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CATALYTIC ASYMMETRIC AZIRIDINATION -- PREPARATION OF LIGAND, EXPLORATION OF MECHANISM AND DISCOVERY OF NEW METHODOLOGY

VOLUME 1

By

Yu Zhang

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ABSTRACT

CATALYTIC ASYMMETRIC AZIRIDINATION
-- PREPARATION OF LIGAND, EXPLORATION OF MECHANISM AND DISCOVERY OF NEW METHODOLOGY

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Yu Zhang

The large scale preparation of racemic VANOL ligand by oxidative coupling and the improved resolution of VANOL were examined in the first part of this thesis. A highly efficient and enantioselective deracemization process of the vaulted and linear biaryl ligands was developed for the preparation of optically pure *S*-VAPOL and *S*-VANOL ligands

The mechanism of the chiral ligand-borate catalyzed asymmetric aziridination reaction of N-benzhydryl aldimines and ethyl diazoacetate as well as the origin of the enantioselectivity was studied in detail. It was proposed that the active catalyst was generated from one molecule of the chiral ligand and one equivalent of triphenyl borate. Modeling suggested that the coordination of the N-benzhydryl imine with the chiral borate Lewis acid catalyst involves two CH-π (face-edge) interactions between the catalyst and the substrate.

In the second part of this thesis, aldimines with various symmetrically and/or asymmetrically substituted N-protecting groups were designed and prepared to examine this proposal, and the effects of electronics and sterics of these imines on the reaction outcome were studied. These mechanistic studies eventually led to the discovery of the aziridination methodology with the N-BUDAM and N-MEDAM imines, which exhibit significantly improved stereoselectivity and reactivity over the unsubstituted benzhydryl imines. The study on the α-alkylbenzyl imines suggested possible applications of the

observed match/mismatched pair, whereas the studies of the relative reaction rates of various substrates suggested possible non-bonding interactions between the substrate and catalyst, provided insights into the mechanism of the aziridination reaction.

The exploration of the structures of the catalysts derived from the chiral ligand and triphenyl borate led to the discovery of two active borate species. The identification of the actual active aziridination catalyst species, along with the studies of match/mismatched relationships with chiral benzhydryl imines suggested that the aziridination reaction involves a bis-borate catalyst species which is different from the original proposal.

To my dearest grandparents, my parents and my wife

without whom everything would be impossible

Preface

My memory of chemistry can be traced back to 22 years ago. As a child I was always curious, and always tried to find something interesting to do at my spare time. It was lucky for me as there was not internet and video game available at that time, and I found that several of the "Chemistry for Kids" books bought by my dad were more interesting than just hanging around the street with other equally over-energetic kids. As a chemistry lecturer for a small college and a devoted scholar, my father bought various books for me on every trip to Shanghai and my personal bookshelves quickly filled with all kind of stories about mathematics, physics and mostly, chemistry. Meanwhile, as a chemist my father was never hesitated to show me the interesting part of his lab work, such as how to change the color of the solution from yellow to black. As a result I read so much of these books that I nowadays almost regret that I should have spent more time with my friends.

Life for a high school student was not easy, as the admission to a good university seemed to be (and still is) the only best choice for a kid. My interest in chemistry was quickly quenched with tons of homework of several subjects. I never found the text of chemistry to be difficult, however, under the extreme pressure of study and exams, the "love" for chemistry was more like an "instinct for survival". When my parents told me to apply for East China University of Science and Technology, which was well-known for its chemical engineering and chemistry program, I agreed without any thinking.

Finally I indeed ended up in the chemical engineering program in this university. The first two years in college passed without a glimpse. As a typical college student I took or skipped the standard classes related to chemical engineering, crammed for the exams. However, somehow I knew I was not ready for an engineer. I wanted to study

something more curious, more creative, something not just related to the calculation of flow rate. With some help, I transferred to Department of Chemistry as I wished. As a result of this choice, I was not only able to study many courses which were much more appealing, but also ended up in a class where I met my future wife, Zhenjie, for the first time.

The chemistry lab = fun, at least that was what I was thinking when I started to do the undergraduate thesis lab work in Professor Guobin Rong's lab. Prof. Rong was a patient and knowledge advisor, on the other hand he also looked after me like a father. Dr. Rujian Ma, a former graduate student in the group was kind and generous, he was willing to teach a novice like me all the details about one certain operation. In these four years I did find some spare time to study English as a second major. My English was quite horrible when I entered the program, however I was lucky enough to met several almost "legendary" professors, and my special thanks should go to Professor Shichang Zhu, who was known to be a "pushy" professor. However, I was lucky that this aggressive yet patient, energetic and meticulous old lad found something in me and gave me so much encouragement and help, after three years my understanding of English was never the same. The memory in the college was quite happy, if not counting my failed attempt to enter the graduate program in the same university. Yes as a result of my total fiasco in the admission exams, I was unable to be a graduate student as I wished and had to find a job.

The job in a state-run research institute was comfortable and almost too idle for a young man who wanted to do something. It was then that I started to think about graduate program in United States. Should I say that I was fortunate because there were always helpful people around? My department manager, Mr. Yunguang Hu, apparently did not think that I should get stuck there forever, and he suggested I should pursue my dream and do something more significant. It was so gratifying that Mr. Hu even offered

to write recommendation letters for me, even though the department of human resource was apparently quite unhappy due to the fact that he let me leave "so easily".

And then I was in United States, finally. The first year, should I say, was almost "overwhelmingly difficult". I thought I was ready, but it seemed that I was never ready enough. After four years of brainless working experience, my memory was dilute and my response was slow, I could hardly follow the course and hardly handle the homework let alone the exams. I used to think I was smart but the harsh reality forced me to doubt myself for once. However, behind every man there is always a strong woman, and with the help of my wife I slowly, staggeringly caught up and found myself back into chemistry. There will always be some regret, but I can look back and tell myself: "not bad"!

On a beautiful fall morning, I walked along the hallway of 5th of Chemistry building, and on the end of hallway I saw an old gentleman in an office, he was studying a book as careful and devoted as a child studying his most precious toy. I did not know who he was, until days later somebody told me it was Professor Wulff. A quick background check suggested that he just moved from University of Chicago, he was good, actually very good in research and he had almost perfect reputation (isn't that important!). Since he is a synthetic organic chemist and I wanted to do something in the same area, my choice seemed quite obvious. Until I screwed up with the winter time change and came to Professor Wulff's office one hour after when I was supposed to meet him. However he was not annoyed by my ignorance and quite happily talked with me about the weather, the school and most importantly, the chemistry that was going on in his lab. It took me just 0.5 second to decide that I wanted to work in his lab. And after some persistent talk and emails, I did end up in Professor Wulff's group as I wished.

As usual, the first year in the lab was tough, if not extremely tough as my bench skill was limited to undergraduate level. The former postdoctoral fellows Dr. Hongqiao Wu, Dr. Xuejun Liu and former graduate student Dr. Xiaowu Jiang helped me bit by bit,

from running the TLC to the more formidable silica gel chromatography. Specifically thanks to Hongqiao, who was so generous that he was willing to tell me anything he knew about chemistry, yet was also so ridiculously funny for being a guy that was much older than me. With the kind help of all these people, I finished the projects of oxidative coupling and deracemization before the oral.

I thought I learned everything from others and should be able to handle everything in this lab. I just finished my oral and first two projects, and Professor Wulff just told me to write the first paper. I was joyful, almost too joyful about my research, until the inevitable result of aziridination came to me. Being unable to repeat some former group members' result was an insult and a great shame for a junior student. Being a third-year student, I just began to know what I was doing, what I wanted to do. However, the feeling of defeat was, overwhelming. For the 8-10 months that I worked on the project of the reinvestigation of the aziridination, I asked for an answer but the real answer seemed to be so elusive that the investigation was more like a chase of a phantom. However I am glad that I showed the real result that I obtained, regardless of the pressure from the other group members. Now I am glad that this fruitless chase is over, and even gladder that even during those days professor Wulff still had confidence in me.

When I joined professor Wulff's group, the real big project for my graduate program was the investigation of the detailed mechanism of the VAPOL-borate or VANOL-borate catalyzed aziridination reaction of benzhydryl imine and ethyl diazoacetate. The working model involves two CH-π interactions between the proposed catalyst and benzhydryl imine. The whole model was based on the literature precedence and was reasonable enough to account for the enantioselectivity and diastereoselectivity of the reaction. Like any unrealistically ambitious new students I took the project and decided to find the mechanism and prove our hypothesis. The hollow remark such as "I'm gonna make all the substrates before my oral" made myself laugh even now. But, even a little step is

still a step, and step by step I was closer to the real mechanism of the catalytic asymmetric aziridination reaction. Years passed quickly and most of the substrates I tested did not yield too much insight into our originally proposed mechanism. However one day it was almost astonishing to find that one substrate which I thought should kill the reaction actually gave the best enantioselectivity. This substrate eventually was further developed into a general methodology of highly enantioselective aziridination reaction, the stereoselectivity and reactivity observed for this substrate was significantly improved over the original benzhydryl imines. Every step, ridiculous or not, eventually led us to the better understanding of the nature of the reaction.

I was so fortunate to have professor Wulff as my research advisor. The profound knowledge of organic chemistry possessed by professor Wulff was a result of so many years of hard-working and was beyond my imagination. This knowledge helps, in the sense that it not only led to the discovery of the most active substrate in the catalytic asymmetric aziridination, but also resulted in the reconsideration of the whole working model. After some of the most crucial tests of our originally proposed model failed to yield conclusive results, I went back to the catalyst and found that there are actually two catalyst species in the solution generated from chiral ligand and triphenyl borate. Our original working model was based on the proposed structure of one of the VAPOL-borate catalyst species. This working model was sufficient enough to explain the enantioselectivity and/or diastereoselectivity of aziridination as well as the aza Diels-Alder reaction of benzhydryl imines and this model was almost too perfect to give up. However some lab work quickly showed that this working model was actually based on the wrong structure of the active VAPOL-borate catalyst. The discovery of the real aziridination active catalyst species answered our longtime question about what is really in the catalyst mixture, provided access to two ligand-borate catalyst species. However it also raised more questions about the mechanism of this catalytic asymmetric reaction as

the origin of stereoselectivity provided by this catalyst species is not quite clear based on either the CPK or the computational modeling. It will be my greatest pleasure if one day in the near future, somebody in this group can solve the mystery of the mechanism of this aziridination reaction.

I personally do not think that a graduate student need to publish tons of paper to be regarded as successful, I think maybe the process is more important than the product. Although in the end I was unable to completely unlock the key of the door toward detailed mechanism of aziridination reaction, I tried hard and learned so much and all these studies (at least partially) satisfied my curiosity for the chemistry.

I was always lucky to have some great mentors since my study in elementary schools, over thirty years these mentors encouraged me, criticized me, and step by step I was finally able to come to the graduate school. During this graduate study, I cannot imagine to have better a research advisor than professor Wulff. The enlightening discussions and the absolute confidence provided by professor Wulff were so significant that my understanding of chemistry as well science was never the same. I don't think I can accomplish anything discussed in this thesis without his patient guidance. However, it is not only the valuable chemistry-related knowledge that I obtained from professor Wulff will be greatly helpful for the rest of my life, his attitude toward science and life also taught me a possibly more important lesson.

The help provided by other members of my committee Professor Robert Maleczka, Babak Borhan, Gary Blanchard is also greatly appreciated. Professor Maleczka as my second reader provided me with some very helpful suggestions to my oral exam, he also meticulously read my thesis and his feedback contributes much to the clarity of my thesis. On the other hand, the chemistry that I learned from the Organic Synthesis course, the Spectroscopic Analysis course given by Professor Maleczka and Borhan really led me to the doorstep of synthetic organic chemistry.

The understanding of chemistry is just one aspect of what I learned from the life in graduate school. As I grew up I also learned from the stories of my colleagues and friends. And it is all these stories that made my life so colorful and joyful. My lab mates not only taught me a great deal of knowledge, but also brought so much fun to the lab. I wish to thank Hongqiao Wu for his ridiculous horseplay, Xuejun Liu and Xiaowu Jiang for being good chat mates, Jie Huang for sharing the stories of her beautiful sons, Mannish Rawat and Vijay Gopalsamuthiram for all the interesting talk about India and chemistry, Glenn Philips for his kind joke and blessing, Chunrui Wu (and her husband Feng Shi) and Gang Hu for being nice labmates, Zhensheng Ding for all the dirty jokes, Keith Korthals for being a quite neighbor and sharing of Budlight at night, Cory Newman for all the talking about fishing tips, Kostas Rampalakos, Alex Predeus and Mike for all the interesting talk about their countries, Victor Prutyanov for the discussion of computational chemistry. I should specially thank Aman Desai for taking my project, I appreciate his efforts to be a good student and wish him good luck in the future.

I was not expecting to find many good friends here in MSU, I was wrong. I'm so privileged to have the company of so many friends who are willing to share my joy and my pain. I should thank Yana Cen for being so noisily funny, Jason Dahl for sharing so many lunches with me and talking about everything, Feng Jing for sharing the wonderful world of photography, Lei Sun for being a nice sister (did I congratulate her for being a happy bride?), Jun Yan for being a nice sister and sharing her beautiful life with me, Tao Zheng for being a not-so-nice sister and sharing her excellent cooking skill with me, and finally Ying Zheng for being such a interesting girl.

I appreciate Dr. Rui Huang for his help with the MS analysis, elemental analysis and X-ray analysis, he not only run every one of my numerous samples as careful as possible, but also provided many valuable suggestions to improve my purification and crystallization skill. I would also like to thank Daniel Holmes for his help on the NMR

analysis, and acknowledge Lijun Chen of MSU mass spectrometry facility for the HRMS analysis of my sensitive samples.

Finally I wish to express my gratitude to my family. For every single day in these 11 years since we met each other, my beloved wife Zhenjie Lu has been my strongest supporter and did everything for me, I can not ask for a more perfect wife than her. I should thank my parents for their 30 years of support and encouragement, I feel so sorry that for six years I was unable to go home and see them once. My grandparents passed away during my graduate study and I am so regretful that I could not be their side for the last days in their life.

Sometimes I do looked back and think who or what I would be if I have stayed in that comfortable institute for the rest of my life. I was always glad that I made the choice to come here, made the choice to study chemistry and prove myself. Any of my success never belongs to me along, it belongs to you – all those who ever loved me.

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ABBREVIATIONS

Ac	acetyl
BINOL	1,1'-binaphthol
BUDAM	3,3',5,5'-tetra-*tert*-butyl-4,4'-dimethoxybenzhydryl
DMF	N, N-dimethylformamide
DMPU	1,3-dimethyl 3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
EI	electron ionization
FAB	fast atom bombardment
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
MS	mass spectrometry
MEDAM	3,3',5,5'-tetra-methyl-4,4'-dimethoxybenzhydryl
NMR	nuclear magnetic resonance
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
VANOL	3,3'-diphenyl-[2,2'-binaphthalene]-1,1'-diol
VAPOL	2,2'-diphenyl-[3,3'-biphenanthrene]-4,4'-diol

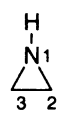
CHAPTER ONE

INTRODUCTION

1.1 Physical properties of aziridine

Aziridines, the nitrogen analogues of epoxides, have until recently received much less interest from organic chemists than their oxygenated counterparts. Aziridine **1** is the simplest of the three-membered saturated nitrogen-containing heterocyles (Figure 1.1).[1]

Figure 1.1 Simple aziridine



1

The structures of aziridines have been the focus of both extensive theoretical calculations and experimental studies in the past 20 years.[2a-b] X-ray diffraction study and other spectroscopic methods suggested that the C-C bond (1.46 Å) of aziridine is about 0.06 Å shorter than a normal open chain C-C bond, whereas its C-N bond (1.48 Å) is 0.03 Å longer than an open chain C-N bond.[2c-f] The endocyclic angles of the simple aziridine are all close to 60° and the geometry at nitrogen is pyramidal. The calculated structures are generally in good agreement with experimental data. The deformation of normal bond angles within the aziridine ring resulted in 26-27 kcal/mol strain energy, which is about 1

kcal/mol less than the cyclopropane ring.[2g]

Due to the increased s-character of the nitrogen lone pair, the nitrogen atom on aziridine exhibits weaker basicity than that of alkylamines. The conjugate acid of aziridine has a pKa value of 7.98, which is ~3 pKa units less than that of an acyclic secondary amine. The reactivity of aziridine nitrogen is similar to secondary amines with alkylating reagents.[1]

The inversion barrier of the nitrogen atom of aziridines is considerably higher than that of the secondary cyclic and acyclic amines. The activation enthalpy of nitrogen inversion of aziridines ranges from 17 kcal/mol in simple 2-methylaziridine to 27 kcal/mol in N-chloro-2-methylaziridine, and the latter aziridine can be separated into two diastereomers which do not racemize at room temperature.[2g]

Due to the combined effects of bond shortening and angle compression as well as the presence of the electron rich nitrogen atom, the highly strained three-membered aziridines exhibit high reactivity in a variety of reactions.

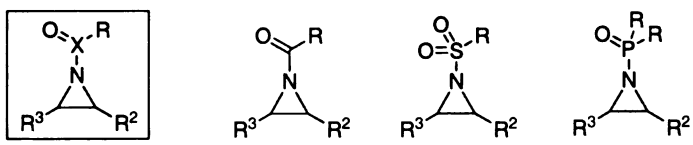
1.2 Reactions of aziridine

Aziridines, especially chiral aziridines have been widely used in organic synthesis. The highly strained aziridines generally exhibits good reactivity toward several cycloadditions as well as various ring opening reactions.[1-3] The highly stereo- and regioselective ring opening reactions of chiral aziridines can provide a large variety of chiral products. In addition, chiral aziridines have also found applications as chiral ligands

and auxiliaries in asymmetric synthesis. In the past ten years several excellent reviews have been published on the synthetic applications and reactions of aziridines,[2-4] thus this area will not be discussed in detail.

As aforementioned, the 26 kcal/mol ring strain energy and the electronegativity of the nitrogen atom determine that it is feasible for the ring opening reaction to occur under relatively mild conditions. However, because of the diminished electronegativity of nitrogen compared to oxygen, the reactions of aziridines are generally more difficult than those of epoxides. This problem can be overcome by two methods: 1) attachment of an "activating group" to the nitrogen; or 2) activation of the nitrogen via Bronsted acid or Lewis acid catalysis.

Figure 1.2 Oxygenated aziridine activating groups

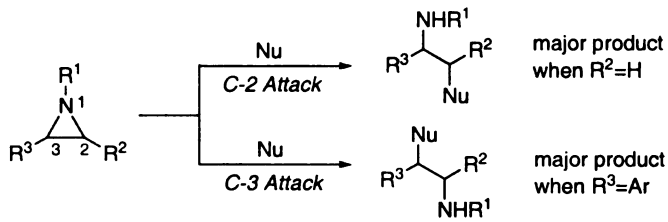


The incorporation of an electron-withdrawing group not only effectively activates the aziridine toward nucleophilic ring-opening, but also addresses the issue of N-H deprotonation under basic conditions. The activating groups are generally oxygenated substituents such as various carbonyl, sulfonyl or phosphoryl groups (Figure 1.2). It is worth mentioning that the resonance interaction between the nitrogen lone pair and the X=O bond is minimal. Since resonance delocalization would lead to a highly strained structure. The activation provided by these N-substituents are two-fold: the inductive effect results in kinetic activation, which leads to the increased polarization of C-N bond;

whereas the thermodynamic activation is provided by the resonance stabilization of amide-like anion generated after ring-opening reaction.

Another important issue of the ring-opening reaction is the regioselectivity of the nucleophilic attack. As in the case of an unsymmetrically-substituted aziridine, the reaction with nucleophile may in theory lead to either C-2 attack or C-3 attack (Scheme 1.1). The regioselectivity generally depends on the ring substituents, with most nucleophiles preferentially attacking at the less substituted position. Introduction of an aryl group at either carbon will make the ring-opening at that particular carbon much more facile.[3] In the case of the aziridine-2-carboxylates that this work involves, the majority of the nucleophilic ring-opening reactions occur at C-3.

Scheme 1.1 Nucleophilic ring opening of aziridine

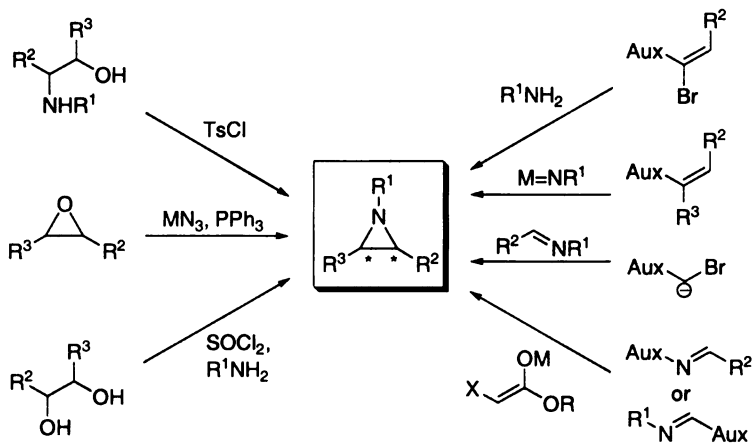


1.3 Catalytic asymmetric synthesis of chiral aziridines

Aziridines as chiral building blocks for organic synthesis have been the focus of extensive study over the last few decades. In many ways, aziridines rival epoxides in their versatility as excellent electrophilic reagents. However, compared with the great progress made in asymmetric epoxidations, especially the area of enantioselective catalytic

epoxidations, the field of asymmetric aziridination until recently remained relatively undeveloped.[5] The lack of suitable, general methods for the preparation of chiral aziridines greatly hindered the development of aziridine chemistry.

Scheme 1.2 Preparation of aziridines from chiral starting materials

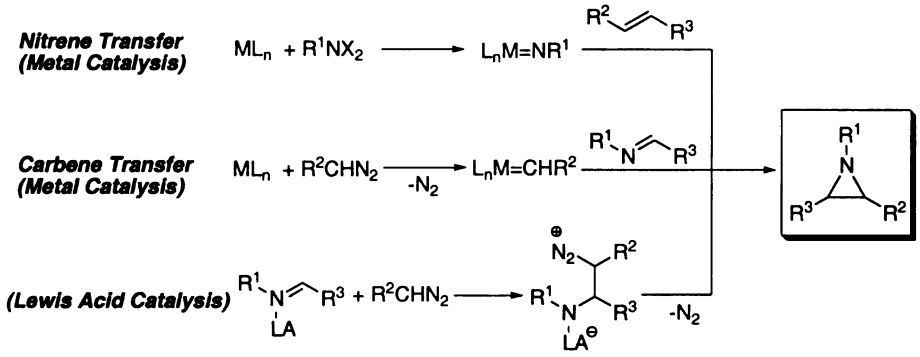


Before the discovery of catalytic systems for enantioselective aziridinations, the preparation of chiral aziridines solely relied on the presence of pre-existing stereogenic centers in the chiral starting material.[1,4] The chiral centers of the aziridines are either derived from chiral amino alcohols, epoxides or diols via various substitution reactions, or from the chiral auxiliary controlled Grabiel-Growell reactions, nitrene insertion reactions and aza-Darzens reactions (Scheme 1.2). The asymmetric syntheses of aziridines from the "chiral pool" have been reviewed extensively,[4] and thus will not be discussed in detail here. These syntheses generally gave good diastereo- and/or enantioselectivities. However the biggest drawback is that all the asymmetric synthesis outlined in Scheme 1.2 involve stiochiometric amount of chiral starting materials, and the preparations of

these starting material and/or chiral aziridine from these precursors generally require multiple step synthesis.

In the last twenty years substantial efforts were devoted to the study of effective asymmetric catalyst system for aziridination, however this area turned out to be exceedingly difficult.[5,6] In one review, Jacobsen described that the difficulty is probably due to the fact that while epoxidation catalysts were thoroughly studied from the biological and industrial aspects, the aziridination catalysts are relatively much less understood.[5] Thus the design of aziridination catalysts does not benefit from a comprehensive foundation of knowledge. It is not until mid- to late-90's that successful asymmetric aziridination catalysis began to be reported, and until now examples of general, highly enantioselective catalytic systems are rare.

Scheme 1.3 Three approaches to catalytic aziridination



Depending on the reaction pathway and catalyst used, catalytic aziridination reactions can be classified according to three different approaches: metal catalyzed nitrene transfer to olefins, metal-catalyzed carbene transfer to imines, and Lewis acid catalyzed addition of diazo compound to imines (Scheme 1.3). This introduction will

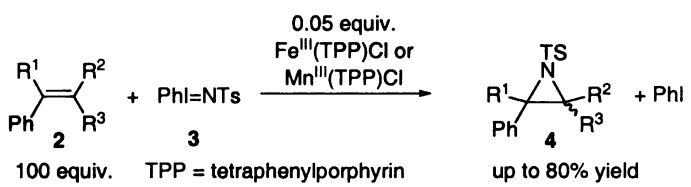
briefly review the most important publications in these three categories.

1.3.1 Catalytic aziridination via nitrene transfer to olefins

The classical direct aziridination of alkenes involves the addition of nitrene to the C=C double bond. The early methods for nitrene generation included thermal and photochemical decomposition of azides, and the oxidation of hydrazines. These methods generally require harsh conditions and suffer from poor stereoselectivity in the aziridination reaction due to the non-selective formation of singlet and triplet nitrenes.

It was discovered in the mid- 1980's that metal-stabilized nitrenes could be used for efficient alkene aziridination. The first catalytic aziridination reaction of alkenes was reported by Mansuy, who found that iron- and manganese-based porphyrin complexes could catalyze the nitrene transfer from N-p-(tosyl)imino phenyliodinane (PhI=NTs) **3** to alkenes **2** (Scheme 1.4).[7] Although PhI=NTs is expensive, insoluble and generates a heavy stoichiometric by-product PhI, it has since then proven to be one of the most effective reagents for nitrene transfer reactions and is used in various metal catalyzed aziridination systems.

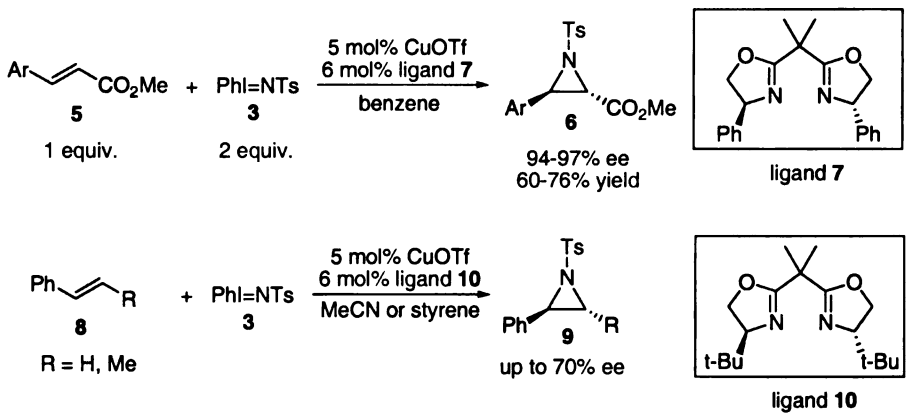
Scheme 1.4 First metal catalyzed aziridination



In the early 1990's, Evans was the first to report that the low-valent metal catalysts

typically used for cyclopropanation reactions of alkenes were equally effective for the nitrene transfer from PhI=NTs to alkenes.[8] Simple Cu(I) and Cu(II) salts were found to be efficient catalysts for the preparation of a wide range of aziridines. As these metal ions were also useful catalysts for asymmetric catalytic cycloporpanation reactions via carbene transfer to alkenes, this discovery lead chemists to explore the possibility of similar asymmetric catalysts for aziridinations. Subsequently, Evans and Jacobsen simultaneously reported the independent discovery of new copper-catalyzed asymmetric aziridination reactions.[9,10]

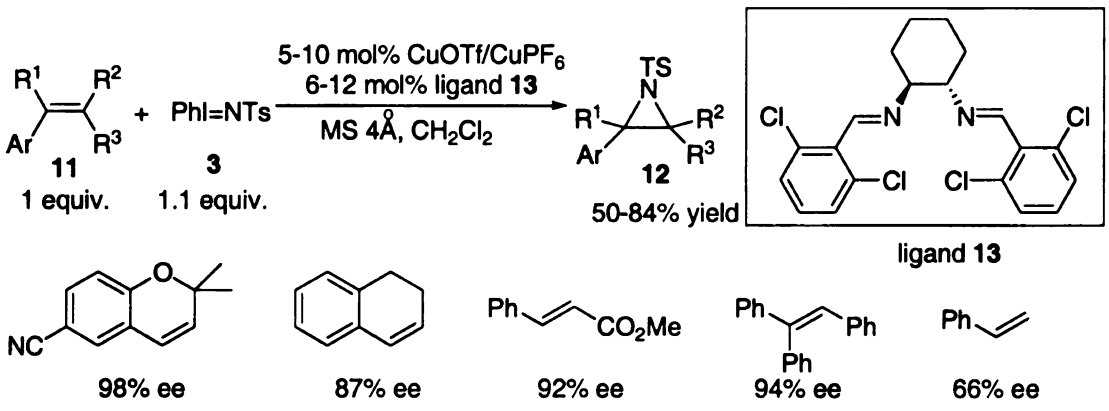
Scheme 1.5 Evans' catalytic asymmetric aziridination



The Evans' catalysts were prepared from the chiral bisoxazoline ligands **7** and **10** with copper(I) triflate (Scheme 1.5).[9] Highly enantioselective nitrene transfer was achieved when *trans*-cinnamate esters were used as substrates. In the presence of a catalyst generated from ligand **7** and CuOTf, the *trans*- aziridine-2-carboxylates **6** could be obtained in excellent ee%. However simpler alkenes such as styrene gave much lower selectivity even with a sterically more bulky ligand such as **10**.

The Jacobsen catalyst system employs chiral 1,2-diimine derivates as the chiral ligand for copper(I) salts (Scheme 1.6).[5,10] The most important catalyst design feature was the recognition that multiple coordination sites, in this case two sites on copper was crucial for the success. Ligand optimization revealed that the most efficient ligand was the diimine **13** derived from 1,2-diaminocyclohexane and 2,6-dichlorobenzaldehyde. The Jacobsen catalyst system afforded excellent enantioselectivities with several *cis*-alkenes, which is complementary to Evans *trans*-alkene aziridination system. However, the scope of Jacobsen system is again limited in the sense that the substrates require at least one aromatic group in conjugation with the alkene for high selectivity, and simple alkene such as styrene resulted in much lower chiral induction.

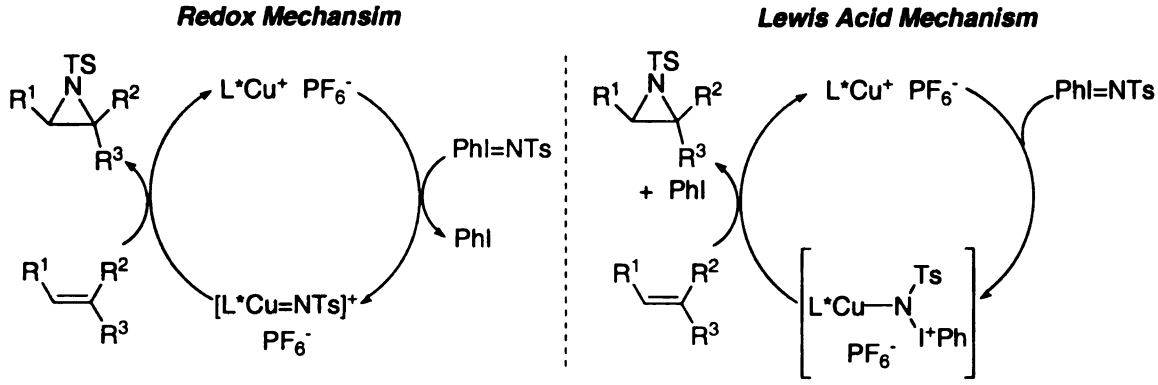
Scheme 1.6 Jacobsen's catalytic asymmetric aziridination



Subsequently, Jacobsen reported the mechanism studies of diimine-copper catalyzed aziridination reaction.[11] They proposed two possible mechanisms, the first is a redox mechanism that involves a discrete Cu-nitrenoid intermediate (Scheme 1.7). An alternative mechanism involves the copper complex functioning only as a Lewis acid catalyst. Jacobsen postulated that the role of aryl iodide moiety in PhI=NTs is

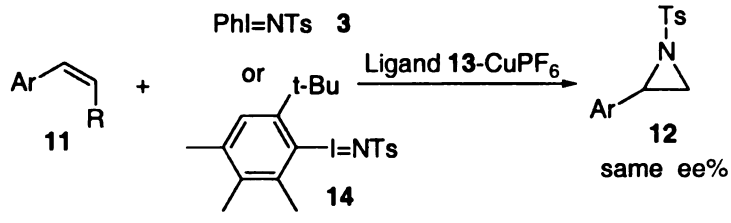
fundamentally different in these two mechanisms. In the redox mechanism, PhI is fully dissociated from the active copper-nitrenoid, whereas in the Lewis acid mechanism it is covalently attached to the copper complex. Thus it is expected that in the Lewis acid mechanism, structural modification of the aryl iodide would result in change of enantioselectivity.

Scheme 1.7 Proposed mechanisms of copper catalyzed aziridination



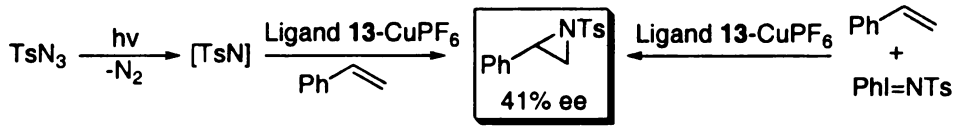
However, control experiments demonstrated that the use of substituted tosylimino iodoarene **14** produced results indistinguishable with PhI=NTs for several alkenes (Scheme 1.8). Thus, the Lewis acid mechanism was excluded.

Scheme 1.8 Control experiments using various ArI=NTs



Meanwhile, Jacobsen provided compelling evidence for the discrete L*Cu=NTs intermediate. The photochemical reaction of TsN_3 with styrene in the presence of the chiral copper catalyst afforded aziridine with same induction as observed for the reaction with PhI=NTs (Scheme 1.9).

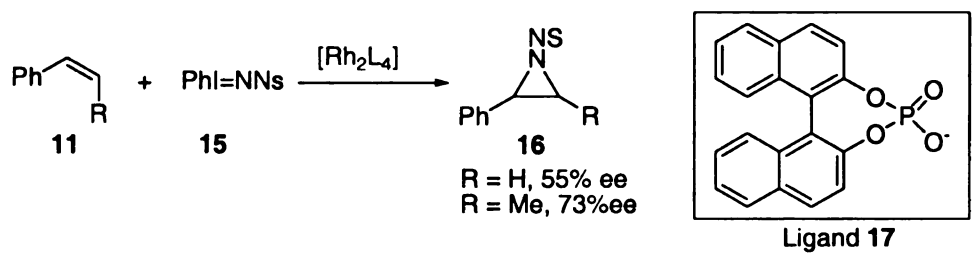
Scheme 1.9 Control experiments in asymmetric aziridination



Another piece of evidence in support of a discrete, monomeric copper-nitrene intermediate came from the comparison of enantioselective aziridinations and cyclopropanations. The $CuPF_6$-catalyzed cyclopropanation of 1,2-dihydronaphthalene with ethyl diazoacetate was compared with the aziridination of the same substrate with PhI=NTs as a function of different diimine ligands. A surprisingly close correlation was observed between the enantioselectivities obtained in two reactions, which suggests that the two different reactions might proceed through similar mechanisms and similar transition state structural geometries.

Compared with the copper catalyzed aziridination, the use of other metals is much less studied and only a few successful examples have been reported in literature. While copper is superior to rhodium when PhI=NTs **3** was used as aziridination reagent, it was later found that the combination of $[Rh_2L_4]$ with PhI=NNs **15** was also efficient. Müller's group found that the catalyst generated from the phosphoric ester of BINOL and Rh(II) could give up to 73% ee for the aziridine **16** (Scheme 1.10).[12]

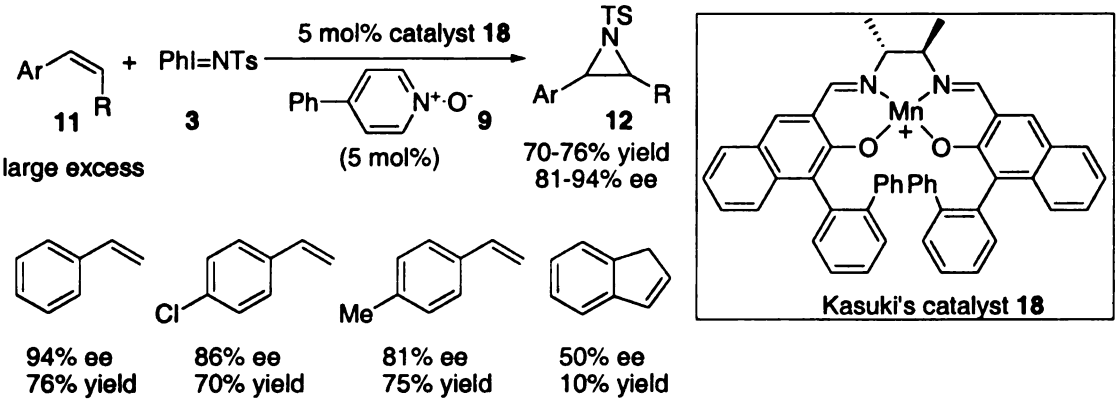
Scheme 1.10 Muller's asymmetric aziridination system



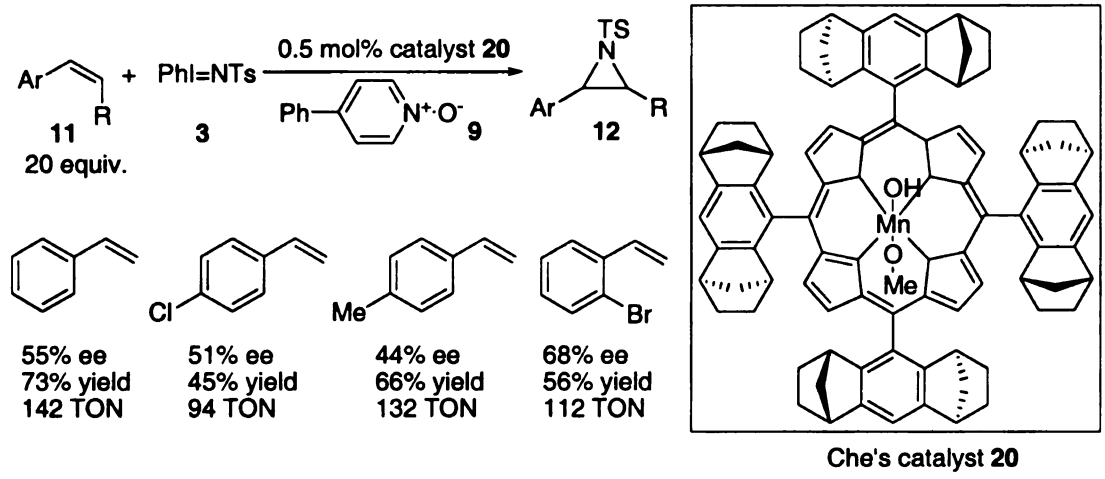
Ligand **17**

Following the initial success of manganese catalyzed aziridination reaction (Scheme 1.4), Katsuki reported an optimized chiral Mn-salen catalyst system **18** and up to 94% ee was obtained for the reaction of **3** with several alkenes (Scheme 1.11).[13] In another example, Che used a chiral manganese(III)-porphyrin catalyst **19** (Scheme 1.12). The enantioselectivities with Che's system were moderate, but the catalyst turnover numbers were good.[14] Although these manganese catalyst systems showed some promise and potential, their biggest limitations lie in the low enantioselectivities, the small substrate scope and the use of large excesses of alkene.

Scheme 1.11 Kasuki's asymmetric aziridination system



Scheme 1.12 Che's catalytic asymmetric aziridination system



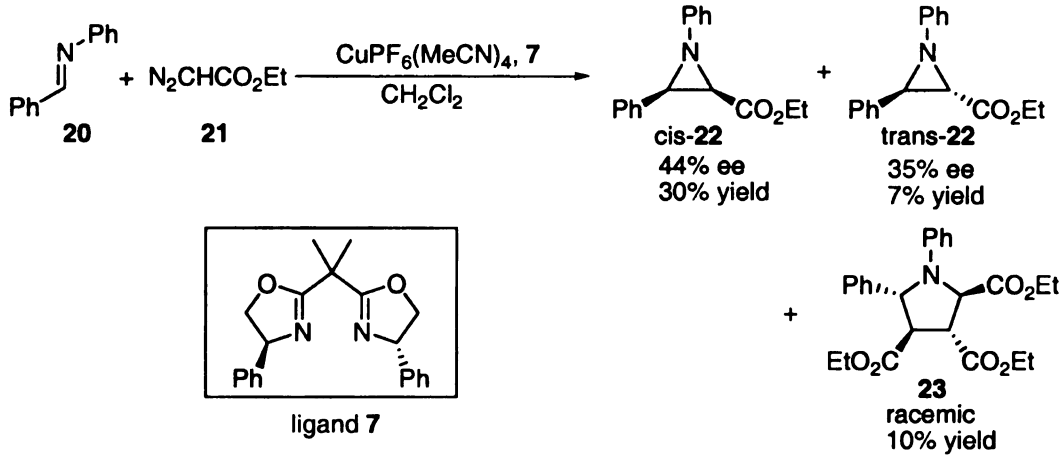
1.3.2 Catalytic aziridination via carbene transfer to imines

The addition of carbenes to imines to afford aziridines is a well-known process, and the catalytic transfer of carbene to imine can be regarded as a method complementary to the nitrene transfer to alkene. Both imines and diazocarbonyl compounds are more readily available than the sulfonyliminoiodinanes. This transformation involves much "cleaner" reaction conditions and could, in theory, be used in the preparation of more complex products compared with the nitrene addition to alkene. However, so far successful examples of asymmetric catalytic reactions in this area are limited.

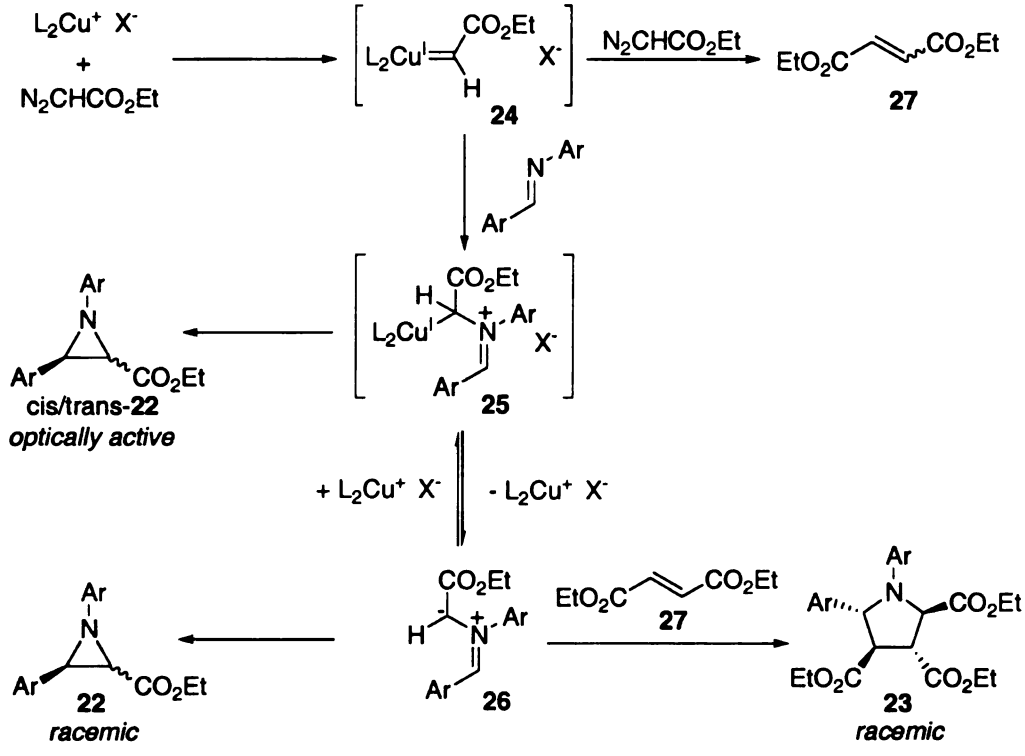
One of the earliest metal catalyzed examples was reported by Baret back in 1972, who described that copper powder could catalyze the aziridination between an imine and ethyl diazoacetate. Various carbene transfer catalysts have been discovered since then.[15] However, over the next 20 years, progress toward enantioselective aziridination of imines with diazo esters was not realized. Various chiral Rh(II) and Cu(II) catalysts were reported to produce aziridines with <15% ee.[6]

A significant improvement in the asymmetric aziridination of imines with diazo compounds was reported by Jacobsen in 1995 (Scheme 1.13).[16] In the presence of a Cu(I)-bisoxazoline catalyst, the reaction of ethyl diazoacetate **21** and imine **20** afforded a mixture of cis/trans aziridines **22**. Even though an improvement over existing method, this catalyst only delivers moderate yields and enantioselectivities along with small amounts of the oxazoline byproduct **23** as racemate.

Scheme 1.13 Jacobsen's Cu(I)-bisoxazoline catalyst system



Scheme 1.14 Proposed mechanism of copper catalyzed aziridination

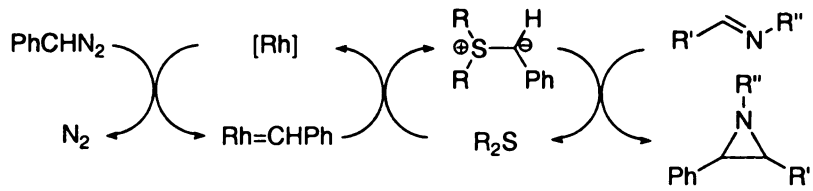


Based on the observation of the products produced in his catalytic system, Jacobsen proposed the mechanism shown in Scheme 1.14. The overall process involves initial formation of a copper-complexed azomethine ylide intermediate **25** from carbene **24**, which subsequently collapses to give optically active aziridine **22**. Alternatively, this

intermediate undergoes dissociation to a free azomethine ylide **26**, which either cyclizes to racemic aziridine or undergoes cycloaddition with fumarate **27** (formed upon diazo decomposition of ethyl diazoacetate) to furnish the racemic pyrrolidine **24**.

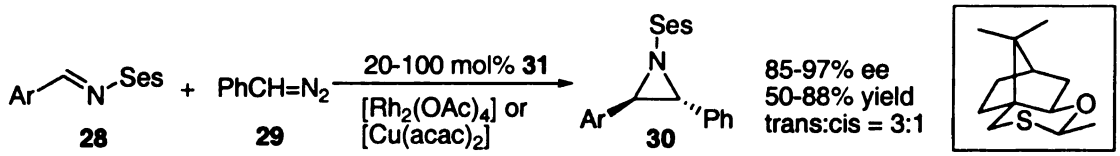
A different strategy for asymmetric carbene transfer to imines was developed by Aggarwal, who employed a chiral, in situ generated sulfonium ylide as aziridination reagent.[17] The overall process involves the generation of a carbene complex via diazo decomposition with Rh catalyst, followed by carbene transfer to a chiral sulfide to give an ylide. The enantiogenic step is the transfer of the ylide carbon to the imine to give an aziridine (Scheme 1.15).

Scheme 1.15 Catalytic cycles of Aggarwal's aziridination system



In Aggarwal's first report, the reaction between N-Ses-aldimines **28** and phenyldiazomethane **29** in the presence of a chiral sulfide ligand and a non-chiral Rh or Cu catalyst was found to furnish aziridines with a 3:1 trans/cis ratio and with 85-95%ee for the trans isomer (Scheme 1.16). $Cu(acac)_2$ is less enantioselective due to non-selective background aziridination resulting from direct transfer of the carbene from the copper to the imine. The drawbacks of this system include the high loading of the chiral ligand **31** (20-100 mol%), and this method is limited to the preparation of stilbene derivatives.

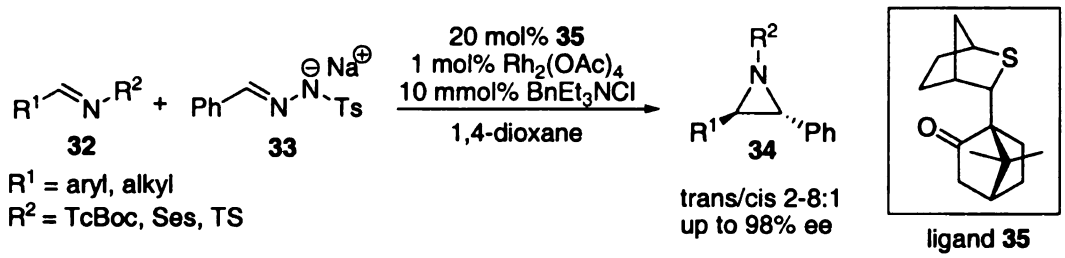
Scheme 1.16 Aggarwal's asymmetric azirdination system



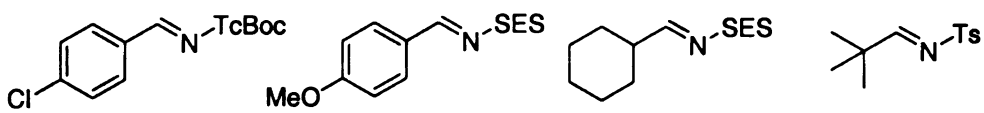
Ar = Ph, *p*-MeC_6H_4, *p*-ClC_6H_4
Ses = β-(trimethylsilyl)ethanesulfonyl

An interesting improvement in the chiral sulfonium ylide system was subsequently reported (Scheme 1.17).[18] The diazo precursor was generated in situ via deprotonation of the more stable tosyl hydrazones. The imine nitrogen substituents include tosyl, Ses, TcBOc, and "activated" aziridines could be obtained with excellent ee in the presence of 20 mol% chiral ligand. The major limitations of Aggarwal's new catalysis system include low diastereoselectivities and moderate yields.

Scheme 1.17 Aggarwal's chiral sulfonium ylide aziridination system



R^1 = aryl, alkyl
R^2 = TcBoc, Ses, TS



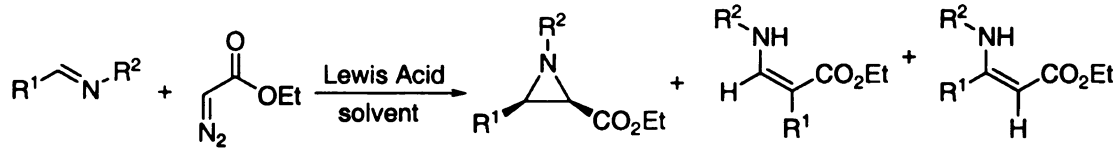
94% ee	92% ee	98% ee	73% ee
56% yield	60% yield	50% yield	53% yield
6:1 trans/cis	2.5:1 trans/cis	2.5:1 trans/cis	2:1 trans/cis

1.3.3 Catalytic aziridination with Lewis acid catalysis

The last approach toward catalytic aziridination involves the Lewis acid catalyzed reaction between diazo compounds and imines. In 1996 Brookhart and Templeton

reported a general process for this type of aziridination catalyzed by a variety of simple Lewis acids (Scheme 1.18).[19] In the presence of Lewis acids such as BF_3-OEt_2, $AlCl_3$, and $TiCl_4$, the reaction between ethyl diazoacetate **21** and imines **36** afforded *cis*-aziridine **37** in 42-93% yield. The cis/trans ratio was moderate to very high (up to 98:2). The two enamine side products were observed in various yields (5-100%) depending on the substitution of R^1 and R^2, with an electron withdrawing R^1 producing the least enamines.

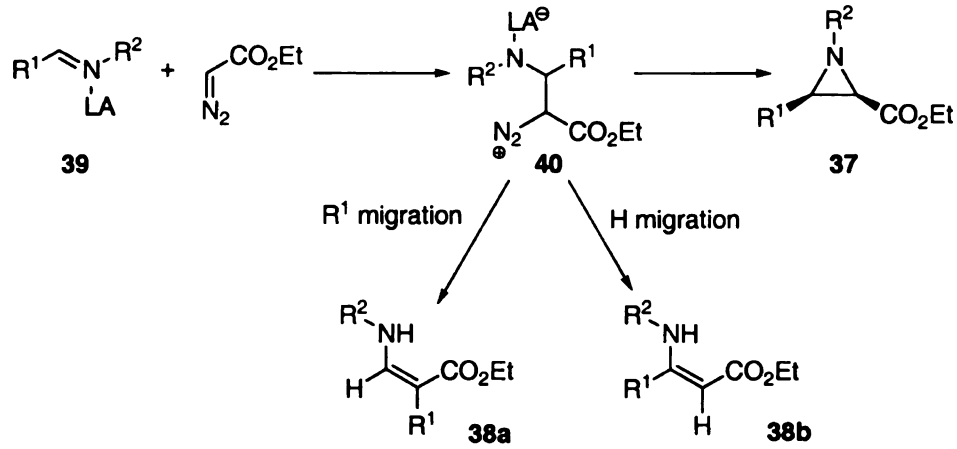
Scheme 1.18 Templeton's Lewis acid catalyzed aziridination



36 **21** **37** **38a** **38b**

R^2 = Ph, $PhCH_2$, P-$CH_3OC_6H_4$

Scheme 1.19 Proposed mechanism of Lewis acid catalyzed aziridination



39 **40** **37** **38a** **38b**

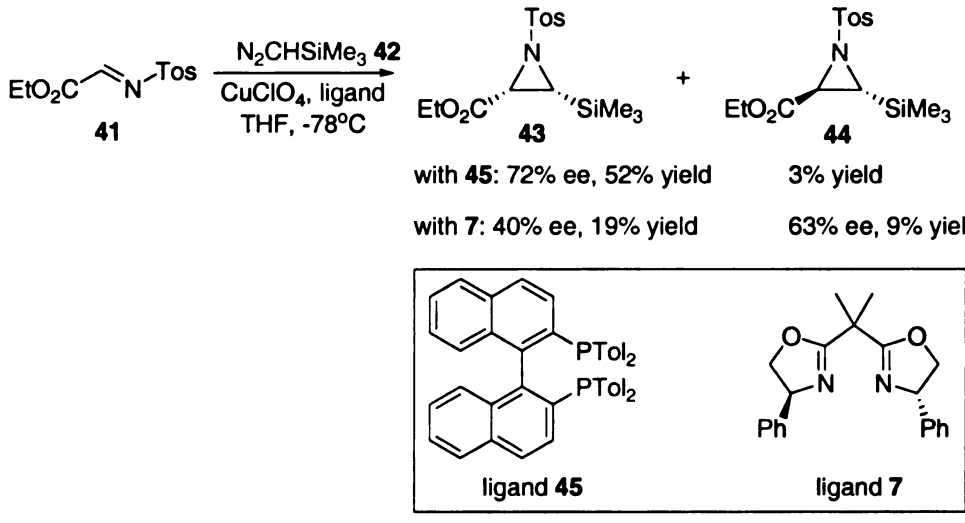
The typical side products (diethyl fumarate or maleate) of carbenoid reactions were never observed under the Lewis acid catalyzed condition.[9] The authors proposed a mechanism which involves nucleophilic attack of the diazo compound on the Lewis acid activated imine. Subsequent ring closure of **40** and loss of N_2 would give *cis*-aziridine **37**.

Alternatively the 1,2 migration of either R^1 or H to the incipient carbocation would produce the two enamine products (Scheme 1.19).

Shortly after Brookhart and Templeton's publication, Jorgensen reported in 1997 a similar Lewis acid catalyzed aziridination reaction between imines and EDA.[20] $Zn(OTf)_2$ and $Yb(OTf)_3$ were found to be the optimal catalysts for the aziridination, and *cis*-aziridines could be isolated in 40-50% yield. In the same paper Jorgensen also reported the attempted asymmetric aziridination using various C2-symmetric chiral ligands, however despite the wide range of chiral ligands he screened, the highest chiral induction they observed was 15% ee. Furthermore, a reduced catalytic activity of the chiral metal complexes was often observed.

Subsequently, in 1999 Jorgensen reported that a catalyst prepared from a copper salt and BINAP ligand **45** is effective for the addition of trimethylsilydiazomethane **42** to imino ester **41** (Scheme 1.20).[21] *Cis*-aziridine **43** could be isolated with up to 72% ee with this ligand, while the bisoxazoline ligand **7** resulted in much reduced chiral induction. Jorgensen suggested that this reaction involves a Lewis acid catalysis mechanism, while he had previously reported an aziridination of imines and diazoacetate that occurred with a mechanism involving a metallocarbene (not shown).[22]

Scheme 1.20 Jorgensen's Lewis acid catalyzed asymmetric aziridination system

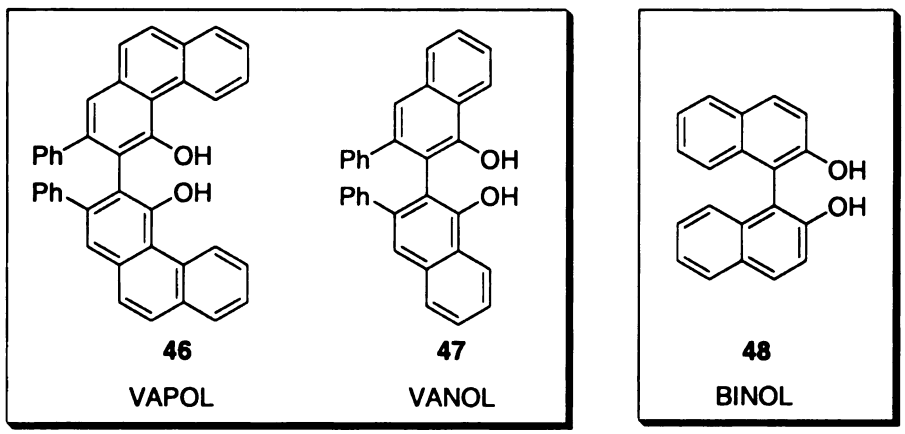


Compared with the metal catalyzed addition of nitrenes to alkenes, the metal carbene mediated reaction and the Lewis acid catalyzed reactions of the imines and diazo compounds are clearly underdeveloped. Besides the above-mentioned catalyst systems, numerous publications which described the addition of diazo compound to imines have appeared in literature within the last twenty years or so, which clearly indicates the amount of effort devoted to this area.[15-23] However, almost all the asymmetric catalytic systems suffered from either low to moderate diastereo- and enantioselectivity, high catalyst loading or very limited substrate scope.

In the early to mid- 1990's, our group started the development of two vaulted biaryl ligands VAPOL **46** and VANOL **47** (Figure 1.3).[24] The design of these ligands was based on BINOL **48**, one of the most successful chiral biaryl ligands. One of the major drawbacks of BINOL is it does not project enough chiral "shielding" to the complexed metal, which significantly decreases its chiral induction in some catalytic reactions. We

envisioned that the vaulted biaryl ligands **46** and **47** should provide a much more effective chiral pocket for various metal/Lewis acid catalyzed reactions. After the successful enantiomeric synthesis of these ligands, we started exploring the possible applications of these ligands in various catalytic asymmetric reactions including aziridination reactions.

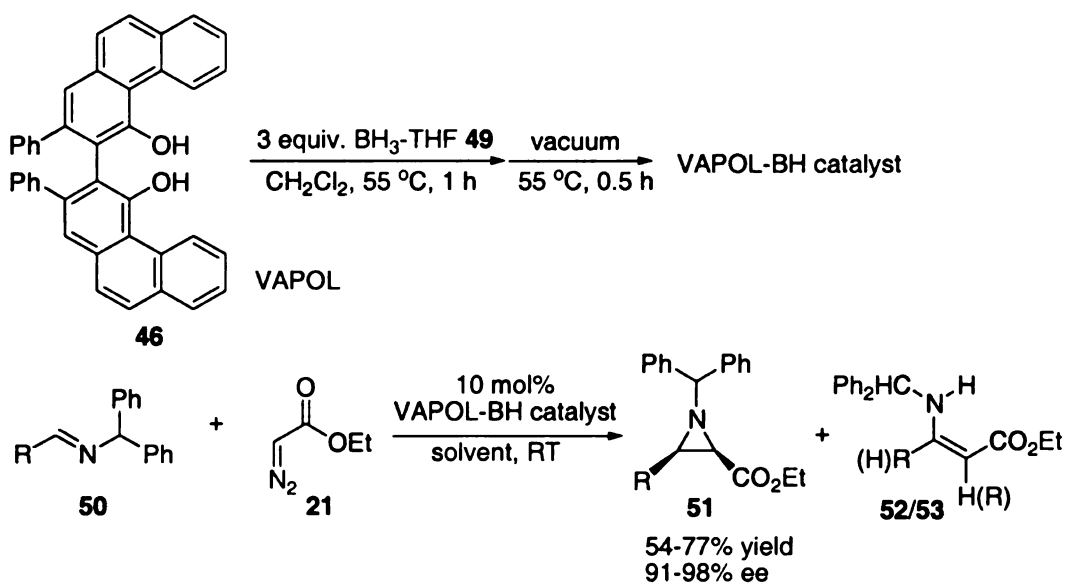
Figure 1.3 Vaulted and linear biaryl ligands



Inspired by Templeton's work on non-chiral Lewis acids, in 1999 our group reported a highly enantioselective catalyst systems generated from the VAPOL ligand and a boron Lewis acid which emerged from an initial screening of numerous Lewis acids (Scheme 1.21).[25a] The active catalyst was prepared from 1 equivalent of the VAPOL ligand and 3 equivalents of BH_3-THF **49**. The aziridination reaction between N-benzhydryl imine **50** and EDA in the presence of 10 mol% VAPOL-BH catalyst afforded aziridines **51** with very high cis diastereoselectivity and up to 98% ee. In most cases <5% of enamines **52/53** were observed. BINOL **48** was found to be a much less effective ligand for this transformation and gave inferior selectivity (17% ee, R = Ph). This asymmetric aziridination system represented a breakthrough in aziridine chemistry, and the level of

asymmetric induction in the aziridination is still among the highest for all systems published so far.

Scheme 1.21 Wulff's VAPOL-BH_3 catalyzed asymmetric aziridination system

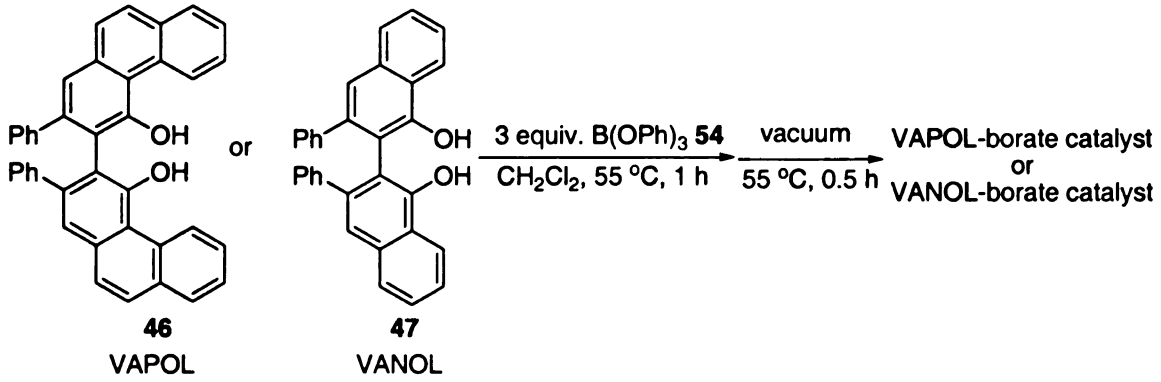


Subsequently, our group found that the success of the reaction is dependent on the purity of the BH_3-THF complex used for catalyst generation.[25b] An old batch of BH_3-THF complex would lead to a catalyst which gave much higher ee than pure BH_3-THF. Further investigation indicated that one of the impurities in commercially available BH_3-THF, especially in a sample that was stored for long periods, was tributylborate. This observation prompted a study of a variety of borate esters. Further optimization resulted in an improved catalysts which could be generated from triphenyl borate **54** and either the VAPOL or VANOL ligand (Scheme 1.22).

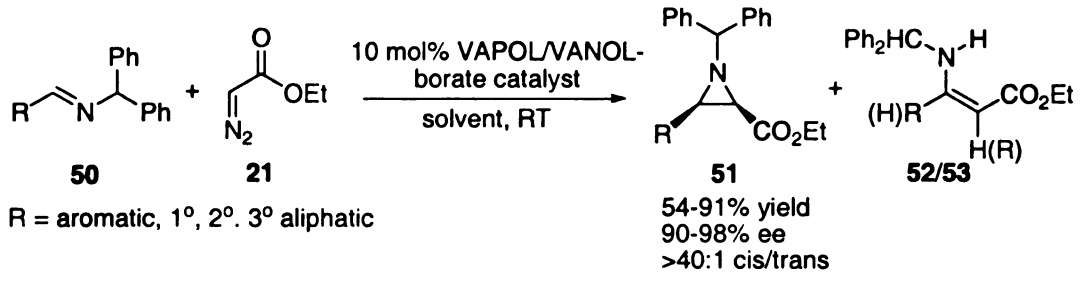
These new catalysts were found to afford much higher cis/trans selectivity (>50:1 cis/trans ratio) and improved yields for most substrates, and the enamine side products **52/53** were generally suppressed to less than 2%. Furthermore, the substrates previously

unreactive toward the VAPOL-BH_3 catalyst, such as the imine derived from pivaldehyde and 1-naphthylaldehyde, also gave excellent enantioselectivities and yields (Scheme 1.23).

Scheme 1.21 Wulff's VAPOL/VANOL-borate catalyst system

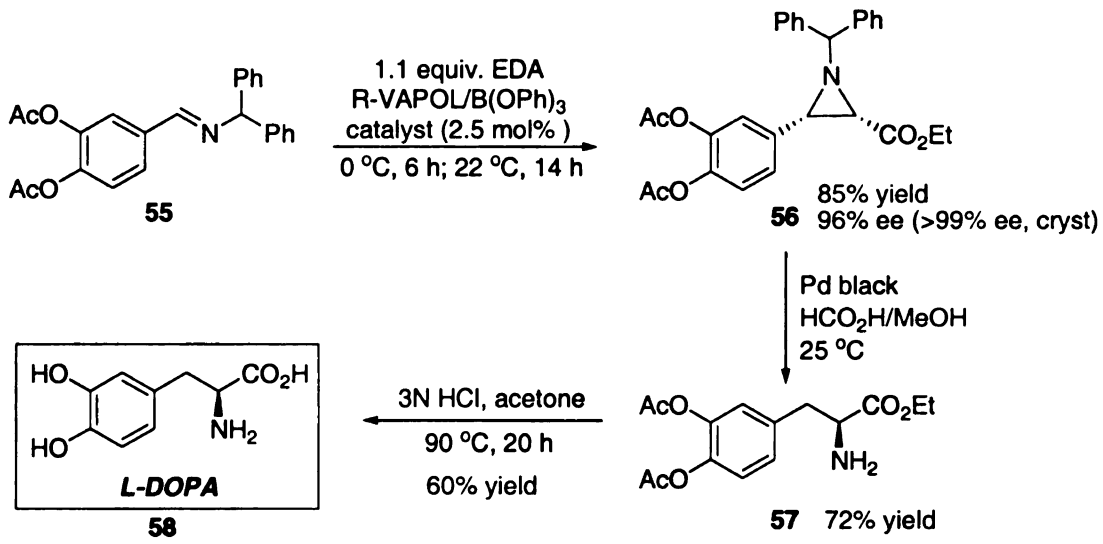


Scheme 1.23 VAPOL/VANOL-borate catalyzed asymmetric aziridination



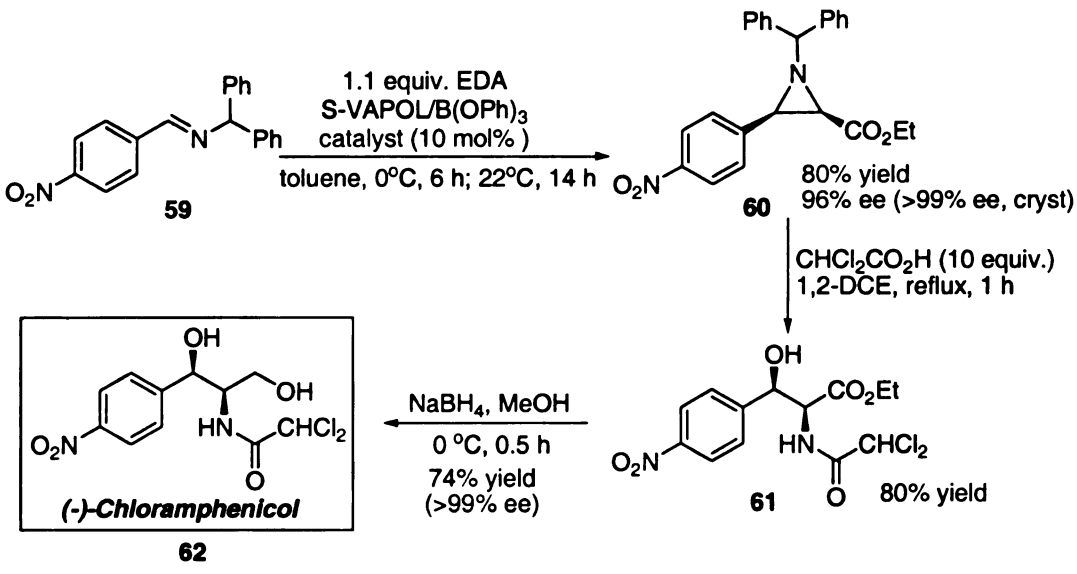
This enantioselective aziridination system was successfully applied to the efficient asymmetric synthesis of L-DOPA in the same communication (Scheme 1.24). The aziridine **56** could be obtained in excellent yield and enantioselectivity in the presence of only 2.5 mol% catalyst. Reductive ring-opening and deprotection happened simultaneously with Pd black and formic acid and then acid hydrolysis of three ester groups in **57** gave L-DOPA **58** in good yield.

Scheme 1.24 Enantioselective synthesis of L-DOPA



Employing this aziridination methodology, our group subsequently reported an efficient synthesis of (-)-Chloramphenicol (Scheme 1.25).[26] Initial screening of several ligands indicated that various ligands such as BINOL and BANOL gave good yield but much inferior selectivity. The most effective catalyst was again generated from VAPOL and three equivalent of triphenyl borate **54**. In the event, 10 mol% of the VAPOL-borate catalyst was found to catalyze the aziridination of *para*-nitrobenzaldimine **59** and gave the desired aziridine **60** in 96% ee and with a 30:1 cis/trans diastereoselectivity. Refluxing the aziridine with excess dichloroacetic acid gave the ring-opened product **61** as a single diastereomer. Reduction of the ester group with $NaBH_4$ completed the synthesis of (-)-Chloramphenicol **62** in 38% overall yield for four steps from the commercially available *p*-nitrobenzaldehyde.

Scheme 1.25 Enantioselective synthesis of (-)-Chloramphenicol



1.4 Conclusion

Catalytic asymmetric aziridination reactions have been studied extensively in the last 20 years. Three different approaches toward the aziridine have been advanced, the most successful examples of each approach were reviewed briefly. Despite the numerous efforts, at this stage highly enantioselective aziridination remains a challenge for organic chemists. The VAPOL-borate and VANOL-borate chiral Lewis acid catalysts developed in our group represents a breakthrough in this area and is still the most diastereo- and enantioselective catalytic aziridination system in all three approaches. In Wulff's group research will focus on the further application of the chiral aziridines, increasing the scope of the asymmetric aziridination reaction, and on the understanding of the mechanism of our chiral catalyst system.

CHAPTER TWO

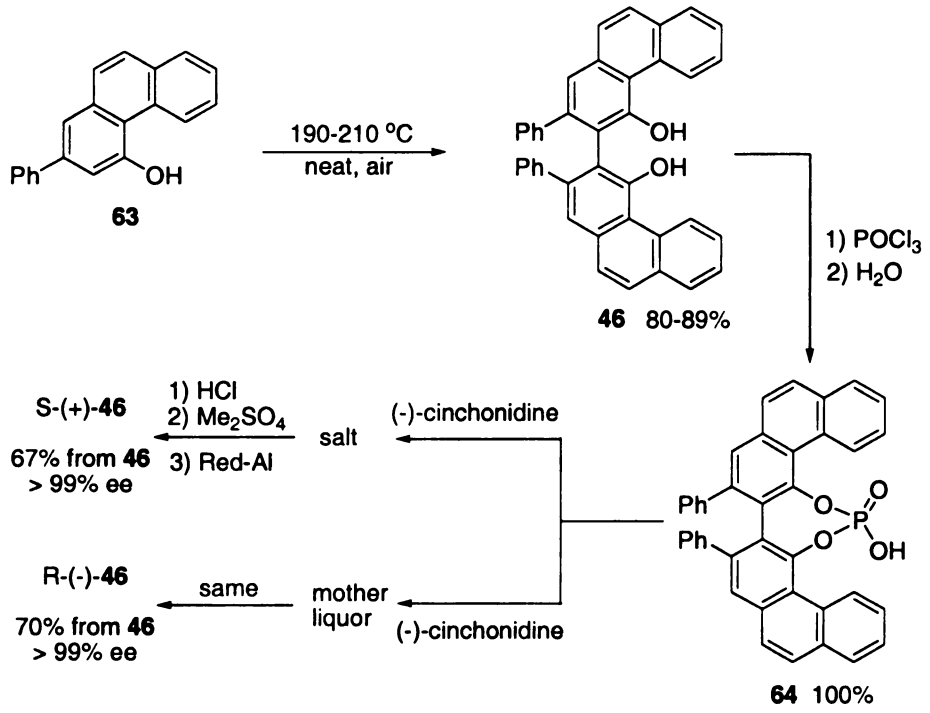
LARGE SCALE SYNTHESIS OF ENANTIOMERICALLY PURE VANOL

2.1 Introduction

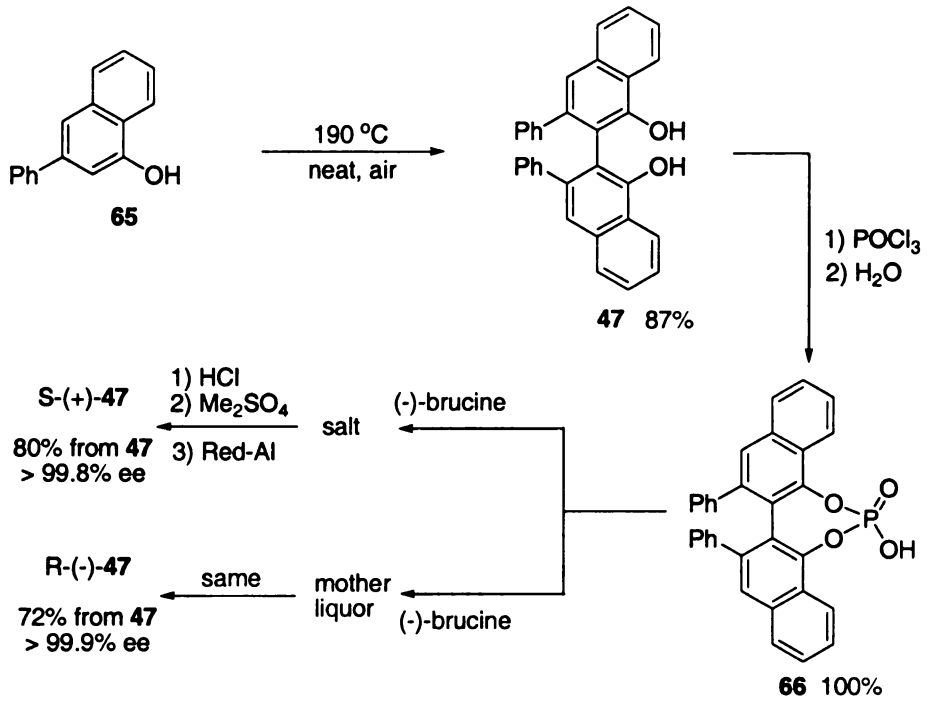
The development of highly efficient catalytic asymmetric reactions has been a major focus in modern synthetic organic chemistry and the design and synthesis of effective ligands necessarily plays an important role in this endeavor.[27] The *C*2-symmetric vaulted biaryl ligands VAPOL **46** and VANOL **47** developed in our laboratories[24] have proved to be excellent ligands for several important catalytic asymmetric reactions such as Diels-Alder reactions,[28] imino aldol reactions,[29] aziridination reactions,[25-26] and Baeyer-Villager oxidations.[30]

The resolution procedures that are published for VAPOL and VANOL follow a four-step procedure developed for BINOL that involves the bis-ester of phosphoric acid.[31] Salt formation of the BINOL bis-ester with (+)-cinchonidine leads to diastereomers which can be separated by crystallization. Adaptation of this protocol to the resolution of VANOL and VAPOL was successful provided that (-)-brucine was used in salt formation with VANOL and (-)-cinchonidine was used with VAPOL (Scheme 2.1 and 2.2).[24]

Scheme 2.1 Enantioselective preparation of VAPOL



Scheme 2.2 Enantioselective preparation of VANOL



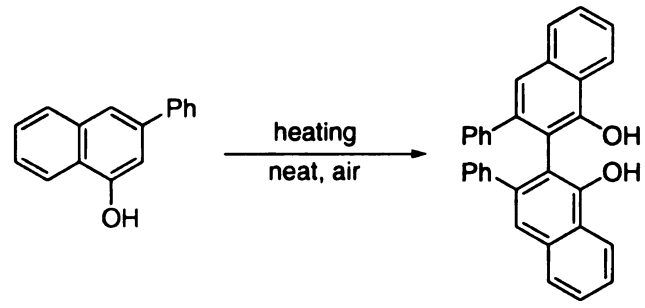
Upon formation of the salt, crystallization of the diastereomeric salts from ethanol will

afford the enantiomerically pure salt and mother liquor, respectively. Liberation of the pure VAPOL and VANOL was achieved by hydrolysis of the salt, ester formation followed by Red-Al reduction of the methyl ester. This published protocol could afford both enantiomers of VAPOL and VANOL in good to excellent yield. The major drawback of this resolution protocol lies with the fact that it is a four-step sequence. Although the preparation of VAPOL **46** via oxidative coupling can be performed on > 10 gram scale, the preparation of racemic VANOL **47** via the same reaction from 3-phenyl-1-naphthol **65** was limited to 1 gram scale. Thus finding a more efficient procedure for the large scale preparation of VANOL will be viral to the borader development of its chemistry.

2.2 Large scale preparation of VANOL by oxidative coupling

In Bao's original procedure,[24] oxidative coupling of 3-phenyl-1-naphthol **65** was performed by simply heating **65** in a culture tube at 190°C for 32 hours which afforded an 87% yield of the VANOL **47** after chromatography separation. Following the procedure discribed by Bao, coupling of **65** was carried out on different scales in test tubes, and the preliminary results are summarized in Table 2.1.

Table 2.1 Oxidative coupling of unpurified 3-phenyl-1-naphthol **65**



65 **47**

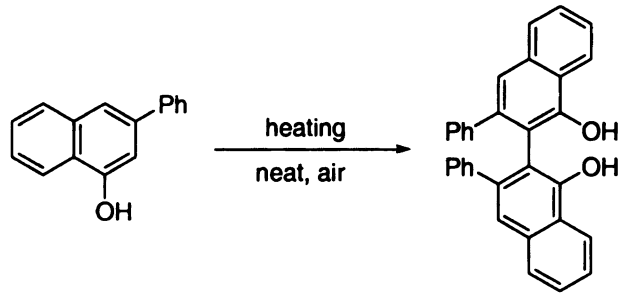
entry	scale	yield	reaction condition
1[a]	1.0 g	32%	190°C, 42 h
2[a]	1.0 g	39%	1)195°C, 20 h; 2) 200°C, 22 h
3	2.0 g	26%	1)190°C, 24 h; 2) 200°C, 24 h
4	4.0 g	23%	1)180°C, 36 h; 2) 187°C, 26 h

[a] Average of two runs

Various conditions were attempted, but the even the best result obtained (39% yield) was much inferior to the reported result. It was quickly found out that the purity of **65** is crucial for the success of the coupling reaction. The particular batch of **65** used for the coupling was clean by ^{1}H-NMR, but TLC showed it was contaminated with several impurities. Thus 3-phenyl-1-naphthol **65** was purified by flash column and then examined again under various reaction conditions. The results are summarized in Table 2.2.

It was pleasing to find that the yield of coupling reaction was greatly improved with purified **65**. Very good yield was obtained on 3 gram scale. In order to reduce the by-product of the coupling reaction, temperature ranges lower than the reported temperature were tested. It was found that the reaction was not very sensitive to temperature changes of 10-25 °C.

Table 2.2 Oxidative coupling of purified 3-phenyl-1-naphthol **65**



65 **47**

entry[a]	scale	yield[b]	condition
1[b]	1 g	70%	180-185°C, 72 h
2	3 g	84%	170-175°C, 43 h
3	5 g	76%	170-175°C, 46 h
4	5 g	60%	185°C, 40 h
5	5 g	70%	1) 170°C, 48 h; 2)180°C, 12 h
6	5 g	63%	1) 160°C, 36 h; 2) 180°C, 24 h; 3) 190°C, 12 h
7	8 g	65%	185°C, 35 h
8[c]	8 g	73%	1) 175°C, 12 h; 2) 175°C, 6 h
9[c]	12 g	78%	1) 175°C, 12 h; 2) 175°C, 6 h
10[c]	17.55 g	78%	1) 175°C, 19 h; 2) 175°C, 12 h

[a] The reaction was performed in a Pyrex test tube or three-neck round bottom flask of different sizes depending on the scale. The reaction was heated in oil bath at indicted temperature. Air was slowly introduced into the flask through needle or glass tube. [b] Combined isolated yield from chromatography and/or filtration. See experimental for details. [c] After the first 12-19 hours of reaction, the crude mixture was stirred with small amount of cold CH_2Cl_2 and racemic VANOL was obtained as a solid after filtration. Upon removal of solvent, the remaining crude mixture was reacted for anther 6-12 hours.

However, the success of entry 2 was unable to be repeated on 5 gram scale. Various conditions (entry 3, 4, 5) including different temperatures, different reaction times were

attempted, however, the highest recovery was only 76% (entry 3), and the yield dropped further to 65% at on gram scale (entry 7).

It was found that strong stirring and the proper air flow was critical for the success of the reaction. On large scale, a big round bottom flask and a big stirring bar was necessary to ensure sufficient air contact. During the reaction, air was introduced via needle or glass tube and slowly blown to the surface of the melted starting material. An airflow that is too fast is detrimental to the reaction. Under the reaction conditions, 3-phenyl-1-naphthol **65** was a liquid as its melting point is only 96-97.5 °C. During the reaction it is slowly oxidized to VANOL, and due to the high melting point of VANOL (231-232 °C), the reaction mixture solidifies slowly and after 12-16 hours the stir bar will stop. Some of the starting material is trapped in the solid and is no longer exposed to oxygen and therefore can not undergo further reaction. The product VANOL formed on the surface of solid mixture would be exposed to too much oxygen and can be further oxidized to by-products at this high temperature.

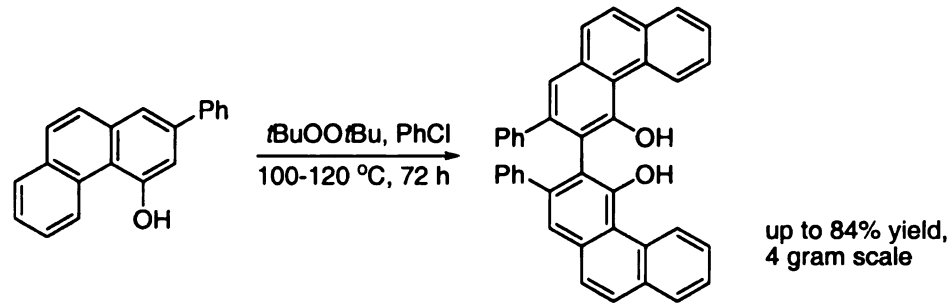
Another problem lies in the purification of racemic VANOL. Separation of VANOL from the crude reaction mixture by chromatography is complicated by the low solubility of the product and by the existence of several impurities of similar polarity. Thus silica gel chromatography on >10 grams of reaction mixture would not be a convenient process. It would be much desirable to find a more feasible and economical purification method.

After numerous attempts, an efficient procedure for the large-scale reaction and purification was finally found. The optimal condition involves a two-step reaction process.

In order to suppress over-oxidation and drive the reaction toward complete conversion, the heating was stopped as soon as the reaction mixture solidified and the stir bar stopped (entry 8-10). Upon cooling the solidified crude mixture was crushed into small granules, mixed with a small amount of cold (0 °C) CH_2Cl_2 and stirred at 0 °C for 10-30 minutes. Because racemic VANOL has a much lower solubility in cold CH_2Cl_2 than the starting material and the impurities, a simple filtration can afford up to an 85% yield (entry 9, based on total recovery) of VANOL with good purity. Upon removal of solvent, the residue from the filtrate was subjected to same reaction conditions for another 6-12 hours. The final reaction mixture was again extracted with cold CH_2Cl_2 to collect the racemic VANOL. The remaining VANOL in the CH_2Cl_2 solution can be purified by silica gel chromatography. With this two-step reaction method, good yield of VANOL could be obtained on up to an 18 gram scale (entry 10). The light yellow VANOL product obtained by this method is pure enough for the resolution step. If desired it can be further purified by washing with cold CH_2Cl_2 and/or crystallization from CH_2Cl_2 or EtOAc. The resulting VANOL is a white powder and can be used in the deracemization reaction.

According to unpublished work by Siu Man Yeung in the Wulff group, VAPOL can be prepared by the stoichiometric oxidative coupling of 2-phenyl-4-phenanthrol **65** using *tert*-butyl peroxide (Scheme 2.3).[32] In the best condition, VAPOL was obtained in up to 93% yield on a 0.1g scale and 84% yield on a 4 gram scale. The major drawback of this method lies in the fact that when this reaction was run on 5 gram scale, the yield dropped to 77% and a significant increase in several side products was observed.

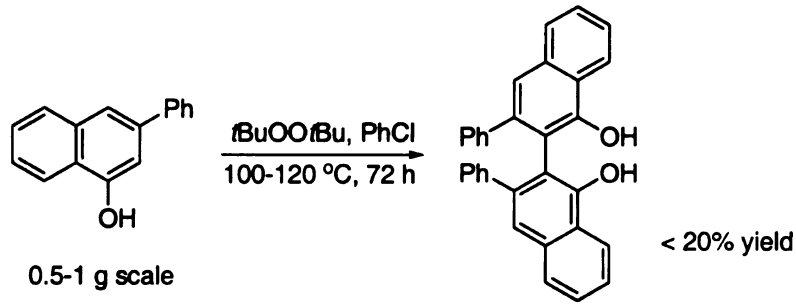
Scheme 2.3 Oxidative coupling of 2-phenyl-4-phenanthrol **63**



63 **46**

Following Yeung's best result, the same condition was used to examine this *tert*-butyl peroxide coupling for the preparation of VANOL. However, it was quickly found that the stoichiometric oxidative coupling of 3-phenyl-1-naphthol **65** using *t*-butyl peroxide gave unsatisfactory results (Scheme 2.4). In all experiments, VANOL was isolated in less than 20% yield, and the major product isolated from the reaction was unable to be identified because of it's complex ^{1}H NMR. The failure of the reaction is presumably due to the much lower oxidative stability of VANOL compared to VAPOL.

Scheme 2.4 Oxidative coupling of 3-phenyl-1-naphthol **65** with *tert*-butyl peroxide



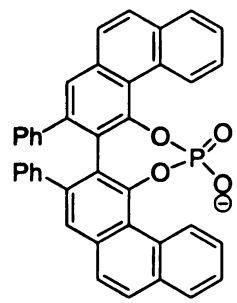
0.5-1 g scale

65 **47**

2.3 Improved large scale resolution of VANOL

Recent work in our lab demonstrated that the resolution of VAPOL could be greatly simplified by direct reduction of VAPOL-cinchonidine salt **67** (Scheme 2.5). Instead of hydrolysis of salt and methylation of the phosphate oxygen, the resolved salt could be directly subjected to the Red-Al reduction. (S)- and (R)- VAPOL could be obtained in 76% and 90% isolated yield from the corresponding salt, respectively, without loss of optical purity. It is thus desirable to determine whether this new cleavage procedure could be applied in the resolution of VANOL.

Scheme 2.5 Direct reduction of VAPOL-cinchonidine salt



67

Cinchonidine-H$^{\oplus}$

(Resolved)

Red-Al
Tol, 0 °C

(S)-VAPOL
76% from salt
62% from rac-**46**
99% ee

&

(R)-VAPOL
90% from salt
68% from rac-**46**
99% ee

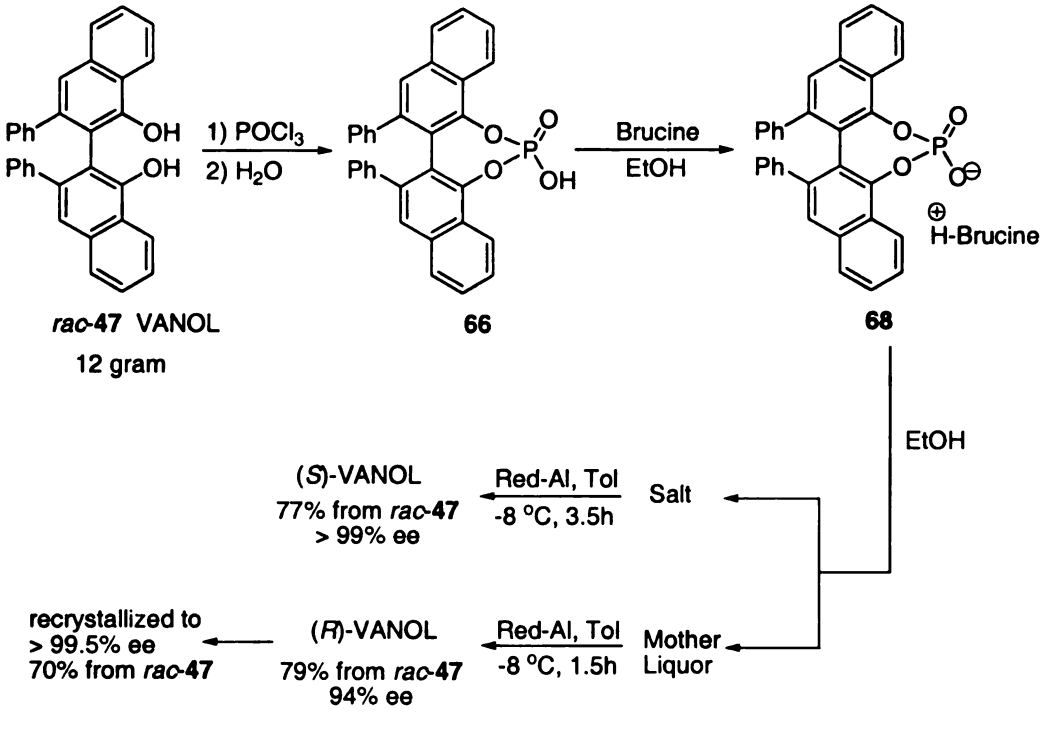
VANOL-phosphoric acid **66** was prepared by refluxing VANOL with $POCl_3$ in pyridine, followed by acid hydrolysis of the resulting acid chloride. The acid **66** was dried and used directly in the following steps.

Resolution was carried out by refluxing **66** with (-)-Brucine dihydrate using ethanol as solvent (Scheme 2.6). Upon cooling, small crystals precipitated from solution. It was found that the enantiomeric purity of the salt or mother liquor could not be determined by examining the ^{1}H or ^{13}C NMR of the salt **68**, as the diastereomers of **68** were completely

indistinguishable by both NMR methods. The reported phosphorous NMR method was not very helpful either,[24] as the two diastereomeric ^{31}P signal peaks overlap.

Subsequently, the salt obtained from the resolution was collected and a small portion was subjected to Red-Al reduction. It was pleasing to find that direct reduction of the salt **68** was successful and that the (*S*)-VANOL obtained was of 99% ee. The optimal procedure for the large scale (> 10 mmol) reduction involves syringe pump addition of diluted Red-Al solution to a suspension of the salt in toluene at -8 °C. It was essential to add Red-Al slowly (in a period of 1 hour) and keep the temperature below 0 °C. Partial racemization had been observed at higher temperature. It was found that the reduction could occur at temperatures as low as -78 °C, although the operation at this temperature would be less convenient.

Scheme 2.6 Large scale resolution of VANOL



In the event, the large scale direct reduction of the resolved salt using Red-Al worked smoothly; (*S*)-VANOL was produced in 77% overall yield from racemic VANOL **47** (12 gram scale) with greater than 99% ee. The mother liquor was concentrated and the same reduction conditions afforded (*R*)-VANOL in 79% yield with 94% ee. The enantiomeric purity of (*R*)-VANOL could be readily enriched by a single crystallization from ethyl acetate and hexane. (*R*)-VANOL was obtained in 70% overall yield from racemic VANOL with greater than 99.5% ee.

2.4 Conclusion

The large scale preparation of racemic VANOL **47** by oxidative coupling of 3-phenyl-1-naphthol **65** using air can be achieved on up to an 18 gram scale with good yield. It was found that the purity of **65** was crucial for the success of the coupling, and a two-step reaction sequence is vital for large scale reactions. Separation of VANOL from the crude reaction mixture could be greatly simplified by washing with cold CH_2Cl_2 and the product could be obtained in good yield and purity.

The direct Red-Al reduction of the VANOL phosphorate ester-Brucine salt could be performed on reasonably large scale. Both enantiomers of VANOL were isolated in good overall yield with greater than 99% ee. It is projected that the reaction can be performed on larger scale (> 50 gram) without modification of the procedure.

After the discovery and optimization of this large scale synthesis of enantiomerically pure VANOL, another group member was able to repeat the overall process on a larger

scale employing the same procedure. The oxidative coupling could be carried out on 100 gram scale and racemic VANOL could be isolated in 80% yield. In addition, the large scale resolution and reduction of the VANOL-brucine salt could also be performed on >30 gram scale following the same protocol.

As a conclusion, the large scale oxidative coupling and resolution reported herein represent a more economical, convenient, higher yielding process compared with the published procedure. It is expected that this efficient process will contribute to the large scale production and commercialization of the VANOL ligand.

CHAPTER THREE

HIGHLY ENANTIOSELECTIVE DERACEMIZATION OF LINEAR AND VAULTED BIARYL LIGANDS

3.1 Introduction

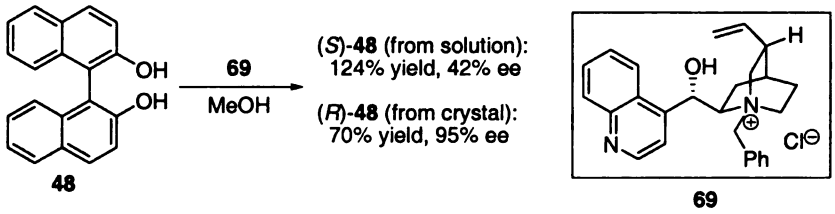
Since the discovery of 2,2'-binaphthol (BINOL) and its derivatives, the stereoselective synthesis of compounds containing axial chirality has been regarded as one of the most significant fields in synthetic organic chemistry. Once regarded as merely "academic curiosity", the axially chiral biaryl compounds exhibit excellent chirality transfer properties in a large number of catalytic asymmetric reactions, and the preparation of enantiomerically pure biaryl compounds has been the focus of extensive studies over the last two decades.[33]

As aforementioned in chapter two, the published resolution procedures for the *C*2-symmetric vaulted biaryl ligands VAPOL **46** and VANOL **47** follow a four-step process that involves the bis-ester of phosphoric acid.[24] Salt formation of the bis-ester with (+)-cinchonidine (for VAPOL) or (-)-brucine (for VANOL) leads to diastereomers which can be separated by crystallization. The drawbacks of this procedure include difficulty in the crystallization of the diastereomers, the use of large amounts of different reagents, and most importantly, the long four-step reaction sequence.

Owing to the importance of chiral biaryl compounds, various alternative methods for obtaining optically pure BINOL derivatives have been developed.[33] These approaches including the optical resolution of diastereomeric salts prepared directly from the ligands,[34] asymmetric coupling of 2-naphthol derivatives,[35] asymmetric biaryl synthesis via benzannulation,[36] and the desymmetrization (deracemization) of biaryl compounds.[37-38]

The optical resolution of diastereomeric salts directly from the ligands involves host-guest complexation between a chiral compound and one enantiomer of the BINOL. Toda et al reported that N-benzylcinchonidium chloride **69** was an efficient resolving reagent for BINOL (Scheme 3.1).[34] X-ray diffraction study indicated directional hydrogen bonding and aryl-aryl interaction modes in the 1:1 complexation of (R)-BINOL and **69**. BINOL could be obtained in up to 100% ee, and in most cases the host compound could be recovered. The biggest limitation of this approach lies in its substrate scope, only a few chiral biaryl compounds have been reported to be resolved by this method.

Scheme 3.1 Direct optical resolution of BINOL

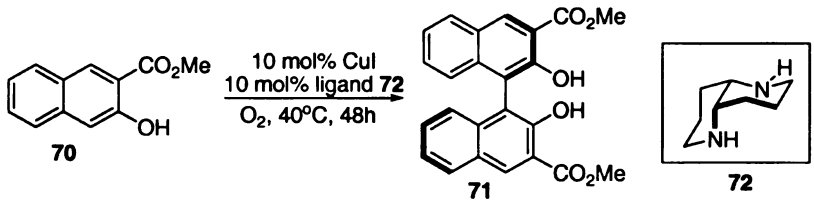


48 **69**

The enantioselective C-C coupling of 2-naphthol derivatives has been the most extensively studied approach.[33,35] Various chiral-tether induced diastereoselective couplings, metal-catalyzed asymmetric cross-couplings and oxidative couplings were

developed. The chirality of the biaryl axis is introduced by either a chiral auxiliary or in the case of catalytic reactions, by chiral ligands. As an example of the latter, Kozlowski et al demonstrated that 2-naphthol compounds such as **70** undergo enantioselective oxidative homocoupling in the presence of catalytic amount of CuI and C2-symmetric chiral diamine **72** (Scheme 3.2).[35e] The most attractive aspects of the enantioselective coupling include that the axial chirality is introduced concomitantly during the formation of aryl-aryl C-C bond, and the "monomeric" substrates are generally easy to prepare. Also in the case of catalytic reactions, only substoichiometric amounts of the chiral reagents are employed. However, despite the great amount of effort in this area, preparation of optically pure biaryl compounds using this method do not generally give high asymmetric induction and are not yet the method of choice for chiral biaryl synthesis.

Scheme 3.2 Catalytic asymmetric oxidative coupling of 2-naphthol derivatives



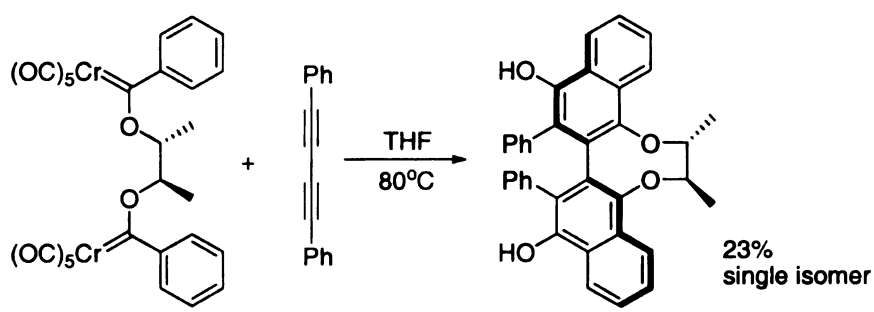
70 **71** **72**

85% yield
91-93% ee

The synthesis of chiral biaryl compounds via the construction of an aromatic ring is a fundamentally new strategy, in which a preformed aryl-carbon single bond is transformed into chiral biaryl axis upon formation of the second arene ring, in some cases two arene rings have been constructed at the same time.[36] The axial chirality is generally introduced by the chiral auxiliary or by the ligand in the enantioselective catalysis.

One such examples was reported by our group in the asymmetric synthesis of axially chiral compound **75** (Scheme 3.3).[36a] The two chromium carbene complexes in **73** are connected by a chiral tether and were reacted with the 1,4-butadiyne **74** via a double Wulff-Dotz benzannulation reaction, and afforded the axially chiral product **75** as a single stereoisomer in low yield. Other benzannulation reactions that involved central-to-axial chirality transfer generally gave very good enantio- or diasteroselectivity.[36] This highly efficient and innovative strategy is still relatively under-developed and its substrate scope is limited.

Scheme 3.3 Asymmetric synthesis of axially chiral **75** via double benzannulation



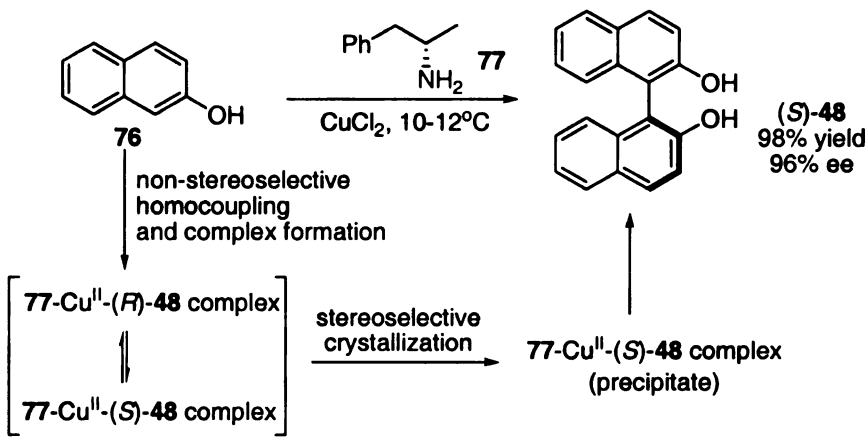
73 **74** **75**

In the process of desymmetrization of biaryl compounds, a non-stereoselective C-C coupling reaction would be used to first form the aryl-aryl bond, and a second step would be necessary to establish the absolute stereochemistry at the biaryl axis. Despite the extra desymmetrization step, this method is not necessarily more labor-intensive than the direct asymmetric coupling procedures.

An interesting example involving an enantioselective dynamic kinetic resolution was published by Brussee et al (Scheme 3.4).[37] The Cu(II) induced non-stereoselective oxidative coupling of 2-naphthol **76** would give racemic BINOL **48**. In the presence of

chiral amine **77**, each enantiomer of **48** formed a diastereomeric complex with Cu(II) and amine **77**. Only the Cu(II)-(S)-**48** complex crystallized, whereas the soluble diastereomeric (*R*)-**48** complex slowly underwent deracemization (second-order asymmetric transformation)[39] into the (*S*)-complex which then precipitated. The overall process afforded (*S*)-**48** in excellent yield and ee. However BINOL was the only ligand reported, and the stereoselective crystallization only occurs within the narrow temperature range of 10-12°C.

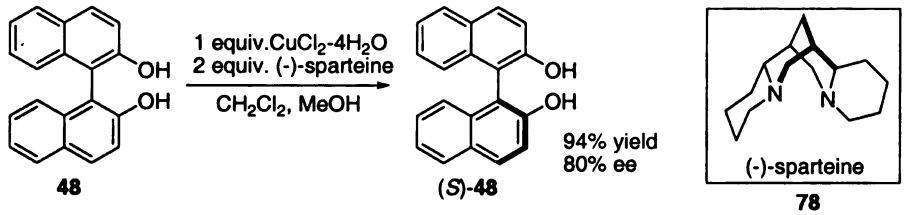
Scheme 3.4 Cu(II)-mediated deracemization of BINOL



Subsequent, Kocovsky et al reported a copper(II)-(-)-sparteine mediated deracemization of BINOL and its derivatives (Scheme 3.5).[38] The asymmetric oxidative coupling of 2-naphthol **76** using $CuCl_2$ and (-)-sparteine **78** gave less satisfactory result. However, in the presence of a reagent generated from 1 equivalent of $CuCl_2$-$4H_2O$ and 2 equivalents of (-)-sparteine **78**, the reaction of 1mmol of racemic BINOL **48** afforded (*S*)-**48** in 94% yield and 80% ee. The authors proposed that this deracemization also involves a second-order asymmetric transformation,[39] since the (S)-**48** isolated from the

reaction precipitate was more optically enriched than the (S)-**48** from the solution.

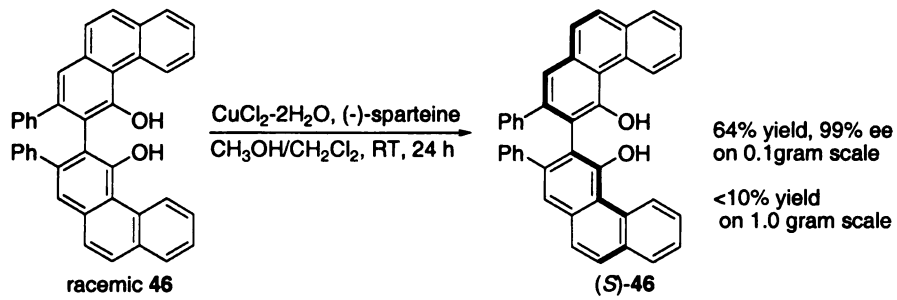
Scheme 3.5 Cu(II)-(-)-sparteine mediated deracemization of BINOL



48 (*S*)-**48** **78**

Inspired by Kocovsky's work, Dr. Yeung, a former group member found that a complex generated from 1.4 equivalent of $CuCl_2$-$2H_2O$ and 2.8 equivalents of (-)-sparteine **78** was also effective for the deracemization of VAPOL **46**.[32] However, the best result Yeung obtained (64% yield, 99% ee) can only be reproduced on a 0.1 gram scale. For example, when an attempt was made to scale this reaction to 1.0 gram, VAPOL was only recovered in <10% yield (Scheme 3.6).

Scheme 3.6 Cu(II)-sparteine mediated deracemization of VAPOL **46**



racemic **46** (*S*)-**46**

Although this Cu(II)-sparteine mediated deracemization process involves the use of an excess amount of chiral base, this one-step preparation of (*S*)-VAPOL would be useful if good recovery and optical purity could be obtained on a reasonably large scale, as this process would avoid the tedious and unpredictable resolution sequence. An efficient

deracemization process would be a valuable tool for the rapid synthesis of chiral biaryl ligands.

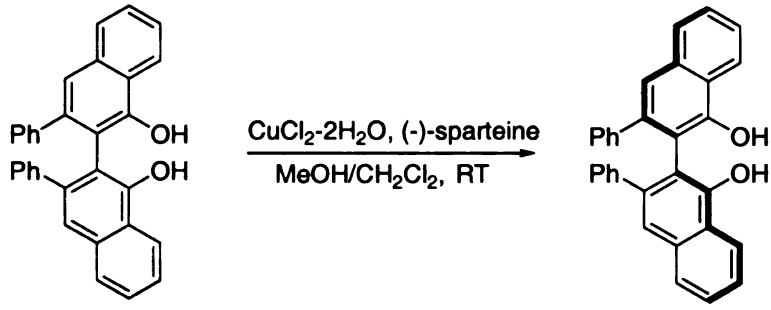
3.2 Highly enantioselective deracemization of linear and vaulted biaryl ligands

3.2.1 Deracemization of VANOL using $CuCl_2$ and (-)sparteine

The initial attempts at deracemization of VANOL encountered several problems (Table 3.1). First, it was found that the reaction was extremely sensitive to oxygen, as the product decomposed completely within 24 hours if the reaction was performed in the presence of air. Another curious problem that was encountered was that even if reaction was performed under an inert atmosphere, satisfactory results were not obtained (entry 1, 2). However, if argon gas was slowly purged through the reaction system during the indicated reaction period, much higher recovery and ee was observed (entry 3-8).

For the argon-purging method, the best result was obtained on a 0.2 gram scale, and (*S*)-VANOL could be isolated in 67% yield and 99% ee (entry 3). However, when the scale was increased to 0.8 gram, the isolated yield dropped to around 40% (entry 8). It was suspected that a small amount of oxygen remained in solution and was responsible for the decomposition of the product. Thus a more strict deoxygenation using the freeze-thaw method was employed to more throughly deoxygenate the solution. It was pleasing to find that the recovery was greatly improved (entries 9 vs 5), and the product could be isolated in 77% yield and 99% ee on a 0.6 gram scale (entry 9).

Table 3.1 Deracemization of racemic VANOL with $CuCl_2$ and (-)-sparteine



racemic **47** (*S*)-**47**

entry[a]	scale (g)	solvent system ($MeOH:CH_2Cl_2$)	concn (mM)	time (h)	yield (%)	ee (%)
1[b]	0.4	2:1	7.6	48	22	66
2[b]	0.8	2:1	7.6	48	17	98
3[c]	0.2	2:1	7.6	57	67	99
4[c,d]	0.4	2:1	7.6	46	45	99
5[c]	0.6	2:1	7.6	46	42	98
6[c,e]	0.6	2:1	7.6	48	60	98
7[c]	0.6	2:1	7.6	20	71	90
8[c]	0.8	2:1	7.6	50	42	98
9[f]	0.6	2:1	7.6	50	77	99
10[d,f]	0.6	2:1	7.6	50	66	90
11[f,g]	0.6	2:1	7.6	50	55	93
12[f]	0.6	2:1	15	50	61	93
13[f]	1.0	2:1	7.6	50	59	93

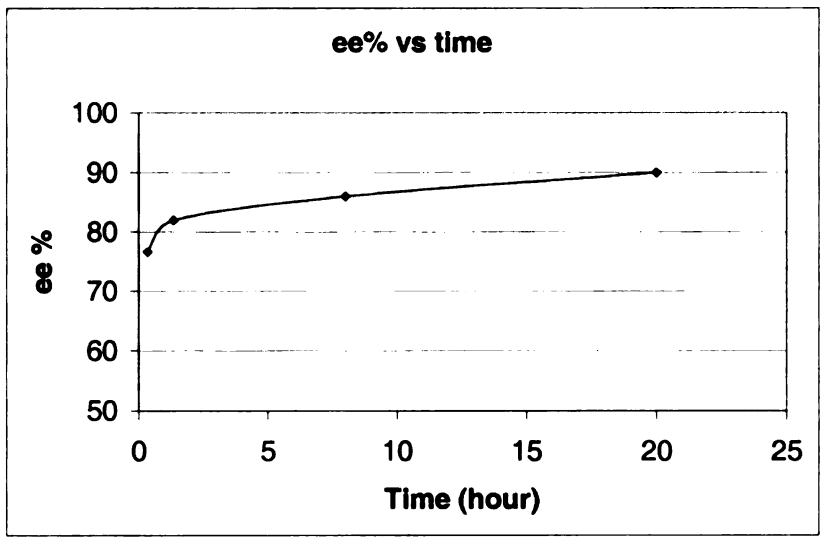
[a] Unless otherwise specified, 1 equiv. of racemic VANOL in deoxygenated CH_2Cl_2 and methanol was transferred to a mixture of 1.4 equiv. of $CuCl_2 \cdot H_2O$ and 2.8 equiv. of (-)-sparteine in deoxygenated methanol at room temperature under argon. [b] The reaction was run under an Ar atmosphere with an Ar ballon attached to the flask. [c] The reaction was purged with argon during the whole reaction period. [d] Average of three runs. [e] $CuCl_2$-(-)-sparteine solution was sonicated for 1 hour using an ultrasonic bath. [f] The reaction solution was deoxygenated using the freeze-thaw

method two to three times. [g] The reaction solution was deoxygenated using the freeze-thaw method two to three times, reaction was run in 40°C.

However, the inductions were still variable as indicated by the fact that the reaction in entry 9 was repeated three times and the average of those three runs (entry 10) was 90% ee. When the reaction was performed on 1.0 gram (entry 13), the recovery of (S)-**47** dropped significantly. Thus, although the use of the freeze-thaw deoxygenation technique generally gave better results, the procedure is time consuming, the results are variable, and it would be impractical on a larger scale.

Time and temperature effects were also examined. Higher temperature (40°C, entry 11) was found to be detrimental to the reaction, and shorter reaction times (entry 7) afforded good recovery, but the chiral induction was low.

Figure 3.1 Study of time-%ee relationship



Time (hour)	0.333	1.333	8	20
ee (%)	77	82	86	90

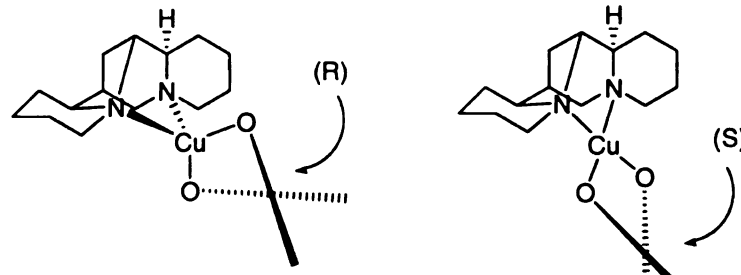
During one experiment, a small amount of the sample was taken from the reaction solution at various reaction time, quenched with HCl and then examined by chiral HPLC to determine the ee% as the reaction progress (Figure 3.1). The plot of ee% versus time clearly indicated that reaction was relatively fast during the first 30 minutes, as the chiral induction reached 77% after only 20 minutes. However, the rate of deracemization dropped dramatically after 30 minutes. After 20 hours, the induction only increased to 90% ee. In another example, the reaction profile displayed a similar pattern, with the induction reaching 90% within 10 hours, but it then took almost another 40 hours to reach 98% ee. Prolonged reaction time generally leads to higher ee, however significantly reduced recovery was observed if the reaction time was longer than 48 hours. In most cases, the low yields were accompanied by the formation of a yellow colored side-product. The possible side reaction and the possible structure of the side product will be discussed later in this chapter.

As a conclusion, we found that the reagent generated from $CuCl_2$ and (-)-sparteine was effective for the deracemization of VAPOL and VANOL on small scale, where good induction and recovery could be observed. However, the reactions were generally slow, and the degree of induction and the yield were variable. The biggest drawback of this process was the poor recovery on large scale.

3.2.2 Deracemization of biaryl ligands using CuCl and (-)-sparteine

In Kocovsky's report on the deracemization of BINOL[38], it was suggested, but not demonstrated, that (*R*)-BINOL could be produced from a copper(I) complex with (-)-sparteine. They proposed that a complex between (-)-sparteine, a tetrahedral copper (presumably Cu^{I}) and BINOL should strongly favor the (*R*)- configuration of BINOL unit (**A**) (Figure 3.2). By contrast, an analogous complex containing square-planar copper (presumably Cu^{II}) should prefer the (*S*)- configuration of BINOL (**B**). Since (+)-sparteine was not available from nature, this suggestion takes on great significance since it could provide for a direct route from racemic bis-phenols to either desired enantiotropic atroposomer.

Figure 3.2 Suggested preferential formation of (*R*)-BINOL with terahedral Cu(I)-sparteine complex **A** and of (*S*)-BINOL with square-planar Cu(II)-sparteine complex **B**



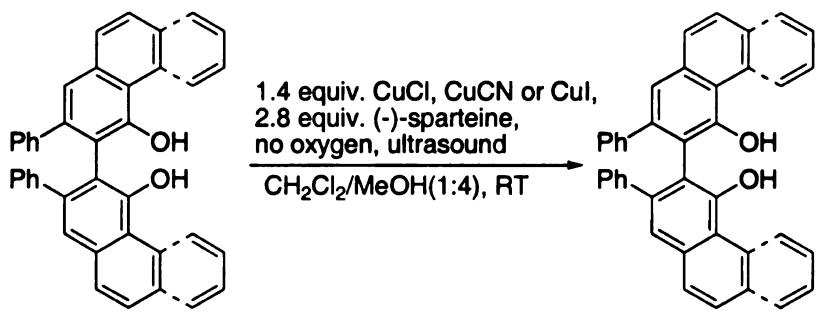
A Cu(I), tetrahedral,

B Cu(II), square-planar

In order to verify Kocovsky's proposed selectivity, the deracemization was examined with various Cu(I) salts (Scheme 3.7). The reaction was conducted by deoxygenating a solution of 1.4 equiv of CuCl, followed by addition of 2.8 equiv of (-)-sparteine. The reaction flask was placed in an ultrasonic bath to speed up the dissolution of cuprous

chloride. After the CuCl was dissolved the resulting clear solution of Cu(I)-(-)-sparteine complex was then transferred to a deoxygenated racemic VAPOL solution. The homogeneous faint yellow reaction mixture was allowed to stir under slow argon flow for 6 hours in the absence of ultrasound. Upon workup VAPOL was recovered in 93% and was found to be racemic. The same reaction conditions employing CuCN or CuI also led to racemic ligand. In these examples, exposing the reaction system to air lead to the formation of (*S*)-VANOL due to the generation of Cu(II) by oxidation, whereas at the same time significant decomposition of VANOL was observed. The reason why this Cu(I)-sparteine mediated deracemization did not occur is not clear. However, due to its great synthetic potential, this proposed transformation may be worth further investigating.

Scheme 3.7 Attempted deracemization of racemic VAPOL and VANOL using Cu(I)-(-)-sparteine complex



racemic **46/47** racemic **46/47**

Meanwhile, we found that if the sonication of CuCl and (-)-sparteine was conducted in the presence of air, there was a rapid dissolution of CuCl along with concomitant formation of a green solution, presumably a copper (II) species. If this solution was deoxygenated by purging with argon and then added to the solution of VANOL, (*S*)-VANOL could be isolated with excellent results (Table 3.2, entry 1, 90% yield, 99% ee)

within much shorter reaction times than when preformed Cu(II) salts were used. If Kocovsky's proposal is correct, then the fact that the isolated enantiomer was found to be (*S*)-VANOL indicated that the active reagent was indeed a Cu(II)-sparteine species resulted from the oxidation of CuCl in the presence of ultrasound and air.

We quickly found out that this in-situ generated Cu(II)-sparteine complex was a much more efficient deracemization reagent. The optimized conditions for the reaction involves sonication of the methanol solution of 1.4 equivalent of CuCl and 2.8 equivalent of (-)-sparteine in the presence of air. This process resulted in the oxidation of the insoluble Cu(I)Cl to Cu(II), which gave a murky green solution as a result of coordination with (-)-sparteine. The homogeneous Cu(II)-sparteine complex solution that was obtained was then deoxygenated by purging with argon and then transferred to a deoxygenated VANOL solution. The resulting black solution was allowed to stir under slow argon flow for the indicated time before work-up with concentrated HCl.

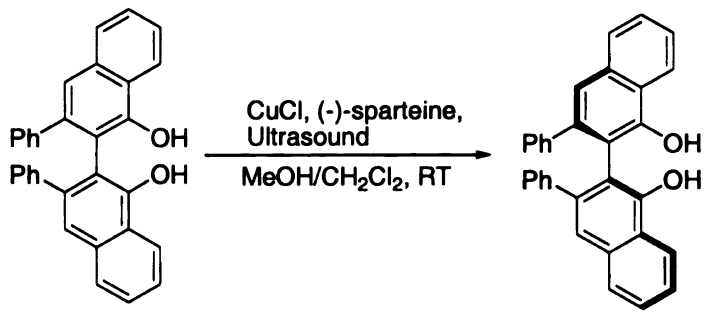
The deracemization of VANOL was subsequently examined on larger scale and under different conditions. This in-situ generated Cu(II)-sparteine complex was found to react approximately twenty times faster than the previous $CuCl_2$-sparteine mediated process. The relatively low recovery of entry 3 should be attributed to prolonged reaction time. In order to suppress the decomposition, a shorter reaction time (2-2.75 hours) was used. Variation of the ratio of MeOH to CH_2Cl_2 on 1 gram scale (entry 4-7) showed that a mixed solvent of 1:4 MeOH/CH_2Cl_2 (entry 5) was the optimal solvent system and afforded optically pure (*S*)-VANOL in good yield. Higher proportions of MeOH (entry 4) or of

CH_2Cl_2 (entry 6) gave lower yield, and the reaction in CH_2Cl_2 alone was very sluggish (entry 7). An attempt to reduce the amount of (-)-sparteine lead to much lower yield and induction (entry 8), and the reaction at higher concentration produced a diminished yield (54% in entry 11, average of two runs), although the chiral induction was still excellent.

It was gratifying to find that by employing this improved procedure, the reactions were much more reproducible and could be successfully scaled up to 5 gram scale with virtually no loss of recovery and %ee (entry 10). Since the optimal concentration was 7.6mM, this reaction was not further pursued on a larger scale due to the limitation of reaction flask size and also due to the limited quantity of racemic VANOL that was available.

The success of the improved procedure can not be attributed to the ultrasonic bath alone, as the complex generated from $CuCl_2 \cdot 2H_2O$ and (-)-sparteine in an ultrasonic bath gave (*S*)-VANOL in a lower yield (60%) and with incomplete chiral induction (98% ee) after 48 hours on a 600mg scale (Table 3.2, entry 6).

Table 3.2 Deracemization of racemic VANOL with CuCl-(-)-sparteine



racemic **47** (*S*)-**47**

entry[a]	scale (g)	solvent ($MeOH:CH_2Cl_2$)	concn (mM)	time (h)	yield (%)[b]	ee (%)[c]
1	0.2	1:4	7.6	12	90	99
2	0.3	1:4	7.6	1.75	79	99
3	0.6	1:4	7.6	24	52	99
4	1.0	2:1	7.6	2.5	62	99
5	1.0	1:4	7.6	2.75	72	99
6	1.0	1:9	7.6	2.5	48	98
7	1.0	CH_2Cl_2 only	7.6	48	49	84
8[d]	1.0	1:4	7.6	2	43	88
9	2.0	1:4	7.6	2	70	99
10	5.0	1:4	7.6	2	69	99
11[e]	4.0	1:4	15	2	54	99

[a] Unless otherwise specified, in all the experiments, 1.4 equiv. of CuCl and 2.8 equiv. of (-)-sparteine was dissolved in methanol. After sonication open to air in ultrasonic bath for 10-15 minutes, the reaction mixture was then purged with argon for 30 minutes. The copper-(-)-sparteine solution was transferred to a solution of VANOL in deoxygenated CH_2Cl_2 and stirred under a slow argon flow for the stated time. [b] Isolated yield by chromatography. [c] Determined by chiral HPLC on a D-Phenylglycine column. [d] 1.4 equiv. of sparteine was used. [e] The yield was the average of two runs.

This improved procedure was then applied to the deracemizaion of VAPOL to examine the scope of this process on the sterically more hindered ligand. The results are shown in Table 3.3.

It was found that under the same conditions, deracemization of VAPOL using the in situ generated Cu(II)-(-)-sparteine complex was slower than that of VANOL. The decreased rate was presumably due to the slower complexation of Cu(II)-sparteine with the bulkier VAPOL. However, the reaction was still much faster than the original $CuCl_2$-(-)-sparteine mediated process. As shown in Figure 3.3, the induction rose to 97% ee after 9 hours (Table 3.3, entry 1). The low yield was possibly due to the long reaction time and associated decomposition. The reaction was then stopped after 5 hours to ensure high yield (75%, entry 2) to give the product of 95% ee, which can be readily recrystallized to give >99% ee.

Figure 3.3 Plot of time-%ee relationship in reaction of deracemization of VAPOL

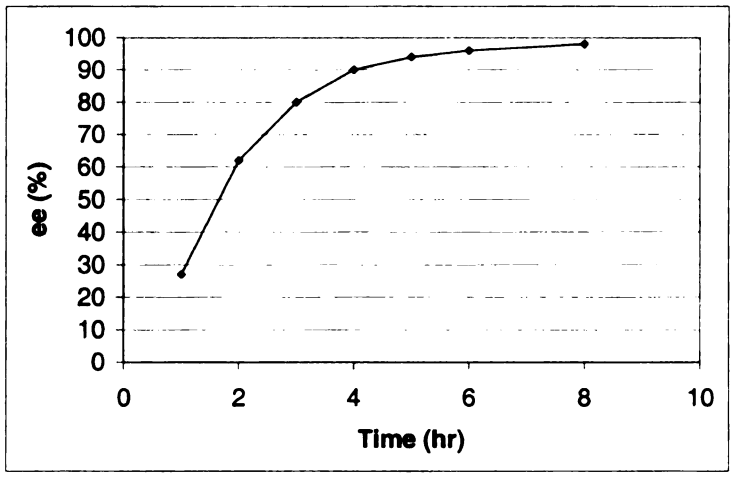
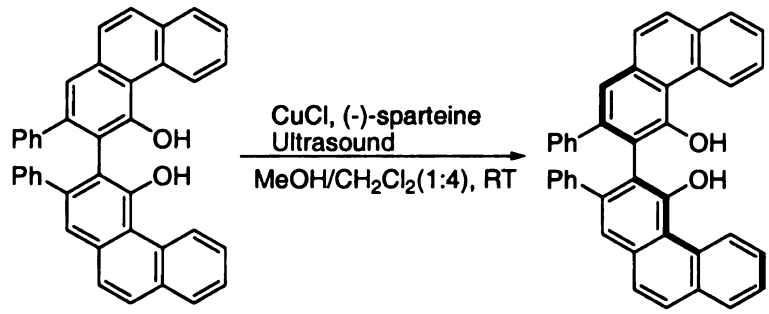


Table 3.3 Deracemization of racemic VAPOL with CuCl and (-)-sparteine



racemic **46** (*S*)-**46**

entry[a]	scale (g)	solvent system ($MeOH:CH_2Cl_2$)	concn (mM)	time (h)	yield (%)[b]	ee (%)[c]
1[d]	1.0	1:4	6.2	9	36	97
2[d,e]	1.0	1:4	6.2	5	75	95
3[d]	2.0	1:4	6.2	4	74	98
4[d,f,g]	5.0	1:4	6.2	24	73	99
5[d,f,g]	5.0	1:4	6.2	48	60	95
6[e,f,h]	5.0	1:4	6.2	25	89	96
7[f,i]	5.0	1:4	6.2	6	84	99

[a] Unless otherwise specified, in all the experiments, 1.4 equiv. of CuCl and 2.8 equiv. of (-)-sparteine were added to a flask containing methanol in ultrasonic bath. After being sonicated open to air for 10-45 min and then purged with argon for 30 min, the copper-sparteine solution was transferred to a solution of VAPOL in deoxygenated CH_2Cl_2 and then stirred at room temperature for stated time. The final product was purified by chromatography. [b] Isolated yield by chromatography. [c] Determined by chiral HPLC on a D-Phenylglycine column. [d] The starting racemic VAPOL was recrystallized from EtOAc once. [e] The yield was the average of two runs. [f] 1.67 equiv. of CuCl and 3.3 equiv. of (-)-sparteine was used. [g] Product was purified by crystallization using CH_2Cl_2/hexane. [h] The starting racemic VAPOL was crystallized from EtOAc twice. [i] The starting racemic VAPOL was crystallized from EtOAc three times.

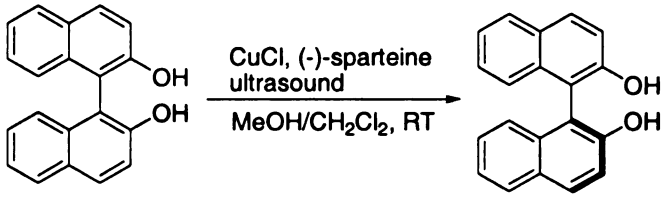
The success of entry 2 could be extended to 2.0 gram scale (74% yield, 98% ee). However, when the scale was increased to 5.0 grams, the reaction became very sluggish (entry 4), and it took 24 hours to reach 99% ee. In a second run under exactly the same condition the induction was only 95% ee after 48 hours (entry 5), even though 1.67 equivalent of CuCl and 3.3 equivalent of sparteine were used in both cases. We found that the only difference between entry 5 and entry 4 was that different batches of racemic VAPOL were used. Thus it was possible that the slower rate of entry 5 was due to a small amount of impurity in racemic VAPOL.

Therefore, the racemic VAPOL was crystallized from EtOAc twice before use. For larger scales, a solution of CuCl and sparteine was sonicated for 45 minutes under constant purge with air introduced into the solution via a needle to ensure the complete oxidation of CuCl. This slightly modified procedure did afford better results (entry 6, average of two runs), although it still required 24 hours for complete conversion. After the racemic VAPOL was crystallized three times before use, the induction reached 99% ee within only 5 hours, and the (*S*)-VAPOL could be isolated in 84% yield (entry 7).

The deracemization of BINOL was also examined with the in situ generated Cu(II) procedure (Table 3.4). Employing conditions previously reported with $CuCl_2$-$2H_2O$,[38] the in situ generated Cu(II) procedure gave a 77% recovery of BINOL with 93.5% ee (entry 1). Further optimization of the reaction time, concentration and solvent system are presented in entries 2-6 which lead to higher yields (~85%) but same ee. In entry 7, after the reaction was carried out at room temperature for 8 hours, the solution was cooled down

to -20°C for 16 hours in order to drive the equilibrium toward the proposed thermodynamically more stable (*S*)-complex. Quenching the reaction at -20°C didn't afford higher enantioselectivity, but the crude reaction mixture was much cleaner and reproducible excellent yields (97-98%) could be obtained. The reaction can also be scaled up to 5 gram without significant loss of ee.

Table 3.4 Deracemization of racemic BINOL with CuCl and (-)-sparteine



racemic **48** (*S*)-**48**

Entry[a]	scale (g)	solvent CH_2Cl_2/MeOH	concn. (mM)	time (h)	yield[b] (%)	ee[c] (%)
1	0.286	MeOH	33	20	77	93
2	0.2	4:1	7.6	8.5	94	92
3	0.2	4:1	7.6	16	90	91
4	0.2	4:1	7.6	24	81	91
5	0.2	2.5:1	7.6	24	83	92
6	0.2	2.5:1	15	24	93	92
7[d]	0.2	2.5:1	15	24	97	92
8[d]	0.2	2.5:1	30	24	97	92
9[d]	5.0	2.5:1	30	24	98	87

[a] Unless otherwise specified, all reactions were performed with 1.4 equiv of CuCl and 2.8 equiv of (-)-sparteine according to the general procedure. [b] Isolated yield by flash chromatography on silica gel. [c] Determined by HPLC on a Chirapak AS column. [d] Reaction at 25°C for 8 h and then -20°C for 16 h before quench at -20°C.

Unlike the observation with VANOL and VAPOL, the deracemization of BINOL at higher concentration (30 mM) has little effect on the outcome of the reaction (entry 8-9).

The deracemization of BINOL was not further optimized to scales larger than 5 grams. Nonetheless, the asymmetric induction observed with this new procedure represents a significant improvement over that previously reported[38] for BINOL (Scheme 3.4). The observed lower enantioselectivity for BINOL compared with that from the deracemizations of VANOL and VAPOL is presumably due to the shallower chiral pocket projected by BINOL.

Bao et al found that there is a large solubility difference between the racemate and each pure enantiomer of VAPOL and VANOL. As a result, a practical method was described for the enrichment of VAPOL by simple extraction with hexane.[24]

We subsequently discovered that the enantiomeric enrichment of VANOL could be conducted by simple precipitation of the racemate due to the extraordinary good solubility of enantiomerically pure VANOL. In the event, 4 g of (*S*)-VANOL with 90% ee was dissolved in a minimal amount of ethyl acetate. Hexane was added slowly until the racemate (< 25% ee) precipitated and the ee% of the VANOL in solution was optically pure as determined by chiral HPLC. Upon concentration the resulting solution gave an 88% recovery of S-VANOL which was determined to be >99.5% ee.

Due to the smaller solubility difference between racemic and optically pure VAPOL, purification of (*S*) or (*R*)-VAPOL using recrystallization was more capricious than that of VANOL. The hexane extraction method was used for the enrichment of (*S*)-VAPOL. It was found that after several extractions, it became more and more difficult to separate

the remaining solid from the hexane solution as the solid particles become increasingly finer and precipitation times became unduly extended.

Continuous labor-free extraction using a Soxhlet extractor was then examined for its utility in the enrichment of (*S*)-VAPOL. VAPOL of 97% ee was placed into the extraction thimble and extracted with pentane under inert atmosphere. After 24 hours, HPLC confirmed that the VAPOL extracted by pentane was of >99.5% ee. The major problem with this method lies in the fact that it took more than 48 hours to extract 4.0 g VAPOL (>3.0 g optically pure VAPOL was recovered), and during this period some decomposition was observed due to the low stability of the optically pure ligand in solution.

3.2.3 Mechanistic study of Cu(II)-(-)-sparteine mediated deracemization

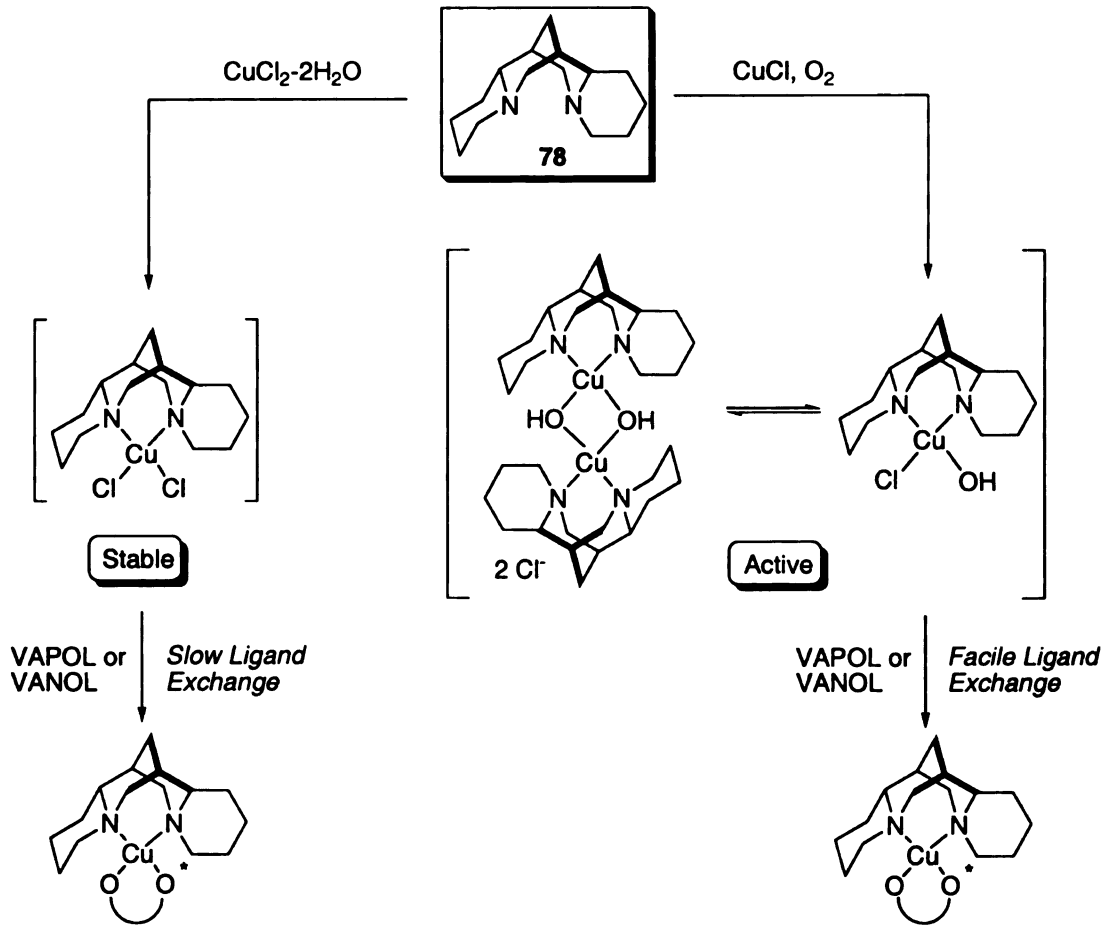
In his study on the deracemization of BINOL[38], Kocovsky proposed that a second-order asymmetric transformation was operating as the main stereodifferentiating process. This transformation was thought to occur via the preferential crystallization of enantiomerically pure (*S*)-BINOL-Cu(II)-(-)-sparteine complex accompanied by an in situ racemization of the diastereomeric complexes in solution under the equilibrium conditions. It should be noted that it is not necessary for the complex which crystallizes out to be the predominant one in equilibrium in solution.

Dr. Yeung in our group proposed that for the deracemization of VAPOL with $CuCl_2$ and (-)-sparteine, the mechanism is probably more consistent with a first-order

asymmetric transformation, since under the reaction conditions no preferential crystallization occurs.[32] The reactions described above involving the in situ generated Cu(II) species were also homogeneous even at much higher concentrations. In this deracemization process, the (*S*)-VANOL-Cu(II)-(-)-sparteine complex and the corresponding (*R*)-VANOL complex exist in equilibrium. The (*S*)-VANOL complex is presumably more thermodynamically stable and thus favored due to the "better fit" of (*S*)-VANOL with (-)-sparteine. The (*R*)-VANOL complex is then transformed into the (*S*)-VANOL complex via a first-order asymmetric transformation. We found that (*S*)-VANOL of 98% ee slowly racemized to 19% ee in 48 hours in the presence of nBu$_3$N and $CuCl_2$, whereas (*R*)-VAPOL with 93% ee can be transformed to (*S*)-VAPOL with 27% ee by Cu(II)- (-)-sparteine complex. These results supported the nature of deracemization. However, the details of transformation remain unclear.

In the deracemization process described above, a Cu(I) source was found to be much more efficient than a Cu(II) source. In a related study of oxidative coupling of naphthol derivatives, Nakajima's also discovered that a Cu(II) salt was less reactive than Cu(I)Cl.[35d] These results could possibly be explained by the fact that the Cu(II)-sparteine complex generated by coordination of (-)-sparteine to $CuCl_2$-2H_2O is a more stable species (Scheme 3.8), and that exchange of both halides by a bisphenol will be slow and formation of the proposed sparteine-Cu(II)-bisphenol complex will be sluggish.

Scheme 3.8 Rationale for the reactivity difference from different Cu sources

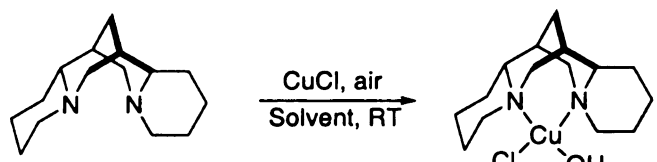


In the case of the in situ generated Cu(II)-sparteine complex from the oxidation of CuCl in the presence of (-)-sparteine, bridging υ-oxo dimers or trimers of Cu(diamine)X(OH) with dissociated chloride anions may well have been formed based on X-ray structures of relative studies with different chiral diamines.[35, 40] In solution, these dimers are possibly in equilibrium with coordinatively unsaturated monomers which can readily bind with VAPOL (Scheme 3.8). In addition, exchange of VAPOL with the hydroxo ligand on the sparteine-Cu(OH)Cl complex should be facile since water is released via direct proton transfer. On the other hand, it is possible that the complex generated from (-)-sparteine and CuCl in the absence of air still has the chloride tightly bound to Cu(I),

and that ligand exchange of this chloride with VAPOL would be slow, thus accounting for the lack of any deracemization observed for VAPOL with the Cu(I)-(-)-sparteine complex.

It was found that the reaction of CuCl with 1 equiv of (-)-sparteine in the presence of air afforded a green solid **79** that was assumed to be Cu-(-)-(sparteine)Cl(OH) (Table 3.5).[35e, 35i] Optimization of the reaction conditions revealed that the use of an ultrasonic bath is more efficient than conventional stirring. Complex **79** was obtained in 50-70% yield upon removal of solvent and used without further purification.

Table 3.5 Preparation of Sparteine-Cu(OH)Cl complex **79**



78
(-)-sparteine

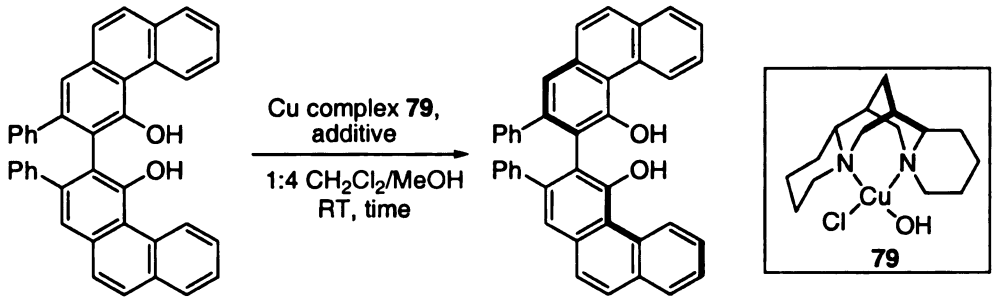
79

entry	solvent	CuCl/sparteine	condition	time	yield (%)
1	95% MeOH	1:2	stirring	> 4h	<5
2	MeOH	1:2	ultrasound	20 min	33
3	CH_2Cl_2	1:2	stirring	1h	30
4	CH_2Cl_2	1:1	ultrasound	20 min	71
5	MeOH	1:1	stirring	20 min	55
6	MeOH	1:1	ultrasound	20 min	63

Deracemization reaction of racemic VAPOL using complex **79** was not as effective as the in situ generated complex (Table 3.6). When 1.1 equiv of **79** was used as the deracemization reagent, the reaction was sluggish and afforded only 70% ee after 23 hours. The addition of an inorganic base was ineffective (entry 2), but the addition of an

extra 1.2 equivalent of an organic base such as (-)-sparteine or triethylamine effectively facilitated the reaction and afforded (*S*)-VAPOL in 54-57% yield and up to 97% ee within 6 hours. The role of the excess amount of organic base is quite possibly to absorb the HCl generated during the ligand exchange.

Table 3.6 Deracemization of racemic VAPOL using pre-generated Cu-complex **79**



racemic **46** (*S*)-**46**

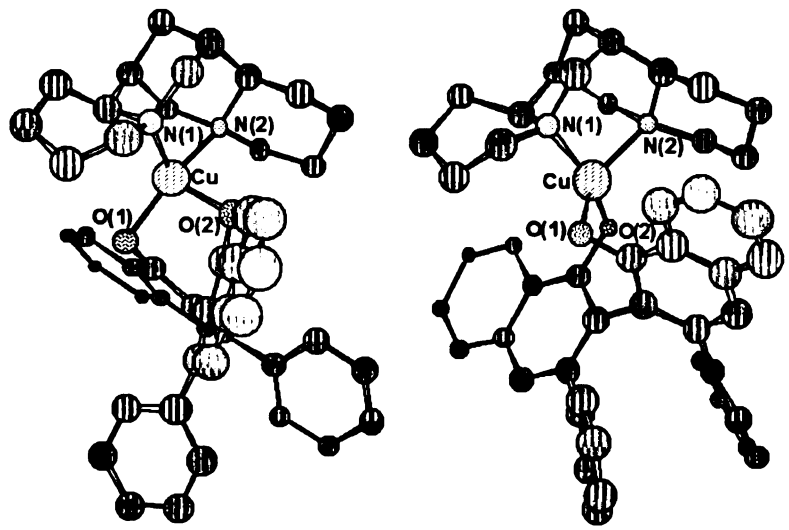
entry	equiv. of **79**	additive	time (h)	yield (%)	ee (%)
1	1.1	none	23	47	70
2	1.2	1.2 equiv. Cs_2CO_3	3.5		28
3	1.2	1.2 equiv. sparteine	6	57	97
4	1.2	1.2 equiv. Et_3N	6	54	90

The preferential formation of the (*S*)-enantiomer was observed in the deracemization of racemic BINOL, VANOL and VAPOL. To probe the origin of this selectivity we have performed calculations with the Spartan program on the copper (II) complexes of (-)-sparteine and (*R*)- and (*S*)-VANOL (Figure 3.4).[41]

As has been observed experimentally for copper (II) complexes of (-)-sparteine,[40] the geometry about copper in both the (*R*)-VANOL-Cu-(-)-sparteine and the (*S*)-VANOL-Cu-(-)-sparteine complexes is seriously distorted from the normal square planar geometry. The angle between the N-Cu-N plane and the O-Cu-O planes is 85.5°

for the R-complex and only 40.6° for the S-complex, revealing that the R-complex is much more distorted from planarity (Table 3.7).

Figure 3.4 Calculated geometry of VANOL-Cu(II)-sparteine complexes



R-VANOL-Cu(II)-sparteine S-VANOL-Cu(II)-sparteine

Table 3.7 Representative data for the (*R*)- and (*S*)-VANOL-Cu(II)-sparteine complexes[a]

Angles	(*R*)-VANOL-Cu Complex	(*S*)-VANOL-Cu Complex
N(1)-Cu-N(2)	94.1	93.8
N(1)-Cu-O(1)	112.7	89.4
O(1)-Cu-O(2)	96.7	98.4
N(2)-Cu-O(2)	92.0	93.5
N(1)-Cu-O(2)	101.8	157.8
N(2)-Cu-O(1)	149.2	139.8
Distortion dihedral angle	85.5	40.6

[a] PM3(tm) semi-empirical calculations with Spartan SGI v 5.1.3 (Wavefunction, Inc.: 18401 Von Karman Avenue, Suite 370; Irvine, CA 92612)

If the computational results are close to the structures of the actual complexes, then the difference in the dihedral angles should be induced by the steric interactions between

(-)-sparteine and the VANOL ligand. These interactions distort the geometry about the Cu(II) center and increase the energy of the complexes.

Calculation using the Spartan 5.0 program with the PM3tm model indicated that the (*S*)-VANOL-Cu-(-)-sparteine complex is more stable than the (*R*)-VANOL complex. Subsequently, the calculations were also performed with the latest Spartan 04' program at higher theoretical level (Table 3.8). Density functional calculations with BLYP/6-31G* and B3LYP/6-31G** models gave very similar results as those from the semi-empirical calculation. From the results of all the three models the heat of formation of (*S*)-VANOL complex is predicted to be approximately 4-5 kcal/mol lower than that of (*R*)-VANOL complex, which is more than enough to account for the selectivities seen ($K_{S/R} > 700$).

Table 3.8 Calculated heat of formation for the (*R*)- and (*S*)-VANOL-Cu(II)-sparteine complexes[a]

Calculation Model	(*R*)-VANOL-Cu Complex	(*S*)-VANOL-Cu Complex	ΔH_f (kcal/mol)
PM3tm	-10.867 kcal/mol	-14.781 kcal/mol	-3.91
BLYP/6-31G*	-3718.1279100 au	-3718.1303451 au	-5.29
B3LYP/6-31G**	-3719.1266659 au	-3719.1343849 au	-4.06

[a] Semi-empirical calculations with PM3(tm) model were performed with Spartan SGI v 5.1.3. Density functional calculations with BLYP/6-31G* and B3LYP/6-31G** models were performed with Spartan '04 (Wavefunction, Inc.: 18401 Von Karman Avenue, Suite 370; Irvine, CA 92612). 1 au = 627.5 kcal/mol.

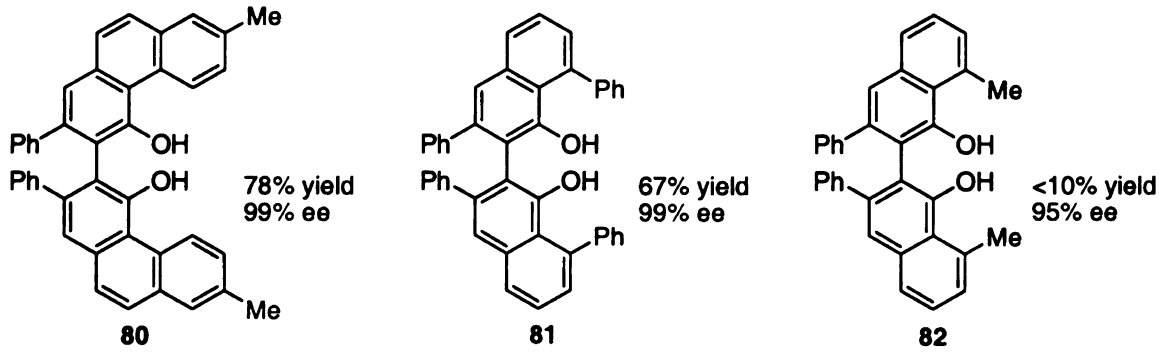
We imagine that the deracemization could involve keto forms of the naphthol and phenanthrol units. The transferring of central chirality to axial chirality has been

suggested previously for BINOL type ligands to occur via rotation about the biaryl bond that is facilitated in the keto tautomer of one of the naphthol rings.[35,38] The detailed mechanism of deracemization of biaryl compounds is still unknown, and it deserves more in-depth investigation.

3.2.4 Latest development of the in situ generated Cu(II)-(-)-sparteine mediated deracemization

After the publication of the in situ generated Cu(II) mediated deracemization of biaryl ligands described in this chapter, more recent work by other group members demonstrated that this process is equally efficient for other ligands include the VAPOL and VANOL derivatives **80** and **81** (Scheme 3.9).[42,43] The sterically more hindered VAPOL derivative **80** and the VANOL derivative **81** could be isolated in optically pure form in good yield following the standard condition. However, curiously ligand **82** suffered from rapid decomposition under the same condition.

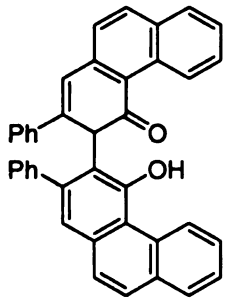
Scheme 3.9 Deracemization of other vaulted biaryl ligands



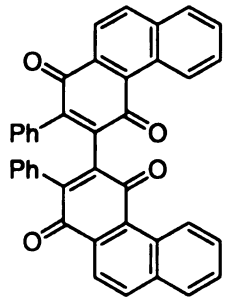
A yellow side product was observed in most of the deracemization reactions of VAPOL and VANOL.[32, 43] Depending on the conditions, this side product was isolated in variable yield, however we noticed that prolonged reaction time produced more of this side product. A tentative structure **83** was originally proposed by Dr. Yeung based on ^{1}H NMR, ^{13}C NMR and mass spectrum (Figure 3.5). Compound **83** was unstable and slowly transformed to VAPOL in $CDCl_3$. It was also found that **83** could also be converted to racemic VAPOL readily in the presence of an organic base such as Triton B.[32] It was shown that quinine **84** was not produced in the deracemization reactions of VAPOL mediated by copper(II). An authentic sample of **84** was obtained in 30-40% yield by the oxidation of VAPOL with cerric ammonium nitrate, and was shown to be non-identical with the side-product obtained from the deracemization of VAPOL.[43]

Recently, Mr. Hu successfully characterized this side product from the deracemization of VANOL by means of various NMR methods.[42b] In contrast to the original proposed structure **83**, the side product was determined to be the dimer **85** which presumably resulted from the coupling of a radical species formed in the Cu(II) oxidation of VANOL. It was also found that upon reaction with Zn/AcOH, **85** could be cleanly reduced to enantiomerically pure (*S*)-VANOL. Thus, the oxidation of VANOL (or VAPOL) by Cu(II) must have occurred after the deracemization of the ligands. The extra 0.4 equivalent of free Cu(II) complex could be responsible for this oxidation. The formation of **85** is after all not so surprising as Cu(II) species are generally strong oxidants whereas the biaryl ligands are readily oxidizable.

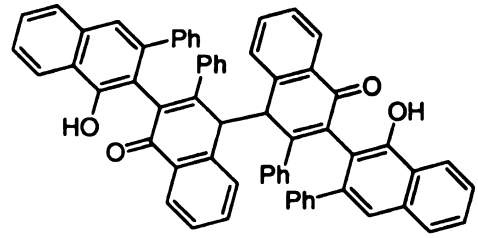
Figure 3.5 Possible structures of the deracemization side-product



83 (Tentative structure)



84

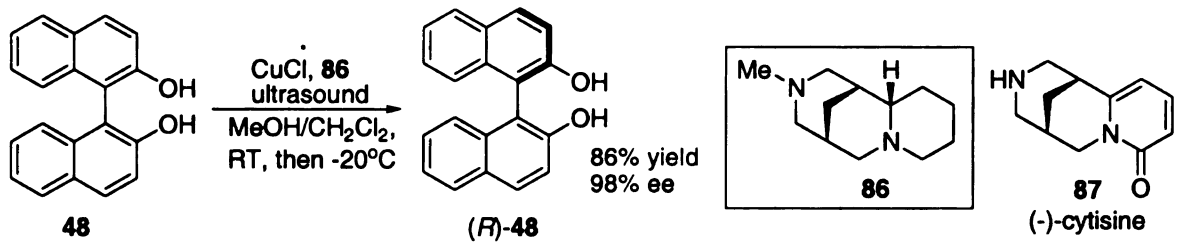


85

Subsequently, Mr. Hu further optimized the deracemization procedure.[42b] The original developed procedure involves quenching the reaction with concentrated HCl. Mr. Hu found that by using saturated sodium bicarbonate solution as quenching reagent, the isolated yield of (*S*)-VAPOL/VANOL could be increased by 10-15% on ~500 mg scale, and the dimer was observed in minimal amounts. The other advantage of the $NaHCO_3$ quench lies in that the deracemization can now be performed at much higher concentration (100 mM for VANOL) without loss of yield.

Since (+)-sparteine is not commercially available, this deracemization method is limited to the preparation of (S)-enantiomers. In 2002, O'Brien et al introduced an elegant synthesis of the readily accessible (+)-sparteine surrogate **86** from the naturally occurring alkaloid (-)-cytisine **87**.[44] This (+)-sparteine surrogate was successfully used by O'Brien in several asymmetric transformations including asymmetric lithiation and oxidative kinetic resolution. The level of enantioselectivity displayed by **86** for these reactions was comparable with that observed for (-)-sparteine. Subsequently, O'Brien reported that **86** was equally effective for the deracemization of BINOL following our in situ generated Cu(II) procedure (Scheme 3.10).[44c]

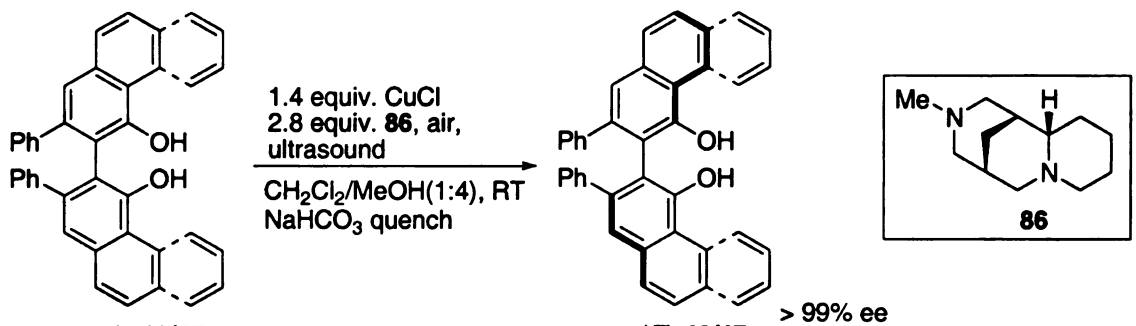
Scheme 3.10 Deracemization of racemic BINOL with (+)-sparteine surrogate **86**



48 (*R*)-**48** **86** **87** (-)-cytisine

Employing O'Brien's chiral amine **86**, Mr. Hu demonstrated that both VAPOL and VANOL could undergo efficient deracemization with Cu(II)-**86** complex with the in-situ generated Cu(II) complex described in this chapter to give optically pure (*R*)-VAPOL and (*R*)-VANOL in excellent yield on 300-500 mg scale (Scheme 3.11).

Scheme 3.11 Deracemization of racemic VAPOL and VANOL with (+)-sparteine surrogate **86**



racemic **46/47** (*R*)-**46/47** > 99% ee > 95% yield **86**

Another issue in the deracemization reaction is the use of excess (-)-sparteine. Considering the cost of sparteine in a large scale deracemization, reducing its equivalents and recovering used sparteine will make the process more attractive. It was proposed that the function of the extra 1.4 equivalent of (-)-sparteine is to absorb the HCl produced during ligand exchange. Mr. Hu found that the amount of chiral base could be reduced to 1.4 equivalent by adding 1.05 equivalent of an inorganic base such as

Na_2CO_3, which resulted in a level of enantioselectivity and yield for VAPOL and VANOL that was comparable to that observed with 2.8 equivalents of (-)-sparteine. It was also found that (-)-sparteine could be recovered in up to 80% yield during the chromatography purification of biaryl ligands.

3.3 Conclusion

The $CuCl_2 \cdot 2H_2O$-(-)-sparteine mediated deracemization of VAPOL (**46**) and VANOL (**47**) affords the (*S*)- ligands in good to excellent yield. However, this process suffers from long reaction time, low yield and selectivity, variable results and most importantly, failure on larger scale reactions. The deracemization mediated by the in situ generated Cu(II)-(-)-sparteine complex is a much more efficient method for the preparation of (*S*)-VANOL and VAPOL ligands. Optically pure ligands could be obtained in good yield on up to 5 gram scale. This method is also superior to the previous $CuCl_2$-$2H_2O$ mediated deracemization of BINOL. This procedure is particularly attractive for the rapid synthesis of enantiomerically pure biaryl ligands, as it is more efficient than the time-consuming and unpredictable resolution which often involves separation of diastereomers by crystallization.

The drawbacks of this method lie in that the reaction is limited to low concentrations, and requires the use of excess of (-)-sparteine. Also the reaction seems to be fairly sensitive to oxygen and to impurities in the starting material. Recently improvements by

other members of the research group successfully addressed some of these issues and greatly improved the efficiency of this methodology.

The origin of the stereoselectivity of this deracemization process was studied by theoretical calculations. The preferential formation of (*S*)-VANOL-Cu(II)-sparteine complex was confirmed, and the energy difference between the two complexes was enough to account for the selectivities. However, the detailed mechanism of this deracemization remains unclear. Future study in this area will be focused on the detailed mechanism of this deracemization and on the possibility of preparing VAPOL and VANOL in optically pure form via catalytic asymmetric oxidative coupling.

CHAPTER FOUR

MECHANISTIC STUDY ON THE ALKYLATION OF AZIRIDINE-2-CARBOXYLATE ESTERS

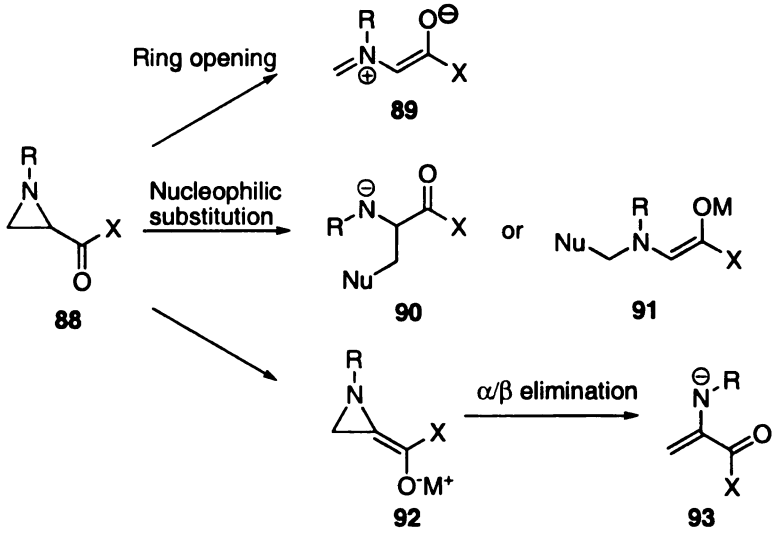
4.1 Introduction

Aziridines are very useful intermediates that possess great value in the synthesis of some important organic compounds such as unnatural amino acids. [1-4] However, until recently, almost all the chiral aziridines have been prepared from acyclic members of the chiral pool.[1,4] In a search for catalytic asymmetric methods for the synthesis of chiral aziridines that was general for *cis*-aziridines, previous members of the Wulff research group discovered a process for the catalytic asymmetric synthesis of aziridines with a chiral boron Lewis acid prepared from VAPOL and VANOL ligands.[25-26] In the presence of this catalyst system, benzhydryl imines reacted efficiently with ethyl diazoacetate to afford *cis*-aziridines with good to excellent yields and excellent enantioselectivities (90-98% ee).

α-Amino acids that bear a tetra-substituted α-carbon are commonly used synthons for the peptides, ligands and pharmaceutical compounds. The synthesis of tetra-substituted α-amino acids is of great interest and a large number of methods have been reviewed recently.[45] However, aziridines were not commonly used for the synthesis

of these amino acids and this may be partly due to the fact that the alkylation of aziridine-2-carboxylates is virtually an unknown process. Deprotonation of aziridine carboxylic acid derivatives **88** is not readily achieved. Typically, attempts to alkylate aziridine-2-carboxylate esters **88** lead to a variety of processes including thermal ring opening of the enolate, or nucleophilic attack followed by ring opening, or α-/β-elimination of the desired enolate and all of these have been documented in the literature.[46] (Scheme 4.1)

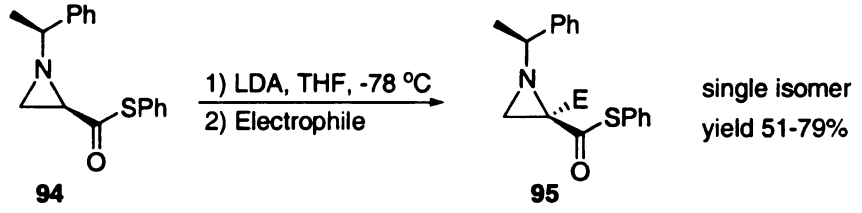
Scheme 4.1 Possible side reactions in the alkylation of aziridine-2-carboxylates



Seebah et al described that the aziridine thiol esters **94** could be deprotonated by LDA and the resulting enolate could be alkylated with several electrophiles (Scheme 4.2).[46] The alkylation of the aziridines with the chiral nitrogen substituent in **94** afforded only one stereoisomer. The biggest drawback of this process is that these aziridines were prepared in several steps from chiral acyclic starting materials and the overall yield was poor. Most curiously, while the thiol esters of the type **94** could be alkylated, if the

aziridine-2-methyl or ethyl esters were subjected to the same alkylation conditions, decomposition of the aziridines was observed.

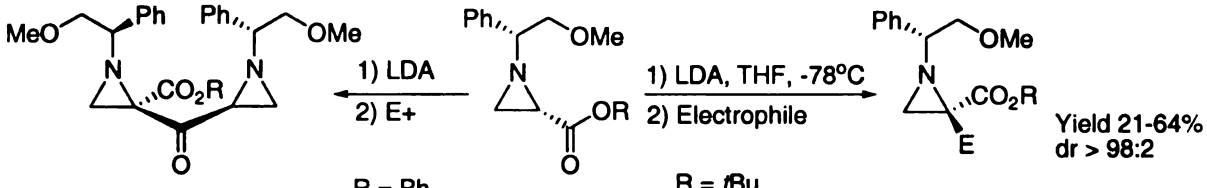
Scheme 4.2 Alkylation of aziridine-2-thiol esters



94 **95**

Aside from thioesters, the only known examples of aziridine-2-carboxylate alkylations employ a 2-methoxy-1-phenylethyl substituent on nitrogen to stabilize the metal enolate intermediate. Husson et al found that aziridine-2-*tert*-butyl esters **96** could be deprotonated and undergo alkylation, to give the corresponding aziridine **98** with good diasteroselectivity (Scheme 4.3).[47] However, the corresponding aziridine-2-phenyl ester only gave the self-condensation product **97** under the same reaction conditions. Furthermore the alkylation of (*2R*)-aziridine was only successful in a 5:1 mixture of DME/Et_2O.

Scheme 4.3 Alkylation of aziridine-2-carboxylates.

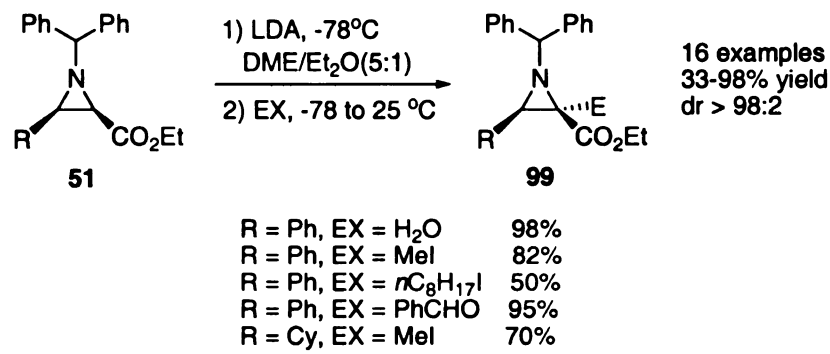


97 **96** **98**

Subsequently, Patwardhan in the Wulff research group found that the alkylations of the readily available chiral *cis*-aziridines **51** occur efficiently by treatment with 2 equivalents of LDA and subsequent reaction with electrophiles. The tri-substituted

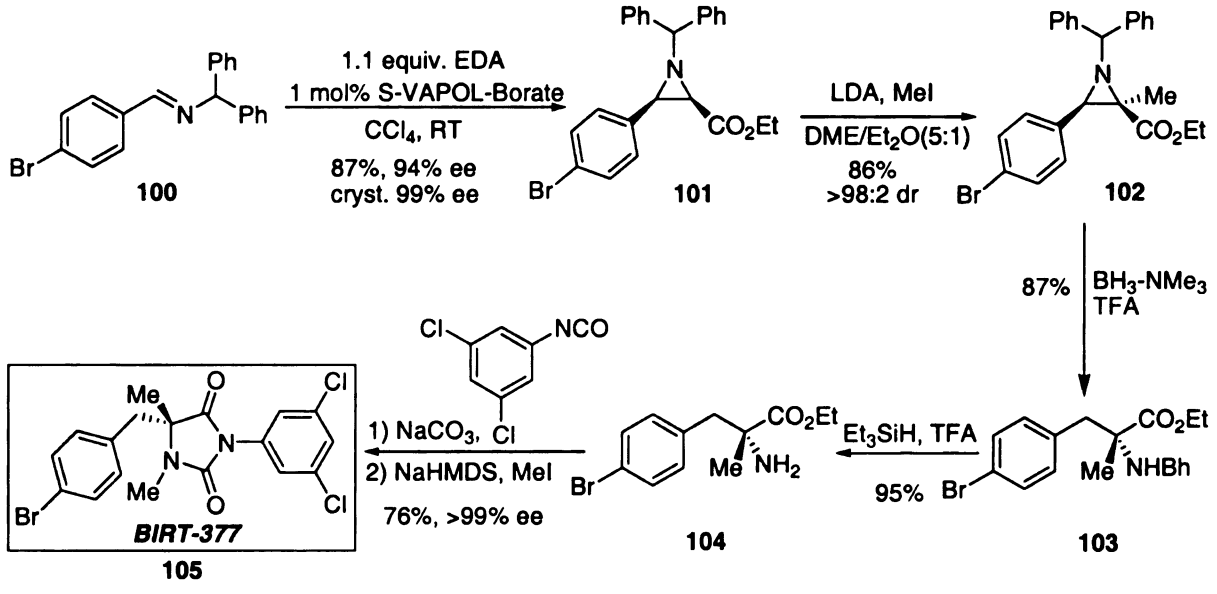
aziridines **99** were isolated in good to excellent yield with exclusive formation of single diastereomer (Scheme 4.4).[48] The reactions with activated electrophiles generally gave higher yield, primary alkyl iodides gave moderate yields, while aldehydes gave good yield but no stereoselectivity at the alcohol stereogenic center. In all cases a single C2 epimer of **99** was observed and, on the basis of the NOE experiments and by an X-ray diffraction, was assigned as that formed from retention at the 2-position. Attempts to epimerize the enolate of **51** failed. Deprotonation of ethyl-3-phenyl aziridine-2-carboxylate **51** at 78 °C and then warming to 0 °C for 2 hours before quenching with water at 78 °C led to a 98% recovery of **99** with complete retention of stereochemistry.

Scheme 4.4 Highly diastereoselective alkylation of aziridine-2-carboxylate esters.



The utility of the alkylation of aziridine-2-carboxylate esters in the synthesis of tetra-substituted α-amino acids was demonstrated by the successful enantioselective synthesis of the leukointegrin LFA-1 antagonist BIRT-377 **105** (Scheme 4.5). In the event, the chiral N-benzhydryl aziridine **101** underwent the diastereoselective alkylation under standard alkylation conditions, to give aziridine **102** as a single isomer in excellent yield. Upon reductive ring-opening and removal of benzhydryl group, **102** was converted to the α-amino ester **104**, which was subsequently converted to BIRT-377.

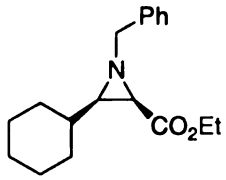
Scheme 4.5 Enantioselective synthesis of BIRT-377.



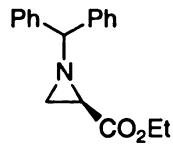
4.2 Mechanistic study of alkylation reaction of aziridines

The alkylation of aziridine-carboxylate esters developed by Patwardhan was much more efficient than the examples described by Seebach and Husson.[46,47] However, it was not clear in the cases of aziridines **51**, why side reactions of the type shown in Scheme 4.1 were never observed. The alkylations of aziridine-2-carboxylates with a benzhydryl group on the nitrogen have not been previously reported, nor have the alkylations of aziridine-2-carboxylates with a substituent at the 3- position. In order to investigate the effects of the substituents and solvent system, we decided to study the alkylation of substrates **106** and **107** in an effort to understand some mechanistic aspects of this alkylation.

Figure 4.1 Substrates for the mechanism study of alkylation reaction



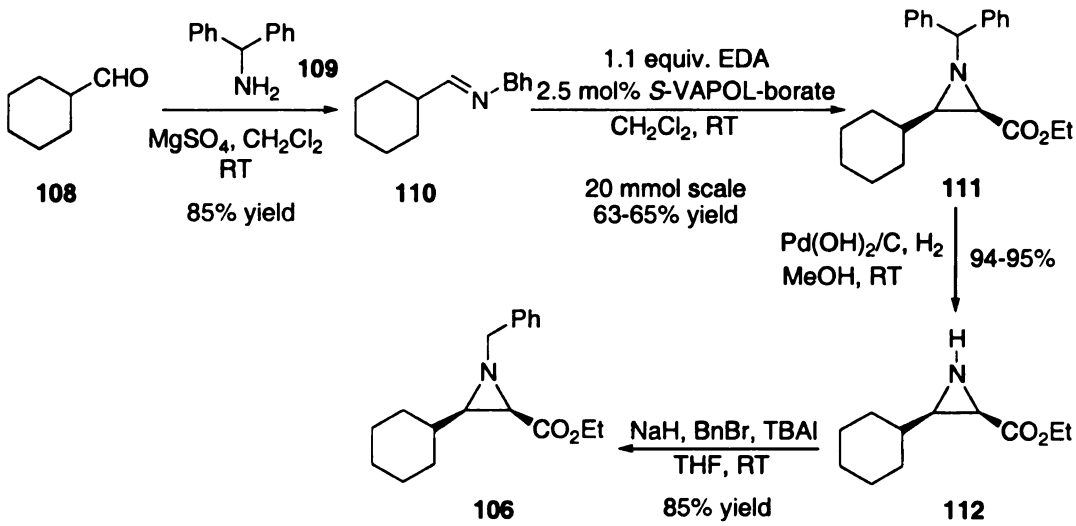
106



107

Aziridine **106** bears a smaller N-benzyl protecting group instead of the normal benzhydryl group, whereas **107** does not possess a substituent at the 3-position but contains a N-benzhydryl group. It was expected that the substituent at C-3 was more important than the nature of the N-substituent, thus it was predicted that the alkylation of **106** will be successful due to the 2,3-disubstitution and the steric bulkiness of the cyclohexyl group, on the other hand alkylation of **107** was predicted to suffer from self-condensation or decomposition.

Scheme 4.6 Synthesis of N-benzyl aziridine **106**



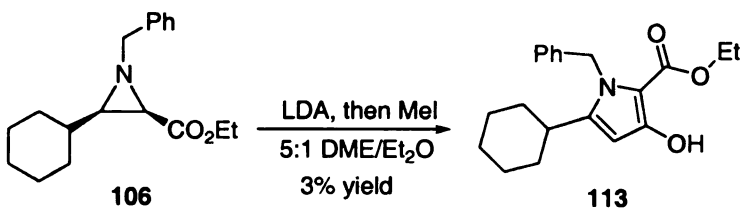
The synthesis of **106** started from imine **110,** which was prepared from commercially available starting materials. Catalytic aziridination of **110** applying 2.5 mol% VAPOL-borate catalyst afforded *cis*-aziridine **111** in 63-65% isolated yield after

chromatography and recrystallization. The optical purity of **111** was not determined. The benzhydryl group of **111** was removed by $Pd(OH)_2/C$ catalyzed hydrogenation and the deprotected N-H aziridine **112** was isolated in 94-95% yield. Aziridine **112** was subsequently treated with sodium hydride and benzyl bromide to afford desired aziridine **106** in excellent yield.

It was surprising to find that when aziridine **106** was subjected to the standard alkylation condition, neither **106** nor the desired alkylated aziridine could be detected or isolated from the crude reaction mixture. The only product that could be isolated from the reaction was a very small amount of the pyrrole-2-carboxylate **113** whose structure was confirmed by X-ray diffraction analysis (Figure 4.2). The failed alkylation of **106** clearly indicated that the benzhydryl group was vital for the successful alkylation.

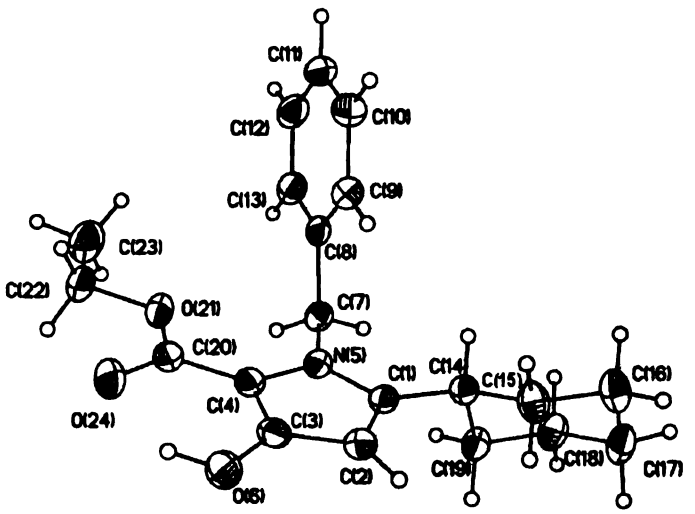
The origin of **113** remains unknown. It was suspected that a small amount of 1,1,2-trimethoxyethane in DME solvent gave an alkene upon treatment with LDA via elimination, which subsequently underwent an [3+2] cycloaddition with aziridine **106** to give the pyrrole carboxylate product. However, reactions performed in the presence of 1.2 equivalent of 1,1,2-trimethoxyethane and/or diisopropylketene acetal under the same conditions failed to yield any pyrrole-2-carboxylate products.

Scheme 4.7 Alkylation of N-benzyl aziridine **106**

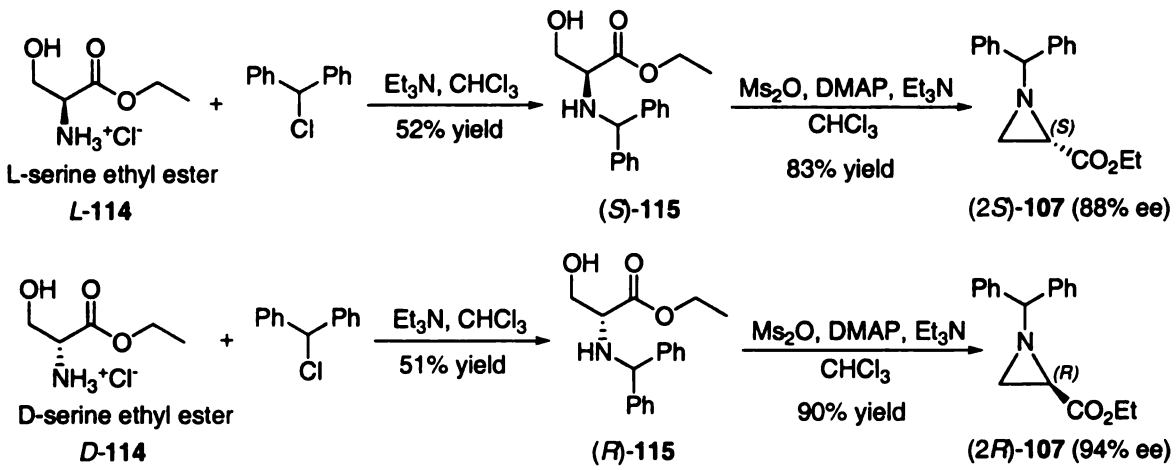


106 **113**

Figure 4.2 X-ray structure of pyrrole **113**



Scheme 4.8 Synthesis of N-benzhydryl aziridine **107**

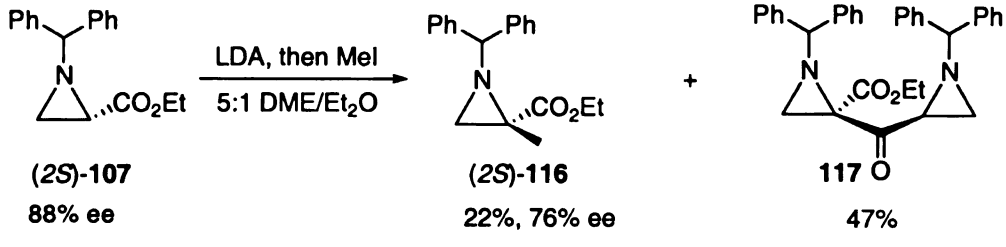


The synthesis of aziridine **107** started with the nitrogen protection of D- or L-serine ethyl ester **114**.[49] The attempted protection using excess amount of benzhydryl bromide only resulted in the undesired protection of both amino and hydroxyl groups. When a sub-stoichiometric amount of the less active benzhydryl chloride was used, the desired N-benzhydryl serine ester **115** could be isolated in 51-52% yield (Scheme 4.8). Subsequent mesylation of the free hydroxyl group followed by the in-situ intramolecular displacement of OMs with the amino group gave the desired aziridine **107** in good yield

with diminished optical purity. The synthesis started from optically pure **114**, and thus some racemization must have occurred during the protection or aziridine formation.

It was interesting to find that employing the standard alkylation procedure, the reaction of aziridine **107** gave the desired alkylated product **116**, albeit in low isolated yield (Scheme 4.9). Aziridine **116** was found to exist as 2:1 ratio of N-invertomers at room temperature. The major product **117** isolated from the alkylation was found to be the Claisen condensation product of starting material **107** with itself. Aziridine **117** was indicated by ^{1}H NMR to be mostly a single diastereomer (>20:1 dr). Interestingly, HPLC analysis indicated that the optical purity of the alkylated aziridine **116** (76% ee) was significantly lower than that of the starting material **107** (88% ee).

Scheme 4.9 Alkylation of aziridine (*2S*)-**107**



(*2S*)-**107** 88% ee

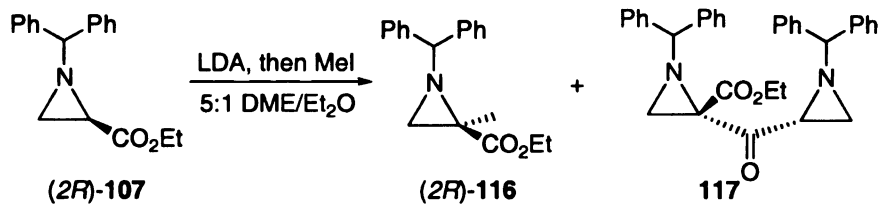
(*2S*)-**116** 22%, 76% ee

117 47%

After examining various conditions for the alkylation of **107**, we found that the loss of optical purity does not dependent on the reaction procedure (Table 4.1). The standard conditions for the alkylation shown in Scheme 4.4 involves transfer of aziridine **107** to a solution of LDA at -78 °C over 2 minutes, and then the resulting enolate solution was allowed to age for 30 minutes before reacted with methyl iodide at -78 °C (entry 1). If the enolate was allowed to age for only two minutes, the optical purity of **116** was found to be 73% ee (entry 2). On the other hand, the slow addition of **107** to LDA over 30 minutes led

to **116** with 78% ee (entry 3). In the last two entries, only a slight increase in the proportion of alkylated product **116** to the Claisen product **117** was observed.

Table 4.1 Alkylation of N-benzhydryl aziridine (*2R*)-**107**

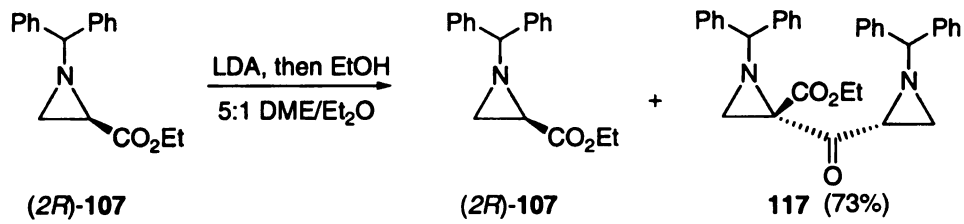


(*2R*)-**107** (94% ee) | (*2R*)-**116** | **117**

entry	addition time (min)[a]	reaction time (min)[b]	yield of **116** (%)[c]	ee of **116** (%)[d]	yield of **117** (%)[c]
1	2	30	15	81	74
2	2	2	29	73	44
3	30	30	29	78	48

[a] The time used for the addition of **107** to the LDA solution. [b] Enolate age time before the addition of MeI. [c] Isolated yield from silica gel chromatography. [d] Determined by chiral HPLC analysis on a Chiracel OD-H column.

Scheme 4.10 Deprotonation-protonation of N-benzhydryl aziridine **107**

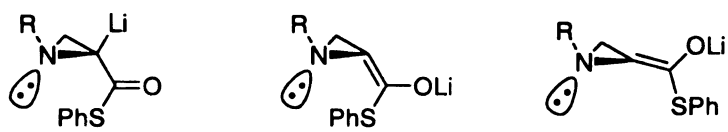


(*2R*)-**107** 94% ee | (*2R*)-**107** 14%, 47% ee | **117** (73%) 73%

Subsequently, it was found that if the enolate of aziridine (*2R*)-**107** was quenched with ethanol, the protonation of the enolate occurred with retention of absolute stereochemistry. Significant loss of optical purity was observed for **107**, which was isolated with only 47% ee (Scheme 4.10). Specific rotation measurement also showed that inversion of the C-2 stereogenic center did not occur.

The exact structure of an aziridine enolate has not been extensively studied. Seebach and coworkers previously observed that the enolates of aziridine thioesters **94** can be alkylated with retention (Scheme 4.2). They proposed that the enolates either exist as the *C*-lithiated species **118** or the *O*-lithiated species **119** with pronounced pyramidalization of the enolate carbon (Scheme 4.11). The planar species **120** would be highly unlikely to exist, as it could not explain the stereo-retention observed for the alkylation of **94**.[46b]

Scheme 4.11 Proposed structure of enolates of aziridine thioesters



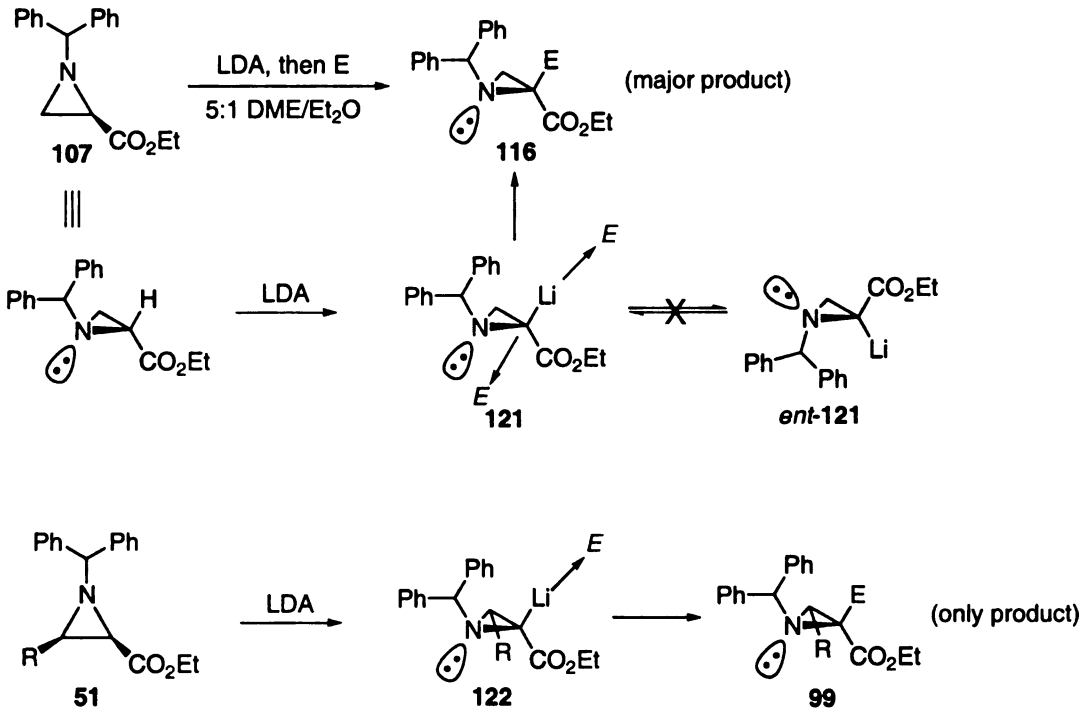
118 **119** **120**

In the case of aziridine **107**, if the structure of the enolate was planar (as it is for **120**), attack of the electrophile could in theory occur from either face to give racemic material. Electrophiles such as EtOH should preferentially attack from the opposite side of the bulky benzhydryl group on nitrogen, and thus the C-2 inversion product *ent*-**107** should be isolated as the major product. However the deprotonation-protonation experiment in Scheme 4.8 indicated that the C-2 retention product was the major product.

The observed results are interpreted as involving a configurationally stable enolate (drawn as the *C*-enolate **121** but could also be the pyramidal *O*-enolate) that does not racemize to *ent*-**121** with time but rather reacts with either retention or inversion, the proportion of which is electrophile dependant (Scheme 4.12). Thus the alkylation of **107** with smaller electrophile such as H^+ would be less selective and result in more inversion product than the bulkier electrophile MeI. This rationale would also be consistent with the

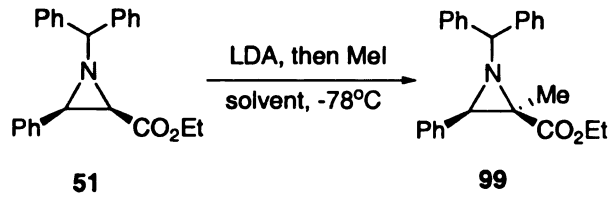
observation that all the *cis*-aziridines **51** give the alkylated product with exclusive retention of configuration. The R group in enolate **122** would be expected to strongly disfavor alkylation with inversion by approach of the electrophile from the rear side *syn*- to the R group.

Scheme 4.12 Rationale for the alkylation of N-benzhydryl aziridine-2-carboxylate esters.



The alkylation of N-benzhydryl aziridine ester **51** was performed in a 5:1 mixture of DME/Et_2O, because Husson et al demonstrated that it was a superior solvent system for their substrates.[47] However, it was subsequently found that comparable yield of **99** could be achieved in either DME (79%) or THF (85%). Surprisingly, the use of diethyl ether lead to a complicated reaction mixture with the formation of only a trace amount of the product (Scheme 4.13).

Scheme 4.13 Study of solvent effect



51 99

solvent	% yield of **99**
5:1 DME/Et_2O	82
DME	79
THF	85
Et_2O	trace

Finally the effect of the number of equivalents of LDA was studied. The procedure developed by Patwardhan involves use of 2 equivalents of LDA. The attempts to reduce the amount of LDA were not successful. The use of 1.1 equivalent of LDA lead to capricious results, and the product **99** was isolated in only 20-48% yield.

4.3 Conclusion

The fact that N-benzhydryl aziridine-2-carboxylates can be readily alkylated at 2-position with excellent diastereoselectivity greatly enhances the synthetic utility of asymmetric aziridination reaction. To understand the mechanistic aspects of the alkylation reaction, two substrates bearing different substituents were synthesized and their alkylation reactions were studied.

The bulky N-benzhydryl group on the nitrogen was found to have the most significant impact on the success of the alkylation, as the smaller N-benzyl group resulted in complete destruction of the aziridine. These studies also demonstrated that the substituent at the C3 position on the aziridine is also responsible for the complete retention of the stereochemistry and the suppression of side reactions, whereas the solvent effect is less profound.

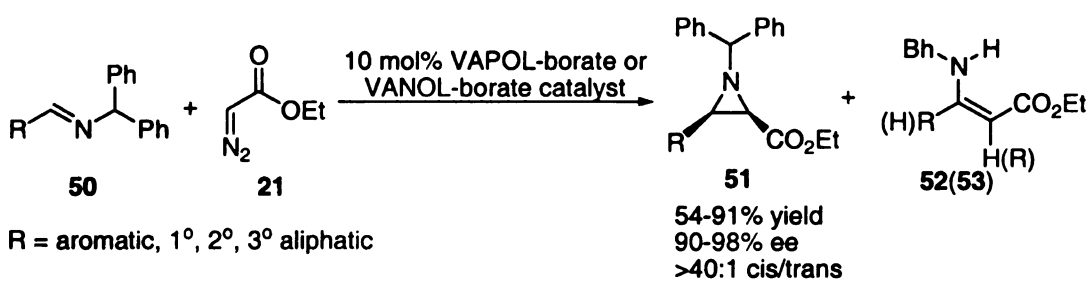
CHAPTER FIVE

REINVESTIGATION OF VAPOL OR VANOL-BORATE CATALYZED ASYMMETRIC AZIRIDINATION

5.1 Introduction

Aziridines are very useful intermediates that possess great value in the synthesis of some important organic compounds such as unnatural amino acids.[1] In a search for catalytic asymmetric methods for the synthesis of chiral aziridines that are general for *cis*-aziridines, Wulff's group recently discovered the VAPOL or VANOL-boron Lewis acid catalyzed aziridination reaction (Scheme 5.1).[25,26] In the presence of 10 mol% catalyst generated from 10 mol% of VAPOL or 10 mol% VANOL and 30 mol% of triphenyl borate, benzhydryl imines **50** reacted efficiently with ethyl diazoacetate **21** to afford *cis*-aziridines **51** with good to excellent yields (50-91%) and excellent enantioselectivities (90-98% ee) along with only very small amounts of enamine byproducts **52** and **53**.

Scheme 5.1 Catalytic asymmetric aziridination



50 **21** **51** **52(53)**

R = aromatic, 1°, 2°, 3° aliphatic

54-91% yield
90-98% ee
>40:1 cis/trans

Subsequently, Dr. Reddy in Wulff's group discovered that the level of chiral induction was not reduced even when the catalyst loading was decreased ten folds in the reaction of benzaldehyde derived imine **50** (R = Ph).[50] This reaction went to complete conversion within 24 hours in the presence of 1 mol% VAPOL-borate catalyst. Both the yields and enantioselectivities were comparable with the previously reported results using 10 mol% catalyst. Thus it was desirable to determine if the aziridination of other imine substrates could be performed using 1 mol% catalyst. This study would not only improve the efficiency of the VAPOL or VANOL-borate catalyst system, but also help to gather further understanding of the scope and limitation of this catalytic asymmetric aziridination.

5.2 Catalytic asymmetric aziridination using VAPOL or VANOL-borate catalyst

5.2.1 Study of achiral Lewis acid catalysts in racemic aziridination

In the exploration of the asymmetric aziridination reaction with a variety of imine substrates, it is necessary in each case to prepare the racemic aziridines and determine the HPLC retention time of each enantiomer. The reported achiral Lewis acids for the aziridination reaction between imine and ethyl diazoacetate include BF_3, $AlCl_3$, $TiCl_3$,[19] $Zn(OTf)_2$,[20] $Yb(OTf)_3$,[20, 23ak] $CuClO_4$,[21] $SnCl_4$,[15g], $InCl_3$,[23aa] and various metal complexes.[23] However, almost all of these Lewis acids either give low cis/trans ratios of the desired aziridines, or produce large amounts of the enamine side-products.

The most successful result was reported by Kobayashi et al, who described that $Yb(OTf)_3$ was an efficient catalyst for the aziridination of N-benzhydryl imines.[23ak] The

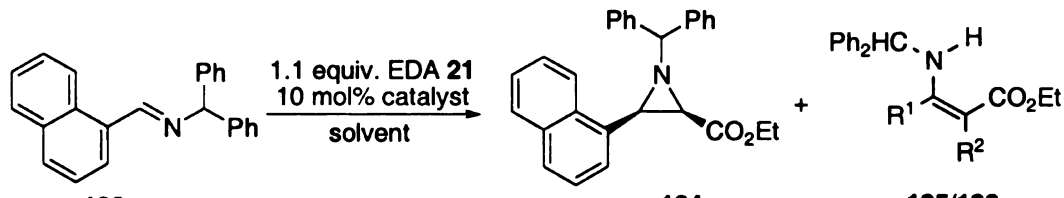
aziridination between imine **123** and EDA with hexane as solvent in the presence of 10 mol% of $Yb(OTf)_3$ was reported to furnish the aziridine **124** in 82% yield with 94:6 cis/trans ratio, and no enamine side products were observed.

The condition that Wulff's group developed employs the catalyst generated from racemic VAPOL or VANOL and triphenyl borate. This catalyst generally affords racemic aziridines in good to excellent yield and produces minimal amounts of undesired side-products.

The reactions of three different achiral or racemic Lewis acid catalysts, namely $Yb(OTf)_3$, BF_3-OEt_2, $B(OPh)_3$ and the VAPOL-Borate were examined with imine **123** in various solvents, and the results are shown in Table 4.1. BF_3-OEt_2 only afforded complete conversion with CH_2Cl_2 as solvent to give **124** in low isolated yield (entry 2). $Yb(OTf)_3$ resulted in complete conversion of **123** in both CH_2Cl_2 and CCl_4, however large amounts of enamine products were observed in both solvents (entry 4,5). Surprisingly, following Kobayashi's published procedure,[23ak] the reaction in hexane only afforded 70% conversion and 37% yield of **124** (entry 6). This inferior result is not totally unexpected, as the imine, catalyst and product aziridine were almost completely insoluble in hexane. Increasing the amount of solvent only resulted in lower conversion. Finally, the catalyst generated from racemic VAPOL and triphenyl borate very cleanly furnished aziridine **124** in 88% yield and with the highest cis/trans ratio, the reaction produced a minimum amount of enamine products, and thus proved to be the most efficient catalyst for the generation of racemic aziridines (entry 8). Interesting, triphenyl borate itself was not an

efficient catalyst. The aziridinations employing only triphenyl borate were much slower, and gave significant amounts of enamine products (entry 9).

Table 5.1 Preparation of racemic aziridine **124** using achiral or racemic Lewis acids



123 **124** **125/126**

125: R^1 = H, R^2 = 1-naphthyl
126: R^1 = 1-naphthyl, R^2 = H

entry	Lewis acid	solvent	concn (M)	convn. (%)[a]	yield of **124**(%)[b]	*cis/trans*-**124**[a]	**124**:**125**:**126**[a]
1	BF_3-OEt_2	hexane	0.1	60	--	17:1	1:--[c]:0.17
2	BF_3-OEt_2	CH_2Cl_2	0.5	100	43	25:1	1:0.35:0.02
3	BF_3-OEt_2	CCl_4	0.5	74	--	16:1	1:0.18:0.07
4	$Yb(OTf)_3$	CH_2Cl_2	0.5	100	--	25:1	1:0.30:0.05
5	$Yb(OTf)_3$	CCl_4	0.5	100	--	20:1	1:0.17:0.06
6	$Yb(OTf)_3$	hexane	0.5	70	37	10:1	1:--[c]:0.04
7	$Yb(OTf)_3$	hexane	0.1	58	--	10:1	1:--[c]:0.17
8	*rac*-VAPOL-B	CH_2Cl_2	0.5	100	88	33:1	1:0.03:0.01
9	$B(OPh)_3$	CH_2Cl_2	0.5	70	--	30:1	1:0.17:0.21

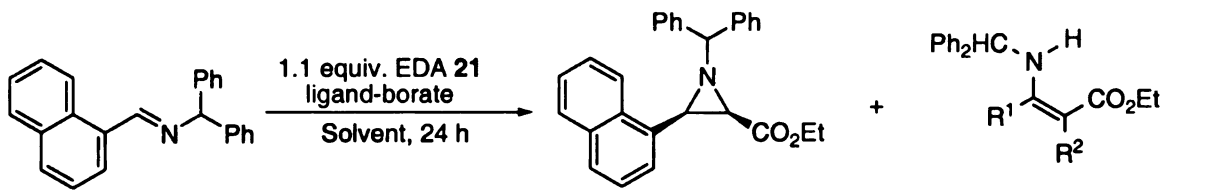
[a] The conversion of **123**, the cis/trans ratio of **124** and the ratio of product and enamines were determined by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield from chromatography. [c] The signal was obscured by unknown peaks and not determined.

5.2.2 Catalytic asymmetric aziridination under low catalyst loading

The catalytic asymmetric aziridination under low catalyst loading began with the reaction of N-benzhydryl 1-naphthylaldimine **123** (Table 5.2). The previously reported

condition involves the reaction of 0.5 M of imine substrates in the presence of 10 mol% catalyst in CH_2Cl_2.[25b] Employing slightly different conditions, the aziridination of **123** was carried out in the presence of 1 mol% catalyst with 1.0 M of imine **123** in CH_2Cl_2 to give 88% ee and 90% ee with the catalysts generated from VAPOL and VANOL (entry 1-2). Reaction at lower concentration of imine **123** (0.5 M) only led to incomplete conversion and lower selectivity.

Table 5.2 Aziridination of 1-naphthyl aldimine **123**



123 → **124** (cis/tran > 30:1) + **125/126**

125: R^1 = H, R^2 = 1-naphthyl
126: R^1 = 1-naphthyl, R^2 = H

entry	catalyst (mol%)	ligand	temp. (°C)	solvent	yield of **124**(%)[a]	ee of **124**(%)[b]	yield of **125/126**(%)[c]
1	1	VAPOL	25	CH_2Cl_2	86	88	<1/<1
2	1	VANOL	25	CH_2Cl_2	85	90	<1/<1
3	1	VANOL	0	CH_2Cl_2	88	93	<1/2
4	1	VAPOL	25	toluene	90	95	<1/<1
5	1	VANOL	0	toluene	93	93	<1/<1
6	10	VAPOL	25	CH_2Cl_2	87	93	3/5
7	10	VANOL	25	CH_2Cl_2	85	88	<1/4

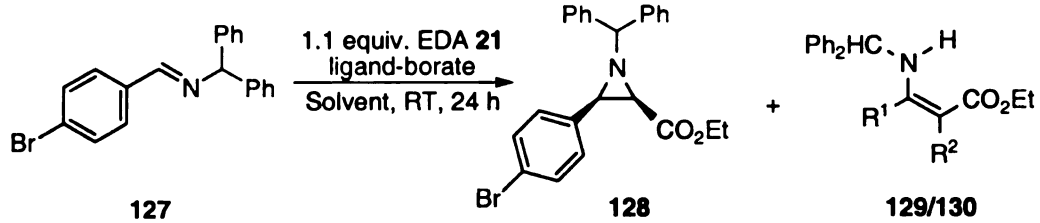
[a] Isolated yield from silica gel chromatography. [b] Determined by chiral HPLC. [c] The cis/trans ratio of **124** and the yield of enamines were determined by ^{1}H NMR of the crude reaction mixture.

The effects of solvent and temperature on the aziridination of **123** were also studied. Reactions at low temperature (0 °C) generally gave higher selectivity (93% ee) when

VANOL was used (entry 3), however the VAPOL catalyst only gave incomplete conversion under the same condition. A significant solvent effect was observed with the VAPOL catalyst (entry 4), as the reaction in toluene increased the chiral induction to 95% ee. Curiously, while reactions in the presence of higher catalyst loading (10 mol%) afforded higher ee with VAPOL (entry 6 vs. entry 1), no such increase in selectivity was observed with the VANOL ligand (entry 7 vs. entry 2).

Surprisingly, the reaction of *para*-bromobenzaldimine **127** with ethyl diazoacetate in dichloromethane afforded much lower selectivity with 1 mol% catalyst (78% ee and 88% ee, Table 5.3, entry 1 and 2) than previously reported with 10 mol% catalyst (98% ee with either VAPOL or VANOL-borate catalyst).[25b] Toluene as solvent significantly improved the enantioselectivity of the VAPOL catalyst at 1 mol% catalyst loading (88% ee, entry 3). Reactions at temperatures below room temperature only lead to incomplete conversion. Higher catalyst loadings (entry 5-10) and decreased concentrations resulted in only a slightly increase in selectivity. Surprisingly, even in toluene the observed chiral inductions were significantly lower than the previously reported value (98% ee).[25b]

Table 5.3 Aziridination of *p*-bromobenzaldimine **127**



127 **128** **129/130**

cis/trans = 20-50:1

129: R^1 = H, R^2 = p-BrC_6H_4
130: R^1 = p-BrC_6H_4, R^2 = H

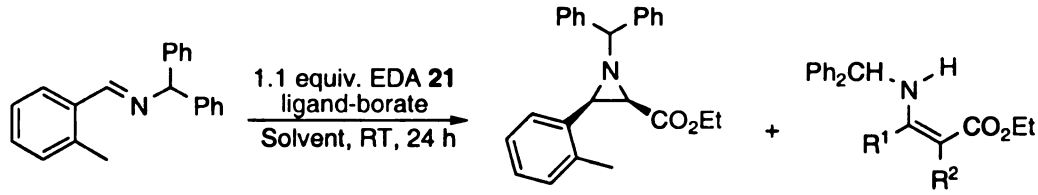
entry	catalyst (mol%)	ligand	solvent	concn (M)[a]	yield of **128**(%)[b]	ee of **128**(%)[c]	yield of **129/130**(%)[d]
1	1	VAPOL	CH_2Cl_2	1	82	78	4/2
2	1	VANOL	CH_2Cl_2	1	84	88	4/6
3	1	VAPOL	toluene	1	83	88	1/1
4	1	VANOL	toluene	1	90	90	4/4
5	2.5	VAPOL	toluene	1	85	90	2/1
7	2.5	VAPOL	toluene	0.5	84	91	<1/<1
8	2.5	VANOL	toluene	0.5	91	90	<1/2
9	5	VAPOL	toluene	0.5	84	91	5/3
10	5	VANOL	toluene	0.5	88	90	<1/<1

[a] Concentration of imine in solvent. [b] Isolated yield from chromatography. [c] Determined by chiral HPLC. [d] The cis/trans ratio of **128** and the yield of enamines were determined by ^{1}H NMR of the crude reaction mixture.

Aziridination of o-tolylbenzaldimine **131** with reduced catalyst loading gave results similar to those for imines **123** and **127** (Table 5.4). Toluene was again a better solvent for the reaction (entry 3 and 4). The asymmetric induction observed for the aziridination of **131** was not sensitive to the catalyst loading, as increasing the amount of catalyst from 1 mol% to 10 mol% afforded nearly identical enantioselectivity. Most unexpectedly, an attempt to perform the reaction of **131** with 10 mol% VAPOL or VANOL-borate catalyst in

toluene (entry 7 and 8) gave the aziridine **132** with chiral inductions (90% ee and 84% ee with VAPOL and VANOL as ligand) that were significantly lower than the previously reported for the reactions which were performed in CH_2Cl_2 (94% ee and 91% ee).

Table 5.4 Aziridination of o-tolylbenzaldimine **131**



131 | **132** cis/tran > 20:1 | **133/134** **133**: R^1 = H, R^2 = o-tolyl **134**: R^1 = o-tolyl, R^2 = H

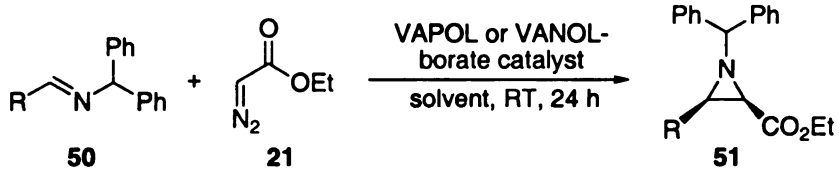
entry	catalyst (mol%)	ligand	concn (M)[a]	solvent	yield of **132**(%)[b]	ee of **132**(%)[c]	yield of **133/134**(%)[d]
1	1	VAPOL	1	CH_2Cl_2	65	81	4/1
2	1	VANOL	1	CH_2Cl_2	64	83	4/10
3	1	VAPOL	1	toluene	60	88	8/4
4	1	VANOL	1	toluene	70	83	2/8
5	2.5	VAPOL	1	toluene	71	89	3/1
6	2.5	VANOL	1	toluene	74	85	2/9
7	10	VAPOL	0.5	toluene	69	90	3/2
8	10	VANOL	0.5	toluene	76	84	1/10

[a] Concentration of imine in corresponding solvent. [b] Isolated yield from silica gel chromatography. [c] Determined by chiral HPLC. [d] The cis/trans ratio of **132** and the yield of enamines were determined by ^{1}H NMR of the crude reaction mixture.

Subsequently, the asymmetric aziridination reactions with several other substrates were conducted under various catalyst loadings in CH_2Cl_2 and the results are presented in Table 5.5. It was most disappointing to find that although the isolated yields were always comparable or higher than the reported yields, for all the substrates shown in

Table 5.5, the chiral inductions were 5-10% lower than those in the report appearing from the Wulff group in 2000 under the exact same conditions.[25b]

Table 5.5 Summary of catalytic asymmetric aziridinations.



50 **21** **51**

entry[a]	R	ligand	catalyst (mol %)	solvent	ee of *cis*-**51**(%)[b]	ee (%) (reported)[c]
1	Ph	VAPOL	10	CH_2Cl_2	88	95[d]
2		VANOL	10	CH_2Cl_2	88	96
3	1-naphthyl	VAPOL	10	CH_2Cl_2	93	92[e]
4		VANOL	10	CH_2Cl_2	88	N/A
5	*p*-BrC_6H_4	VAPOL	5	toluene	91	98[f]
6		VANOL	5	toluene	90	98
7	*o*-tolyl	VAPOL	10	toluene	90	94
8		VANOL	10	toluene	84	91
9	3,4-$(OAc)_2$ -C_6H_3	VAPOL	1	CH_2Cl_2	90	96
10		VANOL	1	CH_2Cl_2	93	97
11	2-furyl	VAPOL	1	toluene	84	N/A
12		VANOL	10	toluene	N/A	93

[a] Unless otherwise specified, the aziridination was conducted under same conditions as reported in reference 25b. [b] This work. [c] Unless otherwise specified, the reported aziridinations (reference 25b) were conducted in CH_2Cl_2 with 10 mol% catalyst and 0.5 M in imine. [d] Reactions with 2 mol% catalyst (entry 1) or 2.5 mol% catalyst (entry 9) and 1.0 M in imine. [e] The reported ee% was not accurate due to the identification of the wrong minor isomer in the chiral HPLC analysis. [f] Reaction in 1:1 toluene/dichloromethane.

By the time this serious problem was discovered, no definitive explanation was available for the observed difference in chiral inductions with the previously reported data. Prior to 2003, the reaction of entry 1 has been repeated numerous times by several group members and constantly gave 95±2 % ee with the VAPOL-borate catalyst. It could only be assumed that during the 3-4 years since our aziridination process was published, presumably the qualities of one or several reagents have changed. However it was not certain when these changes occurred. Subsequently, a series of experiments were conducted to determine what changes had occurred that resulted in these conflicting results.

5.2.3 Optimization of catalytic asymmetric aziridination reactions

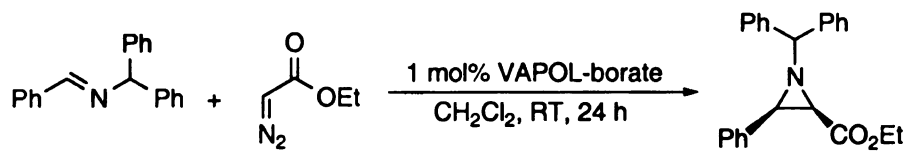
Considering all the reagents involved, possible reasons for low enantioselectivity would include: 1) the purity of imine; 2) the purity of the commercially available triphenyl borate; 3) the purity of the commercially available ethyl diazoacetate; 4) the optical/chemical purity of the ligands. 5) The experimental techniques, including introduction or exclusion of water/air from the reaction system.

In order to determine the real cause for the low asymmetric induction, studies were undertaken to explore the aziridination of benzaldehyde derived imine **135** in CH_2Cl_2 with 1 mol% catalyst prepared from VAPOL and triphenyl borate.

According to the procedure developed by Antilla, the preparation of VANOL or VAPOL-borate catalyst involves heating of one equivalent of the ligand and three

equivalent of triphenyl borate at 55°C for 1 hour, followed by removal of volatile material under reduced pressure at this temperature (Scheme 1.21).[25b] The residue was heated under high vacuum (~0.2 mm Hg) at 55°C for 30 minutes before being dissolved in an appropriate solvent and transferred to the imine. This procedure was employed to the study of aziridination shown in Table 5.6 and Table 5.7.

Table 5.6 Experimental parameters for the aziridination of imine **135** using 1 mol% VAPOL catalyst.



135 **21** **136**

entry[a]	condition	yield of **136**(%)[b]	ee of **136**(%)[c]
1	$B(OPh)_3$ purchased from TCI	76	86
2	Freshly prepared $B(OPh)_3$, imine crystallized three times	82	86
3	Freshly prepared $B(OPh)_3$, distilled EDA	83	88
4	Old bottle of EDA from Aldrich	83	88
6	Distilled EDA, freshly prepared $B(OPh)_3$	83	88
7	Old bottle of EDA from Aldrich, freshly prepared $B(OPh)_3$	84	87
8	Freshly prepared $B(OPh)_3$, distilled EDA, freshly distilled CH_2Cl_2	83	87
10	Reaction performed in Schlenk flask	82	86
11	Result from reference 25b with 2 mol% VAPOL-borate catalyst	77	95

[a] Unless otherwise specified, EDA and $B(OPh)_3$ were purchased from Aldrich. [b] Isolated yield from silica gel chromatography. [b] Determined by chiral HPLC on a Chiralcel OD-H column.

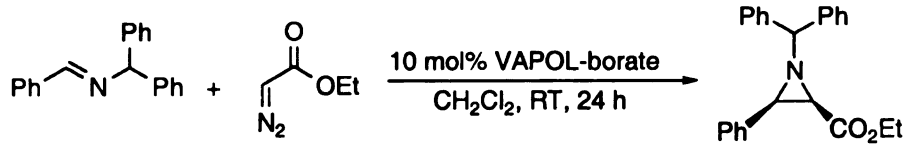
As indicated by the results in Table 5.6, several experimental parameters were examined including various samples of triphenyl borate, EDA and imine. Several different

bottles (batches) of triphenyl borate purchased from different companies were tested as well as a freshly prepared sample from boric acid and phenol was used.[51a] Ethyl diazoacetate was either used as purchased from Aldrich or purified by distillation or silica gel chromatography. Imine **135** was prepared from freshly purified benzhydryl amine and benzaldehyde and was crystallized multiple times to ensure its purity. However, under all these parameters, the induction obtained always fell in the range of 86-88% ee, which is significantly lower than the reported value (95% ee with 2 mol% VAPOL-borate, entry 11).[25b] The isolated yields were generally higher than the reported value (77%).

Subsequently, it was decided that the aziridination with 10 mol% catalyst would be easier to perform and thus allow faster screening of all the variable. Some selected results are shown in Table 5.7.

Variations in the source and purities of all the reagents and solvents used were examined extensively. These variations include using both old and purified samples of VAPOL, triphenyl borate, ethyl diazoacetate and imine. The ethyl diazoacetate was also prepared and purified according to two different procedures.[51b,c] Changes in the operational techniques include stringent removal of water and air from the reaction system or introduction of small amounts of water and/or air to the reaction by not drying the reaction flasks or solvents.

Table 5.7 Selected conditions of aziridination of imine **135** using VAPOL-borate catalyst.



135 **21** **136**

entry[a]	condition	yield of **136**(%)[b]	ee of **136**(%)[c]
1	2 mol% catalyst, prepared $B(OPh)_3$, imine crystallized three times	85	88
2	prepared $B(OPh)_3$, imine crystallized three times	76	89
3	freshly distilled EDA	79	87
4	5 mol% catalyst, distilled EDA, reaction under nitrogen	77	88
5	freshly distilled EDA, reaction in Schlenk flask	78	86
6	imine prepared from purified amine	80	88
7	catalyst from purified VAPOL	78	88
8	catalyst from purified VAPOL, different batch of EDA	78	88
9	different batch of VAPOL & EDA	82	88
10	different batch of VAPOL, EDA & $B(OPh)_3$	77	89
11	Re-purified VAPOL, $B(OPh)_3$ from TCI, distilled EDA	77	89
12	Re-purified VAPOL, $B(OPh)_3$ from TCI, glass syringe	80	89
13	different batch of VAPOL, EDA & $B(OPh)_3$, glass syringe	78	86
14	different batch of VAPOL, EDA, imine and $B(OPh)_3$, glass syringe	78	86
15	flasks not flame-dried, glass syringe cooled in air	74	87
16	new bottle of EDA from Aldrich	81	88
17	flasks not flame-dried, new EDA, reaction run sealed under air	78	89
18	flasks not flame-dried, new EDA, reaction run under argon	75	89
19	flasks not flame-dried, new EDA, non-distilled CH_2Cl_2 used	77	89
20	EDA freshly prepared from ethyl glyoxylate[d]	--	86
21	EDA freshly prepared from ethyl glycine[51b]	78	88
22	Result from reference 25b with 10 mol% VAPOL-borate	81	95

[a] Unless otherwise specified, $B(OPh)_3$ and EDA were purchased from Aldrich. [b] Isolated yield from silica gel chromatography. [c] Determined by chiral HPLC. [d] See experimental for details.

All the conceivable variables were tested by making one or a combination of changes. The aziridination of imine **135** was performed under more than 40 different conditions and some of these are shown in Table 5.7. However, despite the exhaustive exploration of the various conditions, all these reactions consistently afforded aziridine **136** with 86-89% ee, far below the reported value of 95% ee.[25b]

The most useful information obtained from these reactions is that the asymmetric catalytic aziridination was not as sensitive as originally suspected. The purity of all the tested reagents has no obvious effect on the enantioselectivity. On the other hand, it is still possible that detrimental effects of air/impurity will be more obvious at lower catalyst loading.

After all these unsuccessful attempts, by the end of 2003 the conclusion was made that the reported data are no longer reproducible and this issue was not further pursued. Up until the time of writing this thesis, the source of this discrepancy remains a mystery.

5.2.4 Study of solvent effect of aziridination reaction

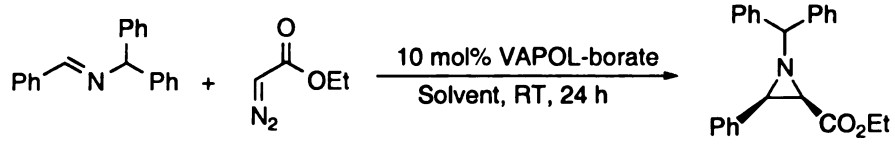
During the development of VAPOL and VANOL borate mediated catalytic asymmetric aziridination, the effect of solvent was never studied systematically. The reported conditions generally employed CH_2Cl_2 or in several cases, toluene as solvent.[25b] It is thus possible that the aziridination may be further improved by applying the optimal solvent.

In chapter six, a model will be presented for the catalytic asymmetric aziridination

reaction using VAPOL-borate or VANOL-borate catalysts, two edge-face arene-arene interactions are thought to be involved that occur between the benzhydryl group and ligand arene system (Figure 6.2). These interactions were used to account for the origin of the enantioselectivity of VAPOL and VANOL-borate catalyzed aziridination and they will be discussed in detail in chapter six. Solvent dependency of these CH-π arene-arene interactions are well-documented in literature.[52] The effect of solvent on these interactions could play an important role in catalytic asymmetric reactions.[53] In one case, by simply switching the solvent from CH_3CN to CH_2Cl_2, the enantioselectivity of an asymmetric allylation was increased by 12%. The authors attributed this enhancement of selectivity to a more favored arene-arene interactions.[53a]

Hunters has published studies that indicate the solvophobic arene-arene interactions are strongest in polar solvents (such as CD_3OD) which are unable to properly solvate the nonpolar surfaces of the aromatic rings.[52d] Hunter found that as the solvent polarity decreases, the strength of the aromatic interaction goes through a minimum with DMSO and then starts to increase again. In chloroform, the magnitude of the interaction is comparable to that in D_2O. Solvents less polar than chloroform were not studied, however, it is possible that the arene-arene interactions can be maximized by using the even less polar solvent such as CS_2 or CCl_4. If the proposed interactions in Wulff's catalytic system do exist, then an increase in the enantioselectivity may be observed due to the better complexation between catalyst and substrates in an optimal non-polar solvent.

Table 5.8 Study of solvent effect of catalytic asymmetric aziridination.



135 21 136

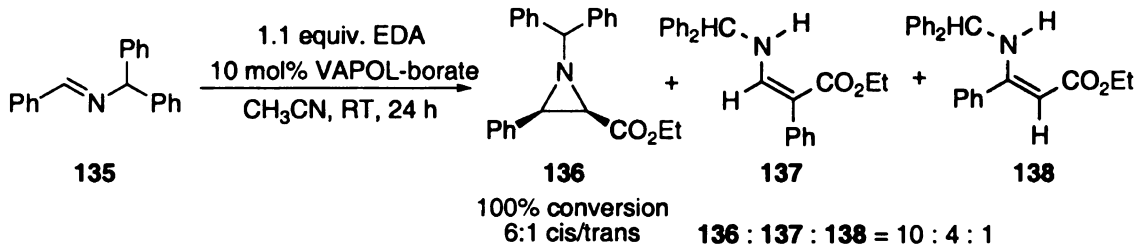
entry[a]	solvent	yield of **136** (%)[b]	ee of **136** (%)[c]
1	CH_2Cl_2	83	86-89
2	α,α,α-trifluorotoluene	82	89.5
3	$CHCl_3$	81	90
4	$CH_3C_6H_5$	83	91
5	CS_2	73	91
6	C_6H_6	83	92
7	CCl_4	84	93

[a] The standard procedure was used for the catalyst preparation and aziridination. [b] Isolated yield from silica gel chromatography. [c] Determined by chiral HPLC on a Chiralcel OD-H column.

Subsequently, different solvents were examined for the aziridination of **135** (Table 5.8). All the reactions were conducted according to the standard procedure which involves the transfer of the prepared catalyst solution in an appropriate solvent to the flask containing the imine. Upon mixing, the colorless solution turned yellow or light orange, indicating a π-acceptor/donor interaction.[54] After the syringe addition of EDA, bubbling was observed in most of the solvents. Depending on the solvent system, the bubbling would stop after 2-4 hours and the color of the original orange solution would turn to a pale yellow or colorless, indicating the complete consumption of the starting materials. However, the reaction time was not optimized and for the convenience the workup was generally done after 16-24 hours.

It was found that all the nonpolar solvents examined gave higher chiral induction than CH_2Cl_2 (Table 5.8). The reactions performed in chloroform, toluene and benzene afforded higher than 90% ee (entry 3,4,6). The reaction in CCl_4 gave the best result with regard to yield and chiral induction (entry 7). After the addition of EDA to the mixture of catalyst and imine in this solvent, vigorous bubbling was observed. Based on the color change of the solution and the rate at which bubbles were formed, the reaction in CCl_4 was complete within approximate two hours, and aziridine **136** was isolated with 93% ee and in very good yield (84%).

Scheme 5.2 Catalytic asymmetric ziridination of imine **135** in acetonitrile



135 **136** **137** **138**

100% conversion
6:1 cis/trans

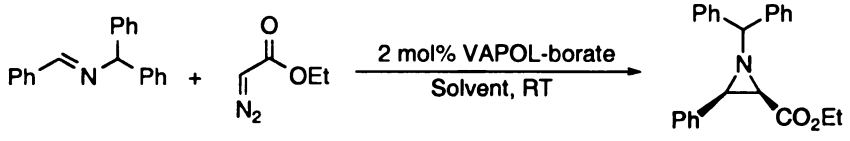
136 : **137** : **138** = 10 : 4 : 1

It is worthwhile to note that the aziridination performed in the polar solvent CH_3CN was also fast. Vigorous bubbling was observed immediately after the addition of ethyl diazoacetate. The ^1H NMR spectrum of the crude product indicated a much lower cis-selectivity (cis:trans = 6:1) and substantially increased amounts of the enamine products (~30% by crude ^1H NMR). The observed inferior selectivity was presumably due to the following reasons: 1) the addition of ethyl diazoacetate occurred via a less-defined transition state involving the catalyst-substrate complex in this polar solvent, which resulted in a lower cis/trans selectivity; 2) the stabilization of the proposed zwitterion **40** (Scheme 1.19) intermediate by the polar solvent, which would result in a retardation of

the ring closure, and thus lead to an increased amounts 1,2-migration of phenyl or hydrogen enamine products.

During the solvent study on the aziridination, it was observed that reactions performed in CCl_4 were faster than those in CH_2Cl_2 by visually comparing the rate of bubbling and the rate of the color change in the reaction solution. A more quantitative study was performed in these two solvents. The reactions in the presence of 2 mol% VAPOL-borate catalyst were set up side-by-side and the crude reaction mixture was examined by ^1H NMR after 0.5 or 1 hour. It was determined that the reactions in CCl_4 were roughly 1.5-2 times faster than those in CH_2Cl_2 (Table 5.9). Based on Hunter's study,[52d] it was proposed that the reaction acceleration was induced by the stronger arene-arene interactions between the arene systems in VAPOL ligand and the benzhydryl groups of the substrate when the solvent is CCl_4.

Table 5.9 Study of relative rate in CH_2Cl_2 and CCl_4.



135 **21** **136**

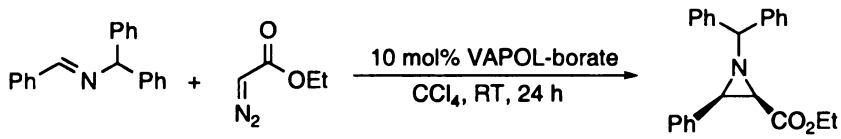
entry[a]	solvent	time (h)	conversion (%)[b]
1	CH_2Cl_2	1	64
2	CCl_4	1	95
3	CH_2Cl_2	0.5	30
4	CCl_4	0.5	60

[a] In entry 1 and 3, catalyst was prepared in CH_2Cl_2 at 55°C. In entry 2 and 4, the catalyst was prepared in CCl_4 by heating at 80°C. [b] Determined by ^1H NMR integration of the crude product.

According to a published procedure,[55] the purification of CCl_4 can be achieved by distillation over P_2O_5, and it was found that CCl_4 dried by this process generally works well in most aziridination reactions. However, the solvent still turned brown slowly upon refluxing even under dry nitrogen atmosphere. After one month the color of still turned black, and the CCl_4 from this distill gave only 76% ee in the aziridination of imine **135**. After examining several drying reagents, it was found that the distillation of CCl_4 over CaH_2 was the optimal drying condition. The still remains clear and colorless even after several months, and the CCl_4 dried by this method afforded aziridine **136** with reproducible chiral induction and yield.

With the discovery of CCl_4 as the optimal solvent, a series of reactions were performed to further optimize the reaction (Table 5.10). It was found that the catalyst prepared at 80°C could lead to a 3-5% higher yield of aziridine than the standard condition, in which the catalyst was prepared at 55°C. It was also found that the slow addition of ethyl diazoacetate could slightly increase the enantioselectivity. Other attempts at optimization included the reaction at lower temperature and the slow addition of imine, however, both resulted in no significant improvement. It was thus decided that the standard condition for aziridination will involve the preparation of the catalyst at 80°C, and for convenience the aziridination will be performed at room temperature with addition of the ethyl diazoacetate all at once.

Table 5.10 Optimization of aziridination in CCl_4.



135 **21** **136**

entry[a]	condition	yield of **136** (%)[b]	ee of **136** (%)[c]
1	catalyst prepared at 55°C	84	93
2	catalyst prepared at 80°C	85-89	93
3	catalyst prepared at 110°C	85	92
5	reaction at 0°C	87	93
6[d]	400 mg MS 4Å added	88	82
7[d]	syringe addition of EDA over 2h	90	93.5
8[d]	syringe addition of EDA over 4h	88	93.5
9[d]	syringe addition of imine over 5h	87	93

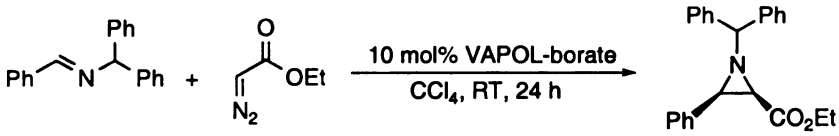
[a] Unless otherwise specified, all the reactions were run in CCl_4 containing 1.0 mmol imine at room temperature, concentration of imine was 0.5M. [b] Isolated yield. [c] Determined by chiral HPLC on a Chiralcel OD-H column. [d] Catalyst was prepared at 80°C.

5.2.5 Catalyst loading study of asymmetric aziridination

The asymmetric aziridination of benzhydryl imine **135** was performed with both enantiomers of the VAPOL and VANOL ligands in CCl_4 (Table 5.11). Since carbon tetrachloride is the optimal solvent and it would be important to determine how both ligands will perform under these optimized conditions. For the reaction with each ligand, the enantiomeric excess will be determined by the average of the results of both enantiomers of each ligand. In the event, the catalyst generated from VAPOL consistently

gave 92.5% ee, and the VANOL catalyst gave identical chiral induction. The reactions with VANOL catalyst were faster than those with VAPOL catalyst based on the observed color change of the reaction solution.

Table 5.11 Aziridination of N-benzhydryl imine **135**



135 **21** **136**

entry[a]	ligand	solvent	yield of **136**(%)[b]	ee of **136** (%)[c]
1	*S*-VAPOL	CCl_4	87	93
2	*R*-VAPOL	CCl_4	78	92
3	*S*-VANOL	CCl_4	87	93
4	*R*-VANOL	CCl_4	88	92

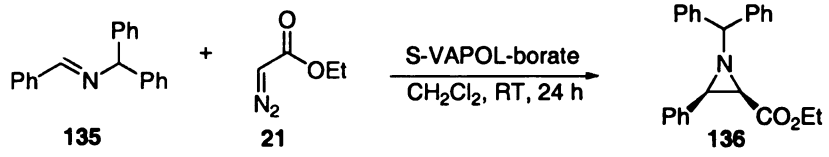
[a] Unless otherwise specified, all the reactions were run in CCl_4 containing 1.0 mmol imine at room temperature, concentration of imine was 0.5M. Catalyst was prepared at 80°C. [b] Isolated yield from chromatography. [c] Determined by chiral HPLC on a Chiralcel OD-H column.

After the optimization of the reaction in CCl_4, we decided to study the effect of the catalyst loading on the aziridination reaction in CCl_4 and CH_2Cl_2. This study should serve to further explore the limit and performance of the catalytic system. The experiments started with 1 mol% catalyst, and then catalyst loading was gradually decreased. This was effected by increasing the amount of substrates while maintaining a constant amount of catalyst (0.1 mmol). The results are summarized in Table 5.12 and 5.13.

As shown in Table 5.12, the aziridination of **135** in CH_2Cl_2 resulted in good yield and enantioselectivity. It was found that: 1) the reactions performed with 10 mol% or 1 mol%

VAPOL catalyst gave almost identical enantioselectivity; 2) the catalyst loading could be decreased to as low as 0.5 mol% and the overall ee was still as high as 85.5%. 3) the limit of catalyst loading in CH_2Cl_2 was 0.5 mol%, as the reaction with 0.25 mol% catalyst gave <50% conversion.

Table 5.12 Catalyst loading study on the aziridination of **135** in CH_2Cl_2



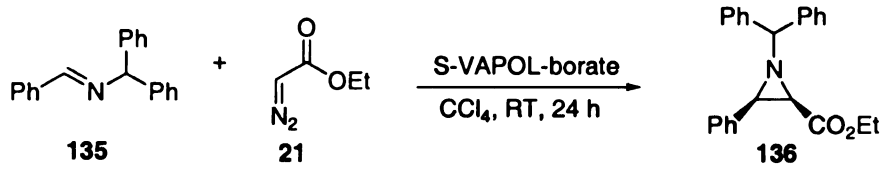
entry[a]	catalyst (mol%)	purification and result[b]	combined yield (%)[c]	combined ee (%)[d]
1	1	1st crystallization, 61.5% yield, 98% ee 2nd crystallization, 16% yield, 60% ee chromatography, 5% yield, 59% ee	82.5	88.5
2	0.5	1st crystallization, 53% yield, 98% ee 2nd crystallization, 22% yield, 59% ee chromatography, 4% yield, 66% ee	79	85.5
3	0.25		44% conversion	

[a] The reactions were 0.5 M in imine. [b] Crystallization of crude reaction mixture was performed in mixture of CH_2Cl_2/hexane. After two crystallizations, the mother liquor was purified by silica gel chromatography. [c] Combined yield from crystallization and chromatography. [d] Determined from the combined product by chiral.

Because these reactions were performed on large scale, silica gel chromatography purification would be very expensive and inconvenient. Furthermore, the silica gel chromatographic separation of the N-benzhydryl aziridines from the crude reaction mixture was complicated by the difficulty in their separation from the enamines side product and from the VAPOL ligand. In these large scale reactions, crystallization

became the preferred purification method. In the event, a simple crystallization of the crude reaction mixture from CH_2Cl_2/hexane was found to give optically pure (>98% ee) aziridine of at least 98% chemical purity in 50-60% yield. After a second crystallization of **136** and chromatographic purification of the remaining **136** in the mother liquor, the remaining 20-25% aziridines was isolated with low chiral induction.

Table 5.13 Catalyst loading study on the aziridination of **135** in CCl_4



entry[a]	catalyst (mol%)	scale (mmol)	purification and result[b]	combined yield (%)[c]	combined ee (%)[d]
1	1	10	1st crystallization, 59% yield, 99% ee 2nd crystallization, 24% yield, 77% ee chromatography, 4% yield, 62% ee	86	91
2	0.5	20	1st crystallization, 58% yield, 98% ee 2nd crystallization, 25% yield, 65% ee chromatography, 6% yield, 65% ee	88	86
3	0.25	40	1st crystallization, 64% yield, 98% ee 2nd crystallization, 19% yield, 50% ee chromatography, 5% yield, 66%ee	88	86
4[e]	0.125	80		68% convn	

[a] The reactions were 0.5 M in imine. [b] Crystallization of crude product was performed in mixture of CH_2Cl_2/hexane. After two crystallizations, the mother liquor was purified by silica gel chromatography. See experimental for details. [c] Combined yield from crystallization and chromatography. [d] Determined from combined product by chiral HPLC on a Chiralcel OD-H column. [e] The reaction was 1.0 M in imine

It was gratified to find that the aziridination of **135** in CCl_4 afforded better results than those in CH_2Cl_2 (Table 5.13). The reactions were generally faster, gave better yield and chiral induction and produced less side products. Most importantly, the catalyst loading could be decreased to as low as 0.25 mol%, which is equal to 400 turnovers within 24 hours. The aziridination in CCl_4 gave 91% ee with 1 mol% catalyst, 86% ee with 0.5 mol% and with 0.25 mol% catalyst. Again, a single crystallization of the crude aziridine consistently afforded highly enantiomerically pure (≥ 98% ee) aziridine **136** in ~60% yield in all cases. For example, the reaction in entry 3 employed 54 mg (0.1 mmol) of VAPOL and 11 g (40 mmol) of imine **135** in a reaction that was complete within 24 hours, and a single crystallization from which gave 9 g (25 mmol) of aziridine **136** with 98% ee.

Upon decreasing the catalyst loading to 0.125 mol%, the conversion of **135** was only 3%. It was suspected that at this scale and loading, small amount of impurities in the imine, ethyl diazoacetate and/or the solvent may destroy the active catalyst. It was found that increasing the imine concentration to 1.0 M from 0.5 M indeed gave better conversion at 0.125 mol% catalyst (68%, entry 4). The crystallizations in entries 1-3 represent optimized procedures for the collection of the first crop. Attempted isolation of more aziridine using less solvent was not successful, as it only led to the crystallization of enantiomerically less pure (89-92% ee) aziridine. Finally, this catalyst loading study may not be representative of what will be found for other imine substrates. Depending on their electronic and/or steric properties, various benzhydryl imines will in theory respond differently to changes in the catalyst loading.

5.3 Conclusion

During the course of the study of the catalytic asymmetric aziridination reaction, it was found for some unknown reasons, the level of chiral induction that had been previously reported from the Wulff research group could not be repeated. Despite a large amount of effort dedicated to the exploration all the conceivable variables, the exact reason for the lack of reproducibility could not be determined.

Carbon tetrachloride was discovered to be a more efficient solvent system after screening of various non-polar solvents. The aziridinations in this solvent are cleaner, give higher yields and higher enantioselectivity. This improved profile of the reaction is proposed to be the result of better edge-face interactions between ligand and substrate in this solvent. On the other hand, the high price, toxicity and decreasing availability of CCl_4 also significantly inhibit its application.

The aziridination of imine **135** at low catalyst loading in different solvents were explored. These studies provided further definition of the scope of Wulff's catalytic system and greatly improved the practical value of asymmetric catalytic aziridination reaction.

CHAPTER SIX

MECHANISTIC STUDIES ON CATALYTIC ASYMMETRIC AZIRIDINATION

6.1 Introduction

Over the last two decades, catalytic asymmetric reactions have received a great deal of attention from organic chemists and have undergone an explosive growth.[5] Numerous excellent enantioselective catalytic systems have been developed which have taken their place in the standard repertoire of synthetic methods. The area of asymmetric catalysis has undoubtedly become one of the most dynamic aspects of modern synthetic chemistry.

One of the most important aspects of the study of catalytic asymmetric reactions is the exploration of the detailed mechanism of these transformations, and more specifically, the study of transition-state structure and the study of the structure of the catalyst-substrate complex. Understanding the origin of the enantioselectivity will not only satisfy the curiosity of chemists, but more importantly, it may be helpful for the improvement of the existing catalytic systems and the development of new methodology. The latter issue is of particular interest to the chemists, as almost all of the modern asymmetric catalytic systems were discovered by the extensive screening of a variety of combinations of chiral ligands and metals/Lewis acids. It was only in rare cases that

synthetic chemists did benefit from the insights into the mechanistic studies and successfully fine-tuned their catalyst system.

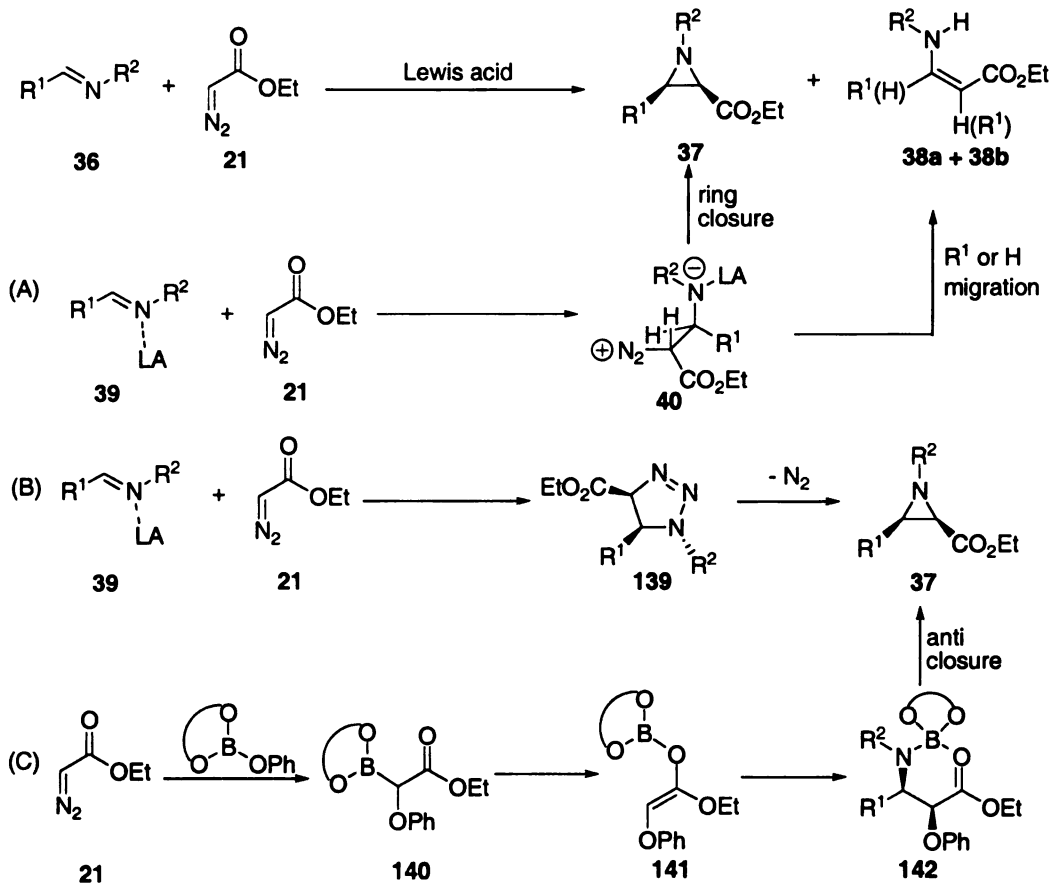
In 2000 our group reported a highly enantioselective catalytic aziridination system and this methodology has been applied in the synthesis of several natural products or pharmaceutically important compounds.[25,26] The discovery of this methodology was the result of screening of numerous catalysts generated from various Lewis acids and ligands. However, the exact structure of the catalyst and the transition state of the aziridination reaction remained a mystery. It is thus desirable to explore these areas and the knowledge obtained from this study should be invaluable for the further improvement of our existing aziridination system and for the possible discovery of new methodologies.

6.1.1 Mechanisms of Lewis acid catalyzed aziridination reaction

The mechanism of the Lewis acid mediated aziridination reactions of diazo compounds and imines has never been thoroughly studied. There are three possible mechanisms for this reaction (Scheme 6.1). The first mechanism was proposed in 1996 by Brookhart and Templeton based on their study of Lewis acid catalyzed reactions of ethyl diazoacetate and imines (Scheme 6.1, mechanism A).[19] An almost identical mechanism was subsequently suggested by Jorgensen.[20] In mechanism A, the Lewis acid activated imine **39** is attacked by the negatively polarized carbon of ethyl diazoacetate, leading to the formation of zwitterion **40**, which then undergoes backside

attack by nitrogen to furnish aziridine **37** upon releasing of nitrogen gas. Alternatively, 1,2-shifts of hydride or R^1 will lead to the formation of the two enamine by-products **38a** and **38b**. On the other hand, mechanism B and C are also plausible based on literature. In mechanism B, the Lewis acid activated imine undergoes [3+2] cycloaddition to give triazoline **139**,[56a] which subsequently decomposes to give aziridine. Mechanism C involves the formation of the boron enolate **141** in the first stage,[56b] which then reacts with imine followed by anti ring-closure to give aziridine product.

Scheme 6.1 Three possible mechanisms for the Lewis acid catalyzed aziridination



The studies from Templeton and Brookhart as well as the studies from Jorgensen's suggested that mechanism A is most likely the correct pathway. Several observations were consistent with this mechanism:[19]

1) In the reactions of aromatic imines, the ratios of aziridines to 1,2-migration products were strongly dependent of the nature of the aryl ring. The unsubstituted benzaldimine (R^1 = Ph) gave a 65:35 ratio of **37**:(**38a**+**38b**), the electron-rich aromatic imines (R^1 = *p*-$CH_3OC_6H_4$) gave exclusively migration products, while the same reaction of electron-withdrawing group substituted (R^1 = *p*-$NO_2C_6H_4$) imines increased the proportion of aziridine product, giving **37** in 82% yield.

2) The reactions of alkyl imines were much faster, which may be attributed to the higher nucleophilicity of imine nitrogen. In the reaction of these substrates the alkyl (R^1) migration product was not observed.

Interestingly, Jorgensen found that electron-rich imines (R^2 = *p*-$CH_3OC_6H_4$) reacted significantly slower, and he proposed that the nucleophilic attack of EDA on the C=N double bond is the rate-determining step.[20]

Mechanism B is unlikely to be operative in the borate catalyzed reaction. Reports of [3+2] cycloadditions of imines and diazo compounds are few and examples of the conversion of triazolines to aziridines are rare. The only publication of such addition involves the addition of diazoacetonitrile to electron-rich imines in the absence of any catalyst, and the electron-deficient imines directly lead to aziridines in low conversion and yield.[55a] This reaction generally gave *cis*/*trans*- triazolines nonselectively in about the

same proportion. Decomposition of the stable triazoline was performed under photochemical or thermal conditions. As a matter of fact, the triazoline product has never detected in all of the reported catalyst systems involving the reaction of ethyl diazoacetate and imines.[19,20,25,26]

The possibility of a reaction between triphenyl borate and ethyl diazoacetate in mechanism C is also small. The literature suggests that although the reaction between alkyldichloroborane and EDA was facile, the similar reaction between boronic esters and EDA was extremely slow due to the decreased electrophilicity of boron.[56b] Mechanism C could not be applied to the VAPOL/VANOL-BH catalyzed reaction either (Scheme 6.1). In this case even if the insertion occurred, the subsequent ring closure via loss of hydride would be highly unlikely.

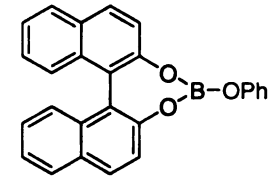
6.1.2 Proposed structure of active catalyst and catalyst-imine complex

The complexes generated from BINOL and borate esters or boronic acids are well known in literature. The structures of these complexes are dependent on the boron substituents and the structure of biaryl ligands.[57] Yamamoto suggested that **143** is most likely the catalyst generated from a 1:1 molar ratio of BINOL and triphenyl borate in CH_2Cl_2 at room temperature (Figure 6.1), although in the same paper he also commented that other possible structures for the active species may not be excluded.[57a] Similar structures were also observed in the reactions of BINOL with several boranes and boronic acids.[56c] Yamamoto also reported that the catalyst generated from 2:1 molar ratio

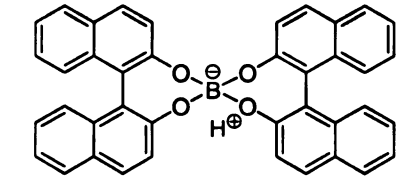
of BINOL and triphenyl borate was **144** and its structure was confirmed by X-ray analysis.[57b] Kaufmann found that when BINOL was reacted with several borane complexes, hydrohaloboranes or boric acid, the bicylic homochiral bisborate compound **145** was observed exclusively.[57c]

On the other hand, it was also reported that the introduction of bulky substituents at 3,3'- position of BINOL would exclusively lead to the formation of the seven-membered complexes of the type **143** to avoid the steric strain observed in **145**.[57c] CPK modeling with the VAPOL or VANOL ligand also indicates severe steric strain in the complexes related to **144** and **145**. Thus, the active catalysts are mostly likely **146** or **147**, which were generated from one molecule of the VAPOL or VANOL ligand and one equivalent of a boron Lewis acid such as BH_3 or $B(OPh)_3$.

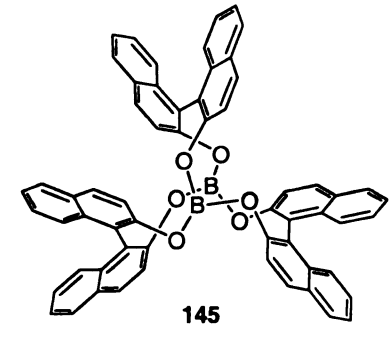
Figure 6.1 Various structures for the chiral biaryl borate catalysts



143



144



145

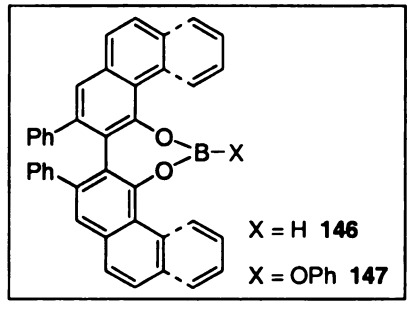
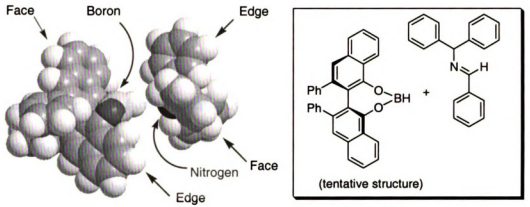


Figure 6.2 Proposed two edge-face interactions between an N-benzhydryl imine and the VANOL-BH catalyst



A model to account for the chiral induction of the VANOL and VAPOL catalysts is shown in Figure 6.2 with space-filling models and is illustrated with the VANOL catalyst (for simplicity the catalyst is shown as generated from BH_3). The benzhydryl imine exists as two enantiomeric low energy conformers, one of which is shown in the scheme. When the imine nitrogen bonds to the boron, the close contact between the benzhydryl group and aromatic system of the ligand creates two edge-face arene interactions (CH/π interactions). More specifically, one phenyl ring acts as edge ring and points toward the naphthalene ring of the ligand, while the other naphthalene ring of the ligand acts as an edge ring in its interaction with the second phenyl ring of benzhydryl group on the imine. The magnitude of these interactions are unknown in this system, but for the interaction of two benzenes in chloroform, this is 0.7 kcal/mol.[52] Very similar face-edge interactions are observed with CPK models for the VAPOL catalyst, but not for the BINOL borate species. It was proposed that these interactions provide an additional organizing effect to the structure of the imine-catalyst complex. This model thus explains why N-benzyl imines

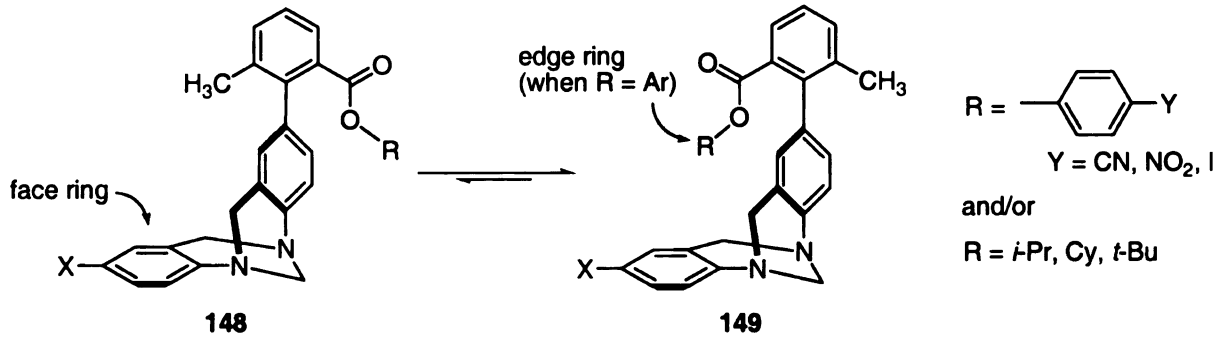
(see Table 6.6) or the catalyst prepared from BINOL[25b] is not very effective, the asymmetric induction in these cases was fairly low as the face-edge interactions would be weak or non-exist.

6.1.3 Experimental and theoretical studies of CH-π interaction

The working model shown in Figure 6.2 is supported by and is based on the extensive experimental and theoretical studies that have examined the effects of substituent on CH-π interactions over the past ten years.

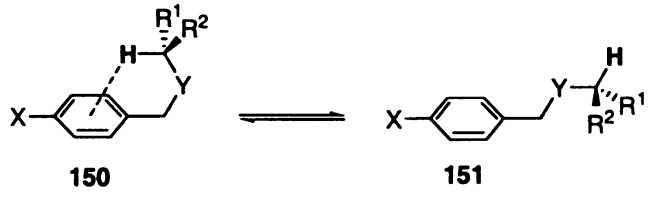
In Wilcox's pioneering experimental work, he employed the molecular torsion balance to study the relative population of the "unfolded" and "folded" conformations **148** and **149**, respectively, as a function of R (Scheme 6.2).[58] It was found that when R was a substituted phenyl group (edge ring), strong edge-face interaction (**149** was preferred) could be observed in the case of Y = cyano, nitro and iodo. There was almost no effect when an electron-withdrawing substituent X was on the face ring. Electron-releasing groups were found to have no effect on the edge or face ring (X or Y). Another surprising observation was that when R was isopropyl, cyclohexyl or *tert*-butyl, the interactions of the bulky alkyl groups with the face arene ring was even stronger than those of the substituted edge arene rings. Finally, Wilcox found that placing two *meta*-methyl groups on the edge ring would lead to a preference for the unfolded state **148**, presumably due to the loss of rotational degree of freedom.[58]

Scheme 6.2 Wilcox's experimental study of edge-face interaction.[58c]



Houk et al later performed molecular mechanics calculations on Wilcox's molecular torsion device.[58c] These theoretical studies conformed that most aromatic groups (R = Ar) prefer the folded conformation **149**, and in addition, that cyclohexyl and *tert*-butyl groups show the same level of preference for the folded conformation. However, he suggested that the preference was a result of a balance between intramolecular van der Waals interactions and solvation effects, with the latter favoring the unfolded conformation **148**. Houk also suggested that in the case of *meta*-methyl substituted edge rings, the preference to unfolded **148** was caused by steric repulsion between the methyl group and the face ring.

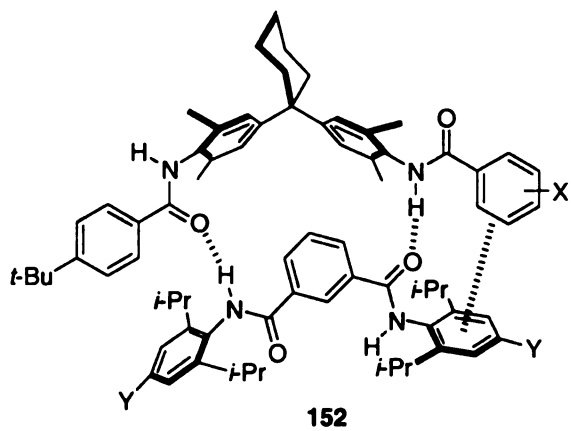
Scheme 6.3 Suezawa's study of substituents effect by NOE experiment.[59a,b]



Subsequently, a different system was developed for the study of substituent effects on CH-π interactions by Hirota and Suezawa et al.[59a,b] They studied the effect of substituents on CH/π interactions by the measurement of NOE enhancement of aromatic

protons induced by the irradiation of CH donor proton (shown in bold) (Scheme 6.3). They found that for all of the compounds they studied, the introduction of electron-donating groups on the phenyl ring resulted in a greater NOE enhancement than with electron-withdrawing groups. This discovery indicated that the CH/π contiguous folded conformer **150** became more favorable than the unfolded conformer **151** with increased electron density on the benzene ring. The authors suggested that an electron-withdrawing group on the CH carbon should lower the level of the antibonding CH orbital, whereas the electron-donating substituents on the π system should raise the highest occupied π orbital. Both effects should increase the partial charge transfer from the highest occupied π orbital to the lowest unoccupied σ^* orbital of the CH bond and thus favor the CH/π interaction by narrowing the energy gap of the interacting orbitals.

Figure 6.3 Hunter's study of substituent effects with double mutant cycles.[59c,d]



152

Hunter et al used a "chemical double mutant cycle" to measure the magnitude of the edge to face aromatic interactions in hydrogen-bonded zipper complexes **152** as a function of substituents on both aromatic rings (Figure 6.3).[59c,d] Hunter's observation was very similar to that of Suezawa. It was found that electron-donating substituents on the

face ring favor the edge-face interaction, whereas the electron-withdrawing groups on the edge ring also enhance the interaction.

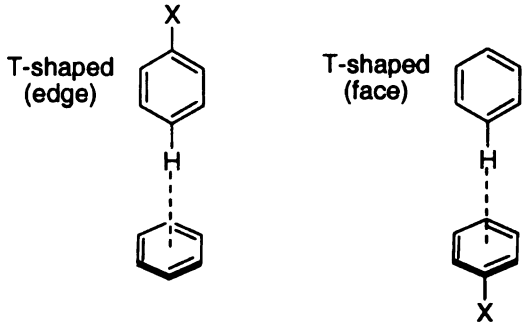
Over the last ten years, owing to the rapid development of modern computer technology and increased availability of more mature theoretical calculation programs, the effects of substituent on the arene-arene interactions have received increased attention from theoretical chemists.

Orozo et al described their results from theoretical studies on alkyl-π and aryl-π interactions.[60] The calculations on alkyl-π interactions confirmed Wilcox's experimental results. However, the calculations on the aryl-π interaction in the simple benzene-benzene dimer and on Wilcox's folding models revealed significant backbone effects in Wilcox's system. In contrast to Wilcox's experimental results, Orozo suggested that the introduction of polar substituents on face ring will induce important interactions in the T-shaped benzene-benzene dimer.

Recently, Sherrill and Kim independently published their theoretical studies on substituent effects in edge-face aromatic interactions.[61,62] Both groups utilized various high level *ab initio* calculations to predict the magnitude and direction of edge face interactions. Sherill found that these interactions are dependant on whether the substitution is on the face or edge ring (Figure 6.4).[61] In concert with Wilcox's discovery, the calculations indicated that an electron-withdrawing group on the edge ring will increase the interaction between the two rings. However, if the same groups are placed on the face ring, there will be a decrease in the binding relative to the benzene dimer. It

was also found that electron-donating groups such as OH or CH_3 will have an impact on the interaction, and that their effects are opposite from those of electron-withdrawing groups. Kim's work involves a larger set of substituents including nitro, amino, bromo and chloro groups.[62] The overall results from Kim's calculation on substituent effects are very similar to those described by Orozo and Sherrill.

Figure 6.4 Theoretical calculations of substituent effect of edge-face interactions.[61]



	X = H	OH	CH_3	F	CN
Δ E (kcal/mol)	T-shaped (edge)				
	0	0.04	0.07	-0.15	-0.63
Δ E (kcal/mol)	T-shaped (face)				
	0	-0.05	-0.33	0.24	0.42

6.1.4 Design of the substrates for mechanistic studies

To test the edge-face interaction in our proposed model, the aziridination reactions with various chiral imines shown in Figure 6.5 will be examined. Based on the experimental and theoretical results discussed above, it was expected that one enantiomer of the chiral imines (**153-156**) should constitute a matched or mismatched pair with one particular enantiomer of the VANOL-borate or VAPOL-borate catalyst.

Figure 6.5 Chiral imines for match/mismatch study

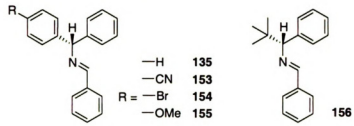
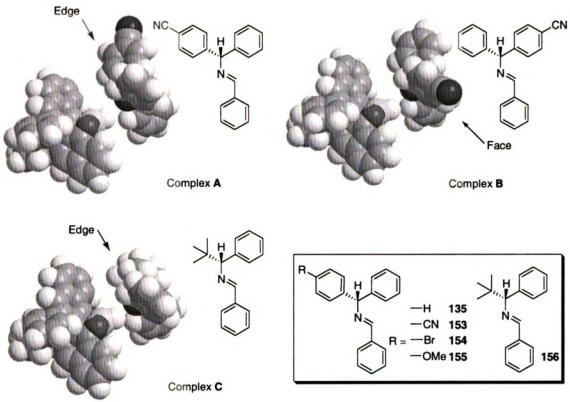


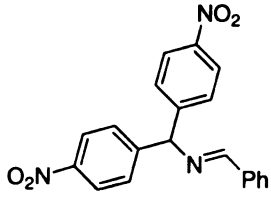
Figure 6.6 Proposed match/mismatch study using chiral imines



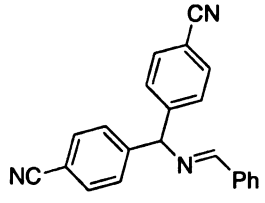
If one enantiomer of the chiral imines (**153-155**, Figure 6.5) can coordinate with one enantiomer of the VANOL-borate or VAPOL-borate complex in such a way that the R-substituted phenyl ring (R = electron-withdrawing group) acts as edge ring (Figure 6.6, complex **A**, shown with *S*-VANOL-BH catalyst), higher asymmetric induction should be observed than with the non-substituted benzhydryl imine **135**. On the other hand, the

other enantiomer of **153** should constitute a mismatched pair with the same *S*-VANOL catalyst as the electron-withdrawing group would now reside on the face ring (complex **B**, Figure 6.6). In the case of the electron-rich imine **155**, same asymmetric induction as benzhydryl imine **135** should be observed if Wilcox's result was correct, as his result suggested that the electron-releasing groups have no effect on the edge or face ring.[57,58] Based on other experimental and computational results which suggested that the electron-releasing groups should induce opposite effect from the electron-withdrawing groups,[59-62] it is also possible that imine **155** will exhibit a matched/mismatched pair opposite from **153** with the same enantiomer of catalyst. Finally the α-*tert*-butylbenzyl amine **156** should create a more pronounced matched/mismatched pair with the VAPOL or VANOL derived catalysts based on Wilcox's observations (complex **C**).

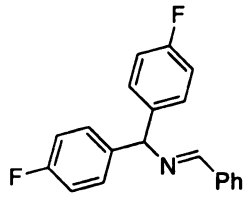
Figure 6.7 Substrates for the study of electronic effect



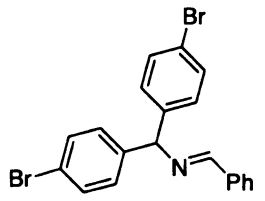
157



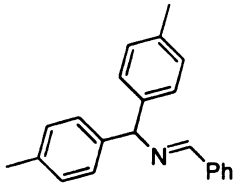
158



159



160



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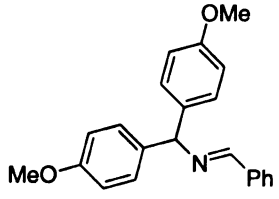
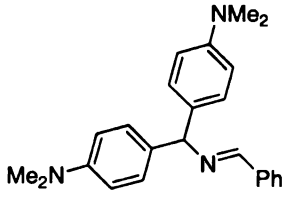


162

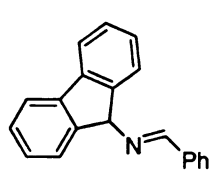


163

This study will be widened to include reactions of the symmetrical imines **157-163**, which will be examined to probe for the electronic effects induced by the two *para*-

substituents on the benzhydryl group (Figure 6.7). Based on Wilcox's study,[58] imines **157-160** that bear two strong electron-withdrawing groups should induce stronger face-edge interaction with VAPOL or VANOL, and their reaction should afford higher chiral induction than imines **161** and **163**. On the other hand, if the more recent finding by Hunter,[59d] Suezawa[59a,59b] and the results from the calculations[60-62] apply, then a large differences in the chiral inductions between these imines would not be expected. Here the two rings would act independently as one edge ring and one face ring and their effects would be opposite and cancel each other.

Figure 6.8 Substrates for the study of steric/geometric effect



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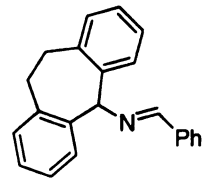
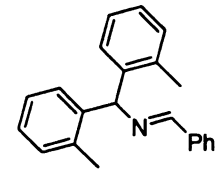
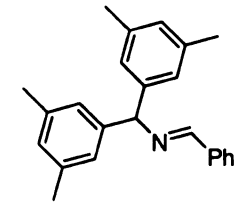


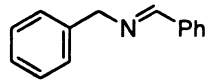
165



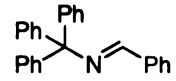
166



167



168



169

The set of imines **164-169** will be studied to probe the effects of sterics and the effect of changes in conformations of the aryl groups in the imine substrates because of the various size/geometry of their nitrogen protecting groups (Figure 6.8). Imine **164** has a planar N-protecting group, thus lower selectivity is expected to be observed for this substrate due to the lack of possibility of two edge-face interactions. The N-protecting group in imine **165** and **166** may adopt different dihedral angles from the benzhydryl group and their results would be difficult to predict but could be informative. Imine **167**

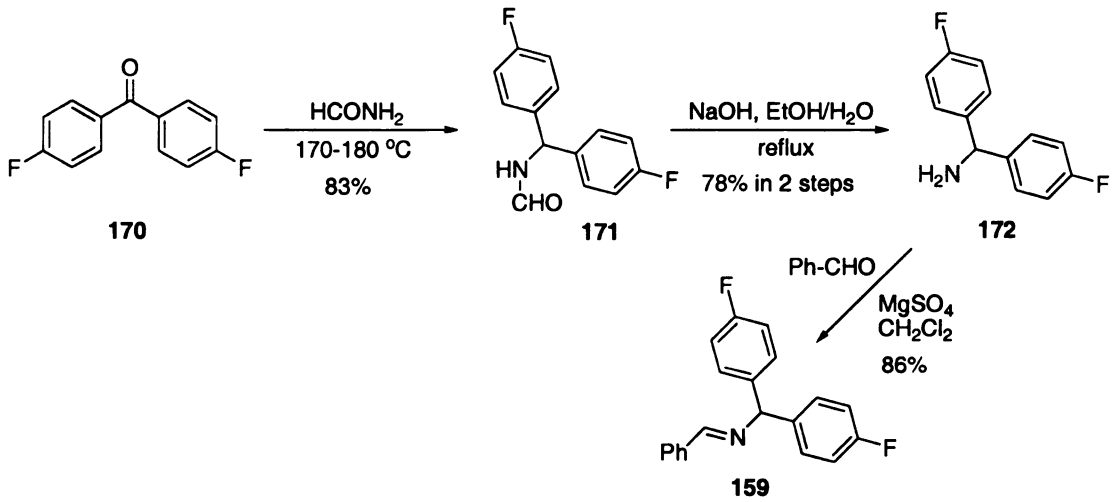
was designed as a "negative" test based on Wilcox's finding that the *meta*-methyl groups on the edge ring would disfavor the edge-face interaction. CPK modeling also indicated that in the VANOL-borate or the VAPOL-borate catalyst, one of the four meta-methyl groups would prevent the edge ring on the benzhydryl group from interacting with the catalyst. Thus imine **167** is expected to afford lower enantioselectivity than the non-substituted benzhydryl imines. Additionally, imines **168** and **169** will be tested for their steric effects.

6.2 Preparation of the imine substrates

6.2.1 Preparation of symmetric N-benzhydryl imines

The synthesis of the achiral imine **159** began with the preparation of fluorinated amine **172** (Scheme 6.4). The commercially available 4,4'-difluorobenzophenone **170** was transformed into amide **171** via a Leukhart reaction in 83% yield.[63] Purification of **171** was difficult, and as a result, it was much easier to use the unpurified amide directly in the next step. After base hydrolysis the product amine **172** was purified by vacuum distillation to give 78% overall yield from **170**. Condensation of **172** with benzaldehyde afforded the desired imine **159** in good yield.

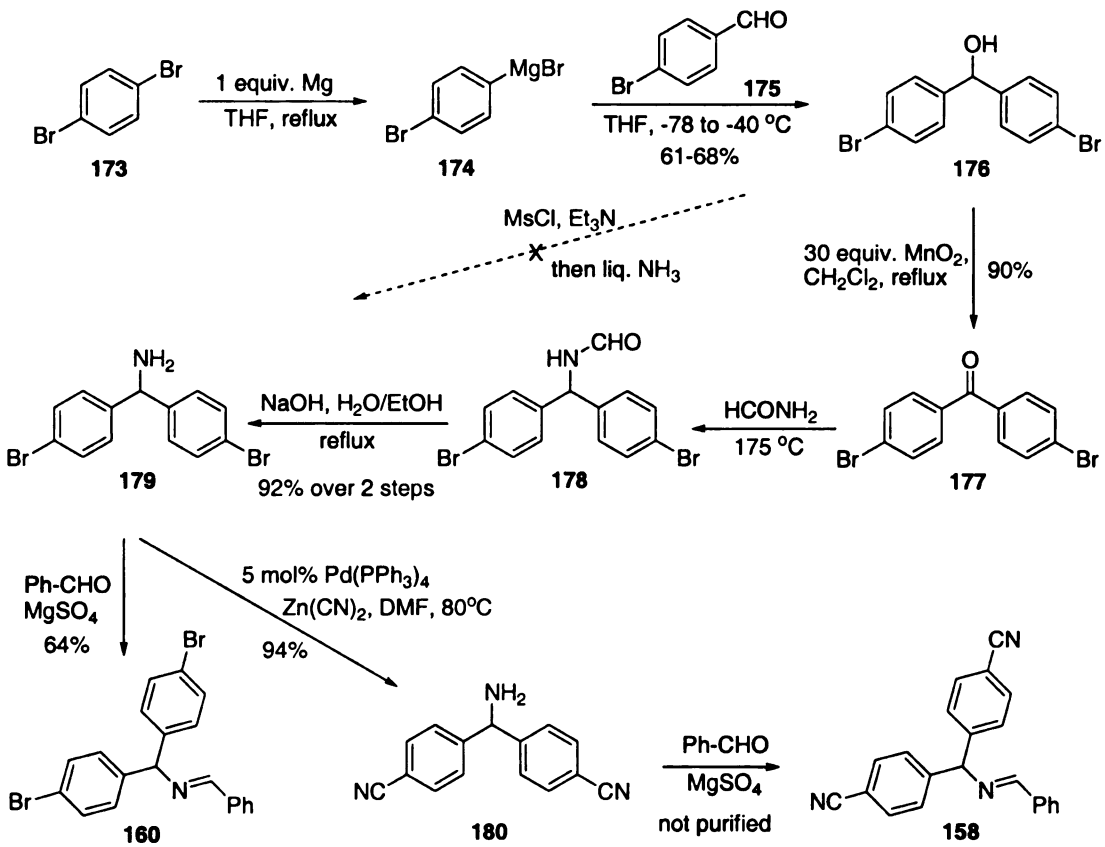
Scheme 6.4 Synthesis of 4,4'-difluorobenzhydryl imine **159**



170 **171** **172** **159**

The 4,4'-dibromobenzhydryl and 4,4'-dicyanobenzhydryl imines were envisioned to be derived from 1,4-dibromobenzene **173** and aldehyde **175** (Scheme 6.5). Reaction of **173** with 1 equivalent of magnesium afforded the Grignard reagent **174**, which upon addition to *para*-bromobenzaldehyde **175** at low temperature furnished the desired 4,4'-dibromobenzhydrol **176** in good yield. The attempted one-pot mesylation-amination was not successful, thus a three step sequence was adopted for the preparation of amine **179**. Oxidation of the benzhydrol **176** was slow, 30 equivalents of MnO_2 was necessary to ensure complete conversion, however the desired ketone **177** could be isolated in excellent yield. Leukhart reaction between **177** and formamide at 175 °C afforded the N-formyl amide **178**, which was not purified, but rather directly subjected to base hydrolysis. As a result the dibromobenzhydryl amine **179** was isolated in excellent yield over two steps.

Scheme 6.5 Synthesis of dibromobenzhydryl and dicyanobenzhdryl imine **158** & **160**

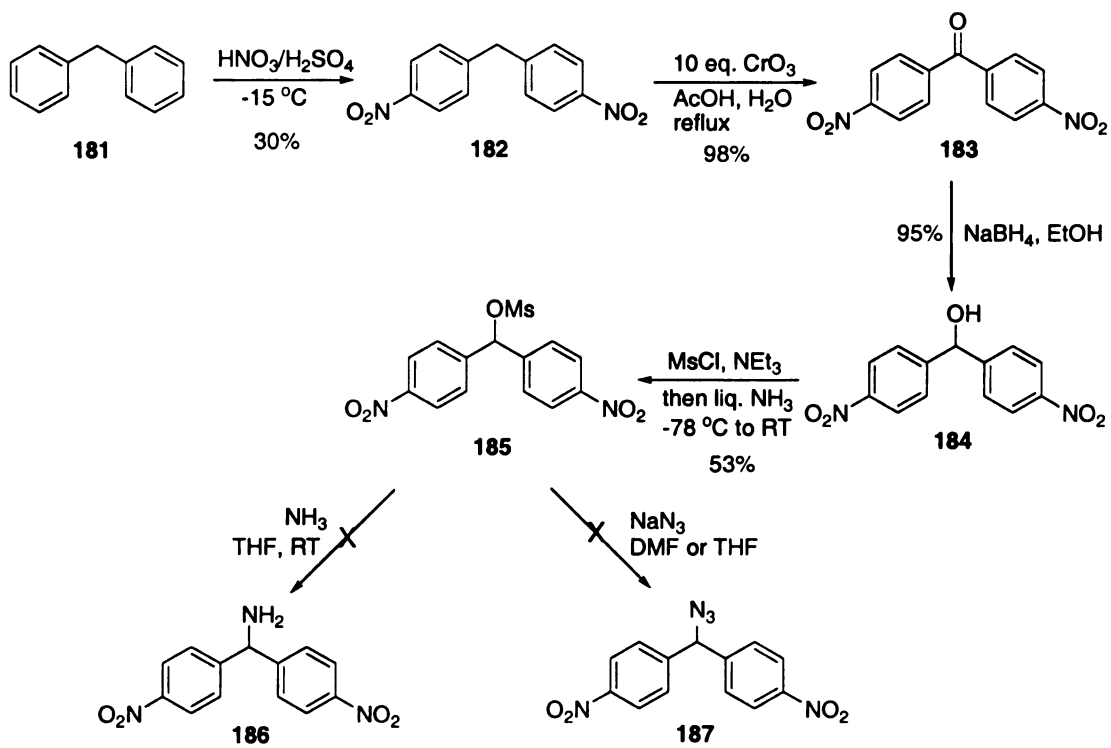


Subsequently, the palladium catalyzed coupling reaction between **179** and zinc cyanide cleanly afforded the 4,4'-dicyanobenzhydryl amine **180** in excellent yield.[64] Condensation of the amine **180** with benzaldehyde yielded the desired imine **158** as a foam-like amorphous solid. Despite extensive efforts, **158** could not be purified by crystallization and thus was used in crude form without purification since chromatography leads to hydrolysis and distillation leads to decomposition.

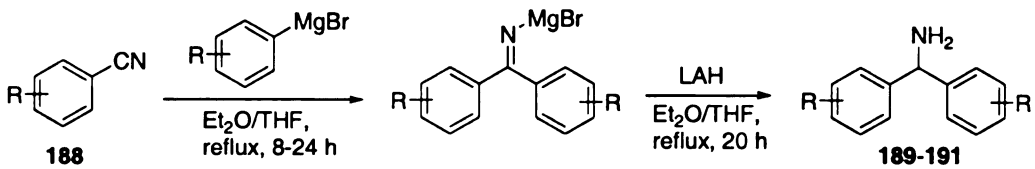
The preparation of 4,4'-dinitrobenzhydryl amine **187** started with the nitration of diphenylmethane **181** (Scheme 6.6).[65] This reaction gave a 1.7:1 mixture of 4,4'-dinitrophenylmethane **182** and its 2,4'-dinitro- isomer. Crystallization from EtOAc

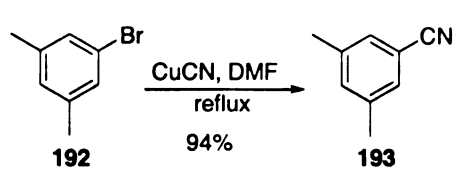
afforded pure **182** in low overall yield. Oxidation of **182** with a large excess of CrO_3 furnished the desired ketone **183**, which was reduced to benzhydrol **184** with $NaBH_4$ in excellent overall yield. The attempted one-pot mesylation-substitution with mesyl chloride and ammonia did not furnish the desired amine, only the mesylate **185** was isolated in moderate yield. Further attempted substitution with either ammonia or sodium azide also failed. The attempt to prepare **186** was not further pursued because all of the intermediates with the 4,4'-dinitrobenzhydryl group exhibit extremely poor solubility in common nonpolar solvents such as CH_2Cl_2. This problem is very likely to result in difficulty with the aziridination even if the preparation of **186** would be successful.

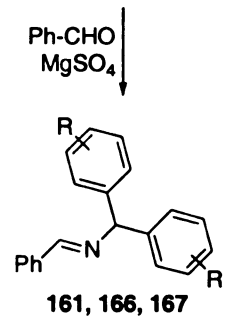
Scheme 6.6 Attempted synthesis of 4,4'-dinitrobenzhydryl amine



Scheme 6.7 Synthesis of methyl-substituted benzhydryl amines and imines







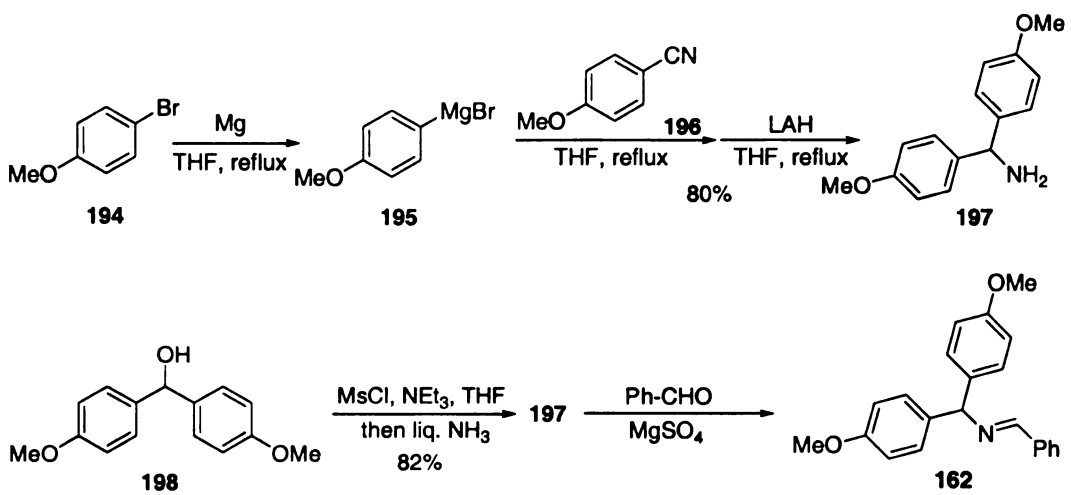
entry	R	yield of amines	yield of imines
1	R = 4-Me	**189**: 79%	**161**: 91%
2	R = 2-Me	**190**: 91%	**166**: 82%
3	R = 3,5-di-Me	**191**: 73%	**167**: 84%

Synthesis of symmetric methyl-substituted amines **189-191** could be achieved using the method developed by Pohland and Sullivan.[66] This procedure involves the one-pot addition of methyl-substituted phenyl Grignard reagent to the corresponding benzonitriles followed by LAH reduction of the imine salt intermediates. Upon workup, the amines could be isolated in good to excellent yields (Scheme 6.7). The 3,5-dimethylbenzonitrile **193** was not commercially available and it was prepared by the Rosenmund-von Braun reaction on 5-bromo-m-xylene **192**.[67] Nitrile **193** sublimes readily under high vacuum and thus it was quickly dried and subjected to the reaction with the Grignard reagent prepared from **192**. All the amines were converted to their imine derivatives in good yields by condensation with benzaldehyde following the standard procedure.

4,4'-Dimethoxybenzhydryl amine **197** could be prepared by two methods (Scheme 6.8). The first method involves the same process that was used in the preparation of the methyl substituted benzhydryl amines[66], which gave the desired amine **197** in 80% yield.

However the amine prepared in this way was sometimes contaminated with small amounts of an impurity which was difficult to remove. Alternatively, a more efficient and simpler process was developed for the preparation of **197** based on a reported procedure.[68] It was found that the commercially available benzhydrol **198** could be transformed to **197** by a more convenient one-pot mesylation-amination process in good yield on large scale, and the isolated amine does not contain the inseparable impurity. Furthermore, the benzhydrol **198** could be obtained in quantitative yield from the reduction of the corresponding benzophenone which is much cheaper than the alcohol **198**.

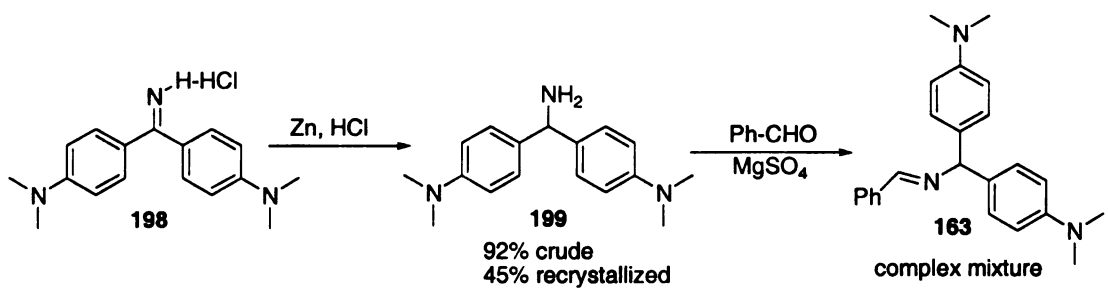
Scheme 6.8 Synthesis of 4,4'-dimethoxybenzhydryl imine **162**



As will be described in latter in this chapter, the aziridination reactions of 4,4'-dimethoxybenzhydryl imines indicated that this group exhibit slightly better chiral induction than the unsubstituted benzhydryl imines, and in addition, this electron rich benzhydryl group could be removed under mild acidic condition which leaving the

aziridine ring intact. Thus, it was expected that the 4,4'-bis-dimethylaminobenzhydryl group may exhibit similar or better selectivity and possibly would be more labile toward cleavage. The attempted synthesis from the commercially available 4,4'-bis-dimethylamino- benzhydrol using the one-pot mesylation-amination failed. Alternatively, reduction of the commercially available imine hydrochloride salt **198** with zinc and hydrochloric acid did afford the desired amine **199** which was contaminated with several unknown impurities (Scheme 6.9). It was found that **199** could not be purified by chromatography as it decomposed immediately upon exposure to TLC plate. Thus the crude amine **199** was crystallized from ethanol and directly condensed with benzaldehyde. The resulting imine **163** was found to be a complex mixture by ^{1}H NMR and could not be purified by crystallization. The aziridination of imine **163** was thus not pursued.

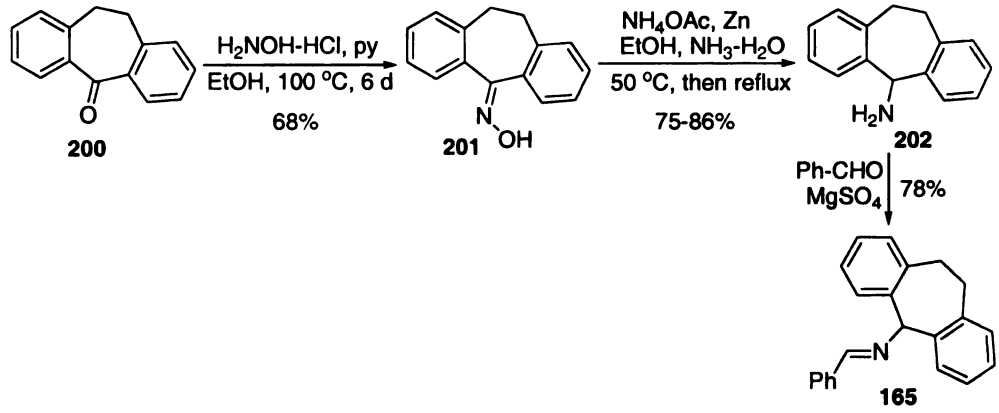
Scheme 6.9 Attempted synthesis of 4,4'-di(dimethylamino)benzhydryl imine



N-dibenzosuberonyl imine **165** was prepared from the commercially available dibenzosuberone **200** (Scheme 6.10). The attempted Leukart reaction of **200** was not successful. Thus **200** was converted to oxime **201** via a known procedure.[69] Although the catalytic hydrogenation of **201** using Pd catalyst was not successful, reduction of oxime

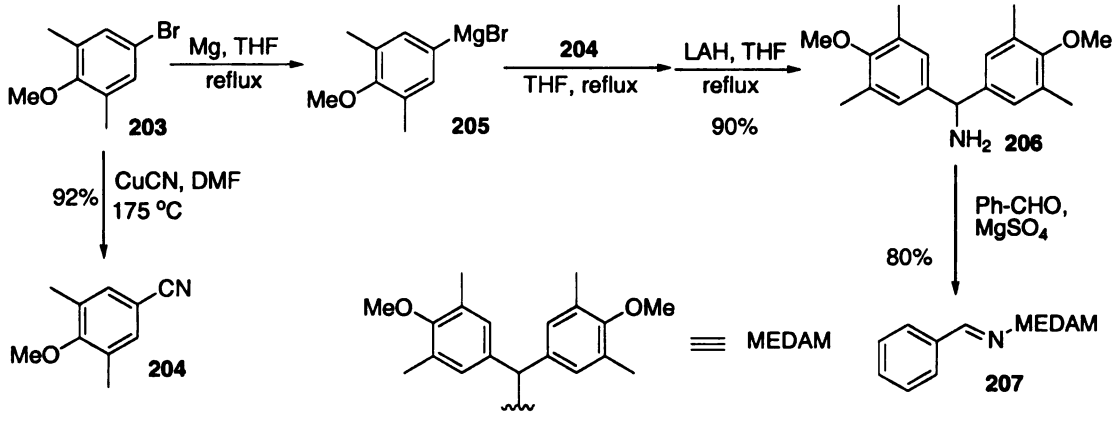
using zinc and ammonia at elevated temperature gave the desired 5-aminodibenzosuberane **202** in good yield.

Scheme 6.10 Synthesis of N-dibenzosuberonyl amine and imine



The N-9-fluorenyl Imine **164** was prepared from the commercially available 9-fluorenylamine hydrochloride and benzaldehyde according to a published procedure (not shown).[70]

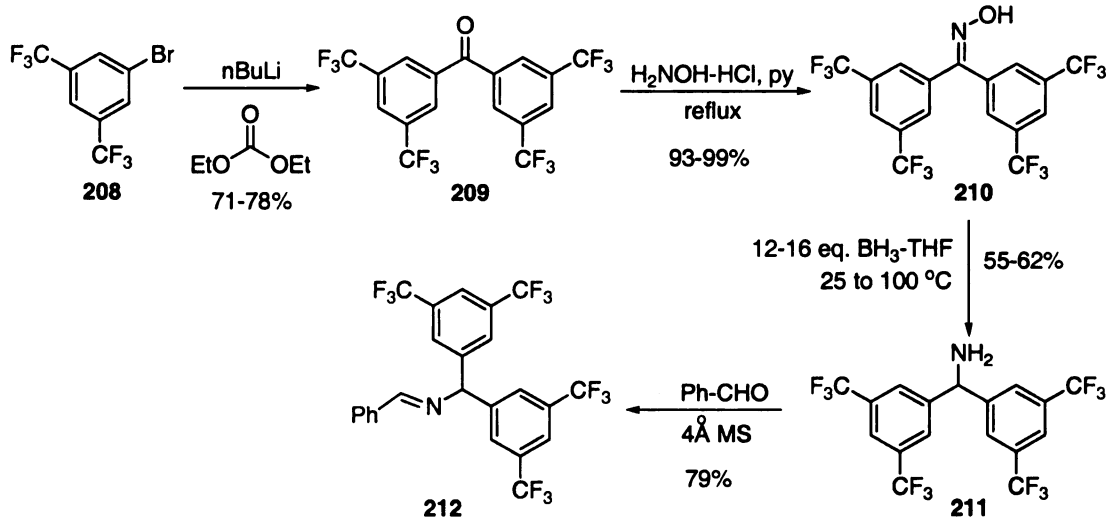
Scheme 6.11 Synthesis of N-MEDAM imine **207**



The synthesis of 3,3',5,5'-tetramethyl-4,4'-dimethoxyl benzhydrylamine **206** (Scheme 6.11) followed the same addition-reduction protocol as the preparation of amine **189-191** (Scheme 6.7). It was found that the preparation of Grignard reagent **205** required

refluxing **203** and Mg^0 in THF as no reaction was observed in ether. The Grignard addition of **205** to benzonitrile **204** followed by the in-situ LAH reduction occurred smoothly and the desired N-MEDAM amine **206** was isolated in excellent yield.

Scheme 6.12 Synthesis of 3,3',5,5'-tetra-trifluoromethyl benzhydryl imine **212**



The preparation of tetra-trifluoromethyl benzhydrylamine **211** was much more difficult than originally anticipated. Several conditions such as the addition of a Grignard reagent prepared from **208** to a benzonitrile followed by LAH reduction of the resulting iminium salt, the Leukart reaction of ketone **209** followed by hydrolysis of the amide, mesylation-amination of a benzhydrol which was prepared from **208** (not shown) all failed to yield any desired product. After numerous attempts, a method to prepare amine **211** was finally developed (Scheme 6.12). In the event, bromobenzene **208** was subjected to lithium-halide exchange and the resulting aryllithium was added to diethyl carbonate to furnish benzophenone **209** in 71-78% yield.[71a] Ketone **209** was transformed into oxime **210** by the condensation with hydroxylamine in pyridine.[71b] After the screening of several

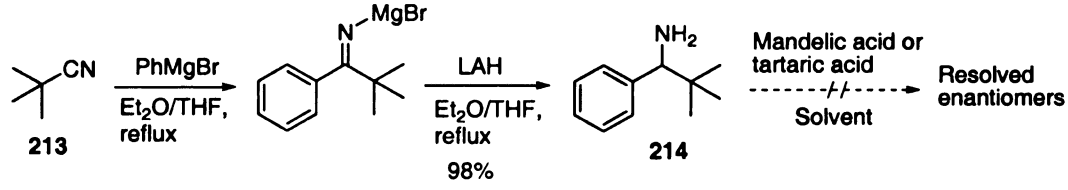
reducing reagents including $NaBH_4/TiCl_4$, Zn/NH_3-H_2O, H_2/Pd and $LiAlH_4$, it was found that a large excess of BH_3-THF complex was the only reagent which could give the desired amine **211** in good yield.[72]

On the other hand, the condensation of amine **211** with benzaldehyde was very sluggish in the presence of the standard drying reagent $MgSO_4$. A stronger drying reagent was required and it was found that 4Å molecular sieve was more efficient and gave the desired imine **212** in good yield within 24 hours. The slow condensation was probably due to the diminished nucleophilicity of the amine nitrogen induced by the strong electron-withdrawing groups. The molecular sieve may also serve as a Lewis acid catalyst to activate the carbonyl of the benzaldehyde and accelerate the condensation.

6.2.2 Preparation of chiral imines

The preparation of racemic α-*tert*-butylbenzylamine **214** involved addition of phenyl magnesium bromide to trimethylacetonitrile **213** followed by in-situ LAH reduction (Scheme 6.13), which gave amine **214** in quantitative isolated yield.

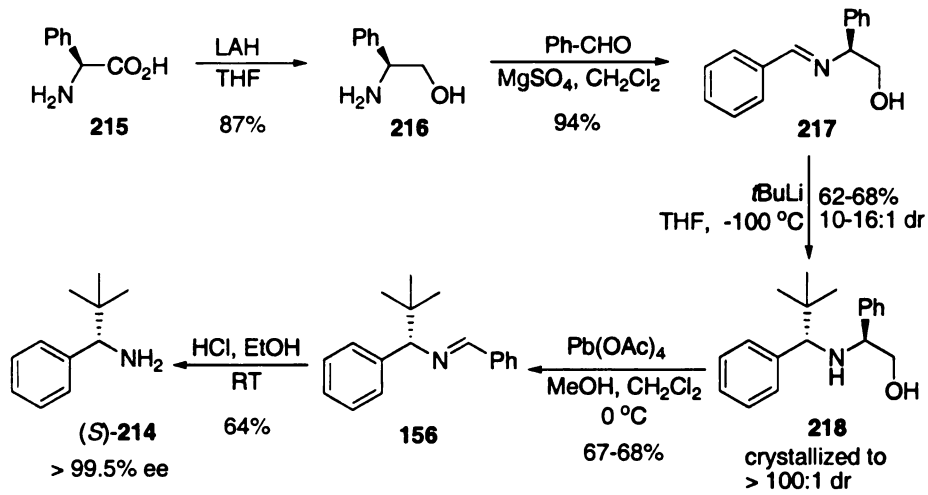
Scheme 6.13 Attempted resolution of α-*tert*-butylbenzylamine **214**



The resolution of amine **214** followed the method reported for the resolution of 1-phenylethylamine.[73] This method used mandelic acid as resolving reagent and water as

solvent. However, applying the same conditions, crystallization always produced crystals that contained equal amounts of the diastereoisomeric salts. Different solvent systems including EtOH/H_2O, EtOAc, MeOH, CH_2Cl_2 and acetone were examined for the selective crystallization of the diastereomeric salts derived from either mandelic acid or tartaric acid, but all attempts failed to produce a successful resolution.

Scheme 6.14 Synthesis of chiral α-*tert*-butyl benzyl amine **214**

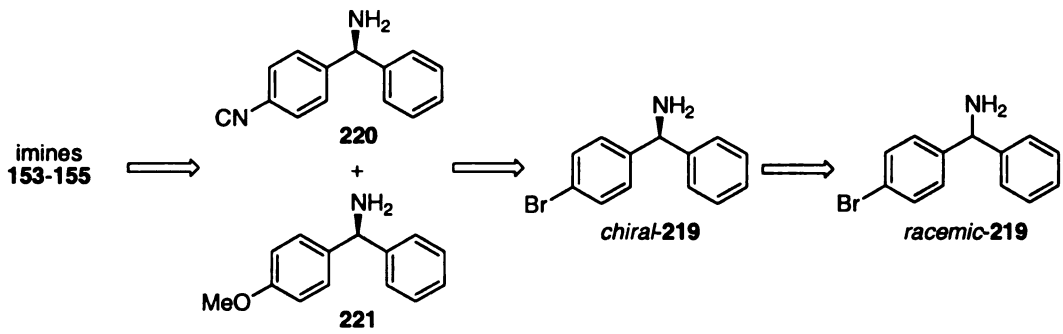


Subsequently, a chiral-auxiliary based asymmetric synthesis was employed for the preparation of optically pure **214** (Scheme 6.14). The chiral auxiliary, (*S*)-2-phenylglycinol **216**, was prepared from the inexpensive D-phenylglycine **215** by LAH reduction.[74] Upon condensation with benzaldehyde, imine **217** was isolated in good yield. The addition of *tert*-butyl lithium to imine **217** at low temperature (-100 °C)[75] afforded a mixture of diastereoisomers of amino alcohol **218** in a 10-16 to 1 ratio. The two isomers could be separated by silica gel chromatography, and the desired major isomer **218** was isolated in 62-68% yield with enriched dr. The diastereopurity of **218** was further improved to >100:1

by crystallization from ethyl acetate and hexane. Subsequent lead tetraacetate mediated oxidation[75c] of amino alcohol **218** afforded the desired chiral imine **156**, which upon crystallization could be used in asymmetric aziridinations. Acid hydrolysis of **156** afforded the chiral amine *S*-**214**, whose enantiomeric excess was determined by chiral HPLC analysis to be > 99.5% ee.

The chiral benzhydryl imines **153-155** (Scheme 6.5) should all be preparable from one starting material, 4-bromobenzhydrylamine **219** (Scheme 6.15). It was envisioned that amine **220** and **221** could be synthesized from the chiral amine **219** via C-C and C-O coupling reactions. The synthesis and resolution of one compound will be easier and cheaper to perform. Since the resolution of chiral amines of this type has been reported to involve multiple recrystallizations,[63] this was expected to be the most difficult step. It would thus be desirable to first resolve **219**, and then convert it to the optically active imines **153-155**.

Scheme 6.15 Planned synthesis of chiral amines

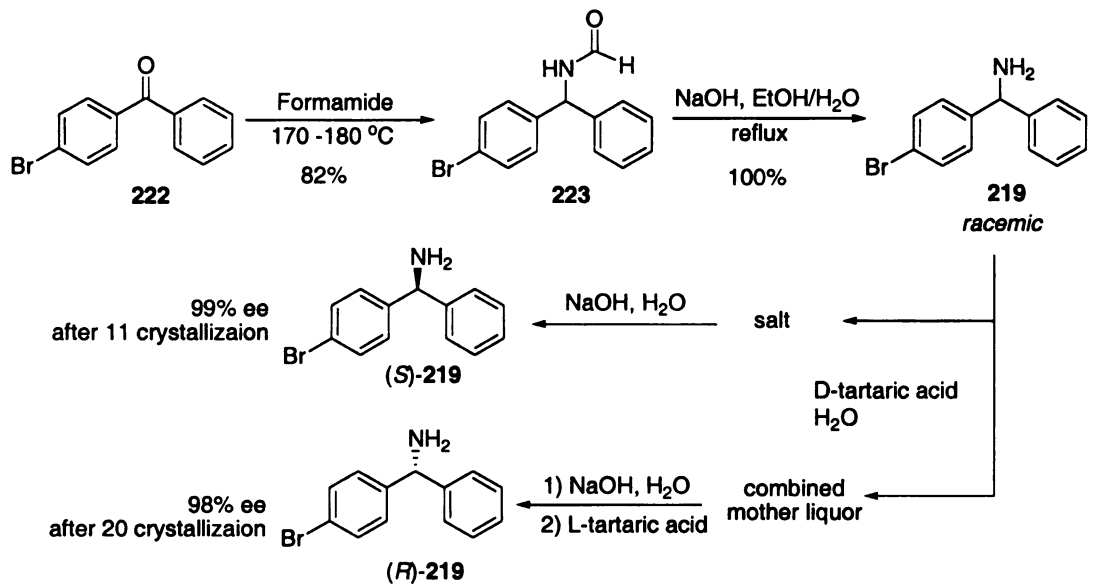


The reported preparation of **219** involved Leukhart reaction of 4-bromobenzophenone **222** with formamide followed by hydrolysis to afford racemic **219**.[63] Other possible routes

were also examined to find which would be the most efficient method. However, it was quickly found that the direct reductive amination of ketone **222** using $NaCNBH_3$, NH_4OAc and CSA only afforded **219** in low yield. The reduction of oxime derived from **222** also failed.

As a result, the original reported method for the preparation of **219** was adopted (Scheme 6.16).[63] Ketone **222** was heated with formamide at 170-180 °C for 18 hours, which afforded N-formyl-amide **223** in 82% yield after two crystalizations. The reported hydrolysis condition involves acid hydrolysis of the amide and only gave a 55% yield of the amine **219**. After examining different hydrolysis conditions, it was found that hydrolysis with NaOH in ethanol/H_2O afforded quantitative yield of amine **219**.

Scheme 6.16 Preparation and resolution of chiral amine **219**

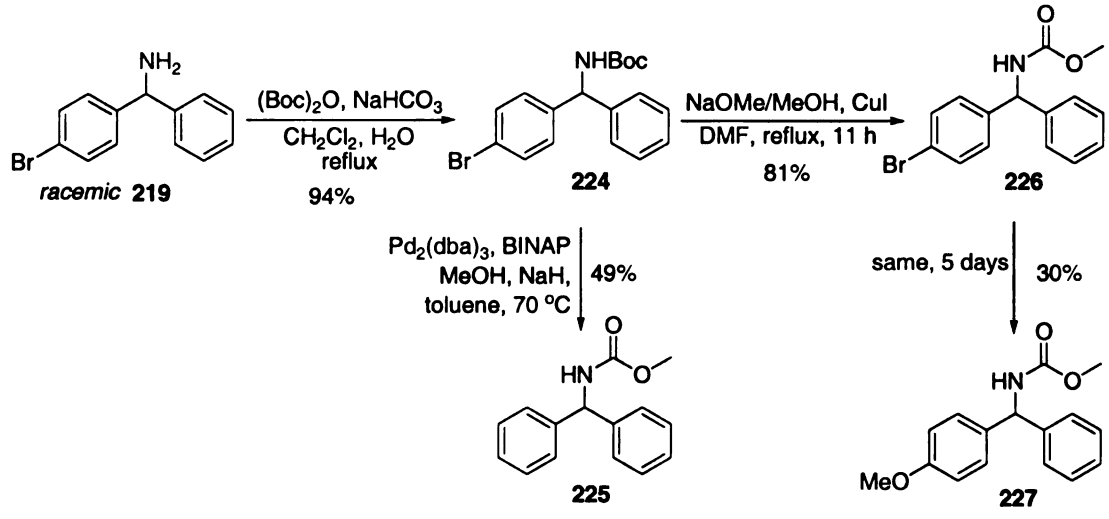


The resolution of amine **219** required multipule recrystallizations with enantiomerically pure tartaric acid. It was found that after four crystallizations with D-tartaric acid, the amine

(*S*)-**219** had only reached 78% ee. After eleven crystallizations, enantiomerically pure (> 99% ee by HPLC analysis) (*S*)-**219** was obtained. After the crystallizaiton of the salt of (*S*)-**219,** the mother liquors containing enriched (*R*)-**219** were combined and concentrated. The free amine was liberated with aqueous sodium hydroxide solution, distilled and then crystallized using L-tartaric acid. The resolution of (*R*)-**219** took even longer. After twenty crystallizations from water, (*R*)-**219** was obtained with 98% ee.

Before the limited quantity of chiral amine **219** was further converted to imines **145-147**, these transformation were first examined with achiral starting material in an attempt to find the optimized conditions.

Scheme 6.17 Attempted synthsis of 4-methoxybenzhydryl amine



The synthesis of 4-methoxy benzhydrylamine **221** started with the protection of the free amino group as it was expected to be imcompatible with the reagents used for the requisite functional group transformations (Scheme 6.17). Protection of amine **219** with $(Boc)_2O$ and $NaHCO_3$ occurred smoothly and afforded N-Boc amine **224** in excellent

yield.[76] The conversion of the aryl bromide to the aryl methyl ether was first attempted by refluxing a DMF solution of **224** with sodioum methoxide in the presence of CuI.[77] After complete consumption of the starting material, protected amine **226** was isolated with the bromo group untouched and the Boc group was converted to a methl carbamate. This is a rather surprising result as the Boc group was expected to be resistant toward the nucleophilic attack of sodium alkoxide. After the amine **226** was heated with same reagents for a much longer time, the corresponding amide **227** was only isolated in low yield.

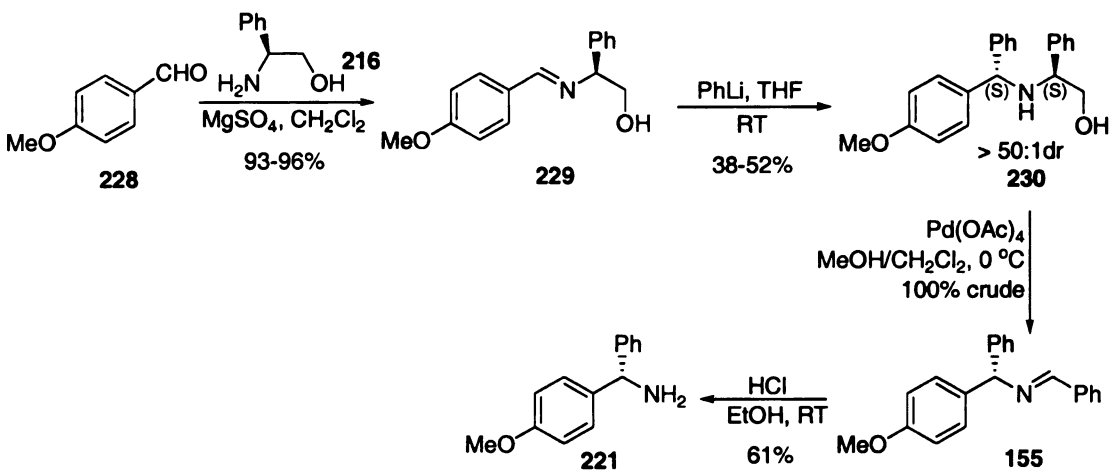
Subsequently, the palladium catalyzed C-O coupling reaction developed by Buchwald et al was examined.[78] In the event, it was found that the catalytic coupling reaction using methanol and sodium hydride only afforded the undesired side product **225**. In this case, not only was the butoxy group on Boc was subtituted by a methoxy group, but dehalogenation also occured presumably due to a β-hydride elimination in an intermediate palladium methoxide complex. Changing MeONa/MeOH to *t*BuONa/toluene (which does not contain β-H) and/or switching the Pd source to $Pd(OAc)_2$ did not afford any isolable product.

After the unsuccessful attempts at the synthesis of 4-methoxy benzhydrylamine **221** from 4-bromobenzhydrylamine **219**, an asymmetric synthesis was utilized for the preparation of amine **221** and imine **155** (Scheme 6.18).

Condensation of 4-methoxylbenzaldehyde **228** with chiral auxiliary **216** afforded imine **229**, which was subjected to phenyl lithium addition. The isolated yield of amino

alcohol **230** was only moderate even after extensive optimization of the reaction temperature. It was surprising to find that only one diastereoisomer of **230** was observed by ^{1}H NMR in the crude reaction mixture even if the PhLi was added at room temperature. Amino alcohol **230** was then oxidized with lead tetraacetate to afford chiral imine **155** in quantitative yield of unpurified product. Acid hydrolysis of **155** gave amine **221** in 61% yield.

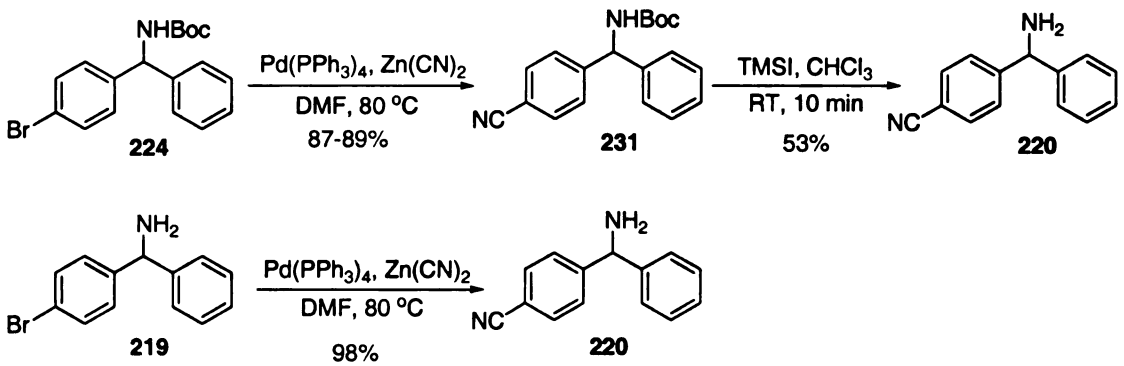
Scheme 6.18 Asymmetric synthesis of amine **221**



The synthesis of 4-cyanobenzhydrylamine **220** started from Boc- protected amine **224** (Scheme 6.19). Typical Rosenmund-von Braun reaction condition[67] which involves refluxing a DMF solution of **224** in the presence of CuCN didn't afford any product, presumably due to the decomposition of starting material at high reaction temperature. An improved Pd-catalyzed C-C coupling procedure[79] using NaCN as cyanide source and CuI as co-catalyst also failed to give any of the desired product **231**. Switching the Pd source from $Pd(PPh_3)_4$ to the more robust $Pd(dppf)Cl_2$ still didn't give any trace of the nitrile **231**. However, when zinc cyanide was used as the cyanide source,[64] the reaction

occurred smoothly with $Pd(PPh_3)_4$ to give the desired product **231** in excellent isolated yields. Deprotection of N-Boc group of **231** using HCl in ether only gave back starting material even after 48 hours. The more active reagent TMSI efficiently removed the Boc group,[80] but the yield of isolated amine **220** was low.

Scheme 6.19 Synthesis of 4-cyanobenzhydryl amine **220**



Subsequently, it was found that the Pd-catalyzed coupling reaction of unprotected amine **219** with zinc cyanide afforded 4-cyanobenzhydrylamine **220** in almost quantitative yield. This result was surprising since the free amino group was expected to coordinate with palladium catalyst and interfere with the catalytic reaction. In any event, this result was rather welcome as synthesis of **220** can now be accomplished without the protection/deprotection sequence.

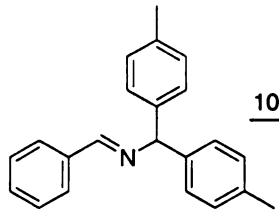
6.3 Study of electronic and steric effects on the catalytic asymmetric aziridination reaction

After the successful synthesis of all the required imine substrates, the stage was set for the exploration of the catalytic asymmetric aziridination reaction on these imines. The electronic and steric effects of the various nitrogen protecting groups will be studied. Due to the significant solvent effects observed in the aziridination reactions of benzhydryl imine **135** (Table 5.8), reactions of all imines will be studied in both CH_2Cl_2 and CCl_4. In addition, some substrates will be examined with catalysts generated from both enantiomers of the chiral ligand to ensure the reproducibility of the reactions.

6.3.1 Electronic effects on the catalytic asymmetric aziridination reaction

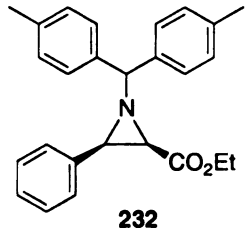
The catalytic asymmetric aziridination reactions of 4,4'-dimethylbenzhydryl imine **161** are presented in Table 6.1. The reactions of imine **161** were generally very stereoselective and the *cis*-aziridine **232** was isolated in higher yields than the reactions of benzhydryl imine **135**. Only very small amounts of *trans*-**232** and enamine products were observed. The chiral inductions of this substrate were found to be slightly higher than those of imine **135**. With CH_2Cl_2 as solvent, the catalyst generated from VAPOL and VANOL gave 90.5% ee and 91.5% ee, respectively. Slightly higher inductions were observed with CCl_4 as solvent, with the VAPOL-borate and the VANOL-borate catalysts giving 95% ee and 93.5% ee, respectively.

Table 6.1 Aziridination of 4,4'-Dimethylbenzhydryl imine **161**

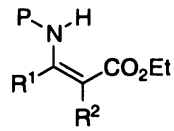


161

1.1 equiv. EDA
10 mol% ligand-borate
solvent, RT, 24 h



232



233/234
233: R^1=H, R^2=Ph
234: R^1=Ph, R^2=H
P = 4,4'-dimethylbenzhydryl

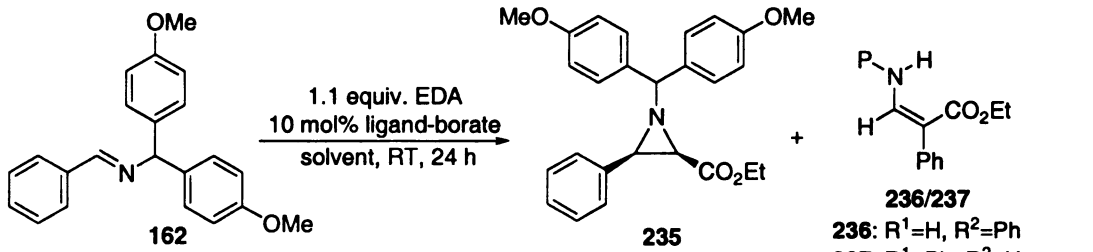
entry[a]	ligand	solvent	yield of **232** (%)[b]	ee of **232**(%)[c]	*cis*:*trans*-**232**[d]	yield of **233/234** (%)[d]
1	*S*-VAPOL	CH_2Cl_2	82	92	>50:1	<1/<1
2[e]	*R*-VAPOL	CH_2Cl_2	80	89	>50:1	<1/<1
3	*S*-VAPOL	CCl_4	85	95	>50:1	<1/<1
4[e]	*R*-VAPOL	CCl_4	88	94	>50:1	<1/<1
5	*S*-VANOL	CH_2Cl_2	80	90	>50:1	1/<1
6	*R*-VANOL	CH_2Cl_2	88	93	>50:1	1/<1
7	*S*-VANOL	CCl_4	92	92	>50:1	1/<1
8	*R*-VANOL	CCl_4	95	95	>50:1	1/<1

[a] Unless otherwise specified, all the reactions were run in the indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5 M. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral HPLC on a Chiralpak AD column. [d] Determined by ^{1}H NMR on the crude reaction mixture, see experimental for details [e] Results are the average of two runs.

The reactions of the more electronically rich 4,4'-dimethoxybenzhydryl imine **162** (Table 6.2) gave slightly higher chiral induction than its dimethylbenzhydryl analogue **161** (Table 6.1). The reactions in CH_2Cl_2 gave aziridine **235** in 90% ee and 92.5% ee with the VAPOL and VANOL-borate catalysts, respectively. With CCl_4 as solvent, the catalysts generated from VAPOL and VANOL resulted in aziridine **235** with 93.5% ee and 94.5%

ee, respectively. The reactions performed in CCl_4 and the reactions with the VANOL-borate catalyst were generally more rapid, since the bubbling due to the loss of N_2 was more vigorous for these reactions after the addition of ethyl diazoacetate to the mixture of imine and catalyst.

Table 6.2 Aziridination of 4,4'-Dimethoxybenzhydryl imine **162**



entry[a]	ligand	solvent	yield of **235** (%)[b]	ee of **235** (%)[c]	*cis/trans*-**235**[d]	yield of **236/237**(%)[d]
1	*S*-VAPOL	CH_2Cl_2	78	90	>50:1	3/2
2	*R*-VAPOL	CH_2Cl_2	85	90	>50:1	<1/<1
3	*S*-VAPOL	CCl_4	85	94	>50:1	3/2
4	*R*-VAPOL	CCl_4	89	93	>50:1	--/2
5	*S*-VANOL	CH_2Cl_2	91	93	>50:1	<1/<1
6	*R*-VANOL	CH_2Cl_2	89	92	>50:1	3/<1
7	*S*-VANOL	CCl_4	93	95	>50:1	<1/<1
8	*R*-VANOL	CCl_4	89	94	>50:1	<1/<1

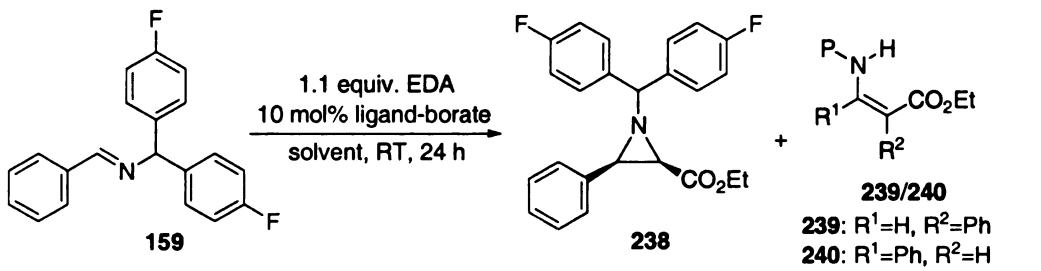
[a] Unless otherwise specified, all the reactions were run in the indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5M. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral HPLC on a Chiralpak AD column. [d] Determined by ^1H NMR on the crude reaction mixture, see experimental for details.

Recently, Ms. Zhenjie Lu found that the 4,4'-dimethoxybenzhdryl group on aziridine **235** could be removed by an efficient acid-mediated deprotection.[81] This discovery is of

great synthetic value as the only published procedure for the cleavage of the N-benzhydryl group on the C3-aryl aziridines involves ozonolysis conditions and suffers from low to moderate yields.[82] It was found that in the presence of TfOH or TFA/H_2SO_4 with anisole as solvent, the dimethoxybenzhydryl group on aziridine **235** could be readily cleaved, and the resulting N-H aziridine could be isolated in excellent yield. The feasibility of this deprotection can be attributed to the combined inductive and resonance effects of the two *para*-methoxy groups, which efficiently stabilize the incipient dimethoxy benzhydryl cation.

Next, the aziridinations of the electron-deficient substrates were conducted. The reactions of the 4,4'-difluorobenzhydyl imine **159** gave almost identical chiral inductions as the unsubstituted benzhydryl imine **135**. The catalysts generated from VAPOL and VANOL gave 88% ee and 91% ee in CH_2Cl_2, respectively. As was seen with other imines, the chiral inductions in CCl_4 were higher, with 93% ee and 93.5% ee measured for the VAPOL and VANOL-borate catalysts, respectively.

Table 6.3 Aziridination of 4,4'-Difluorobenzhydryl imine **159**

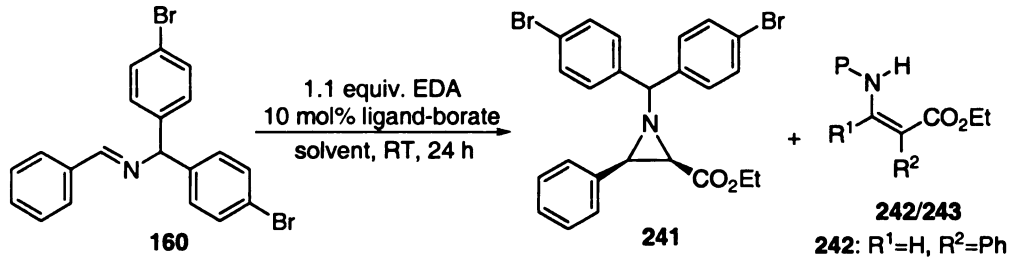


entry[a]	ligand	solvent	yield of **238** (%)[b]	ee of **238** (%)[c]	*cis*:*trans*-**238**[d]	yield of **239/240** (%)[d]
1	*S*-VAPOL	CH_2Cl_2	70	88	>50:1	2/<1
2	*R*-VAPOL	CH_2Cl_2	89	88	>50:1	3/<1
3	*S*-VAPOL	CCl_4	73	93	>50:1	<1/<1
4	*R*-VAPOL	CCl_4	<90[e]	94	>50:1	2/<1
5	*S*-VANOL	CH_2Cl_2	89	92	>50:1	<1/<1
6	*R*-VANOL	CH_2Cl_2	89	90	>50:1	2/<1
7	*S*-VANOL	CCl_4	<90[e]	93	>50:1	<1/<1
8	*R*-VANOL	CCl_4	83	94	>50:1	2/<1

[a] Unless otherwise specified, all reactions were run in the indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5M. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC on a Chiralpak AD column. [d] Determined by ^1H NMR on the crude reaction mixture. [e] The isolated product was contaminated with a small amount of an unknown impurity.

The aziridination of the 4,4'-dibromobenzhydryl imine **160** (Table 6.4) also gave very similar results with regard to chiral induction and yield when compared with the reactions of difluorobenzhydryl imine **159** (Table 6.3).

Table 6.4 Aziridination of 4,4'-dibromobenzhydryl imine **160**



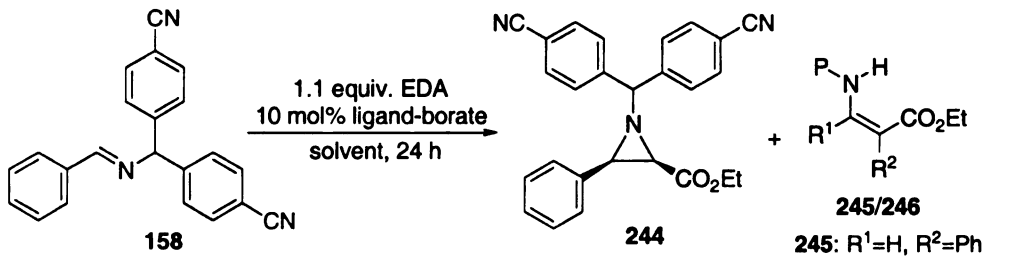
entry[a]	ligand	solvent	yield of **241**(%)[b]	ee of **241** (%)[c]	*cis*:*trans*-**241**[d]	yield of **242/243** (%)[d]
1	*rac*-VAPOL	CCl_4	78	--	>50:1	3/3
2	*S*-VAPOL	CH_2Cl_2	80	88	>50:1	2/2
3	*S*-VAPOL	CCl_4	85	93	>50:1	1/1
4	*S*-VANOL	CH_2Cl_2	81	91	>50:1	2/1
5	*S*-VANOL	CCl_4	83	93	>50:1	1/1

[a] Unless otherwise specified, all reactions were run in indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5M. [b] Isolated yield from chromatography on silica gel. [c] Determined by chiral HPLC on a Chiralcel OD-H column. [d] Determined by ^{1}H NMR on the crude reaction mixture.

As discussed in section 6.2.1 (Scheme 6.5), the 4,4'-dicyanobenzhydryl imine **158** could not be purified and was used as the crude product. In the event, the reactions of **158** under standard condition afforded the desired product **244** in excellent yield, however inferior chiral inductions were observed (Table 6.5). The effect of solvents on the reactions of this substrate was negligible. The same reactions run at 0 °C did give improved yields over those at room temperature but the induction only increased by 1-2% ee. The unexpected low level of chiral inductions for this substrate will be discussed later

in this chapter. On the other hand the possible detrimental effect of the small amount of impurities in the unpurified imine **158** could also contribute to the inferior chiral induction.

Table 6.5 Aziridination of 4,4'-Dicyanobenzhydryl imine **158**



entry[a]	ligand	temp (°C)	solvent	yield of **244**(%)[b]	ee of **244**(%)[c]	*cis*:*trans*-**244**[d]	yield of **245/246**(%)[d]
1	*S*-VAPOL	25	CH_2Cl_2	83	79.5	33:1	6/4
2	*R*-VAPOL	25	CH_2Cl_2	81	78.5	30:1	3/2
3	*S*-VAPOL	25	CCl_4	88	81	>50:1	3/2
4	*S*-VAPOL	0	CH_2Cl_2	89	82	30:1	4/3
5	*S*-VAPOL	0	CCl_4	95	81	>50:1	4/2

[a] Unless otherwise specified, all reactions were run in indicated solvent containing 1.0 mmol unpurified imine at room temperature, concentration of imine was 0.5M. [b] Isolated yield from chromatography on silica gel. [c] Determined by chiral HPLC on Chiralpak AD column. [d] Determined by ^{1}H NMR on the crude reaction mixture, see experimental for details

The results of the electronic effects studies described above are summarized in Figure 6.9 and Figure 6.10 in which the chiral inductions are plotted as a function of the substituent. The reactions with the catalyst generated from VAPOL displayed very similar trends to those with the VANOL catalyst. With the exception of the nitrile substituent, the imines with electron-withdrawing groups generally produced similar or slightly higher chiral inductions than the unsubstituted benzhydryl imine **135**, whereas the imines with

the electron-donating group always gave higher selectivity. The lower induction with the nitrile substituted imine **158** may be associated with the fact that this imine could not be purified.

Figure 6.9 Study of electronic effects with the VAPOL-borate catalyst

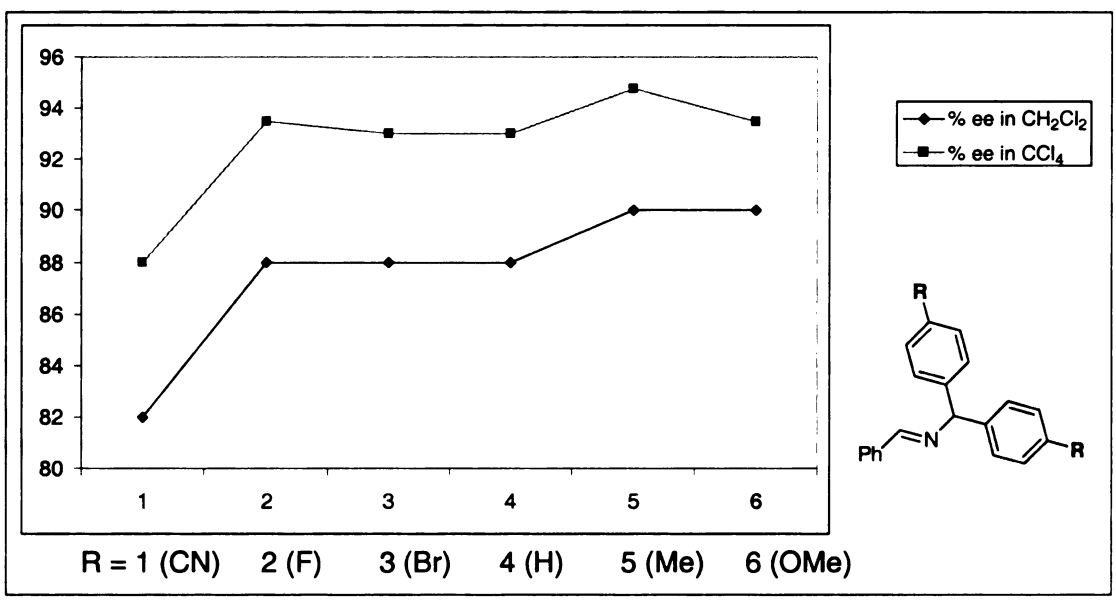
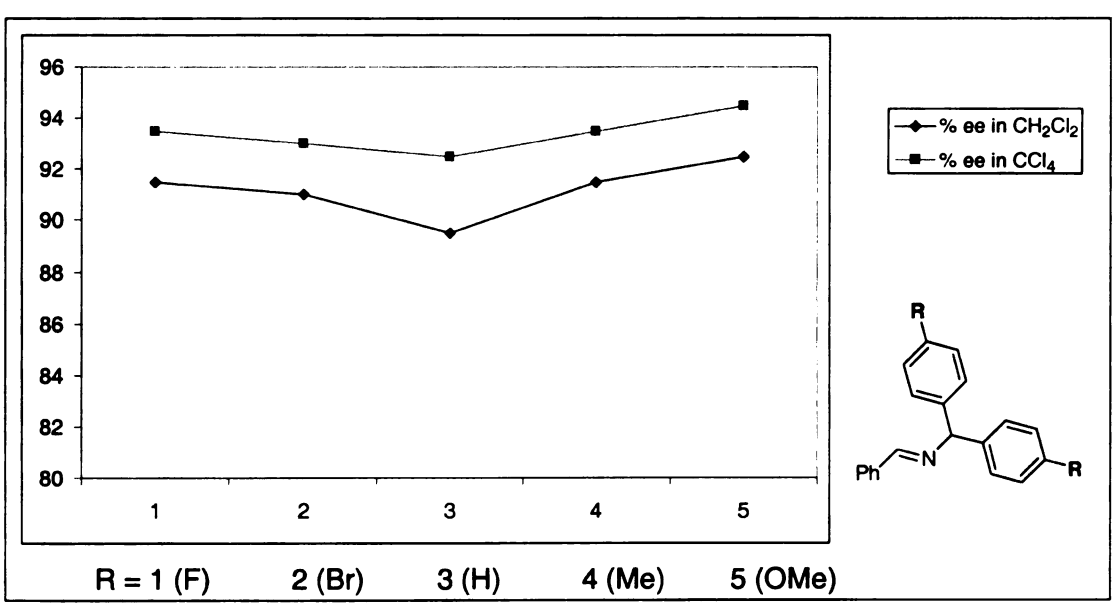


Figure 6.10 Study of electronic effects with the VANOL-borate catalyst



As discussed in section 6.1.3, Wicox's model for CH-π interactions (Scheme 6.2) revealed that electron-withdrawing groups on the edge ring lead to greater edge-face interactions, whereas, no effect was seen on the face ring.[58] In addition, Wilcox's model showed no effect for an electron-donating group on either the edge or face rings. Therefore, Wilcox's model would predict that the electron-deficient imines **158-160** would bind more tightly to the catalyst and lead to higher inductions, while this model also predicts that the electron-rich imines **161** and **162** should give the same selectivity as the unsubstituted **135**. According to other experimental and recent theoretical studies,[59-62] the two electron-deficient phenyl rings would act independently as one edge ring (increased interaction) and one face ring (decreased interaction), and as a result, the two opposing effects would result in very small changes in the stabilization energy and thus the asymmetric induction. The results of the substituent effect observed with both VAPOL and VANOL-borate catalysts are very close to the prediction based on the studies of Suezawa, Hunter, Sherill and Kim et al[59-62], but in any event these results do not agree with Wilcox's suggestion.[58]

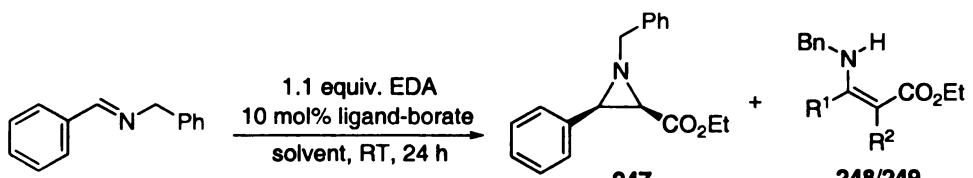
In considering an analysis of the above results, one should not neglect the fact that the 4,4'-substituents could also effectively change the electronic property on the imine nitrogen. Two electron-withdrawing groups would undoubtedly reduce the electron density on the imine nitrogen, and as a result, the coordination of the nitrogen with the Lewis acid would be weakened. On the other hand, the diminished electron density of the C=N double bond may also accelerate the nucleophilic attack of ethyl diazoacetate. At

this stage, it is not clear which effect will dominate the stereo-genic step of the aziridination reaction. Related studies and discussion will be presented in section 6.5.

6.3.2 Study of the effects of sterics and conformational constraints on the imine nitrogen substituent

N-Benzyl imine **168** was prepared from benzyl amine and its reactivity in the catalytic asymmetric aziridination was studied since it lacks one of the phenyl rings of the benzhydryl group and thus it cannot have two edge-face interactions with the catalyst. Thus, it was anticipated that imine **168** would give much lower selectivities than the benzhydryl imine.

Table 6.6 Aziridination of N-benzyl imine **168**



168 **247** **248/249**

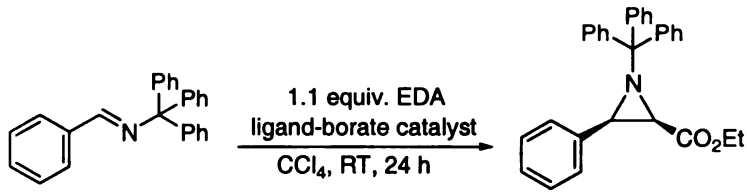
248: R^1=H, R^2=Ph
249: R^1=Ph, R^2=H

entry[a]	ligand	solvent	yield of **247**(%)[b]	ee of **247**(%)[c]	*cis*:*trans* **247**[d]	yield of **248/249**(%)[d]
1	*rac*-VAPOL	CH_2Cl_2	44	--	9-10:1	4/4
2	*S*-VAPOL	CH_2Cl_2	51	43	25:1	5/7
3[e]	*S*-VAPOL	CCl_4/CH_2Cl_2 (4:1)	54	48	12:1	5/6

[a] Unless otherwise specified, all reactions were run in indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5 M. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC on a Chiralpak OD-H column. [d] Determined by ^{1}H NMR on the crude reaction mixture. [e] Concentration of imine was 0.2 M.

In the event, the aziridination reaction of **168** furnished the desired aziridine **247** in moderate yield with 100% conversion (Table 6.6), and as expected the asymmetric inductions (~45% ee) were much lower than those for the benzhydryl imine **135**. Significantly more *trans*-aziridine and enamine products were observed than in the reaction of the benzhydryl imine **135**. The reaction in CCl_4/CH_2Cl_2 mixed solvent was performed at slightly lower concentration due to the reduced solubility of the imine-catalyst complex in pure CCl_4.

Table 6.7 Aziridination using N-trityl imine **169**



169 **250**

entry[a]	catalyst & loading	conversion (%)[b]
1	10 mol% VAPOL-borate	7
2	30 mol% VAPOL-borate	9-11
3	30 mol% VANOL-borate	9-10

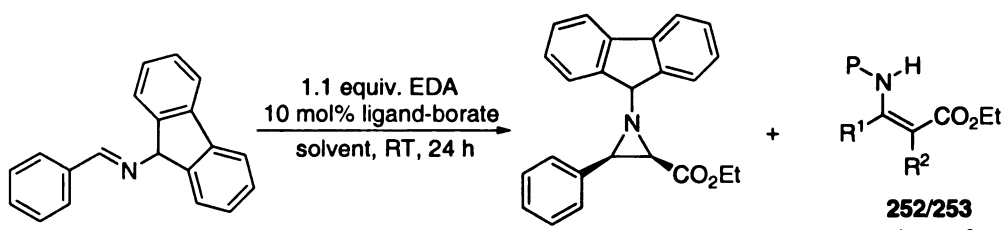
[a] Unless otherwise specified, all reactions were run in indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5 M. [b] Determined by ^1H NMR on the crude reaction mixture.

It was found that the aziridination of the sterically bulky N-trityl imine **169** was extremely sluggish. Only 9-10% conversion was observed even in the presence of 30 mol% VANOL-borate catalyst. Thus for this substrate, the bulky N-trityl group must significantly interfere with the coordination between the imine nitrogen and the chiral

Lewis acid. Due to the low reactivity of **169**, its aziridination reactions were not studied further.

The N-9-fluorenyl imine **164** has two benzene rings as does the N-benzhydryl imine **135**. However, because the two rings are directly connected, the planar N-9-fluorenyl group cannot participate in two edge-face interactions with the ligand in the catalyst.

Table 6.8 Aziridination of N-9-fluroenyl imine **164**



164 **251** **252/253**

252: R^1=H, R^2=Ph
253: R^1=Ph, R^2=H
P = 9-fluoroenyl

entry[a]	ligand	concn (M)	solvent	yield of **251**(%)[b]	ee **251**(%)[c]	*cis*:*trans* **251**[d]	yield of **252/253**(%)[d]
1	*rac*-VAPOL	0.5	CH_2Cl_2	53	--	50:1	8/2
2	*S*-VAPOL	0.5	CH_2Cl_2	64	80	50:1	11/6
3	*S*-VAPOL	0.25	CCl_4	58	81	50:1	--[e]

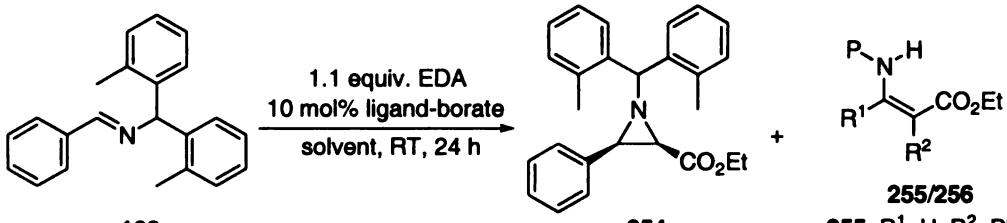
[a] Unless otherwise specified, all reactions were run in the indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5 M. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC analysis on a Chiralpak AD column. [d] Determined by ^{1}H NMR on the crude reaction mixture. [e] Enamine signals obscured by unknown peaks.

The reaction of imine **164** did produce the desired aziridine **251** but only in moderate yield. The observed asymmetric inductions were approximately 10% lower than those from benzhydryl imine **135**. On the other hand, the asymmetric inductions were significantly higher than those with the N-benzyl imine **168**. CPK models suggest that it is

possible that the imine-catalyst complex could be stabilized by one face-edge interaction and one face-face interaction.

The benzhydryl imine **166** which bears two *ortho*-methyl groups was studied to probe the effects of sterics and possible conformational differences with of the benzhydryl group. The two methyl groups may change the dihedral angles of the two benzene rings and thus either increase or decrease any possible face-edge interactions with the catalyst.

Table 6.9 Aziridination of 2,2'-dimethylbenzhydryl imine **166**



166 **254** **255/256**

255: R^1=H, R^2=Ph
256: R^1=Ph, R^2=H

P = 2,2'-dimethyl benzhydryl

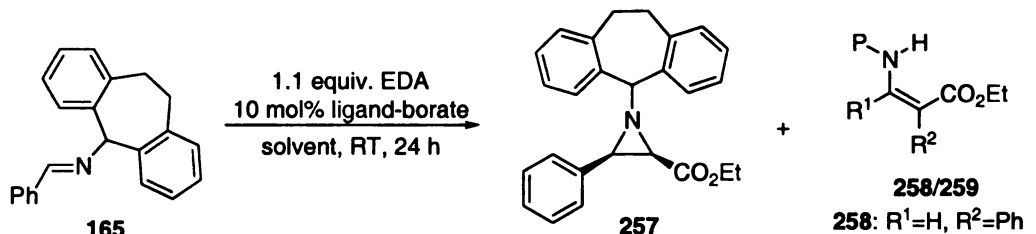
entry[a]	ligand	solvent	yield of **254**(%)[b]	ee of **254** (%)[c]	*cis*:*trans*-**254**[d]	yield of **255/256**(%)[d]
1	*rac*-VAPOL	CH_2Cl_2	60	--	30:1	4/2
2	*S*-VAPOL	CH_2Cl_2	63	86	50:1	8/3
3	*S*-VAPOL	CCl_4	67	90	50:1	5/1

[a] Unless otherwise specified, all reactions were run in the indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5 M. [b] Isolated yield after chromatography on silica gel. [c] Determined by HPLC on a Chiralcel OD-H column. [d] Determined by ^{1}H NMR on the crude reaction mixture, see experimental for details.

The results of the catalytic asymmetric aziridination of imine **166** are shown in Table 6.9 and it was revealed to have comparable asymmetric induction as the benzhydryl

imine **135**, although the isolated yields were about 15% lower. CPK modeling of imine **166** suggests that the two methyl groups may project away from the ligand via rotation of the phenyl ring, and as a result, the methyl groups may not directly interfere with any face-edge interactions, and may not significantly change the conformation of the aryl groups.

Table 6.10 Aziridination of N-dibenzosuberonyl imine **165**



165 **257** **258/259**

258: R^1=H, R^2=Ph
259: R^1=Ph, R^2=H
P = dibenzosuberonyl

entry[a]	ligand	solvent	yield of **257** (%)[b]	ee of **257** (%)[c]	yield of **258/259** (%)[d]
1	*S*-VAPOL	CH_2Cl_2	75	95	5/1
2	*S*-VAPOL	CCl_4	84	96.5	2/3
3	*R*-VAPOL	CH_2Cl_2	75	95	2/1
4	*R*-VAPOL	CCl_4	82	96	4/1

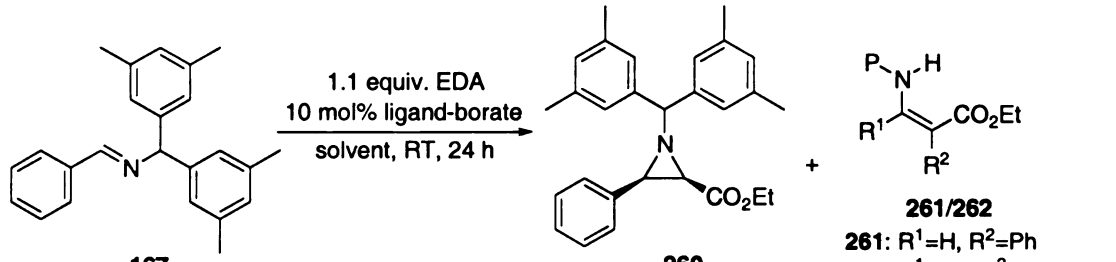
[a] Unless otherwise specified, all reactions were run in the indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5 M. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC analysis on a Chiralcel OD-H column. [d] Determined by ^{1}H NMR on the crude reaction mixture, see experimental for details. The cis/trans ratio of the aziridine was obscured by signals of conformational isomers of the product.

Surprisingly, the reaction of the N-dibenzosuberonyl imine **165** gave higher asymmetric inductions than the benzhydryl imine. The aziridine **257** was isolated from the reactions in CH_2Cl_2 in 95% ee. Based on the time required for color changes during the

reaction, it did not appear that **165** reacted faster than benzhydryl imine **135**. Upon switching the solvent to CCl_4, the improvement in the enantioselectivity was very small, although the isolated yield increased by 7-9%. The reason why substrate **165** gives better asymmetric induction is not understood, but the fact itself is curious, since the steric bulkiness of **165** should be similar to that of benzhydryl imine **135**. CPK modeling didn't provide much insight into the enhanced selectivity. It is suspected that the $-CH_2CH_2-$ tether between the two phenyl rings locks the conformation of the two phenyl groups at an angle that better accommodates an edge-face interaction with the ligand. However, due to the difficulty in the preparation of dibenzosuberonyl amine from the dibenzosuberone (Scheme 6.10), this discovery is unlikely to be adopted into further developments of this aziridination methodology.

The last substrate examined was the 3,3',5,5'-tetramethylbenzhydryl imine **167**. Wilcox's experimental data indicated that the 3,5-dimethyl groups on the edge ring of his molecular torsion balance would disfavor the CH-π interaction (Scheme 6.2).[57] CPK modeling of imine **167** docking with the VAPOL-BH catalyst also indicated that by placing two *meta*-methyl groups on each benzene ring, one of the methyl groups on the edge ring will point toward the face ring of VAPOL. It was thus expected that one of the desired edge-face interactions between this substituted phenyl ring of the benzhydryl group and the ligand arene system would be disrupted, resulting in diminished asymmetric induction in the aziridination.

Table 6.11 Aziridination of 3,3',5,5'-tetramethylbenzhydryl imine **167**



167 **260** **261/262**

261: R^1=H, R^2=Ph
262: R^1=Ph, R^2=H
P = 3,3',5,5'-tetramethylbenzhydryl

entry[a]	ligand	solvent	yield of **260** (%)[b]	ee of **260** (%)[c]	*cis*:*trans*-**260**[d]	yield of **261/262**(%)[d]
1	*rac*-VANOL	CH_2Cl_2	86	--	>50:1	<1/<1
2	*S*-VAPOL	CH_2Cl_2	89	95	>50:1	<1/<1
3	*S*-VAPOL	CCl_4	94	98	>50:1	<1/<1
4	*R*-VAPOL	CH_2Cl_2	91	95.5	>50:1	<1/<1
5	*R*-VAPOL	CCl_4	94	97.5	>50:1	<1/<1

[a] Unless otherwise specified, all reactions were run in the indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5 M. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC analysis on a Chiralcel OD-H column. [d] Determined by ^{1}H NMR on the crude reaction mixture, see experimental for details.

It was most surprising to find that the imine **167** not only reacted efficiently with 10 mol% of VAPOL-borate catalyst to furnish the desired aziridine **260** in excellent yield, but this imine also afforded the highest asymmetric induction ever observed for any of the substrates that have been examined. The asymmetric induction is 95% ee in CH_2Cl_2 and 98% ee in CCl_4, and minimal amounts of the *trans*-aziridine and enamine products were observed. This was indeed an unexpected yet much welcomed result. Obviously, the *meta*-methyl groups are not interfering with the proposed edge-face interaction, leading

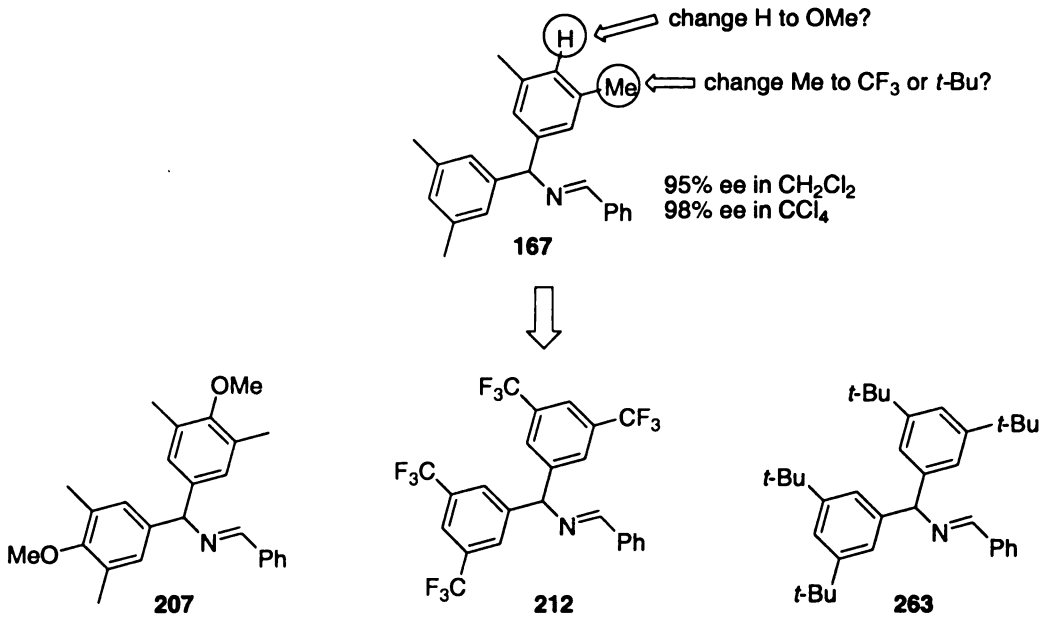
to lower inductions, but rather, they must somehow be enhancing the catalyst-imine association.

The possibility of an acid-mediated cleavage of this tetramethylbenzhydryl group was explored, since the four electron-donating methyl groups may contribute to the formation of a sufficiently stable benzhydryl cation and thus facilitate an acid-mediated deprotection. It was found that when aziridine **260** was subjected to the same conditions[81] for the deprotection of dimethoxybenzhydryl group in aziridine **235**, the two best conditions (TfOH and TFA/H_2SO_4, both with anisole as solvent) only resulted in complete decomposition of **260**.

The surprising discovery of the enhanced selectivity with 3,3',5,5'-tetramethylbenzhydryl imine **167** prompted a re-investigation of the original proposal for the selectivity of the benzhydryl group (Figure 6.2). One plausible explanation would be that in this system, the methyl group may act as a good π–acceptor which results in an even stronger CH-π interaction with the arene ring of the ligand system than a simple arene-arene interaction. Wilcox indeed suggested that the CH-π interaction of a *tert*-butyl group or *iso*-propyl group with the face ring in his model system (Scheme 6.2) is stronger than the benzene-benzene CH-π interaction and this suggestion was subsequently supported by Houk and Orozo's independent theoretical study.[58,60] However, the CH-π interactions between a methyl group and an arene ring have not been studied by experimental methods. Theoretical calculations suggested that a methane/benzene interaction is approximately 1 kcal/mol weaker than the

benzene/benzene interaction.[50a] On the other hand, Wilcox also suggested that the *iso*-propyl-benzene and *tert*-butyl-benzene are both more favorable interactions than benzene-benzene interaction in his experiments. These observations are consistent with the dominance of dispersion forces in both types of CH-π interactions, since there is more surface contact in a bulky alkyl-phenyl interaction than in a phenyl-phenyl edge-to-face interaction.[57b]

Figure 6.11 Study of CH-π interactions using meta-alkyl benzhydryl group

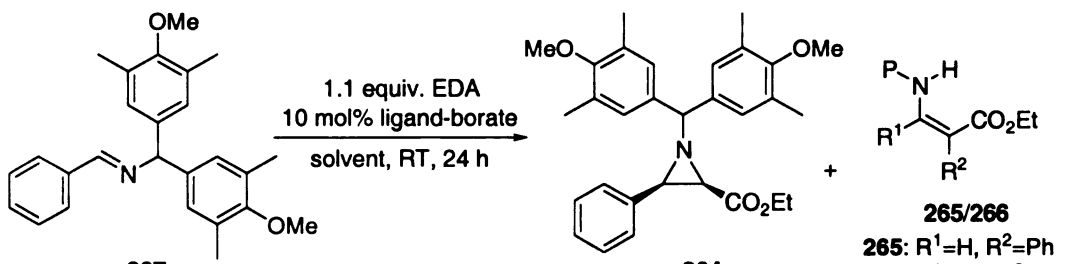


The unexpected effect of the four methyl groups was further explored by the study of the substrates in Figure 6.11. Imine **207** should benefit from the high selectivity of **167**, while the two *para*-methoxy groups should facilitate the acid-mediated deprotection of benzhydryl group, and in addition, may further increase the asymmetric induction as suggested by the study of electronic effect. Imine **263** may in theory result in a stronger alkyl-benzene interaction due to the large surface of the *tert*-butyl group. Finally, the

trifluoromethyl group in imine **212** is sterically similar to the *iso*-propyl group, however, the electron-deficient CF_3 group should significantly change the magnitude of the interaction.

The synthesis of imine **207** and **212** were discussed early in this chapter. The preparation and reaction imine **263** will be discussed in detail in section 6.4 of this chapter.

Table 6.12 Aziridination of 3,3',5,5'-tetramethyl-4,4'-dimethoxybenzhydryl imine **207**



207 **264** **265/266**

265: R^1=H, R^2=Ph
266: R^1=Ph, R^2=H

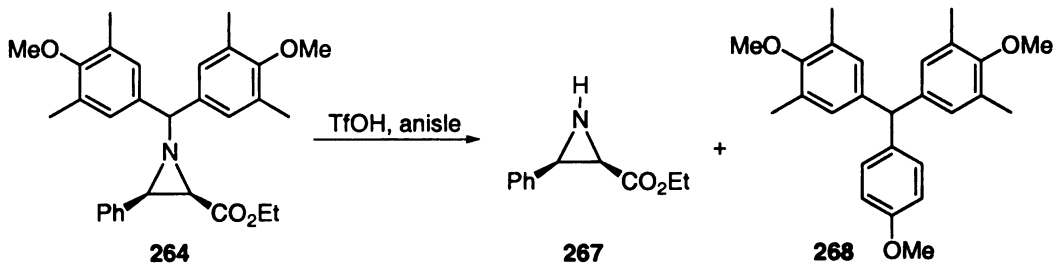
P = 3,3',5,5'-tetramethyl-4,4'-dimethoxybenzhydryl

entry[a]	ligand	solvent	yield of **264** (%)[b]	ee of **264** (%)[c]	*cis*:*trans*-**264**[d]	yield **265/266**[d]
1	*S*-VAPOL	CH_2Cl_2	89	97.5	>50:1	<1/<1
2	*R*-VAPOL	CH_2Cl_2	88	97	>50:1	2/<1
3	*S*-VAPOL	CCl_4	81	99	>50:1	<1/<1
4	*R*-VAPOL	CCl_4	86	98.5	>50:1	<1/<1
5	*S*-VANOL	CH_2Cl_2	93	97	>50:1	<1/<1
6	*R*-VANOL	CH_2Cl_2	88	98	>50:1	<1/<1
7	*S*-VANOL	CCl_4	81	98.5	>50:1	<1/<1
8	*R*-VANOL	CCl_4	91	98.5	>50:1	<1/<1

[a] Unless otherwise specified, all reactions were run in the indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5 M. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC analysis on a Chiralcel OD-H column. [d] Determined by ^{1}H NMR on the crude reaction mixture.

It was gratified to find that the aziridination of imine **207** indeed afforded improved enantioselectivity and yield over both the tetramethyl substituted imine **162** (Table 6.11) and the 4,4'-dimethoxy substituted imine **167** (Table 6.2). The reactions were notably cleaner and more selective than all the imine substrates tested so far. In the presence of 10 mol% catalyst derived from either VAPOL or VANOL, the reactions of imine **207** in CCl_4 gave optically pure aziridine **264** in very good yield.

Table 6.13 Deprotection of 3,3',5,5'-tetramethyl-4,4'-dimethoxybenzhydryl group



264 **267** **268**

entry[a]	equiv. of TfOH	time (h)	conversion (%)[b]	yield of **267** (%)[c]	yield of **268** (%)[c]
1	5	0.5	40	38	
2	5	2	90	83	
3	5	3	100	89	90
4	5	4	100	72	89
5	8	4	100	70	92

[a] Unless otherwise specified, all reactions were run in anisole containing 1.0 mmol **264** at room temperature. [b] Determined by ^1H NMR on the crude reaction mixture. [c] Isolated yield after chromatography on silica gel.

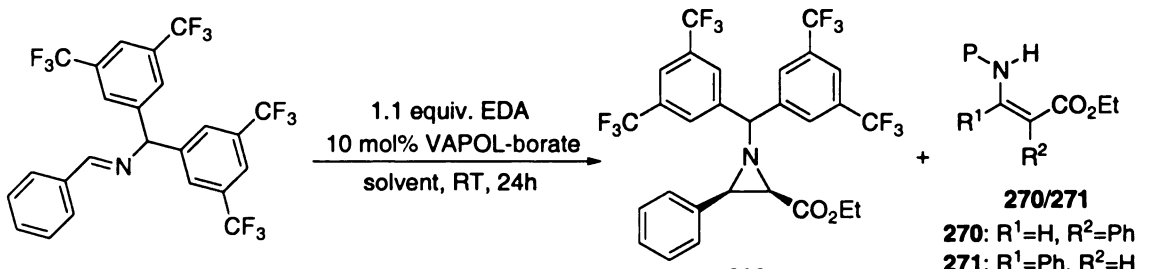
The nitrogen deprotection reaction of aziridine **264** (Table 6.13) was conducted with the same condition for the cleavage of dimethoxybenzhydryl group in **235** (section 6.3.1).[81] It was found that the original procedure developed for the deprotection of **235**

could be applied to aziridine **264** with minor modification. The reaction of **264** was several times slower than that of **235**. After optimization of the time and the number of equivalents of triflic acid, it was found that the best condition involves using anisole as solvent and 5 equivalent of TfOH as cleaving reagent. With these conditions the N-H aziridine **267** could be isolated in 89% yield. The triaryl methane **268** which resulted from the trapping of the benzhydryl carbocation by anisole was also isolated in good yield.

In contrast to the tetramethyl imine **167** (Table 6.11) or the tetramethyldimethoxy imine **207** (Table 6.12), the reactions of the tetra-trifluoromethyl substituted benzhydryl imine **212** were very sluggish (Table 6.14). Standard conditions employing 10 mol% VAPOL-borate catalyst only resulted in 56-67% conversion of imine **212**, and the *cis*-aziridine **269** was isolated and found to be merely 40-60% ee. The reactions with the smaller VANOL catalyst were significantly faster and more selective. Up to 91% ee was observed with the VANOL-borate catalyst in CCl_4, but the conversion was still less than 100%.

The greatly reduced reaction rate for imine **212** is presumably due to one or more of the following reasons: 1) CF_3 group does not interact with the face of the arene ring of the ligand and thus the proposed alkyl-π interaction is interrupted; 2) the four CF_3 groups significantly decrease the electron density on the imine nitrogen, and as a result, the nitrogen is unable effectively coordinate with boron Lewis acid; 3) the considerably increased size of this substituted benzhydryl group causes steric repulsion upon interaction with the ligand thus inhibiting the coordination between nitrogen and boron.

Table 6.14 Aziridination of 3,3',5,5'-tetratrifluromethylbenzhydryl imine **212**



212

269

270/271

270: R^1=H, R^2=Ph

271: R^1=Ph, R^2=H

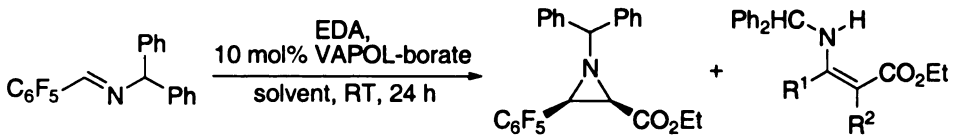
P = 3,3',5,5'-tetra-trifluoro methylbenzhydryl

entry[a]	ligand	solvent	convn (%)[b]	yield of **269**(%)[c]	ee of **269** (%)[d]	*cis*:*trans*-**269**[b]	yield **270/271**(%)[b]
1	*rac*-VAPOL	CH_2Cl_2	60	43	--	12:1	4/5
2	*S*-VAPOL	CH_2Cl_2	56	48	36.5	20:1	4/4
3	*S*-VAPOL	CCl_4	67	62	61	25:1	4/4
4	*S*-VANOL	CH_2Cl_2	87	73	75	50:1	6/4
5	*S*-VANOL	CCl_4	94	84	91	50:1	2/2

[a] Unless otherwise specified, all reactions were run in the indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5 M. [b] Determined by ^{1}H NMR on the crude reaction mixture, see experimental for details. [c] Isolated yield after chromatography on silica gel. [d] Determined by chiral HPLC on a Chiralpak AD column.

It is not clear whether only one or more of the reasons cited above contribute to the diminished reactivity of **212**. As suggested by a study on the tetra-*tert*-butyl benzhydryl group (Section 6.4), the size of imine **212** should not deter the imine-borate coordination. In a perhaps related observation, it was also found that the aziridination reaction of imine **272** which has an electron deficient substituent attached to the carbon of the imine was also considerably slower than that of benzhydryl imine of benzaldehyde **135** (Table 6.15).

Table 6.15 Aziridination of N-benzhydryl pentafluorobenzaldimine **272**



272 **273** **274/275**

274: R^1=H, R^2=C_6F_5
275: R^1=C_6F_5, R^2=H

entry[a]	ligand	solvent	convn (%)[b]	yield of **273**(%)[c]	ee of **273**(%)[d]	*cis*:*trans* **273**[b]	yield of **274/275**(%)[b]
1	*rac*-VAPOL	CH_2Cl_2	60	35		>50:1	
2	*S*-VAPOL	CH_2Cl_2	61	43	76	>50:1	2/5
3	*S*-VAPOL	CCl_4	53	41	90	>50:1	4/9

[a] Unless otherwise specified, all reactions were run in the indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.5 M. [b] Determined by ^{1}H NMR on the crude reaction mixture, see experimental for details. [c] Isolated yield after chromatography on silica gel. [d] Determined by chiral HPLC on a Chiralcel OD-H column.

The reaction of the imine **272** only went to 60% conversion with the VAPOL-borate catalyst after 24 hours. Surprisingly the chiral inductions were not significantly decreased as in the case of imine **212** (Table 6.14). The reaction of **272** in CCl_4 gave only a slightly lower asymmetric induction than benzhydryl imine of benzaldehyde **135**. Thus in the case of imine **272**, although the overall reaction rate was slow, the transition state structure of this imine-catalyst complex appears to only be determined by the benzhydryl group, and the imine-catalyst complex was not significantly affected by the electron-deficient imine nitrogen.

The observed differences in asymmetric inductions and the similarity in reactivity between imines **212** and **272** with the VAPOL-borate catalyst suggests that the

enantioselectivity-determining step is possibly independent of the overall reaction rate. In the case of imine **212**, it was suspected that an electron-deficient CF_3-substituted benzhydryl group was unable to participate in the positive non-bonding interactions (presumably alkyl-face interactions) with the face of the arene groups on the ligand. A less-organized transition state for imine **212**-catalyst complex leads to a less selective nucleophilic attack of EDA and results in lower asymmetric induction. These and other related issues will be discussed in detail in section 6.5 of this chapter.

6.3.3 Conclusion

A comprehensive study of the electronic and steric effects of the imine in the catalytic asymmetric aziridination reaction was conducted and the results from various substituted benzhydryl imines were compared to those from the reaction of unsubsituted N-benzhydryl imine **135**. The observed electronic effects are that electron-rich benzhydryl imines generally provide higher asymmetric inductions than their electron-deficient counterparts, although the observed differences are small.

The results from the study of the effects of sterics of various nitrogen protecting groups provided mixed information. From the reactions of N-benzyl and N-trityl imines, it was clear that a protecting group of appropriate size is necessary for the efficient coordination between the nitrogen and the Lewis acid. The reactions of N-dibenzosuberonyl and N-9-fluroenyl imine indicated that appropriate angles (geometry) between the phenyl rings of the benzhydryl group play an important role.

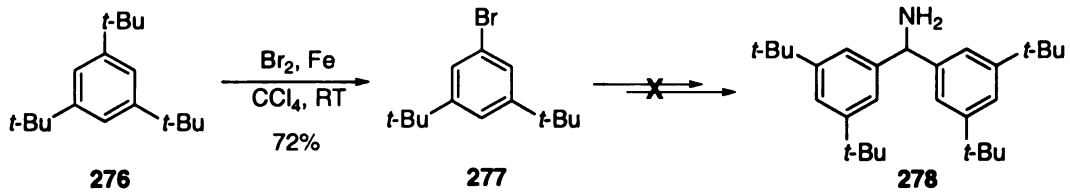
The surprising excellent asymmetric induction provided by 3,3',5,5'-tetramethylbenzhydryl group provided some insight into the positive alkyl-π interactions between the substrates and the ligand. The improved enantioselectivity and increased yield coupled with the ease of deprotection provided by the 3,3',5,5'-tetramethyl-4,4'-dimethoxybenzhydryl group may indeed lead to a more efficient and versatile aziridination methodology.

Based on the information obtained from these studies, it is still difficult to draw a definitive conclusion about whether the proposed edge-face interactions between the imines and catalyst actually play a role in the asymmetric induction. Before the crucial match/mismatch studies with chiral imines, it was decided that the possible alkyl-π interactions in the catalytic asymmetric aziridination reaction would be further explored.

6.4 Preparation and aziridination of N-BUDAM imines

After the successful exploration of the reactions of tetra-methyl substituted benzhydryl imine **167** (Table 6.11) and **207** (Table 6.12), the preparation of tetra-*tert*-butylbenzhydryl imine **263** was subsequently examined (Figure 6.11). It was found that the 3,5-di-*tert*-butylbromobenzene **277** could be prepared from 1,3,5-tri-*tert*-butylbenzene **276** in good yield (Scheme 6.20).[83a] However, the transformation of **277** to **278** was found to be difficult. In addition, due to the high cost of **276** ($ 70 for 10 g from Aldrich) and some of the required reagents, the further development of **278** did not appear to be practical even if the imine **263** turned out to be an excellent substrate.

Scheme 6.20 Attempted synthesis of amine **278**

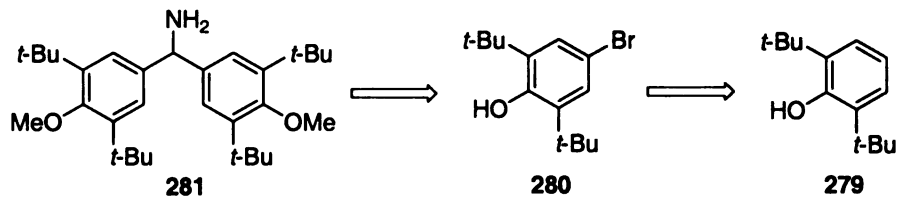


276 **277** **278**

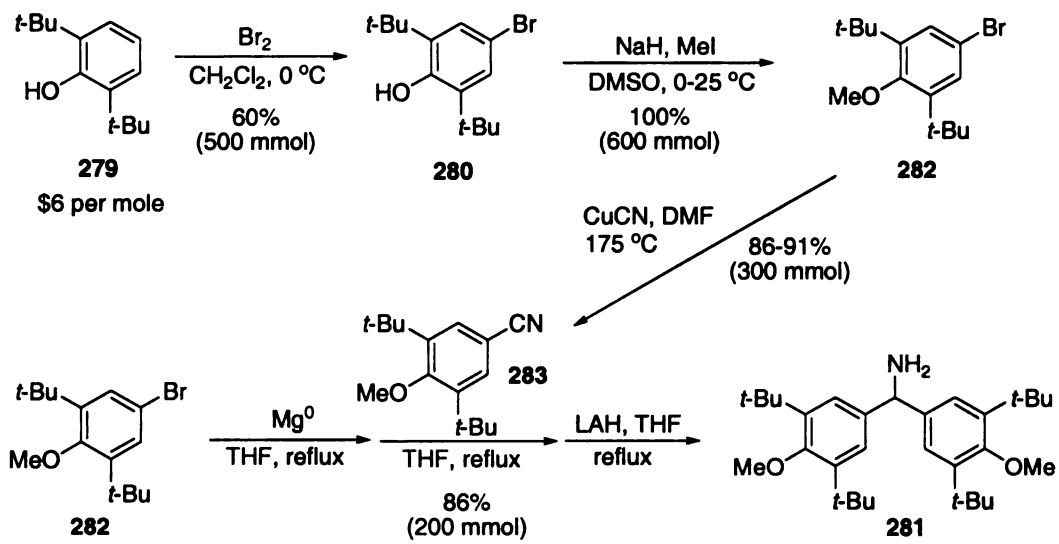
Meanwhile, it was envisioned that the tetra-*tert*-butyldimethoxy benzhydrylamine **281** could be prepared from phenol **280** which is the analogue of bromobenzene **277**, with the only difference being the presence of the hydroxyl group in **280** is one hydroxyl group (Scheme 6.21). 4-Bromo-2,6-di-*tert*-butylphenol **280** is commercially available at a much lower price than **276** ($ 70 for 100 g from Aldrich). Alternatively, phenol **280** could be prepared from the very inexpensive 2,6-di-*tert*-butylphenol **279** ($ 29 for 1 kg from Aldrich) according to a convenient Organic Syntheses procedure reported by Yamamoto.[83b] Synthesis of amine **281** from **280** was expected to be similar to the

synthesis of amine **207** (Scheme 6.11). In addition, if the preparation of amine **281** can be performed readily on a reasonable scale and the aziridination of imines derived from **281** give satisfactory results, then the acid-mediated deprotection of this nitrogen protecting group would be expected to be successful based on the results from the cleavage of dimethoxybenzhydryl group[81] and on the tetramethyl dimethoxy group in aziridine **264** (Table 6.12). Therefore, this would greatly add to the synthetic value of the amine **281** in the catalytic asymmetric aziridination reaction.

Scheme 6.21 Proposed synthesis of amine **281** from **279/280**



Scheme 6.22 Large scale synthesis of amine **281**



After considerable optimization of the conditions, an efficient large-scale synthesis of amine **281** was finally developed. This synthesis began with 2,6-Di-*tert*-butylphenol **279** due to its much lower cost than **280**. In the event, **279** was brominated according to

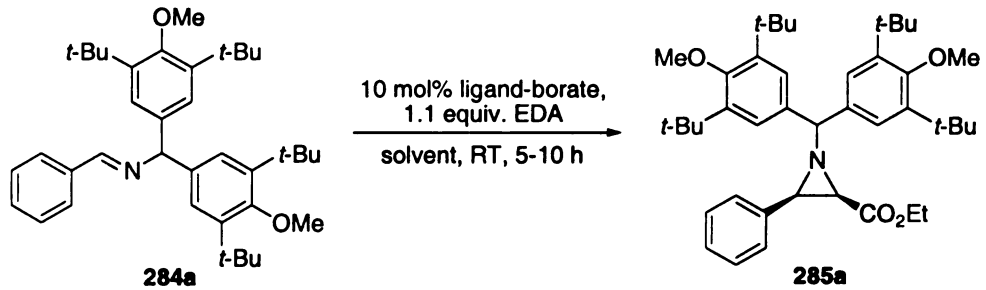
Yamamoto's procedure and, upon crystallization, 4-bromo-2,6-di-*tert*-butylphenol **280** could be isolated in good yield.[83a] The hydroxyl group of the bromobenzene **280** was subsequently methylated in the presence of sodium hydride and methyl iodide to furnish **282** in quantitative yield. These two steps could be performed routinely on 500-600 mmol scale.

The anisole **282** was converted to benzonitrile **283** in excellent yield via the coupling with CuCN in refluxing DMF.[67] Finally, the addition of a Grignard reagent prepared from **282** to benzonitrile **283** followed by the in-situ LAH reduction of the salt occurred smoothly and afforded amine **281** in excellent isolated yield. The product **281** was always contaminated with a trace amount of a yellow impurity (undetectable by ^{1}H NMR) which could not be removed even after chromatography on silica gel. However, this impurity can be easily removed by crystallization. The synthesis of amine **281** could be performed on 200 mmol scale.

After the successful synthesis of tetra-*tert*-butyl-dimethoxy benzhydryl amine (N-BUDAM amine) **281** and its conversion to the corresponding benzaldimine **284a**, this imine was evaluated in the catalytic asymmetric aziridination reaction under the standard protocol (Table 6.16). It was found that the aziridination of imine **284a** gave the highest selectivity ever observed. In the presence of 10 mol% catalyst generated from VAPOL or VANOL and triphenyl borate, essentially optically pure (≥ 99% ee) *cis*-aziridine **285a** could be isolated in 95% yield in either CH_2Cl_2 or CCl_4 as solvent. Meanwhile, the *trans*-aziridine and the enamine products were never detected by ^{1}H NMR for all the reactions

in Table 6.16. The crude reaction mixture was remarkably clean and contained only the product and ligand as determined by NMR and TLC.

Table 6.16 Catalytic asymmetric aziridination of imine **284a**.



284a **285a**

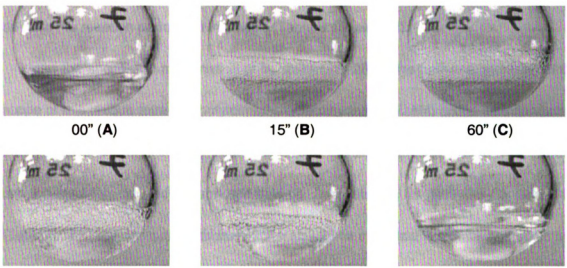
entry[a]	ligand	solvent	yield of **285a** (%)[b]	ee of **285a** (%)[c]
1	*S*-VAPOL	CH_2Cl_2	84	99
2	*R*-VAPOL	CH_2Cl_2	96	98
3	*S*-VAPOL	CCl_4	94	99
4	*R*-VAPOL	CCl_4	96	99
5	*S*-VANOL	CH_2Cl_2	97	99
6	*S*-VANOL	CCl_4	96	99
7	*S*-BINOL	CH_2Cl_2	71	67

[a] Unless otherwise specified, all reactions were run in the indicated solvent containing 0.5 mmol imine at room temperature, concentration of imine was 0.25 M. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC on a Pirkle covalent (R,R) Whelk-O 1 column.

It was also found that the aziridination of imine **284a** was significantly faster than any of the substrate examined to this point. In the reaction of **284a** with 10 mol% VAPOL or VANOL-borate catalyst in CCl_4 as solvent, mixing the catalyst solution with imine **284a** gave an orange solution **A** (Figure 6.12), which was presumably due to the strong π-

acceptor/donor interaction between the substrate and ligand.[54] Upon addition of ethyl diazoacetate, vigorous bubbling (due to the generation of nitrogen gas) was observed within seconds (**B**). After 90 seconds the orange color started to fade (**D**), and after 3 minutes there was only trace of the orange color left, and the bubbling was almost stopped (**E**). Finally after 5 minutes the bubbling stopped completely (**F**), the solution was almost colorless, indicating the complete consumption of the starting material **284a**. However, all the reactions shown in Table 6.16 were generally worked up after 5-10 hours to ensure the complete conversion of **284a**.

Figure 6.12 Progress of aziridination of **284a** as indicated by change of color



00" (**A**) 15" (**B**) 60" (**C**)

1'30" (**D**) 3'00" (**E**) 5'00" (**F**)

The extraordinary reaction rate for imine **284a** was indeed a surprise. For the N-benzhydryl imine **135**, the disappearance of the orange color was generally observed 3 hours after the addition of ethyl diazoacetate, thus the reaction of **284a** must be several

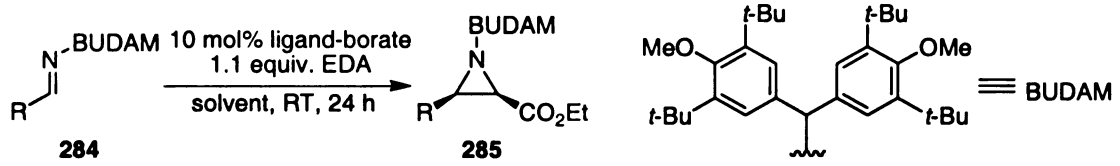
times faster than that of **135**. The study of the relative rate of various imines will be discussed later in details section 6.5 of this chapter.

It was found that imine **284a** only exhibited such excellent reactivity and selectivity in the presence of the VAPOL and VANOL-borate catalysts. The catalyst generated from BINOL and one equivalent of triphenyl borate in the presence of 4Å molecular sieve according to Yamamoto's procedure[57a] was found to be completely inactive for the aziridination of **284a**. If the catalyst was generated from BINOL and three equivalents of triphenyl borate at elevated temperature according to the procedure used for the VAPOL-borate catalyst,[25b] then aziridine **285a** could be isolated in 71% yield with 67% ee from the reaction performed in CH_2Cl_2 (Table 6.16, entry 7).

After the successful aziridination of benzaldimine **284a**, the further exploration of the scope of this unique tetra-*tert*-butyldimethoxybenzhydryl (BUDAM) group was conducted. The reactions of imines derived from cyclohexanecarboxaldehyde, *para*-bromobenzaldehyde and 1-naphthylaldehyde were studied in both CH_2Cl_2 and CCl_4 (Table 6.17). The aromatic aldimines **284c** and **284d** exhibited reactivity and selectivity similar to that of **284a** (Table 6.17). Excellent yield and asymmetric induction were observed for both substrates. The reactions in CCl_4 are more enantioselective than in CH_2Cl_2, where the asymmetric inductions of both substrates dropped to 97-98% ee. In contrast, a much slower rate and selectivity was observed for the cylcohexanecarboxaldehyde derived imine **284b**. The isolated yield and cis/trans ratio of aziridine **285b** were still excellent, but small amounts of the enamine products were

observed, and the asymmetric induction was significantly lower than that of **284a**. Despite the lower induction observed with imine **284b**, the results from imine **284c** and **284d** were very promising, and prompted further investigation of the catalytic aziridination of other N-BUDAM imines.

Table 6.17 Study of the substrate scope for N-BUDAM imines



entry[a]	imine	R	ligand	solvent	yield of **285** (%)[b]	ee of **285** (%)[c]	enamines[d]
1		cyclohexyl	*S*-VAPOL	CH_2Cl_2	88	72	2-3/<1
2	**284b**	cyclohexyl	*S*-VANOL	CH_2Cl_2	89	77	2-3/<1
3		cyclohexyl	*S*-VAPOL	CCl_4	95	80	<1/<1
7		1-naphthyl	*S*-VAPOL	CH_2Cl_2	92	99	<1/<1
8	**284c**	1-naphthyl	*S*-VANOL	CH_2Cl_2	92	97.5	<1/<1
9		1-naphthyl	*S*-VAPOL	CCl_4	91	99.5	<1/<1
4		4-BrC_6H_4	*S*-VAPOL	CH_2Cl_2	96	97.7	<1/<1
5	**284d**	4-BrC_6H_4	*S*-VANOL	CH_2Cl_2	94	97.4	<1/<1
6		4-BrC_6H_4	*S*-VAPOL	CCl_4	99	99	<1/<1

[a] Unless otherwise specified, all reactions were run in the indicated solvent containing 1.0 mmol imine at room temperature, concentration of imine was 0.25 M. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC analysis on a Pirkle covalent (R,R) Whelk-O 1 column. [d] Determined by ^1H NMR on the crude reaction mixture.

Before the comprehensive studies of other substrates were initiated, it was decided to take a closer look at the issues of catalyst loading and solvent. Owing to the

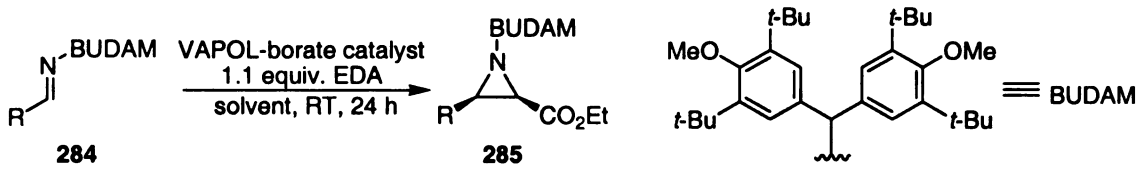
extraordinary reactivity of the N-BUDAM imines, 10 mol% catalyst loading seemed excessive. Furthermore, although the reactions in CCl_4 generally afford higher selectivity than those performed in CH_2Cl_2, the relatively lower solubility of these imines in CCl_4, along with the expense and toxicity of this solvent significantly detracted from a protocol that use CCl_4. Thus a more readily available, environmentally benign solvent would be greatly desirable, and in fact preferable, if the aziridination reactions retained the same level of selectivity and reactivity.

It was found that under various loadings of the VAPOL-borate catalyst (2-10 mol%), the aziridinations of imines **284c** and **284d** in CCl_4 consistently gave aziridines **285** with 99% ee (Table 6.18). The catalyst loading could be reduced to as low as 2 mol % and the efficiency of the reaction was not affected. However incomplete conversion (after 24 hours) was observed for both substrates when the catalyst was decreased to 1 mol % (entry 5, 9). Meanwhile, although the reactions with 10 mol% VAPOL-borate catalyst in CH_2Cl_2 furnished the aziridines with 97-99% ee (Table 6.16), reduction of the catalyst loading to 2-2.5 mol % gave the aziridines with reduced asymmetric inductions in this solvent (96-97% ee, entry 2, 10).

The study of the effect of solvents on the aziridination of imine **135** (Chapter 5.2.4, Table 5.8) indicated that toluene was second only to CCl_4 with regard to yield and selectivity for N-benzhydryl imines, therefore, the aziridinations of **284** were also examined in toluene. It was gratifying to find that the reactions of imines **284c** and **284d** in toluene afforded the same level of selectivity and yield as in CCl_4. Furthermore, the

enantioselectivity with a reduced catalyst loading (2 mol % VAPOL-borate catalyst) was same as that with 10 mol % catalyst (entry 7, 12). It is worth mentioning that no *trans*-aziridine or enamine products were observed in any of the reactions shown in Table 6.18.

Table 6.18 Optimization of the aziridination of N-BUDAM imines.



284 **285**

entry[a]	imine	R	loading (mol %)	solvent	concn. (M)	yield of **285** (%)[b]	ee of **285** (%)[c]
1		1-naphthyl	5	CH_2Cl_2	0.25	90	99
2		1-naphthyl	2.5	CH_2Cl_2	0.25	91	97
3		1-naphthyl	5	CCl_4	0.25	94	99
4	**284c**	1-naphthyl	2	CCl_4	0.2	92	99
5		1-naphthyl	1	CCl_4/CH_2Cl_2	0.2	<70% convn[d]	
6		1-naphthyl	10	toluene	0.25	93	99
7		1-naphthyl	2	toluene	0.25	93	99
8		4-Br-C_6H_4	2	CCl_4	0.25	99	99
9		4-Br-C_6H_4	1	CCl_4	0.25	<10% convn[d]	
10	**284d**	4-Br-C_6H_4	2	CH_2Cl_2	0.25	93	96
11		4-Br-C_6H_4	10	toluene	0.25	99	99
12		4-Br-C_6H_4	2	toluene	0.25	99	99

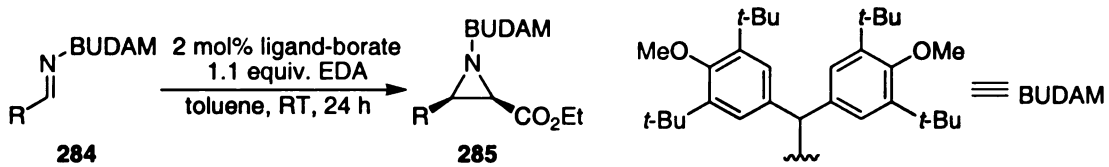
[a] Unless otherwise specified, all reactions were run in the indicated solvent containing 0.5-2 mmol imine at room temperature, concentration of imine was 0.25 M. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC analysis on a Pirkle covalent (R,R) Whelk-O 1 column. [d] Determined by ^{1}H NMR on the crude reaction mixture.

Upon completion of the catalyst loading and solvent study, the scope of the catalytic asymmetric aziridination reaction was expanded to various N-BUDAM imine substrates. All reactions were performed in the presence of 2 mol % catalyst generated from the VAPOL or VANOL ligand and triphenyl borate with toluene as solvent.

It was remarkable to find that all the N-BUDAM imines **284** derived from a variety of aromatic aldehydes underwent highly enantioselective and diastereoselective aziridination with only 2 mol% catalyst generated from either the VANOL or VAPOL ligand (Table 6.19). The reactions of imines **284** produced very clean crude reaction mixtures from which the *trans*-aziridine and enamine side products were never detected by either ^{1}H NMR or TLC for nearly all the substrates. In the aziridination of N-benzhydryl imines, the separation of the product aziridines from the ligand and from the enamines by silica gel chromatography was always complicated by the similar polarity of these compounds. In contrast the purification of N-BUDAM substituted aziridines was much easier due to the virtual non-existence of the enamine products and to the fact that the polarities of aziridines **285** were significantly different from those of the ligands.

The scope of the reaction is quite general. In those reactions with VAPOL as ligand, aziridines **285** were isolated with at least 96% ee and in several cases essentially optically pure **285** were produced (≥ 99% ee). With one exception, the catalyst generated from VANOL produced slightly lower asymmetric inductions, although same excellent level of isolated yields (83-99%) were observed with both ligands.

Table 6.19 Catalytic asymmetric aziridination of N-BUDAM aldimines



284 **285**

entry[a]	imine	R	ligand	yield of **285** (%)[b]	ee of **285** (%)[c]
1	**284a**	C_6H_5	*S*-VAPOL	98	99
2		C_6H_5	*S*-VANOL	97	98
3	**284c**	1-naphthyl	*S*-VAPOL	93	99
4		1-naphthyl	*S*-VANOL	96	98
5	**284d**	4-BrC_6H_4	*S*-VAPOL	99	99
6		4-BrC_6H_4	*S*-VANOL	99	98
7	**284e**	2-BrC_6H_4	*S*-VAPOL	84	96
8		2-BrC_6H_4	*S*-VANOL	83	90
9	**284f**[d]	4-$NO_2C_6H_4$	*S*-VAPOL	92	96
10		4-$NO_2C_6H_4$	*S*-VANOL	91	97
11	**284g**	2-MeC_6H_4	*S*-VAPOL	97	99
12		2-MeC_6H_4	*S*-VANOL	96	96
13	**284h**	4-MeC_6H_4	*S*-VAPOL	95	99
14		4-MeC_6H_4	*S*-VANOL	98	98
15	**284i**	4-$MeOC_6H_4$	*S*-VAPOL	87	98
16		4-$MeOC_6H_4$	*S*-VANOL	90	98

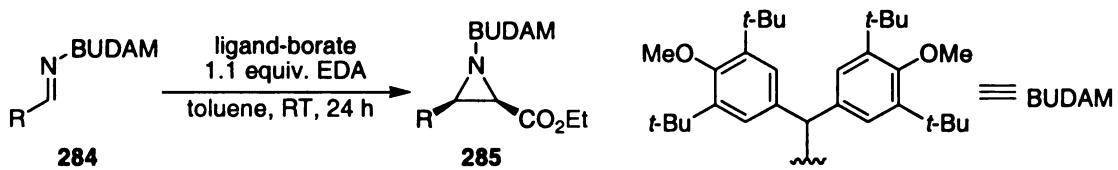
[a] Unless otherwise specified, all reactions were run in toluene containing 2.0 mmol imine at room temperature, concentration of the imine was 0.25 M. Reaction time was not optimized. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC on a Pirkle covalent (R,R) Whelk-O 1 column. [d] Imine was 0.22 M in a mixture of 5:1 toluene/CH_2Cl_2.

Several sterically hindered imines including **284c**, **284e** and **284g** also gave excellent results. Only the reaction of the 2-bromobenzaldimine **284e** produced small amount of enamines, and in addition its asymmetric induction was lower than 95% ee with the VANOL-borate catalyst (entry 7, 8). It is impressive that excellent asymmetric inductions were observed from imines derived from both electron-rich and electron-poor aryl aldehydes, including 4-nitrobenzaldimine **284f** and 4-methoxybenzaldimine **284l** which both gave the same level of enantioselectivity.

Encouraged by the success of N-BUDAM imines derived from aromatic aldehydes, the reactions of imines derived from aliphatic and other unsaturated aldehydes were subsequently studied. It was found that although the imine **284j** derived from a primary aliphatic aldehydes produced aziridine **285j** in good yield with excellent chiral induction (entry 1, 2, Table 6.20), the reaction rate and chiral inductions of the sterically more hindered imines **284b** and **284k** decreased considerably (entry 3-6). In the case of tertiary aldimine **284k**, incomplete conversion was observed even in the presence of 10 mol % catalyst (entry 5, 6). The imine **284l** which was generated from an alkynyl-aldehyde afforded the corresponding aziridine in excellent yield, and the observed asymmetric induction was significantly improved over similar substrates generated from benzhydryl amine (entry 7, 8). Other substrates examined that are not in the table include the N-BUDAM imine derived from cinnamaldehyde, which was found to be completely inactive under the same reaction condition for reasons that remain unknown.

In addition, the imine generated from 2-furyl aldehyde gave a complex mixture of products of which the expected aziridine was a minor component.

Table 6.20 Catalytic asymmetric aziridination of N-BUDAM imines



284 **285**

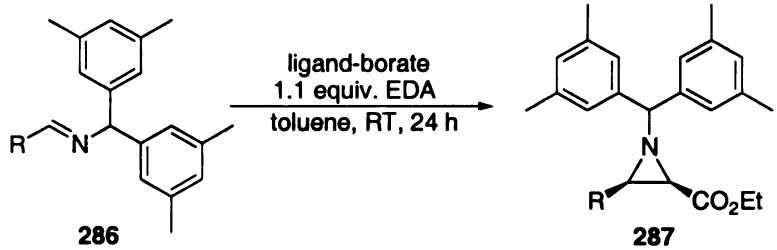
entry[a]	imine	R	ligand	catalyst (mol %)	yield of **285** (%)[b]	ee of **285** (%)[c]
1	**284j**	ethyl	*S*-VAPOL	2	62	93
2		ethyl	*S*-VANOL	2	57	87
3	**284b**	cyclohexyl	*S*-VAPOL	4	89	89
4		cyclohexyl	*S*-VANOL	4	87	84
5	**284k**	*tert*-butyl	*S*-VAPOL	10	60 (75)[d]	78
6		*tert*-butyl	*S*-VANOL	10	76 (95)[d]	80
7	**284l**	TIPS-C≡C-	*S*-VAPOL	2	97	83
8		TIPS-C≡C-	*S*-VANOL	2	97	78

[a] Unless otherwise specified, all reactions were run in toluene containing 1-2 mmol imine at room temperature, concentration of imine was 0.25 M. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC on a Pirkle covalent (R,R) Whelk-O 1 column. [d] Numbers in parenthesis indicate percent conversion determined by ^{1}H NMR on the crude reaction mixture.

It was suspected that in the cases of imine **284b** and **284k**, the decrease of reactivity was the result of the combined increased steric bulk of both the N-protecting group and the α-position of imines. This proposal was supported by several observations: 1) similar reactions with imines generated from benzhydryl amine and a tertiary aldehyde always lead to complete conversion[25b]; 2) the reaction rate decreased gradually from primary

aldimine to tertiary aldimine; and 3) the sterically less demanding VANOL-borate catalyst gave better conversion (entry 6). If this proposal is true, then switching the nitrogen protecting group from N-BUDAM to a smaller tetramethylbenzhydryl group should in theory decrease the undesired steric repulsion and increase the reactivity, but still retain a high level of chiral induction.

Table 6.21 Asymmetric aziridination of tetramethylbenzhydryl imines **286**



286 **287**

entry[a]	imine	R	ligand	catalyst (mol %)	yield of **287** (%)[b]	ee of **287** (%)[c]
1	**286a**	cyclohexyl	*S*-VAPOL	4	87	91
2		cyclohexyl	*S*-VANOL	4	93	92
3	**286b**[d]	*tert*-butyl	*S*-VAPOL	10	94	96
4		*tert*-butyl	*S*-VANOL	10	94	96

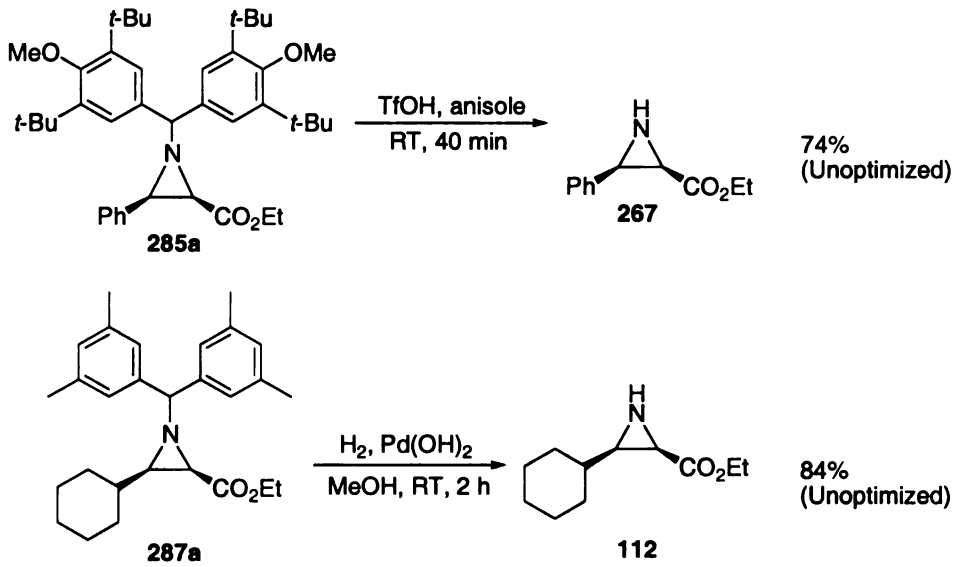
[a] Unless otherwise specified, all reactions were run in toluene containing 1-2 mmol imine at room temperature, concentration of imine was 0.25 M. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC on a Pirkle covalent (R, R) Whelk-O 1 column. [d] Imine was used as crude without crystallization.

In the event, the imines **286** derived from secondary and tertiary aldehydes and tetramethylbenzhydryl amine indeed resulted in significantly improved enantioselectivity over the corresponding N-BUDAM imine **284** (Table 6.21). The observed improvements with regard to reactivity and selectivity for tertiary aldimine **286b** were remarkable even

though **286b** could not be crystallized and was used in unpurified form. The same reaction conditions that were used with N-BUDAM imine **284k** (Table 6.20) were employed in the reaction of **288b**. In the presence of 10 mol % catalysts, complete conversions were observed for **286b**, and the aziridine **287b** could be isolated with excellent yield and asymmetric induction (entry 3, 4). Furthermore, it is expected on the basis of observations presented earlier in this chapter (section 6.3), that the use of 3,3',5,5'-tetramethyl-4,4'-dimethoxyl benzhydrylamine (MEDAM-aimine) **206** should provide even better results with the imine from pivaldehyde. However, due to the limited quantity of **206** this experiment was not pursued.

In the design of the N-BUDAM protecting group, two methoxy groups were implanted at the 4,4'- positions of the benzhydryl rings. Based on extensive studies of the 4,4'-dimethoxybenzhdryl (DAM) group,[81] the two methoxy groups should not only enhance the selectivity in the aziridination reaction, but also provide access to the N-H aziridines via the acid-mediated deprotection. The N-BUDAM group should also be able to serve this function. Indeed, it was found that the standard conditions for the deprotection of N-DAM group could be applied directly to the cleavage of BUDAM group (Scheme 6.23). The deprotection of **285a** in anisole as solvent in the presence of triflic acid smoothly gave N-H aziridine **267** in good but unoptimized yield. In the case of 3-alkyl aziridine **287a**, the tetramethylbenzhydryl group could also be removed by hydrogenolysis in the presence of Pearlman's catalyst.[81]

Scheme 6.23 Deprotection of BUDAM and TMBh group



The aziridination-deprotection sequence established here represents an efficient and highly enantioselective access to N-H aziridines. The overall process benefits from the simple and high-yielding preparation of N-BUDAM and/or TMBh amine and imines, the highly enantioselective aziridination and the ease of which the nitrogen can be deprotected to give the optically active aziridines.

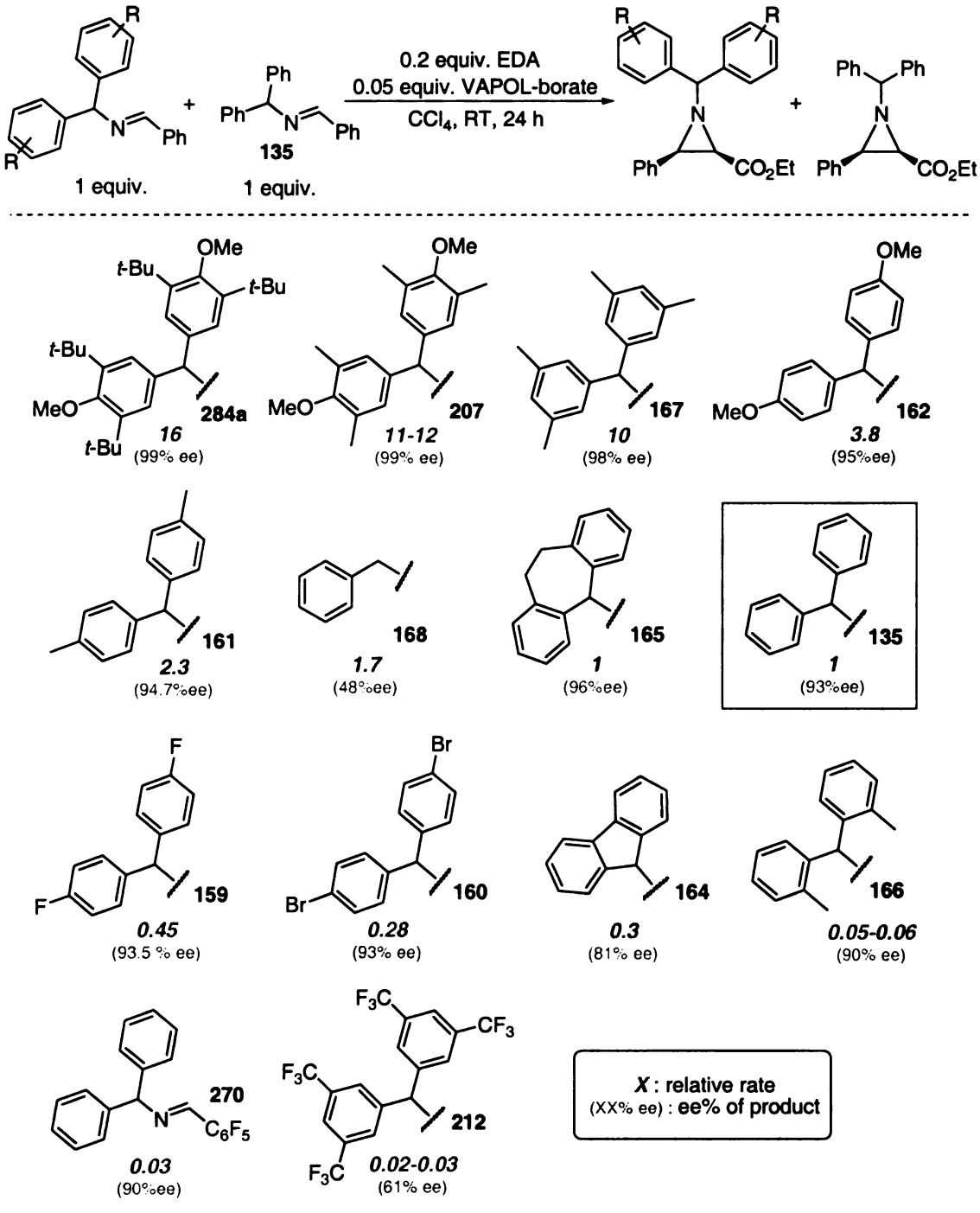
6.5 Study of kinetics and relative rate competition

During the study of the aziridination of N-BUDAM imines, it was found that the substrates such as N-BUDAM imine **284a** exhibited extraordinary reactivity, appearing to react several times faster than the benzhydryl imine **135** based on the visual observation. It was also found that several other substrates with strong electron-withdrawing groups exhibited diminished reactivity compared with **135**. However, at that point the detailed relationship between the substitution pattern and reactivity remained unclear. As part of

the study on the mechanism of the catalytic asymmetric aziridination reaction several issues needed to be addressed: 1) The reactivity difference between substrates with various substituents; 2) the relationship between structure and reactivity; 3) the possible correlation of reactivity with selectivity.

It was decided that the study of the relative reaction rates of various imine substrates should provide insights to these questions. This study was conducted by the competition of two imine substrates for 0.05 equivalent of catalyst in the presence of a substoichiometric amount (0.2 equivalent) of ethyl diazoacetate. The N-benzhydryl benzaldimine **135** would be used as the standard substrate and the rate competition of all the examined imines would be performed against **135** under the same aziridination conditions. The relative rate would be determined by ^{1}H NMR of the crude product mixture via the integration of C2 and C3 protons of the two aziridines. Due to the slightly different reactivity and/or selectivity induced by the VAPOL and VANOL derived catalysts, the rate competition was also studied with both ligands. Finally, at this stage the exact rate-determining step of the reaction was unknown, thus this competition study was only representative of the overall reaction rates differences of the substrates.

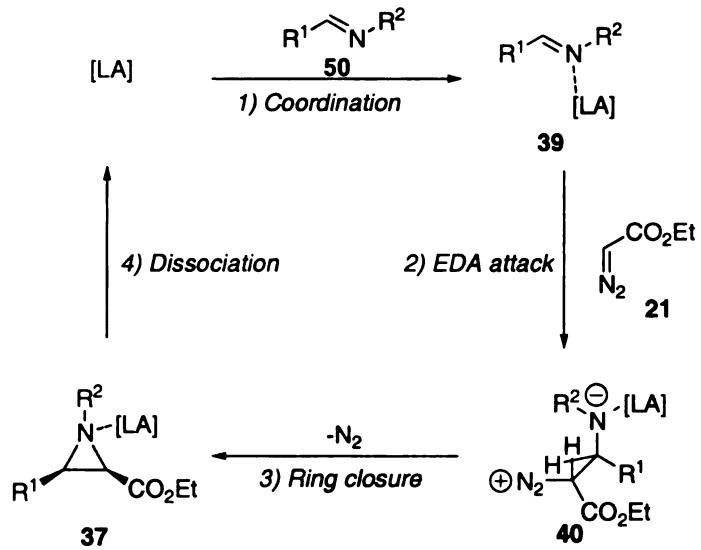
Scheme 6.24 Rate competition studies with the VAPOL-borate catalyst



The results from these relative ratio studies with VAPOL-borate catalyst are shown in Scheme 6.4, and very large differences in the relative rate of various imines were observed to cover a range of 3000. The imines with the *meta*-alkyl-substituted

benzhydryl groups all react much faster than the corresponding imine without the *meta*-alkyl groups. The N-BUDAM imine **284a** is the most reactive imine, reacting 16 times faster than the benzhydryl imine **135**. The imines **161** and **162** with *para*-electron-donating groups generally reacted 2-4 times faster than the electron-neutral imine **135**, whereas the presence of electron-withdrawing groups on either the benzhydryl group (**159**, **160**, **212**) or on the aldehyde (**270**) always slowed down the reaction.

Scheme 6.25 Proposed catalytic cycle of aziridination reaction



Correlation of the electronic properties of various imines and their relative rates provided some additional information. The fact that the electron-deficient imines reacted slower is contradictory to the common notion that these imines are considered "activated" substrates toward nucleophilic attack. Thus in the case of either the VAPOL or VANOL-borate Lewis acid catalyzed aziridinations, the attack of ethyl diazoacetate on C=N bond (Step 2, Scheme 6.25) is unlikely to be the rate-determining step of the catalytic cycle. For the same reason, the dissociation of the Lewis acid catalyst from the

product aziridine (Step 4, Scheme 6.27) would not be expected to be the rate-determining step either. This determination is based on the fact that both of these two steps should be facilitated by strong electron-withdrawing groups.

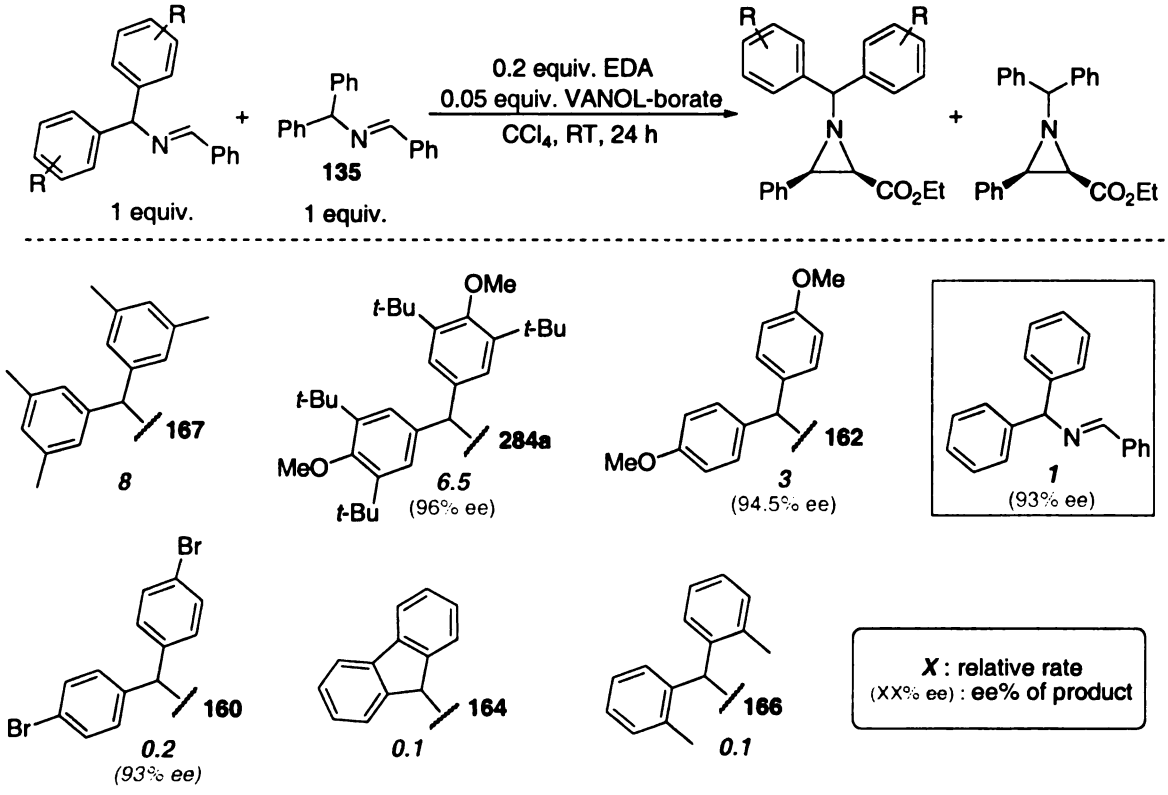
Most of the substrates in scheme 6.24 including **159-162**, **165** and **270** would be expected to have very similar steric encumberences with regard to the N-protecting groups. If this were true, then it can be conclude that their asymmetric inductions were not significantly affected by the electronic properties of the N-substituents, since the reactions of these imines gave 93±3% ee. On the other hand, very large rate differences were observed with these substrates. This observation may not be surprising since once the active catalyst coordinates with the imine, the direction of nucleophilic attack (as the ee% determining step) would solely depend on the structure of the imine-catalyst complex.

Of related interest, it was found that the much smaller N-benzyl imine **168** only reacted slightly faster (1.7x) than the benzhydryl imine **135**. The di-*ortho*-methyl substituted benzhydryl imine **166** exhibited significantly diminished reactivity, presumably due to steric hinderance. However, the reactions of the tetra-alkyl substituted benzhydryl imines **167**, **207** and **284a** demonstrate that sterically bulky substrates do not necessarily react slower. This fact raises an interesting question about the origin of rate acceleration of these imines, because from just the point of view of sterics, the bulky of these substrates should significantly disfavor their coordination with

the catalyst, and the subsequent nucleophilic attack of EDA and also possibly the final ring-closing event.

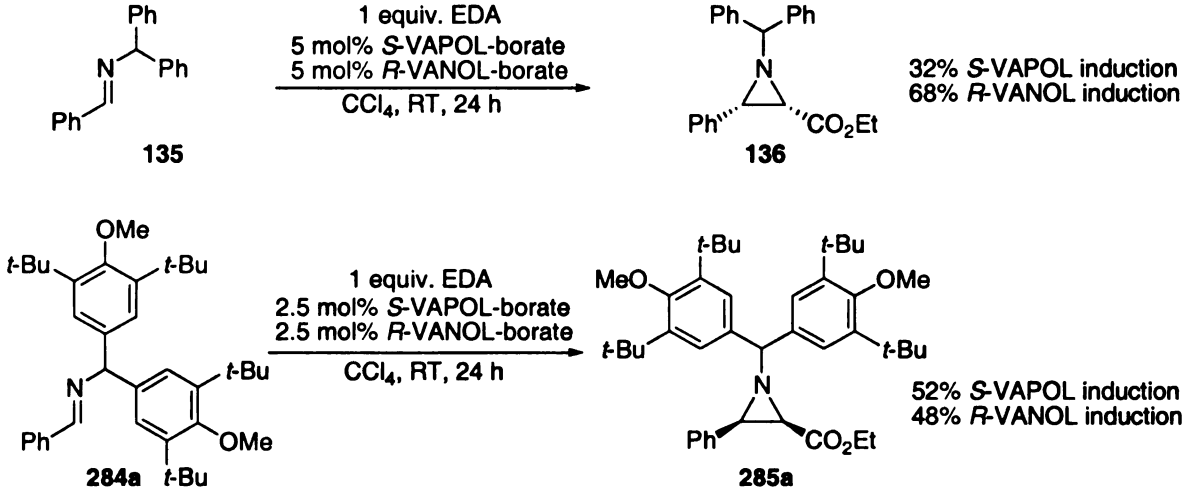
Interestingly, with few exceptions, a good correlation was observed between the reactivity and the selectivity. The imines that reacted the fastest also generally produced aziridines with the highest asymmetric induction. The reactions of the tetra-*meta*-substituted benzhydryl imines are especially intriguing. The N-BUDAM imine **284a** is clearly the most sterically hindered substrate, however, it displays the highest reactivity and it gave rise to the highest selectivity, while the sterically similar tetra-CF_3 substituted imine **212** exhibited the lowest reactivity and the lowest asymmetric induction.

Scheme 6.26 Rate competition study with the VANOL-borate catalyst



The rate competition study using the VANOL-borate catalyst gave relative rates similar to the VAPOL-borate catalyst for most substrates (Scheme 6.26). However, the magnitude of the observed rate differences is smaller. Surprisingly, with this catalyst the N-BUDAM imine **284a** reacted slower than the N-TMBh imine **167**, although both substrates still reacted significantly faster than benzhydryl imine **135**. Considering the similarity of the two ligands, the exact reason for the observed differences between the VAPOL and VANOL catalysts are not clear. At this stage it can only be assumed that the different rates are the result of minor differences in the electronic and/or steric differences between the ligands.

Scheme 6.27 Study of relative reactivity between VAPOL and VANOL catalysts



A study of relative reactivity of the catalysts generated from VAPOL and VANOL was also conducted (Scheme 6.27). The aziridination of N-benzhydryl imine **135** in the presence of catalysts generated from a 1:1 mixture of *S*-VAPOL and *R*-VANOL produced aziridine **136**, which was determined to be consist of a 32:68 mixture of enantiomers where the (*2S*, *3S*)-enantiomer was major and thus resulted from the *R*-

VANOL ligand. Thus in the case of **135**, its reaction with the VANOL-borate catalyst was roughly 2 times faster than that with the VAPOL-borate catalyst. This reaction indicates that the catalyst is affecting the rate-determining step in the aziridination of **135**. On the other hand, very similar reaction rates were observed for reaction of the N-BUDAM imine **284a** since there was essentially no difference in asymmetric induction with the two catalysts. As with the relative rate studies presented in Scheme 6.24, these results presented seemly contradictory data that the smaller imine was converted faster with the smaller catalyst, whereas the rate of the bulkier substrate was not sensitive to the steric differences in the ligand.

Based on the information obtained from the rate competition studies presented in Scheme 6.24 and Scheme 6.26, Scheme 6.27, the following set of rationales were developed to account for the observed results:

1) The coordination of the imine to the catalyst is most likely to be the rate-determining step (step 1, scheme 6.25). The relative rate of this step is determined by the electronic and steric properties of the imine nitrogen substituents. Electron-donating substituents on the benzhydryl group should increase the basicity of the imine nitrogen and favor the Lewis acid-Lewis base coordination. A similar observation was also made by Brookhart and Templeton during their study of the aziridination with imines with non-chiral Lewis acids.[19] The presence of *meta*-alkyl substituents on the benzhydryl rings significantly facilitates the substrate-catalyst complexation, presumably via non-bonding interactions (alkyl-π interaction) of the alkyl group with the arene system of the ligand. In

the case of N-BUDAM imine **284a**, it is proposed that the larger surface area of *tert*-butyl groups induces interactions with the arene rings of the ligand that is stronger than those of the methyl-arene and/or arene-arene interaction.

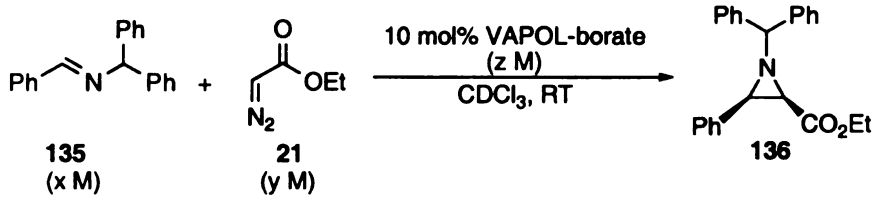
2) After the coordination of the imine to the catalyst, the attack of ethyl diazoacetate to the C=N double bond occurs rapidly. The positive non-bonding interactions between the substrate and catalyst effectively restrict the rotation about the Lewis acid-Lewis base bond between nitrogen and boron. The combination of nitrogen-boron coordination and the proposed non-bonding interactions (as in the case of N-BUDAM imine **284**) determine that the imine-catalyst complex will have a defined structure, which leads to a highly stereofacial nucleophilic attack by ethyl diazoacetate.

3) The ring closure of zwitterion **40** is also unlikely to be the rate-determining step (step 3, Scheme 6.25). This step involves the nucleophilic attack of the negatively polarized nitrogen on the C-3 carbon of the incipient aziridine. A sterically bulky nitrogen substituent should significantly slow down this intramolecular substitution step, and, when this occurs, phenyl and hydrogen migrations should be increased leading to greater amounts of enamine products. However, the relative rate between the two electronically similar substrates N-MEDAM imine **207** and N-BUDAM imine **284a** indicated that the bulkier imine reacted faster and produced less enamine products. Thus the ring-closure of zwitterion must be facile and is not hindered by the size of nitrogen substituent.

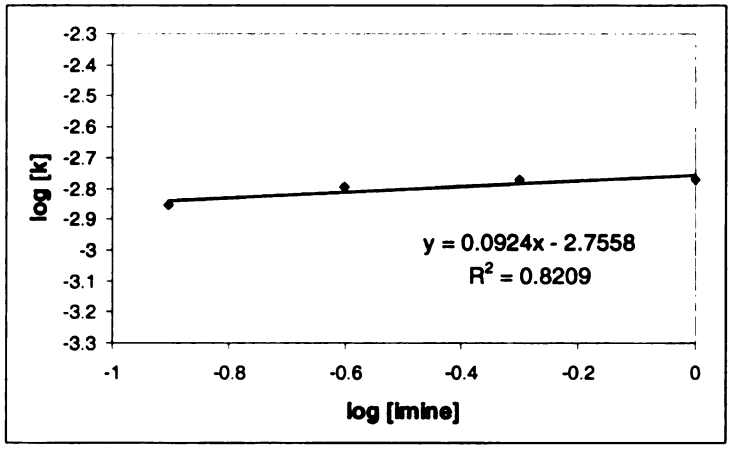
4) The rate of catalyst dissociation from the aziridine product (step 4, scheme 6.25) is determined by the relative stability between the imine-catalyst complex **39** and aziridine-catalyst complex **37**. It was observed in the studies of relative rate competition that the electron-rich imines always react fast, thus this step is also unlikely the rate-determining step since the aziridine products which contain more electron-rich substituents will coordinate with the chiral Lewis acid tighter. On the other hand the sterically more bulky group such as N-BUDAM may also facilitate the dissociation of product aziridine from the catalyst.

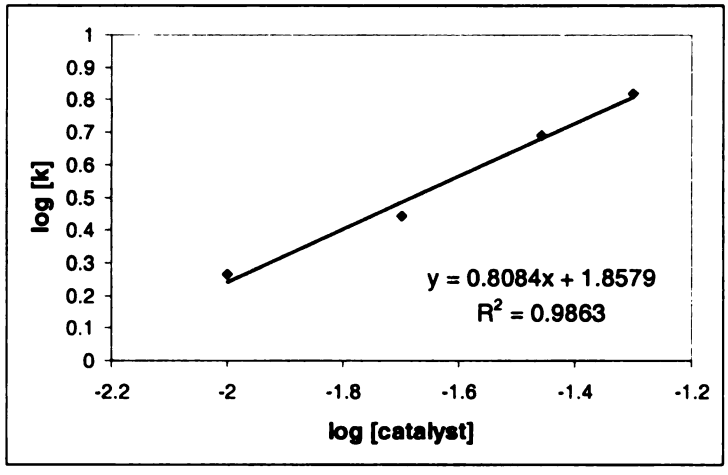
Finally, it needs to be noted that the study of relative rates for different imines assumes that the aziridination of the two different imines occur via two totally independent processes within the same reaction vessel, and that these processes do not interfere with each other. However, during the competition reactions the free catalyst may in theory not only coordinate with two imines, but also complex with either of the product aziridines. It is possible that the "matched" aziridine product may coordinate with the active catalyst and in some way inhibit the complexation of the other imine substrate. Thus the competition studies should only be considered as providing an approximate glimpse of the relationship between structure and reactivity, and in no way should they be regarded as an exact quantification of the reactivity.

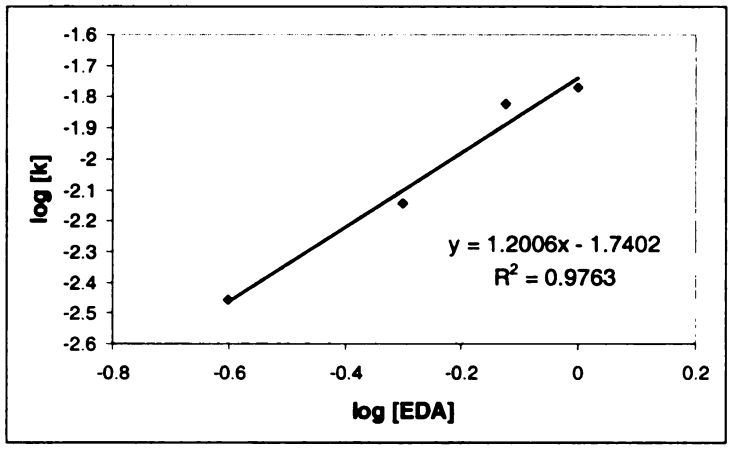
Figure 6.13 Initial rate kinetics of imine **135**, VAPOL-borate catalyst and EDA



135 (x M) **21** (y M) **136**







In an effort to obtain more definitive information on the mechanism of the catalytic asymmetric aziridination, the initial reaction rate kinetics were determined for the reaction of imine **135** ethyl diazoacetate with the VAPOL-borate catalyst (Figure 6.13).[84] Interestingly, the results of the initial reaction rate studies indicated that the VAPOL-borate catalyzed aziridination reaction has a zero-order dependency on the benzhydryl imine **135**, a 0.8 order dependency on the concentration of the VAPOL-borate catalyst and a 1.2 order dependency on the concentration of ethyl diazoacetate. These studies on the initial reaction rate kinetics suggests that the rate-determining step of the catalytic aziridination of the benzhydryl imine **135** involves the reaction of the VAPOL-borate catalyst and ethyl diazoacetate, these rate studies furthermore indicate that imine **135** is not involved in the rate limiting step.

The initial rate studies (Figure 6.13) seem to be in contradiction to the results from the studies of the relative rate competition of various imines (Scheme 6.24), the source of this contradiction is not clear and certainly deserves further investigation. However, it should be noted that the VAPOL-borate catalyzed aziridinations of different imine substrates may follow completely different reaction profiles. As an example, in Shibasaki's studies of the catalytic asymmetric Mannich-type reactions of hydroxyketones, it was noticed that the reactions of N-diphenylphosphinoyl and N-Boc imines in the presence of the same nucleophile and catalyst exhibited two different initial rate kinetic profiles.[84b]

6.6 Match/mismatched study using chiral imines

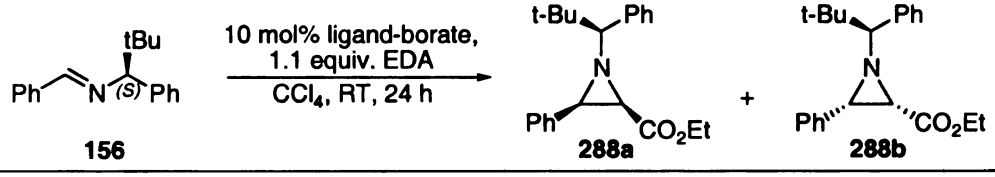
The steric and electronic effects of symmetrically substituted imines were presented in section 6.3. While the study of the symmetrically substituted imines provide a wealth of information on the aziridination reaction, it can be anticipated that the study of unsymmetrically (chiral) substituted imines would provide new information about the reaction, especially from matched and mismatched situations.

The optically pure α-*tert*-butylbenzylimine **156** was the first substrate examined under the standard aziridination condition (Table 6.22). The aziridination with $B(OPh)_3$ as catalyst gave a 1:12 ratio of two aziridine diastereomers **288a** and **288b**. The formation of unequal amounts of the two diastereomers with the racemic catalyst is a measure of the inherent 1,3-induction of the chiral nitrogen substituent. In fact, nucleophilic additions of organometallic compounds to similar chiral imine substrates are well-documented in the literature and various models have been proposed to account for the diastereoselectivity.[85]

The aziridination of *S*-**156** was conducted with both enantiomers of the VAPOL and VANOL catalysts (Table 6.22). The results showed there is a strong match/mismatched relationship for both ligands. In the presence of the catalysts generated from *R*-VAPOL and *R*-VANOL, the aziridination of the *S*-enantiomer of the chiral imine **156** gave almost exclusively the (*2S*, *3S*)-aziridine **288b** as the matched product. These reactions were generally very clean and produced less than 2% of the mismatched aziridine **288a** and only trace amounts of enamine side-product. However, the same reaction with the *S*-

catalysts resulted in significantly reduced selectivity. The *S*-VAPOL catalyst afforded a 2.2:1 mixture of **288a/288b**, along with significant amount of enamine products. The reaction of (*S*)-**156** in the presence of the *S*-VANOL catalyst gave a 1.1:1 ratio of the two products, however, less enamine products were observed than with the *S*-VAPOL catalyst.

Table 6.22 Match/mismatched study with chiral α-*tert*-butylbenzylimine



156 **288a** **288b**

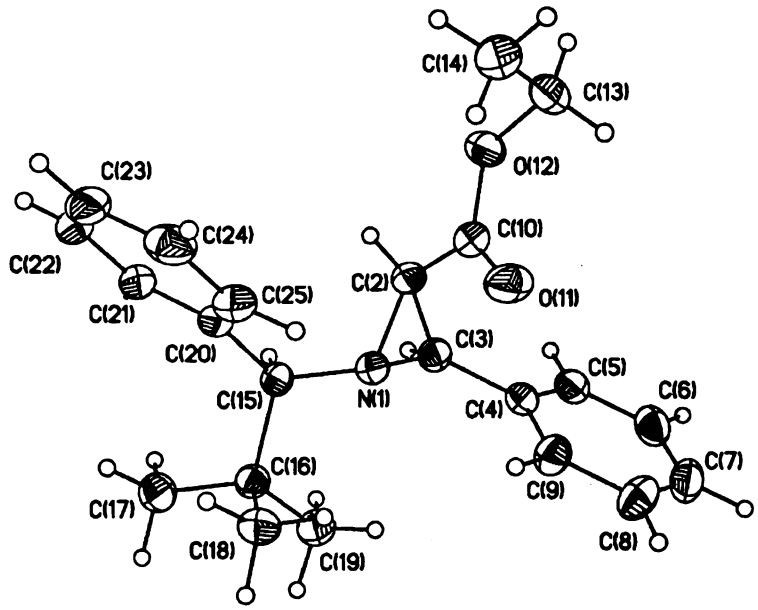
entry[a]	ligand	**288a** : **288b**[b]	yield of **288** (%)[c]	cis/trans **288**[b]	enamines (%)[b]
1	$B(OPh)_3$ only	1 : 12	NA	NA	24/11
2	*S*-VAPOL	2.2 : 1	56 (**288a**)	>50:1	44/2
3	*R*-VAPOL	< 1 : 50	80 (**288b**)	>50:1	<2
4	*S*-VANOL	1.1 : 1	36 (**288a**)	>50:1	11/2
5	*R*-VANOL	< 1 : 50	85 (**288b**)	>50:1	<2

[a] Unless otherwise specified, all reactions were run with 1.0 mmol imine at room temperature, concentration of imine was 0.5 M. [b] Determined by ^1H NMR on the crude reaction mixture. The yields of enamine (Ph/H migration) products were the relative yield compared with the major aziridine product. [c] Isolated yield of the major product after chromatography on silica gel.

The absolute stereoselectivity of the major product from the mismatched reaction of the *S*-enantiomer of **156** with the *S*-VAPOL catalyst was further proved by an X-ray diffraction analysis of aziridine (*2R*, *3R*)-**288a** (Figure 6.14). This analysis indicated that

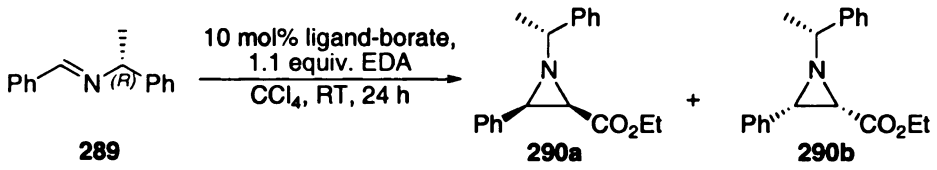
the major product of the mismatched reaction was a result of the catalyst-controlled aziridination of imine **156**.

Figure 6.14 X-ray structure of aziridine **288a**



The significant match/mismatch effects observed in the reaction of imine **156** prompted a further investigation of the α-alkyl benzylimine substrates. Imine **289** was prepared by the condensation of benzaldehyde and the inexpensive and commercially available α-(*R*)-methyl-benzylamine. It was surprising to find that the aziridinations of α-(*R*)-methyl-benzylimine **289** gave essentially the same level of match/mismatch selectivity with both ligands as the α-*tert*-butyl-benzylimine **156** (Table 6.23).

Table 6.23 Match/mismatched study with chiral α-methylbenzylimine **289**



289 **290a** **290b**

entry[a]	ligand	**290a** : **290b**[b]	yield of **290** (%)[c]	cis/trans[b]	enamines (%)[b]
1	$B(OPh)_3$ only	6 : 1	NA	>50:1	22/15
2	*S*-VAPOL	> 50 : 1	79 (**290a**)	>50:1	2/2
3	*R*-VAPOL	1 : 2	40 (**290b**)	>50:1	27/17
4	*S*-VANOL	> 50 : 1	86 (**290a**)	>50:1	4/3
5	*R*-VANOL	1 : 2.2	26 (**290b**)	>50:1	33/19

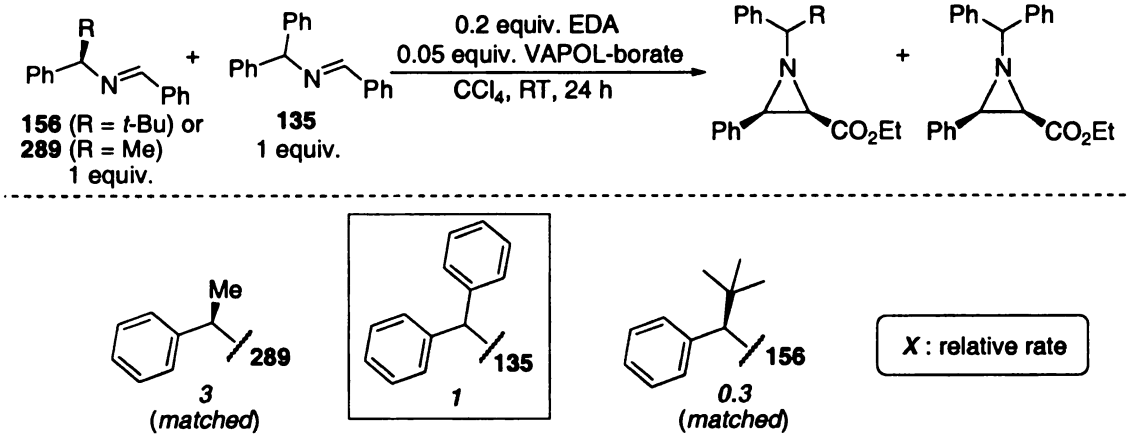
[a] Unless otherwise specified, all reactions were run with 1.0 mmol imine at room temperature, concentration of imine was 0. 5 M. [b] Determined by ^1H NMR on the crude reaction mixture. The yields of enamine (Ph/H migration) products were the relative yield compared with the major aziridine product. [c] Isolated yield of the major product after chromatography on silica gel.

The match/mismatched studies with imines **156** and **289** provide further information of the mechanism of the aziridination reaction. CPK modeling of the interaction between α-(*S*)-*tert*-butylbenzylimine **156** and *R*-VAPOL-borate catalyst **147** indicates potential alkyl-π interaction between the *tert*-butyl group and the face arene ring system of the *R*-ligand. In addition, similar interactions between the methyl group and ligand were also observed in modeling between imine (*R*)-**289** and *S*-ligand.

The relative reaction rates of both chiral imines were measured against benzhydryl imine **135** under the standard competition conditions (Scheme 6.28). Curiously, it was found that the α-*tert*-butylbenzylimine **156** (matched case) reacted three times slower

than imine **135**, while the smaller imine **289** reacted three times faster. According to Wilcox's study and related theoretical calculations[58], the bulky *tert*-butyl group should act as a more efficient π-acceptor,[58] as a result, **156** should have a stronger interaction with catalyst than the smaller imine **289** and the overall reaction rate for **156** should be higher if the formation of the imine-catalyst complex is the rate-determining step. At this stage, a reasonable explanation for the greater rate of **289** is not available.

Scheme 6.28 Relative rates of chiral imines with the VAPOL-borate catalyst



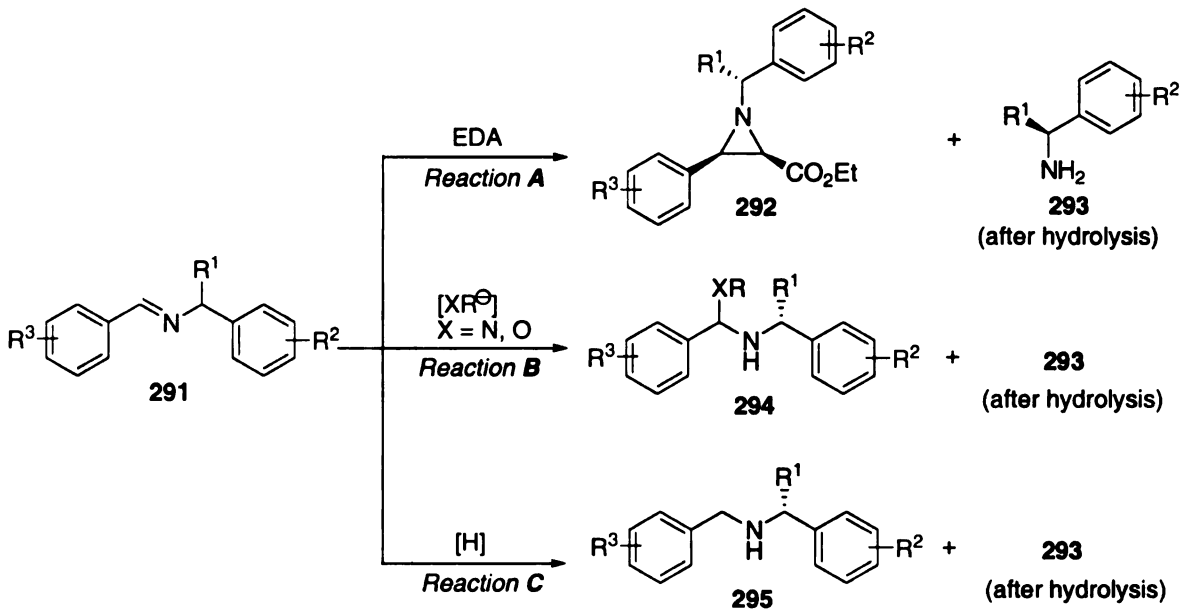
The reactions of the chiral imines **156** and **289** represent a successful example of double stereodiffferentiation,[86] in which the existing stereogenic center on the chiral imines recognize the chirality of the VAPOL and VANOL-borate catalysts. The chiral center of the imine either reinforces the chiral environment projected by the chiral VAPOL or VANOL-borate catalyst (matched asymmetric catalysis) and gives high stereoselectivity, or oppose the chiral environment of the catalyst (mismatched asymmetric catalysis) and gives low stereoselectivity.

The investigation of match/mismatched aziridinations of the chiral imines **156** and **289** was driven by an intent to the study of mechanism of the catalytic asymmetric aziridination reaction and to probe any possible and the CH-π interactions. However, the results of the investigation may have provided access to a new direction of research, namely, the kinetic resolution of racemic α-alkyl benzylimines. The kinetic resolution of alcohols has been extensively studied over the last twenty years, and as a result, some highly selective systems have emerged in literature.[87] In contrast, the kinetic resolution of amines remains virtually undeveloped. Most of the enantioselective kinetic resolution methods for amines utilize enzymes. Prior to 2004 there was only one report of a highly selective catalyst system and that was by Fu et al.[88a] Subsequently, in 2005 Mioskowski and Wager published their chiral diamine acetyl-transfer reagent,[88b-d] and Backvall reported an efficient chemoenzymatic dynamic kinetic resolution process.[88f] However, these methods have their limitations, Fu's system requires an exotic acylation reagent, Wagner and Mioskowski's system requires 0.5 equivalent of chiral reagent, whereas Backvall's system utilizes an enzyme as an acyl donor. The lack of progress in this area is not due to the lower synthetic value of chiral amines, instead, it is a clear indication of the difficulty in the development of successful catalytic kinetic resolution processes for these valuable synthons.

It was envisioned that a process for the kinetic resolution of α-alkylbenzylimines could be developed with the VANOL and VAPOL-borate catalysts and would utilize the mutual recognition between the α-alkyl benzyl moiety on the nitrogen and the VAPOL or

VANOL borate catalyst. The ideal resolution would be the direct reaction between the amine and another reagent, however, currently this process would be unlikely due to the lack of the appropriate methodology. A more likely process would have the α-alkyl benzyl amine masked as the corresponding imine which would participate in reactions with various nucleophiles (Scheme 6.29).

Scheme 6.29 Proposed kinetic resolutions of racemic imine **291**.

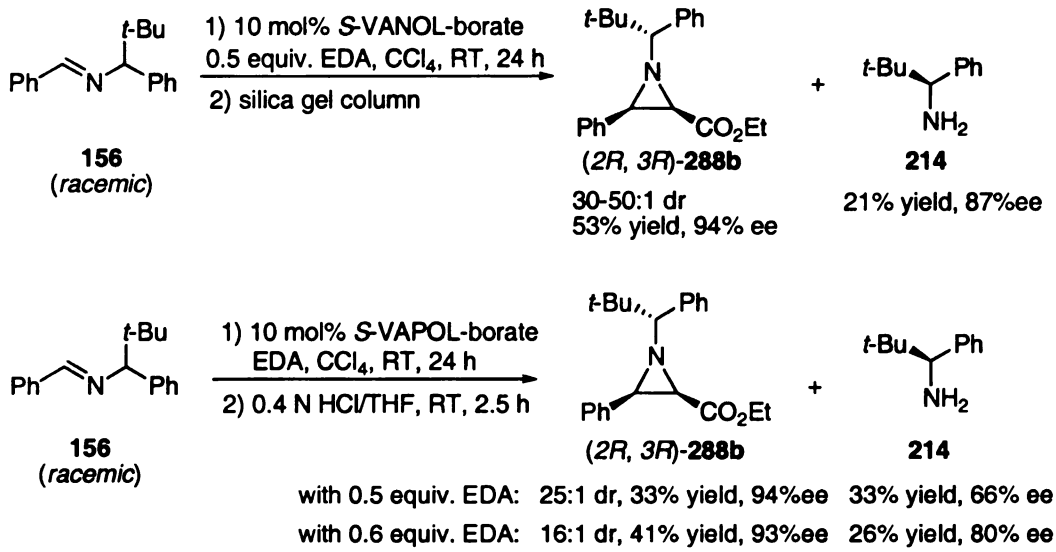


The direct adaptation of the current aziridination process to the reaction between imine **291** and a substoichiometric amount of ethyl diazoacetate would lead to the chiral aziridine **292** and chiral amine **293** after the hydrolysis of the remaining imine (Reaction A). On the other hand, the addition of an oxygen/nitrogen nucleophile to the imine would provide the aminal type product **294**, which upon hydrolysis would afford the enantiomer of amine **293** (Reaction B), and thus both enantiomers of the amine would be accessible. Finally, a more ideal approach involves the reduction of the C=N bond (Reaction C),

which in the case when R_3 = 4-OMe, oxidative cleavage of the PMB group of **295** should also give *ent*-**293**.

The investigation of reaction B and C would require the development of the methodologies currently unknown to this research group. Thus the kinetic resolution employing the already mature aziridination reaction was studied (Scheme 6.30).

Scheme 6.30 Kinetic resolution of racemic imine **156**



In the event, the reaction of racemic **156** with 0.5 equivalent of ethyl diazoacetate in the presence of 10 mol% VANOL-borate catalyst gave the aziridine (*2R*, *3R*)-**288b** in 53% yield and 94% ee. The diastereomeric ratio of **288b** was determined to be 30-50:1 by ^{1}H NMR on the unpurified reaction mixture. Upon chromatography and concomitant hydrolysis of the remaining imine on silica gel, the aziridine (*2R*, *3R*)-**288b** was isolated as well as the desired chiral amine **214** with good optical purity (87% ee) but in low yield. Alternatively, the crude reaction mixture could be hydrolyzed by dilute HCl before chromatography. However, in the reactions with the VAPOL catalyst and 0.5 equivalent

of ethyl diazoacetate the isolated amine **214** was found to be only 66% ee. Reaction with more ethyl diazoacetate (0.6 equivalent) increased the chiral induction of **214** to 80%.

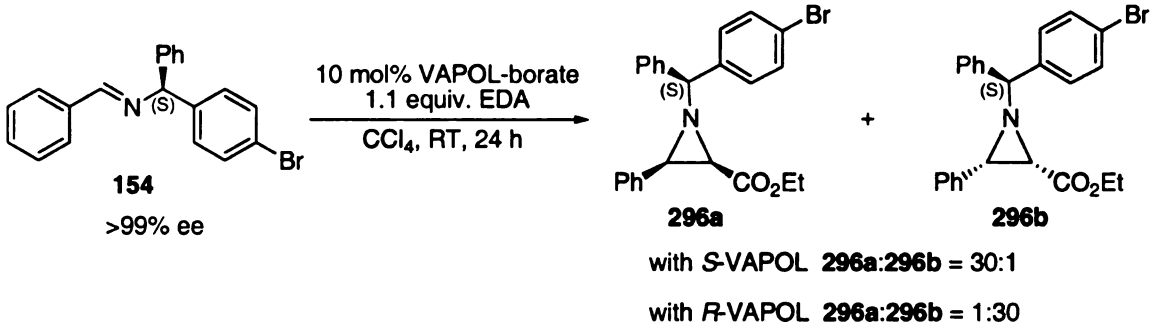
The kinetic resolution with other α-alkylbenzylimines were not studied, although based on the result from match/mismatched aziridination reactions, the reactions with other substrates are expected to give results similar to that with imine **156**.

This preliminary study of the kinetic resolution of imines showed its potential as a successful methodology, but several problems remain to be solved: 1) the low isolated yield of the amine, which was quite possibly due to the low stability of amine toward silica gel and air; 2) the exact stoichiometry of EDA, as the commercially available ethyl diazoacetate was purchased as a mixture with ~10% dichloromethane. Due to the limitation of time, this work will be further pursued by anther group member. It is believed that with careful optimization, this work can be developed into a valuable method for the preparation of a large variety of chiral aziridines and amines.

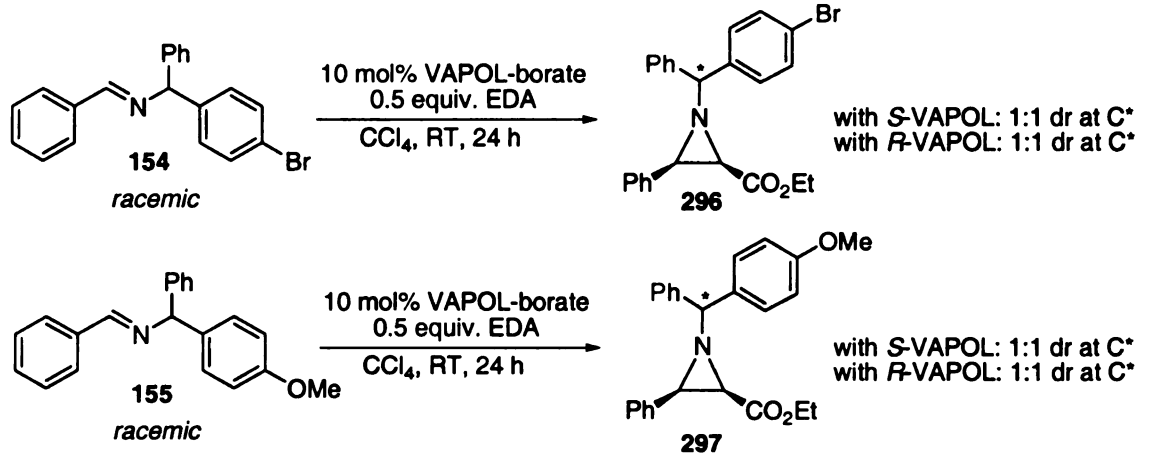
After the studies of the unsymmetrical chiral α-alkyl benzylimines, the reactions of unsymmetrical chiral benzhydryl imines were subsequently conducted. The imines were chosen such that the two phenyl rings are nearly sterically identical. Therefore, the outcome of the reactions of these chiral benzhydryl imines should solely be a function of the by the difference in the electronic property of the two phenyl groups. Thus the observation of match/mismatched pair would provide compelling evidence for the proposed CH-π interactions between the arene rings of the substrate and ligand.

It was very surprising and disappointing to find that in the aziridination of chiral benzhydryl imine **154**, aziridine **296a** and **296b** were obtained almost exclusively in ratios expected from catalyst controlled process. Both enantiomers of the VAPOL-borate catalysts gave a 30:1 ratio of products with no evidence for a match/mismatched pair with the substrate (Scheme 6.31).

Scheme 6.31 Match/mismatched study with chiral benzhydryl imine **154**



Scheme 6.32 Attempted kinetic resolution of chiral benzhydryl imines



An alternative method of examining the match/mismatched relationship between benzhydryl imines and the catalyst is via kinetic resolution. If the proposed CH-π interaction indeed exists, then the matched enantiomer of the imine should bind with one enantiomer of the catalyst more strongly, and as a result, this imine should react with

ethyl diazoacetate at a higher rate. This idea was examined with racemic imines **154** and **155** (Scheme 6.32). As was the case with optically pure **154**, neither enantiomer of the VAPOL-borate catalyst was able to differentiate between the two enantiomers of the either benzhydryl imines. With 0.5 equivalent of ethyl diazoacetate, both reactions were non-selective, giving a 1:1 mixture of the aziridines which were diastereomeric at the benzhydryl carbon position.

The absence of a match/mismatched relationship in the reactions of chiral benzhydryl imines demands a rationale to account for this surprising observation. One plausible explanation involves the limits in the extension of background knowledge of the experimental systems that have been described above. Almost all the theoretical and experimental studies of the effects of substituent on edge-face interactions in arene systems that have been published were conducted with much more simplified benzene-benzene systems.[58-62] In the only known case, Tsuzuki et al performed theoretical studies to the naphthalene dimer and found that the parallel configuration was favored over the T-shaped configuration.[59e] The proposed edge-face interactions in the VAPOL-borate catalyst-benzhydryl imine complex involves the interactions between the substituted benzene rings of the imine on the naphthalene or phenanthrene ring systems of the ligands. Interactions between such complex systems have never been published.

On the other hand, the originally proposed model in Scheme 6.2 may not accurately represent the real complex between the catalyst and substrates. The complexation between the active catalyst species and the imine may actually be quite different from

the model in Scheme 6.2. Although the reactions with α-alkylbenzyl imines indicated a significant match/mismatched relationship, it is possible that the observed double stereo-differentiation was only induced by the chiral pocket of the active catalyst and that the proposed alkyl-π interactions were not involved. This possibility is supported by the puzzling observation that the smaller α-methylbenzyl imine **289** reacts faster than α-*tert*-butylbenzyl imine **156** (Scheme 6.28). The difference in the rate could be the result of the unfavorable steric repulsion between the bulky *tert*-butyl group and ligand.

As discussed in chapter 6.1, the structure of the catalysts **146** and **147** were proposed based on literature precedent[57] and several other possible structures have been excluded based on the consideration of steric interactions (Figure 6.1). However, it is possible that neither **146** nor **147** are the real active catalyst species in the complex generated from the proper ligand with 1 equivalent of triphenyl borate. A related study directed to determining the structure of the VAPOL and VANOL-borate catalysts will be discussed in detail in chapter seven.

6.7 Conclusion

During the studies of the mechanism of the catalytic asymmetric aziridination, a model was proposed to account for the enantioselectivity of this reaction. In this model, the VAPOL or VANOL-borate catalyst is generated from the chiral ligand and one equivalent of triphenyl borate. During the association of the catalyst with the N-benzhydryl imines, two CH-π (edge-face) interactions between the benzhydryl group of

the imine and the arene system of the ligand were proposed as the additional organizing element of the imine-catalyst complex. Based on this model, various imines with different electronic or steric properties were designed to examine these edge-face interactions.

The preparations of various chiral or symmetric imines were discussed and their catalytic asymmetric aziridinations in the presence of the VAPOL or VANOL-borate catalyst were studied in detail. The study of the electronic effect revealed that the N-benzhydryl imines with electron-donating substituents are more reactive and more selective substrates for the aziridination. It was found during the study of the steric effect that the benzhydryl imine with four *meta*-methyl substituents exhibited much better enantioselectivity than the unsubsituted benzhydryl imine. This discovery subsequently led to the new aziridination methodology using N-tetra-*tert*-butyl-dimethoxybenzhydryl (N-BUDAM) and N-tetramethyl-dimethoxybenzhydryl (N-MEDAM) imines. The N-BUDAM imines exhibit extraordinary reactivity in the catalytic asymmetric aziridination reactions with only 2 mol% VAPOL-borate or VANOL-borate catalyst, and the corresponding aziridines were produced in remarkably excellent yields and chiral inductions. The N-MEDAM group is complementary to N-BUDAM group in the reactions of secondary and tertiary alkyl aldimines. Finally, the N-BUDAM and N-MEDAM group on the aziridines can by removed by a mild acid-mediated deprotection process, which provides an easy access to the optically active N-H aziridines.

The study of the relative aziridination reaction rate of various imines via competition reactions indicated large rate differences between imines with different nitrogen protecting groups. Good correlation was observed between the reactivity and the

enantioselectivity of various imines. This study provided further insight into the detailed mechanism of the aziridination reaction. On the other hand, the study of initial reaction kinetics provided seemingly contradictory information about the rate-determining step.

Significant match/mismatched relationship was observed in the aziridination reactions of chiral α-alkylbenzyl imines. These reactions represent a successful example of double stereo-differentiation, and were further applied in the kinetic resolution of racemic α-alkylbenzyl imines via the VAPOL-borate catalyzed aziridination reaction. The preliminary study of this kinetic resolution process gave good results with regard to the asymmetric inductions of aziridine and amine. It is believed that with careful optimization, this discovery may lead to a valuable methodology for the preparation of chiral amines and aziridines.

The study of match/mismatched relationship using chiral benzhydryl imines suggested that the VAPOL or VANOL-borate catalyst can not differentiate the chiral benzhydryl group. The exact reason for the absence of selectivity will be discussed in chapter seven.

At this stage the originally proposed edge-face interactions between the VAPOL or VANOL-borate catalyst and the benzhydryl imine as well as the detailed mechanism of catalytic asymmetric aziridination reaction still await further investigation. However, the new methodologies developed as well as the wealth of information obtained during these mechanistic studies will be invaluable to the broader understanding of the aziridination chemistry.

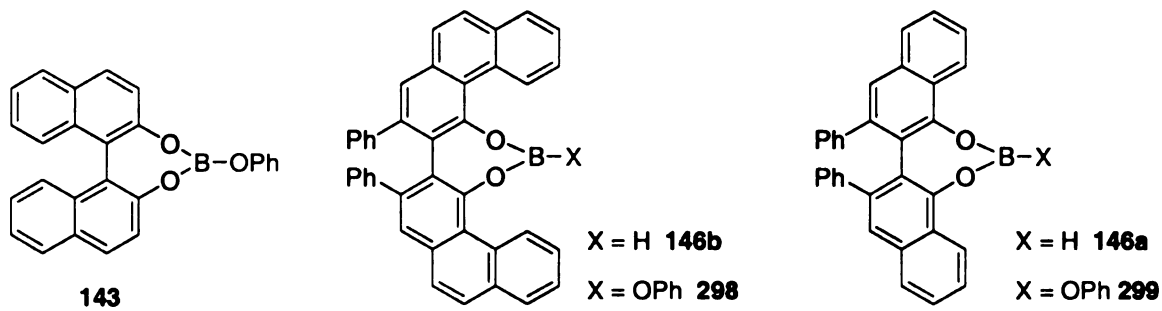
CHAPTER SEVEN

STUDIES OF THE VANOL AND VAPOL-BORATE CATALYSTS

7.1 Introduction

The proposed structure of the aziridination catalysts generated from the reactions of VAPOL and VANOL with triphenyl borate was presented in chapter 6 and these structures were subsequently used to account for the enantioselectivity in the catalytic asymmetric aziridination reaction of benzhydryl imines.

Figure 7.1 Proposed structures of the VAPOL and VANOL-borate catalysts



It was believed that the active catalysts **298** and **299** were generated from the VAPOL and VANOL ligands respectively when reacted with one equivalent of triphenyl borate (Figure 7.1). These proposed structures are based on studies by Yamamoto,[57a] who described that **143** was the most probable structure for the catalyst generated from BINOL and 1 equivalent of triphenyl borate. However, no spectroscopic evidence for **143** was provided by Yamamoto or others.[57a, 57d] Several other possible structures for the

VAPOL-borate catalyst were excluded based on the analysis of sterics and on the similar reports by Yamamoto and Kaufmann and these were previously discussed in chapter 6 (Figure 6.1).[57a, 57c]

During the mechanistic studies on the catalytic asymmetric aziridination that were presented in chapter 6, it was proposed that the complexation between **147** and benzhydryl imine **135** involves two edge-face interactions between the aromatic system of chiral ligand and the phenyl rings of the benzhydryl group (Figure 6.2). These interactions were considered to provide an additional organizing factor for the imine-catalyst complex. A study of match/mismatched pair using various chiral imines was subsequently designed and tested (Figure 6.5, Figure 6.6). Although the reactions with chiral α-alkylbenzylimines exhibited significant match/mismatched relationships with the chiral catalysts (Table 6.22, Table 6.23), the reactions with chiral benzhydryl imines suggested that the chiral VAPOL-borate catalyst was unable to differentiate between the two sterically similar but electronically different phenyl rings (Scheme 6.31, Scheme 6.32).

The unexpected lack of match/mismatched pairs with chiral benzhydryl imines prompted a reinvestigation of the originally proposed model (Figure 6.2) and more specifically, a reconsideration of the structure of the active VAPOL and VANOL-borate catalysts for the catalytic asymmetric aziridination reaction. The complexes generated from either the VAPOL, VANOL or BINOL ligands with triphenyl borate have never been

studied comprehensively by means of spectroscopic methods. It is thus desirable to investigate this issue, and the identification of the actual active catalyst and accurate information on the catalyst structure should provide important insights into the mechanism of asymmetric catalytic aziridination developed in this lab.

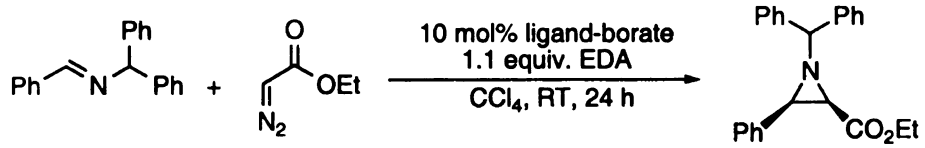
7.2 Study of nonlinear effects with VAPOL-borate and VANOL-borate catalyst

In most reactions involving the chiral Lewis acids or transition metal catalysts, the catalyst is generated from one equivalent of the metal (or Lewis acid) and one or more equivalents of the chiral ligand to give catalysts that are either a 1:1 complex (ML type, such as **147**) or a 1:n complex (ML_n type, n>1). Although based on the literature, catalysts generated from more than one equivalent of the VAPOL or the VANOL ligand such as **144** (ML_2 type) or **145** (M_2L_3 type) (Figure 6.1) are considered unlikely to form due to anticipated steric interactions,[57c] their existence remains to be excluded by real evidence.

The identification of the possibility of an ML_n type catalyst can be achieved following the pioneering work of Kagan on nonlinear effects,[89] it was described that a plot of ee_{prod} versus ee_{ligand} can be a simple way to obtain information about the structure of a catalyst. An aggregation state or the formation of a species which includes more than one chiral ligand as in the case of ML_n is indicated by an abnormal curve in the plot. The details of this phenomenon will not be discussed here. On the other hand, Kagan also pointed out

that an observed linearity does not fully disprove the association between metal and two or more ligands, because under certain conditions, the catalyst (such as ML_2 type) could in theory still produce a linear effect.

Table 7.1 Study of nonlinear effect with VAPOL/VANOL-borate catalyst



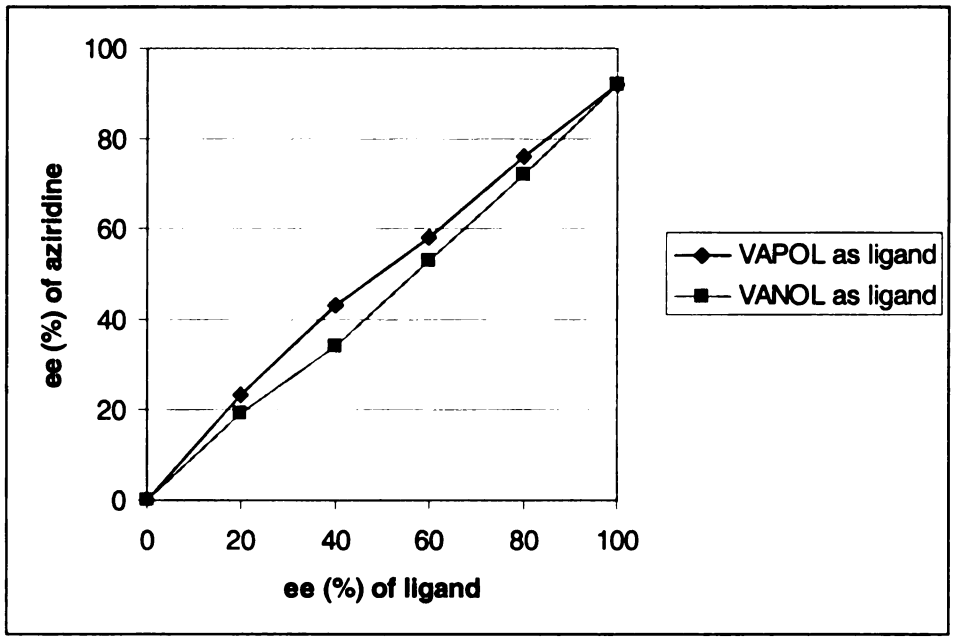
135 **21** **136**

entry[a]	ligand	ee of ligand (%)	yield of **136** (%)[b]	ee of **136** (%)[c]
1	*R*-VAPOL	20	84	23
2	*R*-VANOL		86	19
3	*R*-VAPOL	40	84	43
4	*R*-VANOL		83	34
5	*R*-VAPOL	60	82	58
6	*R*-VANOL		87	53
7	*R*-VAPOL	80	85	76
8	*R*-VANOL		83	72
9	*R*-VAPOL	>99.5	78	92
10	*R*-VANOL		88	92

[a] Reactions were performed with the ligand generated from the proper mixture of racemic and enantiomerically pure ligand. The catalysts were prepared from the ligand and three equivalents of triphenyl borate at 80°C according to the standard condition. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC on a Chiralcel OD-H column.

The study of nonlinear effects of the VANOL-borate and VAPOL-borate catalysts was conducted with benzhydryl imine **135** under the standard catalytic aziridination conditions. In the preparation of the catalysts the optically pure and racemic ligand was mixed according to various ratios so that the optical purity of the resulting ligand was 20, 40, 60 and 80% ee, respectively. As a result, both the VAPOL-borate and VANOL-borate catalyzed reactions showed a gradual increase in the asymmetric induction of **136** with an increase of optical purity of the ligand (Table 7.1).

Figure 7.2 Plot of optical purity of aziridine versus optical purity of ligands



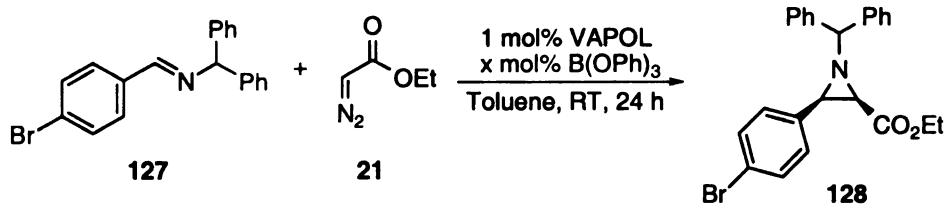
The optical purity of the aziridine **136** was plotted against that of the chiral ligand (Figure 7.2). The reaction profiles with both VAPOL and VANOL-derived catalysts indicated a fairly good linear relationship between the optical purities of the aziridine and those of the chiral ligands. Thus based on the numerous literature examples of nonlinear

effects in various catalysis systems,[89] the active VAPOL and VANOL borate catalysts are most likely generated from only one equivalent of the chiral ligand.

7.3 Studies on the VAPOL-borate catalyst by MS, NMR and theoretical methods

The standard condition for the generation of VAPOL or VANOL borate catalyst involves the reaction of one equivalent of ligand with three equivalents of triphenyl borate at 55 or 80°C for one hour, followed by removal of volatile material under high vacuum. It was suspected that because the formation of one molecule of the proposed catalyst **298** or **299** (Figure 7.1) only requires one equivalent of triphenyl borate, the excess amount of racemic triphenyl borate may catalyze the background racemic reaction and result in reduced chiral induction in the aziridination. Thus a systematic study of the loading of triphenyl borate was conducted in order to find the optimal ratio of the chiral ligand and triphenyl borate (Table 7.2). In this study, 1 mol% of VAPOL was used for each reaction and the amount of $B(OPh)_3$ was gradually increased from 1.5 equivalent to 30 equivalent, and the efficiency of the resulting catalyst in each case was evaluated for the aziridination of the *para*-bromobenzaldimine **127**.

Table 7.2 Study of loading of triphenyl borate by aziridination of *p*-bromobenzaldimine



127 21 128

Entry[a]	$B(OPh)_3$ **54** (mol %)	conversion (%)[b]	yield of **128** (%)[c]	ee of **128** (%)[d]
1	1.5	26	25	83
2	2	98	82	85
3	2.5	97	82	88
4	3	100	85	88
5	5	100	85	89
6	10	100	85	87
7	30	100	84	83
8[e]	3	26	--	--

[a] Unless otherwise specified, the catalyst was prepared from 1 mol% of VAPOL and the indicated amount of triphenyl borate according to standard procedure. [b] Determined by ^1H NMR on the crude reaction mixture. [c] Isolated yield after chromatography on silica gel. [d] Determined by chiral HPLC. [e] VAPOL was not used, only 3 mol% $B(OPh)_3$ was used as catalyst.

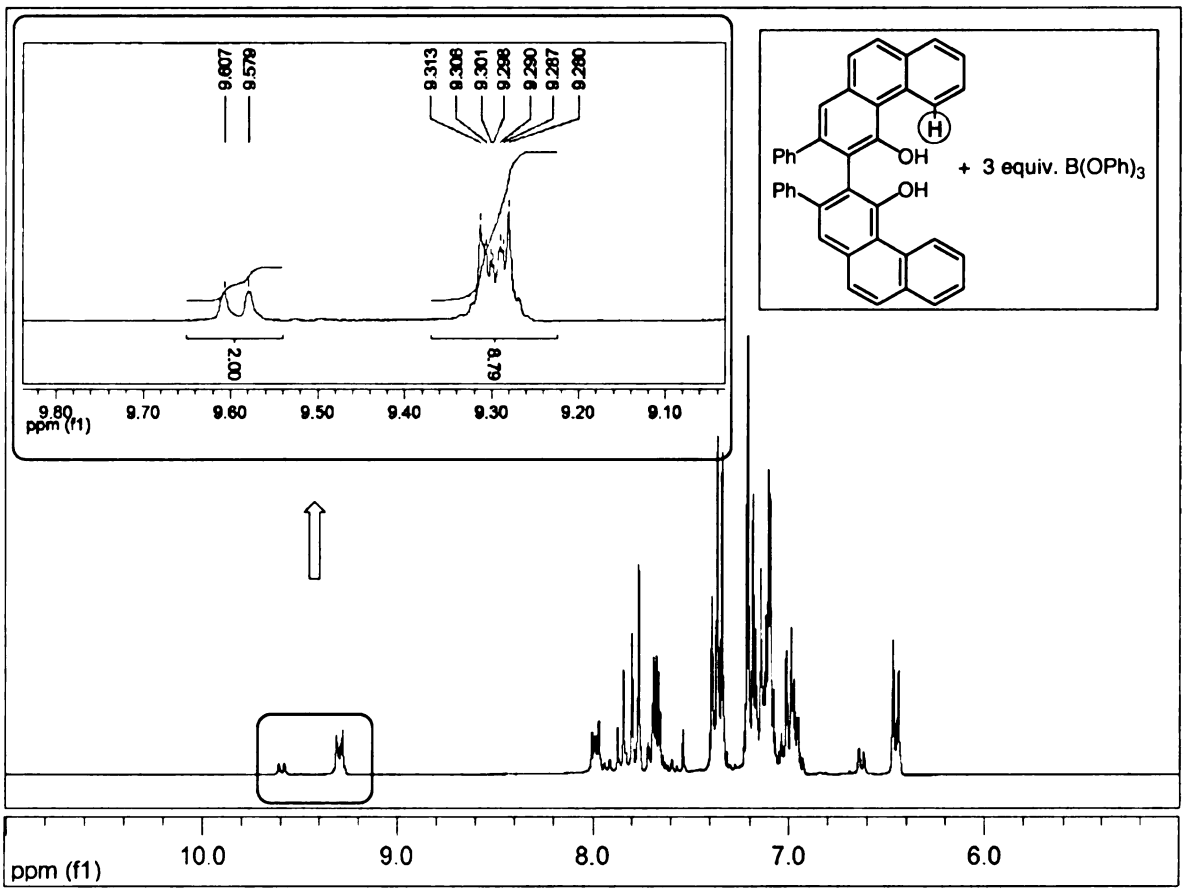
In sharp contrast to the original proposal, the use of less than 2.5 equivalents of triphenyl borate **54** led to incomplete conversion of imine **127**, produced lower asymmetric induction in aziridine **128** gave and reduced isolated yield of **128** (entry 1, 2). The conversion of the imine as well as the yield and asymmetric induction of aziridine increased gradually when the amount of triphenyl borate was raised from 1.5 to 2.5 equivalents. The use of 3 to 5 equivalents of triphenyl borate led to the highest yields and enantioselectivities (88-89% ee, entry 4, 5). Interestingly, even 10 equivalents of

$B(OPh)_3$ had little significant detrimental effect on the chiral induction (87% ee, entry 6). It was not until the amount of triphenyl borate was increased to 30 equivalents that moderate loss of in the asymmetric induction was observed (entry 7). On the other hand, a control experiment that employed 3 mol% triphenyl borate as the sole Lewis acid catalyst revealed that there is a certain degree of background reaction. As indicated in entry 8, 3 mol% of $B(OPh)_3$ catalyzed the reaction of **127** and gave 26% conversion under the standard reaction time (24 h). Thus, the relative rate of the VAPOL-borate catalyst must be significantly higher than that of triphenyl borate in the cases of entry 4-7. This is not completely surprising as cyclic boronate esters have been reported to have increased boron Lewis acidity over their corresponding acyclic analogues.[57d]

The triphenyl borate loading study raised one intriguing question: If only one equivalent of triphenyl borate **54** is necessary, why did the catalyst prepared from less than 2 equivalents of $B(OPh)_3$ give worse results than the catalyst prepared from 5 equivalents of $B(OPh)_3$?

The catalyst prepared from VAPOL and three equivalents of triphenyl borate under the standard condition was subsequently examined by ^1H NMR. The bay protons of VAPOL (shown as the bold red H in red circle, Figure 7.3) are significantly more downfield (doublet at 9.8 ppm for VAPOL, not shown in spectrum) than all the other aromatic protons, which makes for the convenient identification of VAPOL by ^1H NMR.

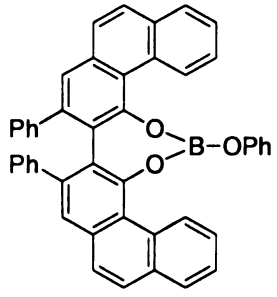
Figure 7.3 ^{1}H NMR spectrum (in $CDCl_3$) of the VAPOL-borate catalyst



Shown in Figure 7.3 is the ^{1}H NMR spectrum of the $CDCl_3$ solution of the VAPOL-borate catalyst from 3 equivalents of $B(OPh)_3$ and in this particular spectrum the VAPPOL ligand has been completely consumed. Curiously, two sets of bay protons within the 9-10 ppm region were always observed in every batch of catalyst examined. These two sets of signals include a doublet at 9.59 ppm and a multplet between 9.28 and 9.32 ppm with a relative integral of ratio in Figure 7.3 is 1:4.4. The ratio of the doublet/multiplet may vary even with the same catalyst generation procedure, but in most cases the ratio falls into the range of 1:3-5, with the multiplet always being the

major component in the catalyst mixture. These signals suggest that there are two catalyst species.

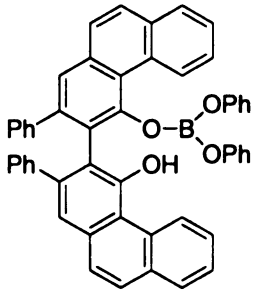
Figure 7.4 Mass spectral analysis of VAPOL-borate catalyst species



298

Calcd mass: 640.2210
Found mass: 640.2214

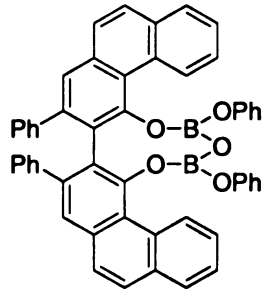
(4.6% rel intensity)



300

Calcd mass: 734.26

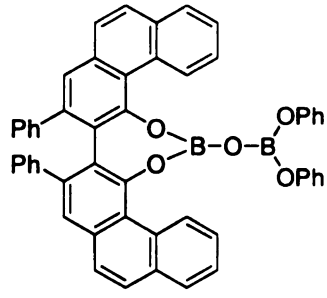
Not Found



301

Calcd mass: 760.2592
Found mass: 760.2596

(12% rel intensity)



302

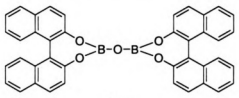
From first appearances it was though that the bay proton doublet at 9.59 ppm is of a C2 symmetrical species and the multiplet at 928-9.32 ppm is of a species where the two bay protons have become non-identical. Initial assignments were that the doublet at 9.59 ppm was the signal of the bay protons of C2-symmetric species **298**, whereas, the multiplet at 9.28-9.32 ppm was of the a borate ester species **300** generated from the condensation of only one hydroxyl group of VAPOL with triphenyl borate (Figure 7.4). To confirm these two proposed structures the catalyst solution was subjected to MS-FAB analysis. Consistent with the ^{1}H NMR spectrum, only two species were detected in the mass spectrum, and as expected, the originally proposed structure **298** was indeed found as the minor species. However, surprisingly the major species detected in the mass spectrum of the catalyst mixture was an unexpected species whose molecular

weight was 760, and a peak at m/z = 734 expected for **300** was not observed. The complex with a mass of 760 could be a species derived from one molecule of VAPOL and two molecule of triphenyl borate, and two possibilities for this would be either **301** or **302**. The species **298** and **301/302** were also confirmed by high-resolution mass spectral analysis.

The oxygen bridge between the two boron atoms in **301** or **302** indicated that during the formation of this species, one molecule of water must have participated in the reaction. As the procedure for the preparation of the catalyst involves moisture-free conditions and is performed in oven and flame dried Schlenk flasks and employ freshly distilled solvents, this oxygen atom was though to most likely to result from partially hydrolyzed triphenyl borate. This conclusion was not surprising as it was found that the purity of commercially available triphenyl borate from various suppliers was never higher than 85%. Triphenyl borate is susceptible to hydrolysis by moisture and presumably during its manufacture, packaging, weighing and/or transfer some hydrolysis occurred.

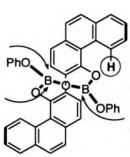
Distinguishing between structures **301** and **302** would be more difficult as the two species have the same molecular weight. Compounds composed of one chiral diol ligand and two boron atoms have never been reported. The only report of a chiral diol contained in a boronic anhydride is the pyroborate **303** (Figure 7.5) prepared from BINOL and boric acid.[57e,f]

Figure 7.5 Boric anhydride prepared from BINOL



303

Figure 7.6 Proposed rationale for the observed multiplets of bay proton in $CDCl_3$



301

$CDCl_3$ from same face:
-- Not C2 symmetric

$CDCl_3$ from opposite face:
-- C2 symmetric

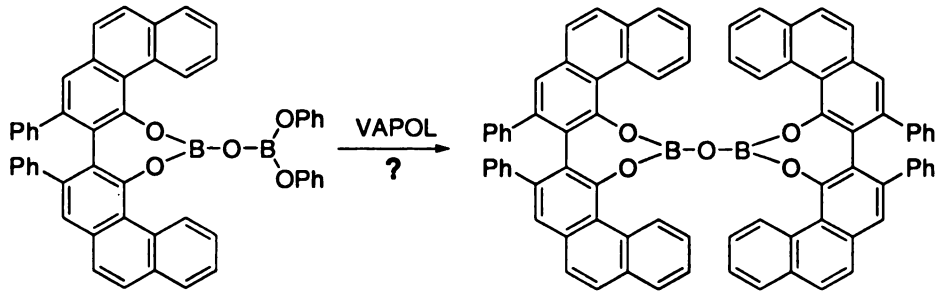
(Two Ph groups ommited)

Several observations were consistent with the structure **301** rather than **302** (Figure 7.4). The multiplet signal of the bay proton at 9.28-9.32 ppm in the $CDCl_3$ solution suggests that it is not a C2 symmetric structure. This could be explained by the coordination of one $CDCl_3$ molecule to each of the two boron atoms in the C2 symmetric structure **301** which can occur from either the opposite face or the same face of B-O-B plane (Figure 7.6). The former leads to a C2 symmetrical structure and the latter leads to a non-C2 symmetric structure. The non-selective coordination of $CDCl_3$ will lead to a mixture of two diastereomeric complexes, whose bay-protons will be non-identical. In the case of structure **302**, the coordination of both boron atoms with $CDCl_3$ can only lead to a single diastereomer, whose bay protons would thus appear as a doublet. This

hypothesis was further supported by the fact that when the ^{1}H NMR spectrum was taken in d_6-bezene, the multiplet at 9.28-9.32 ppm became a clear doublet, indicating a C2-symmetric structure.

The piece of second evidence supporting structure **301** is that it doesn't exhibit reactivity that would be expected for structure **302**. The proposed complex **302** has two phenoxy groups on one boron atom, and these two phenoxy groups might be expected to further react with another molecule of ligand and give the structure **304** (Scheme 7.1). Due to the two extra oxygen-boron bonds structure **304** should not suffer from the steric hinderance expected for **144** (Scheme 6.2). However, and m/z expected for **304** was never observed in the MS analysis. In those cases where less than two equivalents of triphenyl borate was used for the preparation of the catalyst, significant amounts of the free VAPOL ligand were always observed in the ^{1}H NMR spectrum, along with **298** and **301/302**, which indicated that further reaction between the proposed structure **302** and VAPOL did not occur.

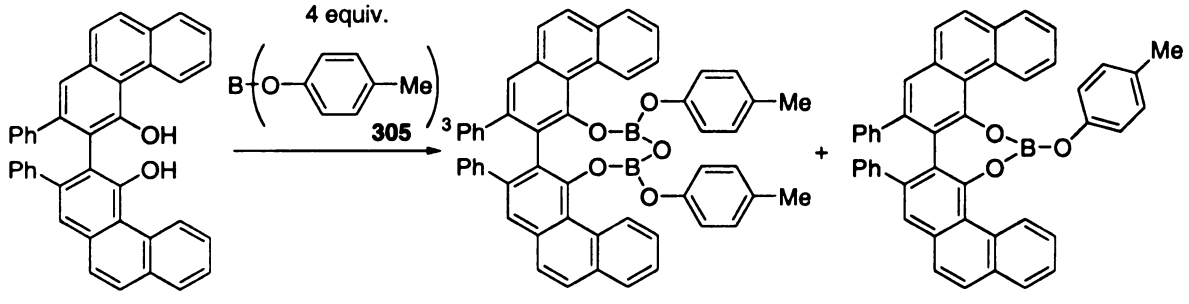
Scheme 7.1 Proposed formation of **304** from borate **302**



302 **304**
Not observed

The last piece of evidence in favor of structure **301** over **302** came from the theoretical calculation which will be discussed in detail in the next few pages. The borate **302** is structurally similar to **298** and both species were determined by various calculation methods to be less stable than **301**.

Table 7.3 ^{1}H NMR and MS analysis of the catalysts prepared from tri-*p*-tolyl borate and VAPOL



46

306
Calcd mass: 788.2905
Found mass: 788.2918
(14% rel intensity)

307
Calcd mass: 654.2366
Found mass: 654.2376
(9.2% rel intensity)

entry[a]	temp. (°C)	solvent	H_2O (equiv.)	**306:307** (by bay H)[b]	**306:307** (by methyl H)[b]	conversion (%)[b]
1	55	CH_2Cl_2	none	1.3:1	1.2:1	>95
2	55	CH_2Cl_2	0.5	3.3:1	3.3:1	80
3	80	toluene	1.0	8.5:1	8:1	100

[a] The catalyst was prepared from one equivalent of **46** and 4 equivalent of **305** at indicated temperature in the appropriate solvent, water was added before the heating. [b] Determined by ^{1}H NMR integration of the bay proton or methyl group in $CDCl_3$.

The assignment of the bay proton doublet at 9.59 ppm as due to the structure **298** and the bay proton multiplet at 9.28-9.32 ppm as due to the structure **301** is a result of the expected symmetry of each as well as the fact that the most intense ion in the mass

spectrum was for m/z = 760. Since the mass spectrum is not a reliable quantization tool, it was decided that further evidence in support of this assignment was needed. Thus the borate derivatives **306** and **307** were prepared from *para*-methylphenyl borate **305** such that methyl groups could be integrated against the bay protons. Borate **305** was prepared from the azeotropic refluxing of boric acid and cresol, and the crude borate was carefully purified under moisture-free environment to avoid partial hydrolysis, the chemical purity of **304** used was determined to be at least 95% by ^{1}H NMR. As a result, the corresponding VAPOL catalyst prepared from this non-hydrolyzed triphenyl borate gave a lower ratio of **306**:**307** (Table 7.3, entry 1) with all the efforts to taken to avoid contamination by H_2O, it is surprising that **306** was formed at all. While efforts were made to ensure that all reagents and solvent were dry, and the reaction was carried out in a Schlenk flask, the transfer of some reagents was done with brief exposure to air. Fortunately, the methyl groups of **306** and **307** were distinct. Integration confirmed that borate with the bay proton doublet at 9.63 ppm had only one phenoxy group present and the borate with the bay proton multiplet at 9.34-9.37 ppm had two phenoxy groups in the molecule, thus confirming the assignments of **298** and **301** (Figure 7.4). MS-FAB analysis again confirmed the existence of the two species by both low-resolution and high-resolution mass spectra. Borates **306** and **307** were the only two major species detectable by both NMR and MS.

During the preparation of the catalysts from borate **305**, small amounts of water was added to the reaction mixture. It was found that the addition of 0.5 to 1 equivalent of water significantly increased the proportion of di-borate **306** (entry 2, 3). This observation is compelling evidence for the proposal that the formation of di-borate species **306** (or **301**) is due to the partial hydrolysis of triphenyl borate.

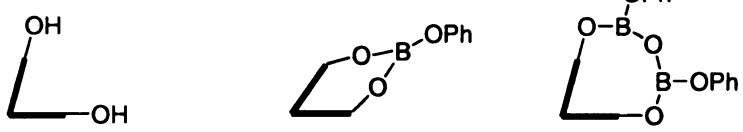
After the successful identification of the two species present in the VAPOL catalyst mixture by NMR and MS, the two catalyst species were further explored by other methods. To further understand the properties of the two catalyst species, theoretical calculations of the ligands and their corresponding catalysts were subsequently conducted.

The calculations were performed by geometry optimization of the molecules with Spartan '04 program. Several methods at different theoretical levels were employed which include semi-empirical calculations, the Hartree-Fock calculations and more advanced density functional calculations.[41] All of the above methods should in theory provide a generally credible accounting of the experimental structural data. Semi-empirical methods such as PM3 are considered the most cost-effective methods for larger molecules. The Hartree-Fock methods can give considerably more accurate results with regard to bond length and angle. The density functional (DFT) methods generally provide further improvement over HF methods and their mean absolute errors are smaller. DFT methods such as EDF1/6-31G** are considered to be the best

compromise of speed and accuracy for calculations of large molecules. However, the biggest obstacle with the more desirable high level (such as DFT) methods lies in the significantly increased computational times.

The first observation from the optimized geometry of various molecules was the significant difference in the dihedral angles between the two naphthyl/phenanthrol rings of the free ligands, and their di-borate and mono-borate complexes (Table 7.4). Regardless of the calculation methods employed, the dihedral angles of all three ligands (**L**) vary from 85 to 90 degrees. The same angles of the corresponding di-diborate catalysts (**B**) are only slightly larger than those of the free ligands and the difference is generally less than 5-6 degrees. However, the dihedral angles of the mono-borate catalysts (**A**) are significantly (~ 25-30 degree) smaller than those of the free ligands. In the case of VAPOL and VANOL, such a dramatic change in dihedral angles from the free ligands (**L**) or the di-borates (**B**) to the mono-borate catalyst (**A**) leads to one question: is this decrease in dihedral angle affecting the overall stability of the mono-borate catalysts?

Table 7.4 Calculated dihedral angle of the free ligands and their corresponding catalysts[a]



ligands **L** | ligand-mono-borate **A** | ligand-di-borate **B**

ligand	calculation model	dihedral angle of **L**	dihedral angle of **A**	dihedral angle of **B**
VAPOL	PM3	91.42	58.63	94.26
	HF3-21G	90.18	61.15	95.44
	HF/6-31G*	83.83	59.42	91.63
	EDF1/6-31G**	84.19	61.41	91.84
VANOL	PM3	92	53.09	83.76
	HF/3-21G	89.90	53.75	92.51
	HF/6-31G*	83.03	52.58	88.13
	EDF1/6-31G**	81.97	53.99	87.85
BINOL	PM3	96.82	48.81	77.51
	HF/3-21G	90.93	51.81	92.52
	HF/6-31G*	90.54	50.15	88.84
	EDF1/6-31G**	89.71	51.27	88.48

[a] Calculations were performed with Spartan '04 program. The equilibrium geometries of the molecules (in gas phase) were optimized with the indicated computational methods.

Calculations of strain energy using computational method are well-documented in literature.[90] The commonly used methods include the isodesmic method and the homodesmotic method.[91] Both methods were originally developed for the calculation of

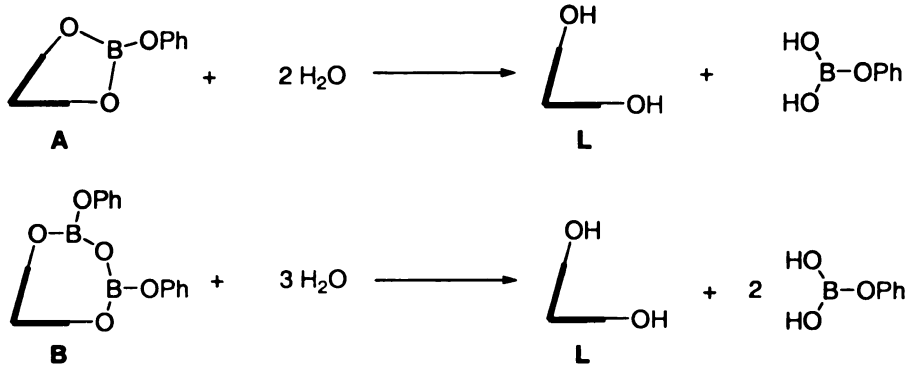
the strain energy of various molecules using the experimental value of H_f known for that compound.

In the isodesmic method, the strained molecules undergo proposed "isodesmic reactions". These reactions "are examples of chemical changes in which there is retention of the number of bonds of a given formal type (e.g., C-O, B-O) but with a change in their formal relation to one another."[91]

The homodesmotic method is a conceptually more satisfactory method. In the homodesmotic method, there are "(a) equal numbers of C atoms in their various states of hybridization in the reactants and products, and (b) equal number of C atoms with zero, one, two, and three atoms attached in the reactants and products."[91] The homodesmotic method is commonly used for the calculation of strained molecules by the means of either experimental or theoretical methods.[90a,b]

Applying these two methods, the calculations with various theoretical models were conducted and the results are shown in Table 7.5 and Table 7.6. Despite the possibility that various computational models may overestimate or underestimate the overall energy of different molecules, almost all the models indicated a higher strain energy for the mono-borate catalyst (**A**) than that for di-borate catalyst (**B**). Only the PM3 calculation from the isodesmic method gave the opposite prediction, and this particular result is probably due to the low level of the computational model and energy calculation methods.

Table 7.5 Calculation of strain energy using the isodesmic method[a]



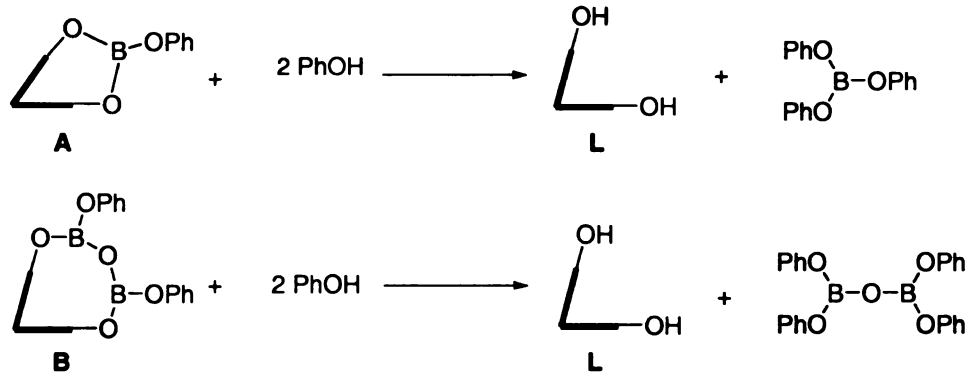
	calculation model	strain energy of **A**	strain energy of **B**	relative strain (kcal/mol)
VAPOL	PM3	-27.52	-30.45	-2.93
	HF/3-21G	-28.01	-13.35	14.66
	HF/6-31G*	-16.69	-7.21	9.48
	EDF1/6-31G**	-24.26	-21.54	2.72
VANOL	PM3	-26.17	-28.37	-2.2
	HF/3-21G	-25.02	-12.09	12.93
	HF/6-31G*	-14.60	-6.38	8.22
	EDF1/6-31G**	-20.42	-18.58	1.84
BINOL	PM3	-24.77	-30.15	-5.38
	HF/3-21G	-22.47	-11.81	10.66
	HF/6-31G*	-15.49	-7.36	8.13
	EDF1/6-31G**	-20.52	-18.71	1.81

[a] Calculations were performed with Spartan '04 program. The equilibrium geometries of the molecules (in gas phase) were optimized with the indicated calculation models.

Interestingly, calculations with the homodesmotic method using various theoretical models gave very similar results for all three of the ligands (Table 7.5). The estimated relative strain energy of catalyst (**A**) over (**B**) varied from 4-6 kcal/mol with PM3, HF/6-

31G* and EDF1/6-31G** models, with the exception of HF/3-21G* model which seemed to overestimate the strain energy (and the energy difference) of all the molecules.

Table 7.6 Calculation of strain energy using the homodesmotic method[a]



	calculation model	strain energy of **A**	strain energy of **B**	relative strain (kcal/mol)
VAPOL	PM3	-10.13	-5.129	5.00
	HF/3-21G	-25.93	-13.63	12.30
	HF/6-31G*	-13.89	-7.28	6.61
	EDF1/6-31G**	-13.95	-9.44	4.51
VANOL	PM3	-8.785	-3.054	5.73
	HF/3-21G	-22.934	-12.382	10.55
	HF/6-31G*	-11.80	-6.45	5.35
	EDF1/6-31G**	-10.11	-6.48	3.63
BINOL	PM3	-7.39	-4.83	2.56
	HF/3-21G	-20.38	-12.10	8.28
	HF/6-31G*	-12.69	-7.43	5.26
	EDF1/6-31G**	-10.21	-6.61	3.60

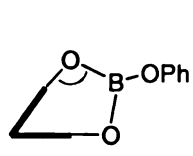
[a] Calculations were performed with Spartan '04 program. The equilibrium geometries of the molecules (in gas phase) were optimized with the indicated calculation models.

The calculated relative strain energy of the BINOL-borate was comparable to those of VAPOL and VANOL-borates. This value (3-5 kcal/mol with homodesmotic method)

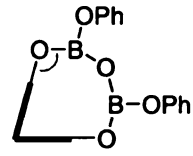
was surprisingly high, considering that the strain energy was primarily a result of steric repulsion between the two C8 and C8' hydrogen atoms of BINOL.

The exact reason why the di-borate catalysts **B** are more stable than the mono-borates **A** is not clear. One plausible explanation again came from the examination of the optimized structure of both catalyst species (Table 7.7). It was found that for all the three ligands, the carbon-oxygen-boron bond angles in borate **A** are considerably smaller than the same angles in borates **B** and triphenyl borate **54**. Thus it is possible that the compression of the C-O-B angle contributes to the overall higher energy of borates **A**.

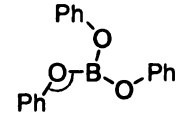
Table 7.7 Average C-O-B bond angles in **A**, **B** and triphenyl borate[a]



A



B



54

entry	ligand	C-O-B bond angle of **A**	C-O-B bond angle of **B**	C-O-B bond angle of **54**
1	BINOL	118.22	123.70	125.72
2	VANOL	117.96	124.66	125.72
3	VAPOL	116.51	124.17	125.72

[a] Calculations were performed with Spartan '04 program. The equilibrium geometries of the molecules (in gas phase) were optimized with EDF1/6-31G** model. The bond angle of **A** and **B** is the average of two angles and that of **54** is the average of three angles.

The results from these calculations suggest that the mono-borate catalysts **A** are indeed less stable than di-borate catalysts **B**. Although the detailed mechanism by which

the two borate species form is not known, it is reasonable to postulate that during the nucleophilic attack of one of the C2-oxygen of the ligand on a boron attached to the other oxygen of the ligand is difficult due to the strain energy in species **A**. Thus the formation of catalyst **A** is probably more difficult due to the combined effects of the unfavorably high kinetic barrier and lower thermodynamic stability. This proposal agrees with the experimental observation that the di-borate catalysts **B** are always the major component of the catalyst mixture. Likewise, the results from these theoretical studies also suggest that structure **302** (Figure 7.4) is less likely to form than the di-borate **301**.

7.4 Identification of the active aziridination catalyst species

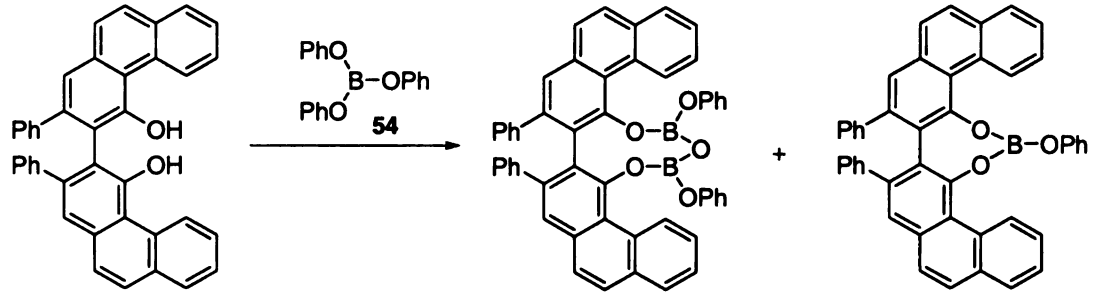
Now that a compelling case has been made that the aziridination catalyst consists of a mixture of the species **298** and **301**, the emphasis of the mechanistic study was then focused on the identification of the active aziridination catalyst. It was suspected that the di-borate species **301** was an inactive catalyst, since CPK modeling indicated that each of the two boron atoms was shielded by the protruding phenoxy group of the opposite boron. The computer optimized structure shown in Figure 7.6 also reveals that the two phenoxy may possibly block access of the imine to either boron. In the preparation of the VAPOL-borate catalyst, species **301** is always observed as the major component (~ 80%) and **298** is always the minor component (~ 20%). If complex **301** is indeed an inactive species, it would be very desirable to suppress its formation and increase the proportion

of the active mono-borate species **298**. For example, if the ratio of **298/301** could be increased from 1:4 to 4:1, the actual catalyst loading could be decreased by four times.

Subsequently, a series of experiment was conducted to study how the ratio of the two VAPOL-borate catalysts **298** and **301** responds to variations in the conditions under which they are generated (Table 7.8). It was found that three equivalents of triphenyl borate **54** were necessary for catalyst generation. Less than three equivalents of $B(OPh)_3$ always led to incomplete conversion of VAPOL (entry 1). The use of 1.5 equivalents of $B(OPh)_3$ gives a ratio of **301/298** which is lower (1-2:1) than the standard procedure for catalyst generation which employs 3 equivalent (entry 1 vs 2). The use of 3 equivalents of $B(OPh)_3$ gives a ratio of 3-5:1 (average of 5 runs) and it was found that a prolonged heating time did not affect this ratio (entry 3), the ratio of **301:298** could increased to 8-12:1 with the use of ten equivalents of $B(OPh)_3$ (entry 4).

The catalyst prepared at room temperature under various conditions always suffered from low conversion (< 50%) (entry 5, 6), and the conversion was not improved after prolonged reaction period (entry 7). However in all three cases the observed ratio of **301/298** was significantly higher than that for the catalyst generated under the standard conditions (entry 2). This result may not be surprising as the calculations suggested that **298** is the relatively higher-energy species and thus its formation may be quite possibly more difficult at room temperature.

Table 7.8 ^{1}H NMR studies of the VAPOL-borate catalyst



46 301 298

entry[a]	solvent	temp. (°C)	equiv. of $B(OPh)_3$	time (h)	equiv. of H_2O	**301:298**[b]	convn. (%)[b]
1[c]	CCl_4	80	1.5	1	0	1.2-2.2:1	< 90
2[d]	CCl_4	80	3-4	1	0	3-5:1	100
3	CCl_4	80	4	26	0	4.5:1	100
4[c]	CCl_4	80	10	1	0	8-12:1	100
5	CH_2Cl_2	25	3	1	0	10:1	< 50
6	$CDCl_3$	25	3	1	0	8:1	< 50
7	$CDCl_3$	25	3	6	0	8:1	< 50
8	$CDCl_3$	25	3	1	3	>10:1	6
9	$CDCl_3$	25	3	1	1	>10:1	30
10	CH_2Cl_2	80	3	1	3	10:1	70
11	CH_2Cl_2	80	3	1	1	15:1	100

[a] The catalyst was generated from one equivalent of VAPOL and the indicated equivalents of $B(OPh)_3$ in the indicated solvent at 25°C or 80°C for indicated time before applying vacuum to remove volatile material. [b] Determined by ^{1}H NMR integration of the catalyst mixture in $CDCl_3$. [c] Average of two runs. [d] Average of five runs.

The most interesting observation came from the study of the effect of added H_2O. The addition of three equivalents of H_2O at various temperatures led to incomplete conversion of VAPOL (entry 8, 10). However if only one equivalent of H_2O was added

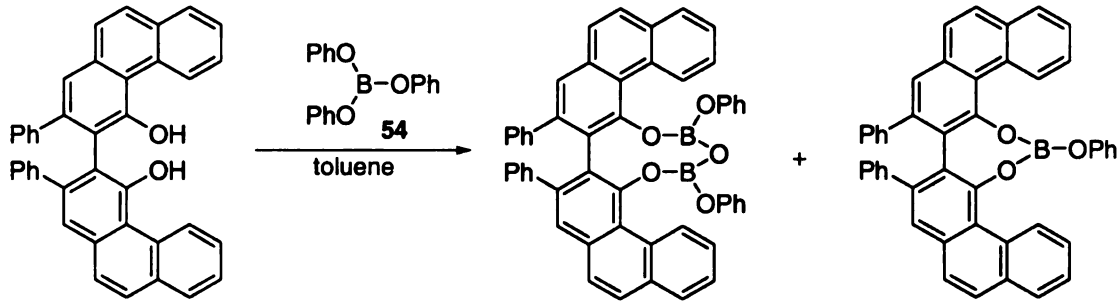
along with three equivalent of triphenyl borate and the mixture was allowed to stir at 80°C for one hour, a very high ratio of **301/298** was observed along with complete conversion of VAPOL (entry 11). Again this result agrees with the proposal that the generation of **301** requires a molecule of water.

After the comprehensive study of the relationship between the catalyst generation conditions and the product ratio of **301:298**, efforts were then extended to the development of conditions for selective generation of **301** over **298** and for the selective generation of **298** over **301**. The observations in Table 7.8 suggest that less than three equivalents of triphenyl borate generally lead to a higher proportion of **298**, however the conversion of VAPOL became an issue under these conditions. On the other hand, calculations suggested that due to the relative higher strain energy of **298** it may be more difficult to form, and thus, a higher reaction temperature may favor the formation of this species. Based on the above information, it was believed that higher ratio of VAPOL/triphenyl borate and a higher reaction temperature would be crucial for the selective formation of **298**.

In the event, it was pleasing to find that the syringe pump addition of a solution of 1.5 equivalent of triphenyl borate slowly to a solution of VAPOL at 100°C produced a 4:1 mixture of catalyst species which contains 80% **298** (Table 7.9, entry 3). Under this condition more than 95% of the VAPOL ligand was converted to one of the two catalyst species. Using greater or lesser amounts of $B(OPh)_3$ led to either decreased ratio or

incomplete conversion of VAPOL. On the other hand, the slow addition of VAPOL to a solution of $B(OPh)_3$ led to an inverted ratio (1:11) of **298/301** (entry 4).

Table 7.9 Selective preparation of VAPOL-borate catalyst **298** or **301**



46 **301** **298**

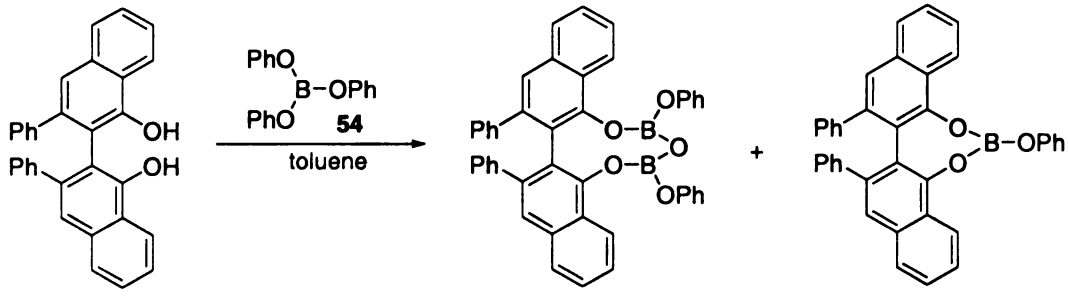
entry[a]	temp. (°C)	**54** (equiv.)	condition	**301:298**[b]	convn (%)[b]
1[c]	80	1	addition of **54** in once in 2 mL toluene	1:0.7	50
2[c]	80	2.5	syringe addition of 2.5 mL solution of **54** to 8 mL solution of VAPOL	0.9:1	>95
3[c,d]	100	1.5	syringe addition of 1.5 mL solution of **54** to 9 mL solution of VAPOL	1:4	>95
4	80	5	syringe addition of 1 mL solution of VAPOL to 9 mL solution of **54**	11:1	100

[a] Unless otherwise specified, the catalyst was prepared by addition of triphenyl borate to the solution of VAPOL stirred at the indicated temperature. [b] Determined by ^1H NMR in $CDCl_3$. [c] The $B(OPh)_3$ stock solution (~1M) was prepared by dissolving **54** in dry toluene and stored over MS 4Å under an argon atmosphere. [d] Average of two runs.

The procedure developed for the selective preparation of the VAPOL-borate catalysts **298** and **301** were applied to the selective preparation of two VANOL-borate catalysts. It was found that the two conditions developed for the VAPOL catalysts could also selectively produce the two corresponding VANOL-borate catalysts **299** and **308** (Table 7.10). The difference observed between the VAPOL and VANOL ligands is that

under the same condition the VANOL ligand generally gave a slightly higher proportion of the mono-borate catalyst **299**.

Table 7.10 Selective preparation of VANOL-borate catalyst **308** or **299**



47 **308** **299**

entry	temp. (°C)	**54** (equiv.)	condition	**308:299**[b]	convn (%)[b]
1[a,c]	100	1.5	syringe addition of 1.5 mL solution of **54** to 9 mL solution of VANOL	1:5	100
2	80	5	syringe addition of 1 mL solution of VANOL to 9 mL solution of **54**	2.8-2.9:1	100

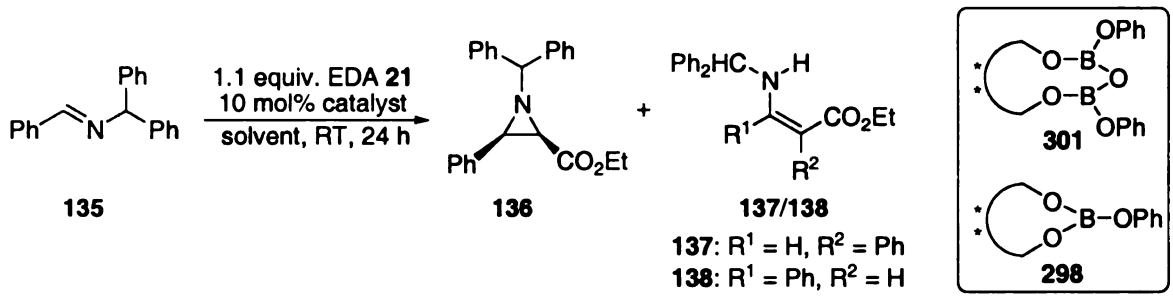
[a] The catalyst was prepared by addition of triphenyl borate to a solution of VANOL stirred at the indicated temperature. [b] Determined by ^{1}H NMR in $CDCl_3$. [c] The $B(OPh)_3$ stock solution (~1M) was prepared by dissolving **54** in dry toluene and stored over MS 4Å under an argon atmosphere.

The catalyst generated from BINOL and triphenyl borate was not studied. Although based on the experimental results for catalyst generation from the VAPOL and VANOL ligands and from the theoretical studies described above, there may be two possible BINOL-borate species as well. This particular issue may be worth further investigation.

Following the successful selective preparation of the two VAPOL-borate species, the aziridination of imine **135** was conducted with the enriched sample of both catalyst species. The reactions of **135** with either catalyst species were repeated twice. Due to the fact that neither of the procedures was completely selective, the catalyst mixture

generated under either condition was always contaminated with 8-20% of the other undesired catalyst species. Therefore, the results of the aziridination reactions do not reflect the exact activity of either pure catalyst species. Nonetheless, the results were definitive since considerably different diastereo- and enantioselectivity was observed between the reactions with two the catalyst species (Table 7.11).

Table 7.11 Aziridination of imine **135** using selectively generated VAPOL catalysts



135 **136** **137/138**

137: R^1 = H, R^2 = Ph
138: R^1 = Ph, R^2 = H

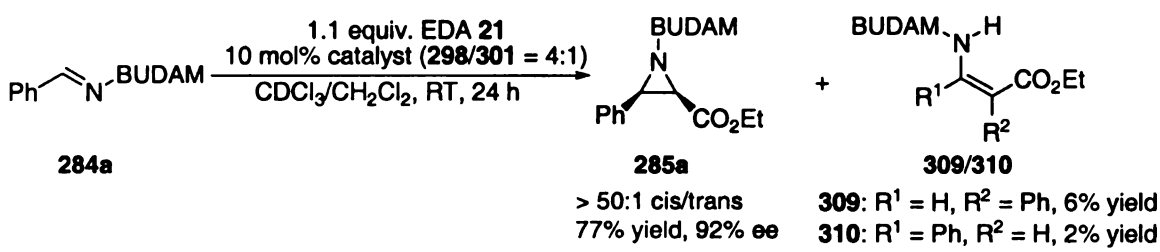
entry	**301:298**[a]	solvent	yield of **136** (%)[b]	ee of **136** (%)[c]	cis/trans **136**[d]	yield of **137/138**(%)[d]
1[e,f]	1:4	$CDCl_3/CH_2Cl_2$	68	75	20:1	17/4
2[e]	N/A	CH_2Cl_2	66	72	16:1	18/5
3[f,g]	12:1	$CDCl_3/CH_2Cl_2$	79	91.5	> 50:1	2/<1
4[g]	N/A	CH_2Cl_2	75	91	> 50:1	4/<1

[a] The ratio of **301:298** was determined by ^{1}H NMR in $CDCl_3$. The ratio of **301:298** in entry 2 and 4 was not determined. [b] Isolated yield after chromatography on silica gel. [c] Determined by chiral HPLC analysis. [d] Determined by ^{1}H NMR on the crude reaction mixture. [e] The catalyst was prepared from VAPOL and 1.5 equivalent of $B(OPh)_3$ as in entry 3 in Table 7.9. [f] Aziridination was performed in a 1:1 mixture of $CDCl_3/CH_2Cl_2$. [g] The catalyst was prepared from VAPOL and 5 equivalent of $B(OPh)_3$ as in entry 4 in Table 7.9.

The biggest surprise came from the aziridination in the presence of the catalyst which contains 80% of the mono-borate **298**. Much larger amounts of the enamine and *trans*-aziridine side-products were observed in the crude reaction mixture. After chromatographic separation, the isolated aziridine **136** was determined by chiral HPLC analysis to be only 72-75% ee. In contrast, the aziridination reactions with the di-borate **301** catalyst (> 92% purity) were significantly cleaner and produced less than 5% of the side products. Most importantly, with this catalyst the chiral induction of **136** was 91% ee in CH_2Cl_2 as solvent.

It was also found that the reaction of N-BUDAM imine **284a** with 10 mol% of the VAPOL catalyst which contains 80% of the mono-borate **298** produced aziridine **285a** in only 92% ee along with about 8% enamine products (Scheme 7.2). In contrast, the reaction of this substrate in CH_2Cl_2 with 10 mol% catalyst generated under standard conditions afforded **285a** in 85-94% yield and in 99% ee with undetectable amounts of the enamines (Table 6.15).

Scheme 7.2 Aziridination of imine **284a** using selectively generated VAPOL catalysts



284a

285a

> 50:1 cis/trans
77% yield, 92% ee

309/310

309: R^1 = H, R^2 = Ph, 6% yield
310: R^1 = Ph, R^2 = H, 2% yield

The results of the aziridinations shown in Table 7.11 and Scheme 7.2 not only unambiguously demonstrated that the di-borate catalyst **301** is the active and

stereoselective aziridination catalyst, but also suggested the role of the mono-borate **298**. The data in entry 1 and 2 in Table 7.11 indicates that borate **298** also catalyzes the aziridination of imine **135**, however this species is much less stereoselective. This suggestion is based on the fact that a 72% ee was obtained with 4:1 ratio of **298/301** (prepared from 10 mol% VAPOL), which means there were 2 mol% **301** and 8 mol% **298**. The extensive studies in chapter five indicated that 2 mol% of the VAPOL-borate generated according to the standard conditions[25b] (which contains ~ 80% **301**) consistently gives 86-88% ee. The only explanation for the observed diminished chiral induction in entry 1 and 2 of Table 7.11 is that both **298** and **301** are active catalysts in the aziridination reaction, however, **298** is a much less stereoselective catalyst species and the overall stereoselectivity is determined by the combined catalysis of both species. Thus, a lower ratio of **301/298** (in entry 1, 2, Table 7.11) would result in significantly decreased stereoselectivity. This suggestion is further supported by the fact that a higher proportion of **301** (**301/298** = 12:1) led to an improved chiral induction (91% ee in entry 4) over the catalyst generated under the standard conditions (87-89% ee with a 3-5:1 mixture of **301/298**).

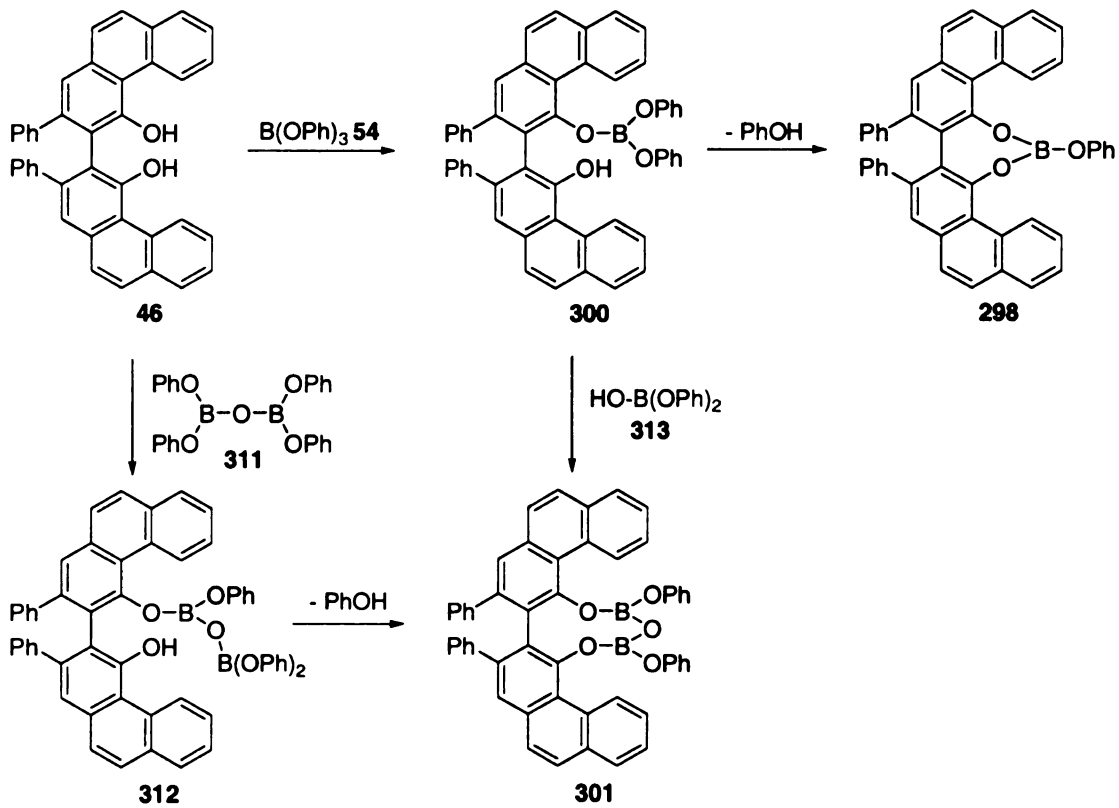
The results in Table 7.9 and Table 7.11 further suggests that the original procedure[25b] developed for catalyst generation is not the optimal condition, as this procedure produces as much as 17-25% of less selective mono-borate catalyst **298**. Although the catalyst generated from more than 5 equivalents of triphenyl borate **54**

generally contains a higher proportion of **301**, the large excess of $B(OPh)_3$ would inevitably catalyze the racemic reaction while phenol from the hydrolyzed $B(OPh)_3$ would also complicate the separation process (Table 7.8, entry 4). Benefiting from the knowledge that three equivalents of $B(OPh)_3$ and a small amount of water increases the proportion of di-borate species **301** (Table 7.8, entry 11), Zhenjie Lu screened a series of conditions for catalyst generation that included variations in the reaction temperature and/or the stoichiometry of triphenyl borate and water.[81] The optimized conditions for the catalyst preparation that she developed involves heating the VAPOL ligand with four equivalents of triphenyl borate and one equivalent of water at 80°C for 1 hour, followed by removal of volatile material and subsequent heating 80°C under a high vacuum. As a result this procedure consistently gave catalyst with a 15:1 ratio of **301/298**. Given the results in Table 7.11, the catalyst prepared in this way should provide aziridines with slightly increased chiral inductions than those in Table 5.5.

At this stage, the exact details concerning the formation of the di-borate species **301** is not clear. In theory there are several pathways which may lead to **301** (Scheme 7.3). The free VAPOL may first react with triphenyl borate **54** to give mono-borate **299**, which either undergoes the less favorable intramolecular substitution to generate the seven-membered ring species **298**, or further react with partially hydrolyzed borate **313** followed by another substitution to give **301**. Alternatively, VAPOL may directly react with the boric anhydride **311** (which presumably results from the condensation between **54**

and **313**) to afford boric anhydride **312**, which subsequently undergoes another substitution to give the nine-membered ring species **301**. On the other hand, it is also possible that VAPOL may react the partially hydrolyzed borate **313**.

Scheme 7.3 Possible pathways for the generation of VAPOL-borate **298** and **301**



The discovery that **301** is the more selective catalyst also provides possible explanations of several early intriguing observations. In the study on $B(OPh)_3$ loading (Table 7.2), the significantly reduced selectivity (and reactivity) with the catalyst generated from less than two equivalent of $B(OPh)_3$ is now understood to be due to the formation of a larger proportion of mono-borate **298** along with the incomplete conversion of ligand.

On the other hand, the lack of match/mismatched pairs in the reactions of chiral benzhydryl imines (Scheme 6.30, 6.31) can be explained by the significantly different catalyst structures. CPK and/or computational modeling suggests that the proposed CH-π interaction between the benzhydryl imine and mono-borate catalyst **298** do not exist in the case of di-borate catalyst **301**, thus the sterically "symmetric" chiral benzhydryl imines would not be differentiated by the two enantiomer of the chiral catalyst. The match/mismatched cases observed with α-alkyl benzylimines **156** and **289** may possibly be simply induced by the chiral environment of the ligand and not be related to alkyl-π interaction.

Interestingly, although the VAPOL and VANOL-mono-borate species are inferior catalysts for the aziridination of benzhydryl imines and EDA, it was found recently that the mono-borate species give higher asymmetric inductions than the di-borate species in the aziridination reaction between N-aryl imines and trimethylsilyl diazomethane.[42b]

The successful identification of the bis-borate **301** as the active catalyst was particularly important with regard to understanding of the mechanism of the VAPOL or VANOL-borate catalyzed aziridination reaction. However, after the exclusion of the working model in Figure 6.2 more questions were raised than answered: 1) Is the bis-borate catalyst **301** acting as two separate boron Lewis acid with both borons capable of coordinating with (and activating) the imine? 2) What is the enantioselective-determining

transition-state structure of catalyst-imine complex? 3) Why does the N-BUDAM imine react more selectively than benzhydryl imine?

The most direct approach to both questions seems to be the isolation and characterization of the catalyst-imine complex. The VAPOL and VANOL-borates are highly moisture-sensitive, thus the ideal isolation method may involve the crystallization of the borate/imine or borate/amine complexes. The X-ray diffraction analysis of the complex should provide some definitive information of the transition-state structure of the aziridination, and possibly explain the greatly enhanced reactivity/selectivity of the N-BUDAM imines.

7.5 Conclusion

The lack of a match/mismatched relationship for the aziridination of chiral benzhydryl imines prompted a re-investigation of originally proposed catalyst structure. The study of nonlinear effects in the aziridination reaction indicated that the active catalyst contains only one ligand. The MS and NMR studies suggested two species are present in the catalyst generated from either VAPOL or VANOL and triphenyl borate. An unprecedented bis-borate catalyst species was successfully identified along with the originally proposed mono-borate catalyst.

Theoretical studies were employed to further understand the properties of the two species. Calculations of the strain energy with various theoretical models suggest that the mono-borate species is a less stable complex than the di-borate species.

Methods for the selective preparations of each catalyst species were developed based on extensive studies of catalyst generation, and both species were examined in the catalytic aziridination. The more active and more selective aziridination catalyst was unexpectedly determined to be the di-borate catalyst which is generated from two equivalents of triphenyl borate, one equivalent of ligand and one equivalent of water. The mono-borate species was found to be the less stereoselective catalyst. This work subsequently led to an improved procedure for the preparation of the VAPOL-borate catalyst.

Although the discovery of the new active catalyst renders obsolete the original model for the VAPOL or VANOL-borate catalyzed asymmetric aziridination, the exploration of the active aziridination catalyst led to the better understanding of the mechanism of this powerful asymmetric transformation, and provided further insights which should serve to guide future developments of catalytic asymmetric aziridination reaction.

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CATALYTIC ASYMMETRIC AZIRIDINATION -- PREPARATION OF LIGAND, EXPLORATION OF MECHANISM AND DISCOVERY OF NEW METHODOLOGY

VOLUME 2

By

Yu Zhang

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

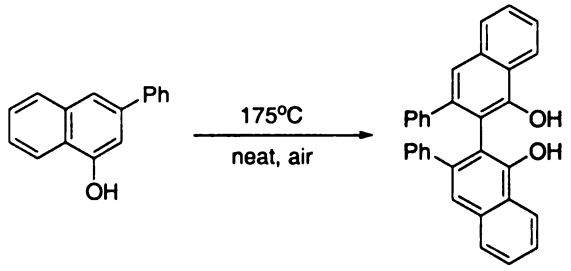
Department of Chemistry

2006

EXPERIMENTAL SECTION

Experimental for Chapter Two:

Preparation of VANOL 47 by oxidative coupling of 65 with air.



65 **47**

To a 1L three neck round bottom flask attached with a condenser was loaded purified 3-phenyl-1-naphthol **65**[24] (17.55 g, 79.77 mmol). The starting material was stirred at 175°C in oil bath, neat air was slowly blown through needle or glass tube into the flask and to the surface of the reaction mixture from one of the flask neck. The evaporated **65** which condensed on condenser was rinsed back into the flask using small amount of EtOAc after 12 hours. After 19 hours, stirring stopped as the reaction mixture solidified. The flask was allowed to cool down to room temperature and was then put into ice bath. The crude mixture was crushed into small granule with a spatula. To this mixture was added ~20 mL of cold (0°C) CH_2Cl_2 and the slurry was stirred at <0°C until there are no large solid pieces visible in the slurry. The solution was filtered through a Buchner funnel, the light yellow powder collected in the funnel was washed with a small amount of cold CH_2Cl_2 twice to afford 11.62 g racemic VANOL as a light yellow solid powder. The filtrate was concentrated *in vacuo* and

loaded into the reaction flask again and stirred at 175°C for another 12 hours. The obtained reaction mixture was mixed with a small amount of cold CH_2Cl_2, stirred at 0°C and then filtered again to afford 0.90 g light yellow racemic VANOL. Upon removal of solvent the remaining filtrate was loaded onto a silica gel column and eluted with 1:15 mixture of EtOAc/hexane to afford 1.12 g of a light yellow solid as product. The combined VANOL product **47** was 13.64 g (31.14mmol, 78% yield).

Spectral data for **47**:[24] white solid; mp = 231-232 °C; R_f=0.36 (1:9 EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 300MHz) δ 5.83 (s, 2 H), 6.61 (d, 4 H, *J* = 7.2 Hz), 6.93 (t, 4 H, *J* = 7.7 Hz), 7.03 (t, 2 H, *J* = 7.3 Hz), 7.29 (s, 2 H), 7.50-7.54 (m, 4 H), 7.73-7.75 (m, 2 H), 8.30-8.32 (m, 2 H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 112.64, 122.00, 122.78, 122.86, 125.66, 126.59, 127.43, 127.51, 127.67, 128.86, 134.56, 140.12, 140.65, 150.33;

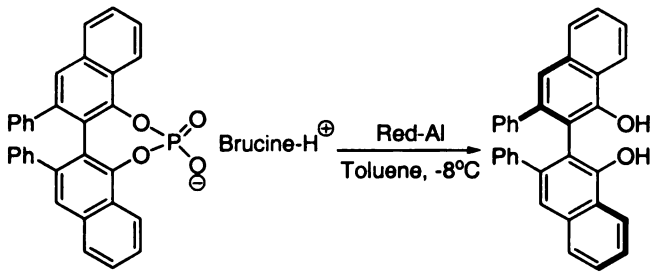
IR (neat) 3508 s, 3054 m, 3030 w, 1948 w, 1630 w, 1502 m, 1569 m, 1493 s, 1439 w, 1383 s, 1285 m, 1233 m, 1221 m, 1192 m, 1140 m, 1062 m, 1020 w, 947 m, 908 s, 879 m, 853 w, 798 w, 759 s cm^{-1};

mass spectrum, m/z (% rel intensity), 438 M^+ (100), 420 (6), 361 (9), 231 (11), 219 (23), 202 (14), 180 (20), 157(16);

exact mass calcd for $C_{32}H_{22}O_2$: m/z 438.1620, exact m/z 438.1610.

Anal. Calcd for $C_{32}H_{22}O_2$: C, 87.65; H, 5.06. Found: C, 87.89; H, 5.10;

Representative procedure for the Red-Al reduction of VANOL-brucine salt:

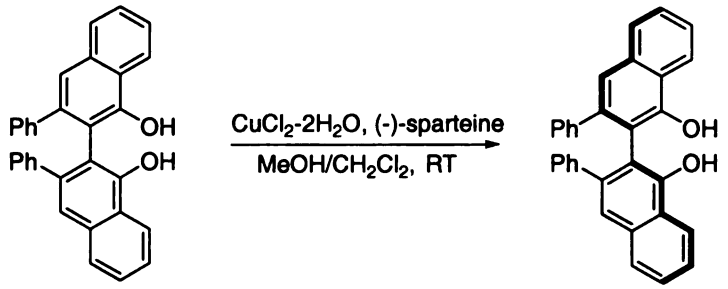


68 (salt) **S-47**

To an oven dried 500 mL round bottom flask filled with argon was added resolved (S)-VANOL-brucine salt **68**[24] (11.26g, 12.60 mmol) and 200 mL dry toluene. The suspension was stirred at -8°C. Red-Al (12 mL, 38.5 mmol) was diluted with 50 mL dry toluene and added dropwisely by syringe pump over a period of 60 minutes. Upon addition, the solid dissolved and the release of hydrogen gas was observed. After complete addition, the solution was stirred at -8°C for 2.5 hours. The reaction was quenched by adding 1N HCl dropwisely at -8°C until Ph level reached <2~3. The reaction mixture was transferred to separatory funnel, the aqueous layer was extracted with 3 × 100 mL EtOAc. The combined organic layer was washed with 3 × 50 mL brine, dried over $MgSO_4$. Upon removal of solvent the crude (*S*)-VANOL was purified by silica gel chromatography, eluted with 1:9 EtOAc/hex or 1:2 CH_2Cl_2/hexane to give 4.72 g (10.77 mmol, 77% yield from racemic VANOL) white solid as pure product. The optical purity of (*S*)-VANOL **47** was found to be of 99.4% by HPLC analysis using following conditions: Pirkle D-Phenylglycine column with a 98:2 mixture of hexane/isopropanol (254nm, flow rate: 1 mL/min to 2 mL/min in 30 min), under this condition, the retention time of (*R*)-VANOL was 16.14 min and that of (*S*)-VANOL was 17.32 min.

Experimental for Chapter Three:

Typical experimental procedure for deracemization of racemic VANOL 47 using $CuCl_2 \cdot 2H_2O$ and (-)-sparteine:



racemic **47** (S)-**47**

To a 500 mL Schlenk flask was added 100 mL MeOH, 333 mg of $CuCl_2 \cdot 2H_2O$ (1.95 mmol) and 942 mg of (-)-sparteine **78** (4.01 mmol). A solution of racemic VANOL (**47**) (620 mg, 1.42 mmol) in a 250 mL round bottom flask containing 60 mL of CH_2Cl_2 and 20 mL of MeOH was deoxygenated by purging with argon for 40 min and then this solution was transferred via cannula to the 500 mL Schlenk flask containing the $CuCl_2 \cdot 2H_2O$ and sparteine. After the VANOL solution was transferred, the Schlenk flask was deoxygenated by the freeze-thaw method (2 cycles). The flask was then sealed under argon and stirred at room temperature for 50 hours. The reaction was quenched by slow addition of 20 mL of concentrated HCl and then stirring for 10 minutes. The mixture was concentrated on rotavapor. Upon removal of most of the organic solvents, the mixture was poured into a separatory funnel. The CH_2Cl_2 layer was collected and the upper MeOH/H_2O layer was washed with 2 × 30 mL of CH_2Cl_2. The CH_2Cl_2 solutions were combined and dried over $MgSO_4$. Upon removal of solvent, the crude reaction mixture was loaded onto a silica gel column and eluted with a 1:10 mixture of EtOAc/hexane to give 479 mg (1.09 mmol, 77% yield) of (*S*)-**47** as a white foam-like solid. The optical purity of (*S*)-**47** was determined to be of ≥ 99 % ee by HPLC on a Pirkle D-Phenylglycine

column with a 98:2 mixture of hexane/isopropanol (254 nm, flow rate: 1 mL/min to 2 mL/min over 30 min). Under these conditions, the retention time of (*R*)-**47** was 16.14 min and that of (*S*)-**47** was 17.32 min.

Spectral data for (*S*)-**47**:[24]

white solid; mp = 231-232 °C; R_f=0.36 (1:9 EtOAc/hexane). $[\alpha]_D$ = -372.3 (THF, *c* = 1.0).

^{1}H NMR ($CDCl_3$, 300MHz) δ 5.83 (s, 2 H), 6.61 (d, 4 H, *J* = 7.2 Hz), 6.93 (t, 4 H, *J* = 7.7 Hz), 7.03 (t, 2 H, *J* = 7.3 Hz), 7.29 (s, 2 H), 7.50-7.54 (m, 4 H), 7.73-7.75 (m, 2 H), 8.30-8.32 (m, 2 H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 112.64, 122.00, 122.78, 122.86, 125.66, 126.59, 127.43, 127.51, 127.67, 128.86, 134.56, 140.12, 140.65, 150.33;

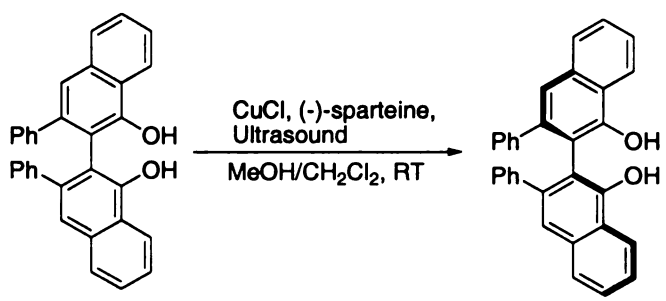
IR (neat) 3508 s, 3054 m, 3030 w, 1948 w, 1630 w, 1502 m, 1569 m, 1493 s, 1439 w, 1383 s, 1285 m, 1233 m, 1221 m, 1192 m, 1140 m, 1062 m, 1020 w, 947 m, 908 s, 879 m, 853 w, 798 w, 759 s cm^{-1};

mass spectrum, m/z (% rel intensity), 438 M^+ (100), 420 (6), 361 (9), 231 (11), 219 (23), 202 (14), 180 (20), 157(16);

exact mass calculated for $C_{32}H_{22}O_2$: m/z 438.1620, exact m/z 438.1610.

Anal. Calcd for $C_{32}H_{22}O_2$: C, 87.65; H, 5.06. Found: C, 87.89; H, 5.10.

Typical experimental procedure for deracemization of racemic VANOL 47 using CuCl and (-)-sparteine:



racemic **47** (*S*)-**47**

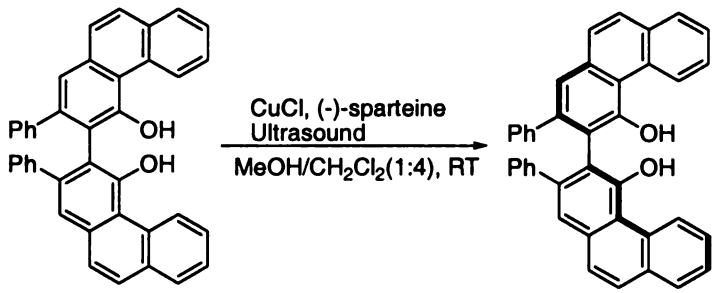
To a 500 mL round bottom flask was added 300 mL MeOH, 1.55 g of CuCl (15.66 mmol) and 7.6 g of (-)-sparteine **78** (32.4 mmol). The reaction was sonicated in an ultrasonic water bath with air bubbled via needle into the solution. The temperature of the ultrasonic bath was maintained at or below 25 °C by the addition of ice to the water in the bath. The flask was sealed with a septum after 20 minutes and purged with argon for 60 minutes. The green Cu(II)-sparteine solution was transferred via cannula to the solution of racemic **47** (5 g, 11.4 mmol) in 1200 mL CH_2Cl_2 in a 2L round bottom flask which had previously been purged with argon and sonicated for 60 minutes. The combined solution was sonicated for 15 more minutes and then the flask was removed from ultrasonic bath, covered with aluminum foil and the reaction mixture allowed to stir at room temperature for 105 minutes under a positive pressure of argon maintained by slow flow through the head space of the flask. The reaction was quenched by slowly adding 100 mL of concentrated HCl and then stirring for 10 minutes. Approximately 1 L of the solvent was removed by rotavapor and then the solution was poured into a 500 mL separatory funnel. The lower CH_2Cl_2 layer was collected and the upper MeOH/H_2O layer was washed with 2 × 50 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were dried over $MgSO_4$. Upon removal of solvent, the crude reaction mixture was loaded to a silica gel column and eluted with a 1:10 mixture of EtOAc/hexane to give 3.43 g (7.8 mmol, 69 % yield) of (*S*)-**47** as a white foam-like solid. The optical purity of (*S*)-**47** was determined to be ≥ 99 % ee by HPLC.

Enrichment of (*S*)-VANOL (47) by precipitation of racemate.

(*S*)-**47** (4.0 g, 9.13mmol) with 90 % ee was introduced into a 250 mL round bottom flask. Ethyl acetate was added dropwise until all the solid had dissolved. Hexane (100 mL) was added and the flask was manually shaken for one or two minutes. A white solid appeared in the flask which was then allowed to stand still for 2 hours. The VANOL in the solution was checked by HPLC and it was found to be greater than 99.5% ee.

Removal of the solid by filtration followed by concentration of the solution in vacuo afforded 3.5 g white foam-like (*S*)-**47** solid with > 99.5 % ee.

Typical experimental procedure for deracemization of racemic VAPOL 46 using CuCl and (-)-sparteine:



racemic **46** (*S*)-**46**

To a 500 mL round bottom flask was added 300 mL of MeOH, 1.55 g of CuCl (15.66 mmol) and 7.6 g of (-)-sparteine **78** (32.42 mmol). The reaction was sonicated in an ultrasonic bath with air purged into the solution via a needle. The temperature was maintained at or below 25 °C by the addition of ice to the water in the bath. The flask was sealed with a septum after 45 minutes and then purged with argon for 60 minutes in the ultrasonic bath. The green Cu(II)-sparteine solution was transferred via cannula to the solution of racemic **46** (5 g, 9.29 mmol) in 1.2 L of CH_2Cl_2 in a 2 L round bottom flask which was had previously been purged with argon and sonciated for 60 minutes. The combined solution was sonicated for 10 minutes and then the flask was removed from ultrasonic bath, covered with aluminum foil and stirred at room temperature for 6 hours under a positive pressure of argon maintained by slow flow through the head space of the flask. The reaction was quenched by adding 120 mL of concentrated HCl and then stirring for 10 minutes. Approximately 1 L of the solvent was removed by rotavapor and then the solution was poured into a 500 mL separatory funnel. The lower CH_2Cl_2 layer was collected, the upper MeOH/H_2O layer was washed with 2 × 50 mL of CH_2Cl_2. The

combined CH_2Cl_2 layer was dried over $MgSO_4$. Upon removal of solvent, the crude reaction mixture was loaded to silica gel column and eluted with a 1:2 mixture of CH_2Cl_2/hexane to give 4.19 g (7.79 mmol, 84% yield) (*S*)-**46** as a white solid. The optical purity of (*S*)-**46** was found to be of ≥ 99 % by HPLC on a Pirkle D-Phenylglycine column with a 75:25 mixture of hexane/isopropanol (260 nm, flow rate: 2 mL/min). Under these conditions the retention time of (*R*)-**46** was 12.50 min and that of (*S*)-**46** was 18.54 min.

Spectral data for (*S*)-**46**:[24]

white solid; mp > 250 °C; R_f = 0.40 (1:2 CH_2Cl_2/hexane); $[\alpha]_D$ = 124.96 (THF, *c* = 1.0).

^{1}H NMR ($CDCl_3$) δ 6.59 (s, 2 H), 6.66 (d, 4 H, *J* = 7.7 Hz), 6.93 (t, 4 H, *J* = 7.5 Hz), 7.04 (t, 2 H, *J* = 7.4 Hz), 7.42 (s, 2 H), 7.61 (t, 2 H, *J* = 7.3 Hz), 7.64-7.67 (m, 4 H), 7.79 (d, 2 H, *J* = 8.8 Hz), 7.91 (d, 2 H, *J* = 7.7 Hz), 9.71 (d, 2 H, *J* = 8.4 Hz);

^{13}C NMR ($CDCl_3$) δ 115.77, 118.09, 123.23, 126.36, 126.81, 126.99, 127.03, 127.53, 128.44, 128.82, 129.29, 130.28, 132.80, 135.27, 139.70, 141.56, 153.41 (one carbon not located);

IR (neat) 3473 s, 3049 m, 1611 w, 1590 w, 1555 w, 1372 m, 1330 m, 1246 w, 1210 w, 1175 m, 1027 w, 816 w, 774 m, 731 m, 665 m cm^{-1};

mass spectrum, *m/z* (rel intensity), 538 (18) M^+, 520 (5), 370 (3), 270 (100), 241 (30), 215 (7), 165 (10);

exact mass calculated for $C_{40}H_{26}O_2$ *m/z* 538.1933, found *m/z* 538.1933.

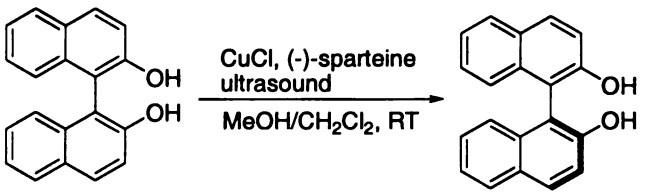
Anal. Calcd for $C_{40}H_{26}O_2$: C, 89.19; H, 4.87. Found: C, 88.43, H, 5.29.

Enrichment of (*S*)-VAPOL (46) using Soxhlet extraction.

To a Soxhlet thimble (33 x 94 mm) was added (4.0 g, 7.43 mmol) (*S*)-**46** of 97% ee. The thimble was placed in the extractor and 250 mL of pentane was added to a 500 mL round bottom flask attached to the bottom of the extractor. The pentane solution was

heated at 55 °C in an oil bath and allowed to reflux. Off-white VAPOL precipitate appeared in the flask within 12 hours. After 24 hours, removal of the solvent from the pentane solution afforded 3.0 g (5.57 mmol) **46** which was determined by HPLC to be ≥ 99.5 % ee.

Typical experimental procedure for deracemization of racemic BINOL 48 using CuCl and (-)-sparteine:

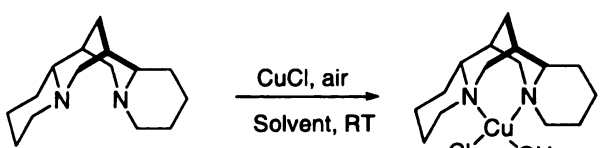


racemic **48** (*S*)-**48**

To a 50 mL round bottom flask was added 6.5 mL MeOH, 97 mg of CuCl (0.98 mmol) and 464 mg of (-)-sparteine **78** (1.96 mmol). The flask was sonicated in an ultrasonic bath open to air. The temperature was maintained at or below 25 °C by the addition of ice to the water in the bath. The flask was sealed with a septum after 25 minutes and the solution purged with argon for 60 minutes in the ultrasonic bath. The green Cu(II)-sparteine solution was transferred via cannula to the solution of racemic **48** (200 mg, 0.70 mmol) in 16.5 mL CH_2Cl_2 in a 50 mL round bottom flask which had been previously purged with argon and sonciated for 60 minutes. Upon transferring, the flask was sonicated for 10 more minutes. The flask was removed from the ultrasonic bath, covered with aluminum foil and the reaction mixture allowed to stir at room temperature for 8 hours and then at –20 °C for 16 hours. The reaction was quenched by slow addition of 10 mL of a pre-cooled concentrated HCl at –20 °C and then the mixture was stirred for 5 minutes. The solution was poured into a separatory funnel, the lower CH_2Cl_2 layer was collected and the upper MeOH/H_2O layer was washed with 2 × 30 mL of CH_2Cl_2. The

combined CH_2Cl_2 layers were washed with 30 mL water and dried over $MgSO_4$. Upon removal of solvent, the crude reaction mixture was loaded onto a silica gel column and eluted with a 15:1 mixture of CH_2Cl_2/hexane to give 194 mg (0.68 mmol, 97 % yield) of (*S*)-**48** as a white solid. The material obtained was identical to that commercially available from Aldrich. The optical purity of (*S*)-**48** was found to be of 92 % ee by HPLC on a Chirapak AS column with a 90:10 mixture of hexane/isopropanol (260 nm, flow rate: 1 mL/min). Under these conditions, the retention time of (*S*)-**48** was 10.3 min and that of (*R*)-**48** was 16.2 min.

Preparation of (-)-sparteine-copper complex 79:

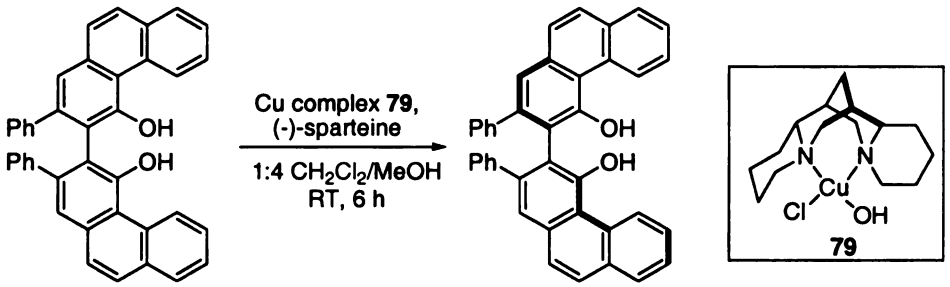


78
(-)-sparteine

79

To a 50 mL round bottom flask was added 20 mL of appropriate solvent (MeOH or CH_2Cl_2) followed by CuCl (200 mg, 2 mmol) and (-)-sparteine **78** (469 mg, 2 mmol). The mixture was sonicated open to air for 20 min. The solid CuCl dissolved within 15 min. The resulting green solution was filtered to remove any insoluble solid and concentrated in vacuo to give a green solid. This solid was dissolved in 12 mL CH_2Cl_2 and then 250 mL of hexane was added to cause precipitation. Filtration and drying of the precipitate afforded a lime-green solid (440 mg, 1.26 mmol, 63 % yield) which, based on literature precedent, was expected to be Cu(-spartiene)Cl(OH): mp 148-151°C.

Deracemization of racemic VAPOL 46 using (-)-sparteine-copper complex 79:

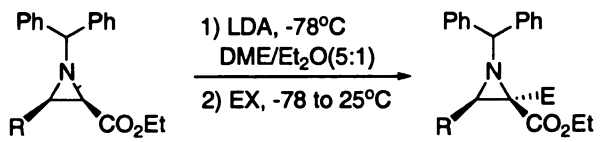


racemic **46** (*S*)-**46**

To a 250 mL round bottom flask filled with argon was added 12 mL of MeOH and 48 mL of CH_2Cl_2 and the resulting mixture was sparged with argon for 1 h. To this solvent mixture was added racemic VAPOL (**46**) (200 mg, 0.37 mmol) and (-)-sparteine copper complex **79** (155 mg, 0.44 mmol) which afforded a light green solution. This solution turned black upon addition of (-)-sparteine **78** (103 mg, 0.44 mmol). The dark solution was stirred under argon and at room temperature for 6 hours. The reaction was quenched by adding 10 mL of concentrated HCl and then stirred for 10 minutes. The mixture was transferred to separatory funnel. The lower CH_2Cl_2 layer was collected and the upper MeOH/H_2O layer was washed with 2 × 50 mL of CH_2Cl_2. The combined CH_2Cl_2 layer was dried over $MgSO_4$. Upon removal of solvent, the crude reaction mixture was loaded onto a silica gel column and eluted with a 1:1 mixture of CH_2Cl_2/hexane to give 114 mg (0.21 mmol, 57 % yield) (*S*)-**46** as a white solid. The optical purity of (*S*)-**46** was found to be of 97% ee as described in the VAPOL deracemization procedure above.

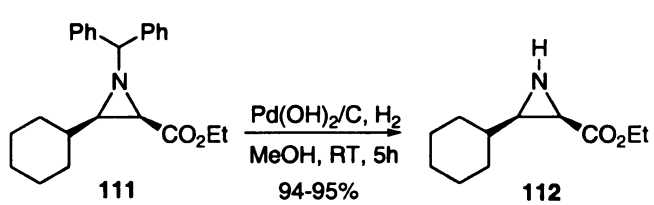
Experimental for Chapter Four:

Typical procedure for the alkylation of aziridine:



To a flame-dried round-bottomed flask equipped with a magnetic stir bar and a septa was added 4-ml dry 1,2-dimethoxyethane, 2 equiv. dry diisopropylamine and 2 equiv. *n*-butyl lithium at –78 °C. Then 1 equiv. of the appropriate aziridine dissolved in a mixture of 1 mL DME and 1 mL diethyl ether was transferred to the reaction flask via a cannula. The final concentration of the aziridine is 0.08 M. The color of the reaction turned to a transparent brown. The reaction was stirred at –78 °C for 30 min and then 3 equiv. of the electrophile was added via syringe. The reaction was then gradually allowed to reach room temperature under constant stirring. The reaction was quenched with brine and extracted with 3 x 15 mL Et_2O. The ethereal phases were combined and dried over anhydrous $MgSO_4$, filtered and the solvent removed on a rotary evaporator. The crude product was then purified on a silica gel column eluting with a mixture of hexanes and ethyl acetate.

Synthesis of N-H aziridine 112:



111 94-95% **112**

To an oven-dried 500 mL round bottom flask filled with argon was added aziridine **111**[25b] (2.5 g, 6.89 mmol) and 800 mg $Pd(OH)_2/C$, followed by 250 mL of MeOH. The

flask was vacuumed and then flushed with hydrogen gas, the procedure was repeated for four times, then a hydrogen gas ballon was attached to the flask and the suspension was stirred for five hours at room temperature. After the reaction finished, the solution was filtered to remove the Pd catalyst, concentrated *in vacuo*. Silica gel chromatography (50:50 Et_2O/hexane to 100% Et_2O) afforded **112** (1.291 g, 6.55 mmol, 95% yield) as white solid.

Spectral data of **112**: White solid, mp 59-61 °C, R_f = 0.16 (1:4 EtOAc/hexane), $[\alpha]_D$ = -45.4 (c = 1.0, $CHCl_3$);

^1H NMR (300 MHz, $CDCl_3$) δ 0.77(br, 1H), 0.99-1.20 (m, 6H), 1.13 (t, 3H, J = 7.1 Hz), 1.30-1.82 (m, 6H), 2.48 (d, 1H, J = 5.8 Hz), 4.07 (q, 2H, J = 7.1 Hz);

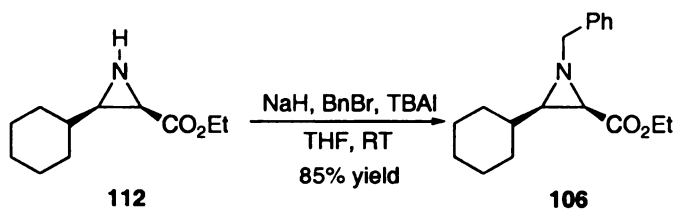
^{13}C NMR (75 MHz, $CDCl_3$) δ 14.20, 25.44, 26.05, 30.89, 31.67, 34.31, 36.96, 44.02, 61.12, 171.04 (one carbon not located); (75 MHz, C_6D_6) δ 14.20, 25.87, 26.44, 31.38, 31.97, 34.45, 37.33, 44.45, 60.87, 171.30 (one carbon not located);

IR (thin film, cm^{-1}) ; 3165 w, 2924 vs, 2849 s, 1730vs, 1194 s, 1180 s;

Mass spectrum *m/z* (% rel intensity) 197 (4) M^+, 168 (32), 124 (100), 95 (84);

Anal calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.98; H 9.30; N 7.08;

Synthesis of N-benzyl aziridine 106:



112 **106**

To an oven-dried 250mL flask filled with argon was added aziridine **112** (1.291 g, 6.55 mmol), 80 mL dry THF. The solution was stirred at 0°C and NaH (943 mg of 60% dispersion, 23.58 mmol) was added. The mixture was stirred at 0°C for 1 hour, then benzyl bromide (4.48 g, 26.19 mmol) and tetrabutyl ammonium iodide (4.94 g, 13.10

mmol) was added. The mixture was stirred at 0°C for 15 minutes, then warmed up to room temperature and stirred for 48 hours. The reaction was quenched by adding 1 mL H_2O via syringe dropwisely, followed by addition of 50 mL saturated NH_4Cl solution. The mixture was loaded to separatory funnel, and extracted with 3 × 60 mL Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, concentrated *in vacuo*. Silica gel chromatography (1:10 EtOAc/hexane) afforded **106** (1.605 g, 5.6 mmol, 85% yield) as white solid.

Spectral data of **106**: White solid, mp 39-42 °C, R_f = 0.27 (1:9 EtOAc/hexane), $[\alpha]_D$ = 47.3 (*c* = 1.0, $CHCl_3$);

^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (dq, 2H, *J* = 11.8, 3.0 Hz), 1.04-1.71 (m, 10H), 1.22 (t, 3H, *J* = 7.1 Hz), 2.19 (d, 1H, *J* = 6.9 Hz), 3.51 (d, 2H, *J* = 4.4 Hz), 4.17 (m, 2H), 7.23-7.29 (m, 5H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 14.21, 25.38, 25.49, 26.11, 30.04, 31.30, 36.19, 42.43, 51.94, 60.73, 64.22, 127.18, 128.22, 128.33, 137.71, 169.84;

IR (thin film, cm^{-1}) 2926 vs, 2851 s, 1745 vs, 1720 s, 1178 vs;

Mass spectrum *m/z* (% rel intensity) 287 M^+ (7), 286 (7), 214 (51), 91 (100);

Anal calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.63; H, 9.11; N, 4.75;

Synthesis of pyrrole-2-carboxylate 113:

106 **113**

Pyrrole-2-carboxylate **113** was prepared from N-benzyl aziridine **106** according to standard alkylation procedure.

Spectral data of **113**: Colorless needle, mp = 119-120°C (CH_2Cl_2/hexane); R_f = 0.26 (1:15 EtOAc/hexane)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14-1.77 (m, 10H), 1.23 (t, 3H, *J* = 6.9 Hz), 2.43 (qq, 1H, *J* = 1.6 Hz, *J* < 1 Hz), 4.18 (q, 2H, *J* = 6.9 Hz), 5.3 (s, 2H), 5.7 (s, 1H), 6.88 (d, 2H, *J* = 7.5 Hz), 7.19-7.29 (m, 5H) ;

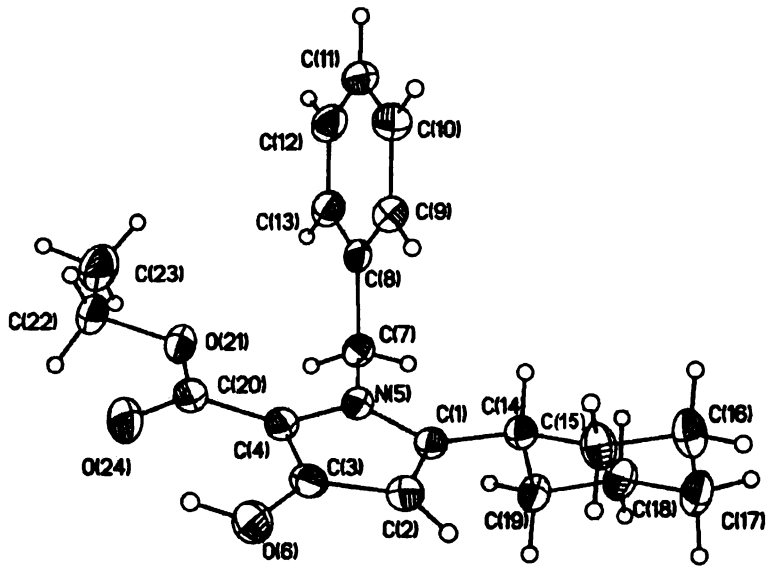
^{13}C NMR (75 MHz, $CDCl_3$) δ 14.26, 25.82, 26.35, 33.26, 35.57, 47.87, 59.62, 77.20, 94.04, 104.72, 125.37, 126.86, 128.51, 139.12, 146.83 (one carbon not located).

IR (thin film, cm^{-1}) 3330 br, 2928 vs, 1647vs;

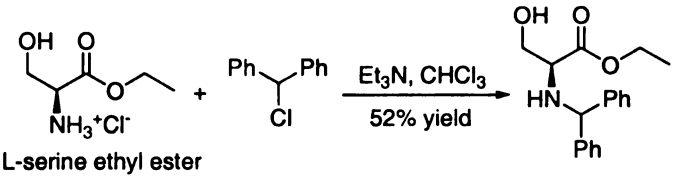
Mass spectrum *m/z* (% rel intensity) $(M)^+$ 327 (100), 281 (46), 91 (38);

Anal calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28; O, 14.66. Found: C, 72.99; H, 7.48; N, 4.49;

30 mg of **113** was dissolved in ~0.2 mL of CH_2Cl_2 and transferred to a NMR tube, the CH_2Cl_2 solution was covered with 1mL of hexane. After one week needle-like crystal was grown in the tube and an X-ray crystal structure was obtained.



Synthesis of N-benzhydryl serine ester 115:



L-serine ethyl ester
L-**114**

(*S*)-**115**

To a Schlenk flask filled with argon was added L-serine ethyl ester salt L-**114** (1.2 g, 7.1 mmol), followed by 12 mL $CHCl_3$. The suspension was stirred at 0°C. Triethyl amine (1.72 g, 16.8 mmol) was added via syringe, followed by benzhydryl chloride (1.01 g, 4.86 mmol), which was added via syringe slowly over 10 minutes. The flask was then sealed under argon and the solution was heated to reflux for 3 days, allowed to cool to room temperature, quenched with saturated aqueous ammonium chloride solution, and extracted with 3 × 30 mL CH_2Cl_2. The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel chromatography (1:3 EtOAc/hexane) afforded **115** (756 mg, 2.52 mmol, 52 % yield) as a colorless oil.

Spectral data of (*S*)-**115**: Colorless oil, R_f = 0.24 (1:3 EtOAc/hexane), $[\alpha]_D$ = -44.1 (*c* = 1.6, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3H, *J* = 7.1 Hz), 2.65 (s, 2H, br), 3.39 (t, 1H, *J* = 4.4 Hz), 3.63-3.77 (m, 2H), 4.19 (q, 2H, *J* = 7.1Hz), 4.94 (s, 1H), 7.22-7.43 (m, 10H);

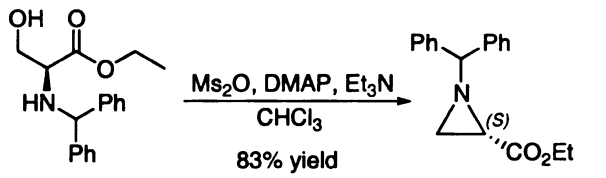
^{13}C NMR (75 MHz, $CDCl_3$) δ 14.15, 60.40, 61.13, 63.12, 65.23, 127.23, 127.29, 127.50, 128.53, 142.21, 143.53, 173.15 (two aryl carbons not located).

IR (thin film, cm^{-1}) 3420 vs, 1725 vs, 1190vs;

Mass spectrum *m/z* (% rel intensity) $(M+H)^+$ 300 (<1), 226 (17), 182 (80), 167 (100);

Anal calcd for $C_{18}H_{21}NO_2$: C, 72.22; H, 7.077; N, 4.68. Found: C, 72.10; H, 7.04; N, 4.77;

Synthesis of (*2S*)-aziridine 107:



(*S*)-**115** (*2S*)-**107** (88% ee)

To a Schlenk flask filled with argon was added N-benzhydryl serine ester (*S*)-**115** (756 mg, 2.53 mmol) and 40 mL chloroform, followed by 4-(dimethylamino)pyridine (32 mg, 0.27 mmol) and triethyl amine (614 mg, 6.07 mmol). The solution was cooled to 0°C. Methanesulfonic anhydride (681 mg, 3.79 mmol) in 5 mL chloroform was added via syringe dropwise over 30 minutes. The solution was stirred at 0°C for 1 h, the allowed to reach room temperature and heated to reflux for 44 h. The solution was allowed to cool to room temperature and quenched with water, the mixture was extracted with 3 × 50 mL CH_2Cl_2. The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. Silica gel chromatography (1:9 EtOAc/hexane) afforded (*2S*)-**107** (588 mg, 2.09 mmol, 83% yield) as white solid.

Spectral data of (*2S*)-**107**: White solid, mp = 93-95 °C, R_f = 0.24 (1:9 EtOAc/hexane), $[\alpha]_D$ = -84.5 (*c* = 1.0, $CHCl_3$);

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H, *J* = 7.1 Hz), 1.82 (d, 1H, *J* = 6.3 Hz), 2.23 (dd, 1H, *J* = 6.3, 3.0 Hz), 2.29 (d, 1H, *J* = 2.8 Hz), 3.6 (s, 1H), 4.19 (q, 2H, *J* = 7.1 Hz), 7.20-7.42 (m, 10H);

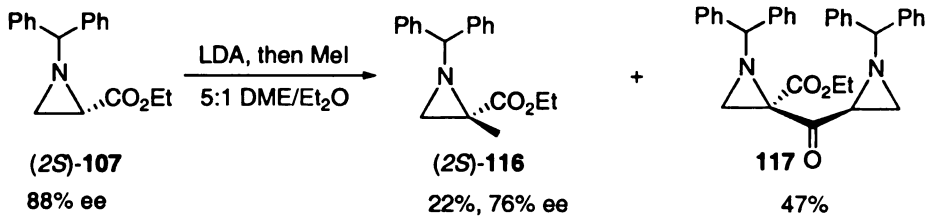
^{13}C NMR (75 MHz, $CDCl_3$) δ 14.12, 34.73, 38.26, 60.97, 77.76, 127.07, 127.16, 127.36, 127.60, 128.41, 142.41, 142.44, 170.52 (one aryl carbon not located);

IR (thin film, cm^{-1}) 1728 vs, 1186vs;

Mass spectrum *m/z* (% rel intensity) 281 M^+ (1), 280 (11), 252 (38), 167 (100), 165 (70);

Anal calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.92; H, 6.61; N, 4.60;

Synthesis of aziridine 116 and 117:

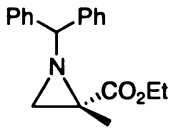


(*2S*)-**107**
88% ee

(*2S*)-**116**
22%, 76% ee

117
47%

To a flame-dried 100 mL flask cooled under argon was added diisopropylamine (627 mg, 6.2 mmol), followed by 33 mL DME. The solution was cooled to -78°C, followed by addition of nBuLi (3.85 mL, 6.2 mmol) via syringe. The LDA solution was stirred at -78°C for 5 min, then warmed up to 0°C and stirred for 15 min then cooled down to -78°C. The solution of (2S)- aziridine **107** (847 mg, 3.03 mmol) in 22 mL DME and 11 mL Et_2O was also cooled to -78°C and transferred via cannula to the flask containing LDA, gave a light brown solution. After stirring at -78°C for 30 min, iodomethane (1.31 g, 9.2 mmol) was added via syringe. The solution was then stirred at -78°C for 1 h, then allowed to warm up to room temperature slowly. After 2 h, the reaction was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with 3 × 100 mL Et_2O, the combined organic solution was dried over $MgSO_4$, concentrated *in vacuo*. Silica gel chromatography (1:15 to 1:3 EtOAc/hexane) afforded (*2S*)-**116** (200 mg, 0.68 mmol, 22% yield) as colorless oil and **117** (367 mg, 0.71 mmol, 47 % yield) as white solid.



(*2S*)-**116**

Spectral data of (*2S*)-**116**: $[\alpha]_D$ = -35.4 (*c* = 2.13, $CHCl_3$);

^1H NMR (300 MHz, $CDCl_3$) (2:1 ratio of N-invertomers) major N-invertomer: δ 0.93 (t, 3H, *J* = 6.9 Hz), 1.52 (s, 3H), 2.01 (s, 1H), 2.44 (s, 1H), 3.90 (m, 2H), 4.66 (s, 1H), 7.19-7.50

(m, 10H); minor N-invertomer: ^{1}H NMR (300 MHz, $CDCl_3$) 1.29 (t, 3H, J = 6.9 Hz), 1.42 (s, 3H), 4.66 (m, 2H), other peaks and aromatic protons were obscured by major inveromer; ^{13}C NMR of major invertomer (75 MHz, $CDCl_3$) δ 13.62, 20.33, 41.26, 60.90, 69.17, 126.70, 127.00, 127.10, 127.67, 128.04, 128.33, 143.20, 143.61, 170.29;

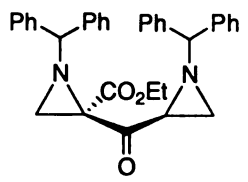
Upon heating the sample to 110°C, the two invertomers emerged: (300 MHz, d_8-toluene) δ 0.83 (t, 3H, J = 6.8 Hz), 1.38 (s, 3H), 1.60(s, 1H), 2.32 (s, 1H), 3.81 (q, 2H, J = 6.8 Hz), 7.05-7.44 (m, 10H);

IR (thin film, cm^{-1}) 2980 s, 1720 vs, 1176 vs;

Mass spectrum *m/z* (% rel intensity) 295 M^+ (2), 294 (11), 266 (32), 180 (55), 167 (100);

Anal calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found:C, 77.11; H, 7.21; N, 4.77; Rf = 0.29 (1:15 EtOAc/hexane)

The optical purity by HPLC of aziridine (*2S*)-**116** was found to be 76% by using a Chiralcel OD-H column with the following conditions: 254nm, 0.6 mL/min, 99.5:0.5 mixture of hexane and 2-propanol. (t_R = 5.52 min for major isomer and t_R = 6.63 for minor isomer)



117

Spectral data of **117**: mp = 52-56 °C (decomposed), R_f = 0.28 (1:5 EtOAc/Hexane), $[\alpha]_D$ = 17.9 (*c* = 1.0, $CHCl_3$) (prepared from *2S*-**107**);

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 3H, J = 7.3 Hz), 1.88 (d, 1H, J = 6.3 Hz), 1.98 (s, 1H), 2.41 (d, 1H), 2.42 (s, 1H), 2.82 (dd, 1H, J = 6.3, 2.9 Hz), 3.64 (s, 1H), 3.99 (m, 2H), 4.51 (s, 1H), 7.22-7.50 (m, 20H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 13.51, 37.60, 39.01, 40.41, 51.84, 61.73, 69.33, 78.14, 127.19, 127.21, 127.28, 127.40, 127.42, 128.28, 128.34, 128.36, 128.44, 142.17, 142.40, 142.55, 142.60, 165.88, 199.73 (three aryl carbon not located);

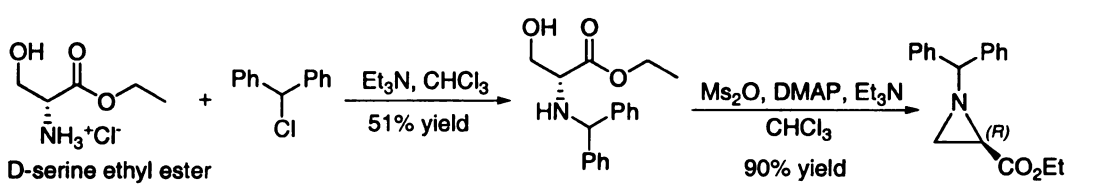
IR (thin film, cm^{-1}): 3028 s, 1720 vs;

Mass spectrum *m/z* (% rel intensity) 516 M+ (<1), 349 (8), 248 (31), 167 (100), 165 (100);

HRMS calcd for $C_{34}H_{33}N_2O_3$ (M+H) m/z 517.2491, meas 517.2495(FAB);

Anal calcd for $C_{34}H_{32}N_2O_3$: C, 79.04; H, 6.24; N, 5.42. Found: C, 78.82; H, 6.10; N, 5.38;

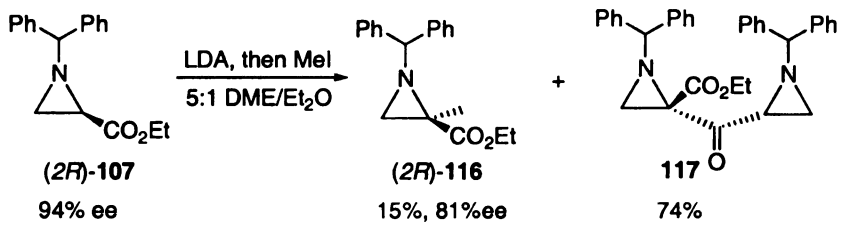
Synthesis of (*2R*)-aziridine 107:



N-benzhydryl serine ester (*R*)-**115** and (*2R*)-aziridine **107** were prepared from D-serine ethyl ester according to the procedure used for the synthesis of N-benzhydryl ester (*S*)-**115** and aziridine (*2R*)-**107**.

The optical purity by HPLC of aziridine (*2R*)-**107** was found to be 94% by using a Chiralpak AD column with the following conditions: 221nm, 0.5 mL/min, 99.6:0.4 mixture of hexane and 2-propanol. (t_R = 31.44 min for minor isomer and t_R = 37.48 for major isomer). Optical rotation: $[\alpha]_D$ = -95.5 (*c* = 1.0, $CHCl_3$)

Alkylation of (*2R*)-aziridine 107:



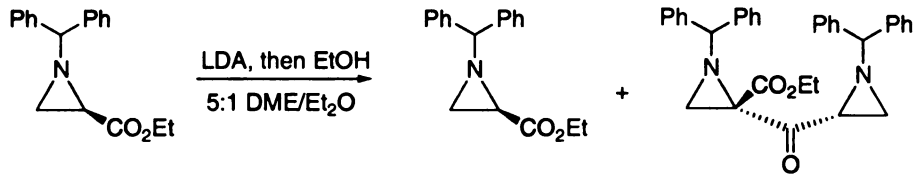
(*2R*)-**107**
94% ee

(*2R*)-**116**
15%, 81%ee

117
74%

To a flame-dried 100 mL flask cooled under argon was added diisopropylamine (314 mg, 3.1 mmol), followed by 16 mL DME. The solution was cooled to -78°C, then n-BuLi (1.93 mL, 3.1 mmol) was added via syringe. The LDA solution was stirred at -78°C for 5 min, then warmed up to 0°C and stirred for 15 min and finally cooled to -78°C. The solution of aziridine (*2R*)-**107** (423 mg, 1.51 mmol) in 11 mL DME and 5 mL Et_2O was also cooled to -78 C and transferred via cannula to the flask containing LDA giving a light brown solution. After stirring at -78°C for 30 min, iodomethane (642 mg, 4.6 mmol) was added via syringe. The solution was then stirred at -78°C for 1 h, then allowed to warm up to room temperature slowly over 2 h before quenching with saturated $NaHCO_3$ solution. The mixture was extracted with 3 × 100 mL Et_2O and the combined organic solution was dried over $MgSO_4$ and concentrated in vacuo. Silica gel chromatography (1:15 to 1:5 EtOAc/hexane) afforded (*2R*)-**116** (65 mg, 0.22 mmol, 15 % yield) as colorless oil and **117** (290 mg, 0.56 mmol, 74 % yield) as white solid. The optical purity by HPLC analysis of aziridine (*2R*)-**116** was found to be 81% with the same method as described above for (*2S*)-**116**.

Deprotonation-protonation of (*2R*)-107:



(*2R*)-**107** 94% ee

(*2R*)-**107** 14%, 47% ee

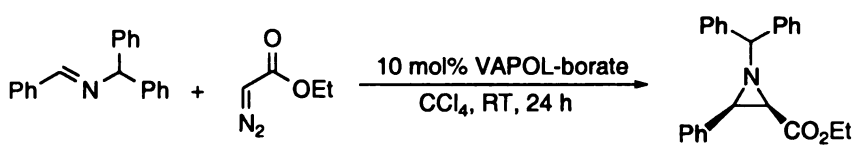
117 (73%) 73%

To a flame-dried 100 mL flask cooled under argon was added diisopropylamine (314 mg, 3.1 mmol), followed by 16 mL DME. The solution was cooled to -78°C, then n-BuLi (1.93 mL, 3.1 mmol) was added via syringe. The LDA solution was stirred at -78°C for 5 min, then warmed up to 0°C and stirred for 15 min and finally cooled to -78°C. The solution of aziridine (*2R*)-**107** (423 mg, 1.51 mmol) in 11 mL DME and 5 mL Et_2O was also cooled to -78 C and transferred via cannula to the flask containing LDA giving a light brown solution. After stirring at -78°C for 30 min, ethanol (348 mg, 7.55 mmol) was added via syringe. The solution was then stirred at -78°C for 1 h, then allowed to warm up to room temperature slowly over 2 h before quenching with saturated $NaHCO_3$ solution. The mixture was extracted with 3 × 100 mL Et_2O and the combined organic solution was dried over $MgSO_4$ and concentrated in vacuo. Silica gel chromatography (1:15 to 1:5 EtOAc/hexane) afforded (*2R*)-**107** (60 mg, 0.20 mmol, 14 % yield) as colorless oil and **117** (285 mg, 0.55 mmol, 73 % yield) as white solid. HPLC analysis of (*2R*)-**107** indicated its optical purity was 47% ee. Optical rotation of recovered (*2R*)-**107**: $[\alpha]_D$ = +45.0 (*c* = 1.0, $CHCl_3$)

Experimental for Chapter Five:

Experimental procedure for the preparation of VAPOL-borate catalyst: To a flame-dried Schlenk flask cooled under argon was added VAPOL (54 mg, 0.1 mmol) and $B(OPh)_3$ (87 mg, 0.3 mmol) followed by 2 mL of dry CCl_4. The flask was sealed under argon and the mixture was stirred at 80°C for 1 hour, then a vacuum (0.2-0.5 mm Hg) was applied to remove the solvent and the remained mixture was heated at 80°C for 30 minutes. The catalyst was then dissolved in appropriate solvent and transferred to the reaction flask.

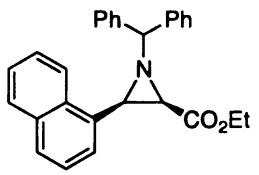
Typical experimental procedure for the asymmetric aziridination in CCl_4:



135 **21** **136**

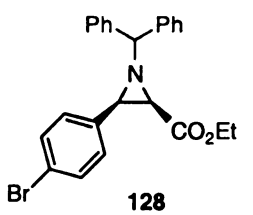
To a flame-dried 25 mL round bottom flask cooled under argon was added imine **135** (271 mg, 1 mmol). The catalyst prepared from *S*-VAPOL and $B(OPh)_3$ was dissolved in 2 × 1 mL CCl_4 and added to the reaction flask via syringe. Stirring for 5 minutes gave an orange solution. To this solution was added ethyl diazoacetate **21** (115 μL, 1.1 mmol) via syringe. Vigorous bubbling was observed after the addition and continued for approximately 2 hours. The solution was stirred at room temperature for 24 hours, then quenched by addition of 10 mL hexane. Removal of the solvent afforded an off-white solid. The cis/trans ratio and the amount of enamine products were determined by ^{1}H-NMR as described in reference 25b. Silica gel chromatography (1:19 to 1:15 EtOAc/hexane) of the crude product afforded aziridine (*2R*, *3R*)-**136** as a white solid (316 mg, 0.89 mmol), 89% yield. An optical purity of 93 % ee was determined by HPLC

analysis using a Chiralcel OD-H column with 9:1 hexane/2-propanol as eluent, flow rate = 0.7 mL/min. Retention times: R_t = 4.33 min (minor *2S, 3S*-isomer) and R_t = 9.48 min (major *2R, 3R*-isomer from S-ligand). All the characterization details of **136** can be found in reference 25b.



124

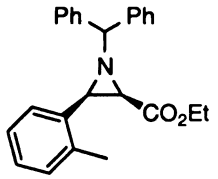
(*2R, 3R*)-aziridine **124**: The aziridine was prepared from 1 mmol imine **123** with 10 mol% *S*-VAPOL borate catalyst in CH_2Cl_2. 335 mg aziridine **124** was isolated as product (0.87 mmol, 87% yield). An optical purity of 93 % ee was determined by HPLC analysis using a Chiralcel OD-H column with 9:1 hexane/2-propanol as eluent, flow rate = 1.0 mL/min. Retention times: R_t = 3.4 min (minor isomer) and R_t = 4.0 min (major *2R, 3R*-isomer). All the characterization details of **124** can be found in reference 25b.



128

(*2R, 3R*)-aziridine **128**: The aziridine was prepared from 2 mmol imine **127** with 5 mol% *S*-VAPOL borate catalyst in toluene. 734 mg aziridine **128** was isolated as product (1.68 mmol, 84% yield). An optical purity of 91 % ee was determined by HPLC analysis using a Chiralcel OD-H column with hexane/2-propanol as eluent (96:4 to 90:10 in 30 minutes), flow rate = 1.0 mL/min. Retention times: R_t = 4.11 min (minor isomer) and R_t = 7.02 min

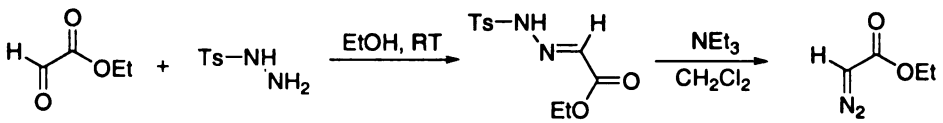
(major *2R*, *3R*-isomer). All the characterization details of **128** can be found in reference 25b.



132

(*2R*, *3R*)-aziridine **132**: The aziridine was prepared from 1 mmol imine **131** with 10 mol% *S*-VAPOL borate catalyst in toluene as solvent. 256 mg aziridine **128** was isolated as product (0.69 mmol, 84% yield). An optical purity of 90 % ee was determined by HPLC analysis using a Chiralcel OD-H column with hexane/2-propanol (99:1 in 30 minutes) as eluent, flow rate = 1.0 mL/min. Retention times: R_t = 4.9 min (minor isomer) and R_t = 5.8 min (major *2R*, *3R*-isomer). All the characterization details of **132** can be found in reference 25b.

Preparation of ethyl diazoacetate from ethyl glyoxalate:

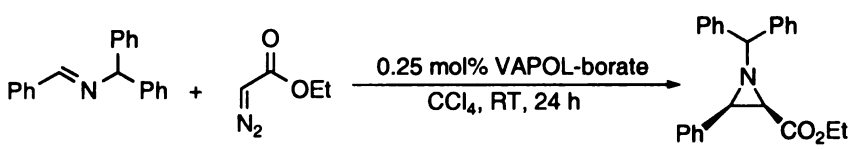


To a 100 mL round bottom flask was added p-tolusulfonyl hydrazide (2 g, 10.4 mmol), followed by 10 mL absolute ethanol. The slurry was stirred at room temperature. Ethyl glyoxalate (50% in toluene, 2.13 g, 10.4 mmol) was added via syringe. The mixture was stirred at room temperature for 12 hours. The solution was then concentrated in vacuo, and the crude reaction mixture was obtained as a light yellow oil, which slowly solidified to

give an off-white solid. The crude hydrozone[51c] was not purified and used directly in the next step.

The crude hydrozone (~ 10.4 mmol) was dissolved in 20 mL CH_2Cl_2 and stirred at 0°C. NEt_3 (1.05 g, 10.4 mmol) was diluted with 5 mL CH_2Cl_2 and added to the hydrozone solution dropwisely in a period of 5 minutes. The solution turned yellow upon addition. After the addition finished, the solution was stirred at 0°C for 30 minutes, then the ice bath was removed and the solution was stirred for another 15 minutes. The organic solution was washed with 50 mL 0.3 M HCl solution, then 2 × 50 mL saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated in vacuo to give a yellow oil. The crude product was purified by flash chromatography with 1:1 pentane/CH_2Cl_2, gave 0.69 g ethyl diazoacetate (6 mmol, 58 % yield). The material obtained was identical to that commercially available from Aldrich.

Experimental procedure for the large scale aziridination of 135 in CCl_4:



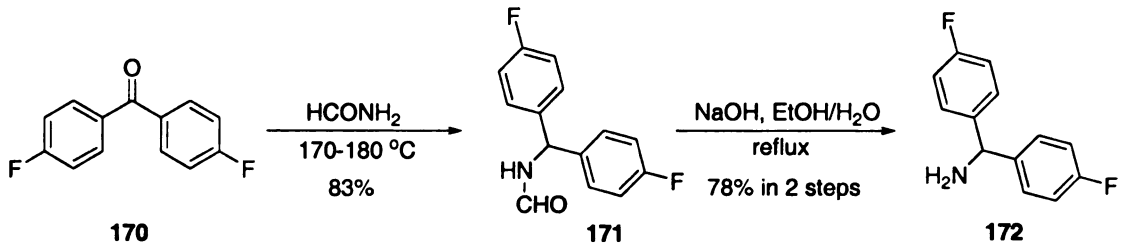
135 **21** **136**

To a flame-dried 250 mL round bottom flask cooled under argon was added imine **135** (10.854 g, 40 mmol), followed by 76 mL CCl_4. The catalyst prepared from 0.1 mmol VAPOL and 0.3 mmol $B(OPh)_3$ was dissolved in 2 × 2 mL CCl_4 and added to the reaction flask via syringe. Stirring for 5 minutes gave a light yellow solution. To this solution was added ethyl diazoacetate **21** (4.6 mL, 46 mmol) via syringe. Vigorous bubbling was observed after the addition. The solution was stirred at room temperature for 24 hours, then quenched by addition of 80 mL hexane. The mixture was stirred open to air for 15 minutes, then filtered through celite to remove insoluble solid. Removal of the solvent and

excess of EDA *in vacuo* afforded an off-white solid. The crude product was recrystallized from 360 mL boiled 98:2 hexane/CH_2Cl_2, first crop afforded 9.127 g aziridine with 98.2% ee. The mother liquor was concentrated *in vacuo* and recrystallized from 65 mL hexane/CH_2Cl_2 again, afforded 2.694 g aziridine **136** with 50% ee. The remaining mother liquor was again concentrated *in vacuo* and purified by chromatography (1:19 to 1:15 EtOAc/hexane) to give 0.728 g aziridine **136** with 66% ee. The combined yield for aziridine **136** was 12.55 g (35.2 mmol, 88% yield) and the overall ee was determined to be 86% ee by chiral HPLC analysis on the combined product.

Experimental for Chapter Six:

Preparation of amines



170 171 172

***N*-Formyl-4,4'-difluorobenzhydrylamine 171:** To a 100 mL round bottom flask was charged ketone **170** (5 g, 22.7 mmol) and 30 mL formamide. The flask was stirred under argon in 170-180 °C oil bath for 15 hours. The hot mixture was poured into 200 mL H_2O. A dark brown mixture was obtained, after mixed with 300 mL EtOAc and vigorously stirred for 5 minutes, it was filtered through a plug of celite to remove insoluble material. The solution was loaded to separation funnel and the organic layer was collected, the aqueous layer was washed with 2 × 100 mL EtOAc. The combined organic layer was dried over $MgSO_4$, boiled with 3 g of active carbon for 5 minutes to remove the color, and concentrated *in vacuo* to give a yellow oil. To this yellow oil was added 200 mL of hexane, the flask was loaded to rotavapor to remove solvent. Off-white solid appeared when solvent was evaporated, 7.83 g of this solid was collected as the crude product. The crude mixture can be used in next step without further purification. From the 7.83 g crude mixture, 1 g was purified with flash chromatography and eluted with 1:35 MeOH/CH_2Cl_2. The product was isolated as 0.6 g (2.42 mmol) off-white solid, which corresponded to 83% yield. Spectral data for **171**: White solid; R_f = 0.30 (1:30 CH_2Cl_2/MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ = 6.21 (d, J = 8 Hz, 1H), 6.76 (d, J = 8 Hz, 1H), 6.96-7.20 (m, 8H), 8.16 (s, 1H); Mass spectrum: m/z (% rel intensity) 247 M^+ (93), 246 (71), 203 (18), 201 (100), 183 (21), 152 (11), 122 (71);

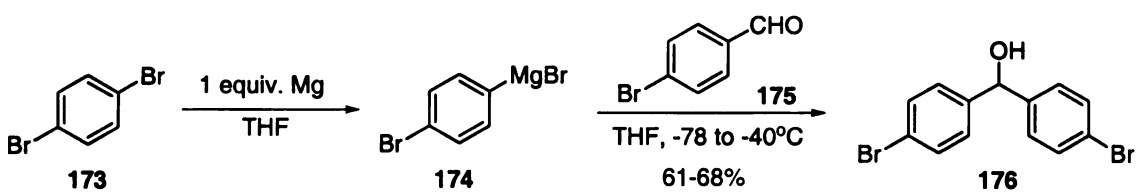
4,4'-Difluorobenzhydrylamine 172: The crude *N*-formyl-benzhydrylamine **171** obtained in the Leukhart reaction from (15 g, 68 mmol) of ketone **170** was added to a 500 mL round bottom flask equipped with condenser. To the flask was also added 60 mL 40% NaOH solution and 300 mL EtOH. The mixture was heated to reflux for 3.5 hours. The solution was cooled down, concentrated on rotavapor to remove most solvent. Then the mixture was loaded to separation funnel, and the mixture was extracted with 3 × 100 mL CH_2Cl_2. The combined CH_2Cl_2 was dried over $MgSO_4$, concentrated *in vacuo* to give a red oil. Vacuum distillation gave 11.59 g (53 mmol) colorless oil as product, which solidified slowly in freezer. Amine **172** boiled at 102–105 °C (0.2 mm Hg). The overall yield from ketone **170** over two steps was 78%.

Spectral data for **172**:[92] Colorless oil; m.p. 31-32 °C;

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.72 (br, s, 2H), 5.16 (s, 1H), 6.90-7.05 (m, 4H), 7.24-7.34 (m, 4H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 58.23, 115.10 (d, J_{CF} = 22Hz), 128.17 (d, J_{CF} = 8.0 Hz), 141.11 (d, J_{CF} = 3.5 Hz), 161.66 (d, J_{CF} = 245 Hz);

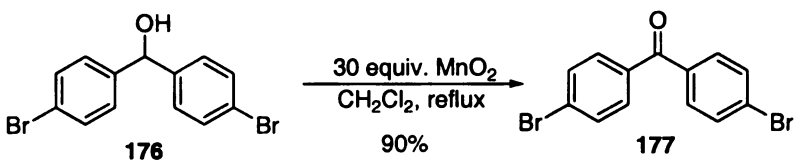
Mass spectrum: m/z (% rel intensity) 219 M^+ (8), 201 (10), 124 (83), 123 (100);



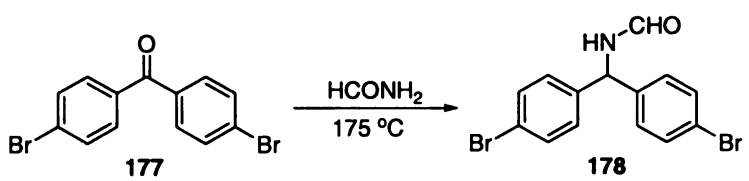
173 **174** 61-68% **176**

4,4'-Dibromobenzhydrol 176: A 250 mL three-neck round bottom flask attached with reflux condenser was flame-dried and cooled under argon. To this flask was added 1,4-dibromobenzene **173** (18 g, 75 mmol), 100 mL dry THF and magnesium (1.25g, 50 mmol) followed by a small iodine crystal. The flask was heated to reflux for 1 h, then cooled down to 0°C. To another flame-dried 500 mL round bottom flask cooled under

argon was added *p*-bromobenzaldehyde **175** (9.25 g, 50 mml) and 100 mL dry THF. The solution of **175** was cooled to -78 °C. The Grignard reagent **174** prepared from **173** was transferred via cannula to the -78 °C solution of **175** slowly. The resulting solution was stirred at -78 °C and allowed to warm up very slowly to -40°C in two hours, then quenched at -40 °C by addition of 50 mL 1N HCl. The mixture was extracted with 3 × 50 mL ether. The organic layer was dried over $MgSO_4$, concentrated *in vacuo*. The crude mixture was purified by flash chromatography and eluted with 1:6 EtOAc/hexane, gave product **176**[93] as a white solid (10.42 g, 30.5 mmol), 61% yield.



4,4'-Dibromobenzophenone 177: To an oven-dried 500 round bottom flask equipped with reflux condenser and filled with argon was added 4,4'-dibromobenzhydrol **176** (4g, 11.7 mmol), activated MnO_2 (30.24 g, 348 mmol) and 150 mL CH_2Cl_2. The suspension was refluxed for 18 h. TLC showed complete consumption of the starting material. The mixture was filtered and concentrated on rotary evaporator, and absorbed on 24 g silica gel, purified by flash chromatography and eluted with 1:3 CH_2Cl_2/hexane (R_f = 0.33), afforded the desired product **177** was a white solid (3.573 g, 10.5 mmol), 90% yield. The material obtained was identical to that commercially available from Aldrich.



N-(Bis(4-bromophenyl)methyl)formamide 178: To a 500 mL round bottom flask was added ketone **177** (7 g, 20.6 mmol) and 160 mL formamide. The mixture was heated

open to air at 175 °C for 18 hours. The solution turned dark gradually. After 18h, the dark solution while hot was poured into 1L of H_2O, 300 mL CH_2Cl_2 was then added to dissolve the organic product. The emulsified mixture was filtered through celite to remove insoluble material. The water layer was extracted with 3 × 80 mL CH_2Cl_2, and the combined organic layer was washed with 50 mL H_2O once, dried over $MgSO_4$, concentrated *in vacuo*, gave a light yellow solid. The crude product does not require further purification and could be subjected to hydrolysis directly.

Spectral data for amide **178**: White solid; mp 156-158 °C. R_f = 0.33 (10:10:1 hexane/ CH_2Cl_2/MeOH).

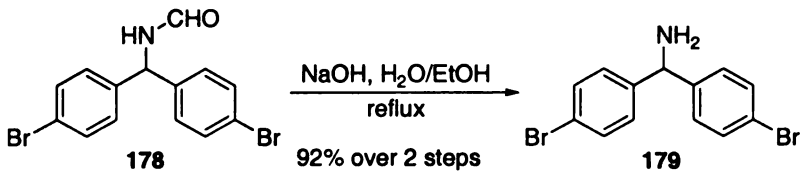
^1H NMR ($CDCl_3$, 300 MHz) δ = 6.20 (s, 2H), 7.06 (d, *J* = 8.5 Hz, 4H), 7.45 (d, *J* = 8.5 Hz, 4H), 8.26 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 54.69, 121.95, 129.03, 132.0, 139.27, 160.11;

IR (thin film, cm^{-1}) 3270 br, 1659 vs, 1487 vs;

Mass spectrum: m/z (% rel intensity) 372 (2, $(M+1)^+$, $^{81}Br_2$), 371 (18, M^+, $^{81}Br_2$), 370 (26, $(M+1)^+$, $^{81}Br^{79}Br$), 369 (50, M^+, $^{81}Br^{79}Br$), 368 (47, $(M+1)^+$, $^{79}Br_2$), 367 (30, M^+, $^{79}Br_2$), 245 (38), 243 (35), 184 (90), 165 (100), 163 (96);

Anal calcd for $C_{14}H_{11}Br_2NO$: C, 45.56; H, 3.00; N, 3.80. Found: C, 45.55; H, 2.88; N, 3.84;



4,4'-Dibromobenzhydryl amine 179: To a 500 mL round bottom flask was added ~20 mmol crude amide **178** which was prepared from Leukarht reaction of 20.6 mmol benzophenone **177**, followed by 28 mL 40% aqueous NaOH solution and 140 mL EtOH. The solution was heated to reflux for 2h before cooled down to room temperature and

loaded to rotary evaporator. Most solvent (~ 120 mL) was removed *in vacuo*. The remaining mixture was extracted with 3 × 80 mL CH_2Cl_2. The combined organic layer was washed with 50 mL H_2O once, dried over $MgSO_4$ and concentrated *in vacuo* to give a light yellow solid. The crude mixture was purified by flash chromatography, eluted with 1:1 EtOAc/hexane, gave product **179** as a white solid (6.52 g, 19.2 mmol), 93% yield for two steps).

Spectral data for 4,4'-dibromobenzhydryl amine **179**: White soild; mp 73-75 °C. R_f = 0.5 (1:1 hexane/EtOAc).

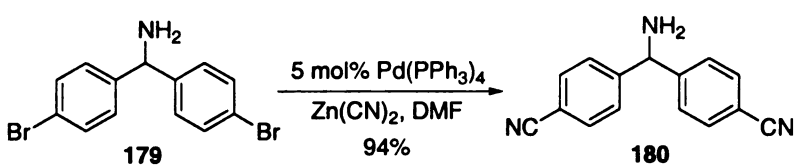
^1H NMR ($CDCl_3$, 300 MHz) δ = 1.69 (s, 2H), 5.10 (s, 1H), 7.20 (d, 4H, *J* = 8.5 Hz), 7.40 (d, 4H, *J* = 8.5 Hz);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 58.62, 120.95, 128.50, 131.59, 144.04;

IR (thin film, cm^{-1}) 3380 brs, 1481s;

Mass spectrum: m/z (% rel intensity) 344(<1, $(M+1)^+$, $^{81}Br_2$), 343 (3, M^+, $^{81}Br_2$), 342 (3, $(M+1)^+$, $^{81}Br^{79}Br$), 341 (6, M^+, $^{81}Br^{79}Br$), 340 (5, $(M+1)^+$, $^{79}Br_2$), 339 (4, M^+, $^{79}Br_2$), 186 (51), 185 (84), 184 (100), 165 (13), 164 (12);

Anal calcd for $C_{13}H_{11}Br_2N$: C, 45.78; H, 3.25; N, 4.11. Found: C, 46.16; H, 3.22; N, 4.15;



4,4'-Dicyanobenzhydryl amine 180: To a flame-dried 50 mL Schlenk flask filled with argon was added 4,4'-dibromobenzhydryl amine **179** (6.52g, 19.12 mmol), $Pd(PPh_3)_4$ catalyst (1.10g, 0.956 mmol) and zinc cyanide (3.20 g, 26.77 mmol), followed by 30 mL dry DMF. The flask was deoxygenated by three freeze-thaw cycles before sealed under argon. The yellow suspension was stirred at 80 °C for 24h, then cooled down to room

temperature, diluted with 200 mL toluene. The organic layer was washed with 3 × 50 mL 2N ammonium hydroxide solution, then washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow solid. The crude product was purified by flash chromatography, eluted with 20:5:1 EtOAc/hexane/MeOH and gave product **180** as a white solid (4.115 g, 17.6 mmol), 92% yield.

Spectral data for 4,4'-dicyanobenzhydryl amine **180**: White solid; mp 99-101 °C. R_f = 0.34 (20:5:1 EtOAc/hexane/MeOH).

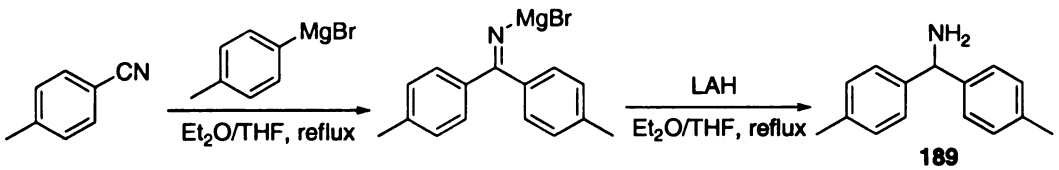
^1H NMR ($CDCl_3$, 300 MHz) δ = 1.79 (s, 2H), 5.29 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 4H), 7.57 (d, *J* = 8.2 Hz, 4H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 59.20, 111.28, 118.51, 127.54, 132.49, 149.38;

IR (thin film, cm^{-1}) 3379 s, 2229 vs, 1603s;

Mass spectrum: m/z (% rel intensity) 233 M^+ (27), 232 (21), 131 (100), 130 78);

Anal calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 77.18; H, 4.65; N, 17.68;



189

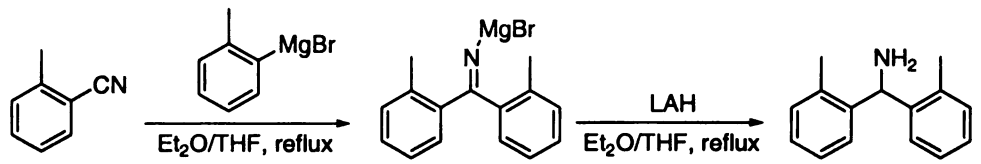
4,4'-Dimethylbenzhydryl amine 189: To a flame-dried 500 mL three-neck round bottom flask cooled under argon was added 1 M solution of p-tolylmagnesium bromide (51 mL, 50.69 mmol), followed by 30 mL of dry THF. The solution of *para*-methylbenzonitrile (5.05 g, 42.24 mmol) in 20 mL dry THF was transferred via syringe to the flask containing Grignard reagent. The resulting solution was heated to reflux for 9 hours before cooled down to room temperature. Then a suspension of LAH (1.95 g, 51 mmol) in 60 mL dry THF was transferred to the reaction flask via cannula. The resulting solution was reheated to reflux for 12 hours. The solution was cooled down to room temperature,

quenched carefully with 2 mL H_2O, 2 mL 20% NaOH solution, then 6 mL H_2O. The mixture was filtered through sand funnel and the solid was washed with Et_2O until there was no presence of detectable amine in the filtered Et_2O. The organic solution was concentrated *in vacuo* to give a yellow solid. The crude product was purified by crystallization from ether, gave white solid as pure product after four crops (7.03 g, 33.3 mmol), 79% yield.

Spectral data for **189**:[92] White solid;

^1H NMR ($CDCl_3$, 300 MHz) δ = 1.75 (s, 2H), 2.30 (s, 6H), 5.13 (s, 1H), 7.10 (d, J = 8.0 Hz, 4H), 7.24 (d, J = 8.0 Hz, 4H) ;

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 20.98, 59.14, 126.66, 129.07, 136.36, 142.85;



190

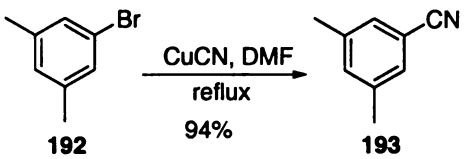
2,2'-Dimethylbenzhydrylmine 190: To a flame-dried 500 mL three-neck round bottom flask cooled under argon was added 1 M solution of o-tolylmagnesium bromide (51 mL, 50.69 mmol). The solution of o-methylbenzonitrile (5.05 g, 42.24 mmol) in 50 mL dry THF was transferred via syringe to the flask containing Grignard reagent. The resulting solution was heated to reflux for 24 hours before cooled down to room temperature. Then a suspension of LAH (1.95 g, 51 mmol) in 40 mL dry THF was transferred to the reaction flask via cannula. The resulting solution was reheated to reflux for 19 hours. The solution was cooled down to room temperature, quenched carefully with 2 mL H_2O, 2 mL 20% NaOH solution, then 8 mL H_2O. The mixture was filtered through sand funnel and the solid was washed with Et_2O until there was no presence of detectable amine in the filtered Et_2O. The organic solution was concentrated *in vacuo* to give a light yellow oil.

The crude product was purified by vacuum distillation, gave a colorless oil as pure product (8.14 g, 38.5 mmol), 91% yield.

Spectral data for product amine **190**:[92] Colorless oil; bp 119-122 °C at 0.1 mm Hg;

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.69 (br, s, 2H), 2.34 (s, 6H), 5.51 (s, 1H), 7.20-7.36 (m, 8H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 18.99, 52.53, 126.02, 126.08, 126.65, 130.28, 135.44, 142.88;



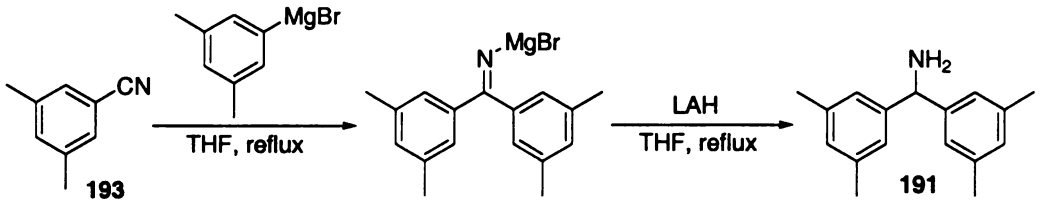
192 **193**

3,5-Dimethylbenonitrile 193: To a 250 round bottom flask equipped with condenser was charged 5-bromo-m-xylene **192** (12 g, 63 mmol), CuCN (6.76 g, 75 mmol) and 80 mL DMF. The solution was deoxygenated by flushing with argon for 10 minutes, and heated to reflux under argon for 6 hours. Workup was done by adding a solution of 20 mL ethylenediamine in 100 mL H_2O to the reaction flask. The mixture was stirred at room temperature for 10 minutes, then extracted with 3 × 100 mL benzene. The combined benzene solution was washed with 50 mL 10 NaCN solution, the washed with 50 mL H_2O, dried over $MgSO_4$. Removal of solvent on rotavapor afforded a light yellow solid, which was purified by flash column. Elution with 1:35 EtOAc/hexane afforded 7.73 g (59 mmol) white solid as product, yield 94%.

Spectral data for benzonitrile **193**:[94] White solid;

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.35 (d, J = 0.55 Hz, 6H), 7.23 (s, 1H), 7.25 (d, J = 0.55 Hz, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 20.88, 111.85, 119.07, 129.48, 134.49, 138.89.



3,3',5,5'-Tetramethylbenzhydryl amine 191: To a flame-dried 100 mL three-neck round bottom flask was added 50 mL THF, magnesium tunning (1.96 g, 80.73 mmol), followed by one crystal of iodine. To this flask was then added the bromide **192** (6.16 g, 32.29 mmol) via syringe. The mixture was heated to reflux for 1.5 hours. The obtained light amber solution was transferred via syringe to a 500 mL round bottom flask. A solution of nitrile **193** (3.86 g, 29.35 mmol) in 50 mL THF was added via cannula to the flask containing Grignard solution. The solution was heated to reflux for 8 hours, the cooled down. A suspension of $LiAlH_4$ (1.23 g, 32.29 mmol) in 60 mL THF was added to the reaction flask via cannula, the obtained solution was reheated to reflux for 14 hours. The mixture was cooled down to room temperature, then it was quenched by careful addition of 1.2 mL of H_2O, 1 mL of 20% NaOH solution and then 3 mL H_2O carefully. The white mud like mixture was loaded to funnel and filtrated, the solid was washed with Et_2O (~ 500 mL) until there was no presence of detectable compound in the filtered Et_2O (monitored by TLC spotting). The ether layer was dried over Na_2SO_4. The yellow solid obtained was crystallized from CH_2Cl_2/hexane, afforded 5.15 g (21.51 mmol) white solid as product **191**, yield 73%.

Spectral data for 3,3',5,5'-tetramethylbenzhydrylamine **191**: White solid; mp 58-60 °C

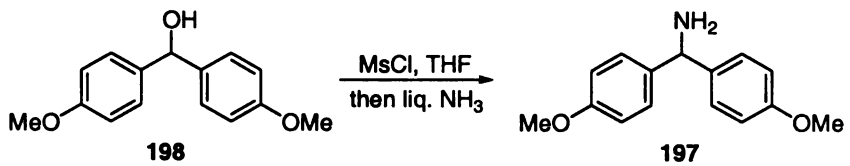
^1H NMR ($CDCl_3$, 300 MHz) δ = 1.99 (br, s, 2H), 2.29 (s, 12H), 5.05 (s, 1H), 6.86 (s, 2H), 6.99 (s, 4H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 21.30, 59.50, 124.56, 128.51, 137.86, 145.45;

IR (thin film, cm^{-1}) 2946 vs;

Mass spectrum: m/z (% rel intensity) 239 M^+ (21), 193 (7), 135 (100), 107 (22);

Anal calcd for $C_{22}H_{21}N$: C, 85.30; H, 8.84; N, 5.85. Found: C, 84.94; H, 8.92; N, 5.82;



198 197

4,4'-Dimethoxybenzhydryl amine:[68] To a 500 mL flame-dried three-neck round bottom flask filled with argon was added 4,4'-dimethoxybenzhydrol **198** (19.1 g, 78.2 mmol) and 250 mL dry THF, the solution was cooled to –78 °C. Et_3N (10.28 g, 101.7 mmol) was added dropwisely, followed by mesyl chloride (11.62 g, 101.7 mmol) dropwisely via syringe with vigorous stirring at –78 °C. The mixture was warmed up to –20 °C maximum, stirred for 30 minutes at this temperature, then cooled back to –78 °C, Liquid ammonia was directly added dropwisely via a dry ice condenser from ammonia cylinder in a period of 20 minutes. The reaction mixture was allowed to warm up gradually to room temperature, and stirred for another 20 h. Upon completion, the reaction contents was quenched by adding 200 mL NH_4OH solution, followed by extraction with ethyl acetate (100 mL × 3), the organic layer was dried over $MgSO_4$ and concentrated to afford a white solid as crude product, purified by 2% Et_3N pre-neutralized column chromatography, 1:1 ethyl acetate and hexane was first used as eluent, after the first fraction elucidated, the eluent was changed to pure ethyl acetate to afford product amine as white solid (15.59 g, 64 mmol), 82% yield.

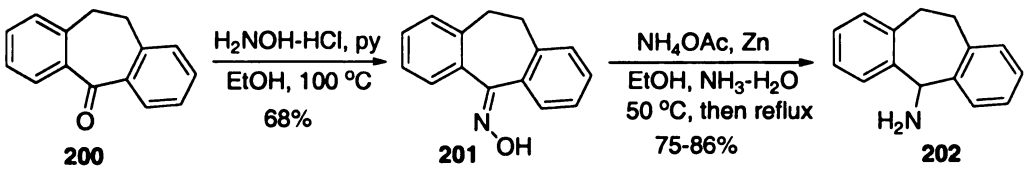
Spectral data for amine **197**:[68] white solid; mp: 60-61 °C; R_f = 0.17 (1:1 hexane/EtOAc).

^1H NMR ($CDCl_3$, 300 MHz) δ = 1.97 (br s, 2H), 3.75 (s, 6H), 5.11 (s, 1H), 6.82 (d, J = 8.6, 4H), 7.25 (d, J = 8.5Hz, 4H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 55.08, 58.33, 113.60, 127.68, 138.03, 158.26;

IR (thin film, cm^{-1}) 3395 br, 3345 m, 1610 s, 1508 vs, 1245 vs,;

Mass spectrum: m/z (% rel intensity) 243 M^+ (23), 242 (27), 227 (14), 136 (72), 135 (100), 109 (17);



200 201 202

Dibenzosuberone oxime 201:[69] To a 50 mL Schlenk flask was added dibenzosuberone **200** (6 g, 28.8 mmol), hydroxylamine hydrochloride (6 g, 86 mmol), 6 mL pyridine and 30 mL EtOH. The solution was deoxygenated by three freeze-thaw cycle and sealed under argon, then heated at 100 °C for 6 days. Upon heating the color of the solution turned dark red slowly. After 6 days, the solvent was removed under reduced pressure and the residue was partitioned between 40 mL EtOAc and 40 mL water. The aqueous layer was extracted with 2 × 20 mL EtOAc. The combined organic layer was dried over $MgSO_4$, concentrated *in vacuo* to give crude oxime as pale yellow solid, which was crystallized from 3:1 cyclohexane/EtOAc. Two crops gave product **201** as pale yellow solid (4.36 g, 19.5 mmol), 68% yield.

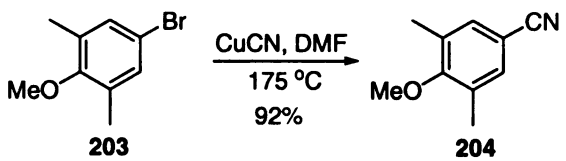
5-Aminodibenzosuberane 202: To a stirred suspension of dibenzosuberone oxime **201** (3.94 g, 17.7 mmol) in 25 mL EtOH and 100 mL concentrated ammonia solution was added NH_4OAc (690 mg, 8.95 mmol), followed by portionwise addition of zinc powder (6.42 g, 98 mmol). The mixture was heated to 50 °C. Once the vigorous bubbling stopped, the solution was heated to reflux for 18 h. The mixture was then cooled down to room temperature and diluted with 100 mL of EtOAc, stirred for 30 mins and filtered. The filtrate was transferred to separatory funnel, the EtOAc was collected and the aquesous layer extracted with 2 × 50 mL EtOAc. The combined organic layer was dried over

$mgSO_4$, concentrated *in vacuo* to give a light yellow solid, which was purified by flash chromatography (3:1:0.2 EtOAc/hexane/MeOH, R_f = 0.3) to give pure amine **202** (3.18 g, 15.2 mmol), 86% yield.

All the spectral data for **202** were identical to the reported data.[69]

^1H NMR ($CDCl_3$, 300 MHz) δ = 1.81 (s, 2H), 3.15-3.25 (m, 2H), 3.34-3.45 (m, 2H), 5.46 (s, 1H), 7,11-7.20 (m, 6H), 7.38-7.44 (m, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 32.56, 58.45, 126.11, 126.42, 127.11, 130.10, 138.82, 142.20;



203 **204**

3,5-Dimethyl-4-methoxybenzonitrile 204: To a 250 three neck round bottom flask equipped with condenser and filled with argon was charged 4-bromo-2,6-dimethyl anisole **203** (10 g, 46.5 mmol), CuCN (5 g, 55.8 mmol) and 100 mL distilled DMF. The solution was purged with argon for 30 minutes before being heated in oil batch. The solution was then heated to reflux under argon for 6 hours. Solid CuCN dissolved after approximately 1-2 hours. After 6 hours of heating, the solution was allowed to cool down, and poured into 500 mL H_2O containing 20 mL of ethylene diamine. The mixture was stirred at room temperature for 10 minutes, then extracted with 3 × 100 mL benzene. The combined benzene solution was washed with 100 mL 10% NaCN solution, then washed with 100 mL H_2O and dried over $MgSO_4$. Removal of solvent on rotavapor afforded an off-white solid, which was purified by flash chromatography. Elution with 1:15 EtOAc/hexane afforded 6.82 g (42.3 mmol) white solid as product, yield 92%.

Spectral data for benzonitrile **204**: White solid, R_f = 0.32 (1:15 EtOAc/hexane), mp = 48-49 °C

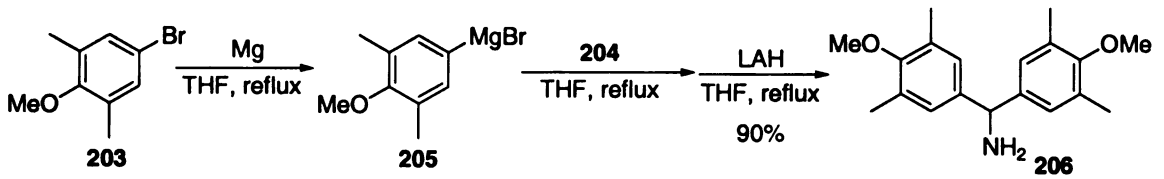
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.26 (s, 6H), 3.72 (s, 3H), 7.29 (s, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 15.93, 59,73, 107.25, 118.99, 132.46, 132.70, 160.75;

IR (thin film, cm^{-1}) 2225 vs, 2960 vs;

Mass spectrum: m/z (% rel intensity) 161 M^+ (80), 145 (100), 116 (24);

Anal calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.67; H, 6.87; N, 8.58.



203 205 206

3,3',5,5'-Tetramethyl-4,4'-dimethoxy benzhydrylamine 206: To a flame-dried 250 mL three-neck round bottom flask attached with a reflux condenser and cooled under argon was added magnesium (2.07 g, 85 mmol), 100 mL dry THF followed by one crystal of iodine. Bromoanisole **203** (7.33 g, 34 mmol) was added via syringe slowly. The mixture was heated to reflux under argon for 1.5 hours, allowed to cool down to room temperature. The clear amber solution was transferred to a flame-dried 500 mL three-neck round bottom flask equipped with condenser via cannula. Benzonitrile **204** (5 g, 31 mmol) was dissolved in 100 mL of dry THF and transferred to the 500 mL flask containing Grignard reagent via cannula. The resulting solution was heated to reflux under argon for 6 hours, then cooled down to room temperature. A suspension of $LiAlH_4$ (1.36 g, 34 mmol) in 60 mL dry THF was transferred via cannula to the reaction flask. The resulting light yellow mixture was heated to reflux for 12 hours, then cooled down to room temperature, quenched carefully with the addition of 1.4 mL H_2O, 1.4 mL 10% NaOH solution and then 4.2 mL H_2O slowly. The resulting suspension was diluted with 100 mL of Et_2O and filtered to remove salts, the solid was washed with Et_2O until there was no presence of detectable amine in the filtered Et_2O. The combined ether was

concentrated *in vacuo* to give crude product as a light yellow oil, which was purified by silica gel chromatography, eluted with 5:1:0.2 EtOAc/Hexane/MeOH, gave 8.33 g (27.8 mmol) colorless oil, which solidified upon standing, 90% yield.

Spectral data for product **206**: White solid, R_f = 0.3 (5:1:0.2 EtOAc/Hexane/MeOH), mp = 59-61 °C;

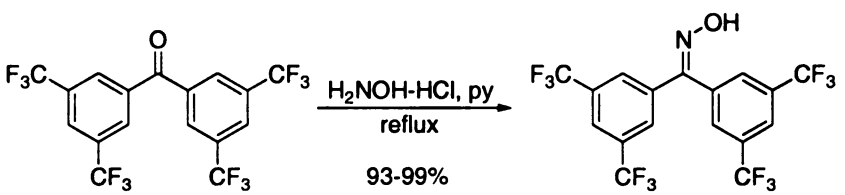
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.73 (s, 2H), 2.26 (s, 12H), 3.69 (s, 6H), 5.00 (s, 1H), 7.01 (s, 4H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 16.10, 58.77, 59.50, 126.96, 130.56, 140.88, 155.65;

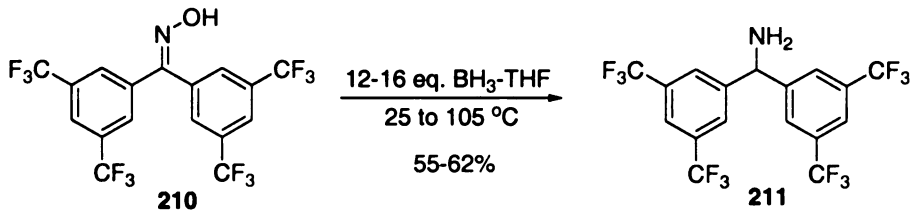
IR (thin film, cm^{-1}) 2943 vs;

Mass spectrum: m/z (% rel intensity) 299 M^+ (35), 298 (54), 283 (47), 268 (94), 163 (100);

Anal calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 75.89; H, 8.54; N, 4.62.



3,3',5,5'-Tetra-trifluoromethyl benzhydrylamine 210: To a 250 mL round bottom flask equipped with refluxing condenser and filled with argon, was added 10 g (22 mmol) ketone **209**,[71a] hydroxyl ammonium chloride (2.6 g, 37.4 mmol) and 100 mL pyridine. The solution was heated to reflux for 45 minutes, cooled down and concentrated *in vacuo*. 100 mL H_2O was added, and the mixture was extracted with 3 × 50 mL EtOAc. The combined EtOAc was washed with 50 mL 2N HCl, 50 mL H_2O, 50 mL saturated $NaHCO_3$ solution and brine. The EtOAc solution was dried over $MgSO_4$ and concentrated to give a white solid, which was crystallized from hexane to give product **210**[71b] (10.19 g, 21.8 mmol) as white solid, 99% yield.



210 **211**

3,3',5,5'-Tetra-trifluoromethyl benzhydrylamine 211: To an oven-dried 250 mL Schlenk flask filled with argon was added 10 mL dry THF and oxime **210** (4 g, 8.5 mmol), BH_3-THF (100 mL, 100 mmol) was added slowly at room temperature. The solution turned yellow and bubbling was observed. After stirring at room temperature of 15-20 minutes, the solution was sealed under argon, heated to 105 °C and stirred at that temperature for 24 hours. The solution was then cooled to room temperature, carefully quenched by slow addition of 25 mL H_2O, 60 mL 10% NaOH solution. The mixture was stirred at room temperature for 15 minutes, then loaded to separatory funnel and extracted with 3 × 100 mL Et_2O. The combined organic layer was washed with brine until neutral, dried over $MgSO_4$ and concentrated *in vacuo*. The crude reaction mixture was heated at 50 °C under high vacuum (0.2 mm Hg) to remove butanol. Purification by silica gel chromatography with 1:1 CH_2Cl_2/hexane gave 2.28 g product (5 mmol) as white solid, 59% yield.

Spectral data for **211**: White solid, R_f = 0.28 (1:1 CH_2Cl_2/hexane), mp = 110-112 °C;

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.86 (s, 2H), 5.48 (s, 1H), 7.79 (s, 2H), 7.88 (s, 4H);

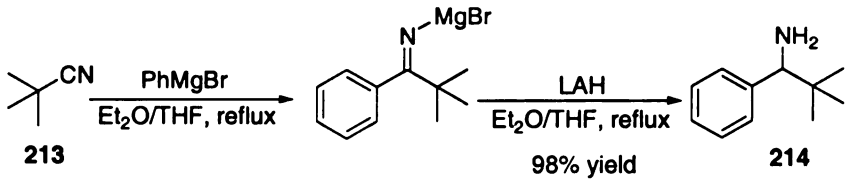
^{13}C NMR ($CDCl_3$, 75 MHz) δ = 58.79, 123.14 (q, $J_{C\text{-}F}$ = 273 Hz), 121.99 (t, $J_{C\text{-}F}$ = 4.5 Hz), 127.06 (d, $J_{C\text{-}F}$ = 2.3 Hz), 132.31 (q, $J_{C\text{-}F}$ = 33.2 Hz), 146.30;

^{19}F NMR ($CDCl_3$, 282 MHz) δ = -62.97;

IR (thin film, cm^{-1}) 1279 vs;

Mass spectrum: m/z (% rel intensity) 455 M^+ (1), 454 (4), 242 (100), 241 (83);

Anal calcd for $C_{17}H_9F_{12}N$: C, 44.85; H, 1.99; N, 3.08. Found: C, 44.95; H, 1.90; N, 3.04.



213 214

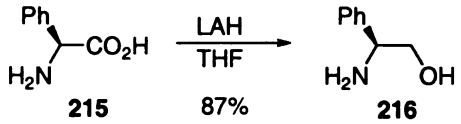
Racemic α-*tert*-butylbenzylamine 214: To a 500 mL flamed-dried three-neck round bottom flask filled with argon was added 40 mL PhMgBr (3M solution in ether) (0.12 mmol) and 80 mL dry Et_2O via syringe. Trimethyl acetonitrile **213** (8.48 g, 0.1 mol) was added to the flask dropwisely via syringe with stirring of Grignard reagent. The solution was heated to reflux after addition was finished. After being refluxed for 4 hours, a solution of 4.80 g $LiAlH_4$ (0.12 mol) in 80 mL dry THF was transferred to the reaction flask via cannula. The solution was heated and refluxed for another 20 hours. After reaction finished, the solution was allowed to cool down. To the flask was carefully added 5 mL of H_2O, 5 mL of 20% NaOH solution and then 15 mL H_2O. The white mud like mixture was filtered, the solid was washed with Et_2O until there was no presence of detectable amine in the filtered Et_2O (monitored by TLC spotting). The ether layer was dried over Na_2SO_4. Removal of solvent afforded a light yellow liquid, which was further purified by vacuum distillation. Distillation at 48 °C (0.15 mm Hg), afforded 15.94 g (97.8 mmol) product **214** as colorless oil, yield 98%.

Spectral data for **214**:[92]

^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (s, 9H), 1,42 (sbr, 2H), 3.69 (s, 1H), 7.20-7.29 (m. 5H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.42, 34.89, 65.20, 126.60, 127.37, 128.13, 143.68;

Mass spectrum, m/z (% rel intensity), 163 (M^+, <1), 148 (16), 107(39), 106(100).



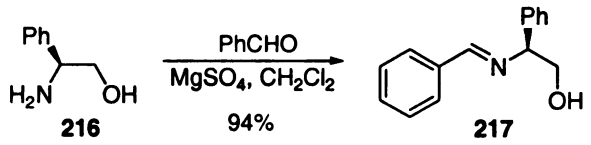
215 87% **216**

(S)-2-Phenylglycinol 216:[74] To an oven-dried 1L round bottom flask filled with argon was added $LiAlH_4$ (9.86 g, 260 mmol), then 500 mL anhydrous THF was added via cannula. The flask was placed in 0 °C ice bath, upon stirring, S-phenylglycine **215** (20.2 g, 132 mmol) was added portionwisely. After addition was complete, the mixture was allowed to slowly warm up to room temperature. Large amount of gas was produced during warming up, and the solution turned into a yellowish-green color. The mixture was stirred at room temperature for 1.5 hours, then a condenser equipped with nitrogen inlet and outlet was attached. The mixture was heated to reflux under nitrogen and refluxed for 15 hours. The mixture was then cooled down to 0 °C, to the flask was carefully added 10 mL H_2O, 10 mL 15% NaOH solution and 30 mL of H_2O. The obtained orange mixture was refluxed for 20 minutes, then filtered through a sand funnel. Organic solution was collected, the solid in the funnel was washed with THF until the elutant was clean. Organic solution was combined, dried over $MgSO_4$. Removal of solvent gave a yellow, viscous oil, which solidified slowly under high vacuum. The crude solid was crystallized from 25 mL toluene, afforded 15.7 g (114 mmol) colorless crystal as product, yield 87%.

Spectral data for **216**: m.p. 76-78 °C (Aldrich 75-78 °C).

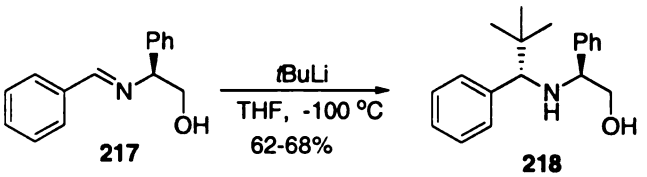
^1H NMR (300MHz, $CDCl_3$): δ = 2.61 (br, s, 3H), 3.53 (dd, J = 8.3 Hz, 10.9 Hz, 1H), 3.69 (dd, J = 4.2 Hz, 10.9 Hz, 1H), 4.01 (dd, J = 4.2 Hz, 8.3 Hz, 1H), 7.02-7.36 (m, 5H);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.32, 67.79, 126.46, 127.37, 128.49, 142.48.



216 **217**

Imine 217:[75] To a 100 mL round bottom flask was added (S)-2-phenylglycinol **216** (2.5 g, 17.86 mmol), benzaldehyde (1.895 g, 17.86mmol), 5 g $MgSO_4$ and 40 mL of CH_2Cl_2. The mixture was stirred at room temperature for 20 hours. Upon removal of $MgSO_4$ and solvent, the light yellow solid was crystallized from 1:30 EtOH/hexane. Two crops afforded 3.77 g (16.73 mmol) white solid as product, yield 94%. Spectral data for **217**: White solid, ^{1}H-NMR (300MHz, $CDCl_3$): δ = 2.26 (br, s, 1H), 3.92 (d, J = 4.6 Hz, 1H), 3.97(d, J = 8.3 Hz, 1H), 4.51 (dd, J = 4.6 Hz, J = 8.3 Hz, 1H), 7.26-7.46 (m, 10H), 8.39 (s, 1H);



217 **218**

Amino alcohol 218: To a flame-dried 250 mL round bottom flask filled with argon was added imine **217** (5 g, 22.2 mmol) and 125 mL dry THF. After the solid dissolved, the flask was placed in liquid nitrogen to freeze the THF solution. After the liquid solidified, 28.7 mL of 1.7M *t*BuLi solution (48.8 mmol) was added slowly through the syringe. The flask was manually swirled in the liquid nitrogen bath. After addition finished, the flask was moved to a –96 °C MeOH/liquid nitrogen bath attached to a cooler. The mixture was stirred at –100 °C for 2 hours, then slowly warmed up to –85 °C and stirred at that temperature for 6 hours. The mixture was then slowly warmed up to –5 °C, then quenched by 42 mL of saturated NH_4Cl solution, followed by addition of 50 mL of H_2O. The mixture was loaded to separation funnel, the organic layer was separated, and the water layer was washed with 50 mL ether. The combined organic layer was washed with

brine, dried over $MgSO_4$. Removal of solvent afforded a light yellow solid, which was determined by ^1H NMR as of 10:1 dr (Based on integration of *tert*-butyl proton at 0.97 ppm and 0.873 ppm). The crude product was purified by flash chromatography and eluted with 1:9 EtOAc/hexane, afforded 4.3 g (15.17 mmol) colorless solid as product (dr > 50:1 on ^1H NMR), yield 68%. This product can be crystallized from 1:9 EtOAc/hexane to afford 3.5 g colorless crystal which was of > 100:1 dr.

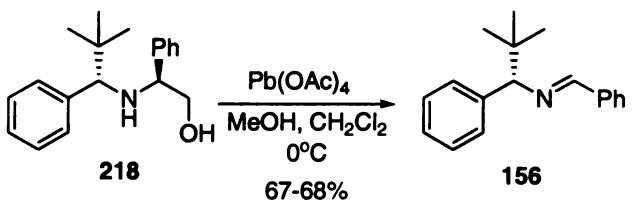
Spectral data for **218**: Colorless crystal, mp = 76-78 °C, R_f = 0.23 (1:9 EtOAc/hexane), $[\alpha]_D$ = 5.5 (*c* = 1.0, $CHCl_3$);

^1H NMR (300MHz, $CDCl_3$): δ = 0.95 (s, 9H), 3.44 (s, 1H), 3.51-3.56 (m, 2H), 3.80 (m, 1H), 7.08-7.27 (m, 10H) (two exchangeable protons not located);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.16, 35.20, 61.21, 63.73, 69.92, 126.70, 127.16, 127.20, 127.52, 128.31, 128.52, 141.19, 142.29;

Mass spectrum: m/z (% rel intensity) 284 $M+H^+$ (<1), 252 (9), 226 (51), 121 (12), 106 (100), 105 (25), 103 (16), 91 (39);

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89, N, 4.94. Found: C, 80.70; H, 8.89; N, 5.26.



218 156

Imine 156: To a 500 mL oven-dried flask in ice bath was added 150 mL MeOH. Then $Pb(OAc)_4$ (13.78 g, 31 mmol) was added to the flask bulkwisely. The yellow mixture was stirred at 0 °C. To an oven-dried 100 mL flask was added amino alcohol **218** (3 g, 10.5mmol), 10 mL CH_2Cl_2 and 50 mL MeOH. The amino alcohol solution was also cooled to 0 °C, then transferred to the $Pb(OAc)_4$ solution by syringe in 10 minutes. The obtained mixture was stirred at 0 °C for 8.5 hours, then 100 mL CH_2Cl_2 was added and

the solution was stirred for 3 minutes. The reaction was quenched by addition of 120 mL 10% $NaHCO_3$ solution. The mixture was loaded to separation funnel, organic layer was separated, the aqueous layer was extracted with 2 × 50 mL CH_2Cl_2, the combined organic layer was dried over $MgSO_4$, removal of solvent afforded 2.52 g white solid, which was pure by ^1H NMR. Two crystallization from hexane afforded 1.76 g (7 mmol) colorless needle crystal as product, yield 67%.

Spectral data for **156**: Colorless needle crystal, mp = 69-71 °C, $[\alpha]_D$ = 101.4 (*c* = 1.0, $CHCl_3$);

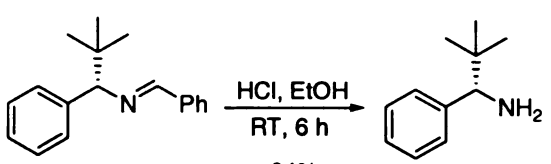
^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (s, 9H), 3.93 (s, 1H), 7.18-7.43 (m, 8H), 7.75-7.78 (m, 2H), 8.23 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.98, 35.73, 84.85, 126.58, 127.42, 128.21, 128.42, 128.87, 130.29, 136.68, 142.44, 159.27;

Mass spectrum: m/z (% rel intensity) 251 M^+ (<1), 194 (100), 165(9), 116(16).

IR (thin film, cm^{-1}) 2953 vs, 1647 vs;

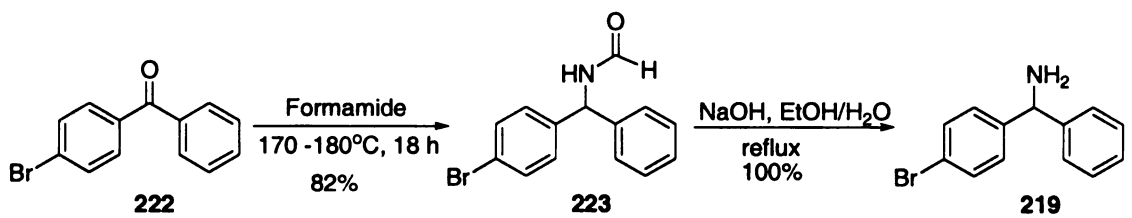
Anal. Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42, N, 5.57. Found: C, 86.07; H, 8.49 ; N, 5.55



156 (S)-**214**

(*S*)-α-*tert*-Butylbenzylamine 214: To a 500 mL round bottom flask filled with argon was charged imine **156** (4.83 g, 19.2 mmol), 15 mL concentrated HCl and 300 mL EtOH. The mixture was stirred at room temperature for 6 hours, then concentrated *in vacuo*. The obtained white solid was fractioned between 300 mL H_2O and 30 mL ether. The aqueous layer was collected, basified with solid Na_2CO_3, and extracted with 3 × 100 mL ether. The combined ether layer was dried over $MgSO_4$, concentrated *in vacuo*. The crude

amine was purified by flash chromatography, eluted with 1:15 to 1:10 MeOH/CH_2Cl_2, 2.5 g light yellow oil was obtained, which was further purified by vacuum distillation. The product boiled at 48-50 °C at 1mm Hg. Distillation afforded 2.0 g (12.25 mmol) colorless oil was obtained as pure product, yield 64%. The enantiomeric excess of amine **214** was determined by chiral HPLC analysis as of > 99.5%. (Chiralcel OD-H column, 250 nm, 99:1 hexane/iPrOH, flow rate: 1 mL/min, under this condition, the retention time of minor (*R*)-isomer was 4.18 min and that of major (*S*)-isomer was 7.86 min.)



N-Formylamide 223:[63] To a 100 mL round bottom flask equipped with an air condenser and dying tube was charged 9 gram 4-bromobenzophenone **222** (33.78 mmol). The flask was heated in 170-180 °C oil bath for 18 hours. The hot dark solution was poured into 300 mL cold water. A dark muddy suspension was obtained. The emulsified solution was filtered through a Celite layer to remove the insoluble material. The mixture was loaded to a separation funnel, and the organic compound was extracted with 2 × 100 mL EtOAc. The combined EtOAc solution was washed with brine once, upon dried over Na_2SO_4, concentrated to 300 mL. The solution was heated to reflux with 3 gram of active carbon to remove color. The obtained yellow solution was concentrated *in vacuo*, and the obtained light yellow solid was crystallized from EtOAc twice, afforded 7.99 g (27.54 mmol) amide **223** as white solid, yield 81.5%. Spectral data for **223**: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.24 (s, 1H), 6.31 (sbr, 1H), 7.07-7.45 (m, 9H), 8.24 (s, 1H); m.p. 127-129°C.

4-Bromobenzhydrylamine 219:[63] To a 1 L round bottom flask equipped with condenser, was added amide **223** (30 g, 103 mmol), 450 mL EtOH and 100 mL 50% NaOH solution.

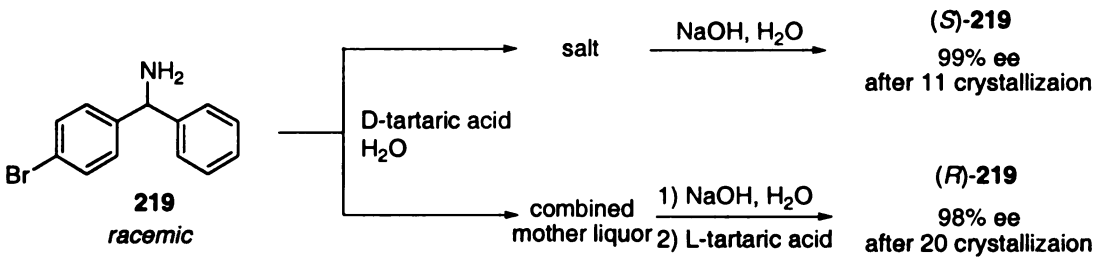
The mixture was heated under reflux for 3 hours. After reaction finished, the flask was loaded to rotavapor to remove ~400 mL ethanol. The solution was then extracted with 3 × 100 mL CH_2Cl_2. The combined CH_2Cl_2 solution was dried over Na_2SO_4. Removal of solvent afforded a light yellow oil. The yellow oil was further purified by vacuum distillation (138-140 °C, 0.1 mm Hg), afforded 27 g (103 mmol) amine **219** as colorless oil, yield 100%.

Spectral data for amine **219**:

^1H NMR ($CDCl_3$, 300 MHz) δ 1.77 (s, 2H), 5.19 (s, 1H), 7.27-7.48 (m, 9H);

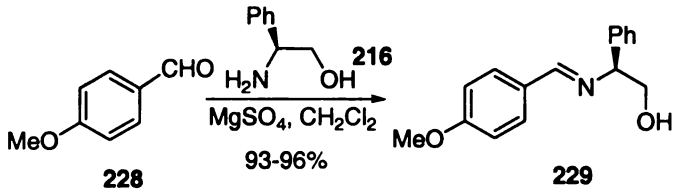
^{13}C NMR ($CDCl_3$, 75 MHz) δ 58.96, 120.47, 126.58, 126.95, 128.37, 128.47, 131.25, 144.44, 144.96;

Mass spectrum: m/z (% rel intensity) 263 (10, M^+, ^{81}Br), 261 (11, M^+, ^{79}Br), 186 (31, ^{81}Br), 184 (44, ^{79}Br), 165 (17), 105 (100), 104 (54), 79 (17), 77 (39), 51 (10);



Resolution of 4-bromobenzhydrylamine 219: To a 500 mL round bottom flask equipped with condenser was added 11 g (42 mmol) amine **219**, 6.3 g d-tartaric acid (42 mmol) and 50 ml H_2O. The flask was heated and stirred until a white solid salt formed. The solution was heated to refluxing, H_2O was added until all the solid dissolved. The clear solution was allowed to cool down slowly. After 24 hours the solid was filtered and crystallized with hot water again. After ten more crystallizations, the (*S*)-**219** in the precipitate was liberated by aqueous NaOH solution and determined by chiral HPLC analysis to be 99% ee (Chiralcel OD-H column, 265 nm, 90:10 hexane/isopropanol, flow

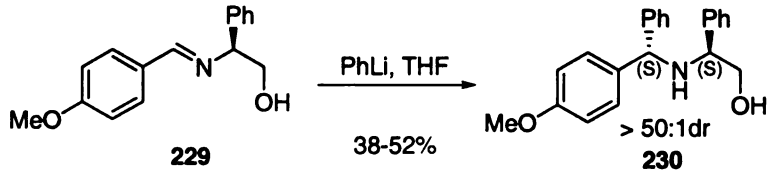
rate: 1 mL/min, under this condition, the retention time of (*R*)-**219** was 6.64 min and that of (*S*)-**219** was 8.16 min). The mother liquor recovered from ten crystallizations was concentrated to 500 mL, to the flask was added 10 g of NaOH (0.25 mmol) and 100 mL ether. The solution was stirred until no solid was visible. The solution was then loaded to separation funnel, ether layer was collected, and the water layer was washed with 2 × 100 mL ether. The combined ether was dried over $MgSO_4$, removal of ether afforded a brown oil which was purified by vacuum distillation. The recovered amine **219** rich in (*R*)-isomer was then crystallized with L-tartaric acid in water again. Twenty crystallization gave (*R*)-**219** with 98% ee.



Imine 229:[75] Prepared from aldehyde **228** and (S)-2-phenylglycinol **216** with the standard imine preparation procedure.

Spectral data for **229**: White solid;

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 3.09 (br, s, 1H), 3.82 (s, 3H), 3.89 (d, *J* = 4.1 Hz, 1H), 3.97 (d, *J* = 8.8 Hz, 1H), 4.44 (dd, *J* = 4.1 Hz, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.22-7.45 (m, 5H), 7.65 (d, *J* = 8.8 Hz, 2H), 8.22 (s, 1H);



Amino alcohol 230:[75] To an oven-dried 250 mL round bottom flask filled with argon was charged imine **229** (5 g, 19.6 mmol) and 120 mL dry THF. The solution was stirred at

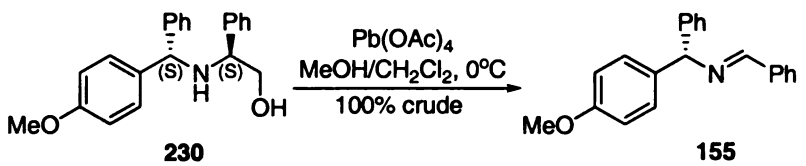
room temperature. Then 33 mL of 1.8 M PhLi solution (59 mmol) was added by syringe in a period of 5 minutes. The obtained dark purple solution was stirred at room temperature of 15 minutes. The reaction was quenched by adding 70 mL saturated NH_4Cl solution and stirred for 5 minutes. The mixture was loaded to separation funnel, the organic layer was collected, the aqueous layer was basified with 1N NaOH solution, washed with 2 × 50 mL Et_2O. The organic layer was combined, washed with brine, dried over $MgSO_4$, removal of solvent afforded an orange oil. The crude mixture was purified with flash column, eluted with 1:3 EtOAc/hexane, afforded 2.86 g (8.58 mmol) light yellow viscous oil as product, yield 44%.

Spectral data for **230**: R_f = 0.16 (1:5 EtOAc/hexane);

^1H NMR ($CDCl_3$, 300 MHz) δ = 2.36 (sbr, 2H), 3.58-3.75 (m, 3H), 3.76 (s, 3H), 4.69 (s, 1H), 6.81 (d, *J*= 8.0 Hz, 2H), 7.22-7.39 (m, 12H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 55.20, 61.55, 62.77, 66.90, 113.83, 127.08, 127.28, 127.57, 127.64, 128.21, 128.57, 128.69, 136.59, 140.45, 142.93, 158.61;

Mass spectrum: m/z (% rel intensity) 333 M^+ (<1), 302 (29), 198 (41), 197 (100), 165 (23), 153 (22);



230 **155**

Imine 155: To a flame-dried 500 mL round bottom flask was added 200 mL MeOH. The flask was stirred at 0 °C for 10 minutes, then $Pb(OAc)_4$ (16.7 g, 38 mmol) was added bulkwisely. The obtained yellow solution was stirred at 0 °C for 15 minutes. Then a 0°C solution of amino alcohol **230** (4.2 g, 12.59 mmol) in 50 mL MeOH and 30 mL CH_2Cl_2 was transferred via cannula to the flask containing $Pb(OAc)_4$. The addition finished in 5

minutes, and the solution was stirred at 0 °C for 30 minutes. To this flask was then added 100 mL CH_2Cl_2 and the solution was stirred for 2 minutes. The reaction was quenched by addition of 100 mL 10% Na_2CO_3 solution. The mixture was loaded to separation funnel, the organic layer was collected, and the aqueous layer was washed with 3 × 50 mL CH_2Cl_2. The organic layer was combined, washed with brine, dried over $MgSO_4$, concentrated *in vacuo* and gave a yellow oil, which slowly solidified in 3 days. The crude mixture was identified by ^1H NMR as product, afforded 3.8 g (12.59 mmol) crude product **155**, yield 100%.

Spectral data of **155**: White solid, mp 64-66 °C;

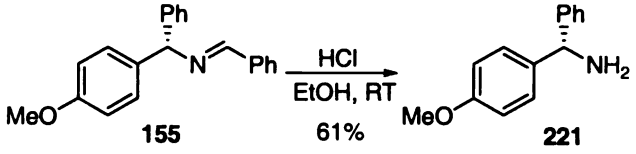
^1H NMR ($CDCl_3$, 300 MHz) δ = 3.82 (s, 3H), 5.63 (s, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 7.23-7.48 (m, 10H), 7.88-7.91 (m, 2H), 8.46 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 55.18, 77.18, 113.77, 126.86, 127.55, 128.37, 128.42, 128.48, 128.74, 130.70, 136.08, 136.30, 144.08, 158.53, 160.53;

Mass spectrum: m/z (% rel intensity) 301 M^+ (2), 197 (100), 182 (6), 165 (16), 153(14);

IR (thin film, cm^{-1}) 2835 vs, 1642 vs, 1510 vs;

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35, N, 4.65. Found: C, 83.57; H, 6.36; N, 4.65.



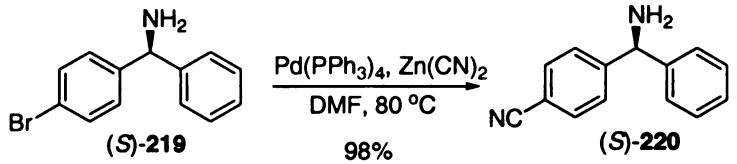
Amine 221:[92] To a 500 mL round bottom flask was charged imine **155** (3.8 g, 12.6 mmol), 10 mL concentrated HCl and 250 mL EtOH. The flask was filled with argon and stirred at room temperature. After 4.5 hours, the solution was concentrated on rotavapor. The obtained yellow solid was fractioned between 300 mL H_2O and 30 mL ether. The aqueous layer was collected, basified with solid Na_2CO_3, then extracted with 3 × 100 mL ether. The combined ether layer was dried over $MgSO_4$, concentrated *in vacuo*. The

crude amine was purified by flash chromatography, eluted with 100% CH_2Cl_2 to 1:30 MeOH/CH_2Cl_2, 1.64 g (7.69 mmol) red oil was obtained, yield 61%.

Spectral data for **221**: Colorless oil; $[\alpha]_D$ = -11.7 (*c* = 1.0, EtOAc);

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.81 (br, s, 2H), 3.81 (s, 3H), 5.22 (s, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 7.27-7.43 (m, 7H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 55.09, 58.99, 113.69, 126.68, 126.74, 127.85, 128.33, 137.79, 145.82, 158.40;



4-Cyanobenzhydrylamine (*S*)-220: To a flame-dried Schlenk flask was added amine (*S*)-**219** (4 g, 15.3 mmol), $Pd(PPh_3)_4$ (0.8 g, 0.69 mmol), $Zn(CN)_2$ (1.2 g, 9.9 mmol) followed by 20 mL dry DMF. The mixture was deoxygenated by two freeze-thaw cycles, then sealed under argon, and heated in 80 °C oil bath for 7 hours. The mixture was cooled to room temperature, diluted with 50 mL toluene. The organic layer was washed with 3 × 30 mL 2N ammonium hydroxide solution, the 2 × 30 mL brine. The orange organic layer was dried and concentrated *in vacuo*, afforded a red solid, which was purified by flash chromatography, eluted with 100% CH_2Cl_2 until all the early fractions comes out, then eluted with 1:30 to 1:20 MeOH/CH_2Cl_2, afforded product amine (*S*)-**220** (3.137 g, 15.06 mmol) as light yellow oil, yield 98 %.

Spectral data for (*S*)-**220**: Light yellow oil; $[\alpha]_D$ = -37.1 (*c* = 1.0, EtOAc);

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.81 (s, 2H), 5.24 (s, 1H), 7.20-7.53 (m, 9H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 59.14, 110.21, 118.66, 126.54, 127.18, 127.34, 128.45, 131.93, 144.19, 150.62;

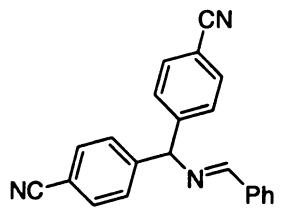
Mass spectrum: m/z (% rel intensity) 208 M^+ (89), 192 (11), 131 (79), 106 (100):

IR (thin film, cm^{-1}) 3378 br, 2228 vs;

Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81, N, 13.45. Found: C, 80.23; H, 5.67; N, 13.16.

Preparation of Imines

Typical experimental procedure for the synthesis of aldimines: Aldehydes and amines were purified by chromatography or distillation before use. To an oven dried 100 mL round bottom flask was added 30 mmol of amine, followed by 50 mL of CH_2Cl_2 and 4 g of $MgSO_4$, 30 mmol of benzaldehyde was added via syringe. The reaction was stirred for 12-24 hours. Upon completion of the reaction the mixture was filtered and concentrated by rotary evaporation to give the crude imine. These imines were generally crystallized from hexane/CH_2Cl_2 or EtOAc/hexane and only the first crop was used.



158

Imine 158: Prepared from 4,4'-dicyanobenzhydryl amine **180** and benzaldehyde using the standard procedure. Imine **158** was not purified and was used as crude material.

Spectral data for **158**: White amorphous solid, mp = 51-54 °C;

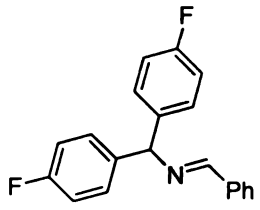
^1H NMR ($CDCl_3$, 300 MHz) δ = 5.61 (s, 1H), 7.42-7.62 (m, 11H), 7.82-7.85 (m, 2H), 8.44 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 76.80, 111.28, 118.54, 128.13, 128.51, 128.66, 131.48, 132.46, 135.34, 147.86, 162.66;

IR (thin film, cm^{-1}) 1644 vs, 2228 vs;

Mass spectrum: m/z (% rel intensity) 321 M^+ (30), 320 (21), 217 (100), 190 (78);

Anal calcd for $C_{22}H_{15}N_3$: C, 82.22; H, 4.70; N, 13.08. Found: C, 82.63; H, 4.74; N, 12.63;



159

Imine 159: Prepared from 4,4'-difluorobenzhydryl amine **172** and benzaldehyde using the standard procedure. Crystallization from hot hexane gave **159** in 86% yield.

Spectral data for **159**: Colorless crystal; mp 64-66 °C;

^1H NMR ($CDCl_3$, 300 MHz) δ = 5.53 (s, 1H), 6.99 (dd, J_{HH} = 8.8 Hz, J_{HF} = 8.8 Hz, 4H), 7.39 (dd, J_{HH} = 8.6 Hz, J_{HF} = 5.5 Hz, 4H), 7.40-7.45 (m, 3H), 7.8-7.85 (m, 2H), 8.39 (s, 1H);

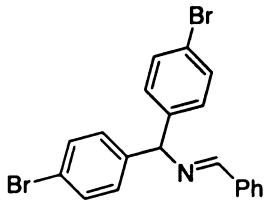
^{13}C NMR ($CDCl_3$, 75 MHz) δ = 76.37, 115.30 (d, J_{CF} = 21.76 Hz), 128.47, 128.61, 129.08 (d, J_{CF} = 8.0 Hz), 131.0, 136.01, 139.50 (d, J_{CF} = 3.4 Hz), 161.02, 161.88 (d, J_{CF} = 246.2 Hz);

19F NMR ($CDCl_3$, 300 MHz) δ = -115.64 (m);

IR (thin film, cm^{-1}): 1643 vs, 1506 vs;

Mass spectrum: m/z (% rel intensity) 307 M^+ (4), 204 (24), 203 (100), 183 (40);

Anal calcd for $C_{20}H_{15}F_2N$: C, 78.16; H, 4.92; N, 4.56. Found: C, 77.92; H, 5.03; N, 4.60;



160

Imine 160: Prepared from 4,4'-dibromobenzhydryl amine **179** and benzaldehyde using the standard procedure. Crude imine was crystallized from 10:1 hexane/EtOAc, the product was crystallized as a mixture of 6 equivalent of imine 1 equivalent of hexane, yield was 64%.

Spectral data for **160**: White small needle; mp 64-67 °C;

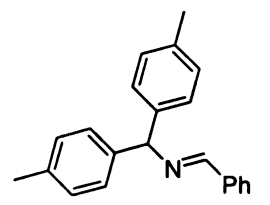
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 5.48 (s, 1H), 7.25 (d, J = 8.5 Hz, 4H), 7.42-7.46 (m, 7H), 7.82-7.85 (m, 2H), 8.39 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 76.45, 121.09, 128.45, 128.59, 129.22, 131.08, 131.58, 135.84, 142.40, 161.40;

IR (thin film, cm^{-1}) 1648 vs, 1485 vs, 1010 vs;

Mass spectrum: m/z (% rel intensity) 429 M^+ (2), 325 (44), 165 (100);

Anal calcd for $6C_{20}H_{15}Br_2N$-C_6H_{14}: C, 56.87; H, 3.16; N, 3.26. Found: C, 56.55; H, 3.58; N, 3.01;



161

Imine 161: Prepared from 4,4'-dimethylbenzhydryl amine and benzaldehyde using the standard procedure. Crystallization from hexane gave **161** in 91% yield.

Spectral data for **161**: Colorless crystal; mp 73-74.5 °C;

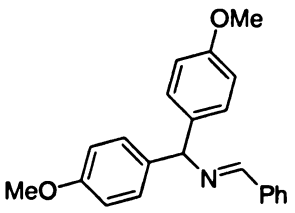
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.34 (s, 6H), 5.57 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 4H), 7.30 (d, *J* = 8.0 Hz, 4H), 7.41-7.43 (m, 3H), 7.84-7.87 (m, 2H), 8.42 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 21.04, 77.42, 127.49, 128.45, 129.07, 130.62, 136.39, 136.43, 141.09, 160.43 (one aromatic carbon was not located);

IR (thin film, cm^{-1}) 1642 vs;

Mass spectrum: m/z (% rel intensity) 299 M^+ (3), 298 (3), 208 (2), 195 (100), 180 (20), 165 (32);

Anal calcd for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 87.95; H, 7.41; N, 4.67;



162

Imine 162: Prepared from 4,4'-dimethoxybenzhydryl amine **197** and benzaldehyde using the standard procedure. Crystallization (1:8 CH_2Cl_2/hexanes) afforded white solid in 91% isolated yield.

Spectral data for **162**: White small needle; mp: 60-61 °C.

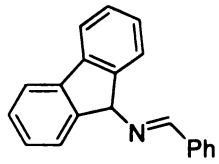
^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 6H), 5.51(s, 1H), 6.84 (d, *J* = 8.8 Hz, 4H), 7.25-7.27 (m, 4H), 7.37-7.40 (m, 3H), 7.79-7.82 (m, 2H), 8.37 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.17, 76.55, 113.71, 128.35, 128.43, 128.61, 128.70, 130.60, 136.28, 158.43, 160.24;

IR (thin film, $CDCl_3$) 1641 m, 1608 m, 1510 vs, 1246 vs, 1172 s, 1036 s, 829 m cm^{-1};

Mass spectrum: m/z (% rel intensity) 331 M^+ (<1), 243 (11), 227 (100), 212 (8), 141 (9), 136 (38), 135 (58), 77 (14).

Anal calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.38; H, 6.53; N, 4.29.

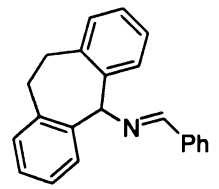


164

Imine 164:[70] Prepared from 9-fluorenylamine hydrochloride (purchased from Aldrich) and benzaldehyde. The amine hydrochloride salt was dissolved in CH_2Cl_2, stirred with aqueous $NaHCO_3$ solution for 10 minutes, dried over $MgSO_4$ and then subjected to the standard imine preparation condition. Crystallization gave 90% yield. Spectral data for **164**: Colorless solid,

^1H NMR ($CDCl_3$, 300 MHz) δ = 5.47 (s, 1H), 7.34-7.49 (m, 9H), 7.80-7.89 (m, 4H), 8.84 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 74.7, 120.06, 125.20, 127.39, 128.40, 128.48, 128.56, 130.94, 135.96, 141.00, 144.69, 163.46;



165

Imine 165: Prepared from dibenzosuberonyl amine **202** and benzaldehyde using the standard procedure. Crystallization from 100:1 hexane/EtOAc gave 78% yield.

Spectral data for **165**: Colorless needle; mp: 86-88 °C.

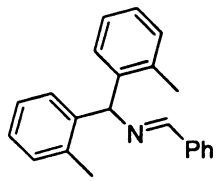
^1H NMR ($CDCl_3$, 300 MHz) δ = 3.21-3.26 (m, 2H), 3.62-3.67 (m, 2H), 5.74 (s, 1H), 7.20-7.24 (m, 6H), 7.44-7.48 (m, 5H), 7.87-7.90 (m, 2H), 8.46 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 32.46, 78.15, 126.08, 127.37, 128.10, 128.45, 130.16, 130.67, 136.33, 139.15, 140.86, 159.99 (one aryl carbon not located);

IR (thin film, cm^{-1}) 1640.35 vs, 1638.84 vs;

Mass spectrum: m/z (% rel intensity) 297 M^+ (1), 192 (100), 178 (27), 165 (12), 106 (22).

Anal calcd for $C_{22}H_{19}N$: C, 88.85; H, 6.44; N, 4.71. Found: C, 88.89; H, 6.43; N, 4.73.



166

Imine 166: Prepared from 2,2'-dimethylbenzhydryl amine **190** and benzaldehyde using the standard procedure. Crystallization from hexane/CH_2Cl_2 gave 82% yield.

Spectral data for **166**: Colorless crystal; mp 118-119 °C;

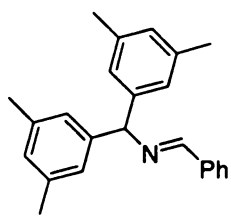
^1H NMR ($CDCl_3$, 300 MHz) δ = 2.25 (s, 6H), 6.11 (s, 1H), 7.15-7.40 (m, 11H), 7.77-7.80 (m, 2H), 8.16 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 19.42, 69.67, 126.02, 126.96, 128.29, 128.37, 128.49, 130.34, 130.68, 135.94, 126.29, 140.39, 160.41;

IR (thin film, cm^{-1}) 1641 vs,;

Mass spectrum: m/z (% rel intensity) 299 M^+ (3), 298 (3), 195 (100), 180 (20), 165 (32);

Anal calcd for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.03; H, 7.08; N, 4.66;



167

Imine 167: Prepared from 3,3',5,5'-tetramethylbenzhydryl amine **191** and benzaldehyde using the standard procedure. Crystallization from 6:1 hexane/CH_2Cl_2 gave 84% yield.

Spectral data for **167**: Colorless crystal; mp 126-128 °C;

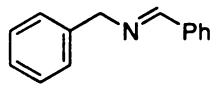
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.36 (s, 12H), 5.52 (s, 1H), 6.93 (s, 2H), 7.09 (s, 4H), 7.45-7.47 (m, 3H), 7.90-7.93 (m, 2H), 8.45 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 21.36, 78.12, 125.35, 128.40, 128.44, 128.55, 130.54, 136.41, 137.76, 143.88, 160.36;

IR (thin film, cm^{-1}) 1645 vs;

Mass spectrum: m/z (% rel intensity) 327 M^+ (9), 326 (6), 223 (100), 208 (18), 193 (32);

Anal calcd for $C_{24}H_{25}N$: C, 88.03; H, 7.70; N, 4.28. Found: C, 88.09; H, 7.70; N, 4.28;



168

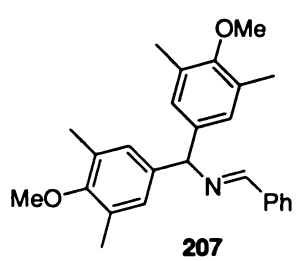
Imine 168: Prepared from benzylamine and benzaldehyde using the standard procedure. Imine was purified by distillation, yield 87%.

Spectral data for **168**: Colorless oil, bp 119-120 °C at 0.1 mm Hg;

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 4.79 (s, 2H), 7.20-7.40 (m, 8H), 7.75-7.78 (m, 2H), 8.35 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 64.94, 126.89, 127.88, 128.18, 128.40, 128.50, 130.67, 136.05, 139.20, 161.88;

All the other spectral data were identical to that commercially available from Aldrich.



207

Imine 207: Prepared from amine **206** and benzaldehyde using the standard procedure. Crystallization from 9:1 hexane/EtOAc gave **207** in 80% yield.

Spectral data for **207**: Colorless crystal; mp 144-146 °C;

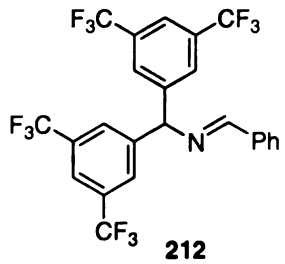
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 2.28 (s, 12H), 3.70 (s, 6H), 5.39 (s, 1H), 7.04 (s, 4H), 7.41-7.43 (m, 3H), 7.84-7.87 (m, 2H), 8.39 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 16.17, 59.52, 77.41, 127.78, 128.40, 130.57, 136.33, 139.18, 155.75, 160.25 (two aryl carbons not located);

IR (thin film, cm^{-1}) 2944 w, 1643 vs, 1483 vs;

Mass spectrum: m/z (% rel intensity) 387 M^+ (3), 283 (100);

Anal calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.42; H, 7.24; N, 3.55;



212

Imine 212: Prepared from amine **211** and benzaldehyde with standard procedure except that 4 Å molecular sieve was used as the dehydrating reagent. Crystallization from 100:1 hexane/EtOAc gave **212** in 79% yield.

Spectral data for **212**: Colorless crystal; mp 116-118 °C;

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 5.77 (s, 1H), 7.49-7.52 (m, 3H), 7.85-7.92 (m, 8H) 8.54, (s, 1H);

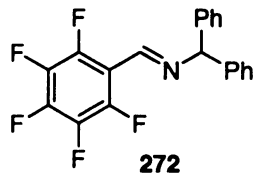
^{13}C NMR ($CDCl_3$, 75 MHz) δ = 76.44, 123.18 (q, $J_{C\text{-}F}$ = 273 Hz), 121.94 (t, $J_{C\text{-}F}$ = 4.0 Hz), 127.56 (d, $J_{C\text{-}F}$ = 3.0 Hz), 128.87, 131.91, 132.28 (q, $J_{C\text{-}F}$ = 33.2 Hz), 135.15, 145.01, 163.62;

^{19}F NMR ($CDCl_3$, 282 MHz) δ = -62.89

IR (thin film, cm^{-1}) 1277 vs, 1129 vs;

Mass spectrum: m/z (% rel intensity) 544 $M+1^+$ (7), 543 M^+ (29), 542 (17), 440 (16), 439 (100), 350 (13), 301 (32);

Anal calcd for $C_{24}H_{13}F_{12}N$: C, 53.05; H, 2.41; N, 2.58. Found: C, 53.09; H, 2.25; N, 2.56;



272

Imine 272: Prepared from benzhydryl amine and penta-fluorobenzaldehyde using the standard procedure. Crystallization from 50:1 hexane/EtOAc gave **272** in 83% yield.

Spectral data for **272**: small white needle; mp 95-97 °C;

^1H NMR ($CDCl_3$, 300 MHz) δ = 5.65 (s, 1H), 7.30-7.49 (m, 10H), 8.60 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 79.70, 127.28, 127.37, 128.57, 142.97, 149.03 (the fluorinated carbons merged into baseline and were indistinguishable from noise);

^{19}F NMR ($CDCl_3$, 282 MHz) δ = -142.10 to -142.00 (m, 2F), -150.90 to -150.74 (dt, J = 4.0 Hz, 21.8 Hz, 1F), -161.98 to -161.78 (m, 2F);

IR (thin film, cm^{-1}) 1522 vs, 1495 vs;

Mass spectrum: m/z (% rel intensity) 361 M^+ (1), 360 (3), 237 (11), 167 (100), 152 (64);

Anal calcd for $C_{20}H_{12}F_5N$: C, 66.48; H, 3.35; N, 3.88. Found: C, 66.49; H, 3.22; N, 3.86;

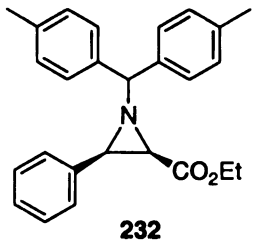
Preparation of Aziridines

Typical experimental procedure for the aziridination reaction:

Preparation of VAPOL-borate catalyst: To a flame dried Schlenk flask cooled under argon was added triphenyl borate (87 mg, 0.3 mmol) and S-VAPOL (54 mg, 0.1 mmol), followed by 2 mL of dry CCl_4. The flask was sealed under argon and the solution was stirred at 80 °C for 1 hour. A partial vacuum was then applied to the flask and the solvent was removed slowly. After complete removal of solvent, the catalyst was heated under high vacuum (~ 0.2 mm Hg) at 80 °C for 0.5 hour to remove the volatile material. The prepared catalyst was then dissolved in CCl_4 and transferred to the reaction flask.

Asymmetric aziridination procedure: To a flame-dried 25 mL round bottom flask cooled under argon was added imine (1 mmol). The catalyst prepared as above was dissolved in 2 × 1 mL dry CCl_4 and transferred via syringe to the flask containing imine. The resulting orange solution was allowed to be stirred at room temperature for 5 minutes, then EDA (115 μL, 1.15 mmol) was added via syringe in once. The solution was then stirred at room temperature for 24 hours. The reaction was quenched by addition of 15 mL hexane. Removal of solvent afforded an off-white to yellow solid. The cis/trans ratios of aziridine were determined by comparing the ^{1}H-NMR integration values for the relative aziridine methane protons. The cis (J = 7-8 Hz) and the trans (J = 2-3 Hz) coupling constants were used to differentiate the two isomers. Acyclic enamine products were also determined by ^{1}H NMR of the crude mixture by N-H proton integration relative to the integration of the aziridine methane protons. The crude aziridine was purified by chromatography on a 3.5 × 32 cm silica gel column (~400-500

mL silica gel), elution with the appropriate solvent to afford product. The enantiomeric excess was determined by HPLC on a chiral column.



232

***Cis*-(*2R, 3R*)-aziridine 232**: The standard aziridination condition with the *S*-VAPOL-borate catalyst in CCl_4 was employed. The crude mixture was purified by flash chromatography and eluted with 1:15 EtOAc/hexane. Product **232** was isolated as a white solid (327 mg, 0.85 mmol), 85% yield. An optical purity of 95.5% ee was determined by HPLC analysis.

HPLC condition: Chiralpak AD column, 223nm, 90:10 hexane/iPrOH as eluent at 0.8 mL/min. The retention time for the major (*2R, 3R*)-enantiomer from *S*-ligand was 5.74 min and that of the minor enantiomer was 9.81 min.

Spectral data for **232**: White solid; mp 140-142 °C; R_f = 0.26 (1:15 EtOAc/hexane); $[\alpha]_D$ = 45.3 (*c* = 1.0, $CHCl_3$) on 95.5 % ee material from *S*-VAPOL;

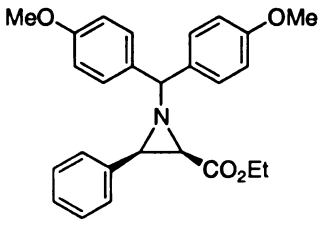
^1H NMR ($CDCl_3$, 300 MHz) δ = 0.95 (t, *J* = 7.1 Hz, 3H), 2.23 (s, 3H), 2.29 (s, 3H), 2.62 (d, *J* = 6.9 Hz, 1H), 3.16 (d, *J* = 6.9 Hz, 1H), 3.86 (s, 1H), 3.90 (q, *J* = 7.1 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 2H,), 7.11 (d, *J* = 7.7 Hz, 2H), 7.16-7.40 (m, 7H), 7.45 (d, *J* = 7.9 Hz, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.89, 20.98, 21.03, 46.36, 47.95, 60.47, 77.20, 126.96, 127.22, 127.28, 127.69, 127.78, 129.12, 135.13, 136.61, 136.81, 139.66, 139.80, 167.77 (one aryl carbon not located);

IR (thin film, cm^{-1}) 2980w, 1746 vs, 1200vs;

Mass spectrum: m/z (% rel intensity) 385 M^+ (<1), 195 (100), 165 (14);

Anal calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 80.73; H, 6.83; N, 3.71;



235

***Cis*-(*2R, 3R*)-aziridine 235**: The standard aziridination procedure with the *S*-VANOL-borate catalyst in CCl_4 was employed. The crude mixture was purified by flash chromatography. Product **235** was isolated as a white solid (389 mg, 0.93 mmol), 93% yield. An optical purity of 95% ee was determined by HPLC analysis.

HPLC condition: Chiralpak AD column with a 90:10 mixture of hexane/iPrOH at 1 mL/min, 226nm. The retention time of the major (*2R*, *3R*)-enantiomer from *S*-ligand was 7.94 min and that of the minor enantiomer was 13.84 minute.

Spectral data for **235:** m.p. 89.5-90.5 °C; R_f =0.26 (1:5 EtOAc/hexane), $[\alpha]_D$ = 43.0 (*c* = 1.0, $CHCl_3$) on 95% ee material prepared from *S*-VANOL.

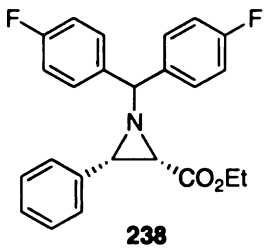
^{1}H-NMR ($CDCl_3$, 300 MHz) δ = 0.99 (t, 3H, *J* = 7.0 Hz), 2.68 (d, 1H, *J* = 6.9 Hz), 3.21 (d, , 1H *J* = 6.9 Hz), 3.69 (s, 3H), 3.76 (s, 3H), 3.89 (s, 1H), 3.94 (q, 2H, *J* = 7.1 Hz), 6.80 (d, 2H, *J* = 8.8 Hz), 6.89 (d, 2H, *J* = 8.8Hz), 7.26 (m, 3H), 7.41 (m, 4H), 7.52 (d, 2H, *J* = 8.5 Hz);

^{13}C-NMR ($CDCl_3$, 75 MHz) δ = 13.66, 46.15, 47.75, 54.77, 54.85, 60.22, 76.13, 113.54, 127.02, 127.49, 127.52, 127.91, 128.21, 134.68, 134.88, 134.91, 158.39, 158.46, 167.52 (one aryl carbon not located);

IR (thin film, cm^{-1}) 2957 br, 1746 m, 1611 m, 1510 vs, 1248 s;

Mass spectrum: m/z (% rel intensity) 417 M^+(<1), 227 (100), 212 (6), 169 (5), 149 (21);

Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.42; H, 6.27; N, 3.53;



238

***Cis*-(*2S, 3S*)-aziridine 238**: The standard aziridination procedure with the *R*-VANOL-borate catalyst in CCl_4 was employed. The crude mixture was purified by flash chromatography and eluted with 1:9 EtOAc/hexane, afforded 373 mg light yellow oil as a mixture of product and small amount of ligand. The obtained mixure was further purified by flash chromatography and eluted with 1:1 CH_2Cl_2/hexane, afforded pure **238** (328 mg, 0.83 mmol) as a colorless oil (83% yield). An optical purity of 94% ee was determined by HPLC analysis.

HPLC condition: Chiralpak AD column, 220nm, 98:2 hexane/iPrOH as eluent at 0.6 mL/min. The retention time for the minor enantiomer was 21.77 min and that of the major (*2S, 3S*)-enantiomer from R-ligand was 26.13 min.

Spectral data for **238**: Racemic material was white solid, mp 107-109 °C, optically active material was colorless oil; R_f = 0.26 (1:15 EtOAc/hexane), $[\alpha]_D$ = -47.5 (*c* = 1.0, $CHCl_3$) on 94% ee material prepared from *R*-VANOL;

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.97 (t, *J* = 7.1 Hz, 3H), 2.65 (d, d = 6.9 Hz, 1H), 3.18 (d, *J* = 6.9 Hz, 1H), 3.90 (s, 1H), 3.94 (q, *J* = 7.1 Hz, 2H), 6.99 (dd, J_{HH} = 8.8 Hz, J_{HF} = 8.8 Hz, 4H), 7.39 (dd, J_{HH} = 8.6 Hz, J_{HF} = 5.5 Hz, 4H), 7.40-7.45 (m, 3H), 7.8-7.85 (m, 2H);

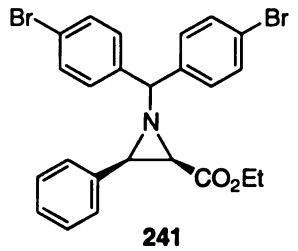
^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.86, 46.43, 47.97, 60.64, 76.03, 115.37 (d, J_{CF} = 21.8 Hz), 115.40 (d, J_{CF} = 21.8 Hz), 127.46, 127.60, 127.81, 128.60 (d, J_{CF} = 8.1 Hz), 128.90 (d, J_{CF} = 8.1 Hz), 134.64, 137.94 (d, J_{CF} = 3 Hz), 138.15 (d, d, J_{CF} = 3 Hz), 161.99 (d, J_{CF} = 246.2 Hz), 162.03 (d, J_{CF} = 246.2 Hz), 167.42;

^{19}F NMR ($CDCl_3$, 282 MHz) δ = -115.25 (m), -114.90 (m)

IR (thin film, cm^{-1}) 1744 vs, 1500vs;

Mass spectrum: m/z (% rel intensity) 393 M^+ (<1), 203 (52), 190 (100), 162 (14);

Anal calcd for $C_{24}H_{21}F_2NO_2$: C, 73.27; H, 5.38; N, 3.56. Found: C, 73.54; H, 5.33; N, 3.50;



241

***Cis*-(*2R, 3R*)-aziridine 241**: The standard aziridination procedure with the *S*-VAPOL-borate catalyst in CCl_4 was employed. The crude mixture was absorbed on 4 g of silica gel and purified by flash chromatography and eluted with 1:1 CH_2Cl_2/hexane, afforded 437 mg **241** as white solid (0.85 mmol), 85% yield. An optical purity of 93% ee was determined by HPLC analysis.

HPLC conditions: Chiralcel OD-H column, 220nm, 99.5:0.55 hexane/iPrOH as eluent at 0.7 mL/min. The retention time for the major (*2R, 3R*)-enantiomer from *S*-ligand was 4.79 min and that of the minor enantiomer was 5.86 min.

Spectral data for **241**: White solid, mp 158-159 °C; R_f = 0.3 (1:1 CH_2Cl_2/hexane), $[\alpha]_D$ = -37.6 (c = 1.0, CH_2Cl_2) on 93% ee material prepared from *S*-VAPOL;

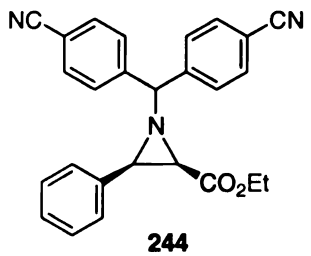
^1H NMR ($CDCl_3$, 300 MHz) δ = 0.96 (t, J = 7.1 Hz, 3H), 2.63 (d, J = 6.9 Hz, 1H), 3.16 (d, J = 6.9 Hz, 1H), 3.84 (s, 1H), 3.92 (d, J = 7.1 Hz, 2H), 7.22-7.38 (m, 9H), 7.44 (s, 4H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.90, 46.40, 47.91, 60.73, 76.23, 121.39, 121.59, 127.57, 127.86, 128.74, 129.00, 131.73, 134.41, 140.85, 140.96, 167.24, 186.26 (one aryl carbon not located);

IR (thin film, cm^{-1}) 2980 s, 1743 vs;

Mass spectrum: m/z (% rel intensity) 518(<1, $(M+1)^+$, $^{81}Br_2$), 517(<1, M^+, $^{81}Br_2$), 516(<1, $(M+1)^+$, $^{81}Br^{79}Br$), 515(<1, M^+, $^{81}Br^{79}Br$), 514(<1, $(M+1)^+$, $^{79}Br_2$), 513(<1, M^+, $^{79}Br_2$), 325 (17), 191 (39) 190 (100), 117 (100);

Anal calcd for $C_{24}H_{21}Br_2NO_2$: C, 55.95; H, 4.11; N, 2.72. Found: C, 55.85; H, 4.35; N, 2.70;



244

***Cis*-(*2R, 3R*)-aziridine 244**: The standard aziridination procedure with the *S*-VAPOL-borate catalyst in CCl_4 was employed. Crude mixture was purified by flash chromatography and eluted with 2:1 hexane/EtOAc. Product **244** was isolated as a white solid (359 mg, 0.88 mmol), 88% yield. An optical purity of 81% ee was determined by HPLC analysis.

HPLC conditions: Chiralpak AD column, 241nm, 70:30 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor enantiomer was 9.03 min and that of the major (*2R, 3R*)-enantiomer from *S*-ligand was 12.88 min.

Spectral data for **244**: White solid; mp 78-82 °C; R_f = 0.27 (2:1 hexane/EtOAc), $[\alpha]_D$ = -43.6 (*c* = 1.0, CH_2Cl_2) on 79 % ee material from *R*-VAPOL;

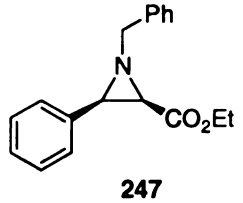
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.94 (t, *J* = 7.1 Hz, 3H), 2.67 (d, *J* = 6.9 Hz, 1H), 3.19 (d, *J* = 6.9 Hz, 1H), 3.90-3.93 (m, 2H), 4.01(s, 1H), 7.19-7.36 (m, 5H), 7.55-7.59 (m, 4H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.83, 46.43, 47.72, 60.91, 76.27, 111.76, 111.92, 118.28, 118.45, 127.36, 127.81, 127.98, 128.04, 132.64, 133.81, 146.13, 146.16, 166.76;

IR (thin film, cm^{-1}) 2230 vs, 1744 vs, 1204 vs;

Mass spectrum: m/z (% rel intensity) 407 M^+ (<1), 217 (13), 190 (100), 162 (16);

Anal calcd for $C_{26}H_{21}N_3O_2$: C, 76.64; H, 5.19; N, 10.31. Found: C, 76.51; H, 5.01; N, 9.95;



247

***Cis*-(*2R, 3R*)-aziridine 247**: The standard aziridination procedure with the *S*-VAPOL-borate catalyst was employed except that a mixture of 4 mL CCl_4 and 2 mL CH_2Cl_2 was used as solvent. Crude mixture was purified by flash chromatography and eluted with 1:9 hexane/EtOAc. Product **247** was isolated as a light yellow oil (151mg, 0.48 mmol), 48% yield. An optical purity of 48% ee was determined by HPLC analysis.

HPLC condition: Chiralcel OD-H column, 225 nm, 98:2 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor enantiomer was 5.77 min and that of the major (*2R, 3R*)-enantiomer from *S*-ligand was 10.02 min.

Spectral data for **247**: Light yellow oil; R_f = 0.23 (1:9 EtOAc/hexane); $[\alpha]_D$ = 12.8 (*c* = 1.0, $CHCl_3$) on 48 % ee material from *S*-VAPOL;

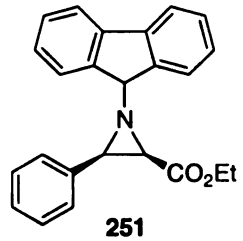
^1H NMR ($CDCl_3$, 300 MHz) δ = 0.95 (t, *J* = 7.1 Hz, 3H), 2.63 (d, *J* = 6.9 Hz, 1H), 3.05 (d, *J* = 6.9 Hz, 1H), 3.63 (d, *J* = 13.8 Hz, 1H), 3.94 (d, *J* = 13.8 Hz, 1H), 3.90-3.97 (m, 2H), 7.20-7.44 (m, 10H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.83, 45.87, 47.60, 60.61, 63.40, 127.18, 127.34, 127.77, 127.87, 128.34, 134.95, 137.62, 168.0 (one aryl carbon not located);

IR (thin film, cm^{-1}): 2982w, 1748 vs;

Mass spectrum: m/z (% rel intensity) 281 M^+ (14), 206 (19), 190 (19), 91 (100);

Anal calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.81; H, 6.86; N, 4.98;



251

***Cis*-(*2R, 3R*)-aziridine 251**: Standard aziridination procedure with the *S*-VAPOL-borate catalyst was employed except that the concentration of imine in solvent was 0.25 M (4 mL of CCl_4 was added). Crude mixture was purified by flash chromatography and eluted with 1:9 hexane/EtOAc. Product **251** was isolated as a white solid (206 mg, 0.58 mmol), 58% yield. An optical purity of 81% ee was determined by HPLC analysis.

HPLC conditions: Chiralpak AD column, 225 nm, 98:2 hexane/iPrOH as eluent at 1.5 mL/min. The retention time for the minor enantiomer was 8.24 min and that of the major (*2R, 3R*)-enantiomer from *S*-ligand was 11.68 min.

Spectral data for **251**: white solid, mp = 139-141 °C, R_f = 0.29 (1:9 EtOAc/hexane); $[\alpha]_D$ = -41.8 (*c* = 1.0, $CHCl_3$) on 81 % ee material from *S*-VAPOL;

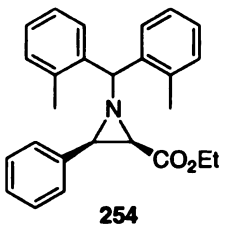
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.85 (t, *J* = 7.0 Hz, 3H), 3.14 (d, *J* = 7.0 Hz, 1H), 3.52 (d, *J* = 7.0 Hz, 1H), 3.80-3.85 (m, 1H), 3.87-4.04 (m, 1H), 4.24 (s, 1H), 7.20-7.41 (m, 9H), 7.51 (m, 1H), 7.76-7.71 (m, 3H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.76, 43.57, 45.55, 60.75, 70.81, 120.09, 120.15, 124.62, 124.78, 127.37, 127.45, 127.52, 127.89, 128.01, 128.74, 128.77, 134.78, 140.99, 141.21, 142.79, 143.08, 168.20;

IR (thin film, cm^{-1}): 1713 vs, 1450 s ;

Mass spectrum: m/z (% rel intensity) 355 M^+ (<1), 190 (92), 165 (75), 116 (100);

Anal calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.12; H, 6.03; N, 3.87;



254

***Cis*-(*2R, 3R*)-aziridine 254**: Standard aziridination procedure with the *S*-VAPOL-borate catalyst in CCl_4 was employed. Crude mixture was absorbed on 4 g of silica gel, purified by flash chromatography and eluted with 15:1 hexane/EtOAc. Product **254** was isolated as a colorless oil (257 mg, 0.67 mmol), 67% yield. An optical purity of 90 % ee was determined by HPLC analysis.

HPLC conditions: Chiralcel OD-H column, 225 nm, 98:2 to 90:10 hexane/iPrOH in 30 minutes at 1 mL/min. The retention time for the minor enantiomer was 3.78 min and that of the major (*2R, 3R*)-enantiomer from *S*-ligand was 9.96 min.

Spectral data for **254**: Colorless oil; R_f = 0.21 (1:15 EtOAc/hexane); $[\alpha]_D$ = 89.2 (*c* = 1.0, $CHCl_3$) on 90 % ee material prepared from *S*-VAPOL;

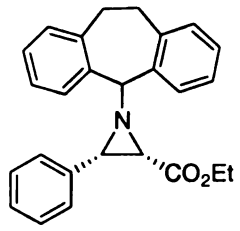
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.98 (t, *J* = 7.1 Hz, 3H), 2.17 (s, 3H), 2.39 (s, 3H), 2.65-2.68 (m, 1H), 3.28 (d, *J* = 6.8 Hz, 1H), 3.95 (q, *J* = 7.1 Hz, 2H), 4.46 (s, 1H), 7.09-7.33 (m, 11H), 7.56 (d, *J* = 6.6 Hz, 1H), 8.07 (d, *J* = 7.07 Hz, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.89, 19.78, 19.95, 45.64, 46.92, 60.49, 70.09, 125.91, 126.00, 126.96, 127.13, 127.24, 127.72, 128.40, 129.69, 130.35, 130.53, 135.14, 135.39, 135.49, 138.57, 139.62, 167.88 (one aryl carbon not located);

IR (thin film, cm^{-1}): 2959 br, 1745 bs, 1196 vs;

Mass spectrum: m/z (% rel intensity) 385 M^+ (<1), 196 (90), 195 (100), 190 (48), 180 (37), 165 (28);

Anal calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 81.20; H, 7.32; N, 3.60;



257

***Cis*-(*2S, 3S*)-aziridine 257**: Standard aziridination procedure with the *R*-VAPOL-borate catalyst in CCl_4 was employed. Crude mixture was purified by flash chromatography and eluted with 1:1 to 1:2 hexane/CH_2Cl_2, the impure fraction was purified by chromatography with 1:9 EtOAc/hexane. Product **257** was isolated as a white solid (322 mg, 0.82 mmol) 67% yield. An optical purity of 96 % ee was determined by HPLC analysis.

HPLC conditions: Chiralcel OD-H column, 222 nm, 90:10 hexane/iPrOH in 30 minutes at 1 mL/min. The retention time for the major (*2S, 3S*)-enantiomer from *R*-ligand was 3.23 min and that of the minor enantiomer was 7.20 min.

Spectral data for **257**: White solid, mp = 128-130 °C; R_f = 0.27 (1:1 CH_2Cl_2/hexane), $[\alpha]_D$ = -12.6 (*c* = 1.0, $CHCl_3$) on 96 % ee material prepared from *R*-VAPOL;

Aziridine **257** exists as two conformers (1:1 ratio) at room temperature, the NMR spectrum of **257** was difficult to interpret as the signals of the two conformers overlap in both aliphatic and aromatic region. Upon heating the d^6-DMSO solution of **257** to 95 °C the two conformers merged. Due to the significantly decreased shimming quality some coupling were not observed at that temperature.

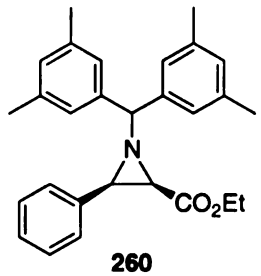
^1H NMR (d^6-DMSO at 95 °C, 300 MHz) δ = 0.90 (s, 3H), 2.49 (s, 1H), 2.90 (d, *J* = 6.9 Hz, 1H), 3.17 (s, br, 2H), 3.37 (d, *J* = 6.8 Hz, 1H), 3.84 (s, br, 4H), 7.00-7.40 (m, 13H);

^{13}C NMR (d^6-DMSO at 95 °C, 75 MHz) δ = 13.17, 31.01, 31.28, 45.67, 47.27, 59.29, 125.13, 125.20, 126.55, 126.90, 127.11, 129.28, 129.50, 135.13, 166.67 (two aryl carbons not located);

IR (thin film, cm^{-1}): 1744 bs, 1204 vs;

Mass spectrum: m/z (% rel intensity) 383 M^+ (<1), 193 (94), 192 (100), 191 (33), 178 (29);

Anal calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.17; H, 6.57; N, 3.65;



260

***Cis*-(*2R, 3R*)-aziridine 260**: Standard aziridination procedure with the *S*-VAPOL-borate catalyst in CCl_4 was employed. Crude mixture was absorbed on 4 g of silica gel and purified by flash chromatography and eluted with 1:15 EtOAc/hexane. Product was isolated as a mixture (414 mg) of aziridine **260** and small amount of impurity. The mixture was purified again by chromatography and eluted with 1:1 CH_2Cl_2/hexane, pure product was isolated as a colorless oil (390 mg, 0.94 mmol), 94% yield. An optical purity of 98 % ee was determined by HPLC analysis.

HPLC conditions: Chiralcel OD-H column, 225 nm, 99.5:0.5 hexane/iPrOH as eluent at 0.6 mL/min. The retention time for the major (*2R, 3R*)-enantiomer from *S*-VAPOL was 6.72 min and that of the minor enantiomer was 8.52 min.

Spectral data for **260**: Colorless oil; $[\alpha]_D$ = 60.9 (*c* = 1.0, $CHCl_3$) on 98 % ee material prepared from *S*-VAPOL;

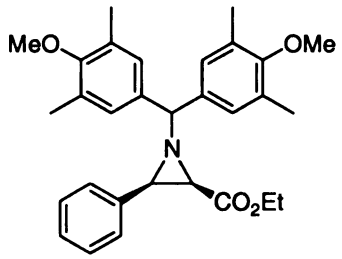
^1H NMR ($CDCl_3$, 300 MHz) δ = 1.03 (t, *J* = 7.1 Hz, 3H), 2.26 (s, 6H), 2.33 (s, 6H), 2.65 (d, *J* = 6.8 Hz, 1H), 3.19 (d, *J* = 6.7 Hz, 1H), 3.81 (s, 1H), 3.94-4.01 (m, 2H), 6.83 (s, 1H), 6.90 (s, 1H), 7.16 (s, 2H), 7.21-7.30 (m, 5H), 7.43 (d, *J* = 7.7 Hz, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.96, 21.26, 21.34, 46.21, 48.04, 60.41, 77.80, 124.87, 125.32, 127.16, 127.65, 127.80, 128.72, 128.98, 135.20, 137.69, 137.75, 142.40, 142.49, 169.91;

IR (thin film, cm^{-1}): 2980 s, 1748 vs, 1199 vs ;

Mass spectrum: m/z (% rel intensity) 413 M^+ (<1), 223 (100), 193 (11);

Anal calcd for $C_{28}H_{31}NO_2$: C, 81.32; H, 7.56; N, 3.39. Found: C, 81.38; H, 7.28; N, 3.41;



264

***Cis*-(*2R, 3R*)-aziridine 264**: Standard aziridination procedure with the *S*-VANOL-borate catalyst in CCl_4 was employed. Crude mixture was purified by flash chromatography and eluted with 20:20:1 hexane/EtOAc/CH_2Cl_2, gave the pure product as a foam-like solid (383 mg, 0.81 mmol), 81% yield. An optical purity of 98.5 % ee was determined by HPLC analysis.

HPLC condition: Chiralcel OD-H column, 225 nm, 99:1 hexane/iPrOH as eluent at 1 mL/min. The retention time for the major (*2R, 3R*)-enantiomer from *S*-VANOL was 5.98 min and that of the minor enantiomer was 8.43 min.

Spectral data for **264**: White foam-like solid, mp = 56-60 °C; R_f = 0.33 (20:20:1 hexane/EtOAc/CH_2Cl_2), $[\alpha]_D$ = 47.5 (*c* = 1.0, $CHCl_3$) on 98.5 % ee material prepared from *S*-VANOL;

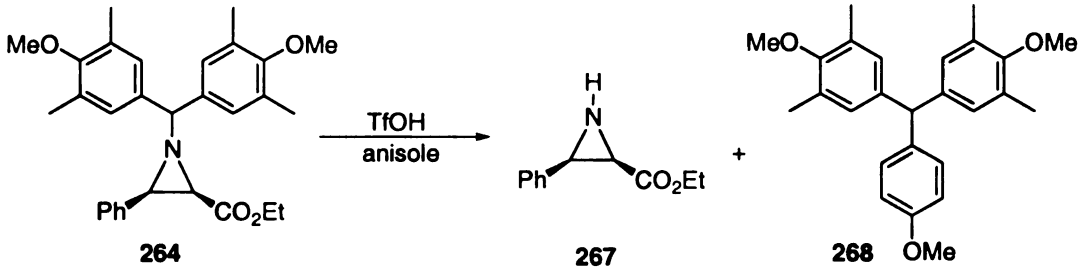
^1H NMR ($CDCl_3$, 300 MHz) δ = 0.99 (t, *J* = 7.1 Hz, 3H), 2.21 (s, 6H), 2.27 (s, 6H), 2.59 (d, *J* = 6.9 Hz, 1H), 3.14 (d, *J* = 6.9 Hz, 1H), 3.63 (s, 3H), 3.69 (s, 3H), 3.85 (s, 1H), 3.93-3.96 (m, 2H), 7.13 (s, 2H), 7.18-7.27 (m, 5H), 7.39 (d, *J* = 6.9 Hz, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.96, 16.11, 16.17, 46.18, 48.15, 59.46, 59.52, 60.46, 76.95, 127.17, 127.33, 127.66, 127.74, 127.78, 130.54, 135.22, 137.75, 137.92, 155.84, 155.99, 168.00 (one aryl carbon not located);

IR (thin film, cm^{-1}): 2930 vs, 1747 vs, 1221 vs ;

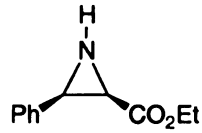
Mass spectrum: m/z (% rel intensity) 473 M^+ (<1), 284 (78), 283 (100), 268 (34), 253 (20), 237 (11);

Anal calcd for $C_{30}H_{35}NO_4$: C, 76.08; H, 7.45; N, 2.96. Found: C, 76.31; H, 7.28; N, 2.82;



264 **267** **268**

Deprotection of N-MEDAM aziridine 264: To an oven-dried 25 mL round bottom flask filled with argon was added aziridine **264** (406 mg, 0.86 mmol) and 10 mL distilled anisole. The solution was stirred at 0 °C, then 406 μL triflic acid (689 mg, 4.59 mmol) was added by syringe in 1 minute. After addition, the solution was stirred at 0°C for 10 minutes, then the ice bath was removed and the light brown solution was stirred at room temperature for 3 h before quenched with saturated $NaHCO_3$ solution until PH>9. The mixture was extracted with 3 × 20 mL ether, the combined organic layer washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluted with 1:1 Et_2O/hexane to give **268** (302 mg, 0.77 mmol, 90% yield), then the column was eluted with pure Et_2O to give aziridine **267** as white solid (145 mg, 0.76 mmol), 89% yield.



267

Spectral data for **267**: White solid, mp = 67-68 °C, R_f = 0.13 (1:1 Et_2O/hexane); $[\alpha]_D$ = -12.4 (*c* = 1.0, EtOAc) on 99 % ee material prepared from *S*-VAPOL;

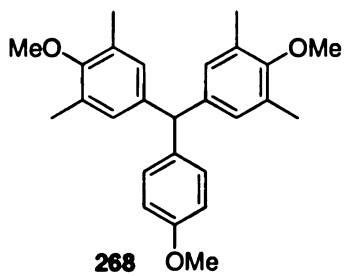
^1H NMR ($CDCl_3$, 300 MHz) δ = 0.99 (t, *J* = 7.1 Hz, 3H), 1.87 (br, s, 1H), 3.00 (d, *J* = 6.1 Hz, 1H), 3.47 (d, *J* = 6.1 Hz, 1H), 3.99 (m, 2H), 7.33 (m, 5H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.90, 29.65, 37.14, 61.07, 127.47, 127.62, 128.01, 134.80, 169.02;

IR (thin film, cm^{-1}): 3218 w, 1738 vs, 1186 vs ;

Mass spectrum: m/z (% rel intensity) 191 M^+ (<1), 162 (58), 118 (100), 91 (100);

Anal calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.74; H, 6.91; N, 7.25;



268

Spectral data for **268**: Viscous oil, R_f = 0.28 (1:9 EtOAc/hexane);

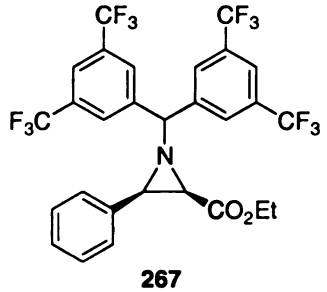
^1H NMR ($CDCl_3$, 300 MHz) δ = 2.23 (s, 12H), 3.72 (s, 6H), 3.79 (s, 3H), 5.28 (s, 1H), 6.75 (s, 4H), 6.83 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 16.16, 54.90, 55.10, 59.56, 113.47, 129.53, 130.20, 130.29, 136.61, 139.57, 155.15, 157.77;

IR (thin film, cm^{-1}): 2946 w, 1510 vs, 1485 vs ;

Mass spectrum: m/z (% rel intensity) 391 $(M+1)^+$ (19), 390 M^+ (70), 389 $(M-1)^+$ (10), 376 (24), 375 (90), 360 (26), 359 (100), 331 (22), 283 (21);

Anal calcd for $C_{26}H_{30}O_3$: C, 79.97; H, 7.74. Found: C, 79.89; H, 7.70;



267

***Cis*-(*2R, 3R*)-aziridine 267**: Standard aziridination procedure with the *S*-VANOL-borate catalyst in CCl_4 was employed. Crude reaction mixture was absorbed on 4 g of silica gel, purified by flash chromatography and eluted with 9:1:1 hexane/Et_2O/CH_2Cl_2, gave the pure product **267** (529 mg, 0.84 mmol) as a white solid 84% yield. An optical purity of 91 % ee was determined by HPLC analysis.

HPLC conditions: Chiralpak AD column, 225 nm, 98:2 hexane/iPrOH as eluent at 1 mL/min. The retention time for the major (*2R, 3R*)-enantiomer from *S*-VANOL was 4.16 min and that of the minor enantiomer was 5.98 min.

Spectral data for **267**: White solid; mp = 108-110 °C, R_f = 0.33 (9:1:1 hexane/Et_2O/CH_2Cl_2), $[\alpha]_D$ = 28.0 (c = 1.0, $CHCl_3$) on 91 % ee material prepared from *S*-VANOL;

^1H NMR ($CDCl_3$, 300 MHz) δ = 1.09 (t, J = 7.1 Hz, 3H), 2.79 (d, J = 7.1 Hz, 1H), 3.31 (d, J = 7.1 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 4.25 (s, 1H), 7.29-7.36 (m, 3H), 7.43-7.47 (m, 2H), 7.82 (s, 1H), 7.90 (s, 1H), 8.05 (s, 2H), 8.21 (s, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.77, 46.77, 47.92, 61.26, 75.27, 122.29 (m), 122.47 (m), 122.96 (q, $J_{C\text{-}F}$ = 273 Hz), 123.11 (q, $J_{C\text{-}F}$ = 273 Hz), 127.36, 127.55 (d, $J_{C\text{-}F}$ = 2.3 Hz),

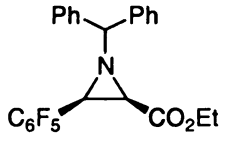
128.07, 128.15, 128.37, 132.41 (q, $J_{C\text{-}F}$ = 32 Hz), 132.44 (q, $J_{C\text{-}F}$ = 32 Hz), 133.40, 143.29, 143.34, 166.69;

^{19}F NMR ($CDCl_3$, 282 MHz) δ = -62.97, -62.85;

IR (thin film, cm^{-1}): 1738 vs, 1373 vs, 1279 vs;

Mass spectrum: m/z (% rel intensity) 629 M^+ (<1), 439 (5), 300 (4), 191 (11), 190 (100), 162(12);

Anal calcd for $C_{28}H_{19}F_{12}NO_2$: C, 53.43; H, 3.04; N, 2.23. Found: C, 53.50; H, 3.09; N, 2.14;



273

***Cis*-(*2R, 3R*)-aziridine 273**: Standard aziridination procedure with the *S*-VAPOL-borate catalyst in CCl_4 was employed. Crude mixture was absorbed on 4 g of silica gel and purified by flash chromatography and eluted with 15:1 hexane/EtOAc, gave the pure product as a colorless oil (183 mg, 0.41 mmol), 41% yield). An optical purity of 90 % ee was determined by HPLC analysis.

HPLC condition: Chiralcel OD-H column, 225 nm, 98:2 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor enantiomer was 4.30 min and that of the major (*2R, 3R*)-enantiomer from *S*-VAPOL was 6.49 min.

Spectral data for **273**: White solid, mp = 102-105 °C; R_f = 0.29 (15:1 hexane/EtOAc), $[\alpha]_D$ = 47.7 (*c* = 1.0, $CHCl_3$) on 90 % ee material prepared from *S*-VAPOL;

^1H NMR ($CDCl_3$, 300 MHz) δ = 1.14 (t, *J* = 7.1 Hz, 3H), 2.67 (d, *J* = 6.3 Hz, 1H), 3.11 (d, *J* = 6.3 Hz, 1H), 3.99 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 7.23-7.33 (m, 6H), 7.42-7.46 (m, 4H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.91, 38.44, 42.97, 61.25, 78.23, 127.07, 127.40, 127.84, 128.18, 128.40, 128.57, 141.17, 141.37, 167.95 (the fluorinated carbons merged into baseline and were indistinguishable from noise);

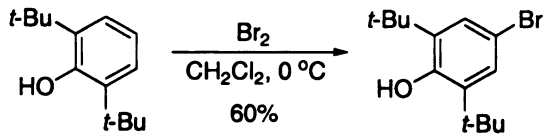
^{19}F NMR ($CDCl_3$, 282 MHz) δ = -162.77 (dt, J = 8.2 Hz, J = 21.7 Hz, 2F), -155.20 (dt, J = 1.5 Hz, J = 21.1 Hz, 1F), -140.25 (dd, J = 8.2 Hz, J = 20.8 Hz, 2F);

IR (thin film, cm^{-1}): 1744 vs, 1526 vs, 1502 vs;

Mass spectrum: m/z (% rel intensity) 447 M^+ (<1), 374 (6), 197 (13), 168 (60), 167 (100), 166 (51), 165(76), 152 (47);

Anal calcd for $C_{24}H_{18}F_5NO_2$: C, 64.43; H, 4.06; N, 3.13. Found: C, 64.24; H, 4.07; N, 3.09;

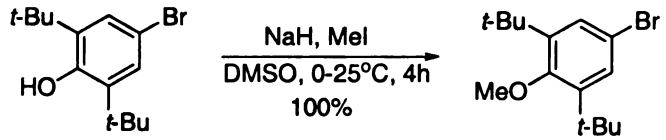
Preparation of N-BUDAM amine and imines



279 **280**

2,6-di-*tert*-butyl-4-bromophenol 280[83b]: To an flame-dried 2L three neck round bottom flask equipped with a gas inlet, rubber septum, pressure-equalizing dropping funnel was charged with 2,6-di-*tert*-butylphenol **279** (206 g, 1 mol) and flushed with argon, after which 400 mL dry CH_2Cl_2 was added. The gas outlet tube was connected to a gas trap containing 0.5 M sodium hydroxide. The dropping funnel was charged with bromine (53 mL, 1.05 mol) and 40 mL of dry CH_2Cl_2. The reaction vessel is immersed in an ice-water bath, stirring is initiated, and bromine in dichloromethane is added over 80 mins. The reaction mixture is stirred at 0°C for 20 min after the addition. Then 120 mL of saturated aqueous sodium sulfite (Na_2SO_3) was added slowly at that temperature and the stirring is continued at room temperature until the light orange color of bromine was discharged. The mixture was poured into a 3 L separation funnel containing 800 mL of saturated aqueous sodium bicarbonate. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by crystallization from ethanol-water (mixture of 260 mL ethanol and 36 mL water) to afford product **280** as light yellow crystal in 78% yield (225 g, 780 mmol).

Characterization of the product was reported in reference 83b.



280 **282**

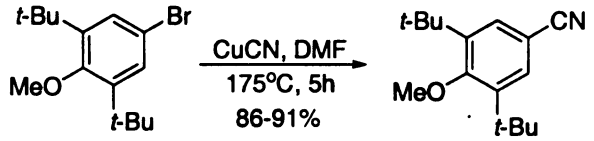
Methylation of phenol 282: To an flame-dried 2L three neck round bottom flask equipped with mechanical stirring device was added 1.4 L anhydrous DMSO (dried over 4A MS), purged with argon and slowly added sodium hydride (56 g, 1.4 mol) (60% suspension in oil) to give a suspension. The flask was then submerged into a 0°C ice bath for at least 10 min before the addition of **280**. With rapid stirring, 4-bromo-2,6-di-*tert*-butyl phenol **280** (167 g, 588 mmol) was added portion wise in 20 min. After the addition, the suspension was stirred at 0 °C for 15 min, followed by the addition of methyl iodide (150 mL, 2.3 mol) via addition funnel in 15 min. Upon addition, the mixture was stirred at 0 °C for 15 more min before the ice bath was removed, and the reaction mixture was allowed to warm up to room temperature gradually. After 3 hours, the red mixture was cooled to 0 °C and 400 mL of hexane was added, the mixture was poured into a 4 L Erlenmeyer flask containing 500 mL hexane. The flask that contains reaction mixture was put into the 0 ºC ice bath, with the continuing mechanical stirring, 500 mL water was slowly added until it appeared two layers. The hexane layer was collected, and the water layer was extracted with 3 × 200 mL hexane. The combined hexane was then washed with 3 × 400 mL water, dried over $MgSO_4$ and concentrated under reduced pressure to give a light yellow solid. Purification by silica gel chromatography (two 80mm × 800 mm column, hexane as elute) to give **282** as white solid in about 100% yield (181 g, 588 mmol).

Spectral data for **282**:

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 18H), 3.66 (s, 3H), 7.31 (s, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 31.86, 35.90, 64.36, 116.40, 129.50, 145.98, 158.73;

Characterization of the product was reported in reference 83c.



282 **283**

Preparation of benzonitrile 283: To an flame-dried 2 L three neck round bottom flask filled with argon and equipped with refluxing condenser was charged with compound **282** (91.7 g, 308 mmol), copper cyanide (32.7 g, 365 mmol) and 600 mL distilled anhydrous DMF. The reaction mixture was purged with argon for 15 minutes, then the argon inlet was removed and a argon balloon was attached on the top of the condenser through a rubber septum stopper. The mixture was heated to reflux in 180 °C oil bath for 8 hours. The solid CuCN dissolved after approximately 2 hours and red precipitate appeared slowly. After 8 h of heating, the mixture was allowed to cool down gradually to room temperature, and was then poured into a Erlenmeyer flask containing a solution of ethylene diamine aqueous solution (280 mL ethylene diamine in 2500 mL water), followed by the addition of 1000 mL benzene. The mixture was stirred at room temperature for 20 minutes and then loaded into a separation funnel, the benzene layer was collected, the aqueous layer was extracted with 4 × 400 mL benzene. The combined benzene layer was washed with 500 mL 6% NaCN solution, then 2 × 600 mL water, dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a brown semi-solid. Purification by silica gel chromatography (two times with 80mm × 800 mm column, 1:3 CH_2Cl_2/hexane as elute) to give **283** as white solid in 91% yield (68 g, 280 mmol).

Spectral data for **283**: White solid, mp 72-74 °C, R_f = 0.30 (1:3 CH_2Cl_2/hexane)

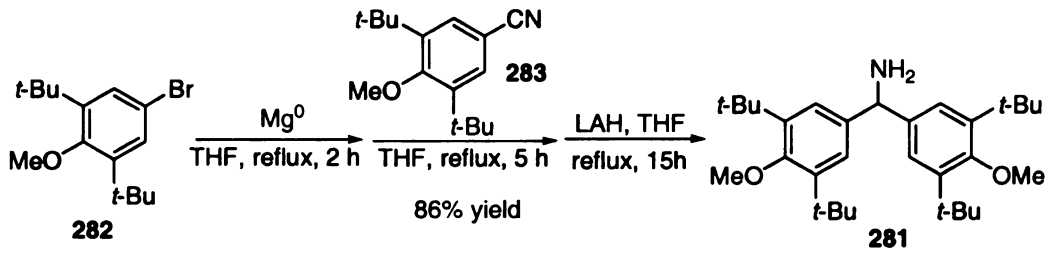
^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 18H), 3.69 (s, 3H), 7.51 (s, 2H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 31.67, 35.94, 64.63, 106.72, 119.75, 130.74, 145.48, 163.55;

IR (thin film, cm^{-1}) 2965 vs, 2230 vs, 1410 s, 1229 s;

Mass spectrum *m/z* (% rel intensity) 245 (30) M^+, 230 (100), 188 (12);

Anal calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.40; H 9.54; N 5.68;



Preparation of N-BUDAM amine 281: To a flame-dried 1 L three neck round bottom flask filled with argon and equipped with refluxing condenser was added magnesium metal (13.2 g, 550 mmol), 500 mL dry THF, bromobenzene **282** (65.6 g, 220 mmol) and a few crystals of iodine. The mixture was heated to reflux under the protection of argon for 3 h. The resulting light brown solution was allowed to cool down to room temperature, transferred via cannula to a flame-dried 2 L three neck round bottom flask equipped with refluxing condenser under the protection of argon. At the same time, to a flame-dried 1L flask filled with argon was added benzonitrile **283** (49 g, 200 mmol) and 500 mL dry THF, the solution of **283** in THF was then transferred via cannula to the 2 L flask containing Grignard reagent in 10 min at room temperature. The resulting mixture was heated to reflux for 5 hours under the protection of argon, then allowed to cool down to room temperature, and then submerged into a 0 °C ice bath. To this mixture was added via cannula a suspension of $LiAlH_4$ (8.79 g, 220 mmol) in 300 mL dry THF which was in a flame-dried 500 mL flask filled with argon and pre-cooled at 0 °C. After the addition, the ice bath was removed, and the reaction mixture was heated to reflux for 15 h. Upon

completion, the greenish slurry was cooled down to room temperature, and carefully quenched with slow addition of 9 mL water, then 9 mL 10% NaOH solution, followed by 25 mL of water. The resulted slurry was filtered through a cilite pad, the gray solid was washed with excess of ether until no amine left. The combined organic layer was concentrated under reduced pressure to give crude **281** as a white solid. Silica gel chromatography purification (2 times 80mm × 800 mm column, 1:5 to 1:2 EtOAc/hexane as elute) gave **281** as two fractions, the first fraction was pure by ^{1}H NMR but it was contaminated with small amount of yellow impurity, the second fraction was white solid, both fractions were further purified by crystallization (1:25 EtOAc/hexane). The overall yield of **281** was 86% (81 g, 172 mmol) as white crystals.

Spectral data for N-BUDAM amine **281**: Small white crystal, mp 179-180 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 36H), 1.76 (s, 2H), 3.66 (s, 6H), 5.07 (s, 1H), 7.21 (s, 4H);

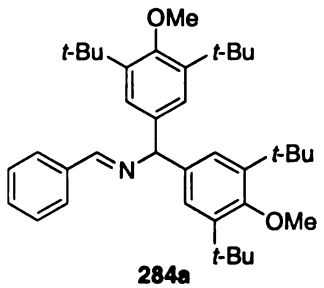
^{13}C NMR (75 MHz, $CDCl_3$) δ 32.09, 35.77, 59.81, 64.10, 125.17, 139.54, 143.14, 158.17;

IR (thin film, cm^{-1}): 2961 vs, 1410 s;

Mass spectrum *m/z* (% rel intensity) 467 (4) M^+, 410 (16), 247 (100);

Anal calcd for $C_{31}H_{49}NO_2$: C, 79.60; H, 10.56; N, 2.99. Found: C, 79.65; H 10.78; N 3.09;

Typical experimental procedure for the synthesis of all aldimines: Aldehyde and amine were purified by chromatography or distillation before use. To an oven dried 100 mL round bottom flask was added 30 mmol of amine, followed by 50 mL of CH_2Cl_2, 5 g of $MgSO_4$, and 30 mmol of aldehyde. The reaction was stirred for 12-24 hours. Upon completion of the reaction the mixture was filtered and concentrated by rotary evaporation to give the crude imine. These imines were generally crystallized from hexane/CH_2Cl_2 or EtOAc/hexane and only the first crop was used.



284a

Imine 284a: Imine was prepared by the standard procedure. The crude product was crystallized from 1:100 EtOAc/hexane, two crops gave 87% yield.

Spectral data for **284a**: Small white needle, mp 127-129 °C.

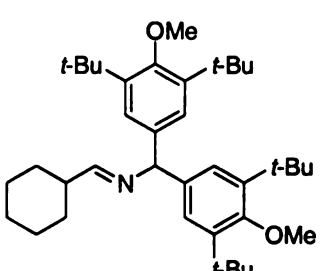
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.429 (s, 18H), 1.433 (s, 18H), 3.70 (s, 3H), 3.70 (s, 3H), 5.51 (s, 1H), 7.27 (s, 4H), 7.42-7.44 (m, 3H), 7.86-7.89 (m, 2H), 8.52 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 32.08, 35.77, 64.13, 78.20, 126.02, 128.40, 128.47, 130.50, 136.55, 137.42, 143.10, 158.29, 160.23;

IR (thin film, cm^{-1}): 2981 vs, 1410 s, 1221 s;

Mass spectrum *m/z* (% rel intensity) 555 (1) M^+, 451 (100), 218 (16), 182 (29);

Anal calcd for $C_{38}H_{53}NO_2$: C, 82.11; H 9.61; N 2.52. Found: C, 81.85; H, 9.65; N, 2.48;



284b

Imine 284b: Imine was prepared by the standard procedure. The crude product was crystallized from 1:25 EtOAc/hexane, 76% yield.

Spectral data for **284b**: White solid, mp 142-144°C.

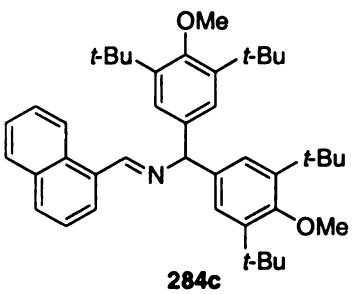
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25-1.89 (m, 10H), 1.37 (s, 36H), 2.27 (m, 1H), 3.66 (s, 6H), 5.21 (s, 1H), 7.05 (s, 4H), 7.73 (d, J = 5.5 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 25.40, 26.04, 29.82, 32.06, 35.77, 43.46, 64.13, 126.11, 137.06, 142.90, 158.18, 168.56 (one aliphatic carbon not located);

IR (thin film, cm^{-1}): 2961 vs, 2930 vs, 1414 vs, 1221 vs;

Mass spectrum *m/z* (% rel intensity): 562 M+ (<1), 453 (31), 452 (100), 451 (29), 218 927), 184 (21);

Anal calcd for $C_{38}H_{59}NO_2$: C, 81.23; H, 10.58; N, 2.49. Found: C, 81.44; H, 10.79; N, 2.54;



284c

Imine 284c: Imine was prepared by the standard procedure. The crude product was crystallized from 1:20 EtOAc/hexane, 89 % yield. The product was isolated as a 4:1 mixture of imine and trapped hexane solvent.

Spectral data for **284c**: White solid, mp 137-140 °C.

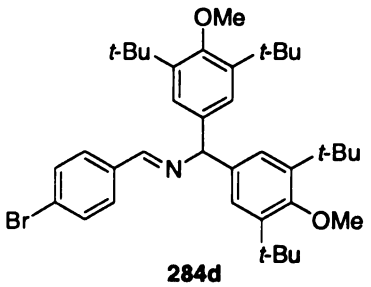
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 36H), 3.70 (s, 6H), 5.59 (s, 1H), 7.38 (s, 4H), 7.50-7.61 (m, 3H), 7.88-7.94 (m, 3H), 9.19 (s, 1H), 9.26 (d, J = 8.5 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 32.11, 35.81, 64.15, 79.35, 125.08, 125.16, 126.02, 126.99, 128.50, 129.65, 130.91, 131.38, 131.99, 133.85, 137.65, 143.17, 158.30, 160.23 (one aryl carbon not located);

IR (thin film, cm^{-1}): 2961 vs, 1643 s, 1412 vs, 1221 vs;

Mass spectrum *m/z* (% rel intensity): 606 $(M+1)^+$ (9), 605 M^+ (5), 453 (50), 452 (100), 422 (22), 379 (22);

Anal calcd for $4C_{42}H_{55}NO_2$-C_6H_{14}: C, 83.27; H, 9.40; N, 2.23. Found: C, 83.32; H, 9.82; N, 2.18;



284d

Imine 284d: Imine was prepared by the standard procedure. The crude product was crystallized from 1:17 EtOAc/hexane, 81% yield.

Spectral data for **284d**: White solid, mp 172-174 °C.

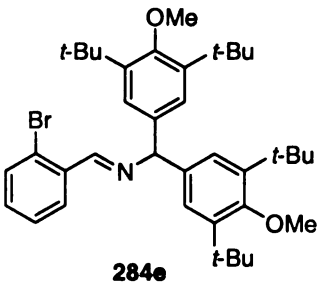
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 36H), 3.67 (s, 6H), 5.46 (s, 1H), 7.21 (s, 4H), 7.54 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 8.42 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 32.09, 35.78, 64.13, 78.17, 124.91, 125.96, 129.80, 131.74, 135.48, 137.24, 143.22, 158.38, 158.93;

IR (thin film, cm^{-1}): 2963 vs, 1412 vs, 1221 vs, 1011 vs;

Mass spectrum *m/z* (% rel intensity): 635 M^+ (<1, ^{81}Br), 633 M+ (<1, ^{79}Br), 453 (29), 452 (100), 184 (20);

Anal calcd for $C_{38}H_{52}BrNO_2$: C, 71.91; H, 8.26; N, 2.21. Found: C, 71.99; H, 8.53; N, 2.18;



284e

Imine 284e: Imine was prepared by the standard procedure. The crude product was crystallized from 1:1.5 EtOAc/hexane, 77% yield.

Spectral data for **284e**: White solid, mp 173-174 °C.

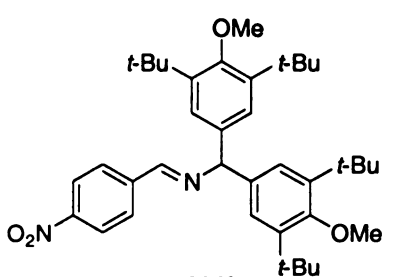
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 36H), 3.67 (s, 6H), 5.58 (s, 1H), 7.23 (s, 4H), 7.21-7.27 (m, 1H), 7.32-7.36 (m, 1H), 7.55 (dd, *J* = 8, 1.4 Hz, 1H), 8.13 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.82 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 32.11, 35.81, 64.15, 77.99, 125.04, 126.13, 127.54, 129.25, 131.62, 132.85, 135.05, 136.87, 143.22, 158.42, 159.32;

IR (thin film, cm^{-1}): 2963 vs, 1412 vs, 1223 vs;

Mass spectrum *m/z* (% rel intensity): 635 M^+ (<1, ^{81}Br), 633 M^+ (<1, ^{79}Br), 453 (58), 451 (100), 379 (11);

Anal calcd for $C_{38}H_{52}BrNO_2$: C, 71.91; H, 8.26; N, 2.21. Found: C, 72.07; H, 8.60; N, 2.19;



284f

Imine 284f: Imine was prepared by the standard procedure. The crude product was crystallized from CH_2Cl_2/hexane (bi-layer). Two crops gave 82% yield.

Spectral data for **284f**: Light yellow solid, mp 228-229 °C.

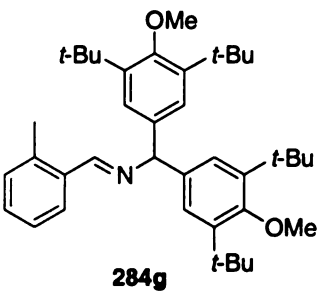
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 36H), 3.69 (s, 6H), 5.55 (s, 1H), 7.25 (s, 4H), 8.02 (d, *J* = 8.8 Hz, 2H), 8.29 (d, *J* = 8.8 Hz, 2H), 8.58 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 32.05, 35.78, 64.13, 78.49, 123.81, 125.87, 129.00, 136.84, 142.00, 143.38, 149.01, 157.82, 158.52;

IR (thin film, cm^{-1}): 2959 vs, 1528, 1339, 1219;

Mass spectrum *m/z* (% rel intensity): 600 M^+ (5), 452 (74), 451 (100), 421 (17), 379 (13), 218 (24), 184 915);

Anal calcd for $C_{38}H_{52}N_2O_4$: C, 75.96; H, 8.72; N, 4.66. Found: C, 75.94; H, 9.10; N, 4.77;



284g

Imine 284g: Imine was prepared by the standard procedure. The crude product was crystallized from 1:5 EtOAc/hexane, 94% yield.

Spectral data for **284g**: White solid, mp 174-175 °C.

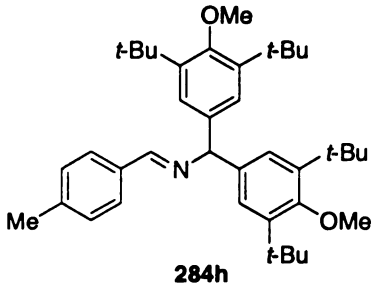
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 36H), 2.61 (s, 3H), 3.69 (s, 6H), 5.49 (s, 1H), 7.18-7.30 (m, 3H), 7.28 (s, 4H), 7.92-7.95 (m, 1H), 8.75 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.91, 32.11, 35.78, 64.12, 78.85, 125.96, 126.04, 128.66, 129.94, 130.79, 134.55, 137.68, 137.74, 143.10, 158.26, 159.24;

IR (thin film, cm^{-1}): 2963 vs, 1412 vs, 1221 vs;

Mass spectrum *m/z* (% rel intensity): 569 M^+ (<1), 451 (67), 84 (100);

Anal calcd for $C_{39}H_{55}NO_2$: C, 82.20; H, 9.73; N, 2.46. Found: C, 82.18; H, 10.10; N, 2.41;



284h

Imine 284h: Imine was prepared by the standard procedure. The crude product was crystallized from 1:25 EtOAc/hexane, 83% yield.

Spectral data for **284h**: White solid, mp 131-132 °C.

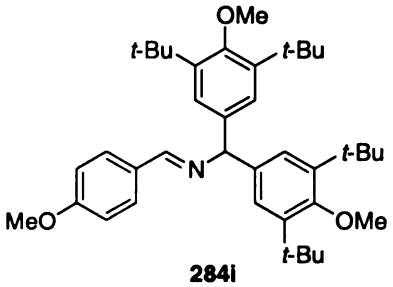
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 36H), 2.41 (s, 3H), 3.72 (s, 6H), 5.51 (s, 1H), 7.25 (d, J = 8.2 Hz, 2H), 7.27 (s, 4H), 7.79 (d, J = 8.2 Hz, 2H), 8.50 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.48, 32.11, 35.78, 64.12, 78.11, 126.08, 128.40, 129.21, 134.07, 137.57, 140.68, 143.07, 158.29, 160.15;

IR (thin film, cm^{-1}): 2961 vs, 1412 vs, 1221 vs;

Mass spectrum *m/z* (% rel intensity): 569 M+ (2), 453 (53), 452 (100), 392 (5), 219 (15);

Anal calcd for $C_{39}H_{55}NO_2$: C, 82.20; H, 9.73; N, 2.46. Found: C, 82.36; H, 9.85; N, 2.72;



284i

Imine 284i: Imine was prepared by the standard procedure. The crude product was crystallized from 1:50 EtOAc/hexane, two crops gave 86% yield.

Spectral data for **284i**: White solid, mp 132-133 °C.

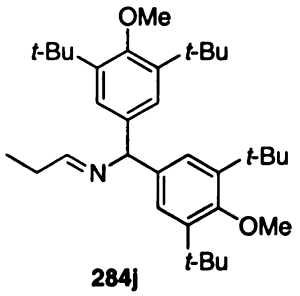
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 36H), 3.71 (s, 6H), 3.85 (s, 3H), 5.49 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 7.27 (s, 4H), 7.83 (d, J = 8.8 Hz, 2H), 8.47 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 32.09, 35.77, 55.24, 64.10, 78.06, 113.87, 126.07, 129.60, 129.94, 137.66, 143.03, 158.24, 159.53, 161.55;

IR (thin film, cm^{-1}): 2959 vs, 1607 vs, 1250 vs;

Mass spectrum *m/z* (% rel intensity): 585 M^+ (2), 529 (2), 452 (100), 411 (6), 380 (7), 247 (37), 183 (18);

Anal calcd for $C_{39}H_{55}NO_3$: C, 79.95; H, 9.46; N, 2.39. Found: C, 80.06; H, 9.88; N, 2.39;



284j

Imine 284j: Imine was prepared by the standard procedure. The crude product was crystallized from hexane, two crops gave 56% yield.

Spectral data for **284j**: White solid, mp 126-128 °C.

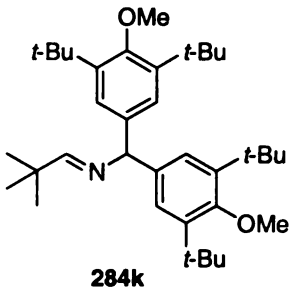
^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J = 7.6 Hz, 3H), 1.36 (s, 36H), 2.33-2.38 (m, 2H), 3.64 (s, 6H), 5.21 (s, 1H), 7.06 (s, 4H), 7.89 (t, J = 4.7 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 10.48, 29.13, 32.06, 35.77, 64.12, 77.79, 126.08, 137.15, 143.00, 158.26, 165.41;

IR (thin film, cm^{-1}): 2693 vs, 1412 vs, 1221 vs;

Mass spectrum *m/z* (% rel intensity): 507 M^+ (<1), 452 (29), 247 (20), 218 (22), 183 (43), 57 (100);

Anal calcd for $C_{34}H_{53}NO_2$: C, 80.42; H, 10.52; N, 2.76. Found: C, 80.57; H, 10.52; N, 2.83;



284k

Imine 284k: Imine was prepared by the standard procedure. The crude product was crystallized from 1:10 EtOAc/hexane.

Spectral data for **284k**: White solid, mp 121-124 °C.

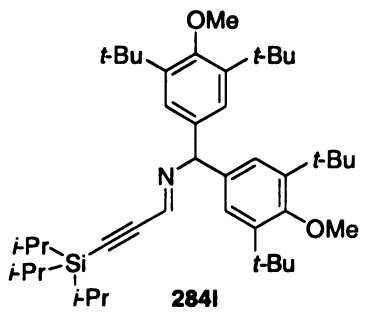
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 9H), 1.41 (s, 36H), 3.70 (s, 6H), 5.27 (s, 1H), 7.12 (s, 4H), 7.79 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 27.19, 32.08, 35.78, 36.28, 64.10, 76.71, 126.01, 137.30, 142.84, 158.14, 171.42;

IR (thin film, cm^{-1}): 2959 vs, 1414 vs, 1221 vs;

Mass spectrum *m/z* (% rel intensity): 535 M^+ (<1), 453 (25), 451 (100), 218 (55), 197 (22), 183 (89);

Anal calcd for $C_{36}H_{57}NO_2$: C, 80.69; H, 10.72; N, 2.61. Found: C, 80.82; H, 11.16; N, 2.66;



284l

Imine 284l: Imine was prepared by the standard procedure. The crude product was crystallized from 1:30 EtOAc/hexane, 78% yield.

Spectral data for **284l**: White solid, mp 145-147 °C.

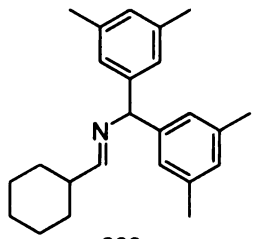
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 21H), 1.40 (s, 36H), 3.68 (s, 6H), 6.28 (s, 1H), 7.67 (s, 4H), 7.67 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 11.13, 18.65, 32.05, 35.75, 64.10, 73.19, 98.95, 100.66, 126.10, 136.66, 140.93, 143.23, 158.47;

IR (thin film, cm^{-1}): 2959 vs, 2869 vs, 1412 vs, 1221 vs;

Mass spectrum *m/z* (% rel intensity): 660 M^+ (<1), 451 (9), 183 (10), 155 (100), 108 (30);

Anal calcd for $C_{43}H_{69}NO_2Si$: C, 78.24; H, 10.54; N, 2.12. Found: C, 78.62; H, 10.97; N, 2.15;



286a

Imine 286a: Imine was prepared by the standard procedure except that 1.05 equivalent of aldehyde was used. The crude product was crystallized from 1:100 EtOAc/hexane, 63% yield.

Spectral data for **286a**: White solid, mp 87-88 °C.

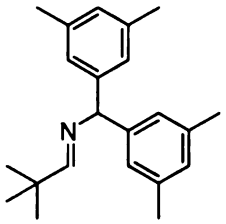
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21-1.34 (m, 6H), 1.68-1.86 (m, 5H), 2.27 (s, 12H), 5.14 (s, 1H), 6.84 (s, 2H), 6.92 (s, 4H), 7.62 (d, J = 5.5 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.32, 25.38, 25.99, 29.74, 43.47, 78.29, 125.25, 128.36, 137.65, 144.10, 168.64;

IR (thin film, cm^{-1}): 2924 vs, 1665 vs, 1599 vs, 1449 vs;

Mass spectrum *m/z* (% rel intensity): 333, M^+ (4), 266 (43), 265 (38), 223 (100), 208 (45), 193 (66), 179 (14);

Anal calcd for $C_{23}H_{31}N$: C, 86.43; H, 9.37; N, 4.20. Found: C, 86.34; H, 9.52; N, 4.19;



286b

Imine 286b: Imine was prepared by the standard procedure except that 1.1 equivalent of aldehyde was use. The crude product was a viscous oil and was purified by drying under high vacuum (~ 0.2 mm Hg) for 48 hours to remove excess of aldehyde, 100% crude yield.

Spectral data for **286b**: Viscous oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 9H), 2.31 (s, 12H), 5.20 (s, 1H), 6.87 (s, 2H), 6.97 (s, 4H), 7.68 (s, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.38, 27.02, 36.33, 77.67, 125.25, 128.33, 137.59, 144.39, 171.11;

IR (thin film, cm^{-1}): 2961 vs, 1664 vs, 1599 vs;

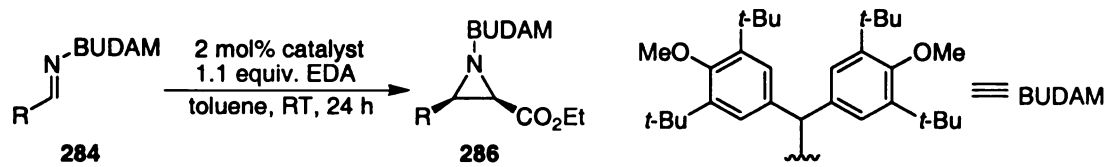
Mass spectrum *m/z* (% rel intensity): 307 M+ (<1), 208 (19), 223 (100), 193 (43), 178 (15), 103 (14);

Anal calcd for $C_{22}H_{29}N$: C, 85.94; H, 9.51; N, 4.56. Found: C, 85.64; H, 9.83; N, 4.50;

Preparation of N-BUDAM Aziridines

Typical experimental procedure for the aziridination reaction:

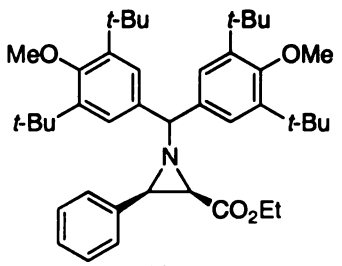
Preparation of VAPOL-borate catalyst: To a flame dried Schlenk flask cooled under argon was added triphenyl borate (45 mg, 0.16 mmol) and *S*-VAPOL (22 mg, 0.04 mmol), followed by 2 mL of dry toluene. The flask was sealed under argon and the solution was stirred at 80 °C for 1 hour. A partial vacuum was then applied to the flask and the solvent was removed slowly. After complete removal of solvent, the catalyst was heated under high vacuum (~ 0.2 mm Hg) at 80 °C for 0.5 hour to remove the volatile material. The prepared catalyst was then dissolved in toluene and transferred to the reaction flask.



284 286

Typical asymmetric aziridination procedure: To a flame-dried 25 mL round bottom flask cooled under argon was added imine **284** (2 mmol). The catalyst prepared as above was dissolved in 2 × 4 mL dry toluene and transferred via syringe to the flask containing imine. The resulting orange solution was allowed to be stirred at room temperature for 5 minutes, then EDA (250 μL, 2.25 mmol) was added via syringe in once. Vigorous bubbling was observed after 3-5 minutes. The solution was then stirred at room temperature for 24 hours. The reaction was quenched by addition of 15 mL hexane. Removal of solvent afforded the crude product. The cis/trans ratios of aziridine were determined by comparing the ^{1}H NMR integration values for the relative aziridine methane protons. The cis- (7-8 Hz) and the trans- (2-3 Hz) coupling constants were

used to differentiate the two isomers. Acyclic enamine products were also determined by ^{1}H NMR of the crude mixture by N-H proton integration relative to the integration of the aziridine methane protons. The crude aziridine was purified by silica gel chromatography, elution with the appropriate solvent to afford product. The enantiomeric excess was determined by HPLC on a chiral column.



285a

Cis-aziridine 285a: The standard aziridination procedure with 2 mol% *S*-VAPOL catalyst was employed. The crude reaction mixture was purified by flash chromatography and eluted with 20:1 hexane/EtOAc. Product **285a** was isolated as a white solid (1.259 g, 1.96 mmol), 98% yield. An optical purity of 99% ee was determined by HPLC analysis. HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225nm, 99:1 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor (*2S*, *3S*)-enantiomer was 5.15 min and that of the major (*2R*, *3R*)-enantiomer was 9.3 min.

Spectral data for **285a**: White solid; mp 156-158 °C; R_f = 0.26 (20:1 hexane/EtOAc), $[\alpha]_D$ = -16.1 (c = 1.0, CH_2Cl_2) on 99 % ee (*2R*, *3R*)-**285a** from *S*-VAPOL;

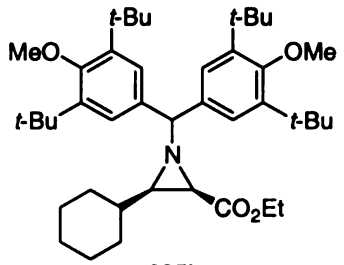
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.99 (t, J = 7.1 Hz, 3H), 1.34 (s, 18H), 1.43 (s, 18H), 2.67 (d, J = 6.9 Hz, 1H), 3.19 (d, J = 6.9 Hz, 1H), 3.61 (s, 3H), 3.68 (s, 3H), 3.85 (s, 1H), 3.90-3.96 (m, 2H), 7.19-7.28 (m, 3H), 7.35 (s, 2H), 7.45 (s, 2H), 7.50 (m, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.93, 32.02, 32.11, 35.67, 35.75, 46.33, 48.77, 60.49, 63.90, 63.98, 77.21, 125.32, 125.43, 127.22, 127.55, 128.12, 135.29, 136.68, 136.83, 142.96, 143.03, 158.20, 168.24 (one aryl carbon not located);

IR (thin film, cm^{-1}) 2961 vs, 1750 vs, 1414 vs, 1202 vs;

Mass spectrum: m/z (% rel intensity) 641 M^+ (1), 568 (3), 453 (70), 451 (100), 421 (27), 379 (20), 116 (23);

Anal calcd for $C_{42}H_{59}NO_4$: C, 78.58; H, 9.26; N, 2.18. Found: C, 78.41; H, 9.09; N, 2.18;



285b

Cis-aziridine 285b: The aziridination was conducted with 1 mmol of imine **283b** and 4 mol% *S*-VAPOL catalyst. The crude reaction mixture was purified by flash chromatography and eluted with 30:1 hexane/EtOAc. Product **285b** was isolated as a white solid (1.136 g, 1.76 mmol), 88% yield. An optical purity of 89% ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225nm, 99.7:0.3 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor (*2S*, *3S*)-enantiomer was 4.51 min and that of the major (*2R*, *3R*)-enantiomer was 5.44 min.

Spectral data for **285b**: White amorphous solid; mp 48-52 °C; R_f = 0.25 (30:1 hexane/EtOAc), $[\alpha]_D$ = 67.3 (*c* = 1.0, EtOAc) on 89 % ee (*2R*, *3R*)-**285b** from *S*-VAPOL;

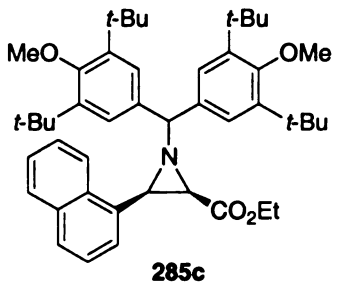
^1H NMR ($CDCl_3$, 300 MHz) δ = 0.82-1.64 (m, 11H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 18H), 1.37 (s, 18H), 1.74-1.79 (m, 1H), 2.24 (d, *J* = 6.8 Hz, 1H), 3.50 (s, 1H), 3.60 (s, 3H), 3.63 (s, 3H), 4.08-4.25 (m, 2H), 7.07 (s, 2H), 7.30 (s, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 14.27, 25.23, 25.55, 26.20, 30.12, 31.20, 31.99, 32.09, 35.60, 35.70, 36.28, 43.25, 52.38, 60.53, 64.01, 64.12, 77.90, 125.52, 126.66, 136.19, 136.92, 142.70, 142.82, 158.18, 158.88, 170.02;

IR (thin film, cm^{-1}) 2959 vs, 1414 vs, 1221 vs, 1179 vs;

Mass spectrum: m/z (% rel intensity) 647 M^+ (8), 590 (3), 564 (27), 451 (100), 421 (29), 391 (11), 379 (25), 183 (37);

Anal calcd for $C_{42}H_{65}NO_4$: C, 77.85; H, 10.11; N, 2.16. Found: C, 7.91; H, 10.48; N, 2.15;



285c

Cis-aziridine 285c: The standard aziridination procedure with 2 mol% *S*-VAPOL catalyst was employed. The imine was used as a mixture of imine **285c** and trapped hexane solvent (4:1) which is of 96.5% chemical purity. The crude reaction mixture was purified by flash chromatography and eluted with 15:1 hexane/EtOAc. Product **285c** was isolated as a white solid (1.293 g, 1.86 mmol), 96% yield based on starting material. An optical purity of 99% ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225 nm, 90:10 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor (*2S*, *3S*)-enantiomer was 4.01 min and that of the major (*2R*, *3R*)-enantiomer was 8.00 min.

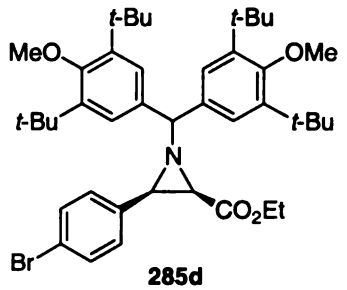
Spectral data for **285c**: White amorphous solid; mp 64-120 °C; R_f = 0.25 (15:1 hexane/EtOAc), $[\alpha]_D$ = -22.3 (*c* = 1.0, CH_2Cl_2) on 99% ee (*2R*, *3R*)-**285a** from *S*-VAPOL; ^1H NMR ($CDCl_3$, 300 MHz) δ = 0.70 (t, *J* = 7.1 Hz, 3H), 1.45 (s, 18H), 1.49 (s, 18H), 2.98 (d, *J* = 6.6 Hz, 1H), 3.67 (s, 3H), 3.74 (s, 3H), 3.73-3.81 (m, 3H), 4.04 (s, 1H), 7.42-7.52 (m, 3H), 7.50 (s, 2H), 7.55 (s, 2H), 7.75 (d, *J* = 8 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.61, 32.09, 32.14, 35.72, 35.78, 45.92, 47.03, 60.21, 63.93, 64.01, 77.82, 122.94, 125.07, 125.37, 125.76, 125.84, 127.05, 127.51, 128.51, 130.76, 131.56, 133.06, 136.66, 136.93, 143.13, 158.29, 158.45, 168.21 (two aryl carbons not located);

IR (thin film, cm^{-1}) 2961 vs, 1414 vs, 1221 vs;

Mass spectrum: m/z (% rel intensity) 691 M^+ (<1), 453 (36), 451 (100), 379 (6), 193 (6), 167 (23);

Anal calcd for $C_{46}H_{61}NO_4$: C, 79.84; H, 8.89; N, 2.02. Found: C, 79.93; H, 8.93; N, 1.86;



285d

Cis-aziridine 285d: The standard aziridination procedure using 2 mol% *S*-VAPOL catalyst was employed. The crude reaction mixture was purified by flash chromatography and eluted with 20:1 hexane/EtOAc. Product **285d** was isolated as a white solid (1.42 g, 1.97 mmol), 99 % yield. An optical purity of 99% ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225 nm, 99:1 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor (*2S*, *3S*)-enantiomer was 5.43 min and that of the major (*2R*, *3R*)-enantiomer was 9.15 min.

Spectral data for **285d**: White solid; mp 146-148 °C; R_f = 0.32 (20:1 hexane/EtOAc), $[\alpha]_D$ = 3.0 (*c* = 1.0, CH_2Cl_2) on 99 % ee (*2S*, *3S*)-**285d** from *R*-VAPOL;

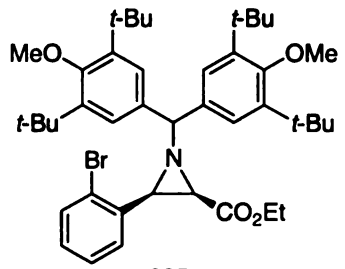
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.02 (t, *J* = 6.9 Hz, 3H), 1.33 (s, 18H), 1.41 (s, 18H), 2.67 (d, *J* = 6.6 Hz, 1H), 3.12 (d, *J* = 6.6 Hz, 1H), 3.61 (s, 3H), 3.67 (s, 3H), 3.84 (s, 1H), 3.91-3.97 (m, 2H), 7.30 (s, 2H), 7.37 (s, 4H), 7.41 (s, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.99, 32.03, 32.11, 35.69, 35.77, 46.33, 48.04, 60.61, 63.93, 63.98, 77.15, 121.21, 125.29, 125.38, 129.88, 130.68, 134.44, 136.40, 136.62, 143.11, 158.29, 158.33, 169.88 (one aryl carbon not located);

IR (thin film, cm^{-1}) 2691 vs, 1740 vs, 1412 vs, 1221 vs;

Mass spectrum: m/z (% rel intensity) 721 (M^+, ^{81}Br, <1), 719 (M^+, ^{79}Br, <1), 453 (^{81}Br, 51), 451 (^{79}Br, 100), 421 (13), 379 (12)

Anal calcd for $C_{42}H_{58}BrNO_4$: C, 69.98; H, 8.11; N, 1.94. Found: C, 70.05; H, 8.10; N, 1.95;



285e

Cis-aziridine 285e: The standard aziridination procedure with 2 mol% *S*-VAPOL catalyst was employed. The crude reaction mixture was precipitated on 6 g silica gel and purified by gravity column and eluted with 30 to 20:1 hexane/EtOAc. Product **285e** was isolated as a white solid (1.212 g, 1.68 mmol), 84 % yield. An optical purity of 96 % ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225 nm, 99:1 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor enantiomer was 4.70 min and that of the major (*2R*, *3R*)-enantiomer was 8.31 min.

Spectral data for **285e**: White solid; mp 120-121 °C; R_f = 0.25 (25:1 hexane/EtOAc), $[\alpha]_D$ = 11.5 (*c* = 1.0, CH_2Cl_2) on 96 % ee (*2R*, *3R*)-**285e** from *S*-VAPOL;

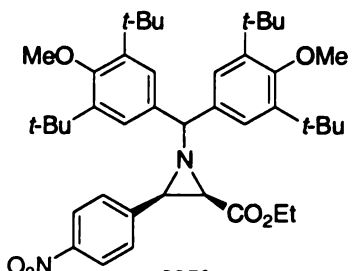
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.94 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 18H), 1.39 (s, 18H), 2.76 (d, *J* = 6.6 Hz, 1H), 3.31 (d, *J* = 6.6 Hz, 1H), 3.60 (s, 3H), 3.65 (s, 3H), 3.88 (s, 1H), 3.85-3.92 (m, 2H), 7.05-7.08 (m, 1H), 7.18-7.24 (m, 1H), 7.34 (s, 2H), 7.38 (s, 2H), 7.35-7.40 (m, 1H), 7.73 (dd, *J* = 7.7, 1.6 Hz, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.88, 32.06, 32.09, 35.70, 35.75, 45.68, 49.45, 60.44, 63.95, 63.99, 77.24, 123.35, 125.26, 125.57, 126.40, 128.69, 131.36, 131.52, 134.75, 136.48, 136.72, 143.11, 143.14, 158.26, 167.94 (one aryl carbon not located);

IR (thin film, cm^{-1}) 2961 vs, 1751 vs, 1414 vs, 1221 vs, 1200 vs;

Mass spectrum: m/z (% rel intensity) 721 (M^+, ^{81}Br, <1), 719 (M^+, ^{79}Br, <1), 453 (^{81}Br, 81), 451 (^{79}Br, 100), 421 (20), 379 (14);

Anal calcd for $C_{42}H_{58}BrNO_4$: C, 69.98; H, 8.11; N, 1.94. Found: C, 69.85; H, 7.98; N, 1.78;



285f

Cis-aziridine 285f: The standard aziridination procedure with 2 mol% *S*-VAPOL catalyst was employed. The crude reaction mixture was purified by flash chromatography and eluted with 15-12:1 hexane/EtOAc. Product **285f** was isolated as a white solid (1.325 g, 1.92 mmol), 96% yield. An optical purity of 96% ee was determined by HPLC analysis. HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225 nm, 96:4 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor (*2S*, *3S*)-enantiomer was 7.09 min and that of the major (*2R*, *3R*)-enantiomer was 9.04 min.

Spectral data for **285f**: White solid; mp 143-145 °C; R_f = 0.23 (12:1 hexane/EtOAc), $[\alpha]_D$ = -14.7 (*c* = 1.0, CH_2Cl_2) on 96 % ee (*2R*, *3R*)-**285f** from *S*-VAPOL;

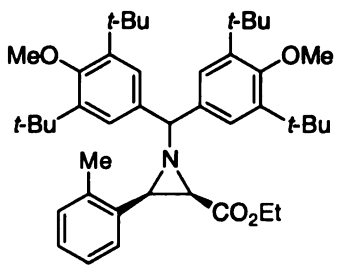
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.02 (t, J = 7.1 Hz, 3H), 1.33 (s, 18H), 1.41 (s, 18H), 2.79 (d, J = 6.7 Hz, 1H), 3.24 (d, J = 6.7 Hz, 1H), 3.60 (s, 3H), 3.68 (s, 3H), 3.88 (s, 1H), 3.90-3.96 (m, 2H), 7.29 (s, 2H), 7.40 (s, 2H), 7.67 (d, J = 8.8 Hz, 2H), 8.13 (d, J = 8.8 Hz, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.99, 32.01, 32.08, 35.69, 35.76, 46.85, 47.71, 60.81, 63.94, 63.99, 77.06, 122.79, 125.19, 125.27, 129.05, 136.09, 136.31, 142.93, 143.25. 147.24, 158.37, 158.44, 167.32 (one aryl carbon not located);

IR (thin film, cm^{-1}) 2963 vs, 1748 vs, 1524 vs, 1412 vs;

Mass spectrum: m/z (% rel intensity) 687 M^+ (1), 453 (58), 451 (100), 421 (13), 391 (4), 233 (7);

Anal calcd for $C_{42}H_{58}N_2O_6$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.56; H, 8.61; N, 4.13;



285g

Cis-aziridine 285g: The standard aziridination procedure with 2 mol% S-VAPOL catalyst was employed. The crude reaction mixture was purified by gravity chromatography and eluted with 15:1 hexane/EtOAc. Product **285g** was isolated as a foam-like white solid (1.275 g, 1.94 mmol), 97% yield. An optical purity of 99 % ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225nm, 99:1 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor (*2S*, *3S*)-enantiomer was 4.47 min and that of the major (*2R*, *3R*)-enantiomer was 8.20 min.

Spectral data for **285g**: White foam-like solid; mp 144-147 °C; R_f = 0.29 (15:1 hexane/EtOAc), $[\alpha]_D$ = 18.0 (c = 1.0, $CHCl_3$) on 99 % ee (*2R*, *3R*)-**285g** from *S*-VAPOL;

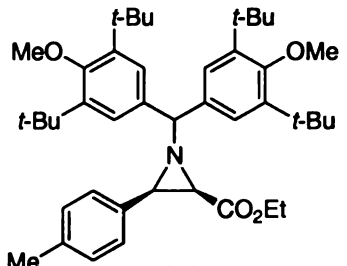
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.87 (t, *J* = 7.1 Hz, 3H), 1.37 (s, 18H), 1.40 (s, 18H), 2.29 (s, 3H), 2.69 (d, *J* = 6.6 Hz, 1H), 3.16 (d, *J* = 6.6 Hz, 1H), 3.61 (s, 3H), 3.66 (s, 3H), 3.81 (s, 1H), 3.78-3.91 (m, 2H), 7.01-7.11 (m, 3H), 7.39 (s, 2H), 7.42 (s, 2H), 7.68-7.71 (m, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.79, 18.78, 32.09, 32.12, 35.72, 35.77, 45.37, 47.60, 60.29, 63.90, 63.98, 77.73, 125.04, 125.29, 125.63, 127.02, 129.01, 129.12, 133.46, 135.98, 136.84, 137.02, 143.07, 158.20, 158.36, 168.46 (one aryl carbon not located);

IR (thin film, cm^{-1}) 2961 vs, 1414 vs, 1221 vs;

Mass spectrum: m/z (% rel intensity) 655 M^+ (2), 453 (68), 421 (20), 379 (16), 131 (27);

Anal calcd for $C_{43}H_{61}NO_4$: C, 78.73; H, 9.37; N, 2.14. Found: C, 78.87; H, 9.75; N, 2.04;



285h

Cis-aziridine 285h: The standard aziridination procedure with 2 mol% *S*-VAPOL catalyst was employed. The crude reaction mixture was precipitated on 6 g of silica gel and purified by flash chromatography and eluted with 25:1 hexane/EtOAc. Product **285h** was isolated as a white foam-like solid (1.249 g, 1.90 mmol), 95% yield. An optical purity of 99% ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225 nm, 98:2 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor (*2S*, *3S*)-enantiomer was 4.81 min and that of the major (*2R*, *3R*)-enantiomer was 8.72 min.

Spectral data for **285h**: White solid; mp 152-155 °C; R_f = 0.21 (25:1 hexane/EtOAc), $[\alpha]_D$ = 11.8 (*c* = 1.0, $CHCl_3$) on 99 % ee (*2R*, *3R*)-**285h** from *S*-VAPOL;

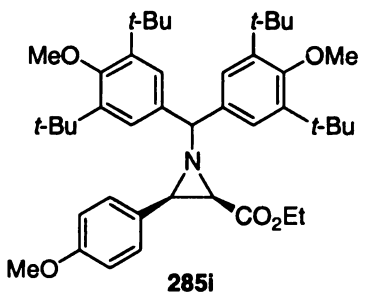
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.02 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 18H), 1.43 (s, 18H), 2.39 (s, 3H), 2.64 (d, *J* = 6.6 Hz, 1H), 3.17 (d, *J* = 6.6 Hz, 1H), 3.62 (s, 3H), 3.69 (s, 3H), 3.84 (s, 1H), 3.90-3.99 (m, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 7.36 (s, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.44 (s, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.97, 21.09, 32.05, 32.12, 35.67, 35.75, 46.18, 48.76, 60.14, 63.89, 63.96, 77.30, 125.37, 125.51, 128.01, 128.25, 132.30, 136.74, 136.89, 142.93, 143.00, 158.21, 168.30 (two aryl carbons not located);

IR (thin film, cm^{-1}) 2961 vs, 1412 vs, 1221 vs, 1220 vs;

Mass spectrum: m/z (% rel intensity) 655 M^+ (<1), 452 (68), 233 (5), 204 (15);

Anal calcd for $C_{43}H_{61}NO_4$: C, 78.73; H, 9.37; N, 2.14. Found: C, 78.82; H, 9.26; N, 2.24;



285i

Cis-aziridine 285i: The standard aziridination procedure with 2 mol% *S*-VAPOL catalyst was employed. Crude mixture was precipitated on 6 g of Et_3N buffered silica gel, purified by flash chromatography with Et_3N buffered silica gel and eluted with 15:1 hexane/EtOAc. Product **285i** was isolated as a white solid (1.164 g, 1.74 mmol), 87% yield. An optical purity of 98% ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225nm, 95:5 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor (*2S, 3S*)-enantiomer was 5.44 min and that of the major (*2R, 3R*)-enantiomer was 9.21 min.

Spectral data for **285i**: White solid; mp 160-162 °C; R_f = 0.23 (15:1 hexane/EtOAc), $[\alpha]_D$ = 8.6 (*c* = 1.0, CH_2Cl_2) on 98 % ee (*2R, 3R*)-**285i** from *S*-VAPOL;

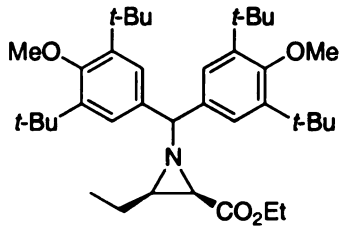
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.02 (t, *J* = 7.1 Hz, 3H), 1.33 (s, 18H), 1.42 (s, 18H), 2.61 (d, *J* = 6.6 Hz, 1H), 3.14 (d, *J* = 6.6 Hz, 1H), 3.61 (s, 3H), 3.67 (s, 3H), 3.75 (s, 3H), 3.83 (s, 1H), 3.91-3.97 (m, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 7.33 (s, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.43 (s, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 14.00, 32.05, 32.12, 35.69, 35.75, 46.25, 48.48, 55.16, 60.43, 63.90, 63.98, 77.24, 113.05, 125.38, 125.48, 127.48, 129.22, 136.71, 136.87, 142.94, 143.03, 158.21, 158.93, 168.33 (one aryl carbon not located);

IR (thin film, cm^{-1}) 2961 vs, 1414 vs, 1221 vs;

Mass spectrum: m/z (% rel intensity) 671 M^+ (<1), 452 (100), 421 (11), 339 (15), 220 (30), 173 (12);

Anal calcd for $C_{43}H_{61}NO_5$: C, 76.86; H, 9.15; N, 2.08. Found: C, 76.60; H, 8.99; N, 2.08;



285j

Cis-aziridine 285j: The standard aziridination procedure with 2 mol% *S*-VAPOL catalyst was employed. Crude mixture was purified by gravity chromatography and eluted with 25:1 hexane/EtOAc. Product **285j** was isolated as a viscous oil (736 mg, 1.24 mmol), 62% yield. An optical purity of 93% ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225nm, 99.9:0.1 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor (*2S*, *3S*)-enantiomer was 6.98 min and that of the major (*2R*, *3R*)-enantiomer was 7.91 min.

Spectral data for **285j**: Viscous oil; R_f = 0.23 (20:1 hexane/EtOAc), $[\alpha]_D$ = 66.3 (*c* = 1.0, EtOAc) on 93 % ee (*2R*, *3R*)-**285j** from *S*-VAPOL;

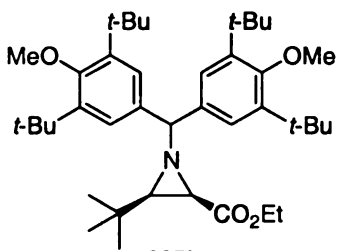
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.72 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.37 (s, 18 H), 1.38 (s, 18H), 1.51-1.65 (m, 2H), 2.04 (dd, *J* = 6.7 Hz, 13.2 Hz, 1H), 2.29 (d, *J* = 6.7 Hz, 1H), 3.61 (s, 1H), 3.63 (s, 3H), 3.64 (s, 3H), 4.12-4.19 (m, 2H), 7.13 (s, 2H), 7.28 (s, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 11.33, 14.29, 21.29, 32.05, 32.08, 35.66, 35.69, 43.13, 48.89, 60.59, 63.99, 64.05, 77.33, 125.55, 126.11, 136.25, 136.90, 142.79, 142.85, 158.20, 158.56, 169.87;

IR (thin film, cm^{-1}) 2961 vs, 1748 vs, 1180 vs;

Mass spectrum: m/z (% rel intensity) 594 M^+ (<1), 453 (13), 452 (54), 218 (22), 197 (13), 183 (31), 57 (100);

Anal calcd for $C_{38}H_{59}NO_4$: C, 76.85; H, 10.01; N, 2.36. Found: C, 76.75; H, 10.18; N, 2.30;



285k

Cis-aziridine 285k: The aziridination reaction was conducted with 1 mmol imine **285k** and 10 mol% *S*-VANOL catalyst. A 95% conversion of starting material was determined by ^{1}H NMR. The crude reaction mixture was purified by gravity chromatography and eluted with 35:1 hexane/EtOAc. Product **285k** was isolated as a white amorphous solid (475 mg, 0.76 mmol), 76 % yield. An optical purity of 80% ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225nm, 99.8:0.2 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor (*2S*, *3S*)-enantiomer was 4.65 min and that of the major (*2R*, *3R*)-enantiomer was 5.76 min.

Spectral data for **285k**: White amorphous solid; mp 42-48 °C; R_f = 0.3 (35:1 hexane/EtOAc), $[\alpha]_D$ = 58.2 (*c* = 1.0, $CHCl_3$) on 80 % ee (*2R*, *3R*)-**285k** from *S*-VANOL;

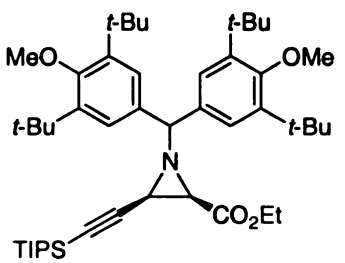
^1H NMR ($CDCl_3$, 300 MHz) δ = 0.66 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.38 (s, 18H), 1.41 (s, 18H), 1.63 (d, *J* = 7.1 Hz, 1H), 2.15 (d, *J* = 7.1 Hz, 1H), 3.39 (s, 1H), 3.60 (s, 3H), 3.64 (s, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 7.24 (s, 2H), 7.47 (s, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 14.12, 27.49, 31.64, 32.09, 32.17, 35.67, 35.75, 43.37, 56.18, 60.47, 63.99, 64.15, 79.47, 125.49, 126.33, 136.72, 137.86, 142.84, 158.04, 158.56, 169.96 (one aryl carbon not located);

IR (thin film, cm^{-1}) 2959 vs, 1750 vs, 1221 vs;

Mass spectrum: m/z (% rel intensity) 622 M^+ (1), 453 (54), 451 (100), 379 (11), 183 (11);

Anal calcd for $C_{40}H_{63}NO_4$: C, 77.25; H, 10.21; N, 2.25. Found: C, 77.36; H, 10.36; N, 2.22;



285l

Cis-aziridine 285l: The standard aziridination procedure with 2 mol% *S*-VAPOL catalyst was employed. The crude reaction mixture was purified by gravity chromatography and eluted with 40:1 hexane/EtOAc. Product **285l** was isolated as a white amorphous solid (1.44 g, 1.94 mmol), 97% yield. An optical purity of 83 % ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225 nm, 99.8:0.2 hexane/iPrOH as eluent at 1 mL/min. The retention time for the major (*2R*, *3R*)-enantiomer was 5.11 min and that of the minor (*2S*, *3S*)-enantiomer was 5.88 min.

Spectral data for **285l**: White amorphous solid; mp 50-56 °C; R_f = 0.24 (40:1 hexane/EtOAc), $[\alpha]_D$ = -14.7 (*c* = 1.0, CH_2Cl_2) on 83 % ee (*2R*, *3R*)-**285l** from *S*-VAPOL;

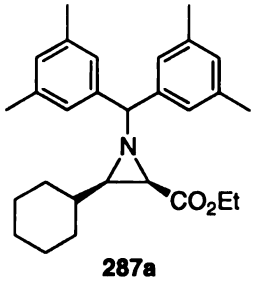
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.03 (s, 18H), 1.04 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.37 (s, 18H), 1.38 (s, 18H), 2.52 (d, *J* = 6.7 Hz, 1H), 2.62 (d, *J* = 6.7 Hz, 1H), 3.64 (s, 3H), 3.65 (s, 3H), 3.66 (s, 1H), 4.11-4.22 (m, 2H), 7.25 (s, 2H), 7.26 (s, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 11.16, 14.21, 18.55, 32.09, 32.12, 35.45, 35.73, 45.07, 61.03, 64.00, 64.02, 76.68, 83.66, 102.36, 125.57, 125.60, 135.86, 135.96, 143.00, 143.10, 158.44, 167.1 (one aryl carbon not located);

IR (thin film, cm^{-1}) 2961 vs, 2867 vs, 1414 vs, 1221 vs;

Mass spectrum: m/z (% rel intensity) 746 M^+ (2), 745 (5), 658 (2), 453 (36), 451 (100), 421 (18), 380 (14);

Anal calcd for $C_{47}H_{75}NO_4Si$: C, 75.65; H, 10.13; N, 1.88. Found: C, 75.45; H, 10.34; N, 1.90;



287a

Cis-aziridine 287a: The standard aziridination procedure was employed except that 1 mmol imine **286a** and 4 mol% *S*-VAPOL catalyst was used. The crude reaction mixture was precipitated on 3 g of silica gel and purified by gravity chromatography, eluted with

20:1 hexane/EtOAc. Product **287a** was isolated as a viscous oil (364 mg, 0.87 mmol), 87 % yield. An optical purity of 91 % ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R, R) Whelk-O 1 column, 225nm, 99:1 hexane/iPrOH as eluent at 1 mL/min. The retention time for the major (*2R*, *3R*)-enantiomer was 5.6 min and that of the minor (*2S*, *3S*)-enantiomer was 6.7 min.

Spectral data for **287a**: Viscous oil; R_f = 0.23 (20:1 hexane/EtOAc), $[\alpha]_D$ = 126.4 (*c* = 1.0, $CHCl_3$) on 91 % ee (*2R*, *3R*)-**287a** from *S*-VAPOL;

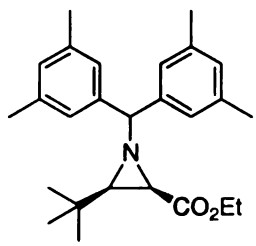
^1H NMR ($CDCl_3$, 300 MHz) δ = 0.48-0.62 (m, 1H), 0.95-1.65 (m, 10H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.77-1.82 (m, 1H), 2.24 (d, *J* = 6.9 Hz, 1H), 2.26 (s, 6H), 2.27 (s, 6H), 3.46 (s, 1H), 4.17-4.26 (m, 2H), 6.85 (s, 2H), 6.96 (s, 2H), 7.13 (s, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 14.20, 21.12, 21.21, 25.28, 25.48, 26.08, 30.04, 30.74, 36.25, 43.32, 52.14, 60.47, 78.28, 124.79, 126.01, 128.37, 128.92, 137.39, 137.53, 142.23, 142.50, 169.64;

IR (thin film, cm^{-1}) 2926 vs, 1746, 1181 vs;

Mass spectrum: m/z (% rel intensity) 419 M^+ (<1), 224 (100), 223 (100), 196 (53), 178 (13), 102 (27);

Anal calcd for $C_{28}H_{37}NO_2$: C, 80.15; H, 8.89; N, 3.34. Found: C, 80.09; H, 9.24; N, 3.30;



287b

Cis-aziridine 287b: The aziridination reaction was conducted with 1 mmol imine **286b** and 10 mol% *S*-VAPOL catalyst. The crude reaction mixture was precipitated on 3 gram of silica gel and purified by gravity chromatography and eluted with 25:1 hexane/EtOAc.

Product **287b** was isolated as a viscous oil (371 mg, 0.94 mmol), 94 % yield. An optical purity of 96 % ee was determined by HPLC analysis.

HPLC conditions: Pirkle covalent (R,R) Whelk-O 1 column, 225nm, 99.5:0.5 hexane/iPrOH as eluent at 1 mL/min. The retention time for the major (*2R*, *3R*)-enantiomer was 6.6 min and that of the minor (*2S*, *3S*)-enantiomer was 7.5 min.

Spectral data for **287b**: Colorless viscous oil; R_f = 0.22 (25:1 hexane/EtOAc), $[\alpha]_D$ = 121.8 (*c* = 1.0, $CHCl_3$) on 96 % ee (*2R*, *3R*)-**287b** from *S*-VAPOL;

^1H NMR ($CDCl_3$, 300 MHz) δ = 0.71 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.71 (d, *J* = 7.1 Hz, 1H), 2.11 (d, *J* = 7.1 Hz, 1H), 2.27 (s, 6H), 2.29 (s, 6H), 3.42 (s, 1H), 4.06-4.26 (m, 2H), 6.84 (s, 2H), 7.00 (s, 2H), 7.28 (s, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 14.12, 21.24, 21.35, 27.45, 31.58, 43.31, 56.19, 60.47, 79.37, 125.02, 125.92, 128.42, 128.81, 137.45, 137.50, 142.64, 143.35, 169.91;

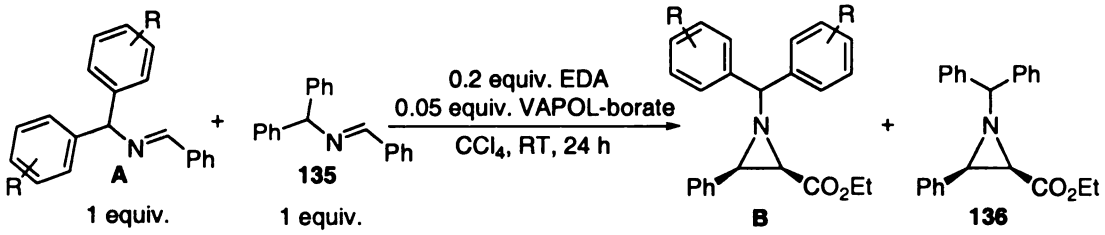
IR (thin film, cm^{-1}) 2956 vs, 1749 vs, 1186 vs;

Mass spectrum: m/z (% rel intensity) 393 M+ (<1), 224 (19), 223 (100), 193 (28), 170 (43), 142 (6);

Anal calcd for $C_{26}H_{35}NO_2$: C, 79.35; H, 8.96; N, 3.56. Found: C, 79.62; H, 9.32; N, 3.56;

Rate competition studies

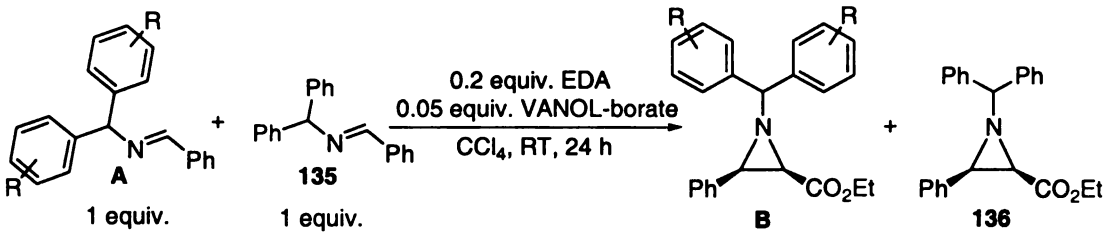
Rate competition studies with VAPOL-borate catalyst:



To a flame-dried 25 mL round bottom flask filled with argon was added 1 mmol of benzhydryl imine **135** and 1 mmol of imine **A**. The VAPOL-borate catalyst (0.05 mmol) prepared according to the standard procedure was dissolved in 4 mL of CCl_4 and transferred to the flask containing imines. Ethyl diazoacetate (0.2 mmol) was added via syringe in once. The mixture was stirred at room temperature for 24 hours. The reaction was worked up by addition of 10 mL of hexane, concentrated in vacuo. The ratio of the two aziridines (**B** vs. **136**) was determined by the ^1H NMR integration of the C-2 and C-3 methine protons of **B** and **136** in appropriate solvent.

entry	imine **A**	NMR solvent	δ of **136** (PPM)	δ of **B** (PPM)	**B** : **136**
1	**284a**	d6-benzene	2.61, 2.90	2.57, 2.87	16:1
2	**207**	$CDCl_3$	2.61, 3.51	2.69, 3.22	12:1
3	**167**	d6-benzene	2.49, 2.82	2.59, 2.92	10:1
4	**162**	d6-benzene	2.48, 2.82	2.54, 2.89	3.8:1
5	**161**	d6-benzene	2.48, 2.82	2.53, 2.86	2.3:1
6	**168**	d6-benzene	2.28, 2.55	2.48, 2.82	1.7:1
7	**165**	d6-benzene	5.36 (Ar_2CH)	5.49 (Ar_2CH)	1:1
8	**159**	d6-benzene	2.48, 2.82	2.40, 2.74	0.45:1
9	**160**	$CDCl_3$	2.76, 3.29	2.72, 3.24	0.28:1
10	**164**	$CDCl_3$	3.25	3.19	0.30:1
11	**166**	$CDCl_3$	3.37	2.72, 3.24	0.05:1
12	**270**	$CDCl_3$	3.25	3.16	0.03
13	**212**	d6-benzene	2.48, 2.82	2.35, 2.68	0.02

Rate competition studies with VANOL-borate catalyst:

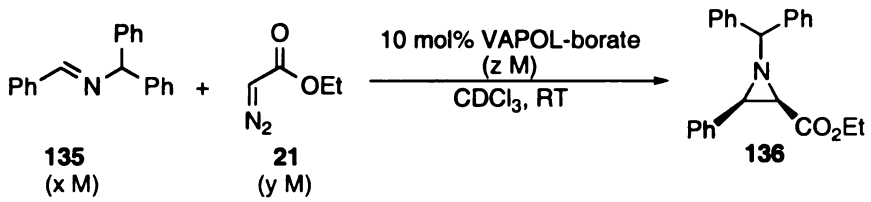


To a flame-dried 25 mL round bottom flask filled with argon was added 1 mmol of benzhydryl imine **135** and 1 mmol of imine **A**. The VANOL-borate catalyst (0.05 mmol) prepared according to the standard procedure was dissolved in 4 mL of CCl_4 and transferred to the flask containing imines. Ethyl diazoacetate (0.2 mmol) was added via syringe in once. The mixture was stirred at room temperature for 24 hours. The reaction was worked up by addition of 10 mL of hexane, concentrated in vacuo. The ratio of the two aziridines (**B** vs. **136**) was determined by the ^1H NMR integration of the C-2 and C-3 methine protons of **B** and **136** in appropriate solvent.

entry	imine **A**	NMR solvent	δ of **136** (PPM)	δ of **B** (PPM)	**B** : **136**
1	**167**	d6-benzene	2.49, 2.83	2.59, 2.92	8:1
2	**284a**	d6-benzene	2.49, 2.83	2.58, 2.88	6.5:1
3	**162**	d6-benzene	2.49, 2.83	2.54, 2.89	3:1
4	**160**	d6-benzene	2.49, 2.83	2.36, 2.71	1:5
5	**164**	d6-benzene	2.49, 2.83	2.87, 3.04	1:10
6	**166**	d6-benzene	2.49, 2.83	2.53, 2.98	1:10

Kinetic studies of catalytic aziridination

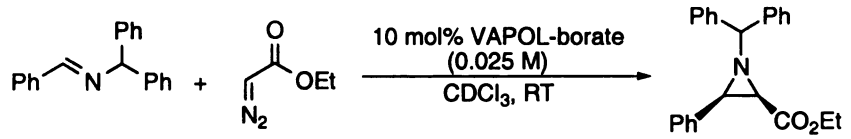
Typical experimental procedure for the kinetic studies:



135 (x M) **21** (y M) **136**

To a flame dried 25 mL round bottom flask cooled under argon was added imine **135** and Ph_3CH (final concentration of Ph_3CH = 0.25 M). The VAPOL-borate catalyst prepared according to the standard procedure was dissolved in appropriate amount of dry $CDCl_3$ (purified by filtered through basic alumina and stored over MS 4Å under argon), and transferred to the flask containing imine. After being stirred at room temperature for 3-5 minutes, the solution was transferred via syringe to an oven-dried NMR tube under argon atmosphere. Ethyl diazoacetate was added via syringe in once. The concentration of aziridine **136** was measured by ^1H NMR via integrations of the aziridine C-2, C-3 methine protons and the methine protons of Ph_3CH as in the kinetics of imine and catalyst, or measured by ^1H NMR via integrations of the aziridine C-2, C-3 methine protons and the imine CH protons as in the kinetics of EDA.

Initial rate kinetics of [imine]



135 0.125 M, 0.25 M, 0.5 M, 1.0 M

21 0.25 M

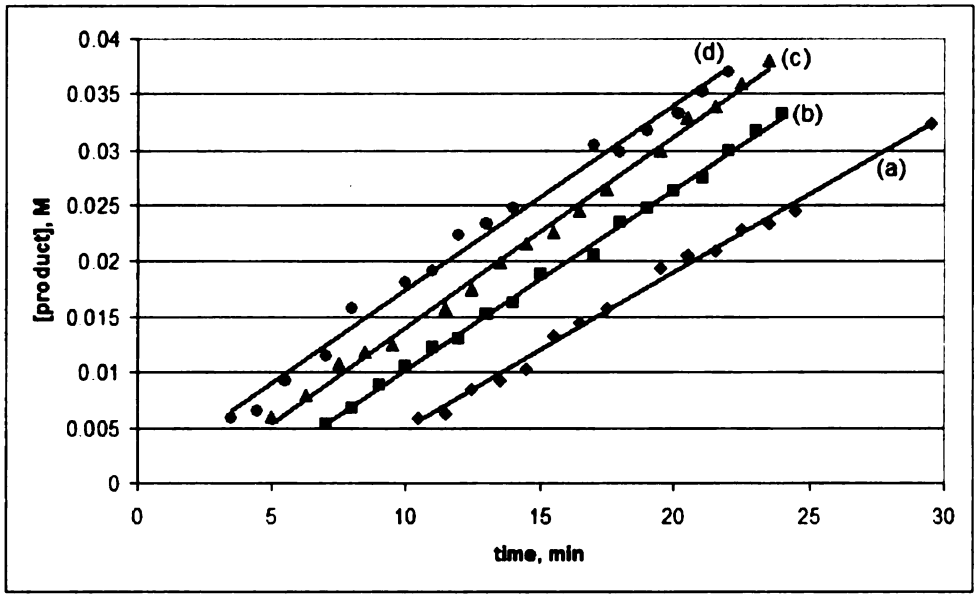
136

Concentration of product at various imine concentration:

[**135**] = 0.125 M		[**135**] = 0.25 M		[**135**] = 0.5 M		[**135**] = 1.0 M	
time (min)	[**136**] (M)	time (min)	[**136**] (M)	time (min)	[**136**] (M)	time (min)	[**136**] (M)
10.5	0.0058	7	0.0053	5	0.006	3.5	0.0058
11.5	0.0063	8	0.0068	6.25	0.008	4.5	0.0065
12.5	0.0085	9	0.0088	7.5	0.0108	5.5	0.0093
13.5	0.0093	10	0.0105	8.5	0.0118	7	0.0115
14.5	0.0103	11	0.0123	9.5	0.0125	8	0.0158
15.5	0.0133	12	0.013	11.5	0.0158	9	0.0188
16.5	0.0145	13	0.0153	12.5	0.0175	10	0.018
17.5	0.0158	14	0.0163	13.5	0.0198	11	0.019
18.5	0.0158	15	0.0188	14.5	0.0215	12	0.0223
19.5	0.0193	17	0.0205	15.5	0.0225	13	0.0233
20.5	0.0205	18	.0235	16.5	0.0245	14	0.0248
21.5	0.0208	19	0.0248	17.5	0.0265	17	0.0305
22.5	0.0228	20	0.0263	19.5	0.03	18	0.0298
23.5	0.0233	21	0.0275	20.5	0.033	19	0.0318
24.5	0.0245	22	0.03	21.5	0.034	20.17	0.0333
29.5	0.0325	23	0.0318	22.5	0.036	21	0.0353
		24	0.0333	23.5	0.038	22	0.037

Ph_3CH was used as internal standard for ^1H NMR integration, [Ph_3CH] = 0.25 M

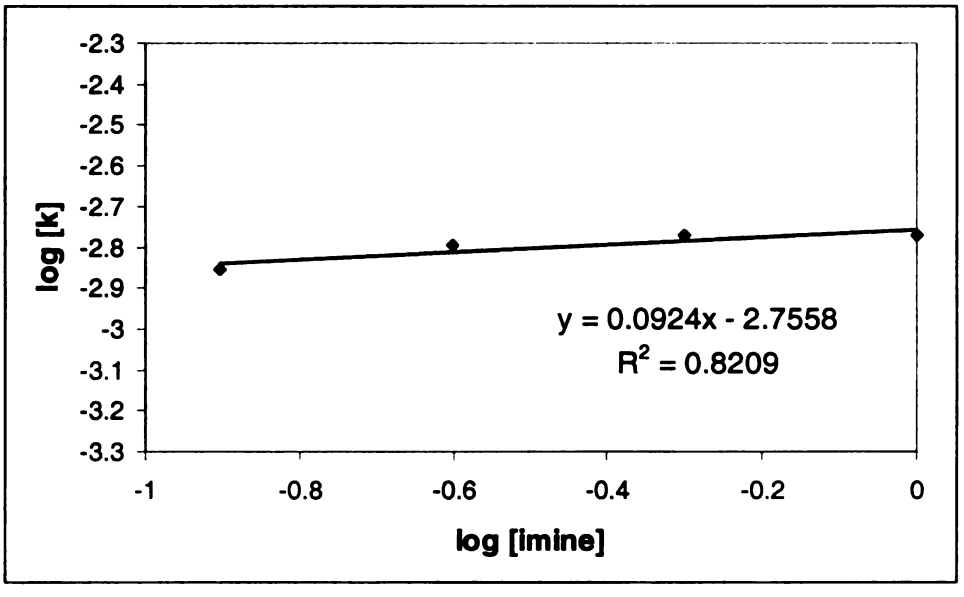
Reaction rate at various imine concentrations:



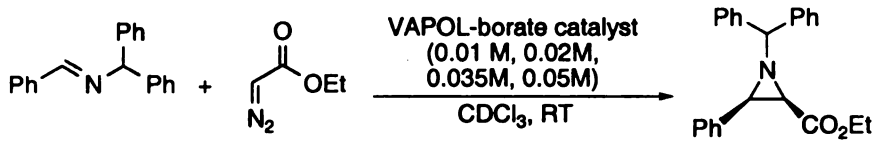
(a) [imine] = 0.125 M, y = 0.0014x - 0.0093, R^2 = 0.9936
(b) [imine] = 0.25 M, y = 0.0016x - 0.0061, R^2 = 0.9976
(c) [imine] = 0.50 M, y = 0.0017x - 0.0032, R^2 = 0.9957
(d) [imine] = 1.0 M, y = 0.0017x + 0.0006, R^2 = 0.9896

[imine]	log[imine]	k	log[k]
0.125	-0.903	0.0014	-2.854
0.25	-0.602	0.0016	-2.796
0.5	-0.301	0.0017	-2.770
1	0	0.0017	-2.770

Initial Reaction rate kinetics of imine:



Initial rate kinetics of [catalyst]



135 0.5 M

21 0.5 M

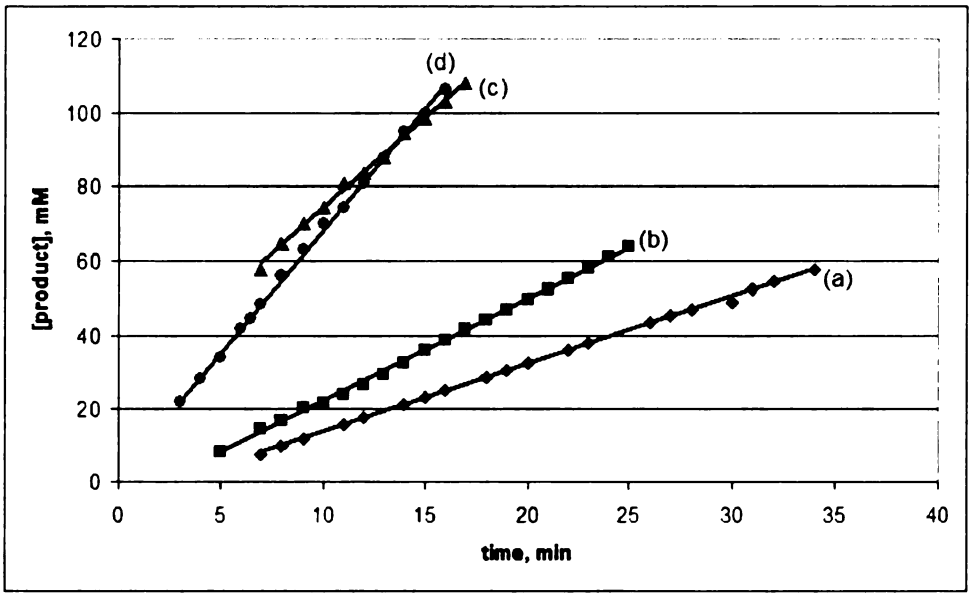
136

Concentration of product at various catalyst concentration:

[catal] = 0.01 M		[catal] = 0.02 M		[catal] = 0.035 M		[catal] = 0.05 M	
time (min)	[**136**] (mM)	time (min)	[**136**] (mM)	time (min)	[**136**] (mM)	time (min)	[**136**] (mM)
7	7.5	5	8.25	7	57.5	3	22
8	9.75	7	14.5	8	64.5	4	28
9	11.75	8	17	9	70	5	34
11	15.5	9	20.25	10	74.25	6	41.75
12	17.75	10	21.5	11	81	6.5	44.5
14	21.25	11	24	12	83.5	7	48.5
15	23.25	12	26.5	13	88	8	55.75
16	25	13	29.5	14	94.5	9	63
18	28.5	14	32.25	15	98.5	10	70
19	30.5	15	36	16	103	11	74.25
20	32.5	16	38.75	17	108	12	81
22	36	17	41.75			13	88
23	37.75	18	44			14	95
26	43.5	19	46.75			15	100
27	45.5	20	49.75			16	106.5
28	47	21	52.25				
30	48.75	22	55.25				
31	52.25	23	58				
32	54.25	24	61				
34	57.5	25	63.75				

PH_3CH was used as internal standard for ^1H NMR integration, $[Ph_3CH] = 0.25$ M

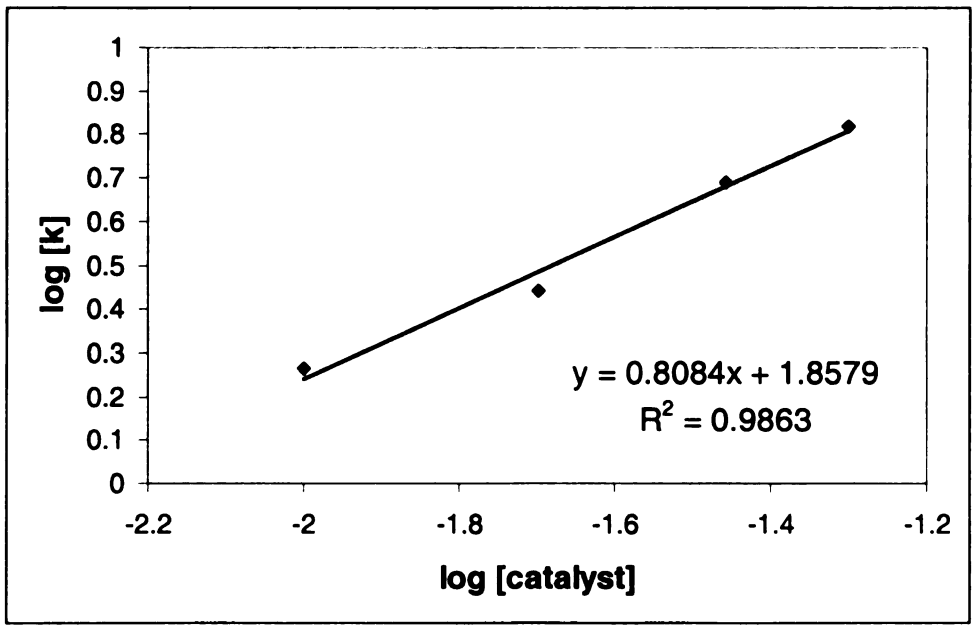
Reaction rate at various catalyst concentrations:



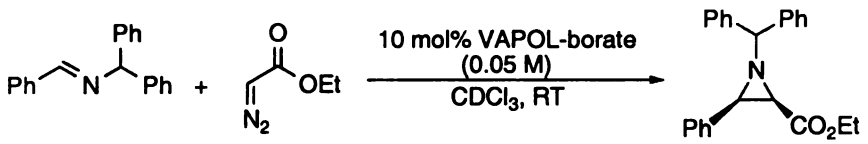
(a) [catal] = 0.01 M, $y = 1.834x - 4.5764$, $R^2 = 0.999$
(b) [catal] = 0.02 M, $y = 2.7652x - 5.6729$, $R^2 = 0.9989$
(c) [catal] = 0.035 M, $y = 4.9045x + 25.032$, $R^2 = 0.9962$
(d) [catal] = 0.05 M, $y = 6.5751x + 2.3346$, $R^2 = 0.9989$

[catalyst]	log[catalyst]	k	log[k]
0.01	-2	1.834	0.2634
0.02	-1.699	2.7652	0.4417
0.035	-1.456	4.9045	0.6906
0.05	-1.30	6.5751	0.8179

Initial Reaction rate kinetics of catalyst:



Initial rate kinetics of [EDA]



135 0.5 M

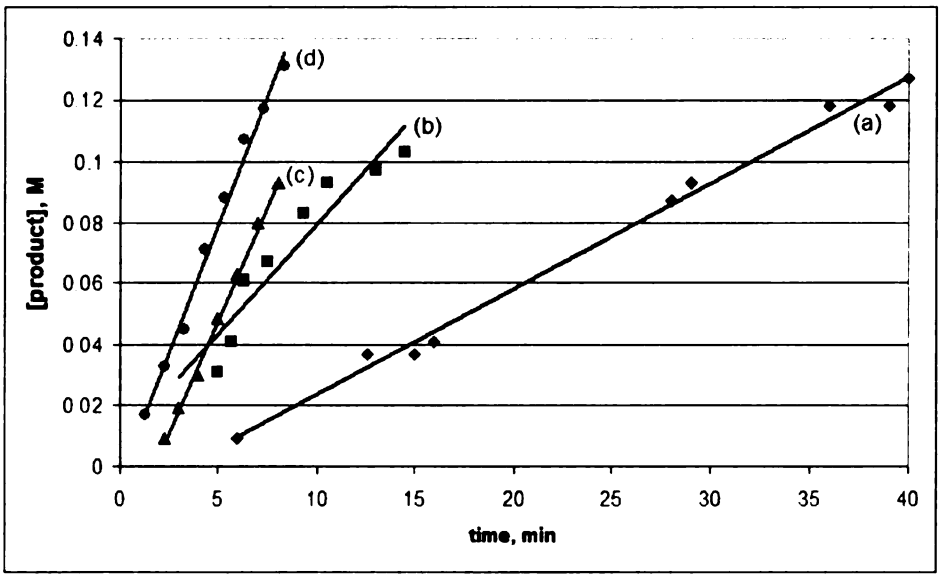
21 0.25 M, 0.5 M, 1.0 M, 1.5M

136

Concentration of product at various EDA concentration:

[EDA] = 0.25 M			[EDA] = 0.5 M		
time (min)	ratio of **136/135**	concn **136** (M)	time (min)	ratio of **136/135**	concn **136** (M)
6	0.02	0.009	5	0.065	0.031
12.6	0.08	0.037	5.67	0.09	0.041
15	0.08	0.037	6.33	0.14	0.061
16	0.09	0.041	7.50	0.155	0.067
28	0.21	0.087	9.33	0.20	0.083
29	0.23	0.093	10.50	0.23	0.093
36	0.31	0.118	13	0.24	0.097
39	0.31	0.118	14.50	0.26	0.103
40	0.34	0.127			
[EDA] = 0.75 M			[EDA] = 1 M		
time (min)	ratio of **136/135**	concn **136** (M)	time (min)	ratio of **136/135**	concn **136** (M)
2.25	0.02	0.009	1.3	0.035	0.017
3	0.04	0.019	2.3	0.07	0.033
4	0.064	0.030	3.3	0.10	0.045
5	0.11	0.049	4.3	0.165	0.071
6	0.145	0.063	5.3	0.215	0.088
7	0.19	0.080	6.3	0.273	0.107
8	0.227	0.093	7.3	0.305	0.117
			8.3	0.355	0.131

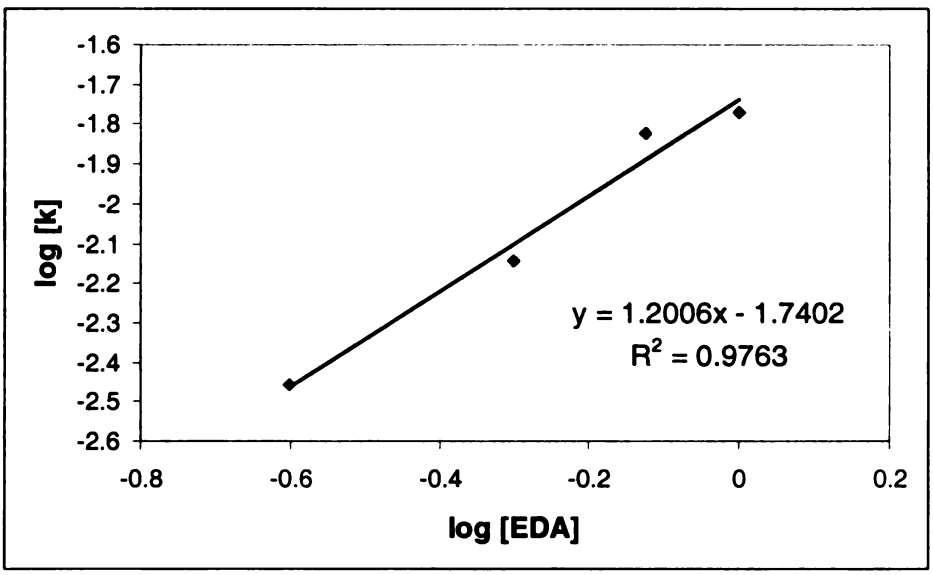
Reaction rate at various EDA concentrations:



(a) [EDA] = 0.25 M, $y = 0.0035x - 0.0112$, $R^2 = 0.9924$
(b) [EDA] = 0.5 M, $y = 0.0072x + 0.0076$, $R^2 = 0.8853$
(c) [EDA] = 0.75 M, $y = 0.015x - 0.0263$, $R^2 = 0.9969$
(d) [EDA] = 1.0 M, $y = 0.0169x - 0.0051$, $R^2 = 0.9911$

[EDA]	log[EDA]	k	log[k]
0.25	-0.602	0.0035	-2.456
0.5	-0.301	0.0072	-2.143
0.75	-0.125	0.015	-1.824
1	0	0.0169	-1.772

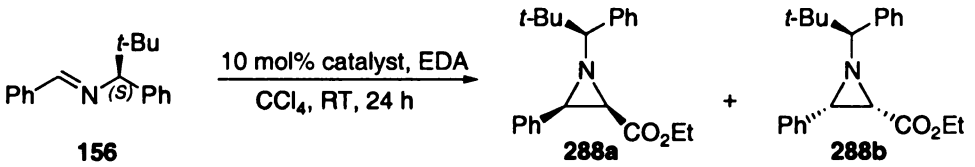
Initial Reaction rate kinetics of EDA:



Match/mismatched studies:

Typical experimental procedure for the aziridination reaction of chiral imines:

Preparation of VAPOL-borate catalyst: To a flame dried Schlenk flask cooled under argon was added triphenyl borate (120 mg, 0.4 mmol) and *S*-VAPOL (54 mg, 0.1 mmol), followed by 2 mL of dry CCl_4. The flask was sealed under argon and the solution was stirred at 80 °C for 1 hour. A partial vacuum was then applied to the flask and the solvent was removed slowly. After complete removal of solvent, the residue was heated under high vacuum (~ 0.2 mm Hg) at 80 °C for 0.5 hour to remove the volatile material. The prepared catalyst was then dissolved in CCl_4 and transferred to the reaction flask.



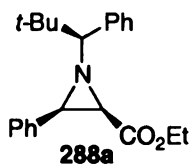
(*S*)-catalyst: **288a**:**288b** = 1-2.5 : 1

(*R*)-catalyst: **288a**:**288b** < 1 : 50

Reaction of chiral imine 156 with *S*-VAPOL-borate catalyst: The *S*-VAPOL-borate catalyst (0.1 mmol) prepared according to the standard procedure was dissolved in 2 × 1 mL dry CCl_4 and transferred via syringe to the flask containing chiral imine **156** (251 mg, 1 mmol). The resulting light yellow solution was allowed to be stirred at room temperature for 5 minutes, then EDA (115 μL, 1.15 mmol) was added via syringe in once. No bubbling was observed. The solution was then stirred at room temperature for 24 hours. Upon workup, ^1H NMR of the crude product showed it's a mixture of 1:0.45:0.44:0.02 of **288a/288b**/Ph migration enamine/H migration enamine. The crude product was purified by silica gel chromatography, eluted with 1:35 EtOAc/hexane. The

major product (*2R*, *3R*)-**288a** was isolated as a white solid (189 mg, 0.56 mmol), 56% yield.

Reaction of chiral imine 156 with *R*-VAPOL-borate catalyst: The *R*-VAPOL-borate catalyst (0.1 mmol) prepared according to the standard procedure was dissolved in 2 × 1 mL dry CCl_4 and transferred via syringe to the flask containing chiral imine **156** (251 mg, 1 mmol). The resulting light yellow solution was allowed to be stirred at room temperature for 5 minutes, then EDA (115 μL, 1.15 mmol) was added via syringe in once. Vigorous bubbling was observed. The solution was then stirred at room temperature for 24 hours. Upon workup, ^{1}H NMR of the crude product showed it's a mixture of >50:1 of **288b/288a**, along with small amount of Ph migration /H migration enamine product (1%, 2%). The crude product was purified by silica gel chromatography, eluted with 1:35 to 1:25 EtOAc/hexane. The major product (*2S*, *3S*)-**288b** was isolated as a white solid (271 mg, 0.80 mmol), 80% yield.



288a

Cis-(*2R*, *3R*)-aziridine 288a:

Spectral data for **288a**: White foam-like solid; mp = 107-109 °C, R_f = 0.12 (35:1 hexane/EtOAc), $[\alpha]_D$ = 52.9 (*c* = 1.0, $CHCl_3$);

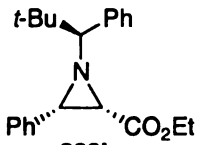
^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.91 (t, *J* = 7.1 Hz, 3H), 0.94 (s, 9H), 2.22 (d, *J* = 6.6 Hz, 1H), 2.60 (s, 1H), 3.14 (d, *J* = 6.6 Hz, 1H), 3.82-3.85 (m, 2H), 7.23-7.33 (m, 8H), 7.53 (m, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.90, 27.30, 36.04, 44.20, 52.91, 60.25, 83.48, 126.90, 127.34, 127.78, 127.96, 129.38, 135.31, 140.50, 168.08, 180.57;

IR (thin film, cm^{-1}) 1736 vs;

Mass spectrum: m/z (% rel intensity) 337 M^+ (<1), 281 (12), 280 (72), 206 (36), 190 (48), 130 (31), 91 (100);

Anal calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.22; H, 8.31; N, 4.15;



288b

Cis-(*2S, 3S*)-aziridine 288b:

Spectral data for **288b**: White amorphous solid; mp = 46-56 °C; R_f = 0.12 (35:1 hexane/EtOAc), $[\alpha]_D$ = 85.6 (*c* = 1.0, $CHCl_3$);

^1H NMR ($CDCl_3$, 300 MHz) δ = 0.99 (t, *J* = 7.1 Hz, 3H), 1.03 (s, 9H), 2.60 (s, 1H), 2.68 (d, *J* = 6.6 Hz, 1H), 2.73 (d, *J* = 6.6 Hz, 1H), 3.95 (q, *J* = 7.1 Hz, 2H), 7.11-7.39 (m, 10H);

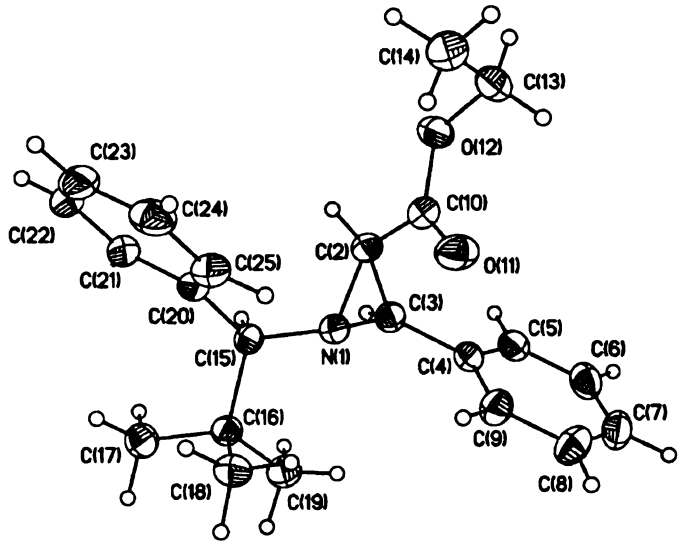
^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.94, 27.27, 36.45, 44.52, 51.73, 60.43, 83.47, 126.84, 126.93, 127.22, 127.48, 127.68, 129.22, 135.54, 140.12, 167.82;

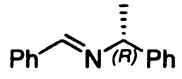
IR (thin film, cm^{-1}) 1748 vs, 1200 vs;

Mass spectrum: m/z (% rel intensity) 337 M^+ (2), 281 (17), 280 (100), 206 (57), 190 (40), 189 (51), 116 (72);

Anal calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.40; H, 8.36; N, 4.10;

(*2R, 3R*)-aziridine **288a** (~ 40 mg) was dissolved in small amount of CH_2Cl_2 (< 0.5 mL), and transferred to NMR tube. The CH_2Cl_2 layer was covered with ~2 mL pentane. After one week, half of the solvent evaporated, large needle-like colorless crystal in the NMR tube was collected and the structure of **288a** was determined by X-ray diffraction analysis.





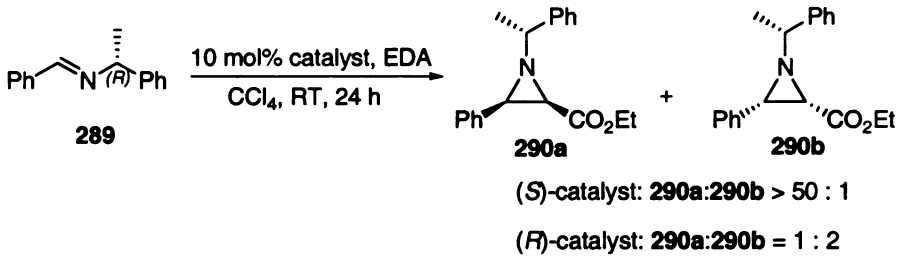
289

Imine 289: The imine was prepared from the corresponding (*R*)-α-methyl benzylamine (> 99% ee, purchased from Aldrich) and benzaldehyde. Crude imine was purified by vacuum distillation. The product boiled at 105 °C under 0.5 mm Hg and the isolated yield was 80%.

Spectral data for **289**:[95] Colorless oil;

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 1.63 (d, *J* = 6.6 Hz, 3H), 4.57 (q, *J* = 6.6 hz, 1H), 7.23-7.48 (m, 8H), 7.78-7.83 (m, 2H), 8.39 (s, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 24.95, 69.69, 126.58, 126.77, 128.21, 128.37, 128.48, 130.51, 136.36, 145.14, 159.38;

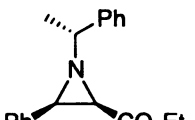


(*S*)-catalyst: **290a**:**290b** > 50 : 1

(*R*)-catalyst: **290a**:**290b** = 1 : 2

Reaction of chiral imine 289 with *S*-VAPOL-borate catalyst: The *S*-VAPOL-borate catalyst (0.1 mmol) prepared according to the standard procedure was dissolved in 2 × 1 mL dry CCl_4 and transferred via syringe to the flask containing chiral imine **289** (209 mg, 1 mmol). The resulting slightly yellow solution was allowed to be stirred at room temperature for 5 minutes, then EDA (115 μL, 1.15 mmol) was added via syringe in once. Vigorous bubbling was observed. The solution was then stirred at room temperature for 24 hours. Upon workup, ^{1}H NMR of the crude product showed it's a mixture of >50:1 of **290a/290b**, along with small amount of Ph migration /H migration enamine product (2%, 2%). The crude product was purified by silica gel chromatography, eluted with 1:1:8 Et_2O/CH_2Cl_2/hexane. The major product **290a** was isolated as a white solid (233 mg, 0.79 mmol), 79% yield.

Reaction of chiral imine 289 with *R*-VAPOL-borate catalyst: The *R*-VAPOL-borate catalyst (0.1 mmol) prepared according to the standard procedure was dissolved in 2 × 1 mL dry CCl_4 and transferred via syringe to the flask containing chiral imine **289** (209 mg, 1 mmol). The resulting light yellow solution was allowed to be stirred at room temperature for 5 minutes, then EDA (115 μL, 1.15 mmol) was added via syringe in once. No bubbling was observed. The solution was then stirred at room temperature for 24 hours. Upon workup, ^{1}H NMR of the crude product showed it's a mixture of 1:2:0.13:0.08 of **290a/290b**/Ph migration enamine/H migration enamine. The crude product was purified by silica gel chromatography, eluted with 1:20 EtOAc/hexane. The major product **290b** was isolated as a white solid (118 mg, 0.40 mmol), 40% yield.



290a

Cis-(*2R, 3R*)-aziridine 290a: White solid, mp = 87-88 °C; R_f = 0.33 (1:1:8 Et_2O/CH_2Cl_2/hexane), $[\alpha]_D$ = -35.0 (*c* = 1.0, $CHCl_3$);

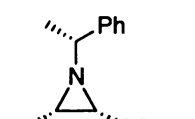
^1H NMR ($CDCl_3$, 300 MHz) δ = 0.96 (t, *J* = 7.1 Hz, 3H), 1.54 (d, *J* = 6.6 Hz, 3H), 2.60 (d, *J* = 6.8 Hz, 1H), 2.86 (q, *J* = 6.6 Hz, 1H), 2.97 (d, *J* = 6.8 Hz, 1H), 3.93-4.00 (m, 2H), 7.15-7.34 (m, 8H), 7.43-7.46 (m, 2H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.88, 22.88, 45.96, 47.30, 60.58, 69.71, 126.87, 127.13, 127.22, 127.62, 127.69, 128.33, 135.13, 143.22, 168.18;

IR (thin film, cm^{-1}) 1744 vs, 1200 vs;

Mass spectrum: m/z (% rel intensity) 295 M^+ (<1), 191 (13), 190 (95), 144 (14), 117 (95), 116 (100), 105 (90);

Anal calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.14; N, 4.74. Found: C, 77.18; H, 7.29; N, 4.69;



290b

Cis-(*2S, 3S*)-aziridine 290b: White solid, mp = 87-88 °C; R_f = 0.3 (15:1 hexane/EtOAc), $[\alpha]_D$ = -55.9 (*c* = 1.0, $CHCl_3$);

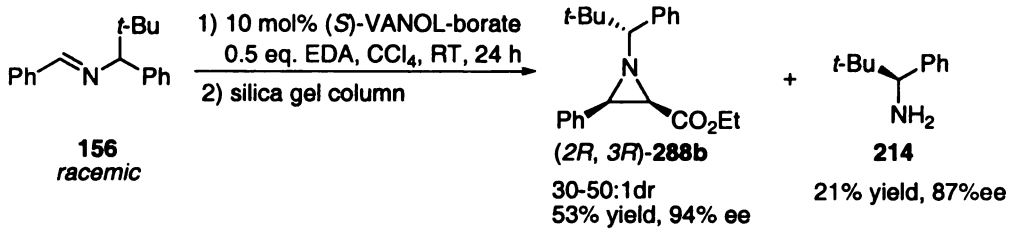
^1H NMR ($CDCl_3$, 300 MHz) δ = 0.93 (t, *J* = 7.1 Hz, 3H), 1.51 (d, *J* = 6.6 Hz, 3H), 2.50 (d, *J* = 6.8 Hz, 1H), 2.91 (q, *J* = 6.6 Hz, 1H), 3.11 (d, *J* = 6.8 Hz, 1H), 3.89 (q, *J* = 7.1 Hz, 2H), 7.24-7.38 (m, 6H), 7.50-7.53 (m, 4H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.85, 23.85, 45.49, 47.97, 60.40, 69.12, 126.61, 127.04, 127.39, 127.86, 128.36, 135.48, 143.66, 167.91 (one aryl carbon not located);

IR (thin film, cm^{-1}) 1738 vs;

Mass spectrum: m/z (% rel intensity) 295 M^+ (<1), 190 (96), 162 (18), 117 (100), 116 (98);

Anal calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.14; N, 4.74. Found: C, 77.37; H, 7.32; N, 4.72;



156
racemic

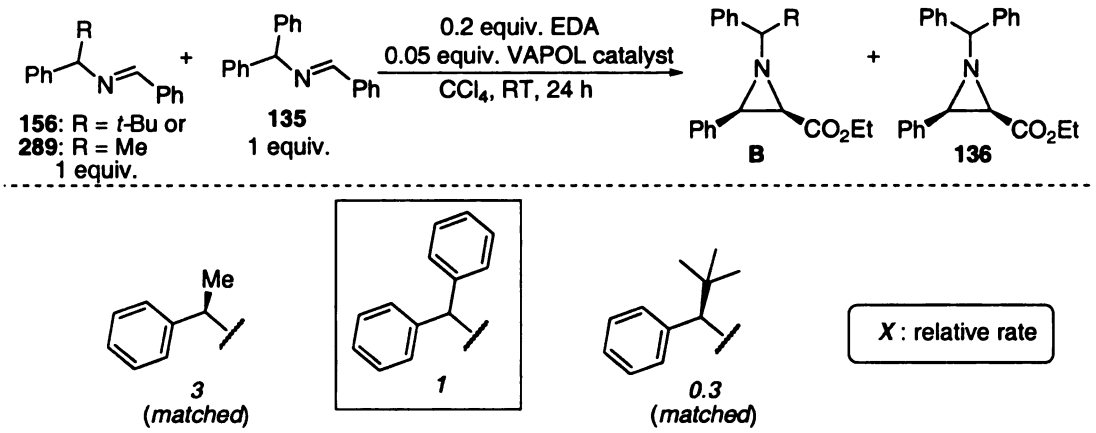
(*2R*, *3R*)-**288b**
30-50:1dr
53% yield, 94% ee

214
21% yield, 87%ee

Kinetic resolution of racemic imine 156: The *S*-VANOL-borate catalyst (0.1 mmol) prepared according to the standard procedure was dissolved in 2 × 1 mL dry CCl_4 and transferred via syringe to the flask containing racemic imine **156** (251 mg, 1 mmol). The resulting slightly yellow solution was allowed to be stirred at room temperature for 5 minutes, then EDA (55 μL, 0.5 mmol) was added via syringe in once. Vigorous bubbling was observed. ^1H NMR of the crude product indicated 50% conversion of **156** and no enamine was observed. The crude product was absorbed one 3 g of silica gel and purified by silica gel chromatography, eluted with 1:35 EtOAc/hexane to give aziridine (*2R*, *3R*)-**288b** (157 mg, 0.53 mmol, 53% yield), the chiral induction of (*2R*, *3R*)-**286b** was found to be 94% ee by chiral HPLC analysis. After aziridine (*2R*, *3R*)-**288b** was isolated, the column was eluted with 4:1:0.1 EtOAc/hexane/MeOH, gave amine **214** as a colorless oil (35 mg, 0.21 mmol, 21% yield). The chiral induction of **214** was found to be 87% ee by chiral HPLC analysis.

HPLC conditions for aziridine **288b**: Chiralcel AD column, 225nm, 99.5:0.5 hexane/iPrOH as eluent at 1 mL/min. The retention time for the minor (*2S*, *3S*)-enantiomer was 6.8 min and the major (*2R*, *3R*)-enantiomer from *S*-ligand was 8.8 min. HPLC conditions for amine **214**: Chiralcel OD-H column, 250 nm, 99:1 hexane/iPrOH, flow rate: 1 mL/min, under this condition, the retention time of minor isomer was 4.18 min and that of major (*S*)-isomer was 7.86 min.)

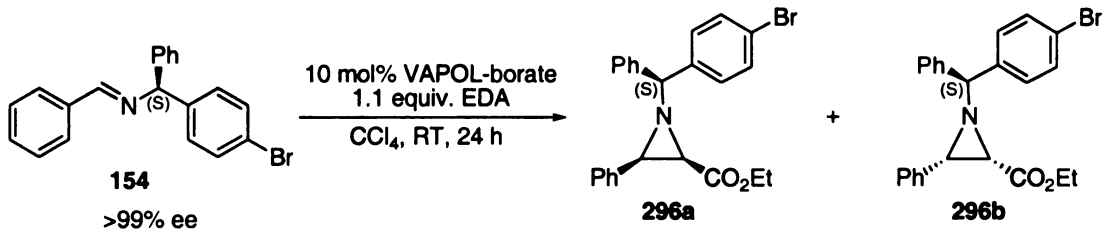
Rate competition study of chiral α-alkyl benzylimines with VAPOL-borate catalyst



To a flame-dried 25 mL round bottom flask filled with argon was added 1 mmol of benzhydryl imine **135** and 1 mmol of imine **156** or **289**. The VAPOL-borate catalyst (0.05 mmol) prepared according to the standard procedure was dissolved in 4 mL of CCl_4 and transferred to the flask containing imines. Ethyl diazoacetate (0.2 mmol) was added via syringe in once. The mixture was stirred at room temperature for 24 hours. The reaction was worked up by addition of 10 mL of hexane and concentrated in vacuo. The ratio of the two aziridines (**B** vs. **136**) was determined by the ^1H NMR integration of the crude product in appropriate solvent by comparing the C-2 and C-3 methine protons or benzhydryl methine protons of **B** and **136**.

entry	imine	NMR solvent	δ of **136** (PPM)	δ of **B** (PPM)	**B** : **136**
1	**156**	d6-benzene	2.48, 2.83	2.60, 2.93	3:1
2	**289**	d6-benzene	2.49, 2.83	2.58, 2.28(Ph_2CH)	1:3

Reaction of chiral benzhydryl imine 154 with VAPOL catalyst:



154

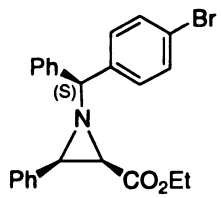
>99% ee

296a **296b**

with *S*-VAPOL **296a**:**296b** = 30:1

with *R*-VAPOL **296a**:**296b** = 1:30

Reaction of 154 with *S*-VAPOL-borate catalyst: The standard aziridination procedure with *S*-VAPOL-borate catalyst was employed except that 0.5 mmol chiral imine **154** was used and the concentration of imine was 0.2 M. The reaction was worked up after 24 hours. ^{1}H NMR of the crude reaction mixture indicated that the ratio of the two aziridine diastereoisomers (**296a**:**296b**) was 30:1. The crude product was precipitated on 3 g of silica gel and purified by chromatography, eluted with 1:10 EtOAc/hexane, gave 164 mg white solid as product **296a** (0.375 mmol, 75% yield).



296a

Cis-(*2R*, *3R*)-aziridine 296a: White solid, mp = 140-141 °C; R_f = 0.28 (10:1 hexane/EtOAc), $[\alpha]_D$ = 44.0 (c = 1.0, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 300 MHz) δ = 0.96 (t, J = 7.1 Hz, 3H), 2.67 (d, J = 6.8 Hz, 1H), 3.17 (d, J = 6.8 Hz, 1H), 3.89-3.94 (m, 2H), 3.90 (s, 1H), 7.21-7.41(m, 12H), 7.55-7.57 (m, 2H);

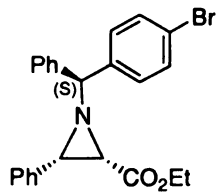
^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.88, 46.33, 47.99, 60.58, 76.88, 121.29, 127.04, 127.43, 127.63, 127.81, 128.57, 129.12, 131.58, 134.67, 141.58, 141.74, 167.44 (one aryl carbon not located);

IR (thin film, cm^{-1}) 1744 vs, 1202 vs;

Mass spectrum: m/z (% rel intensity) 437 (M^+, Br^{81}, <1), 435 (M^+, Br^{79}, <1), 247 (Br^{81}, 14), 245 (Br^{79}, <1), 190 (100), 165 (48), 117 (44);

Anal calcd for $C_{24}H_{22}BrNO_2$: C, 66.06; H, 5.08; N, 3.21. Found: C, 65.86; H, 5.03; N, 3.28;

Reaction of 154 with *R*-VAPOL-borate catalyst: The standard aziridination procedure with *R*-VAPOL-borate catalyst was employed except that 0.5 mmol chiral imine **154** was used and the concentration of imine was 0.2 M. The reaction was worked up after 24 hours. ^1H NMR of the crude reaction mixture indicated that the ratio of the two aziridine diastereoisomers (**296a**:**296b**) was 1:30. The crude product was precipitated on 3 g of silica gel and purified by chromatography, eluted with 1:10 EtOAc/hexane, gave 161 mg white solid as product **296a** (0.37 mmol, 74% yield).



296b

Cis-(*2S*, *3S*)-aziridine 296b: White solid, mp = 63-65 °C; R_f = 0.225 (10:1 hexane/EtOAc), $[\alpha]_D$ = -35.1 (*c* = 1.0, EtOAc);

^1H NMR ($CDCl_3$, 300 MHz) δ = 0.96 (t, *J* = 7.1 Hz, 3H), 2.62 (d, *J* = 7.1 Hz, 1H), 3.19 (d, *J* = 7.1 Hz, 1H), 3.87 (s, 1H), 3.87-3.93 (q, *J* = 7.1 Hz, 2H), 7.17-7.34 (m, 6H), 7.36-7.49 (m, 8H);

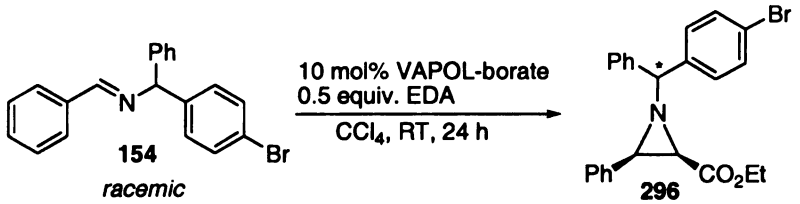
^{13}C NMR ($CDCl_3$, 75 MHz) δ = 13.90, 46.40, 47.88, 60.61, 76.97, 121.12, 127.39, 127.62, 127.68, 127.77, 128.57, 128.89, 131.58, 134.76, 141.47, 141.88, 167.45 (one aryl carbon not located);

IR (thin film, cm^{-1}) 1741 vs, 1202 vs;

Mass spectrum: m/z (% rel intensity) 437 (M^+, Br^{81}, <1), 435 (M^+, Br^{79}, <1), 247 (Br^{81}, 14), 245 (Br^{79}, <1), 190 (100), 165 (41), 117 (35);

Anal calcd for $C_{24}H_{22}BrNO_2$: C, 66.06; H, 5.08; N, 3.21. Found: C, 66.24; H, 5.30; N, 3.12;

Attempted kinetic resolution of racemic imine 154:

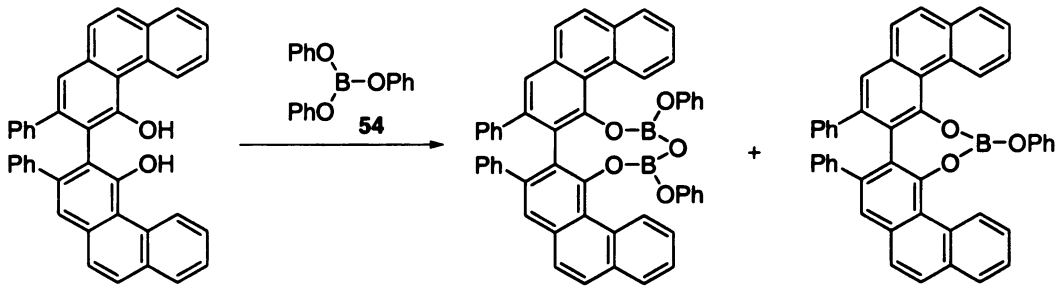


with *S*-VAPOL: **296a**:**296b**=1:1
with *R*-VAPOL: **296a**:**296b**=1:1

The *S*-VAPOL-borate catalyst (0.1 mmol) prepared according to the standard procedure was dissolved in 2 × 2 mL dry CCl_4 and transferred via syringe to the flask containing racemic imine **154** (355 mg, 1 mmol). The resulting slightly yellow solution was allowed to be stirred at room temperature for 5 minutes, then EDA (55 μL, 0.5 mmol) was added via syringe in once. Vigorous bubbling was observed. The reaction was worked up after 24 hours. ^1H NMR of the crude reaction product in d6-acetone indicated 50% conversion of **154** and the ratio of **296a**:**296b** was 1:1.

Experimental for Chapter Seven:

^{1}H NMR and MS Study of the VAPOL and VANOL-borate catalysts:



46 301 298

Preparation of VAPOL-borate catalyst: To a flame-dried Schlenk flask cooled under argon was added VAPOL **46** (54 mg, 0.1 mmol) and $B(OPh)_3$ **54** (87 mg, 0.3 mmol, purchased from Aldrich, ~80% purity) followed by 2 mL of dry CCl_4. The flask was sealed under argon and the mixture was stirred at 80 °C for 1 hour, then a vacuum (0.2-0.5 mm Hg) was applied to remove the solvent and volatile material and the residue was heated at 80 °C under high vacuum for 30 minutes. The prepared catalyst was dissolved in an appropriate deuturated solvent and examined by ^{1}H NMR. NMR indicated that the ratio of the two catalyst species (**301**:**298**) ranges from 3-5:1.

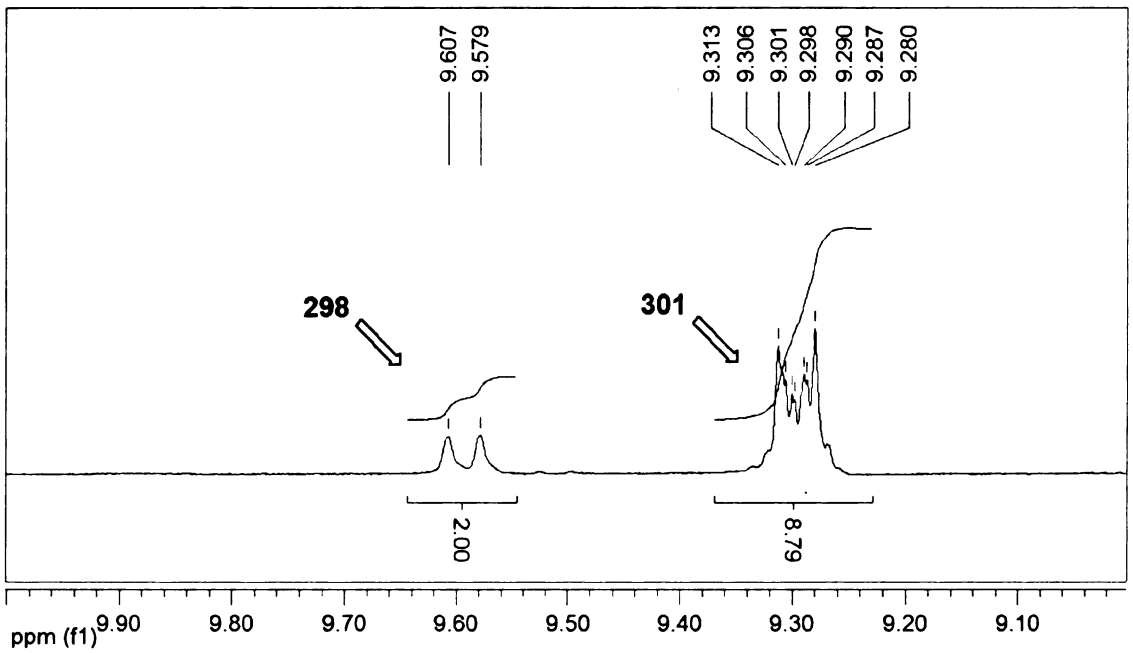
MS analysis of VAPOL-borate catalysts 298 and 301:

Low resolution in FAB, NPOE matrix: Relative intensity of **298** is 4.6% and relative intensity of **301** is 12%.

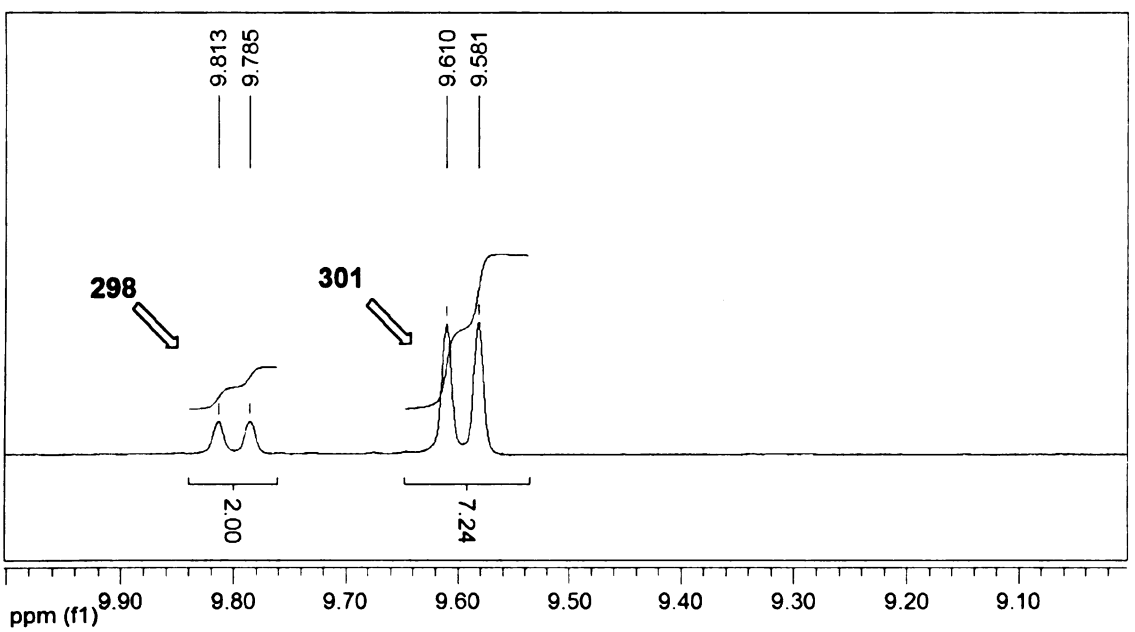
High resolution analysis of **298**: Calculated, 640.2210; Found, 640.2214

High resolution analysis of **301**: Calculated, 760.2592; Found, 760.2596

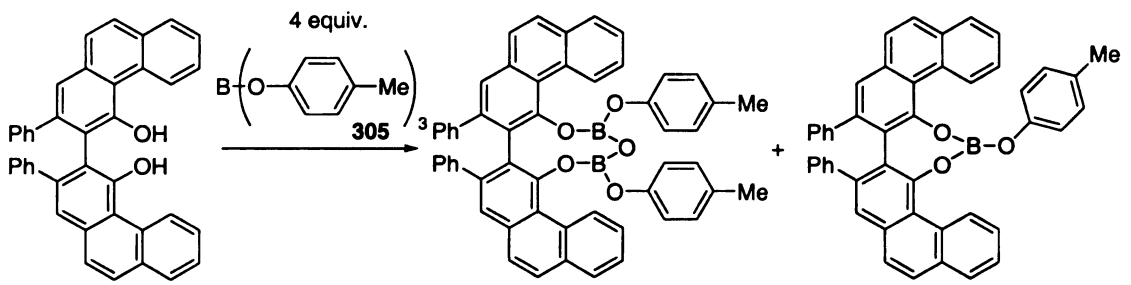
Bay proton region of the VAPOL-borate catalyst in $CDCl_3$:



Bay proton region of the VAPOL-borate catalyst in d6-benzene:



Preparation of tri-p-tolyl borate 305: To a 250 mL round bottom flask attached with Dean-Stark column and refluxing condenser was charge boric acid (3.09 g, 50 mmol), cresol (18.9 g, 175 mmol) and 50 mL toluene. The solution was refluxed under argon for 48 hours, and the water produced in the reaction was removed until complete conversion which was indicated by no more generation of water. The solvent was removed *in vacuo* and the crude product was distilled under high vacuum. The product **305** boiled at 181 °C (0.1 mm Hg), and the viscous oil collected solidified upon standing. The product was isolated as white solid (13.54 g, 41 mmol, 82% yield). ^{1}H NMR of the isolated indicated that the isolated **305**[51d] was higher than 95% chemical purity.



46 **306** **307**

Preparation of VAPOL-(p-tol)-borate catalyst (without water): To a flame-dried Schlenk flask cooled under argon was added VAPOL (54 mg, 0.1 mmol) and borate **305** (133 mg, 0.4 mmol) followed by 2 mL of dry CH_2Cl_2. The flask was sealed under argon and the mixture was stirred at 55 °C for 1 hour, then a vacuum (0.2-0.5 mm Hg) was applied to remove the solvent and volatile material and the residue was heated at 55 °C under high vacuum for 30 minutes. The prepared catalyst was dissolved in $CDCl_3$ and examined by ^{1}H NMR. NMR indicated that the ratio of the two catalyst species (**306:306**) is 1.3:1.

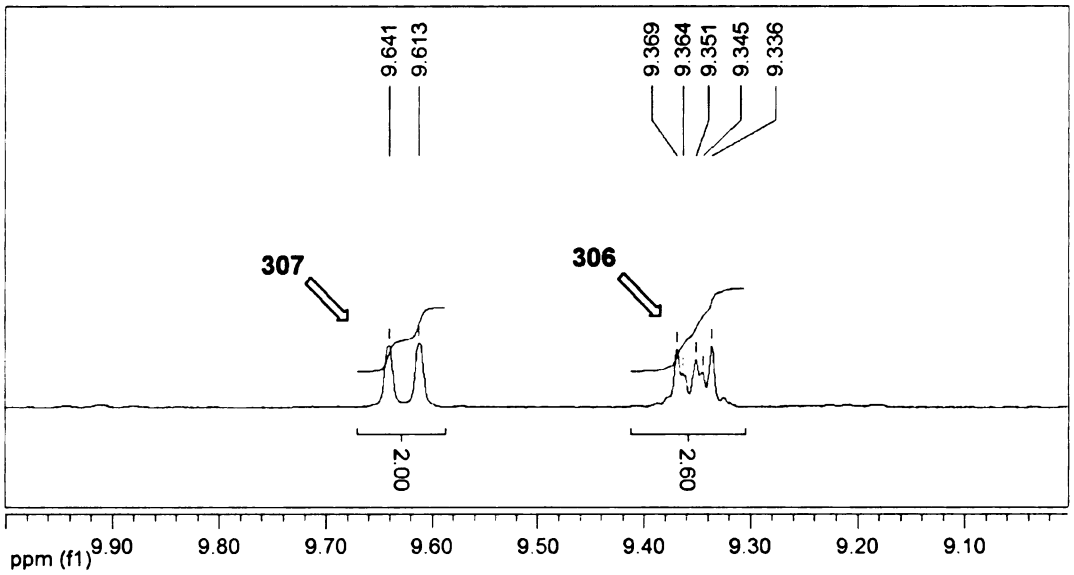
MS analysis of VAPOL-(p-tol)-borate catalysts 306 and 307:

Low resolution in FAB, NPOE matrix: Relative intensity of **306** is 14% and relative intensity of **307** is 11%.

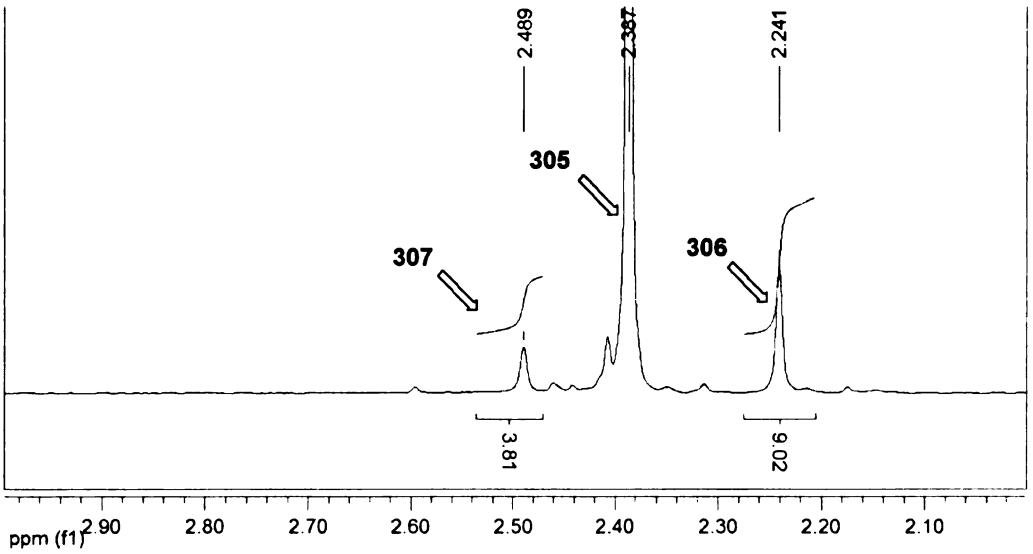
High resolution analysis of **306**: Calculated, 788.2905; Found, 788.2918

High resolution analysis of **307**: Calculated, 654.2366; Found, 654.2376

Bay proton region of the VAPOL-(p-toyl)-borate catalyst in $CDCl_3$:

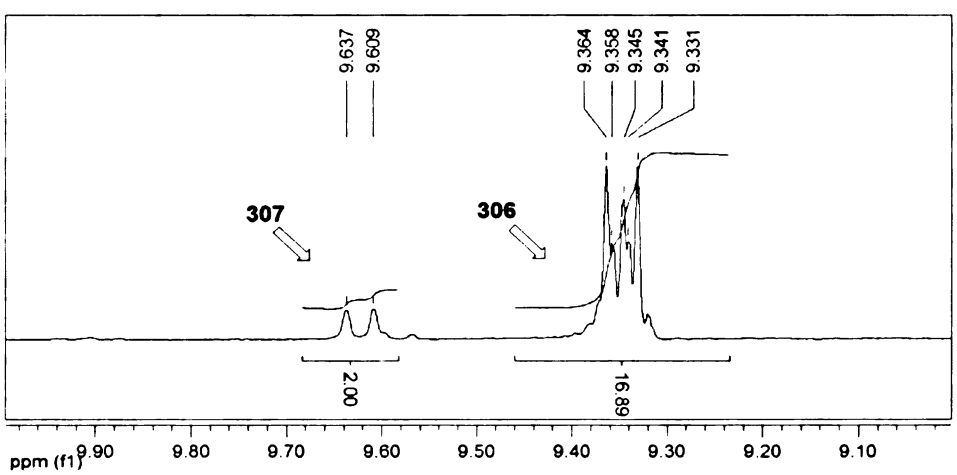


Methyl proton region of the VAPOL-(p-toyl)-borate catalyst in $CDCl_3$:

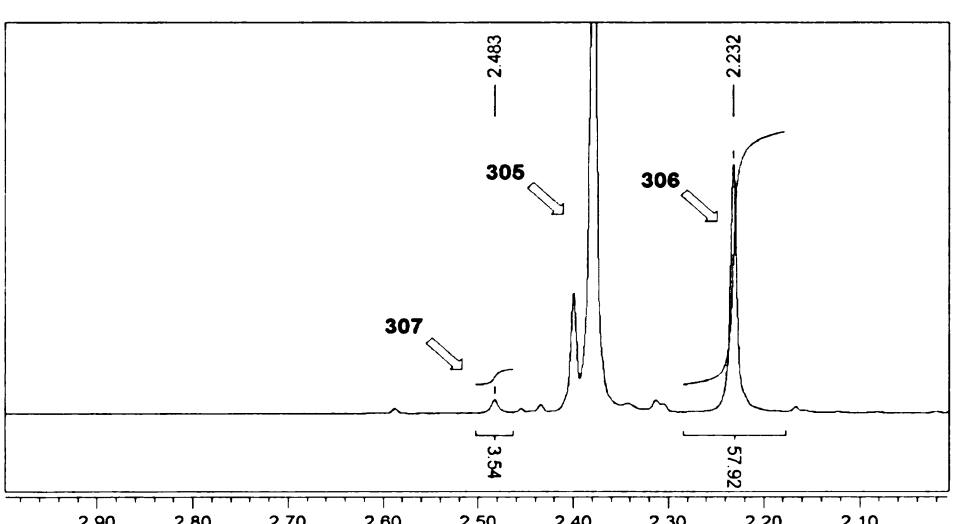


Preparation of VAPOL-(o-Tol)-borate catalyst (with water): To a flame-dried Schlenk flask cooled under argon was added VAPOL (54 mg, 0.1 mmol) and $B(OC_6H_4CH_3)_3$ (133 mg, 0.4 mmol) followed by 1.8 μL of water (0.1 mmol) and 2 mL of dry toluene. The flask was sealed under argon and the mixture was stirred at 80 °C for 1 hour, then a vacuum (0.2-0.5 mm Hg) was applied to remove the solvent and volatile material and the residue was heated at 80 °C under high vacuum for 30 minutes. The prepared catalyst was dissolved in $CDCl_3$ and examined by ^1H NMR. NMR indicated that the ratio of the two catalyst species (**306:307**) is 8-9:1

Bay proton region of the VAPOL-(p-toyl)-borate catalyst in $CDCl_3$:



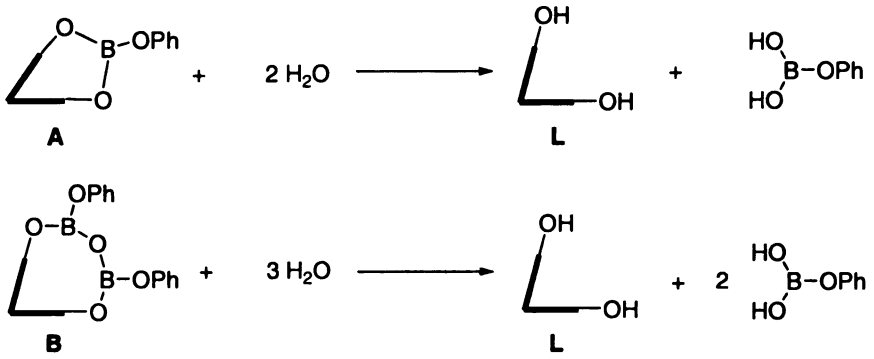
Methyl proton region of the VAPOL-(p-toyl)-borate catalyst in $CDCl_3$:



Calculation of the ligand and ligand-borates:

All the calculations were performed with Spartan '04 program. The gas phase equilibrium geometries of the molecules were optimized with the indicated computational methods.

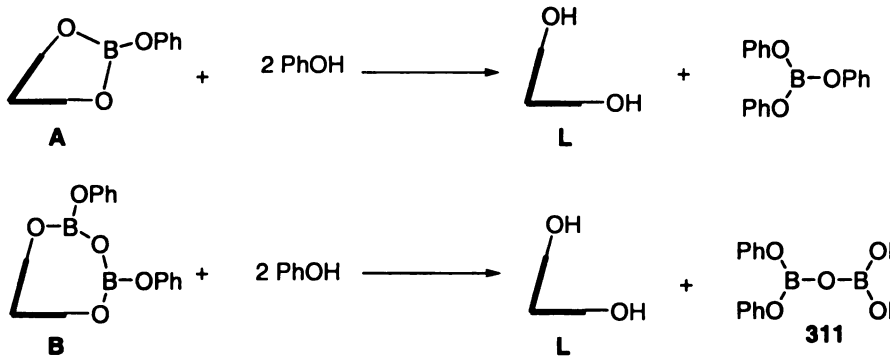
Optimized energy of the molecules (Isodesmic calculation): [a]



VAPOL:	A	B	H_2O	L	boric acid
PM3	28.4089	-106.8543	-53.4266	85.6579	-191.6187
HF/3-21G	-1997.151344	-2399.651648	-75.585960	-1670.305035	-478.062872
HF/6-31G*	-2008.322903	-2413.037359	-76.010746	-1679.660915	-480.710084
EDF1/6-31G**	-2021.365497	-2428.528054	-76.431585	-1690.677520	-483.589807
VANOL:	A	B	H_2O	L	boric acid
PM3	-7.882	-143.871	-53.4266	50.716	-191.6187
HF/3-21G	-1693.563347	-2096.060864	-75.585960	-1366.712271	-478.062872
HF/6-31G*	-1703.028309	-2107.740758	-76.010746	-1374.362990	-480.710084
EDF1/6-31G**	-1714.042784	-2121.203933	-76.431585	-1383.348686	-483.589807
BINOL:	A	B	H_2O	L	boric acid
PM3	-65.1603	-197.9746	-53.4266	-5.1684	-191.6187
HF/3-21G	-1237.027196	-1639.521095	-75.585960	-910.172047	-478.062872
HF/6-31G*	-1243.932807	-1648.645097	-76.010746	-915.268904	-480.710084
EDF1/6-31G**	-1251.873588	-1659.034694	-76.431585	-921.179648	-483.589807

[a] The unit of the energy in the PM3 calculation is kcal/mol and the unit for other methods is au (1 au = 627.5 kcal/mol)

Optimized energy of the molecules (Homodesmotic calculation):

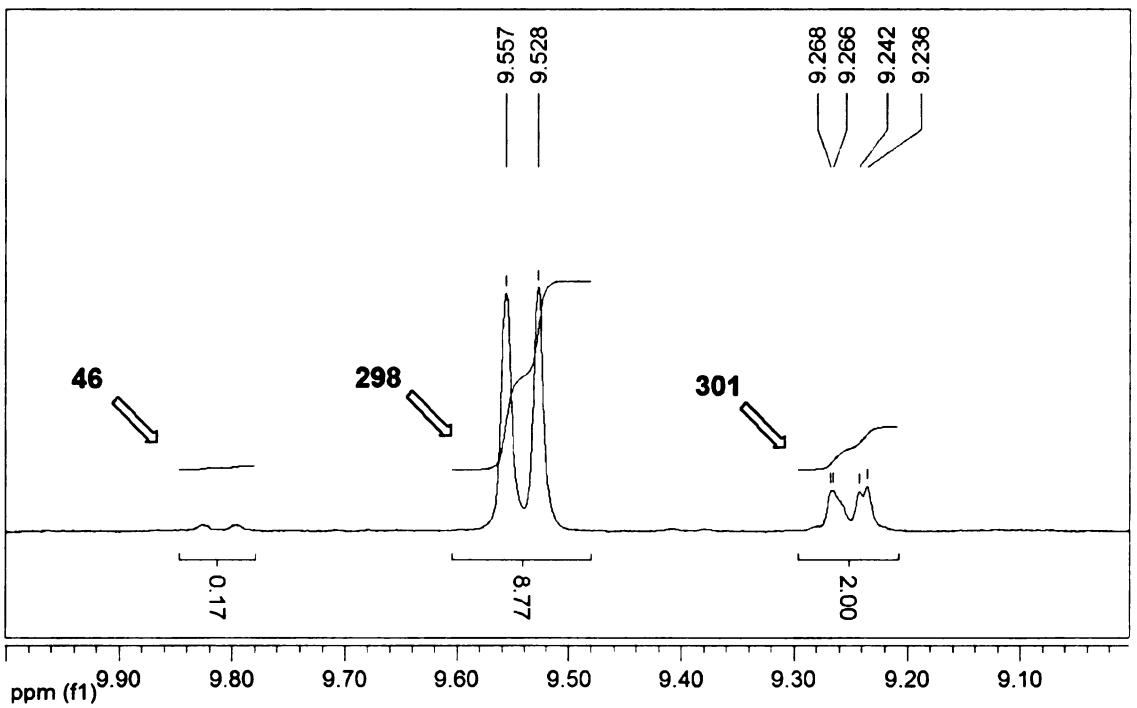


VAPOL:	A	B	PhOH	L	$B(OPh)_3$	311
PM3	28.4089	-106.8543	-21.6716	85.6579	-110.726	-240.9841
HF/ 3-21G	-1997.151344	-2399.651648	-303.860103	-1670.305035	-934.60783	-1337.088532
HF/ 6-31G*	-2008.322903	-2413.03736	-305.558064	-1679.660915	-939.800249	-1344.504172
EDF1/ 6-31G**	-2021.365497	-2428.528054	-307.519058	-1690.677520	-945.748320	-1352.903690
VANOL:	A	B	PhOH	L	$B(OPh)_3$	311
PM3	-7.882	-143.871	-21.6716	50.716	-110.726	-240.9841
HF/ 3-21G	-1693.563347	-2096.060864	-303.860103	-1366.712271	-934.60783	-1337.088532
HF/ 6-31G*	-1703.028309	-2107.740758	-305.558064	-1374.362990	-939.800249	-1344.504172
EDF1/ 6-31G**	-1714.042784	-2121.203933	-307.5190575	-1383.348686	-945.748320	-1352.903690
BINOL:	A	B	PhOH	L	$B(OPh)_3$	311
PM3	-65.1603	-197.9746	-21.6716	-5.1684	-110.726	-240.9841
HF/ 3-21G	-1237.027196	-1639.521095	-303.860103	-910.1720475	-934.607830	-1337.088532
HF/ 6-31G*	-1243.932807	-1648.645097	-305.558064	-915.2689041	-939.800249	-1344.504172
EDF1/ 6-31G**	-1251.873588	-1659.034694	-307.5190575	-921.1796478	-945.748320	-1352.903690

[a] The unit of the energy in the PM3 calculation is kcal/mol and the unit for other methods is au (1 au = 627.5 kcal/mol)

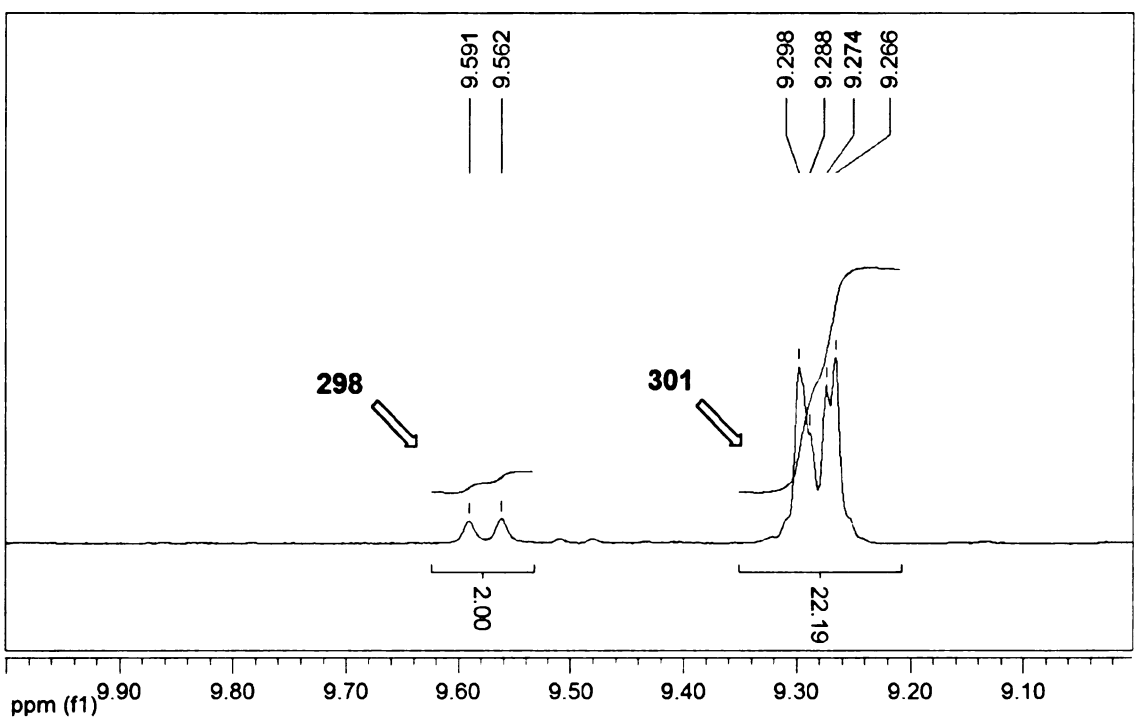
Selective preparation of the VAPOL-mono-borate 298: To a flame-dried Schlenk flask cooled under argon was added VAPOL **46** (54 mg, 0.1 mmol) and 9 mL of dry toluene. The flask was stirred at 100 °C under argon protection. A solution of triphenyl borate (0.15 mmol, 1.5 mL of 1 M solution in toluene) was added via syringe pump to the VAPOL solution over 30 minutes. After the addition, the solution was stirred for 40 minutes, then a vacuum (0.2-0.5 mm Hg) was applied to remove the solvent and volatile material and the residue was heated at 100 °C under high vacuum for 30 minutes. The prepared catalyst was dissolved in $CDCl_3$ and examined by ^1H NMR. NMR indicated that the conversion of VAPOL was > 95% and the ratio of the two catalyst species (**298:301**) is 4.3:1.

Bay proton region of the VAPOL-borate catalyst in $CDCl_3$:

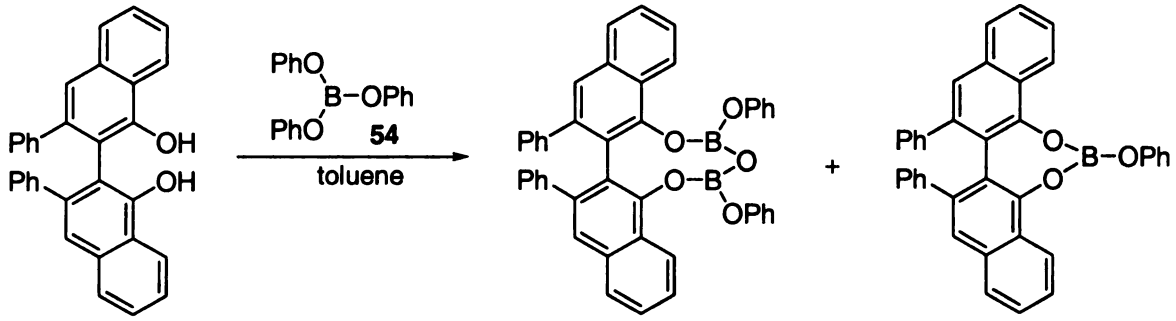


Selective preparation of the VAPOL-di-borate 301: To a flame-dried Schlenk flask cooled under argon was added and triphenyl borate **54** (145 mg, 0.5 mmol) and 9 mL of dry toluene. The flask was stirred at 80 °C under argon protection. A solution of triphenyl VAPOL **46** (54 mg, 0.1 mmol) in 1 mL toluene was added via syringe pump to the solution of **54** over 30 minutes. After the addition, the solution was stirred for 40 minutes, then a vacuum (0.2-0.5 mm Hg) was applied to remove the solvent and volatile material and the residue was heated at 80 °C under high vacuum for 30 minutes. The prepared catalyst was dissolved in $CDCl_3$ and examined by ^1H NMR. NMR indicated that the conversion of VAPOL was 100% and the ratio of the two catalyst species (**298**:**301**) is 1:11.

Bay proton region of the VAPOL-borate catalyst in $CDCl_3$:



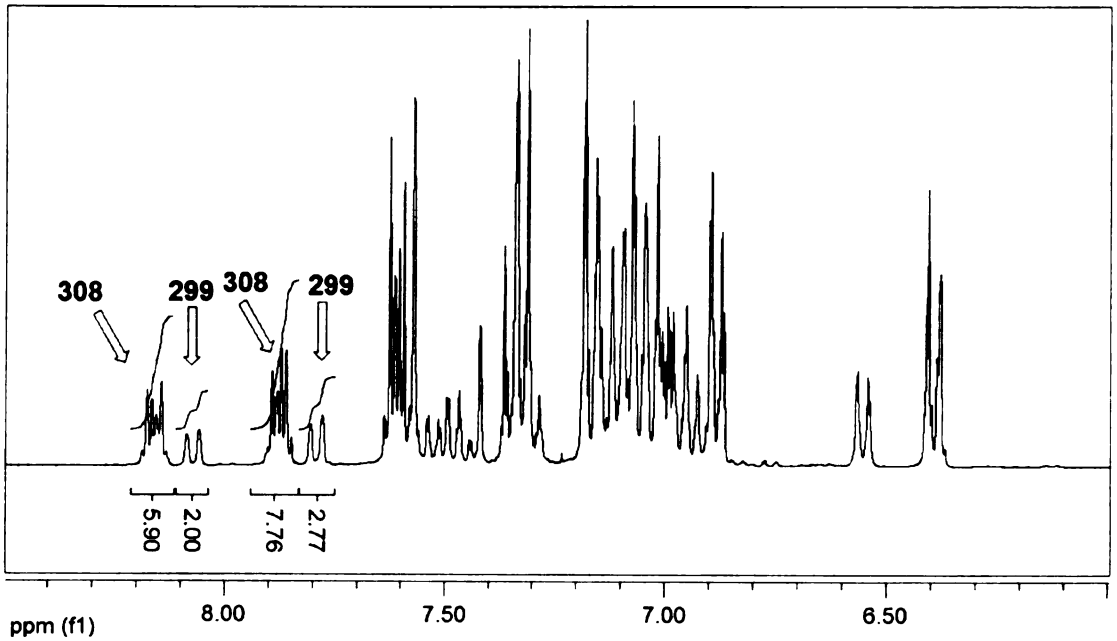
Selective preparation of the VANOL-borate species 308 and 299:



47 308 299

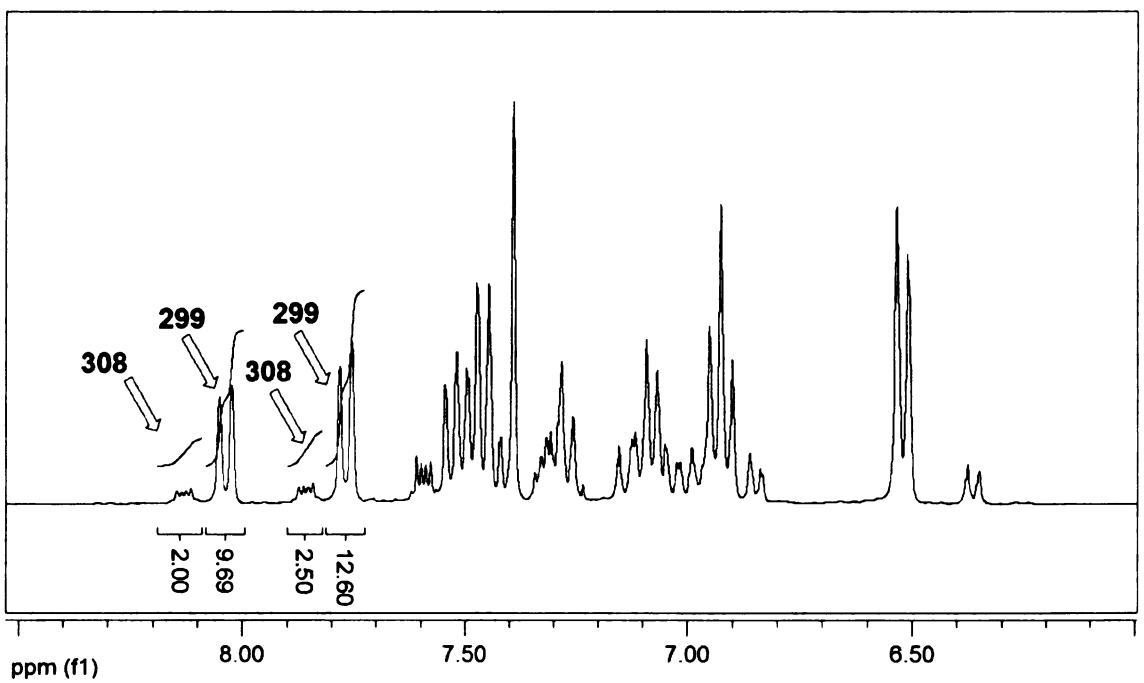
Preparation of VANOL-di-borate 308: To a flame-dried Schlenk flask cooled under argon was added VANOL **47** (44 mg, 0.1 mmol) and $B(OPh)_3$ **54** (87 mg, 0.3 mmol, purchased from Aldrich, ~80% purity) followed by 2 mL of dry CH_2Cl_2. The flask was sealed under argon and the mixture was stirred at 80 °C for 1 hour, then a vacuum (0.2-0.5 mm Hg) was applied to remove the volatile material and the residue was heated at 80 °C under high vacuum for 30 minutes. The prepared catalyst was dissolved in $CDCl_3$ and examined by ^1H NMR. NMR indicated that the ratio of the two catalyst species (**308**:**299**) is approximately 3:1.

Aromatic region of VANOL-borate catalyst in $CDCl_3$:

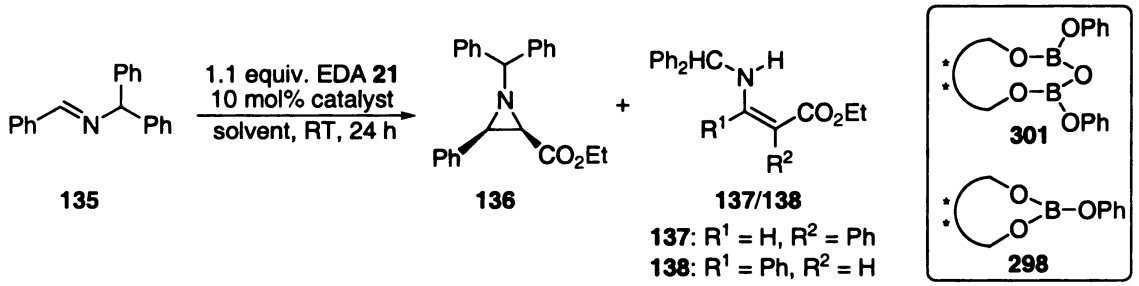


Selective preparation of the VANOL-mono-borate 299: To a flame-dried Schlenk flask cooled under argon was added VANOL **47** (54 mg, 0.1 mmol) and 9 mL of dry toluene. The flask was stirred at 100 °C under argon protection. A solution of triphenyl borate (0.15 mmol, 1.5 mL of 1 M solution in toluene) was added via syringe pump to the VANOL solution over 30 minutes. After the addition, the solution was stirred for 40 minutes, then a vacuum (0.2-0.5 mm Hg) was applied to remove the solvent and volatile material and the residue was heated at 100 °C under high vacuum for 30 minutes. The prepared catalyst was dissolved in $CDCl_3$ and examined by ^1H NMR. NMR indicated that the conversion of VANOL was 100% and the ratio of the two catalyst species (**308:299**) is approximately 1:4-5.

Aromatic region of VANOL-borate catalyst in $CDCl_3$:



Aziridination of imine 135 using selectively generated VAPOL-borate catalysts:



135 136 137/138

137: R^1 = H, R^2 = Ph
138: R^1 = Ph, R^2 = H

Aziridination with VAPOL-mono-borate 298: To a flame-dried 25 mL round bottom flask was added imine **135** (271 mg, 1 mmol) and 1 mL CH_2Cl_2. The VAPOL-borate catalyst was generated from 0.1 mmol of VAPOL and 0.15 mmol of $B(OPh)_3$ according to the procedure described above (which contains 80% VAPOL-mono-borate **298** and 20% di-borate **301** as determined by ^1H NMR), was dissolved in 1 mL of $CDCl_3$ and transferred to the flask containing imine. EDA (115 μL, 1.1 mmol) was added via syringe in once. The mixture was allowed to be stirred at room temperature for 24 hours before workup. The crude reaction mixture was concentrated in vacuo. ^1H NMR indicated that the cis/trans ratio of aziridine **136** was 20:1, and the yield of the enamine products (relative to **136**) was 17% for **137** and 4% for **138**. The crude product was purified by chromatography, gave 243 mg 136 (0.68 mmol, 68% yield). The chiral induction was determined to be 75% ee by chiral HPLC analysis using the condition described in Chapter 5.

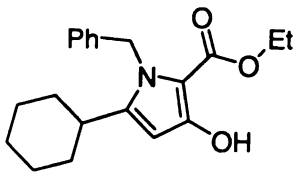
Aziridination with VAPOL-di-borate 301: To a flame-dried 25 mL round bottom flask was added imine **135** (271 mg, 1 mmol) and 1 mL CH_2Cl_2. The VAPOL-borate catalyst was generated from 0.1 mmol of VAPOL and 0. 5 mmol of $B(OPh)_3$ according to the procedure described above (which contains 7.7% VAPOL-mono-borate **298** and 92.3% di-borate **301** as determined by ^1H NMR), was dissolved in 1 mL of $CDCl_3$ and transferred to the flask containing imine. EDA (115 μL, 1.1 mmol) was added via syringe

in once. The mixture was allowed to be stirred at room temperature for 24 hours before workup. The crude reaction mixture was concentrated in vacuo. ^{1}H NMR indicated that the cis/trans ratio of aziridine **136** was > 50:1, and the yield of the enamine products (relative to **136**) was 2% for **137** and <1% for **138**. The crude product was purified by chromatography, gave 281 mg 136 (0.79 mmol, 79% yield). The chiral induction was determined to be 91.5% ee by chiral HPLC analysis using the condition described in Chapter 5.

APPENDICES

Crystallographic Data of Selected Compounds

Figure A.1 ORTEP Drawing of Compound 113



113

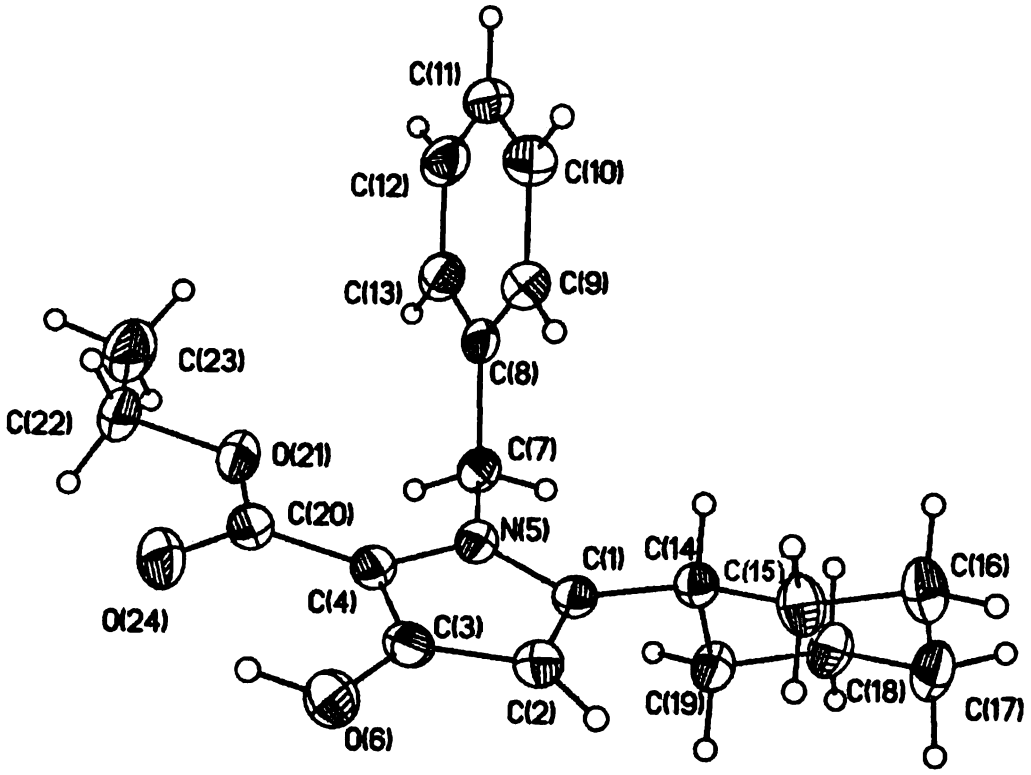


Table A.1.1 Crystal data and structure refinement for **113**

Identification code	p21n
Empirical formula	C20 H25 N O3
Formula weight	327.41
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Monoclinic
Space group	P2(1)/n
Unit cell dimensions	a = 8.7829(18) A
	b = 6.1391(12) A
	c = 32.373(7) A
	alpha = 90 deg.
	beta = 93.08(3) deg.
	gamma = 90 deg.
Volume	1743.0(6) A^3
Z	4
Density (calculated)	1.248 Mg/m^3
Absorption coefficient	0.083 mm^-1
F(000)	704
Crystal size	0.7 x 0.3 x 0.15 mm
Theta range for data collection	2.37 to 28.28 deg.
Index ranges	-11<=h<=11, -7<=k<=7, -41<=l<=41
Reflections collected / unique	19969 / 4167 [R(int) = 0.0331]
Completeness to theta = 28.28	96.6%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4167 / 0 / 317
Goodness-of-fit on F^2	0.868
Final R indices [I>2sigma(I)]	R1 = 0.0393, wR2 = 0.1116
R indices (all data)	R1 = 0.0657, wR2 = 0.1268
Largest diff. peak and hole	0.245 and -0.228 e.A^{-3}

Table A.1.2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for **113**

	x	y	z	U(eq)	Occ.
C(1)	4556(1)	-2288(2)	1536(1)	24(1)	1
C(2)	5268(1)	-4136(2)	1392(1)	28(1)	1
C(3)	5051(1)	-4145(2)	961(1)	27(1)	1
C(4)	4217(1)	-2310(2)	840(1)	26(1)	1
N(5)	3929(1)	-1161(2)	1203(1)	25(1)	1
O(6)	5574(1)	-5741(2)	716(1)	36(1)	1
C(7)	3067(1)	872(2)	1222(1)	26(1)	1
C(8)	1352(1)	582(2)	1188(1)	25(1)	1
C(9)	44(2)	-1325(2)	1306(1)	31(1)	1
C(10)	-946(2)	-1463(3)	1289(1)	40(1)	1
C(11)	-1825(2)	288(3)	1152(1)	41(1)	1
C(12)	-1123(2)	2177(3)	1032(1)	38(1)	1
C(13)	54(2)	2330(2)	1049(1)	32(1)	1
C(14)	4425(2)	-1559(2)	1976(1)	25(1)	1
C(15)	4561(2)	-3509(2)	2273(1)	34(1)	1
C(16)	4394(2)	-2819(3)	2722(1)	40(1)	1
C(17)	5541(2)	-1066(3)	2853(1)	40(1)	1
C(18)	428(2)	877(2)	2560(1)	35(1)	1
C(19)	612(2)	175(2)	2111(1)	30(1)	1
C(20)	3751(2)	-1829(2)	416(1)	30(1)	1
O(21)	2921(1)	-24(2)	352(1)	34(1)	1
C(22)	2404(2)	406(3)	-77(1)	40(1)	1
C(23)	1560(2)	2520(3)	-83(1)	52(1)	1
O(24)	4107(1)	-3031(2)	135(1)	41(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table A.1.3 Bond lengths [A] and angles [deg] for **113**

C(1)-N(5)	1.3714(16)
C(1)-C(2)	1.3874(18)
C(1)-C(14)	1.5030(17)
C(2)-C(3)	1.3990(18)
C(3)-C(4)	1.3884(18)
C(3)-O(6)	1.3561(16)
C(4)-N(5)	1.4032(16)
C(4)-C(20)	1.4420(18)
N(5)-C(7)	1.4626(16)
C(7)-C(8)	1.5153(18)
C(8)-C(9)	1.3881(19)
C(8)-C(13)	1.3922(19)
C(9)-C(10)	1.398(2)
C(10)-C(11)	1.382(2)
C(11)-C(12)	1.380(2)
C(12)-C(13)	1.387(2)
C(14)-C(15)	1.5367(19)
C(14)-C(19)	1.5366(18)
C(15)-C(16)	1.527(2)
C(16)-C(17)	1.520(2)
C(17)-C(18)	1.524(2)
C(18)-C(19)	1.5320(19)
C(20)-O(24)	1.2263(16)
C(20)-O(21)	1.3364(17)
O(21)-C(22)	1.4611(16)
C(22)-C(23)	1.494(3)
N(5)-C(1)-C(2)	108.57(11)
N(5)-C(1)-C(14)	123.16(11)
C(2)-C(1)-C(14)	128.27(12)
C(1)-C(2)-C(3)	107.33(12)
C(4)-C(3)-O(6)	127.69(12)
C(4)-C(3)-C(2)	108.59(11)
O(6)-C(3)-C(2)	123.71(12)
C(3)-C(4)-N(5)	106.80(11)
C(3)-C(4)-C(20)	123.56(12)
N(5)-C(4)-C(20)	129.63(12)

C(1)-N(5)-C(4)	108.71(10)
C(1)-N(5)-C(7)	125.76(10)
C(4)-N(5)-C(7)	125.51(10)
N(5)-C(7)-C(8)	114.31(10)
C(9)-C(8)-C(13)	118.98(12)
C(9)-C(8)-C(7)	122.54(11)
C(13)-C(8)-C(7)	118.43(12)
C(8)-C(9)-C(10)	120.11(14)
C(11)-C(10)-C(9)	120.36(15)
C(10)-C(11)-C(12)	119.60(14)
C(13)-C(12)-C(11)	120.38(14)
C(12)-C(13)-C(8)	120.57(14)
C(1)-C(14)-C(15)	110.73(11)
C(1)-C(14)-C(19)	113.04(10)
C(15)-C(14)-C(19)	109.44(11)
C(16)-C(15)-C(14)	111.81(12)
C(15)-C(16)-C(17)	111.50(13)
C(18)-C(17)-C(16)	111.09(12)
C(17)-C(18)-C(19)	111.35(12)
C(18)-C(19)-C(14)	111.12(11)
O(24)-C(20)-O(21)	122.81(12)
O(24)-C(20)-C(4)	120.87(13)
O(21)-C(20)-C(4)	116.31(11)
C(20)-O(21)-C(22)	115.92(11)
O(21)-C(22)-C(23)	107.37(13)

Symmetry transformations used to generate equivalent atoms:

Table A.1.4 Anisotropic displacement parameters (A^2 x 10^3) for **113**

	U11	U22	U33	U23	U13	U12
C(1)	21(1)	27(1)	24(1)	2(1)	0(1)	-3(1)
C(2)	26(1)	29(1)	29(1)	0(1)	1(1)	1(1)
C(3)	22(1)	31(1)	29(1)	-6(1)	4(1)	-1(1)
C(4)	23(1)	32(1)	25(1)	-4(1)	1(1)	-2(1)
N(5)	24(1)	28(1)	23(1)	-2(1)	0(1)	1(1)
O(6)	37(1)	40(1)	31(1)	-9(1)	3(1)	9(1)
C(7)	27(1)	25(1)	25(1)	-2(1)	-2(1)	0(1)
C(8)	27(1)	31(1)	18(1)	-4(1)	0(1)	2(1)
C(9)	29(1)	35(1)	29(1)	1(1)	-1(1)	0(1)
C(10)	33(1)	49(1)	36(1)	0(1)	2(1)	-10(1)
C(11)	26(1)	64(1)	32(1)	-8(1)	0(1)	2(1)
C(12)	34(1)	48(1)	33(1)	-4(1)	-4(1)	14(1)
C(13)	34(1)	34(1)	28(1)	-1(1)	-1(1)	5(1)
C(14)	26(1)	26(1)	24(1)	1(1)	1(1)	0(1)
C(15)	46(1)	27(1)	29(1)	2(1)	6(1)	-3(1)
C(16)	54(1)	36(1)	29(1)	7(1)	9(1)	2(1)
C(17)	50(1)	44(1)	24(1)	1(1)	-4(1)	6(1)
C(18)	44(1)	34(1)	28(1)	-3(1)	-6(1)	-3(1)
C(19)	34(1)	30(1)	25(1)	2(1)	-3(1)	-5(1)
C(20)	25(1)	38(1)	26(1)	-3(1)	1(1)	-4(1)
O(21)	36(1)	42(1)	23(1)	1(1)	-2(1)	4(1)
C(22)	38(1)	57(1)	23(1)	5(1)	-4(1)	-3(1)
C(23)	58(1)	58(1)	38(1)	13(1)	-6(1)	3(1)
O(24)	45(1)	53(1)	27(1)	-11(1)	2(1)	6(1)

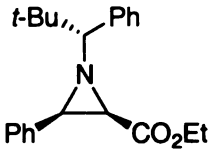
The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

Table A.1.5 Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for **113**

	x	y	z	U(eq)	Occ.
H(2)	5821(17)	-5240(20)	1569(5)	31(4)	1
H(6)	5280(20)	-5400(40)	448(7)	72(7)	1
H(7A)	3328(15)	1550(20)	1483(4)	25(3)	1
H(7B)	3368(15)	1850(20)	1002(4)	22(3)	1
H(9)	1245(18)	-2470(30)	1397(5)	37(4)	1
H(10)	-1420(20)	-2840(30)	1365(6)	51(5)	1
H(11)	-2920(20)	180(30)	1139(5)	51(5)	1
H(12)	-1670(20)	3380(30)	930(5)	49(5)	1
H(13)	954(19)	3630(30)	960(5)	43(4)	1
H(14)	3412(18)	-910(30)	2002(5)	38(4)	1
H(15A)	5570(20)	-4190(30)	2242(5)	41(4)	1
H(15B)	3790(20)	-4560(30)	2188(5)	50(5)	1
H(16A)	3340(20)	-2260(30)	2758(5)	50(5)	1
H(16B)	4510(20)	-4110(30)	2905(6)	53(5)	1
H(17A)	6600(20)	-1650(30)	2855(6)	57(5)	1
H(17B)	5340(18)	-610(30)	3138(5)	43(4)	1
H(18A)	4343(19)	1580(30)	2582(5)	38(4)	1
H(18B)	6200(20)	2020(30)	2640(5)	46(5)	1
H(19A)	5519(19)	1470(30)	1924(6)	46(4)	1
H(19B)	6639(18)	-510(20)	2082(5)	33(4)	1
H(22A)	1710(20)	-820(30)	-170(5)	47(5)	1
H(22B)	3300(20)	450(30)	-238(6)	55(5)	1
H(23A)	710(30)	2500(40)	96(8)	79(7)	1
H(23B)	1150(20)	2820(30)	-367(6)	58(5)	1
H(23C)	2230(30)	3640(40)	-3(8)	89(8)	1

Figure A.2 ORTEP Drawing of Compound 288b



(*2R, 3R*)-**288b**

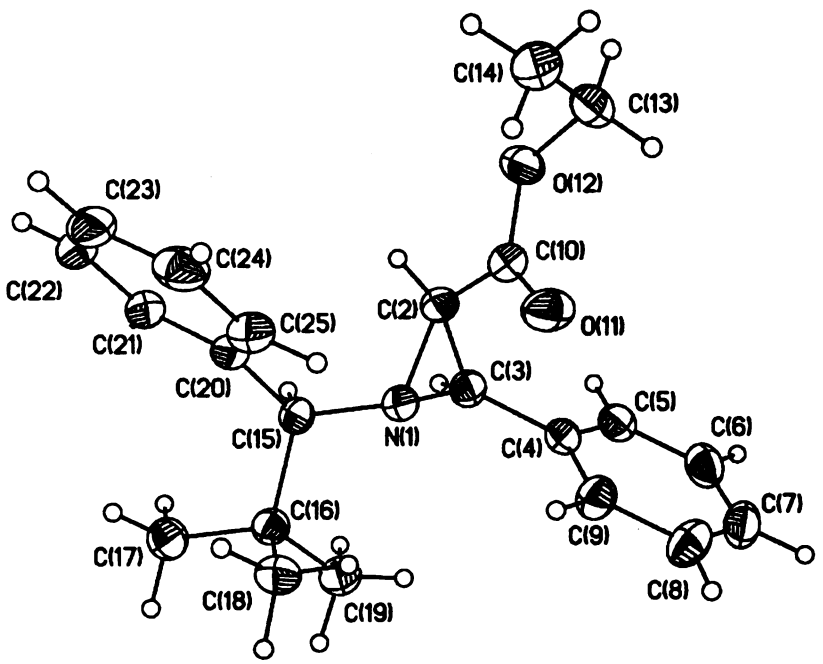


Table A.2.1 Crystal data and structure refinement for **288b**

Identification code	
Empirical formula	$C_{22}H_{27}NO_2$
Formula weight	337.45
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Orth.
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 6.0555(12) A
	b = 15.265(3) A
	c = 20.895(4) A
	alpha = 90 deg.
	beta = 90 deg.
	gamma = 90 deg.
Volume	1931.5(7) A^3
Z	4
Density (calculated)	1.160 Mg/m^3
Absorption coefficient	0.073 mm^-1
F(000)	728
Crystal size	0.7 x 0.2 x 0.2 mm
Theta range for data collection	1.65 to 28.29 deg.
Index ranges	-8<=h<=8, -20<=k<=20, -27<=l<=27
Reflections collected / unique	23164 / 4656 [R(int) = 0.0316]
Completeness to theta = 28.29	98.8%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4656 / 0 / 334
Goodness-of-fit on F^2	0.804
Final R indices [I>2sigma(I)]	R1 = 0.0344, wR2 = 0.0938
R indices (all data)	R1 = 0.0463, wR2 = 0.1039
Absolute structure parameter	0.4(10)
Largest diff. peak and hole	0.136 and -0.185 e.A^-3

Table A.2.2 Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for **288b**

	x	y	z	U(eq)	Occ.
N(1)	8945(2)	4326(1)	1888(1)	25(1)	1
C(2)	9686(2)	3558(1)	1534(1)	27(1)	1
C(3)	10808(2)	4440(1)	1458(1)	26(1)	1
C(4)	10595(2)	5016(1)	884(1)	27(1)	1
C(5)	12437(3)	5133(1)	495(1)	31(1)	1
C(6)	12306(3)	5672(1)	-44(1)	38(1)	1
C(7)	10356(3)	6096(1)	-192(1)	41(1)	1
C(8)	8521(3)	5987(1)	199(1)	40(1)	1
C(9)	8636(2)	5446(1)	737(1)	33(1)	1
C(10)	8119(2)	3206(1)	1043(1)	29(1)	1
O(11)	6498(2)	3576(1)	844(1)	42(1)	1
O(12)	8804(2)	2416(1)	848(1)	33(1)	1
C(13)	7427(3)	1980(1)	367(1)	36(1)	1
C(14)	5496(3)	1528(1)	672(1)	40(1)	1
C(15)	9380(2)	4310(1)	2585(1)	25(1)	1
C(16)	8799(2)	5228(1)	2871(1)	27(1)	1
C(17)	9375(3)	5238(1)	3585(1)	37(1)	1
C(18)	6335(3)	5428(1)	2785(1)	33(1)	1
C(19)	10166(3)	5931(1)	2527(1)	34(1)	1
C(20)	8108(2)	3559(1)	2885(1)	26(1)	1
C(21)	8985(3)	3107(1)	3408(1)	33(1)	1
C(22)	7815(3)	2424(1)	3694(1)	42(1)	1
C(23)	5772(3)	2187(1)	3463(1)	45(1)	1
C(24)	4881(3)	2621(1)	2942(1)	42(1)	1
C(25)	6040(2)	3301(1)	2652(1)	33(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table A.2.3 Bond lengths [A] and angles [deg] for **288b**

N(1)-C(3)	1.4527(17)
N(1)-C(2)	1.4572(16)
N(1)-C(15)	1.4794(16)
C(2)-C(10)	1.4970(19)
C(2)-C(3)	1.5177(18)
C(3)-C(4)	1.4931(18)
C(4)-C(9)	1.3899(19)
C(4)-C(5)	1.391(2)
C(5)-C(6)	1.396(2)
C(6)-C(7)	1.382(2)
C(7)-C(8)	1.389(3)
C(8)-C(9)	1.397(2)
C(10)-O(11)	1.2063(18)
C(10)-O(12)	1.3393(16)
O(12)-C(13)	1.4652(17)
C(13)-C(14)	1.500(2)
C(15)-C(20)	1.5170(18)
C(15)-C(16)	1.5644(17)
C(16)-C(17)	1.5325(19)
C(16)-C(19)	1.5335(19)
C(16)-C(18)	1.534(2)
C(20)-C(21)	1.3973(19)
C(20)-C(25)	1.400(2)
C(21)-C(22)	1.394(2)
C(22)-C(23)	1.376(3)
C(23)-C(24)	1.383(3)
C(24)-C(25)	1.393(2)
C(3)-N(1)-C(2)	62.87(9)
C(3)-N(1)-C(15)	118.15(10)
C(2)-N(1)-C(15)	115.52(10)
N(1)-C(2)-C(10)	116.18(11)
N(1)-C(2)-C(3)	58.42(8)
C(10)-C(2)-C(3)	122.03(11)
N(1)-C(3)-C(4)	120.06(11)
N(1)-C(3)-C(2)	58.71(8)
C(4)-C(3)-C(2)	124.60(11)
C(9)-C(4)-C(5)	119.65(12)

C(9)-C(4)-C(3)	121.91(12)
C(5)-C(4)-C(3)	118.43(12)
C(4)-C(5)-C(6)	120.08(14)
C(7)-C(6)-C(5)	120.32(14)
C(6)-C(7)-C(8)	119.74(14)
C(7)-C(8)-C(9)	120.25(15)
C(4)-C(9)-C(8)	119.95(14)
O(11)-C(10)-O(12)	124.65(13)
O(11)-C(10)-C(2)	125.73(12)
O(12)-C(10)-C(2)	109.61(11)
C(10)-O(12)-C(13)	116.24(12)
O(12)-C(13)-C(14)	111.19(12)
N(1)-C(15)-C(20)	109.24(10)
N(1)-C(15)-C(16)	108.72(10)
C(20)-C(15)-C(16)	113.87(10)
C(17)-C(16)-C(19)	109.03(12)
C(17)-C(16)-C(18)	109.45(12)
C(19)-C(16)-C(18)	109.34(12)
C(17)-C(16)-C(15)	109.28(11)
C(19)-C(16)-C(15)	109.05(11)
C(18)-C(16)-C(15)	110.66(11)
C(21)-C(20)-C(25)	118.30(13)
C(21)-C(20)-C(15)	120.25(13)
C(25)-C(20)-C(15)	121.46(11)
C(22)-C(21)-C(20)	120.69(15)
C(23)-C(22)-C(21)	120.22(15)
C(22)-C(23)-C(24)	120.05(15)
C(23)-C(24)-C(25)	120.22(16)
C(24)-C(25)-C(20)	120.52(14)

Symmetry transformations used to generate equivalent atoms:

Table A.2.4 Anisotropic displacement parameters (A^2 x 10^3) for **288b**

	U11	U22	U33	U23	U13	U12
N(1)	27(1)	23(1)	26(1)	0(1)	-1(1)	0(1)
C(2)	30(1)	24(1)	28(1)	1(1)	-3(1)	6(1)
C(3)	25(1)	28(1)	27(1)	1(1)	-2(1)	4(1)
C(4)	30(1)	26(1)	25(1)	-3(1)	-2(1)	-1(1)
C(5)	33(1)	31(1)	29(1)	-4(1)	1(1)	1(1)
C(6)	44(1)	41(1)	28(1)	-2(1)	7(1)	-6(1)
C(7)	55(1)	40(1)	28(1)	6(1)	-4(1)	-6(1)
C(8)	39(1)	40(1)	42(1)	10(1)	-10(1)	3(1)
C(9)	31(1)	36(1)	32(1)	5(1)	-2(1)	3(1)
C(10)	34(1)	25(1)	27(1)	2(1)	0(1)	1(1)
O(11)	45(1)	32(1)	49(1)	-5(1)	-19(1)	7(1)
O(12)	39(1)	28(1)	33(1)	-6(1)	-1(1)	2(1)
C(13)	46(1)	32(1)	30(1)	-7(1)	1(1)	-4(1)
C(14)	44(1)	35(1)	40(1)	1(1)	0(1)	-4(1)
C(15)	26(1)	26(1)	23(1)	1(1)	-3(1)	2(1)
C(16)	29(1)	24(1)	26(1)	0(1)	-2(1)	-2(1)
C(17)	48(1)	34(1)	29(1)	-3(1)	-6(1)	-2(1)
C(18)	33(1)	30(1)	37(1)	-2(1)	2(1)	4(1)
C(19)	39(1)	28(1)	37(1)	1(1)	1(1)	-5(1)
C(20)	30(1)	23(1)	27(1)	-1(1)	3(1)	2(1)
C(21)	41(1)	28(1)	30(1)	2(1)	3(1)	7(1)
C(22)	63(1)	28(1)	35(1)	6(1)	12(1)	9(1)
C(23)	62(1)	26(1)	48(1)	1(1)	22(1)	-6(1)
C(24)	41(1)	32(1)	53(1)	-9(1)	11(1)	-8(1)
C(25)	34(1)	27(1)	38(1)	-1(1)	0(1)	-1(1)

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

Table A.2.5 Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for **288b**

	x	y	z	U(eq)	Occ.
H(2)	10550(30)	3123(11)	1766(7)	32(4)	1
H(3)	12320(30)	4456(10)	1668(7)	29(4)	1
H(5)	13790(30)	4825(12)	604(7)	38(4)	1
H(6)	13630(40)	5739(13)	-308(9)	47(5)	1
H(7)	10290(30)	6469(12)	-572(9)	44(5)	1
H(8)	7210(30)	6299(14)	129(9)	45(5)	1
H(9)	7350(30)	5370(12)	1005(8)	40(5)	1
H(13A)	6940(30)	2392(12)	59(8)	29(4)	1
H(13B)	8430(30)	1561(13)	184(9)	49(5)	1
H(14A)	4590(30)	1240(14)	338(10)	53(6)	1
H(14B)	4560(30)	1958(13)	874(9)	45(5)	1
H(14C)	5960(30)	1111(13)	1011(9)	43(5)	1
H(15)	11010(30)	4184(11)	2667(7)	31(4)	1
H(17A)	10950(40)	5046(14)	3643(9)	52(5)	1
H(17B)	8460(30)	4831(11)	3851(8)	34(4)	1
H(17C)	9120(30)	5837(14)	3773(10)	51(5)	1
H(18A)	6030(30)	6029(12)	2951(8)	39(5)	1
H(18B)	5860(30)	5393(12)	2325(8)	42(5)	1
H(18C)	5400(30)	5020(12)	3058(9)	45(5)	1
H(19A)	9760(30)	6009(11)	2092(9)	40(5)	1
H(19B)	9870(40)	6505(14)	2741(10)	58(6)	1
H(19C)	11670(40)	5788(14)	2538(9)	50(5)	1
H(21)	10460(30)	3265(11)	3553(8)	32(4)	1
H(22)	8510(30)	2131(12)	4042(8)	41(5)	1
H(23)	5030(40)	1718(14)	3673(10)	67(6)	1
H(24)	3420(40)	2461(16)	2748(10)	65(6)	1
H(25)	5430(30)	3607(12)	2272(8)	40(4)	1

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