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A UNIVERSAL ASYMMETRIC CATALYTIC AZIRIDINATION SYSTEM, AND OTHER FORAYS IN CHIRAL CATALYSIS

presented by

AMAN ASHVIN DESAI

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of the requirements for the

Doctoral degree in Chemistry

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A UNIVERSAL ASYMMETRIC CATALYTIC AZIRIDINATION SYSTEM, AND OTHER FORAYS IN CHIRAL CATALYSIS

By

Aman Ashvin Desai

A DISSERTATION

Submitted to
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ABSTRACT

A UNIVERSAL ASYMMETRIC CATALYTIC AZIRIDINATION SYSTEM, AND OTHER FORAYS IN CHIRAL CATALYSIS

By

Aman Ashvin Desai

A universal asymmetric catalytic aziridination system is described. Contributions were made to the development of a robust, efficient and scalable *cis*-selective aziridination of imines and diazoacetates. By simply switching to diazoacetamides, the diastereoselectivity could be cleanly reversed, and the corresponding *trans*-aziridines could be accessed efficiently. Thus, employing the same imine and the same chiral catalyst, we can now independently access both *cis*- and *trans*- aziridines with excellent yields, diastereoselectivities and asymmetric inductions. The substrate scope is broad for both the *cis*- and *trans*-selective aziridination protocols, and includes imines prepared from both electron rich and electron deficient aromatic aldehydes, and also from 1°, 2° and 3° aliphatic aldehydes. The face selectivity of the addition to the imine was found to be independent of the diazo compounds. The (*S*)-VANOL or (*S*)-VAPOL catalyst will cause both diazoesters and diazoacetamides to add to the *Si*-face of the imine when *cis*-aziridines are formed, and both to add to the *Re*-face of the imine when *trans*-aziridines are formed.

The stereochemistry determining step of the universal aziridination reactions was studied using ONIOM(B3LYP/6-31G*:AM1) calculations in collaboration with Dr. Mathew Vetticatt. The origin of *cis*-selectivity in reactions of ethyldiazoacetate, and *trans*-selectivity in reactions of *N*-phenyldiazoacetamide, was understood on the basis of the difference in specific non-covalent interactions at the stereochemistry determining transition state. An H-bonding interaction between the amidic hydrogen and an oxygen atom of the chiral counterion was identified as the key interaction responsible for this reversal in diastereoselectivity. KIE experiments subsequently provided evidence for a rate limiting ring closure for the step-wise mechanism in the universal aziridination reaction.

Other forays in chiral catalysis were also made. New structurally distinct chiral Brønsted acids and ligands were prepared based on the framework of VAPOL and VANOL. Development of other catalytic asymmetric reactions was initiated, including the Darzens reaction, the transfer hydrogenation of quinolines, and the rhodium catalyzed aziridination of olefins, with varying degrees of success.

To,

Mom and Dad

(words would never be enough)

ACKNOWLEDGEMENTS

It is difficult to put the last five years in perspective, life has changed so much. A PhD in the organic area at the Department of Chemistry, Michigan State University has certainly been a life changing experience, and there are numerous people to thank. Before getting to individuals, I must thank all the faculty, especially the organic ones, for making the department a wonderful, no-nonsense, and absolutely science driven institution. The friendly and completely informal atmosphere between the professors and students makes it an absolute pleasure and a lot of fun to work in this department. I must say I will be very sorry to go away from this place which has taught me and given me so much.

The same feelings exist for my research group, that of Professor William Wulff. Not only have I learned a tremendous amount of science from being under his tutelage, but I have grown a lot in his group too. His completely hands-off approach towards running his research group has helped me develop as a researcher, and as a person. Right from the first year, he gave me a free hand to pursue my wild dreams in asymmetric catalysis. Looking back, some of these ideas of mine were pretty ludicrous, but he always encouraged me to pursue them. At the same time, his door was always open and he has always been available and ready to offer sound advice. Dr. Wulff has also infused in me an appreciation of the fine things in life; be it fine wine, good fresh coffee, or fine cheese. I have really enjoyed interacting with him, scientifically as well as socially; he has been a great boss. In what has been the most important stage of

my education, I am sure I could not have learned more and grown more in any other place than the research group of Professor William Wulff, and I will always be extremely grateful.

Babak. Professor Babak Borhan. I vividly remember him patiently talking to me for hours in his office in my first year in the program, and telling me that I was an idiot for not pursing a PhD. His advice and those conversations were instrumental in me deciding to stay for the PhD, and it has been the best decision that I have made for my career so far. Babak has always been ready to offer help, be it for chemistry or for anything else. His organic spectroscopy and bioorganic chemistry courses were two of the best courses I have ever taken; Babak is a great teacher and I have learned a lot from him. After a few glasses of wine or margaritas, that Babak was Professor Babak Borhan would usually be the farthest thought in my mind – it has truly been a pleasure interacting with, working with and learning from Babak. I thank him for everything.

I also thank Professor Robert Maleczka was all the assorted help he has provided through the years. I have bugged him quite a bit with questions about the pharmaceutical / fine chemical industry, and other research related problems, and he has always been spontaneous and very generous with his advice, recommendations and suggestions.

I also thank Dr. Borhan and Dr. Maleczka for organizing the Wednesday night mechanism clubs that I attended religiously until my fourth year. One of the fondest memories I will take from this department will be sitting in a room, drinking beer, joking with them, and proposing ridiculous structures and

mechanisms, but learning an amazing amount of synthetic organic chemistry at the same time. I am guessing that I will never be able to live down my "S_N2's on sp^2 centers" reaction mechanisms.

I thank Professor Aaron Odom for taking the time to be on my committee, and I also apologize for failing in our collaborative project. I assure him it was not due to a lack of effort on my part. I would like to thank Dr. Dan Holmes for being an amazingly considerate boss, when I was the NMR TA under him for a few years. I thank Ms. Lijun Chen in the Mass Spectrometry Facility at the Department of Biochemistry for her kind help whenever I needed to get some HRMS samples.

I must thank our collaborator, Dr. Mathew J. Vetticatt. Mathew is one of my best friends from college and also my roommate from college. To be able to collaborate with one of your best friends in science – I don't think it can get better than that. I would also like to thank our other collaborators. Dr. Xiaoyong Li and Professor Babak Borhan, and Dr. Supriyo Majumder and Professor Aaron Odom – it was a lot of fun working with all of them.

The Wulff group has been just an amazing and rocking place to pursue a PhD in, and there are quite a few Wulff group members to thank – past and present. I would like to thank Dr. Keith Korthals for being my lab neighbor in my early years, and patiently answering the million stupid questions that I used to ask him all the time. Keith truly went out of his way to help me and train me in the ways of organic synthesis; without his help I would have been a complete idiot in the lab. Dr. Zhenjie Lu also helped me tremendously in the early years. She was

always ready to drop whatever she was doing, and answer my questions. Zhenjie was the perfect senior in the lab, always ready to help with a smile. I would also like to thank Dr. Zhensheng Ding for his friendship, and his absolutely hilarious jokes and drawings. Many a depressing day were lightened by Ding's humor and laughter. I thank Dr. Yu Zhang for his help and advice in my first year; it was Yu's project that I took up initially. Dr. Konstantinos Rampalakos (Kostas) and Dr. Cory Newman were good friends, and good lab mates. I have had quite a few wild memories in the company of Dr. Alex Predeus, we had fun hanging out together.

From the present Wulff group, a big thank-you goes out to my two favorite Chinese girls in the world – Li Huang and Hong Ren. They have been wonderful companions in the group in the last few years. We have had great parties together, and we have had countless heated discussions, arguments and talks. Hong and Li have helped me a lot in my research, and they have helped me a lot in my personal life too. There have been quite a few times when I was about to do something very stupid that I would definitely regret later, and they have held me back, quite forcefully at times. They have been extremely good friends, and I do hope they will remain that way.

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fortune to work with two post-doctoral research associates who had come to our group for short periods of time. Dr. María Pascual and Dr. Roberto Morán-Ramallal were fun to work with, and have become good friends. I thank all the group members, past and present, for making the group a rocking place to be in.

I have been lucky to have numerous good friends through these years. Allison Brown was one of my first friends in the chemistry department, and has remained a close friend. We have had great times, partying, hanging out and going through the rigors of grad school together. At the mention of hanging out with friends, I have to mention our Cancun gang – Aman Kulshrestha, Luis Mori Quiroz and Luis Sanchez – for all those Friday nights arguing about everything under the moon over margaritas, chips and salsa, and Pollo Locos. They have been wonderful friends, for multiple reasons, and grad school would have been very boring without them. Hovig has been a good friend in the last few years, and has thrown some amazing parties. Maryam and Borzoo have been good friends too, and along with Monica, Alli, Hovig and Luis Mori formed our Crunchy's gang. Buckets of beer, perfect company, wonderful songs and rock and roll on the karaoke will remain a hard combination to beat for a long time.

Monica Norberg. One of the most courageous and stubborn girls I have ever met. It has been just wonderful having her by my side in the last few years. My fondest memories from these years will be those shared with Monica. I have learned a lot from her; she has made me a better person, both personally and professionally. For all the love and support she has given me in these years, and for all the great times we have had, I will always be grateful.

I have been very fortunate to have a wonderful family. My brother and my sister-in-law have been solid supporters for whatever I have done, and I am sure they will continue being so for all my life.

Finally, all of this would be meaningless if not for my Mom and Dad. Words would never be enough for me to thank them, and I will not even try to do it. All those hour long conversations on Sundays have gone a long way in getting me to where I am today. Without Mom's constant supply of wonderful food, I would have probably starved before I got anywhere close to my PhD. They have always believed in me, and have been absolutely selfless in their love, encouragement and support, to the point where I have taken it for granted at times. I only hope that I can give back to them a fraction of what they have given to me in my life. This thesis and my PhD are dedicated to my Mom and Dad.

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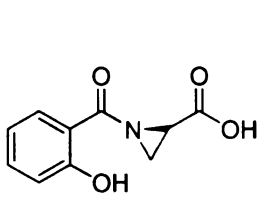
CHAPTER ONE

CHIRAL AZIRIDINES IN ORGANIC CHEMISTRY

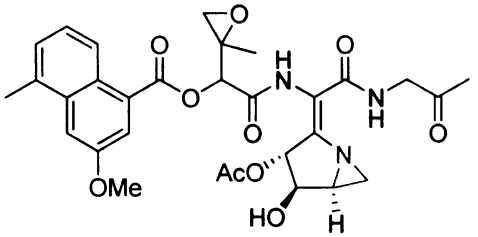
1.1 Chiral aziridines as invaluable motifs in organic chemistry

Aziridines are important 3-membered heterocycles, found in numerous natural products with promising biological activities (Scheme 1.1).[1] Aziridines are also invaluable building blocks in organic synthesis; by virtue of their inherent ring strain, they participate readily in a multitude of stereoselective ring opening and ring expansion reactions.[2,3] Scheme 1.2 provides a snapshot of the multi-dimensional reactivity of aziridine-2-carboxylates,[2a] which is the general motif that we have targeted in our research.

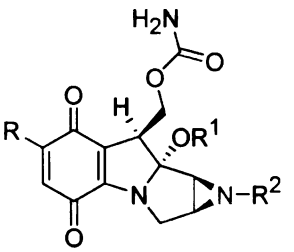
Scheme 1.1 Chiral aziridines in natural products



Madurastatin B1
anti-bacterial activity

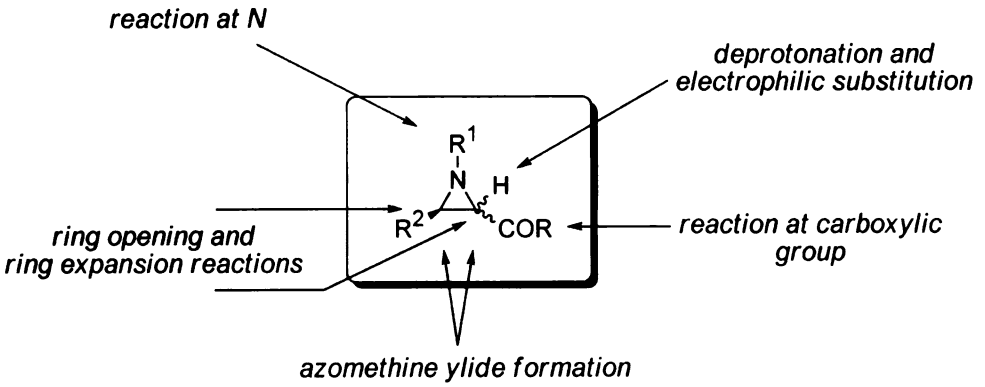


Azinomycin A
anti-tumor activity



Mitomycins
anti-tumor activity

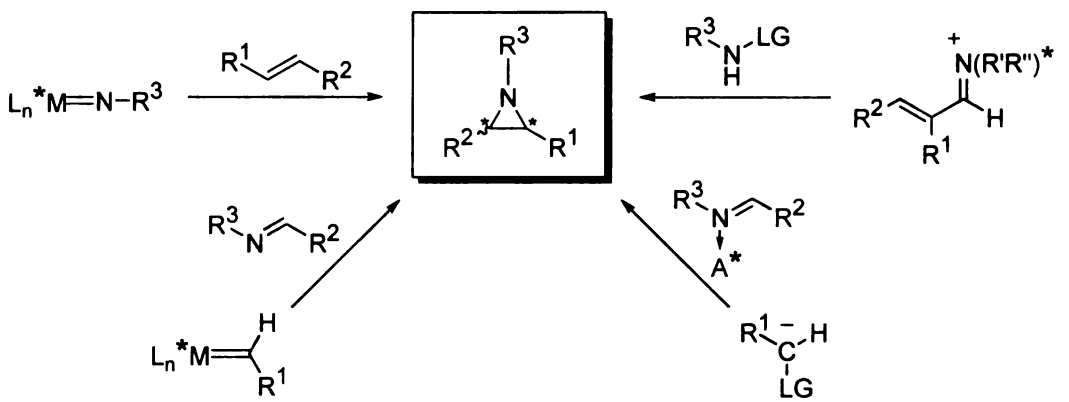
Scheme 1.2 Aziridine-2-carboxylates as versatile synthetic intermediates



1.2 Major approaches towards chiral aziridines

Chiral aziridines could be conceptually obtained in one of two different ways. The first approach would be to start from optically pure starting material, i.e. utilize the chiral pool, and construct the aziridine motif thereon. The second and alternative approach would be the way of catalytic asymmetric synthesis, i.e. induce chirality with the help of chiral catalysts. There has been tremendous growth in both these fields over the last few decades, and this growth has been extensively detailed in several excellent reviews.[2,4]

Scheme 1.3 Major approaches towards catalytic asymmetric aziridination



Approaches towards catalytic asymmetric aziridination could be chiefly differentiated into four categories (Scheme 1.3). From left to right, the first approach involves the transfer of a nitrene from a chiral metal center to an alkene. The second approach involves the transfer of a carbene from a chiral metal center to an imine. Imine activation by a chiral Lewis or Brønsted acid catalyst and subsequent attack of a carbenoid species provides the third approach towards the catalytic asymmetric synthesis of aziridines. The final, and

the most recently developed, approach entails the use of chiral enamine organocatalysis.

The Wulff group has pioneered the third approach towards catalytic asymmetric aziridination viz. the chiral Brønsted acid catalyzed imine aziridination approach. A detailed discussion on the state-of-art in the literature for this approach will be included in subsequent sections of this chapter. Several efficient and successful systems exist in the literature which furnish chiral aziridines utilizing the other approaches depicted in Scheme 1.3. For details on these systems, reference is given to two comprehensive reviews. Muller has published an excellent compilation which reviews the entire field of catalytic asymmetric aziridination till 2003,[4b] and Pellissier has done the same for the time period between 2003 and 2009.[4c]

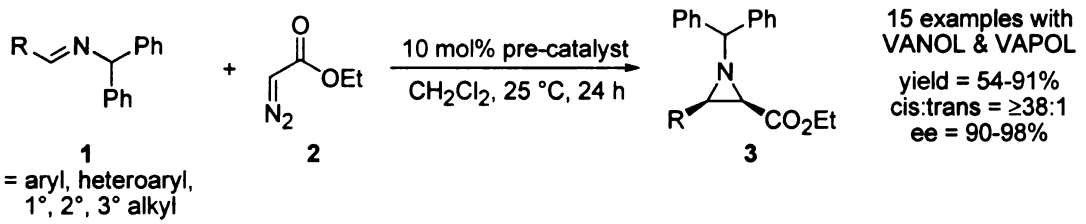
1.3 The Wulff catalytic asymmetric aziridination system

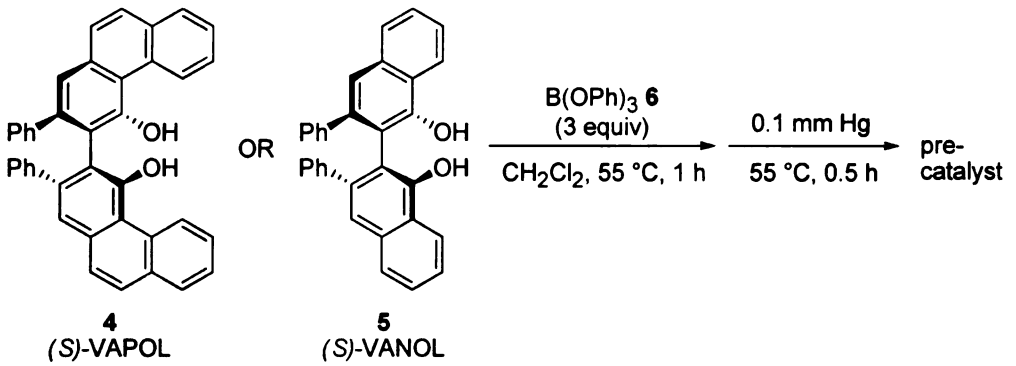
Based on the pioneering studies of Brookhart and Templeton with achiral Lewis acids in 1996,[5a] our group in 1999 developed an efficient aziridination protocol which was originally thought to involve a chiral Lewis acid catalyzed addition of ethyl diazoacetate **2** to imines **1** (Scheme 1.4).[6] The catalyst was prepared *in-situ* from the reaction of the vaulted ligands VAPOL **4** or VANOL **5** and triphenyl borate **6**.

In the years since this aziridination protocol was discovered, an enormous amount of work has been carried out in our group towards further developing this methodology. Efforts towards fine-tuning numerous aspects of the reaction, increasing the scope, elucidating the mechanism and the active catalyst

structure, and applying the reaction towards use in organic synthesis and towards total synthesis of natural products have been undertaken.[7-11] Contributions to these efforts made during the period of this dissertation will be discussed further in Chapter 2. A review of our early work in this field has been published.[12] The Wulff catalytic asymmetric cis-aziridination system, as it stands today, is arguably the most studied and the most efficient and general catalytic asymmetric aziridination protocol in the literature.

Scheme 1.4 The seminal Wulff catalytic asymmetric aziridination system



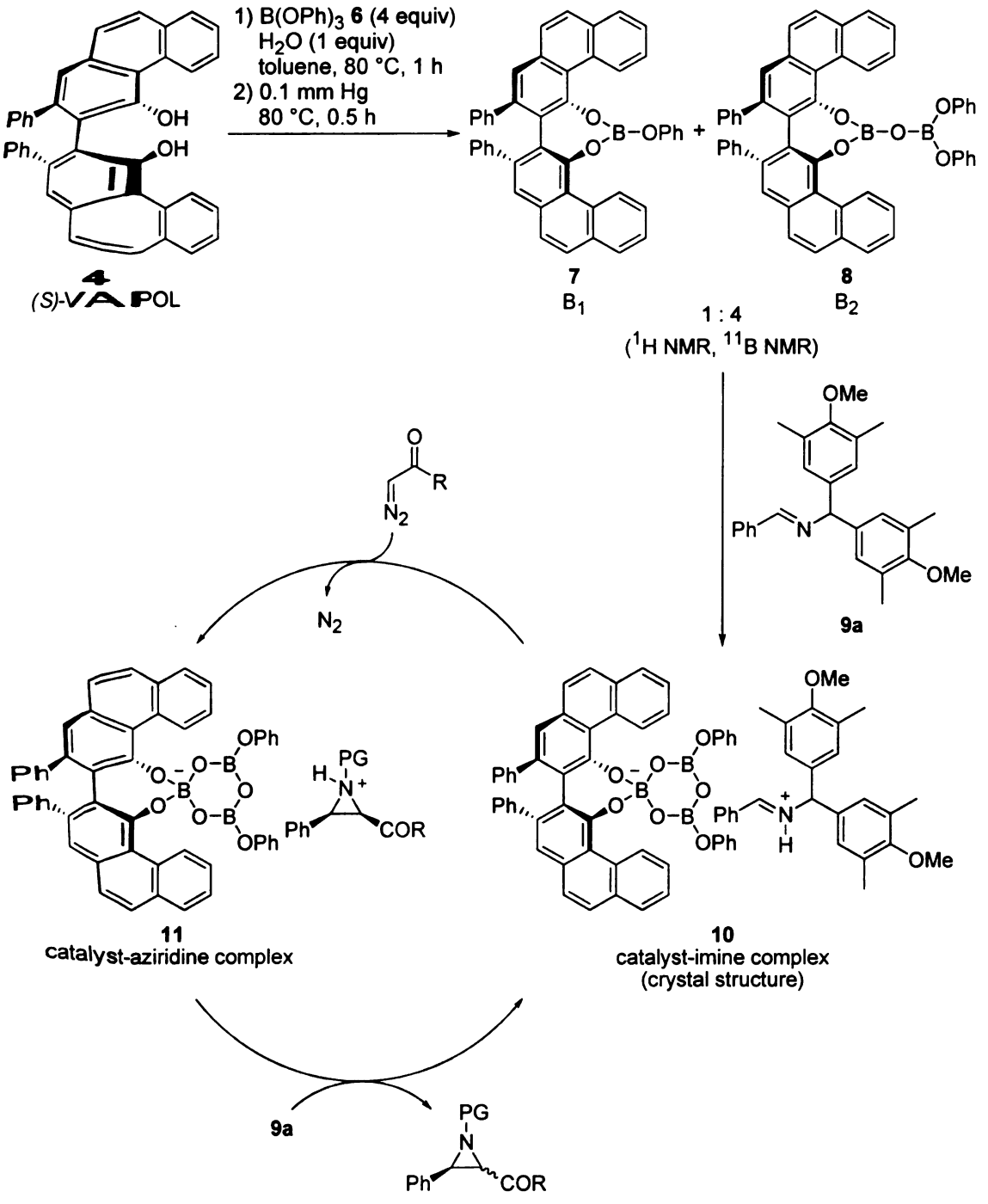


1.3.1 Proposed catalytic cycle in the Wulff aziridinations

A significant part of this dissertation has been devoted to the study of the mechanism of the Wulff aziridination. The origins of the enantio- and diastereo-selections in our cis-selective as well as the newly developed trans- selective aziridination systems have been studied in detail with the aid of computational chemistry. While these studies will be discussed in later chapters, they merit at

this stage a brief discussion of the proposed catalytic cycle in our aziridination reactions. Two previous group members, Yu Zhang and Gang Hu, spent a considerable amount of time during their dissertations in attempting to solve the structure of the active catalyst in our aziridination reactions. Their findings were quite remarkable, and these are depicted in our proposed catalytic cycle, exemplified for the *(S)*-VAPOL ligand **4**, the imine **9a** and a general diazo compound in Scheme 1.5.

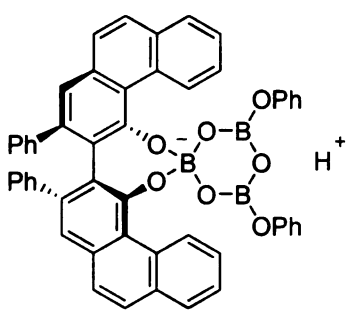
***Scheme* 1.5** Proposed catalytic cycle in the Wulff aziridinations



The active catalyst is prepared *in-situ* in the reaction from VAPOL **4** and triphenyl borate **6**. In the initial years after the discovery of the aziridination

reaction, it was believed in our group that the active catalyst in our reactions would resemble the meso-monoborate **7** (B_1). However, we had no evidence to support this hypothesis. After an extensive study based on high resolution mass spectrum analysis, ^{1}H NMR and ^{11}B NMR,[8] Yu Zhang was able to ascertain that the product of the initial reaction between VAPOL and triphenylborate was actually a mixture of two species, the monoborate **7** (B_1) as well as a linear pyroborate **8** (B_2). The pyroborate **8** (B_2) was formed as the major species in the reaction. Yu Zhang and Zhenjie Lu, another previous group member, were then able to obtain evidence that suggested that the pyroborate **8** (B_2) was actually the active catalytic species in our reaction.[8] Subsequently, Gang Hu tried to gather solid state evidence for this proposal by attempting to grow crystals of the complex formed between the pyroborate **8** (B_2) and a substrate imine **9a**.[11b] Much to our surprise, the crystals that he solved the structure for revealed an entirely different complex – the spiroboroxinate catalyst-imine complex **10**.[11b]

Figure 1.1 (*S*)-VAPOL-B_3 catalyst – *the active catalyst in Wulff aziridinations*



12
(S)-VAPOL-B_3 catalyst

This discovery, and subsequent studies,[11] have since led us to believe that the active catalyst in the Wulff aziridination reactions is actually a spiroboroxinate Brønsted acid catalyst (Figure 1.1, *(S)*-VAPOL-B_3 catalyst **12**), and

not a Lewis acid catalyst as we had believed for several years. In our catalytic cycle then, the catalyst-imine complex **10** reacts with the diazo compound to give the catalyst-aziridine complex **11** (Scheme 1.5). It was not possible to detect species **11** and this was presumed to be due to a more favorable binding of the imine to the catalyst than the aziridine which leads to turnover.[11b]

1.4 Other chiral Brønsted acid catalyzed imine aziridination systems

Till 2008, the Wulff cis-aziridination system was the only example of a chiral Brønsted acid catalyzed imine aziridination protocol. Since 2008, there has been a flurry of activity in this field, and three research groups have reported imine aziridination systems catalyzed by different chiral Brønsted acid catalysts.

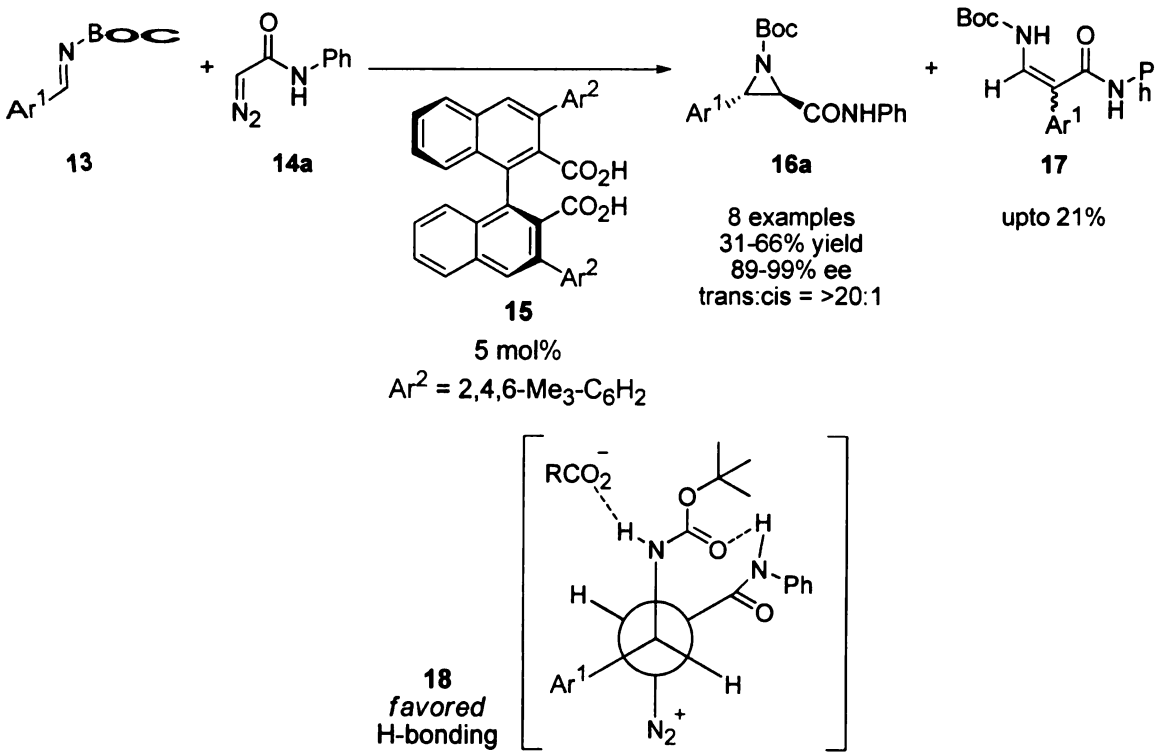
1.4.1 Maruoka's trans-aziridination system

In 2008, Maruoka reported the first trans-selective chiral Brønsted acid catalyzed aziridination of imines (Scheme 1.6).[13] In their system, the reactions between aryl *N*-Boc imines **13** and *N*-phenyldiazoacetamide **14a** mediated by the chiral BINOL dicarboxylic acid catalyst **15** furnished the corresponding trans-aziridines **16a** with excellent control of enantio- and diastereo- selectivities. It was a beautiful system for the first example, but there were several significant drawbacks. Only 8 examples were reported for the imine substrate scope, all of which were derived from aromatic aldehydes with a fixed substitution pattern and electronic allowance. The yields were strictly moderate, and significant amounts of the enamines **17** were formed as side products. They proposed that transition state **18** was favored due to hydrogen bonding between the Boc group of the

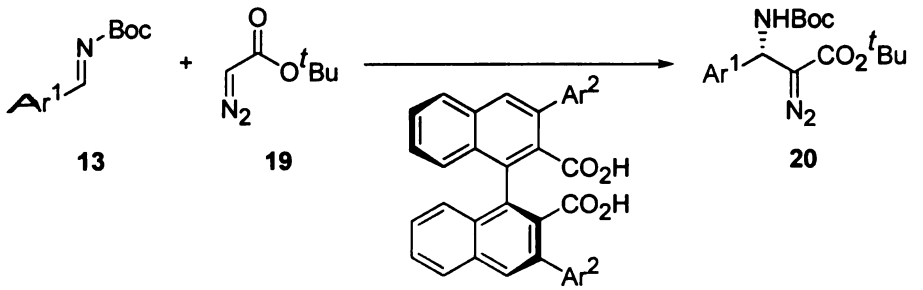
imine and the diazoacetamide *N*-H bond, which provided the observed trans *diastereo*selectivity.

In a separate study, Maruoka has reported that if they use diazoacetates instead of diazoacetamides, and use the same aryl *N*-Boc imines **13** and the same BINOL dicarboxylic acid catalyst **15** as in their trans-aziridination system, they obtain the corresponding alkylation products (Scheme 1.7).[14a]

Scheme 1.6 Maruoka's trans-aziridination system with *N*-phenyldiazoacetamide



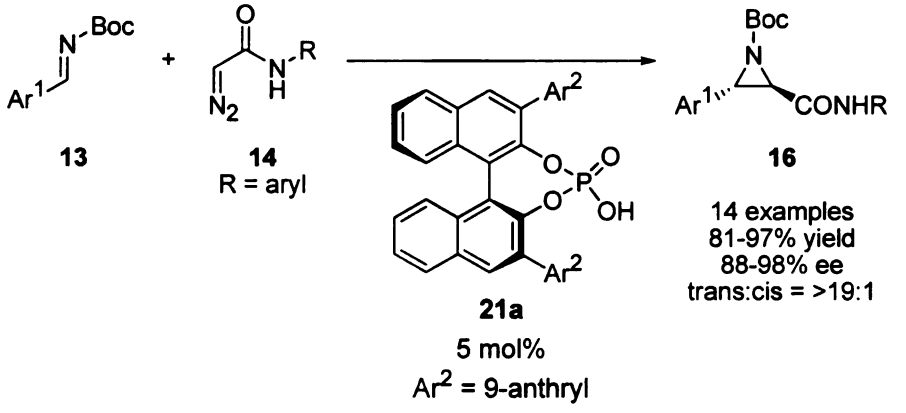
Scheme 1.7 Use of diazoacetate **19** by Maruoka furnishes the alkylation product



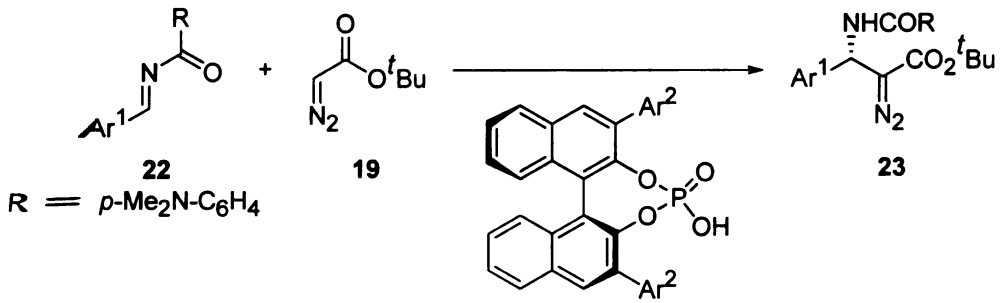
1.4.2 Zhong's trans-aziridination system

Presumably taking the initiative from Maruoka's seminal report,[13] Zhong in 2009 reported a similar trans-selective aziridination protocol catalyzed by the chiral BINOL phosphoric acid catalyst **21a** (Scheme 1.8).[15] Excellent control over the enantio- and diastereo- selectivities was demonstrated, but the significant improvements in Zhong's system over that of Maruoka's were the higher yields for the trans-aziridine products and the extremely short reaction times (10 min for most substrates).

Scheme 1.8 Zhong's trans-aziridination system with *N*-aryldiazoacetamides **14**



***Scheme* 1.9** Use of diazoacetate **19** by Terada furnishes the alkylation product



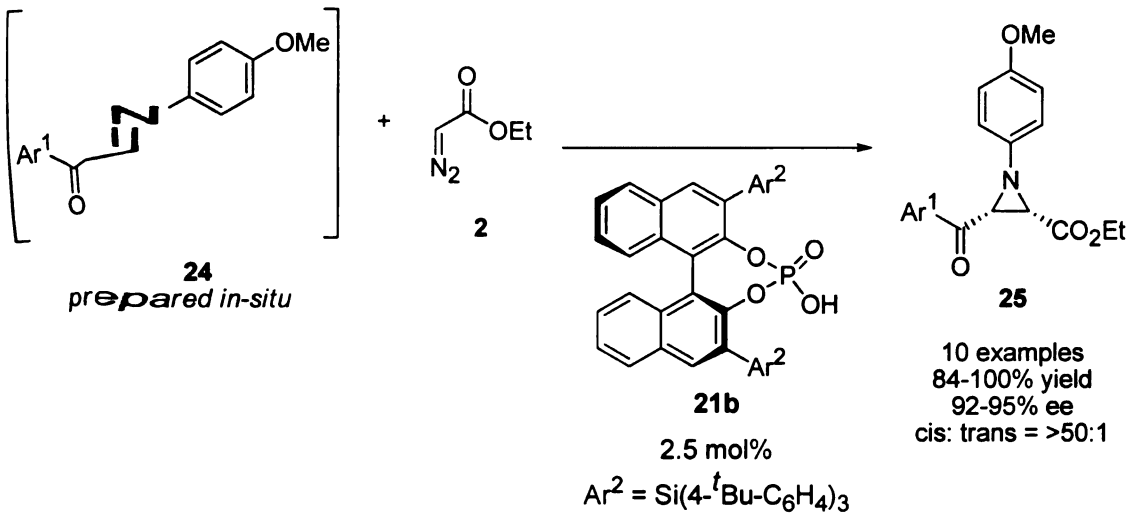
However, as with Maruoka's trans-aziridination system, Zhong's protocol was also limited to imines prepared from aromatic aldehydes with a fixed substitution pattern and electronic allowance. Furthermore, in analogy to Maruoka's system again, Terada in a separate study has demonstrated that if they use diazoacetates instead of diazoacetamides, and use similar imines and the same chiral BINOL phosphoric acid catalyst **21a** as in Zhong's trans-aziridination study, they obtain the corresponding alkylation products (Scheme 1.9).[16]

1.4.3 Akiyama's cis-aziridination system

Akiyama in 2009 reported a cis-aziridination system between activated imines **24** and ethyldiazoacetate **2**, mediated by the chiral BINOL phosphoric acid catalyst **21b** (Scheme 1.10).[17] The imines **24** were prepared *in-situ* in the reaction from the corresponding phenyl glyoxal derivatives and *p*-anisidine. Excellent results were obtained for the cis-aziridine products (Scheme 1.10). However, it was a very specific system; the major drawback was the need for activated imines i.e. only imines prepared from phenyl glyoxal derivatives were

reported. They speculated that having an electron rich group on the imine nitrogen facilitates the nucleophilic aziridine formation, as against the alkylation pathway reported by Maruoka[14a] (Scheme 1.7) and Terada[16] (Scheme 1.9) in their reactions between diazoacetates and imines with electron deficient groups on the nitrogen.

Scheme 1.10 Akiyama's cis-aziridination system with ethyldiazoacetate **2**



1.5 Conclusions

Aziridines are invaluable motifs in organic chemistry; by virtue of their widespread presence in natural products, and more importantly, by virtue of their incredible versatility as building blocks in organic synthesis.

The oxygen analogs of aziridines are the epoxides, and numerous extremely general and efficient systems for catalytic asymmetric epoxidation exist in the literature.[18] The corresponding progress in catalytic asymmetric aziridination has lagged behind considerably, and although this field has seen significant growth in the last few decades, catalytic asymmetric aziridination to this day remains largely an unsolved problem. Several reasonably efficient

catalytic systems exist for the asymmetric synthesis of cis-aziridines, as do those *for trans*-aziridines; but there is *no* example in the literature of a protocol that *could provide* efficient access to both cis- as well as trans- aziridines, utilizing the same starting material and the same chiral catalyst. The development of such a *universal catalytic asymmetric aziridination* protocol has remained an elusive, albeit an actively pursued goal in the field.

CHAPTER TWO

CATALYTIC ASYMMETRIC CIS-AZIRIDINATION:

STRENGTHENING OLD FRONTIERS, AND BUILDING NEW ONES

2.1 Revisiting the aziridinations with benzhydryl imines

The seminal Wulff catalytic asymmetric cis-aziridination system involved imines prepared from the commercially available benzhydryl amine (Chapter 1, Scheme 1.4).[6] Early on during this dissertation, it was decided to revisit this seminal system.[8]

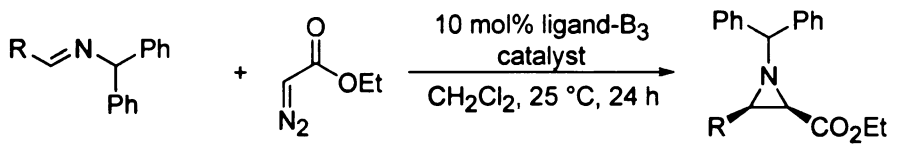
2.1.1 The reasons behind the revisit

Yu Zhang, a previous group member, discovered a serious problem with our basic aziridination system around 2003.[19] He found that when he tried to repeat the aziridinations from our seminal report,[6b] the corresponding cis-aziridine products were obtained with asymmetric inductions which were consistently lower by 4-5% ee as compared to the originally reported values. This led Yu Zhang to launch a comprehensive study of all the possible parameters involved in the reaction to account for the lowering of the observed inductions and to regain the previously obtained inductions.[19] However, to the disappointment of everybody involved, neither a reason to account for the low inductions evolved, nor a solution to get them back to the original values. To this day, this discrepancy remains a mystery.

At the start of the work done for this project during this dissertation, it was desired to confirm these differences from our seminal report. Thus, several

reactions were repeated under the exact conditions as originally reported,[6b] and sure enough, consistently lower asymmetric inductions were obtained (Table 2.1).

Table 2.1 Repeating the aziridinations under the exact original conditions[a]



Entry	R (series)	Ligand	Yield **3** (%) (this work)[b]	ee **3** (%) (this work)[c]	Yield **3** (%) (ref. 6b)[b]	ee **3** (%) (ref. 6b)[c]
1	Ph (**b**)	*(S)*-VAPOL	83	89	77[d]	95
2[e]	*p*-BrC_6H_4 (**f**)	*(S)*-VAPOL	85	90	91	98
3	*p*-BrC_6H_4 (**f**)	*(R)*-VANOL	86	90	85	98
4	*o*-MeC_6H_4 (**c**)	*(S)*-VAPOL	68	88	69	94
5	*o*-MeC_6H_4 (**c**)	*(R)*-VANOL	69	83	65	91
6	*t*-butyl (**l**)	*(S)*-VAPOL	83	83	78	91
7[f]	*t*-butyl (**l**)	*(R)*-VANOL	93	83	77	97
8	*c*-C_6H_{11} (**k**)	*(S)*-VAPOL	74	78	74	94

[a] Unless otherwise specified, all reactions were run with 1 mmol of imine **1** in dichloromethane (0.5 M in imine **1**) with 1.2 equiv of **2**. The catalyst was prepared by heating 1 equiv of ligand with 3 equiv of $B(OPh)_3$ in dichloromethane at 55 °C for 1 h, followed by removing all volatiles under high vacuum (0.1 mm Hg) for 0.5 h at 55 °C. These reaction conditions were identical to those reported in ref. 6b. Reaction with *(R)*-VANOL gives ent. **3**. [b] Isolated yield after chromatography on silica gel. [c] Chiral HPLC. [d] Reaction with 2 mol% of catalyst and 1.0 M imine. [e] Reaction in toluene:dichloromethane (1:1). [f] Toluene, 0 °C for 4 h, then 25 °C for 20 h.

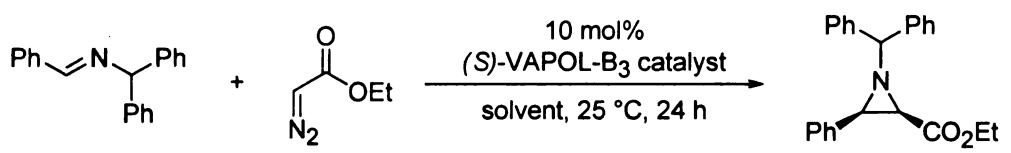
Thus, the primary reason behind revisiting our seminal aziridination system was to determine and report the actual values of the asymmetric inductions obtained for all reactions contained in the original report[6b], and thus

set the record straight. There were a few secondary reasons. It was desired to try toluene also as the solvent for the main substrate scope; dichloromethane had been used in the original reports. It was also desired to add a few more substrates to the original study. The catalyst loading would also be reduced to 5 mol% from 10 mol%. Furthermore, the work reported in Sections 2.1.2, 2.1.4, 2.1.5, and 2.1.6 was also new to this study.

2.1.2 A solvent study

It was initially desired to carry out a thorough solvent study for our basic aziridination system (Table 2.2).

Table 2.2 A solvent study for the basic aziridination system with imine **1b**[a]



Entry	Solvent	Yield **3b** (%)[b]	ee **3b** (%)[c]	Reference
1	THF	79	90	This work
2	Et_2O	83	95	This work
3[d]	CH_3CN	60	26	This work
4	CH_2Cl_2	83	89	This work
5	$CH_3C_6H_5$	83	91	This work
6	CCl_4	84	93	This work
7	$CF_3C_6H_5$	82	90	Ref. 19
8	$CHCl_3$	81	90	Ref. 19
9	CS_2	73	91	Ref. 19
10	C_6H_6	83	92	Ref. 19

[a] Unless otherwise specified, all reactions were run in the mentioned solvent containing 0.5 M imine **1b** with 1.2 equiv of ethyl diazoacetate with respect to imine **1b**. The catalyst was prepared

(Table 2.2 continued...)

by heating 1 equiv of ligand with 3 equiv of $B(OPh)_3$ in dichloromethane at 55 °C for 1 h, followed by removing all volatiles under high vacuum (0.1 mm Hg) for 0.5 h at 55 °C. [b] Isolated yield after chromatography on silica gel. [c] Chiral HPLC. [d] 77% completion.

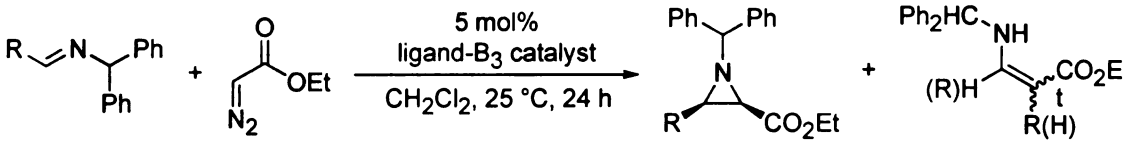
2.1.3 The substrate scope in dichloromethane and toluene

The study of our basic aziridination with VAPOL and VANOL in dichloromethane (Table 2.3) and in toluene (Table 2.4) was carried out, and a few insights were obtained: (1) In dichloromethane, VANOL is superior to VAPOL for all substrates. (2) In toluene, the general trend is that VANOL is similar to or slightly better than VAPOL, with the exception of imine **1j**. (3) In the original report,[6b] dichloromethane was the solvent used. However, this study proves that toluene is better for all substrates, with the exception of imine **1e**, where dichloromethane offered the best asymmetric induction. (4) VANOL and toluene emerged as the best combination for our basic catalytic asymmetric aziridination system. Exceptions to this were the imine **1e** and imine **1j**. (5) Asymmetric inductions as high as those originally reported[6b] were never obtained. However, for all the aromatic substrates from the original report, similar albeit slightly lower inductions were obtained (>90% ee in each case). (6) For all aliphatic substrates, >90% ee was observed in the original report.[6b] However, in this study, even the best inductions for these substrates were in the range of 80-90% ee. (7) For the new imines introduced in this study, the best asymmetric inductions were encouraging (85-94% ee, imines **1d**, **1e**, **1g** and **1h**).

Interestingly, aziridinations with imines derived from *n*-propanal failed in this study while those with imines derived from *n*-butanal were successful,

although the yields obtained were low. Additionally, aziridinations with imines derived from 2-furaldehyde also failed in this study.

Table 2.3 The substrate scope in dichloromethane[a]



1 **2** **3** **26**

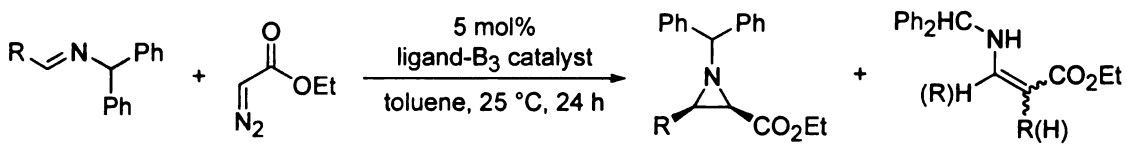
Entry	Imine	R_1	Ligand	Yield **3** (%)[b]	ee **3** (%)[c]	cis:trans[d]	Yield **26** (%)[e]
1	**1b**	Ph	*(S)*-VAPOL	67	91	≥33:1	2/<1
2	**1b**	Ph	*(R)*-VANOL	77	91	≥50:1	<1/5
3	**1c**	*o*-MeC_6H_4	*(S)*-VAPOL	56	85	10:1	7/3
4	**1c**	*o*-MeC_6H_4	*(R)*-VANOL	57	88	11:1	4/10
5	**1d**	*p*-MeC_6H_4	*(S)*-VAPOL	80	88	≥50:1	6/2
6	**1d**	*p*-MeC_6H_4	*(R)*-VANOL	82	93	≥50:1	<1/2
7	**1e**	*o*-BrC_6H_4	*(S)*-VAPOL	40[f]	75	2.0:1	6/7
8	**1e**	*o*-BrC_6H_4	*(R)*-VANOL	41[f]	85	2.2:1	4/9
9	**1f**	*p*-BrC_6H_4	*(S)*-VAPOL	71	84	20:1	2/<1
10	**1f**	*p*-BrC_6H_4	*(R)*-VANOL	81	92	34:1	4/8
11	**1g**	*p*-$NO_2C_6H_4$	*(S)*-VAPOL	61[g]	61	13:1	9/2
12	**1g**	*p*-$NO_2C_6H_4$	*(R)*-VANOL	76[h]	86	34:1	<1/4
13	**1h**	*p*-$OMeC_6H_4$	*(S)*-VAPOL	42[i]	77	5:1	2/<1
14	**1h**	*p*-$OMeC_6H_4$	*(R)*-VANOL	51[j]	88	6:1	2/3
15	**1i**	3,4-$(OAc)_2C_6H_3$	*(S)*-VAPOL	83	86	≥50:1	4/3
16	**1i**	3,4-$(OAc)_2C_6H_3$	*(R)*-VANOL	88	91	≥50:1	3/7
17	**1a**	1-naphthyl	*(S)*-VAPOL	76	89	26:1	2/3
18	**1a**	1-naphthyl	*(R)*-VANOL	73	93	21:1	3/5
19	**1k**	*c*-C_6H_{11}	*(S)*-VAPOL	76	76	≥50:1	<1/<1
20	**1k**	*c*-C_6H_{11}	*(R)*-VANOL	80	83	≥50:1	4/<1

(Table 2.3 continued...)

21	**1l**	*t*-butyl	*(S)*-VAPOL	66[k]	74	≥18:1	1/2
22	**1l**	*t*-butyl	*(R)*-VANOL	85	84	≥50:1	6/<1
23	**1j**	*n*-propyl	*(S)*-VAPOL	24	73	8:1	10/5
24	**1j**	*n*-propyl	*(R)*-VANOL	55	81	14:1	8/9

[a] Unless otherwise specified, all reactions were run with 1 mmol of **1** at 0.5 M in **1** with 1.2 equiv of **2**. The catalyst was prepared by heating 1 equiv of ligand, 4 equiv of $B(OPh)_3$ and 1 equiv of water in toluene at 80 °C for 1 h, followed by removing all volatiles under high vacuum at 80 °C for 0.5 h. Reaction with *(R)*-VANOL gives ent. **3**. [b] Isolated yield after chromatography on silica gel. [c] Chiral HPLC. [d,e] Determined from ^{1}H NMR spectrum of the crude reaction mixture. [f] Reaction time was 48 h. [g] 81% conversion. [h] 97% conversion. [i] 70% conversion. [j] 81% conversion. [k] 86% conversion.

Table 2.4 The substrate scope in toluene[a]



1 **2** **3** **26**

Entry	Imine	R	Ligand	Yield **3** (%)[b]	ee **3** (%)[c]	cis:trans[d]	Yield **26** (%)[e]
1	**1b**	Ph	*(S)*-VAPOL	82	94	≥50:1	<1/<1
2	**1b**	Ph	*(R)*-VANOL	87	93	≥50:1	<1/2
3	**1c**	*o*-MeC_6H_4	*(S)*-VAPOL	63	91	10:1	9/5
4	**1c**	*o*-MeC_6H_4	*(R)*-VANOL	67	90	12:1	2/9
5	**1d**	*p*-MeC_6H_4	*(S)*-VAPOL	80	92	≥50:1	<1/<1
6	**1d**	*p*-MeC_6H_4	*(R)*-VANOL	79[f]	94	≥50:1	<1/2
7	**1e**	*o*-BrC_6H_4	*(S)*-VAPOL	37[g]	82	1.6:1	5/5
8	**1e**	*o*-BrC_6H_4	*(R)*-VANOL	43[g]	82	1.9:1	11/13
9	**1f**	*p*-BrC_6H_4	*(S)*-VAPOL	78[f]	90	20:1	<1/<1
10	**1f**	*p*-BrC_6H_4	*(R)*-VANOL	86	94	≥20:1	6/10

(Table 2.4 continued...)

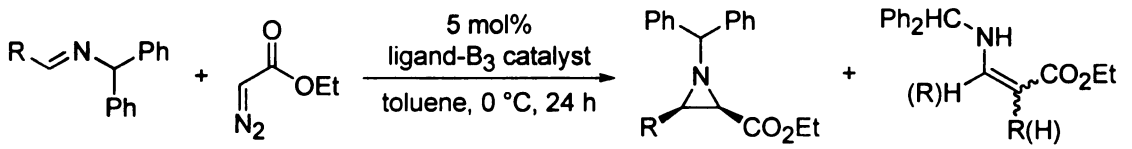
11	**1g**	*p*-$NO_2C_6H_4$	*(S)*-VAPOL	79[h]	79	15:1	<1/<1
12	**1g**	*p*-$NO_2C_6H_4$	*(R)*-VANOL	86	89	≥50:1	<1/<1
13	**1h**	*p*-$OMeC_6H_4$	*(S)*-VAPOL	51[f,i]	86	6:1	13/10
14	**1h**	*p*-$OMeC_6H_4$	*(R)*-VANOL	61	87	34:1	<1/<1
15	**1i**	3,4-$(OAc)_2C_6H_3$	*(S)*-VAPOL	87	89	≥50:1	3/3
16	**1i**	3,4-$(OAc)_2C_6H_3$	*(R)*-VANOL	84	93	≥50:1	<1/<1
17	**1a**	1-naphthyl	*(S)*-VAPOL	76	93	34:1	<1/<1
18	**1a**	1-naphthyl	*(R)*-VANOL	80	93	51:1	<1/2
19	**1k**	*c*-C_6H_{11}	*(S)*-VAPOL	73	81	≥50:1	<1/<1
20	**1k**	*c*-C_6H_{11}	*(R)*-VANOL	79	82	≥ 50:1	6/< 1
21	**1l**	*t*-butyl	*(S)*-VAPOL	72[j]	87	≥50:1	<1/<1
22	**1l**	*t*-butyl	*(R)*-VANOL	89	85	≥50:1	4/<1
23	**1j**	*n*-propyl	*(S)*-VAPOL	40	81	14:1	4/3
24	**1j**	*n*-propyl	*(R)*-VANOL	54	77	14:1	10/9

[a] Unless otherwise specified, all reactions were run with 1 mmol of **1** at 0.5 M in **1** with 1.2 equiv of **2**. The catalyst was prepared by heating 1 equiv of ligand, 4 equiv of $B(OPh)_3$ and 1 equiv of water in toluene at 80 °C for 1 h, followed by removing all volatiles under high vacuum at 80 °C for 0.5 h. Reaction with *(R)*-VANOL gives ent. **3**. [b] Isolated yield after chromatography on silica gel. [c] Chiral HPLC. [d,e] Determined from ^1H NMR of the crude mixture. [f] Reaction run in toluene:dichloromethane (4:1). [g] Reaction time was 48 h. [h] 95% conversion. [i] 73% conversion. [j] 93% conversion.

2.1.4 Enhancement of asymmetric inductions at 0 °C

For some imines, an attempt was made to enhance their asymmetric inductions by conducting the reactions at 0 °C in toluene (Table 2.5). Comparing with the corresponding entries in Table 2.4 for the reactions at room temperature, it can be seen that significantly better results were obtained at 0 °C.

Table 2.5 Enhancement of asymmetric inductions at 0 °C[a]



1 **2** **3** **26**

Entry	Imine	R_1	Ligand	Yield **3** (%)[b]	ee **3** (%)[c]	cis:trans[d]	Yield **26** (%)[e]
1	**1g**	*p*-$NO_2C_6H_4$	*(S)*-VAPOL	90	95	33:1	<1/<1
2	**1g**	*p*-$NO_2C_6H_4$	*(R)*-VANOL	93	93	≥50:1	<1/<1
3	**1k**	*c*-C_6H_{11}	*(S)*-VAPOL	70	85	33:1	9/4
4	**1k**	*c*-C_6H_{11}	*(R)*-VANOL	81	82	≥50:1	5/<1
5	**1l**	*t*-butyl	*(S)*-VAPOL	75[f]	93	33:1	<1/2
6	**1l**	*t*-butyl	*(R)*-VANOL	58[f]	83	≥50:1	<1/<1
7	**1j**	*n*-propyl	*(S)*-VAPOL	54[f]	86	25:1	2/11
8	**1j**	*n*-propyl	*(R)*-VANOL	60[f]	83	33:1	<1/4

[a] Unless otherwise specified, all reactions were run with 1 mmol of **1** at 0.5 M in **1** with 1.2 equiv of **2**. The catalyst was prepared by heating 1 equiv of ligand, 4 equiv of $B(OPh)_3$ and 1 equiv of water in toluene at 80 °C for 1 h, followed by removing all volatiles under high vacuum at 80 °C for 0.5 h. Reaction with *(R)*-VANOL gives ent. **3**. [b] Isolated yield after chromatography. [c] Chiral HPLC. [d,e] ^1H NMR of the crude reaction. [f] Reaction time was 48 h with 10 mol% catalyst loading.

2.1.5 Optically pure benzhydryl aziridines via crystallization

A pleasant discovery in this study was that all aziridines **3** could be crystallized to afford almost optically pure aziridines (≥99% ee) with excellent recoveries (Table 2.6).

Table 2.6 Optically pure benzhydryl aziridines via crystallization[a]

Entry	Aziridine	R_1	ee (%) **3** before crystallization[b]	ee (%) **3** after crystallization[b]	Recovery (%) from crystallization
1	**3b**	Ph	94	99.4	62

(Table 2.6 continued...)

2	**3c**	*o*-MeC_6H_4	91	99.3	74
3	**3d**	*p*-MeC_6H_4	94	99.2	80
4	**3e**	*o*-BrC_6H_4	85	98.6	65
5	**3f**	*p*-BrC_6H_4	94	99.4	76
6	**3g**	*p*-$NO_2C_6H_4$	95	99.7	74
7	**3h**	*p*-$OMeC_6H_4$	87	99.9	81
8	**3i**	3,4-$(OAc)_2C_6H_3$	93	99	67
9	**3a**	1-naphthyl	89	99.9	55
10	**3k**	*c*-C_6H_{11}	83	99.1	80
11	**3l**	*t*-butyl	87	99.7	76
12	**3j**	*n*-propyl	86	96.6	40

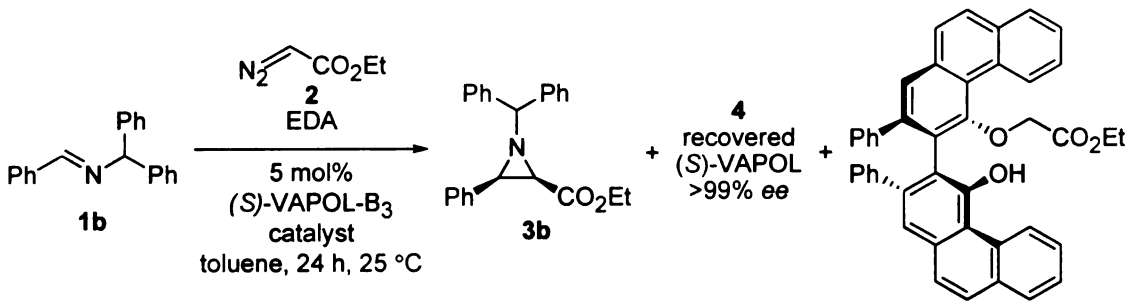
[a] See experimental information for information on solvent mixtures used for crystallization. [b] Chiral HPLC.

2.1.6 Recovery of the VAPOL ligand post-aziridination

The VAPOL **4** could be recovered from the aziridination reaction in high optical purity, however, usually part or all of the VAPOL is recovered as the ethyl diazoacetate (EDA) adduct **27**.[7e] The ratio of VAPOL **4** to the VAPOL-EDA adduct **27** that is recovered at the end of the reaction depends on the amount of excess EDA **2** that is used in the reaction (Table 2.7). For example, with 1.1 equivalents of EDA, the reaction performed with the catalyst prepared by the procedure outlined in Table 2.4 gave, after purification by silica gel chromatography, a 46% recovery of (*S*)-VAPOL with >99% ee along with a 49% yield of the EDA adduct **27** (Entry 2). The same reaction with 1.2 equivalents of EDA gave only the EDA adduct **27** in 98% yield (Entry 3). The aziridination with 1.0 equivalent of EDA lead to an incomplete reaction (Entry 1), however this was

an expected result as the commercially available EDA (Aldrich) contains up to 15% dichloromethane.

Table 2.7 Recovery of **4** and **27** based on the equivalents of EDA **2** used[a]

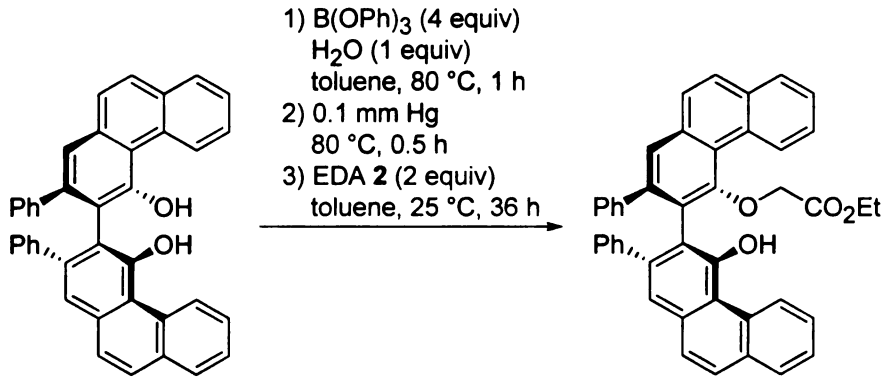


Entry	Equiv of EDA **2** used	conversion of **1b** to **3b** (%)[b]	yield **4** (%)[c]	yield **27** (%)[c]
1	1.0	81	ND	ND
2	1.1	100	46	49
3	1.2	100	0	98

[a] Reaction conditions and catalyst preparation were exactly identical to those outlined in Table 2.4. ND = not determined. [b] Crude ^{1}H NMR. [c] Isolated yield after chromatography.

First, an independent route was sought to synthesize the adduct **27**. Surprisingly, it was found there was no reaction to form the adduct **27** when the reagents, *viz.* *(S)*-VAPOL, 20-30 mol% triphenyl borate, toluene and 1.2 equivalents of EDA, were simply mixed. However, when a procedure similar to the aziridination protocol was followed, albeit without adding the imine, it was found that the reaction proceeded smoothly to give the VAPOL-EDA adduct in 93% isolated yield after flash column chromatography (Scheme 2.1).

Scheme 2.1 Independent synthesis of VAPOL-EDA adduct **27**



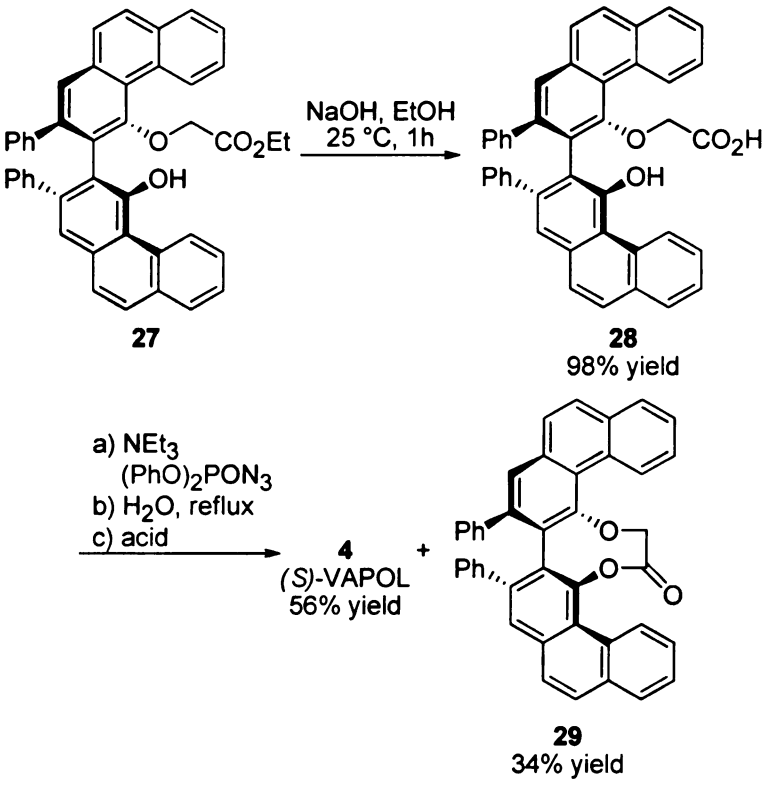
4 **27**
93% yield

One of the first routes tested to recycle the VAPOL-EDA adduct **27** back to VAPOL **4** was a zinc/glacial acetic acid reduction. However, even when the reaction was pushed (90 °C for 16 h), no progress for the reaction was observed by TLC.

The EDA adduct **27** could be recycled to optically pure *(S)*-VAPOL **4** via a Curtius rearrangement (Scheme 2.2).[20] Hydrolysis of **27** afforded the carboxylic acid **28**, essentially as a single compound in the reaction, which could be used in the next step without purification. Acid **28** was then treated with diphenylphosphoryl azide (DPPA) and triethylamine and the resulting acyl azide was rearranged to an isocyanate. Trapping the isocyanate with H_2O gave a carbamate that decarboxylated to give a hemiaminal that hydrolyzed to *(S)*-VAPOL. However, some of the acyl azide was trapped intramolecularly by the phenol to give the lactone **29**. The overall result was a mixture of free *(S)*-VAPOL (56%) and the lactone **29** (34%). Although the lactone **29** could be recycled to the ethyl ester **27** (see experimental information), a more efficient method for the liberation of VAPOL was found to be the direct reduction of **27**

with samarium diiodide[21] which gave (*S*)-VAPOL in 91% yield and 99.8% ee (Scheme 2.3).

Scheme 2.2 The Curtius rearrangement for the recovery of VAPOL

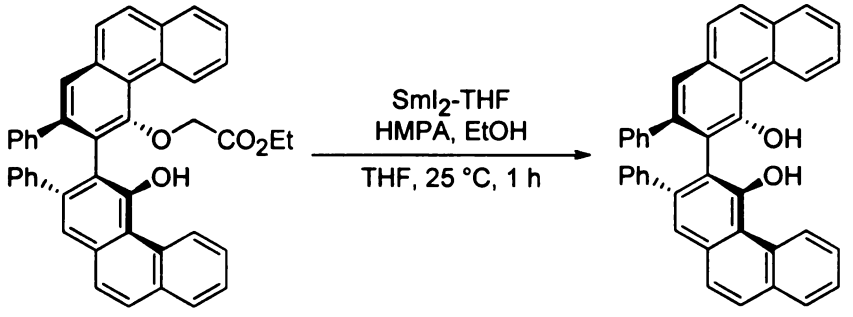


27

28
98% yield

29
34% yield

Scheme 2.3 The SmI_2 mediated reduction for the recovery of VAPOL



27

4
91% yield
99.8% ee

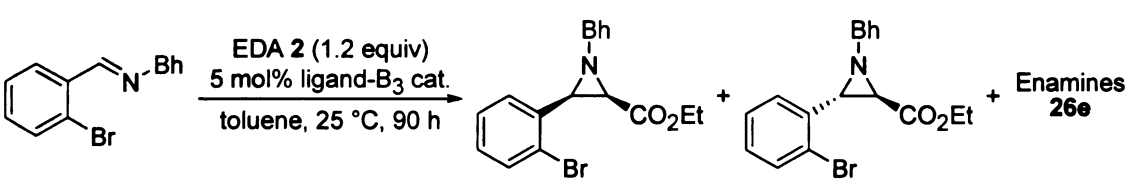
A good outcome of the Curtius rearrangement study (Scheme 2.2) was the discovery that selective manipulation and functionalization of one of the

hydroxyl groups of VAPOL was indeed possible, and could be done with reasonably simple reactions and excellent yields. This chemistry could possibly be explored in the future for the development of new ligands based on VAPOL/VANOL, perhaps in the domain of dual-functional catalysis.

2.2 Aziridinations with *o*-bromophenyl benzhydryl imine: First glimpses of trans-aziridines

While screening different benzhydryl imines for the Wulff catalytic asymmetric cis-aziridination, it was found that the reaction with the *o*-bromophenyl benzhydryl imine **1e** gave significant amounts of the trans-aziridine isomer (cis:trans = 2:1, Table 2.4, Entry 7 and 8). This was the first time that trans-aziridines, in isolable ratios, were observed in our aziridination reactions. While the reason for the low diastereoselectivity was not clear at the time, it was desired to isolate the trans-aziridine isomer, quantify its yield and asymmetric induction, and characterize it completely. This was done, and the results are presented in Table 2.8.

Table 2.8 Cis- and trans-aziridines from aziridination of imine **1e**[a]



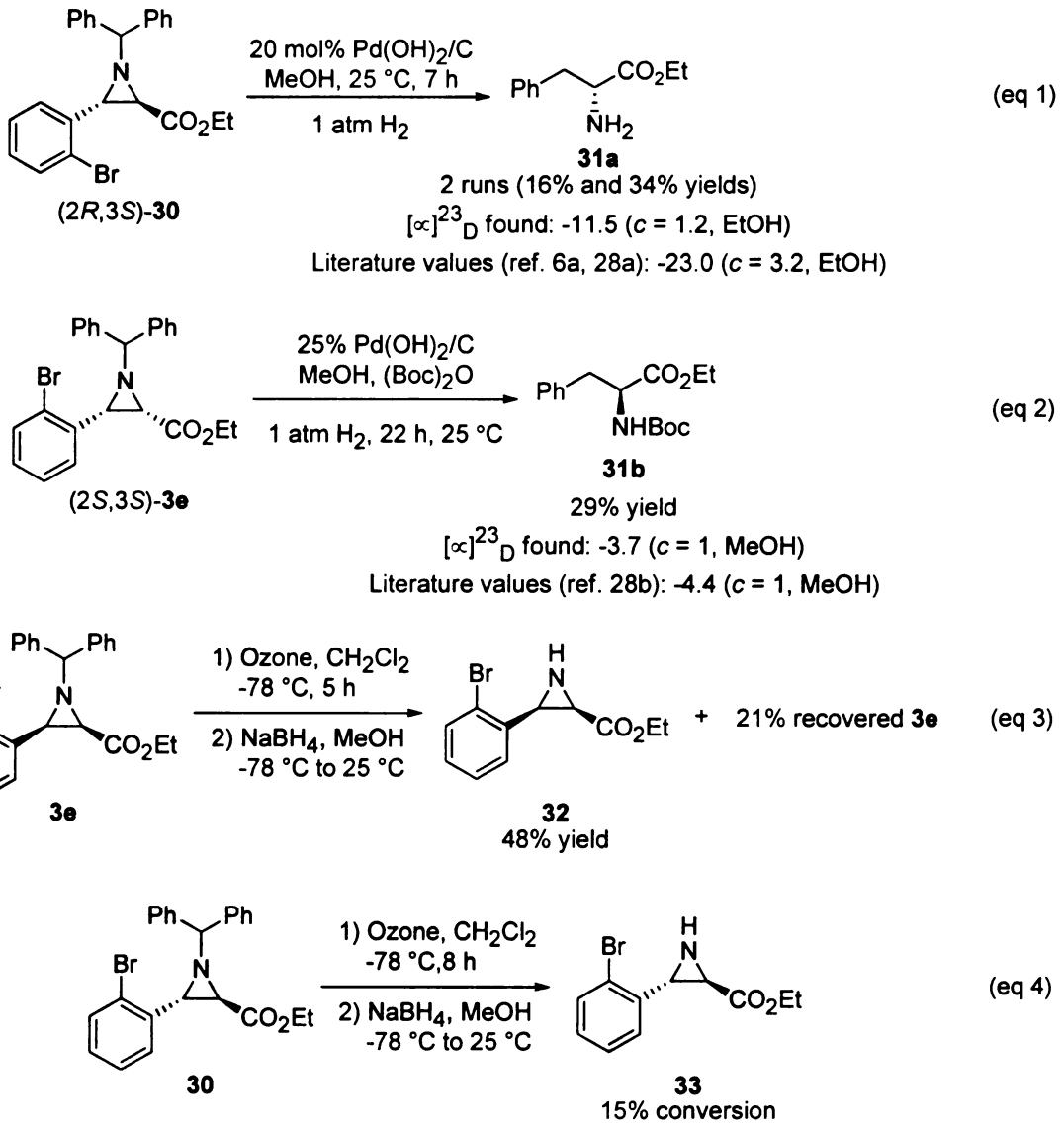
1e *(2R,3R)*-**3e** *(2R,3S)*-**30**

Entry	Ligand	cis:trans[b]	Yield (%) **3e**[c]	ee (%) **3e**[d]	Yield (%) **30**[c]	ee (%) **30**[d]	Yield (%) **26e**[b]
1	*(S)*-VAPOL	1.10:1	42	80	36	36	15
2	*(R)*-VANOL	1.75:1	47	82	24	35	22

(Table 2.8 continued...)

[a] Unless otherwise specified, all reactions were run with 4 mmol of **1e** at 0.5 M in **1e** with 1.2 equiv of **2**. The catalyst was prepared by heating 1 equiv of ligand, 4 equiv of $B(OPh)_3$ and 1 equiv of water in toluene at 80 °C for 1 h, followed by removing all volatiles under high vacuum at 80 °C for 0.5 h. Reaction with *(R)*-VANOL gives ent. **3e** and ent. **30**. [b] Determined from ^1H NMR of the crude reaction mixture. [c] Isolated yield after chromatography. [d] Chiral HPLC.

Scheme 2.4 Absolute configuration determination and attempts at ozonalysis



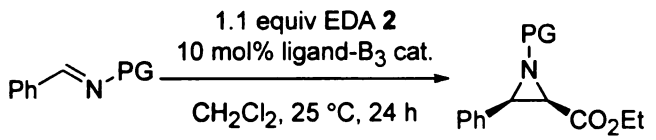
The absolute configurations of the cis-aziridine **3e** and the trans-aziridine **30** were determined by chemical correlation, and subsequently comparing the optical rotation of the products to literature values (Scheme 2.4, eq 1 and 2). Interestingly, opposite facial selectivity was observed for the cis-aziridine **3e** and the trans-aziridine **30** with the same enantiomer of the ligand. For example, in the reaction with the catalyst prepared from *(S)*-VAPOL (Scheme in Table 2.8), the cis-aziridine **3e** was configured (2*R*,3*R*), which results from a *Si* face attack of the diazoacetate. The trans-aziridine **30** from the same reaction however was configured (2*R*,3*S*), which results from a *Re* face attack of the diazoacetate. Furthermore for this study, the cleavage of the benzhydryl group via ozonalysis was also attempted (Scheme 2.4, eq 3 and eq 4).

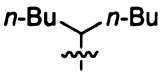
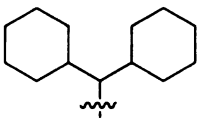
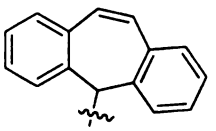
2.3 Aziridinations with 5-nonylimine, dicyclohexylmethylimine and *5H*-dibenzo[*a,d*]cyclohepten-5-imine

Yu Zhang and Zhenjie Lu from our group, around 2006, carried out an elegant study to map out the active site of the catalyst in our aziridination reactions.[9] To do this, they synthesized numerous diarylmethylamines of varying electronic and steric properties, and prepared the corresponding imines with benzaldehyde. These imines were then subjected to our standard aziridination reactions, and the effects of the different *N*-protecting groups studied. It was in this study that Yu and Zhenjie discovered the tetra-*tert*-butyldianisylmethyl (BUDAM) and tetramethyldianisylmethyl (MEDAM) groups, which have since then been established as the protecting groups of choice in our catalytic asymmetric aziridination reactions.

A small contribution to this study was made during the period of this dissertation. To confirm the importance of the diaryl groups on the *N*-protecting group for our aziridination reactions, it was desired to test the di-*n*-butylmethyl and the dicyclohexylmethyl *N*-protecting groups. To test the importance of relative orientation of the diaryl groups, it was desired to test the imine prepared from *5H*–dibenzo[*a,d*]cyclohepten-5-amine. The amines for this study were prepared according to, or in an analagous manner to, literature procedures, and the corresponding imines were subsequently made with benzaldehyde (see experimental information). These were then subjected to our standard aziridination reaction conditions, and the results are presented in Table 2.9. The aziridination reactions of the imine **1b** with the benzhydryl protecting group are shown for comparison (Entries 1-2). The reactivity, yields and asymmetric inductions with imines **34** and **35** dropped significantly (Entries 3-6), thus confirming our belief that diaryl groups are indeed important in the *N*-protecting group for our aziridination protocol. However, the results improved slightly with the imine **36** (Entries 7-8). The exact reasons behind this are unclear at this time, but these results suggest that the relative orientation of these diaryl groups is important in our aziridination protocol.

Table 2.9 Contributions to the study to map the active site of our catalyst[a]



imine	PG	aziridine
34		**37**
35		**38**
36		**39**

Entry	imine	ligand	azir.	conversion (%)[b]	yield azir. (%)[c]	ee azir.(%)[d]	rel. rate (**1b**:imine)[e]
1	**1b**	*(S)*-VAPOL	**3b**	100	83	89	1:1
2	**1b**	*(R)*-VANOL	**3b**	100	81	88	1:1
3	**34**	*(S)*-VAPOL	**37**	29	27	84	1:0.23
4	**34**	*(R)*-VANOL	**37**	45	40	79	ND
5	**35**	*(S)*-VAPOL	**38**	23	18	74	1:0.04
6	**35**	*(R)*-VANOL	**38**	42	35	70	ND
7	**36**	*(S)*-VAPOL	**39**	100	65	96	1:2.2
8	**36**	*(R)*-VANOL	**39**	100	66	94	ND

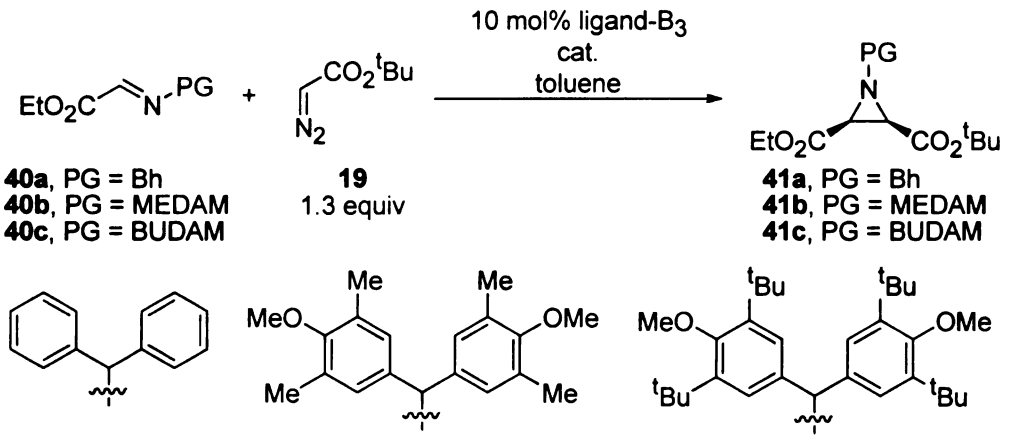
[a] Reactions were run with 1 mmol of imine at 0.5 M in imine. The catalyst was prepared by heating 1 equiv ligand and 3 equiv $B(OPh)_3$ at 80 °C in toluene for 1 h, then all volatiles were removed under high vacuum for 0.5 h at 80 °C. *(R)*-VANOL gives ent. aziridine shown. [b] Crude ^1H NMR. [c] Isolated yield. [d] Chiral HPLC. [e] Relative rate studies were carried out in pairwise competitions in CCl_4 with 1 equiv of **1b**, 1 equiv of competitor imine, 0.2 equiv of **2**, and 5 mol% catalyst at 25 °C for 24 h.

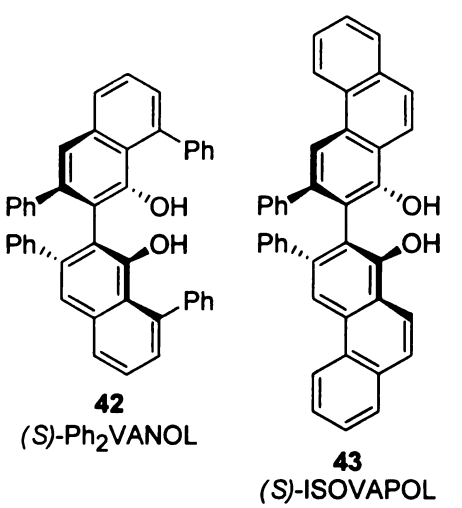
2.4 cis-2,3-Dicarbonylaziridines from the Wulff aziridination

cis-2,3-Dicarbonylaziridines would be attractive targets for a catalytic asymmetric aziridination protocol. A Brønsted acid catalyzed reaction providing racemic cis-aziridine-2,3-dicarboxylate derivatives has been previously reported

by Johnston.[22] Shortly after the promising attempts reported in this section were carried out, a chiral Brønsted acid catalyzed aziridination protocol affording cis-2,3-dicarbonylaziridines was reported by Akiyama (Chapter 1, Scheme 1.10).[17]

Table 2.10 cis-2,3-Dicarbonylaziridines from the Wulff aziridination protocol[a]





42
(S)-Ph_2VANOL

43
(S)-ISOVAPOL

#	PG	ligand	Temp (Time) (°C, h)	cis:trans[b]	Yield **41** (%)[c]	ee **41** (%)[d]
1	Bh	no catalyst	25 (24)	5% conversion		
2	Bh	VAPOL	-40 (24) to 25 (24)	>50:1	65	4
3	Bh	VANOL	-40 (24) to 25 (24)	>50:1	75	34
4	Bh	VANOL	-40 (24)	>50:1	ND	ND
5	Bh	VANOL	0 (24)	>50:1	55	42

(Table 2.10 continued...)

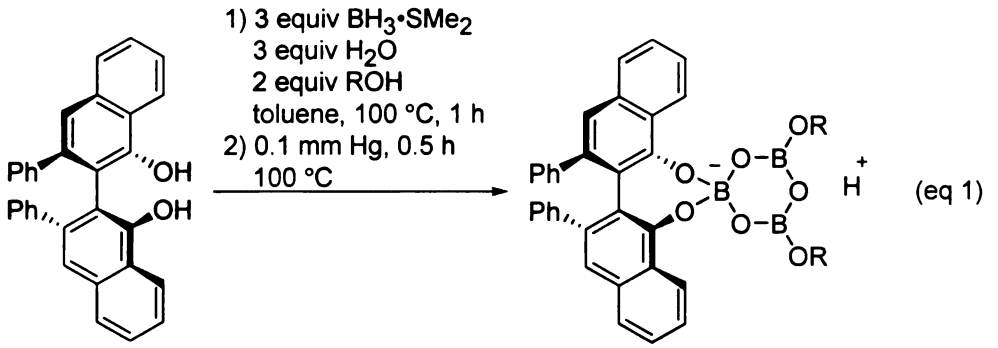
6	Bh	VANOL	25 (24)	>50:1	64	31
7	Bh	Ph_2VANOL[e]	-20 (48) to 25 (12)	>50:1	57	8
8	MEDAM	VAPOL	0 (24)	20:1	80	14
9	MEDAM	VANOL	0 (24)	20:1	77	46
10	MEDAM	VANOL	-20 (24)	25:1	74	45
11	MEDAM	VANOL	-40 (24)	25:1	77	42
12	MEDAM	ISO-VAPOL[f]	-20 (24)	33:1	80	46
13	MEDAM	Ph_2VANOL[e]	-20 (64) to 25 (24)	>50:1	42	5
14	BUDAM	VAPOL-B_3	0 (24)	15:1	58	15
15	BUDAM	VANOL-B_3	0 (24)	15:1	<76	11

[a] All reactions were run with 0.25 mmol of imine **40** at 0.125 M in imine **40**. The catalyst was prepared by heating 1 equiv of ligand, 4 equiv of $B(OPh)_3$ and 1 equiv of water at 80 °C in toluene for 1 h, followed by removing all volatiles at high vacuum (0.1 mm Hg) for 0.5 h at 80 °C. ND = not determined. [b] Crude ^{1}H NMR analysis. [c] Isolated yield after chromatography. [d] Chiral HPLC. [e] See chapter 6 for ligand preparation. [f] Provided by Anil Gupta.

A significant amount of time was devoted during this dissertation in trying to access cis-2,3-dicarbonyl aziridines via the Wulff catalytic asymmetric aziridination. A systematic optimization was undertaken, and although excellent diastereo-control and reactivity was observed, the best asymmetric induction obtained was only 46% ee. These results are summarized in Table 2.10.

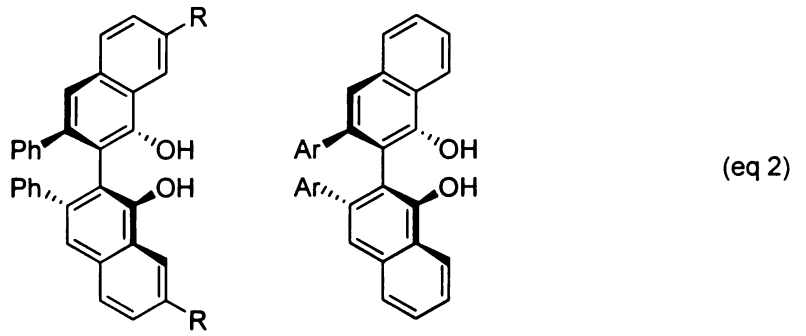
cis-2,3-Dicarbonylaziridines have never been accessed before from the Wulff catalytic asymmetric aziridination. If successfully obtained, they would be a nice addition to the already wide repertoire of the cis-aziridines available from our protocol. It is proposed that the asymmetric inductions obtained during this dissertation could be further improved in the future in one of three ways (Scheme 2.5).

Scheme 2.5 Proposals to further improve the asymmetric inductions in this study

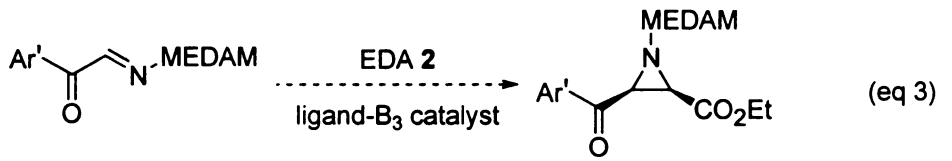


5
(S)-VANOL

44
new VANOL B_3 catalysts



New members of the VANOL ligand family



The BH_3•SMe_2/phenol route could be utilized for preparing the B_3 catalyst, which provides an additional handle with which the active site of catalysis could be tweaked i.e. electronically and sterically different phenols/alcohols could be used to generate a large number of B_3 catalysts from VANOL (eq 1), since VANOL offered the best inductions during this study. Alternately, the B_3 catalyst for this reaction could be prepared from the new members of the VANOL ligand family, which are being actively pursued in our laboratory (eq 2). Finally, a last avenue for improving the asymmetric inductions in this system could be switching

from MEDAM imines prepared from ethyl gloxylate to MEDAM imines prepared from phenyl glyoxal derivatives (eq 3), similar to those used in Akiyama's protocol (Chapter 1, Scheme 1.10).[17] Having an aromatic group on the imine might help in establishing better non-covalent interactions in the catalyst-imine complex and thus further fine-tune the active site of catalysis to engender higher asymmetric inductions.

2.5 A gram scale catalytic asymmetric aziridination process

To make our cis-aziridination protocol easily accessible to the scientific community at large, it was desired to scale up one example and convert the reaction into an easy and practical process. Thus, it was decided to develop a procedure with one example from our catalytic asymmetric cis-aziridination protocol for submission to the journal *Organic Synthesis.* Procedures submitted to *Organic Synthesis* (usually on a larger scale than the discovery chemistry scale) are independently verified in the laboratories of the board of editors before publication, and thus are widely accepted as robust and reliable procedures.

This study was carried out with Dr. Roberto Morán-Ramallal, a post-doctoral research associate in our group for a short period in 2009. It was decided to scale up an example from our full report in 2008 (Section 2.1);[8] the aziridination reaction of *p*-bromophenyl benzhydryl imine **1f** and ethyldiazoacetate **2** mediated by the *(S)*-VANOL-B_3 catalyst was chosen (Table 2.4, Entry 10). VANOL was chosen since it afforded better results with imine **1f** as compared to VAPOL (86% yield and 94% ee with VANOL for aziridine **3f**). The imine prepared from *p*-bromobenzaldehyde was chosen as the substrate

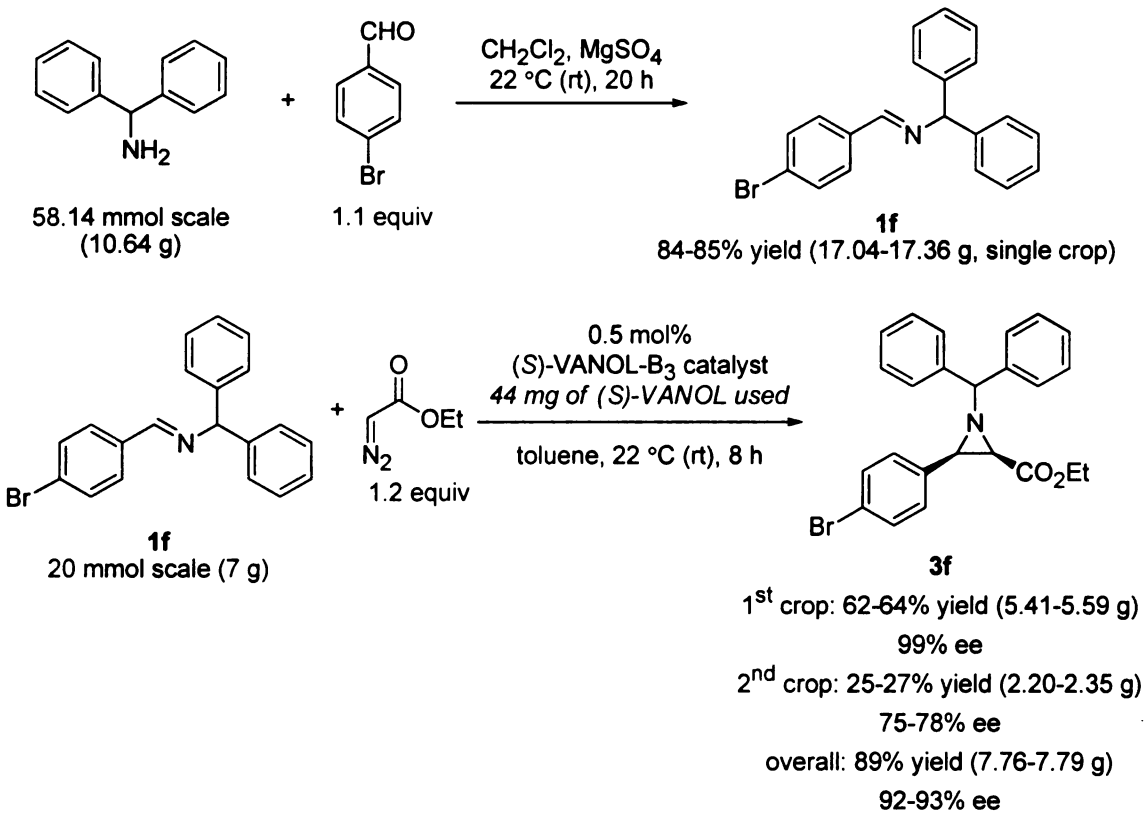
since the presence of bromine would offer a convenient handle in the product cis-aziridine for further synthetic transformations *viz.* cross-coupling reactions. The benzhydryl group was chosen as the *N*-protecting group since it is commercially available, and since the benzhydryl aziridines are solids and can be readily crystallized up to almost optical purity with excellent recovery (Table 2.6).

Initially a catalyst loading study was pursued with both VAPOL and VANOL ligands. At 1% catalyst loading, the above mentioned reaction with the catalyst prepared from VAPOL gave incomplete completion, whereas that with the catalyst prepared from VANOL went to full completion. Thus VAPOL was dropped from the study at that point. The catalyst loading with VANOL could be further reduced to 0.5 mol% without affecting the reaction outcome. The reaction time at this catalyst loading was optimized to 8 h.

Scheme 2.6 depicts the optimized large scale procedure that evolved from this study. The imine **1f** was prepared under extremely mild conditions at a 58.14 mmol scale from commercially available starting materials. After just one crop of crystallization, 17.04-17.36 g of imine **1f** was obtained as white crystals (84-85% yield). The subsequent aziridination reaction was carried out at a 20 mmol scale in the imine. 0.5 mol% of the B_3 catalyst prepared from *(S)*-VANOL was used, which corresponds to only 44 mg of *(S)*-VANOL being used. The reaction was complete at room temperature in 8 h, and the first crop of crystallization afforded the aziridine product **3f** as a white solid in 62-64% yield (5.41-5.59 g). Almost optically pure aziridine **3f** (99% ee) was obtained in the first crop. A second crop could be taken, and this afforded the aziridine **3f**, again as a white solid, in 25-

27% yield (2.20-2.35 g) and 75-78% ee. Thus, the overall yield for the reaction was 89% (7.76-7.79 g) and the overall asymmetric induction was 92-93% ee.

Scheme 2.6 A gram scale catalytic asymmetric aziridination process

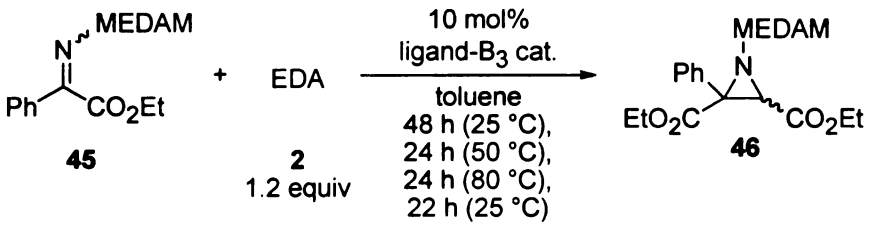


Worthy of note is that no column chromatography is used in this entire process, which makes it attractive from a process chemistry point of view. The entire process involves commercially available starting materials; even the ligand VANOL is now commercially available from Aldrich as well as Strem Chemicals, Inc. The reactions proceed under mild conditions, and essentially optically pure aziridine product is obtained in good yield in just one crop. That such an operationally simple and highly efficient catalytic asymmetric aziridination process could be evolved from this study was very gratifying.

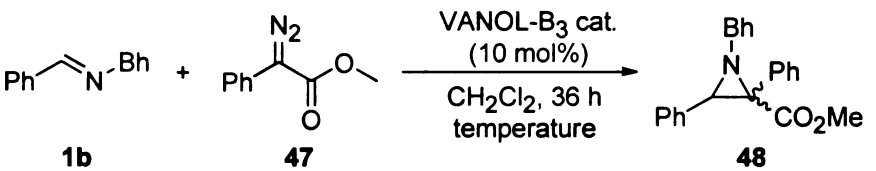
2.6 Failed attempts for the direct access to tri-substituted aziridines

A few attempts were made to directly access tri-substituted aziridines via the Wulff catalytic asymmetric aziridination, either by using di-substituted imines or di-substituted diazo compounds. All these reactions failed, and are summarized in Scheme 2.7.

Scheme 2.7 Failed attempts for the direct access to tri-substituted aziridines



entry	catalyst	result
1	VAPOL-B_3	only s.m. recovered
2	VANOL-B_3	only s.m. recovered



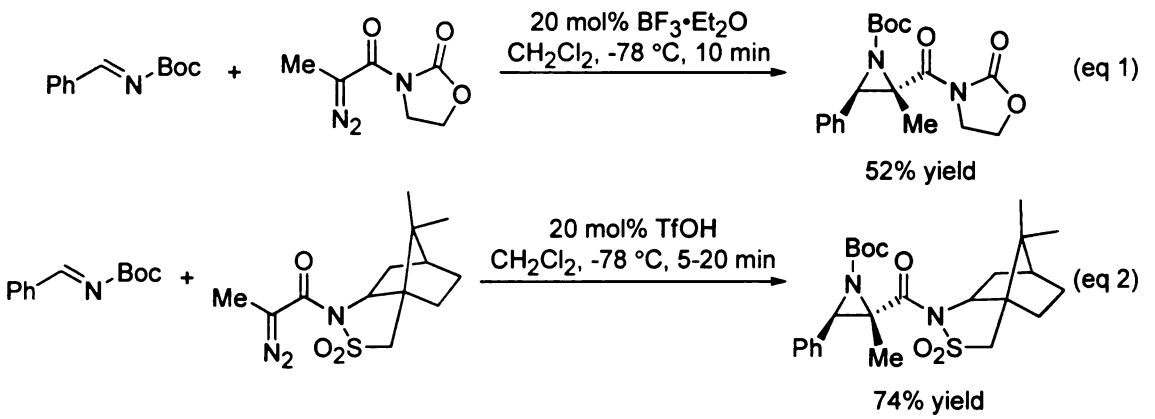
entry	temperature	result
1	25 °C	only s.m. + junk + diazo
2	80 °C	dimer - no aziridine

A gigantic amount of work has been devoted to the catalytic asymmetric synthesis of aziridines by numerous research groups all over the world since the last two decades. In spite of this, there are *no* reports in the literature to access tri-substituted aziridines in a catalytic asymmetric fashion. If such a system could be developed using our VAPOL/VANOL-B_3 catalysts, it would undoubtedly be a

big addition to the utility of our catalytic asymmetric aziridination system. It would also be a standalone high impact research project.

Very recently in 2010, Maruoka has reported a diastereoselective synthesis of tri-substituted aziridines from imines and disubstituted diazo compounds, catalyzed by triflic acid (Scheme 2.8).[14b] This constitutes the first stereoselective synthesis of tri-substituted aziridines in the literature.

Scheme 2.8 Examples from Maruoka's tri-substituted aziridination study



The reaction shown in eq 1 of Scheme 2.8 is catalyzed by $BF_3 \bullet Et_2O$. They mention in a footnote that the same reaction could be catalyzed smoothly by camphorsulfonic acid; however the product was obtained in racemic form. Our trans-selective aziridination protocol (described in Chapter 3) was inspired from Maruoka's trans-aziridination[13] between *N*-Boc imines and *N*-phenyldiazoacetamide catalyzed by chiral Brønsted acids. Compiling the above three sentences makes a very sound argument to attempt the aziridination reaction shown in eq 1 of Scheme 2.8, mediated by our VAPOL/VANOL-B_3 catalysts and with the diarylmethyl imines used in our protocol.

CHAPTER THREE

CATALYTIC ASYMMETRIC TRANS-AZIRIDINATION:

DEVELOPMENT OF A UNIVERSAL AZIRIDINATION PROTOCOL

3.1 Introduction

The Wulff catalytic asymmetric cis-aziridination was discovered around 2000, and all through the long years of developing that system, a constant effort had been made in our laboratories to access the corresponding trans-aziridines. As mentioned in Chapter 1, there is no example in the literature of a protocol that could provide efficient access to both cis- as well as trans- aziridines, utilizing the same starting imine and the same chiral catalyst. The development of such a *universal catalytic asymmetric aziridination* protocol has remained an elusive, albeit an actively pursued goal in the field.

One of the early hopes in our laboratories towards realizing this goal was to do this by epimerization of the ester group on the cis-aziridine, but it was found that the enolate was configurationally stable. This proved to be synthetically quite valuable since the cis-aziridine-2-carboxylate ester could be alkylated with complete retention of configuration at the 2-position.[7c]

After the work towards developing the cis-aziridination protocol described in this dissertation ended, attention was turned to the tantalizing goal of expanding this protocol to include trans-aziridines, thereby creating the first universal catalytic asymmetric aziridination protocol in literature. Quite a few of

what started out as very promising avenues were initially explored in this regard; however all these efforts were in vain.

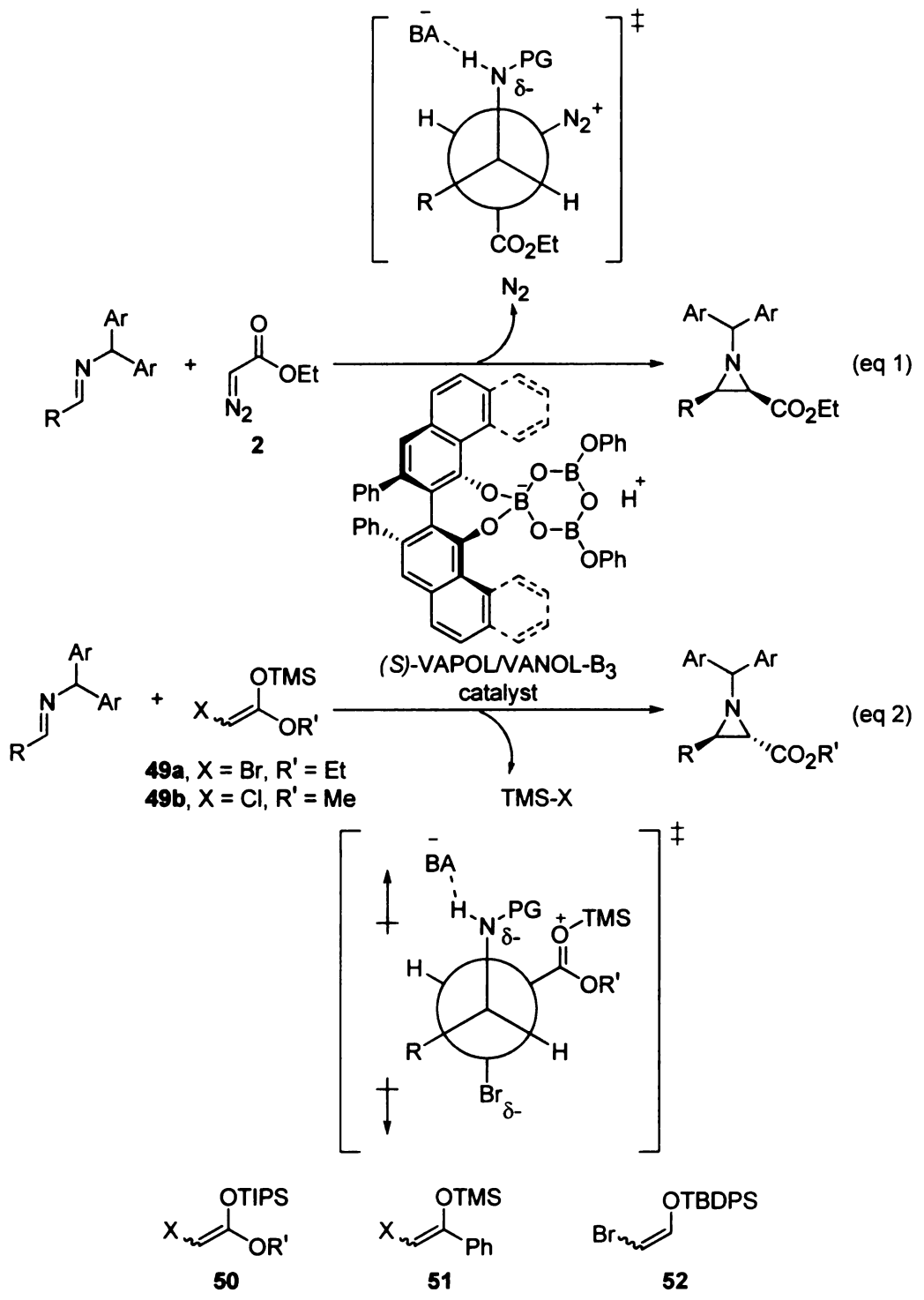
3.2 Initial attempts towards a catalytic asymmetric trans-aziridination

Eq 1 in Scheme 3.1 depicts the proposed stereochemistry determining transition state in the Wulff catalytic asymmetric cis-aziridination reaction. The high cis diastereoselectivity has been presumed to be due to the stabilization of the developing charges in the zwitterionic intermediate at the transition state. It was hypothesized that if ethyldiazoacetate **2** was then switched with a different aziridinating nucleophile, such as the α-halogenated silylketene acetals **49** depicted in eq 2, an analogous Newman projection of the zwitterionic transition state would predict the opposite trans diastereoselectivity. The trans selectivity would be favored not only due to a similar charge stabilization at the transition state, but also due to the additional opposing dipoles indicated.

Thus, it was thought to be very interesting to prepare and test various α-halogenated trimethylsilylketene acetals as aziridinating agents in a catalytic asymmetric aziridination protocol of the same diarylmethylimines as in our original aziridination, catalyzed by the same VANOL/VAPOL-B_3 catalysts (Scheme 3.1). For this purpose, the trimethylsilylketene acetals of α-bromoethylacetate (**49a**)[35] and α-chloromethylacetate (**49b**)[36] were chosen to be prepared and tested. However, although literature procedures existed for making these compounds, attempts at repeating these procedures resulted in polymerized crude products. Numerous permutations and combinations of the

reaction parameters were subsequently tried, but all failed miserably, giving only polymerized crude products or polymerized products after distillation.

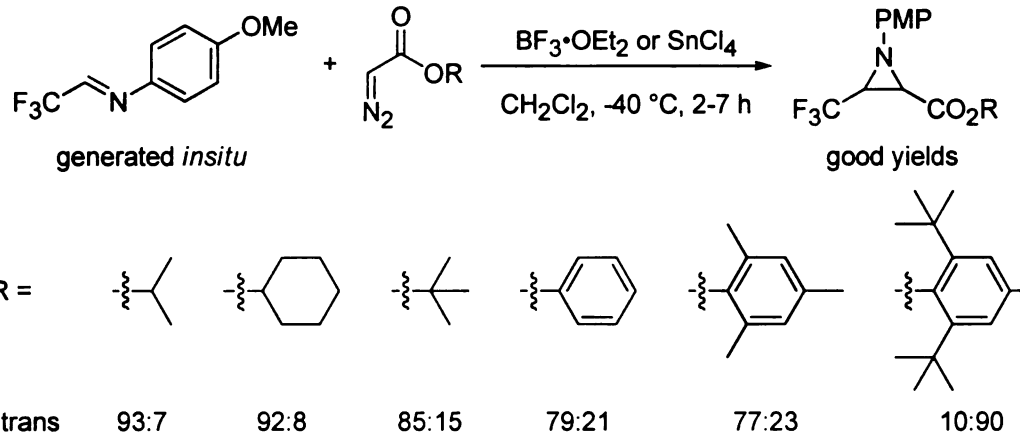
Scheme 3.1 Proposed trans-aziridination with α-halosilylketene acetals



Thus, the α-halogenated trimethylsilylketene acetals **49** for this project could never be prepared during this dissertation, and the essence of the project *i.e.* the actual catalytic asymmetric aziridination could not be attempted. If successfully realized, this method would represent an unprecedented protocol for preparing chiral aziridines. Since the high reactivity, and thus the instability, of **49** is probably the cause of the failure behind its preparation, this might be attenuated by either increasing the bulk of the silyl protecting group (**50**) or by switching to the α-halogenated silyl enol ethers (**51** or **52**) (Scheme 3.1). Silyl enol ether **52** has actually been previously prepared in our laboratories by Nilanjana Majumdar, for research related to carbene complexes.

A separate attempt at developing a trans-selective aziridination protocol was inspired by a report by Akiyama and co-workers[37], who found that they could stereoselectively obtain trans-aziridines if they used an extremely bulky diazoacetate compound *viz.* 4-methyl-2,6-di-*tert*-butylphenyldiazoacetate (Scheme 3.2). Thus, this particular diazoacetate was prepared according to a literature procedure.[38] Disappointingly however, when this diazoacetate was evaluated under our standard aziridination conditions (imine **1b**, 10 mol% of B_3 catalyst prepared from either VAPOL or VANOL, 25 °C or 50 °C), there was no reaction at all, presumably due to the extreme steric bulk of the diazoacetate. No further work was done for this trans-aziridination approach.

Scheme 3.2 Akiyama's protocol for racemic trifluoromethyl aziridines

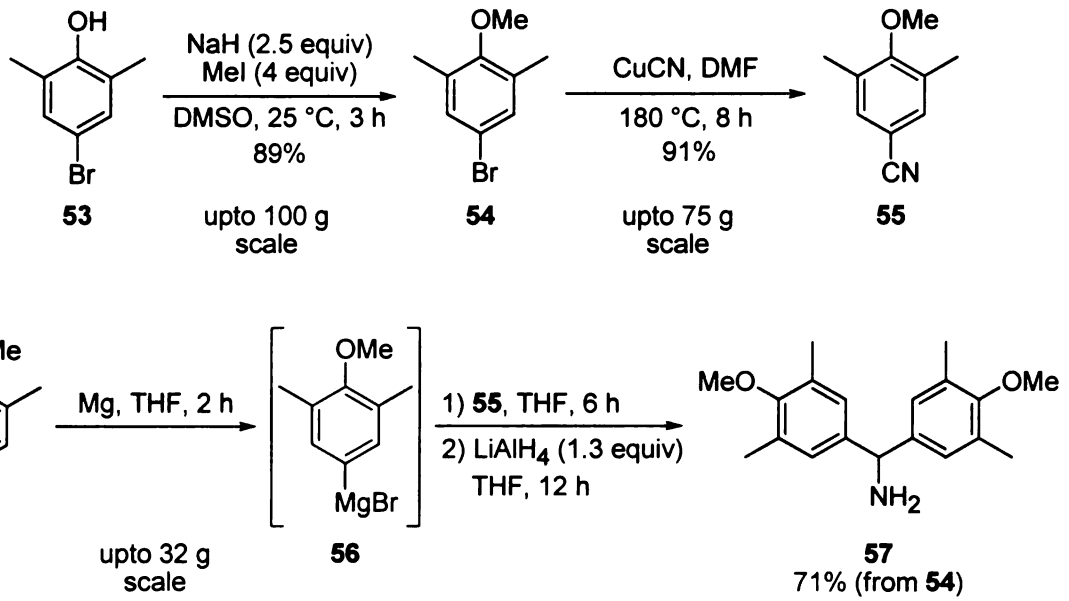


3.3 Large scale preparation of the MEDAM amine

The *N*-protecting group of choice in our cis-selective aziridinations is the tetramethyldianisylmethyl (MEDAM) group.[10] In the trans-selective aziridinations that will be discussed in the subsequent sections of this chapter, the MEDAM group also proved to be the protecting group of choice for the aryl imines.

The small scale synthesis of the MEDAM amine **57** was developed by Yu Zhang from our group.[9,19] This synthesis was scaled up for the first time early on during this dissertation (Scheme 3.3), and was accomplished in three overall steps starting from the commercially available phenol **53**. Thus, 100+ g of the MEDAM amine **57** was prepared with excellent yields at each step. Each reaction was carried out at least 4 times at different scales; the average yields are reported in Scheme 3.3.

Scheme 3.3 Large scale synthesis of the MEDAM amine



3.4 Catalytic asymmetric trans-aziridination: *Development of a universal aziridination protocol*

During the period in this dissertation when the futile attempts (Section 3.2) towards developing a trans-selective aziridination protocol were being carried out, Maruoka reported the first chiral Brønsted acid catalyzed trans-selective aziridination of imines (Scheme 1.6, Chapter 1). In their system, the reaction of aryl *N*-Boc imines and *N*-phenyldiazoacetamide mediated by a chiral BINOL dicarboxylic acid catalyst furnished the corresponding trans-aziridines. They proposed that H-bonding between the Boc group of the imines and the *N*-H of the diazoacetamide at the carbon-carbon bond forming transition state was responsible for the observed trans diastereoselectivity (**18**, Scheme 1.6, Chapter 1). If this proposal were true, having an electron rich protecting group on the imine nitrogen such as the diarylmethyl groups we have in our cis-aziridination

reactions, instead of the electron deficient Boc group, would not offer such an H-bonding opportunity, and thus would not us provide any trans selectivity.

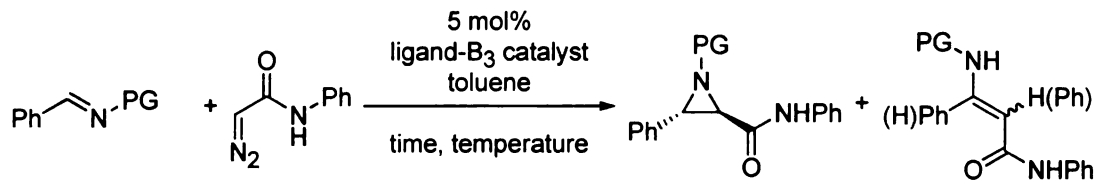
3.4.1 The initial optimization of the trans-aziridination protocol

R. B. Woodward had once said "...faced with a decision based solely upon hypothetical arguments, consider all reasons *not* to perform an experiment, and disregard them."[39] Keeping in spirit with these words, around November 2008, the reactions between imine **1b** and *N*-phenyldiazoacetamide **14a** mediated by 20 mol% of the B_3 catalyst prepared from VAPOL and VANOL were set up (Table 3.1, Entry 2 and 5). Much to our pleasure, both reactions furnished trans-aziridines with very encouraging results. Borrowing from the abundance of experience gleaned from fine-tuning our cis-selective aziridinations, we were able to optimize the trans-selective aziridination protocol. These optimization details are presented in Table 3.1. In the final optimized system, MEDAM was the protecting group of choice, VANOL was the ligand of choice, and the reaction temperature was either 0 ° or -20 °C. This optimized system is represented by Entries 8 and 17 in Table 3.1.

An intriguing outcome of these reactions was that the catalyst prepared from VAPOL was consistently, and significantly, inferior to that prepared from VANOL. This is quite contrary to our cis-selective aziridinations,[6-12] where both VAPOL and VANOL have always afforded very similar results. The minor diastereomer, the cis aziridine, was isolated from the reaction in Entry 19 in 14% yield and with 77% ee (see Section 3.4.10).

Furthermore in this study, an extensive solvent screen convinced us that toluene was indeed our solvent of choice (Table 3.2).

Table 3.1 Optimization study for the trans-aziridination protocol[a]

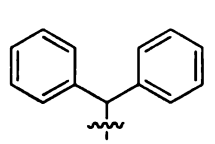


1b, PG = Bh
9a, PG = MEDAM
58a, PG = BUDAM

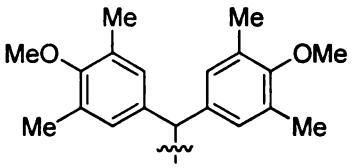
14a
1.3 equiv

59a, PG = Bh
60a, PG = MEDAM
61a, PG = BUDAM

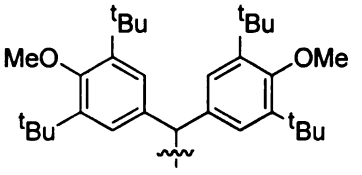
62a, PG = Bh
63a, PG = MEDAM
64a, PG = BUDAM



Bh



MEDAM



BUDAM

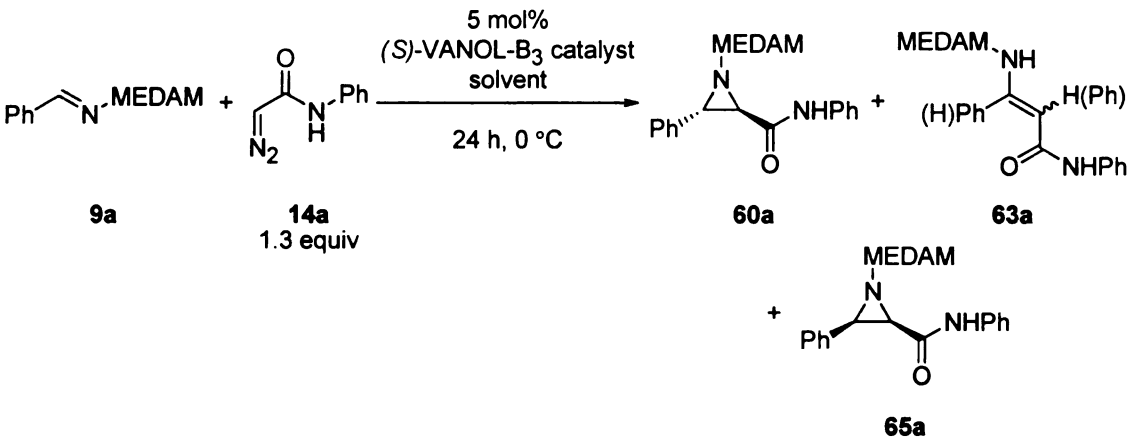
#	PG	ligand	temp. (°C)	time (h)	conv. (%)[b]	trans:cis[b]	yield of trans-azi (%)[c]	ee (%)[d]	yield of enamines (%)[b]
1	Bh	*(R)*-VAPOL	0	19	91	12:1	65	69	17
2[e,f]	Bh	*(R)*-VAPOL	0 25	12 24	100	13:1	72	70	19
3[e,f]	Bh	*(S)*-VAPOL	25	6	100	4:1	49	71	28
4	Bh	*(S)*-VANOL	0	19	65	9:1	47	77	12
5[e,f]	Bh	*(S)*-VANOL	0 25	12 24	100	6:1	59	80	22
6[e]	MEDAM	*(S)*-VANOL	0	23	100	7:1	69	91	10
7[g]	MEDAM	*(S)*-VANOL	0	23	100	7:1	73	87	<1
8[h]	MEDAM	*(S)*-VANOL	0	24	100	12:1	84	90	10
9	MEDAM	*(R)*-VANOL	0	19	100	11:1	81	89	9
10	MEDAM	*(S)*-VANOL	0	4	83	ND	ND	ND	ND
11	MEDAM	*(S)*-VANOL	0	9	100	13:1	83	89	9
12[i]	MEDAM	*(R)*-VANOL	0	24	100	12:1	81	92	10

(Table 3.1 continued...)

13[f]	MEDAM	*(S)*-VANOL	0	18	100	10:1	84	90	7
14[i]	MEDAM	*(S)*-VANOL	0	16	100	14:1	87	92	7
15[j]	MEDAM	*(S)*-VANOL	0	18	100	8:1	75	84	2
16	MEDAM	*(S)*-VANOL	-40	24	100	18:1	90	94	6
17	MEDAM	*(S)*-VANOL	-20	24	100	21:1	90	96	5
18	MEDAM	*(S)*-VANOL	22 (rt)	18	100	5:1	69	67	16
19[k,l]	MEDAM	*(S)*-VANOL	22 (rt)	16	100	5:1	71	88	8
20	MEDAM	*(S)*-VAPOL	0	20	100	4:1	63	70	20
21	BUDAM	*(R)*-VAPOL	0	19	100	5:1	35	51	21
22	BUDAM	*(S)*-VANOL	0	20	100	16:1	75	91	10
23[h]	BUDAM	*(S)*-VANOL	-20	24	100	27:1	74	89	13
24	BUDAM	*(S)*-VANOL	-40	24	100	19:1	73	92	11

[a] Unless otherwise specified, all reactions were carried out with 0.1-0.3 mmol of imine at 0.1-0.2 M in imine. The catalyst was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \bullet SMe_2$ (2 *M* in toluene), 2 equiv PhOH and 3 equiv of water at 100 °C for 1 h in toluene, followed by removing all volatiles at high vacuum (0.1 mm Hg) for 0.5 h at 100 °C. Stock solution of catalyst used. Reaction with *(R)*-ligand gives ent. trans-aziridine shown. ND = not determined. Reaction times have not been optimized. Crystallized imines used. [b] ^1H NMR analysis of crude reaction mixture. [c] Isolated yield after chromatography. [d] Chiral HPLC. [e] 20 mol% catalyst loading. [f] Catalyst prepared by heating 1 equiv of ligand, 4 equiv of $B(OPh)_3$ and 1 equiv of water at 80 °C in toluene, followed by removing all volatiles at high vacuum (0.1 mm Hg) for 0.5 h at 80 °C. [g] 10 mol% catalyst. [h] Average of two runs. [i] 1 day old stock solution of catalyst used. [j] 10 day old stock solution of catalyst used. [k] The cis aziridine was isolated in 14% yield and 77% ee (see Section 3.4.10). [l] Reaction run with 1 mmol of imine at 0.2 M in imine.

Table 3.2 Solvent study for the trans-aziridination protocol[a]



9a **14a** 1.3 equiv **60a** **63a** **65a**

#	solvent	conv. (%)[b]	trans:cis[b]	yield **60a** (%)[c]	ee **60a** (%)[d]	yield **63a** (%)[b]	yield **65a** (%)[c]	ee **65a** (%)[d]
1[e]	toluene	100	12:1	84	90	7	ND	ND
2	xylenes	100	11:1	83	90	8	ND	ND
3	$C_6H_5CF_3$	100	5:1	74	91	10	ND	ND
4	C_6H_5Cl	100	4:1	75	91	6	16	85
5	CH_2Cl_2	100	7:1	69	86	2	ND	ND
6	$CHCl_3$	100	6:1	77	89	7	ND	ND
7	CCl_4	100	5:1	78	88	6	ND	ND
8	THF	80	2:1	28	-25	12	14	10
9	Et_2O	100	4:1	60	41	26	ND	ND
10	CH_3CN	98	1:1	22	39	24	31	21
11	EtOAc	100	1:1	37	39	25	32	13
12[f]	cyclopentane	18	ND	15	90	ND	ND	ND
13[f,g]	*n*-hexane	0	ND	ND	ND	ND	ND	ND
14[f,g,h]	*n*-hexane	5	ND	ND	ND	ND	ND	ND

[a] Unless otherwise specified, all reactions were carried out with 0.1-0.2 mmol of imine at 0.1-0.2 M in imine. The catalyst was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \bullet SMe_2$ (2 *M* in toluene), 2 equiv PhOH and 3 equiv of water at 100 °C for 1 h in toluene, followed by removing all volatiles at high vacuum (0.1 mm Hg) for 0.5 h at 100 °C. Stock solution of catalyst used. ND =

(Table 3.2 continued...)

not determined. Reaction times have not been optimized. Crystallized **9a** used. [b] ^{1}H NMR analysis of crude reaction mixture. [c] Isolated yield after chromatography. [d] Chiral HPLC. [e] Average of two runs, reaction complete in 9 h. [f] Very poor solubility of catalyst-imine complex in solvent. [g] Reaction time was 48 h. [h] Reaction was carried out at room temperature.

3.4.2 The issue of trans-aziridine invertomers

^{1}H NMR analysis of almost all isolated pure trans-aziridines reveals the presence of aziridine invertomers (two species). The ratio of these invertomers depends on the deuterated NMR solvent used, and also on the aziridine substrate itself. The ratio of invertomers for the trans-aziridine **60a** in various deuterated NMR solvents is presented in Table 3.3. The ratio of invertomers for aziridine **60a** in $CDCl_3$ is usually 1:0.31, while the same ratio in DMSO-d_6 is 1:0.06. DMSO-d_6 gives predominantly one invertomer for almost all trans-aziridines, and is the solvent of choice for characterization of the trans-aziridines by NMR analysis. However, there have been certain trans-aziridines in this study for which even DMSO-d_6 indicates a significant presence of both invertomers in the NMR analysis.

NMR temperature experiments were carried out to check whether the signals from the invertomers for aziridine **60a** would coalesce at high temperatures. Thus, solutions of **60a** were made in C_6D_6 and toluene-d_8, and heated from 15 °C → 25 °C → 50 °C → 70 °C and from 21 °C → 40 °C → 50 °C → 60 °C → 80 °C respectively, and ^{1}H NMR analysis was carried out at each stage. While the respective peaks for the two aziridine invertomers were sharp at lower temperatures, the same peaks broadened at higher temperatures and

gradually disappeared into the baseline. These peaks did not coalesce at higher temperatures as expected.

Table 3.3 Ratio of invertomers for **60a** in deuterated NMR solvents

Entry	Solvent	Ratio of invertomers for **60a**[a]	Polarity of solvent[b]
1	DMSO-d_6	1:0.06	
2	CD_3CN	1:0.4	
3	CD_3OH	1:0.22	
4	acetone-d_6	1:0.25	
5	THF-d_8	1:0.32	
6	CD_2Cl_2	1:0.35	
7	$CDCl_3$	1:0.31	
8	Et_2O-d_{10}	1:0.08	
9	C_6D_6	1:0.65	
10	toluene-d_8	1:0.63	

[a] Invertomers have not been assigned. [b] Taken from "Solvent selection guide", Pirrung, M. C. *The Synthetic Organic Chemist's Companion*, John Wiley & Sons, Inc., Hoboken, New Jersey, 2007.

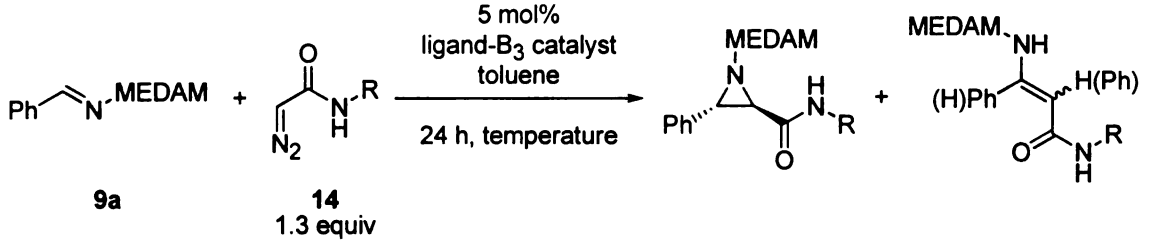
The conversions, trans:cis ratios and yields of enamines for the trans-selective aziridinations are usually calculated on the basis of the ^1H NMR analysis of the crude reaction mixture in $CDCl_3$. For the relative integrations, the trans-aziridine ring methine proton signals are taken into consideration. For the major invertomer, these methines usually exhibit sharp doublets (J = 2-3 Hz) in the region of 2-4 ppm. For the minor invertomer, these are small broad singlets in the same region. The minor diastereomers, the cis aziridines, are single species and do not show invertomers as do the trans-aziridines. Thus, for the relative integrations, the cis-aziridine ring methine proton signals (sharp doublets, J = 6-8 Hz, 2-4 ppm) are taken into consideration. For the enamines, the signals from the

N-H proton (doublets or doublet of doublets, 8-10 ppm) are considered. Before the practitioners get comfortable with the trans-aziridination protocol, they are advised to isolate the trans-aziridine, confirm the location of the signals from the two invertomers, and then revert to the crude ^{1}H NMR analysis to calculate the necessary ratios of products.

3.4.3 The diazoacetamide substrate scope

After the completion of the initial optimization, we set out to explore the generality of our new trans-aziridination protocol. In the secondary diazoacetamide screen (Table 3.4), both aryl and alkyl groups performed well. Both electron rich and electron deficient phenyl rings gave excellent results (Entries 9, 10, 12). Alkyl diazoacetamides were outstanding substrates, and gave near perfect asymmetric inductions under their optimized conditions (Entries 19, 22). These are the first examples for alkyl groups on the diazoacetamide component in the asymmetric trans-selective imine aziridination literature[13,15].

Table 3.4 The diazoacetamide substrate scope[a]



9a **14** 1.3 equiv

#	R (**diazo**)	ligand	temp (°C)	conv. (%)[b]	trans: cis[b]	azir.	yield azir. (%)[c]	ee azir. (%)[d]	yield enamines (%)[b]
1[e]	Ph (**14a**)	*(S)*-VANOL	0	100	12:1	**60a**	84	90	10
2		*(S)*-VANOL	-20	100	21:1		90	96	5

(Table 3.4 continued...)

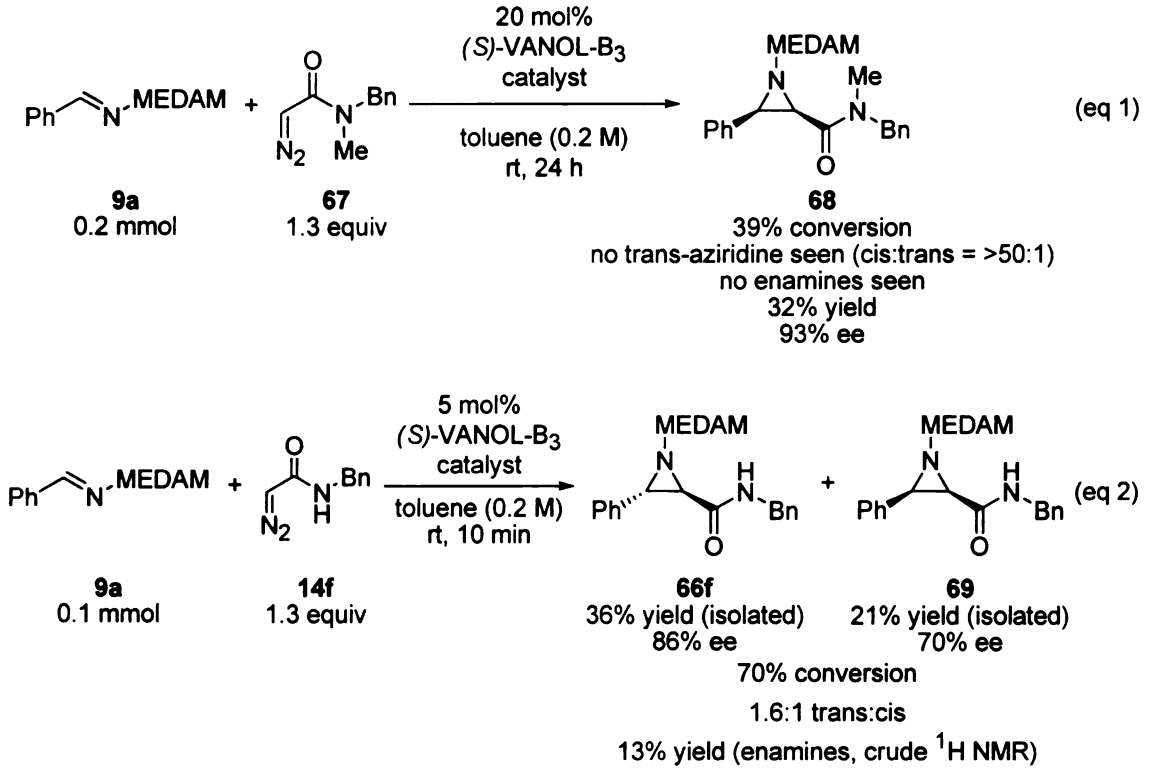
3[f,g]		*(S)*-VANOL	0	7	ND		ND	ND	ND
4[f]	*p*-$NO_2C_6H_4$ **(14b)**	*(S)*-VANOL	22	23	4:1	**66b**	ND	ND	ND
5[f]		*(R)*-VAPOL	0	0	ND		ND	ND	ND
6		*(S)*-VANOL	0	53	9:1		40	80	6
7[h,i]	*p*-$CF_3C_6H_4$ **(14c)**	*(R)*-VANOL	0	54	8:1	**66c**	30	78	6
8[j,k]		*(S)*-VANOL	0	77	8:1		58	78	13
9		*(S)*-VANOL	0	100	13:1		75	91	11
10	*p*-$OMeC_6H_4$ **(14d)**	*(R)*-VANOL	0	100	13:1	**66d**	84	93	10
11		*(R)*-VANOL	-20	74	19:1		ND	ND	ND
12	*p*-ClC_6H_4 **(14e)**	*(S)*-VANOL	0	100	13:1	**66e**	82	92	8
13		*(R)*-VANOL	-20	53	18:1		ND	ND	ND
14		*(S)*-VANOL	0	100	3:1		62	94	8
15		*(R)*-VANOL	0	100	3:1		60	94	9
16	Bn **(14f)**	*(S)*-VANOL	-20	100	5:1	**66f**	78	97	5
17		*(R)*-VANOL	-40	76	10:1		ND	ND	ND
18[j]		*(S)*-VANOL	-40	81	10:1		73	98	1
19[l]		*(S)*-VANOL	-40	100	10:1		88	98	3
20		*(S)*-VANOL	0	100	3:1		62	95	10
21	*n*-Bu **(14g)**	*(R)*-VANOL	0	100	4:1	**66g**	66	96	13
22		*(R)*-VANOL	-20	100	8:1		84	98	6
23		*(S)*-VANOL	-40	68	11:1		ND	ND	ND

[a] Unless otherwise specified, all reactions were carried out with 0.2 mmol of imine at 0.2 M in imine. The catalyst was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \bullet SMe_2$ (2 *M* in toluene), 2 equiv PhOH and 3 equiv of water at 100 °C for 1 h in toluene, followed by removing all volatiles at high vacuum (0.1 mm Hg) for 0.5 h at 100 °C. Stock solution of catalyst used. ND = not determined. Reaction times have not been optimized. Reaction with (*R*)-ligand gives ent.

(Table 3.4 continued...)

trans-aziridine shown. Crystallized **9a** used. [b] ^{1}H NMR analysis of crude reaction mixture. [c] Isolated yield after chromatography. [d] Chiral HPLC. [e] Average of two runs, reaction complete in 9 h. [f] Low conversion probably due to very poor solubility of diazo in toluene. [g] Average of two runs. [h] Reaction time 66 h. [i] Some compound spilled during work-up leading to low yield. [j] Reaction time 48 h. [k] 10 mol% catalyst. [l] 0.1 mmol imine scale, 0.1 M in imine, 10 mol% catalyst.

Scheme 3.4 Cis-aziridination with *N*-methyl-*N*-benzyldiazoacetamide **67**



In our original aziridination protocol, the reactions between various diarylmethylimines and ethyldiazoacetate provided the corresponding cis-aziridines (Chapter 2). In the work discussed in this chapter, simply switching to diazoacetamides affords the opposite diastereomers, the trans-aziridines. The *N*-H bond of the diazoacetamide has been found to play a pivotal role in this reversal of diastereoselectivity (further discussion in Chapter 7). Indeed, if the *N*-

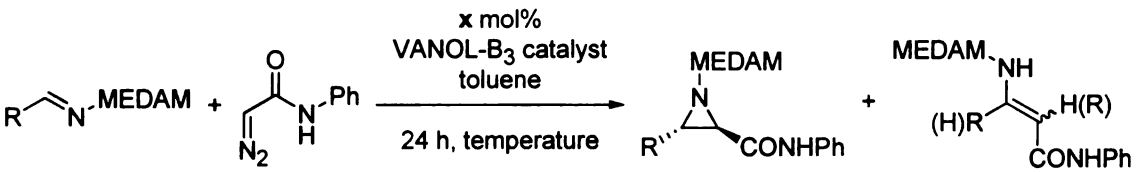
H bond is removed from the diazoacetamide, and replaced with a group not capable of H-bonding, the diastereoselectivity of the reaction reverts again to afford the corresponding cis-aziridines. This is exemplified in Scheme 3.4, where the reaction of *N*-methyl-*N*-benzyldiazoacetamide[10,31] **67** and imine **9a** gives exclusively the corresponding cis-aziridine **68** with excellent asymmetric induction (eq 1). This reaction is quite sluggish, and is compared to the corresponding reaction of diazoacetamide **14f** (eq 2).

3.4.4 The aryl imine substrate scope

For the imine substrate scope, those prepared from aryl aldehydes were explored first (Table 3.5). A wide range of aromatic imines with varying electronic and steric demands gave excellent diastereoselectivities, yields and asymmetric inductions for the corresponding trans-aziridines. Both electron rich and electron deficient aryl imines were well tolerated. The imine **9e** bearing the 4-methoxyphenyl moiety had completely failed for the other trans-selective imine aziridination systems in the literature[13,15], giving messy mixtures and low conversions. In our protocol however, this substrate performed very well, giving the corresponding trans-aziridine **60e** in 66% yield and 94% ee (average from Entries 14, 15). Sterically demanding substrates have also not been reported in these other trans-selective aziridination systems in the literature[13,15]. We took up this challenge and designed a substrate possessing a 2-chlorophenyl moiety (**9g**) and an ortho-*di-substituted* substrate with a 4-bromo-2-fluorophenyl moiety (**9j**). Both these imines performed exceedingly well, the former providing 84% yield

and 98% ee (Entry 25) and the latter providing 74% yield and 95% ee (Entry 37) for their corresponding trans-aziridine products.

Table 3.5 The aryl imine substrate scope[a]



9 **14a** 1.3 equiv **60** **63**

#	R (series)	ligand	x (%)	temp. (°C)	conv. (%)[b]	trans: cis[b]	yield **60** (%)[c]	ee **60** (%)[d]	yield **63** (%)[b]
1[e]	Ph (**a**)	*(S)*-VANOL	5	0	100	12:1	84	90	10
2		*(S)*-VANOL	5	-20	100	21:1	90	96	5
3	*p*-$CH_3C_6H_4$ (**b**)	*(S)*-VANOL	5	0	100	14:1	84	95	6
4		*(S)*-VANOL	5	-20	19	ND	ND	ND	ND
5	*p*-BrC_6H_4 (**c**)	*(S)*-VANOL	5	0	100	18:1	87	97	5
6		*(R)*-VANOL	5	0	100	16:1	85	94	7
7		*(S)*-VANOL	5	-20	82	36:1	74	99	3
8	*p*-$NO_2C_6H_4$ (**d**)	*(S)*-VANOL	5	0	100	11:1	80	92	11
9		*(S)*-VANOL	5	-20	96	18:1	85	93	7
10		*(R)*-VANOL	5	-20	92	19:1	81	93	6
11		*(S)*-VANOL	5	-40	22	ND	ND	ND	ND
12		*(R)*-VANOL	5	0	37	9:1	ND	ND	ND
13	*p*-$OMeC_6H_4$ (**e**)[f]	*(S)*-VANOL	10	0	100	6:1	61	89	9
14[g]		*(S)*-VANOL	15	0	100	8:1	69	96	8
15[h,i]		*(S)*-VANOL	15	0	100	6:1	62	91	7
16[h,i]		*(S)*-VANOL	20	-20	70	16:1	ND	ND	ND

(Table 3.5 continued...)

17[g,j]		*(S)*-VANOL	5	0	100	11:1	82	87	8
18[g,j]		*(R)*-VANOL	5	0	100	9:1	79	81	10
19[g,j]	*m*-$CH_3C_6H_4$ (**f**)	*(R)*-VANOL	5	-20	12	ND	ND	ND	ND
20[g,j]		*(S)*-VANOL	10	-20	55	9:1	ND	ND	ND
21[h,j,k]		*(S)*-VANOL	20	-20	100	12:1	87	90	4
22[g,j]		*(S)*-VANOL	5	0	100	14:1	78	90	16
23	*o*-ClC_6H_4 (**g**)	*(R)*-VANOL	5	0	100	11:1	75	89	17
24		*(R)*-VANOL	5	-20	82	30:1	ND	ND	ND
25		*(R)*-VANOL	10	-20	100	26:1	84	98	13
26[j]		*(S)*-VANOL	5	0	100	11:1	76	92	10
27[j]	*m*-$OMeC_6H_4$ (**h**)	*(R)*-VANOL	5	0	100	9:1	75	93	9
28[j]		*(S)*-VANOL	10	-20	100	9:1	74	97	6
29[j]		*(R)*-VANOL	5	0	62	11:1	ND	ND	ND
30[j]		*(R)*-VANOL	5	-20	26	ND	ND	ND	ND
31[j]	2-naphthyl (**i**)	*(R)*-VANOL	10	-20	33	ND	ND	ND	ND
32[j]		*(R)*-VANOL	10	0	100	7:1	81	81	8
33[j]		*(S)*-VANOL	10	0	100	7:1	79	81	9
34		*(S)*-VANOL	5	0	84	5:1	62	92	10
35	4-Br-2-F-C_6H_3 (**j**)	*(R)*-VANOL	5	0	91	5:1	66	90	10
36		*(S)*-VANOL	5	-20	82	8:1	ND	ND	ND
37		*(S)*-VANOL	10	-20	100	7:1	74	95	11

[a] Unless otherwise specified, all reactions were carried out with 0.2 mmol of imine at 0.2 M in imine. The catalyst was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \bullet SMe_2$ (2 *M* in toluene), 2 equiv PhOH and 3 equiv of water at 100 °C for 1 h in toluene, followed by removing all volatiles at high vacuum (0.1 mm Hg) for 0.5 h at 100 °C. Stock solution of catalyst used. ND = not determined. Reaction times have not been optimized. Reaction with *(R)*-VANOL gives ent. **60**. Crystallized imines used. [b] ^1H NMR analysis of crude reaction mixture. [c] Isolated yield after

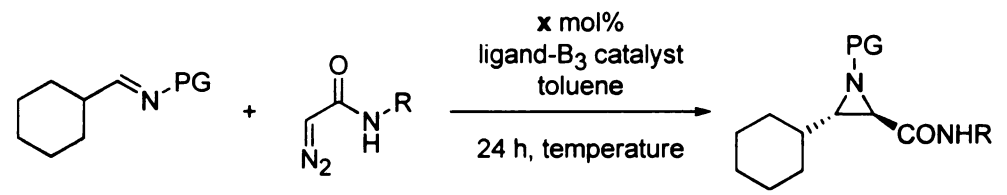
(Table 3.5 continued...)

chromatography. [d] Chiral HPLC. [e] Average of two runs, reaction complete in 9 h. [f] The chiral HPLC conditions were verified by running two additional experiments (not shown), with *(S)*- and *(R)*-VANOL, which gave unreliable trans:cis ratios, but identical ee's. [g] 0.133 M in imine. [h] 0.1 mmol scale in imine. [i] 0.1 M in imine. [j] Crude imine used. [k] 0.07 M in imine.

3.4.5 The alkyl imine substrate scope

We knew that the real test of our trans-selective aziridination would be the imines prepared from alkyl aldehydes; such examples are unprecedented in this field[13,15]. Imines prepared from 1°, 2° as well as 3° alkyl aldehydes provide excellent results in our cis-selective aziridinations;[6-12] we strongly felt that these should be successful in our trans-selective aziridinations too, for us to be able to develop a universal catalytic asymmetric aziridination protocol.

Table 3.6 Trans-aziridination of the cyclohexyl (2° alkyl) imine substrate[a]



9k, PG = MEDAM
1k, PG = Bh
58k, PG = BUDAM

1.3 equiv
14a, R = Ph
14f, R = Bn
14g, R = *n*-Bu

#	PG	R	ligand	x (%)	temp. (°C)	azir.	conv. (%)[b]	yield of trans-azi (%)[c]	ee (%)[d]
1	MEDAM	Ph	*(S)*-VANOL	5	0	**60k**	0	-	-
2	MEDAM	Bn	*(S)*-VANOL	5	0	**70f**		low conversion	
3	MEDAM	Ph	*(R)*-VAPOL	10	22	**60k**	100	73	59
4	MEDAM	Ph	*(S)*-VAPOL	10	22	**60k**	100	70	52

(Table 3.6 continued...)

5[e]	MEDAM	Ph	*(R)*-VANOL	10	22	**60k**	100	57	25
6	MEDAM	Bn	*(R)*-VANOL	10	22	**70f**	100	34	22
7	MEDAM	*n*-Bu	*(R)*-VANOL	10	22	**70g**	100	28	8
8	MEDAM	Ph	*(S)*-VAPOL	10	0	**60k**	35	19	68
9	MEDAM	Ph	*(R)*-VANOL	10	0	**60k**	69	43	32
10	MEDAM	Ph	*(S)*-VANOL	10	0	**60k**	82	50	30
11	Bh	Ph	*(R)*-VAPOL	20	0	**59k**	100	61	43
12	Bh	Ph	*(S)*-VANOL	20	0	**59k**	100	57	47
13	BUDAM	Ph	*(S)*-VANOL	20	0	**61k**	100	62	26
14	BUDAM	Ph	*(R)*-VAPOL	20	0	**61k**	100	61	70
15	BUDAM	Ph	*(R)*-VAPOL	20	0	**61k**	100	66	70
16	BUDAM	Ph	*(R)*-VAPOL	10	0	**61k**	100	66	73
17	BUDAM	Ph	*(S)*-VAPOL	20	-20	**61k**	100	67	50
18	BUDAM	Ph	*(R)*-VAPOL	20	-20	**61k**	100	72	49
19[f]	BUDAM	Ph	*(S)*-VAPOL	20	-40	**61k**	69	55	53
20	BUDAM	Ph	*(R)*-VAPOL	20	rt (22)	**61k**	100	62	69

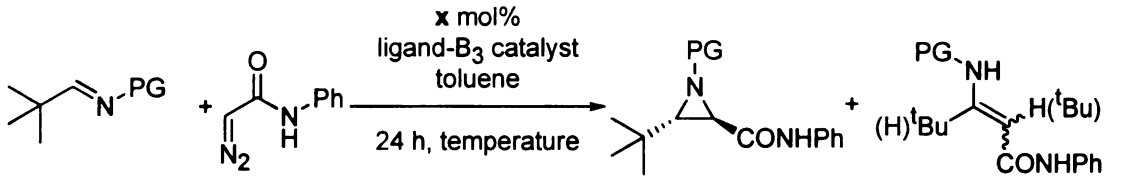
[a] Unless otherwise specified, all reactions were carried out with 0.2 mmol of imine at 0.2 M in imine. The catalyst was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \bullet SMe_2$ (2 *M* in toluene), 2 equiv PhOH and 3 equiv of water at 100 °C for 1 h in toluene, followed by removing all volatiles at high vacuum (0.1 mm Hg) for 0.5 h at 100 °C. Stock solution of catalyst used. Trans:cis ratios and yields of enamines = not determined, due to overlapping/unidentified signals in crude ^{1}H NMR. Reaction times have not been optimized. Reaction with *(R)*-ligand gives ent. trans-aziridine shown. Crystallized imines used. [b] ^{1}H NMR analysis of crude reaction mixture. [c] Isolated yield after chromatography. [d] Chiral HPLC. [e] Trans:cis = 11:1, determined from isolated yields of the cis- and trans-aziridines. [f] 48 h reaction time.

Initial results in this regard were disappointing. Under our optimized conditions (MEDAM protecting group, 5 mol% VANOL catalyst, 0 °C), the imine

with a cyclohexyl group (2° alkyl) gave no reaction at all (Table 3.6, Entry 1)! This made us launch an extensive optimization for this substrate, and the results are presented in Table 3.6. The best result that could be obtained for this substrate was only 66% yield and 73% ee (Entry 16). The optimized conditions for this alkyl imine substrate were surprisingly different as compared to those for the aryl imine model substrate **9a** (Table 3.1). BUDAM gave better results for the reaction rates as compared to MEDAM (compare Entries 16 vs. 8), and VAPOL was superior to VANOL for the asymmetric inductions (compare Entries 14 vs. 13).

The first 3° alkyl substrate (*t*-butyl) examined was outstanding in its performance, and afforded exclusively the trans-aziridine product in 90% yield and 90% ee (Table 3.7, Entry 3). The BUDAM/VAPOL combination again was better for this substrate, albeit by a much smaller margin as compared to the cyclohexyl imine substrate.

Table 3.7 Trans-aziridination of the *t*-butyl (3° alkyl) imine substrate[a]



9l, PG = MEDAM
58l, PG = BUDAM

1.3 equiv
14a

60l, PG = MEDAM
61l, PG = BUDAM

#	imine	ligand	x (%)	temp. (°C)	conv. (%)[b]	trans: cis[b]	yield trans-azi (%)[c]	ee (%)[d]	yield enamines (%)[b]
1	**58l**	*(S)*-VANOL	20	0	81	17:1	65	80	<1
2	**58l**	*(R)*-VAPOL	20	0	100	26:1	85	83	2
3	**58l**	*(S)*-VAPOL	20	-20	100	>50:1	90	90	<1
4	**58l**	*(R)*-VAPOL	10	-20	100	>50:1	88	89	2

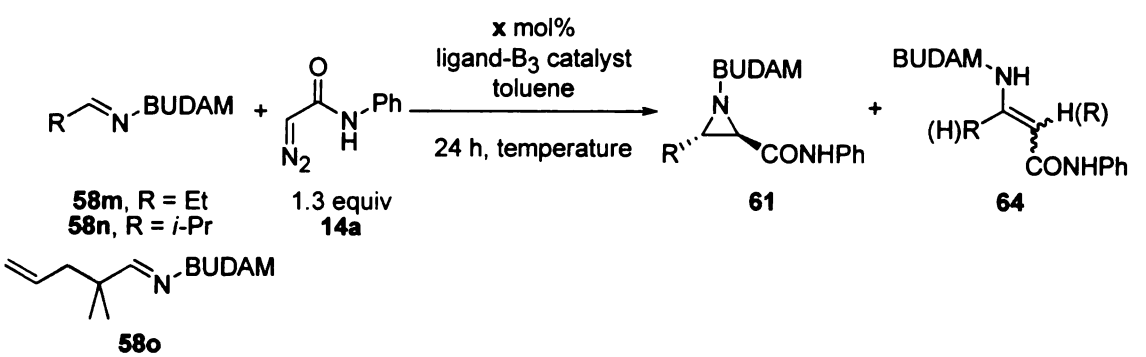
(Table 3.7 continued...)

5	**9l**	*(R)*-VAPOL	20	0	66	8:1	49	75	<1
6	**9l**	*(S)*-VANOL	20	0	95	17:1	68	88	3

[a] Unless otherwise specified, all reactions were carried out with 0.2 mmol of imine at 0.2 M in imine. The catalyst was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \bullet SMe_2$ (2 *M* in toluene), 2 equiv PhOH and 3 equiv of water at 100 °C for 1 h in toluene, followed by removing all volatiles at high vacuum (0.1 mm Hg) for 0.5 h at 100 °C. Stock solution of catalyst used. Reaction times have not been optimized. Reaction with *(R)*-ligand gives ent. trans-aziridine shown. Crystallized imines used. [b] ^1H NMR analysis of crude reaction mixture. [c] Isolated yield after chromatography. [d] Chiral HPLC.

Other 1°, 2° and 3° alkyl imines were subsequently evaluated with the BUDAM protecting group, and all could be optimized to provide good to excellent results for their corresponding trans-aziridine products (Table 3.8).

Table 3.8 Trans-aziridination of other 1°, 2° and 3° alkyl BUDAM imines[a]



#	imine	ligand	x (%)	temp. (°C)	conv. (%)[b]	trans: cis[b]	yield **61** (%)[c]	ee **61** (%)[d]	yield **64** (%)[b]
1	**58m**	*(S)*-VANOL	20	0	100	ND[e]	66	88	27
2	**58m**	*(R)*-VANOL	20	0	100	ND[e]	68	87	27
3	**58m**	*(R)*-VANOL	10	0	100	ND[e]	67	82	17
4	**58m**	*(R)*-VANOL	20	-20	100	ND[e]	63	80	21
5	**58m**	*(R)*-VAPOL	20	0	100	ND[e]	51	2	27
6	**58m**	*(S)*-VAPOL	20	0	100	ND[e]	57	54	27

(Table 3.8 continued...)

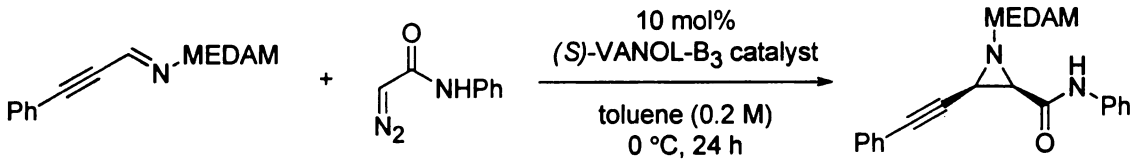
7[f]	**58o**	*(R)*-VAPOL	20	0	55	ND	ND	ND	ND
8[f]	**58o**	*(S)*-VANOL	20	0	28	ND	ND	ND	ND
9[f]	**58o**	*(R)*-VAPOL	20	rt	25	ND	ND	ND	ND
10[f,g]	**58o**	*(R)*-VAPOL	20	0	70	5:1	53	81	6
11	**58n**	*(S)*-VANOL	20	0	100	ND[e]	60	58	ND[e]
12	**58n**	*(R)*-VAPOL	20	0	100	ND[e]	73	81	ND[e]
13	**58n**	*(S)*-VAPOL	20	0	100	ND[e]	68	83	ND[e]
14	**58n**	*(S)*-VAPOL	10	0	100	ND[e]	67	83	ND[e]
15	**58n**	*(S)*-VAPOL	20	-20	100	ND[e]	69	74	ND[e]
16	**58n**	*(S)*-VAPOL	10	-20	100	ND[e]	70	75	ND[e]

[a] Unless otherwise specified, all reactions were carried out with 0.2 mmol of imine at 0.2 M in imine. The catalyst was prepared by heating 1 equiv of ligand, 3 equiv of $BH_3 \bullet SMe_2$ (2 *M* in toluene), 2 equiv PhOH and 3 equiv of water at 100 °C for 1 h in toluene, followed by removing all volatiles at high vacuum (0.1 mm Hg) for 0.5 h at 100 °C. Stock solution of catalyst used. Reaction times have not been optimized. Reaction with *(R)*-ligand gives ent. trans-aziridine shown. Crystallized imines used. ND = not determined. [b] ^{1}H NMR analysis of crude reaction mixture. [c] Isolated yield after chromatography. [d] Chiral HPLC. [e] Not determined, due to overlapping/unidentified signals in crude ^{1}H NMR. [f] Crude imine used, 0.08 M in imine. [g] 67 h reaction time.

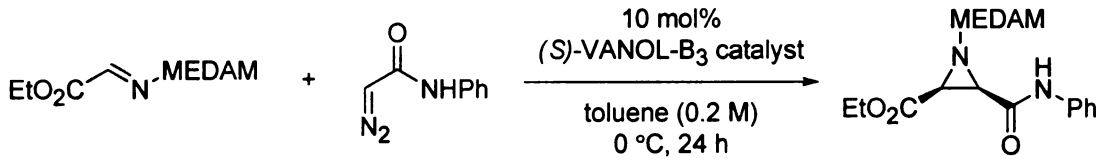
3.4.6 Puzzling aziridination reactions of two substrates

When the aziridination reactions of imines **9p**[40] and **40b** were attempted, the ^{1}H NMR analysis of the crude reaction mixture revealed the presence of the corresponding cis-aziridines as the major diastereomers (Scheme 3.5). The reaction with imine **9p** was especially very clean, and a 90% NMR yield was observed for the cis-aziridine product. The reasons behind the reversal of diastereoselection for these imines are not understood at the moment; these reactions were not pursued any further.

Scheme 3.5 Puzzling aziridination reactions of two substrates



9p 0.2 mmol | **14a** 1.3 equiv | 100% conversion, 1:9 trans:cis | **71** 90% NMR yield



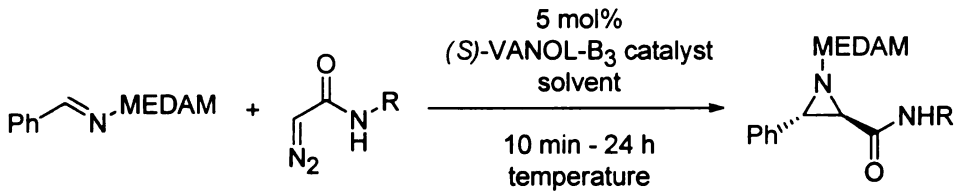
40b 0.2 mmol | **14a** 1.3 equiv | 100% conversion, 1:2 trans:cis | **72**

3.4.7 Temperature vs. diastereoselectivity in the trans-aziridinations

A study to monitor the diastereoselectivities in the trans-aziridination reactions as a function of the reaction temperature was carried out, and the results for the aziridines **60a** and **66f** are presented in Table 3.9. The trans:cis diastereoselectivity gradually decreased with increasing temperature, and eventually switched over to marginally favor the cis aziridines under refluxing conditions. However, this was accompanied by concomitant erosion in the quality of the reactions; the reaction conversions to the aziridine products decreased significantly and the imine was recovered unreacted, presumably due to the decomposition of the diazoacetamide at high temperatures.

Decomposition of related trans-aziridine carboxylate esters has been previously noted by Hossain[5b] and Mayer[5c], which might be a factor affecting the observed diastereoselectivies in the present study. However, this idea was not investigated any further.

Table 3.9 Temperature vs. diastereoselectivity in the trans-aziridinations



9a

14a, R = Ph
14f, R = Bn
1.3 equiv

60a, R = Ph
66f, R = Bn

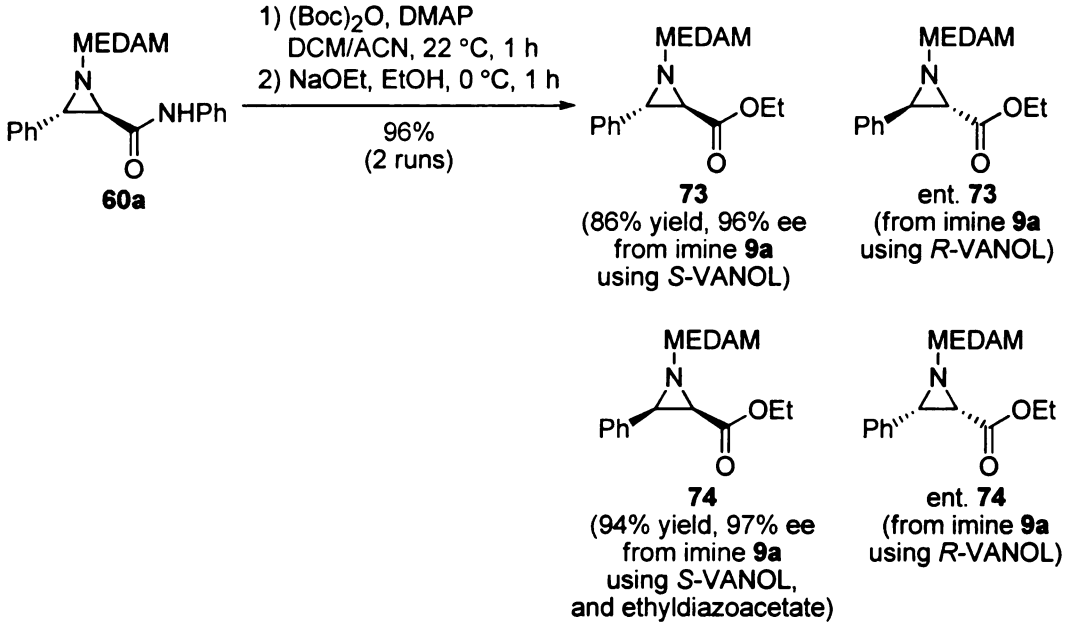
Entry	R	solvent	temp. (°C)	trans:cis[a]
1[b]	Ph	toluene	-40	18:1
2[b]	Ph	toluene	-20	21:1
3[b]	Ph	toluene	0	12:1
4[c]	Ph	xylenes	0	11:1
5[b]	Ph	toluene	22 (rt)	5:1
6	Ph	xylenes	60	3:1
7[d]	Ph	xylenes	100	1:1.5
8[c]	Ph	CH_3CN	0	1:1
9[e]	Ph	CH_3CN	22 (rt)	1:1.3
10[e]	Ph	CH_3CN	60	1:2
11[f]	Bn	toluene	-40	10:1
12[f]	Bn	toluene	-20	5:1
13[f]	Bn	toluene	0	3:1
14[g]	Bn	toluene	22 (rt)	1.6:1
15[d]	Bn	xylenes	100	1:2

[a] Crude ^1H NMR analysis. [b] Table 3.1. [c] Table 3.2. [d] Mostly diazoacetamide decomposition, traces of aziridines. [e] Enamines were the major products. [f] Table 3.4. [g] Scheme 3.4.

3.4.8 All four stereoisomers of 3-aziridine-2-carboxylates

After confirming the generality of our substrate scope, we sought to demonstrate the universality of our aziridination protocol. The amide group in trans-aziridine **60a** was smoothly converted to the corresponding ethyl ester (Scheme 3.6).[41] Thus, the trans-aziridine **73** could be obtained with an overall yield of 86% and 96% ee from imine **9a** via our trans-aziridination protocol. Of course, switching the enantiomer of the VANOL ligand in the trans-aziridination would give us access to the enantiomer of **73**.

Scheme 3.6 All four stereoisomers of 3-aziridine-2-carboxylates



Through our previous work, we have shown that we can access the diastereomers of **73**, the cis-aziridine **74** and its enantiomer, in 94% yield and 97% ee *starting from the same imine **9a** and using 5 mol% of the same catalyst prepared from the VANOL ligand*, by simply switching to ethyldiazoacetate instead of phenyldiazoacetamide.[10]

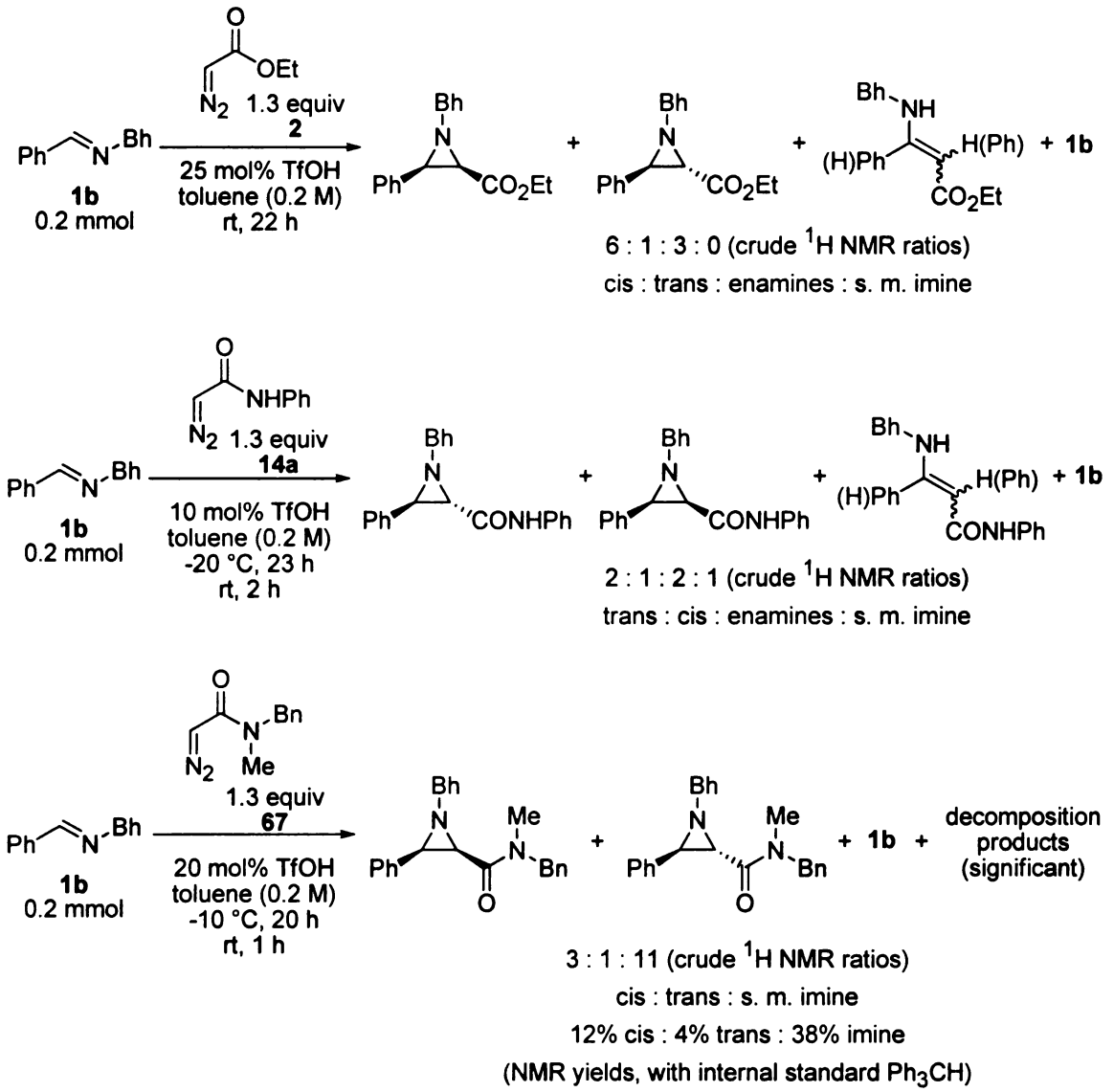
Thus, we can now access, in an efficient and straightforward manner,[42] all four possible stereoisomers of these 3-aziridine-2-carboxylates – synthetic intermediates of seminal importance in organic synthesis[2,3] – via our universal catalytic asymmetric aziridination protocol (Scheme 3.6).

3.4.9 TfOH catalyzed aziridination reactions

Switching from a diazoacetate to a diazoacetamide completely reversed the diastereoselectivity of our aziridination reactions. We were interested to check if this reversal was specific to our B_3 catalysts. Thus, the imine **1b** was reacted with ethyldiazoacetate **2** and *N*-phenyldiazoacetamide **14a** in the presence of catalytic amounts of TfOH (Scheme 3.7).[22] The reaction with **2** furnished the corresponding cis-aziridine as the major diastereomer, while the trans-aziridine was formed as the major diastereomer in the reaction of **14a**. Thus, the reversal of diastereoselectivity in our catalytic asymmetric aziridinations was not specific to our B_3 catalysts only; rather it seemed to be solely due to the diazo component.

Removal of the *N*-H from the *N*-phenyldiazoacetamide **14a**, via the use of *N*-methyl-*N*-benzyldiazoacetamide **67**, had resulted in the re-reversal of the diastereoselectivity for the reaction of imine **9a** catalyzed by the VANOL-B_3 catalyst, furnishing the cis-aziridine **68** exclusively as the major diastereomer (Scheme 3.4). The same re-reversal was seen with diazoacetamide **67** for the triflic acid catalyzed reactions also, where again the cis-aziridine was observed as the major diastereomer (Scheme 3.7).

Scheme 3.7 TfOH catalyzed aziridination reactions



3.4.10 General absolute configurations in the universal aziridination

The absolute configuration of the major diastereomer, the cis aziridine, in our cis-selective aziridinations with ethyldiazoacetate has been previously determined by chemical derivatization.[6] The cis aziridine in these reactions results from a *Si* face attack of the diazoacetate on the (*S*)-catalyst-imine complex; the same facial selectivity was also determined for the cis-aziridine **3e** formed from the reaction of the *o*-bromophenyl benzhydryl imine **1e** (see Section

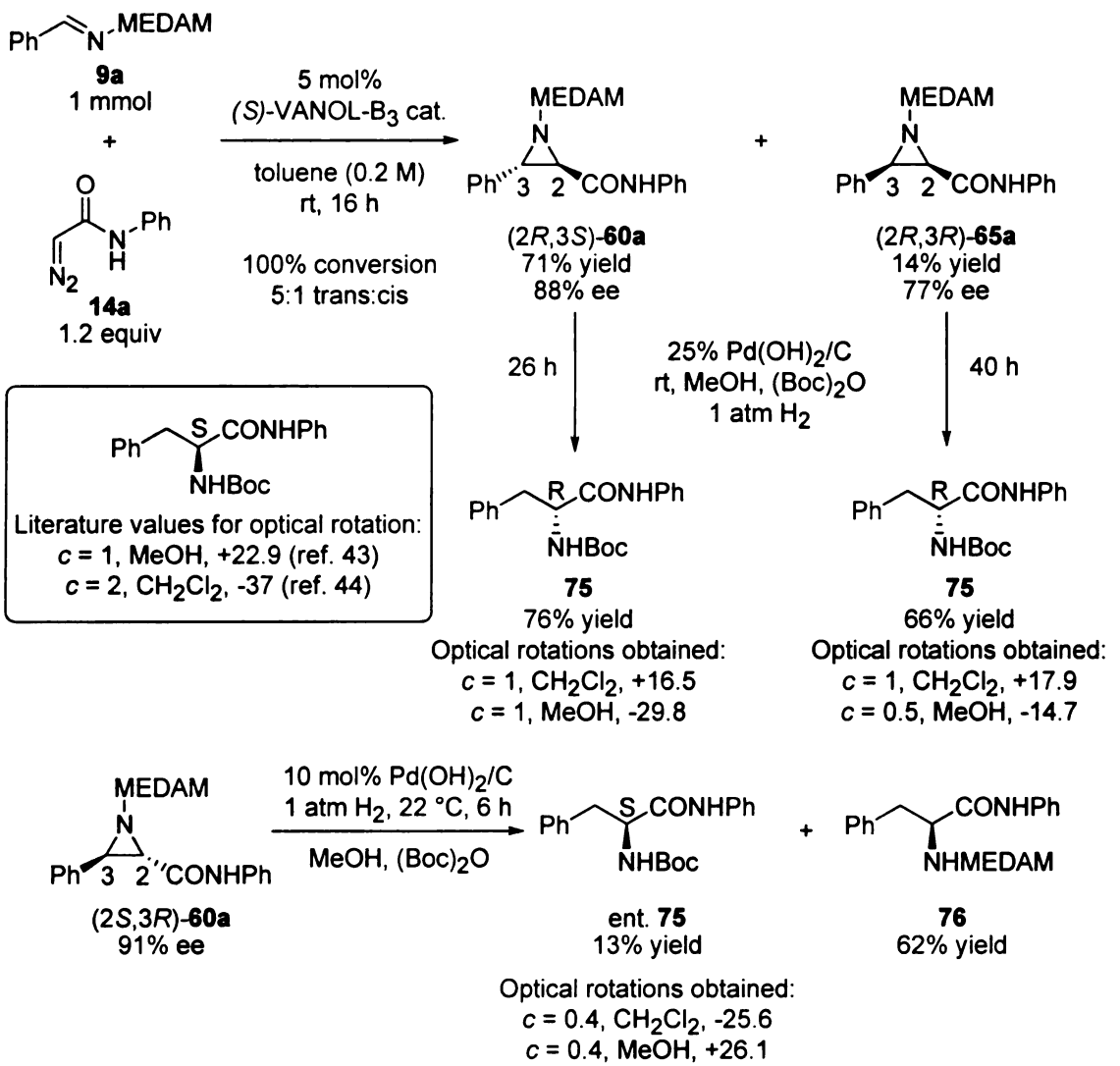
2.2, Chapter 2). The reaction with the *o*-bromophenyl benzhydryl imine **1e** has been the only reaction in our cis-selective aziridinations with ethyldiazoacetate that has given us isolable quantities of the minor diastereomer, the trans-aziridine **30** (see Section 2.2, Chapter 2). Determination of the absolute configuration then surprisingly led to the discovery that the trans-aziridines in this protocol result from a *Re* face attack of the diazoacetate on the (*S*)-catalyst-imine complex. Thus, the facial selectivity of the aziridinations with ethyldiazoacetate is opposite for the cis- and trans-aziridine diastereomers with the same enantiomer of the catalyst-imine complex.

In the present study of the trans-selective aziridinations with diazoacetamides, the absolute configurations of both the major and minor diastereomers, the trans- and cis-aziridines respectively, have been determined by chemical derivatization (Scheme 3.8). The aziridines were converted to the corresponding Boc protected α-aminoamides, and their optical rotations were compared to literature values. Surprisingly again, opposite facial selectivity was observed for the trans- and cis-aziridine diastereomers with the same enantiomer of the catalyst-imine complex. The trans-aziridines in this protocol result from a *Re* face attack of the diazoacetamide on the (*S*)-catalyst imine complex, whilst the cis-aziridines result from a *Si* face attack of the diazoacetamide on the same catalyst-imine complex.

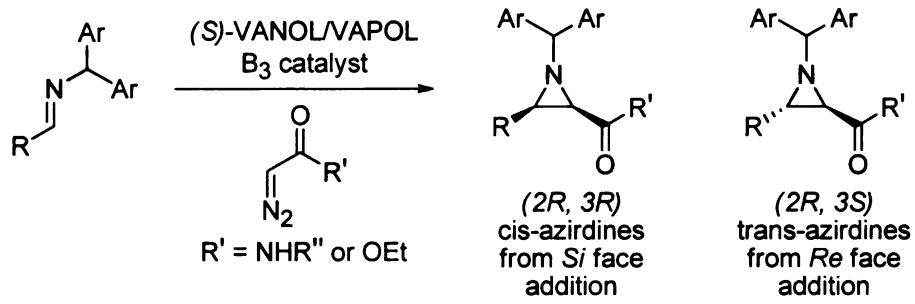
Thus, the absolute configurations in our universal aziridination protocol can be generalized as follows. Irrespective of the diazo compound (ethyldiazoacetate or diazoacetamides) and irrespective of the

diastereoselectivity of the aziridination reaction (cis- or trans-selective), all cis aziridines in our protocol result from a *Si* face attack of the diazo compound on the (*S*)-catalyst-imine complex, whilst all trans aziridines result from a *Re* face attack of the diazo compound on the same catalyst-imine complex. This generalization is exemplified for the aziridination reactions with the *(S)*-VAPOL/VANOL-B_3 catalyst in Scheme 3.9.

Scheme 3.8 Absolute configurations in the trans-selective aziridinations



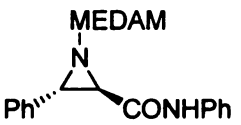
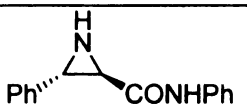
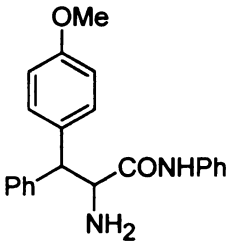
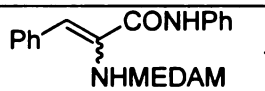
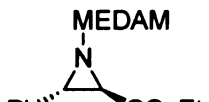
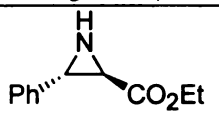
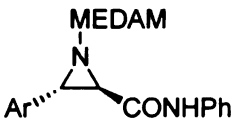
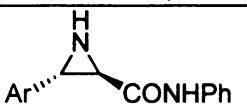
Scheme 3.9 General absolute configurations in the universal aziridination



3.4.11 Attempts at deprotection of the trans-aziridines

The cis-aziridines from our aziridination reactions with ethyldiazoacetate and imines derived from the MEDAM/BUDAM amine have been previously shown by others in our group to undergo smooth and efficient deprotection with TfOH, revealing the corresponding *N*-H aziridines.[9,10] All attempts at deprotecting the trans-aziridines obtained in the study described in this chapter under similar conditions did not give clean reactions or the same high yields. Quite a few other variations were attempted for the deprotection, however none were found to work satisfactorily; these attempts are summarized in Table 3.10.

Table 3.10 Attempts at deprotection of the trans-aziridines[a]

#	Substrate	Conditions	Results
1	 **60a**	5 equiv TfOH anisole, rt, 30 min	 **77** 22% yield  **78** 49% yield
2		10 equiv (8% H_2SO_4 in TFA) 0 °C to rt, 2 h 60 °C, 45 min, anisole	mostly ring-opened products no desired product in crude ^{1}H NMR
3		5 equiv TfOH, CH_3CN 0 °C, 1.5 h rt, 1 h	**77** (35% yield) + **60a** (50% yield)
4		5 equiv TfOH, CH_3CN rt, 20 h	**77** (21% yield) + mostly ring opened products
5		5 equiv TfOH, CH_3CN 48 h, 0 °C	**77** (44% yield)
6		DDQ (1.2 equiv) DCM:H_2O (5:1), rt, 20 h	 + **77** **79** 27% yield (tentative assignment) 5% yield
7	 **73**	5 equiv TfOH, 0 °C to rt, 3 h, anisole	 **80** ~14% yield (isolated with impurities)
8	 **60j** Ar = 4-Br-2-FC_6H_3	8 equiv TfOH, CH_3CN 0 °C, 24 h	 **81** 67% conversion Ar = 4-Br-2-FC_6H_3
9		8 equiv TfOH, CH_3CN 0 °C to rt, 3 h	**81** (53% yield)

[a] Isolated yields reported after chromatography on silica gel.

3.4.12 Puzzling origins of the stereoselections in our universal aziridination

Thus, switching from a diazoacetate to a diazoacetamide completely and cleanly reversed the diastereoselectivity as well as the face selectivity of imine addition in our aziridination reactions. While this result was very welcome, and helped us develop the first universal aziridination protocol in the literature, the mechanistic origins of these opposite diastereo- and facial- selections fascinated us, and intrigued us to great ends. We decided to seek answers with the aid of computational chemistry, and thus initiated a collaborative project with Dr. Mathew Vetticatt (Albert Einstein College of Medicine, New York). The results from this separate study have been remarkably satisfying, and will be reported in Chapter 7.

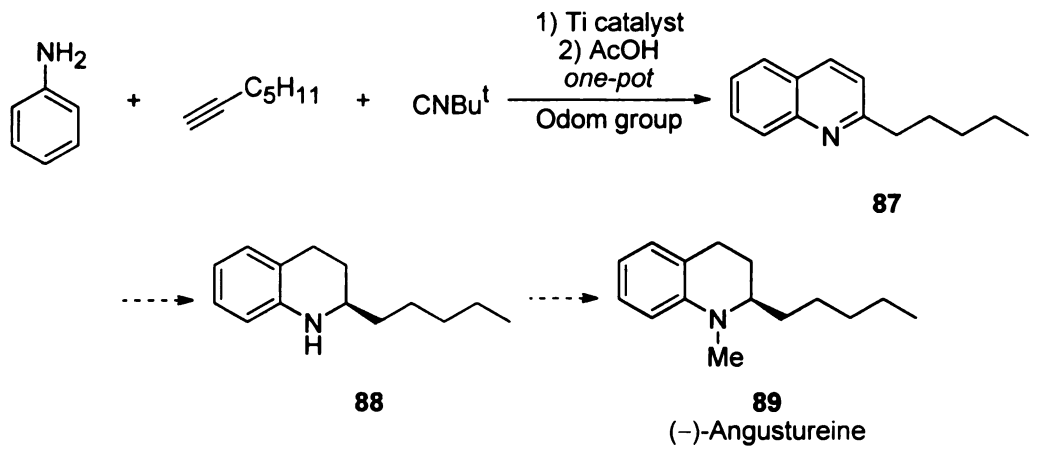
CHAPTER FOUR

CATALYTIC ASYMMETRIC TRANSFER HYDROGENATION OF 2-QUINOLINES: *AN EXPERIMENTAL AND COMPUTATIONAL STUDY*

4.1 Introduction

A considerable amount of time during this dissertation was spent trying to develop a catalytic asymmetric transfer hydrogenation of quinolines, mediated by the VAPOL/VANOL spiro-boroxinate Brønsted acid catalysts. The products of such a protocol would be 1,2,3,4-tetrahydroquinolines, structural motifs of significant importance in the pharmaceutical and fine chemical industry, as well as in the material sciences.[47] This core is also common in numerous alkaloid natural products.[48] Several successful systems exist for the asymmetric reduction of quinolines using organometallic catalysts.[49] Successful organocatalytic systems for the asymmetric transfer hydrogenation of quinolines using the Hantzsch ester as the hydrogen source have been recently reported, mediated by phosphoric acid catalysts derived from the BINOL ligand.[50]

Scheme 4.1 A collaborative effort with the Odom group



This project initially started out as a collaborative effort between our group and that of Professor Aaron Odom at Michigan State University (Scheme 4.1). The Odom group had developed an elegant titanium catalyzed multicomponent coupling sequence to directly access substituted quinolines.[51] Our group took up the task of developing a catalytic asymmetric transfer hydrogenation protocol, to transform the quinolines obtained from the Odom protocol into the corresponding 1,2,3,4-tetrahydroquinolines. The 2-pentylquinoline substrate **87** was initially chosen, since the corresponding reduced tetrahydroquinoline **88** was a simple *N*-methylation step away from a natural product **89**, (–)-Angustureine.[48c,50a]

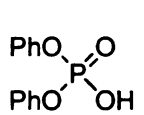
4.2 The different attempts in the optimization study

Numerous Brønsted acid and H-bonding catalysts, based on the parent ligands VAPOL and VANOL, were initially evaluated for the catalytic asymmetric transfer hydrogenation of 2-pentylquinoline **87** (Table 4.1). The preparation of these new derivatives of VAPOL and VANOL will be discussed in Chapter 5. Promising leads obtained from this catalyst screen were the VAPOL phosphoric acid catalyst **91** (Entry 2) and the VAPOL-B_3 catalyst **12** (Entries 7, 8). These provided the product **88** in 63% ee and 72-79% ee respectively, and were chosen for further optimization.

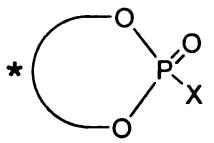
Quite a few parameters in the reaction conditions were then systematically varied with these two catalysts, in an attempt to increase the asymmetric inductions. All efforts were in vain; the asymmetric inductions could not be increased above the initial 72-79% ee value. These efforts are summarized herein: temperature/additives/other variations screen (Table 4.2), the Hantzsch

ester screen (Table 4.3), the solvent screen for the VAPOL-B_3 catalyst **12** (Table 4.4), and the solvent screen for the VAPOL phosphoric acid catalyst **91** (Table 4.5).

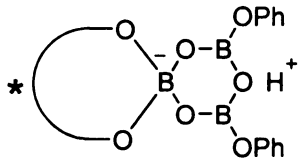
Table 4.1 The catalyst screen[a]



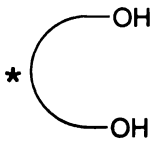
90



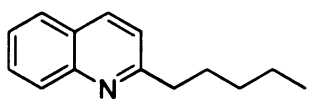
91 : VAPOL, X = OH
92 : VAPOL, X = $NHSO_2CF_3$
93 : VANOL, X = OH
94 : VANOL, X = $NHSO_2CF_3$
95 : 8,8'-Ph_2VANOL, X = OH



12 : VAPOL-B_3
96 : VANOL-B_3
97 : 8,8'-Ph_2VANOL-B_3

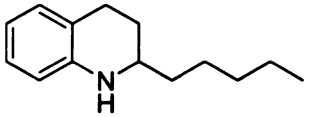


4 : VAPOL
5 : VANOL

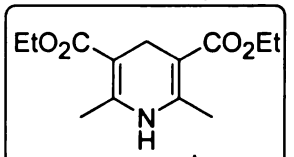


87
0.05 mmol

x mol% catalyst
Hantzsch's ester **98a**
(2.4 equiv)
benzene, time, temperature



88



Hantzsch's ester **98a**

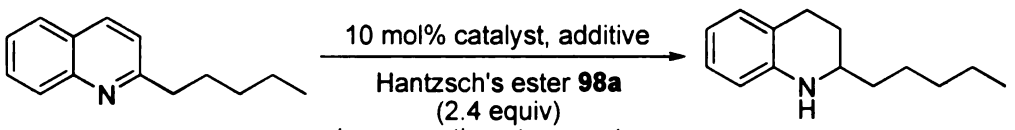
Entry	Catalyst	x	Time (h)	Temperature (°C)	Conversion (%)[b]	Yield **88** (%)[c]	ee **88** (%)[d]
1	**90**	20	10	60	100	>99	-
2	*(R)*-**91**	5	10	60	100	>99	63
3	*(R)*-**92**	10	12	60	100	>99	37
4	*(S)*-**93**	10	12	60	100	>99	50
5	*(S)*-**94**	10	12	60	100	>99	31
6	*(S)*-**95**	10	31 6	60 70	~90	88	17
7	*(R)*-**12** (3 runs)	10	12	60	100	>99	72
8	*(S)*-**12**	10	12	60	100	ND	79
9	*(S)*-**96**	10	12	60	100	88	20

(Table 4.1 continued...)

10	*(S)*-**97**	10	12	60	100	ND	9
11	*(R)*-**4**	20	39 14	60 70	incomplete	~80	0
12	*(S)*-**5**	20	39 14	60 70	incomplete	78	0

[a] ND = not determined. [b] ^{1}H NMR analysis of crude reaction mixture. [c] Isolated yield after chromatography. [d] Chiral HPLC.

Table 4.2 Temperature/additives screen[a]



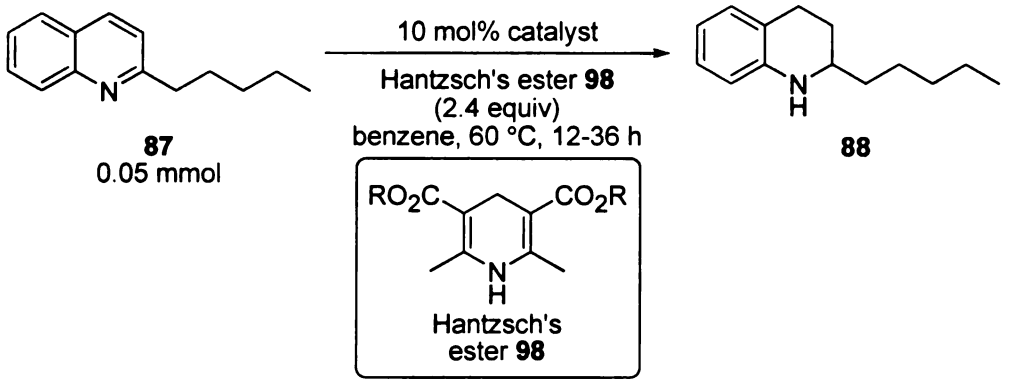
87
0.05 mmol

88

Entry	Catalyst	Additive	Time (h)	Temperature (°C)	Conversion (%)[b]	ee **88** (%)[c]
1	**12**[d]	none	12	60	100	73
2		none	24	35	100	72
3		none	76	rt	incomplete	ND
4		activated 4Å MS	12	60	100	48
5		1.2 equiv BnOH	12	60	100	3
6		1.2 equiv gla. AcOH	12	60	100	~15
7	**91**	none	18	60	100	61
8		none	24 46	rt 35	incomplete	58
9		activated 4Å MS	68	60	incomplete	ND
10		1.2 equiv gla. AcOH	18	60	100	56
11		1.2 equiv BnOH	18	60	100	56

[a] Product **88** was isolated by pipette column chromatography, usually in >99% isolated yield. ND = not determined. [b] Determined by TLC. [c] Chiral HPLC on isolated **88**. [d] Catalyst prepared by heating 1 equiv of VAPOL, 4 equiv of $B(OPh)_3$ and 1 equiv of water at 80 °C for 1 h in toluene (2 mL), followed by removing all volatiles under high vacuum (0.1 mm Hg) at 80 °C for 0.5 h. Stock solution of catalyst used.

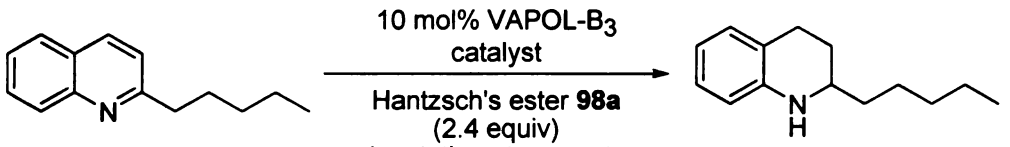
Table 4.3 The Hantzsch ester screen[a]



Entry	Catalyst	Hantzsch's ester (R)	ee **88** (%)[b]
1	**12**[c]	Et (**98a**)	73
2		^{t}Bu (**98b**)	43[d]
3		Me (**98c**)	76
4		Bn (**98d**)	75
5	**91**	Et (**98a**)	63
6		^{t}Bu (**98b**)	53
7		Me (**98c**)	60
8[e]		Bn (**98d**)	<50

[a] Product **88** was isolated by pipette column chromatography, usually in >99% isolated yield. Conversion usually 100%, determined by TLC. [b] Chiral HPLC on isolated **88**. [c] Catalyst prepared by heating 1 equiv of VAPOL, 4 equiv of $B(OPh)_3$ and 1 equiv of water at 80 °C for 1 h in toluene (2 mL), followed by removing all volatiles under high vacuum (0.1 mm Hg) at 80 °C for 0.5 h. Stock solution of catalyst used. [d] Average of 4 runs. [e] Incomplete conversion, by TLC.

Table 4.4 Solvent screen for VAPOL-B_3 catalyst **12**[a]



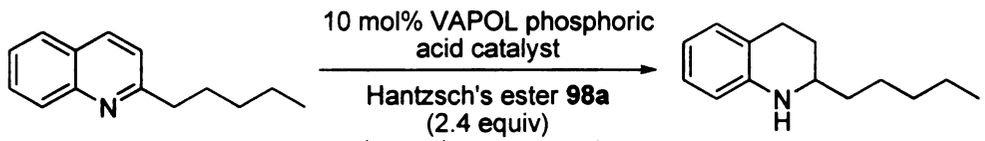
87
0.05 mmol

88

Entry	Solvent	Time (h)	Temperature (°C)	ee **88** (%)[b]
1	benzene	12	60	73
2	toluene	15	60	65
3	C_6H_5Cl	13	60	64
4	$CHCl_3$	15	60	46
5	$ClCH_2CH_2Cl$	15	60	16
6	CCl_4	13	60	3
7	EtOAc	23 12	60 70	3
8	CH_3CN	13	60	0
9	THF	15	60	12
10[c]	1,4-dioxane	23 12	60 70	ND
11[d]	Et_2O	100	35	ND
12	*n*-Bu_2O	41 15	60 70	5
13	DMSO	41 15	60 70	0

[a] Product **88** was isolated by pipette column chromatography, usually in >99% isolated yield. Conversion usually 100%, determined by TLC. Catalyst prepared by heating 1 equiv of VAPOL, 4 equiv of $B(OPh)_3$ and 1 equiv of water at 80 °C for 1 h in toluene (2 mL), followed by removing all volatiles under high vacuum (0.1 mm Hg) at 80 °C for 0.5 h. Stock solution of catalyst used. ND = not determined. [b] Chiral HPLC on isolated **88**. [c] No reaction. [d] Incomplete reaction, by TLC.

Table 4.5 Solvent screen for the VAPOL phosphoric acid catalyst **91**[a]



87
0.05 mmol

88

Entry	Solvent	Time (h)	Temperature (°C)	ee **88** (%)[b]
1	benzene	10	60	63
2	toluene	12	60	64
3	C_6H_5Cl	12	60	63
4	$ClCH_2CH_2Cl$	12	60	48
5	$CHCl_3$	12	60	51
6	CCl_4	12	60	19
7	1,4-dioxane	18	60	37
8	*n*-Bu_2O	18	60	48
9[c]	Et_2O	46	35	57
10	THF	32 23	60 70	42
11	CH_3CN	32 44	60 70	19
12	EtOAc	32 23	60 70	41
13[c]	DMSO	32 44 24	60 70 90	ND

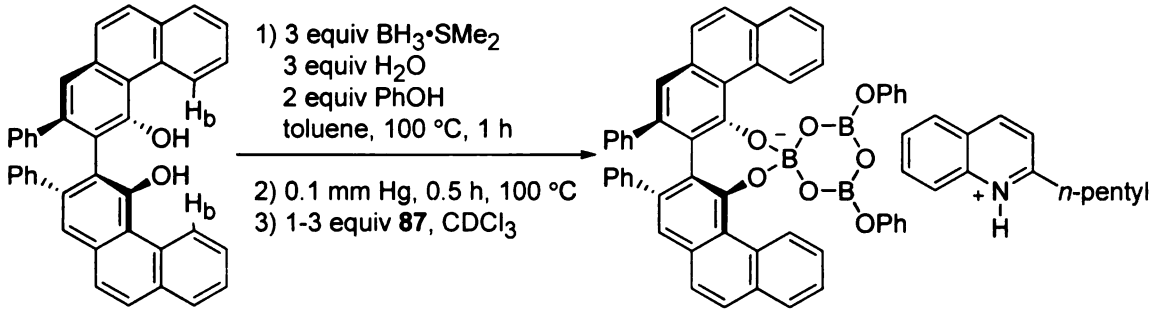
[a] Product **88** was isolated by pipette column chromatography, usually in >99% isolated yield. Conversion usually 100%, determined by TLC. ND = not determined. [b] Chiral HPLC on isolated **88**. [c] Incomplete conversion.

4.3 Confirmation of the VAPOL-B_3 spiro-boroxinate active catalyst

Since so far the best result was with the VAPOL-B_3 catalyst **12** (73% ee vs. 63% ee for VAPOL phosphoric acid catalyst **91**), we decided to remove the VAPOL phosphoric acid catalyst from subsequent screens. We had initially

assumed the VAPOL-B_3 spiro-boroxinate active catalyst structure for our quinoline reduction studies (Scheme 4.2), in analogy with the active catalyst/catalytic cycle in our aziridination studies[11] (Section 1.3.1, Chapter 1). We next decided to seek evidence for this assumption.

Scheme 4.2 The active catalyst-quinoline complex in quinoline reductions



4
(S)-VAPOL

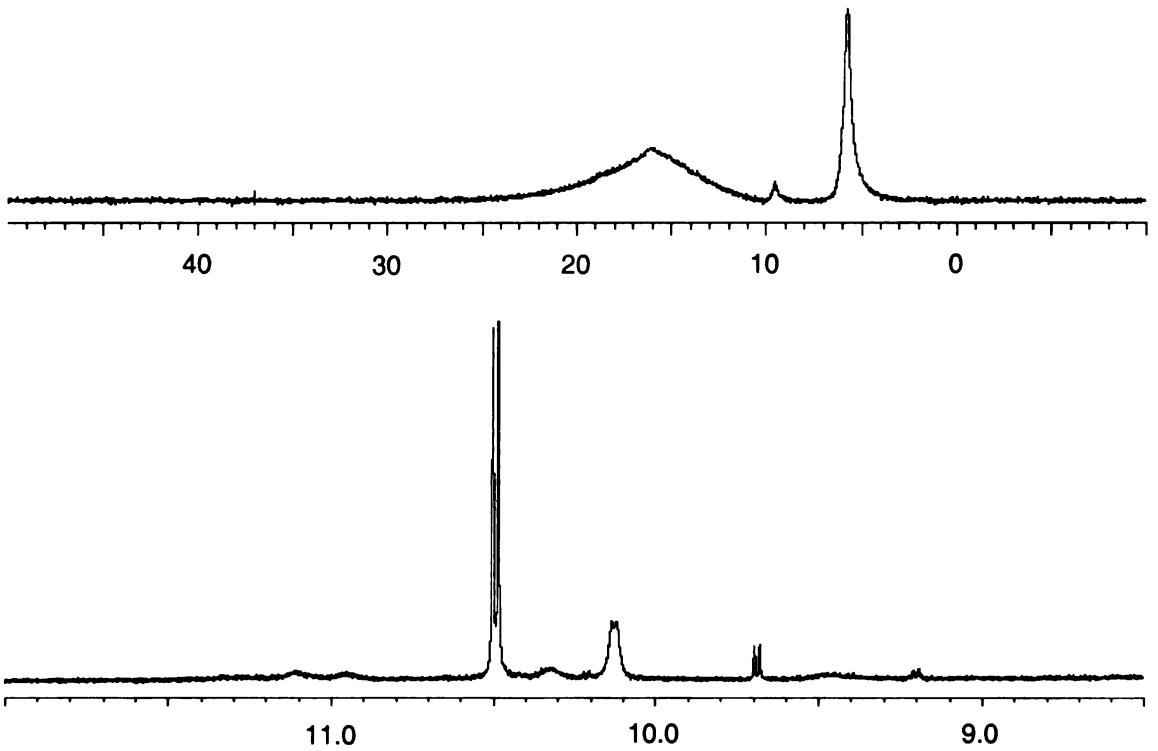
99
(S)-VAPOL-B_3 - quinoline complex

For our aziridination studies, the method of choice for confirming the spiro-boroxinate B_3 motif in the active catalyst is by way of ^{11}B and ^{1}H NMR analyses,[11] which were carried out for our quinoline reduction studies too. The catalyst was prepared as indicated in Scheme 4.2. The ^{11}B and ^{1}H NMR spectra of the boroxinate-quinoline complex **99** are quite distinctive (Figure 4.1).

Three-coordinate borate esters typically have broad absorptions for the boron between 16-20 ppm in $CDCl_3$.[11a] Since ^{11}B is a quadrapole, the sharpness of the absorption is related to the spherical symmetry around the boron, and this is reflected in the appearance of the ^{11}B NMR spectrum of the boroxinate-quinoline complex **99** (Figure 4.1, top). The two three-coordinate borons in **99** appear as a very broad absorption at 15.97 ppm, and the four-coordinate boron as a very sharp peak at 5.76 ppm, with an integration of 2:1 respectively (not shown). This is in perfect accord with the ^{11}B NMR spectrums obtained in our

aziridination studies.[11] The most distinctive absorption for the complex **99** in the ^{1}H NMR spectrum is the bay-region doublet (H_b in **4**, Scheme 4.2) at 10.49 ppm (Figure 4.1, bottom), again in good agreement with that observed in our aziridination studies[11]. These NMR studies thus confirmed the presence of the spiro-boroxinate B_3 active catalyst in our quinoline reduction studies.

Figure 4.1 *Top:* ^{11}B NMR of complex **99** ($CDCl_3$, 160 MHz); *bottom:* ^{1}H NMR of complex **99** ($CDCl_3$, 500 MHz)



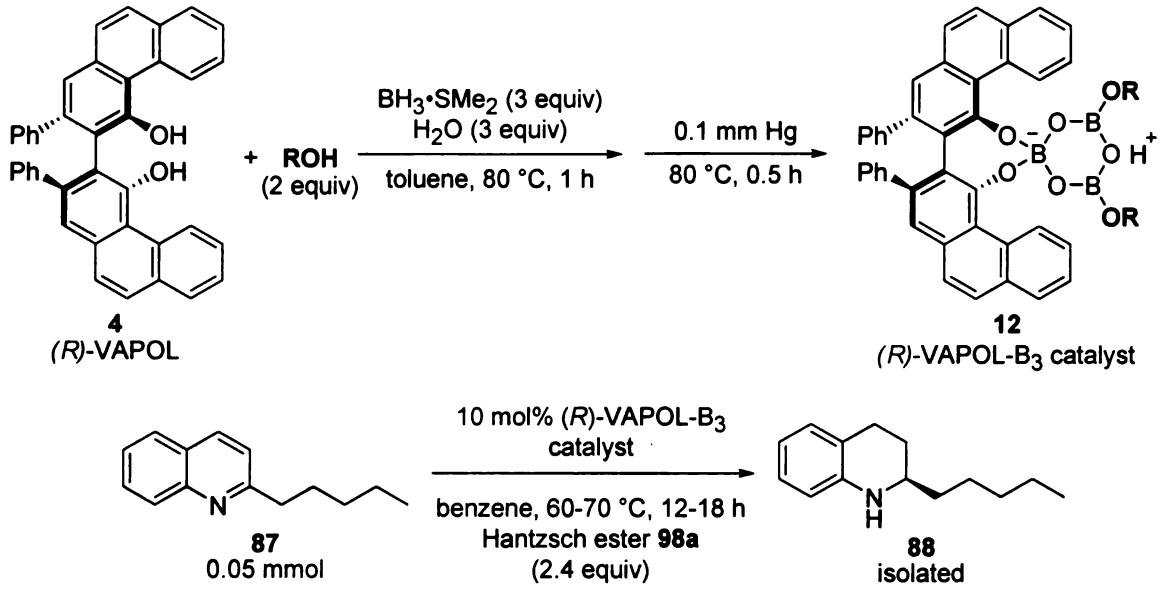
Furthermore, the absolute configuration of the tetrahydroquinoline product **88** from the reaction of the VAPOL-B_3 catalyst was determined by comparison of the optical rotations to literature values, and is shown in Scheme 4.3 (see Experimental Information for details).

4.4 Self-assembly of a family of B_3 catalysts for the quinoline reductions

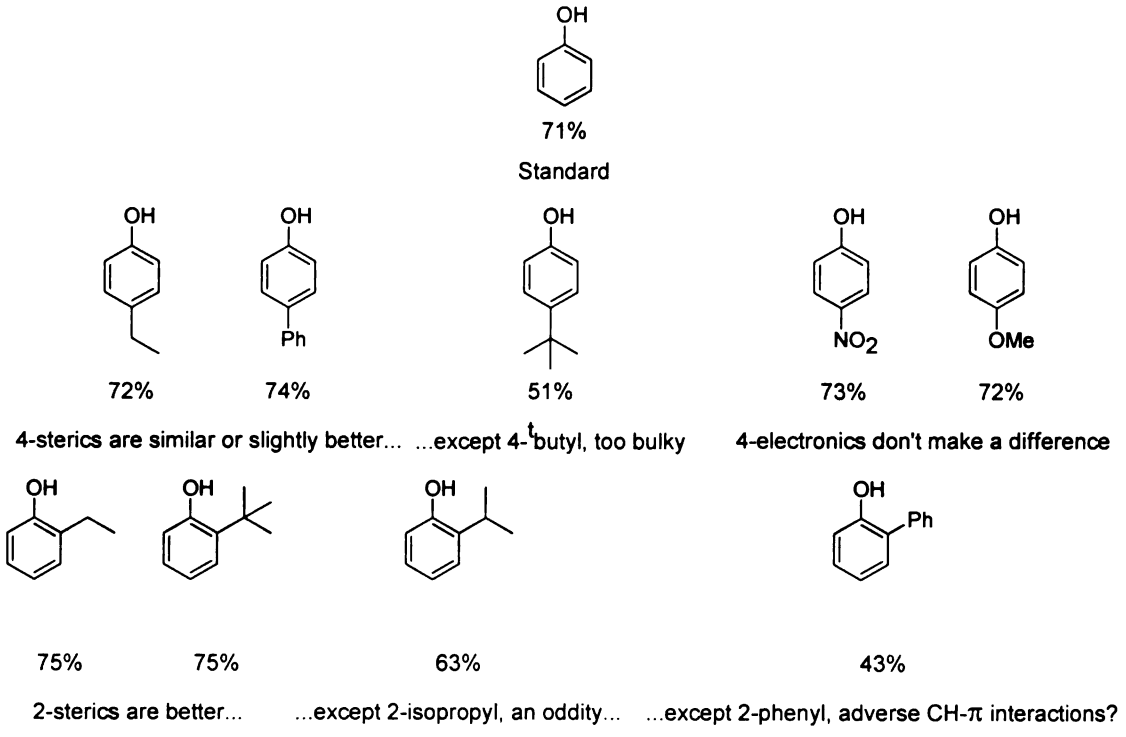
The spiro-boroxinate catalysts from VAPOL/VANOL can be generated via two different methods, either using $B(OPh)_3$ (Table 4.4) or using $BH_3 \bullet SMe_2$ (Scheme 4.2). The catalyst prepared from either method affords identical results in both our aziridination studies as well as in the quinoline reduction studies. However, that the catalyst can be prepared using the $BH_3 \bullet SMe_2$ route lends us the distinct opportunity to generate a large family of B_3 catalysts by simply incorporating different phenols and alcohols during the catalyst self-assembly.

This was the approach taken to further enhance the asymmetric inductions in the reduction of quinolines study discussed in this chapter. A broad range of sterically and electronically different phenols and alcohols were screened, and the resulting asymmetric inductions and trends obtained are presented in Scheme 4.3. Unfortunately, in spite of all our efforts, we were never able to increase the asymmetric inductions beyond the initially obtained 72-79% ee range.

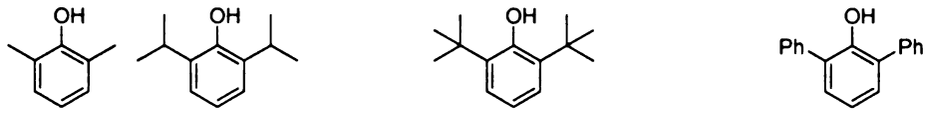
Scheme 4.3 Self-assembly of a family of B_3 catalysts for the quinoline reductions



ee values:

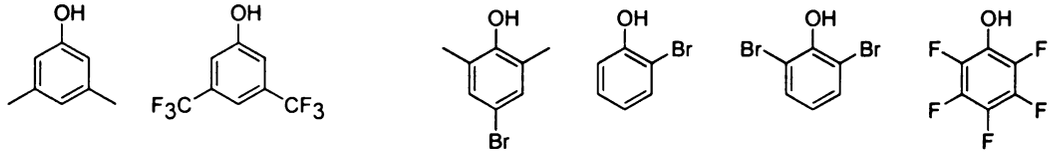


(Scheme 4.3 continued...)



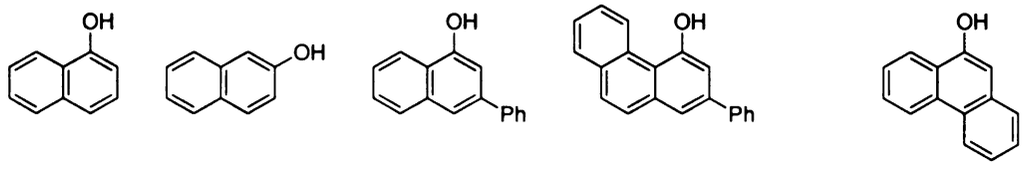
78% 71% 8% (slow reaction) 41%

2,6-sterics are better or similar... ...except 2,6-di-^{t}butyl, too bulky... ...except 2,6-di-phenyl, adverse CH-π interactions?



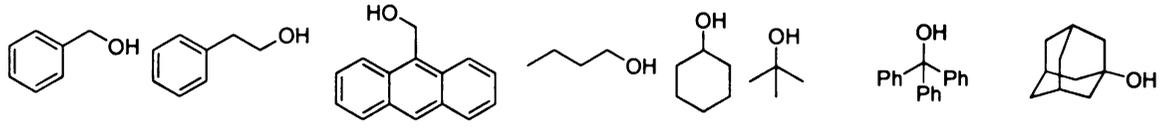
40% 51% 67% 58% 61% 33%

3,5-sterics or 3,5-electronics are worse Halogens are consistently deleterious, adverse halogen-bonding?



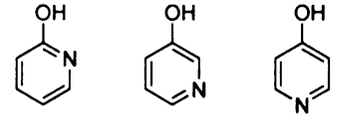
78% 73% 74% 76% 19%

Bicyclic and tricyclic aromatics (up to "tri-substituted" phenols) are better... ...except "tetra-substituted" phenols, too bulky



19% 19% 2% (slow reaction) 25% 22% 15% 35% (slow reaction) 70%

Several diverse aliphatic/benzyl alcohols tried, all are consistently worse... ...except one oddity



-12% 2% 5%

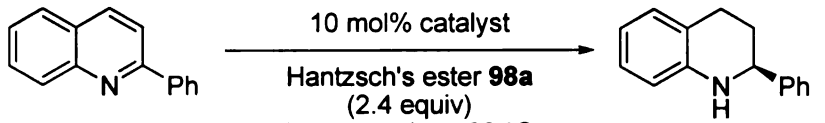
Pyridyl hydroxides are slow and disastrous

VAPOL-B_3 catalyst probably does not form, maybe due to the extra coordination site

4.5 Asymmetric transfer hydrogenation of 2-phenylquinoline

The catalytic asymmetric transfer hydrogenation of a different substrate, 2-phenylquinoline, was also attempted (Table 4.6). The best asymmetric induction obtained with this substrate was also 67% ee, with the VAPOL-B_3 catalyst.

Table 4.6 Asymmetric transfer hydrogenation of 2-phenylquinoline **100**[a]



100
0.1 mmol

101

Entry	Catalyst	Time (h)	Yield **101** (%)[b]	ee **101** (%)[c]
1	*(R)*-VAPOL-B_3	58	>99	67
2	*(S)*-VANOL-B_3	14	>99	36

[a] Catalyst prepared by heating 1 equiv of ligand, 4 equiv of $B(OPh)_3$ and 1 equiv of water at 80 °C for 1 h in toluene (2 mL), followed by removing all volatiles under high vacuum (0.1 mm Hg) at 80 °C for 0.5 h. Stock solution of catalyst used. *(S)*-ligand gives ent. **101** shown. [b] Isolated yield after column chromatography. [c] Chiral HPLC.

4.6 Transition state analysis via computational chemistry

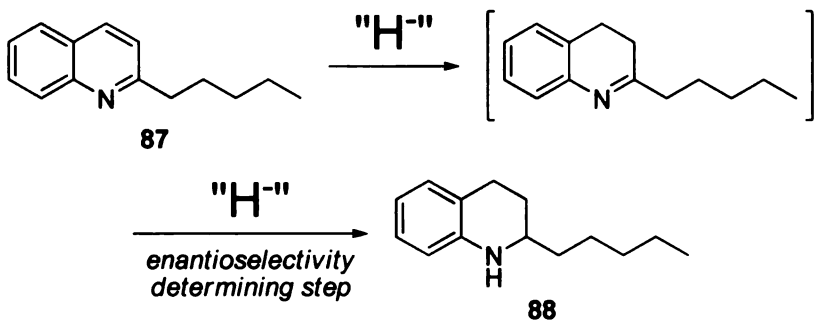
As with our aziridination studies (Chapter 7), we entered into a collaboration with Dr. Mathew Vetticatt to study the origins of the stereoselections in the asymmetric reduction of quinolines also, using computational chemistry. Numerous transition states were located, and a detailed study based on theoretical calculations was conducted.

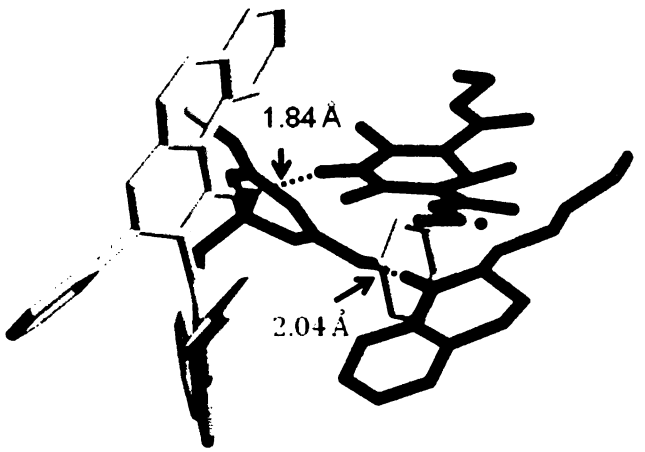
Shown in Figure 4.2 is the preferred enantioselectivity determining transition state, corresponding to the final transfer hydrogenation step. As seen in the transition states for our aziridination studies (Chapter 7), multiple non-

covalent interactions are seen in this transition state also. The protonated quinoline H-bonds to oxygen O-3 of the boroxinate catalyst, whilst the Hantzsch ester H-bonds to oxygen O-1 of the catalyst. The additive effect of these interactions leads to a tight organization at the transition state, consequently lowering the energy of the transition state.

The full details of the computational studies in the collaborative effort with Dr. Vetticatt, along with the experimental details for this project, will be published shortly.

Figure 4.2 The enantioselectivity determining step, and the enantioselectivity determining transition state calculated via ONIOM(B3LYP/6-31G*:AM1)

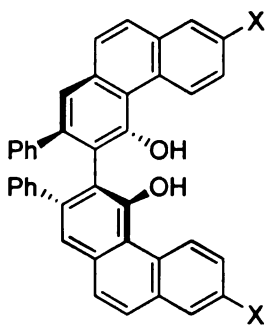




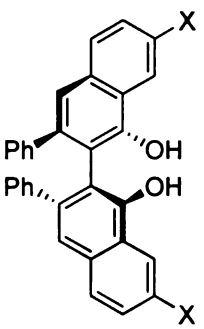
4.7 Future directions for the project

While a reasonable level of asymmetric induction was achieved for the catalytic asymmetric transfer hydrogenation of quinolines during this dissertation (up to 78% ee), and a satisfying collaborative computational study carried out for the same, this cannot be billed as a successful protocol for the asymmetric reduction of quinolines. In our opinion, any catalytic asymmetric system to be called successful should provide >90% ee for at least two substrates. All efforts to reach this level during this dissertation have ended in frustration; however, for the future generations of the boroxinate-catalyst users, a few suggestions are made to convert this protocol into a successful system (Scheme 4.4).

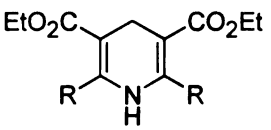
Scheme 4.4 Future directions for the project



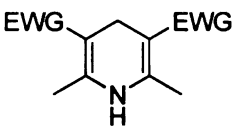
102



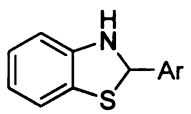
103



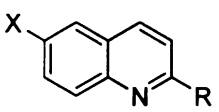
104



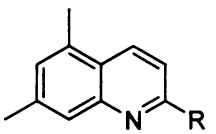
105
(EWG = COPh, NO_2)



106



107



108

There was a distinct difference between the boroxinate catalysts prepared from VAPOL and VANOL in the initial catalyst screen (Table 4.1). Thus, since the system seems to respond to changes in the ligand structure (unlike our cis-aziridination studies, Chapter 2), it might be interesting to screen the newer

derivatives of both VAPOL (**102**) and VANOL (**103**) being actively developed in our laboratories (Scheme 4.4). There is a tight H-bond between the Hantzsch ester and the catalyst core at the enantioselectivity determining transition state (Figure 4.2). Numerous transition states without this H-bond were located, but they were all significantly higher in energy (15-20 kcal/mol). Thus, the hydrogen transfer reagent is intimately involved in the enantioselectivity determining step; varying its steric and electronic environment should definitely produce a variation in the asymmetric inductions. In this regard, it might be interesting to try Hantzsch ester derivatives of type **104** (R > Me),[52] which would be sterically different. The H-bonding capability of the Hantzsch ester could be tuned by using derivatives of type **105**.[53] Alternately, the hydrogen transfer reagent could be completely switched. Akiyama has recently introduced benzothiazolines **106** as effective reducing agents for the asymmetric organocatalytic transfer hydrogenation of ketimines;[54] it would be very interesting to try these for our system. There seems to be a stabilizing CH-π interaction between the hydrogen at the C-7 position of the partially reduced quinoline and the catalyst at the transition state (Figure 4.2). It might be worthwhile to examine substituted quinolines of type **107** and **108** (Scheme 4.4), in an attempt to exploit this interaction.

Furthermore, catalytic asymmetric transfer hydrogenation is a vast and practically useful field, one which is untapped as of yet by our spiro-boroxinate B_3 Brønsted acid catalysts. The quinoline reduction study could serve as a proof of principle; efforts towards the asymmetric transfer hydrogenation of other

substrates, especially those not successfully realized yet, could be initiated. One such example is that of pyridines, pioneered by Rueping in 2007.[55a] The Rueping protocol is the first organocatalytic example, one though with definite limitations and considerable room for improvement. For leads into the literature for the asymmetric hydrogenation of aromatic/heteroaromatic compounds, a few references are provided.[55b-d]

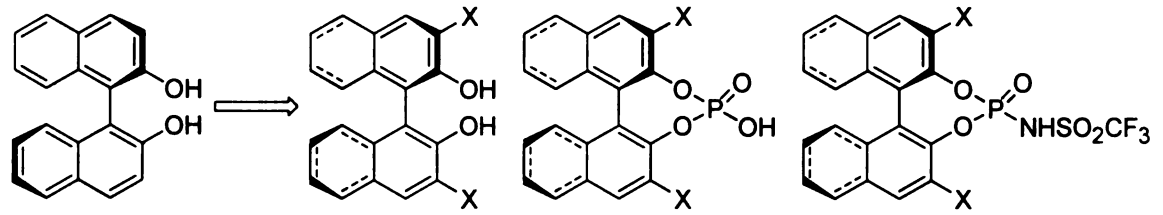
CHAPTER FIVE

NEW DERIVATIVES OF VAPOL AND VANOL: *STRUCTURALLY DISTINCT VAULTED CHIRAL LIGANDS AND BRØNSTED ACID CATALYSTS*

5.1 Introduction

The field of chiral Brønsted acid catalysis has witnessed an exponential growth in the last decade.[57] Countless efficient asymmetric reaction systems mediated by these organocatalysts have been developed by numerous research groups around the world, and this growth continues unabated till date. The BINOL ligand scaffold has been ubiquitous in the realm of organocatalysis, and is entitled to the label of a "privileged" ligand.[58]

Scheme 5.1 Chiral Brønsted acid catalysts from the BINOL scaffold



109 **110** **111**

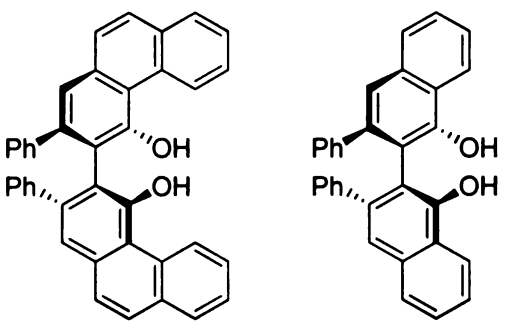
"privileged" BINOL scaffold

Chiral BINOL Brønsted acid catalysts

Shown in Scheme 5.1 are the three most extensively utilized groups of chiral Brønsted acids derived from the BINOL scaffold. As weakly acidic Brønsted acids, a variety of BINOL derivatives **109** have been developed and utilized in asymmetric organocatalysis.[59] In 2004, the research groups of Akiyama[60a] and Terada[60b] independently introduced the 3,3'-disubstituted BINOL phosphoric acids **110** for asymmetric Mannich-type reactions. These phosphoric acids have since then proven to be extremely versatile chiral Brønsted acid

catalysts, and a multitude of successful catalytic asymmetric systems have been developed under their aegis.[61] Chiral BINOL *N*-triflyl phosphoramide catalysts **111** were subsequently introduced by Yamamoto in 2006 for an asymmetric Diels-Alder reaction.[62] These are stronger Brønsted acids (pKa of -3 in water)[57c] as compared to the corresponding BINOL phosphoric acids (pKa of 1 in water)[57c]; these *N*-triflyl phosphoramides have also found considerable success in asymmetric organocatalysis in recent years.[63]

Scheme 5.2 Structurally distinct vaulted biaryl diol ligands



4 (*S*)-VAPOL **5** (*S*)-VANOL

The vaulted biaryl diol ligands VAPOL (**4**) and VANOL (**5**) were introduced by our group in 1993 (Scheme 5.2).[64,65] These ligands possess a unique vaulted structure, and are thus structurally distinct from the BINOL ligands. Since their discovery, VAPOL and VANOL have served as the basis for a number of successful catalytic asymmetric systems by several research groups. Catalysts prepared from VAPOL/VANOL and various boron compounds have been shown to mediate extremely efficient and general asymmetric aziridinations,[6-12] as well as asymmetric hetero-Diels-Alder cycloadditions.[66] VAPOL/VANOL catalysts containing aluminum or zirconium have successfully catalyzed asymmetric Diels-Alder reactions,[64,67] imino-aldol reactions,[68] and Baeyer-Villiger reactions[69].

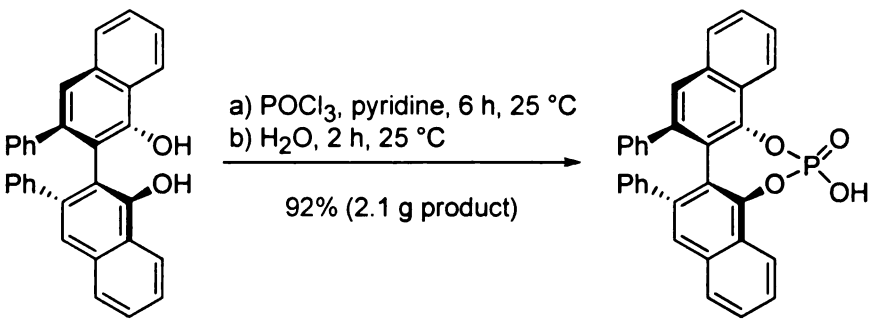
Phosphoramidite derivatives of VAPOL and VANOL have been shown to be effective ligands in rhodium catalyzed enantioselective intramolecular hydroarylation of alkenes.[70] VAPOL as a standalone species can mediate asymmetric Petasis reactions, affording chiral α-amino acid esters with high asymmetric inductions.[71] An increasing number of systems in recent years have showcased the use of the chiral phosphoric acid catalysts prepared from VAPOL and VANOL. Imine amidations,[72] imino ester reductions,[73] imine imidations,[74] as well as desymmetrization of *meso*-aziridines to afford vicinal diamines[75] and vicinal amidophenylthioethers[76] have been all shown to proceed with excellent levels of asymmetric inductions under their catalysis.

The utility of VAPOL and VANOL is poised to increase as both antipodes of these ligands are now commercially available.[42,65] Despite the significant use of catalysts derived from VAPOL and VANOL in asymmetric catalysis, a dearth of information exists in the literature for the preparation of derivatives of these ligands. In the present study, we thus wish to report efficient, reproducible and multi-gram scale syntheses of several new derivatives of VAPOL and VANOL. These are structurally novel chiral ligands and Brønsted acid catalysts; the asymmetric active sites created by these derivatives will be electronically and sterically very different from those created from the corresponding BINOL derivatives, thus resulting in a profile for reactivity and asymmetric inductions that could be quite singular. We believe that the uniqueness of their structure, and the subsequent promise of radically different reactivity profiles, warrants the inclusion of these derivatives in any screen comprised of chiral Brønsted acids.

5.2 New Brønsted acid derivatives of VANOL

VANOL phosphoric acid **93** was prepared at a multi-gram scale from VANOL **5**, in an excellent yield and under mild conditions (Scheme 5.3). Thus, VANOL was reacted with $POCl_3$ at room temperature, followed by the addition of water, which upon work-up and purification afforded pure VANOL phosphoric acid **93** in 92% isolated yield (2.1 g product). The stronger Brønsted acid, *N*-triflyl VANOL phosphoramide **94**, was prepared in 76% isolated yield (2.2 g product) in a one-pot two-step sequence[62] starting from VANOL **5** (Scheme 5.4).

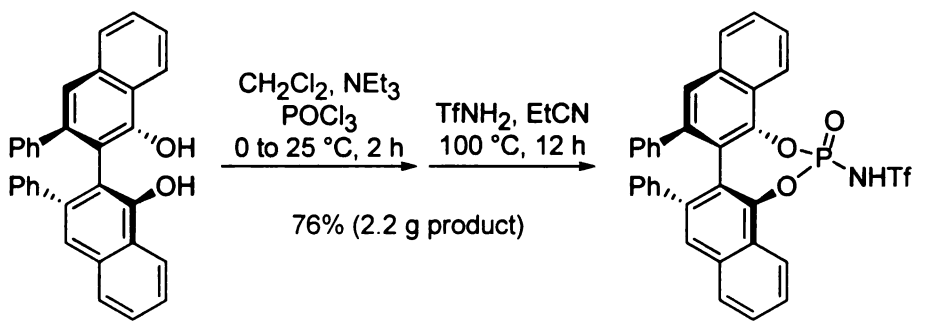
Scheme 5.3 Multi-gram scale synthesis of VANOL phosphoric acid **93**



5
(*S*)-VANOL

93
(*S*)-VANOL phosphoric acid

Scheme 5.4 Multi-gram scale synthesis of *N*-triflyl VANOL phosphoramide **94**



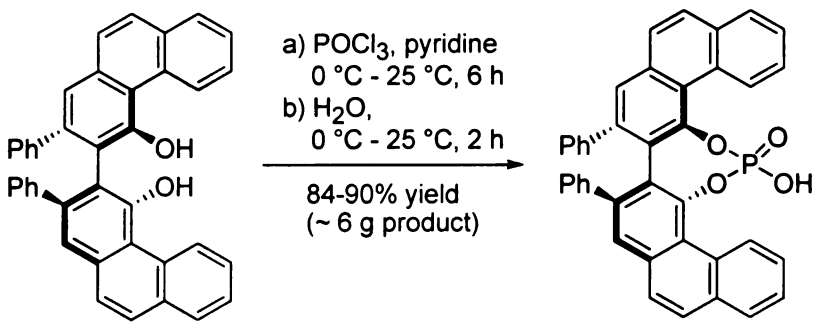
5
(*S*)-VANOL

94
(*S*)-*N*-triflyl VANOL phosphoramide

5.3 New Brønsted acid derivatives of VAPOL

As with VANOL, the phosphoric acid **91**[77] (Scheme 5.5) and the *N*-triflyl phosphoramide **92** (Scheme 5.6) Brønsted acid derivatives of VAPOL were also prepared at multi-gram scales, and with excellent yields.

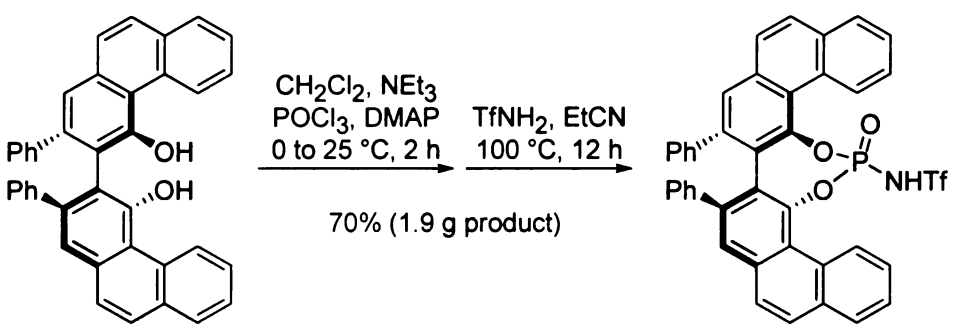
Scheme 5.5 Multi-gram scale synthesis of VAPOL phosphoric acid **91**



4
(*R*)-VAPOL

91
(*R*)-VAPOL phosphoric acid

Scheme 5.6 Multi-gram scale synthesis of *N*-triflyl VAPOL phosphoramide **92**



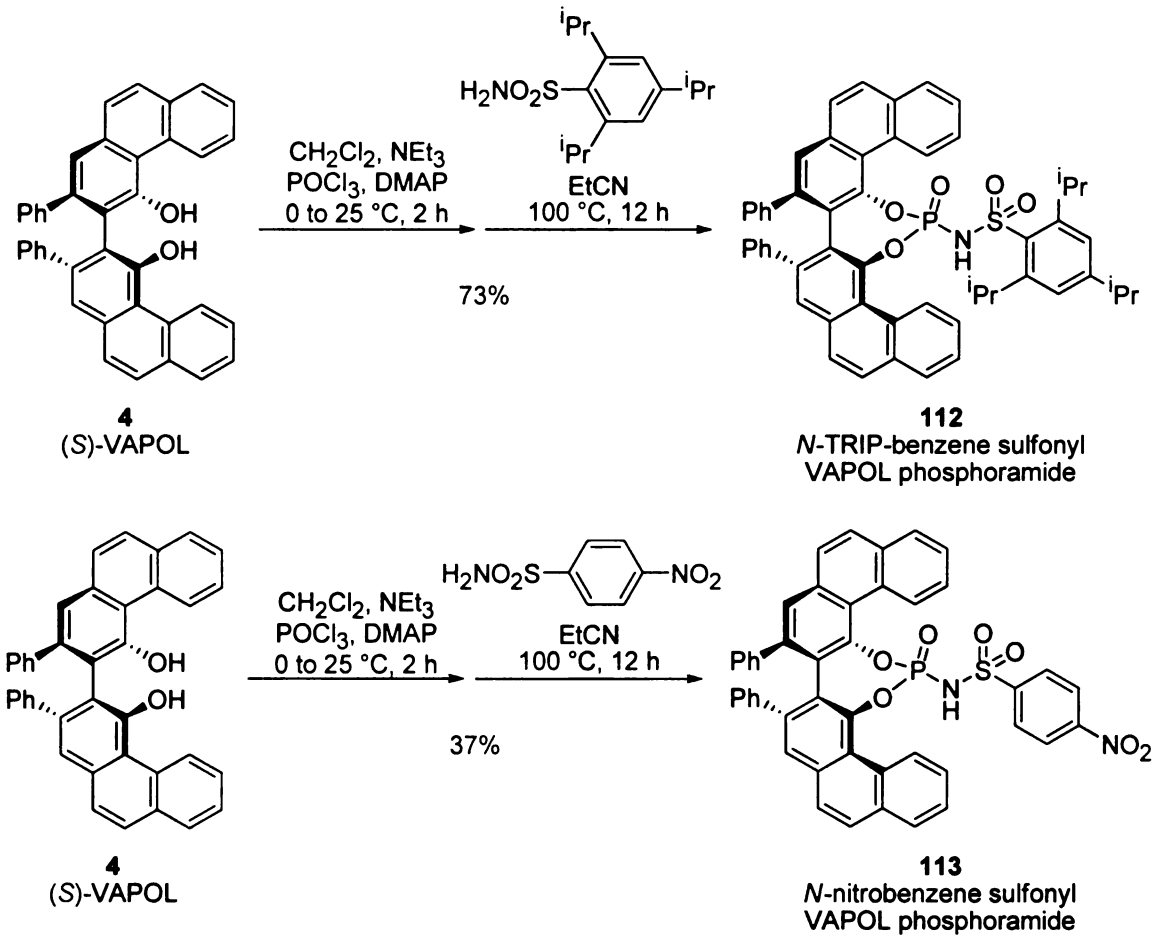
4
(*R*)-VAPOL

92
(*R*)-*N*-triflyl VAPOL phosphoramide

It was realized that the *N*-triflyl phosphoramide derivatives offered yet another handle with which to tune the asymmetric active sites of these catalysts – the triflate side chain. If the trifluoromethyl group in these derivatives was to be replaced with a bulky aromatic group, it would add yet another element of steric bulk into the system. Thus, the *N*-TRIP-benzene sulfonyl VAPOL phosphoramide **112** and the *N*-nitrobenzene sulfonyl VAPOL phosphoramide **113** Brønsted acids

were also prepared in an efficient manner using similar procedures (Scheme 5.7).

Scheme 5.7 *N*-benzene sulfonyl VAPOL phosphoramide Brønsted acid catalysts

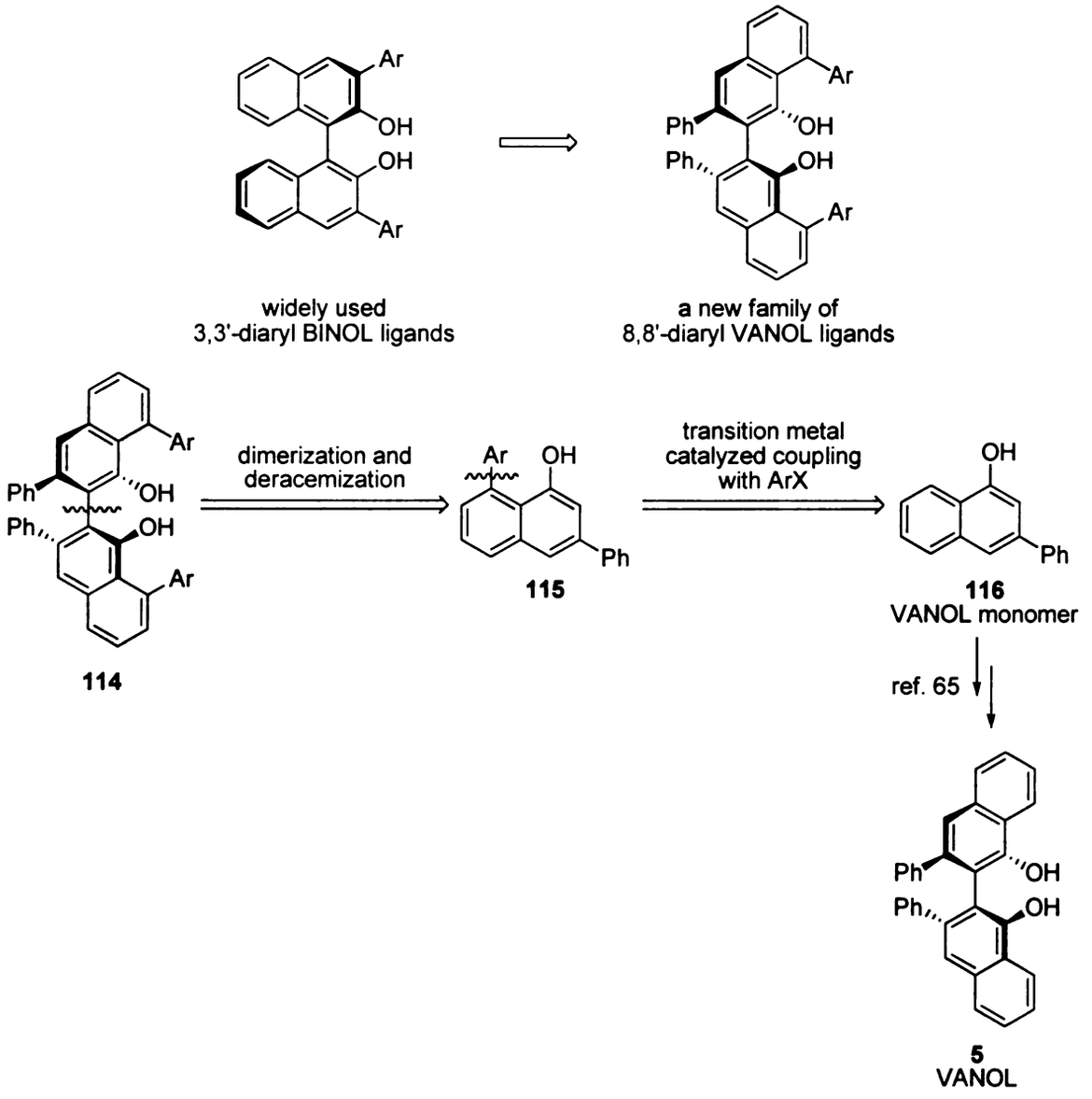


5.4 A new family of vaulted ligands – 8,8'-diaryl VANOL derivatives

Gaining inspiration from the enormous success of various 3,3'-diaryl BINOL derivatives in asymmetric catalysis, we were drawn towards the prospect of creating a new family of structurally distinct vaulted ligands, the 8,8'-diaryl VANOL derivatives (Scheme 5.8). These would be unique ligands, and could again be completely orthogonal in their reaction profiles as compared to the 3,3'-diaryl BINOL ligands. Not only would they be interesting chiral scaffolds for

standalone weak Brønsted acid catalysis, but their phosphoric acid and phosphoramide derivatives would be attractive in the realm of strong Brønsted acid catalysis too.

Scheme 5.8 A new family of structurally distinct vaulted ligands



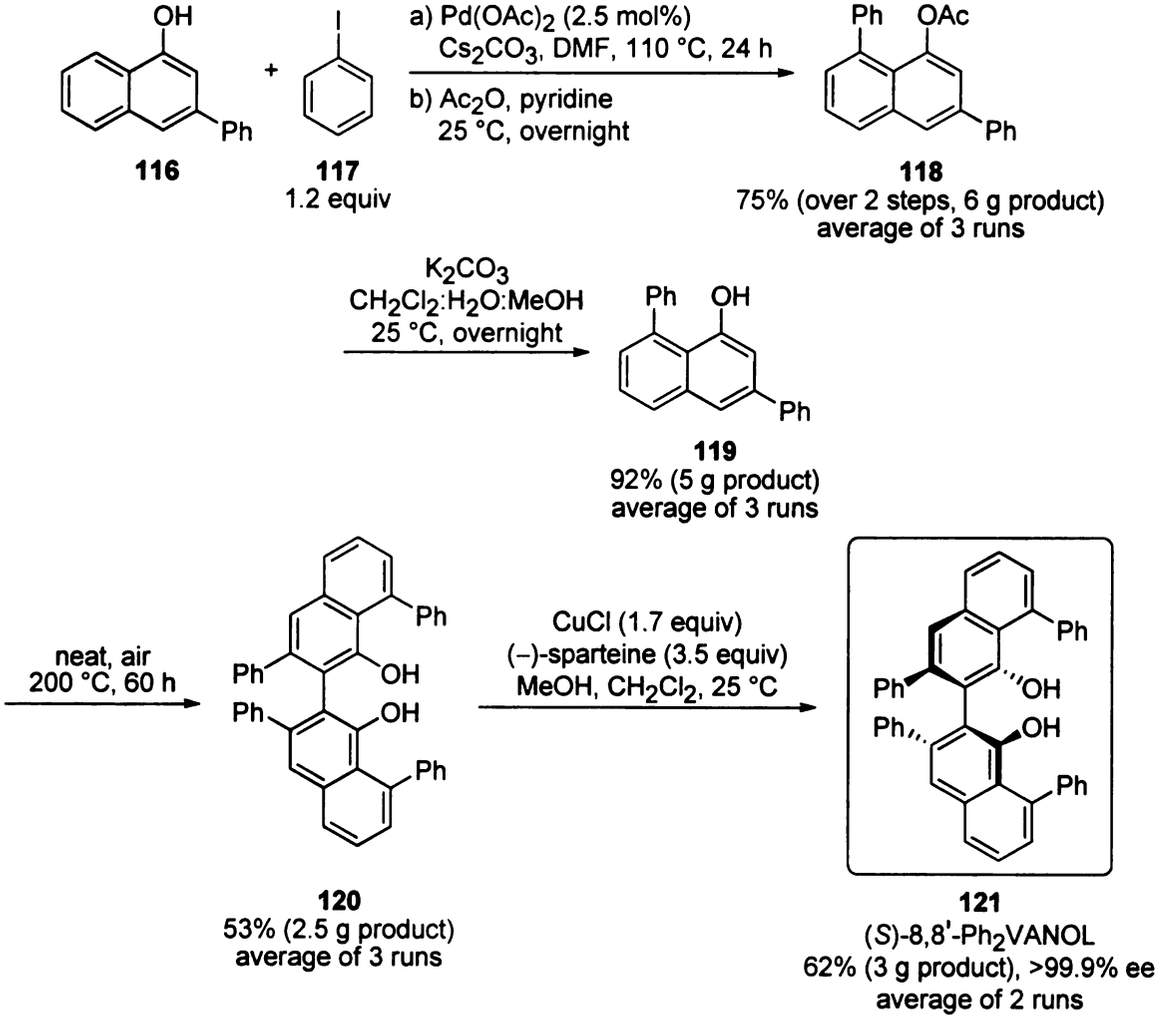
At the outset, it was desired to have a general route towards these new derivatives, which should make it possible to generate a large number of family members using similar reaction conditions. The ideal retrosynthetic analysis for

the preparation of a large family of these ligands is presented in Scheme 5.8. The syntheses would start from compound **116**, which is the monomer used for the synthesis of the VANOL ligand. We have already reported an efficient multi-gram scale synthesis for this compound,[65] and this was thus thought to be an attractive starting point for the present work. A transition metal catalyzed coupling reaction should then be able to install sterically and electronically different aromatic substituents on the 8-position of the VANOL monomer, thereby providing the requisite monomers **115** for the new ligands. Subsequent dimerization and deracemization, in a similar fashion as done during our previous syntheses of VAPOL and VANOL,[65] should then afford the new family of 8,8'-diaryl VANOL ligands **114**.

The expectations from this retrosynthetic analysis were borne out quite satisfyingly when the multi-gram synthesis of (*S*)-8,8'-Ph_2VANOL **121** was carried out as a proof of principle (Scheme 5.9). All reactions were optimized on a small scale first, and then demonstrated on larger scales for multiple times. The yields reported are the average of all runs on larger scales. The initial transition metal catalyzed coupling step was the key for the synthesis; it was our synthetic handle to be able to rapidly prepare the entire family of these new ligands. To our pleasure, a Pd-catalyzed α-arylation protocol developed by Miura and co-workers[78] worked smoothly from the VANOL monomer **116** to afford the corresponding new acetylated monomer **118**, in 75% isolated yield over 2 steps at a multi-gram scale. Attempts to purify the monomer after the initial Pd-coupling reaction by silica gel chromatography failed,[78] thus requiring the subsequent

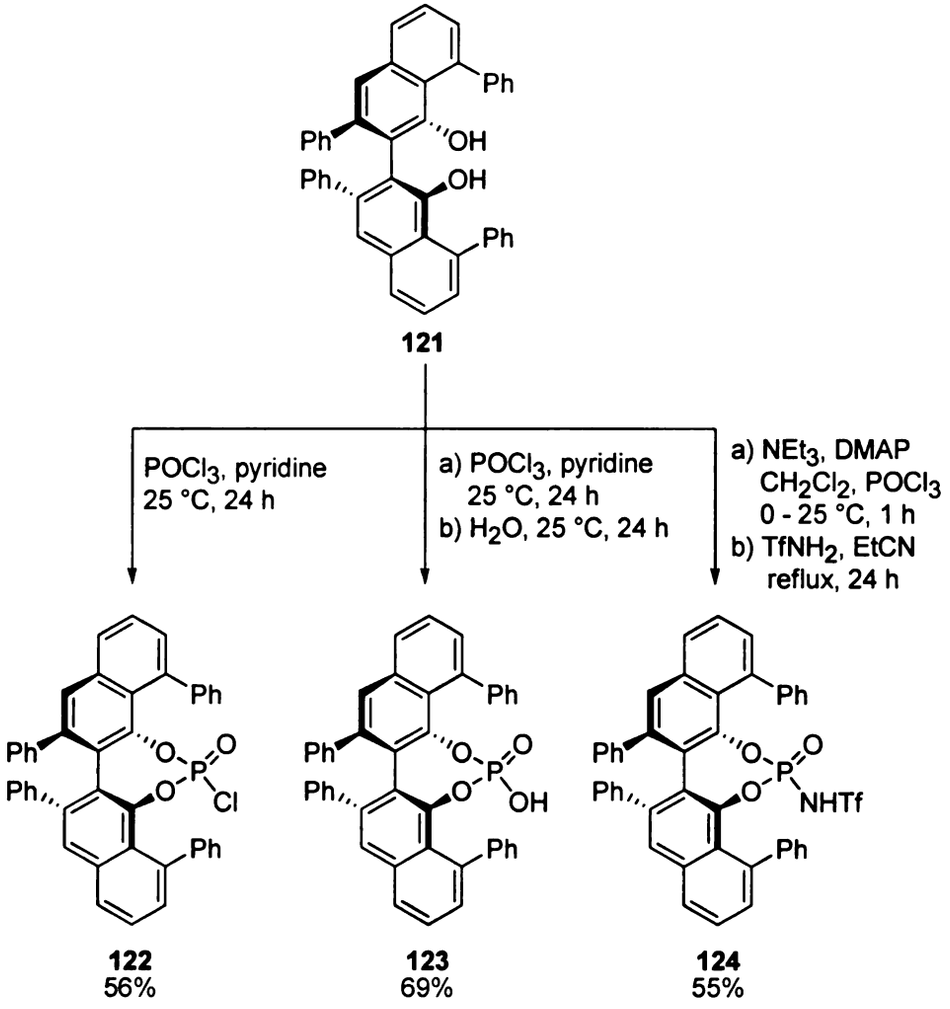
acetylation of the crude material to afford the acetylated monomer **118**. This could then be isolated as a pure compound after silica gel column chromatography, and a simple de-acetylation was then optimized to afford the pure new monomer **119** in excellent yield, again at a multi-gram scale. The monomer was dimerized in air with acceptable yields; the dimer was then subjected to a deracemization protocol with CuCl and (–)-sparteine to afford the optically pure (*S*)-8,8'-Ph_2VANOL ligand **121** in good yields in multi-gram quantities.

Scheme 5.9 Multi-gram scale synthesis of (*S*)-8,8'-Ph_2VANOL **121**



Thus, a lean, efficient and multi-gram scale synthesis of **121** could be devised, and a proof of principle demonstrated for the synthesis of a new family of biaryl diol ligands in the future; this should in principle be easily achieved by simply substituting iodobenzene in the initial Pd-coupling reaction in the above synthetic route with a variety of electronically and sterically distinct aryliodides, and the rest of the synthesis should be identical as for **121**.

Scheme 5.10 Preparation of Brønsted acid derivatives of 8,8'-Ph_2VANOL



We were subsequently interested in demonstrating the preparation of the phosphoric acid (**123**) and the *N*-triflyl phosphoramide (**124**) derivatives of the

new 8,8'-Ph_2VANOL ligand. This was done using our standard procedures in acceptable yields, and is presented in Scheme 5.10. An interesting outcome during the optimization of these syntheses was that the phosphorous chloride intermediate **122** could also be isolated by silica gel chromatography in good yields (Scheme 5.10). Displacement of chloride from this intermediate should be facile, to introduce other functionality such as urea/thiourea groups, thus paving the way towards other novel Brønsted acid catalysts or H-bonding ligands for use in asymmetric catalysis.

5.5 Conclusions

By the virtue of their unique vaulted structure, the biaryl diol ligands VAPOL and VANOL have carved a special niche for themselves in asymmetric catalysis. A multitude of different catalytic asymmetric reactions have been mediated by the catalysts prepared from these ligands, affording excellent selectivities, yields and asymmetric inductions.[6-12,64,66-76] The use of these ligands in the future will be further facilitated by that they are now commercially available.[42,65]

Anticipating an increased use of these ligands in asymmetric catalysis in the near future, we have initiated a program to prepare novel derivatives of these ligands. Herein, we have reported our preliminary results from this study; efficient, reproducible and multi-gram scale syntheses of several new chiral ligands and Brønsted acid catalysts based on the framework of VAPOL and VANOL have been presented. These are structurally distinct as compared to the traditional BINOL scaffolds, and should generate singular profiles for reactivity

and asymmetric inductions. We hope that this expectation gets borne out in our laboratories in the near future, and in those of others actively engaged in the science of asymmetric catalysis.

CHAPTER SIX

OTHER FORAYS IN CHIRAL CATALYSIS

During the first year of this dissertation, Professor Wulff had commented that nine out of ten projects that a synthetic organic chemist evaluates during a PhD will fail. Those words were certainly borne out during this dissertation; behind each working project mentioned in this dissertation, there were quite a few dead ends. Two of these projects will be detailed briefly in this chapter, and so will be another exciting project which was initiated towards the end of this dissertation.

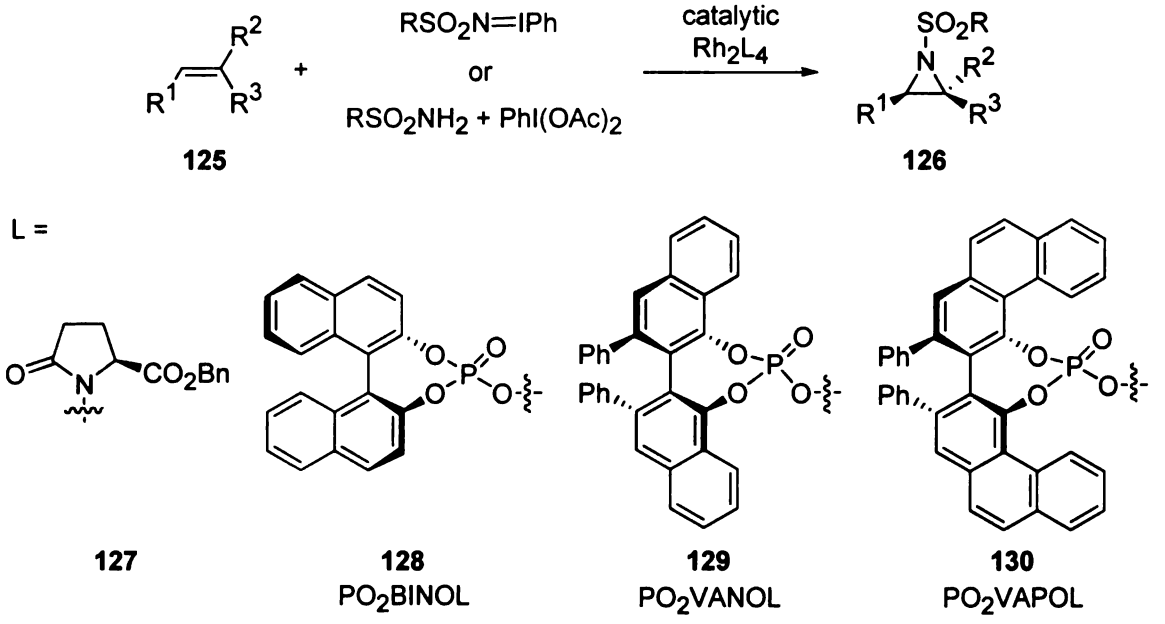
6.1 Asymmetric catalysis via chiral dirhodium catalysts

One of the most widely studied approaches towards catalytic asymmetric aziridination has been the one in which a chiral metal nitrene intermediate is utilized to transfer a nitrene to an olefin. The best system till date in this approach has been reported by Katsuki, who utilized a highly modified salen ligand to provide high chiral inductions with aryl olefins (85-99% ee).[79] Aliphatic substrates gave good inductions but low yields (20-30%).

Enormous success has been achieved in the development of chiral dirhodium catalysts for the asymmetric carbene transfer to olefins to give cyclopropanes.[80] In contrast, the only known example for the use of chiral dirhodium catalysts for the asymmetric nitrene transfer to olefins to give aziridines is by Muller.[81] The highest induction he reported involves a dirhodium catalyst Rh_2L_4 where L is the phosphoric acid ester **128** prepared from the BINOL

ligand (Scheme 6.1). The aziridination of *cis*-β-methylstyrene can be achieved with 2 mol% of this catalyst and nosyliminoiodinane (NsN=IPh) to give the corresponding aziridine in 73% ee. This is to be compared with his second best catalyst, which is derived from the pyrolidinone **127**, which gave an asymmetric induction of 35% ee for the same reaction. That the best chiral dirhodium catalyst developed so far involves a BINOL ligand thus gives encouragement for the evaluation of the corresponding dirhodium compounds derived from the VANOL and VAPOL phosphoric acid esters, **129** and **130** respectively (Scheme 6.1).

Scheme 6.1 Proposed asymmetric aziridination with chiral dirhodium catalysts



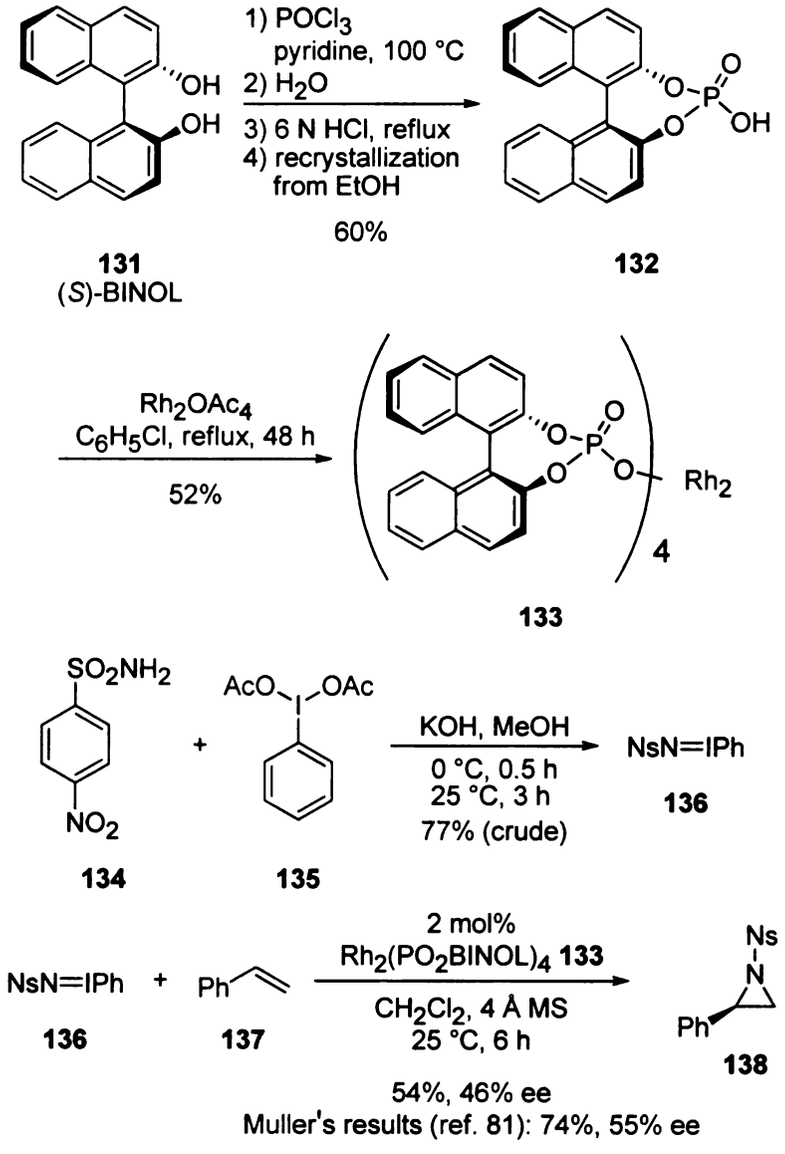
125 **126**

127 **128** PO_2BINOL **129** PO_2VANOL **130** PO_2VAPOL

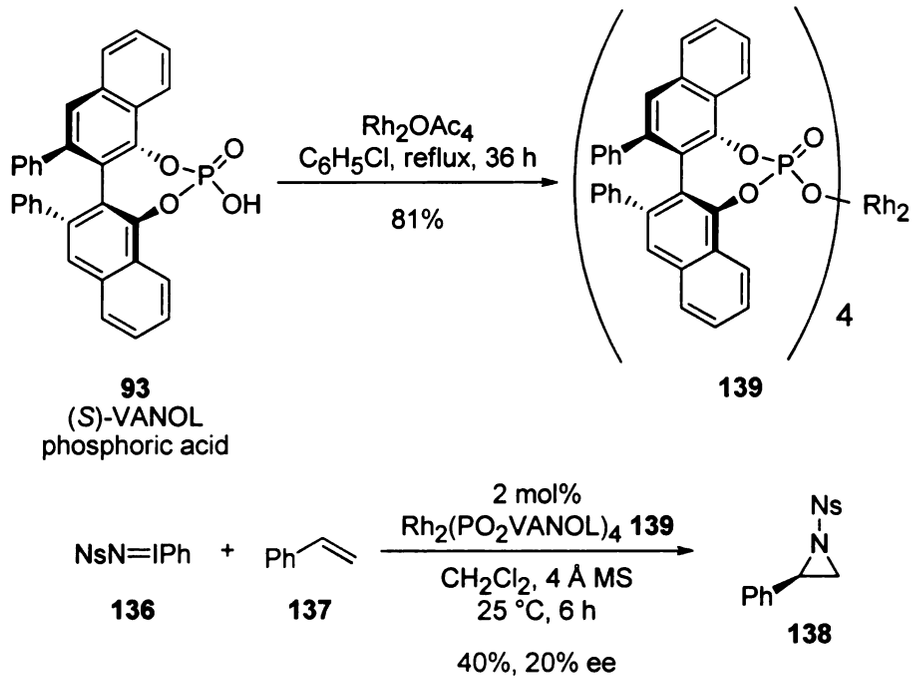
To initiate the investigation, it was desired to reproduce Muller's results[81] with the $Rh_2(PO_2BINOL)_4$ complex **133**. Thus, the requisite catalyst **133** and the starting materials were prepared as indicated in Scheme 6.2, and Muller's results could subsequently be reproduced up to a satisfying degree (Scheme 6.2). It was then desired to explore the corresponding dirhodium catalyst **139** prepared from the VANOL ligand. Disappointingly, the dirhodium VANOL catalyst **139**

performed inferior to the corresponding BINOL catalyst **133**, providing the aziridine **138** in only 20% ee (Scheme 6.3 vs. Scheme 6.2).

Scheme 6.2 Asymmetric aziridination with the $Rh_2(PO_2BINOL)_4$ complex **133**



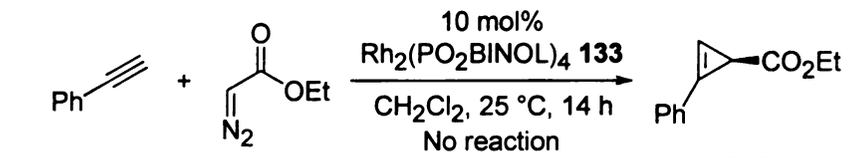
Scheme 6.3 Asymmetric aziridination with the $Rh_2(PO_2VANOL)_4$ complex **139**



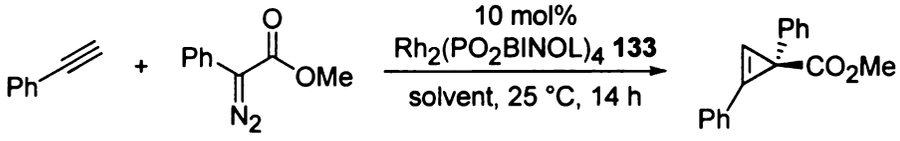
The next steps in this project could have been a temperature study with the dirhodium VANOL catalyst **139**, or trying a substrate other than styrene, such as *cis*-β-methylstyrene, which in fact performed better in Muller's system[81] than styrene. Alternately, the same asymmetric aziridination could have been attempted with the corresponding dirhodium catalyst prepared from the VAPOL ligand. Unfortunately at this stage in this dissertation, other projects were deemed to be of higher priority, and the asymmetric aziridination project mediated by chiral dirhodium catalysts was relegated to the back burner, where it has remained since then.

The $Rh_2(PO_2BINOL)_4$ complex **133** was also evaluated briefly for an asymmetric cyclopropenation reaction.[82] A few variations were attempted (Scheme 6.4), however no encouraging results were obtained.

Scheme 6.4 Asymmetric cyclopropenation with $Rh_2(PO_2BINOL)_4$ complex **133**



140 **2** **141**



140 **47** **142**

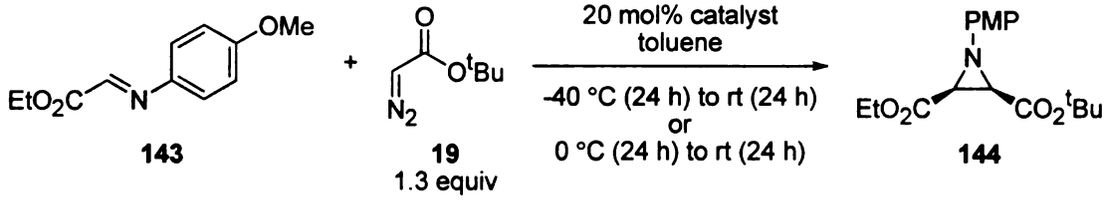
Entry	Solvent	Yield (%)	ee (%)
1	CH_2Cl_2	< 7	nd
2	hexanes	12	15

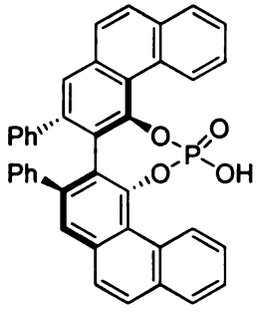
6.2 Organocatalytic asymmetric aziridination mediated by chiral Brønsted acid catalysts

The field of chiral phosphoric acid catalysis has grown exponentially since the pioneering reports by Akiyama[60a] and Terada[60b] in 2004. Chiral phosphoric acids[60,61] and their *N*-triflyl phosphoramide derivatives[62,63] have successfully catalyzed a plethora of nucleophilic additions to imines and carbonyl compounds. Surprisingly, at the stage of this dissertation when attention was focused towards this area, no report of an asymmetric aziridination protocol mediated by these versatile organocatalysts existed. Thus, a considerable amount of time during this dissertation was spent trying to develop an aziridination protocol catalyzed by the chiral phosphoric acid and phosphoramide derivatives of VAPOL and VANOL, the preparation of which has been discussed in Chapter 5. These efforts largely ended in vain, and subsequent to the end of work for this project during this dissertation, Akiyama and co-workers reported a successful asymmetric

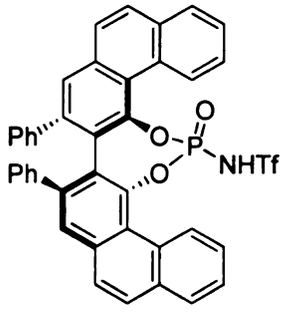
aziridination protocol mediated by a chiral phosphoric acid catalyst derived from a 3,3'-disubstituted BINOL ligand (Scheme 1.10, Chapter 1).[17]

Scheme 6.5 Asymmetric aziridination with VAPOL/VANOL chiral Brønsted acids

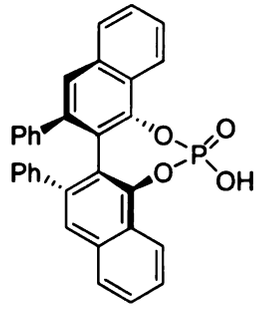




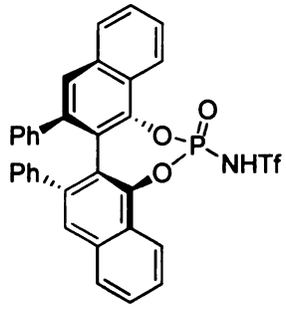
91
6:1 cis:trans, 48% yield
24% ee



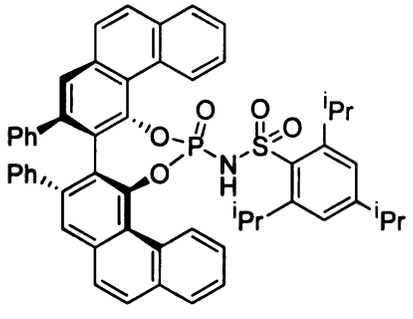
92
15:1 cis:trans, 65% yield
8% ee



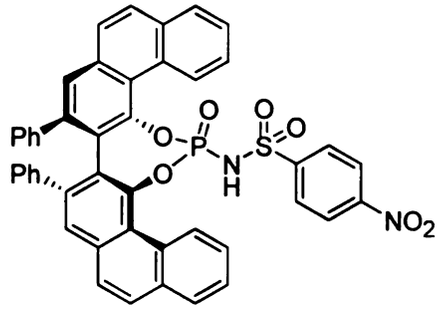
93
5:1 cis:trans, 36% yield
5% ee



94
11:1 cis:trans, 73% yield
<10% ee



112
4:1 cis:trans, 41% yield
5% ee



113
12:1 cis:trans, 60% yield
15% ee

During the initial part of this investigation, the VAPOL/VANOL derived chiral Brønsted acid catalysts **91-94** and **112-113** (Chapter 5) were evaluated for the aziridination reaction between various imines and ethyldiazoacetate. Imines derived from various benzaldehydes, and with numerous electron

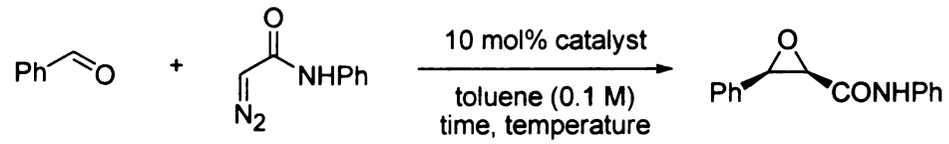
rich/neutral/deficient protecting groups were evaluated. However, all reactions resulted mostly in low conversion to the desired aziridine products.

It was only when we switched to activated imines that we started getting good reactivity in our system, and good conversions to the desired aziridine products were observed. The important results from this investigation are summarized in Scheme 6.5, and as can be seen, although excellent reactivity and diastereoselectivity was observed, the asymmetric induction for this project could never be increased beyond 24% ee.

6.3 Asymmetric catalytic Darzens reaction

Gong and co-workers have recently reported an efficient asymmetric catalytic Darzens reaction between aldehydes and *N*-phenyldiazoacetamide **14a**, mediated by Lewis acid catalysts prepared from BINOL ligands and either $Ti(O^iPr)_4$[41] or $Zr(O^nBu)_4$[83]. All successful systems till date for the asymmetric catalytic Darzens reaction are mediated by chiral Lewis acids involving metals.[41] There are no examples with a chiral Brønsted acid. After successfully utilizing *N*-phenyldiazoacetamide **14a** in our trans-selective aziridination protocol (Chapter 3), we became interested in evaluating the same for the Darzens reaction under catalysis of our VAPOL/VANOL-B_3 boroxinate catalysts. If successfully established, this would represent the first protocol for an asymmetric catalytic Darzens reaction mediated by a chiral Brønsted acid. It would also be exciting from that this would be the first time that our B_3 catalysts were successfully able to activate carbonyl compounds, which is an entire realm of chiral acid catalysis that has been untapped as of yet by our research group.

Table 6.1 Proof of principle for the asymmetric catalytic Darzens reaction[a]



145 1.2 equiv

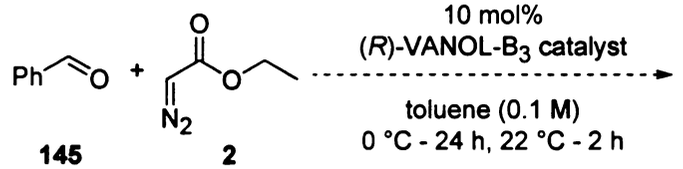
14a 0.2 mmol (1 equiv)

146

Entry	Ligand	Temperature (°C)	Time (h)	cis:trans[b]	Yield (%)[c]	ee (%)[d]
1	(*R*)-VAPOL-B_3[e]	0 22	18 1	17:1	44	4
2	(*S*)-VANOL-B_3[e]	0 22	19 2	20:1	60	-32
3	(*R*)-VANOL-B_3[e]	0 22	24 2	13:1	47	40
4	no catalyst	22	19		no reaction	
5	only VANOL	22	19		no reaction	
6	only $B(OPh)_3$	22	19		no reaction	

[a] Reaction with (*S*)-VANOL-B_3 catalyst gives *ent.* **146** shown. [b] Determined from ^{1}H NMR analysis of crude reaction mixture. [c] Isolated yield after column chromatography, of approximately 97% pure product. [d] Chiral HPLC. [e] Catalyst prepared by heating 1 equiv of ligand, 3 equiv BH_3•SMe_2, 2 equiv phenol and 3 equiv water at 100 °C in toluene for 1 h, following by removing all volatiles at 100 °C under high vacuum (0.1 mm Hg) for 0.5 h.

Scheme 6.6 Attempted Darzens reaction with ethyldiazoacetate **2**



No reaction (TLC & crude ^{1}H NMR)
Only an EDA decomposition product observed in the crude ^{1}H NMR - possibly the dimerization product.

145 1.2 equiv

2 0.2 mmol (1 equiv)

A proof of principle for the asymmetric catalytic Darzens reaction was established during this dissertation (Table 6.1), when the reaction of benzaldehyde **145** and *N*-phenyldiazoacetamide **14a** mediated by the VANOL-B_3

catalyst was shown to afford the corresponding cis-epoxide **146** with a cis:trans ratio of 17:1, 54% yield and 36% ee (average from Entries 2 and 3). The corresponding reaction mediated by the VAPOL-B_3 catalyst afforded the cis-epoxide **146** with only 4% ee (Entry 1). Interestingly, no reaction was observed when the same reaction was conducted with ethyldiazoacetate **2** instead of *N*-phenyldiazoacetamide **14a** (Scheme 6.6).

The reactions in Table 6.1 were the first few reactions conducted for the Darzens reaction project. Work was stopped due to a lack of time in this dissertation. This is an exciting project, the reasons for which have been mentioned above. There are quite a few parameters that could be easily tweaked in an attempt to convert this proof of principle into a successful system. A few suggestions that come to the mind instantly are as follows: (1) The results in Table 6.1 should be reproduced once, especially the reaction with the VAPOL-B_3 catalyst (Entry 1). (2) A systematic solvent screen should be conducted, particularly with halogenated hydrocarbons and ethereal solvents. (3) An entire family of *N*-substituted diazoacetamides has been prepared and screened for the trans-selective aziridination protocol (Chapter 3, Table 3.4), the procedures for which have also been detailed in this dissertation (experimental information for Chapter 3). These should be screened for the Darzens system; it is thought that especially the *N*-alkyl substituted diazoacetamides (**14f** and **14g**) should produce a marked difference in the Darzens reaction results. (4) Different phenols could be used to generate a varied family of the VANOL-B_3 boroxinate catalysts, which could be tested (see Section 4.4, Chapter 4). (5) Finally, the new derivatives of

VAPOL and VANOL being developed in our laboratory could be evaluated, especially since there is a distinct difference between the results obtained from the VAPOL and VANOL boroxinate catalysts (Table 6.1, Entry 1 vs. Entries 2 and 3).

Several research groups (Maruoka,[13] Zhong,[15] Gong[41]) are familiar with the chemistry of *N*-substituted diazoacetamides. All these groups also practice chiral Brønsted acid catalysis extensively. The asymmetric catalytic Darzens reaction is an attractive project since there is no example of a chiral Brønsted acid catalyzed system, yet.

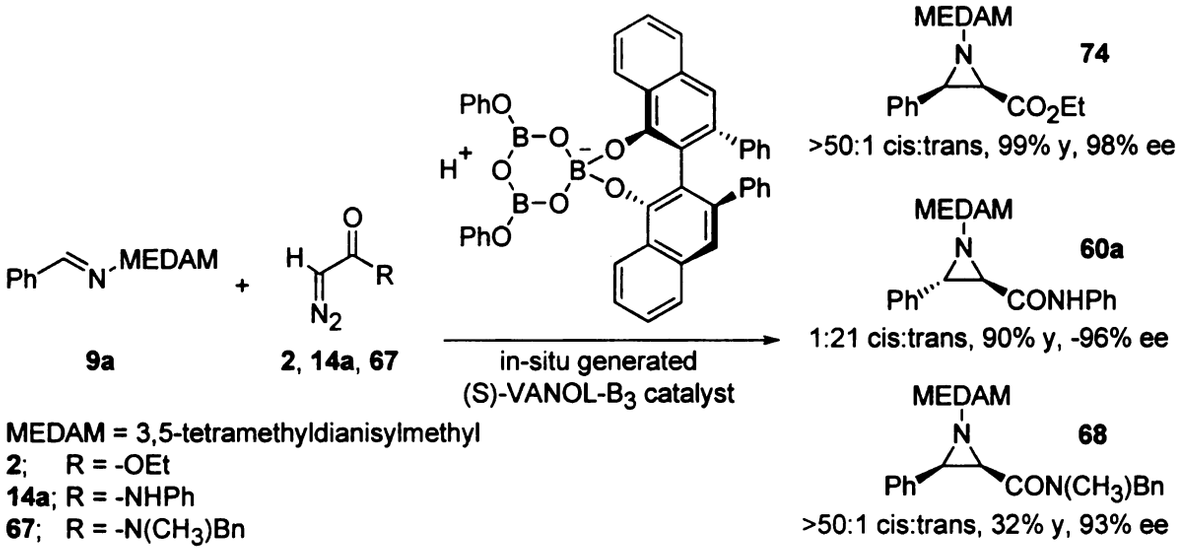
CHAPTER SEVEN

COMPUTATIONAL CHEMISTRY AND UNIVERSAL AZIRIDINATION

7.1 Background and significance

Chapter 3 describes the extension of our catalytic asymmetric cis-aziridination methodology[6-12] to now selectively form trans-aziridines. This reversal of diastereoselectivity, accomplished by a simple change in one of the substrates used, was accompanied by the observation of the opposite facial selectivity to the imine (Scheme 7.1). This chapter describes a combined experimental and computational study that examines the mode of catalysis of this unique catalyst and the origins of the enantio- and diastereo- selection in this unprecedented universal catalytic asymmetric aziridination methodology. This work was carried out in collaboration with Dr. Mathew Vetticatt.

Scheme 7.1 Universal catalytic asymmetric aziridination

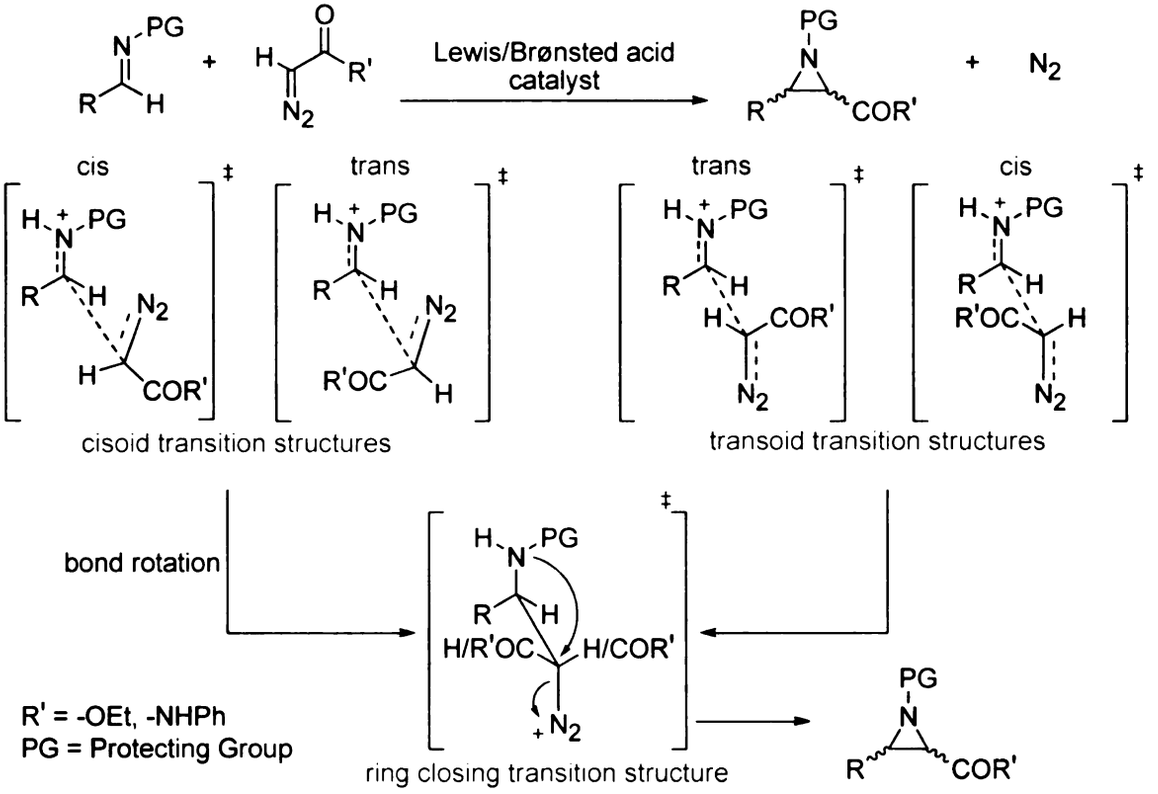


MEDAM = 3,5-tetramethyldianisylmethyl
2; R = -OEt
14a; R = -NHPh
67; R = -N(CH_3)Bn

The universal catalytic asymmetric aziridination is a computationally challenging system to explore. Each of the reactions studied computationally had

over 150 atoms. Exploring the conformational space and transition state geometries is a tedious task, if performed at a high level of theory. So we opted for the hybrid DFT:semi-emperical ONIOM method to obtain quality results in a reasonable time. Our primary goal was to gain a qualitative idea of the interactions between the catalyst and substrates at the transition states.

Scheme 7.2 General mechanism of aziridination reaction of imines and diazo nucleophiles catalyzed by Lewis/Brønsted acid



The mechanism of Lewis/Brønsted acid catalyzed aziridination reaction of imines and diazo compounds has received little experimental and no calculational scrutiny.[86] The widely accepted mechanism invokes initial nucleophilic attack of the diazo compound at the iminium carbon to form a diazonium intermediate. There are four limiting orientations for this attack – two

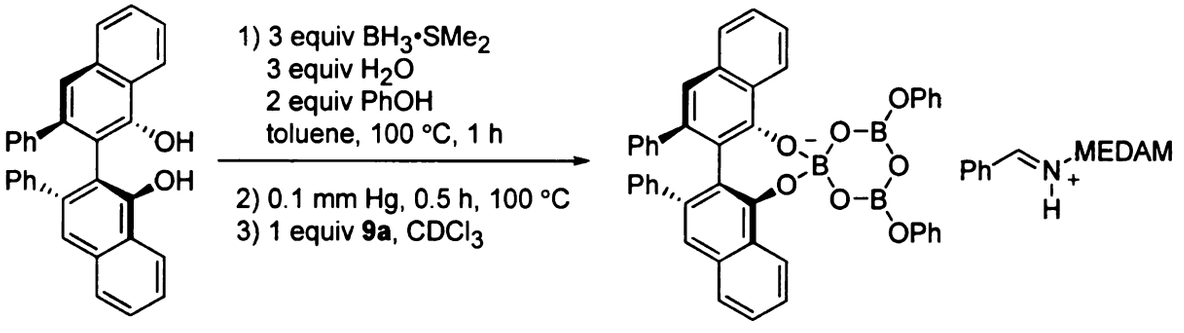
cisoid approaches (quasi 3+2) and two anti-periplanar transoid approaches as shown in Scheme 7.2. This carbon-carbon bond forming step is the enantioselectivity and diastereoselectivity determining step of the reaction.

Diastereoselection can be achieved if one of these approaches is preferred. This step is rendered enantioselective if the nucleophile can effectively discriminate between the *Si* and *Re* faces of the activated imine. Having formed the carbon-carbon bond, N_2 is eliminated in an S_N2 fashion from the diazonium intermediate (directly from the transoid intermediates and after bond rotation from the cisoid intermediates) to form the three-membered aziridine ring.

7.2 Spectral data in support of the VANOL-B_3 boroxinate complex

The VANOL-B_3 boroxinate complex was generated according to Scheme 7.3, and was analyzed by ^{11}B NMR and ^{1}H NMR.

Scheme 7.3 Generation of the VANOL-B_3 boroxinate complex



(*S*)-VANOL

(*S*)-VANOL-B_3 boroxinate
(catalyst-imine complex)

The ^{11}B NMR spectrum of the VANOL-B_3 boroxinate complex is quite distinctive (Figure 7.1). Three-coordinate borate esters typically have broad absorptions for the boron between 16-20 ppm in $CDCl_3$. Since ^{11}B is a quadrapole, the sharpness of the absorption is related to the spherical symmetry

around the boron, and this is reflected in the appearance of the ^{11}B NMR spectrum of the VANOL-B_3 boroxinate complex (Figure 7.1). The two three-coordinate borons in the complex appear as a very broad absorption at 16.16 ppm, and the four-coordinate boron as a very sharp peak at 6.10 ppm, with an integration of 2:1 respectively (not shown). This is in perfect accord with the ^{11}B NMR spectrums obtained previously for the VAPOL-B_3 boroxinate complexes.[11]

Figure 7.1 ^{11}B NMR spectrum of the VANOL-B_3 boroxinate complex ($CDCl_3$, 160 MHz) (top: complete spectrum, bottom: expanded view)

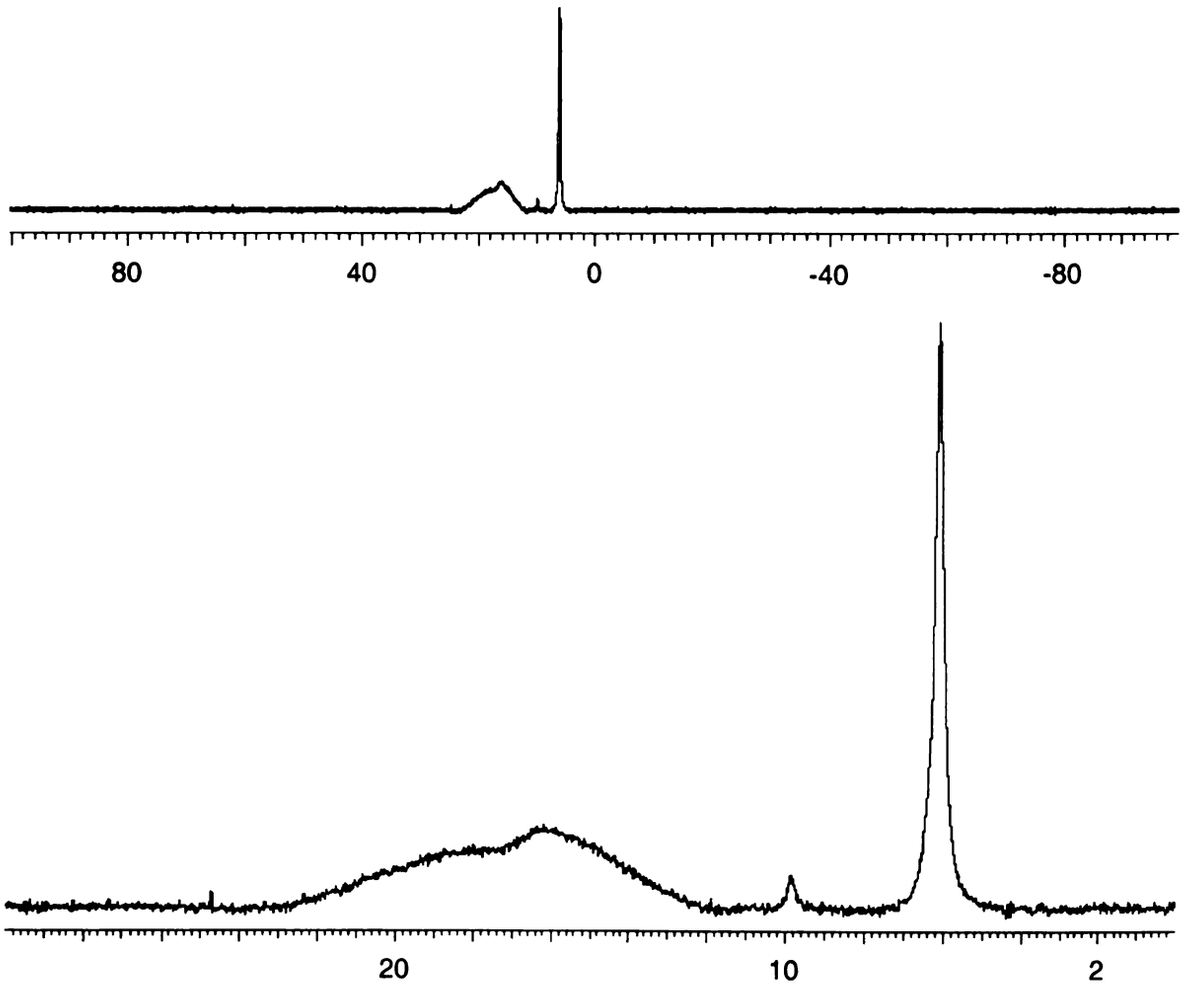
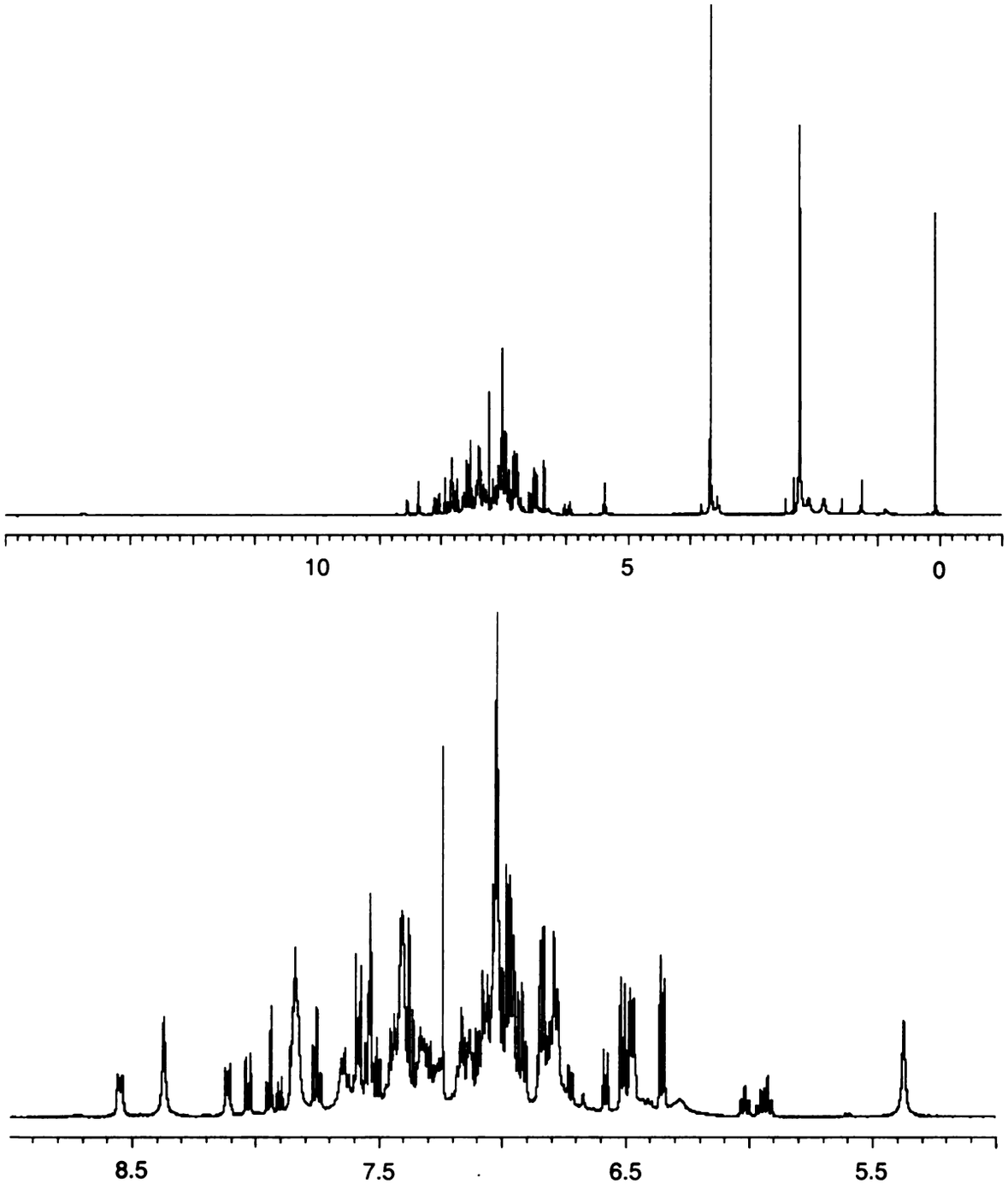


Figure 7.2 ^{1}H NMR spectrum of the VANOL-B_3 boroxinate complex ($CDCl_3$, 500 MHz) (top: complete spectrum, bottom: expanded view)



The ^{1}H NMR spectrum of the VANOL-B_3 boroxinate complex is presented in Figure 7.2. The ^{1}H NMR spectrum of the VANOL-B_3 boroxinate complex shows the absence of the signature doublet for VANOL at 8.34 ppm (J = 9.5 Hz),

and the presence of a new doublet at 8.55 ppm (J = 8.8 Hz). The singlet signals from the methines of the iminium were found at 5.38 and 8.37 ppm. The proton on the protonated iminium was located at 13.74 ppm. The complexity of the aromatic region suggests that the iminium is complexed to one face of the ligand and exchange with the other face is slow on the NMR time scale. While temperature studies were not performed to probe this, this was found to be the case for a related VAPOL complex at -40 °C.[11b]

7.3 Exploring the geometry of the catalyst-imine complex

The active catalyst in our universal aziridination protocol is a self assembled chiral polyborate Brønsted acid of unique structure.[11] The iminium ion can potentially be bound to one of the four oxygen atoms O1, O2, O3 or O4 of the chiral counterion. NBO (Natural Bond Order) analysis performed on the (*R*)-VANOL counterion (B3LYP/6-31G*//RHF/3-21G) revealed that electron densities on these oxygen atoms follow the order O2>O4>O1>O3 (Figure 7.3).

Figure 7.3 NBO analysis of the (*R*)-VANOL-counterion

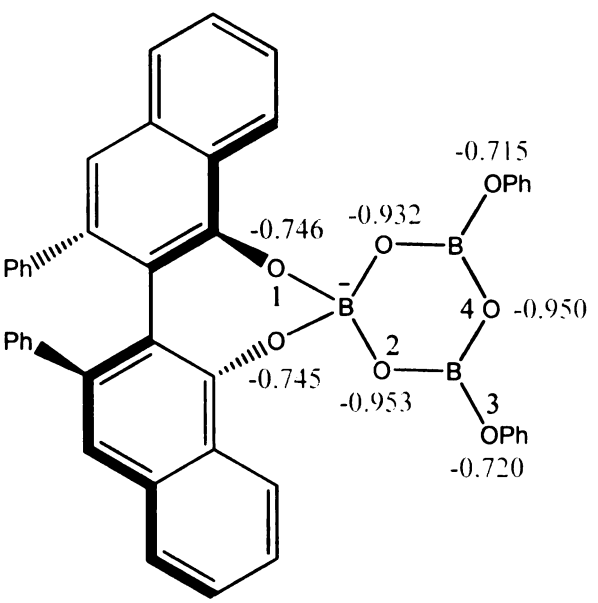
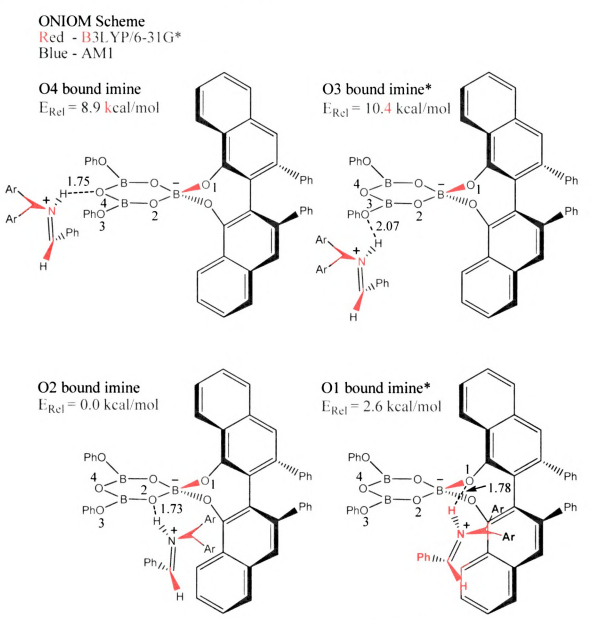


Figure 7.4 Division of ONIOM layers; Final geometries and relative energies of four possible catalyst-imine complexes



The starting geometry for the four possible points of coordination of the iminium ion and the boroxinate core of the (*S*)-VANOL-B_3 catalyst is shown in Figure 7.4. These geometries were minimized and the ONIOM extrapolated energies were compared in order to determine the lowest energy complex.

Interestingly, the optimizations initiated from the O1, O2 and O3 bound iminium ion converged to the same O2 bound minimized geometry. In order to obtain a geometry corresponding to the iminium ion bound to O3 and O1, two calculations were initiated with the iminium ion in proximity to O3 and O1 respectively, with the distance of the iminium proton to O2 fixed at 3 Å. This calculation gives us a crude idea of what the energy of these species would be, if indeed they could be located as local minima. Starting from the optimized geometries from these fixed distance calculations and releasing the iminium proton-O2 distance resulted in the O2 bound species. This preference for the O2 bound species probably results from a combination of the stronger H-bonding to the oxygen atom with the highest electron density and favorable interactions with the VANOL ligand. The O4 bound species lacked these catalyst interactions and was consequently found to be significantly higher in energy. The O1 bound species, though H-bonded to a less electron rich oxygen, probably benefits from intimate stabilizing interactions with the catalyst making it the second most preferred geometry of the catalyst imine complex. The relative energy of each of the four species either from complete minimization or fixed distance minimizations is also shown in Figure 7.4.

The biaryl system with the *S*-configuration appears to effectively shield the *Re* face of the iminium ion, keeping the *Si* face accessible for nucleophilic attack. This is consistent with the absolute configuration of the cis-aziridine **74** in reactions of **9a** and **2**. However one cannot rationalize, based on the O2 bound species in Figure 7.4, the *Re* facial attack that must occur in order to form the

observed enantiomer of the trans-aziridine **60a** in reactions of **9a** and **14a**. There clearly has to be some interaction between **14a** and the catalyst, that is absent in reactions of **2**, at the stereochemistry determining transition state, that reverses both the diastereoselectivity and the facial selectivity to the imine in this reaction.

7.4 Transition state models

Transition structures for the key carbon-carbon bond forming step of the reactions of **9a** and either **2**, **14a** or **67** catalyzed by the (*S*)-VANOL-B_3 catalyst were located using ONIOM(B3LYP/6-31G*:AM1) calculations.[87] The color scheme in Figure 7.4 illustrates the division of layers for the ONIOM calculations. In addition to the portions shown in red, the diazo nucleophile was also calculated using the DFT method. All distances are reported in angstroms. All reported energetics are single point energies of fully optimized geometries from the ONIOM calculations computed at the B3LYP/6-31+G* level of theory. This approach has been reasonably successful in qualitative predictions of stereoselectivity in similar reactions.[88]

The lowest energy transition structures leading to the observed enantiomer of the *cis*- (TS1) and *trans*- (TS2) aziridine in the reaction of **9a** and **2** are shown in Figure 7.5. The key observation in both these structures (and in all structures discussed below) is that, unlike in the catalyst-imine complex depicted in Figure 7.4 (O2-bound species), the iminium proton is no longer closest to O2. As a general trend, protonated **9a** is H-bonded to O1 in all *cis*-, and to O3 in all *trans*- transition structures. There also exists a stabilizing non-covalent interaction between the acidic α-CH of **2** and O2/O1 of the catalyst core in TS1

and TS2. The acidity of the α-CH of diazo compounds is well established (even a simple base such as DBU has been shown to cause deprotonation).[89] Numerous other transition structures similar to TS1 and TS2 were located that did not have this non-covalent interaction. While they reproduced the diastereoselectivity, they were on an average 2-4 kcal/mol higher in energy than either TS1 or TS2. In order to accommodate this interaction, attack of **2** occurs via a syn-clinical approach relative to the iminium double bond in TS1 and via a trans-antiperiplanar approach in TS2 (similar to the cisoid and transoid transition structures in Scheme 7.2). TS1 is 3.1 kcal/mol lower in energy than TS2 and this difference is qualitatively consistent with the experimentally observed >50:1 cis:trans ratio for this reaction at room temperature.

TS1 (*ent.*) in Figure 7.5 is the transition structure leading to the minor enantiomer of the *cis*-aziridine **74** and corresponds to a *Re*-facial attack of **2** with **9a** H-bonded to O3. This geometry is similar to TS2 with regard to the points of contact of the two key non-covalent interactions (**9a** bound to O3 and the α-CH of **2** bound to O1), the only difference being that the face of **2** is now switched with respect to TS2 to now give the cis-aziridine. The energy of this transition structure relative to TS1 is shown and it is in good agreement to the 98% ee observed experimentally.

Figure 7.5 Transition structures TS1, TS2 and TS1 (*ent.*) accounting for the diastereoselectivity and enantioselectivity in reactions of **9a** and **2**

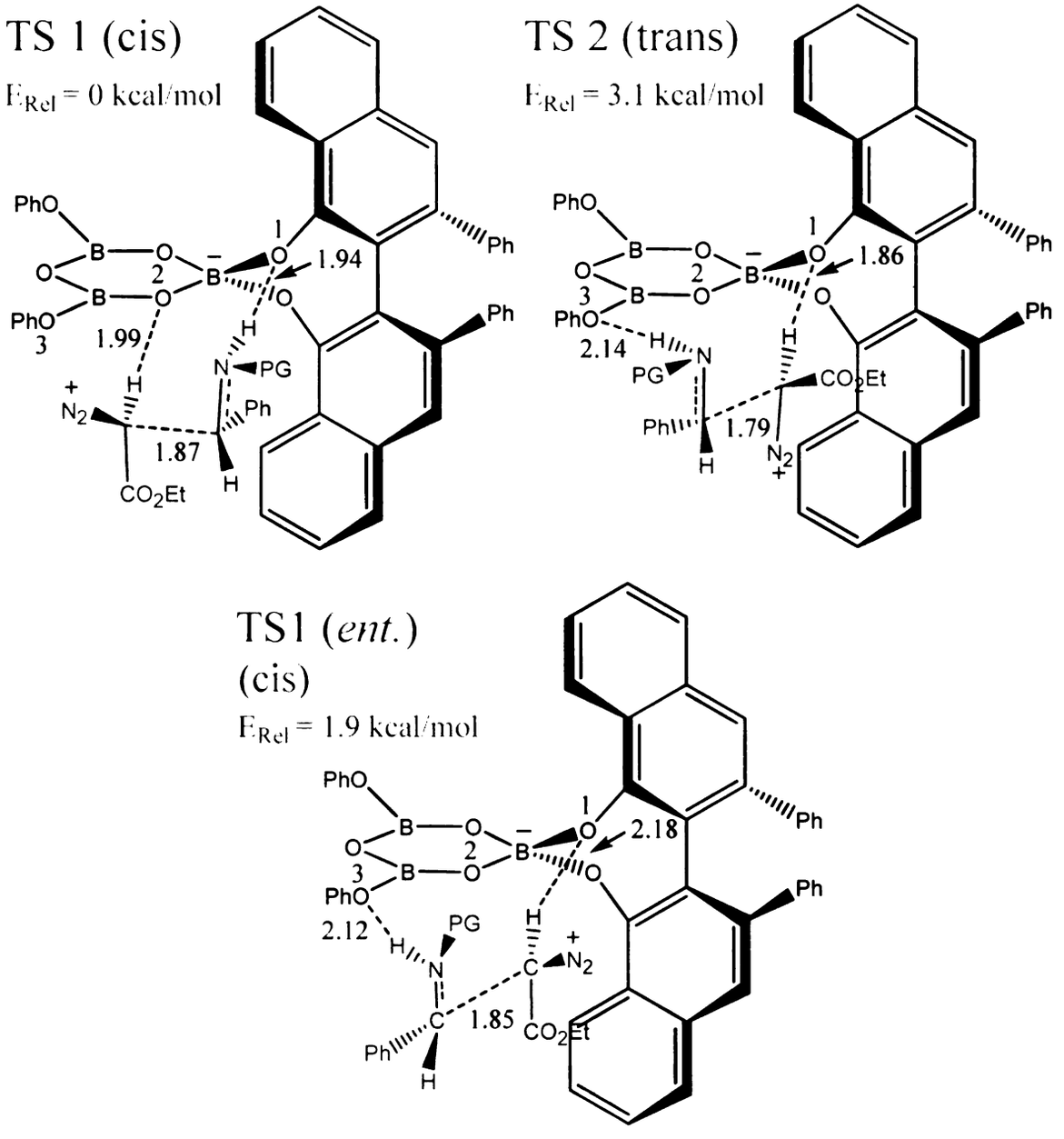
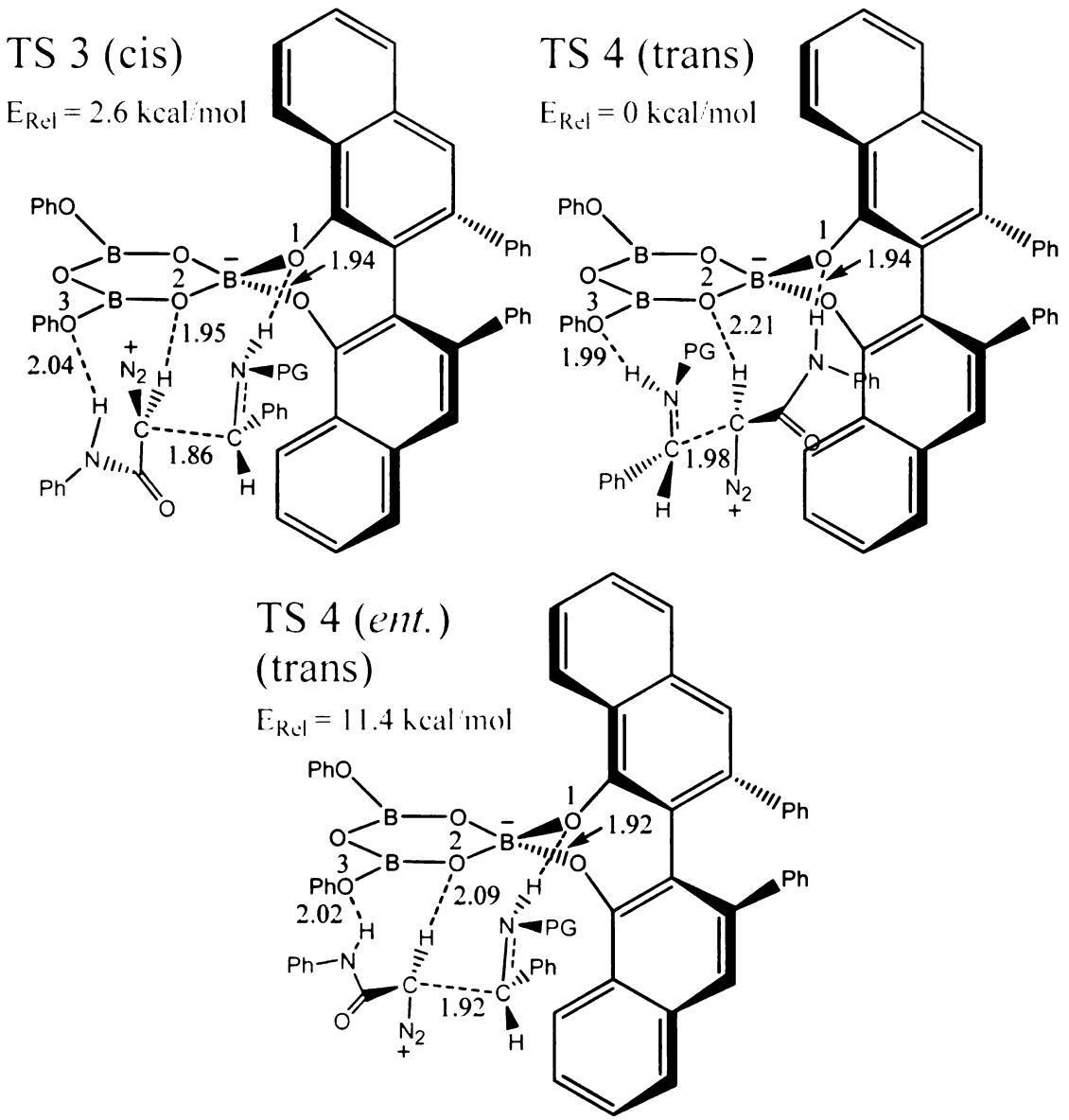


Figure 7.6 Transition structures TS3, TS4 and TS4 (*ent.*) accounting for the diastereoselectivity and enantioselectivity in reactions of **9a** and **14a**



Transition structures TS3 and TS4 were then located for the reaction of **9a** and **14a** (Figure 7.6). Both TS3 and TS4 are characterized by non-covalent H-bonding interactions between (a) the iminium proton and O1/O3, (b) the α-CH of **14a** and O2, and (c) the amidic hydrogen of **14a** and O3/O1. While H-bonding interactions (a) and (b) are also present in TS1 and TS2, (c) is exclusive to TS3

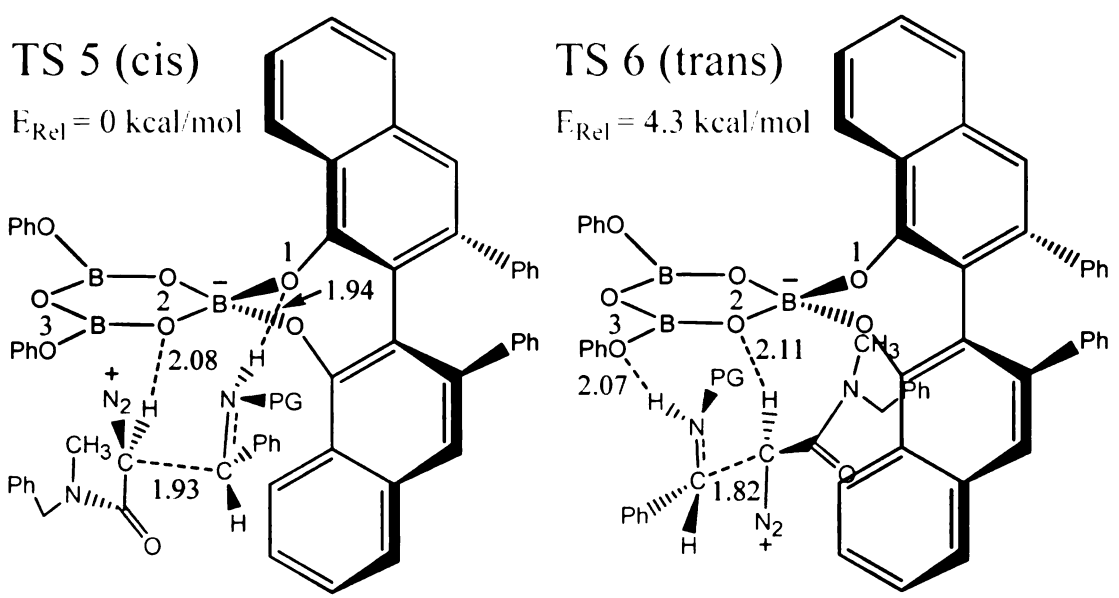
and TS4. Therefore, the reversal of diastereoselectivity must have its origins in the relative strength of the H-bonding interaction (c) in TS3 versus TS4. Hydrogen bond strengths are characterized both by the bond distances and the donor-H-acceptor angle – with short, linear hydrogen bonds being the strongest interactions.[90] The amide hydrogen-oxygen H-bond is shorter (1.94 Å versus 2.04 Å) and closer to linearity (176° versus 159°) in TS4 as compared to TS3. Consequently, TS4 is 2.6 kcal/mol lower in energy than TS3 and this is consistent with the experimental *trans*-selectivity. TS4 (*ent.*) is the transition structure leading to the minor enantiomer of the *trans*-aziridine **60a** and corresponds to a *Si*-facial attack of **14a** with **9a** H-bonded to O1. This geometry is similar in all respects to TS3 with the only difference being that the face of **14a** is now switched with respect to TS3. The energy of this transition structure relative to TS4 is shown. This difference is qualitatively consistent with the experimentally observed >95% ee.

7.5 Mechanistic probes for the proposed transition state models

As a mechanistic probe for the importance of this third H-bonding interaction in impacting diastereoselectivity, we decided to explore the aziridination reaction of **9a** and *N*-methyl-*N*-benzyldiazoacetamide **67** (Scheme 7.1). Being a 3° diazoamide, **67** lacks the key amide proton and we expected to see the reaction of **9a** and **67** to revert to a *cis*-selective reaction, analogous to the reaction of **9a** and **2**. Not surprisingly, this was indeed the case – the reaction carried out at room temperature gave almost exclusively the *cis*-aziridine (Scheme 7.1). Transition structures TS5 and TS6 were then located for the

reaction of **9a** and **67** (Figure 7.7). Comparing the pairs of transition structures TS3/TS5 and TS4/TS6, all key distances are almost identical and clearly the only difference of note is the absence of the H-bond between the amide hydrogen and O3/O1 in TS5 and TS6. Remarkably, TS5 is now favored over TS6 by 4.3 kcal/mol, once again in complete accord with the experimental (>50:1) cis:trans ratio.

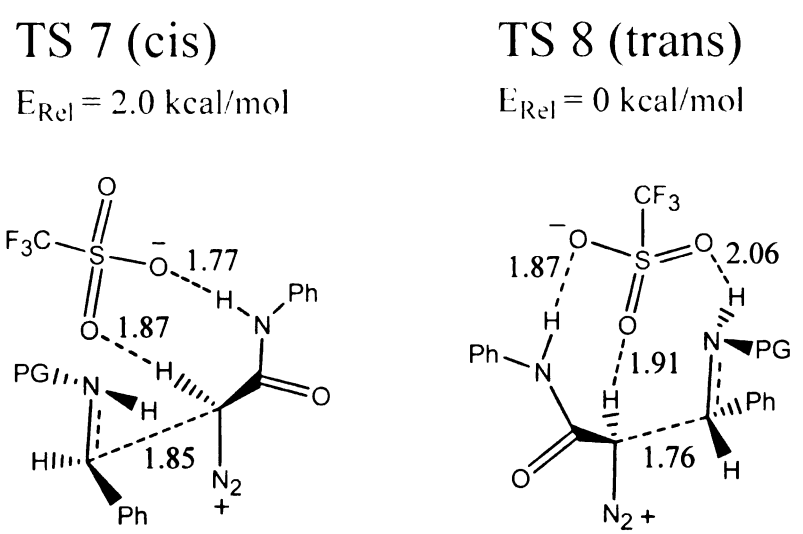
Figure 7.7 Transition structures TS5 and TS6 accounting for the diastereoselectivity in reaction of **9a** and **67**



Jacobsen and co-workers have recently illustrated the concept of 'cooperative catalysis' in Brønsted acid catalyzed reactions using chiral ureas/thioureas in a series of elegant publications.[91] Based on our understanding of the non-covalent interactions that stabilize the transition states in the aziridination reactions catalyzed by the B_3-catalyst, and the idea that triflic acid could function as a H-bonding counterion (as in the Jacobsen system),[91d] we decided to explore the aziridination reactions of **1b** and **2**,[86b] **14a** or **67** catalyzed

by triflic acid (Chapter 3, Section 3.4.9, Scheme 3.7). Our hypothesis was that in the event that the three oxygen atoms of the triflate anion could stabilize the aziridination transition state in a manner similar to our B_3-catalyst, we could have tunable diastereoselectivity even in this simple reaction, depending on the diazo nucleophile used. To our delight, identical to the trends observed in our system, we observed *trans*-selective aziridination in the reaction of **1b** and **14a** and *cis*-selective aziridination in reactions of **1b** and **2/67** (Chapter 3, Section 3.4.9, Scheme 3.7).

Figure 7.8 Transition structures TS7 and TS8 accounting for the diastereoselectivity in reaction of **1b** and **14a**



We then sought to reproduce this experimental observation based on the transition state model for the B_3-catalyzed reaction (Figure 7.8). The trans-antiperiplanar orientation of the double bonds of **1b** and **14a** in TS8 sets up the three strong H-bonding interactions with the triflate anion, virtually identical to TS4. The only transition structure located for the formation of the *cis*-aziridine in the reaction of **1b** and **14a** is TS7 and it lacks one of the three H-bonding

interactions present in TS8. Consequently it is 2.0 kcal/mol higher in energy than TS8. While this result reinforces the validity of our model, it also emphasizes the importance of considering multiple non-covalent interactions as a control element in the other Brønsted acid catalyzed aziridinations.[13,15,17]

7.6 Conclusions and future direction

Ours is a unique template in asymmetric catalysis. We have shown that the polyborate catalyst self-assembles *only* in the presence of the imine substrate.[11] During a catalytic cycle, the boroxinate core executes key functions that are quintessential for asymmetric catalysis. It activates the imine electrophile by protonation and imparts enantioselection in nucleophilic additions to the imine by serving as a chiral counterion. Diastereoselection is achieved when the polyborate core *directs* the orientation and approach of the diazo nucleophile to the 'active site'. It also lowers the energy of the transition state via multiple stabilizing H-bonding interactions with both substrates. Finally, it disassembles upon product formation and enters into another catalytic cycle by self-assembling with another molecule of the imine. This mode of catalysis is reminiscent of nature's strategy of lowering reaction barriers.

'Counterion catalysis' has emerged as a powerful strategy in asymmetric proton catalysis.[92] The mode of catalysis described in this chapter adds a new dimension to counterion catalysis by integrating into it some of the key features of H-bonding catalysis. This theoretical analysis of the catalyst-substrate interactions lays the groundwork for the rational development of newer reaction

types using our catalyst. Experimental characterization of the transition state geometry and the rate-limiting step in these reactions is detailed in Chapter 8.

CHAPTER EIGHT

KINETIC ISOTOPE EFFECTS AND MECHANISM OF THE AZIRIDINATION REACTION

The work described in this chapter was carried out in collaboration with Dr. Mathew Vetticatt (Albert Einstein College of Medicine, New York).

8.1 Transition state theory and kinetic isotope effects

Within the framework of conventional transition state theory (TST), selectivity observed in reactions is associated with relative energies of competing transition states, with the preferred product in a reaction arising from the lower energy transition state. Catalysis is explained in terms of lowering of the energy of the transition state relative to that of the uncatalyzed reaction. In short, TST has formed the basis of our understanding of how reactions work.

Kinetic isotope effect (KIE) measurements are powerful mechanistic probes. The origin of KIEs lies in how isotopic substitution affects the vibrational modes associated with the reaction coordinate. The magnitude of the change in the vibrational normal modes, caused by isotopic substitution, is different at the stage of reactants and at the transition state. It is this difference that results in an isotope effect. It follows therefore that KIEs can be used to experimentally probe the transition state geometry, i.e. the extent of bond formation/bond breaking occurring as the reaction goes over the transition state.

Each individual carbon and hydrogen atom in an organic molecule contains at natural abundance 1.109% of ^{13}C and 0.015% of ^{2}H. As a reaction

progresses, the starting materials are enriched in the slower reacting isotope and the products in the faster reacting ones. If this isotopic enrichment at every position in a molecule can be measured, KIEs can be determined without the use of explicitly labeled substrates. The Singleton method uses ^{13}C NMR at natural abundance in order to measure this isotopic change that determines the magnitude of the KIEs.[93] This method has been used for the elucidation of several important organic and organometallic reactions.[94]

There are mainly two approaches to measure KIEs by this method; these are described below.

(A) Intermolecular starting material KIEs: Reactions are taken to high conversion (typically ~80%) and the starting material of interest is recovered. The isotopic composition of this recovered material is determined by NMR methodology at natural abundance and compared to that of unreacted starting material (drawn from the bottle originally used for the reaction). The enrichment (depletion) thus measured can be used to determine the KIEs.

(B) Intermolecular product KIEs: Reactions are taken to low conversion (typically ~20%) and the product of interest is isolated. The isotopic composition of this isolated product is compared to that of a product isolated from a 100% conversion reaction (no isotopic fractionation), and the KIEs are thus determined.

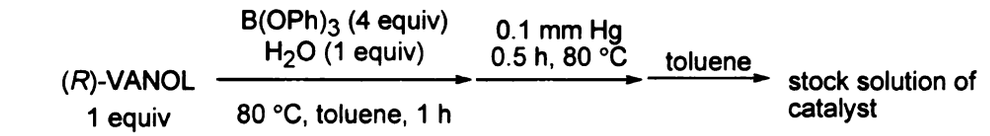
Having measured the experimental KIEs, the next step is to assume a mechanism, develop a theoretical model and make predictions for the isotope effects. These calculations will be used to predict KIEs for a variety of mechanistic possibilities. The match of experimental and theoretical KIEs gives

valuable insight to the reaction mechanism and provides an 'experimental' picture of the transition state geometry of the KIE determining step of the reaction. This step is either the first irreversible step or the rate-limiting step of the reaction.

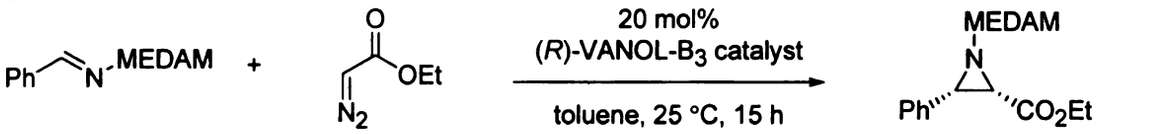
8.2 Design of experiment

The aziridination reaction of imine **9a** and ethyldiazoacetate **2** provides us with a robust reaction to measure ^{13}C KIEs. At room temperature, this reaction has been shown to give 97% yield of the *cis*-aziridine **74** with 99% ee, with a cis:trans ratio of >50:1.[10] The advantage of such high diastereoselection and asymmetric induction is that one needs to consider only one transition state for the theoretical interpretation of KIEs.

Scheme 8.1 Design of intermolecular product KIE measurement

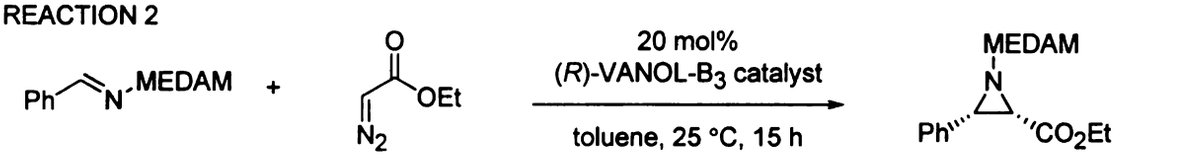


REACTION 1



9a 1.0 equiv (5.29 mmol) | **2** 0.2 equiv (1.06 mmol) | **74** (0.2 equiv) 1st run: 95% yield, 99% ee 2nd run: 93% yield, 99% ee

REACTION 2



9a 0.2 equiv (1.06 mmol) | **2** 1.0 equiv (5.29 mmol) | **74** (0.2 equiv) 1st run: 90% yield, 99% ee 2nd run: 94% yield, 99% ee

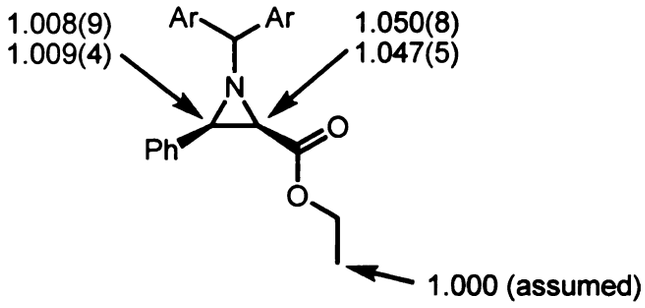
Isolation of **9a** or **2** from a reaction mixture is a tedious task and hence intermolecular starting material KIEs was excluded as a possible strategy. However **74** can be isolated relatively easily by column chromatography and hence we chose to perform intermolecular product KIE measurements to determine the isotope effects and thereby the mechanism of this reaction. Shown in Scheme 8.1 is the design of experiment for making this measurement. The first reaction shown in this scheme is run using **2** as the limiting reagent (0.2 equiv with respect to 1 equiv of **9a**). The sample of **74** isolated from this reaction will correspond to a 20% reaction of imine and 100% reaction of ethyldiazoacetate. In the second reaction the stoichiometry is reversed and we will now have a sample that corresponds to 20% reaction of ethyldiazoacetate and 100% reaction of imine. By comparing the ^{13}C composition of the carbon atoms that originally belonged to **9a**, in the sample of **74** isolated from reaction 1 versus reaction 2, one can determine the ^{13}C KIE for *all* the carbon atoms belonging to **9a**. From the same two NMR spectra by simply reversing the standard for comparison, one can also get the ^{13}C KIE for all the carbon atoms belonging to **2** (i.e. by comparing the ^{13}C composition of the carbon atoms that originally belonged to **2** in the sample of **74** isolated from reaction 2 versus reaction 1). One can thus calculate the experimental ^{13}C KIEs at every position (with separated ^{13}C NMR signal) of **74**, using the fractional conversion and the relative abundance of ^{13}C in sample versus standard NMR spectra. This measurement is made in duplicate (from two independent sets of samples). This novel process eliminates the need

for extra product isolation and analysis, and provides all of the ^{13}C KIEs for the reaction from the analysis of two product samples.

8.3 Experimental KIEs

The reactions of imine **9a** with ethyldiazoacetate **2** proceeded smoothly at room temperature and afforded the *cis*-aziridine **74** in near-quantitative yields and asymmetric inductions (Scheme 8.1). The ^{13}C KIEs for both components in this reaction were determined from NMR analysis of the products at natural abundance. Separate reactions were run to low conversion (~20%) in **9a** (using limiting **2**) and in **2** (using limiting **9a**). The KIEs were then determined by comparison of the ^{13}C composition of the product **74** to product samples derived from reactions in which the same starting material was taken to 100% conversion as described in the previous section.

Figure 8.1 Experimental ^{13}C KIEs (*k*12C/*k*13C, 25 °C) for the reactions of **9a** with **2**, with 95% confidence limits on the last digit shown in parentheses.



The ^{13}C KIEs based on two independent sets of reactions of **9a** and **2** as described in the previous section are shown in Figure 8.1. The methyl group on the ester moiety was used as the standard for the measurement under the assumption that there is no isotopic fractionation at this position at the transition state. For clarity, only the KIEs of the key bond forming centers are shown. The

results are remarkable and help to qualitatively eliminate two mechanistic possibilities. The near unity KIE on the carbon that originally belonged to the imine suggests that it is not involved in the rate limiting transition state. This would imply that the carbon-carbon bond forming event is not rate-limiting. It does not tell us anything about the stepwise or concerted nature of this first necessary event in the reaction. The KIE on the ethyldiazoacetate carbon is large and answers this question. A large KIE on one of the bond forming centers and a minimal KIE on the other is clear indication that a two-step process is operational. And by extension, a two-step process precludes a concerted mechanism. The qualitative interpretation of this set of KIEs is that carbon-carbon bond formation is *not* rate-limiting and that ring closure to form the aziridine ring is likely the rate-limiting step of the reaction. The large carbon KIE on the diazoacetate carbon onto which the imine nitrogen ring closes is consistent with this scenario. One can now predict the KIEs for these two events being rate-limiting and a match between experimental and theoretical KIEs will lend support to this qualitative analysis.

8.4 Predicted KIEs and interpretation

As a first step in the interpretation of the experimental KIEs, the reactions of **9a** with **2** were explored using ONIOM(B3LYP/6-31G*:AM1) calculations. Transition structures for the carbon-carbon bond forming step ($TS1_{C\text{-}C}$) and the ring-closing step ($TS1_{RC}$) are shown in Figure 8.2. KIEs were predicted assuming each of these TSs as rate-limiting.

Figure 8.2 Relevant transition structures for the theoretical interpretation of experimental KIEs

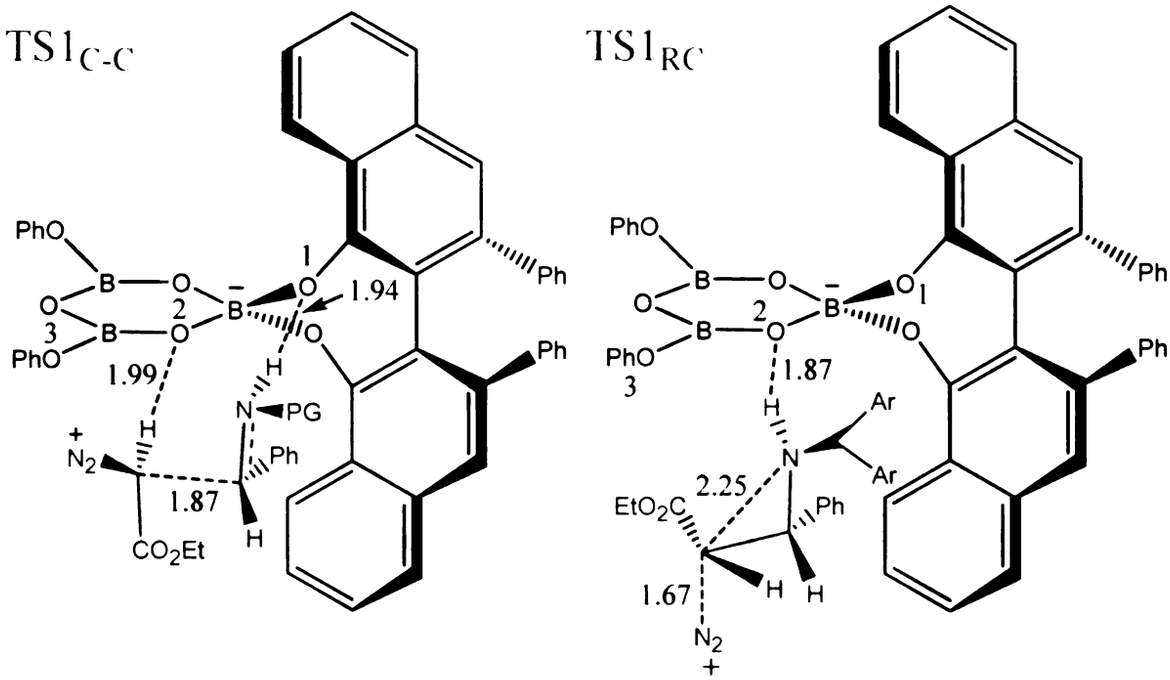
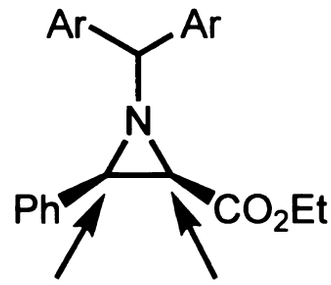


Figure 8.3 Comparison of experimental and predicted KIEs for the two key transition structures



Exp.	1.008(9) 1.009(4)	1.050(8) 1.047(5)
$TS1_{C-C}$	1.033	1.031
$TS1_{RC}$	1.006	1.050

Figure 8.3 shows the predicted KIEs for each of the transition structures shown in Figure 8.2. Consistent with our qualitative analysis of the KIEs, the predicted KIEs for $TS1_{C-C}$ are significantly different from our experimentally

determined values. The predicted KIE (1.033) for the bond-forming carbon of the imine **9a** in $TS1_{C\text{-}C}$ is significantly higher than experiment. The predicted KIE for the bond-forming carbon of the diazoacetate **2** in $TS1_{C\text{-}C}$ is 1.031, almost 2% lower than the observed KIE at this position. These results clearly lend no support to the carbon-carbon bond forming event being the rate-limiting step of the reaction.

Once the initial bond is formed, the carbon atom of the imine does not undergo rehybridization at the transition state for the ring closure to the aziridine. The bond-forming event in $TS1_{RC}$ is between the imine nitrogen and the carbon atom of the diazo nucleophile. There is also a slight loss of bond order between the same carbon and the N_2 leaving group. This concomitant bond-making and bond-breaking event at the diazo carbon should amplify the KIE at this position. The KIEs predicted for TS_{RC} are consistent with this analysis and are shown in Figure 8.3 in blue. These values are distinct from those for $TS1_{C\text{-}C}$ and are in remarkable agreement with our experimental KIEs at both positions. Thus our experimental KIEs are *qualitatively and quantitatively* consistent with the ring-closure step being rate limiting.

8.5 Discussion and future experiments

We have presented compelling evidence that the rate-limiting step in the Wulff aziridination is the second bond-forming event in the catalytic mechanism – the S_N2 type elimination of N_2 and ring closure to form the aziridine. In a multi-step reaction, one imagines the slow step to be the one with the largest entropic cost. Bringing together two molecules that are free in solution into a near-attack

conformation requires significant organization at the transition state. An intramolecular step in a catalytic mechanism, like the ring-closing step, is expected to be much faster and is rarely thought of as the rate-limiting event. We believe that the answer to this puzzle lies in the unique structure and mode of catalysis of the self-assembled B_3 catalyst. From the theoretical analysis of the key interactions occurring at the transition state for the initial carbon-carbon bond formation (Chapter 7), we know that in forming the *cis*-aziridine **74**, the diazo nucleophile approaches the catalyst-imine complex in a *syn*-clinical geometry. The anionic oxygen atoms of the boroxinate core form key H-bonding interactions with both **9a** and **2** and significantly lower the barrier of this transition state. Now, having formed the bond, the α-diazonium β-amino ester intermediate also enjoys the same interactions with the catalyst, leading to a stabilized intermediate. In order to eliminate N_2 and ring-close to form the aziridine, this intermediate needs to rotate and orient the leaving group N_2 in a trans-antiperiplanar orientation to the carbon-nitrogen bond of the original imine. There are two factors that make this bond rotation unfavorable: (1) The α-CH to O interaction that stabilizes TS1 and the intermediate has to be compromised as the bond-rotation occurs and (2) in the anti-periplanar orientation, the ester group might have steric interactions with the boroxinate core. The combined effect of stabilizing the carbon-carbon bond forming transition state (and the resulting intermediate) by non-covalent interactions with the catalyst and the energetic penalty of bond rotation and completion of the ring closure likely makes the second step rate-limiting.

One final question needs to be addressed here and will be the subject of future mechanistic work of this reaction. If the ring-closing step is slow because of the energetic penalty of bond rotation, then what about the *trans*-selective aziridinations where bond rotation is not required since the initial attack itself is in the trans-antiperiplanar orientation? Is there a possibility that the rate-limiting step for the formation of the *trans*-aziridine is *different* from the *cis*-selective reactions? This is an intriguing question and can quite easily be addressed by performing the same experiments described in this chapter, but using *N*-phenyl diazoacetamide instead of ethyldiazoacetate and analyzing the *trans*-aziridine product. A change in the rate-limiting step for two similar reactions mediated by the same catalyst is rare in solution chemistry but is often the hallmark of enzymatic catalysis.

CHAPTER NINE

RAMBLING FANTASIES OF AN ASYMMETRIC CATALYSIS AFICIONADO

A doctoral degree is a long drawn process which usually involves the following steps: proposal of an idea, the design of experiments, subsequent execution of these experiments, analysis of data, and validation of the initial proposal. This process more often than not breaks down along the chain, and the student has to start from the first step all over again, which is the proposal of a new idea. Having gone through this process several times, quite a few ideas were generated during the course of the present dissertation, many straight out absurd, some with slim chances of success. A few ideas belonging to the latter class, which have not been evaluated in this dissertation, will be briefly summarized here. There have been several sections in this dissertation where potential future work has been suggested, these will be mentioned first.

(1) Ways to further improve the asymmetric inductions in the 2,3-dicarbonyl cis-aziridination project have been suggested (Chapter 2, Section 2.4, Scheme 2.5). An interesting idea would be to combine this with the study of the aziridination of the same imines with diazoacetamides, where surprisingly the cis-aziridine was observed as the major diastereomer (Chapter 3, Section 3.4.6, Scheme 3.5). An entire project could be constructed by combining these two experimental studies with a mechanistic understanding of the origins of the strange cis-selectivity with the diazoacetamides, with the aid of computational chemistry in collaboration with Dr. Mathew Vetticatt.

(2) An unprecedented catalytic asymmetric synthesis of tri-substituted aziridines has been proposed (Chapter 2, Section 2.6). Evaluating this should be straightforward, once the requisite diazo compound is prepared.

(3) An aziridination protocol with a different "carbene" source has been proposed, mediated by the VAPOL/VANOL-B_3 catalysts (Chapter 3, Section 3.2, Scheme 3.1).

(4) Previously our laboratory has studied the reactions of alkynyl imines with diazoacetates to afford cis-aziridines.[31,40] Surprisingly again, the reaction of an alkynyl imine and a diazoacetamide, with the same B_3 catalyst, also afforded the corresponding cis-aziridine as the major diastereomer (Chapter 3, Section 3.4.6, Scheme 3.5). These reactions were especially clean. If pursued satisfactorily, this could make a nice addition to the experimental alkynyl imine aziridination study. Again with this project, a theoretical investigation could be initiated in collaboration with Dr. Mathew Vetticatt, to understand this strange switch in diastereoselectivity to favor the cis-aziridine in the reaction of diazoacetamides.

(5) More efficient deprotection of the trans-aziridines, than what has been obtained during this dissertation (Chapter 3, Section 3.4.11), should be developed.

(6) A few suggestions for further optimization and development of asymmetric transfer hydrogenation mediated by the VAPOL/VANOL-B_3 catalysts have been made (Chapter 4, Section 4.7).

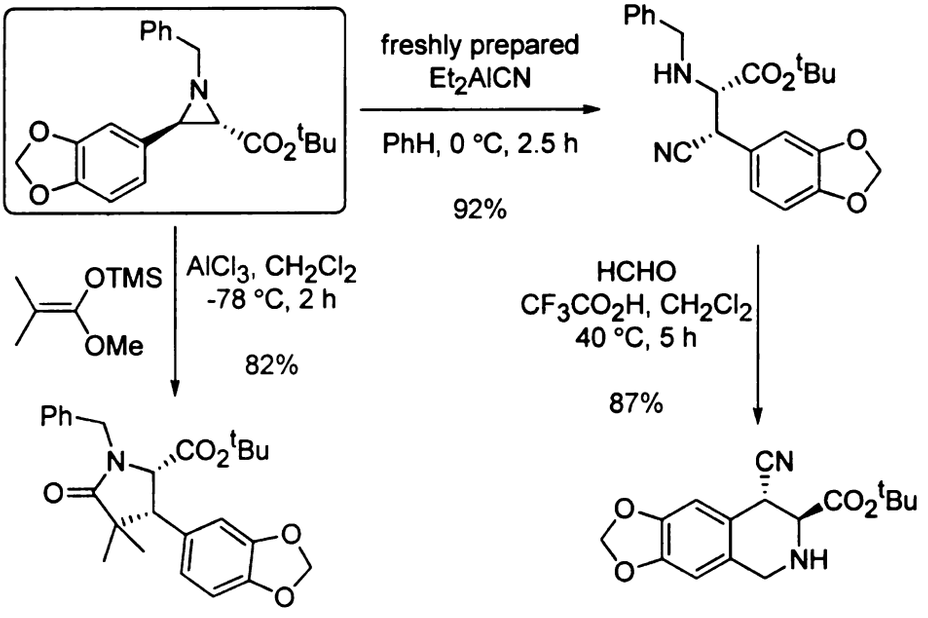
(7) Multi-gram quantities of the new chiral ligands and Brønsted acid catalysts based on the framework of VAPOL and VANOL have been made (Chapter 5). These will be available in the research group. Detailed procedures have been described. These are structurally distinct ligands and catalysts, and should give singular profiles for reactivity and asymmetric inductions as compared to the traditionally used BINOL derivatives. It would be interesting to screen them for different reactions.

(8) Ways to further improve the catalytic asymmetric Darzens reaction have been suggested (Chapter 6, Section 6.3).

There have been several ideas that have been generated from general literature reading through these years, which are related to the kind of asymmetric catalysis being pursued in our group. Some of these ideas will be summarized herein.

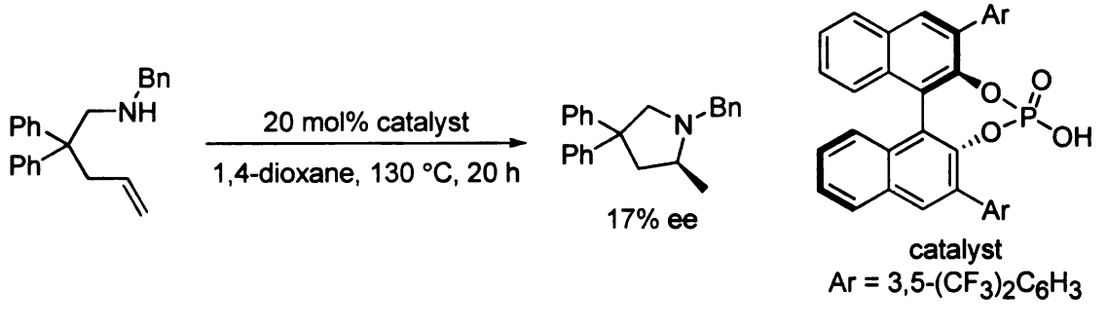
(1) Ishikawa and co-workers have recently reported interesting applications of non-activated trans-ester aziridines of the type shown in Scheme 9.1.[95] Their starting aziridines are very similar to the aziridines of the type **73** prepared in Chapter 3 (Section 3.4.8, Scheme 3.6); thus these would make for worthwhile applications of our trans-selective aziridination protocol.

Scheme 9.1 Ishikawa's applications of non-activated trans-ester aziridines



(2) Ackermann in 2008 reported an intramolecular (racemic) hydroamination protocol for non-activated alkenes, catalyzed by racemic chiral phosphoric acid catalysts prepared from 3,3'-disubstituted BINOL ligands.[96] They had one enantioselective example, providing the product in only 17% ee (Scheme 9.2).

Scheme 9.2 Ackermann's proof of principle for intramolecular hydroamination

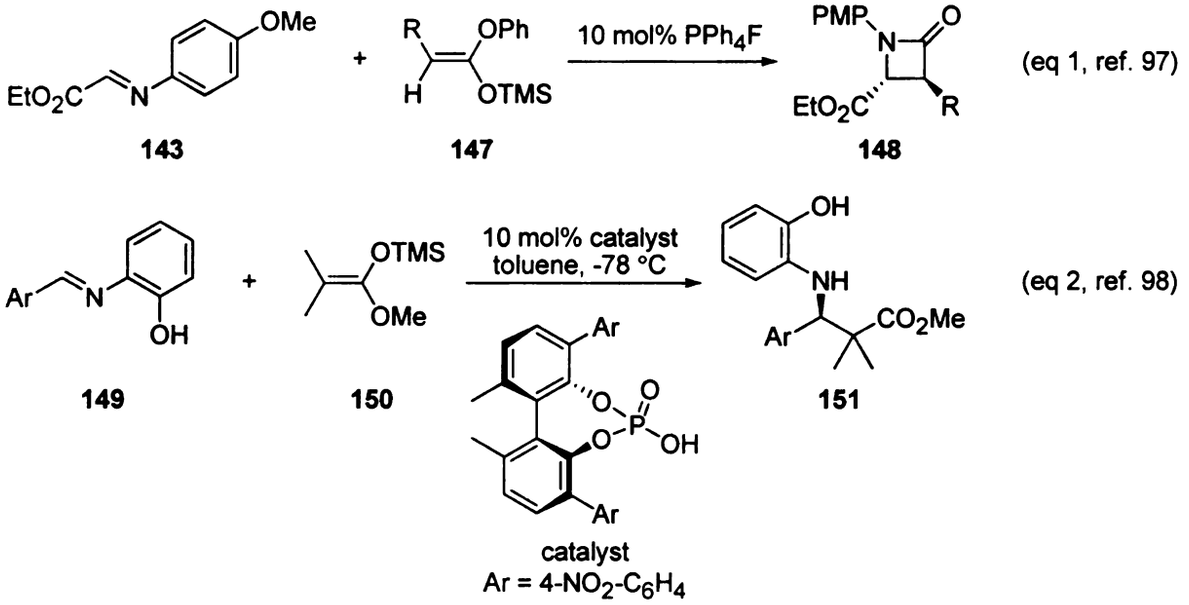


There is *no* example of a metal-free catalytic asymmetric hydroamination of non-activated alkenes in the literature. Thus, Ackermann's study is a proof of principle for this field. With the appropriate *N*-substitution (benzyl, benzhydryl,

MEDAM or even no substitution), it would definitely be worthwhile to attempt to catalyze the above reaction with our VAPOL/VANOL-B_3 catalysts. Alternately, the phosphoric acid and *N*-triflyl phosphoramide derivatives of VAPOL/VANOL prepared in Chapter 5 would be interesting to evaluate under the same reaction conditions.

(3) Lectka and co-workers in 2009 reported an interesting synthesis of *trans*-β-lactams catalyzed by fluoride salts (Scheme 9.3, eq 1).[97] In the proposed mechanism, the fluoride from the catalyst cleaves the trimethylsilyl ketene acetal **147** generating the enol *in-situ* which attacks the imine **143**, leading to an intermediate which subsequently cyclizes on what was originally the trimethylsilyl ketene acetal carbon eliminating phenoxide, and leading to the formation of the β-lactam **148**. To the best of our knowledge, an enantioselective variant of this reaction would be unprecedented in the field of β-lactam synthesis.

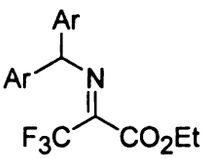
Scheme 9.3 Lectka's β-lactam and Akiyama's Mannich-type systems



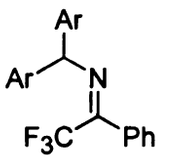
In a separate report for a Mannich-type reaction (Scheme 9.3, eq 2), Akiyama and co-workers have shown that chiral Brønsted acids can cleave trimethylsilyl ketene acetals and also activate imines at the same time.[98] A rather intriguing idea emerges when one combines the above two systems. Using our VAPOL/VANOL-B_3 chiral Brønsted acid catalysts (or the new chiral Brønsted acids prepared in Chapter 5), would it then be possible to create a catalytic asymmetric variant of the reaction between **143** and **147** to afford the corresponding β-lactams **148**?

(4) Finally, the failure in the attempts to directly access tri-substituted aziridines (Chapter 2, Section 2.6) could be attributed to the unreactive nature and the steric bulk of the disubstituted imines evaluated.

Scheme 9.4 Potential substrates for tri-substituted aziridination



152



153

It might be possible to overcome both these disadvantages by screening trifluoromethyl imines of type **152** or **153** (Scheme 9.4). Similar imines have been reported previously in the literature.[99]

APPENDICES

EXPERIMENTAL INFORMATION

Appendix A

General Information

All experiments were performed under an Argon atmosphere. Flasks were flame dried and cooled under argon before use. All solvents used were dried appropriately. Both VAPOL and VANOL ligands are commercially available from Aldrich as well as Strem Chemicals, Inc. If desired, they could be purified using column chromatography on regular silica gel using an eluent mixture of 2:1 dichloromethane:hexanes. Phenol was sublimed and stored under Argon in a dry desiccator; each batch was used for a maximum of 20 days. Solid aldehydes were used as purchased from Aldrich. Liquid aldehydes and benzhydryl amine were either used as purchased from Aldrich or distilled before use. The tetramethyldianisylmethyl (MEDAM) amine and the tetra-*tert*-butyldianisylmethyl (BUDAM) amine were prepared according to procedures previously reported by our group.[9,10,19,31] All other reagents were used as freshly purchased either from Aldrich or other commercial sources, or purified appropriately.

The silica gel for column chromatography was purchased from Sorbent Technologies with the following specifications: standard grade, 60 Å porosity, 230 X 400 mesh particle size, 500 – 600 m^2/g surface area and 0.4 g/mL bulk density. Melting points were determined on a Thomas Hoover capillary melting point apparatus. IR spectra were taken on a Nicolet IR/42 spectrometer. ^1H and

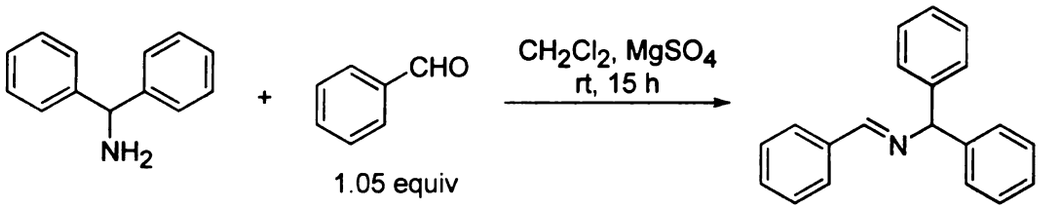
^{13}C NMR spectra were recorded on a VXR-500 MHz instrument in DMSO-*d*6 or $CDCl_3$ unless otherwise noted, wherein either DMSO-*d*5 was used as the internal standard for both ^{1}H NMR (δ = 2.49) and ^{13}C NMR (δ = 39.5) or $CHCl_3$ was used as the internal standard for both ^{1}H NMR (δ = 7.24) and ^{13}C NMR (δ = 77), respectively. Low resolution mass spectra analysis and elemental analysis was performed at the Department of Chemistry at Michigan State University. High resolution mass spectra analysis was performed at the Department of Biochemistry at Michigan State University. Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with phosphomolybdic acid reagent (20% wt in ethanol, Aldrich). HPLC was carried out using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0 decimeter cell with a total volume of 1.0 mL. Specific rotations are reported in degrees per decimeter at 25 °C and the concentrations are given in grams per 100 mL of the solvent indicated.

Appendix B

Experimental Information for Chapter Two

Section 2.1 Revisiting the aziridinations with benzhydryl imines

General procedure for the preparation of the imines 1 – illustrated for the synthesis of *N*-benzylidene-1,1-diphenylmethanamine 1b

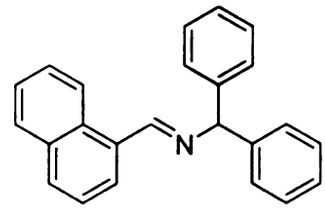


1b

All imines **1** could be purified by crystallization except imine **1j** which was a liquid at room temperature and was used in the aziridination reaction without further purification. The reaction time for the formation of imine **1h** was 24 h.

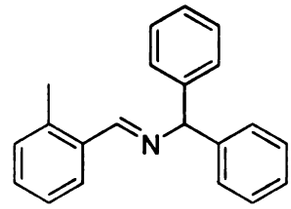
*N-benzylidene-1,1-diphenylmethanamine **1b**.*[6] To a flame-dried 100 mL round bottom flask filled with argon was added 4 g $MgSO_4$ (33.3 mmol) and 40 mL dry CH_2Cl_2. This was followed by the addition of diphenylmethanamine (3.46 g, 18.9 mmol, 1 equiv). After stirring for 5 minutes, benzaldehyde (2.10 g, 19.8 mmol, 1.05 equiv) was added. The reaction mixture was stirred for 15 h at room temperature. Thereafter, the reaction mixture was filtered through Celite and the Celite bed was washed with CH_2Cl_2 (15 mL x 3). The filtrate was then concentrated by rotary evaporation and placed under high vacuum (0.05 mm Hg) for 1 h to give the crude imine **1b** as an off-white solid. Crystallization (1:9 ethyl acetate:hexanes) afforded **1b** in 77% isolated yield (3.9 g, 14.5 mmol) as white crystals: mp. 99–101 °C (lit[23] 98-100 °C). Spectral data for **1b**: ^{1}H NMR ($CDCl_3$,

300 MHz) δ 5.64 (s, 1H), 7.20-7.90 (m, 15H), 8.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 77.62, 126.69, 127.40, 128.15, 128.19, 128.24, 130.47, 136.07, 143.64, 160.48.



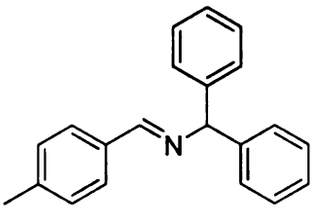
1a

N-(1-Naphthylidene)-1,1-diphenylmethanamine ***1a.***[6] Crystallization (1:5 ethyl acetate/hexanes) afforded **1a** in 85% isolated yield as a white solid (mp. 105 °C). Spectral data for **1a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.62 (s, 1H), 7.18-7.55 (m, 12H), 7.84-7.91 (m, 3H), 9.00 (s, 1H), 9.06 (d, 1H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 79.33, 121.35, 124.71, 125.15, 126.02, 126.97, 127.22, 127.66, 128.48, 128.57, 129.83, 131.24, 131.53, 133.85, 144.02, 160.91.



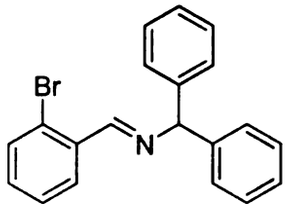
1c

N-(2-methylbenzylidene)-1,1-diphenylmethanamine ***1c.***[6] Crystallization (1:5 ethyl acetate/hexanes) afforded **1c** in 92% isolated yield as white crystals (mp. 99-100 °C). Spectral data for **1c**: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.48 (s, 3H), 5.52 (s, 1H), 7.10-7.40 (m, 12H), 7.93 (d, 2H, J = 7 Hz), 8.67 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) (1 sp^2 carbon missing) δ 19.64, 78.74, 126.03, 126.88, 127.60, 128.39, 130.22, 130.81, 134.18, 137.87, 144.09, 159.65.



1d

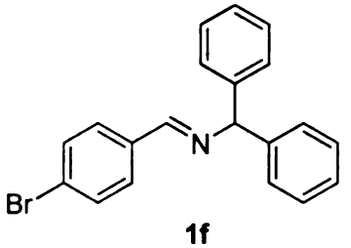
N-(4-methylbenzylidene)-1,1-diphenylmethanamine ***1d***.[24] Crystallization (1:5 ethyl acetate/hexanes) afforded **1d** in 79% isolated yield as white crystals (mp. 73-74 °C). Spectral data for **1d**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 5.64 (s, 1H), 7.26-7.48 (m, 12H), 7.80 (d, 2H, *J* = 8 Hz), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.50, 76.57, 126.89, 127.66, 128.38, 128.41, 129.21, 133.88, 141.01, 143.98, 160.67; IR (thin film) 3026s, 2853s, 1639vs, 1599s, 1452s, 1383s, 1030s, 700s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 285 M^+ (14), 168 (16), 167 (100), 152 (27), 76 (9). Anal calcd for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.23; H, 6.88; N, 4.82.



1e

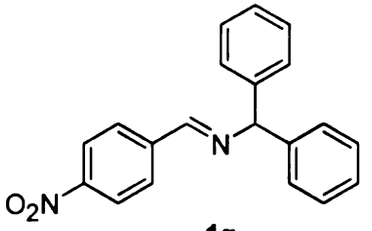
N-(2-bromobenzylidene)-1,1-diphenylmethanamine ***1e***.[25] Crystallization (1:5 ethyl acetate/hexanes) afforded **1e** in 81% isolated yield as a white solid (mp. 113-114 °C). Spectral data for **1e**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.71 (s, 1H), 7.27-7.61 (m, 13H), 8.27 (dd, 1H, *J* = 8, 2 Hz), 8.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 78.06, 127.06, 127.53, 127.61, 128.47, 129.23, 131.89, 132.96, 143.58, 159.80; IR (thin film) 3061m, 3026m, 1631s, 1493s, 1028s, 756s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 351 M^+ (4, ^{81}Br), 349 M^+ (5, ^{79}Br), 165

(100), 152 (53), 151 (84), 88 (52). Anal calcd for $C_{20}H_{16}BrN$: C, 68.58; H, 4.60; N, 4.00. Found: C, 68.39; H, 4.73; N, 3.93.



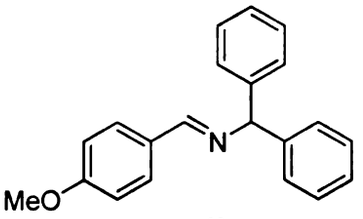
1f

N-(4-bromobenzylidene)-1,1-diphenylmethanamine ***1f***.[6,26] Crystallization (1:5 ethyl acetate/hexanes) afforded **1f** in 70% isolated yield as a white solid (mp. 96-97 °C). Spectral data for **1f**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.23 (s, 1H), 7.15-7.35 (m, 10H), 7.47 (d, 2H, *J* = 7 Hz), 7.64 (d, 2H, *J* = 7 Hz), 8.28 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 77.85, 127.05, 127.60, 128.46, 129.84, 131.75, 143.62, 159.51.



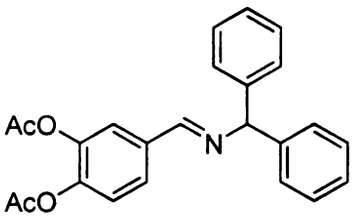
1g

N-(4-nitrobenzylidene)-1,1-diphenylmethanamine ***1g***.[26] Crystallization (1:1 ethyl acetate/hexanes) afforded **1g** in 80% isolated yield as an off-white solid: mp. = 132-134 °C (lit[27] 134-135 °C). Spectral data for **1g**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.76 (s, 1H), 7.30-7.40 (m, 10H), 8.08 (d, 2H, *J* = 8 Hz), 8.31 (d, 2H, *J* = 8 Hz), 8.52 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) (1 sp^2 carbon missing) δ 78.09, 123.80, 127.28, 127.55, 128.57, 129.10, 141.65, 143.14, 158.51.



1h

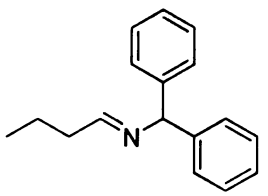
N-(4-methoxybenzylidene)-1,1-diphenylmethanamine ***1h.*** Crystallization (1:5 ethyl acetate/hexanes) afforded **1h** in 85% isolated yield as white crystals: mp. 108-109 °C (lit[27] 108-109 °C). Spectral data for **1h**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.82 (s, 3H), 5.55 (s, 1H), 6.91 (d, 2H, J = 8.8 Hz), 7.28-7.40 (m, 10H), 7.78 (d, 2H, *J* = 8.8 Hz), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.32, 77.77, 113.88, 126.85, 127.67, 128.37, 129.99, 144.11, 160.01; IR (thin film) 2849m, 1632s, 1493m, 1028m, 756s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 301 M^+ (16), 168 (10), 167 (100), 164 (41), 152 (22), 76 (11). Anal calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.60; H, 6.35; N, 4.52.



1i

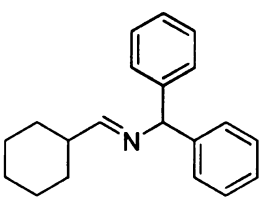
4-((benzhydrylimino)methyl)-1,2-phenylene diacetate ***1i.***[6] Crystallization (1:5 ethyl acetate/hexanes) afforded **1i** in 66% isolated yield as white crystals (mp. 138-139 °C). Spectral data for **1i**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H), 2.30 (s, 3H), 5.62 (s, 1H), 7.24 (m, 3H), 7.33 (t, 4H, *J* = 8 Hz), 7.38 (d, 4H, *J* = 8 Hz), 7.68 (dd, 1H, *J* = 8, 2 Hz), 7.77 (d, 1H, *J* = 2 Hz), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.64, 20.70, 77.62, 122.88, 123.60, 126.99, 127.11, 127.68, 128.50, 135.16, 142.44, 143.59, 144.07, 158.85, 168.02, 168.22; IR (thin film)

1775s, 1640s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 387 M^+ (10), 167 (100). Anal calcd for $C_{24}H_{21}NO_4$: C, 74.46; H, 5.47; N, 3.62. Found: C, 74.17; H, 5.66; N, 3.58.



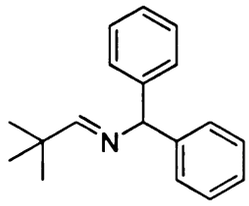
1j

N-butylidene-1,1-diphenylmethanamine ***1j***.[6] Crude product obtained as a light yellow oil in 74% yield. Spectral data for **1j**: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95 (t, 3H, *J* = 7.5 Hz), 1.60 (q, 2H, *J* = 7.5 Hz), 2.33 (dt, 2H, *J* = 7.5, 5 Hz), 5.35 (s, 1H), 7.1-7.4 (m, 10H), 7.84 (t, 1H, *J* = 5 Hz).



1k

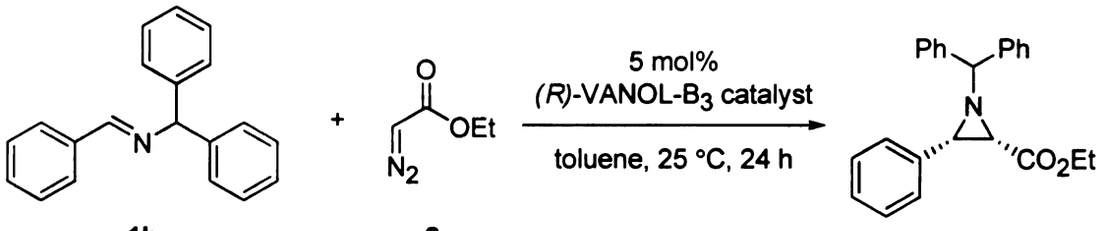
N-(cyclohexylmethylene)-1,1-diphenylmethanamine ***1k***.[6,23] Crystallization (1:5 ethyl acetate/hexanes) afforded **1k** in 74% isolated yield as an off-white solid: mp. 49-51 °C (lit[23] 48-49 °C). Spectral data for **1k**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10-1.90 (m, 10H), 2.20 (bs, 1H), 5.21 (s, 1H), 7.00-7.60 (m, 10H), 7.59 (d, 1H, *J* = 5.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.82, 26.41, 30.13, 43.91, 78.35, 127.20, 127.97, 128.73, 144.41, 169.51.



1l

N-(2,2-dimethylpropylidene)-1,1-diphenylmethanamine ***1l***.[6] Crystallization (1:9 ethyl acetate/hexanes) afforded **1l** in 35% isolated yield as white crystals (mp. 51-51.5 °C). Spectral data for **1l**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 9H), 5.50 (s, 1H), 7.34 (t, 2H, J = 7 Hz), 7.44 (t, 4H, J = 7 Hz), 7.49 (d, 4H, J = 7 Hz), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 26.94, 36.38, 77.36, 126.68, 127.44, 128.25, 144.23, 171.48; IR (thin film) 1666s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 251 M^+ (<1), 167 (100). Anal calcd for $C_{18}H_{21}N$: C, 86.08; H, 8.43; N, 5.58. Found: C, 85.82; H, 8.58; N, 5.53.

General procedure for the Wulff catalytic asymmetric cis-aziridination – illustrated for the synthesis of *(2S,3S)-ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate 3b*



1b **2** (2*S*,3*S*)-**3b**

(2S,3S)-ethyl 1-benzhydryl-3-phenylaziridine-2-carboxylate ***3b***.[6] The catalyst was prepared by the following method. A magnetic stir bar was added to a 25 mL pear shaped flask that had its 14/20 joint replaced by a high vacuum threaded T-shaped Teflon valve and then the flask was flame-dried and cooled

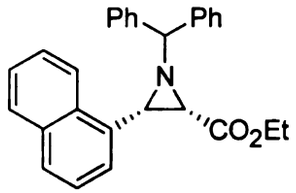
under argon. To the flask was added (*R*)-VANOL (21.9 mg, 0.05 mmol) and triphenylborate (58 mg, 0.2 mmol). Under an argon flow, dry toluene (2 mL) was added to dissolve the two reagents and this was followed by the addition of water (0.9 μL, 0.05 mmol). The Teflon value was closed and the flask was heated at 80 °C for 1 h. The threaded Teflon value was opened to gradually apply high vacuum (0.05 mm Hg) and to remove the solvent. The vacuum is maintained for a period of 30 min at a temperature of 80 °C. The flask was then filled with argon and the catalyst mixture was allowed to cool to room temperature.

To the flask containing the catalyst was first added the imine **1b** (271 mg, 1 mmol) and then dry toluene (2 mL). Upon addition of the imine and solvent the reaction mixture turned a yellow color. Ethyl diazoacetate (124 μL, 1.2 mmol) was added via syringe and the Teflon value was closed and the reaction mixture was stirred at room temperature for 24 h. Immediately upon addition of ethyl diazoacetate the reaction mixture became an intense yellow and the formation of bubbles from the release of nitrogen was noted. The mixture was then diluted with 15 mL of hexanes and transferred to a 100 mL round bottom flask. The reaction flask was rinsed twice with 5 mL of dichloromethane and the rinse was added to the round bottom flask. Rotary evaporation of the solvent followed by exposure to high vacuum (0.05 mm Hg) for 30 minutes gave the crude aziridine as an off-white solid. The conversion was determined from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the aziridine ring methine protons relative to either the imine benzhydryl methine proton or the methine of the imine carbon. The cis:trans ratio was determined on the crude reaction mixture to be

≥100:1 by ^{1}H NMR integration of the ring methine protons for each aziridine. The cis (J = 7-8 Hz) and the trans (J = 2-3 Hz) coupling constants were used to differentiate the two isomers. The yields of the acyclic enamine products (**26b**) were determined from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the N-H proton of the enamine relative to the aziridine ring methine protons with the aid of the isolated yield of the cis-aziridine: 2% yield of **26b**. Purification of the crude aziridine by chromatography (35 mm x 400 mm column) on silica gel with an eluent mixture of ethyl acetate:hexanes (1:9) gave the pure aziridine **3b** in 87% isolated yield (310.2 mg, 0.87 mmol). The optical purity of (2*S*,3*S*)-**3b** was determined to be 93% ee by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexanes/2-propanol, 222 nm, flow rate 0.7 mL/min). Retention times: R_t = 4.44 min (major enantiomer) and R_t = 8.18 min (minor enantiomer). Spectral data for (2*S*,3*S*)-**3b**: R_f = 0.3 (1:9 ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, 3H, J = 7 Hz), 2.76 (d, 1H, J = 7 Hz), 3.30 (d, 1H, J = 7 Hz), 4.00 (m, 2H), 4.08 (s, 1H), 7.25 (m, 2H), 7.33 (m, 5H), 7.41 (t, 2H, J = 7 Hz), 7.49 (d, 2H, J = 7 Hz), 7.57 (d, 2H, J = 7 Hz), 7.69 (d, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 13.88, 46.34, 47.98, 60.48, 77.64, 127.17, 127.27, 127.35, 127.49, 127.71, 127.74, 128.43, 135.00, 142.35, 142.48, 167.65; IR (thin film) 3030m, 2981m, 1737s, 1600s, 1200s, 1097s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 357 M^+ (<1), 190 (100), 167 (60), 117 (34). Anal calcd for $C_{24}H_{23}NO_2$: C, 80.84; H, 6.48; N, 3.92. Found: C, 80.92; H, 6.70; N, 3.88. $[\alpha]^{23}_D$ -41.0 (*c* 1.0, CH_2Cl_2) on 99.4% *ee* material (HPLC). White solid: mp. 128-129 °C on 99.4% ee material.

Optical purity enhancement by crystallization. The chemically pure aziridine (2*S*,3*S*)-**3b** (261 mg, 0.73 mmol, 94% ee) obtained from column chromatography was placed in a 100 mL round bottom flask. An air condenser with an argon balloon was attached to the round bottom flask. A small amount of a 1:9 mixture of EtOAc:hexanes (~10-20 mL) was added via syringe and the solvents brought to boil with a heat gun as the flask was swirled. Additional solvent mixture was added and mixture was returned to a boil. This process was continued until a clear solution was obtained (10-20 mL solvent mixture). The flask was then kept in an insulated place untouched for 10-15 h, upon which the aziridine **3b** crystallized out. The first crop was collected (162 mg, 0.45 mmol, 62% recovery) and determined to be 99.4% *ee* by HPLC (see conditions above).

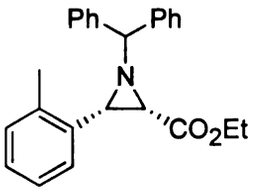
The above procedure for the preparation of the aziridine **3b** was also repeated with a slight modification of the procedure in which the catalyst solution was transferred to a solution of the imine and identical results were obtained. Each imine **1a-l** was subjected to the catalytic asymmetric aziridination reaction with the procedure described above in four different variations: with catalysts derived from (*R*)-VANOL and (*S*)-VAPOL ligands and with the solvents toluene and CH_2Cl_2. The results for all these reactions can be found in Tables 2.3 and 2.4 (in Chapter 2). Imines **1g**, **1j**, **1k** and **1l** were also subjected to the catalytic asymmetric aziridination reaction at a reaction temperature of 0 °C and these results are presented in Table 2.5 (in Chapter 2).



(2*S*,3*S*)-**3a**

(2S,3S)-ethyl 1-benzhydryl-3-(naphthalen-1-yl)aziridine-2-carboxylate ***3a***.[6] Imine **1a** (321 mg, 1 mmol) was reacted according to the general procedure described above with (*R*)-VANOL as ligand. Purification by column chromatography on silica gel (1:9 ethyl acetate/hexanes) gave the pure aziridine (2*S*,3*S*)-**3a** in 80% isolated yield (325 mg, 0.80 mmol); cis/trans*:* 51:1. Enamine side products: 2% yield of **26a**. The optical purity of (2*S*,3*S*)-**3a** was determined to be 93% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes/2-propanol, 222 nm, flow rate 0.7 mL/min). Retention times: R_t = 32.89 min (major enantiomer) and R_t = 25.62 min (minor enantiomer). A single crystallization (1:15 ethyl acetate:hexanes) of 89% *ee* material gave **3a** with 55% recovery and 99.9% *ee*. Spectral data for (2*S*,3*S*)-**3a**: R_f = 0.25 (1:9 ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.65 (t, 3H, *J* = 7 Hz), 2.94 (d, 1H, *J* = 7 Hz), 3.75 (m, 2H), 3.77 (d, 1H, *J* = 7 Hz), 4.10 (s, 1H), 7.22 (m, 1H), 7.30 (m, 3H), 7.38 (m, 3H), 7.48 (m, 2H), 7.58 (d, 2H, *J* = 7 Hz), 7.70 (m, 4H), 7.81 (d, 1H, *J* = 7 Hz), 8.12 (d, 1H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.55, 45.98, 46.36, 60.35, 77.91, 122.93, 125.29, 125.40, 125.82, 126.51, 127.10, 127.14, 127.58, 127.85, 128.48, 128.54, 130.48, 131.38, 133.01, 142.22, 142.45, 167.75; IR (thin film) 3030w, 2980w, 1737s, 1598m, 1191s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 407 M^+ (5), 240 (59), 167 (100), 139 (9). Anal calcd for $C_{28}H_{25}NO_2$: C, 82.59; H,

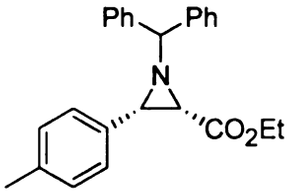
6.19; N, 3.44. Found: C, 81.86; H, 6.37; N, 3.26. $[\alpha]^{23}_D$ = +16.0 (*c* 1.0, CH_2Cl_2) on 99.9% *ee* material. White solid: mp 128-129 °C on 99.9% ee material.



(2*S*,3*S*)-**3c**

(2S,3S)-ethyl 1-benzhydryl-3-o-tolylaziridine-2-carboxylate ***3c***.[6] Imine **1c** (285 mg, 1 mmol) was reacted according to the general procedure described above with (*R*)-VANOL as ligand. Purification by column chromatography on silica gel (1:9 ethyl acetate/hexanes) gave the pure aziridine **3c** in 67% isolated yield (250 mg, 0.67 mmol); cis/trans: 12:1. Enamine side products: 11% yield of **26c**. The optical purity of (2*S*,3*S*)-**3c** was determined to be 90% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes/2-propanol, 222 nm, flow rate 1 mL/min). Retention times: R_t = 6.02 min (major enantiomer) and R_t = 7.47 min (minor enantiomer). A single crystallization (1:19 ethyl acetate:hexanes) of 91% *ee* material gave **3c** with 74% recovery and 99.3% *ee*. Spectral data for (2*S*,3*S*)-**3c**: R_f = 0.33 (1:9 ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00 (t, 3H, *J* = 7 Hz), 2.43 (s, 3H), 2.86 (d, 1H, *J* = 7 Hz), 3.34 (d, 1H, *J* = 7 Hz), 4.00 (q, 2H, *J* = 7 Hz), 4.07 (s, 1H), 7.15 (d, 1H, *J* = 7 Hz), 7.22 (m, 2H), 7.28 (m, 1H), 7.38 (m, 3H), 7.45 (t, 2H, *J* = 7 Hz), 7.65 (d, 2H, *J* = 7 Hz), 7.68 (d, 1H, *J* = 7 Hz), 7.75 (d, 2H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 Hz) δ 13.73, 18.70, 45.53, 46.81, 60.33, 77.76, 125.26, 127.04, 127.06, 127.43, 127.63, 128.39, 128.41, 129.01, 133.05, 135.90, 142.33, 142.48, 167.80; IR (thin film) 3054m, 2982m, 1740s, 1600m, 1184s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 371 M^+ (<1),

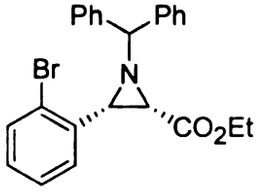
204 (100), 167 (43), 131 (41). Anal calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.37. Found: C, 80.84; H, 6.94; N, 3.64. $[\alpha]^{23}_D$ = -42.6 (*c* 1.0, CH_2Cl_2) on 99.3% *ee* material. White solid: mp 164-165 °C on 99.3% ee material.



(2*S*,3*S*)-**3d**

(2S,3S)-ethyl 1-benzhydryl-3-p-tolylaziridine-2-carboxylate ***3d.*** Imine **1d** (285 mg, 1 mmol) was reacted according to the general procedure described above with (*R*)-VANOL as ligand. The only difference in the procedure was that 2 mL of a 4:1 toluene:CH_2Cl_2 solvent system was used for the reaction. Purification by column chromatography on silica gel (1:9 ethyl acetate/hexanes) gave the pure aziridine **3d** in 79% isolated yield (293 mg, 0.79 mmol); cis/trans: ≥50:1. Enamine side products: 2% yield of **26d.** The optical purity of (2*S*,3*S*)-**3d** was determined to be 94% *ee* by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexanes/2-propanol, 222 nm, flow rate 0.7 mL/min). Retention times: R_t = 4.29 min (major enantiomer) and R_t = 7.60 min (minor enantiomer). A single crystallization (1:19 ethyl acetate:hexanes) of 94% *ee* material gave **3d** with 80% recovery and 99.2% *ee* (HPLC). Spectral data for (2*S*,3*S*)-**3d**: R_f = 0.30 (1:9 ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (t, 3H, *J* = 7.1 Hz), 2.28 (s, 3H), 2.64 (d, 1H, *J* = 6.9 Hz), 3.17 (d, 1H, *J* = 6 Hz), 3.93 (s, 1H), 3.95 (q, 2H, *J* = 7.2 Hz), 7.05 (d, 2H, *J* = 8 Hz), 7.13-7.36 (m, 8H), 7.48 (d, 2H, *J* = 7.2 Hz), 7.60 (d, 2H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 Hz) δ 13.94, 21.09, 46.29, 47.98, 60.47, 76.57, 127.13, 127.19, 127.31, 127.47, 127.63, 128.41, 131.94,

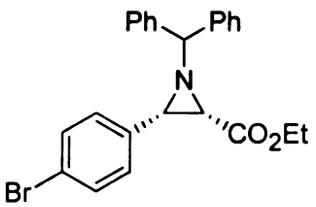
136.84, 142.41, 142.51, 167.75; IR (thin film) 3030m, 2980m, 1739s, 1454m, 1197s, 1178s, 1066m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 371 M^+ (<1), 204 (83), 203 (58), 167 (40), 164 (46), 131 (58), 130 (100), 129 (58), 77 (26). Anal calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.67; H, 6.50; N, 3.66. $[\alpha]^{23}_D$ = -27.8 (*c* 1.0, CH_2Cl_2) on 99.2% *ee* material. White solid: mp 164-165 °C on 99.2% ee material.



(2*S*,3*S*)-**3e**

(2S,3S)-ethyl 1-benzhydryl-3-(2-bromophenyl)aziridine-2-carboxylate ***3e***. Imine **1e** (349 mg, 1 mmol) was reacted according to the general procedure described above with (*R*)-VANOL as ligand, the only difference being the reaction time which was 48 h for this reaction. Purification by column chromatography (1:9 ethyl acetate/hexanes) gave the pure aziridine **3e** in 43% isolated yield (188 mg, 0.43 mmol); *cis/trans*: ≥100:1. Enamine side products: 24% yield of **26e**. The optical purity of (2*S*,3*S*)-**3e** was determined to be 82% *ee* by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexanes/2-propanol, 222 nm, flow rate 0.7 mL/min). Retention times: R_t = 6.06 min (major enantiomer) and R_t = 7.91 min (minor enantiomer). A single crystallization (1:19 ethyl acetate) of 85% *ee* material gave **3e** with 65% recovery and 98.6% *ee*. Spectral data for (2*S*,3*S*)-**3e**: R_f = 0.33 (1:9 ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H, *J* = 7.1 Hz), 2.77 (d, 1H, *J* = 7.0 Hz), 3.32 (d, 1H, *J* = 6.8 Hz), 3.92 (q, 2H, *J* = 7.2 Hz), 3.98 (s, 1H), 7.12 (t, 1H, *J* = 7.6 Hz), 7.22-7.44 (m, 7H), 7.48 (d,

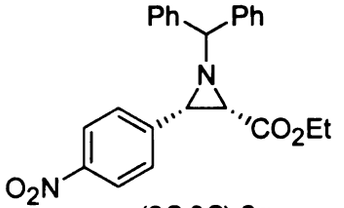
1H, J = 8.0 Hz), 7.56 (d, 2H, J = 7.1 Hz), 7.64 (d, 3H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.85, 45.86, 48.77, 60.58, 76.57, 123.22, 126.71, 126.98, 127.18, 127.57, 127.65, 128.49, 128.54, 128.77, 130.78, 131.54, 134.40, 142.11, 142.34, 167.54; IR (thin film) 1738s, 1199s, 1028m, 748m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 437 M^+ (<1, ^{81}Br), 435 M^+ (<1, ^{79}Br), 270 (22), 268 (31), 167 (100), 165 (50). Anal calcd for $C_{24}H_{22}BrNO_2$: C, 66.06; H, 5.08; N, 3.21. Found: C, 66.01; H, 4.98; N, 3.06. $[\alpha]^{23}_D$ = -26.0 (*c* 1.0, CH_2Cl_2) on 98.6% *ee* material (HPLC). White solid: mp 147-148 °C on 98.6 % ee material.



(2*S*,3*S*)-**3f**

(2S,3S)-ethyl 1-benzhydryl-3-(4-bromophenyl)aziridine-2-carboxylate ***3f***.[6] Imine **1f** (349 mg, 1 mmol) was reacted according to the general procedure described above with (*R*)-VANOL as ligand. Purification by column chromatography on silica gel (1:9 ethyl acetate/hexanes) gave the pure aziridine **3f** in 86% isolated yield (373 mg, 0.86 mmol); cis/trans: ≥20:1. Enamine side products: 14% yield of **26f**. The optical purity of (2*S*,3*S*)-**3f** was determined to be 94% *ee* by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexanes/2-propanol, 222 nm, flow rate 1 mL/min). Retention times: R_t = 5.37 min (major enantiomer) and R_t = 13.48 min (minor enantiomer). A single crystallization (1:19 ethyl acetate:hexanes) of 94% *ee* material gave **3f** with 76% recovery and 99.4% *ee*. Spectral data for (2*S*,3*S*)-**3f**: R_f = 0.33 (1:9 ethyl acetate/hexanes). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.07 (t, 3H, J = 7 Hz), 2.74 (d, 1H, J = 7 Hz), 3.19 (d, 1H, J =

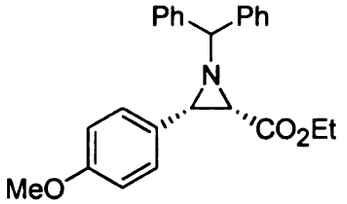
7 Hz), 4.00 (q, 2H, J = 7 Hz), 4.01 (s, 1H), 7.23 (t, 1H, 7 Hz), 7,29-7.45 (m, 9H), 7.50 (d, 2H, J = 7 Hz), 7.65 (d, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) (1 sp^2 carbon missing) δ 13.96, 46.44, 47.31, 60.67, 77.55, 121.31, 127.11, 127.25, 127.40, 127.46, 128.49, 129.52, 130.86, 134.06, 142.12, 142.29, 167.37; IR (thin film) 1734s, 1201s, 1067m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 437 M^+ (<1, ^{81}Br), 435 M^+ (<1, ^{79}Br), 270 (42, ^{81}Br), 268 (43, ^{79}Br), 167 (100, ^{81}Br), 165 (19, ^{79}Br). Anal calcd for $C_{24}H_{22}BrNO_2$: C, 66.06; H, 5.27; N, 3.09. Found: C, 66.06; H, 5.08; N, 3.21. $[\alpha]^{23}_D$ = -12.5 (*c* 1.0, CH_2Cl_2) on 99.4% *ee* material. White solid: mp 155-157 °C on 99.4% ee material.



(2*S*,3*S*)-**3g**

(2S,3S)-ethyl 1-benzhydryl-3-(4-nitrophenyl)aziridine-2-carboxylate ***3g***.[6] Imine **1g** (316 mg, 1 mmol) was reacted according to the general procedure described above with (*R*)-VANOL as ligand. The only difference was that the reaction was carried out at 0 °C. Purification by column chromatography on silica gel (1:5 ethyl acetate:hexanes) gave the pure aziridine **3g** in 93% isolated yield (371 mg, 0.92 mmol); cis/trans:100:1. Enamine side products: <1% yield of **26g**. The optical purity of (2*S*,3*S*)-**3g** was determined to be 93% *ee* by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexanes:2-propanol, 222 nm, flow rate 0.7 mL/min). Retention times: R_t = 8.70 min (major enantiomer) and R_t = 11.37 min (minor enantiomer). A single crystallization (1:15 ethyl acetate:hexanes) of 94.5% *ee* material gave **3g** with 74% recovery and 99.7% *ee*. Spectral data for (2*S*,3*S*)-

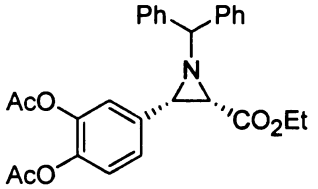
3g: R_f = 0.3 (1:5 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (t, 3H, *J* = 7 Hz), 2.84 (d, 1H, *J* = 7 Hz), 3.30 (d, 1H, *J* = 7Hz), 3.98 (q, 2H, *J* = 7 Hz), 4.04 (s, 1H), 7.23 (t, 1H, *J* = 7 Hz), 7.29 (m, 3H), 7.38 (t, 2H, *J* = 7 Hz), 7.55 (d, 2H, *J* = 8 Hz), 7.63 (m, 4H), 8.15 (d, 2H, *J* = 8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.96, 29.64, 46.88, 47.02, 60.89, 123.00, 127.02, 127.34, 127.40, 127.64, 128.57, 128.60, 128.74, 141.09, 142.03, 142.49, 166.92; IR (thin film) 2980w, 1742s, 1605s, 1520s, 1346s, 1340s, 1202s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 402 M^+ (<1), 167 (100), 165 (12), 152 (8), 89 (3). Anal calcd for $C_{24}H_{22}N_2O_4$: C, 71,63; H, 5.51; N, 6.96. Found: C, 71.58; H, 5.71; N, 6.82. $[\alpha]^{23}_D$ = +11.2 (*c* 1.0, CH_2Cl_2) on 99.7% *ee* material. White solid: mp 139-140 °C on 99.7% ee material.



(2*S*,3*S*)-**3h**

(2S,3S)-ethyl 1-benzhydryl-3-(4-methoxyphenyl)aziridine-2-carboxylate ***3h***. Imine **1h** (301 mg, 1 mmol) was reacted according to the general procedure described above with (*R*)-VANOL as ligand. The silica gel for column chromatography was pre-conditioned by preparing a slurry in a 1:9 mixture of Et_3N:CH_2Cl_2 which was loaded into a column, the solvent was drained and then the silica gel was dried by flushing with nitrogen for one hour. The silica gel column was then saturated with a 1:9 mixture of ethyl acetate:hexanes, the crude aziridine was loaded onto the column and then elution with the same solvent mixture gave the pure aziridine **3h** in 61% isolated yield (236 mg, 0.61 mmol);

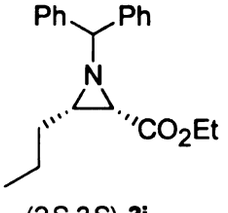
cis/trans: 34:1. Enamine side products: <1% yield of **26h**. The optical purity of (2*S*,3*S*)-**3h** was determined to be 87% *ee* by HPLC analysis (CHIRALCEL OD-H column, 95:5 hexanes:2-propanol, 222 nm, flow rate 0.7 mL/min). Retention times: R_t = 6.35 min (major enantiomer) and R_t = 15.00 min (minor enantiomer). A single crystallization (1:25 ethyl acetate:hexanes) of 87% *ee* material gave **3h** with 81% recovery and 99.9% *ee*. Spectral data for (2*S*,3*S*)-**3h**: R_f = 0.2 (1:9 ethyl acetate:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.03 (t, 3H, *J* = 7.0 Hz), 2.66 (d, 1H, *J* = 6.8 Hz), 3.19 (d, 1H, *J* = 6.7 Hz), 3.74 (s, 3H), 3.96 (s, 1H), 3.97 (q, 2H, *J* = 7.2 Hz), 6.82 (d, 2H, *J* = 8.8 Hz), 7.15-7.39 (m, 8H), 7.51 (d, 2H, *J* = 7.3 Hz), 7.63 (d, 2H, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.94, 46.26, 47.67, 55.06, 60.45, 76.57, 113.16, 127.05, 127.15, 127.31, 127.46, 128.40, 128.82, 142.38, 142.53, 158.84, 167.80; IR (thin film) 3030w, 2934w, 1738s, 1614m, 1516s, 1250s, 1033s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 388 M+1 (0.9), 315 (10), 222 (12), 221 (100), 167 (21), 166 (20), 147 (25), 146 (19), 91 (19). Anal calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.67; H, 6.63; N, 3.58. $[\alpha]^{23}_D$ = -27.6 (*c* 1.0, CH_2Cl_2) on 99.9% ee material. White solid: mp 136-137 °C on 99.9% ee material.



(2*S*,3*S*)-**3i**

4-((2S,3S)-1-benzhydryl-3-(ethoxycarbonyl)aziridin-2-yl)-1,2-phenylene diacetate ***3i***.[6] Imine **1i** (387 mg, 1 mmol) was reacted according to the general procedure described above with (*R*)-VANOL as ligand. Purification by column

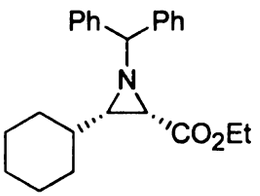
chromatography on silica gel (1:2 ethyl acetate:hexanes) gave the pure aziridine **3i** in 84% isolated yield (214 mg, 0.45 mmol); cis/trans: ≥100:1. Enamine side products: <1% yield of **26i**. The optical purity of (2*S*,3*S*)-**3i** was determined to be 93% *ee* by HPLC analysis (CHIRALCEL OD column, 85:15 hexanes:2-propanol, 222 nm, flow rate 0.7 mL/min). Retention times: R_t = 28.62 min (major enantiomer) and R_t = 25.38 min (minor enantiomer). A single crystallization (1:5 ethyl acetate:hexanes) of 92.5% *ee* material gave **3i** with 67% recovery and 99% *ee*. Spectral data for (2*S*,3*S*)-**3i**: R_f = 0.28 (1:2 ethyl acetate:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, 3H, *J* = 7 Hz), 2.24 (s, 3H), 2.25 (s, 3H), 2.68 (d, 1H, *J* = 7 Hz), 3.18 (d, 1H, *J* = 7 Hz), 3.95 (s, 1H), 3.95 (m, 2H), 7.07 (d, 1H, *J* = 9 Hz), 7.19 (m, 1H), 7.28 (m, 7H), 7.45 (d, 2H, *J* = 7 Hz), 7.81 (d, 2H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.84, 20.64, 46.57, 47.03, 60.89, 77.49, 122.75, 122.78, 126.05, 127.18, 127.30, 127.45, 127.61, 128.55, 128.65, 133.97, 141.35, 141.57, 142.21, 167.45, 168.07, 168.24; IR (thin film) 3030w, 2980w, 1770w, 1731s, 1600m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 474 M+1 (21), 306 (12), 195 (10), 167 (100). Anal calcd for $C_{28}H_{27}NO_6$: C, 71.02; H, 5.75; N, 2.96. Found: C, 71.23; H, 5.88; N, 2.94. $[\alpha]^{23}_D$ = -19.7 (*c* 1.0, CH_2Cl_2) on 99% *ee* material. White solid: mp 141-143 °C on 99% ee material.



(2*S*,3*S*)-**3j**

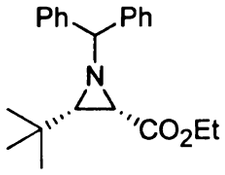
(2S,3S)-ethyl 1-benzhydryl-3-propylaziridine-2-carboxylate ***3j***.[6] Imine **1j** (237 mg, 1 mmol) was reacted according to the general procedure described

above with (*R*)-VANOL as ligand. The only differences were that the reaction was carried out at 0 °C, 10 mol% catalyst loading was used and the reaction time was 48 h. Purification by column chromatography (1:19 ethyl acetate:hexanes) gave the pure aziridine **3j** in 60% isolated yield (194 mg, 0.60 mmol); cis/trans: 33:1. Enamine side products: 4% yield of **26j**. The optical purity of (2*S*,3*S*)-**3j** was determined to be 83% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes:2-propanol, 222 nm, flow rate 1 mL/min). Retention times: R_t = 3.51 min (major enantiomer) and R_t = 7.44 min (minor enantiomer). A single crystallization (hexanes) of 86% *ee* material gave **3j** with 40% recovery and 96.6% *ee*. Spectral data for (2*S*,3*S*)-**3j**: R_f = 0.33 (1:9 ethyl acetate:hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.74 (t, 3H, *J* = 7 Hz), 1.05 (m, 1H), 1.10 (m, 1H), 1.25 (t, 3H, *J* = 7 Hz), 1.45 (m, 1H), 1.52 (m, 1H), 2.05 (q, 1H, *J* = 7 Hz), 2.28 (d, 1H, *J* = 7 Hz), 3.66 (s, 1H), 4.17 (m, 2H), 7.27 (m, 2H), 7.33 (m, 4H), 7.39 (d, 2H, *J* = 7 Hz), 7.49 (d, 2H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.57, 14.21, 20.26, 29.85, 43.32, 46.62, 60.62, 77.88, 126.94, 127.10, 127.30, 127.82, 128.27, 128.29, 142.42, 142.77, 169.46; IR (thin film) 3040m, 2959m, 1732s, 1194s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 323 M^+ (2), 167 (100), 156 (91), 152 (15), 128 (23), 82 (17). Anal calcd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 78.06; H, 7.94; N, 4.21. $[\alpha]^{23}_D$ = -112.2 (*c* 1.0, CH_2Cl_2) on 96.6% *ee* material. White solid: mp 93-95 °C on 96.6% ee material.



(2*S*,3*S*)-**3k**

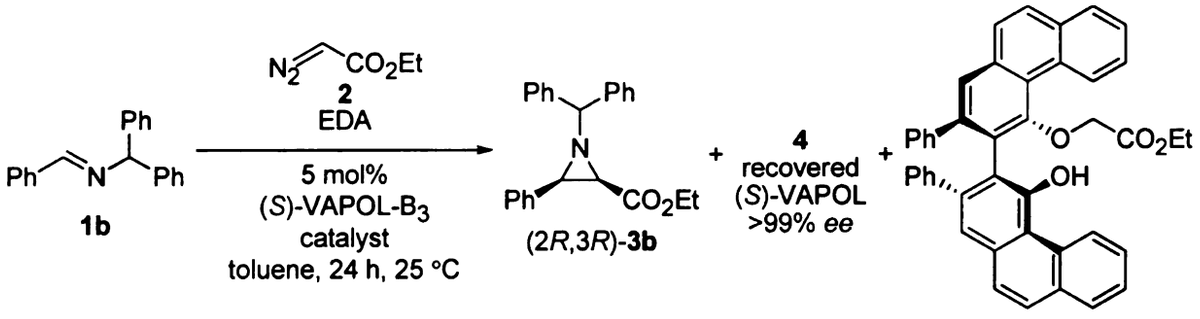
(2S,3S)-ethyl 1-benzhydryl-3-cyclohexylaziridine-2-carboxylate ***3k***.[6] Imine **1k** (277 mg, 1 mmol) was reacted according to the general procedure described above with (*R*)-VANOL as ligand. The only difference was that the reaction was carried out at 0 °C. Purification by column chromatography on silica gel (1:15 ethyl acetate:hexanes) gave the pure aziridine **3k** in 81% isolated yield (295 mg, 0.81 mmol); cis/trans: 100:1. Enamine side products: 6% yield of **26k**. The optical purity of (2*S*,3*S*)-**3k** was determined to be 82% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes:2-propanol, 222 nm, flow 1 mL/min). Retention times: R_t = 3.45 min (major enantiomer) and R_t = 6.99 min (minor enantiomer). A single crystallization (1:19 ethyl acetate:hexanes) of 83% *ee* material gave **3k** with 80% recovery and 99.1% *ee*. Spectral data for (2*S*,3*S*)-**3k**: R_f = 0.2 (1:15 ethyl acetate:hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.52 (dq, 1H, *J* = 10, 3 Hz), 0.95-1.66 (m, 10H), 1.28 (t, 3H, *J* = 7 Hz), 1.83 (dd, 1H, *J* = 7, 3 Hz), 2.29 (d, 1H, *J* = 7 Hz), 3.63 (s, 1H), 4.25 (m, 2H), 7.24 (m, 2H), 7.31 (m, 4H), 7.37 (m, 2H), 7.45 (d, 2H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.27, 25.34, 25.53, 30.11, 30.71, 36.27, 43.39, 52.12, 60.67, 78.18, 126.80, 126.82, 127.06, 127.49, 128.26, 128.30, 128.35, 142.33, 142.72, 169.63; IR (thin film) 2927m, 2917m, 2850m, 1731s, 1190s, 1180s; mass spectrum, *m/z* (% rel intensity) 363 M^+ (1), 196 (100), 167 (64), 102 (18), 95 (29). Anal calcd for $C_{24}H_{29}NO_2$: C, 79.44; H, 8.07; N, 3.64. Found: C, 79.30; H, 8.04; N, 3.85. $[\alpha]^{23}_D$ = -145.2 (*c* 1.0, CH_2Cl_2) on 99.1% *ee* material. White solid: mp 165-166 °C on 99.1% ee material.



(2*S*,3*S*)-**3l**

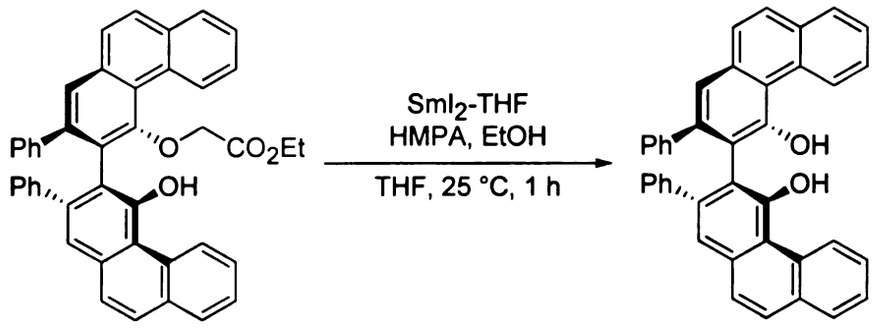
(2S,3S)-ethyl 1-benzhydryl-3-tert-butylaziridine-2-carboxylate ***3l***.[6] Imine **1l** (251 mg, 1mmol) was reacted according to the general procedure described above with (*R*)-VANOL as ligand. Purification by column chromatography on silica gel (1:9 ethyl acetate:hexanes) gave the pure aziridine **3l** in 89% isolated yield (300 mg, 0.89 mmol); cis/trans: ≥100:1. Enamine side products: 4% yield of **26l**. The optical purity of (2*S*,3*S*)-**3l** was determined to be 85% *ee* by HPLC analysis (CHIRALCEL OD-H, 99:1 hexanes:2-propanol, 222 nm, flow rate 1 mL/min). Retention times: R_t = 3.60 min (major enantiomer) and R_t = 9.76 min (minor enantiomer). A single recrysallization (1:19 ethyl acetate:hexanes) of 87% *ee* material gave **3l** with 76% recovery and 99.7% *ee*. Spectral data for (2*S*,3*S*)-**3l**: R_f = 0.33 (1:9 ethyl acetate:hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.70 (s, 9H), 1.29 (t, 3H, *J* = 7 Hz), 1.76 (d, 1H, *J* = 7 Hz), 2.16 (d, 1H, *J* = 7 Hz), 3.59 (s, 1H), 4.09 (m, 1H), 4.24 (m, 1H), 7.20 (m, 2H), 7.28 (m, 4H), 7.40 (d, 2H, *J* = 7 Hz), 7.67 (d, 2H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.09, 27.39, 31.59, 43.37, 56.07, 60.58, 79.19, 126.83, 127.24, 127.36, 128.17, 128.19, 128.26, 142.07, 143.43, 169.72; mass spectrum, *m/z* (% rel intensity) 338 M+1 (14), 195 (15), 167 (100). Anal calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.27; H, 8.27; N, 4.13. $[\alpha]^{23}_D$ = -149.4 (*c* 1.0, CH_2Cl_2) on 99.7% *ee* material. White solid: mp 150-152 °C on 99.7% ee material.

General procedures for the recovery and recycling of VAPOL from the catalytic asymmetric aziridination reaction



*Recovery of VAPOL-EDA adduct **27**.* The aziridination reaction of the imine **1b** (542 mg, 2 mmol) with ethyl diazoacetate **2** (250 μL, 2.4 mmol) was carried out in toluene, for 24 h at room temperature and with 5 mol% of the *(S)*-VAPOL-borate catalyst generated according to the general procedure described above. Thus for the preparation of the catalyst, (*S*)-VAPOL (54 mg, 0.1 mmol), $B(OPh)_3$ (116 mg, 0.4 mmol), H_2O (1.8 μL, 0.1 mmol) and toluene (2 ml) were heated at 80 °C for 1 h, then a vacuum (0.2 mm Hg) was applied carefully. Upon removal of solvent, the vacuum was kept for 30 minutes with continual heating at 80 °C. After the aziridination reaction, the crude reaction mixture obtained was subjected to separation by column chromatography with an eluent mixture of 1:9 EtOAc:hexanes, which afforded the pure aziridine **3b** in 73% yield (522 mg, 1.46 mmol) as well as the VAPOL-EDA adduct **27** in 98% yield (61 mg, 0.098 mmol). No VAPOL was detected under these reactions conditions. The R_f values for VAPOL, the aziridine **3b** and the VAPOL-EDA adduct **27** with the eluent mixture of 1:9 EtOAc:hexanes are 0.34, 0.30 and 0.25 respectively. The characterization data for **27** was identical to that previously reported by our group.[7e] The amount

of the VAPOL-EDA adduct **27** that is formed is variable and depends on the amount of excess ethyl diazoacetate that is used. For example, if 1.1 equivalents of ethyl diazoacetate is used then the adduct **27** is isolated in 49% yield along with a 46% recovery of unreacted VAPOL that is >99% ee.

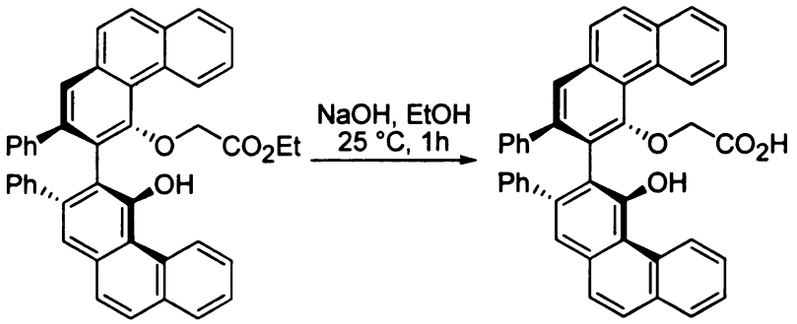


27 **4**
91% yield
99.8% ee

Samarium Diiodide[21] *Reduction of EDA-Adduct* ***27***. A 25 mL round-bottom flask was flame dried and cooled under argon and charged with samarium metal (128 mg, 0.85 mmol) and dry THF (5.2 ml). The flask was then fitted with a rubber septum and an argon balloon. Freshly distilled diiodomethane (63 μL, 0.784 mmol) was then added via syringe. The reaction mixture was stirred for 2 h at room temperature to give a dark blue slurry. To another 25 mL round-bottom flask which had been flame dried and cooled under argon was added the VAPOL-EDA adduct **27** (61 mg, 0.098 mmol) and dry THF (1 mL). After fitting the flask with a rubber septum and an argon balloon, ethanol (reagent grade, 17 μL, 0.294 mmol) and hexamethylphosphoramide (HMPA, 153 μL, 0.882 mmol) were added via syringe. The SmI_2-THF solution (0.392 mmol, 2.6 mL) was then transferred via syringe to the solution of **27**. The reaction mixture was stirred at room temperature for 1 h, during which time the reaction went to

completion (TLC, 1:9 ethyl acetate:hexanes). To the reaction flask was then added saturated $NaHCO_3$ solution (20 mL) and the mixture extracted with ethyl acetate (4 x 20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed by rotary evaporation to afford the crude VAPOL ligand **4**. The ligand was then purified by column chromatography on silica gel with an eluent mixture of 1:19 ethyl acetate/hexanes, which afforded the pure *(S)*-VAPOL product **4** in 91% yield (48 mg, 0.089 mmol). The optical purity of the recovered VAPOL was determined to be 99.8% *ee* by chiral HPLC analysis (Regis Pirkle Covalent D-Phenylglycine column, 75:25 hexanes:2-propanol, 260 nm, flow rate 2 mL/min). Retention times: (*S*)-VAPOL = 18.54 min, (*R*)-VAPOL = 12.50 min.

Liberation of the VAPOL Ligand via Curtius rearrangement.[20]

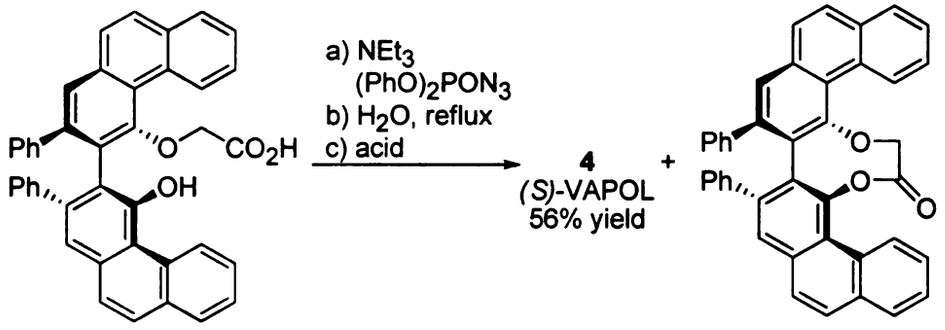


27 **28**
98% yield

*Hydrolysis of the EDA-Adduct to the Acid **28**.* A 100 mL round bottom flask was flame dried and cooled under argon and then the VAPOL-EDA adduct **27** (232 mg, 0.372 mmol) was introduced into the flask. The adduct was dissolved in ethanol (20 mL) and then 20 mL of 20% (w/v) aqueous solution of NaOH was added. This resulted in an instant color change from colorless to intense yellowish green. The reaction mixture was stirred at room temperature for

1 h. Thereafter, 140 mL 1 N HCl was added to adjust the pH of the mixture to pH = 1, upon which the product carboxylic acid **28** precipitated from the reaction mixture. The product was isolated by vacuum filtration and then dissolved in ethyl acetate. The filtrate was extracted once with ethyl acetate (30 mL) and the organic layers combined, washed with brine (2 X 30 mL), dried over $MgSO_4$ and then the solvent was removed via rotary evaporation to afford the crude carboxylic acid product **28** as a yellow solid in 98% yield (217.2 mg, 0.36 mmol).

Spectral data for **28**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.29 (d, 1H, J = 15.7 Hz), 4.39 (d, 1H, J = 15.7 Hz), 6.51 (bs, 1H), 6.78-6.86 (m, 4H), 6.95-7.04 (m, 4H), 7.04-7.13 (m, 2H), 7.43 (s, 1H), 7.47-7.64 (m, 7H), 7.71-7.64 (m, 3H), 7.82 (d, 1H, J = 8.7 Hz), 7.92 (d, 1H, J = 7.7 Hz), 9.31 (d, 1H, J = 8.1 Hz), 9.71 (d, 1H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) (1 sp^2 C missing) δ 67.72, 115.25, 118.70, 119.92, 120.74, 123.01, 123.13, 126.03, 126.09, 126.63, 126.73, 126.84, 126.99, 127.05, 127.12, 127.30, 127.62, 127.71, 127.73, 128.08, 128.19, 128.53, 128.77, 128.86, 128.90, 129.02, 129.07, 129.23, 129.61, 130.40, 132.84, 133.10, 134.55, 135.15, 139.19, 139.76, 140.41, 142.32, 152.07, 154.63, 171.64.

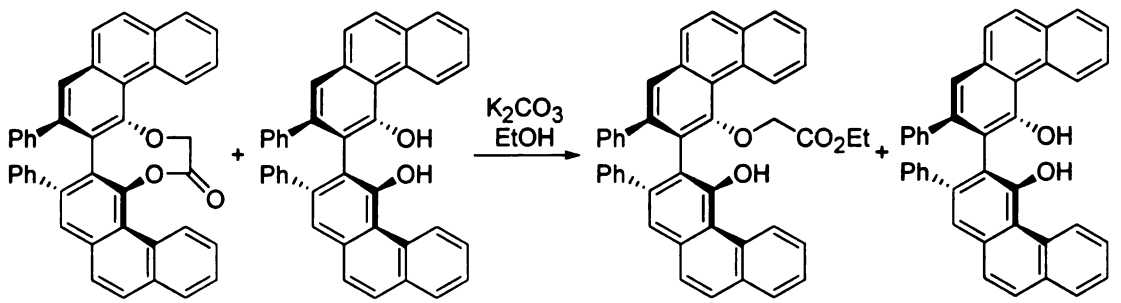


28
98% yield

29
34% yield

Curtius Rearrangement[20] *of Acid* ***28***. A 25 mL round bottom flask was flame dried and cooled under argon and then charged with the crude carboxylic acid **28** (41.2 mg, 0.069 mmol). The solid was then dissolved by the addition of toluene (3 mL) and DMF (1 mL). This was followed by the addition of triethyl amine (11 μL, 0.079 mmol) and diphenylphosphoryl azide (DPPA, 15.7 μL, 0.072 mmol). The flask was then fitted with a water condenser and an argon balloon and the reaction mixture was refluxed for 3 h. After cooling down to room temperature, water (3 mL) was added via syringe and the reaction mixture was refluxed again for 2 h. After cooling to room temperature, 2 N HCl (5 mL) and ethyl acetate (10 mL) were added and the layers separated. The aqueous layer was extracted with ethyl acetate (2 x 10 mL), the organic layers combined, washed twice with brine, dried over $MgSO_4$ and the solvent evaporated by rotary evaporation to afford the crude reaction product. This crude product was then subjected to column chromatography on silica gel with an eluent mixture of 1:9 ethyl acetate:hexanes to afford *(S)*-VAPOL **4** (56% yield, 20.8 mg, 0.039 mmol, >99% ee) and the lactone **29** (34% yield, 13.6 mg, 0.024 mmol). Spectral data for **29**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.92 (d, 1H, J = 13.5 Hz), 5.25 (d, 1H, J = 13.5 Hz), 6.54 (d, 2H, J = 7.1 Hz), 6.67 (d, 2H, J = 7.1 Hz), 6.89-6.98 (m, 4H), 7.04-7.10 (m, 2H), 7.60 (s, 1H), 7.64-7.76 (m, 7H), 7.79-7.85 (m, 2H), 7.95-8.0 (m, 2H), 9.29-9.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 71.29, 121.14, 122.01, 126.74, 126.82, 126.93, 127.01, 127.10, 127.25, 127.40, 127.49, 127.55, 127.83, 128.28, 128.37, 128.67, 128.84, 128.93, 128.94, 128.99, 129.12, 129.18, 129.21, 133.21, 133.47, 134.20, 135.03, 139.14, 139.24, 140.06, 140.45, 147.74, 154.25,

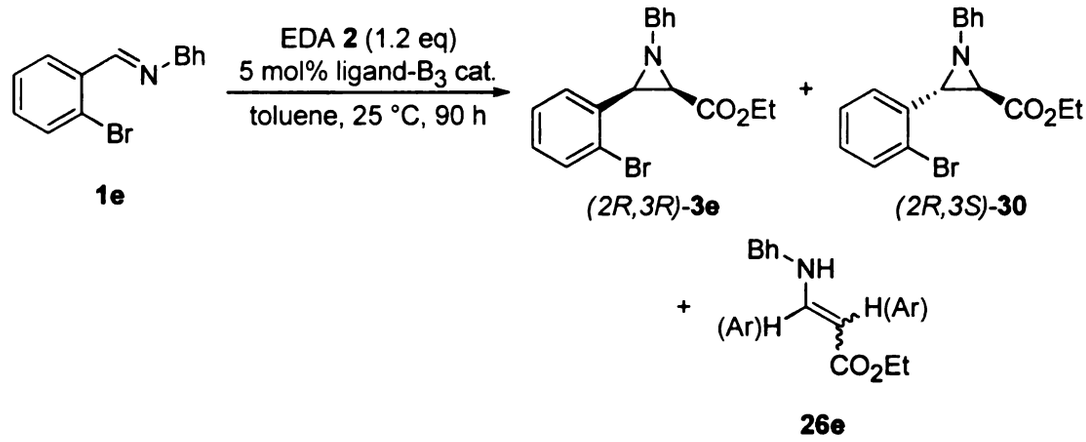
166.31; IR (thin film) 3055w, 2920w, 1761m, 1641m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 578 M^+ (32), 295 (17), 294 (100), 221 (25).



29 **4** **27** **4**

*Ethanolysis of the Lactone **29**.* A 25 mL round bottom flask was flame dried and cooled under argon and then the crude reaction mixture (**29**+**4**) from the Curtius rearrangement reaction (77.8 mg, 0.0975 mmol (scale determined from the amount of the original starting material – the carboxylic acid **28**)) was added which was dissolved in EtOH (4 mL) and THF (1.2 mL) to obtain a clear yellow solution. To this mixture was added K_2CO_3 (134.7 mg, 0.975 mmol) and the reaction mixture stirred for 6 h to obtain a brownish green slurry at which point the TLC indicated complete disappearance of the lactone **29**. To this solution was then added 2N HCl (5 mL) and diethyl ether (10 mL) and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 10 mL), the organic layers combined and washed twice with brine, dried over $MgSO_4$ and the solvent removed by rotary evaporation to give the crude reaction mixture. This was then subjected to purification by column chromatography on silica gel with an eluent mixture of 1:19 ethyl acetate:hexanes to afford *(S)*-VAPOL **4** (38% yield, 26.1 mg, 0.042 mmol, >99% ee) and the VAPOL-EDA adduct **27** (32% yield, 26.7 mg, 0.05 mmol).

Section 2.2 Aziridinations with *o*-bromophenyl benzhydryl imine: First glimpses of trans-aziridines



1e *(2R,3R)*-**3e** *(2R,3S)*-**30**

26e

The general aziridination procedure described for Section 2.1 was followed for this aziridination reaction. Thus, imine **1e** (1.4 g, 4 mmol) was reacted with 1.2 eq ethyl diazoacetate **2** (0.5 mL, 4.8 mmol) in the presence of the (*S*)-VAPOL-B_3 catalyst prepared as described in the general procedure to furnish the aziridination reaction. ^{1}H NMR analysis of the crude reaction mixture indicated a cis:trans ratio of 1.1:1. Column chromatography with an eluent system of 1:19 EtOAc:hexanes afforded the *cis*-aziridine **3e** in 42% isolated yield (725 mg, 1.66 mmol) as a white solid, the *trans*-aziridine **30** in 36% isolated yield (632 mg, 1.45 mmol) as a colorless oil and the enamines **26e** in 15% isolated yield (250.5 mg, 0.57 mmol) as a colorless oil.

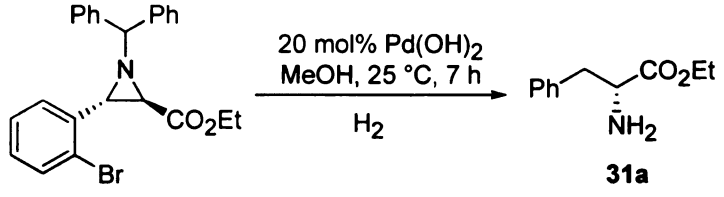
(2R,3R)-ethyl 1-benzhydryl-3-(2-bromophenyl)aziridine-2-carboxylate ***3e.*** Complete characterization data for *cis*-aziridine **3e** can be found above in the experimental information for Section 2.1.

(2R,3S)-ethyl 1-benzhydryl-3-(2-bromophenyl)aziridine-2-carboxylate ***30.*** The optical purity of the *trans*-aziridine **30** was determined to be 36% *ee* by

HPLC analysis (CHIRALCEL OD-H column, 99:1 hexanes/2-propanol, 222 nm, flow rate 0.7 mL/min). Retention times: R_t = 4.32 min (major enantiomer) and R_t = 10.84 min (minor enantiomer). Spectral data for **30**: R_f = 0.32 (1:19 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (t, 3H, *J* = 7.1 Hz), 2.83 (d, 1H, *J* = 2.7 Hz), 3.84 (d, 1H, *J* = 2.4 Hz), 4.05 (q, 2H, *J* = 7.1 Hz), 5.28 (s, 1H), 7.11 (t, 1H, *J* = 7.8 Hz), 7.22-7.38 (m, 8H), 7.52 (d, 1H, *J* = 7.0 Hz), 7.59 (t, 4H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 13.78, 44.62, 48.96, 60.98, 67.99, 123.48, 126.88, 127.20, 127.27, 127.30, 127.79, 127.92, 128.18, 128.41, 128.72, 131.96, 137.29, 142.78, 143.23, 168.09; IR (thin film) 3028m, 1726s, 1414m, 1332m, 1188s, 1026s cm^{-1}; mass spectrum *m/z* (% rel intensity) 437 M^+ (<1, ^{81}Br), 435 M^+ (<1, ^{79}Br), 364 (5, ^{81}Br), 362 (6, ^{79}Br), 270 (13, ^{81}Br), 268 (13, ^{79}Br), 193 (17), 167 (100), 165 (53), 84 (26); HRMS calcd for $C_{24}H_{23}NO_2Br$ (M+H) *m/z* 436.0912, meas 436.0897; $[\alpha]^{20}_D$ = -8.5 (*c* 1.0, CH_2Cl_2) on 36% *ee* (2*R*,3*S*)-**30**.

Determination of absolute configurations of trans-aziridine 30 and cis-aziridine 3e

Procedure for the hydrogenation[7b] of (2*R*,3*S*)-30 to give (*R*)-phenyl alanine ethyl ester 31a



(2R,3S)-**30** **31a**

Aziridine (2*R*,3*S*)-**30** with 36% *ee* (165 mg, 0.38 mmol) was added to a 100 mL round bottom flask, which had been previously flame-dried and cooled under Argon. It was then dissolved by the addition of 40 mL MeOH, which was

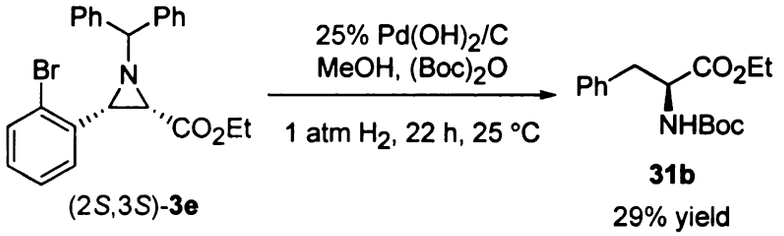
followed by the addition of $Pd(OH)_2$ (133 mg, 0.076 mmol, $Pd(OH)_2$ on carbon powder, 20% Pd, moisture *ca.* 60%). The flask was then equipped with a vacuum transfer adapter connected to vacuum and a balloon filled with hydrogen. The valve to vacuum (15-20 mm Hg) was opened for a few seconds, and then switched to the hydrogen balloon; this process was repeated 5 times. The suspension was then stirred at room temperature for 7 h. It was then filtered through a pad of Celite, washed with MeOH (20 mL), subjected to rotary evaporation until dryness and put on high vacuum for 5 minutes. To the resulting crude material was then added 10 mL diethyl ether and 8 mL sat. $NaHCO_3$ solution. This was extracted, and the aqueous layer extracted again with 5 X 10 mL ether. The organic layers were combined, dried with Na_2SO_4, filtered through a pad of Celite, subjected to rotary evaporation until dryness and put on high vacuum. The resulting crude product (a yellow oil) was then purified by column chromatography on regular silica gel with an eluent system of 1:6 hexanes:EtOAc to afford the product **31a** in 16% isolated yield (12 mg, 0.06 mmol) as a colorless/light yellow oil.

Spectral data for **31a**: R_f = 0.14 (1:6 hexanes:EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 2.53 (t, 3H, J = 7.1 Hz), 1.49 (br s, 2H), 2.87 (dd, 1H, J = 7.9, 13.6 Hz), 3.09 (dd, 1H, J = 5.4, 13.3 Hz), 3.72 (dd, 1H, J = 5.4, 7.7 Hz), 4.17 (q, 2H, J = 7.1 Hz), 7.20-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.14, 41.15, 55.85, 60.87, 126.74, 128.49, 129.27, 137.29, 175.01. Specific rotation found: $[\alpha]^{23}_D$ = -11.5 (*c* 1.2, EtOH). Literature rotations: $[\alpha]^{23}_D$ = -23.0 (*c* 3.2, EtOH) for *(R)*-

phenyl alanine ethyl ester.[6a] $[\alpha]^{23}_D$ = +23.8 (*c* 3.2, EtOH) for *(S)*-phenyl alanine ethyl ester.[28a]

The *trans*-aziridine (2*S*,3*R*)-**30** was also hydrogenated in a similar procedure as described above to give the *(S)*-phenyl alanine ethyl ester **31a** in 34% isolated yield. Specific rotation found: $[\alpha]^{20}_D$ = +6.6 (*c* 2.0, EtOH).

Procedure for the hydrogenation of (2*S*,3*S*)-3e to give 31b



(2*S*,3*S*)-**3e**

31b

29% yield

$[\alpha]^{23}_D$ found: -3.7 (*c* = 1, MeOH)

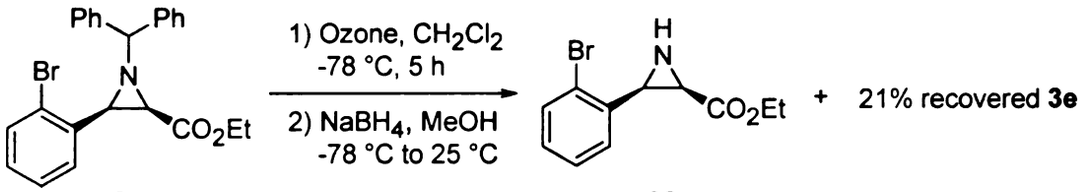
Literature values (ref. 28b): -4.4 (*c* = 1, MeOH)

(S)-ethyl 2-(tert-butoxycarbonylamino)-3-phenylpropanoate ***31b***. The procedure was identical to that followed for the conversion of **60a** to **75** (Chapter 3, Experimental Information). Thus, the cis-aziridine (2*S*,3*S*)-**3e** (200 mg, 0.46 mmol, 82% ee), $Pd(OH)_2/C$ (202 mg, 0.115 mmol, $Pd(OH)_2$ on carbon powder, 20% Pd, moisture *ca.* 60%), $(Boc)_2O$ (300 mg, 1.38 mmol) and MeOH (15 mL) were reacted accordingly at room temperature for 22 h to afford crude **31b**. Column chromatography with regular silica gel and an eluent mixture of 1:5 EtOAc:hexanes afforded pure **31b** as a colorless oil in 29% isolated yield (38 mg, 0.13 mmol).

Data for ***31b***: R_f = 0.30 (1:5 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24 (t, 3H, *J* = 7.0 Hz), 1.44 (s, 9H), 3.05-3.15 (m, 2H), 4.17 (q, 2H, *J* = 7.1 Hz), 4.58 (bd, 1H, *J* = 7.4 Hz), 5.00 (bd, 1H, *J* = 6.4 Hz), 7.15 (d, 2H, *J* = 6.9 Hz),

7.24-7.32 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.08, 28.28, 38.39, 54.43, 61.23, 79.80, 126.93, 128.45, 129.34, 136.09, 155.07, 171.84; For optical rotations, see Scheme above.

Cleavage of the benzhydryl group by ozonalysis



3e **32** 48% yield

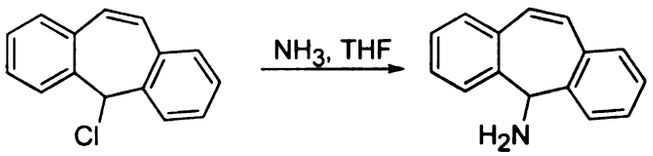
(2R,3R)-ethyl 3-(2-bromophenyl)aziridine-2-carboxylate ***32.*** The ozonolysis reaction was carried out according to a procedure previously published by our group.[7b] Thus, the cis-aziridine **3e** (436 mg, 1 mmol) of 88% ee was subjected to ozone under the reported conditions, and the resulting crude mixture was subjected to regular column chromatography with an eluent system of 2:1 ether:pentane to afford the *N*-H aziridine **32** in 48% isolated yield (130 mg, 0.48 mmol), as a colorless oil, which became a white solid (mp 55-57 °C) upon applying high vacuum (0.1 mm Hg). The reaction went to 71% conversion (determined by the ^1H NMR analysis of the crude reaction mixture), and 21% starting material (**3e**) was isolated after column chromatography.

Spectral data for **32**: R_f = 0.27 (2:1 ether:pentane); ^1H NMR (*d*-DMSO, 500 MHz, 110 °C) δ 0.91 (t, 3H, *J* = 7.1 Hz), 2.58 (bs, 1H), 3.06 (m, 1H), 3.42 (m, 1H), 3.84 (q, 2H, *J* = 7.1 Hz), 7.16 (t, 1H, *J* = 5.6 Hz), 7.29 (t, 1H, *J* = 6.1 Hz), 7.31-7.52 (m, 2H); ^{13}C NMR (*d*-DMSO, 500 MHz, 110 °C) (1 aryl sp^2 carbon not located) δ 13.00, 35.93, 38.52, 59.13, 122.89, 126.04, 128.17, 129.70, 130.90,

167.77; IR (thin film) 3310m, 3063w, 2982m, 1736s, 1439m, 1201s, 1026m, 750m cm^{-1}; mass spectrum *m/z* (% rel intensity) M^+ 272 (100, ^{81}Br), 270 (97, ^{79}Br); HRMS calcd for $C_{11}H_{13}NO_2Br$ *m/z* 270.0130, meas 270.0136; $[\alpha]^{23}_D$ = -87.8 (*c* = 1.0, CH_2Cl_2).

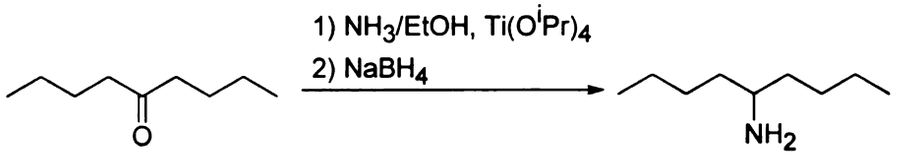
Section 2.3 Aziridinations with 5-nonylimine, dicyclohexylmethylimine and *5H*–dibenzo[*a,d*]cyclohepten-5-imine

The amines dicyclohexylmethylamine[29], 5-aminononane[29], and 5*H*-dibenzo*[a,d]*cyclohepten-5-amine[30], for imines **35**, **34** and **36** respectively, are all known compounds and were prepared according to or in an analogous manner to literature procedures.



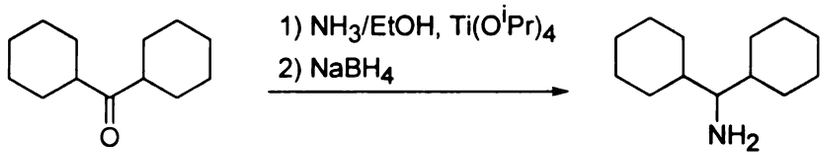
5H–dibenzo[a,d]cyclohepten-5-amine.[30] A 1 L three neck round bottom flask equiped with a magnetic stirring bar, a dropping funnel and a dry ice isopropanol cooler fitted with an oil bubbler in a dry ice isopropanol bath was charged with 5 mL dry THF. Then 20 mL ammonia was condensed in. 5-Chloro-5*H*-dibenzo*[a,d]*cycloheptene (1 g, 4.41 mmol) dissolved in 20 mL dry THF was added dropwise over 30 min. The yellowish solution was stirred for another 30 min and then warmed to room temperature. All volatiles were removed under reduced pressure and the residue dissolved in 20 mL diethylether. The organic phase was washed twice with brine, dried over sodium sulfate and the solvent removed under reduced pressure. The yellow oil was recrystallized from hot hexanes or flash chromatographed over silica gel with dichloromethane:ethanol

20:1 to give the product as a white solid (mp. 112°C) in 83% yield (0.76 g, 3.67 mmol). 5*H*–dibenzo*[a,d]*cyclohepten-5-amine in solution exists as endo and exo forms which leads to a doubling of some of the signals in the NMR spectrum. The signals have not been assigned. Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.96 (bs, 2 H), 4.74 (bs, 0.5 H), 5.15 (bs, 0.5 H), 7.16 (s, 2 H), 7.29-7.81 (m, 8 H).

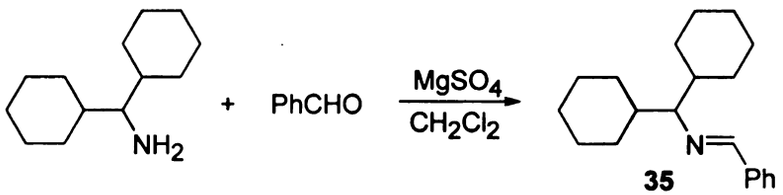


5-aminononane.[29] A 100 mL RBF, flame dried and cooled under Argon, was fitted with a rubber septum and an Argon balloon. To it was added sequentially, 5-nonanone (2.5 g, 17.6 mmol), freshly distilled $Ti(O^iPr)_4$ (2 g, 35.2 mmol) and 2 M NH_3•EtOH solution (44 mL, 88 mmol), and the reaction mixture was stirred at room temperature for 10 h. $NaBH_4$ (1 g, 26.4 mmol) was then added, and the reaction mixture stirred at room temperature for 6 h. The reaction mixture was then added to 50 mL 2 M NH_4Cl solution and filtered through a plug of Celite. The resulting liquid was then extracted with EtOAc and the aqueous layer washed twice with EtOAc. The organic layers were combined and extracted with 80 mL 1 M HCl. The aqueous layer from this extraction was extracted once with EtOAc, and then treated with 2 M NaOH solution till a pH of 10-12 was attained, and was then extracted with EtOAc thrice. All organic layers were combined, washed with brine, twice with sat. $NaHCO_3$ solution, again with brine and finally dried over Na_2SO_4. This was then filtered through a plug of Celite, subjected to rotary evaporation and high vacuum (20 mm Hg) for 5 minutes to get the crude product as a yellow liquid. This crude liquid was then subjected to

vacuum distillation (~20 mm Hg pressure) to isolate the pure product (bp. 90 °C, 40 mm Hg) as a colorless liquid in 36% yield (0.92 g, 6.43 mmol). Spectral data: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84-0.90 (m, 6H), 1.15-1.59 (m, 14H), 2.60-2.78 (m, 1H).



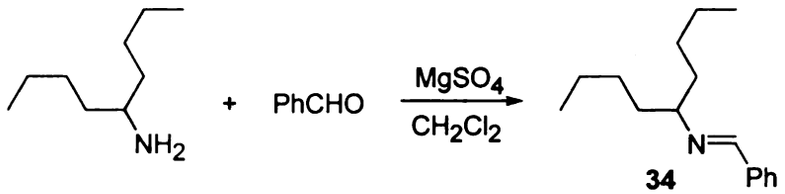
Dicyclohexylmethylamine.[29] This was prepared in an analogous manner to the preparation of 5-aminononane described above. The only difference in the procedure was that during the first step (NH_3/EtOH and $Ti(O^iPr)_4$), the reaction mixture was refluxed for 18 h. Thus, dicyclohexyl ketone (1.86 g, 9.6 mmol) was reacted as described above, to obtain the crude product as a viscous yellow liquid. The crude product was purified by a Kugeror bulb-to-bulb distillation (at ~1-2 mm Hg pressure) to afford the pure product (bp. ~277 °C, 760 mm Hg) as a light yellow oil in 74% yield (1.39 g, 7.13 mmol). Spectral data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90-1.38 (m, 14 H), 1.53-1.78 (m, 10H), 2.17 (t, 1H, J = 5.9 Hz).



N-benzylidene-1,1-dicyclohexylmethanamine ***35.*** The standard procedure described above for the preparation of imine **1b** was followed with the dicyclohexylmethylamine (1.39 g, 7.13 mmol). The crude product was purified by

crystallization (pure hexanes, single crop) to give **35** as a pale white solid (mp 74-76 °C) in 53% yield (1.08 g, 3.8 mmol).

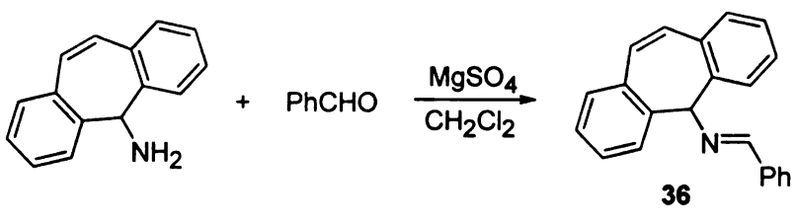
Spectral data for **35**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84-1.30 (m, 10H), 1.56-1.76 (m, 12H), 2.54 (t, 1H, *J* = 5.9 Hz), 7.37-7.40 (m, 3H), 7.71-7.73 (m, 2H), 8.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.45, 26.61, 26.66, 28.87, 30.80, 38.48, 82.19, 128.12, 128.46, 130.08, 136.56, 159.08; IR (thin film) 2928s, 2851s, 1645m, 1448m, 1307w cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 284 $M+1^{+}$ (100), 102 (5); Anal calcd for $C_{20}H_{29}N$: C, 84.75; H, 10.31; N, 4.94. Found: C, 84.44; H, 10.73; N, 4.97.



34

N-benzylidenenonan-5-amine ***34***. The standard procedure described above for the preparation of imine **1b** was followed with 5-aminononane (0.92 g, 6.42 mmol). The crude product was obtained as a colorless oil after work-up in 95% yield (1.4 g, 6.1 mmol), and was used in the aziridination reaction as such.

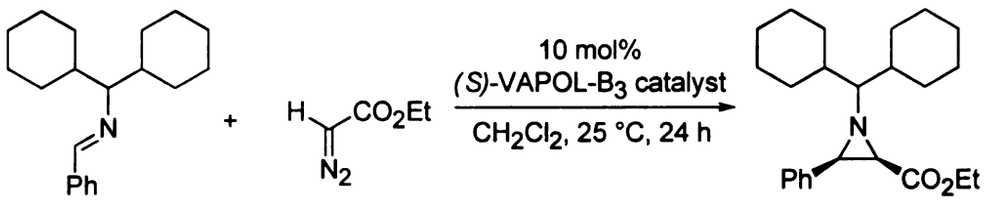
Spectral data for **34**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.85 (t, 6H, *J* = 7.2 Hz), 1.09-1.34 (m, 8H), 1.54-1.65 (m, 4H), 3.01-3.06 (m, 1H), 7.37-7.40 (m, 3H), 7.71-7.73 (m, 2H), 8.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.08, 22.65, 28.77, 36.05, 71.99, 128.09, 128.50, 130.25, 136.49, 159.02.



36

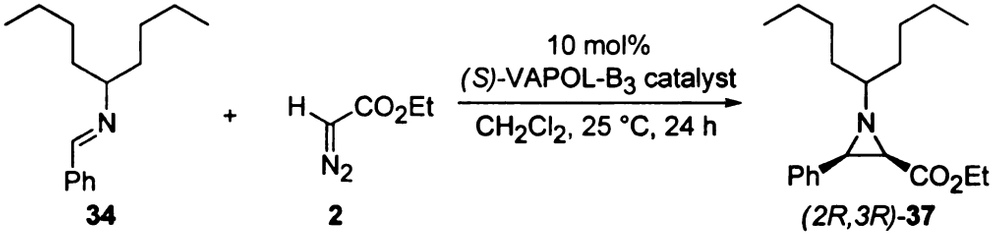
Imine ***36***. The standard procedure described above for the preparation of imine **1b** was followed with 5*H*-dibenzo*[a,d]*cyclohepten-5-amine (0.75 g, 3.63 mmol). The crude product was purified by crystallization (1:10 EtOAc:hexanes, 2 crops) to give **36** as white crystals (mp 136-139 °C) in 49% yield (0.62 g, 2.10 mmol).

Spectral data for **36**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.96 (bs, 1H), 7.14 (bs, 2H), 7.21 (t, 2H, J = 7.4 Hz), 7.33-7.36 (m, 4H), 7.46 (bs, 3H), 7.75-7.94 (m, 4H), 8.33 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 72.13, 124.59, 125.97, 127.84, 128.51, 128.52, 128.63, 130.88, 131.23, 133.29, 136.39, 141.36, 161.52; IR (thin film) 3063w, 3024w, 1649m, 1483w, 796m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 296 M+1^{+} (19), 192 (37), 191 (100); Anal calcd for $C_{22}H_{17}N$: C, 89.46; H, 5.80; N, 4.74. Found: C, 89.16; H, 5.84; N, 4.59.



(2R,3R)-ethyl 1-(dicyclohexylmethyl)-3-phenylaziridine-2-carboxylate ***38***. The standard procedure for the preparation of aziridine **3b** described above was followed from imine **35** (283 mg, 1 mmol). The crude product was purified by silica gel chromatography (1:40 EtOAc/hexanes as elute) to give **38** as a white solid (mp 64-66 °C) in 18% yield (65 mg, 0.18 mmol). An optical purity of 74% ee was determined by HPLC analysis (Chiralcel OD-H column, 222 nm, 99:1 hexane/*i*-PrOH, flow rate: 0.7 mL/min). Retention times: R_t = 3.43 min for *(2R,3R)*-**38** and R_t = 3.86 min for *(2S,3S)*-**38**.

Spectral data for **38**: R_f = 0.32 (1:19 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.99 (t, 3H, *J* = 7.1 Hz), 1.13-1.35 (m, 10H), 1.58-1.94 (m, 13H), 2.46 (d, 1H, *J* = 6.7 Hz), 2.88 (d, 1H, *J* = 6.8 Hz), 3.92-3.99 (m, 2H), 7.21-7.24 (m, 1H), 7.27-7.30 (t, 2H, *J* = 7.2 Hz), 7.41-7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.96, 26.56, 26.70, 26.91, 26.94, 27.06, 27.18, 29.98, 30.03, 31.85, 32.48, 41.56, 42.03, 46.30, 46.90, 60.30, 79.29, 127.02, 127.63, 128.00, 135.74, 168.55; IR (thin film) 2948s, 1743s, 1195vs cm^{-1}; Mass spectrum: *m/z* (% rel intensity) M+1$^+$ 370 (100), 301 (27), 217 (10); HRMS calcd for $C_{24}H_{36}NO_2$ (M+H) *m/z* 370.2746, meas 370.2764; $[\alpha]^{23}_D$ = +4.1 (*c* 1.0, CH_2Cl_2) on 70% ee *(2S,3S)*-**38**.

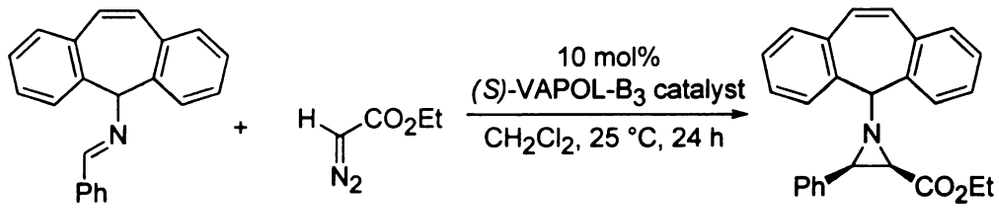


34 **2** *(2R,3R)*-**37**

(2R,3R)-ethyl 1-(nonan-5-yl)-3-phenylaziridine-2-carboxylate ***37.*** The standard procedure for the preparation of aziridine **3b** described above was followed from imine **34** (231 mg, 1 mmol). The crude product was purified by silica gel chromatography and prep TLC (1:19 EtOAc/hexanes as elute) to give **37** as a colorless oil in 27% yield (86 mg, 0.27 mmol). An optical purity of 84% ee was determined by HPLC analysis (Chiralcel OD-H column, 222 nm, 100% hexanes, flow rate: 1 mL/min). Retention times: R_t = 2.59 min for *(2R,3R)*-**37** and R_t = 2.90 min for *(2S,3S)*-**37**.

Spectral data for **37**: R_f = 0.30 (1:25 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86-1.00 (m, 9H), 1.26-1.68 (m, 13H), 2.52 (d, 1H, *J* = 6.8 Hz), 2.96

(d, 1H, J = 6.8 Hz), 3.88-4.09 (m, 2H), 7.25-7.34 (m, 3H), 7.43-7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.84, 13.90, 13.99, 22.93, 23.05, 27.96, 28.03, 33.78, 34.05, 45.52, 47.11, 60.39, 69.55, 127.13, 127.71, 127.81, 135.70, 168.53; IR (thin film) 2986s, 1751s, 1297vs, 946m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) $M+1^+$ 318 (100), 217 (9); HRMS calcd for $C_{20}H_{32}NO_2$ (M+H) *m/z* 318.2433, meas 318.2428; $[\alpha]^{23}_D$ = +3.6 (*c* 1.0, CH_2Cl_2) on 79% ee *(2S,3S)*-**37**.



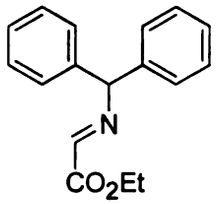
*Aziridine **39**.* The standard procedure for the preparation of aziridine **3b** described above was followed from imine **36** (147 mg, 0.5 mmol). The crude product was purified by silica gel chromatography (1:19 EtOAc:hexanes as elute) to give **39** as a white solid (mp 174-176 °C) in 65% yield (124 mg, 0.33 mmol). An optical purity of 96% ee was determined by HPLC analysis (Chiralcel OD-H column, 222 nm, 95:5 hexanes:*i*-PrOH, flow rate: 1 mL/min). Retention times: R_t = 6.1 min for *(2R,3R)*-**39** and R_t = 3.2 min for *(2S,3S)*-**39**.

Spectral data for **39**: R_f = 0.21 (1:19 EtOAc/hexanes); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (t, 3H, J = 7.1 Hz), 2.60 (d, 1H, J = 7.1 Hz), 3.05 (d, 1H, J = 6.8 Hz), 3.36 (s, 1H), 4.03-4.10 (m, 2H), 7.13 (d, 2H, J = 2.2 Hz), 7.16-7.20 (m, 1H), 7.24-7.36 (m, 5H), 7.41 (t, 2H, J = 7.6 Hz), 7.50 (t, 1H, J = 7.1 Hz), 7.69 (d, 2H, J = 7.1 Hz), 7.91 (d, 1H, J = 7.8 Hz), 8.31 (d, 1H, J = 8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.02, 47.68, 48.47, 60.68, 72.72, 124.03, 124.47, 125.99, 126.13,

127.46, 127.49, 127.51, 127.78, 127.93, 128.69, 127.88, 131.06, 131.11, 133.29, 133.32, 134.99, 138.92, 139.15, 167.44; IR (thin film) 3084s, 3049s, 1746m, 1263m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) $M+1^+$ 382 (100), 301 (26), 192 (25), 191 (83); HRMS calcd for $C_{26}H_{24}NO_2$ (M+H) *m/z* 382.1807, meas 382.1798; $[\alpha]^{23}_D$ = -61.1 (*c* 1.0, CH_2Cl_2) on 96% ee *(2R,3R)*-**39**.

Section 2.4 cis-2,3-Dicarbonylaziridines from the Wulff aziridination

The procedures for the formation of the imines **40** and the aziridines **41** were identical to the general procedures reported above for the imine **1b** and the aziridine **3b** respectively. ^{t}Butyl diazoacetate **19** is commercially available from Aldrich, and can also be prepared according to previously reported procedures.[31,32]

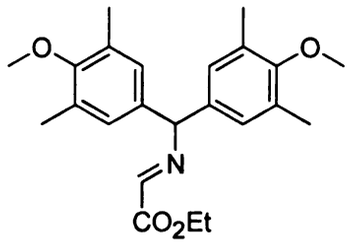


40a

*Ethyl 2-(benzhydrylimino)acetate **40a**.* This imine was prepared in a similar manner as described in the general procedure, from diphenylmethanamine (0.94 g, 5.16 mmol) and freshly distilled ethyl glyoxalate solution (50% in toluene), and was obtained as a viscous yellow oil from the reaction in 95% yield (1.31 g, 4.90 mmol). However, it solidified when kept in the refrigerator for 2 days and this light yellow crude solid was used in the aziridination reaction as such without further purification.

Spectral data for **40a**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (t, 3H, *J* = 7.1 Hz), 4.37 (q, 2H, *J* = 7.1 Hz), 5.71 (s, 1H), 7.27-7.30 (m, 2H), 7.33-7.37 (m, 8H),

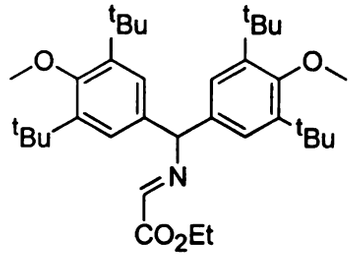
7.80 (d, 1H, J = 1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.09, 61.75, 77.42, 127.46, 127.77, 128.56, 141.53, 153.70, 163.10.



40b

Ethyl 2-(bis(4-methoxy-3,5-dimethylphenyl)methylimino)acetate ***40b.*** This imine was prepared in a similar manner as described in the general procedure, from the MEDAM amine (1.54 g, 5.16 mmol) and freshly distilled ethyl glyoxalate solution (50% in toluene), and was obtained as a viscous yellow oil from the reaction in 93% yield (1.83 g, 4.78 mmol). However, it solidified when kept in the refrigerator for 2 days and this light yellow crude solid was used in the aziridination reaction as such without further purification.

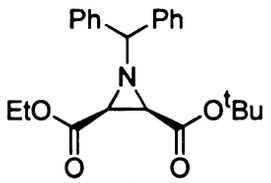
Spectral data for **40b**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.33 (t, 3H, J = 7.1 Hz), 2.23 (s, 12H), 3.67 (s, 6H), 4.32 (q, 2H, J = 7.1 Hz), 5.42 (s, 1H), 6.92 (s, 4H), 7.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.15, 16.14, 59.61, 61.74, 77.25, 127.97, 130.93, 136.99, 153.22, 156.24, 163.27.



40c

Ethyl 2-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methylimino)acetate ***40c.*** This imine was prepared in a similar manner as described in the general procedure, from the BUDAM amine (2.84 g, 6.10 mmol) and freshly distilled ethyl glyoxalate solution (50% in toluene). Crystallization (1:20 ethyl acetate/hexanes) afforded imine **40c** in 75% isolated yield as white crystals (mp 118-120 °C).

Spectral data for **40c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.33 (t, 3H, J = 7.2 Hz), 1.36 (s, 36H), 3.62 (s, 6H), 4.33 (q, 2H, J = 7.1 Hz), 5.53 (s, 1H), 7.07 (s, 4H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 14.14, 32.01, 35.79, 61.68, 64.22, 77.79, 126.35, 134.97, 143.45, 152.94, 158.80, 163.52; IR (thin film) 2961s, 2912w, 1753m, 1724m, 1414s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) $M+1^{+}$ 552 (10), 452 (100); Anal calcd for $C_{35}H_{53}NO_4$: C, 76.18; H, 9.68; N, 2.54. Found: C, 75.94; H, 10.12; N, 2.53.

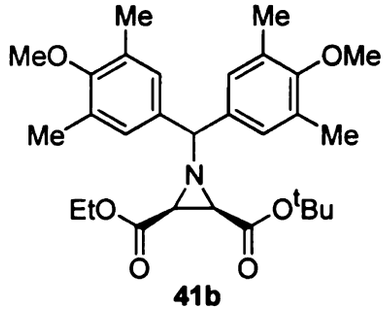


41a

(2R,3S)-tert-butyl 1-benzhydryl-3-propionylaziridine-2-carboxylate ***41a.*** The standard procedure for the aziridination was followed from imine **40a** (66 mg, 0.25 mmol). The reaction temperature was -40 °C for 24 h followed by room temperature for 12 h. The crude product was purified by silica gel chromatography with an eluent system of 1:9 EtOAc:hexanes to afford the pure product **41a** as a white solid (mp 144-146 °C) in 65% isolated yield (62 mg, 0.16 mmol). An optical purity of 4% ee was determined by HPLC analysis (Chiralcel

OD-H column, 222 nm, 95:5 hexanes:^{i}PrOH, flow rate: 1 mL/min). Retention times: R_t = 3.6 min for *(2S,3R)*-**41a** and R_t = 7.5 min for *(2R,3S)*-**41a**.

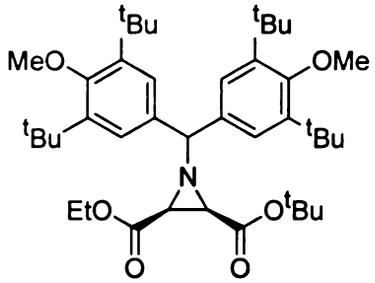
Spectral data for **41a**: R_f = 0.09 (1:15 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, 3H, *J* = 7.1 Hz), 1.42 (s, 9H), 2.60-2.66 (m, 2H), 3.88 (s, 1H), 4.09-4.23 (m, 2H), 7.19-7.23 (m, 2H), 7.26-7.31 (m, 4H), 7.49-7.54 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.08, 27.90, 43.52, 44.59, 61.13, 76.74, 81.80, 127.33, 127.37, 127.38, 127.41, 128.34, 128.39, 141.76, 141.78, 166.02, 167.19; IR (thin film) 3065w, 2980w, 1745s, 1732m, 1238m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) M+1$^+$ 382 (100), 326 (32), 167 (50); HRMS calcd for $C_{23}H_{28}NO_4$ (M+H) *m/z* 382.2018, meas 382.2016.



41b

(2R,3S)-tert-butyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-propionylaziridine-2-carboxylate ***41b.*** The standard procedure for the aziridination was followed from imine **40b** (96 mg, 0.25 mmol). The reaction temperature was 0 °C for 24 h. The crude product was purified by silica gel chromatography with an eluent system of 1:5 EtOAc:hexanes to afford the pure product **41b** as a light yellow solid (mp 82-85 °C) in 80% isolated yield (100 mg, 0.2 mmol). An optical purity of 14% ee was determined by HPLC (Chiralcel OD-H column, 222 nm, 99:1 hexanes:^{i}PrOH, flow rate: 0.7 mL/min). Retention times: R_t = 12.5 min for *(2S,3R)*-**41b** and R_t = 18.2 min for *(2R,3S)*-**41b**.

Spectral data for **41b**: R_f = 0.1 (1:9 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, 3H, *J* = 7.1 Hz), 1.41 (s, 9H), 2.22 (s, 12H), 2.44-2.51 (m, 2H), 3.54 (s, 1H), 3.65 (s, 6H), 4.08-4.24 (m, 2H), 7.11 (s, 2H), 7.12 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.16, 16.14, 27.93, 43.93, 44.57, 59.56, 61.11, 76.24, 81.71, 127.52, 127.66, 130.55, 130.57, 137.12, 137.22, 156.04, 156.10, 166.29, 167.31; IR (thin film) 2980s, 2934s, 2866w, 2826w, 1751s, 1483m, 1369s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) M+1$^+$ 498 (100), 283 (45); HRMS calcd for $C_{29}H_{40}NO_6$ (M+H) *m/z* 498.2856, meas 498.2847; $[\alpha]^{23}_D$ = +0.6 (*c* 1.0, CH_2Cl_2) on 46% ee *(2S,3R)*-**41b**.



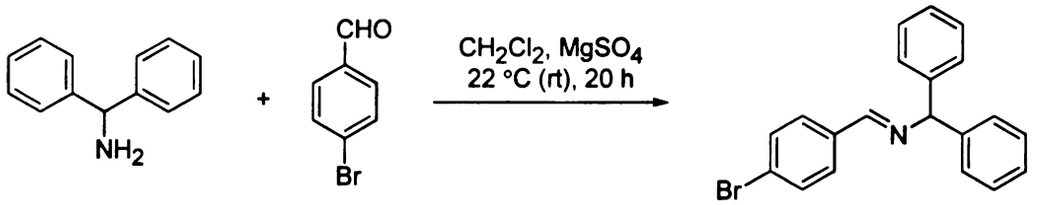
41c

(2R,3S)-tert-butyl 1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-propionylaziridine-2-carboxylate ***41c***. The standard procedure for the aziridination was followed from imine **40c** (138 mg, 0.25 mmol). The reaction temperature was 0 °C for 24 h. The crude product was purified by silica gel chromatography with an eluent system of 1:19 EtOAc:hexanes to afford the pure product **41c** as a light yellow solid (mp 96-99 °C) in 58% isolated yield (97 mg, 0.14 mmol). An optical purity of 15% ee was determined by HPLC analysis (Pirkle Covalent *(R,R)* Whelk O1 column, 222 nm, 99:1 hexanes:^{i}PrOH, flow rate:

0.7 mL/min). Retention times: R_t = 9.4 min for *(2S,3R)*-**41c** and R_t = 10.3 min for *(2R,3S)*-**41c**.

Spectral data for **41c**: R_f = 0.2 (1:19 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.27 (t, 3H, *J* = 7.1 Hz), 1.41 (s, 36H), 1.44 (s, 9H), 2.60-2.64 (m, 2H), 3.67 (s, 6H), 3.76 (s, 1H), 4.14-4.24 (m, 2H), 7.27 (s, 2H), 7.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.19, 27.96, 32.09, 35.74, 44.26, 44.77, 61.15, 64.03, 76.60, 81.60, 125.65, 125.76, 135.67, 135.86, 143.03, 143.04, 158.43, 158.46, 166.17, 167.32; IR (thin film) 2983s, 2870w, 1757s, 1730m, 1414m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) M+1$^+$ 666 (2), 451 (100); HRMS calcd for $C_{41}H_{64}NO_6$ (M+H) *m/z* 666.4734, meas 666.4742; $[\alpha]^{23}_D$ = +0.5 (*c* 1.0, CH_2Cl_2) on 15% ee *(2R,3S)*-**41c**.

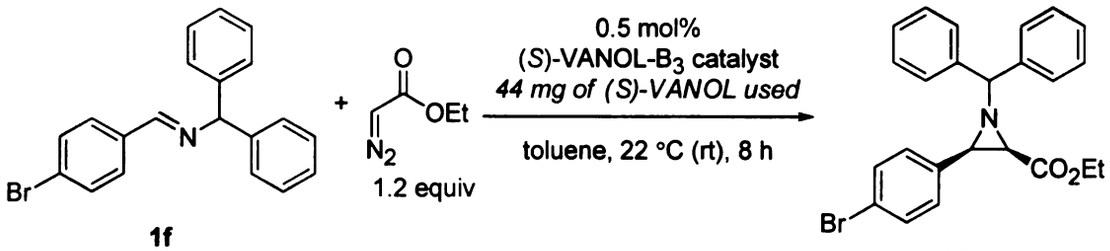
Section 2.5 A gram scale catalytic asymmetric aziridination process



58.14 mmol scale
(10.64 g)

1.1 equiv

1f
84-85% yield (17.04-17.36 g, single crop)



1f
20 mmol scale (7 g)

1.2 equiv

3f
1st crop: 62-64% yield (5.41-5.59 g)
99% ee
2nd crop: 25-27% yield (2.20-2.35 g)
75-78% ee
overall: 89% yield (7.76-7.79 g)
92-93% ee

*N-(4-bromobenzylidene)-1,1-diphenylmethanamine (**1f**).*[8] A 250 mL round-bottom flask with a single 24/40 neck was fitted with a pear-shaped magnetic stir bar (2.5 × 1.3 × 1.3 cm) and a 24/40 vacuum adapter. This assembly was flame dried under high vacuum (0.1 mm Hg) and cooled under a slight positive pressure of Argon. To this flask was then sequentially added 4-bromobenzaldehyde (11.84 g, 63.95 mmol, 1.1 equiv) and $MgSO_4$ (14 g, 116.28 mmol, 2 equiv) (Note 1). This was followed by the addition of 60 mL dry dichloromethane (Note 1), via a plastic syringe fitted with a metallic needle, along the neck and the sides of the flask such that all solids could be brought to the bottom of the flask. The vacuum adapter was then replaced with a rubber septum and an Argon balloon. The mixture was stirred at room temperature (22 °C) to get a white slurry. Aminodiphenylmethane (10 mL, 58.14 mmol, 1 equiv) was then added to the solution through the rubber septum, via a plastic syringe fitted with a metallic needle (Note 1). The resulting white slurry was stirred at room temperature (22 °C) for 20 h, at which time the reaction was complete (Note 2). A different 250 mL round bottom flask (24/40 single neck) was fitted with a filter adapter and a glass fritted funnel (60 mL, 4.5 × 5.5 cm) packed with Celite (1 cm height). The reaction mixture was then filtered through the fritted funnel; the reaction flask was rinsed with 15 mL dichloromethane three times and the rinse added to the funnel each time (Note 3). The fritted funnel and the Celite bed were then washed twice with 15 mL dichloromethane. The fritted funnel was removed, the filter adapter rinsed with 10 mL dichloromethane and the solution of the crude product was then subjected to rotary evaporation until drynress (20 mm Hg, 35-

45 °C) followed by high vacuum (0.1 mm Hg) for 3 h. This afforded the crude imine product **1f** as an off-white solid (21.25-21.41 g). For crystallization, the 250 mL round bottom flask containing the crude product was fitted with a water condenser, a rubber septum and an Argon balloon. A mixture of 20 mL of 1:5 ethyl acetate:hexanes was added via a plastic syringe fitted with a metallic needle (Note 4). This solution was brought to a boil while swirling by hand over a heat gun. An additional 15 mL portion of the 1:5 ethyl acetate:hexanes mixture was then added slowly with continued boiling and swirling (total volume 35 mL). At this time, a clear pale yellow solution of the crude product was obtained; this was placed on a wooden cork and left untouched for 19 h. The resulting crystals were then broken up into small pieces by a spatula, and these were collected by filtration on a Büchner funnel (6 cm d × 3.5 cm h). The crystallization flask was rinsed twice with 10 mL cold (0 °C) hexanes and the rinse added each time to the Büchner funnel. The resulting crystals were transferred to a 50 mL single neck round bottom flask and subjected to high vacuum (0.1 mm Hg) for 4 h. This afforded the product imine **1f** as white crystals (mp. 95-97 °C) in 84-85% yield (17.04-17.36 g, 48.69-49.60 mmol) (Notes 5, 6).

*(2R,3R)-ethyl 1-benzhydryl-3-(4-bromophenyl)aziridine-2-carboxylate (**3f**).*[8] A 100 mL glass Schlenk flask fitted with a magnetic stir bar (3.8 × 1 × 1 cm) was connected via a rubber tube to a double manifold vacuum line with an Argon ballast (Note 7, 8). The flask was then flame dried under high vacuum (0.05 mm Hg) and cooled under a slight positive pressure of Argon. To the flask was added sequentially (*S*)-VANOL (44 mg, 0.1 mmol, 0.005 equiv) and triphenyl borate

(116 mg, 0.4 mmol, 0.02 equiv) under a slight positive pressure of Argon (Note 9). Thereafter, 4 mL dry toluene (Note 1) was added along the sides of the Schlenk flask via a plastic syringe fitted with a magnetic needle which had been pre-flushed with Argon. This was followed by the addition of water (1.8 μL, 0.1 mmol, 0.005 equiv) via a glass syringe. The flask was then sealed and stirred at 80 °C in an oil bath (bath temperature) for 1 h. Thereafter, the valve on the double manifold connected to the Schlenk flask was turned to high vacuum (0.05 mm Hg). The threaded valve on the Schlenk flask was then carefully and gradually opened to the high vacuum, and the solvent was removed (Note 10). After all solvent was removed, the Schlenk flask was allowed to remain at 80 °C in the oil bath for an additional 0.5 h exposed to high vacuum. The flask was then removed from the oil bath and cooled to room temperature under a slight positive pressure of Argon (*ca.* 20 min) to afford the pre-catalyst as a colorless/off-white oil stuck to the sides of the Schlenk flask. To this was then added, under a slight positive pressure of Argon, the imine **1f** (7.00 g, 20 mmol, 1 equiv), followed by the addition of 20 mL dry toluene along the sides of the Schlenk flask via a plastic syringe fitted with a magnetic needle (pre-flushed with Argon). The magnetic stir bar at this point was stuck to the Schlenk flask, the flask was swirled by hand until the stir bar became free (Note 11). Additional dry toluene (5 mL) was then added along the sides of the Schlenk flask, and the solution was stirred at room temperature for 5-10 min to obtain a clear pale yellow solution of the catalyst-imine complex. Under a slight positive pressure of Argon, ethyldiazoacetate (2.5 mL, 24 mmol, 1.2 equiv) was then added to the

Schlenk flask via a plastic syringe fitted with a magnetic needle (pre-flushed with Argon) (Note 9). The clear solution in the Schlenk flask turned dark yellow/orange with this addition, and vigorous nitrogen evolution was observed. Within 1 h, the product aziridine started precipitating out, and the entire reaction mixture turned into a pale yellow semi-solid mass. The reaction was stirred at room temperature under a slight positive pressure of Argon for a total of 8 h, at which point the reaction was complete (Note 12).

Dichloromethane (30 mL) was added to the Schlenk flask (Note 3) and the resulting mixture was stirred to obtain a clear yellow solution of the crude aziridine product. This was then added, via a plastic funnel, to a pre-weighed 250 mL round bottom flask with a single neck (24/40 joint). The Schlenk flask was rinsed twice with 20 mL dichloromethane, the plastic funnel with 5 mL dichloromethane, and the rinse added each time to the round bottom flask. This was then subjected to rotary evaporation (20 mm Hg, 35-45 °C) until *ca.* 25 mL of the crude product solution was left in the flask. Hexanes (50 mL) were added to the flask at this point, and the solution was again subjected to rotary evaporation to dryness and finally to high vacuum (0.1 mm Hg) for 12 h to afford the crude aziridine product **3f** as an off-white solid (8.89-8.91 g). This was then dissolved in 30 mL dichloromethane to obtain a clear yellow solution and was allowed to stand at room temperature for 15 min. A different pre-weighed 250 mL round bottom flask (24/40 single neck) was fitted with a filter adapter and a glass fritted funnel (30 mL, 3.5 × 5.0 cm) packed with Celite (1 cm height). The crude product solution was filtered through the fritted funnel; the flask was rinsed twice with 20

mL dichloromethane and the rinse added to the funnel. The sides of the fritted funnel and the Celite bed were then washed with 20 mL dichloromethane. The fritted funnel was removed and the filter adapter rinsed with 10 mL dichloromethane and this crude product solution was then subjected to rotary evaporation to dryness (20 mm Hg, 35-45 °C) followed by high vacuum (0.1 mm Hg) for 4 h. This afforded the crude aziridine product **3f** again as an off-white solid.

For crystallization, the 250 mL round bottom flask containing the crude product was fitted with a water condenser, a rubber septum and an Argon balloon. A mixture of 1:3 dichloromethane:hexanes (30 mL) was added via a plastic syringe fitted with a metallic needle (Note 3, 4). This solution was brought to a boil while swirling by hand over a heat gun. An additional portion (60 mL) of the 1:3 dichloromethane:hexanes solvent mixture was then added slowly (total volume 90 mL). The solution was continually heated at boil over the heat gun and swirled by hand until all the solids had dissolved and a clear pale yellow solution of the crude product was obtained; this was placed on a wooden cork and left untouched for 1 h. The condenser was then removed, and the crystallization flask allowed to stand open to air at room temperature for an additional 27 h. During this time, a very small amount of light cloudy material appeared at the bottom of the flask, followed by needle-like white crystals. After a total of 28 h, the supernatant was then carefully decanted, so as to not disturb the crystals, into another 500 mL round bottom flask (24/40 single neck) via a plastic funnel. Cold hexanes (-20 °C, 50 mL) was gently added to the

crystallization flask, the flask gently swirled by hand, and the supernatant solution was again added via decantation to the 500 mL round bottom flask. The hexane wash was repeated once more. Then, 80 mL of dichloromethane was added to the crystallization flask to completely dissolve the product crystals and afford a clear slightly pale yellow solution. A small aliquot (*ca.* 0.5 mL) was taken from this solution, diluted with ethyl acetate and hexanes, and subjected to chiral HPLC analysis, which revealed 99% ee for the first crop of aziridine **3f** (Note 13). The solution of the first crop in the 250 mL round bottom flask was then subjected to rotary evaporation until dryness (35-45 °C, 20 mm Hg) and finally to high vacuum for 3-4 h to afford the first crop of aziridine **3f** as a white solid (mp. 152-154 °C) in 62-64% yield (5.41-5.59 g, 12.41-12.82 mmol) (Note 13).

The 500 mL round bottom flask with the mother liquor and the washes was then subjected to rotary evaporation to dryness (35-45 °C, 20 mm Hg) and the resulting solids were dissolved in 50 mL dichloromethane, and transferred to a different pre-weighed 250 mL round bottom flask (24/40 single neck) via a plastic funnel. The 500 mL round bottom flask was rinsed twice with 20 mL dichloromethane, the plastic funnel with 10 mL dichloromethane and the rinse added each time to the 250 mL round bottom flask. This mother liquor solution was then subjected to rotary evaporation until dryness (35-45 °C, 20 mm Hg) and finally to high vacuum for 3-4 h to afford the crude aziridine product **3f** as a pale yellow solid (3.37-3.54 g). A second crop was then taken from this material in the same manner as the first crop, except that a total volume of 35 mL of a 1:4 mixture of dichloromethane:hexanes was used for the crystallization. Two similar

cold hexanes (-20 °C) washes were employed as in the first crop, with 25 mL hexanes each time. The second crop of aziridine **3f** was obtained as a white/off-white solid (mp. 134-142 °C) in 25-27% yield (2.20-2.35 g, 5.05-5.39 mmol) and 75-78% ee. Thus, the overall yield of the reaction was 89% (7.76-7.79 g, 17.80-17.87 mmol) and the overall asymmetric induction was 92-93% ee (Note 14).

Notes

1. Aminodiphenylmethane (97%) and 4-bromobenzaldehyde (99%) were obtained from Aldrich, used as received and stored under nitrogen on the bench. $MgSO_4$ (98+%, anhydrous) was obtained from Jade Scientific and used as received. Dichloromethane (99.5+%) was obtained from Mallinckrodt Chemicals and distilled from calcium hydride under nitrogen. Toluene (99.5+%) was obtained from Mallinckrodt Chemicals and distilled from sodium under nitrogen.

2. Determined from ^1H NMR analysis of the crude reaction mixture. The stirring was stopped and the solids were allowed to settle from the reaction mixture to the bottom of the reaction flask. A small aliquot (<0.5 mL) was then taken from the solution with a glass pipette, which was subjected directly to high vacuum (0.01 mm Hg) for 15 min, and analyzed by ^1H NMR. The disappearance of the singlet signal from the methine proton of aminodiphenylmethane was observed (δ = 5.22 ppm, $CDCl_3$); the reaction was judged complete.

3. The dichloromethane was not dried, regular dichloromethane (99.5+%) obtained from Mallinckrodt Chemicals was used.

4. Ethyl acetate (99.5+%) was obtained from Mallinckrodt Chemicals and used as received. Hexanes (98.5+%, total hexane isomers and methylcyclopentane) was obtained from EMD Chemicals and used as received.

5. Imine **1f** can be stored for a long period of time sealed under Argon in a dry desiccator. Spectral data for imine **1f**:[8] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.59 (s, 1H), 7.22-7.25 (m, 2H), 7.30-7.34 (m, 4H), 7.37-7.40 (m, 4H), 7.54 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 77.86, 125.17, 127.06, 127.61, 128.47, 129.85, 131.76, 135.20, 143.64, 159.52; IR (thin film) 3026w, 2845w, 1643s, 1485m, 700s cm^{-1}; HRMS calcd for $C_{20}H_{16}{}^{79}BrN$ (M+H) *m/z* 350.0544, meas 350.0558; white crystals: mp. 95-97 °C.

6. A second crop of crystals could be taken to afford imine **1f** in 6% yield (1.27 g, 3.63 mmol), but this was found to contain ~1% of 4-bromobenzaldehyde by ^{1}H NMR analysis.

7. The Schlenk flask was made in a glass blowing shop by fusing together a high vacuum threaded Teflon valve (Chemglass, CG-960-03, Valve, Chem-Vac™, Chem-Cap®, Hi-Vac, 1-Arm, 0-12 mm Bore) and a 100 mL recovery flask (Chemglass, CG-622-04, 100 mL Glassblowers Flask Blank, Recovery). The side-arm of the high vacuum valve was modified with a piece of 3/8th inch glass tubing to fit with the rubber tube attached to the double manifold. The double manifold had two-way high-vacuum valves, which could be alternated between high vacuum (0.05 mm Hg) and an Argon supply (ultra high purity, 99.999%). The large stir bar is needed for efficient stirring during the actual aziridination reaction.

8. For pictures of the set up after addition of ethyldiazoacetate, see published procedure.

9. (*S*)-VANOL is commercially available from Aldrich as well as Strem Chemicals, Inc. It was sealed under Argon and stored in a refrigerator away from light. Triphenyl borate was obtained from Aldrich, used as received and stored under nitrogen in a dry desiccator. Ethyl diazoacetate was obtained from Aldrich, used as received and stored under nitrogen in a refrigerator. Commercially available ethyldiazoacetate usually contains ≤15% dichloromethane, which was the reason behind using 1.2 equivalents in the procedure.

10. If the threaded valve on the Schlenk flask is not opened with care under high vacuum, the solvent might bump into the manifold and result in loss of catalyst.

11. If needed, the Schlenk flask may be gently tapped on a hard surface to aid in freeing the stir bar stuck inside.

12. Determined from ^{1}H NMR analysis of the crude reaction mixture. A glass pipette was dipped into the Schlenk flask, and a small amount of the semi-solid reaction mass was collected at the tip of the pipette. This was directly rinsed with $CDCl_3$ and analyzed by ^{1}H NMR. The disappearance of the singlet signals from the methine protons of imine **1f** was observed (δ = 5.59, 8.36 ppm, $CDCl_3$); the conversion was ≥95% as determined from the relative integration of the aforementioned imine methine protons vs. the aziridine ring methine protons.

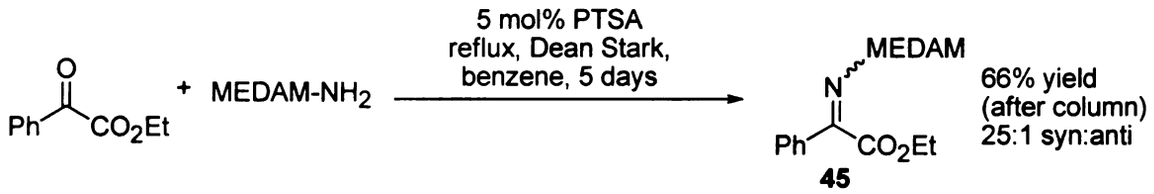
13. Aziridine **3f** can be stored for a long period of time sealed under nitrogen on the bench. The optical purity of the first crop of (2*R*,3*R*)-**3f** was determined to

be 99% ee by HPLC analysis (Chiralcel OD-H column, hexanes/2-propanol 98:2, 222 nm, flow rate 1 mL min^{-1}). Retention times: t_R = 5.5 min (minor enantiomer) and t_R = 13.3 min (major enantiomer). Spectral data for (2*R*,3*R*)-**3f**:[8] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05 (t, *J* = 7.1 Hz, 3H), 2.72 (d, *J* = 6.6 Hz, 1H), 3.17 (d, *J* = 6.8 Hz, 1H), 3.98 (s, 1H), 3.98 (q, *J* = 7.1 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.26-7.42 (m, 9H), 7.48 (d, *J* = 7.1 Hz, 2H), 7.61 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.98, 46.46, 47.33, 60.69, 77.58, 121.33, 127.13, 127.27, 127.41, 127.48, 128.50, 128.51, 129.53, 130.88, 134.07, 142.13, 142.30, 167.39; IR (thin film) 1734s, 1201s, 1067m cm^{-1}; Mass spectrum: *m/z* (%) 437 (<1, ^{81}Br) $[M]^+$, 435 (<1, ^{79}Br) $[M]^+$, 270 (42, ^{81}Br), 268 (43, ^{79}Br), 167 (100, ^{81}Br), 165 (19, ^{79}Br); elemental analysis calcd (%) for $C_{24}H_{22}BrNO_2$: C 66.06; H 5.27; N 3.09. Found: C 66.06; H 5.08; N, 3.21; $[\alpha]^{23}_D$ = +12.5 (*c* = 1.0, CH_2Cl_2) on 99% ee material; white solid: mp. 152-154 °C on 99% ee material.

14. During the optimization of this procedure, one particular run afforded the 1st crop of aziridine **3f** in 59% yield (5.13 g, 11.77 mmol) and 99% ee, and the 2nd crop in 24% yield (2.07 g, 4.75 mmol) and 78% ee. At this time, a 3rd crop was taken by simply washing the crude material remaining after the 2nd crop with cold hexanes (-20 °C, 2 × 10 mL) and swirling by hand followed by decantation. Thus, the 3rd crop of aziridine **3f** was obtained in 5% yield (0.40 g, 0.92 mmol) and 96% ee. Subjecting the crude material remaining after collection of the 3rd crop to purification by column chromatography on regular silica gel (1:9 EtOAc:hexanes) afforded negligible quantities of pure aziridine **3f** (0.07 g, 0.16 mmol, <1% yield).

Section 2.6 Failed attempts for direct access to tri-substituted aziridines

The di-substituted diazo compound **47** was prepared according to a reported procedure.[33] The di-substituted MEDAM imine **45** was prepared in a similar manner to a reported procedure.[34]



Ethyl 4,4-bis(4-methoxy-3,5-dimethylphenyl)-2-phenylbut-2-enoate ***45***. A 50 mL RBF, fitted with a Dean-Stark apparatus, was flame dried and cooled under Argon. The MEDAM amine (2.37 g, 7.92 mmol) was added to the flask and was dissolved in 20 mL of dry benzene. Thereafter, ethyl benzoylformate (0.89 mL, 5.618 mmol) was added via a syringe, which was followed by the addition of *p*-toluene sulfonic acid (54 mg, 0.28 mmol). The reaction mixture was heated to reflux with azeotropic distillation of water for 5 days, following which the reaction was judged complete by TLC. The reaction mixture was then cooled down to room temperature, all organic volatiles removed by rotary evaporation and subjected to high vacuum to afford the crude product **45** as a viscous oil. This was then subjected to column chromatography with an eluent mixture of 1:9 EtOAc:hexanes to afford the pure product **45** as a colorless viscous oil in 66% isolated yield (1.69 g, 3.69 mmol) and with a *syn:anti* ratio of 25:1 (the diastereomers were not assigned).

Spectral data for **45**: R_f = 0.25 (1:9 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34 (t, 3H, *J* = 7.1 Hz), 2.24 (s, 12H), 3.67 (s, 6H), 4.41 (q, 2H, *J* = 7.1

Hz), 5.47 (s, 1H), 6.99 (s, 4H), 7.38-7.43 (m, 3H), 7.80-7.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 14.23, 16.22, 59.56, 61.30, 70.79, 127.59, 127.80, 128.45, 130.57, 130.94, 134.56, 138.59, 155.95, 158.45, 165.55; IR (thin film) 3063w, 2982w, 2943w, 1732s, 1633m, 1483m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) $M+1^+$ 460 (100), 283 (85); Anal calcd for $C_{29}H_{33}NO_4$: C, 75.79; H, 7.24; N, 3.05. Found: C, 75.34; H, 7.44; N, 3.03.

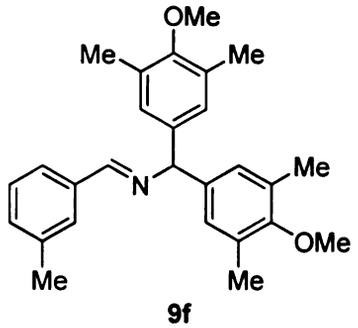
Appendix C

Experimental Information for Chapter Three

Section 3.4 Catalytic asymmetric trans-aziridination: *Development of a universal aziridination protocol*

General procedure for the preparation of imines, and characterization data for new imines

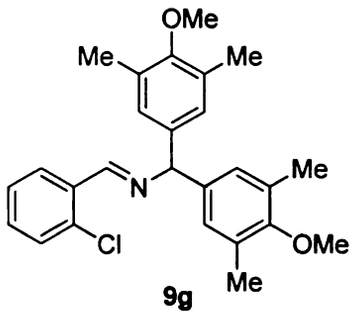
Procedures for the preparation of benzhydryl[8], MEDAM[10], and BUDAM[9] imines have been previously published by our group. All these procedures are similar in the reaction conditions, and that for the benzhydryl imines is also detailed in the experimental information for Chapter 2 of this dissertation. The new imines for the present study were also prepared using this general procedure. Benzhydryl imines **1b** and **1k** have been previously reported by our group (see also experimental information for Chapter 2).[8] MEDAM imines **9a-e** and **9k-l** have been previously reported by our group.[10] BUDAM imines **58a** and **58k-m** have also been previously reported by our group.[9]



9f

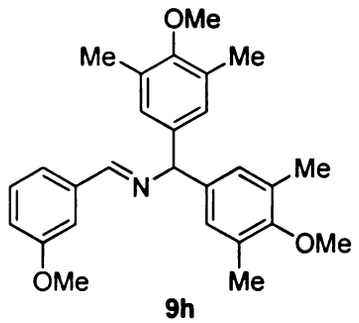
1,1-bis(4-methoxy-3,5-dimethylphenyl)-N-(3-methylbenzylidene)methanamine ***9f***. The MEDAM amine (1.00 g, 3.34 mmol) and *m*-methylbenzaldehyde (0.42 mL, 3.51 mmol) were reacted according to the

general procedure to afford crude **9f**. The crude imine **9f** was obtained as a thick colorless oil in quantitative yield (1.34 g, 3.34 mmol), and was used in the aziridination reaction as such. Spectral data for **9f**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.24 (s, 12H), 2.38 (s, 3H), 3.68 (s, 6H), 5.35 (s, 1H), 6.99 (s, 4H), 7.21-7.30 (m, 2H), 7.57 (d, 1H, J = 7.5 Hz), 7.68 (s, 1H), 8.33 (s, 1H).



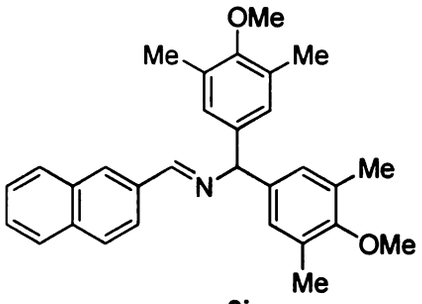
9g

N-(2-chlorobenzylidene)-1,1-bis(4-methoxy-3,5-dimethylphenyl)methanamine ***9g***. The MEDAM amine (1.00 g, 3.34 mmol) and *o*-chlorobenzaldehyde (0.40 mL, 3.51 mmol) were reacted according to the general procedure to afford crude **9g**. Crystallization (1:10 CH_2Cl_2:hexanes) afforded **9g** as a pale yellow solid (mp. 100-102 °C) in 78% isolated yield (1.10 g, 2.61 mmol). Spectral data for **9g**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.25 (s, 12H), 3.68 (s, 6H), 5.42 (s, 1H), 7.02 (s, 4H), 7.28-7.35 (m, 3H), 8.22-8.24 (m, 1H), 8.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.22, 59.60, 77.79, 126.87, 127.78, 128.90, 129.67, 130.71, 131.49, 133.35, 135.27, 139.03, 155.90, 156.99; IR (thin film) 2941m, 1633m, 1483s, 1221s, 1142s, 1016s cm^{-1}; HRMS calcd for $C_{26}H_{29}{}^{35}ClNO_2$ (M+H, ES+) *m/z* 422.1887, meas 422.1898.



9h

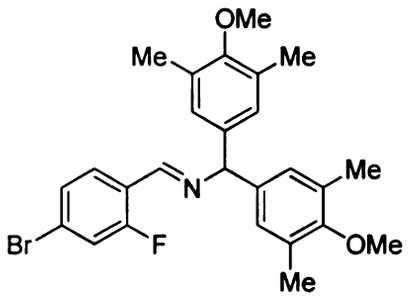
1,1-bis(4-methoxy-3,5-dimethylphenyl)-N-(3-methoxybenzylidene)methanamine ***9h.*** The MEDAM amine (0.50 g, 1.67 mmol) and *m*-methoxybenzaldehyde (0.22 mL, 1.76 mmol) were reacted according to the general procedure to afford crude **9h**. The crude imine **9h** was obtained as a thick colorless oil in quantitative yield (0.70 g, 1.67 mmol), and was used in the aziridination reaction as such. Spectral data for **9h**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.24 (s, 12H), 3.67 (s, 6H), 3.84 (s, 3H), 5.36 (s, 1H), 6.94-6.96 (m, 1H), 6.99 (s, 4H), 7.28-7.34 (m, 2H), 7.42-7.43 (m, 1H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.22, 55.41, 59.60, 77.32, 112.53, 116.95, 121.67, 127.89, 129.44, 130.64, 137.90, 139.12, 155.85, 159.82, 160.23.



9i

1,1-bis(4-methoxy-3,5-dimethylphenyl)-N-(naphthalen-2-ylmethylene)methanamine ***9i.*** The MEDAM amine (0.50 g, 1.67 mmol) and 2-napthaldehyde (0.27 g, 1.76 mmol) were reacted according to the general procedure to afford crude **9l**. The crude imine **9i** was obtained as a non-

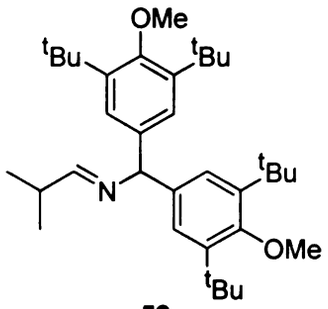
crystallizable white foamy solid in quantitative yield (0.73 g, 1.67 mmol), and was used in the aziridination reaction as such. Spectral data for **9i**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.26 (s, 12H), 3.69 (s, 6H), 5.44 (s, 1H), 7.05 (s, 4H), 7.47-7.52 (m, 2H), 7.83-7.89 (m, 3H), 8.07 (s, 1H), 8.15 (dd, 1H, *J* = 1.7, 8.5 Hz), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.23, 59.59, 77.45, 124.32, 126.36, 127.06, 127.84, 127.91, 128.27, 128.57, 130.16, 130.67, 133.07, 134.15, 134.73, 139.22, 155.86, 160.42.



9j

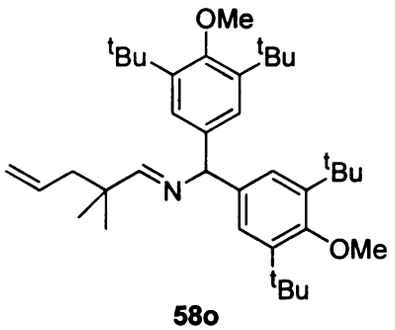
N-(4-bromo-2-fluorobenzylidene)-1,1-bis(4-methoxy-3,5-dimethylphenyl)methanamine ***9j.*** The MEDAM amine (0.50 g, 1.67 mmol) and 4-bromo-2-fluorobenzaldehyde (0.36 g, 1.76 mmol) were reacted according to the general procedure to afford crude **9j**. Crystallization (hexanes, seeded with crude solid imine) afforded **9j** as a light yellow solid (mp. 137-139 °C) in 80% isolated yield (0.65 g, 1.34 mmol). Spectral data for **9j**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.25 (s, 12H), 3.68 (s, 6H), 5.37 (s, 1H), 6.98 (s, 4H), 7.25 (dd, 1H, *J* = 1.7, 9.6 Hz), 7.32 (dd, 1H, *J* = 1.7, 8.5 Hz), 8.05 (t, 1H, *J* = 8.1 Hz), 8.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.23, 59.61, 77.92, 119.28 (d, 1C, *J* = 24.4 Hz), 123.13 (d, 1C, *J* = 9.2 Hz), 125.14 (d, 1C, *J* = 9.7 Hz), 127.74, 127.79 (d, 1C, *J* = 3.7 Hz), 129.29 (d, 1C, *J* = 3.7 Hz), 130.78, 138.82, 152.61 (d, 1C, *J* = 4.6 Hz), 155.96,

161.84 (d, 1C, J = 256.8 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz) δ -119.62; IR (thin film) 2941m, 1639m, 1481s, 1219s, 1016m cm^{-1}; HRMS calcd for $C_{26}H_{28}{}^{79}BrFNO_2$ (M+H, ES+) *m/z* 484.1287, meas 484.1284.



58n

*1,1-bis(3,5-di-tert-butyl-4-methoxyphenyl)-N-(2-methylpropylidene)methanamine **58n**.* The BUDAM amine (2.00 g, 4.28 mmol) and isobutyraldehyde (0.45 mL, 4.92 mmol) were reacted according to the general procedure to afford crude **58n**. Crystallization (1:39 EtOAc:hexanes) afforded **58n** as a white solid (mp. 128-130 °C) in 61% isolated yield (1.36 g, 2.61 mmol). Spectral data for **58n**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.14 (d, 6H, J = 7.0 Hz), 1.36 (s, 36H), 2.53-2.60 (m, 1H), 3.65 (s, 6H), 5.21 (s, 1H), 7.05 (s, 4H), 7.72 (d, 1H, J = 5.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.57, 32.07, 34.11, 35.78, 64.13, 77.29, 126.10, 137.12, 142.95, 158.22, 169.31; IR (thin film) 2983s, 1666m, 1414m, 1221m, 1014m cm^{-1}; HRMS calcd for $C_{35}H_{56}NO_2$ (M+H, ES+) *m/z* 522.4311, meas 522.4317.



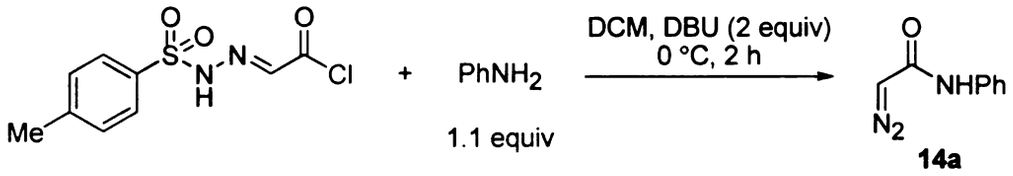
58o

*1,1-bis(3,5-di-tert-butyl-4-methoxyphenyl)-N-(2,2-dimethylpent-4-enylidene)methanamine **58o**.* The BUDAM amine (1.50 g, 3.20 mmol) and 2,2-dimethyl-4-pentenal (0.53 mL, 3.52 mmol) were reacted according to the general procedure to afford crude **58o**. The crude imine **58o** was obtained as a thick colorless oil in quantitative yield (1.79 g, 3.20 mmol), and was used in the aziridination reaction as such. Spectral data for **58o**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.11 (s, 6H), 1.36 (s, 36H), 2.24 (d, 2H, J = 7.3 Hz), 3.65 (s, 6H), 4.97-5.01 (m, 2H), 5.23 (s, 1H), 5.76-5.84 (m, 1H), 7.06 (s, 4H), 7.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.97, 32.09, 35.78, 39.21, 44.72, 64.11, 76.88, 117.14, 126.01, 135.10, 137.34, 142.87, 158.13, 170.61.

General procedures for the preparation of the diazoacetamides, and their characterization data

Diazoacetamides **14a** and **14d-e** were prepared in an identical manner as previously reported in the literature,[13] and diazoacetamides **14b-c** were prepared in an analogous manner. Diazoacetamide **14b** is a known compound.[45] Diazoacetamides **14f-g** were prepared in an identical manner as previously reported in the literature.[46] The starting material for the syntheses of **14f-g** was succinimidyl diazoacetate[31,32b], and the starting material for the preparation of

succinimidyl diazoacetate was *p*-toluenesulfonylhydrazone of glyoxylic acid[31,32a]; these were all prepared in an identical manner as previously reported in the literature. *N*-methyl-*N*-benzyldiazoacetamide **67** was prepared in an identical manner as previously reported by our group.[10,31]

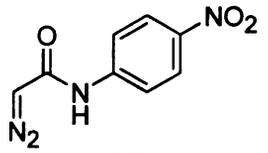


14a

*2-diazo-N-phenylacetamide **14a**.*[13] A 100 mL round bottom flask fitted with a magnetic stir bar was flame dried and cooled under Argon. The *p*-toluenesulfonylhydrazone of glyoxylic acid chloride[31,32a] (3.6 g, 13.82 mmol, 1 equiv) was added to this flask followed by the addition of 30 mL dry dichloromethane. The flask was then fitted with a rubber septum and an Argon balloon and cooled to 0 °C in an ice-bath. The reaction mixture was stirred at 0 °C for 15 min. Aniline (1.4 mL, 15.2 mmol, 1.1 equiv) and DBU (4.2 mL, 27.6 mmol, 2 equiv) were then added sequentially to the reaction flask at 0 °C via plastic syringes. The reaction mixture was stirred at 0 °C for 2 h, and then warmed up to room temperature. It was then added to sat. NH_4Cl (~ 30 mL), and the layers separated. The aqueous layer was extracted with dichloromethane once, the organic layers combined, washed with brine once, dried over Na_2SO_4, and filtered. The product solution thereafter was transferred to a 250 mL round bottom flask and enough silica gel was added for subsequent column chromatography ("dry load"). This was then subjected to rotary evaporation till dryness, and directly loaded on a silica gel column (3 × 27 cm). An eluent mixture

of 1:50 MeOH:CH_2Cl_2 was used for the flash chromatography, all yellow colored fractions were collected, and subjected to rotary evaporation till dryness and finally high vacuum to afford the impure product **14a** as a yellow solid. This was then washed with ether 1-4 times until a single spot was observed on TLC (1:29 MeOH:CH_2Cl_2), this afforded pure **14a** as a bright yellow solid in 40-52% yield (1.0 g, 6.2 mmol, 45% yield).

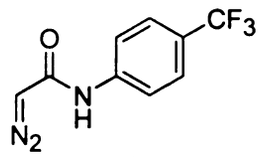
Data for **14a**:[13] R_f = 0.18 (1:50 MeOH:CH_2Cl_2); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 5.48 (s, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 7.6 Hz, 2H), 9.69 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 48.01, 118.58, 122.66, 128.75, 139.52, 163.53; IR (thin film): 3086w, 2099s, 1635w, 1371m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 161 M^+ (4), 133 (60), 105 (55), 104 (100); Anal calcd for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.21; H, 4.15; N, 25.52; bright yellow solid: m.p. dec. 147-149 °C.



14b

2-diazo-N-(4-nitrophenyl)acetamide ***14b.*** The general procedure for the preparation of **14a** described above was followed for the synthesis of **14b**, starting from the *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (1.80 g, 6.91 mmol) and *p*-nitroaniline (1.05 g, 7.6 mmol). After the reaction, only column chromatography on regular silica gel with an eluent system of 1:50 MeOH:CH_2Cl_2 was sufficient to afford pure **14b** as a yellow solid in 39% isolated yield (0.56 g, 2.72 mmol). The ether washes described for **14a** were not necessary for **14b**.

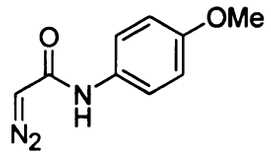
Data for **14b**:[45] R_f = 0.30 (1:50 MeOH:CH_2Cl_2); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 5.59 (s, 1H), 7.75 (d, 2H, *J* = 8.5 Hz), 8.18 (d, 2H, *J* = 8.5 Hz), 10.33 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 49.11, 118.06, 125.06, 141.59, 145.70, 164.39.



14c

2-diazo-N-(4-(trifluoromethyl)phenyl)acetamide ***14c.*** The general procedure described above for the preparation and purification of **14a** was followed for the preparation and purification of **14c**, starting from the *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (1.18 g, 4.52 mmol) and *p*-trifluoromethylaniline (0.62 mL, 4.97 mmol). This afforded pure **14c** as a yellow solid in 34% isolated yield (0.36 g, 1.55 mmol).

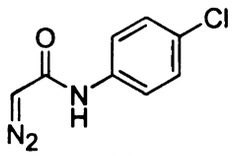
Data for **14c**: R_f = 0.20 (1:50 MeOH:CH_2Cl_2); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 5.54 (s, 1H), 7.63 (d, 2H, *J* = 8.9 Hz), 7.72 (d, 2H, *J* = 8.9 Hz), 10.08 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 48.58, 118.34, 122.57 (q, 1C, *J* = 32.1 Hz), 124.38 (q, 1C, *J* = 270.8 Hz), 126.07 (q, 1C, *J* = 3.7 Hz), 143.04, 164.15; ^{19}F NMR ($CDCl_3$, 283 MHz) δ -60.21; IR (thin film) 3418 bm, 3092w, 2105s, 1605m, 1321m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 229 M^+ (18), 202 (10), 201 (95), 173 (79), 172 (100); Anal calcd for $C_9H_6F_3N_3O$: C, 47.17; H, 2.64; N, 18.34. Found: C, 46.67; H, 2.45; N, 17.66; HRMS calcd for $C_9H_7F_3N_3O$ (M+H, ES+) *m/z* 230.0541, meas 230.0544; yellow solid.



14d

2-diazo-N-(4-methoxyphenyl)acetamide ***14d.***[13] The general procedure described above for the preparation and purification of **14a** was followed for the preparation and purification of **14d**, starting from the *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (1.34 g, 5.14 mmol) and *p*-methoxyaniline (0.70 g, 5.66 mmol). This afforded pure **14d** as a yellow solid in 21% isolated yield (0.21 g, 1.10 mmol).

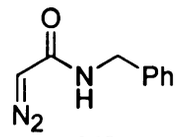
Data for **14d**:[13] R_f = 0.30 (1:50 MeOH:CH_2Cl_2); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 3.70 (s, 3H), 5.42 (s, 1H), 6.85 (d, 2H, *J* = 8.8 Hz), 7.42 (d, 2H, *J* = 8.8 Hz), 9.55 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 47.61, 55.11, 113.89, 120.20, 132.70, 154.86, 163.01.



14e

N-(4-chlorophenyl)-2-diazoacetamide ***14e.***[13] The general procedure described above for the preparation and purification of **14a** was followed for the preparation and purification of **14e**, starting from the *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (1.80 g, 6.91 mmol) and *p*-chloroaniline (0.97 g, 7.60 mmol). This afforded pure **14e** as a yellow solid in 30% isolated yield (0.41 g, 2.10 mmol).

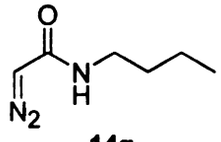
Data for **14e**:[13] R_f = 0.32 (1:50 MeOH:CH_2Cl_2); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 5.48 (s, 1H), 7.32 (d, 2H, *J* = 8.7 Hz), 7.54 (d, 2H, *J* = 8.7 Hz), 9.84 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 48.23, 120.08, 126.15, 128.64, 138.47, 163.68.



14f

*N-benzyl-2-diazoacetamide **14f**.* Diazoacetamide **14f** was prepared in an identical manner as previously reported in the literature.[46] The starting material for the synthesis of **14f** was succinimidyl diazoacetate[31,32b], and the starting material for the preparation of succinimidyl diazoacetate was *p*-toluenesulfonylhydrazone of glyoxylic acid[31,32a]; these were all prepared in an identical manner as previously reported in the literature. Thus, pure **14f** was obtained as a yellow solid in 85% isolated yield (0.41 g, 2.33 mmol), starting from succinimidyl diazoacetate (0.50 g, 2.73 mmol) and benzylamine (0.60 mL, 5.46 mmol).

Data for **14f**:[46] R_f = 0.33 (1:1 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.37 (d, 2H, *J* = 5.5 Hz), 4.82 (s, 1H), 6.22 (bs, 1H), 7.23-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$,125 MHz) δ 43.74, 46.99, 127.34, 127.43, 128.56, 138.36, 165.51.



14g

*N-butyl-2-diazoacetamide **14g**.* Diazoacetamide **14g** was prepared in an identical manner as previously reported in the literature.[46] The starting material

for the synthesis of **14g** was succinimidyl diazoacetate[31,32b], and the starting material for the preparation of succinimidyl diazoacetate was *p*-toluenesulfonylhydrazone of glyoxylic acid[31,32a]; these were all prepared in an identical manner as previously reported in the literature. Thus, pure **14g** was obtained as a yellow solid in 80% isolated yield (0.31 g, 2.20 mmol), starting from succinimidyl diazoacetate (0.50 g, 2.73 mmol) and *n*-butylamine (0.54 mL, 5.46 mmol).

Data for **14g**:[46] R_f = 0.33 (1:1 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, 3H, J = 7.3 Hz), 1.29-1.36 (m, 2H), 1.44-1.50 (m, 2H), 3.26 (bs, 2H), 4.68 (bs, 1H), 5.10 (bs, 1H); ^{13}C NMR ($CDCl_3$,125 MHz) δ 13.69, 19.96, 32.01, 39.76, 46.95, 165.34.

The issue of trans-aziridine invertomers

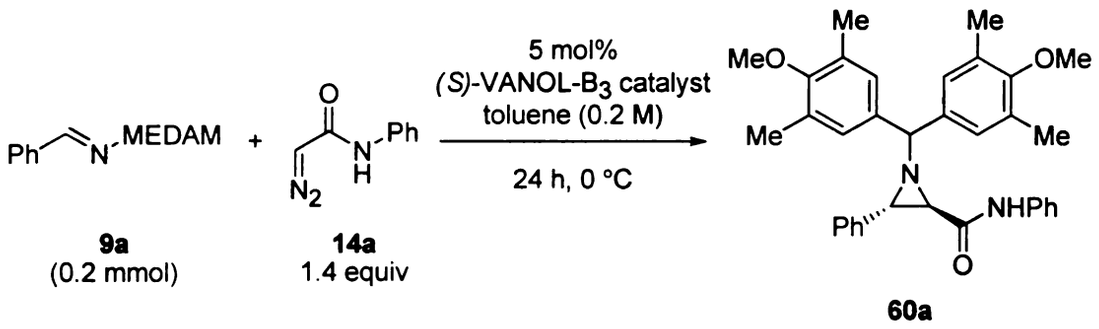
^{1}H NMR analysis of almost all isolated pure trans-aziridines reveals the presence of aziridine invertomers (two species). The ratio of these invertomers depends on the deuterated NMR solvent used, and also on the aziridine substrate itself. The ratio of invertomers for aziridine **60a** in $CDCl_3$ is usually 1:0.31, while the same ratio in DMSO-d_6 is 1:0.06. DMSO-d_6 gives predominantly one invertomer for almost all trans-aziridines, and is the solvent of choice for characterization of the trans-aziridines by NMR analysis. However, there have been certain trans-aziridines in this study for which even DMSO-d_6 indicates a significant presence of both invertomers in the NMR analysis.

The conversions, trans:cis ratios and yields of enamines for the trans-selective aziridinations are usually calculated on the basis of the ^{1}H NMR

analysis of the crude reaction mixture in $CDCl_3$. For the relative integrations, the trans-aziridine ring methine proton signals are taken into consideration. For the major invertomer, these methines usually exhibit sharp doublets (J = 2-3 Hz) in the region of 2-4 ppm. For the minor invertomer, these are small broad singlets in the same region. The minor diastereomers, the cis aziridines, are single species and do not show invertomers as the trans-aziridines. Thus, for the relative integrations, the cis-aziridine ring methine proton signals (sharp doublets, J = 6-8 Hz, 2-4 ppm) are taken into consideration. For the enamines, the signals from the *N*-H proton (doublets or doublet of doublets, 8-10 ppm) are considered. Before the practitioners get comfortable with the trans-aziridination protocol, they are advised to isolate the trans-aziridine, confirm the location of the signals from the two invertomers, and then revert to the crude ^1H NMR analysis to calculate the necessary ratios of products.

General procedure for the catalytic asymmetric trans-aziridination (illustrated for the preparation of trans-aziridine 60a), and characterization data for the products

All trans-aziridines (major diastereomers) have been characterized. Two cis-aziridines (minor diastereomers, **65a** and **69**) and one enamine side-product (from the reaction of imine **9a** and diazoacetamide **14c**) have been characterized. Cis-aziridine **68** has been previously reported by our group.[10,31]



(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N,3-diphenylaziridine-2-carboxamide ***60a***.

Preparation of catalyst stock solution. A 50 mL glass Schlenk flask fitted with a magnetic stir bar was connected via a rubber tube to a double manifold with an Argon ballast. The Schlenk flask was made in a glass blowing shop by fusing together a high vacuum teflon valve and a 50 mL recovery flask. The side-arm of the high vacuum valve was modified with a piece of 3/8th inch glass tubing to fit with the rubber tube attached to the double manifold. The double manifold had two-way high-vacuum valves, which could be alternated between high vacuum (0.1 mm Hg) and an Argon supply (ultra high purity, 99.999%). The Schlenk flask was then flame dried under high vacuum and cooled under a low flow of Argon. To the flask was added sequentially (*S*)-VANOL (44 mg, 0.1 mmol), phenol (19 mg, 0.2 mmol), dry toluene (2.5 mL), $BH_3 \bullet SMe_2$ (2 *M* solution in toluene, 150 μL, 0.3 mmol) and water (5.4 μL, 0.3 mmol) under a low flow of Argon. The threaded Teflon valve on the Schlenk flask was then closed, and the mixture heated at 100 °C for 1 h. The valve was opened to gradually apply high vacuum (0.1 mm Hg) and the solvent was removed. The vacuum was maintained for a period of 30 min at 100 °C. The flask was then removed from the oil bath

and allowed to cool to room temperature under a low flow of Argon. This was then completely dissolved in 10 mL of dry toluene to afford the stock solution of the catalyst.

The actual aziridination reaction. A 5 mL round-bottom single-neck (14/20) flask fitted with a magnetic stir bar was flame dried under high vacuum and cooled down under a low flow of Argon. For the aziridination reactions at -20 °C, a 14/20 glass extender was attached to the round bottom flask with a Teflon sleeve to prevent moisture from entering the reaction medium. To the flask was then added imine **9a** (77 mg, 0.2 mmol, 1 equiv). The flask was then fitted with a rubber septum and an Argon balloon. To this flask was added 1.00 mL of the catalyst stock solution (5 mol% catalyst) via a plastic syringe fitted with a metallic needle. This catalyst-imine complex was cooled to 0 °C with the help of a chiller for 15-20 min. Diazoacetamide **14a** (45 mg, 0.28 mmol, 1.4 equiv) was then added to the reaction flask, and the reaction stirred at 0 °C for 24 h.

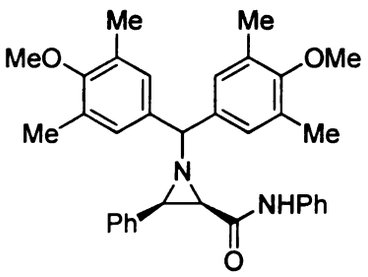
The work-up and crude ^{1}H NMR analysis. The reaction mixture was added to *ca.* 7-10 mL of cold saturated aq. $NaHCO_3$. The reaction flask was rinsed three times with EtOAc and the rinse added each time to the aq. $NaHCO_3$ solution. The layers were separated, the aqueous layer was washed once with EtOAc and the organic layers were then combined. This was dried over Na_2SO_4, filtered through a pad of Celite, rinsed with EtOAc, subjected to rotary evaporation till dryness and finally to high vacuum to afford the crude product as a foamy light yellow solid. Crude ^{1}H NMR analysis was performed in $CDCl_3$ to calculate the conversion, trans:cis ratio and yields of the enamine side-products (vide supra).

The purification. Column chromatography with regular silica gel and an eluent mixture of 1:6 EtOAc:hexanes afforded the trans-aziridine **60a** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of 1:25 EtOAc:benzene afforded analytically pure **60a** as a white foamy solid in 84% isolated yield (87 mg, 0.17 mmol). The optical purity of **60a** was determined to be 90% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 97:3, 222 nm, flow rate 0.7 mL min^{-1}). Retention times were 22 min (minor enantiomer, (2*S*,3*R*)-**60a**) and 31 min (major enantiomer, (2*R*,3*S*)-**60a**).

The absolute configurations for the major diastereomer of this reaction, the trans-aziridine **60a**, and the minor diastereomer of this reaction, the cis-aziridine **65a**, were determined by chemical correlation (*vide infra*). The absolute configurations for the rest of the aziridines in this study were assigned by analogy.

*Data for **60a**:* R_f = 0.2 (1:6 EtOAc:hexanes); R_f = 0.27 (1:25 EtOAc:benzene); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.01 (s, 6H), 2.06 (s, 6H), 2.91 (d, 1H, *J* = 2.6 Hz), 3.34 (d, 1H, *J* = 2.5 Hz), 3.48 (s, 3H), 3.54 (s, 3H), 5.04 (s, 1H), 6.98 (s, 2H), 7.04 (s, 2H), 7.04-7.06 (m, 1H), 7.25-7.35 (m, 7H), 7.48 (d, 2H, *J* = 7.7 Hz), 10.28 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 15.70, 15.88, 45.89, 47.41, 58.94, 59.07, 65.35, 119.21, 123.51, 126.02, 127.21, 127.30, 127.84, 128.31, 128.62, 129.64, 129.68, 138.59, 138.67, 138.84, 138.87, 155.11, 155.23, 164.83; IR (thin film) 3318m, 2941m, 1684s, 1539s, 1485s, 1444s, 1221m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 520 M^+ (1), 401 (9), 400 (31),

298 (25), 284 (78), 283 (100); Anal calcd for $C_{34}H_{36}N_2O_3$: C, 78.43; H, 6.97; N, 5.38. Found: C, 77.77; H, 6.78; N, 5.32; HRMS calcd for $C_{34}H_{37}N_2O_3$ (M+H, ES+) *m/z* 521.2804, meas 521.2823; $[\alpha]^{23}_D$ = +5.1 (*c* = 1, CH_2Cl_2) on 96% ee (2*R*,3*S*)-**60a**; white foamy solid: mp. 92-96 °C.

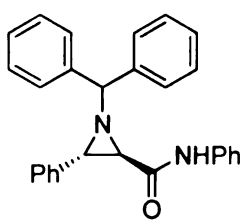


65a

(2R,3R)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N,3-diphenylaziridine-2-carboxamide ***65a***. Cis-aziridine (the minor diastereomer) **65a** was isolated (74 mg, 0.14 mmol, 14% yield) in a reaction run as described above with (*S*)-VANOL-B_3 catalyst (5 mol%), at room temperature and at a 1 mmol scale of imine **9a** (Section 3.4.10, Chapter 3). The trans:cis ratio of the reaction was 5:1. The optical purity of **65a** was determined to be 77% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 97:3, 222 nm, flow rate 0.7 mL min^{-1}). Retention times were 10 min (major enantiomer, (2*R*,3*R*)-**65a**) and 24 min (minor enantiomer, (2*S*,3*S*)-**65a**).

Data for ***65a****:* R_f = 0.25 (1:3 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.25 (s, 12H), 2.73 (d, 1H, *J* = 7.2 Hz), 3.28 (d, 1H, *J* = 7.1 Hz), 3.67 (s, 6H), 3.81 (s, 1H), 7.01 (t, 1H, *J* = 7.4 Hz), 7.08 (s, 2H), 7.10-7.12 (m, 2H), 7.13 (s, 2H), 7.15-7.24 (m, 5H), 7.28-7.29 (m, 2H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.24, 16.33, 47.30, 48.73, 59.61, 59.63, 76.72, 120.30, 124.42, 127.49, 127.55,

127.64, 127.72, 128.28, 128.79, 130.91, 131.12, 134.92, 136.66, 137.16, 137.23, 156.27, 156.34, 165.96; IR (thin film) 3360w, 2926w, 1684s, 1525s, 1442s, 1223m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 520 M^+ (<1), 400 (10), 384 (8), 400 (10), 284 (78), 283 (100); Anal calcd for $C_{34}H_{36}N_2O_3$: C, 78.43; H, 6.97; N, 5.38. Found: C, 77.95; H, 7.11; N, 5.32; HRMS calcd for $C_{34}H_{37}N_2O_3$ (M+H, ES+) *m/z* 521.2804, meas 521.2814; $[\alpha]^{23}_D$ = +4.0 (*c* = 1, CH_2Cl_2) on 13% ee (2*R*,3*R*)-**65a**; white solid: mp. 168-172 °C.

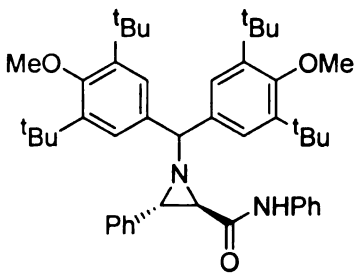


59a

(2R,3S)-1-benzhydryl-N,3-diphenylaziridine-2-carboxamide ***59a.*** Imine **1b** (54 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude product **59a**. Column chromatography with regular silica gel and an eluent mixture of 1:9 EtOAc:hexanes afforded pure **59a** as a white foamy solid in 47% isolated yield (38 mg, 0.09 mmol). The optical purity of **59a** was determined to be 77% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 95:5, 222 nm, flow rate 0.7 mL min^{-1}). Retention times were 13 min (minor enantiomer, (2*S*,3*R*)-**59a**) and 18 min (major enantiomer, (2*R*,3*S*)-**59a**).

Data for ***59a:*** R_f = 0.22 (1:9 EtOAc:hexanes); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.98 (d, 1H, *J* = 2.5 Hz), 3.44 (d, 1H, *J* = 2.2 Hz), 5.41 (s, 1H), 7.03 (t,

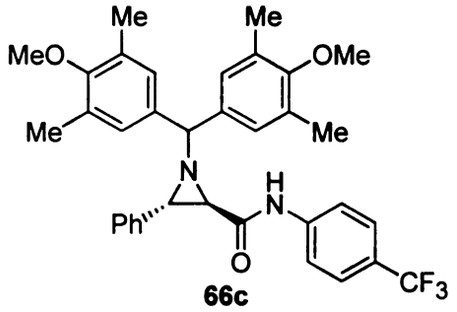
1H, *J* = 7.5 Hz), 7.11-7.14 (m, 2H), 7.20-7.28 (m, 7H), 7.31-7.36 (m, 4H), 7.43-7.45 (m, 6H), 10.28 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) (2 sp^2 carbons missing) δ 45.96, 47.31, 65.85, 119.33, 123.60, 125.94, 126.78, 127.15, 127.30, 128.13, 128.25, 128.37, 128.66, 138.46, 138.82, 143.65, 143.88, 165.00; IR (thin film) 3308m, 3030m, 2924w, 1662s, 1601s, 1531s, 1444s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 404 M^+ (<1), 283 (15), 236 (36), 181 (30), 166 (100); HRMS calcd for $C_{28}H_{25}N_2O$ (M+H, ES+) *m/z* 405.1967, meas 405.1982; $[\alpha]^{23}_D$ = -7.5 (*c* = 1, CH_2Cl_2) on 78% ee (2*R*,3*S*)-**59a**; white foamy solid: mp. 68-72 °C.



61a

(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-N,3-diphenylaziridine-2-carboxamide ***61a***. Imine **58a** (111 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **61a**. Column chromatography with regular silica gel and CH_2Cl_2 as an eluent afforded pure **61a** as a white foamy solid in 75% isolated yield (103 mg, 0.15 mmol). The optical purity of **61a** was determined to be 91% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99:1, 222 nm, flow rate 0.7 mL min^{-1}). Retention times were 18 min (minor enantiomer, (2*S*, 3*R*)-**61a**) and 28 min (major enantiomer, (2*R*, 3*S*)-**61a**).

*Data for **61a**:* R_f = 0.38 (CH_2Cl_2); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 1.21 (s, 18H), 1.22 (s, 18H), 2.98 (d, 1H, *J* = 2.2 Hz), 3.37 (d, 1H, *J* = 2.2 Hz), 3.41 (s, 3H), 3.52 (s, 3H), 5.21 (s, 1H), 7.01 (t, 1H, *J* = 7.3 Hz), 7.18 (s, 2H), 7.22-7.26 (m, 3H), 7.29 (s, 2H), 7.31-7.36 (m, 4H), 7.49 (d, 2H, *J* = 8.1 Hz), 10.26 (s, 1H); ^{13}C NMR (DMSO-*d*6:$CDCl_3$ 2:1, referenced with DMSO-*d*5, 125 MHz) δ 31.62, 31.64, 35.04, 35.08, 46.33, 46.38, 47.52, 63.44, 63.49, 63.59, 63.65, 65.35, 65.42, 118.89, 123.13, 125.03, 125.64, 125.90, 126.93, 127.98, 128.21, 137.58, 137.59, 138.61, 138.89, 142.00, 142.05, 157.18, 157.28, 165.08; IR (thin film) 3325w, 2961s, 1684s, 1539s, 1444s, 1221m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 688 M^+ (1), 568 (24), 568 (24), 452 (48), 451 (100); Anal calcd for $C_{46}H_{60}N_2O_3$: C, 80.19; H, 8.78; N, 4.07. Found: C, 79.62; H, 8.81; N, 4.07; HRMS calcd for $C_{46}H_{61}N_2O_3$ (M+H, ES+) *m/z* 689.4682, meas 689.4709; $[\alpha]^{23}_D$ = +11.2 (*c* = 1, CH_2Cl_2) on 91% ee (2*R*, 3*S*)-**61a**; white foamy solid: mp. 98-100 °C.

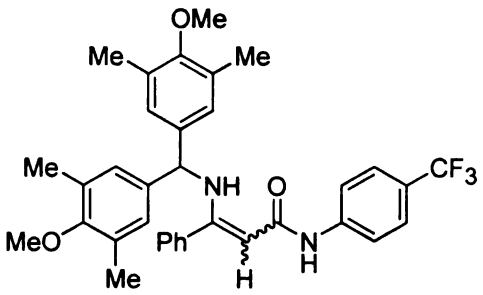


66c

*(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenyl-N-(4-(trifluoromethyl)phenyl)aziridine-2-carboxamide **66c**.* Imine **9a** (77 mg, 0.2 mmol) and diazoacetamide **14c** (64 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **66c**. Column chromatography with regular silica gel and an eluent

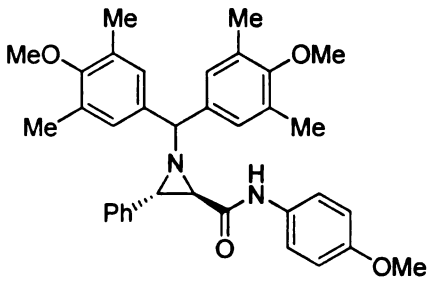
mixture of 1:5 EtOAc:hexanes afforded **66c** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of 1:25 EtOAc:benzene afforded analytically pure **66c** as a white foamy solid in 40% isolated yield (47 mg, 0.08 mmol). The optical purity of **66c** was determined to be 80% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 98:2, 222 nm, flow rate 1 mL min^{-1}). Retention times were 14 min (minor enantiomer, (2*S*,3*R*)-**66c**) and 53 min (major enantiomer, (2*R*,3*S*)-**66c**).

Data for ***66c***: R_f = 0.3 (1:5 EtOAc:hexanes); R_f = 29 (1:25 EtOAc:benzene); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 1.98 (s, 6H), 2.06 (s, 6H), 2.93 (d, 1H, *J* = 2.2 Hz), 3.39 (d, 1H, *J* = 2.4 Hz), 3.44 (s, 3H), 3.54 (s, 3H), 4.96 (s, 1H), 6.97 (s, 2H), 7.05 (s, 2H), 7.26-7.35 (m, 5H), 7.65-7.70 (m, 4H), 10.62 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 15.70, 15.97, 46.26, 47.44, 58.92, 59.11, 65.72, 118.96, 123.49 (q, 1C, *J* = 31.8 Hz), 124.37 (q, 1C, *J* = 271.1 Hz), 126.06, 126.10, 127.31, 127.39, 127.83, 128.42, 129.75, 129.82, 138.56, 138.65, 138.78, 142.12, 155.20, 155.28, 165.50; ^{19}F NMR (DMSO-*d*6, 283 MHz) δ -60.33; IR (thin film) 3424m, 2928w, 1674m, 1529m, 1325s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 588 M^+ (<1), 400 (25), 284 (58), 283 (100); HRMS calcd for $C_{35}H_{36}N_2O_3F_3$ (M+H, ES+) *m/z* 589.2678, meas 589.2697; $[\alpha]^{23}_D$ = +8.0 (*c* = 1, CH_2Cl_2) on 80% ee (2*R*, 3*S*)-**66c**; white foamy solid: mp. 94-98 °C.



3-(bis(4-methoxy-3,5-dimethylphenyl)methylamino)-3-phenyl-N-(4-(trifluoromethyl)phenyl)acrylamide. Enamines are common side products in all acid catalyzed aziridinations of imines. The enamine shown above was isolated in 2% yield (2.0 mg, 0.0034 mmol) as a white solid, during the reaction between imine **9a** and diazoacetamide **14c**; only the clean fractions were collected from the column chromatography.

Data for enamine side product: R_f = 0.32 (1:5 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 12H), 3.67 (s, 6H), 4.56 (s, 1H), 5.24 (d, 1H, *J* = 9.7 Hz), 6.75 (s, 4H), 6.81 (s, 1H), 7.19-7.21 (m, 2H), 7.30-7.39 (m, 3H), 7.52 (d, 2H, *J* = 8.5 Hz), 7.58 (d, 2H, *J* = 8.8 Hz), 9.84 (d, 1H, *J* = 9.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) (1 carbon – CF_3 missing) δ 16.24, 59.63, 61.27, 88.82, 118.84, 126.15, 127.41, 127.77, 128.24, 128.32, 129.14, 130.81, 136.09, 137.93, 142.06, 155.91, 163.35, 168.22; IR (thin film) 3319w, 2926w, 1593m, 1317s, 1066m cm^{-1}; HRMS calcd for $C_{35}H_{36}N_2O_3F_3$ (M+H, ES+) *m/z* 589.2678, meas 589.2657; white solid.

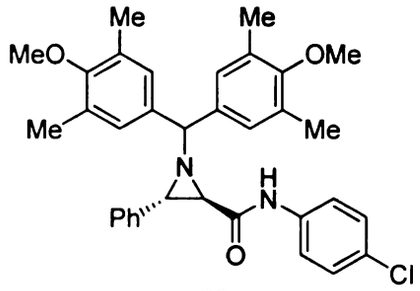


66d

(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N-(4-methoxyphenyl)-3-phenylaziridine-2-carboxamide ***66d.*** Imine **9a** (77 mg, 0.2 mmol) and diazoacetamide **14d** (53 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to

afford crude **66d**. Column chromatography with regular silica gel and an eluent mixture of 1:5 EtOAc:hexanes afforded **66d** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of 1:15 EtOAc:benzene afforded analytically pure **66d** as a white foamy solid in 75% isolated yield (83 mg, 0.15 mmol). The optical purity of **66d** was determined to be 91% ee by HPLC analysis (Chiralpak AD column, hexanes:2-propanol 95:5, 222 nm, flow rate 1 mL min^{-1}). Retention times were 28 min (major enantiomer, (2*R*,3*S*)-**66d**) and 49 min (minor enantiomer, (2*S*,3*R*)-**66d**).

*Data for **66d**:* R_f = 0.2 (1:5 EtOAc:hexanes); R_f = 0.21 (1:15 EtOAc:benzene); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.04 (s, 6H), 2.06 (s, 6H), 2.86 (d, 1H, *J* = 2.7 Hz), 3.31 (d, 1H, *J* = 2.4 Hz), 3.50 (s, 3H), 3.54 (s, 3H), 3.71 (s, 3H), 5.05 (s, 1H), 6.86 (d, 2H, *J* = 9.1 Hz), 6.98 (s, 2H), 7.03 (s, 2H), 7.25-7.37 (m, 7H), 10.13 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) (1 sp^2 carbon missing) δ 15.74, 15.86, 45.72, 47.37, 55.15, 58.97, 59.06, 65.24, 113.75, 120.85, 126.00, 127.16, 127.30, 127.82, 128.27, 129.60, 129.64, 131.75, 138.74, 138.91, 155.08, 155.22, 155.43, 164.34; IR (thin film) 3306m, 2932m, 1653s, 1512s, 1223s, 1016s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 550 M^+ (2), 384 (16), 298 (35), 284 (65), 283 (100); HRMS calcd for $C_{35}H_{39}N_2O_4$ (M+H, ES+) *m/z* 551.2910, meas 551.2933; $[\alpha]^{23}_D$ = +14.5 (*c* = 1, CH_2Cl_2) on 91% ee (2*R*,3*S*)-**66d**; white foamy solid: mp. 89-92 °C.

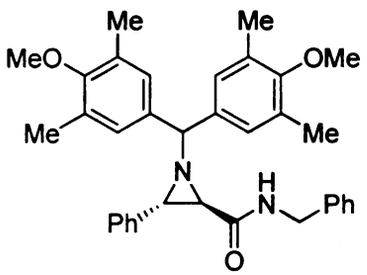


66e

(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N-(4-chlorophenyl)-3-phenylaziridine-2-carboxamide ***66e***. Imine **9a** (77 mg, 0.2 mmol) and diazoacetamide **14e** (55 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **66e**. Column chromatography with regular silica gel and an eluent mixture of 1:6 EtOAc:hexanes afforded **66e** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of 1:50 EtOAc:benzene afforded analytically pure **66e** as a white foamy solid in 82% isolated yield (91 mg, 0.16 mmol). The optical purity of **66e** was determined to be 92% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 97:3, 222 nm, flow rate 1 mL min^{-1}). Retention times were 15 min (minor enantiomer, (2*S*,3*R*)-**66e**) and 39 min (major enantiomer, (2*R*,3*S*)-**66e**).

Data for ***66e****:* R_f = 0.22 (1:6 EtOAc:hexanes); R_f = 0.27 (1:50 EtOAc:benzene); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.01 (s, 6H), 2.06 (s, 6H), 2.89 (d, 1H, *J* = 2.4 Hz), 3.35 (d, 1H, *J* = 2.6 Hz), 3.48 (s, 3H), 3.54 (s, 3H), 4.99 (s, 1H), 6.97 (s, 2H), 7.03 (s, 2H), 7.24-7.29 (m, 1H), 7.34-7.35 (m, 6H), 7.50 (d, 2H, *J* = 8.8 Hz), 10.41 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) (1 sp^2 carbon missing) δ 15.70, 15.87, 46.02, 47.34, 58.94, 59.06, 65.50, 120.67, 126.02,

127.08, 127.27, 127.80, 128.31, 128.55, 129.65, 129.69, 137.51, 138.58, 138.70, 138.77, 155.13, 155.25, 164.95; IR (thin film) 3319w, 2924m, 1666m, 1597m, 1493m, 1221m cm^{-1}; Anal calcd for $C_{34}H_{35}ClN_2O_3$: C, 73.56; H, 6.36; N, 5.05. Found: C, 72.74; H, 6.27; N, 4.86; HRMS calcd for $C_{34}H_{36}ClN_2O_3$ (M+H, ES+) *m/z* 555.2414, meas 555.2420; $[\alpha]^{23}_D$ = +17.2 (*c* = 1, CH_2Cl_2) on 92% ee (2*R*,3*S*)-**66e**; white foamy solid: mp. 88-94 °C.

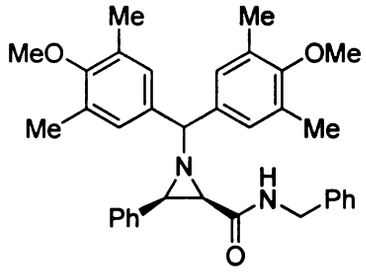


66f

(2R,3S)-N-benzyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxamide ***66f.*** Imine **9a** (77 mg, 0.2 mmol) and diazoacetamide **14f** (35 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **66f**. Column chromatography with regular silica gel and an eluent mixture of 1:5 EtOAc:hexanes afforded pure **66f** as a white foamy solid in 62% isolated yield (66 mg, 0.12 mmol). The optical purity of **66f** was determined to be 94% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 92:8, 222 nm, flow rate 0.4 mL min^{-1}). Retention times were 32 min (minor enantiomer, (2*S*,3*R*)-**66f**) and 35 min (major enantiomer, (2*R*,3*S*)-**66f**).

Data for ***66f:*** R_f = 0.18 (1:5 EtOAc:hexanes); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.06 (s, 6H), 2.17 (s, 6H), 2.82 (d, 1H, *J* = 2.5 Hz), 3.27 (d, 1H, *J* = 2.4

Hz), 3.53 (s, 3H), 3.62 (s, 3H), 4.03 (dd, 1H, J = 4.7, 15.4 Hz), 4.43 (dd, 1H, J = 7.1, 15.2 Hz), 5.16 (s, 1H), 6.85-6.87 (m, 2H), 7.03 (s, 2H), 7.08 (s, 2H), 7.16-7.31 (m, 8H), 8.75 (t, 1H, J = 4.6 Hz); ^{13}C NMR (DMSO-d6, 125 MHz) (1 sp^2 carbon missing) δ 15.86, 16.03, 42.11, 45.42, 46.62, 59.03, 59.12, 64.88, 125.99, 126.66, 126.89, 127.05, 127.39, 128.07, 128.21, 129.64, 129.66, 138.72, 139.13, 139.17, 137.37, 155.09, 155.29, 166.25; IR (thin film) 3310w, 2945w, 1653m, 1483m, 1221m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 534 M$^+$ (<1), 400 (26), 309 (18), 283 (88), 91 (100); Anal calcd for $C_{35}H_{38}N_2O_3$: C, 78.62; H, 7.16; N, 5.24. Found: C, 78.06; H, 6.90; N, 4.98; HRMS calcd for $C_{35}H_{39}N_2O_3$ (M+H, ES+) *m/z* 535.2961, meas 535.2974; $[\alpha]^{23}_D$ = -40.1 (c = 1, CH_2Cl_2) on 98% ee (2*R*,3*S*)-**66f**; white foamy solid: mp. 74-84 °C.

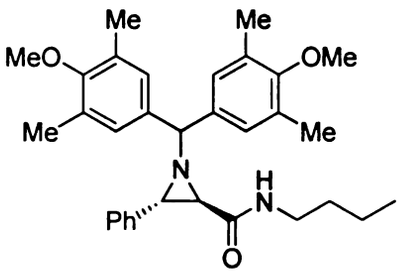


69

*(2R,3R)-N-benzyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxamide **69**.* Cis-aziridine (the minor diastereomer) **69** was isolated, in a reaction run as above at room temperature and at a 0.1 mmol scale in imine **9a**, as a white solid in 21% isolated yield (11 mg, 0.02 mmol). The optical purity was determined to be 70% ee by HPLC analysis (Regis Rexchrom Pirkle Covalent D-Phenylglycine column, hexanes:2-propanol 90:10, 222 nm, flow

rate 1 mL min^{-1}). The retention times were 42 min (major enantiomer, (2*R*,3*S*)-**69**) and 49 min (minor enantiomer, (2*S*,3*R*)-**69**).

*Data for **69**:* R_f = 0.25 (1:2 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.23 (s, 6H), 2.25 (s, 6H), 2.71 (d, 1H, *J* = 7.1 Hz), 3.24 (d, 1H, *J* = 7.2 Hz), 3.68 (s, 3H), 3.72 (s, 3H), 3.75 (s, 1H), 4.08 (dd, 1H, *J* = 6.1, 15.3 Hz), 4.23 (dd, 1H, *J* = 6.1, 15.2 Hz), 6.63 (t, 1H, *J* = 6.1 Hz), 6.78-6.80 (m, 2H), 7.02 (s, 2H), 7.11 (s, 2H), 7.20-7.27 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) (1 sp^2 carbon missing) δ 16.18, 16.23, 29.69, 42.57, 46.91, 48.44, 59.61, 77.09, 127.08, 127.11, 127.50, 127.80, 127.83, 128.25, 128.49, 130.81, 130.92, 130.93, 135.23, 137.21, 137.43, 137.86, 156.28, 167.76; IR (thin film) 3404m, 2924w, 1653s, 1525m, 1485m, 1221m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 534 M^+ (<1), 400 (22), 309 (24), 283 (100); HRMS calcd for $C_{35}H_{39}N_2O_3$ (M+H, ES+) *m/z* 535.2961, meas 535.2937; white solid: mp. 178-180 °C.

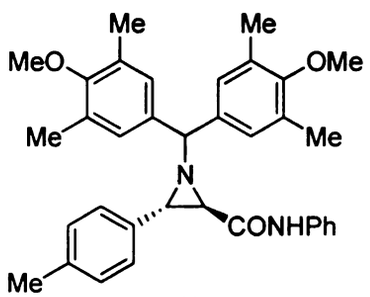


66g

*(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N-butyl-3-phenylaziridine-2-carboxamide **66g**.* Imine **9a** (77 mg, 0.2 mmol) and diazoacetamide **14g** (40 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **66g**. Column chromatography with regular silica gel and an eluent mixture

of 1:5 EtOAc:hexanes afforded pure **66g** as a white foamy solid in 62% isolated yield (62 mg, 0.12 mmol). The optical purity was determined to be 95% ee by HPLC analysis (Regis Rexchrom Pirkle Covalent D-Phenylglycine column, hexanes:2-propanol 98:2, 222 nm, flow rate 1 mL min^{-1}). Retention times were 79 min (major enantiomer, (2*R*,3*S*)-**66g**) and 91 min (minor enantiomer, (2*S*,3*R*)-**66g**).

*Data for **66g**:* R_f = 0.2 (1:5 EtOAc:hexanes); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 0.77 (t, 3H, *J* = 7.4 Hz), 1.03-1.22 (m, 4H), 2.04 (s, 6H), 2.16 (s, 6H), 2.70 (d, 1H, *J* = 2.4 Hz), 2.79-2.85 (m, 1H), 3.08-3.14 (m, 1H), 3.19 (d, 1H, *J* = 2.5 Hz), 3.53 (s, 3H), 3.58 (s, 3H), 5.06 (s, 1H), 7.00 (s, 4H), 7.21-7.32 (m, 5H), 8.21 (t, 1H, *J* = 5.3 Hz); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 13.52, 15.84, 15.92, 19.28, 30.87, 38.32, 45.15, 46.83, 59.02, 59.04, 64.94, 125.94, 126.99, 127.31, 127.62, 128.20, 129.45, 129.58, 139.05, 139.21, 139.28, 155.02, 155.22, 165.86; IR (thin film) 3316w, 2930m, 1647m, 1483m, 1221m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 500 M^+ (2), 401 (31), 400 (82), 384 (40), 309 (27), 283 (100); HRMS calcd for $C_{32}H_{41}N_2O_3$ (M+H, ES+) *m/z* 501.3117, meas 501.3113; $[\alpha]^{23}_D$ = +39.8 (*c* = 1, CH_2Cl_2) on 98% ee (2*S*,3*R*)-**66g**; white foamy solid: mp. 74-80 °C.

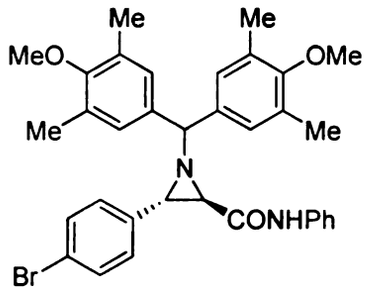


60b

(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N-phenyl-3-p-tolylaziridine-2-carboxamide ***60b.*** Imine **9b** (80 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **60b**. Column chromatography with regular silica gel and an eluent mixture of 1:6 EtOAc:hexanes afforded **60b** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of 1:40 EtOAc:benzene afforded analytically pure **60b** as a foamy white solid in 84% isolated yield (90 mg, 0.17 mmol). The optical purity of **60b** was determined to be 95% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 97:3, 222 nm, flow rate 1 mL min^{-1}). Retention times were 9 min (major enantiomer, (2*R*,3*S*)-**60b**) and 14 min (minor enantiomer, (2*S*,3*R*)-**60b**).

Data for ***60b:*** R_f = 0.22 (1:6 EtOAc:hexanes); R_f = 0.22 (1:50 EtOAc:benzene); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.00 (s, 6H), 2.07 (s, 6H), 2.28 (s, 3H), 2.87 (d, 1H, *J* = 2.5 Hz), 3.30 (m, 1H, with DMSO water peak), 3.47 (s, 3H), 3.55 (s, 3H), 5.01 (s, 1H), 6.97 (s, 2H), 7.02-7.05 (m, 3H), 7.14 (d, 2H, *J* = 7.8 Hz), 7.22 (d, 2H, *J* = 8.1 Hz), 7.28 (t, 2H, *J* = 7.8 Hz), 7.46 (d, 2H, *J* = 8.3 Hz), 10.24 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 15.67, 15.89, 20.67, 45.81, 47.25, 58.92, 59.05, 65.38, 119.19, 123.46, 125.91, 127.30, 127.81, 128.58, 128.84, 129.58, 129.65, 135.80, 136.28, 138.59, 138.69, 138.89, 155.10, 155.19, 164.91; IR (thin film) 3320w, 2924w, 1680m, 1601m, 1529m, 1444m, 1221m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 534 M^+ (<1), 414 (15), 298 (17), 284 (23), 283 (100); HRMS calcd for $C_{35}H_{39}N_2O_3$ (M+H, ES+) *m/z* 535.2961, meas

535.2959; $[\alpha]^{23}_D$ = -3.1 (*c* = 1, CH_2Cl_2) on 95% ee (2*S*,3*R*)-**60b**; white foamy solid: mp. 82-90 °C.

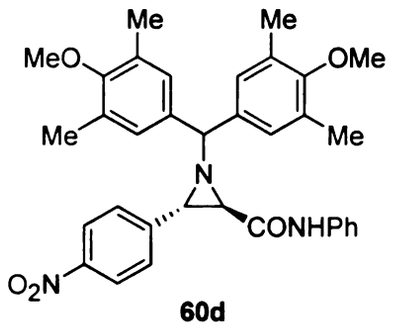


60c

(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-bromophenyl)-N-phenylaziridine-2-carboxamide ***60c***. Imine **9c** (93 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **60c**. Column chromatography with regular silica gel and an eluent mixture of 1:6 EtOAc:hexanes afforded pure **60c** as a white foamy solid in 87% isolated yield (104 mg, 0.17 mmol). The optical purity of **60c** was determined to be 97% ee by chiral HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 97:3, 222 nm, flow rate 1 mL min^{-1}). The retention times were 12 min (major enantiomer, (2*R*,3*S*)-**60c**) and 28 min (minor enantiomer, (2*S*,3*R*)-**60c**).

Data for ***60c****:* R_f = 0.28 (1:6 EtOAc:hexanes); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.00 (s, 6H), 2.07 (s, 6H), 2.89 (d, 1H, *J* = 2.5 Hz), 3.36 (d, 1H, *J* = 2.4 Hz), 3.47 (s, 3H), 3.55 (s, 3H), 5.02 (s, 1H), 6.97 (s, 2H), 7.03 (s, 2H), 7.05 (t, 1H, *J* = 7.3 Hz), 7.27-7.33 (m, 4H), 7.46 (d, 2H, *J* = 7.8 Hz), 7.53 (d, 2H, *J* = 8.6 Hz), 10.27 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 15.67, 15.87, 45.11, 47.57, 58.92, 59.05, 65.30, 119.21, 120.14, 123.53, 127.23, 127.76, 128.21, 128.59,

129.63, 129.74, 131.19, 138.39, 138.49, 138.51, 138.72, 155.16, 155.23, 164.52; IR (thin film) 3318m, 2963s, 1668s, 1601s, 1533s, 1444s, 1263s, 1010s cm^{-1}; HRMS calcd for $C_{34}H_{36}N_2O_3{}^{79}Br$ (M+H, ES+) *m/z* 599.1909, meas 599.1891; $[\alpha]^{23}_D$ = +12.6 (*c* = 1, CH_2Cl_2) on 99% ee (2*R*,3*S*)-**60c**; white foamy solid: mp. 98-104 °C.

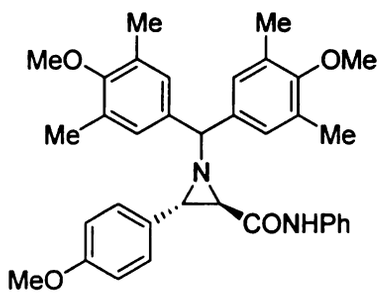


60d

(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-nitrophenyl)-N-phenylaziridine-2-carboxamide ***60d.*** Imine **9d** (86 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **60d**. Column chromatography with regular silica gel and an eluent mixture of 1:6 EtOAc:hexanes afforded pure **60d** as a pale yellow foamy solid in 80% isolated yield (90 mg, 0.16 mmol). The optical purity of **60d** was determined to be 92% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 93:7, 222 nm, flow rate 1 mL min^{-1}). Retention times were 15 min (major enantiomer, (2*R*,3*S*)-**60d**) and 54 min (minor enantiomer, (2*S*,3*R*)-**60d**).

Data for ***60d****:* R_f = 0.18 (1:6 EtOAc:hexanes); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.01 (s, 6H), 2.07 (s, 6H), 3.00 (d, 1H, *J* = 2.4 Hz), 3.48 (s, 3H), 3.54 (s, 3H), 3.55 (d, 1H, *J* = 2.5 Hz), 5.07 (s, 1H), 6.99 (s, 2H), 7.04 (s, 2H), 7.05 (t, 1H,

J = 7.3 Hz), 7.29 (t, 2H, J = 7.6 Hz), 7.46 (d, 2H, J = 7.6 Hz), 7.65 (d, 2H, J = 8.8 Hz), 8.21 (d, 2H, J = 8.7 Hz), 10.32 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 15.67, 15.85, 44.96, 48.36, 58.93, 59.05, 65.35, 119.24, 123.54, 123.63, 127.16, 127.25, 127.73, 128.62, 129.70, 129.83, 138.29, 138.43, 138.55, 146.68, 146.97, 155.20, 155.29, 164.09; IR (thin film) 3323w, 2928w, 1686m, 1601s, 1522s, 1444m, 1346s, 1223m cm^{-1}; HRMS calcd for $C_{34}H_{36}N_3O_5$ (M+H, ES+) *m/z* 566.2655, meas 566.2638; $[\alpha]^{23}_D$ = +6.8 (*c* = 1, CH_2Cl_2) on 93% ee (2*R*,3*S*)-**60d**; pale yellow foamy solid: mp. 104-110 °C.

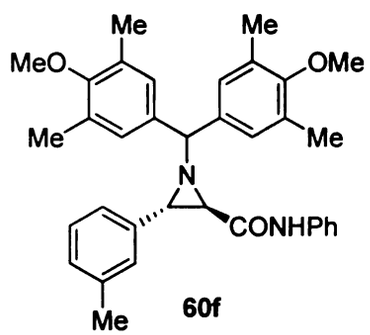


60e

(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-methoxyphenyl)-N-phenylaziridine-2-carboxamide ***60e.*** Imine **9e** (83 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 10 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **60e**. For chromatography, the column was packed with regular silica gel with a solvent mixture of 1:9 NEt_3:CH_2Cl_2, completely dried and then re-slurried in the column with a solvent mixture of 1:15 EtOAc:hexanes. Subsequent column chromatography with an eluent mixture of 1:3 EtOAc:hexanes afforded pure **60e** as a white foamy solid in 61% isolated yield (67 mg, 0.12 mmol). The optical purity of **60e** was determined to be 89% ee by HPLC analysis (Chiralcel

OD-H column, hexanes:2-propanol 97:3, 222 nm, flow rate 0.7 mL min^{-1}). Retention times were 22 min (major enantiomer, (2*R*,3*S*)-**60e**) and 36 min (minor enantiomer, (2*S*,3*R*)-**60e**).

*Data for **60e**:* R_f = 0.22 (1:3 EtOAc:hexanes); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.00 (s, 6H), 2.07 (s, 6H), 2.86 (d, 1H, *J* = 2.2 Hz), 3.28 (d, 1H, *J* = 2.4 Hz), 3.48 (s, 3H), 3.55 (s, 3H), 3.73 (s, 3H), 5.01 (s, 1H), 6.90 (d, 2H, *J* = 8.5 Hz), 6.96 (s, 2H), 7.02 (s, 2H), 7.04 (t, 1H, *J* = 7.6 Hz), 7.24-7.30 (m, 4H), 7.47 (d, 2H, *J* = 8.1 Hz), 10.24 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 15.68, 15.89, 45.59, 47.05, 55.05, 58.93, 59.06, 65.33, 113.75, 119.18, 123.45, 127.13, 127.32, 127.83, 128.59, 129.58, 129.64, 130.67, 138.61, 138.72, 138.91, 155.09, 155.19, 158.52, 165.00; IR (thin film) 3315w, 2937m, 1679m, 1601m, 1514s, 1443m, 1249m cm^{-1}; HRMS calcd for $C_{35}H_{39}N_2O_4$ (M+H, ES+) *m/z* 551.2910, meas 551.2896; $[\alpha]^{23}_D$ = +61.1 (*c* = 1, EtOAc) on 90% ee (2*R*,3*S*)-**60e**; white foamy solid: mp. 84-92 °C.

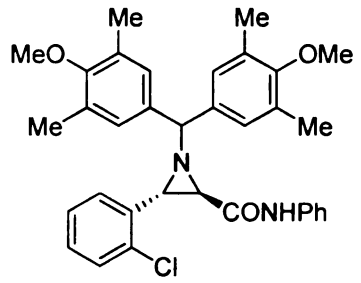


60f

*(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-N-phenyl-3-m-tolylaziridine-2-carboxamide **60f**.* Imine **9f** (80 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **60f**.

Column chromatography with regular silica gel and with an eluent mixture of 1:5 EtOAc:hexanes afforded **60f** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of 1:35 EtOAc:benzene afforded pure **60f** as a white foamy solid in 82% isolated yield (88 mg, 0.16 mmol). The optical purity of **60f** was determined to be 87% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 98:2, 222 nm, flow rate 1 mL min^{-1}). Retention times were 18 min (minor enantiomer, (2*S*,3*R*)-**60f**) and 22 min (major enantiomer, (2*R*,3*S*)-**60f**).

*Data for **60f**:* R_f = 0.25 (1:5 EtOAc:hexanes); R_f = 0.28 (1:35 EtOAc:benzene); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.01 (s, 6H), 2.07 (s, 6H), 2.29 (s, 3H), 2.90 (d, 1H, *J* = 1.7 Hz), 3.30 (m, 1H, with DMSO water peak), 3.48 (s, 3H), 3.55 (s, 3H), 5.02 (s, 1H), 6.97 (s, 2H), 7.03-7.08 (m, 4H), 7.13 (bs, 2H), 7.21-7.24 (m, 1H), 7.28 (t, 2H, *J* = 8.5 Hz), 7.47 (d, 2H, *J* = 8.3 Hz), 10.25 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 15.68, 15.88, 20.94, 45.99, 47.14, 58.93, 59.06, 65.42, 109.24, 119.19, 123.08, 123.48, 126.76, 127.36, 127.80, 128.20, 128.60, 129.60, 129.65, 137.37, 138.59, 138.63, 138.71, 138.88, 155.13, 155.20, 164.89; IR (thin film) 3313w, 2925m, 1669m, 1602m, 1527s, 1484s, 1443s, 1221s cm^{-1}; HRMS calcd for $C_{35}H_{39}N_2O_3$ (M+H, ES+) *m/z* 535.2961, meas 535.2938; $[\alpha]^{23}_D$ = +55.8 (*c* = 1, EtOAc) on 80% ee (2*R*,3*S*)-**60f**; white foamy solid: mp. 78-86 °C.

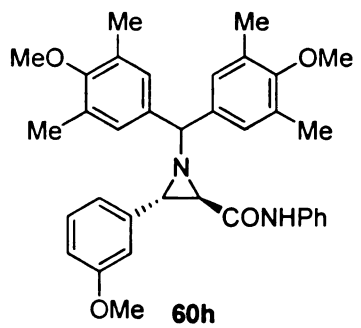


60g

(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(2-chlorophenyl)-N-phenylaziridine-2-carboxamide ***60g***. Imine **9g** (84 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **60g**. Column chromatography with regular silica gel and an eluent mixture of 1:5 EtOAc:hexanes afforded **60g** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of 1:35 EtOAc:benzene afforded pure **60g** as a white foamy solid in 78% isolated yield (87 mg, 0.16 mmol). The optical purity of **60g** was determined to be 90% ee by HPLC analysis (Chiralcel OD column, hexanes:2-propanol 95:5, 222 nm, flow rate 1 mL min^{-1}). Retention times were 17 min (minor enantiomer, (2*S*,3*R*)-**60g**) and 21 min (major enantiomer, (2*R*,3*S*)-**60g**).

Data for ***60g****:* R_f = 0.2 (1:5 EtOAc:hexanes); R_f = 0.28 (1:35 EtOAc:benzene); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.03 (s, 6H), 2.12 (s, 6H), 2.85 (d, 1H, *J* = 2.7 Hz), 3.47 (s, 3H), 3.56 (s, 3H), 3.61 (d, 1H, *J* = 2.7 Hz), 5.03 (s, 1H), 7.03 (s, 2H), 7.05 (t, 1H, *J* = 7.6 Hz), 7.13 (s, 2H), 7.27-7.30 (m, 3H), 7.37-7.41 (m, 2H), 7.46 (d, 2H, *J* = 7.5 Hz), 7.51 (dd, 1H, *J* = 1.5, 7.8 Hz), 10.27 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 15.71, 15.86, 43.56, 46.88, 58.93,

59.08, 65.61, 119.23, 123.59, 127.04, 127.37, 127.43, 127.61, 128.62, 128.82, 128.93, 129.67, 129.90, 132.46, 136.05, 138.38, 138.48, 138.65, 155.24, 155.32, 164.37; IR (thin film) 3310w, 2925w, 1685s, 1601s, 1539s, 1444s, 1221s cm^{-1}; HRMS calcd for $C_{34}H_{36}N_2O_3{}^{35}Cl$ (M+H, ES+) *m/z* 555.2414, meas 555.2428; $[\alpha]^{23}_D$ = +48.1 (*c* = 1, EtOAc) on 85% ee (2*R*,3*S*)-**60g**; white foamy solid: mp. 86-94 °C.

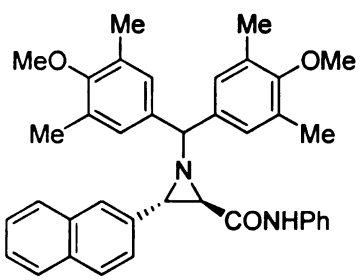


60h

(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(3-methoxyphenyl)-N-phenylaziridine-2-carboxamide ***60h.*** Imine **9h** (83 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **60h**. Column chromatography with regular silica gel and an eluent mixture of 1:5 EtOAc:hexanes afforded pure **60h** as a white foamy solid in 76% isolated yield (84 mg, 0.15 mmol). The optical purity of **60h** was determined to be 92% ee by HPLC analysis (Chiralcel OD column, hexanes:2-propanol 98:2, 222 nm, flow rate 1 mL min^{-1}). Retention times were 52 min (minor enantiomer, (2*S*,3*R*)-**60h**) and 61 min (major enantiomer, (2*R*,3*S*)-**60h**).

Data for ***60h:*** R_f = 0.2 (1:4 EtOAc:hexanes); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.01 (s, 6H), 2.08 (s, 6H), 2.89 (d, 1H, *J* = 2.4 Hz), 3.34 (d, 1H, *J* = 2.4

Hz), 3.47 (s, 3H), 3.55 (s, 3H), 3.74 (s, 3H), 5.01 (s, 1H), 6.81 (dd, 1H, J = 2.2, 8.1 Hz), 6.89 (s, 1H), 6.93 (d, 1H, J = 7.5 Hz), 6.98 (s, 2H), 7.04 (t, 1H, J = 7.6 Hz), 7.06 (s, 2H), 7.23-7.30 (m, 3H), 7.46 (d, 2H, J = 7.8 Hz), 10.25 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 15.68, 15.89, 45.87, 47.26, 54.97, 58.92, 59.05, 65.43, 111.46, 112.98, 118.15, 119.20, 123.49, 127.35, 127.78, 128.59, 129.39, 129.61, 129.69, 138.57, 138.60, 138.86, 140.50, 155.15, 155.21, 159.32, 164.78; IR (thin film) 3313w, 2939w, 1670m, 1601s, 1529s, 1487s, 1444s, 1221s cm^{-1}; HRMS calcd for $C_{35}H_{39}N_2O_4$ (M+H, ES+) *m/z* 551.2910, meas 551.2905; $[\alpha]^{23}_D$ = -64.2 (*c* = 1, EtOAc) on 93% ee (2*S*,3*R*)-**60h**; white foamy solid: mp. 76-84 °C.

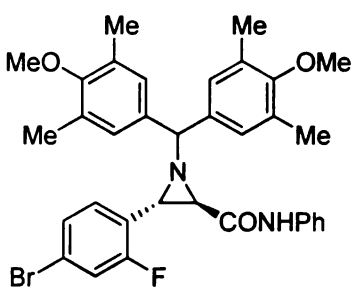


60i

(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(naphthalen-2-yl)-N-phenylaziridine-2-carboxamide ***60i.*** Imine **9i** (87 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 10 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **60i**. Column chromatography with regular silica gel and an eluent mixture of 1:6 EtOAc:hexanes afforded pure **60i** as a white foamy solid in 79% isolated yield (90 mg, 0.16 mmol). The optical purity of **60i** was determined to be 81% ee by HPLC analysis (Chiralcel OD column, hexanes:2-propanol 97:3, 222 nm, flow

rate 1 mL min^{-1}). Retention times were 39 min (major enantiomer, (2*R*,3*S*)-**60i**) and 54 min (minor enantiomer, (2*S*,3*R*)-**60i**).

*Data for **60i**:* R_f = 0.25 (1:5 EtOAc:hexanes); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.03 (s, 6H), 2.04 (s, 6H), 3.03 (d, 1H, *J* = 2.0 Hz), 3.49 (s, 3H), 3.52-3.53 (m, 4H), 5.09 (s, 1H), 7.02 (s, 2H), 7.05 (t, 1H, *J* = 7.4 Hz), 7.09 (s, 2H), 7.29 (t, 2H, *J* = 8.0 Hz), 7.47-7.52 (m, 5H), 7.87-7.92 (m, 4H), 10.30 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 15.70, 15.87, 46.16, 47.36, 58.95, 59.03, 65.47, 119.22, 123.52, 123.86, 125.10, 125.73, 126.28, 127.33, 127.47, 127.55, 127.83, 127.98, 128.61, 129.64, 129.69, 132.34, 132.78, 136.43 ,138.59, 138.63, 138.88, 155.13, 155.24, 164.81; IR (thin film) 3313w, 2928w, 1666m, 1601s, 1529s, 1485s, 1444s, 1221s cm^{-1}; HRMS calcd for $C_{38}H_{39}N_2O_3$ (M+H, ES+) *m/z* 571.2961, meas 571.2954; $[\alpha]^{23}_D$ = +62.3 (*c* = 1, EtOAc) on 80% ee (2*R*,3*S*)-**60i**; white foamy solid: 98-108 °C.

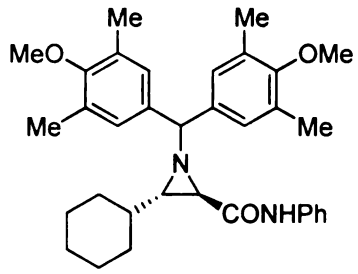


60j

*(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-bromo-2-fluorophenyl)-N-phenylaziridine-2-carboxamide **60j**.* Imine **9j** (97 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 5 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **60j**. Column chromatography with regular silica gel and an eluent

mixture of 1:6 EtOAc:hexanes afforded **60j** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of 1:40 EtOAc:benzene afforded pure **60j** as a white foamy solid in 62% isolated yield (77 mg, 0.12 mmol). The optical purity of **60j** was determined to be 92% ee by HPLC analysis (Chiralcel OD column, hexanes:2-propanol 97:3, 222 nm, flow rate 1 mL min^{-1}). Retention times were 16 min (major enantiomer, (2*R*,3*S*)-**60j**) and 52 min (minor enantiomer, (2*S*,3*R*)-**60j**).

*Data for **60j**:* R_f = 0.22 (1:6 EtOAc:hexanes); R_f = 0.26 (1:40 EtOAc:benzene); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 2.01 (s, 6H), 2.10 (s, 6H), 2.97 (d, 1H, *J* = 2.6 Hz), 3.47 (m, 4H), 3.56 (s, 3H), 4.98 (s, 1H), 6.99 (s, 2H), 7.04-7.06 (m, 3H), 7.89 (t, 2H, *J* = 7.6 Hz), 7.35-7.39 (m, 1H), 7.45-7.51 (m, 4H), 10.31 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) (1 sp^3 carbon missing) δ 15.67, 15.87, 46.83, 58.93, 59.07, 65.57, 118.39, 118.59, 119.27, 120.23 (d, 1C, *J* = 9.0 Hz), 123.64, 125.34 (d, 1C, *J* = 13.0 Hz), 127.34, 127.67, 127.86 (d, 1C, *J* = 3.0 Hz), 128.56 (d, 1C, *J* = 4.5 Hz), 128.62, 129.69, 129.89, 138.24, 138.41, 138.48, 155.28, 160.44 (d, 1C, *J* = 248.1 Hz), 164.13; ^{19}F NMR (DMSO-*d*6, 283 MHz) δ -117.99; IR (thin film) 3340w, 2926w, 1660s, 1603s, 1531m, 1467s, 1444s, 1221s cm^{-1}; HRMS calcd for $C_{34}H_{35}N_2O_3F^{79}Br$ (M+H, ES+) *m/z* 617.1815, meas 617.1804; $[\alpha]^{23}_D$ = +72.9 (*c* = 1, EtOAc) on 94% ee (2*R*,3*S*)-**60j**; white foamy solid: mp. 90-98 °C.

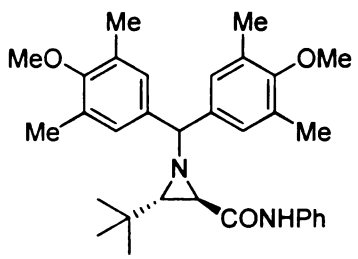


60k

(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexyl-N-phenylaziridine-2-carboxamide ***60k***. Imine **9k** (79 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 10 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **60k**. Column chromatography with regular silica gel and an eluent mixture of 1:5 EtOAc:hexanes afforded **60k** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of (1:50 EtOAc:CH_2Cl_2 followed by 1:20 EtOAc:CH_2Cl_2) afforded analytically pure **60k** as a white foamy solid in 50% isolated yield (53 mg, 0.1 mmol). The optical purity of **60k** was determined to be 30% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 97:3, 222 nm, flow rate 0.7 mL min^{-1}). Retention times were 9 min (minor enantiomer, (2*S*,3*R*)-**60k**) and 13 min (major enantiomer, (2*R*,3*S*)-**60k**).

Data for ***60k****:* R_f = 0.19 (1:5 EtOAc:hexanes); R_f = 0.3 (1:50 EtOAc:CH_2Cl_2); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 0.69-1.61 (m, 11H), 2.01 (s, 6H), 2.13 (dd, 1H, *J* = 2.9, 7.1 Hz), 2.18 (s, 6H), 2.67 (d, 1H, *J* = 2.9 Hz), 3.07 (s, 3H), 3.59 (s, 3H), 4.69 (s, 1H), 6.94 (s, 2H), 7.00 (t, 1H, *J* = 7.3 Hz), 7.05 (s, 2H), 7.20-7.25 (m, 2H), 7.41 (d, 2H, *J* = 7.6 Hz), 10.12 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 15.72, 15.85, 25.08, 25.29, 25.81, 29.43, 29.87, 39.77, 41.41, 49.80,

58.90, 59.18, 65.68, 119.13, 123.20, 127.41, 127.96, 128.48, 129.35, 129.57, 138.76, 138.78, 139.26, 154.91, 155.31, 166.07; IR (thin film) 3316w, 2926s, 2853m, 1664s, 1601s, 1533s, 1485s, 1444s, 1221s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 526 M^+ (1), 443 (18), 350 (45), 322 (52), 284 (56), 283 (100); HRMS calcd for $C_{34}H_{43}N_2O_3$ (M+H, ES+) *m/z* 527.3274, meas 527.3264; white foamy solid: mp. 186-189 °C.

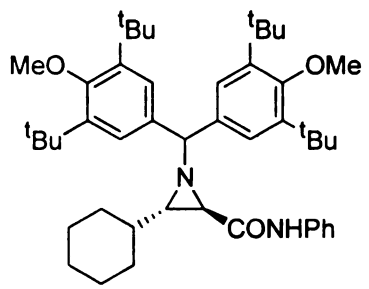


60l

(2R,3S)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-tert-butyl-N-phenylaziridine-2-carboxamide ***60l***. Imine **9l** (73 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 20 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **60l**. Column chromatography with regular silica gel and an eluent mixture of 1:8 EtOAc:hexanes afforded pure **60l** as a white foamy solid in 68% isolated yield (68 mg, 0.14 mmol). The optical purity of **60l** was determined to be 88% ee by HPLC analysis (Chircalcel OD-H column, hexanes:2-propanol 98:2, 222 nm, flow rate 1 mL min^{-1}). Retention times were 10 min (minor enantiomer, (2*S*,3*R*)-**60l**) and 28 min (major enantiomer, (2*R*,3*S*)-**60l**).

Data for ***60l:*** R_f = 0.17 (1:8 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.73 (s, 9H), 2.09 (s, 6H), 2.23 (s, 6H), 2.38 (d, 1H, *J* = 2.7 Hz), 2.49 (d, 1H, *J* = 2.7 Hz), 3.55 (s, 3H), 3.64 (s, 3H), 4.50 (s, 1H), 7.03 (t, 1H, *J* = 7.5 Hz), 7.07 (s,

2H), 7.20 (s, 2H), 7.13-7.23 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.01, 16.11, 26.73, 30.42, 40.86, 54.60, 59.35, 59.57, 67.76, 119.86, 124.22, 127.56, 128.39, 128.69, 130.12, 130.20, 137.50, 139.17, 139.27, 155.48, 155.88, 166.15; IR (thin film) 3318m, 2953s, 2866w, 1658s, 1601s, 1541s, 1500s, 1444s, 1221s cm^{-1}; HRMS calcd for $C_{32}H_{41}N_2O_3$ (M+H, ES+) *m/z* 501.3117, meas 501.3095; $[\alpha]^{23}_D$ = -37.3 (*c* = 1, EtOAc) on 88% ee (2*R*,3*S*)-**60l**); white foamy solid: mp. 78-86 °C.

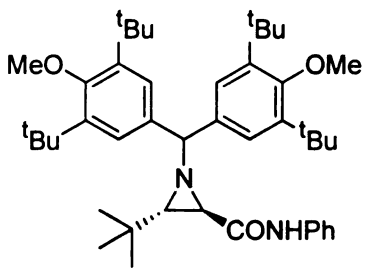


61k

(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-cyclohexyl-N-phenylaziridine-2-carboxamide ***61k.*** Imine **58k** (112 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 20 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **61k**. Column chromatography with regular silica gel and an eluent mixture of 1:13 EtOAc:hexanes afforded **61k** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of (1:1 CH_2Cl_2:hexanes followed by CH_2Cl_2 only) afforded analytically pure **61k** as a white foamy solid in 62% isolated yield (86 mg, 0.12 mmol). The optical purity of **61k** was determined to be 26% ee by HPLC analysis (Regis Pirkle Covalent (*R,R*) Whelk-O1 column, hexanes:2-propanol 98:2, 222 nm, flow rate 1 mL min

[1]). Retention times were 15 min (major enantiomer, (2*R*,3*S*)-**61k**) and 22 min (minor enantiomer, (2*S*,3*R*)-**61k**).

*Data for **61k**:* R_f = 0.24 (1:13 EtOAc:hexanes); ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 0.63-1.66 (m, 11H), 1.22 (s, 18H), 1.36 (s, 18H), 2.14 (dd, 1H, *J* = 2.2, 6.5 Hz), 2.72 (d, 1H, *J* = 2.7 Hz), 3.37 (s, 3H), 3.57 (s, 3H), 4.79 (s, 1H), 6.96 (t, 1H, *J* = 7.3 Hz), 7.19 (t, 2H, *J* = 8.0 Hz), 7.21 (s, 2H), 7.34 (s, 2H), 7.41 (d, 2H, *J* = 8.0 Hz), 10.06 (s, 1H); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 25.06, 25.25, 25.77, 29.27, 29.68, 31.74, 31.83, 31.92, 35.09, 35.27, 41.08, 50.00, 63.59, 64.03, 66.54, 118.91, 123.07, 125.26, 125.85, 128.35, 137.59, 138.11, 138.81, 141.85, 142.14, 157.17, 157.69, 166.25; IR (thin film) 3333w, 2981s, 2926s, 2853m, 1676s, 1603s, 1527s, 1444s, 1221s cm^{-1}; HRMS calcd for $C_{46}H_{67}N_2O_3$ (M+H, ES+) *m/z* 695.5152, meas 695.5133; $[\alpha]^{23}_D$ = +32.2 (*c* = 1, EtOAc) on 73% ee (2*S*,3*R*)-**61k**; white foamy solid: mp. 192-198 °C.

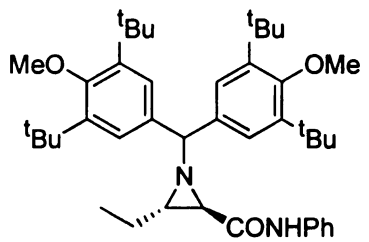


61l

*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-tert-butyl-N-phenylaziridine-2-carboxamide **61l**.* Imine **58l** (107 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 20 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **61l**. Column chromatography with regular silica gel and an eluent mixture

of 1:15 EtOAc:hexanes afforded pure **61l** as a white solid in 65% isolated yield (87 mg, 0.13 mmol). The optical purity of **61l** was determined to be 80% ee by HPLC analysis (Regis Pirkle Covalent (*R,R*) Whelk-O1 column, hexanes:2-propanol 99:1, 222 nm, flow rate 1 mL min^{-1}). Retention times were 14 min (major enantiomer, (2*R*,3*S*)-**61l**) and 18 min (minor enantiomer, (2*S*,3*R*)-**61l**).

*Data for **61l**:* R_f = 0.28 (1:15 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.68 (s, 9H), 1.30 (s, 18H), 1.39 (s, 18H), 2.37 (d, 1H, *J* = 2.7 Hz), 2.44 (d, 1H, *J* = 2.7 Hz), 3.45 (s, 3H), 3.60 (s, 3H), 4.52 (s, 1H), 6.89 (bs, 1H), 7.00 (t, 1H, *J* = 6.8 Hz), 7.17-7.22 (m, 4H), 7.38 (s, 2H), 7.39 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.49, 30.49, 32.05, 32.11, 35.57, 35.69, 41.00, 54.67, 63.86, 64.14, 68.87, 119.31, 124.16, 125.36, 126.47, 128.78, 137.55, 137.86, 138.14, 142.64, 142.69, 157.85, 158.39, 166.03; IR (thin film) 3294w, 2959s, 2868w, 1662m, 1601m, 1541m, 1442m, 1414m, 1219m cm^{-1}; HRMS calcd for $C_{44}H_{65}N_2O_3$ (M+H, ES+) *m/z* 669.4995, meas 669.4973; $[\alpha]^{23}_D$ = -15.2 (*c* = 1, EtOAc) on 80% ee (2*R*,3*S*)-**61l**; white solid: mp. 178-180 °C.

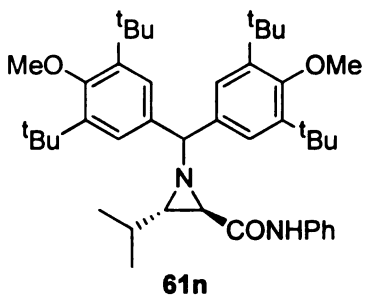


61m

*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-ethyl-N-phenylaziridine-2-carboxamide **61m**.* Imine **58m** (101 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 20 mol% (*S*)-VANOL-B_3 catalyst) to afford

crude **61m**. Column chromatography with regular silica gel and an eluent mixture of 1:8 EtOAc:hexanes to afford pure **61m** as a white solid in 66% isolated yield (85 mg, 0.13 mmol). The optical purity of **61m** was determined to be 88% ee by HPLC analysis (Regis Pirkle Covalent (*R,R*) Whelk-O1 column, hexanes:2-propanol 99:1, 222 nm, flow rate 1 mL min^{-1}). Retention times were 26 min (minor enantiomer, (2*S*,3*R*)-**61m**) and 49 min (major enantiomer, (2*R*,3*S*)-**61m**).

*Data for **61m**:* R_f = 0.22 (1:8 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, 3H, *J* = 7.3 Hz), 1.33 (s, 18H), 1.42 (s, 18H), 1.63-1.73 (m, 2H), 2.20 (d, 1H, *J* = 2.2 Hz), 2.37 (bs, 1H), 3.61 (s, 3H), 3.66 (s, 3H), 4.28 (s, 1H), 7.06 (t, 1H, *J* = 7.3 Hz), 7.26 (s, 2H), 7.29 (t, 2H, *J* = 7.6 Hz), 7.34 (s, 2H), 7.48 (d, 2H, *J* = 7.8 Hz), 8.56 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.35, 19.81, 32.04, 32.13, 35.68, 35.76, 45.13, 49.04, 63.99, 64.16, 68.33, 119.17, 123.90, 125.20, 125.27, 128.92, 136.98, 137.12, 137.58, 143.24, 143.51, 158.34, 158.47, 168.81; IR (thin film) 3310w, 2983s, 2872w, 1676m, 1603m, 1529s, 1444s, 1412s, 1221s cm^{-1}; HRMS calcd for $C_{42}H_{61}N_2O_3$ (M+H, ES+) *m/z* 641.4682, meas 641.4667; $[\alpha]^{23}_D$ = +61.0 (*c* = 1, EtOAc) on 88% ee (2*R*,3*S*)-**61m**; white solid: mp. 186-192 °C.

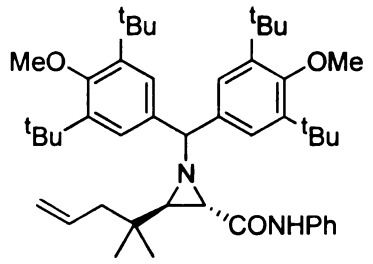


61n

*(2R,3S)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-isopropyl-N-phenylaziridine-2-carboxamide **61n**.* Imine **58n** (104 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general

procedure described above (0 °C, 20 mol% (*S*)-VANOL-B_3 catalyst) to afford crude **61n**. Column chromatography using regular silica gel and an eluent mixture of 1:9 EtOAc:hexanes afforded **61n** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of 1:100 EtOAc:benzene afforded analytically pure **61n** as a white solid in 60% isolated yield (78 mg, 0.12 mmol). The optical purity of **61n** was determined to be 58% ee by HPLC analysis (Regis Pirkle Covalent (*R,R*) Whelk-O1 column, hexanes:2-propanol 98:2, 222 nm, flow rate 1 mL min^{-1}). Retention times were 12 min (major enantiomer, (2*R*,3*S*)-**61n**) and 19 min (minor enantiomer, (2*S*,3*R*)-**61n**).

*Data for **61n**:* R_f = 0.20 (1:9 EtOAc:hexanes); R_f = 0.29 (1:100 EtOAc:benzene); ^{1}H NMR (DMSO-*d*6:$CDCl_3$ 3:1, referenced to DMSO-*d*5, 500 MHz) δ 0.60 (d, 3H, *J* = 6.6 Hz), 0.77 (d, 3H, *J* = 6.8 Hz), 1.21 (s, 18H), 1.35 (s, 18H), 1.39-1.48 (m, 1H), 2.13 (dd, 1H, *J* = 3.0, 6.6 Hz), 2.66 (d, 1H, *J* = 2.7 Hz), 3.35 (s, 3H), 3.56 (s, 3H), 4.77 (s, 1H), 6.93 (t, 1H, *J* = 7.4 Hz), 7.15 (t, 2H, *J* = 7.5 Hz), 7.19 (s, 2H), 7.32 (s, 2H), 7.41 (d, 2H, *J* = 7.8 Hz), 10.02 (s, 1H); ^{13}C NMR (DMSO-*d*6:$CDCl_3$ 3:1, referenced to DMSO-*d*5, 125 MHz) δ 18.86, 19.24, 29.65, 31.69, 31.81, 35.04, 35.23, 41.11, 51.22, 63.45, 63.86, 66.61, 118.84, 122.88, 125.25, 125.77, 128.15, 137.52, 138.05, 138.77, 141.77, 142.08, 157.12, 157.62, 166.18; IR (thin film) 3327w, 2261s, 2870s, 1670m, 1603m, 1529s, 1444s, 1414s, 1221s cm^{-1}; HRMS calcd for $C_{43}H_{63}N_2O_3$ (M+H, ES+) *m/z* 655.4839, meas 655.4827; $[\alpha]^{23}_D$ = -37.3 (*c* = 1, EtOAc) on 76% ee (2*R*,3*S*)-**61n**; white solid: mp. 182-186 °C.



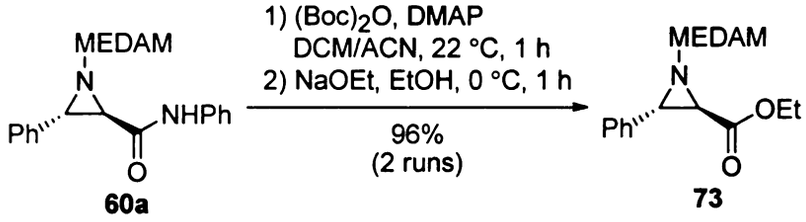
61o

(2S,3R)-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-(2-methylpent-4-en-2-yl)-N-phenylaziridine-2-carboxamide ***61o***. Imine **58o** (112 mg, 0.2 mmol) and diazoacetamide **14a** (45 mg, 0.28 mmol) were reacted according to the general procedure described above (0 °C, 20 mol% (*R*)-VAPOL-B_3 catalyst) to afford crude **61o**. Column chromatography with regular silica gel and an eluent mixture of 1:15 EtOAc:hexanes afforded **61o** which was 95% pure. Subsequent column chromatography with regular silica gel and an eluent mixture of 1:1 CH_2Cl_2:hexanes afforded analytically pure **61o** as a white foamy solid in 53% isolated yield (74 mg, 0.11 mmol). The optical purity of **61o** was determined to be 81% ee by HPLC analysis (Regis Pirkle Covalent (*R,R*) Whelk-O1 column, hexanes:2-propanol 99:1, 222 nm, flow rate 1 mL min^{-1}). Retention times were 14 min (minor enantiomer, (2*R*,3*S*)-**61o**) and 21 min (major enantiomer, (*2S*,3*R*)-**61o**).

Data for ***61o****:* R_f = 0.24 (1:15 EtOAc:hexanes); R_f = 0.3 (1:1 CH_2Cl_2:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.62 (s, 3H), 0.74 (s, 3H), 1.29 (s, 18H), 1.40 (s, 18H), 1.68-1.84 (m, 2H), 2.45 (d, 1H, *J* = 2.7 Hz), 2.48 (d, 1H, *J* = 2.7 Hz), 3.45 (s, 3H), 3.61 (s, 3H), 4.53 (s, 1H), 4.74 (d, 1H, *J* = 16.9 Hz), 4.88 (d, 1H, *J* = 8.5 Hz), 5.57-5.65 (m, 1H), 6.88 (bs, 1H), 7.01 (t, 1H, *J* = 6.9 Hz), 7.17-7.23 (m, 4H), 7.39 (s, 2H), 7.41 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.11,

24.10, 32.08, 32.12, 33.43, 35.60, 35.71, 41.02, 45.14, 53.73, 63.84, 64.14, 69.01, 117.07, 119.34, 124.18, 125.31, 126.45, 128.79, 134.86, 137.59, 137.98, 138.17, 142.73, 142.84, 157.89, 158.50, 165.90; IR (thin film) 3341w, 2983s, 1666m, 1601m, 1529m, 1442s, 1412s, 1219s cm^{-1}; HRMS calcd for $C_{46}H_{67}N_2O_3$ (M+H, ES+) *m/z* 695.5152, meas 695.5131; $[\alpha]^{23}_D$ = +21.5 (*c* = 1, EtOAc) on 81% ee (2*S*,3*R*)-**61o**; white foamy solid: mp. 70-78 °C.

Conversion of the trans-amide aziridine 60a to the trans-ester aziridine 73[41]



(2R,3S)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate ***73***. To a 25 mL round bottom flask fitted with a magnetic stir bar, previously flame dried and cooled under Argon, was added sequentially the trans-aziridine (2*R*,3*S*)-**60a** (120 mg, 0.23 mmol, 1 equiv, 90% ee), 9 mL dry CH_3CN, and 1.5 mL dry CH_2Cl_2 to get a clear solution. The flask was then fitted with a rubber septum and an Argon balloon. This was followed by the addition of DMAP (57 mg, 0.46 mmol, 2 equiv) and $(Boc)_2O$ (151 mg, 0.69 mmol, 3 equiv), and the reaction mixture was then stirred at room temperature for 1 h, at which time the reaction was judged complete by TLC. The reaction mixture was then subjected to rotary evaporation to afford a yellow oil, which was subjected to flash column chromatography with regular silica gel and an eluent mixture of 1:5 EtOAc:hexanes (R_f = 0.33). This afforded the intermediate product as a white foamy solid (147 mg). This was taken in a 25 mL round bottom flask

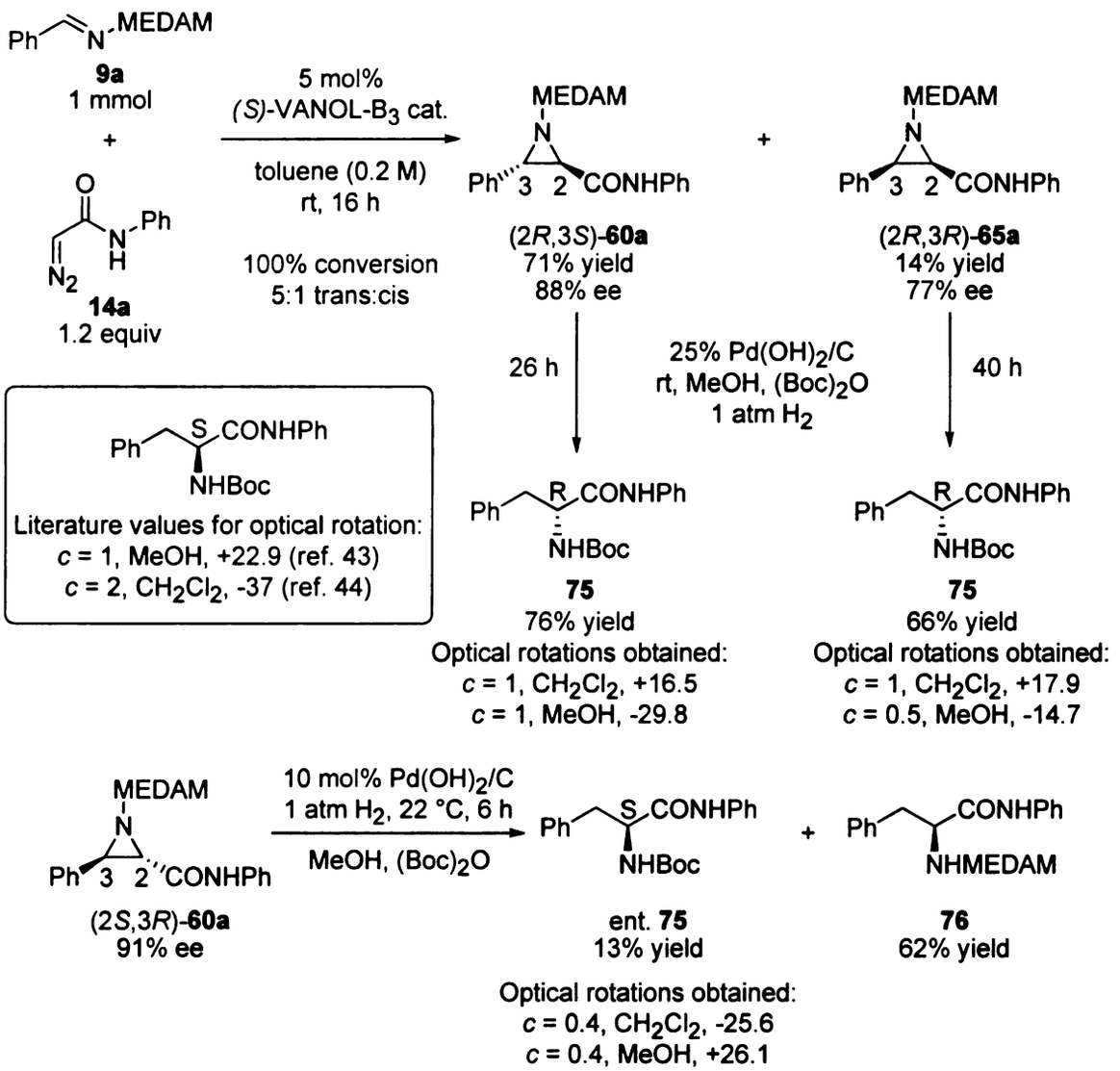
fitted with a magnetic stir bar, to which was then added 6 mL EtOH. The flask was fitted with a rubber septum and an Argon balloon and the solution was cooled to 0 °C in an ice bath, followed by the addition of NaOEt (21 wt% solution of NaOEt in EtOH, 132 μL, 0.35 mmol, 1.5 equiv). This reaction mixture was stirred at 0 °C for 1 h, at which time the reaction was complete by TLC. The reaction was then quenched with the addition of 9 mL sat. aq. NH_4Cl solution, and the reaction mixture was concentrated by rotary evaporation. This was followed by the addition of 30 mL water, which was extracted three times with CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered through a pad of Celite, subjected to rotary evaporation till dryness and finally to high vacuum to afford the crude product **73**. This was then subjected to column chromatography with regular silica gel and an eluent mixture of 1:9 EtOAc:hexanes to afford the pure product **73** as a white semi-solid in 96% isolated yield (average of two runs, 105 mg, 0.22 mmol).

*Data for **73**:* R_f = 0.23 (1:9 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.03 (t, 3H, *J* = 7.1 Hz), 2.15 (s, 6H), 2.24 (s, 6H), 2.82 (d, 1H, *J* = 2.4 Hz), 3.39 (d, 1H, *J* = 2.4 Hz), 3.62 (s, 3H), 3.66 (s, 3H), 3.96-4.05 (m, 2H), 4.89 (s, 1H), 7.05 (s, 2H), 7.07 (s, 2H), 7.22-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.89, 16.14, 16.17, 45.09, 48.71, 59.50, 59.52, 60.90, 67.04, 126.47, 127.36, 127.77, 127.89, 128.21, 130.24, 130.34, 138.34, 138.50, 138.75, 155.73, 155.81, 168.66; IR (thin film) 2932m, 1724s, 1483s, 1221s, 1108s cm^{-1}; HRMS calcd for $C_{30}H_{36}NO_4$ (M+H, ES+) *m/z* 474.2644, meas 474.2656; $[\alpha]^{23}_D$ = -4.4 (*c* = 1, EtOAc) on 90% ee (2*R*,3*S*)-**73**; white semi-solid.

TfOH catalyzed aziridination reactions

For experimental details, see published work (Vetticatt, M. J.; Desai, A. A.; Wulff, W. D. **2010**, *submitted*).

Determination of absolute configuration in the trans-selective aziridination



As indicated in the Scheme above, the major and minor diastereomers in the trans-selective aziridination reaction, trans-**60a** and cis-**65a**, were isolated from the aziridination reaction performed according to the general procedure described above. These were then subjected to a reductive ring-

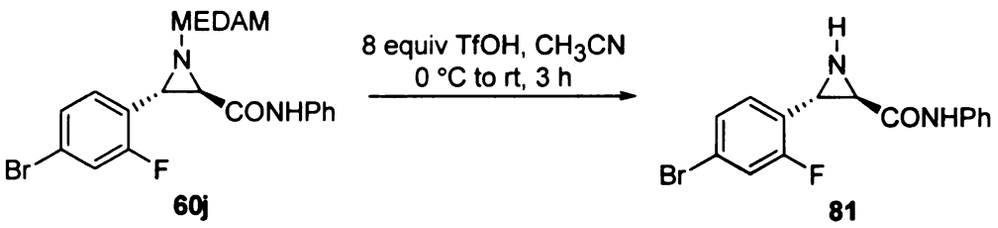
opening/deprotection/Boc-protection sequence, and transformed to the corresponding Boc-protected aminoamides **75**. The optical rotations of these products were compared to literature values (indicated in the Scheme above), and the absolute configurations were assigned.

*Representative procedure for the reductive ring-opening/deprotection/Boc-protection sequence for conversion of **60a** to **75**:* A 25 mL round bottom flask fitted with a magnetic stir bar was flame dried under vacuum and cooled under Argon. To this flask was then added, the trans-aziridine **60a** (80 mg, 0.154 mmol), $Pd(OH)_2$ (68 mg, 0.0385 mmol, $Pd(OH)_2$ on carbon powder, 20% Pd, moisture *ca.* 60%), $(Boc)_2O$ (100 mg, 0.462 mmol) and MeOH (5 mL), and a black suspension was obtained. The flask was then equipped with a vacuum transfer adapter connected to vacuum and a balloon filled with hydrogen. The valve to vacuum (5-10 mm Hg) was opened for a few seconds, and then switched to the hydrogen balloon; this process was repeated 5 times. This entire process of vacuum/hydrogen was repeated for a total of three times (at time t = 0 h, 4 h, and 18 h). The reaction mixture was stirred at room temperature for 26 h. It was then filtered through a pad of Celite, subjected to rotary evaporation until dryness and put on high vacuum for 5 minutes to afford the crude product **75**. Column chromatography with regular silica gel and an eluent mixture of 1:5 EtOAc:hexanes afforded pure **75** as a white solid in 76% isolated yield (40 mg, 0.118 mmol).

*Data for **75**:* ^1H NMR ($CDCl_3$, 500 MHz) δ 1.43 (s, 9H), 3.12-3.17 (m, 2H), 4.55 (bs, 1H), 5.36 (bs, 1H), 7.09 (t, 1H, J = 7.3 Hz), 7.24-7.32 (m, 7H), 7.38 (d,

2H, J = 7.8 Hz), 8.07 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 28.25, 36.64, 39.49, 38.65, 120.07, 120.18, 124.42, 126.98, 128.72, 128.84, 129.29, 136.67, 137.32, 169.72. Optical rotations indicated in Scheme above.

Deprotection to the *N*-H aziridine



(2R,3S)-3-(4-bromo-2-fluorophenyl)-N-phenylaziridine-2-carboxamide ***81***.

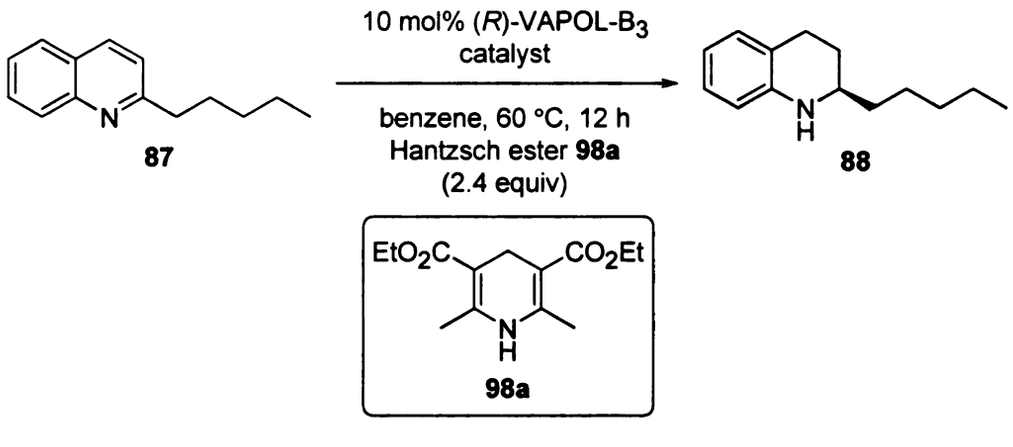
A 25 mL round bottom flask fitted with a magnetic stir bar was flame dried under vacuum and cooled under Argon. To this was added aziridine **60j** (55 mg, 0.092 mmol), which was dissolved in 2 mL dry CH_3CN. The flask was then fitted with a rubber septum and an Argon balloon, and cooled to 0 °C in an ice bath. TfOH (65 μL, 0.74 mmol, 8 equiv) was added to the reaction mixture, the ice bath was removed and the reaction mixture stirred for a total of 3 h. For the work-up, sat. aq. Na_2CO_3 was added till pH > 9, the reaction mixture was diluted with water and ether, and the layers were separated. The aqueous layer was extracted with ether three times, the organic layers combined, washed with brine, dried over $MgSO_4$, filtered through a pad of Celite, subjected to rotary evaporation till dryness and finally to high vacuum to afford the crude product **81**. Column chromatography with regular silica gel and an eluent mixture of 1:3 EtOAc:hexanes afforded pure **81** as a white solid in 53% isolated yield (16 mg, 0.049 mmol).

*Data for **81**:* R_f = 0.24 (1:3 EtOAc:hexanes); ^{1}H NMR (acetone-*d*6, 500 MHz) (invertomers observed) δ 2.19 (t, 1H, *J* = 8.5 Hz), 2.63-2.65 (m, with invertomer, 1H), 2.79-2.82 (m, with invertomer, 1H), 3.31-3.33 (m, with invertomer, 1H), 7.09 (t, 1H, *J* = 7.3 Hz), 7.25-7.38 (m, 5H), 7.68 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR (acetone-*d*6, 125 MHz) (invertomers observed) δ 33.49 (m, invertomers/F-splitting), 41.51 (m, invertomers/F-splitting), 119.20 (d, *J* = 24.9 Hz), 120.07, 120.15, 121.28 (d, *J* = 9.7 Hz), 124.73, 126.97 (d, *J* = 13.3 Hz), 128.52 (d, *J* = 3.7 Hz), 129.48 (d, *J* = 4.6 Hz), 129.69, 139.69 (m, invertomers), 161.27, 163.26, 168.35 (m, invertomers); ^{19}F NMR (acetone-*d*6, 283 MHz) δ -119.46; IR (thin film) 3283w, 1651s, 1603m, 1545m, 1487m, 1446m, 1404m cm^{-1}; HRMS calcd for $C_{15}H_{13}N_2OFBr$ (M+H, ES+) *m/z* 335.0195, meas 335.0187; white solid.

Appendix D

Experimental Information for Chapter Four

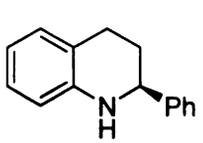
2-pentylquinoline **87** was kindly provided by Dr. Supriyo Majumder, from the research group of Prof. Aaron Odom.[51] 2-phenylquinoline **100** was used as purchased from Aldrich. The requisite Hantzsch esters **98** were prepared according to, or in a similar manner as, previously published procedures.[56] Hantzsch ester **98a** is commercially available. The boroxinate B_3 catalysts were prepared according to the procedures detailed in the experimental information for Chapters 2 and 3.



*(R)-2-pentyl-1,2,3,4-tetrahydroquinoline **88**.* A small vial (3.7 mL), fitted with a Teflon liner, was flame dried and cooled under Argon. 2-pentylquinoline **87** (10 mg, 0.05 mmol, 1 equiv) was added from a stock solution in CH_2Cl_2. The vial was directly subjected to gradual high vacuum to remove the CH_2Cl_2. Hantzsch ester **98a** was then added (31 mg, 0.12 mmol, 2.4 equiv) to the vial. The vial was evacuated and back-filled with Argon. 10 mol% of the *(R)*-VAPOL-B_3 catalyst was added from a stock solution in benzene (1 mL). The reaction mixture was flushed

with Argon above the solvent surface; the vial was capped and stirred at 60 °C for 12 h. The reaction was judged complete by TLC; the crude reaction mixture was subjected to rotary evaporation till dryness and finally to high vacuum to afford crude **88**. This was then subjected to column chromatography with regular silica gel and an eluent mixture of 1:50 EtOAc:hexanes to afford pure **88** as a colorless oil in >99% isolated yield (10 mg, 0.05 mmol). The optical purity was determined to be 73% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99.5:0.5, 222 nm, flow rate 0.5 mL min^{-1}). Retention times were 10 min (major enantiomer) and 12 min (minor enantiomer).

*Data for **88**:* R_f = 0.26 (1:39 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, 3H, *J* = 7.0 Hz), 1.24-1.42 (m, 6H), 1.45-1.50 (m, 2H), 1.54-1.62 (m, 1H), 1.92-1.97 (m, 1H), 2.69-2.83 (m, 2H), 3.19-3.24 (m, 1H), 3.75 (bs, 1H), 6.46 (d, 1H, *J* = 7.4 Hz), 6.58 (t, 1H, *J* = 7.5 Hz), 6.92-6.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.03, 22.62, 25.38, 26.42, 28.10, 31.94, 36.66, 51.57, 114.00, 116.85, 121.37, 126.66, 129.21, 144.71; IR (thin film) 3406m, 3053w, 3015w, 2928s, 2853s, 1608s, 1583s, 1487s, 1275s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 203 M^+ (31), 133 (29), 132 (100); HRMS calcd for $C_{14}H_{22}N$ (M+H, ES+) *m/z* 204.1752, meas 204.1743; $[\alpha]^{23}_D$ = +37.0 (*c* = 1, $CHCl_3$) on 72% ee (*R*)-**88**, literature values: +60.7 (*c* = 1.2, $CHCl_3$, 92% ee)[50b] and +51.4 (*c* = 1, $CHCl_3$)[50a]; colorless oil.



101

(S)-2-phenyl-1,2,3,4-tetrahydroquinoline ***101***. The general procedure described above was followed for the reaction of 2-phenylquinoline **100** to afford crude **101**. Column chromatography with regular silica gel and an eluent mixture of 1:50 EtOAc:hexanes afforded pure **101** as a colorless oil in >99% isolated yield (10 mg, 0.05 mmol). The optical purity was determined to be 67% ee by HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 95:5, 222 nm, flow rate 0.6 mL min^{-1}). Retention times were 9 min (major enantiomer) and 13 min (minor enantiomer).

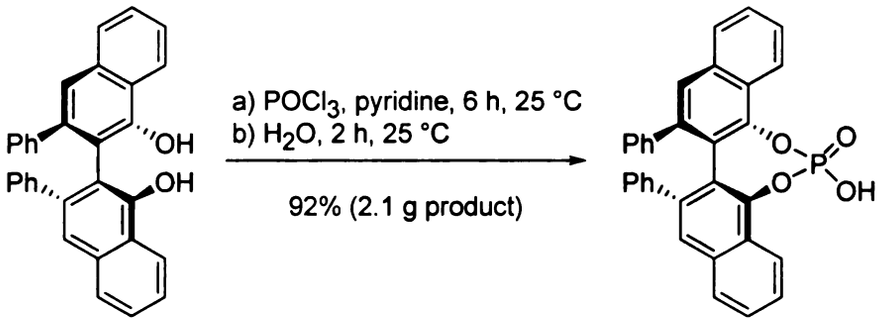
Data for ***101****:* R_f = 0.49 (1:9 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.95-2.03 (m, 1H), 2.09-2.14 (m, 1H), 2.74 (dt, 1H, *J* = 4.7, 16.3 Hz), 2.89-2.95 (m, 1H), 4.02 (s, 1H), 4.43 (dd, 1H, *J* = 3.2, 9.3 Hz), 6.53 (d, 1H, *J* = 7.6 Hz), 6.65 (t, 1H, *J* = 7.3 Hz), 6.99-7.02 (m, 2H), 7.27-7.29 (m, 1H), 7.33-7.39 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.36, 30.96, 56.24, 113.94, 117.13, 120.85, 126.52, 126.87, 127.41, 128.55, 129.27, 144.70, 144.79; IR (thin film) 3404w, 3026w, 2922w, 2841w, 1606m, 1585m, 1483m, 1309m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 209 M^+ (41), 208 (22), 132 (59), 117 (22), 103 (25), 91 (37), 77 (100); HRMS calcd for $C_{15}H_{16}N$ (M+H, ES+) *m/z* 210.1283, meas 210.1281; $[\alpha]^{23}_D$ = -27.5 (*c* = 1, $CHCl_3$) on 67% ee (*S*)-**101**, literature values:[50a,b] -37.7 (*c* = 1, $CHCl_3$); colorless oil.

Appendix E

Experimental Information for Chapter Five

General considerations

Both antipodes of VAPOL and VANOL are commercially available from Aldrich and Strem Chemicals, Inc. Alternately, they can be prepared according to a procedure described in literature.[65] Phosphorus oxychloride was purchased from Aldrich, and pyridine from Jade Scientific, and both were used as obtained. Other reagents were used as purchased from commercial sources. Dichloromethane and triethylamine were dried from calcium hydride under nitrogen. Propionitrile and DMF were distilled appropriately before use. The VANOL monomer **116** can be prepared on a multi-gram scale according to a procedure described in literature.[65]



5
(*S*)-VANOL

93
(*S*)-VANOL phosphoric acid

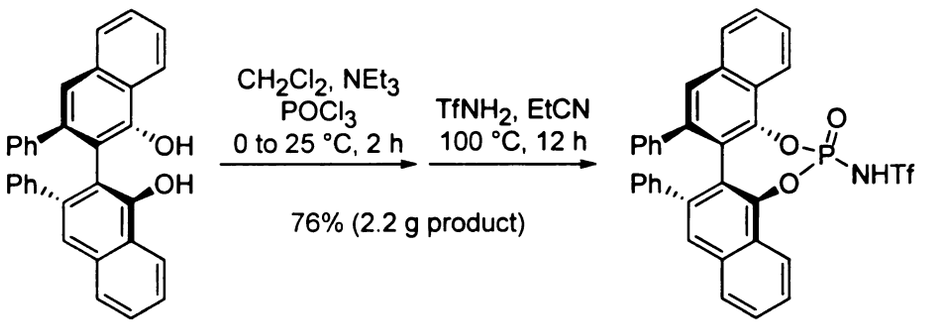
*(S)-VANOL phosphoric acid **93**.* To a 50 mL round bottom flask, flame-dried and cooled under Argon, was added (*S*)-VANOL (2 g, 4.57 mmol, 1 equiv) and 8 mL pyridine to obtain a clear yellow solution. The round bottom flask was fitted with a rubber septum and an Argon balloon. Thereafter, $POCl_3$ (0.85 mL, 9.13 mmol, 2 equiv) was added slowly via a syringe. The reaction mixture was

stirred at room temperature then for 6 h, in which time salts started precipitating out. Thereafter, 8 mL water was added via a syringe, and the reaction mixture was stirred at room temperature for 2 h. For the workup then, the reaction mixture was taken in a separatory funnel and 350 mL CH_2Cl_2 was added. This was then extracted with 4 X 350 mL 1 N HCl. The organic layer was collected, dried over Na_2SO_4, filtered through a pad of Celite, subjected to rotary evaporation and finally high vacuum to afford the crude product **93** as a white solid. The purification was a simple precipitation. The crude solid was dissolved in a minimum amount of CH_2Cl_2 to obtain a clear yellow solution, which was followed by the addition of excess pentane to precipitate the product as a white solid in the solution. Filtration off a Buchner funnel then provided the pure (*S*)-VANOL phosphoric acid product **93**, which was subjected to high vacuum to completely remove all organic volatiles. Thus, (*S*)-VANOL phosphoric acid **93** was obtained as a white solid (mp. decomposes >250 °C) in 92% yield (2.1 g, 4.2 mmol).

It was found that (*S*)-VANOL phosphoric acid decomposed on regular silica gel column chromatography.

*Spectral data for **93**:* ^{1}H NMR (THF-*d*8, 500 MHz) δ 6.50 (d, 4H, *J* = 8.2 Hz), 6.92 (t, 4H, *J* = 7.7 Hz), 7.07 (t, 2H, *J* = 7.4 Hz), 7.53 (s, 2H), 7.54-7.61 (m, 4H), 7.86 (d, 2H, *J* = 7.6 Hz), 8.46 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR (THF-*d*8, 125 MHz) δ 123.78, 123.84 (d, 1C, *J* = 2.0 Hz), 127.08 (d, 1C, *J* = 2.6 Hz), 127.13, 127.20, 127.38, 128.15, 128.43, 128.46, 129.84, 135.31, 141. 14, 141.27, 147.40 (d, 1C, *J* = 9.8 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 7.03 (s); IR (thin film) 3435s,

3057w, 1634m, 1489m, 1026m cm^{-1}; Mass spectrum, *m/z* (% rel intensity) 500 M^+ (13), 83 (14), 73 (20), 57 (22), 44 (100), 41 (25); HRMS calcd for $C_{32}H_{20}O_4P$ (M-H, ESI-) *m/z* 499.1099, meas 499.1118; $[\alpha]^{23}_D$ = +43.0 (*c* 1.0, CH_2Cl_2) for (*S*)-VANOL phosphoric acid **93**.



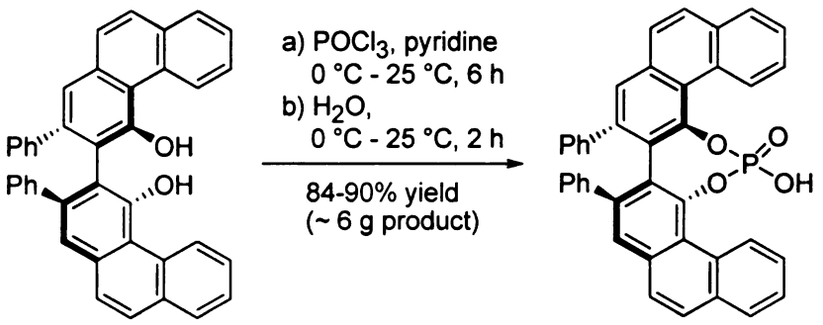
5
(*S*)-VANOL

94
(*S*)-*N*-triflyl VANOL phosphoramide

*(S)-N-triflyl VANOL phosphoramide **94***. This was prepared in the same manner as the preparation of the (*R*)-*N*-triflyl VAPOL phosphoramide **92** described below. The entire process was similar, except that DMAP was not utilized in the synthesis of **94**. Thus, (*S*)-VANOL (2 g, 4.57 mmol) was reacted accordingly to afford crude **94**. This was also purified and precipitated accordingly to afford the pure product **94** as a white solid (mp. decomposes >250 °C) in 76% isolated yield (2.2 g, 3.49 mmol).

*Spectral data for **94***: ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 6.38-6.40 (m, 4H), 6.96 (dt, 4H, *J* = 2.6, 5.6 Hz), 7.12 (t, 2H, *J* = 7.4 Hz), 7.56 (d, 2H, *J* = 8.3 Hz), 7.60-7.70 (m, 4H), 7.95-7.99 (m, 2H), 8.27 (d, 1H, *J* = 8.3 Hz), 8.35-8.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 120.10 (CF_3(q), *J* = 318.2 Hz), 122.13, 122.51, 122.95, 123.20, 125.69, 125.73, 125.75, 126.29, 126.52, 126.57, 126.71, 126.86, 127.17, 127.35, 127.48, 127.60, 127.72, 127.65, 128.87, 128.96, 133.82, 134.22,

139.85, 139.90, 140.00, 140.16, 145.30 (d, 1C, J = 8.7 Hz), 146.34 (d, 1C, J = 9.7 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 0.75 (s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ -78.69 (s); IR (thin film) 3430s, 3055w, 1284m, 1217s, 1084s, 760m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) M^+ 631 (11), 420 (14), 170 (17), 80 (81), 79 (48), 44 (100); HRMS calcd for $C_{33}H_{20}NO_5F_3PS$ (M-H, ESI-) *m/z* 630.0752, meas 630.0785; $[\alpha]^{23}_D$ = +137.3 (*c* 1.0, CH_2Cl_2) for (*S*)-*N*-triflyl VANOL phosphoramide **94**.



4
(*R*)-VAPOL

91
(*R*)-VAPOL phosphoric acid

*(R)-VAPOL phosphoric acid **91**.*

Procedure for the reaction

A one-neck 100 mL round-bottom flask, fitted with a magnetic stirrer (2.50 X 1.30 X 1.10 cm), was flame-dried and cooled under Argon to room temperature. (*R*)-VAPOL (6.00 g, 11.15 mmol) was added to this flask followed by the addition of pyridine (24.50 g, 25.00 mL, 0.31 mol). The flask was then fitted with a rubber septum and an Argon balloon. The mixture was stirred to completely dissolve the (*R*)-VAPOL, and a clear intense yellow solution was obtained. The flask was then placed in an ice-bath and the solution stirred at 0 °C for 20 min. $POCl_3$ (3.42 g, 2.08 mL, 22.30 mmol) was added slowly via a plastic

syringe over a period of 10 min at 0 °C. The ice-bath was removed and the flask was allowed to warm up to room temperature. The reaction mixture was then stirred at room temperature for another 6 h. Over this period, the color of the solution changed from intense clear yellow to a cloudy pale yellow, and solid salts started precipitating out. The flask was then placed in an ice-bath again, and stirred for 10 min at 0 °C. Water (25.00 mL, 1.39 mol) was added slowly via a plastic syringe into the flask over 5 min at 0 °C. The ice-bath was removed, the flask warmed up to room temperature and the reaction mixture was stirred at room temperature for 2 h.

Procedure for work-up

The reaction mixture was transferred to a 2 L separatory funnel. The round-bottom flask was rinsed twice with 15 mL dichloromethane and once with 15 mL water, and the rinse was transferred to the separatory funnel each time. 750 mL dichloromethane was added to the separatory funnel, followed by the addition of 1000 mL 1 N HCl. The mixture was vigorously shaken for 3 min, and the organic layer collected. This organic layer was washed again, vigorously each time, with 6 X 1000 mL 1 N HCl. Towards the end of this process, the organic layer changed from a clear pale yellow to a white cloudy composition. Thereafter, the organic layer was washed with 2 X 900 mL saturated NaCl solution (brine), towards the end of which the organic layer regained its clear pale yellow composition. This was then dried over 80 g anhydrous sodium sulfate, filtered through a sintered glass frit covered with a layer of Celite, washed with 150 mL dichloromethane and all volatiles were then removed via rotary

evaporation. The resulting light brown solid was subjected to high vacuum (0.1 mm Hg) overnight to afford the crude product in 94% yield (6.30 g, 10.50 mmol).

Procedure for column chromatography

A 3" diameter column was packed to a depth of 17" with 1700 mL silica gel, in the form of a slurry with 1:14 MeOH:$CHCl_3$ (Note 1). The crude product was dissolved in 35 mL 1:1 MeOH:$CHCl_3$ (Note 2) to obtain a cloudy yellow solution, and added to the top of the silica gel layer via a pipette. The round-bottom flask, which previously contained the crude product, was rinsed twice with 3 mL 1:1 MeOH:$CHCl_3$, and the rinse was added to the top of the silica gel layer each time. The top of the product solution layer was brought to the top of the silica gel layer, and then a layer of sand (0.5″ X 3″) was added on the top of the silica gel layer. The top of the column was then rinsed twice with 10 mL 1:14 MeOH:$CHCl_3$, and the solution let run into the sand layer each time. The column was run under gravity with a 1:14 mixture of MeOH:$CHCl_3$ as eluent. During this time, two bands could be observed travelling down the column, visible under long wave UV (365 nm), and these bands appeared to be bright purple in color under the long wave UV. The first band, the smaller band, is a side-product formed during the reaction (Note 3), and the second band, a much broader band, is the product of the reaction. After the elution started, *ca.* 900 mL of a void volume was collected under gravity as the first fraction. Thereafter, a second fraction was collected under gravity, *ca.* 350 mL (1:14 MeOH:$CHCl_3$), which was the side-product. After the side-product completely eluted (confirmed by the disappearance of the purple band on the column under long wave UV), a void

volume of *ca.* 200 mL (1:14 MeOH:$CHCl_3$) was collected under gravity before the product began to elute. Once the product started eluting, the eluent system was changed to 1:3 MeOH:$CHCl_3$, and N_2 pressure was applied and the column was flushed. The product continued to elute for *ca.* 3600 mL of the eluent (1:3 MeOH:$CHCl_3$). At that point, the product stopped eluting, as observed by the disappearance of an intense purple spot on TLC, observed under short wave UV (254 nm) (Note 4). All product fractions were then collected, the volatiles removed by rotary evaporation and subjected to high vacuum (0.1 mm Hg) overnight, to afford the product as a light brown solid in 109% yield (7.30 g, 12.17 mmol). ^{1}H NMR analysis of this product revealed substantial amounts of residual methanol and chloroform solvents, which explained the >100% yield.

Procedure for removal of residual solvents

The product, in a one-neck 500 mL round-bottom flask, was dissolved in a minimum amount of CH_2Cl_2 to get a clear yellow solution (Note 5). Then the 500 mL RBF was filled almost completely with pentanes while swirling by hand, during which time the product VAPOL hydrogenphosphate started precipitating out. The resulting solution was swirled by hand for a few minutes. This was then filtered with a Büchner funnel, the solid product dried under a stream of N_2 on the Büchner funnel, collected and subjected to high vacuum (0.1 mm Hg) for at least 3-4 h. This precipitation cycle was repeated (usually 6-7 times) until ^{1}H NMR analysis of the product showed complete (or almost complete) removal of the residual solvent peaks.

Procedure for drying of the product (Note 6)

The VAPOL hydrogenphosphate obtained from the above procedure was placed on an aluminum foil boat into an Abderhalden drying gun. It was then dried under high vacuum (0.1 mm Hg) over refluxing benzene for 48 h.

The above procedure affords the product (*R*)-VAPOL hydrogenphosphate as a white solid (mp >300 °C) in 84-90% isolated yield (for 87% yield – 5.83 g, 9.72 mmol).

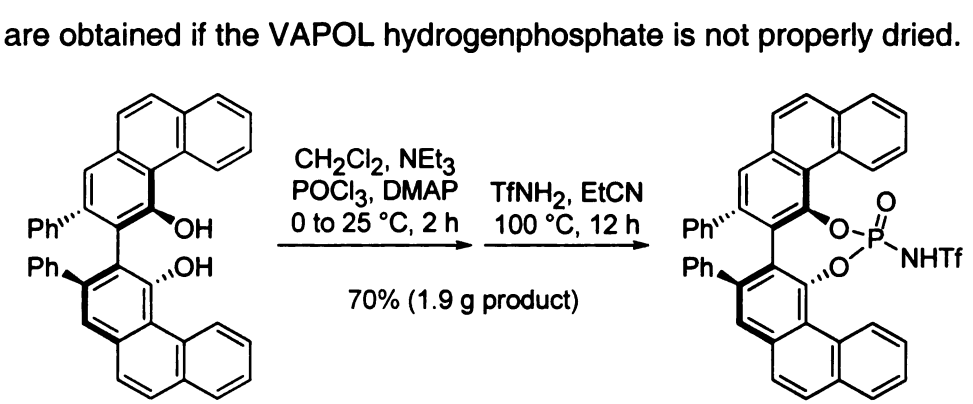
Spectral data for VAPOL phosphoric acid ***91***: ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 6.44 (d, 4H, *J* = 8.2 Hz), 6.96 (t, 4H, *J* = 7.6 Hz), 7.11 (t, 2H, *J* = 7.4 Hz), 7.64 (s, 2H), 7.70-7.76 (m, 4H), 7.89 (d, 2H, *J* = 8.8 Hz), 7.94 (d, 2H, *J* = 8.8 Hz), 8.05 (d, 2H, *J* = 7.8 Hz), 9.75 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR (DMSO-*d*6, 125 MHz) (1 carbon not located) δ 121.23, 125.98, 126.46, 126.58, 126.79, 126.92, 127.51, 128.03, 128.48, 128.58, 128.88, 129.13, 132.81, 133.91, 139.34, 140.55, 149.2 (d, 1C, *J* = 9.3 Hz); ^{31}P NMR (DMSO-*d*6, 121 MHz) δ 1.05 (s); IR (thin film) 3854s, 1653s, 1558s; Mass spectrum (% rel intensity) M^{+} 600 (43), 520 (21), 221 (64), 44 (100); HRMS calcd for $C_{40}H_{24}O_4P$ (M-H, ESI-) *m/z* 599.1412, meas 599.1434; $[\alpha]^{23}_{D}$ = -146.5 (*c* 1.0, CH_2Cl_2) for (*R*)-VAPOL phosphoric acid **91**.

Notes

1. Commercial chloroform stabilized with amylene was used; and NOT the chloroform stabilized with ethanol. It was found that if the latter is used, it becomes extremely difficult to remove the residual ethanol from the product.
2. Sometimes it is difficult to dissolve the crude product in 35 mL of 1:1 MeOH:$CHCl_3$. In such cases, a little pure MeOH could be added to help the

dissolution. Alternately, the mixture could be heated at *ca.* 30 °C to aid the dissolution.

3. The side-product was collected, subjected by rotary evaporation to dryness and high vacuum (0.1 mm Hg) for 2 hours. Its weight was 21 mg, and ^{1}H NMR analysis showed a mixture of unidentified products.
4. The product, when spotted on a TLC and observed under short wave UV (254 nm), is an intense purple spot.
5. Sometimes, the VAPOL hydrogenphosphate obtained after column chromatography did not dissolve in CH_2Cl_2 to give a clear solution. In such cases, the crude product should be left on high vacuum (0.1 mm Hg) overnight again, which might solve the problem. If not, then the precipitation should be carried out with the emulsion obtained on the addition of CH_2Cl_2 to the crude product – it was found that it proceeded just fine even if a clear solution was not obtained.
6. It has been observed in some reactions[72] that lower asymmetric inductions are obtained if the VAPOL hydrogenphosphate is not properly dried.



4
(*R*)-VAPOL

92
(*R*)-*N*-triflyl VAPOL phosphoramide

(R)-N-triflyl VAPOL phosphoramide ***92***. To a 100 mL RBF, flame-dried and cooled under Argon, was added (*R*)-VAPOL (2 g, 3.72 mmol) and dry CH_2Cl_2 (20

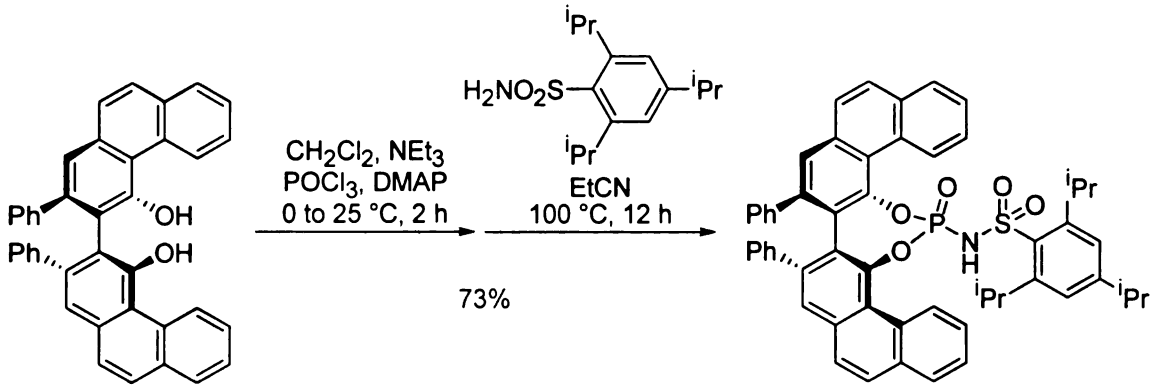
mL) to obtain a clear solution. The RBF was fitted with a rubber septum and an Argon balloon. It was then cooled to 0 °C in an ice-bath. Thereafter, dry NEt_3 (3.62 mL, 26 mmol) and $POCl_3$ (0.42 mL, 4.46 mmol) were added sequentially via a syringe, which was followed by the addition of DMAP (0.91 g, 7.44 mmol), all at 0 °C. The reaction flask was then warmed up to room temperature, and stirred for 2 h. Thereafter, $TfNH_2$ (1.11 g, 7.44 mmol) and distilled EtCN (20 mL) were added, and a water condenser (flame-dried and cooled under Argon separately) was attached. The reaction mixture was then heated at 100 °C for 12 h and cooled down to room temperature thereafter. For the work-up, 100 mL water and 150 mL diethyl ether were then added, and the mixture extracted. The aqueous layer was extracted with 2 X 100 mL ether, the organic layers combined and washed with 300 mL sat. $NaHCO_3$ solution, 2 X 300 mL 4N HCl, dried over Na_2SO_4, filtered through a pad of Celite and subjected to rotary evaporation and high vacuum (0.1 mm Hg) to afford the crude product **92** as a light brown solid.

Crude TLC (EtOAc) showed a long product streak in the middle of the TLC plate and a baseline impurity spot. For purification thus, the crude product was dissolved in EtOAc, flushed through a glass frit packed with 1:1 Celite:silica gel and rinsed with EtOAc. Different fractions were collected and analyzed by TLC. All product fractions showed absence of the baseline impurity. This process was repeated if the fractions were not pure and contained the baseline impurity. All fractions were collected, subjected to rotary evaporation and high vacuum.

The pure product was then subjected to precipitation. It was dissolved in a minimum amount of CH_2Cl_2 and an excess of pentane was added to precipitate

the product. It was then filtered off a Buchner funnel; the solid product was collected and subjected to high vacuum. This precipitation cycle was repeated until ^{1}H NMR analysis indicated complete (or almost complete) removal of all residual solvent peaks. This process thus afforded the pure product **92** as a white solid (mp. decomposes >250 °C) in 70% isolated yield (1.9 g, 2.60 mmol).

*Spectral data for **92***: ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 6.43 (t, 4H, *J* = 7.8 Hz), 6.96 (t, 4H, *J* = 7.6 Hz), 7.11 (t, 2H, *J* = 7.5 Hz), 7.62-7.73 (m, 6H), 7.88-7.96 (m, 4H), 8.03-8.06 (m, 2H), 9.67-9.69 (m, 1H), 9.91 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 120.24 (CF_3 (q), *J* = 323.6 Hz), 121.40, 121.17, 121.42, 121.44, 125.98, 125.99, 126.43, 126.49, 126.57, 126.58, 126.64, 126.68, 126.73, 126.77, 126.91, 126.92, 126.94, 127.52, 127.53, 128.28, 128.36, 128.48, 128.68, 128.73, 128.85, 128.92, 128.95, 132.77, 133.96, 134.00, 139.18, 139.33, 140.54, 140.59, 147.91 (d, 1C, *J* = 8.7 Hz), 148.96 (d, 1C, *J* = 11 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 1.07 (s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ -79.69 (s); IR (thin film) 3424s, 1653m, 1635m, 1213w cm^{-1}; Mass spectrum: *m/z* (% rel intensity) $(M-1)^{-}$ 730 (100), 630 (3); HRMS calcd for $C_{41}H_{24}NO_5F_3PS$ (M-H, ESI-) *m/z* 730.1065, meas 730.1080; $[\alpha]^{23}_{D}$ = -476.1 (*c* 1.0, CH_2Cl_2) for (*R*)-*N*-triflyl VAPOL phosphoramide **92**.



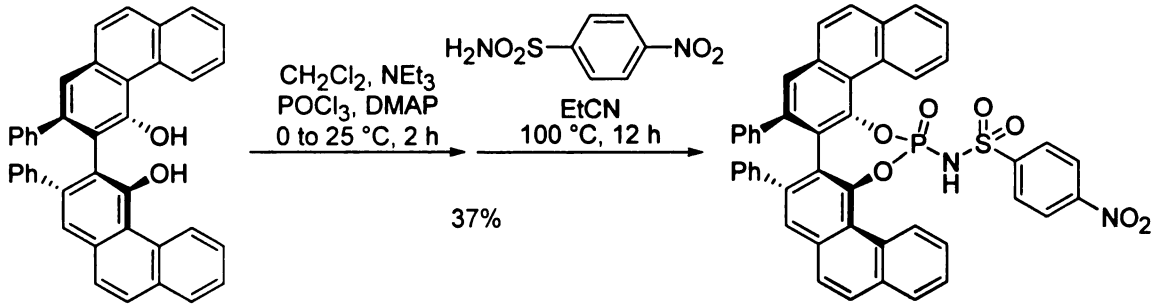
4
(*S*)-VAPOL

112
N-TRIP-benzene sulfonyl
VAPOL phosphoramide

(S)-N-(2,4,6-triisopropylbenzene sulfonyl) VAPOL phosphoramide ***112.*** This was prepared in the same manner as the preparation of the (*R*)-*N*-triflyl VAPOL phosphoramide **92** described above. The reaction and work-up was identical, but the purification was different. Thus, (*S*)-VAPOL (0.30 g, 0.56 mmol) was reacted and worked-up accordingly to afford crude **112**. After work-up, crude TLC showed presence of 2,4,6-triisopropylbenzene sulfonamide. Thus, the crude solid product **112** was subjected to column chromatography with an eluent system of 1:3 EtOAc:hexanes to elute the sulfonamide first (R_f = 0.3). Once the sulfonamide was completely eluted from the column (as judged by TLC), the column was flushed with EtOAc to elute the product **112**. This afforded the pure product **112** as a light brown solid (mp. decomposes >250 °C) in 73% isolated yield (0.35 g, 0.41 mmol).

*Spectral data for **112**:* ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 0.91 (t, 12H, *J* = 7.1 Hz), 1.20 (t, 6H, *J* = 6.8 Hz), 2.81-2.87 (m, 1H), 4.42-4.50 (m, 2H), 6.37 (d, 2H, *J* = 7.1 Hz), 6.44 (d, 2H, *J* = 7.1 Hz), 7.52 (t, 1H, *J* = 7.1 Hz), 7.56 (d, 2H, *J* = 3.4 Hz), 7.64-7.68 (m, 2H), 6.93 (t, 4H, *J* = 7.3 Hz), 6.97-7.02 (m, 3H), 7.06-7.10

(m, 2H), 7.81-7.87 (m, 3H), 7.89-7.94 (m, 2H), 8.00-8.02 (m, 1H), 9.55 (d, 1H, J = 8.8 Hz), 9.90-9.92 (m, 1H); ^{13}C NMR (DMSO-$d6$, 125 MHz) (1 sp^2 carbon missing) δ 23.72, 23.75, 24.52, 24.81, 28.02, 33.37, 121.48, 121.50, 121.62, 121.65, 122.20, 125.68, 125.90, 126.03, 126.16, 126.48, 126.60, 126.65, 126.86, 126.95, 127.01, 127.02, 127.34, 127.41, 127.97, 128.15, 128.38, 128.87, 128.91, 129.04, 129.35, 132.52, 132.73, 133.72, 133.79, 139.51, 139.67, 140.51, 140.54, 142.17, 142.20, 147.64, 148.33, 148.91, 148.98, 148.94 (d, 1C, J = 9.2 Hz), 150.02 (d, 1C, J = 10.9 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 0.78 (s); IR (thin film) 3414s, 3057w, 2961m, 1626s, 1599s, 1226s, 1126s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) $(M+1)^+$ 866 (100), 301 (60); HRMS calcd for $C_{55}H_{47}NO_5PS$ (M-H, ESI-) *m/z* 864.2913, meas 864.2951; $[\alpha]^{23}_D$ = +270.5 (*c* 1.0, CH_2Cl_2) for (*S*)-**112**.

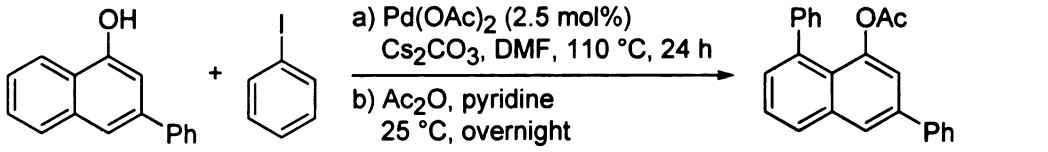


4
(*S*)-VAPOL

113
N-nitrobenzene sulfonyl
VAPOL phosphoramide

(S)-N-(4-nitrobenene sulfonyl) VAPOL phosphoramide ***113.*** This was prepared in the same manner as the preparation of the (*R*)-*N*-triflyl VAPOL phosphoramide **92** described above. The entire process was similar, except that the precipitation was not done. Thus, (*S*)-VAPOL (0.30 g, 0.56 mmol) was reacted and purified accordingly to afford the pure product **113** as a yellow solid (mp. decomposes >250 °C) in 37% isolated yield (0.16 g, 0.21 mmol).

*Spectral data for **113**:* ^{1}H NMR (DMSO-*d*6, 500 MHz) δ 6.29 (d, 2H, *J* = 7.3 Hz), 6.36 (d, 2H, *J* = 7.3 Hz), 6.91 (q, 4H, *J* = 7.9 Hz), 7.06-7.09 (m, 2H), 7.48 (d, 2H, *J* = 8.8 Hz), 7.54 (s, 1H), 7.58 (s, 1H), 7.61-7.72 (m, 4H), 7.84-7.94 (m, 6H), 8.02-8.06 (m, 2H), 9.67 (d, 1H, *J* = 8.1 Hz), 10.05 (d, 1H, *J* = 8.5 Hz); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 121.20, 121.46, 122.95, 124.42, 126.01, 126.09, 126.17, 126.35, 126.50, 126.56, 126.60, 126.66, 126.73, 126.76, 126.81, 127.03, 127.19, 127.35, 127.45, 128.17, 128.44, 128.53, 128.57, 128.82, 128.87, 128.98, 129.06, 129.35, 132.66, 132.72, 133.79, 133.83, 139.18, 139.24, 140.41, 140.48, 147.33, 148.30 (d, 1C, *J* = 9.9 Hz), 149.10 (d, 1C, *J* = 10.8 Hz), 153.18; ^{31}P NMR ($CDCl_3$, 121 MHz) δ -0.11 (s); Mass spectrum: *m/z* (% rel intensity) $(M-1)^-$ 783 (100), 771 (7); HRMS calcd for $C_{46}H_{28}N_2O_7PS$ (M-H, ESI-) *m/z* 783.1355, meas 783.1342; $[\alpha]^{23}_D$ = +257.4 (*c* 1.0, MeOH) for (*S*)-**113**.



116 **117** 1.2 equiv **118** 75% (over 2 steps, 6 g product) average of 3 runs

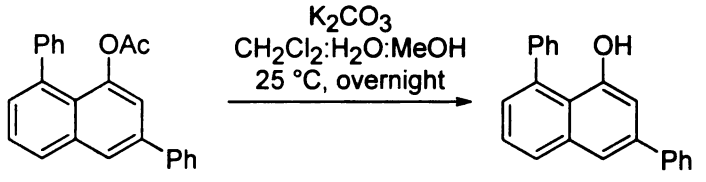
*3,8-diphenylnaphthalen-1-yl acetate **118**.* A 250 mL round bottom flask, equipped with a magnetic stir bar and a water condenser, was flame dried and cooled under Argon. To the flask was added Cs_2CO_3 (14.81 g, 45.45 mmol, 2 equiv), and the assembly was then heated at 150 °C for 2 h under high vacuum (0.1 mm Hg). This was subsequently cooled to room temperature, and the VANOL monomer (5.00 g, 22.73 mmol, 1 equiv) was added, which was followed by the addition of $Pd(OAc)_2$ (127.5 mg, 0.57 mmol, 0.025 equiv), DMF (120 mL)

and iodobenzene (3.04 mL, 27.28 mmol, 1.2 equiv). The assembly was then fitted with a rubber septum and an Argon balloon, and stirred in an oil bath at 110 °C for 24 h. The reaction mixture was subsequently cooled to room temperature, and added to a separatory funnel. Also added to the funnel were 200 mL EtOAc, 200 mL water and 50 mL brine solution. The layers were separated, the aqueous layer extracted with 4 × 200 mL EtOAc, the organic layers were combined, and washed with 2 × 500 mL water, 2 × 500 mL 0.5 N HCl, and brine. The organic layer was dried over Na_2SO_4, filtered through a pad of Celite, subjected to rotary evaporation till dryness and finally to high vacuum (0.1 mm Hg) overnight to afford the crude intermediate product.

To the flask containing the crude product was then added pyridine (120 mL) to dissolve the crude product. The flask was equipped with a rubber septum and an Argon balloon. Ac_2O (11.00 mL, 113.65 mmol, 5 equiv) was then added slowly via a syringe and the reaction mixture stirred at room temperature for 12 h. The reaction mixture was added to a separatory funnel, with 700 mL dichloromethane. This was then extracted with 4 × 700 mL 1 N HCl, the organic layers combined, washed with brine, dried over Na_2SO_4, filtered through a pad of Celite, subjected to rotary evaporation till dryness and finally to high vacuum to afford crude product **118**. Column chromatography with regular silica gel and an eluent system of 1:19 EtOAc:hexanes afforded pure **118** as a light yellow solid in 76% isolated yield (5.86 g, 17.34 mmol).

*Data for **118**:* R_f = 0.24 (1:19 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.38 (s, 3H), 7.25 (dd, 1H, *J* = 1.2, 7.1 Hz), 7.34-7.51 (m, 10H), 7.68-7.70 (m,

2H), 7.93 (d, 1H, J = 8.3 Hz), 8.02 (d, 1H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.72, 119.83, 123.85, 124.67, 125.86, 126.60, 127.28, 127.62, 127.73, 128.60, 128.89, 129.47, 130.19, 136.02, 137.30, 138.45, 139.75, 143.40, 147.17, 169.86; IR (thin film) 3055w, 3028w, 1785s, 1367m, 1203s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) M^+ 338 (10), 297 (28), 296 (100); HRMS calcd for $C_{24}H_{19}O_2$ (M+H, ESI+) *m/z* 339.1385, meas 339.1393; light yellow solid, mp. 117-119 °C.



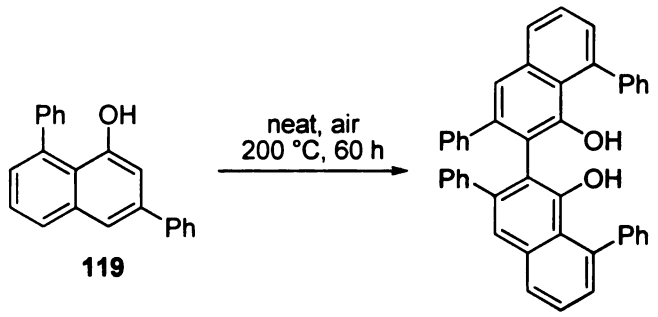
118

119
92% (5 g product)
average of 3 runs

3,8-diphenylnaphthalen-1-ol ***119.*** To a 500 mL round bottom flask, fitted with a magnetic stir bar, was added compound **118** (5.76 g, 17.04 mmol, 1 equiv) and dry dichloromethane (25 mL) to obtain a clear yellow solution. To this was added slowly a clear solution of K_2CO_3 (4.71 g, 34.08 mmol, 2 equiv) in water (18 mL). To the reaction flask was then added MeOH (110 mL), and the reaction mixture was stirred at room temperature for 15 h. During the course of the reaction, the color of the solution changed from yellow to an intense green and finally to light brown/orange, and salts precipitated out. For the work-up, the reaction mixture was added to a separatory funnel, and 150 mL of water and 150 mL dichloromethane were also added. The layers were separated, and the aqueous layer was washed with 3 × 150 mL dichloromethane and 2 × 150 mL diethylether. The organic layers were combined, washed with brine solution, dried over Na_2SO_4, filtered through a pad of Celite, subjected to rotary

evaporation till dryness and finally to high vacuum to afford crude product **119**. Column chromatography with regular silica gel and an eluent mixture of 1:19 EtOAc:hexanes afforded pure **119** as a colorless oil in 94% isolated yield (4.80 g, 16.22 mmol).

*Data for **119**:* R_f = 0.22 (1:19 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.47 (s, 1H), 7.18-7.20 (m, 2H), 7.36 (tt, 1H, *J* = 1.2, 7.4 Hz), 7.44-7.48 (m, 3H), 7.50-7.54 (m, 5H), 7.70-7.72 (m, 3H), 7.90 (dd, 1H, *J* = 1.0, 8.3 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 111.19, 118.86, 120.46, 125.30, 127.24, 127.53, 128.45, 128.66, 128.80, 129.02, 129.04, 129.46, 135.95, 136.11, 139.58, 140.45, 141.12, 153.34; IR (thin film) 3490s, 3055w, 1628m, 1496m, 1373m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) M^+ 296 (100); HRMS calcd for $C_{22}H_{17}O$ (M+H, ESI+) *m/z* 297.1279, meas 297.1274; colorless oil.



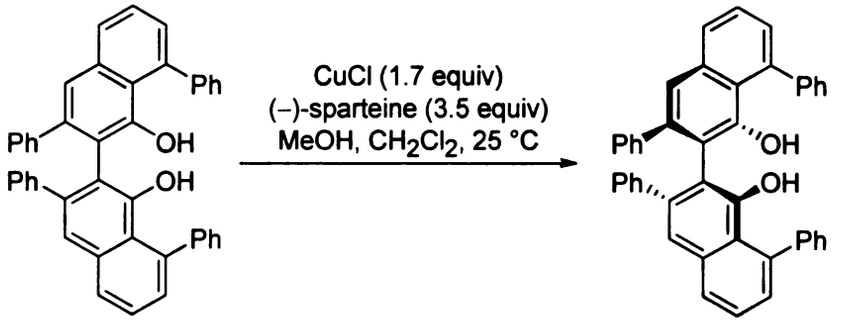
119

120
53% (2.5 g product)
average of 3 runs

3,3',8,8'-tetraphenyl-2,2'-binaphthyl-1,1'-diol (racemic 8,8'-Ph_2VANOL) ***120.*** The monomer **119** (4.65 g, 15.71 mmol) was dissolved in diethylether and divided equally into 5 glass test tubes (18 d × 150 h mm). The diethylether in all test tubes was then evaporated by heating slightly on a water bath in a fume hood. All test tubes were fitted with magnetic stir bars, and subsequently heated

in an oil bath at 200 °C with rapid stirring for 60 h. The test tubes were then allowed to cool down to room temperature, the crude product in the test tubes dissolved in dichloromethane, combined, and subjected to rotary evaporation till dryness and finally to high vacuum to afford crude product **120**. Careful column chromatography with regular silica gel and an eluent mixture of 1:19 EtOAc:hexanes afforded pure **120** as a light yellow solid in 54% isolated yield (2.50 g, 4.24 mmol).

*Data for **120**:* R_f = 0.15 (1:19 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.46 (s, 2H), 6.98 (d, 2H, *J* = 7.2 Hz), 7.00-7.02 (m, 4H), 7.11 (t, 4H, *J* = 7.5 Hz), 7.14-7.17 (m, 4H), 7.30-7.45 (m, 12H), 7.74 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 117.46, 120.64, 121.17, 125.16, 125.84, 126.30, 126.88, 127.06, 127.58, 128.57, 128.63, 129.39, 135.05, 138.49, 140.89, 141.23, 144.18, 152.20; IR (thin film) 3524s, 3053w, 1568m, 1493m, 1348s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) M^+ 590 (100), 295 (44); HRMS calcd for $C_{44}H_{31}O_2$ (M+H, ESI+) *m/z* 591.2324, meas 591.2309; light yellow solid, mp. 222-226 °C.



120

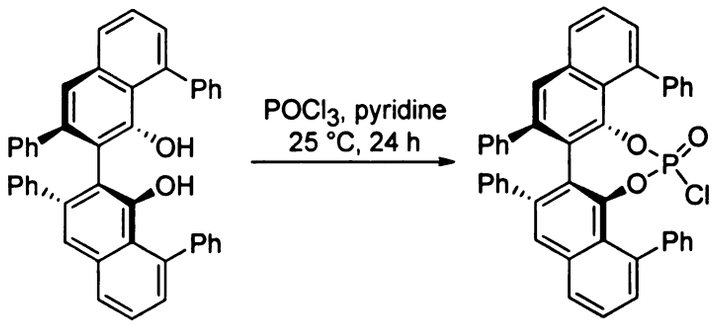
121
(*S*)-8,8'-Ph_2VANOL
62% (3 g product), >99.9% ee
average of 2 runs

(S)-3,3',8,8'-tetraphenyl-2,2'-binaphthyl-1,1'-diol ***121***. A 250 mL round bottom flask was flame dried and cooled under Argon. After the flask had cooled to room temperature, it was opened to air. To the flask were then added CuCl (1.38 g, 13.9 mmol, 1.7 equiv), MeOH (125 mL), and (–)-sparteine (6.64 mL, 28.88 mmol, 3.5 equiv), and this mixture was sonicated open to air in an ultrasound water bath at room temperature for 1 h. A dark green solution was obtained at this stage; the flask was then fitted with a rubber septum, and the solution was deoxygenated by bubbling in Argon via a metallic needle (1 h inside the solution and 0.5 h above the solution). A different 1 L round bottom flask fitted with a magnetic stir bar was flame dried and cooled under Argon. To this flask was added the racemic ligand **120** (4.9 g, 8.3 mmol, 1 equiv), which was dissolved in 400 mL dry dichloromethane to obtain a clear yellow solution. The flask was then fitted with a rubber septum, and the solution was deoxygenated with Argon in a similar way as above. The copper-sparteine complex prepared above was added to this 1 L reaction flask via a cannula under Argon pressure. The cannula was replaced with an Argon balloon; the flask was sonicated in an ultrasound water bath for 15 min, covered with aluminum foil, and subsequently stirred at room temperature with a magnetic stirrer for 3 h.

The reaction mixture was then quenched with 70 mL aq. sat. $NaHCO_3$ solution, stirred for 10 min and then added to a separatory funnel, which was followed by the addition of 200 mL water. The layers were separated, the aqueous layer extracted with 3 × 200 mL dichloromethane, the organic layers combined, dried over Na_2SO_4, filtered through a pad of Celite, subjected to rotary

evaporation till dryness and finally to high vacuum to afford a dark green crude product. This was dissolved in a minimum amount of dichloromethane, and subjected to flash column chromatography with regular silica gel and dichloromethane as the eluent, to separate the copper salts and other baseline impurities. This afforded again the crude product **121**, which was subjected to careful column chromatography with regular silica gel and an eluent mixture of 1:9 EtOAc:hexanes to afford pure **121** as a light yellow solid (mp. 130-134 °C) in 60% isolated yield (2.92 g, 4.95 mmol).

The optical purity of the product, (*S*)-**121**, was determined to be >99.9% ee by chiral HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 99:1, flow rate 0.5 mL/min, 222 nm). Retention times were 12.15 min (major enantiomer) and 19.37 min (minor enantiomer). Optical rotation: $[\alpha]^{23}_{D}$ = -43.2 (*c* 1.0, CH_2Cl_2) for >99.9% ee (*S*)-**121**.



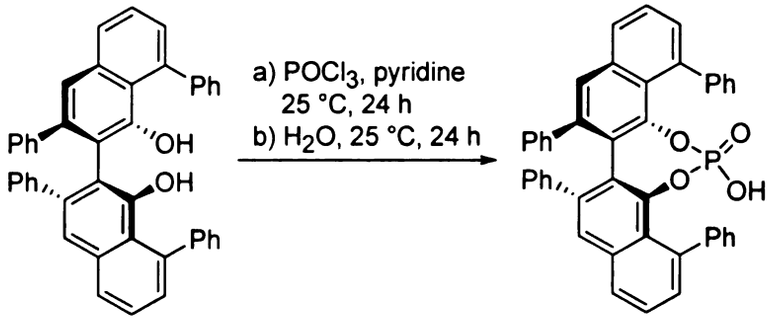
121 **122** 56%

*(S)-8,8'-Ph$_2$VANOL phosphorus oxychloride **122**.* A 10 mL round bottom flask, fitted with a magnetic stir bar, was flame dried and cooled under Argon. To this flask was then added the ligand **121** (100 mg, 0.17 mmol), which was followed by the addition of pyridine (1 mL) and $POCl_3$ (32 μL, 0.34 mmol). The

flask was fitted with a rubber septum and an Argon balloon, and stirred at room temperature for 24 h, at which the reaction was judged complete by TLC. The reaction mixture was then diluted with dichloromethane, filtered through a pad of Celite, subjected to rotary evaporation till dryness and finally to high vacuum overnight. Dichloromethane was added to the thus obtained solid crude product to get a slurry, which was again filtered through a pad of Celite. The resulting solution was subjected to rotary evaporation till dryness and finally to high vacuum to afford the crude product **122**. This was then subjected to column chromatography with regular silica gel and an eluent mixture of 1:9 EtOAc:hexanes to afford pure product **122** as a white foamy solid in 56% isolated yield (64 mg, 0.095 mmol).

*Data for **122**:* R_f = 0.17 (1:9 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.54 (dd, 4H, *J* = 7.3, 11.4 Hz), 7.02 (q, 4H, *J* = 7.6 Hz), 7.17 (q, 2H, *J* = 7.5 Hz), 7.27-7.39 (m, 6H), 7.47-7.54 (m, 5H), 7.57-7.65 (m, 5H), 7.84 (t, 2H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) (2 sp^2 carbons missing) δ 122.62 (d, 1C, *J* = 3.4 Hz), 123.40 (d, 1C, *J* = 2.9 Hz), 124.49 (d, 1C, *J* = 2.9 Hz), 124.58 (d, 1C, *J* = 3.4 Hz), 126.37, 126.64, 126.82, 126.91, 127.23, 127.77, 127.84, 127.94, 127.98, 128.18, 128.21, 128.50, 128.55, 128.58, 129.02, 129.15, 129.37, 129.96, 130.69, 130.97, 131.23, 135.55, 135.57, 135.62, 135.65, 138.16, 138.20, 138.35, 138.37, 139.25, 139.92, 139.95, 140.14, 140.17, 142.06, 142.58, 144.67 (d, 1C, *J* = 11.5 Hz), 144.91 (d, 1C, *J* = 13.2 Hz); ^{31}P NMR ($CDCl_3$, 121 MHz) δ 7.30 (s); IR (thin film) 3057w, 1314s, 760s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) M^+ 673 (15, ^{37}Cl), 672 (40, ^{37}Cl), M^+ 671 (42, ^{35}Cl), 670 (100, ^{35}Cl); HRMS calcd for $C_{44}H_{29}O_3PCl$

(M+H, ESI+) *m/z* 671.1543, meas 671.1572; $[\alpha]^{23}_D$ = +313.7 (*c* 1.0, CH_2Cl_2) for (*S*)-**122**; white foamy solid, mp. decomposes 180-200 °C.



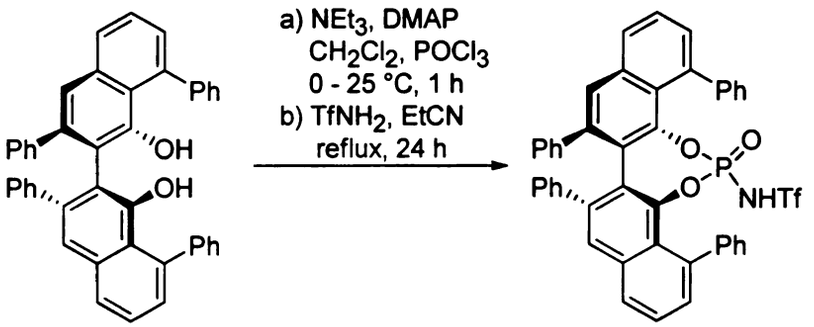
121 **123** 69%

(S)-8,8'-Ph$_2$VANOL phosphoric acid ***123.*** A 50 mL round bottom flask, fitted with a magnetic stir bar, was flame dried and cooled under Argon. To this flask was added the ligand **121** (442 mg, 0.75 mmol) and pyridine (3 mL) to obtain a clear solution. The flask was then fitted with a rubber septum and an Argon balloon. $POCl_3$ (140 μL, 1.5 mmol) was then added dropwise via a syringe, and the resulting reaction mixture was stirred at room temperature for 24 h. Water (3 mL) was then added dropwise via a syringe, and the reaction mixture stirred at room temperature for an additional 24 h. The reaction mixture was then added to a separatory funnel, along with 75 mL dichloromethane. This was washed seven times with 75 mL 1 N HCl, once with brine solution, dried over Na_2SO_4, filtered through a pad of Celite, subjected to rotary evaporation till dryness and finally to high vacuum to afford crude **123**.

The crude product was subjected to column chromatography with regular silica gel and an eluent mixture of 1:9 MeOH:CH_2Cl_2. The product fractions were collected, subjected to rotary evaporation till dryness and finally to high vacuum

to afford product **123**. This was dissolved in a minimum amount of dichloromethane, and precipitated with the addition of excess pentane. Filtration off a Büchner funnel afforded product **123** again. This was again dissolved in dichloromethane, washed four times with 100 mL 1 N HCl, dried over Na_2SO_4, filtered through a pad of Celite, subjected to rotary evaporation till dryness and finally to high vacuum. The solid **123** thus obtained was again dissolved in a minimum amount of dichloromethane, and precipitated with the addition of excess pentane. Filtration once again off a Büchner funnel afforded the final pure product **123** as a white solid in 69% isolated yield (335 mg, 0.51 mmol).

*Data for **123**:* R_f = 0.3 (streak, 1:9 MeOH:CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.50 (d, 4H, *J* = 7.2 Hz), 6.96 (t, 4H, *J* = 7.8 Hz), 7.11 (t, 2H, *J* = 7.4 Hz), 7.19 (t, 2H, *J* = 7.2 Hz), 7.25-7.30 (m, 6H), 7.36-7.37 (m, 4H), 7.43-7.47 (m, 4H), 7.73 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR (DMSO-*d*6, 125 MHz) δ 123.26, 124.58, 125.72, 125.99, 126.17, 126.57, 127.59, 127.72, 128.11, 128.69, 130.06, 130.23, 135.06, 138.36, 139.46, 139.52, 142.99, 146.58; ^{31}P NMR (DMSO-*d*6, 121 MHz) δ 0.91 (s); IR (thin film) 3446s, 3055w, 1495m, 1334s, 1263s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) M^+ 652 (100); HRMS calcd for $C_{44}H_{30}O_4P$ (M+H, ESI+) *m/z* 653.1882, meas 653.1863; $[\alpha]^{23}_D$ = +362.4 (*c* 1.0, CH_2Cl_2) for (*S*)-**123**; white solid, mp. decomposes >230 °C.



121 **124** 55%

(S)-8,8'-Ph_2VANOL N-triflyl phosphoramide ***124***. A 25 mL round bottom flask, fitted with a magnetic stir bar, was flame dried and cooled under Argon. To the flask was added the ligand **121** (100 mg, 0.17 mmol, 1 equiv) and 2 mL dry dichloromethane to obtain a clear yellow solution. The flask was fitted with a rubber septum and an Argon balloon, and cooled to 0 °C in an ice bath. Triethylamine (165 μL, 1.19 mmol, 7 equiv) and $POCl_3$ (19 μL, 0.20 mmol, 1.2 equiv) were added via a syringe, followed by the addition of DMAP (42 mg, 0.34 mmol, 2 equiv). The reaction was then allowed to warm up to room temperature, and stirred at room temperature for 1 h; TLC at this stage indicated complete consumption of **121**. EtCN (2 mL) was added to the reaction flask, followed by the addition of $TfNH_2$ (50 mg, 0.34 mmol, 2 equiv). A water condenser, separately flame dried and cooled under Argon, was then attached to the reaction flask, and the mixture heated at 100 °C in an oil bath for 24 h. The reaction mixture was allowed to cool to room temperature, and stirred at room temperature for an additional 12 h.

For the work up, the reaction mixture was diluted with water and dichloromethane, and the layers were separated. The aqueous layer was

extracted with dichloromethane, the organic layers were combined, washed with sat. $NaHCO_3$ once, 4 N HCl twice, dried over Na_2SO_4, filtered through a pad of Celite, subjected to rotary evaporation till dryness and finally to high vacuum to afford crude product **124**. This crude product was subjected to column chromatography with regular silica gel and an eluent mixture of 1:9 MeOH:CH_2Cl_2. The product fractions were collected, subjected to rotary evaporation till dryness and finally to high vacuum to afford **124** again, which was subsequently subjected to yet another round of column chromatography with regular silica gel and an eluent mixture of 5:1 EtOAc:hexanes to afford product **124**. The solid product obtained was dissolved in dichloromethane, washed twice with 4 N HCl, dried over Na_2SO_4, filtered through a pad of Celite, subjected to rotary evaporation till dryness and finally to high vacuum to afford solid product **124**. This was finally dissolved in a minimum amount of dichloromethane, and precipitated with excess pentane, which upon filtration off a Büchner funnel afforded the final pure product **124** as a white solid in 55% isolated yield (72 mg, 0.092 mmol).

*Data for **124**:* R_f = 0.3 (streak, 1:9 MeOH:CH_2Cl_2 as well as 5:1 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.46 (bs, 1H), 5.71 (bs, 1H), 6.47 (d, 2H, *J* = 7.3 Hz), 6.62 (d, 2H, *J* = 7.3 Hz), 6.84 (bs, 1H), 6.96 (t, 2H, *J* = 7.9 Hz), 7.02 (t, 3H, *J* = 7.9 Hz), 7.10-7.16 (m, 2H), 7.19 (d, 1H, *J* = 6.9 Hz), 7.31-7.53 (m, 8H), 7.61 (s, 1H), 7.65-7.70 (m, 2H), 7.77 (d, 1H, *J* = 8.4 Hz), 7.87 (d, 1H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) (4 sp^2 carbons and CF_3 missing) δ 117.92, 118.03, 120.46, 120.57, 123.00, 124.32, 124.34, 124.75, 125.27, 126.23,

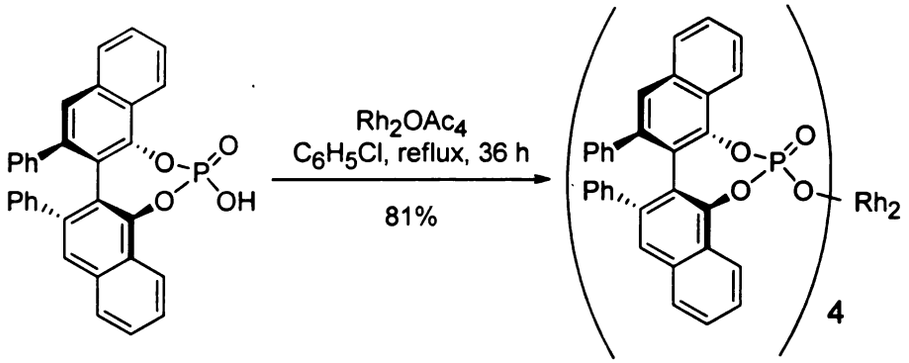
126.59, 126.80, 126.89, 126.97, 127.27, 127.75, 127.81, 127.87, 127.97, 128.08, 128.36, 128.86, 129.42, 129.69, 130.52, 131.58, 132.73, 135.59, 135.65, 136.42, 138.64, 139.34, 139.67, 140.14, 142.84, 145.19, 145.33, 145.41, 145.60, 145.68; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 2.82 (s); ^{19}F NMR ($CDCl_3$, 283 MHz) δ -79.18 (s); IR (thin film) 3435s, 3055w, 1215s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) M^+ 783 (<1), 572 (90), 246 (33), 39 (100); HRMS calcd for $C_{45}H_{28}NO_5F_3PS$ (M-H, ESI-) *m/z* 782.1378, meas 782.1374; $[\alpha]^{23}_D$ = +309.5 (*c* 1.0, CH_2Cl_2) for (*S*)-**124**; white solid, mp. decomposes >255 °C.

Appendix F

Experimental Information for Chapter Six

6.1 Asymmetric catalysis via chiral dirhodium catalysts

BINOL phosphoric acid **132** was prepared using an *Organic Synthesis* procedure.[84] The $Rh_2(PO_2BINOL)_4$ complex **133** was prepared using a procedure developed by Pirrung.[85] Nosyliminoiodinane (NsN=IPh) was prepared according to a report by Muller.[81] The preparation of VANOL phosphoric acid **93** has been detailed in Chapter 5.



93
(*S*)-VANOL
phosphoric acid

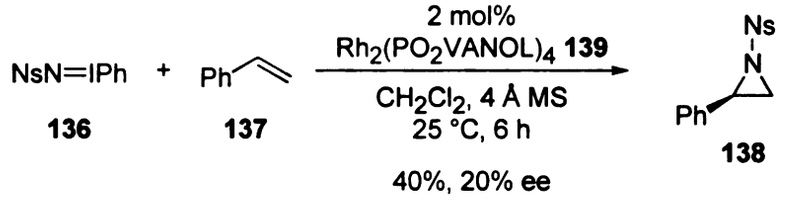
139

*The $Rh_2(PO_2VANOL)_4$ complex **139**.* A Soxhlet extractor (25 mL), flame dried and cooled under argon, was set up with a 1:1 mixture of sand:Na_2CO_3 (1.59 g, 15 mmol, Na_2CO_3) in the thimble. Under an Argon flow, **93** (1.5 g, 3 mmol), Rh_2OAc_4 (92 mg, 0.21 mmol) and freshly distilled chlorobenzene (15 mL) were then added. The resulting green slurry was stirred at reflux (165 °C) for 36 h. It was then cooled to room temperature. Rotary evaporation of the solvent followed by applying high vacuum (0.1 mm Hg) afforded crude **139** as a green non-homogenous solid. Purification by column chromatography on regular silica

gel with an eluent mixture of ethyl acetate:hexanes (1:2) gave pure **139** as a green solid in 81% isolated yield (370 mg, 0.17 mmol).

It was found that these dirhodium complexes decompose slowly with regular silica gel chromatography. They were also found to decompose slowly (green to red color) under exposure to light and excessive heat. The assignment of the structure of **139** is tentative at best.

*Spectral data for **139**:* R_f = 0.3 (streak, 1:2 ethyl acetate:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.49 (d, 4H, *J* = 7.0 Hz), 6.88 (t, 4H, *J* = 8.0 Hz), 7.04 (q, 4H, *J* = 7.5 Hz), 7.30 (t, 2H, *J* = 8.0 Hz), 7.48 (s, 2H), 7.70 (d, 2H, *J* = 8.5 Hz), 8.56 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 122.27, 123.89, 125.92, 126.33, 126.59, 126.81, 127.03, 127.44, 127.71, 129.05, 133.96, 139.92, 140.29, 146.39 (t, 1C, *J* = 4.6 Hz).



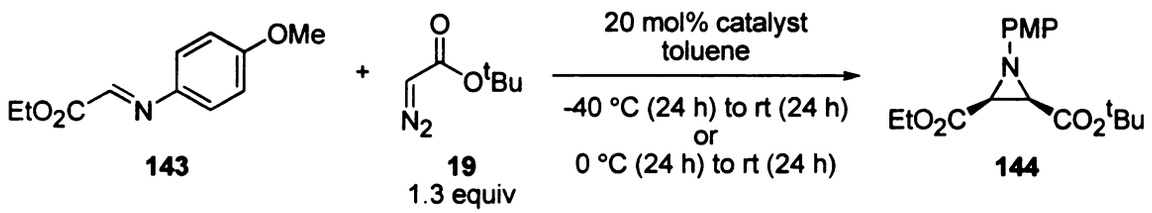
*1-(4-nitrophenylsulfonyl)-2-phenylaziridine **138**.* To a 100 mL round bottom flask, flame dried and cooled under argon, was added sequentially: (*S*)-$Rh_2(PO_2VANOL)_4$ **139** (44 mg, 0.02 mmol), dry CH_2Cl_2 (10 mL), 4 Å molecular sieves (6 g, activated previously at 190 °C under 0.1 mm Hg high vacuum for 4 h), styrene **137** (2.3 mL, 20 mmol) and **136** (404 mg, 1 mmol). The resulting green slurry was stirred at room temperature for 6 h. It was then filtered through a pad of Celite and washed exhaustively with CH_2Cl_2. Rotary evaporation of the solvent following by applying high vacuum (0.1 mm Hg) afforded crude aziridine

138 as an off-white solid. Purification by column chromatography on silica gel with an eluent mixture of diethylether:hexanes (1:2) afforded the pure aziridine **138** as an off-white solid in 40% isolated yield (121 mg, 0.4 mmol). The optical purity of **138** was determined to be 20% ee by chiral HPLC analysis (Pirkle Covalent (*R,R*) Whelk-O1 column, 99:1 hexanes:2-propanol, 222 nm, flow rate 0.7 mL min^{-1}). Retention times: R_t = 63 min (major enantiomer) and R_t = 78 min (minor enantiomer).

*Spectral data for **138**:* R_f = 0.27 (1:2 diethylether:hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.54 (d, 1H, *J* = 4.5 Hz), 3.15 (d, 1H, *J* = 7.2 Hz), 3.94 (dd, 1H, *J* = 7.2, 4.5 Hz), 7.24-7.36 (m, 5H), 8.22 (d, 2H, *J* = 9.0 Hz), 8.41 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.51, 41.86, 124.31, 126.42, 128.71, 128.72, 129.14, 134.13, 143.96, 150.65; Mass spectrum: *m/z* (% rel intensity) 304 M^+ (<1), 167 (4), 118 (100), 89 (15).

6.2 Organocatalytic asymmetric aziridination mediated by chiral Brønsted acid catalysts

Imine **143** is a commonly known compound, and was prepared in a similar manner as the preparation of the benzhydryl imines **1** described in Chapter 2. ^{t}Butyl diazoacetate **19** is commercially available from Aldrich, and can also be prepared according to previously reported procedures.[31,32]



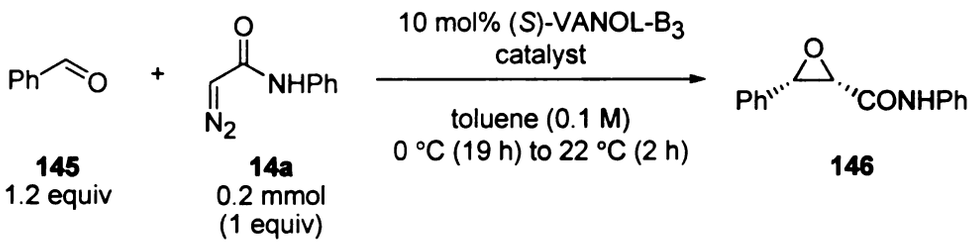
(2R,3S)-2-tert-butyl 3-ethyl 1-(4-methoxyphenyl)aziridine-2,3-dicarboxylate ***144.*** A 5 mL round bottom flask, fitted with a magnetic stir bar, was flame dried and cooled under Argon. To this flask was sequentially added: the imine **143** (52 mg, 0.25 mmol), the catalyst **113** (39 mg, 0.05 mmol, 20 mol%), and dry toluene (1 mL). The flask was then fitted with a rubber septum and an Argon balloon, and was cooled to 0 °C with the help of a chiller. Diazoacetate **19** (46 mg, 0.325 mmol) was then added to the reaction flask, and the reaction mixture stirred at 0 °C for 24 h. The flask was allowed to warm up to room temperature, and the reaction mixture stirred at room temperature for an additional 24 h. Dilution with dichloromethane and hexanes, and subsequent rotary evaporation of the crude solution led to crude product **144**. Column chromatography with regular silica gel and an eluent mixture of 1:5 EtOAc:hexanes afforded pure **144** as a light yellow oil in 60% isolated yield (48 mg, 0.15 mmol). The enantiomer for **144** has been assumed. The optical purity of **144** was determined to be 15% ee by chiral HPLC analysis (Chiralcel OD-H column, hexanes:2-propanol 95:5, flow rate 0.7 mL min^{-1}, 222 nm). Retention times were 9 min (minor enantiomer) and 10 min (major enantiomer).

*Data for **144**:* R_f = 0.26 (1:4 EtOAc:hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.30 (t, 3H, J = 7.1 Hz), 1.47 (s, 9H), 2.88 (d, 1H, J = 6.9 Hz), 2.93 (d, 1H, J = 6.9 Hz), 3.72 (s, 3H), 4.21-4.28 (m, 2H), 6.75 (d, 2H, J = 8.8 Hz), 6.92 (d, 2H, J = 9.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.11, 27.91, 43.18, 44.05, 55.41, 61.57, 82.43, 114.26, 120.88, 144.48, 156.08, 165.92, 167.11; IR (thin film) 2982s,

2936m, 2837w, 1751vs, 1510s, 1369s, 1244s cm^{-1}; HRMS calcd for $C_{17}H_{24}NO_5$ (M+H, ESI+) *m/z* 322.1654, meas 322.1666; light yellow oil.

6.3 Asymmetric catalytic Darzens reaction

The preparation of *N*-phenyldiazoacetamide **14a** has been described in the experimental information for Chapter 3. The B_3 catalysts were also prepared as described in the experimental information for Chapter 3.



145 1.2 equiv

14a 0.2 mmol (1 equiv)

146

*(2S,3S)-N,3-diphenyloxirane-2-carboxamide **146**.* A 5 mL round bottom flask, fitted with a magnetic stir bar, was flame dried and cooled under Argon. To this flask was then added benzaldehyde **145** (25 μL, 0.24 mmol, 1.2 equiv) and 2 mL from a stock solution of the (*S*)-VANOL-B_3 catalyst in toluene (corresponding to 10 mol% catalyst loading). The flask was fitted with a rubber septum and an Argon balloon, and was then cooled to 0 °C with a chiller. Diazoacetamide **14a** (0.2 mmol, 32 mg) was then added in one portion, and the reaction mixture stirred at 0 °C for 19 h. This was allowed to warm up to room temperature, and stirred at room temperature for an additional 2 h. Dilution with hexanes and dichloromethane, followed by rotary evaporation of the crude reaction mixture afforded crude product **146**. Column chromatography with regular silica gel and an eluent mixture of 1:3 EtOAc:petroleum ether afforded approximately 97% pure product **146** as a white solid in 60% yield (29 mg, 0.12 mmol). The optical purity of **146** was determined to be 32% ee by chiral HPLC analysis (Chiralcel OD-H

column, hexanes:2-propanol 90:10, flow rate 1 mL min^{-1}, 222 nm). Retention times were 9 min (major enantiomer) and 11 min (minor enantiomer).

Data for ***146***:[41] R_f = 0.32 (1:3 EtOAc:petroleum ether); ^1H NMR ($CDCl_3$, 500 MHz) δ 3.94 (d, 1H, *J* = 4.6 Hz), 4.44 (d, 1H, *J* = 4.7 Hz), 7.07 (t, 1H, *J* = 7.1 Hz), 7.17-7.25 (m, 4H), 7.28-7.35 (m, 3H), 7.43 (d, 2H, *J* = 7.3 Hz), 7.55 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 56.51, 58.65, 120.21, 124.86, 126.39, 128.55, 128.69, 128.85, 132.78, 135.96, 164.40; IR (thin film) 3321w, 3061w, 2922w, 1672s, 1599m, 1529s, 1444s cm^{-1}; HRMS calcd for $C_{15}H_{14}NO_2$ (M+H, ESI+) *m/z* 240.1025, meas 240.1034; $[\alpha]^{23}_D$ = +3.7 (*c* 1.0, CH_2Cl_2) on 32% ee (2*S*,3*S*)-**146**. Literature value:[41] $[\alpha]^{23}_D$ = +19.1 (*c* 0.9, CH_2Cl_2) on 99% ee (2*S*,3*S*)-**146**; white solid, mp. 100-104 °C.

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