub>), 1.36 (s, 6H, **2CH**<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 134.16, 129.56, 127.48, 124.84, 121.25, 113.98, 55.29, 44.36, 32.63, 26.29. IR (film) 2967, 2912, 2846, 2233, 1605, 1513, 1465, 1252, 1032, 801 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>14</sub>H<sub>17</sub>NO [M+H]<sup>+</sup>: 216.1383, found: 216.1373

#### General LiAlH<sub>4</sub> Reduction Procedure

(*E*)-5-(4-Methoxyphenyl)-2,2-Dimethylpent-4-en-1-Amine (**148d**)

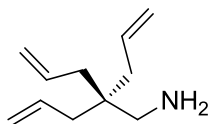


To a mixture of LiAlH<sub>4</sub> (0.294 g, 7.75 mmol) and anhydrous Et<sub>2</sub>O (30 mL) was added a solution of (*E*)-5-(4-methoxyphenyl)-2,2-dimethylpent-4-enenitrile (0.83 g, 3.87 mmol) in Et<sub>2</sub>O (10 mL) at 0 °C. The reaction mixture was stirred at 21°C overnight and was then re-cooled to 0 °C. Water was slowly added dropwise until hydrogen evolution ceased. The resulting suspension was diluted with diethyl ether (50 mL) and subsequently

was dried with Na<sub>2</sub>SO<sub>4</sub>. The white solid was removed by vacuum filtration.

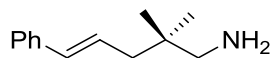
Concentration in vacuo followed by bulb to bulb distillation from CaH<sub>2</sub> afforded (*E*)-5-(4-methoxyphenyl)-2,2-dimethylpent-4-en-1-amine (**148d**) (0.76 g, 3.5 mmol, 92%) as a colorless oil. <sup>1</sup>H-NMR (500 MHz; CDCl<sub>3</sub>): δ 7.26 (d, *J* = 8.7 Hz, 2H, 2Ar-H), 6.82 (d, *J* = 8.7 Hz, 2H, 2Ar-H), 6.31 (d, *J* = 15.7 Hz, 1H, Ar-CH=C), 6.07 (dt, *J* = 15.6, 7.6 Hz, 1H, Ar-C=CH), 3.77 (s, 3H, OCH<sub>3</sub>), 2.46 (s, 2H, CH<sub>2</sub>NH<sub>2</sub>), 2.07 (d, *J* = 7.6 Hz, 2H, C=C-CH<sub>2</sub>), 1.00 (s, 2H, NH<sub>2</sub>), 0.88 (s, 6H, 2CH<sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 158.73, 131.47, 130.60, 127.04, 125.04, 113.91, 55.25, 52.77, 43.10, 35.60, 24.73.; IR (film) 3375, 2957, 1609, 1513, 1465 1296, 1245, 1175, 1032, 970 cm<sup>-1</sup>; HRMS (ESI): Calcd for C<sub>14</sub>H<sub>21</sub>NO [M+H]<sup>+</sup>: 220.1696, found: 220.1683

### 2,2-Diallylpent-4-en-1-Amine (148b)



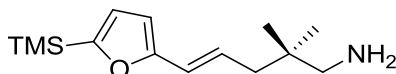
The title compound 2,2-diallylpent-4-en-1-amine (**148b**) (1.35 g, 8.2 mmol, 88%) was obtained as a colorless oil from 2,2-diallylpent-4-enenitrile ( 1.50 g, 9.32 mmol) by the general LiAlH<sub>4</sub> reduction procedure. <sup>1</sup>H-NMR (500 MHz; CDCl<sub>3</sub>): δ 5.88-5.79 (m, 3H, 3CH<sub>2</sub>-CH=C), 5.10-5.06 (m, 6H, 3CH<sub>2</sub>-CH=CH<sub>2</sub>), 2.03 (dd, *J* = 7.5, 0.8 Hz, 6H, 3CH<sub>2</sub>-CH=C), 0.99 (s, 2H, NH<sub>2</sub>). <sup>13</sup>C NMR (126 MHz; CDCl<sub>3</sub>): δ 134.9, 117.9, 47.8, 41.0, 39.5

(E)-2,2-Dimethyl-5-Phenyl  
Pent-4-en-1-Amine (148c)



The title (*E*)-2,2-dimethyl-5-phenylpent-4-en-1-amine (**148c**) (1.31 g, 6.92 mmol, 85%) was obtained as a colorless oil from (*E*)-2,2-dimethyl-5-phenylpent-4-enenitrile (1.51 g, 8.15 mmol) by the general  $\text{LiAlH}_4$  reduction procedure.  $^1\text{H-NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.38 (d,  $J = 7.4$  Hz, 2H, 2Ar-H), 7.33 (t,  $J = 7.6$  Hz, 2H, 2Ar-H), 7.23 (t,  $J = 7.3$  Hz, 1H, Ar-H), 6.42 (d,  $J = 15.7$  Hz, 1H, Ar-CH=C), 6.27 (dt,  $J = 15.6, 7.7$  Hz, 1H, Ar-C=CH), 2.53 (s, 2H,  $\text{CH}_2\text{NH}_2$ ), 2.16 (d,  $J = 7.4$  Hz, 2H, C=C- $\text{CH}_2$ ), 1.14 (s, 2H,  $\text{NH}_2$ ), 0.94 (s, 6H, 2 $\text{CH}_3$ ).  $^{13}\text{C NMR}$  (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  138.1, 132.6, 128.9, 127.7, 127.3, 126.4, 53.2, 43.5, 36.0, 25.2

(E)-2,2-Dimethyl-5-(5-(Trimethylsilyl)  
Furan-2-yl)Pent-4-en-1-Amine (148e)

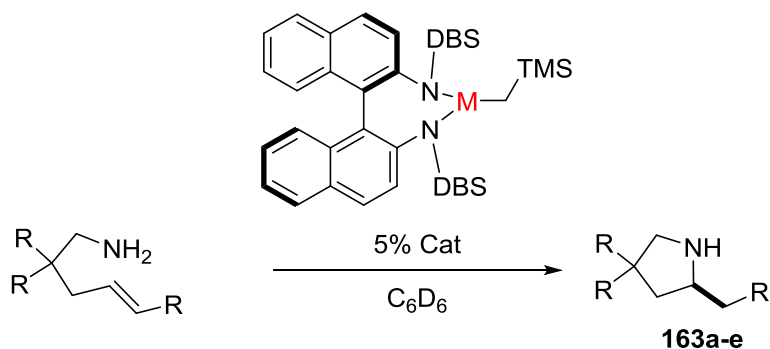


The title compound (*E*)-2,2-dimethyl-5-(5-trimethylsilyl-furan-2-yl)-pent-4-enylamine (**148e**) (0.48 g, 1.9 mmol, 95%) was obtained as colorless oil from (*E*)-2,2-dimethyl-5-(5-trimethylsilyl-furan-2-yl)-pent-4-enenitrile (0.52 g, 2.1 mmol) by the general  $\text{LiAlH}_4$  reduction procedure.  $^1\text{H-NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  6.59 (d,  $J = 3.1$  Hz, 1H, Ar-H), 6.29-6.16 (m, 4H, 2Ar-C=CH and 2Ar-H), 2.53 (s, 2H,  $\text{CH}_2\text{-NH}_2$ ), 2.13 (d,  $J = 7.2$  Hz, 2H, C=C- $\text{CH}_2$ ), 1.37 (s, 2H,  $\text{NH}_2$ ), 0.94 (s, 6H, 2 $\text{CH}_3$ ), 0.29 (s, 9H, 3Si $\text{CH}_3$ ).

$^{13}\text{C}$  NMR (126 MHz;  $\text{CDCl}_3$ ):  $\delta$  159.7, 157.4, 126.9, 121.54, 121.46, 106.8, 53.1, 43.5, 36.0, 25.1, -1.1

### General Hydroamination Procedure

The catalytic complex **145a** or **145b** was prepared in-situ according to the formation of complexes (**145a** and **145b**) or (**147a** and **147b**) procedure. The aminoalkene (0.2 mmol) was added to the preformed complex and the reactant mixture was subsequently held at indicated temperature until the cyclization of aminoalkenes was judged complete ( $\geq 95\%$  conversion by  $^1\text{H}$  NMR integration).



**148a:**  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{H}$

$\text{M} = \text{Y}$ :  $23^\circ\text{C}$ , 5.6 d,  $>95\%$  conv, **85%ee**

$\text{M} = \text{La}$ :  $23^\circ\text{C}$ , 5 h,  $>95\%$  conv, **88%ee**

**148b:**  $\text{R}^1 = \text{Allyl}$ ,  $\text{R}^2 = \text{H}$

$\text{M} = \text{Y}$ :  $23^\circ\text{C}$ , 18 h,  $>95\%$  conv, **74%ee**

$\text{M} = \text{La}$ :  $23^\circ\text{C}$ , 15 min,  $>95\%$  conv, **82% ee**

**148c:**  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{Phenyl}$

$\text{M} = \text{Y}$ :  $60^\circ\text{C}$ , 6 d,  $>95\%$  conv, **59%ee**

$\text{M} = \text{La}$ :  $45^\circ\text{C}$ , 10 h,  $>95\%$  conv, **77%ee**

**148d:**  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = 4\text{-(MeO)C}_6\text{H}_4$

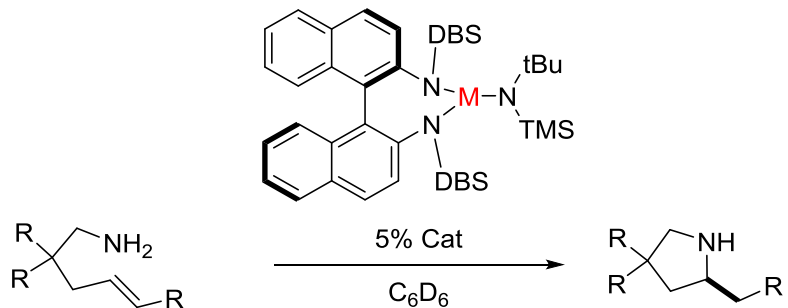
$\text{M} = \text{Y}$ :  $90^\circ\text{C}$ , 12.1 d,  $>95\%$  Conv, **61%ee**

$\text{M} = \text{La}$ :  $45^\circ\text{C}$ , 9.1 d,  $>95\%$  conv, **87%ee**

**148e:**  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = 5\text{-(TMS)-2-furanyl}$

$\text{M} = \text{Y}$ :  $60^\circ\text{C}$ , 29 h,  $>95\%$  conv, **58%ee**

$\text{M} = \text{La}$ :  $35^\circ\text{C}$ , 9 h,  $>95\%$  conv, **87%ee**



**148a:** R<sup>1</sup> = Me, R<sup>2</sup> = H

M = Y: 23°C, 53 h, >95%conv, **57%ee**

M = La: 23°C, 3 h, >95%conv, **87%ee**

**148c:** R<sup>1</sup> = Me, R<sup>2</sup> = Phenyl

M = Y: 60°C, 132 h, >95%conv, **48%ee**

M = La: 35°C, 89 h, >95%conv, **82%ee**

**148d:** R<sup>1</sup> = Me, R<sup>2</sup> = 4-(MeO)C<sub>6</sub>H<sub>4</sub>

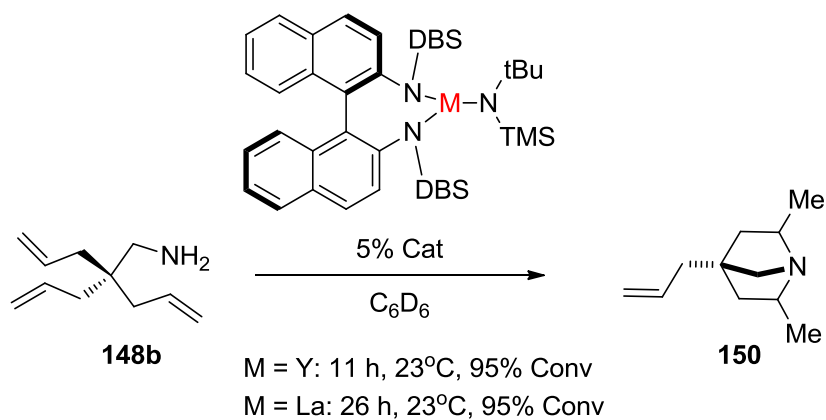
M = Y: 90°C, 97 h, >95% Conv, **70%ee**

M = La: 35°C, 93 h, >95% conv, **84%ee**

**148e:** R<sup>1</sup> = Me, R<sup>2</sup> = 5-(TMS)-2-furanyl

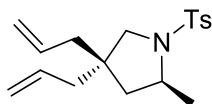
M = Y: 60°C, 9 h, >95% conv, **78%ee**

M = La: 35°C, 12 h, >95%conv, **84%ee**



General Large Scale (≥1 mmol)  
Hydroamination Procedure

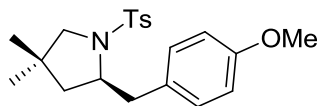
(S)-4,4-Diallyl-2-Methyl-1-Tosylpyrrolidine



In an argon-filled glove box,  $\text{YCl}_3(\text{THF})_3$  (8.21 mg, 0.02 mmol) and THF (0.5 mL) were added into a J. Young NMR tube equipped with teflon screw cap. (Trimethylsilyl)methyl lithium (5.8 mg, 0.06 mmol) was added and reactant mixture was kept at room temperature for 30 min. *N,N'*-Bis(10,11-dihydro-5H-dibenzo[a,d][7]annulen-5-yl)-[1,1'-binaphthalene]-2,2'-diamine (**143**) (13.84 mg, 0.021 mmol) was added and the solution was maintained at room temperature overnight. Removal of THF in vacuo was then followed by addition of  $\text{C}_6\text{D}_6$  (0.5 mL). The 2,2-diallylpent-4-en-1-amine (**147b**) (0.18 g, 1.1 mmol) were added to the preformed complex and the reactant mixture was subsequently kept at 21°C for 21h. Following pyrrolidine formation, the teflon screw cap was removed, the contents were diluted with anhydrous  $\text{CH}_2\text{Cl}_2$  (4 mL) and then transferred into a 5-mL, round-bottomed flask.  $\text{TsCl}$  (0.36 g, 1.6 mmol) and pyridine (0.2 mL, 1.64 mmol) were added in succession. The reactant mixture was stirred at 21°C for 12h. The reactant mixture was diluted with diethyl ether (20 mL), washed with saturated  $\text{NaHCO}_3$  (10 mL) and brine (10 mL). The organic phase was subsequently dried with  $\text{MgSO}_4$ . Concentration in vacuo followed by flash chromatography on silica gel (20:1 hexane/EtOAc for elution) afforded (*S*)-4,4-diallyl-2-methyl-1-tosylpyrrolidine (0.24 g, 0.75 mmol, 68%)  $^1\text{H-NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.68 (d,  $J = 7.9$  Hz, 2H, 2Ar-**H**), 7.28 (d,  $J = 7.9$  Hz, 2H, 2Ar-**H**), 5.66 (ddt,  $J = 17.5, 10.3, 7.4$  Hz, 1H,  $\text{CH}_2\text{-CH=C}$ ), 5.50 (ddt,  $J = 17.5, 10.3, 7.4$  Hz, 1H,  $\text{CH}_2\text{-CH=C}$ ), 5.04-4.99 (m, 2H,  $\text{CH}_2\text{-CH=CH}_2$ ), 4.94 (d,  $J = 10.6$  Hz, 1H,  $\text{CH}_2\text{-CH=CH}_2$ ), 4.77 (d,  $J = 16.9$  Hz, 1H,  $\text{CH}_2\text{-CH=CH}_2$ ), 3.66-3.49 (m, 1H,  $\text{CH}_2\text{-CH-CH}_3$ ), 3.17 (d,  $J = 10.6$  Hz, 1H,  $\text{CH}_2\text{-N}$ ), 3.09 (d,  $J = 10.6$  Hz, 1H,  $\text{CH}_2\text{-N}$ ), 2.39 (s, 3H, Ar- $\text{CH}_3$ ), 2.07 (d,  $J = 7.4$  Hz,

2H,  $\text{CH}_2\text{-CH-CH}_3$ ), 1.81 (dd,  $J = 12.9, 7.4$  Hz, 1H,  $\text{CH-CH}_3$ ), 1.67 (dd,  $J = 14.1, 6.9$  Hz, 1H,  $\text{CH-CH}_3$ ), 1.53 (dd,  $J = 14.1, 7.9$  Hz, 1H,  $\text{CH-CH}_3$ ), 1.36 (d,  $J = 6.1$  Hz, 4H,  $2\text{CH}_2\text{-CH=C}$ .;  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  143.21, 135.29, 133.78, 133.74, 133.47, 129.51, 129.44, 127.40, 118.27, 58.16, 55.30, 44.46, 43.22, 40.93, 39.45, 29.66, 22.51, 21.46. IR (film) 3072, 2972, 2920, 1638, 1601, 1442, 1342, 1158, 1095, 917, 658, 585  $\text{cm}^{-1}$ ; HRMS (ESI): Calcd for  $\text{C}_{18}\text{H}_{25}\text{NO}_2\text{S}$   $[\text{M}+\text{H}]^+$ : 320.1679, found: 320.1660

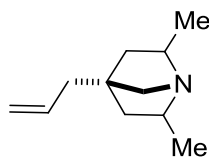
(S)-2-(4-Methoxybenzyl)-4,4-Dimethyl-1-Tosylpyrrolidine



The title (S)-2-(4-methoxybenzyl)-4,4-dimethyl-1-tosylpyrrolidine (0.28 g, 0.75 mmol, 71%) was obtained as a light yellow oil from  $\text{LaCl}_3\text{THF}_{1.5}$  (17.6 mg, 0.05 mmol), and (E)-5-(4-methoxyphenyl)-2,2-dimethylpent-4-en-1-amine (**162d**) (0.23 g, 1.0 mmol) by the general large scale ( $\geq 1$  mmol) hydroamination procedure.  $^1\text{H-NMR}$  (500 MHz;  $\text{CDCl}_3$ ):  $\delta$  7.76 (d,  $J = 7.9$  Hz, 2H, 2Ar-H), 7.30 (d,  $J = 7.9$  Hz, 2H, 2Ar-H), 7.12 (d,  $J = 8.3$  Hz, 2H, 2Ar-H), 6.86 (d,  $J = 8.3$  Hz, 2H, 2Ar-H), 3.76 (s, 3H, O- $\text{CH}_3$ ), 3.74-3.69 (m, 1H, N- $\text{CH-CH}_2$ ), 3.44 (d,  $J = 13.3, 3.4$  Hz, 1H,  $\text{CH}_2\text{-Ar}$ ), 3.11, 3.04 (ABq,  $J = 7.3$  Hz, 2H,  $\text{CH}_2\text{-NTs}$ ) 2.73 (dd,  $J = 13.2, 9.6$  Hz, 1H,  $\text{CH}_2\text{-Ar}$ ), 2.40 (s, 3H, Ar- $\text{CH}_3$ ), 1.45 (dd,  $J = 7.9, 3.0$  Hz, 2H,  $\text{CH}_2\text{-CH-NTs}$ ), 0.95 (s, 3H,  $\text{CH}_3$ ), 0.42 (s, 3H,  $\text{CH}_3$ ).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  158.16, 143.26, 135.33, 130.46, 129.57, 127.48, 113.77, 61.64, 55.19, 45.62, 41.76, 37.17, 26.43, 25.80, 21.50. IR (film) 2957, 2872, 1609, 1509, 1465, 1345,

1245, 1157, 1095, 1036, 661, 588  $\text{cm}^{-1}$ ; HRMS (ESI): Calcd for  $\text{C}_{21}\text{H}_{27}\text{NO}_3\text{S}$   $[\text{M}+\text{H}]^+$ :  
374.1761, found: 374.1761

(1*s*,4*s*)-4-Allyl-2,6-Dimethyl-1-  
Azabicyclo[2.2.1] Heptane (150)



The title (1*s*,4*s*)-4-allyl-2,6-dimethyl-1-azabicyclo[2.2.1]heptane (**150**) was obtained as a colorless oil from Complex **147a** or **147b** (0.01mmol), and 2,2-Diallylpent-4-en-1-amine (**148b**) (33 mg, 0.2 mmol) by the General hydroamination procedure.  $^1\text{H-NMR}$  (500 MHz;  $\text{C}_6\text{D}_6$ ):  $\delta$  5.79 (ddt,  $J = 17.2, 10.1, 7.4$  Hz, 1H,  $\text{CH}_2\text{-CH}$ ), 5.06-4.88 (m, 2H,  $\text{CH}_2\text{-CH}$ ), 2.77-2.65 (m, 2H, 2N- $\text{CH}$ ), 2.77 (d,  $J = 7.4$  Hz, 2H, N- $\text{CH}_2$ ), 2.19 (s, 2H, C- $\text{CH}_2$ ), 1.34 (dd,  $J = 11.2, 7.9$  Hz, 2H,  $\text{CH-CH}_2$ ), 1.03 (d,  $J = 6.3$  Hz, 6H, 2C- $\text{CH}_3$ ), 0.90 (dd,  $J = 9.9, 4.2$  Hz 2H,  $\text{CH-CH}_2$ ).  $^{13}\text{C NMR}$  (126 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  136.03, 115.99, 61.85, 55.25, 42.94, 36.78, 22.74. IR (film) 2957, 2920  $\text{cm}^{-1}$ ; HRMS (ESI): Calcd for  $\text{C}_{11}\text{H}_{19}\text{N}$   $[\text{M}+\text{H}]^+$ : 166.1590, found: 166.1602

General Procedure for  
Determination of Enantiomeric  
Excess via Mosher Amide Formation

To a solution of the hydroamination product (0.05 mmol) and *N,N*-Diisopropylethylamine (0.075 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 mL) was added (*R*)-(+)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetyl chloride (0.055 mmol). The reactant mixture was stirred

overnight and filtered through a silica gel plug (pipette column, and 10:1 Hexane: EtOAc for elution). The filtrate solution was concentrated in vacuo to give a yellow residue. The % ee was determined by  $^{19}\text{F}$  NMR.