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CATALYTIC ASYMMETRIC *AZA*-DIELS-ALDER REACTION:
REGULATION OF ORTHOGONAL FUNCTIONS IN A DUAL
CHIRAL/NON-CHIRAL CATALYST SYSTEM

presented by

CORY ALLAN NEWMAN

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of the requirements for the

Ph.D. degree in Chemistry

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CATALYTIC ASYMMETRIC *AZA*-DIELS-ALDER REACTION: REGULATION OF ORTHOGONAL FUNCTIONS IN A DUAL CHIRAL/NON-CHIRAL CATALYST SYSTEM

By

Cory Allan Newman

A DISSERTATION

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ABSTRACT

CATALYTIC ASYMMETRIC *AZA*-DIELS-ALDER REACTION:
REGULATION OF ORTHOGONAL FUNCTIONS IN A DUAL
CHIRAL/NON-CHIRAL CATALYST SYSTEM

By
Cory Allan Newman

The subject of this thesis is the catalytic asymmetric *aza*-Diels-Alder reaction and a new method using a dual catalyst system. The optimization studies as well as the generality of the reaction will be discussed in detail. In addition, NMR titrations were done to obtain binding constants to gain insight into the role of the non-chiral Lewis acid $B(OPh)_3$. Lastly, efforts toward the total synthesis of cylindricine C will be discussed where the *aza*-Diels-Alder was used as the key step.

A catalytic asymmetric *aza*-Diels-Alder reaction has been developed using the catalyst derived from the chiral C2 symmetric ligand VAPOL and $B(OPh)_3$. Optimization studies found that the catalyst prepared from 5 mol% VAPOL and 100 mol% $B(OPh)_3$ was optimal. This method was found to be widely general for imines generated from aromatic and secondary aliphatic aldehydes, however, attempts to expand the scope to primary aliphatic substrates failed. Several other surrogate imines for the primary aliphatic substrates were attempted and success was limited with these substrates as well. A second class of substrate that was studied were imines containing a substituted benzhydryl group on the nitrogen of the imine. The TMB, DAM, and BUDAM imines

were studied and with few exceptions, the substitution on the benzhydryl group proved to be detrimental to the outcome of the reaction

During optimization studies, a unique observation was made with the non-chiral Lewis acid $B(OPh)_3$, where it was found that the asymmetric induction of the product remained constant (90% ee) as the amount of $B(OPh)_3$ was increased and the ee did not diminish until the ratio of $B(OPh)_3$ to VAPOL was 100:1 (82% ee). To determine the mechanistic role of $B(OPh)_3$, an NMR titration study was conducted to determine the affinity for binding of the VAPOL-$B(OPh)_3$ catalyst and $B(OPh)_3$ to both the imine **150** and the Diels-Alder cycloadduct **151**. It was found that the excess triphenylborate was competing for binding to the product of the reaction, resulting in chiral catalyst turnover, and the rate of the achiral background reaction was determined to be about 9 times slower than chiral reaction.

Also discussed are efforts towards the asymmetric total synthesis of cylindricine C using an *aza*-Diels-Alder reaction with the bis-TMS diene **278** to install its core decalin structure. Unfortunately, all attempts to afford the Diels-Alder adduct with this diene using a zirconium catalyst with a variety of chiral ligands failed. A racemic synthesis was then carried out using $BF_3{\cdot}OEt_2$ as the catalyst and an optimized yield of 69% was achieved. A 1,4-addition of a butenyl side-chain was proposed as the second step in the synthesis but all attempts to install that group failed. Another route was proposed where the diene **227** containing the butenyl side chain could be employed. One attempt was made with this diene and only the Mannich type product **296** was observed. The details of these studies as well as a discussion of the results will be the focus of this thesis.

To:

George L. Newman

(my grandfather)

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First and foremost I would like to thank professor William D. Wulff, my research advisor. I thank him for allowing me to join his research group and giving me the freedom to take any idea I had and explore it in the lab no matter how foolish or brilliant it might have sounded. It has been a pleasure not only learning from him and interacting on a professional level but also in a less formal setting as well. We have also shared many great conversations over a bottle (or two) of wine and he has given me an appreciation for the taste of wine, which I did not have before joining his group.

I would now like to send my greatest appreciation to a few people, without whom I would not have ventured to graduate school. The first person to thank is Anne Wilson, my undergraduate research advisor. I first was exposed to organic chemistry in 1998 in the general organic lectures taught by Anne Wilson. She was a great professor and if I had been taught by someone else, I might not have enjoyed the experience, and would not have chosen organic as my major field of study in graduate school. I also had the opportunity to do research for Anne in my senior year, which was my first exposure to academic research in organic chemistry. She again made this experience a great one and without her advice, I probably would not have decided to apply to graduate school.

I owe it also to my parents (Tim and Diane) as well as my grandfather for helping me decide to go to graduate school. I had many discussions with them and I have distinct memories of them telling me "just go to graduate school...you have nothing holding you

back." So, without them, I may have just received my B.S. degree and took a job in industry, which would have been much less fulfilling than my experience here at Michigan State University.

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I owe the secretaries in the department an acknowledgement as well. Lisa Dillingham (graduate secretary) was always helpful when I needed to take care of the formalities or just little things that come up during the graduate school process. If I needed something mailed or printed out in a timely fashion, Deanne Pierce (organic secretary) would always take care of what I needed immediately. Nancy Lavrik was a great joy to work with during the semesters when I had to teach and she would always be there to help when it was needed. These are just a few secretaries that I have worked closely with at times, but experiences with all other secretaries, as they came up have been very pleasurable as well.

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I also want to thank Daniel Whitehead for reading my entire thesis for proofreading purposes, this was a great help to me. In addition to Dan, Stewart Hart also

proofread a chapter for me as well. I thank them for that and for also being great friends during my time here.

During my time here, I have met many people and developed many friendships. In my second year I met Janelle Secl who became my best friend and ultimately my wife. I owe her a great deal of gratitude for her patience when dealing with all that graduate school throws at you. Her support throughout and the motivation she has given me definitely played some role in my success here (the $80 bottle of port for getting my cume points did not hurt). There have been some stressful times throughout graduate school and being able to go home to someone as special as Janelle has gotten me through it. I cannot say enough about her but I will stop here otherwise these acknowledgements will be about 100 pages.

Now I will just mention some names of other friends and express my thanks to them: Yiqian Lian, my lab mate for 3 years is awesome and he is a great colleague and friend. It was great to share the good times and hardships in lab together. Hopefully one of these years, I will be able to fill out the NCAA basketball pools better than him. I have spent my entire graduate career in the same lab as Kieth Korthals and he too has shared in the frustrations that occur in graduate school. Dr. Patwardan, I owe thanks to for teaching me all the basics of organic research and for being patient when I first started in the lab. Glenn Phillips was a great deal of help when things were not going well in the lab and he was kind enough to share some good stories to make me feel better about myself when I did stupid things in the lab. Vijaygopal Gopalsamuthirim was also a lab mate of mine for a few years and he was very knowledgeable and I took advantage of this many times. Zhengzheng Ding, how can I say enough about this guy. First, I will say he

is a little "dorky" (inside joke) but he is witty and is always ready with a good joke. I only worked in the same lab as him for about a year, but it was a fantastic year hopefully our friendship will last a long time. Many good conversations have been had with Alex Predus, Kostas Rabalakos, Aman Desai, and all the other Wulff group members (past and present) and I thank all of them for that and I wish them continued success in their careers.

I will end my acknowledgements by thanking again my parents and my wife who have been my lifeline for the past several years. They have been great supporters, great friends, and my stress relief when needed. Thank you all very very much.

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KEY TO SYMBOLS AND ABREVIATIONS

Bh	benzhydryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Dinaphthalene-2,2'-diol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BUDAM	bis-(3,5-di*tert*-butyl-*p*-anisyl)methylamine
Cbz	benzyloxycarbonyl
CSA	camphor sulfonic acid
DAM	*p*-dianisylmethylamine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIB	(diacetoxyiodo)benzene
DIBAL	diisopropyl aluminum hydride
DME	1,2-dimethoxy ethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
EDA	ethyl diazoacetate
EDG	electron donating group
ee	enantiomeric excess

EWG	electron withdrawing group
HOMO	highest occupied molecular orbital
KHMDS	potassium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
M.S.	molecular sieves
MeCN	acetonitrile
MEDAM	bis-(3,5-dimethyl-*p*-anisyl)methylamine
Ms	Methanesulfonyl
NCS	*N*-chlorosuccinimide
NMI	*N*-methylimidazole
NMO	*N*-methyl morpholine
TBAF	tetrabutylammonium floride
TBAT	tetrabutylammonium triphenyldifluorosilicate
TBDME	*tert*-butyl methyl ether
TBDPS	*tert*-butyldiphenylsilyl
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMB	bis(3,5-dimethylphenyl)methylamine
TMS	trimethylsilyl

TON	turn over number
TPAP	tetrapropylammonium chloride
VANOL	3,3'-Diphenyl-2,2'-binaphthalene-1,1'-diol
VAPOL	2,2'-Diphenyl-[3,3'-biphenanthrene]-4,4'-diol

CHAPTER 1
INTRODUCTION

The main focus of this dissertation is the development of new methodology for the heteroatom Diels-Alder reaction of imino-dienophiles with Danishefsky's diene. Before getting into the details of this research, several items need to be explained and defined before the methodology can be understood. Discussed herein are the basics of the Diels-Alder reaction, incorporation of a heteroatom, and how the use of a chrial Lewis acid or Brønsted acid allows access to enantioselectivity. In addition, to understanding how this reaction adds to or contributes to the heteroatom-Diels-Alder reaction field, the methods already present in the literature will be described.

1.1 Diels-Alder Reaction

The Diels-Alder reaction is arguably the most useful organic transformation ever discovered in organic chemistry (Scheme 1.1). When the phrase "Diels-Alder" is typed

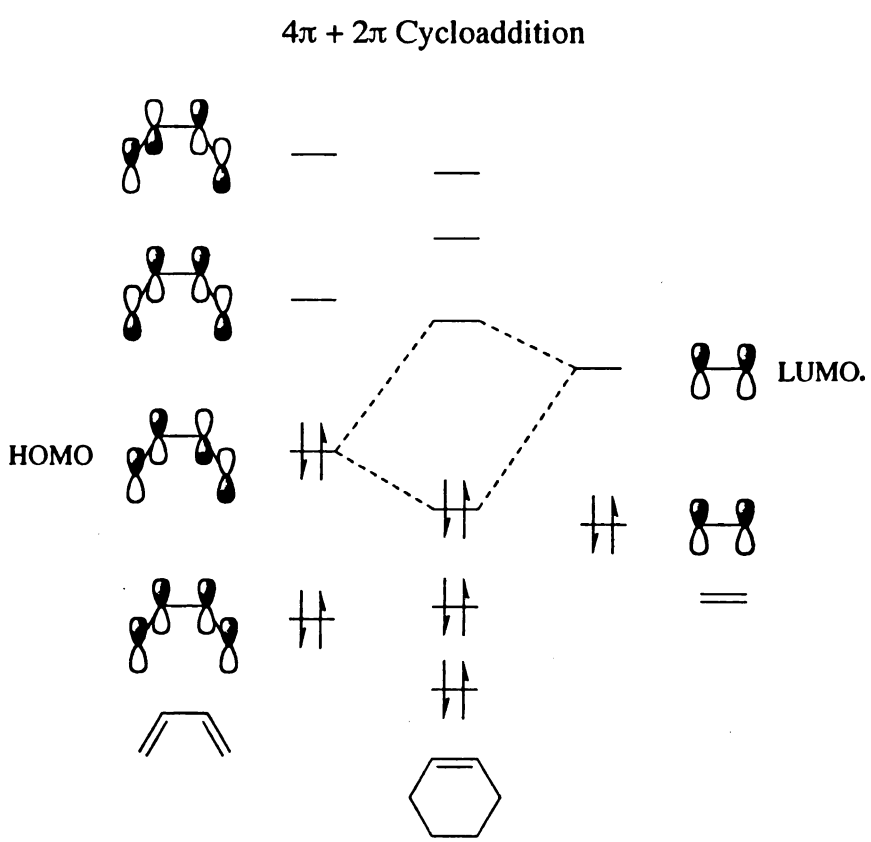
Scheme 1.1 Diels-Alder [4+2] Cycloaddition

1 **2** **3**

into the Scifinder search engine, the search reveals over 29000 items containing the concept Diels-Alder. The reaction was discovered in 1928[1] by the German chemists Otto Diels and Kurt Alder. There are many things about this reaction that make it so useful, and all have contributed to its popularity. First, the reaction forms a six-membered ring,

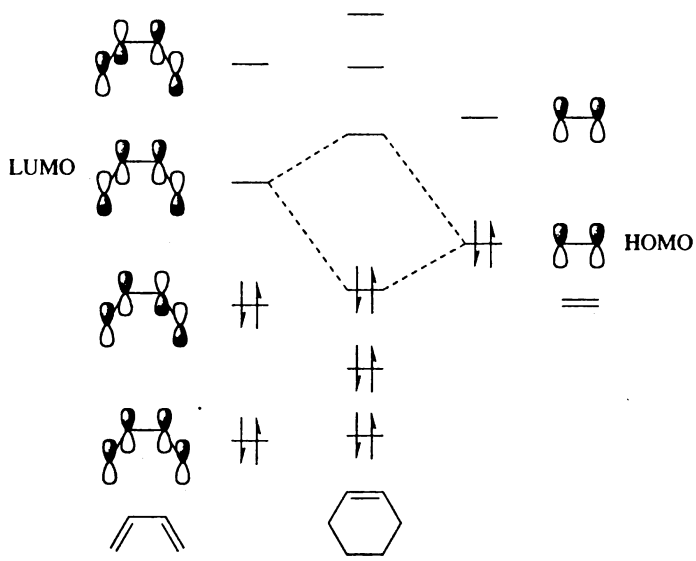
which is the most common cyclic structure in nature. In addition, one or more six-membered rings make up the core structure of vast numbers of these important and naturally occurring compounds. The reaction has another desirable characteristic that is very important in synthesis in that it is 100% atom economic. Every atom of the two reactants are incorporated into the product. For example, when butadiene is added to ethylene the reaction gives cyclohexene ($C_4H_6 + C_2H_4 \rightarrow C_6H_{10}$), thus all of the six carbons and 10 hydrogens in the starting materials are present in the product. The mechanism of the Diels-Alder reaction occurs with rare exception as a concerted process especially when there are no heteroatoms involved in the reaction. The mechanism[2] is a $4\pi e^- + 2\pi e^-$ process (Figure 1.1) where normally the HOMO of the diene reacts with the

Figure 1.1 Molecular Orbital Diagram of a Normal [4+2] Cycloaddition



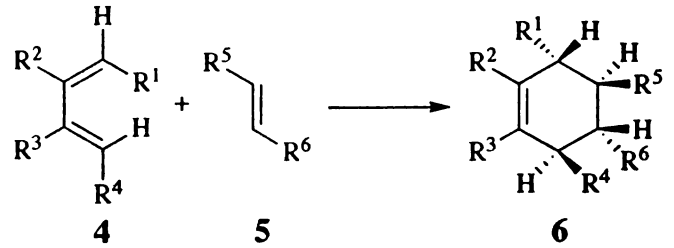
LUMO of the dienophile. Other examples are known where an electron donating substituent on the dienophile raises the energy of the HOMO high enough to interact with the LUMO of the diene. This is called an inverse electron demand Diels-Alder reaction (Figure 1.2). The concerted nature of the reaction allows for the ability to set the relative

Figure 1.2 Molecular Orbital Diagram of the Inverse Electron Demand 4+2 Cycloaddition



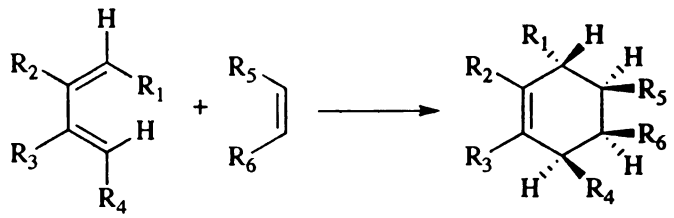
stereochemistry of 4 out of the 6 carbons of the six-membered ring (Scheme 1.2).

Scheme 1.2 Stereospecificity of the Diels-Alder Reaction



4 5 6

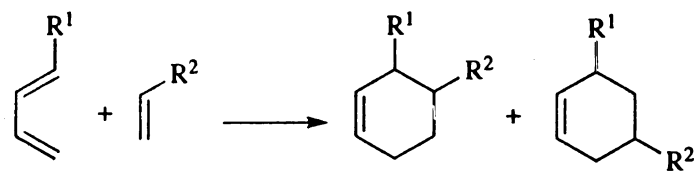
OR



4 7 8

One issue that can present a problem for this reaction is the aspect of regiochemistry. When the diene and dienophile are both unsymmetrical, then mixtures of two regioisomers can be produced (Scheme 1.3). This issue can be resolved, however by

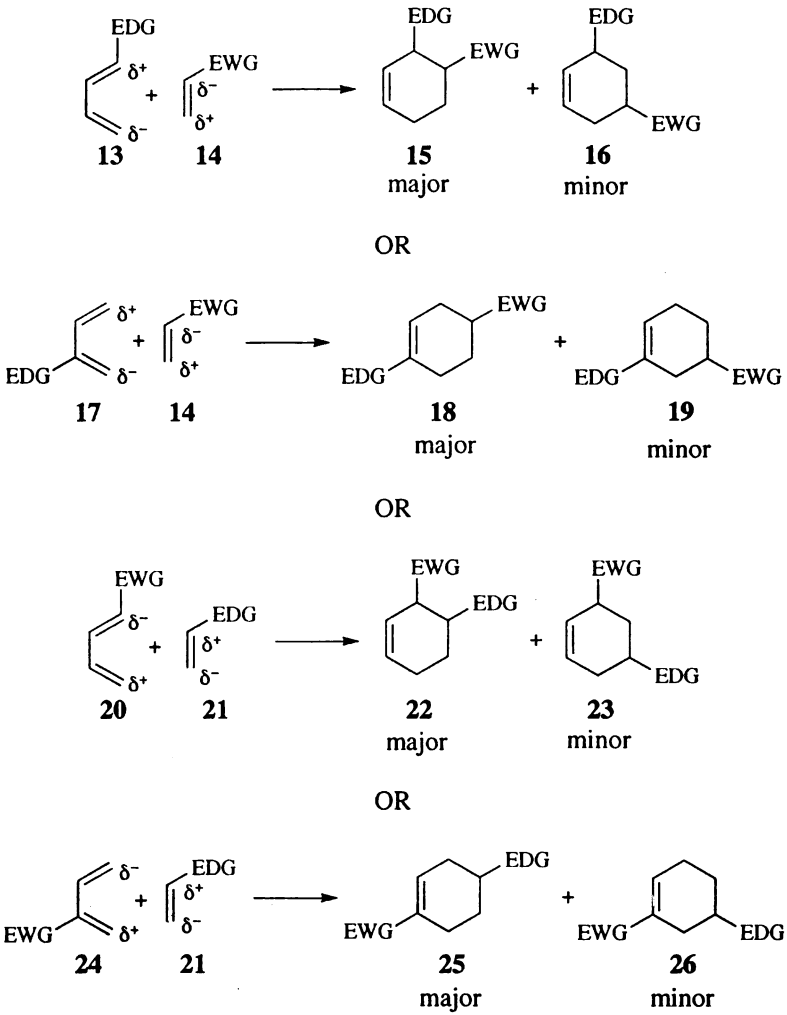
Scheme 1.3 Possible Regiochemical Outcomes of the Diels-Alder Reaction



9 10 11 12

placing an electron donating group (EDG) on the diene and an electron withdrawing group (EWG) on the dienophile or visa versa (Scheme 1.4). In the case where the EDG

Scheme 1.4 Effect of EWG's and EDG's on Regiochemistry

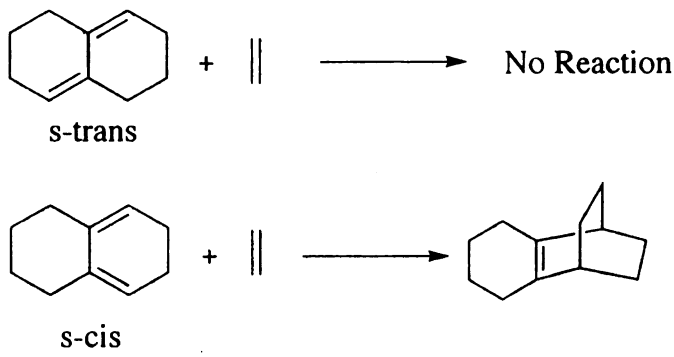


is on the diene (**13** and **17**) and the EWG is on the dienophile (**14**), the normal Diels-Alder reaction occurs. However, when the EWG is on the diene (**20** and **24**) and the EDG is on the dienophile (**21**), the inverse electron demand situation can be realized.

In order for the Diels-Alder reaction to occur, there has to be sufficient orbital overlap (as seen above), but what was not mentioned previously concerns the orientation

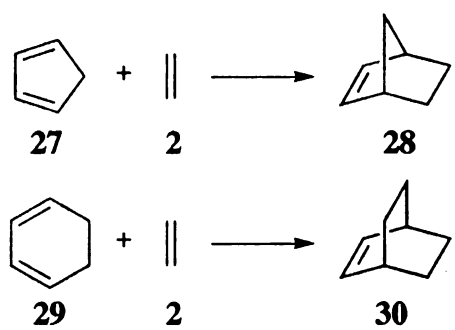
of the two double bonds with respect to the rotation about the single bond of the diene. For the orbital overlap to be favorable (Scheme 1.5) the double-bonds have to be pointing

Scheme 1.5 s-cis Versus s-trans



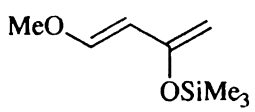
in the same direction (s-cis as opposed to s-trans). If they are not, the reaction will not occur. The reaction rates can thus be greatly increased by using dienes with the conformation of the diene locked in the s-cis conformation as in cyclopentadiene (**27**) or 1,3-cyclohexadiene (**29**) (Scheme 1.6).

Scheme 1.6 Examples of the Diene Locked s-cis



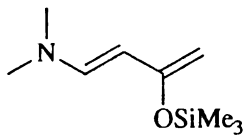
Another way to increase the rate of the Diels-Alder reaction is to make the diene or the dienophile very electron rich or poor. During the history of the Diels-Alder reaction, several electron rich dienes have been developed to increase reactivity, which in turn increased the regioselectivity (Figure 1.3). In 1974[3] Samuel Danishefsky published

Figure 1.3 Activated Dienes



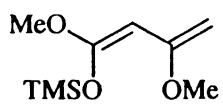
31

Danishefsky's diene



32

Rawal's Diene



33

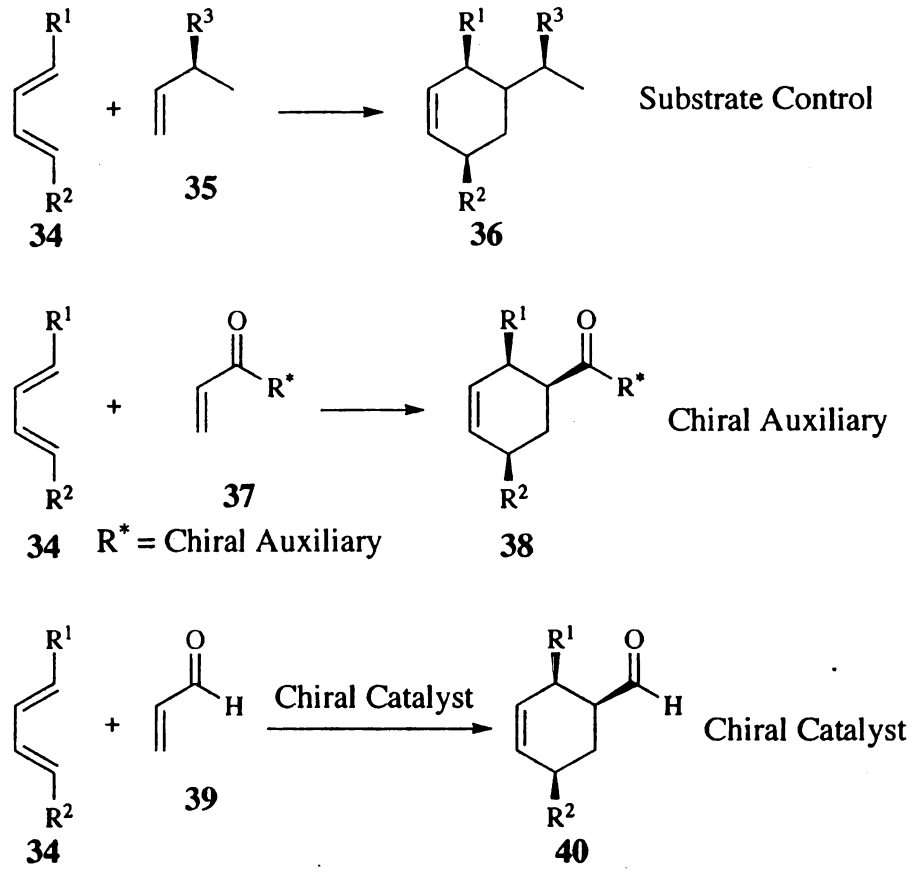
Brassard's diene

an article where he employed the *trans*-4-methoxy-2-trimethylsilyloxybutadiene (**31**) as a useful diene in the Diels-Alder reaction. This diene was found to be much more reactive due to its very electron rich nature. This enhanced electron density also aids in the regiochemical outcome of reactions using this diene with dienophiles containing EWG's. Thirty-four years later, Rawal, et. al. published an article using an amino version of Danishefksy's diene[4, 5] (**32**). This diene was found to be about twenty-five times more reactive[4, 5] than Danishefsky's diene. Brassard also developed an electron rich diene[6] (**33**). The diene developed in his lab allowed access to β-methoxy cyclohexenone derivatives. The increased electron density of this diene also gives increased reactivity as well as regioselectivity compared to other dienes.

It is well known that many naturally occurring compounds exist as a single enantiomer. In addition, pharmaceutical agents have different mechanisms of action when one enantiomer is used versus another. As mentioned before, the Diels-Alder reaction is attractive due to its ability to set four stereocenters in a single transformation. The diastereoselectivity of this reaction is very good, but due to the issues just mentioned, the ability to obtain a single enantiomer would also be desirable. For these reasons, the development of methods using the Diels-Alder reaction in an enantioselective manner has been actively pursued.

There are several ways to achieve asymmetric induction for the Diels-Alder reaction (Scheme 1.7). One is the use of substrate control, as in the case where a

Scheme 1.7 Possible Ways to Induce Stereochemistry in the Diels-Alder Reaction



stereocenter in either the diene or dienophile relays the stereochemistry into the product. Another option would be to use a chiral auxiliary that could be incorporated in either reagent and ultimately removed in a later step. Lastly, an external chiral catalyst that could coordinate to the diene or dienophile could be used. The chiral catalyst, when coordinated to either reagent theoretically only allows the carbon-carbon bond formation to occur preferably from one face over the other. There are pros and cons of each method, but in order to produce enantiopure substrates the use of one of these methods is necessary.

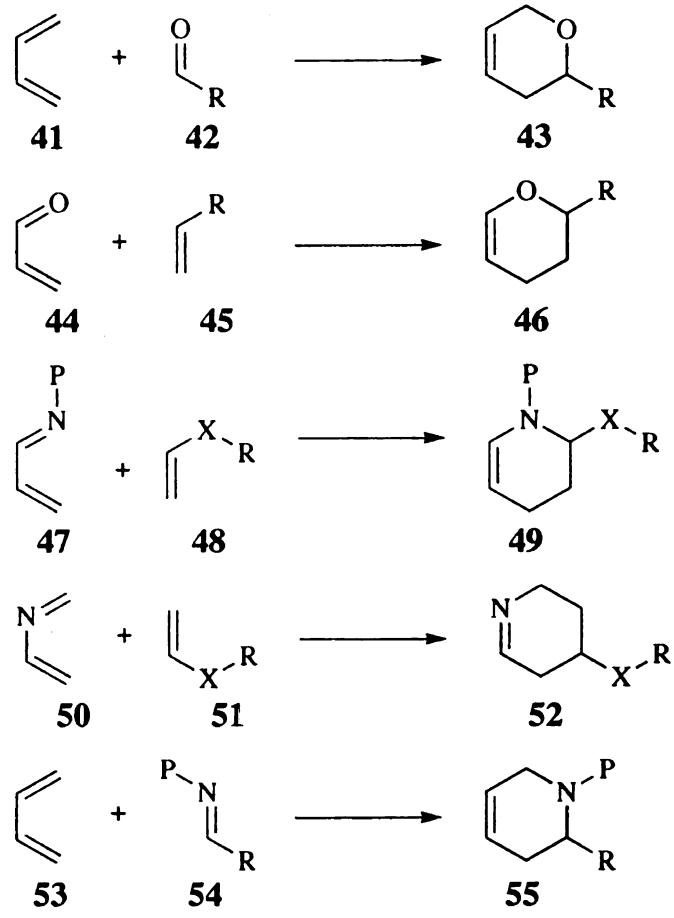
Each of these options will now be discussed in greater detail to provide insight into the advantages and disadvantages of each. Using substrate control requires the use of a substrate with a stereocenter previously incorporated. Some enantiopure compounds are commercially available, but if they are not, then one must prepare the substrate with the desired stereochemistry prior to executing the Diels-Alder reaction. This means that the same issues need to be faced to make that stereocenter before attempting the Diels-Alder reaction. Although extra effort is required, if that original stereocenter is incorporated into the target compound or could be used later in a synthetic route, then the substrate control method would be attractive. When a chiral auxiliary or chiral catalyst is used, the issues of the atom economy of the reaction become compromised. In the case of the chiral auxiliary, the group is first put on and then removed later. The down side to this method is that extra steps, time, and effort are needed to recover the chiral auxiliary. When using a chiral catalyst, the recoverability of the catalyst is also an issue. Even though a covalent bond is not necessarily needed to promote the reaction, the catalyst is not incorporated into the product. In many cases these chiral catalysts use expensive metals and/or ligands. It would be undesirable if in the end the expensive catalyst was lost during the workup. Despite these challenges, successful installation of up to four chiral centers make the effort and/or expense worth it.

1.2 Heteroatom-Diels-Alder Reaction

The discussion to this point has dealt with the general aspects of the Diels-Alder reaction and its utility in organic synthesis. The discussion will now turn to the heteroatom Diels-Alder reaction, as this topic is the main focus of this thesis. As discussed above, the Diels-Alder reaction produces a six-membered cycloalkene. When

a heteroatom is involved, the resulting product contains a six-membered heterocycle (Scheme 1.8). There are many types of heteroatom Diels-Alder reactions in

Scheme 1.8 Heteroatom Diels-Alder Reaction

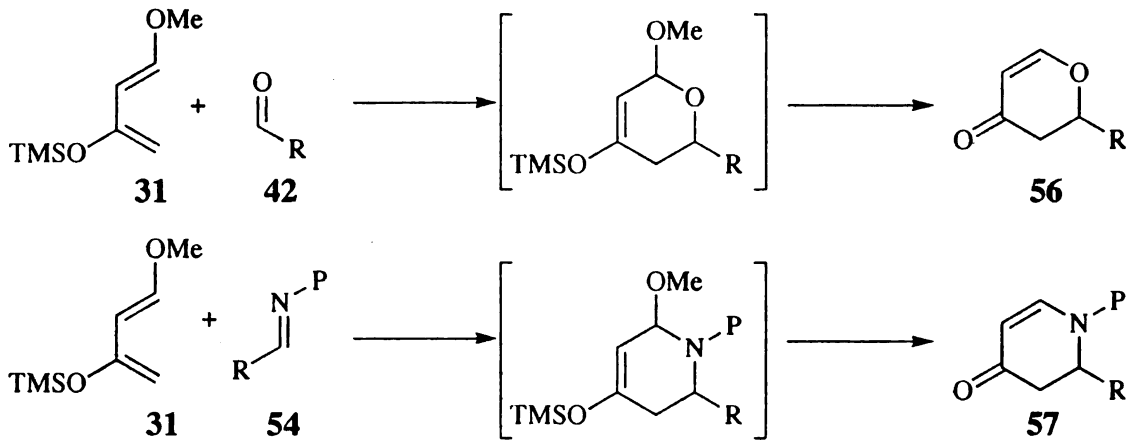


the literature[7-11] and probably the most common are ones in which an oxygen[12, 13] or nitrogen[14-16] is incorporated. The oxygen and nitrogen can be included in either the diene or dienophile and depending on the heteroatom location, the reaction will proceed to give different substitution patterns around the heterocyclic ring.

Regioselectivity is usually very predictable in the heteroatom Diels-Alder reactions due to the polarized nature of the imine and aldehyde carbon-nitrogen or carbon-oxygen double bond. The reactivity of these type of starting materials, especially in the case of the more sterically hindered imine also becomes an issue. However if the

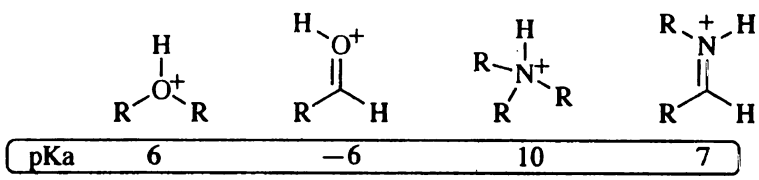
dienes such as those reported by Danishefsky, Rawal, or Brassard are used to react with aldehyde or imino dienophiles (Scheme 1.9) the rate of the reaction can be increased.

Scheme 1.9 Regioselectivity in the Heteroatom Diels-Alder Reaction



Another difficult challenge deals with the basicity of the starting materials and products and arises when developing methodologies for the heteroatom Diels-Alder reaction. When an imine or aldehyde dienophile is used, the product contains an sp^3 oxygen or nitrogen that is more basic (Figure 1.4) than the sp^2 oxygen or nitrogen in the aldehyde or

Figure 1.4 pKa of sp^2 and sp^3 Oxygen and Nitrogen



imine. When catalytic amounts of the chiral Lewis acid is used, turnover problems occur as a result of this issue.

1.3 Previous Examples of Lewis acid/Brønsted Acid Catalyzed *aza*-Diels-Alder Reaction

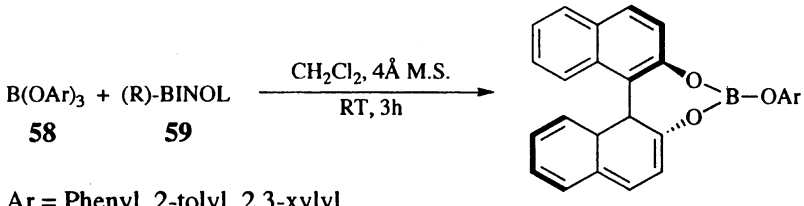
The main focus of the work in this thesis has been the development of a catalytic asymmetric Diels-Alder reaction of imino dienophiles with Danishefsky's diene. Before

this work can be discussed, it is necessary to review examples that already exist in the literature utilizing chiral catalysts to facilitate this class of reaction. There have been many researchers contributing work to this field and their successes and limitations will be discussed at this time.

1.3.1 Stoichiometric Catalyst

Yamamoto's studies using catalysts prepared from triarylborates and BINOL[17-19] (Scheme 1.10) represents the first example when a chiral catalyst was used in the *aza*-

Scheme 1.10 Pioneering Work by Yamamoto

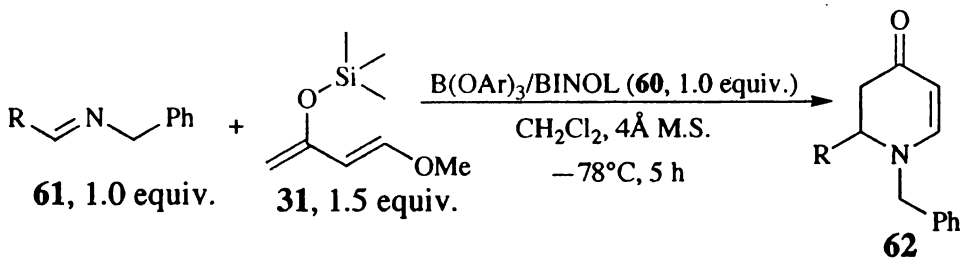


Ar = Phenyl, 2-tolyl, 2,3-xylyl

Proposed Catalyst (60)

Diels-Alder of imino dienophiles. In his studies, he found that a stoichiometric amount of catalyst **60** was needed to facilitate the reaction. He screened reactions of Danishefsky's diene with several imines (**61**) prepared from various aldehydes and benzyl amine[19] (Scheme 1.11). When R=Ph (**61a**), 86% ee could be achieved when the

Scheme 1.11 Substrate Scope for B(OAr)$_3$/BINOL Catalyst



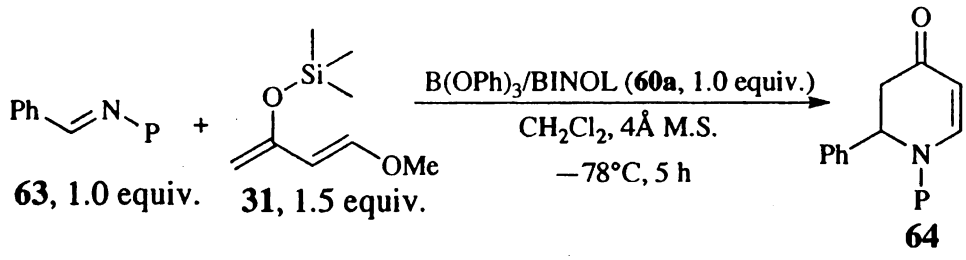
61, 1.0 equiv. **31**, 1.5 equiv. **62**

Entry	R	Ar (cat.)	Yield **62** (%)	ee **62** (%)
1	Ph (**61a**)	Phenyl (**60a**)	75	82
3	Ph (**61a**)	2-tolyl (**60b**)	76	84
4	Ph (**61a**)	3,5-xylyl (**60c**)	75	86
5	3-pyridyl (**61b**)	Phenyl (**60a**)	70	90
6	Cy (**61c**)	Phenyl (**60a**)	45	76
7	Cy (**61c**)	3,5-xylyl (**60c**)	49	72
8	3,5-dimethoxy-Ph (**61d**)	Phenyl (**60a**)	89	74
9	2-naphthyl (**61e**)	Phenyl (**60a**)	83	84

catalyst was prepared from tri-3,5-xylylborate (**60c**) and for the other substrate/catalyst combinations, a range of ee's from 72-90% could be reached with yields ranging from 45 to 89%. In a subsequent paper[18], several other metals with BINOL (**59**) were screened for the reaction of the imine prepared from benzaldehyde and benzylamine and Danishefsky's diene. This study indicated that all other metals screened (Al, Ti, Zn, other borates) were inferior to B(O-3,5-xylyl)$_3$. In this publication, he also screened several substrates as well as different solvents. He found that using propionitrile, THF, and toluene all gave results far inferior to those obtained with CH_2Cl_2.

In this study he also screened imines (**63**) prepared from benzaldehyde and other amines (Scheme 1.12). Entry 3 is very relevant to the present work as the imine

Scheme 1.12 Screening Different Imine Protecting Groups for the $B(OAr)_3$/BINOL Catalyst



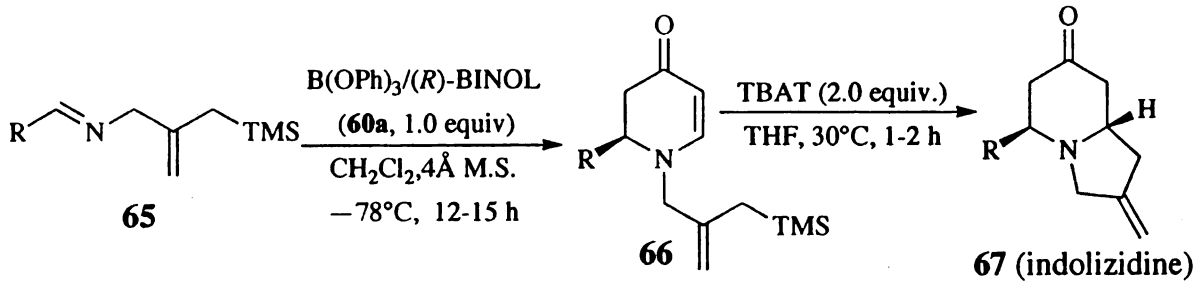
63, 1.0 equiv. **31**, 1.5 equiv. **64**

Entry	P	Yield **64** (%)	ee **64** (%)
1	3,4-dimethoxy-Bn (**63a**)	73	85
2	$-CH_2$-CH=CH_2 (**63b**)	97	70
3	Bh (**63c**)	0	—
4	Ph (**63d**)	77	24
5	*i*-Pr (**63e**)	13	4

used (**63c**) is identical to that used in optimization studies discussed in the next chapter. It is interesting to note that when Yamamoto screened this substrate using a stoichiometric amount of catalyst **60a**, no reaction was observed.

Although this system required 1.0 equivalent of the chiral catalyst, it was interesting to find that Furman used this system 13 years later[20] (Scheme 1.13) in attempt

Scheme 1.13 Furman's use of Yamamoto's Catalyst

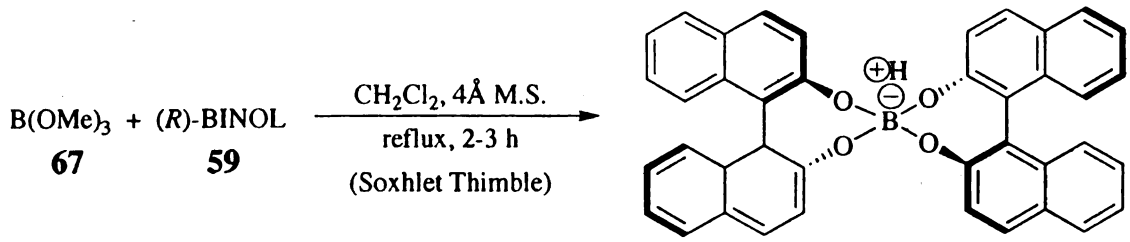


Entry	R	Yield **66** (%)	ee **66** (%)
1	C_6H_5 (**65a**)	75	90
2	4-MeC_6H_4 (**65b**)	70	86
3	4-$MeOC_6H_4$ (**65c**)	68	60
4	4-ClC_6H_4 (**65d**)	75	95
5	2-pyridyl (**65e**)	57	62
6	$CH_3CH_2CH_2$ (**65f**)	70	72
7	$CH_3(CH_2)_7CH_2$ (**65g**)	70	64
8	Cy (**65h**)	80	71
9	$(CH_3)_3C$ (**65i**)	0	—

to provide the Diels-Alder adduct (**66**) which could be further transformed into indolizidines (**67**). The initial step in his syntheses of the indolizidines was the *aza*-Diels-Alder reaction. All of the imines screened produced Diels-Alder product with the exception of the substrate where R = *t*-butyl (**65i**). For all the others, a range of 57-80% yield and 62-95% ee could be achieved for this class of imines. Ultimately each of these substrates were successfully taken on to do a fluoride mediated Hosomi-Sakurai allylation to afford the *trans*-indolizidines (**67**) diastereoselectively[21] (64-85% yield).

In 1994, Yamamoto reported an *aza*-Diels-Alder reaction using a chiral Brønsted acid[22] (Catalyst **68**) prepared by simply adding 2 equivalents BINOL with one equivalent of a trimethylborate (Scheme 1.14). When catalyst **68** was employed in the *aza*-Diels-

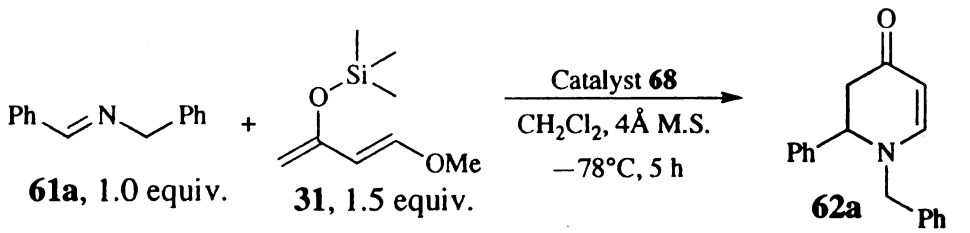
Scheme 1.14 Yamamoto's Chiral Brønsted Acid Catalyst



Catalyst **68**

Alder reaction of the imine **61a** prepared from benzaldehyde and benzylamine with Danishefsky's diene, a 78% yield and 86% ee was realized for **62a** (Scheme 1.15).

Scheme 1.15 *aza*-Diels-Alder Reaction Using the Brønsted Acid Catalyst

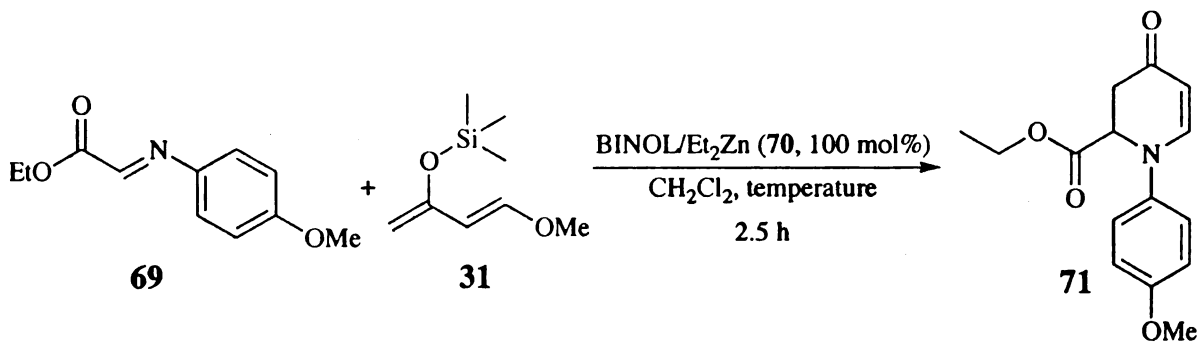


75% yield
86% ee

It is worthy of mention that this work has been repeated by Bull and James[23] for probing the structure of the catalyst proposed by Yamamoto. They found non-linear effects for the catalyst prepared from BINOL operate and that dynamic ligand exchange occurs for these types of catalysts. Since the non-linear effects were observed using scalemic BINOL, it was concluded that two equivalents of BINOL were included in the active catalyst even for the case when only one equivalent of BINOL was used (Scheme 1.10). If only one BINOL was incorporated, then the resulting ee would drop linearly with respect to the ee of BINOL used whereas the incorporation of two equivalents of BINOL in the active catalyst structure allows for the observation of a nonlinear relationship with the ee of BINOL used.

Another report in the literature where a stoichiometric amount of catalyst was used in a heteroatom Diels-Alder reaction was that by Whiting using a zinc catalyst[24] (**70**) (Scheme 1.16). The catalyst he used also involved BINOL. In this work the catalyst was

Scheme 1.16 Use of Stoichiometric Catalyst Derived from Et_2Zn and BINOL



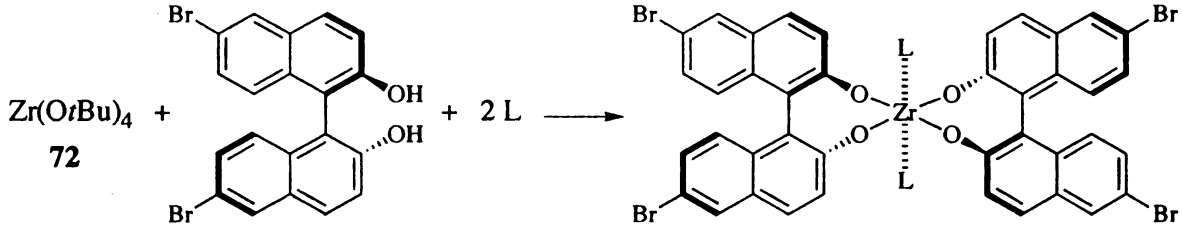
Entry	Temperature (°C)	Yield **71** (%)	ee **71** (%)
1	22	78	93
2	0	72	92
3	−40	66	88
4	−78	63	72

prepared using Et_2Zn and the more reactive imine (**69**) prepared from ethylglyoxylate and 4-methoxy-aniline was the substrate. Whiting found that when the temperature of the reaction was raised, an increase in yield and ee was observed. When the reaction was done at −78°C (entry 4) the reaction gave 63% yield and only 72% ee, however, when done at room temperature (entry 1) the yield was 78% and the ee surprisingly was 93%. This trend is opposite from that which is usually observed in asymmetric catalysis, but has been observed in other cases before.[25, 26] This kind of trend indicates the possibility for more than one catalytic species in the reaction that have different reactivity at different temperatures. Whiting also did several reactions using substoichiometric amounts of catalyst and these results will be discussed in the next section.

1.3.2 Sub-Stoichiometric Catalyst

As discussed earlier, it is not desirable to use stoichiometric amounts of the catalyst to accomplish these reactions. Since the initial reports by Yamamoto using a stoichiometric chiral Lewis acid, many other researchers developed systems that were able to achieve turnover with asymmetric induction. One of the major contributors in this area is Shu Kobayashi at the University of Tokyo, who mainly focused on catalysts that are zirconium BINOL derivatives[27-31]. In his first report[30] he describes the use of a catalyst prepared from $Zr(OtBu)_4$ and 6,6'-dibromoBINOL (Catalyst **74**) (Scheme 1.17).

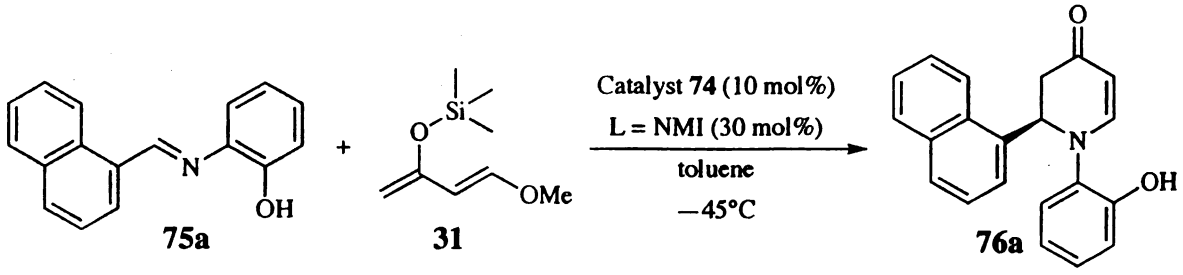
Scheme 1.17 Catalyst Derived from $Zr(OtBu)_4$ and 6,6'-dibromoBINOL



73 Catalyst **74**

He also attempted to use Hf and Ti derivatives but they both gave results that were inferior to Zr. His optimization studies were done using the imine **75a** prepared from 1-naphthaldehyde and 2-aminophenol (Scheme 1.18). The requirement for the phenol

Scheme 1.18 Optimal Conditions Using the Naphthyl Derived Imine

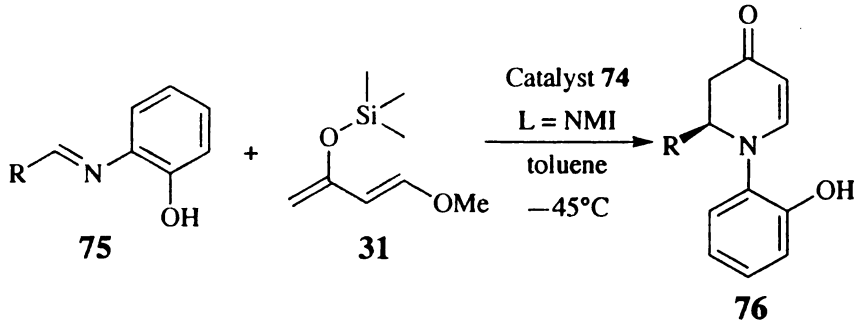


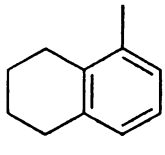
75a **31** **76a**

86% yield
82% ee

group on the imine was proposed to be a result of the fact that zirconium has binding sites available that can accommodate a bidentate substrate. When the imine approaches the metal it will coordinate through the imine nitrogen and the phenol oxygen, activating the imine allowing it to react with the diene. He found that the optimal conditions were those where the catalyst was prepared in toluene using *N*-methyl imidazole (NMI) as the additive L. With the optimal results in hand, he then screened several imines with varying R groups and found that this catalyst was quite good for most substrates (Scheme 1.19). When the catalyst loading was increased to 20 mol%, the ee

Scheme 1.19 Screening of Substrates with the Zr/Br-BINOL Catalyst

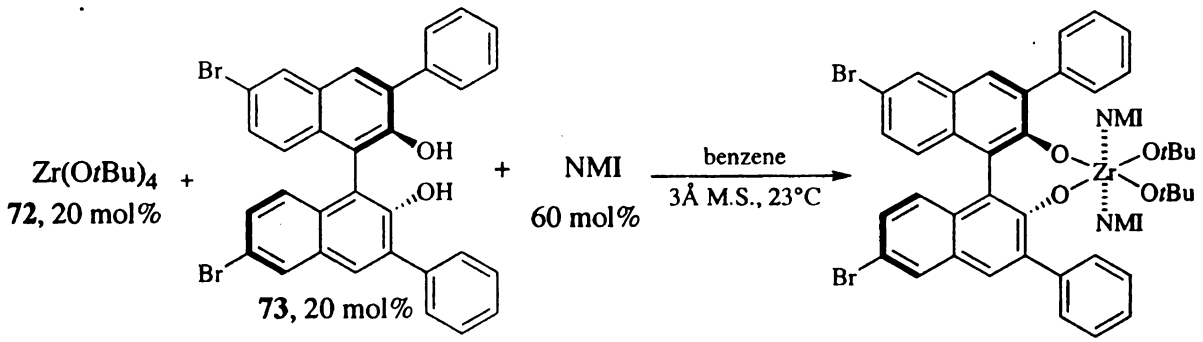


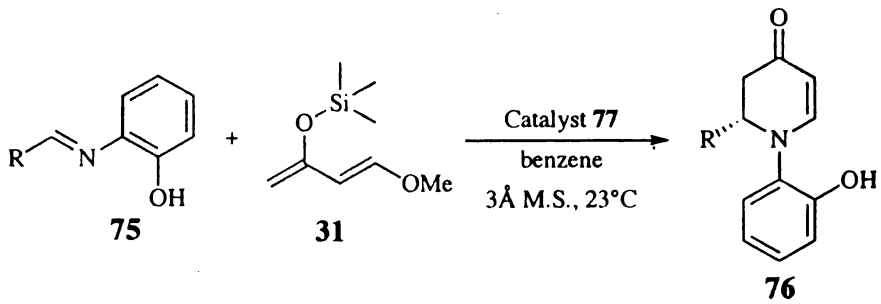
Entry	R	Cat. 74 (mol%)	Yield 76 (%)	ee 76 (%)
1	1-naphthyl (75a)	5	72	67
2	1-naphthyl (75a)	10	86	82
3	1-naphthyl (75a)	20	96	88
4	1-naphthyl (75a)	30	98	89
5	1-naphthyl (75a)	50	88	90
6	 (75b)	10	92	80
7	*o*-tol (75c)	10	81	76
8	*o*-tol (75c)	20	83	82
9	2-thienyl (75d)	10	86	64

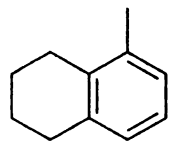
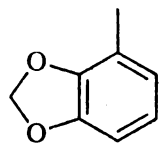
reached 88% for the 1-naphthyl substrate (**75a**) and could only be increased to 90% using 50 mol% catalyst. For the other substrates, moderate ee's were also produced and the yields were all high. The lowest observed ee was when R= 2-thienyl (**75d**) and only gave 64% ee. This was found when 10 mol% catalyst was used and the reaction with increased catalyst loading for this substrate was not reported.

About one year later, Kobayashi reported similar catalysts using different BINOL derivatives.[28] It was observed from this work that a switch in enantioselectivity could be achieved by simply by putting an aryl group in the 3 and 3'-positions of the BINOL ligand (**73**) (Scheme 1.20). This catalyst proved to be just as efficient and selective as the

Scheme 1.20 Switched Enantioselectivity with Different BINOL Derivative





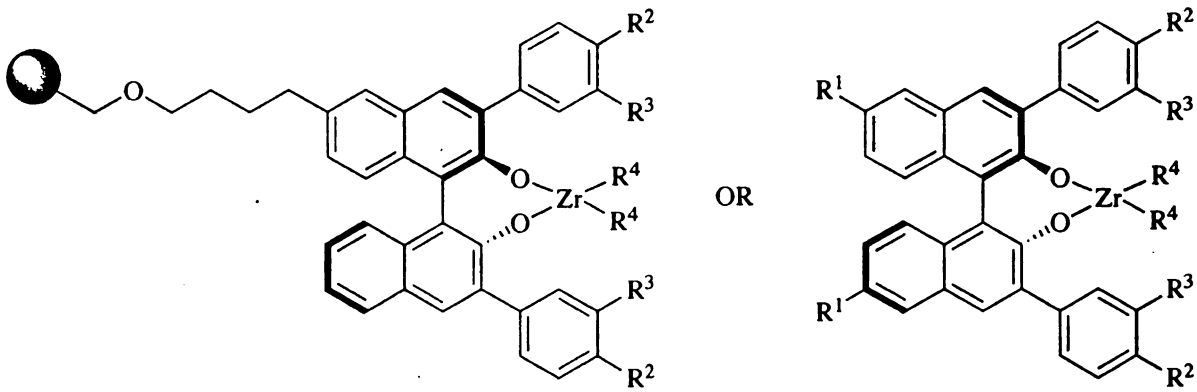
Entry	R	Yield **76** (%)	ee **76** (%)
1	Ph (**75e**)	94	82
2	*o*-tol (**75c**)	93	91
3	1-naphthyl (**75a**)	88	84
4	2-thienyl (**75d**)	74	86
5	cyclohexyl (**75f**)	64	81
6	 (**75b**)	67	85
7	 (**75g**)	90	90

original catalyst and a range of ee's from 81-91% was observed and yields from 64-94% could be achieved for a range of substrates. It is worth mentioning that a major difference between the two reaction conditions was that in the second report, the

reactions could be run at ambient temperature whereas the first system needed much colder conditions (—45°C) in order to achieve acceptable selectivities.

In 2000, Kobayashi reported many other variations of the zirconium/BINOL based catalysts[29] (Figure 1.5). In this report he discussed the use of catalysts where the

Figure 1.5 Other Zirconium/BINOL Catalysts

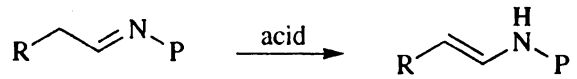


Catalyst **78** Catalyst **79**

BINOL had a variety of different groups in the 3,3' and 6,6' positions (Catalyst **78** and **79**) including one where the BINOL was tethered to a solid support (Catalyst **78**). In addition, he also explored zirconium catalysts where R^4=O*t*Bu or R^4=CN. He screened many combinations of R^1, R^2, R^3, and R^4 and discovered that yields and enantioselectivites around 90% could be achieved. When 20 mol% of the polymer supported catalyst (**78**) where R^2=H and R^3=F was used, the reaction gave 99% yield of **76** and 91% ee was observed. The catalyst was easily recovered by simple filtration and used in subsequent reactions. Using the recovered catalyst for the second run, the reaction gave 97% yield and 90% ee, and the third gave 97% yield and 90% ee. This appears to be the first literature example where a polymer-supported Lewis acid was used to catalyze the *aza*-Diels-Alder reaction. This is a desirable system due to its ease in recoverability and efficiency when reused.

In the previously described work by Kobayashi, it should be noted that he did not report the use of any primary aliphatic aldimines. One issue that arises when attempting reactions using this class of imines is that in the presence of an acid, they are prone to isomerization to the enamine (**81**) (Scheme 1.21). When this isomerization takes place,

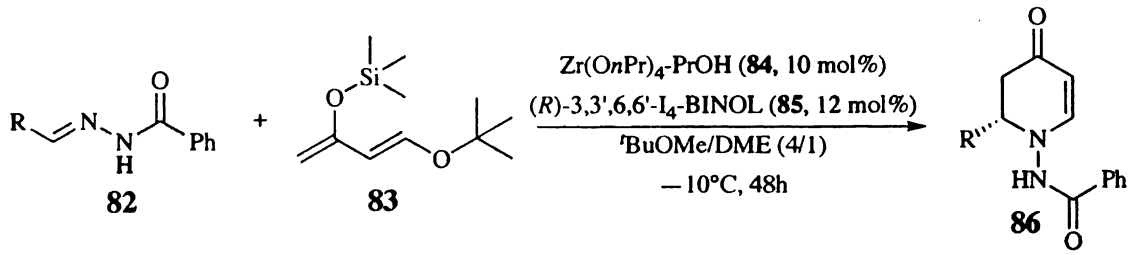
Scheme 1.21 Isomerization of Aliphatic Imines to the Enamine

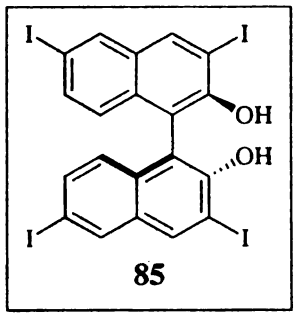


80 **81**

the nitrogen becomes much more basic and will ultimately bind preferentially to the catalyst over the imine eliminating the possiblility for the heteroatom Diels-Alder reaction to occur. This problem was solved by Kobayashi and in a report published in 2005[31]; he described the *aza*-Diels-Alder reaction of the C-N double bond of the hydrazone **82** as a surrogate for an imine. The hydrazones were prepared from primary aliphatic aldehydes and benzoylhydrazines (Scheme 1.22). The hydrazones are stable

Scheme 1.22 *aza*-Diels-Alder Reaction of Hydrazones





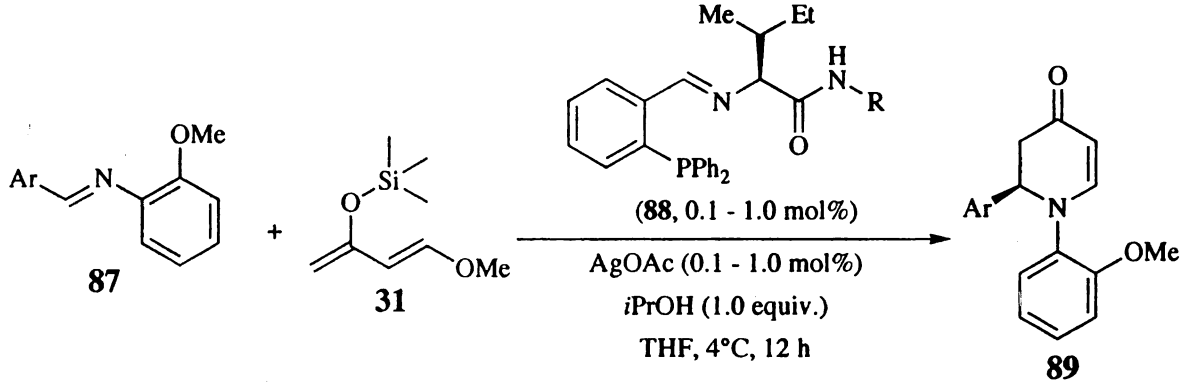
Entry	R	Yield **86** (%)	ee **86** (%)
1	(**82a**)	44	89
2	(**82b**)	31	92
3	(**82c**)	70	91
4	(**82d**)	70	93

and it was found that the rate of the *aza*-Diels-Alder reaction exceeded that of the isomerization of the imine to the enamine. For this reaction, he again used a zirconium catalyst, but this time found it was best to use Zr(O*n*Pr)$_4$-PrOH **84** utilizing (*R*)-3,3',6,6'-tetraiodoBINOL **85** as the ligand. Using 20 mol% Zr and 24 mol% ligand, he optimized this system in toluene at 0°C using the imine prepared from dihydrocinnamaldehyde and benzoylhydrazine (**82c**). Reaction of **82c** with Danishefsky's diene only gave 19% yield and 90% ee. However, if the methoxy group on the diene was replaced with a *t*-butoxy group (**83**), the yield could be increased to 35% with 93% ee observed. Using this diene he screened several solvents and found that a 4:1 ratio of *t*-butyl methyl ether (TBME) and dimethoxyethane (DME) was optimal. Finally, he screened other substrates and all were found to be successful (see Scheme 1.22). The best result was observed when

R=propyl (**82d**) and 93% ee was achieved with good yield. The other substrates gave ee's around 90 but the yield dropped significantly when cyclohexyl (**82a**) and isobutyl (**82b**) groups were on the hydrazone.

All examples discussed to this point used at least 10 mol% catalyst. Prior to a report by Snapper and Hoveyda in 2003[32], ~10 turnovers was the most that was achieved by any catalyst. The silver catalyst developed by Snapper and Hoveyda (Scheme 1.23)

Scheme 1.23 *aza*-Diels-Alder Reaction Using a Silver Catalyst

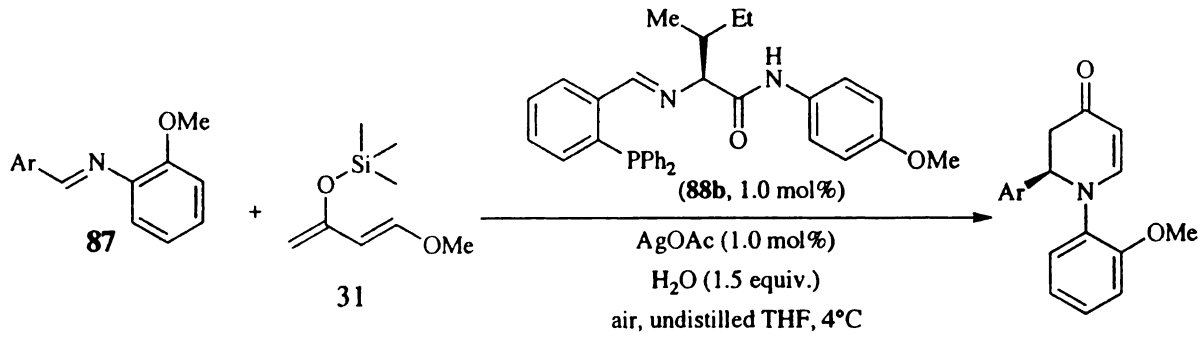


Entry	Ligand/AgOAc (mol%)	Ar	R	Yield **89** (%)	ee **89** (%)
1	1.0	Ph (**87a**)	*o*-$OMeC_6H_4$ (**88a**)	94	93
2	0.5	Ph (**87a**)	*o*-$OMeC_6H_4$ (**88a**)	92	92
3	0.1	Ph (**87a**)	*o*-$OMeC_6H_4$ (**88a**)	78	88
4	1.0	1-naphth (**87b**)	*o*-$OMeC_6H_4$ (**88a**)	94	90
5	0.5	2-naphth (**87c**)	*o*-$OMeC_6H_4$ (**88a**)	>98	95
6	1.0	*p*-$OMeC_6H_4$ (**87d**)	*o*-$OMeC_6H_4$ (**88a**)	86	91
7	1.0	*p*-ClC_6H_4 (**87e**)	*o*-$OMeC_6H_4$ (**88a**)	98	90
8	1.0	*o*-Br C_6H_4 (**87f**)	*o*-$OMeC_6H_4$ (**88a**)	91	89
9	1.0	*m*-$NO_2C_6H_4$ (**87g**)	*o*-$OMeC_6H_4$ (**88a**)	92	91
10	1.0	*p*-$NO_2C_6H_4$ (**87h**)	*o*-$OMeC_6H_4$ (**88a**)	>98	92
11	1.0	2-furyl (**87i**)	*o*-$OMeC_6H_4$ (**88a**)	89	92
12	1.0	*p*-ClC_6H_4 (**87e**)	*p*-$OMeC_6H_4$ (**88b**)	>98% conv.	92
13	1.0	*p*-ClC_6H_4 (**87e**)	*p*-$CF_3C_6H_4$ (**88c**)	75% conv.	88
14	1.0	*p*-ClC_6H_4 (**87e**)	2,6-$Me_2C_6H_4$ (**88d**)	53% conv.	28
15	1.0	*p*-ClC_6H_4 (**87e**)	NHBu (**88e**)	>98% conv.	80
16	1.0	*p*-ClC_6H_4 (**87e**)	Bn (**88f**)	>98% conv.	80
17	1.0	*p*-ClC_6H_4 (**87e**)	NH(OMe) (**88g**)	52% conv.	20

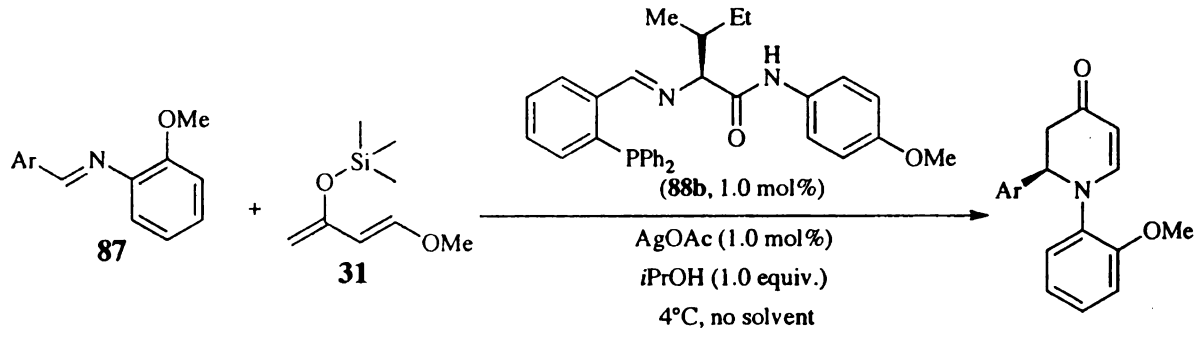
using a chiral phosphoryl-aryl imine amide ligand (**88**) is capable of turning over the *aza*-Diels-Alder reaction of the imine **87a** prepared with benzaldehyde and 2-methoxyaniline with Danishefsky's diene 780 times (i.e. using 0.1 mol% catalyst, the yield was 78%). The reaction was very general for aromatic imines when R on the ligand was *ortho*-$OMeC_6H_4$ (**88a**). Using 0.5 or 1.0 mol% of this catalyst/ligand combination, a range of yields from 86% to nearly quantitative could be achieved with ee's ranging from 89 to 95%. Reactions were then studied to test the effect of the R group on the amide nitrogen of the ligand. The selectivity remained in the 80's for each of the different R groups with the exception of the bulky aryl group (2,6-$Me_2C_6H_4$) (**88d**) and R = NH(OMe) (**88g**) which dropped the ee into the 20's. The results from the screening and catalyst loading studies demonstrate that this reaction is an attractive one from the standpoint of turnovers and asymmetric induction.

Two other reactions were also attempted which makes this system even more attractive. One is the reaction run in air using undistilled THF and the other without the use of any solvent (Scheme 1.24). The reaction using undistilled solvent still gave ee's in

Scheme 1.24 Use of Silver Catalyst with No Solvent or Undistilled THF in Air



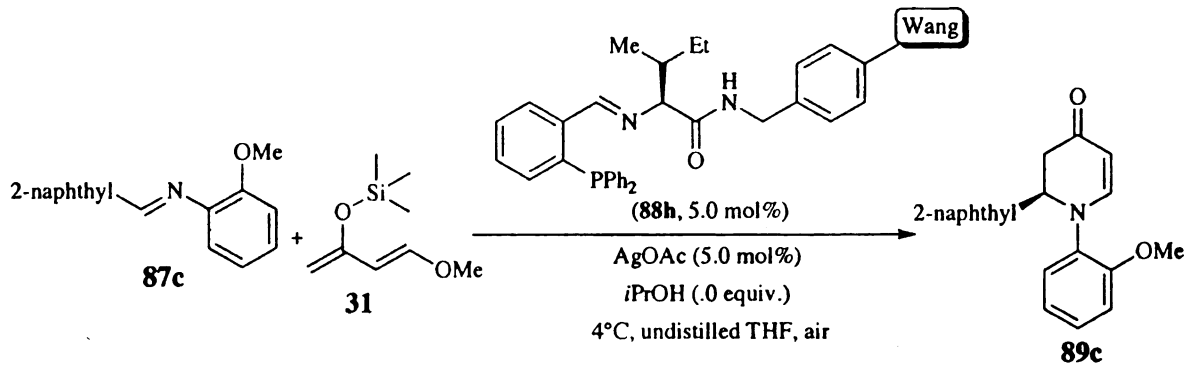
Ar = 2-Naphth (**87c**) 82% yield, 94% ee (**89c**)
Ar = *p*-Cl-C_6H_4 (**87e**) 81% yield, 90% ee (**89e**)



Ar = *p*-OMe-C_6H_4 (**87d**) 66% yield, 90% ee (**89d**)
Ar = *p*-NO_2-C_6H_4 (**87h**) 88% yield, 80% ee (**89h**)

the 90's with good yields. When no solvent was used, the yields were still good, and for *p*-OMe-C_6H_4 (**88b**) 90% ee was achieved. Lastly, Hoveyda, et. al. attempted to use a ligand tethered to solid support (**88h**) which could be easily recovered, similar to the work done by Kobayashi in 2000 (Scheme 1.25). This catalyst was used for the reaction

Scheme 1.25 *aza*-Diels-Alder Reaction Using Silver Catalyst with a Recoverable Ligand

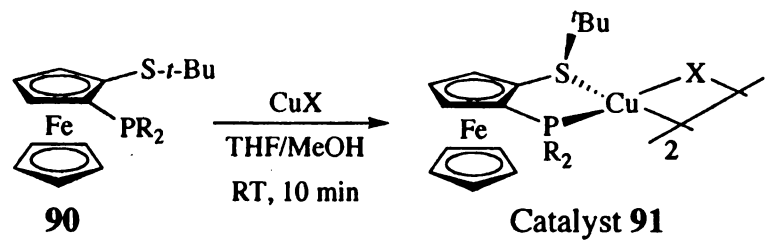


96% yield, 86% ee
after ligand recycled 5 times

and recycled five times and when used again, 96% yield and 86% ee was achieved.

Each of the remaining Lewis acid catalyzed *aza*-Diels-Alder reactions to be discussed will deal with the use of activated imines. The imines used contain either an electron-withdrawing group on the nitrogen or an ester on the imine carbon, making the imine carbon more electrophilic and thus more reactive. The work done by Carrretero, et. al. employed a copper (I) complex with planar chiral phosphinò sulfenyl ferrocene[33] (**90**) (Scheme 1.26). Using the tosyl imine prepared from benzaldehyde (**92a**) he

Scheme 1.26 Copper Phosphino Sulfenyl Ferrocene Catalyst



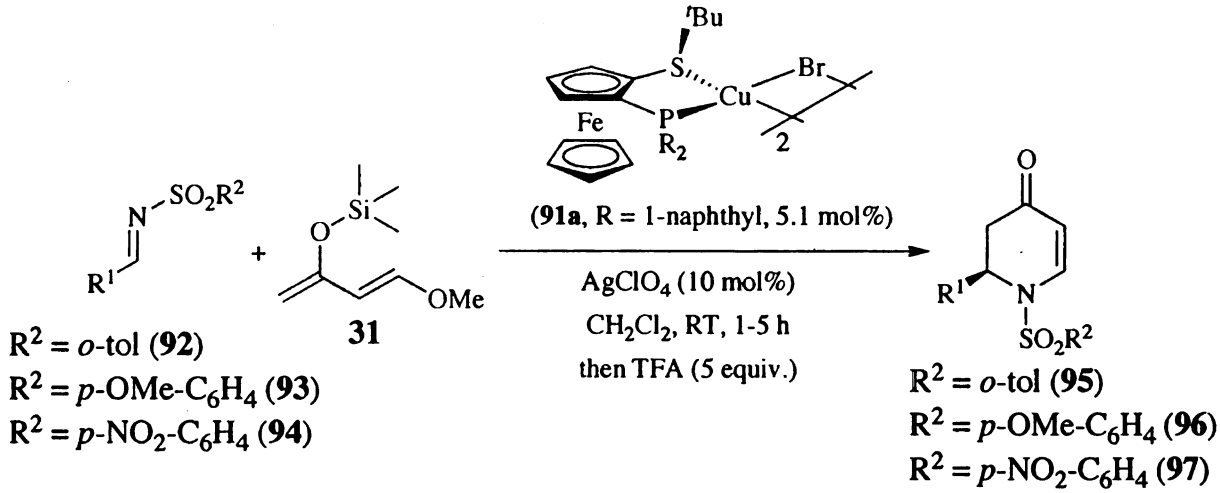
90 Catalyst **91**

X = Cl or Br
R = *p*-F-C_6H_4, 2-furyl, Cy, *o*-Tol, or 1-naphthyl

discovered that the best catalyst was where X=Br and R=1-naphthyl (**91a**). Using 5.1 mol% of this catalyst and 10 mol% $AgClO_4$ as a halogen scavenger, a 93% ee for **95a**

could be obtained when the reaction was run at room temperature and 97% ee was observed at −20°C. Using this catalyst, he then screened several different imines (Scheme 1.27). The reaction was found to be fairly general for the imines screened and a

Scheme 1.27 Substrate Scope Using Copper Phosphino Sulfenyl Ferrocene Catalyst

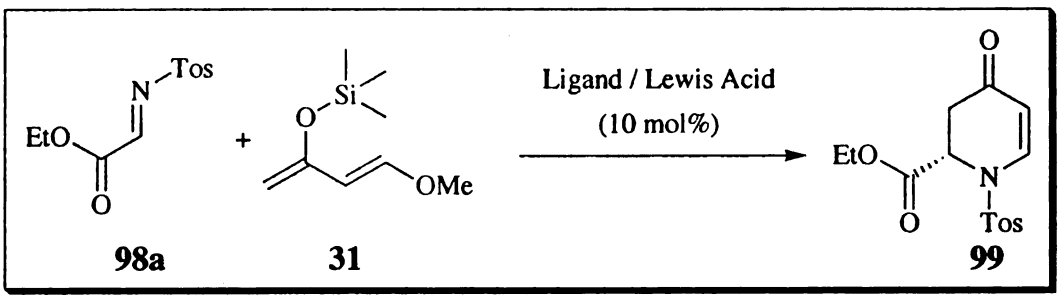


Entry	R^1	R^2	Product	Yield (%)	ee (%)
1	Ph (**92a**)	*p*-tol	**95a**	90	93
2	*o*-tol (**92b**)	*p*-tol	**95b**	82	93
3	*p*-F-C_6H_4 (**92c**)	*p*-tol	**95c**	78	88
4	*p*-OMe-C_6H_4 (**92d**)	*p*-tol	**95d**	76	91
5	*p*-NMe_2-C_6H_4 (**92e**)	*p*-tol	**95e**	39	93
6	2-naphthyl (**92f**)	*p*-tol	**95f**	85	86
7	PhCH=CH (**92g**)	*p*-tol	**95g**	66	83
8	*n*-Pr (**92h**)	*p*-tol	**95h**	65	73 (−20°C)
9	Ph (**93a**)	*p*-OMe- C_6H_4	**96a**	61	94
10	*o*-tol (**93b**)	*p*-OMe- C_6H_4	**96b**	78	90
11	2-naphthyl (**93c**)	*p*-OMe- C_6H_4	**96c**	56	82
12	PhCH=CH (**93d**)	*p*-OMe- C_6H_4	**96e**	58	76
13	Ph (**94a**)	*p*-NO_2- C_6H_4	**97a**	58	90

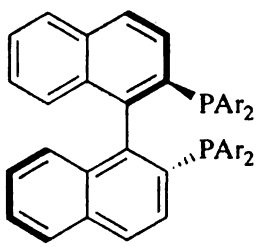
range of yields from 39-90% was achieved with ee's ranging from 73-94%. It was also found that in some cases, the lower ee's could be increased by simply running the reaction at lower temperature (i.e. entry 7, at −20°C gave 96% ee).

Jorgensen, et. al. also published catalytic versions of the *aza*-Diels-Alder reaction with the extremely reactive imines derived from and bearing a tosyl group on the nitrogen[34, 35] (**98a**). Using a wide variety of chiral ligands (Scheme 1.28) he screened

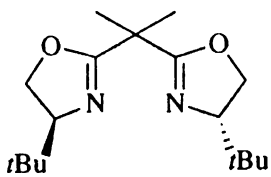
Scheme 1.28 Ligands Screened by Jorgensen



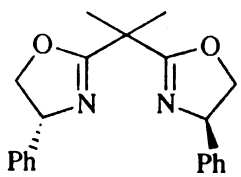
98a **31** **99**



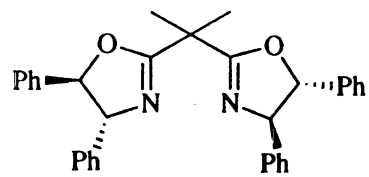
Ar = Ph (**100**)
Ar = *p*-Tol (**101**)



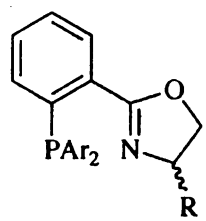
102



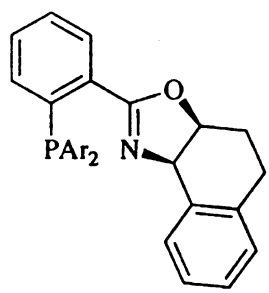
103



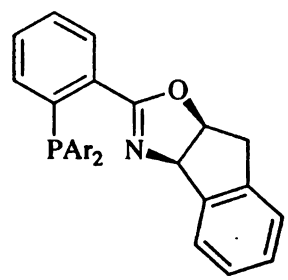
104



Ar = Ph, R = Ph (*R*) (**105**)
Ar = Ph, R = *i*Pr (*S*) (**106**)
Ar = Ph, R = *t*Bu (*S*) (**107**)
Ar = *p*-tol, R = *t*Bu (*S*) (**108**)



Ar = Ph (**109**)
Ar = *p*-tol (**110**)
Ar = 2,4-xylene (**111**)

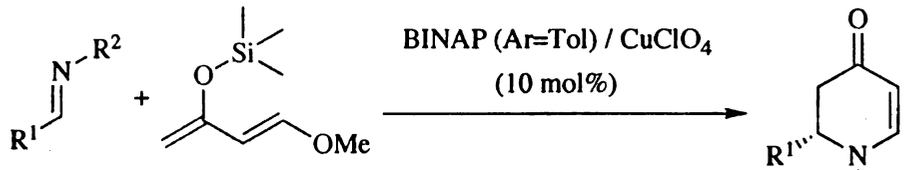


Ar = Ph (**112**)
Ar = *p*-tol (**113**)
Ar = 2,4-xylene (**114**)

$CuClO_4 \cdot 4$ MeCN, 2 $CuOTf \cdot C_6H_6$, $Cu(OTf)_2$, $AgSbF_6$, AgOTf, $AgClO_4$, $Pd(SbF_6)_2$, $Pd(ClO_4)_2$, $Pd(OTf)_2$, $RuSbF_6$, and $Zn(OTf)_2$ as Lewis acids for this reaction. The copper (I) Lewis acids gave the best enantioselectivities (61-80%) followed by the silver Lewis acids which gave ee's from 30% to 34%. Zn, Pd, and Cu (II) all gave ee's in the teens or less. In his initial publication,[34] he found that the best ligand and Lewis acid combination

was the BINAP ligand (**101**) where Ar= Tol with $CuClO_4 \cdot 4$ MeCN giving 68% yield and 80% ee. In a subsequent publication[35], he studied the effectiveness of the phosphino-oxazoline ligands (**105-114**) with the Lewis acid $CuClO_4 \cdot 4$ MeCN. Using chiral ligands **107** and **108**, the ee's could be increased to 87%, which is slightly better than the 80% produced using the BINAP ligand. He then used the BINAP ligand (**101**) where Ar = Tol with $CuClO_4$ to screen different imines using THF or CH_2Cl_2 as the solvent (Scheme 1.29). The effect of solvent proved to be purely substrate dependant as indicated by entry

Scheme 1.29 Screening of Substrates using the Cu/BINAP Catalyst



R^2 = Tos (**98**) **31**
R^2 = COOEt (**115**)
R^2 = *o*-MeO-Ph (**116**)
R^2 = Ph (**117**)

99

Entry	R^1	R^2	Temperature (°C)	Yield/ee **99** (%) (THF)	Yield/ee **99** (%) (CH_2Cl_2)
1	COOEt (**98a**)	Tos	—78	80/79	89/26
2	COOEt (**115a**)	COOEt	—78	10/79	23/77
3	COOEt (**116a**)	*o*-MeO-Ph	RT	25/60	23/58
4	COOEt (**117a**)	Ph	RT	61/86	78/91
5	COOEt (**116a**)	*o*-MeO-Ph	RT	93/15	89/72
6	COOEt (**116a**)	*o*-MeO-Ph	—78 to RT	82/16	75/78
7	Ph (**98b**)	Tos	RT	65/46	65/48

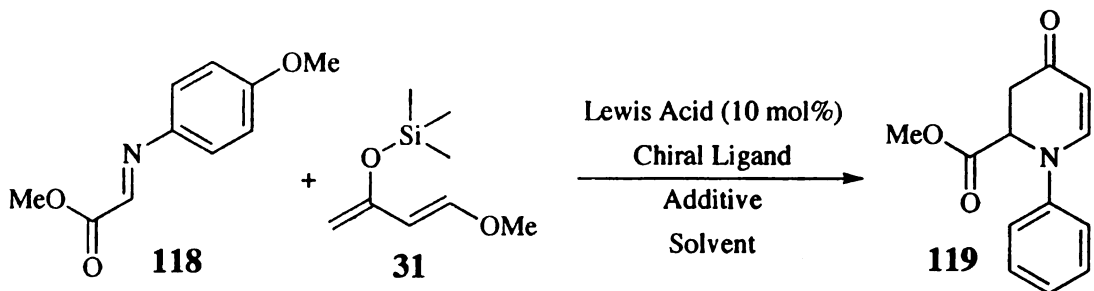
1 versus entry 6. In entry 1, the ee went from 79% to 26% by switching from THF to CH_2Cl_2 and in entry 6, the opposite effect was observed as the ee went from 16% in THF to 78% in CH_2Cl_2.

With respect to the yield, it changed from 82% to 75% upon switching from THF to CH_2Cl_2 for R^1 = COOEt, R^2 = *o*-MeO-Ph (**116a**, entry 6) but for R^1 = COOEt, R^2 = Tos

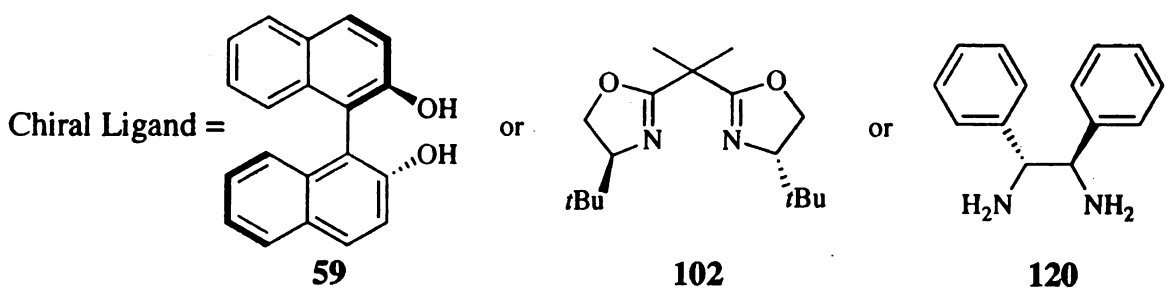
(**98a**, entry 1), the yield went from 80% in THF to 89% in CH_2Cl_2. Jorgensen's work has proven the effectiveness of copper (I) Lewis acids with a variety of different ligands for the *aza*-Diels-Alder reaction of activated imines.

Andrew Whiting has also contributed to the field studying the reactive imines (**118**) prepared from the glyoxylate aldehydes and 4-methoxy aniline[24, 36]. In his initial report[36], he screened $Yb(OTf)_3$, $Cu(OTf)_2$, MgI_2, and $FeCl_3$ as possible Lewis acids in conjunction with BINOL (**59**), a bis-oxazoline (**102**) and a chiral diamine (**120**). Using a combinatorial approach, he explored different combinations of solvents, additives, Lewis acids and ligands (Scheme 1.30). He found that the chiral diamine (**120**) was the best

Scheme 1.30 Whiting's Combinatorial Approach



Lewis acid = $Yb(OTf)_3$, $Cu(OTf)_2$, MgI_2, or $FeCl_3$
Additive = 2,6-Lutidine, 4Å M.S., or none
Solvent = Toluene, MeCN, or CH_2Cl_2



ligand in conjunction with MgI_2, $Yb(OTf)_3$, and $Cu(OTf)_2$, whereas the bis-oxazoline (**102**) was best for $FeCl_3$. The effects of additives and solvents used for these ligand/Lewis acid combinations are presented in the following table (Table 1.1) with

Table 1.1 Best Results from Combinatorial Study

Entry	Lewis Acid	Ligand	Additive	Solvent	Yield **119** (%)	ee **119** (%)
1	MgI_2	**120**	2,6-Lutidine	MeCN	64	97
2	$Yb(OTf)_3$	**120**	2,6-Leutidine	Toluene	60	87
3	$Cu(OTf)_2$	**120**	none	MeCN	58	86
4	$FeCl_3$	**102**	4Å M.S.	CH_2Cl_2	67	92

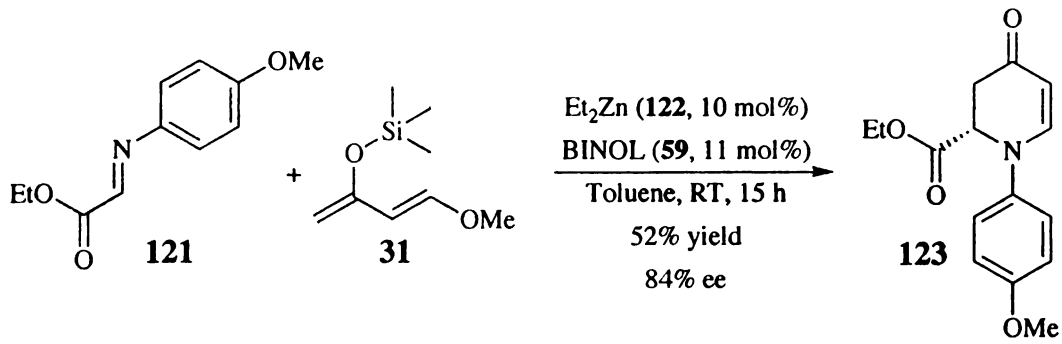
yields ranging from 58-67% and ee's from 86-97%.

Interestingly, about 5 years later the same author published a corrigendum to this paper[37] indicating that the results in Table 1.1 were not reproducible. For MgI_2 only a range of ee's from 0% to 55% could be obtained and the remainder of the entries when repeated only gave racemic product.

In a subsequent report in 2004[24], Whiting attempted to find a metal Lewis acid that would produce acceptable yields and/or ee's when BINOL (**59**) was used as the ligand for the *aza*-Diels-Alder reaction of the imine **121** derived from ethylglyoxylate and 4-methoxyaniline and Danishefsky's diene. Initially Whiting screened Et_3Al, Et_2AlCl, Et_2Zn, Et_3B, $(i\text{PrO})_3B$, $(PhO)_3B$, and $(i\text{PrO})_4Ti$. He found that the only two Lewis acids that gave any asymmetric induction were Et_3Al and Et_2Zn. Et_3Al gave 65% yield and 15% ee whereas Et_2Zn gave 57% yield and 36% ee. One entry relevant to the present work was the attempt made using triphenylborate. This reaction failed to produce any product. There was not a detailed experimental procedure outlined for this reaction so it was not clear at what temperature he ran this reaction.

Due to the better selectivity with Et_2Zn, Whiting prepared a catalyst from Et_2Zn and BINOL and optimized the reaction of imine **121** with Danishefsky's diene using 10 mol% catalyst (Scheme 1.31). He found that the best ee of **123** that could be achieved

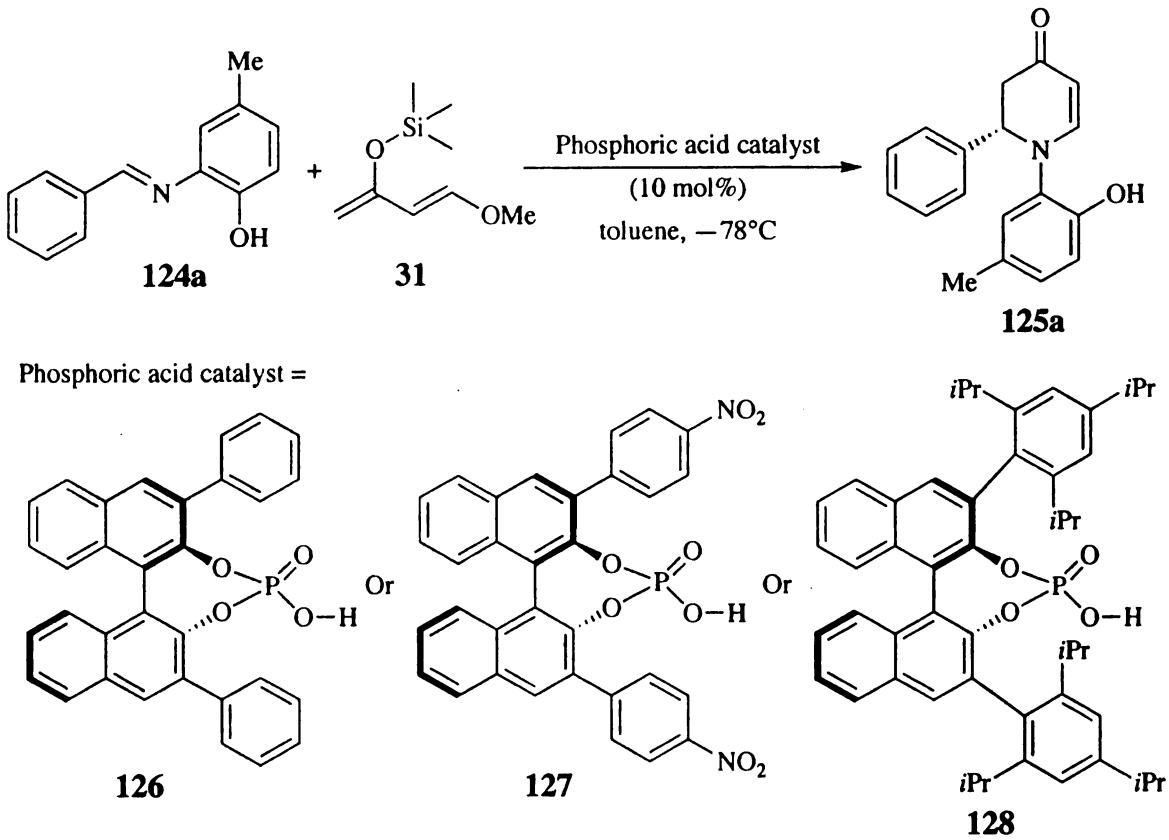
Scheme 1.31 Whiting's Substoicheometric Approach



was 84% with 52% isolated yield using toluene as the solvent and running the reaction at room temperature for 15 hours. Comparing this work from Whiting to the work of Jorgensen with the BINAP ligand[34, 35] on this class of imine, it can be determined that Jorgensen's system is slightly better since he has examples where ≥90% ee could be achieved.

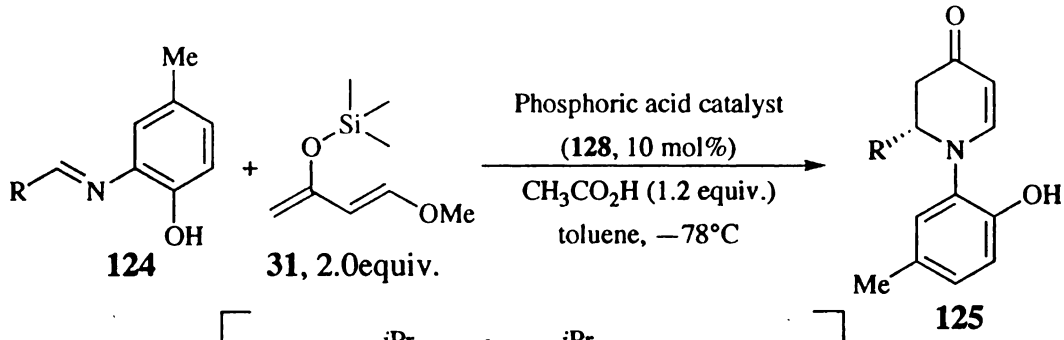
This concludes the discussion of work previously done using chiral Lewis acid catalysts. However, recent reports with organocatalysts also have described systems that can produce good asymmetric induction with sub-stoichiometric amounts of catalyst. Akiyama, et. al. have reported success with chiral Brønsted acids[38] (Scheme 1.32) that are

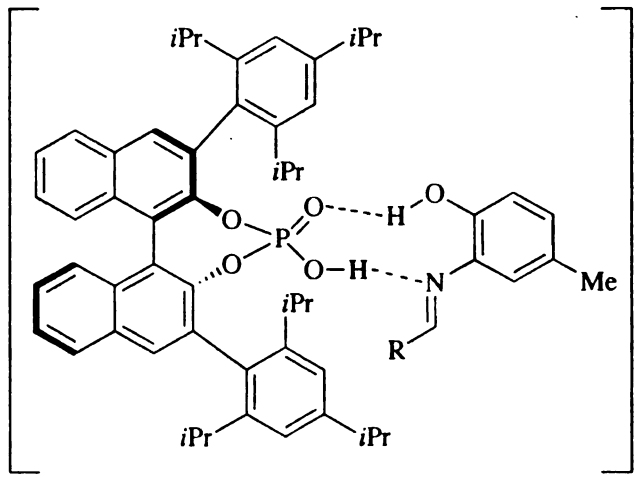
Scheme 1.32 *aza*-Diels-Alder Using Catalytic Chiral Brønsted Acid



phosphoric acid derivatives of a 3,3'- diarylBINOLs (**126-128**). Upon initial screening of the reactions using 10 mol% of each of these catalysts, it was found that catalyst **128** with the bulky tri-isopropyl aryl groups in the 3,3'-positions gave much better selectivity (42% versus <5% ee). This reaction was run at −78°C in toluene but only gave 32% yield. In order to optimize the yield as well as the ee, several additives and solvents were screened. The optimization studies ultimately indicated that toluene was the best solvent for the reaction using 10 mol% phosphoric acid (**128**), 1.2 equivalents acetic acid, and a reaction temperature of −78°C. Using these optimal conditions, he then studied the substrate scope for the *aza*-Diels-Alder reaction using the chiral phosphoric Brønsted acid **128** (Scheme 1.33). All the reactions produced significant quantities of product with yields

Scheme 1.33 Substrate Scope using the Chiral Phosphoric Brønsted Acid





Proposed transition state

Entry	R	Reaction time (h)	Yield **125** (%)	ee **125** (%)
1	Ph (**124a**)	18	99	80
2	*p*-IC_6H_4 (**124b**)	24	86	84
3	*p*-BrC_6H_4 (**124c**)	13	100	84
4	*p*-ClC_6H_4 (**124d**)	35	72	84
5	*p*-FC_6H_4 (**124e**)	13	77	78
6	*p*-$CF_3C_6H_4$ (**124f**)	21	82	81
7	*o*-BrC_6H_4 (**124g**)	10	96	80
8	*o*-ClC_6H_4 (**124h**)	12	100	76
9	1-naphthyl (**124i**)	12	100	91

ranging from 72% to quantitative. The selectivities were also quite good for this catalyst ranging from 76 to 91% ee. The first application of a chiral Brønsted acid catalyst to the *aza*-Diels-Alder reaction proved to be successful and is a nice addition to the Lewis acid based catalyst systems.

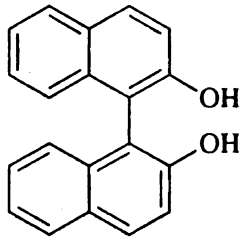
1.4 VAPOL and VANOL Ligands

As discussed above, there have been many catalysts used successfully in the *aza*-Diels-Alder reaction with most derived from a range of Lewis acidic metals and a diverse array of chiral ligands. However, there is still room for improvement via either continued development of existing catalyst systems or the development of a new catalyst system. As can be seen from the history of the catalytic asymmetric *aza*-Diels-Alder reaction, summarized above, BINOL and its many derivatives have been key to many successful catalytic systems.

The C2 symmetric ligand BINOL is very popular and has been shown to be very successful in many areas of asymmetric catalysis[39, 40] beyond the *aza*-Diels-Alder reaction. The way BINOL ligand function is through the coordination or binding of the diol to a metal center. The substrate then coordinates to the metal and the chiral ligand should preferentially allow the approach of another reactant from one face. However, the bulk of the space that is asymmetrically discriminated is on the opposite side of the chiral axis of BINOL as the metal center. The Wulff group developed the vaulted biaryl ligands VANOL and VAPOL[41-46] (Figure 1.6) to surmount this limitation of BINOL.

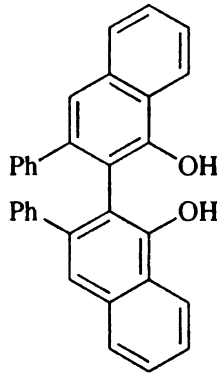
Figure 1.6 C-2 Symmetric Biaryl Ligands

Linear Biaryl

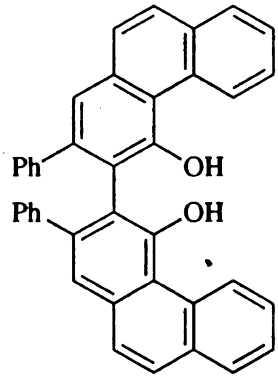


BINOL
Binaphthol
59

Vaulted Biaryls



VANOL
Vaulted Binaphthol
129

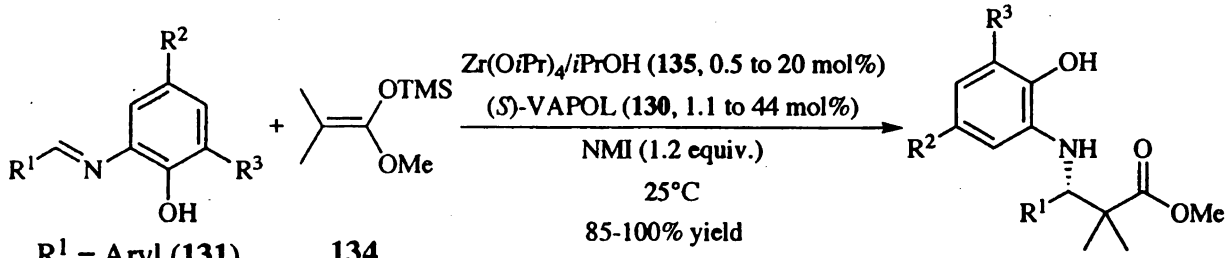


VAPOL
Vaulted Biphenanthrol
130

The vaulted nature of VANOL and VAPOL was envisioned to create a chiral pocket around the coordinated substrate that would aid in the facial selectivity of reaction. Before the present work on the *aza*-Diels-Alder reaction, the success of these ligands was limited to the Diels-Alder reaction,[47-49] imino-aldol reaction,[50] Baeyer Villager reaction,[51] and the aziridination reaction.[52-57]

For each of these reactions, a variety of Lewis acids were used including zirconium, aluminum, and boron. In the imino-aldol reaction[50] (Scheme 1.34), a catalyst

Scheme 1.34 Imino-Aldol Reaction



R^1 = Aryl (**131**)
R^2 = H or Me (**132**)
R^3 = H or Me (**133**)

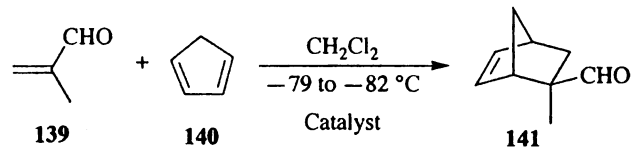
134

R^1 = Aryl (**136**)
R^2 = H or Me (**137**)
R^3 = H or Me (**138**)

similar to those described for Kobayashi's *aza*-Diels-Alder work was employed using VAPOL. The utility of VANOL for this reaction has not been studied.

Scheme 1.35 Diels-Alder Reaction and Baeyer Villager Reaction

Diels-Alder Reaction

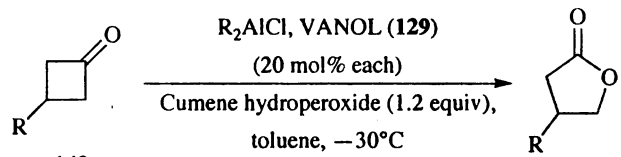


139 **140** **141**

Catalyst = Et_2AlCl + Ligand

Ligand	exo/endo	% ee exo **141**	yield **141** (endo + exo)
(S)-VAPOL (**130**)	98:2	97.8	100
(S)-VANOL (**129**)	92:8	17	85
(*R*)-BINOL (**59**)	???	???	???

Baeyer Villager Reaction



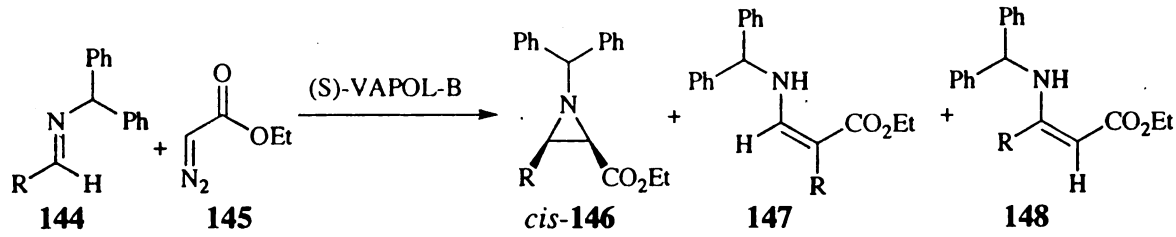
142 **143**

up to 96% yield
up to 84% ee
14% ee with VAPOL (**130**)

The Diels-Alder reaction[47-49] and Baeyer Villager[51] reactions (Scheme 1.35) both employed R_2AlCl as the Lewis acid. For the Diels-Alder reaction, both VANOL (**129**) and VAPOL (**130**) were screened and it was found that VAPOL was clearly the superior ligand for this transformation. The reaction with VAPOL gave 98% ee with quantitative yield whereas VANOL only gave 17% ee and a slightly worse *exo* to *endo* selectivity. For the Baeyer Villager reaction, upon initial screening, VAPOL gave only 14% ee whereas VANOL gave 80% ee. With further optimization, the VANOL catalyst was able to provide yields of up to 96% and the maximum ee observed was 84%.

The other reaction that was found to be very successful using VANOL and VAPOL derived catalyst was the aziridination reaction[52-57] (Scheme 1.36). For this

Scheme 1.36 Aziridination Reaction

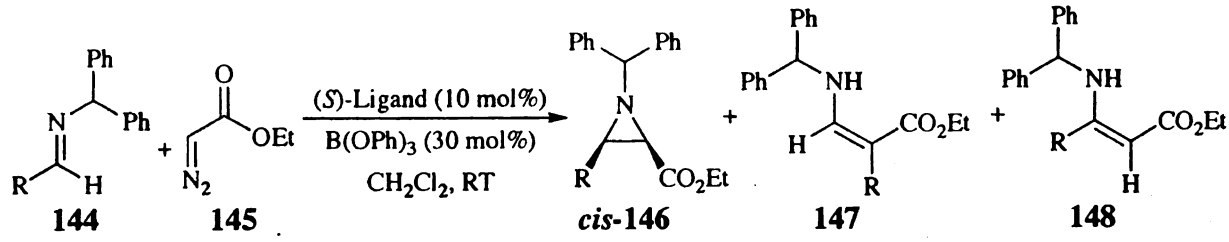


reaction, the ligand was combined with a boron species to prepare the chiral Lewis acid. In the initial report[57], it was discovered that the benzhydryl protecting group on the nitrogen in imine **144** was important for asymmetric induction to be realized in any substantial amount. VAPOL was combined with BH_3·THF to prepare the catalyst and the reaction proved to be very successful. For this catalyst, the *cis/trans* selectivity was found to be 3:1 to >50:1 for a range of substrates with ee's all in the 90's for the *cis* isomer. The reaction of imines with ethyl diazoacetate are known to give enamine side products, however the yield of the enamines was always less than or equal to 15% with the VANOL and VAPOL catalysis.

It was later discovered that the BH_3·THF slowly decomposes to produce significant amounts of tributylborate. Subsequent work[56] revealed that catalysts derived from $B(OPh)_3$ are superior to those from the BH_3·THF complex.

Upon screening many different imines **144**, that were prepared from aldehydes and aminodiphenylmethane, it was surprising to find that for this reaction that there is not much difference between the VAPOL and VANOL catalysts in terms of selectivity or turnovers (Scheme 1.37)[56].

Scheme 1.37 Comparison of VAPOL and VANOL in the Aziridination Reaction



144 **145** ***cis*-146** **147** **148**

Entry	R	Ligand	reaction time (h)	Yield *cis*-**146** (%)	ee *cis*-**146** (%)	**146** *cis/trans* ratio	Yield **147** (%)	Yield **148** (%)
1	Ph (**144a**)	VAPOL	48	77	95	>50:1	4.4	1.7
2	Ph (**144a**)	VANOL	0.5	85	96	>50:1	3.3	1
3	*p*-BrC_6H_4 (**144b**)	VAPOL	5	91	98	>50:1	3.4	2.2
4	*p*-BrC_6H_4 (**144b**)	VANOL	1	85	98	>50:1	8	3
5	*o*-$OMeC_6H_4$ (**144c**)	VAPOL	14	69	94	40:1	11.1	7.1
6	*o*-$OMeC_6H_4$ (**144c**)	VANOL	16	65	91	>50:1	6	4
7	3,4-$(OAc)_2C_6H_3$ (**144d**)	VAPOL	20	85	96	>50:1	<1	<1
8	3,4-$(OAc)_2C_6H_3$ (**144d**)	VANOL	5	83	97	>50:1	<1	<1
9	2-furyl (**144e**)	VANOL	16	55	93	>50:1	<1	<1
10	1-naphthyl (**144f**)	VAPOL	12	87	92	>50:1	3.8	0.3
11	*n*-propyl (**144g**)	VAPOL	20	54	91	>50:1	8.3	9.2
12	*n*-propyl (**144g**)	VANOL	5	60	90	>50:1	6.7	9.2
13	*tert*-butyl(**144h**)	VAPOL	12	78	91	40:1	<1	<1
14	*tert*-butyl (**144h**)	VANOL	5	77	97	>50:1	<1	<1
15	cyclohexyl (**144i**)	VAPOL	8	74	94	38:1	<1	<1

Although the structures of VAPOL and VANOL are very similar with the only difference being the extra fused benzene ring in the phenanthrene unit of VAPOL, their utility as ligands has been shown to be quite different, and somewhat unpredictable. It was found that VAPOL was significantly better in the Diels-Alder reaction but in the Baeyer Villager reaction VANOL was much better. In the aziridination reaction, the two catalysts were very similar in their effiency, however VANOL was able to produce slightly better enantioselectivity in some cases.

The inspiration for the *aza*-Diels-Alder reaction stemmed from the results observed in the aziridination. Success for the aziridination was observed when studying

the imines prepared from benzaldehyde and aminodiphenylmethane using boron as the Lewis acid in conjunction with the chiral ligands VANOL and VAPOL. The study of the *aza*-Diels-Alder reaction was then undertaken for this class of imines using the vaulted ligands in conjunction with metal Lewis acids as the catalyst.

CHAPTER 2

OPTIMIZATION OF THE *AZA*-DIELS-ALDER REACTION

As discussed in the previous chapter, the *aza*-Diels-Alder reaction has gained significant attention in the past 15 years[15, 58-61]. Since the first example of the catalytic asymmetric Lewis acid catalyzed example in 1992,[19] many groups have contributed to the field. The main problem with Yamamoto's work was that he was unable to get the reaction to turnover and hence needed a stoicheometric amount of the catalyst. As is the case with many asymmetric reactions, the metals and/or ligands can be very expensive. In this respect, it is desirable in any case, to be able to obtain the highest possible turn over numbers (TONs) and since 1992, contributions have been made from groups all around the world towards finding a solution to this problem. In addition to increasing TONs, it is desirable to develop high yielding reactions, which produce high asymmetric induction. With the appropriate combination of protecting group on the nitrogen, and catalyst, it has been shown that high yields and high asymmetric induction can be afforded with good TONs as well. The bar has been set high for this reaction class as both yields and ee's have been achieved near 100% and the best TONs achieved being 780.[32] The TON of 780 achieved by Hoveyda was very high and uses an exceptional silver catalyst system, but most other examples produced TONs of 5 to 20 with catalyst loadings around 5-20 mol%. In order to have a reaction that is on par with systems in the

literature, it is important to try and obtain numbers equal to or higher than those in systems previously reported.

When beginning to think about developing a new reaction, several items need to be considered in reaction optimization. For a catalytic asymmetric reaction, the first, and probably most important item is which catalyst is going to be employed. The catalyst can either be developed specifically for the type of substrate that is going to be studied or a substrate has to be used which can be predicted to interact favorably with the catalyst. In the work done by Kobayashi,[28-31] for example, he used zirconium as the metal. In this case, he used the phenolic protecting group on the nitrogen of the imine so that the substrate could occupy two free sites on the metal. The opposite scenario was seen in the Wulff group in the development of the aziridination.[53, 55-57] The catalyst was developed first and studies then indicated that some version of a benzhydryl protecting group was needed on the imine nitrogen to induce a favorable interaction of the imine with the catalyst. In any event, the catalyst and substrate interaction is a very important aspect of these reactions. It is this interaction that will ultimately activate the substrate making it more reactive in asymmetric reactions. It is also important that the lowest energy (or most favorable) substrate-catalyst complex allow the second reagent to approach the coordinated substrate only from one face. One other issue for reactions of imines is that the resulting products are in many cases amines, which brings up the importance of catalyst loading. As discussed in Chapter 1, the sp^3 nitrogen in amines is more basic than the sp^2 nitrogen of the imine, which oftentimes makes turnover difficult to achieve causing the need for higher catalyst loading. When using metals with several coordination sights, it can also be valuable to think about different additives and how

they may help or hurt the reaction. As mentioned before, the desirable situation is that where the catalyst-substrate coordination is such that the reaction will happen preferentially from one face over the other. Although there are exceptions, it is often observed that reactions will give increased selectivity at lower temperatures. This is presumably due to the fact that at colder temperatures, the rate of the reaction slows down, leading to a greater differentiation between the opposing transition states. Another variable, which can prove to be very important, is the solvent or solvent combination that is used in the reaction. Solubility is probably the first issue to consider. If the reagents were insoluble in the solvent, the reaction would only be able to occur at the interface of the phases, which makes the reaction much less efficient. In addition to solubility, the type of solvent used can play an important role in the reaction. In cases where the metal catalyst has sufficient coordination sites, coordinating solvents could potentially be favorable for the reaction, but for lower coordination metals, the presence of a coordinating solvent could compete with the substrate for binding to the metal center. For boron or aluminum catalysts, there is only one binding site available so a coordinating solvent such as THF, ether, acetonitrile, or ethanol, etc. would be expected to be detrimental to the outcome of the reaction. Concentration can also influence the outcome of a reaction. It is expected that when the concentration is increased, the reaction rates would increase and thus potentially produce a higher yield of the desired product in less reaction time. However, at increased concentration, solubility could present a problem especially when reactions are run at low temperatures. A few other items to keep in mind when developing conditions for a new reaction are stoichiometry of reagents, how the reagents are added, the order in which reagents are added, and lastly,

reaction time. All of these items need to be considered when developing a new system for a reaction and each can effect the yield or selectivity either in a positive or negative way depending on the variable.

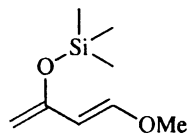
The VAPOL (**130**) and VANOL (**129**) ligands were developed in the Wulff group and have been previously used as ligands in several catalytic asymmetric reactions including Diels-Alder[47-49], imino-aldol-reaction[50], Baeyer Villager[51], and aziridination[52, 55-57] reactions. In addition to trying to add to the collection of catalytic asymmetric *aza*-Diels-Alder reactions present in the literature, it was also desirable to find another reaction where one or both of the ligands developed in our group could be utilized. When this thesis work was begun in 2001, one of the goals was to determine if VAPOL (**130**) and VANOL (**129**) could be used as efficient ligands for the catalytic asymmetric *aza*-Diels-Alder reaction.

Preliminary results, which were obtained by Jon Antilla just before he graduated in 2000, indicated that it would be worthwhile to explore this reaction (see appendix).

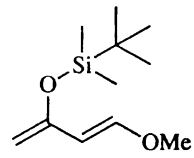
2.1 The TBS Version of Danishefsky's Diene

The preliminary studies done by Antilla, along with previous observations using Boron-VAPOL or boron-VANOL catalysts, indicated that the TBS version (**149**) of Danishefsky's diene (Figure 2.1) was going to produce better results than the original diene with the TMS group group (**31**). One could expect that the bulkier diene should be

Figure 2.1 Danishefsky's dienes



31
Danishefsky's diene

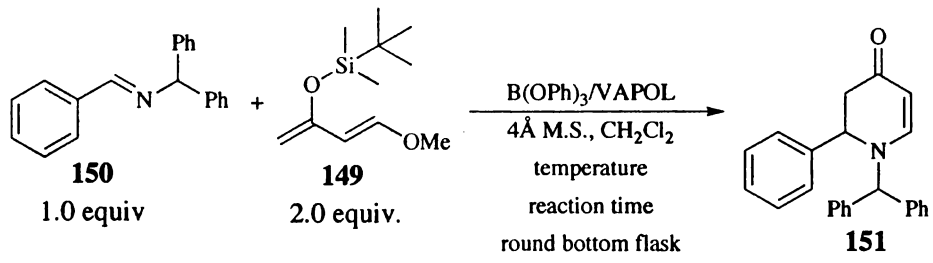


149
TBS version of
Danishefsky's diene

more selective for one face of the imine simply due to steric interactions between the diene and the ligand. Jon Antilla only used a catalyst prepared from BH_3·THF and VAPOL for his initial screening of the *aza*-Diels-Alder reaction. However, since the catalyst prepared using a 3:1 ratio of $B(OPh)_3$ to (*S*)-VAPOL was found to be most effective for the aziridination reaction than was the catalyst prepared from BH_3·THF and VAPOL, the former was used for most of the initial attempts of the *aza*-Diels-Alder reaction. The imine (**150**) prepared from benzaldehyde (**152**) and aminodiphenylmethane (**153**, Bh-NH_2) was used exclusively for the optimization of the *aza*-Diels-Alder reaction.

Several reactions were run using 2.0 equivalents of the TBS version (**149**) of Danishefsky's diene in the presence of 4Å molecular sieves (Scheme 2.1) where the

Scheme 2.1 *aza*-Diels-Alder in the Prescence of 4Å Molecular Sieves



150 1.0 equiv

149 2.0 equiv.

151

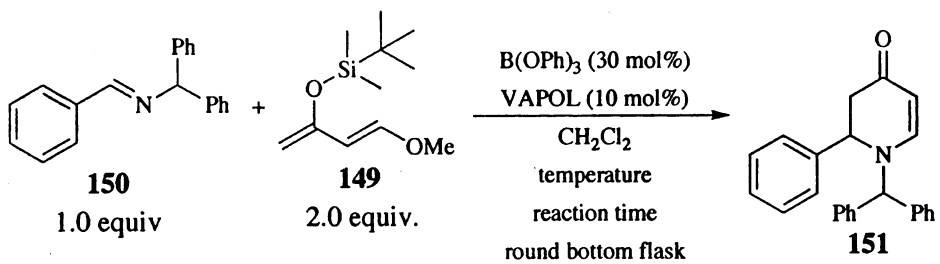
Entry	**149** addition time (h)	$B(OPh)_3$ (mol%)	VAPOL (mol%)	temperature (°C)	reaction time (h)	concentration (M)	conversion (%)
1	3	30	10	−50 to RT	41	0.22	44
2	3	30	10	0	22	0.20	10
3	4	30	10	−40	36	0.20	20
4	10	30	10	−20	36	0.14	17
5	3	10	10	−45	25	0.22	21

temperature, reaction time and rate of addition of the diene were varied. At this time, the isolated yield and enantiomeric excess were not measured and only the conversion was measured by looking at the crude ^1H NMR. The ratio of the final product and the starting imine was measured to calculate the conversion. When the diene was added over 3 hours and the temperature was allowed to warm from −50°C to room temperature and stir for 41 hours (entry 1), the conversion was 44%. When the reaction was run at 0°C or −40°C (entries 2 and 3) for the entire reaction, the conversion dropped to 10 and 20% respectively. If the reaction was run at −20°C and the diene was added over 10 hours (entry 4), the conversion was only 17%. One other reaction was performed in the presence of molecular sieves using the catalyst prepared from 10 mol% $B(OPh)_3$ and 10 mol% VAPOL (entry 5). When this reaction was stirred for 25 hours at −45°C, only

21% conversion was observed. All of these reactions were very slow and the best conversion was achieved when the reaction was allowed to stir for 41 hours.

Next, a few reactions were accomplished where molecular sieves were not put in the reaction (Scheme 2.2). 25% conversion was achieved (entry 1) when the reaction was

Scheme 2.2 *aza*-Diels-Alder Reaction Without 4Å Molecular Sieves



150
1.0 equiv

149
2.0 equiv.

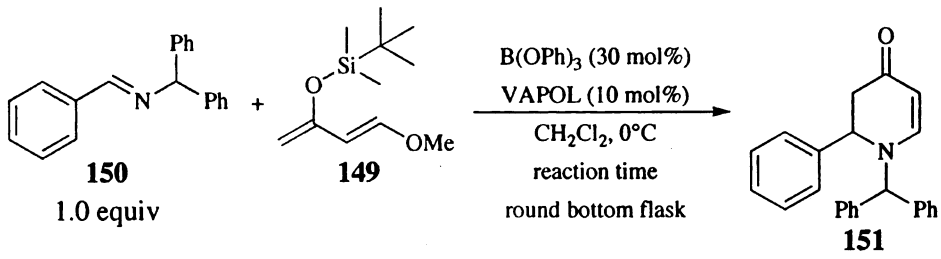
151

Entry	**149** addition time (h)	temperature (°C)	reaction time (h)	concentration (M)	conversion (%)
1	3.5	0 to RT	43	0.25	25
2	2.5	−40	23	0.33	20
3	3	−40	19	0.2	40

allowed to warm from 0°C to room temperature immediately after the addition of the diene was complete. If the reaction was allowed to stir at −40°C, at slightly different concentrations, for about one day (entries 2 and 3), it was found that the slightly less concentrated (0.2 M with respect to imine) reaction was better, resulting in 40% conversion.

Since the reactions all seemed to be very sluggish at this point, a series of experiments were performed where the reaction temperature was held constant at 0°C (Scheme 2.3). In this set of experiments, the amount of diene, addition time of diene,

Scheme 2.3 Effect Diene Equivalents and Addition Time in the *aza*-Diels-Alder Reaction



150
1.0 equiv

149

151

Entry	**149** (equiv.)	**149** addition time (h)	reaction time (h)	concentration (M)	yield **151** (%)	ee **151** (%)	conversion (%)
1	2	0	24	0.2	ND	ND	21
2	1.5	0	6	0.5	ND	ND	10
3	2	2.5	45	0.45	ND	ND	20
4	1.58	2.5	21	0.2	ND	ND	12
5	1.58	3	24	0.2	ND	ND	59
6	1	3	24	0.29	36	68	ND
7	1.5	4.5	24	0.5	ND	ND	17
8	2	12	17	0.2	29.8	66	30
9	2	21	21	0.29	ND	ND	24
10	2	21	45	0.22	ND	ND	33

concentration, and reaction time were all varied. When the diene was added all at once (entries 1 and 2) it was observed that only 21% conversion could be achieved even when 2 equivalents of the diene were added and the reaction allowed to stir for one day. Increasing the addition time to 2.5 hours (entry 3 and 4) was not that helpful. Using 1.58 equivalents of the diene and stirring for 21 hours gave only about 12% conversion (entry 4) and doubling the concentration and allowing the reaction to stir for 45 hours still only gave 20% conversion (entry 3). Two reactions were done where the diene was added over 3 hours, one using 1.58 equivalents of the diene and the other using 1 equivalent of the diene (entries 5 and 6 respectively). After one day of stirring, the one with 1.58

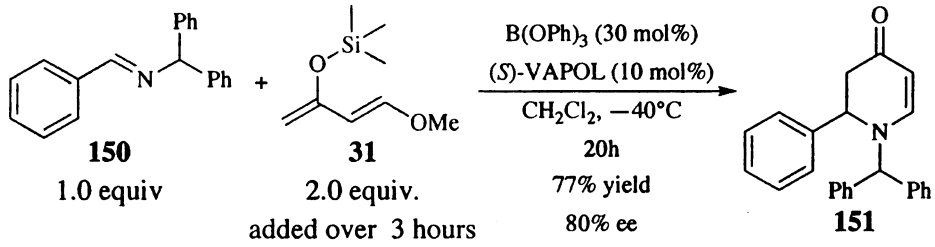
equivalents showed 59% conversion. For the reaction where 1.0 equivalents of the diene was used, the conversion was not measured, but the product was isolated and the selectivity measured. This reaction resulted in 36% yield and an enantiomeric excess of 68% was observed. A 17% conversion could be achieved if 1.5 equivalents of diene were added over 4.5 hours and the reaction allowed to stir for 24 hours (entry 7). One reaction was performed where the conversion, isolated yield, and ee was measured (entry 8). The isolated yield was 30% with 66% ee observed. The reaction was again slow, but it was reassuring to see that the yield was corresponding nicely to the conversion. The conversion in this reaction was 30%, so this seemed to indicate that the only reaction that the imine was undergoing was the desired *aza*-Diels-Alder reaction. If the amount of conversion was high and the isolated yield was much lower, then it would indicate that some competing reaction was taking place, but this was not observed. Lastly, two other experiments were done where the 2.0 equivalents of the diene were added over 21 hours. The reaction was stopped immediately after the addition was complete (entry 9), and only 24% conversion was observed. If allowed to stir an additional 24 hours, the conversion could only be increased to 33%.

It can be concluded from these sets of experiments that the *aza*-Diels-Alder reaction with the TBS version (**149**) of Danishefsky's diene was very slow. The highest conversion observed was 59% and the rest of these reactions showed conversions that were significantly lower.

Some time was spent trying to synthesize a diene that contained even more steric bulk, thinking that the increase in size would possibly help facilitate this reaction.

Meanwhile, while attempting to prepare the bulkier diene, Danishefsky's diene (**31**) was also prepared and one reaction was attempted (Scheme 2.4). The approach of the diene

Scheme 2.4 First Attempt Using Danishefsky's Diene



150
1.0 equiv

31
2.0 equiv.
added over 3 hours

151

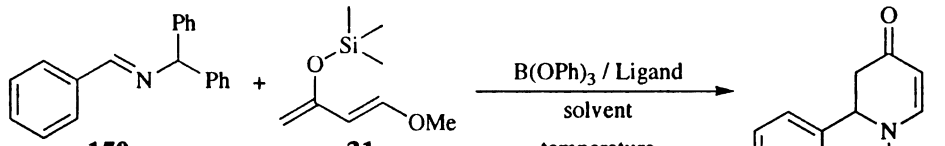
31, due to its less sterically hindered nature, allowed for an easier approach towards the dienophile and the reaction worked well! Using this diene, the optimization of the *aza*-Diels-Alder reaction using the benzhydryl-imine and Danishefsky's diene was begun.

2.2 Danishefsky's Diene

2.2.1 VAPOL vs. VANOL vs. BINOL

As mentioned before it was not clear which ligand would perform the best for the *aza*-Diels-Alder reaction. The first item to be investigated was a comparison of VANOL (**129**), VAPOL (**130**), and BINOL (**59**) ligands used in catalysts prepared from $B(OPh)_3$ (Scheme 2.5). Two reactions were done in toluene (entries 1 and 2) where the catalyst

Scheme 2.5 Comparison of VANOL, VAPOL, and BINOL



150 1.0 equiv

31 2.0 equiv. added over 3.0 h

151

Entry	$B(OPh)_3$ (mol%)	Ligand (mol%)	temperature (°C)	Solvent	flask type	reaction time (h)	Yield **151** (%)	ee **151** (%)
1[a]	30	(*S*)-VANOL (10)	−48	Toluene	rbf	24	<5	ND
2[b]	30	(*S*)-VAPOL (10)	−45	Toluene	rbf	48	78	85
3[c]	100	(*S*)-VANOL (10)	−45	CH_2Cl_2/Tol (1:1)	COIL[d]	24	41	56
4[b]	100	(*S*)-VAPOL (10)	−45	CH_2Cl_2/Tol (1:1)	COIL[d]	24	94	90
5[b]	100	(*R*)-BINOL (10)	−45	CH_2Cl_2/Tol (1:1)	COIL[d]	24	26	23

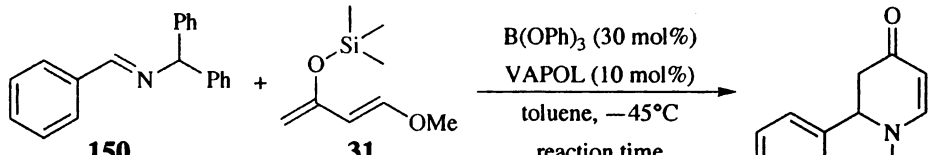
a) 0.25 M with respect to imine
b) 0.2 M with respect to imine
c) 0.1 M with respect to imine
d) For discussion and picture of the COIL flask see Scheme 2.21 and Figure 2.4

was prepared from 10 mol% VANOL or VAPOL and 30 mol% $B(OPh)_3$. The reaction with the VANOL catalyst gave little or no product while the VAPOL catalyst produced a 78% yield. It is easy to see from these results that VAPOL was the superior ligand when toluene was used as the solvent. These same two reactions were repeated in the same way except 100 mol% $B(OPh)_3$ was used to prepare the catalyst and a 1:1 mixture of CH_2Cl_2 /toluene was used as the solvent. The results with VAPOL (entry 4) were 94% yield and 90% ee. These results are significantly higher than those with VANOL (entry 3), which only gave 41% yield and 56% ee. Another reaction was attempted using BINOL as the ligand and it proved to be even worse than VANOL resulting in 26% yield

and 23% ee. The results of this series of experiments showed clearly that VAPOL was in fact the best ligand to use in pursuit of the optimal conditions of the reaction. With the exception of the temperature studies, all the reactions discussed in this chapter will involve the use of VAPOL as the chiral ligand.

Another important variable that was found to be an important consideration for this reaction was the purity of VAPOL used for the preparation of the catalyst. A few reactions were carried out using VAPOL sources with different purities (Scheme 2.6),

Scheme 2.6 Effects of the Purity of VAPOL



150 1.0 equiv

31 2.0 equiv. added over 3.0 h

151

Entry	VAPOL (condition)	reaction time (h)	yield **151** (%)	ee **151** (%)
1[a]	Yellow[b]	48	43	86
2[a]	Light Yellow[c]	48	54	87
3[a]	White[d]	20	35	86
4[a]	White[e]	20	45	89

a) 0.2 M reactions with respect to imine
b) VAPOL from an old vial that was yellow in color was used
c) Light yellow VAPOL that had been purified by running two columns was used
d) Very white VAPOL that TLC analysis showed one extra minor spot was used
e) Very white VAPOL that TLC analysis showed only one spot was used

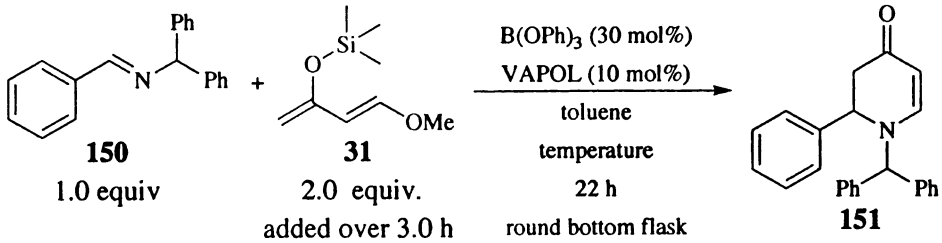
the purity of VAPOL was indeed very important to the outcome of these reactions. In order to determine this, a vial of VAPOL that had been sitting around for an undetermined amount of time was used in the preparation of the catalyst (entry 1). When the catalyst was prepared from 30 mol% $B(OPh)_3$ and 10 mol% of that VAPOL and the reaction allowed to run for two days in toluene, 43% yield and 86% ee was obtained.

Two columns were then run to purify the VAPOL to a light yellow color. The reaction with this VAPOL (entry 2) resulted in 54% yield and 87% ee. The VAPOL was then purified to whiteness, but two spots were still visible by TLC analysis. This reaction after 20 hours only gave 35% yield and 86% ee was observed again. Finally the VAPOL was further purified and pristine white VAPOL was obtained. The reaction using this VAPOL (entry 4) gave the best results and 89% ee was obtained. This series of experiments indicated that the purity of the VAPOL has an effect on the selectivity of the reaction but it is unclear whether the yield is affected because the reaction times were not the same. It is important to note at this time that later in the course of these studies, several reactions were repeated at random times using identical conditions and analysis of the data collected from those experiments showed that the variation of yield was ±7 and a variation of ee was ±1 (using the optimal conditions the error was 83.5±7% yield and 89±1% ee). This indicates that the increase in ee for the experiments conducted in Scheme 2.6 indeed exceeded experimental error and thus carefully purified, extremely clean VAPOL was used for the optimization of this reaction.

2.2.2 Temperature Effects

In asymmetric catalysis, temperature can have a significant effect on the outcome of the reaction. Two temperature studies were accomplished using both VAPOL and VANOL, where the temperatures were varied from −70°C to room temperature. The temperature effect on the reaction using VAPOL was studied first (Scheme 2.7). From

Scheme 2.7 Temperature Effect Using VAPOL



150
1.0 equiv

31
2.0 equiv.
added over 3.0 h

151

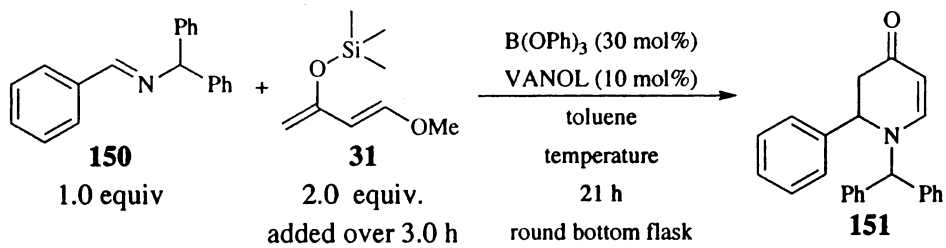
Temperature (°C)	yield **151** (%)	ee **151** (%)
−70	21	91
−60	16	81
−50	27	88
−40	51	89
−30	40	86
−20	34	80
−10	36	85
RT	21	58

the results of the series of temperatures, it was found that the yield reached a maximum at −40°C. It makes perfect sense that the yield would drop going to lower temperatures and this can be explained by a decrease in the rate of the reaction at lower temperatures. If this same argument was used for warmer temperatures, then it would be expected that warming the temperature above −40°C would result in increased yields. This effect was not observed, and in fact the yields dropped significantly as the temperature was warmed to room temperature. One explanation for this observation could be that at warmer temperatures some side reaction could start to occur at a faster rate and effectively reduce the amount of desired product produced. Another explanation could be that if at warmer reaction temperatures the stability of the reagents under the reaction conditions were compromised, then decomposition of the reagents could occur. If this happened, then the

yields would drop in this case as well. This explanation is probably the correct one as it was observed during the course of the reactions at warmer temperatures that the solution became dark red and material could be observed at the base line in TLC analysis. The thought was that the reactive diene could be decomposed or possibly polymerize in the presence of Lewis acid. One reaction was done where only the catalyst and diene were added to the flask in the absence of imine and the reaction again turned very dark red. TLC analysis showed only baseline material was present and when purification was attempted using column chromatography, all attempts to retrieve the material, using any solvent, were unsuccessful. The dark red material just stuck at the top of the column and could not be eluted. In conclusion, the best compromise between the rate of reaction and minimal decomposition of the diene was a temperature of −40°C where the highest yield was observed. The other factor to consider when selecting the optimal temperature is its effect on the selectivity of the reaction. When the reaction was run at room temperature, 58% enantiomeric excess was observed. This is only a moderate selectivity and it was desired to find a temperature where the ee would be as high as possible. It was found that going to lower temperatures, the ee could be increased to 86% and 89% at −30°C and −40°C respectively. Unfortunately, going to lower temperatures seemed to have little effect on the ee. From this study it can be concluded that the optimal reaction temperature was −40°C, however after running this reaction many times over the past few years, and the observation of temperature fluctuations above and below this mark, the optimal reaction temperature was decided to be −45°C.

VANOL was also subjected to the same temperature study (Scheme 2.8). Based

Scheme 2.8 VANOL Temperature Study



150
1.0 equiv

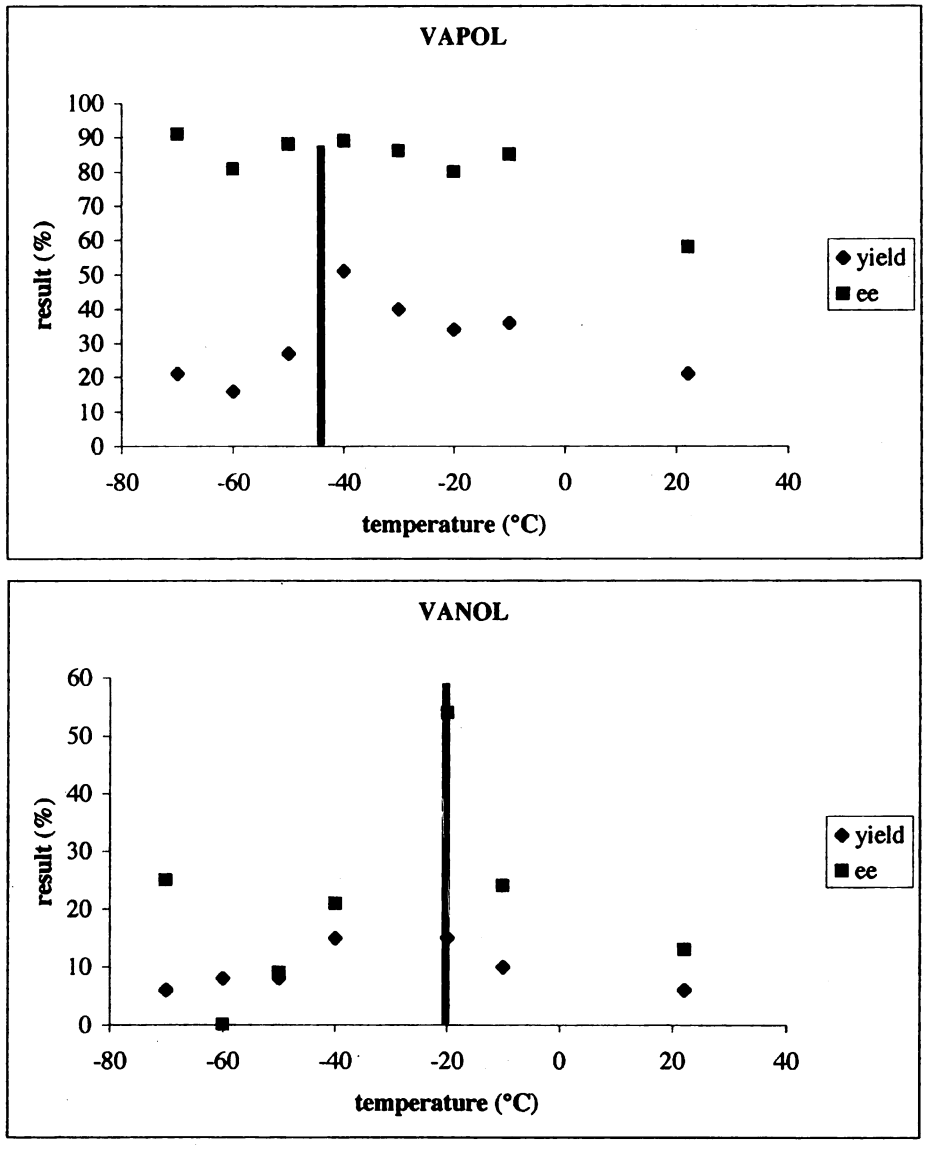
31
2.0 equiv.
added over 3.0 h

151

temperature (°C)	yield **151** (%)	ee **151** (%)
−70	6	25
−60	8	0
−50	8	9
−40	15	21
−20	15	54
−10	10	24
RT	6	13

on the results in Scheme 2.5, it was not unexpected to find that the results were not as good as those from VAPOL. Nonetheless, it revealed interesting differences between VAPOL and VANOL. This study indicated that the best yield and ee could be achieved at −20°C where 15% yield and 54% ee was observed. In a manner similar to that observed for VAPOL, both higher and lower temperatures had a negative effect on yield of the reaction. It was interesting to find that the same negative effect was not observed for the ee. When the temperature was decreased to −40°C, 21% ee was observed and when the temperaure was increased to −10, 24% ee was observed. It is not clear why this effect is observed, nontheless, it seemed that there was a narrow window of temperatures around −20°C where the reaction was most efficient. The effect of temperature on the reactions using VANOL and VAPOL are expressed in the following plots (Figure 2.2). The bold bar indicates the optimal temperature in each case. Again, it

Figure 2.2 Summary of Temperature Effects

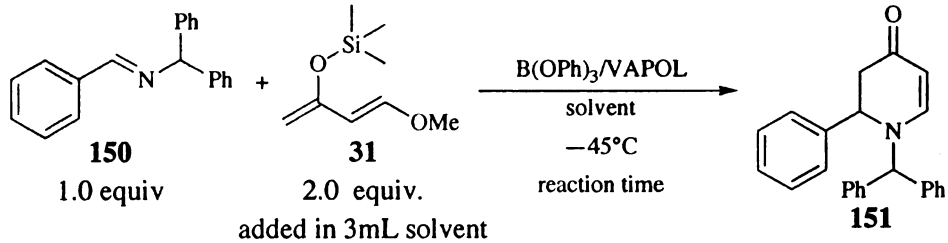


was found that VAPOL was indeed the superior ligand and the optimal temperature for VAPOL was determined to be —45°C.

2.2.3 Solvent Effects

As expected, it was found that the choice of solvent or solvent combination also played a major role in the outcome of the reaction. Several reactions using different conditions were performed for the purpose of providing a comparison of toluene and CH_2Cl_2 as the solvent (Scheme 2.9). The first set of reactions were done using 5 mol%

Scheme 2.9 Toluene Versus CH_2Cl_2 as Solvent



150 1.0 equiv

31 2.0 equiv. added in 3mL solvent

151

Entry	solvent	$B(OPh)_3$ (mol%)	VAPOL (mol%)	**31** addition time (h)	reaction time (h)	yield **151** (%)	ee **151** (%)
1	CH_2Cl_2	100	5	3[a]	24	95	76
2	Toluene	100	5	3[a]	24	60	90
3	CH_2Cl_2	100	1	3[b]	49	78	47
4	Toluene	100	1	3[b]	49	53	80
5	CH_2Cl_2	30	10	3[b]	47	81	73
6	Toluene	30	10	3[b]	48	78	85
7	CH_2Cl_2	30	10	0[b]	47	82	70
8	Toluene	30	10	0[b]	47	54	88

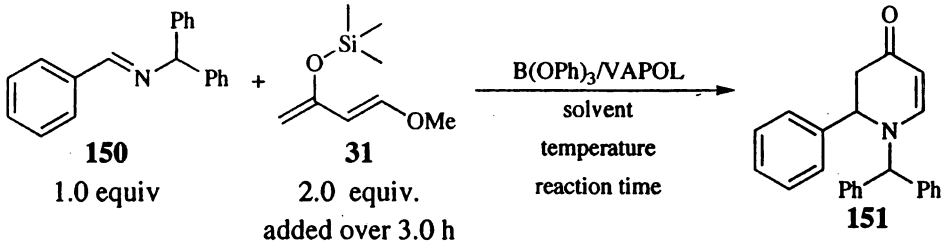
a) A cooling addition coil flask was used (For discussion and picture of the flask see Scheme 2.21 and Figure 2.4).
b) A traditional 25 mL round bottom flask was used.

VAPOL and 100 mol% $B(OPh)_3$ as the catalyst (entries 1 and 2). When CH_2Cl_2 was used, the reaction gave 95% yield and 76% ee, whereas when toluene was used, the reaction produced 60% yield and 90% ee. It seemed from this experiment that the reaction was slower in toluene but the selectivity was much better. In another set of experiments where 1 mol% VAPOL and 100 mol% $B(OPh)_3$ were used (entries 3 and 4), the same effect was observed. With this low level of VAPOL loading (1 mol%), the

difference in the selectivity was even greater when switching from toluene to CH_2Cl_2, as the ee dropped from 80% to 47%. Two additional sets of experiments were carried out with 30 mol% $B(OPh)_3$ and 10 mol% VAPOL (entries 5-8). These results also examine the effect of the diene addition time, which will be discussed in much more detail later in the chapter. When the diene was added over 3 hours and CH_2Cl_2 was used as the solvent, the reaction produced 81% yield and 73% ee in two days (entry 5). On the contrary, the reaction in toluene gave 78% yield and 85% ee (entry 6). Again, the increase in ee when switching to toluene was observed. Switching from CH_2Cl_2 to toluene, when the diene was added all at one time showed an increase from 70% ee to 88% ee and a decrease in yield from 82% to 54%. In this series of experiments, all data was in agreement that toluene was a better solvent for creating the desired selectivity and CH_2Cl_2 was the better solvent for enhancing the rate of turnover of the reaction.

THF and CCl_4 were also examined as solvents for this reaction (Scheme 2.10) and

Scheme 2.10 CCl_4 and THF as the Solvent



150
1.0 equiv

31
2.0 equiv.
added over 3.0 h
in 3 mL solvent

151

Entry	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	temperature (°C)	reaction time (h)	yield **151** (%)	ee **151** (%)
1[a]	150	2.5	CCl_4	−45	24	38	75
2[b]	30	10	THF	−50	48	43	20

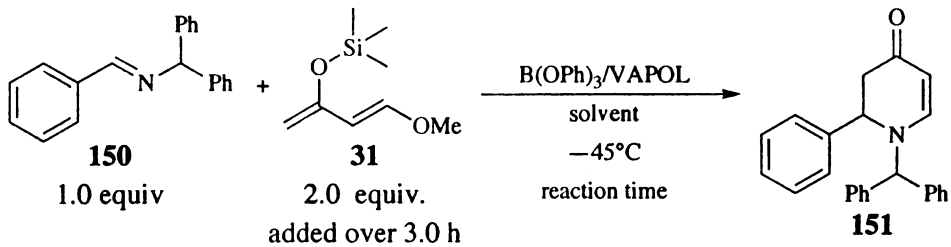
a) A cooling addition coil flask was used (For discussion and picture of the flask see Scheme 2.21 and Figure 2.4).
b) A traditional 25 mL round bottom flask was used.

each proved to be a much poorer choice for solvent in this reaction. When CCl_4 was used, the reaction gave 38% yield and 75% ee (entry 1). It is not so surprising that this reaction failed to produce good results. In fact this was a poorly designed experiment because the melting point of CCl_4 is $-23°C$. When the reaction was attempted at $-45°C$, the solvent did in fact freeze which cannot be good for the reaction. Also, at the end of 24 hours, the reaction was allowed to warm to temperature where the solvent would melt and stirred about 30 minutes before the workup was accomplished. This warmer temperature could also have affected the outcome of the reaction. When THF was used, it was also not surprising to find that this solvent produced inferior results. THF contains an oxygen which could, and probably does compete with the imine for binding to the catalyst. This competition for binding would at the very least lead to the expectation that the reaction would slow down. This was indeed observed and the reaction only produced 43% yield after 48 hours reaction time. In addition to the lower yield, the reaction was much less selective when THF was used as the solvent and produced only 20% ee.

Carbon tetrachloride is very expensive and very toxic and is therefore not a conventional solvent that is used very often in chemical laboratories. During the course of these studies, some issues occurred for the reproducibility of the aziridination reaction, and some previous results could not be duplicated. In order to obtain ee's that were as high as those seen previously, it was discovered that CCl_4 was helpful in obtaining higher ee' for this reaction. It was for these reasons, that the carbon tetrachloride reaction above was attempted at all. The desire to determine the effect of CCl_4 for the *aza*-Diels-Alder reaction prompted the use of solvent combinations using CCl_4 and CH_2Cl_2. In addition to

this, since the reactions in toluene gave good selectivity and CH_2Cl_2 gave good yields, it was also desired to try CH_2Cl_2 and toluene mixtures as well. The discussion will now turn to the studies of different solvent combinations (Scheme 2.11). It was determined

Scheme 2.11 Effects of Solvent Combinations



150 1.0 equiv

31 2.0 equiv. added over 3.0 h

151

Entry	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	reaction time (h)	Yield **151** (%)	ee **151** (%)	Conc. (M)
1[a]	100	5	CH_2Cl_2/CCl_4 (1:5)	24	67	90	0.11
2[a]	100	5	CH_2Cl_2/CCl_4 (1:2)	24	83	94	0.2
3[b,c]	100	10	CH_2Cl_2/Tol (2:3)	24.5	86	84	0.2
4[b,d]	100	10	CH_2Cl_2/Tol (3:2)	24.5	94	81	0.2
5[b,e]	100	10	CH_2Cl_2/Tol (1:1)	22.5	90	86	0.2
6[a,e]	100	10	CH_2Cl_2/Tol (1:1)	24	90	94	0.2

a) A cooling addition coil flask was used (For discussion and picture of the flask see Scheme 2.21 and Figure 2.4).
b) A traditional 25 mL round bottom flask was used.
c) The catalyst was transferred in 2 mL DCM and the diene added in 3 mL toluene.
d) The catalyst was transferred in 2 mL toluene and the diene added in 3 mL DCM.
e) The catslyst was transferred and the diene added in DCM/toluene (1:1).

from this study that if 1:5 ratio of CCl_4 to CH_2Cl_2 was cooled to −45°C, that the solution would not freeze. The *aza*-Diels-Alder reaction was then attempted with this solvent (entry 1). For this solvent it was found that twice as much solvent was required to

maintain solubility of the reagents and catalyst. The outcome of this reaction was really good, resulting in 67% yield and 90% ee. Some precipitate was observed in the flask at that reaction temperature which indicated that solubility at —45°C was possibly still an issue and could be the reason for the modest yield produced in that reaction. One reaction was then attempted where an increased amount of CH_2Cl_2 was used (entry 2). When the ratio of CH_2Cl_2 to carbon tetrachloride was changed to 1:2 (i.e. ~1.75 mL CH_2Cl_2 and 3.25 mL CCl_4 as opposed to ~0.8 mL CH_2Cl_2 and 4.2 mL CCl_4), the reaction was more efficient giving 83% yield and 94% ee. This was the best selectivity seen for this reaction throughout the course of these studies but was not chosen as the optimal conditions simply due to the toxic nature and expense of CCl_4.

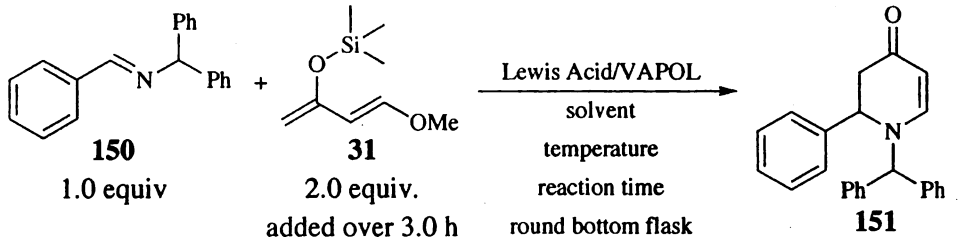
Now, thinking back to the interesting results from the toluene versus CH_2Cl_2 studies, it was thought that high yields and selectivity could be achieved if a mixture of these solvents was used. In order to test this hypothesis, several reactions were done using a combination of CH_2Cl_2 and toluene. One reaction was attempted where the catalyst was transferred to the imine in 2 mL CH_2Cl_2 and upon cooling to —45°C, the diene was then added in 3 mL toluene (entry 3). This reaction gave 86% yield and 84% ee. If the solvents were switched in this reaction where the catalyst was transferred in toluene and the diene added in CH_2Cl_2 (entry 4) the reaction produced 94% yield and 81% ee. Again, a similar effect of the two solvents was observed. When more CH_2Cl_2 was present, the yield went up and the ee down and when more toluene was present, the yield went down and the ee went up. One attempt was then done where a 1:1 ratio of toluene and CH_2Cl_2 was used for both the catalyst transfer and the addition of the diene. When this was attempted, it was found that a good ee and yield could be achieved as the

reaction produced 90% yield and 86% ee. When that same reaction was performed using special coil addition glassware (discussed later in the chapter) (entry 6), it was found that the ee could be increased to 90% and 94% yield was obtained. With these results observed, toluene/CH_2Cl_2 (1:1) was then decided to be the optimal solvent for this *aza*-Diels-Alder reaction.

2.2.4 Different Lewis Acid Sources

Before moving on to discuss the effects of catalyst loading and various ratios of $B(OPh)_3$ to VAPOL, it is important to note that several other Lewis acid sources were studied and their affects on the outcome of the reactions were recorded (Scheme 2.12).

Scheme 2.12 Different Lewis Acid Sources



150 1.0 equiv

31 2.0 equiv. added over 3.0 h

151

Entry	Lewis acid (mol%)	VAPOL (mol%)	solvent	temperature (°C)	reaction time (h)	Conc. (M)	yield **151** (%)	ee **151** (%)
1	$Al(Me)_3$ (30)	10	Toluene	−45	19	0.2	0	ND
2	$Al(OiPr)_3$ (30)	10	Toluene	−45	46.5	0.2	0	ND
3	$B(OnBu)_3$ (30)	10	CH_2Cl_2	−40	71	0.2	41	ND
4	$B(OPh)_3$ (30)	10	CH_2Cl_2	−40	47	0.2	81	73
5	$B(OPh)_3$ (30)	10	Toluene	−40	48	0.2	78	85
6	$B(O\text{-}2,6\text{-}di\text{-}Me\text{-}Ph)_3$ (30)	10	CH_2Cl_2	−40	26	0.2	69	75
7	$B(O\text{-}4\text{-}F\text{-}Ph)_3$ (30)	10	CH_2Cl_2	−45	20	0.2	45	58
8	$B(O\text{-}4\text{-}F\text{-}Ph)_3$ (30)	10	CH_2Cl_2	−78	22.5	0.2	28	52
9	$B(O\text{-}4\text{-}Me\text{-}Ph)_3$ (30)	10	CH_2Cl_2	−40	22	0.2	80	88
10	$B(O\text{-}4\text{-}Me\text{-}Ph)_3$ (30)	10	Toluene	−40	20	0.2	68	90
11	$B(O\text{-}4\text{-}OMe\text{-}Ph)_3$ (30)	10	Toluene	−45	23.5	0.2	45	84
12	$Yb(OTf)_3$ (20)	10	CH_2Cl_2/Tol (1:1)	−45	22	0.2	76	10*
13	$Yb(OTf)_3$ (10)	20	Toluene	−45	24	0.125	24	10

Two attempts were made with catalysts prepared from aluminum Lewis acids. One catalyst was prepared in the normal fashion by heating $AlMe_3$ (30 mol%) and VAPOL (10 mol%) in CH_2Cl_2 to 55°C for one hour and then heating under high vacuum for 30 minutes. Another catalyst was prepared in the same way from $Al(OiPr)_3$ (entries 1 and 2). Neither of these reactions with these catalysts produced any Diels-Alder adduct. In the first case, the excess $AlMe_3$ was probably not necessary to drive catalyst formation

to completion because aluminum is so oxophilic and the methyl groups were likely readily protonated by the acidic oxygens of VAPOL. $AlMe_3$ is a strong enough Lewis acid that with excess around, the diene may decompose at a faster rate than the desired *aza*-Diels-Alder reaction. Although the triisopropoxy aluminum is not as strong of a Lewis acid, a similar situation could have occurred, explaining the failure to produce the product. It is entirely possible if a 1:1 ratio of aluminum to VAPOL had been used, a more favorable result would have been observed, but this investigation never occurred.

In addition to studying aluminum catalysts, a series of experiments were done using four different borate species. The slightly less Lewis acidic tributyl borate (purchased from Aldrich) was used to prepare a catalyst first (entry 3) and its reaction turned out to be much slower compared to the $B(OPh)_3$ catalysts. In CH_2Cl_2 at $-40°C$ this reaction only gave 41% yield in 71 hours (entry 3). Due to the slow reaction, the ee was not determined and $B(OnBu)_3$ was not considered further. Next, a more sterically hindered triarylborate was prepared from 2,6-dimethylphenol and boric acid by azeotropic distillation. This triarylborate was used for the preparation of the catalyst (entry 6) and the reaction gave 69% yield of **151**, but the selectivity was not very good (75% ee). A triarylborate with an electron withdrawing fluorine in the *para*-position was then prepared in similar fashion as the 2,6-dimethylphenol. An initial attempt was made where the reaction was run at $-45°C$ (entry 7) and this gave 45% yield and 58% ee. Having an electron-withdrawing group on the aryl group should increase the Lewis acidic nature of the boron and make the catalyst more active. This argument indicates that the reaction might be faster and this could account for the drop in enantiomeric excess. On the other hand, the increased Lewis acidity could also potentially slow down the rate of

turn over if the boron was coordinating more strongly to the more basic *aza*-Diels-Alder adduct, thus lowering the yield. If the Lewis acid was more acidic and the rate was faster, then presumably cooling the reaction down would slow the reaction and more selectivity would be observed. This was not the case as only 52% ee was observed for the reaction at −78°C (entry 8). It was interesting to find that by switching to an electron-donating group (tris-4-methoxyphenylborate, entry 11), the selectivity went back up and 84% ee was observed. The reaction was done in toluene so the moderate yield of 45% was not unexpected. Two reactions were then done using tris-4-methylphenylborate, a triarylborate species that is only slightly more electron rich than $B(OPh)_3$ (entries 9 and 10). One reaction was done in toluene and one in CH_2Cl_2 and again, the same trend as seen before with these two solvents was observed. When the reaction was done in CH_2Cl_2 the yield was 80% and in toluene the yield was 68% for reactions that were allowed to stir for about one day. A similar trend was also observed for the outcome of the ee as well, only with this catalyst, the ee was only 2% less in pure CH_2Cl_2 than in toluene (88% and 90% ee respectively). This is probably the most intriguing result from the study of different borates because it would not have been expected that a borate that similar to $B(OPh)_3$would give such a dramatic increase in ee using CH_2Cl_2 as the solvent. When this same reaction was done using $B(OPh)_3$, only 73% ee was observed (entry 4) and with the *para*-methylphenyl group, the ee was increased to 88% (entry 9).

The synthesis of racemic mixtures of the *aza*-Diels-Alder products for the screening of substrates were accomplished using $Yb(OTf)_3$. The yields of these reactions were moderate to good so it was curious to find out what would happen if

VAPOL were attached to the Ytterbium and the *aza*-Diels-Alder reaction was attempted. One reaction was attempted where $Yb(OTf)_3$ (20 mol%) and VAPOL (10 mol%) was used to prepare the catalyst in the same way as for $B(OPh)_3$ (entry 12). The reaction was quite efficient, giving 76% yield, but the background reaction predominated and only 10% ee was observed. This reaction, interestingly enough, produced the opposite enantiomer from the VAPOL-$B(OPh)_3$ catalyst. In order to be sure that there was no $Yb(OTf)_3$ around to facilitate the racemic reaction, a catalyst was prepared using 10 mol% $Yb(OTf)_3$ and 20 mol% VAPOL (entry 13). This reaction was done in toluene under slightly less concentrated conditions and the reaction only gave 24% yield and 10% ee. The major enantiomer in this case was the same as that produced for the VAPOL-$B(OPh)_3$ catalyst.

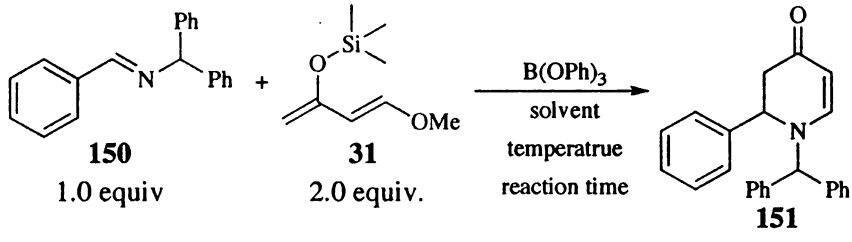
Although some interesting results were observed from this series of experiments, the readily available $B(OPh)_3$ was still the desired Lewis acid for this reaction. However, more exploration of the *para*-methylphenylborate may be interesting to study for its effect on this and other substrates in the *aza*-Diels-Alder reaction.

2.2.5 Catalyst Loading: $B(OPh)_3$/VAPOL Ratios

As mentioned in the introduction to this chapter, catalyst loading is a very important aspect to catalytic asymmetric reactions. In many cases the metal and/or ligands used for these transformations can be very expensive or difficult to prepare. If a lot of money or time is spent to achieve these catalysts, it is desirable to use as little of the catalyst as possible. The discussion will now turn to the catalyst loading needed for this particular reaction. In this section, not only will the catalyst/ligand loading be discussed but also the effects of different ratios of VAPOL to $B(OPh)_3$ used to prepare the catalyst.

In almost all cases for this study, an excess amount of $B(OPh)_3$ was used for the preparation of the catalyst. This leads to inevitability that there will be at least some opportunity for the reaction to be catalyzed by the $B(OPh)_3$ to give racemic product. A few reactions were attempted to determine how efficient $B(OPh)_3$ alone would be at facilitating this reaction (Scheme 2.13). If 30 mol% triphenylborate was used and the

Scheme 2.13 Reactions Using $B(OPh)_3$[a]



150 1.0 equiv

31 2.0 equiv.

151

Entry	**31** addition time (h)	$B(OPh)_3$ (mol%)	solvent	temperature (°C)	flask type	reaction time (h)	Yield **151** (%)
1	3	30[b]	CH_2Cl_2	RT	rbf	16	30
2	0	100[b]	CH_2Cl_2/Tol (1:1)	−45	rbf	24	46
3	3	100[c]	CH_2Cl_2/Tol (1:1)	−45	COIL	24	25

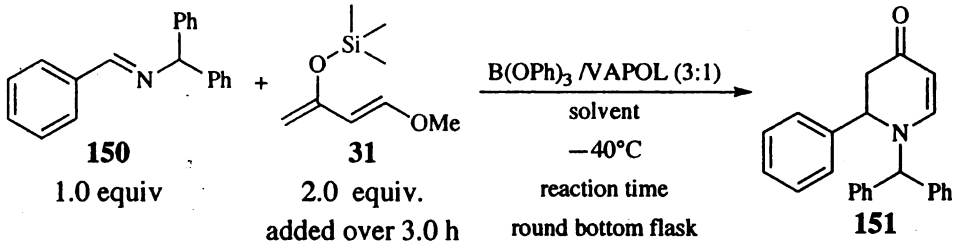
a) All reactions 0.2 M with respect to the imine.
b) $B(OPh)_3$ was purchased from Aldrich and used right from bottle
c) $B(OPh)_3$ was heated to 55°C in CH_2Cl_2 for one hour and heated under vacuum for 0.5 hours.

reaction was done in CH_2Cl_2 at room temperature the reaction produced 30% yield of the desired product (entry 1). Two reactions were then done using one equivalent of $B(OPh)_3$ with the optimal solvent and temperature (DCM/toluene (1:1) and −45°C). In one reaction, triphenylborate was used as purchased from Aldrich (entry 2). This reaction gave 46% yield in one day. If the $B(OPh)_3$ was taken through the normal catalyst preparation procedure only without VAPOL, the reaction slowed down and only gave

25% yield (entry 3). The results prove that the possibility exists for significant background reaction to occur, however it is not clear why the reaction using $B(OPh)_3$ directly from the bottle gave better results. It is possible that the bottle may contain other boron species such as phenylboronic acid or phenylboricacid that could also potentially catalyze the reaction. By distilling the material or taking it through the catalyst preparation cycle, these other potential catalysts may be eliminated thus the reaction has to be catalyzed by $B(OPh)_3$ resulting in lower yields.

The original plan was to use the same catalyst that was found to be successful for the aziridination reaction.[56] This catalyst was prepared using a 1:3 ratio of VAPOL to $B(OPh)_3$. A series of experiments was then carried out using this 1:3 ratio of VAPOL to $B(OPh)_3$ in the catalyst preparation for a study directed at exploring the catalyst loading (Scheme 2.14). The total catalyst loading of VAPOL was varied from 10 mol% to 50

Scheme 2.14 Reactions Using $B(OPh)_3$/VAPOL (3:1)



150 1.0 equiv

31 2.0 equiv. added over 3.0 h

151

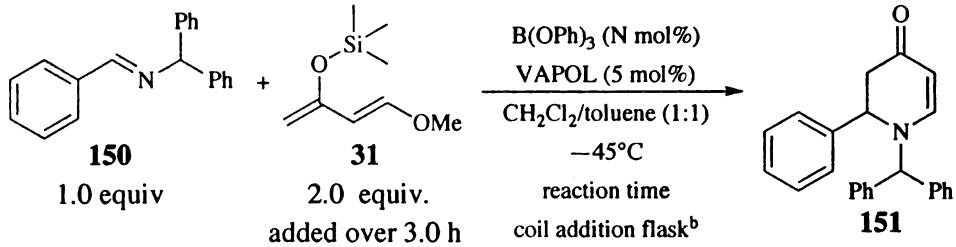
Entry	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	reaction time (h)	concentration (M)	yield **151** (%)	ee **151** (%)
1	30	10	toluene	22.5	0.2	58	93
2	60	20	toluene	20	0.14	84	91
3	90	30	toluene	17	0.13	74	92
4	30	10	CH_2Cl_2	20	0.2	61	90
5	60	20	CH_2Cl_2	15	0.14	84	83
6	90	30	CH_2Cl_2	21	0.13	85	89
7	150	50	CH_2Cl_2	5	0.08	95	58

mol% adjusting the amount of $B(OPh)_3$ accordingly to maintain the proper ratio. Three reactions were done in toluene using 10 mol%, 20 mol% and 30 mol% VAPOL respectively. It was observed from these three experiments that increasing the amount of catalyst had little effect on the outcome of the reaction. The enantiomeric excess of the reactions ranged from 91% to 93% with the reaction using 10 mol% being the best. The yield was effected slightly going from 10 mol% to 20 mol% VAPOL as the yield increased from 58% in 22 hours for 10 mol% VAPOL to 84% yield for 20 mol% VAPOL in 20 hours. When 30 mol% VAPOL was employed, the yield was 74% after 17 hours, so not a drastic difference from 20 mol% VAPOL. A similar observation was observed in the outcome of the reactions with respect to yield for the same series of experiments in CH_2Cl_2 (entries 4-7). In this solvent one additional experiment was included using 50 mol% VAPOL. The yield of the reaction increased from 61% to 84% going from 10 mol% VAPOL to 20 mol%. Increasing the loading to 30 mol% did not effect the yield but when 50 mol% VAPOL was employed the yield was nearly quantitative. The data for the selectivity of these reactions was not very consistent and should be taken lightly, but the ee was 90% when 10 mol% VAPOL was used, went down to 83% when 20 mol% was used and then back up to 89% when 30 mol% was used. It was interesting though to find that the enantiomeric excess dropped to 58% when 50 mol% VAPOL was used. If the formation of the catalyst was complete, and the predominant catalyst species in the reaction was the active VAPOL-boron species, one would expect the ee to increase. However, it can be reasoned that this drop in selectivity is in fact due to unformed catalyst at this loading. It is possible that the preparation of the catalyst might not be going to completion using the standard catalyst preparation time and temperature. At this

catalyst loading, there is also significantly more $B(OPh)_3$ present that if not reacted with VAPOL to form the catalyst, could potentially catalyze the background reaction and thus account for the observed lower enantiomeric excess.

The focus will now turn to the effect of the VAPOL to $B(OPh)_3$ ratio. A set of experiments was carried out where the amount of VAPOL was maintained at 5 mol% and the amount of $B(OPh)_3$ was varied from 5 mol% to 500 mol% (Scheme 2.15). As a

Scheme 2.15 $B(OPh)_3$ to VAPOL Ratio Effects



150
1.0 equiv

31
2.0 equiv. added over 3.0 h through cooling addition coil

151

Entry[a]	$B(OPh)_3$ (N mol%)	reaction time (h)	yield **151** (%)	ee **151** (%)
1	5	24	50	65
2	10	24	52	84
3	15	24	59	89
4	30	24	68	87
5	60	24	71	90
6	100	30	85	90
7	150	22.5	96	92
8	500	24	98	83

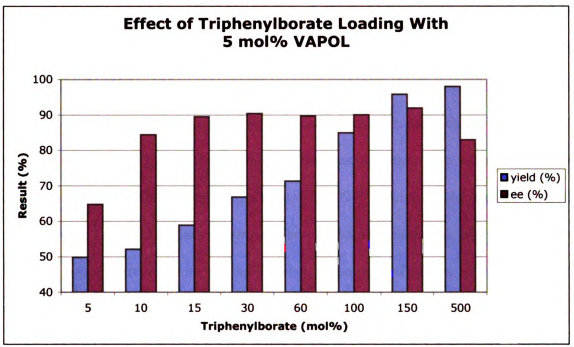
a) All reactions run at 0.2 M with respect to the imine
b) For discussion and picture of the coil addition flask see Scheme 2.21 and Figure 2.4.

starting point, a reaction was performed using a 1:1 ratio of $B(OPh)_3$ and VAPOL (5 mol% each, entry 1). This reaction gave 50% yield and 65% ee which is obviously not a very good result compared to what has been observed before. It can be see from the data

in Scheme 2.15 that as the amount of triphenyborate was increased, so did the yield. The yield could be increased to nearly quantitative when 500 mol% triphenylborate was used (entry 8). This effect was not surprising, as it would be expected that upon introducing more catalyst to the system, the reaction would proceed at a more rapid rate. It was very interesting, however, to find that the same increasing trend was observed for the selectivity of these reactions. The ee increased from 65% to 90% when the amount of $B(OPh)_3$ was increased from 5 mol% to 60 mol%. The highest induction of 92% ee was observed when 150 mol% $B(OPh)_3$ was used (entry 7) . The asymmetric induction did not drop off until a 100:1 ratio of $B(OPh)_3$ to VAPOL was used (entry 8).

This series of experiments proved to be quite intriguing. It was significant that an ee of 92% could be obtained with good yield, but further analysis of the results may reveal other information about this reaction. The results of this series of experiments are displayed in an easier to follow bar graph shown in Figure 2.3 below. It is not hard to

Figure 2.3 Summary of $B(OPh)_3$ Loading Effects

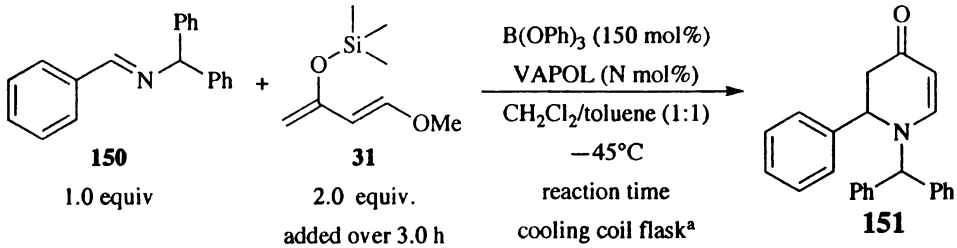


surmise why the yield goes up upon addition of more $B(OPh)_3$. By adding more of the achiral catalyst, there is more Lewis acid in the reaction mixture, and the possibility for the racemic background reaction increases significantly. However, if the increase in yield were due to background racemic reaction, then it would be expected that the enantiomeric excess would drop off as the yield was increased. This effect was not observed and even when a 30:1 ratio of $B(OPh)_3$ to VAPOL was used, 92% ee was still observed. An even more amazing result comes from the reaction where a 100:1 ratio of achiral catalyst to chiral catalyst was used and the reaction still produced an astonishing 83% ee. In order to rationalize these observations, a study was done to determine the association constants each of the catalysts (chiral and achiral) to both the imine and the product of the reaction. The results and discussion of these experiments will be discussed in Chapter 4. This phenomenon, however, where an achiral catalyst plays an orthogonal

role in the reaction to increase TONs without depleting the selectivity of the reaction, is one that has not been observed to date in the *aza*-Diels-Alder reaction or for any other asymmetric catalytic reaction. It is worthy of mention that Yu and coworkers[62] have used $B(OMe)_3$ to accelerate the catalytic asymmetric allylation of aldehydes with allyl stannanes using a BINOL-titanium catalyst. This differs from the present work because the $B(OMe)_3$ is forming a covalent bond with the product rather than acting as a Lewis acid. In addition, Shibasaki published a review in 1999[63] discussing the use of additives in asymmetric catalysis. Many examples therein display increased selectivity and/or yield, but again there were no examples where a non-chiral Lewis acid was used to enhance the reaction efficiency.

The best result observed for the above series of experiments was where 150 mol% $B(OPh)_3$ was used with 100 mol% a close second. A series of experiments was then performed to determine the minimum loading of VAPOL in the presence of 150 and 100 mol% $B(OPh)_3$. As seen in scheme 2.16, the reaction using 5 mol% VAPOL in the presence of 150 mol% $B(OPh)_3$ produced 96% yield and 92% ee.

Scheme 2.16 VAPOL Loading with 150 mol% $B(OPh)_3$



150
1.0 equiv

31
2.0 equiv.
added over 3.0 h
through cooling
addition coil

151

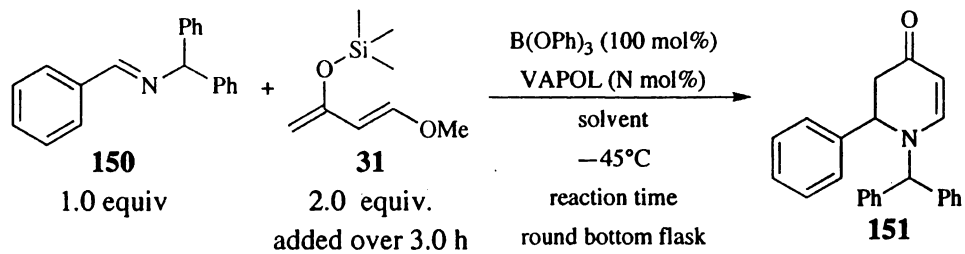
Entry[b]	VAPOL (N mol%)	reaction time (h)	yield **151** (%)	ee **151** (%)
1	5	22.5	96	92
2	2.5	26.5	91	87
3	1	24	86	83
4	0.5	24	68	66
5	0.2	23.5	56	7

a) For discussion and picture of the coil addition flask see Scheme 2.21 and Figure 2.4.
b) All reactions run at 0.2 M with respect to imine.

When half as much VAPOL was used (entry 2), the reaction was still quite efficient and resulted in 91% yield and 87% ee. It was not until the loading was decreased to 0.5 mol% VAPOL (entry 4) that the ee started to significantly drop off. This reaction (300:1 ratio achiral catalyst/chiral catalyst) resulted in 68% yield with a measured enantiomeric excess of 66%. It was not until the ratio of achiral to chiral catalyst reached 750:1 (0.2 mol% VAPOL) that the background reaction became dominant. In this case only 7% ee was observed with 56% isolated yield.

A similar study on the minimum loading of VAPOL was carried out using 100 mol% $B(OPh)_3$ (Scheme 2.17). The results are similar to those observed using 150 mol%

Scheme 2.17 VAPOL Loading with 100 mol% $B(OPh)_3$



150
1.0 equiv

31
2.0 equiv.
added over 3.0 h

151

Entry	VAPOL (N mol%)	solvent	reaction time (h)	yield **151** (%)	ee **151** (%)
1	10	CH_2Cl_2/toluene	24	94	90
2	7.5	CH_2Cl_2/toluene	24	90	90
3	5	CH_2Cl_2/toluene	24	85	90
4	5	Toluene	24	70	88
5	2.5	CH_2Cl_2/toluene	24	78	85
6	1	CH_2Cl_2/toluene	24	66	82
7	1	toluene	24	33	78
8	1	toluene	49	53	80
9	1	CH_2Cl_2	49	78	47

a) All reactions were done at 0.2 M with respect to the imine.

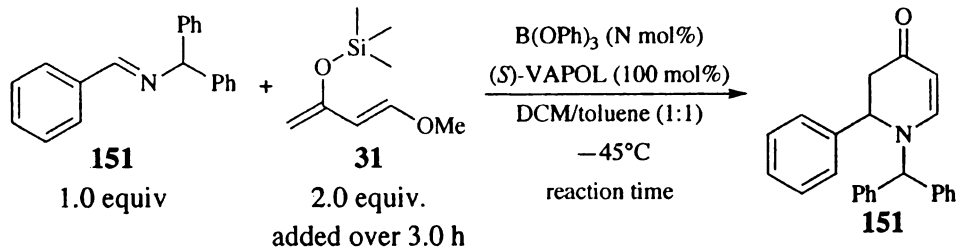
$B(OPh)_3$ (Scheme 2.16). It was not until the VAPOL loading was decreased to 2.5 mol% that the ee dropped below 90%. This reaction gave 78% yield and 85% ee (entry 5). Decreasing VAPOL loading to 1 mol% (entry 6), resulted in 66% yield and 82% ee. A few other experiments were done using 1 mol% VAPOL in pure toluene or CH_2Cl_2. When the reaction was done in pure toluene (entry 7 and 8), 33% yield and 78% ee was observed for the reaction that was allowed to stir for one day and 53% yield and 80% ee was observed for the two day reaction. Allowing the reaction to stir longer increased the yield, which shows again that reactions in toluene are slower than those in CH_2Cl_2. The two-day reaction was repeated in CH_2Cl_2 and the yield increased to 78%, but it was not

surprising that the ee dropped to 47% as this difference in solvent has been seen several times before (i.e. Scheme 2.9).

The best reaction conditions from the catalyst loading experiments was found to be 150 mol% $B(OPh)_3$ and 5 mol% VAPOL which gave 96% yield and 92% ee. This reaction was only attempted one time and similar results were obtained from reactions using 100 mol% $B(OPh)_3$. $B(OPh)_3$ is readily available and very cheap so cost was not taken into consideration when deciding the optimal catalyst loading for this reaction. It was unclear how other types of substrates would behave in the presence of excess $B(OPh)_3$, so it was decided that 5 mol% VAPOL and 100 mol% $B(OPh)_3$ would be used as the optimal catalyst loading for this reaction.

Some information was desired about what the outcome of the reaction would be if only the chiral catalyst was involved. In other words, what is the asymmetric induction in the absence of any background reaction, is it 90% ee or is it higher? A set of experiments was performed using a stoichiometric amount of VAPOL (Scheme 2.18) to

Scheme 2.18 Reactions Using 100 mol% VAPOL



151
1.0 equiv

31
2.0 equiv.
added over 3.0 h
in 3 mL solvent

151

Entry	$B(OPh)_3$ (N mol%)	flask type	reaction time (h)	yield **151** (%)	ee **151** (%)
1[a]	100	COIL[d]	24	65	11
2[b]	300	rbf	18	71	28
3[b]	1000	COIL[d]	39	28	74

a) Reaction run at 0.03 M with respect to the imine.
b) Reaction run at 0.2 M with respect to the imine.
c) Reaction run at 0.02 M with respect to the imine.
d) For discussion and picture of the COIL flask see Scheme 2.21 and Figure 2.4.

find the answer and the results were quite interesting. The first experiment was done using a catalyst prepared with 100 mol% VAPOL and 100 mol% $B(OPh)_3$ (entry 1). As was seen for the reaction using 5 mol% VAPOL and 5 mol% $B(OPh)_3$ in the preparation of the catalyst (Scheme 2.15, entry 1), the reaction was not efficient at all and in this case an even worse result was obtained (65% yield and 11% ee). The cause for this poor results could be due to the incomplete formation of the catalyst and significant background reaction with the non-chiral $B(OPh)_3$ catalyst (see Scheme 2.13 for reactions with $B(OPh)_3$). It was found during concurrent studies by Gang Hu in the Wulff group that the active catalyst contains three boron atoms (see discussion in Chapter 6). This finding offers insight as to why the reactions using a catalyst prepared from a 1:1 ratio of $B(OPh)_3$ and VAPOL is inferior. In order to prepare the active catalyst, three equivalents of boron are needed thus when less than three equivalents of $B(OPh)_3$ is used, the

likelihood that the catalyst is formed is much less probable. Another reaction was performed where a 3:1 ratio of $B(OPh)_3$ to VAPOL was used (entry 2) and 71% yield and 28% ee was observed in this reaction. The concentration for this reaction was 0.2 M and with the large amount of catalyst present, solubility became a major issue, which could have been the cause for the inefficiency of that reaction. Lastly, one reaction was carried out where a 10:1 ratio of $B(OPh)_3$ to VAPOL (1000 mol% and 100 mol% respectively) was used to prepare the catalyst (entry 3). The concentration in this reaction was 10 times more dilute, but still the reaction only gave 28% yield and 71% ee. Other reactions using lower catalyst loadings were done during the course of these studies where the concentration of the reaction was studied over the range of 0.4 M to 0.024 M and little effect on the selectivity of the reaction although the very dilute reactions were slightly slower. Unfortunately, these experiments with stoichiometric amounts of VAPOL ligand employed did not provide any information about whether the 89-91% ee represents the maximum asymmetric induction for this catalyst in the absence of background reaction.

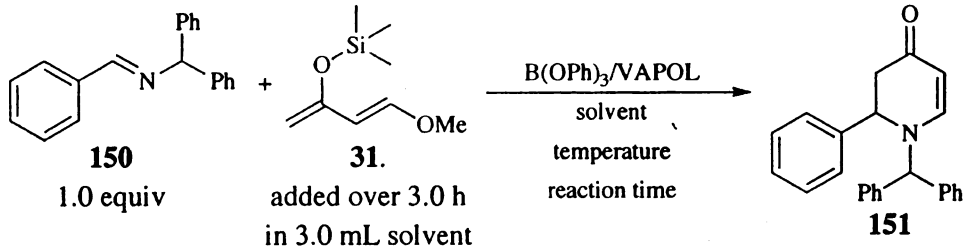
2.2.6 Danishefsky's Diene: Quality, Equivalents, and Addition Time and Temperature

Another aspect of the reaction that needed to be considered was the purity and source of materials used as well as how many equivalents of each were used. Purity was found to be important for VAPOL as well as how much of it was used (catalyst loading). Some exploration was done looking at the purity of the diene, diene equivalency, and addition method. The general experimental procedure for the reaction was to prepare the catalyst, transfer it to the imine, cool the reaction to the desired temperature, and finally add the diene to the reaction mixture. This experimental protocol allowed for the

modification of how the diene was added and in this section, this and the other aspects dealing with the diene will be discussed.

The discussion will first examine the effect of purity and source of the diene and on how many equivalents were needed to produce the best results (Scheme 2.19). The

Scheme 2.19 Source and Equivalents of Diene[a]



150
1.0 equiv

31.
added over 3.0 h
in 3.0 mL solvent

151

Entry	**31** (equiv)	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	temperature (°C)	flask type	reaction time (h)	yield **151** (%)	ee **151** (%)
1	2[b]	30	10	CH_2Cl_2	−40	rbf	20	12	ND
2	1.1[c]	100	5	CH_2Cl_2/Tol (1:1)	−45	COIL[d]	24	72	90
3	1.5[c]	100	5	CH_2Cl_2/Tol (1:1)	−45	COIL[d]	24	76	89
4	2[c]	100	5	CH_2Cl_2/Tol (1:1)	−45	COIL[d]	24	85	90

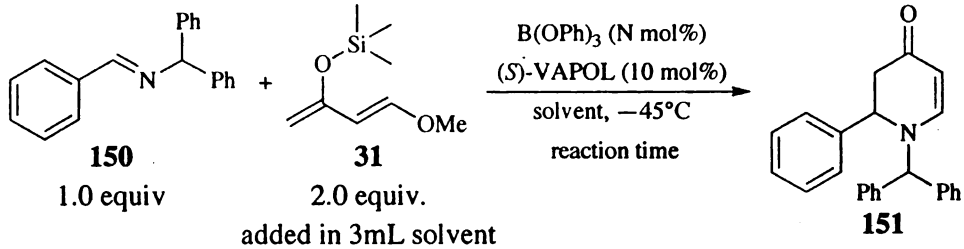
a) All reactions were done at 0.2 M with respect to the imine
b) Danishefsky's diene was purchased from Aldrich and used without further purification.
c) Danishefsky's diene was independently prepared and purified by distillation.
d) For discussion and picture of the COIL flask see Scheme 2.21 and Figure 2.4.

diene used for all the optimization studies discussed prior to this point was prepared by treating *trans*-4-methoxy-butene-2-one with KHMDS and trapping the enolate with TMSCl. The resulting diene (**31**) was purified by bulb-to-bulb distillation before use in the reaction. When the reaction was performed with 2.0 equivalents of Danishefsky's diene purchased from Aldrich (entry 1), only a 12% yield could be obtained after 20 hours. Since this reaction was terrible with respect to yield, the ee was not determined. It was found that the material purchased from Aldrich could be purified and the reaction

would work just fine, but due to the expense of the diene ($108/5g), and since it would have to be purified anyway, it was far better to independently prepare Danishefsky's diene. A series of experiments were then performed using 1.1, 1.5, and 2.0 equivalents of the diene (entries 2, 3, and 4 respectively). It was found that the amount of diene had no effect on the selectivity of the reaction. This is consistent with a control experiment, which revealed that in the absence of catalyst, there was no reaction between the diene and imine. On the other hand, the amount of Danishefsky's diene used did have a slight effect on the yield. The reaction using 1.1 equivalents of the diene gave 72% yield and increasing the amount to 1.5 equivalents resulted in 76% yield. The yield of the reaction was increased further to 85% when 2.0 equivalents of diene were used. Even when the diene was independently prepared, the starting materials needed were relatively expensive so it was not desirable to use a large excess of this reagent. Thus, no reactions for this series of experiments were done using more than 2.0 equivalents, which was chosen as the optimized amount.

The temperature studies described earlier showed that temperature played a very important role in the outcome of the reaction (Scheme 2.7). These reactions for the temperature studies were performed, as mentioned above, by adding the diene to a premixed and precooled solution (−45°C) of the imine and catalyst. If the diene solution were added at room temperature all at one time in 3 mL solvent, the temperature in the reaction vessel would rise significantly at least for a short period of time. In order to alleviate this problem, one could add the diene solution slowly using a syringe pump. Several reactions were done to determine if the slow addition would have a significant effect on the outcome of the reaction (Scheme 2.20). When the diene solution was added

Scheme 2.20 Danishefsky's Diene Addition Times[a]



150 1.0 equiv

31 2.0 equiv. added in 3mL solvent

151

Entry	**31** addition time (h)	$B(OPh)_3$ (N mol%)	solvent	temperature (°C)	reaction time (h)	Yield **151** (%)	ee **151** (%)
1	0	30	CH_2Cl_2	−45	24	69	78
2	3	30	CH_2Cl_2	−40	20	77	80
3	18	30	CH_2Cl_2	−40	20	23	ND
4	0	30	Toluene	−45	96	70	86
5	3	30	Toluene	−45	18	22	89
6	9	30	Toluene	−45	48	63	86
7	12	30	Toluene	−45	48	61	87
8	3[b]	100	Toluene	−45	22.5	68	83

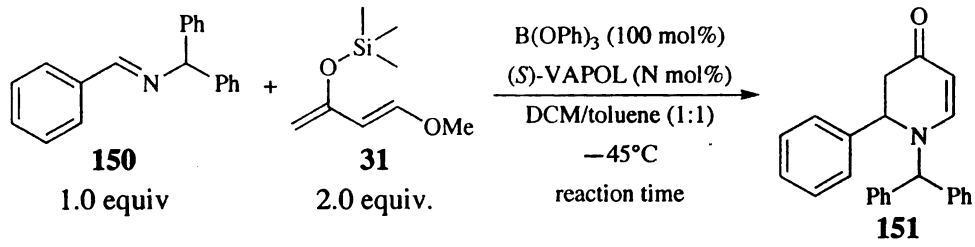
a) All reactions were done at 0.2 M with respect to the imine.
b) For this reaction, the catalyst was transferred to the imine in 2 mL solvent and the resulting solution was added to the diene (solution in 3 mL solvent) over 3 hours.

all at one time (entry 1), the reaction in CH_2Cl_2 gave 69% yield and 78% ee. When the diene was added dropwise over 3 hours under the same conditions (entry 2) both the yield and ee increased slightly to 77% and 80% respectively. However, when diene was added over 18 hours (entry 3) the reaction was very poor and only gave 23% yield. Since the yield was so low, the ee was not determined. When adding the diene very slowly, the diene solution has to be in a syringe for the entire addition time. The longer the diene is in the syringe, the possibility becomes greater for the diene to decompose. Also, since plastic syringes were used, it is possible that some contaminants from the syringe or plunger could dissolve in the organic solvent and get added to the reaction also having a negative effect on the outcome of the reaction.

A similar series of experiments were done using toluene as the solvent (Scheme 2.20, entries 4-7). A small increase in % ee from 86% to 89% was observed upon going from addition of the diene all at one time to addition over three hours, which was similar to that seen in CH_2Cl_2. The yield of these two reactions in toluene are dramatically different but the reaction time for one is five times longer. Slowing the addition down even more to 12 hours did not have a positive effect on the selectivity of the reaction as the outcome was within the ±1 experimental error. The effect of adding a solution of the catalyst and imine slowly (three hours) to the diene was also examined and this gave a good yield but a slightly depressed induction (83% ee) (entry 8). It can be concluded from this set of experiments that a 3 hour addition of the diene to the catalyst/imine solution was best for the efficiency of the reaction.

It was found that a slow addition of the diene was necessary and presumably this slow addition of a room temperature solution of the diene could cause the temperature of the reaction mixture to rise slightly and thus influence the selectivity of the reaction. For the ease of physically performing this addition, it would be desirable to not have to use the syringe pump. If it was indeed a temperature issue, then cooling down the solution of the diene before it was added would fix the problem and a few reactions were performed to determine this effect (Scheme 2.21). First, the diene solution was cooled to the exact

Scheme 2.21 Temperature of the Addition of Danishefsky's Diene[a]



150 1.0 equiv

31 2.0 equiv.

151

Entry	**31**, addition time (h) / temperature (°C)	VAPOL (N mol%)	flask type	reaction time (h)	Yield **151** (%)	ee **151** (%)
1	0 / −45[b]	5	rbf	24	84[c]	86[c]
2	0 −78[d]	5	rbf	23	85	88
3	0.08 / −45[e]	5	COIL[f]	22	83	88
4	3 / −45[f]	5	COIL[f]	30	93	90

a) All the reactions were run at 0.2 M with respect to the imine.
b) The diene solution was cooled to −45°C in a separate flask and transferred quickly via syringe to the reaction vessel.
c) Average of two runs.
d) The diene solution was cooled to −78°C in a separate flask and transferred quickly via syringe to the reaction vessel.
e) These reactions were done side by side and the room temperture solution of the diene was added dropwise over 5 minutes.
f) The diene was added through the cooling coil.

reaction temperature (−45°C) and then transferred all at one time to the reaction vessel via syringe (entry 1). This reaction gave 84% yield and 86% ee. Its possible that the temperature of the diene solution increased slightly during the transfer process so another reaction was done where the diene solution was cooled to −78°C before it was transferred (entry 2). The yield remained about the same, but the ee increased two percent to 88% ee. These results indicated that temperature was probably an issue. The additional effort to cool the diene solution again raised the question of ease of operation of the reaction. It was thought that it would be nice if there were some way to add a room temperture solution of the diene and have it be cold before it came into contact with the rest of the reaction mixture. It was envisioned that one way to accomplish this would

be to submerge the reaction vessel very deep into the cooling bath and when adding the diene solution to the flask, be sure that the tip of the needle touched the side of the flask, so the solution runs down the side of the flask, and be cooled to the reaction temperature before it reached the contents of the flask. This proved to be not very easy to do and also leads to some variability in how the reaction was done each time. Inspired by an invited seminar speaker at Michigan State University who discussed the use of a flask with a side arm coil through which a solution could be added that would be cooled to the reaction temperature before it transversed the length of the coil and reached the reaction flask. This particular flask appeared to be very fragile and probably not very convenient to use. In collaboration with the glass blower at Michigan State University (Scott Bankroff), a modified, more robust, version of this flask was developed (Figure 2.4). The flask is

Figure 2.4 Glassware with Cooling Addition Coil

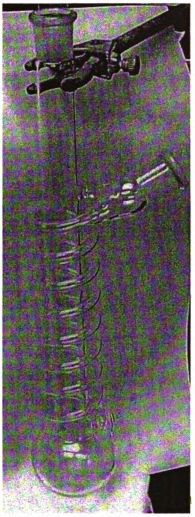


Image 1

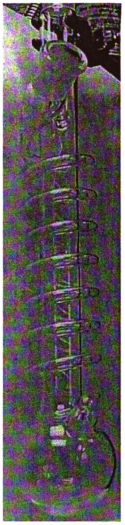
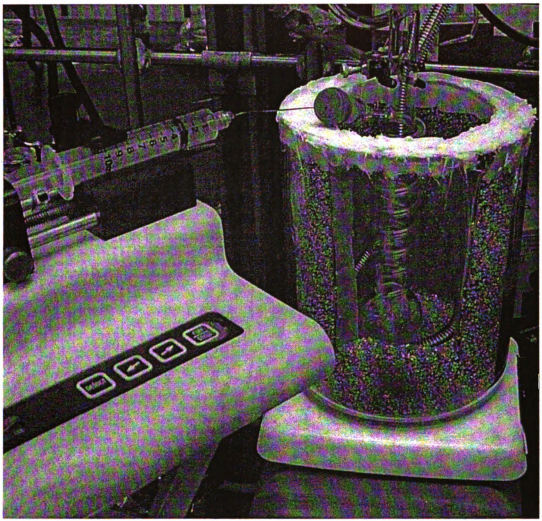


Image 2

simply a 50 mL round bottom flask with an extended neck and wrapped around it is a glass coil that is topped with a 14/20 ground glass joint and the bottom of which opens into the top side of the round bottom flask. In addition, to make the flask slightly less fragile, a glass support connects the top of the coil to the neck of the flask.

In order to use this glassware effectively, a deep cooling bath was needed such that a major portion of the coil could be submerged allowing for the solution of the diene to properly cool as it runs down the coil and into the flask. The entire setup is depicted in Figure 2.5. With the flask and cooling bath in hand, two experiments were attempted,

Figure 2.5 Reaction Setup

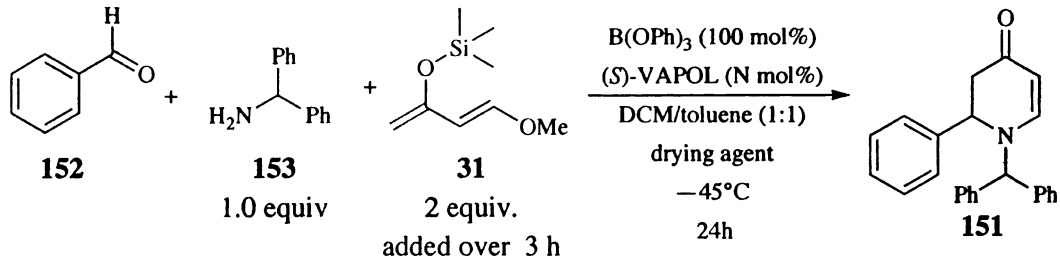


one where the diene solution was added all at one time through the addition coil (table 2.20, entry 3) and the other where the diene was added over 3 hours (Table 2.20, entry 4). The result for the addition all at once was about the same as for the −78°C addition for the traditional round bottom flask giving 83% yield and 88% ee. However, when the

diene was added slowly over three hours via syringe pump through the cooling addition coil, the ee increased to 90%. The difference in ee from the round bottom flask to the coil flask is small, however, it was found that using the coil flask that the results were slightly more reproducible and eliminated the need to cool the diene solution before addition. This flask and reaction setup seen in Figure 2.5 was determined to be the optimal setup for this *aza*-Diels-Alder reaction and was used later for testing the generality of this reaction.

For every reaction described in this chapter up to this point, the imine used was prepared by treating benzaldehyde (**152**) with Bh-NH_2 (**153**) in the presence of magnesium sulfate and the crude solid material was purified by recrystallization to ensure high purity of the imine. To make this reaction even more attractive, it would be desirable to find conditions where the imine could be prepared *in situ* and the reaction run without further purification of the imine. Several attempts using a variety of drying agents were made to determine if this would be feasible (Scheme 2.22). These reactions

Scheme 2.22 *In Situ* Preparaton of the Imine[a]



152 **153** 1.0 equiv **31** 2 equiv. added over 3 h in 3 mL solvent through cooling coil **151**

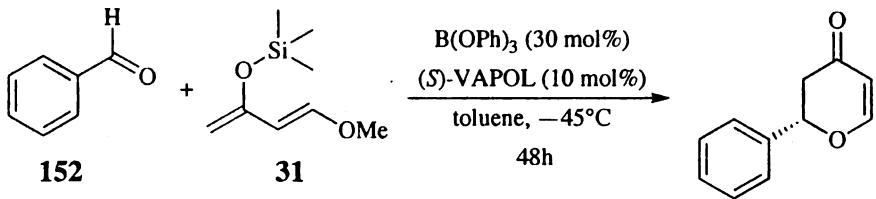
Entry	**152** (equiv)	VAPOL (N mol%)	Drying agent	yield **151** (%)	ee **151** (%)
1	1.0	5	4Å M.S.[b]	81	56
2	1.0	10	4Å M.S.[b]	80	72
3	1.1	10	4Å M.S.[b]	85	74
4	1.1	10	$MgSO_4$[b]	81	70
5	1.1	10	Na_2SO_4[c]	82	70
6	1.1	10	$CaSO_4$[d,e]	75	79
7	1.1	10	$CaSO_4$[e,f]	79	83
8	1.1	10	$CaSO_4$[d,g]	82	77
9	1.1	10	$CaSO_4$[f,g]	92	78

a) All reactions were done at 0.14 M with respect to the amine.
b) 0.15 g of the drying agent was used.
c) 0.16 g of the drying agent was used.
d) $CaSO_4$ that contained blue indicator was used.
e) 0.22 g of the drying agent was used.
f) $CaSO_4$ without the indicator was used.
g) 0.136 g of the drying agent was used.

performed by first allowing benzaldehyde and aminodiphenylmethane to stir with the drying agent overnight. The catalyst was then transferred directly to the flask containing the imine solution, cooled to −45°C and then the diene added. The first drying agent attempted using this procedure for this reaction was 4Å molecular sieves. When 5 mol% VAPOL was employed (entry 1), the reaction only gave 81% yield and 56% ee. The same reaction with 10 mol% VAPOL gave the same yield but an improved induction (72% ee) (entry 2). In these reactions, the amine and benzaldehyde are both Lewis bases

that could potentially compete for binding to the catalyst if the formation of the imine was not complete. The amine **153** would be the strongest Lewis base, thus the rest of the reactions were run using 1.1 equivalents of benzaldehyde. Benzaldehyde also has the potential to participate in the heteroatom Diels-Alder reaction with Danishefsky's diene and in fact, one reaction was attempted with the VAPOL-boron catalyst (Scheme 2.23).

Scheme 2.23 Heteroatom Diels-Alder Reaction of Benzaldehyde



152

31
2 equiv.
added over 3 h
in 3 mL solvent
through cooling coil

151-O
67% yield
28% ee

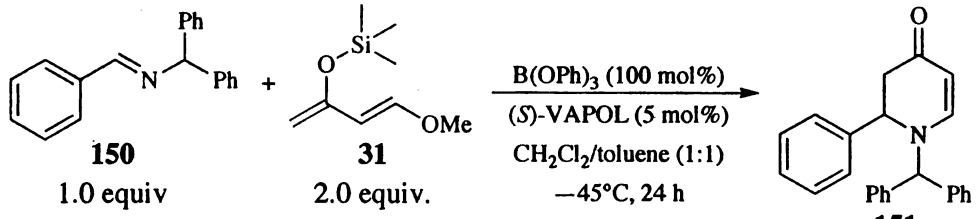
The reaction was run in toluene for 48 hours at −45°C and gave 67% yield of **151-O** and 28% ee. Other than possibly using up 0.1 equivalent of the diene, this was not a problem because if the *oxo*-Diels-Alder adduct was formed it could be separated at the end of the reaction (no attempts were made to determine if this product was formed). When 1.1 equivalents of benzaldehyde was used for the reaction in the presence of 4Å molecular sieves, 85% yield and 74% ee was observed (Scheme 2.21, entry 3). Although this was slightly better than with 1.0 equivalents of benzaldehyde (entry 2), it is not as good as seen in the optimization studies using the preformed imine (Scheme 2.21, entry 4). For this reason, magnesium sulfate, sodium sulfate, and calcium sulfate were examined as other potential drying agents. Magnesium sulfate and sodium sulfate both gave 70% ee with yields in the low 80's (entries 4 and 5). The last drying agent attempted was calcium sulfate. In order to test this drying agent, Dri-rite with the blue indicator on the

calcium sulfate was first examined. This reaction was attempted using 0.22 g of Dri-rite (entry 6) and surprisingly this gave a significantly better result (79% ee) than the other drying agents. Inspired by this result, the same reaction was repeated with calcium sulfate without the indicator (entry 7), which gave 83% ee. The asymmetric induction for all the drying agents was lower than for the preformed imine (Scheme 2.21, entry 4) and it was thought that this could be due to the Lewis acidic nature of the drying agents. As a result, two more reactions were attempted where half the amount (0.136 g) of the drying agent was used with and without the indicator (entries 8 and 9 respectively). The yield in each case was excellent, but the selectivity still remained unsatisfactory. Unfortunately, this set of experiments lead to the conclusion that the preparation of the imine *in situ* was not the optimal way to do this reaction.

2.2.7 Optimal Conditions

The discussion in this chapter has focused on the many variables that could have an effect on the catalytic asymmetric *aza*-Diels-Alder reaction. There are almost infinite possibilities for different combinations when so many variables exist for a catalytic asymmetric reaction. The effects of many conditions as well as various combinations thereof were explored and the optimal conditions found are expressed in Scheme 2.24.

Scheme 2.24 Optimal Conditions



150
1.0 equiv

31
2.0 equiv.
added over 3.0 h
through cooling
addition coil

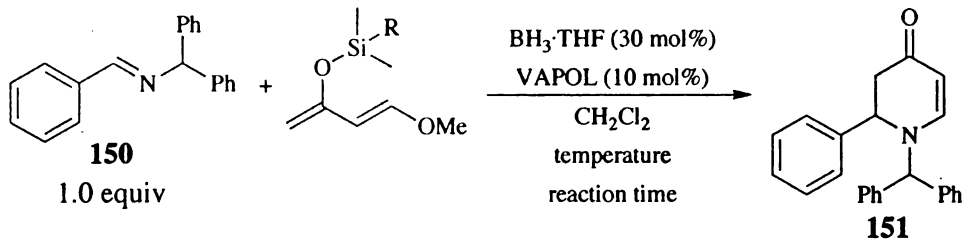
151
85% yield
90% ee

It was found that using the catalyst prepared from **5 mol% VAPOL** and **100 mol% $B(OPh)_3$** was best for this reaction. Although the yield could be increased from 85% to 94% using 10 mol% VAPOL, the ee remained the same. In order to preserve the expensive ligand, it was decided that 5 mol% VAPOL would be used as the optimal loading for the screening of additional substrates. Very low temperatures resulted in low reaction yields and reactions run below −40°C, failed to produce higher ee's. In addition, if the reaction temperature was increased above −40°C, both the selectivity and yield drop off significantly. It was then concluded from the temperature studies as well as many of the other reactions run around this temperature that **−45°C** was optimal for the *aza*-Diels-Alder reaction using the VAPOL-$B(OPh)_3$ catalyst. With respect to solvent, it was found that using a mixture of CH_2Cl_2/CCl_4 (1:2), resulted in a selectivity of 94% ee. However, since 90% ee could still be achieved using **CH_2Cl_2/toluene (1:1)**, the less expensive and less toxic solvent combination, was chosen as the desired optimal solvent for this reaction. As far as the diene is concerned, it was found that **2.0 equivalents of Danishefsky's diene** were necessary to produce yields in the middle 80s. It was also found that the addition time and temperature was important to the outcome of the reaction. A **three-hour addition of the diene** using a syringe pump was found to be the optimal addition time for obtaining the best selectivity. The **cooling coil addition glassware** was found to slightly enhance this selectivity (2% to give 90% ee), but more importantly the cooling coil flask obviated the need to precool the diene solution and lead to improved reproducibility. Satisfactory results could also be achieved using a traditional round bottom flask, but for the optimal results and ease of reproducibility, it was best to use the special glassware. Several reactions were performed using these

optimal conditions with the finding that the reaction gave **83.5±7% yield** and **89±1% ee**. The stage was now set to test these reaction conditions by exploring a broad range of substrates.

2.3 Appendix

Scheme 2.25 Jon Antilla's Results



150
1.0 equiv

151

Entry	Diene (equiv)	Diene addition time (h)	temperature (°C)	reaction time (h)	yield **151** (%)	ee **151** (%)	Conversion (%)
1[a]	1.3	0	−20	18	ND	ND	62
2[a]	1.3	0	−20 to RT[e]	overnight	ND	ND	60
3[a]	2	0	−40	22	55	84	100
4[a]	2	0	−40	17	46	82	89
5[a,g]	2	0	−40	24	43	80	80
6[b]	2	3	−40	6	67	77	80
7[b]	2	3[d]	−40	18	0	ND	0
8[b]	1.2	3	−40	7	ND	ND	35
9[b]	2	3	−40	16	63	80	90
10[b]	2	1	−40	18	ND	ND	67
11[b]	2	1	−75	18	31	ND	50
12[b]	2	4	−40	45	ND	ND	30
13[a]	2	0	−40	1	ND	ND	low
14[b]	2	3	−40	overnight	ND	ND	30
15[c]	1.13	0	−40 to RT	18+24[f]	ND	ND	17%
16[b,h]	2	3	−40 to RT	18	ND	ND	0

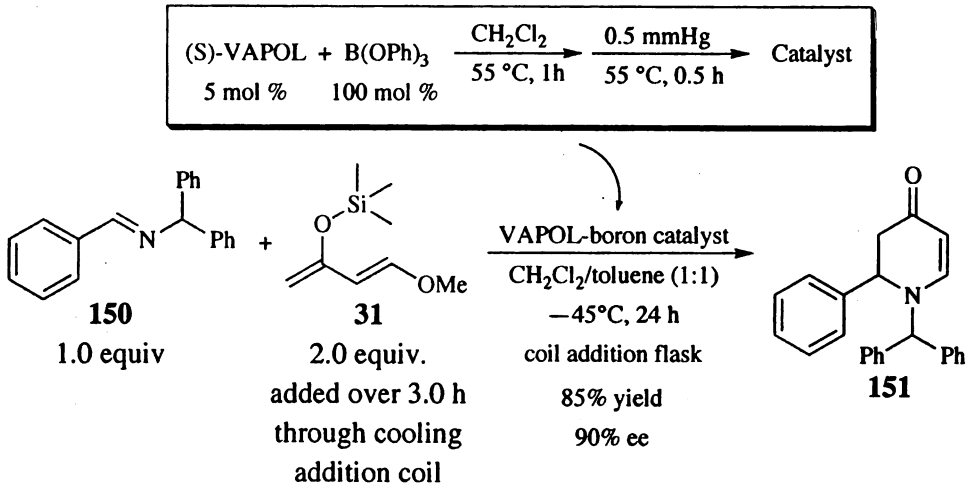
a) R = Me and the reaction run at 0.5 M with respect to the imine.
b) R = Me and the reaction run at 0.33 M with respect to the imine.
c) Reaction run at 0.1 M with respect to the imine.
d) The imine was added over 3 hours to a previously prepared solution of the catalyst and the diene.
e) The reaction was stirred at −20°C until the diene addition was complete and then warmed immediately to room temperature.
f) The reaction was stirred at −40°C for 18 hours and then 24 hours at room temperature.
g) 4Å molecular sieves were added to the reaction vessel.
h) R = *t*-Bu.

CHAPTER 3

SUBSTRATE SCOPE

It was seen in the previous chapter that the optimization of the catalytic asymmetric *aza*-Diels-Alder reaction utilizing the catalyst derived from triphenylborate and VAPOL proved to be quite tedious. The optimization for the said reaction was accomplished using the imine (**150**) derived from aminodiphenylmethane (**153**, Bh-NH_2) and benzaldehyde (**152**) (as described in chapter 2) and the optimal conditions are outlined in Scheme 3.1. It is desired for any new methodology that the conditions be

Scheme 3.1 Optimal Conditions for the *aza*-Diels-Alder



sufficiently general to accommodate many functional groups and multiple substrate classes using the optimized conditions. With the optimal conditions found, the stage was set to screen a variety of substrates to test the generality of the reaction.

In an ideal circumstance, studying the substrate generality of the reaction should be facile whereby using the optimal conditions would give satisfactory results without further optimization. It is also well known that, in the world of chemistry, rarely does the ideal circumstance exist and this reaction proved to be no different.

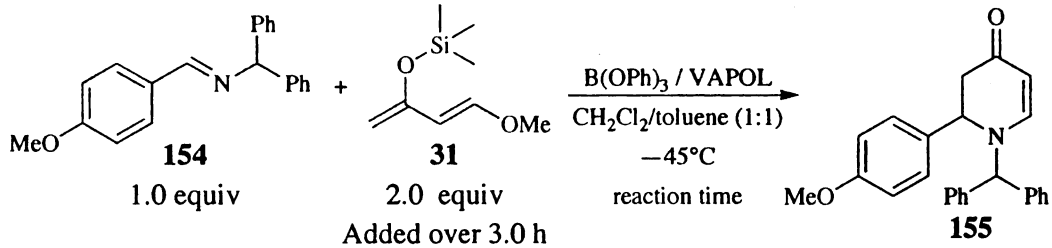
The initial screening process was accomplished by first using the optimal conditions (Scheme 3.1). Two runs were performed for each substrate and the average of the two runs was taken to determine if these conditions gave satisfactory results. If the two reactions gave dissimilar results, then a third run was performed. If the average reaction yields or enantioselectivity for any particular substrate was not satisfactory or if it was thought that the results could be improved, substrate specific optimization was undertaken. For most substrates it was found that by either doubling the loading of (*S*)-VAPOL to 10 mol% or by increasing the reaction time, satisfactory results could be achieved. This was not the case for all substrates and for those exceptions a broader range of conditions were explored to enhance the efficiency of the reaction. A discussion of all substrates and the necessary optimization for each will be discussed in this chapter.

3.1 Aromatic Substrates

The first class of substrates studied was imines prepared from aromatic aldehydes. The scope included examples to determine the effect of electron donating groups, electron withdrawing groups on the aryl ring, and the effect of increasing the steric bulk by placing a substituent in the *ortho* position of the arene. The first substrate to be

discussed is the imine (**154**) prepared from 4-methoxybenzaldehyde and Bh-NH_2 (Scheme 3.2). For the initial screening using the optimal conditions (entries 1 and

Scheme 3.2 *aza*-Diels-Alder Reaction of 4-methoxybenzaldimine (154)



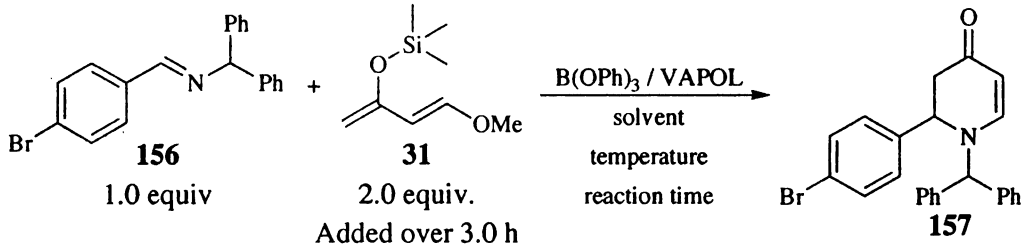
Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	reaction time (h)	yield **155** (%)	ee **155** (%)
1	A	100	5	24	45	82
2	A	100	5	24	41	71
3	A	100	5	24	43	84
4	B	100	5	47	58	77
5	C	100	10	24	60	88
6	D	100	10	48	71	90

2), a yield of 45 and 41% was observed, but there was a 9% difference in the enantiomeric excess. Due to this significant discrepancy in the enantiomeric excess, the reaction was repeated (entry 3) and 43% yield and 84% ee was obtained. This result more closely represented entry 1 so these results were considered to be the true values. However, analysis of these results indicated that both the enantiomeric excess and yield were unacceptable. Attempting to increase the yield, another reaction was carried out, which was allowed to stir for 47 hours. The yield increased to 58%, but only a 77% ee was observed. In an effort to increase the ee, the loading of (*S*)-VAPOL was increased to 10 mol% (entries 5 and 6). When the reaction was allowed to stir for 24 hours, the reaction produced 60% yield and 88% ee whereas a two day reaction time gave only slightly higher yield (71%) and enantiomeric excess (90%). Although the yield was only

moderately high, the enantiomeric excess reached an acceptable level so no further optimization of this substrate was attempted.

The focus was then turned to electron withdrawing groups on the aryl imine. First, the imine (**156**) prepared from Bh-NH_2 and 4-bromobenzaldehyde was studied (Scheme 3.3) followed by the imine (**159**) prepared from 4-nitrobenzaldehyde

Scheme 3.3 *aza*-Diels-Alder Reaction of 4-bromobenzaldimine (156)

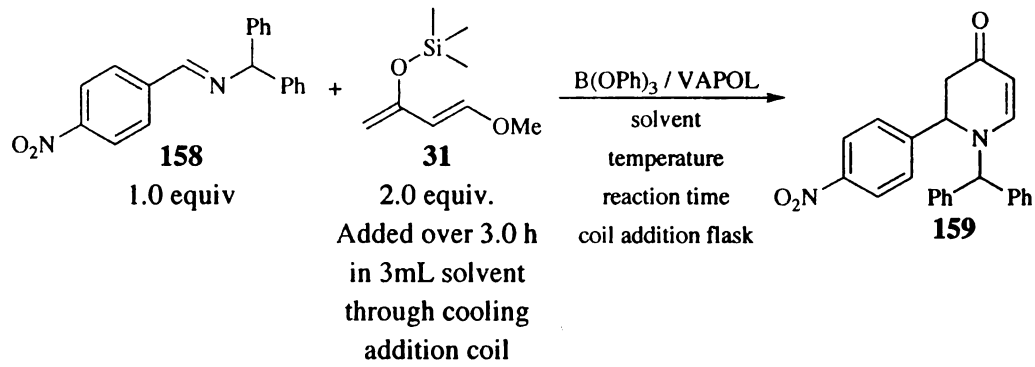


Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	temperature (°C)	flask type	reaction time (h)	yield **157** (%)	ee **157** (%)
1	A	100	5	CH_2Cl_2/toluene (1:1)	−45	COIL	24	82	90
2	A	100	5	CH_2Cl_2/toluene (1:1)	−45	COIL	24	86	88
3	B	30	10	CH_2Cl_2	−40	rbf	26	69	68

(Scheme 3.4). For the 4-bromo substrate **156**, the two initial runs (entries 1 and 2) gave similar and satisfactory results with and average of 84% yield and 89% ee. One other reaction was accomplished much earlier while the optimization studies were ongoing where 30 mol% $B(OPh)_3$ and 10 mol% VAPOL was used to prepare the catalyst. CH_2Cl_2 was used as the solvent and the reaction was carried out at −40°C for 26 hours. The reaction resulted in inferior results giving 69% yield and only 68% ee.

The 4-nitrobenzaldimine **158** was not a very good substrate and the best yield obtained was 71% and the best ee was 75%. The initial two runs (entries 1and 2) using the optimal conditions gave an average of 65% yield and 73% ee. Several attempts were then made to try and increase both the yield and ee. First, the VAPOL loading was increased to 10 mol% (entries 3 and 4). This did not make the reaction more efficient and only gave 69% and 64% yield and both gave 73%

Scheme 3.4 *aza*-Diels-Alder Reaction of 4-nitrobenzaldimine (158)

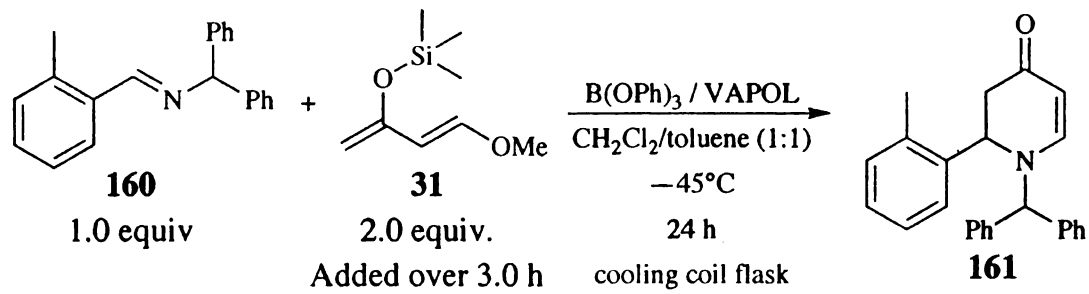


Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	temperature (°C)	reaction time (h)	Yield **159** (%)	ee **159** (%)
1	A	100	5	CH_2Cl_2/toluene (1:1)	—45	24	59	75
2	A	100	5	CH_2Cl_2/toluene (1:1)	—45	24	71	71
3	B	100	10	CH_2Cl_2/toluene (1:1)	—45	24	69	73
4	B	100	10	CH_2Cl_2/toluene (1:1)	—45	24	64	73
5	C	100	10	CH_2Cl_2/toluene (1:1)	—78 to —45	42	64	75
6	D	30	10	CH_2Cl_2/toluene (1:1)	—45	24	49	64
7	E	100	10	toluene	—45	24	27	66

enantiomeric excess. It was thought that it might be possible to increase the asymmetric induction by cooling the reaction to a colder temperature and thus the reaction was started at −78°C and after 3 hours was allowed to warm slowly to −45°C. After a total of 42 hours reaction time, a 64% yield and 75% ee was obtained for the adduct **159**. One explanation for the low asymmetric induction could be that the background reaction may be competing with this substrate. However, when the catalyst was prepared from 30 mol% $B(OPh)_3$ and 10 mol% VAPOL (entry 6), the asymmetric induction fell to 64% ee. During the optimization studies it was observed that reactions run in toluene, gave higher enantiomeric excess although they were slower. Therefore, the reaction of imine **158** was carried out in toluene (entry 7), and as expected, the reaction was much slower giving only 27% yield, but unfortunately the ee remained low giving only 66% ee. The reason for the inefficient nature of the reaction for this substrate is unclear at this point. One possible explanation could be that the oxygens of the nitro group compete with the imine nitrogen for binding with the catalyst. Another possibility could be that the strong electron withdrawing nature of the nitro group effectively pulls enough electron density out of the imine nitrogen causing it to be a much weaker Lewis base causing coordination to the catalyst to be much weaker. This could result in increased conformational flexibility of the bound imine and as a result, less facial discrimination of the imine. Ultimately this effect would cause the reaction to be much less efficient.

It was also of interest to probe the effect of sterics by introducing substituents on the aryl group in the *ortho*-position. The first substrate studied was imine **160** with a methyl group in the *ortho* position of the aromatic ring (Scheme 3.5). The imine was

Scheme 3.5 *aza*-Diels-Alder Reaction of 2-methylbenzaldimine (160)



160
1.0 equiv

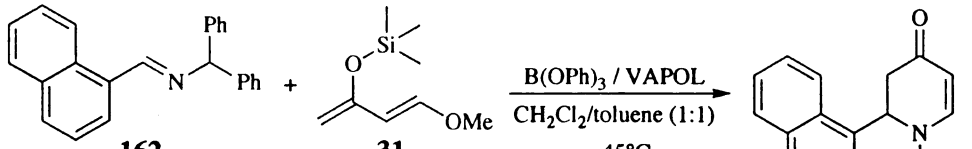
31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

161

Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	yield **161** (%)	ee **161** (%)
1	A	100	5	83	94
2	A	100	5	82	93

prepared in the usual fashion from 2-methylbenzaldehyde and Bh-NH_2. It was found that when the optimal conditions were employed, the reaction gave better than satisfactory results; 83% and 82% yield with 94% and 93% ee, respectively, was observed for two separate runs. From this result, it seems that the increased steric bulk close to the imine aided in the efficiency of the reaction. Another sterically bulky aryl substrate derivative (**162**) studied was that prepared from 1-naphthaldehyde and Bh-NH_2 (Scheme 6). The initial attempts using the optimal conditions gave reproducible results

Scheme 3.6 *aza*-Diels-Alder Reaction of 1-naphthaldimine (162)



162
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through cooling
adidtion coil

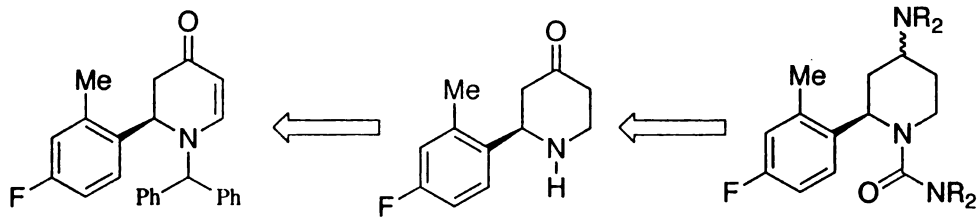
163

Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	yield **163** (%)	ee **163** (%)
1	A	100	5	75	86
2	A	100	5	78	86
3	B	100	10	79	90

with an average yield of 76.5% yield and both reactions resulted in 86% enantiomeric excess. After observing an increased asymmetric induction for the *ortho*-methyl (**160**) substrate, it was difficult to discern why the ee would drop to 86% for this substrate. Increasing the loading of VAPOL to 10 mol% gave 79% yield and 90% ee, which is a slightly better result than with 5 mol% VAPOL.

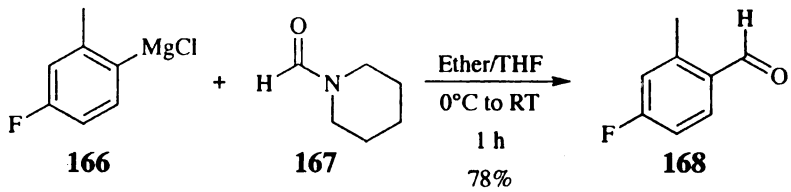
The second to last aromatic substrate screened was imine **169,** which contains a methyl group in the *ortho*-position and fluorine in the *para*-position. This substrate was selected in order to determine the absolute configuration of the *aza*-Diels-Alder product. In 2004, Hayashi, at Kyoto University in Japan, synthesized a key intermediate in the synthesis of a tachykinin antagonist[64] (Figure 3.1). A simple hydrogenation of the *aza*-

Figure 3.1 Tachykinin Antatonist and Key Intermediate



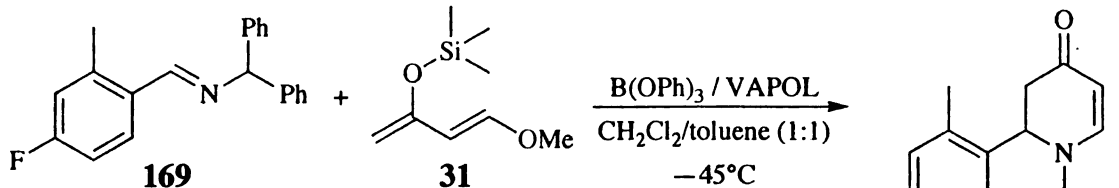
Diels-Alder product **170** would produce the same key intermediate **164**. Under the hydrogenation conditions, the benzhydryl group would be removed and the double bond reduced. All the previous imines were prepared from commercially available aldehydes, were used to prepare the imine, however the 4-fluoro-2-methylbenzaldehyde **168** is not commercially available so it had to be prepared (Scheme 3.7). A known procedure[65] was

Scheme 3.7 Preparation of 4-fluoro-2-methylbenzaldehyde (168)



followed where 1-formylpiperidine was treated with the commercially available 4-fluoro-2-methyl-phenylmagnesiumchloride as a solution in THF to give the aldehyde **168**. The resulting aldehyde was then transformed into the imine **169** in the standard way by condensing it with Bh-NH_2 and it was then screened in the *aza*-Diels-Alder reaction (Scheme 3.8). Using the optimal conditions (entry 1) it was found that the reaction

Scheme 3.8 *aza*-Diels-Alder Reaction of 4-fluoro-2-methylbenzaldimine (169)



169
1.0 equiv

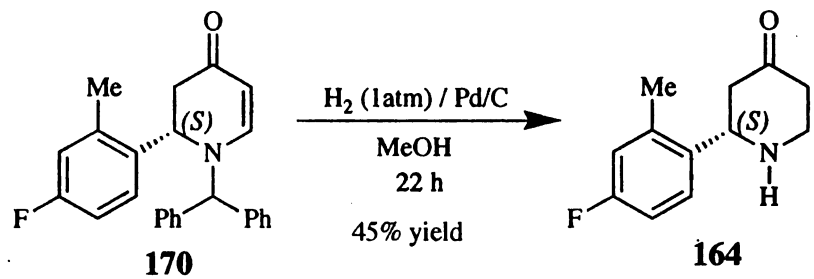
31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through cooling
adidtion coil

170

Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	reaction time (h)	yield **170** (%)	ee **170** (%)
1	A	100	5	24	68	90
2	B	100	5	50	84	89
3	C	100	10	24	78	91

produced 68% yield and 90% ee. The yield was a little low, so the same reaction was repeated and allowed to stir for 50 hours (entry 2). The ee remained about the same, but the yield showed an increase to 84%. One attempt was also made using 10 mol% VAPOL (entry 3) and in this reaction the ee only increased one percent to 91%. With the cycloadduct **170** in hand, it was then converted to the key intermediate **164**, which had previously been prepared by Hayashi[64] in a catalytic asymmetric Michael reaction. (Scheme 3.9).

Scheme 3.9 Reduction of 4-fluoro-*2*-methylphenyl-Diels-Alder Adduct (164)



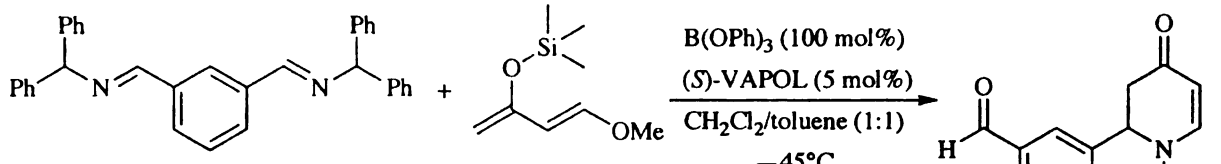
170

164

The product was dissolved in methanol and treated with hydrogen gas in the presence of palladium on carbon to give the desired deprotected and reduced product (*S*-**164**). The optical rotation of this product was then determined to be $[\alpha]^{20}_{D}$ —77° (c 0.18, DMSO). The measured optical rotation of the Hayashi intermediate (*R*-enantiomer) was $[\alpha]^{20}_{D}$ +77° (c 0.18, DMSO). Therefore from this experiment it was determined that the (*S*)-enantiomer was produced in the reaction when (*S*)-VAPOL was used for the preparation of the catalyst.

The last aromatic substrate explored was the imine (**171**) prepared from isophthalaldehyde and two equivalents of Bh-NH_2 (Scheme 3.10). Only one reaction was

Scheme 3.10 *aza*-Diels-Alder Reaction of Phthalaldimine (171)



171
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through cooling
adidtion coil

172
48% yield
74% ee

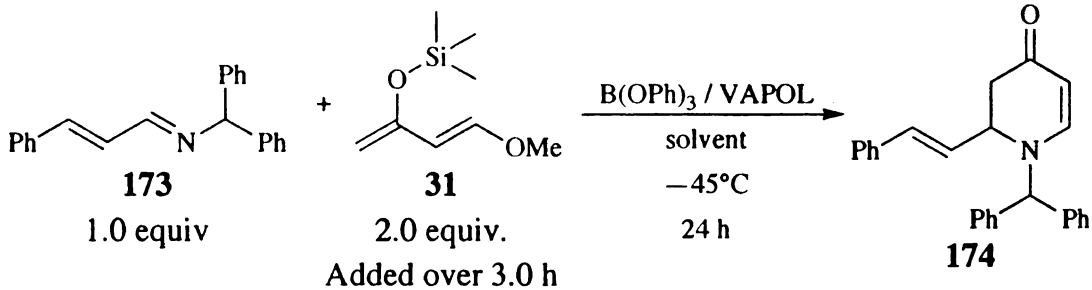
attempted for this reaction. It was expected that the reaction would produce the bis-*aza*-Diels-Alder adduct, but none of that product was observed. What actually was observed was that the mono-Diels-Alder adduct **172**. Apparently, during the workup conditions, the second imine was hydrolyzed to the aldehyde giving product **172**. Employing the optimal conditions using two equivalents of the diene per imine (4 total equivalents), 48% yield of the mono-Diels-Alder product **172** was observed with 74% ee.

3.2 α, β-Unsaturated Substrates

In order to determine if the scope of the reaction could be expanded to imines

containing α,β -unsaturated substituents, three different compounds were examined. The first was the imine **173** prepared from Bh-NH_2 and *trans*-cinnamaldehyde (Scheme 3.11).

Scheme 3.11 *aza*-Diels-Alder Reaction of *trans*-cinnamaldimine (173)



173
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent

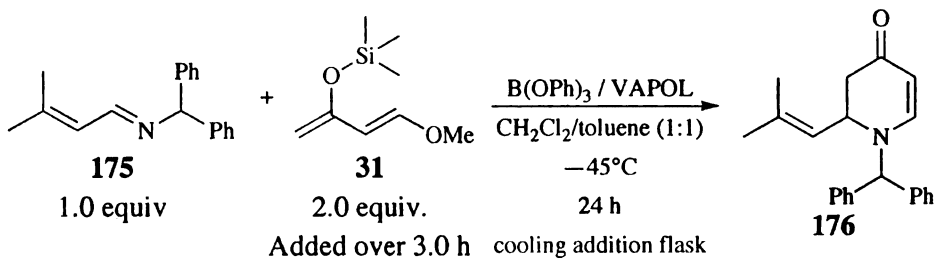
174

Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	flask type	reaction time (h)	yield **174** (%)	ee **174** (%)
1	A	100	5	CH_2Cl_2/toluene (1:1)	COIL	28	11	0
2	B	30	10	toluene	rbf	48	11	49

Using the optimal conditions, it was found that this reaction was very inefficient giving an 11% of cycloadduct **174** with 0% ee (entry 1). However, when the reaction was run in toluene using 10 mol% catalyst (3:1 $B(OPh)_3$/VAPOL, entry 2), the reaction, albeit slow, gave 49% ee.

The next α,β -unsaturated imine **175** that was studied was that prepared from 3-crotanaldehyde (Scheme 3.12). As can be seen in the table, none of the attempted

Scheme 3.12 *aza*-Diels-Alder Reaction of 3-methylcrotanaldimine (175)



175
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

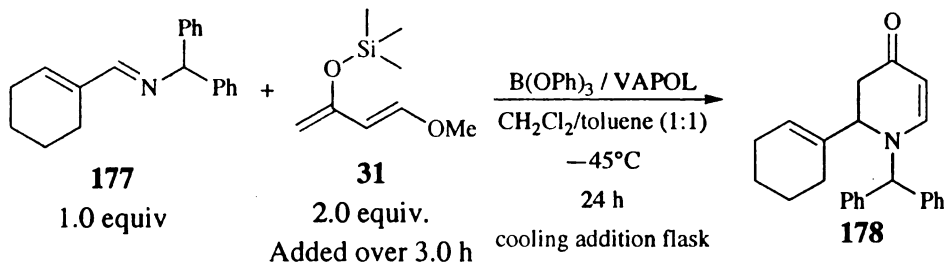
176

Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	yield **176** (%)	ee **176** (%)
1	A	100	5	0	N.D.
2	A	100	5	0	N.D.
3	A	100	5	0	N.D.
4	B	100	10	0	N.D.

reactions with this substrate produced any cycloadduct at all. This included reactions under the optimal conditions and a reaction with the catalyst prepared using 10 mol% VAPOL.

Lastly, for this class of substrate, the imine (**177**) prepared from cyclohexene carboxaldehyde was studied (Scheme 3.13). This substrate is different than imines **173** and **175** in that there is a substituent in the α-position of the α,β-unsaturated imine.

Scheme 3.13 *aza*-Diels-Alder Reaction of Cyclohexenecarboxaldimine (177)



177
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

178

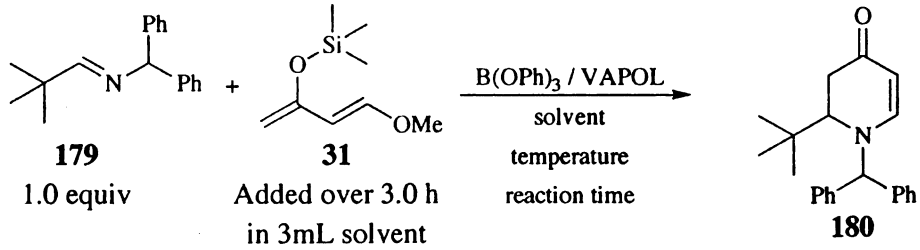
Entry	Conditions	$B(OPh)_3$ (mol%)	VAPOL (mol%)	reaction time (h)	yield **178** (%)	ee **178** (%)
1	A	100	5	24	29	93
2	B	100	10	24	32	93
3	C	100	10	48	45	94

This caused the reaction to behave quite differently from those attempted with imines **173** and **175**, and in fact proved to be similar to the secondary aliphatic substrates (discussed later). The optimal conditions produced a low yield (29%), but the ee was outstanding (93%) (entry 1). In attempt to increase the yield, 10 mol% VAPOL was employed (entry 2) but the yield only increased to 32%. When the reaction was repeated following these conditions, only allowing the reaction run for 48 hours, the yield increased to 45% and again excellent asymmetric induction (94%) was observed. It is not clear why imine **177** gives high asymmetric induction and why imines **173** and **175** either give low asymmetric induction or fail to react. It may perhaps be related to the fact that imine **177** has a substituents in the α-position of the α,β-unsaturated imine. A clear answer will have to await further studies on this class of substrates.

3.3 Tertiary Aliphatic Substrates

The next class of substrates studied was the aliphatic substituted imines. The first and only tertiary aliphatic substrate studied was the imine **179** containing a *tert*-butyl substituents, which was prepared from pivalaldehyde and Bh-NH_2 (Scheme 3.14). As

Scheme 3.14 *aza*-Diels-Alder Reaction of *tert*-butyl-aldimine (179)



179 1.0 equiv

31 Added over 3.0 h in 3mL solvent

180

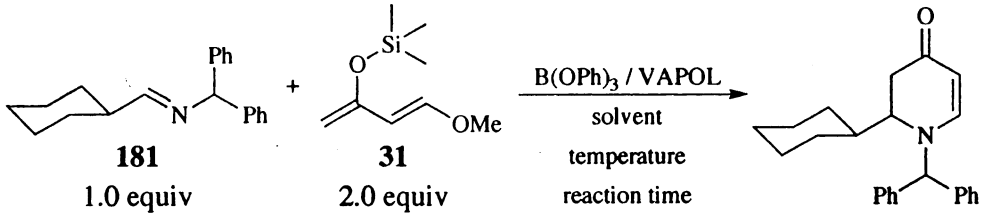
Entry	Condition	**31** (equiv)	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	temperature (°C)	flask type	reaction time (h)	yield **180** (%)
1	A	2	100	5	CH_2Cl_2/toluene (1:1)	—45	COIL	24	0
2	B	2+1	30	10	toluene	—40	rbf	16	0
3	C	2	30	10	toluene	—45	rbf	48	0
4	D	2	30	10	toluene	RT	rbf	22	0

seen from the data in the table, all attempts to effect the reaction of imine 179 and Danishefsky's diene were unsuccessful. One possible explanation could be that the bulkier *tert*-butyl group would limits the necessary interaction between the catalyst and the imine. If this were the case, then the imine would not be activated and thus no reaction would occur. Another explanation could be that even if the imine is coordinated to the catalyst, the *tert*-butyl group could be too sterically bulky to allow the relatively large nucleophile (the diene) to get close enough for the *aza*-Diels-Alder reaction to occur.

3.4 Secondary Aliphatic Substrates

Two secondary aliphatic substrates were studied, the first being the imine **181** prepared from cyclohexanecarboxaldehyde and Bh-NH_2 (Scheme 3.15). The two initial

Scheme 3.15 *aza*-Diels-Alder Reaction of Cyclohexane Carboxaldimine (181)



181 1.0 equiv

31 2.0 equiv Added over 3.0 h in 3mL solvent

182

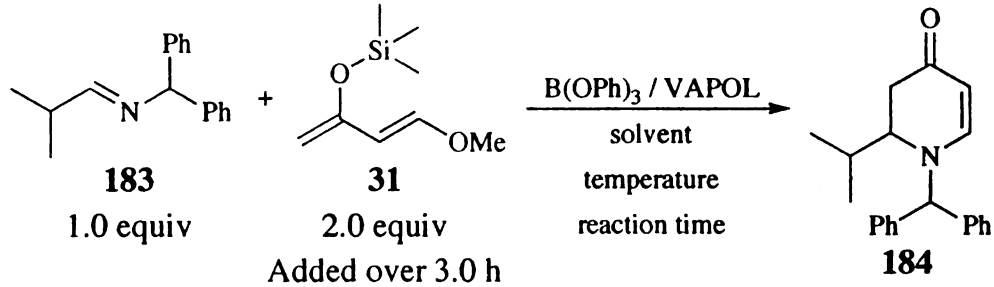
Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	temperature (°C)	flask type	reaction time (h)	yield **182** (%)	ee **182** (%)
1	A	100	5	CH_2Cl_2/toluene (1:1)	−45	COIL	24	56	74
2	A	100	5	CH_2Cl_2/toluene (1:1)	−45	COIL	24	57	78
3	B	100	10	CH_2Cl_2/toluene (1:1)	−45	COIL	24	54	91
4	C	100	10	CH_2Cl_2/toluene (1:1)	−45	COIL	46	91	93
5	D	100	10	CH_2Cl_2/toluene (1:4)	−45	COIL	24	54	94
6	E	100	10	CCl_4/ CH_2Cl_2 (2:1)	−45	COIL	46	50	93
7	E	100	10	CCl_4/ CH_2Cl_2 (2:1)	−45	COIL	48	46	90
8	F	30	10	Toluene	−45	COIL	24	45	95
9	G	30	10	Toluene	−45	rbf	43.5	76	93
10	H	30	10	Toluene	0	rbf	48	42	80

reactions were performed utilizing the optimal conditions developed for the imine from benzaldehyde (entries 1 and 2). These reactions gave an average of 56.5% yield and 76% enantiomeric excess. Due to the poor ee observed for this reaction, the VAPOL loading was increased to 10 mol% (entry 3) and as a result the % ee increased to 91%. This reaction was slow and increasing the reaction time from 24 to 46 hours increased the yield from 54% to 91% (entries 3 and 4). It was seen in the optimization studies on the phenyl imine **150** that reactions in toluene produced higher ee's and lower yields than in CH_2Cl_2. For the cyclohexyl substrate **181**, using a smaller amount of CH_2Cl_2 (1:4 CH_2Cl_2/toluene) (entry 5) increased the ee to 94% however the yield remained unchanged. During the course of this study, work was being done simultaneously in our laboratory to study the details of the aziridination reaction using a similar catalyst[56]. It was found that the ee's could be raised slightly using CCl_4 as the solvent for that reaction. Due to the fact that the melting point of carbon tetrachloride is —23°C it would not be a suitable solvent for the *aza*-Diels-Alder reaction at —45°C. It was found, however, that if a ratio of 2:1 of CCl_4/CH_2Cl_2 was used, the reaction would not freeze at —45°C. Using this solvent ratio (entries 6 and 7), the reaction of **181** gave **182** in 48% yield and 91.5% ee (average of two runs) and thus, this solvent system was not as good as the 1:1 ratio of CH_2Cl_2/toluene (entry 4). The ee of the product could be increased to 95% (entry 8) when pure toluene was used as the solvent and the catalyst was prepared using only 30 mol% triphenylborate and 10 mol% VAPOL. As expected, the reaction was slow in pure toluene and increasing the reaction time to 43.5 hours increased the yield to 76% (entry 9). Finally an attempt was made to increase the yield by raising the temperature. Thus repeating the reaction in entry 9 at 0°C (entry 10) actually lead to a decrease in yield and

in the asymmetric induction.

In addition to the cyclohexyl substrate, one more secondary aliphatic group was tested. The imine **183** was prepared from isobutyraldehyde and Bh-NH_2 and its reaction with diene 31 was examined (Scheme 3.16). All prior imine substrates were crystalline

Scheme 3.16 *aza*-Diels-Alder Reaction of Isopropylaldimine (183)



183
1.0 equiv

31
2.0 equiv
Added over 3.0 h
in 3mL solvent

184

Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	temperature (°C)	flask type	reaction time (h)	yield **184** (%)	ee **184** (%)
1	A	100	5	CH_2Cl_2/toluene (1:1)	−45	COIL	24	61	90
2	A	100	5	CH_2Cl_2/toluene (1:1)	−45	COIL	24	54	88
3	B	100	10	CH_2Cl_2/toluene (1:1)	−45	COIL	24	64	90
4	C	30	10	toluene	−50	rbf	48	57	91

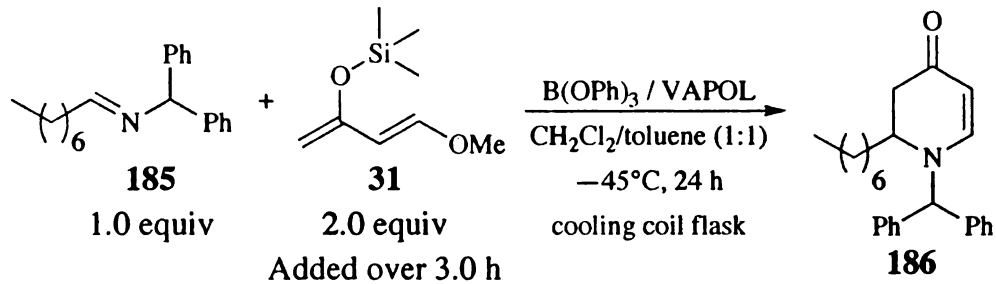
and could be purified by recrystallization, however the isopropyl substrate **183** was produced as an oil which was used in this form without further purification. The first two runs with this substrate using the optimized conditions gave an average of 57.5% yield and 89% ee (entries 1 and 2). In order to increase the yield, a third reaction was performed using 10 mol% VAPOL (entry 3). This reaction gave a slightly higher yield of 64% but the ee remained about the same at 90%. The reaction of imine **183** was also carried out in pure toluene to see if the asymmetric induction could be enhanced (entry

4). As had been seen before the reaction was slower in toluene and the increase in % ee was within experimental error and perhaps not significant.

3.5 Primary Aliphatic Substrates

The next logical step was to then look at primary aliphatic substrates to see if the optimized protocol was applicable to this substrate class. The first choice was the imine prepared from octanal and Bh-NH_2 (Schemes 3.17-3.19). Employing the optimal

Scheme 3.17 *aza*-Diels-Alder Reaction of *n*-heptylaldimine (185)

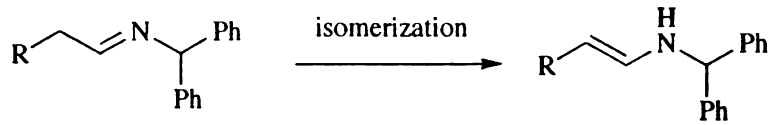


Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	yield **186** (%)	ee **186** (%)
1	A	100	5	45	0
2	A	100	5	37	5
3	B	100[a]	0	31	N.A.
4	C	100[b]	0	40	N.A.

a) triphenylborate used directly from bottle without further purification
b) triphenylborate used after going through the catalyst preparation cycle (55°C, 1 h and 0.1 mmHg, 0.5 h)

conditions (entries 1 and 2), the cycloadduct **186** was obtained only in moderate yield with an average of 41% yield over two runs, and even more disappointingly the ee was less than or equal to 5% for both runs. One possible explanation for the lack of ee could be that under these conditions, enamine formation (Figure 3.2) could be taking place to

Figure 3.2 Isomerization of Primary Alkyl Imines to Enamines

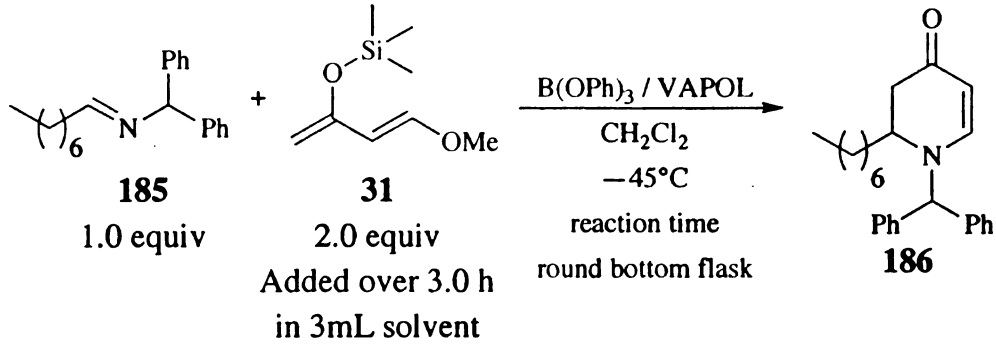


187 188

give a much stronger Lewis base which in turn would bind much stronger to the active catalyst only allowing the background reaction to occur. To get a feel for whether or not this was the case, two reactions were done using $B(OPh)_3$ alone with no VAPOL. First, one reaction was carried out using $B(OPh)_3$ right out of the bottle (entry 3). This reaction gave 31% yield of the product, which was lower than the yield when the VAPOL catalyst was employed. During the preparation of the VAPOL-boron catalyst, any excess $B(OPh)_3$ would of course be taken through the catalyst preparation cycle. Therefore, to insure the same boron species were present as would be during the attempted asymmetric reaction, another reaction was performed using $B(OPh)_3$ that had been treated to the same catalyst preparation procedure (entry 4). This reaction gave 40% yield, which is about the same as observed when the VAPOL catalyst was used. This suggests that it is indeed possible that the background reaction could be the only one taking place for this primary substrate. It is also entirely possible that the VAPOL catalyst for these substrates does not produce any selectivity.

To decrease the possibility of any background reaction, the amount of $B(OPh)_3$ in the reaction was lowered and several reactions were attempted using 30 mol% $B(OPh)_3$ and 10 mol% VAPOL for the preparation of the catalyst (Scheme 3.18). The first attempt

Scheme 3.18 *aza*-Diels-Alder Reaction of *n*-heptylaldimine (185) (more attempts)



Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	reaction time (h)	yield **186** (%)	ee **186** (%)
1	A	30	10	24	9.4	N.D.
2	B[a]	30	10	24	15.5	0
3	B[a]	30	10	24	21	0
4	C	30	10	22	24	4
5	D[b]	30	10	21	21	0
6	E[b,c]	30	10	24.5	34	0
7	F[b,d]	30	10	21.5	47	4
8	G[b]	60	20	20	30	0

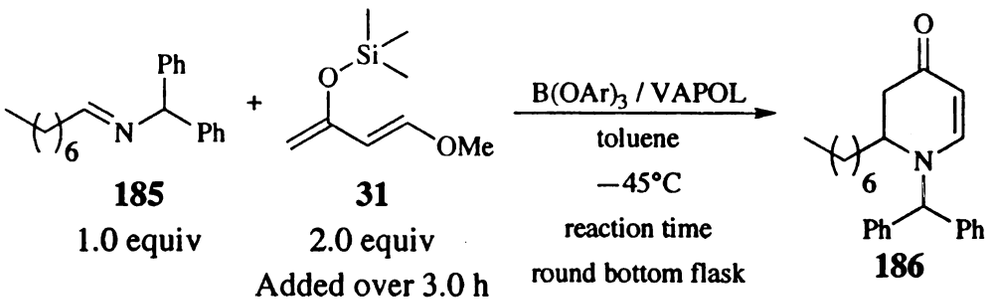
a) Aminodiphenylmethane was redistilled just before used for the *in situ* preparatioin of the imine.
b) 1.1 equivalent of the aldehyde was used for the *in situ* preparation of the imine.
c) The aldehyde was distilled and aminodiphenylmethane was purified by first distillation, then column chromatography, and distillation once more before the *in situ* preparation of the imine.
d) The aldehyde was distilled and aminodiphenylmethane was purified by column chromatography before the *in situ* preparation of the imine.

(entry 1) was done using the imine **185**, prepared in the usual fashion and used as the crude oil without purification. The reaction was quite poor and only gave 9% yield. For the rest of the entries, the imine was prepared *in situ* and the reactions were performed without removal of the magnesium sulfate. Using this method, the yield could be increased to 18% (average of two runs, entries 2 and 3) but still no asymmetric induction was observed. An additional attempt was made with the same conditions (entry 4) and this time the reaction produced a 24% yield and 4% ee. Since the imine was being prepared *in situ* with no purification, it was thought that the imine conversion might not be 100% and that that the Bh-NH_2 could be still present during the reaction and compete

for binding with the catalyst. To push the imine formation to completion, 1.1 equivalents of the aldehyde was added and any excess aldehyde was removed under high vacuum before the *aza*-Diels-Alder reaction was attempted. The first reaction where this was attempted gave only 21% yield and no enantiomeric excess (entry 5). Two reactions were attempted where careful purification of the aldehyde and BH-NH_2 was accomplished prior to the reaction (entries 6 and 7). Even when the aldehyde was distilled and the amine purified three times before use, the reaction still only gave 47% yield and 0% ee. Another reaction was attempted using double the catalyst loading where 20 mol% VAPOL and 60 mol% triphenylborate was used to prepare the catalyst. No ee was observed again for this reaction and the yield (30%) was still unsatisfactory.

Imine **185** is the first substrate that failed to produce any asymmetric induction with the VAPOL catalyst and thus other ligands (VANOL and BINOL) were examined. In addition, another triarylborate was explored as well (Scheme 3.19). In this series of

Scheme 3.19 *aza*-Diels-Alder Reaction of *n*-heptylaldimine (185) (final attempts)

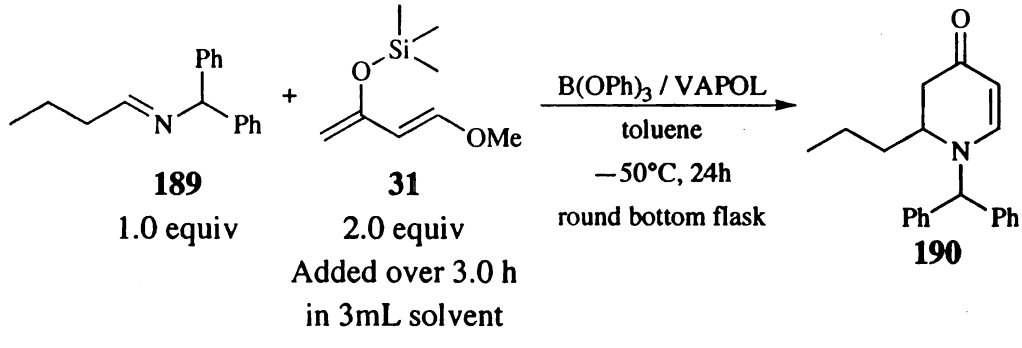


Entry	Condition	Ar (mol%)	Ligand (mol%)	reaction time (h)	yield **186** (%)	ee **186** (%)
1	A	Ph (30)	VAPOL (10)	20	17	20
2	B	Ph (30)	VANOL (10)	51	21	0
3	C	Ph (30)	BINOL (10)	51	15	18
4	D	*o*,*o*-di-Me (30)	VAPOL (10)	48	23	16

experiments, toluene was used, as it was known to be the best solvent for achieving high enantiomeric excess. The first attempt was done using 10 mol% VAPOL and 20% ee was observed, which is still low, but at least some selectivity was finally seen for this substrate. When VANOL was used (entry 2), about the same yield was obtained, but no enantioselectivity occurred using this ligand for the reaction. BINOL proved to be just about as selective as VAPOL and gave 15% yield and 18% ee (entry 3). In the last entry (entry 4), the catalyst was prepared using 30 mol% tris-(2,6-dimethylphenyl)borate and 10 mol% VAPOL. It was curious to find that this hindered triarylborate had little effect on the reaction since it gave 23% yield and 16% ee.

The imine **189** prepared from butyraldehyde and Bh-NH_2 was then looked at to determine if a shorter alkyl chain would have any effect on the reaction (Scheme 3.20). It

Scheme 3.20 *aza*-Diels-Alder Reaction of *n*-propylaldimine (189)



Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	yield **190** (%)	ee **190** (%)
1	A	30	10	35	22

was not so surprising to find that this substrate behaved similarly to the longer straight chain imine **185**. The yield of **190** was 35% and 22% ee was obtained for this substrate. The study of the primary aliphatic substrates **185** and **189** further establishes the importance of substitution at the position α to the imine.

The study of primary aliphatic substrates raises the question of why the enantioselectivity drops off so drastically when there is no substitution at the α-position. To be able to give a good explanation of this, it is necessary to know the structure of the catalyst. Just as the studies in this thesis were coming to a close, studies within the group were beginning to shed light on the structure of the catalyst (see Chapter 6 for discussion of the catalyst). It could be that the imine is binding to the catalyst in two different orientations, each of which results in a different stereochemical outcome. Furthermore, it is possible that by increasing the steric bulk at the α-position one of the orientations is favored leading to a majority of one stereochemical outcome and the high ee's that are observed. These are all speculations and once the catalyst structure is determined, hopefully a reasonable explanation for the drop in ee will be evident. As mentioned earlier, it is also known that primary aliphatic imines are not particularly stable and are prone to isomerize to an enamine (Figure 3.2). Lewis acids can influence the rate of isomerization and if the imines are indeed isomerizing, it is also possible that the enamine competes with the imine for binding to the catalyst thus inhibiting the chiral catalyst and leaving predominantly a non-asymmetric background reaction.

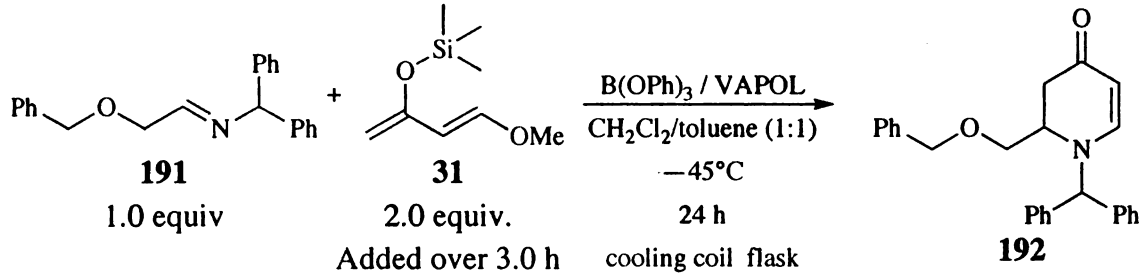
3.6 Modifiable Substrates

To make this methodology more attractive, it would be desirable to at least have a successful reaction using a substrate containing functionality that could be easily modified to give a primary aliphatic side chain in separate operations. In addition, expanding the generality to substrates containing heteroatoms would also be desirable from the aspect that they provide an easily modified handle for further modification.

3.6.1 α-Alkoxy Substrates

Two substrates containing oxygen at the α-position were studied, the first being the imine **191** prepared from commercially available benzyloxyacetaldehyde and the second being the imine **197** prepared from *tert*-butyl-diphenylsilyloxy acetaldehyde. The benzyloxy substrate (**191**), when subjected to the optimal conditions (Scheme 3.21),

Scheme 3.21 *aza*-Diels-Alder Reaction of α-benzyloxyaldimine (191)



191
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

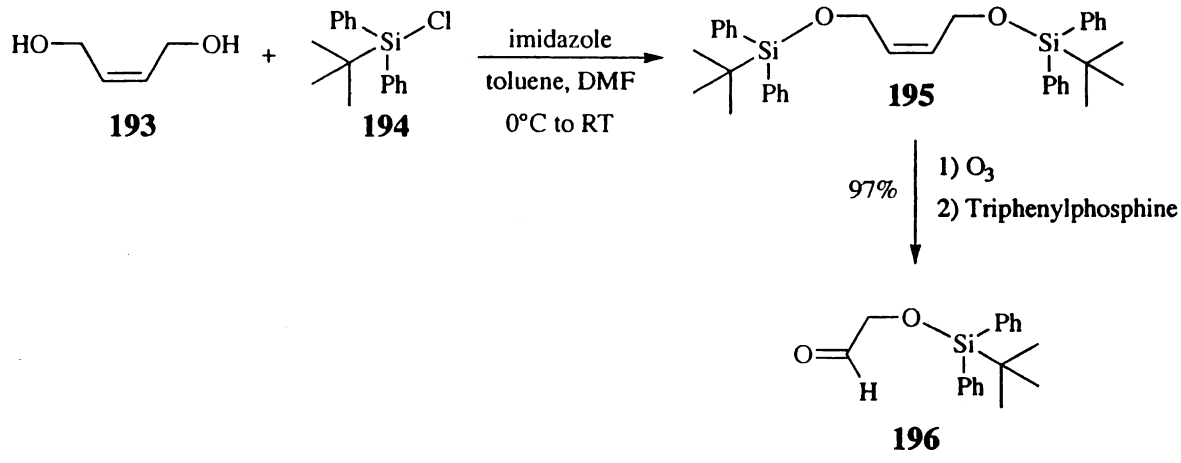
24 h
cooling coil flask

192

Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	yield **192** (%)	ee **192** (%)
1	A	100	5	37 (complex mixture)	0
2	A	100	5	51 (complex mixture)	0

gave a complex mixture compounds which were one spot by TLC analysis. The average yield of the mixture in the two runs (entries 1 and 2) was 44% and since pure product could not be isolated, this imine was not explored further. The focus then turned to the silyloxy substituents. The aldehyde **196** needed for preparation of the imine **197** is not commercially available and its synthesis is outlined in Scheme 3.22. The bis protection

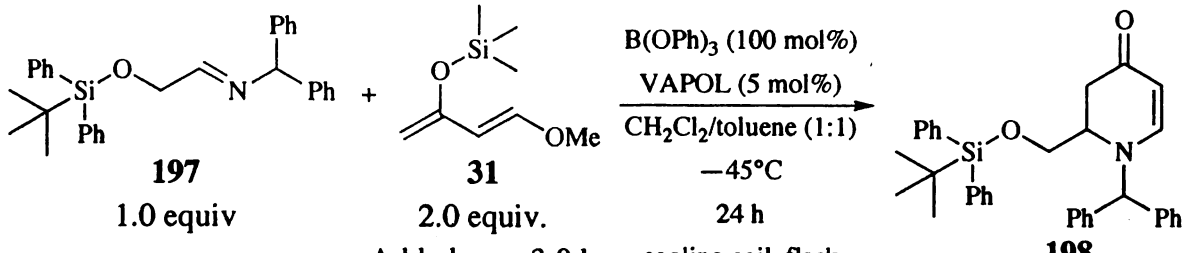
Scheme 3.22 Preparation of 2-*tert*-butyl-diphenylsilyloxyethanal (196)



193 **194** **195** **196**

of *cis*-2-butene-1,4-diol (**193**) was accomplished by treatment with TBDPSCl (**194**) and imidazole in DMF. In the second step, ozonolysis was carried out to afford the desired aldehyde (**196**) in 97% yield. The imine **197** was prepared from **196** and benzhydryl amine over $MgSO_4$ and the resulting crude oil was used in the *aza*-Diels-Alder reaction without further purification (Scheme 3.23). Only one reaction was attempted for this

Scheme 3.23 *aza*-Diels-Alder Reaction of α-*tert*-butyl-diphenylsilyloxyaldimine (197)



197
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

198
0% yield

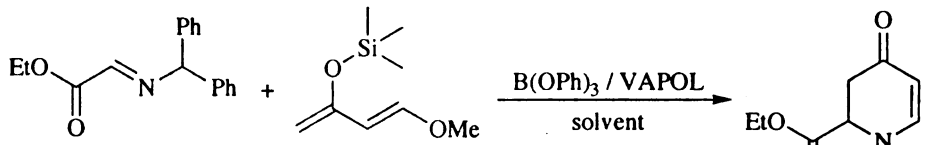
substrate following the optimal conditions. The reaction failed to produce any of the desired product.

3.6.2 Glyoxylate Ester Substrates

It was envisioned that if the *aza*-Diels-Alder reaction was successful with the

imine prepared from ethylglyoxylate or isopropylglyoxylate that the ester could be reduced and the resulting alcohol could be further functionalized in order to install other functional groups. The first substrate to be investigated was the imine **199** prepared from Bh-NH_2 and ethylglyoxylate and purified by recrystallization. This substrate was studied in detail and several reaction conditions were attempted to try and obtain high stereoselectivity (Scheme 24). For this substrate, the optimal conditions were attempted

Scheme 3.24 *aza*-Diels-Alder Reaction of Ethylglyoxaldimine (199)



199
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

200

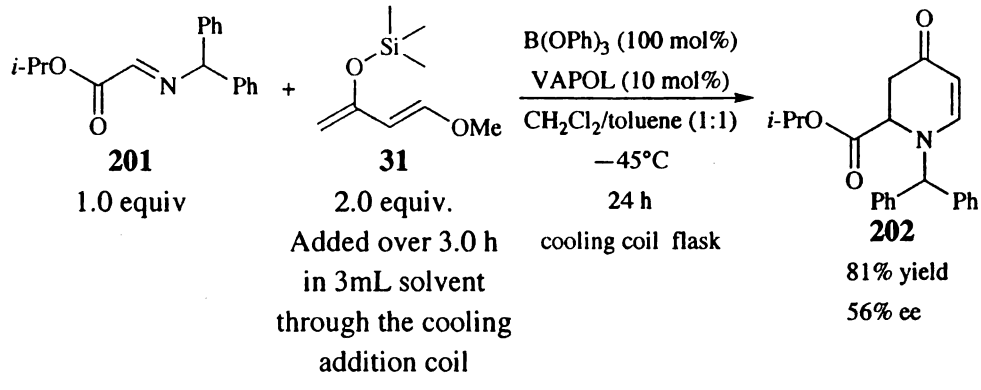
Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	temperature (°C)	reaction time (h)	yield **200** (%)	ee **200** (%)
1	A	100	10	CH_2Cl_2/toluene (1:1)	−45	24	80	52
2	B	100	10	CH_2Cl_2/toluene (1:1)	−60	24	72	35
3	C	100	10	CH_2Cl_2/toluene (1:1)	−30	24	83	55
4	D	30	10	CH_2Cl_2/toluene (1:1)	−45	24	88	53
5	E	100	10	CCl_4/ CH_2Cl_2 (2:1)	−45	24	74	60
6	F	100	10	CCl_4/ CH_2Cl_2 (2:1)	−78	48	39	30

with the exception that 10 mol% VAPOL was employed instead of 5 mol% (entry 1). This reaction gave 80% yield and 52% ee. The ester functionality is potentially an

activating group due to its electron withdrawing nature, so it was thought that imine **199** might be more reactive than the corresponding imine of benzaldehyde and lower temperatures might lead to higher selectivity. When this reaction was carried out at −60°C (entry 2), in fact, the opposite was found and the ee dropped to 35%. After observing this negative effect, an adjustment was made by varying the temperature in the other direction. The reaction at −30°C was performed (entry 3) and it was surprising to find that the yield and ee increased, albeit not significantly, to 83% and 55% respectively. To decrease the opportunity for background reaction, one attempt was made where the catalyst was prepared using only 30 mol% $B(OPh)_3$ (entry 4). The yield increased to 88% but the ee was still only 55%. Inspired by the increase in %ee observed for the reaction of imine **150** when CCl_4/CH_2Cl_2 (2:1) was used as the solvent (Scheme 2.11), two more reactions were attempted for imine **199** where this solvent mixture was used. When the reaction was carried out at −45°C for 24 hours (entry 5), the yield dropped to 74% and the ee did increase slightly to 60%. The last effort to increase the asymmetric induction involved a reaction at −78°C for about 2 days (entry 6). These conditions proved to be the worst for this substrate and only gave 39% yield and 30% ee.

To determine if steric bulk on the ester of the glyoxylate might have an impact on the outcome of the reaction, the imine **201** prepared from isopropylglyoxylate and purified by recrystallization was screened (Scheme 3.25). The optimal conditions were

Scheme 3.25 *aza*-Diels-Alder Reaction of Isopropylglyoxaldimine (201)

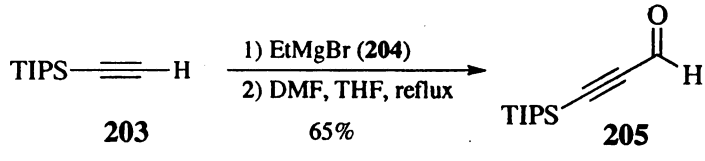


employed except that 10 mol% VAPOL and 100 mol% $B(OPh)_3$ were used to prepare the catalyst and the yield and ee were determined to be 81% and 56% respectively. This result was not significantly different from the ethyl ester substrate (Scheme 3.24, entry 1), so no other conditions were studied for this substrate.

3.6.3 Silyl-acetylene Substrate

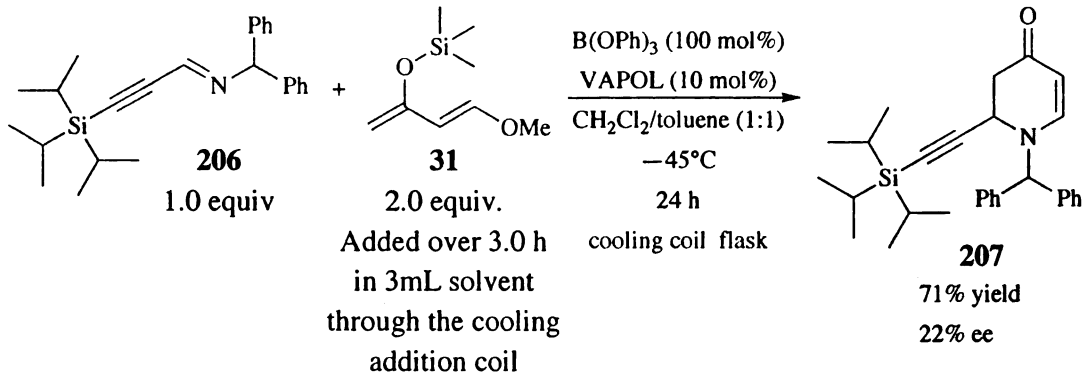
The next substrate investigated was the imine prepared from an aldehyde containing a TIPS-protected acetylene. This aldehyde was prepared (Scheme 3.26) by

Scheme 3.26 Preparation of 3-triisopropylsilyl-2-propynal (205)



treatment of TIPS acetylene (**203**) with ethylmagnesium bromide (**204**) followed by DMF in refluxing THF. This reaction gave 65% yield of the desired aldehyde **205**. The imine **206** was then prepared in the usual fashion and used as the crude oil in the *aza*-Diels-Alder reaction attempted (Scheme 3.27). The optimal conditions were used except that

Scheme 3.27 *aza*-Diels-Alder Reaction of Triisopropylsilyl-acetyleneylaldimine (206)

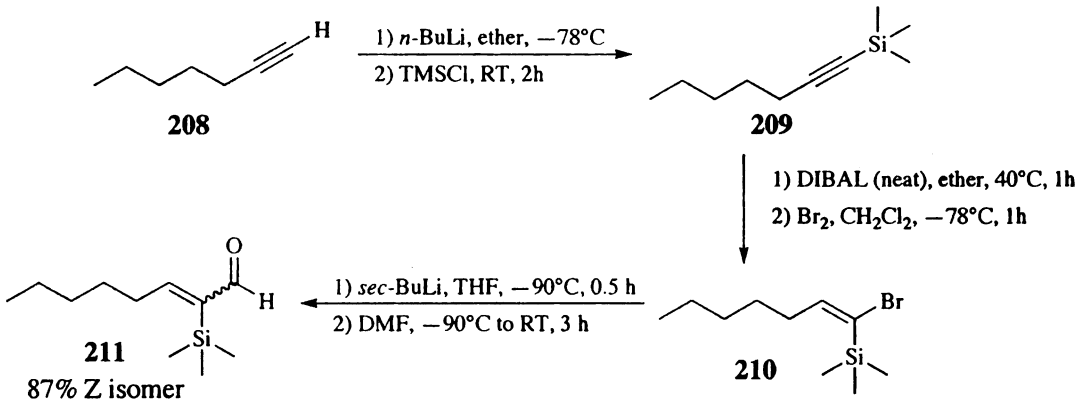


10 mol% VAPOL was employed rather than 5 mol%. Imine **206** proved to be an inefficient substrate and only gave a 71% yield of cycloadduct **207** in 22% ee. These results were also not very promising so no further optimization was attempted for this substrate.

3.6.4 α-Silyl-α,β-unsaturated Substrate

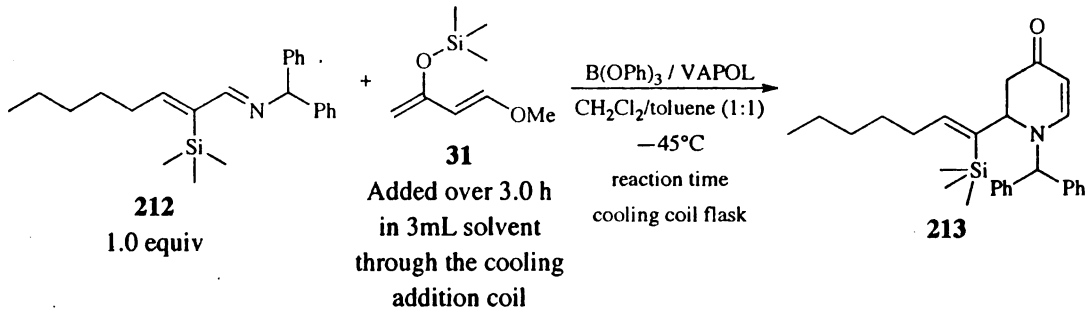
Of the three α,β-unsaturated imines that were discussed in section 3.2, the only substrate that gave high asymmetric induction was imine **177** (Scheme 3.13). This was the only substrate that had an α-substituent and this was suggestive that an α,β-unsaturated substrate containing a silyl-group in the α-position might be successful. In addition, this substrate would be useful because the silyl-group could be easily removed allowing access to the aliphatic side chain, which could not be obtained directly from the *aza*-Diels-Alder reaction of primary aliphatic imines. Preparation of the α-silylaldehyde **211** was accomplished in three steps from 1-heptyne (**208**) (Scheme 3.28). 1-Heptyne

Scheme 3.28 Preparation of Z-2-trimethylsilyl-2-ocetnal (211)



was first silylated by treatment with *n*-BuLi followed by chlorotrimethylsilane giving **209**. The regioselective bromination was then accomplished by treating 1-trimethylsilyl-1-heptyne (**209**) with neat DIBAL and subsequent quenching with bromide to give **210**. A lithium halogen exchange was then carried out followed by trapping with DMF to introduce the aldehyde functionality (**211**). It was important to ensure that the reaction temperature was kept below −85°C while adding the reagents because if not, the stereomeric purity of the olefin would be depleted. As it turned out, even when the reaction was kept very cold, only an 87% retention of the geometry of the alkene was observed. Imine **212** was then prepared from this aldehyde by treatment with Bh-NH_2. The resulting imine was an oil so this had to be used without further purification for the *aza*-Diels-Alder reaction (Scheme 3.29). The first attempt at the reaction of **212** with

Scheme 3.29 *aza*-Diels-Alder Reaction of *Z*-α-trimethylsilyl-heptenylaldimine (212)



Entry	Conditions	31 (equiv)	$B(OPh)_3$ (mol%)	VAPOL (mol%)	reaction time (h)	yield 213 (%)	ee 213 (%)
1	A	2	100	10	24	0	N.D.
2	B[a]	2.72	113	13.6	96	0	N.D.
3	C[b]	1.87	100	10	96	0	N.D.
4	D[c]	2	100	10	96	0	N.D.

a) The imine was prepared *in situ* using magnesium sulfate as the drying agent.
b) The imine was prepared *in situ* using as the 4Å molecular sieves as the drying agent.
c) The imine was prepared *in situ* using sodium sulfate as the drying agent.

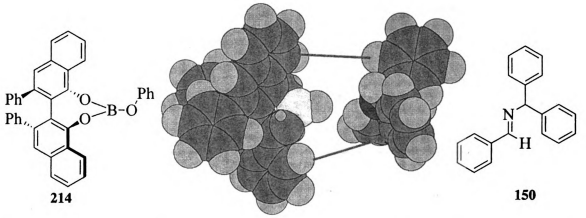
Danishefsky's diene (entry 1) was made using 10 mol% VAPOL and in 24 hours, the reaction failed to give any product. Three reactions were performed where the imine was prepared *in situ* using three different drying agents. Magnesium sulfate, 4Å molecular sieves, and sodium sulfate were all examined (entries 2-4 respectively), but neither of these reactions gave the desired product even after 3 days reaction time. It was unfortunate that this reaction did not work because this would have been a great solution to the problem of the failure of primary aliphatic imines to give significant asymmetric induction for this reaction. The solution to this problem remains unsolved and awaits future investigations.

3.7 Benzhydryl Derivatives

As mentioned before, during the course of this study, efforts were being made in the group to determine the structure of the catalyst prepared from VAPOL and $B(OPh)_3$.

In conjunction with this, other studies were being conducted to learn about the interaction of the imine with the catalyst. The originally proposed catalyst was a species that contained one boron atom where the two oxygen atoms of the ligand replaced two of the phenoxy groups on triphenylborate. It was thought that if this structure was correct, the benzhydryl group on the nitrogen of the imine **150** could have C-H edge/face pi interactions with the pi system of the ligand (see Figure 3.3). In order to test this

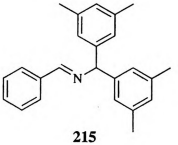
Figure 3.3 Original Propsed VANOL-Boron Catalyst/Benzaldimine Interactions



214 **150**

hypothesis, Yu Zhang (former Wulff group member) prepared imines from benzaldehyde and benzhydryl amines with a wide variety of substituents. It was anticipated that the methyl groups in the 3,3',5,5'-tetramethylbenzhdryl substituted imine **215** (Figure 3.4),

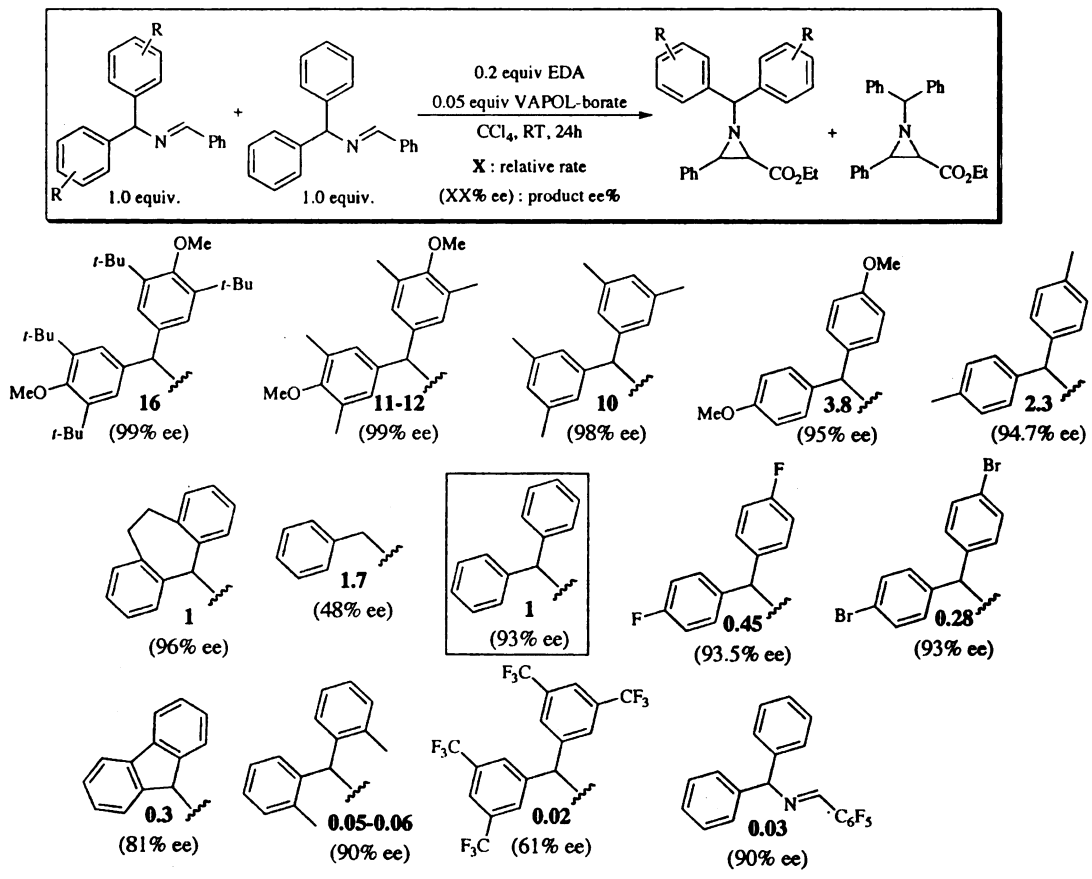
Figure 3.4 Tetramethylbenzhydrylbenzaldimine (TMB-benzaldimine) (215)



215

would block the possibility of C-H pi interactions and thus make the substrate/catalyst interaction less favorable and ultimately cause the reaction to be much less efficient. When this imine was used in the aziridination reaction, the opposite effect was observed. The ee was raised from 93% to 98% and the rate was 10 times faster. This observation prompted the synthesis of several other benzhydryl derivatives, which were also evaluated in the aziridination reaction (Scheme 3.30). The relative rates and % ee for the

Scheme 3.30 Relative Rates and Selectivity of the Azirdination Reactions of Substituted Benzhydryl Protected Benzaldimines



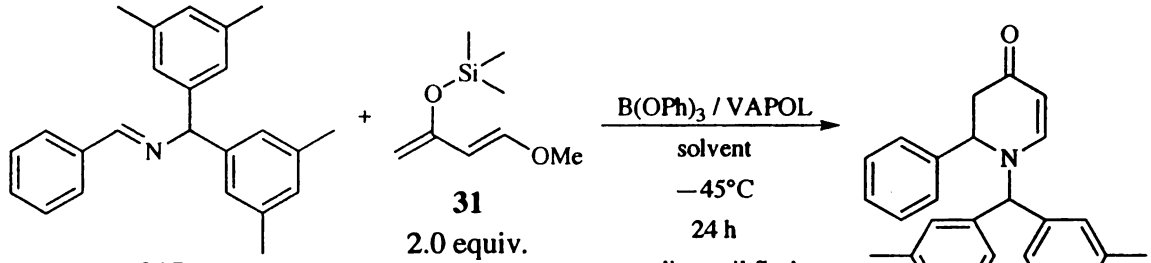
aziridination with many of these substrates are shown in Scheme 3.30. Since the rates were much faster and the reactions were more selective for some of these substituted

benzhydryl groups in the aziridination reaction, it was decided to determine if the same positive effects would be observed in the *aza*-Diels-Alder reaction. The tetramethyl (TMB), tetra-*tert*-butyl-dimethoxy (BUDAM), and dimethoxy (DAM) substituted benzhydryl groups were selected for study in the *aza*-Diels-Alder reaction.

3.7.1 Tetramethyl Benzhydryl (TMB) Substrates

First, the TMB imine **215** was studied (Scheme 3.31). Initially, the optimal

Scheme 3.31 *aza*-Diels-Alder Reaction of TMB-benzaldimine (215)



215
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

216

Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	yield **216** (%)	ee **216** (%)
1	A	100	5	CH_2Cl_2/toluene (1:1)	70	93
2	B	100	5	CCl_4/ CH_2Cl_2 (2:1)	56	91
3	C	100	10	CH_2Cl_2/toluene (1:1)	84	93
4	D	100	10	CH_2Cl_2	66	76
5	E	100	10	CCl_4/ CH_2Cl_2 (2:1)	75	95
6	F	100	10[a]	CH_2Cl_2/toluene (1:1)	79	96
7	G	100	10[a]	CCl_4/ CH_2Cl_2 (2:1)	63	93
8	H	100	10[a]	toluene	27*	82

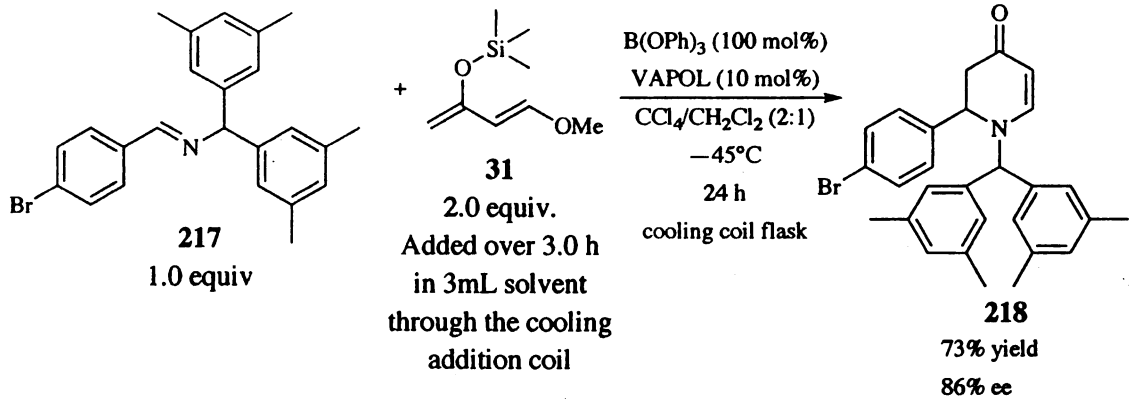
a) The catalyst was prepared in CCl_4

conditions were examined (entry 1) and the cycloadduct **216** was obtained with slightly higher asymmetric induction (3% ee) than the corresponding benzhydryl imine **150** (Scheme 3.1) but in lower yield. The same reaction was repeated using CCl_4/CH_2Cl_2

(2:1) as the solvent (entry 2) and this gave 56% yield and 91% ee. It was found that the yield could be increased to 84% by doubling the amount of VAPOL and the induction remained the same (entries 1 vs. 3). When the solvent was changed to CCl_4/CH_2Cl_2 (2:1), the ee could be increased to 95% with 10 mol% VAPOL (entry 5). Interestingly, if the catalyst was prepared in CCl_4 at 80°C rather than in CH_2Cl_2 at 55°C, and the reaction run in DCM/toluene (1:1), a 79% yield of the Diels-Alder adduct was obtained in 96% ee which is the highest achieved to date. Other solvents were explored and all were found to be inferior (entries 4, 7, and 8).

Due to the enhanced asymmetric induction observed for imine **215**, it was decided to determine if this effect was general for other substrates containing the TMB group as well. First, the 4-bromo-phenyl-TMB imine **217** was easmined (Scheme 3.32). The

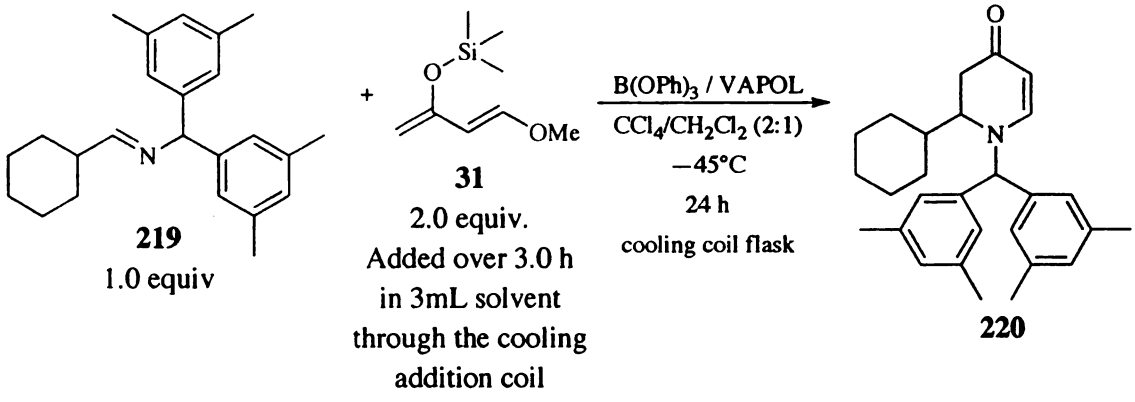
Scheme 3.32 *aza*-Diels-Alder Reaction of TMB-4-bromobenzaldimine (217)



reaction of the 4-bromo substrate **156** with the benzhydryl imine gave 89% ee (Scheme 3.3), and the corresponding TMB imine **217** gave the Diels-Alder product with 86% ee. It was also desired to determine the effect of the TMB protecting group on the reaction of aliphatic substrates. The imine **219** was then prepared from cyclohexane carboxaldehyde and the results of the *aza*-Diels-Alder reaction of this substrate are shown in Scheme

3.33. When the optimal conditions with 10 mol% VAPOL) were employed (entry 1), the

Scheme 3.33 *aza*-Diels-Alder Reaction of TMB-cyclohexane carboxaldimine (219)



Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	yield **220** (%)	ee **220** (%)
1	A	100	10	30	70
2	B	100	10[a]	28	80

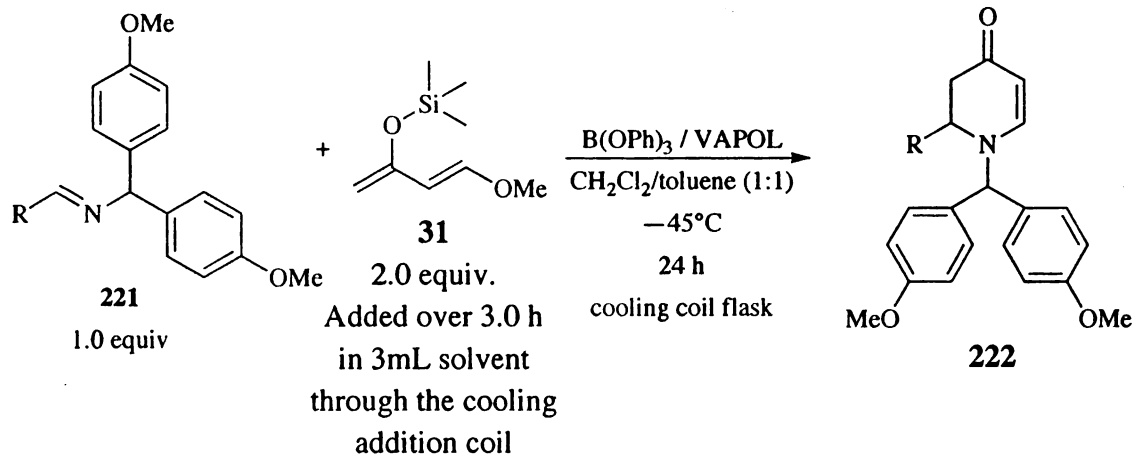
a) The catalyst was prepared in CCl_4 at 80°C.

reaction gave 30% yield of **220** with an asymmetric induction (70% ee) that was much lower than that for the unsubstituted benzhydryl imine **181** (93% ee) under the same conditions (Scheme 3.15, entry 6). The ee could be increased to 80% when the catalyst was prepared in CCl_4 at 80°C (entry 2). Although the reaction with the TMB imine **215** from benzaldehyde showed increased induction (Scheme 3.31), this proved to not be a general effect as the reactions of the cyclohexyl and 4-bromophenyl derivatives both produced poorer results.

3.7.2 DAM Substrates

The next benzhydryl derivative studied was the DAM-imines (**221**) (Scheme 3.34). For each of the substrates, the yields were on par with those produced for the

Scheme 3.34 *aza*-Diels-Alder Reaction of DAM-protected Imines (221a-d)



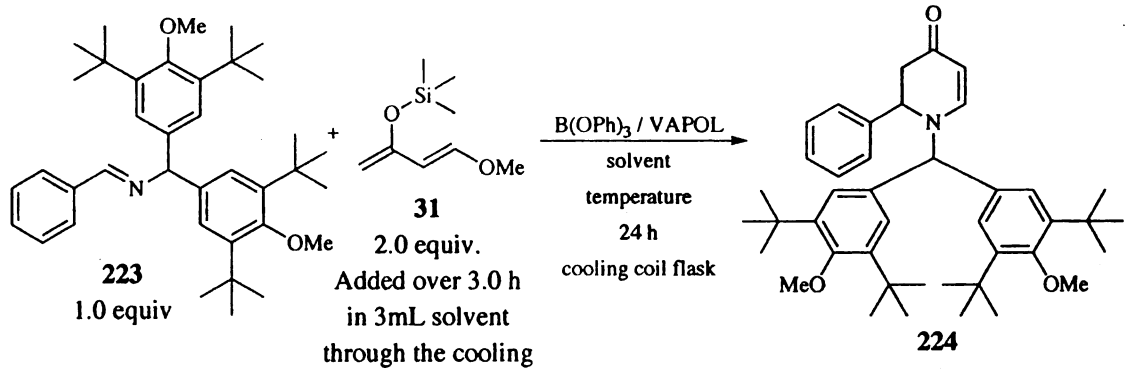
Entry	Condition	R	$B(OPh)_3$ (mol%)	VAPOL (mol%)	Product	Yield 222 (%)	ee 222 (%)
1	A	phenyl (**221a**)	100	10	**222a**	93	84
2	A	4-bromophenyl (**221b**)	100	10	**222b**	100	90
3	A	4-nitrophenyl (**221c**)	100	10	**222c**	68	81
4	A	cyclohexyl (**221d**)	100	10	**222d**	66	56

corresponding benzhydryl imines. The ee for the phenyl (**221a**) and cyclohexyl (**221d**) derivatives were lower, however for the 4-bromophenyl (**221b**) substrate the ee increased 1% to 90% and for the 4-nitrophenyl (**221c**) substrate, the ee was increased from 75% to 81%. The DAM group, therefore is not generally a better choice for the *aza*-Diels-Alder reaction but may be useful for specific substrates.

3.7.3 BUDAM Substrates

In the aziridination reaction, it was discovered that the best benzhydryl derivative was BUDAM. The observed rate was 16 times faster than the unsubstituted benzhydryl group and reactions with imines derived from aryl aldehydes generally gave 96-99% ee with very high yields. The imine **223** prepared from BUDAM amine and benzaldehyde was prepared and the results from its Diels-Alder reactions are shown in Scheme 3.35.

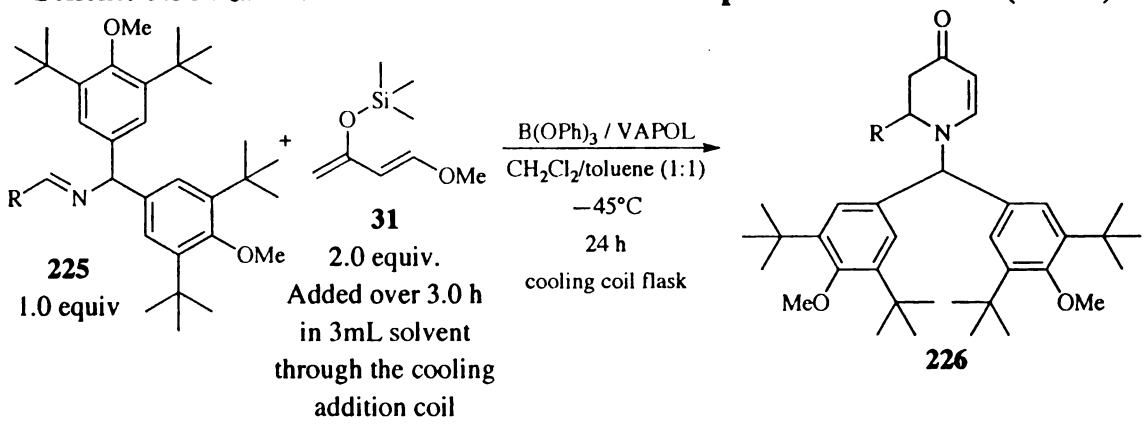
Scheme 3.35 *aza*-Diels-Alder Reaction of BUDAM-benzaldimine (223)



Entry	Condition	$B(OPh)_3$ (mol%)	VAPOL (mol%)	solvent	temperature (°C)	yield **224** (%)	ee **224** (%)
1	A	100	5	CH_2Cl_2/toluene (1:1)	—45	58	20
2	B	100	10	CH_2Cl_2/toluene (1:1)	—45	35	40
3	C	30	10	CCl_4	RT	9	29

When the optimal conditions were employed, the reaction gave 58% yield and 20% ee (entry 1). Obviously, this is much worse than the reaction of imine **150** with the benzhydryl group (Scheme 3.1). One attempt was made using 10 mol% VAPOL (entry 2) and although the ee increased to 40%, the reaction was still much less efficient than the unsubstituted benzhydryl imine. The best conditions for the aziridination reaction employed 30 mol% $B(OPh)_3$ and 10 mol% VAPOL in the catalyst preparation and then carrying out the reactions in CCl_4 at room temperature. When these conditions were utilized for the *aza*-Diels-Alder reaction, the yield dropped to 9% and the ee to 29%. It is definitely clear from these results that the BUDAM group does not have the same positive effect on the *aza*-Diels-Alder reaction as it does on the aziridination reaction. Nonetheless, substrates were screened with the BUDAM group to see if this effect is general (Scheme 3.36). As indicated by the data in Scheme 3.36 the tetra-*t*-butyl

Scheme 3.36 *aza*-Diels-Alder Reaction of BUDAM-protected Aldimines (225a-c)



Entry	Condition	R	$B(OPh)_3$ (mol%)	VAPOL (mol%)	Product	yield **226** (%)	ee **226** (%)
1	A	4-bromophenyl (**225a**)	100	10	**226a**	15	29
2	A	4-nitrophenyl (**225b**)	100	10	**226b**	0	N.D.
3	A	cyclohexyl (**225c**)	100	10	**226c**	21	30

dimethoxy benzhydryl (BUDAM) appears to be uniformly detrimental to the *aza*-Diels-Alder reaction.

Obviously, the *aza*-Diels-Alder reaction is clearly a different reaction than the aziridination reaction. Although the catalyst is the same and the imines are the same, the major difference is the nucleophile that is involved in the carbon-carbon bond forming reaction. Danishifsky's diene and ethyldiazoacetate clearly have significantly different effects on the outcome of these reactions. With the BUDAM imines, it seems that the large steric demand of this group does not allow the diene to approach the imine in a selective manner. The smaller ethyldiazoacetate, on the other hand, is able to approach the bound substrate and the formation of the carbon-carbon bond is more facile thus giving the outstanding enantiomeric excesses observed.

In conclusion, the *aza*-Diels-Alder reaction with the VAPOL/$B(OPh)_3$ catalyst described in this chapter is general for aromatic substrates and secondary aliphatic

groups. Yields and ee's in the 90s could be achieved for most of the substrates. The imines prepared from *trans*-cinnamaldehyde (**173**) and 3-methyl crotonaldehyde (**175**) gave poor results, however that prepared from cyclohexene carboxaldehyde (**177**) was successful. Unfortunately the generality of the *aza*-Diels-Alder reaction could not be expanded to imines bearing primary aliphatic groups. These substrates give only moderate yields and they fail to produce any enantiomeric excess. Attempts were made using other substrates that would allow access to primary alkyl side chains, but none of these substrates proved to be viable. The best result in this regard came from the imines **199** and **201** prepared from ethylglyoxylate and isopropylglyoxylate respectively, however, the ee's for these substrates was only around 60%. The TIPS acetylene substituted imine **206** was also examined, but its reaction gave only 22% ee. Lastly, one attempt was made with imine **212** which had an α,β-unsaturated group with a trimethylsilyl group in the α-position, but this substrate failed to give any of the desired Diels-Alder adduct.

Other benzhydryl derivatives were also surveyed and a much different outcome was seen for these substrate in the *aza*-Diels-Alder reaction than in the aziridination reaction. The TMB imine was better for the phenyl substituted substrate (**215**), but this was not the case for the cyclohexyl (**219**) or 4-bromophenyl (**217**) substrates. The DAM and BUDAM imines were also studied and it was found that these were also not useful for the *aza*-Diels-Alder reaction. The DAM imines gave similar yields as the benzhydryl imines, but with the exception of the electron withdrawing phenyl substrates, the ee's were not better. BUDAM imines were found to be very poor substrates for this reaction and all of the results with the BUDAM imines were much inferior to those with

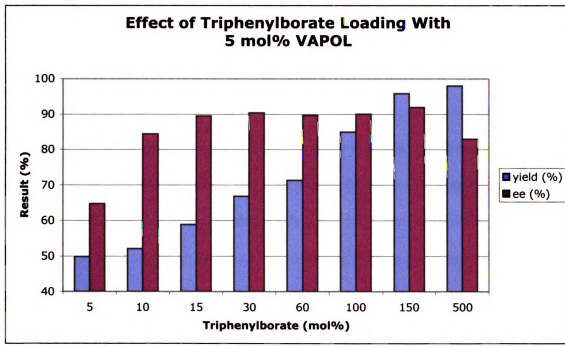
unsubstituted benzhydryl imines. The highest ee observed for a reaction with a BUDAM imine was 40%.

CHAPTER 4

EFFECTS OF TRIPHENYLBORATE

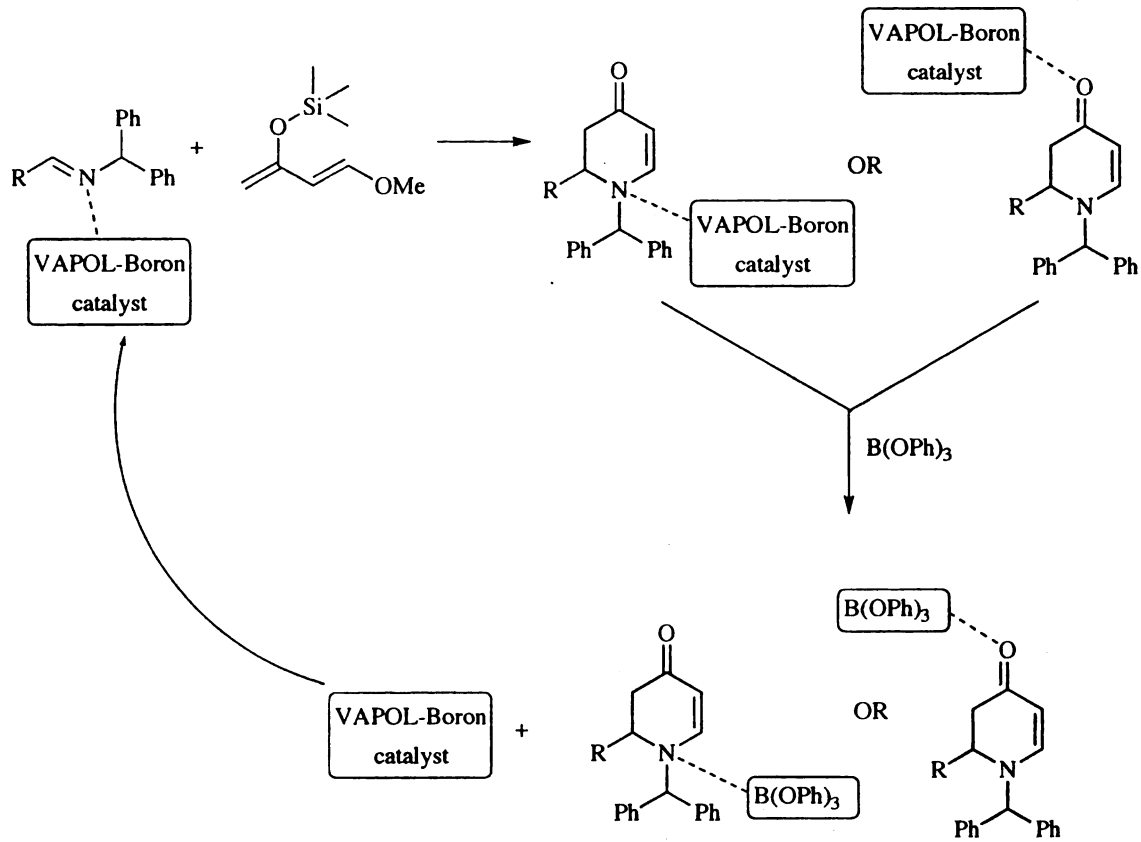
Discussed in chapters two and three was the development and generality of the catalytic asymmetric *aza*-Diels-Alder reaction of iminodienophiles with Danishefsky's diene using the catalyst prepared from VAPOL and $B(OPh)_3$. An interesting discovery during these studies was the use of excess $B(OPh)_3$ (a non-chiral Lewis acid) which led to increased yields without any loss of asymmetric induction. As indicated in Figure 4.1, an

Figure 4.1 Summary of $B(OPh)_3$ Effects



an increased rate of the reaction could be achieved without the loss of induction until a ratio of 100:1 $B(OPh)_3$ to VAPOL was used to prepare the catalyst. To our knowledge, this type of system, which involves two Lewis acid catalysts that can serve in orthogonal capacities, has not been demonstrated before. Several examples do exist, however, where non-chiral additives have been used in asymmetric catalysis[63, 66, 67] where an increase of ee's and/or yield could be observed, but this is the first example of where an achiral Lewis acid has had the observed effect of increasing yield without changing the ee's. Yu and coworkers have noted that $B(OMe)_3$ will accelerate the catalytic asymmetric allylation of aldehydes with allyl stannanes using a BINOL-titanium complex[62] as the chiral catalyst. The mechanism of this process is not known but is thought to involve an alkoxide exchange between titanium and boron on the product. So, for Yu's allylation reaction, there is a covalent bond formed between the product and either of two catalysts. The idea they propose is that the boron-oxygen bond is much stronger than the titanium-oxygen bond and in the presence of $B(OMe)_3$, the product will preferentially bind to the boron thus releasing the titanium species to catalyze the reaction. This is different, however, than the system developed for the VAPOL/$B(OPh)_3$ catalyst because both the starting imine and the product of the *aza*-Diels-Alder reaction are neutral and thus only Lewis acid/Lewis base interactions can take place. In order to account for the results shown in Figure 4.1, when the product is formed, the chiral catalyst would have to exchange with the non-chiral $B(OPh)_3$ thus liberating the chiral catalyst to catalyze the reaction, allowing turnover without loss of asymmetric induction (Scheme 4.1). This

Scheme 4.1 Turnover Induced by Triphenylborate



system is even more interesting in that it has two boron catalysts that are competing for interaction with the imine and product. To explain the results, there must be a very large difference in the rate for the two catalysts in favor of the chiral catalyst, or there must be a very large difference in the binding constantas for the two catalysts for the imine in favor of the chiral catalyst, or a combination of the two. A possible source of these effects could be due to a greater Lewis acidity for boron if it were to form a borate complex with a VAPOL that contained a 7-membered ring. It has been found in recent studies in the Wulff group that the catalyst is actually a Brønsted acid (see discussion in Chapter 6). The Brønsted acid would presumably have a stronger interaction to the imine

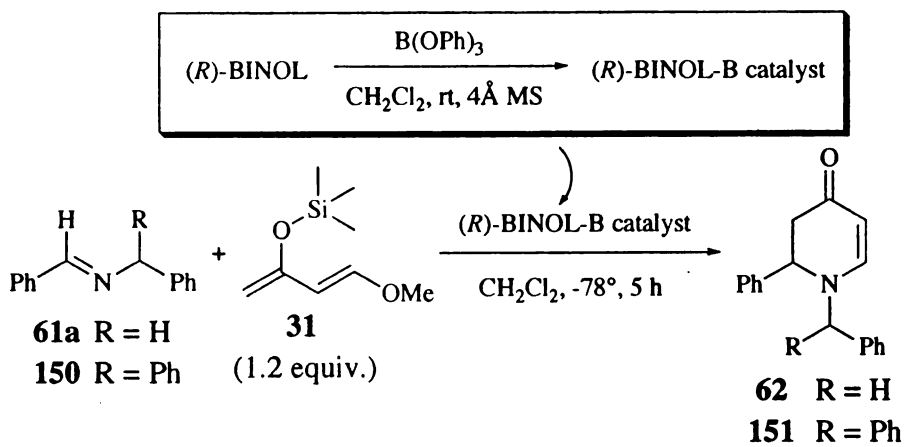
or product than the $B(OPh)_3$ Lewis acid, but this still offers no solution to the question about the role of triphenylborate.

4.1 Exploration and Explanation of the VAPOL-$B(OPh)_3$ Catalyst System

The question that arises from these results is why does the rate of the reaction increase without the lowering of the ee when excess $B(OPh)_3$ is used? It was seen earlier (see Scheme 2.13) that the reaction can indeed be catalyzed by $B(OPh)_3$ so a concern when using the large excess of $B(OPh)_3$ is that the ee's would decrease. However, it can be concluded, based on experimental results, that whatever role the $B(OPh)_3$ is playing in this reaction, the rate of the background reaction where the $B(OPh)_3$ is catalyzing the reaction must be very small compared to the VAPOL-boron catalyst. However, before studies were undertaken to develop an explanation of this effect, studies were done to compare this work to Yamamoto's work in order develop an understanding of what kind of interactions were necessary to make the reaction successful. In order to do this, several experiments were done using Yamamoto's conditions as well as the conditions developed in this work using both VAPOL and BINOL and with both the imines **61a** and **150** prepared from benzylamine (Bn-NH_2) and benzhydrylamine (Bh-NH_2) respectively.

First, a series of experiments were done using Yamamoto's system where the catalyst was prepared at room temperature, stirring in the presence of 4Å molecular sieves in CH_2Cl_2 for three hours (Scheme 4.2). After the catalyst preparation was

Scheme 4.2 Comparison of Bn and Bh Using the BINOL-boron Catalyst Prepared using Yamamoto's Conditions



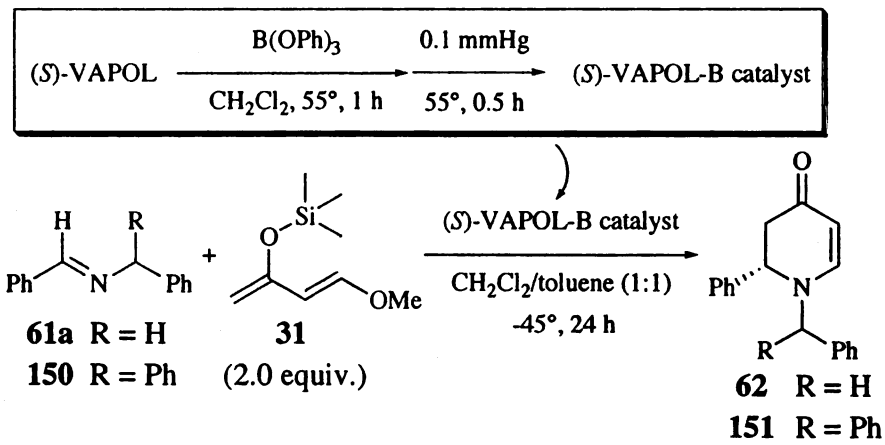
Entry	R	(*R*)-BINOL (mol%)	$B(OPh)_3$ (mol%)	Product	Yield (%)	ee (%)	Reference
1	H	100	100	**62**	68-75	77-86	Yamamoto[18], Bull[23], this work
2	H	10	100	**62**	41	15-50	Bull[23], this work
3	H	10	10	**62**	<5	—	Bull[23]
4	Ph	100	100	**151**	0	—	Yamamoto[18], this work
5	Ph	10	100	**151**	0	—	this work

complete, the solution was cooled to 0°C and imine was added. Stirring commenced for 10 minutes, then the resulting catalyst-imine solution was cooled to —78°C at which time Danishefsky's diene (**31**) was added and the reaction was allowed to stir 5 hours. In Yamamoto's publication[19], he reported 75% yield and 82% ee for the benzyl imine **61a** under these conditions with 100 mol% catalyst. This reaction was repeated by Bull, et. al.[23] and also in this work. Bull was able to obtain the product **62** that measured 77% ee while when the reaction was repeated for the present study, the product **62** was obtained

with 86% ee. Using 10 mol% BINOL and 100 mol% $B(OPh)_3$ to prepare the catalyst (as a corollary to the optimal conditions discovered in this work), it was not surprising to find that that the ee dropped. Under these conditions, Bull reported 15% ee, but did not mention the yield. When this reaction was carried out for the present study, the product **62** could be obtained in 41% yield with 50% ee. Lastly, two reactions were attempted using Yamamoto's catalyst preparation protocol for the benzhydryl imine (**150**). Whether 10 mol% BINOL or 100 mol% BINOL was used with 100 mol% $B(OPh)_3$, the reaction failed to give any product.

The next series of experiments was done using the catalyst preparation method determined to be optimal for the *aza*-Diels-Alder reaction of the imine **150** (see chapter 2) using the VAPOL-$B(OPh)_3$ catalyst (Scheme 4.3). For this study, however, 10 mol%

Scheme 4.3 Comparison of Bn and Bh Using the VAPOL-Boron or BINOL-Boron Catalyst Prepared Using my Optimal Conditions

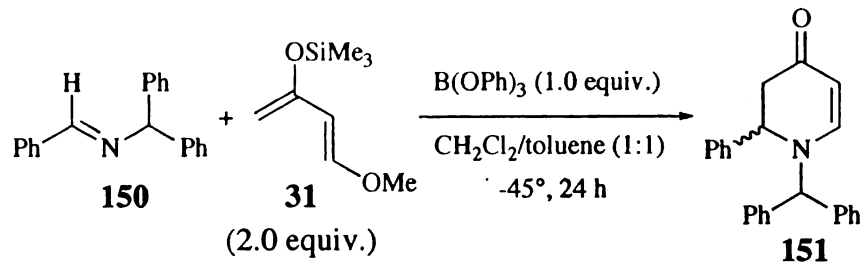


Entry	R	(*S*)-VAPOL (mol%)	(*R*)-BINOL (mol%)	$B(OPh)_3$ (mol%)	Product	Yield (%)	ee (%)
1	H	10	—	100	**62**	50	36
2	Ph	10	—	100	**151**	94	90
3	Ph	—	10	100	**151**	26	23

of the ligand was used rather than 5 mol%. The first reaction was done using the imine **61a** and after observing the results from the experiments following Yamamoto's protocol, it was not unexpected to find that using the VAPOL-boron catalyst that the reaction produced poor asymmetric induction (36% ee). Interestingly, under the same conditions, using the benzhydryl imine (**150**), 94% yield of **151** was obtained in 90% ee. Lasty, one reaction was done with the benzhydryl imine (**150**) using (*R*)-BINOL instead of (*S*)-VAPOL and this reaction only gave 26% yield and 23% ee.

Clearly, it can be seen from these results, that VAPOL is far superior to BINOL when the benzhydryl imine is used indicating that there is something special about the catalyst imine interaction that leads to high asymmetric induction. The cause for reduced enantioselectivity in these reactions would be presumably due to achiral background reaction. For these systems, it is the reaction catalyzed by $B(OPh)_3$ that would lead to racemic product so three reactions were performed to determine the effectiveness of $B(OPh)_3$ as a catalyst for this reaction (Scheme 4.4). The first reaction was carried out using $B(OPh)_3$ that had been taken through the catalyst preparation cycle, heating to 55°C for an hour and then evacuating under high vacuum at 55°C for 30 minutes (entry 1).

Scheme 4.4 Reactions with $B(OPh)_3$



Entry	$B(OPh)_3$ (source)	Yield **151** (%)
1	Cat Prep Cycle[1]	26
2	Aldrich[2]	46
3	Distilled[3]	25

1) $B(OPh)_3$ was heated to 55°C in CH_2Cl_2 for one hour and then heated at 55°C for 30 minutes under high vacuum. 2) $B(OPh)_3$ was used directly as purchased from Aldrich. 3) $B(OPh)_3$ was purified by distillation and stored in a glove box immediately before used.

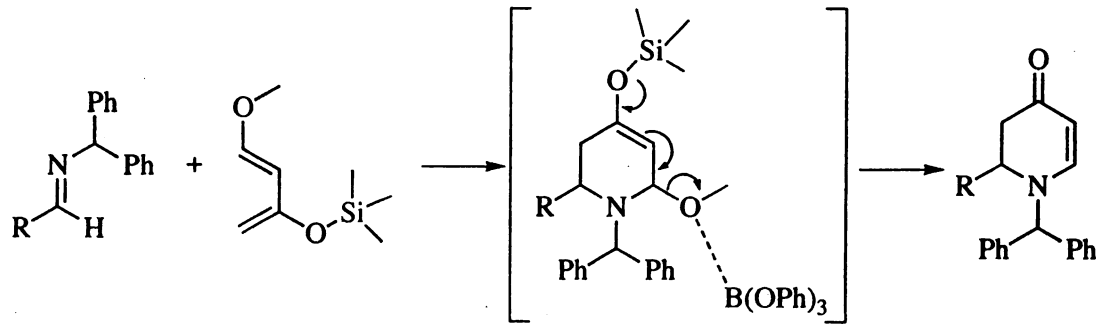
This reaction only gave 26% yield of the desired product **151**. Performing the reaction under the same conditions only using $B(OPh)_3$ taken directly from the bottle purchased from Aldrich, the reaction gave 46% yield of the desired product **151** (entry 2). Lastly, a reaction was attempted using $B(OPh)_3$ that had been purified by distillation and stored in a glove box before use and the reaction gave a 25 % yield of **151**. It is obvious from these experiments that there is definitely the possibility for the background reaction to occur indicating that there must be something special about this system to account for enhanced rates without loss of induction observed when significant excess $B(OPh)_3$ was used. In any event, an explanation of the results in Figure 4.1 is still needed.

One explanation consistent with these results is that $B(OPh)_3$ can compete with the chiral catalyst for binding to the product and thus liberate the sequestered chiral Lewis acid to turn over more starting material. This explanation still does not, however, explain why the increasing amounts of $B(OPh)_3$ does not lead to background reaction and

loss of asymmetric induction. These observations could be explained simply by an increase in Lewis acidity that would be expected if the VAPOL-boron catalyst were a cyclic borate ester, which has been demonstrated in other systems.[68] It was mentioned earlier and will be expanded upon in chapter 6 that the VAPOL-boron catalyst is actually a Brønsted acid, which does in fact indicate that it would be the stronger catalyst. According to this argument, this catalyst should also bind stronger to the more basic product (once it is formed) and thus not allow the catalyst to turn over the reaction as rapidlly. The question really is how is the $B(OPh)_3$ able to aid in the rate of turnover without catalyzing the reaction itself? In order to distinguish between the theories described above, it was decided to measure the binding constants of the VAPOL/$B(OPh)_3$ catalyst and also that of $B(OPh)_3$ with both the imine starting material and the product.

Before discussing the results of the binding study, it is worth mentioning some mechanistic considerations for this reaction. Whether the reaction occurs via a stepwise or concerted mechanism, the intermediate of the *aza*-Diels-Alder reaction with Danishefsky's diene is a TMS protected enolate with a β-methoxy group (Scheme 4.5),

Scheme 4.5 Possible Mechanism Involving $B(OPh)_3$



which upon hydrolysis leads to the elimination of the methoxy group to give the final dihydropyridinone (vinylogous amide) product. One theory for the role of $B(OPh)_3$ is

that it could be coordinating to the methoxy oxygen thus aiding in the elimination of the methoxy group giving the final product. Attempts were made to isolate this intermediate so that it could be exposed to $B(OPh)_3$ to see if the elimination of the methoxy group could be facilitated. Unfortunately, all attempts to isolate the intermediate were unsuccessful and this experiment could not be conducted. During the attempts to isolate this intermediate, several NMR's of crude material were taken and it was interesting to find that during the course of the reaction, the major species that was observed in the crude reaction mixture was the eliminated final product.

Another theory for the role of $B(OPh)_3$ could be that it could be competing for binding with the product thus liberating the VAPOL-boron catalyst to turnover the reaction. In order to determine if there were any merits to this possibility, NMR titration experiments were conducted to determine the binding constants for the VAPOL-boron catalyst with both the imine **150** and product **151** as well as binding constants for $B(OPh)_3$ with the imine **150** and product **151**. The study was carried out in collaboration with Lee Fielding at Organon Laboratories Ltd., Newhouse, Lanarkshire, Scotland, ML1 5SH. These experiments were conducted by maintaining a constant concentration of the imine or product while adding different concentrations of $B(OPh)_3$ or VAPOL-boron catalyst. A non-linear least squares evaluation of the data obtained from the NMR titrations by plotting the chemical induced shift versus the concentration allowed for the determination of the binding constant and the results from this analysis are outlined in Table 4.1. It was found that the complex of $B(OPh)_3$ with the imine **150** had a binding

Table 4.1 Binding Constants for Complexes of the Imine and Product with $B(OPh)_3$ and the VAPOL-Boron Catalyst

Entry	Complex	Binding Constant (M^{-1})
1	$B(OPh)_3$ / imine	0.32 ±0.12
2	$B(OPh)_3$ / product	2.7 ±0.4
3	VAPOL-B / imine	2.1 ±0.4
4	VAPOL-B / product	4.9 ±0.8

constant of 0.32 ±0.12 M^{-1} and the complex of $B(OPh)_3$ with the product **151** had a binding constant of 2.7 ±0.4 M^{-1}. The complexes of the VAPOL-boron catalyst with the imine **150** and product **151** gave binding constants of 2.1 ±0.4 M^{-1} and 4.9 ±0.8 M^{-1} respectively.

Interpretation of this data would have been straight forward if the binding of the $B(OPh)_3$ to the product **151** would have been much stronger than the VAPOL-boron catalyst to the product **151**, and the binding of the VAPOL-boron catalyst to the imine **150** much stronger than $B(OPh)_3$. As can be seen from the data, although the later is true, the former is not, and in fact the binding of the $B(OPh)_3$ to the product **151** is about half as strong VAPOL-boron catalyst. However, since there is no product at the beginning of the reaction, the binding of the two catalyst species to the product cannot totally explain this phenomenon anyhow. Due to this, the binding of the catalysts to the imine must be significant at the beginning of the reaction. It was found that the binding of the VAPOL-boron catalyst to the imine **150** was about seven times as strong as $B(OPh)_3$. While the VAPOL-$B(OPh)_3$ catalyst binds to the imine 7 times stronger than $B(OPh)_3$, it is also true that there is at the very least 85 mol% $B(OPh)_3$ and only 5 mol% VAPOL-boron catalyst if three boron atoms are incorporated into the catalyst (a 17:1 ratio of nonchiral to chiral

catalyst). Another issue that must be considered is that it is not clear which catalyst, when bound to the imine, would cause the reaction to happen at a faster rate.

Using the following analysis in conjunction with our experimental data, it was found that the rate of the reaction of the VAPOL-boron catalyst must be at least 9 times as fast to account for the trend in Figure 2.1 when a 20 to 30 fold excess of $B(OPh)_3$ is used.

4.2 Binding Constant Data Analysis

The ultimate goal of the following analysis is to develop an explanation for why the use of excess $B(OPh)_3$ does not result in lower asymmetric induction. As mentioned earlier, either the rate of the reaction with the VAPOL-boron catalyst had to be significantly greater, or the binding constant much larger, or both to account for the experimental observation. The binding constants were measured but no information about the rates of these reactions was collected. Due to the fact that the catalyst is prepared from VAPOL and triphenylborate, it becomes difficult to obtain the VAPOL-boron catalyst without any triphenylborate still present and it was for this reason that the rate constant could not be obtained for the reaction of the VAPOL-boron catalyst. However, using the binding constants, a correlation was made between the constants and the rates of the reaction. The following analysis will be made for conditions present at the beginning of the reaction.

The first question to be answered is what would the expected enantiomeric excess of the reaction be if the rates of the chiral and racemic reaction were the same? The binding constants were measured (Table 4.1) and using these numbers and the following analysis the answer to this question was elucidated.

For the following analysis, VAPOL-boron catalyst will be abbreviated "B*" and $B(OPh)_3$ will be abbreviated "B" (as in the following reactions). First, the following rate equations were developed for this specific reaction:

$$\text{B-imine} + \text{Danishefsky's Diene} \xrightarrow{k_{rac}} \text{Product} + \text{B}$$

$$\text{B}^*\text{-imine} + \text{Danishefsky's Diene} \xrightarrow{k_{ch}} \text{Product} + \text{B}^*$$

$$\text{Rate}_{racemic} = k_{rac}\,[\text{B-imine}]^*[\text{diene}]$$

$$\text{Rate}_{chiral} = k_{ch}\,[\text{B}^*\text{-imine}]^*[\text{diene}]$$

In order to determine what the ee would be if the rates of the reactions were the same, then the assumption has to be made that $k_{ch}=k_{rac}$. Having made this assumption, the following correlation can be made between the rates of the reactions and [B*-imine] and [B-imine] and thus the binding constants $K_{a(chiral)}$ and $K_{a(racemic)}$:

$$\text{Rate}_{chiral}/\text{Rate}_{racemic} \propto [\text{B}^*\text{-imine}] / [\text{B-imine}]$$

$$[\text{B}^*\text{-imine}] = K_{a(chiral)} * [\text{imine}] * [\text{B}^*]$$

$$[\text{B-imine}] = K_{a(racemic)} * [\text{imine}] * [\text{B}]$$

At the beginning of the reaction there is 17 times excess of B over B* in the reaction so it was decided to do this analysis on the situation where [B] is 17 times more than [B*]. Before the final analysis could be done, one must understand what the enantiomeric excess of the reaction would be for each of the two catalysts. The reaction that occurs when $B(OPh)_3$ (B) is acting as the catalyst, the reaction gives 0% ee (50:50 ratio of *S*/*R*). In order to determine what the maximum ee that could be achieved for the VAPOL-boron catalyst (B*), attempts to run the reaction using 100 mol% VAPOL (Scheme 2.18) were made. It is difficult to prepare the VAPOL-boron catalyst in abscense of $B(OPh)_3$ and

due to this and other reasons that are unclear, the results of this study were quite ambiguous and instead, the data from Figure 4.1 was used to determine the maximum ee for this catalyst. It was found for the reactions using 15 mol%-150 mol% $B(OPh)_3$ that a constant ee of 90% was observed with an error on these measurements of ±1. Based on these experimental observations, the maximum possible ee produced by the chiral catalyst was assumed to be 90%.

For the chiral reaction a ratio of 95% *S* and 5% *R* is produced.

So a $K_{a(chiral)}$=2.1 M^{-1} gives 95% *S* and 5% *R*

For the racemic reaction, a ratio of 50% *S* and 50% *R* is produced.

So a $K_{a(racemic)}$=0.32 M^{-1} gives 50% *S* and 50% *R*

When [B] and [B*] are equal, the production of each enantiomer would be a sum of the binding constants and the asymmetric induction for each catalyst:

[*S*] (2.1 * 95) + (0.32 * 50) = 199.5 + 16 = **215.5 *S* enantiomer**

[*R*] (2.1 * 5) + (0.32 * 50) = 10.5 + 16 = **26.5 *R* enantiomer**

However, at the beginning of the reaction, there is minimum of a 17 fold excess of the racemic catalyst. This leads to the weighted equations shown below. When this was done, it was found that at the beginning of the reaction, based on the binding constants, and the relative concentrations of the two catalyst species, the actual ee expected would be 25.1% ee.

[*S*] (2.1 * 95) + (17* 0.32 * 50) = 199.5 + 272 = **471.5 *S* enantiomer**

[*R*] (2.1 * 5) + (17* 0.32 * 50) = 10.5 + 272 = **282.5 *R* enantiomer**

Using the correlation of $K_{a(chiral)}$ / $K_{a(racemic)}$ α $Rate_{chiral}$ / $Rate_{racemic}$ and a similar analysis where 25.1% ee was used as a starting point, a table was constructed (Table 4.2) to

Table 4.2 Relative Rates of the Two Catalysts and ee Prediction

X	ee (%)
1	25.1
1.67	35
2.10	40
2.62	45
3.24	50
4.10	55
5.19	60
6.76	65
9.10	70
12.95	75
20.76	80
44.05	85
55.71	86
75.14	87
114.00	88
230.57	89
∞	90

a) $X = k_{ch}/k_{rac}$

determine the minimum difference in rate between the two catalysts that could account for the experimental observations. As mentioned before, the error for the ee in this study was ±1% and because of this the calculation was extrapolated to the relative rate where 89% ee would be observed. The minimun amount faster (as seen in Table 4.2) that the chiral reaction had to be in order to observe the asymmetric induction for the reaction would have to be about 230 times faster.

The discussion will now turn to what is happening as the product is formed. Assuming the extreme case where only product is in the solution (100% conversion), there would be a ratio of about 4.9 to 2.7 of B*-product complex to B-product complex (1.8 times as much B*-product) based on the measured binding constants. As mentioned before, there is 17 times as much $B(OPh)_3$ in the solution during the reaction. Due to this, the ratio would switch to 17 * 2.7 = 45.9 B-product to 4.9 B*-product (9.37 times as

much B-product complex). In addition to the comparison of binding of the two catalysts to the product it is worthwhile to compare the binding of $B(OPh)_3$ to the product and imine itself. Looking at the binding constants for these two, it can be seen that the ratio of B-product to B-imine is 8.44 (K_a B-prod / K_a B-imine = 2.7 / 0.32 = 8.44). It can be concluded that the combination of the weak binding interaction of $B(OPh)_3$ with the imine and the presumed much slower rate (based on experiment and K_a interpretation) of background reaction indicates that there would not be significant background reaction to lower the asymmetric induction.

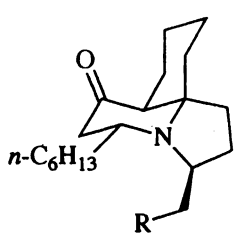
This interpretation of the binding constants provides sufficient evidence and to account for the experimental results present in Figure 4.1. It can be concluded that it is a combination of the smaller rate of the background reaction as well as the fact that the excess $B(OPh)_3$ coordinates to the product enough to not allow the chiral catalyst to be sequestered by the product. This in turn shows that the two catalysts are working orthogonally to facilitate an efficient reaction giving enhanced rates without the loss of enantiomeric excess.

CHAPTER 5: EFFORTS TOWARD THE SYNTHESIS OF CYLINDRICINE C

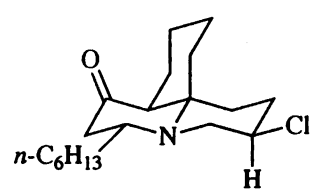
5.1 Cylindricine C History

Cylindricine C was isolated in 1991 from the sea squirt (*Clavalina Cylindrica)* off the coast of Tasmania and was fully characterized in 1994 by Li and Blackman[69]. Cylindricine C is only one of many cylindricine molecules that have been isolated from the marine ascidia[70]. Cylindricines A and B[71] and D-K[69, 72] (Figure 5.1) have a similar

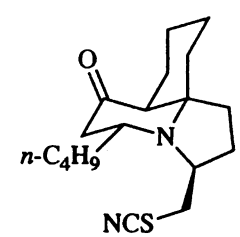
Figure 5.1 Cylindricines A-K



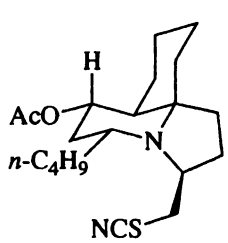
R=Cl Cylindricine A (**227**)
R=OH Cylindricine C (**228**)
R=OMe Cylindricine D (**229**)
R=OAc Cylindricine E (**230**)
R=SCN Cylindricine F (**231**)



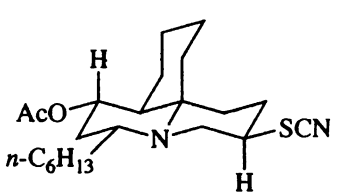
Cylindricne B (**232**)



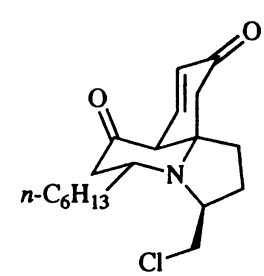
Cylindricine G (**233**)



R=SCN Cylindricne H (**234**)
R=NCS Cylindricine I (**235**)



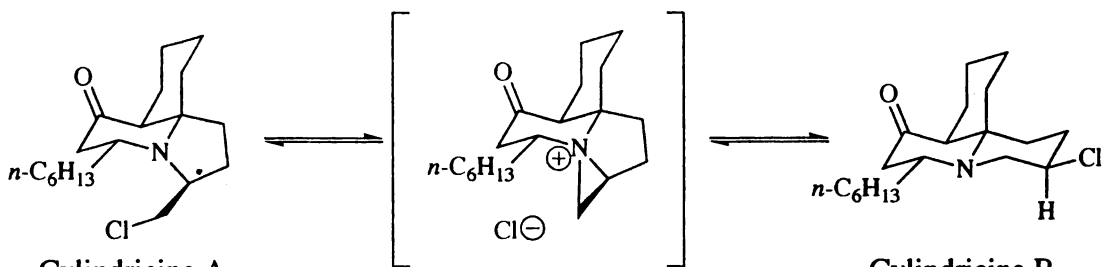
Cylindricine J (**236**)



Cylindricine K (**237**)

core tricyclic ring structure and contain minor structural differences. Cylindricine B and J are ring expanded isomers of Cylindricine A and F respectively. It is thought that Cylindricine B is in equalibrium with Cylindricine A (Figure 5.2) via the quaternary

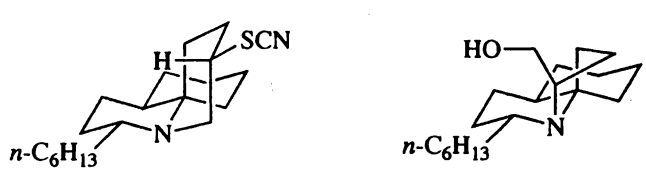
Figure 5.2 Isomerization of Cylindricine A to B



Cylindricine A **227** — **238** — Cylindricine B **232**

ammonium salt **238** formed by attack of the nitrogen on the carbon containing the chlorine followed by subsequent nucleophilic ring opening by the chlorine to give the ring expanded Cylindricine B (**232**). All species in the Cylindricine class of compounds have the *cis* fused *aza*-decaline system which is structurally unique compared to the related compounds, Fasicularin[73] and Lepadiformine,[74] a class of compounds which contain the *trans* fused *aza*-decalin system (Figure 5.3). In addition to the *trans* fused

Figure 5.3 Fasicularin and Lepadiformine

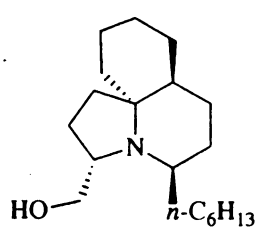


Fasicularin (**239**) Lepadiformine (**240**)

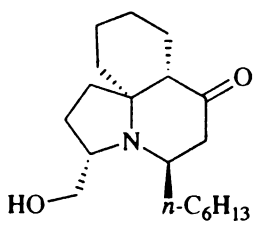
aza-decalin system, Fasicularin and Lepadiformine differ from Cylindricine C also in that the carbonyl functionality on the 6-membered ring containing the alkyl side chain is fully

reduced to a CH_2. A side-by-side comparison of these three compounds drawn in the flat representation shows these differences nicely (Figure 5.4).

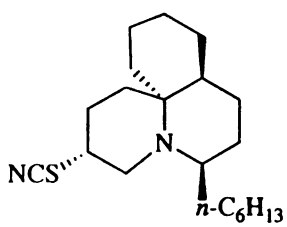
Figure 5.4 Flat representation of Lepadiformine, Fasicularin, and Cylindricine C



Lepadiformine (**239**)



Cylindricne C (228)



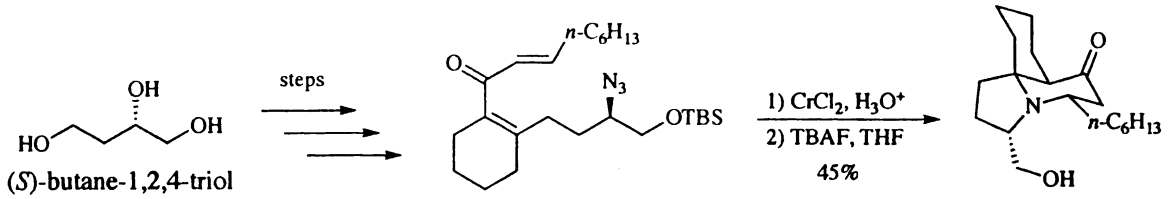
Fasicularin (**240**)

There have not been significant studies reported on the the biological activity of Cylindricine C but it has been shown that a 3:2 mixture of Cylindricine A and B have some toxicity in the brine shrimp assay.[75] However, Fasicularin has been shown to be an alkylating agent and has the ability to damage DNA[73, 76] and Lepadiformine has shown moderate cyctotoxicity against several cancer cell lines and has been shown to block the cardiac muscle K_{ir} channel.[74, 77, 78] In any event, the Cylindricine family, due to unique structural features, has gained significant attention in the literature and many syntheses have been accomplished in recent years. The focus of this chapter will be Cylindricine C and presented herein will be a brief summary of prior efforts towards Cylindricine C as well as the discussion of a different approach and efforts toward the total synthesis of Cylindricine C using said approach.

5.2 Previous Syntheses of Cylindricne C

Five years after its structure was determined, the first synthesis of Cylindricine C was reported by Molander[79]. He was able to accomplish the synthesis with the longest linear sequence being 15 steps achieving a 10.4% overall yield from (*S*)-1,2,4-butanetriol **241** (Scheme 5.1). The key step in Molander's synthesis was the $CrCl_2$ reduction of the

Scheme 5.1 Molander Total Synthesis of (—)-Cylindricine C



(*S*)-butane-1,2,4-triol
241

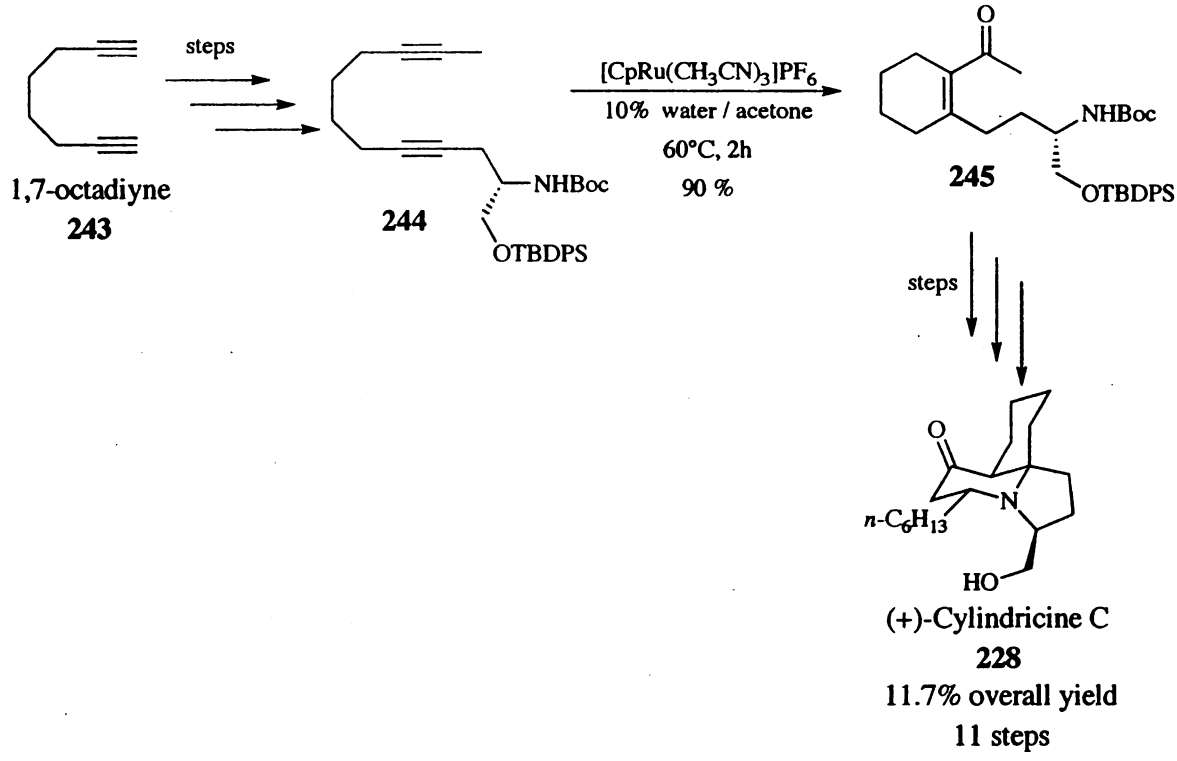
242

(—)-Cylindricine C
228
10.4% overall yield
15 steps

azide **242** followed by Michael addition of the resulting amine to form the tricyclic core of (—)-Cylindricine C.

It was not until 5 years after Molander's synthesis that Barry Trost at Stanford University contributed his synthesis of Cylindricine C[80]. Trost started with 1,7-octadiyine (**243**) and was able to complete the synthesis in 11 steps achieving 11.7% overall yield for the longest linear sequence (Scheme 5.2). The key step in his synthesis was the

Scheme 5.2 Trost Total Synthesis of (+)-Cylindricine C



1,7-octadiyine
243

244

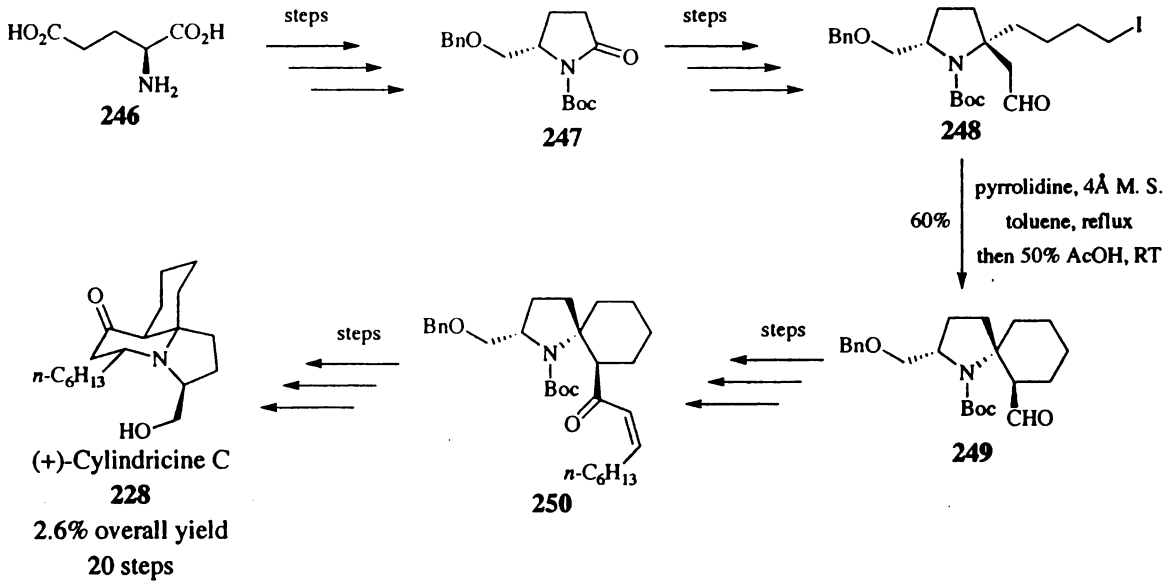
245

(+)-Cylindricine C
228
11.7% overall yield
11 steps

ruthenium-catalyzed hydrative diyne cyclization of **244** to give **245** in 90% yield. The enone **245** could then be further modified by a subsequent Michael addition to give the tricyclic core, which upon deprotection gave Cylindricine C.

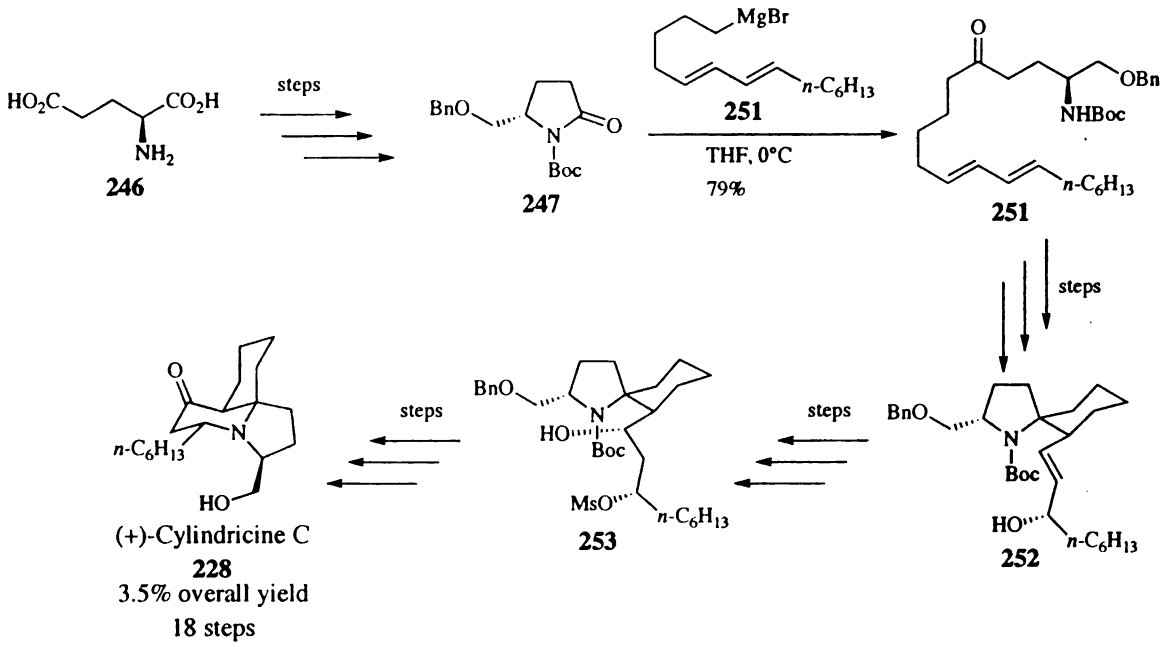
Concurrently in the past 3 years, Kibayashi[81-83], Ciufolini[84, 85] and Hsung[86-88] have also been working towards the total synthesis of Cyindricine C, each having success taking very different synthetic approaches. In Kibayashi's first total synthesis[83] (Scheme 5.3), he prepared (*S*)-*N*-Boc-2-pyrrolidinone **247** from the amino diacid **246**

Scheme 5.3 Kibayashi's First Total Synthesis of (+)-Cycindricine C



after which was modified to the advanced intermediate **248**. The key step was then the spirocyclization of **248**, which was carried out in the presence of pyrrolidine and 4Å molecular sieves to give the desired spirocyclic compund **249** in 60% yield. Modification of the aldehyde to give **250** introduced a substrate that was able to undergo a Michael addition followed by deprotection to give (+)-Cylindricine C. A second synthesis by Kibayashi[82] (Scheme 5.4) was accomplished using the same starting material (**246**).

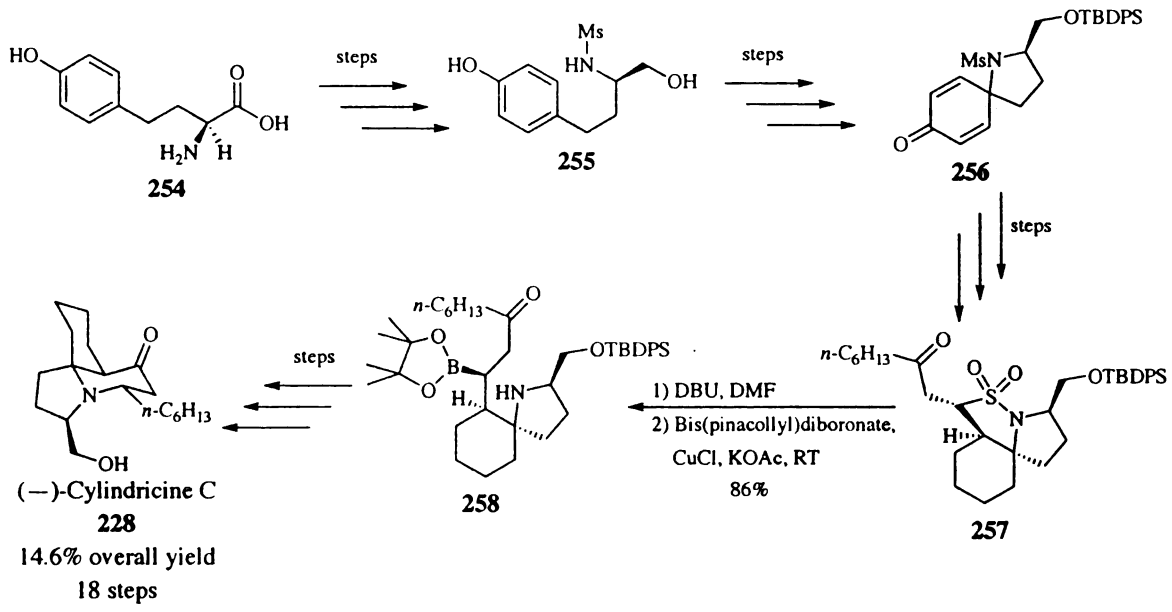
Scheme 5.4 Kibayashi's Second Total Synthesis of (+)-Cycindricine C



Grignard addition to (*S*)-*N*-Boc-2-pyrrolidinone (**247**) gave the ring opened advanced intermediate **251**, which underwent subsequent cycilzation by treatment with formic acid to give the conjugate spirocyclization product **252**. Epoxidation, followed by epoxide opening gave a diol, which was then mesylated selectively at the alcohol farthest away from the spirocycle to give advanced intermediate **253**. The mesylated oxygem atom was then displaced by the nitrogen leading to the tricyclic core, and subsequent oxidation and deprotection gave (+)-Cylindricine C in 3.5% overall yield over 18 steps.

Ciufolini used a different approach starting with D-Homotyrosine[85] **254** (Scheme 5.5). D-homotyrosine could be modified to the N-mesylated and TBDPSO-protected

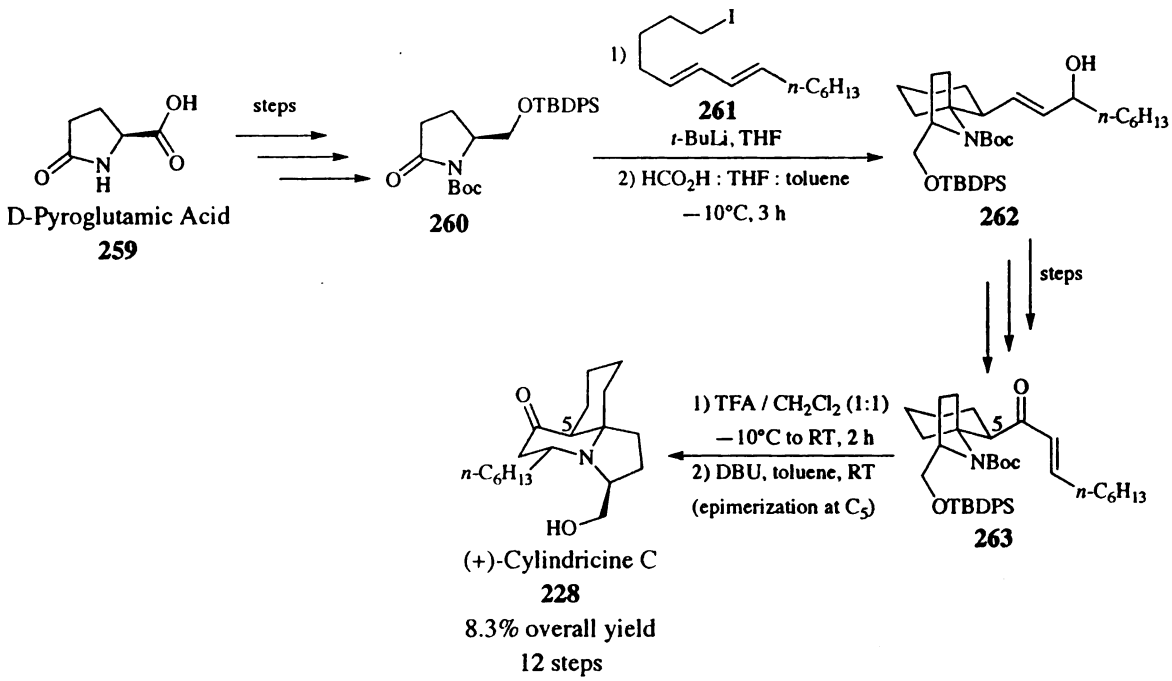
Scheme 5.5 Ciufolini's Total Synthesis of (—)-Cylindricine C



intermediate **255** and cyclization to **256** was accomplished by oxidation in the presence of DIB in hexafluoro-2-propanol. After protection of the alcohol, **256** was transformed into **257** several steps including treatment with KHMDS at —100°C first, followed by treatment with PhSH and $BF_3 \cdot OEt_2$ and subsequent reduction with Raney Ni to perform the desulferization. After desulferization, treatment with base and (±)-1-octene oxide in the presence of $BF_3 \cdot OEt_2$ led to a compound, which could finally be oxidized under Dess-Martin conditions to give the advanced intermediate **257**. The boronate **258** could then be prepared from **257** by treatment with DBU followed by bis(pinacollyl)diboronate. The last steps in Ciufolini's synthesis involved an oxidation and deprotection to give (—)-Cylindricine C in 14.6% overall yield (18 step longest linear sequence).

Richard Hsung has published two different approaches toward Cylindricine C. In his first approach he starts from D-Pyroglutamic acid[87, 88] using an *aza*-Prins cyclization and a Wharton rearrangement (Scheme 5.6).

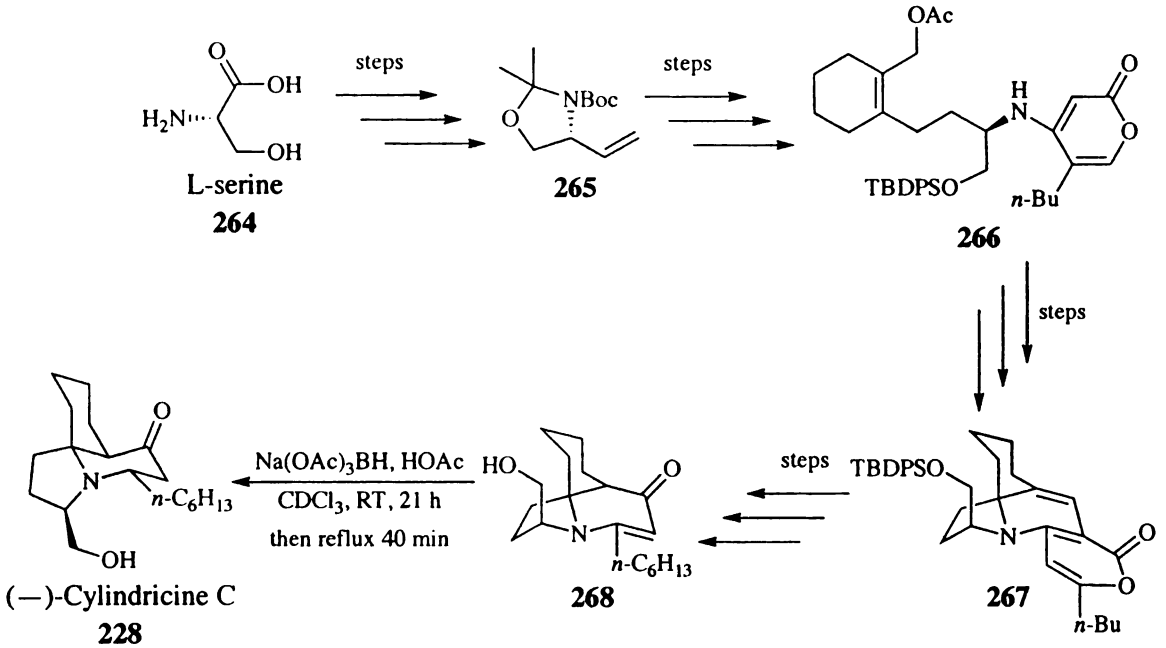
Scheme 5.6 Hsung's Total Synthesis of (+)-Cylindricine C from D-Pyroglutamic Acid



The nitrogen of D-Pyroglutamic acid was protected with a Boc group and reduction of the carboxylic acid gave an alcohol, which was protected to give **260**. Ring opening of **260** by addition of the lithiated diene **261** gave a compound that subsequently underwent the *aza*-Prins cyclization resulting in the advanced intermediate **262**. Derivatization of **262** allowed for a Wharton rearrangement to give a more advanced intermediate **263**. The Boc group was then removed and the 1,4-addition took place readily to give the C_5-epimeric tricyclic core of Cylindricine C. Treatment with DBU in toluene allowed for the epimerization at C_5 to give (+)-Cylindricine C in 8.3% yield over 12 steps.

Hsung's second approach used an *aza*-[3+3] annulation strategy[86] to prepare (—)-Cylindricine C (Scheme 5.7). This strategy proved to be a much longer process (22

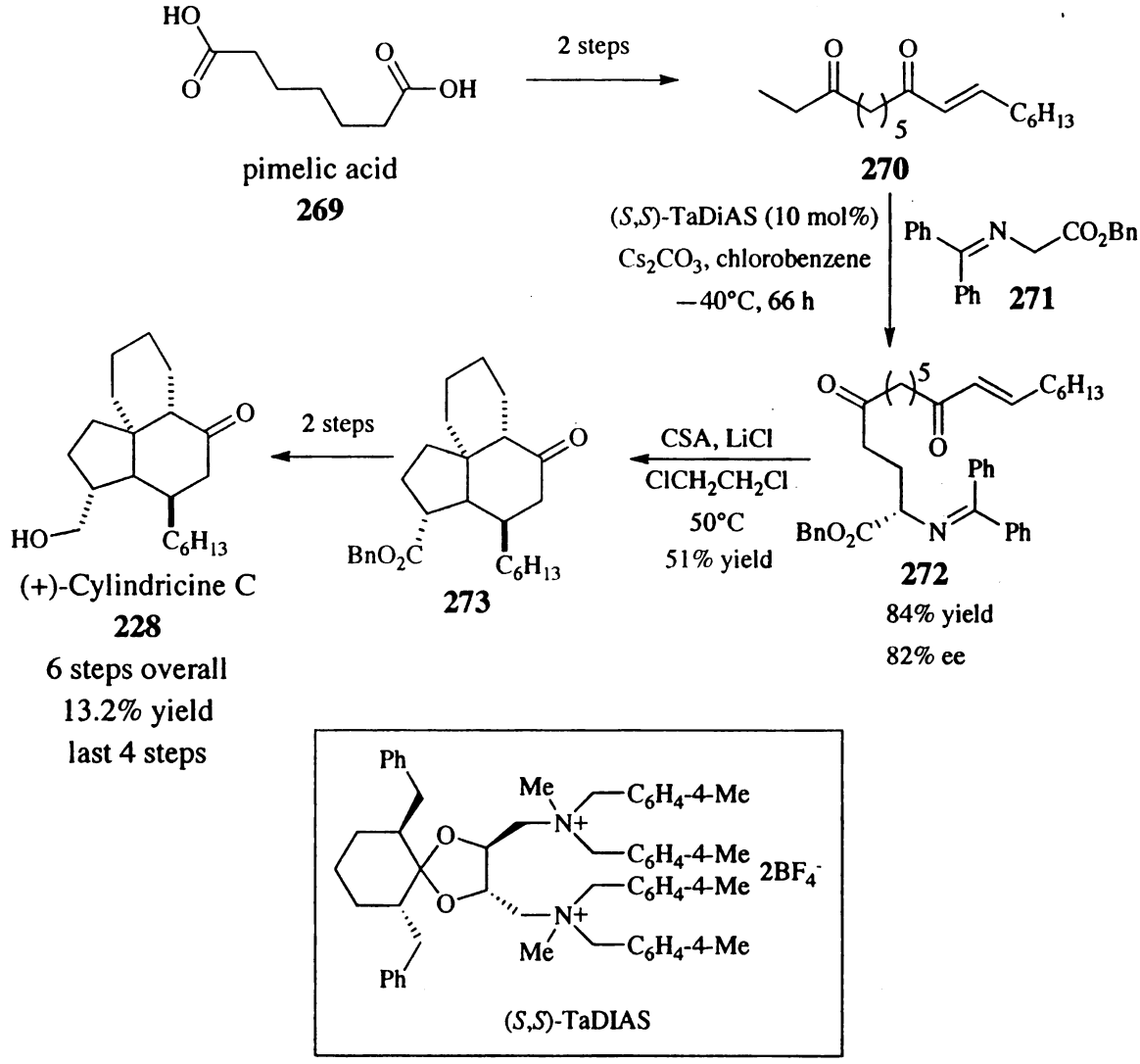
Scheme 5.7 Hsung's Total Synthesis of (—)-Cylindricine C from L-Serine



steps in the longest linear sequence), but the overall yield was still 4.5%. This synethesis started from *L*-serine (**264**), which was easily transformed to the vinyloxazoline **265**. Several organic transformations were then needed to prepare precursor **266** which was setup for the key intramolecular [3+3]-*aza*-annulation step, which upon treatment with 0.5 equivalents of piperidinium acetate and heating to 150°C for 12 hours gave the desired annulation product **267**. Going through a chlorohydrin intermediate, **267** was transformed into the desired ketone **268** by treatment with NCS and *t*-BuOH/H_2O (1:1) followed by TPAP/NMO in the presence of 4Å molecular sieves. Finally, a facile reduction of **268** gave (—)-Cylindricine C.

The most recent and shortest synthesis was published in 2006 and was carried out in the laboratories of Shibasaki[89] using a catalytic asymmetric Michael reaction with a two-center organocatalyst (Scheme 5.8). Pimelic acid (**269**) was easily modified in two

Scheme 5.8 Shibasaki's Total Synthesis of (+)-Cylindricine C



steps giving the ene-dione **270**, which was treated with the imine **271** in the presence of 10 mol% (*S*,*S*)-TaDiAS to give the asymmetric Michael addition product **272** in 84% yield and 82% ee. Cyclization was then accomplished by treating **272** with CSA in the presence of LiCl to give 51% yield of the desired isomer **273**. Finally, deprotection and reduction of the advanced intermediate **273** gave (+)-Cylindricine C (13.2% yield from **270**).

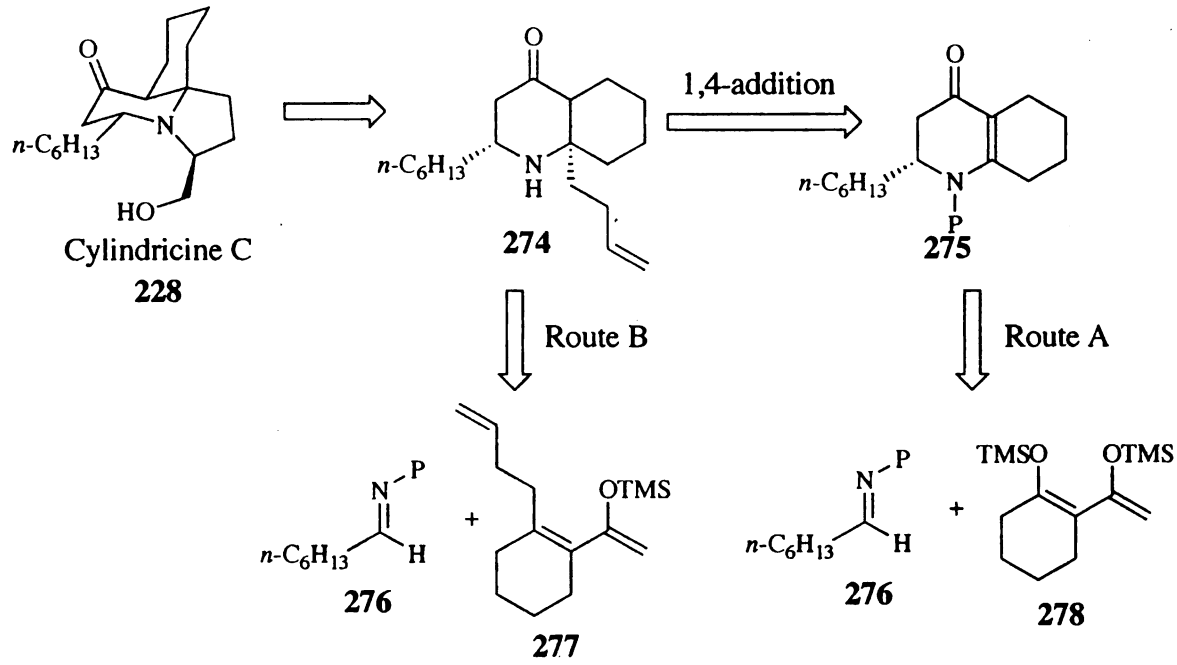
As can be seen in the discussion above, Cylindricine C has definitely gained significant attention in the past several years. Molander, Trost, Kibayashi, Hsung, Ciufolini and Shibasaki have all published unique syntheses, but choosing which is the best, is a matter of opinion. There are several aspects to be considered when determining the attractiveness of a particular synthesis. The two most important aspects are probably the length and overall yield of the synthesis. With respect to the number of steps involved in a synthesis, of course the shortest synthesis will be the more desirable one. However, if the materials are very expensive, a longer synthesis might become more attractive if the synthesis is more efficient. Of the syntheses of Cylindricine C reported to date, Ciufolini has accomplished the synthesis giving the best overall yield, as he was able to complete the synthesis in 14.6% yield from from D-Homotyrosine. This synthesis took 18 steps, which is third largest number of synthetic steps needed by any of the scientists that have published a synthesis Cylindricine C. Interestingly, however, the shortest synthesis (6 steps) that was done by Shibasaki gave a slightly lower overall yield (13.2% in the last four steps). This was only 1.4% lower than the former, so of the two, the latter would likely be the attractive with respect to length and overall yield. The latter also used an organocatalyst that was not commercially available, which may take significant time and money to prepare, which could make this synthesis slightly less attractive. All things considered, an attractive synthesis should involve few synthetic steps with high yields starting from cheap readily available materials.

5.3 Retrosynthetic Analysis

The goal of the present work was to develop a new synthesis of Cylindricine C that was not only shorter, but also more efficient than the previously reported syntheses.

The *aza*-Diels-Alder reaction is an atom economic and highly desired reaction to utilize because of its ability to form carbon-carbon and carbon-nitrogen bonds in one reaction. Another attractive feature of the *aza*-Diels-Alder reaction is if a concerted pathway is followed, a stereoselective reaction will occur allowing for relative stereochemistry to be set. In the retrosynthetic analysis (Figure 5.5), it was envisoned that the *aza*-Diels-Alder

Figure 5.5 Retrosynthetic Analysis

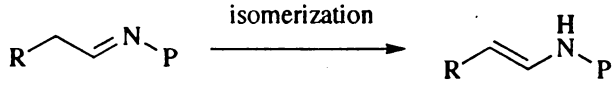


reaction would allow for the formation of the fused *aza*-decaline system in one transformation. Route A employs the *aza*-Diels-Alder reaction of an iminodienophile **276** and the known bis-TMS diene[90-97] **278**. Using the appropriate organocuprate, a 1,4-addition to the vinylogous amide produced from this *aza*-Diels-Alder reaction could be envisioned to add the butenyl side chain. After incorporaton of the butenyl side chain, a deprotection of the nitrogen and treatment with I_2 and water should afford Cylindricine C. A shorter synthesis could be envisioned using an alternate diene is outlined in route B. This route undergoes an *aza*-Diels-Alder reaction of an iminodienophile as well, but in

this route, the diene already contains the butenyl side chain. Deprotection would give the cyclization precursor **274** as discussed immediately before. In this retrosynthetic analysis, the stereochemistry could be set in the initial *aza*-Diels-Alder reaction, however, in route A, the butenyl side chain needs to be added *cis* to the *n*-hexyl side chain. Literature precedent exists[98] for the addition of a cuprate to a vinylogous amide containing a Cbz-protected nitrogen, where the *cis*-addition of an alkyl side chain preferentially occured. The reaction in that report deals with a di-substituted olefin and our proposed synthesis deals with a tetrasubstituted olefin, which could potentially result in reactivity and selectivity problems. Nonetheless, the end cyclization process is known on similar systems[99] and should not be a problem.

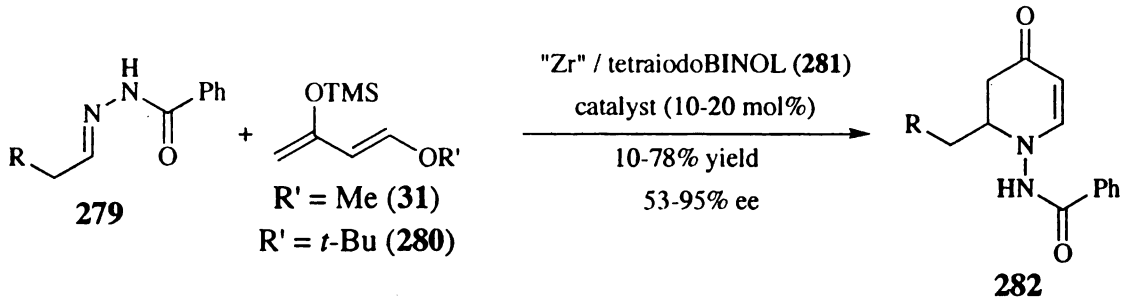
An issue that arises from the proposed synthesis is the imine needed is one that has to be prepared from heptanal. It is known that primary imines are not very stable and are prone to isomerization (Figure 5.6). In 2005[31], Kobayashi reported that the imines

Figure 5.6 Isomerization of Primary Alkyl Imines to Enamines



prepared from primary aliphatic aldehydes and benzoyl hydrazine were stable, and no isomerization occurred even under his zirconium Lewis acidic conditions. He showed that these imines could be used effectively in the *aza*-Diels-Alder reactions with Danishefsky's type dienes with the catalyst prepared from $Zr(OnPr)_4$ and tetraiodoBINOL (Scheme 5.9). Not only did this report by Kobayashi show that this

Scheme 5.9 *Aza*-Diels-Alder Reaction of Hydrazine Imines



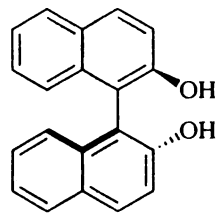
class of imines could be easily prepared but also indicated that they might be useful in the asymmetric synthesis of Cylindricine C using his zirconium catalyst system.

5.4 Efforts Toward Cylindricine C

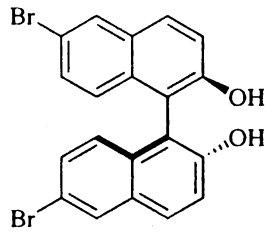
5.4.1 Catalytic Asymmetric *aza*-Diels-Alder Reaction

The zirconium catalyst utilized by Kobayashi seemed promising for facilitating the *aza*-Diels-Alder reaction that could eventually lead to the asymmetric synthesis of Cylindricine C. Before the zirconium catalyzed *aza*-Diels-Alder reaction could be attempted, tetraiodoBINOL (**281**) was prepared along with several other BINOL derivatives (Figure 5.7). In order to ensure tetraiodo-BINOL was properly prepared,

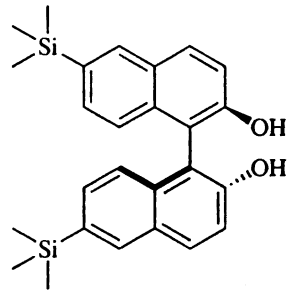
Figure 5.7 BINOL Derivatives



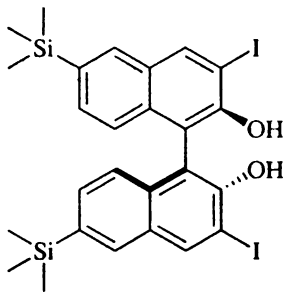
(S)-BINOL(**59**)



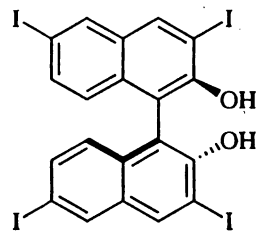
(S)-6,6'dibromo-BINOL (**282**)



(S)-6,6'di(trimethylsilyl)-BINOL (**283**)



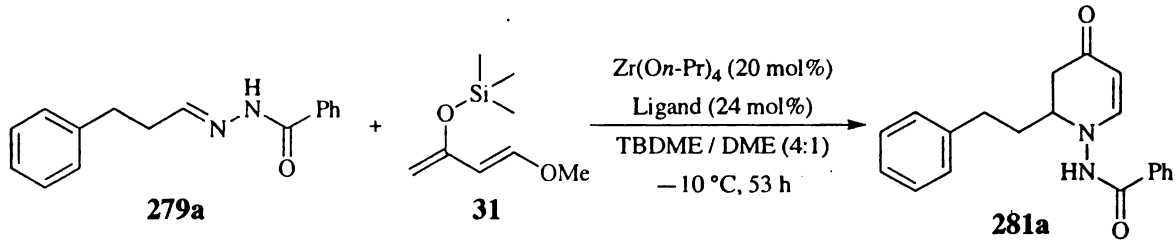
(S)-6,6'di(trimethylsilyl)-3,3'diiodo-BINOL (**284**)



(S)-3,3',6,6'-tetraiodo-BINOL (**281**)

the reaction of imine **279a** with diene **31** was repeated with Kobayashi's catalyst using his conditions. In addition, having prepared all the above-mentioned BINOL derivatives, they in addition to (*S*)-VAPOL (**130**), (*S*)-VANOL (**129**), and (*S*)-3,3'-dinitro-VANOL (**285**) were all screened (Scheme 5.10) to determine if they were viable ligands for this reaction.

Scheme 5.10 Screening of Ligands for the *aza*-Diels-Alder Reaction Using Kobayashi's Conditions



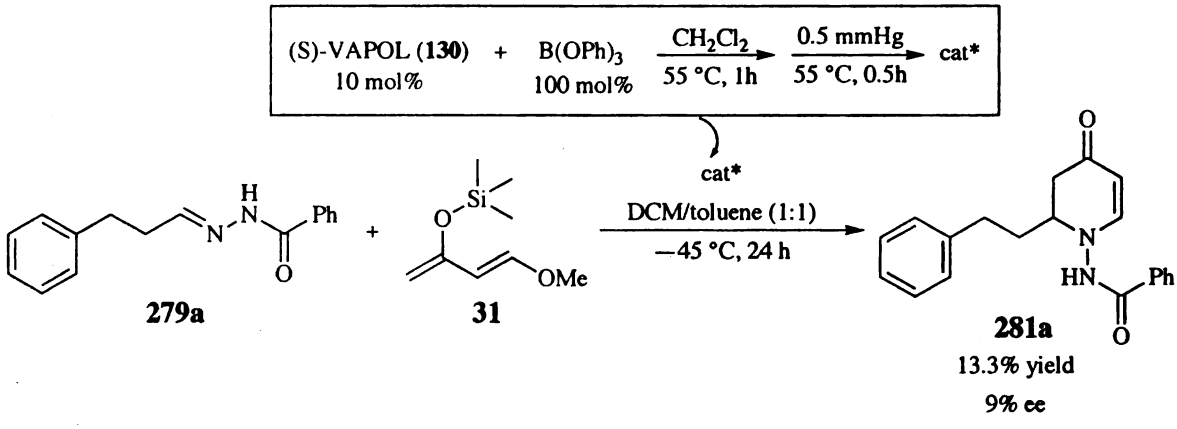
279a 31 281a

Entry	Ligand	Yield (%)	ee (%)
1	(S)-VAPOL (**130**)	0	N.D.
2	(S)-VANOL (**129**)	0	N.D.
3	(S)-BINOL (**59**)	0	N.D.
4	(S)-6,6'-dibromo-BINOL (**282**)	6.3	42.2
5	(S)-6,6'-di(trimethylsilyl)-BINOL (**283**)	<5	N.D.
6	(S)-6,6'-di(trimethylsilyl)-3,3'-diiodo-BINOL (**284**)	11.7	74.5
7	(S)-3,3',6,6'-tetraiodo-BINOL (**281**)	41	94
8	(S)-3,3'-dinitro-VANOL (**285**)	21	87

The electron neutral ligands, (*S*)-VAPOL, (*S*)-VANOL, and (*S*)-BINOL (entries 1-3 respetively) all failed to produce any of the desired Diels-Alder adduct **281a**. Using the ligand **283**, with trimethylsilyl groups in the 6,6'-positions, the reaction only gave trace amount of the desired product **281a** (entry 5). When electron-withdrawing groups were incorporated, the reaction was accelerated and produced enough material to determine the ee of the product from the reaction. The BINOL derivative **282** containing bromine atoms in the 6,6'-positions (entry 4) gave 6.3% yield and 42% ee, which was significantly inferior to the results published by Kobayashi for tetraiodoBINOL **281**. The selectivity could, however, be increased to 74.5% ee when the (S)-6,6'-di(trimethylsilyl)-3,3'-diiodo-BINOL **284** derivative was used as the ligand (entry 6). This reaction was reluctant to turn over and gave only about 12% yield. Repeating exactly the conditions

that Kobayashi reported for tetraiodoBINOL (**281**), the reaction gave 46% yield and 92% ee (entry 7, average of two runs), which is very close to what he achieved (70% yield and 91%ee using 10 mol% "Zr" and 12 mol% **284**). Interestingly, it was found that when 3,3'-dinitroVANOL **285** was used, the reaction gave 21% yield and 87% ee. Although the reaction did not turnover, the asymmetric induction was excellent when compared to Kobayashi's tetraiodoBINOL ligand and it may be worth while to explore this ligand in more detail to find conditions to improve the selectivity as well as induce turnover. One last attempt was made for this reaction using the optimal conditions developed for the *aza*-Diels-Alder reaction of **150** with Danishefsky's diene (see chapter 2). The VAPOL-$B(OPh)_3$ catalyst (Scheme 5.11) prepared using 100 mol%

Scheme 5.11 Reaction using (*S*)-VAPOL/$B(OPh)_3$ as the Catalyst

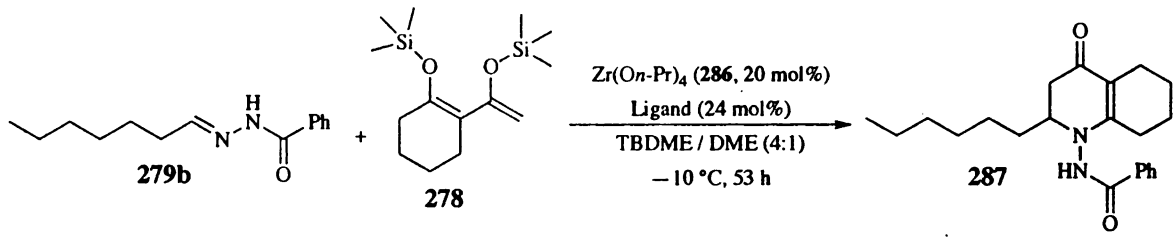


$B(OPh)_3$ and 10 mol% (*S*)-VAPOL was used and the reaction only gave 13% yield of the desired product **281a** with 9% ee. Although this catalyst system worked well for benzhydryl imines, it is clear from this reaction that there is no utility in using this catalyst when the dienophile is a benzoylhydrazone.

From the series of experiments described above, it was decided that tetraiodoBINOL was indeed the superior ligand for the reaction using the hydrazone **279a**

prepared from dihydrocinnamaldehyde and benzoyl hydrazine with Danishefsky's diene. The *aza*-Diels-Alder reaction desired for the synthesis of Cylindricine C, however, requires the use of the imine (**279b**) prepared from benzoyl hydrazine and heptanal and the bis-TMS diene **278**. Although tetraiodoBINOL proved to be better for Kobayashi's reaction, it was not clear that this would be the case for the desired system so attempts were made to accomplish the reaction asymmetrically using $Zr(OnPr)_4$ with BINOL, VAPOL, VANOL, and all the previously prepared BINOL derivatives (Scheme 5.12). It

Scheme 5.12 Catalytic Asymmetric *aza*-Diels-Alder Reactions using the bis-TMS Diene 278

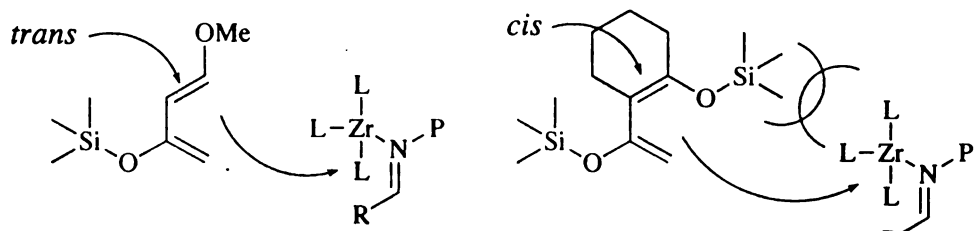


Entry	Ligand	Yield **287** (%)
1	(S)-VAPOL (**130**)	0
2	(S)-VANOL (**129**)	0
3	(S)-BINOL (**59**)	0
4	(S)-6,6'-dibromo-BINOL (**282**)	0
5	(S)-6,6'-di(trimethylsilyl)-BINOL (**283**)	0
6	(S)-6,6'-di(trimethylsilyl)-3,3'-diiodo-BINOL (**284**)	0
7	(S)-3,3',6,6'-tetraiodo-BINOL (**281**)	0

was dissappointing to find none of these ligands in conjunction with $Zr(OnPr)_4$ catalyzed the reaction to give the Diels-Alder adduct **287** using the imine **279b** and diene **278**. Knowing that tetraiodoBINOL was superior to the other ligands, two more reactions were carried out using this ligand at higher temperatures (see Experimental). Even heating the

reaction to reflux in toluene (see experimental section for details) for 25 hours failed to produce any of the desired product. The diene **278** in this reaction is significantly bulkier than Danishefsky's diene (**31**) as it contains two trimethylsilyloxy groups. In addition to containing more steric bulk, the bis-TMS diene has one of the trimethylsilyloxy groups locked in the *cis* position (Figure 5.8), which makes the orbital overlap that is

Figure 5.8 Danishefsky's Diene Versus bis-TMS Diene



Danishefsky's Diene (**31**) bis-TMS Diene (**278**)

necessary for the reaction even more difficult. This effect is enhanced even more when a sterically bulky catalyst is bound to the imine. The lack of success of these reactions is probably due to the fact that when the imine is coordinated to the zirconium with these relatively large ligands, the approach of the diene is too hindered and cannot get close enough for sufficient orbital overlap to occur and hence the reaction cannot happen. The outcome of these reactions was disappointing because the asymmetric synthesis would have to await further investigation of other chiral catalysts, however the synthesis of (±)-Cylindricine C was still persued.

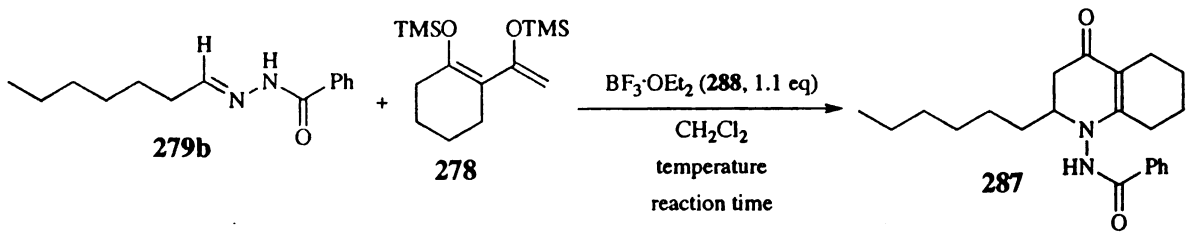
5.4.2 Efforts Toward the Synthesis of (±)-Cylindricine C

5.4.2.1 Optimization of the *aza*-Diels-Alder Reaction

Kobayashi's report in Tetrahedron[31], described the use of $BF_3{\cdot}OEt_2$ (**288**) to perform the racemic *aza*-Diels-Alder reaction of the hydrazone **279a** and Danishefsky's diene. Even for the racemic synthesis of Cylindricne C, the *aza*-Diels-Alder reaction is

the key step, so several reactions were carried out to try and find optimal conditions using $BF_3{\cdot}OEt_2$ (**288**) as the catalyst for the reaction of the bis-TMS diene **278** with imine **279b** (Scheme 5.13).

Scheme 5.13 Optimization of the Racemic *aza*-Diels-Alder Reaction



Entry	Condition	Temperature (°C)	Reaction time (h)	Yield **287** (%)
1	AA[1]	−45[3]	2	0
2	BB[1]	−45[4]	20	0
3	CC[1]	−45[5]	2	29
4	DD[1]	−78 to −45[6]	19	29
5	EE[1]	−78 to RT[7]	19	36
6	FF[2]	−78 to −45[6]	19	32
7	GG[1,8]	−78 to RT[7]	20	64
8	HH[1,8]	−78 to RT[9]	20	58.5
9	II[1,8,10]	−78 to RT[7]	20	42
10	JJ[1,8,11]	−78 to RT[7]	20	68
11	JJ[1,8,12]	−78 to RT[7]	20	63
12	KK[1,8,13]	−78 to −20 to RT[14]	19	>40

1) Reaction run at 0.1 M with respect to imine. 2) Reaction run at 0.025 M with respect to imine. 3) Imine and BF_3 combined at room temperature then cooled to −45°C before the diene was added. 4) Imine cooled to −45°C before BF_3 was added followed by the diene. 5) Imine was cooled to −45°C and then the diene was added followed by BF_3. 6) Imine was cooled to −78°C and then the diene was added followed by BF_3 and then warmed to −45°C. 7) Imine was cooled to −78°C and the diene was added followed by BF_3 then warmed slowly to room temperature. 8) Diene redistilled immediately before use. 9) imine was cooled to −78°C and the diene was added followed by BF_3 then warmed immediately to room temperature. 10) BF_3 redistilled immediately before use. 11) 0.45 g imine used. 12) 6.21 g imine used. 13) 16.3 g imine used. 14) The imine was cooled to −78°C and the diene was added followed by BF_3 then the reaction was allowe to warm slowly to −20°C over15 hours and then to room temperature for 4 hours.

The first two reactions involved the combination of the imine and $BF_3{\cdot}OEt_2$ before the addition of the diene (entries 1 and 2) and neither reaction gave the Diels-Alder

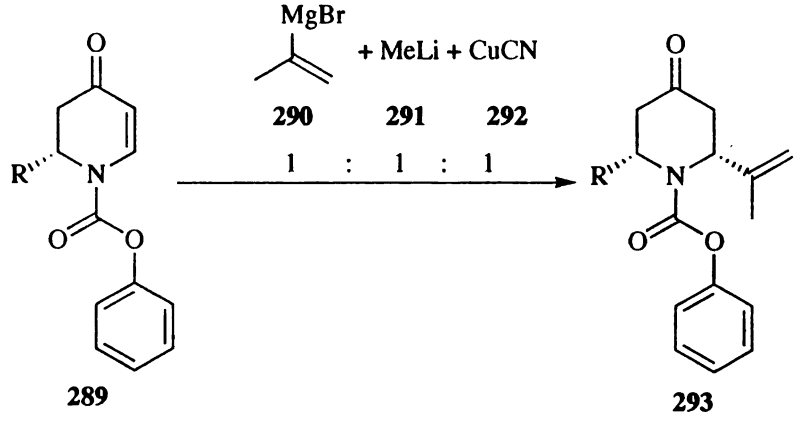
product **287**. It was found that when the solution of the imine was cooled to −45°C first and then adding the diene and $BF_3{\cdot}OEt_2$ in that order, the reaction produced 29% yield of **287** in only 2 hours (entry 3). A subsequent reaction was then attempted where the imine solution was cooled to −78°C before the diene and $BF_3{\cdot}OEt_2$ were added (entry 4) and then warmed to −45°C and no improvement was observed (29% yield) even when the reaction was allowed to run for 20 hours. This reaction was repeated except that the reaction was allowed to warm to room temperature after all reagents were added (entry 5) and 36% yield of **287** was produced. Another reaction was performed at lower concentration (0.025 M, entry 6) using the conditions where the reaction warmed from −78°C to −45°C, but still, the reaction gave a low yield (32%) of the desired product **287**. The highest yield obtained (36%) was not satisfactory since this was the key step in the synthesis of Cylindricine C. In an attempt to increase the yield, a new batch of the diene was prepared and distilled immediately before use. Repeating the reaction where it was cooled to −78°C before the diene and $BF_3{\cdot}OEt_2$ were added and then warming to room temperature, using the freshly prepared diene, the reaction gave 64% yield (entry 7). The yield dropped to 58.5% (entry 8) if the temperature was immediately allowed to warm to room temperature rather than slowly over several hours. The same conditions as for entry 7 were followed only redistilled $BF_3{\cdot}OEt_2$ was used (entry 9) and the reaction only gave 42% yield of **287**. Lastly, three reactions were then carried out on larger scale (0.45g, 6.21g, and 16.3g of imine **279b**). The reaction performed on a 0.45 g scale gave 68% yield (entry 10), 6.21 g scale gave 63% yield (entry 11), and 16.3 g scale gave at least 40% yield (entry 12). The 40% yield in the last reaction was after one recrystalization and more of the crude product was isolated from the mother liquor but

another recrystalization was not accomplished at that time. It is encouraging that the reaction could be scaled up and this scalability makes this route even more attractive.

5.4.2.2 1,4-Addition to Incorporate the Butenyl Side Chain

With plenty of the Diels-Alder product **287** in hand, attempts were made to find conditions to facilitate the 1,4-addition of the butenyl side chain. Work published by Martin[98] showed that the reaction took place between an organomagnesiumcuprate prepared from a mixture of vinylmagnesium bromide, MeLi, and CuCN (1:1:1) with the Cbz-protected vinylogous amide **289** (Scheme 5.14). Not only did the reaction work

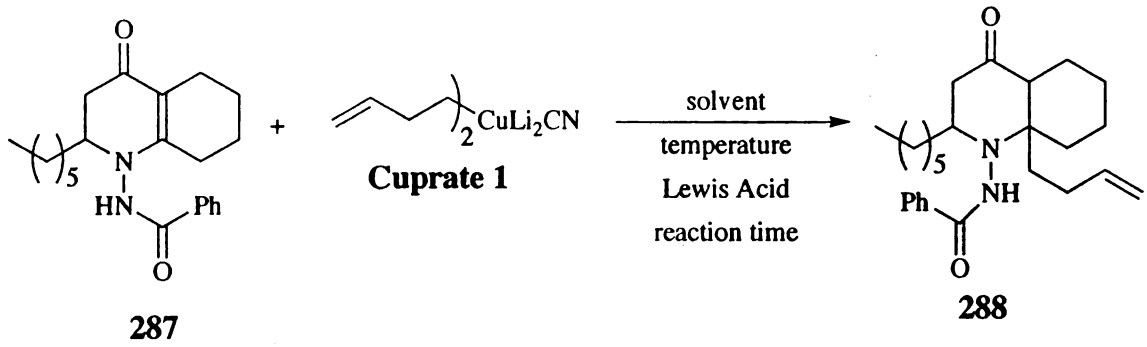
Scheme 5.14 *cis* 1,4-Addition as Reported by Martin[98]



289 **293**

well, but the major isomer of the product was where *cis*-addition of the vinyl side chain occurred. The vinylogous amide (**278**) resulting from *aza*-Diels-Alder using the present strategy contains hydrazine functionality rather than the Cbz carbamate functionality. The hydrazine is not as electron withdrawing as the Cbz group, but in order to minimize the amount of steps needed in the synthesis, several attempts were made to facilitate the 1,4-addition on the hydrazine adduct **287** (Scheme 5.15). Two reactions were first

Scheme 5.15 1,4-Addition to the Vinylogous Hydrazine Using Cuprate 1



287 **288**

Entry	Cuprate 1 (equiv.)	solvent	Temperature (°C)	Lewis Acid	reaction time (h)	yield (%)
1	1.5	Et_2O	−78 to −25	none	19	0
2	1.5	Et_2O	−78 to −25	none	16	0
3	2.5	Et_2O	−78 to −10	none	22	0
4	1.5	Et_2O/CH_2Cl_2 (4:3)	−78 to −50 to −25	$Zr(OnPr)_4$	67	0

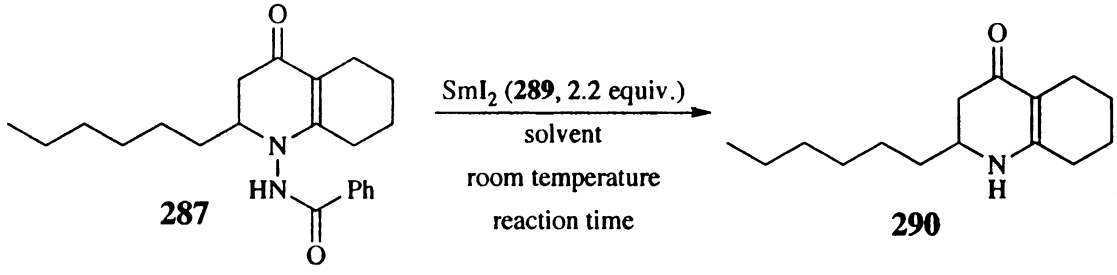
attempted using 1.5 equivalents of the cyanocuprate (**cuprate 1**) prepared *in situ* from two equivalents of the butenyl lithium and one equivalent of copper cyanide. Both reactions were allowed to warm from −78°C to −25°C and one was stirred for for 19 hours and one for 16 hours, but neither reaction produced the desired product **288**. When 2.5 equivalents of the cyanocuprate was used and the reaction allowed to warm to −10°C (entry 3) also failed to produce the desired product. The lack of reactivity could either be due to steric hindrance of the tetrasubstitutted double bond or the electron rich nature of the double bond. It was thought then that the benzoyl hydrazine in the product **287** could coordinate to $Zr(OnPr)_4$ (as in the *aza*-Diels-Alder published by Kobayashi) and pull electron density out of the vinylogous amide's carbon-carbon double bond.

When $Zr(OnPr)_4$ was added to the reaction and the resulting mixture warmed slowly from—78°C to —25°C over 67 hours (entry 4), no reaction was observed.

5.4.2.3 N-N Bond Cleavage and Protection with Cbz

The 1,4-addition did not take place on the hydrazine moiety **287** but the work done by Martin (Scheme 5.13) indicated that if the nitrogen was protected with a Cbz group, the reaction can occur readily and give the desired *cis* stereochemistry as the major product. Before the 1,4-addition could be attempted, the hydrazine N-N bond had to be cleaved and the Cbz group incorporated. Initial efforts to reductively cleave the N-N bond were done using SmI_2 (Scheme 5.16). The first two attempts (entries 1 and 2)

Scheme 5.16 Reductive Cleavage Using SmI_2



Entry	solvent	reaction time (h)	yield 290 (%)
1[a]	THF	0.67	12
2[a]	THF/MeOH (3.5:1)	0.67	7.6
3[b]	THF/MeOH (4:1)	7	38

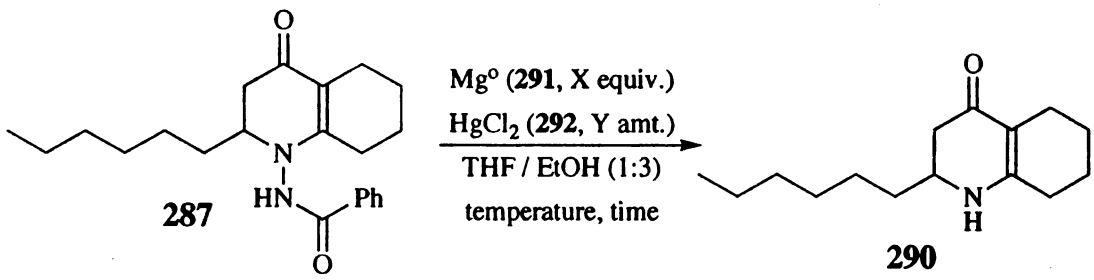
a) SmI_2 was prepared using Sm° and I_2 refluxing in THF.
b) SmI_2 was prepared using Sm° and CH_2I_2 at room temperature in THF.

used SmI_2 that had been prepared by diluting samarium metal and iodine in THF and refluxed until the solution turned blue. When only THF was used as the solvent (entry 1), the reaction produced 12% yield of the free amine **290** in 45 minutes, however when THF/MeOH was used as the solvent, the reaction only gave 7.6% yield. The last attempt was carried out using SmI_2 that had been prepared by stirring samarium metal in the

presence of CH_2I_2 at room temperature for several hours in THF. The resulting blue solution was used for the reductive cleavage of the N-N bond and after 7 hours the reaction produced 38% of the desired amine **290**. This series of experiments indicated that SmI_2 was not a good choice for this reaction and another method was needed to perform the reductive cleavage that would give higher yields.

In 1993, Pak published a method to efficiently mediate desulfonylation reactions in methanol[100]. His method used 10 equivalents of magnesium with catalytic amount of mercuric chloride as the reducing agent and was able to obtain the reduced product in high yields. It was thought that this reducing agent may be able to facilitate the N-N bond cleavage desired for production of the free amine **290**. The reaction conditions mentioned in Pak's publication were vague and only mentioned that he used catalytic amounts of $HgCl_2$. In order to determine if this method would be feasible for the cleavage of the N-N bond in **287**, a few preliminary reactions were attempted (Scheme 5.17). When 10 equivalents of Mg and a few spatula tips of $HgCl_2$ were used (entry 1),

Scheme 5.17 Initial Attempts for the Reductive Cleavage Using Mg° and $HgCl_2$

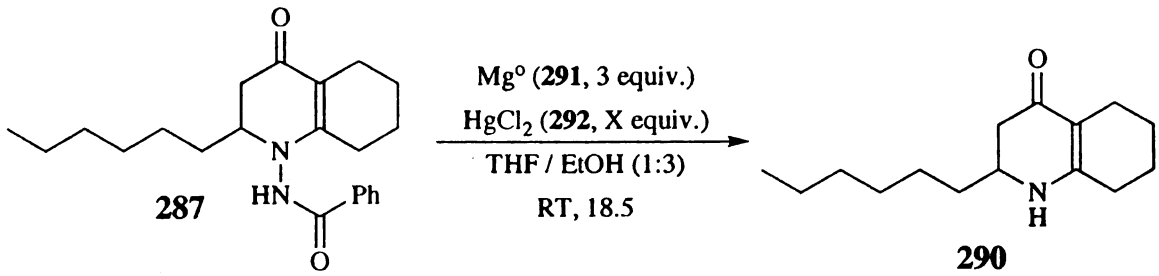


Entry	Mg° (equiv)	$HgCl_2$ (amt.)	temperatrue	reaction time (h)	Yield **290** (%)
1	10	3 spatula tips	RT	3	18.2
2	10	3 spatula tips	0°C to RT	3	16.7
3	3	0.7 equiv.	RT	6	69

an exothermic reaction occurred when the $HgCl_2$ was added. After 3 hours, TLC analysis showed the starting material had been consumed but only 18.2 % yield of the product **290** was isolated. During the previous reaction, it was exothermic enough that the solvent started to boil, so another reaction was done cooling to the hydrazine and magnesium to 0°C before the $HgCl_2$ was added (entry 2). After the the addition of $HgCl_2$, the reaction was warmed to room temperature and stirred for 3 hours, and only 17% yield of **290** was obtained. One possible explanation of the low yield could be due to the large excess of the reducing agent degrading the product after the N-N bond cleavage took place. With 10 equivalents of the reducing agent, it is not unreasonable to believe that reduction of the carbonyl and possibly the double bond could also occur. In addition to over reduction, it is possible that the excess reducing agent could also facilitate some radical type polymerization reaction. Finally, a reaction was carried out using only 3 equivalents of magnesium and 0.7 equivalents of the $HgCl_2$ (entry 3) and the reaction proceeded smoothly giving 69% yield of **290** in only 6 hours.

In order to determine the optimal amount of $HgCl_2$ needed to give good conversions, a series of experiments was conducted using $HgCl_2$ amounts ranging from 0.1 equivalent to 1.0 equivalent (Scheme 5.18). It was found that the reaction was quite

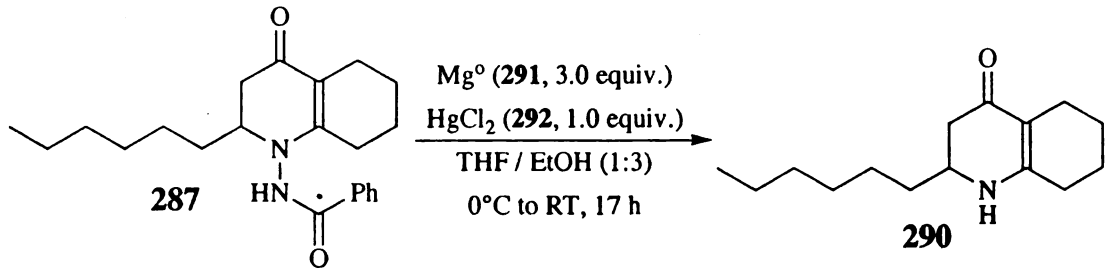
Scheme 5.18 Determination of the Optimal Amount of $HgCl_2$



Entry	$HgCl_2$ (equiv)	Conversion
1	0.1	<5
2	0.2	<5
3	0.3	19
4	0.5	80
5	0.6	70
6	0.8	>95
7	1	>95

slow (19% conversion or less) when less than 0.5 equivalents of $HgCl_2$ were used. However when 0.8 and 1.0 equivalents of $HgCl_2$ were used, only trace amounts of the starting material were observed in the crude ^1H NMR after 18.5 hours. Since only conversions were measured for these reactions and the isolated yields were not determined, a reaction was carried out using 1.0 equivalent of the $HgCl_2$ to determine the isolable yield from this reaction (Scheme 5.19). Using these conditions on a 0.355 g

Scheme 5.19 Optimal Reduction Condition and Scalability



Entry	Scale (g)	Yield **290** (%)
1	0.355	80
2	1.0	62
3	1.2	62
4	9.0	60

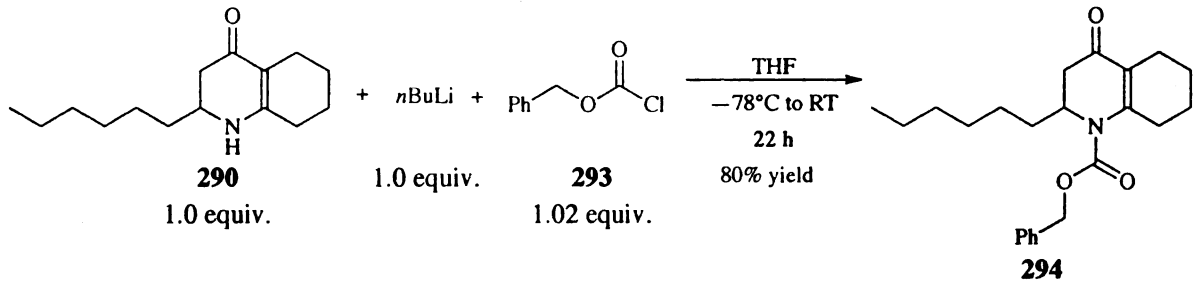
scale, the reaction gave 80% yield of the desired free amime **290**. To determine the scalability of this reaction, three other reactions were carried out on larger scale. When the scale was increased to 1.0 g the yield dropped slightly to 62% (entry 2), but scaling up even more to 9.0 g (entry 4), showed no detrimental effects and the reaction still gave 60% yield of the desired product **290**.

5.4.2.4 Protection of the Amine with Cbz

With a significant amount of the free amine **290** in hand, the stage was set for protecting the amine with the Cbz protecting group and ultimately attempting the 1,4-addition with the Cbz protected product **294**. Literature precedent indicated that either sodium hydride[101] or Hunig's base[102] could be used as an efficient base for deprotonation of the nitrogen. Subsequent treatment of the nitrogen anion with CbzCl (**293**) should have given the desired Cbz protected vinylogous amide **294**, however, using these conditions, the desired product was not obtained (see experimental). Fortunately, it was

found that treatment with *n*BuLi followed by the addition of CbzCl gave the desired product (Scheme 5.20) in 80% yield. It is worthy to note that the reagents all need to be

Scheme 5.20 Cbz Protection of the Amine

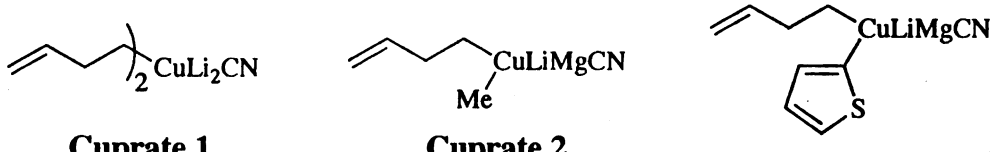


added slowly at −78°C before the reaction could be warmed to room temperature or the yield of the reaction was significantly decreased. An additional reaction was done where the reaction was only allowed to stir for 30 minutes after reaching room temperature, and the yield for this reaction was 98% based on recovered starting material.

5.4.2.5 1,4-Addition of the Butenyl Side Chain Using the Cbz Protected Vinylogous Amide

With the Cbz protected vinylogous amide **294** in hand, the 1,4-addition of the butenyl side chain could be attempted. The three different cuprates depicted in Figure 5.9

Figure 5.9 Cuprates 1-3

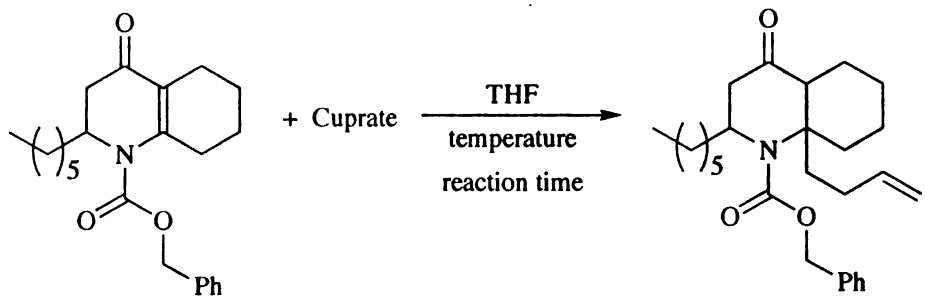


Cuprate 1 **Cuprate 2** **Cuprate 3**

were explored for this reaction. The lithium cyanocuprate (**Cuprate 1**) is the most reactive of the three and only contains the butenyl groups so the possibility only exists for a butenyl group to be incorporated. A less reactive lithium cyanomagnesium cuprate (**Cuprate 2**), similar to the one used by Martin,[98] contains a methyl group also, which

may compete with the aliphatic butenyl group for the 1,4 addition. To alleviate this problem, a second lithium cyanomagnesium cuprate (**Cuprate 3**) was prepared that contains the "dummy" thiophenyl ligand. This group takes up one site on the cuprate but will transfer much slower, only allowing for the addition of the butenyl group. Each of these cuprates was then tested in the 1,4-addition reaction (Scheme 5.21). All attempts

Scheme 5.21 Screening of Cuprates 1, 2 and 3



294 **295**

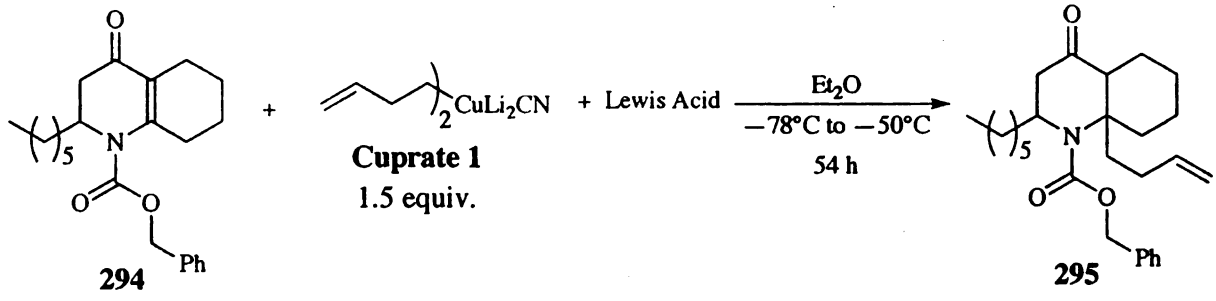
Entry	Cuprate (equiv.)	temperature (°C)	reaction time (h)	Conversion (%)
1	**Cuprate 2** (1.5)	−78	20	<5
2	**Cuprate 3** (1.5)	−78 to RT	17	0
3	**Cuprate 3** (1.5)	−78 to −20 to 10	42	0
4	**Cuprate 1** (1.5)	−78 to RT	2	0
5	**Cuprate 1** (1.5)	−78 to −20	53	58[a]
6	**Cuprate 1** (1.5)	−78 to −25	19	0
7	**Cuprate 1** (2.45)	−78 to −10	48	38[a]

a) none of the desired product was isolated

using Cuprates 2 and 3 (entries 1-3) failed to install the butenyl side chain even when the reaction was increased to room temperature. When cuprate 1 was used and the reaction was allowed to warm slowly from −78°C to −20°C (entry 5), 58% conversion was observed, but none of the desired product **295** was isolated. A second reaction was performed using 2.45 equivalents of cuprate 1 (entry 7) and the conversion of the reaction was still low (38%), and again, the desired product **295** was not isolated. The results from this set of experiments indicated that the reaction using the tetrasubstituted double

bond was going to be a bigger challenge than originally anticipated. Three different Lewis acids ($BF_3{\cdot}OEt_2$, $ZnCl_2$, and TMSCl) were then used in an attempt to activate the double bond by decreasing its electon density (Scheme 5.22). $BF_3{\cdot}OEt_2$ and $ZnCl_2$

Scheme 5.22 Lewis Acid Promoted 1,4-Addition



Entry	Lewis acid	Conversion (%)
1	$BF_3{\cdot}OEt_2$	0
2	$ZnCl_2$	0
3	TMSCl	68.5

a) none of the desired product was isolated

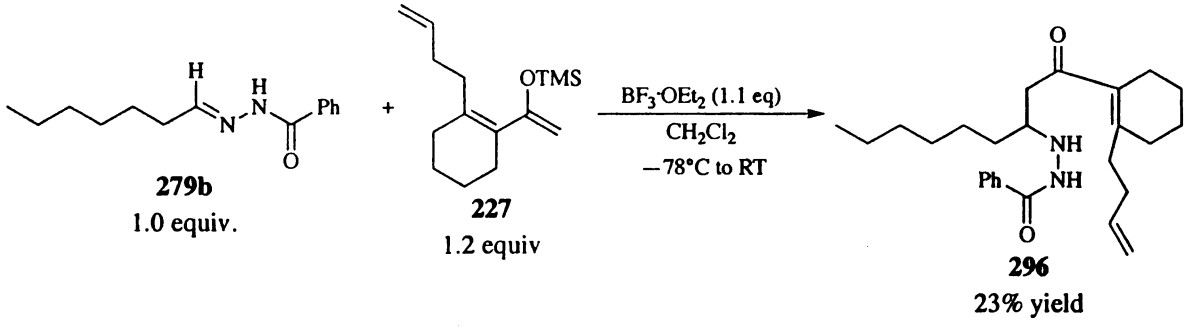
(entries 1 and 2 respectively) both failed to facilitate the reaction and only starting material was observed in the crude ^1H NMR for these reactions. When TMSCl was used (entry 3), 68.5% of the starting material was consumed, but none of the 1,4-addition product **295** was isolated.

5.4.3 Synthesis of Cylindricine C via Route B

After problems occurred with the originally proposed 1,4-addition following route A for the synthesis of Cylindricine C, the alternative route B was investigated. The proposed route B (Figure 5.5) involved the use of the diene **227**, which already has the butenyl side chain incorporated. It was envisioined that if the *aza*-Diels-Alder reaction were to occur with this diene, then the only other steps would be the deprotection and cyclization. Presumably, the cleavage of the hydrazine N-N bond should not pose a

problem, as that issue was previously solved for route A, and as mentiomed earlier, the final cyclization step is known[99] and has been carried out on a similar substrate. One attempt was made to perform the *aza*-Diels-Alder reaction using the alternate diene **227** (Scheme 5.23) under the optimal conditions found for diene **278** (scheme 5.13, entry 10)

Scheme 5.23 *Aza*-Diels-Alder Attempt Using Alternate Diene 227

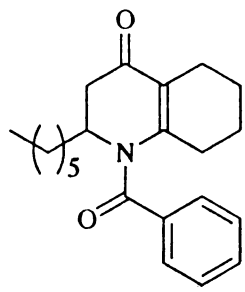


The reaction proceeded to give 23% yield of the non-cyclized Mannich type product **296**, which is of course not the desired *aza*-Diels-Alder adduct. It is possible that heating the Mannich product or treating it with a weak acid or base could facilitate the cyclization to give the core decalin system of Cylindricne C but this was not attempted. Another issue that may present a problem using this diene is if the process is not concerted, the relative stereochemistry at the fused six-membered rings might not be exclusively *cis* after the cyclization step. However, if this reaction can be optimized and the issues of stereochemistry can be solved, then this route to Cylindricine C seems very promising and is shorter than the originally proposed route A.

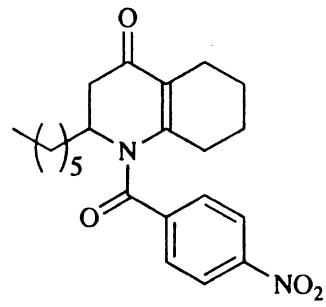
Efforts toward the racemic synthesis of Cylindricine C unfortunately were halted at this point. It was found that the 1,4-addition of the butenylside chain is a difficult problem and could be due to the more hindered tetrasubstituted double bond causing the addition of the butenyl group to be unfavorable. It could also be that even with the Cbz group on the nitrogen, the tetrasubstituted olefin is not electrophilic enough to allow the

1,4-addition to take place. A solution to the latter issue would be to put a more electron-withdrawing group on the nitrogen and attempt the 1,4- addition again. The compounds with a benzoyl group on the nitrogen and a 4-nitro-benzoyl group on the nitrogen were synthesized (Figure 5.10) but the 1,4- addition on these compounds was not attempted. If

Figure 5.10 Alternate Substrates for the 1,4-Addition



294b



294c

the 1,4-addition could be carried out on one of these compunds, the synthesis should be easily completed by simple deprotection of the nitrogen followed by cyclization to incorporate the final 5-membered ring in the tricyclic core of Cylindricine C. Alternatively, route B also seems promising and if the *aza*-Diels-Alder reaction can be optimized or the cyclization to be induced, this route may provide an even shorter synthesis of Cylindricine C (6 steps) including the preparation of the diene.

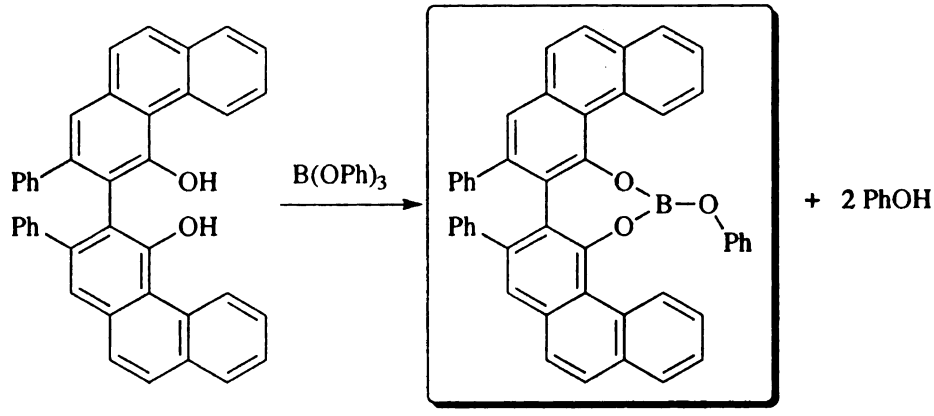
CHAPTER 6

CATALYST STRUCTURE, CONCLUSIONS AND FUTURE WORK

6.1 Structure of the (*S*)-VAPOL-Boron Catalyst

In order to obtain a clear idea of how a catalyst is functioning and to be able to predict the stereochemical outcome of an asymmetric reaction, one must have a good understanding of the actual catalyst structure. The VAPOL-boron catalyst utilized in the *aza*-Diels-Alder reaction and previously in the aziridination reaction was prepared using an excess triphenylborate (≥3:1 $B(OPh)_3$/VAPOL). It was originally assumed that the excess $B(OPh)_3$ was simply driving the catalyst formation to completion and that the catalyst was formed by the replacement of two phenoxy groups on triphenylborate with the two oxygen atoms on VAPOL (Figure 6.1). A related catalyst structure was originally proposed by Yamamoto in 1993[18] for his catalyst prepared from BINOL and $B(OPh)_3$.

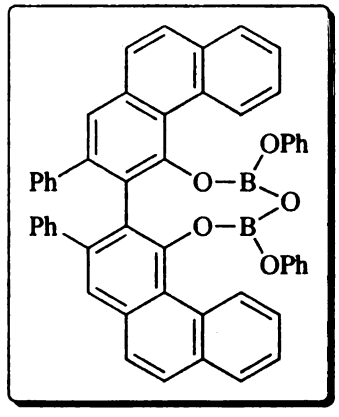
Figure 6.1 Original Proposed Catalyst



Original Proposed Catalyst

During the time that the work presented in this thesis was going on, studies in the Wulff group were being directed at determining the exact structure of the active catalyst prepared from VAPOL and $B(OPh)_3$. Towards the beginning of these studies, mass spectral data was obtained that indicated that the active catalyst species contained two boron atoms (Figure 6.2).

Figure 6.2 Two Boron Catalyst Structure

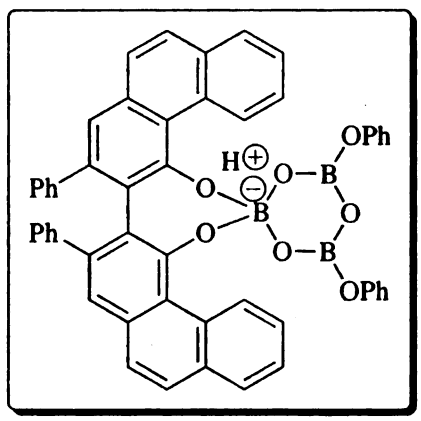


Proposed Catalyst 2

With the assumption that the active catalyst contained two boron atoms, a method was developed to prepare this catalyst by using 1 equivalent of VAPOL, 2 equivalents of BH_3·THF, 2 equivalents of phenol, and 1 equivalent of H_2O. This method was developed

because it uses the appropriate number of atoms needed to prepare the proposed catalyst 2. In addition, a method was also developed to prepare the originally proposed one boron catalyst species using 1 equivalent of VAPOL, 1 equivalent of BH_3·THF, and 1 equivalent of phenol. The two catalysts could be distinguished from each other by observing different chemical shifts for the bay proton in the ^1H NMR. Interestingly, recent data has indicated that neither of the proposed catalysts 1 or 2 described above are actually the active catalyst in the aziridination reaction. Based on crystallographic data, it is now believed that the actual active catalyst species contains three boron atoms (Figure 6.3). This catalyst contains a boroxazine ring with one of the

Figure 6.3 Boroxazine (H^+) Catalyst



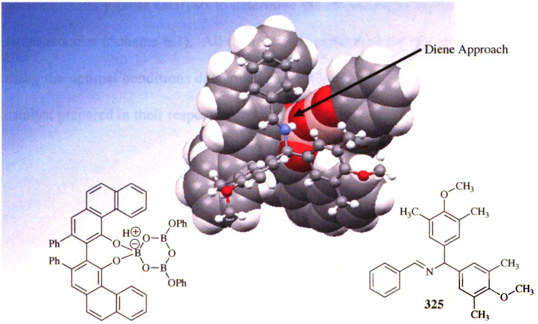
Active Catalyst Species

borons attached to two oxygens in the boroxazine ring and two oxygen atoms from VAPOL. It was found that this boroxazine catalyst forms readily in the presence of an imine and by just placing the imine. Specifically, it was found that the boroxazine catalyst spontaneously forms when the imine, VAPOL, and triphenylborate are simply placed in a flasak and dissolved. This VAPOL-boroxazine catalyst is negatively charged with a proton as the counter ion. Knowing that this is the actual catalyst structure, one

can imagine that the imine is either activated by the proton (Brønsted acid) or possibly it could be one of the neutral boron atoms in the boroxazine ring (Lewis acid).

In order to determine how the imine is coordinating to the catalyst, crystals were grown by Gang Hu in the group using the imine **325** prepared from benzaldehyde and bis(4-methoxy-3,5-dimethylphenyl)methanamine (MEDAM). The crystals were grown by first preparing the catalyst by adding $B(OPh)_3$ (3.0 equiv.), VAPOL (1 equiv.) and water (3.0 equiv.) to a Schlenk flask and heating to 80°C in THF. After 1 hour of heating, the flask was placed under high vacuum and heated to 80°C to remove any volatiles. To this active catalyst was then added the MEDAM imine and the crystals were grown using a mixture of pentane, CH_2Cl_2, and $CDCl_3$ as the solvent (see crystal structure in Figure 6.4, solvent

Figure 6.4 Crystal Structure of the Three Boron Catalyst and MEDAM Imine



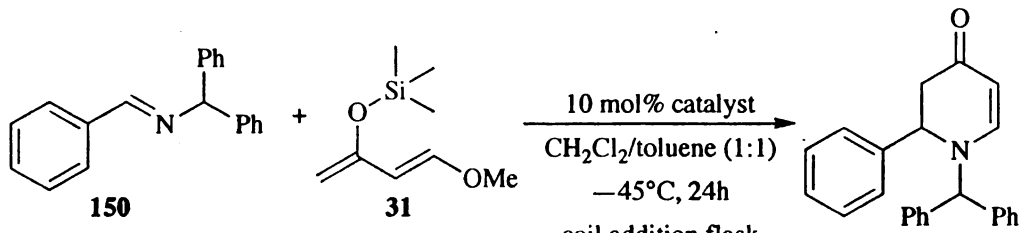
molecules removed for clarity). As can be seen from the crystal structure, it is indeed the proton that is coordinated to the imine. So, after many years of thinking that the catalyst

was a Lewis acid, it appears now that it is in fact a Brønsted acid that is facilitating these reactions. The crystal structure shown was grown using the (*S*)-VAPOL ligand, which was the ligand used in *aza*-Diels-Alder work discussed in this thesis. It was found that the absolute stereochemistry of the product **170** was *S* (see Scheme 3.8 and 3.9) when using (*S*)-VAPOL and this is precisely what the crystal structure would predict. Although the catalyst is actually a "chiral proton" and it is a Brønsted acid catalyzed reaction, it does not change the fact that a new successful method has been developed for the *aza*-Diels-Alder reaction.

6.1.1 *aza*-Diels-Alder Reaction Using Alternate Catalyst Preparations

Previously, mention was made of studies carried out in the Wulff research group by Gang Hu to optimize conditions to prepare the VAPOL-boron catalyst containing one boron atom (Figure 6.1) as well as the catalyst with two boron atoms (Figure 6.2). It was decided to study these catalysts to determine the effectiveness of each for the *aza*-Diels-Alder reaction (Scheme 6.1). All the reactions performed for this study were carried out using the optimal conditions developed and described in Chapter 2 only 10 mol% of the catalyst prepared in their respective methods.

Scheme 6.1 *aza*-Diels-Alder Reaction Using the One (B1) and Two Boron (B2) Catalyst



Entry	Catalyst	Yield **151** (%)	ee **151** (%)
1	B1[a]	35	30
2	B2[b]	82	71
3	B2[c]	31	75

a) catalyst prepared using 1.0 eq. $BH_3{\cdot}SMe_2$, 1.0 eq. (*S*)-VAPOL, and 1.0 eq. phenol by heating to 100°C in toluene for 1 hour and then heated to 100°C under high vacuum for 30 minutes.

b) catalyst prepared using 4.0 eq. of $B(OPh)_3$, 1.0 eq. (*S*)-VAPOL, and 1.0 eq. of H_2O by heating to 80°C in toluene for 1 hour and then heated to 80°C under high vacuum for 30 minutes.

c) catalyst prepared using 2.0 eq. $BH_3{\cdot}SMe_2$, 1.0 eq. (*S*)-VAPOL, 3.0 eq. phenol, and 1.0 eq. H_2O by heating to 100°C in toluene for 1 hour and then heated to 100°C under high vacuum for 30 minutes.

The first reaction was attempted using the B1 catalyst prepared using 1.0 equivalents of $BH_3{\cdot}SMe_2$, 1.0 equivalents of (*S*)-VAPOL, and 1.0 equivalent of phenol (entry 1). The reagents were combined and heated to 100°C in toluene for 1 hour and then heated to 100°C under high vacuum for 30 minutes. When the reaction was attempted using this catalyst, only 35% yield of the desired product **151** was obtained with 30% ee. The second two reactions were attempted using the B2 catalyst. The reaction in entry 2 was carried out using the catalyst prepared by heating 4.0 equivalents of $B(OPh)_3$, 1.0 equivalents of (*S*)-VAPOL, and 1.0 equivalent of water to 80°C for one hour and placed under high vacuum at 80°C for 0.5 hour. This reaction produced 82% yield of the desired product **151** with 71% ee. The last reaction was attempted using another method

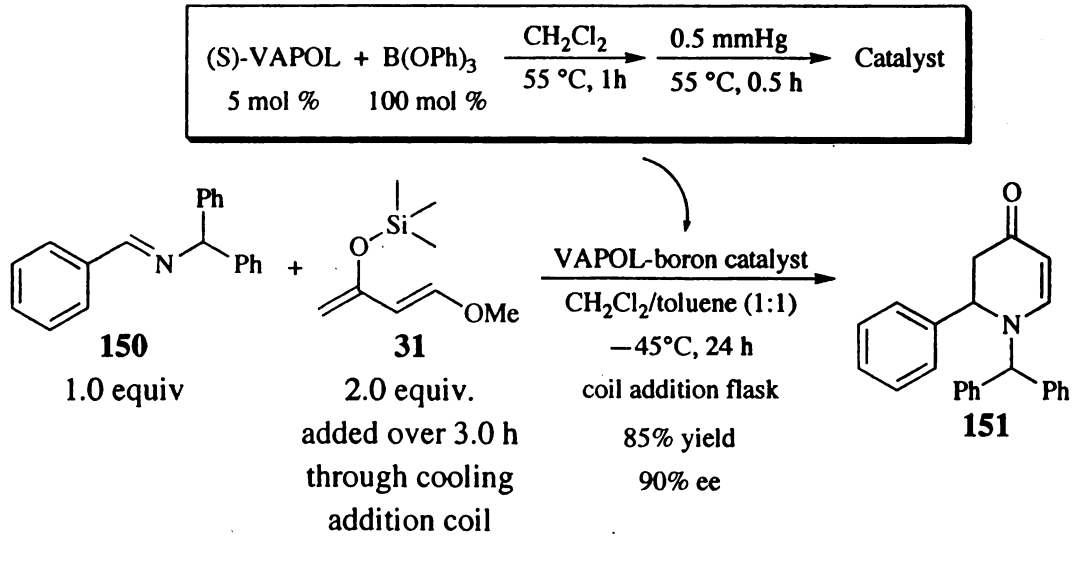
to prepare the B2 catalyst. For this reaction, 2.0 equivalents of $BH_3 \cdot SMe_2$, 1.0 equivalents of (*S*)-VAPOL, 3.0 equivalents of phenol, and 1.0 equivalent of water was used for the preparation of the catalyst (entry 3). The reagents were combined and heated to 100°C in toluene for 1 hour and then heated to 100°C under high vacuum for 30 minutes. When the reaction was attempted using this catalyst, only 31% yield of the desired product **151** was obtained with 75% ee. It is clear from these experiments that the B1 and B2 catalysts are not as effective in producing asymmetric induction as high as for the optimal conditions.

The next few sections will contain a biref summary of the work that has been described in this thesis. Conclusions can be drawn from the results observed during the course of the study and along with those conclusions several questions arise as well. Some of these questions will be discussed as well as the future work that needs to be done to gain a better understanding of this catalyst and reaction system.

6.2 Conclusions and Future work

6.2.1 *Aza*-Diels-Alder Optimization

Scheme 6.2 Optimal Reaction Conditions



A significant amount of effort was spent on the exploration of the *aza*-Diels-Alder reaction of benzhydryl (Bh) protected imino dienophiles during these studies. Several ligand/Lewis acid combinations were explored and it was found that the catalyst derived from $B(OPh)_3$ and (*S*)-VAPOL was optimal. Using this catalyst, a broad range of conditions had to be explored to find those that would give the highest yield and asymmetric induction. Originally the TBS version (**149**) of Danishefsky's diene was studied but later it was found that the less bulky original Danishefsky's diene (**31**) produced better results. Studies were then done to determine how other important variables such as time, temperature, solvent, catalyst preparation, catalyst loading, equivalents of reagents, order of addition of reagents, and how the reagents are added would effect the outcome of the reaction. In order to determine the optimal conditions for this reaction many different combinations of these variables were explored. This task was found to be quite daunting, but in the end, the optimal results obtained were 85% yield and 90% ee using only 5% loading of the chiral ligand. The catalyst was prepared by heating 5 mol% (*S*)-VAPOL and 100 mol% $B(OPh)_3$ in CH_2Cl_2 to 55°C for one hour followed by heating to 55°C under high vacuum for 30 minutes. The optimal temperature for the reaction was determined to be —45°C and using a 1:1 mixture of CH_2Cl_2/toluene as the solvent was optimal. An interesting effect was observed when studying how the reagents were added and it was found that when the diene was added over a period of three hours as a 0.33 M solution in CH_2Cl_2/toluene (1:1) was optimal. In addition, the use of a home-made round bottom flask equipped with a coil that allowed the solution of the diene to be cooled down to the reaction temperature as it was added

was able to increase the ee's by about 2%. More importantly, however, it was observed that the reproducibility of the reaction was slightly better when using this special flask.

6.2.2 Substrate Screening

The optimal conditions described above were used for the screening of a wide variety of imines to test the generality of the reaction. Many substrates afforded good results when using the optimal conditions, but some imines either needed increased reaction time to achieve higher yields or increased catalyst loading (10 mol% VAPOL) to aid in the asymmetric induction of the reaction. For most of the imines screened, when one or both of these modified conditions were employed, the ee's as well as the yield could be increased. The increased reaction time or catalyst loading was only used when the optimal conditions failed to provide satisfactory results.

The reaction was found to be general for aromatic substrates with yields from 71-85% and ee's from 89-95%. The only exception was the *p*-nitrobenzaldimine substrate **159** that gave only 69% yield and 73% ee even when 10 mol% (*S*)-VAPOL was used. The α,β-unsaturated imines proved to be interesting as it was found that when there was no substituents in the α-position (i.e. *trans*-β-styryl **173** and β,β-dimethyl **175**) the reaction failed to produce any enantiomeric excess and low yields were obtained. However, when the double bond was substituted at the α-position (i.e. cyclohexenyl **175**), the reaction was very successful giving 45% yield and 93% ee using 10 mol% (*S*)-VAPOL. It is still not clear whether it is the substituent at the α-position or the fact that the double bond is contained in a ring that is causing the asymmetric induction. One substrate that could be looked at to determine which is true would be that with just a methyl group in the α-position. It was found when studying the aliphatic substrates that

secondary aliphatic groups worked quite well (64-90% yield and 90-93% ee), but the primary aliphatic imines gave only racemic products. Due to the lack of success with the primary substrates, several other imines could function as surrogates for the imines with a primary aliphatic side chain were also examined and success was limited with these compounds as well. The best results from these studies were found when imines **199** or **201** prepared from ethylglyolylate or isopropylglyoxylate were used and although yields were around 80%, the reactions only gave around 60% ee. A substrate with a silyl-group incorporated into the α-position (**212**) of an α,β-unsaturated substrate was also attempted, but failed undergo the *aza*-Diels-Alder reaction and no product was formed. Lastly, a substrate containing a silyl-substituted acetylene (**207**) was studied and the product **208** with only 22% ee was obtained from the reaction.

In addition to the benzhydryl imines, several other imines were studied that were prepared using substituted benzhydryl amines. Those studied were the 3,3'5,5'-tetramethyl benzhydryl (TMB), 4,4'-dimethoxy bezhydryl (DAM), and 3,3',5,5' tetra-*t*-butyl-4,4'-dimethoxy benzhydryl (BUDAM) groups. For each of the different benzhydryl amines, the corresponding imines were prepared using benzaldehyde, 4-nitrobenzaldehyde, 4-bromobenzaldehyde, and cyclohane carboxaldehyde. The first class of benzhydryl derivatives studied was the TMB imines. The TMB imine **215** (phenyl) was better than the original Bh group (**150**) for the phenyl substrate but this was not observed for cyclohexyl (**219**) or 4-bromophenyl (**217**) substrates. The other two benzhydryl derivatives studied were the di-4-methoxy benzhydryl group (DAM) and the di-tetra-*t*-butyl-dimethoxy benzhydryl group (BUDAM) and they were also found to be have an effect on the outcome in the *aza*-Diels-Alder reaction where the optimal

conditions were employed. The DAM imines gave similar yields as their corresponding benzhydryl imines, but the effect on the assymetric induction varied. The phenyl DAM-imine **221a** and the cyclohexyl DAM imine **221d** gave lower ee's (84% and 56% respectively). For the aromatic substrates with electron withdrawing groups, 4-bromophenyl DAM imine **221b** gave about the same ee (90%) but for the 4-nitrophenyl DAM imine, the ee increased from 73% (Bh) to 81% (DAM). All of the BUDAM imines that were studied were found to be inferior to the benzhydryl-substituted substrates and 40% ee was the highest asymmetric induction observed for this class of imines.

When developing a new methodology, it is important to compare results from that study to those that have already been published in the literature. Arguably, the best system in the literature was developed by Snapper and Hoyveda,[32] and using a silver catalyst were able to achieve >98% yield and 95% ee. One detail that is impressive about their system is that they were able to get these results using only 1 mol% catalyst, which means that they were getting almost 100 turnovers. In addition they also developed a recoverable catalyst, which could be used effectively several times in subsequent reactions. The highest ee in the literature was 97% and this was observed by Whiting[36] using 10 mol% of the catalyst prepared from MgI_2 and the chiral diamine (*R*,*R*)-1,2-diphenyl-ethylenediamine (**120**).

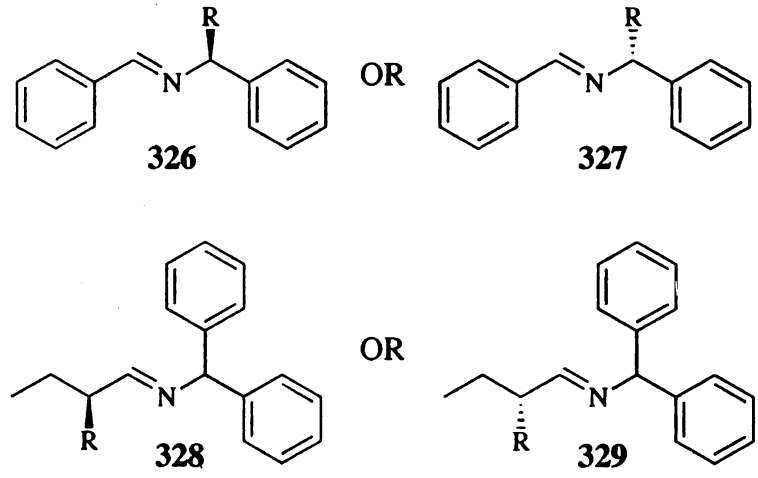
The work by Whiting and Hoyveda, just discussed, is the best that has been achieved to date, however several other successful systems have been reported where ee's in the low 90's with moderate to excellent yields have been achieved. The (*S*)-VAPOL/$B(OPh)_3$ system used for the studies described in this thesis gave similar results to those in the literature, and yields and ee's could both be achieved in the upper 80's to

low 90's. In addition, this catalyst system was able to achieve about 66 TONs with minimal loss of asymmetric induction (1 mol% catalyst gave 66% yield and 82% ee).

6.2.2.1 Other Possible Substrates to Screen

When developing a new reaction or catalyst system, it is important to be as exhaustive as possible when testing the generality of the reaction. As seen above, the method developed and described in this thesis has proven to be quite general with a few exceptions. The substrate scope has primarily dealt with the modification of the aldehyde used to prepare the imine using aminodiphenylmethane. Some other benzhydryl derivatives were screened as well, but future work needs to be done to explore chiral imine derivatives. Both imines derived from chiral amines (**326** and **327**) or chiral aldehydes (**328** and **329**) should be examined as substrates for the *aza*-Diels-Alder reaction (Figure 6.5). This study would indicate whether it was the catalyst or imine that

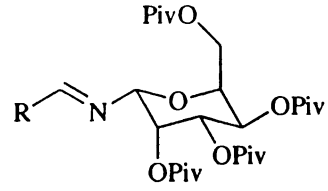
Figure 6.5 Chiral Imines



had a greater influence on the asymmetric induction of the reaction. In addition, one may discover a matched or mismatched case where one specific enantiomer combination would be favorable.

In 1989 Kunz et al reported the use of a pivaloylated carbohydrate derivative where the anomeric alcohol was replaced by an NH_2 which in turn was used to to prepare imines (**330**, Figure 6.6)

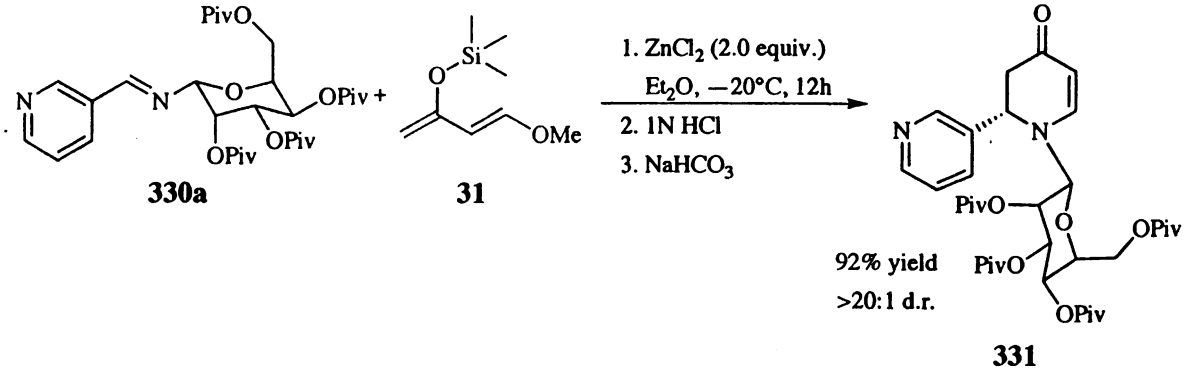
Figure 6.6 Sugar Derived Imine



330

for the *aza*-Diels-Alder reaction.[103] In the decade thereafter, Kunz also published other work using the carbohydrate as a template to incorporate chiral centers in other reactions as well.[104-106] The *aza*-Diels-Alder reaction worked quite well when $ZnCl_2$ was used as the catalyst giving high yields and moderate diastereoselectivity. More specifically, the reaction run with Danishefsky's diene and the imine **330a** prepared from 3-pyridinecarboxaldehyde, gave 92% yield of **331** and a diastereomeric ratio of >20:1 (Scheme 6.3). The results of Kunz's studies as well as the observations seen in the

Scheme 6.3 Kunz's Reaction Using Danishefsky's Diene[103]

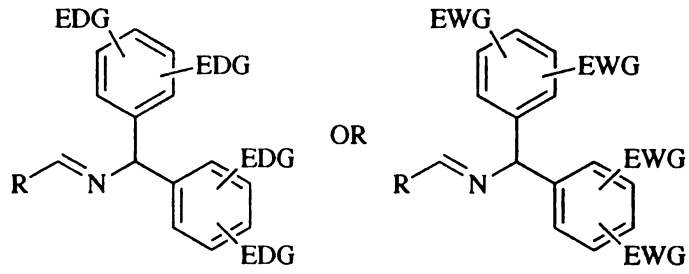


aziridination reaction that the size of the group on nitrogen may be important in the reactions using the VAPOL-boron catalyst indicate that this class of imine should be

studied for the aziridination reaction as well as *aza*-Diels-Alder reaction VAPOL-boron catalyst. In addition to exploring the double stereodifferentiation in these reactions, the chiral group on the nitrogen may lead to selectivity in subsequent modification reactions as well.

As mentioned before it has been shown in the aziridination reaction (unpublished results) that the size of the group on nitrogen of the imine is important to the outcome of the reaction. Although this was not particularly true for the *aza*-Diels-Alder reaction, it would still be interesting to explore in more detail the effects of the size of Bh group and the electron donating (**332**) or electron withdrawing (**333**) nature of the benzhydryl group on the nitrogen (Figure 6.7).

Figure 6.7 Electron Donating and Withdrawing Bh Derivatives

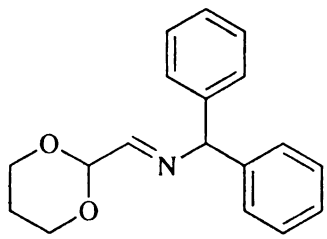


332 **333**

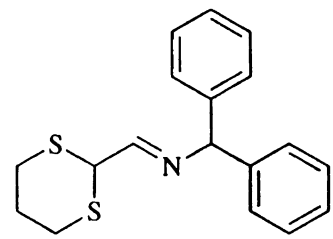
A limitation of this catalyst system for the *aza*-Diels-Alder reaction was the failure of imines prepared from primary aliphatic aldehydes to give any asymmetric induction. In addition, all attempts to find suitable substrates that could be modified to primary alkyl groups failed. To make this reaction more attractive for use in the synthesis of more advanced compounds, it would be a great achievement to be able to add this type of substrate to the list of successful imines for this reaction. One possible class of imine that could provide access to the primary aliphatic side chain would be ones

containing a cyclic ketal (**334**) or thioketal (**335**) attached directly to the imine carbon (Figure 6.8). These substrates contain a

Figure 6.8 Ketal or Thioketal Imines



334

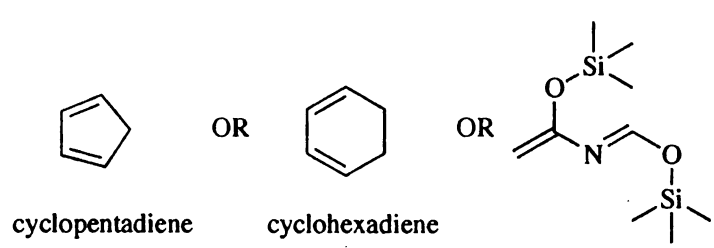


335

secondary α-carbon, which may be necessary for this reaction to be successful. Should the reaction work well, the cyclic ketal or thioketal could be easily removed and the resulting aldehydes modified to a linear carbon chain. Although incorporation of heteroatoms may prove to be detrimental to the reaction, if this class of imines were successful, it would be a nice addition to the scope of this reaction.

The other participant in the *aza*-Diels-Alder reaction is the diene and to date the only dienes that have been studied using the VAPOL-boron catalyst were Danishefsky's diene (**31**) and its TBS derivative **149**. It would be interesting to determine the effectiveness of the VAPOL-boron catalyst using other dienes as well (Figure 6.9).

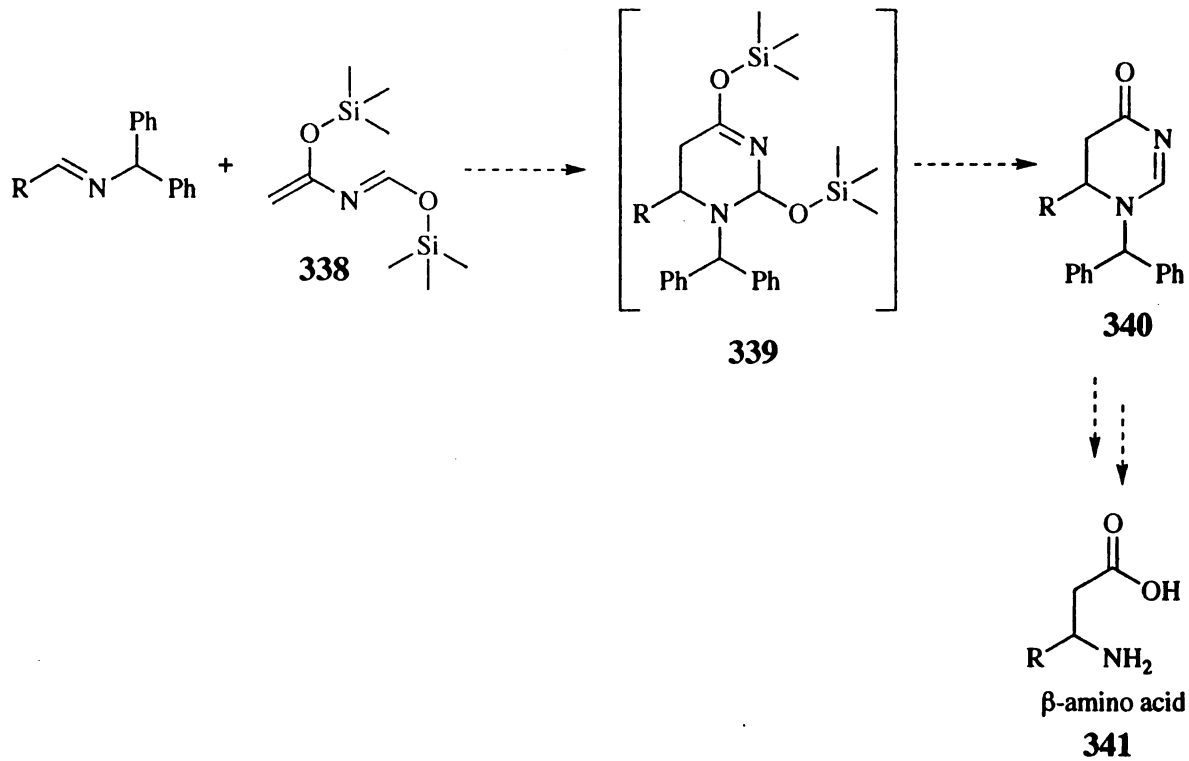
Figure 6.9 Dienes to be Screened



cyclopentadiene **336** OR cyclohexadiene **337** OR 2-*aza*-Diene **338**

Especially of interest would be the use of unactivated dienes such as cyclopentadiene (**336**) or 1,3-cyclohexadiene (**337**), which are locked in the s-*cis* conformation. It would also be interesting to look into the possibility of using aza-dienes as well. Should the reaction work with activated 2-aza-diene **338**, one could potentially use the cycloadduct to access β-amino acid derivatives **341** (Figure 6.10).

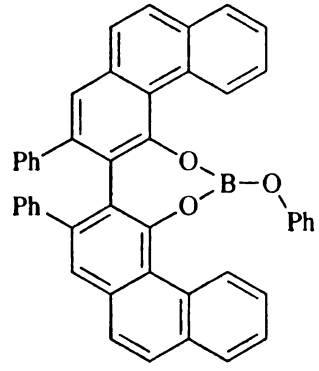
Figure 6.10 Access to β-Amino Acids



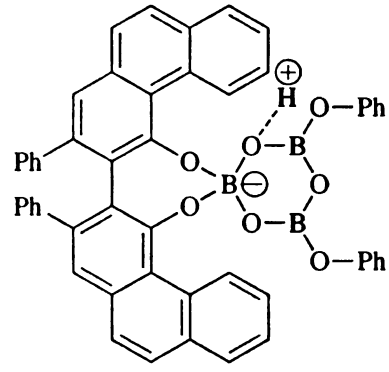
6.2.2.2 Exploration of Other Boron Catalysts

As discussed earlier, work has been going on in the Wulff group to determine the structure of the active catalyst. During these studies, new methods of catalyst preparation have been developed where the catalyst containing only one boron atom (B1-catalyst) can be made selectively as well as the catalyst containing three boron atoms (B3-Catalyst) (Figure 6.11). Using these alternate methods, the catalysts can be made without the use of

Figure 6.11 B1 and B3 Catalysts



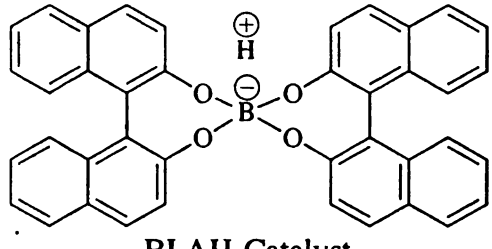
B1-Catalyst



B3-Catalyst

excess triphenylborate, which would eliminate the possibility of background reaction. Although the excess triphenylborate was found to have great utility in the *aza*-Diels-Alder reaction described in this thesis, it would still be informative to determine the effectiveness of these catalysts without the use of excess $B(OPh)_3$. In addition to the catalysts prepared using VAPOL, the same catalysts prepared using VANOL or BINOL could also be explored. It may also be interesting to further explore the the BLAH catalyst (Figure 6.12) utilized by Yamamoto[22] for the *aza*-Diels-Alder reaction. Several

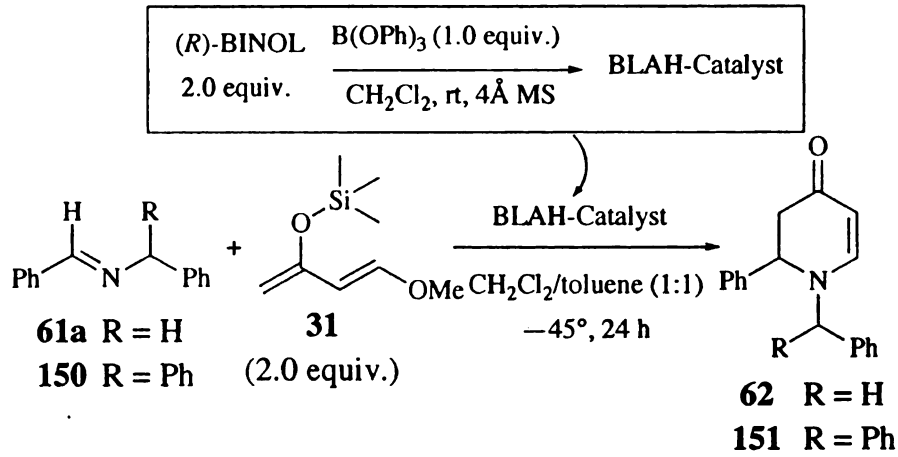
Figure 6.12 BLAH Catalyst



BLAH-Catalyst

preliminary reactions have been run to determine if this catalyst was worth exploring (Scheme 6.4). The first imine that was studied was **61a** in order to compare the reactions

Scheme 6.4 Results Using BLAH-Catalyst



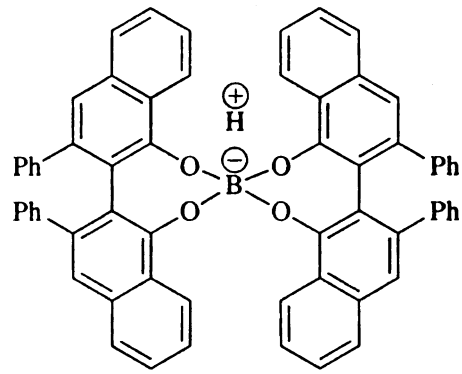
Entry	R	(*R*)-BINOL (mol%)	$B(OPh)_3$ (mol%)	Product	Yield (%)	ee (%)	Configuration
1	H	200	100	**62**	75	~80-88[a]	***R***
2	Ph	200	100	**151**	92	89	***R***
3	Ph	20	10	**151**	39	90	***R***
4	Ph	20	100[b]	**151**	54	60	***R***

a) Approximation because baseline separation could not be achieved in HPLC analysis. b) The imine was premixed with 20 mol% BINOL and 10 mol% $B(OPh)_3$, dissolved in solvent, cooled to −45°C and to it was added 90 mol% $B(OPh)_3$ immediately before the diene was added.

carried out using the optimal conditions found for the *aza*-Diels-Alder reaction (see Chapter 2) and those reported by Yamamoto. For these reactions, BINOL, $B(OPh)_3$ and the imine were premixed in a glove box, taken out and dissolved in solvent. The resulting mixture was stirred for about 10 minutes and then cooled to −45°C. Using imine **61a** (entry 1), the reaction gave 75% yield and ~80-88% ee (approximation, HPLC not baseline resolved). This result is comparable to those achieved by Yamamoto[22] (78% yield and 86% ee) only he used different conditions (1.2 equiv. diene, 4Å M.S., CH_2Cl_2, −78°C, and the reaction was only run for 12 hours). Yamamoto also reported that imine **150** prepared from benzaldehyde and aminodiphenylmethane failed to produce the product **151** using the catalyst prepared from a 1:1 ratio of BINOL and $B(OPh)_3$ but he

never attempted this reaction using the BLAH catalyst. To determine if this catalyst was going to be worth exploring further, an attempt was made with imine **150** using a stoichiometric amount of the BLAH catalyst (entry 2). The reaction worked quite well at −45°C in CH_2Cl_2/toluene (1:1) and after the reaction was stirred for 24 hours, it gave 92% yield of the desired product **151** with 89% ee. The reaction was then attempted using 10 mol% of the BLAH catalyst (entry 3) and surprisingly the reaction turned over about 4 times giving 39% yield and 90% ee. Lastly, one reaction was attempted (entry 4) to mimic the optimal conditions found for the *aza*-Diels-Alder using 5 mol% VAPOL and 100 mol% $B(OPh)_3$ to determine if the turnover could be increased without lowering the induction. The imine was premixed with 10 mol% of the BLAH catalyst and stirred after diluting with solvent for about 10 minutes. The reaction was cooled to −45°C and solution containing 90 mol% more $B(OPh)_3$ was added followed immediately by the slow addition of the diene. The outcome of this reaction was inferior to those in entries 2 and 3 and only gave 54% yield and 60% ee indicating that the background reaction must be competing with the BLAH catalyst under these conditions. Exploration of reaction conditions for this catalyst may lead to more turnover numbers and another successful use of BINOL. Although the VAPOL ligand might be too bulky to form this 2:1 ligand/boron (BLAH type) catalyst, it may be worthwhile to explore the slightly less bulky VANOL ligand for this type of catalyst (VANOL-BLAH-catalyst, Figure 6.13)

Figure 6.13 VANOL-BLAH Catalyst



VANOLBLAH-Catalyst

6.2.3 Triphenylborate Effects

The most interesting discovery during these studies was the fact that the success of this reaction depended on the use of excess $B(OPh)_3$ (a non-chiral Lewis acid) (see Figure 6.1). As Figure 6.1 indicates, an increased rate of the reaction was observed without a loss of ee until the ratio of 100 to 1 $B(OPh)_3$:VAPOL was used to prepare the catalyst. In effort to determine the role of $B(OPh)_3$ in the reaction, attempts were made to isolate intermediates formed during the course of the reaction. All of these attempts failed so the role of $B(OPh)_3$ had to be determined using a different method. Eventually, determination of the association constants (Table 6.1) for the VAPOL-boron catalyst and

Table 6.1 Binding Constants for Complexes of the Imine and Product with $B(OPh)_3$ and the VAPOL-Boron Catalyst

Entry	Complex	Binding Constant (M^{-1})
1	$B(OPh)_3$ / imine	0.32 ±0.12
2	$B(OPh)_3$ / product	2.7 ±0.4
3	VAPOL-B / imine	2.1 ±0.4
4	VAPOL-B / product	4.9 ±0.8

$B(OPh)_3$ with both the imine (**150**) and product (**151**) gave some indication of what was actually going on during this reaction. After careful analysis of the data in table 6.1, it

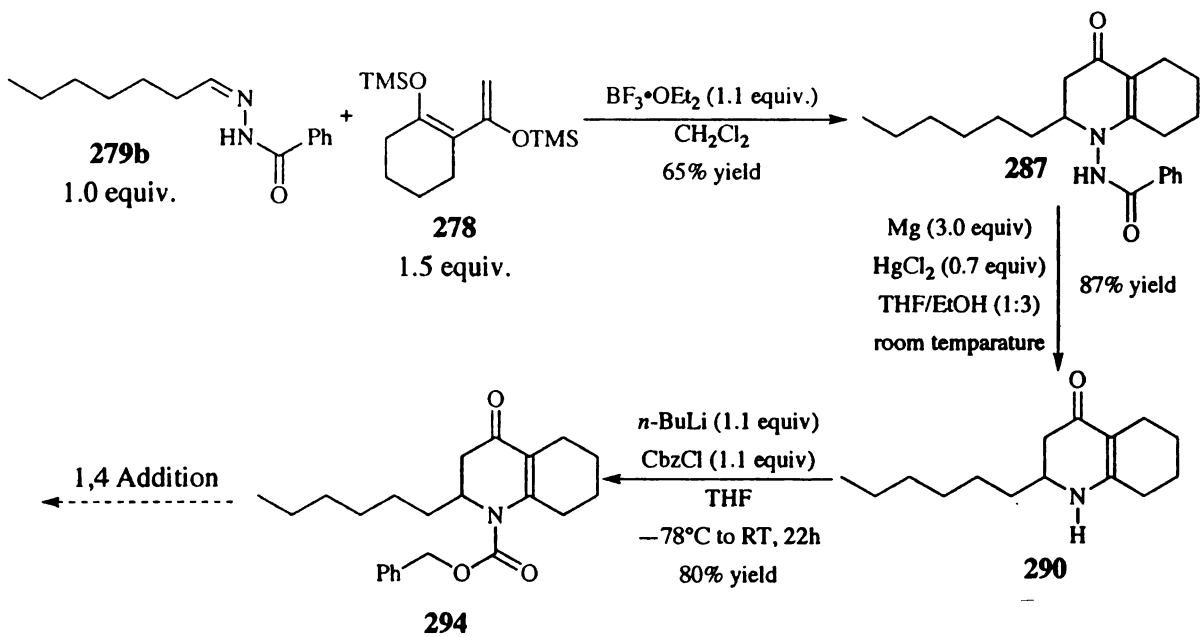
was determined that the rate of the chiral reaction must be at least 9 times faster than the background reaction.

The experimental results are still very intriguing and to our knowledge, this is the only catalytic asymmetric reaction where two similar catalysts, one chiral (substoichiometric) and the other achiral (stoichiometric), are playing separate roles (in acid-base interactions) making the reaction more efficient.

6.2.4 Progress Towards Cylindricine C

While studying the *aza*-Diels-Alder reaction, significant progress was also made toward the total synthesis of (±)-Cylindricine C (Scheme 6.5). The key step in the

Scheme 6.5 Progress Towards Cylindricine C

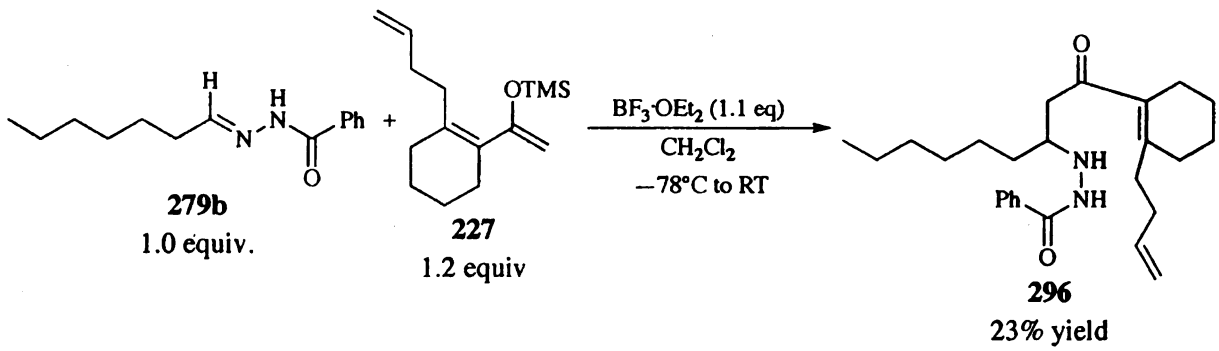


synthesis was envisioned to be the *aza*-Diels-Alder reaction to produce two of the three rings that make up the core structure of the Cylindricine C. Although all attempts to discover an asymmetric version of this reaction failed, the racemic reaction catalyzed by $BF_3{\cdot}OEt_2$ was optimized. It was found that this reaction could give up to 68% yield and even on a 6.2 g scale, 63% yield of the desired product **287** could be obtained. The next

step was to install the butenyl side chain and all attempts to accomplish the conjugate addition on the hydrazine moiety failed. Literature precedent[98] indicated that the incorporation of a Cbz protecting group would facilitate this reaction, so the hydrazine needed to be cleaved and the Cbz group added. The hydrazine was easily reduced off by the addition of magnesium and mercuric chloride to give the free amine **290** in up to 80% yield and even on a 9.0 g scale, 60% yield could be obtained. The Cbz group was then introduced by treatment of the secondary vinylogous amide **290** with *n*-butyl lithium followed by Cbz-Cl to give the Cbz-protected vinylogous amide **294** in 80% yield. Unfortunately, all attempts to facilitate the conjugate addition on this substrate failed as well. This is where progress, using the original route A, halted and this problem still needs to be solved before the synthesis can be completed.

An alternate route B has been envisioned where the butenyl side chain could be incorporated into the diene (**227**), which would eliminate the need for the conjugate addition. Also, if this route could be employed the total synthesis would take only 6 steps (including diene preparation) as opposed to 7 steps (not including diene preparation) for the original route. The *aza*-Diels-Alder reaction employing this diene was attempted only one time (Scheme 6.6) and the reaction failed to give the Diels-Alder cyclo adduct,

Scheme 6.6 Alternate Diene *aza*-Diels-Alder Attempt

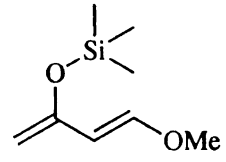


however, the Mannich product **296** was obtained in 23% yield. If this issue surrounding the *aza*-Diels alder reaction of **227** and **279b** in route B can be solved, and the synthesis completed, it would match the shortest synthesis reported to date reported by Shibasaki,[89] (only 6 steps longest linear sequence).

CHAPTER 7

EXPERIMENTAL SECTION

7.1 Experimental Procedures and Characterizations Data for Chapter Two

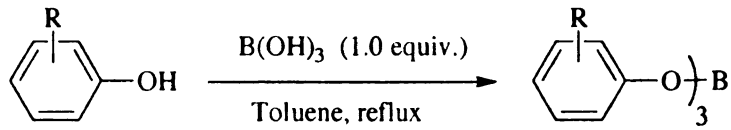


31

Preparation of Danishefsky's diene (31):

To a flame dried 500 mL three neck round bottom flask equipped with a magnetic stir bar and a pressure equalizing liquid addition funnel was added KHMDS (80 mL, 40 mmol, 0.5M solution in toluene) and diluted with THF (50 ml). The solution was then cooled to –78°C and the ketone (4.0 mL, 39.2 mmol) was added dropwise in 50 mL THF over 15 min. through the liquid addition funnel. This was allowed to stir for 1.5 hours and then warmed up to –30°C for 30 minutes. The reaction mixture was then cooled back to –78°C at which time TMSCl (6.19 mL, 48.8 mmol) was added dropwise in 50mL THF over 30 minutes through the liquid addition funnel. The reaction was then allowed to warm up slowly to room temperature and stir for 1 hour. The solvent was then removed under reduced pressure. The crude orange reaction mixture was diluted with ether and filtered through Celite. The Celite was washed several times with ether to ensure the product was recovered. Finally the ether was removed under reduced pressure and the product was purified by distillation (65-69°C, 13 mmHg) to give 4.87 g of the desired

diene **31** (72% yield). The spectral data matched perfectly to that in the literature.[3] All reactions involving the use of the diene **31** used diene prepared by this method unless noted otherwise.



3.0 equiv.

Preparation of triarylborates:

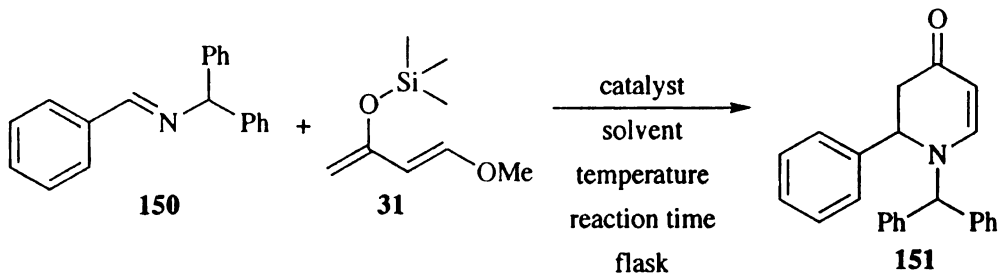
To a round bottom flask equipped with a magnetic stir bar and an azeotropic distillation apparatus (Dean-Stark trap) was added toluene (100 mL/163 mmol) the phenol (3.0 equiv), and boric acid (1.0 equiv). The solution was heated to reflux and allowed to stir overnight. The toluene was then removed by distillation to give the crude triarylborate.

When R= 2,6-dimethyl, the product was purified by distillation (160-170°C, 0.05 mmHg) using an air condenser to give a solid which contained only 5% free 2,6-dimethylphenol. This mixture was used for the preparation of the VAPOL-boron catalyst.

When R= 4-fluoro, after removal of the toluene the crude oil was heated under high vacuum to remove any of the volatiles and the resulting oil was then used for the preparation of the VAPOL-boron catalyst.

When R= 4-OMe, the crude solid was heated until melted and placed under high vacuum to remove any of the volatiles and the resulting solid was then used for the preparation of the VAPOL-boron catalyst.

When R= 4-Me, the crude solid was heated until melted and placed under high vacuum to remove any of the volatiles and the resulting solid was then used for the preparation of the VAPOL-boron catalyst.

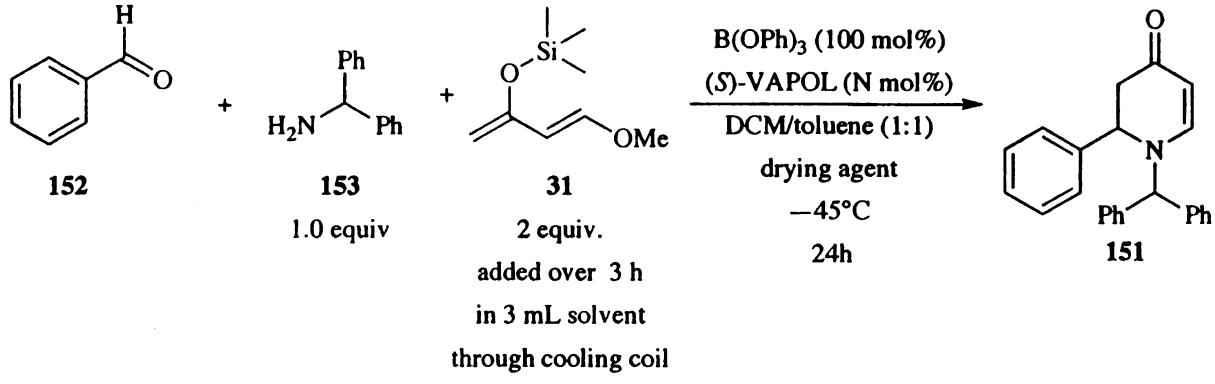


General reaction procedure:

To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ and (S)-VAPOL (**130**). To this was added CH_2Cl_2 (2 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours yielding the VAPOL-boron catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of solvent. The catalyst solution was transferred by syringe to a flask containing the imine prepared as immediately below.

To a flame dried, argon purged round bottom flask or homemade flask with a cold addition coil (see Figure 2.4) equipped with a stir bar was added the imine (**150**) (1.0 mmol). The flask was topped with a rubber septum and the VAPOL-boron catalyst was transfered in two 1.0 mL portions of solvent directly to the bottom of the flask by a syringe equipped with a long needle. This was allowed to stir for 5-10 minutes at room

temperature and then cooled to the reaction temperature. Meanwhile, in a separate flame dried 5 or 10 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) and solvent. The diene was taken up in a syringe and added to the solution of imine and VAPOL-boron catalyst. After completion of the reaction, saturated sodium bicarbonate (~20 mL) was added to the reaction flask. This was then transferred to a separatory funnel and diluted with distilled water (25 mL) and extracted with three or four 30-40 mL portions of CH_2Cl_2. The combined organic layers were placed in a 250 mL round bottom flask and the solvent was then removed via rotary evaporation. The flask was then equipped with a stir bar and cooled in an ice bath. To this was then added a previously cooled (0 °C) 20:1 mixture of THF and 1N HCl (50 mL) at which time the flask was removed from the ice bath and allowed to stir (monitored by TLC) until the undesired spots close to the desired product disappeared (usually less than one hour). This was then transferred to a separatory funnel containing water (75-100 mL) followed by extraction of the crude product with four 50 mL portions of CH_2Cl_2. The combined organic layers were then dried with magnesium sulfate, filtered, and solvent was removed via rotary evaporation. Purification was accomplished using flash column chromatography.



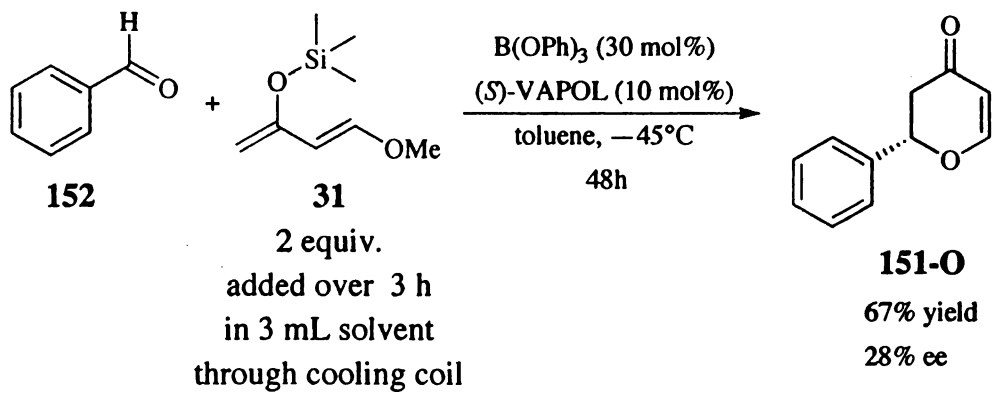
152 + **153** (1.0 equiv) + **31** (2 equiv. added over 3 h in 3 mL solvent through cooling coil) → **151**

Reactions using *in situ* prepared imine 150:

To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (0.3125g, 1.0 mmol) and (S)-VAPOL (**130**) (27mg, 0.05 mmol). To this was added CH_2Cl_2 (2 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours yielding the VAPOL-boron catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 2.0 mL of a 1:1 mixture of toluene and CH_2Cl_2 (in two portions). The catalyst solution was transferred by syringe to a solution of the *in situ* prepared imine prepared as immediately below.

To a flame dried, argon purged homemade flask with a cold addition coil (see Figure 2.4) equipped with a stir bar was added the drying agent. The flask was topped with two rubber septa and to it was added toluene/CH_2Cl_2 (1:1) (2 mL). To the flask was then added benzaldehyde (**152**) (1.0 or 1.1 equivalents) followed immediately by aminodiphenylmethane (**153**) (0.172 mL, 1.0 mmol). The resulting mixture was allowed to stir at room temperature during the ~2.0 hour catalyst preparation and used without further manipulation for the *aza*-Diels-Alder reaction. The VAPOL-boron catalyst was then transferred in two 1 mL portions of CH_2Cl_2/toluene (1:1) directly to the bottom of the flask containing the imine by a syringe equipped with a long needle. This was allowed to stir for 5-10 minutes at room temperature and then cooled to –45 °C. Meanwhile, in a separate flame dried 5 or 10 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) (0.38 mL, 2.0 mmol) and toluene/CH_2Cl_2 (1:1) (3.0

mL). The diene was taken up in a syringe and added over 3.0 hours via syringe pump through the cold addition coil. The reaction was then allowed to stir at –45 °C for the duration of the reaction (24 hours). After completion of the reaction, saturated sodium bicarbonate (~20 mL) was added to the reaction flask at –45 °C. This was then transferred to a separatory funnel and diluted with distilled water (25 mL) and extracted with three or four 30-40 mL portions of CH_2Cl_2. The combined organic layers were placed in a 250 mL round bottom flask and the solvent was then removed via rotary evaporation. The flask was then equipped with a stir bar and cooled in an ice bath. To this was then added a previously cooled (0 °C) 20:1 mixture of THF and 1N HCl (50 mL) at which time the flask was removed from the ice bath and allowed to stir (monitored by TLC) until the undesired spots close to the desired product disappeared (usually less than one hour). This was then transferred to a separatory funnel containing water (75-100 mL) followed by extraction of the crude product with four 50 mL portions of CH_2Cl_2. The combined organic layers were then dried with magnesium sulfate, filtered, and solvent was removed via rotary evaporation. The crude mixture was then purified by flash column chromatography.



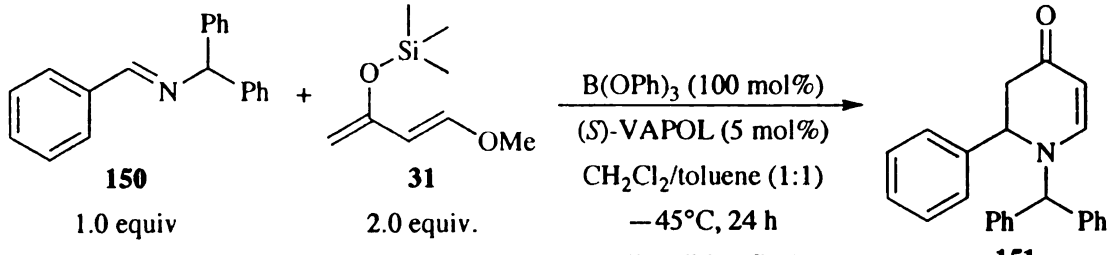
152 + **31** (2 equiv. added over 3 h in 3 mL solvent through cooling coil) → **151-O** (67% yield, 28% ee)

Procedures for Scheme 2.23 (heteroatom Diels-Alder reaction of 152):

To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (87 mg, 0.3 mmol) and (S)-VAPOL (**130**) (54 mg, 0.05 mmol). To this was added CH_2Cl_2 (2 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours yielding the VAPOL-boron catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 2.0 mL of toluene (in two portions).

To a flame dried, argon purged round bottom flask equipped with a stir bar was added the aldehyde (**152**) (0.101 mL, 1.0 mmol). The flask was topped with a rubber septum and the VAPOL-boron catalyst was transfered in two 1.0 mL portions of toluene directly to the bottom of the flask by a syringe equipped with a long needle. This was allowed to stir for 5-10 minutes at room temperature and then cooled to —45°C. Meanwhile, in a separate flame dried 5 or 10 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) and toluene (3.0 mL). The diene was taken up in a syringe and added dropwise to the solution of imine and VAPOL-boron catalyst over 3 hours via syringe pump. The resulting reaction mixture was allowed to stir for 48 hours total reaction time at which time trifluroroacetic acid (several drops) was added to the reaction flask and allowed to stir for a couple hours. At this time, saturated sodium bicarbonate (~20 mL) was added. This was then transferred to a separatory funnel purged with ~25 mL distilled water. Extraction was accomplished using four 25 mL washes of dichloromethane. The product was then isolated by flash column chromatography (4:1 hexanes/ethyl acetate, r_f 0.2) to give 118.7 mg (67% yield) of the

desired product **151-O**. Spectral data matched perfectly to the literature[107] and the absolute configuration was determined by comparison of the HPLC retention times.



150
1.0 equiv

31
2.0 equiv.
added over 3.0 h
through cooling
addition coil

151
85% yield
90% ee

Optimal conditions:

To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (0.3125g, 1.0 mmol) and (S)-VAPOL (**130**) (27mg, 0.05 mmol). To this was added CH_2Cl_2 (2 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours yielding the VAPOL-boron catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 2.0 mL of a 1:1 mixture of toluene and CH_2Cl_2 (in two portions). The catalyst solution was transferred by syringe to a solution of the imine prepared as immediately below.

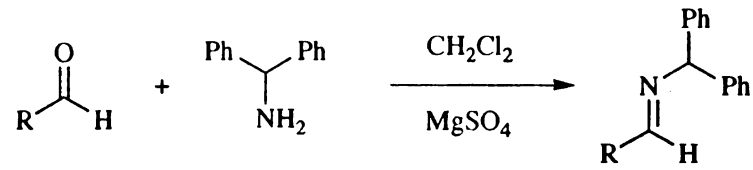
To a flame dried, argon purged homemade flask with a cold addition coil (see Figure 2.4) equipped with a stir bar was added the imine (**150**) (1.0 mmol). The flask was topped with two rubber septa and the VAPOL-boron catalyst was added in two 1.0 mL portions of toluene/CH_2Cl_2 (1:1) directly to the bottom of the flask by a syringe

equipped with a long needle. This was allowed to stir for 5-10 minutes at room temperature and then cooled to –45 °C. Meanwhile, in a separate flame dried 5 or 10 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) (0.38 mL, 2.0 mmol) and toluene/CH_2Cl_2 (1:1) (3.0 mL). The diene was taken up in a syringe and added over 3.0 hours via syringe pump through the cold addition coil. The reaction was then allowed to stir at –45 °C for the duration of the reaction 24 hours. After completion of the reaction, saturated sodium bicarbonate (~20 mL) was added to the reaction flask at –45 °C. This was then transferred to a separatory funnel and diluted with distilled water (25 mL) and extracted with three or four 30-40 mL portions of CH_2Cl_2. The combined organic layers were placed in a 250 mL round bottom flask and the solvent was then removed via rotary evaporation. The flask was then equipped with a stir bar and cooled in an ice bath. To this was then added a previously cooled (0 °C) 20:1 mixture of THF and 1N HCl (50 mL) at which time the flask was removed from the ice bath and allowed to stir (monitored by TLC) until the undesired spots close to the desired product disappeared (usually less than one hour). This was then transferred to a separatory funnel containing water (75-100 mL) followed by extraction of the crude product with four 50 mL portions of CH_2Cl_2. The combined organic layers were then dried with magnesium sulfate, filtered, and solvent was removed via rotary evaporation. The crude mixture was then purified by flash column chromatography (R_f 0.08, 2:1 hexanes/ethyl acetate) to give 288.5 mg pure **151** (85% yield). The enantiomers could be separated by HPLC analysis on Chiralcel OJ-H (75:25 hexane/isopropanol, 1 mL/min). Retention times: 8.55 and 17.61 min. The product **151** obtained from the reaction was determined to be 90% ee (major peak = 17.61 min).

Spectral Data for Compound **151** ($C_{24}H_{21}NO$):

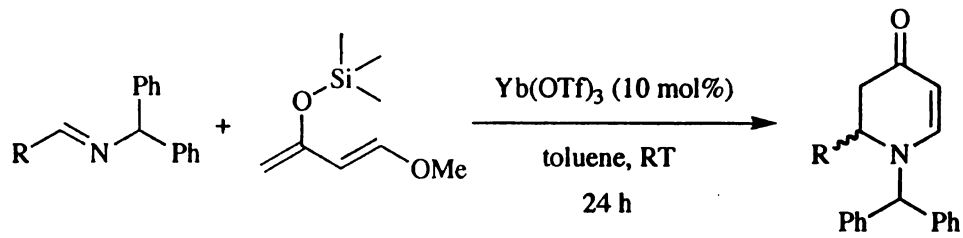
^{1}H NMR ($CDCl_3$) δ 2.77-2.96 (m, 2H), 4.59 (t, 1H, *J*=7.1 Hz), 5.06 (d, 1H, *J*=8 Hz), 5.46 (s, 1H), 7.46-7.06 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 43.51, 62.01, 67.67, 98.60, 127.04, 127.39, 128.01, 128.18, 128.32, 128.68, 128.82, 128.95, 129.36, 137.94, 138.11, 138.74, 151.30, 190.15; IR ($CDCl_3$) 3031m, 2959m, 2926m, 1645vs, 1591vs, 1570m cm^{-1}; mass spectrum *m/z* (% rel intensity) 339 M^+ (5), 338 (13), 168 (14), 167 (100), 165 (31), 152 (17), 104 (12), 103 (10), 77 (8), 51 (5), 50 (3). White solid, mp 136-138 °C. Optical rotation taken on 90% ee sample, $[\alpha]^{20}_D$ +106.2 (c 1.90, CH_2Cl_2).

7.2 Experimental Procedures and Characterizations Data for Chapter Three



Preparation of the aldimines:

All imines were prepared using the following general protocol and spectral data matched that published in the literature.[56, 57, 64, 108-110] To a flame dried round bottom flask equipped with a magnetic stir bar was added the $MgSO_4$ (0.15g/mmol) and CH_2Cl_2 (1.5mL/mL) followed by the aldehyde (1.0 equivalent). To this solution was then added the desired benzhydrylamine (1.0 equivalent). The resulting solution was then allowed to stir at room temperature overnight (18-25 hrs). At the end of the reaction time, the solution was filtered to remove the $MgSO_4$, and the solvent removed under reduced pressure. If the resulting imine was a solid, then it was purified by recrystallization (hexane/CH_2Cl_2). If the resulting imine was an oil, it was simply used as the crude oil without further purification.



General protocol for the preparation of racemic *aza*-Diels-Alder products:

To a flame dried round bottom flask equipped with a magnetic stir bar was added the imine (1 mmol) and ytterbium triflate (62 mg, 0.1 mmol). To the contents of the flask were then added toluene (10 mL) followed by Danishefsky's diene (**31**) (1.1 mmol). The reaction was then allowed to stir for 24 hours at which time the reaction was quenched

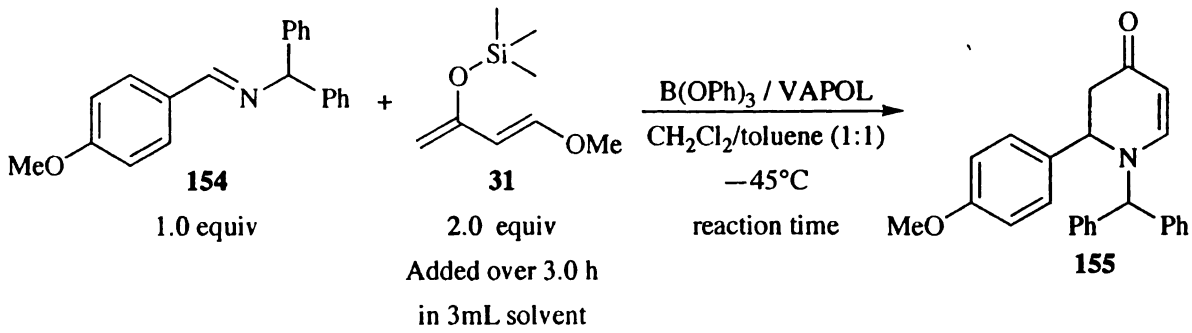
with a mixture of THF and 1N HCl (20:1) and stirred for one hour. The contents were then transferred to a separatory funnel, diluted with distilled water (100 mL) and extracted three times with CH_2Cl_2 (3 x 50 mL). The organic layers were then combined and dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The racemic compounds were then purified via flash column chromatography.

Protocol for the *aza*-Diels-Alder reaction optimal conditions used for screening of substrates:

To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (0.3125g, 1.0 mmol) and (S)-VAPOL (27mg, 0.05 mmol). To this was added CH_2Cl_2 (2 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours yielding the VAPOL-boron catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 2.0 mL of a 1:1 mixture of toluene and CH_2Cl_2 (in two portions). The catalyst solution was transferred by syringe to a flask containing the imine prepared as immediately below.

To a flame dried, argon purged homemade flask with a cold addition coil (see Figure 2.4) equipped with a stir bar was added the imine (1.0 mmol). The flask was topped with two rubber septa and the VAPOL-boron catalyst was added in two 1.0 mL portions of toluene/CH_2Cl_2 (1:1) directly to the bottom of the flask by a syringe equipped with a long needle. This was allowed to stir for 5-10 minutes at room temperature and then cooled to –45 °C. Meanwhile, in a separate flame dried 5 or 10 mL round bottom

flask purged with argon was added Danishefsky's diene (**31**) (0.38 mL, 2.0 mmol) and toluene/CH_2Cl_2 (1:1) (3.0 mL). The diene was taken up in a syringe and added over 3.0 hours via syringe pump through the cold addition coil. The reaction was then allowed to stir at –45 °C for the duration of the reaction (24 total hours). After completion of the reaction, saturated sodium bicarbonate (~20 mL) was added to the reaction flask at –45 °C. This was then transferred to a separatory funnel and extracted with three or four 30-40 mL portions of CH_2Cl_2. The combined organic layers were placed in a 250 mL round bottom flask and the solvent was then removed via rotary evaporation. The flask was then equipped with a stir bar and cooled in an ice bath. To this was then added a previously cooled (0 °C) 20:1 mixture of THF and 1N HCl (50 mL) at which time the flask was removed from the ice bath and allowed to stir (monitored by TLC) until the undesired spots close to the desired product disappeared (usually less than one hour). This was then transferred to a separatory funnel containing distilled water (75-100 mL) followed by extraction of the crude product with four 50 mL portions of CH_2Cl_2. The combined organic layers were then dried over magnesium sulfate, filtered, and solvent was removed via rotary evaporation. The product was then purified via flash column chromatography (36 cm x 2 cm). The enantiomeric excess was determined by chiral HPLC analysis with the aid of an authentic sample of the racemic product.



Procedures for Scheme 3.2 (*aza*-Diels-Alder reaction of imine 154):

Condition A: The protocol for the optimal conditions was followed exactly where 0.3014g (1.0 mmol) of imine **154** was used. The product (**155**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.04). The reaction produced 162.5 mg (44% yield) of the desired product **155** and 83% enantiomeric excess was measured (average of two runs).

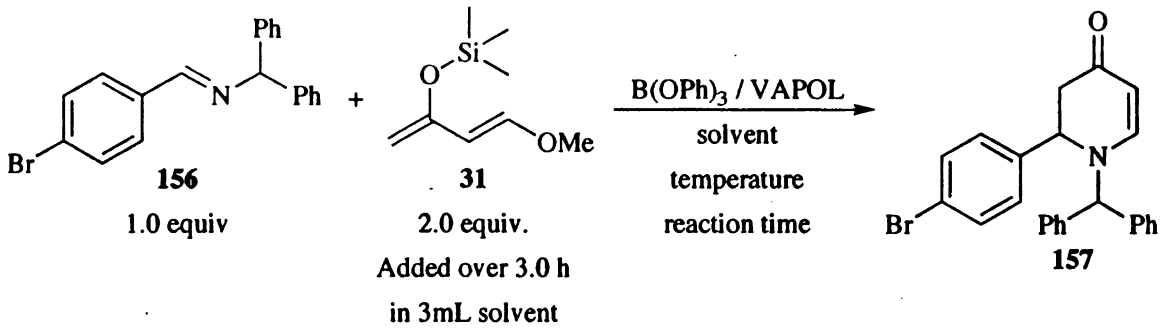
Condition B: The protocol for the optimal conditions was followed exactly except the reaction was allowed to stir for 47 hours. The reaction produced 214.3 mg (58% yield) of the desired product **155** and 77% enantiomeric excess was measured.

Condition C: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 54 mg (*S*)-VAPOL (10 mol%). The reaction produced 221.7 mg (60% yield) of the desired product **155** and 88% enantiomeric excess was measured.

Condition D: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 54 mg (*S*)-VAPOL (10 mol%) and the reaction was allowed to stir for 48 hours. The reaction produced 262.3 mg (71% yield) of the desired product **155** and 90% enantiomeric excess was measured.

Spectral Data for Compound **155** ($C_{25}H_{23}NO_2$):

The enantiomers could be separated by HPLC using a Chiralcel OJ-H column (90:10 hexane/isopropanol, 2 mL/min). Retention times: 17.38 min. (minor) and 33.63 min. (major). ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3H), 2.63-2.79 (m, 2H), 4.77 (t, 1H, *J*=8.8 Hz), 5.05 (d, 1H, *J*=8 Hz), 5.20 (s, 1H), 7.03-7.40 (m, 14H), 7.59 (d, 1H, *J*=7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 18.35, 42.83, 57.93, 67.13, 98.71, 126.33, 126.59, 127.46, 127.81, 127.93, 128.00, 128.55, 128.75, 129.26, 130.90, 135.55, 136.49, 137.55, 137.91, 152.06, 190.38; IR ($CDCl_3$) 3027s, 2953m, 2938m, 2909m, 1642vs, 1582vs cm^{-1}; mass spectrum *m/z* (% rel intensity) M^+ 353 (42), 281 (14), 267 (4), 249 (3), 225 (15), 209 (15), 207 (27), 182 (13), 168 (16), 167 (100), 166 (12), 165 (34), 152 (20), 133 (5), 117 (7), 115 (9), 104 (7), 103 (7), 91 (10), 77 (9), 73 (10), 51 (5). Anal calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N, 3.96. Found: C, 84.96; H, 6.47; N, 3.89. White solid, mp 174-175 °C. Optical rotation was taken on 99.9% ee material (obtained by recrystallization of the 88% ee material in CH_2Cl_2/hexanes), $[\alpha]^{20}_D$ +91.5° (c 1.25, CH_2Cl_2).



Procedures for Scheme 3.3 (*aza*-Diels-Alder reaction of imine 156):

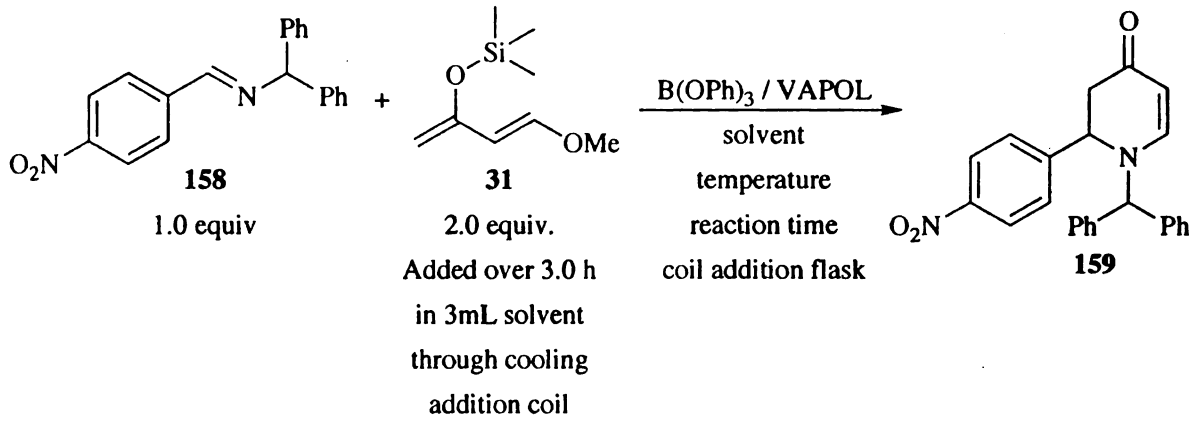
Condition A: The protocol for the optimal conditions was followed exactly where 0.3503 g (1.0 mmol) of imine **156** was used. The product (**157**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.07). The

reaction produced 351.4 mg (84% yield) of the desired product **157** and 89% enantiomeric excess was measured (average of two runs).

Condition B: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 0.09 g $B(OPh)_3$ (30 mol%) and 54 mg (*S*)-VAPOL (10 mol%). The reaction was run using a standard 25 mL round bottom flask, and $CH_2Cl_2$was used as the solvent to transfer the catalyst and add the diene rather than the 1:1 mixture of CH_2Cl_2/toluene. The reaction produced 288.6 mg (69% yield) of the desired product **157** and 68% enantiomeric excess was measured.

Spectral Data for compound **157** ($C_{24}H_{20}BrNO$):

The enantiomers could be separated by HPLC using a Chiralcel OJ-H column (80:20 hexanes/isopropanol, 1mL/min). Retention times: 16.36 min. (minor) and 28.10 min. (major). ^1H NMR ($CDCl_3$) δ 2.62 (dd, 1H, *J*=16.5, 8.4 Hz), 2.81 (dd, 1H, *J*=16.5, 6.9 Hz), 4.47 (t, 1H, *J*=7.5 Hz), 4.96 (d, 1H, *J*=7.8 Hz), 5.34 (s, 1H), 6.98-7.52 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 43.19, 61.20, 67.90, 98.76, 122.07, 127.24, 128.05, 128.22, 128.63, 128.69, 128.82, 129.23, 132.01, 137.53, 137.76, 137.84, 150.95, 189.51; IR ($CDCl_3$) 3028m, 1653vs, 1578vs, 1487s, 1449s, 1221s, 1140s cm^{-1}; mass spectrum *m/z* (% rel intensity) 419 M^+ (18, ^{81}Br), 417 M^+ (19, ^{79}Br), 182 (12), 168 (15), 167 (100), 166 (9), 165 (31), 152 (15), 103 (7), 102 (7), 77 (6), 51 (4), 50 (4). Anal calcd for $C_{24}H_{20}BrNO$: C, 68.91; H, 4.82; N, 3.35. Found: C, 68.97; H, 4.60; N, 3.26. White solid, mp 141-142 °C. Optical rotation was taken on 90% ee material, $[\alpha]^{20}_D$ +117.2° (c 1.285, CH_2Cl_2).



Procedures for Scheme 3.4 (*aza*-Diels-Alder reaction of imine 158):

Condition A: The protocol for the optimal conditions was followed exactly where 0.3164 g (1.0 mmol) of imine **158** was used. The product (**159**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.04). The reaction produced 249.9 mg (65% yield) of the desired product **159** and 73% enantiomeric excess was measured (average of two runs).

Condition B: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 54 mg (*S*)-VAPOL (10 mol%). The reaction produced 257.6 mg (67% yield) of the desired product **159** and 73% enantiomeric excess was observed (average of two runs).

Condition C: The protocol described in condition B was followed exactly except the reaction was cooled to –78°C while the diene was being added and then warmed to —45°C for an additional 39 hours (42 h total reaction time). The reaction produced 246 mg (64% yield) of the desired product **159** and 75% enantiomeric excess was measured.

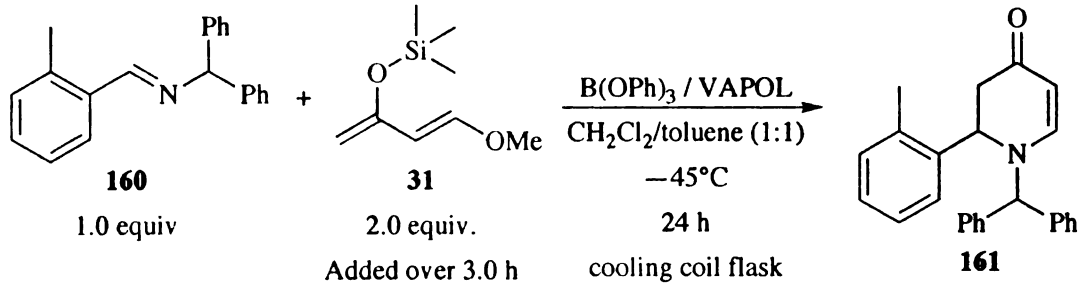
Condition D: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 0.09 g (30 mol%) and 54 mg (*S*)-VAPOL (10 mol%).

The reaction produced 188.4 mg (49% yield) of the desired product **159** and 64% enantiomeric excess was measured.

Condition E: The protocol described in condition B was followed exactly except toluene was used as the solvent to transfer the catalyst to the imine and add the diene rather than the 1:1 mixture of CH_2Cl_2/toluene. The reaction produced 103.8 mg (27% yield) of the desired product **159** and 66% enantiomeric excess was measured.

Spectral Data for compound **159** ($C_{24}H_{20}N_2O_3$):

The enantiomers could be separated by HPLC uaing a Chiralpak AD column (75:25 hexane/isopropanol, 1 mL/min). Retention times: 6.31 min. (minor) and 12.46 min. (major). ^{1}H NMR ($CDCl_3$) δ 2.61 (dd, 1H, *J*=16.5, 6.6 Hz), 2.98 (dd, 1H, *J*=16.5, 7.1 Hz), 4.69 (t, 1H, *J*=6.9 Hz), 5.02 (d, 1H, *J*=8 Hz), 5.39 (s, 1H), 7.00-7.48 (m, 13H), 8.21 (d, 2H, *J*=2 Hz); ^{13}C NMR ($CDCl_3$) δ 42.65, 60.83, 68.86, 99.05, 124.07, 127.18, 127.68, 128.23, 128.44, 128.84, 128.90, 129.14, 137.08, 137.75, 146.09, 147.49, 150.66, 188.60; IR ($CDCl_3$) 3061w, 2910w, 1644s, 1590vs, 1578vs, 1520s, 1346vs, 1219m, 1138m cm^{-1}; mass spectrum *m/z* (% rel intensity) 286 M+2 (2), 285 M+1 (1), 384 M$^+$ (2), 355 (20), 341 (11), 327 (9), 281 (54), 267 (17), 251 (7), 227 (18), 226 (14), 225 (45), 224 (19), 223 (13), 211 (20), 210 (14), 209 (67), 208 (42), 207 (100), 194 (19), 191 (19), 177 (10), 149 (13), 147 (13), 135 (16), 133 (18), 119 (8), 105 (9), 103 (9), 91 (13), 77 (16), 75 (17), 73 (43), 51 (6). Light yellow solid, mp 192-197°C. Optical rotation was taken on a waxy material (99.9 % ee determined by HPLC) that deposited on the side of the flask when attempting to recrystallize the material, $[\alpha]^{20}_D$ +106.5° (c 3.835, CH_2Cl_2).



160
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

161

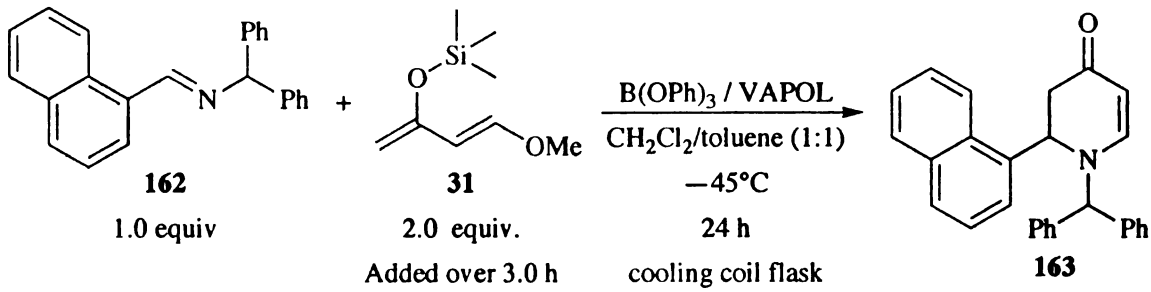
Procedure for Scheme 3.5 (*aza*-Diels-Alder reaction of imine 160):

Condition A: The protocol for the optimal conditions was followed exactly where 0.2854 g (1.0 mmol) of imine **160** was used. The product (**161**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.09). The reaction produced 293.4 mg (65% yield) of the desired product **161** and 94% enantiomeric excess was measured (average of two runs).

Spectral Data for compound **161** ($C_{25}H_{23}NO$):

The enantiomers could be separated by HPLC using a Chiralcel OD column (98:2 hexane/isopropanol, 1 mL/min). Retention times: 47.09 min. (minor) and 51.34 min. (major). ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3H), 2.63-2.79 (m, 2H), 4.77 (t, 1H, *J*=8.8 Hz), 5.05 (d, 1H, *J*=8 Hz), 5.20 (s, 1H), 7.03-7.40 (m, 14H), 7.59 (d, 1H, *J*=7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 18.35, 42.83, 57.93, 67.13, 98.71, 126.33, 126.59, 127.46, 127.81, 127.93, 128.00, 128.55, 128.75, 129.26, 130.90, 135.55, 136.49, 137.55, 137.91, 152.06, 190.38; IR ($CDCl_3$) 3027s, 2953m, 2938m, 2909m, 1642vs, 1582vs cm^{-1}; mass spectrum *m/z* (% rel intensity) M^+ 353 (42), 281 (14), 267 (4), 249 (3), 225 (15), 209 (15), 207 (27), 182 (13), 168 (16), 167 (100), 166 (12), 165 (34), 152 (20), 133 (5), 117 (7), 115 (9), 104 (7), 103 (7), 91 (10), 77 (9), 73 (10), 51 (5). Anal calcd for $C_{25}H_{23}NO$: C, 84.95; H, 6.56; N,

3.96. Found: C, 84.96; H, 6.47; N, 3.89. White solid, mp 174-175 °C. Crystallization from hexanes/CH_2Cl_2 gave **161** that was 99.9% ee. Optical rotation was taken on 99.9% ee material, $[\alpha]^{20}_D$ +91.5° (c 1.25, CH_2Cl_2).



162
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through cooling
adidtion coil

24 h
cooling coil flask

163

Procedures for Scheme 3.6 (*aza*-Diels-Alder reaction of imine 162):

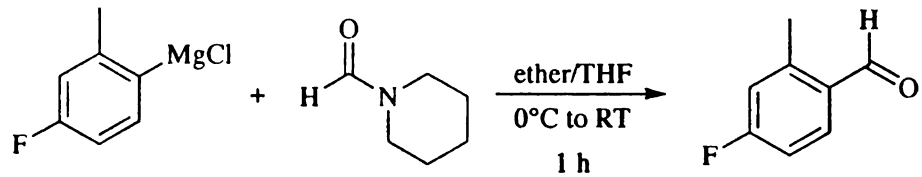
Condition A: The protocol for the optimal conditions was followed exactly where 0.3214 g (1.0 mmol) of imine **162** was used. The product (**163**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.14). The reaction produced 299.9 mg (77% yield) of the desired product **163** and 94% enantiomeric excess was measured (average of two runs).

Condition B: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 54 mg (*S*)-VAPOL (10 mol%). The reaction produced 307.7 mg (79% yield) of the desired product **163** and 90% enantiomeric excess was measured.

Spectral data for compound **163** ($C_{28}H_{23}NO$):

The enantiomers could be separated by HPLC using a Chiralcel OJ-H column (95:5 hexane/isopropanol, 2 mL/min). Retention times: 39.53 min. (minor) and 58.78

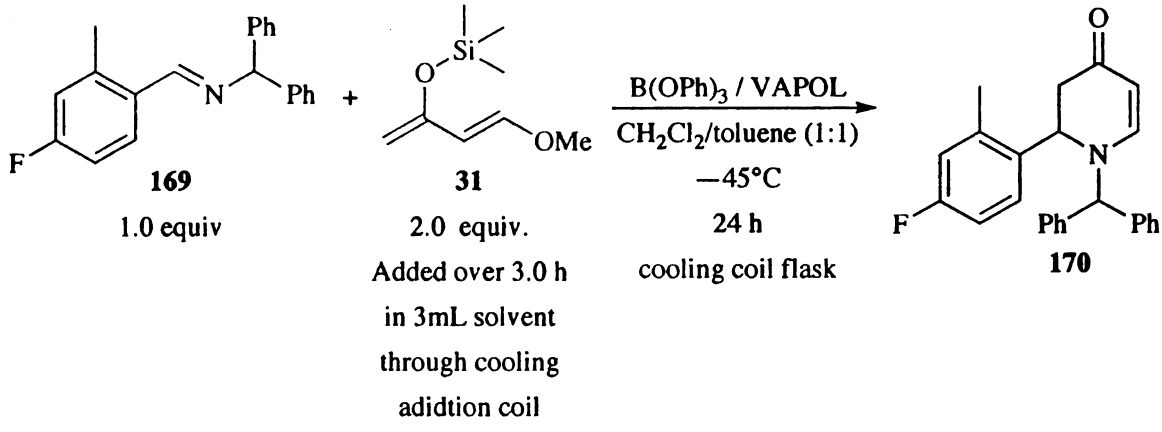
min. (major). ^{1}H NMR ($CDCl_3$) δ 2.96 (br s, 2H), 5.15 (d, 1H, *J*=8 Hz), 5.29 (br s, 1H), 5.45 (s, 1H), 7.02-7.52 (m, 15H), 7.84-7.93 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 42.09, 68.07, 98.30, 122.46, 125.12, 125.67, 126.17, 127.27, 127.94, 128.14, 128.63, 128.72, 128.97, 129.20, 129.43, 130.10, 132.95, 134.15, 137.62, 138.16, 151.30, 190.02 (two aromatic carbons not located); IR($CDCl_3$) 3061s, 3031s, 2901m, 1649vs, 1593vs, 1510s, 1449m, 1389s, 1240m, 1028m, 911m cm^{-1}; mass spectrum *m/z* (% rel intensity) M^+ 389 (33), 308 (8), 281 (5), 248 (4), 222 (6), 207 (12), 182 (12), 167 (100), 166 (11), 165 (37), 152 (32), 128 (4), 115 (6), 77 (5), 51 (4). Yellow solid, mp 73-81 °C. Optical rotation was taken on 90% ee material, $[\alpha]^{20}_D$ −2.9° (c 2.8, CH_2Cl_2)



Preparation of 4-fluoro-2-methylbenzaldehyde (168):

Following the literature protocol,[111] to a flame dried argon purged 250 mL round bottom flask equipped with a magnetic stir bar was added 4-fluoro-2-methyl-phenylmagnesium chloride (**166**, 40 mL, 20 mmol, 0.5 M solution in THF). This was cooled to 0°C and piperadine-1-carbaldehyde (**167**, 2.22 mL, 20 mmol) was added in ether (20 mL) over 2 minutes. The resulting mixture was then allowed to warm to room temperature and stir for 1 hour. To the flask was then added 3N HCl until the reaction was acidic (monitored with litmus paper). The contents of the flask were then transferred to a separatory funnel, extracted 2 times with ether. The ether layers were then combined, washed with water followed by saturated sodium bicarbonate and then brine. The organic layer was then dried over magnesium sulfate, filtered, and the solvent was

removed under reduced pressure. Purification was then accomplished by bulb-to-bulb distillation (63°C, 5 mmHg) to give 2.15 g (78% yield) of the desired aldehyde **168**.



Procedures for Scheme 3.8 (*aza*-Diels-Alder reaction of imine 169):

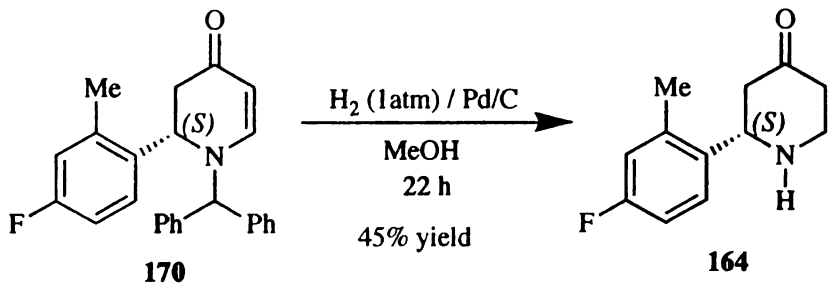
Condition A: The protocol for the optimal conditions was followed exactly where 0.3034 g (1.0 mmol) of imine **169** was used. The product (**170**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.08). The reaction produced 252.6 mg (68% yield) of the desired product **170** and 94% enantiomeric excess was measured (average of two runs).

Condition B: The protocol for the optimal conditions was followed exactly except the reaction was allowed to stir for 50 hours. The reaction produced 312.0 mg of the desired product **170** (84% yield) and 89% enantiomeric excess was measured.

Condition C: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 54 mg (*S*)-VAPOL (10 mol%). The reaction produced 289.7 mg (78% yield) of the desired product **170** and 91% enantiomeric excess was measured.

Spectral Data for compound **170** ($C_{25}H_{22}FNO$):

The enantiomers could be separated by HPLC using a Chiralcel OD column (with guard column) (98:2 hexane/isopropanol, 1 mL/min). Retention times: 55.03 min. (minor) and 63.06 min. (major). ^{1}H NMR ($CDCl_3$) δ 1.83 (s, 3H), 2.63-2.79 (m, 2H), 4.77 (t, 1H, *J*=8.7 Hz), 5.05 (d, 1H, *J*=7.7 Hz), 5.40 (s, 1H), 7.03-7.38 (m, 13H), 7.58 (d, 1H, *J*=7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 18.35, 42.82, 57.93, 67.13, 98.70, 126.33, 126.58, 127.46, 127.81, 127.93, 128.00, 128.55, 128.75, 129.25, 130.89, 135.55, 136.47, 137.55, 137.91, 152.07, 190.35; IR ($CDCl_3$) 3027w, 1645vs, 1578vs, 1443m, 1238s cm^{-1}; mass spectrum *m/z* (% rel intensity) 371 M^+ (91), 342 (1), 294 (1), 262 (7), 248 (8), 206 (9), 182 (25), 168 (13), 167 (100), 166 (14), 165 (40), 152 (8), 133 (10), 115 (9), 77 (6), 51 (5). White solid, 55-59 °C. Optical rotation was taken on 88% ee material, $[\alpha]^{20}_D$ +56.9° (c 2.185, CH_2Cl_2).

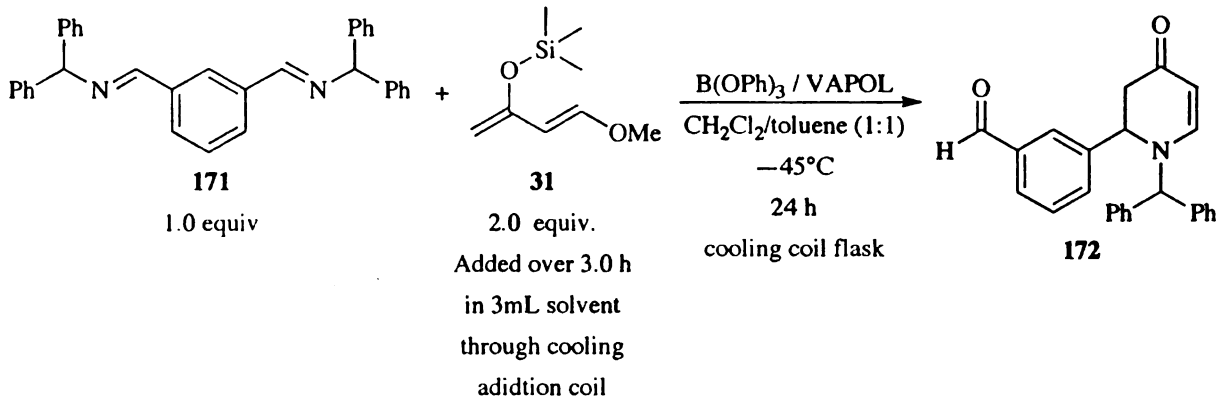


170 **164**

Preparation of cycloadduct 164:

To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added **170** (89% ee as determined by HPLC) (50 mg, 0.135 mmol) and 10% palladium on carbon (28.7 mg, 0.027 mmol) and methanol (2.5 mL). The reaction flask was then flushed with hydrogen gas and kept under 1 atm hydrogen for 22 hours. The reaction mixture was then filtered through Celite was flushed with ether (200 mL). The solvent was then removed under reduced pressure. Purification was accomplished via

flash column chromatography (hexanes/ethyl acetate 1:1, r_f = 0.08) and gave 12.7 mg (45% yield) of the desired product **164**. The ^{1}H-NMR of **164** matched perfectly to that reported in the literature.[64] The absolute configuration was then determined by comparison of the optical rotation to the (*R*)-enantiomer (97% ee, $[\alpha]^{20}_D$ +77.4° (c 0.18, DMSO)[64] of **164** reported in the literature. The configuration of **164** obtained from the reaction described above is thus assigned as the (*S*)-enantiomer based on the optical rotation taken on 89% ee material: $[\alpha]^{20}_D$ —77.0° (c 0.18, DMSO).



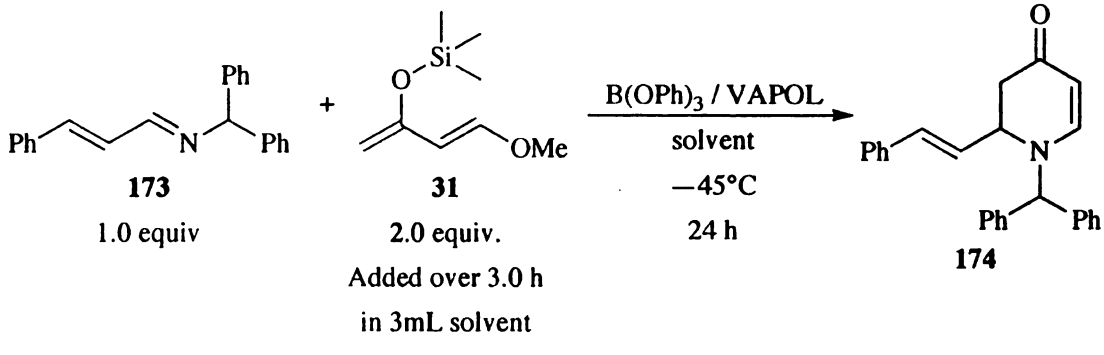
Procedure for Scheme 3.10 (*aza*-Diels-Alder reaction of imine 171):

Condition A: The protocol for the optimal conditions was followed exactly where 0.4646 g (1.0 mmol) of imine **171** was used. The product (**172**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.07). The reaction produced 176.4 mg (48% yield) of the mono-Diels-Alder product **172** and 74% enantiomeric excess was measured.

Spectral data for compound **172** ($C_{25}H_{21}NO_2$):

The enantiomers could be separated by HPLC using a Chiralcel OJ-H column (75:25 hexane/isopropanol, 1 mL/min). Retention times: 31.15 min. (minor) and 40.07 min. (major). ^{1}H NMR ($CDCl_3$) δ2.63-2.71 (dd, 1H, *J*=7.2, 16.5 Hz), 2.91-2.99 (dd, 1H,

J=7.2, 16.5 Hz), 4.66 (t, 1H, *J*=7.2 Hz), 5.02 (d, 1H, *J*=7.5 Hz), 5.39 (s, 1H), 6.98-7.84 (br m, 15H), 9.96 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 42.91, 61.16, 68.48, 98.80, 127.20, 127.55, 128.11, 128.29, 128.75, 128.82, 129.17, 129.69, 132.68, 136.78, 137.37, 137.90, 139.92, 150.92, 189.21, 191.28 (one overlapping sp^2 carbon); IR (neat) 868.08w, 912.45 m, 1001.18w, 1030.12m, 1080.27w, 1138.15 s, 1180.59s, 1223.02s, 1217.55s, 1381.21s, 1410.14m, 1448.73s, 1495.02s, 1756.04vs, 1645.49vs, 1699.50vs, 2375.95w, 2849.22m, 2922.53m, 2971.59m, 3030.56m, 3063.35m; mass spectrum m/z (% rel intensity) M+ 367 (2), 167 (100), 165 (15), 164 (15), 151 (15), 106 (2), 103 (2), 77 (3); Light yellow solid, mp 65-68°C softens and 112-116°C melted. Optical rotation was taken on 75% ee material, $[\alpha]^{20}_D$ +66.7 (c 2.687, CH_2Cl_2).



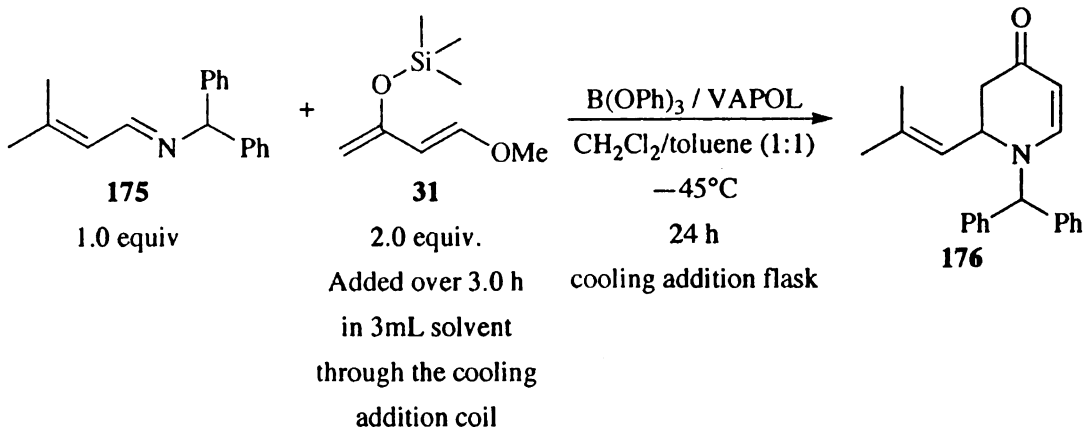
Procedures for Scheme 3.11 (*aza*-Diels-Alder reaction of imine 173):

Condition A: The protocol for the optimal conditions was followed exactly where 0.2974 g (1.0 mmol) of imine **173** was used. The product (**174**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.05). The reaction produced 40.2 mg (11% yield) of the desired product **174** and 0% enantiomeric excess was measured (average of two runs).

Condition B: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 0.09 g $B(OPh)_3$ (30 mol%) and 54 mg (*S*)-VAPOL (10 mol%) and toluene was used as the solvent to transfer the catalyst to the imine and add the diene rather than the 1:1 mixture of CH_2Cl_2/toluene. The reaction was allowed to stir for 48 hours and produced 40.2 mg (11% yield) of the desired product **174** and 0% enantiomeric excess was observed.

Spectral Data for compound **174** ($C_{26}H_{23}NO$):

The enantiomers could be separated by HPLC using a Chiralcel OD column (with guard column) (75:25 hexane/isopropanol, 1mL/min). Retention times: 10.82 and 19.13 min. ^1H NMR ($CDCl_3$) δ 2.52 (dd, 1H, *J*=16.2, 6.0 Hz), 2.86 (dd, 1H, *J*=16.5, 6.6 Hz), 4.14-4.20 (m, 1H), 4.96 (d, 1H, *J*=7.7 Hz), 5.67 (s, 1H), 6.29-47 (m, 2H), 6.87 (d, 1H, *J*=7.7 Hz), 7.09 (d, 2H, *J*=6.0 Hz), 7.24-7.45 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 41.28, 60.60, 68.25, 97.89, 124.19, 126.38, 127.29, 127.93, 128.02, 128.15, 128.40, 128.70, 128.76, 129.28, 133.75, 135.49, 137.87, 138.63, 150.19, 190.11; IR ($CDCl_3$) 3031m, 2926m, 1642vs, 1576vs, 1449m, 1223m, 1140m; mass spectrum *m/z* (% rel intensity) 365 M^+ (54), 363 (11), 288 (7), 207 (11), 198 (11), 168 (34), 167 (100), 166 (12), 365 (35), 152 (27), 115 (10), 102 (7), 101 (7), 91 (14), 76 (8), 64 (6). White solid, mp 148-151 °C.



Procedures for Scheme 3.12 (*aza*-Diels-Alder reaction of imine 175):

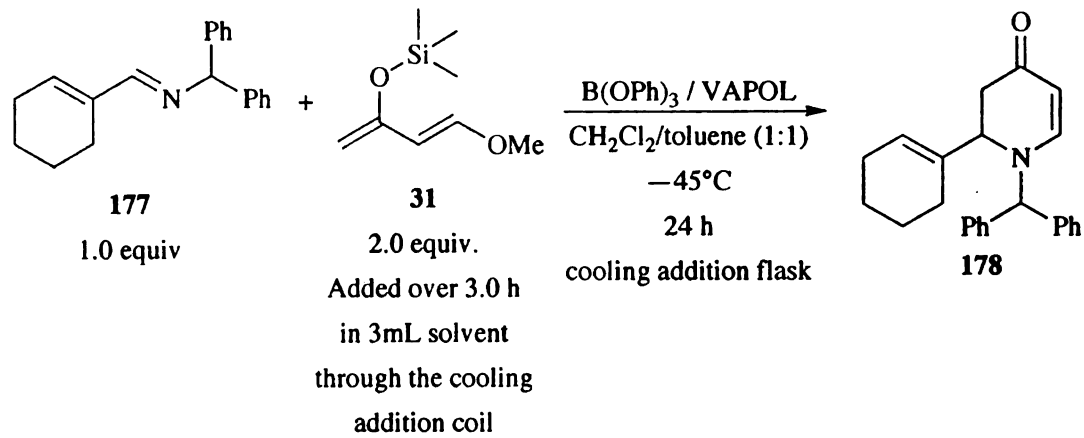
Condition A: The protocol for the optimal conditions was followed exactly where 0.2494 g (1.0 mmol) of imine **175** was used. The reaction failed to produce any of the desired product **176**.

Condition B: The protocol for the optimal conditions were followed exactly except the catalyst was prepared using 54 mg (*S*)-VAPOL (10 mol%). The reaction failed to produce any of the desired product **176**.

Spectral data for compound **176** ($C_{22}H_{23}NO$):

The enantiomers could be separated by HPLC using a Chiralpak AS column (90:10 hexane/isopropanol, 1mL/min). Retention times: 93.12 min. and 109.44 min. ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.72 (s, 3H), 2.34-2.42 (dd, 1H, *J*= 9.0, 16.5 Hz), 2.55-2.62 (dd, 1H, *J*=6.0, 16.2 Hz), 4.19-4.27 (m, 1H), 4.89 (d, 1H, *J*=7.8 Hz), 5.42 (d, 1H, *J*=9.9 Hz), 5.68 (s, 1H), 6.84 (d, 1H, *J*=7.8 Hz), 7.05 (d, 2H, *J*=6.9 Hz), 7.18 (d, 2H, *J*=6.6 Hz), 7.26-7.40 (br m, 6H); ^{13}C NMR ($CDCl_3$) δ 17.36, 25.48, 41.83, 55.99, 67.43, 97.69, 120.88, 127.38, 127.70, 127.90, 128.52, 128.61, 129.19, 137.50, 138.34, 138.46, 150.86, 190.88; IR ($CDCl_3$) 576.79 m, 607.65m, 621.16w, 700.25s, 734.97m, 752.33m, 1030.12w, 1140.08m, 1199.88m, 1242.32m, 1275.11m, 1311.76w, 1377.35w, 1446.80m, 1495.02w, 1577.97vs, 1643.56vs, 2916.74w, 2987.33w, 3051.67w, 3092.40w; mass

spectrum *m/z* (% rel intensity) 318 M+1 (41), 317 M+ (100), 316 (16), 302 (4), 274 (11), 262 (6), 206 (4), 194 (4), 168 (34), 167 (12), 166 (25), 165 (8), 153 (7), 150 (9), 104 (4), 77 (4); White solid, mp 82-93°C.



177
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

178

Procedures for Scheme 3.13 (*aza*-Diels-Alder reaction of imine 177):

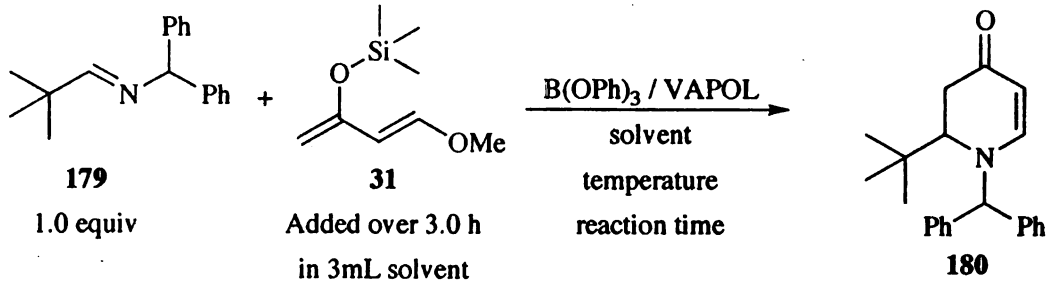
Condition A: The protocol for the optimal conditions was followed exactly where 0.2754 g (1.0 mmol) of imine **177** was used. The product (**178**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.07). The reaction produced 99.6 mg (29% yield) of the desired product **178** and 93% enantiomeric excess was measured (average of two runs).

Condition B: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 54 mg (*S*)-VAPOL (10 mol%). The reaction produced 109.9 mg (32% yield) of the desired product **178** and 93% enantiomeric excess was measured.

Condition C: The protocol described in condition B was followed exactly except the reaction was allowed to stir for 48 hours. The reaction produced 154.6 mg (45% yield) of the desired product **178** and 94% enantiomeric excess was measured.

Spectral data for compound **178** ($C_{24}H_{25}NO$):

The enantiomers could be separated by HPLC using a Chiralcel OJ-H column (90:10 hexane/isopropanol, 1mL/min). Retention times: 11.77 min. (minor) and 15.97 min. (major). ^{1}H NMR ($CDCl_3$) δ 1.53-1.79 (m, 4H), 2.04-2.15 (m, 4H), 2.56-2.69 (m, 2H), 3.88 (t, 1H, *J*=7.7 Hz), 4.87 (d, 1H, *J*=7.7 Hz), 5.50 (s, 1H), 5.57 (s, 1H), 6.93 (d, 1H, *J*=7.7 Hz), 7.04-7.42 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 21.84, 22.81, 23.87, 24.80, 39.78, 64.26, 67.10, 97.45, 127.17, 127.34, 127.70, 127.96, 128.58, 129.25, 134.01, 138.25, 128.58, 151.19, 190.82 (one aromatic carbon not located); IR ($CDCl_3$) 3028w, 2928m, 1643vs, 1589vs, 1578vs, 1449m, 1235m, 1219m, 1142m cm^{-1}; mass spectrum *m/z* (% rel intensity) M^+ 343 (42), 326 (2), 281 (10), 267 (3), 225 (10), 209 (13), 208 (10), 207 (22), 193 (11), 168 (15), 167 (100), 166 (11), 165 (34), 152 (21), 133 (5), 115 (5), 91 (10), 77 (12), 73 (9), 51 (6). White solid, mp 189-191 °C. Crystallization from CH_2Cl_2/hexanes gave **178** that was 98% ee. Optical rotation was taken on a 98% ee sample, $[\alpha]^{20}_D$ +137.2° (c 1.055, CH_2Cl_2).



179
1.0 equiv

31
Added over 3.0 h
in 3mL solvent

180

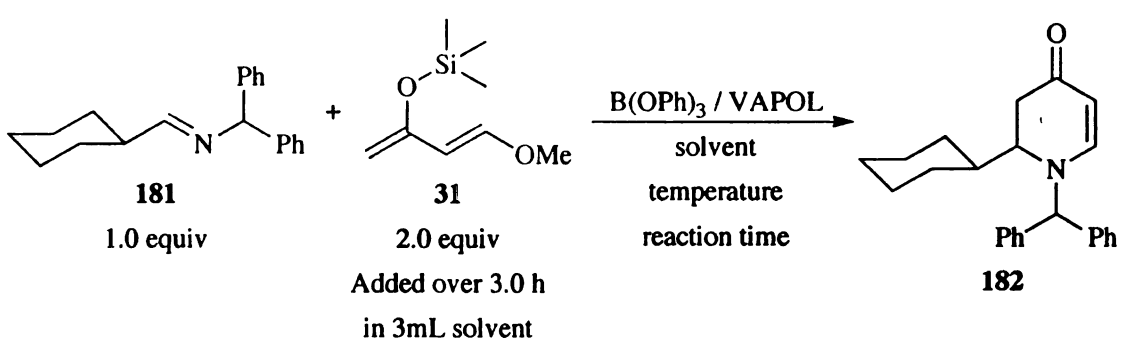
Procedures for Scheme 3.14 (*aza*-Diels-Alder reaction of imine 179):

Condition A: The protocol for the optimal conditions was followed exactly where 0.2514 g (1.0 mmol) of imine **179** was used. Upon analysis of the crude ^{1}H-NMR, it was determined that the reaction failed to give any of the desired product **180**.

Condition B: The protocol for the optimal conditions were followed exactly except the catalyst was prepared using 87 mg (30 mol%) $B(OPh)_3$ and 54 mg (*S*)-VAPOL (10 mol%). A standard 25 mL round bottom flask was used instead of the flask with the cold addition coil and toluene was used for the transfer of the catalyst to the imine and for the addition of the diene rather than a 1:1 mixture of CH_2Cl_2/toluene. The reaction failed to produce any of the desired product **180**.

Condition C: The protocol described in condition B was followed exactly except 3.0 mmol (3 equivalents) of the diene were used. The reaction was stirred for 16 hours failed to produce any of the desired product **180**.

Condition D: The protocol described in condition B was followed exactly except the reaction was stirred at room temperature for 16 hours. The reaction failed to produce any of the desired product **180**.



Procedures for Scheme 3.15 (*aza*-Diels-Alder reaction of imine 181):

Condition A: The protocol for the optimal conditions was followed exactly where 0.2774 g (1.0 mmol) of imine **181** was used. The product (**182**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.09). The reaction produced 196.9 mg (57% yield) of the desired product **182** and 76% enantiomeric excess was measured (average of two runs).

Condition B: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 54 mg (*S*)-VAPOL (10 mol%). The reaction produced 186.6 mg (54% yield) of the desired product **182** and 91% enantiomeric excess was measured.

Condition C: The protocol described for condition B was followed exactly except the reaction was allowed to stir for 46 hours. The reaction produced 314.4 mg (91% yield) of the desired product **182** and 93% enantiomeric excess was measured.

Condition D: The protocol described for condition B was followed exactly except the ratio of CH_2Cl_2 to toluene was changed from 1:1 to 1:4. The reaction produced 186.6 mg (54% yield) of the desired product **182** and 94% enantiomeric excess was measured.

Condition E: The protocol described for condition B was followed exactly except a mixture of CCl_4/CH_2Cl_2 (2:1) was used to transfer the catalyst to the imine and add the diene rather than a 1:1 mixture of CH_2Cl_2/toluene. The reaction was allowed to stir for 47 hours and produced 165.8 mg (48% yield) of the desired product **182** and 91.5% enantiomeric excess was measured (average of two runs).

Condition F: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 0.09 g $B(OPh)_3$ (30 mol%) and 54 mg (*S*)-VAPOL (10 mol%). Toluene was used to transfer the catalyst to the imine and add the diene rather than a 1:1 mixture of CH_2Cl_2/toluene. The reaction produced 155.5 mg (45% yield) of the desired product **182** and 95% enantiomeric excess was measured.

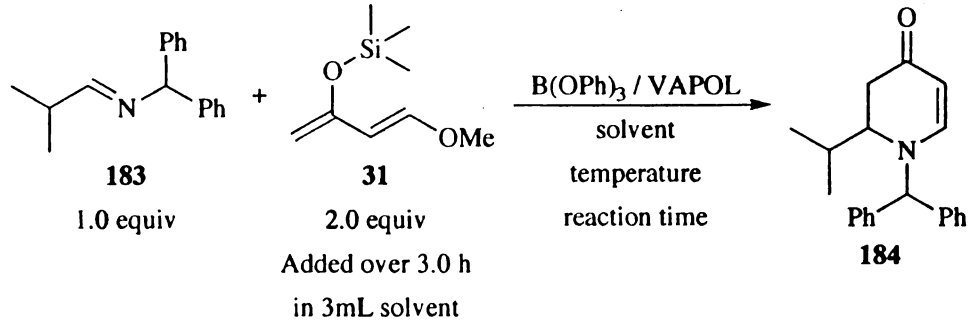
Condition G: The protocol described in condition F was followed exactly except the reaction was performed in a traditional 25 mL round bottom flask stirred for 44 hours.

The reaction produced 262.6 mg (76% yield) of the desired product **182** and 93% enantiomeric excess was measured.

Condition H: The protocol described in condition G was followed exactly except the reaction was stirred at 0°C for 48 hours. The reaction produced 145.1 mg (42% yield) of the desired product **182** and 80% enantiomeric excess was measured.

Spectral Data for compound **182** ($C_{24}H_{27}NO$):

The enantiomers could be separated by HPLC using a Chiralcel OJ-H column (90:10 hexanes/isopropanol, 1mL/min). Retention times: 8.98 min. (minor) and 13.85 min. (major). ^{1}H NMR ($CDCl_3$) δ 0.96-1.20 (m, 5H), 1.59-1.95 (m, 6H), 2.35 (d, 1H, *J*=16.8 Hz), 2.67 (dd, 1H, *J*=17.1, 8.1 Hz), 3.27 (br t, 1H, *J*=1.9 Hz), 4.76 (d, 1H, *J*=7.5 Hz), 5.68 (s, 1H), 6.82 (d, 1H, *J*=7.8 Hz), 7.04 (d, 2H, *J*=7.5 Hz), 7.19-7.37 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 25.76, 26.00, 26.06, 28.08, 29.43, 36.05, 40.51, 61.78, 69.56, 96.71, 126.99, 127.93, 128.17, 128.66, 128.69, 129.31, 137.61, 139.45, 150.21, 190.70; IR ($CDCl_3$) 3063w, 3030w, 2928vs, 2853vs, 1638vs, 1576vs, 1449s, 1223s, 1143s cm^{-1}; mass spectrum *m/z* (% rel intensity) 345 M^+ (63), 346 (19), 344 (9), 262 (12), 208 (4), 182 (16), 168 (15), 167 (100), 166 (9), 165 (31), 152 (19), 115 (5), 91 (4), 77 (6), 51 (4). Anal calcd for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.03; H, 8.11; N, 4.09. White solid, mp 132-134 °C. Optical rotation was taken on 93% ee sample, $[\alpha]^{20}_D$ –127.2° (c 1.13, CH_2Cl_2, 93% ee).



Procedures for Scheme 3.16 (*aza*-Diels-Alder reaction of imine 183):

Condition A: The protocol for the optimal conditions was followed exactly where 0.2374 g (1.0 mmol) of imine **183** was used. The product (**184**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.06). The reaction produced 177.1 mg (58% yield) of the desired product **184** and 89% enantiomeric excess was measured (average of two runs).

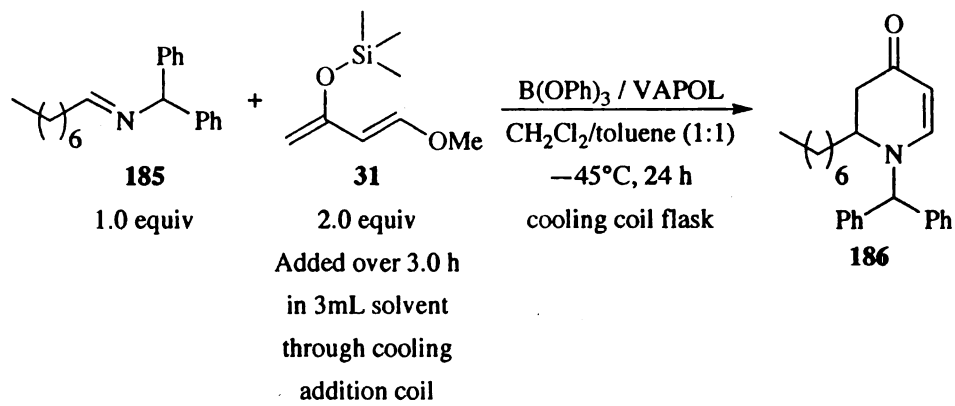
Condition B: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 54 mg (*S*)-VAPOL (10 mol%). The reaction produced 195.5 mg (64% yield) of the desired product **184** and 90% enantiomeric excess was measured.

Condition C: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 0.09 g $B(OPh)_3$ (30 mol%) and 54 mg (*S*)-VAPOL (10 mol%). A traditional 25 mL round bottom flask was used rather than the flask with the cooling addition coil and toluene was used to transfer the catalyst to the imine and add the diene rather than a 1:1 mixture of CH_2Cl_2/toluene. The reaction produced 174.1 mg (57% yield) of the desired product **184** and 91% enantiomeric excess was measured.

Spctral Data for compound **184** ($C_{21}H_{23}NO$):

The enantiomers could be separated by HPLC using a Chiralpak AS column (70:30 hexanes/isopropanol, 1mL/min). Retention times: 14.82 min. (major) and 32.15

min. (minor). ^{1}H NMR ($CDCl_3$) δ 0.98 (d, 6H, *J*=9.3 Hz), 2.34 (d, 1H, *J*=16.5 Hz), 2.34-2.41 (m, 1H), 2.64 (dd, 1H, *J*=17.1, 8.1 Hz), 3.28-3.33 (br m, 1H), 4.78 (d, 1H, *J*=7.2 Hz), 5.70 (s, 1H), 6.83 (d, 1H, *J*=7.8 Hz), 7.05 (d, 2H, *J*=7.5 Hz), 7.24-7.43 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 17.44, 19.32, 29.90, 35.23, 62.06, 69.18, 96.83, 126.99, 127.93, 128.15, 128.64, 128.70, 129.34, 137.66, 139.28, 150.24, 190.77; IR ($CDCl_3$) 2965s, 2932m, 2899m, 2876m, 1640vs, 1578vs, 1449s, 1227s, 1144s; mass spectrum *m/z* (% rel intensity) M+1 306 (19), 305 M^+ (75), 304 (13), 262 (37), 228 (10), 191 (9), 168 (15), 167 (100), 166 (9), 165 (34), 152 (18), 105 (5), 77 (8), 50 (5). Light yellow solid, mp 139-142 °C. Optical rotation was taken a a 84% ee sample, $[\alpha]^{20}_D$ –155.2° (c 0.93, CH_2Cl_2).



Procedures for Scheme 3.17 (*aza*-Diels-Alder reaction of imine 185):

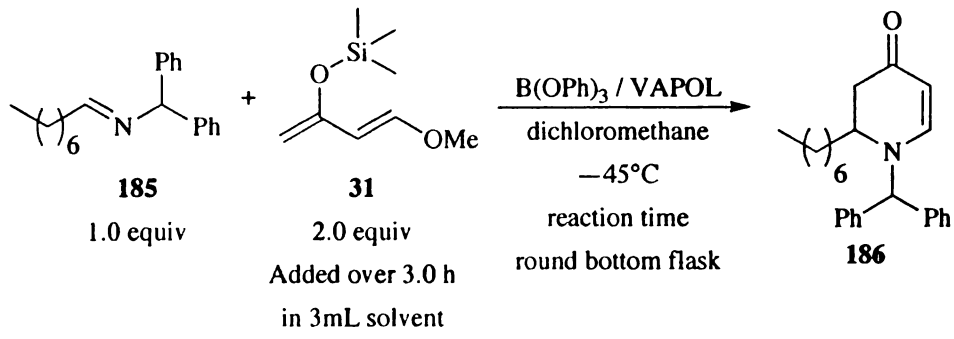
Condition A: The protocol for the optimal conditions was followed exactly where 0.2935 g (1.0 mmol) of imine **185** was used. The product (**186**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.10). The reaction produced 148.2 mg (41% yield) of the desired product **186** and 0% enantiomeric excess was measured (average of two runs).

Condition B: The protocol for the optimal conditions was followed exactly except (*S*)-VAPOL was excluded from the preparation of the catalyst. The reaction produced 144.6 mg (40% yield) of the desired product **186**.

Condition C: The protocol for the optimal conditions was followed exactly except (*S*)-VAPOL was excluded from the reaction and $B(OPh)_3$ was used directly from the bottle with no catalyst preparation. The reaction produced 108.5 mg (30% yield) of the desired product **186**.

Spectral data for compound **186** ($C_{25}H_{31}NO$):

The enantiomers could be separated by HPLC using a Chiralpak AD column (95:5 hexane/isopropanol, 1mL/min). Retention times: 13.25 min. and 16.32 min. ^1H NMR ($CDCl_3$) δ 0.85 (t, 3H, *J*=6.9 Hz), 1.25-1.39 (br m, 10H), 1.68-1.71 (br m, 1H), 1.84-1.94 (br m, 1H), 2.31 (d, 1H, *J*=16.5 Hz), 2.75 (dd, 1H, *J*=16.5, 6.9 Hz), 3.46 (br s, 1H), 4.83 (d, 1H, *J*=7.4 Hz), 5.63 (s, 1H), 6.72 (d, 1H, *J*=6.9 Hz), 7.06 (d, 2H, *J*=9.0 Hz), 7.24-7.43 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 13.75, 22.25, 25.16, 28.79, 29.16, 31.37, 38.44, 57.28, 69.21, 96.50, 126.85, 127.06, 127.91, 128.17, 128.46, 128.67, 129.23, 137.53, 139.26, 149.22, 190.24; IR (neat) 3063w, 3030w, 2928vs, 2857vs, 1645vs, 1576vs, 1456s, 1145s cm^{-1}; mass spectrum *m/z* (% rel intensity) 362 M^{+1} (54), 361 M^+ (100), 304 (4), 276 (3), 262 (7), 206 (3), 182 (16), 167 (75), 165 (30), 152 (14), 77 (3). Light yellow solid, mp 115-117 °C.



Procedures for Scheme 3.18 (*aza*-Diels-Alder reaction of imine 185):

Condition A: The protocol for the optimal conditions was followed exactly except the catalyst was prepared using 0.090 g $B(OPh)_3$ (30 mol%) and 54 mg (S)-VAPOL (10 mol%). A standard 25 mL round bottom flask was used instead of the flask with the cold addition coil and CH_2Cl_2 was used for the transfer of the catalyst to the imine and for the addition of the diene rather than a 1:1 mixture of CH_2Cl_2/toluene. The reaction produced 32.5 mg (9% yield) of the desired product **186** and the enantiomeric excess was not measured.

Condition B: To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (0.090 g, 0.30 mmol) and (S)-VAPOL (54 mg, 0.10 mmol). To this was added CH_2Cl_2 (2 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours yielding the VAPOL-boron catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 2.0 mL of CH_2Cl_2 (in two portions). The catalyst solution was transferred by syringe to the flask containing the imine.

To a flame dried, argon purged 25 mL round bottom flask equipped with a stir bar was added magnesium sulfate (0.17 g) and CH_2Cl_2 (2 mL) followed by octanal (1.0 mmol) and aminodiphenylmethane (redistilled, 1.0 mmol). The reaction was stirred overnight and then placed under high vacuum for 3 hours. The catalyst was added in two 1.0 mL portions of CH_2Cl_2. This was allowed to stir for 5-10 minutes at room temperature and then cooled to –45 °C. Meanwhile, in a separate flame dried 5 or 10 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) (0.38 mL, 2.0 mmol) and CH_2Cl_2 (3.0 mL). Workup was done according to the optimal conditions and the reaction produced 65.1 mg (18% yield) of the desired product **186** and 0% enantiomeric excess was measured (average of two runs).

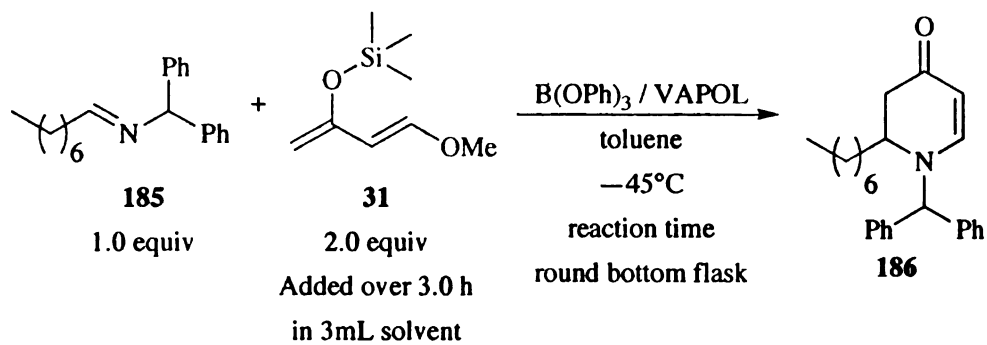
Condition C: The protocol described in condition B was followed exactly except the reaction was only allowed to stir for 22 hours. The reaction produced 86.8 mg (24% yield) of the desired product **186** and 4% enantiomeric excess was measured.

Condition D: The protocol described in condition B was followed exactly except 1.1 equivalents of the aldehyde was used for the *in situ* preparation of the imine. The reaction was only allowed to stir for 21 hours and produced 75.9 mg (21% yield) of the desired product **186** and 0% enantiomeric excess was measured.

Condition E: The protocol described in condition D was followed exactly except the aldehyde was redistilled immediately before use and aminodiphenylmethane was purified by distillation, then running a column, and then distilling one more time before use in the *in situ* preparation of the imine. The reaction was allowed to stir for 24.5 hours and produced 122.9 mg (34% yield) of the desired product **186** and 0% enantiomeric excess was measured.

Condition F: The protocol described in condition D was followed exactly except the aldehyde was distilled and the aminodiphenylmethane purified by column chromatography immediately before use in the *in situ* preparation of the imine. The reaction was allowed to stir for 21.5 hours produced 169.9 mg (47% yield) of the desired product **186** and 4% enantiomeric excess was measured.

Condition G: The protocol described in condition D was followed exactly except 0.18 g $B(OPh)_3$ (60 mol%) and 108 mg (*S*)-VAPOL (20 mol%) were used for the preparation of the catalyst. The reaction was allowed to stir for 20 hours and produced 112.1 mg (30% yield) of the desired product **186** and 0% enantiomeric excess was measured.



Procedures for Scheme 3.19 (*aza*-Diels-Alder reaction of imine 185):

Condition A: To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (0.090 g, 0.30 mmol) and (S)-VAPOL (54 mg, 0.10 mmol). To this was added CH_2Cl_2 (2 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours yielding the VAPOL-boron catalyst.

After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 2.0 mL of toluene (in two portions). The catalyst solution was transferred by syringe to the flask containing the imine as prepared below.

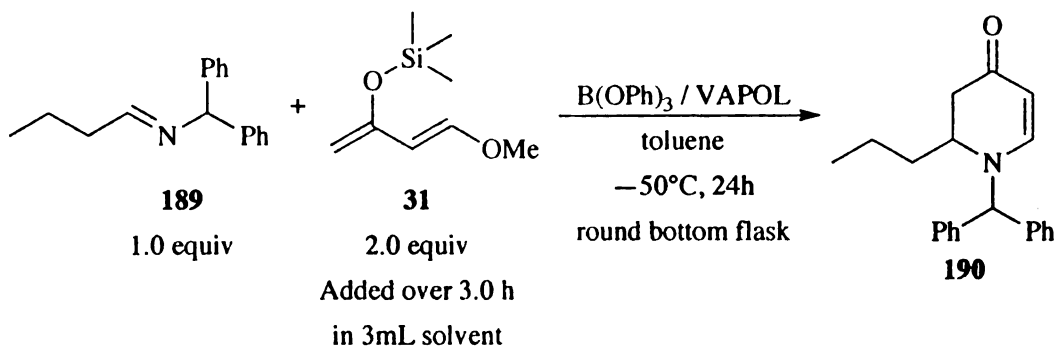
To a flame dried, argon purged 25 mL round bottom flask equipped with a stir bar was added magnesium sulfate (0.17 g) and CH_2Cl_2 (2 mL) followed by octanal (1.0 mmol) and aminodiphenylmethane (redistilled, 1.0 mmol). The reaction was stirred overnight and then placed under high vacuum for 3 hours. The VAPOL-boron catalyst was added in two 1.0 mL portions of toluene. This was allowed to stir for 5-10 minutes at room temperature and then cooled to –45 °C. Meanwhile, in a separate flame dried 5 or 10 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) (0.38 mL, 2.0 mmol) and toluene (3.0 mL). The diene was taken up in a syringe and added over 3.0 hours via syringe pump. The reaction was then allowed to stir at –45 °C for the duration of the reaction (20 hours). Workup was done according to the optimal conditions and the reaction produced 61.5 mg (17% yield) of the desired product **186** and 20% enantiomeric excess was measured.

Conditions B: The protocol described in condition A was followed exactly except (*S*)-VANOL was used instead of (*S*)-VAPOL for the preparation of the catalyst. The reaction was allowed to stir for 51 hours and produced 75.9 mg (21% yield) of the desired product **186** and 0% enantiomeric excess was measured.

Conditions C: The protocol described in condition A was followed exactly except (*S*)-BINOL was used instead of (*S*)-VAPOL for the preparation of the catalyst The

reaction was allowed to stir for 51 hours and produced 54.2 mg (15% yield) of the desired product **186** and 18% enantiomeric excess was measured.

Conditions D: The protocol described in condition A was followed exactly except tris-(2,6-dimethylphenyl)borate was used in place of $B(OPh)_3$ for the preparation of the catalyst. The reaction produced 83.1 mg (23% yield) of the desired product **186** and 16% enantiomeric excess was measured.



189
1.0 equiv

31
2.0 equiv
Added over 3.0 h
in 3mL solvent

190

Procedure for Scheme 3.20 (*aza*-Diels-Alder reaction of imine 189):

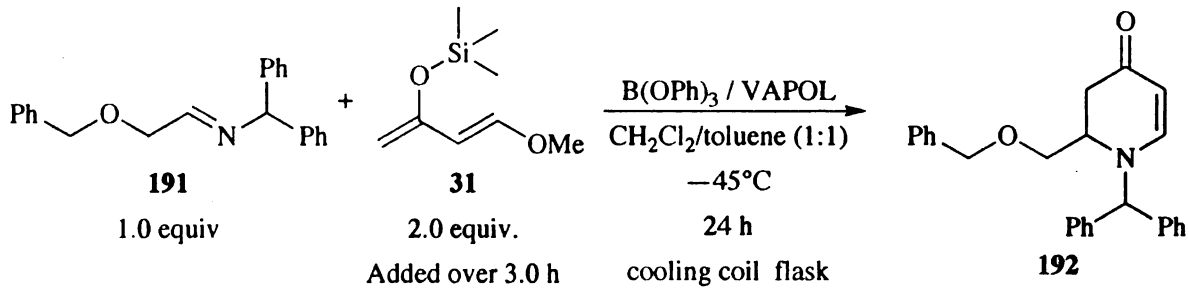
Condition A: To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (0.09g, 0.3 mmol) and (S)-VAPOL (54 mg, 0.10 mmol). To this was added CH_2Cl_2 (2 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours yielding the (*S*)-VAPOL catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 2.0 mL of a toluene (in two portions). The catalyst solution was transferred by syringe to a flask containing the imine prepared as prepared immediately below.

To a flame dried, argon purged 25 mL round bottom flask equipped with a stir bar was added the imine (**189**) (0.2373 g, 1.0 mmol). The flask was topped with a rubber septa and the catalyst was added in two 1.0 mL portions of toluene. This was allowed to stir for 5-10 minutes at room temperature and then cooled to –50 °C. Meanwhile, in a separate flame dried 5 or 10 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) (0.38 mL, 2.0 mmol) and toluene (3.0 mL). The diene was taken up in a syringe and added over 3.0 hours via syringe pump through the cold addition coil. The reaction was then allowed to stir at –50 °C for the duration of the reaction 24 hours. Workup was done according to the optimal conditions and the reaction produced 106.9 mg (35% yield) of the desired product **190** and 22% enantiomeric excess was measured (average of two runs).

Spectral data for compound **190** ($C_{24}H_{23}NO$):

The enantiomers could be separated by HPLC using a Chiralpak AS column (90:10 hexane/isopropanol, 1mL/min). Retention times: 13.25 min. (major) and 16.32 min. (minor). ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H, *J*=7.2 Hz), 1.17-1.32 (br m, 1H), 1.36-1.51 (br m, 1H), 1.60-1.71 (br m, 1H), 1.85-1.98 (br m, 1H), 2.26-2.33 (dd, 1H, *J*=2.4, 16.5 Hz), 2.71-2.79 (dd, 1H, *J*=7.2, 16.8 Hz), 3.42-3.51 (m, 1H), 4.83 (d, 1H, *J*=7.5 Hz), 5.62 (s, 1H), 6.71 (d, 1H, *J*=7.5 Hz), 7.05-7.07 (m, 2H), 7.29-7.43 (br m, 8H); ^{13}C NMR ($CDCl_3$) δ 13.66, 18.443, 30.84, 38.51, 57.10, 62.25, 96.60, 127.06, 127.91, 128.17, 128.69, 129.47, 137.58, 139.34, 149.11, 190.23; IR (neat) 700.25m, 740.76m, 1030.12vw, 1080.27vw, 1124.64w, 1145.86m, 1184.44m, 1215.31m, 1240.39m, 1294.40w, 1319.48w, 1381.21vw, 1415.93vw, 1448.73m, 1495.02vw, 1576.04vs, 1635.84vs, 2860.35w, 2784.30w, 1898.65w, 2927.99m, 2959.18m, 2012.49vw,

3028.63w, 3046.88, 3059.78w, 3088.20w; mass spectrum *m/z* (% rel intensity) 306 M+1 (51), 305 M+ (66), 304 (22), 276 (2), 262 (2), 248 (3), 229 (2), 183 (1), 169 (5), 168 (100), 167 (32), 166 (43), 165 (11), 164 (3), 152 3 (8), 152 (16), 139 (2), 128 (3), 116 (4), 104 (4), 77 (4), 51 (4), 50 (4); light yellow solid, mp 157-159°C.



191
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

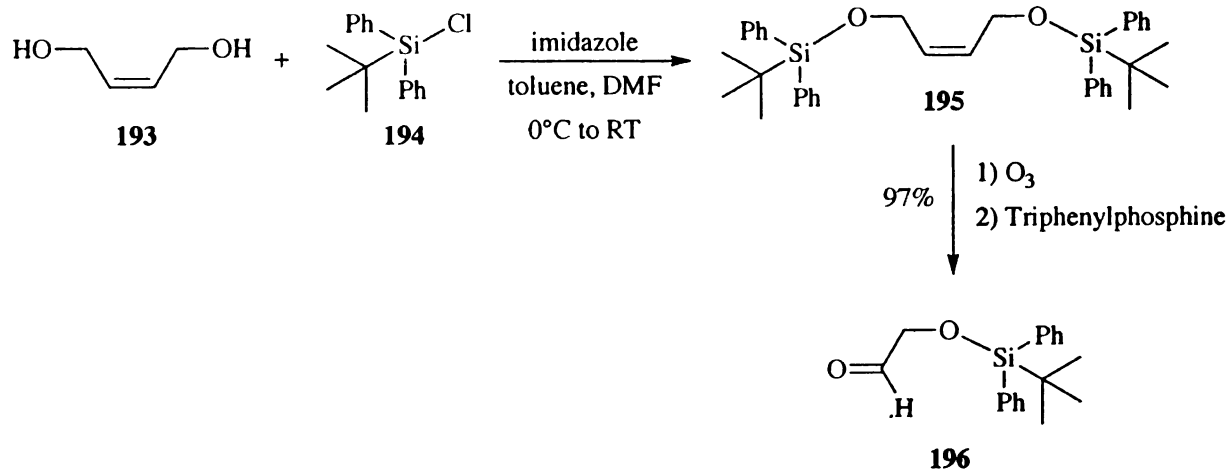
192

Procedure for Scheme 3.21 (*aza*-Diels-Alder reaction of imine 191):

Condition A: The protocol for the optimal conditions was followed exactly where 0.3154 g (1.0 mmol) of imine **191** was used. The product (**192**) was then purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.05). The reaction produced 168.7 mg (one spot by TLC) of a complex mixture of products. The ^{1}H NMR indicated that the desired product **192** may have been formed but could not be isolated (average of two runs).

Spectral Data for compound **192**:

Even after two purifications, a single spot as observed by TLC analysis shows ^{1}H NMR and ^{13}C-NMR that contain a complex mixture of peaks.

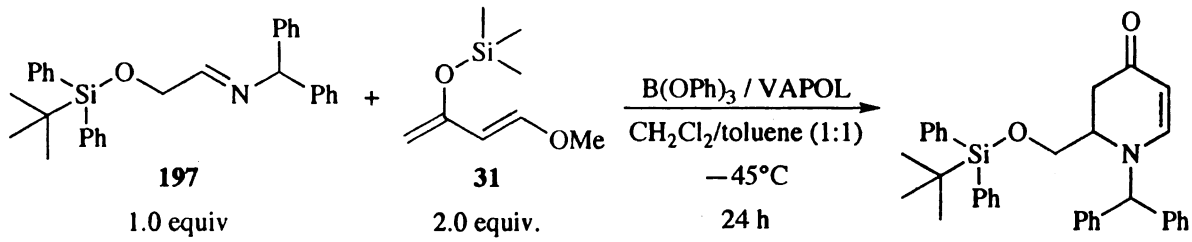


Preparation of 2-*tert*-butyl-diphenylsilyloxyethanal 196:

To a flame dried argon purged 100 mL round bottom flask equipped with a magnetic stir bar was added imidazole (10. 2 g, 150 mmol) and DMF (20 mL). The solution was cooled to 0 °C and the (*Z*)-2-butene-1,4-diol (**193**, 4.12 mL, 50 mmol) was added followed immediately by the addition of a solution of TBDPSCl in 30 mL toluene (**194**, 30.24 g, 110 mmol). The reaction mixture was then allowed to warm up to room temperature and stir for 44 hours. After 44 hours, water (50 mL) was added, the solution transferred to a separatory funnel and extracted three times with ether (3 x 50 mL). The organic layers were combined and washed four times with water (4 x 50mL) and once with brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Distillation was used to remove any volatile compounds and ^{1}H NMR indicated that the material left in the distillation flask was **195**. The unpurified **195** was then used for the ozonolysis step.

Following a literature protocol,[112] to a flame dried argon purged 500 mL round bottom flask equipped with a magnetic stir bar was added the bis-protected diol (**195**, 6.56 g, 11.6 mmol) and a 1:1 mixture of CH_2Cl_2/methanol (220 mL). The solution was cooled to –78 °C and while stirring, ozone was bubbled through the solution until the

color turned light blue (~30 min). To the blue solution was added PPh_3 (4.68 g, 17.85 mmol), it was allowed to warm to room temperature, and stir for 2 hours. The solvent was removed under reduced pressure and the product was purified by flash column chromatography (85:15 hexanes/ethyl acetate) to give 6.7 g (97% yield) of the desired aldehyde **196**.



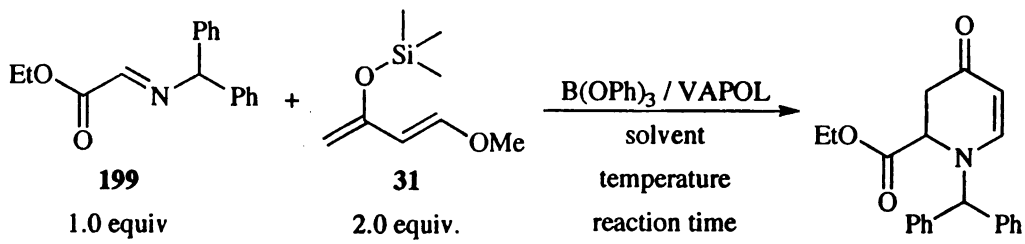
197
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

198

Procedure for Scheme 3.23 (*aza*-Diels-Alder reaction of imine 197):

Condition A: The protocol for the optimal conditions was followed exactly where 0.4637 g (1.0 mmol) of imine **197** was used and the reaction failed to produce any of the desired product **198**.



199
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

200

Procedures for Scheme 3.24 (*aza*-Diels-Alder reaction of imine 199):

Condition A: The protocol for the optimal conditions was followed exactly except 54 mg of (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst. 0.2673 g (1.0 mmol) of imine **199** was used for the reaction. The product (**200**) was purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.07) to give 268.3 mg (80% yield) of the desired product **200** and 52% enantiomeric excess was measured (average of two runs).

Condition B: The protocol described in condition A was followed exactly except the reaction was allowed to take place at −60°C. The reaction produced 241.5 mg (72% yield) of the desired product **200** and 35% enantiomeric excess was measured.

Condition C: The protocol described in condition A was followed exactly except the reaction was allowed to take place at −30°C. The reaction produced 278.4 mg (83% yield) of the desired product **200** and 55% enantiomeric excess was measured.

Condition D: The protocol described in condition A was followed exactly except the catalyst was prepared using 0.09 g $B(OPh)_3$ (30 mol%) and 54 mg (*S*)-VAPOL (10 mol%). The reaction produced 295.2 mg (88% yield) of the desired product **200** and 53% enantiomeric excess was measured.

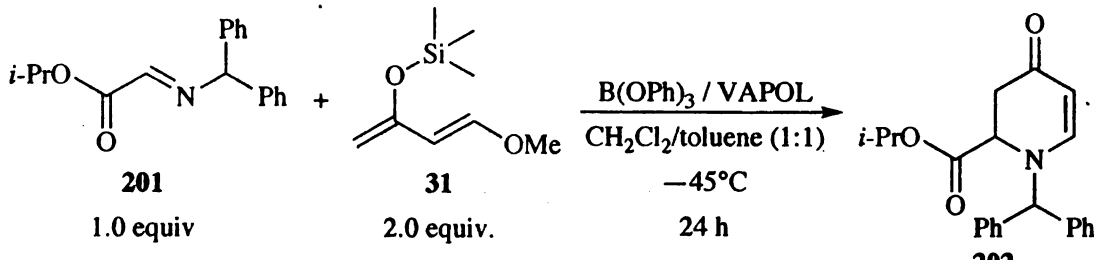
Condition E: The protocol described in condition A was followed exactly except the catalyst was transferred to the imine and the diene was added in CCl_4/CH_2Cl_2 (2:1) rather than a 1:1 mixture CH_2Cl_2/toluene. The reaction produced 248.2 mg (74% yield) of the desired product **200** and 60% enantiomeric excess was measured.

Condition F: The protocol described in condition E was followed exactly except the reaction was allowed to take place at −78°C for 48 hours. The reaction produced

130.8 mg (39% yield) of the desired product **200** and 30% enantiomeric excess was measured.

Spectral data for compound **200** ($C_{21}H_{21}NO_3$):

The enantiomers could be separated by HPLC using a Chiralcel OJ-H column (75:25 hexane/isopropanol, 1.0 mL/min). Retention times: 8.94 min. (major) and 18.61 min. (minor). ^{1}H NMR ($CDCl_3$) δ 1.15 (m, 3H), 2.74 (m, 2H), 4.10 (m, 3H), 4.78 (d, 1H, *J*=7.1 Hz), 5.69 (s, 1H), 6.74 (d, 1H, *J*=7.7 Hz), 7.23 (m, 10H); ^{13}C NMR ($CDCl_3$) δ14.14, 37.78, 59.46, 62.06, 70.87, 98.72, 127.52, 128.39, 128.65, 129.03, 129.11, 129.85, 137.53, 139.11, 150.77, 170.23, 188.75; IR ($CDCl_3$) 3066.49, 3039.11, 2982.33, 2950.10, 2905.67, 1736.16, 1647.42, 1589.55, 1495.02, 1448.73, 1377.35, 1321.41, 1221.10, 184.44, 1140.08, 1032.05, 935.83 cm^{-1}; mass spectrum m/z (% rel intensity) 336 M+1 (29), 335 M+ (44), 289 (10), 262 (5), 260 (4), 169 (4), 168 (32), 167 (100), 166 (28), 153 (12), 152 (4), 115 (4), 51 (3); light yellow wax, the optical rotation was taken on 52% ee material, $[\alpha]^{20}_D$ −34.3° (c 1.782, CH_2Cl_2).

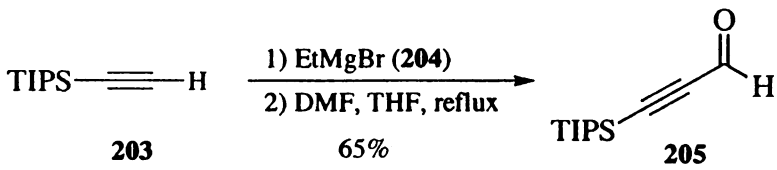


Procedures for Scheme 3.24 (*aza*-Diels-Alder reaction of imine 201):

Condition A: The protocol for the optimal conditions was followed exactly except 54 mg of (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst. 0.2814 g (1.0 mmol) of imine **201** was used for the reaction. The product (**202**) was purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.07). The reaction produced 283.0 mg (80% yield) of the desired product **202** and 52% enantiomeric excess was measured (average of two runs).

Spectral data for compound **202** ($C_{22}H_{23}NO_3$):

The enantiomers could be separated by HPLC using a Chiralcel OJ-H column (75:25 hexane/isopropanol, 1.0 mL/min). Retention times: 7.00 min. (major) and 12.80 min. min. (minor). ^{1}H NMR ($CDCl_3$) δ1.20 (m, 6H), 2.79 (m, 2H), 4.08 (m, 1H), 4.85 (d, 1H, *J*=7.7 Hz), 5.04 (m, 1H), 5.72 (s, 1H), 6.80 (d, 1H, *J*=7.7 Hz) 7.30 (m, 10H); ^{13}C NMR ($CDCl_3$) δ21.4, 37.55, 59.22, 69.74, 70.59, 98.48, 127.20, 128.06, 128.32, 128.70, 128.79, 129.49, 137.22, 138.78, 150.53, 169.44, 188.51; IR ($CDCl_3$) 3081.22, 3047.54, 2982.33, 2946.07, 1734.23, 1653.21, 1591.48, 1448.73, 1375.42, 1321.41, 1221.10, 1128.51, 1140.08, 1105.35, 1010.83, 740.76, 702.18cm^{-1}; mass spectrum m/z (% rel intensity) 350 M+1 (16), 349 M+ (32), 289 (8), 262 (6), 168 (12), 167 (100), 166 (25), 165 (6), 153 (12); White solid, the optical rotation was taken on 56% ee material, $[\alpha]^{20}_D$ −26.2° (c 2.963, CH_2Cl_2).

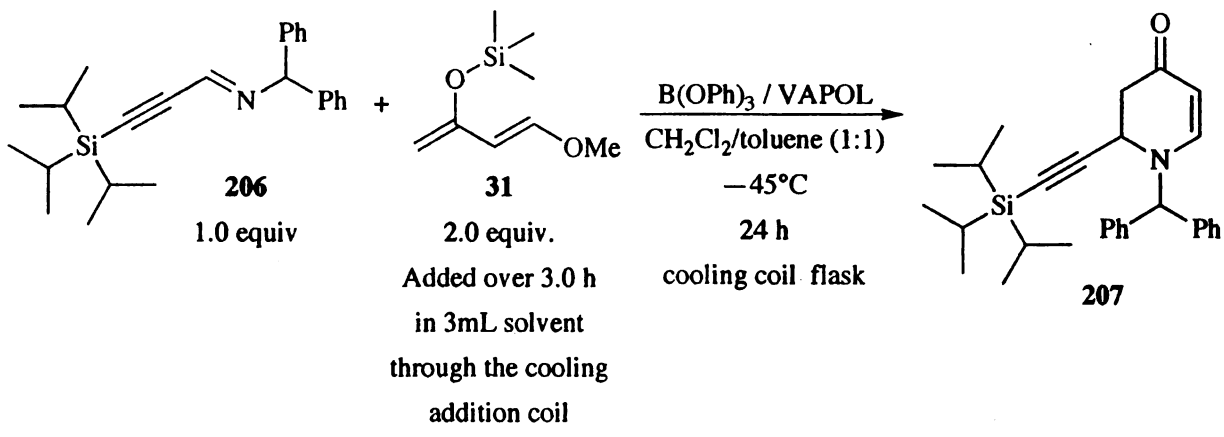


203 65% **205**

Preparation of 3-triisopropylsilyl-2-propynal (205):[113]

To a flame dried argon purged 500 mL round bottom flask was added magnesium turnings (1.07 g, 44.6 mmol) and THF (178 mL). To the flask was then added

bromoethane (3.33 mL, 44.6 mmol). The resulting mixture heated to reflux and allowed to stir overnight. The resulting 0.25M solution of Grignard reagent **204** was then transferred to a flame dried argon purged 1000 mL round bottom flask that had been previously charged with TIPS-acetylene (**203**, 10 mL, 44.6 mmol) and THF (178 mL). The contents were then heated to reflux for 10 minutes and then cooled back to room temperature at which time the solution was transferred to flame dried argon purged 1000 mL round bottom flask that had previously been charged with DMF (21.1 mL, 73.09 mmol) and THF (178 mL). The resulting reaction mixture was then heated to reflux for 10 minutes. Upon cooling to room temperature, 1 N HCl (92 mL) was added and the reaction mixture was then transferred to a 2 L separatory funnel and extracted three times with Et_2O. The organic layers were then combined and dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude oil was then purified by bulb-to-bulb distillation (93-95°C, 2 mmHg) to give 6.12 g (65% yield) of the pure aldehyde **205**. The NMR matched exactly to that in the literature.[113]

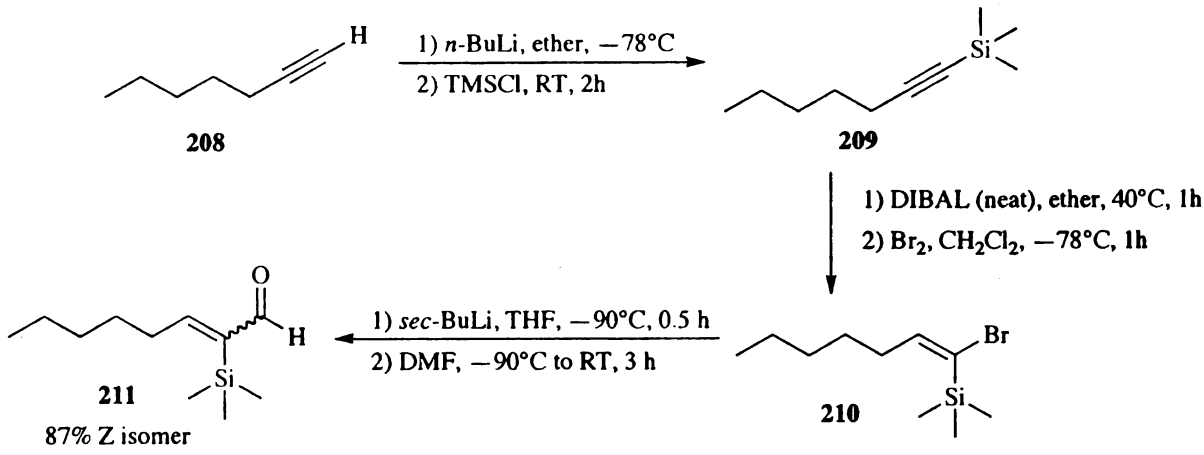


Procedures for Scheme 3.27 (*aza*-Diels-Alder reaction of imine 206):

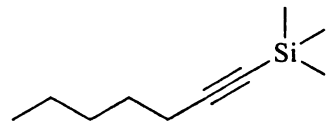
Condition A: The protocol for the optimal conditions was followed exactly except 54 mg of (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst. 0.3756 g (1.0 mmol) of imine **206** was used for the reaction. The product (**207**) was purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.23). The reaction produced 315.0 mg (71% yield) of the desired product **207** and 22% enantiomeric excess was measured.

Spectral data for compound **207** ($C_{30}H_{37}NO$):

The enantiomers could be separated by HPLC using a Chiralcel OJ-H column (98:2 hexane/isopropanol, 1.0 mL/min). Retention times: 10.79 min. (minor) and 14.38 min. (major). ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 21H), 2.70 (dd, 2H, *J*=7.3, 15.9 Hz), 4.31 (m, 1H), 4.98 (d, 1H, *J*=8.0 Hz), 5.98 (s, 1H), 6.77 (d, 1H, *J*=7.9 Hz), 7.25 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 11.00, 18.49, 42.12, 50.81, 68.93, 87.64, 99.74, 103.15, 127.57, 128.15, 128.31, 128.89, 128.95, 129.36, 138.25, 138.41, 150.02, 189.86; IR (neat) 679.03m, 700.25m, 734.97w, 754.26w, 883.51m, 1142.00m, 1180.59w, 1219.17m, 1238.46m, 1275.11w, 1311.76w, 1454.51m, 1591.48vs, 1655.13vs, 2864.66s, 2891.66m, 2943.75s, 3030.56w, 3063.35w cm^{-1}; mass spectrum m/z (% rel intensity) 444 M+1 (54), 443 M+ (100), 415 (27), 400 (25), 373 (12), 276 (11), 235 (7), 168 (26), 167 (98), 166 (34), 165 (11). Colorless wax. Optical rotation was taken on 22% ee material, $[\alpha]^{20}_D$ +60.2° (c 2.233, $CDCl_3$).

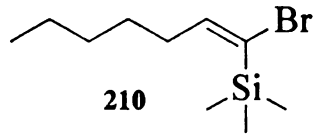


Preparation of *Z*-2-trimethylsilyl-2-ocetnal (211):[114]



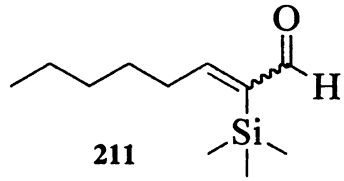
209

*Silylacetylene **209***: To a flame dried 500 mL round bottom flask equipped with a magnetic stir bar was added 1-heptyne (**208**, 30 mL, 0.229 mmol) and Et_2O (125 mL). The solution was then cooled to –78 °C at which time *n*-BuLi (146 mL, 0.233 mmol, 1.6 M solution in hexanes) was added followed by chlorotrimethylsilane (29.5 mL, 0.233 mmol). The reaction mixture was allowed to stir while warming to room temperature for 2 h. After 2 h, the reaction mixture was quenched with ice-cold water and extracted with pentane. The organic layers were combined and washed with water followed by brine. The organic extracts were then dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude oil was then purified via distillation (70°C, 10 mmHg) to give pure **209**. The ^1H NMR spectra matched perfectly with those in the literature.[114]



210

*(E)-1-bromohept-1-enyl)trimethylsilane (**210**)*: To a flame dried 500 mL round bottom flask equipped with a magnetic stir bar was added (hept-1-ynyl)trimethylsilane (**209**, 8.14 g, 48.33 mmol) and Et_2O (25 mL). The reaction flask was then placed in a water bath (room temperature) and to the solution was added neat DIBAL-H (9.87 mL, 53.2 mmol). The reaction mixture was then heated to 40 °C and stirred for 1 h after which it was cooled to 0 °C and added pyridine (7.73 mL, 101.5 mmol) was added. The resulting solution was cooled to −78°C and Br_2 (3.24 mL, 62.8 mmol) was added in CH_2Cl_2 (42 mL) and stirred for 1h. The −78°C solution was transferred to a vigorously stirring mixture of NaOH (7.73 g), pentane (50 mL), and ice (60 g). The resulting solution was then transferred to a separatory funnel and extracted three times with pentane. The organic layers were combined and washed with 1N HCl, 20% solution of $CdCl_3$ (18 g) in H_2O (87 mL), 1N HCl, and then saturated sodium bicarbonate. The organic layers were combined and dried with $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The resulting oil was then filtered through a plug of SiO_2 and flushed with hexanes (~400-500 mL) to give 10.11 g of the desired 100% *E*-isomer product **210** (84% yield) as a pure colorless oil.



211

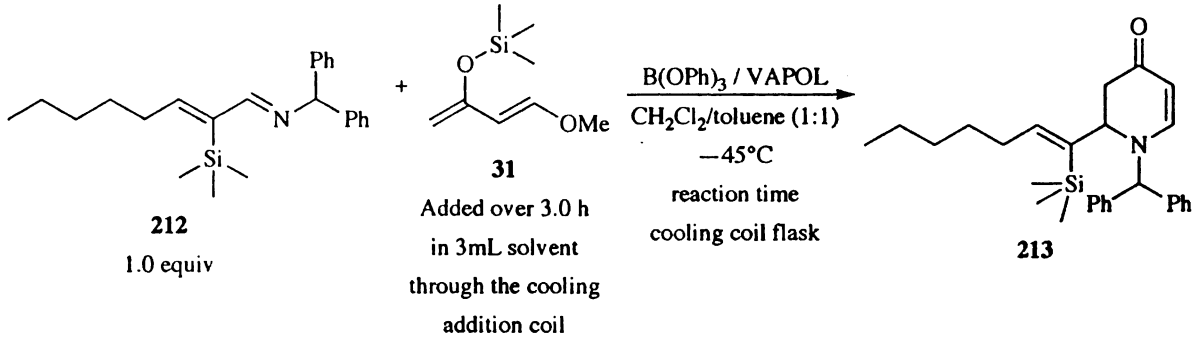
2-(trimethylsilyl)oct-2-enal ***211***: Following a literature protocol[115], to a flame dried 100 mL three-neck round bottom flask equipped with a magnetic stir bar and thermometer was added ((*E*)-1-bromohept-1-enyl)trimethylsilane (**210**, 3.19 g, 12.86 mmol) and THF (30 mL). The solution was then cooled to −90°C (acetone, N_2). To the reaction flask was then added *sec*-BuLi (10.1 mL, 14.15 mmol, 1.4 M solution in cyclohexane) very slowly so as to maintain the temperature of the reaction mixture below −85°C. The resulting solution was then allowed to stir at −90°C for 30 minutes. To the reaction mixture was then added DMF (1.99 mL, 25.72 mmol) very slowly so as to again maintain the temperature below −85°C. After addition of DMF was complete, the reaction was warmed slowly (~2 hrs) to room temperature and stir for an additional 1 h. The reaction was quenched with water (pH 7 buffer) and extracted with ether. The organic layer was then dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. ^{1}H-NMR of the crude mixture indicated that there was only 87% retention of the geometry of the olefin. Purification was done by eluting the product **211** with hexanes/EtOAc (2:1) through a plug of silicagel to give a mixture of the *Z* and *E* isomers as a yellow oil.

Spectral data for compound **211** ($C_{11}H_{22}SiO$):

Z-Isomer: ^{1}H NMR ($CDCl_3$) δ 0.20 (s, 9H), 0.89 (m, 3H, overlap with E-isomer), 1.28 (m, 4H, overlap with E-isomer), 1.48 (m, 2H, overlap with E-isomer), 2.41 (q, 2H, *J*=7.5 Hz), 7.06 (t, 1H, *J*=7.2 Hz), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ; -1.85, 14.06, 25.53, 27.88, 31.51, 32.50, 142.23 (two overlapping peaks).

E-Isomer: ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 9H), 0.89 (m, 3H, overlap with Z-isomer), 1.28 (m, 4H, overlap with Z-isomer), 1.48 (m, 2H, overlap with Z-isomer), 2.57 (q, 2H,

J=7.8 Hz), 6.81 (t, 1H, J=7.5 Hz), 10.27 (s, 1H); ^{13}C NMR ($CDCl_3$) δ; minor isomer C-peaks not detectable after 500 scans); IR (neat) 629.53w, 729.19w, 758.12w, 944.93vs, 972.25m, 1140.08m, 1250.03s, 1379.28w, 1408.21w, 1466.09w, 1697.91vs, 1799.81w, 2731.55 w, 2860.80vs, 2928.32vs, 2957.25vs cm^{-1}; mass spectrum m/z (% rel intensity) 198 M+ (6), 184 (14), 183 (81), 182 (34), 181 (11), 155 (14), 142 (12), 141 (10), 139 (49), 128 (12), 127 (95), 126 (19), 125 (11), 113 (81), 112 (15), 111 (41), 103 (17), 85 (13), 77 (12), 75 (90), 74 (13), 73 (100), 67 (12), 61 (10), 59 (20), 55 (10), 47 (12), 45 (32).



Procedures for Scheme 3.29 (*aza*-Diels-Alder reaction of imine 212):

Condition A: To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (0.3125 g, 1.0 mmol) and (S)-VAPOL (54 mg, 0.10 mmol). To this was added CH_2Cl_2 (2 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours yielding the VAPOL-boron catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 2.0 mL of toluene (in two portions). The

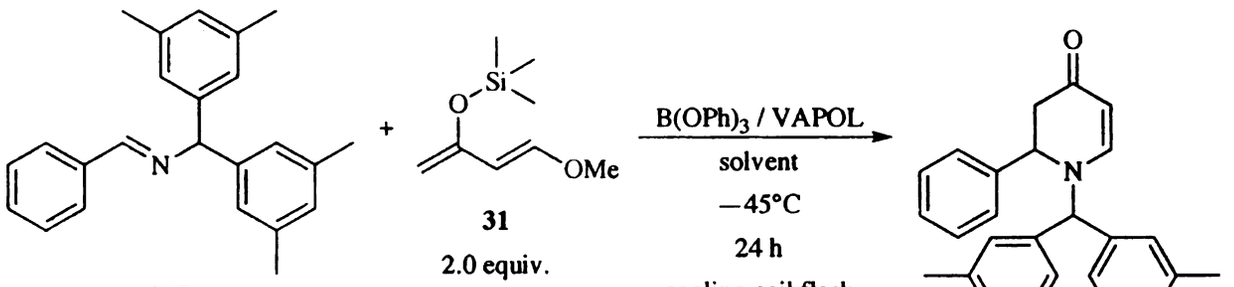
catalyst solution was transferred by syringe to the flask containing the imine as prepared below.

To a flame dried, argon purged 25 mL round bottom flask equipped with a stir bar was added magnesium sulfate (0.17 g) and CH_2Cl_2 (2 mL) followed by the aldehyde **211** (0.1984g, 1.0 mmol) and aminodiphenylmethane (**153**, 0.1833g, 1.0 mmol). The reaction was stirred overnight and then placed under high vacuum for 3 hours. The VAPOL-boron catalyst was added in two 1.0 mL portions of CH_2Cl_2/toluene (1:1). This was allowed to stir for 5-10 minutes at room temperature and then cooled to –45 °C. Meanwhile, in a separate flame dried 5 or 10 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) (0.38 mL, 2.0 mmol) and CH_2Cl_2/toluene (3.0 mL). The diene was taken up in a syringe and added over 3.0 hours via syringe pump. The reaction was then allowed to stir at –45 °C for the duration of the reaction (20 hours). Workup was done according to the optimal conditions and the reaction failed to produce any of the desired product **213**.

Condition B: The protocol described in condition A was followed exactly except the imine was prepared from 0.146 g (0.735 mmol) of the aldehyde **211** and 0.1347 g aminodiphenylmethane (0.735 mmol) using magnesium sulfate as the drying agent. 2.72 equivalents of the diene were used and the reaction was allowed to stir for 96 hours and the reaction failed to produce any of the desired product **213**.

Condition C: The protocol described in condition A was followed exactly except the imine was prepared using 4Å molecular sieves rather than $MgSO_4$ as the drying agent. 1.87 equivalents of the diene were used and the reaction was allowed to stir for 96 hours and the reaction failed to produce any of the desired product **213**.

Condition D: The protocol described in condition A was followed exactly except the imine was prepared using sodium sulfate as the drying agent and the reaction was allowed to stir for 96 hours. The reaction failed to produce any of the desired product **213**.



215
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

216

Procedures for Scheme 3.31 (*aza*-Diels-Alder reaction of imine 215):

Condition A: The protocol for the optimal conditions was followed exactly where 0.3275 g (1.0 mmol) of imine **215** was used. The product (**216**) was purified via flash column chromatography (36 cm x 2 cm, 8:5 hexanes/ethyl acetate r_f 0.17). The reaction produced 280.8 mg (70% yield) of the desired product **216** and 93% enantiomeric excess was measured.

Condition B: The protocol for the optimal conditions was followed exactly except the catalyst was transferred to the imine and the diene was added in CCl_4/CH_2Cl_2 (2:1) rather than a 1:1 mixture of CH_2Cl_2/toluene. The reaction produced 221.5 mg (56% yield) of the desired product **216** and 91% enantiomeric excess was measured.

Condition C: The protocol for the optimal conditions was followed exactly except 54 mg (10 mol%) (*S*)-VAPOL was used for the preparation of the catalyst. The

reaction produced 332.3 mg (84% yield) of the desired product **216** and 93% enantiomeric excess was measured.

Condition D: The protocol described in condition C was followed exactly except the catalyst was transferred to the imine and the diene was added in CH_2Cl_2 rather than the 1:1 mixture of CH_2Cl_2/toluene. The reaction produced 261.1 mg (66% yield) of the desired product **216** and 76% enantiomeric excess was measured.

Condition E: The protocol described in condition C was followed exactly except the catalyst was transferred to the imine and the diene added in CCl_4/CH_2Cl_2 (2:1) rather than a 1:1 mixture of CH_2Cl_2/toluene. The reaction produced 296.7 mg (75% yield) of the desired product **216** and 95% enantiomeric excess was measured.

Condition F: The protocol for the optimal conditions was followed exactly except 54 mg (*S*)-VAPOL (10 mol%) was used and the catalyst was prepared in CCl_4, heating to 80°C for one hour, and then heating under high vacuum at 80°C for 30 minutes. The reaction produced 312.5 mg (79% yield) of the desired product **216** and 96% enantiomeric excess was measured.

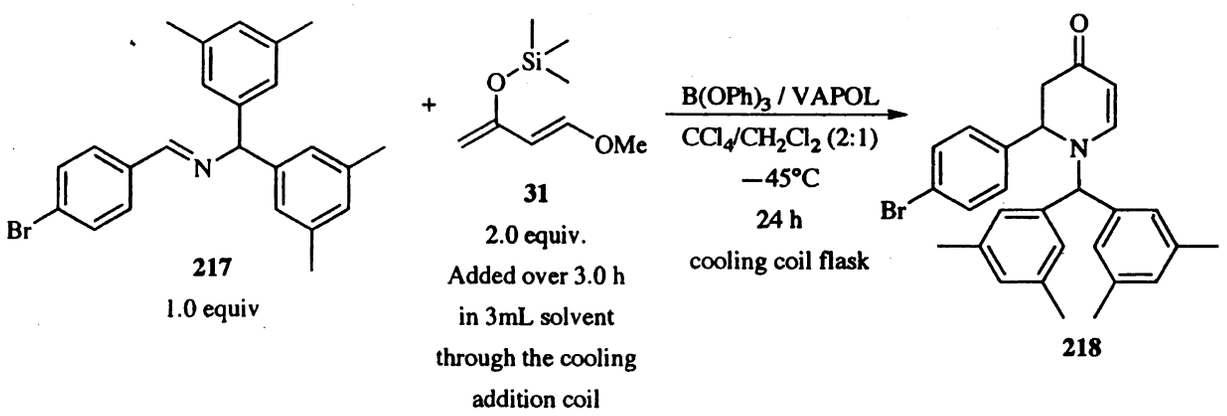
Condition G: The protocol described in condition F was followed exactly except the catalyst was transferred to the imine and the diene added in CCl_4/CH_2Cl_2 (2:1) rather than a 1:1 mixture of CH_2Cl_2/toluene. The reaction produced 249.2 mg (63% yield) of the desired product **216** and 93% enantiomeric excess was measured.

Condition H: The protocol described in condition F was followed exactly except the catalyst was transferred to the imine and the diene added in toluene rather than a 1:1 mixture of CH_2Cl_2/toluene. The reaction produced 106.8 mg (27% yield) (some product

lost during the workup) of the desired product **216** and 82% enantiomeric excess was measured.

Spectral data for compound **216** ($C_{28}H_{29}NO$):

The enantiomers could be separated by HPLC using a Chiralcel OD column (w/guard column) (95:5 hexane/isopropanol, 1.0 mL/min). Retention times: 15.02 min. (major) and 17.02 min. (minor). ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 6H), 2.28 (s, 6H), 2.81 (dd, 2H, *J*=7.1, 16.5 Hz), 2.97 (s, 1H), 4.56 (t, 1H, *J*=9.3 Hz), 5.02 (d, 1H, *J*=7.7 Hz), 6.63 (s, 2H), 6.74 (s, 2H), 6.87 (s, 1H), 6.94 (s, 1H), 7.11 (d, 1H, *J*=7.7 Hz), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.42, 21.54, 43.64, 62.03, 68.36, 98.27, 125.36, 127.32, 127.51, 128.45, 129.09, 129.83, 130.13, 138.12, 138.50, 138.54, 138.71, 139.12, 151.84, 190.20; IR ($CDCl_3$) 3024.77, 2918.67, 1653.21, 1576.04, 1495.02, 1454.51, 1379.28, 1284.75, 1221.10, 1155.51, 1142.00, 910.52 cm^{-1}; mass spectrum m/z (% rel intensity) 396 M^{+1} (22), 395 M^+ (91), 394 (12), 393 (7), 392 (6), 304 (11), 262 (6), 239 (20), 225 (14), 224 (100), 223 (24), 209 (17), 208 (6), 194 (27), 193 (9), 209 (17), 208 (6), 116 (5), 115 (9), 104 (9), 103 (13), 102 (5), 91 (6), 77 (10, 51 (5); White solid, m.p. 61-65°C. Optical rotation was taken on a 96% ee material, $[\alpha]^{20}_D$ +115.7° (c 1.575, CH_2Cl_2).



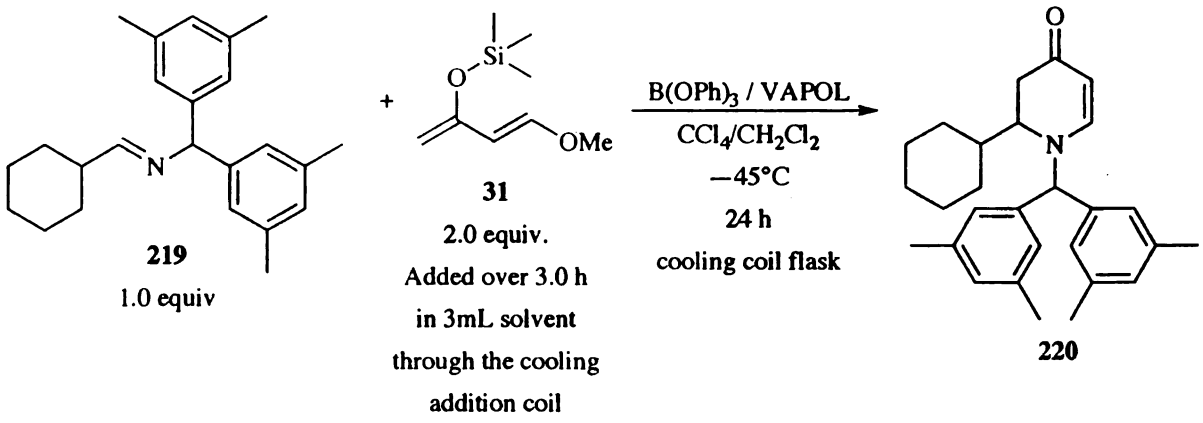
Procedure for Scheme 3.32 (*aza*-Diels-Alder reaction of imine 217):

Condition A: The protocol for the optimal conditions was followed exactly except 54 mg (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst and the catalyst was prepared by heating to 80°C rather than 55°C for one hour and then heated to 80°C rather than 55°C for 30 minutes under high vacuum. 0.4064 g (1.0 mmol) of imine **217** was used, and the catalyst was transferred to the imine and the diene was added in in CCl_4/CH_2Cl_2 (2:1) rather than a 1:1 mixture of CH_2Cl_2/toluene. The product (**218**) was purified via flash column chromatography (36 cm x 2 cm, 8:5 hexanes/ethyl acetate r_f 0.17). The reaction produced 346.3 mg (70% yield) of the desired product **218** and 86% enantiomeric excess was measured.

Spectral data for compound **218** ($C_{28}H_{28}BrNO$):

The enantiomers could be separated by HPLC using a Chiralcel OD column (w/guard column) (80/20 hexane/isopropanol, 1.0 mL/min). Retention times: 17.82 min (major) and 24.66 min (minor). ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 6H), 2.27 (s, 6H), 2.76 (dd, 2H, *J*=7.1, 16.5 Hz), 4.52 (t, 1H, *J*=7.2 Hz), 4.99 (d, 1H, *J*=8.0 Hz), 5.25 (s, 1H), 6.60 (s, 2H), 6.73 (s, 2H), 6.88 (s, 1H), 6.93 (s, 1H), 7.08 (d, 1H, *J*=7.7 Hz), 7.14 (d, 2H, *J*=8.2 Hz), 7.45 (d, 2H, *J*=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.04, 21.14, 42.92, 60.88, 68.33, 98.01, 121.90, 124.92, 127.05, 128.63, 129.57, 129.87, 131.83, 137.41, 137.82, 138.14, 138.22, 138.26, 151.38, 189.42; IR ($CDCl_3$) 3017.05, 2918.67, 1643.56, 1581.83, 1487.31, 1464.16, 1406.29, 1377.35, 1286.68, 1219.17, 1155.51, 1140.08, 1072.56, 1010.83, 910.52, 852.65, 821.78, 733.04, 646.24 cm^{-1}; mass spectrum m/z (% rel intensity) 475 M+ (27), 473 (27), 304 (11), 283 (8), 281 (19), 276 (8), 238 (18), 225 (26), 224 (58), 223 (100), 222 (12), 221 (9), 210 (29), 209 (63), 208 (61), 207 (20), 206 (8), 195 (8), 194 (38), 193 (41), 192 (8), 191 (11), 183 (11), 179 (11), 176 (14), 134 (9), 115

(16), 105 (10), 104 (8), 103 (17), 102 (11), 77 (27), 75 (9), 73 (18), 51 (12); Anal Calcd for Light yellow solid. Mp 82-88°C. Optical rotation was taken on 86% ee material, $[\alpha]^{20}_{D}$+104.0° (c 1.455, CH_2Cl_2).



219
1.0 equiv

31
2.0 equiv.
Added over 3.0 h
in 3mL solvent
through the cooling
addition coil

220

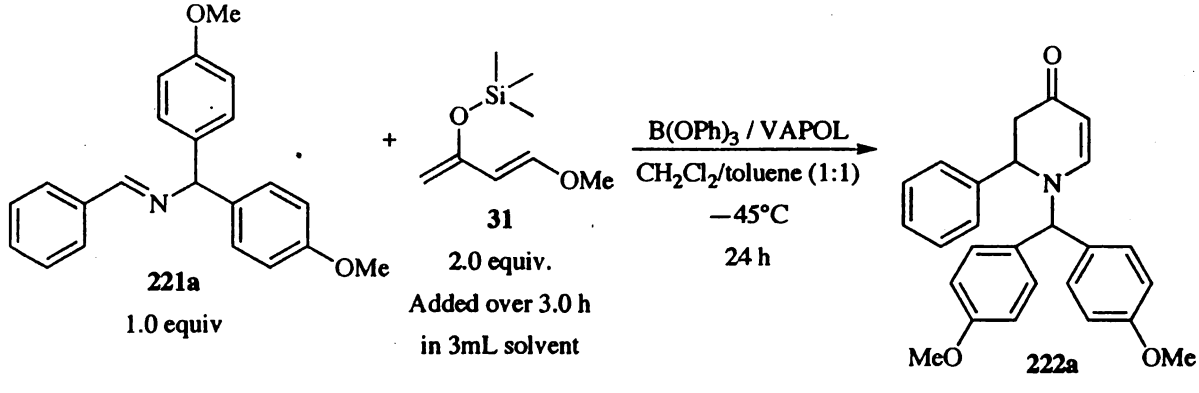
Procedures for Scheme 3.33 (*aza*-Diels-Alder reaction of imine 219):

Condition A: The protocol for the optimal conditions was followed exactly except 54 mg (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst and the catalyst was prepared by heating to 80°C rather than 55°C for one hour and then heated to 80°C rather than 55°C for 30 minutes under high vacuum. 0.3335 g (1.0 mmol) of imine **219** was used, and the catalyst was transferred to the imine and the diene was added in in CCl_4/CH_2Cl_2 (2:1) rather than a 1:1 mixture of CH_2Cl_2/toluene. The product (**220**) was then purified via flash column chromatography (36 cm x 2 cm, 8:5 hexanes/ethyl acetate r_f 0.17). The reaction produced 120.5 mg (30% yield) of the desired product **220** and 70% enantiomeric excess was measured.

Condition B: The protocol described in condition A was followed exactly except the catalyst was prepared in CCl_4 rather than CH_2Cl_2. The reaction produced 112.4 mg (28% yield) of the desired product **220** and 80% enantiomeric excess was measured.

Specctral Data for compound **220** ($C_{28}H_{35}NO$):

The enantiomers could be separated by HPLC using a Chiralcel OD column (w/guard column) (95:5 hexane/isopropanol, 1.0 mL/min). Retention times: 9.5 min. (major) and 12.5 min. (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02-1.34 (br m, 5H), 1.64-1.98 (br m, 6H), 2.04-2.50 (br m, 12H), 2.69-2.77 (dd, 1H, *J*=7.5, 16.8 Hz), 3.28 (t, 1H, *J*=5.7 Hz), 4.77 (d, 1H, *J*=7.5 Hz), 5.55 (s, 1H), 6.67 (s, 2H), 6.83-6.88 (m, 4H), 6.93 (s, 1H), 6.97 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.41, 21.47, 26.16, 26.37, 26.47, 28.52, 29.82, 36.41, 40.81, 62.02, 70.03, 96.59, 125.09, 127.52, 129.82, 130.15, 138.57, 139.97, 151.11, 191.17; IR ($CDCl_3$) 3013.19, 2926.39, 2853.08, 1635.84, 1577.97, 1450.65, 1224.95, 1157.44, 1037.83, 910.52, 852.65, 731.11cm^{-1}; mass spectrum m/z (% rel intensity) 402 M+1 (27), 401 M+ (84), 281 (22), 238 (19), 225 (32), 224 (65), 223 (100), 210 (44), 209 (73), 208 (61), 207 (19), 194 (62), 193 (14), 192 (13), 179 (13), 178 (15), 133 (12), 105 (10), 103 (12), 91 (17), 77 (20), 73 (16), 67 (10), 55 (11); white solid, mp 57-59°C. Optical rotation was taken on 70% ee material, $[\alpha]^{20}_D$ −65.8° (c 1.415, CH_2Cl_2).



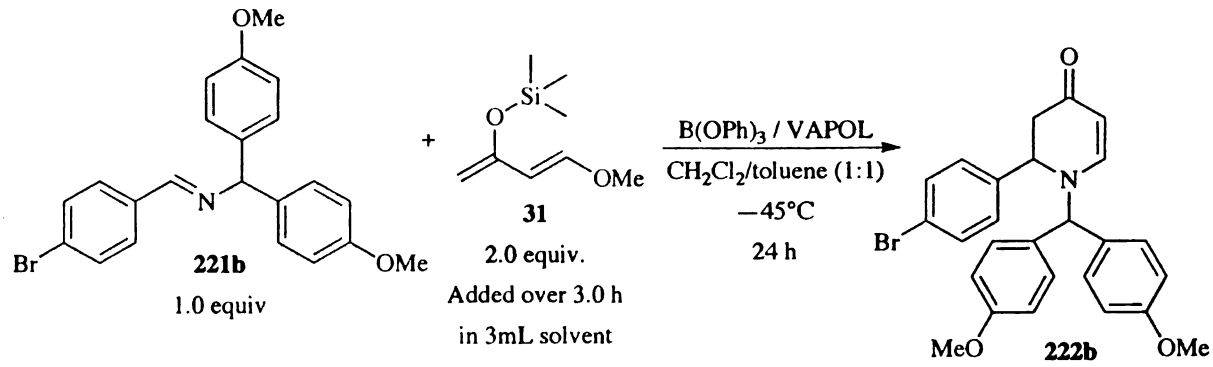
Procedure for Scheme 3.34 entry 1 (*aza*-Diels-Alder reaction of imine 221a):

Condition A: The protocol for the optimal conditions was followed exactly except 54 mg (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst. 0.3314 g (1.0

mmol) of imine **221a** was used and the product (**222a**) was purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate, r_f 0.05). The reaction produced 371.5 mg (93% yield) of the desired product **222a** and 84% enantiomeric excess was measured.

Spectral Data for compound **222a** ($C_{26}H_{25}NO_3$):

The enantiomers could be separated by HPLC using a Chiralpak AD column (95:5 hexane/isopropanol, 2.0 mL/min). Retention times: 18.8 min. (major) and 23.7 min. (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.69-2.74 (dd, 1H, *J*=8.5, 16Hz), 2.82-2.86 (dd, 1H, *J*=7, 16.5 Hz), 3.76 (s, 3H), 3.82 (s, 3H), 4.52 (t, 1H, *J*=7.8 Hz), 4.99 (d, 1H, *J*=7.5 Hz), 5.32 (s, 1H), 6.81-6.83 (m, 2H), 6.90-6.93 (m, 4H), 7.03-7.08 (m, 3H), 7.27-7.29 (m, 2H), 7.33-7.38 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ 43.97, 55.54, 55.58, 62.27, 67.22, 98.83, 114.47, 114.62, 127.48, 128.67, 128.91, 129.36, 130.67, 130.84, 130.96, 139.44, 151.59, 159.64, 159.71, 190.49; IR (neat) 731.11s, 908.59m, 1032.05s, 1136.22s, 1174.80s, 1250.03vs, 1304.05s, 1454.51m, 1512.36vs, 1576.91vs, 1608.84vs, 1643.56vs, 2842.33w, 2898.23w, 2935.45w, 2951.33w, 3003.12w, 3025.67w, 3086.64w cm^{-1}; Mass spectrum m/z (% rel intensity) 399 M+ (5), 355 (7), 342 (6), 327 (5), 289 (14), 281 (18), 268 (7), 252 (8), 228 (6), 210 (6), 209 (17), 208 (100), 207 (27), 194 (9), 191 (14), 178 (8), 147 (6), 133 (12), 115 (5), 73 (20); White solid, mp 58-74 °C. Optical rotation was taken on 93% ee material, $[\alpha]^{20}_D$ +63.7° (c 1.78, CH_2Cl_2).



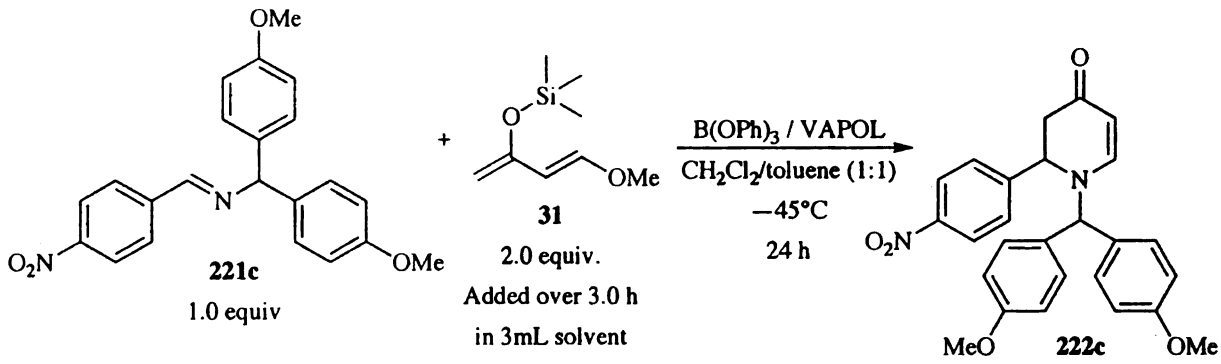
Procedure for Scheme 3.34 entry 2 (*aza*-Diels-Alder reaction of imine 221b):

Condition A: The protocol for the optimal conditions was followed exactly except 54 mg (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst. 0.4103 g (1.0 mmol) of imine **221b** was used and the product (**222b**) was purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate, r_f 0.05). The reaction produced 478.3 mg (100% yield) of the desired product **222b** and 90% enantiomeric excess was measured.

Spectral Data for compound **222b** ($C_{26}H_{24}BrNO_3$):

The enantiomers could be separated by HPLC analysis on Chiralpak AD (95:5 hexane/isopropanol, 2.0 mL/min). Retention times: 20.2 min. (major) and 30.8 min. (minor). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61-2.66 (dd, 1H, *J*=8.5, 16.5 Hz), 2.81-2.86 (dd, 1H, *J*=7.0, 16.5 Hz), 3.76 (s, 3H), 3.82 (s, 3H), 4.86 (t, 1H, *J*=7.5 Hz), 4.99 (d, 1H, *J*=8.0 Hz), 5.28 (s, 1H), 6.81-6.84 (m, 2H), 6.90 (s, 2H), 6.91 (s, 2H), 7.03-7.06 (m, 3H), 7.15 (br s, 1H), 7.16 (br s, 1H), 7.48 (br s, 1H), 7.50 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ 43.72, 55.56, 55.59, 61.59, 67.54, 99.05, 114.56, 114.69, 122.54, 128.86, 129.15, 130.38, 130.63, 130.91, 132.54, 138.54, 151.40, 159.72, 159.80, 190.04; IR (neat); 731.11m, 821.78 m, 908.59w, 1033.98s, 1136.22s, 1174.80s, 1250.03vs, 1304.05 s, 1344.56w, 1462.23m, 1512.36 vs, 1579.9vs, 1610.77s, 1641.63vs, 2816.33w, 2891.56w, 2920.10w,

2963.23w, 3002.72w, 3017.39w cm^{-1}; mass spectrum m/z (% rel intensity) 479 M+2 (4), 477 M+ (4), 452 (11), 437 (5), 280 (5), 271 (19), 253 (28), 252 (49), 251 (100), 227 (100), 212 (18), 183 (17), 169 (12), 141 (16), 115 (10), 77 (8); White solid, mp 58-74 °C. Optical rotation was taken on 93% ee material, $[\alpha]^{20}_{D}$ +63.7° (c 1.78, CH_2Cl_2).



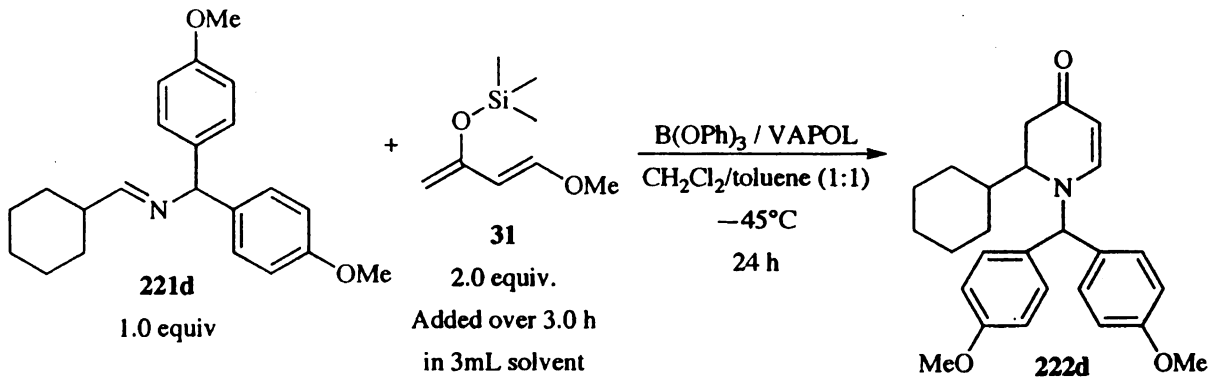
Procedure for Scheme 3.34 entry 1 (*aza*-Diels-Alder reaction of imine 221c):

Condition A: The protocol for the optimal conditions was followed exactly except 54 mg (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst. 0.3764 g (1.0 mmol) of imine **221c** was used and the product (**222c**) was purified via flash column chromatography (36 cm x 2 cm, 2.5:1 hexanes/ethyl acetate, r_f 0.13). The reaction produced 302.2 mg (68% yield) of the desired product **222c** and 81% enantiomeric excess was measured.

Spectral Data for compound **222c** ($C_{26}H_{24}N_2O_5$):

The enantiomers could be separated by HPLC using a Chiralpak AD column (75:25 hexane/isopropanol, 1.0 mL/min). Retention times: 11.79 min. (major) and 23.07 min. (minor). ^{1}H NMR ($CDCl_3$) δ 2.56 (dd, 1H, *J*=16.5, 6.3 Hz), 2.93 (dd, 1H, *J*=16.5, 7.5 Hz), 3.72 (s, 3H), 3.76 (s, 3H), 4.65 (t, 1H, *J*=6.9 Hz), 4.97 (d, 1H, *J*=7.8 Hz), 5.27 (s, 1H), 6.79-7.08 (br m, 9H), 7.43 (d, 2H, *J*=9 Hz), 8.17 (d, 2H, *J*=8.4 Hz); ^{13}C NMR

($CDCl_3$) δ 13.83, 42.57, 54.96, 60.56, 67.84, 98.67, 114.07, 114.16, 124.00, 127.64, 128.20, 129.26, 129.88, 130.26, 146.25, 147.41, 150.60, 159.22, 159.31, 188.56; IR (pure) 1032m, 1136m, 1175m, 1252s, 1348s, 1462w, 1512vs, 1578vs, 1609s, 1642s, 2850w, 2932w, 2956w, 3002w, 3057w cm^{-1}; Mass spectrum *m/z* (% rel intensity) 444 M^+ (9), 414 (5), 294 (32), 266 (17), 242 (33), 228 (64), 227 (100), 212 (32), 169 (59), 141 (60), 115 (39); Light yellow solid, mp 85-90 °C. The optical rotation was taken on an 81% ee material, $[\alpha]^{20}_D$ +69.2° (*c* 1.753, CH_2Cl_2).



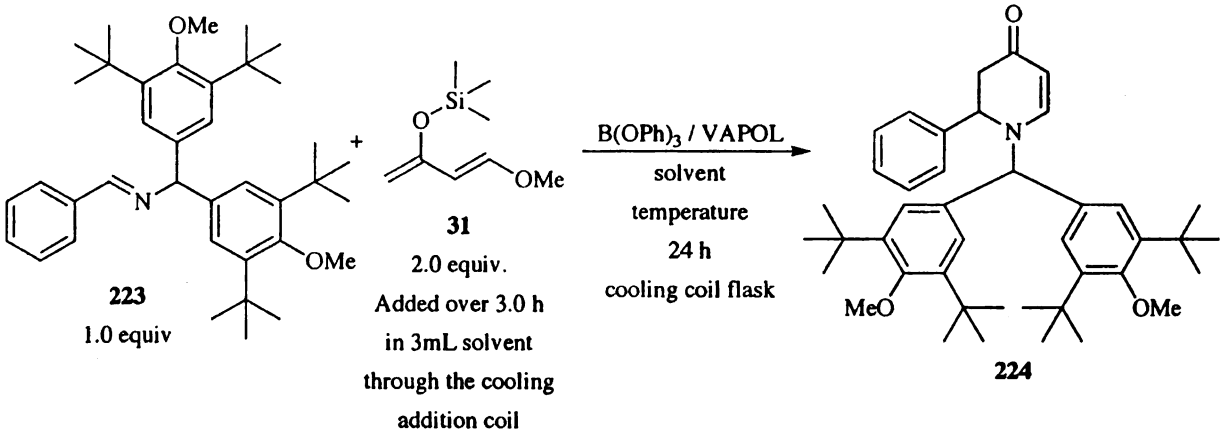
Procedure for Scheme 3.34 entry 4 (*aza*-Diels-Alder reaction of imine 221d):

Condition A: The protocol for the optimal conditions was followed exactly except 54 mg (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst. 0.3375 g (1.0 mmol) of imine **221d** was used and the product (**222d**) was purified via flash column chromatography (36 cm x 2 cm, 2.5:1 hexanes/ethyl acetate, r_f 0.13). The reaction produced 267.6 mg (66% yield) of the desired product **222d** and 56% enantiomeric excess was measured.

Spectral Data for compound **222d** ($C_{26}H_{31}NO_3$):

The enantiomers could be separated by HPLC using a Chiralpak AD column (95:5 hexane/isopropanol, 2.0 mL/min). Retention times: 12.5 min. (major) and 17.2

min. (minor). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.029-1.26 (br m, 6H), 1.66 (br s, 2H, 1.75-1.84 (br m, 3H), 1.97 (br s, 1H), 2.36 (d, 1H, *J*=17.0 Hz), 2.65-2.70 (dd, 1H, *J*=8.0 Hz, *J*=16.5 Hz), 3.27 (br t, 1H, *J*=5.5 Hz), 3.77 (s, 3H), 3.81 (s, 3H), 4.78 (d, 1H, *J*=7.5 Hz), 5.60 (s, 1H), 6.84-6.86 (br m, 2H), 6.91 (br s, 1H), 6.92 (br s, 1H), 6.97 (br s, 1H), 6.99 (br s, 1H), 7.19 (br s, 1H), 7.21 (br s, 1H); clean ^{13}C NMR was not obtained; IR (neat) 1033.98m, 1142.00m, 1174.80s, 1251.98s, 1304.05m, 1462.23m, 1512.38s, 1576.04vs, 1637.77vs, 2851.15m, 2926.39m, 3001.28w, 3025.69w, 3067.41w cm^{-1}; mass spectrum *m/z* (% rel intensity) 406 M+1 (26), 405 M+ (100), 375 (9), 323 (5) 299 (10), 295 (9), 281 (7), 252 (19), 228 (31), 208 (10), 207 (9), 170 (4), 135 (6), 133 (5), 73 (7); White solid, mp 121-125°C. Optical rotation was taken on 56% ee material, $[\alpha]^{20}_D$ −71.9° (c 1.615, CH_2Cl_2).



Procedures for Scheme 3.35 (*aza*-Diels-Alder reaction of imine 223):

Condition A: The protocol for the optimal conditions was followed exactly where 0.5558 g (1.0 mmol) of imine **223** was used. The product (**224**) was purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.34). The reaction produced 361.9 mg (58% yield) of the desired product **224** and 81% enantiomeric excess was measured.

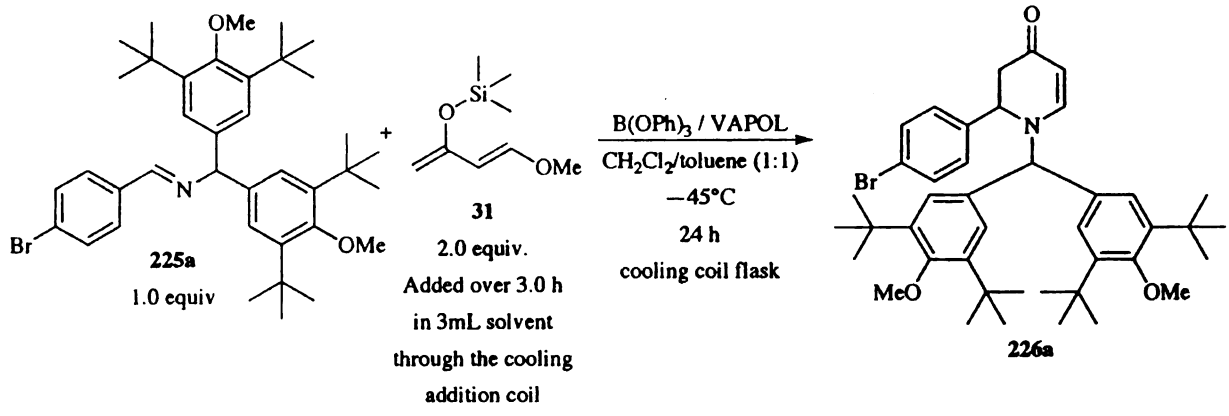
Condition B: The protocol described in condition A was followed exactly except 54 mg (10 mol%) (*S*)-VAPOL was used for the preparation of the catalyst. The reaction produced 218.4 mg (35% yield) of the desired product **224** and 40% enantiomeric excess was measured.

Condition C: The protocol described in condition A was followed exactly except 0.09 g $B(OPh)_3$ (30 mol%) and 54 mg (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst. The catalyst was transferred to the imine and the diene was added in CCl_4 rather than a 1:1 mixture CH_2Cl_2/toluene. The reaction was run at room temperature and produced 56.2 mg (9% yield) of the desired product **224** and 29% enantiomeric excess was measured.

Spectral data for compound **224** ($C_{42}H_{57}NO_3$):

The enantiomers could be separated by HPLC using a Pirckle Covalent (*R,R*) Whelk-O 1 column (75:25 hexane/isopropanol, 1.0 mL/min). Retention times: 8.74 min. (minor) and 11.50 min. (major). ^{1}H-NMR ($CDCl_3$) δ 1.28-1.38 (br m, 36 H), 2.71 (dd, 1H, *J* =16.5, 7.5 Hz), 2.9 (dd, 1H, *J*=16.5, 7.2 Hz), 3.62-3.67 (m, 6H), 4.54 (t, 1H, *J*=7.5 Hz), 5.03 (d, 1H, *J*=7.8 Hz), 5.27 (s, 1H), 6.79 (s, 2H), 6.97 (s, 2H), 7.06 (d, 1H, *J*=7.8 Hz), 7.20-7.36 (br m, 5H); ^{13}C-NMR ($CDCl_3$) δ 29.73, 31.94, 32.06, 32.12, 35.82, 43.56, 61.88, 64.27, 64.37, 68.47, 98.27, 125.86, 127.31, 127.73, 128.38, 129.05, 132.24, 132.43, 143.93, 144.12, 151.60, 190.26; mass spectrum *m/z* (% relative intensity): 624 M+1 (13), 623 M+ (32), 568 (12), 567 (27), 454 (10), 453 (56), 452 (100), 451 (11), 438 (19), 380 (8), 282 (8), 234 (4), 208 (35), 207 (10), 194 (6), 191 (7), 147 (5), 103 (6), 73 (9), 57 (13); IR (neat): cm^{-1}; 1013.72m, 1116.44m, 1225.92s, 1414.00s, 1450m, 1576.53s,

1579.87s, 1635.85m, 2962.56vs, 2892.93m, 3012.45m, 3087.43w; Light yellow wax, the optical rotation was taken on 29% ee material $[\alpha]^{20}_{D}$ +3.3° (c 1.66, $CDCl_3$).



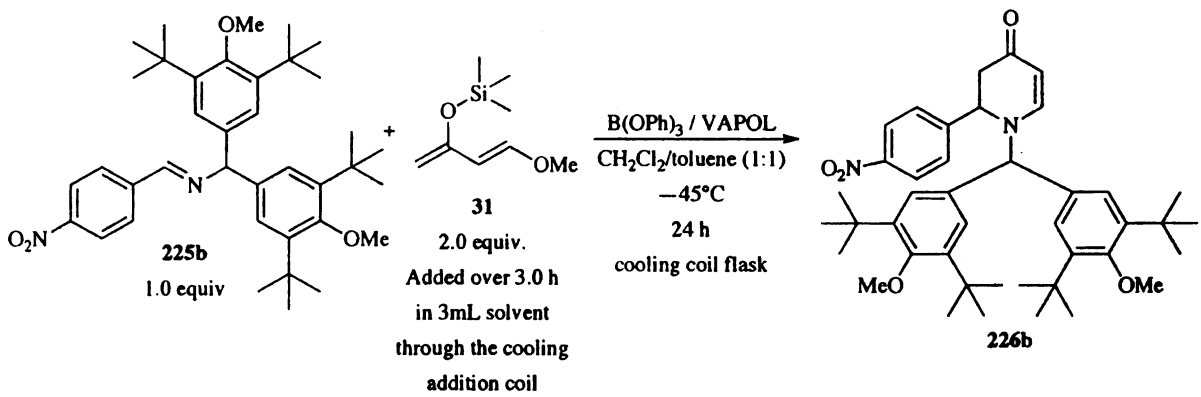
Procedure for Scheme 3.36 entry 1 (*aza*-Diels-Alder reaction of imine 225a):

Condition A: The protocol for the optimal conditions was followed exactly except 54 mg of (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst. 0.6347 g (1.0 mmol) of imine **225a** was used for the reaction and the product (**226a**) was purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.27). The reaction produced 105.4 mg (15% yield) of the desired product **226a** and 29% enantiomeric excess was measured.

Spectral Data for compound **226a** ($C_{42}H_{56}BrNO_3$):

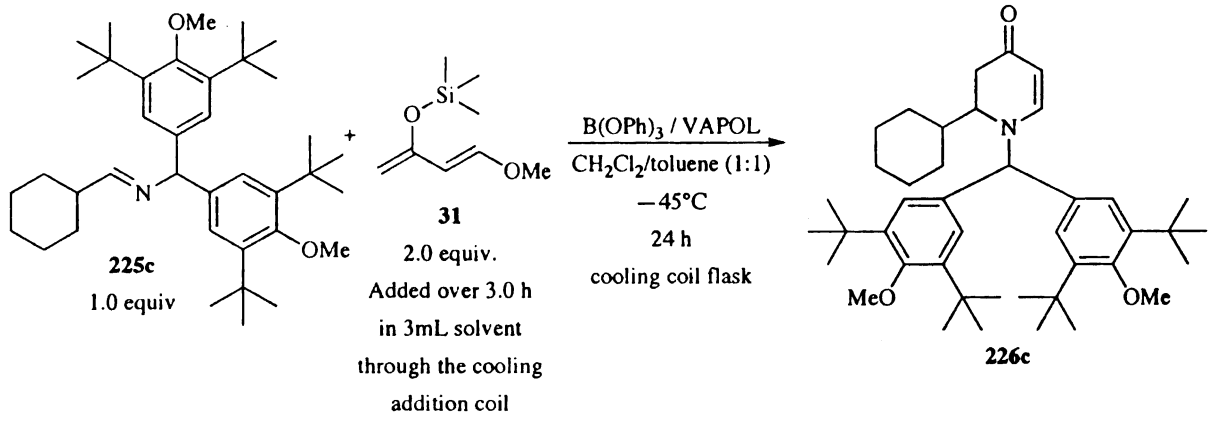
The enantiomers could be separated by HPLC using a Pirckle Covalent (*R*,*R*) Whelk-O 1 column (75:25 hexane/isopropanol, 1.0 mL/min). Retention times: 8.20 min. (minor) and 11.20 min. (major). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.34 (br s, 18H), 1.41 (br s, 18H), 2.65-2.70 (dd, 1H, *J*=7.0, 16.5 Hz), 2.93-2.98 (dd, 1H, *J*=7.0, 16.5 Hz), 3.696 (s, 3H), 3.703 (s, 3H), 4.57 (t, 1H, *J*=7.0 Hz), 5.07 (d, 1H, *J*=8.0 Hz), 5.30 (s, 1H), 6.82 (s, 2H), 7.01 (s, 2H), 7.09 (d, 1H, *J*=8.0 Hz), 7.22 (d, 2H, *J*=8.5 Hz), 7.51 (d, 2H, *J*=8.5 Hz); ^{13}C-NMR ($CDCl_3$) δ 32.16, 32.32, 36.04, 36.08, 43.52, 61.33, 64.50, 64.57, 69.19, 98.68,

122.41, 126.11, 127.75, 129.13, 132.29, 132.37, 132.40, 138.79, 144.28, 144.44, 151.67, 159.48, 159.63, 189.96; IR (neat) 1116.93s, 1143.93m, 1224.95vs, 1265.46m, 1361.92m, 1414.00s, 1448.72m, 1487.31m, 1585.69vs, 1643.56s, 2870.44m, 2908.23s, 2964.97vs, 3009.76m cm^{-1}; Mass spectrum *m/z* (% rel intensity) 703 M+2 (14) 701 M+ (12), 647 (29), 646 (76), 644 (76), 643 (12), 518 (17), 497 (22), 495 (72), 494 (100), 452 (47), 451 (100), 450 (29), 421 (15), 379 (10), 218 (6), 183 (11), 57 (21); Light yellow solid, mp 166-174°C. Optical rotation was taken on 29% ee material, $[\alpha]^{20}_{D}$ +3.6° (c 1.6, CH_2Cl_2).



Procedure for Scheme 3.36 entry 2 (*aza*-Diels-Alder reaction of imine 225b):

Condition A: The protocol for the optimal conditions was followed exactly except 54 mg of (*S*)-VAPOL (10 mol%) was used for the preparation of the catalyst. 0.6008 g (1.0 mmol) of imine **225b** was used for the reaction and a complex mixture of compounds as observed by TLC analysis was produced. None of the desired product **226b** was observed by ^{1}H-NMR.



Procedure for Scheme 3.36 entry 3 (*aza*-Diels-Alder reaction of imine 225c):

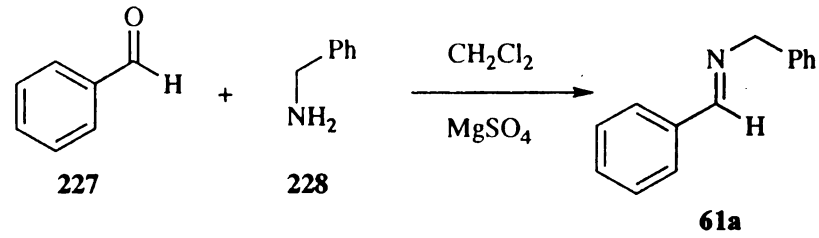
Condition A: The protocol for the optimal conditions was followed exactly except 54 mg of (*S*)-VAPOL was used for the preparation of the catalyst. 0.5619 g (1.0 mmol) of imine **225c** was used and the product (**226c**) was purified via flash column chromatography (36 cm x 2 cm, 2:1 hexanes/ethyl acetate r_f 0.39). The reaction produced 132.3 mg (21% yield) of the desired product **226c** and 30% enantiomeric excess was measured.

Spectral Data for compound **226c** ($C_{42}H_{63}NO_3$):

The enantiomers could be separated by HPLC using a Pirckle Covalent (*R,R*) Whelk-O 1 column (75:25 hexane/isopropanol, 1.0 mL/min). Retention times: 5.80 min. (minor) and 7.30 min. (major). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.17-1.27 (br m, 5H), 1.33 (br s, 18H), 1.41 (br s, 18H), 1.69-1.71 (m, 2H), 1.81-1.85 (m, 2H), 1.92-1.94 (m, 1H), 2.02-2.04 (br s, 1H), 2.43 (d, 1H, *J*=16.5 Hz), 2.73-2.79 (dd, 1H, *J*=9.0, 17.0 Hz), 3.40 (br t, 1H, *J*=7.5 Hz), 3.70 (s, 3H), 3.71 (s, 3H), 4.86 (d, 1H, *J*=7.5 Hz), 5.57 (s, 1H), 6.86 (s, 2H), 6.88 (d, 1H, *J*=7.5 Hz), 7.16 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 26.40, 26.73, 26.78, 28.76, 29.93, 32.14, 32.32, 36.01, 36.08, 36.67, 41.92, 62.15, 64.47, 64.55, 70.31, 96.73, 125.67, 127.94, 132.92, 133.92, 144.14, 144.34, 151.14, 159.38, 159.54, 191.25; IR

(neat) 1116.m 1147.79w, 1224.95vs, 1265.46m, 1361.92w, 1392.78m, 1414.00s, 1448.72m, 1583.76 vs, 1637.77s, 2856.43m, 2881.29w, 2924.69vs, 2963.04vs, 3006.18w cm^{-1}; Mass spectrum *m/z* (% rel intensity) 631 M+1 (13), 630 M+ (100), 629 (30), 575 (13), 574 (39), 573 (83), 453 (19), 452 (25), 411 (5); White solid, mp 93-95°C. Optical rotation was taken on 30% ee material, $[\alpha]^{20}_{D}$ −33.3° (c 1.505, CH_2Cl_2).

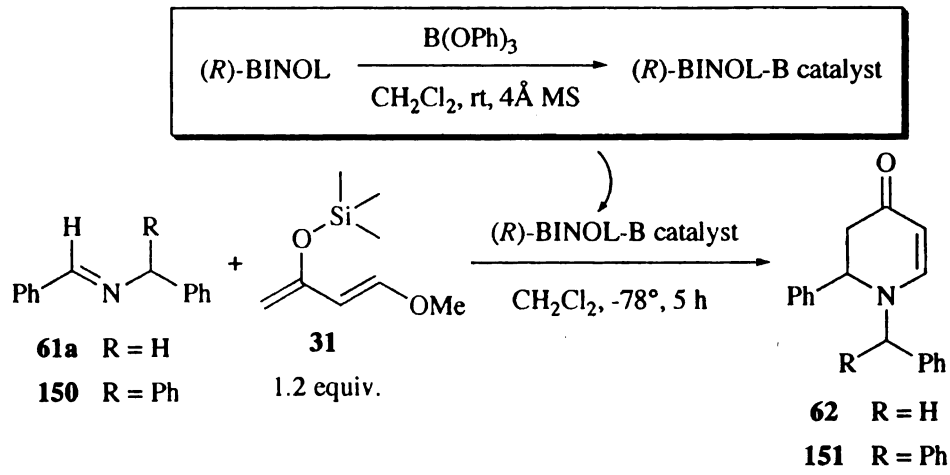
7.3 Experimental Procedures and Characterizations Data for Chapter Four



227 228 61a

Preparation of imine 61a:

To a flame dried round bottom flask equipped with a magnetic stir bar was added benzaldehyde (5.23 g, 49.2 mmol) followed by $MgSO_4$ (7.5 g) and CH_2Cl_2 (100 mL). To this solution was then added benzylamine (5.20 g, 49.2 mmol). The resulting solution was allowed to stir at room temperature for 5.5 hours. At the end of the reaction time, the solution was filtered to remove the $MgSO_4$, and the solvent was removed under reduced pressure. The resulting imine was an oil which was purified by bulb-to-bulb distillation (bp 133 °C, 3 mm Hg) to give 6.24 g of **61a** (67% yield). The spectral data matched those reported in the literature.[1] ^{1}H-NMR ($CDCl_3$) δ 4.86 (s, 2H), 7.28-7.47 (m, 8H), 7.81-7.84 (m, 2H), 8.41 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 64.76, 126.70, 127.70, 128.00, 128.22, 128.32, 130.48, 135.93, 139.07, 161.65.



Procedures for Scheme 4.2 (*aza*-Diels-Alder reactions following Yamamoto's Conditions[19]):

Entry 1: To a flame dried round bottom flask equipped with a magnetic stir bar was added 4 Å molecular sieves (1.0 g), $B(OPh)_3$ (101 mg, 0.35 mmol) and (*R*)-BINOL (100 mg, 0.35 mmol). To this was added CH_2Cl_2 (10 mL) and the reaction mixture was allowed to stir for one hour at room temperature. The reaction was then cooled to 0 °C at which time the imine **61a** (68 mg, 0.35 mmol) was added in CH_2Cl_2 (1.0 mL). This was allowed to stir for 5 minutes and then the reaction mixture was cooled to – 78 °C and the diene (**31**) (84 μL, 0.42 mmol) was added in CH_2Cl_2 (1.0 mL) dropwise over about 3 minutes. The reaction was allowed to stir at —78 °C for an additional 5 hours. Suction filtration was then used to remove the molecular sieves. The resulting mixture was then washed with water (30 mL) and saturated sodium bicarbonate (50 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. The product was purified via flash column chromatography (36 cm x 2 cm), R_f = 0.06 (hexanes/ethyl acetate 2:1), to give 62.3 mg (68% yield) of the desired product **62**. Spectral data was collected and was found to be identical to that in the literature.[19] The enantiomers could be separated by HPLC using a

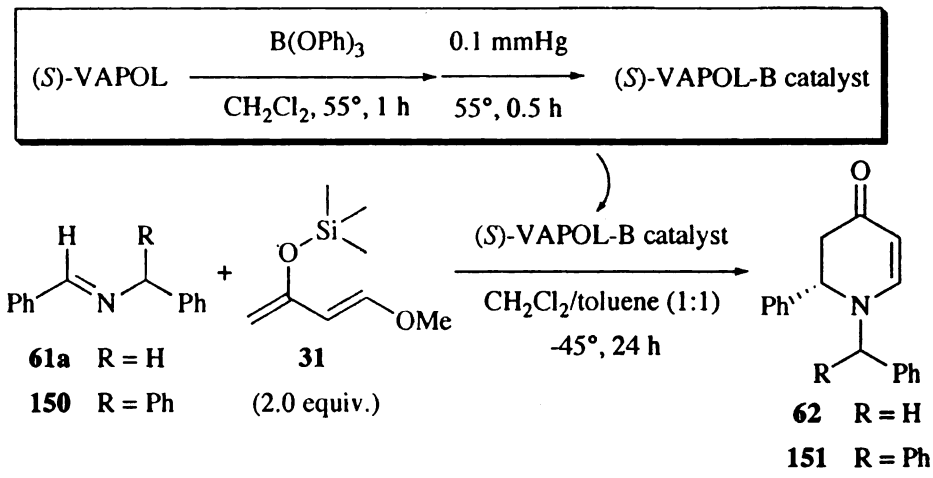
Chiralcel OJ-H column (80:20 hexane/isopropanol, 1mL/min). Retention times: 26.15 min. (major) and 31.81 min. (minor). The product **62** obtained from the reaction was determined to be 85.5% ee.

Entry 2: The protocol as described for entry 1 was followed exactly except 10 mg (*R*)-BINOL (0.035 mmol, 10 mol%) was used for the preparation of the catalyst. This reaction produced 38 mg of **62** (41% yield) and 40% ee was measured.

Entry 3: The protocol as described for entry 1 was followed exactly except 10.1 mg $B(OPh)_3$ (0.035 mmol, 10 mol%) and 10 mg (*R*)-BINOL (0.035 mmol, 10 mol%) was used for the preparation of the catalyst. This reaction produced less than 10 mg of **62** (<5 % yield) and the ee was not measured.

Entry 4: The protocol as described for entry 1 was followed exactly except 94.9 mg (0.35 mmol) of the benzhydryl imine **150** was used rather than imine **61a**. None of the desired product **151** was observed.

Entry 5: The protocol as described for entry 2 was followed exactly except 94.9 mg (0.35 mmol) of the benzhydryl imine **150** was used rather than imine **61a**. None of the desired product **151** was observed.



Procedures for Scheme 4.3 (*aza*-Diels-Alder reactions using the optimal conditions from chapter 2):

Entry 1: To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (0.3125g, 1.0 mmol) and (*S*)-VAPOL (54 mg, 0.1 mmol). To this was added CH_2Cl_2 (2 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours yielding the (*S*)-VAPOL-boron catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 2.0 mL of a 1:1 mixture of toluene and CH_2Cl_2 (in two portions). The catalyst solution was transferred by syringe to a solution of the imine prepared as immediately below.

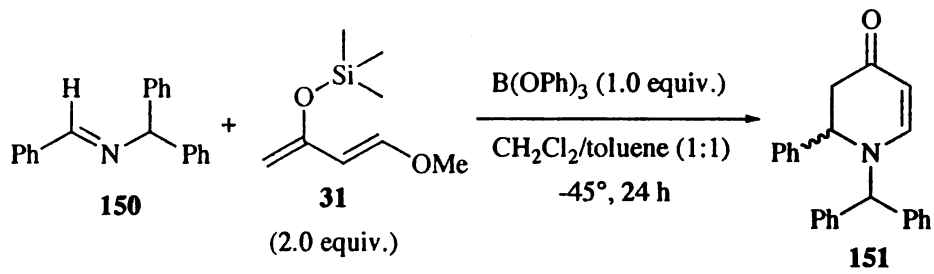
To a flame dried, argon purged homemade flask with a cold addition coil (see Figure 2.4) equipped with a stir bar was added the imine (0.195 mg, 1.0 mmol). The flask was topped with two rubber septa and the (*S*)-VAPOL-boron catalyst was added in two 1.0 mL portions of toluene/CH_2Cl_2 (1:1) directly to the bottom of the flask by a syringe equipped with a long needle. This was allowed to stir for 5-10 minutes at room

temperature and then cooled to –45 °C. Meanwhile, in a separate flame dried 5 or 10 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) (0.38 mL, 2.0 mmol) and toluene/CH_2Cl_2 (1:1) (3.0 mL). The diene was taken up in a syringe and added over 3.0 hours via syringe pump through the cold addition coil. The reaction was then allowed to stir at –45 °C for the duration of the reaction (for reaction times see Table 3). After completion of the reaction, saturated sodium bicarbonate (~20 mL) was added to the reaction flask at –45 °C. This was then transferred to a separatory funnel and diluted with distilled water (25 mL) and extracted with three or four 30-40 mL portions of CH_2Cl_2. TLC analysis of the organic layer after extraction showed a small amount of two compounds in addition to the dihydropyridinone. The crude ^{1}H NMR confirmed that only a small amount of other products were present. Isolation gave small amounts of materials that had very complicated ^{1}H NMR spectra with broad peaks and assignment of structure was not made. These compounds were not observable by TLC after treatment of the reaction mixture with 1N HCl diluted with THF. Therefore, the combined organic layers were placed in a 250 mL round bottom flask and the solvent was then removed via rotary evaporation. The flask was then equipped with a stir bar and cooled in an ice bath. To this was then added a previously cooled (0 °C) 20:1 mixture of THF and 1N HCl (50 mL) at which time the flask was removed from the ice bath and allowed to stir (monitored by TLC) until the undesired spots close to the desired product disappeared (usually less than one hour). This was then transferred to a separatory funnel containing water (75-100 mL) followed by extraction of the crude product with four 50 mL portions of CH_2Cl_2. The combined organic layers were then dried with magnesium sulfate, filtered, and solvent was removed via rotary evaporation. The product **62** was then

purified via flash column chromatography (36 cm x 2 cm) , R_f = 0.06 (hexanes/ethyl acetate 2:1) yielding 131.7 mg of **62** (50% yield). Spectral data was collected and was found to be identical to that in the literature.[19] The enantiomers could be separated by HPLC analysis on Chiralcel OJ-H (80:20 hexane/isopropanol, 1mL/min), retention times: 26.15 min. (major) and 31.81 min. (minor). The product **62** obtained from the reaction was determined to be 36% ee.

Entry 2: The protocol as described for entry 1 was followed exactly except 0.271 g (1.0 mmol) of the benzhydryl imine **150** was used. The reaction produced 319.3 mg (94% yield) of the desired product **150** and 90% enantiomeric excess was measured.

Entry 3: The protocol as described for entry 1 was followed exactly except 0.271 g (1.0 mmol) of the benzhydryl imine **150** was used and 29.1 mg of (*R*)-BINOL (10 mol%) was used for the preparation of the catalyst. The reaction produced 88.2 mg (26% yield) of the desired product **151** and 23% enantiomeric excess was measured.



Procedures for Scheme 4.4 (*aza*-Diels-Alder reactions of imine 150 using $B(OPh)_3$):

Entry 1: To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (0.3125g, 1.0 mmol). To this was added CH_2Cl_2 (2 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one

hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 2.0 mL of a 1:1 mixture of toluene and CH_2Cl_2 (in two portions). The catalyst solution was transferred by syringe to a solution of the imine prepared as immediately below.

To a flame dried, argon purged homemade flask with a cold addition coil (see Figure 2.4) equipped with a stir bar was added the imine (0.195 mg, 1.0 mmol). The flask was topped with two rubber septa and the $B(OPh)_3$ was added in two 1.0 mL portions of toluene/CH_2Cl_2 (1:1) directly to the bottom of the flask by a syringe equipped with a long needle. This was allowed to stir for 5-10 minutes at room temperature and then cooled to –45 °C. Meanwhile, in a separate flame dried 5 or 10 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) (0.38 mL, 2.0 mmol) and toluene/CH_2Cl_2 (1:1) (3.0 mL). The diene was taken up in a syringe and added over 3.0 hours via syringe pump through the cold addition coil. The reaction was then allowed to stir at –45 °C for the duration of the reaction (for reaction times see Table 3). After completion of the reaction, saturated sodium bicarbonate (~20 mL) was added to the reaction flask at –45 °C. This was then transferred to a separatory funnel and diluted with distilled water (25 mL) and extracted with three or four 30-40 mL portions of CH_2Cl_2. TLC analysis of the organic layer after extraction showed a small amount of two compounds in addition to the dihydropyridinone. The crude ^{1}H-NMR confirmed that only a small amount of other products were present. Isolation gave small amounts of materials that had very complicated ^{1}H NMR spectra with broad peaks and assignment of structure was not made. These compounds were not observable by TLC after treatment

of the reaction mixture with 1N HCl diluted with THF. Therefore, the combined organic layers were placed in a 250 mL round bottom flask and the solvent was then removed via rotary evaporation. The flask was then equipped with a stir bar and cooled in an ice bath. To this was then added a previously cooled (0 °C) 20:1 mixture of THF and 1N HCl (50 mL) at which time the flask was removed from the ice bath and allowed to stir (monitored by TLC) until the undesired spots close to the desired product disappeared (usually less than one hour). This was then transferred to a separatory funnel containing water (75-100 mL) followed by extraction of the crude product with four 50 mL portions of CH_2Cl_2. The combined organic layers were then dried with magnesium sulfate, filtered, and solvent was removed via rotary evaporation. The product **151** was then purified via flash column chromatography (36 cm x 2 cm) to give 88 mg (26% yield) of the desired product **151**.

Entry 2: The protocol as described in entry 1 was followed exactly, except $B(OPh)_3$ was purchased from Aldrich and used directly without taking it through the catalyst preparation cycle. This reaction produced 146 mg (46% yield) of the desired product **151**.

Entry 3: The protocol as described in entry 2 was followed exactly, except the reaction was done on a 0.369 mmol (of the imine **150**) scale and the $B(OPh)_3$ was purified by distillation and stored in a glove box before use. This reaction produced 30.9 mg (25 % yield) of the desired product **151**.

NMR Titration Experiment with (*R*)-VAPOL-boron Catalyst and Imine 150:

To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added (*R*)-VAPOL (0.0.957 g, 1.77 mmol) and phenol (0.333g, 3.54 mmol). To this was added CH_2Cl_2 (15 mL) followed by $BH_3{\cdot}SMe_2$ (1.77 mL, 3.54 mmol, 2 M solution in toluene) and water (0.031 mL, 1.77 mmol). The flask was sealed with the stopcock and heated to 75 °C for one hour. After one hour, the solvent was removed via high vacuum and heated to 100°C and left under high vacuum for 0.5 hours yielding the (*R*)-VAPOL-boron catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 5 mL of a $CDCl_3$ (stored over 4Å M.S.) to make a 0.35 M solution. Meanwhile, 50 mg (0.184 mmol) of imine **150** was added to 10 separate flame dried argon purged 2 mL volumetric flasks. To each volumetric flask was then transferred via syringe a different amount of the (*R*)-VAPOL-boron catalyst solution (see table below). After the addition of the catalyst, the solutions were diluted to the 2 mL mark on the volumetric flask to ensure the concentration of the imine was maintained. One separate flask was prepared using only the imine with no catalyst. This was used as the reference sample. Approximately 0.8 mL of each volumetric flask was then transferred via syringe to a clean and dry NMR tube and capped immediately to ensure no air was introduced to the system. The ^1H NMR's were then taken for each of the different catalyst/imine ratios. Recorded in the table are the exact concentrations of imine **150** and (*R*)-VAPOL-boron catalyst, and the observed chemical shifts for the complexed species for the benzhydryl proton (H^1) and the imine sp^2 C-H (H^2).

NMR	[imine **150**] (M)	[(*R*)-VAPOL-boron catalyst] (M)	Obs Chem Shift (H^1, ppm)	Obs Chem Shift (H^2, ppm)
1	0.092	0.0046	under aromatic	under aromatic
2	0.092	0.00575	6.142	under aromatic
3	0.092	0.00775	6.035	8.163
4	0.092	0.0115	5.926	8.255
5	0.092	0.023	5.852	8.317
6	0.092	0.03075	5.791	8.37
7	0.092	0.046	5.735	8.405
8	0.092	0.069	5.713	8.428
9	0.092	0.092	5.7	8.44
10	0.092	0.1505	5.694	8.447

NMR Titration Experiment with (*S*)-VAPOL-boron Catalyst and the Product 151.

To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added (*S*)-VAPOL (0.0.957 g, 1.77 mmol) and phenol (0.333g, 3.54 mmol). To this was added CH2Cl2 (15 mL) followed by $BH_3{\cdot}SMe_2$ (1.77 mL, 3.54 mmol, 2 M solution in toluene) and water (0.031 mL, 1.77 mmol). The flask was sealed with the stopcock and heated to 75 °C for one hour. After one hour, the solvent was removed via high vacuum and heated to 100°C and left under high vacuum for 0.5 hours yielding (*S*)-VAPOL-boron catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 5 mL of a $CDCl_3$ (stored over 4Å M.S.) to make a 0.35 M solution. Meanwhile, 62.5 mg (0.184 mmol) of product **151** was added to 10 separate flame dried argon purged 2 mL volumetric flasks. To each volumetric flask was then transferred via syringe a different amount of the (*S*)-VAPOL-boron catalyst solution (see table below). After the addition of the catalyst, the solutions were diluted to the 2 mL mark on the volumetric flask to

ensure the concentration of the imine was maintained. One separate flask was prepared using only the imine with no catalyst. This was used as the reference sample. Approximately 0.8 mL of each volumetric flask was then transferred via syringe to a clean and dry NMR tube and capped immediately to ensure no air was introduced to the system. The ^{1}H-NMR's were then taken for each of the different catalyst/imine ratios. Recorded in the table are the exact concentrations of product **151** and (*S*)-VAPOL-boron catalyst, and the observed chemical shifts for the complexed species for the vinylic proton adjacent to the carbonyl.

NMR	[product **3b**] (M)	[(*S*)-VAPOL-boron catalyst **8**] (M)	Obs Chem Shift (ppm)
1	0.092	0.0046	5.338
2	0.092	0.00575	5.337
3	0.092	0.00775	5.335
4	0.092	0.0115	5.331
5	0.092	0.023	5.321
6	0.092	0.03075	5.314
7	0.092	0.046	5.301
8	0.092	0.069	5.292
9	0.092	0.092	5.288

NMR Titration Experiment with $B(OPh)_3$ and Imine 150.

50 mg (0.184 mmol) of imine **150** was added to 10 separate flame dried argon purged 2 mL volumetric flasks. To each volumetric flask was then transferred via syringe a different amount of a 0.35 M solution of $B(OPh)_3$ **5** (see table below) prepared using $B(OPh)_3$ that had been distilled immediately before use. After the addition of the $B(OPh)_3$, the solutions were diluted to the 2 mL mark on the volumetric flask to ensure the concentration of the imine was maintained. One separate flask was prepared using only the imine with no catalyst. This was used as the reference sample. Approximately

0.8 mL of each volumetric flask was then transferred via syringe to a clean and dry NMR tube and capped immediately to ensure no air was introduced to the system. The ^{1}H-NMR's were then taken for each of the different catalyst/imine ratios. Recorded in the table are the exact concentrations of imine **150** and $B(OPh)_3$, and the observed chemical shifts for the complexed species for the benzhydryl proton (H^1) and the imine sp^2 C-H (H^2).

NMR	[imine **150**] (M)	[$B(OPh)_3$] (M)	Obs Chem Shift (H^1, ppm)	Obs Chem Shift (H^2, ppm)
1	0.092	0.0046	5.518	8.331
2	0.092	0.00575	5.517	8.329
3	0.092	0.00775	5.52	8.332
4	0.092	0.0115	5.522	8.334
5	0.092	0.023	5.526	8.338
6	0.092	0.03075	5.53	8.342
7	0.092	0.046	5.536	8.347
8	0.092	0.069	5.544	8.353
9	0.092	0.092	5.556	8.364
10	0.092	0.1505	5.59	8.392

NMR Titration Experiment with $B(OPh)_3$ and the Product 151.

62.5 mg (0.184 mmol) of product **151** was added to 10 separate flame dried argon purged 2 mL volumetric flasks. To each volumetric flask was then transferred via syringe a different amount of a 0.35 M solution of $B(OPh)_3$ (see table below) prepared using $B(OPh)_3$that had been distilled immediately before use. After the addition of the $B(OPh)_3$, the solutions were diluted to the 2 mL mark on the volumetric flask to ensure the concentration of the imine was maintained. One separate flask was prepared using only the imine with no catalyst. This was used as the reference sample. Approximately 0.8 mL of each volumetric flask was then transferred via syringe to a clean and dry NMR

tube and capped immediately to ensure no air was introduced to the system. The ^{1}H-NMR's were then taken for each of the different catalyst/imine ratios. Recorded in the table are the exact concentrations of product **151** and $B(OPh)_3$, and the observed chemical shifts for the complexed species for the vinylic proton adjacent to the carbonyl.

NMR	[product **151**] (M)	[$B(OPh)_3$] (M)	Obs Chem Shift (ppm)
1	0.092	0.0046	5.344
2	0.092	0.00575	5.348
3	0.092	0.00775	5.348
4	0.092	0.0115	5.351
5	0.092	0.023	5.354
6	0.092	0.03075	5.359
7	0.092	0.046	5.365
8	0.092	0.069	5.374
9	0.092	0.092	5.383
10	0.092	0.1505	5.408

NMR Titration Analysis[116]

The stability constant comes from the NMR titration data by fitting the data to the two site model. This assumes a 1:1 stoichiometery and fast exchange between the bound and non bound forms of the NMR observed species. In the present case titrations were configured so that the chemical shifts of reporter protons on the starting imine or the product amine (both termed ligand in the following discussion), were followed as a function of varying catalyst concentration.

Any observed ^{1}H chemical shift is the mole fraction weighted average of the shifts observed in the free and complexed molecule.

$$\delta_{obs} = X_L \delta_L + X_{LCat} \delta_{LCat} \quad (1)$$

where X_L and X_{LCat} are the mole fractions of ligand that are free and bound to catalyst and δ_L and δ_{LCat} are the chemical shifts of the reporter protons in the free and bound states. For the formation of a 1:1 complex the following relationships describe the equilibrium conditions.

$$[L] + [LCat] = [L]_o \quad (2)$$

$$[Cat] + [LCat] = [Cat]_o \quad (3)$$

$$K_a = [LCat]/[L][Cat] \quad (4)$$

$[L]_o$ and $[Cat]_o$ are the known solution compositions, and [L], [Cat] and [LCat] are the equilibrium concentration of ligand, catalyst and complex respectively. The following quadratic equation relates the equilibrium conditions to the known total concentrations

$$[LCat] = (a - b^{1/2})/2K_a \quad (5)$$

where

$$a = K_a[L]_o + K_a[Cat]_o + 1 \quad (6)$$

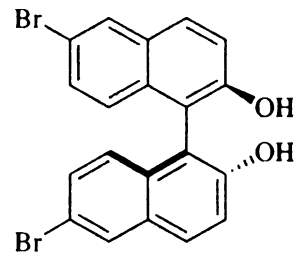
$$b = (K_a[L]_o - K_a[Cat]_o)^2 + 2K_a[L]_o + 2K_a[Cat]_o + 1 \quad (7)$$

This now allows solutions of equation (1) so that δ_{obs} can be calculated for any desired solution composition and K_a.

K_a is obtained from the NMR data by calculating a titration curve and matching it to the experimental data by adjusting K_a and δ_{Lcat}. This is accomplished within an Excel spreadsheet, and using the 'Solver' tool to minimize the global error between the experimental data and the calculated curve.

7.4 Experimental Procedures and Characterizations Data for Chapter Five

Preparation of BINOL Derivatives:[117-119]



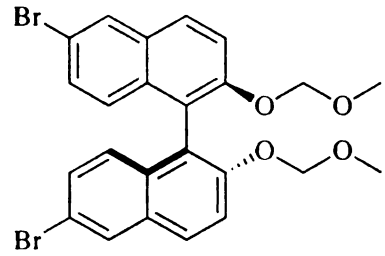
282

Preparation of **282**:

To a flamed dried 500 mL round bottom flask equipped with a magnetic stir bar was added (*S*)-BINOL (**59**, 9.5 g, 33.2 mmol) and CH_2Cl_2 (181 mL) and the reaction mixture was then cooled to −78°C and Br_2 (4.56 mL, 88.6 mmol) was added over 30 min. The reaction mixture was allowed to stir at −78°C for 30 min at which time the cooling bath was removed and the reaction was warmed to room temperature over 2.5 hours. The reaction mixture was then transferred to a separatory funnel and washed with 10% sodium bisulfate, water, and sodium chloride. The organic extracts were combined, dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. Purification was accomplished by recrystallization from benzene/cyclohexane to give 10.66 g of **282** (72% yield) with ^{1}H NMR matching perfectly to the reference.[116]

Spectroscopic data for **282** ($C_{20}H_{12}Br_2O_2$):

^{1}H NMR ($CDCl_3$) δ 4.97 (s, 2H), 6.93 (d, 2H, *J*=9.0 Hz), 7.33-7.38 (m, 4H), 7.87 (d, 2H, *J*=9.0 Hz), 8.03 (d, 2H, *J*=1.8 Hz).



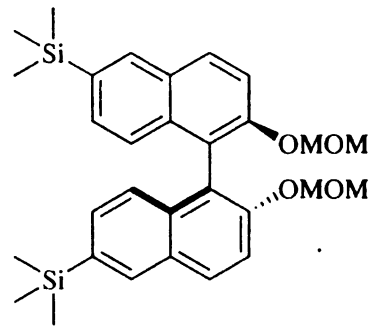
297

Preparation of **297**[118]:

To a flamed dried 500 mL round bottom flask equipped with a magnetic stir bar was added NaH (3.28 g, 82 mmol, 60% by wt. in mineral oil), diluted with DMF (7.7 mL) and cooled to 0°C. To the solution was then added (*S*)-6,6'-dibromo-BINOL (**282**, 5.122 g, 11.5 mmol) as a solution in DMF (76.7 mL). The reaction was allowed to stir at 0°C for 30 min at which time MOMCl (3.07 mL, 40.4 mmol) was added dropwise. Stirring was continued at 0°C for 3 hours. The reaction was quenched with saturated sodium bicarbonate and after workup yielded 6.25g **297** (quantitative yield) with the ^{1}H NMR matching perfectly to the reference[3] and was used in the next step without further purification.

Spectral data for **297** ($C_{24}H_{20}Br_2O_4$):

^{1}H NMR ($CDCl_3$) δ 3.13 (s, 6H), 5.01 (dd, 4H, *J*=33.3, 6.9 Hz), 6.95 (dd, 2H, *J*=9.0, 0.6 Hz), 7.23 (m, 2H), 7.57 (d, 2H, *J*=9 Hz), 7.83 (d, 2H, *J*=9 Hz), 8.00 (d, 2H, *J*=2.0 Hz).



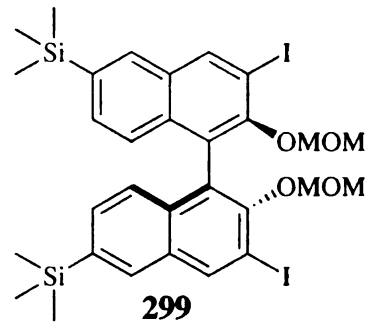
298

Preparation of **298**:[119]

To a flamed dried 500 mL round bottom flask equipped with a magnetic stir bar was added (*S*)-6,6'-dibromo-MOM-BINOL (**297**, 6.25 g, 11.5 mmol) and THF (98 mL) and the reaction mixture was then cooled to −78°C. To the cooled solution was added *n*-BuLi (17.97 mL, 28.75 mmol, 1.6 M solution in hexanes) and was allowed to stir for one hour at which time TMSCl (4.36 mL, 34.5 mmol) was added. The reaction mixture was then allowed to stir for an additional 3 hours and then quenched with water and diluted with ether. The water layer was extracted three times with ether and the organic layers were combined and washed with water followed by brine. The organic extracts were the combined, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification was done by flash column chromatography and the product was eluted with 3:1 hexanes/ethylacetate giving 7.75 g of **298** (91% yield) with ^{1}H NMR matching the data from the reference.[119]

Spectroscopic data for **298** ($C_{30}H_{38}O_4Si_2$):

^{1}H NMR ($CDCl_3$) δ 0.27 (s, 18H), 3.15 (s, 6H), 5.00 (dd, 4H, *J*=6.9, 21.3 Hz), 7.1 (d, 2H, *J*=8.4 Hz), 7.31 (dd, 2H, *J*=0.9, 8.1 Hz), 7.55 (d, 2H, *J*=9.3 Hz), 7.93 (d, 2H, *J*=8.7 Hz), 8.00 (s, 2H).



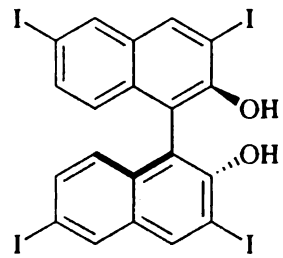
299

Preparation of **299**:[119]

To a flamed dried 500 mL round bottom flask equipped with a magnetic stir bar was added (*S*)-6,6'-ditrimethylsilyl-MOM-BINOL (**298**, 9.10 g, 17.54 mmol) and THF (90 mL) and the resulting solution was cooled to −78°C. To the reaction mixture was then added *sec*-BuLi (50.3 mL, 70.2 mmol, 1.4 M in cyclohexane) and was allowed to stir at −78°C for 1.5 hours. To the reaction was then added I_2 (26.7 g, 105.2 mmol) in THF (50 mL). After stirring for 2 hours, the reaction was diluted with methanol and transferred to a separatory funnel containing water and ethylacetate. The mixture was extracted four times with ethylacetate. The organic layers were combined and washed with 10% sodium bisulfate, water, sodium bicarbonate, and brine. The organic layers were dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give 12.66 g of crude **299** (93.7% yield) with ^{1}H NMR data matching exactly that from the reference[4]. The crude **299** was used without purification for the next step.

Spectroscopic data for **299** ($C_{30}H_{36}I_2O_4Si_2$):

^{1}H NMR ($CDCl_3$) δ 0.28 (s, 18H), 2.62 (s, 6H), 4.71 (dd, 4H, *J*=5.7, 36.6 Hz), 7.10 (dd, 2H, *J*=0.6, 8.4 Hz), 7.38 (dd, 2H, *J*=1.2, 8.7), 7.88 (s, 2H), 8.52 (s, 2H).



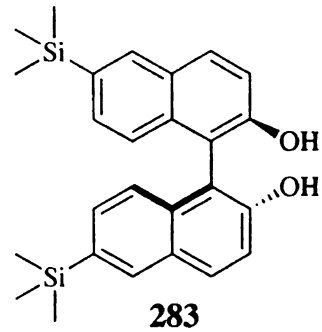
281

Preparation of **281**:[119]

To a flamed dried 500 mL round bottom flask equipped with a magnetic stir bar was added (*S*)-6,6'-ditrimethylsilyl-3,3'-diiodo-MOM-BINOL (**299**, 12.66 g, 16.4 mmol) and CCl_4 (170 mL) and the reaction mixture was then cooled to −15°C. ICl (21g, 165.7 mmol) was then added in 20 ml CCl_4. The reaction was allowed to stir for 10 minutes at which time the reaction mixture was quenched with 10% sodium bisulfate. The mixture was then extracted three times with CH_2Cl_2. The organic extracts were combined and washed with water, sodium bicarbonate, and brine. The solvent was then removed under reduced pressure and the crude mixture was then diluted with CH_2Cl_2 (115 mL), cooled to 0°C, and treated with methanolic HCl (77 mL). This was allowed to stir at 0°C for 24 hours. The reaction mixture was transferred to a separatory funnel and diluted with water and extracted three times with CH_2Cl_2. The organic layers were combined, dried over magnesium sulfate and the solvent was removed under reduced pressure. Purification was then accomplished by flash column chromatography (14:1 hexanes/ethyl acetate) to give **281** with ^{1}H NMR matching exactly to that from the reference.[4]

Spectroscopic data for **281** ($C_{20}H_{10}I_4O_2$):

^{1}H NMR ($CDCl_3$) δ 5.47 (br s, 2H), 6.7 (d, 2H, 9 Hz), 7.49 (dd, 2H, *J*=1.8, 9.3 Hz), 8.13 (d, 2H, *J*=1.5 Hz), 8.34 (s, 2H).



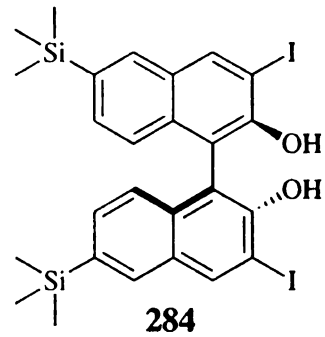
283

Preparation of **283**:

To a flame dried 50 mL round bottom flask equipped with a magnetic stir bar was added 6,6'-di-trimethylsilyl-MOM-BINOL (**298**, 0.48 g, 0.93 mmol) and CH_2Cl_2 (6.5 mL). This was then cooled to 0°C at which time saturated methanolic hydrogen chloride (4.3 mL) was added.[4] The reaction mixture was then allowed to stir overnight and workup was accomplished as described for the preparation of **281**. Purification was accomplished using flash column chromatography with 14:1 hexanes/ethyl acetate used as the eluent (r_f 0.15 2.5:1 hexanes/ethylacetate) to give 253.4 mg (63% yield) of the desired BINOL derivative **283** as a white solid.

Spectroscopic data for **283** ($C_{26}H_{30}O_2Si_2$):

^{1}H NMR ($CDCl_3$) δ 0.31 (s, 18H), 4.99 (s, 2H), 7.11 (d, 2H, *J*=8.7 Hz), 7.33-7.41 (m, 4H), 7.96 (d, 2H, *J*=9.0 Hz), 8.02 (s, 2H); ^{13}C NMR ($CDCl_3$) δ −1.43, 110.32, 117.33, 122.98, 128.67, 131.30, 133.31, 133.89, 135.33, 152.72 (one overlapping sp^2 carbon); IR (pure) 735m, 754m, 839vs, 899s, 1093m, 1134s, 1155s, 1201m, 1219s, 1250vs, 1383m, 1400m, 1466vs, 1615vs, 2955s, 3514br m cm^{-1}; Mass spectrum *m/z* (% rel intensity) 432 M^{+2} (8), 431 M^{+1} (14), 430 M^+ (33), 415 (40), 343 (5), 239 (5), 200 (100), 185 (9), 169 (8), 73 (88); mp 97-103 °C.



284

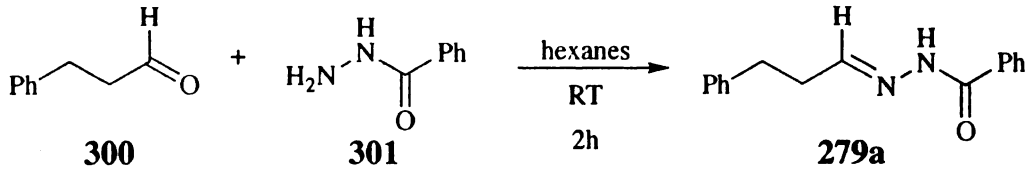
Preparation of **284**:

To a flame dried 50 mL round bottom flask equipped with a magnetic stir bar was added 6,6'di-trimethylsilyl-3,3'-diiodo-MOM-BINOL (**299**, 0.917 g, 1.2 mmol) and CH_2Cl_2 (8.4 mL). This was then cooled to 0°C at which time saturated methanolic hydrogen chloride (5.6 mL) was added[4]. The reaction mixture was then allowed to stir overnight and workup was accomplished as described for the preparation of **281**. Purification was accomplished via flash column chromatography using 535 mL 14.5:1 hexanes/CH_2Cl_2, then 270 mL 12.5:1 hexanes/ CH_2Cl_2, then 250 mL 14:1 hexanes/ethyl acetate as the eluent (r_f 0.4 2.5:1 hexanes/ethyl acetate) to give 662.2 mg (81% yield) of the desired BINOL derivative **284** as a white solid.

Spectroscopic data for **284** ($C_{26}H_{28}I_2O_2Si_2$):

^{1}H NMR ($CDCl_3$) δ 0.28 (s, 18H), 5.43 (s, 2H), 7.06 (d, 2H, *J*=8.4 Hz), 7.41 (d, 2H, *J*=8.4 Hz), 7.93 (s, 2H), 8.52 (s, 2H); ^{13}C NMR ($CDCl_3$) δ −1.49, 85.98, 112.11, 123.12, 129.92, 131.71, 132.72, 133.09, 136.47, 140.30, 150.13; IR 735m, 841vs, 864s, 912s, 1005w, 1070w, 1095m, 1152s, 1190w, 1213w, 1250s, 1379m, 1437s, 1606w, 2953s, 3520s; Mass spectrum *m/z* (% rel intensity) 685 M^{+3} (1), 684 M^{+2} (3), 683 M^{+1} (5), 682 M^+ (10), 670 (1), 669 (3), 668 (5), 667 (10), 610 (2), 595 (2), 556 (2), 541 (2), 326 (68), 262 (17), 199 (11), 128 (14), 73 (100); mp 128-134 °C.

Preparation of hydrazine imines[120]:



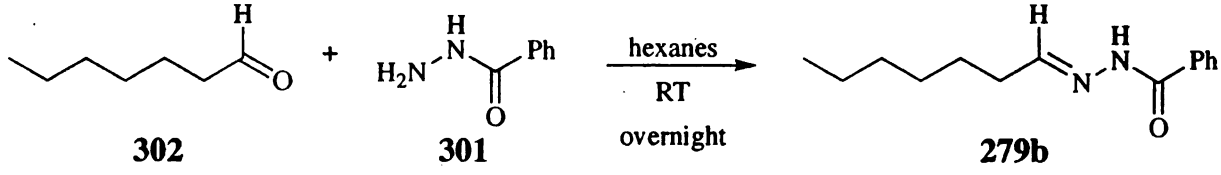
300 **301** **279a**

Preparation of **279a**:

To a 500 mL round bottom flask equipped with a magnetic stir bar was added the dihydrocinnamaldehyde (**300**, 5 mL, 37.9 mmol), and hexanes (250 mL). To the resulting suspension was added benzoylhydrazine (**301**, 3.45g, 25.3 mmol). The resulting reaction mixture was allowed to stir for 2 hours. After 2 hours, the insoluble material was collected and washed with hexanes. The powder was purified via recrystallization from ether/MeOH resulting in 2.77g (44% yield) of the imine **279a** as a crystalline solid. The spectral data matched perfectly to that in the literature.[120]

Spectral data for compound **279a** ($C_{16}H_{16}N_2O$):

^{1}H-NMR ($CDCl_3$) δ 2.62-2.83 (br m, 4H), 7.12-7.48 (br m, 8H), 7.61 (br s, 1H), 7.75-7.78 (m, 2H), 9.60 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ 32.37, 33.53, 125.89, 127.03, 128.02, 128.20, 131.57, 132.80, 140.13, 151.31, 164.05 (one overlapping sp^2 carbon).



302 **301** **279b**

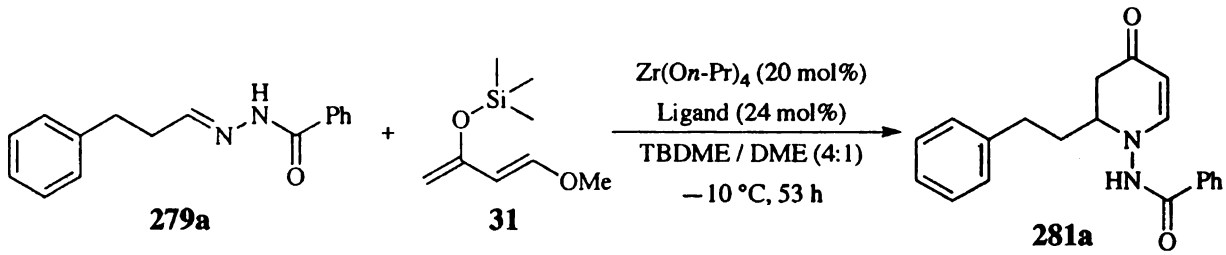
Preparation of **279b**:

To a 500 mL round bottom flask equipped with a magnetic stir bar was added the heptanal (**302**, 15 mL, 107.5 mmol), and hexanes (350 mL). To the resulting suspension

was added benzoylhydrazine (**301**, 9.75g, 71.6 mmol). The resulting reaction mixture was allowed to stir for 18 hours. After 18 hours, the insoluble material was collected and washed with hexanes. The powder was purified via recrystallization from ether/MeOH resulting in 15.5g (93% yield) of the imine **279b** as a crystalline solid.

Spectral data for compound **279b** ($C_{14}H_{20}N_2O$):

^{1}H-NMR ($CDCl_3$) δ 0.822 (t, 3H, *J*=6Hz), 1.22-1.40 (br m, 8H), 2.26 (q, 2H, *J*=6.9 Hz), 7.29-7.45 (br m, 3H), 7.61-7.78 (br m, 3H), 9.96 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ 13.66, 22.13, 26.24, 28.58, 31.19, 32.15, 127.08, 128.14, 131.39, 132.83, 152.82, 164.00; mass spectrum *m/z* (% relative intensity); 233 M+1 (4), 232 M+ (17), 231 (5), 217 (2), 205 (13), 204 (12), 190 (15), 188 (14), 176 (43), 174 (100), 161 (5), 147 (11), 120 (9), 105 (50), 77 (50) 51 (5), 41 (8); IR (neat) 613.17m, 692.53m, 800.56m, 895.08w, 935.59w, 1051.34w, 1076.42w, 1142.00w, 1188.3w, 1268.68m, 1361.92m, 1466.09m, 1495.02m, 1577.97s, 1653.21s, 2581.01s, 2922.53s, 3063.35s, 3227.32s cm^{-1}; mp:103-105 °C.



Procedures for Scheme 5.9 (*aza*-Diels-Alder reaction of imine 279a using Kobayashi's conditions):

General Procedure: To a flame dried 5 mL round bottom flask equipped with a magnetic stir bar was added the ligand (0.098 mmol, 24 mol%) and TBDME (0.4 mL) followed by Zr(O*n*-Pr)$_4$ (0.032 mL, 0.082 mmol, 20 mol%). The reaction mixture was

allowed to stir at room temperature for 3 hours. Meanwhile, in a flame dried 10 mL round bottom flask equipped with a magnetic stir bar was added the imine **279a** (103 mg, 0.41 mmol). The zirconium catalyst was then transferred from the 5 mL round bottom flask to the flask containing **279a**. The 5 mL flask was rinsed with 0.4 mL TBDME to ensure all the catalyst was transferred. The reaction mixture was then cooled to 0°C at which time the DME (0.2 mL) was added followed by the diene (**31**, 0.12 mL, 0.61 mmol). The reaction mixture was then allowed to stir for 53 hours after which, the reaction mixture was transferred to a separatory funnel containing 25 mL saturated sodium bicarbonate. The mixture was extracted three times with CH_2Cl_2, the organic extracts combined, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. Purification was done by flash column chromatography and the enantiomeric excess was measured following the HPLC conditions from Kobayashi.[31]

Entry 1: The general procedure described above was followed exactly using (*S*)-VAPOL (**130**, 53 mg, 0.098 mmol) and the reaction did not produce any of the desired product **281a**.

Entry 2: The general procedure described above was followed exactly using (*S*)-VANOL (**129**, 43 mg, 0.098 mmol) and the reaction did not produce any of the desired product **281a**.

Entry 3: The general procedure described above was followed exactly using (*S*)-BINOL (**59**, 28.1 mg, 0.098 mmol) and the reaction did not produce any of the desired product **281a**.

Entry 4: The general procedure described above was followed exactly using (*S*)-6,6'-dibromo-BINOL (**282**, 43.5 mg, 0.098 mmol) and the reaction gave 8.3 mg (6.3% yield) of the desired product **281a** and 42% ee was measured.

Entry 5: The general procedure described above was followed exactly using (*S*)-6,6'-ditrimethylsilyl-BINOL (**283**, 42.2 mg, 0.098 mmol) and the reaction gave less than 6 mg (<5% yield) of the desired product **281a** and the ee for this reaction was not measured.

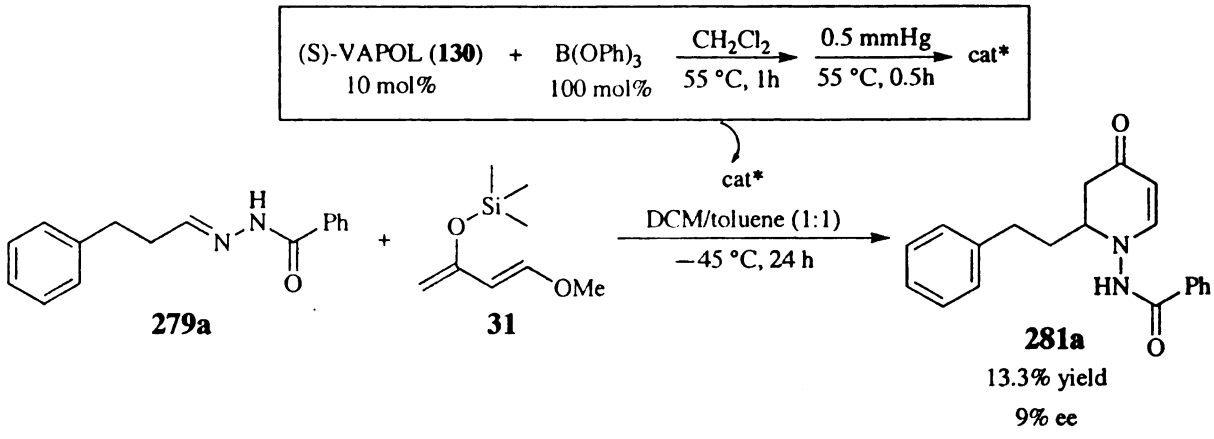
Entry 6: The general procedure described above was followed exactly using (*S*)-6,6'-ditrimethylsilyl-3,3'-diiodo-BINOL (**284**, 67 mg, 0.098 mmol) and the reaction gave 15.4 mg (11.7% yield) of the desired product **281a** and 74.5% ee was measured.

Entry 7: The general procedure described above was followed exactly using (*S*)-3,3',6,6'-tetraiodo-BINOL (**281**, 77.4 mg, 0.098 mmol) and the reaction gave 53.9 mg (41% yield) of the desired product **281a** and 94.2% ee was measured.

Entry 8: The general procedure described above was followed exactly using (*S*)-3,3'-dinitroVANOL (**285**, 51.8 mg, 0.098 mmol) the reaction yielded 27.9 mg (21% yield) of the desired product **281a** and 87.1% ee was measured.

Spectral data for compound **281a** ($C_{20}H_{20}N_2O_2$):

^{1}H NMR ($CDCl_3$) δ 1.89-2.02 (m, 2H), 2.47-2.70 (m, 4H), 4.05 (br s, 1H), 5.00 (d, 1H, *J*=7.8 Hz), 7.01-7.24 (br m, 5H), 7.38-7.55 (m, 4H), 7.72 (d, 2H, *J*=7.8 Hz), 9.04 (s, 1H).

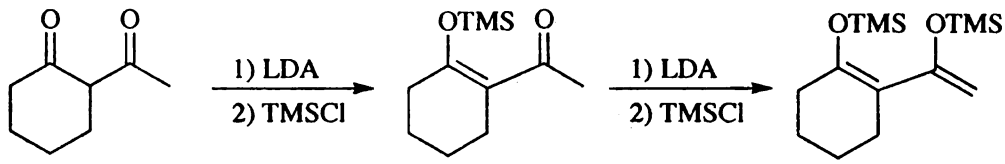


Procedure for Scheme 5.9 (*aza*-Diels-Alder reaction of imine 279a using (*S*)-VAPOL/B(OPh)$_3$ as the Catalyst):

To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (0.128 g, 0.41 mmol) and (S)-VAPOL (**130**, 22 mg, 0.041 mmol). To this was added CH_2Cl_2 (0.8 mL) and then the flask was sealed with the stopcock and heated to 55 °C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 55 °C for 0.5 hours yielding catalyst. After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 1.0 mL of a 1:1 mixture of toluene and CH_2Cl_2 (in two portions). The catalyst solution was transferred by syringe to a solution of the imine **279a** prepared as immediately below.

To a flame dried, argon purged homemade flask with a cold addition coil equipped with a stir bar was added the imine (**279a**, 0.3764 g, 1.0 mmol). The flask was topped with two rubber septa and the catalyst was added in two 0.5 mL portions of toluene/ CH_2Cl_2 (1:1) directly to the bottom of the flask by a syringe equipped with a long needle. This was allowed to stir for 5-10 minutes at room temperature and then

cooled to –45 °C. Meanwhile, in a separate flame dried 5 mL round bottom flask purged with argon was added Danishefsky's diene (**31**, 0.38 mL, 2.0 mmol) and toluene/CH_2Cl_2 (1:1) (1.5 mL). The diene was taken up in a syringe and added over 3.0 hours via syringe pump through the cold addition coil. The reaction was then allowed to stir at –45 °C for 24 h. After completion of the reaction, saturated sodium bicarbonate (~20 mL) was added to the reaction flask at –45 °C. This was then transferred to a separatory funnel containing saturated sodium bicarbonate (25 mL) and extracted with three or four 30-40 mL portions of CH_2Cl_2. The combined organic layers were then dried with magnesium sulfate, filtered, and solvent was removed via rotary evaporation. Purification was then done using flash column chromatography to give 16.8 mg of **281a** (13.3% yield) and 9% ee was measured using the HPLC conditions form Kobayashi.[31]

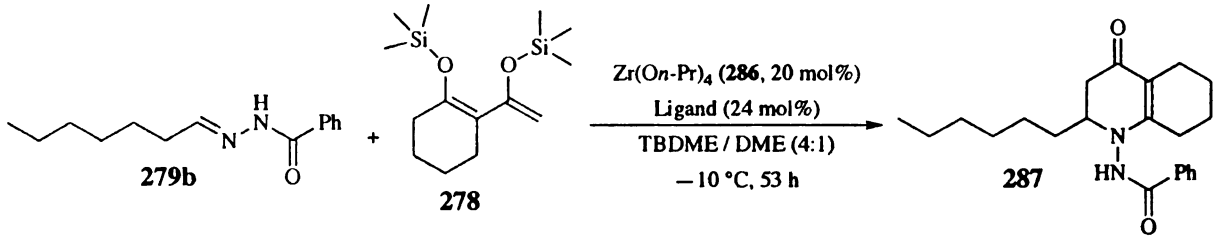


303 **304** **278**

Preparation of the bisTMS diene (278)[90]:

To a flame dried argon purged 500 mL round bottom flask equipped with a magnetic stir bar was added 2-acetyl-cyclohexanone (**303**, 4.95 mL, 37.5 mmol) and THF (60 mL). The solution was cooled to —78°C and LDA (40.5 mL, 45 mmol, 1.11 M solution in THF) was added over 5 minutes. The resulting solution was stirred for 30 minutes at which time TMSCl (7.11 mL, 56.25 mmol) was added over about 10 minutes. After the addition of TMSCl, the reaction was immediately warmed to room temperature to give **304**. The solution containing **304** was cooled back to —78°C and LDA (40.5 mL,

45 mmol, 1.11 M solution in THF) was added over 5 minutes. The resulting solution was stirred for 30 minutes at which time TMSCl (7.11 mL, 56.25 mmol) was added over about 10 minutes. After the addition of TMSCl, the reaction was immediately allowed to warm to room temperature. After the reaction was stirred for one hour at room temperature, the solvent was removed under reduced pressure and the resulting gel was dissolved in ether and filtered through Celite. The Celite was washed with several portions of ether to ensure all the desired material was extracted from the Celite. Purification was accomplished by distillation (94-95°C, 0.6 mmHg) to afford 9.5 g (89% yield) of the desired diene **278**. The spectral data matched perfectly to that in the literature.[90]

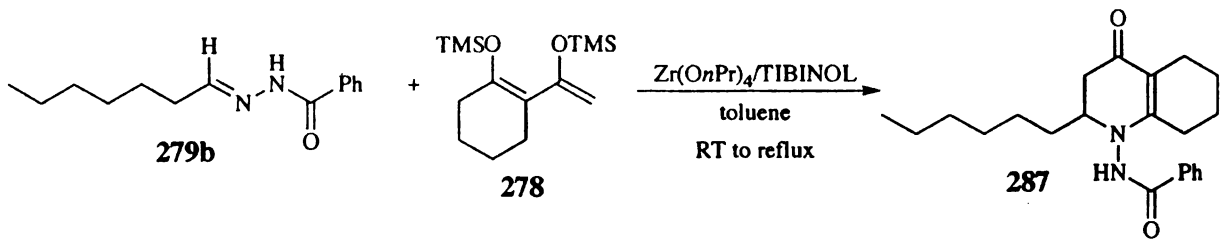


Procedure for Scheme 5.11 (*aza*-Diels-Alder reaction of imine 279a and diene 278):

To a flame dried 5 mL round bottom flask equipped with a magnetic stir bar was added the ligand (0.098 mmol, 24 mol%) and TBDME (0.4 mL) followed by Zr(O*n*-Pr)$_4$ (0.032 mL, 0.082 mmol, 20 mol%). The reaction mixture was allowed to stir at room temperature for 3 hours. Meanwhile, in a flame dried 10 mL round bottom flask equipped with a magnetic stir bar was added the imine (**279b**, 103 mg, 0.41 mmol). The zirconium catalyst was then transferred from the 5 mL round bottom flask to the flask containing **279a**. The 5 mL flask was rinsed with 0.4 mL TBDME to ensure all the catalyst was transferred. The reaction mixture was then cooled to 0°C at which time DME (0.2 mL) was added followed by the diene (**278**, 0.12 mL, 0.61 mmol). The

reaction mixture was then allowed to stir for 53 hours. After stirring for 53 hours, the reaction mixture was transferred to a separatory funnel containing 25 mL saturated sodium bicarbonate. The mixture was then extracted three times with CH_2Cl_2, the organic extracts combined, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure.

(S)-VAPOL (**130**), (S)-VANOL (**129**), (S)-BINOL (**59**), (S)-6,6'-dibromo-INOL (**282**), (S)-6,6'-di(trimethylsilyl)-BINOL (**283**), (S)-6,6'-di(trimethylsilyl)-3,3'-diiodo-BINOL (**284**), and (S)-3,3',6,6'-tetraiodo-BINOL (**281**) were all attempted as ligands for this reaction and none of the reactions using these ligands gave any of the desired product **287**.

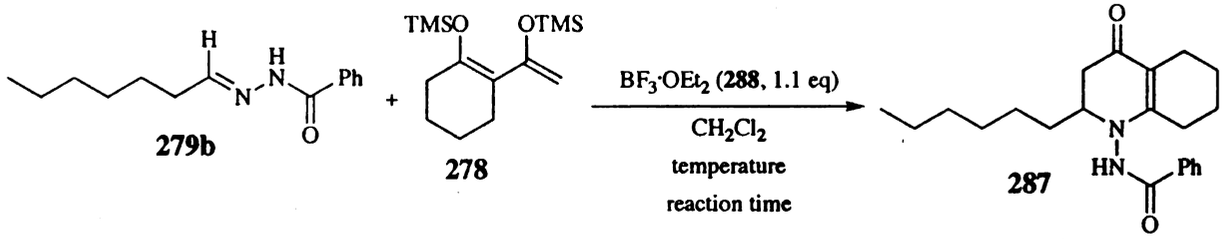


Procedure for attempts at running reaction at warmer temperatures:

Reaction 1: To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added (*S*)-tetraiodoBINOL (**281**, 28.1 mg, 0.098 mmol) followed by toluene (0.4 mL) and $Zr(OnPr)_4$ (0.032 mL, 0.082 mmol). This was then allowed to stir at room temperature for 3 hours. Meanwhile, to a flame dried 10 mL round bottom flask was added the imine **279b** (95.3 mg, 0.41 mmol). The zirconium catalyst was then transferred to the flask containing the imine. The catalyst flask was rinsed with toluene (0.4 mL) to ensure all of the catalyst was transferred. At room temperature, the diene (**278**, 0.175 g, 0.61 mmol) was added in toluene (0.2 mL). The reaction was then allowed

to stir for 48 hours at room temperature. After 48 hours, more diene (0.12 mL, 0.41 mmol) was added to the reaction mixture and it was then heated to reflux for 24 hours. The reaction mixture was then transferred to a separatory funnel containing saturated sodium bicarbonate (25 mL). Extraction was done three times with CH_2Cl_2 and the organic layers were combined, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Analysis of the crude NMR showed that none of the desired product **287** had been produced.

Reaction 2: The conditions as described for reaction 1 were followed exactly except the reaction was diluted with toluene (3mL) and heated to reflux after addition of the first aliquot of the diene **278**. After 21.5 hours, the crude ^1H NMR showed that only starting material was present so another aliquot of the diene **278** (0.15 mL, 0.5 mmol) was added. After refluxing for an additional 12 hours, the reaction was worked up as in reaction 1 but still no product was observed in the crude ^1H NMR.



Procedure for Scheme 5.12 (racemic *aza*-Diels-Alder reactions of imine 279b and diene 278):

Condition AA: To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added the imine 279b (116.2 mg, 0.5 mmol) followed by CH_2Cl_2 (5 mL) and then $BF_3{\cdot}OEt_2$ (288, 0.069 mL, 0.55 mmol). The flask was then cooled to −45°C at which time the diene (278, 0.213 g, 0.75 mmol) was added. A white

precipitate formed before the reaction was cooled and upon addition of the diene, the precipitate disappeared and the reaction turned slightly yellow. The reaction was then allowed to stir at −45°C for 2 hours at which time the reaction was transferred to a separatory funnel. Saturated sodium bicarbonate was added and the extraction was done four times with CH_2Cl_2 (30 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Several new spots were observed by TLC analysis, but none of the desired product 287 was isolated.

Conditions BB: To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added the imine **279b** (116.2 mg, 0.5 mmol) followed by CH_2Cl_2 (5 mL). The reaction was then cooled to −45°C at which time $BF_3{\cdot}OEt_2$ (**288**, 0.069 mL, 0.55 mmol) was added followed immediately by the diene (**278**, 0.213 g, 0.75 mmol). No white precipitate was formed upon addition of $BF_3{\cdot}OEt_2$. The reaction was allowed to stir at −45°C overnight and after 20 hours, the reaction was transferred to a separatory funnel, treated with saturated sodium bicarbonate and extracted four times with CH_2Cl_2 (30 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. None of the desired product **287** was isolated.

Conditions CC: To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added the imine **279b** (116.2 mg, 0.5 mmol) followed by CH_2Cl_2 (5 mL). The reaction was then cooled to −45°C and the diene (278, 0.213 g, 0.75 mmol) was added followed immediately by $BF_3{\cdot}OEt_2$ (**288**, 0.069 mL, 0.55 mmol). The reaction was allowed to stir at −45°C for 2 hours. At this time the reaction was transferred to a separatory funnel, treated with saturated sodium bicarbonate and extracted four times with CH_2Cl_2 (30 mL). The organic layers were combined, dried over magnesium sulfate,

filtered and concentrated under reduced pressure. Purification was accomplished via flash column chromatography, R_f 0.05 (2.5:1 hexanes/ethyl acetate), by ramping the solvent from 10:3 hexanes/EtOAc (500 mL) to 1:1 hexanes/EtOAc to give 51.6 mg (29% yield) of the desired product **287** as a wax-like substance.

Conditions DD: To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added the imine **279b** (116.2 mg, 0.5 mmol) followed by CH_2Cl_2 (5 mL). The reaction was then cooled to −78°C anad the diene (**278**, 0.213 g, 0.75 mmol) was added followed immediately by $BF_3{\cdot}OEt_2$ (**288**, 0.069 mL, 0.55 mmol). The reaction was then allowed to warm to −45°C and stirred for 19 hours. After 19 hours, the reaction was transferred to a separatory funnel, treated with saturated sodium bicarbonate and extracted four times with CH_2Cl_2 (30 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification was accomplished via flash column chromatography, R_f 0.05 (2.5:1 hexanes/ethyl acetate), by ramping the solvent from 10:3 hexanes/EtOAc (500 mL) to 1:1 hexanes/EtOAc to give 51.7 mg (29% yield) of the desired product **287** as a wax-like substance.

Conditions EE: To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added the imine **279b** (116.2 mg, 0.5 mmol) followed by CH_2Cl_2 (5 mL). The reaction was then cooled to −78°C and the diene (**278**, 0.213 g, 0.75 mmol) was added followed immediately by $BF_3{\cdot}OEt_2$ (**288**, 0.069 mL, 0.55 mmol). Immediately after the addition of $BF_3{\cdot}OEt_2$, the cooling bath was removed and the reaction was allowed to warm to room temperature and stirred for 19 hours. After 19 hours, the reaction was transferred to a separatory funnel, treated with saturated sodium bicarbonate

and extracted four times with CH_2Cl_2 (30 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification was accomplished via flash column chromatography, R_f 0.05 (2.5:1 hexanes/ethyl acetate), by ramping the solvent from 10:3 hexanes/EtOAc (500 mL) to 1:1 hexanes/EtOAc to give 63.5 mg (36% yield) of the desired product **287** as a wax-like substance.

Conditions FF: To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added the imine **279b** (116.2 mg, 0.5 mmol) followed by CH_2Cl_2 (20 mL). The reaction was then cooled to −78°C and the diene (**278**, 0.213 g, 0.75 mmol) was added followed immediately by $BF_3{\cdot}OEt_2$ (**288**, 0.069 mL, 0.55 mmol). The reaction was allowed to warm to −45°C and stirred for 19 hours. After 19 hours, the reaction was transferred to a separatory funnel, treated with saturated sodium bicarbonate and extracted four times with CH_2Cl_2 (30 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification was accomplished via flash column chromatography, R_f 0.05 (2.5:1 hexanes/ethyl acetate), by ramping the solvent from 10:3 hexanes/EtOAc (500 mL) to 1:1 hexanes/EtOAc to give 56.3 mg (32% yield) of the desired product **287** as a wax-like substance.

Conditions GG: To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added the imine **279b** (116.2 mg, 0.5 mmol) followed by CH_2Cl_2 (5 mL). The reaction was then cooled to −78°C and the diene **278** (redistilled immediately before use) (0.213 g, 0.75 mmol) was added followed immediately by $BF_3{\cdot}OEt_2$ (**288**, 0.069 mL, 0.55 mmol). Immediately after the addition of $BF_3{\cdot}OEt_2$, the

cooling bath was removed and the reaction was allowed to warm to room temperature and stired for 20 hours. After 20 hours, the reaction was transferred to a separatory funnel, treated with saturated sodium bicarbonate and extracted four times with CH_2Cl_2 (30 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification was accomplished via flash column chromatography, R_f 0.05 (2.5:1 hexanes/ethyl acetate), by ramping the solvent from 10:3 hexanes/EtOAc (500 mL) to 1:1 hexanes/EtOAc to give 114.1 mg (64% yield) of the desired product **287** as a wax-like substance.

Conditions HH: To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added the imine **279b** (116.2 mg, 0.5 mmol) followed by CH_2Cl_2 (5 mL). The reaction was then cooled to −78°C and the diene **278** (redistilled immediately before use) (0.213 g, 0.75 mmol) was added followed immediately by $BF_3{\cdot}OEt_2$ (**288**, redistilled immediately before use) (0.069 mL, 0.55 mmol). Immediately after the addition of $BF_3{\cdot}OEt_2$, the cooling bath was removed and the reaction was allowed to warm to room temperature and stirred for 20 hours. After 20 hours, the reaction was transferred to a separatory funnel, treated with saturated sodium bicarbonate and extracted four times with CH_2Cl_2 (30 mL). The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Puurification was accomplished via flash column chromatography, R_f 0.05 (2.5:1 hexanes/ethyl acetate), by ramping the solvent from 10:3 hexanes/EtOAc (500 mL) to 1:1 hexanes/EtOAc to give 103.7 mg (58.5% yield) of the desired product **287** as a wax-like substance.

Conditions II: The conditions as described for Conditions HH were followed exactly, except 0.2323 g (1.0 mmol) of the imine **279b** was used. The reaction gave 147.5 mg (42% yield) of the desired produt **287** as a wax-like substance.

Conditions JJ (0.446g): To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added the imine **279b** (446 mg, 1.92 mmol) followed by CH_2Cl_2 (20 mL). The reaction was then cooled to —78°C and the diene **278** (redistilled immediately before use) (3 mL, 10.12 mmol) was added followed immediately by $BF_3{\cdot}OEt_2$ (0.265 mL, 2.11 mmol). Immediately after the addition of $BF_3{\cdot}OEt_2$, the cooling bath was removed and the reaction was allowed to warm to room temperature and stir for 20 hours. After 20 hours, the reaction was transferred to a separatory funnel, treated with saturated sodium bicarbonate and extracted four times with CH_2Cl_2. The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification was accomplished via flash column chromatography, R_f 0.05 (2.5:1 hexanes/ethyl acetate), by ramping the solvent from 10:3 hexanes/EtOAc (500 mL) to 1:1 hexanes/EtOAc to give 466.2 mg (68% yield) of the desired product **287** as a wax-like substance.

Conditions JJ (6.21g): To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added the imine 279b (6.21g, 26.75 mmol) followed by CH_2Cl_2 (275 mL). The reaction was then cooled to —78°C and the diene 278 (redistilled immediately before use) (11.4 g, 40.11 mmol) was added followed immediately by $BF_3{\cdot}OEt_2$ (288, 3.7 mL, 29.4 mmol). Immediately after the addition of $BF_3{\cdot}OEt_2$, the cooling bath was removed and the reaction was allowed to warm to room temperature and stir for 20 hours. After 20 hours, the reaction was transferred to a

separatory funnel, treated with saturated sodium bicarbonate and extracted four times with CH_2Cl_2. The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification was accomplished via flash column chromatography, R_f 0.05 (2.5:1 hexanes/ethyl acetate), by ramping the solvent from 10:3 hexanes/EtOAc (500 mL) to 1:1 hexanes/EtOAc to give 5.97 g (63% yield) of the desired product 288 as a wax-like substance.

Conditions KK (16.3 g): To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added the imine 279b (16.3g, 70.3 mmol) followed by CH_2Cl_2 (700 mL). The reaction was then cooled to −78°C and the diene 278 (redistilled immediately before use) (30 g, 105.4 mmol) was added followed immediately by $BF_3{\cdot}OEt_2$ (288, 9.7 mL, 77.33 mmol). Immediately after the addition of $BF_3{\cdot}OEt_2$, the temperature was allowed to warm to −20° overnight. After 15 hours, the cooling bath was removed and the reaction was allowed to warm to room temperature and stirred for an additional 4 hours. After 19 hours total reaction time, the reaction mixture was transferred to a separatory funnel, treated with saturated sodium bicarbonate and extracted four times with CH_2Cl_2. The organic layers were combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. Purification was accomplished via flash column chromatography, R_f 0.05 (2.5:1 hexanes/ethyl acetate), by ramping the solvent from 10:3 hexanes/EtOAc (500 mL) to 1:1 hexanes/EtOAc to give >9.5 g (>40% yield) of the desired product 287 as a wax-like substance.

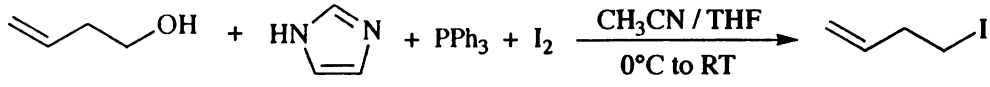
Spectral data for compounds **287** ($C_{22}H_{30}N_2O_2$):

The enantiomers could be separated by HPLC using a Chiralcel OD column (with guard column) (90/10 hexanes/isopropanol, 1 mL/min). Retention times: 14.12 min. and

16.99 min. ^{1}H NMR ($CDCl_3$) δ 0.78 (t, 3H, *J*=6.9 Hz), 1.16-1.66 (br m, 13H), 2.07-2.40 (br m, 6H), 2.60 (dd, 1H, *J*=16.2, 4.5 Hz), 3.89 (s, 1H), 7.38-7.55 (m, 3H), 7.84 (d, 2H 8.4 Hz), 9.27 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.62, 21.19, 21.37, 21.78, 22.14, 24.65, 26.12, 28.91, 30.51, 31.30, 40.95, 59.96, 108.77, 127.06, 128.43, 131.49, 132.13, 161.76, 166.61, 191.50; IR (pure) 1136w, 1262m, 1522s, 1559vs, 1617s, 1653s, 1684s, 2859s, 2930vs, 3254br s cm^{-1}; Mass spectrum *m/z* (% rel intensity) 355 M^+ (83), 269 (19), 234 (100), 163 (30), 105 (71).

Preparation of Cuprates 1, 2, and 3:

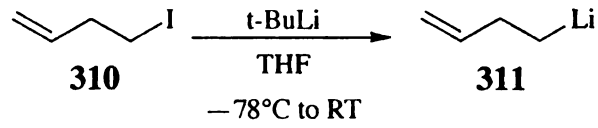
Cuprate 1:



305 **306** **307** **308** **309**

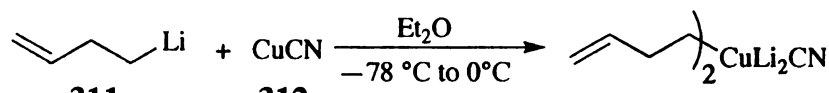
Preparation of 4-iodo-1-butene (**309**):[121] To a flame dried argon purged 250 mL round bottom flask equipped with a magnetic stir bar was added PPh_3 (**307**, 23 g, 87.75 mmol), 3-butene-1-ol (**305**, 5 mL, 58.5 mmol), imidazole (**306**, 8 g, 117 mmol), and a 3.1:1 mixture of THF/CH_3CN (111 mL). The resulting solution was then cooled to 0°C and I_2 (**308**, 25.4 g, 100 mmol) was added in three portions over ~5 minutes. After the addition of I_2 was completed, the ice bath was removed and the reaction mixture was allowed to stir at room temperature for 30 minutes. The dark solution was then transferred to a separatory funnel containing 10% sodium bisulfite (180 mL) and pentane (170 mL). The layers were separated and the organic layer was dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification was

accomplished by flash column chromatography to give 3.82 g (36% yield) of **309** as a light pink oil. The H-NMR matched perfectly to the literature.[121]



310 **311**

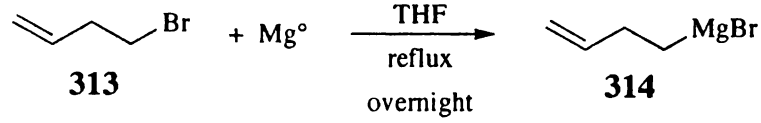
*Preparation of 3-butenyllithium (**311**)*: To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added 4-iodo-1-butene (**310**, 1.0 equiv.) and THF (2.1 mL/mmol). The reaction mixture was then cooled to –78°C at which time *t*-BuLi (1.0 equiv., 1.7 M solution in hexanes) was added. The reaction mixture was then allowed to warm slowly to room temperature. The yield was assumed to be 90% and the entire solution of the resulting lithium species **311** was used directly for the preparation of the cuprate 1.



311 **312** **Cuprate 1**

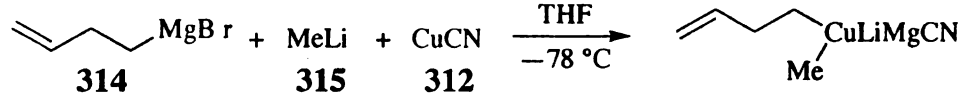
Preparation of cuprate 1: To a round bottom flask equipped with a magnetic stir bar was added CuCN (**312**, 1.0 equiv.). The flask was then flame dried and purged with argon and then Et_2O was added (3 mL/mmol) and cooled to −78°C. To the slurry was then transferred the previously prepared solution 3-butenyllithium **311**. Ether (1.0 mL/mmol) was used to rinse any left over material from the butenyllithium flask. The resulting solution was then warmed to 0°C for one minute to give a 0.13 M solution of **cuprate 1.** The resulting solution of cuprate 1 was then cooled back to −78°C and used immediately for the 1,4-addition reactions.

Cuprate 2:



313 **314**

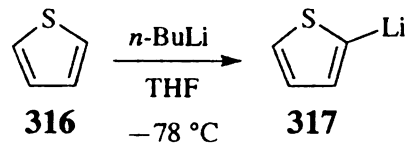
*Preparation of Butenylmagnesiumbromide (**306**):* To a flame dried argon purged round bottom flask equipped with a magnetic stir bar and a reflux condenser was added magnesium (50 mesh, 1.05 equiv.), THF (1.25 mL/mmol), and 4-bromo-1-butene (**313**, 1.0 equiv). The resulting solution was then heated to reflux and stirred overnight. The Grignard reagent **314** was then used immediately for the preparation of the cuprate 2.



314 **315** **312** **Cuprate 2**

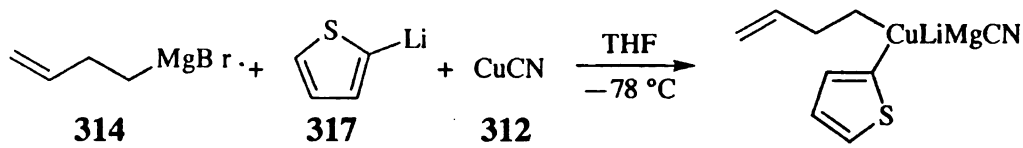
Preparation of Cuprate 2: To a round bottom flask equipped with a magnetic stir bar was added copper cyanide (**312**, 1 equiv.). The flask was then flame dried and purged with argon and to it was added THF (1.5 mL/mmol) and cooled to −78°C. To the slurry was added MeLi (**315**, 1.0 equiv., 1.6 M in ether) over two minutes. The reaction was then placed in a 0°C ice bath for 2-3 minutes and then cooled back to −78°C at which time the freshly prepared butenylmagnesium bromide (**314**, 1.0 equiv, 0.8M in THF) (as prepared above) was added dropwise over 4 minutes. Stirring was allowed for another 10 minutes to give a 0.26 M solution of **cuprate 2**. The resulting solution of cuprate 2 was then used for the 1,4-addition reactions.

Cuprate 3:



316 **317**

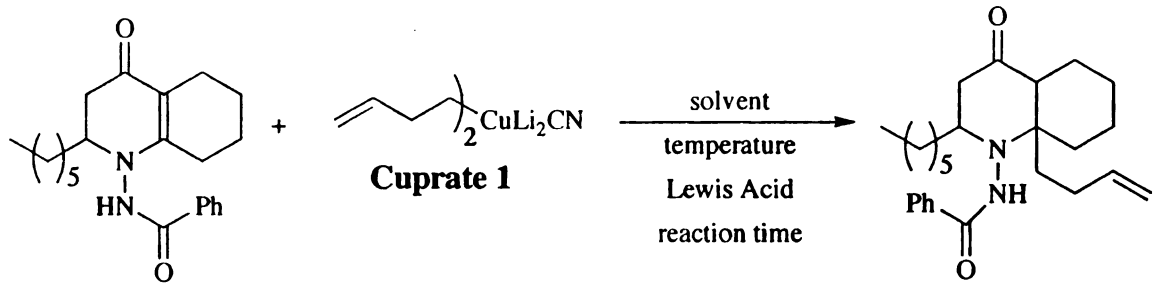
Preparation of thiophenyllithium (**317**):[122] To a flame dried argon purged round bottom flask equipped with a magnetic stir bar was added thiophene (**316**, 1.0 equiv.) and THF (0.9 mL/mmol). The reaction mixture was cooled to –78°C at which time *n*-BuLi (1.0 equiv., 2.5 M solution in hexanes) was added. The temperature was then allowed to warm slowly to 0°C and was stirred for another 30 minutes to give a 0.676 M solution of thiophenyllithium **317**. The resulting solution of **317** was used immediately for the preparation of cuprate 3.



314 **317** **312** **Cuprate 3**

Preparation of Cuprate 3:[122] A round bottom flask was charged with CuCN (**312**, 1.0 equiv.) and a magnetic stir bar. The flask was then flame dried and purged with argon and the contents were diluted with dry THF (1.33mL/mmol) and cooled to −78°C. To the flask was added the freshly prepared thiophenylithium (**317**, 1.0 equiv., 0.676M solution in THF as prepared above) over 30 seconds after which, the reaction mixture was then warmed to room temperature. The resulting amber solution was then cooled back to −78°C and freshly prepared butenylmagnesiumbromide (**314**, 1.0 equiv. 0.8M solution in THF as prepared above) was added over 1 minute. The reaction flask was

then transferred to a 0°C ice bath and remained there for 2 minutes to giving a 0.36 M solution of **cuprate 3**. The resulting solution of cuprate 3 was then cooled back to —78°C and used immediately for the 1,4-addition reactions.



287 **288**

Procedures for Scheme 5.14 (1,4-addition of cuprate 3 to hydrazine 287):

Entry 1: To the previously prepared solution of cuprate 1 (3.7 mL, 0.48 mmol, 0.13 M solution in THF/hexanes/ether) was added the hydrazine **287** (0.1134 g, 0.32 mmol). The reaction was allowed to stir at —78°C for 3 hours and then warmed to —25°C for 16 hours. After 19 hours total reaction time, a 9:1 solution of NH_4Cl/NH_4OH (5.0 mL) was added. The cooling bath was removed and the reaction mixture was allowed to stir for 1 hour. The solution was transferred to a separatory funnel, extracted three times with ethyl acetate. The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. None of the desired product **288** was observed in the crude ^1H NMR.

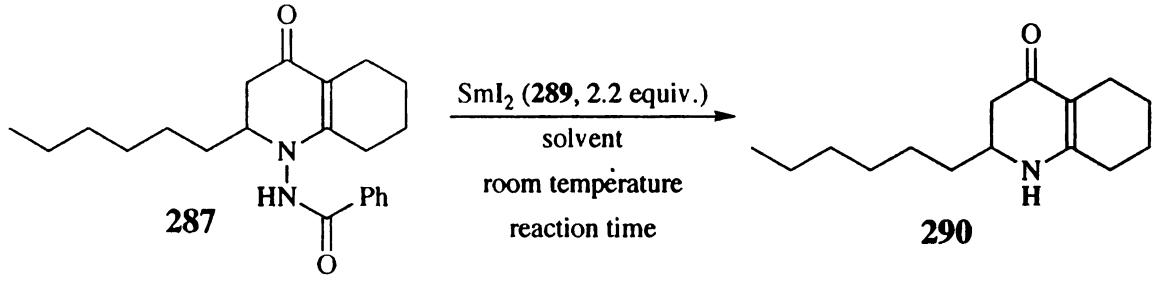
Entry 2: To the previously prepared solution of cuprate 1 (2.75 mL, 0.689 mmol, 0.25 M solution in ether) was added the hydrazine **287** (0.627 g, 0.459 mmol) The cooling bath was then packed with dry ice and the reaction was allowed to warm very slowly to —25°C and stirred for a total of 16 hours. After 16 hours total reaction time, a

9:1 solution of NH_4Cl/NH_4OH (5.0 mL) was added. The cooling bath was removed and the reaction mixture was allowed to stir for 30 minutes. The solution was transferred to a separatory funnel, extracted three times with ethyl acetate, The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. None of the desired product **288** was observed in the crude ^1H NMR.

Entry 3: To the previously prepared solution of cuprate 1 (2.84 mL, 0.71 mmol, 0.25 M solution in ether) was added the hydrazine **287** (0.1008 g, 0.284 mmol). The reaction was allowed to stir at −78°C for 3 hours, then warmed slowly to −10°C for an additional 19 hours. After 22 hours total reaction time, a 9:1 solution of NH_4Cl/NH_4OH (5.0 mL) was added. The cooling bath was removed and the reaction mixture was allowed to stir for 30 minutes. The solution was transferred to a separatory funnel, extracted three times with ethyl acetate, The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. None of the desired product **288** was observed in the crude ^1H NMR. .

Entry 4: To the previously prepared solution of cuprate 1 (1.32 mL, 0.33 mmol, 0.25 M solution in ether) was added a previously prepared solution of the hydrazine **287** (78 mg, 0.22 mmol) and $Zr(O\text{-}nPr)_4$ (0.0686 mL, 0.22 mmol) in a 4:3 mixture of ether/CH_2Cl_2 (3.5 mL) dropwise via syringe over 2-3 minutes. The resulting black reaction mixture was allowed to stir at −78°C for 21 hours and the temperature was raised to −50°C stirring for another 23 hours, and finally the reaction was warmed to −25°C for an additional 24 hours. After a total of 67 hours, a 9:1 solution of

NH_4Cl/NH_4OH (5.0 mL) was added. The cooling bath was removed and the reaction mixture was allowed to stir for 2 hours. The solution was transferred to a separatory funnel, extracted three times with ethyl acetate, The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Only a few minor peaks were observed in the vinyl region of the crude ^1H NMR but none of the desired product **288** was isolated.



Procedures for Scheme 5.15 (reductive cleavage using SmI_2):

Entry 1: To a flame dried argon purged 50 mL 3-neck round bottom flask equipped with a magnetic stir bar and a reflux condenser was added Sm° (0.5 g, 3.33 mmol), I_2 (0.767 g, 3.02 mmol) and THF (9 mL). The resulting solution was heated to reflux for 1.5 hours. The dark blue 0.333 M solution of SmI_2 (**289**) was stored in the dark and used for the reductive cleavage as described immediately below.

To a flame dried argon purged 25 mL round bottom flask was added the hydrazine **287** (0.2331 g, 0.658 mmol) and THF (9.5 mL). To the solution was then added the previously prepared solution of SmI_2 (**289**, 4.35 mL, 1.45 mmol, 0.333 M solution in THF). The reaction was allowed to stir for 45 minutes at which time the solution was treated with 3N HCl (20 mL). The mixture was extracted three times with ether. The aqueous layer was then treated with 10% aqueous sodium hydroxide and this

was then extracted three times with ether. These organic layers of the second extraction were then combined, dried, filtered, and the solvent removed under reduced pressure. Purification was accomplished by flash column chromatography (r_f 0.13 5:2 hexanes/ethyl acetate) using 1:1 hexanes/ethyl acetate as the eluent to give 18 mg (12% yield) of the desired product **290**.

Entry 2: To a flame dried argon purged 50 mL round bottom flask equipped with a magnetic stir bar and a reflux condenser was added Sm° (0.316 g, 2.1 mmol), and THF (30 mL) followed immediately by the addition of CH_2I_2 (0.16 mL, 2.0 mmol). The resulting solution was stirred at room temperature until the solution turned dark blue (~3 hours). The resulting dark blue 0.067 M solution of SmI_2 (**289**) was stored in the dark and used for the reductive cleavage described immediately below.

To a flame dried argon purged 25 mL round bottom flask was added the hydrazine **287** (0.1 g, 0.282 mmol) followed by the addition of the previously prepared solution of SmI_2 (**289**, 9.26 mL, 0.62 mmol, 0.067 M solution in THF). The solution turned brown within 45 minutes but TLC analysis showed that the starting material (**287**) was still present so more SmI_2 (3.0 mL, 0.2 mmol) was added. The resulting mixture was then allowed to stir one hour at which time MeOH (3 mL) was added and stirred for an additional 5 hours. The reaction mixture was then treated with water (20 mL) and extracted three times with Et_2O. The organic extracts were combined and washed with brine, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. Purification was accomplished by flash column chromatography (r_f 0.13 5:2 hexanes/ethyl acetate) using 1:1 hexanes/ethyl acetate as the eluent to give 27.4 mg (38% yield) of the desired product **290**.

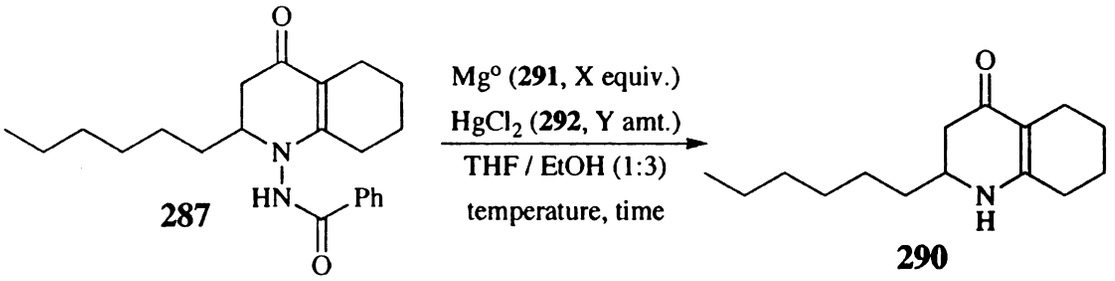
Entry 3: To a flame dried argon purged 50 mL 3-neck round bottom flask equipped with a magnetic stir bar and a reflux condenser was added Sm° (0.5 g, 3.33 mmol), I_2 (0.771 g, 3.02 mmol) and THF (15 mL). The resulting solution was heated to reflux for 1.5 hours. The resulting dark blue 0.2 M solution of SmI_2 (**289**) was stored in the dark and used for the reductive cleavage described immediately below.

To a flame dried argon purged 25 mL round bottom flask was added the hydrazine **287** (0.2792 g, 0.787 mmol) and MeOH (2.5 mL). To the solution was then added the previously prepared solution of SmI_2 (**289**, 8.66 mL, 1.73 mmol, 0.2 M solution in THF). The blue color disappeared immediately and after 45 minutes, TLC analysis showed that the starting material **287** was still present so more SmI_2 (2.0 mL, 0.4 mmol) was added. The resulting mixture was then allowed to stir overnight after which the solution was treated with 3N HCl (20 mL). The mixture was extracted three times with Et_2O. The aqueous layer was then treated with 10% aqueous sodium hydroxide and this was then extracted three times with ether. These organic layers of the second extraction were then combined, dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. Purification was accomplished by flash column chromatography (r_f 0.13 5:2 hexanes/ethyl acetate) using 1:1 hexanes/ethyl acetate as the eluent to give 14 mg (7.6% yield) of the desired product **290** as a white solid.

Spectral data for compound **290** ($C_{15}H_{25}NO$):

^{1}H NMR ($CDCl_3$) δ 0.853 (t, 3H, *J*=6.9 Hz), 1.22-1.27 (m, 10H), 1.46-1.72 (m, 5H), 2.09-2.25 (m, 3H), 2.30 (s, 1H), 2.39 (dd, 1H, *J*=3.6, 15.9 Hz), 3.44-3.55 (m, 1H), 4.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.63, 20.57, 21.73, 22.14, 22.25, 24.89, 28.66, 28.75, 21.28, 34.35, 41.90, 52.68, 106.09, 159.02, 191.82; IR; 1147.79m, 1203.73m, 1219.17m,

1242.32m, 1265.46m, 1307.90m, 1344.56m, 1359.99m, 1412.07m, 1441.01m, 1468.02s, 1502.74s, 1535.53s, 1549.04s, 1566.40s, 1610.77s, 2853.08m, 2922.53s, 3285.19br m; Mass spectrum *m/z* (% rel intensity) 236 M+1 (46) 235 M+ (47), 164 (20), 150 (100), 146 (58), 122 (48); white solid, mp 95-97°C.



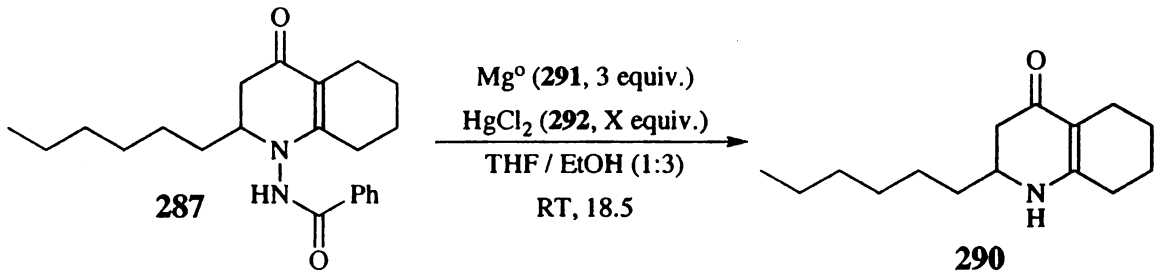
Procedures for Scheme 5.16 (initial attempts for the reductive cleavage using Mg° and $HgCl_2$):

Entry 1: To a flame dried argon purged 5 mL round bottom flask equipped with a magnetic stir bar was added the hydrazine **287** (100 mg, 0.282 mmol) and Mg° (mesh, 67.4 mg, 2.82 mmol) and a spatula tip of $HgCl_2$. The contents of the flask were then diluted with methanol (1.07 mL) and THF (0.36 mL). The mixture was allowed to stir for 18 hours and TLC analysis showed that only the starting material was present. At this time, another two or three spatula tips full of $HgCl_2$ were added and immediately an extremely exothermic reaction was observed heating the solvent to boil. After 30 minutes the TLC analysis showed that the starting material had been consumed. The reaction was quenched with water and extracted 3 times with Et_2O. The ether extracts were then washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification was accomplished by flash column

chromatography (r_f 0.13 5:2 hexanes/ethyl acetate) using 1:1 hexanes/ethyl acetate as the eluent to give 13.2 mg (18.2% yield) of the desired product **290**.

Entry 2: The protocol described for entry 1 was followed exactly except the reaction was cooled to 0°C before the THF and methanol was added. TLC analysis after 20 minutes showed no reaction had taken place so more $HgCl_2$ was added to initiate the reaction. The same workup as described in entry 1 was followed to give 23.3 mg (16.7% yield) of the desired product **290**.

Entry 3: To a flame dried argon purged 5 mL round bottom flask equipped with a magnetic stir bar was added the hydrazine **287** (100 mg, 0.282 mmol) and Mg° (mesh, 67.4 mg, 2.82 mmol) and $HgCl_2$ (54 mg, 0.199 mmol). The contents of the flask were then diluted with methanol (1.07 mL) and THF (0.36 mL). The mixture was allowed to stir for 6 hours and TLC analysis showed that the starting material was consumed. The reaction was quenched with water and extracted 3 times with ether. The ether extracts were then washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification was accomplished by flash column chromatography using (r_f 0.13 5:2 hexanes/ethyl acetate) 1:1 hexanes/ethyl acetate as the eluent to give 45.8 mg (69% yield) of the desired product **290**.



Procedures for Scheme 5.17 (determination of the optimal amount of $HgCl_2$):

Entry 1: The protocol as described for Scheme 5.16 entry 3 was followed exactly where 7.7 mg (0.0282 mmol) of $HgCl_2$ was added and the reaction was allowed to stir for 18.5 hours. Analysis of the crude ^1H NMR showed that the reaction only went to <5% conversion.

Entry 2: The protocol as described for Scheme 5.16 entry 3 was followed exactly where 15.3 mg (0.0564 mmol) of $HgCl_2$ was added and the reaction was allowed to stir for 18.5 hours. Analysis of the crude ^1H NMR showed that the reaction only went to <5% conversion.

Entry 3: The protocol as described for Scheme 5.16 entry 3 was followed exactly where 24.7 mg (0.0846 mmol) of $HgCl_2$ was added and the reaction was allowed to stir for 18.5 hours. Analysis of the crude ^1H NMR showed that the reaction only went to 19% conversion.

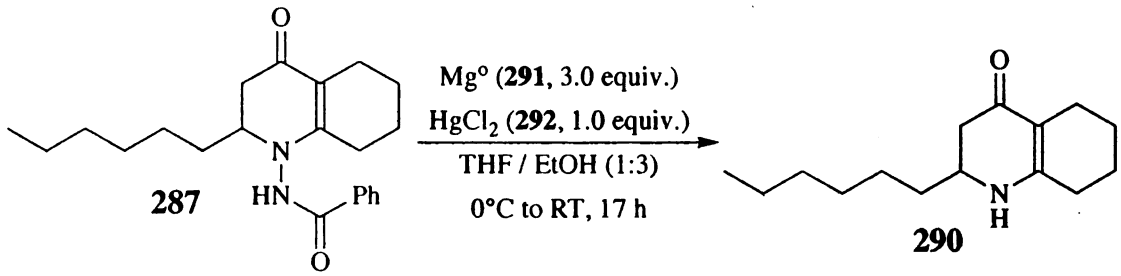
Entry 4: The protocol as described for Scheme 5.16 entry 3 was followed exactly where 38.3 mg (0.141 mmol) of $HgCl_2$ was added and the reaction was allowed to stir for 18.5 hours. Analysis of the crude ^1H NMR showed that the reaction went to 80% conversion.

Entry 5: The protocol as described for Scheme 5.16 entry 3 was followed exactly where 46 mg (0.1692 mmol) of $HgCl_2$ was added and the reaction was allowed to stir for 18.5 hours. Analysis of the crude ^1H NMR showed that the reaction went to 70% conversion.

Entry 6: The protocol as described for Scheme 5.16 entry 3 was followed exactly where 61.3 mg (0.2256 mmol) of $HgCl_2$ was added and the reaction was allowed to stir

for 18.5 hours. Analysis of the crude ^{1}H NMR showed that the reaction only that the reaction went to >95% conversion.

Entry 7: The protocol as described for Scheme 5.16 entry 3 was followed exactly where 78.6 mg (0.282 mmol) of $HgCl_2$ was added and the reaction was allowed to stir for 18.5 hours. Analysis of the crude ^{1}H NMR showed that the reaction went to >95% conversion.



Procedures for Scheme 5.18 (optimization and scalability for reductive cleavage):

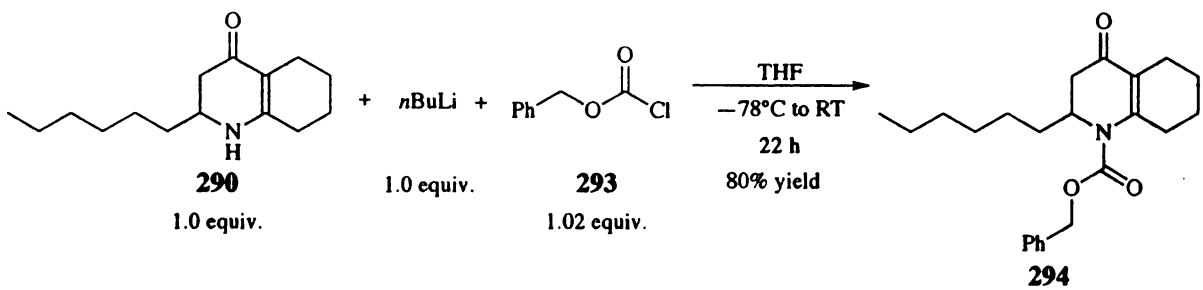
Entry 1 (0.355g): To a flame dried argon purged 10 mL round bottom flask equipped with a magnetic stir bar was added the hydrazine **287** (0.355 g, 1.0 mmol) and Mg° (mesh, 72 mg, 3.0 mmol) and $HgCl_2$ (0.272 g, 1.0 mmol). The contents of the flask were then cooled to 0°C and diluted with methanol (3.5 mL) and THF (1.2 mL). The mixture was allowed to warm to room temperature and stir for 17 hours. TLC analysis showed that the starting material was consumed. The reaction was quenched with cold 0.5 N HCl (20 mL) and extracted 3 times with CH_2Cl_2. The organic extracts were then combined and washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification was accomplished by flash column chromatography (r_f 0.13 5:2 hexanes/ethyl acetate) using 1:1 hexanes/ethyl acetate as the eluent to give 202.2 mg (80% yield) of the desired product **290**.

Entry 2 (1.0 g): To a flame dried argon purged 50 mL round bottom flask equipped with a magnetic stir bar was added the hydrazine **287** (1.0 g, 2.82 mmol) and Mg° (mesh, 203 mg, 8.46 mmol) and $HgCl_2$ (0.766 g, 2.82 mmol). The contents of the flask were then cooled to −20°C and diluted with methanol (10.0 mL) and THF (3.2 mL). The mixture was allowed to warm to room temp and stir for 17 hours. TLC analysis showed that the starting material was consumed. The reaction was quenched with cold 0.5 N HCl (67 mL) and extracted 3 times with CH_2Cl_2. The organic extracts were then combined and washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification was accomplished by flash column chromatography (r_f 0.13 5:2 hexanes/ethyl acetate) using 5:2 hexanes/ethyl acetate ramping to 1:1 hexanes/ethyl acetate as the eluent to give 0.535 g (62% yield) of the desired product **290**.

Entry 3 (1.2g): To a flame dried argon purged 50 mL round bottom flask equipped with a magnetic stir bar was added the hydrazine **287** (1.2 g, 3.376 mmol) and Mg° (mesh, 243 mg, 10.13 mmol) and $HgCl_2$ (0.916 g, 3.376 mmol). The contents of the flask were then cooled to 0°C and then diluted with methanol (11.8 mL) and THF (3.8 mL). The mixture was allowed to warm to room temperature and stir for 17 hours. TLC analysis showed that the starting material was consumed. The reaction was quenched with cold 0.5 N HCl (80 mL) and extracted 3 times with CH_2Cl_2. The organic extracts were then combined and washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification was accomplished by flash column chromatography (r_f 0.13 5:2 hexanes/ethyl acetate) using 5:2 hexanes/ethyl

acetate ramping to 1:1 hexanes/ethyl acetate as the eluent to give 0.535 g (62% yield) of the desired product **290**.

Entry 4 (9.0 g): To a flame dried argon purged 50 mL round bottom flask equipped with a magnetic stir bar was added the hydrazine **287** (9.0 g, 25.39 mmol) and Mg° (mesh, 1.83 g, 76.2 mmol) and $HgCl_2$ (0.766 g, 25.39 mmol). The contents of the flask were then cooled to 0°C and diluted with methanol (90 mL) and THF (30 mL). The mixture was allowed to warm to room temp and stir for 17 hours. TLC analysis showed that the starting material was consumed. The reaction was quenched with cold 0.5 N HCl (550 mL) and extracted 3 times with CH_2Cl_2. The organic extracts were then combined and washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification was accomplished by flash column chromatography (r_f 0.13 5:2 hexanes/ethyl acetate) using 5:2 hexanes/ethyl acetate ramping to 1:1 hexanes/ethyl acetate as the eluent to give 3.6 g (60% yield) of the desired product **290**.



290 1.0 equiv. | 1.0 equiv. | **293** 1.02 equiv. | **294**

Procedures for Scheme 5.19 (preparation of Cbz protected amine 294):

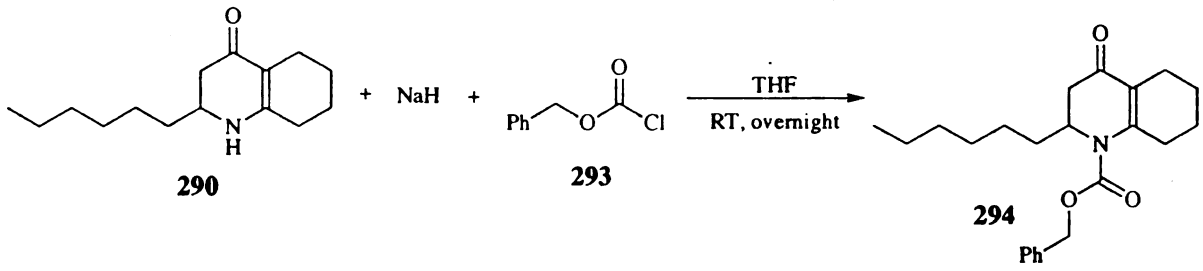
Reaction 1: To a flame dried argon purged 25 mL round bottom flask was added the amine **290** (0.2401 g, 1.02 mmol) and THF (3.5 mL). The solution was then cooled to −78°C and *n*-BuLi (0.37 mL, 1.03 mmol, 2.6 M solution in hexanes) was added over

1.5 hours via syringe pump. After the addition was complete, the resulting mixture was stirred for 30 minutes and to it was then added CbzCl (**293**, 0.15 mL, 1.04 mmol) in THF (1.5 mL) over 30 minutes. This was allowed to stir for 30 minutes and the cooling bath was removed warming the solution to room temperature in about 45 minutes. The reaction was then transferred to a separatory funnel containing saturated ammonium chloride and extracted with ethyl acetate three times, washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification was accomplished using flash column chromatography (5:1 hexanes/ethyl acetate, r_f 0.35) go give 242.4 mg (71.9 % yield) of the desired product **294**. In addition, 82.1 mg of the starting material was recovered (97.7% overall yield based on recovered amine).

Reaction 2: The protocol as described for reaction 1 was followed exactly except the reaction was allowed to stir for 22 hours at room temperature rather than 45 minutes. The reaction gave 238.9 mg (80.1% yield) of the desired product **294**.

Spectral data for compound **294** ($C_{23}H_{31}NO_3$):

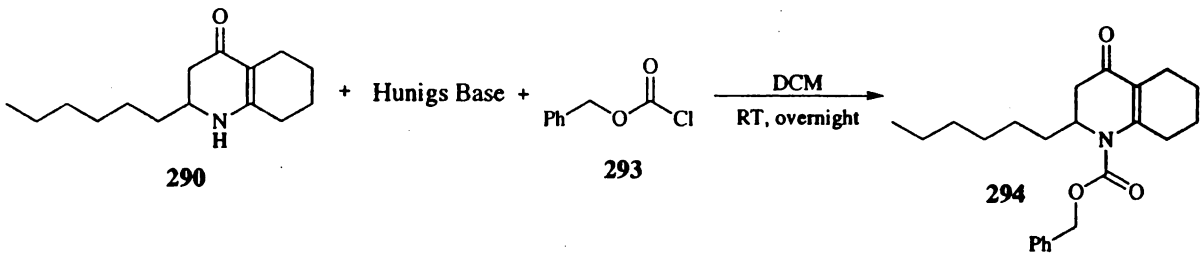
^{1}H NMR ($CDCl_3$) 0.80 (t, 3H, *J*=6.9 Hz), 1.16-1.48 (br m, 11H), 1.62-1.77 (br m, 3H), 2.06-2.41 (br m, 4H), 2.71-2.78 (dd, 1H, *J*=6.0, 17.1Hz), 2.99-3.06 (br m, 1H), 4.63-4.69 (m, 1H), 5.15 (s, 2H), 7.23-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) 13.54, 13.84, 21.25, 22.11, 25.89, 28.55, 30.42, 31.22, 41.49, 41.83, 52.21, 54.90, 55.29, 55.94, 67.75, 120.10, 127.61, 128.06, 128.49, 135.32, 150.60, 153.33, 193.14.



Unsuccessful Attempts for Cbz Protection using NaH:[101]

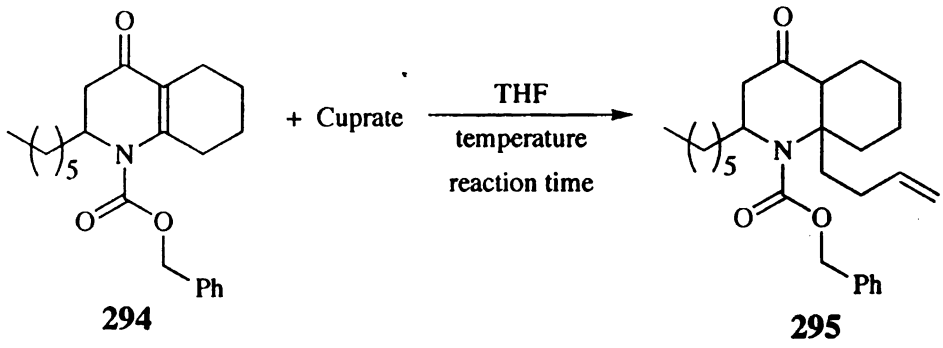
Attempt 1: To a flame dried argon purged 25 mL round bottom flask equipped with a magnetic stir bar was added NaH (16.6 mg, 0.356 mmol, 60% by wt. in mineral oil) and THF (0.5 mL). To the reaction mixture was then added the amine **290** (69.9 mg, 0.297 mmol) and the resulting mixture was allowed to stir at room temperature for 1.5 hours. To the reaction mixture was then added CbzCl·(**293**, 60.7 mg, 0.356 mmol). The solution was then allowed to stir overnight. Purification was then accomplished by flash column chromatography using 1:1 hexane/ethyl acetate as the eluent giving 53.3 mg (~50% yield) of a mixture of material that contained only about 50% **294**.

Attempt 2: The conditions as described for attempt 1 were followed exactly except the reaction was cooled to —78°C before NaH and CbzCl were added. After warming to room temperature and working up the reaction, it was observed that none of the desired product **294** was formed.



Unsuccessful Attempts for Cbz Protection using Hunig's Base:[102]

Following the protocol from the reference,[102] to a flame dried argon purged 25 mL round bottom flask equipped with a magnetic stir bar was added the amine **290** (.2244g, 0.953 mmol) and CH_2Cl_2 (3.6 mL). To the reaction mixture was then added Hunigs base (0.66 mL, 0.3.8 mmol) followed immediately by the addition of CbzCl (**293**, 0.41 mL, 2.86 mmol). The resulting mixture was allowed to stir at room temperature for 19 hours. The solution was then transferred to a separatory funnel containing 30 mL of water and extracted three times with CH_2Cl_2, the organic layers combined, washed with 1N HCl (50 mL), and twice with saturated sodium bicarbonate (2 x 20 mL). None of the desired product **294** was isolated from this reaction.



294 **295**

Procedures for Scheme 5.21 (addition of cuprates 1, 2, and 3 to the Cbz protected amine 294):

Entry 1: To a previously prepared solution of cuprate 2 (2.3mL, 0.599 mmol, 0.25 M solution in THF/Et_2O) (see preparaton of cuprates above) was added the Cbz protected vinylogous amide **294** (0.1474g, 0.399 mmol) in THF (0.5 mL). The reaction was then allowed to stir at −78°C for 10.5 hours at which time the cooling bath was packed with dry ice to ensure that the reaction mixture warmed slowly to room temperature. After 20 h, the reaction was cooled back to −78°C and to it was added 9:1 mixture of

NH_4Cl/NH_4OH (3 mL). The reaction was then allowed to warm to room temperature and stirred for 3h. The resulting blue solution was then transferred to a separatory funnel and extracted three times with ethyl acetate. The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude ^1H NMR indicated that mostly starting material was present with only <5% other material observed in the baseline in the vinyl region.

Entry 2: To a previously prepared solution of cuprate **3**[122] (2.1 mL, 0.75 mmol, 0.36 M solution in THF/Et_2O) (see preparaton of cuprates above) was added the vinylogous amide **294** (0.77 mL, 0.5 mmol, 0.65M solution in THF) was then added all at once. The acetone bath was then packed with dry ice to ensure that the reaction mixture warmed very slowly to room temperature. After 17 h, the reaction was cooled back to −78°C and to it was added 9:1 mixture of NH_4Cl/NH_4OH (2.5 mL). The reaction was then allowed to warm to room temperature and stirred for 3h. The resulting blue solution was then transferred to a separatory funnel and extracted three times with ethyl acetate. The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude ^1H NMR indicated that only starting material was present and none of the desired product **295** was formed.

Entry 3: The protocol as described in entry 2 was followed exactly except after the vinylogous amide **294** was added, the reaction was immediately allowed to warm to −45°C over one hour and stir for 30 minutes, then warmed to −20°C for 30 minutes, and then to 0°C for 14 hours, and finally to 10°C for one more night. After 42 hours total reaction time, the reaction was cooled back to −78°C to it was added 9:1 mixture of

NH_4Cl/NH_4OH (2.5 mL). The reaction was then allowed to warm to room temperature and stirred for 3h. The resulting blue solution was then transferred to a separatory funnel and extracted three times with ethyl acetate. The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. The crude ^1H NMR indicated that only starting material was present and none of the desired product **295** was formed.

Entry 4: To the previously prepared solution of cuprate 1 (4.03 mL, 0.525 mmol, 0.13 M solution in THF/hexanes/ether) (see preparaton of cuprates above) was added the vinylogous amide (0.129g, 0.35 mmol) dropwise in ether (1.0 mL). The reaction was allowed to stir at −78°C for 3 hours and a 9:1 solution of NH_4Cl/NH_4OH (5.0 mL) was added. The cooling bath was removed and the reaction mixture was allowed to stir for 2 hours. The solution was transferred to a separatory funnel, extracted three times with ethyl acetate, The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. None of the desired product **295** was observed in the crude ^1H NMR.

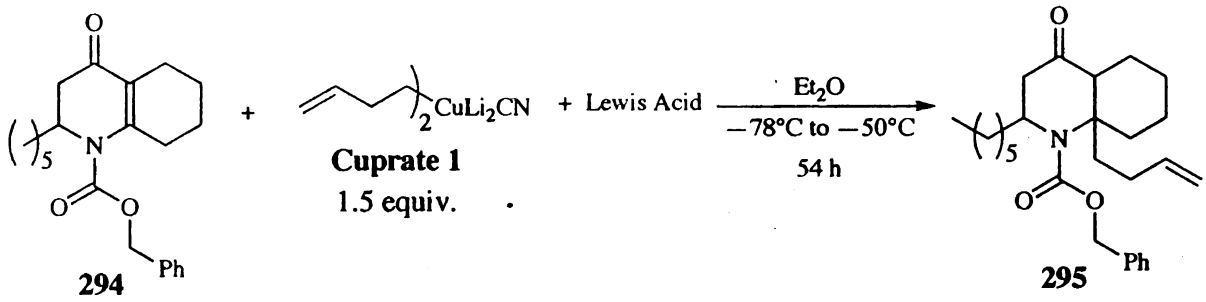
Entry 5: To the previously prepared solution of cuprate 1 (4.03 mL, 0.525 mmol, 0.13 M solution in THF/hexanes/ether) (see preparaton of cuprates above) was added the vinylogous amide **294** (0.129g, 0.35 mmol) dropwise in ether (1.0 mL). The reaction was allowed to stir at −78°C for 3 hours and then warmed to −20°C for 53 hours. After 53 hours, a 9:1 solution of NH_4Cl/NH_4OH (5.0 mL) was added. The cooling bath was removed and the reaction mixture was allowed to stir for 2 hours. The solution was transferred to a separatory funnel, extracted three times with ethyl acetate, The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered

and the solvent was removed under reduced pressure. The starting material was consumed and purification was attempted via flash column chromatrgraphy using 10:3 hexanes/EtOAc to give 37.9 mg of a mixture of two spots by TLC and 36.9 mg of pure uncharacterized material. The two isolated compounds were not the desired product **295** and further characterization was not accomplished.

Entry 6: To the previously prepared solution of cuprate 1 (3.7 mL, 0.48 mmol, 0.13 M solution in THF/hexanes/ether) (see preparaton of cuprates above) was added the vinylogous amide **294** (0.118 g, 0.32 mmol). The reaction was allowed to stir at −78°C for 3 hours and then warmed to −25°C for 16 hours. After 19 total reaction hours, a 9:1 solution of NH_4Cl/NH_4OH (5.0 mL) was added. The cooling bath was removed and the reaction mixture was allowed to stir for 1 hour. The solution was transferred to a separatory funnel, extracted three times with ethyl acetate, the organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. None of the desired product **295** was observed in the crude ^1H NMR.

Entry 7: To the previously prepared solution of cuprate 1 (5.2 mL, 0.671 mmol, 0.13 M solution in THF/hexanes/ether) (see preparaton of cuprates above) was added the vinylogous amide **294** (101.2 mg, 0.274 mmol) dropwise in ether (1.0 mL). The reaction was then allowed to warmed to −10°C and was stirred for 48 hours at which time a 9:1 solution of NH_4Cl/NH_4OH (5.0 mL) was added. The cooling bath was removed and the reaction mixture was allowed to stir for 30 minutes. The solution was transferred to a separatory funnel, extracted three times with ethyl acetate, The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent

was removed under reduced pressure. The starting material was consumed and purification was accomplished via flash column chromatography using 5:1 mixture of hexanes/EtOAc to give 38.8 mg of pure material that was not the desired product **295**. Further characterization was not accomplished.



Procedures for Scheme 5.22 (Lewis Acid Promoted[123-127] addition of cuprate 1 to the Cbz protected amine 294):

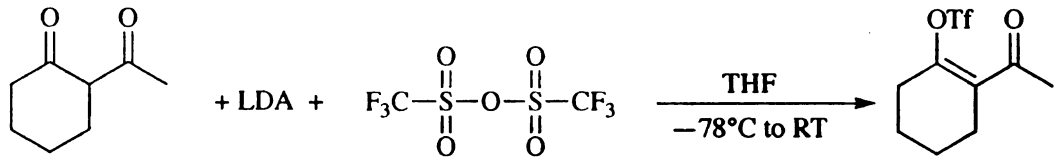
Entry 1 ($BF_3{\cdot}OEt_2$): To the previously prepared solution of cuprate 1 (2.23 mL, 0.29 mmol, 0.13 M solution in THF/hexanes/ether) (see preparaton of cuprates above) was added a previously prepared solution of the vinylogous amide **294** (71.3 mg, 0.193 mmol) and $BF_3{\cdot}OEt_2$ (0.0242 mL, 0.193 mmol) in ether (1.0 mL) dropwise via syringe over 2-3 minutes. The reaction was allowed to stir at −78°C for 21 hours and the temperature was raised to −50°C and the reaction was stirred for another 23 hours. After 44 hours total reaction time, a 9:1 solution of NH_4Cl/NH_4OH (5.0 mL) was added, the cooling bath removed and the reaction mixture was allowed to stir for 2 hours. The solution was transferred to a separatory funnel, extracted three times with ethyl acetate. The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. None of the desired product **295** was observed in the crude ^1H NMR.

Entry 2 ($ZnCl_2$): To the previously prepared solution of cuprate 1 (1.9 mL, 0.251 mmol, 0.13 M solution in THF/hexanes/ether) (see preparaton of cuprates above) was added a previously prepared solution of the vinylogous amide **294** (61.7 mg, 0.167 mmol) and $ZnCl_2$ (0.2 mL, 0.167 mmol, 1.0 M solution in ether) in ether (0.87 mL) dropwise via syringe over 2-3 minutes. The reaction was allowed to stir at −78°C for 21 hours and the temperature was raised to −50°C and the reaction was stirred for another 23 hours after which a 9:1 solution of NH_4Cl/NH_4OH (5.0 mL) was added. The cooling bath was removed and the reaction mixture was allowed to stir for 2 hours. The solution was transferred to a separatory funnel, extracted three times with ethyl acetate. The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. None of the desired product **295** was observed in the crude ^1H NMR.

Entry 3 (TMSCl): To the previously prepared solution of cuprate 1 (2.4 mL, 0.309 mmol, 0.13 M solution in THF/hexanes/ether) (see preparaton of cuprates above) was added a previously prepared solution of the vinylogous amide **294** (76.2mg, 0.206 mmol) and TMSCl (0.026 mL, 0.206 mmol) in ether (1.0 mL) dropwise via syringe over 2-3 minutes. The reaction was allowed to stir at −78°C for 21 hours and the temperature was raised to −25°C over three hours and the reaction was stirred for another 22 hours. After 56 hours total reaction time, a 9:1 solution of NH_4Cl/NH_4OH (5.0 mL) was added and the cooling bath was removed. The reaction mixture was allowed to stir for 2 hours and the solution was transferred to a separatory funnel, extracted three times with ethyl acetate. The organic layers were then combined and washed with brine, dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure.

Purification was attempted via flash column chromatography using 10:1 hexanes/ethyl acetate as the eluent and 24 mg of the starting material **294** was recovered. In addition, 17.8 mg of some other unknown material was isolated that was not the desired product **295**.

Synthesis of the Alternate diene 227:

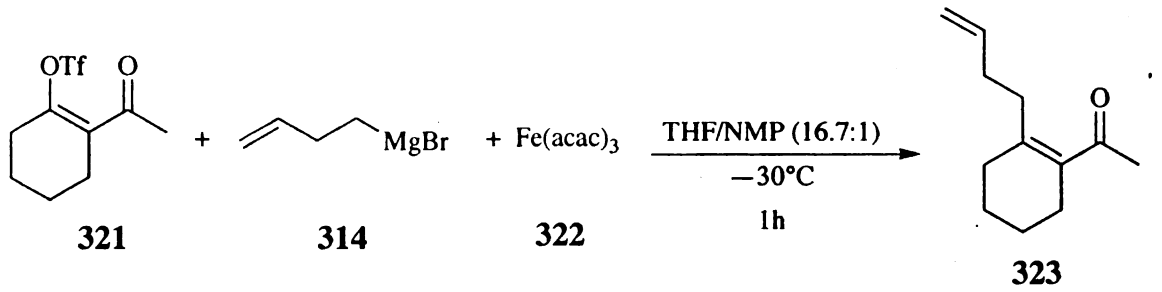


318 **319** **320** **321**

*Preparation of the triflate **321**:* To a flame dried argon purged 250 mL round bottom flask equipped with a magnetic stir bar was added 2-acetyl-cyclohexanone **318** (7.0 mL, 50 mmol) and THF (65 mL). The solution was cooled to —78°C and LDA **319** (45 mL, 44 mmol, 1.0 M solution in THF) was added over 15 minutes. The resulting solution was stirred at —78°C for 30 minutes at which time, trifluoromethyl sulfonic anhydride **320** (8.07 mL, 48 mmol) was added over about 10 minutes. The reaction mixture was then stirred for 30 minutes at —78°C and the cooling bath was removed allowing the reaction to warm to room temperature. After 3 hours at room temperature, the solvent was removed and purification was accomplished by flash column chromatography using 15:1 hexanes/ethyl acetate ramping to 10:1 hexanes/ethylacetate to to give the desired triflate **321** as a colorless oil.

Spectral data for compound **321** ($C_9H_{11}F_3O_3S$):

^{1}H NMR ($CDCl_3$) δ 1.63-1.69 (br m, 2H), 1.73-1.79 (br m, 2H), 2.36 (s, 3H), 2.37-2.46 (br m, 4H). Final structure determination was confirmed by further modification to the diene **227**.



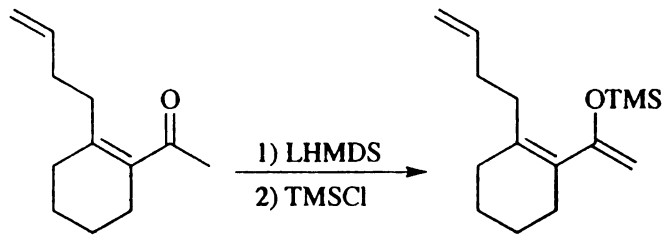
321 **314** **322** **323**

Preparation of 323[128]: To a flame dried argon purged 250 mL round bottom flask equipped with a magnetic stir bar was added the triflate **321** (1.32 g, 4.85 mmol). The triflate was then diluted with THF (70 mL) and $Fe(acac)_3$ **322** (0.171 g, 0.485 mmol) was added followed immediately by N-methylpyrolidinone (NMP, 4.4 mL). The resulting reaction mixture was then cooled to −30°C and to it was added butenylmagnesiumbromide **314** (11 mL, 5.35 mL, 0.5 M solution in THF). The reaction was stirred for 30 minutes and TLC analysis showed that starting material was still present so to the reaction was added more butenylmagnesiumbromide **314** (1.46 mL, 2.92 mmol). The reaction was stirred for an additional 15 minutes and then the reaction mixture was transferred to a separatory funnel containing ammonium chloride. Extraction was done three times with ether and the combined organic layers were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure. Purification was accomplished via flash column chromatography (r_f = 0.37 9:1 hexanes/ethyl acetate) using 15:1 hexanes/ethyl acetate as the eluent to give the desired product **323** as a colorless oil.

Spcetral data for compound **323** ($C_{12}H_{18}O$):

^{1}H NMR ($CDCl_3$) δ 1.50-1.56 (m, 3H), 2.05-2.35 (br m, 12H), 4.85-4.97 (m, 2H), 5.67-5.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.83, 21.96, 26.50, 29.22, 30.01, 32.42, 33.92,

114.19, 133.47, 137.93, 142.5, 204.08; Mass spectrum *m/z* (% rel intensity) 179 M^{+1} (100), 178 M^{+} (17), 163 (12), 150 (14), 149 (65), 136 (18), 135 (55), 121 (10), 107 (13). Final structure determination was confirmed by further modification to the diene **227**.



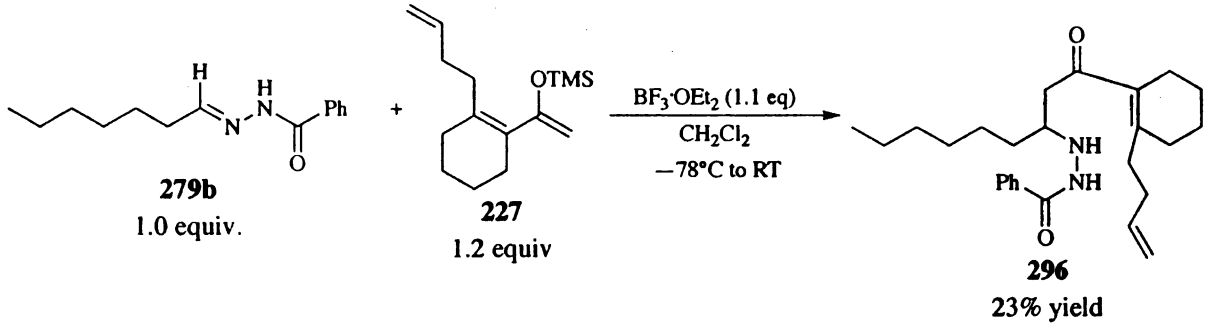
324 **227**

Preparation of diene 227: To a flame dried argon purged 250 mL round bottom flask equipped with a magnetic stir bar was added the ketone **324** (1.682 g, 9.435 mmol) and THF (20 mL). The solution was cooled to −78°C and LHMDS (9.9 mL, 9.91 mmol, 1.0 M solution in THF) was added over 15 minutes. The resulting solution was allowed to warm slowly to −30°C and then cooled back to −78°C. To the reaction was then added TMSCl (1.5 mL, 11.8 mmol) in THF (10 mL) over about 30 minutes. Immediately after the addition was complete, the reaction was allowed to warm to room temperature. The solvent was then removed under reduced pressure and the resulting gel was diluted with ether and filtered through Celite. The Celite was washed with several portions of ether to ensure all the desired material was extracted from the Celite. Purification was accomplished by distillation (75°C, 0.1 mmHg) to afford 1.85 g (78.2% yield) of the diene **227** as a colorless oil.

Spectral data for compound **227**:

^{1}H NMR ($CDCl_3$) δ 0.18 (s, 9H), 1.56 (br s, 4H), 1.99-2.26 (br m, 8H), 4.11 (s, 1H), 4.27 (s, 1H), 4.90-5.02 (m, 2H), 5.75-5.88 (br m, 1H); ^{13}C NMR ($CDCl_3$) δ 0.18,

22.76, 28.83, 28.46, 29.01, 32.73, 34.14, 92.80, 114.08, 130.77, 134.55, 138.89, 157.79; IR (neat) 752.33w, 844.93vs, 864.23s, 910.52m, 1010.83s, 1035.91m, 1074.49w, 1089.92w, 1201.96s, 1282.54 s, 1286.68s, 1361.92vw, 1439.08w, 1448.73w, 1614.62m, 1641.63w, 1686.00vw, 2858.97m, 2930.24s, 3076.85w cm^{-1}; mass spectrum *m/z* (% rel intensity) 250 M+ (5), 236 (21), 235 (42), 222 (60), 221 (68), 205 (18), 179 (13), 145 (22), 132 (22), 120 (31), 117 (52), 75 (100), 73 (99), 45 (72).



Procedure for Scheme 5.23 (*aza*-Diels-Alder attempt using alternate diene 227):

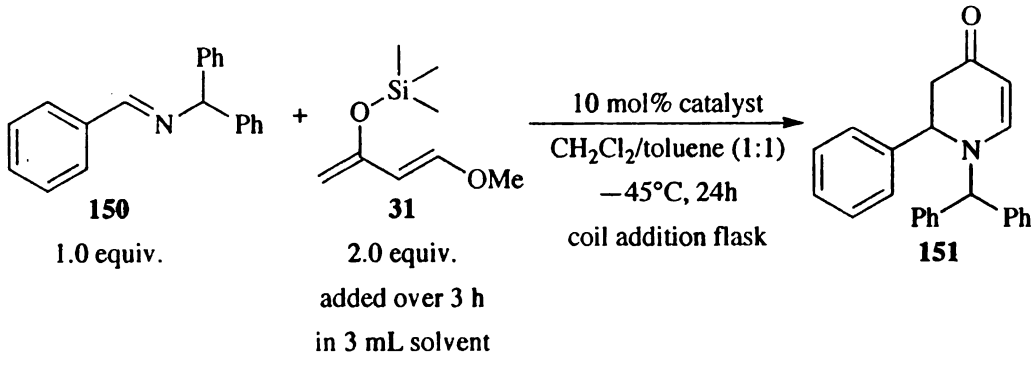
To a flame dried argon purged 25 mL round bottom flask was added the imine **279b** (0.2323 g, 1.0 mmol) and CH_2Cl_2 (5 mL). The contents of the flask were then cooled to −78°C and to the flask was added the diene **227** (0.3008 g, 1.20 mmol) in two 2.5 mL portions of CH_2Cl_2. After 5 minutes, $BF_3{\cdot}OEt_2$ (0.138 mL, 1.10 mmol) was added all at once and the cooling bath was packed with dry ice so the reaction would warm very slowly to room temperature. After 22 hours total reaction time, the solution was transferred to a separatory funnel containing saturated sodium bicarbonate, extracted three times with CH_2Cl_2. The combined organic layers were dried, filtered and the solvent was removed under reduced pressure. Purification was accomplished by flash column chromatography using 6.5:1 hexanes/ethyl acetate (500 mL) and then 3:1

hexanes/ethyl acetate to afford 100 mg (23% yield) of the uncyclized Mannich type product **296**.

Spectral data for compound **296**:

^{1}H NMR ($CDCl_3$) δ 0.83 (t, 3H, *J*=6.9 Hz), 1.23-1.59 (br m, 16H), 2.00-2.18 (br m, 6H), 2.56-2.75 (m, 2H), 3.38 (br s, 1H), 4.86-4.98 (br m, 2H), 5.12 (br s, 1H), 5.68-5.81 (br m, 1H), 7.35-7.49 (br m, 3H), 7.72-7.76 (br m, 2H), 8.09 (br s, 1H); ^{13}C NMR 13.68, 21.77, 21.96, 22.22, 25.67, 26.42, 29.00, 30.01, 31.34, 32.42, 33.00, 34.12, 45.35, 56.73, 114.21, 126.50, 128.23, 131.24, 132.56, 133.33, 137.94, 143.16, 166.08, 205.98; IR (neat) 704.11s, 794.77w, 908.59s, 972.25 w, 995.40m, 1028.19w, 1074.49m, 1140.08m, 1178.66w, 1282.83s, 1363.85m, 1475.73s, 1506.60s, 1579.90m, 1676.35vs, 2855.01vs, 2924.46vs, 3028.63m, 3067.21s, 3289.05vs cm^{-1}.

7.5 Experimental Procedures and Characterizations Data for Chapter Six



Procedure for Scheme 6.1 (*aza*-Diels-Alder Reaction Using the One (B1) and Two Boron (B2) Catalyst)

Entry 1: To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $BH_3 \cdot SMe_2$ (0.1 mmol, 0.5 M solution in toluene), (S)-VAPOL (54 mg, 0.1 mmol), and phenol (9.4 mg, 0.1 mmol). To this was added toluene (2 mL) and then the flask was sealed with the stopcock and heated to 100°C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 100°C for 0.5 hours yielding the B1 VAPOL-boron catalyst (~10:1 B1/B2 as measured by ^1H NMR). After cooling the stopcock was removed and replaced with a rubber septum. The catalyst was dissolved by the injection via syringe of 2.0 mL CH_2Cl_2/toluene (in two portions). The catalyst solution was transferred by syringe to a flask containing the imine prepared as immediately below.

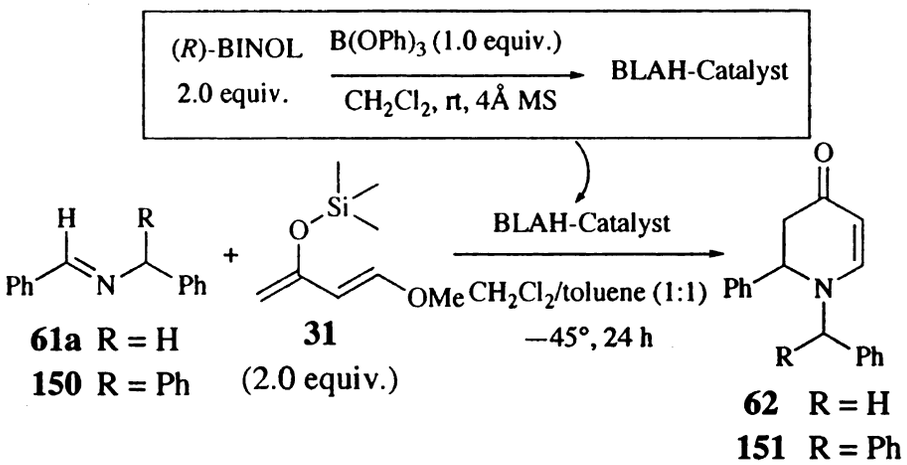
To a flame dried, argon purged homemade flask with a cold addition coil (see Figure 2.4) equipped with a stir bar was added the imine **150** (0.271 g, 1.0 mmol). The flask was topped with two rubber septa and the VAPOL-boron catalyst was added in two

1.0 mL portions of a 1:1 ratio of CH_2Cl_2/toluene directly to the bottom of the flask by a syringe equipped with a long needle. This was allowed to stir for 5-10 minutes at room temperature and then cooled to –45 °C. Meanwhile, in a separate flame dried 5 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) (0.38 mL, 2.0 mmol) and CH_2Cl_2/toluene (1:1) (3.0 mL). The diene was taken up in a syringe and added over 3.0 hours via syringe pump through the cold addition coil. The reaction was then allowed to stir at –45 °C for the duration of the reaction (24 total hours). After completion of the reaction, saturated sodium bicarbonate (~20 mL) was added to the reaction flask at –45 °C. This was then transferred to a separatory funnel and extracted with three or four 30-40 mL portions of CH_2Cl_2. The combined organic layers were placed in a 250 mL round bottom flask and the solvent was then removed via rotary evaporation. The flask was then equipped with a stir bar and cooled in an ice bath. To this was then added a previously cooled (0 °C) 20:1 mixture of THF and 1N HCl (50 mL) at which time the flask was removed from the ice bath and allowed to stir (monitored by TLC) until the undesired spots close to the desired product disappeared (usually less than one hour). This was then transferred to a separatory funnel containing distilled water (75-100 mL) followed by extraction of the crude product with four 50 mL portions of CH_2Cl_2. The combined organic layers were then dried over magnesium sulfate, filtered, and solvent was removed via rotary evaporation. The product was then purified via flash column chromatography (36 cm x 2 cm) to give 117.5 mg (35% yield) of the desired product **151** with 30% ee.

Entry 2: The protocol as described in entry 1 was followed exactly, except the B2 catalyst was used and it was prepared in the following fashion. To a flame dried, argon

purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $B(OPh)_3$ (116 mg, 0.4 mmol), (S)-VAPOL (54 mg, 0.1 mmol), and distilled water (1.8 μL, 0.1 mmol). To this was added toluene (2 mL) and then the flask was sealed with the stopcock and heated to 80°C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 80°C for 0.5 hours yielding the B2 VAPOL-boron catalyst (~19:1 B2/B1 by). The workup was accomplished following the exact procedure from entry 1 and purification using flash column chromatography gave 277.7 mg (82% yield) of the desired product **151** with 71% ee.

Entry 3: The protocol as described in entry 1 was followed exactly, except the B2 catalyst was used and it was prepared in the following fashion. To a flame dried, argon purged single-necked flask that had its 14/20 joint replaced with a threaded Teflon high-vacuum T-shaped stop-cock equipped with a stir bar was added $BH_3 \cdot SMe_2$ (0.2 mmol, 0.5 M solution in toluene), (S)-VAPOL (54 mg, 0.1 mmol), phenol (9.4 mg, 0.1 mmol), and distilled water (1.8 μL, 0.1 mmol). To this was added toluene (2 mL) and then the flask was sealed with the stopcock and heated to 100°C for one hour. After one hour, the solvent was removed via high vacuum and left under high vacuum at 100°C for 0.5 hours yielding the B2 VAPOL-boron catalyst. The workup was accomplished following the exact procedure from entry 1 and purification using flash column chromatography gave 106 mg (31% yield) of the desired product **151** with 75% ee.



Procedure for Scheme 6.4 (*aza*-Diels-Alder attempt using the BLAH-Catalyst):

Entry 1: A 25 mL round bottom flask equipped with a magnetic stir bar was flame dried and purged with argon. The flask was then put in a glove box and to it was added $B(OPh)_3$ (0.291 g, 1.0 mmol, purified by distillation), (*R*)-BINOL (0.573 g, 2.0 mmol), and the imine **61a** (0.195 g, 1.0 mmol). The flask was then taken out of the glove box and to it was then added a 1:1 ratio of CH_2Cl_2/toluene (4.0 mL) and was allowed to stir for 15 minutes at room temperature and then cooled to –45 °C. Meanwhile, in a separate flame dried 5 or 10 mL round bottom flask purged with argon was added Danishefsky's diene (**31**) (0.38 mL, 2.0 mmol) and CH_2Cl_2/toluene (1:1) (3.0 mL). The diene was taken up in a syringe and added over 3.0 hours via syringe pump. The reaction was allowed to stir at –45 °C for an additional 21 hours. After completion of the reaction, saturated sodium bicarbonate (~20 mL) was added to the reaction flask at –45 °C. This was then transferred to a separatory funnel and extracted with three or four 30-40 mL portions of CH_2Cl_2. The combined organic layers were placed in a 250 mL round bottom flask and the solvent was then removed via rotary evaporation. The flask was then equipped with a stir bar and cooled in an ice bath. To this was then added a previously cooled (0 °C) 20:1 mixture of THF and 1N HCl (50 mL) at which time the flask was removed from the ice

bath and allowed to stir (monitored by TLC) until the undesired spots close to the desired product disappeared (usually less than one hour). This was then transferred to a separatory funnel containing distilled water (75-100 mL) followed by extraction of the crude product with four 50 mL portions of CH_2Cl_2. The organic layers were combined, dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure. Purification was accomplished via flash column chromatography (36 cm x 2 cm) to give 197.3 mg of the desired product **62** (75% yield). The enantiomeric excess was determined to be 80-88% (not baseline separated) by chiral HPLC analysis with the aid of an authentic sample of the racemic product.

Entry 2: The protocol as described for entry 1 was followed exactly except 0.271 g (1.0 mmol) of the benzhydryl imine **150** was used rather than the imine **61a**. The reaction gave 311.0 mg (92% yield) of the desired product **151** and 89% enantiomeric excess was measured.

Entry 3: The protocol as described for entry 2 was followed exactly except 29.1 mg (0.1 mmol) of $B(OPh)_3$ and 57.3 mg (0.2 mmol) (*R*)-BINOL (10 mol% BLAH-catalyst) was premixed with the imine. The reaction gave 135 mg (39% yield) of the desired product **151** and 90% enantiomeric excess was measured.

Entry 4: The protocol as described for entry 3 was followed exactly except after the reaction was cooled to −45°C, a previously prepared solution of $B(OPh)_3$ (0.262 g, 0.9 mmol) in CH_2Cl_2/toluene (1:1) (0.5 mL) was added to the reaction vessel immediately before the diene was added. The reaction gave 186 mg (54% yield) of the desired product **151** and 60% enantiomeric excess was measured.

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