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STUDIES ON THE OPTIMIZATION OF CATALYTIC ASYMMETRIC AZIRIDINATION REACTION – TACTICS AND MECHANISM

VOLUME I

By

Zhenjie Lu

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ABSTRACT

STUDIES ON THE OPTIMIZATION OF CATALYTIC ASYMMETRIC AZIRIDINATION REACTION – TACTICS AND MECHANISM

By

Zhenjie Lu

N-DAM imines have been shown to be excellent substrates for the AZ reaction with ethyl diazoacetate mediated by boron catalysts derived from either the VANOL or VAPOL ligand. These reactions produced the *N*-DAM protected *cis*-aziridinyl-2-carboxylate esters with high yields (up to 97%) and high asymmetric inductions (up to 97% ee) and also with high diastereoselectivities. Catalysts derived from both VAPOL and VANOL offer high asymmetric induction and the catalyst loading can be lowered to 0.25 mol% with VANOL derived catalyst. Cleavage of the DAM group can be achieved under several mild acidic conditions to give both 3-aryl and 3-alkyl *cis*-substituted *N*-H aziridines in excellent yields and with no erosion of stereochemistry or evidence of ring opened products. These methods can also be applied to the asymmetric synthesis of tri-substituted *N*-H aziridines by introducing an alkyl group on the C2 position of the *N*-DAM aziridine in a stereospecific fashion followed by the removal of the DAM group.

The AZ reaction can be used effectively in the preparation of optically pure α-amino esters and β-amino esters via regio- selective ring opening reactions of activated aziridines. The activation of *N*-H aziridines was examined with different activating groups, and proved to be highly efficient. For the reactions tested, it was found that the nucleophilic ring opening of *cis*-di-substituted or tri-substituted aziridinyl-2-carboxylates always takes place anti to nitrogen and the reactivity varies greatly depending on type of the nucleophile and the activating group on the aziridine, such as a SmI_2 mediated radical C2-ring opening reaction, a Lewis acid mediated C3-ring expansion reaction to

oxazolidinones and a [3 + 2] cycloaddition reaction with nitrile catalyzed by a Lewis acid for the synthesis of optically pure 2,4,5-tri-substituted imidazolines.

The highly reactive catalytic AZ reaction systems with the *N*-BUDAM or the *N*-MEDAM imines were studied. For most aryl *N*-BUDAM imines, quantitative yields and almost enantio-pure aziridines were obtained. For the bulky alkyl substrates, *N*-MEDAM imines generally afford better enantioselectivities than the corresponding *N*-BUDAM imines. The one-pot imine formation-AZ reaction procedure was shown to be practical, albeit with a slightly higher catalyst loading (4 – 10 mol%). The catalytic asymmetric alkynylaziridination was investigated.

The studies for a better understanding of the mechanism of AZ reaction on the nature of the catalyst-substrate interactions were discussed in the studies of the effects on AZ reaction due to the structurally difference of diazo esters, borates and VANOL derivatives.

To my dearest parents, my brother and my husband

for their understanding, support and help

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Scheme 6.20 Attempted one-pot preparation of **301** from compound **313** 214

ABBREVIATIONS

VAPOL : vaulted 2,2'-biphenanthrol

VANOL : vaulted 2,2'-binaphthol

EDA : ethyl diazoacetate

AZ : asymmetric aziridination

Fmoc : 9-fluorenylmethyloxycarbonyl

Boc : *tert*-butyloxycarbonyl

DMEA : dimethylethanol amine

Bh : benzhydryl

DAM : dianisylmethyl

MEDAM : bis(3,5-di-methyl-4-methoxylphenyl)methyl

BUDAM : bis(3,5-di-*tert*-butyl-4-methoxylphenyl)methyl

TMBh : tetramethylbenzhydryl

DMEA : dimethylethanolamine

TfOH : trifluoromethanesulfonic acid

HMPA : hexamethylphosphoramide

DMAP : 4-*N,N'*-dimethylaminopyridine

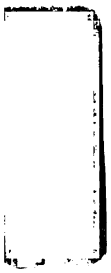
CHAPTER ONE

INTRODUCTION

1.1 Aziridine: an overview

Aziridines are strained three-membered saturated nitrogen-containing heterocycles. Just like their oxygen analogues – epoxides, the synthetic utility of aziridine lies in the fact that they readily undergo ring opening reactions with high or often complete stereoselectivity and regioselectivity. They can be converted to a large variety of 1,2-difunctional products which represent common motifs in many organic molecules. Most of the applications of the ring opening reactions have been focused on mono-substituted or fused ring systems.[1] In addition, chiral aziridines have also found applications as chiral ligands and auxiliaries in asymmetric synthesis.[2] Functionalized chiral aziridines have also been discovered in nature and play a role in their bioactivity because of the electrophilic nature of the aziridine ring in the bioactivation step.[3] The preparation and application of aziridines have received significant interest from organic chemists in the past two decades since their chemistry has not been as well developed as epoxides.

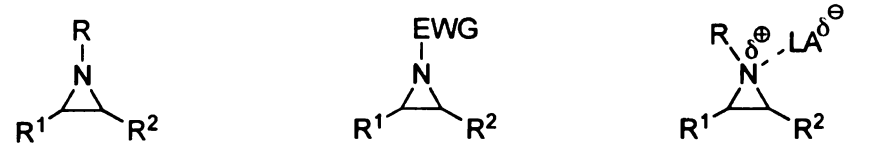
X-ray crystal diffraction studies and other spectroscopic methods suggest that in the aziridine ring structure, the C-C bond is 0.06 Å shorter than a normal open-chain C-C bond, and its C-N bond is 0.03 Å longer than that of an open chain C-N bond.[4] The aziridine has approximately 26 kcal/mol ring strain energy (based on the parent aziridine), which plays a lead role in its utility in the applications of aziridines as building blocks in organic synthesis. Like epoxides, the highly strained ring structure of aziridine also generally show good reactivity towards cycloadditions and ring opening reactions.[1b] Aziridines, especially chiral aziridines, provides a versatile and powerful synthetic



intermediate for the synthesis of a large variety of chiral compounds. As a consequence, a substantial body of work has been accumulated, concerning the highly stereo- and regioselective ring-opening reactions of aziridines.[5]

Although an aziridine has high ring strain energy and the electronegativity of the nitrogen atom facilitates the opening of the ring, the reactions of aziridines are generally not as facile as those of epoxides because of the diminished electronegativity of nitrogen as compared to oxygen. Additionally, the *N*-H bond of the aziridine must be masked to avoid deprotonation as a competitive side reaction, especially when using highly basic carbon centered nucleophiles. The solution to this problem usually involves either a) attachment of an "activating group" to the nitrogen to form an activated aziridine or b) activation of the nitrogen via Brønsted or Lewis acids. (Figure 1.1) Using an aziridine with an activating group is the more common method for effecting ring opening reactions.

Figure 1.1 The activated and non-activated aziridines



non-activated
R = H, alkyl, aryl

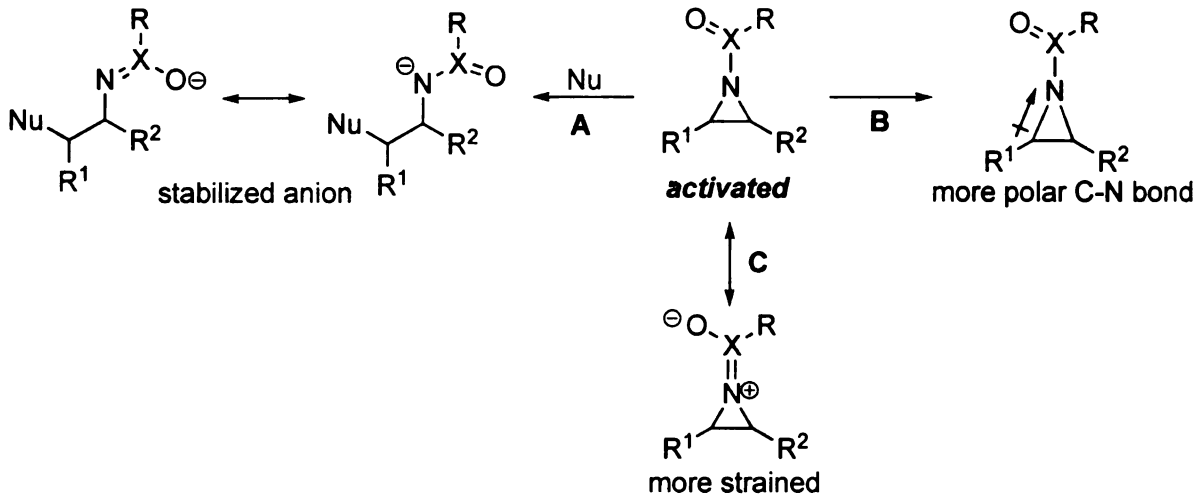
activated
EWG = COR, CO_2R, SO_2R, POR_2

activated by acid

The activating groups are generally carbonyl, sulfonyl or phosphoryl or other oxygenated electron withdrawing groups (Figure 1.1). The resonance interaction between the nitrogen lone pair and the X=O bond of the activating group is diminished due to the increased strain energy of the resulting amidate-like resonance structure (Figure 1.2, C), so the influence of the activating groups is a combination of kinetic and thermodynamic activation. Kinetically, the inductive effect of the X=O increases the

polarization of C-N bond to facilitate the C-N bond cleavage (Figure 1.2, B), and thermodynamically, the electron withdrawing activating group stabilizes the amide-like anion generated after ring opening (Figure 1.2, A).

Figure 1.2 The effect of activating group on aziridines



1.2 Catalytic asymmetric syntheses of chiral aziridines

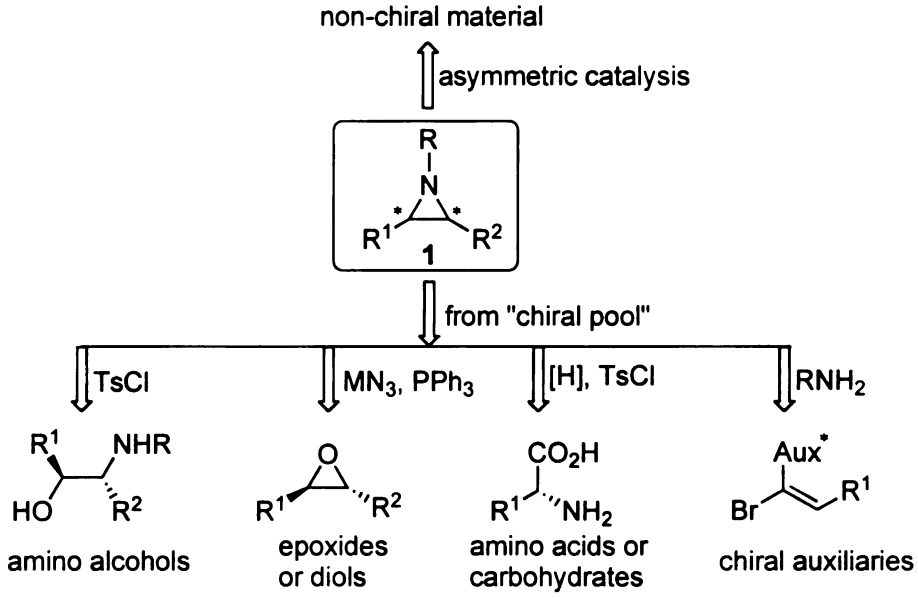
Considering the high utility of aziridines, the formation and the applications of chiral aziridines became an important aspect of the development of their chemistry and has received considerable attention.

As compared to the successes that have been achieved in the development of asymmetric epoxidations, the development of asymmetric aziridination (AZ) reaction has been limited and has proven to be considerably more challenging. This is especially true in the area of catalytic AZ reaction from non-chiral precursors, where reliable and general methods have not been developed to date.[6]

Chiral aziridines can generally be obtained through two different strategies (Scheme 1.1). The first involves an enantiomerically pure starting material, such as a chiral amino acid, carbohydrate, amino alcohol, epoxide, diol or a substrate with a chiral auxiliary present in the molecule.[7] Aziridines derived from the "chiral pool" have been extensively

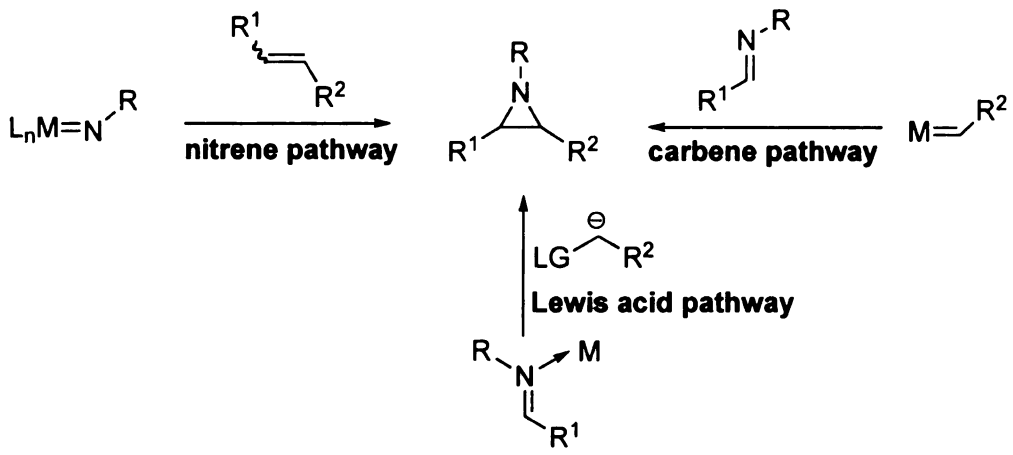
studied and generally can be prepared with good to excellent diastereo- and enantioselectivities. However, this strategy is limited to those starting materials available from chiral pool and often involves multiple steps for the synthesis of desired chiral aziridines. The other strategy, which has developed significantly in the past two decades, is one in which the chiral centers in the aziridines are generated via asymmetric addition to a C=C or C=N double bond using non-chiral precursors and chiral catalysts. Although attractive, this area has proven to be much more difficult to pursue, partly due to a lack of good understanding of the asymmetric catalytic systems for aziridination reactions that exist. Although some successful AZ reaction catalysis were reported in the mid-1990's,[5] examples of a general and highly enantioselective catalytic system are still limited.

Scheme 1.1 Strategies for the preparation of chiral aziridines



Catalytic AZ reactions can be classified into three approaches, which differ by the reaction pathway: the metal catalyzed nitrene transfer to alkenes, the metal catalyzed carbene transfer to imines and the Lewis acid catalyzed carbenoid addition to imines (Scheme 1.2).

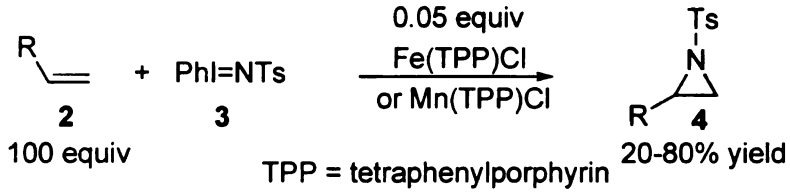
Scheme 1.2 Three approaches for catalytic AZ reaction



1.2.1 Metal catalyzed nitrene addition to alkene

In the mid-1980's, Mansuy was the first to report that a nitrene could be catalytically transferred to an alkene **2** from the *N-p*-(tosyl)iminophenyliodinane (PhI=NTs) **3** to form aziridines in moderate yields,[8] In this system, it was believed that a metal-stabilized nitrene intermediate was generated under catalysis with Fe(TPP)Cl or Mn(TPP)Cl.

Scheme 1.3 The first metal catalyzed aziridination reaction

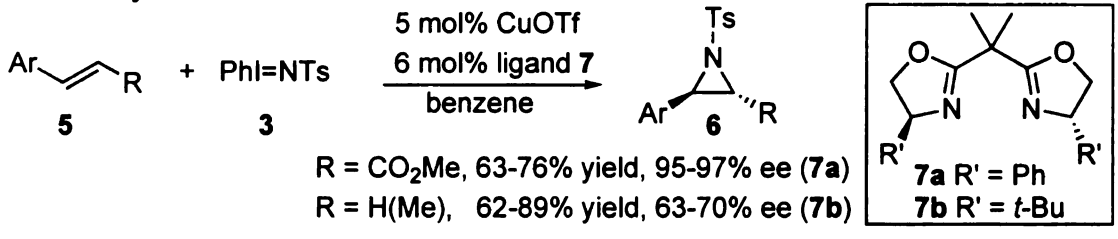


The first successful examples of AZ reaction via the metal nitrene approach were reported simultaneously by Evans and Jacobsen using different copper-catalyst systems (Scheme 1.4).[9] Using chiral ligands which can provide two coordination sites, Cu(I) salts were used to generate efficient catalysts for the synthesis of a wide range of aziridines. In Evans' AZ system, catalysts prepared from the bis(oxazoline) ligands **7** were investigated with different olefins. While cinnamate esters afforded aziridines with excellent enantioselectivity (higher than 94% ee) and moderate yield, the aziridination of

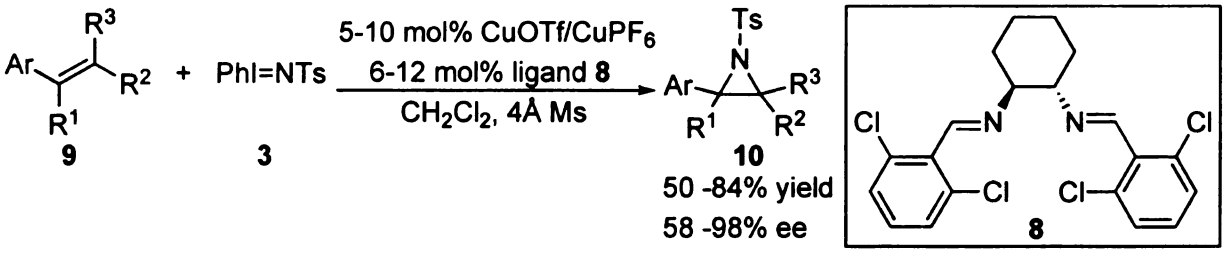
simple olefin like styrene was much less enantioselective (63-70% ee).[9a] Later on, Hutchings' group optimized the catalytic system by using a complex of copper-exchanged zeolite (CuHY) with the bis(oxazoline) **7a**, which increased the selectivity to 85% ee for the aziridination of styrene.[10] In Hutchings' system, a different sulfonyliminoiodinane (NsN=IPh) was found to be a more efficient nitrene source.

Scheme 1.4 Evans' and Jacobsen's aziridination systems

Evans' system



Jacobsen's system

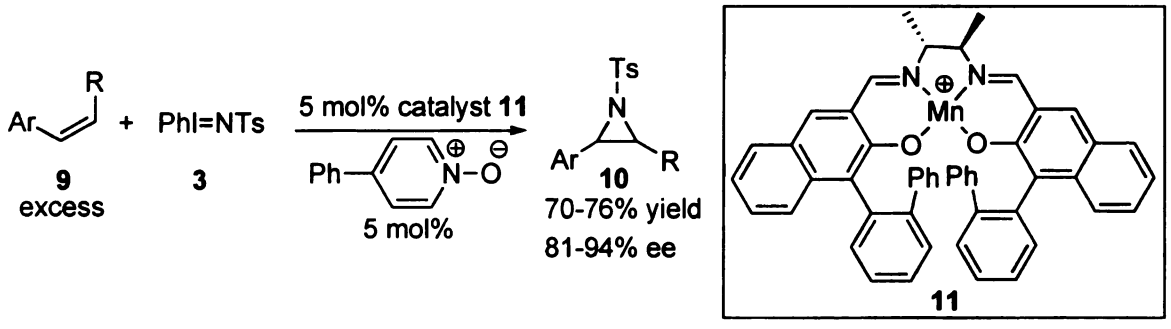


In Jacobsen's Cu(I) catalyzed aziridination system,[9b,c] a different set of olefins was examined using the chiral diimine-based ligand **8**, which afforded the corresponding aziridines **10** with 58-98% ee in 50-84% yield. The excellent enantioselectivity was observed only for one substrate. Similar observations have been made for this reactions with catalysts prepared from various ligands by other groups,[10] where it is generally seen that the asymmetric induction for simple olefin like styrene was low to moderate.

Other metal complexes such as Rh(II) Mn(III) and Ru(II) systems have been less studied and only a few successful examples have been reported.[11] Although several ligand modifications have been made which have resulted in different substrate specificities, a really general catalytic AZ system has not been developed till date. The

best system developed to date around the metal nitrene approach is that by Katsuki,[12] who recently reported a highly modified chiral Mn-salen catalyst system **11**. High asymmetric inductions (85-99% ee) for a number of vinyl arenes were reported, however, alkyl substituted olefins gave good inductions but low yields (20-30%) (Scheme 1.5). Thus, the development of a catalyst for nitrene transfer with a broader substrate scope remains an actively pursued goal.

Scheme 1.5 Katsuki's AZ system

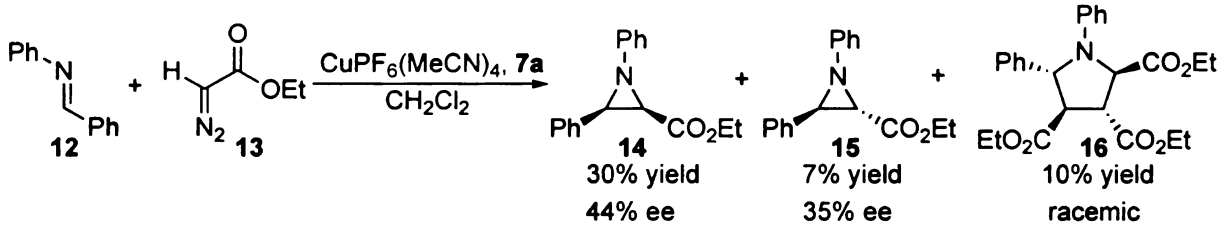


1.2.2 Metal catalyzed carbene addition to imine

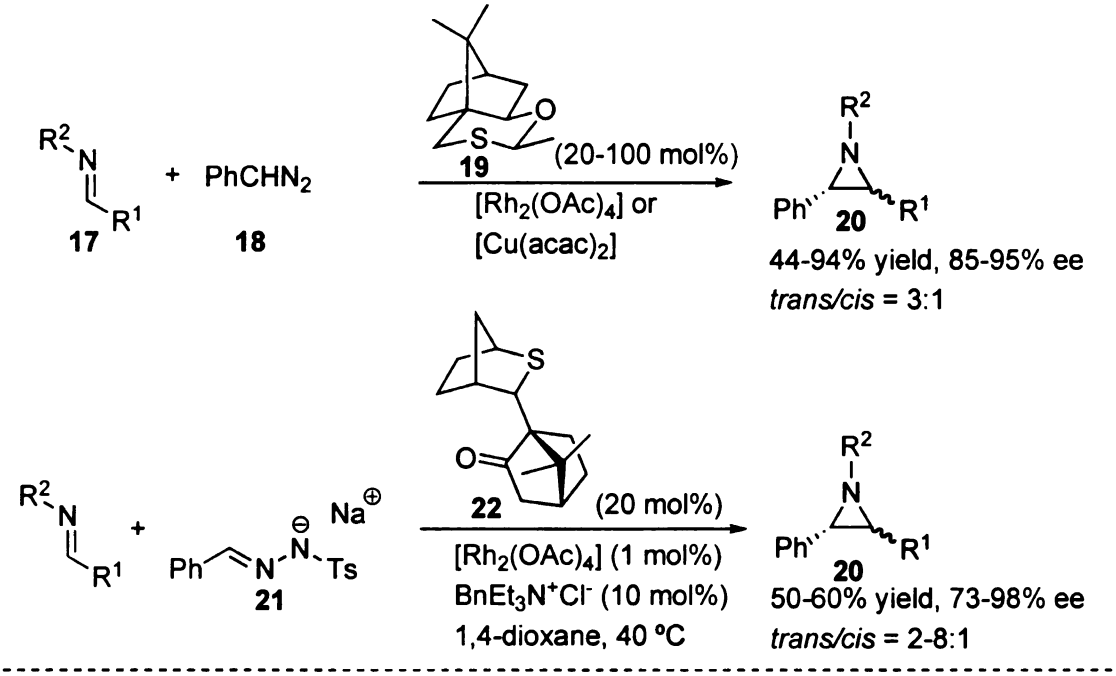
The second and the third approaches toward catalytic AZ reactions (Scheme 1.2) both involve the asymmetric transformation of imines into chiral aziridines.[13] These two methods remain relatively less developed than the analogous epoxides formation from aldehydes. The second approach involves the asymmetric addition of a metallocarbene to an imine and can be regarded as a method complementary to the asymmetric addition of a metal-nitrene to an alkene. Although this approach is well known,[14] and both the imine and carbene precursor are more readily available than the sulfonyliminoiodinanes in the metal-nitrene approach, successful AZ reactions by the metal-carbene approach are limited. The first example was reported by Jacobsen,[15] where a Cu(I) complex of the bis(oxazoline) ligand **7a** was shown to catalyze the reaction of ethyl diazoacetate **13** with N-phenylphenylimine **12** to afford the aziridine as a mixture of *cis/trans* isomers in moderate enantioselectivity along with small amounts of an pyrrollidine by-product **16** as

a racemate.

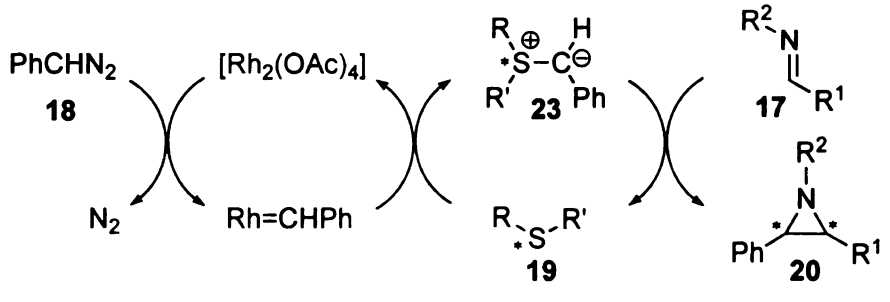
Scheme 1.6 The first AZ reaction via carbene addition to imines (Jacobsen)



Scheme 1.7 Aggarwal's chiral sulfonium ylide aziridination system



Proposed mechanism:



The only highly enantioselective system utilizing this approach involves an ylide transfer to an imine, which is part of an cleverly designed double-catalytic cycle developed by Aggarwal, involving the intermediacy of a chiral *in situ* generated

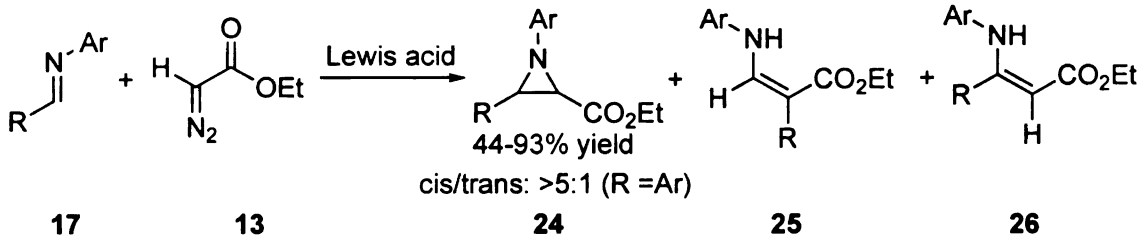
sulfonium ylide (Scheme 1.7).[16]

As shown in Scheme 1.7, the overall process involves the generation of a rhodium carbene complex via a diazo compound, followed by carbene transfer to a chiral sulfide **19** to give an ylide **23**. The enantio determining step is the transfer of the carbene from the chiral ylide to the imine to give the corresponding chiral aziridine **20**. The procedure is applicable to a series of imines bearing electron withdrawing groups to afford the aziridines in 44-94% yield and 85-95% ee with the trans aziridine as the major isomer.[16a] A subsequent improvement involves the *in situ* generation of the diazo compound via deprotonation of the tosyl hydrazone **21**, thus avoiding the handling of an unstabilized diazo compound (Scheme 1.7). The stabilized diazo compound ethyl diazoacetate **13** is not reactive in this system. The subsequent reaction with a modified chiral sulfide **22** followed by aziridine formation results in high enantioselectivity (up to 98% ee) but moderate yields.[16d] The shortcomings of this protocol include the fact that only modest control of the *cis/trans* selectivity of the aziridines could be achieved and that 20 mol% of the chiral sulfide is required for the reaction.

1.2.3 The Lewis acid catalyzed AZ reaction

The third approach towards the AZ reaction (Scheme 1.2) involves the reaction of a carbenoid with an imine that is activated by a chiral Lewis acid. This approach was first developed as a synthetic method by Brookhart and Templeton in 1996 as a general process for aziridine formation with non-chiral Lewis acids with moderate to high yields (Scheme 1.8).[17] In the presence of a variety of simple Lewis acids, such as $BF_3 \cdot Et_2O$, $AlCl_3$ and $TiCl_4$, imines **17** (R = Ar) reacted with ethyl diazoacetate **13** to afford aziridines **24** with the *cis*- isomer as the major product in 42 – 93% yield. Two enamine side products **25** and **26** were observed in various yields (5 – 100%) depending on the aryl substituents on the imines.

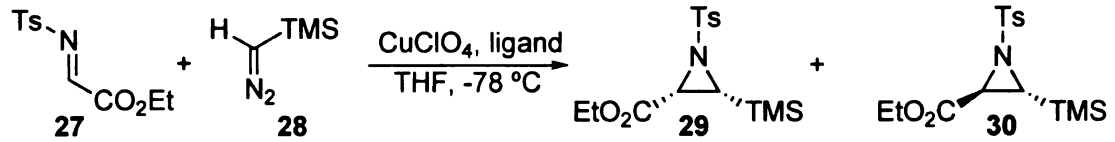
Scheme 1.8 Brookhart and Templeton's Lewis acid catalyzed aziridination



17 **13** **24** **25** **26**

One year later, Jørgensen reported a similar system using $Zn(OTf)_2$ or $Yb(OTf)_3$ as Lewis acids to give aziridines in moderate yields, however, attempts at asymmetric induction using catalysts prepared from different C2-symmetrical chiral ligands gave only 5 – 15% ee.[18a] Then in 1999, they found that the chiral catalyst derived from the reaction of $CuClO_4$ with the C2-symmetrical tol-BINAP ligand **31** gave the highest asymmetric induction of 72% ee for the *cis*-aziridine **29**[18c] made from the imino ester **27** and trimethylsilydiazomethane **28** (Scheme 1.9). The bis(oxazoline) ligand **7a** gave the *trans*-aziridine **30** in low yield (9%) but with 63% ee along with the *cis*-aziridine **29** in 19% yield and 40% ee.

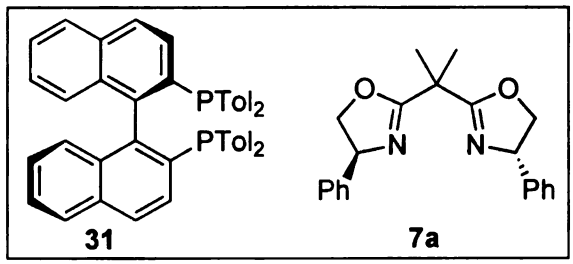
Scheme 1.9 Jørgensen's Lewis acid catalyzed AZ system



27 **28** **29** **30**

with **31**: 52% yield, 72% ee
with **7a**: 19% yield, 40% ee

3% yield
9% yield, 63% ee

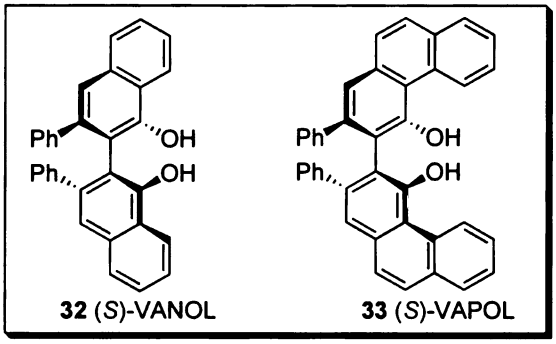


31 **7a**

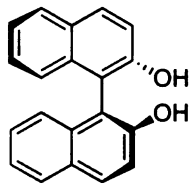
In the area of AZ reaction, the metal catalyzed nitrene addition to alkenes has received more attention than the corresponding carbene addition to imines via either the

metal carbene intermediate or the Lewis acid activated process (Scheme 1.2). Although numerous publications concerning the addition of diazo compounds to imines have emerged in the past few decades,[19] which clearly shows the interest in this field, almost all of the asymmetric catalytic systems suffer from either low to moderate stereoselectivities and / or high catalyst loading and limited substrate scope.

Figure 1.3 The VANOL, VAPOL and BINOL ligands



32 (*S*)-VANOL **33** (*S*)-VAPOL

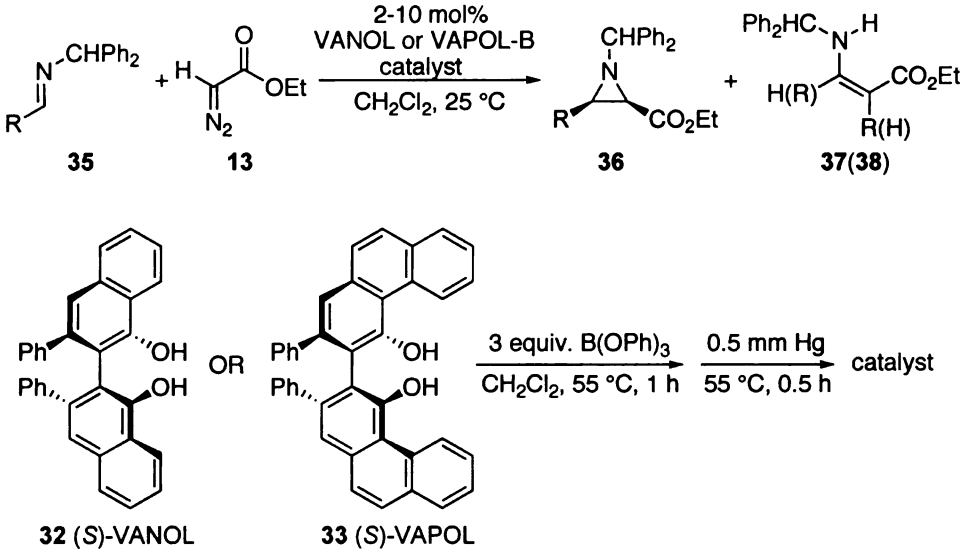


34 *(S)*-BINOL

Our study of the catalytic AZ reaction started in the late 1990's. Inspired by the pioneering study of Brookhart and Templeton of the Lewis acid mediated addition of diazo compound to imines to furnish *cis*- aziridines, we envisioned that an AZ reaction (AZ) approach might be plausible by using shiral Lewis acids derived from C2-symmetrical ligands such as the vaulted binaphthol (VANOL) **32** and the vaulted biphenanthrol (VAPOL) **33** developed previously in our group (Figure 1.3).[20] Previous studies have shown that these two ligands are superior to the linear biaryl ligand BINOL **34** in several asymmetric reactions.[21] It is believed that the successes of VAPOL and/or VANOL ligands verses the well studied BINOL ligand are due to the more effective chiral pocket of these two ligands than that of the BINOL ligand. As a result, they may provide better chiral "shielding" to the active site consisting of a transition metal or a Lewis acid and this in turn may lead to significantly increased chiral induction in some asymmetric reactions.

After an initial screening of various Lewis acids, the most reactive catalyst was determined to be a complex derived from 1 equivalent of the ligand **32** or **33** with 3 equivalents of triphenylborate ($B(OPh)_3$), and using this catalyst system, we reported the first successful AZ reaction that is general for aryl and alkyl aldimines in 2000 (Scheme 1.10).[22b] The reaction was carried out using *N*-benzhydryl imine **35** and ethyl diazoacetate **13** in the presence of 2 – 10 mol% of the VAPOL-borate or VANOL-borate catalyst to afford aziridines **36** with high *cis* diastereoselectivity (> 25:1) and up to 98% ee. The corresponding experiment using the BINOL **34** derived catalyst was found to be much less effective for this transformation and gave only 17% ee when R is a phenyl group. This AZ system represented a breakthrough in aziridine chemistry, and the level of asymmetric induction obtained is still among the highest for all systems published so far.

Scheme 1.10 VANOL/VAPOL boron compounds as catalysts in AZ reactions

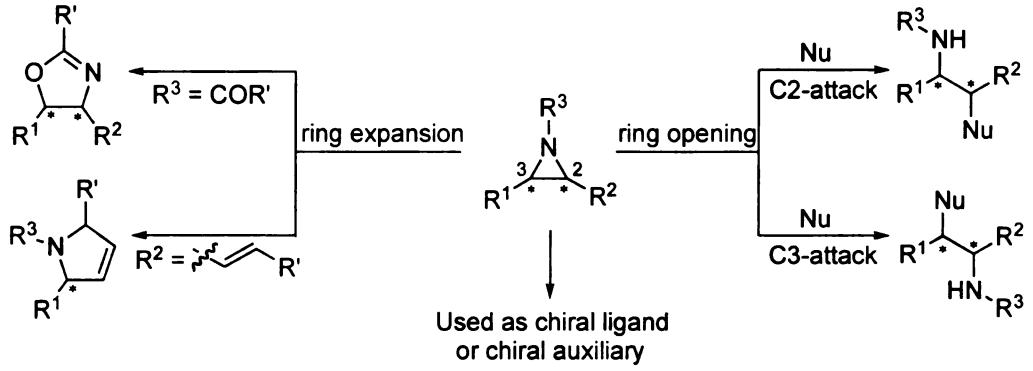


1.3 Synthetic applications of chiral aziridines

As has been mentioned above, the research on chiral aziridines has blossomed in

recent years due to its widely recognized versatility as a useful building block in organic synthesis.[1] The vast amount of publications in the literatures on the asymmetric preparation and on the synthetic applications of aziridines only seem to demonstrate the interest from chemists worldwide in this field.

Figure 1.4 Applications of chiral aziridines

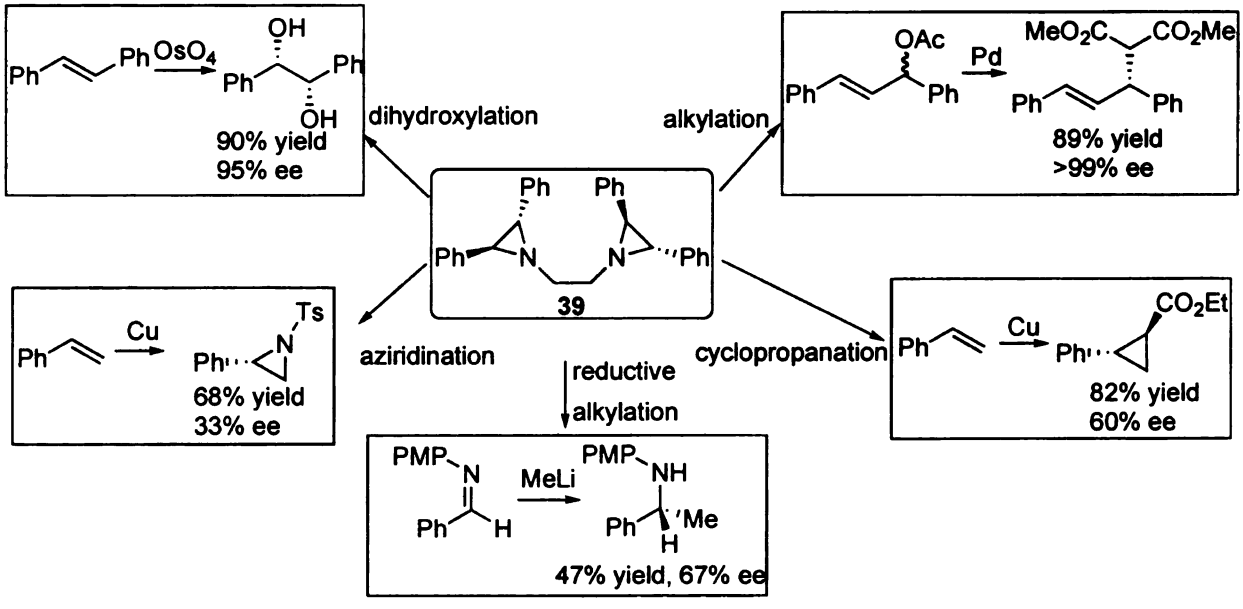


Amongst the numerous applications of chiral aziridines, the application that is most widely practiced is nucleophilic ring opening reactions. The stereo- and regiocontrol in the reaction mainly depends on the substituents on the aziridine nitrogen and on the carbon atoms. Chiral aziridines can be transformed into various useful chiral compounds with a wide variety of nucleophiles. When a nucleophile attacks an asymmetrically substituted aziridine, the reaction with the nucleophile may in theory lead to either C2 attack or C3 attack (Figure 1.4). The regioselectivity generally depends on the ring substituents with most nucleophiles preferentially attacking at the less substituted position. Introduction of an aryl group at either carbon will make the ring-opening at that particular carbon much more facile.[7] In the case of aziridine-2-carboxylates that the work of this thesis involves, the majority of nucleophilic ring-opening reactions occur at the C3 position to give α-amino esters. These nucleophilic ring opening reactions and related ring expansion reactions will be discussed in detail in chapter three.

The ring expansion of activated aziridines can result in the transformation from a three-membered ring to a five-membered ring, which could be further functionalized to add more structural complexity. For example, if the nitrogen of the aziridine is activated by a carbonyl group, the aziridine can undergo ring expansion to an oxazoline in the presence of a Lewis acid.[23] Another common ring expansion reaction is represented in the transformation of vinylaziridines to pyrrolines, which have been increasingly exploited as versatile building blocks in organic synthesis.[24] These ring opening and ring expansion reactions will be discussed in detail in chapter three.

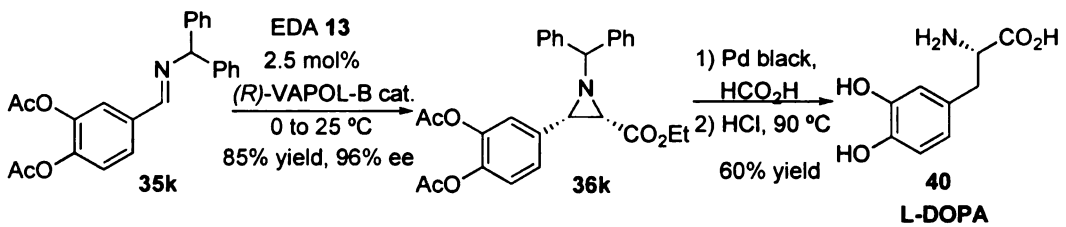
The other application that attracts a lot of interest is the use of chiral aziridines as chiral ligands or chiral auxiliaries in various asymmetric reactions. Their utility in this regard may be due to the high density of the stereochemical environment that is close to the good electron donor nitrogen of the aziridine. This concept has been reduced to practice by the Tanner's group as illustrated in Scheme 1.11, where the bis-aziridine **39** has shown promise in its use as a chiral ligand for various asymmetric transformations.[25]

Scheme 1.11 Examples of the application of aziridine as chiral ligand in asymmetric reaction



As has been described above (Scheme 1.10), a highly selective catalytic AZ reaction was discovered in our group, and following that discovery, work has been done in the group to apply this methodology to several synthetic targets. The success of the VAPOL/VANOL-borate catalyzed AZ reaction requires the presence of the benzhydryl group on the nitrogen to provide high asymmetric inductions and high yields. Although the chiral aziridine products belong to the class of nonactivated aziridines, they can still undergo reductive ring opening with the aid of acid, which is not surprising because the hydrogenolysis ring opening of nonactivated aziridines is well known and is the predominate process for a C3-aryl substituted aziridinyl carboxylate or a mono-substituted aziridine.[7] Based on this concept, three efficient total syntheses have been accomplished in our group by the ring opening of chiral aziridines that were prepared by the VANOL/VAPOL-borate catalyzed AZ reaction.

Scheme 1.12 Asymmetric synthesis of L-DOPA via AZ reaction[22b]

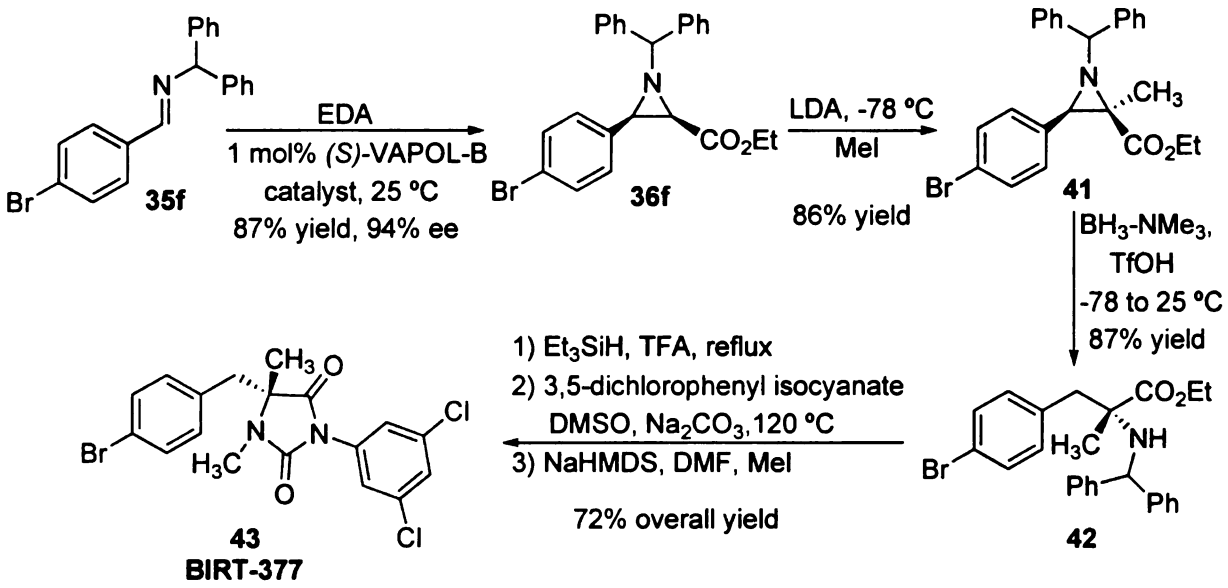


The catalytic hydrogenative ring opening of activated or nonactivated aziridines produce amines as useful synthons for the synthesis of biologically active products. When aziridine-2-carboxylates are used, the reductive ring opening reaction gives α-amino acids. As illustrated in Scheme 1.12, optically pure L-DOPA **40** was synthesized successfully from the nonactivated *(2S, 3S)*- aziridinyl-2-carboxylate **36k**, which was generated from the AZ reaction catalyzed by the VAPOL-borate catalyst. The optical purity of aziridine **36k** could be improved to higher than 99% ee by a single

crystallization. The enantiomerically enriched aziridine **36k** could be transformed efficiently to L-DOPA in 60% isolated yield.

Another successful application of the reductive ring opening of an aziridine was the synthesis of the LFA-1 antagonist BIRT-377, which started from the catalytic AZ reaction of *N*-benzhydryl-*p*-bromophenylimine **35f** and involved a diastereoselective alkylation of the *(2R, 3R)*-ethyl-1-benzhydryl-3-*p*-bromophenyl-aziridinyl-2-carboxylate **36f**. The reductive ring opening of intermediate **41** was achieved with borane-trimethylamine complex in the presence of triflic acid to give compound **42**, which led to the final product BIRT-377 as illustrated in Scheme 1.13. The synthesis was completed in 46% overall yield from the known imine **35f**.

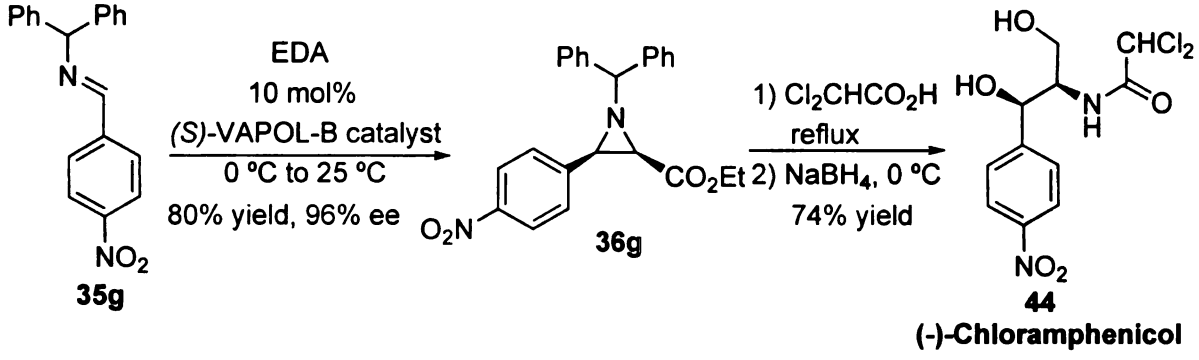
Scheme 1.13 Asymmetric synthesis of BIRT-377 via an AZ reaction[26]



The ring opening reaction via an oxygen nucleophile is possible for both activated and non-activated aziridines, usually under protic or Lewis acid catalyzed conditions. The stereochemical outcome of the ring opening is a consequence of the fact that the attack of the nucleophile occurs with inversion of carbon C3, and the regiochemistry is decided by the reaction conditions and the substituents on the aziridine ring. When *(2R,*

3R)-ethyl-1-benzhydryl-3-*p*-nitrophenyl-aziridinyl-2-carboxylate **36g** was subjected to refluxing dichloroacetic acid, a ring-opened α-amino ester was obtained as an intermediate, which was then easily reduced to the final product (-)-Chloramphenicol **44** in 74% overall yield as shown in Scheme 1.14. This efficient total synthesis was completed in only three steps starting from the simple imine **35g**.

Scheme 1.14 Asymmetric synthesis of (-)-Chloramphenicol via AZ reaction[27]



The development of other applications of this catalytic AZ reaction protocol was limited by the nature of these nonactivated aziridines. Methods for the transformation of the non-activated benzhydryl aziridines to activated aziridines and their subsequent applications will be discussed in detail in the following chapters.

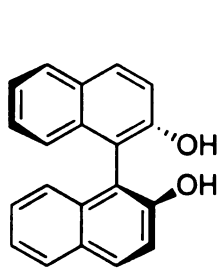
1.4 The VAPOL / VANOL ligands – a brief introduction

1.4.1 Introduction to VANOL / VAPOL ligands

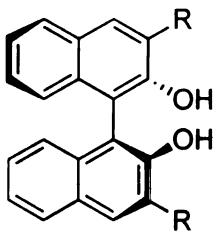
The catalytic AZ reaction of benzhydryl imines and ethyl diazoacetate with the catalyst prepared from triphenylborate and the VAPOL ligand gives a profile for asymmetric induction that is nearly identical to that for the same catalyst generated from the VANOL ligand (Scheme 1.10)[22b]. This kind of parallel inductive effect over several substrates was never observed before for any other reactions using these ligands, which may suggest that the VAPOL-borate or VANOL-borate catalyst systems share some common factors that are unique from BINOL and can result in the high reactivity and

excellent asymmetric induction. This observation encouraged us to carry out further studies for a better understanding of the reaction mechanism, especially to determine the structure of the catalyst because the use of the VANOL **32** or the VAPOL **33** is the key for the high asymmetric inductions and yields, which are much superior to the results when BINOL was used as the ligand.

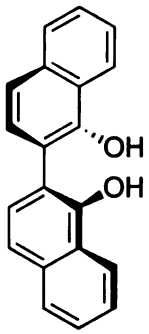
Figure 1.5 Biaryl ligands related to the VANOL and VAPOL ligands



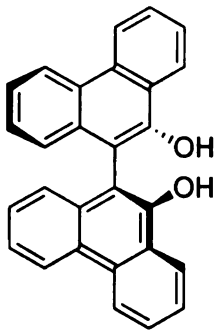
34
1,1'-binaphthol
(S)-BINOL



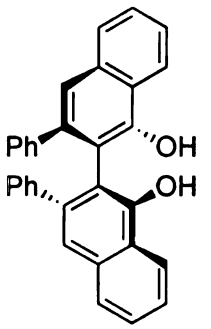
45
R = bulkyl group



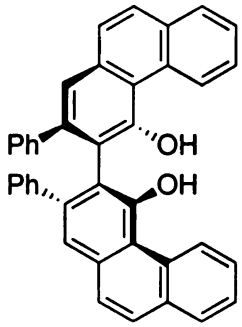
46
2,2'-binaphthol



47
6,6'-biphenanthrol
(S)-BANOL



32
(*S*)-VANOL

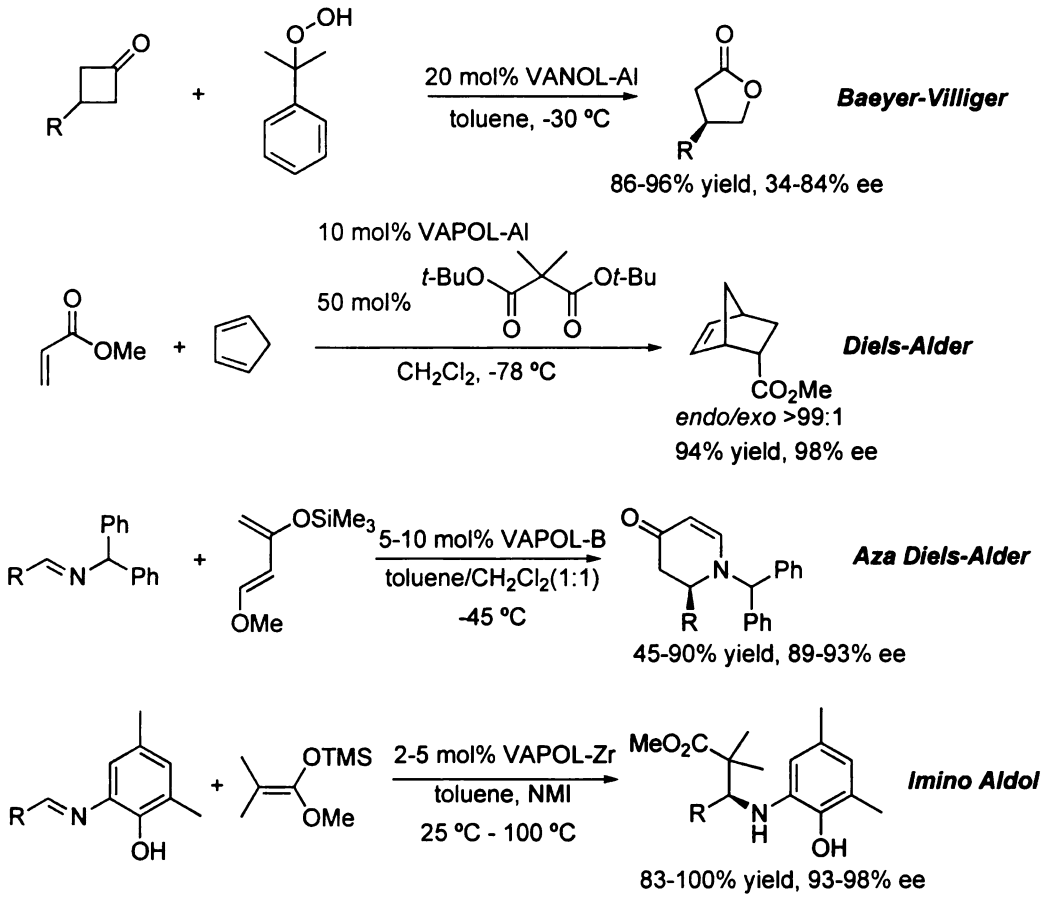


33
(*S*)-VAPOL

The inspiration for the development of the VANOL / VAPOL ligands was derived from the knowledge of the enantiomeric atropisomers of 1,1'-binapth-2-ol (BINOL) **34**, which are widely used as chiral ligands in asymmetric synthesis.[28] The rationale behind the design of the VANOL (**32**) and VAPOL (**33**) ligands will be discussed in chapter six. The VAPOL/VANOL derived asymmetric catalysts have been found to be superior to other binaphthol-derived catalysts in many asymmetric reactions, such as the aziridination[22]

(Scheme 1.10), Baeyer-Villiger,[29a] Diels-Alder,[29b] Aza Diels-Alder,[29c] and imino-aldol reactions[29d] (Scheme 1.15).

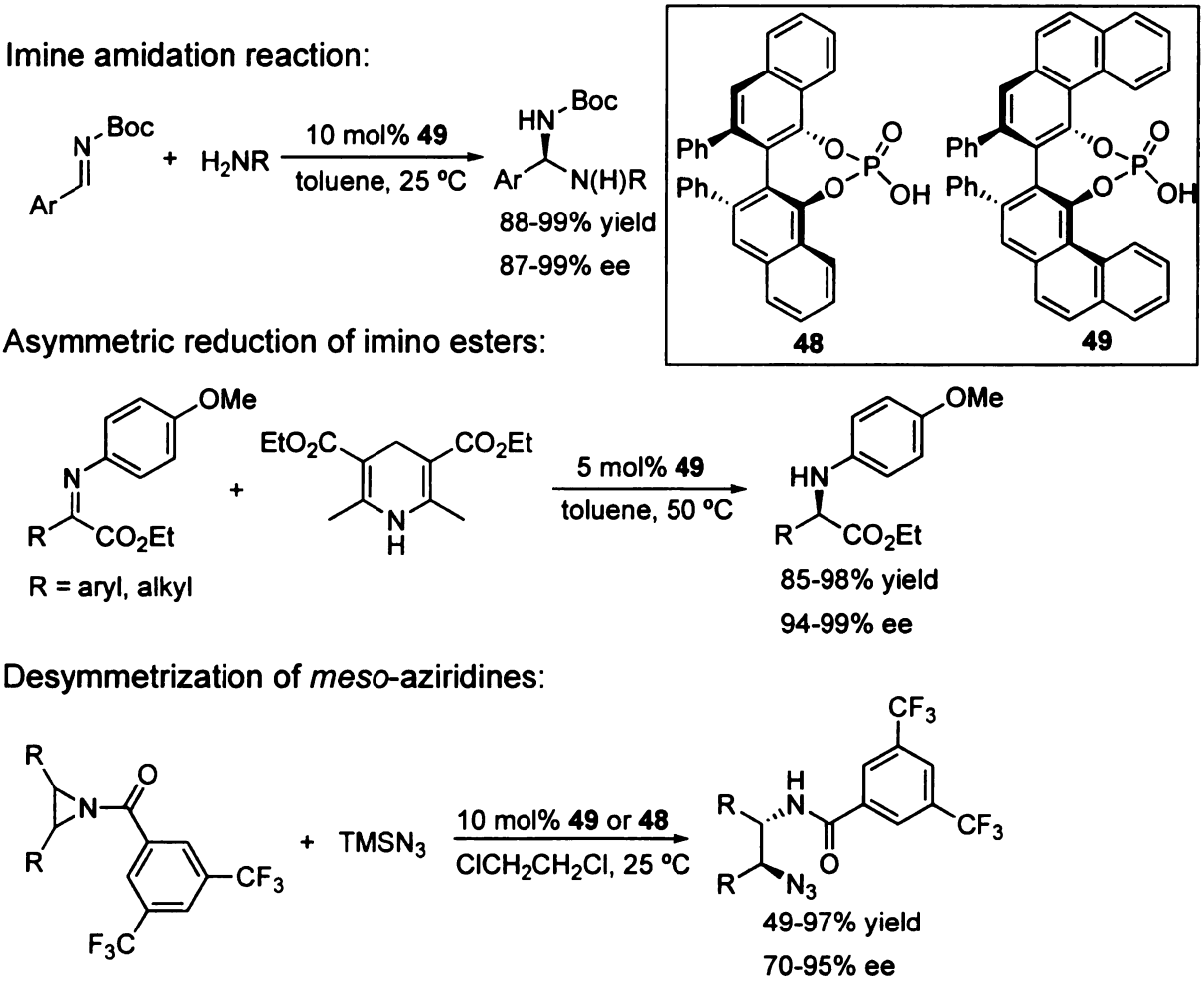
Scheme 1.15 Examples of asymmetric reactions utilizing VANOL or VAPOL ligands



The VAPOL derived Brønsted acid **49** has also been demonstrated to be useful as a chiral catalyst by Antilla's group[30] in the asymmetric imine amidation reaction[30a] and more recently, in an asymmetric reduction of α-imino esters to obtain α-amino esters[30b] and the desymmetrization of *meso*-aziridines[30c] (Scheme 1.16). Considering the many applications of VAPOL and VANOL mentioned above, and the fact that these ligands are now commercially available from Aldrich, it would not be very surprising if more asymmetric reactions catalyzed by a catalyst derived from VANOL or VAPOL were to be

reported in the future.

Scheme 1.16 Asymmetric reactions catalyzed by VAPOL/VANOL-phosphoric acid

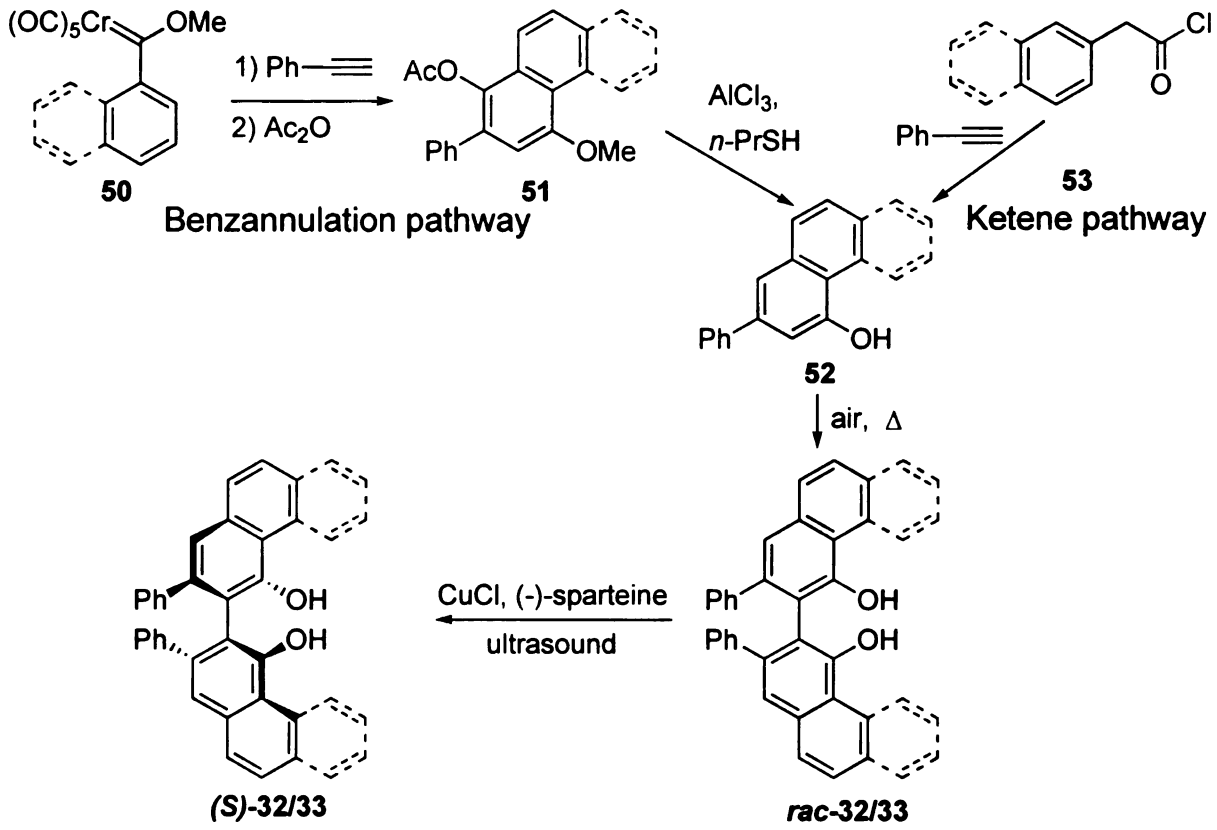


The successful applications of VANOL and VAPOL derived catalysts in asymmetric synthesis have prompted studies toward understanding their unique rigid biaryl structures and some results have recently begun to immerge. Gagne's group examined the coordination chemistry of these ligands with a carbophilic late transition metal complex via the synthesis and the characterization of complexes (dppe)Pt(*S*-VANOL) and (dppe)Pt(*S*-VAPOL),[31] which are quite different from the catalytic complexes of VAPOL or VANOL developed in our group with oxophilic early transition or main group metals. Matzger's group has published a detailed study of the solid state structure of

VAPOL via X-ray crystallographic analysis.[32] The study to understand the superior catalytic character of VAPOL over BINOL and its derivatives is an on-going project in our lab.

1.4.2 Preparation of VANOL/VAPOL ligands

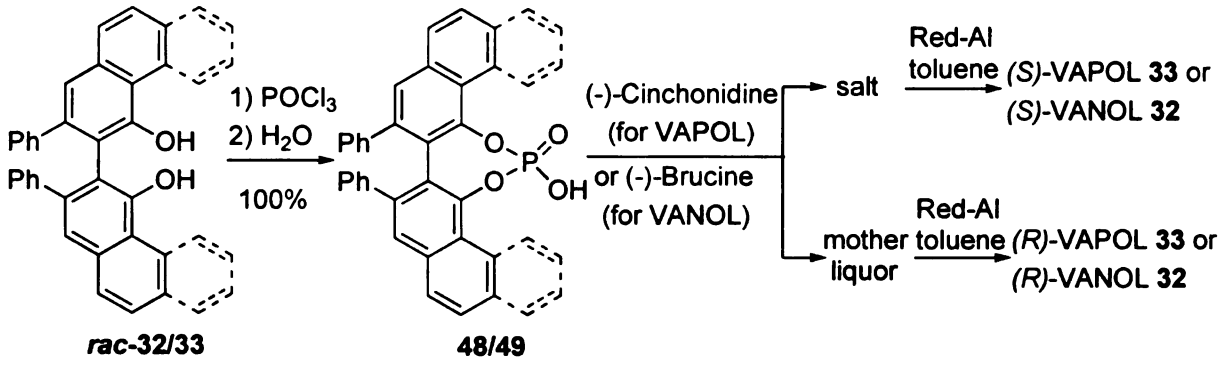
Scheme 1.17 Preparation of VANOL or VAPOL ligands



VANOL and VAPOL ligands can be prepared from the benzannulation reaction of chromium carbene complex **50** with phenylacetylene (Scheme 1.17).[20] They can also be prepared by a second pathway via formation of a ketene intermediate from the acyl chloride **53** (Scheme 1.17).[20] The oxidative coupling of the monomer **52** in air is used to generate racemic VANOL or VAPOL. The *(S)*-enantiomers of VANOL and VAPOL can be obtained by a highly enantioselective deracemization reaction with a Cu(II)-sparteine complex that can be formed *in situ* using Cu(I) and (-)-sparteine by an oxidization via an ultrasound technique.[33]

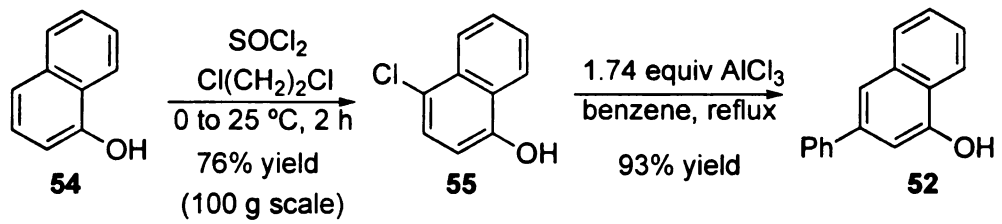
To obtain the *(R)*-enantiomers and for larger scales, a classical resolution has been developed which proceeds via the formation of the phosphoric acid **48** or **49** (Scheme 1.18). A large scale resolution can be accomplished by converting acid **48** or **49** to a diastereomeric pair of salts with (-)-cinchonidine in the case of VAPOL or with (-)-brucine in the case of VANOL,[34] and then separation of the diastereomeric salts by crystallization. The direct Red-Al reduction of the salt for both VANOL and VAPOL gives the *(S)*-enantiomers of the ligands in >99% ee, while the reduction of the mother liquor can afford the *(R)*-enantiomers of VANOL or VAPOL.

Scheme 1.18 Large scale resolution of VANOL and VAPOL



Recently, another approach for the large-scale synthesis of monomer **52** of VANOL has been developed by group member Zhensheng.[35] As shown in Scheme 1.19, the desired monomer **52** of VANOL was synthesized in 71% overall yield starting from 100 g of *1*-naphthol **54**.

Scheme 1.19 Large scale synthesis of VANOL monomer



1.5 Conclusion

Three different approaches toward catalytic AZ reactions have been studied extensively in the last two decades, and the most representative successful examples were briefly reviewed in this chapter. Although studies in this area have increased rapidly with time, relatively few really successful and general systems have emerged. The VAPOL-borate and VANOL-borate chiral Lewis acid catalysts developed in our group represent a breakthrough in this area and provides high enantio- and diastereo-selectivities over a broad range of substrates. The utilization of the aziridines obtained by this method for ring opening and ring expansion reactions in the synthesis of useful chiral materials would serve to enhance the attractiveness of this AZ reaction method. The success of the aziridination protocol has piqued our curiosity for a better understanding of the role of the active VANOL/ VAPOL-borate complex in this reaction and the related mechanistic details.

In the following chapters, we will talk about the studies toward the access to chiral *N*-H aziridines via an efficient acid mediated deprotection of the aziridines obtained from the catalytic AZ reaction (Chapter two), the following activation and applications in ring opening and ring expansion reactions (Chapter three). The optimization of the AZ reaction protocol and some attempted asymmetric reactions utilizing VANOL or VAPOL derived catalysts will also be discussed (Chapter four and five). The detailed study towards understanding the VANOL / VAPOL derived catalysts in catalytic AZ reaction protocol will be discussed in chapter six.

CHAPTER TWO

DIRECT ACCESS TO *N*-H AZIRIDINES VIA CATALYTIC AZ REACTIONS

2.1 Introduction

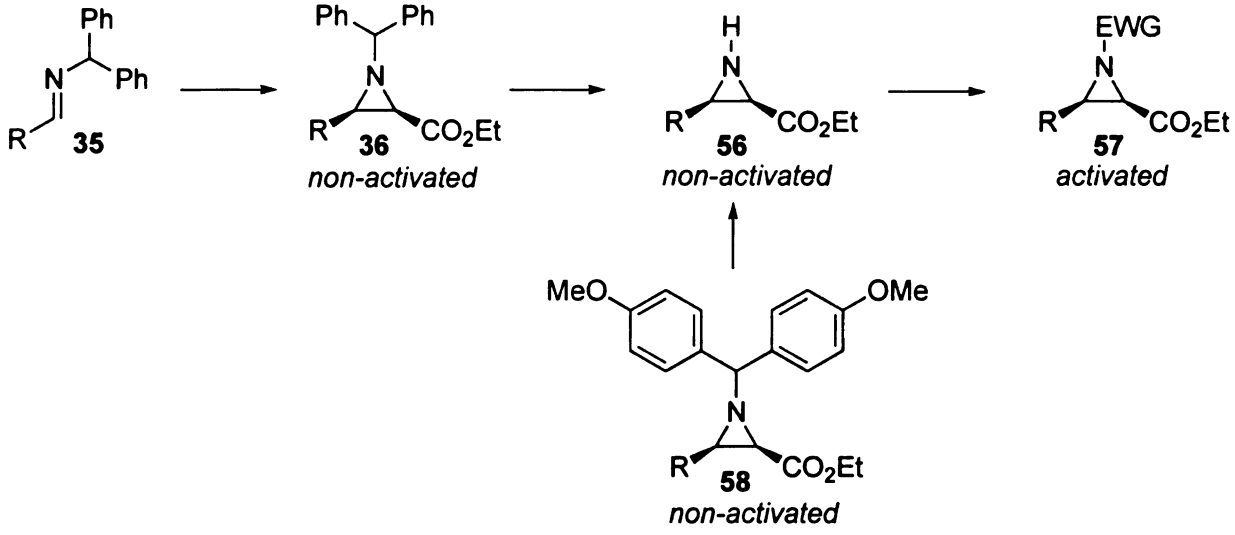
Although it has been known for a long time that Lewis acids can effect the formation of aziridines from imines and diazo compounds, it was not until the work of Brookhart and Templeton[17] and later of Jørgensen[18] that the generality of this process was appreciated. Taking the lead from these studies, it was found that catalysts derived from triphenylborate and either VANOL or VAPOL were effective in catalyzing the formation of *cis*-aziridinyl-2-carboxylates from *N*-benzhydryl imines and ethyl diazoacetate[22] (Scheme 1.10). This AZ reaction has proved to be general for imines derived from aryl and alkyl aldehydes giving the aziridines with high *cis/trans* ratios in good to high yields with excellent enantioselective induction.

The aziridinyl-2-carboxylates have emerged as a special class of aziridines, because they can be easily converted into acyclic α– or β– amino acids via various ring opening reactions. On the other hand, they can also be incorporated into peptides as special amino acid units, which can result in significantly altered biological activities.[24c] In addition, naturally occurring aziridinyl-2-carboxylic acid has also been reported.[36] The work of this chapter is mainly focused on the asymmetric synthesis of chiral *cis*-aziridinyl-2-carboxylates and their transformation to *N*-H aziridines.

The optically active benzhydryl aziridines **36** that are synthesized from our catalytic AZ reaction are non-activated and thus will require transformation to activated aziridines in order to facilitate many of ring opening reactions of synthetic interest. The most straightforward approach would be the removal of the *N*-benzhydryl group to form the *N*-

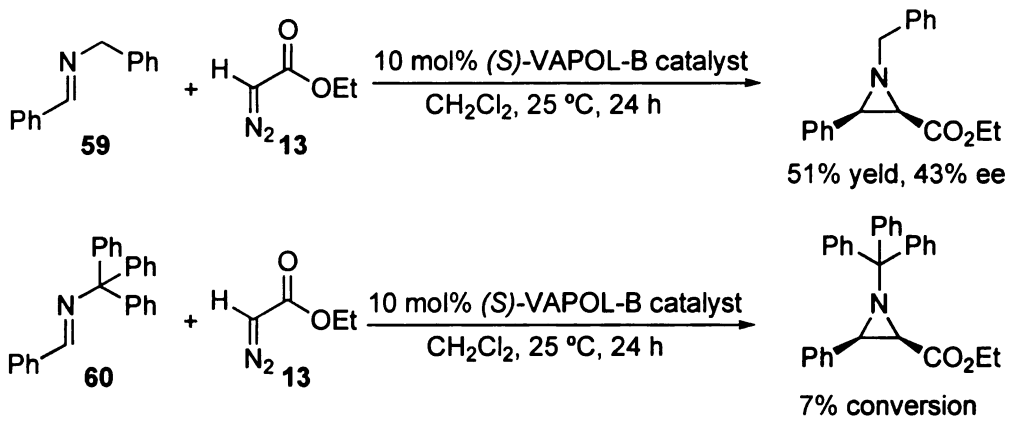
H aziridine **56** followed by the activation with an electron withdrawing group on the nitrogen to give the activated aziridine **57** (Scheme 2.1). Thus, for maximum efficiency in this approach, there arises a need for deprotection methods that allow the clean conversion of the benzhydryl aziridines **36** to the *N*-H aziridines **56**.

Scheme 2.1 Conversion of non-activated aziridines to activated aziridines



Alternatively, a better solution would be to perform the aziridination with an imine already bearing an electron-withdrawing group on the nitrogen. However, it was found that the benzhydryl group was essential for achieving high asymmetric inductions in our AZ reaction protocol. Efforts to replace the benzhydryl group on the imine **35** with a benzyl group (compound **59**) or a trityl group (compound **60**) led to either low reactivities or low asymmetric inductions (Scheme 2.2).[37a] Since the aziridination of imines with an activating group did not work in this catalytic system, we had to focus on the cleavage of benzhydryl group or other benzhydryl derivatives like the dianisylmethyl group as shown in aziridine **58** in Scheme 2.1.

Scheme 2.2 AZ reactions with *N*-benzyl imine **59** and *N*-trityl imine **60**



The most common method for the cleavage of the benzhydryl group is treatment with acid, however, this proceeds with good yields only for certain *N*-benzhydryl aziridines.[38] Aryl substituted *N*-benzhydryl aziridines are more susceptible to acid promoted aziridine ring opening. We thus set out on an endeavor to find a protecting group for the nitrogen of aziridines that could be effectively cleaved and would allow access to *N*-H aziridines in high yields and without any ring opening side reactions. Attention was turned to the dianisylmethyl (DAM) protecting group.[39] It was anticipated that the acid mediated cleavage of the DAM group from aziridine **58** (Scheme 2.1) would be more facile than that of the benzhydryl group due to the increased stability[40] of the dianisyl methyl cation compared to the benzhydryl cation that would be formed during the course of the acid cleavage of the aziridines.

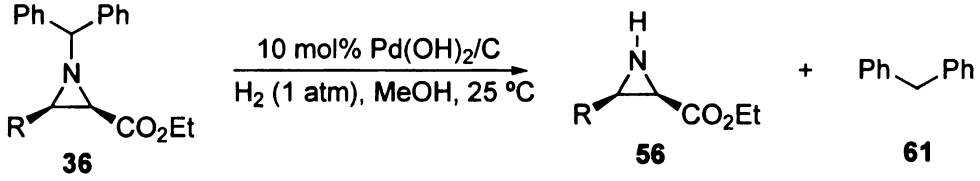
2.2 Cleavage of the benzhydryl group from aziridines 36

Our initial study towards the deprotection of the benzhydryl group from aziridines **36** has resulted in two approaches that were initiated by former group members Dr. Patwardhan, and Dr. Pulgam.

2.2.1 Cleavage of the benzhydryl group by hydrogenolysis

It was known that $Pd(OH)_2$ (Pearlman's catalyst) could cleave benzhydryl groups from amines and selectively cleave benzylamines in the presence of benzyl ethers.[41] This hydrogenation method could be applied successfully to the removal of the benzhydryl group of 3-alkyl substituted aziridines **36**. The hydrogenation was carried out under 1 *atm* of hydrogen in methanol at room temperature with 10 mol% Pearlman's catalyst. The primary, secondary, and tertiary *N*-H aziridinyl-2-carboxylates **56** could be obtained in excellent isolated yields for each substrate (Scheme 2.3). From the crude ^1H NMR spectrum of the reaction, the reaction was clean and no other nitrogenous by-product was observed.

Scheme 2.3 Deprotection of 3-alkyl benzhydryl aziridines via hydrogenolysis



36

36a : R = *c*-C_6H_{11}
36b : R = *t*-Bu
36c : R = *n*-C_3H_7

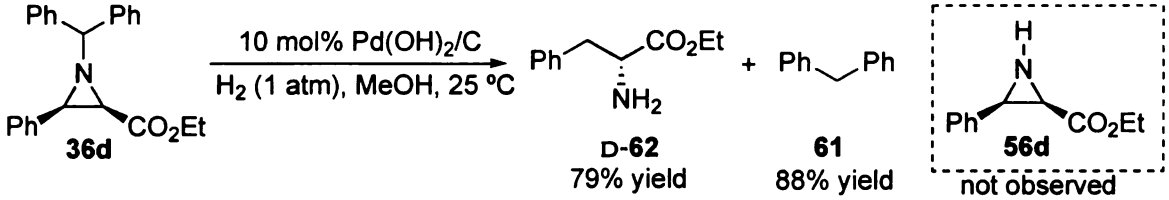
56

56a : 93% yield
56b : 92% yield
56c : 83% yield

61

However, this protocol was not effective for the removal of the benzhydryl group from 3-phenyl substituted aziridine **36d** (Scheme 2.4). Reductive ring opening reaction occurred under the deprotection conditions to give the ethyl ester of D-phenylalanine **62** in 79% yield.

Scheme 2.4 Hydrogenolysis of C3-phenyl aziridine



36d

D-62
79% yield

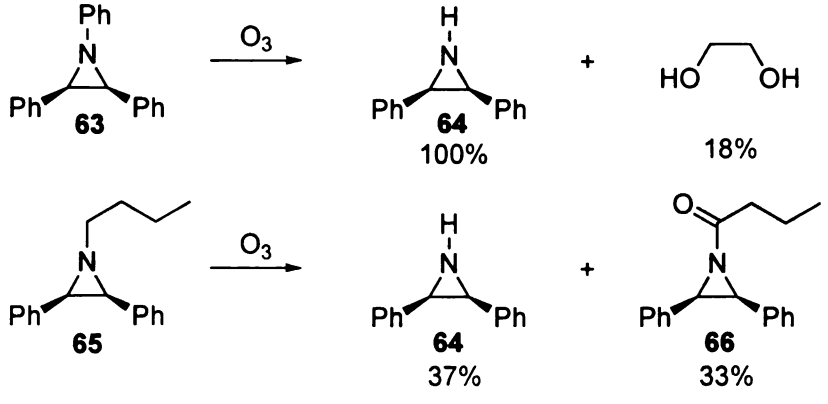
61
88% yield

56d
not observed

2.2.2 Cleavage of the benzhydryl group by ozonolysis

Because of the limitation of the hydrogenolysis method for C3-aryl substituted aziridines, an alternative approach was developed. Back in the late 1970's, Ito and co-workers discovered that the aziridine ring is stable to the presence of ozone,[42] and it was observed that the treatment of *N*-phenyl aziridine **63** with ozone gave the deprotected aziridine **64** in quantitative yield with the aziridine ring untouched, which suggested that the "benzylic" carbon in **63** is inert towards cleavage as a consequence of being in a three-membered ring system (Scheme 2.5). It was also found that when a primary alkyl group was attached to the aziridine nitrogen, the alkyl group was oxidized in preference to the ring carbons under the ozonolysis condition. In the experiment of treating **65** with ozone, the reaction gave a mixture of *N*-H aziridine **64** and the aziridinyl amide **66** as a result of the competition between the oxidation of the intermediate aminal and the collapse of the aminal to the *N*-H aziridine. Considering the stability of the benzylic ring carbon under ozonolysis conditions and the fact that the non-cyclic C-N bond is susceptible to cleavage, ozone, thus, provided the possibility of an alternative way for the deprotection of the benzhydryl aziridines.

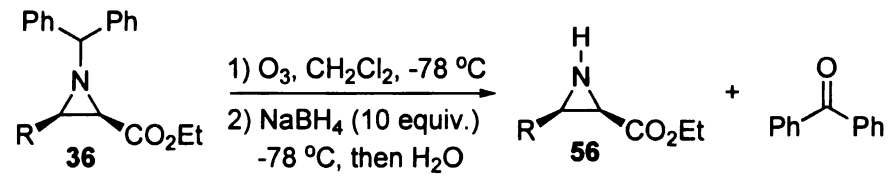
Scheme 2.5 Ito's ozonolysis of aziridine



The initial study on the cleavage of the benzhydryl group via ozonolysis was

performed on the phenyl aziridinyl-2-carboxylate **36d** by Dr. Patwardhan (Scheme 2.6).[38] It was found that methylene chloride was the best solvent and that the yield of the deprotected aziridines depended largely on the reductant used to quench the reaction, 10 equivalents of sodium borohydride was the optimal reagent. The optimized conditions for the deprotection involved using methylene chloride as the solvent at –78 °C and then the reaction was quenched with 10 equivalents of sodium borohydride in methanol. This condition afforded the desired *N*-H aziridines **56** in up to 60% isolated yields, no other nitrogenous side products were observed. This method was general for both 3-alkyl and 3-aryl di- or trisubstituted benzhydryl aziridines **36**, but it's clear that this protocol would not tolerate many functional groups, and the moderate yields for all the substrates were far from satisfactory.

Scheme 2.6 Deprotection of *N*-benzhydryl aziridines via ozonolysis

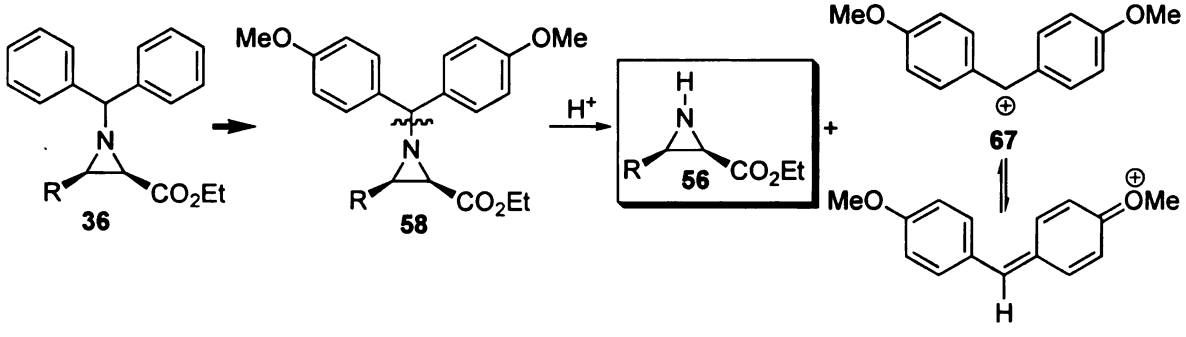


2.3 Formation of the *N*-H aziridine from the cleavage of the dianisylmethyl group

Since the direct removal of the benzhydryl group by either hydrogenolysis or ozonolysis was not very efficient, we began to think of an alternative way for accessing the *N*-H aziridines that would involve the derivitization of the benzhydryl groups, such that more efficient cleavage could be achieved. In a previous study,[37a] it has already been found that the success in the asymmetric induction is highly dependent on the presence of the two phenyl of the benzhydryl group (Scheme 2.2). In order to retain the excellent asymmetric induction and facilitate easier access to the *N*-H aziridines, it was expected that, under the acidic conditions of the cleavage, the dianisylmethyl (DAM)

cation **67** that would be liberated from *N*-bis(dimethoxyphenyl)methyl aziridines **58** would be more stable than the diphenylmethyl cation derived from benzhydryl aziridines **36** (Scheme 2.7).[40] This is because the cation **67** is stabilized by resonance structures that are not available to the diphenylmethyl cation, which should lead to an increased preference for deprotection verses ring opening process.

Scheme 2.7 Overview of the acid mediated cleavage of dianisylmethyl group

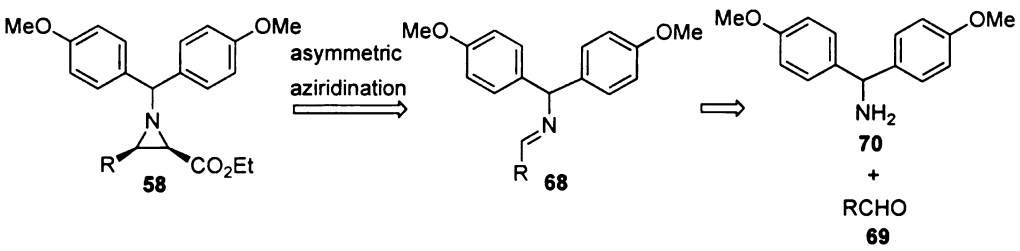


Two questions that had to be considered during the course of this study are: (a) would the increased stability of the DAM cation be enough to overcome the natural tendency of an aryl substituted aziridine to undergo ring opening upon treatment with acid; and (b) would the AZ reaction with the *N*-DAM imines still retain high yields and asymmetric inductions?

2.3.1 Preparation of the dianisylmethyl (DAM) amine

The *N*-DAM imines **68** could be synthesized by the condensation of aldehyde **69** and dianisylmethyl amine **70** according to the general procedure for the preparation of benzhydryl imines (Scheme 2.8).[43] Although amine **70** is commercially available, the price is too high to be make it economically feasible to conduct a detailed study on the aziridination of the imines **68** with a broad range of substrates. Two procedures were developed to prepare **70** and both are comparable in terms of the overall efficiency.

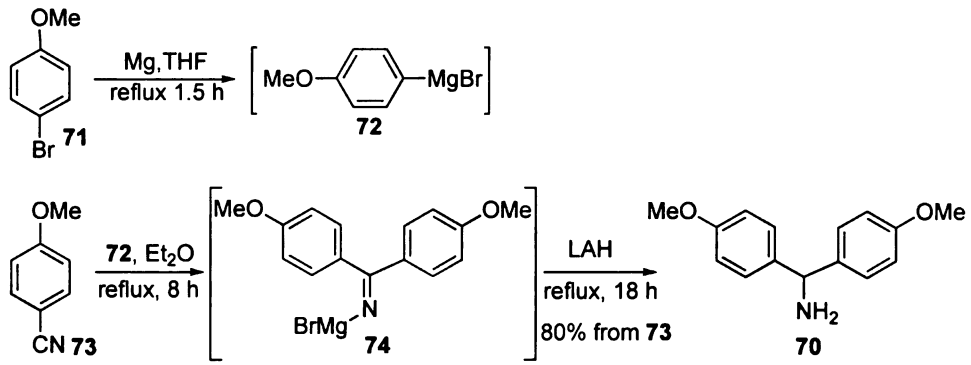
Scheme 2.8 The proposed aziridination of *N*-DAM imines



2.3.1.1 The reductive amination procedure

The lithium aluminum hydride reduction of Grignard-nitrile adducts for the preparation of primary amines was developed by Pohland and Sullivan[44] and was successfully applied by the former group member Dr. Zhang in the synthesis of several benzhydryl derived amines.[37d] It was expected that the dianisylmethyl amine could also be prepared by this route (Scheme 2.9).

Scheme 2.9 Amine formation via reductive amination



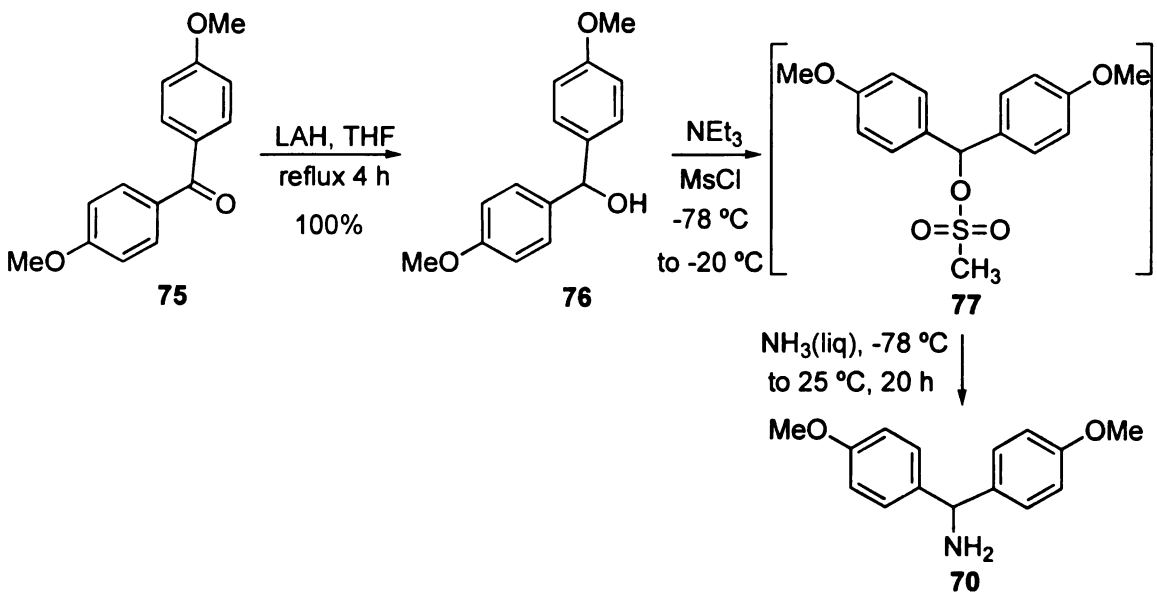
The *para*-bromoanisole **71** was converted to the Grignard reagent **72**, followed by the reaction with *para*-methoxybenzonitrile **73** to form intermediate **74**, which was directly reduced with lithium aluminum hydride to generate the desired amine **70**. The overall process gave the amine **70** in 80% yield from **73** (average of two runs) after silica

gel chromatographic purification. The silica gel was neutralized by adding 2% Et_3N to the elution solvent to avoid loss of the product during chromatography.

2.3.1.2 The one-pot mesylation-amination procedure

Another successful method for the preparation of amine **70** is through a one-pot mesylation-amination reaction[45] that begins with commercially available 4,4'-dimethoxybenzhydrol **76**, as shown in Scheme 2.10. The hydroxyl group in **76** was converted to a good leaving group by using freshly distilled mesylchloride to afford intermediate **77**. Subsequent S_N2 substitution with liquid ammonia resulted directly in amine **70**.

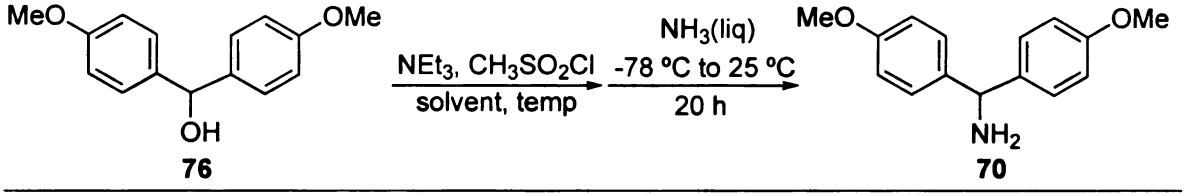
Scheme 2.10 Preparation of amine **70** via mesylation-amination reaction



In the optimization of this method, it was found that the low yields in many runs could be traced to incomplete conversion to the mesylate **77**. In order to effect complete conversion of **76** to **77**, the temperature was increased from –78 °C to –20 °C after the addition of mesylchloride, and kept at –20 °C for at least half an hour.[45a] After cooling the reaction mixture back to –78 °C, liquid ammonia was introduced carefully from an

ammonia cylinder through a dry ice/acetone condenser. The best method for quenching the reaction employed NH_4OH solution (30% assay). To further reduce the overall expense for the preparation of **70**, the alcohol **76** was prepared in the lab by a simple LAH reduction of the inexpensive 4,4'-dimethoxybenzophenone **75** to afford **76** in quantitative isolated yield. Some of the conditions for the optimization of the preparation of amine **70** are listed in Table 2.1, and the best condition is shown in entry 4.

Table 2.1 Optimization of the mesylation-amination procedure[a]



entry	solvent	temp (°C)	time (h)[b]	yield (%)[c]
1	THF	-78	24	<35% conv.
2	THF	-78→-20→-78	24	84
3[d]	THF	-78→-20→-78	24	35
4	THF	-78→-20→-78	16	84
5[e]	CH_2Cl_2	-50→-20→-50	24	68
6	CH_2Cl_2	-78→-20→-78	16	85

[a] Mesyl chloride and triethylamine were freshly distilled. Unless otherwise specified, all reactions were carried out with 1.3 equiv Et_3N, 1.3 equiv MsCl and 1 equiv **76** in 0.3 M in THF. Excess liquid ammonia was used in the second step and NH_4OH (30%) was used to quench the reaction. [b] Time after the addition of liquid ammonia. [c] Isolated yield after silica gel chromatography. [d] The concentration of the reaction mixture was 10 times diluted. [e] After the reaction was done, 1N HCl was added first to quench the reaction, then neutralized by 1N NaOH.

Compared with the Grignard reagent procedure (Scheme 2.9), this one-pot mesylation-amination is milder, easier and less expensive considering the cost of all reagents.

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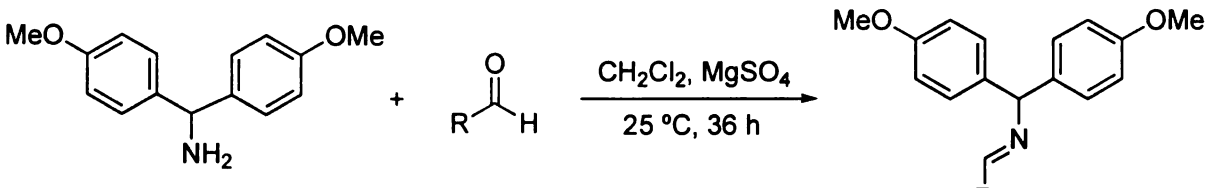
2.3.2 Preparation of *N*-DAM imines

All of the imines **68** were prepared following the procedure that has been reported[22a] for the benzhydryl imines, in which the amine **70** was reacted with aldehyde **69** under argon, and $MgSO_4$ was used as the dehydration reagent (Table 2.2). All liquid aldehydes were freshly distilled, and all solid aldehydes were used as purchased. The product could be purified by crystallization for all of the aryl and all of the alkyl substrates except the *n*-propyl substituted imine **68c** (Table 2.2, entry 3), which is a liquid. Unpurified imine **68c** was used directly in the aziridination step. The solid *para*-nitrobenzaldehyde **69g** was purified by silica gel chromatography to probe a possible difference in the AZ reaction between the unpurified and purified solid aldehyde, which will be discussed in section 2.3.4.2.

Table 2.2 Preparation of *N*-DAM imines **68**[a]



70 **69a - 69i** **68a - 68i**

entry	R	series	yield (%)[b]
1	*c*-C_6H_{11}	**a**	92
2	*t*-Bu	**b**	96
3	*n*-C_3H_7	**c**	nd
4	Ph	**d**	91
5	*o*-CH_3-C_6H_4	**e**	75
6	*p*-Br-C_6H_4	**f**	91
7	*p*-NO_2-C_6H_4	**g**	91
8	*p*-MeO-C_6H_4	**h**	92
9	1-naphthyl	**i**	82

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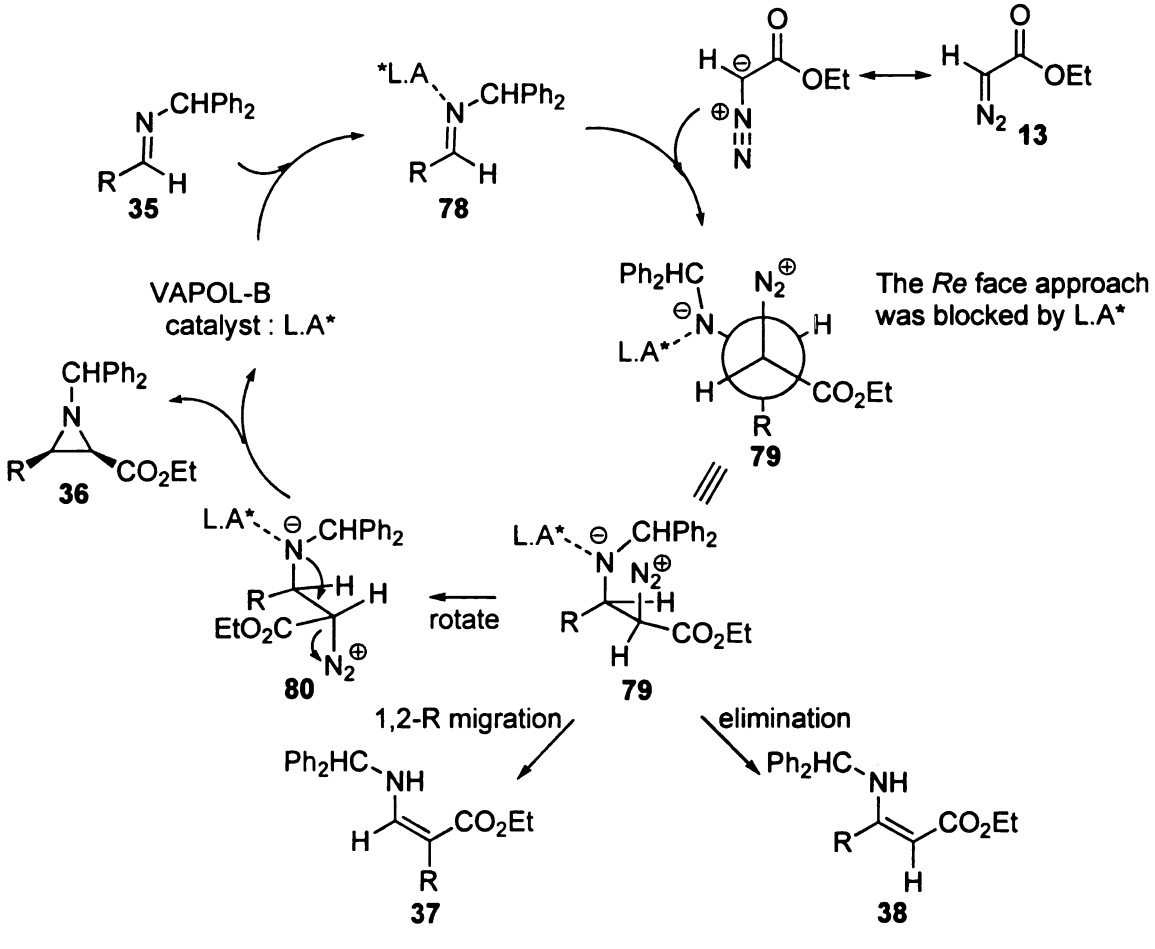
[a] All reactions were carried out with 1 equiv amine and 1.05-1.1 equiv aldehyde. [b] Isolated yield after crystallization in hexanes or the mixed solvent of hexanes and CH_2Cl_2. nd = not determined.

2.3.3 Optimization of conditions for the catalytic AZ reaction

The reaction conditions[22b] that were developed for the aziridination reaction of *N*-benzhydryl imines were examined first. It is believed that this VANOL / VAPOL-borate complex catalyzed AZ reaction has a mechanism similar to that proposed by Brookhart and Templeton for aziridination catalyzed by simple Lewis acids.[17] As shown in Scheme 2.11, the reaction of ethyl diazoacetate with imines mediated by a Lewis acid is normally selective for the formation of the *cis*-substituted aziridines **36**.

Scheme 2.11 Proposed mechanism of Wulff's AZ system



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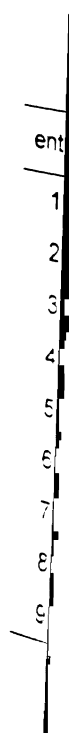
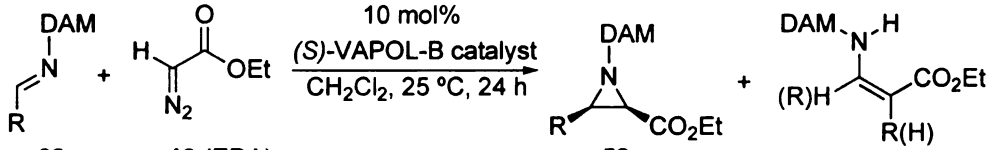


The process is thought to involve coordination of the Lewis acid to the imine and then carbon-carbon bond formation resulting from the attack of the diazo carbon in **13** on the activated imine **78**. From steric considerations, the approach of **13** to **78** may be expected to most favorably generate the zwitterion **79**. This carbon-carbon bond forming step sets both the diastereoselectivity and the absolute configuration of the product. The zwitterion **79** then undergoes rotation along the newly formed C-C bond to its conformer **80** to facilitate the intramolecular *anti-* attack of nitrogen, which releases nitrogen gas and affords the aziridine in a *cis-* configuration as shown in structure **36**. The released chiral Lewis acid catalyst then coordinates with free imine **35** to reform the complex **78** and continue the catalytic cycle. The reaction is also known to give varying amounts of the isomeric enamines **37** and **38**, which are likely the result of nitrogen loss concomitant with a 1,2-carbon or 1,2-hydrogen shift in the zwiterionic intermediate **79**, respectively.

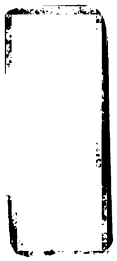
Table 2.3 AZ reaction of *N*-DAM imines **68** in CH_2Cl_2[a]



68 **13** (EDA) **58** **81(82)**

DAM = dianisylmethyl

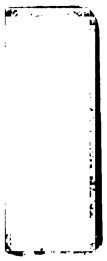
entry	series	R	yield (%) *cis*-**58**[b](c)	ee (%) *cis*-**58**[d](c)	*cis:trans* **58**[e]	yield (%) **81(82)**[f]
1	**a**	*c*-C_6H_{11}	65(74)	67(78)	25:1	3(1)
2	**b**	*t*-Bu	58(83)	80(83)	33:1	1(1)
3	**c**	*n*-Pr	11(52)	nd(78)	nd	nd
4	**d**	Ph	83(83)	91(89)	33:1	1(1)
5	**e**	*o*-MeC_6H_4	76(68)	79(88)	33:1	4(1)
6	**f**	*p*-BrC_6H_4	87(85)	87(90)	25:1	1(1)
7	**g**	*p*-$NO_2C_6H_4$	81(61)	85(61)	15:1	1(1)
8	**h**	*p*-$OMeC_6H_4$	45[g](42)	89(77)	50:1	1(1)
9	**i**	1-Naphthyl	83(87)	93(93)	20:1	1(1)



[a] Unless otherwise specified, all reactions were performed with 10 mol% catalyst in CH_2Cl_2 at 0.5 M in **68** with 1.1 equiv of **13** at 25 °C for 24 h. nd = not determined. [b] Isolated yield after silica gel chromatography. [c] The data in parenthesis is the data from the aziridination of benzhydryl imine **35**.[47] [d] Determined on purified *cis*-**58** by HPLC on a Chiralpak AD column. [e] Ratio determined by integration of the methine protons of the *cis*- and *trans*-aziridines in the ^{1}H NMR spectrum of the crude reaction mixture. [f] Determined by integration of the *N*-H signals of **81** and **82** relative to the methine proton of *cis*-**58** in the ^{1}H NMR spectrum of the crude reaction mixture. [g] Reaction time was 72 h, 50% conversion. Purification of *cis*-**58h** was achieved on Et_3N neutralized silica gel.

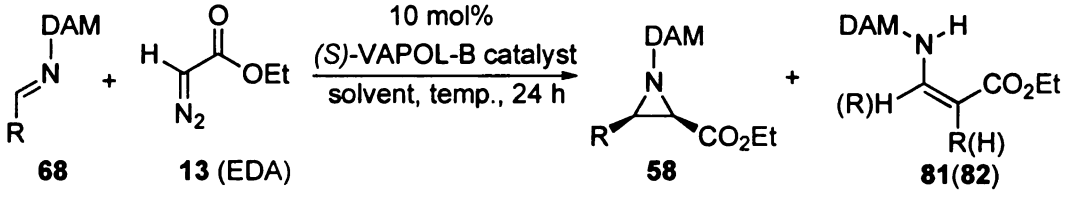
The AZ reaction of the *N*-DAM imine **68** was carried out with a catalyst prepared from VAPOL and triphenylborate according to our previously published procedure[22] (Scheme 1.10), and the results are presented in Table 2.3. The asymmetric inductions observed for the aryl substituted *N*-DAM imines are similar to those reported for the corresponding benzhydryl imines, but in the cases of alkyl substituted imines, the inductions are lower. The *cis/trans* selectivities were comparable as were the yields except for the reactions of the alkyl imines, especially for the imine **68c** that was used without purification, where a sluggish reaction was observed (Table 2.3, entry 3). The amount of the enamine side-products is less than that observed with the benzhydryl imines. The aziridination reaction of the imine **68h** derived from *para*-methoxybenzaldehyde was very slow requiring 72 hours for 50% completion (Table 2.3, entry 8). The resulting aziridine **58h** was unstable to normal silica gel chromatography and could only be purified if the silica gel was buffered with triethylamine.[46]

In an effort to improve the asymmetric inductions, the cyclohexyl imine **68a** and phenyl imine **68d** were selected for the optimization of reaction conditions and the results of variation in the temperature and solvents are presented in Table 2.4. Each imine was screened in toluene, methylene chloride and carbon tetrachloride and at room temperature or 0 °C. As the results show in Table 2.4, there was significant improvement



in the asymmetric induction of the cyclohexyl imine **68a** in carbon tetrachloride as compared to methylene chloride (Table 2.4, entry 1 vs. entry 3), however, when the temperature was decreased to 0 °C, the induction dropped dramatically, which may be related to the fact that imine **68a** was not completely dissolved (Table 2.4, entry 4). The temperature has a negligible effect on the reaction of phenyl imine **68d** (Table 2.4, entry 7 and 8), while CCl_4 was again superior to CH_2Cl_2 (Table 2.4, entry 5 vs. 7). The induction with imine **68d** in carbon tetrachloride could be increased to a value higher than observed for either methylene chloride or toluene, and the yield was slightly improved as well (Table 2.4, entry 5, 6 and 7). The reactions with imine **68d** in both toluene and carbon tetrachloride gave very high diastereoselectivity and the amount of the non-cyclized enamine products **81** and **82** that are formed is less than 2% in each case.

Table 2.4 Optimization of AZ conditions by using *N*-DAM imines **68a** and **68d**[a]



entry	series	R	solvent	temp (°C)	yield (%) *cis*-**58**[b]	ee (%) *cis*-**58**[c]	*cis*/*trans* **58**[d]	yield (%) **81(82)**[e]
1	**a**	*c*-C_6H_{11}	CH_2Cl_2	25	65	67	25:1	3(1)
2[f]	**a**	*c*-C_6H_{11}	toluene	25	58	52	25:1	12(7)
3	**a**	*c*-C_6H_{11}	CCl_4	25	69	77	50:1	3(1)
4[f]	**a**	*c*-C_6H_{11}	CCl_4	0	45	19	33:1	4(1)
5	**d**	Ph	CH_2Cl_2	25	83	91	33:1	1(1)
6	**d**	Ph	toluene	25	88	95	50:1	1(1)
7	**d**	Ph	CCl_4	25	91	96	50:1	1(1)
8	**d**	Ph	CCl_4	0	91	97	33:1	1(1)

[a] Unless otherwise specified, all reactions were performed with 10 mol% catalyst at 0.5 M in **68**

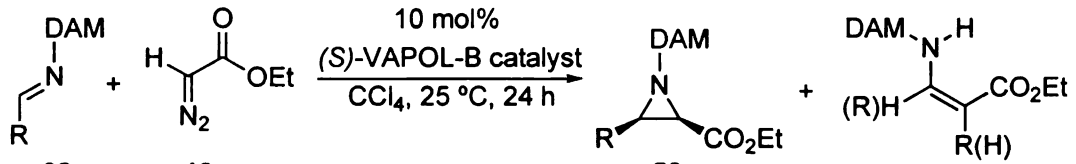
with 1.1 equiv of **13** at 25 °C for 24 h. [b] Isolated yield after silica gel chromatography. [c] Determined on purified *cis*-**58** by HPLC on a Chiralpak AD column. [d] Ratio determined by integration of the methine protons of the *cis*- and *trans*-aziridines in the ^{1}H NMR spectrum of the crude reaction mixture. [e] Determined by integration of the *N*-H signals of **81** and **82** relative to the methine proton of *cis*-**58** in the ^{1}H NMR spectrum of the crude reaction mixture. [f] Imine **68a** was not completely dissolved.

2.3.4 AZ reaction of *N*-DAM imines with optimized conditions

2.3.4.1 AZ reaction catalyzed by VAPOL-borate catalyst

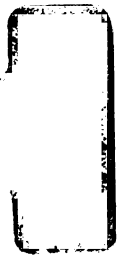
Applying the optimized conditions, the reactions of the *N*-DAM imines **68a-68i** with the VAPOL-borate catalyst were examined in carbon tetrachloride and the results are presented in Table 2.5.

Table 2.5 Aziridination of *N*-DAM imines **68** with VAPOL-borate catalyst in CCl_4[a]



68 **13** **58** **81(82)**

entry	series	R	yield (%) *cis*-**58**[b]	ee (%) *cis*-**58**[c]	*cis:trans* **58**[d]	yield (%) **81(82)**[e]
1	**a**	*c*-C_6H_{11}	69	77	50:1	3(1)
2	**b**	*t*-Bu	47	75	50:1	1(1)
3	**c**	*n*-Pr	11	63	nd	nd
4	**d**	Ph	91	96	50:1	1(1)
5	**e**	*o*-MeC_6H_4	86	89	50:1	1(1)
6	**f**	*p*-BrC_6H_4	92	93	50:1	1(1)
7	**g**	*p*-$NO_2C_6H_4$	88	96	20:1	1(1)
8	**h**	*p*-$OMeC_6H_4$	49[f]	nd	nd	nd
9	**i**	1-Naphthyl	92	94	50:1	1(1)



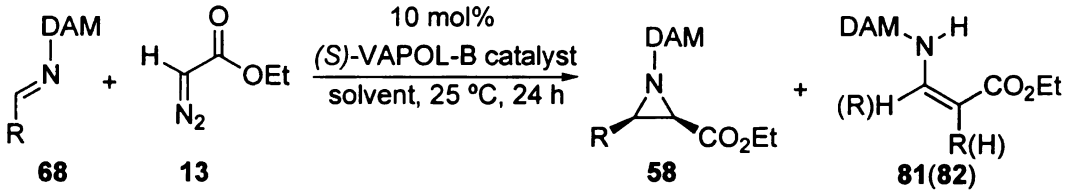
[a] Unless otherwise specified, all reactions were performed with 10 mol% catalyst in CCl_4 at 0.5 M in **68** with 1.1 equiv of **13** at 25 °C for 24 h. nd = not determined. [b] Isolated yield after silica gel chromatography. [c] Determined on purified *cis*-**58** by HPLC on a Chiralpak AD column. [d] Ratio determined by integration of the methine protons of the *cis*- and *trans*-aziridines in the ^{1}H NMR spectrum of the crude reaction mixture. [e] Determined by integration of the *N*-H signals of **81** and **82** relative to the methine proton of *cis*-**58** in the ^{1}H NMR spectrum of the crude reaction mixture. [f] Reaction time was 72 h, 70% conversion. Purification of *cis*-**58h** was achieved on Et_3N neutralized silica gel. The isolated yield was ~10% with untreated silica gel.

The asymmetric inductions are uniformly improved over those in methylene chloride and the yields are better in all cases as well (Table 2.3 vs. Table 2.5). The *cis/trans* selectivities in CCl_4 are also higher than those in CH_2Cl_2. This type of observation is normally the case for these aziridination reactions: the *cis/trans* selectivity usually increases as the asymmetric induction increases. From the data in Table 2.5, it should be noted that the asymmetric inductions for the aryl-substituted imines are excellent, however, the inductions for the alkyl imines are lower. In addition, the reaction with the imine **68c** is poor giving only 11% isolated yield with moderate enantioselectivity (Table 2.5, entry 3). The reaction of the imine **68h** is still slow, but is slightly faster in CCl_4 than in CH_2Cl_2 (Table 2.5, entry 8 vs. Table 2.3, entry 8).

N-DAM imines **68** in many cases are less soluble in toluene and carbon tetrachloride than they are in methylene chloride and, therefore, some reactions were also examined in a mixed solvent system of carbon tetrachloride and methylene chloride as shown in Table 2.6. Phenyl imine **68d** is soluble in CCl_4, but was used in the mixed solvent system as a control experiment (Table 2.6, entry 2). Generally, lower isolated yields were observed in the mixed solvent as compared with the same reactions run in pure CCl_4, while the asymmetric induction increased only in the case of the *tert*-butyl substituted imine **68b** (Table 2.6, entry 1) and the *para*-bromophenyl substituted imine **68f** (Table

2.6, entry 4). At this point, we can only assume that the higher selectivity is caused by the better solubility. A definitive understanding of these solvents effects may have to await the determination of the catalyst structure and of the reaction mechanism.

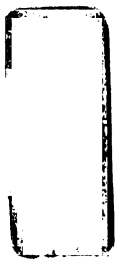
Table 2.6 Aziridination of *N*-DAM imine **68** using a mixed solvent system[a]



entry	imine	R	solvent (CH_2Cl_2:CCl_4)	yield (%)[b] *cis*-**58**	ee (%)[c] *cis*-**58**
1	**b**	*t*-Bu	1:3	74	87
2	**d**	Ph	1:7	83	95
3	**e**	*o*-MeC_6H_4	1:7	62	80
4	**f**	*p*-BrC_6H_4	1:7	89	97
5[d]	**g**	*p*-$NO_2C_6H_4$	1:19	83	96
6	**h**	*p*-$OMeC_6H_4$	1:3	50[e]	nd
7	**i**	*1*-naphthyl	1:7	88	96

[a] Unless otherwise specified, all reactions were performed with 10 mol% catalyst at 0.25 M in **68** with 1.1 equiv of **13** at 25 °C for 24 h. [b] Isolated yield after silica gel chromatography. [c] Determined on purified *cis*-**58** by HPLC on a Chiralpak AD column. [d] The concentration was 0.1 M. [e] NMR yield using Ph_3CH as internal standard.

The AZ reaction of the *n*-propyl imine **68c** gave very poor isolated yield along with much lower enantioselectivity as compared with other imines even under the optimized conditions (Table 2.5, entry 3). The *N*-DAM butylimine **68j**, which has one more carbon than the *n*-propyl imine, was also a liquid and used unpurified in the reaction to give low yield similar to **68c**. These results were not surprising because imines **68c** and **68j** were



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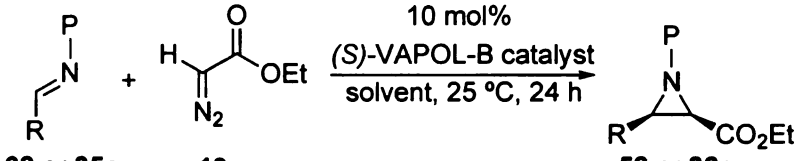
the only imines examined that were not solid and could not be purified by crystallization, and therefore not purified prior to reaction. We suspected that the poor reactivity was caused by the instability of the imine and the presence of impurities. The ^{1}H NMR spectrum of the unpurified imine was not clean. Decomposition in $CDCl_3$ was observed by the ^{1}H NMR spectrum hours after the first NMR spectrum was taken. Interesting, when the unpurified benzhydryl protected imine **35c** that contains the same alkyl substituent as imine **68c** was used in the aziridination reaction, higher yields and enantioselectivities were obtained (Table 2.7, entry 1 vs. entry 4). Although the *N*-benzhydryl imine **35c** and the *N*-dianisylmethyl imine **68c** both showed sign of decomposition within one day, the much faster decomposition rate of **68c** may be due to its higher rate of oxidation caused by the electron rich dianisyl substituent. The imine **68c** is initially a colorless liquid but changes to a light yellow liquid in one hour and then to orange in one day.

Table 2.7 AZ reaction of primary alkyl substituted imines[a]



68 or **35c** **13** **58** or **36c**

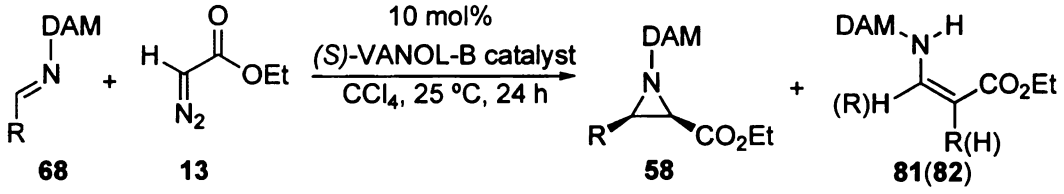
entry	series	R	P	solvent	yield (%) *cis*-**58** or *cis*-**36c**[b]	ee (%) *cis*-**58** or *cis*-**36c**[c]
1	**68c**	*n*-Pr	DAM	toluene	5	nd
2	**68c**	*n*-Pr	DAM	CCl_4	11	63
3	**68j**	*n*-Bu	DAM	CCl_4	25	nd
4	**35c**	*n*-Pr	Bh	toluene	52	78
5	**35c**	*n*-Pr	Bh	CCl_4	54	79

[a] Unless otherwise specified, all reactions were performed with 10 mol% catalyst at 0.5 M in **68** or **35c** with 1.1 equiv of **13** at 25 °C for 24 h. nd = not determined. [b] Isolated yield after silica gel

chromatography. [c] Determined on purified *cis*-**58** by HPLC on a Chiralpak AD column for entry 2 and on purified *cis*-**36c** on a Chiracel OD-H column for entry 4 and 5.

2.3.4.2 AZ reaction catalyzed by VANOL-borate catalyst

Table 2.8 AZ reaction of *N*-DAM imines **68** with VANOL catalyst in CCl_4[a]



68 **13** **58** **81(82)**

entry	series	R	yield (%) *cis*-**58**[b]	ee (%) *cis*-**58**[c]	yield (%) *cis*-**58**[d]	ee (%) *cis*-**58**[c,e]	*cis*/*trans* **58**[f]	yield (%) **81(82)**[g]
1	**a**	*c*-C_6H_{11}	86	84	68	>99	33:1	7(2)
2	**b**	*t*-Bu	70	75	39	99	50:1	6(19)
3	**d**	Ph	92	95	85	>99	33:1	1(1)
4	**e**	*o*-MeC_6H_4	80	89	75	99	50:1	3(1)
5	**f**	*p*-BrC_6H_4	89	80	nd	nd	50:1	1(1)
6[h]	**f**	*p*-BrC_6H_4	95	90	nd	nd	50:1	1(1)
7[i]	**f**	*p*-BrC_6H_4	95	93	86[j]	>99[j]	50:1	1(1)
8	**g**	*p*-$NO_2C_6H_4$	97	97	76[k]	>99[k]	50:1	2(1)
9	**g**[l]	*p*-$NO_2C_6H_4$	96	97	nd	nd	50:1	2(1)
10	**h**	*p*-$OMeC_6H_4$	80	95	nd	nd	50:1	1(1)
11	**i**	1-Naphthyl	98	86	nd	nd	50:1	1(1)
12[h]	**i**	1-Naphthyl	91	97	82	>99	50:1	2(1)

[a] Unless otherwise specified, all reactions were performed with 10 mol% catalyst with 1.1 equiv of **13** at 25 °C for 24 h. nd = not determined. [b] Isolated yield after silica gel chromatography. [c] Determined on purified *cis*-**58** by HPLC on a Chiralpak AD column. [d] Overall yield after chromatography and a single crystallization from CH_2Cl_2:hexanes (see experimental for details). [e] Determined after chromatography and a single crystallization from CH_2Cl_2:hexanes (see

experimental for details). [f] Ratio determined by integration of the methine protons of the *cis*- and *trans*-aziridines in the ^{1}H NMR spectrum of the crude reaction mixture. [g] Determined by integration of the *N*-H signals of **81** and **82** relative to the methine proton of *cis*-**58** in the ^{1}H NMR spectrum of the crude reaction mixture. [h] Reaction temperature was 0 °C for 5 h and then 25 °C for 19 h. [i] Reaction temperature was –10 °C for 5 h and then 25 °C for 19 h. [j] Overall yield and % ee was determined after chromatographic purification of **58** and subsequent conversion to the unprotected aziridine **56** and crystallization. [k] Overall yield and % ee was determined after chromatographic purification of **58** and subsequent conversion to the unprotected aziridine **56** followed by protection with a Boc group and finally a crystallization. [l] The imine **68g** was prepared from purified 4-nitrobenzaldehyde.

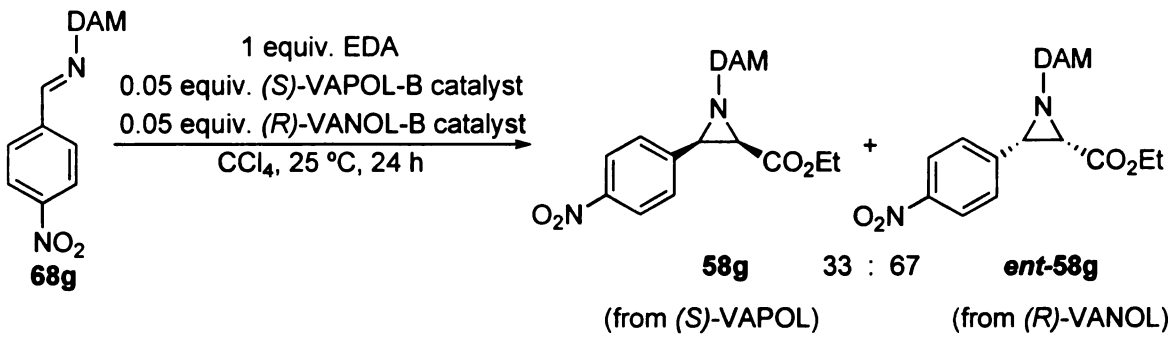
It was reported that the VANOL-borate catalyzed system gave stereoselectivities very similar in the AZ reaction of benzhydryl imines to those of the VAPOL-borate catalyzed system, and this also proved to be the case for the aziridination with *N*-DAM imines **68** in carbon tetrachloride (Table 2.8). The yields and diastereoselectivities were typically higher for the VANOL-borate catalyzed reactions of the aryl-substituted imines than those catalyzed by the VAPOL-borate catalyst (Table 2.5). The asymmetric induction dropped for the *para*-bromophenyl **68f** and 1-naphthyl imine **68i**, but this could be improved if the reactions were performed at lower temperatures (Table 2.8, entries 6, 7 and 12). Each *N*-DAM aziridine could be crystallized to ≥ 99% ee with a single crystallization from methylene chloride and hexanes. For example, the cyclohexyl substituted aziridine **58a** could be obtained in > 99% ee in 68% overall yield from the imine **68a** and the phenyl substituted aziridine **58d** could be obtained in > 99% ee in 85% overall yield from the imine **68d**.

2.3.4.3 Rate competition studies

After analyzing the data obtained from the VAPOL-borate and VANOL-borate catalyzed reactions, it was noted that the reactions with the VANOL-borate catalyst appeared to be slightly faster, especially in the case of the *para*-methoxyphenyl imine

68h. For this imine, the aziridination reaction went to completion in 24 hours with the VANOL-borate catalyst (Table 2.8, entry 10), whereas, with the VAPOL-borate catalyst, it only went to 70% conversion in 3 days (Table 2.5, entry 8). An experiment was designed to quantify this rate difference between the two ligands and the result is shown in Scheme 2.12. The aziridination of the *para*-nitrophenyl substituted imine **68g** was carried out with a mixture of 5 mol% of the catalyst derived from (*R*)-VANOL and 5 mol% of the catalyst derived from (*S*)-VAPOL. Imine **68g** was chosen for this competition study because it gave very high induction with both catalysts (96 – 97% ee, Tables 2.5, entry 7 and Table 2.8, entry 8). This reaction produced a 1:2 mixture of **58g** and *ent*-**58g**, thus revealing that the catalyst derived from VANOL is twice as fast as that derived from VAPOL. This experiment was designed with the knowledge that neither the VANOL-borate nor the VAPOL-borate catalyst formed with $B(OPh)_3$ exhibits any non-linear effects and thus each catalyst is deemed likely to contain only one molecule of the ligand.[47]

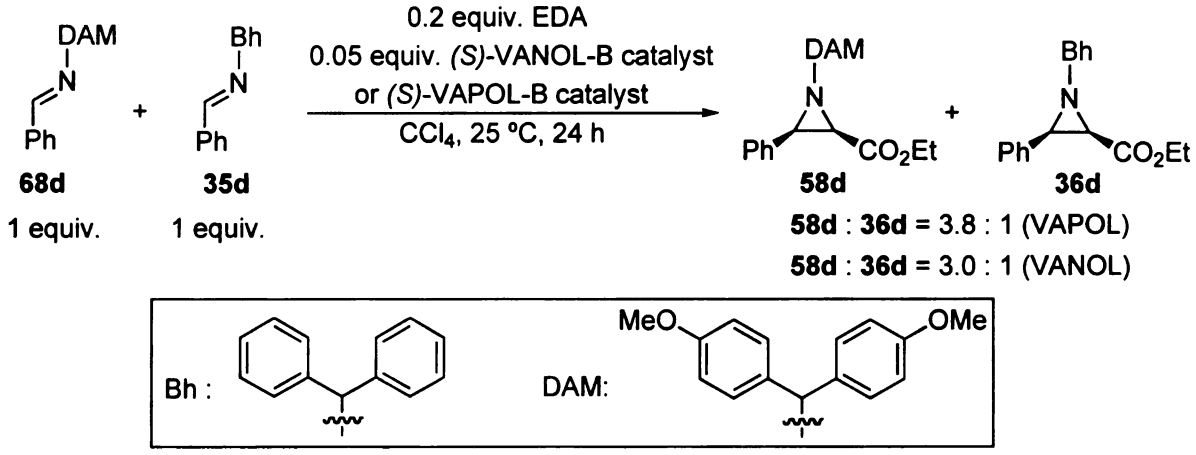
Scheme 2.12 Rate competition between VANOL and VAPOL ligands



Information was also sought on the relative reactivity of the *N*-DAM imines **68** versus the benzhydryl imines **35**. For this experiment, Dr. Yu Zhang, a former group member, designed and carried out a competition study between the two imines (Scheme 2.13). To a 1:1 mixture of the imines **68d** and **35d** was added 0.2 equivalents of ethyl diazoacetate and 5 mol % of either the VANOL-borate or the VAPOL-borate catalyst. Surprisingly, the

N-DAM imine **68d** reacted 3.8 times faster than the benzhydryl imine **35d** with the VAPOL-borate catalyst and 3.0 times faster with the VANOL-borate catalyst. This result is counter-intuitive because one might have expected that the more electron rich *N*-DAM imine would have been less reactive towards the attack by ethyl diazoacetate.

Scheme 2.13 Rate competition between *N*-Bh and *N*-DAM imines



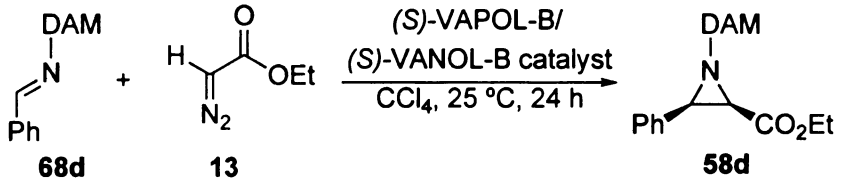
An explanation for the increased reactivity of *N*-DAM imines relative to the benzhydryl imines will have to await further studies focused on the structure and mechanism of the catalyst, and the work directed to these goals will be discussed in chapter six. The reason for the increased rate of reaction with the VANOL-borate catalyst versus the VAPOL-borate catalyst is also not clear at this point, however, it suggests that a lower catalyst loading may be possible for the VANOL-borate catalyst.

2.3.4.4 Catalyst loading study for VAPOL and VANOL ligands

The above results from the studies on the relative rates of catalysts generated form the VANOL and VAPOL ligands prompted a study on catalyst loading to determine the maximum turnover for these catalysts. The study was undertaken on the *N*-DAM phenyl imine **68d** with both the VANOL and VAPOL derived catalysts. The reactions were carried out in carbon tetrachloride at room temperature for 24 hours and all the reactions

indicated in Table 2.9 except entry 8 (80% conversion) and entry 10 (<10% conversion) went to completion under these conditions.

Table 2.9. Catalyst loading study with imine **68d** by VAPOL/VANOL-B catalysis[a]



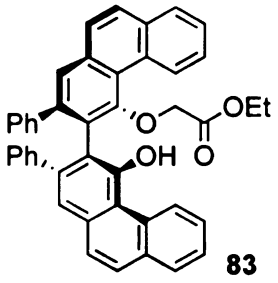
68d **13** **58d**

entry	**68d** (mmol)	ligand[b]	loading (mol%)	crystallized *cis*-**58d**		recrystallized *cis*-**58d**		ee of mother liquor (%)[d,f]	overall *cis*-**58d**	
				yield (%)[c]	ee (%)[d]	yield (%)[e]	ee (%)[d]		yield (%)[g]	ee (%)[d,h]
1	1	VAPOL	10	nd	nd	nd	nd	nd	91	96
2	1	VANOL	10	nd	nd	nd	nd	nd	92	95
3[i]	20	VAPOL	2	79	>99	nd	nd	73	95	96
4	10	VAPOL	1.0	89	92	76	98	81	89	96
5	10	VANOL	1.0	90	93	78	98	81	92	96
6	20	VAPOL	0.5	79	96	72	98	73	82	95
7	30	VANOL	0.5	79	91	68	98	72	92	92
8[i]	40	VAPOL	0.25	69	86	54	89	82	72	87
9	35	VANOL	0.25	76	90	66	97	65	89	90
10	10	VANOL	0.1	< 10% conversion						

[a] Unless otherwise specified, all reactions were performed in CCl_4 at 0.5 M in **68d** with 1.1 equiv of **13** at 25 °C for 24 h. For all reactions, the ratio of *cis*-**58d** / *trans*-**58d** was higher than 33:1, nd = not determined. [b] Ligand: **A** = *(S)*-VAPOL, **B** = *(S)*-VANOL. [c] Yield based on **68d** after crystallization from a 1:5 mixture of CH_2Cl_2 and hexanes. [d] Determined by HPLC on a Chiralpak AD column. [e] Yield based on **68d** after two crystallizations from a 1:5 mixture of CH_2Cl_2 and hexanes. [f] Measured on the product **58d** obtained by silica gel purification of the residue obtained from the combined mother liquors from the first and second crystallizations. [g] Combined yield of recrystallized product **58d** and of **58d** obtained by silica gel chromatography purification of the residue obtained from the combined mother liquors. [h] Calculated from the combined data of the

recrystallized product and the product that was obtained by silica gel chromatography purification of the residue obtained from the combined mother liquors. [i] The *(S)*-VAPOL was recovered in 95% yield (see experimental detail). Without removal of remaining EDA, the compound **83** was isolated in 73% yield as shown in Figure 2.1. [j] The conversion was 80% after 48 h.

Figure2.1 Structure of C-H insertion product from VAPOL and EDA



83

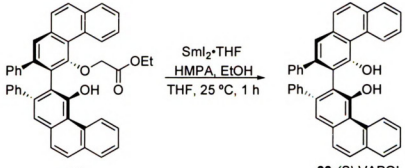
It was found that the amount of both the VANOL and VAPOL catalysts could be reduced to 1 mol% with no detrimental effect on the yield or asymmetric induction. Most of the reactions in Table 8 were performed with the same number of moles of the catalyst and thus, the reactions with decreased loadings were carried out by increasing the amounts of the reagents. For example, the reaction in entry 9 was performed with 11.6 grams (35 mmol) of the imine **68d** and 39 mg (0.09 mmol) of the VANOL ligand. With these large scale reactions, it was most convenient to purify the aziridine **58d** by crystallization first rather than chromatography. Most reactions gave complete conversion, the aziridine **58d** could be obtained in 97 – 98% ee by two crystallizations from methylene chloride/hexanes. In an effort to determine the overall yield and asymmetric inductions for these reactions, the aziridine remaining in the mother liquors from the two crystallizations was purified by silica gel chromatography.

As can be seen from the data in the Table 2.9, no significant loss in yield or induction was observed for either ligand when the catalyst loading was reduced to 0.5 mol%. At 0.25 mol% loading, the reaction with the VANOL catalyst was complete but that with VAPOL only went to 80 % conversion. Even at 400 turnovers, the VANOL derived

catalyst gives an 89% yield and 90% ee for the aziridine **58d** (Table 2.9, entry 9). This is the highest turnover reported for an AZ reaction of an imine. However, it is the limit since further lowering the catalyst loading to 0.1 mol% with the VANOL catalyst gave 10% conversion in 48 hours (Table 2.9, entry 10). Since this catalyst loading study was performed only using the phenyl imine **68d**, the results may not be typical for all imines.

We were also pleased to find that the VAPOL ligand could be recovered after the aziridination reaction. In the experiment shown in entry 3 of Table 2.1, 220 mg *(S)*-VAPOL was used in a reaction with 20 mmol imine and the VAPOL ligand was recovered in 95% yield with ≥ 99% ee. The purification of the recovered ligand and the aziridine **58** from the mother liquor could be achieved on the same silica gel chromatography column because of the lower polarity of VAPOL. However, it is necessary that the crude reaction mixture be directly subjected to high vacuum before crystallization of the aziridine in order to remove the excess ethyl diazoacetate. If vacuum is not applied to the crude reaction mixture, the recovery of VAPOL is only 10% and a 73% yield of the mono O-H insertion[48] product **83** was obtained, which resulted from the reaction of the ligand with the excess EDA **13**. It was found by another group member, Aman Desai, that the by-product **83** can be converted back to *(S)*-VAPOL by a direct reduction with *in situ* generated samarium diiodide to gave *(S)*-VAPOL in 91% yield and 99.8% ee (Scheme 2.14).[47]

Scheme 2.14 Reductive cleavage of C-O bond in **83** to recover the VAPOL ligand

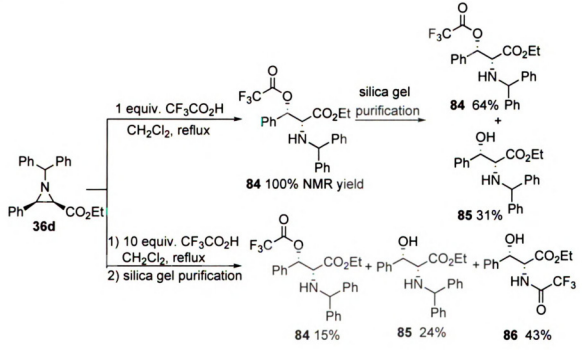


83

33 *(S)*-VAPOL
91% yield, 99.8%ee

2.3.5 Access to *N*-H aziridines under acidic conditions

Scheme 2.15 Acid-mediated ring opening of *N*-benzhydryl aziridine **36d**



The most common method for the deprotection of *N*-benzhydryl amines is by treatment with acid, however, aryl substituted *N*-benzhydryl aziridines are more susceptible to acid promoted aziridine opening, which has been exploited in our group for the total synthesis of some small molecules, and these have been briefly mentioned in chapter one (Schemes 1.12, 1.13, and 1.14). Thus, before examing the acid-mediated

cle

und

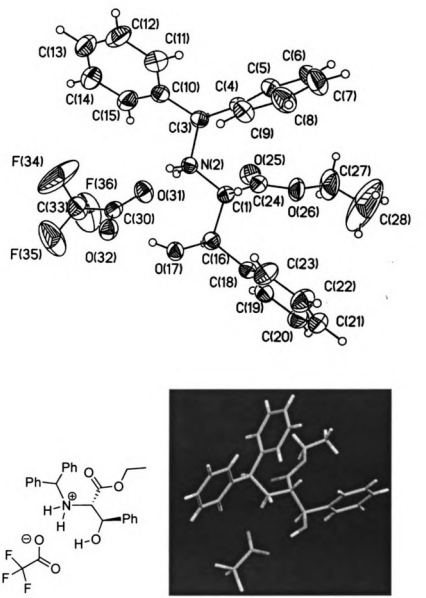
sub

was

Fig

cleavage of the DAM group from aziridine **58** to access *N*-H aziridines, it was desired to understand in more detail of the acid promoted ring opening of the *N*- benzhydryl aryl substituted aziridines **36**. The trifluoroacidic acid mediated ring opening of aziridine **36d** was chosen for this study.

Figure 2.2 X-ray structure of the trifluoroacetate salt of compound **85**



Thus, the treatment of ethyl-*N*-benzhydryl-3-phenyl-aziridinyl-2-carboxylate **36d** with

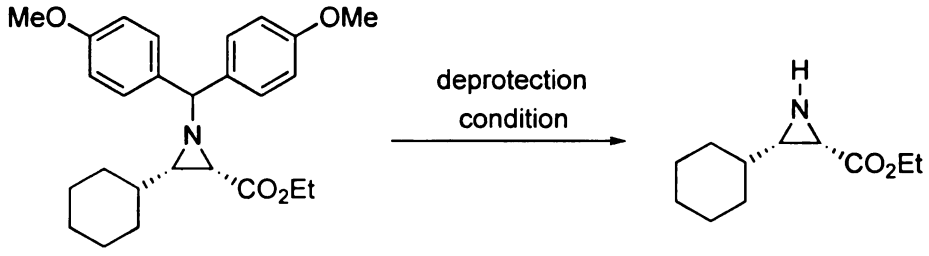
a stoichiometric amount of trifluoroacetic acid resulted in the formation of a single diastereomer of the ring-opened product **84** with the benzhydryl group untouched, which partially hydrolyzed during purification to afford compound **84** along with the deacylated product **85** (Scheme 2.15). The formation of **84** would be expected to result from the inversion at the C-3 carbon when the trifluoroacetate attacked the benzylic position and this was confirmed by X-ray analysis of the salt of **85** with TFA (Figure 2.2). Using an excess amount of acid resulted in a complex mixture of ring opening products (Scheme 2.15). In addition to compounds **84** and **85**, compound **86** with benzhydryl group removed, was isolated in 43% yield.

2.3.5.1 Discovery and optimization of acidic deprotection for DAM-aziridines

The cyclohexyl substituted aziridine **58a** was used as a model system for the determination of the proper acidic deprotection method and subsequent optimization with the hope that these conditions would be general to all of the aziridines **58a-58i**. Considering the relatively high stability of the 4,4'-dimethoxybenzhydryl carbonium ion **67** formed during the course of the acid deprotection (Scheme 2.7), the focus was mainly on the development of a mild but efficient acidic deprotection method.

The standard conditions for the cleavage of the dianisylmethyl group from amines involve exposure to 80% HOAc at 80 °C for 5 minutes.[49] Therefore, the deprotection of **58a** was attempted with a number of different acids under a variety of conditions,[50] however, the starting material **58a** was recovered in most cases, as shown in Table 2.10. The treatment of aziridine **58a** with 80% HOAc at 100 °C for 1 hour resulted in only 20% conversion and the formation of a complex mixture of products, none of which was the desired deprotected *N*-H aziridine **56a** (Table 2.10, entry 1). Although the treatment of **58a** with 100% HOAc at 100 °C for 30 minutes resulted in complete consumption of **58a**, no detectable amount of **56a** was observed.

Table 2.10 Acidic deprotection of aziridine **58a**



58a **56a**

entry	deprotection reagent (amount)	solvent	temp (°C)	time (h)	result
1[a]	HOAc (50 equiv.)	none	reflux	3	**58a** with complex mixtures
2	1:1 HOAc/HBr in H_2O (48%) (100 equiv.)	none	25	6	trace **56a**
3	HBr in HOAc (33 wt%) (10 equiv.)	none	25	0.5	50% **58a** with complex mixtures
4	90% HOAc/HCl (9:1) (140 equiv.)	none	reflux	1.5	complex mixtures
5	$Cl_2CHCOOH$ (10 equiv.)	anisole/CH_2Cl_2	50	3.5	trace **56a**
6	$CH_3CHClOCOCl$ (1.3 equiv.)	CH_2ClCH_2Cl	reflux	5	trace **56a**
7	5%H_2SO_4 in HOAc (10 equiv.)	anisole	80	20	33% **58a** and complex mixtures
8	TFAA (2 equiv.)	TEA/CH_2ClCH_2Cl	50	20	**58a** only
9	TFAA (2 equiv.)	TFA	25	0.7	34% of **56a**
10	TFA (10 equiv.)	anisole	50	0.5	42% of **56a**
11	5%H_2SO_4 in TFA (10 equiv.)	anisole	25	0.5	37% of **56a**

[a] The same results were obtained with HOAc in H_2O.

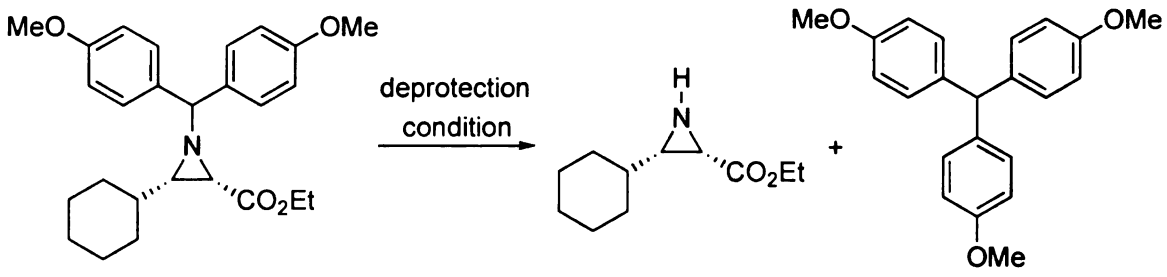
As shown in Table 2.10 (entry 1 to entry 8), a screen of several different inorganic and organic acids was conducted, and the parameters that were varied included the solvent (anisole, CH_2Cl_2, CH_2ClCH_2Cl, THF), the reaction temperature (25 °C, 50 °C, 100 °C, refluxing), the reaction time (10 minutes to 20 h), and the amount of each reagent used. Based on the ^1H NMR spectra of the crude reaction mixtures for these experiments,

more than trace amounts of the desired *N*-H aziridine **56a** was observed in only a few cases. Most of these experiments gave either recovered starting material or a complex mixture of products. These experimental results were consistent with the fact that aziridines are less basic than non-cyclic alkyl amines. The strain of the *cis*-disubstituted aziridine requires that the reagent for the cleavage of the DAM group from **58** be less nucleophilic than for the deprotection of normal *N*-DAM amines. For this purpose, stronger acids with less nucleophilic counter ions were examined, and promising results were obtained when trifluoroacetic acid or trifluoroacetic anhydride were used, which afforded the N-H aziridine **56a** in moderate yield (Table 2.10, entry 9 to 11). These results were different from those with the benzhydryl aziridine **36**, which gave predominantly ring opening products (Scheme 2.15).

It was found that the use of anisole as a solvent with these acids was the key to obtaining complete conversion and the best yields (Table 2.11, entry 14 vs. entry 15). Anisole serves to trap the dianisylmethyl cation that is formed and high yields of the resulting (*tris*)-anisylmethane **87** can be isolated from these reactions. The optimal conditions for the deprotection of *N*-DAM aziridine **58a** were found by screening various conditions and monitoring the ratio of **58a**, **56a**, and **87** by ^{1}H NMR spectrum with triphenylmethane as internal standard (Table 2.11). The reactions were optimized for conversion as well as for a 1 : 1 ratio of **56a** to **87** which can occur only if the aziridine does not undergo any ring opening reactions subsequent to deprotection. Trifluoroacetic acid by itself could not produce complete conversion without leading to some loss of the unprotected aziridine (Tabel 2.11, entry 2). However, following the protocol of Jones,[51] it was found that in combination with concentrated sulfuric acid, the cleavage with TFA was much cleaner and gave higher conversion (Table 2.11, entry 4 to 11). Additionally, it was found that the presence of water in the reaction system resulted in significantly diminished yields. It was also noticed that the deprotected aziridine **56a** sublimed slowly

under high vacuum.

Table 2.11 Optimization of deprotection conditions[a]



58a **56a** **87**

entry	reagent	reagent (equiv)	temp (°C)	time (h)	yield[b] **56a** (%)	ratio of **56a:87:58a**[c]
1	TFA	10	50	0.25	56	1: 1.4: 0.4
2	TFA	10	25	4	nd	1: 1.5: 0.1
3	H_2SO_4	10	25	0.5	nd	1: 1.1: <0.05
4	2% H_2SO_4 in TFA	10	25	0.5	52	1: 1.0: 0.6
5	2% H_2SO_4 in TFA	10	25	1	63	1: 1.2: 0.4
6	5% H_2SO_4 in TFA	10	0	4	<50	1: 1.6: 0.4
7	5% H_2SO_4 in TFA	10	25	0.5	75	1: 1.2: 0.1
8	8% H_2SO_4 in TFA	10	25	0.25	47	1: 1.6: 0.6
9	8% H_2SO_4 in TFA	10	25	0.5	98[e]	1: 1.0: <0.05
10	10% H_2SO_4 in TFA	10	25	0.5	93	1: 1.1: 0.08
11	10% H_2SO_4 in TFA	10	25	1	96	1: 1.0: <0.05
12	CF_3SO_3H	10	0	0.5	52	1: 1.5: 0.7
13	CF_3SO_3H	10	25	0.5	72	1: 1.2: <0.05
14	CF_3SO_3H	5	25	0.7	96[e,f]	1: 1.0: <0.05
15[d]	CF_3SO_3H	5	25	0.5	34	1: 1.1: 2.0
16	CF_3SO_3H	5	25	0.25	32	1: 1.5: 0.3
17	CF_3SO_3H	2	25	0.7	82	1: 1.1: 0.2

[a] Unless otherwise specified, all reactions were performed in anisole at 0.09 M in **58a**. [b] The yield was determined by ^1H NMR with triphenylmethane as an internal standard. [c] Determined by ^1H NMR of the crude reaction mixture. [d] CH_2Cl_2 was used as solvent. [e] Isolated yield after silica gel

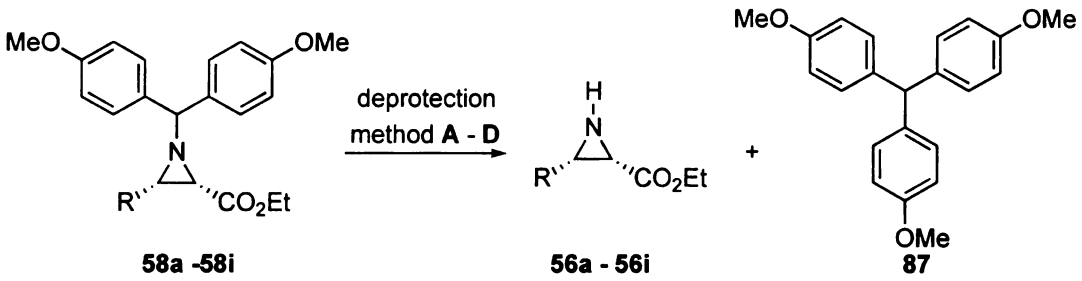
chromatography. [f] Compound **87** was also isolated in 95% yield after silica gel chromatography.

A series of experiments were carried out to study the effects of the concentration of sulfuric acid in trifluoroacetic acid, the temperature and the reaction time on the yield of aziridine **56a**. Better conversion was observed with greater amounts of sulfuric acid (up to 10%, entry 7 to 11). Prolonging the reaction time increases the conversion but also increases the decomposition of product **56a** (Table 2.11, entry 5), and lowering the temperature gave even worse results (Table 2.11, entry 6). The best conditions were with 8-10% sulfuric acid (v/v) in TFA for 30 minutes at room temperature, which reproducibly gives quantitative yields of **56a** (Table 2.11, entry 8 to 11) as determined by ^{1}H NMR spectrum. No decomposition was observed in these cases even with prolonged reaction times. The only drawback of this method is that the mixture of sulfuric acid and trifluoroacetic acid begins to decompose within a few days, which results in 5-10% lower isolated yields. Alternative methods that were found to be equally effective were using triflic acid or sulfuric acid alone, both of which are strong and less nucleophilic acids. The use of triflic acid is more convenient than the combination of trifluoroacetic acid and sulfuric acid and the results are also generally more consistent.

2.3.5.2 Deprotection of *N*-DAM aziridines

The deprotection of eight differently substituted dianisylmethyl aziridines **58** was examined with the three optimized acidic conditions described in the previous section and also, for a point of comparison, with hydrogenolysis conditions. Specifically, these conditions are: Method **A**, 5 equivalents of triflic acid at 25 °C for 40 minutes, Method **B**, 10 equivalents of trifluoroacetic acid containing 8% concentrated sulfuric acid (by volume) at 25 °C for 40 minutes, Method **C**, 10 equivalents of sulfuric acid at 25 °C for 40 minutes, and Method **D**, hydrogenation with Pearlman's catalyst.[38] The results of these studies ware presented in Table 2.12.

Table 2.12 Deprotection of *N*-DAM aziridines **58**[a]



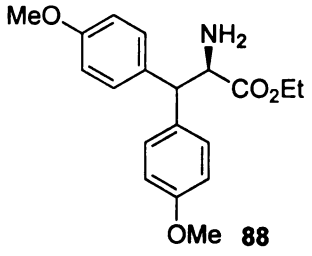
58a -58i **56a - 56i** **87**

entry	series	R	method[b]	NMR yield of **56** (%)	Isolated yield of **56** (%)[c]
1	**a**	*c*-C_6H_{11}	A	95	96
2	**a**	*c*-C_6H_{11}	B	95	96
3	**a**	*c*-C_6H_{11}	C	nd	95
4	**a**	*c*-C_6H_{11}	D	nd	76
5	**b**	*t*-Bu	A	nd	88
6	**b**	*t*-Bu	D	nd	75
7	**d**	Ph	A	97	99
8	**d**	Ph	B	nd	95[d]
9	**d**	Ph	C	nd	81
10	**d**	Ph	D	0	0[e]
11	**e**	*o*-MeC_6H_4	A	100	99
12	**f**	*p*-BrC_6H_4	A	98	99
13	**g**	*p*-$NO_2C_6H_4$	A	95	99
14	**h**	*p*-$OMeC_6H_4$	A	0	0[f]
15	**h**	*p*-$OMeC_6H_4$	B	0	0[f]
16	**i**	1-Naphthyl	A	83	72
17	**i**	1-Naphthyl	B	94	92
18	**i**	1-Naphthyl	C	nd	99

[a] Unless otherwise specified, all reactions were carried out at 0.5 mmol scale in **58** and all reactions went to completion. nd = not determined. 95 – 100% yield of **87** observed for methods A and B. [b] Method **A**: anisole solvent at 0.09 M in **58**, 5 equiv of triflic acid, 25 °C for 40 min.

Method **B**: anisole solvent at 0.09 M in **58**, 10 equiv of trifluoroacetic acid containing 8% (by volume) sulfuric acid, 25 °C for 40 min. Method **C**: anisole solvent at 0.09 M in **58**, 10 equiv sulfuric acid, 25 °C for 40 min. Method **D**: methanol solvent at 0.01 M in **58**, 10 mol% $Pd(OH)_2/C$, 1 atm H_2, 25 °C for 4 – 24 h. [c] Isolated yield after purification by silica gel chromatography. [d] Reaction was carried at a 45 mmol scale. [e] A 66% yield of the ring opening product **62** was isolated. [f] These conditions gave the ring opening product **88** which was isolated from the reaction in entry 14 in 72% yield as shown in Figure 2.3 below.

Figure 2.3 Acid mediated ring opening product of aziridine **58h**



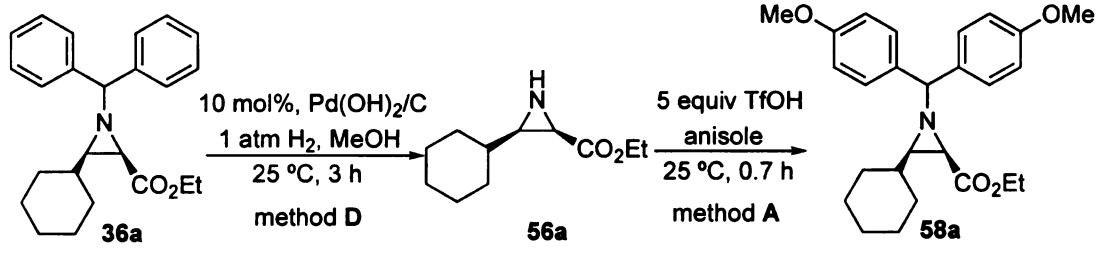
88

The data in Table 2.12 indicate that Method **A** gives very high yields for the deprotected aziridine **56** for most substrates. However, the 1-naphthyl aziridine **58i** was deprotected in higher yields with TFA and H_2SO_4 (Method **B**) or with H_2SO_4 alone (Method **C**) than with just triflic acid (Method **A**) (Table 2.12, entry 17 and 18 vs. entry 16). The *para*-methoxyphenyl substituted aziridine **58h** could not be deprotected without also effecting ring opening. Reaction of **58h** via Method **A** led to a 72% isolated yield of the amino ester **88** that results from an acid mediated opening of the aziridine by anisole (Table 2.12, entry 14). Attempts to deprotect the DAM group from aziridine **58h** via oxidation by using ceric ammonium nitrate (CAN), generally used for the removal of *para*-methoxyphenyl group from amines, resulted in complex mixtures without any trace of the desired *N*-H aziridine **56h**.

The phenyl substituted *N*-DAM aziridine **58d**, like the corresponding phenyl substituted benzhydryl aziridine **36d** (Scheme 2.4), could also not be deprotected by hydrogenation with Pearlman's catalyst (Method **D**) without effecting simultaneous

reductive opening of the aziridine, leading to the isolation of a 66% yield of the ring opening product **62** (Table 2.12, entry 10). Methods **A** and **B** are comparable for the phenyl aziridine **58d**. A large scale deprotection was performed for this substrate with Method **B** which gave a 95% yield of product **56d** from 18.8 grams (45 mmol) of **58d** (Table 2.11, entry 8). It's obvious that method **B** is a better choice for larger scale reactions considering the lower cost of trifluoroacetic acid as compared to that of triflic acid used in method **A**. Methods **A**, **B**, and **C** give comparable results with the cyclohexyl substituted aziridine **58a** (Table 2.12, entries 1, 2, and 3). Hydrogenation of the aziridine **58a** with Pearlman's catalyst did not give as good a yield of **56a** as did any of the other methods and this was also true for the *tert*-butyl substituted aziridine **58b**. It is difficult to separate the aziridine **56b** from anisole by rotary evaporation due to the volatility of this aziridine. Instead, the crude reaction mixture was loaded directly onto a silica gel column without concentration (Table 2.12, entry 5). The optimized Methods **A**, **B** and **C** were not successful with the benzhydryl aziridines **36**, complex mixtures were observed for the attempted deprotection of **36d** and **36i** with these methods.

Scheme 2.16 Determination of absolute stereochemistry of **58a**



79% ee of *(2R, 3R)* obtained from *(S)*-VAPOL

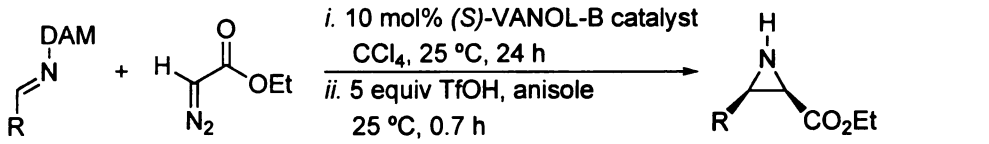
from **36a** : $[\alpha]^{23}_D$ = - 45.7
from **58a** : $[\alpha]^{23}_D$ = - 62.3

99% ee obtained from *(S)*-VANOL

The absolute stereochemistry of the *N*-DAM aziridines (*2R, 3R*) was shown to be the same as that of the aziridines produced from the corresponding reaction with benzhydryl imines (Scheme 2.16). This was confirmed when it was found that the optical rotation of

56a obtained from **58a** (99% ee) prepared with the *(S)*-VANOL-borate catalyst had the same sign as the optical rotation of *(2R, 3R)*-**56a** which was obtained from the hydrogenolysis of *(2R, 3R)* **36a** (Scheme 2.3, R = cyclohexyl), which was in turn prepared by the aziridination reaction of the corresponding *N*-benzhydryl imine **35a** using the *(S)*-VAPOL-borate catalyst. The absolute stereochemistry of the benzhydryl aziridines had been previously confirmed in our group through the synthesis of a natural product L-DOPA.[22a] Additionally, the retention time of the major peak of **56a** obtained from process **A** and process **D** was identical under the same chiral HPLC conditions.

Scheme 2.17 One pot *N*-H aziridine formation from *N*-DAM imines **68**

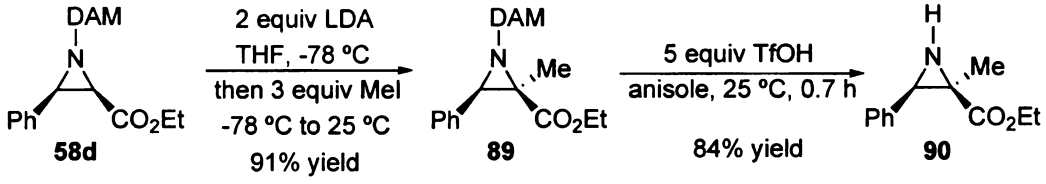


56a R = *c*-C_6H_{11}
89% overall yield, 83% ee
56d R = Ph
92% overall yield, 94% ee

The generation of *N*-H aziridines by the AZ reaction of *N*-DAM imines and ethyl diazoacetate can be greatly simplified by the cleavage of the DAM group without purification of the intermediate *N*-DAM aziridine **58**. This one-pot process was investigated with the phenyl and cyclohexyl imines **68a** and **68d**, respectively (Scheme 2.17). After the aziridination reaction was finished, the volatile material was removed under reduced pressure, and the crude reaction mixture was directly dissolved in anisole and treated with 5 equivalents of triflic acid. Subsequent purification by silica gel chromatography gave the *N*-H aziridines **56a** and **56d** with the same asymmetric inductions and the same or slightly better overall yields as compared to the two-step procedure (Tables 2.12, entries 1 and 9). Thus the purification of the *N*-DAM aziridines **58** becomes unnecessary. Triflic acid was also found to be effective for the deprotection

of the trisubstituted *N*-DAM aziridine **89** to give the *N*-H aziridine **90** in 84% yield (Scheme 2.18). The trisubstituted aziridine **89** was prepared from the aziridine **58d** by a highly diastereoselective alkylation.[26] The alkylation of aziridinyl-2-carboxylates is a rare event, which had previously been observed only under special circumstances.[52] However, we recently reported that this process is quite general for *N*-benzhydryl substituted aziridines, where the steric bulk of the benzhydryl group presumably blocks the normally predominant Claisen condensation pathway.[26] The alkylation of **58d** revealed that this highly diastereoselective alkylation process could be extended to *N*-DAM aziridines and in fact, it occurred in a higher yield than the alkylation of the corresponding benzhydryl aziridine.

Scheme 2.18 Access to tri-substituted *N*-H aziridine **90**

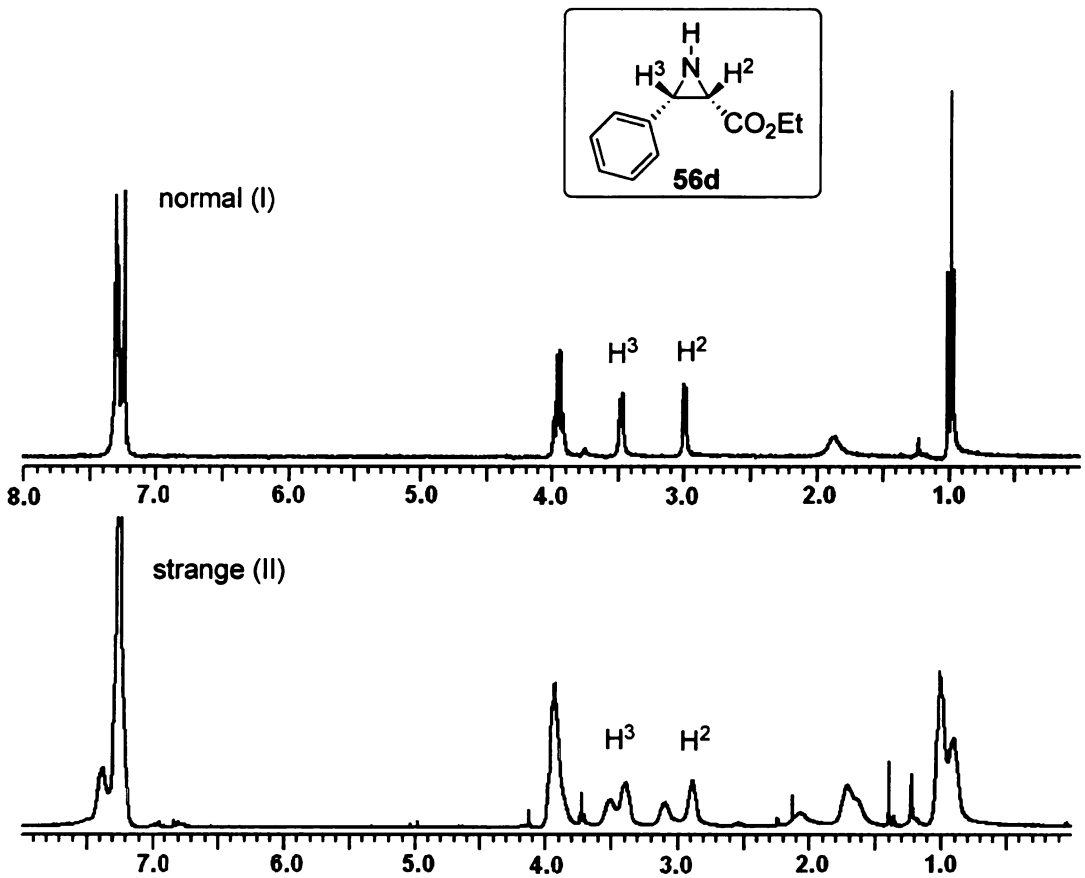


2.3.5.3. Investigation of the unexpected ^{1}H NMR behavior of *N*-H aziridines

During the deprotection of aryl substituted *N*-DAM aziridinyl-2-carboxylates, an interesting phenomenon was observed in the ^{1}H NMR analysis of product **56d**. The expected spectrum for this compound shown in the top of Figure 2.4 was obtained after purification by silica gel chromatography. It was noticed that if the $CDCl_3$ was pretreated with basic K_2CO_3 to remove trace acid and water, the ^{1}H-NMR spectrum of **56d** showed 4 broad peaks instead of the 2 sets of doublets that are expected for the two methine protons on the aziridine ring. The same observation was found if the silica gel was buffered with Et_3N, or if Et_3N was added to the normal NMR sample on purpose. This observation was true for most of the aryl substituted *N*-H aziridines. A typical example of

these spectra of **56d** is shown in Figure 2.4.

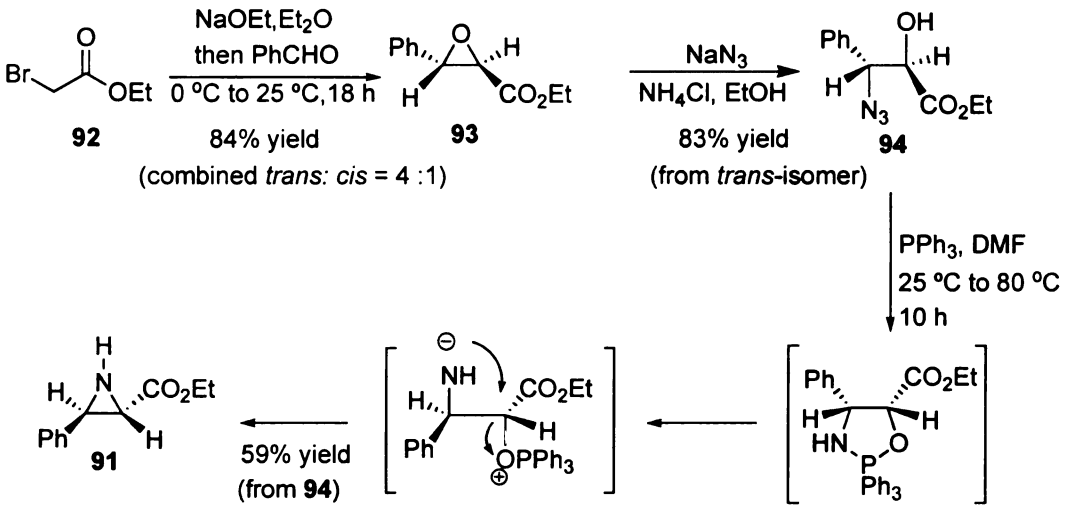
Figure 2.4 Normal and the strange ^{1}H NMR spectra of *N*-H aziridine **56d**



The first possible explanation considered for this observation was that the *cis*-aziridine **56** might isomerize to *trans*-aziridine **91** under basic conditions. In order to determine whether the strange spectrum (Figure 2.4, spectrum II) was indeed due to the presence of the *trans*- aziridine, the *trans*-*N*-H-2-phenylaziridinyl-3-ethylcarboxylate **91** was synthesized[53] from ethyl-2-bromoacetate **92** via a Darzens' reaction to give epoxide **93**, which was isolated as a *trans/cis* mixture (4:1). Subsequent ring opening reaction gave the azide which was isolated as the pure diastereomer **94** that resulted from the *trans*- epoxide **93**. This was followed by a Staudinger reduction/intramolecular aziridine ring formation sequence to afford the racemic *trans*-aziridine **91** (Scheme 2.17). The

comparison of the ^{1}H and the ^{13}C-NMR spectra of compound **91** and the strange spectra of *cis*-aziridine **56d** taken in neutralized $CDCl_3$ did not match, which clearly excluded the possibility of *cis*- to *trans*- isomerization. Furthermore, the isomerization from *cis-N*-H aziridine **56d** to *trans-N*-H aziridine did not happen even when **56d** was treated with triethyl amine on purpose.

Scheme 2.19 Preparation of *trans-N*-H aziridine **91**



Another possible explanation for the spectral data shown in Figure 2.4 is the slow inversion of the nitrogen. The support for this possibility comes from a high temperature ^{1}H NMR experiment in C_6D_6, in which the 4 broad peaks merged back to the two doublets at 80 °C, and upon cooling, the 4 broad peaks appeared again.

2.4 Conclusion

N-DAM imines have been shown to be excellent substrates for the AZ reaction with ethyl diazoacetate mediated by boron catalysts derived from either the VANOL or VAPOL ligand. These reactions produced the *N*-DAM protected 3-substituted aziridinyl-2-carboxylate esters **58** with high yields and high asymmetric inductions and also with high diastereoselectivities. Up to 97% ee was observed for the aziridines, and for all the

substrates examined, the optical purity of the aziridine could be enhanced to > 99% ee with a single crystallization. Catalysts derived from both VAPOL and VANOL offer high asymmetric induction and the catalyst loading can be lowered to 1 mol% with no loss in the asymmetric induction of 95% ee for the *N*-DAM imine of benzaldehyde. With the same imine, the loading for the VANOL catalyst can be lowered to 0.25 mol% and still provide the aziridine in an excellent yield with 90% ee. The VAPOL ligand can be recovered in 95% yield with no loss in optical activity. Competition studies with the *N*-DAM imine of benzaldehyde revealed that the catalyst derived from the VANOL ligand is twice as fast as that derived from the VAPOL ligand. Similar competition studies revealed that the *N*-DAM imines react 3.8 times faster than the corresponding benzhydryl imines with the VAPOL derived catalyst and 3.0 times faster with the VANOL derived catalyst.

Cleavage of the DAM group can be achieved under several mild acidic conditions to give both 3-aryl and 3-alkyl *cis*-substituted *N*-H aziridines **56** in excellent yields and with no erosion of stereochemistry or evidence of ring opened products. Furthermore, the AZ reaction and the acidic deprotection steps could be carried out in a one pot protocol, affording the *N*-H aziridine with the same or higher overall yields and the same asymmetric induction. These methods can also be applied to the asymmetric synthesis of trisubstituted *N*-H aziridines by introducing an alkyl group on the C2 position of the *N*-DAM aziridine in a stereospecific fashion followed by the removal of the DAM group.

CHAPTER THREE

APPLICATION OF ACTIVATED CHIRAL AZIRIDINES

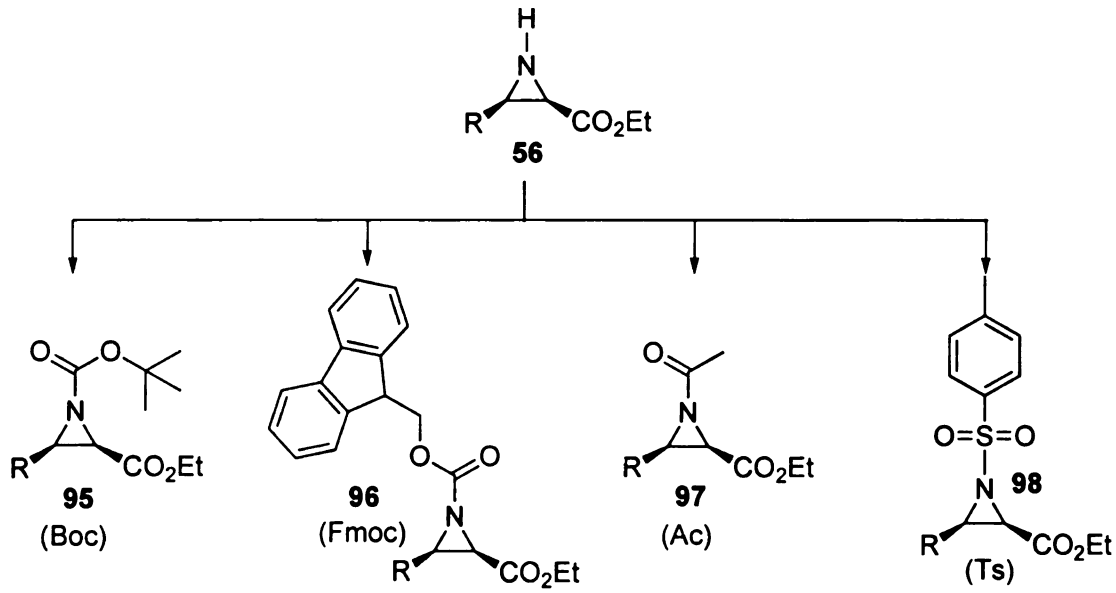
3.1 Activation of chiral aziridines with electron withdrawing groups

The activation of aziridines to enable their applications such as in the ring opening reactions is usually achieved by the installation of carbonyl, sulfonyl, or phosphoryl groups on the aziridine nitrogen.[1] With the development of the method for access to optically active *N*-H aziridines **56** that was discussed in the last chapter, these aziridines can now be activated and their corresponding applications can be examined. Substrates **56a** and **56d** were selected as examples of alkyl and aryl substituted *N*-H aziridines for a study on their activation and subsequent applications in ring opening and ring expansion reactions. The activating groups that were examined include *tert*-butyloxycarbonyl (Boc), 9-fluorenylmethyloxycarbonyl (Fmoc), acetyl (Ac) and tosyl (Ts) groups, which are in the order of increasing electron withdrawing ability, and as a consequence would be expected to show different activating effects toward ring opening and related reactions.

Considering the electronic and steric nature of aryl and alkyl substituents on the C3 position of the activated aziridine, it would be interesting to see how these differences would affect ring opening reactions of the aryl and alkyl substituted aziridinyl carboxylates. The aryl substituted aziridine has a benzylic carbon at the C3 position, which would be favored for nucleophilic attack due to an electron deficiency at this position, while the C2 carbon that is next to an ester group should be disfavored towards nucleophilic attack. As a result, the regioselectivity of nucleophilic ring opening reactions would be expected to be higher for the C3 position for C3-aryl aziridinyl-2-carboxylates than that for the corresponding C3-alkyl substrates. To test this hypothesis, at least one

aryl and one alkyl substituted *N*-activated aziridinyl-2-carboxylates were synthesized and tested.

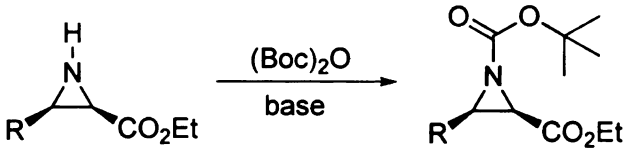
Figure 3.1 From the *N*-H aziridine to activated aziridines



3.1.1 Preparation of *N*-Boc aziridines 95

Of the many methods for the introduction of the *tert*-butyloxycarbonyl group (Boc),[54] the one that uses the ultrasound technique and $NaHCO_3$ as base was found to be the most efficient.[54a] Thermal conditions that involve triethylamine (Table 3.1, entry 1 and 5) or sodium hydride as base (Table 3.1, entry 6) provided comparable yields but the corresponding procedures were less convenient. The *cis-N*-H aziridine **56d** could be converted to N-Boc aziridine **95d** in 98% yield (Table 3.1 entry 3), but when the corresponding *trans*- isomer of **56d** was treated in the same manner, only a 34% yield of the *N*-Boc aziridine was obtained (not shown).

Table 3.1 Activation of the aziridine **56** with the Boc group



56 **95**

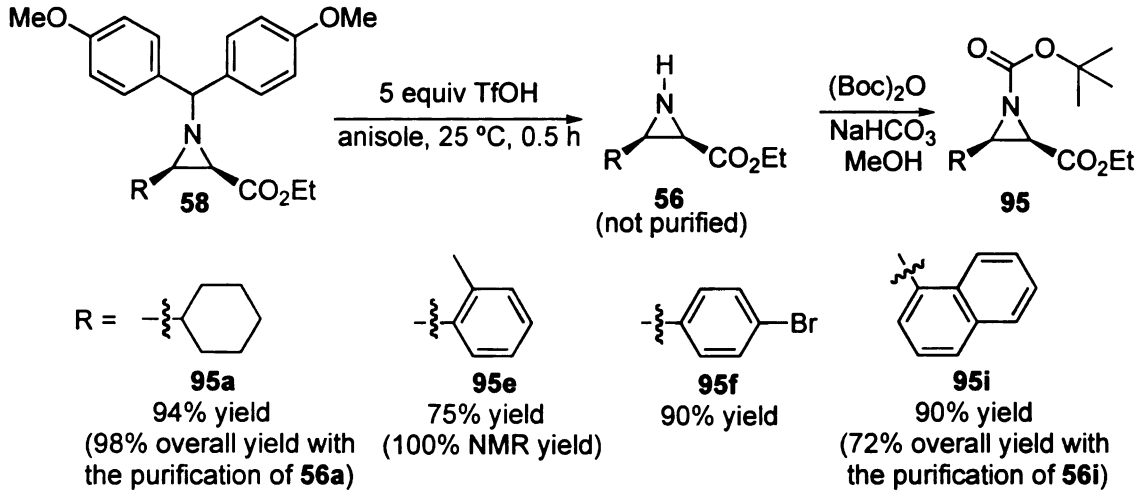
entry	R	series	base	condition	yield of **95** (%)[a]
1	*c*-C_6H_{11}	**56a**	Et_3N	50 °C, 40 mins	99
2	*c*-C_6H_{11}	**56a**	$NaHCO_3$	ultrasound, 25 °C, 2 h	99
3	Ph	**56d**	$NaHCO_3$	ultrasound, 25 °C, 4 h	98
4	*p*-$NO_2C_6H_4$	**56g**	$NaHCO_3$	ultrasound, 25 °C, 8 h	95
5	*1*-Naphthyl	**56i**	Et_3N	50 °C, 3 h	35
6	*1*-Naphthyl	**56i**	NaH	25 °C, 4.5 h	100[b]
7	*1*-Naphthyl	**56i**	$NaHCO_3$	ultrasound, 25 °C, 2 h	100[b]

[a] Unless otherwise specified, the yield is of isolated product **95** after silica gel chromatography. [b] NMR yield using Ph_3CH as internal standard.

To determine whether any possible change in the optical purity occurred during the deprotection of *N*-DAM aziridines and the reprotection of *N*-H aziridines with the Boc group, an investigation was performed using the *N*-DAM aziridines **58d** (R = Ph, >99% ee) and **58g** (R = *p*-$NO_2C_6H_4$, >97% ee). They were converted to the *N*-H aziridines **56d** and **56g** that were purified, and then to the corresponding *N*-Boc aziridines **95d** and **95g**, the corresponding % ee values were examined. In both the deprotection and reprotection steps, no erosion of the % ee was observed and no evidence was found for the isomerization from *cis*-aziridines to *trans*-aziridines. It was also found that the purification of the *N*-H aziridine prior to the activation was unnecessary, so that any loss of the relatively unstable *N*-H aziridines during the purification process could be diminished. After the cleavage of the DAM group from the aziridine **58**, the crude reaction mixture was treated directly with $(Boc)_2O$ in the presence of $NaHCO_3$ in the

ultrasonic bath to afford the *N*-Boc aziridines **95** in high overall yields. Some examples are shown in Scheme 3.1.

Scheme 3.1 Activation of aziridine **58** with the Boc group via the crude **56**



95a
94% yield
(98% overall yield with the purification of **56a**)

95e
75% yield
(100% NMR yield)

95f
90% yield

95i
90% yield
(72% overall yield with the purification of **56i**)

3.1.2 Preparation of *N*-Fmoc aziridines 96

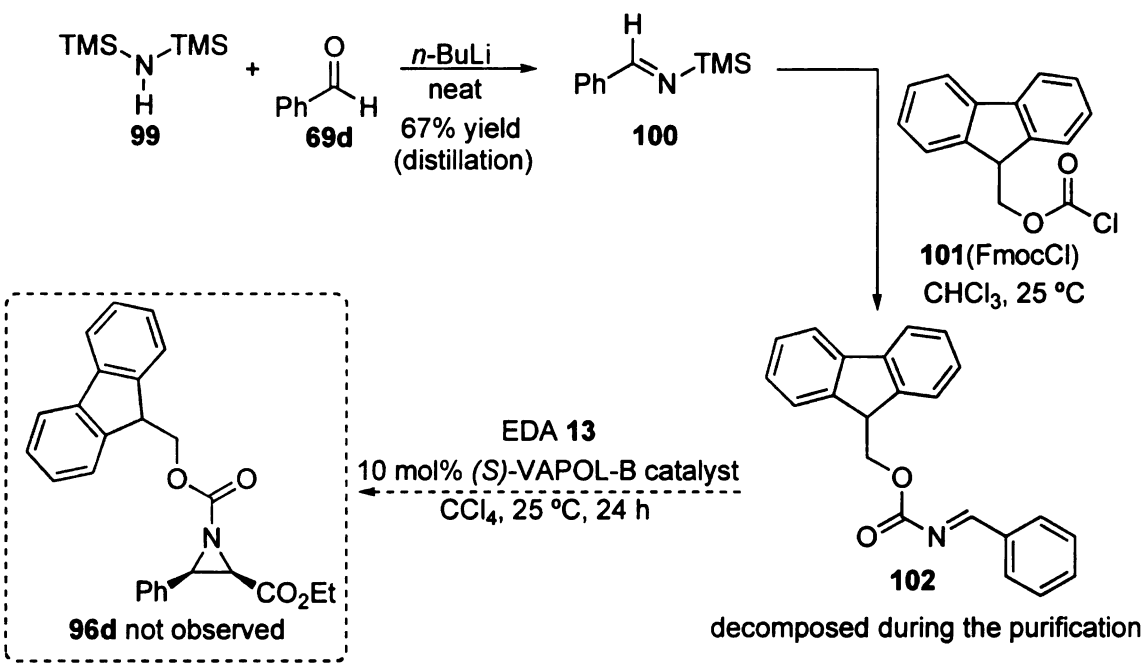
As a versatile amino-protecting group that was developed in 1970's by Carpino's group,[55] the 9-fluorenylmethyloxycarbonyl (Fmoc) group has become a well established tool in organic synthesis. It is especially useful in peptide synthesis[56] due to its unique characteristic of being stable towards acidic conditions and to hydrogenation, however, it can be readily cleaved non-hydrolytically under mild conditions with bases such as piperidine, morpholine. The original Fmoc protected amine is thus liberated as its free base form. This feature makes the selective deprotection of the Fmoc group useful in the presence of other acid sensitive functional groups. We were interested in the preparation of various chiral *N*-Fmoc amino esters / acids from chiral aziridines because these aziridines have been reported to be α-amino acid precursors through ring opening reactions and hydrolysis.[1,2] Two routes were designed for the synthesis of the *N*-Fmoc aziridines. One route is a direct catalytic AZ reaction from the *N*-Fmoc imine **102**, and the other route is by the deprotection of the *N*-DAM aziridine **58** followed by protection

with the Fmoc group.

3.1.2.1 Attempted preparation of aziridine 96d from the *N*-Fmoc imine 102

If the catalytic AZ reaction between the *N*-Fmoc imine **102** and the ethyl diazoacetate **13** could generate the *N*-Fmoc aziridine **96** enantioselectively, this direct *N*-Fmoc aziridine preparation would clearly be more efficient than the aziridination-deprotection-activation protocol. Thus the direct aziridination of the *N*-Fmoc imine **102** was investigated first (Scheme 3.2).

Scheme 3.2 Preparation of the imine **102** and the attempted aziridination reaction



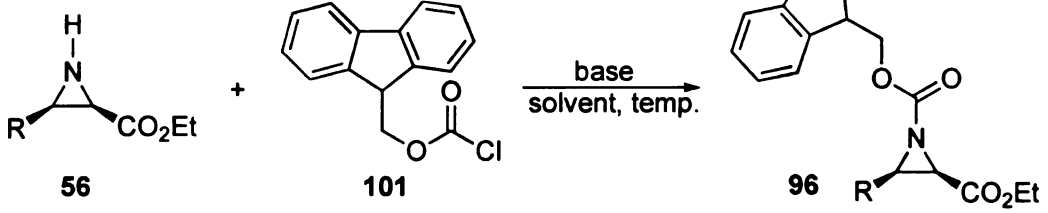
Only a single literature report for the preparation of an *N*-Fmoc imine could be found and it was described without experimental details.[57] We thus tried to synthesize **102** from the bis(trimethylsilyl)amine **99** as shown in Scheme 3.2. The condensation of **99** with benzaldehyde **69d** afforded the *N*-(trimethylsilyl)benzaldimine **100** in 67% yield after purification by distillation.[58] Compound **100** was then treated with 9-fluorenylmethyloxycarbonyl chloride **101** to generate the imine **102** as the major product whose identity could be deduced from the ^{1}H NMR spectrum of the crude reaction

mixture. Attempted purification of this crude imine (white solid) by crystallization only resulted in the isolation of a complex mixture of compound. Utilizing the crude imine **102** in the aziridination reaction did not result in any of the desired product **96d**. The ^{1}H NMR spectrum of the crude material indicated incomplete conversion with the formation of a small amount of a complex mixture of products.

3.1.2.2 Preparation of *N*-Fmoc aziridine from *N*-H aziridines 56

Since the direct aziridination of the *N*-Fmoc imine **102** did not work, effort was then turned to the alternative protocol involving the protection of the *N*-H aziridine **56**. A number of known methods for Fmoc protection[55b,59] were evaluated, all of which involve reacting the aziridine **56d** with the chloroformate **101** under basic conditions. The results from this survey for the preparation of *N*-Fmoc aziridines are listed in the Table 3.2.

Table 3.2 Preparation of *N*-Fmoc aziridines from *N*-H aziridines[a]



entry	R	series	solvent	base	temp, time	yield (%)
1	Ph	**56d**	Et_2O	none	0 to 25 °C, 1 h	100%[b]
2[c]	Ph	**56d**	1,4-dioxane	$NaHCO_3$	25 °C, 40 h	66%
3	Ph	**56d**	Acetone/H_2O (3:1)	$NaHCO_3$	25 °C, 20 h	89%
4[d]	Ph	**56d**	Acetone/H_2O (3:1)	$NaHCO_3$	25 °C, 24 h	94%
5	*c*-C_6H_{11}	**56a**	Acetone/H_2O (3:1)	$NaHCO_3$	25 °C, 48 h	>88%

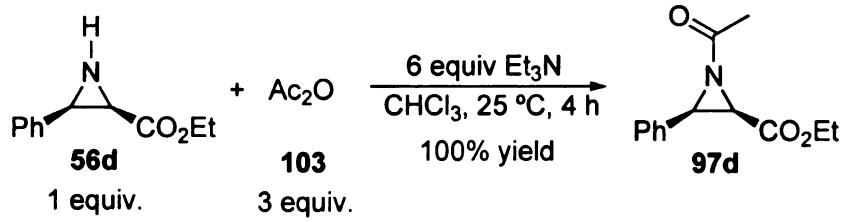
[a] Unless otherwise specified, 0.1 mmol **56**, 0.1 mmol **101** and 0.2 mmol $NaHCO_3$ were used at 0.03 M. [b] 2 equiv of aziridine **56d** was used. [c] The reaction was carried out in ultrasonic bath for

3 h, then stirring for 40 h. [d] 6 mmol scale of **56d** was used.

The reaction of the *N*-H aziridine **56** with the FmocCl **101** can afford the desired *N*-Fmoc aziridine **96d** under all conditions that were tested. Although the quantitative isolated yield (calculated based on the compound **101**) was obtained from the method using no additional base, but 1 one extra equivalent of *N*-H aziridine was used as the alternative of base, which can only be recovered in 10% yield (Table 3.2, entry 1), thus, it's necessary to find a method using other bases. The method reported by Gellman's group can be successfully applied to this system,[59a] which involves $NaHCO_3$ as base and a mixed solvent of acetone and water (Table 3.2, entry 3). The purification by crystallization could be accomplished on a larger scale reaction (Table 3.2, entry 4). The C3-alkyl substituted *N*-Fmoc aziridine **96a** was also synthesized using the same condition (Table 3.2, entry 5).

The acetyl (Ac) protected aziridine **97d** could be obtained from the *N*-H aziridine **56d** using triethylamine as base (Scheme 3.3) to afford the *N*-Ac aziridine **97d** in quantitative yield after purification by silica gel chromatography.

Scheme 3.3 Preparation of the *N*-Ac aziridine **97d** from the *N*-H aziridine **56d**



3.1.3 Preparation of *N*-Ts aziridines 98

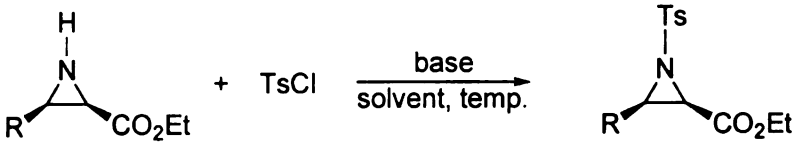
The tosyl group (Ts) is one of the most frequently used nitrogen activating groups in the ring opening reaction of activated aziridines.[1] Amongst the numerous reported ring opening reactions of *N*-Ts aziridines, examples of regioselective nucleophilic ring opening reactions of *cis*-3-substituted aziridinyl-2-carboxylates are limited,[1a] which may

be partly due to the lack of available methods for obtaining these aziridines.

3.1.3.1 Preparation of *N*-tosyl-aziridinyl-2-carboxylates 98

The *N*-H aziridine **56d** was used to find an optimized procedure for the transformation from the *N*-H aziridine **56** to the *N*-Ts aziridine **98**.[60]

Table 3.3 Protection of the *N*-H aziridine **56** with a tosyl group[a]



56a: R = Cy
56d: R = Ph

104

98a: R = Cy
98d: R = Ph

entry	series	TsCl equiv	base (equiv)	solvent	condition	yield (%)[b]
1	**56d**	1	$NaHCO_3$ (1)	THF	ultrasound, 3 h	complex mixture
2	**56d**	1	NaH (1)	DMF	25 °C, 2 h	30% con.
3	**56d**	2	NaH (1)	DMF	ultrasound, 8 h	complex mixture
4	**56d**	1.5	Et_3N (3)	DMF	25 °C, 48 h	80[c]
5	**56d**	1.5	Et_3N (3)	$CHCl_3$	25 °C, 48 h	93[c]
6	**56d**	1.5	Et_3N (3)	CH_2Cl_2	25 °C, 48 h	90[c]
7	**56d**	1	Et_3N	1:1 $CHCl_3/CH_2Cl_2$	0 °C, 60 h	83
8	**56d**	1.5	Et_3N (3)	1:1 $CHCl_3/CH_2Cl_2$	25 °C, 48 h	93
9	**56d**	1	Et_3N(1.5)	1:1 $CHCl_3/CH_2Cl_2$	40 °C, 48 h	50
10	**56d**	1.5	Et_3N (3)	1:1 $CHCl_3/CH_2Cl_2$	0 °C to 25 °C,60 h	93
11[d]	**56d**	1	Et_3N(1.5)	1:1 $CHCl_3/CH_2Cl_2$	0 °C to 25 °C,60 h	40
12[e]	**56d**	1	Et_3N(1.5)	1:1 $CHCl_3/CH_2Cl_2$	25 °C, 64 h	83
13	**56a**	1.5	Et_3N (3)	1:1 $CHCl_3/CH_2Cl_2$	25 °C, 60 h	100

[a] Unless otherwise specified, the base and TsCl were added at 0 °C. All reactions were carried out with 0.25 mmol **56** at 0.1 M. [b] Isolated yield after silica gel chromatography. [c] NMR yield using Ph_3CH as the internal standard. [d] Old TsCl was used. [e] 4 mmol **56d** was used.

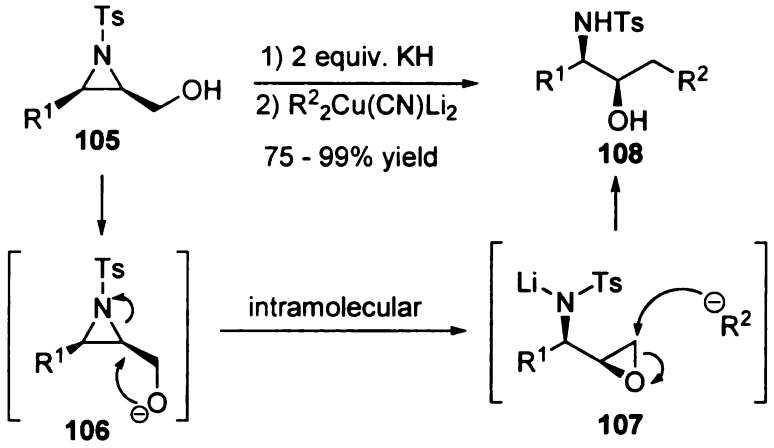
The ultrasound method gave a complex mixture of products without any detectable amount of the *N*-Ts aziridine **98d** (Table 3.3, entry 1). Triethylamine was found to be the best base. In a study of solvents, it was observed that high yields could be obtained in either chloroform or dichloromethane alone, however, a mixed solvent system (1 : 1 mixture of chloroform and dichloromethane) generally gave more consistent results. The reaction is relatively slow and requires at least two days for complete conversion. Attempts at speeding up the reaction by increasing the temperature resulted in decomposition and lower yield (Table 3.3, entry 9), however, a lower temperature (0 °C) has an insignificant effect on the rate and yield (Table 3.3, entry 7). The use of excess amount of TsCl **104** can gave a higher yield (Table 3.3, entry 8 vs. entry 12). It was also found that the quality of TsCl is important for a reproducible high yield. The use of an aged sample of TsCl led to dramatically reduced yield (Table 3.3, entry 11). The final optimized conditions involve the use of 3 equivalents of triethyl amine and 1.5 equivalents of TsCl in a mixed solvent of chloroform and dichloromethane (1:1), where the reaction is started at 0 °C and stirred at that temperature for 3 – 4 h before allowing to warm up to room temperature and stirring for another 45 to 55 h (Table 3.3, entry 10). The *N*-tosyl-cyclohexyl aziridine **98a** was prepared from the *N*-H aziridine **56a** using the same method to give a quantitative isolated yield (Table 3.3 entry 13), where long reaction times (60 h) were required for complete conversion.

3.1.3.2 Preparation of *N*-Ts aziridinyl alcohol

Recently, an interesting intramolecular ring opening reaction of the *N*-tosyl aziridinyl alcohol[61] **105** was reported by Fujii[62] (Scheme 3.4). The base mediated deprotonation of the aziridinyl alcohol **105** generates the oxa anion intermediate **106**, from which the formation of the aza anion **107** via an intramolecular attack of the oxygen anion on a proximal electrophilic carbon center of the aziridine was expected on the basis of

calculations (RHF/3-21G* level[62b], which found that the energy minimum of **107** was predicted to be 18.6 kcal mol^{-1} lower than that of **106**. The subsequent nucleophilic attack of a higher order cuprate reagent on the less substituted carbon of the intermediate **107** provides the amino alcohol **108** in high yield with no loss in diastereomeric purity during the process.

Scheme 3.4 Fujii's intramolecular ring opening of aziridinyl alcohols

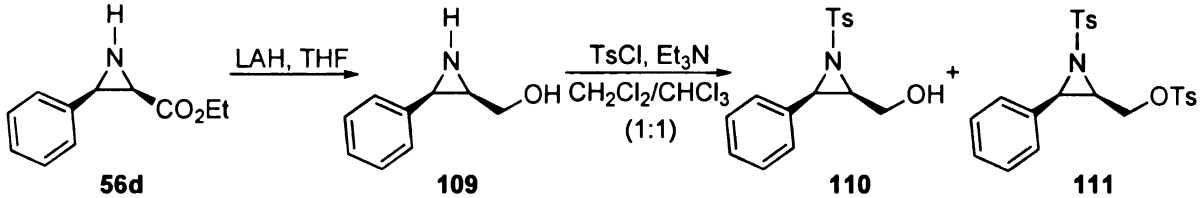


It was envisioned that an asymmetric version of this reaction could be performed from the enantio-rich *N*-tosyl aziridinyl-2-carboxylate **98** because the *N*-tosyl aziridinyl alcohol **105** should be a reduction product of **98**, which is readily available from the AZ reaction via the deprotection, activation protocol. Two possible routes were designed to approach the C3 phenyl aziridinyl alcohol **110** from the *N*-H aziridine **56d**. It should be possible either reduce the carboxylate to alcohol first, then introduce the tosyl group to intermediate **109** to furnish the product **110** as illustrated in route **A**, or to synthesize **110** as shown in route **B** (Scheme 3.5) by reversing the two chemical steps. Potential problems exist for both routes. In route **A**, the free hydroxyl group in **109** may also be deprotonated and react with tosylchloride **104** to give a double tosylated product **111**. Considering the fact that the nucleophilicity of nitrogen is higher than that of oxygen, this problem might be able to be solved with careful control of the reaction conditions. In

route **B**, the problem may come from the step involving LAH reduction of the activated aziridine **98d**. Since lithium aluminum hydride is known to be a useful hydride source in the ring opening reaction of activated aziridines, the reduction of **98d** may produce a mixture of the desired product **110** and the ring opened product **112**.

Scheme 3.5 Preparation of the *N*-tosyl aziridinyl alcohol **110**

Route A:



Route B:

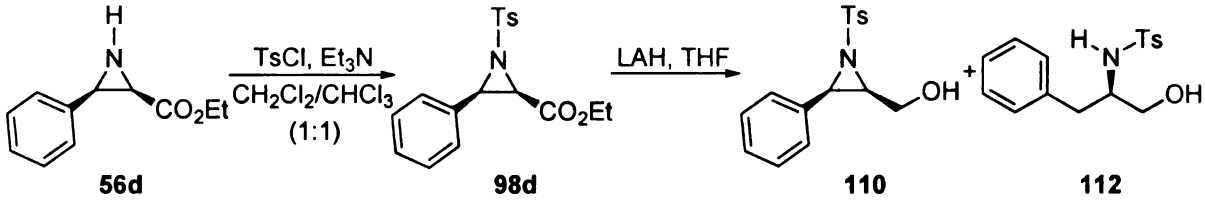


Table 3.4 Synthesis of **110** via two different routes

route	entry	TsCl (equiv)	Et_3N (equiv)	yield of **98d**(**109**) (%)[a]	temp (°C)[b]	result[a]
	1[c]	3	4.5	nd	-20	**110** : **111** = 1 : 1.5
A	2	1	2	(90)	-20	86% yield of **110**, no **111**
	3[c]	1	2	nd	-20	75% yield of **110**, 10% yield of **111**
	4	1.5	3	83	-10	trace **110**, 50% yield of **112**
B	5	1	2	93	-40	48% yield of **110**, 18% yield of **112**
	6	1	2	93	-78	70% recovery of **98d**

[a] Isolated yield after silica gel chromatography. [b] The temperature for the LAH reduction step. The reaction process was monitored by TLC. [c] The intermediate **109** was not purified, and was used in the next step as a crude form.

As the results from route **A** in Table 3.4 (entry 1 to 3) show, the reduction step went smoothly to exclusively give product **109** as indicated by the ^{1}H NMR analysis of the crude reaction mixture. The crude mixture could be directly used in the protection step, which required a careful control of the amount of tosylchloride. An excess amount of tosylchloride causes the formation of the double tosylated product **111** (Table 3.4, entry 1). The product **110** was obtained exclusively in excellent yield when only 1 equivalent of tosylchloride was used (Table 3.4, entry 2). The purity of the aziridinyl alcohol **109** would affect the reaction as well (Table 3.4, entry 3).

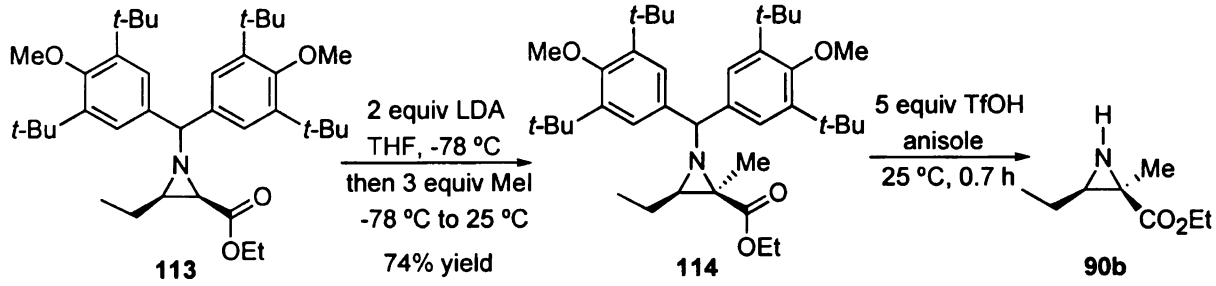
In route **B**, control of the temperature during the reduction step was important to suppress the ring opening process. Only a trace amount of the product **110** was observed along with the ring opening by-product **112** when the reaction was run at –10 °C (Table 3.4, entry 4). Incomplete conversion and the formation of a complex mixture of products was observed at –78 °C (Table 3.4, entry 5). Although–40°C was the best among the temperatures that were tested, less than 50% yield of the desired product was isolated and still there was an 18% yield of the compound **112**.

3.1.4 Preparation of activated tri-substituted aziridines

The selective ring opening reactions of activated tri-substituted aziridines are also attractive, because they may lead to a series of highly functionalized compounds with two adjacent stereo centers. As illustrated in chapter two, the activated tri-substituted chiral aziridinyl-2-carboxylates could be synthesized with a DAM protecting group on nitrogen with a subsequent deprotection and activation protocol illustrated for aziridine **89** (Scheme 2.18). However, the *N*-H C3-alkyl tri-substituted aziridine **90b** was derived from the *N*-bis(3,5-*di-tert*-butyl-4-methoxylphenyl)methyl aziridine (BUDAM aziridine) **113** because alkyl substituted aziridines are formed in higher yielding and with greater

enantioselectivity in the AZ reaction with this *N*-protecting group (Scheme 3.6). The preparation and the reactivity of *N*-BUDAM imines in the aziridination reaction will be discussed in the next chapter. Introduction of the methyl group was achieved following the stereospecific alkylation that was developed for the alkylation of *N*-Bh aziridines[26] and afforded the tri-substituted aziridine **114** in 74% yield (Scheme 3.6).

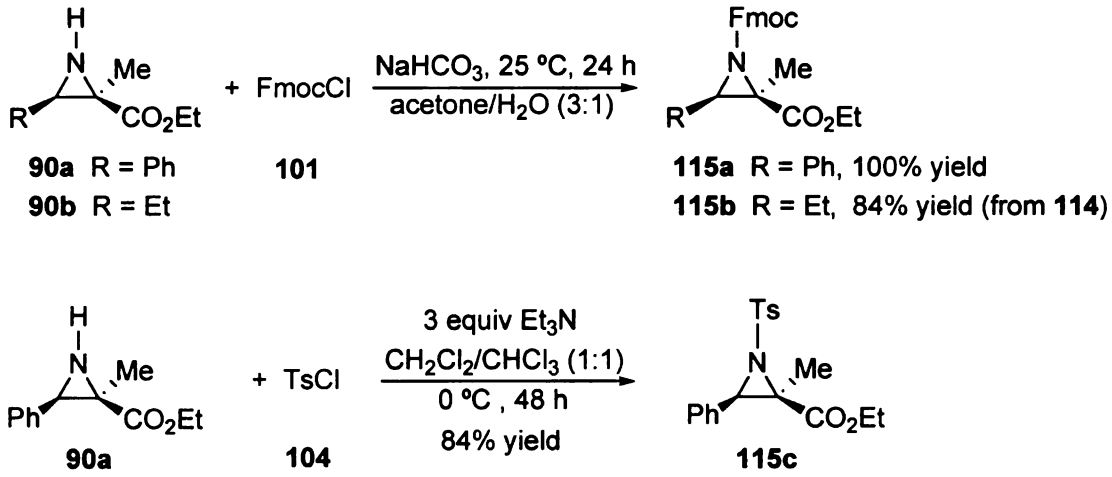
Scheme 3.6 Preparation of the C3-alkyl tri-substituted *N*-H aziridine **90b**



The cleavage of the BUDAM group in compound **114** was carried out with both Method A and Method B, which were described in section 2.3.5.2 and were found to be equally effective for the cleavage of the DAM group from the aziridine **58**. The desired product **90b** was obtained via method A, in which 5 equivalents trifluoromethanesulfonic acid (TfOH) was used. Complete conversion was observed by the ^{1}H NMR spectrum of the crude material. In contract, method B, in which 10 equivalents of a mixture of sulfuric acid and trifluoroacetic acid (1:10 v/v) was used, gave only 50% conversion along with unidentified complex mixture of products. The product **90b** could be purified by silica gel chromatography, but the yield was not determined because this *N*-H aziridine was found to be very volatile, and loses occur when reduced pressure was applied to remove the solvent. To avoid loss of compound **90b**, ethyl ether and pentane were used as eluent during purification and solvents were only partially removed under reduced pressure. The remaining solution of **90b** was directly treated with the Fmoc- protection condition to convert the *N*-H aziridine to the more stable *N*-Fmoc aziridine **115b** (Scheme 3.7).

The introduction of the Fmoc group to aziridine **90a** afforded **115a** in quantitative yield, and the reaction of the aziridine **90b** afforded an 84% overall yield of **115b** from the *N*-BUDAM aziridine **114** (Scheme 3.6). The tri-substituted *N*-tosyl aziridine **115c** was obtained in 84% isolated yield from the tri-substituted *N*-H aziridine **90a**.

Scheme 3.7 Preparation of activated tri-substituted aziridines

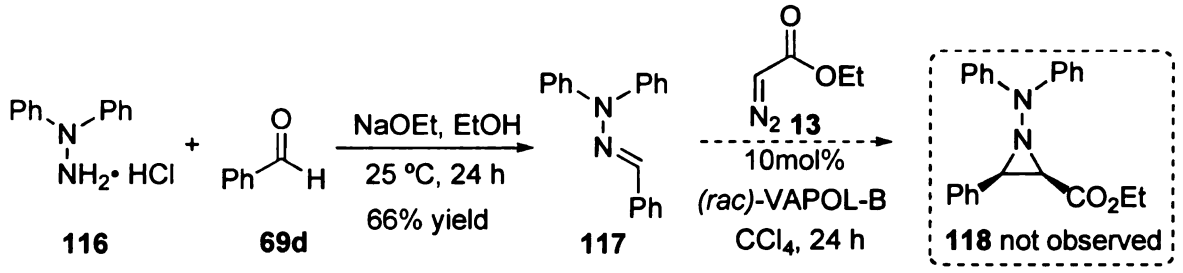


3.1.5 Formation of other aziridines

As an additional study for the access to *N*-H aziridines, another *N*-protecting group that might be easily cleaved is the *N,N*-diphenylhydrazine as shown in the aziridine **118** (Scheme 3.8). The only difference between the *N,N*-diphenylhydrazine and the benzhydryl amine is that in the hydrazine **116**, the two phenyl groups are attached to a nitrogen instead of a carbon (benzhydryl amine). Although the resulting imine **117** may become less reactive towards nucleophiles due to the additional electron-rich nitrogen, the presence of the two phenyl groups is believed to be essential for the success of the VAPOL/VANOL-borate catalyzed AZ reaction. This experiment was designed to answer our curiosity on the effect of an sp^3 nitrogen verses an sp^3 carbon. The *N,N'*-diphenylphenylhydrazone **117** was prepared by the condensation of *N,N'*-diphenylhydrazine•hydrochloride salt **116** with benzaldehyde in the presence of sodium

ethoxide (Scheme 3.8). The reaction went to completion after 24h, and after the extraction it was found that the compound **117** was in the aqueous layer instead of the organic layer as was suggested in the literature.[63] The hydrazone **117** was thus obtained by neutralizing the aqueous layer with 0.1 N NaOH solution (aq), and then extraction with CH_2Cl_2. Purification by crystallization afforded **117** in 66% yield. Unfortunately, the aziridination under standard condition did not work, there was either no reaction at room temperature or a complex mixture was observed at higher temperatures (80 °C). In any case, aziridine **118** was never observed.

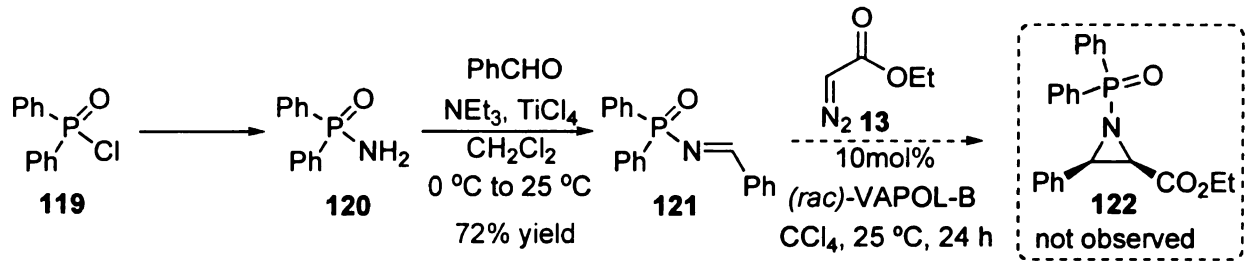
Scheme 3.8 Attempted aziridination of the *N,N*-diphenylhydrazone **117**



Another aziridine of interest is the *N*-diphenylphosphoryl aziridine **122**, because the diphenylphosphoryl group is a widely used activating group for aziridines.[64] Based on similar reasoning that inspired an investigation into the *N,N*-diphenylhydrazone **117**, it was hoped that the two phenyl groups in imine **121** could play the same role as the two phenyls in the benzhydryl group to produce the same good selectivity during the aziridination reaction. The advantage of the aziridination using imine **121** lies in the fact that if the reaction is enantioselective, the aziridine **122** is already an activated aziridine, which can be directly used in ring opening reactions or in other applications of activated aziridines. The diphenylphosphoryl imine **121** was prepared from diphenylphosphorylchloride **119** in two steps[65] and was afforded in 72% yield from the intermediate **120** after crystallization (Scheme 3.9). Unfortunately, the aziridination of **121** failed to occur at room temperature, and only gave complex mixtures if a higher

temperature was applied (80 °C).

Scheme 3.9 Attempted aziridination of the diphenylphosphoryl imine **121**

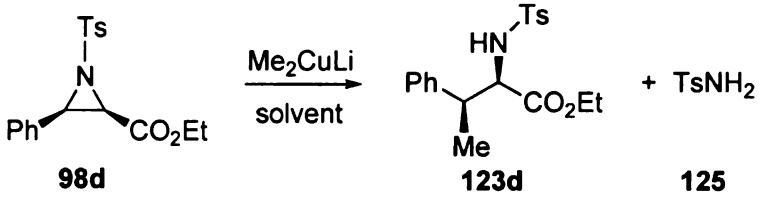


3.2 C3-ring opening by carbon nucleophiles

3.2.1 Regioselective ring opening by alkyl nucleophile

The known examples of aziridine ring opening reactions with carbon nucleophiles involve mainly mono-substituted aziridines or *trans*-di-substituted aziridines.[66] While the reaction of *cis*-di-substituted aziridinyl-2-carboxylates to the best of our knowledge have not studied. Such nucleophilic opening of *cis*-disubstituted aziridines from the AZ reaction would provide access to α-amino esters with two adjacent stereo centers, which thus could serve as precursors to various chiral α-amino acids. With the C3- phenyl substituted aziridine **98d**, a regioselective ring opening at the benzylic carbon was expected because of the electron deficiency on the C3 carbon (Table 3.5). The C3- alkyl substituted aziridine **98a** (Scheme 3.10) was expected to be less selective towards nucleophilic opening because of the lack of a significant electronic difference between the C3 and C2 carbons. To avoid the possible competing side reaction involving nucleophilic addition to the ester group, a cuprate reagent was used as the source of carbon nucleophile. The low order cuprate reagent was first examined as the nucleophile for ring opening reactions of the *N*-Boc aziridine **95** and the *N*-tosyl aziridine **98**, and some of the results are shown in Table 3.5.

Table 3.5 Nucleophilic ring opening of activated aziridines by a low order cuprate reagent[a]



98d **123d** **125**

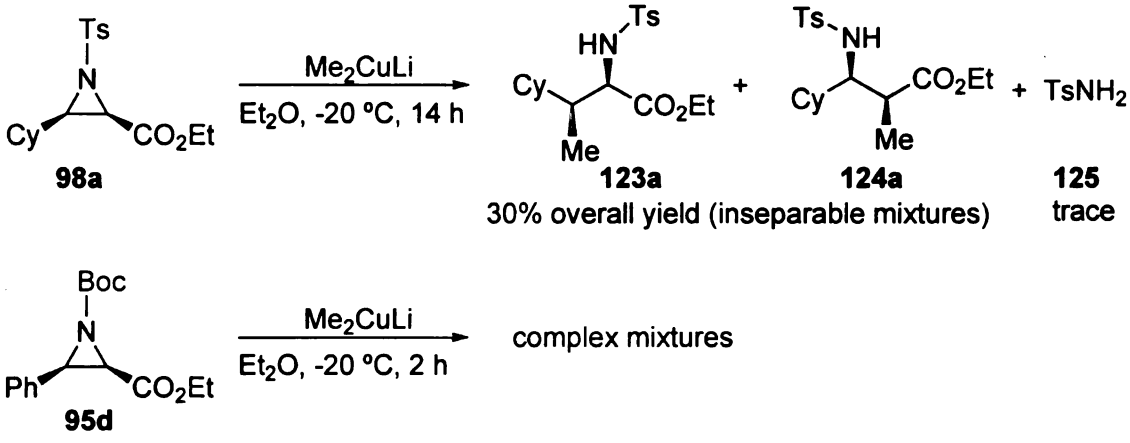
entry	solvent	temp (°C)	time (h)	ratio of **123d** : **125**[b]	yield of **123d** (%)[c]
1	Et_2O	-20	14	1 : 0.8	nd
2[d,e]	Et_2O	-20	8	trace **125**	20
3	THF	-45	2	1 : 2	nd
4	THF	-20	2	1 : 0.8	42
5	THF	0	1	nd	trace of **123**
6[f]	THF	0	2	1 : 1.2	nd
7[g]	THF	-20	2	1 : 0.8	nd
8[d,h]	Et_2O	-78	8	no **125**	28
9[i]	THF	-98	2	1 : 3	nd
10[j]	THF	-78	2	nd	trace of **123**

[a] Unless otherwise specified, 6 equiv of MeLi and 3 equiv of CuI were used to prepare the cuprate reagent. [b] Determined from the ^1H NMR spectrum of the crude reaction mixture. [c] Isolated yield after silica gel chromatography. [d] The crude mixture was directly concentrated and purified without quenching with NH_4Cl solution. [e] 8 equiv of MeLi and 4 equiv CuI was used. [f] The cuprate was prepared in toluene. [g] The cuprate reagent was transferred to the aziridine solution. [h] 1 equiv $BF_3 \cdot Et_2O$ was added. [i] 3 equiv $BF_3 \cdot Et_2O$ was added. [j] 6 equiv $BF_3 \cdot Et_2O$ was added.

As shown in Table 3.5, the aziridine ring in the *N*-tosyl phenylaziridine **98d** was opened regioselectively at the C3 position to give the desired product **123d**, and no C2 ring opening product was observed (Table 3.5, entry 1). Generally, the reaction went faster in THF than that in Et_2O. In most of the ring opening experiments, tosyl amide **125**

was always observed, and the origin of this compound remains unclear, as no other side product could be identified from the crude reaction mixture. The formation of the amide **125** is consistent with the low isolated yield of the desired product **123d**. The best result involves using 3 equivalents of cuprate and the highest isolated yield was only 42% (Table 3.5, entry 4). To further optimize the reaction conditions, several variables were tested, such as changing the solvent (Table 3.5, entry 2, 8), the temperature (Table 3.5, entry 3 and 5), switching the addition sequence of each reagent (Table 3.5, entry 7) and addition of the additives (Table 3.5, entry 8 to 10), but none of these experiments gave improved results. Direct concentration and purification without workup didn't significantly change the outcome (Table 3.5, entry 2 and 8).

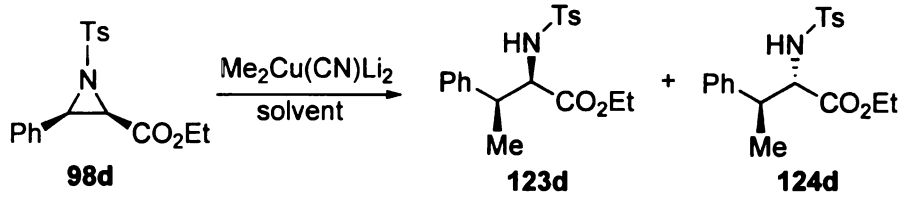
Scheme 3.10 Carbon nucleophilic ring opening of the aziridine **98a**



The *N*-tosyl cyclohexylaziridine **98a** gave a mixture of two products, which are tentatively assigned as the ring opening products resulting from attack at the C2 or the C3 positions (Scheme 3.10). Silica gel chromatography could not separate the mixture of **123a** and **124a**. When the *N*-Boc activated aziridine **95d** was tested, incomplete conversion was observed at –78 °C, and increasing the temperature to –20 °C resulted in complete conversion but in the formation of a complex mixture without any trace of the expected ring opening products (Scheme 3.10).

The ring opening reaction of the aziridine **98d** with a higher order cuprate[67] was also investigated (Table 3.6). The eliminated product **125** observed with Me_2CuLi (Table 3.5) disappeared but the isolated yields of the ring opening products were poorer (<30% overall yield), and a compound **124d** that was tentatively assigned as the diastereomer of compound **123d** was observed as major product (Table 3.6, entry 1). Interestingly, without a work-up process, the product **123d** appeared to be the major product (Table 3.6, entry 2). The clear explanation for such an observation is not clear.

Table 3.6 Carbon nucleophilic ring opening by higher order cuprate reagent

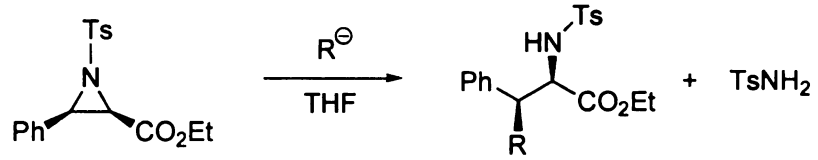


entry[a]	additive	solvent	temp (°C)	time (h)	result[b]
1	none	Et_2O	-78	8	**123d** : **124d** = 1:4
2[c]	none	Et_2O	-78	7	**123d** : **124d** = 3:1
3	1 eq. $BF_3{\cdot}Et_2O$	THF	-78 to -40	24	<5% conv.

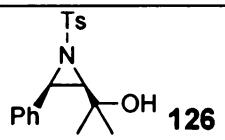
[a] In entry 1 and 2, cuprate reagent was prepared with 3 equiv MeLi and 1.5 equiv CuCN. Entry 3 was with 2 equiv MeLi and 1 equiv CuCN. [b] The silica gel chromatographic purification gave a mixture of compound **123d** and **124d** in 30% overall yield. [c] The crude mixture was directly concentrated and purified without quenching with NH_4Cl (aq.) solution.

Other conditions[68] were also tested for ring opening reactions with carbon nucleophiles, but none of the attempts resulted in better results. Either most of the starting material **98d** was recovered (Table 3.7, entry 4 and 5), the 1,2 addition product was formed (Table 3.7, entry 1) or complex mixtures were observed.

Table 3.7 Results with other conditions for addition of carbon nucleophiles

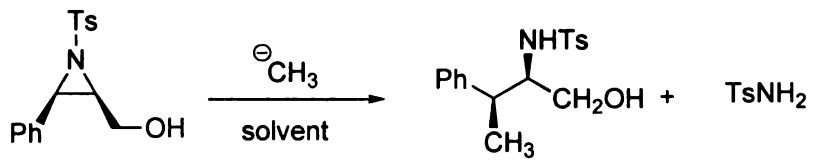


98d **123** **125**

entry	Organometallic regent	CuX	temp (°C)	time (h)	result
1	5eq. MeMgBr	3 eq. CuCN	-78 to -40	1.5	 **126**
2	5eq. *i*-PrMgBr	0.4 eq.CuBr	-40 to 60	1	**125** + complex mixtures
3	3 eq. *n*-BuLi	3 eq. CuI	-78	2	complex mixtures
4	6 eq. *n*-BuLi	3 eq. CuI	-78	2	**98d** + complex mixtures
5	3 eq. *n*-BuLi	1.5 eq. CuI	-78 to -40	24	**98d** only

The ring opening of *N*-tosyl aziridinyl alcohol **110** gave either incomplete conversion or unidentified complex mixtures (Table 3.8).

Table 3.8 Carbon nucleophilic ring opening of the *N*-tosyl aziridinyl methanol **110**



110 **127** **125**

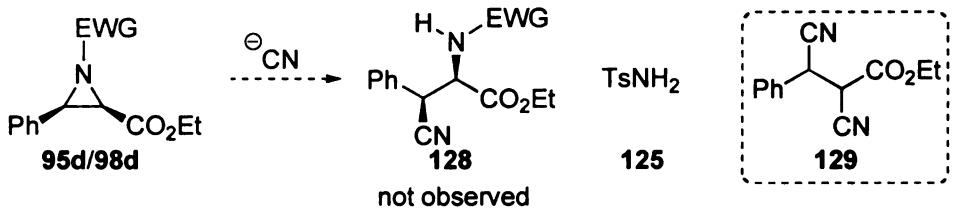
entry	CH_3^- source	solvent	temp (°C)	result
1	3 eq. Me_2CuLi	Et_2O	-20	**110**: **127**: **125** = 4 : 1 : 0.5
2	3 eq. Me_2CuLi	THF	-20 to 25	complex mixtures
3	0.1eq. $Cu(acac)_2$+ 1eq. MeMgBr	THF	0	**110** only

3.2.2 Regioselective ring opening by cyanide

Another carbon nucleophile that was examined in the ring opening of activated

aziridines is cyanide. The successful examples of using cyanide as a nucleophile for the ring opening of aziridines all involve the use of mono substituted aziridines or aziridines that are part of a fused ring system, which in theory will be easier to open due to the release of the strain energy.[69] The corresponding cyanide induced ring opening of di-substituted non-cyclic aziridines are not reported.[70] We were interested in this reaction with the *cis-di*-substituted acyclic aziridinyl-2-carboxylates from our AZ reaction because the resulting adduct **128** might serve as a precursor of *β*-amino acids upon hydrolysis of the cyano group. This cyanide ring opening of the *cis*-di-substituted aziridines was also considered as a model study for our proposed total synthesis of the (-)-Amathaspiramide F,[71] which will be discussed in chapter six.

Table 3.9 Nucleophilic ring opening of activated aziridines by cyanide



entry	series	EWG	reagents	temp (°C)	time (h)	solvent	result
1			KCN, 18-Crown-6	80	24	CH_3CN/H_2O (4:1)	**95d** + complex mixtures
2	**95d**	Boc	TMSCN, TBAF	40-75	24	THF	**95d**
3			NaCN, $LiClO_4$	reflux	36	CH_3CN	**95d** + complex mixtures
4			NaCN, 1 equiv $BF_3•Et_2O$	25[a]	3	HMPA	**125** + **129**
5	**98d**	Ts	NaCN, $LiClO_4$	25-75[b]	24	CH_3CN	**125** + complex mixtures
6			TMSCN, TBAF	40-75	36	THF	**98d** + complex mixtures

[a] The reaction was performed in a ultrasonic bath. [b] The reaction was performed in a ultrasonic bath at 25 °C for 1 h then stirring at 75 °C for 24 h.

The ring opening reaction of the *N*-Boc activated aziridine **95d** gave incomplete

conversion under the conditions indicated in Table 3.9. Increasing the reaction temperature did result in complete conversion, however, it also resulted in the formation of a complex mixture. Possible reasons for the poor reactivity of the *N*-Boc activated aziridine **95d** are : a) the steric hindrance resulting from substituents at both the C2 and C3 positions may block the approach of the relatively weak cyanide nucleophile, b) the activating effect of Boc group is too weak to facilitate ring opening by a weak nucleophile. Some conditions were examined considering these two rationales, one of which involves a more naked CN^- anion that was generated *in-situ* from TMSCN and TBAF[69f] and another that involves the more activated *N*-tosyl aziridine **98d**. Unfortunately, these adjustments still resulted in incomplete conversion (Table 3.9, entry 2 and 6). The additive $LiClO_4$ has been reported to function as a weak Lewis acid,[69d] but for aziridine **95d** also resulted in complex mixtures (Table 3.9, entry 3). As for the ring opening reactions of the **98d** with alkyl cuprates (Table 3.5), the by-product **125** was also observed for the reactions of the *N*-tosyl aziridine **98d** with cyanide (Table 3.9, entry 4 and 5). The NMR, MS and IR spectra of the major fraction from these reactions suggested a possible structure for the products as a mixture of diastereomers of **129** or a mixture of two inseparable unidentified products, while the desired ring opening product **128** was never observed.

The formation of **125** is problematic in most of the ring opening reactions of the aziridine **98d** with carbon nucleophiles. In the future, a possible solution to this problem is to use a nitrogen activating group that is stronger than carbamate (Boc) but that will not change the aziridine nitrogen into a good leaving group as the tosyl group does. One choice could be an acyl activating group that was shown to be easily introduced to an *N*-H aziridine by acetic anhydride in quantitative yield (Scheme 3.3). Alternatively, we can try to use non-activated aziridines (*N*-Bh aziridine **35** or *N*-DAM aziridine **58**) in the presence of Brønsted acid.

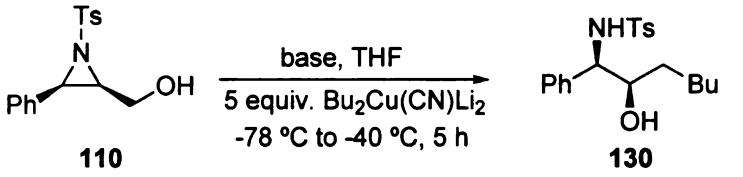
3.3 Regioselective ring opening at the C2 position of aziridines

Few examples are known for the regioselective C2- ring opening of aziridinyl-2-carboxylates.[72] With the aziridinyl-2-methanol **110** and other activated aziridines in hand, the intramolecular C2- ring opening and the radical C2- ring opening reactions were investigated.

3.3.1 Intramolecular C2 ring opening by oxygen

The intramolecular C2 ring opening reaction developed by Fujii[62] was applied to the *N*-tosyl aziridinyl methanol **110**, which was prepared from **56d** through LAH reduction followed by a selective tosylation (Scheme 3.5). A strong non-nucleophilic base like KH was required to achieve complete conversion and afforded product **130** in 81% isolated yield. NaH only gave recovered starting material under the same reaction condition (Scheme 3.11).

Scheme 3.11 Intramolecular C2 ring opening of aziridine



110 **130**

a) 3 equiv NaH, no reaction
b) 2 equiv KH, 81% yield

3.3.2 Approaches for the preparation of β-amino esters

As we mentioned before, the activated chiral 2,3-di-substituted aziridinyl-2-carboxylates can be regarded as precursors to amino acids. Ring opening at the C3 position forms α-amino esters, and ring opening at the C2 position can be a method for the synthesis of optically pure β-amino acids (Figure 3.2), which belongs to another class of important synthons. The preparation of β-amino acids is relatively more difficult

than its α–amino acids analogs.[1] Thus, it would be attractive to develop a general method for the preparation of these molecules applying our AZ reaction methodology. This work will be mainly focused on the study of regioselective ring opening reactions at the C2 carbon of the optically pure *cis*-aziridinyl-2-carboxylates for the purpose of preparing β^3-amino esters. Efforts towards the synthesis of β^2-amino acid derivatives via an asymmetric imino-aldol reaction will also be discussed.

Figure 3.2 β^3-amino acids and β^2-amino acids

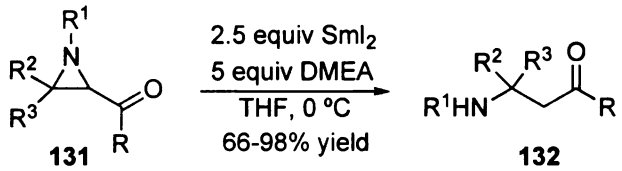
β^3-amino acid β^2-amino acid

3.3.2.1 SmI_2 mediated ring opening of aziridinyl-2-carboxylates

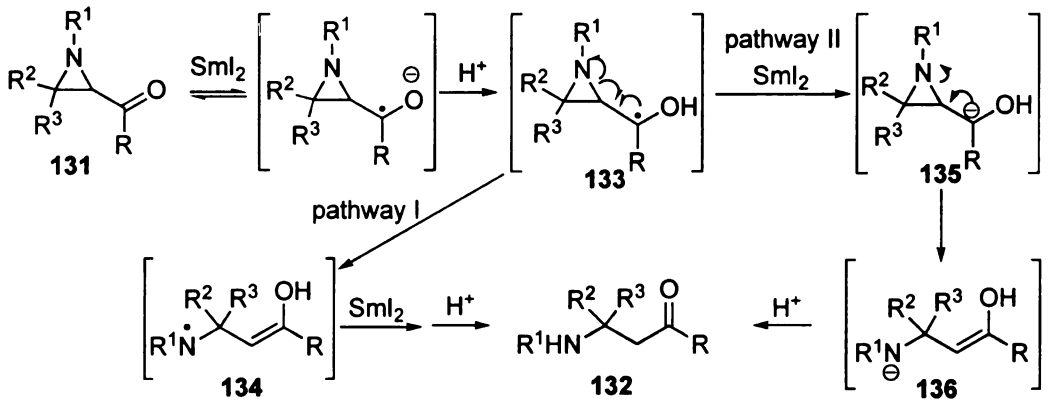
The reductive ring opening of aziridinyl-2-carboxylates at the C-N bond next to the carboxylate group is a convenient method for access to β^3-amino esters,[73] which could be easily converted to β^3-amino acids after hydrolysis. Optically pure β-amino acids bearing an *N*-Fmoc group are useful as was mentioned in Section 3.1.2. The commercially available *N*-Fmoc β–amino acids are expensive and different types that are available are limited, and few synthetic approaches have been developed.[59] Molander studied a series of samarium diiodide (SmI_2) mediated reductive ring opening reactions of *trans*- aziridinyl esters and amides, which were mostly activated by Boc or tosyl groups (Scheme 3.12),[74] but very few examples have been reported for the reactions of *N*-Fmoc activated aziridines.[75,74b] There are no known examples of SmI_2 reductive ring opening of any non-cyclic *cis*-2,3-disubstituted aziridines with any *N*-protecting groups. We were particularly interested in examining the possibility of developing a method for the regioselective ring opening of *cis*- aziridinyl-2-carboxylates, which can be readily

prepared from the VAPOL or VANOL catalyzed AZ reaction, as a direct entry to the synthesis of *N*-Fmoc protected β-amino esters. This would be the first example of the reductive C2 ring opening of monocyclic aziridines with a *cis*-2,3-di-substitution pattern. In this study, other non-activated and activated aziridines were also examined to help understand the reactivity patterns.

Scheme 3.12 Molander's SmI_2 mediated ring opening reaction of aziridines



Proposed mechanism:

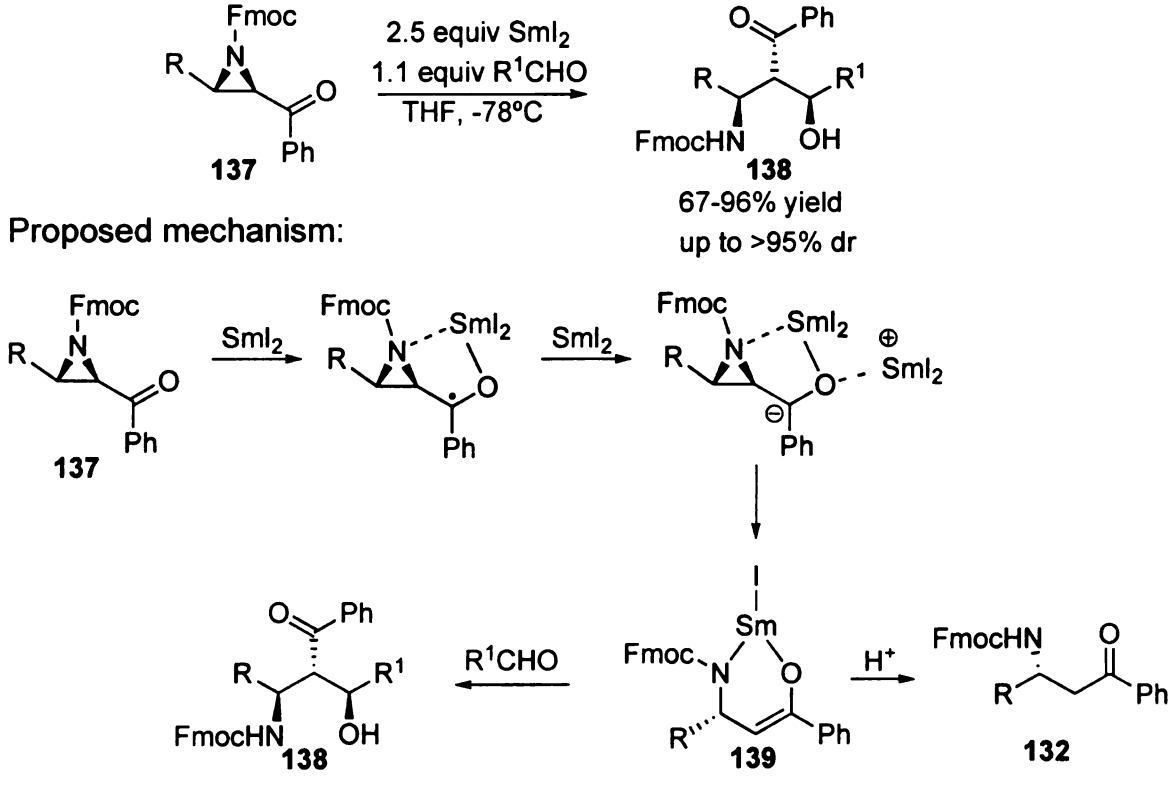


According to Molander's proposed mechanism (Scheme 3.12), the SmI_2 mediated reaction can proceed in two possible pathways from the branch point intermediate **133**, which was generated via a one-electron transfer from SmI_2 to the carbonyl of the aziridine **131** to form a radical anion, followed by subsequent protonation in the presence of proton source (dimethylethanolamine (DMEA)). In pathway I, the aziridine ring of the **133** opens to give the intermediate **134** that has a radical on nitrogen, which gets a second electron from SmI_2, and finally a protonation to furnish the product **132**. In pathway II, the second electron transfer take place prior to the ring opening process, and

then subsequent ring opening and protonation also gives the final product **135**.

The formation of enols **134** or **136** can potentially be taken advantage of in the construction of a new C-C bond, and this has been successfully achieved in Mukaiyama's stereoselective SmI_2 mediated aldol reaction of acylaziridines with aldehydes.[75] In this reaction, the β-aminio-β'-hydroxy ketones **138** were synthesized with high diastereoselectivity. They proposed that the samarium chelates with both oxygen and nitrogen and then electron transfers to the oxygen of the aziridine **137**. The diastereoselectivity was proposed to be controlled via a Sm chelated chair conformation of the enolate **139**, which was generated after the ring opening of the aziridine (Scheme 3.13). In Mukaiyama's mechanistic rationale, the aldehyde is preferred to approach the enolate from the bottom of **139**, which is formed after the second electron transfer and supports the pathway II proposed by Molander.

Scheme 3.13 Mukaiyama's SmI_2 mediated aldol reactions

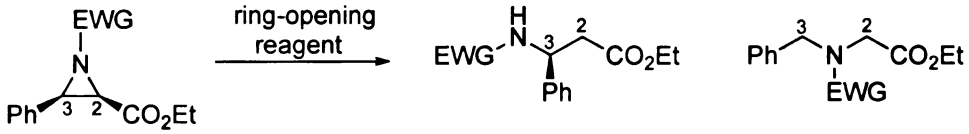


We first investigated this SmI_2 mediated radical ring opening process using the *cis*-*N*-tosyl aziridine **98d** to compare with the results of Molander for the corresponding trans- isomers (87% yield). The aziridine ring was opened selectively at the C2 position to afford the product **140d** by treatment with 2.5 equivalent of *in situ* generated SmI_2 solution (Table 3.10). Commercially available SmI_2 solution could be used only once because of rapid decomposition after the bottle was opened. All SmI_2 that used in this work was generated *in situ* from fresh Sm metal and diiodomethane in THF. The product **140d** could also be obtained via a simple Mg mediated ring opening process,[76] in which Mg was used in large excess. This reaction was clean and easy to perform (Table 3.10, entry 1). However, complications arose when these ring opening conditions were applied to *N*-Fmoc aziridine **96d** as shown in Table 3.10.

As can be rationalized by Molander's mechanism (Scheme 3.12), this reaction is completely regioselective for ring opening at the C2 position, since none of the C3 ring opening product was observed. The C2-ring opening conditions that were successful for the *N*-tosyl aziridine **98d** showed incomplete conversion for the *N*-Fmoc aziridine **96d** (Table 3.10, entry 1, 4 vs. entry 2, 6), which presumably is due to the different electron withdrawing abilities of the tosyl group and the Fmoc group. The weaker electron withdrawing ability of the Fmoc group resulted in the observation of competitive C2-C3 bond breakage and the formation of the undesired product **141a**. Unlike the case with the *N*-tosyl aziridine **98d**, the ring opening of the *N*-Fmoc aziridine **96d** requires a larger amount of SmI_2 to go to completion (Table 3.10, entry 4 vs. entry 10). Many factors may affect this reaction: the amount of dimethylethanol amine (DMEA)[74a] was crucial, the absence or an insufficient amount of DMEA always led to incomplete conversion (Table 3.10, entry 7 to 9). It is thought that the DMEA serves as the proton donor during this process as illustrated in the proposed mechanism in Scheme 3.14. It was found that the amount of DMEA has to be double the amount of the SmI_2. A temperature study showed

that at lower temperature, the amount of the desired product **140a** decreased although the reaction went to completion (Table 3.10, entry 12 to 14). At higher temperature, the C2-C3 bond breakage product **141a** was obtained exclusively as shown in entry 15.

Table 3.10 Optimization of the C2 ring opening conditions



96d: EWG = Fmoc
98d: EWG = Ts

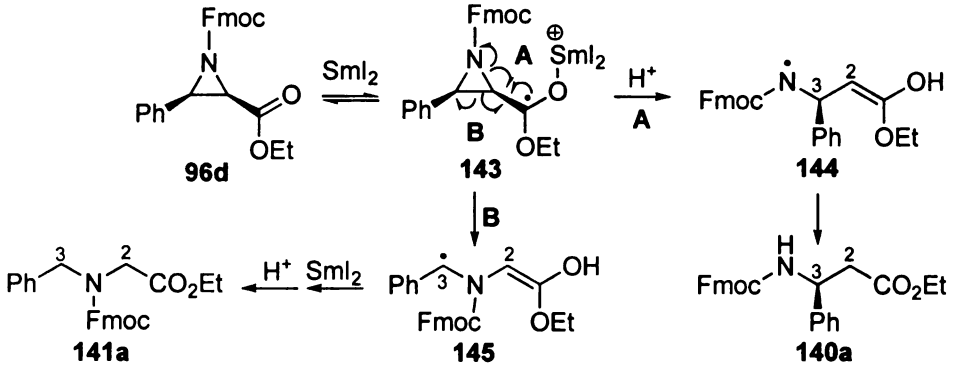
140a EWG = Fmoc
140b EWG = Ts

141a EWG = Fmoc
141b EWG = Ts

entry	EWG	reagent (equiv)	DMEA (equiv)	temp (°C)	time (h)	conv.	yield of **140** (%)[a]
1	Ts	Mg (10)	none	25	4	100%	79
2	Fmoc	Mg (10)	none	25	6	0%	nd
3	Fmoc	Mg (10)	none	55	14	100%	complex mixtures
4	Ts	SmI_2 (2.5)	5	0	0.7	100%	75% (NMR), no **141b**
5	Fmoc	SmI_2 (3)	6	0	0.7	30%	nd
6	Fmoc	SmI_2 (2.5)	5	0	0.7	33%	nd
7	Fmoc	SmI_2 (2.5)	none	0	0.7	12%	nd
8	Fmoc	SmI_2 (5)	2	0	0.7	10%	nd
9	Fmoc	SmI_2 (5)	5	0	0.7	60%	nd
10	Fmoc	SmI_2 (5)	10	0	0.7	100%	40% (NMR)
11[b]	Fmoc	SmI_2 (5)	10	0	1.5	50%	nd
12	Fmoc	SmI_2 (5)	10	-10	1.5	100%	28% (NMR)
13	Fmoc	SmI_2 (5)	10	-40	1.5	100%	20% (NMR)
14	Fmoc	SmI_2 (5)	10	-78	1.5	100%	14% (NMR)
15	Fmoc	SmI_2 (5)	10	40	0.15	100%	0%, **141a** exclusively

[a] Compound **141a** was observed as a by-product in entries 5-15 with the formation of product **140a**. [b] The DMEA was added to SmI_2 and stirred for 5 min before the addition of the aziridine solution.

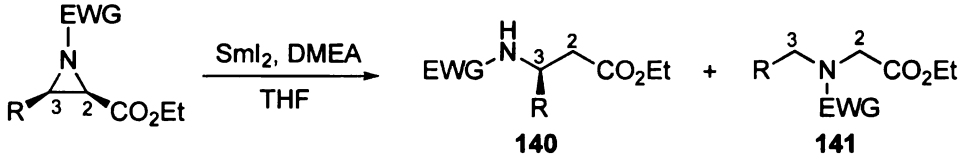
Scheme 3.14 Proposed mechanism for the ring opening of the *N*-Fmoc aziridine **96d**



It was suspected that the ring opening of the *N*-Fmoc aziridine **96d** occurred before the transfer of the second electron from the SmI_2, according to the pathway I that is shown in Scheme 3.12. After the generation of intermediate **143**, there will be a competition between the C2-N bond breakage (**A**) and the C2-C3 bond breakage (**B**). This competition will be determined by the relative stability of either the C3 radical **145** or the nitrogen radical **144**. If the nitrogen is attached to a strong electron withdrawing group, it should be more able to stabilize a radical center and this will result in the C2-N bond breakage product **140a** as the major product, such as in the reaction of the *N*-tosyl aziridine **98d** (Table 3.10, entry 4). Exclusive formation of the C-N bond cleavage product was observed. If there is an aryl substituent at the C3 position, a benzylic radical of the type **145** can be generated, which is stabilized by the aryl substituent to afford C2-C3 bond breakage and the formation of the product **141a**. When the activating group on nitrogen is less electron withdrawing like the Fmoc group, and there is an aryl group at the C3 position, then the competition between the formation of the C3 benzylic radical **145** and the nitrogen radical **144** will be closer with the result that there should be less selectivity between C2-C3 bond breakage and C2-N bond breakage (Table 3.10, entry 6). If this hypothesis is correct, it is reasonable to think that in the absence of a C3 aryl substituent, a stabilized benzylic radical can not form and thus the C2-C3 bond cleavage

might be suppressed even when the nitrogen is activated by a relatively weak electron withdrawing group, and as a result, the C2-N breakage product **140** should be the major product. To test this hypothesis, a series of aziridines with different C3 substituents and *N*-activating groups were investigated for the regioselective ring opening process, and the results are shown in Table 3.11.

Table 3.11 SmI_2 mediated ring opening reaction of aziridines[a]



140 **141**

entry	series	EWG	R	ratio of **140** : **141**	yield of **140** (%)[b]
1[c]	**96d**	Fmoc	Ph	1 : 1	45% of **140a**
2[d,e]	**96d**	Fmoc	Ph	nd	10% conv.
3[d,f]	**96d**	Fmoc	Ph	nd	20% of **140a**
4[d]	**96a**	Fmoc	Cy	1 : 0	89% of **140c**
5	**95d**	Boc	Ph	1 : 0.8	53% **140d**
6[d]	**95d**	Boc	Ph	1 : 1.4	nd
7[d,g]	**95j**	Boc	Ph	1 : 0.2	nd
8[d,h]	**95a**	Boc	Cy	1 : 0.05	84% **140e**
9[d]	**97d**	Ac	Ph	1 : 0	85% overall (**140f** and **140g**)[i]
10[j]	**98d**	Ts	Ph	1 : 0	93% **140b**
11	**56d**	H	Ph	0 : 1	75% **141h**
12	**58d**	DAM	Ph	0 : 1	67% **141i**
13	**36d**	Bh	Ph	0 : 1	69% **141j**

[a] Unless otherwise specified, the reaction was run at 0 °C for 40 min with 5 equiv SmI_2 and 10 equiv DMEA. [b] Isolated yield after silica gel chromatography. [c] The reaction was carried out at 25 °C. [d] 4 equiv. SmI_2 and 8 equiv. DMEA was used. [e] 12 equiv $BF_3 \cdot Et_2O$ was added. [f] 11 equiv $Cu(OTf)_2$ was added. [g] The *trans*-*N*-Boc-3-phenyl aziridinyl-2-carboxylate was used. [h] The

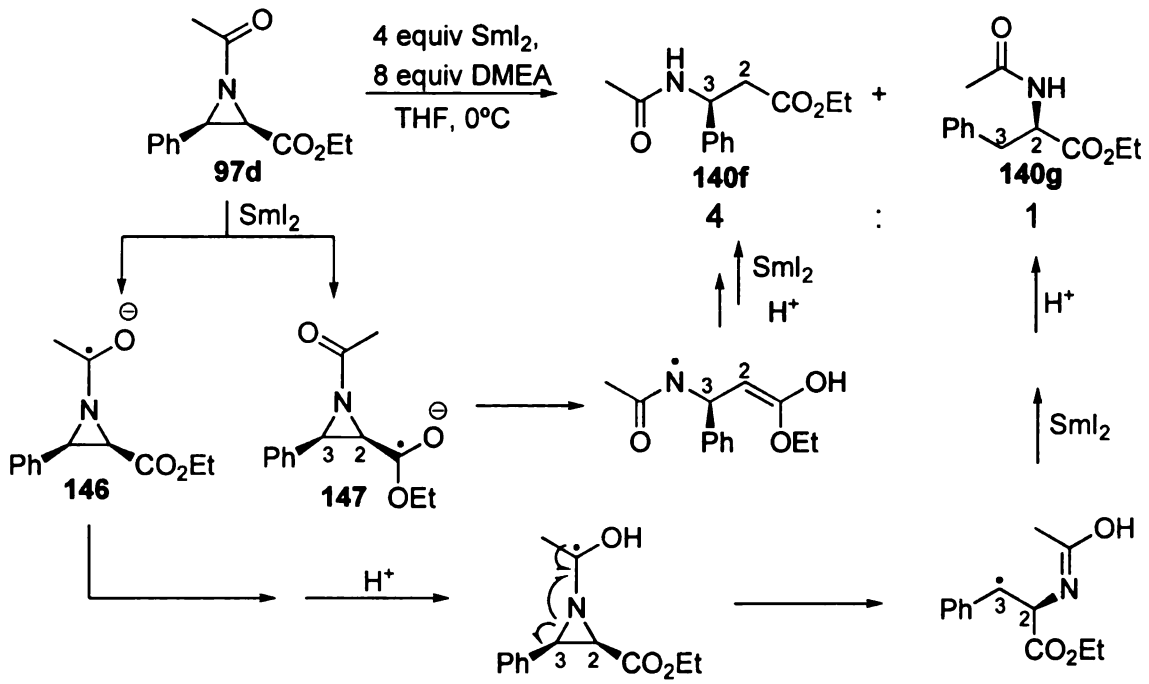
reaction finished in 10 min. [i] See Scheme 3.15, two isomers **140f** and **140g** are inseparable. [j] 2.5 equiv SmI_2 and 5 equiv DMEA was used.

The data shown in Table 3.11 clearly demonstrated that the reaction outcome strongly depends on both of the activating group and the nature of the C3 substituent of the aziridine. As was expected, the C3-alkyl substituted aziridines afforded the C2-N bond breakage product **140c** and **140e** predominantly (Table 3.11, entry 4, 8), which is attributed to the lower stability of secondary alkyl radicals vs. that of the nitrogen radicals. In the case of C3 aryl substituted aziridines, such as **95d** and **96d**, the intermediate benzylic radicals will be more favored than the radicals generated from an aziridine with an alkyl group at the C3 position, and thus the formation of the nitrogen radical may not be favored unless the nitrogen is attached to a strong electron withdrawing group (**98d**) (Table 3.11, entry 1, 5 vs. entry 10). This investigation was further extended to non-activated aziridines and it was not surprising that the C2-C3 bond cleavage product **141** is always the major product when there is an aryl substituent at the C3 position (Table 3.11, entry 11 to 13). Without an activating group, lower reactivities were observed with all C3-alkyl substituted aziridines, and either complex mixtures were observed or there was no reaction (not shown). Using a Lewis acid as an additive to enhance the activating effect of the Fmoc group was not promising (Table 3.11, entry 2 and 3). Molander has reported that the *trans* isomer of the N-Boc aziridine **95j** can be reductively opened to give a single product in 82% yield,[74a] which was assigned as the structure **140d**. This reaction was repeated and as indicated by entry 7 in Table 3.11, this result was confirmed. However, under identical conditions, the *cis-N*-Boc- aziridinyl ester **95d** afforded a mixture of C2-N bond cleavage product **140d** and the C2-C3 bond cleavage product **141d** with the later slightly favored (Table 3.11, entry 6). The reason why there is such a big difference between the *cis*-aziridine and the

trans-aziridine is not clear at this point.

Another interesting observation is that the reaction of the *N*-acetyl activated aziridine **97a** gave none of the C2-C3 bond cleavage product, but instead a mixture of two isomers were isolated in 85% overall yield in a 4: 1 ratio (Table 3.11, entry 9). These compounds were determined to be a mixture of the C2-N bond cleavage product **140f** and the C3-N bond cleavage product **140g** (Scheme 3.15). Since the electron withdrawing ability of the acetyl group is higher than either Boc or Fmoc groups, it is reasonable to expect that the reaction of **97d** would favor C-N bond cleavage over C-C bond cleavage such that compound **141** would not be formed. The C3-N bond cleavage product **140g** was never observed in any of the other SmI_2 mediated ring opening reactions that were examined in this work, one possible explanation for the formation of **140g** is that it may result from the radical intermediate **146** that would be generated from electron transfer to the acetyl group as shown in Scheme 3.15.

Scheme 3.15 Proposed mechanism for the SmI_2 mediated ring opening of the *N*-Ac aziridine **97d**



In summary, reaction conditions that would favor the selective generation of the C-N bond cleavage product **140a** from the *N*-Fmoc-3-phenyl aziridine **96d** remain elusive. However, this should not restrict access to the majority of β^3-analogs of the naturally occurring α-amino acid units, since most have an alkyl substituent at the β–position, and it was found that the C3-alkyl substituted *N*-Fmoc aziridine **96a** undergoes exclusive C-N bond cleavage. In addition, the C-C bond cleavage could be completely avoided for C3-aryl aziridines if the Fmoc group was replaced by the tosyl group (Table 3.11, entry 10).

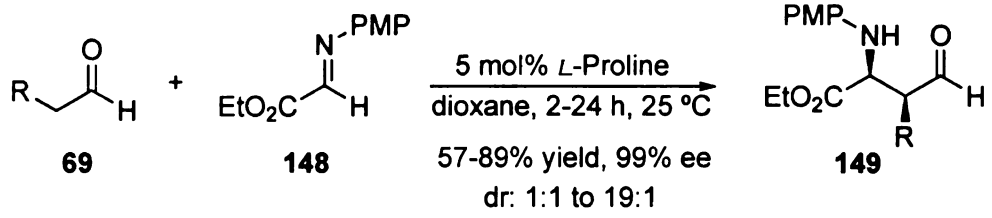
Attempts at the SmI_2 mediated ring opening reaction of the tri-substituted aziridines **115** (Scheme 3.7) all resulted in mixtures of diastereomers with incomplete conversion (not shown). The stereochemistry at the C2 position was lost in all the substrate that were tested that had a quaternary carbon at the C2 position and this is likely a consequence of the intermediacy of a radical enol.

3.3.2.2 β^2-amino ester via asymmetric imino-aldol reaction

Considering Mukaiyama's SmI_2 mediated aldol reaction of aziridines (Scheme 3.13),[75] the SmI_2 mediated C2-ring opening of activated aziridinyl-2-carboxylates might be applied to the synthesis of β^2-amino acids by trapping the enolate **139** with other electrophiles. The work on the attempted asymmetric synthesis of the β^2-amino esters that we will be discussed in this section was inspired by Barbas' study on the asymmetric Mannich-type reaction with α-imino ethyl glyoxylate **148** (Scheme 3.16).[77] In this reaction, aldehydes **69** react with the imino glyoxylate **148** with L-proline as the catalyst to afford the β–amino aldehyde **149** in excellent enantioselectivities and with good diastereoselectivities.

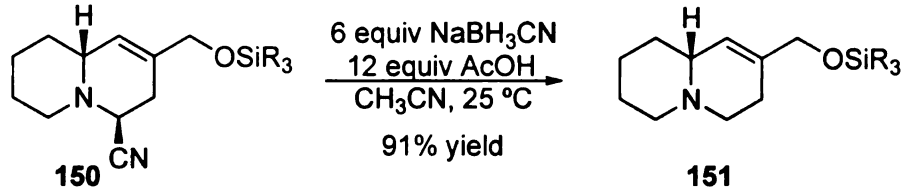
Scheme 3.16 Barbas' Mannich-type reaction and Danheiser's reductive removal of cyanide

Barbas' Mannich reaction :



69 148 149

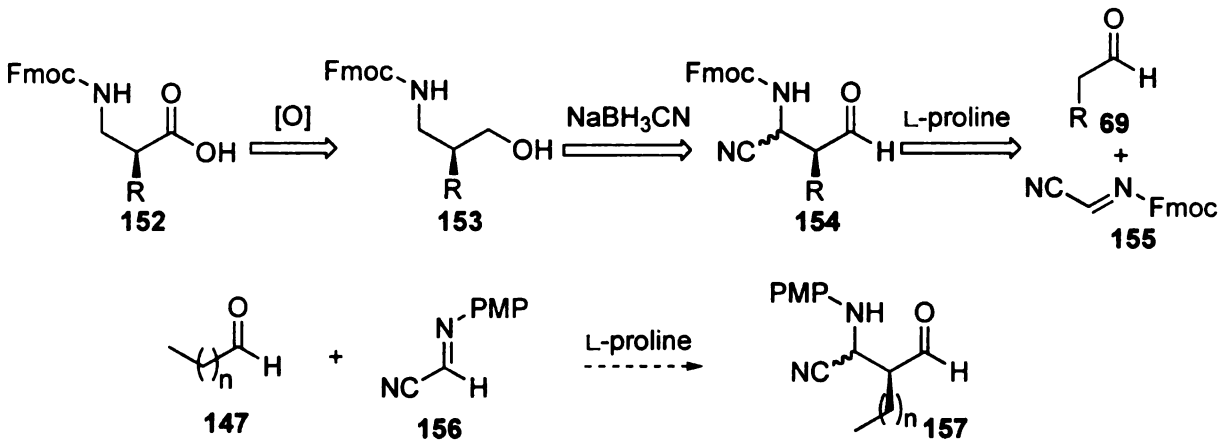
Danheiser's Reductive removal of cyanide:



150 151

Our strategy for the synthesis of the β^2-amino esters **152** is shown in Scheme 3.17. It is proposed to determine if the *N*-Fmoc imine **155** and aldehyde **69** can undergo an asymmetric imino-aldol reaction to give the intermediate **154** under the catalysis of the L-Proline. The reductive decyanation that was reported by Danheiser's group[78] (Scheme 3.16) would be expected to occur to excise the cyanide group and generate the intermediate **153**, which upon subsequent oxidation should afford the *N*-Fmoc β^2-amino acid **152**.

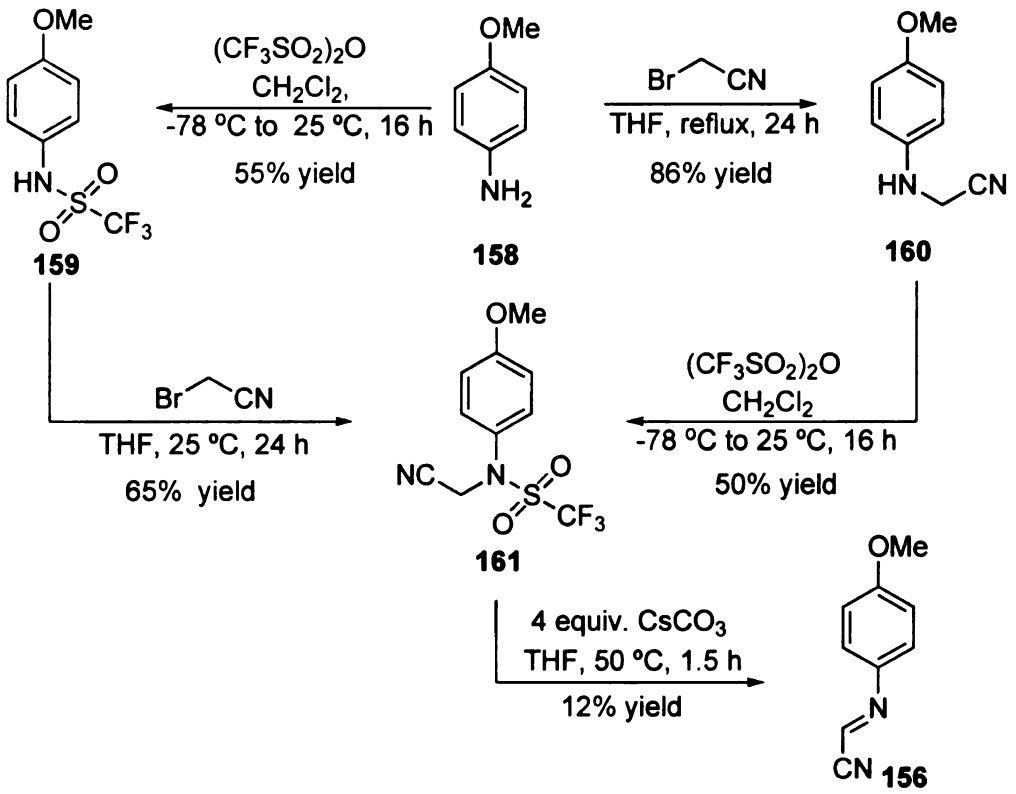
Scheme 3.17 Proposed strategy for the synthesis of the β^2-amino acid



152 153 154 69 155 147 156 157

The key step of this strategy is the catalytic asymmetric imino-aldol reaction of the cyano imine **155** with aldehyde **69**. The investigation started with the imine **156** and aldehyde **69** as a model study based on the following considerations: (a) The cyano group in imine **156** may exhibit a similar or even stronger electronic effect than the carboxyl group in **148**; (b) In Barbas' system, long chain aldehydes provided the best diastereoselectivities; (c) the *para*-methoxyphenyl group was used in the imine **148**, which was claimed to be easily removed after the Mannich reaction.[77a]

Scheme 3.18 Preparation of imine **156**

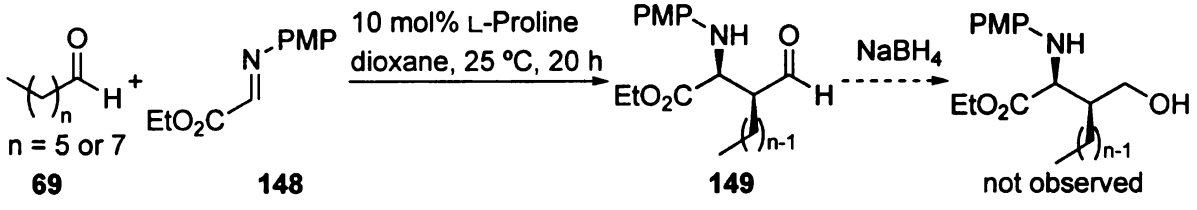


Imine **156** could be prepared in three steps[79] starting from the commercially available *para*-anisidine **158** (Scheme 3.18). The first two steps effected the conversion from the primary amine into the tri-substituted amine **161** that contains a trifluoromethylsulforyl group as a potential good leaving group in next elimination step, which affords the product imine **156**. As shown in Scheme 3.18, the cyanomethyl and

trifluoromethylsulforyl groups could be introduced in either sequence. The overall yield of the intermediate **161** was slightly higher if the cyanomethyl group was introduced first, which may be due to the greater stability of the compound **160** verses the compound **159**. The $CsCO_3$ mediated elimination[78] step afforded the imine **156** in only 12% yield after the chromatographic purification. Despite the low yield of the last step, a sufficient amount of imine **156** was obtained to test the proposed imino-aldol reaction.

Before attempting to extend the Barbas' Mannich reaction to the imine **156**, a control experiment was performed that included a substrate that appeared in Barbas' original report.[77a] Following the published procedure, the imine **148** and the heptaldehyde **69** were reacted under the catalysis of 10 mol% L-proline in freshly distilled dioxane at room temperature for 24h (Scheme 3.19). The best result obtained was around 80% NMR yield of the product **149**. This product could only be observed in the crude ^1H NMR spectrum regardless of the size of aldehydes used. All attempted purifications following Barbas's reported procedure failed to lead to the isolation of compound **149** and instead decomposition was always observed during the purification (neutralized silica gel and normal silica gel were tried). The attempted transformation from the unstable product **149** to the more stable alcohol via the $NaBH_4$ reduction only resulted in complex mixtures.

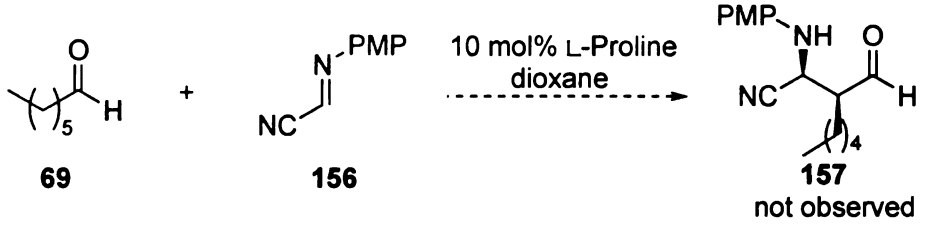
Scheme 3.19 Repeating of Barbas' results by using the imine **148**



Despite the problems that we encountered with the experiments using imine **148**, the reaction of imine **156** was still carried out. As shown in Scheme 3.20, to our surprise, no reaction occurred with the imine **156** at the room temperature even after two days.

Complex mixtures and incomplete conversion were observed if the temperature was increased to 65 °C. The desired addition product **157** was never observed.

Scheme 3.20 Attempted Mannich-type reaction of cyano imine **156** with aldehyde **69**

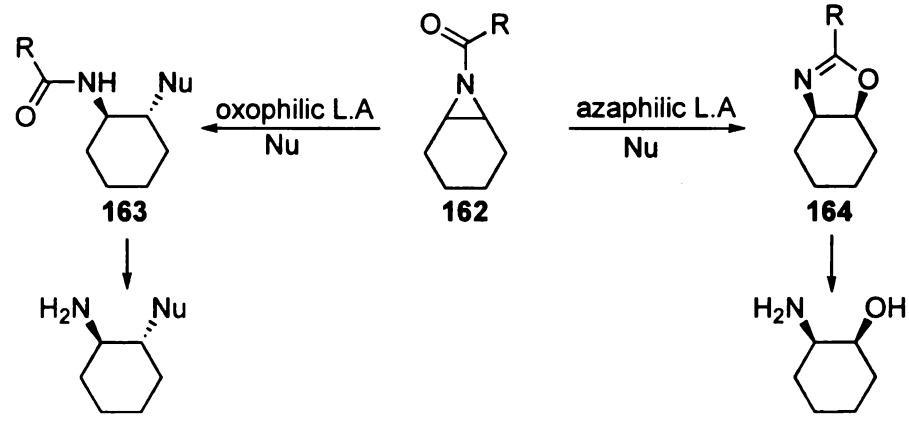


69 **156** **157** not observed

3.4 Synthesis of oxazolidinones and imidazolines

In 1998, Lectka reported a Lewis acid catalyzed Heine[79] reaction, which involves a ring opening and rearrangement of acylaziridines,[23d,e] which featured a catalyst controlled reactivity based on the coordination preference of Lewis acids for either the oxygen or the nitrogen in the acylaziridine **162** (Scheme 3.21). Oxophilic Lewis acids activate **162** predominantly towards external nucleophilic ring opening to afford intermediate **163**, while azaphilic Lewis acids catalyze the ring expansion reaction from **162** to the oxazoline **164** via a ring opening-rearrangement process.

Scheme 3.21 Lectka's ring opening and rearrangement of acylaziridine

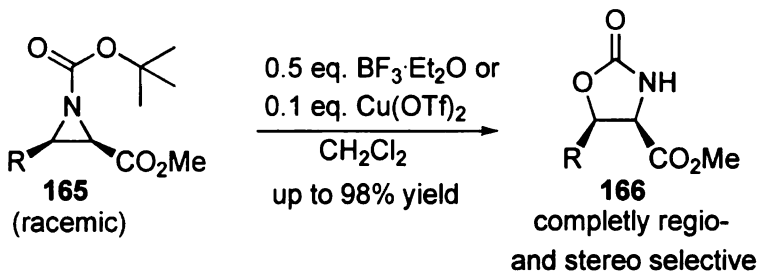


163 **162** **164**

Recently, Tomasini reported an azaphilic Lewis acid catalyzed ring expansion reaction using *N*-Boc aziridines **165**, which afforded oxazolidinone **166** in excellent

yields[23] as shown in Scheme 3.22. This Lewis acid mediated ring expansion caught our attention because it claims complete stereoretention and stereospecificity for *cis*- and *trans*- isomers.

Scheme 3.22 Tomasini's oxazolidinone formation



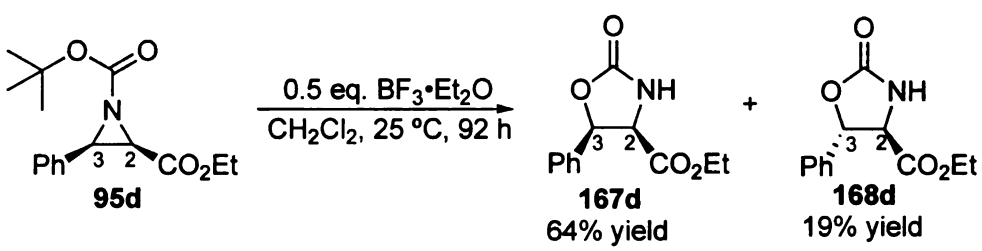
165 (racemic)

166 completly regio- and stereo selective

In the *trans*- series of the aziridine **165**, examples were given where the R group was either aryl or alkyl groups, but for the *cis*- series[23a] only the reactions of alkyl derivatives were reported. To complete the series, the ring expansion reaction of the *cis*- *N*-Boc aziridine **95** was examined with both boron trifluoride etherate and copper(II) triflate as Lewis acids. The aryl and alkyl substituted *N*-Boc aziridine **95d** and **95a** were prepared via the AZ reaction, deprotection and activation protocol.

3.4.1 Observations from the ring expansion of *N*-Boc aziridines

Scheme 3.23 Ring expansion of *N*-Boc phenyl aziridine **95d**



95d

167d 64% yield

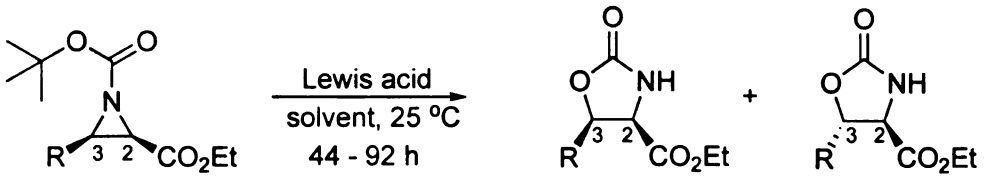
168d 19% yield

The preliminary result for the ring expansion reaction of the *N*-Boc aziridine **95d** is shown in Scheme 3.23. To our surprise, this ring expansion reaction was not stereospecific. Good chemical yields of the ring expansion products were obtained but

as a mixture of *cis*- and *trans*- products. The aziridine ring opened regioselectively at the C3 position, but in addition to the expected *cis*-oxazolidinone **167d**, *trans*-oxazolidinone **168d** was also isolated in 19% yield, which was initially assigned as the structure shown in Scheme 3.23, in which it was suspected that the C3-center was inverted relative to the oxazolidinone **167d**. The assignment of the absolute stereochemistry for each product will be discussed later. This intriguing observation piqued more interest in the Lewis acid catalyzed ring expansion reaction of the *cis*-*N*-Boc aziridines. The results of further investigations are listed in Table 3.12, which include studies on the effect of Lewis acid, solvent, temperature and the ring expansion of 3-alkyl *N*-Boc substituted aziridine **95a**, which was also claimed to be stereospecific by Tomasini.[23a]

As the data listed in Table 3.12 indicate, non-stereospecific ring expansions were observed in all experiments except that in entry 4, where a complex mixture was formed. None of the conditions could exclusively generate either the *cis*- or *trans*- oxazolidinone. Different Lewis acids showed different *cis* / *trans* selectivities. For the C3-phenyl aziridine **95d**, *cis*-oxazolidinone **167d** is the major product when the reaction was catalyzed by $BF_3 \cdot Et_2O$, while the *trans*- oxazolidinone **168d** is the major product with $Cu(OTf)_2$ as catalyst, except for the case where acetonitrile was used as solvent (Table 3.12, entry 8). Polar coordinating solvents such as acetonitrile and tetrahydrofuran resulted in sluggish reactions (Table 3.12, entry 3 and 4). The ratio of *cis*- to *trans*-isomers could be increased to higher than 4 to 1 with complete conversion by using the less Lewis acidic reagent $B(OPh)_3$ (Table 3.12, entry 11), and complete conversion with a slightly higher ratio of the *cis*-oxazolidinone was observed when the reaction was run at 0 °C (Table 3.12, entry 2). Interestingly, it was found that the ring expansion reaction also works well in the presence of Brønsted acid, however, the *cis/trans* selectivity also varied with different acids (Table 3.12, entry 12 to 14).

Table 3.12 Ring expansion reaction of the *N*-Boc aziridine **95**[a]



95a: R = Cy
95d: R = Ph

167a: R = Cy
167d: R = Ph

168a: R = Cy
168d: R = Ph

entry	R	acid	solvent	yield **167** (%)[b]	ratio **167** : **168**[c]
1	Ph	$BF_3.Et_2O$	CH_2Cl_2	64	3 : 1
2[d]	Ph	$BF_3.Et_2O$	CH_2Cl_2	nd	4 : 1
3[e]	Ph	$BF_3.Et_2O$	CH_3CN	nd	**167d** is major
4	Ph	$BF_3.Et_2O$	THF	complex mixtures	
5	Ph	$BF_3.Et_2O$	anisole	nd	2 : 1
6	Ph	$BF_3.Et_2O$	benzene	nd	1 : 1
7	Ph	$Cu(OTf)_2$	CH_2Cl_2	40	0.6 : 1
8	Ph	$Cu(OTf)_2$	CH_3CN	nd	1.5 : 1
9	Ph	$Cu(OTf)_2$	benzene	nd	0.5 : 1
10	Ph	$Cu(OTf)_2$	CCl_4	nd	0.6 : 1
11	Ph	$B(OPh)_3$	CH_2Cl_2	nd	>4 : 1
12[f]	Ph	TFA	CH_2Cl_2	nd	10 : 1
13	Ph	TfOH	benzene	nd	0.7 : 1
14	Ph	8% H_2SO_4 in TFA	CH_2Cl_2	nd	3.5 : 1
15	Cy	$BF_3.Et_2O$	CH_2Cl_2	15	0.5 : 1
16[g]	Cy	$Cu(OTf)_2$	CH_2Cl_2	61	2 : 1

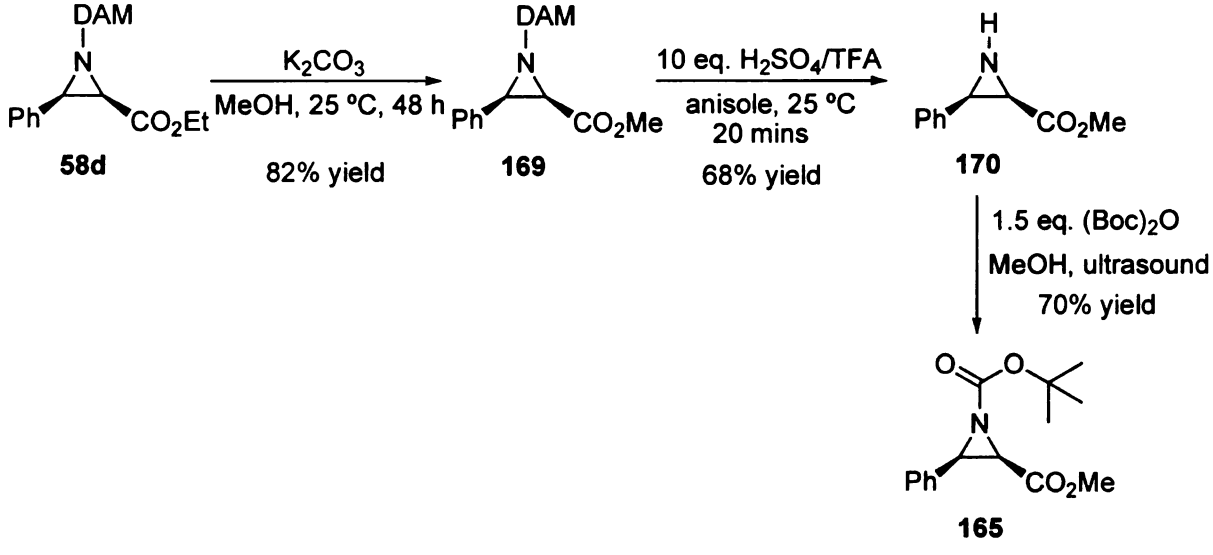
[a] Unless otherwise specified, the reaction was performed at 25 °C for 44 to 92 h. The loading of $Cu(OTf)_2$ was 0.1 equivalent, other catalysts loadings were all 0.5 equivalent. nd = not determined. [b] Isolated yield after silica gel chromatography. [c] The ratio was determined by comparing the methine protons in the oxazolidinones from the ^1H NMR spectrum of the crude reaction mixture. [d] Reaction was performed at 0 °C. [e] 25% conversion. [f] 50% conversion. [g] 40% conversion.

Although the ratio of *cis / trans* products could be increased to 10 : 1 by using trifluoroacetic acid, only 50% conversion was obtained (Table 3.12, entry 12). The ring expansion reaction of the C3- alkyl substituted aziridine **95a** was also not stereospecific (Table 3.12, entry 15 and 16). The *cis / trans* selectivities for the C3-alkyl aziridine **95a** were opposite to that of the C3- aryl aziridine **95d**, where the BF_3•Et_2O catalyzed reaction resulted in *trans*- oxazolidinone **168a** as the major product (Table 3.12, entry 15), and the $Cu(OTf)_2$ catalyzed reaction generated *cis*- isomer **167a** as the major product (Table 3.12, entry 16).

3.4.2 Study on the ring expansion of the aziridine 165

Our observations on the lack of stereospecificity of these ring expansion are quite different from what Tomasini reported, and since the *cis*-aziridines that they used are all methyl carboxylates,[23a] it was decided to prepare the corresponding methyl carboxylate **165** and test the ring expansion reaction before we can draw any definitive conclusions.

Scheme 3.24 Preparation of *N*-Boc methyl aziridinyl ester **165**

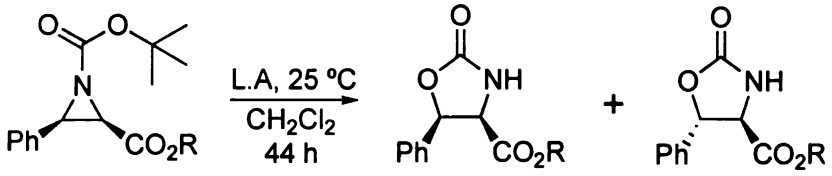


Compound **165** in Tomasini's report was prepared via the synthesis of a β-amino acid intermediate in at least 6 steps. Starting from the readily available aziridine **58d**.

The transesterification[81] in methanol was performed using K_2CO_3 as base,[81a] which resulted in complete conversion with 82% isolated yield of the methyl aziridinyl-ester **169** (Scheme 3.24). The unoptimized transformation from **169** to **165** was completed in two steps in 49% overall yield.

The methyl aziridinyl-carboxylate **165** was tested using the same Lewis acid catalyzed ring expansion conditions described above for **95**. Not surprisingly, the reaction occurred exclusively at the C3 position, but still resulted in a mixture of *cis*- and *trans*- isomers in ratios that were similar to those observed for the ethyl aziridinyl-2-carboxylate **95d** (Scheme 3.25).

Scheme 3.25 Ring expansion of *N*-Boc aziridinyl-2-carboxylates **165** and **95d**



95d R = Et
165 R = Me

167d R = Et
167e R = Me

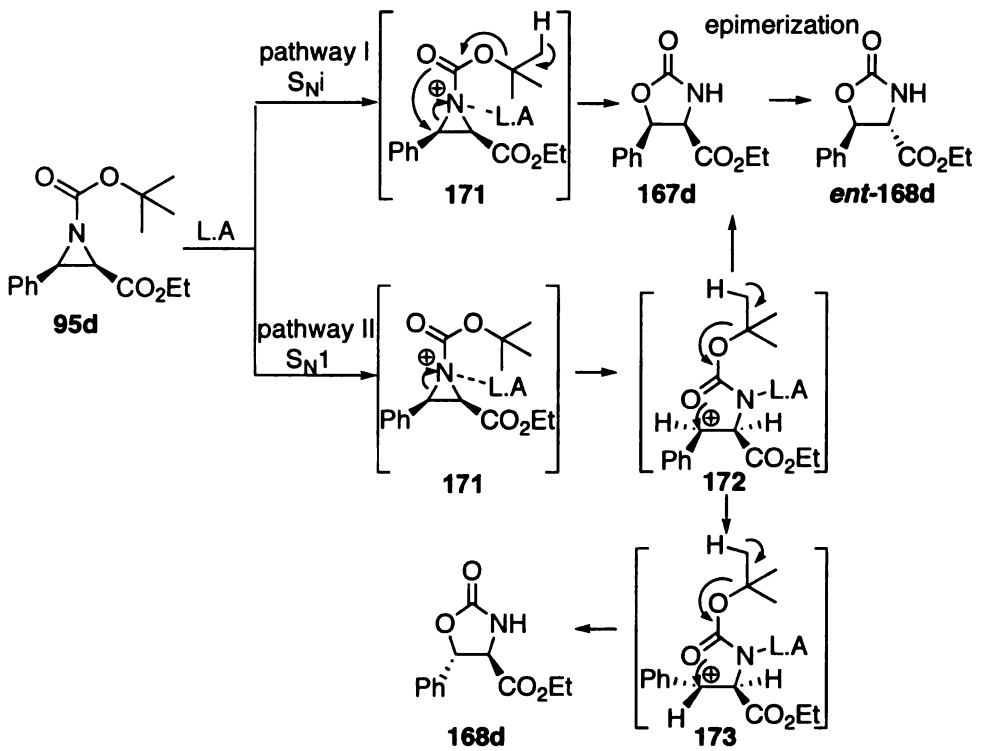
168d R = Et
168e R = Me

R	Lewis acid	% Yield **167+168**	Ratio **167** : **168**
Et	0.5 eq. BF_3•OEt_2	84	3.2 : 1
Et	0.1 eq. $Cu(OTf)_2$	99	0.7 : 1
Me	0.5 eq. BF_3•OEt_2	75	2.1 : 1
Me	0.1 eq. $Cu(OTf)_2$	85	0.5 : 1

3.4.3 Mechanistic study on the ring expansion reaction

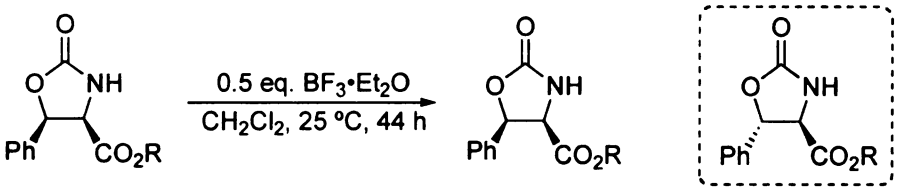
The fact that all of the ring expansion reactions gave a mixture of *cis*- and *trans*-oxazolidinones must be accounted for in any mechanistic proposal and two reasonable possibilities are shown in Scheme 3.26 for aziridine **95d**.

Scheme 3.26 Proposed mechanisms for the ring expansion of the aziridine **95d**



According to pathway I in Scheme 3.26, the ring expansion occurs with the retention of configuration at the benzylic carbon in the intermediate **171** via a concerted S_Ni mechanism to give the *cis*-substituted oxazolidinone **167d**, which is the mechanism Tomasini proposed.[23a] The formation of the *trans*- isomer *ent*-**168d** may be explained by the epimerization at the C2 carbon bearing the ester group under the reaction condition. Pathway II proceeds via a S_N1 mechanism involving the formation of an intermediate benzylic cation **172**, which can result in the *cis*- isomer **167d** through intramolecular nucleophilic attack by the oxygen of the carbonyl group. The intermediate **172** can also rotate along the C2-C3 bond to a steric less hindered intermediate **173**, which followed by the same intramolecular attack by the oxygen affords the *trans*- isomer **168d**. These two pathways can be distinguished since they would lead to different enantiomers of *trans*- isomer **168d**.

Scheme 3.27 Lewis acid mediated isomerization of the *cis*-oxazolidinone **167**



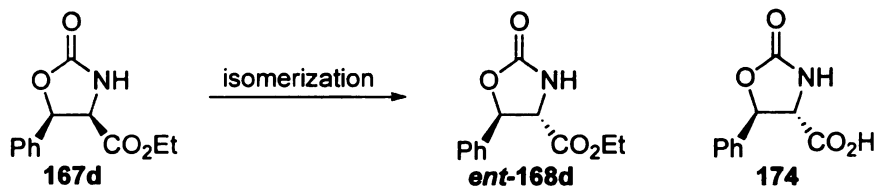
167d : R= Et
167e : R= Me

167d: R = Et
167e: R =Me
recovered

168d : R= Et
168e : R= Me
not observed

To test for the epimerization of **167**, *cis*-isomers of **167d** and **167e** were treated with Lewis acid under the same conditions developed for the ring expansion of aziridine described above, but the generation of either the *trans*-isomer **168d** or **168e** was not observed (Scheme 3.27), which excludes the possibility that the *trans*-oxazolidinone **168** was generated by epimerization of *cis*-oxazolidinone **167**. Thus the compound **168d** or **168e** must be generated during the ring expansion process.

Table 3.13 Base mediated isomerization of the *cis*-oxazolidinone **167d**



167d ***ent*-168d** **174**

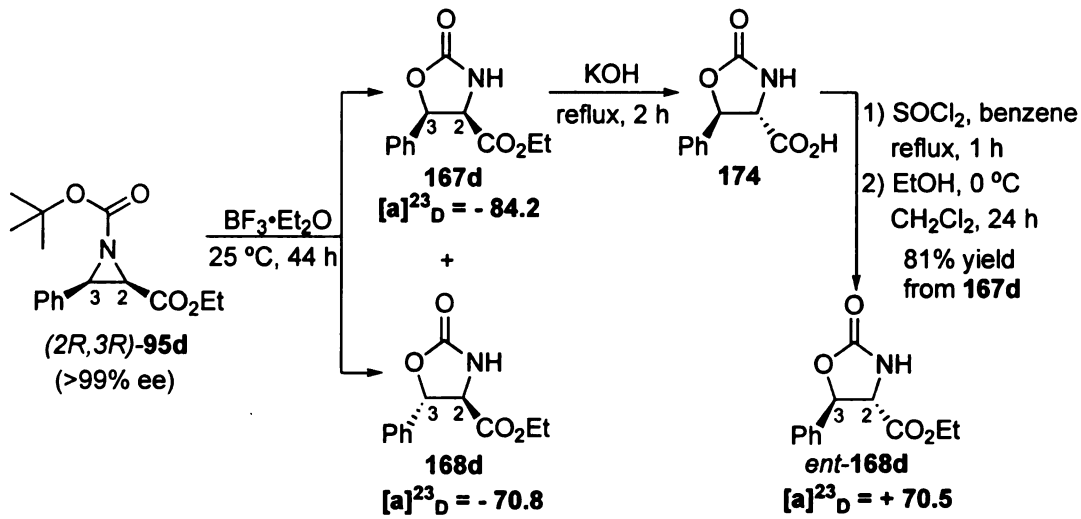
entry	condition	result
1	DBU, CH_2Cl_2, 25 °C, 3 d	**167d** : *ent*-**168d** = 1: 3
2	DBU, CH_2Cl_2, reflux, 1 h	**167d** : *ent*-**168d** = 1: 3
3	KOH, EtOH, reflux, 3 h	**174** exclusively
4	K_2CO_3, THF/EtOH, 25 °C, 1 h then reflux 1 h	**167d** : *ent*-**168d** : **174** = 1: 0.4 : 0.6
6	$CsCO_3$, EtOH, 25 °C, 24 h	complex mixtures

The isomerization of **167d** under the basic condition was also investigated, and the results are listed in Table 3.13. Amongst the bases that we tried, DBU[82a] gave the thermally more stable *trans*- product *ent*-**168d** as the major product, but incomplete

conversion was always observed. When KOH[82b,c] was used, only the acid **174** was isolated, which was assumed to be the hydrolyzed product of the ester *ent*-**168d**.

In order to get the complete isomerization from compounds **167d** to **168d**/*ent*-**168d**, it was decided to use the KOH for the isomerization, because the acid **174** could be converted to oxazolidinone *ent*-**168d** through a simple esterification process as shown in Scheme 3.28, in which the acid **174** was treated with thionylchloride followed by esterification with ethanol. In addition, the use of KOH as base leads to complete conversion and avoids contamination with *cis*-**167d**, which may be present with the use of other bases such as DBU.

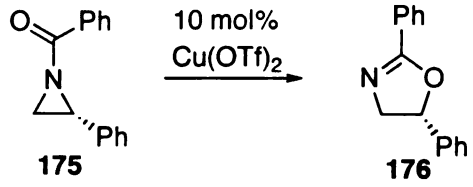
Scheme 3.28 Transformation from **167d** to *ent*-**168d**



The optically pure *(2R, 3R)-N*-Boc aziridine **95d** (> 99% ee) was used in the ring expansion reaction to determine the absolute stereochemistry of each oxazolidinones. As the value of the optical rotation of the three oxazolidinones indicated, the epimerization product **168d** is the enantiomer of the *trans*- **168d** that was originally isolated from the ring expansion reaction (+70.5 vs. –70.8). Thus, it can be concluded that the ring expansion of the aziridine **95d** proceeds mainly by an S_N1 mechanism and that the *trans*- isomer **168d** resulted from C2-C3 bond rotation (Scheme 3.26) from the

zwitterion **172** to give intermediate **173**.

Scheme 3.29 Lectka's ring expansion



175 **176**

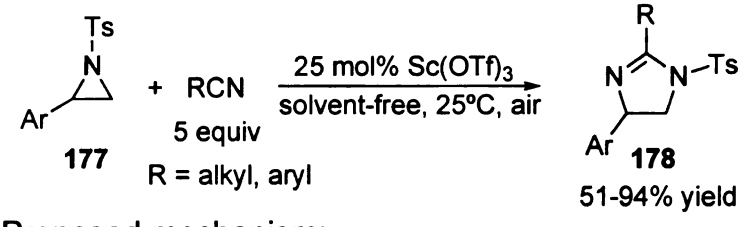
There is evidence in the literature to support both S_N1 and S_Ni mechanisms in the ring expansion of *N*-acyl aziridines.[23e] Lectka and coworkers have found that the ring expansion of the *N*-benzoyl aziridine **175** gives oxazolidine **176** with complete retention of the configuration and he proposed that this occurs via an S_N1 mechanism in which the carbocation undergoes closure faster than bond rotation (Scheme 3.29). The difference in the present case with the *cis*-aziridine **95d** may be attributed to the eclipsing interaction of the phenyl and ester groups in the zwitterion **172** (Scheme 3.26), which leads to bond rotation, and thus the selective formation of the *trans*- oxazolidinone is just a consequence of the fact that the intermediate zwitterion **173** is a more stable conformation. The results of the C3-alkyl aziridine **95a** which also gives a mixture of *cis* and *trans* isomers (Table 3.12, entry 15, 16) are also supported by this S_N1 mechanism, which involves the formation of the *trans*-oxazolidinone **168a** via a zwitterions that has a secondary carbocation.

3.4.4 Synthesis of imidazolines via [3+2] cycloaddition reaction of aziridines

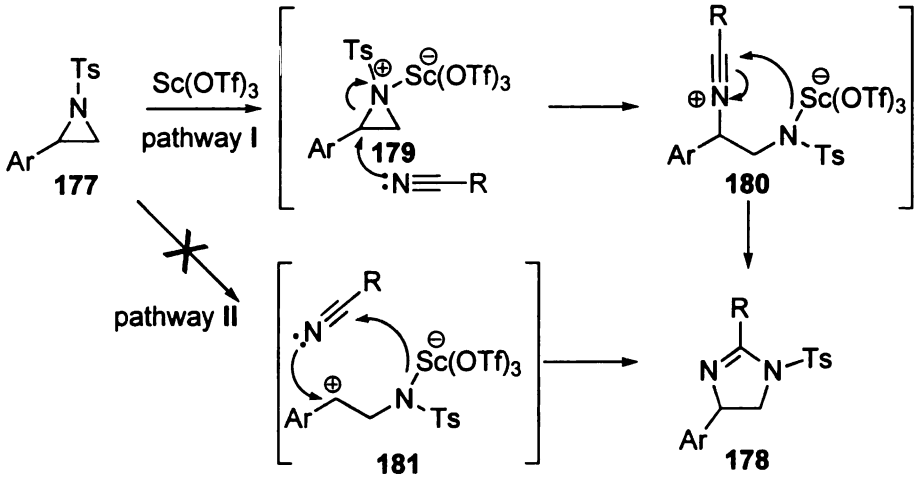
Imidazolines are useful in organic synthesis as synthetic intermediates, or as chiral auxiliaries in asymmetric synthesis,[83] however, the preparation of the stereo-defined imidazolines has been rarely reported and generally they are prepared from enantio-pure 1,2-diamines.[84] Recently, it was reported that aziridines could be used as masked 1,3-dipole in the Lewis acid catalyzed [3+2] cycloaddition reactions with dipolarophiles

such as nitriles, which will generate a five-membered nitrogen containing heterocycle (Scheme 3.30). Racemic imidazolines were obtained in moderate to high yields.[84,85] Several Lewis acids such as $Cu(OTf)_2$, $Sc(OTf)_3$ and $BF_3 \cdot Et_2O$ were found to be effective for this [3+2] cycloaddition. A proposed stepwise addition mechanism is shown in Scheme 3.30. The author claimed that pathway **II** involving the formation of the stabilized zwitterion **181** was unlikely, since *R*-(-)-**177** (> 90% ee) gave non-racemic product **178** ($[\alpha]^{20}$ –10.2, *c* 0.38).[85b] For the reactions reported up to date, only mono substituted aziridines or aziridines contained in a fused ring system were studied.

Scheme 3.30 [3+2] cycloaddition of the aziridine **177** with nitriles and the proposed mechanism



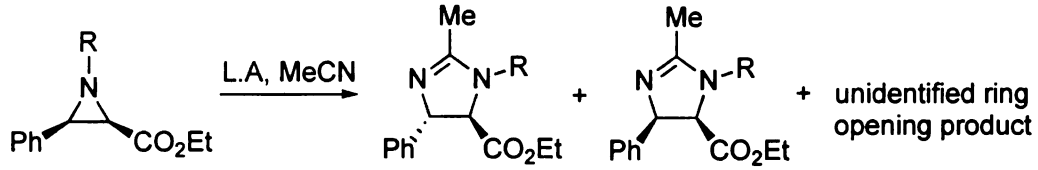
Proposed mechanism:



Our preliminary studies were carried out using di-substituted optically pure aziridines, from which it was envisioned that the optically pure C2, C4, C5 tri-substituted imidazolines could be synthesized via this [3+2] cycloaddition reaction with nitriles.

According to the proposed mechanism shown in Scheme 3.30, the 2,3-*cis*-disubstituted aziridines **36d** and **98d** (Table 3.14) may be expected to be attacked by the nitrile on the benzylic position to generate an intermediate similar to intermediate **180**, which upon the intramolecular ring closure by nitrogen will furnish the imidazoline synthesis.

Table 3.14 The imidazoline synthesis via a [3+2] cycloaddition of aziridines[a]



36d R = Bh, **98d** R = Ts

182a R = Bh, **182b** R = Ts

183a R = Bh, **183b** R = Ts

184

entry	R	Lewis acid	condition	ratio of **182/183**	result[b]
1	Bh	1 eq. $BF_3.Et_2O$	25°C, 48h.	2 : 1	30% conv. (**182a**, *J* = 4.0Hz)
2	Bh	1 eq. $Sc(OTf)_3$	65°C, 6h	0 : 1	**183a** : **184** = 1 : 0.5 (**183a**, *J*=7.2Hz)
3	Bh	1 eq. $Cu(OTf)_2$	65°C, 6h	nd	0 % conv.
4	Ts	1 eq. $BF_3.Et_2O$	25°C, 24h	1: 0.22	73% yield
5	Ts	0.3 eq. $Sc(OTf)_3$	25°C, 24h	4 : 1	45% conv.
6	Ts	1 eq. $Sc(OTf)_3$	25°C, 24h	1 : 0.26	89% yield
7	Ts	1 eq. $Cu(OTf)_2$	65°C, 3h	1 : 0.27	73% yield

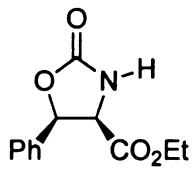
[a] MeCN was used as solvent. [b] The products **182** and **183** couldn't be separated by silica gel chromatography. The yield was the overall isolated yield of **182** and **183**.

As the data listed in Table 3.14 reveal, the [3+2] cycloaddition with acetonitrile took place even for the nonactivated aziridine **36d** to give a mixture of *cis*- and *trans*-imidazolines in favor of the *trans*- imidazoline **182** albeit with incomplete conversion. The *cis*- imidazoline and the *trans*- imidazoline were assigned according to the coupling constants of the vicinal ring protons and comparing them with those for the *cis*-

oxazolidinone **167d** and the *trans*-oxazolidinone **168d** (Figure 3.3). The *cis*- and the *trans*- isomers could not be separated by silica gel chromatography (Table 3.14, entry 1). No C2 regio isomer was observed.

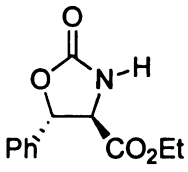
A stoichiometric amount of Lewis acid was required to obtain a complete conversion with aziridine **98d** (Table 3.14, entry 5 vs. entry 6). The facility of this [3 + 2] cycloaddition is very dependent on the different Lewis acid. With non-activated aziridine **36d**, the $Cu(OTf)_2$ catalyzed reaction did not work even at higher temperature (Table 3.14, entry 3), but the $Sc(OTf)_3$ catalyzed reaction resulted in an unidentified ring-opened product along with only one isomer of the imidazoline, which was assigned as the *cis*-imidazoline **183a** based on its coupling constant (Table 3.14, entry 2). Complete conversion was obtained at the room temperature for the activated *N*-tosyl aziridine **98d**, which gave the *trans*- and *cis*-products that were isolated as a 4 : 1 mixture in 73% overall yield (Table 3.14, entry 4). The two isomers could be separated by HPLC. $Cu(OTf)_2$ could effect complete conversion of **98d** but only if the temperature was increased to 65 °C (Table 3.14, entry 7).

Figure 3.3 Coupling constants of oxazolidinones and imidazolines



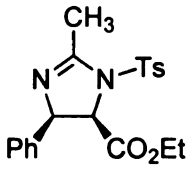
167d

J = 9.1Hz



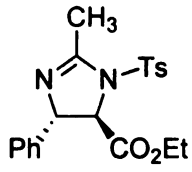
168d

J = 5.0Hz



183b

J = 11.0Hz



182b

J = 5.6Hz

This Lewis acid catalyzed [3+2] cycloaddition could also be applied to other nitriles and aziridines as shown in Scheme 3.31. Isobutyronitrile afforded a 94% isolated yield of a 2 : 1 mixture of imidazolines **182c** and **183c** in favor of the thermodynamically more stable *trans*-imidazoline **182c**. The enantio pure tri-substituted *(2R, 3R)-N*-tosyl aziridine **115c** worked even better than the di-substituted aziridines, 100% overall yield was

obtained for the two separated isomers. The regio chemistry of the products **182d** and **183d** were determined to be C2 ring opening isomers based on the corresponding NOE studies (Figure 3.4). The isolated *cis*- imidazoline **183d** was a colorless crystal and its relative stereochemistry and its regiochemistry was determined by X-ray analysis as shown in Figure 3.5. For all the reactions that we tested so far, none of the C2-ring opened regio-isomer was observed.

Scheme 3.31 Preparation of other imidazolines

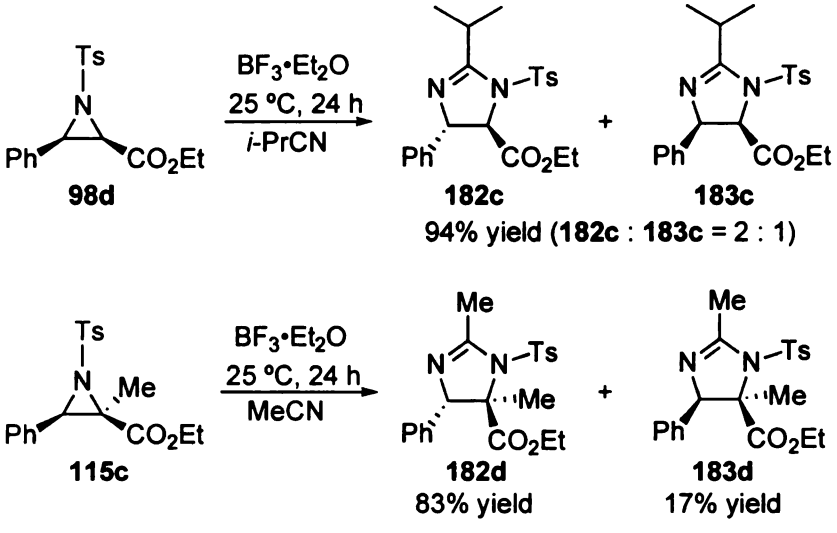


Figure 3.4 NOE studies of compounds **182d** and **183d**

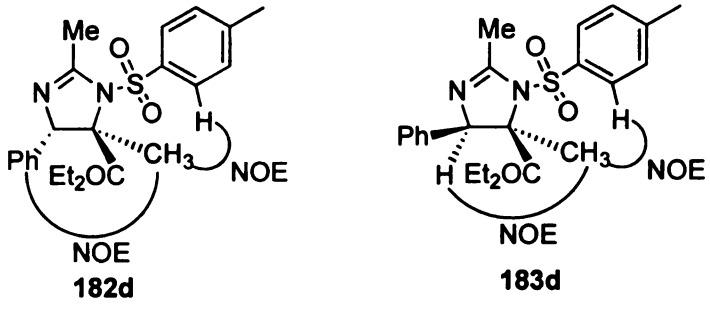
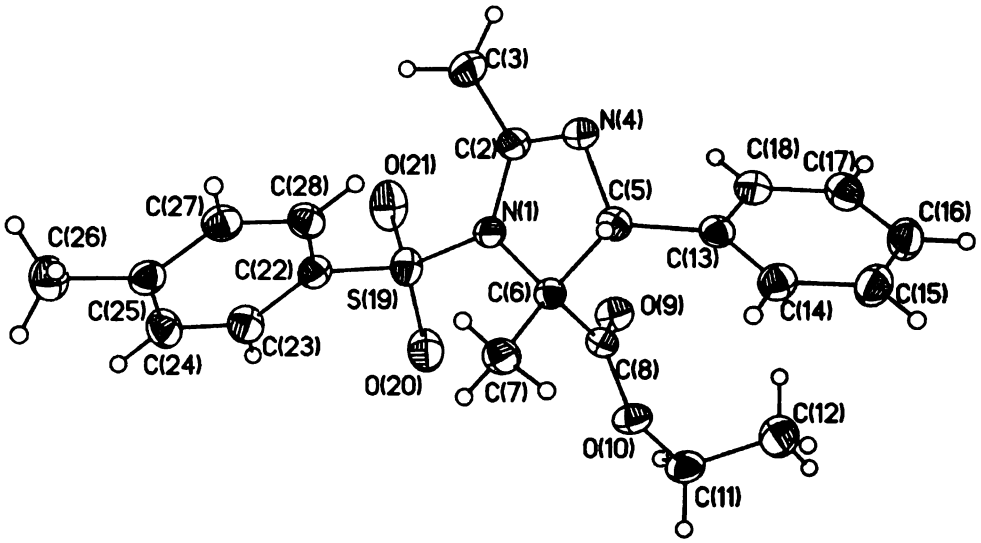
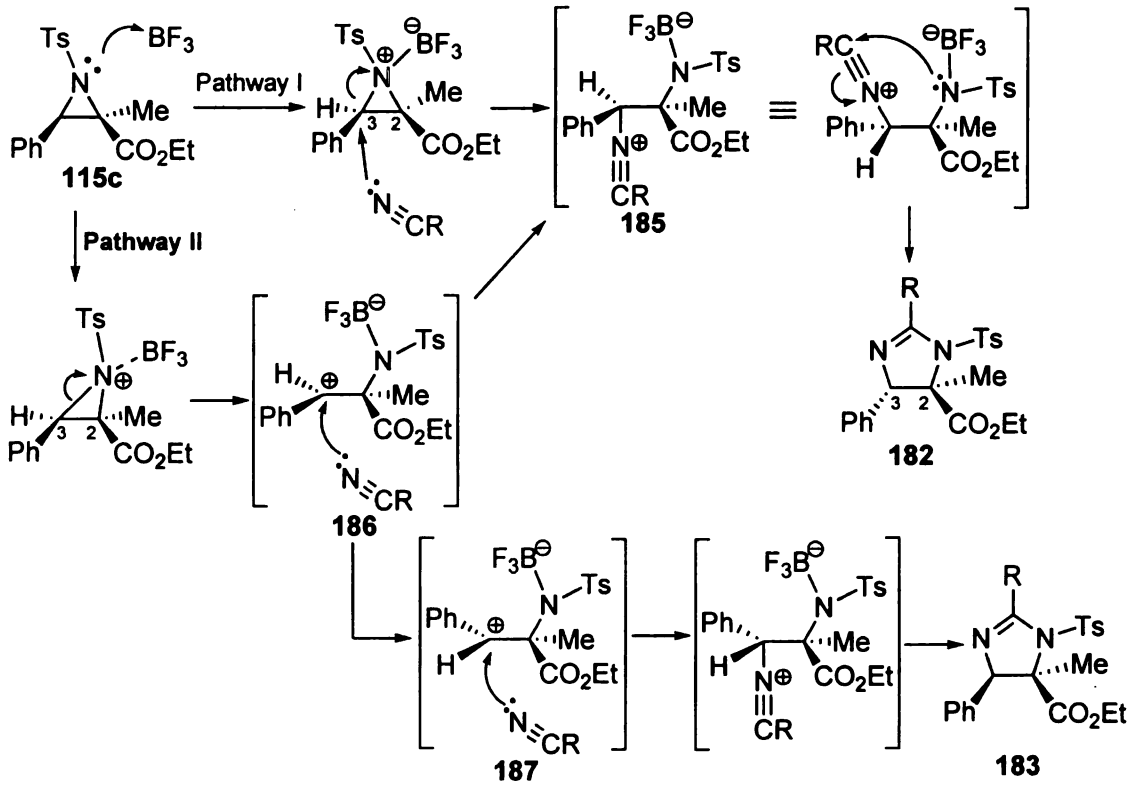


Figure 3.5 The X-ray structure of **183d**



Scheme 3.32 Proposed mechanism for the formation of *cis*- and *trans*- imidazolines

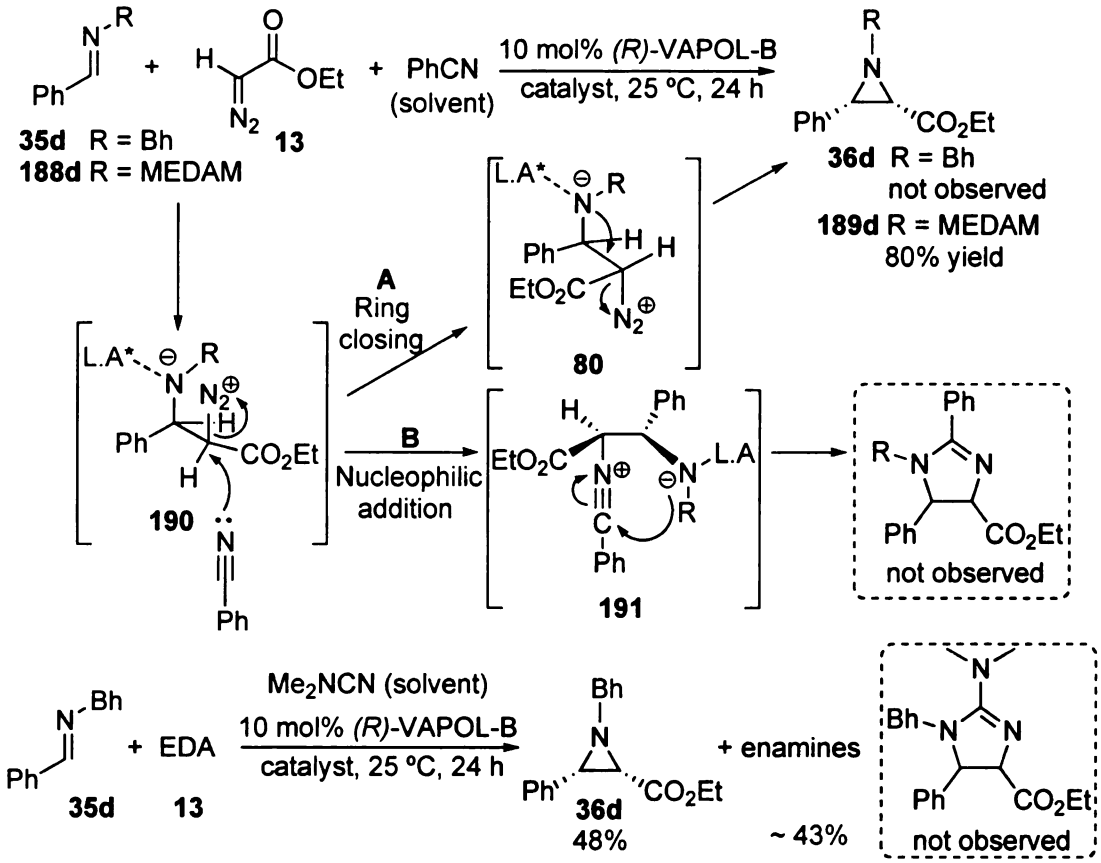


To explain the formation of both *trans*- and the *cis*- imidazolines in this reaction, we proposed the mechanism shown in Scheme 3.32. Pathway II involves the formation of

zwitterion **186** and can explain the observation of the *cis*-imidazoline **183** through the intermediate that is formed via the nucleophilic addition of the nitrile to the zwitterion **187**, which results from rotation about the C2-C3 bond in zwitterion **186**. Pathway I can only generate the *trans*-imidazoline **182** via the intermediate **185**, which can afford the product **182** through a ring closing process, it can be generated from either pathway I or pathway II. Since a mixture of *cis* and *trans* products are always observed from these cycloadditions, it's clear that the pathway II must be involved to some extend although it is not clear if this is the exclusive pathway.

Considering the stepwise mechanism of this imidazoline formation (Scheme 3.32), we became curious about the possibility for a one-pot synthesis of imidazoline as illustrated in Scheme 3.33. In the proposed aziridination mechanism (Scheme 2.11), the VAPOL/VANOL-borate catalyzed stereoselective nucleophilic addition of EDA **13** to the imine generates intermediate **190** first, which can afford an aziridine via a C-C bond rotation and followed by intramolecular ring closure. The same intermediate **190** could also possibly suffer an intermolecular attack by a nucleophile to generate intermediate **191** that could result in imidazoline formation. Although the intramolecular process would be expected to be much faster than the intermolecular process, if the nucleophile is used as solvent, it may be possible for the intermolecular nucleophilic addition (pathway **B**) to overcome the intramolecular aziridine ring formation (pathway **A**). As the results in Scheme 3.31 shown, the ring closure process **A** was much more facile than the intermolecular nucleophilic addition and the only isolable product was aziridine **189d**. No imidazolines were observed, even when the electron-rich *N,N'*-dimethylcyanoamine was used as solvent. The imine **188d** was also tested since it is more reactive than imine **35d** in the catalytic AZ reaction, which will be discussed in the next chapter.

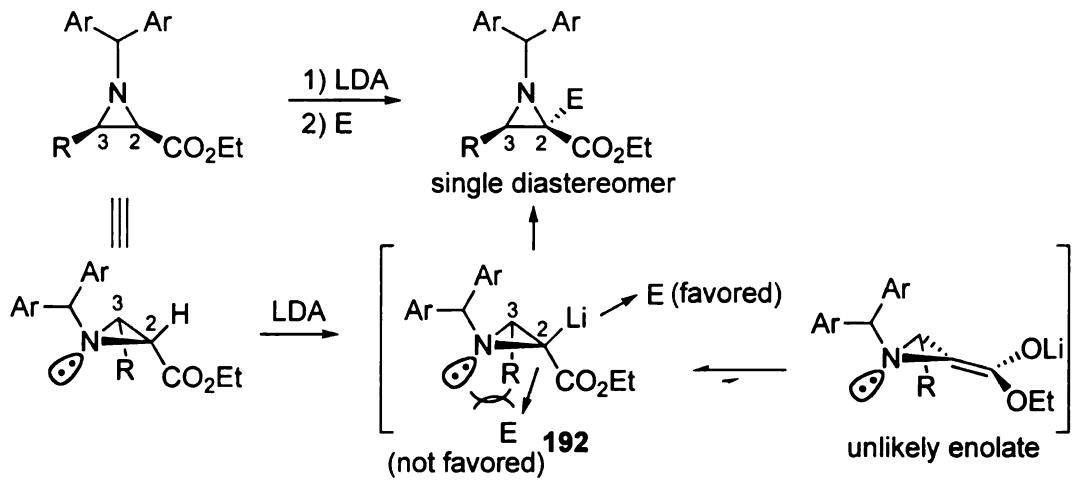
Scheme 3.33 Attempted imidazoline formation starting from imines



3.5. Diastereoselective aldol reaction via aziridine enolates

As was briefly mentioned in the section 3.1.4, the alkylation of *cis*-aziridinyl-2-carboxylates occurs in good to excellent yield and results in the exclusive formation of a tri-substituted aziridine as a single diastereomer with complete retention of the stereochemistry at the C2 position (Scheme 3.34).[26] This alkylation reaction has been successfully applied in the efficient synthesis of the leukointegrin LFA-1 antagonist BIRT-377 **43** where this alkylation step was employed for the introduction of the tetrasubstituted α-amino acid unit (Scheme 1.15). The stereochemical retention of this alkylation reaction was found to be general for many other *cis*-aziridines as long as they have a bulky *N*-benzhydryl or benzhydryl derived groups (Scheme 2.16 and Scheme 3.5). The rationale for the retention of stereochemistry is illustrated in Scheme 3.34.

Scheme 3.34 Rationale for the retention in the C2-alkylation reaction of aziridines

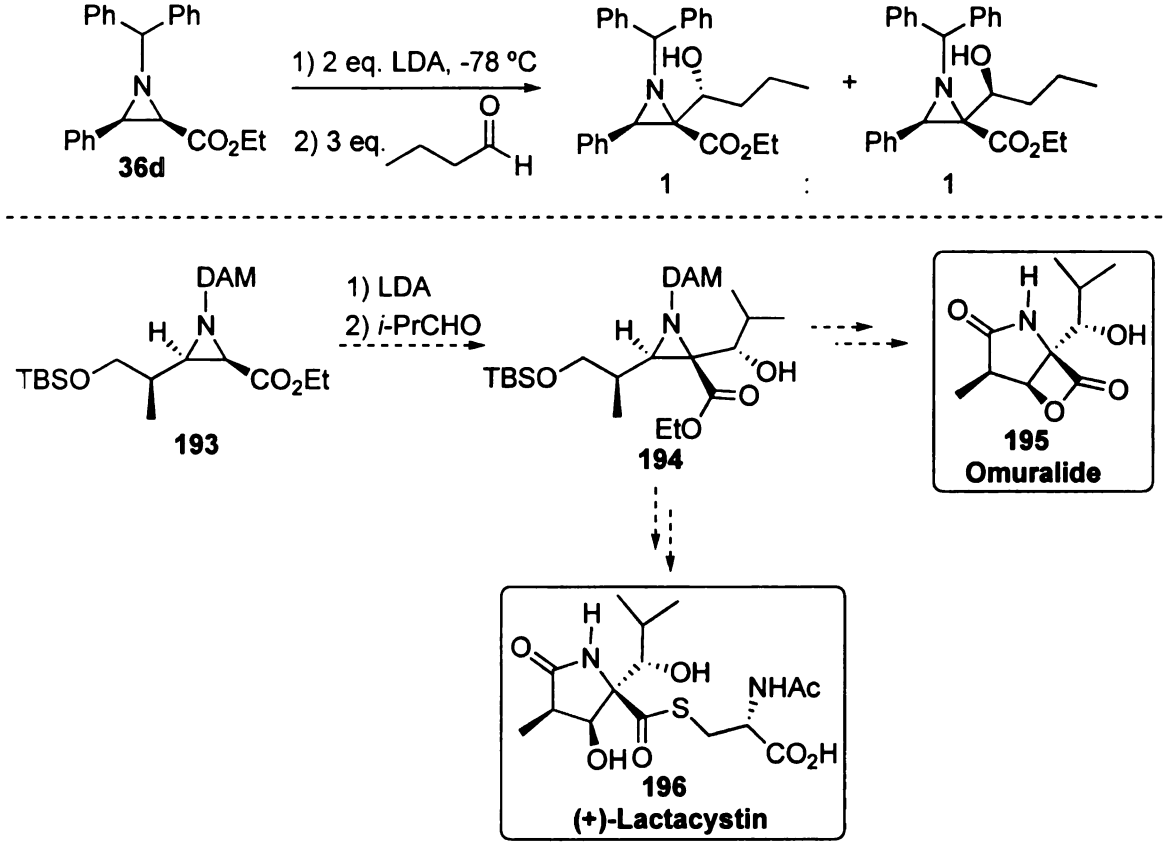


The evidence suggests that the C2- stereo retention is the result of a configurationally stable pyramidalized enolate **192** that reacts with the electrophile with retention of configuration,[86,26] The O-enolate that may give rise to the inversion product is thought to be unfavorable due to the strain of the planar sp^2 carbon on the three-membered ring structure (Scheme 3.34). The experimental results showed that the stereochemistry is electrophile dependant. The R group in enolate **192** is expected to strongly disfavor alkylation with inversion by sterically blocking the approach of the electrophile from the rear side *syn*- to the R group. This rationale is consistent with the observation that all *cis*-aziridines give products with exclusive retention of configuration. It thus can be imagined that a smaller electrophile such as H^+ would be less selective in its approach to the enolate **192** and would give a greater proportion of the inversion product than for the MeI.

In the study of this alkylation reaction of the *N*-Bh aziridine **36**, Dr. Patwardhan found that aldehyde could also serve as an efficient electrophile. Butyraldehyde was tested as electrophile and was found to give a 1 : 1 mixture of diasteromers as shown in Scheme 3.35. Encouraged by this result, an optimization of this aldol reaction via the enolate **192**

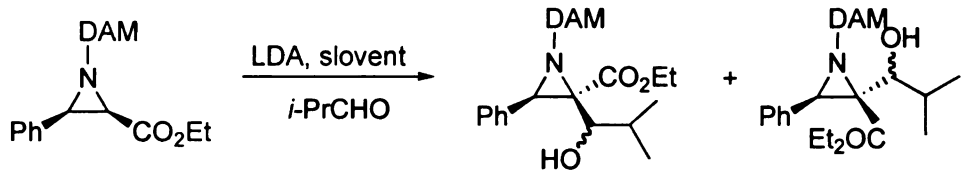
was carried out with hopes to improve the diastereoselectivity, and if successful, this aldol reaction would be one of the key steps in our proposed total synthesis of Omuralide **195** or Lactacystin **196**[87] (Scheme 3.35). The common intermediate **194** is envisioned to be synthesized from the aziridine **193** via an aldol reaction with isobutyraldehyde that occurs with retention.

Scheme 3.35 The previous aldol reaction and the synthetic proposal



The *N*-DAM aziridine **58d** was selected for the optimization of the aldol reaction conditions since the synthesis of Lactacystin will require a removable *N*-protecting group and since *N*-DAM aziridines give higher yields in the alkylation reaction than *N*-Bh aziridines (Scheme 2.18). The results of this optimization study are listed in Table 3.15.

Table 3.15 Optimization of the aldol reaction of the aziridine **58d**[a]



58d **197a/198a** **199a/200a**

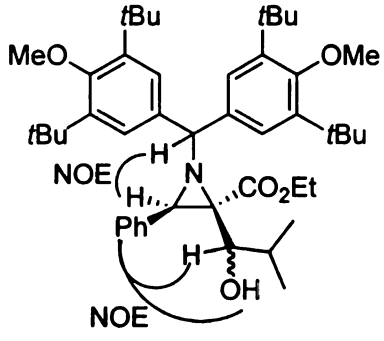
entry	LDA	Additive[b]	condition	conv.	ratio (**197a**:**198a**:**199a**:**200a**)[c]
1	2	none	25 °C	100%	1 : 0.8 : nd : nd
2[d]	2	none	-78°C 4h	100%	3 : 2 : 1.7 : 1
3	2	1 eq. $ZnCl_2$	25 °C 1h	50%	5 : 1 : 5 : 1
4	2	2 eq. $ZnCl_2$	25 °C 14h	40%	5 : 4 : 6 : 1
5[e]	2	2 eq. $ZnCl_2$	25 °C 14h	90%	10 : 2 : 5 : 1
6	2	2 eq. $Zn(OTf)_2$	25 °C 14h	90%	5 : 2 : 2.5 : 1
7	2	2 eq. ZnI_2	25 °C 14h	100%	5: 1.5 : 2.5 : 1
8	4	4 eq. $ZnCl_2$	25 °C 14h	90%	10 : 2 : 3 : 1
9[d]	4	2 eq. $ZnCl_2$	-78 °C 4h	0%	nd
10[f]	6	2 eq. $ZnCl_2$	25°C 14h	50%	1 : 6 : 2 : nd
11[g]	6	2 eq. $ZnCl_2$	25°C 14h	50%	20 : 6 : 6 : 1
12[h]	4	2 eq. $ZnCl_2$	25°C 14h	50%	One major product
13[i]	2	3 eq. AgOAc	-78°C 1h	100%	complex mixtures
14	2	1 eq. $MgCl_2$	-78°C 3h	100%	2.5 : 2 : 1 : 1
15[j]	2	1 eq. $MgBr_2$	–15 °C 3h	0%	nd

[a] Unless otherwise specified, THF was used as solvent. LDA was generated at –78 °C, and the aziridine was transferred to the LDA solution at that temperature and kept for 1h before warmed up to 25 °C. [b] Unless otherwise specified, the additive was used as the solid. [c] Determined by integration of the methine proton of the DAM group in the ^1H NMR spectrum of the crude products. [d] The reaction was quenched at –78 °C. [e] Dried $ZnCl_2$ was used. [f] The $ZnCl_2$ was in THF solution and mixed with the aziridine solution before it was transferred to LDA. [g] The $ZnCl_2$ was in THF solution and added to LDA before the transfer of the aziridine solution. [h] D_2O was

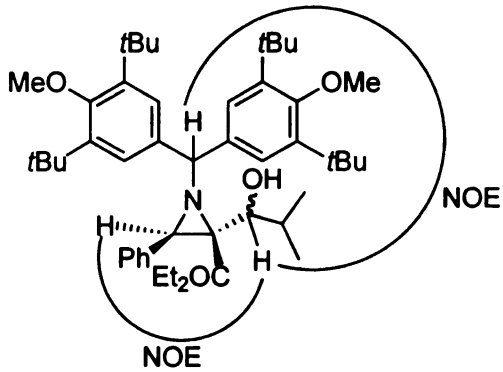
used as the electrophile. [i] 2 equiv KO*t*-Bu was used. [j] The $MgBr_2$ was generated *in situ* from Mg and 1,2-dibromoethane.

To our surprise, unlike all the other results obtained from the alkylation of aziridines using alkyl halides as the electrophile, which give a single diastereomeric product, as the results shown in Table 3.15, the reaction of the enolate of **58d** with isobutyraldehyde gave four diastereomers of the aldol adducts. Since more than two diastereomers are observed, they must include two adducts that result from inversion at C2 and two that result from retention. According to the conclusion deduced from the mechanism shown in Scheme 3.34, the observation of the C2- inversion products should only be possible when the electrophile is small. Repeating the previously reported reaction with butyraldehyde shown in Scheme 3.34 resulted in a mixture of at least three diastereomeric aldol adducts.

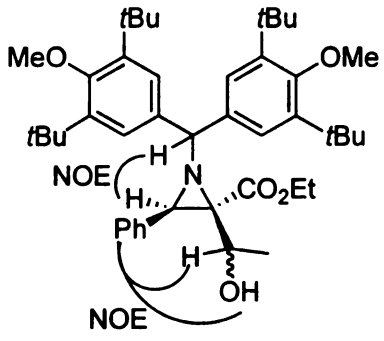
Figure 3.6 NOE studies of the aldol products from *N*-BUDAM aziridine **113d**



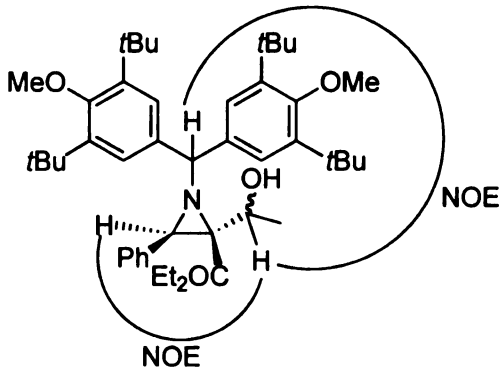
197b/198b



199b/200b

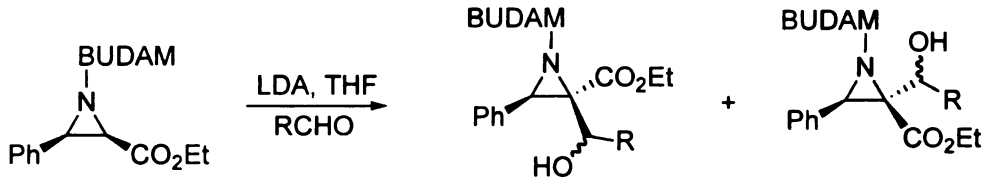


197c/198c



199c/200c

Table 3.16 Aldol reaction of the aziridine **113d**[a]



113d

197b/198b: R = *i*-Pr
197c/198c: R = Me

199b/200b: R = *i*-Pr
199c/200c: R = Me

entry	LDA	R	additive	condition	conv.	ratio (**197**:**198**:**199**:**200**)[b]
1	2	*i*-Pr	none	-78 °C 4h	100%	1: 0.7 : 0.5 : 1
2	2	*i*-Pr	1 eq. $ZnCl_2$	25 °C 3h	0%	nd
3	6	*i*-Pr	2 eq. $ZnCl_2$	25 °C 14h	30%	1: 0.5 : 0.4 : 2.5
4	2	*i*-Pr	1 eq. $MgCl_2$	-78 °C 3h	100%	1: 0.15 : 0.15 : 1
5	2	*i*-Pr	1 eq. $TiCl_4$[c]	-78°C 3h	100%	complex mixture
6	2	Me	none	-78°C 3h	100%	1: nd : 0.3 : 1
7	2	Me	1 eq. $ZnCl_2$[d]	-78°C 3h	20%	nd

[a] Unless otherwise specified, THF was used as solvent. LDA was generated at –78 °C, and the aziridine was transferred at that temperature and kept for 1h before warming up to 25 °C. [b] Determined by integration of the methine proton of the BUDAM group in the ^{1}H NMR spectrum of the crude products. [c] 1 M Solution in toluene. [d] Prepared as a THF solution.

The separation of the four diastereomers was difficult and none of the four isomers could be obtained in completely pure form. The inversion products **197a/198a** and the retention products **199a/200a** were differentiated by comparing the ^{1}H NMR spectra of the partially separated products with that of the products obtained from the aldol reaction of the *N*-BUDAM aziridine **113d** and isobutyraldehyde (Table 3.16, entry 1), where the four diastereomers were isolated. At this point, it is still not possible to assign the absolute stereochemistry of diastereomers **197** and **198** or **199** and **200**, but the retention and inversion diastereomers were assigned by the NOE study (Figure 3.6).

Attempts to improve the selectivity between the C2- retention and the C2- inversion

products or between each of the diastereomers in either the retention or inversion pairs were not promising. Although it was found that the selectivity could be increased by the addition of additives such as $ZnCl_2$, or ZnI_2, this was accompanied by incomplete conversion. In the absence of the additive, the reaction always gave complete conversion even at –78 °C to afford the inversion products and retention products in a ratio of 2 : 1 (Table 3.15, entry 2), In the presence of $ZnCl_2$, the ratio could be increased slightly to 4 : 1 (Table 3.15, entry 8 and 11), but the reaction suffered from incomplete conversion in all cases. The less Lewis acidic species ZnI_2 provided complete conversion and similar ratios of inversion and retention products, but slightly different ratios of the diastereomers of the inversion products (Table 3.15, entry 7). Other additives such as $MgCl_2$, $MgBr_2$, AgOAc were found to be either not effective or completely stop the reaction (Table 3.15, entry 13 to 15).

The aldol reaction of the more bulky *N*-BUDAM aziridine **113d** also afforded four diastereomers as shown in Table 3.16. These were easier to separate than the aldol products generated from the *N*-DAM aziridine **58d** but still difficult to fully separate. The products were not obtained in pure enough form to conclusively allow the structure determination and the absolute stereochemistry. The reactivity and the synthesis of the *N*-BUDAM aziridine **113d** will be discussed in detail in the next chapter. The effects of additives were similar to those for the reaction of the *N*-DAM aziridine **58d**.

3.6 Conclusion

The AZ reaction can be used effectively in the preparation of optically pure α-amino esters and β-amino esters via regio- selective ring opening reactions of activated aziridines. The activation of *N*-H aziridines was examined with different activating groups, and proved to be highly efficient. For the reactions tested, it was found that the nucleophilic ring opening of *cis*-di-substituted or tri-substituted aziridinyl-2-carboxylates

always takes place anti to nitrogen and the reactivity varies greatly depending on type of the nucleophile and the activating group on the aziridine.

Aryl and alkyl substituted *cis*- aziridines showed different reactivities toward the SmI_2 mediated radical ring opening reaction, and this difference was largest when the activating group is not a strong electron withdrawing group. The Lewis acid mediated intramolecular ring expansion reaction was demonstrated to at least partially involve S_N1 mechanism by the determination of the absolute stereochemistry of *cis*- and *trans*-oxazolidinone products. Activated aziridinyl-2-carboxylates can react with a nitrile in a [3 + 2] cycloaddition reaction catalyzed by a Lewis acid and this proceeds through a nucleophilic ring opening followed by an intramolecular ring closing process, to form a 2, 4, 5-tri-substituted optically pure imidazoline. A preliminary study revealed that this reaction is regio selective and favors the *trans*- imidazoline product as the major product.

Finally, the aldol reaction of an enolate of aziridinyl-2-carboxylate was found to be unique from all other related alkylations of the same enolates. Further investigation of this reaction may be most productive with *N*-BUDAM aziridines and simple aldehydes since better separation of the product may be possible and less diastereomers may be generated.

CHAPTER FOUR

FURTHER INVESTIGATION FOR CHIRAL AZIRIDINE FORMATION AND ITS APPLICATIONS

4.1 Introduction

In this chapter, the discussion on the study of the catalytic AZ reaction will be continued, and the focus will be on the optimization of a one-pot protocol and on other aspects of the AZ reaction. Based on the results and observations that had accumulated for the aziridination of the *N*-Bh imines **35** and the *N*-DAM imines **68** with the VAPOL and VANOL derived catalysts, it was clear that the quality of the imine was crucial for obtaining good yields and excellent enantioselectivities. These imines tend to decompose via hydrolysis in the presence of a catalytic amount of acid, with the result that significantly diminished asymmetric induction was observed in the aziridination reaction. Although the quality of the purified imines can remain high for several months if stored in a well-sealed desiccator, there are some imines that can not be purified by either crystallization or distillation, especially primary alkyl substituted imines, which are more prone to decomposition.

It was envisioned that a one-pot imine formation-AZ reaction starting directly from amines and aldehydes might be possible, in which the imines would be generated *in situ*, thus avoiding the decomposition for those unstable imines. Using the same VANOL/VAPOL-borate catalytic system, it was hoped that the aziridination of the *in situ* generated imine and ethyl diazoacetate would still produce the same high yields and enantioselectivities that are obtained from the aziridination of the purified imine. The major concerns for this one-pot protocol are the possible adverse effects on the yield and asymmetric induction that may be caused by the presence of the excess of amine,

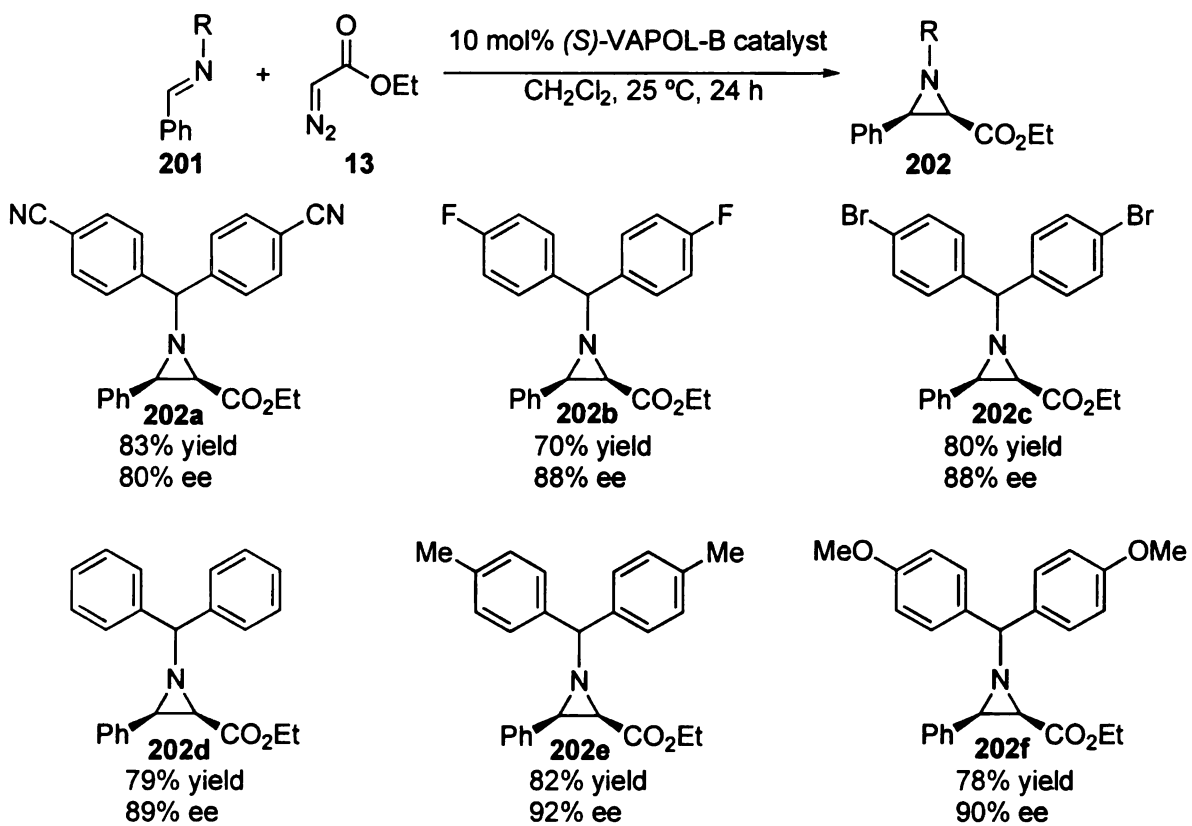
the aldehyde or the presence of the dehydrating reagent that would be required in the imine formation step. The idea for this one-pot procedure was inspired by the discovery of a highly reactive catalytic AZ reaction system.

4.2 Catalytic AZ reaction with other *N*-substituted imines

4.2.1 The discovery of a highly selective AZ reaction system

In an earlier mechanistic study directed by probing the effects of different protecting groups for the imine in the aziridination reaction,[37a] a former group member, Dr. Yu Zhang, found that by tuning the substitution of the biaryl moiety of the benzhydryl group, dramatic changes could be observed for yields, asymmetric inductions and rates of the reaction (Scheme 4.1).

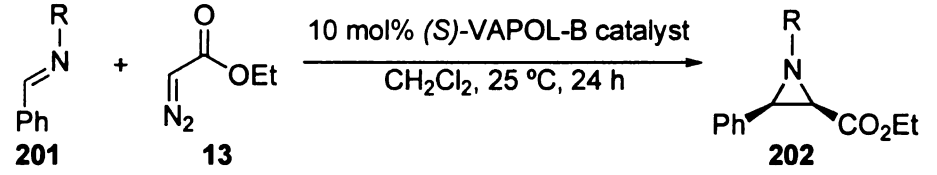
Scheme 4.1 Electronic effects of imines bearing benzhydryl derivatives



Electronic effects were examined by varying the *para*-substitutents on the phenyl

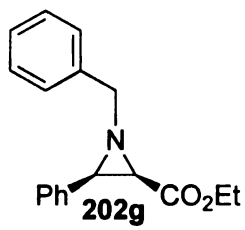
rings of the benzhydryl group (Scheme 4.1). The data suggested a slight preference for electron donating groups (*para*-methyl in **202e** and *para*-methoxy in **202f**) against electron withdrawing groups (*para*-cyano in **202a** and *para*-fluoro in **202b**) with a difference of up to 10% ee.

Scheme 4.2 Steric effects of imines bearing benzhydryl derivatives

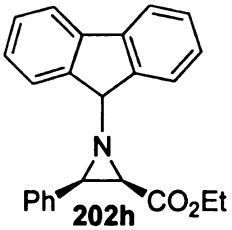


201l: R = *bis*-(2,6-di-*tert*-butyl-4-methoxyphenyl)methine

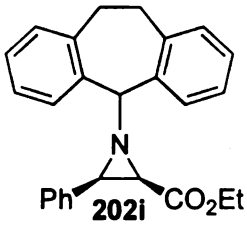
113d: R = *bis*-(2,6-di-*tert*-butyl-4-methoxyphenyl)methine



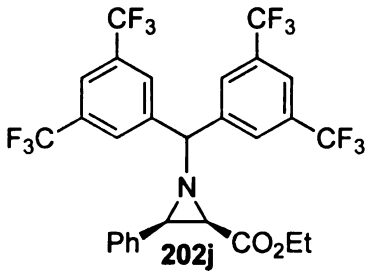
51% yield
43% ee



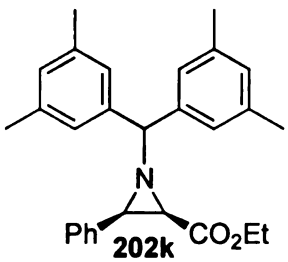
64% yield
80% ee



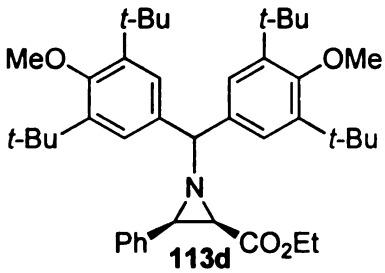
75% yield
95% ee



48% yield
37% ee



89% yield
95% ee

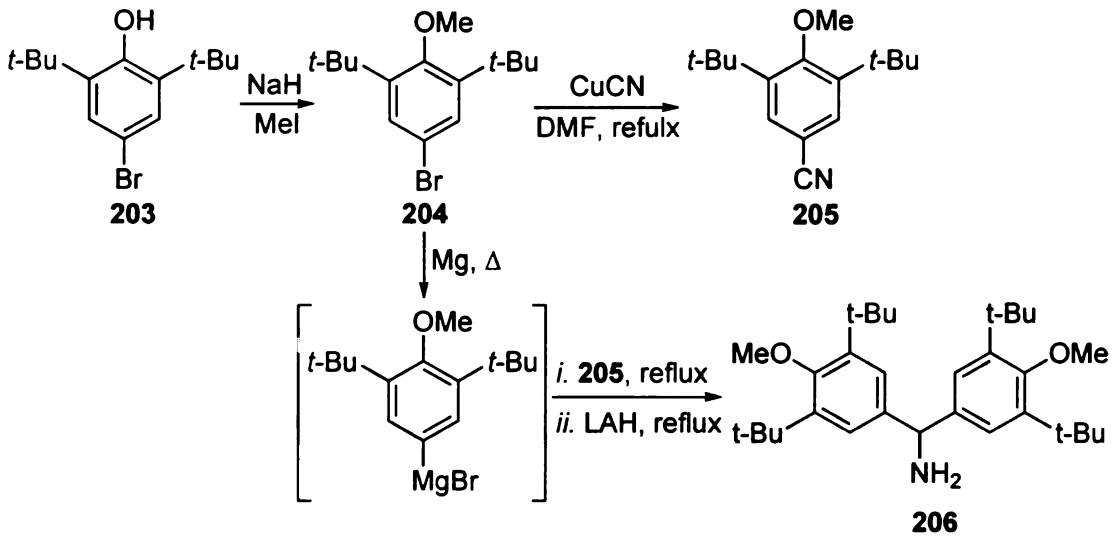


95% yield
99% ee

In addition, a study of the steric effects of substituted benzhydryl imines were under taken by Dr Yu Zhang and some of the results are presented in Scheme 4.2.[37a] It was found that maintaining the proper angles between the two phenyl groups was crucial for high asymmetric inductions. The AZ reaction of the *N*-benzyl imine **201g** gave only 43% ee of the corresponding aziridine **202g**, while the reaction of the *N*-dibenzosulbenonyl imine **201i**, which can maintain the geometry of the benzhydryl protecting group, gave

95% ee of the corresponding aziridine **202i**. Encouraged by the unexpected and significant increase in the yield and enantioselectivity obtained for the hindered bis(3,5-dimethylphenyl)methyl aziridine **202k**, the design for the *N*-protecting groups was reconsidered. The need for a bulky *N*-protecting group has thus emerged from the results of the aziridine **202k**. Combining the positive electronic effect of the *para*-methoxy groups in **202f** and the positive steric effect of the 3,5-dimethyl groups in **202k**, the synthesis of imine **201l** was undertaken. The corresponding 3,3',5,5'-tetra-*tert*-butyl-4,4'-dimethoxybenzhydryl amine (*N*-BUDAM amine) **206** for this imine was prepared in three steps from the commercially available 4-bromo-2,6-di-*tert*-butylphenol **203** (Scheme 4.3).

Scheme 4.3 Synthesis of BUDAM amine **206**



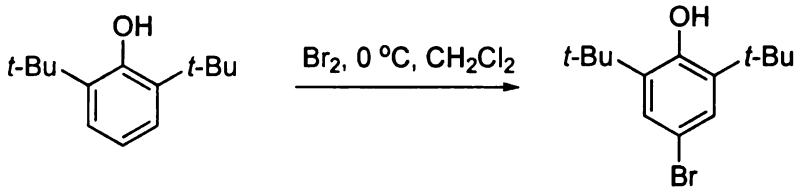
The amine **206** was converted into the *N*-BUDAM benzaldimine **201l**, which was then tested in the catalytic AZ reaction. With 10 mol% of either the VAPOL or VANOL derived catalyst, essentially optically pure (≥ 99% ee) *cis*-aziridine **113d** was isolated in 95% yield in either CH_2Cl_2 or in CCl_4, and these excellent results could also be obtained with less than 2 mol% catalyst loading. To evaluate the substrate scope with different substituted *N*-BUDAM imines in the catalytic AZ reaction, an efficient and affordable

large-scale synthesis of the *N*-BUDAM amine **206** was needed.

4.2.2 Large-scale synthesis of the *N*-BUDAM amine 206

The detailed large-scale procedure was based on the previous small scale synthesis developed by Dr. Zhang as shown in Scheme 4.3.[37d] Since the 4-bromo-3,5-di-*tert*-butylphenol **203** ($70 / 100 g from Aldrich) could be prepared from the inexpensive 2,6-di-*tert*-butylphenol **207** ($29 / 1 kg from Aldrich) via a bromination reaction reported by Yamamoto,[88] it was decided to start the large-scale synthesis from **207** to make the entire protocol more effective (Table 4.1).

Table 4.1 Bromination of 1,6-di-*tert*-butylphenol **207**[a]



207 **203**

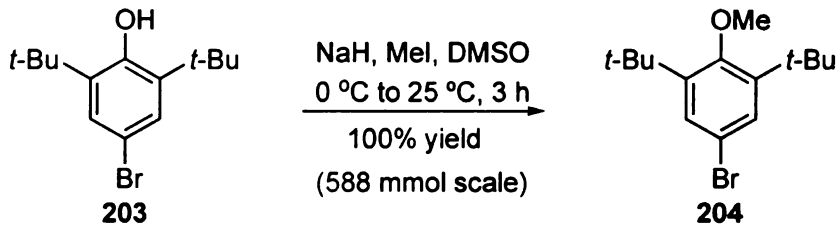
entry	**207** (mmol)	Br_2 (mmol)	time (h)		yield (%)[b]
			addition of Br_2	after addition	
1	50	60	1	0.4	65[c]
2	500	600	1.5	0.8	52 (1st crop)
3	1000	1200	1.2	0.7	60 (1st crop)
4	1000	1050	1.2	0.5	78 (1st crop) + 7 (2nd crop)

[a] The reactions were carried out in 2.5 M in CH_2Cl_2. [b] Isolated yield after crystallization. [c] Yield after two crystallizations.

Following Yamamoto's procedure, the product **203** was prepared successfully in good yields, but it was found to slowly decompose when exposed to light. It was also found that although a slightly excess of bromine was necessary to provide complete conversion, too much bromine resulted in a lower isolated yield of compound **203** along

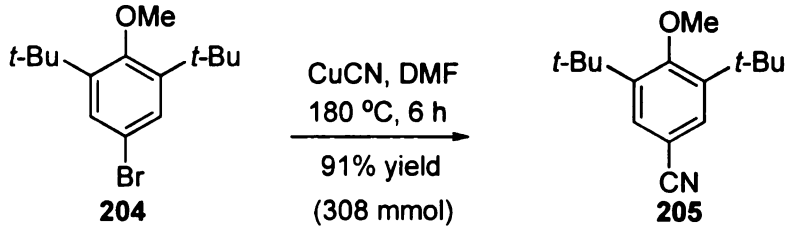
with the formation of an unidentified by-product (Table 4.1, entry 3). Longer reaction time or too much time for the addition of bromine resulted in lower yield (Table 4.1, entry 2). The optimized protocol involves the addition of 1.05 equivalent bromine to phenol **207** through a dropping funnel within 75 minutes at 0 °C, followed by stirring for 30 minutes at 0 °C before the reaction was quenched with aqueous Na_2SO_3. The bromination reaction was carried out on a scale of 206 grams (1 mol) of **207** to afford the product **203** in 85% yield after crystallization (Table 4.1, entry 4).

Scheme 4.4 Methylation of the phenol **203**



The subsequent methylation of the bromo-phenol **203** with sodium hydride and methyl iodide afforded a quantitative isolated yield of the product **204** after purified by silica gel chromatography (Scheme 4.4). The large scale reaction was carried out on a scale of 167 grams (588 mmol) of phenol **203** using dry DMSO that was freshly distilled and stored in the presence of 4Å molecular sieves.

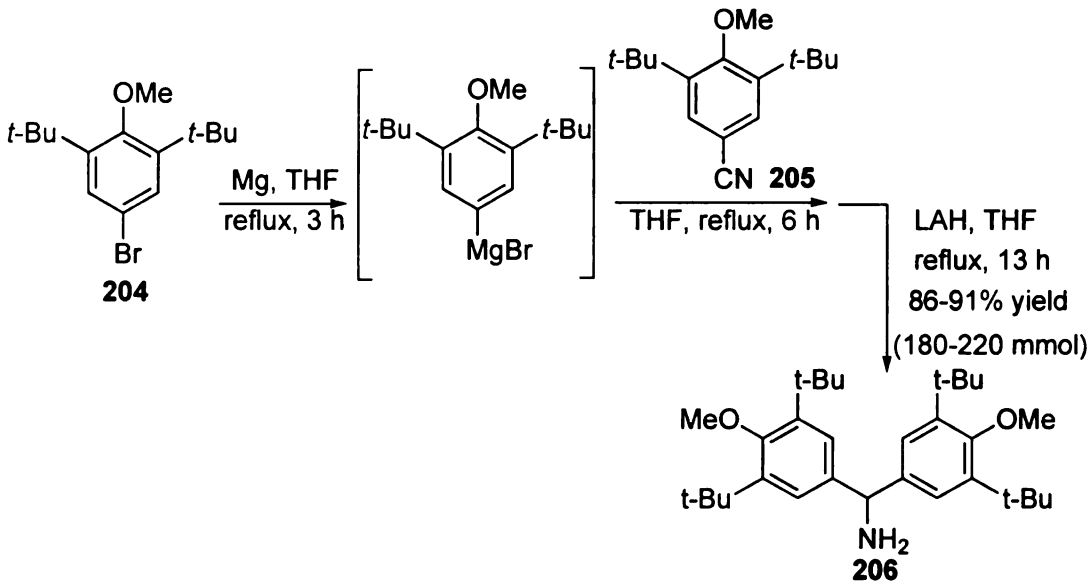
Scheme 4.5 Cyanation of 4-methoxy-3,5-di-*tert*-butylphenylbromide **204**



The preparation of compound **205** was carried out following the procedure published by Friedman and Shechter for related molecules.[89a] In the large scale experiment

(Scheme 4.5), the bromide **204** (92 g, 308 mmol) was coupled with CuCN in refluxing DMF to afford 4-methoxy-3,5-di-*tert*-butylphenylcyanide **205** in 91% isolated yield after silica gel chromatographic purification.

Scheme 4.6 Preparation of the amine **206**



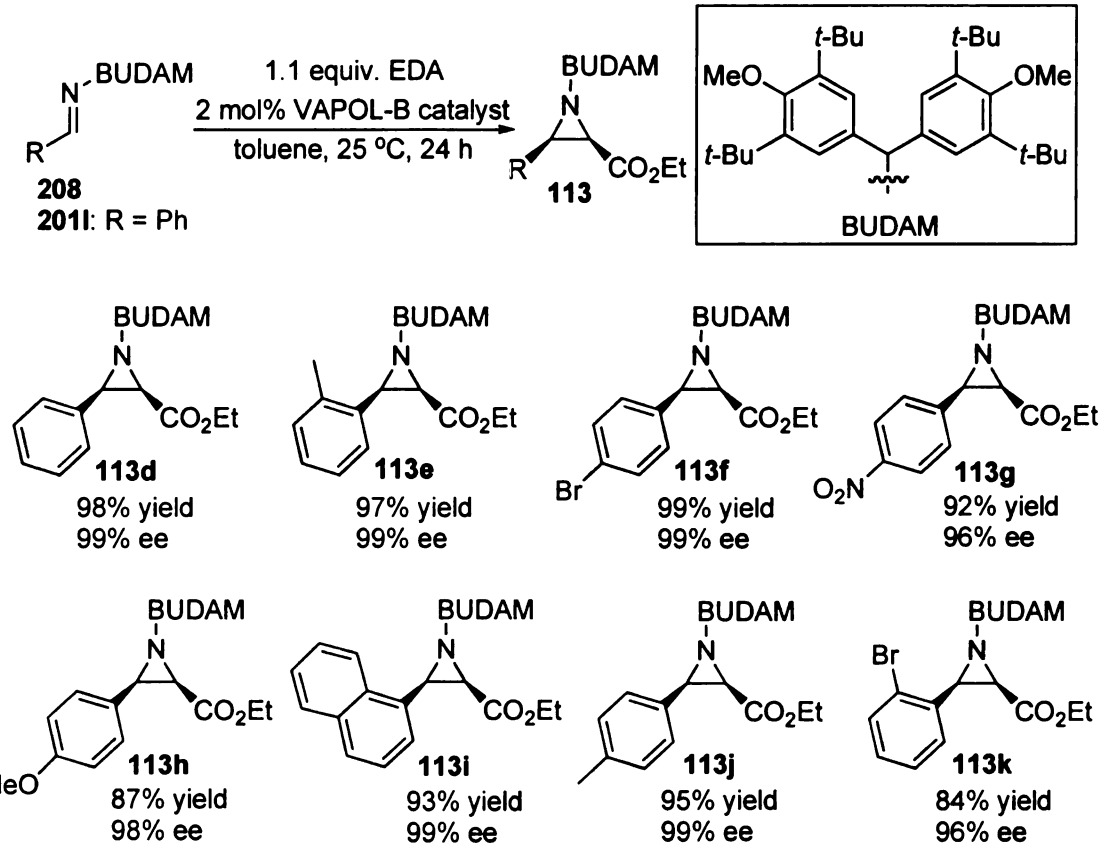
Finally, addition of the Grignard reagent prepared from the bromide **204** to the nitrile **205** followed by a one-pot LAH reduction protocol afforded the product amine **206** in 90% yield (84 g, 180 mmol). In this step, the purity of both starting materials **204** and **205** are important for obtaining good results. The reaction scale was limited to 200 mmol of the nitrile **205** only because of the limitation in the size of the available glassware. Since three reactions on similar scales resulted in consistently high yields for the final product **206**, it is reasonable to expect that comparable yield can be obtained on larger reaction scales. This amine can be easily purified by silica gel chromatography (for 84 grams of amine **206**, only 2.4 L of silica gel was required). If the collected fractions from chromatography are contaminated with small amounts of a light-yellow impurity (undetectable in the ^{1}H NMR spectrum), a single crystallization of the yellow fractions from hexane/CH_2Cl_2 is enough to remove the impurity and afford the pure amine **206** as

white crystal. The remaining amine in the mother liquor can be again purified using a small column.

4.2.3 Catalytic AZ reaction with *N*-BUDAM imines

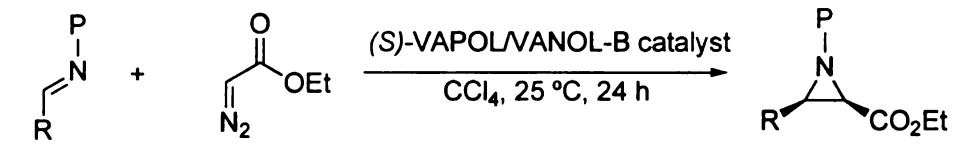
In collaboration with former group member, Dr. Zhang, a series of *N*-BUDAM imines **208** were synthesized using the general procedure.[47] Results for the AZ reaction of these imines are shown in Scheme 4.7. The results from the aziridination of *N*-BUDAM imines **208e** to **208k** clearly demonstrate that excellent asymmetric inductions and yields that we observed for a broad range of aryl substituted *N*-BUDAM imines and not just for the unsubstituted phenyl imine **201l**. However, the same consistently high asymmetric inductions were not obtained with the alkyl substituted *N*-BUDAM imines **208a** to **208c** (Table 4.2).

Scheme 4.7 AZ reaction of *N*-BUDAM aryl substituted imines **208**

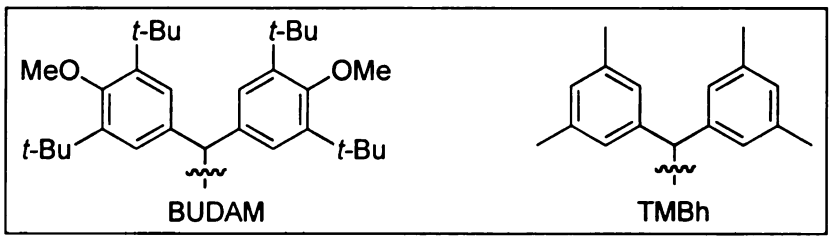


Only the primary alkyl substituted imine **208c** afforded the aziridine **113c** with excellent enantioselectivity (93% ee, Table 4.2, entry 5). The enantioselectivity dropped with the secondary alkyl imine **208a** (89% ee, Table 4.2, entry 1) and dropped even further with the tertiary alkyl imine **208b**, where the aziridine **113b** was obtained with only 78% ee (Table 4.2, entry 3). The decrease in the enantioselectivities was suspected to be the result of the combined steric bulk of both the *N*-BUDAM group and the α-position substituent of the imines. This hypothesis was supported by several observations. For example, the aziridination reaction of imine **35b** (Scheme 4.10) generated from benzhydryl amine and trimethylacetaldehyde always lead to complete conversion,[47,22] while the corresponding reaction of the *N*-BUDAM imine **208b** proceeded with only 75% conversion with the same catalyst loading and the exact same reaction conditions. Based on the rate of evolution of nitrogen gas and the color change of the reaction mixture, it seemed that the reaction rate decreased gradually from the primary aldimine **208c** to the tertiary aldimine **208b**. The reactivity of the imine **208b** appeared to be quite different with the VAPOL derived catalyst and with the VANOL derived catalyst, as the smaller VANOL derived catalyst gave 20% higher conversion in the reaction than the VAPOL derived catalyst (Table 4.2, entry 3 and 4). A possible solution to this problem was expected to be the design of another *N*-protecting group that had a structure similar to the BUDAM group but with less steric bulk.

Table 4.2 Aziridination of alkyl substituted imines[a]



208 P = BUDAM **13** **113** P = BUDAM
209 P = TMBh **210** P = TMBh



entry	imine	R	ligand	catalyst loading	yield (%)[b]	ee (%)[c]
1	**208a**	*c*-C_6H_{11}	VAPOL	4 mol%	89	89
2	**208a**	*c*-C_6H_{11}	VANOL	4 mol%	87	89
3	**208b**	*t*-Bu	VAPOL	10 mol%	60(75)[d]	78
4	**208b**	*t*-Bu	VANOL	10 mol%	76(95)[d]	80
5	**208c**	C_2H_5	VAPOL	2 mol%	62	93
6	**208c**	C_2H_5	VANOL	2 mol%	57	87
7	**209a**	*c*-C_6H_{11}	VAPOL	4 mol%	87	91
8	**209a**	*c*-C_6H_{11}	VANOL	4mol%	93	92
9	**209b**	*t*-Bu	VAPOL	10 mol%	94	96
10	**208b**	*t*-Bu	VANOL	10 mol%	94	96

[a] Unless otherwise specified, all reactions were run in CCl_4 with 1.1 equiv EDA **13**. The catalyst were prepared from 1 equiv. VAPOL or VANOL, 3 equiv. $B(OPh)_3$ at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. [b] Isolated yield after silica gel chromatography. [c] From entry 1 to 6, the % ee was determined by chiral HPLC on a Pirkle covalent (R, R) Whelk-O1 column; from entry 7 to 10, the % ee was determined by chiral HPLC on a Chiralcel OD-H column. [d] Number in parenthesis indicates percent conversion determined by ^1H NMR analysis on the crude reaction mixture.

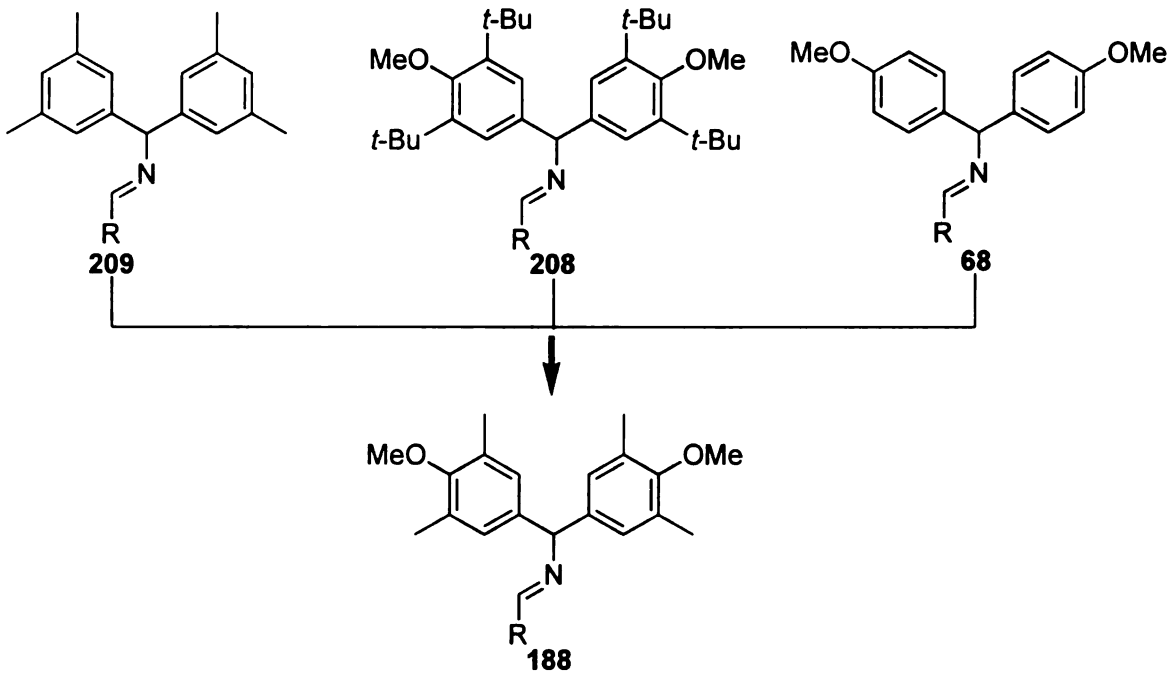
The development of the BUDAM group was mainly inspired from the observations by Dr. Zhang in a previous study outlined in Scheme 4.2. In the same study, the *N*-tetramethylbenzhydryl imine (*N*-TMBh imine) **201k** afforded the aziridine **202k** with just 4% lower ee than the corresponding *N*-BUDAM imine **201l**. Since the TMBh group is sterically smaller than the BUDAM group, the TMBh group was tested as an alternative to the BUDAM group for the aziridination of alkyl substituted imines. The imines **209a** and **209b** derived from secondary and tertiary aliphatic aldehydes and tetramethylbenzhydryl amine (*N*-TMBh amine) were thus tested in the AZ reaction by Dr. Zhang and the data is presented in Table 4.2. As was expected, improved enantioselectivities were obtained, especially in the case of the bulky tertiary alkyl imine **209b** (Table 4.2, entry 3 vs. entry 9). The reactivity was also improved to afford higher yields and with complete conversion under the standard conditions (Table 4.2, entry 7 to 10). However, a major drawback with the *N*-TMBh aziridines **210** was that the attempted deprotection of the *N*-TMBh aziridines **210** to give the *N*-H aziridines **56** using the acid mediated deprotection protocol (Section 2.3.5.2) always resulted in complex mixtures, which limited the subsequent applications of these aziridines. An other reason for not using the TMBh protecting group for imines is due to the expense of the 3,5-dimethylphenylbromide as the starting material for the preparation of the corresponding amine.

4.2.4 Catalytic AZ reaction with *N*-MEDAM imines

From the study for the deprotection of *N*-DAM aziridines **58** described in Section 2.3.5.2, it was known that the presence of *para*-methoxy groups on the *N*-benzhydryl group are essential for facile access to *N*-H aziridines. This was also demonstrated by the fact that the BUDAM group, which also contains *para*-methoxy groups can be readily cleaved under similar acidic conditions (Scheme 3.6). Considering that a) the *para*-

methoxy group in the *N*-DAM aziridine were essential for facile deprotection, b) the bulk of the *N*-BUDAM group was perfect for the aryl substituents but too much for alkyl substituents and c) the bulk of the *N*-TMBh group was good for the hindered alkyl substituents. It became reasonable to design series of imines **188** that had a *N*-protecting group containing both the tetramethyl and the *para*-methoxy units on the phenyl rings as shown in Scheme 4.8.

Scheme 4.8 The *N*-bis(3,5-dimethyl-4-methoxyphenyl)methyl (MEDAM) group

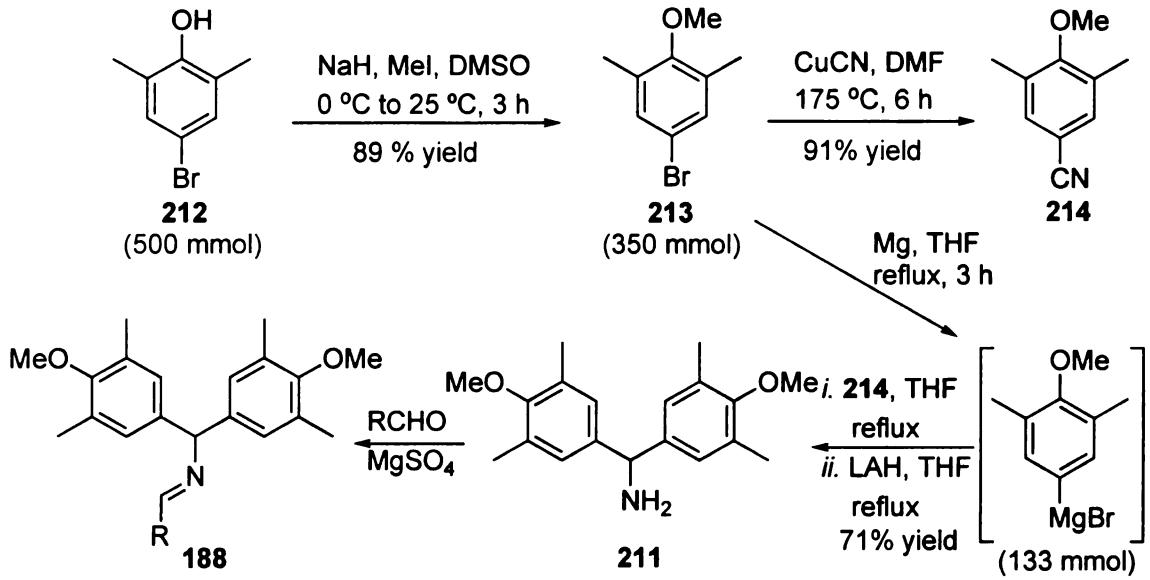


4.2.4.1 Synthesis of *N*-MEDAM imine 188

The preparation of the bis(3,5-dimethyl-4-methoxy-phenyl)methyl amine (*N*-MEDAM amine) **211** could be carried out with a procedure similar to that for the *N*-BUDAM amine **206** (Scheme 4.9). From commercially available 4-bromo-3,5-dimethylphenol **212**, the amine **211** could be obtained in three steps with a 58% overall yield.[37d] The large scale synthesis of the amine **211** was carried out by group member, Aman Desai, at a scale of 28 grams (133 mmol) for the intermediate **214**, which was prepared from the compound **213** at a scale of 75 grams (350 mmol). The *N*-MEDAM imines **188** were then

synthesized from the appropriate aldehyde with removal of water.

Scheme 4.9 Synthesis of *N*-MEDAM imines **188**

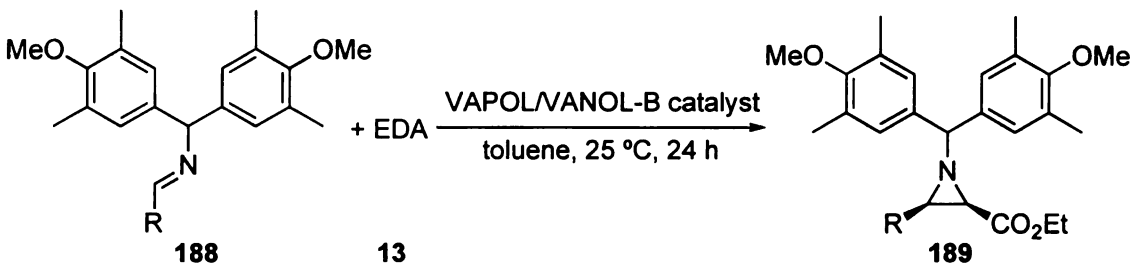


4.2.4.2 AZ reaction with *N*-MEDAM imines

The *N*-MEDAM imines **188a** and **188b** were purified by a single crystallization, while the imines **188c** and **188j** were liquids that could not be purified and were used in their crude form for the catalytic AZ reaction. The results are listed in Table 4.3.

As was expected, the enantioselectivities with the bulky alkyl substituted *N*-MEDAM imines **188a** and **188b** (Table 4.3, entry 1 and 3) were comparable to those obtained with the corresponding *N*-TMBh imines **209** (Table 4.2) and higher than those obtained with the corresponding *N*-BUDAM imines (Table 4.3, entry 1 to 5). Close to quantitative yields were obtained in most cases. However, both the imine **188c** and **188j** that were used in their crude form resulted in incomplete conversion (Table 4.3, entry 6 and 7). The catalyst loading for the imine **188b** could also be reduced to 4 mol% without any adverse effects on the yield and the asymmetric induction (Table 4.3, entry 5).

Table 4.3 Catalytic AZ reaction with *N*-MEDAM imines **188**[a]



188 **13** **189**

entry	series	R	catalyst	yield (%)[b]	ee (%)[c]
1	**a**	*c*-C_6H_{11}	4 mol% *(S)*-VAPOL	99	94
2	**a**	*c*-C_6H_{11}	4 mol% *(R)*-VANOL	96	91
3	**b**	*t*-Bu	10 mol% *(S)*-VAPOL	88	94
4	**b**	*t*-Bu	10 mol% *(R)*-VANOL	97	97
5	**b**	*t*-Bu	4 mol% *(R)*-VANOL	97	96
6[d]	**c**	C_2H_5	5 mol% *(S)*-VAPOL	50% conv.	
7[d]	**j**	C_6H_{13}	4 mol% *(S)*-VAPOL	60% conv.	

[a] Unless otherwise specified, all reactions were run in toluene with 1.1 equiv EDA **13**. The catalyst were prepared from 1 equiv. VAPOL or VANOL, 4 equiv. $B(OPh)_3$ and 1 equiv. H_2O at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. [b] Isolated yield after silica gel chromatography. [c] Determined by chiral HPLC on a Chiralcel OD-H column. [d] The imine was used in crude form.

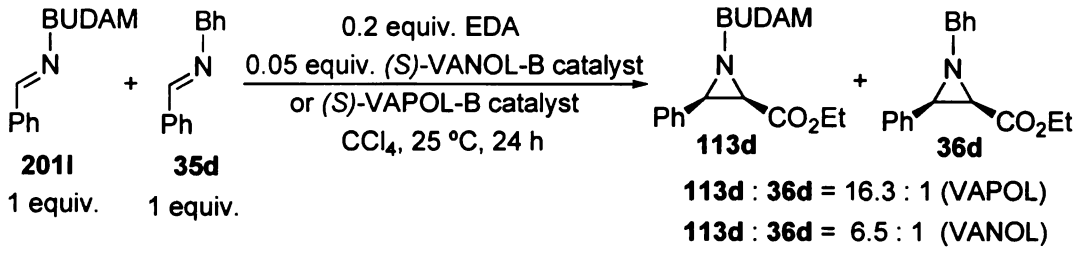
4.3 One-pot imine generation-AZ reaction protocol

4.3.1 Initial studies on the one-pot protocol

The idea for the one-pot catalytic AZ reaction came from the observation that the aziridination reaction of the *N*-BUDAM imine **201l** was significantly faster and proceeded with better asymmetric induction than any of the other *N*-protected imines examined up to that point. A competition study for the relative rate between the *N*-Bh imine **35d** and the *N*-BUDAM imine **201l** was carried out[37c] (Scheme 4.10). The aziridination reaction of the *N*-BUDAM imine **201l** is 16 times faster than that of the *N*-Bh imine **35d** under

VAPOL-borate catalysis, while it is 6.5 times faster under VANOL-borate catalysis.

Scheme 4.10 Rate competition study between the *N*-BUDAM imine **201l** with the *N*-Bh imine **35d**

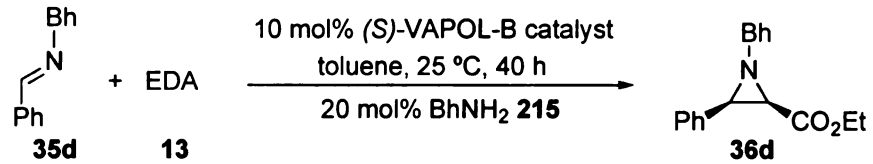


It was envisioned that the one-pot imine generation-aziridination procedure starting from the *N*-BUDAM amine **206** and various aldehydes might be feasible to afforded the corresponding aziridines with reasonable yields and asymmetric inductions. The benefits from such a one-pot procedure would include: (a) simplification of the overall process and (b) prevention of the possible decomposition of imines during the purification step in the synthesis of these imines.

Amongst the factors that could diminish the asymmetric induction of the aziridination step in the one-pot procedure, an excess amount of the amine in the reaction was considered to likely have a major detrimental effect due to the possible strong coordination of the amine nitrogen to the catalyst. To understand the effect of excess amine, control experiments were first carried out by adding excess amounts of *N*-benzhydryl amine **215** to the aziridination system (Scheme 4.11). It was found that the addition of 20 mol% of amine **215** stopped the reaction and gave less than 5% conversion even after 40 h. This was found to be independent of the manner in which the catalyst was prepared. (In the experiment one, the catalyst was prepared from 1 equivalent of VAPOL, 4 equivalent of $B(OPh)_3$ and 1 equivalent of water at 80 °C in toluene for 1 h, followed by high vacuum (0.5 mm Hg) at 80 °C for 0.5 h, then transferred to the imine **35d**. In the experiment two, all the reagents were added together at the

same time with imine **35d**).

Scheme 4.11 Control experiments for the study of the effect of excess amine



35d **13** **36d**

1: The catalyst was prepared first, then transferred to imine, following by the addition of amine **215**. trace **36d** (< 5% conversion)

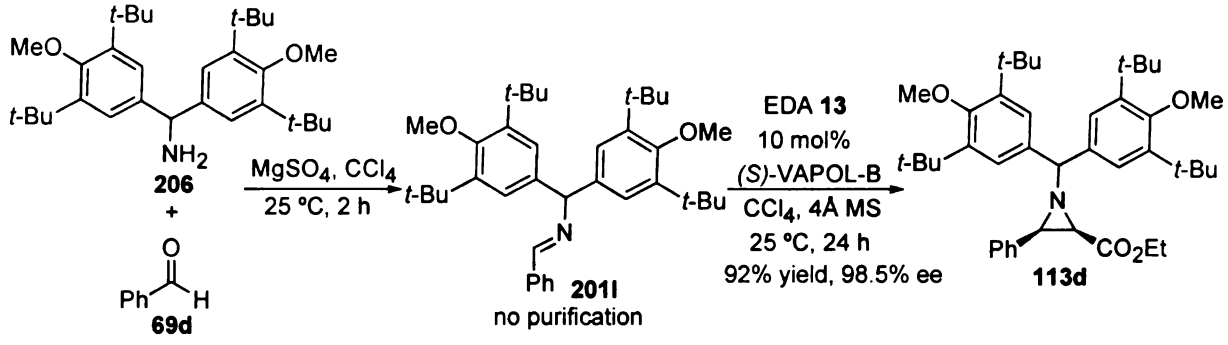
2: The VAPOL, $B(OPh)_3$ and the imine were added all at the same time. followed by the addition of amine **215**. trace **36d** (< 5% conversion)

Considering that most of the aldehydes can be removed by high vacuum due to their high volatility, and that the coordination ability of the aldehyde oxygen would be expected to be lower than the imine nitrogen, it was decided to use a small excess of the aldehyde in the imine formation step. The slight excess of the aldehyde would then be removed under high vacuum before the addition of the chiral catalyst and the ethyl diazoacetate.

The initial experiment was carried out with *N*-BUDAM amine **206** and benzaldehyde **69d** (Scheme 4.12). Carbon tetrachloride was used as the solvent, and 4Å molecular sieves (powder) was used as the dehydrating reagent, a procedure that was inspired by the one-pot reductive amination protocol reported by Macmillan.[90] The imine formation process was monitored by ^1H NMR spectroscopy on an hourly basis by taking a small sample from the reaction mixture. After imine formation was complete (about 2 h), the solvent and excess aldehyde were removed by high vacuum and then catalyst solution of the carbon tetrachloride was transferred to the crude imine followed by the addition of ethyl diazoacetate **13** (The catalyst was prepared as described in the experiment one shown in Scheme 4.11). Bubbling was observed from the reaction mixture seconds after the addition of **13**, indicating the generation of nitrogen gas. Normal work up after 24 h

and purification by silica gel chromatography afforded aziridine **113d** in 92% isolated yield and 98.5% ee. The enantioselectivity was close to that obtained in the two step aziridination protocol (99%ee with purified imine), and the yield was slightly lower (98% with purified imine).

Scheme 4.12 The first one-pot imine formation-AZ reaction



4.3.2 One-pot imine formation-aziridination reaction of *N*-Bh amine and aldehydes

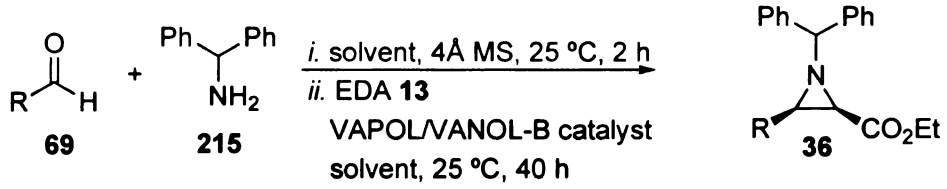
Encouraged by the one-pot protocol with the *N*-BUDAM amine **206**, a study was undertaken to test the generality of this procedure for various aldehydes and amines. The commercially available benzhydryl amine (*N*-Bh amine) **215** was chosen for the optimization of the conditions, since the *N*-Bh imines were the least reactive among the four different aziridination imines that have been developed for the AZ reaction (*N*-Bh, *N*-DAM, *N*-BUDAM, *N*-MEDAM). Presumably, conditions that would work for the *N*-Bh amine would also work for the others.

In the general procedure for the preparation of imines, magnesium sulfate is used as the dehydrating reagent to remove the water generated from the condensation of the amine and the aldehyde. To ensure complete conversion, the reaction is run for 16-24 h and then any impurities are removed by purification. In the one-pot procedure, it was considered desirable to minimize the time for the imine formation step, since longer reaction time could possibly lead to decomposition of the imine and/or excess aldehyde,

which could adversely affect the subsequent aziridination step. In fact, it was noticed that longer reaction times for the imine formation did lead to increasing amounts of several unidentified impurities, as observed by ^{1}H NMR analysis of the reaction mixture containing the imine. For most of the substrates, higher than 99% conversion in the imine formation step was obtained within 2 h.

As the results in Table 4.4 show, the one-pot procedure generally gave results comparable in terms of yields and enantioselectivities to those obtained from the aziridinations with purified imines. The large excess of aldehyde could not be fully pumped out (0.5 mm Hg for 1 h), thus the remaining aldehyde resulted in a lower yield but without affecting the enantioselectivity (Table 4.4, entry 3), this result suggested that there might be a competition between coordination of the aldehyde **69** and the imine **35** to the catalyst, leading to a diminished turnover of for the catalyst. The ideal situation would involve exactly a 1 : 1 ratio of the amine and the aldehyde in the imine formation step, but considering that the coordination of the aldehyde to the catalyst would probably be less favorable than the coordination of the amine, it was decided to continue using a small excess of the aldehyde. The screen with different dehydrating reagents clearly showed that the use of activated 4Å MS afforded better enantioselectivity than that of $MgSO_4$ (Table 4.4, entry 1 vs. entry 2), which might be due to the stronger Lewis acid character of $MgSO_4$ compared to 4Å MS. The reaction in toluene gave a slightly lower yield but higher enantioselectivity as compared to other solvents (Table 4.4, entry 5 vs. entry 1 and 4). This one-pot procedure seemed to be sensitive towards the catalyst loading. The use of 5 mol% catalyst generally resulted in incomplete conversions (Table 4.4, entry 7 and 8). In the corresponding reactions with purified imines, the reactions with 5 mol% catalysts are generally complete within 24 h under the same conditions.

Table 4.4 One-pot aziridination with benzhydryl amine **215** and aldehydes[a]



entry	R	ligand	solvent	yield (%)[b,c]	ee (%)[c,d]
1	Ph	10 mol% *(S)*-VAPOL	CCl_4	79(84)	90(93)
2[e]	Ph	10 mol% *(S)*-VAPOL	CCl_4	85	79
3[f]	Ph	10 mol% *(S)*-VAPOL	CCl_4	35	90
4	Ph	10 mol% *(S)*-VAPOL	CH_2Cl_2	48	91
5	Ph	10 mol% *(S)*-VAPOL	toluene	75(82)	93(94)
6[g]	Ph	10 mol% *(S)*-VAPOL	toluene	62	92
7	Ph	5 mol% *(S)*-VAPOL	toluene	40% conv.	nd
8	Ph	5 mol% *(R)*-VANOL	toluene	45% conv.	nd
9	*p*-$NO_2C_6H_4$	10 mol% *(S)*-VAPOL	toluene	62	92
10	*p*-$NO_2C_6H_4$	5 mol% *(R)*-VANOL	toluene	62(86)	92(89)
11	*p*-$OMeC_6H_4$	10 mol% *(S)*-VAPOL	toluene	41(51)	89(86)
12	*p*-$OMeC_6H_4$	10 mol% *(R)*-VANOL	toluene	65	90
13	*o*-BrC_6H_4	10 mol% *(S)*-VAPOL	toluene	37% conv.	nd
14	*o*-BrC_6H_4	10 mol% *(R)*-VANOL	toluene	20% conv.	nd

[a] Unless otherwise specified, all reactions were performed using 1 equiv amine and 1.05-1.1 equiv aldehyde with activated 4Å MS at 25 °C for 2 h in step *i*, and for 40 h in step *ii*. The AZ step was carried out 0.25 m in toluene with 1.1 equiv EDA **13**. The catalyst were prepared from 1 equiv. VAPOL or VANOL, 4 equiv. $B(OPh)_3$ and 1 equiv. H_2O at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. nd = not determined. [b] Isolated yield after silica gel chromatography. [c] The data in parenthesis is the result from the purified imine. [d] Determined from chiral HPLC on the Chiralcel OD-H column. [e] $MgSO_4$ was used as the dehydrating reagent. [f] 3 equivalents of aldehyde was used. [g] The 4Å MS used was activated and

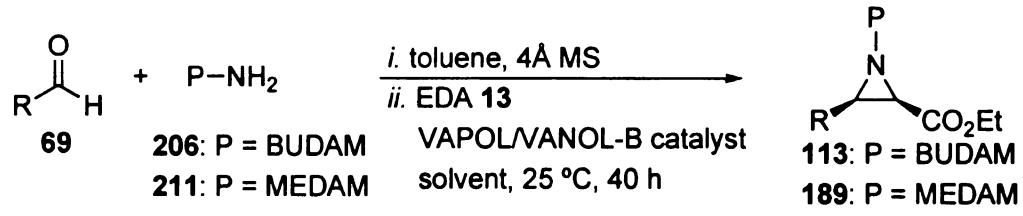
stored in the desiccator for two months.

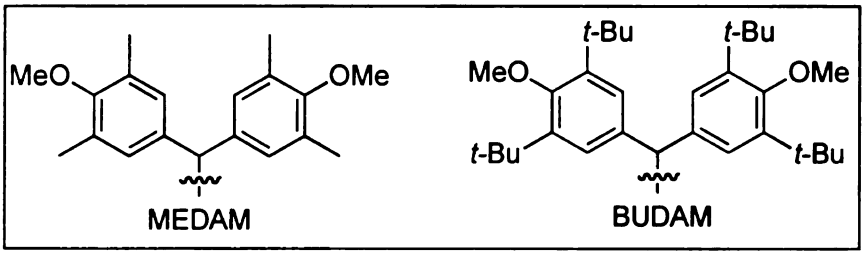
The substrate scope was quite general, both electron poor and electron rich substrates gave slightly higher enantioselectivities than those obtained from the aziridinations of purified imines (Table 4.4, entry 9 to 12). The sterically hindered *o*-bromobenzaldehyde gave incomplete conversion after 40 h (Table 4.4, entry 13 and 14). The optimized conditions for the one-pot imine formation-aziridination that have emerged from this study are: a 1 : 1.05 ratio of amine to aldehyde in the presence of 4Å MS in toluene at room temperature for 2 hours, followed by the addition of catalyst and EDA at the same temperature, and allowing the aziridination reaction to go for 40 hours to ensure complete conversion.

4.3.3 One-pot protocol of *N*-BUDAM and *N*-MEDAM amines with aldehydes

The *N*-BUDAM and *N*-MEDAM amines were also studied for the one-pot procedure and the results are shown in Table 4.5. Here, similar enantioselectivities and slightly higher yields were obtained as compared to the corresponding results employing the purified imines. An excess amount of the aldehyde did not interfere the reactivity of the *N*-BUDAM system (Table 4.5, entry 3) as it did with those of the *N*-Bh system (Table 4.4, entry 3), and this might be related to the fact that the *N*-BUDAM imines react 16.3 times faster than the *N*-Bh imines (Scheme 4.10). For the reactions of the *N*-MEDAM amine **211** and a primary aliphatic aldehyde, incomplete conversions were still observed, but the asymmetric inductions were good (Table 4.5, entry 8 and entry 9). Interestingly, difference were observed for the VANOL derived catalyst and the VAPOL derived catalyst in the reaction of the primary aliphatic imine where lower yields and enantioselectivities were obtained for the reaction with the VANOL-borate catalyst (Table 4.5, entry 8 vs. entry 9).

Table 4.5 One-pot aziridination with *N*-BUDAM / MEDAM amines and aldehydes[a]





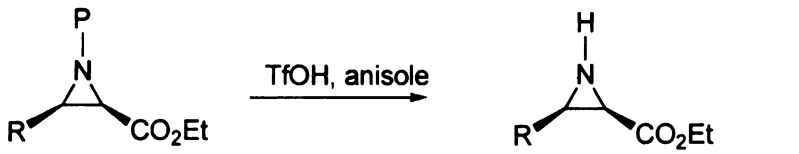
entry	R	P	ligand	solvent	yield (%)[b, c]	ee (%)[c, d]
1	Ph	BUDAM	10 mol% *(S)*-VAPOL	CCl_4	94(98)	99(99)
2[e]	Ph	BUDAM	10 mol% *(S)*-VAPOL	CCl_4	94	99
3[f]	Ph	BUDAM	10 mol% *(S)*-VAPOL	CCl_4	92	99
4	Ph	BUDAM	5 mol% *(S)*-VAPOL	toluene	50% conv.	
5	Et	BUDAM	10 mol% *(S)*-VAPOL	toluene	66(62)	93(93)
6	*i*-Pr	BUDAM	10 mol% *(S)*-VAPOL	toluene	67	nd
7	Ph	MEDAM	4 mol% *(R)*-VANOL	toluene	96(86)[g]	98(99)[g]
8	*n*-C_6H_{13}	MEDAM	4 mol% *(S)*-VAPOL	toluene	66[h]	94
9	*n*-C_6H_{13}	MEDAM	4 mol% *(R)*-VANOL	toluene	48[i]	88
10[j]	*n*-C_6H_{13}	MEDAM	4 mol% *(R)*-VANOL	toluene	complex mixtures	
11	*c*-C_6H_{11}	MEDAM	4 mol% *(S)*-VAPOL	toluene	94	93
12	*t*-Bu	MEDAM	10 mol% *(S)*-VAPOL	toluene	82	94

[a] Unless otherwise specified, all reactions were performed using 1 equiv amine and 1.05-1.1 equiv aldehyde with activated 4Å MS at 25 °C for 2 h in step *i*, and for 40 h in step *ii*. The AZ reaction step was carried out in 0.25 M solution with 1.1 equiv EDA **13**. The catalyst were prepared from 1 equiv. VAPOL or VANOL, 4 equiv. $B(OPh)_3$ and 1 equiv. H_2O at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. [b] Isolated yield after silica gel chromatography based on the amine. [c] The data in parenthesis is that obtained from the

purified imine. [d] From entry 1 to 7, % ee was determined by chiral HPLC on a Pirkle covalent (R, R) Whelk-O1 column. From entry 8 to 13, % ee was determined by chiral HPLC on a Chiralcel OD-H column. [e] The catalyst was prepared without the addition of H_2O. [f] 3 equiv aldehyde was used. [g] Data in parenthesis was obtained from Dr. Zhang. [h] 95% conversion. [i] 90% conversion. [j] Na_2SO_4 was used as the dehydrating reagent.

Furthermore, the subsequent acid mediated deprotection of the *N*-BUDAM and the *N*-MEDAM groups from the aziridines **113** and **189** afforded the corresponding *N*-H aziridines in good yields as shown in Scheme 4.13.

Scheme 4.13 Deprotection of the *N*-MEDAM and the *N*-BUDAM groups



113d: P = BUDAM, R = Ph — **56d**: 97% yield (25 °C, 2 h)

189a: P = MEDAM, R = Cy — **56a**: 90% yield (65 °C, 0.5 h)

189b: P = MEDAM, R = *t*-Bu — **56b**: 88% yield (65 °C, 0.7 h)

189d: P = MEDAM, R = Ph — **56d**: 88% yield (25 °C, 3 h)

The one-pot imine formation-AZ reaction procedure is general for a wide range of substrates to give the results that similar to those of the original two-step protocol. Compared with the aziridination reaction using purified imines, this one-pot procedure is simpler, takes less time and works better for the substrates that can not be purified as their imines. The biggest disadvantage is that the one-pot procedure requires higher catalyst loading than that using purified imines, this is especially true for the synthesis of the *N*-Bh protected aziridines.

4.4 Asymmetric synthesis of alkynylaziridines

4.4.1 Introduction

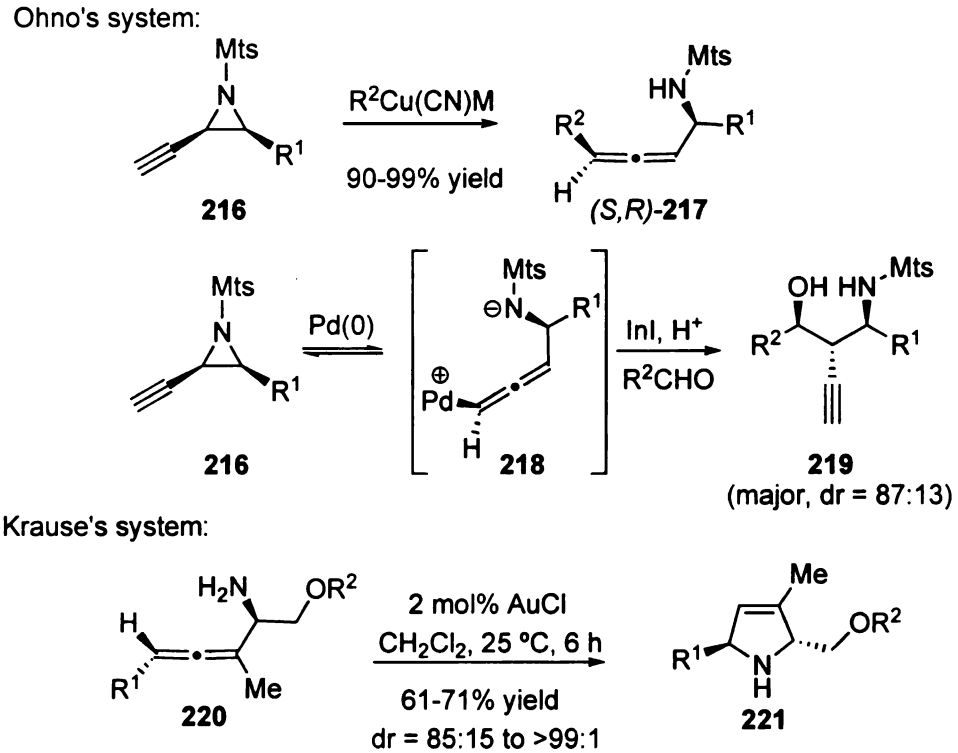
Aziridines bearing an alkynyl group on the aziridine-ring are useful building blocks for the synthesis of various types of natural or synthetic compounds.[91,92] Recently, Ohno found that the 2-ethynylaziridines could be converted to allene species stereospecifically via an *anti*-S_N2' ring opening reaction[93a] (Scheme 4.14). The allenes were generated as single diastereomers in excellent yields, when organocyanocuprates RCu(CN)M•nLiX were used as nucleophiles. An interesting application of this stereoselective amino allene preparation protocol was also reported by the same group (Scheme 4.14),[93b] in which the amino allenes **218** were generated *in situ* from chiral ethynylaziridines **216** via a palladium catalyzed stereoselective ring opening reaction of the aziridine, and then subsequent transmetalation with InI and then addition to various aldehydes to afford 1,3-amino alcohols **219** with three consecutive chiral centers.

Another attractive application for these α-amino allenes is a gold-catalyzed cycloisomerization for the synthesis of Δ^3-pyrrolines reported by the Krause group[94a] (Scheme 4.14). From the optically pure α-amino allenes **220**, they could prepare a series of Δ^3-pyrrolines **221**, which are potentially useful intermediates in natural products synthesis,[95] in good yields and with excellent diastereoslectivities.

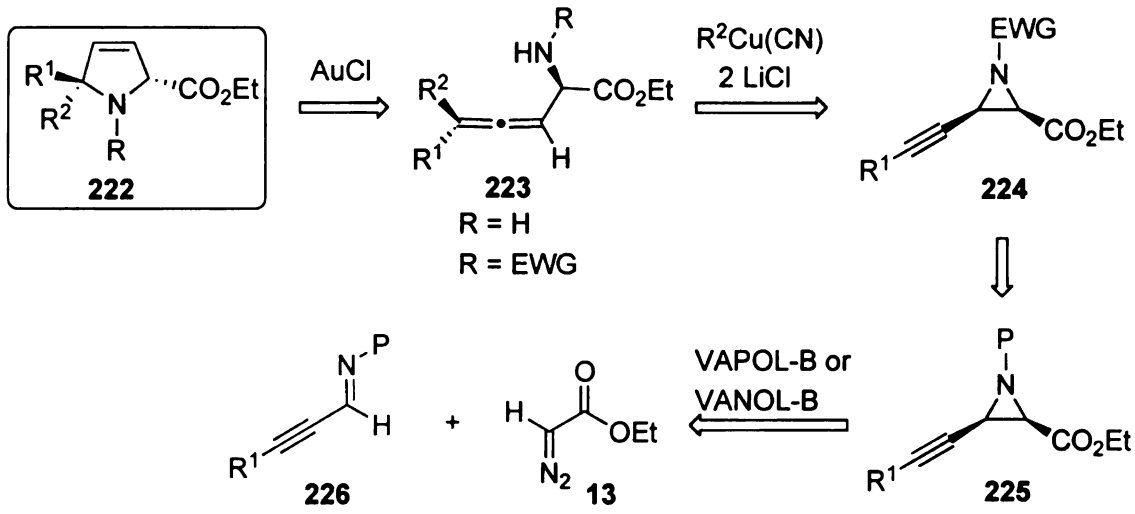
Inspired by the work of Ohno and Krause, it was envisioned that a new synthetic methodology for the preparation of chiral functionalized Δ^3-pyrrolines could be developed utilizing the catalytic AZ reaction (Scheme 4.15). It was hoped that the chiral alkynylaziridine **225** could be synthesized from imine **226** and diazo compound **13** under VAPOL/VANOL-borate catalysis. After transformation to the activated aziridine **224** via the established deprotection and activation protocols described previously in chapter three, the α-amino allene **223** might be obtained stereospecifically by applying

conditions similar to those developed by Ohno.[93] The subsequent transformation to Δ^3-pyrroline **222** is then envisioned employing conditions similar to those developed by Krause.[94] In this proposed Δ^3-pyrroline synthesis, tri-substituted Δ^3-pyrrolines **222** could thus be prepared stereoselectively from simple none chiral starting materials. Compared with Krause's allene **220**, the allene **223** is different in terms of the substituents on the allene, the nitrogen protecting group, and the presence of an ester functionality, and thus success of the Au(I) catalyzed Δ^3-pyrroline formation from allene **223** may be subject to appropriate optimization.

Scheme 4.14 Synthesis of chiral amino allenes from 2-ethynylaziridines and the applications



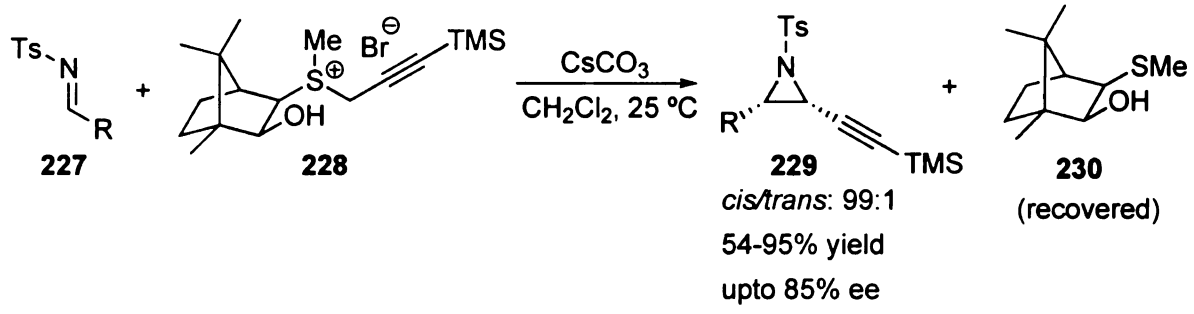
Scheme 4.15 Proposed Δ^3-pyrroline synthesis via catalytic asymmetric alkynylaziridine formation



4.4.2 Catalytic asymmetric alkynyl aziridination from imines

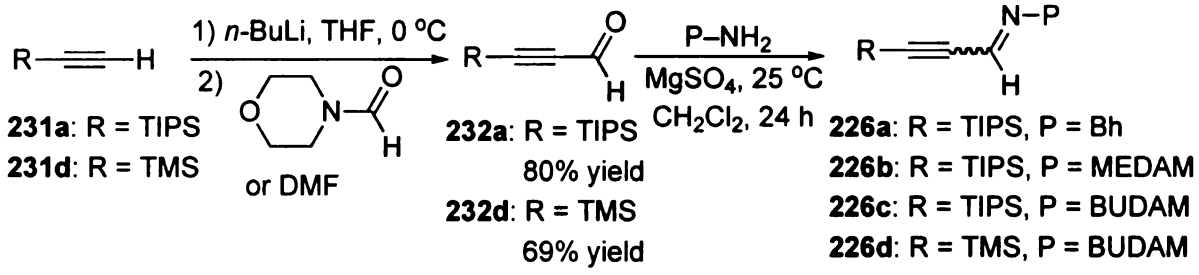
Despite the several established and the even greater potential applications of chiral alkynylaziridines, the lack of methods for the preparation of these aziridines with high diastereoselectivity and enantioselectivity has limited their thorough study.[96] Previous syntheses of enantio-pure alkynylaziridines mostly involve a Mitsunobu reaction on an amino propargyl alcohols that are prepared from optically active amino acids. However, neither *trans*- or *cis*- alkynylaziridines have been synthesized in a general and selective manner.[96] Dai's group reported the first asymmetric alkynylaziridination in 1997,[97] in which *N*-tosylimines **227** reacted with D-(+)-camphor derived chiral sulfinium ylide derived from the salt **228** to afford the alkynylaziridines **229** in moderate to good enantioselectivities (18-85% ee) and with excellent *cis/trans* selectivities (Scheme 4.16). Subsequently, some optimized procedures were developed that involve intramolecular aminations of chiral bromoallenes obtained from chiral amino propargyl alcohols[98] or allenylzinc additions to chiral sulfinimines.[99] However, a catalytic asymmetric alkynylaziridination from non-chiral starting materials has not yet been reported.

Scheme 4.16 Dai's asymmetric alkynylaziridination from *N*-tosylimines



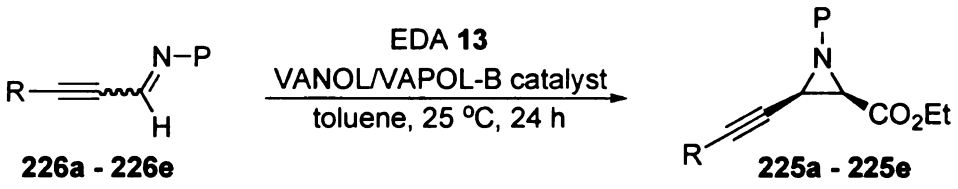
It was envisioned that the VAPOL/VANOL-borate catalyzed AZ reaction protocol could also be applied to the synthesis of chiral alkynylaziridines. The staring alkynylimines **226** for this project were synthesized via the condensation of amines with alkynylaldehydes **232**, which were prepared from the acetylenes **231** (Scheme 4.17). All imines **226** were obtained as mixtures of *trans*- and *cis*- isomers and although the *trans/cis* ratio could be enhanced by crystallization, none of the imines could be obtained in one pure isomeric form. For example, the ratio of *trans/cis* isomers of the imine **226d** could be enhanced from 1.5:1 to 19:1 with a single crystallization. This is the first time that *E* and *Z* isomers of imines were observed in this work. All of the imines described to this point derived from either aryl or alkyl aldehydes were obtained as a single isomer.

Scheme 4.17 Preparation of alkynylimines **226**



The catalytic AZ reactions of the alkynylimine **226** were carried out using 4 mol% VAPOL/VANOL-borate catalyst and the data are summarized in Table 4.6.

Table 4.6 AZ reaction with alkynylimine **226**[a]



226a - 226e **225a - 225e**

entry	P	R	series	*trans/cis* of **226**	ligand	yield (%)[b]	ee (%)[c]
1	Bh	TIPS	**a**	1.3:1	*S*-VAPOL	91	32
2	Bh	TIPS	**a**	nd	*R*-VANOL	87	21
3	MEDAM	TIPS	**b**	1.5:1	*S*-VAPOL	87	44
4	MEDAM	TIPS	**b**	nd	*R*-VANOL	89	40
5[d]	BUDAM	TIPS	**c**	nd	*S*-VAPOL	97[e]	83[e]
6[d]	BUDAM	TIPS	**c**	nd	*S*-VANOL	97[e]	78[e]
7	BUDAM	TMS	**d**	19:1	*S*-VAPOL	93	85
8	BUDAM	TMS	**d**	1.6:1	*S*-VAPOL	86[f]	84
9	BUDAM	TMS	**d**	19:1	*R*-VANOL	91	74
10[d]	BUDAM	TMS	**d**	19:1	*S*-VAPOL	87[f]	80
11	Bh	Ph	**e**	nd	*S*-VAPOL	50[g]	36[g]

[a] Unless otherwise specified, all reactions were performed in 0.5 M in toluene with 1.1 equiv. EDA and with 4 mol% catalyst. The catalyst were prepared from 1 equiv. VAPOL or VANOL, 4 equiv. $B(OPh)_3$ and 1 equiv. H_2O at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. [b] Unless otherwise specified, the yield is the isolated yield of compound **225** after silica gel chromatography. [c] For entries7 to 10, % ee was determined after the conversion of **225d** into the *N*-H aziridine **233d**, all % ee were determined on chiral HPLC from Chiralcel OD-H column. [d] 2 mol% catalyst loading. [e] The data was obtained by Dr. Zhang. [f] Overall yield of **233d** from **226d**. [g] The data was obtained by Dr. Patwardhan.

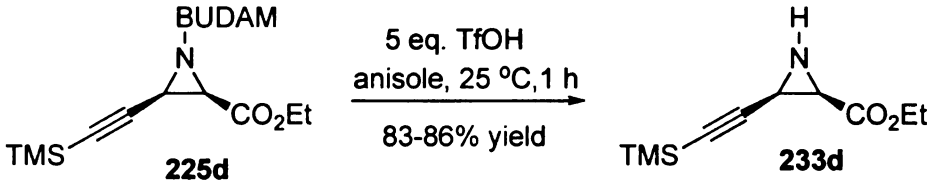
The reactions of the *N*-BUDAM imines **226c** and **226d** afforded the corresponding aziridines with significantly better asymmetric inductions (Table 4.6, entry 5 to 10) than the *N*-Bh imine **226a** (Table 4.6, entry 1 and 2), and also significantly better than those of

the *N*-MEDAM imine **226b** (Table 4.6, entry 3 and 4). The catalyst loading could be even reduced to 2 mol%, albeit with a small decrease in the enantioselectivity (Table 4.6, entries 7 vs. 10). The results with the *N*-MEDAM imine were surprising because in previous experiments with aryl or alkyl substituted imines, the *N*-MEDAM group afforded enantioselectivities similar to those of the *N*-BUDAM group (imine **188** vs. **208** in Table 4.3 and 4.5). Furthermore, unlike the aziridination reactions of most aryl and alkyl imines, these alkynyl imines gave a slightly greater difference in the asymmetric inductions with the VAPOL and VANOL derived catalysts. The inductions with the VANOL-borate catalyst were 5 – 10% ee lower than those with the VAPOL-borate catalyst. An interesting and important observation was that the isomeric ratios of the *trans*- and *cis*- imines did not affect either the yields or the enantioselectivities in the aziridination reaction (Table 4.6, entry 7 vs. entry 8). This is significant because it means the *E* and *Z* isomers of the imine **226** do not need to be separated.

None of the available chiral HPLC columns in our lab would give sufficient separation between the two enantiomers of compound **225d** such that an accurate measure of the enantioselectivity. An alternative way to measure the enantioselectivity was to convert the aziridine **225d** to the *N*-H aziridine **233d** via the acid mediated deprotection method (Scheme 4.18) discussed in chapter two. The enantiomers of the *N*-H aziridine **233d** could then be easily separated on the Chiralcel OD-H column by HPLC analysis. Based on the facts that (a) it was determined that no erosion in the enantiopurity under this acid mediated deprotection condition occurred during the deprotection of *N*-DAM aziridines (Section 2.3.5.2), and (b) the deprotection of **225d** gave only the *cis*-isomer of the product **233d**, as indicated by the crude ^{1}H NMR spectrum, it was believed that the % ee value obtained from the *N*-H aziridine **233d** reflected correctly the enantioselectivity obtained in the prior aziridination reaction. The deprotection of the crude aziridine **225d** was also tested and afforded the *N*-H aziridine **233d** in a higher overall isolated yield

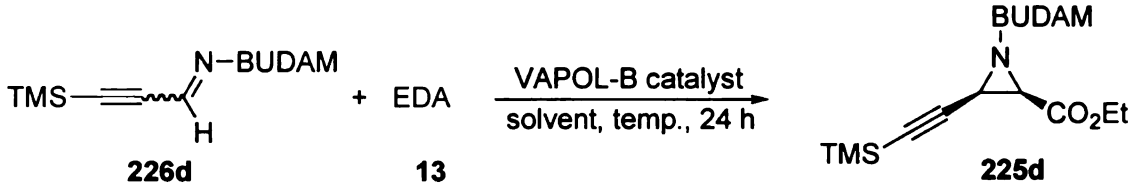
than the two step process (Table 4.6, entry 8 and 10).

Scheme 4.18 Cleavage of the BUDAM group from the aziridine **225d**



The data in Table 4.6 clearly showed that the VAPOL derived catalyst and the bulky BUDAM group are better for the synthesis of alkynyl-aziridinyl-2-carboxylates both in terms of enantioselectivities and yields, thus it was decided to utilize this combination for the optimization of this methodology. This optimization study was carried out together with an exchange student Maria Pascual Lopez-Alberca. The preliminary results are listed in Table 4.7.

Table 4.7 Optimization of conditions for the aziridination of the imine **226d**[a]



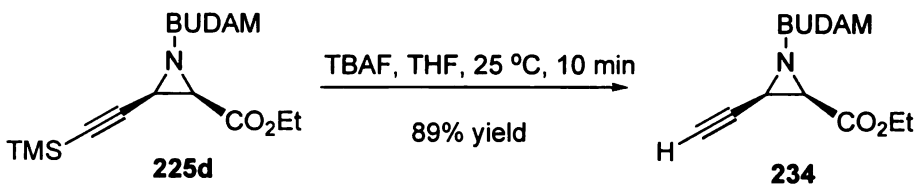
entry	loading	temp (°C)	solvent	yield (%)[b,c]	ee (%)[c,d]
1	4 mol%	25	toluene	81(89)	80(84)
2	4 mol%	0	toluene	86	83
3	4 mol%	-20	toluene	90	87
4	4 mol%	-40	toluene	69	75
5	10 mol%	-20	toluene	90	90
6	10 mol%	-20	CCl_4	86	74
7	10 mol%	-20	Et_2O	86	95

[a] Unless otherwise specified, all reactions were performed in 0.5 M in toluene with 1.1 equiv.

EDA. The catalyst were prepared from 1 equiv. VAPOL or VANOL, 4 equiv. $B(OPh)_3$ and 1 equiv. H_2O at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. [b] Isolated yield after silica gel chromatography. [c] The data in parenthesis was from the author. [d] Determined by chiral HPLC on the Chiralcel OD-H column after the conversion to the *N*-H aziridine **233d**.

The temperature study indicates that the enantioselectivity can be increased as the temperature is lowered (Table 4.7, entry 3), but a diminishing return in both the enantioselectivity and yield at –40 °C (Table 4.7, entry 4). The enantioselectivity could also be slightly enhanced by increasing the catalyst loading from 4 mol% to 10 mol% (Table 4.7 entry 3 vs. entry 5). The most exciting result came from the solvent screen, a 95% ee was obtained when ethyl ether was used as the solvent (Table 4.7, entry 7). This study indicates that the best conditions for the asymmetric synthesis of the *N*-BUDAM alkynylaziridine **225d** involves the use of 10 mol% VAPOL-borate catalyst in Et_2O at –20 °C.

Scheme 4.19 Deprotection of the TMS group from the ethynylaziridine **225d**

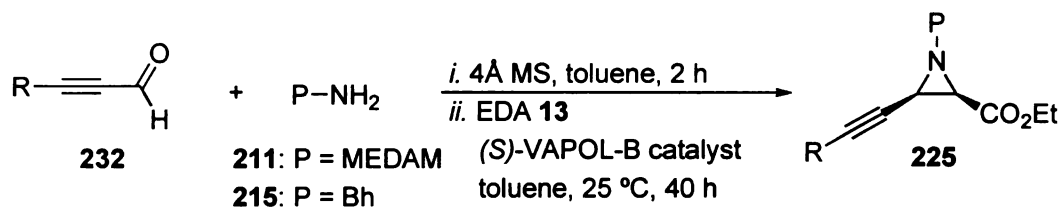


The TMS group can also be readily removed from the aziridine **225d** by using TBAF to give a good isolated yield as shown in Scheme 4.19. This opens the door to a number of subsequent applications of this protocol.

The corresponding one-pot variations of this catalytic asymmetric alkynylaziridination reaction can also be performed starting with the corresponding amines and aldehydes (Table 4.8). These one-pot reaction results are comparable with the results obtained

from the reaction using purified imines (Table 4.6). Although this one-pot study was carried out before the optimization study, it is reasonable to expect that the results from this one-pot study can be used to further improve the application of the optimized conditions revealed by the data in Table 4.7.

Table 4.8 One-pot aziridination from amines and alkynylaldehydes[a]



entry	R	P	*trans/cis* ratio of imine **226**[b]	yield of **225** (%)[c,d]	ee of **225** (%)[d,e]
1	TMS	Bh	nd	78	32
2	TIPS	Bh	5:1	93 (91)	34 (32)
3	TIPS	MEDAM	10:1	90 (87)	44 (44)

[a] Unless otherwise specified, all reactions were performed using 1 equiv amine and 1.05-1.1 equiv aldehyde with activated 4Å MS at 25 °C for 2 h in step *i*, and for 40 h in step *ii*. The AZ reaction step was carried out in 0.25 M solution with 1.1 equiv EDA **13** with 10 mol% catalyst. The catalyst were prepared from 1 equiv. VAPOL or VANOL, 4 equiv. $B(OPh)_3$ and 1 equiv. H_2O at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. nd = not determined. [b] Determined by the ^1H NMR analysis of a sample from the crude reaction mixture after 2 h. [c] Isolated yield after silica gel chromatography. [d] The data in parenthesis are that from the purified imine. [e] Determined by chiral HPLC on the Chiralcel OD-H column.

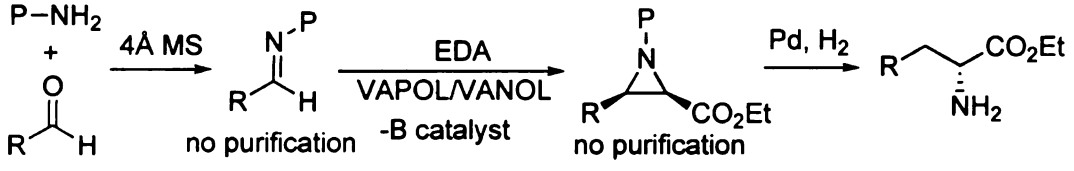
With the optimized conditions, it is expected that a series of chiral *N*-BUDAM C3-alkynylaziridines bearing aryl- and alkyl- groups on the end of the acetylene can be synthesized in good to excellent yields and enantioselectivities. And as proposed in Scheme 4.14, the asymmetric synthesis of di- or tri-substituted Δ^3-pyrrolines via stereospecific formation of the allene intermediate from the corresponding activated *cis*-

alkynylaziridinyl-2-carboxylates **224** is an ongoing project in the group.

4.5 One-pot synthesis of optically pure α-amino esters from amines and aldehydes

The preliminary studies mentioned in this chapter have clearly demonstrated that the one-pot imine formation-AZ reaction protocol is practical, and the subsequent same-pot deprotection is also feasible as shown in Scheme 2.1. Further activation of the crude *N*-H aziridines also gave good yields (Scheme 3.1). Since all these studies could be carried out without intermediate purification, a one-pot optically active α-amino ester synthesis protocol was envisioned, in which, the imine formation, AZ reaction, reductive ring opening and deprotection steps are all carried out in the same pot without the purification of any of the intermediates (Scheme 4.20).

Scheme 4.20 Proposed one-pot synthesis of optically active α-amino ester

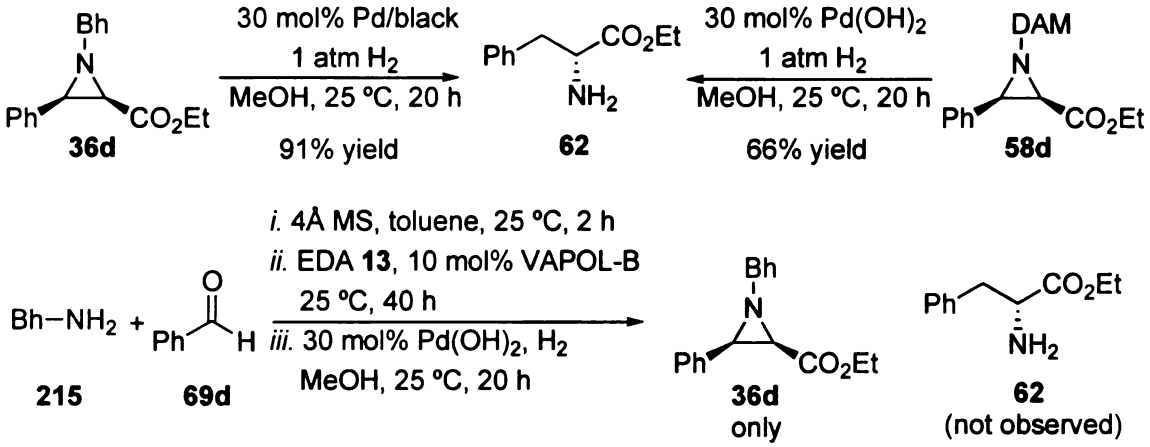


4.5.1 Preliminary investigation on the one-pot amino ester synthesis

Since the ring opening of the *N*-benzhydryl aziridine **36** via hydrogenolysis was previously shown in our group to be highly effective in exclusively providing the deprotected α-amino ester[22b] (Scheme 2.4), the aziridine **36d** was chosen for the preliminary investigation for the one-pot amino ester synthesis. Considering the availability of the reducing reagents and their efficiency towards the reductive ring opening of the aziridines, some hydrogenolysis[1] catalysts such as the Pearlman's catalyst ($Pd(OH)_2$), Pd black, and Pd/C were examined. Even though these catalysts work well with the purified aziridines (Scheme 4.22), they might be deactivated by the presence of other compounds in the crude reaction mixture from the one-pot reaction

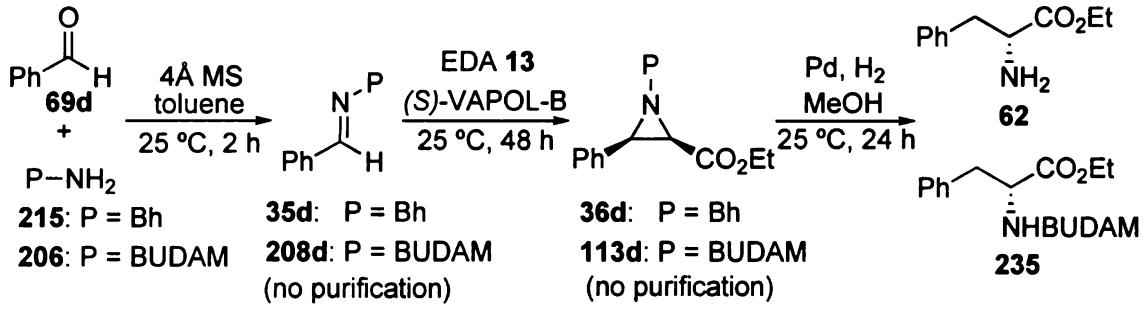
from the amine and the aldehyde. This was found to be true in the case of the one-pot experiment using Pearlman's catalyst, where the aziridine **36d** was isolated without a trace of the desired ring opening product **62** (Scheme 4.21).

Scheme 4.21 Reductive ring opening of aziridine **36d**



The results of the one-pot reaction with different amines and reductants are shown in Table 4.9. If the benzhydryl amine **215** was used as the starting material, the product α-amino ester **62** with the benzhydryl group cleaved was always observed (Table 4.9, entry 1 to 4), while in the case of the *N*-BUDAM amine **206**, the *N*-BUDAM amino ester **235** was isolated (Table 4.9, entry 5). The one-pot procedure gave a good overall isolated yield of the desired product **62** (Table 4.9, entry 1). The hydrogenolysis of the crude product from the *N*-BUDAM amine **206** could be performed with a sub-stoichiometric amount of Pd(0) (Table 4.9, entry 5), whereas a stoichiometric amount of Pd(0) was required for the reaction of the benzhydryl amine **215** to obtain a good yield (Table 4.9, entry 1 vs. 2). The outcome was not significantly effected whether hydrogen or formic acid was used as reductant (Table 4.9, entries 1 and 3).

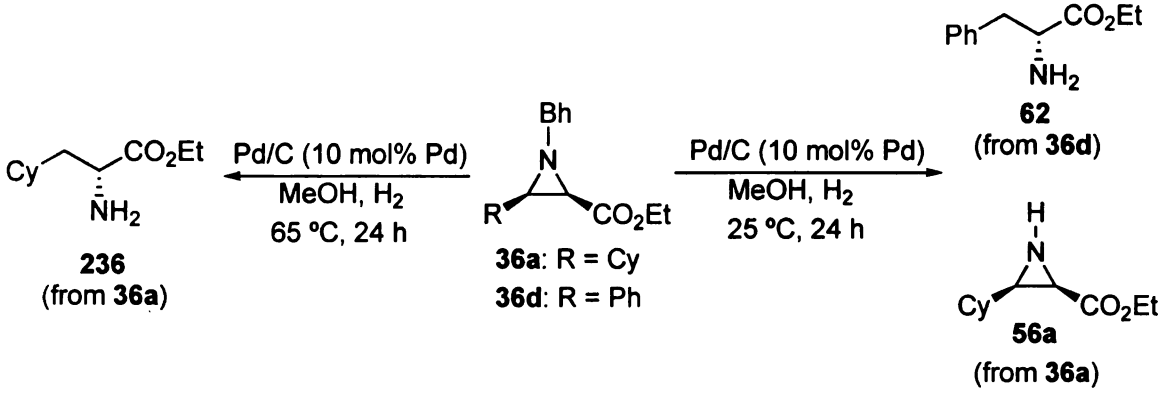
Table 4.9 One-pot amino ester synthesis[a]



entry	P	VAPOL (mol%)	Pd black (equiv)	reductant	yield of **62** (%)[b]
1	Bh	10	1	H_2	69
2	Bh	10	0.3	H_2	<50% conv.
3	Bh	10	1	HCO_2H	72
4	Bh	10	0.3	HCO_2H	14
5	BUDAM	2	0.3	HCO_2H	76[c]

[a] Unless otherwise specified, all reactions were performed using 1 equiv amine and 1.05-1.1 equiv aldehyde with activated 4Å MS at 25 °C for 2 h in step *i*, and for 40 h in step *ii*. The AZ reaction step was carried out in 0.25 M solution with 1.1 equiv EDA **13**. The catalyst were prepared from 1 equiv. VAPOL or VANOL, 4 equiv. $B(OPh)_3$ and 1 equiv. H_2O at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. [b] Overall isolated yield from the amine after chromatography using neutralized silica gel. [c] The yield of the compound **235**, product **62** was not observed.

Scheme 4.22 Hydrogenolysis of the *N*-Bh aziridines catalyzed by Pd/C

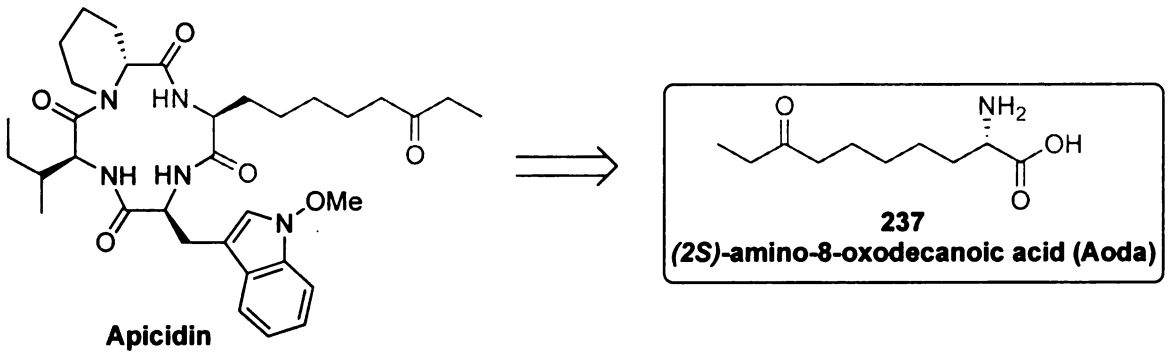


The Pd/C catalyzed ring opening reaction was examined on the purified 3-phenyl aziridine **36d** and the purified 3-cyclohexyl aziridine **36a** (Scheme 4.22). The preliminary experiments indicated that the Pd/C could be used at 10 mol% Pd, and the ring opening reaction along with the cleavage of the benzhydryl group was obtained at room temperature for aziridine **36d**. The C3-cyclohexyl substituted aziridine **36a** under the same conditions generated the *N*-H aziridine **56a** exclusively (a similar reaction was discussed in Section 2.2.1), while increasing the temperature from 25 °C to 65 °C resulted in the formation of the desired amino ester **236.**

4.5.2 Proposed synthesis of *(2S)*-amino-8-oxodecanoic acid (Aoda)

The *(2S)*-amino-8-oxodecanoic acid **237** (Aoda) and its derivatives are common units in natural products such as Apicidin[100] (Figure 4.1), which belongs to a new family of natural cyclic tetrapeptides that have been recently identified as antiprozoal agents. These compounds can be used as inhibitors of the histone deacetylase (HDAC), which is a class of enzymes implicated in epigenetic disorders. All previous total syntheses[101] of Aoda start from the chiral pool and take more than 8 steps except the most recent approach by Barrett,[101f] which takes 4 steps from the Schollkopf's auxiliary.

Figure 4.1 Example of *(2S)*-amino-8-oxodecanoic acid as a structure moiety in natural products

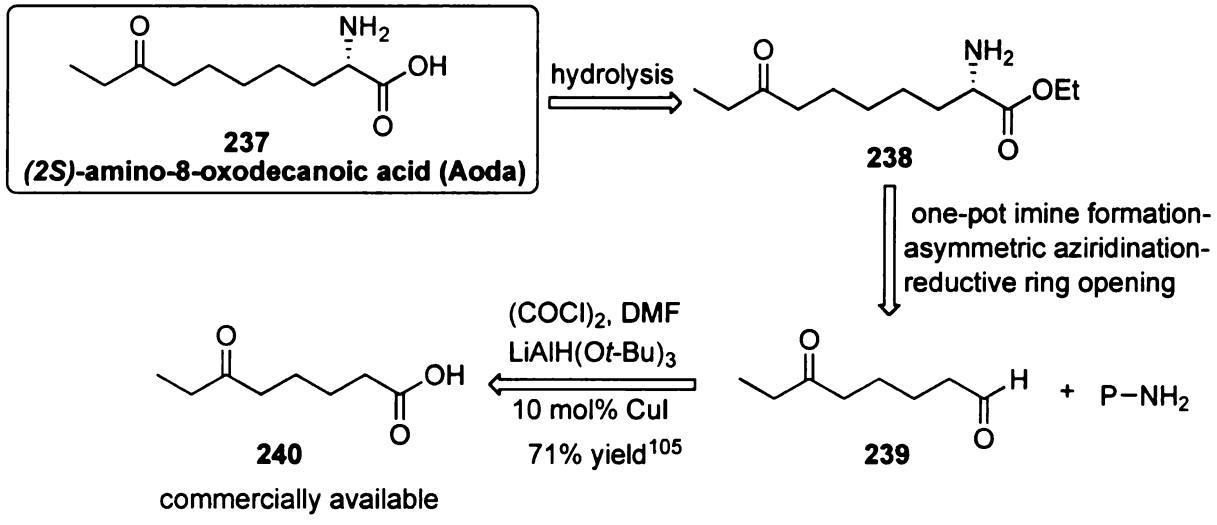


Apicidin

237
(2S)-amino-8-oxodecanoic acid (Aoda)

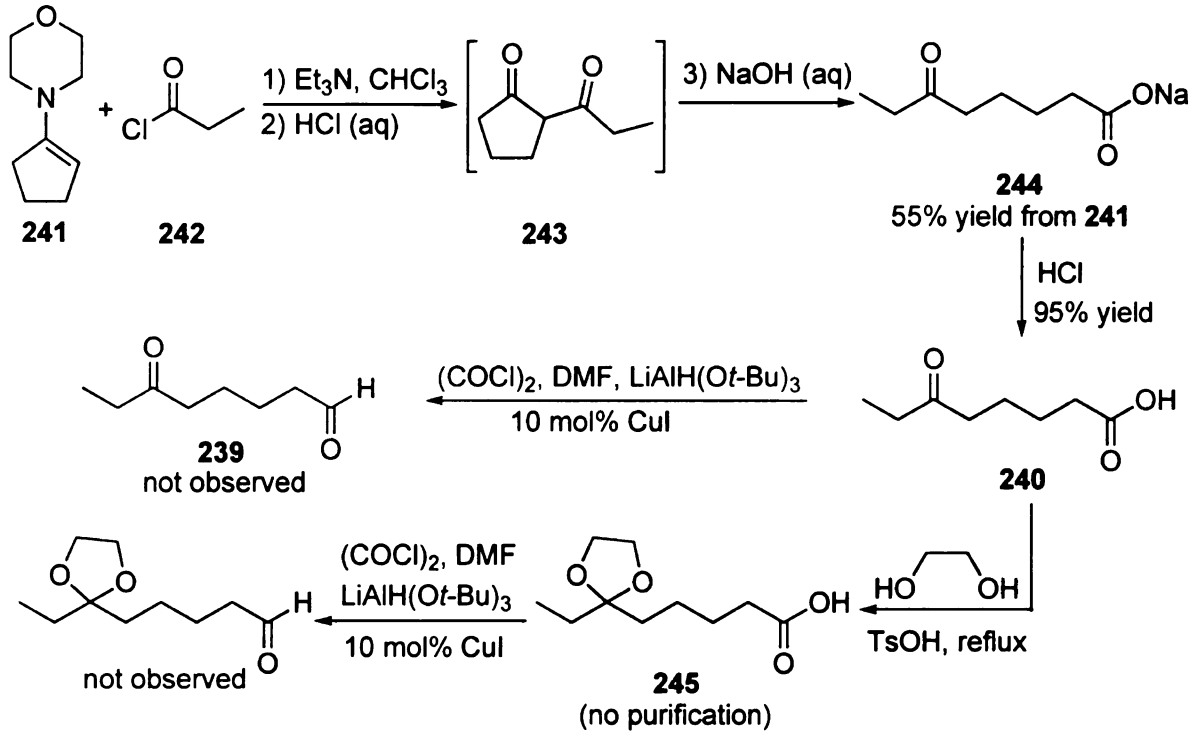
It was envisioned that the one-pot α-amino ester synthesis protocol could be applied to the asymmetric total synthesis of Aoda **237** as proposed in Scheme 4.23.

Scheme 4.23 Proposed total synthesis for Aoda



From the commercially available acid **240**, the aldehyde **239** can be obtained in good yields, according to the procedure reported by Fujisawa.[102] For the subsequent one-pot reaction, the *N*-MEDAM and the *N*-BUDAM amines will be used because they gave the best enantioselectivities and yields for the aziridination of the primary alkyl substituted aldehydes, and their one-pot aziridination reactions were also successful (Table 4.5, entry 5 and 8). The use of 10 mol% catalyst may be necessary to obtain the highest yield and asymmetric induction in the synthesis of the intermediate **238**, which upon hydrolysis should furnish the target molecule Aoda **237**. The entire total synthesis may take only three steps from the acid **240**. The ketone unit in the aldehyde **239** may need to be protected, however, this is not expected to be required considering the significant weaker reactivity of ketones towards amines as compared to aldehydes. In addition, the poorer coordination ability of the oxygen verses the imine nitrogen for the catalyst may allow for the presence of the ketone in the aziridination step.

Scheme 4.24 Preparation of the aldehyde **239**



Considering the cost of the acid **240**, it was decided to prepare it based on reported procedures.[103] As shown in Scheme 4.24, starting from 1-morpholino-1-cyclopentene **241** and propionyl chloride **242** in dry chloroform, the ketoenamine adduct 2-propionyl-1-cyclopentanone **243** was generated *in situ*,[103a] which upon alkaline cleavage led to the formation of the sodium salt of 6-ketooctanoic acid **244**.[103b] Subsequent acidification with aqueous hydrochloric acid afforded the desired acid **240** in 52% overall yield from compound **241**. The ketone unit in acid **240** was protected using ethylene glycol to give the protected acid **245**, which was carried on to the reduction.[103] At the same time, the unprotected acid **240** was also subjected to the same reduction conditions. Both acids **240** and **241** were recovered after these experiments without any detectable amount of the desired aldehyde products. The possible explanation for this failure might be the quality of the reducing reagents used. However, this one small obstacle notwithstanding, based on the information obtained from the one-pot aziridinations and ring opening

reactions described in this work, it is reasonable to expect that this total synthesis will be finished in the near future.

4.6 Conclusion

The highly reactive catalytic AZ reaction systems with the *N*-BUDAM or the *N*-MEDAM imines were studied. For most aryl *N*-BUDAM imines, quantitative yields and almost enantio-pure aziridines were obtained. For the bulky alkyl substrates, *N*-MEDAM imines generally afford better enantioselectivities than the corresponding *N*-BUDAM imines. The one-pot imine formation-AZ reaction procedure was shown to be practical, albeit with a slightly higher catalyst loading (4 – 10 mol%). As an ongoing project, the BUDAM group was found to be the best nitrogen protecting group for the investigation of the catalytic asymmetric alkynylaziridination, and a substrate screen with various alkynyl aldehydes should be performed in the future with the optimized reaction conditions. The attempted one-pot synthesis of α–amino esters and its further application to the total synthesis of Aoda is promising and should be finished in the near future.

CHAPTER FIVE

CATALYTIC ASYMMETRIC STRECKER REACTION AND KINETIC RESOLUTION OF AMINES

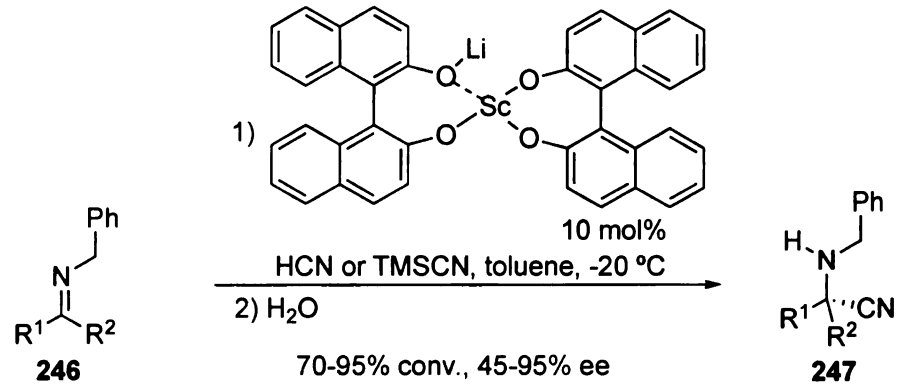
5.1. The catalytic asymmetric Strecker reaction

5.1.1 Introduction

The classic Strecker reaction[104] is one of the most convenient methods for the preparation of α-amino acids. Asymmetric approaches for this reaction usually involve using an imine bearing a chiral unit.[105] Since Lipton reported the first catalytic asymmetric Strecker-type reaction in 1996[106a] using a dipeptide ligand as the chiral catalyst, a variety of different catalytic asymmetric Strecker-type reactions have emerged.[106] While several different ligands have been employed the ones that have been examined to the largest extent in recent years are BINOL or its derivatives.[28] However, all systems involving BINOL and/or BINOL derivatives gave low to moderate asymmetric inductions, while excellent enantioselectivities have been obtained only for some specific substrates.[107] The best result involving the use of a BINOL derivative as the chiral ligand has been reported by the Vallee's group,[107d] in which a chiral heterobimetallic complex $Sc(BINOL)_2Li$ was used as the catalyst and up to 95% ee's were obtained (Scheme 5.1).

During the course of our studies on various catalytic asymmetric reactions, it was expected that VANOL and/or VAPOL derived catalysts, which had proven to be superior catalysts for several asymmetric reactions,[29] might be also able to induce asymmetry for the Strecker reaction. It was thus decided to investigate the asymmetric Strecker reaction using either the VANOL or VAPOL-borate complex as a chiral Lewis acid catalyst or the VANOL or VAPOL phosphoric acid as a chiral Brønsted acid catalyst.

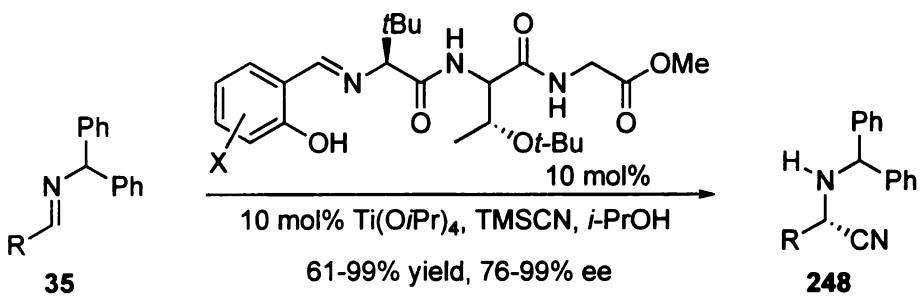
Scheme 5.1 Vallee's catalytic asymmetric Strecker reaction



5.1.2 Asymmetric Strecker reaction catalyzed by VAPOL or VANOL–borate catalyst

The *N*-benzhydryl imine **35d** were chosen for the initial study, since it had proven to be successful substrate in our aziridination protocol using the VANOL/VAPOL derived catalyst systems, and it had also been shown to be a good substrate in Hoveyda's asymmetric Strecker reaction system[106n] (Scheme 5.2). In Hoveyda's report, a large variety of *N*-benzhydryl substituted imines gave Strecker products **248** in good yields and good to excellent enantioselectivities under catalysis by a chiral peptide-Ti complex (85-99% ee when R is an aryl group, 76-90% ee when R is a aryl group).

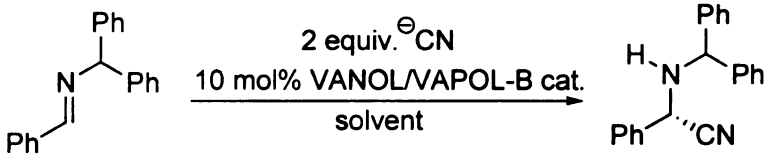
Scheme 5.2 Hoveyda's Strecker reaction with *N*-benzhydryl imines



The results of our studies for the asymmetric Strecker reaction using the VAPOL/VANOL-borate catalysts are listed in Table 5.1. When TMSCN was used as a cyanide source, incomplete conversions were always obtained (Table 5.1, entry 1, 2),

while HCN, which was generated *in situ* from TMSCN and methanol, afforded complete conversions. However, low enantioselectivities were obtained with the best result being 20% ee (Table 5.1, entry 5). The background reaction without the catalyst gave 10% conversion (Table 5.1, entry 7). An attempt to increase the asymmetric induction by lowering the reaction temperature suffered from both incomplete conversion and low enantioselectivity (Table 5.1, entry 6).

Table 5.1. Asymmetric Strecker reaction catalyzed by VAPOL/ VANOL-B catalyst[a]



35d **249a**

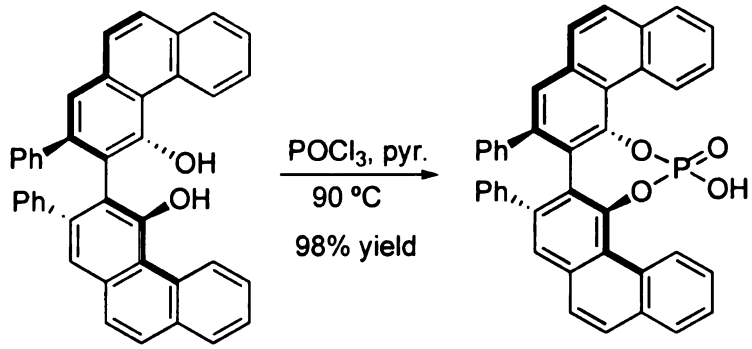
entry	$^{-}$CN source	ligand	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	TMSCN	*rac*-VAPOL	CCl_4	-20	24	25% conv.	nd
2[d]	TMSCN	*rac*-VANOL	CH_2Cl_2	-40	44	<50% conv.	nd
3	HCN	*(S)*-VAPOL	CCl_4	-15	24	94	1
4	HCN	*(S)*-VANOL	CCl_4	-15	24	92	2
5	HCN	*(S)*-VAPOL	CH_2Cl_2	-78 °C, 6h, then -15 °C,18h		85	20
6	HCN	*(S)*-VANOL	CH_2Cl_2	-78	20	49[e]	14
7	HCN	none	CCl_4	-15	24	10% conv.	nd

[a] Unless otherwise specified, HCN was generated *in situ* from TMSCN and MeOH. All reactions were carried out with 1 mmol imine and 2 mmol cyanide in 0.12 M solution with 10 mol% catalyst, the catalyst was generated from 1 equiv VANOL/VAPOL and 3 equiv $B(OPh)_3$ at 80 °C for 1 h, followed by high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. nd = not determined. [b] Isolated yield after silica gel chromatography. [c] Determined from chiral HPLC on Chiralpak AD column. [d] 0.2 equiv PhOH was added as an additive. [e] 60% conversion.

5.1.3 Asymmetric Strecker reaction catalyzed by the VAPOL-phosphoric acid

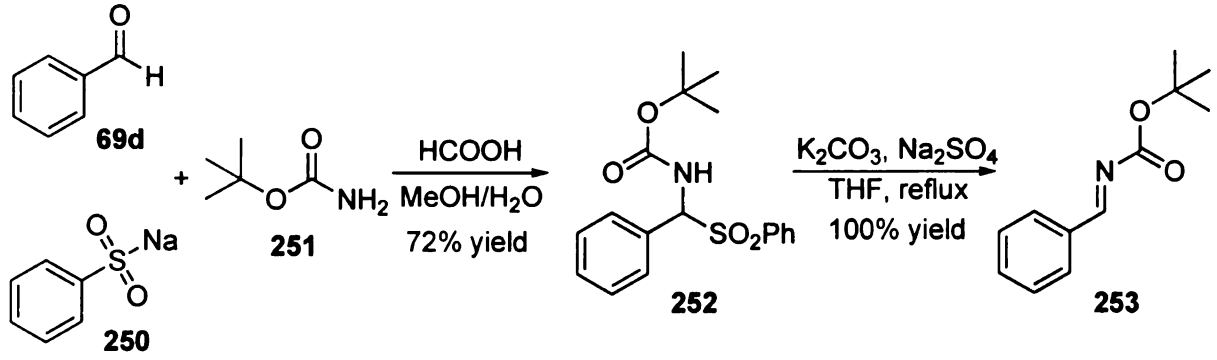
Since Terada[108a] and Akiyama[108b] independently reported their asymmetric reactions catalyzed by optically pure phosphoric acids derived from BINOL, this type of catalyst has emerged as highly effective chiral Brønsted acids in a variety of catalytic asymmetric reactions.[108] Antilla's group has reported several catalytic asymmetric reactions catalyzed by the VAPOL-phosphoric acid **49** (Section 1.4.1, Scheme 1.16).[30] Encouraged by these successful applications of chiral phosphoric acids, it was decided to examine the effect of VAPOL-phosphoric acid as a chiral Brønsted acid catalyst for the Strecker reaction. The catalyst *(S)*-**49** was prepared in 98% yield from *(S)*-VAPOL, following our previous published procedure[20] (Scheme 5.3).

Scheme 5.3 Preparation of the VAPOL-phosphoric acid **49**



(S)-VAPOL *(S)*-**49**

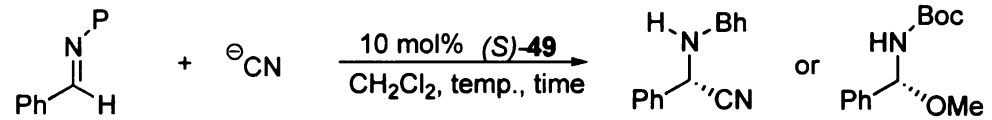
Scheme 5.4 Preparation of the *N*-Boc imine **253**



As an alternative to the imine **35d**, the *N*-Boc imine **253** was also prepared and

tested in the Strecker reaction, since it was employed in the imine amination reaction catalyzed by **49** (Scheme 1.16).[30a] The *N*-Boc imine could be easily prepared in high overall yield by following a reported procedure[109] (Scheme 5.4). The condensation of aldehyde **69d**, the Boc amine **251** and the sodium sulfinate **250** in the presence of formic acid afforded the intermediate **252** in good yield, which underwent an elimination reaction resulting in the formation of the *N*-Boc imine **253** as a colorless liquid in quantitative recovery.

Table 5.2. Strecker reaction catalyzed by the VAPOL-phosphoric acid **49**[a]



35d: P = Bh
253: P = Boc
1equiv.

2 equiv

249a

254

entry	imine	$^-$CN source	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**35d**	TMSCN	0 to 25	24	0% conv.	nd
2	**35d**	TMSCN	55	14	33% (**249a**)	2
3	**35d**	HCN	0 to 25	24	0% conv.	nd
4	**35d**	HCN	55	14	76% (**249a**)	12
5[d]	**253**	HCN	-78	6	35% (**254**)	nd
6	**253**	HCN	-78	8	40% (**254**)	0

[a] Unless otherwise specified, all reactions were carried out with 1 mmol imine and 2 mmol cyanide in 0.12 M solution with 10 mol% *(S)*-**49**. The HCN was generated *in situ* from TMSCN and MeOH. nd = not determined. [b] Isolated yield after silica gel chromatography. [c] Determined from chiral HPLC on the Chiralpak AD column. [d] Racemic VAPOL-phosphoric acid was used.

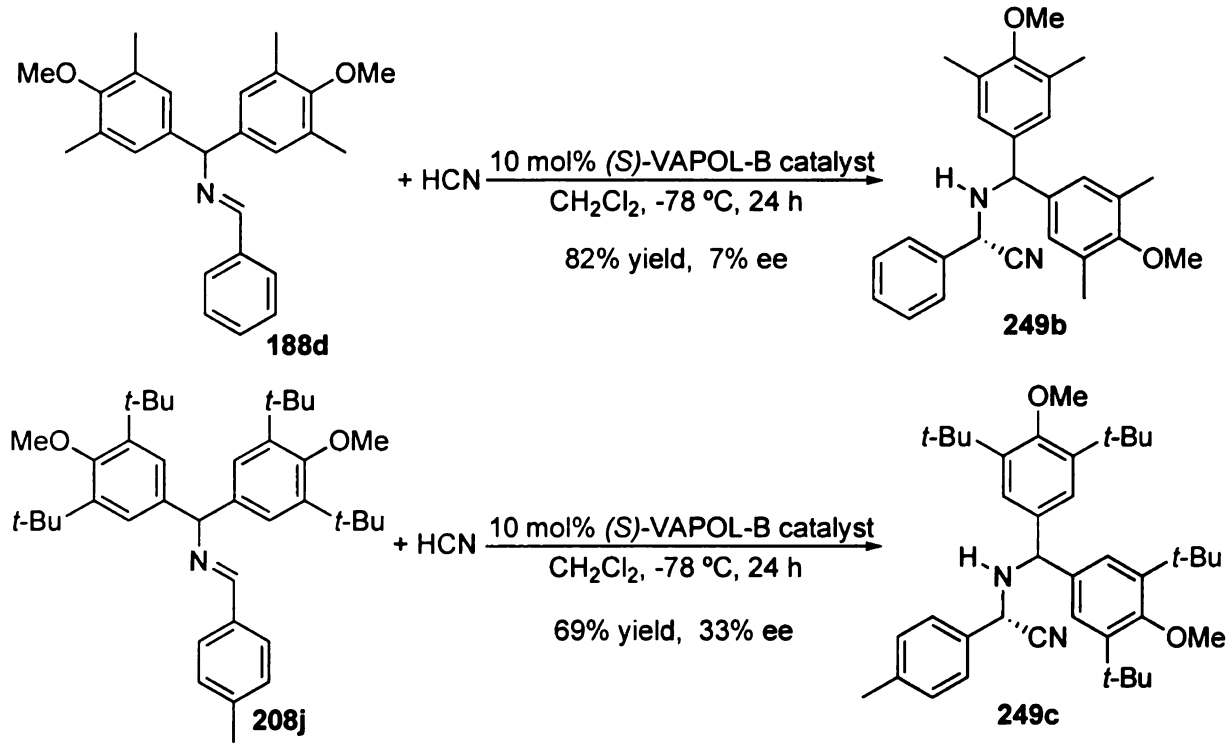
The *N*-Bh imine **35d** and the *N*-Boc imine **253** were then examined for the asymmetric Strecker reaction catalyzed by the optically pure VAPOL-phosphoric acid **49**

(Table 5.2). When **35d** was used, reactions catalyzed by the phosphoric acid **49** were much slower than those catalyzed by the VAPOL-borate catalyst (Table 5.2 vs. Table 5.1). With the phosphoric acid **49**, higher temperature was required (55 °C) for complete conversions, while the same imine gave complete conversion at –15 °C with the VAPOL-borate catalyst (Table 5.1, entry 5 vs. Table 5.2, entry 4). For all reactions catalyzed by the VAPOL-phosphoric acid, low to moderate yields were obtained along with low enantioselectivities. When the activated *N*-Boc imine **253** was used, instead of the normal Strecker reaction product, an unexpected aminal product **254** was isolated in moderate yield (Table 5.2, entry 5). This compound might have resulted from the nucleophilic addition of methanol to the imine **253**, since the HCN used in this reaction was generated *in situ* from methanol and TMSCN in toluene. Unfortunately, no asymmetric induction was obtained in this aminal formation (Table 5.2, entry 6).

The above mentioned results indicated that the asymmetric induction in this catalytic asymmetric Strecker system was far from satisfactory (Table 5.1 and 5.2). If this was due to the small size of the cyano group, it was hoped that the asymmetric induction might be improved by increasing the size of the imines, which can be done either by using a bulky *N*-protecting group or by using ketimines, which have previously been successfully applied in some Strecker type reactions.[106k,r,q,107c,d]

Thus, the asymmetric Strecker reaction was performed by using bulky *N*-BUDAM imine **208j** and the VAPOL-borate catalyst. The asymmetric induction was improved from 20% ee (*N*-Bh imine **35d** in Table 5.1, entry 5) to 32% ee (Scheme 5.5, product **249c**). Surprisingly, the bulky *N*-MEDAM imine **188d** gave even lower induction (7% ee). These results demonstrate that changing the size of the *N*-protecting group in imines is not sufficient for achieving high asymmetric inductions in our VAPOL/VANOL derived catalytic asymmetric Strecker systems.

Scheme 5.5 Strecker reactions of bulky imines

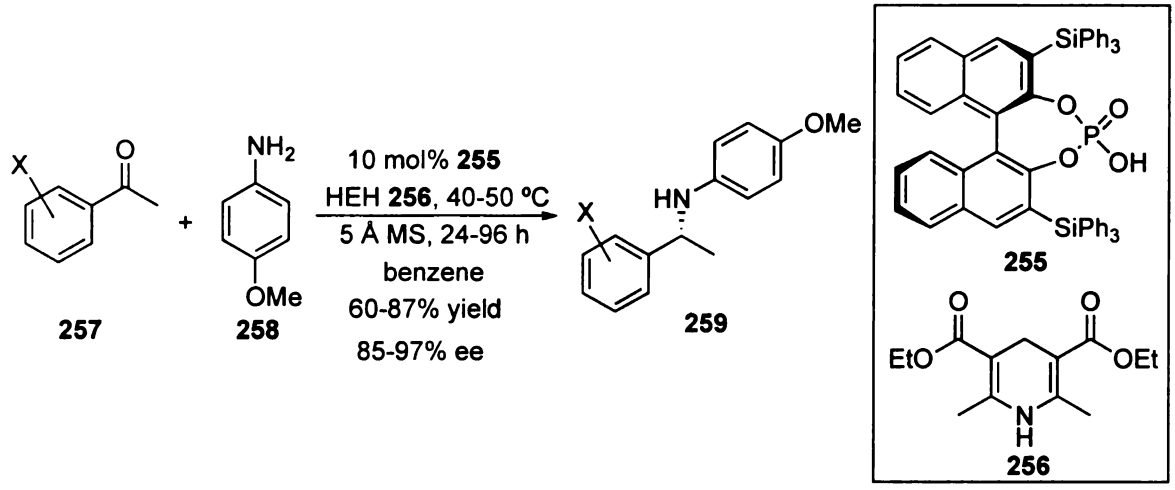


5.2 Kinetic resolution of amines

5.2.1 Introduction

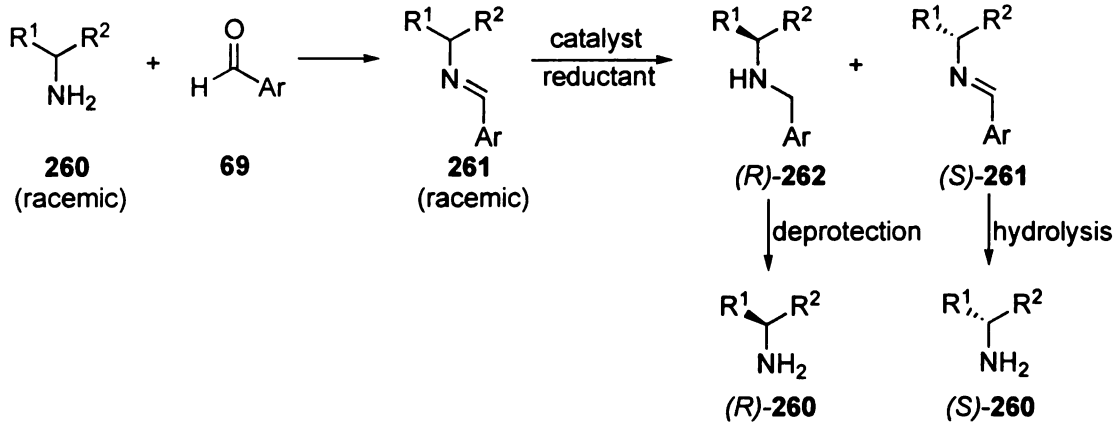
The kinetic resolution of amines is a relatively rare event and only a few successful examples have been reported recently.[110] We started our investigation in this area inspired by a report from MacMillan[90] (Scheme 5.6), in which an asymmetric reduction of *in situ* generated imines with the Hantzsch ester[111] **256** afforded amines **259** in excellent yields and enantioselectivities under the catalysis of the optically pure BINOL-derived phosphoric acid **255**.

Scheme 5.6 MacMillan's asymmetric amination reaction using phosphoric acid catalyst **255**



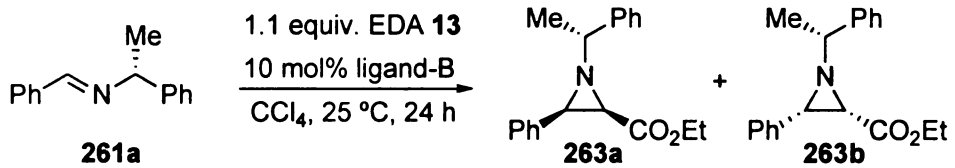
It was expected that this type of asymmetric reduction of imines could be applied to the kinetic resolution of amines. As illustrated in Scheme 5.7, by using a VAPOL or VANOL derived optically pure catalyst, the kinetic resolution of amines could be carried out via the enantioselective reduction on one enantiomer of the racemic imine **261** (generated *in situ*) in the matched case. Subsequent hydrolysis of the mismatched enantiomer of the imine **261** should give the enantiomerically enriched amine **260**. Deprotection of the reduction product **262** (matched case) would then release the other enantiomer of the amine **260**.

Scheme 5.7 Proposed kinetic resolution of amines



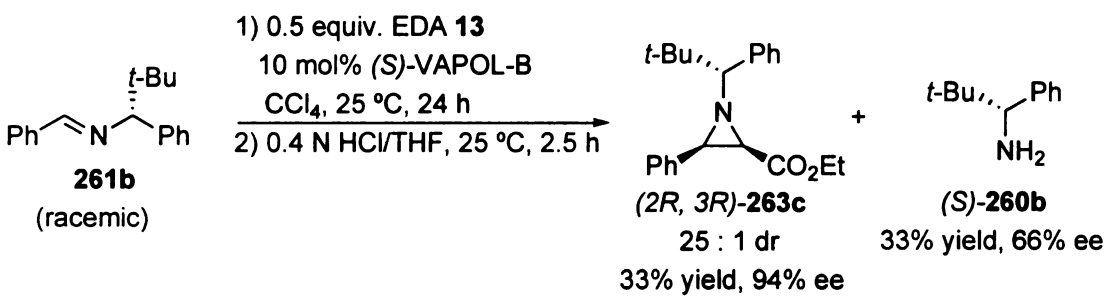
Scheme 5.8 Previous studies on the matched and mismatched AZ reactions and the corresponding study on the kinetic resolution

Match and mismatch results:



entry	ligand	**263a** : **263b**	yield of **263** (%, major)
1	*(S)*-VAPOL	>50 :1	79 (**263a**)
2	*(R)*-VAPOL	1 : 2	40 (**263b**)

Kinetic resolution via aziridination reaction:



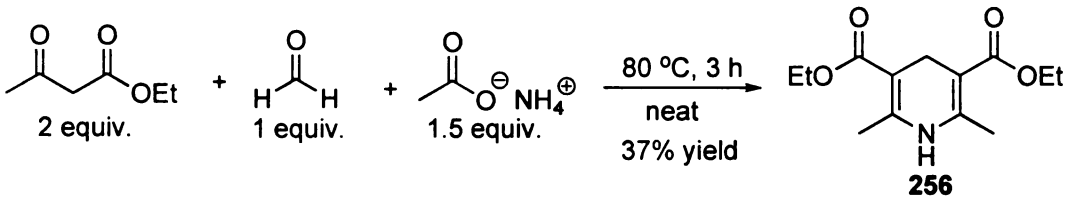
The rationale for the design of this kinetic resolution strategy was based on two previous observations. One observation was the match/mismatch study[37e] performed by a former group member, Dr. Yu Zhang, for the VAPOL/VANOL-borate catalyzed AZ reaction of the chiral imine **261**. This was then successfully applied in a preliminary study towards the kinetic resolution of imine **261b** via the aziridination reaction (Scheme 5.8). The other observation was that the VAPOL/VANOL-borate catalyst works well for the one-pot imine formation-AZ reaction (section 4.3).

5.2.2 Asymmetric reduction of the imine 35d

We decided to start the investigation by using the VAPOL-phosphoric acid **49** or the VAPOL/VANOL-borate complex as the chiral catalyst and the Hantzsch ester **256** as the reductant. The Hantzsch ester (HEH), was easily prepared by following a published

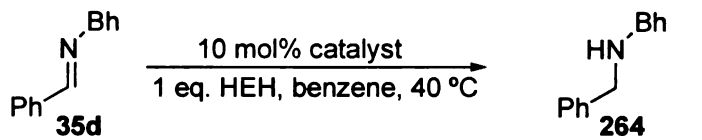
procedure[112] (Scheme 5.9). The HEH was afforded in moderate yield and was used in the subsequent reduction experiments without purification.

Scheme 5.9 Preparation of the Hantzsch ester **256**



The HEH reduction reaction was first tested on the simple *N*-benzhydryl imine **35d** under the catalysis of both the VAPOL-borate complex and the VAPOL-phosphoric acid **49** (Scheme 5.10). Although the reaction catalyzed by the phosphoric acid **49** gave incomplete conversions, both the VAPOL-borate complex and the phosphoric acid could indeed catalyze the HEH reduction.

Scheme 5.10 Reduction of the imine **35d** using HEH as the reductant



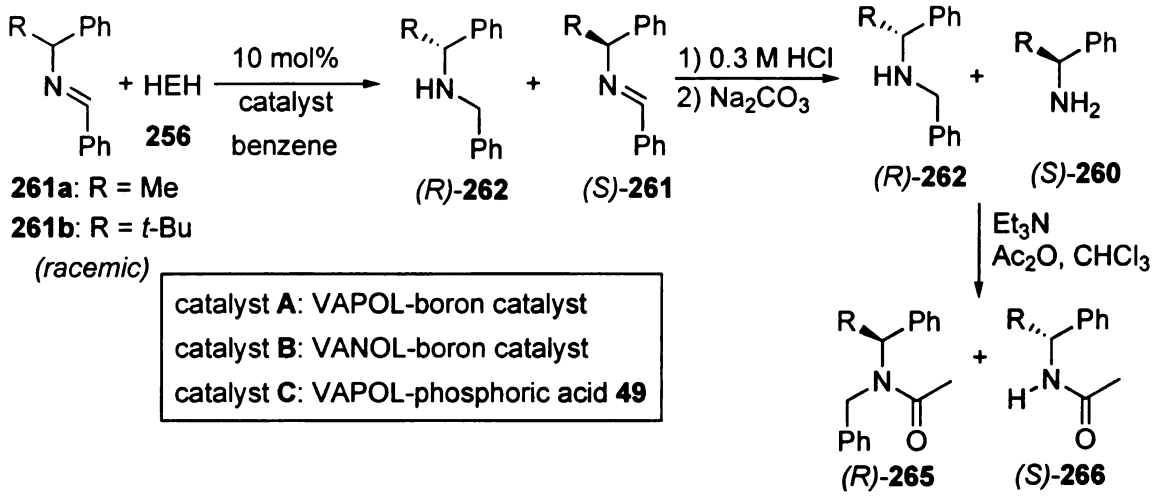
1) *(S)*-VAPOL-B, 96 h
2) *(S)*-**49**, 72 h

80% yield
40% conversion

5.2.3 Asymmetric reduction catalyzed by the VAPOL-borate catalyst

The investigation for the kinetic resolution of amines catalyzed by either the VAPOL-borate complex or the VAPOL-phosphoric acid was carried out first with the racemic imine **261** and the results are shown in Table 5.3. Both the reduction product **262** and the amine **260**, which was obtained from the hydrolysis of the unreacted imine **261**, were converted to their corresponding *N*-Ac protected products **265** and **266**, since the enantiomers of these compounds gave better separation on chiral HPLC.

Table 5.3 Kinetic resolution with imine **261**



entry	HEH (equiv)	catalyst	series of imine	condition	conv. [a]	yield (%)[b]	ee (%)[c]
1	1.1	*rac*- **A**	**a**	60°C, 48h	67%	nd	nd
2	0.55	(*S*)- **A**	**a**	60°C, 20h	100%	36 (**265a**) 30 (**266a**)	17 18
3	1.1	*rac*- **B**	**a**	45°C, 72h	50%	nd	nd
4	0.55	(*R*)- **C**	**a**	25°C, 20h	100%	22 (*ent*-**265a**)	27
5	0.55	*rac*- **C** + 1 eq.TFA	**a**	25°C, 20h	100%	70 (**265a**)	nd
6	0.55	(*S*)- **C** + 0.5 eq. TFA	**a**	25°C, 20h	100%	45 (**265a**)	9
7	1.1	1 eq. TFA	**a**	25°C, 20h	95%	nd	nd
8	1.1	*rac*- **A**	**b**	60°C, 48h	64%	nd	nd
9	1.1	*rac*- **C**	**b**	45°C, 72h	45%	nd	nd
10	1.1	(*S*)- **A**	**b**	45°C, 72h	100%	70 (**262b**)	nd
11	0.55	(*S*)- **A**	**b**	65°C, 20h	100%	42 (**262b**) 5 (**260b**)	nd

[a] The conversion was calculated based on the consumption of HEH. [b] Isolated yield after silica gel chromatography and calculated based on the imine **261**. nd = not determined. [c] Determined from the chiral HPLC on the Chiralpak AD column for the compounds **265** and **266**. nd = not determined.

When the racemic catalysts were used, all reactions gave incomplete conversion (Table 5.3, entry 1, 3, 8 and 9). Both the optically pure VAPOL-borate catalyst and the optically pure VAPOL phosphoric acid could reduce one enantiomer of the racemic imine **261a** to give an enantio-enriched amine **262a** in the matched case, but the selectivities were low (up to 27% ee) (Table 5.3, entry 4), and the isolated yields of either the reduction product **262** or the protected product **265** were low (upon to 36% yield, Table 5.3, entry 2). The other enantiomer of the amine **260** that was obtained after the hydrolysis of the mismatched enantiomer of imine **261** was also isolated in low yield with low % ee (Table 5.3, entry 2 and 11).

Using trifluoroacetic acid (TFA) as an additive increased the reactivity (>95% conversion after 2 h at 25 °C), but decreased the enantioselectivity (Table 5.3, entry 6). If TFA was used alone, a 95% conversion was obtained (Table 5.3, entry 7), which indicated that TFA itself could mediate the reduction of the imine **261a** with HEH. Another imine **261b** was also tested in this reaction and the enantioselectivity might also be low (the chiral HPLC conditions for separating the enantiomers of the amine **262b** have not been found yet). Although the two enantiomers of the amine **260b** could be separated on chiral HPLC, only trace amounts of this compound was obtained after the hydrolysis (Table 5.3, entry 11).

5.3 Conclusion

The studies on the asymmetric Strecker reaction of imines and the kinetic resolution of amines under catalysis by the VAPOL/VANOL-borate complex or the VAPOL-phosphoric acid were discussed. The Strecker reactions generally gave complete conversions but low enantioselectivities (<20% ee) with these catalytic system. The bulky *N*-BUDAM imine **208d** could only improve the asymmetric induction to 32% ee.

The kinetic resolution of amines via the asymmetric reduction of the *in situ* generated

imine **261** could only give up to 27% ee for the matched amine product. A better method for the recovery of the other enantiomer of the amine **260** from the unreacted imine **261** is desirable because the original hydrolysis procedure gave only low to moderate recovery.

CHAPTER SIX

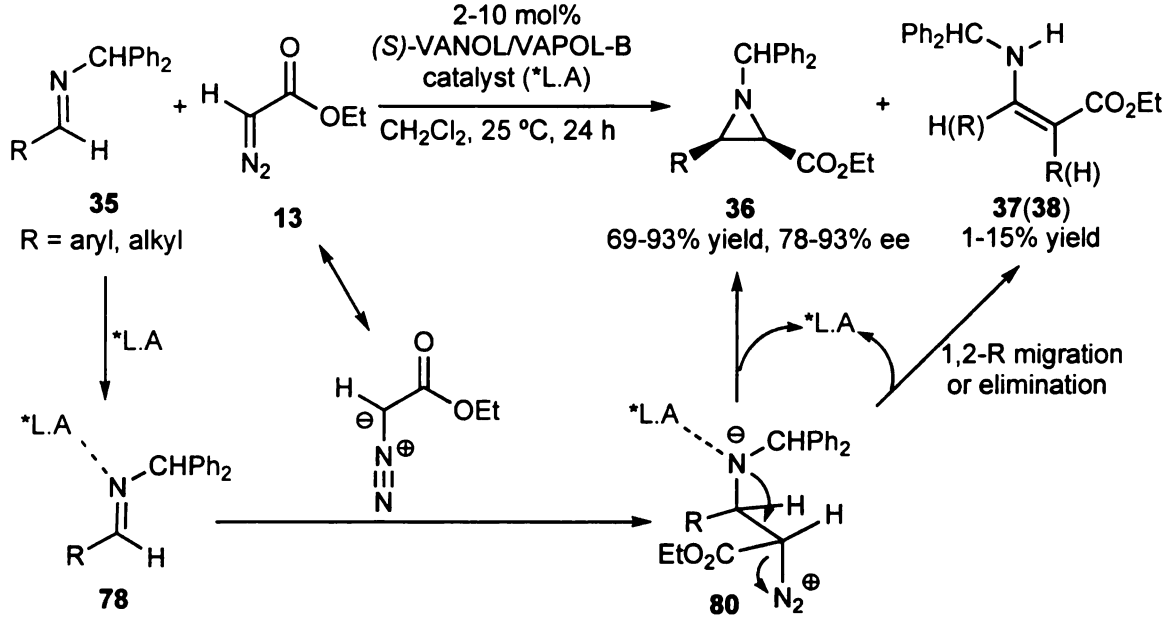
STUDY OF VAPOL/VANOL-BORATE COMPLEX IN THE AZ REACTION

6.1 Introduction

6.1.1 Catalytic AZ reaction with VAPOL/VANOL-borate catalyst

In early 2000, our group reported a highly enantioselective catalytic asymmetric aziridination (AZ) reaction methodology involving either a VAPOL-borate or a VANOL-borate complex mediated addition of a diazo compound to an imine.[22] This method is general for Schiff bases generated from a variety of aldehydes as shown in Scheme 6.1, and is still the most effective Lewis acid catalyzed AZ reaction.[19] As was discussed in previous chapters, by varying the *N*-protecting groups, product aziridines can be readily converted to activated aziridines which in turn can be used in various aziridine ring-opening reactions (Chapter 3).

Scheme 6.1 Previous AZ reaction with VANOL/VAPOL-borate catalyst



However, the aziridination conditions were not extensively optimized and this was partly due to the lack of understanding of the details of this transformation. These details include the structure of the possible active catalyst, the interaction between the catalyst and the imine substrate and how the electronic and/or steric properties of the catalyst and the substrate could be used in the fine-turning of the reaction. Understanding the mechanism of this reaction would be helpful for the improvement of the existing catalytic system and the design of other chiral catalysts.

It was believed that the VANOL/VAPOL-borate catalyst system is a Lewis acid mediated process (Scheme 6.1), and this was based on a mechanism proposed by Brookhart and Templeton[17] from their studies of non-chiral Lewis acid catalyzed reactions of ethyl diazoacetate and imines. In this mechanism, the imine **35** is activated by the chiral Lewis acid to form the complex **78**, which is attacked by the negatively polarized carbon of the ethyl diazoacetate **13** leading to the formation of the zwitterion **80**. The positively polarized carbon in **80** is then attacked by the electron-enriched nitrogen to furnish the aziridine **36** upon releasing the chiral catalyst and nitrogen gas. Alternatively, a 1,2-shift of a hydride or the R group in **80** will lead to the formation of the two enamine by-products **37** and **38**.

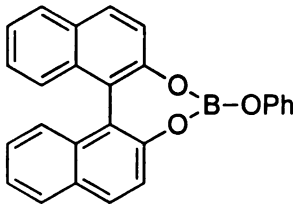
6.1.2 Original proposed structure of the VANOL/VAPOL-borate catalyst

According to known structures of complexes generated from BINOL and borate esters or boronic acids,[114] the original proposal for the VANOL/VAPOL-boron complex was structure **271** shown in Figure 6.1. Yamamoto reported the first example of a catalyst prepared from a borate ester and a biaryl ligand and proposed the structure **267** since it was generated from a 1:1 ratio of BINOL and triphenyl borate in CH_2Cl_2 at room temperature.[114a] A number of other complex structures have also been suggested as active catalysts in asymmetric reactions, and it is believed that structures of these

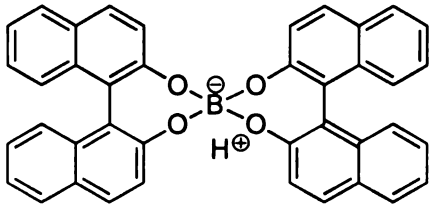
complexes are dependent on substituents on boron and the nature of the different biaryl ligand. Amongst these, the structure of complex **268** was confirmed by X-ray analysis,[114b] and was prepared from a 2:1 molar ratio of BINOL and triphenyl borate. It was reported by Kaufmann[114c] that the bicylic homochiral bisborate compound **269** was observed exclusively when BINOL reacted with several borane complexes, hydrohaloboranes or boric acid.

Further studies by Kaufmann revealed that the introduction of bulky substituents at 3,3'- positions of the BINOL would exclusively lead to the formation of the seven-membered complexes of the type **267** rather than **269** presumably to avoid steric strain.[114c] Analysis of CPK models with the VAPOL or VANOL ligand indicated severe steric strain in the complexes analogous **268** and **269**. Thus, it was believed that the active catalysts from VANOL and VAPOL are most likely **270** or **271**, which incorporate one equivalent VAPOL or VANOL ligand and one equivalent boron Lewis acid such as BH_3 or $B(OPh)_3$.

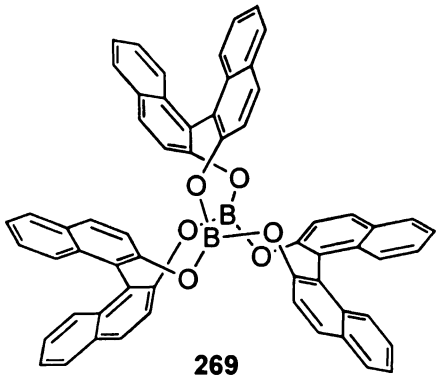
Figure 6.1 Various structures of the chiral biaryl borate complexes



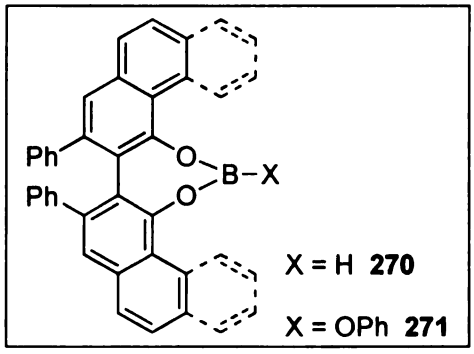
267



268

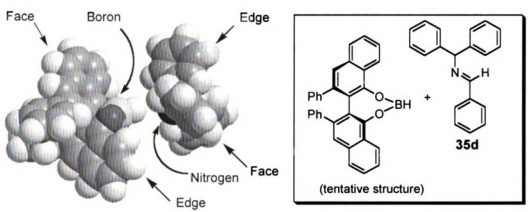


269



If the structure of **270** or **271** reflects the active chiral catalyst in the AZ reaction, then space-filling CPK models suggested that the interactions between the catalyst and the imine **35d** might be these shown in Figure 6.2 (for simplicity, the catalyst is shown as that generated from BH_3 and VANOL). When the imine nitrogen coordinates with the boron, close contacts are established between the benzhydryl group and the aromatic system of the ligand where two edge-face arene interactions may possible be created. More specifically, one phenyl ring of the benzhydryl group acts as an edge ring and points to one of naphthalene rings of the ligand, while another phenyl ring of the benzhydryl group acts as an face ring and points to the edge of the second naphthalene ring of the ligand.

Figure 6.2 Proposed edge-face interactions between the imine **35d** and the VANOL-boron catalyst



The CPK model for the VAPOL-boron catalyst also revealed very similar face-edge interactions with the benzhydryl imine, however, these same interactions could not be observed for the BINOL-boron species. Face-edge interactions between arene systems belongs to a class of weak hydrogen bonds called CH-π interactions.[115] It was proposed that the presence of these interactions in our catalyst-imine complex provides an additional organizing effect, and this is responsible at least in part to the high asymmetric

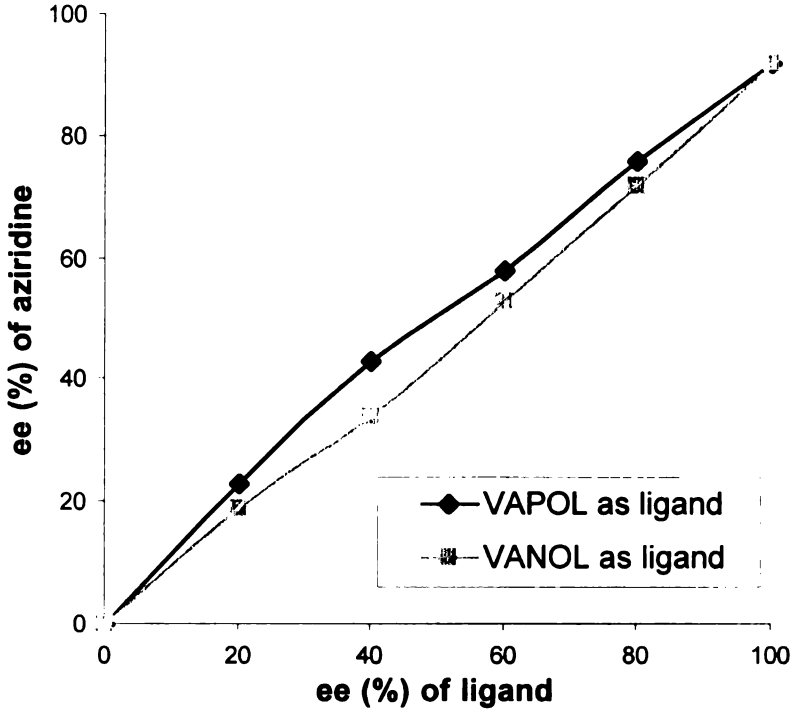
inductions observed for the AZ reaction. This model is consistent with the much lower enantioselectivity observed for the *N*-benzyl imine **201g** (51% yield, 43% ee, Scheme 4.2) or for the catalyst prepared from BINOL[22b] (61% yield, 20% ee), because the face-edge interactions would be weaker or non-existent in these cases.

To test these proposed "face-edge" interactions in the original model for the catalyst-imine complex, a series asymmetric *N*-substituted imines were synthesized and examined in the aziridination reactions by Dr. Zhang.[37a,g] In his work, it was found that some of results were not consistent with the "face-edge" interactions in the proposed model **271** (Figure 6.2) (for detailed discussion see Dr. Zhang's thesis).[37g] These "unsatisfactory" observations thus prompted a reinvestigation to our original proposed model, especially with regard to the structure of the VANOL/VAPOL-borate complex.

6.1.3 Revised structure of VANOL/VAPOL-borate complex

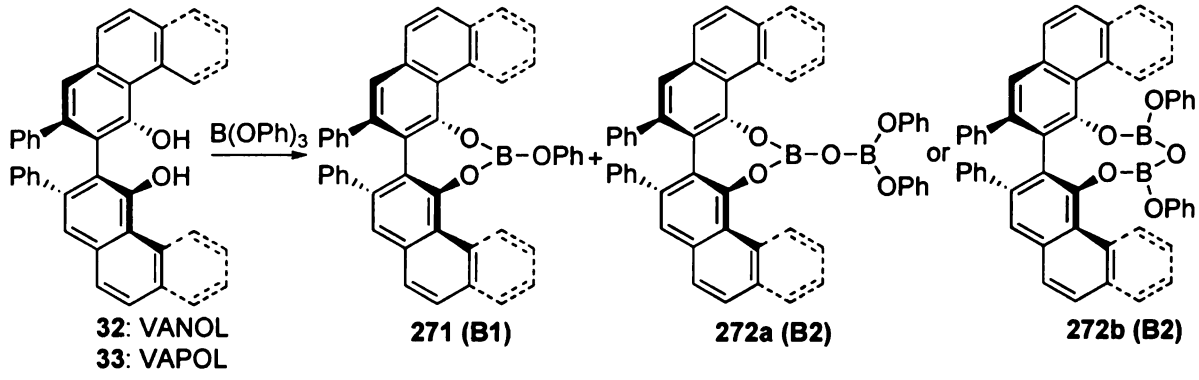
To probe for the possibility of 2 : 1 adducts of the type **268** (Figure 6.1) for the structure of the VANOL/VAPOL-borate catalyst, a study of the non-linear effect[116] of the VANOL/VAPOL-borate catalyst was conducted by Dr. Zhang.[47] As the results in Figure 6.3 show, the relationship between the optical purity of each ligand and the product is essentially linear. This is consistent with the incorporation of only one molecule of the ligand in the active catalyst. This observed linearity does not fully exclude the association between the boron and two or more ligands,[117] it is most suggestive of a 1 : 1 complex.

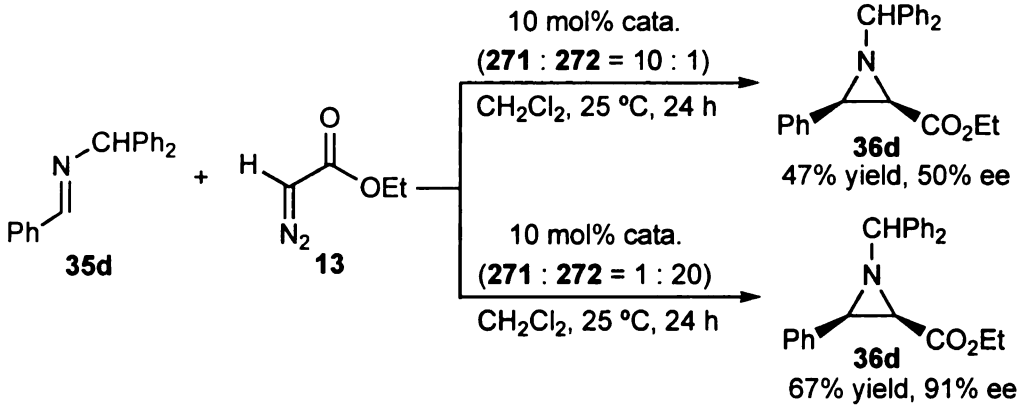
Figure 6.3 Study of the non-linear effect of the VANOL/VAPOL-borate catalyst



Spectroscopic analyses of the catalyst prepared by the original published procedure[22a] (Scheme 1.10) revealed the presence of two species in a ratio that ranges from 3:1 to 5:1 (as determined by the ^{1}H NMR spectra of the catalyst). The high resolution mass spectrum of the catalyst mixture gives two ions with the molecular formulas $C_{46}H_{29}BO_3$ and $C_{52}H_{34}B_2O_5$. Catalyst structures consistent with these formulas are the borate **271** for the former and either of the pyroborates **272a** or **272b** for the latter (Scheme 6.2).[116] The pyroborate was assigned as the major catalyst species by examining the ^{1}H NMR spectrum and the high resolution mass spectrum of the mixture of the two species generated from *p*-tolylborate and VAPOL.[47]

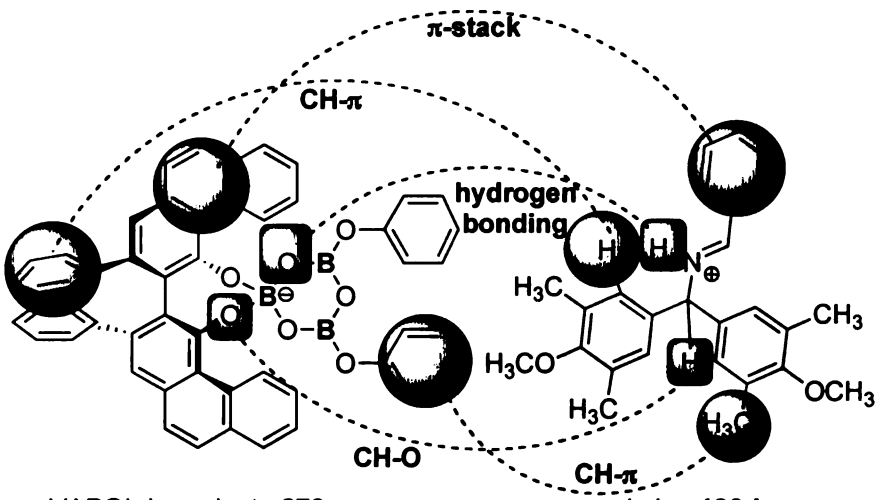
Scheme 6.2 Possible catalyst structures and the aziridination results





Following the discovery of the pyroborates in the catalyst mixture, different procedures were designed to selectively generate enriched samples of either the B1 or B2 catalysts from the VANOL and/or VAPOL ligands.[37h] These enriched catalysts were then examined in the AZ reaction and some typical results are shown in Scheme 6.2. These results clearly indicate that the pyroborate species B2 is responsible for the high asymmetric induction in the aziridination reaction and that the B1 species is not the active catalyst as it had been anticipated (91% ee vs. 50% ee in Scheme 6.2). Support for the structure assignment of the B2 catalyst as the species **272a** comes from the ^{11}B NMR analysis, in which two boron peaks were observed with the similar intensities.[47]

Figure 6.4 Crystal structure of the complex generated from the VAPOL-borate catalyst and imine **188d**

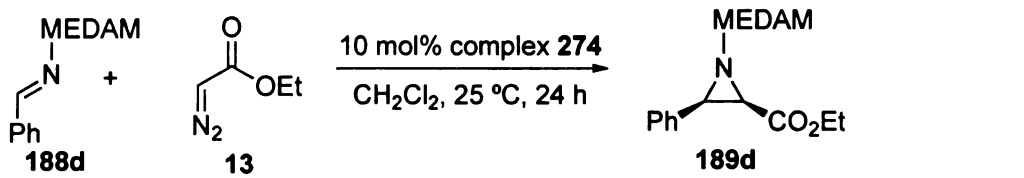


In order to gain further evidence in support of the pyroborate structure **272**, efforts were undertaken to grow crystals for X-ray analysis. Since the pyroborate **272** was not crystalline, a number of adducts with Lewis bases were prepared and a number of these were crystalline. To our surprise, all of the structures from these adducts revealed a VAPOL-boroxinate core.[118a] The crystal structure from the pyroborate **272** enriched VAPOL-borate complex with the MEDAM imine **188d** (Figure 6.4) showed a complex consisting of a protonated imine and a chiral counterion in the form of a VAPOL boroxinate. A diverse array of multiple noncovalent catalyst-substrate contacts can be identified and the most important interaction of these may be the hydrogen bonding between the hydrogen (green) of the protonated imine and one of the oxygens (green) of the boroxine ring (N–O distance is 2.84 Å). There is a π-π stacking interaction between the phenyl group (blue) of the protonated imine and the central ring of the phenanthrene (blue) of the catalyst (3.50 Å). The π-π stacking interaction plays an important role in self-assembly and molecular recognition processes.[119] In addition, several different CH-π

interactions (3.59 Å-4.42 Å, in red) and a CH-O interaction between the methine hydrogen (pink) of the benzhydryl group and the oxygen (3.28Å, pink) of the VAPOL ligand were observed from this X-ray structure (see the detailed illustration of this crystal structure in Gang Hu's thesis).[118a]

An important piece of evidence that support the catalyst-imine complex **274** as the actual catalyst in the AZ reaction is the result shown in Scheme 6.3, in which the complex **274** was applied as the catalyst in the AZ reaction. The aziridine **189d** was obtained with the same asymmetric induction and slightly higher yield when crystals of **274** were used as the catalyst.

Scheme 6.3 The AZ reaction catalyzed by the complex **274**

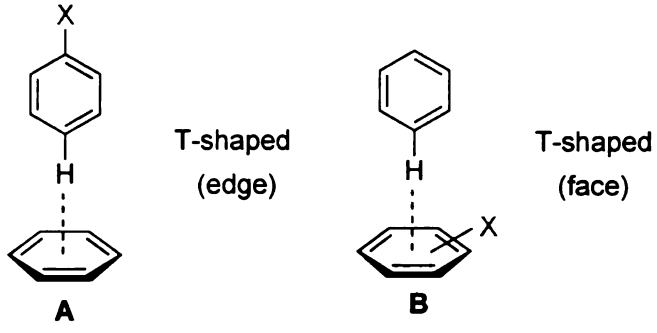


94% yield, 97% ee
(89% yield, 97% ee with*in situ* generated VAPOL-boron catalyst)

In this work, the main focus will be on the investigation of the CH-π interactions between the catalyst and the substrate that are suggested by crystal structure of **274**. Litaka *et al.* gave the first suggest that the CH-π interactions[120] could operate as a weak non-covalent force between molecules as a result of their crystallographic studies. Experimental[121,122] studies have emerged rapidly in the past two decades and a general trend has emerged for the factors that can effect this CH-π (face-edge) interaction that is summarized in Figure 6.5. If the edge ring is electron deficient (with an electron withdrawing substituent on the edge ring), the interaction can be increased. Hirota and Suezawa also reported that the same enhancement could be observed when the face ring is electron rich (with an electron donating substituent on the face ring)[122a,b], while

Wilcox found no effect for the electron donating substituents on either the face or the edge rings[121].

Figure 6.5 Experimental studies of the edge-face interaction



The CH-π interaction is enhanced when:

a) electron withdrawing group on the edge ring (**A**)

b) electron donating group on the face ring (**B**)

In the past decade, more and more computational studies on CH-π interactions have appeared with the help of the rapid development of the modern computer technology.[123] High level *ab initio* calculations were used to predict the magnitude and direction of edge-face interactions by Sherrill's group and kim's group.[124] The calculations indicated that an electron-withdrawing group on the edge ring will increase the interaction between face and edge rings. Electron-donating groups such as OH or CH_3 on the face ring will also increase the interaction, while electron-withdrawing groups on the face ring will have opposite effect.

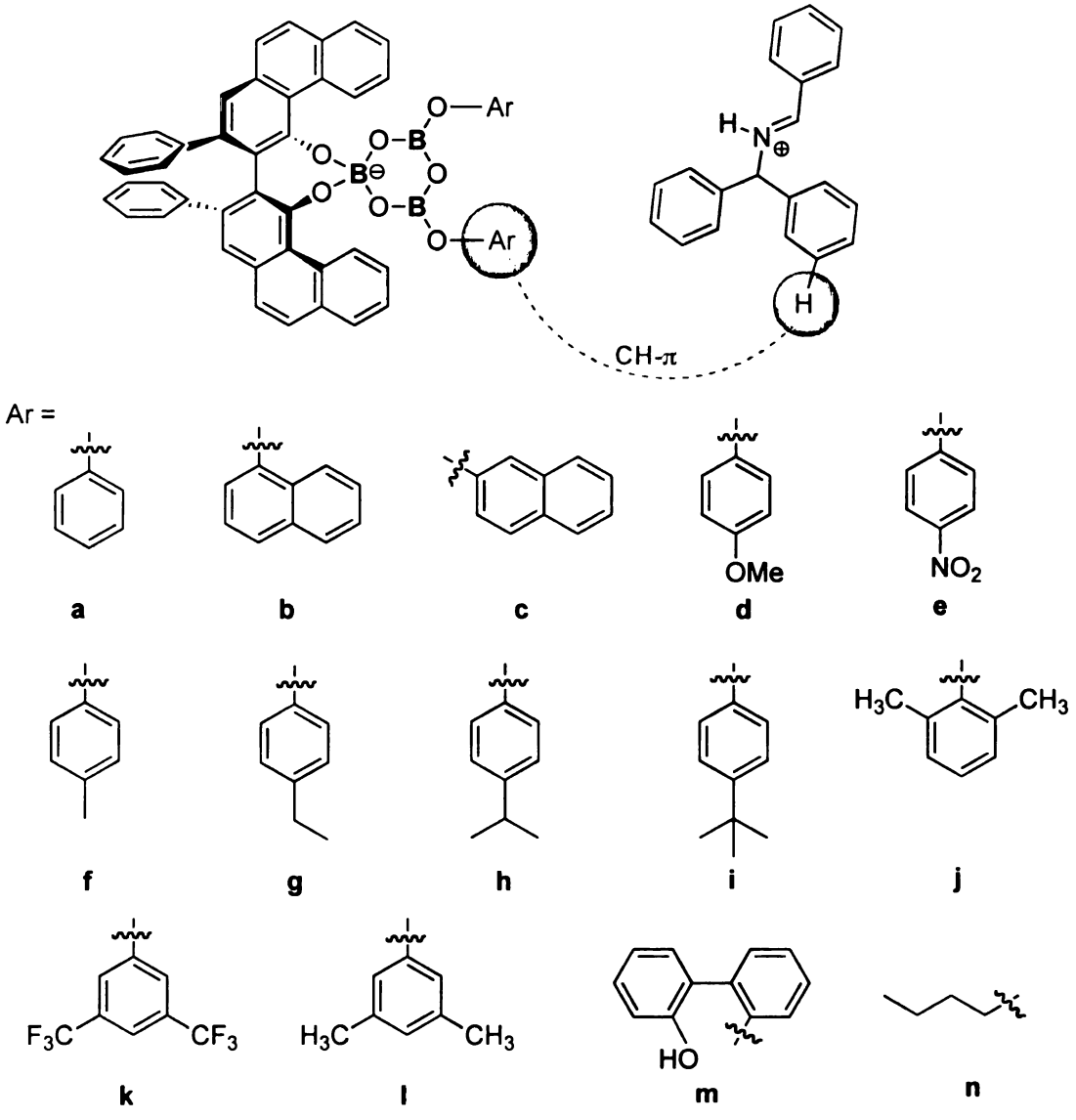
Although non-covalent interactions can be observed in the crystal structure of the complex **274**, the real interactions between the catalyst and imines in solution may be different. Nonetheless, it provides a lead for further investigation of the structure of the active catalyst and of interactions between the catalyst and imines in solution.

6.1.4 Investigation of the mechanism of the AZ reaction

Considering all that is now known about the mechanism for the aziridination of

imines with ethyl diazoacetate mediated by the VANOL/VAPOL-borate catalysis, it is now considered likely that carbon-carbon bond formation is the rate-limiting step, and results from the attack of ethyl diazoacetate on the iminium-boroxinate complex **274**. The biggest difference from the original proposed mechanism is that we now know that this reaction is catalyzed by a chiral Brønsted acid rather than a chiral Lewis acid.

Scheme 6.4 Investigation of CH-π interactions by varying the aryl borate

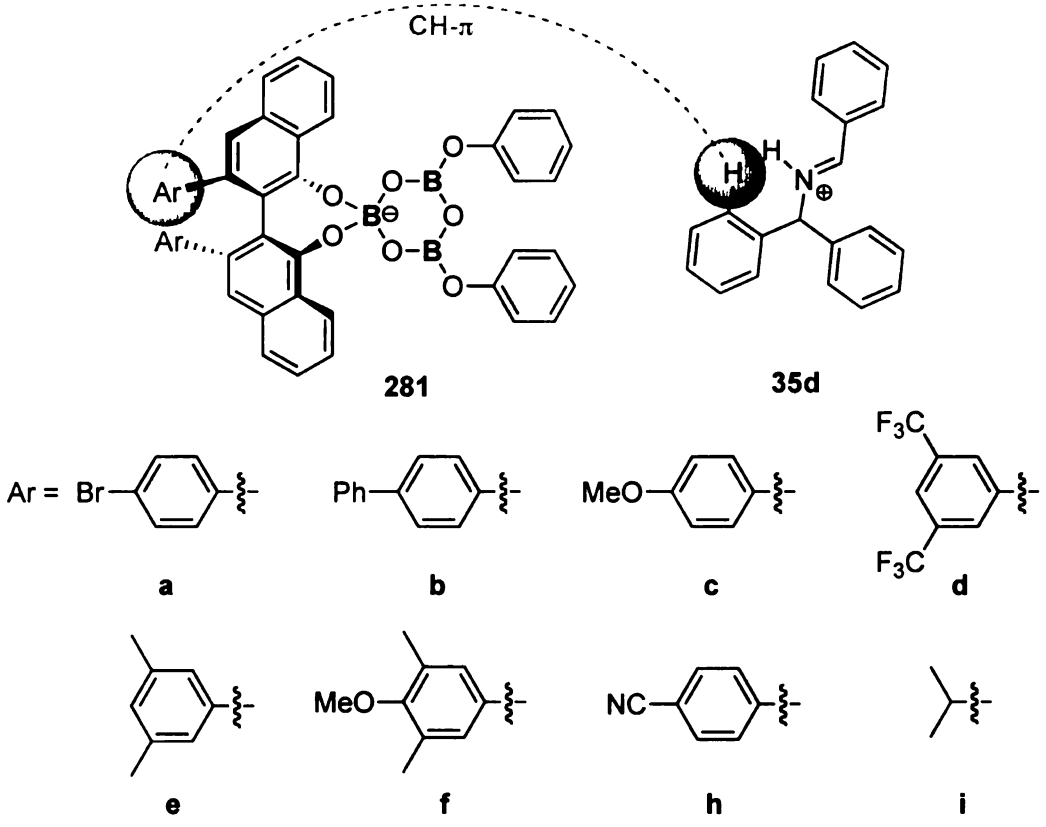


Two major CH-π interactions are observed in the crystal structure of the catalyst-substrate complex **274**, if they are real, the substituent on the face and/or edge rings

should have some effect on these non-covalent interactions (Figure 6.4), and as a result, they may be responsible in part to the asymmetric inductions observed in the AZ reaction. According to the electronic effects reported for face-edge CH-π interactions,[121-124] it should be possible to probe the CH-π interactions in the catalyst-substrate complex **274** by fine-tuning the structure of the catalyst complex or the structure of imine. The studies on varying the structure of the imine at both the *N*-protecting group and on the α-substituents were discussed in chapters two and four. Effects directed to fine-tuning the catalyst structure will be discussed in this chapter. Specifically, the catalyst structure will be modified by varying the electronic and steric character of a) the face ring on the borate substituent, and b) the phenyl group of the VANOL or VAPOL ligands. These experiments will be performed to look for any correlation of these changes with the asymmetric induction in the AZ reaction.

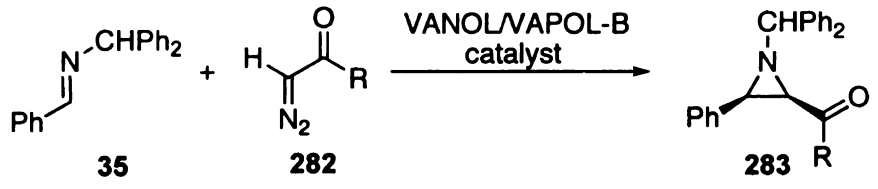
Most studies on CH-π interactions[121-125] reveal that a stronger interaction occurs when the face ring is substituted with electron donating groups and a weaker interaction occurs when the face ring is substituted with electron withdrawing groups. Therefore, a series of electron-rich and electron-deficient borates will be used to generate *in situ* a chiral catalyst with VAPOL/VANOL ligand to give boroxinates of the type **280** (Scheme 6.4). In addition, the new VANOL derivatives indicated in Scheme 6.5 will be synthesized as chiral ligands for a new series of catalysts of the type **281**. All the new catalytic systems indicated in Scheme 6.4 and Scheme 6.5 will be evaluated in the aziridination reaction with the imine **35d**. It is hoped that this work can provide valuable information for understanding of the mechanism of the aziridination reaction and a useful library of ligands for screening new asymmetric reactions.

Scheme 6.5 Investigation of CH-π interactions with VANOL derivatives



To further probe the mechanism of the aziridination reaction, it is thought that it may be useful to understand the effects resulting from variation in steric and electronic properties of the diazo compound. Various sterically and electronically modified diazoacetates and diazo amide were synthesized and examined in the AZ reaction (Scheme 6.6).

Scheme 6.6 AZ reactions with different diazo compounds



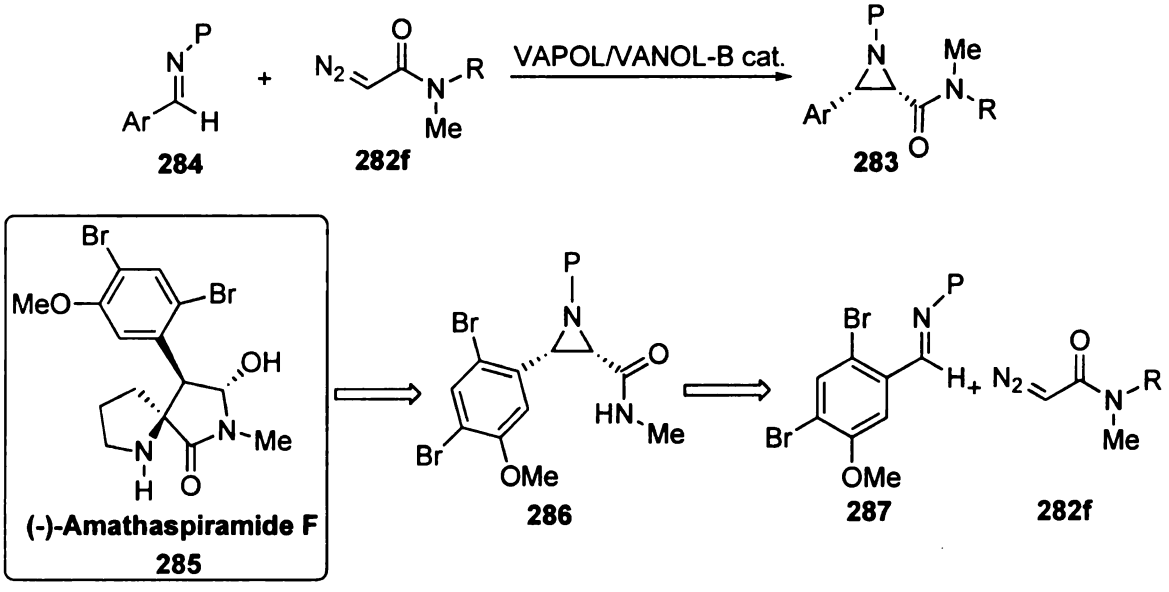
R = OMe, OEt, O*i*-Pr, O*t*-Bu, OPh, N(Me)Bn

a **b** **c** **d** **e** **f**

6.2 Steric and electronic effects of diazo compounds in AZ reactions

The study of effects of changes in the diazo compound as shown in Scheme 6.6 on the catalytic AZ reaction was carried out before the structure of the catalyst was known. This work also served as a model study for the proposed total synthesis of (-)-Amathaspiramide F[125] **284**, which requires the asymmetric synthesis of *cis*-aziridinyl amides as a key step as shown in Scheme 6.7.

Scheme 6.7 Asymmetric synthesis of *cis*-aziridinyl amide in the proposed total synthesis of (-)-Amathaspiramide F



Amathaspiramide F **285** was first isolated from a New Zealand collection of the bryozoan *Amathia Wilsoni* by Blackman.[125] Further investigation on the structural elucidation and the biological activity were done by Prinsep in 1999.[71] The first and the only total synthesis of Amathaspiramide F was reported by Trauner in 2002.[126] This natural product has a novel spirobicyclic core consisting of pyrrolidine and pyrrolidinone ring with three contiguous chiral centers. The intriguing molecular architecture of Amathaspiramide F has attracted our interest in a design of an asymmetric total synthesis through a diastereoselective alkylation[26] and regio selective ring opening of

the aziridinyl amide **286**, which is expected to be prepared enantioselectively utilizing our catalytic AZ reaction from the imine **287** and the diazo amide **282f**.

6.2.1 Preparation of diazo compounds 282

The diazo-compounds were synthesized via diazo-transfer methods[127] shown in Scheme 6.8. From the commercially available glyoxylic acid **288** and the hydrazine **289**, the glyoxylic acid *para*-toluenesulfonylhydrazone **290** was obtained in 79% yield.[128] The diazo compounds **292/282** were obtained in moderate yields by the conversion of **290** into the acid chloride **291**, and then subsequent elimination of the arylsulfonyl group in compound **291** afforded the product **292** in 34% yield or the diazo compounds **282a-d** as the results in Table 6.1 show. The diazo esters were purified by silica gel chromatography using ether/pentane as eluent, however, the solvent could only be removed by careful fractional distillation due to the high volatilities of **282a-d**. As a result, these diazo compounds were used as mixtures with pentane.

Scheme 6.8 Preparation of diazo compounds

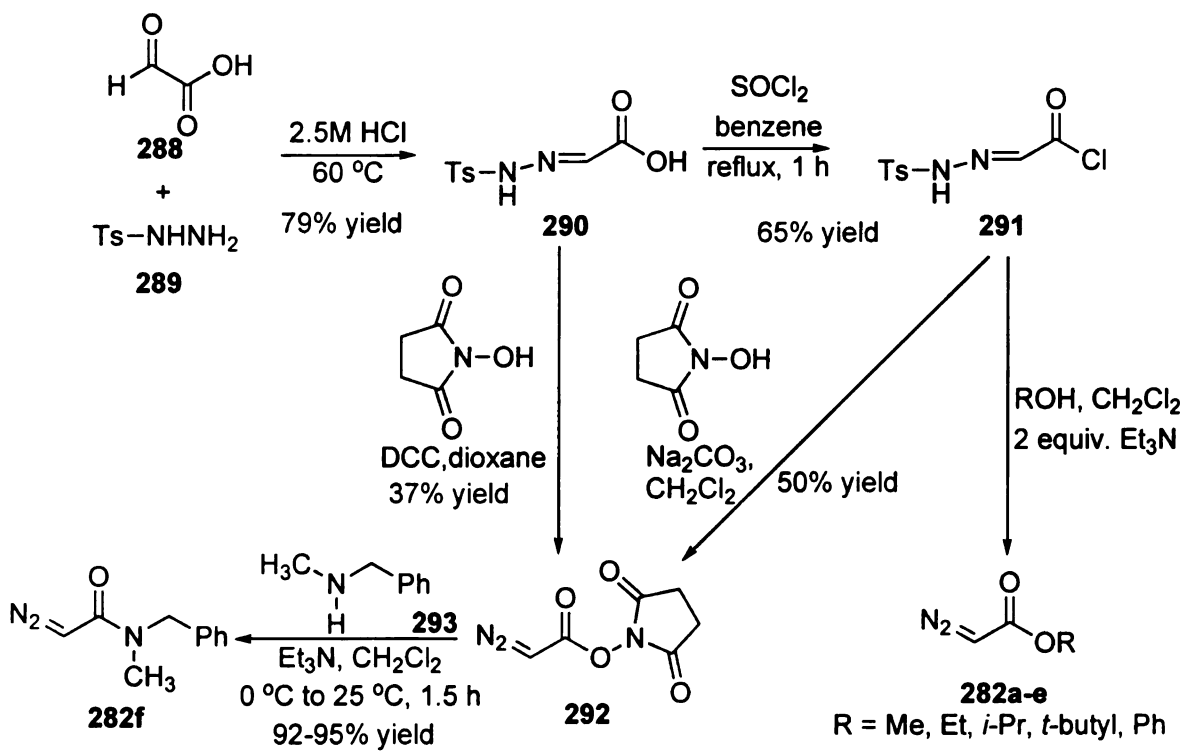
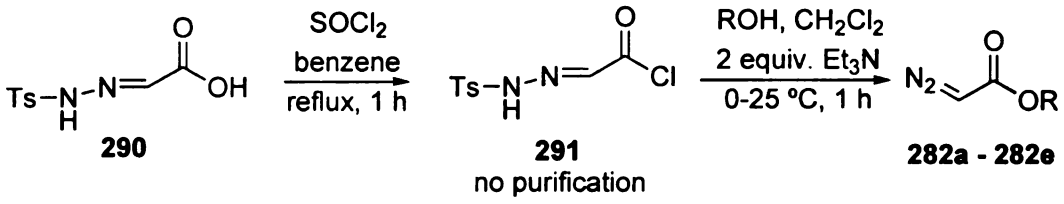


Table 6.1 Preparation of diazo esters **282a-d**



entry	series	R	molar ratio of **282**/pentane	overall yield of **282** form **290** (%)[a]
1	**a**	Me	1 : 1	80
2	**b**	Et	1 : 1	85
3	**c**	*i*-Pr	1 : 2	83
4	**d**	*t*-Bu	1 : 1	80
5	**e**	Ph	4 : 3	86

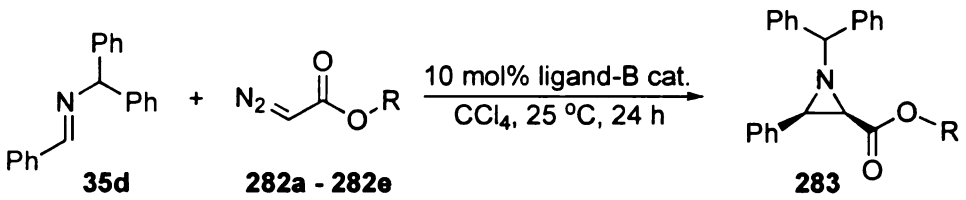
[a] Isolated yield after silica gel chromatography, calculated based on the mixture of **282** and pentane.

As shown in Scheme 6.8, the succinimidyl diazoacetate **292** could be prepared via two routes, either from the acid **290** in the presence of dicyclohexylcarbodiimide,[128a] or from the acyl chloride **291** in the presence of sodium carbonate.[128c] Both routes gave low overall yields of the product **292**. The diazoacetamides **282f** was obtained in high yield via diazoacetylation of amine **293** from succinimidyl diazoacetate **292**[128c] (Scheme 6.8). The *N*-benzyl-*N'*-methylamine **293** was chosen because the resulting aziridine is a potential intermediate for the natural product Amathaspiramide F (Scheme 6.7).

6.2.2 AZ reaction of diazo acetates 282

The diazo acetates **282a-e** were examined in the aziridination reaction with imine **35d** under the catalysis of the VAPOL-borate complex.

Table 6.2 AZ reaction of different diazo acetates[a]



entry	R	series of **282**	ligand	yield (%)[b]	ee (%)[c]
1	Me	**a**	*(S)*-VAPOL	90	91
2	Et	**b**	*(S)*-VAPOL	84	93
3[d]	Et	**b**	*(S)*-VAPOL	85	93
4	*i*-Pr	**c**	*(S)*-VAPOL	86	92
5	*t*-Bu	**d**	*(S)*-VAPOL	95	89
6	Ph	**e**	*(S)*-VAPOL	88	91

[a] Unless otherwise specified, all reactions was carried out in 0.5 M in imine in CCl_4 with 10 mol% catalyst loading. The catalyst were prepared from 1 equiv. VAPOL or VANOL, 3 equiv. $B(OPh)_3$ at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. [b] Isolated yield after silica gel chromatography. [c] Determined from chiral HPLC on a Chiralcel OD-H column. [d] Ethyl diazoacetate was purchased from Aldrich.

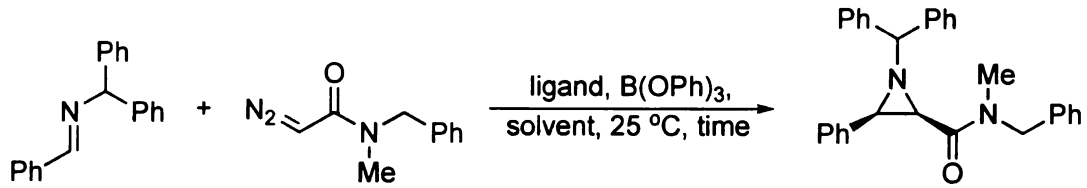
As the results in Table 6.2 show, the steric and the electronic changes on the diazo acetates only affected the asymmetric inductions in a range of 1-4% ee with comparable isolated yields. All aziridinations gave higher than 50 : 1 *cis/trans* ratio. The most sterically hindered *tert*-butyl diazo acetate **282d** gave the lowest enantioselectivity but the highest yield (89% ee, 95% yield) (Table 6.2, entry 5), and the electron-deficient phenyl diazo acetate **282e** gave the corresponding aziridine in slightly lower enantioselectivity and similar yield (91% ee, 88% yield) (Table 6.2, entry 6). The highest enantioselectivity was observed from the reaction of ethyl diazo acetate **282c** either as the commercially available material or as the compound independently prepared by the

same method as all the other diazo esters (Table 6.2, entry 2 and 3).

6.2.3 AZ reaction of diazo amide 282f

Since the study of the AZ reaction using sterically and electronically different diazo acetates indicated that the asymmetric induction would not be significantly affected by the ester substituents, a similar result was thus expected for the aziridination of diazo amide **282f**. As the results in Table 6.3 shown, although the enantioselectivity was still high, incomplete conversion and low isolated yield was always observed under standard reaction conditions (Table 6.3, entry 2). It was thought that the low conversion might be due to the competitive coordination of the nitrogen in the aziridinyl amide **283f** with the catalyst. A similar competition was also observed in the study of the VAPOL-borate catalyzed hetero-Diels-Aldol reaction,[29c] and in that case, the problem was solved by the addition of an excess amount of $B(OPh)_3$ as a co-catalyst to coordinate with product and release the catalyst to achieve good turn over. The same strategy was examined here, however, to our disappointment, no improvement was observed (Table 6.3, entry 5 to 7). In the absence of the ligand, only a trace amount of the product was observed in the ^1H NMR spectrum of the crude reaction mixture (Table 6.3, entry 8). Curiously, higher catalyst loadings failed to improve the yields (Table 6.3, entry 3 and entry 7). A solution to the unreactivity of amide **282f** would be to introduce the amide functional group after the aziridination reaction, however, this was shown to be unusable because no aziridination was observed between the imine **35d** and the succinimidyl diazoacetate **292** under the standard condition (Scheme 6.9).

Table 6.3 AZ reaction with diazo amide **282f**[a]

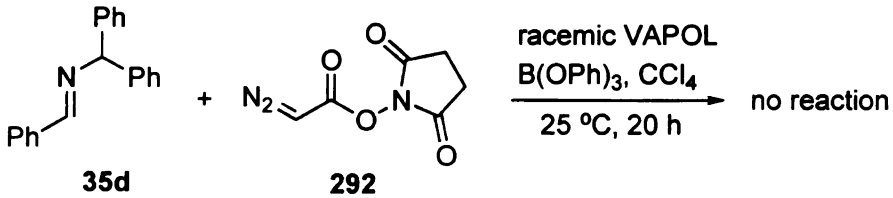


35d **282f** **283f**

entry	ligand (mol%)	amount of $B(OPh)_3$	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	*rac*-VAPOL (10%)	30%	CCl_4	24	14	nd
2	*(S)*-VAPOL (10%)	30%	CCl_4	24	14	88
3[d]	*(S)*-VAPOL (20%)	60%	CCl_4	64	18	88
4[d]	*(R)*-VANOL (10%)	30%	CCl_4	64	16	77
5	*(S)*-VAPOL (10%)	200%	CCl_4	40	16	85
6	*(S)*-VAPOL (10%)	200%	Toluene	40	18	88
7	*(S)*-VAPOL (100%)	300%	CCl_4	24	5	nd
8	none	200%	CCl_4	24	5% conv.	

[a] Unless otherwise specified, all reactions were carried out in 0.5 M in imine with 1.1 equiv **282f**. The catalyst were prepared from 1 equiv. VAPOL or VANOL, 3 equiv. $B(OPh)_3$ at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. <50% conversion was observed in each case. [b] Isolated yield after silica gel chromatography. [c] Determined from chiral HPLC on the Chiralcel OD-H column. [d] The diazo amide **282f** was added slowly over 5 h.

Scheme 6.9 AZ reaction of succinimidyl diazoacetate **292**

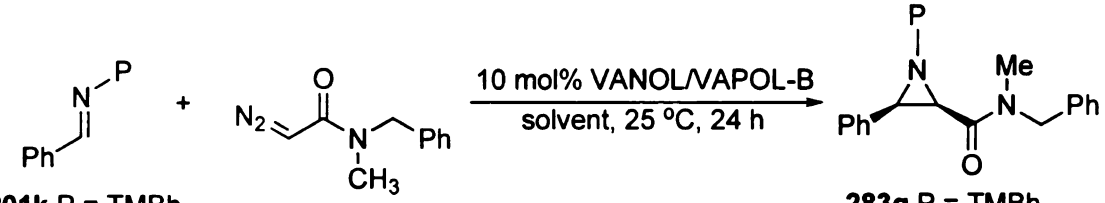


35d **292**

The aziridination reaction of diazo amide **282f** was then optimized by using other *N*-substituted imines (Table 6.4). The more reactive *N*-tetra-methyl benzylhydryl imine **201k** was examined first because it was found to react 10 times faster than **35d** in the

aziridination reaction with ethyl diazoacetate.[37c] As expected the reaction of **201k** gave a higher yield than **35d** (57% yield, Table 6.4, entry 1). The *N*-MEDAM imine **188d** was found to be better than the N-BUDAM imine **208d** (Table 6.4, entry 5 and entry 7), and aziridine **283i** could obtained in 77% yield with 98% ee when 20 mol% catalyst loading (Table 6.4, entry 9). It was also noticed that the reactions with VAPOL as ligand gave higher yields than those with VANOL as ligand.

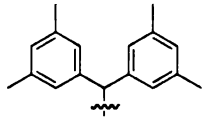
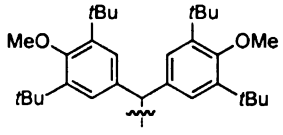
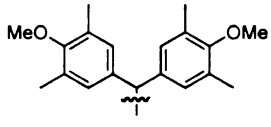
Table 6.4 AZ reaction of substituted benzhydryl imines with diazoamide **282f**[a]



201k P = TMBh
208d P = BUDAM
188d P = MEDAM

282f

283g P = TMBh
283h P = BUDAM
283i P = MEDAM

entry	solvent	ligand	series of imine	P	yield (%)[b]	ee (%)[c]
1	CCl_4	*(S)*-VAPOL			57	nd
2	toluene	*(R)*-VAPOL	**201k**		66	nd
3	toluene	*(S)*-VANOL			49	nd
4	CCl_4	*rac*-VAPOL			39	nd
5	toluene	*(R)*-VAPOL	**208d**		40	nd
6	toluene	*(S)*-VANOL			26	nd
7	toluene	*(R)*-VAPOL			60	96
8	toluene	*(S)*-VANOL	**188d**		53	nd
9[d]	toluene	*(S)*-VAPOL			77	98

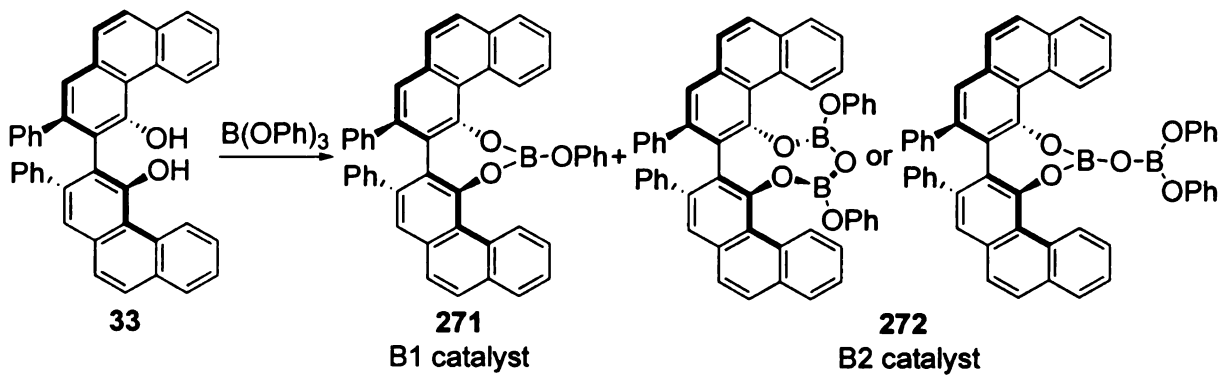
[a] Unless otherwise specified, all reactions were carried out in 0.5 M in imine with 1.1 equiv **282f** and 10 mol% catalyst. The catalyst were prepared from 1 equiv. VAPOL or VANOL, 4 equiv. $B(OPh)_3$ and 1 equiv. H_2O at 80 °C in toluene for 1 h, followed by the high vacuum (0.5 mm Hg) at 80 °C for 0.5 h. Incomplete conversion was observed for all the reactions except the entry 9. nd = not determined. [b] Isolated yield after silica gel chromatography. [c] Determined from chiral HPLC on

Chiralcel OD-H column. [d] 20 mol% catalyst loading was used.

6.3 Optimization of the catalyst generation procedure

It was recently found that the reaction of VAPOL and $B(OPh)_3$ under the standard conditions for the preparation of the catalyst for the AZ reaction produced two species, the mono-borate and the pyroborate **272** with the latter giving the highest induction.[118a] The formation of the pyroborate requires the presence of water, however, the original procedure for the preparation of the catalyst[22a] involves moisture-free conditions and is performed in a flame dried Schlenk flask with freshly distilled dry solvents. Thus, it was considered most likely that the water came from the commercially available $B(OPh)_3$. In fact, $B(OPh)_3$ is prone to hydrolysis and most samples of commercially available $B(OPh)_3$ are partially hydrolyzed and contain free phenol. The purity of $B(OPh)_3$ obtained from a variety of suppliers was never higher than 85%. Thus, perhaps it would be possible to increase the proportion of the B2 catalyst if water was added during the catalyst preparation process. Since the boroxinate is only observed in the crystal structure, and the pyroborate B2 is observed in solution, B2 species was examined to monitor the formation of the active catalyst. The results from the effect of varying the stoichiometry of $B(OPh)_3$, and H_2O, and varying the temperature on the ratio of **271** to **272** are summarized in Table 6.5 and Table 6.6.

Table 6.5 Optimization of the preparation of the catalyst at 55 °C[a]



33 **271** B1 catalyst **272** B2 catalyst

Table 6.5 (con't) Optimization of the preparation of the catalyst at 55 °C[a]

entry	$B(OPh)_3$ (equiv)	H_2O (equiv)	**272** : **271** : **33**[b]
1	2	0	4.5 : 1 :1.2
2	2	0.5	9.3 : 1 :7.4
3	2	1.0	8.2 : 1 :8.7
4	2	1.5	7.4 : 1 :16.9
5	3	0	11.4 : 1 :3.0
6	3	0.5	13.8 : 1 :7.5
7	3	1.0	12.4 : 1 :3.8
8	3	1.5	9.9 : 1 :19.1
9	5	0	10.6 : 1 :0.1
10	5	0.5	13.6 : 1 :0.4
11	5	1.0	15.4 : 1 :1.3
12	5	1.5	16.2 : 1 :6.2

[a] The catalyst was prepared by heating the VAPOL ligand in CH_2Cl_2 at 55 °C for 1 h with the indicated amount of H_2O and $B(OPh)_3$ (newly opened bottle), and then exposure to high vacuum (0.5 mm Hg) for 0.5 h at 55 °C. [b] Determined from the ^1H NMR spectrum of the crude mixture of the preformed catalysts by integration of the bay proton for each species: **272** δ = 9.24 ppm, **271** δ = 9.54 ppm and **33** δ = 9.81ppm.

As the results in Table 6.5 show, when the catalyst was prepared at 55 °C without H_2O, the ratio of B2 : B1 could be driven to a 10.6:1 in favor of B2 by increasing the amount of $B(OPh)_3$ to 5 equiv (Table 6.5, entries 9). As expected, the addition of H_2O led to an increase in the B2:B1 ratio (Table 6.5, entries 2 vs. 1, entry 10 vs. 9) but too much water lead to substantial amounts of unreacted VAPOL (Table 6.5, entry 4, 8 and 12).

Table 6.6 Optimization for the preparation of the catalyst at 80 °C[a]

entry	$B(OPh)_3$ (equiv)	H_2O (equiv)	**272** : **271** : **33**[b]
1	3	0.5	13.9 : 1 :0.8
2	3	1.0	12.5 : 1 :0.4
3	4	0	13.2 : 1 :0
4	4	0.5	13.4 : 1 :0
5	4	1.0	19.6 : 1 : <0.1
6	5	0.5	14.2 : 1 :0.01
7	5	1.0	14.6 : 1 :0.06
8	5	1.5	19.3 : 1 : <0.1
9[c]	4	1.0	11.8 : 1 :0.03
10[d]	4	1.0	11.8 : 1 :0.02
11[e]	4	1.0	12.8 : 1 :0

[a] The catalyst was prepared by heating the VAPOL ligand with the indicated amount of $B(OPh)_3$ and H_2O in toluene at 80 °C for 1 h and then exposure to high vacuum (0.5 mm Hg) for 0.5 h at 80 °C. Unless otherwise specified, a newly opened bottle of $B(OPh)_3$ was used. [b] Determined from the ^1H NMR spectrum of the crude mixture of the preformed catalysts. [c] A one year old bottle of $B(OPh)_3$ was used which had been stored in a desiccator. [d] A three year old bottle of $B(OPh)_3$ was used which had been stored in a desiccator. [e] A three year old bottle of $B(OPh)_3$ was used that had been stored on the bench.

Increased temperature (80 °C) gave higher conversion of the VAPOL to give the active catalyst (Table 6.6 vs. Table 6.5), and complete conversion was observed in almost all cases. The optimal conditions for effecting high conversion and high selectivity for the B2 species includes the use of 4 equivalents of $B(OPh)_3$, 1 equivalent of H_2O and 1 equivalent of ligand at 80 °C (Table 6.6, entry 5). Different bottles of triphenyl borates were also examined using this optimized procedure, and a ratio close to 12 : 1 (B2/B1) could always be obtained independent of the history of the $B(OPh)_3$ (Table 6.6, entry 9 to

11). The catalyst prepared in this procedure was used in the aziridination reaction of imine **35d** with ethyl diazoacetate **13** using CH_2Cl_2 as solvent, and a higher asymmetric induction was obtained (91% ee vs. 89% ee using the original published procedure).

6.4 Steric and electronic effects of borates on the CH-π interactions in the catalyst-imine complex

The crystal structure of the catalyst-substrate complex **274** suggested the possibility of a CH-π interaction between the phenoxy group of the boroxinate ring and the phenyl rings of the benzhydryl group of the imine **188d** (Figure 6.4). This observation promoted an investigation of the electronic and steric effects of this phenoxy group on the interactions between the catalysts and the imine.

Scheme 6.10 Preparation of VANOL and VAPOL-borate catalysts with different borates

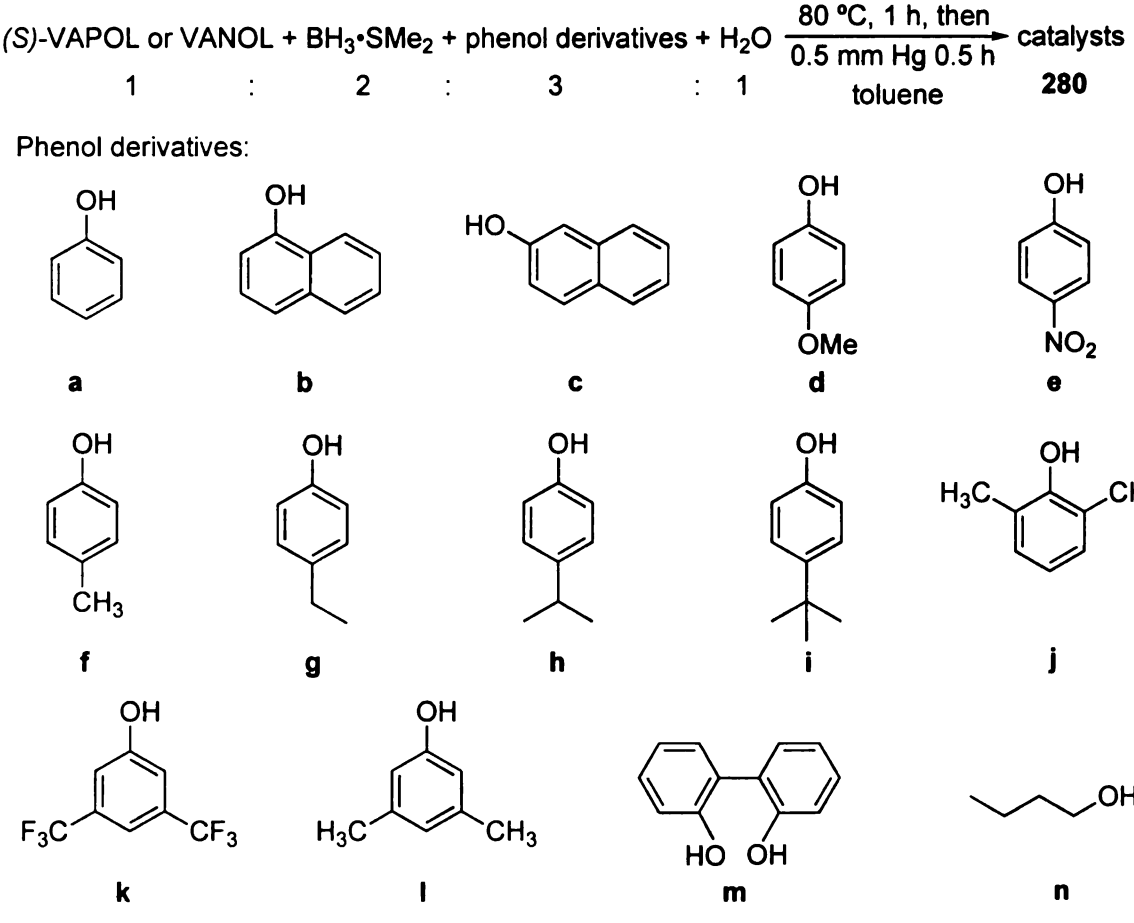
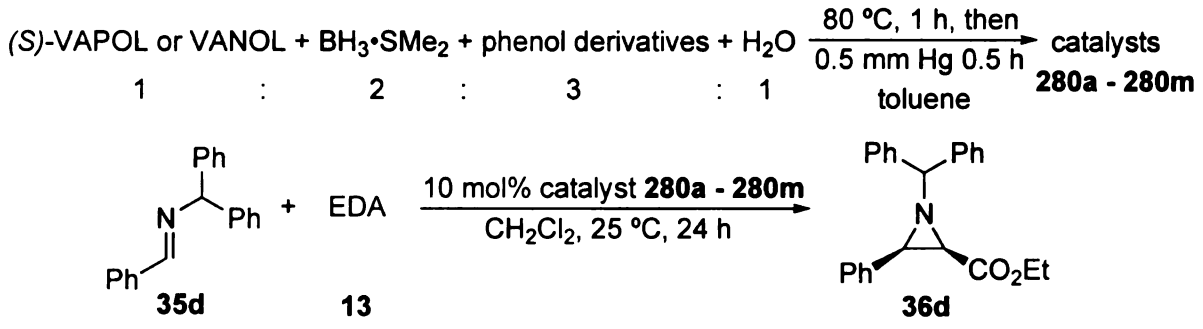


Table 6.7 The AZ reaction in CH_2Cl_2 with catalyst **280**[a]



entry	series	phenol derivatives	ligand	B2 :B1 :ligand[b]	yield of **36d** (%)[c]	ee of **36d** (%)[d]
1	**a**	phenol	VAPOL	9.0 : 1 : 0.1	70	89
2	**a**	phenol	VANOL	1.6 : 1: nd	73	92
3	**b**	1-naphthol	VAPOL	19.9 : 1 : 0.7	77	84
4	**b**	1-naphthol	VANOL	nd	77	88
5	**c**	2-naphthol	VAPOL	13.0 : 1 : 2.5	77	89
6	**c**	2-naphthol	VANOL	2.5 : 1 : nd	66	89
7	**d**	4-methoxyphenol	VAPOL	10.2 : 1 : 0.9	71	89
8	**d**	4-methoxyphenol	VANOL	2.5: 1 : nd	76	93
9	**e**	4-nitrophenol	VAPOL	6.7 : 1 : 0.1	55	52
10	**e**	4-nitrophenol	VANOL	2.4 : 1 : nd	63	49
11	**f**	4-methylphenol	VAPOL	10.0 : 1 : 1	74	89
12	**f**	4-methylphenol	VANOL	2.4 : 1 : nd	79	94
13	**j**	2,6-dimethylphenol	VAPOL	0.01 : 1 : 0.1	76	84
14	**j**	2,6-dimethylphenol	VANOL	3.8 : 1 : nd	83	89
15	**k**	3,5-trifluoromethylphenol	VAPOL	19.3 : 1 : 0.1	62	80
16	**k**	3,5-trifluoromethylphenol	VANOL	nd	68	80
17	**m**	2,2-biphenol	VAPOL	0.1 : 1 : 3.5	37	13
18	**m**	2,2-biphenol	VANOL	0 : 0 : 1	45	2

[a] Unless otherwise specified, all reactions were run in CH_2Cl_2 in 0.5 M of imine with 1.1 equiv EDA **13** and 10 mol% catalyst loading. The catalyst was prepared by heating 1 equiv. ligand with

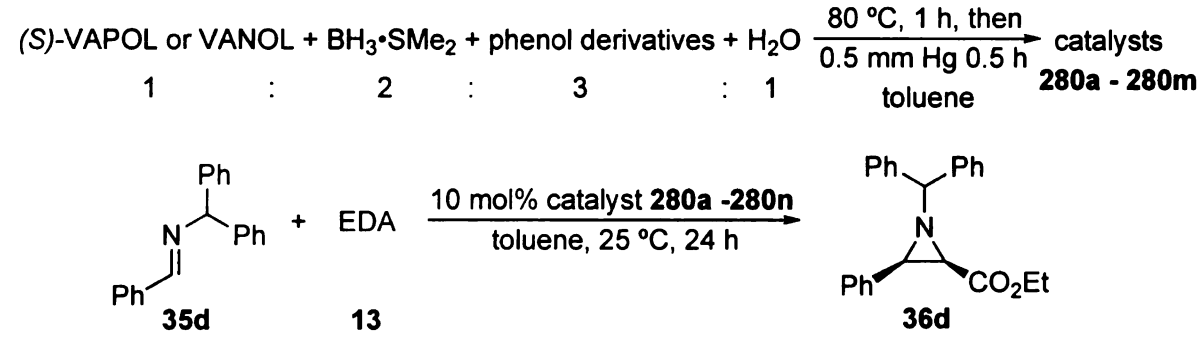
2 equiv. $BH_3 \cdot SMe_2$, 3 equiv. phenol derivatives, and 1 equiv. H_2O in toluene at 80 °C for 1 h and then exposure to high vacuum (0.5 mm Hg) for 0.5 h at 80 °C. [b] Determined from the ^1H NMR spectrum on the crude mixture of the preformed catalyst. [c] Isolated yield after silica gel chromatography. [d] Determined from chiral HPLC on a Chiralcel OD-H column.

As the data in Table 6.7 show, electron withdrawing groups on the phenoxy ring of the borate (face ring) gave much lower enantioselectivities and yields for both VANOL and VAPOL catalysts (Table 6.7, entry 9 and 10). This effect was partially diminished when the electron withdrawing group was not conjugated to the phenol oxygen (Table 6.7, entry 15 and 16). But lower asymmetric induction was still observed. The diminished CH-π interaction between the phenoxy ring of the borate (face) and the phenyl ring of the benzhydryl group (edge) may account for these low enantioselectivities. The electron donating groups on the phenoxy ring gave very similar results in terms of the yields and the enantioselectivities (Table 6.7, entry 7, 8 and entry 11, 12). Steric hindrance in the ortho position has a small effect on the asymmetric induction (5% ee lower, Table 6.7, entry 3 vs. entry 5, entry 13 vs. entry 1).

The study on the effect of the phenoxy group on the catalyst was also carried out in toluene (Table 6.8). The steric bulk on the *para*- position of the phenoxy ring has almost no effect on the asymmetric induction, and this is not surprising as this position is quite far away from the sites of interaction in the catalyst-imine complex as revealed by the structure **274** (Figure 6.4). As has always been the case for the AZ reaction, VANOL and VAPOL showed similar trends for all the derivatives examined. The surprising result came from the experiment where the phenol was replaced by butanol, which obviously could not function as a face ring in a CH-π interaction in a catalyst-imine complex. Nonetheless, comparable asymmetric inductions were obtained using both VAPOL and VANOL derived catalysts (Table 6.8, entry 12 and 13). At this point, there is no other experimental

evidence that would help explain this observation.

Table 6.8 The AZ reaction in toluene with the catalyst **280**[a]

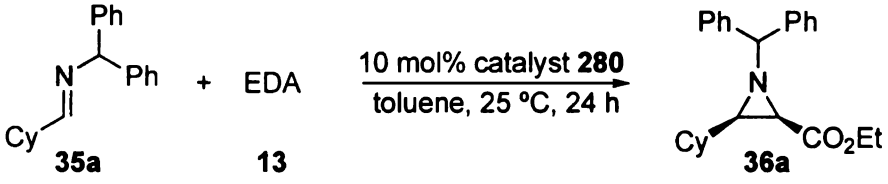


entry	series of **280**	substrate	ligand	B2 :B1 : ligand[b]	yield (%)[c]	ee (%)[d]
1	**a**	phenol	VAPOL	nd	83	95
2	**a**	phenol	VANOL	nd	87	95
3	**f**	4-methylphenol	VAPOL	10 : 1 : 1	78	94
4	**g**	4-ethylphenol	VAPOL	9.0: 1 : 1.1	85	94
5	**g**	4-ethylphenol	VANOL	2.1 : 1 : nd	87	95
6	**h**	4-isopropylphenol	VAPOL	5.7 : 1 : 0.5	81	94
7	**h**	4-isopropylphenol	VANOL	2.0 : 1 : nd	81	95
8	**i**	4-*t*-butylphenol	VAPOL	4.1 : 1 : 0.5	85	94
9	**i**	4-*t*-butylphenol	VANOL	1.4 : 1 : nd	90	95
10	**l**	3,5-dimethylphenol	VAPOL	12.4 : 1 : 0.5	68	95
11	**l**	3,5-dimethylphenol	VANOL	3.6 : 1 : nd	89	91
12	**n**	butanol	VAPOL	nd	85	94
13	**n**	butanol	VANOL	nd	89	91

[a] Unless otherwise specified, all reactions were run in toluene in 0.5 M of imine with 1.1 equiv EDA **13** and 10 mol% catalyst loading. The catalyst was prepared by heating 1 equiv. ligand with 2 equiv. $BH_3•SMe_2$, 3 equiv. phenol derivatives, and 1 equiv. H_2O in toluene at 80 °C for 1 h and then exposure to high vacuum (0.5 mm Hg) for 0.5 h at 80 °C. [b] Determined from the ^1H NMR spectrum on the crude mixture of the performed catalysts. [c] Isolated yield after silica gel chromatography. [d] Determined from chiral HPLC on Chiralcel OD-H column.

The cyclohexyl aldimine **35a** was also examined using the catalysts generated from the borate derivatives and *(S)*-VAPOL shown in Scheme 6.11. Similar effects were observed as these for reactions with the imine **35d** (Table 6.8). The catalyst prepared from $B(OPh)_3$ gave **36a** with 81% ee.

Scheme 6.11 AZ reaction of *N*-Bh imine **35a** catalyzed by **280**

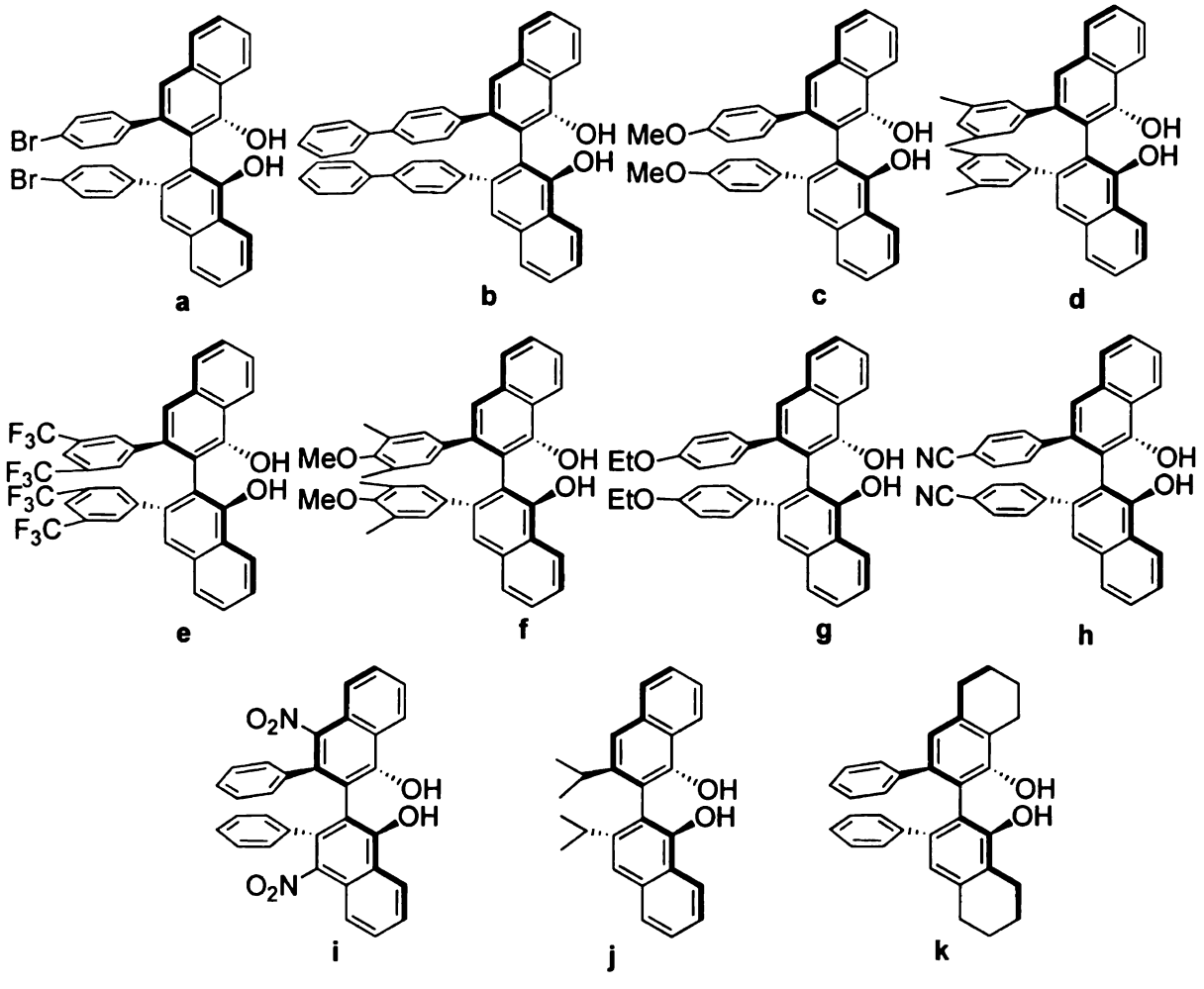


catalyst	phenol derivative	yield of **36a** (%)	ee of **36a** (%)
280b	1-naphthol	72	83
280h	4-isopropylphenyl	86	83
280k	3,5-trifluoromethylphenol	63	51

6.5 Evolving the CH-π interactions with the C3-phenyl group of VANOL ligand

The crystal structure of the complex **274** reveals another possible CH-π interaction between the C3-phenyl group of the VAPOL ligand and the ortho hydrogen of the MEDAM group of the imine (4.42 Å) (Figure 6.4). The investigation of this possible interaction involves varying the electronics and steric properties of the C3-phenyl group on the VANOL or VAPOL ligand and looking for a correlation with the asymmetric induction in the aziridination reaction. Since the VANOL and VAPOL derived catalyst showed a very similar profile in AZ reactions, the focus will be on examination of a series of VANOL derivatives. The VANOL derivatives chosen for this study are indicated in Scheme 6.12, and the evaluation of these ligands was planed to be carried out in the aziridination reaction with the imine **35d** as well as with the *para*-nitrophenyl substituted imine **35g** and the *para*-methoxyphenyl substituted imine **35h** in an effort to survey imines with different electronic properties.

Scheme 6.12 VANOL derivatives **281** for probing CH-π interactions



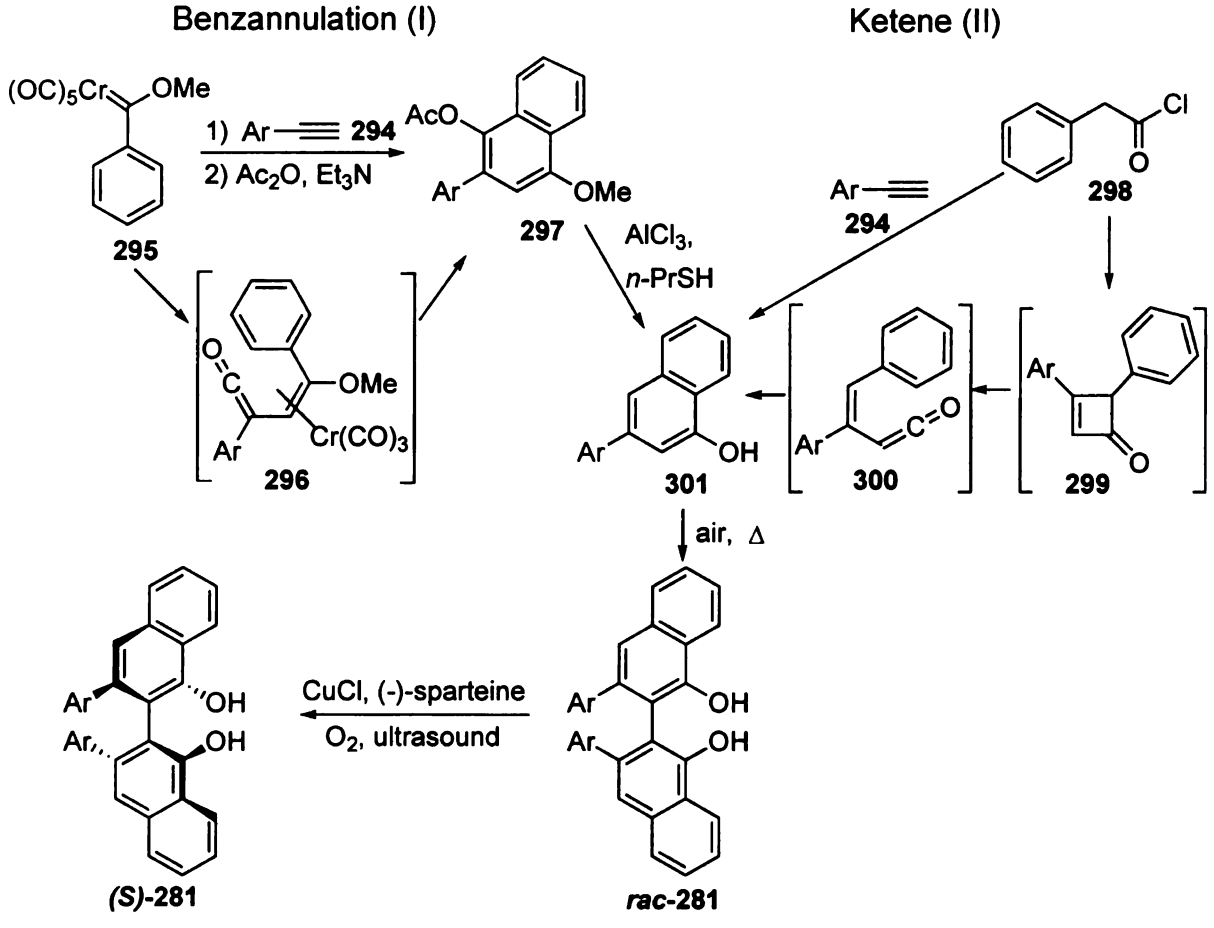
6.5.1 Preparation of various VANOL derivatives 281

The racemic VANOL derivatives **281** in Scheme 6.12 can be easily synthesized by following our published procedures for the preparation of VAPOL and VANOL ligands[20] and the optically pure *(S)*-isomers of these ligands can be obtained by our previously reported deracemization method[33] as shown in Scheme 6.13.

The monomeric intermediate **301** can be prepared either through the benzannulation method (I) or the ketene insertion method (II). In the method I, the carbene complex **295** reacts with various acetylenes **294** to give a naphthol, which is subsequently acylated to give the naphthene **297**, which upon deprotection of the methyl aryl ether and the simultaneous reductive cleavage of the acetate group gives the product **301**. In method

II, the phenylacetyl chloride **298** generates an aryl ketene at high temperature, which reacts with the acetylene **294** via a [2+2] cycloaddition to give the intermediate **299**, and then subsequent electrocyclic ring opening and electrocyclic ring closure of the second ketene intermediate **300** generates the monomer **301**. The thermal coupling of the monomer **301** in the presence of air gives the ligand **281** in racemic form, which can be converted to *(S)*-**281** via a Cu(II)-(-)-sparteine mediated deracemization procedure.

Scheme 6.13 General procedure for the preparation of VANOL derivatives **281**

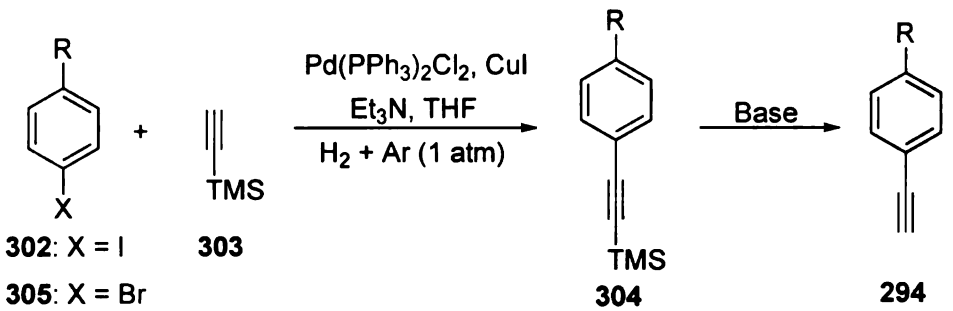


6.5.1.1 Preparation of *para*-substituted phenyl acetylenes

Since the acetylene **294** is required in either pathway for the preparation of the intermediate **301**, our first task was to find a general method for the syntheses of all the desired acetylenes. The strategy that we used was a palladium (II) catalyzed coupling of

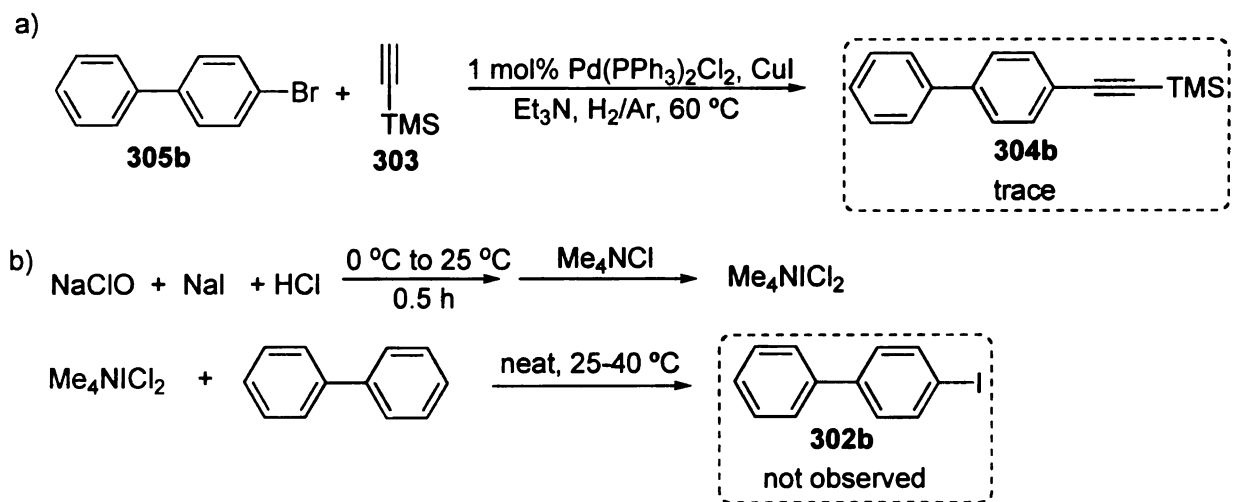
aryl halide **302** and/or **305** with the simple acetylene **303** that has been commonly applied to the preparation of aryl acetylenes[129] (Scheme 6.14).

Scheme 6.14 General strategy for the preparation of different aryl acetylenes



The attempted coupling of bromide **305b** with trimethylsilylacetylene **303** using the reported procedure[129a] only gave a trace amount of the desired product **304b** with most of the starting material recovered (Scheme 6.15, a). It was thus decided to pursue the syntheses of the acetylene **304** from iodoarenes **302** instead of the cheaper and readily available bromides **305** due to the higher reactivity of iodides in these coupling reactions.

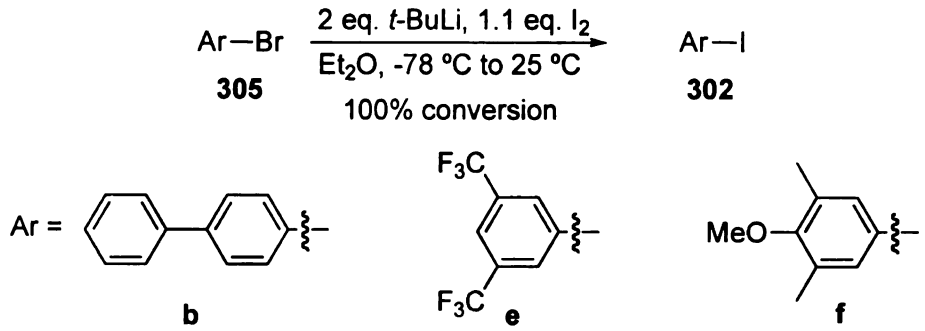
Scheme 6.15 Preparation of the biphenyl iodide



Iodoarenes **302a**, **c**, **d** were used as purchased, and iodoarenes **302b**, **e**, **f** were prepared in lab. The conversion of biphenyl to the iodobiphenyl **302b** following a

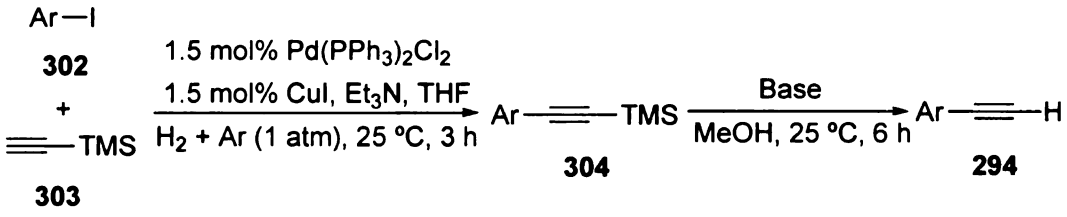
reported procedure[130b] did not give any product (Scheme 6.16, b). Halide exchange from the corresponding bromides as shown in Scheme 6.16 gave complete conversion[130a]. Aryl halides **302** was purified by a short silica gel column and were used directly in the next coupling reaction without further characterization.

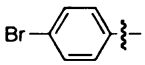
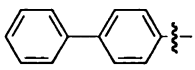
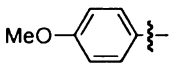
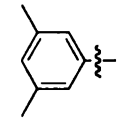
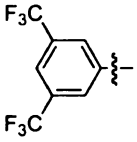
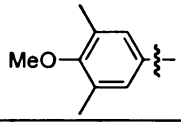
Scheme 6.16 Preparation of substituted iodides from bromides



As the data listed in Table 6.9 show, the Sonogashira coupling reaction[129] works well for all the substrates that were examined. The trimethylsilyl (TMS) protected products **304** were obtained in good isolated yields and the subsequent cleavage of the TMS group under basic conditions gave desired aryl acetylenes **294** in excellent overall isolated yields. It was found that if the silylacetylene **304** was purified, a slightly higher overall yield of **294** could be achieved (Table 6.9, entry 2 vs. 3, entry 4 vs. 5). In the preparation of 4-bromophenylacetylene **304a**, the amount of **303** should be exactly equal to the amount of the aryl iodide, or the bromide in aryl iodide **302a** would also couple with **303** to give a by-product that has two trimethylsilyl acetylene groups, and this is the cause of the lower yield for the silylacetylene **304a**. (Table 6.9, entry 1 vs. 3).

Table 6.9 Preparation of acetylenes **294**[a]



entry	series	Ar	scale[b] (mmol)	yield of **304** (%)[c]	base	yield of **294** (%)[c]
1	**a**		1	82	K_2CO_3	nd
2	**a**		1	nd	K_2CO_3	82 (from **302**)
3[d]	**a**		57	92	K_2CO_3	91 (from **304**)
4	**b**		60	98 (from **305**)	K_2CO_3	92 (from **304**)
5	**b**		1	nd	K_2CO_3	88 (from **302**)
6	**c**		1	73	TBAF	72(from **302**)
7	**c**		73	98	K_2CO_3	94 (from **302**)
8	**d**		107	100	K_2CO_3	86 (from **304**)
9	**e**		50	87 (from **305**)	K_2CO_3	77 (from **304**)
10	**f**		100	nd	K_2CO_3	78 (from **305**)

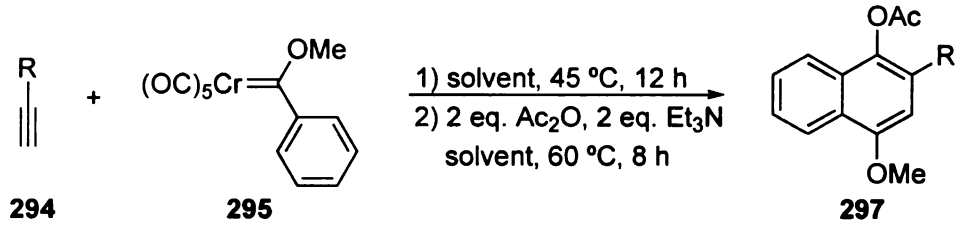
[a] Unless otherwise specified, all coupling reactions were carried out in THF with 1.1 equivalent of **303**, 1.5 mol% $Pd(PPh_3)_2Cl_2$ and CuI at 25 °C for 3 h in the coupling reaction step, and methanol was used as solvent in the deprotection step at 25 °C for 6 h. nd = not determined. [b] The scale in entries 4, 9 and 10 is for **305**, and the others are for **302**. [c] Isolated yield after silica gel chromatography. [d] 1.0 equivalent of **303** was used.

6.5.1.2 Preparation of intermediate 301 via benzannulation reaction

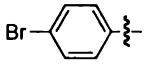
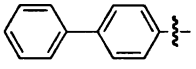
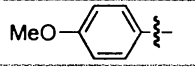
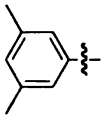
Based on our published procedure for the preparation of the VANOL and VAPOL monomeric intermediates,[20,131] the benzannulation method was examined for the

synthesis of the intermediate **301** (Scheme 6.13). A brief solvent study was undertaken for the benzannulation of substrates **294a, b,** and **d**, which showed that benzene was the best (Table 6.10, entry 1, 4, and 8). Therefore, benzene was used as the solvent for other substrates that gave moderate to good isolated yields of the naphthalenes **297** for all the substrates.

Table 6.10 Preparation of compound **297** via the benzannulation reaction[a]



294 **295** **297**

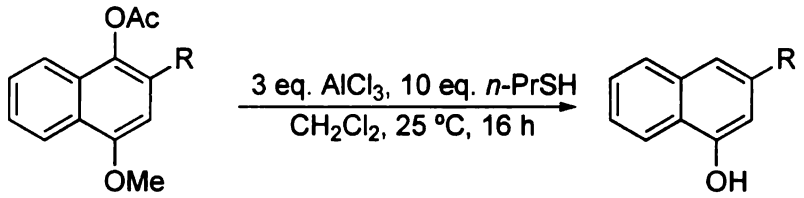
entry	series	R	solvent	yield of **295** (%)[b]
1	**a**		benzene	65
2	**a**		THF	61
3	**a**		hexanes	66
4	**b**		benzene	56
5	**b**		THF	56
6	**b**		hexanes	47
7	**c**		benzene	42
8	**d**		benzene	67
9	**d**		THF	51
10	**d**		hexanes	50
11	**j**		benzene	67

[a] Unless otherwise specified, all reactions were carried out with 1.3 equivalents of acetylene **294** with 1 equivalent of carbene complex **295** in 0.2 M solution. [b] Isolated yield after silica gel chromatography.

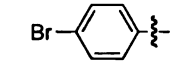
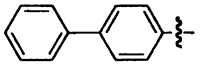
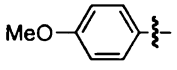
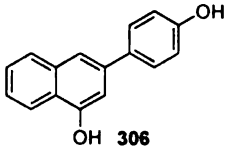
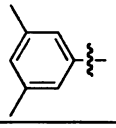
With the benzannulated products **297** in hand, the stage was then set for the

deprotection and the reductive cleavage of the acetate group that were achieved in the same pot (Table 6.11). Good yields of the desired monomers **301** were obtained in all cases. In the case of compound **297c**, the product **306** (Table 6.11, entry 3) that has two phenyl groups was isolated exclusively in 81% yield. This is a result of the fact that the two methoxyl groups in compound **297c** could not be differentiated under these reaction condition.

Table 6.11 Conversion of compound **297** to the monomer **301**



297 **301**

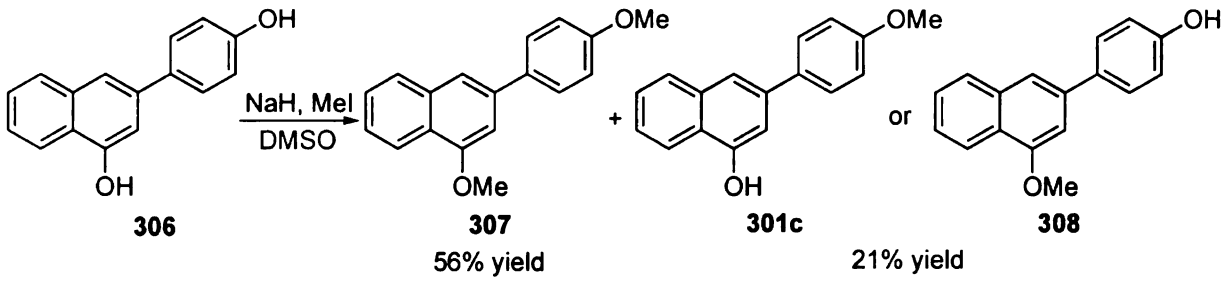
entry	series	R	yield (%)[a]
1	**a**		66-75
2	**b**		69
3	**c**		 **306** 81
4	**d**		75

[a] Isolated yield after silica gel chromatography.

The attempted selective methylation of the C3-phenolic group of **306** gave a mixture of the dimethylated product **307** (56% isolated yield), and the mono-methylated product that could be either the desired product **301c** or the isomer **308** as shown in Scheme 6.17. It was thus decided to synthesize an alternative derivative **301g** that has an ethoxyl group on the C3-phenyl in the hope that the ethoxyl and methoxyl groups could be differentiated in the following deprotection step on the corresponding compound **297g**

(Scheme 6.18). The VANOL derivative **281g** will be used as an alternative to the electron-donating methoxyl derivative **281c** (Scheme 6.12).

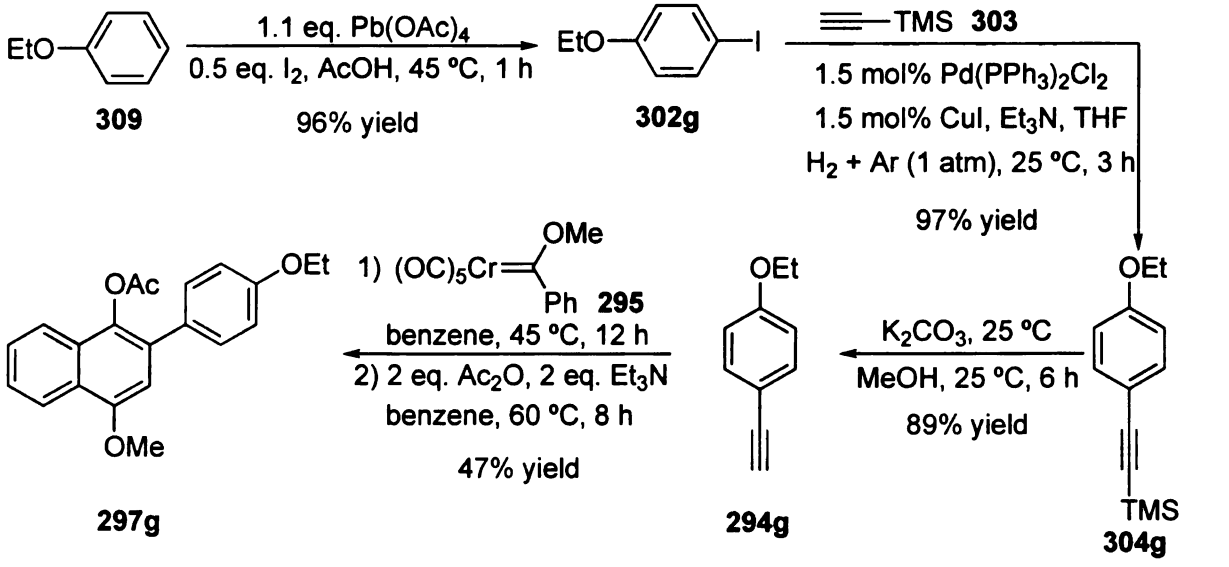
Scheme 6.17 Methylation of the compound **306**



306 **307** 56% yield **301c** **308** 21% yield

Following procedures similar to those for the coupling and benzannulation reactions in the synthesis of **295c** (Tables 6.9 and 6.10), the acetate **297g** was synthesized as illustrated in Scheme 6.18. The iodide **302g** was prepared from the ethoxylbenzene **309** in 96% isolated yield via a lead acetate mediated iodination reaction.[132a] The palladium catalyzed coupling reaction gave the protected acetylene **304g** in excellent isolated yield. Subsequent cleavage of the trimethylsilyl group afforded the acetylene **294g** in 89% isolated yield. The one-pot benzannulation and acetylation reactions using the same protocol as that for other substrates afforded the desired arene acetate **297g** in moderate isolated yield.

Scheme 6.18 Synthesis of the compound **297g**

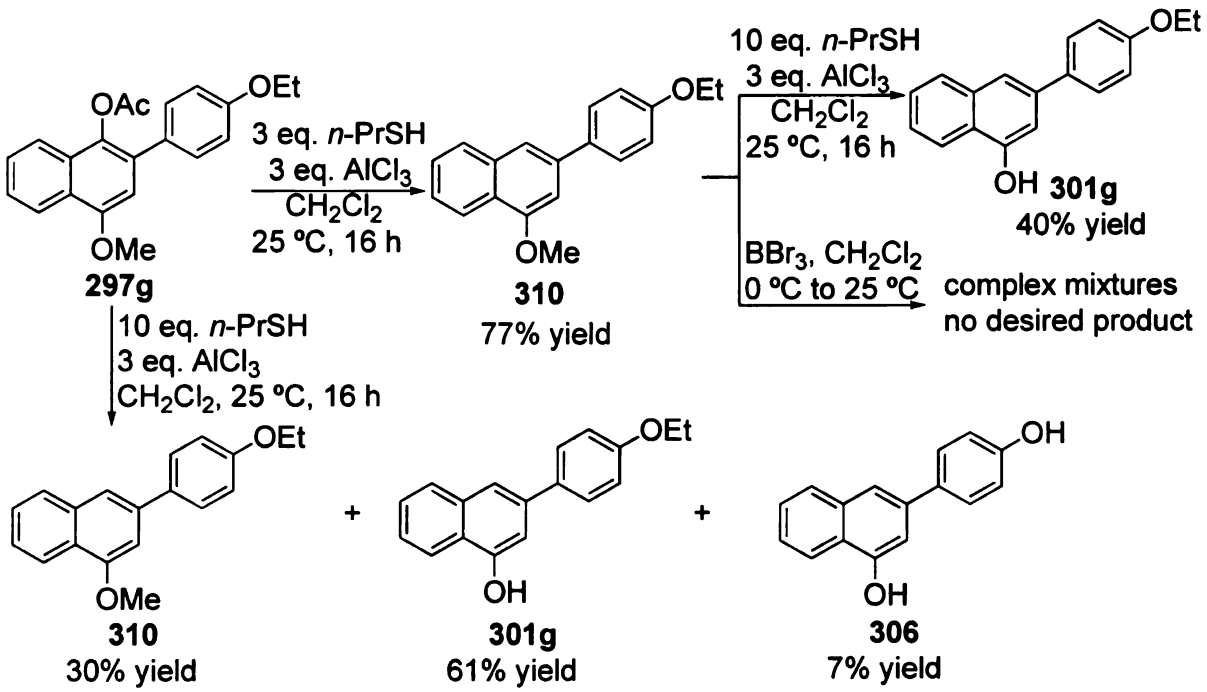


309 96% yield **302g** **304g** **294g** **297g**

The arene acetate **297g** was then examined in the key selective demethylation step. Instead of using the original conditions involving 10 equivalents of propanethiol, only 3 equivalents of the thiol was used together with 3 equivalents aluminum chloride (Scheme 6.19).

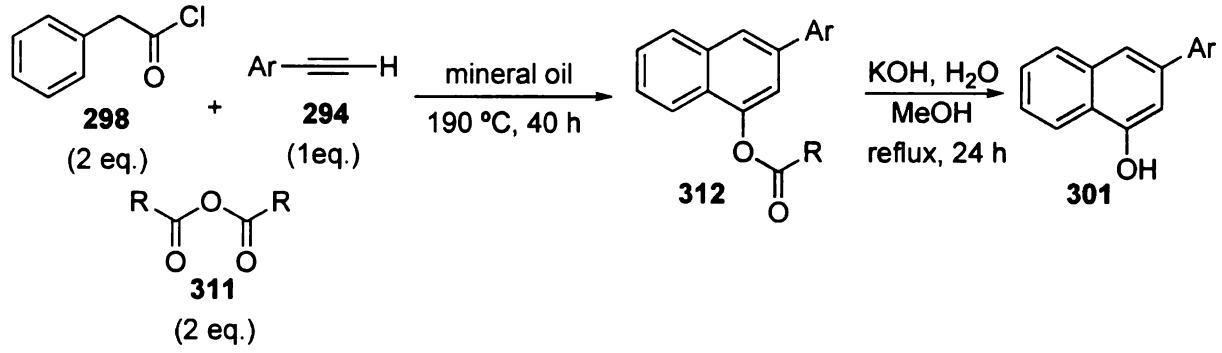
This resulted in the isolation of deacetylated product **310** in 77% yield without any detectable amount of the desired product **301g**. Compound **310** was then examined for the selective deprotection of the methyl group. It was found that the use of BBr_3 only resulted in a complex mixture, while the original deprotection conditions with 10 equivalents of thiol and 3 equivalents of $AlCl_3$ gave the desired product **301g** in 40% yield as the only isolable product. Later, the intermediate **297g** was tested by directly using the original deprotection procedure, and it was pleasing to find that the ethoxyl group was indeed more robust than the methoxyl and the desired intermediate **301g** was obtained in 61% isolated yield. The by-product **310** was isolated in 30% yield, and it could be recycled to the monomer **301g**.

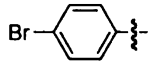
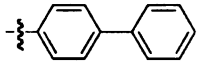
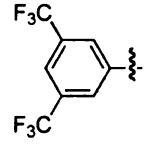
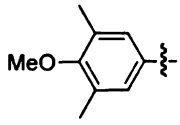
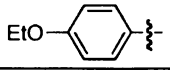
Scheme 6.19 The deprotection and the reductive cleavage of acetyl group for **297g**



6.5.1.3 Preparation of intermediate 301 via the ketene insertion reaction

Table 6.12 Preparation of monomer **301** via the ketene insertion reaction[a]



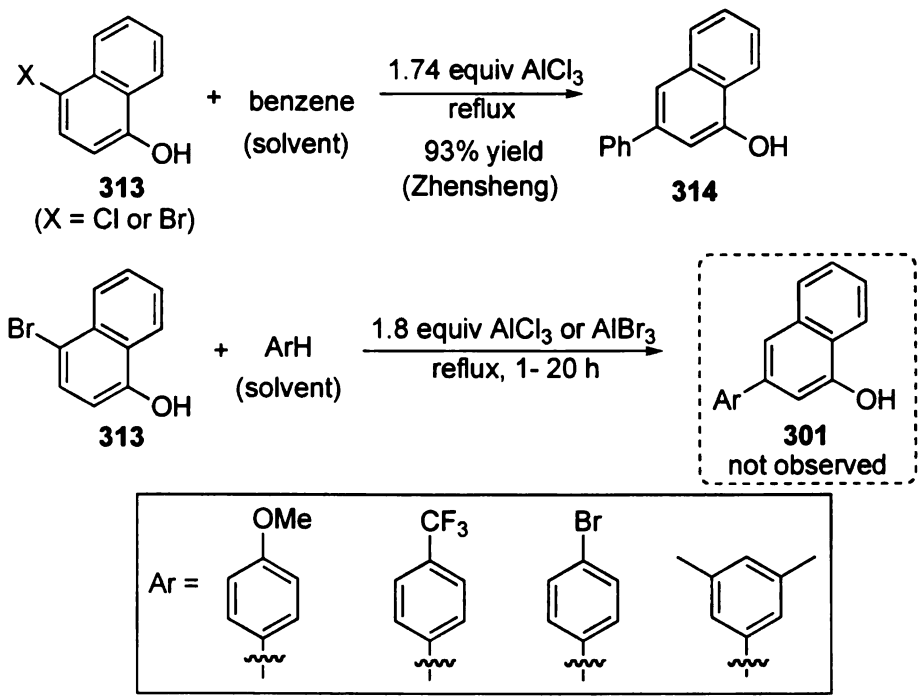
entry	series	Ar	R	yield of **301** (%)[b]
1	**a**		Et	45
2	**b**		*i*-Pr	61
3	**e**		Et	25
4	**e**		*i*-Pr	51
5	**f**		*i*-Pr	65
6	**g**		Et	61

[a] Unless otherwise specified, all reactions were carried out with 2 equiv **298**, 2 equiv **311**, 1 equiv **294** in 2 equiv mineral oil at 190 °C for 40 h in the first step. The intermediate **312** was roughly purified on a short silica gel column. A 1:1 ratio of methanol and water was used in the second step, the process of the progress was monitored by TLC. [b] Isolated yield over two steps after silica gel chromatography.

Our original reported procedure[20] for the preparation of VANOL and VAPOL monomers via the ketene insertion reaction (method II, Scheme 6.13) gave lower overall isolated yield than the benzannulation method and 2 equivalents of the aryl acetylene was required. Recently, this procedure has been optimized by group member

Zhensheng Ding in his study on the preparation of the VAPOL monomer.[35] The yield was found to be dramatically improved by the addition of an anhydride as a trapping reagent. This improved procedure was evaluated for the preparation of monomers **301** with slight change on the equivalents of reagents in this work, and the results are listed in Table 6.12. Moderate overall isolated yields of products **301** were obtained after the hydrolysis of the intermediate **312**. It was found that it is important to be roughly purify the ester **312** by running it through a short column of silica gel to remove the polar tar-like material, otherwise lower yields along with a difficult purification would be encountered during the isolation of **312**. The ketene insertion reaction requires a high temperature (190 °C), and as a result, it was not surprising that the reactions with isobutyric anhydride (bp. 182 °C) gave better results than those with propionic anhydride (bp. 167 °C) (Table 6.12, entry 4 vs. entry 3).

Scheme 6.20 Attempted one-pot preparation of **301** from compound **313**



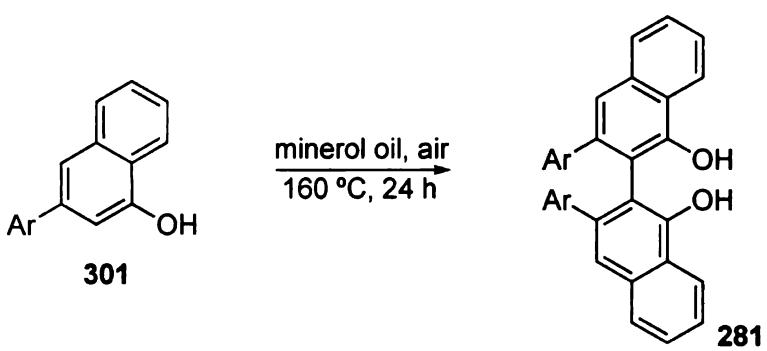
Another one-pot aromatic substitution procedure, also developed by Zhensheng Ding in the large scale preparation of the VANOL monomer **314**, involves reaction between

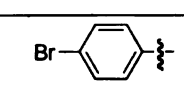
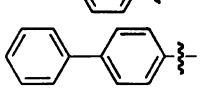
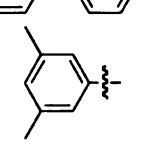
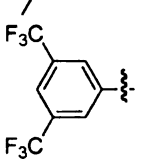
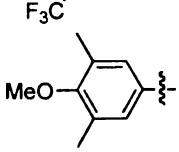
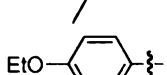
halonaphthol **313** and benzene (Scheme 6.20). However, attempts to extend this reaction to the substituted benzenes shown in Scheme 6.20 gave no detectable product. Either the starting material was recovered or complex mixtures were observed.

6.5.1.4 Preparation of the VANOL derivatives 281

With the monomers **301** in hand, the racemic VANOL derivatives **281** were prepared via a oxidative thermal coupling reaction in air. As the results in Table 6.13 show, moderate yields were obtained for all substrates except for the intermediate **301e** (Table 6.13, entry 4), where complex mixtures were obtained and none of the desired product **281e** was observed.

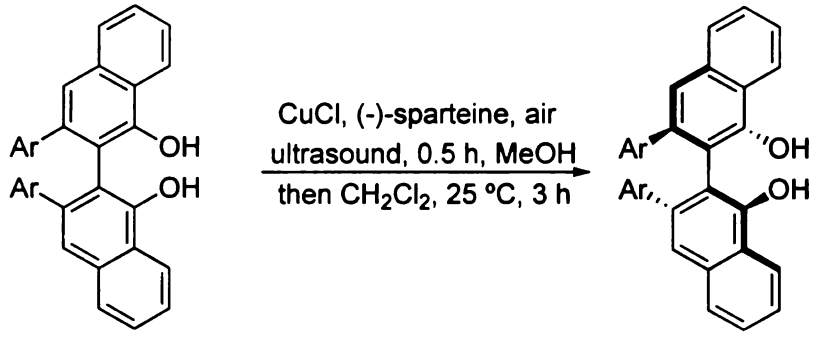
Table 6.13 Preparation of the VANOL derivatives **281** via the thermal coupling reaction[a]



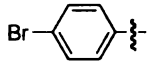
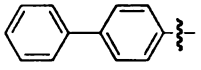
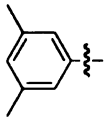
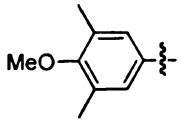
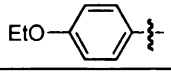
entry	series	Ar	yeld (%)[b]
1	**a**		56
2	**b**		40
3	**d**		69
4	**e**		0
5	**f**		67
6	**g**		60

[a] Unless otherwise specified, all reactions were carried out in mineral oil at 160 °C for 24 h. [b] Isolated yield after silica gel chromatography.

Table 6.14 Deracemization of the VANOL derivatives **281**[a]



rac-**281** → *(S)*-**281** >99% ee

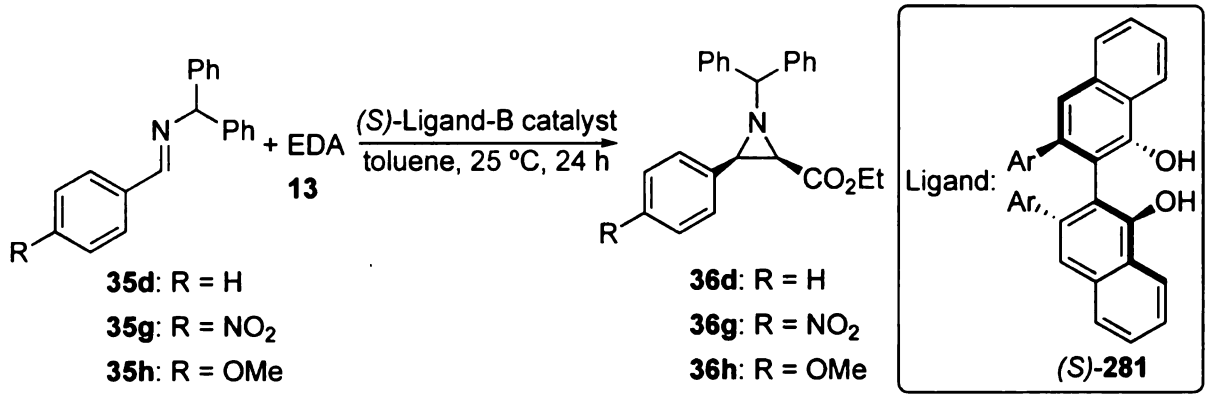
entry	series	Ar	yield (%)[b]
1	**a**		92
2	**b**		91
3	**d**		89
4	**f**		93
5	**g**		55

[a] See experimental for details. [b] Isolated yield after silica gel chromatography.

The unpublished copper(II) mediated deracemization method[118b] that was optimized in our group by Gang Hu was employed for the preparation of enantio enriched ligands *(S)*-**281**. The racemic compounds **281** were thus converted to the *(S)*-isomer with >99% ee in all cases and in good isolated yields in most cases (Table 6.14).

6.5.2 AZ reaction catalyzed by *(S)*-281-borate complexes

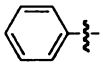
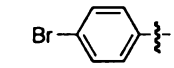
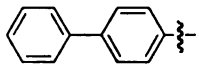
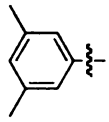
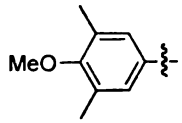
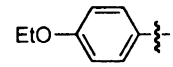
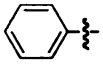
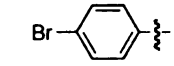
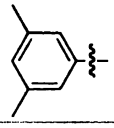
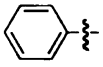
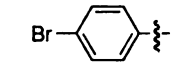
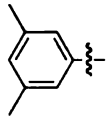
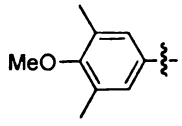
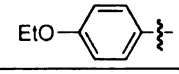
Table 6.15 AZ reaction in toluene catalyzed by ligand-borate catalysts[a]



35d: R = H
35g: R = NO_2
35h: R = OMe

36d: R = H
36g: R = NO_2
36h: R = OMe

(S)-**281**

entry	catalyst (mol%)	imine	Ar	ligand	yield (%)[b]	ee (%)[c]
1	10	**35d**		**32**	87	93
2	10	**35d**		**281a**	92	91
3	10	**35d**		**281b**	92	89
4	10	**35d**		**281d**	91	94
5	10	**35d**		**281f**	84	96
6	10	**35d**		**281g**	81	94
7	5	**35g**		**32**	86	89
8	5	**35g**		**281a**	86	89
9	5	**35g**		**281d**	85	88
10	5	**35h**		**32**	61	87
11	5	**35h**		**281a**	68	85
12	5	**35h**		**281d**	54	92
13	5	**35h**		**281f**	62	96
14	5	**35h**		**281g**	58	88

[a] Unless otherwise specified, all reactions were carried out in 0.5 M in imine in toluene at 25 °C for 24 h with 1.1 equiv EDA **13**. The catalyst was generated from 1 equiv ligand, 4 equiv $B(OPh)_3$, and 1 equiv H_2O at 85 °C for 1 h, then 0.5 mm Hg vacuum was applied at 85 °C for 0.5 h. [b] Isolated yield after silica gel chromatography. [c] Determined from chiral HPLC on a Chiralcel OD-H column.

Five chiral VANOL derivatives were prepared and ready for the evaluation of the CH-π interactions that are suggested by the crystal structure of the complex **274** (Scheme 6.5). The ligands **281a** and **281b** will serve to test the effects of an electron deficient face ring, ligand **281g** will serve to test the effects of an electron donating face ring, ligand **281d** was synthesized to test for possible steric effects, and the ligand **281f** was designed to test for combined steric and electronic effects.

The 4,4'-di-nitro-VANOL **281i** was made by Dr. Hu and will be used to test how an electron deficient naphthalene ring system will effect the catalyst-substrate binding. It might be expected to result in a diminished π-π stacking interaction with the substrate. The *N*-benzhydryl imine **35d** was used as the standard imine in these aziridination reactions, and to span a broader range of catalyst-substrate interactions, imines with different electronic properties such as the *para*-nitrophenyl imine **35g** and the *para*-methoxylphenyl imine **35h** were also examined with some of ligands. The results are listed in Table 6.15.

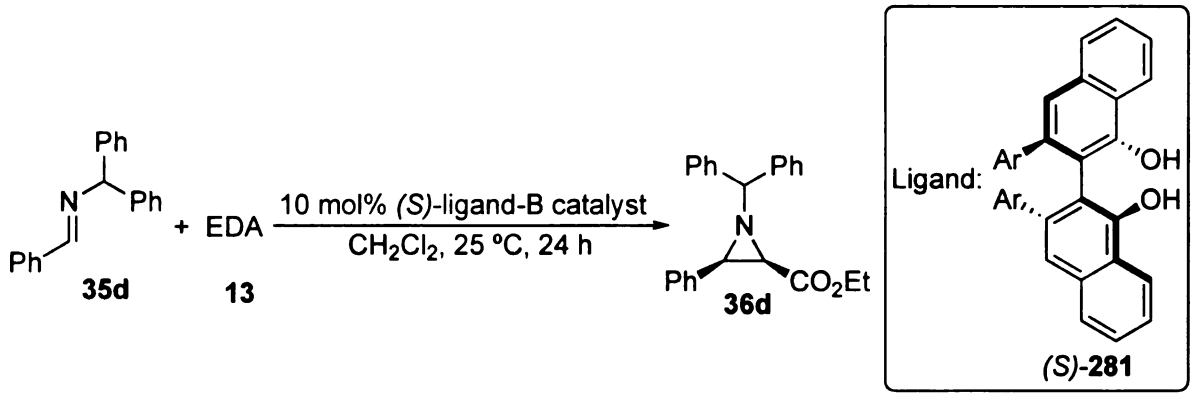
For the reactions with imine **35d**, there was a small but measurable variation in the asymmetric inductions over the range of VANOL ligands (89-96% ee). The lowest enantioselectivities were observed (Table 6.15, entry 2 and entry 3) for the ligands with the most electron withdrawing groups on the ligand and this might be due to the weakened CH-π interaction between the catalyst (face ring) and the imine (edge ring) (Figure 6.4).

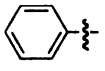
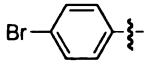
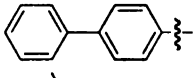
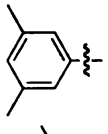
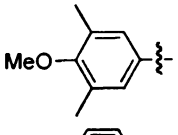
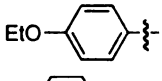
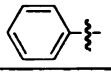
Considering the weak electron withdrawing effects of both the bromide in **281a** and the phenyl in **281b**, it might be interesting in future work to examine the cyano substituted VANOL **281g** (Scheme 6.12) that has a strong electron withdrawing group thus might be expected to give lower asymmetric induction in the aziridination reaction with the imine **35d** (Scheme 6.12). Another substrate **281j** would also be interesting to examine since it has the phenyl ring replaced by an isopropyl group and therefore, it should not be able to function as a face ring in the catalyst-imine complex. The preparation and examination of these ligands will await future experiments.

The electron donating substrate **281g** that was expected to enhance the CH-π interaction only gave a 1% higher ee than that obtained from the VANOL **32** (Table 6.15, entry 6 vs. entry 1). To our surprise, the 3,5-dimethyl substituted derivative **281d** also gave slightly higher yield and % ee value and yield, while the substrate **281f** that was designed to probe the combined effects of **281d** and **281g** provided highest enantioselectivity (Table 6.15, entry 5). The advantageous effect of **281f** was even more significant in the reaction with imine **35h** (Table 6.15, 96% ee in entry 13 vs. 87% ee using VANOL in entry 10).

The effects of different VANOL derivatives on the asymmetric induction in aziridination reactions were also examined in dichloromethane, and the results are listed in Table 6.16. In the reactions carried out in CH_2Cl_2, all of the ligand with electron withdrawing and with electron donating groups gave nearly the same asymmetric inductions as did the unsubstituted VANOL ligand **32**. As in toluene, the best ligand in CH_2Cl_2 was **281f** (Table 6.16, entry 5). The 4,4'-di-nitro-VANOL **281i** (Scheme 6.12) was obtained from Dr. Hu and gave racemic aziridine **36d** but in comparable yield. It was determined to be >99% ee when prepared years ago,[118c] and the only explanation for this observation is that the nitro-VANOL may have slowly racemized. This ligand will need to be further investigated.

Table 6.16 AZ reaction in CH_2Cl_2 catalyzed by ligand-borate catalysts[a]



entry	series of ligand	Ar	yield (%)[b]	ee (%)[c]
1	**32**		77	91
2	**281a**		84	91
3	**281b**		84	92
4	**281d**		76	91
5	**281f**		84	95
6	**281g**		82	91
7	**281i**[d]		73	0

[a] Unless otherwise specified, all reactions were carried out in 0.5 M in imine in CH_2Cl_2 with 1.1 equiv EDA **13** and 10 mol% catalyst at 25 °C for 24 h. The catalyst was generated from 1 equiv ligand, 4 equiv $B(OPh)_3$, and 1 equiv H_2O at 85 °C for 1 h, then 0.5 mm Hg vacuum was applied at 85 °C for 0.5 h. [b] Isolated yield after silica gel chromatography. [c] Determined from chiral HPLC on a Chiralcel OD-H column. [d] 4,4'-di-nitro-VANOL ligand (Scheme 6.12).

Based on the results of the AZ reactions with catalysts generated from VANOL derivatives, the electron donating substituent (**281g**), which was expected to enhance the CH-π interaction and thus give higher asymmetric induction, does not gave

significantly increased induction. The electron withdrawing substituent (**281a** and **281b**) does decrease the enantioselectivity to a small extent. On the other hand, the substituents **281d** and **281f** enhance the enantioselectivity to a significant degree giving the highest asymmetric inductions for both imines **35d** and **35h**. This may be the result of enhanced CH-π interactions since both methoxyl and methyl are electron donating groups.

6.6 Conclusion

The studies for a better understanding of the mechanism of AZ reaction on the nature of the catalyst-substrate interactions were discussed. Structurally different diazo esters will only affect the asymmetric inductions in the range of 1-4% ee, while the diazo amide reacted much slower and incomplete conversions could not be avoided under the standard conditions unless the very reactive *N*-MEDAM imine was used as the substrate along with 20% catalyst loading.

Based on the discovery of both B1 and B2 species in the reactions of VANOL and VAPOL with $B(OPh)_3$ and their selectivity differences in the AZ reaction, the catalyst preparation procedure was further optimized by the introduction of 1 equivalent of H_2O, together with 1 equivalent of the ligand and 4 equivalents of $B(OPh)_3$ with the optimal temperature of 80 °C. This optimized procedure was then used in the later studies of the CH-π interactions.

The presence of the CH-π interactions between the imine and the phenoxy group on the boroxinate ring of the catalyst suggest that electron withdrawing groups on the phenoxy ring (face) should weaken these interactions and result in low enantioselectivities and electron rich substituents should strengthen these CH-π interactions and thus the asymmetric inductions. Amongst the VANOL derivatives shown in Scheme 6.12, five ligands were prepared and examined in the aziridination reactions

of imines with different electronic properties. The preliminary results suggest that electron withdrawing groups on the face ring may slightly diminish the proposed CH-π interactions, while the most electron enriched ligand (**281f**) gave superior asymmetric inductions for imines that were examined.

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STUDIES ON THE OPTIMIZATION OF CATALYTIC ASYMMETRIC AZIRIDINATION REACTION – TACTICS AND MECHANISM

VOLUME II

By

Zhenjie Lu

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

2008

CHAPTER SEVEN

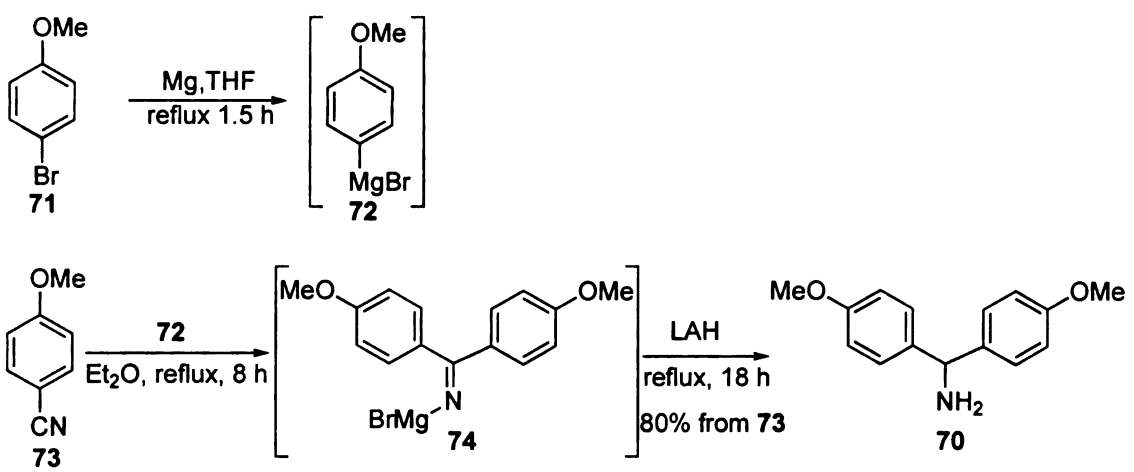
EXPERIMENTAL PART

All experiments were performed under an argon atmosphere. Flasks were flame-dried and cooled under argon before use. All solvents such as dichloromethane, carbon tetrachloride, triethylamine, Toluene, benzene, ether, THF, DMF and DMSO are dried if used in the reaction.

7.1 Experimental for chapter two

Synthesis of *bis*(4-methoxyphenyl)methylamine 70:

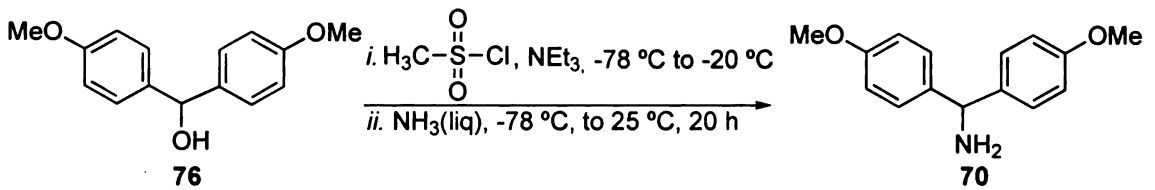
Method A: (reductive amination)[44]



To a flame-dried 100 mL three-neck round bottom flask attached with a reflux condenser and cooled under argon was added Mg (1.22 g, 50 mmol), 50 mL THF followed by one crystal of iodine. Bromoanisole **71** (5.6 g, 30 mmol) was added via syringe slowly. The mixture was heated to reflux under argon for 1.5 hours, allowed to cool down to room temperature. The clear amber solution was transferred to a flame-dried 250 mL three-neck round bottom flask equipped with condenser via cannula. Benzonitrile **73** (3.33 g, 25 mmol) was dissolved in 20 mL of THF and transferred to the

250 mL flask containing Grignard reagent via cannula. The resulting solution was heated to reflux under argon for 8 hours, then cooled down to room temperature. A suspension of $LiAlH_4$ (1.14g, 30 mmol) in 50 mL THF was transferred via cannula to the reaction flask. The resulting light yellow mixture was heated to reflux for 20 hours, then cooled down to room temperature, quenched carefully with the addition of 1.2 mL H_2O, 1.2 mL 10% NaOH solution and then 3.0 mL H_2O slowly. The resulting suspension was diluted with 50 mL of Et_2O and filtered to remove salt, the solid was washed with Et_2O until there was no presence of detectable amine in the filtered Et_2O. The combined ether was concentrated under reduced pressure to give crude product as a light yellow oil, which was purified by silica gel chromatography using 1:1 EtOAc/Hexane as eluent to give amine **70** as white solid in 80% yield (4.86 g, 20 mmol).

Method B: (mesylation-amination)[45a]

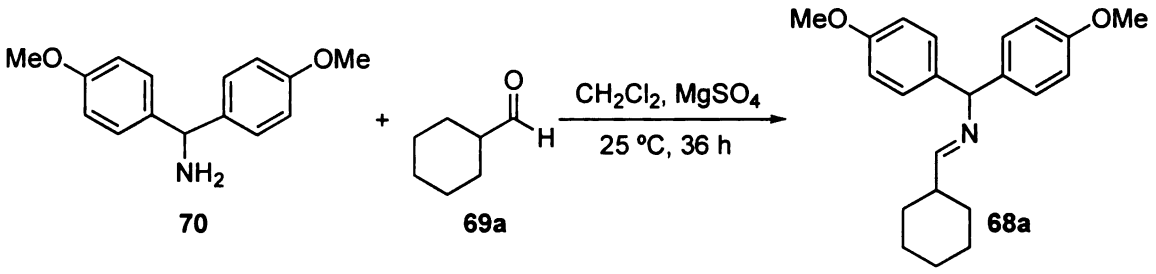


To a 500 mL flame-dried three-neck round bottom flask equipped with a condenser filled with argon was added 4,4'-dimethoxybenzhydrol **76** (19.1 g, 78.2 mmol) and 250 mL THF. Et_3N (10.28 g, 101.7 mmol) was added dropwise at –78 °C followed by dropwise addition of mesylchloride (11.62 g, 101.7 mmol) via syringe with vigorous stirring. The mixture was warmed up to –20 °C and stirred for 40 minutes at this temperature, then cooled to –78 °C. Gaseous ammonia was introduced at a rate such that a dry-ice cooled condenser provided steady drop-wise addition of liquid NH_3 and this addition was continued for a period of 20 minutes. The reaction mixture was allowed to warm gradually to ambient temperature after which it was stirred for an additional 20

hours. The reaction was quenched by addition of 200 mL of concentrated NH_4OH then extracted with EtOAc (100 mL × 3). The combined organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation to give the crude product as a white solid. The amine **70** was purified by chromatography on a column (65 mm × 400 mm, with pre-neutralized (2% Et_3N) silica gel, 1:1 EtOAc/hexanes as eluent). An initial band containing a yellow impurity along with a small amount of alcohol **76** was discarded and elution continued to give the product **70** as white solid (mp. 60-61°C) in 82% yield (15.59 g, 64 mmol).

Spectral data for **70**: R_f = 0.17 (1:1 hexane/EtOAc). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.78 (br s, 2H), 3.82 (s, 6H), 5.18 (s, 1H), 6.90 (d, 4H, *J* = 8.8 Hz), 7.33 (d, 4H, *J* = 8.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 55.14, 58.39, 113.67, 127.74, 138.11, 158.35; IR (thin film) 3395m, 3345m, 1610s, 1508vs, 1245vs, 1174s, 1034s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 244 M^+ +1 (4), 243 M^+ (23), 242 (27), 227 (14), 135 (100), 109 (17), 94 (8), 77 (10).

General procedure for the preparation of imines 68 - illustrated for the synthesis of *N*-cyclohexylmethylidene-*bis*(4-methoxyphenyl)methylamine 68a.

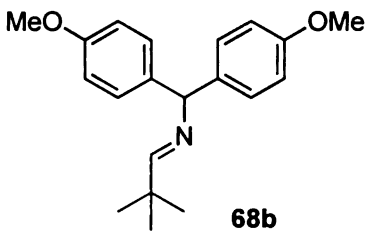


All liquid aldehydes were distilled before use and the solid aldehydes were used as purchased from Aldrich. The commercial available 4-nitrobenzaldehyde was not pure and gave the imine **68g** as a yellow solid. If the 4-nitrobenzaldehyde was purified via chromatography the imine **68g** could be obtained as an off-white solid, however, no

difference was observed in the results of the AZ reaction. All imines **68** could be purified by crystallization except **68c**, which is light-yellow liquid and decomposed when purification was attempted by vacuum distillation. Imine **68c** was used without purification.

***N*-cyclohexylmethylidene-bis(4-methoxyphenyl)methylamine 68a.** To a 100 mL flame-dried round bottom flask filled with argon was added bis(4-methoxyphenyl)methylamine **70** (2.43 g, 10 mmol), $MgSO_4$ (2.0 g, 16.7 mmol) and 30 mL CH_2Cl_2. After stirring for 10 minutes, aldehyde **69a** (1.13 g, 10.1 mmol) was added. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was filtered through celite and the celite bed was washed with CH_2Cl_2 (10 mL × 3) and then the filtrate was concentrated by rotary evaporation to give the crude imine **68a** as an off-white solid. Crystallization (1: 20 CH_2Cl_2/hexanes) afforded **68a** as a white solid (mp. 77.5-78.5 °C) in 92% isolated yield (3.1 g, 9.2 mmol).

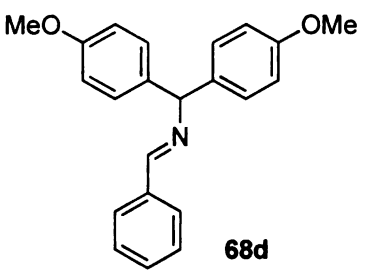
Spectral data for **68a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25-1.37 (br m, 6H), 1.68-1.90 (br m, 4H), 2.31-2.33 (m, 1H), 3.82 (s, 6H), 5.27 (s, 1H), 6.87 (d, 4H, *J* = 8.8 Hz), 7.22 (d, 4H, *J* = 8.8 Hz), 7.68 (d, 1H, *J* = 5.1 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 25.34, 25.94, 29.67, 43.39, 55.09, 76.58, 113.58, 128.46, 136.39, 158.28, 168.48; IR (thin film) 2928vs, 1664m, 1608s, 1510vs, 1246vs, 1035s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 337 M^+ (0.3), 227 (100), 682 (7), 141 (8), 113 (17), 77 (4), 55 (15), 41 (16). Anal calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.28; H, 8.11; N, 4.11.



68b

***N*-(1,1-Dimethylethylidene)-bis(4-methoxyphenyl)methylamine 68b.** Crystallization (1:10 CH_2Cl_2/hexanes) afforded white solid (mp. 75.5-76.5 °C) in 96% isolated yield (2.98 g, 9.6 mmol).

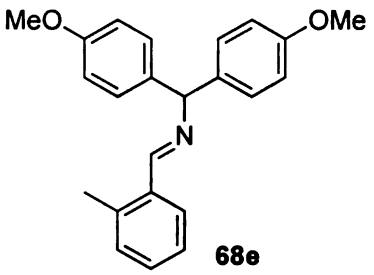
Spectral data for **68b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.08 (s, 9H), 3.76 (s, 6H), 5.24 (s, 1H), 6.81 (d, 4H, *J* = 8.8 Hz), 7.18 (d, 4H, *J* = 8.8 Hz), 7.62 (s, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 26.94, 36.31, 55.16, 75.99, 113.59, 128.43, 136.70, 158.25, 171.09; IR (thin film) 2957w, 1664m, 1610m, 1510vs, 1246vs, 1172s, 1036s, 827w cm^{-1}; mass spectrum, *m/z* (% rel intensity) 311 M^+ (0.2), 227 (100), 212 (5), 141 (9), 113 (13), 86 (12), 84 (12). Anal calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.75; H, 8.24; N, 4.51.



68d

***N*-Benzylidene-bis(4-methoxyphenyl)methylamine 68d.** Crystallization (1:8 CH_2Cl_2/hexanes) afforded white solid (mp. 60.0-61.0 °C) in 91% isolated yield (3.01 g, 9.1 mmol).

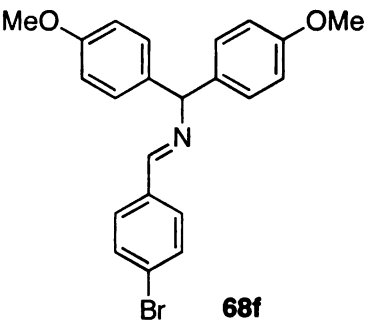
Spectral data for **68d**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 6H), 5.51(s, 1H), 6.84 (d, 4H, *J* = 8.8 Hz), 7.25-7.27 (m, 4H), 7.37-7.40 (m, 3H), 7.79-7.82 (m, 2H), 8.37 (s, 1H); ^{13}C (CDCl3, 75 MHz) δ 55.17, 76.55, 113.71, 128.35, 128.43, 128.61, 128.70, 130.60, 136.28, 158.43, 160.24; IR (thin film) 2955w, 1641m, 1608m, 1510vs, 1246vs, 1172s, 1036s, 829m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 331 M^+ (0.6), 243 (11), 227 (100), 212 (8), 141 (9), 136 (38), 135 (58), 77 (14). Anal calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.38; H, 6.53; N, 4.29.



68e

***N*-(*o*-Tolylbenzylidene)-bis(4-methoxyphenyl)methylamine 68e.** White solid (mp. 64.0-65.0 °C) in 75% isolated yield (2.58 g, 7.5 mmol) after recrystallization three times (1: 8 CH_2Cl_2/hexanes).

Spectral data for **68e**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.55 (s, 3H), 3.78 (s, 6H), 5.53 (s, 1H), 6.88 (d, 4H, *J* = 8.8 Hz), 7.14-7.16 (m, 1H), 7.21-7.25 (m, 2H), 7.29 (d, 4H, *J* = 8.5 Hz), 7.95-7.98 (m, 1H), 8.72 (s, 1H). ^{13}C ($CDCl_3$, 75 MHz) δ 19.64, 55.21, 77.41, 113.73, 126.02, 128.28, 128.55, 130.15, 130.78, 134.22, 136.57, 137.79, 158.43, 159.09; IR (thin film) 2836m, 1635m, 1608m, 1500vs, 1246vs, 1173s, 1036s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 345 M^+ (0.4), 227 (100), 212 (5), 169 (8), 141 (6), 115 (5). Anal calcd for $C_{23}H_{23}NO_2$: C, 79.97; H, 6.71; N, 4.05. Found: C, 79.54; H, 6.93; N, 4.09.

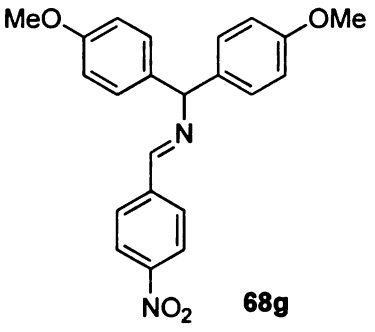


68f

***N*-(4-Bromobenzylidene)-bis(4-methoxyphenyl)methylamine 68f**. Crystallization (1:10 CH_2Cl_2/hexanes) afforded white solid (mp. 125.5-126.5 °C) in 91% isolated yield (3.73 g, 9.1 mmol).

Spectral data for **68f**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 6H), 5.51 (s, 1H), 6.85 (d, 4H, *J* = 8.8 Hz), 7.26 (d, 4H, *J* = 8.8 Hz), 7.52 (d, 2H, *J* = 8.3 Hz), 7.67 (d, 2H, *J* = 8.5 Hz), 8.31 (s, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 55.20, 76.56, 113.77, 125.02, 128.58, 129.78,

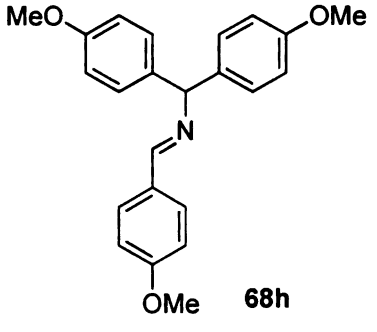
131.70, 135.20, 136.02, 158.51, 159.01; IR (thin film) 2835m, 1641m, 1609m, 1510vs, 1240vs, 1171s, 1036s, 826w cm^{-1}; mass spectrum, *m/z* (% rel intensity) 411 M^+ (^{81}Br, 0.3), 409 M^+ (^{79}Br, 0.3), 227 (100), 212 (5), 169 (6), 89 (5). Anal calcd for $C_{22}H_{20}BrNO_2$: C, 64.40; H, 4.91; N, 3.41. Found: C, 64.15; H, 5.09; N, 3.50.



68g

***N-(*4-Nitrobenzylidene)-bis(4-methoxyphenyl)methylamine 68g.** Crystallization (1:5 EtOAc / hexanes) afforded a light yellow solid (mp. 99-100 °C) in 91% isolated yield (3.42 g, 9.1 mmol).

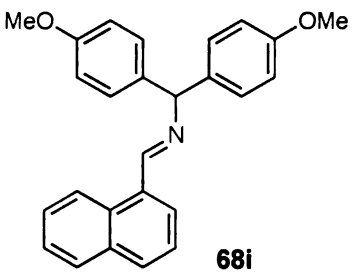
Spectral data for **68g**: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 6H), 5.57 (s, 1H), 6.85 (d, 4H, *J* = 8.8 Hz), 7.26 (d, 4H, *J* = 8.8 Hz), 7.96 (d, 2H, *J* = 8.8 Hz), 8.24 (d, 2H, *J* = 8.8 Hz), 8.44 (s, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 55.19, 76.75, 113.84, 123.73, 128.55, 129.01, 135.52, 141.73, 148.95, 157.98, 158.65; IR (thin film) 2838m, 1644m, 1603m, 1510vs, 1340vs, 1248vs, 1173s, 1034s, 831s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 376 M^+ (0.7), 227 (100), 212 (5), 169 (7), 141 (6), 113 (10). Anal calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 70.05; H, 5.31; N, 7.38.



68h

***N*-(4-Methoxybenzylidene)-bis(4-methoxyphenyl)methylamine 68h.** Crystallization (1:8 CH_2Cl_2/hexanes) afforded white powder (mp. 129.5-130.5 °C) in 92% isolated yield (3.32 g, 9.2 mmol).

Spectral data for **68h**: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 6H), 3.81 (s, 3H), 5.47 (s, 1H), 6.83 (d, 4H, *J* = 8.8 Hz), 6.89 (d, 2H, *J* = 8.8 Hz), 7.25 (d, 4H, *J* = 8.5 Hz), 7.75 (d, 2H, *J* = 8.8 Hz), 8.29 (s, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 55.20, 55.29, 76.40, 113.68, 113.81, 128.47, 128.63, 129.92, 136.52, 158.37, 159.54, 161.30; IR (thin film) 2838m, 1633m, 1607m, 1510vs, 1246vs, 1167s, 1034s, 831w cm^{-1}; mass spectrum, *m/z* (% rel intensity) 361 M^+ (0.5), 227 (100), 212 (3), 169 (5), 141 (5), 86 (10), 84 (10), 77 (6). Anal calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.05; H, 6.20; N, 4.03.

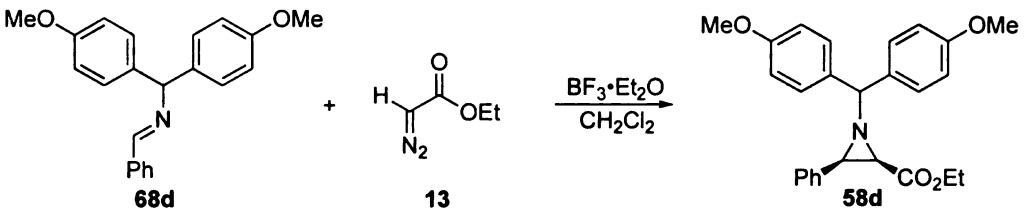


68i

***N*-(1-Naphthylidene)-bis(4-methoxyphenyl)methylamine 68i.** Crystallization (1:8 CH_2Cl_2/hexanes) afforded white solid (mp. 92.5-93.5 °C) in 82% isolated yield (3.12 g, 8.2 mmol).

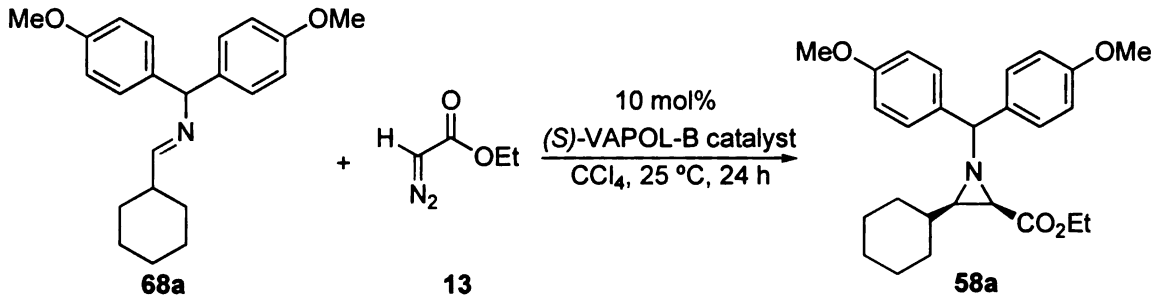
Spectral data for **68i**: ^1H NMR ($CDCl_3$, 300 MHz) δ 3.77 (s, 6H), 5.60 (s, 1H), 6.86 (d, 4H, *J* = 8.8 Hz), 7.35 (d, 4H, *J* = 8.5 Hz), 7.47-7.58 (m, 3H), 7.85-7.95 (m, 3H), 9.02 (s, 1H), 9.09 (d, 1H, *J* = 8.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 55.20, 77.98, 113.79, 113.88, 124.68, 125.16, 125.98, 127.16, 128.56, 128.65, 128.74, 129.66, 131.10, 133.81, 136.48, 158.48, 160.35; IR (thin film) 2836m, 1640m, 1609m, 1510vs, 1246vs, 1173s, 1034s, 777m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 381 M^+ (1.2), 228 (10), 227 (100), 169 (6), 153 (4), 141 (7), 127 (8), 115 (5). Anal calcd for $C_{26}H_{23}NO_2$: C, 81.86; H, 6.08; N, 3.67. Found: C, 81.55; H, 6.07; N, 3.81.

General procedure for the preparation of racemic aziridines – illustrated for *rac-cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-phenylaziridine 15d.



To a 25 mL flamed-dried round bottom flask filled with argon was added *N*-phenylmethylidene-bis(4-methoxyphenyl)methylamine **68d** (166 mg, 0.5 mmol) and 2 mL CH_2Cl_2. This mixture was stirred for 10 minutes and then $BF_3 \cdot Et_2O$ (36 μL, 0.3 mmol) was added. To this solution was added ethyl diazoacetate (EDA) (58 μL, 0.55 mmol). The reaction mixture was stirred for 24 hours at room temperature. Removal of the solvent by rotary evaporation afforded the crude aziridine **58d** as an off-white semi-solid. The crude aziridine was purified by silica gel chromatography to give racemic **58d** as a white solid in 44% isolated yield (90 mg, 0.22 mmol). The chromatography was performed on a 15 mm column filled to a depth of 400 mm with silica gel and eluted with 9:1 hexanes / EtOAc which was switched to 5:1 hexanes / EtOAc after the excess ethyl diazoacetate had eluted. The racemic aziridine was used to determine the HPLC separation conditions and help identify the presence of both enantiomers.

General procedure for the AZ reaction with *N*-DAM imines – illustrated for the preparation of *(2R, 3R)-Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-cyclohexylaziridine 58a.



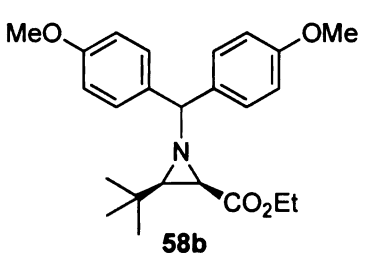
68a **13** **58a**

To a 25 mL flame-dried Schlenk flask flushed with argon was added (*S*)-VANOL (44 mg, 0.1 mmol) and $B(OPh)_3$ (87 mg, 0.3 mmol). The mixture was dissolved in 2 mL CCl_4, the flask was sealed, and then placed in an 85 °C oil bath. After 1 hour, a vacuum (0.5 mm Hg) was applied carefully and lasted for 30 minutes while the flask was still heated at 85 °C. In a separate similar 25 mL flame-dried round bottom flask filled with argon was added *N*-cyclohexylmethylidene-bis(4-methoxyphenyl)methylamine **68a** (337 mg, 1 mmol) and 2 mL CCl_4. The flask containing the catalyst was cooled to room temperature and then 2 mL CCl_4 was added. The catalyst solution was transferred via syringe to the flask containing imine **68a.** The reaction mixture was stirred for 5 minutes to give a light orange solution. To this solution was rapidly added EDA **13** (114 μL, 1.1 mmol) and the resulting mixture was stirred for 24 hours at room temperature. The reaction was quenched by addition of 4 mL hexane. Removal of the solvent by rotary evaporation afforded the crude aziridine as an off-white solid.

The *cis/trans* ratio of aziridine **58a** was determined by comparing the ^1H NMR integration of the methine protons of the aziridine in the crude reaction mixture. The relative amounts of the acyclic enamine side products **81a** and **82a** were determined by ^1H NMR analysis of the crude reaction mixture by integration of the *N*-H proton relative to the that of the *cis*-aziridine methine proton. The crude aziridine was purified by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes / EtOAc as eluent, after elution of the first fraction, which contains EDA and / or enamine side products **81** and **82**, the eluent was changed to 5:1 hexanes / EtOAc). The aziridine **58a** was obtained as

a white solid (mp. 119.5-121 °C) in 86% isolated yield (364 mg, 0.86 mmol). The *cis/trans* ratio was > 33:1 and <7% yield of **81a** and <2% yield of **82a** was observed by ^{1}H NMR analysis. The optical purity of **58a** was determined to be 84% ee by HPLC analysis (Chiralpak AD column, 98:2 hexane/*i*PrOH at 226 nm, flow-rate: 1.0 mL/min). Retention times: R_t = 9.63 min **58a** and R_t = 15.31 min *ent*-**58a**. The assignment of the retention times was aided by a racemic sample of **58a** prepared from BF_3•Et_2O as described above. A single crystallization (1:5 CH_2Cl_2/hexanes) gave (*2R*, *3R*)-**58a** in an overall 68% isolated yield (287 mg, 0.68 mmol) with 99% optical purity.

Spectral data for (*2R*, *3R*)-**58a**: R_f = 0.3 (1:5 EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.50-0.53 (m, 1H), 0.89-1.11 (m, 4H), 1.22 (t, 3H, *J* = 7.1 Hz), 1.22-1.24 (m, 2H), 1.31-1.66 (m, 4H), 1.75 (dd, 1H, *J* = 6.9, 9.0 Hz), 2.20 (d, 1H, *J* = 6.9 Hz), 3.50 (s, 1H), 3.74 (s, 6H), 4.12-4.24 (m, 2H), 6.78 (d, 2H, *J* = 8.8 Hz), 6.80 (d, 2H, *J* = 8.8 Hz), 7.21 (d, 2H, *J* = 8.5 Hz), 7.34 (d, 2H, *J* = 8.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 14.25, 25.35, 25.52, 26.11, 30.10, 30.80, 36.29, 43.35, 52.21, 55.17, 60.64, 76.99, 113.53, 113.62, 127.97, 129.26, 134.82, 135.41, 158.36, 158.78, 169.71; IR (thin film) 2922w, 1734s, 1610m, 1510vs, 1244s, 1174s, 1035m, 816s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 423 M^+ (2), 394 (6), 340 (13), 227 (100), 212 (34), 196 (10), 168 (27), 141 (20), 115 (10), 95 (10). Anal calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.43; H, 7.90; N, 3.38. $[\alpha]^{23}_D$ +116.3 (*c* 1.0, EtOAc) on 99% ee material (HPLC).

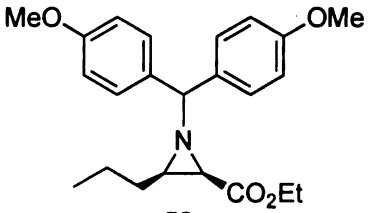


58b

***(2R, 3R)-Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-1,1-dimethylethylaziridine 58b.** The general procedure for the synthesis of **58a** was

followed with the following difference: the catalyst was prepared from 54 mg (*S*)-VAPOL (0.1 mmol), the imine **68b** (1 mmol) was dissolved in 2 mL mixed solvent (1:1 CH_2Cl_2 / CCl_4) and to this was added a solution of the catalyst in 2 mL CCl_4. After purification, the product was obtained as a white solid (mp. 81-83 °C) in 74% isolated yield (293 mg, 0.74 mmol). The crude reaction mixture indicated that a *cis/trans* ratio of >50:1 and <1% **81b** and <5% **82b**. The optical purity was determined to be 87% ee by HPLC analysis (Chiralpak AD column, 98:2 hexane/*i*PrOH at 226nm, flow-rate: 1.0 mL/min). Retention times: R_t = 8.81 min for **58b** and R_t = 10.59 min for *ent*-**58b**. A single crystallization (1:5 CH_2Cl_2/hexanes) gave (*2R*, *3R*)-**58b** in 39% overall isolated yield (154 mg, 0.39 mmol) with 99% optical purity.

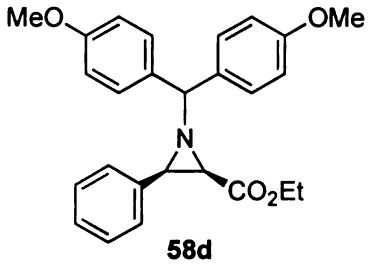
Spectral data for (*2R*, *3R*)-**58b**: R_f = 0.4 (1:5 EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (s, 9H), 1.33 (t, 3H, *J* = 7.1 Hz), 1.78 (d, 1H, *J* = 7.2 Hz), 2.18 (d, 1H, *J* = 7.2 Hz), 3.55 (s, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 4.09-4.31 (m, 2H), 6.83-6.89 (m, 4H), 7.33 (d, 2H, *J* = 8.7 Hz), 7.60 (d, 2H, *J* = 8.7 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 14.15, 27.54, 31.71, 43.46, 55.22, 56.26, 60.65, 78.03, 113.64, 128.26, 129.13, 135.30, 136.25, 158.46, 158.84, 170.01 (one sp^2 carbon and one sp^3 carbon not located); IR (thin film) 2955w, 1745m, 1610m, 1510vs, 1248s, 1174s, 1035m, 819m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 397 M^+ (2), 340 (4), 227 (100), 212 (13), 169 (24), 141 (17), 115 (12), 41 (18). Anal calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.30; H, 7.77; N, 3.68. $[\alpha]^{23}_D$ +142.6 (*c* 1.0, EtOAc) on 99% ee material (HPLC).



58c

***(2R)-Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-propylaziridine 58c.** The general procedure for the synthesis of **58a** was followed with the following difference: the catalyst was prepared from (*S*)-VAPOL with CH_2Cl_2 as solvent. After purification, the product was obtained as a white solid (mp. 98-100 °C) in 11% isolated yield (42 mg, 0.11 mmol). An optical purity of 63% ee was determined by HPLC analysis (Chiralpak AD column, 90:10 hexane/*i*PrOH at 226nm, flow-rate: 1.0 mL/min): retention times; R_t = 5.58 min for **58c** and R_t = 7.69 min for *ent*-**58c**. A single crystallization (1:5 CH_2Cl_2/hexanes) gave (*2R*, *3R*)-**58c** in 8% overall isolated yield (31 mg, 0.08 mmol) with 73% optical purity.

Spectral data for (*2R*, *3R*)-**58c**: R_f = 0.28 (1:5 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.74 (t, 3H, *J* = 7.4 Hz), 1.02-1.16 (m, 2H), 1.23 (t, 3H, *J* = 7.1 Hz), 1.40-1.54 (m, 2H), 1.99 (q, 1H, *J* = 6.6 Hz), 2.23 (d, 1H, *J* = 6.9 Hz), 3.56 (s, 1H), 3.74 (s, 6H), 4.11-4.21 (m, 2H), 6.77-6.82 (m, 4H), 7.26 (d, 2H, *J* = 8.5 Hz), 7.34 (d, 2H, *J* = 8.8 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.65, 14.26, 20.35, 29.91, 43.35, 46.74, 55.16, 60.65, 76.70, 113.61, 113.67, 128.09, 128.81, 134.98, 135.46, 158.47, 158.73, 169.60 (one sp^3 carbon not located); IR (thin film) 2930w, 1741s, 1604s, 1510s, 1248s, 1170s, 1036m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 383 M^+ (0.4), 354 (3), 227 (100), 212 (6), 169 (6), 141 (8), 43 (5). Anal calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65. Found: C, 71.87; H, 7.60; N, 3.49. $[\alpha]^{23}_D$ +70.7 (*c* 1.0, EtOAc) on 73% ee material (HPLC).



58d

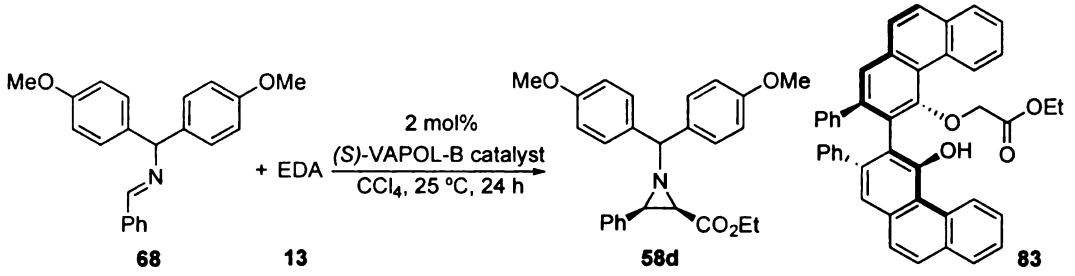
***(2R, 3R)-Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-phenylaziridine 58d.** The general procedure for the synthesis of **58a** was followed. After purification, the

product was afforded as white solid (mp. 89.5-90.5 °C) in 91% isolated yield (379 mg, 0.91 mmol). Analysis of the crude reaction mixture indicated that the *cis/trans* ratio was >33:1 and the presence of <1 % **81d** and <1% **82d**. The optical purity of the purified product was determined to be 96% ee by HPLC analysis (Chiralpak AD column, 90:10 hexane/*i*PrOH at 226nm, flow-rate: 1.0 mL/min), retention times: R_t = 8.14 min for **58d** and R_t = 13.73 min for *ent*-**58d**. A single crystallization (1:4 CH_2Cl_2/hexanes) gave (*2R*, *3R*)-**58d** in an overall isolated yield of 85% (353 mg, 0.85 mmol) and 99% optical purity.

Spectral data for (*2R*, *3R*)-**58d**: R_f = 0.26 (1:5 EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, 3H, *J* = 7.0 Hz), 2.68 (d, 1H, *J* = 6.9 Hz), 3.21 (d, 1H, *J* = 6.8 Hz), 3.69 (s, 3H), 3.76 (s, 3H), 3.89 (s, 1H), 3.94 (q, 2H, *J* = 7.1 Hz), 6.80 (d, 2H, *J* = 8.5 Hz), 6.89 (d, 2H, *J* = 8.5 Hz), 7.21-7.29 (m, 3H), 7.37-7.42 (m, 4H), 7.52 (d, 2H, *J* = 8.7 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.81, 46.30, 47.90, 54.92, 55.00, 60.37, 76.28, 113.69, 127.17, 127.64, 127.67, 128.06, 128.36, 134.83, 135.03, 135.06, 158.54, 158.61, 167.67 (one sp^2 carbon not located); IR (thin film) 2957w, 1746m, 1611m, 1510vs, 1248s, 1174s, 1036m, 818m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 417 M^+ (0.1), 227 (100), 212 (6), 169 (5), 149 (21), 117 (5), 85 (5), 57 (10), 43 (8). Anal calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.42; H, 6.27; N, 3.53. $[\alpha]^{23}_D$ = +43.8 (*c* 1.0, EtOAc) on 99% ee material (HPLC).

The preparation of **58d** was also carried out on a 32-fold increased scale with 0.5 mol% catalyst instead of 10 mol% catalyst. The general procedure for the synthesis of **58a** was followed with the following differences. In a 250 mL flame dried flask was added **68d** (10.6 g, 32 mmol) dissolved in 64 mL CCl_4. To this was added a solution of the *(S)*-VANOL-boron catalyst (0.16 mmol) in 3 mL of CCl_4. After the addition of ethyl diazoacetate (3.65 mL, 35 mmol) the reaction mixture was stirred for 24 hours at room temperature under the protection of argon. The reaction mixture was diluted with 20 mL hexanes and then the solvent was removed under reduced pressure to give the crude

product as a white solid. The purification was effected by crystallization from 1:5 CH_2Cl_2/hexanes and the partially purified product was crystallized again to give **58d** in 68% yield (9.08 g, 21.7 mmol) as a white solid in 98.1% ee. The combined mother liquors from the two crystallizations were loaded onto a silica gel column (80 mm x 600 mm column, 6" SiO_2, 9:1 hexanes / EtOAc as eluent) and elution gave **58d** (3.17 g, 7.6 mmol) as a white solid in 72.2% ee. The overall yield and enantiomeric excess for the reaction was calculated to be 91.8% yield and 91.5% ee.



68 **13** **58d** **83**

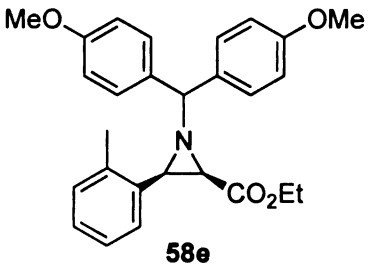
The general procedure described for the preparation of **58a** was followed beginning with (*S*)-VAPOL (216 mg 0.4 mmol) and $B(OPh)_3$ (350 mg, 1.2 mmol). The mixture was dissolved in 8 mL CCl_4 and then heated in an oil bath at 85 °C for 1 hour. A vacuum (0.2 mmHg) was applied to remove the volatiles with the temperature maintained at 85 °C and after the volatiles were removed, residue was heated an additional 30 minutes at 85 °C. Meanwhile, in a separate 100 mL flame-dried round bottom flask filled with argon was added imine **68d** (6.62 g, 20 mmol) and 35 mL CCl_4. The catalyst was cooled to room temperature and then dissolved in 5 mL CCl_4. This solution of catalyst was transferred to the flask that containing **68d** via syringe. The reaction mixture was stirred for 5 minutes to give a light orange solution. To this solution was added EDA **13** (2.3 mL, 22 mmol) and the resulting mixture was stirred for 24 hours at room temperature. The reaction mixture was diluted by addition of 10 mL hexane. Removal of the solvent by rotary evaporation afforded the crude aziridine as an off-white solid, which was exposed to high vacuum (0.5 mmHg) for 24h to remove the excess EDA. Analysis of the ^1H NMR

of the crude aziridine revealed a *cis/trans* ratio of >50:1 and <% **81d** and <1% **82d**. The purification of the aziridine was the same as the large-scale aziridination procedure except that a single crystallization (1:5 CH_2Cl_2/hexanes) was employed to give **58d** (6.73 g) as a white solid with >99% ee. The residue from the mother liquor was purified by silica gel chromatography (80 mm × 600 mm column, 6" SiO_2, 1: 2: 20 EtOAc / CH_2Cl_2 / hexanes as eluent) to afford **58d** (1.32 g) as a white solid with 73% ee. The overall yield and enantiomeric excess of **58d** for the reaction was calculated to be 95% yield and 96% ee. The VAPOL was also recovered during the purification of the mother liquor collection via silica gel chromatography. The optically pure *(S)*-VAPOL (>99% ee) was obtained in 95% recovery (205mg, 0.38 mmol).

The VAPOL ligand can only be effectively recovered if the excess diethyl diazoacetate is removed under high vacuum prior to purification. In a separate experiment where this step was eliminated, the *(S)*-VAPOL was only recovered in 10% yield (24mg, 0.04 mmol) after chromatography on silica gel. In this experiment, a new product was obtained from the chromatography column which was identified as the modified VAPOL ligand **83** as a white solid (mp. 100-102 ºC) in 73% isolated yield (180 mg, 0.29mmol).

Spectral data for *(S)*-**83**: R_f = 0.2 (1:9 EtOAc/hexane), ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.77 (t, 3H, *J* = 7.1Hz), 1.25 (br, s, 1H), 3.68-2.74 (m, 2H), 4.40 (d, d, 2H, *J* = 14.8, 37.6Hz), 6.70 (s, 1H), 6.79-6.85 (m, 4H), 6.93-7.12 (m, 6H), 7.44 (s, 1H), 7.56-7.82 (m, 8H), 7.88-7.94 (m, 2H), 9.55-9.58 (m, 1H), 9.83 (d, 1H, *J* = 8.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.48, 60.91, 68.44, 120.48, 123.01, 123.19, 125.97, 126.35, 126.50, 126.67, 126.91, 126.96, 127.13, 127.48, 127.55, 127.64, 127.76, 128.19, 128.36, 128.66, 128.90, 129.08, 129.19, 129.33, 130.66, 132.79, 133.08, 134.41, 135.05, 139.37, 140.10, 140.62, 142.27, 152.26, 155.04, 167.66 (four sp^2 carbons not located); IR (thin film) 3512vs, 1759s, 1209s, 1136s, 908m, 812m cm^{-1}; mass spectrum, *m/z* (% rel intensity)

624 M^+ (51), 520 (28), 294 (58), 281 (35), 275 (27), 265 (20), 222 (74), 141 (100), 105 (81), 43 (20). $[\alpha]^{23}_D$ +212.3 (*c* 1.0, EtOAc) on 99% ee material (HPLC). (The optical purity was assumed to be unchanged from *S*-VAPOL.)

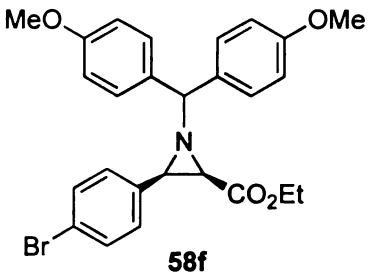


58e

***(2R, 3R)-Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-*o*-tolylaziridine 58e.** The general procedure for the synthesis of **58a** was followed with following differences. Imine **68e** (345 mg, 1mmol) was dissolved in 4 mL CCl_4 before the transfer of catalyst to the imine. After purification, the product was obtained as a white solid (mp. 122.5-124 °C) in 80% isolated yield (344 mg, 0.8 mmol). The optical purity was determined to be 89% ee by HPLC analysis (Chiralpak AD column, 90:10 hexane/*i*PrOH at 226nm, flow-rate: 1.0 mL/min); retention times: R_t = 6.48 min for **58e** and R_t = 9.44 min for *ent*-**58e**. From the crude reaction mixture the cis/trans selectivity for the reaction was >50:1, and <1 % **81e** and <1% **82e** were formed in the reaction. The optical purity of the product could be enhanced by a single crystallization (1:4 CH_2Cl_2/hexanes), which gave (*2R*, *3R*)-**58e** in 75% overall isolated yield (323 mg, 0.75 mmol) from **68e** and with 99% optical purity.

Spectral data for (*2R*, *3R*)-**58e**: R_f = 0.24 (1:5 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, 3H, *J* = 7.1 Hz), 2.27 (s, 3H), 2.67 (d, 1H, *J* = 6.9 Hz), 3.14 (d, 1H, *J* = 6.9 Hz), 3.71 (s, 3H), 3.76 (s, 3H), 3.84 (s, 1H), 3.87 (q, 2H, *J* = 7.1 Hz), 6.79 (d, 2H, *J* = 8.8 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 7.01-7.08 (m, 3H), 7.36 (d, 2H, *J* = 8.8 Hz), 7.47 (d, 3H, *J* = 8.8 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.88, 18.82, 45.72, 46.97, 55.20, 55.26, 60.47, 76.72, 113.88, 113.92, 125.39, 127.15, 128.16, 128.57, 128.73, 129.14, 133.31, 135.01,

135.27, 136.05, 158.67, 158.89, 168.10; IR (thin film) 2957w, 1746m, 1609m, 1510vs, 1248s, 1173s, 1033m, 820m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 431 M^+ (0.1), 229 (11), 227 (100), 212 (8), 169 (6), 130 (11), 115 (5). Anal calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 74.86; H, 6.98; N, 3.28. $[\alpha]^{23}_D$ +53.7 (*c* 1.0, EtOAc) on 99% ee material (HPLC).

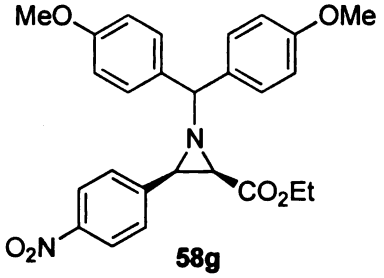


58f

***(2R, 3R)-Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-*p*-bromophenylaziridine 58f.** The general procedure for the synthesis of **58a** was followed with following differences. The catalyst was prepared from (*S*)-VAPOL and imine **68f** (410 mg, 1mmol) was dissolved in 2 mL of a mixed solvent (1:3 CH_2Cl_2/CCl_4) before the catalyst was transferred to the imine solution. After purification, the product was obtained as light yellow solid (mp. 49-50 °C) in 89% isolated yield (384 mg, 0.89 mmol). The optical purity of **58f** was determined to be 97% ee by HPLC analysis (Chiralpak AD column, 90:10 hexane/*i*PrOH at 226nm, flow-rate: 1.0 mL/min); retention times, R_t = 7.64 min for **58f** and R_t = 20.49 min for *ent*-**58f**. Analysis of the crude reaction mixture revealed that the cis/trans ratio of **58f** from the reaction was >50:1 and that <1% yield of **81f** and <1% yield of **82f** were formed in the reaction.

Spectral data for (*2R, 3R*)-**58f**: R_f = 0.24 (1:5 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, 3H, *J* = 7.1 Hz), 2.61 (d, 1H, *J* = 6.9 Hz), 3.06 (d, 1H, *J* = 6.9 Hz), 3.65 (s, 3H), 3.71 (s, 3H), 3.81 (s, 1H), 3.89 (q, 2H, *J* = 7.1 Hz), 6.72 (d, 2H, *J* = 8.8 Hz), 6.80 (d, 2H, *J* = 8.8 Hz), 7.24-7.33 (m, 6H), 7.41 (d, 2H, *J* = 8.8 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ

14.13, 46.64, 47.50, 55.16, 55.23, 60.76, 76.39, 113.98, 121.40, 128.28, 128.54, 129.73, 131.00, 134.43, 134.87, 135.08, 158.85, 158.93, 167.59 (one sp^2 carbon not located); IR (thin film) 1744m, 1611m, 1510vs, 1240s, 1174s, 1036m, 828m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 497 M^+ (^{81}Br, 0.1), 495 M^+ (^{79}Br, 0.1), 227 (100), 212 (11), 197 (^{81}Br, 3), 195 (^{79}Br, 4), 169 (10), 141 (7), 89 (8). Anal calcd for $C_{26}H_{26}BrNO_4$: C, 62.91; H, 5.28; N, 2.82. Found: C, 63.02; H, 5.47; N, 2.80. $[\alpha]^{23}_D$ +14.9 (*c* 1.0, EtOAc) on 97% ee material (HPLC).

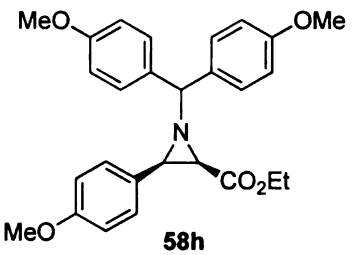


58g

***(2R, 3R)-Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-*p*-nitrophenylaziridine 58g.** The general procedure for the synthesis of **58a** was followed except the following difference. The imine **68g** (376 mg, 1 mmol) was dissolved in 8 mL CCl_4 before the catalyst was added. After purification, the title aziridine was obtained as a yellow powder (mp. 55-56 °C) in 97% isolated yield (448 mg, 0.97 mmol). The optical purity of **58g** was determined to be 97% ee by HPLC analysis (Chiralpak AD column, 90:10 hexane/*i*PrOH at 226nm, flow-rate: 1.0 mL/min), retention times: R_t = 14.53 min for **58g** and R_t = 42.81 min for *ent*-**58g**. Analysis of the crude reaction mixture revealed that the cis/trans selectivity for **58g** was >50:1 and that <2% yield of **81g** and <1% yield of **82g** were formed in the reaction.

Spectral data for (*2R*, *3R*)-**58g**: R_f =0.12 (1:5 EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (t, 3H, *J* = 7.1 Hz), 2.80 (d, 1H, *J* = 6.9 Hz), 3.26 (d, 1H, *J* = 6.9 Hz), 3.76 (s, 3H), 3.83 (s, 3H), 3.94 (s, 1H), 3.98 (q, 2H, *J* = 7.2 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 6.92 (d, 2H, *J* = 8.8 Hz), 7.38 (d, 2H, *J* = 8.5 Hz), 7.50 (d, 2H, *J* = 8.5 Hz), 7.62 (d, 2H, *J* = 8.5

Hz), 8.15 (d, 2H, J = 8.8 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.69, 46.61, 46.75, 54.82, 54.90, 60.59, 75.95, 113.60, 122.72, 127.71, 128.03, 128.46, 134.04, 134.30, 142.34, 146.91, 158.46, 158.57, 166.75 (one sp^2 carbon not located); IR (thin film) 2959w, 1744m, 1609m, 1510vs, 1344s, 1248s, 1174s, 1034m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 462 M^+ (1.2), 389 (3), 253 (4), 227 (100), 212 (11), 169 (8), 141 (7), 115 (5), 89 (4). Anal calcd for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.37; H, 5.77; N, 5.99. $[\alpha]^{23}_D$ -2.2 (*c* 1.0, EtOAc) on 97% ee material (HPLC).

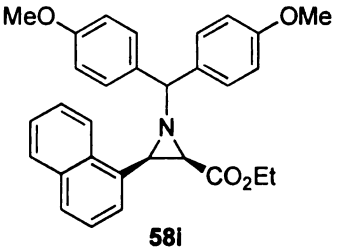


58h

***(2R, 3R)-Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-*p*-methoxyphenylaziridine 58h.** The general procedure for the synthesis of **58a** was followed with one change: the imine **68h** (361 mg, 1 mmol) was dissolved in 10 mL CCl_4 before the catalyst was added. Purification of the product by column chromatography required that the silica gel was pretreated with Et_3N. This was affected by the addition of 20 mL Et_3N to a slurry of 500 mL silica gel in 200 mL CH_2Cl_2. The CH_2Cl_2 was then removed by rotary evaporation and the silica gel was then dried overnight in an oven. After purification, the aziridine **58h** was afforded as semi solid in 80% isolated yield (352 mg, 0.8 mmol). The optical purity of **58h** was determined to be 95% ee by HPLC analysis (Chiralpak AD column, 90:10 hexane/*i*PrOH at 226nm, flow-rate: 1.0 mL/min); retention times, R_t = 9.50 min for **58h** and R_t = 26.45 min for *ent*-**58h**. Analysis of the crude reaction mixture revealed that the cis/trans selectivity for **58h** was >50:1 and that <1% **81h** and <1% **82h** were formed in the reaction. The ^1H NMR of the crude reaction

mixture was extremely clean and the yield of **58h** may have been higher than the 80% isolated yield, which might have resulted from some loss from the silica gel column.

Spectral data for (*2R, 3R*)-**58h**: R_f = 0.17 (1:5 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, 3H, *J* = 7.1 Hz), 2.56 (d, 1H, *J* = 6.9 Hz), 3.10 (d, 1H, *J* = 6.9 Hz), 3.70 (s, 3H), 3.73 (s, 3H), 3.76 (s, 3H), 3.81 (s, 1H), 3.92 (q, 2H, *J* = 7.1 Hz), 6.75 (d, 4H, *J* = 8.8 Hz), 6.83 (d, 2H, *J* = 8.8 Hz), 7.22-7.33 (m, 4H), 7.44 (d, 2H, *J* = 8.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.94, 46.27, 47.68, 55.06, 55.09, 55.13, 60.43, 76.38, 113.15, 113.73, 127.18, 128.12, 128.41, 128.82, 134.92, 135.13, 158.56, 158.64, 158.81, 167.90 (one sp^2 carbon not located); IR (thin film) 2957w, 1744m, 1611m, 1512vs, 1240s, 1173s, 1034m, 820w cm^{-1}; mass spectrum, *m/z* (% rel intensity) 447 M^+ (0.1), 227(100), 220(5), 212(8), 169(6), 148(13), 121(19), 77(6). Anal calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.13; H, 6.71; N, 3.04. $[\alpha]^{23}_D$ +27.1 (*c* 2.0, EtOAc) on 95% ee material (HPLC).



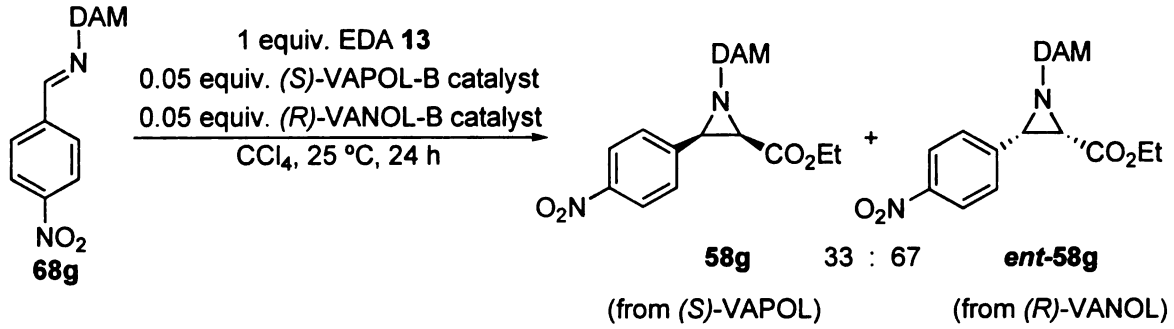
58i

***(2R, 3R)-Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-1-naphthylaziridine 58i.** The general procedure for the synthesis of **58a** was employed with the following differences. The imine **68i** (382 mg, 1 mmol) was dissolved in 6 mL CCl_4 before the catalyst was added. The ethyl diazoacetate was added at 0 °C and during the first 4 hours of the reaction, the temperature was maintained at 0 °C and subsequently the temperature was gradually increased to 25 °C and then the reaction continued for another 20 hours. After purification, the title compound was obtained as a white solid (mp. 153-154 °C) in 91% isolated yield (425 mg, 0.91 mmol). The optical

purity of **58i** was determined to be 97% ee by HPLC analysis (Chiralpak AD column, 90:10 hexane/*i*PrOH at 226nm, flow-rate: 1.0 mL/min); retention times: R_t = 13.99 min for **58i** and R_t = 16.97 min for *ent*-**58i**. A single crystallization (1:3 CH_2Cl_2/hexanes) gave (*2R*, *3R*)-**58i** with > 99% optical purity an overall isolated yield of 82% (383 mg, 0.82 mmol) from **68i**. Analysis of the crude reaction mixture revealed a *cis/trans* selectivity of **58i** as >50:1 and that <2% of **81i** and <1% of **82i** were formed in the reaction.

Spectral data for (*2R*, *3R*)-**58i**: R_f =0.22 (1:5 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.62 (t, 3H, *J* = 7.2 Hz), 2.88 (d, 1H, *J* = 6.8 Hz), 3.66 (d, 1H, *J* = 6.6 Hz), 3.72 (s, 3H), 3.70-3.74 (m, 2H), 3.78 (s, 3H), 4.00 (s, 1H), 6.81 (d, 2H, *J* = 8.5 Hz), 6.89 (d, 2H, *J* = 8.8 Hz), 7.35-7.47 (m, 5H), 7.53 (d, 2H, *J* = 8.8 Hz), 7.64-7.70 (m, 2H), 7.79 (d, 1H, *J* = 7.4 Hz), 8.09 (d, 1H, *J* = 7.7 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.58, 46.04, 46.39, 55.13, 55.21, 60.36, 76.72, 113.84, 113.88, 123.01, 125.36, 125.42, 125.83, 126.57, 127.57, 128.14, 128.50, 128.88, 130.78, 131.44, 133.05, 134.78, 135.15, 158.63, 158.88, 167.90; IR (thin film) 1746m, 1611m, 1510vs, 1240s, 1175s, 1034m, 816m, 775m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 467 M^+ (0.1), 241 (1), 227 (100), 212 (6), 166 (11), 141 (5), 139 (7). Anal calcd for $C_{30}H_{29}NO_4$: C, 77.06; H, 6.25; N, 3.00. Found: C, 76.86; H, 6.30; N, 2.96. $[\alpha]^{23}_D$ +6.3 (*c* 1.0, EtOAc) on 99% ee material (HPLC).

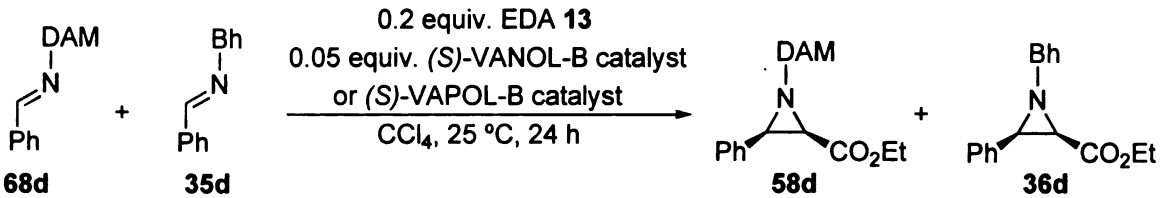
Rate competition in the aziridination catalyzed by VANOL and VAPOL ligands



The general procedure for the synthesis of **58a** was followed with certain changes. The catalysts were prepared from *(S)*-VAPOL (27 mg, 0.05 mmol) and *(R)*-VANOL (22

mg, 0.05 mmol)), $B(OPh)_3$ (106 mg, 0.4 mmol) and H_2O (1.8 μL, 0.1 mmol). The competition experiment was conducted by the addition of **68g** (376 mg, 1 mmol) to a 25 mL flame dried flask filled with argon, then dissolved in 2 mL CCl_4. A solution of the catalyst in 2 mL CCl_4 was then added followed by EDA **13** (114 μL, 1 mmol). The reaction mixture was stirred at 25 °C for 24 hours and then quenched with 5 mL hexane. After purification, the optical purity of **58g** was determined to be 34% ee of *ent*-**58g** by HPLC analysis, which indicated that this reaction produced a 1:2 mixture of **58g** and *ent*-**58g**, thus revealing that the catalyst derived from VANOL is twice as fast as that derived from VAPOL.

Competition study in the aziridinations of benzhydryl imine 35d and dianisylmethyl imine 68d.



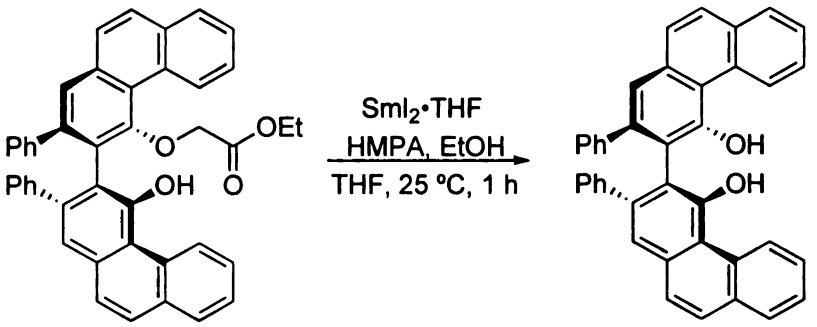
58d : **36d** = 3.8 : 1 (VAPOL)

58d : **36d** = 3.0 : 1 (VANOL)

The general procedure for the synthesis of **58a** was followed with certain changes. The catalyst was prepared from VAPOL (27 mg, 0.05 mmol) or VANOL (22 mg, 0.05 mmol)) and $B(OPh)_3$ (44 mg, 0.15 mmol). The competition experiment was conducted by the addition of **68d** (331 mg, 1 mmol) and **35d** (271 mg, 1mmol) to a 25 mL flame dried flask filled with argon, then dissolved in 3 mL CCl_4. A solution of the catalyst in 2 mL CCl_4 was then added followed by EDA (24 μL, 0.2 mmol). The reaction mixture was stirred at 25 °C for 24 hours. The reaction mixture was diluted with 5 mL hexane, after the removal of solvent, the crude ^1H NMR analysis revealed that the ratio of products **36d** and **58d** was 1 : 3.8 (the ratio was 1 : 3.0 when VANOL was used) upon integration

of the protons on aziridine ring (^{1}H NMR (C_6D_6, 300 MHz) for **36d** : δ 2.48, 2.82, for **58d** : δ 2.54, 2.89.)

Samarium diiodide reduction of the EDA-adduct 83.

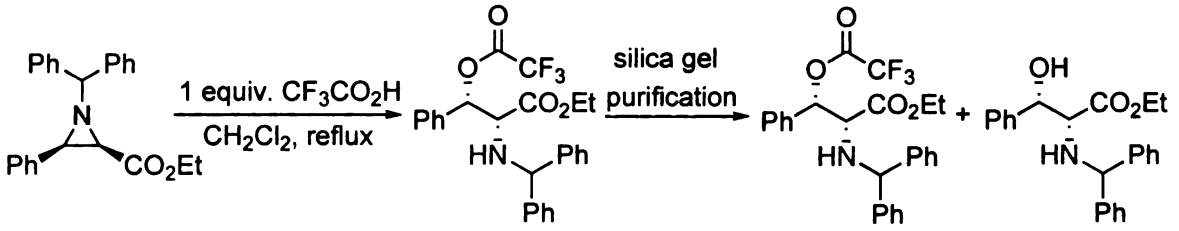


83 **33** *(S)*-VAPOL

A 25 mL round-bottom flask was flame dried and cooled under argon and charged with samarium metal (128 mg, 0.85 mmol) and 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 **83** (61 mg, 0.1 mmol) and 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 **83**. The reaction mixture was stirred at room temperature for 1 h, during which time the reaction went to completion (TLC monitor, 1:9 EtOAc:hexanes). To the reaction flask was then added saturated $NaHCO_3$ solution (20 mL) and the mixture extracted with EtOAc (4 x 20 mL). The organic layers were combined, washed with NaCl (aq. sat.), dried over $MgSO_4$ and the solvent removed by rotary evaporation to afford the crude VAPOL ligand **33**. The ligand was then purified by column chromatography on silica gel

with an eluent mixture of 1:19 EtOAc/hexanes, which afforded the pure *(S)*-VAPOL product **33** 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: R_t = 12.50 min for (*R*)-VAPOL and R_t = 18.54 min for (*S*)-VAPOL.

Attempted deprotection of the benzhydryl aziridine 36d via acidic condition.



36d **84** 100% NMR yield **84** 64% **85** 31%

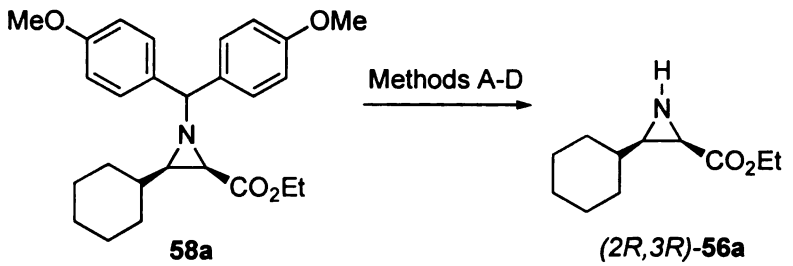
To a 25 mL flame-dried round bottom flask filled with argon was charged with (*2R, 3R*)-aziridine **36d** (357 mg, 1 mmol, 97% ee) and 8 mL CH_2Cl_2 at room temperature, followed by drop-wise addition of trifluoroacetic acid (80 μL, 1 mmol) and the mixture was stirred at room temperature for 5 minutes and then heated to reflux for 48 hours. The reaction mixture was allowed to gradually cool to room temperature and then quenched with saturated aq Na_2CO_3 followed by the addition of 3 mL ether and 1 mL H_2O. The organic layer was collected and the aqueous layer was extracted with ether (5 mL x 3). The combined organic layer was washed with 10 mL NaCl (aq. sat.), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a white solid. The ^1H NMR analysis of the crude material revealed that only compound **84** present. However, purification by silica gel chromatography (18 mm x 230 mm column, 6" SiO_2, 1:1 ether / hexanes as eluent) afforded **84** as white solid (mp. 78-80 °C) in 64% isolated yield (300 mg, 0.64 mmol) along with compound **85** as a colorless semi-solid in

31% isolated yield (115 mg, 0.32 mmol). The relative stereochemistry of **84** was confirmed by the X-ray analysis, which is in appendices.

Spectral data for **84**: R_f = 0.6 (1:1 Et_2O/hexane), ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, 3H, *J* = 7.1 Hz), 2.73 (br, s, 1H), 3.71 (d, 1H, *J* = 5.5 Hz), 4.05-4.38 (m, 2H), 4.90 (s, 1H), 6.33 (d, 1H, *J* = 5.5 Hz), 7.18-7.45 (m, 15H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.79, 61.37, 63.37, 65.43, 79.85, 114.54 (q, *J* = 286 Hz), 127.00, 127.05, 127.29, 128.36, 128.39, 128.54, 141.62, 143.73, 156.40 (q, *J* = 43 Hz), 171.26; IR (thin film) 3327br m, 1790vs, 1734s, 1223m, 1152s, 698m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 471 M^+ (0.03), 398 (2), 268 (28), 182 (71), 167 (100), 165 (100), 152 (93), 102 (11), 91 (10), 77 (17). Anal calcd for $C_{26}H_{24}F_3NO_4$: C, 66.24; H, 5.13; N, 2.97. Found: C, 66.61; H, 5.24; N, 3.02. $[\alpha]^{23}_D$ = +47.2 (*c* 1.0, EtOAc) on 97% ee material (HPLC) (The optical purity was assumed to be unchanged from *(2R,3R)*-**36d**).

Spectral data for **85**: R_f = 0.4 (1:1 Et_2O/hexane), ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, 3H, *J* = 7.1 Hz), 2.65 (br, s, 1H), 3.34 (d, 1H, *J* = 6.6 Hz), 3.87 (br, s, 1H), 3.98 (q, 2H, *J* = 7.1 Hz), 4.69 (s, 1H), 4.73 (d, 1H, *J* = 6.6 Hz), 7.19-7.30 (m, 15H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.90, 60.92, 65.45, 66.05, 74.74, 126.54, 127.24, 127.27, 127.36, 127.41, 127.94, 128.15, 128.53, 128.56, 140.08, 141.82, 143.28, 173.04; IR (thin film) 3478br vs, 1728s, 1452m, 1188s, 1026s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 375 M^+ (0.1), 302 (4), 269 (26), 182 (36), 167 (100), 149 (57), 102 (40), 77 (43). Anal calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.37; H, 6.79; N, 3.59. $[\alpha]^{23}_D$ +47.7 (*c* 1.0, EtOAc) on 97% ee material (HPLC) (The optical purity was assumed to be unchanged from *(2R,3R)*-**36d**).

General procedure for the deprotection of the *N*-DAM aziridines – illustrated in the preparation of *(2R, 3R)-Cis*-2-carboxyethyl-3-cyclohexylaziridine 56a.



58a *(2R,3R)*-**56a**

Method A: To a 25 mL flame-dried round bottom flask filled with argon was added (*2R, 3R*)-**58a** (212 mg, 0.5 mmol, 99% ee) and 5.4 mL of freshly distilled anisole at room temperature. The flask was cooled to 0 °C and triflic acid (200 μL, 2.5 mmol) was added. The ice-bath was removed and the reaction mixture was stirred for 40 minutes. The reaction mixture was quenched by addition of saturated aq Na_2CO_3 until the pH was greater than 9. After addition of 3 mL ether and 1 mL water, the organic layer was separated and the water layer was extracted with ether (5 mL x 3). The combined organic layer was washed with NaCl (aq. sat.) (2 x 10 mL) and dried over $MgSO_4$. The ether was removed by rotary evaporation and most of the anisole was removed by high vacuum for a short period leaving an off-white sticky residue. Exposure to high vacuum for extended periods results in loss of **56a** to sublimation. Purification by silica gel chromatography (18 mm x 230 mm, 1:1 ether / hexanes as eluent) afforded **56a** as a white solid (mp. 58-59 °C) in 96% isolated yield (95 mg, 0.48 mmol). The optical purity of **56a** was determined to be 99% ee by HPLC analysis (Chiralcel OD-H column, 98:2 hexane/*i*PrOH at 228nm, flow-rate: 1.0 mL/min), retention times: R_t = 3.47 min for *(2S, 3S)*-**56a** and R_t = 3.99 min for *(2R, 3R)*-**56a**.

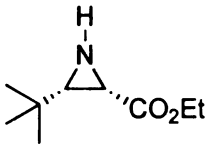
Method B: The procedure for method A was followed except that 400 μL of a solution of 8% (v/v) H_2SO_4 in TFA (1 mL concentrated H_2SO_4 dissolved in 11 mL

trifluoroacetic acid) was used instead of triflic acid. Purification afforded **56a** in 96% isolated yield (95 mg, 0.48 mmol).

Method C: The procedure for method A was followed except that concentrated H_2SO_4 (266 μL, 5 mmol) was used instead of triflic acid. Purification afforded **56a** in 95% isolated yield (94 mg, 0.48 mmol).

Method D: This hydrogenation procedure was adapted from the one that was developed for the deprotection of benzhydryl aziridines.[38] To a 250 mL flame-dried round bottom flask filled with argon was added (*2R, 3R*)-**58a** (212 mg, 0.5 mmol) (99% ee), $Pd(OH)_2$ (85 mg, 0.05 mmol) ($Pd(OH)_2$ on carbon 20%, moisture ca 60%) and 40 mL MeOH. The flask was equipped with a vacuum transfer adapter connected to vacuum and to a balloon filled with hydrogen. The valve to vacuum was opened for a few seconds, then switched to the hydrogen balloon. This process was repeated four times. The suspension was stirred at room temperature under hydrogen for 4 hours and then filtered through a pad of celite, washed with ether (20 mL). The filtrate was concentrated by rotary evaporation and the product was purified to give **56a** in 75% isolated yield (75 mg, 0.38 mmol).

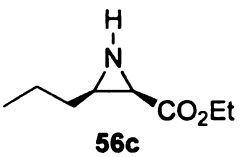
Spectral data for *(2R, 3R)*-**56a**: R_f =0.19 (1:1 Et_2O/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (br, s, 1H), 1.09-1.20 (m, 6H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.43-1.46 (m, 1H), 1.61-1.70 (m, 3H), 1.86-1.92 (m, 2H), 2.60 (d, 1H, *J* = 6.1 Hz), 4.18 (q, 2H, *J* = 7.1 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 14.14, 25.39, 25.40, 26.01, 30.84, 31.61, 34.24, 36.91, 43.98, 61.06, 170.95; IR (thin film) 3165w, 2924vs, 2849s, 1730vs, 1194s, 1180s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 197 M^+ (4), 168 (32), 124 (100), 95 (84). Anal calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.98; H, 9.30; N, 7.08. $[\alpha]^{23}_D$ –62.3 (*c* 1.0, EtOAc) on 99% ee material (HPLC).



(2S,3S)-**56b**

***(2S, 3S)-Cis*-2-carboxyethyl-3-1,1-dimethylethylaziridine 56b.** The same procedure for the synthesis of **56a** was followed. Starting from aziridine (*2S, 3S*)-**58b** (199 mg, 0.5 mmol) (97% ee), after extraction and removal of ether on rotary evaporator, the crude reaction mixture was directly loaded on silica gel column without the removal of anisole due to the high volatility of **56b**. Product **56b** was obtained as colorless liquid in 88% isolated yield (75 mg, 0.43 mmol) via method A and 75% isolated yield (64 mg, 0.38 mmol) via method D in 24 hours. The optical purity of **56b** in each case was determined to be 97% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/*i*PrOH at 228nm, flow-rate: 1.0 mL/min). Retention times: R_t = 8.38 min for (*2S, 3S*)-**56b** and R_t = 9.95 min for (*2R, 3R*)-**56b**).

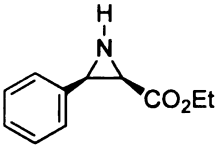
Spectral data for *(2S, 3S)*-**56b:** R_f =0.10 (1:1 Et_2O/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.89 (s, 9H), 1.23 (t, 3H, *J* = 6.9 Hz), 1.48 (br, s, 1H), 2.09 (d, 1H, *J* = 6.1 Hz), 2.61 (d, 1H, *J* = 6.6 Hz), 4.04-4.23 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 14.00, 27.42, 31.46, 35.25, 47.36, 60.98, 170.20; IR (thin film) 3277(br, m), 2957s, 1745vs, 1200s, 1034m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 171 M^+ (0.2), 156 (43), 114 (30), 97 (63), 82 (100), 70 (88), 55 (63). Anal calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.10; H, 9.94; N, 8.32. $[\alpha]^{23}_D$ –23.7 (*c* 1.0, EtOAc) on 97% ee material (HPLC).



56c

***Cis*-2-carboxyethyl-3-*n*-propylaziridine 56c.** The same procedure for the synthesis of **56b** was followed. Starting from *rac*-aziridine **58c** (192 mg, 0.5 mmol), **56c** was obtained as light yellow liquid in 83% isolated yield (65 mg, 0.41 mmol) via method D.

Spectral data for **56c**: R_f =0.13 (1:1 Et_2O/hexane). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, 3H, *J* = 7.1 Hz), 1.16 (t, 3H, *J* = 7.1 Hz), 1.22-1.40 (m, 3H), 1.40-1.50 (m, 2H), 2.04-2.10 (m, 1H), 2.49 (d, 1H, *J* = 6.0 Hz), 4.08 (q, 2H, *J* = 7.1 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.46, 13.99, 20.73, 29.60, 34.27, 38.31, 60.97, 170.73; IR (thin film) 3269(br), 2963m, 1728s, 1196s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 157 M^+ (0.2), 128 (31), 68 (29), 54 (100), 41 (38). Anal calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.17; H, 10.09; N, 9.06.

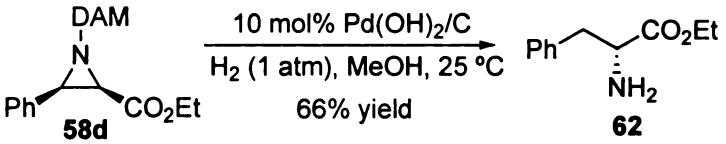


(2R,3R)-**56d**

***(2R, 3R)-Cis*-2-carboxyethyl-3-phenylaziridine 56d.** The same procedure for the synthesis of **56a** was followed. Starting from aziridine (*2R, 3R*)-**58d** (209 mg, 0.5 mmol) (99% ee), (*2R, 3R*)-**56d** was obtained as white solid (mp. 67-68 °C) in 99% isolated yield (94 mg, 0.49 mmol) via method A. The optical purity of (*2R, 3R*)-**56d** was determined to be 99% ee by HPLC analysis (Chiralcel OD-H column, 90:10 hexane/*i*PrOH at 228nm, flow-rate: 0.7 mL/min). Retention times: R_t = 6.16 min (*2S, 3S*)-**56d** and R_t = 9.47 min for (*2R, 3R*)-**56d**.

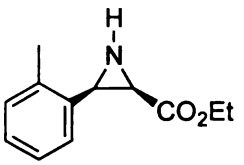
A large-scale experiment was carried out via method B. To a solution of aziridine (*2R, 3R*)-**58d** (18.76 g, 45 mmol) in 400 mL anisole was added 36 mL of a solution of 8% (v/v) H_2SO_4 in TFA. Workup and purification gave **56d** in 95% isolated yield (8.16 g, 42.8 mmol). Applying method D to aziridine **58d** (209 mg, 0.5 mmol) gave the ring-opening product **62** in 66% yield (64 mg, 0.33 mmol) and no **56d** was observed.

Spectral data for (*2R, 3R*)-**56d:** R_f = 0.13 (1:1 Et_2O/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, 3H, *J* = 7.1 Hz), 1.87 (br, s, 1H), 3.00 (d, 1H, *J* = 6.1 Hz), 3.47 (d, 1H, *J* = 6.1 Hz), 3.90-4.00 (m, 2H), 7.24-7.33 (m, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.90, 29.65, 37.14, 61.07, 127.47, 127.62, 128.01, 134.80, 169.02; IR (thin film) 3218w, 1738s, 1186s, 698s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 191 M^+ (0.1), 162 (58), 118 (100), 104 (12), 91 (100), 88 (21), 77 (8). Anal calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.74; H, 6.91; N, 7.25. $[\alpha]^{23}_D$ –12.4 (*c* 1.0, EtOAc) on 99% ee material (HPLC).



ethyl-2-amino-3-phenylpropanoate 62. Starting from the aziridine **58d** (212 mg, 0.5 mmol), applying the method D gave the ring-opening product **62** as a colorless liquid in 66% isolated yield (64 mg, 0.33 mmol).

Spectral data for **62**: R_f = 0.07 (1:3 EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, 3H, *J* = 7.1 Hz), 1.74 (br, s, 2H), 2.83 (dd, 1H, *J* = 5.7, 7.8 Hz), 3.04 (dd, 1H, *J* = 5.5, 7.9 Hz), 3.66-3.70 (m, 1H), 4.12 (q, 2H, *J* = 7.1 Hz), 7.15-7.29 (m, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 14.10, 41.08, 55.77, 60.82, 126.71, 128.45, 129.24, 137.24, 174.94; IR (thin film) 3383w, 3280w, 1734s, 1184s cm^{-1}. (Identical to that from Aldrich)

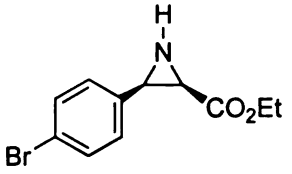


(2R,3R)-**56e**

***(2R, 3R)-Cis*-2-carboxyethyl-3-*o*-tolylaziridine 56e.** The synthesis of **56a** using method A was followed. Starting from aziridine (*2R, 3R*)-**58e** (215 mg, 0.5 mmol) (99% ee), **56e** was obtained as white solid (mp. 84.5-85.5 °C) in 99% isolated yield (102 mg,

0.49 mmol). The optical purity of (*2R, 3R*)-**56e** was determined to be 99% ee by HPLC analysis (Chiralcel OD-H column, 90:10 hexane/*i*PrOH at 228nm, flow-rate: 0.7 mL/min). Retention times: R_t = 5.50 min for (*2S, 3S*)-**56e** and R_t = 6.40 min for (*2R, 3R*)-**56e**.

Spectral data for (*2R, 3R*)-**56e**: R_f =0.11 (1:1 Et_2O/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, 3H, *J* = 7.1 Hz), 1.72 (br, s, 1H), 2.32 (s, 3H), 3.04 (d, 1H, *J* = 6.1 Hz), 3.35 (d, 1H, *J* = 6.1 Hz), 3.92 (q, 2H, *J* = 7.1 Hz), 7.09-7.17 (m, 3H), 7.23-7.24 (m, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.85, 18.83, 29.66, 36.48, 61.05, 125.49, 127.16, 127.60, 129.53, 133.26, 136.86, 169.29; IR (thin film) 3214(br, m), 1734s, 1181s, 877w cm^{-1}; mass spectrum, *m/z* (% rel intensity) 205 M^+ (2), 160 (17), 131 (100), 117 (23), 104 (24), 77 (30). Anal calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.89; H, 7.82; N, 6.72. $[\alpha]^{23}_D$ –96.9 (*c* 1.0, EtOAc) on 99% ee material (HPLC).

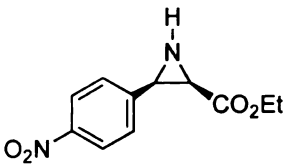


(2R,3R)-**56f**

***(2R, 3R)-Cis*-2-carboxyethyl-3-*p*-bromophenylaziridine 56f.** The synthesis of **56a** using method A was followed. Starting from aziridine (*2R, 3R*)-**58f** (248 mg, 0.5 mmol) (93% ee), **56f** was obtained as white solid (mp. 78.5-79 °C) in 99% isolated yield (134 mg, 0.5 mmol). The optical purity of this material was determined 93% ee by HPLC analysis (Chiralcel OD-H column, 90:10 hexane/*i*PrOH at 228nm, flow-rate: 0.7 mL/min). Retention times: R_t = 7.07 min for (*2S, 3S*)-**56f** and R_t = 8.24 min for (*2R, 3R*)-**56f**. A single crystallization (1:4 CH_2Cl_2/hexanes) gave (*2R, 3R*)-**56f** an overall isolated yield of 91% (122 mg, 0.45 mmol) with an optical purity of 99%.

Spectral data for (*2R, 3R*)-**56f:** R_f =0.12 (1:1 Et_2O/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, 3H, *J* = 7.1 Hz), 1.67 (br, s, 1H), 3.01 (d, 1H, *J* = 6.6 Hz), 3.40 (d, 1H, *J* = 6.4 Hz), 3.93-3.98 (m, 2H), 7.20 (d, 2H, *J* = 8.5 Hz), 7.41 (d, 2H, *J* = 8.5 Hz); ^{13}C ($CDCl_3$,

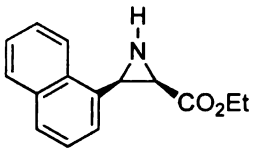
75 MHz) δ 13.88, 37.05, 38.98, 61.06, 121.45, 129.18, 130.98, 133.85, 168.62; IR (thin film) 3222br s, 1734vs, 1194vs, 1170s, 843w cm^{-1}; mass spectrum, *m/z* (% rel intensity) 271 M^+ (^{81}Br, 2), 269 M^+ (^{79}Br, 2), 226 (^{81}Br, 8), 224 (^{79}Br, 11), 197 (^{81}Br, 100), 195 (^{79}Br, 100), 116 (96), 89 (97), 88 (21), 77 (13), 63 (26). Anal calcd for $C_{11}H_{12}BrNO_2$: C, 48.91; H, 4.48; N, 5.19. Found: C, 48.88; H, 4.50; N, 5.13. $[\alpha]^{23}_D$ +11.9 (*c* 1.0, EtOAc) on 99% ee material (HPLC).



(2R,3R)-**56g**

***(2R, 3R)-Cis*-2-carboxyethyl-3-*p*-nitrophenylaziridine 56g.** The synthesis of **56a** using method A was followed. Starting from aziridine (*2R, 3R*)-**58g** (232 mg, 0.5 mmol) (97% ee), compound **56g** was obtained as yellow solid (mp. 89-90.5 °C) in 99% isolated yield (118 mg, 0.5 mmol). The optical purity of (*2R, 3R*)-**56g** was determined to be 97% ee by HPLC analysis (Chiralcel OD-H column, 90:10 hexane/*i*PrOH at 228nm, flow-rate: 0.7 mL/min), retention times: R_t = 11.92 min for (*2S, 3S*)-**56g** and R_t = 13.75 min for (*2R, 3R*)-**56g**.

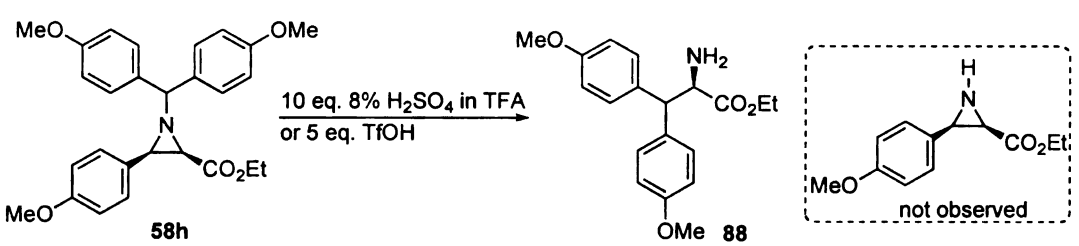
Spectral data for (*2R, 3R*)-**56g**: R_f =0.07 (1:1 Et_2O/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 (t, 3H, *J* = 7.1 Hz), 1.80 (br, s, 1H), 3.13 (d, 1H, *J* = 6.3 Hz), 3.56 (d, 1H, *J* = 6.6 Hz), 3.92-3.97 (m, 2H), 7.54 (d, 2H, *J* = 8.3 Hz), 8.15 (d, 2H, *J* = 8.8 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.80, 29.45, 37.39, 61.09, 122.94, 128.55, 142.58, 147.08, 168.08; IR (thin film) 3316m, 1738vs, 1520s, 1346s, 1200br s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 236 M^+ (3), 191 (18), 163 (21), 161 (100), 145 (23), 116 (100), 104 (29), 89 (100), 77 (23), 63 (27). Anal calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.82; H, 5.06; N, 11.70. $[\alpha]^{23}_D$ –15.6 (*c* 1.0, EtOAc) on 97% ee material (HPLC).



(2R,3R)-**56i**

***(2R, 3R)-Cis*-2-carboxyethyl-3-1-naphthylaziridine 56i.** The synthesis of **56a** using method C was followed. Starting from aziridine (*2R, 3R*)-**58i** (234 mg, 0.5 mmol, 99% ee), compound **56i** was obtained as white solid (mp. 116-117 °C) in 99% isolated yield (119 mg, 0.5 mmol). Method B gave **56i** in 92% isolated yield (111 mg, 0.46 mmol). When the method A was used, **56i** was isolated in 72% yield (87 mg, 0.36 mmol). The optical purity of (*2R, 3R*)-**56i** was determined 99% ee by HPLC analysis (Chiralcel OD-H column, 90:10 hexane/*i*PrOH at 228nm, flow-rate: 0.7 mL/min), retention times: R_t = 7.58 min for (*2S, 3S*)-**56i** and R_t = 9.95 min for (*2R, 3R*)-**56i**.

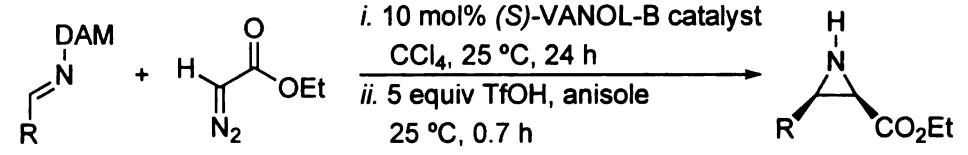
Spectral data for (*2R, 3R*)-**56i:** R_f =0.13 (1:1 Et_2O/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.65 (t, 3H, *J* = 7.1 Hz), 1.90 (br, s, 1H), 3.18 (d, 1H, *J* = 6.3 Hz), 3.70-3.74 (m, 3H), 7.42-7.51 (m, 4H), 7.72 (d, 1H, *J* = 8.0 Hz), 7.78 (d, 1H, *J* = 7.9 Hz), 8.10 (d, 1H, *J* = 8.0 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.34, 36.41, 38.34, 60.64, 123.17, 124.84, 125.17, 125.56, 125.89, 127.86, 128.29, 131.13, 131.49, 132.89, 169.01; IR (thin film) 3185br s, 3045w, 2849s, 1742vs, 1184vs, 783s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 241 M^+ (1), 196 (8), 167 (100), 139 (40), 115 (12), 83 (21), 63 (6). Anal calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.62; H, 6.41; N, 5.73. $[\alpha]^{23}_D$ –278.6 (*c* 1.0, EtOAc) on 99% ee material (HPLC).



***(R)*-ethyl-2-amino-3,3-bis(4-methoxyphenyl)propanoate 88.** Starting from aziridine (*2R, 3R*)-**58h** (224 mg, 0.5 mmol) (95% ee), both methods A and B (see preparation of **56a** above) gave the ring-opening product **88** as a light yellow liquid. Isolation of **88** from the reaction with method A gave (*R*)-**88** in 72% isolated yield (118 mg, 0.36 mmol).

Spectral data for **88**: R_f = 0.07 (1:3 EtOAc/hexane); ^{1}H NMR (C_6D_6, 300 MHz) δ 0.74 (t, 3H, *J* = 7.1 Hz), 1.25 (br, s, 2H), 3.23 (s, 6H), 3.75-3.80 (m, 2H), 4.02 (d, 1H, *J* = 7.4 Hz), 4.22 (d, 1H, *J* = 7.9 Hz), 6.65-6.69 (m, 4H), 7.09 (d, 2H, *J* = 8.3 Hz), 7.21 (d, 2H, *J* = 8.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.80, 54.76, 55.06, 58.96, 60.57, 113.62, 113.98, 129.02, 129.43, 132.81, 133.80, 158.12, 158.31, 174.46 (one sp^3 carbon not located); IR (thin film) 3381(br, w), 2936m, 2835m, 1734vs, 1510vs, 1248s, 1178s, 825m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 329 M^+ (0.03), 256 (9), 227 (100), 212 (18), 169 (21), 141 (17); HRMS (FAB): Calculated for $C_{19}H_{23}NO_4$ ion (M+H) 330.1705. Found: 330.1705. $[\alpha]^{23}_D$ –40.4 (*c* 2.0, EtOAc) on 95% ee material (HPLC). (The optical purity was assumed to be unchanged from *(2R,3R)*-**58h**.)

One pot *N*-H aziridine formation from *N*-DAM imine 68



68a: R = Cy
68d: R = Ph

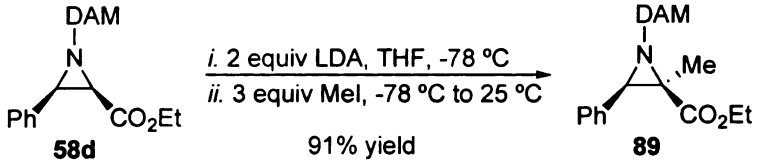
13

56a: R = Cy
56d: R = Ph

The general procedure for the synthesis of **58a** and the deprotection method A were followed with following differences: Upon the completion of the AZ reaction, anisole (11 mL) was added to the reaction mixture by syringe, then the flask was cooled to 0 °C under the protection of argon, and triflic acid (500 μL, 5 mmol) was added. The same workup and purification procedure as the preparation of **56a** from the pure **58a** was

followed to afford **56a** as a white solid in 89% isolated overall yield from **68a**. The same procedure for the imine **68d** afforded the *N*-H aziridine **56d** in 92% isolated overall yield.

Methylation of (*2R, 3R*)-*Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-phenylaziridine 58d.

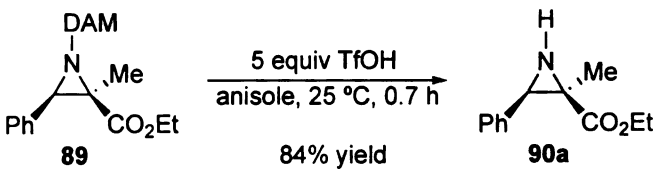


58d 91% yield **89**

The following procedure is the same as that developed for the alkylation of benzhydryl aziridines.[26] To a flame-dried 25 mL round bottom flask filled with argon was added diisopropylamine (57 mg, 0.56 mmol) and 3 mL THF. The solution was cooled to –78 °C and then a 1.6 M solution of *n*BuLi (0.4 mL, 0.56 mmol) in hexanes was added via syringe. The LDA solution was stirred at –78 °C for 5 minutes and then warmed to 0 °C and stirred for 15 minutes, then cooled back to –78°C. A solution of aziridine *(2R,3R)*-**58d** (115 mg, 0.28 mmol, 99% ee) in 3 mL THF was cooled to –78 °C and then transferred via cannula to the flask containing the LDA solution at -78 °C. The resulting light brown solution was stirred at -78 °C for 30 minutes and then MeI (118 mg, 0.8 mmol) was added via syringe. After stirring at -78 °C for 1 hour, the reaction mixture was allowed to warm slowly to room temperature over a period of 2 hours. The reaction was quenched with 10 mL saturated aq. $NaHCO_3$ and the organic layer was separated, the aqueous layer was extracted with ether (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification by silica gel chromatography (18 mm × 230 mm, 6" SiO_2, 1:5 EtOAc / hexanes as eluent) afforded **89** as a colorless liquid in 91% isolated yield (107 mg, 0.25 mmol) which later solidified (mp. 72-73 °C).

Spectral data for **89**: R_f =0.25 (1:5 EtOAc / hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, *J* = 7.1 Hz), 1.57 (s, 3H), 2.98 (s, 1H), 3.68 (s, 3H), 3.77 (s, 3H), 3.80-3.97 (m, 2H), 4.42 (s, 1H), 6.76 (d, 2H, *J* = 8.2 Hz), 6.88 (d, 2H, *J* = 8.5 Hz), 7.14-7.23 (m, 3H), 7.30 (d, 2H, *J* = 7.2 Hz), 7.39 (d, 2H, *J* = 8.5 Hz), 7.62 (d, 2H, *J* = 8.8 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.23, 13.75, 50.23, 52.60, 54.98, 55.04, 60.39, 69.10, 113.66, 126.83, 127.23, 127.54, 127.71, 128.70, 135.95, 136.20, 136.33, 158.28, 158.54, 170.10 (one sp^2 carbon not located); IR (thin film) 1740s, 1610m, 1510vs, 1248s, 1172m, 1149m, 1034m, 819m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 431 M^+ (0.1), 242 (3), 227 (100), 212 (35), 204 (47), 195(11), 184 (14), 168 (38), 152 (17), 130 (76), 115 (33), 107 (55), 89 (40), 79 (27), 43 (12). Anal calcd. for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 74.96; H, 6.84; N, 3.14. $[\alpha]^{23}_D$ +131.6 (*c* 1.0, EtOAc) on 99% ee material (HPLC). (The optical purity was assumed to be the same as the starting material *(2R,3R)*-**58d**.)

Deprotection of (*2R, 3R*)-*Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-2-methyl-3-phenylaziridine 89.

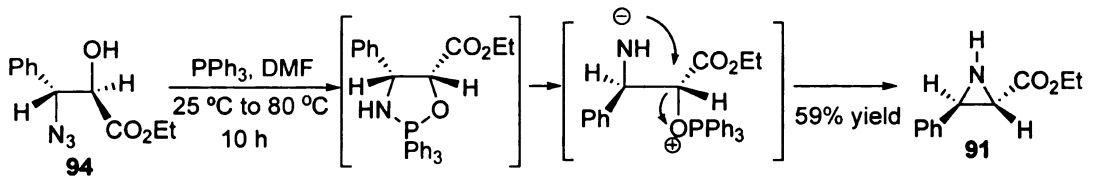


89 84% yield **90a**

The synthesis of **56a** using method A was followed. Starting from aziridine (*2R, 3R*)-**89** (107 mg, 0.25 mmol, 99% ee), (*2R, 3R*)-**90a** was obtained as colorless liquid in 84% isolated yield (43 mg, 0.21 mmol).

Spectral data for (*2R, 3R*)-**90a:** R_f =0.17 (1:3 EtOAc / hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, *J* = 7.1 Hz), 1.60 (s, 3H), 2.03 (br, s, 1H), 3.17 (s, 1H), 3.86 (q, 2H, *J* = 7.1 Hz), 7.20 (s, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.79, 20.01, 42.82, 47.51, 61.22, 127.24, 127.43, 127.98, 135.43, 170.93; IR (thin film) 3303br m, 2978m, 1726s, 1454m, 1192s,

1091m, 1026m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 205 M^+ (16), 176 (3), 160(30), 131 (100), 117 (15), 107 (18), 90 (28), 79 (16), 51 (16), 42 (32). $[\alpha]^{23}_D$ +14.1 (*c* 1.0, EtOAc) on 99% ee material (HPLC). (The optical purity was assumed to be the same as the aziridine **58d**.)

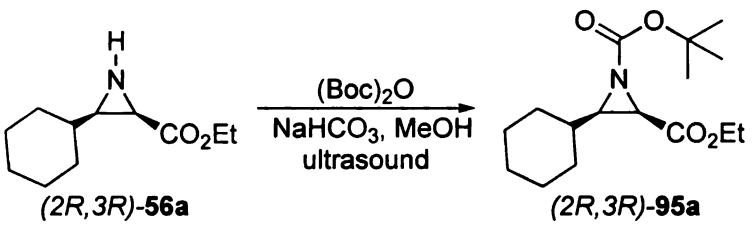


***Trans*-2-carboxyethyl-3-phenylaziridine 91.** Starting from compound **94** (0.45 g, 1.9 mmol), after purification by silica gel chromatography (25 mm × 300 mm, 6" SiO_2, 1:40 EtOAc / hexanes as eluent) afforded **91** as a colorless liquid in 59% isolated yield (215 mg, 1.1 mmol).

Spectral data for **91**:[53] R_f =0.17 (1:3 EtOAc / hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, 3H, *J* = 7.1 Hz), 1.92 (t, 1H, *J* = 8.0 Hz), 2.53 (dd, 1H, *J* = 2.0, 8.0 Hz), 3.21 (dd, 1H, *J* = 2.0, 9.0 Hz), 4.16-4.24 (m, 2H), 7.19-7.30 (m, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 14.44, 39.81, 40.62, 62.04, 126.42, 128.01, 128.71, 138.15, 172.00; IR (thin film) 3287w, 1727s, 1217s cm^{-1}; mass spectrum, m/z (% rel intensity) 191 M^+ (0.03), 162 (22), 118 (60), 91 (100), 88 (15), 65 (10).

7.2 Experimental for chapter three:

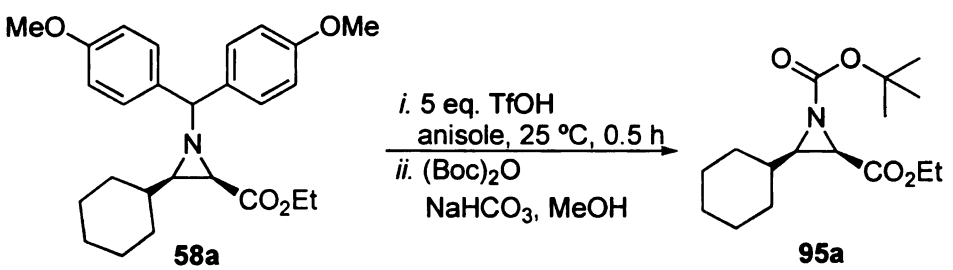
General procedure for the preparation of Boc protected aziridines – illustrated for (*2R, 3R*)-*N*-Boc-*cis*-2-carboxyethyl-3-cyclohexylaziridine 95a



(2R,3R)-**56a** *(2R,3R)*-**95a**

To a 25 mL flame-dried round bottom flask filled with argon was added (*2R, 3R*)-**56a** (30 mg, 0.15 mmol, 99% ee) and 1 mL MeOH followed by $NaHCO_3$ (38 mg, 0.45 mmol). The flask was put in an ultrasonic bath for 5 minutes and then $(Boc)_2O$ (50 mg, 0.23 mmol) was added. The mixture was left in the ultrasonic-bath for 2 hours with a needle in the rubber septum to release the generated CO_2 gas. The reaction mixture was filtered through celite and the solid residue was washed with Et_2O. The cloudy filtrate was filtered again through celite and then concentrated by rotary evaporation to afford the crude product as a colorless liquid. Purification by silica gel chromatography (9 mm × 200 mm column, 1:9 EtOAc/hexanes as eluent) afforded **95a** as a colorless liquid in 99% isolated yield (44 mg, 0.15 mmol).

Preparation of *N*-Boc aziridine 95a from the *N*-DAM aziridine 58a:

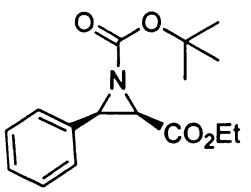


58a **95a**

The same procedure of method A for the synthesis of **56a** was followed using **58a** (105 mg, 0.25 mmol). Upon the completion, the reaction was quenched with $NaHCO_3$ (aq. sat.), after the extraction with ethyl ether and the removal of the solvent, the crude product of **56a** was dissolved in 2 mL MeOH followed by addition of $NaHCO_3$ (76 mg, 0.9

mmol). The flask was then put in an ultrasonic bath for 5 minutes and then $(Boc)_2O$ (100 mg, 0.45 mmol) was added. Other operations were the same as the above mentioned procedure. After purification, product **95a** was obtained as a colorless liquid in 94% isolated overall yield (69 mg, 0.23 mmol),

Spectral data for (*2R, 3R*)-**95a**: R_f = 0.40 (1:9, EtOAc/hexane). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01-1.20 (m, 4H), 1.24 (t, 3H, *J* = 7.1 Hz), 1.38 (s, 9H), 1.44-1.47 (m, 2H), 1.59-1.67 (m, 4H), 1.99-2.00 (m, 1H), 2.30 (dd, 1H, *J* = 6.6, 9.2 Hz), 3.06 (d, 1H, *J* = 6.6 Hz), 4.15-4.24 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 14.15, 25.19, 25.23, 26.01, 27.72, 29.39, 30.92, 36.22, 39.63, 48.35, 61.26, 81.71, 160.67, 167.70; IR (thin film) 2930s, 1753s, 1728s, 1298s, 1155vs, 1037m, 852m, 800m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 225 (M^+ - 72) (0.1), 196 (4), 124 (19), 95.2 (13), 57 (100), 41 (15). Anal calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.43; H, 9.10; N, 4.55. $[\alpha]^{23}_D$ +21.8 (*c* 2.0, EtOAc) on 99% ee material (HPLC). (The optical purity was assumed to be unchanged based on the measured optical purities of **95d** and **95g**.)

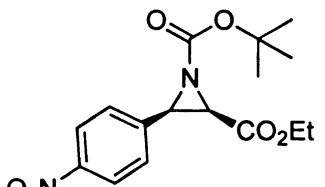


(2R,3R)-**95d**

***(2R, 3R)-N*-Boc-*cis*-2-carboxyethyl-3-benzylaziridine 95d.** The preparation of **95a** was followed from aziridine (*2R, 3R*)-**56d** (29 mg, 0.15 mmol, 99% ee). Product **95d** was obtained as white solid (mp. 62-64 °C) in 98% isolated yield (43 mg, 0.14 mmol). The optical purity of **95d** was determined to be 99% ee by HPLC analysis (Chiralcel OD-H column, 98:2 hexane/*i*PrOH at 228nm, flow-rate: 1.0 mL/min); retention times: R_t = 5.23 min for (*2S, 3S*)-**95d** and R_t = 12.68 min for (*2R, 3R*)-**95d**.

Spectral data for (*2R, 3R*)-**95d**: R_f = 0.20 (1:9, EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, 3H, *J* = 7.1 Hz), 1.52 (s, 9H), 3.45 (d, 1H, *J* = 6.9 Hz), 3.86 (d, 1H, *J* =

6.8 Hz), 3.97-4.04 (m, 2H), 7.30-7.35 (m, 3H), 7.44-7.47 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.82, 27.87, 42.62, 44.40, 61.17, 82.46, 127.54, 128.04, 128.09, 133.08, 160.57, 166.13; IR (thin film) 2924m, 1726vs, 1284s, 1153vs, 1039s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 291 M^+ (0.02), 191 (37), 190 (23), 146 (60), 117 (100), 90 (74), 77 (23), 59 (100), 41 (83). Anal calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 66.03; H, 7.33; N, 4.73. $[\alpha]^{23}_D$ –47.0 (*c* 1.0, EtOAc) on 99% ee material (HPLC).

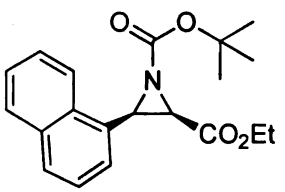


(2R,3R)-**95g**

***(2R, 3R)-N*-Boc-*cis*-2-carboxyethyl-3-p-nitrobenzylaziridine 95g.** The preparation of **95a** was followed from aziridine (*2R, 3R*)-**56g** (108 mg, 0.5 mmol, 97% ee). Product **95g** was obtained as a white solid (mp. 92-93 °C) in 95% isolated yield (160 mg, 0.47 mmol). The optical purity of **95g** was determined to be 97% ee by HPLC analysis (Chiralcel OD-H column, 98:2 hexane/*i*PrOH at 228nm, flow-rate: 1.0 mL/min), retention times: R_t = 11.93 min for (*2S, 3S*)-**95g** and R_t = 19.12 min for (*2R, 3R*)-**95g**. A single crystallization (1:4 CH_2Cl_2/hexanes) gave an overall isolated yield of 83% of (*2R, 3R*)-**95g** (139 mg, 0.42 mmol) with 99% optical purity.

Spectral data for (*2R, 3R*)-**95g**: R_f = 0.19 (1:9, EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, 3H, *J* = 7.1 Hz), 1.47 (s, 9H), 3.46 (d, 1H, *J* = 6.6 Hz), 3.85 (d, 1H, *J* = 6.6 Hz), 3.93-3.98 (m, 2H), 7.58 (d, 2H, *J* = 8.6 Hz), 8.17 (d, 2H, *J* = 8.8 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.91, 27.81, 42.73, 43.41, 61.55, 83.14, 123.27, 128.72, 140.30, 147.75, 159.85, 165.42; IR (thin film) 2982w, 1730vs, 1606w, 1524s, 1348s, 1154s, 850m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 264 (M^+ - 72) (0.1), 236 (32), 219 (23), 191 (33), 162 (89), 116 (57), 89 (100). Anal calcd for $C_{16}H_{20}N_2O_6$: C, 57.14; H, 5.99; N, 8.33.

Found: C, 57.47; H, 6.06; N, 8.06. $[\alpha]^{23}_D$ –74.5 (*c* 1.0, EtOAc) on material of 99% ee (HPLC).

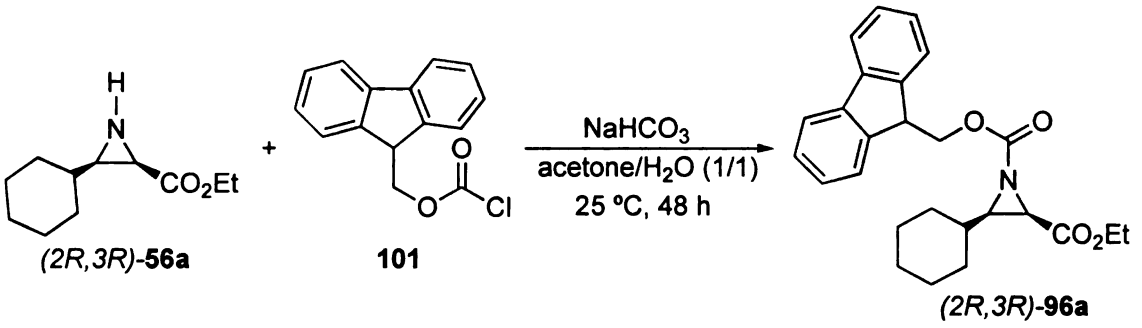


(2R,3R)-**95i**

***(2R, 3R)-N*-Boc-*cis*-2-carboxyethyl-3-1-naphthylaziridine 95i.** The preparation of **95a** was followed from aziridine (*2R, 3R*)-**56i** (36 mg, 0.15 mmol, 99% ee). Product **95i** was obtained as white solid (mp. 104-105 °C) in 98% isolated yield (50 mg, 0.14 mmol). The preparation of **95i** from *N*-DAM aziridine **58i** (116 mg, 0.25 mmol) following the same procedure described for the preparation of **95a** from **58a**, product **95i** was obtained in 90% overall yield (76 mg, 0.22 mmol).

Spectral data for (*2R, 3R*)-**95i:** R_f = 0.28 (1:5, EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.58 (t, 3H, *J* = 7.1 Hz), 1.50 (s, 9H), 3.66 (d, 1H, *J* = 6.6 Hz), 3.65-3.79 (m, 2H), 4.24 (d, 1H, *J* = 6.8 Hz), 7.42-7.51 (m, 3H), 7.73-7.84 (m, 3H), 8.07 (d, 1H, *J* = 8.0 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.45, 27.91, 42.13, 43.27, 60.99, 82.60, 122.86, 125.26, 125.77, 126.27, 126.55, 128.47, 128.61, 128.96, 131.16, 133.13, 160.74, 166.20; IR (thin film) 2980w, 1753w, 1727vs, 1298s, 1154s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 284 (M^+ - *t*-Bu) (0.2), 240 (10), 167 (94), 139 (28), 83 (32), 57 (100), 41 (33). Anal calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.15; H, 6.81; N, 4.02. $[\alpha]^{23}_D$ –189.4 (*c* 1.0, EtOAc) on material of 99% ee (HPLC). (The optical purity was assumed to be unchanged based on the measured optical purity of **95d** and **95g**.)

General procedure for Fmoc protected aziridines – illustrated for *(2R,3R)-N*-9-fluorenylmethyl-carbamate-*cis*-2-carboxyethyl-3-cyclohexylaziridine 96a.

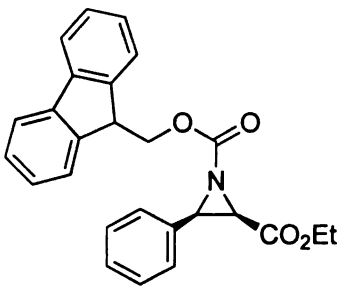


(2R,3R)-**56a** **101** *(2R,3R)*-**96a**

To a 250 mL round bottom flask was added aziridine **56a** (591 mg, 3 mmol, 89% ee), $NaHCO_3$ (510 mg, 6 mmol), 100 mL of a 3 : 1 mixture of acetone and H_2O. The mixture was stirred at 25 °C for 5 minutes and then 9-fluorenylmethylchloroformate **101** (777 mg, 3 mmol) was added. The reaction mixture was stirred at 25 °C for 20 h. The acetone was removed by rotary evaporation and the aqueous residue was extracted with EtOAc (20 mL × 3). The combined organic layer was washed with NaCl (aq. sat.), dried over $MgSO_4$ and concentrated on rotary evaporator to give a light yellow liquid. Purification by silica gel chromatography (15 mm × 250 mm, 1:5 EtOAc/ hexanes as eluent) afforded **96a** as white solid (mp. 129-130 °C) in 92% isolated yield (1.15 g, 2.76 mmol),

Spectral data for (*2R, 3R*)-**96a**: R_f =0.22 (1:5 EtOAc / hexane). ^1H NMR ($CDCl_3$, 300 MHz) δ 0.93-1.01 (m, 2H), 1.10-1.22 (m, 4H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.32-1.45 (m, 1H), 1.60-1.70 (m, 3H), 1.83-1.87 (m, 1H), 2.10 (dd, 1H, *J* = 6.9, 9.7 Hz), 3.02 (d, 1H, *J* = 6.9 Hz), 4.15-4.25 (m, 3H), 4.40-4.54 (m, 2H), 7.25-7.31 (m, 2H), 7.35-7.39 (m, 2H), 7.55 (dd, 2H, *J* = 5.2, 6.8 Hz), 7.72 (d, 2H, *J* = 7.6 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 14.06, 25.08, 25.13, 25.90, 29.24, 30.76, 35.95, 39.59, 46.84, 48.36, 61.26, 67.85, 119.77, 119.80, 124.75, 124.82, 126.90, 126.98, 127.63, 141.21, 141.34, 143.20, 143.38, 161.63, 167.20 (one sp^2 carbon not located); IR (thin film) 1741s, 1714s, 1591m, 1506s, 1251s, 1161m, 1032 cm^{-1}; mass spectrum, *m/z* (% rel intensity) 196 (1.1), 178 (100), 165 (9), 152 (3), 95 (11), 67 (11), 57 (13), 41 (15). Anal calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34.

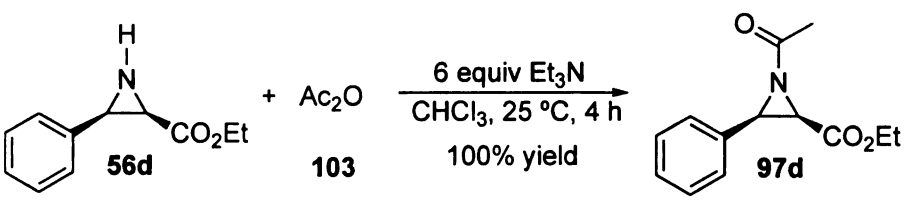
Found: C, 74.37; H, 7.34; N, 3.27. $[\alpha]^{23}_D$ +26.2 (c 1.0, EtOAc) on 89% ee material (HPLC). (The optical purity was assumed to be unchanged from **56a**.)



(2R,3R)-**96d**

***(2R, 3R)-N*-9-fluorenylmethyl-carbamate-*cis*-2-carboxyethyl-3-phenylaziridine 96d.** The preparation of **96a** was followed from **56d** (573 mg, 3 mmol, 98% ee). Purification by silica gel chromatography (15 mm × 250 mm, 1:5 EtOAc/ hexanes as eluent) afforded **96d** as white solid (mp. 96-98 °C) in 94% isolated yield (1.16 g, 2.82 mmol).

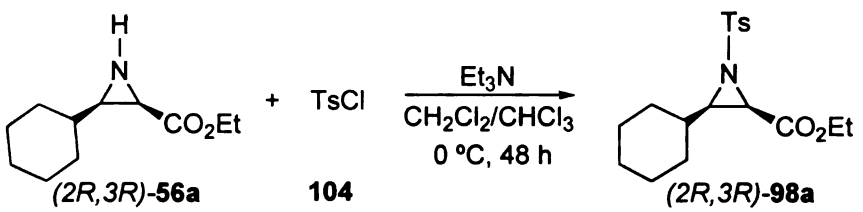
Spectral data for (*2R, 3R*)-**96d**: R_f =0.5 (1:3 EtOAc / hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, 3H, *J* = 7.1 Hz), 3.40 (d, 1H, *J* = 6.6 Hz), 3.77 (d, 1H, *J* = 6.8 Hz), 3.92-4.04 (m, 2H), 4.26 (t, 1H, *J* = 7.1 Hz), 4.44-4.52 (m, 2H), 7.23-7.43 (m, 9H), 7.58 (t, 2H, *J* = 7.1 Hz), 7.74 (d, 2H, *J* = 7.4 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.84, 42.65, 44.39, 46.78, 61.30, 68.74, 120.02, 125.12, 125.15, 127.12, 127.46, 127.88, 128.14, 128.32, 141.30, 143.29, 161.47, 165.66; IR (thin film) 1734vs, 1450m, 1273s, 1175s, 1037m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 413 M^+ (0.05), 190 (6), 178 (100), 165 (11), 117 (41), 89 (19), 76 (8), 44 (6). Anal calcd for $C_{26}H_{23}NO_4$: C, 75.53; H, 5.61; N, 3.39. Found: C, 75.48; H, 5.62; N, 3.48. $[\alpha]^{23}_D$ –31.7 (*c* 1.0, EtOAc) on 98% ee material (HPLC). (The optical purity was assumed to be unchanged from **56d**.)



Preparation of Ethyl-3-phenyl-1-acetylaziridine-2-carboxylate 97d. To a 25 mL flame-dried round bottom flask filled with argon was added (*2R, 3R*)-**56d** (38 mg, 0.2 mmol), 1 mL $CHCl_3$ and Et_3N (90 μL, 0.65 mmol) at room temperature. The mixture was stirred at room temperature for 4 h, and the solvent was directly removed under reduced pressure to give the crude product of **97d** as a white solid. Purification by silica gel chromatography (9 mm × 250 mm, 1:5 EtOAc/ hexanes as eluent) obtained **97d** as white solid in 100% yield (106 mg, 0.2 mmol).

Spectral data for (*2R, 3R*)-**98a**: R_f = 0.35 (1:5, EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, *J* = 7.1 Hz), 2.20 (s, 3H), 3.47 (d, 1H, *J* = 6.6 Hz), 3.81 (d, 1H, *J* = 6.6 Hz), 3.85-3.97 (m, 2H), 7.24-7.31 (m, 3H), 7.35-7.39 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.68, 23.06, 42.05, 43.46, 61.08, 127.32, 128.04, 128.24, 132.50, 165.60, 181.13; IR (thin film) 1747s, 1713s cm^{-1}; mass spectrum, m/z (% rel intensity) 233 M^+ (0.09), 191 (14), 146 (11), 117 (100), 91 (18), 79 (10), 55 (12), 43 (44). Anal calcd for $C_{18}H_{25}NO_4S$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.87; H, 6.85; N, 5.94.

General procedure for the preparation of Tosyl protected aziridines – illustrated for (*2R, 3R*)-ethyl-3-cyclohexyl-1-tosylaziridine-2-carboxylate 98a

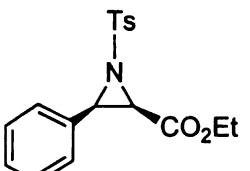


(*2R,3R*)-**56a** **104** (*2R,3R*)-**98a**

To a 25 mL flame-dried round bottom flask filled with argon was added (*2R, 3R*)-**56a** (49 mg, 0.25 mmol, 89% ee), 2 mL $CH_2Cl_2/CHCl_3$ (1:1) and Et_3N (100 μL, 0.75 mmol) at 0 °C. The mixture was stirred for 5 minutes, followed by the addition of TsCl (70 mg, 0.40 mmol), the mixture was then stirred at 0 °C for 48 h. The reaction was quenched by the addition of 4 mL NH_4Cl (aq. sat.) and 1 mL H_2O. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with the following reagents in the

indicated sequence: 1 mL H_2O, 2 mL citric acid (aq. sat.), 1 mL H_2O, 2 mL $NaHCO_3$ (aq. sat.), and 5 mL NaCl (aq. sat.). The collected organic layer was dried over $MgSO_4$ and concentrated by rotary evaporation to afford the crude product as colorless oil. Purification by silica gel chromatography (9 mm × 250 mm, 1:6 EtOAc/ hexanes as eluent) afforded **98a** as white solid (mp. 94-96 °C) in 100% isolated yield (86 mg, 0.25 mmol).

Spectral data for (*2R, 3R*)-**98a**: R_f = 0.36 (1:5, EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88-1.14 (m, 5H), 1.19 (t, 3H, *J* = 7.1 Hz), 1.21-1.34 (m, 1H), 1.43-1.61 (m, 5H), 2.38 (s, 3H), 2.65 (dd, 1H, *J* = 7.7, 9.6 Hz), 3.34 (d, 1H, *J* = 7.5 Hz), 4.14 (q, 2H, *J* = 7.1 Hz) , 7.28 (d, 2H, *J* = 8.5 Hz), 7.79 (d, 2H, *J* = 8.3 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.97, 21.54, 24.97, 25.09, 25.73, 29.33, 30.78, 35.28, 40.85, 49.25, 61.56, 128.14, 129.57, 133.99, 144.85, 165.77; IR (thin film) 2930vs, 1753s, 1333s, 1198s, 1163s, 1092m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 351 M^+ (0.02), 278 (4), 196 (81), 155 (9), 122 (31), 102 (51), 95 (100), 91 (63), 86 (19), 67 (33), 55 (29). Anal calcd for $C_{18}H_{25}NO_4S$: C, 61.51; H, 7.17; N, 3.99. Found: C, 61.28; H, 7.19; N, 3.76. $[\alpha]^{23}_D$ +16.2 (*c* 1.0, EtOAc) on 89% ee material (HPLC). (The optical purity was assumed to be unchanged from **56a**.)

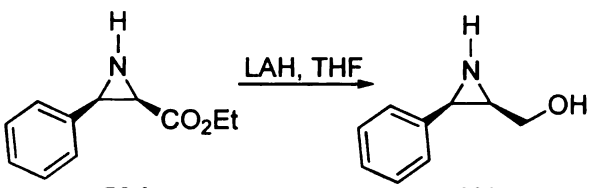


(2R,3R)-**98d**

***(2R, 3R)*-ethyl-3-phenyl-1-tosylaziridine-2-carboxylate 98d.** The general procedure for the preparation of **98a** was followed from aziridine (*2R, 3R*)-**56d** (45 mg, 0.25 mmol, 98% ee). Product **98d** was obtained as white solid (mp. 78-80 °C) in 93% isolated yield (80 mg, 0.23 mmol).

Spectral data for (*2R, 3R*)-**98d**: R_f = 0.25 (1:6, EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, 3H, *J* = 7.1 Hz), 2.41 (s, 3H), 3.66 (d, 1H, *J* = 7.7 Hz), 3.89-3.94 (m, 2H),

4.09 (d, 1H, J = 7.7 Hz), 7.21-7.28 (m, 5H), 7.32(d, 2H, J = 8.5 Hz), 7.90 (d, 2H, J = 8.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.67, 21.61, 43.31, 45.13, 61.45, 127.42, 128.04, 128.10, 128.44, 129.82, 131.09, 133.96, 145.12, 164.33; IR (thin film) 2984w, 1753s, 1333s, 1163vs, 1092m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 345 M^+ (0.02), 190 (95), 162 (15), 116 (100), 91 (65), 65 (20). Anal calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.39; H, 5.79; N, 4.02. $[\alpha]^{23}_D$ –21.8 (*c* 1.0, EtOAc) on 98% ee material (HPLC). (The optical purity was assumed to be unchanged from **56d**.)

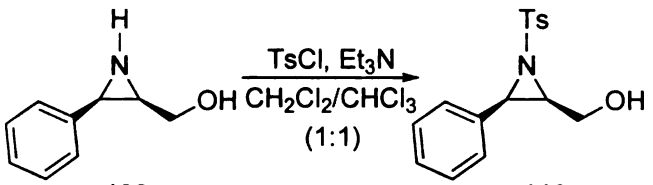


56d **109**

***N*-H-*cis*-2-hydroxymethyl-3-phenylaziridine 109.** To a 25 mL flame-dried round bottom flask filled with argon was added **56d** (191 mg, 1 mmol) and 5 mL THF, followed by a slow addition of LAH solution (2 mL, 2 mmol) (1 M in THF) at -20 °C in 5 minutes. The reaction mixture was stirred at -20 °C for 20h, upon completion, the reaction was quenched at that temperature by carefully addition of 100 μL H_2O, then 140 μL 1.5 M NaOH solution, followed by 200 μL H_2O. The white solid was removed by filtration, the filtrate was washed by ether, dried over $MgSO_4$ and concentrated by rotary evaporation to afford crude product as white solid. Purification by silica gel chromatography (9 mm × 250 mm, 6" SiO_2, 3:1 EtOAc/ hexanes as eluent) afforded **109** as white solid (mp. 87-89 °C) in 90% isolated yield (133 mg, 0.9 mmol).

Spectral data for **109**:[133] R_f = 0.07 (1:1, EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.54 (br, s, 3H), 3.10-3.16 (m, 1H), 3.32-3.41 (m, 2H), 7.17-7.31 (m, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 36.63, 37.81, 61.11, 126.84, 127.36, 127.98, 136.52; IR (thin film) 3281br,vs,

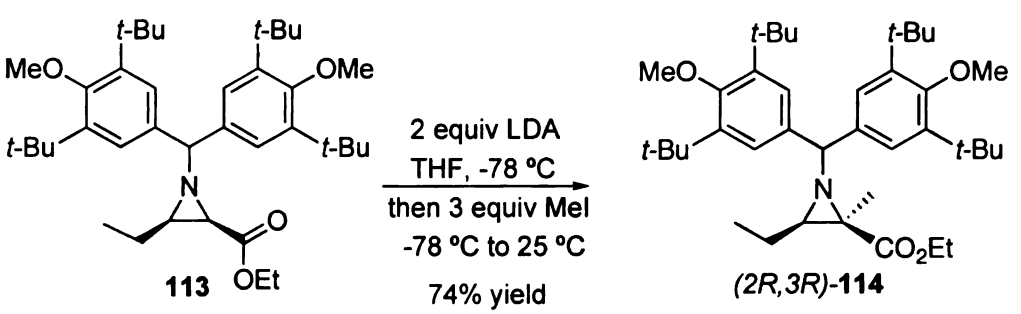
1497m, 1449m, 1039s, 1028s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 149 M^+ (1), 148 (8), 130 (57), 104 (100), 91 (40), 77 (28), 65(22), 51 (27), 39 (19).



109 **110**

***(2R, 3R)-Cis-N*-tosyl-2-hydroxymethyl-3-phenylaziridine 110.** The same procedure of the preparation of **98a** was followed except the following difference: Only 1 equiv. TsCl and 2 equiv. Et_3N was used to avoid the second tosyl group on the oxygen of hydroxyl group. Purification by silica gel chromatography (9 mm × 250 mm, 6" SiO_2, 1:3 EtOAc/ hexanes as eluent) afforded **110** as white solid (mp. 81-82 °C) in 86% isolated yield (63 mg, 0.42 mmol).

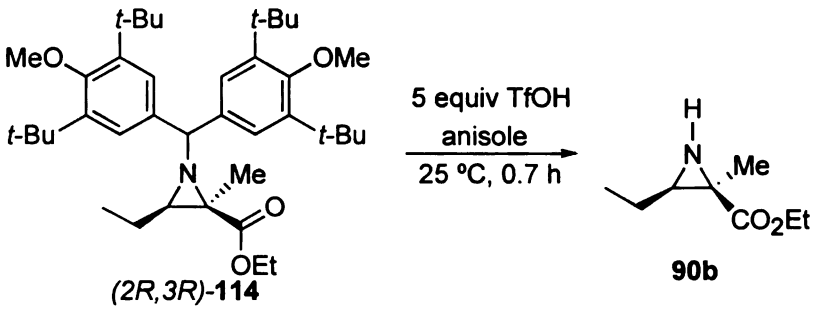
Spectral data for *(2R,3R)*-**110**:[62] R_f = 0.25 (1:3, EtOAc/hexane); ^{1}H-NMR($CDCl_3$, 300 MHz) δ 1.55 (br, s, 1H), 2.42 (s, 3H), 3.24-3.37 (m, 2H), 3.42-3.48 (m, 1H), 4.00 (d, 1H, *J* = 6.9Hz), 7.17-7.29 (m, 5H), 7.32 (d, 2H, *J* = 8.0Hz), 7.87 (d, 2H, *J* = 8.2Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 21.65, 45.28, 45.84, 59.40, 127.19, 128.04, 128.12, 128.45, 129.82, 132.09, 134.40, 144.87; IR (thin film) 3520br, vs, 1325m, 1163s, 675m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 302 M^+-1 (0.1), 148 (50), 118 (40), 91 (100), 65(14). Anal. calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.33; H, 6.03; N, 4.39. Specific rotation: $[\alpha]^{23}_D$ –132.7 (*c* 1.0 in CH_2Cl_2) (on 95% ee material, assumed not changed from **109**).



113 *(2R,3R)*-**114**

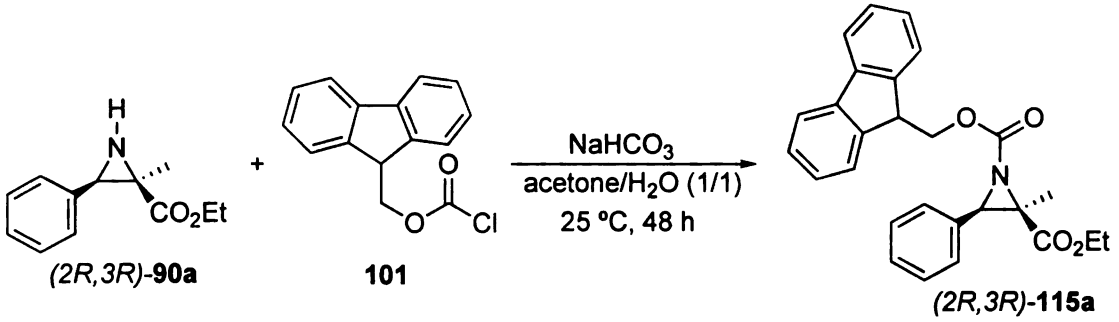
***(2R,3R)-Cis*-1-(*N*-1-bis(4-methoxy-3,5-di-*tert*-butylphenyl)methyl)-2-carboxyethyl-2-methyl-3-ethylaziridine 114.** The similar procedure as the preparation of compound **89** was followed (chapter two) from aziridine **113i** (3.53 g, 5.9 mmol, 93% ee). Product **114** was obtained as a colorless semi-solid in 74% isolated yield (2.68 g, 4.4 mmol).

Spectral data for *(2R,3R)*-**114**: R_f =0.7 (1:9 EtOAc / hexane); ^{1}H-NMR($CDCl_3$, 300 MHz) δ 0.65 (t, 3H, *J* = 7.4 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.40 (s, 18H), 1.41 (s, 18H), 1.45-1.62 (m, 5H), 1.78 (t, 1H, *J* = 6.6Hz), 3.64 (s, 6H), 4.14 (s, 1H), 4.16-4.25 (m, 2H), 7.24 (s, 2H), 7.40 (s, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 11.15, 13.41, 14.23, 22.38, 32.02, 32.11, 35.58, 35.63, 45.47, 53.75, 60.49, 63.94, 70.38, 125.30, 126.24, 137.62, 137.91, 142.61, 142.66, 157.83, 158.32, 171.96 (one sp^3 carbon not located); IR (thin film) 2963vs, 1743m, 1721m, 1414s, 1221s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 608 M^+ (0.2), 451 (100), 156 (27), 128 (13), 82 (13), 68 (13), 57 (98), 41 (29). Anal calcd for $C_{39}H_{61}NO_4$: C, 77.05; H, 10.11; N, 2.30. Found: C, 77.35; H, 10.38; N, 2.20. $[\alpha]^{23}_D$ +66.2 (*c* 1.0, CH_2Cl_2) on 93% ee material (HPLC). (The optical purity was assumed to be unchanged from **113i**.)



***Cis*-*N*-H-2-carboxyethyl-2-methyl-3-ethylaziridine 90b.** The Method A for the preparation of **56a** was used from aziridine **114** except that the reaction requires 4 h for a complete conversion. After the chromatography purification, the product **90b** was obtained as a colorless liquid in a mixed form with small amount of pentane (the product is too volatile).

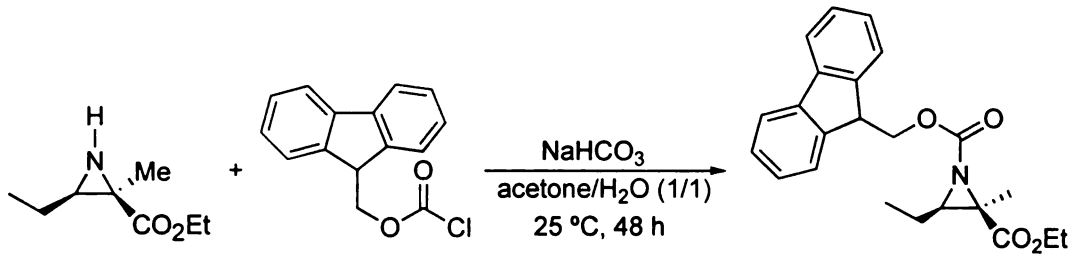
Spectral data for **90b**: R_f =0.3 (1:1 Et_2O / hexane); ^{1}H-NMR($CDCl_3$, 300 MHz) δ 0.90 (t, 3H, *J* = 7.4 Hz), 1.21 (t, 3H, *J* = 7.1 Hz), 1.36 (s, 3H), 1.38-1.52 (m, 3H), 1.84 (t, 1H, *J* = 6.7Hz), 4.10-4.17 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 11.89, 14.14, 20.15, 21.77, 40.08, 47.68, 61.34, 172.51.



(2R,3R)-**90a** **101** *(2R,3R)*-**115a**

***(2R, 3R)* - *N*-9-fluorenylmethyl-carbamate-*cis*-2-carboxyethyl-2-methyl-3-phenylaziridine 115a.** The general procedure for the preparation of **96a** was followed from **90a** (102 mg, 0.5 mmol, 98% ee). Purification by silica gel chromatography (15 mm × 250 mm, 1:5 EtOAc/ hexanes as eluent) obtained **115a** as a white solid (mp. 82-83 °C) *in* 100% isolated yield (215 mg, 0.5 mmol).

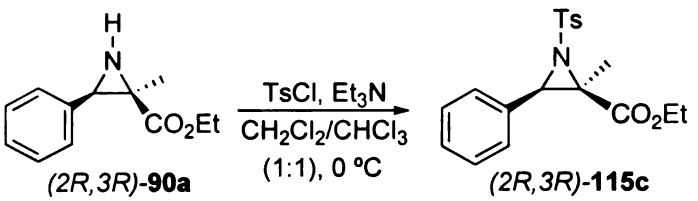
Spectral data for (*2R, 3R*)-**115a**: R_f =0.29 (1:5 EtOAc / hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 3H, *J* = 7.1 Hz), 1.54 (s, 3H), 3.58 (s, 1H), 3.91 (q, 2H, *J* = 7.1 Hz), 4.26 (t, 1H, *J* = 6.6 Hz), 4.50-4.64 (m, 2H), 7.26-7.42 (m, 9H), 7.60-7.66 (m, 2H), 7.74 (d, 2H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.52, 17.27, 46.80, 49.78, 49.85, 61.01, 67.90, 119.80, 124.89, 125.04, 126.94, 127.06, 127.65, 127.88, 133.29, 141.16, 141.20, 143.17, 143.36, 159.72, 167.34 (4 sp^2 carbons not located); IR (thin film) 1726vs, 1450m, 1267s, 1176m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 427 M^+ (0.5), 204 (42), 178 (100), 165 (14), 152 (7), 131 (34), 107 (20), 89 (19), 79 (15). Anal calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: C, 75.84; H, 6.30; N, 3.15. $[\alpha]^{23}_D$ –4.6 (c 1.0, EtOAc) on 98% ee material (HPLC). (The optical purity was assumed to be unchanged from **58d**.)



(2R,3R)-**90b** **101** *(2R,3R)*-**115b**

***(2 R , 3 R) - N*-9-fluorenylmethyl-carbamate-*cis*-2-carboxyethyl-2-methyl-3-ethylaziridine 115b.** The general procedure for the preparation of **96a** was followed from **90b** (mixed form with pentane). Purification by silica gel chromatography (9 mm × 250 mm, 1:5 EtOAc/ hexanes as eluent) obtained **115b** as colorless liquid in 84% overall yield from **114** (160 mg, 0.4 mmol).

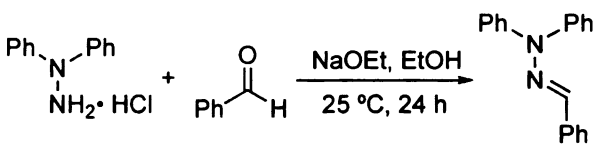
Spectral data for (*2R, 3R*)-**115b**: R_f =0.27 (1:5 EtOAc / hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3H, *J* = 7.4 Hz), 1.26 (t, 3H, *J* = 7.1 Hz), 1.32 (s, 3H), 1.43-1.54 (m, 2H), 2.22 (t, 1H, *J* = 7.1 Hz), 4.17-4.19 (m, 1H), 4.20 (q, 2H, *J* = 7.1 Hz), 4.40-4.46 (m, 1H), 4.55-4.60 (m, 1H), 7.23-7.39 (m, 4H), 7.53-7.61 (m, 2H), 7.72 (d, 2H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.97, 14.11, 17.54, 21.44, 46.71, 46.99, 50.29, 61.43, 67.55, 119.82, 124.84, 124.98, 126.97, 127.01, 127.65, 141.29, 143.45, 143.51, 159.99, 168.80 (3 sp^2 carbons not located); IR (thin film) 1725vs, 1451m, 1238s, 1175m cm^{-1}; mass spectrum, m/z (% rel intensity) 379 M^+ (0.21), 180 (19), 178 (100), 165 (47), 156 (16), 152 (13), 128 (20), 89 (15), 82 (15), 68 (19), 59 (23), 42 (29). $[\alpha]^{23}_D$ +52.0 (c 1.0, CH_2Cl_2) on 93% ee material (HPLC). (The optical purity was assumed to be unchanged from **114**.)



(2R,3R)-**90a** *(2R,3R)*-**115c**

***(2R, 3R)* Ethyl-1-tosyl-2-methyl-3-phenylaziridinyl-2-carboxylate 115c.** The general procedure for the preparation of **98a** was followed from **90a** (197 mg, 0.96 mmol, 98% ee). The reaction was carried out at 0 °C for 48 h, purification by silica gel chromatography (9 mm × 250 mm, 1:5 EtOAc/ hexanes as eluent) obtained **115c** as white solid (mp. 55-56 °C) in 84% yield (289 mg, 0.8 mmol).

Spectral data for (*2R, 3R*)-**115c**: R_f =0.31 (1:5 EtOAc / hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, 3H, *J* = 7.1 Hz), 2.06 (s, 3H), 2.38 (s, 3H), 3.83 (q, 2H, *J* = 6.3Hz), 4.09 (s, 1H), 7.08-7.16 (m, 5H), 7.28 (d, 2H, *J* = 8.5Hz), 7.89 (d, 2H, *J* = 8.5Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.50, 16.05, 21.47, 52.13, 54.63, 61.25, 126.80, 127.44, 127.97, 128.06, 129.52, 132.28, 137.20, 144.28, 166.68; IR (thin film) 1751s, 1728s, 1331s, 1161vs cm^{-1}; mass spectrum, m/z (% rel intensity) δ 314 M^+ –OEt (0.2), 204 (100), 176 (9), 130 (54), 107 (56), 90 (40), 79 (34), 65 (12). Anal calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.49; H, 6.08; N, 3.70. $[\alpha]^{23}_D$ –22.3 (*c* 1.0, CH_2Cl_2) on 98% ee material (HPLC). (The optical purity was assumed to be unchanged from **58d**.)

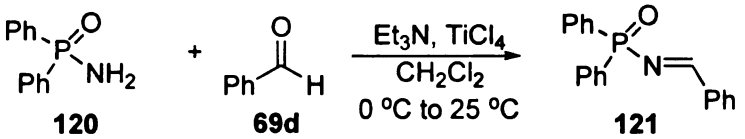


116 **69d** **117**

Preparation of *(E)*-2-benzylidene-1,1-diphenylhydrazine 117: To a 100 mL flame-dried round bottom flask filled with argon was added Na metal (1.05 g, 50 mmol) and 50 mL EtOH, stirring at the room temperature until all sodium dissolved. To an 250 mL flame-dried flask was added hydrazine hydrochloride **116** (11.8 g, 52 mmol) and 50 mL EtOH, followed by the slow addition of **69d** (5.3 g, 50 mmol), the purple solution turned to brown, followed by a slow transfer of the NaOEt solution via cannula. The reaction mixture was stirred at room temperature for 24 h before quenched by addition of 0.1 N NaOH solution until basic. The mixture was extracted with CH_2Cl_2, the organic collection

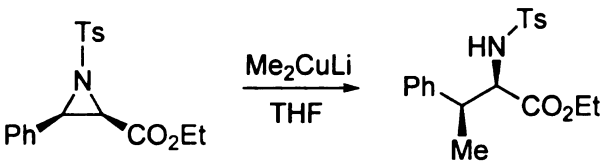
was dried over $MgSO_4$ and concentration by rotary evaporation to give the crude product as light yellow solid, which was purified by crystallization to give product **117** as light yellow solid (mp. 124-125 °C) in 66% yield (9.02 g, 33 mmol).

Spectral data for **117**:[63] ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.15-7.28 (m, 8H), 7.30-7.36 (m, 2H), 7.40-7.45 (m, 4H), 7.61 (d, 1H, *J* = 7.2Hz), 7.62 (s, 1H); ^{13}C (CDCl3, 75 MHz) δ 122.49, 124.49, 126.26, 128.09, 128.50, 129.77, 135.43, 136.11, 143.60; IR (thin film) 1589s, 1495vs, 1203m, 752m, 693s cm^{-1}.



Preparation of *(E)-N*-benzylidene-*N,N*-diphenylphosphinamide 121: To a 250 mL flame-dried round bottom flask filled with argon was added amine **120** (2.12 g, 9.76 mmol), benzaldehyde **69d** (1.95 mL, 19.5 mmol), Et_3N (4.1 mL, 29.3 mmol) and 44 mL CH_2Cl_2, the reaction mixture was stirred at room temperature for 5 minutes, then cooled to 0 °C, followed by the slow addition of $TiCl_4$ (5.4 mL, 5.4 mmol, 1 M solution in toluene) in 3 minutes. After the addition, the ice bath was removed and the reaction mixture was allowed to stirring at room temperature for 2 h. The reaction was then quenched by adding 150 mL toluene, followed by the filtration and the solid residue was washed with CH_2Cl_2, the collected filtrate was concentrated under the reduced pressure to give crude product as white solid. Purification by crystallization (1:2 CH_2Cl_2/hexane) afforded compound **121** as white solid (mp. 141-143 °C) in 72% yield (2.13 g, 7.0 mmol).

Spectral data for **121**:[65] ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.42-7.56 (m, 9H), 7.89-8.01 (m, 6H), 9.31 (d, 1H, *J* = 32.2Hz); ^{13}C (CDCl3, 75 MHz) δ 128.34, 128.50, 128.87, 130.13, 131.43, 131.57, 131.72, 133.60, 173.63; IR (thin film) 1614vs, 1577s, 1476m, 1439(s), 1397m, 1206s, 851m, 828m cm^{-1}.

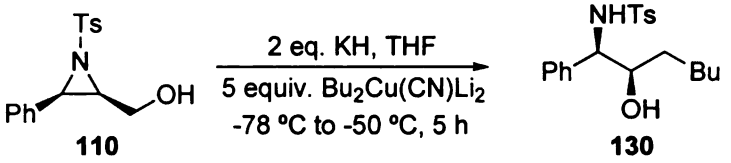


98d **123d**

***(2R, 3S)*-(4-Methylphenylsulfonamido)-3-phenyl-ethylbutanoate 123d.** To a 25 mL flame-dried round bottom flask filled with argon was added freshly dried CuI (236 mg, 1.2 mmol), 2 mL THF, then the flask was put into a –20 °C bath, followed by addition of MeLi (1.6 mL, 2.4 mmol, 1.6 M in Et_2O), after stirring for 10 minutes, yellow slurry turned to colorless solution. At the same time, the *N*-Ts aziridine **98d** (138 mg, 0.4 mmol, 95% ee) was dissolved in 3 mL THF in a flame-dried 10 mL flask under the protection of argon. The **98d** solution was then slowly transferred to the prepared cuprate reagent by syringe, and the reaction mixture was stirred at –20 °C for 2 h. The reaction was quenched by addition of 10 mL aqueous saturated NH_4Cl solution, bubbling with air until no solid exist, the organic layer was collected and the aqueous layer was extracted with Et_2O (5 mL × 3). The combined organic layer was washed with NaCl (aq. sat.), dried over $MgSO_4$ and concentrated by rotary evaporation to afford crude product as yellow oil. Purification by silica gel chromatography (9 mm × 250 mm, 6" SiO_2, 1:5 EtOAc/ hexanes as eluent) afforded **123d** as a colorless liquid in 42% isolated yield (61 mg, 0.17 mmol).

Spectral data for *(2R,3R)*-**123d**: R_f = 0.18 (1:3 EtOAc/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, 3H, *J* = 7.1Hz), 1.15 (d, 3H, *J* = 6.9Hz), 2.28 (s, 3H), 2.77-2.82 (m, 1H), 3.83-3.91 (m, 2H), 4.44-4.50 (m, 1H), 5.84 (d, 1H, *J* = 9.0Hz (N-H)), 6.93-7.23 (m, 7H), 7.47 (d, 2H, *J* = 8.4Hz); ^{13}C (CDCl3, 75 MHz) δ 13.71, 13.82, 21.34, 45.99, 59.93, 60.65, 126.99, 127.02, 127.41, 128.07, 129.16, 137.38, 138.20, 142.91, 173.35; IR (thin film) 3281br, vs, 1732s, 1456s, 1161vs, 1094s, 1049s, 918m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 361 M^+ (0.05), 260 (97), 206 (11), 155 (90), 117 (23), 104 (34), 91 (100),

77(20), 65(27); Anal. calcd for $C_{19}H_{23}NO_4S$: C, 63.13; H, 6.41; N, 3.88. Found: C, 63.15; H, 6.70; N, 3.78. Specific rotation: $[\alpha]^{23}_D$ –74.5 (*c* 1.8 in CH_2Cl_2) (on 95% ee material assumed not changed from **98d**).



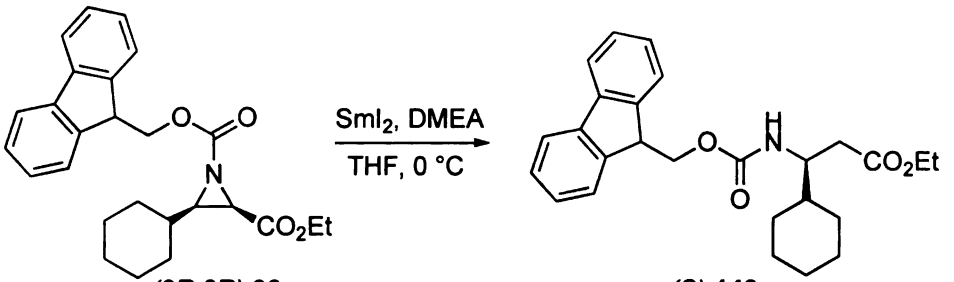
110 **130**

1-(4-Methylphenyl)sulfonylamino-1-phenyl-2-heptanol 130.

To a stirred suspension of KH (80 mg, approximately 1 mmol) in 2 mL of THF at –78 °C filled with argon was added alcohol **110** (30 mg, 0.1 mmol) in 1 mL THF, and the mixture was allowed to warm up to 0 °C and stirred for 1 h, then the flask was cooled back to –78 °C. At the same time, the $CuBu_2LiCN$ solution was prepared by addition of CuCN (45 mg, 0.5 mmol), MeLi (0.6 mL, 1 mmol) (1.6 M in Et_2O) and 1 mL Et_2O to a 20 mL flame-dried flask filled with argon at –78 °C, the mixture was then warmed up to -35 °C for 10 minutes and cooled back to -78 °C. The $CuBu_2LiCN$ solution was then transferred to the alcohol-KH slurry via syringe at -78 °. The reaction mixture was stirred at –78 °C for 0.5 h before it was warmed to –50 °C and stirred for 5 h for a complete conversion. The reaction was quenched with 2 mL of a mixed solution (sat. NH_4Cl / NH_4OH (28%) (1:1)) with vigorous stirring at –78 °C. After the extraction with Et_2O, the collected organic layer was dried over $MgSO_4$ and concentrated on rotary evaporator to give the crude product as a yellow liquid. Purification by silica gel chromatography (9 mm × 250 mm, 6" SiO_2, 1:1 ether/ hexanes as eluent) afforded **130** as a white solid in 83% yield (29 mg, 0.08 mmol).

Spectral data for **130**:[62] R_f =0.25 (1:3 EtOAc/ Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, 3H, *J* = 6.9 Hz), 1.15-1.41 (m, 8H), 2.21 (br, s, 1H), 2.30 (s, 3H), 3.66 (s, 1H), 4.19-4.23 (m, 1H), 5.74 (d, 1H, *J* = 7.7 Hz), 7.00-7.14 (m, 7H), 7.48-7.52 (m, 2H).

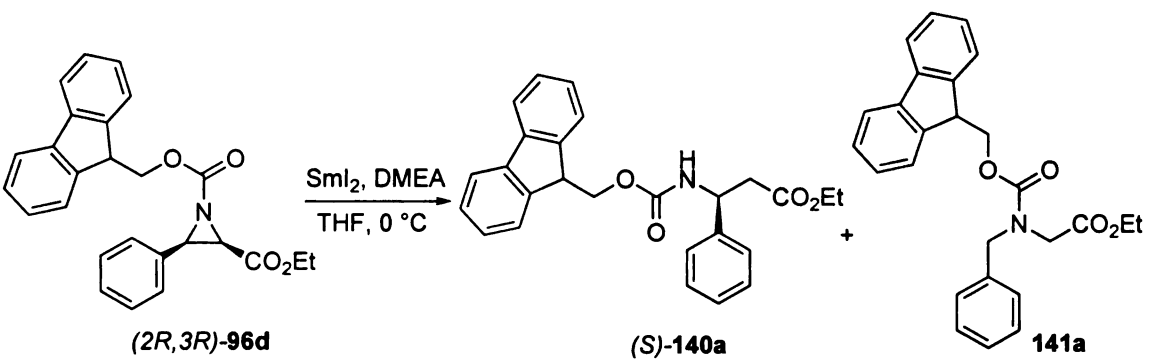
General procedure for the reductive opening of Fmoc aziridines with samarium diiodide – illustrated for *(2R, 3R)-N*-9-fluorenylmethyl-carbamate-*cis*-2-carboxyethyl-3-cyclohexylaziridine 96a.



(2R,3R)-**96a** *(S)*-**140c**

To a 10 mL flame-dried round bottom flask filled with argon was charged with Sm metal (98 mg, 0.65 mmol) and 1.5 mL THF, then the addition of CH_2I_2 (48 μL, 0.6 mmol), the mixture was stirred at room temperature for 2 h to give a dark blue slurry. (To generate the SmI_2 solution successfully, the Sm should be fresh that appears like silver-flashing metal (the grey powder appearance is the oxidized Sm that can't be used), and the glassware should be clean, free of any base or acid contaminates, the good quality of the diiodomethane was also required (SmI_2 does not generate in Et_2O or benzene)). To this slurry was added a solution of *(2R, 3R)-N*-Fmoc aziridine **96a** (84 mg, 0.2 mmol, 89% ee) and *N,N*-dimethylethanolamine (DMEA) (120 μL, 1.2 mmol) in 1.5 mL THF at 0 °C. The reaction mixture was stirred at 0 °C for 40 minutes and then quenched by the addition of $NaHCO_3$ (sat. aq.) at 0 °C. The organic layer was collected and the aqueous layer was extracted with EtOAc (5 mL × 3). The combined organic layer was washed with 10 mL NaCl (aq. sat.) and dried over $MgSO_4$. The solvent was removed by rotary evaporation to give a light yellow solid. Purification by silica gel chromatography (18 mm × 230 mm, 1:3 EtOAc / hexanes as eluent) afforded **140c** as white solid (mp. 129-130 °C) in 89% isolated yield (75 mg, 0.18 mmol).

Spectral data for (*S*)-**140c**: R_f = 0.18 (1:5 EtOAc/Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.86-1.01 (m, 2H), 1.08-1.24 (m, 3H), 1.23 (t, 3H, *J* = 7.1 Hz), 1.42-1.53 (m, 1H), 1.65-1.74 (m, 5H), 2.52 (d, 2H, *J* = 6.0 Hz), 3.74-3.84 (m, 1H), 4.12 (q, 2H, *J* = 7.1 Hz), 4.20 (t, 1H, *J* = 7.2 Hz), 4.32-4.48 (m, 2H), 5.20 (d, 1H, *J* = 9.9 Hz), 7.29 (t, 2H, *J* = 7.4 Hz), 7.38 (t, 2H, *J* = 7.4 Hz), 7.58 (d, 2H, *J* = 7.4 Hz), 7.74 (d, 2H, *J* = 7.4 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 14.13, 25.90, 25.97, 26.15, 29.05, 29.72, 36.75, 41.29, 47.33, 52.85, 60.53, 66.48, 119.89, 125.06, 126.97, 127.58, 141.30, 143.94, 155.96, 171.87; IR (thin film) 3333s, 1730vs, 1531s, 1448s, 1242s, 738m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 422 (M^++1) (0.8), 198 (26), 178 (100), 165 (88), 152 (22), 137(17), 116 (13), 95 (17), 67 (10), 55 (19), 41 (23). Anal. calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.10; H, 7.87; N, 3.22. $[\alpha]^{23}_D$ –2.9 (*c* 2.0, EtOAc) on 89% ee material (HPLC). (The optical purity was assumed to be unchanged from **96a**.)



(2R,3R)-**96d** *(S)*-**140a** **141a**

C2-ring opening of *(2R, 3R)-N*-9-fluorenylmethyl-carbamate-*cis*-2-carboxyethyl-3-phenylaziridine 96d. The general procedure for the cleavage of **96a** was followed except that 4 equivalents of SmI_2 and 8 equivalent of DMEA were used. Starting from **96d** (82 mg, 0.2 mmol, 98% ee), purification by silica gel chromatography (18 mm x 300 mm, 1:5 EtOAc/ hexanes as eluent) gave **140a** as white solid (mp. 128-129 °C) in 45 % isolated yield (37 mg, 0.09 mmol) and **141a** as white solid (mp. 95-97 °C) in 46 % isolated yield (38 mg, 0.09 mmol).

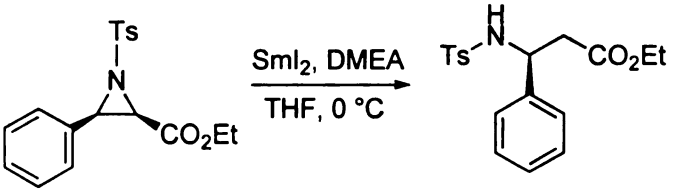
Spectral data for *(S)*-**140a**: R_f = 0.17 (1:5 EtOAc/Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.19 (t, 3H, *J* = 7.1 Hz), 2.88-2.92 (m, 2H), 4.11 (q, 2H, *J* = 7.1 Hz), 4.24 (t, 1H, *J* = 6.6 Hz), 4.43 (d, 2H, *J* = 6.6 Hz), 5.21 (s, 1H), 5.83 (d, 1H, *J* = 6.4 Hz), 7.28-7.43 (m, 9H), 7.59-7.63 (m, 2H), 7.78 (d, 2H, *J* = 7.3 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.03, 40.59, 47.22, 51.65, 60.74, 66.77, 119.92, 125.01, 126.11, 127.00, 127.01, 127.63, 128.68, 141.27, 143.85, 143.88, 155.56, 170.89; IR (thin film) 3337m, 1730vs, 1695s, 1532s, 1451m, 1244s, 1030m, 741m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 219 (0.39), 196 (16), 178 (59), 165 (100), 145 (20), 132 (53), 103(26), 88 (36), 77 (49), 68 (15), 51 (12). $[\alpha]^{23}_D$ −11.4 (*c* 1.0, CH_2Cl_2) on 98% ee material (HPLC). (The optical purity was assumed to be unchanged from **96d**.)

The compound **141a** appeared to be a mixture of two rotamers at room temperature in a ratio of 1 : 1. Spectral data for **141a**: R_f = 0.25 (1:5 EtOAc/Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24 (t, 3H, *J* = 7.1 Hz), 1.26 (t, 3H, *J* = 7.1 Hz), 3.83 (s, 2H), 3.98 (s, 2H), 4.14 (q, 2H, *J* = 7.1 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 4.26-4.30 (m, 2H), 4.53 (d, 2H, *J* = 6.7 Hz), 4.55 (s, 2H), 4.56 (d, 2H, *J* = 6.6 Hz), 4.62 (s, 2H), 7.11-7.13 (m, 2H), 7.26-7.36 (m, 12H), 7.38-7.43 (m, 4H), 7.52 (d, 2H, *J* = 7.4 Hz), 7.58 (d, 2H, *J* = 7.4 Hz), 7.75 (d, 2H, *J* = 7.6 Hz), 7.78 (d, 2H, *J* = 7.6 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.12, 47.15, 47.33, 47.37, 47.99, 51.09, 51.49, 61.16, 67.75, 67.86, 119.94, 124.91, 124.92, 127.02, 127.05, 127.51, 127.58, 127.65, 128.15, 128.62, 128.69, 136.67, 141.30, 143.81, 143.87, 156.33, 156.47 169.38, 169.51 (two sp^3 and five sp^2 carbon not located); IR (thin film) 1750vs, 1707vs, 1453s, 1238s, 1198s, 1122m, 741m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 236 (0.05), 178 (100), 165 (18), 91 (44).

Spectral data for **141a**: ^{1}H NMR (C_6D_6, 500 MHz, 75°C) δ 0.88 (t, 3H, *J* = 7.1 Hz), 3.68 (br, s, 1H), 3.82 (br, s, 1H), 3.87 (q, 2H, *J* = 7.1 Hz), 4.01 (t, 1H, *J* = 6.3 Hz), 4.39 (br, s, 1H), 4.43 (d, 2H, *J* = 6.3 Hz), 4.55 (br, s, 1H), 6.94-7.18 (m, 9H), 7.37-7.43 (m,

2H), 7.53 (d, 2H, *J* = 7.3 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.06, 47.53, 47.97, 51.95, 60.78, 67.86, 120.13, 125.28, 127.27, 127.59, 127.90, 128.29, 128.79, 137.69, 141.87, 144.64, 156.48, 169.26.

Spectral data for **141a**: ^1H NMR (C_6D_6, 500 MHz, 25°C) δ 0.81 (t, 3H, *J* = 7.1 Hz), 0.84 (t, 3H, *J* = 7.1 Hz), 3.60 (s, 2H), 3.81-3.85 (m, 6H), 3.94 (t, 1H, *J* = 6.3 Hz), 3.99 (t, 1H, *J* = 6.4 Hz), 4.38 (s, 2H), 4.39 (d, 2H, *J* = 6.5 Hz), 4.42 (d, 2H, *J* = 6.4 Hz), 4.59 (s, 2H), 6.84-6.86 (m, 2H), 7.00-7.10 (m, 8H), 7.13-7.20 (m, 8H), 7.27 (d, 2H, *J* = 7.4 Hz), 7.40 (d, 2H, *J* = 7.3 Hz), 7.49 (d, 2H, *J* = 7.5 Hz), 7.53 (d, 2H, *J* = 7.4 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.10, 14.07, 47.52, 47.57, 47.79, 48.36, 51.36, 51.85, 60.83, 60.88, 67.72, 67.74, 120.14, 125.30, 127.28, 127.52, 127.64, 127.74, 127.81, 128.26, 128.43, 128.76, 128.82, 137.55, 141.72, 144.42, 144.49, 156.42, 169.29, 169.39 (six sp^2 carbon not located).

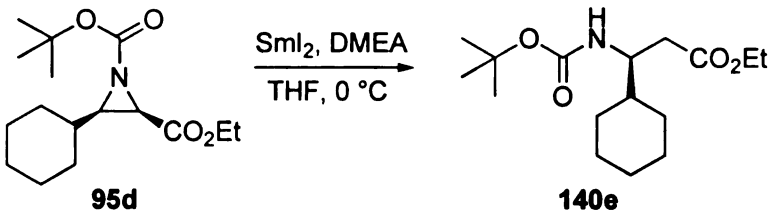


(2R,3R)-**98d** *(S)*-**140b**

C2-ring opening of *(2R, 3R)*-ethyl-3-phenyl-1-tosyl-aziridine-2-carboxylate 98d. The procedure of C2-ring opening for **96a** was followed by using 2.5 equiv of *in situ* generated SmI_2. Starting from **98d** (34 mg, 0.1 mmol, 98% ee), purification by silica gel chromatography (18 mm × 150 mm, 1:5 EtOAc/ hexanes as eluent) gave **140b** as colorless liquid in 93% isolated yield (32 mg, 0.09 mmol).

Spectral data for *(S)*-**140b**:[74] R_f = 0.25 (1:3 EtOAc/Hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.13 (t, 3H, *J* = 7.1 Hz), 2.37 (s, 3H), 2.74 (dd, 1H, *J* = 6.2, 15.7 Hz), 2.83 (dd, 1H, *J* = 6.2, 15.7 Hz), 3.99-4.04 (m, 2H), 4.72-4.76 (m, 1H), 5.80 (d, 1H, *J* = 7.7 Hz), 7.10-7.16 (m, 2H), 7.17-7.27 (m, 5H), 7.61 (d, 2H, *J* = 8.2 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ

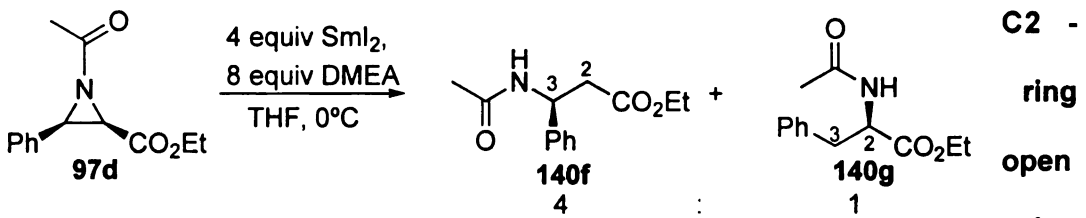
13.94, 21.41, 41.27, 54.34, 60.84, 126.42, 127.06, 127.66, 128.45, 129.38, 137.42, 139.31, 143.15, 170.58; The ^{1}H and ^{13}C spectra match those reported for this compound.[78] $[\alpha]^{23}_{D}$ –51.4 (*c* 1.0, CH_2Cl_2) on 98% ee material (HPLC). (The optical purity was assumed to be unchanged from **98d**.)



95d **140e**

C2-ring opening of ethyl-3-cyclohexyl-1-Boc-aziridine-2-carboxylate 95d. The procedure for the C2-ring opening of **96a** was followed except that 4 equiv Sm and 8 equiv DMEA was used. Starting from **95d** (38 mg, 0.12 mmol), purification by silica gel chromatography (18 mm x 150 mm, 1:5 EtOAc/ hexanes as eluent) gave **140e** as white solid in 84% isolated yield (30 mg, 0.1 mmol).

Spectral data for **140e**:[74] R_f = 0.25 (1:5 EtOAc/Hexane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83-0.99 (m, 2H), 1.01-1.17 (m, 3H), 1.21 (t, 3H, *J* = 7.1 Hz), 1.38 (s, 9H), 1.31-1.40 (m, 1H), 1.61-1.75 (m, 5H), 2.38-2.51 (m, 2H), 3.63-3.75 (m, 1H), 4.08 (q, 2H, *J* = 7.1 Hz), 4.88 (d, 1H, *J* = 7.1 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.12, 25.98, 26.02, 26.19, 28.33, 28.94, 29.73, 37.04, 41.50, 52.22, 60.41, 78.96, 155.48, 171.98; IR (thin film) 3360br, s, 2930s, 1719vs, 1504m, 1173s cm^{-1}.



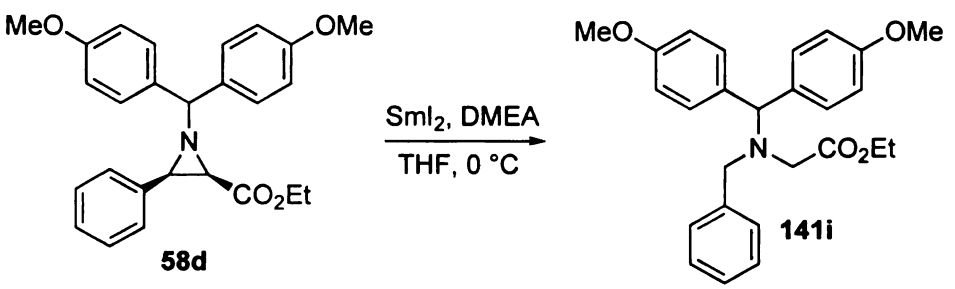
97d **140f** 4 : **140g** 1

C2-ring opening

of *cis*-*N*-acetyl-2-carboxyethyl-3-phenylaziridine 97d. The general procedure for the C2-ring opening of **96a** was followed except that 2.5 equivalents of SmI_2 and 5 equivalents of DMEA were used. Starting from **97d** (47 mg, 0.19 mmol), purification by silica gel chromatography (18 mm × 300 mm, 1:5 EtOAc/ hexanes as eluent) gave **140f** as colorless semi-solid in 52 % isolated yield (24 mg, 0.1 mmol) and **140g** as colorless semi-solid in 13 % isolated yield (6 mg, 0.025 mmol).

Spectral data for **140f**: R_f = 0.15 (1:5 EtOAc/Hexane); ^1H NMR ($CDCl_3$, 500 MHz,) δ 1.12 (t, 3H, *J* = 7.1 Hz), 1.98 (s, 3H), 2.77 (dd, 1H, *J* = 6.0, 15.4 Hz), 2.87 (dd, 1H, *J* = 6.0, 15.7 Hz), 4.04 (q, 2H, *J* = 7.1 Hz), 5.36-5.43 (m, 1H), 6.60 (d, 1H, *J* = 8.0 Hz), 7.20-7.32 (m, 5H).

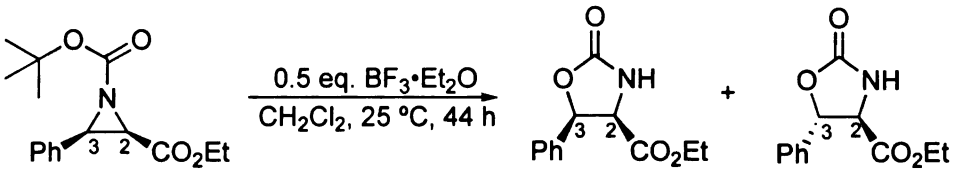
Spectral data for **140g**: R_f = 0.2 (1:1 EtOAc/Hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.22 (t, 3H, *J* = 7.1 Hz), 1.96 (s, 3H), 3.09 (dd, 2H, *J* = 2.2, 5.5 Hz), 4.15 (q, 2H, *J* = 7.1 Hz), 4.84 (dt, 1H, *J* = 5.8, 7.7 Hz), 5.87 (d, 1H, *J* = 6.6 Hz), 7.07 (d, 2H, *J* = 8.0 Hz), 7.21-7.29 (m, 3H). (identical to that from Aldrich).



Ring opening of *cis*-*N*-bis(dimethoxylphenyl)methyl-2-carboxyethyl-3-phenylaziridine 58d. The general procedure for the C2-ring opening of **96a** was applied except that 5 equiv Sm and 10 equiv DMEA was used. Starting with **58d** (42 mg, 0.1 mmol), after purification by silica gel chromatography (18 mm × 300 mm, 1:5 EtOAc/ hexanes as eluent), the reaction gave **141i** as colorless liquid in 67 % isolated yield (29 mg, 0.07 mmol).

Spectral data for **141i**: R_f = 0.45 (1:1:4 Et_2O/CH_2Cl_2/Hexane); ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (t, 3H, *J* = 7.1 Hz), 3.22 (s, 2H), 3.75 (s, 6H), 3.79 (s, 2H), 4.05 (q, 2H, *J* = 7.1 Hz), 5.15 (s, 1H), 6.82 (d, 4H, *J* = 8.5 Hz), 7.22-7.41 (m, 5H), 7.38 (d, 4H, *J* = 8.5 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.19, 50.36, 54.81, 55.16, 59.88, 68.86, 123.80, 126.90, 128.25, 128.67, 129.27, 134.47, 139.39, 158.56, 171.70. m/z (% rel intensity) 419 M^+ (0.01), 328 (7), 227 (100), 212 (9), 169 (10), 141(10), 91 (67), 65 (9).

Ring expansion of the Boc-protected aziridine 95d.



(2R,3R)-**95d** *(4R,5R)*-**167d** *(4R,5S)*-**168d**

Method A: The $BF_3•Et_2O$ was distilled before use. To a 10 mL flame-dried round bottom flask filled with argon was added *(2R, 3R)*-**95d** (76 mg, 0.25 mmol, 99% ee) and 2.5 mL CH_2Cl_2. The reaction mixture was stirred to effect dissolution followed by the addition of $BF_3•Et_2O$ (16 μL, 0.125 mmol). The reaction mixture was stirred for 44 hours at room temperature and was quenched by addition of 2 mL saturated aq. Na_2CO_3. The aqueous layer was separated and extracted with CH_2Cl_2 (2 mL × 4). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to afford a mixture of **167d** and **168d**. Purification by silica gel chromatography (11 mm × 250 mm, 1:3 EtOAc/ hexanes as eluent) gave **167d** as white solid (mp. 116-117 °C) in 64% isolated yield (37 mg, 0.16 mmol) and **168d** as colorless liquid in 19% isolated yield (12 mg, 0.05 mmol).

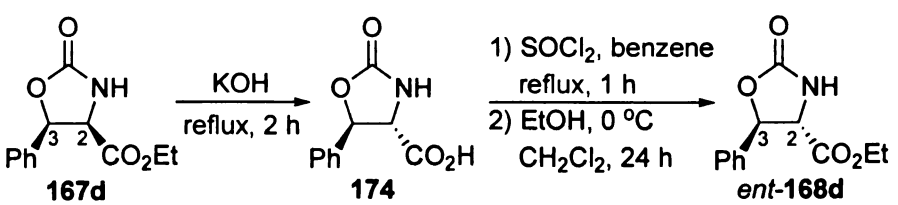
Method B: The same procedure was followed except that the $Cu(OTf)_2$ (10 mg, 0.025 mmol) was used as Lewis acid. After the addition of $Cu(OTf)_2$, the color of the solution changed slowly from colorless to green, then to light blue. Purification by silica gel

chromatography gave **167d** in 39% isolated yield (22 mg, 0.10 mmol) and **168d** in 60% isolated yield (35 mg, 0.15 mmol).

Spectral data for (*4R, 5R*)-**167d**: R_f = 0.10 (1:1, EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (t, 3H, *J* = 7.1 Hz), 3.55-3.75 (m, 2H), 4.64 (d, 1H, *J* = 9.1 Hz), 5.80 (d, 1H, *J* = 9.1 Hz), 6.44(s, 1H), 7.31(s, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.36, 59.85, 61.61, 79.24, 126.37, 128.36, 129.22, 134.08, 159.12, 168.65; IR (thin film) 3348m, 3258s, 1746vs, 1204s, 1018s, 698m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 235 M^+ (1.9), 192 (5), 161 (24), 129 (64), 118 (100), 107 (26), 101 (33), 91 (55). Anal calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.32; H, 5.63; N, 5.91. $[\alpha]^{23}_D$ –84.2 (*c* 1.0, EtOAc) on 99% ee material (HPLC). (The optical purity was assumed to be unchanged from **95d**.)

Spectral data for (*4R, 5S*)-**168d**: R_f = 0.15 (1:1, EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, 3H, *J* = 7.1 Hz), 4.25 (d, 1H, *J* = 5.0 Hz), 4.26-4.31 (m, 2H), 5.62 (d, 1H, *J* = 5.0 Hz), 6.51(s, 1H), 7.38(s, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 13.97, 61.38, 62.36, 79.37, 125.29, 128.88, 129.01, 138.06, 158.44, 169.66; IR (thin film) 3304br vs, 1771vs, 1219vs, 1016s, 765m, 700m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 235 M^+ (4), 192 (14), 163 (13), 161 (11), 129 (18), 119 (13), 105 (20), 101 (8), 91 (31), 77 (17). Anal calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.44; H, 5.30; N, 5.78. $[\alpha]^{23}_D$ –70.8 (*c* 1.0, EtOAc) on 99% ee material (HPLC). (The optical purity was assumed to be unchanged from **95d**.)

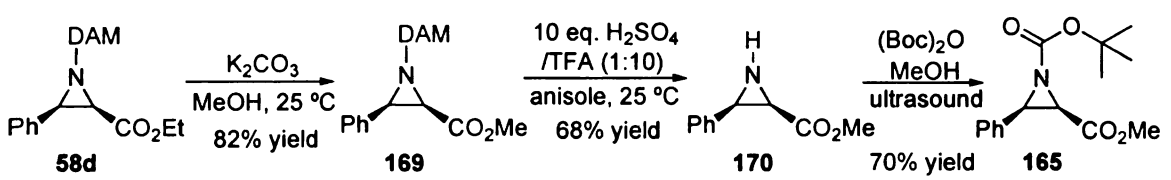
Isomerization from *(4R, 5R)-cis*-oxazolidinone 167d to *ent*-168d.



167d **174** ***ent*-168d**

To a 25 mL round bottom flask was added *(4R, 5R)*-**167d** (100 mg, 0.42 mmol, 99% ee), 4 mL EtOH and 0.6 M KOH (0.7 mL 0.42 mmol, aq.). The reaction mixture was heated to reflux for 2 hours. After cooling to room temperature, 2 mL of 0.3 N aq. HCl was added to neutralize the reaction mixture. The aqueous layer was extracted with EtOAc (5 mL × 3) and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude acid **174** as a white semi-solid. A condenser was then attached to the flask that containing the crude product **174** under the protection of argon. After the addition of 3 mL THF and $SOCl_2$ (59 mg, 0.5 mmol), the reaction mixture was heated to reflux for 1 h under the protection of argon before it was cooled to room temperature. Removal of the solvent by rotary evaporation gave the crude product as a white solid, which was put on high vacuum for at least 4 hours to remove the remaining $SOCl_2$. To the flask containing the crude reaction mixture was then added 3 mL EtOH and DMAP (50 mg, 0.4 mmol) stirred at room temperature for 10 h. The reaction mixture was extracted with CH_2Cl_2 (2 mL × 4), the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (11 mm × 250 mm, 1:4 EtOAc/ hexanes as eluent) gave *ent*-**168d** as colorless liquid in 81% isolated yield (81 mg, 0.34 mmol). All data of *ent*-**168d** are the same as the compound **168d** except the optical rotation: $[\alpha]^{23}_D$ +70.5 (*c* 1.0, EtOAc) on 99% ee material (HPLC). (The optical purity was assumed to be unchanged from **167d**.)

Preparation of *N*-Boc-*cis*-2-carboxymethyl-3-benzylaziridine 165:



Transesterification of the *cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-phenylaziridine 58d. To a 50 mL flame-dried round bottom flask filled with argon was added **58d** (330 mg, 0.78 mmol) and 30 mL MeOH to effect dissolution, followed by the addition of K_2CO_3 (0.5 g, 3.7 mmol). The reaction mixture was stirred at room temperature for 48 h, and the conversion was monitored by TLC. To avoid the fact that the product **169** will change back to the starting material **58d** if all the methanol solvent is removed due to the equilibrium between the carboxylates **58d** and **169**, upon the reaction was done, the methanol was removed partially by reduced pressure and the remaining crude material was loaded directly on silica gel column for the purification, which still has large excess of methanol compared with the generated ethanol from the transesterification reaction. Purification by silica gel chromatography (11 mm × 300 mm, 1:5 EtOAc/ hexanes as eluent) gave **169** as white solid (mp. 115-116 °C) in 82% isolated yield (260 mg, 0.64 mmol).

Spectral data for **169**: R_f = 0.36(1:3, EtOAc/hexanes); ^{1}H-NMR($CDCl_3$, 300 MHz) δ 2.70 (d, 1H, *J* = 6.9Hz), 3.21 (d, 1H, *J* = 6.9Hz), 3.47 (s, 3H), 3.70 (s, 3H), 3.77 (s, 3H), 3.88 (s, 1H), 6.80 (d, 2H, *J* = 8.5Hz), 6.88 (d, 2H, *J* = 8.8Hz), 7.26 (m, 3H), 7.38 (m, 4H), 7.50 (d, 2H, *J* = 8.8Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 46.18, 48.17, 51.56, 54.99, 55.06, 76.45, 113.72, 113.75, 127.28, 127.62, 127.75, 128.10, 128.38, 134.77, 134.97, 135.00, 158.57, 158.65, 168.13.

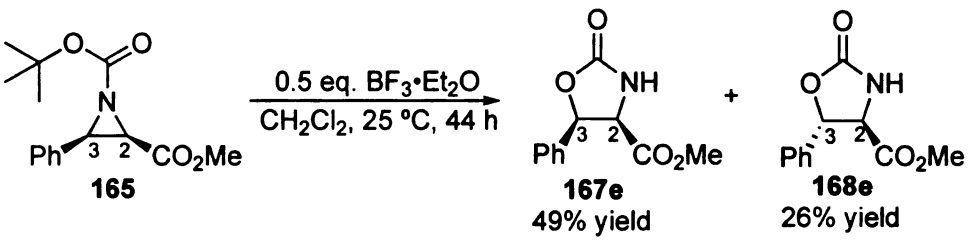
Deprotection of *cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxymethyl-3-phenylaziridine 169. The method B for the synthesis of **56a** was followed starting from **169** (250 mg, 0.6 mmol). After purification, the product **170** was obtained as white solid in 68% isolated yield (74 mg, 0.42 mmol).

Spectral data for **170**: R_f = 0.08(1:3, EtOAc/hexanes); ^{1}H-NMR($CDCl_3$, 300 MHz) δ 1.67 (br, s, 1H), 3.0 (br, m, 1H), 3.48 (m, 4H), 7.24 (s, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 29.60,

37.06, 52.00, 127.36, 127.63, 128.02, 134.70; IR (thin film) 3204br, s, 1741vs, 1443m, 1196vs, 1008m, 868m cm^{-1}.

Protection of *cis*-*N*-H-2-carboxymethyl-3-phenylaziridine 170 with Boc group. The procedure for the synthesis of **95a** was followed from **170** (61 mg, 0.35mmol). After purification, the product **165** was obtained as white solid in 70% yield (69 mg, 0.25 mmol).

Spectral data for **165**:[23a] R_f = 0.18(1:9, EtOAc/hexanes); ^{1}H-NMR($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 3.41 (d, 1H, *J* = 6.9Hz,), 3.47 (s, 3H), 3.80 (d, 1H, *J* = 6.9Hz,), 7.26 (m, 3H), 7.36 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 27.79, 42.53, 44.42, 52.03, 82.46, 127.38, 128.05, 128.11, 132.96, 160.40, 166.49.

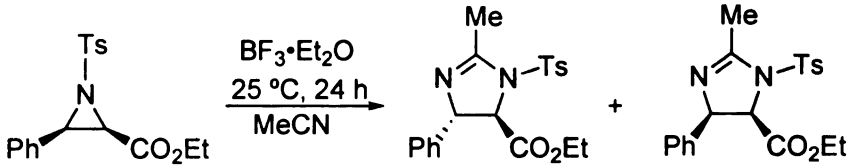


165 → **167e** 49% yield + **168e** 26% yield

Ring Expansion of the Boc-Protected Aziridine 165. The procedure for the ring expansion of compound **95d** was followed starting from **165** (30 mg, 0.1 mmol). After purification, the compound **167e** was obtained as white solid in 49% yield (11 mg, 0.05 mmol) and **168e** as colorless liquid in 26% yield (6 mg, 0.026 mmol).

Spectral data for **167e**:[23a] R_f = 0.27(1:1, EtOAc/hexanes). ^{1}H-NMR($CDCl_3$, 300 MHz) δ 3.19 (s, 3H), 4.66 (d, 1H, *J* = 9.1Hz), 5.81 (d, 1H, *J* = 9.1Hz), 6.21 (br, s, 1H), 7.33 (m, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 52.11, 59.94, 79.18, 126.14, 128.39, 129.25, 133.91, 158.89, 169.00; IR (thin film) 3279br, s, 1746vs, 1207s, 1180m, 1119m, 1007m cm^{-1}; mass spectrum, m/z (% rel intensity) 221 M^+ (3), 178 (2), 161 (12), 118 (100), 107 (55), 91 (50), 83 (11), 77 (29), 65 (14), 59 (16), 51 (15).

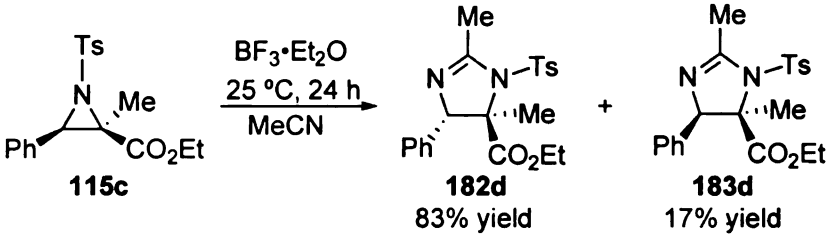
Spectral data for **167e**:[23a] R_f = 0.36(1:1, EtOAc/hexanes). ^{1}H-NMR($CDCl_3$, 300 MHz) δ 3.84 (s, 3H), 4.27 (d, 1H, J = 5.0Hz), 5.64 (d, 1H, J = 5.0 Hz), 6.15 (br, s, 1H), 7.40 (m, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 53.23, 61.26, 79.36, 125.32, 129.04, 129.19, 138.01, 158.01, 170.06; IR (thin film) 3001br, s, 1769vs, 1223s, 1115(m), 1016m, 989m cm^{-1}; mass spectrum, m/z (% rel intensity) 221 M^+ (6), 178 (34), 162 (23), 118 (100), 107 (27), 91 (34), 83 (11), 77 (31), 65 (22), 59 (25), 51 (17).



[3+2] cycloaddition of aziridine 98d with acetonitrile. To a 10 mL flame-dried round bottom flask filled with argon was added **98d** (43 mg, 0.125 mmol), acetonitrile (1 mL) followed the addition of BF_3•Et_2O (16 μL, 0.125 mmol). The reaction mixture was stirred for 24 hours at room temperature and was quenched by addition of 2 mL $NaHCO_3$ (aq. sat.). The aqueous layer was separated and extracted with EtOAc (2 mL × 4). The combined organic layer was washed with NaCl (aq. sat.), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude products as colorless liquid. Purification by silica gel chromatography (9 mm × 250 mm, 6" SiO_2, 1:1 Et_2O/ hexanes as eluent) gave a mixture of product **182b** and **183b** as colorless semi solid in 73% overall isolated yield in a ratio of 5 : 1 (35 mg, 0.09 mmol). The mixture could be separated by HPLC (MCROSORB-MV™ 100Å, Silica R0086100C8 column, 95:5 isopropanol/hexane, 0.7 mL, retention times: R_t = 16.85 min for **182b** and R_t = 19.86 min for **183b**).

Spectral data for **182b**: R_f = 0.15 (1:3, EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (t, 3H, J = 7.1 Hz), 2.31 (s, 3H), 2.40 (s, 3H), 4.22-4.35 (m, 2H), 4.51 (d, 1H, J = 5.6 Hz), 4.96 (dd, 1H, J = 1.4, 5.5 Hz), 6.92-6.96 (m, 2H), 7.19-7.23 (m, 3H), 7.27 (d, 2H, J =

8.5 Hz), 7.74 (d, 2H, J = 8.4 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 14.02, 16.46, 21.47, 61.92, 68.56, 71.86, 125.98, 127.53, 127.83, 128.60, 129.89, 135.58, 140.52, 144.89, 156.25, 170.34. IR (thin film,) 1748vs, 1599vs, 1497s, 1094s, 891s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 386 M^+ (0.03), 231 (60), 155 (35), 127 (52), 116 (16), 99 (42), 91 (100), 65 (17), 42 (11).



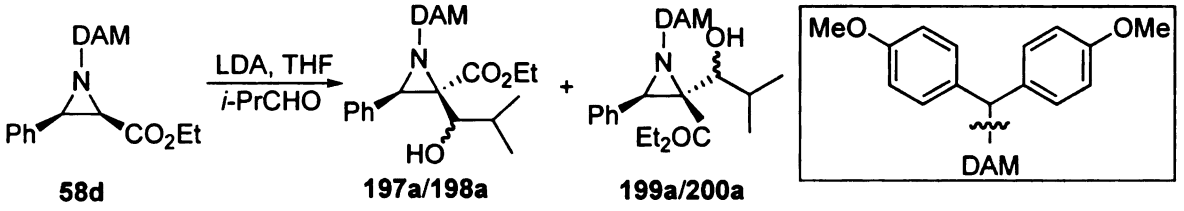
[3+2] cycloaddition of aziridine 115c with acetonitrile. The same procedure was followed as the cycloaddition reaction for **98d** from *(2R,3R)*-**115c** (60 mg, 0.16 mmol, 98% ee) and BF_3•Et_2O (35 μL). The product **182d** was obtained as colorless liquid in 83% yield (56 mg, 0.13 mmol) and **183d** was obtained as white solid in 17% yield (12 mg, 0.03 mmol).

Spectral data for *(4S,5R)*-**182d**: R_f = 0.55 (1:1, EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 3H), 1.41 (t, 3H, J = 7.1 Hz), 2.15 (s, 3H), 2.46 (s, 3H), 4.39-4.42 (m, 2H), 5.27 (s, 1H), 7.17 (d, 2H, J = 8.3 Hz), 7.31-7.38 (m, 5H), 7.97 (d, 2H, J = 8.3 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 14.08, 16.55, 19.35, 21.55, 62.24, 75.00, 76.14, 127.78, 127.98, 128.03, 128.21, 129.81, 136.16, 137.59, 144.69, 156.08, 172.96; IR (thin film) 1740vs, 1657s, 1343s, 1251s, 1156s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 401 M^+ (0.1), 327 (8), 245 (93), 155 (16), 142 (58), 130 (51), 114 (100), 104 (12), 77 (11), 73 (23), 65 (23), 54 (15), 43 (33). Specific rotation: $[\alpha]^{23}_D$ +24.8 (*c* 2.0 in CH_2Cl_2) (on 98% ee material, assumed not changed from **115c**).

Spectral data for **183d**: R_f = 0.40 (1:1, EtOAc/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.96 (t, 3H, J = 7.2 Hz), 2.04 (s, 3H), 2.28 (s, 3H), 2.48 (s, 3H), 3.61-3.67 (m, 2H), 4.92

(s, 1H), 7.19-7.20 (m, 2H), 7.28-7.33 (m, 3H), 7.38 (d, 2H, J = 8.5 Hz), 7.93 (d, 2H, J = 8.5 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 13.47, 16.86, 21.57, 25.10, 61.44, 75.41, 79.25, 127.76, 127.93, 128.21, 129.87, 136.68, 138.14, 144.55, 156.93, 169.59 (one sp^2 carbon not located); IR (thin film) 1742vs, 1659s, 1352s, 1154s cm^{-1}.

Aldol reaction of (*2R, 3R*)-*Cis*-1-(*N*-1-bis(4-methoxyphenyl)methyl)-2-carboxyethyl-3-phenylaziridine 58d using isobutyraldehyde as electrophile:

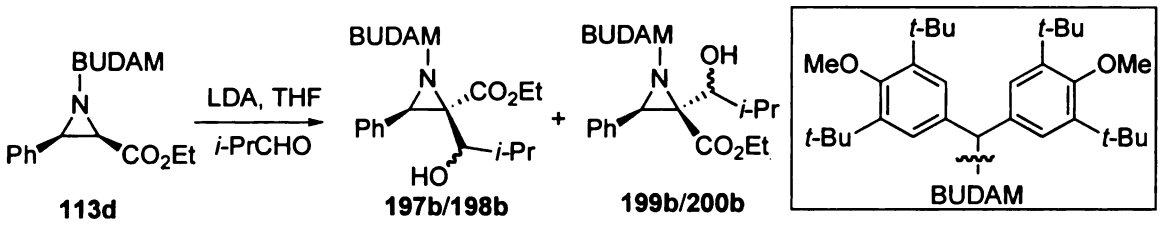


58d **197a/198a** **199a/200a**

The same procedure for the methylation of **58d** was followed except that isobutyraldehyde was used as the electrophile. After silica gel chromatography purification, four aldol products were obtained that could not be fully separated from each other, the diastereomer **197a** or **198a** was the major, the C2-stereo chemistry inversion was determined by comparing the spectra with compound **197b** or **198b**.

Spectral data for **197a** or **198a**: R_f =0.19 (1:5 EtOAc / hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.60 (d, 3H, J = 6.8Hz,), 0.84 (d, 3H, J = 6.8 Hz,), 0.96 (t, 3H, J = 7.1 Hz,), 1.42-1.53 (m, 1H), 3.34 (s, 1H), 3.39 (s, 1H), 3.54-3.59 (m, 1H), 3.64 (s, 3H), 3.76 (s, 3H), 3.77-3.99 (m, 2H), 4.66 (s, 1H), 6.71 (d, 2H, J = 8.8 Hz,), 6.87 (d, 2H, J = 8.8 Hz,), 7.12-7.21 (m, 3H), 7.30 (d, 4H, J = 8.8 Hz,), 7.69 (d, 2H, J = 8.5 Hz,); ^{13}C ($CDCl_3$, 75 MHz) δ 13.64, 17.11, 20.00, 32.59, 49.52, 54.93, 55.06, 57.37, 60.60, 67.46, 75.82, 113.60, 113.74, 126.97, 127.09, 127.59, 127.87, 128.82, 135.74, 135.88, 136.03, 158.46, 158.60, 169.71; IR (thin film) 3500br, vs, 1730m, 1610m, 1510s, 1248s, 1173m, 1034m, 823m cm^{-1}; mass spectrum, m/z (% rel intensity) 446 M^+ -OEt (0.07), 262 (5), 227 (100), 212 (5), 169 (7), 141 (6), 117 (11), 91 (10), 43 (5).

Aldol reaction of (*2R, 3R*)-*Cis*-1-(*N*-1-bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-2-carboxyethyl-3-phenylaziridine 113d using isobutyraldehyde as electrophile:



113d **197b/198b** **199b/200b**

The same procedure for the aldol reaction of **58d** was followed from the aziridine **113d** (80 mg, 0.125 mmol). After silica gel chromatography purification, four aldol products were obtained in a ratio of 1 : 0.5 : 0.7 : 1 in an 81% overall isolated yield (71 mg, 0.1 mmol) (the retention and inversion aldol products were assigned by NOE study).

Spectral data for **197b** or **198b** (fraction 1): R_f =0.45 (1:9 EtOAc / hexane); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.46 (d, 3H, *J* = 6.8 Hz,), 0.79 (d, 3H, *J* = 6.4 Hz,), 1.12 (t, 3H, *J* = 7.1 Hz,), 1.34 (s, 18H), 1.47 (s, 18H), 1.74-1.78 (m, 1H), 2.08 (d, 1H, *J* = 7.1 Hz,), 2.95 (dd, 1H, *J* = 7.3, 8.8 Hz,), 3.58 (s, 3H), 3.70 (s, 3H), 3.87 (s, 1H), 3.89-3.97 (m, 1H), 4.20-4.27 (m, 1H), 4.37 (s, 1H), 7.26-7.30 (m, 3H), 7.37 (s, 2H), 7.44-7.47 (m, 2H), 7.50 (s, 2H).

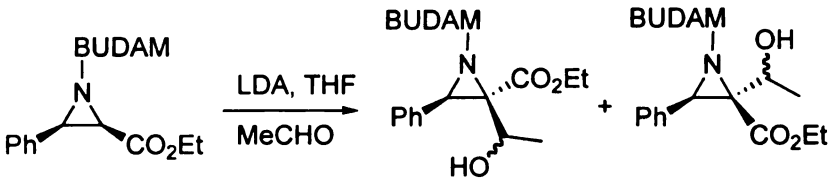
Spectral data for **199b** or **200b** (fraction 2): R_f =0.41 (1:9 EtOAc / hexane); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.85 (d, 1H, *J* = 2.7 Hz,), 0.95 (t, 3H, *J* = 7.1 Hz,), 1.03 (d, 3H, *J* = 6.6 Hz,), 1.15 (d, 3H, *J* = 6.6 Hz,), 1.33 (s, 18H), 1.47 (s, 18H), 2.16-2.21 (m, 1H), 3.03 (s, 1H), 3.32 (dd, 1H, *J* = 2.7, 9.5 Hz,), 3.59 (s, 3H), 3.67 (s, 3H), 3.90-3.95 (m, 2H), 4.45 (s, 1H), 7.18-7.26 (m, 3H), 7.35-7.40 (m, 2H), 7.42 (s, 2H), 7.75 (s, 2H).

Spectral data for **198b** or **197b** (fraction 3): R_f =0.35 (1:9 EtOAc / hexane); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.72 (d, 3H, *J* = 6.6Hz,), 0.75 (d, 3H, *J* = 7.0Hz,), 1.06 (t, 3H, *J* = 7.1Hz,), 1.35 (s, 18H), 1.44 (s, 18H), 3.48 (d, 1H, *J* = 3.4 Hz,), 3.62 (s, 3H), 3.68 (s, 3H), 3.82 (dd, 1H, *J* = 3.4, 8.4 Hz,), 3.86-3.92 (m, 1H), 4.08-4.10 (m, 1H), 4.11 (s, 1H), 4.69

(s, 1H), 7.17-7.24 (m, 3H), 7.25-7.28 (m, 2H), 7.31 (s, 2H), 7.33 (s, 2H) (one H of isopropyl methine proton not located).

Spectral data for **200b** or **199b** (fraction 4): R_f =0.30 (1:9 EtOAc / hexane); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.47 (d, 3H, *J* = 6.8 Hz,), 0.78 (d, 3H, *J* = 6.6 Hz,), 0.97 (t, 3H, *J* = 7.1 Hz,), 1.36 (s, 18H), 1.48 (s, 18H), 3.33 (s, 1H), 3.36 (d, 1H, *J* = 10.5 Hz), 3.49 (dd, 1H, *J* = 4.5, 11.3 Hz), 3.59 (s, 3H), 3.66 (s, 3H), 3.81-3.95 (m, 2H), 4.48 (s, 1H), 7.15-7.29 (m, 3H), 7.33-7.37 (m, 2H), 7.41 (s, 2H), 7.65 (s, 2H).

Aldol reaction of (*2R, 3R*)-*Cis*-1-(*N*-1-bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-2-carboxyethyl-3-phenylaziridine 113d using acetaldehyde as electrophile:



113d **197c/198c** **199c/200c**

The same procedure for the aldol reaction of **113d** was followed using acetaldehyde as electrophile. After silica gel chromatography purification, three aldol products were obtained in a ratio of 1 : 1 : 0.3, as fraction 1 in 35% yield (30 mg, 0.04 mmol), fraction 2 in 33% yield (29 mg, 0.04 mmol) and fraction 3 in 10% yield (8 mg, 0.01 mmol) (the retention and inversion aldol products were assigned by NOE study).

Spectral data for **197c** or **198c** (fraction 1): R_f =0.40 (1:9 EtOAc / hexane); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.95 (d, 3H, *J* = 6.8 Hz,), 1.11 (t, 3H, *J* = 7.1 Hz,), 1.37 (s, 18H), 1.45 (s, 18H), 2.51 (d, 1H, *J* = 9.0 Hz,), 3.35 (qd, 1H, *J* = 6.8, 9.1 Hz,), 3.62 (s, 3H), 3.68 (s, 3H), 3.90 (s, 1H), 3.92-3.99 (m, 1H), 4.12-4.19 (m, 1H), 4.52 (s, 1H), 7.21-7.28 (m, 3H), 7.38-7.40 (m, 2H), 7.42 (s, 2H), 7.49 (s, 2H). ^{13}C ($CDCl_3$, 75 MHz) δ 14.04, 18.92, 32.05, 32.11, 35.70, 35.73, 52.42, 54.07, 61.24, 63.89, 64.07, 69.11, 70.77, 125.69,

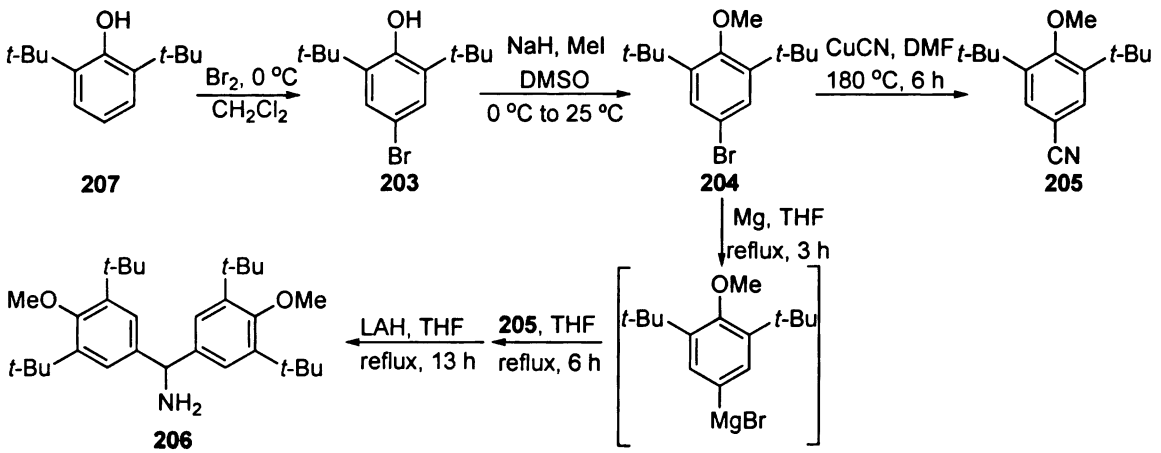
127.31, 127.82, 127.98, 135.51, 136.97, 137.59, 142.99, 143.06, 158.21, 158.37, 168.39 (one sp^2 carbon not located); IR (thin film) 3596m, 2961vs, 1728m, 1412s, 1221s cm^{-1}.

Spectral data for **199c** or **200c** (fraction 2): R_f =0.25 (1:9 EtOAc / hexane); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.77 (br, s, 1H), 0.93 (t, 3H, *J* = 7.1 Hz,), 1.36 (s, 18H), 1.46 (s, 18H), 1.58 (d, 3H, *J* = 6.6 Hz,), 2.98 (s, 1H), 3.62 (s, 3H), 3.66 (s, 3H), 3.83-3.97 (m, 2H), 4.01 (qd, 1H, *J* = 2.7, 5.8 Hz,), 4.48 (s, 1H), 7.17-7.20 (m, 3H), 7.33-7.35 (m, 2H), 7.45 (s, 2H), 7.74 (s, 2H). ^{13}C ($CDCl_3$, 75 MHz) δ 13.90, 20.89, 32.03, 32.06, 35.71, 35.93, 51.10, 58.05, 60.35, 63.89, 64.27, 65.86, 70.60, 125.37, 125.39, 127.03, 127.15, 127.79, 136.11, 137.06, 137.31, 143.09, 144.24, 158.28, 158.61, 167.29; IR (thin film) 3551m, 2961vs, 1742m, 1412s, 1223s cm^{-1}.

Spectral data for **200c** or **199c** (fraction 3): R_f =0.15 (1:9 EtOAc / hexane); ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.63 (d, 3H, *J* = 6.4 Hz), 0.98 (t, 3H, *J* = 7.1 Hz,), 1.37 (s, 18H), 1.44 (s, 18H), 3.41 (s, 1H), 3.51 (d, 1H, *J* = 11.3 Hz), 3.62 (s, 3H), 3.64 (s, 3H), 3.77-3.83 (m, 1H), 3.90 (q, 2H, *J* = 7.1 Hz,), 4.45 (s, 1H), 7.16-7.23 (m, 3H), 7.37-7.38 (m, 2H), 7.43 (s, 2H), 7.56 (s, 2H). ^{13}C ($CDCl_3$, 75 MHz) δ 13.82, 20.77, 32.02, 32.07, 32.15, 35.71, 35.77, 52.41, 60.68, 63.93, 64.25, 67.39, 71.06, 125.40, 125.52, 127.12, 127.56, 127.60, 135.77, 137.26, 137.42, 143.08, 143.44, 158.35, 158.49, 170.08; IR (thin film) 3550br, m, 2963vs, 1699m, 1414s, 1221s cm^{-1}.

7.3 Experimental for chapter four

Large scale preparation of the *N*-BUDAM amine 206:



Preparation of 2,6-di-*tert*-butyl-4-bromophenol 203. A flame-dried 2L three neck round bottom flask equipped with a gas inlet, rubber septum, and a pressure-equalizing dropping funnel was charged with phenol **207** (206 g, 1.0 mol) and CH_2Cl_2 (400 mL) under the protection of argon. The gas outlet tube was connected to a gas trap containing 0.5 M NaOH to absorb the generated HBr. The dropping funnel was charged with bromine (53 mL, 1.05 mol) and CH_2Cl_2 (40 mL). The reaction vessel was immersed into a 0 °C bath, and the bromine-CH_2Cl_2 solution was added dropwise to the phenol solution over 80 minutes through the dropping funnel. After the addition, the reaction mixture was stirred at 0 °C for additional 20 minutes, then Na_2SO_3 (120 mL, aq. sat.) was added slowly at 0 °C, and the mixture was allowed to warm up to room temperature until the light orange color disappeared. The reaction mixture was poured slowly into a 3 L separation funnel containing $NaHCO_3$ (800 mL, aq. sat.), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product **203** as light yellow solid. Purification by crystallization from ethanol-water (mixture of 260 mL ethanol and 36 mL water) afforded product **203** as light yellow

crystals (mp. 80-81 °C) in 78% yield (225 g, 780 mmol) from the first crop. R_f = 0.4 (hexane). Other data see reference.[91]

2,6-di-*tert*-butyl-4-bromoanisole 204.[89a] To a flame-dried 2 L three neck round bottom flask equipped with a mechanical stirring device was added anhydrous DMSO (1.4 L, freshly distilled and stored over 4Å MS), NaH (56 g, 1.4 mol) (60% suspension in oil) under the protection of argon. The flask was then submerged into a 0 °C ice bath and stirred vigorously to avoid DMSO freezing at 0 °C, then compound **203** (167 g, 588 mmol) was slowly added portion-wise over 20 minutes. After the addition, the suspension was stirred at 0°C for 15 minutes, followed by the addition of MeI (150 mL, 2.3 mol) via addition funnel over 15 minutes, then the mixture was stirred at 0 °C for 15 minutes before the ice bath was removed. The reaction mixture was allowed to gradually warm up to room temperature (for about 2 h), and was then stirred at room temperature for an additional 3 h. The reaction mixture was cooled to 0°C, and diluted with hexane (400 mL), and then the mixture was poured into a 4 L Erlenmeyer flask containing 500 mL hexane at 0 °C, the mixture was stirred with a mechanical stirrer and the 500 mL water was added slowly until two layers appeared. The organic layer was collected, and the aqueous layer was extracted with hexane (200 mL × 3). The combined organic layer was then washed with water (400 mL × 4), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product **204** as a light yellow solid. The crude product was divided into two parts and each was purified by silica gel chromatography (80mm × 600 mm columns, hexane as eluent) to give **204** as white solid in 100% yield (181 g, 588 mmol). R_f = 0.4 (hexane).

2,6-di-*tert*-butyl-4-cyanoanisole 205. A flame-dried 2 L three neck round bottom flask filled with argon and equipped with a refluxing condenser was charged with compound **204** (91.7 g, 308 mmol), CuCN (32.7 g, 365 mmol) and anhydrous DMF (600 mL, freshly distilled and stored over 4Å MS). The reaction mixture was purged with argon under the

surface of the solution for 15 minutes, then the argon inlet was removed and a argon balloon was attached on the top of the condenser through a rubber septum stopper (the flask was sealed with Teflon stoppers). The mixture was heated to reflux in a 180 °C oil bath for 8 h. During the refluxing, the solid CuCN dissolved after approximately 2 h and a red precipitate appeared slowly. The reaction mixture was then slowly cooled gradually to room temperature, and then poured into a Erlenmeyer flask containing a solution of ethylene diamine (280 mL ethylene diamine in 2500 mL water) at 0 °C, then the ice-bath was removed and 1000 mL benzene was added and the resulting mixture was stirred at room temperature for 20 minutes and loaded into a separation funnel. The water layer was extracted with benzene (400 mL × 4). The combined organic layer was washed with 6% NaCN solution (500 mL), and then water (600 mL × 2), dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product as a brown semi-solid. The crude product was divided into two parts, and each was purified by silica gel chromatography (80mm × 600 mm columns, 1:3 CH_2Cl_2/hexane as elute) gave **205** as white solid (mp. 72-74 °C) in 91% yield (68 g, 280 mmol). The light yellow color that was present in some of the earlier fractions could be removed by crystallization (Hexane).

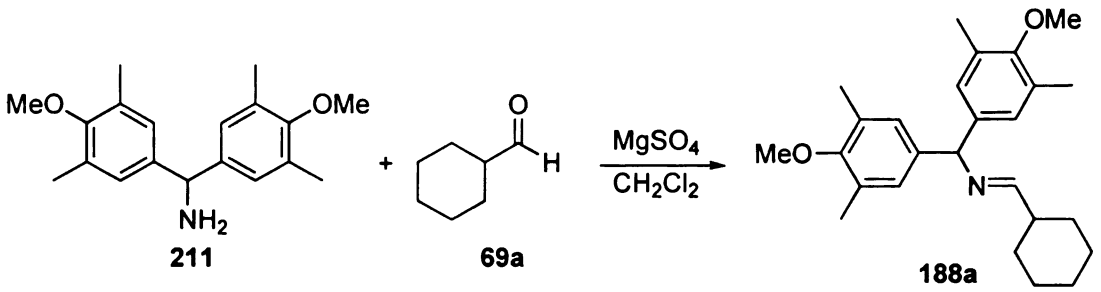
Spectral data for **205**:[89a] R_f = 0.3 (1:3 CH_2Cl_2/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 18H), 3.69 (s, 3H), 7.51 (s, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 31.67, 35.94, 64.63, 106.72, 119.75, 130.74, 145.48, 163.55.

***Bis*-(2,6-di-*tert*-butyl-4-methoxyphenyl)methineamine 206.** To a flame-dried 1 L three neck round bottom flask filled with argon and equipped with refluxing condenser was added magnesium (13.2 g, 550 mmol), THF (500 mL), compound **204** (65.6 g, 220 mmol) and a few crystals of iodine. The mixture was slowly heated to reflux under the protection of argon and kept at reflux for 3 h. The resulting light brown solution was allowed to cool down to room temperature and transferred via cannula to a flame-dried 2 L three neck flask equipped with refluxing condenser under the protection of argon. At

the same time, to a flame-dried 1L flask filled with argon was added compound **205** (49 g, 200 mmol) and THF (500 mL), and then this solution was then transferred via cannula to the 2 L flask containing the Grignard reagent over 10 min at room temperature. The resulting mixture was heated to reflux, which was maintained for 5 h under the protection of argon, then allowed to cool down to room temperature, and then to 0°C. To this mixture was transferred a suspension of $LiAlH_4$ (8.79 g, 220 mmol) in THF (300 mL) via cannula. The $LiAlH_4$ suspension was prepared in a flame-dried 500 mL flask filled with argon and pre-cooled at 0 °C. The ice bath was then removed, and the reaction mixture was heated to reflux, which was maintained for 15 h. Upon completion, the greenish slurry was cooled down to room temperature, and carefully quenched by the slow addition of water (9 mL), then 10% NaOH solution (9 mL), and then H_2O (25 mL). The resulting slurry was filtered through a Celite pad and washed with ether until no amine was left (monitored by TLC). If filtration took too long a time, a white solid may appear in the organic phase, which may be the bicarbonate salt of amine **206** formed from CO_2 and H_2O, and can be recovered by treating with 0.5 M NaOH and a subsequent extraction. The combined organic layer was washed with NaCl (aq. sat.) and concentrated under reduced pressure to give the crude product **206** as a white solid. The crude product was washed with hexanes before purification by crystallization (1:15 EtOAc / Hexane). Which gave **206** as white crystals (mp. 179-180 °C). The mother liquor and the hexane washing were combined and concentrated under reduced pressure and the residual product was purified by silica gel chromatography (50mm × 400 mm column, 1:5 to 1:2 EtOAc/hexane as elute) to give **206** as a white solid. The overall yield of product **206** after crystallization and chromatography is 91% (84 g, 182 mmol).

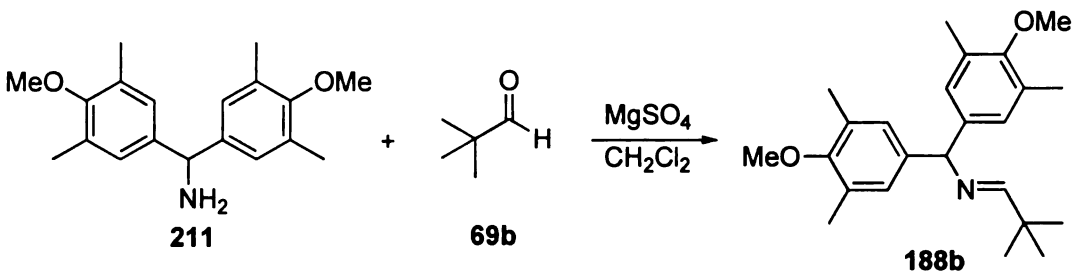
Spectral data for **206**:[37d] R_f = 0.25 (1:5 EtOAc/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 36H), 1.76 (s, 2H), 3.66 (s, 6H), 5.07 (s, 1H), 7.21 (s, 4H); ^{13}C ($CDCl_3$, 75 MHz) δ 32.09, 35.77, 59.81, 64.10, 125.17, 139.54, 143.14, 158.17.

***N*-Cyclohexylmethylidene-*bis*(3,5-dimethyl-4-methoxyphenyl)methylamine 188a.**



The standard procedure described for the preparation of imine **68a** was followed with amine **211** (5.09 g, 17 mmol). The crude product was purified by crystallization (1: 60 EtOAc / hexane) to give **188a** as white solid (mp. 108-109 °C) in 71% yield (4.74 g, 12 mmol).

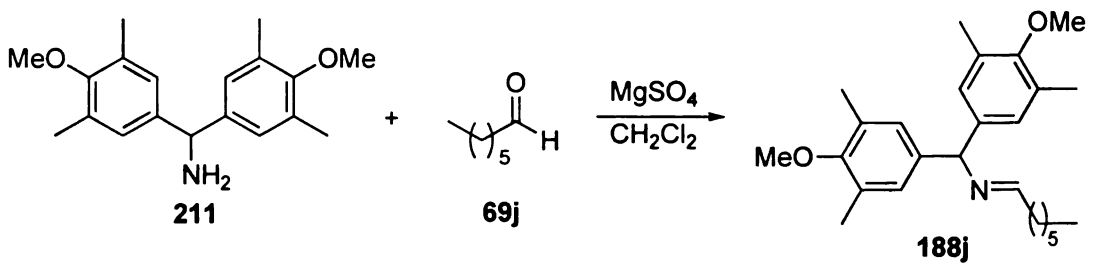
Spectral data for **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17-1.34 (m, 5H), 1.64-1.84 (m, 5H), 2.19-2.35 (m, 1H), 2.23 (s, 12H), 3.67 (s, 6H), 5.05 (s, 1H), 6.91 (s, 4H), 7.59 (d, 1H, *J* = 5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.17, 25.41, 25.99, 29.78, 43.50, 59.58, 77.42, 127.74, 130.48, 139.39, 155.69, 168.59; IR (thin film): 2926s, 1665m, 1483s 1221s, 1142m, 1017s cm^{-1}; Mass spectrum *m/z* (% rel intensity) 393 M^+ (0.22), 283 (100), 268 (15), 163 (54), 142 (24), 134 (15), 77 (11), 44 (10).



***N*-(1,1'-dimethylethylidene)-bis(4-methoxy-3,5-dimethylphenyl)methylamine 188b.**

The standard procedure described for the preparation of imine **68a** was followed with amine **211** (5.56 g, 18.5 mmol). The crude product was purified by crystallization (1: 60 EtOAc / hexane) to give **188b** as white solid (mp. 90-91 °C) in 70% yield (4.78 g, 13 mmol).

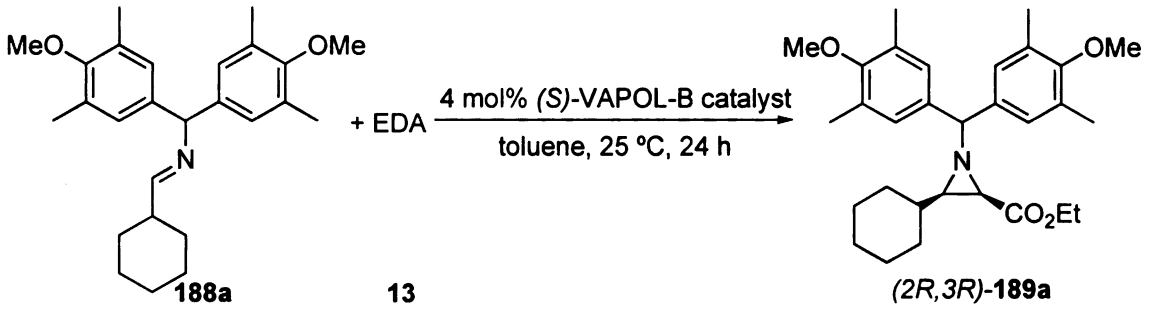
Spectral data for **188b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 2.23 (s, 12H), 3.68 (s, 6H), 5.08 (s, 1H), 6.91 (s, 4H), 7.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.20, 27.02, 36.31, 59.56, 76.71, 127.69, 130.39, 139.60, 155.60, 171.10; IR (thin film): 2955vs, 1663m, 1483s, 1221s, 1017s cm^{-1}; Mass spectrum *m/z* (% rel intensity) 367 M^+ (0.8), 283 (100), 268 (22), 253 (12), 210 (11), 195 (14), 178 (8), 141 (34), 133 (11), 118 (19), 41 (10).



***N*-hexylidene-bis(4-methoxy-3,5-dimethylphenyl)methylamine 188j**: The standard procedure described for the preparation of imine **68a** was followed with amine **211**. The crude product was a light yellow oil with 95% mass recovery, and was used in the next step without purification.

Spectral data for **188j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, 3H, *J* = 6.7 Hz), 1.25-1.33 (m, 6H), 1.50-1.55 (m, 2H), 2.22 (s, 12H), 2.28-2.34 (m, 2H), 3.66 (s, 6H), 5.08 (s, 1H), 6.91 (s, 4H), 7.74 (t, 1H, *J* = 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.97, 16.14, 22.55, 26.02, 28.94, 31.59, 35.87, 59.56, 77.68, 127.74, 130.53, 139.21, 155.71, 165.03; IR (thin film): 2928s, 1667m, 1483s 1219s, 1014vs cm^{-1}; Mass spectrum *m/z* (% rel intensity) 395 M^+ (0.45), 325 (24), 283 (100), 268 (42), 253 (32), 237 (24), 210 (25), 163 (23), 141 (51), 134 (21), 126 (27), 118 (21), 111 (14), 43 (16).

General procedure for the asymmetric aziridination illustrated for the synthesis of *(2R, 3R)-Cis*-1-(*N*-1-bis(3,5-dimethyl-4-methoxyphenyl)methyl)-2-carboxyethyl-3-cyclohexylaziridine 189a.

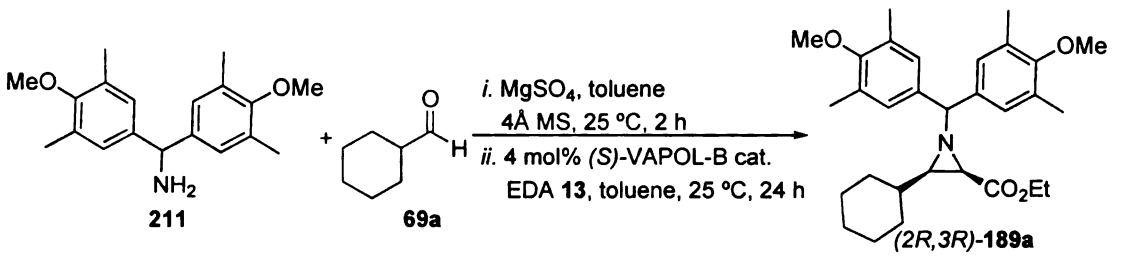


188a 13 (2R,3R)-189a

Method A: Aziridine formation from pure imine 188a.

The procedure for the synthesis of **58a** was followed with the following difference: the catalyst was prepared by a new catalyst generation method: A magnetic stir bar was added to a 25 mL flame-dried Schlenk flask filled with argon. To the flask was added (*S*)-VAPOL (22 mg, 0.04 mmol) and $B(OPh)_3$ (43 mg, 0.16 mmol), toluene (1.5 mL) and H_2O (0.7 μL, 0.04 mmol). The Teflon valve of the flask was closed and the flask was heated at 80 °C for 1 h. The threaded Teflon valve was opened to gradually apply high vacuum (0.5 mm Hg) and to remove the solvent. The vacuum was maintained for a period of 30 min at 80 °C. The flask was then filled with argon and allowed to cool to room temperature, then 1 mL toluene was added to dissolve the catalyst, the catalyst solution was transferred to the flame-dried flask that containing imine **188a** (491 mg, 1 mmol) via syringe. The reaction mixture was stirred for 5 minutes to give an orange solution. To this solution was rapidly added ethyl diazoacetate (114 μL, 1.1 mmol). The product was obtained after silica gel chromatography (35 mm × 400 mm column, 40:20:1 hexanes / CH_2Cl_2 / EtOAc as eluent) as a colorless semi solid (mp. 47- 49 °C) in 99% yield (475 mg, 0.99 mmol). An optical purity of 94% ee was determined by HPLC analysis using Chiralcel OD column, (223nm, 99:1 hexane/*i*PrOH as eluent at 0.7 mL/min). Retention times: R_t = 10.06 min for *(2R, 3R)*-**189a** and R_t = 12.37 min for *(2S, 3S)*-**189a**.

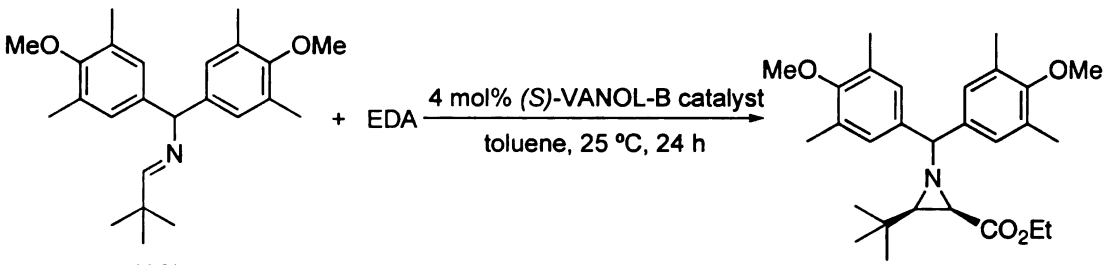
Method B: One-pot aziridine formation from amine and aldehyde



To a 25 mL flame-dried round bottom flask filled with argon was added amine **211** (299 mg, 1 mmol), 4Å MS (1 g, activated) and toluene (2 mL). After stirring for 2 minutes, aldehyde **69a** (133 μL, 1.1 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours under the protection of argon. At the same time, the catalyst was prepared *in situ* using the new catalyst generation method as described in method A from (*S*)-VAPOL (22 mg, 0.04 mmol), triphenyl borate (43 mg, 0.15 mmol) and H_2O (0.7 μL, 0.04 mmol). The catalyst was then dissolved in 2 mL toluene and transferred to the flask containing solution of the *in situ* generated imine **188a** via syringe (the extention of imine formation was monitored by the ^1H NMR analysis from a small sample (<2% by volume) taken from the reaction mixture). The mixture was stirred for 5 minutes before the addition of EDA **13** (114 μL, 1.1 mmol) and the resulting mixture was stirred at room temperature for 40 hours. Upon completion, 3 mL hexane was added and the solvent was removed under reduced pressure. To the remainder, 5 mL CH_2Cl_2 and 3 g silica gel was added, and then the solvent was removed for dry loading onto to a silica gel column, and purification using the same condition that was used in method A. Product **189a** was obtained in 94% yield (450 mg, 0.94 mmol) with 93% ee as determined by HPLC analysis.

Spectral data for *(2R, 3R)*-**189a**: R_f = 0.21 (40:20:1 hexane/CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.46-0.57 (m, 1H), 0.87-1.19 (m, 4H), 1.21 (t, 3H, *J* = 7.1 Hz), 1.22-1.32 (m, 2H), 1.40-1.60 (m, 4H), 1.71-1.76 (m, 1H), 2.16 (m, 1H), 2.19 (s, 6H), 2.20 (s, 6H), 3.35 (s, 1H), 3.60 (s, 3H), 3.63 (s, 3H), 4.10-4.25 (m, 2H), 6.95 (s, 2H), 7.10 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.85, 15.56, 15.67, 24.91, 25.09, 25.73, 29.65, 30.38,

35.88, 42.97, 51.76, 59.01, 59.07, 60.12, 77.01, 126.90, 128.10, 129.84, 129.95, 137.16, 137.71, 155.31, 155.83, 169.30; IR (thin film) 2928vs, 1744s, 1483s, 1221s, 1181s, 1017m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 479 M^+ (0.7), 283 (100), 268 (25), 253 (12), 237 (7), 210 (7), 195 (9), 141 (8), 95 (10), 67 (16), 55 (10), 41 (16); $[\alpha]^{23}_D$ +119.0 (c 1.0, CH_2Cl_2) on 94 % ee material (HPLC).



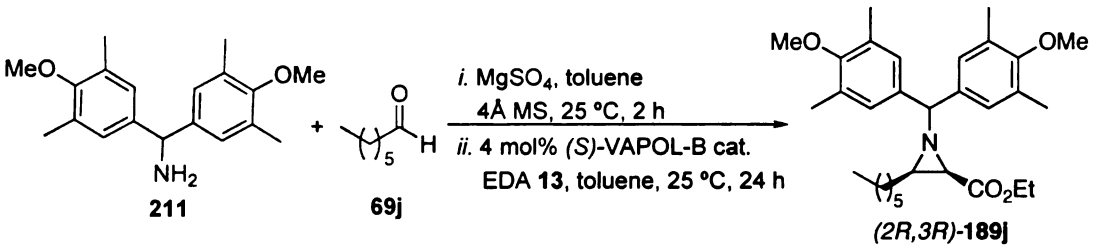
188b **13** *(2R,3R)*-**189b**

***(2R, 3R)-Cis*-1-(*N*-1-bis(4-methoxy-3,5-di-methylphenyl)methyl)-2-carboxyethyl-3-(1,1-dimethylethyl)aziridine 189b**: The method A for the preparation of **189a** was followed except the following difference: The *(S)*-VANOL catalyst was used. Purification by silica gel chromatography gave product **189b** as colorless semi-liquid in 97% yield (439 mg, 0.97 mmol). An optical purity of 96% ee was determined by HPLC analysis using Chiralcel OD column, (225nm, 99:1 hexane/*i*-PrOH as eluent at 1.0 mL/min). Retention times: R_t = 6.80 min for *(2R, 3R)*-**189b** and R_t = 10.55 min for *(2S, 3S)*-**189b**.

One-pot preparation of 189b: The method B for the preparation of **189a** was followed except for the following difference: The catalyst loading was 10 mol% and was prepared from *(S)*-VAPOL (54 mg, 0.1 mmol), triphenyl borate (116 mg, 0.4 mmol) and H_2O (1.8 μL, 0.1 mmol). Purification by silica gel chromatography gave product **189b** as colorless semi-liquid in 82% yield (374 mg, 0.8 mmol). An optical purity of 94% ee was determined by HPLC analysis.

Spectral data for *(2R, 3R)*-**189b**: R_f = 0.28 (40:20:1 hexane/CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.72 (s, 9H), 1.29 (t, 3H, *J* = 7.1 Hz), 1.70 (d, 1H, *J* = 7.3 Hz), 2.11 (d, 1H, *J* = 7.2 Hz), 2.24 (s, 6H), 2.26 (s, 6H), 3.38 (s, 1H), 3.63 (s, 3H), 3.66 (s, 3H),

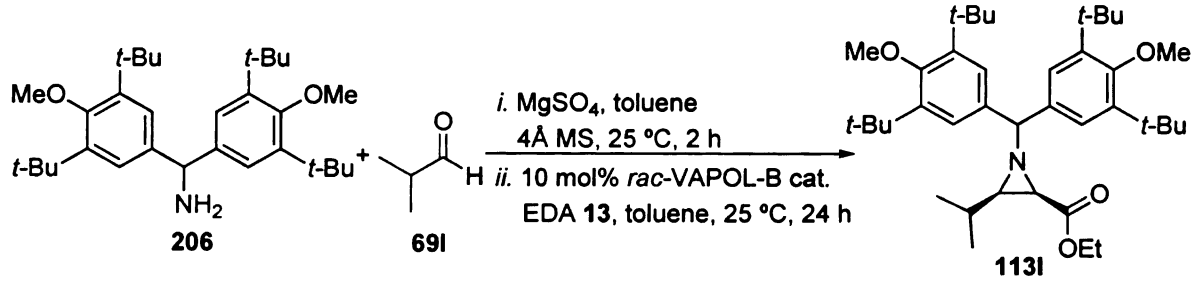
4.05-4.26 (m, 2H), 7.04 (s, 2H), 7.30 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.92, 15.84, 15.96, 27.24, 31.39, 43.16, 55.94, 59.20, 59.27, 60.24, 78.20, 127.30, 128.18, 130.01, 137.77, 138.74, 155.51, 155.98, 169.66 (one sp^2 carbon not located); IR (thin film) 2953vs, 1747s, 1481s, 1221s, 1181s, 1017m cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 453 M^+ (1), 283 (100), 268 (45), 253 (26), 237 (17), 225 (11), 210 (13), 195 (17), 164 (9), 141 (26), 132 (11), 127 (12), 91 (11), 69 (18), 55 (37), 41 (55); $[\alpha]^{23}_D$ +110.0 (c 1.0, CH_2Cl_2) on 94 % ee material (HPLC).



One-pot preparation of *(2R, 3R)-cis*-1-(*N*-1-bis(4-methoxy-3,5-dimethylphenyl)methyl)-2-carboxyethyl-3-hexylaziridine 189j: The method B for the preparation of **189a** was used. Purification by silica gel chromatography (40:10:1 hexane/CH_2Cl_2/EtOAc) gave product **189j** as a semi-liquid (318 mg, 0.66 mmol) in 66% yield. An optical purity of 94% ee was determined by HPLC analysis using Chiralcel OD column, (223nm, 99:1 hexane/*i*PrOH as eluent at 0.7 mL/min). Retention times: R_t = 9.27 min for *(2R, 3R)*-**189j** and R_t = 11.17 min for *(2S, 3S)*-**189j**.

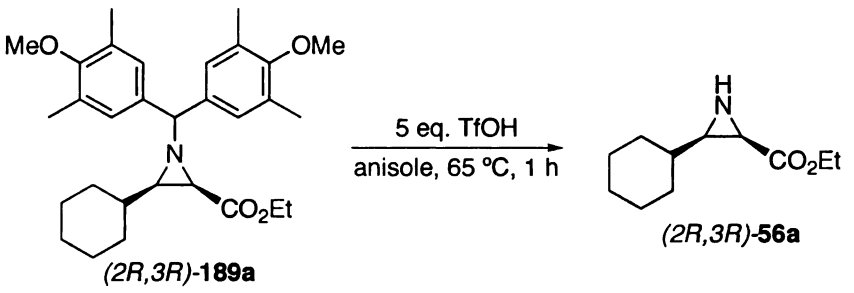
Spectral data for *(2R, 3R)*-**189j**: R_f = 0.30 (40:20:1 hexane/CH_2Cl_2/EtOAc); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, *J* = 7.2 Hz), 0.99-1.03 (m, 1H), 1.14-1.24 (m, 7H), 1.27 (t, 3H, *J* = 7.1 Hz), 1.48-1.56 (m, 2H), 1.97-2.00 (m, 1H), 2.23 (d, 1H, *J* = 6.8 Hz), 2.26 (s, 12H), 3.43 (s, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 4.16-4.25 (m, 2H), 7.04 (s, 2H), 7.12 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.90, 14.22, 15.99, 16.05, 22.33, 27.08, 27.83, 28.70, 31.69, 43.46, 46.88, 59.42, 60.53, 77.24, 127.27, 128.01, 130.31, 130.36, 137.68, 138.10, 155.69, 156.04, 169.57 (one sp^3 carbon not located); IR (thin film) 2928vs, 1746s, 1483s, 1221s, 1181s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 481 M^+ (0.5),

283 (100), 268 (13), 253 (7), 142 (7), 55 (13), 41 (16); $[\alpha]^{23}_D$ +81.8 (c 1.0, CH_2Cl_2) on 94 % ee material (HPLC).



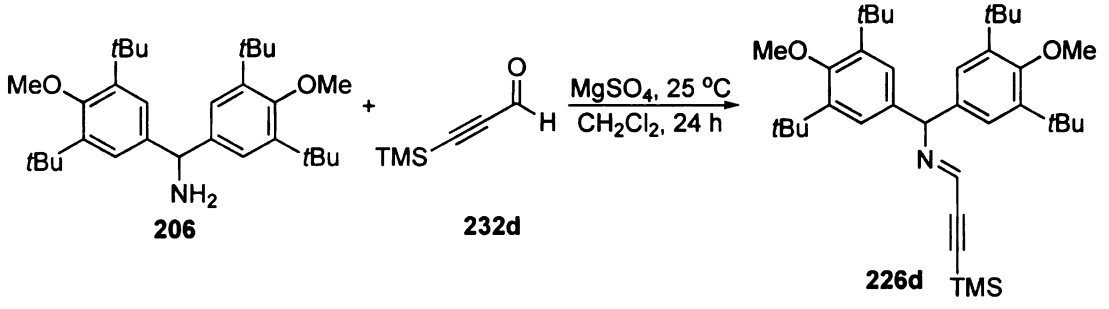
One-pot preparation of *cis*-1-(*N*-1-bis(4-methoxy-3,5-di-*tert*-butylphenyl)methyl)-2-carboxyethyl-3-ethylaziridine 113l: The method B for the preparation of **189a** was employed except the following difference: The catalyst was prepared from *rac*-VAPOL (54 mg, 0.1 mmol), $B(OPh)_3$ (116 mg, 0.4 mmol) and H_2O (1.8 μL, 0.1 mmol). Purification by silica gel chromatography (19:1 hexane/EtOAc as eluent) gave product **113l** as viscous liquid in 67% yield (410 mg, 0.67 mmol).

Spectral data for **113l**: R_f = 0.3 (1:20 EtOAc/Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.55 (d, 3H, *J* = 6.3Hz,), 0.79 (d, 3H, *J* = 7.5Hz,), 1.24 (t, 3H, *J* = 7.1Hz,), 1.37 (s, 18H), 1.39 (s, 18H), 1.58-1.65 (m, 1H), 1.75 (dd, 1H, *J* = 6.6, 9.3Hz,), 2.27 (d, 1H, *J* = 6.6Hz,), 3.53 (s, 1H), 3.61 (s, 3H), 3.64 (s, 3H), 4.17 (q, 2H, *J* = 7.1Hz,), 7.10 (s, 2H), 7.32 (s, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 14.22, 19.61, 20.43, 27.26, 31.98, 32.06, 35.58, 35.67, 43.50, 53.91, 60.50, 63.97, 64.09, 77.89, 125.47, 126.62, 136.20, 136.90, 142.70, 142.77, 158.13, 158.81, 169.88; IR (thin film) 2961vs, 1747s, 1414s, 1221m, 1192m, 1115m, 1015m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 607 M^+ (0.12), 451 (98), 421 (7), 379 (7), 218 (28), 183 (24), 81 (17), 57 (100), 41 (38).



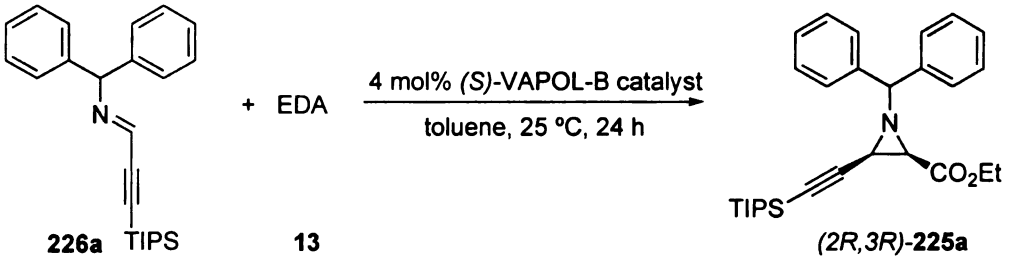
(2R,3R)-**189a** *(2R,3R)*-**56a**

General procedure for the deprotection of *N*-BUDAM or *N*-MEDAM aziridines – illustrated in the preparation of *(2R, 3R)-cis*-2-carboxyethyl-3-cyclohexylaziridine 56a. To a 25 mL flame-dried round bottom flask filled with argon was added (*2R, 3R*)-**189a** (140 mg, 0.29 mmol) and freshly distilled anisole (2 mL) at room temperature. The mixture was stirred, after all was dissolved, triflic acid (120 μL, 1.5 mmol) was added drop-wise. The reaction mixture was stirred at room temperature for 10 minutes and then put into a 65 °C bath for 1 h under the protection of argon to give a dark red solution. Upon completion (monitored by TLC), the reaction mixture was cooled to room temperature and quenched by addition of Na_2CO_3 (aq. sat.) until the pH was higher than 9. After the addition of 3 mL ether and 1 mL water, the organic layer was separated and the water layer was extracted with ether (5 mL × 3). The combined organic layer was washed with NaCl (aq. sat.) (10 mL), dried over $MgSO_4$. The ether was removed by rotary evaporation and the remaining anisole solution was directly loaded onto a silica gel column for purification (18 mm × 230 mm, Et_3N neutralized silica gel. 1:1 ether / hexanes as eluent) The product **56a** was afforded as a white solid in 90% isolated yield (51 mg, 0.26 mmol). The spectral data see the same compound reported in chapter two.



***N*-(4-trimethylsilyl)ethynyl)-bis(4-methoxy-3,5-di-*tert*-butylphenyl)methylamine 226d.** The standard procedure described for the preparation of imine **68a** was followed with amine **206** (7 g, 15 mmol) and aldehyde **232d** (2.07 g, 16.5 mmol). The crude product was a mixture of *trans/cis* imines in a ratio of 1.5 : 1, and was purified by crystallization (1: 30 EtOAc / hexane) to give **226d** as white solid as a mixture of *trans/cis* in a ratio of 19 : 1 (mp. 142-143 °C) in 75% yield (6.46 g, 11 mmol).

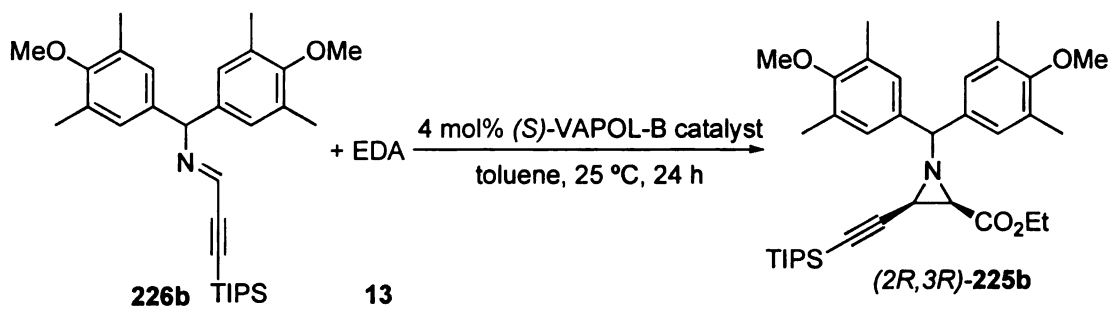
Spectral data for **226d**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 0.32 (s, 9H), 1.43 (s, 36H), 3.71 (s, 6H), 6.21 (s, 1H), 7.21 (s, 4H), 7.68 (s, 1H); ^{13}C ($CDCl_3$, 125 MHz) δ -0.42, 32.06, 35.75, 64.15, 72.55, 76.57, 97.12, 126.22, 136.62, 141.25, 143.16, 158.44; IR (thin film) 2959s, 2180w, 1412m, 1221s, 844s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 575 M$^+$ (10), 451 (100), 421 (9), 379 (7), 218 (15), 197 (11), 182 (30), 168 (11), 128 (10), 110 (10), 83 (19), 73 (64), 57 (97), 41 (45).



226a **13** *(2R,3R)*-**225a**

***(2R,3R)-Cis*-1-benzhydryl-2-carboxyethyl-3-(2-(triisopropylsilyl)ethynyl)aziridine 225a.** The method A for the preparation of aziridine **189a** was followed with imine **226a** (375 mg, 1 mmol) and *(S)*-VAPOL (22 mg, 0.04 mmol). Purification by silica gel chromatography (35mm × 400 mm column, 40:20:1 hexane/CH_2Cl_2/EtOAc as eluent) gave product **225a** as colorless semi-liquid in 91% yield (420 mg, 0.91 mmol). An optical purity of 32% ee was determined by HPLC analysis using Chiralcel OD-H column, (225nm, 95:5 hexane/*i*PrOH as eluent at 0.7 mL/min). Retention times: R_t = 3.79 min for *(2S, 3S)*-**225a** and R_t = 7.24 min for *(2R, 3R)*-**225a**.

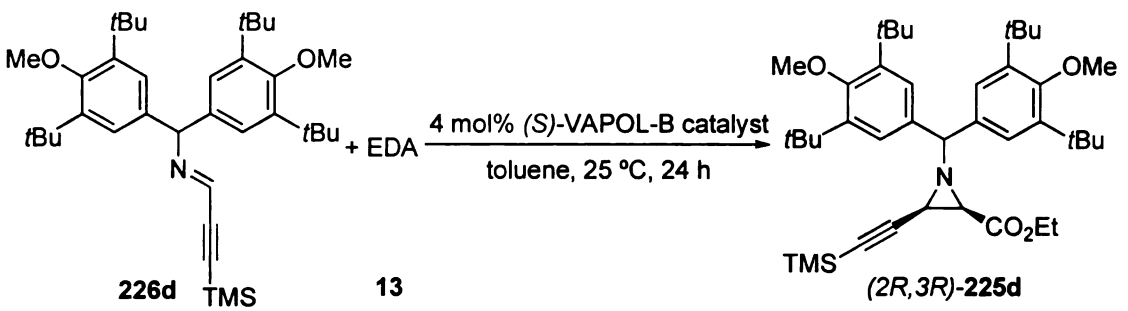
Spectral data for **225a**: R_f = 0.42 (1:9 EtOAc/Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.14-1.17 (m, 3H), 1.16 (d, 18H, *J* = 0.9 Hz), 1.31 (t, 3H, *J* = 7.1 Hz), 2.58 (d, 1H, *J* = 6.5Hz), 2.61 (d, 1H, *J* = 6.5 Hz), 3.85 (s, 1H), 4.14-4.17 (m, 1H), 4.28-4.32 (m, 1H), 7.25-7.30 (m, 2H), 7.32-7.38 (m, 4H), 7.53 (d, 2H, *J* = 7.8Hz), 7.60 (d, 2H, *J* = 7.7Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 11.01, 14.08, 18.41, 18.42, 34.52, 44.48, 60.88, 76.60, 83.93, 101.99, 127.11, 127.18, 127.34, 127.42, 128.21, 128.34, 141.77, 166.90 (one sp^2 carbon not located); IR (thin film) 2944vs, 2888s, 2150w, 1755s, 1184s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 461 M^+ (0.1), 294 (16), 167 (100), 152 (68), 138 (11), 110 (12), 95 (10), 83 (11), 59 (19), 43 (24). $[\alpha]^{23}_D$ –14.6 (c 1.0, CH_2Cl_2) on 32% ee *(2R, 3R)*-**225a** (HPLC).



***(2R, 3R)-Cis*-(*N*-1-bis(4-methoxy-3,5-dimethylphenyl)methyl)-2-carboxyethyl-3-(2-(triisopropylsilyl)ethynyl)aziridine 225b.** The method A for the preparation of aziridine **225a** was followed with imine **226b** (491 mg, 1 mmol). Purification by silica gel chromatography gave product **225b** as a colorless semi-liquid in 87% yield (505 mg, 0.87 mmol). An optical purity of 44% ee was determined by HPLC analysis using Chiralcel OD-H column, (223nm, 99:1 hexane/*i*PrOH as eluent at 0.7 mL/min). Retention times: R_t = 9.43 min for *(2R, 3R)*-**225b** and R_t = 11.23 min for *(2S, 3S)*-**225b**.

Spectral data for **225b**: R_f = 0.35 (1:9 EtOAc/Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.04-1.09 (m, 3H), 1.07 (d, 18H, *J* = 1.8 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 2.24 (s, 6H), 2.26 (s, 6H), 2.46 (d, 1H, *J* = 6.5Hz), 2.49 (d, 1H, *J* = 6.5Hz), 3.53 (s, 1H), 3.67 (s, 3H), 3.68 (s, 3H), 4.08-4.12 (m, 1H), 4.23-4.28 (m, 1H), 7.08 (s, 2H), 7.15 (s, 2H); ^{13}C ($CDCl_3$, 75

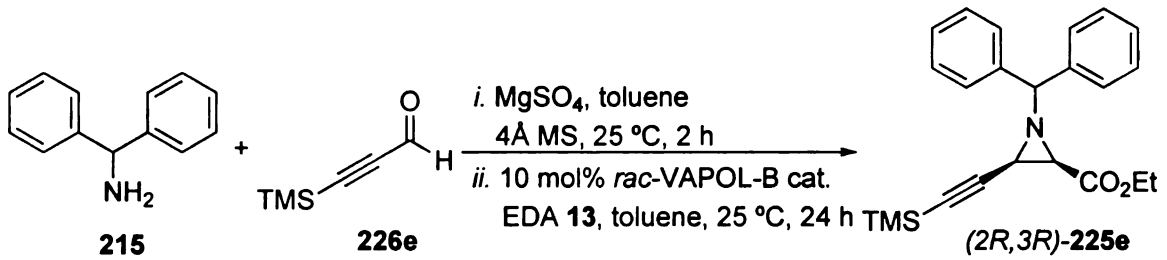
MHz) δ 11.42, 14.54, 16.42, 18.83, 18.86, 35.13, 45.10, 59.77, 59.80, 61.24, 76.62, 84.00, 102.49, 127.74, 128.04, 130.83, 130.90, 137.55, 137.56, 156.26, 156.45, 167.54; IR (thin film) 2944vs, 2180w, 1757s, 1728m, 1483s, 1221s cm^{-1}; mass spectrum, m/z (% rel intensity) 577 M^+ (0.1), 283 (100), 268 (7), 43 (11). $[\alpha]^{23}_D$ −18.4 (c 1.0, CH_2Cl_2) on 44% ee *(2R, 3R)*-**225b** (HPLC).



***(2R, 3R)-Cis*-(*N*-1-bis(4-methoxy-3,5-di-*tert*-butylphenyl)methyl)-2-carboxyethyl-3-(2-(trimethylsilyl)ethynyl)aziridine 225d.** The method A for the preparation of aziridine **225a** was followed with imine **226d** (576 mg, 1 mmol) (*trans/cis* = 19 : 1). Purification by silica gel chromatography (35mm × 400 mm column, 30:1 hexane/EtOAc as eluent) gave product **225d** as white solid (mp. 58-60 °C) in 93% yield (615 mg, 0.93 mmol). After converting the compound **225d** to **233d**, an optical purity of 85% ee was determined by HPLC analysis using Chiralcel OD-H column, (225nm, 99:1 hexane/*i*PrOH as eluent at 1.0 mL/min). Retention times: R_t = 3.46 min for *(2S, 3S)*-**233d** and R_t = 4.05 min for *(2R, 3R)*-**233d**.

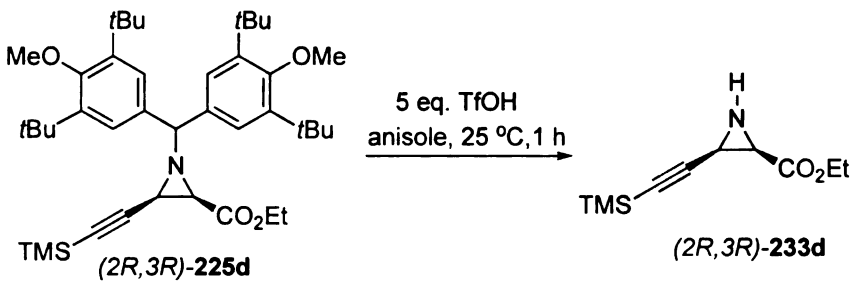
Spectral data for *(2R,3R)*-**225d**: R_f = 0.53 (1:9 EtOAc/Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.17 (s, 9H), 1.34 (t, 3H, *J* = 7.1 Hz), 1.42 (s, 18H), 1.44 (s, 18H), 2.58 (d, 1H, *J* = 6.6 Hz), 2.66 (d, 1H, *J* = 6.6 Hz), 3.69 (s, 3H), 3.70 (s, 3H), 3.78 (s, 1H), 4.24-4.29 (m, 2H), 7.26 (s, 2H), 7.28 (s, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ -0.23, 14.46, 32.04, 32.09, 35.45, 35.71, 35.74, 44.79, 61.09, 64.01, 76.28, 87.67, 100.32, 125.69, 125.71, 135.38, 135.71, 142.94, 143.11, 158.45, 158.53, 167.81 (one sp^3 carbon not located); IR (thin film) 2961vs, 1757m, 1730m, 1414s, 1223s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 661

M^+ (0.4), 451 (92), 421 (15), 379 (9), 218 (10), 183 (15), 96 (13), 73 (27), 57 (100), 43 (36); Anal calcd for $C_{41}H_{63}NO_4Si$: C, 74.38; H, 9.59; N, 2.12. Found: C, 74.10; H, 10.04; N, 2.11. $[\alpha]^{23}_D$ -1.9 (c 1.0, CH_2Cl_2) on 84% ee material (HPLC).



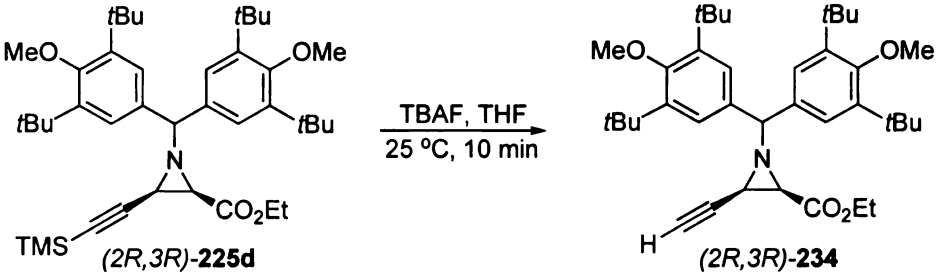
***Cis*-1-benzhydryl-2-carboxyethyl-3-(2-(trimethylsilyl)ethynyl)aziridine 225e.** The method B for the preparation of aziridine **189a** was followed with amine **215** (183 mg, 1 mmol) and *(S)*-VAPOL (54 mg, 0.1 mmol). Purification by silica gel chromatography (35mm x 400 mm column, 20:1 hexane/EtOAc as eluent) gave product **225e** as a white solid (mp. 124-125 °C) in 78% yield (294 mg, 0.78 mmol). An optical purity of 32% ee was determined by HPLC analysis using Chiralcel OD-H column, (225nm, 95:5 hexane/*i*PrOH as eluent at 0.7 mL/min). Retention times: R_t = 4.19 min for *(2S, 3S)*-**225e** and R_t = 8.50 min for *(2R, 3R)*-**225e**.

Spectral data for **225e**: R_f = 0.35 (1:9 EtOAc/Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.20 (s, 9H), 1.31 (t, 3H, *J* = 7.1 Hz), 2.57-2.60 (m, 2H), 3.80 (s, 1H), 4.17-4.33 (m, 2H), 7.24-7.36 (m, 6H), 7.49-5.53 (m, 4H); ^{13}C ($CDCl_3$, 75 MHz) δ -0.34, 14.24, 34.41, 44.65, 60.95, 76.97, 87.79, 99.92, 127.24, 127.32, 127.34, 127.35, 128.26, 128.32, 141.45, 167.02 (one sp^2 carbon not located); IR (thin film) 2178w, 1742vs, 1194s cm^{-1}; mass spectrum, m/z (% rel intensity) 377 M^+ (0.3), 304 (9), 210 (17), 181 (20), 165 (100), 151 (40), 99 (15), 75 (14), 43 (23). $[\alpha]^{23}_D$ –0.2 (c 1.0, CH_2Cl_2) on 32% ee *(2R, 3R)*-**225e** (HPLC).



***(2R, 3R)-Cis-N*-1-H-2-carboxyethyl-3-(2-(trimethylsilyl)ethynyl)aziridine 233d.** The method A for the preparation of *N*-H aziridine **56a** was followed with aziridine **225d** (330 mg, 0.5 mmol) and the reaction was monitored by TLC. Purification by silica gel chromatography (18 mm × 250 mm column, 5:1 hexane/Et_2O as eluent) gave product **233d** as a colorless liquid in 83% yield (87 mg, 0.41 mmol). An optical purity of 85% ee was determined by HPLC analysis. See the conditions described for **225d**. (The product **233d** is volatile, will be lost under high vacuum if last for long time.)

Spectral data for *(2R,3R)*-**233d**: R_f = 0.22 (1:5 EtOAc/Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.08 (s, 9H), 1.26 (t, 3H, *J* = 7.1 Hz), 1.33-1.38 (m, 1H), 2.58 (dd, 1H, *J* = 6.8, 8.6 Hz), 2.70 (dd, 1H, *J* = 6.8, 8.5 Hz), 4.13-4.28 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ -0.38, 14.27, 26.07, 37.45, 61.66, 87.88, 100.33, 168.59; IR (thin film) 3273br, m, 2174m, 1740vs, 1209s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 211 M^+ (1.2), 137 (22), 110 (21), 95 (13), 84 (100), 52 (15), 49 (57). $[\alpha]^{23}_D$ +1.8 (c 1.0, CH_2Cl_2) on 84% ee material (HPLC) (the optical purity was assumed not changed from aziridine **225d**).

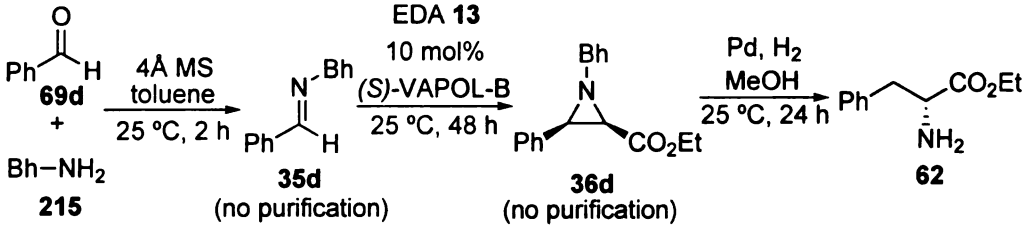


***Cis*-(*N*-1-bis(4-methoxy-3,5-di-*tert*-butylphenyl)methyl)-2-carboxyethyl-3-ethynylaziridine 234.** To a 10 mL flame-dried round bottom flask filled with argon was

added aziridine **225d** (70 mg, 0.1 mmol) and THF (2 mL) at room temperature. To this solution was slowly added TBAF (0.2 mL, 0.2 mmol, 1 M in THF), after stirring for 10 minutes, TLC indicated complete conversion. The reaction was quenched by adding 3 mL NaCl (aq. sat.) and 2 mL Et_2O. The organic layer collected after the extract was concentrated and purified by silica gel chromatography (18 mm × 200 mm, 1:20 EtOAc/ hexanes as eluent) to give product **234** as colorless liquid in 89% yield (55 mg, 0.09 mmol).

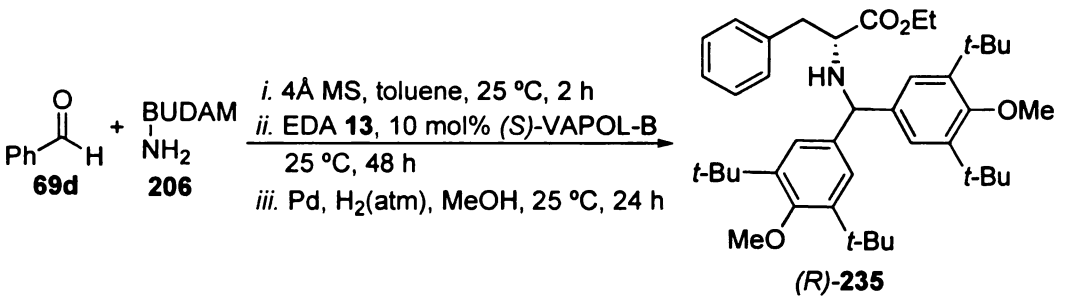
Spectral data for **234**: R_f = 0.42 (1:9 EtOAc/Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.30 (t, 3H, *J* = 7.1 Hz), 1.40 (s, 18H), 1.41 (s, 18H), 2.19 (d, 1H, *J* = 1.8 Hz), 2.55 (d, 1H, *J* = 6.4 Hz), 2.63 (dd, 1H, *J* = 1.7, 6.4 Hz), 3.67 (s, 3H), 3.68 (s, 3H), 3.76 (s, 1H), 4.25 (q, 2H, *J* = 7.1 Hz), 7.23 (s, 2H), 7.28 (s, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 14.37, 32.07, 34.45, 35.76, 44.18, 61.22, 64.04, 64.05, 70.80, 76.41, 78.87, 125.68, 125.74, 135.38, 135.70, 143.10, 143.22, 158.57, 167.64 (two sp^3 and one sp^2 carbons not located); IR (thin film) 3275m, 2961vs, 2210w, 1755s, 1728s, 1414s, 1223s cm^{-1}. mass spectrum, *m/z* (% rel intensity) 589 M^+ (2.4), 517 (28), 451 (78), 421 (25), 219 (10), 183 (26), 167 (12), 144 (12), 57 (100), 41 (28).

General procedure for the one-pot synthesis of α-amino ester – illustrated for the synthesis of ethyl-2-amino-3-phenylpropanoate 62



The method B for the preparation of **189a** was employed except the following difference: The catalyst was prepared from *(S)*-VAPOL (54 mg, 0.1 mmol), $B(OPh)_3$ (116 mg, 0.4 mmol) and H_2O (1.8 μL, 0.1 mmol). After 48 h, the toluene was removed under high vacuum, then 30 mL MeOH and Pd black (106 mg, 1 mmol) were added to the

same flask, which was then purged with H_2 gas by switch between the vacuum and H_2 source for three times and stopped at the last time with the H_2 source connected to the flask. The reaction mixture was stirred at room temperature for 20 h. After that, most of the MeOH was removed under reduced pressure and 20 mL EtOAc was added to the residue, the collected organic layer after filtration was concentrated under reduced pressure and purified by silica gel chromatography (18 mm × 200 mm column, 1:2 EtOAc/hexane as eluent) to give the product **62** as colorless liquid in 69% yield (133 mg, 0.69 mmol). The spectral data are reported in chapter two.



(R)-**235**

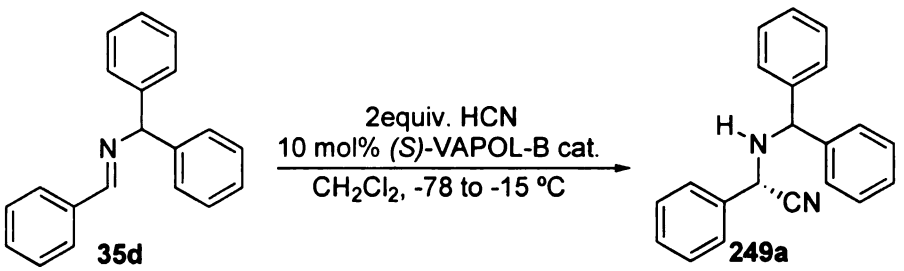
Ethyl-2-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methylamino)-3-phenylpropanoate 235. The procedure for the one-pot preparation of **62** was followed except the following difference. The reaction started from amine **206** (468 mg, 1 mmol) with *(S)*-VAPOL (11 mg, 0.02 mmol), $B(OPh)_3$ (22 mg, 0.075 mmol) and H_2O (0.4 μL, 0.02 mmol). Purification by silica gel chromatography (35 mm × 400 mm column, 1:19 EtOAc/hexane as eluent) gave the product **235** white solid (mp. 114-116 °C) in 76% yield (487 mg, 0.76 mmol).

Spectral data for **235**: R_f = 0.56 (1:9 EtOAc/Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.17 (t, 3H, *J* = 7.1Hz), 1.35 (s, 18H), 1.38 (s, 18H), 2.10 (s, 1H), 2.94 (d, 2H, *J* = 6.9Hz), 3.41 (t, 1H, *J* = 6.8Hz), 3.64 (s, 6H), 4.12 (q, 2H, *J* = 7.1Hz), 4.62 (s, 1H), 7.14-7.29 (m, 9H); ^{13}C ($CDCl_3$, 75 MHz) δ 14.26, 32.06, 32.10, 35.65, 35.71, 40.31, 60.28, 60.37, 64.00, 65.26, 77.40, 125.51, 125.69, 126.48, 128.18, 129.48, 136.47, 137.79, 138.48, 143.01, 143.05, 158.23, 174.92 (one sp^2 carbon not located); IR (thin film) 3320w, 2961vs, 1734s, 1412m, 1221s, 1115m, 1014m, 700m cm^{-1}; mass spectrum, *m/z* (% rel

intensity) 586 M^+-*t*-Bu (0.31), 466 (10), 452 (33), 421 (5), 379 (5), 226 (16), 218 (32), 199 (12), 185 (30), 168 (13), 120 (17), 91 (30), 57 (100), 41 (17).

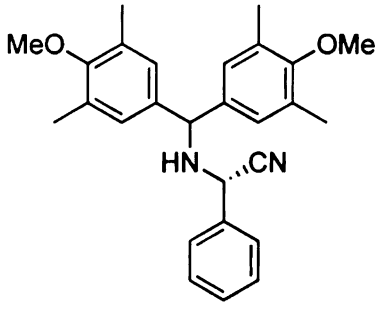
7.4 Experimental for chapter five

General procedure for the preparation of amine 249 - illustrated for the synthesis of *(S)*-*N*-Benzhydryl-cyanobenzylamine 249a.



To a 25 mL flame-dried round bottom flask filled with argon was added imine **35d** (271 mg, 1 mmol) and 8 mL CH_2Cl_2, followed by the transfer of the catalyst prepared following the same procedure as mentioned in the preparation of aziridine **58a** from *(S)*-VAPOL (54 mg, 0.1 mmol) and $B(OPh)_3$ (116 mg, 0.4 mmol) in toluene at 80 °C. The reaction mixture was cooled down to –78 °C and stirred for 30 minutes at –78 °C under the protection of argon, followed by drop-wise addition of HCN (1.3 mL, 2 mmol) (1.5 M in toluene: 1.35 mL TMSCN and 0.4 mL methanol dissolved in 5 mL toluene and stirred at room temperature for 2 h). The reaction mixture was stirred at –78 °C for 6 h, then allowed to warm up to –15 °C and kept stirring for an additional 18 h. Upon completion, 1 mL $NaHCO_3$ (aq. sat.) was added at –15 °C and kept stirring for 30 minutes, after warming up to room temperature, 2 mL CH_2Cl_2 and 3 mL $NaHCO_3$ were added. The mixture was then extracted with CH_2Cl_2 (3 mL × 3), the organic collection was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product as white solid. Purification by silica gel chromatography (15 mm × 300 mm column, 6" SiO_2, 1: 30 EtOAc/hexanes as eluent) gave **249a** as a white solid in 85% yield (255 mg, 0.85 mmol). An optical purity of 20% ee was determined by HPLC analysis (Chiralpak AD column, 95:5 hexane/*i*PrOH at 228nm, flow-rate: 1.0 mL/min). Retention times: R_t = 11.98 min for *(R)*-**249a** and R_t = 22.61 min for *(S)*-**249a**.

Spectral data for **249a**:[107e] R_f = 0.15 (1:25 EtOAc/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.21 (d, 1H, *J* = 11.8 Hz), 4.65 (d, 1H, *J* = 12.0 Hz), 5.34 (s, 1H), 7.29-7.68 (m, 15H); ^{13}C ($CDCl_3$, 75 MHz) δ 52.14, 65.37, 118.57, 126.93, 127.07, 127.28, 127.49, 127.73, 128.57, 128.77, 128.84, 134.76, 140.97, 142.56 (one sp^2 carbon not located); IR (thin film) 3314s, 1493s, 1452s, 737vs cm^{-1}; mass spectrum, *m/z* (% rel intensity) 298 M^+ (0.1), 271 (5), 221 (8), 182 (9), 167 (100), 151 (9), 116 (11), 77 (9).

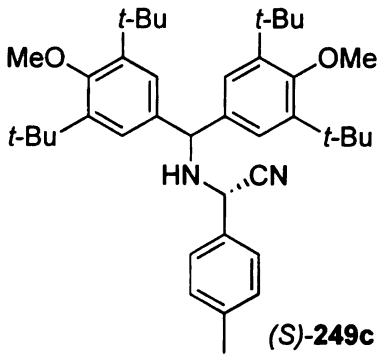


(S)-**249b**

***(S)*-*N*-bis(4-methoxy-3,5-dimethylphenyl)methyl)-cyanobenzylamine 249b.** The same procedure for the preparation of **249a** was applied with the following difference: The catalyst was prepared following the procedure in the synthesis of **189a**, imine **188d** (194 mg, 0.5 mmol) was used. Purification by silica gel chromatography (15 mm × 300 mm column, 6" SiO_2, 1: 20 EtOAc / hexanes as eluent) afforded **249b** as a white solid in 82% yield (170 mg, 0.4 mmol). An optical purity of 7% ee was determined by HPLC analysis (Chiralpak AD column, 99:1 hexane/2-propanol at 228nm, flow-rate: 1.0 mL/min). Retention times: R_t = 13.89 min for *(R)*-**249b** and R_t = 26.72 min *(S)*-**249b**.

Spectral data for **249b**: R_f = 0.25 (1:9 EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.19 (d, 1H, *J* = 12.0 Hz), 2.33 (s, 6H), 2.38 (s, 6H), 3.72 (s, 3H), 3.77 (s, 3H), 4.68 (d, 1H, *J* = 12.2 Hz), 5.12 (s, 1H), 7.18 (s, 2H), 7.29 (s, 2H), 7.40-7.49 (m, 3H), 7.61 (d, 2H, *J* = 7.6 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 16.04, 16.18, 52.23, 59.38, 59.41, 64.70, 118.76, 127.12, 127.20, 127.47, 128.77, 128.80, 130.90, 131.13, 135.11, 136.31, 138.14, 156.18, 156.38; IR (thin film) 3298s, 2943s, 2253w, 1485s, 1453s, 1221vs cm^{-1}; mass

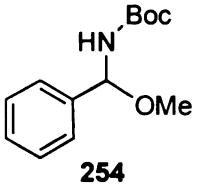
spectrum, *m/z* (% rel intensity) 414 M^+ (0.1), 283 (100), 268 (7), 253 (10), 162 (15), 141 (14).



(S)-**249c**

***(S)*-*N*-bis(4-methoxy-3,5-di-*tert*-butylphenyl)methyl)-1-cyano-1-*p*-tolylamine 249c.** The same procedure for the preparation of **249b** was followed from imine **208j** (278 mg, 0.5 mmol). Purification by silica gel chromatography (15 mm × 300 mm column, 6" SiO_2, 1: 30 EtOAc / hexanes as eluent) afforded **249c** as a white solid in 69% yield (202 mg, 0.35 mmol). An optical purity of 33% ee was determined by HPLC analysis (Pirkle covalent (*R, R*) Whelk-O1 column, 99:1 hexane/2-propanol at 223nm, flow-rate: 0.7 mL/min). Retention times: R_t = 10.64 min *(R)*-**249c** and R_t = 12.04 min for *(S)*-**249b**.

Spectral data for **249c**: R_f = 0.6 (1:9 EtOAc/hexane); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.51 (s, 18H), 1.57 (s, 18H), 2.15 (d, 1H, *J* = 8.0 Hz), 2.44 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 4.67 (d, 1H, *J* = 8.2 Hz), 5.19 (s, 1H), 7.30 (d, 2H, *J* = 8.0 Hz), 7.40 (s, 2H), 7.52 (d, 2H, *J* = 7.8 Hz), 7.58 (s, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 21.06, 32.03, 32.16, 35.74, 35.79, 52.25, 64.01, 64.04, 65.77, 119.07, 125.49, 125.54, 127.15, 129.52, 132.41, 135.02, 137.08, 138.65, 143.53, 143.74, 158.62, 158.80; IR (thin film) 3316w, 2963vs, 2255w, 1447m, 1223s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 569 M^+ -CN (3), 451 (100), 421 (11), 182 (15), 57 (62), 41 (32). Specific rotation: $[\alpha]^{23}_D$ –3.7 (*c* 1.0 in CH_2Cl_2) on 33% ee material (HPLC).



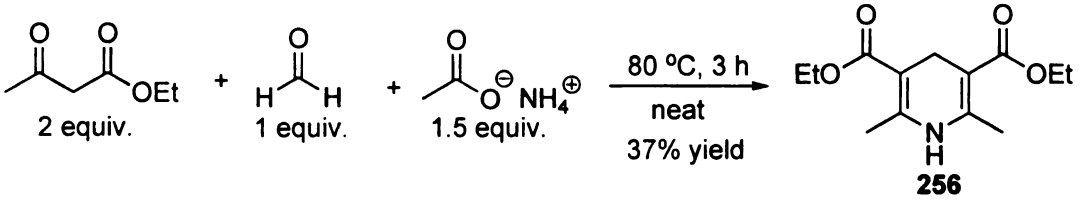
254

***Tert*-butyl methoxyl(phenyl)methylcarbamate 254**

The same procedure for the preparation of **249a** was followed with the following difference: *(S)*-VAPOL-phosphoric acid **49** (30 mg, 0.05 mmol) was used as catalyst and added directly to the flask containing *N*-Boc imine **253** (100 mg, 0.5 mmol) and 4 mL CH_2Cl_2 at –78 °C under the protection of argon. After the addition of HCN (0.65 mL, 1 mmol) and stirred at –78 °C for 8 h, the reaction mixture was allowed to warm up gradually to 0 °C and kept stirring for 16 h. Purification by silica gel chromatography (15 mm × 250 mm, 6" SiO_2, 1:15 EtOAc/ hexanes as eluent) obtained compound **254** as the only isolable product as white solid in 40% yield (47 mg, 0.2 mmol). And 0%ee was determined by HPLC analysis (Chiralpak AD column, 99:1 hexane/2-propanol at 223nm, flow-rate: 0.7 mL/min). Retention times: R_t = 12.46 min and R_t = 14.71 min.

Spectral data for **254**: R_f = 0.2 (1:9 EtOAc/Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 3.42 (s, 3H), 5.09-5.12 (m, 1H), 5.79 (d, 1H, *J* = 9.6 Hz,), 7.25-7.41 (m, 5H); ^{13}C ($CDCl_3$, 75 MHz) δ 28.28, 53.83, 55.52, 83.48, 125.87, 128.41, 128.54, 139.41, 155.27; IR (thin film) 3331br, m, 1719s, 1495s, 1169m cm^{-1}.

Preparation of the Hantzsch ester 256:[112]

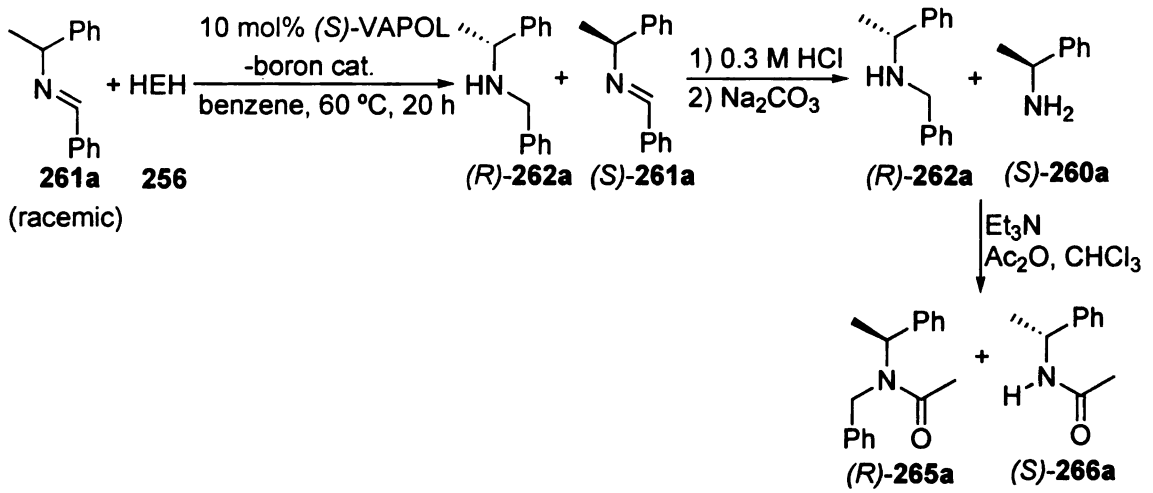


256

To a 100 mL flask was added ethyl acetoacetate (52 mL, 400 mmol), formaldehyde (16.6 g, 200 mmol) (37% wt in H_2O) and ammonium acetate (23.6 g, 306 mmol), the yellow reaction mixture was purged with N_2, then submerged into a 80 °C bath and

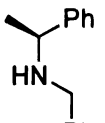
stirred for 45 minutes to give a yellow solid, which was cooled down and added H_2O (100 mL) to afford a slurry, followed by additional H_2O (100 mL) and CH_2Cl_2 (400 mL). Extraction with CH_2Cl_2 (100 mL × 3), the organic collection was washed with NaCl (aq. sat.), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product **256**. Purification by crystallization (1:5 CH_2Cl_2/hexane) obtained product **256** as yellow solid (mp. 179-183 °C) in 37% yield (19.2 g, 74 mmol).

Asymmetric reduction of racemic imine 261 and the following conversion to the acetyl protected amides:



To a 25 mL flame-dried round bottom flask filled with argon was added imine **261a** (104 mg, 0.5 mmol), 5 mL benzene, and the catalyst following that was prepared by following the same procedure as mentioned in the preparation of aziridine **189a** from *(S)*-VAPOL (27 mg, 0.05 mmol), $B(OPh)_3$ (60 mg, 0.2 mmol) and H_2O (0.9 μL, 0.05 mmol) in toluene at 80 °C. To this mixture was added HEH **256** (70 mg, 0.27 mmol). The reaction mixture was stirred at room temperature for 10 minutes, then moved to a 60 °C bath and kept stirring for 20 h. Upon completion, the reaction mixture was cooled to room temperature, followed by addition of 1 mL 0.3 M HCl solution (aq.) slowly and then kept stirring for 30 minutes. After extraction, the collected aqueous layer was neutralized with

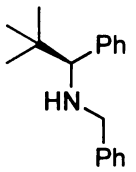
Na_2CO_3 (aq. sat.). The mixture was then extracted again with EtOAc (3 mL × 3), and the collected organic layer was washed with NaCl (aq. sat.), dried over Na_2SO_4 and concentrated under reduced pressure. To this mixture was added 5 mL $CHCl_3$, Et_3N (140 μL, 1 mmol) and acetic anhydride (71 μL, 0.7 mmol), the reaction mixture was stirred at room temperature for 16 h. Upon removal of the solvent under reduced pressure, the reaction mixture was purified by silica gel chromatography (15 mm × 300 mm column, 6" SiO_2, 1:5 EtOAc/hexanes as eluent, after the compound **265a** came out, the eluent was changed to 1:3 EtOAc/ hexane) to afford product **265a** as colorless semi liquid in 36% yield (44 mg, 0.17 mmol) and product **266a** as white solid in 30% yield (24 mg, 0.14 mmol). A 17% ee of product **265a** was determined by HPLC analysis (Chiralpak AD column, 95:5 hexane/*i*PrOH at 225nm, flow-rate: 1.0 mL/min). Retention times: R_t = 15.35 min (minor) and R_t = 20.10 (major) min. A 18% ee of product **266a** was determined by HPLC analysis (Chiralpak AD column, 95:5 hexane/*i*PrOH at 225nm, flow-rate: 0.7 mL/min). Retention times: R_t = 16.82 min (minor) and R_t = 19.98 (major) min.



262a

***(S)-N*-benzyl-1-phenylethanamine 262a.** Colorless liquid.

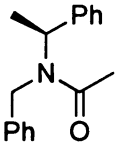
Spectral data for **262a**: R_f = 0.18 (1:5 Et_2O/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.40 (d, 3H, *J* = 6.6Hz), 1.47 (br, s, 1H), 3.62 (d, 1H, *J* = 13.2Hz), 3.69 (d, 1H, *J* = 13.2Hz), 3.84 (q, 1H, *J* = 6.6Hz), 7.25-7.42 (m, 10H); ^{13}C ($CDCl_3$, 75 MHz) δ 24.38, 51.57, 57.42, 126.62, 126.75, 126.83, 128.04, 128.27, 128.38, 140.58, 145.50. (identical to that from Aldrich)



262b

***(S)-N*-benzyl-2,2-dimethyl-1-phenylpropan-1-amine 262b.** Colorless liquid.

Spectral data for **262b**:[134] R_f = 0.55 (1:5 EtOAC/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.90 (s, 9H), 1.91 (br, s, 1H), 3.35 (s, 1H), 3.40 (d, 1H, *J* = *13.2* Hz), 3.62 (d, 1H, *J* = *13.2* Hz), 7.25-7.42 (m, 10H); ^{13}C ($CDCl_3$, 75 MHz) δ 27.10, 34.75, 52.01, 71.74, 126.66, 126.69, 127.50, 128.12, 128.18, 129.14, 141.14, 141.49. IR (thin film) 2950br,s, 1452m, 704s cm^{-1}.

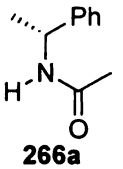


265a

***(S)-N*-benzyl-*N*-(1-phenylethyl)acetamide 265a.**[135] White solid, the product has a rotamer at the room temperature in a ratio of 2:1, R_f = 0.15 (1:5 EtOAc/hexane).

Rotamer 1 (major): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.41 (d, 3H, *J* = 7.2Hz), 2.03 (s, 3H), 4.18 (d, 1H, *J* = 17.9Hz), 4.38 (d, 1H, *J* = 17.8Hz), 6.17 (q, 1H, *J* = 7.1Hz), 7.19-7.31 (m, 10H).

Rotamer 2 (minor): ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.45 (d, J = 7.2Hz, 3H), 2.26 (s, 3H), 3.94 (d, 1H, *J* = 15.4Hz), 4.95 (d, 1H, *J* = 15.6Hz), 5.15 (q, 1H, *J* = 7.1Hz), 7.05-7.21 (m, 10H).



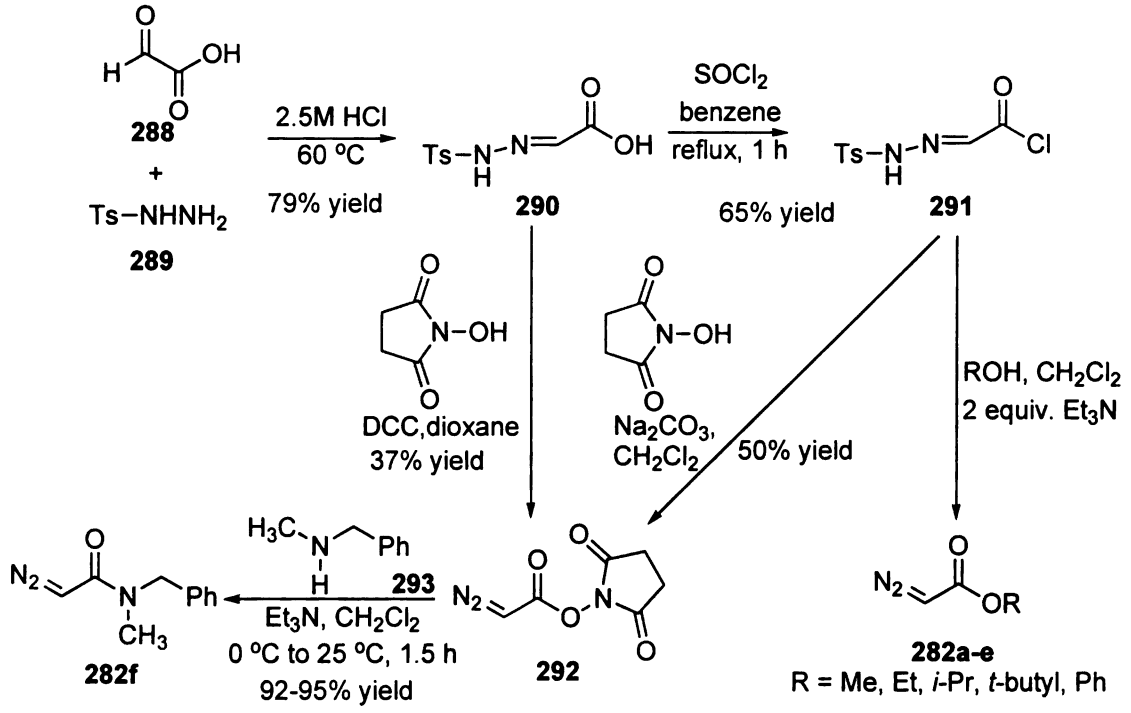
266a

***N*-(1-phenylethyl)acetamide 266a.** White solid. R_f = 0.13 (1:3 EtOAC/hexane).

Spectral data for **266a**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.40 (d, 3H, *J* = 6.9Hz), 1.88 (s, 3H), 5.02-5.07 (m, 1H), 6.57 (d, 1H, *J* = 6.6Hz), 7.17-7.30 (m, 5H). (identical to that from Aldrich)

7.5 Experimental for chapter Six

Preparation of diazo compounds 282:



Preparation of glyoxylic acid *p*-toluenesulfonylhydrazone 290. To a 1 L round bottom flask was added glyoxylic acid monohydrate **288** (46.3 g, 0.5 mol) and 500 mL water, stirred to dissolve in a 65 °C oil bath. To this solution was then added a warm suspension (at approximately 60 °C) of *p*-toluenesulfonylhydrazide **289** (93.1 g, 0.5 mol) in 300 mL 2.5 M hydrochloric acid (aq.). The reaction mixture was stirred at 65 °C for 15 minutes, then allowed to cool to room temperature gradually until all the oil solidified and then kept in a refrigerator for overnight. The crude product was collected on a filter paper, washed with cold water, and dried for 2 days in air. Crystallization from EtOAc/hexanes (1:2) afforded **290** as white solid (mp. 150-152 °C) in 79% isolated yield (96.4 g, 0.4 mol).

Spectral data for **290**:[127] R_f = 0.45 (1:1, EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39(s, 3H), 7.29 (s, 1H), 7.40 (d, 2H, *J* = 8.5Hz), 7.78 (d, 2H, *J* = 8.3Hz), 10.05 (br s,

1H), 11.00 (br s, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 21.37, 128.42, 130.57, 136.81, 137.28, 145.28, 163.72.

Preparation of glyoxylic acid chloride *p*-toluenesulfonylhydrazone 291. To a suspension of acid **290** (4.85g, 20 mmol) in 25 mL benzene is added $SOCl_2$ (freshly distilled) (5.8 mL, 40 mol). The reaction mixture was heated to reflux until vigorous gas evolution has ceased and most of the suspended solid has dissolved (1-2 h). The reaction mixture then was cooled under nitrogen and filtrated through a Celite mat on a sintered-glass funnel. The filtrate was concentrated under reduced pressure, the residual solid was broken up and brought to a fine suspension in 5 mL of warm benzene. The suspension was cooled and filtered quickly and then the solid was washed with cold benzene (3 mL ×2). The combined filtrates were stripped of solvent on the rotovapor and the residual was washed with cold benzene to give a second crop of the crude product. Purification by crystallization was achieved by dissolving the crude product in 10 mL boiling benzene, followed by the addition of 10 mL petroleum ether (bp. 60-90 °C). The mixture was allowed to cool down, and stand overnight. The product **291** was collected as a white solid (mp. 100-103 °C) in 65% isolated yield (3.38 g, 13 mmol).

Spectral data for **291**:[128c] R_f = 0.5 (1:1, EtOAc/hexane); ^1H-NMR(CD_3COCD_3, 300 MHz) δ 2.42 (s, 3H), 7.44 (d, 2H, *J* = 8.5Hz), 7.46 (s, 1H), 7.83 (d, 2H, *J* = 8.3Hz,), 9.08 (br s, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 20.41, 127.55, 129.75, 135.18, 136.09, 144.89, 164.47.

Succinimidyl diazoacetate 292

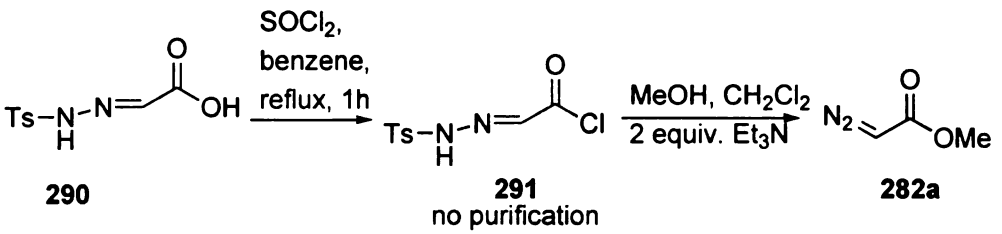
Method A:[128a] To a 250 mL flame-dried flask containing a suspension of acid **290** (2.42 g, 10 mmol) in 80 mL cold dry dioxane was added *N*-hydroxysuccinimide (1.15 g, 10 mmol), followed by drop-wise addition of a solution of DCC (2.06 g, 10mmol) in 20

mL of cold dry dioxane. After addition, the reaction mixture was allowed to warm up to room temperature and stirred for 4 h. Upon completion, DCU was filtered off, the collected filtrate was concentrated under reduced pressure to give the crude product **292** as a brown solid. Purification by column chromatography (3:1, Et_2O/hexanes as eluent) gave product **292** as a light yellow solid in 50% isolated yield (0.91 g, 5 mmol).

Method B:[128c] To a suspension of *N*-hydroxysuccinimide (2.3 g, 20 mmol) and sodium carbonate (3.18 g, 30mmol) in 30 mL dry CH_2Cl_2 was added a solution of compound **291** (~20mmol) in 40 mL dry CH_2Cl_2 at 0 °C over 2 h by syringe pump. The reaction mixture was stirred for an additional 1 h at 0 °C, then warmed to room temperature and stirred for 3 h. Upon completion, the mixture was filtered through a pad of Celite topped with a layer of sand. The collected filtrate was concentrated under reduced pressure to give the crude product as a light brown solid. Purification by silica gel chromatography afforded product **292** as light yellow crystals (mp. 114-115 °C) in 37% yield (1.36 g, 7 mmol).

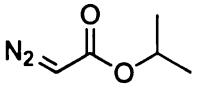
Spectral data for **292**:[128a] R_f = 0.13 (3:1, ether/hexanes); ^{1}H-NMR($CDCl_3$, 300 MHz) δ 2.80 (s, 4H), 5.10 (br, s, 1H); ^{13}C NMR (CD_3COCD_3, 75 MHz) δ 25.44, 45.11, 169.37 (one sp^2 carbon not located); IR (thin film) 3105w, 2135s, 1736vs, 1375s, 1206s, 1105s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 183 M^+ (1), 155 (3), 69 (100), 56 (16), 42 (11).

General procedure for the preparation of diazo acetates – illustrated for the preparation of methyl diazoaectate 282a



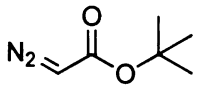
290 **291** no purification **282a**

The acyl chloride **291** was prepared as mentioned above from acid **290** (4.85 g, 20 mmol) and used without purification. The volatile materials in the crude **291** were removed under high vacuum (0.5 mm Hg, 2~4 h), then the crude mixture was dissolved in 60 mL CH_2Cl_2, and to this solution was added MeOH (1.5 mL, 40 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 minutes, followed by slow addition of dry Et_3N (5.6 mL) over a 20 minutes period at 0 °C. The reaction mixture was stirred for 40 minutes at 0 °C and then allowed to warm up to room temperature and stirred for 30 minutes. The reaction was quenched by adding 0.3 M HCl (120 mL, aq.), the organic layer was collected and neutralized by $NaHCO_3$ (aq. sat.) (15 mL × 2). The aqueous layer was extracted with ether (3 mL × 2), the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure (use cold water bath for the rotary evaporation to avoid the lose of product) to give crude product **282a** as a brown liquid. After purification by silica gel chromatography (20 mm × 350 mm column, 1:9 EtOAc/pentane as eluent), the solvent was removed by fractional distillation under the protection of nitrogen to give product **282a** as a yellow liquid in 80% overall isolated yield from **290** (2.38 g, 16 mmol, as a mixture with pentane in a 1 : 1 molar ratio). R_f = 0.50 (1:3, EtOAc/hexanes). Spectral data for **282a**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.73 (s, 3H), 4.72 (br, s, 1H).



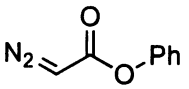
282c

***Iso*-propyl diazoaectate 282c.** The same procedure for the preparation of **282a** was followed from isopropanol (2.6 mL, 34 mmol) and acid **290** (4.73 g, 19 mmol). Compound **282c** was obtained as a yellow liquid in 83% overall yield from **290** (4.27 g, 28 mmol, as a mixture of **282c** with pentane in a 1:2 molar ratio). R_f = 0.67 (1:3, EtOAc/hexanes). Spectral data for **282c**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.23 (m, 6H), 4.67 (br, s, 1H), 5.06 (m, 1H).



282d

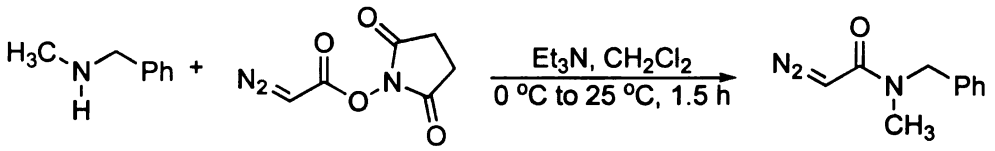
***tert*-Butyl diazoaectate 282d.** The same procedure for the preparation of **282a** was followed from *tert*-butanol (0.4 mL, 4 mmol) and acid **290** (0.48 g, 2 mmol). Compound **282d** was obtained as a yellow liquid in 80% overall yield from **290** (0.34 g, 1.6 mmol, as a mixture of **282d** with pentane in 1:1 molar ratio). R_f = 0.65 (1:3, EtOAc/hexanes). Spectral data for **282d**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9H), 4.58 (br, s, 1H).



282e

Phenyl diazoaectate 282e. The same procedure for the preparation of **282a** was followed from phenol (3.76 g, 40 mmol) and acid **290** (4.85 g, 20 mmol). Compound **282e** was obtained as a yellow liquid in 86% overall yield from **290** (4.1 g, 17 mmol, as a mixture of **282e** with pentane in 4:3 molar ratio). R_f = 0.29 (1:9, EtOAc/hexanes).

Spectral data for **282e**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.94 (br, s, 1H), 7.10 (m, 2H), 7.21 (m, 1H), 7.36 (m, 2H). IR (thin film) 2120vs, 1707vs, 1370s, 1202s, 1150s cm^{-1}.

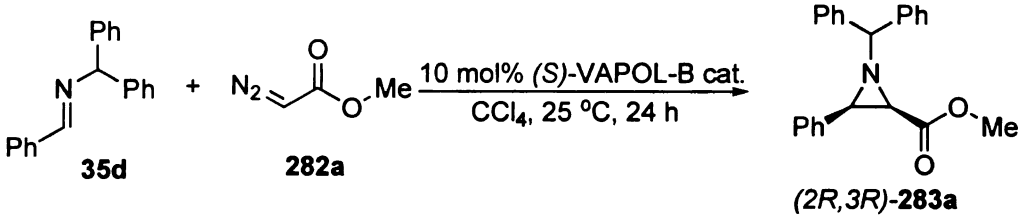


293 **292** **282f**

***N*-benzyl-*N*-methyldiazoacetamide 282f.** To a flame-dried 50 mL round bottom flask filled with argon was added amine **293** (0.85 mL, 6.55 mmol) and 5 mL CH_2Cl_2, followed by dry Et_3N (1.15 mL, 8.19 mmol) at 0 °C. After stirring for 5 minutes, the solution of succinimidyl diazoacetate **292** (1 g, 5.6 mmol) in 10 mL CH_2Cl_2 was added slowly over a 10 minutes period. The reaction mixture was stirred for 0.5 h at 0 °C, then allowed to warm up to room temperature and stirred for another 1 h. The reaction was complete

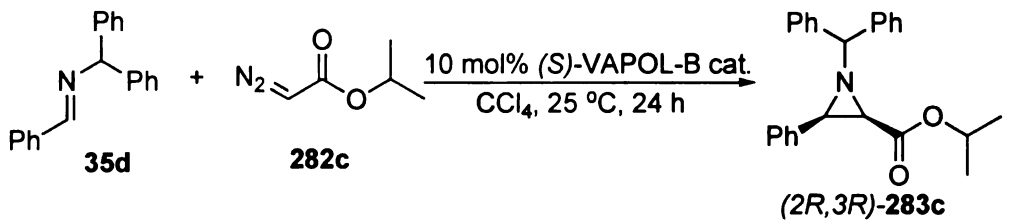
and the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography (25 mm x 450 mm, 6" SiO_2, 1:1 EtOAc/ hexanes as eluent) to afford product **282f** as a yellow liquid in 92% yield (0.97 g, 5.1 mmol).

Spectral data for **282f**: R_f = 0.38 (1:1, EtOAc/hexanes). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.84 (br s, 3H), 4.47 (br s, 2H), 4.96 (s, 1H), 7.19-7.34 (m, 5H). ^{13}C ($CDCl_3$, 75 MHz) δ 46.34, 51.72, 127.39, 128.62, 136.84, 166.00 (two sp^2 carbon not located); IR (thin film) 3065s, 2100vs, 1611vs, 1477s, 1408s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 161 M^+ -N_2 (2), 117 (45), 103 (97), 91 (100), 64 (24), 50 (17).



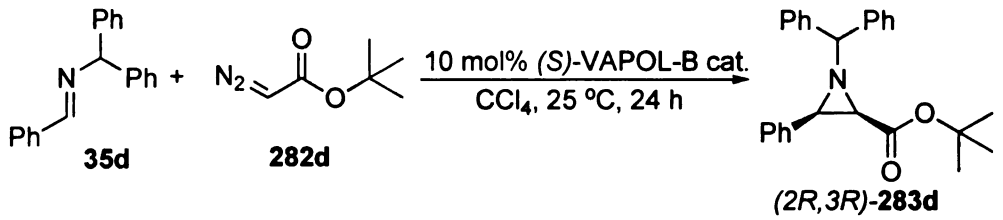
***(2R, 3R)*-1-benzhydryl-3-phenylaziridine-2-methylcarboxylate 283a:** The procedure for the preparation of aziridine **58a** (chapter two) was followed from imine **35d** (271 mg, 1 mmol) and methyl diazoacetate **282a** (155 mg, 1.1 mmol, as a mixture with pentane in a 1 : 1 molar ratio). Purification by silica gel chromatography (35 mm x 400 mm column, 1:1:20 EtOAc/CH_2Cl_2/hexanes as eluent) gave aziridine **283a** as a white solid (mp. 179-180 °C) in 89% isolated yield (307 mg, 0.89 mmol). The *cis/trans* ratio was >50:1 as observed from the ^{1}H NMR spectrum of the crude reaction mixture. The optical purity of **283a** was determined to be 91% ee by HPLC analysis (Chiralcel OD-H column, 95:5 hexane/*i*PrOH at 228nm, flow-rate: 0.5 mL/min). Retention times: R_t = 7.70 min *(2R, 3R)*-**283a** and R_t = 24.69 min *(2S,3S)*-**283a**. The assignment of the retention times was aided by a racemic sample of **283a** prepared from racemic VAPOL-boron catalyst using the same procedure.

Spectral data for *(2R, 3R)*-**283a**: R_f = 0.22 (1:9 EtOAc/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.67 (d, 1H, *J* = 6.7 Hz), 3.21 (d, 1H, *J* = 6.7 Hz), 3.45 (s, 3H), 3.92 (s, 1H), 7.15-7.38 (m, 11H), 7.46 (d, 2H, *J* = 8.0 Hz), 7.56 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 46.20, 48.18, 51.69, 77.76, 127.15, 127.21, 127.39, 127.47, 127.66, 127.80, 128.48 134.89, 142.25, 142.39, 168.13 (two sp^2 carbon not located); IR (thin film) 1736s, 1208s, 1173m, 698m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 343 M^+ (0.02), 176 (95), 167 (100), 144(14), 152 (21), 116 (78), 77 (10). Anal. calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 79.98; H, 5.96; N, 4.04; Specific rotation: $[\alpha]^{23}_D$ +14.6 (*c* 1.0 in EtOAc) on 91% ee material (HPLC).



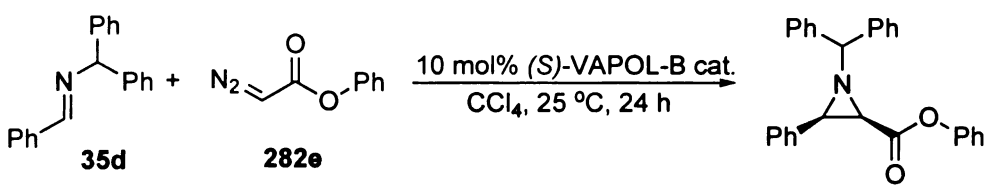
***(2R, 3R)*-1-benzhydryl-3-phenylaziridine-2-isopropylcarboxylate 283c.** The procedure for the preparation of aziridine **283a** was followed from imine **35d** (271 mg, 1 mmol) and isopropyl diazoacetate **282c** (270 mg, 1.1 mmol, as a mixture with pentane in a 1 : 2 molar ratio). Purification by silica gel chromatography (35 mm × 400 mm column, 1:1:20 EtOAc/CH_2Cl_2/hexanes as eluent) gave aziridine **283c** as a white solid (mp 114.5-115.5 °C) in 84% isolated yield (310 mg, 0.84 mmol). The *cis/trans* ratio was >50:1 as observed from the ^{1}H NMR spectrum of the crude reaction mixture. An optical purity of 92% ee was determined by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/*i*PrOH at 230nm, flow-rate: 0.5 mL/min). Retention times: R_t = 15.11 min for *(2R,3R)*-**283c** and R_t = 17.69 min for *(2S,3S)*-**283c**. A single crystallization (1:5 CH_2Cl_2/hexanes) gave a 61 % recovery of *(2R, 3R)*-**283c** with >99.9% ee.

Spectral data for *(2R, 3R)*-**283c**: R_f = 0.13 (1:1:20 EtOAc/CH_2Cl_2/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.94 (dd, 6H, *J* = 2.3, 6.2 Hz), 2.61 (d, 1H, *J* = 6.9 Hz), 3.18 (d, 1H, *J* = 6.9 Hz), 3.92 (s, 1H), 4.76-4.80 (m, 1H), 7.15-7.40 (m, 11H), 7.47 (d, 2H, *J* = 8.5 Hz), 7.60 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.36, 21.52, 46.51, 47.74, 67.99, 77.49, 127.18, 127.24, 127.37, 127.51, 127.69, 127.80, 128.42, 128.47, 135.05, 142.47, 142.58, 167.30 (one sp^2 carbon not located); IR (thin film) 1734s, 1209s, 1099m, 1064m, 750m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 371 M^+ (0.02), 204 (71), 167 (100), 162 (100), 152 (33), 144 (18), 116 (100), 90 (24), 43 (47). Anal. calcd for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.46; H, 6.25; N, 3.70; Specific rotation: $[\alpha]^{23}_D$ +42.0 (*c* 1.0 in EtOAc) on >99.9% ee material (HPLC).



***(2R, 3R)*-1-benzhydryl-3-phenylaziridine-2-*t*-butylcarboxylate 283d.** The procedure for the preparation of aziridine **283a** was followed from imine **35d** (271 mg, 1 mmol) and tert-butyl diazoacetate **282d** (212 mg, 1.1 mmol, as a mixture with pentane in a 1 : 1 molar ratio). Purification by silica gel chromatography (35 mm × 400 mm column, 1:1:20 EtOAc/CH_2Cl_2/hexanes as eluent) gave aziridine **283d** as a white solid (mp. 174.5-175.5 °C) in 89% isolated yield (379 mg, 0.89 mmol). The *cis/trans* ratio was >50:1 as observed from the ^{1}H NMR spectrum of the crude reaction mixture. An optical purity of 92% ee was determined by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/*i*PrOH at 221nm, flow-rate: 0.5 mL/min). Retention times: R_t = 6.89 min for *(2R,3R)*-**283d** and R_t = 8.29 min for *(2S,3S)*-**283d**.

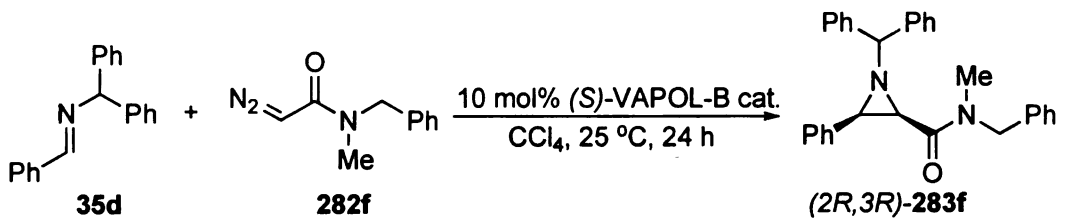
Spectral data for *(2R, 3R)*-**283d**: R_f = 0.2 (1:1:20 EtOAc/CH_2Cl_2/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.14 (s, 9H), 2.54 (d, 1H, *J* = 6.9 Hz), 3.14 (d, 1H, *J* = 6.9 Hz), 3.90 (s, 1H), 7.14-7.34 (m, 9H), 7.38 (d, 2H, *J* = 7.7 Hz), 7.46 (d, 2H, *J* = 7.9 Hz), 7.60 (d, 2H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.71, 47.14, 47.35, 77.32, 80.94, 127.10, 127.18, 127.33, 127.51, 127.62, 127.83, 128.40, 128.45, 135.32, 142.65, 142.72, 166.91(one sp^2 carbon not located); IR (thin film) 1730s, 1366m, 1223s, 1150s, 698s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 386 M+1$^+$ (0.01), 218 (1), 167 (85), 162 (100), 152 (15), 116 (31), 90 (7), 57 (59). Anal. calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 81.09; H, 6.49; N, 3.49; Specific rotation: $[\alpha]^{23}_D$ +39.1 (*c* 1.0 in EtOAc) on 92% ee material (HPLC).



(2R,3R)-**283e**

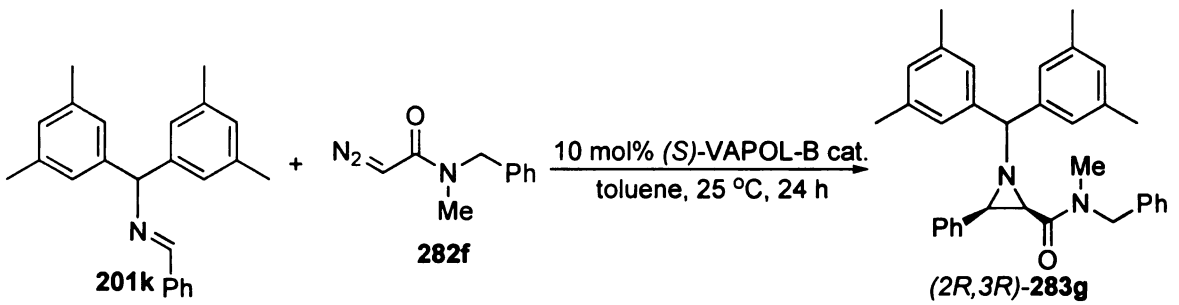
***(2R, 3R)*-1-benzhydryl-3-phenylaziridine-2-phenylcarboxylate 283e:** The procedure for the preparation of aziridine **283a** was followed from imine **35d** (271 mg, 1 mmol) and phenyl diazoacetate **282e** (230 mg, 1.1 mmol, as a mixture with pentane in a 4 : 3 molar ratio). Purification by silica gel chromatography (35 mm × 400 mm column, 1:1:20 EtOAc/CH_2Cl_2/hexanes as eluent) gave aziridine **283e** as a white solid (mp. 159-160 °C) in 85% isolated yield (345 mg, 0.85 mmol). The *cis/trans* ratio was >50:1 as observed from the ^{1}H NMR spectrum of the crude reaction mixture. An optical purity of 91% ee was determined by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/*i*PrOH at 234nm, flow-rate: 0.5 mL/min). Retention times: R_t = 12.40 min for *(2R,3R)*-**283e** and R_t = 16.36 min for *(2S,3S)*-**283e**. A single crystallization (1:5 CH_2Cl_2/hexanes) gave 89 % recovery of *(2R, 3R)*-**283e** with 96% ee.

Spectral data for *(2R, 3R)*-**283e**: R_f = 0.11 (1:1:20 EtOAc/CH_2Cl_2/hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.89 (d, 1H, *J* = 6.9 Hz), 3.38 (d, 1H, *J* = 6.9 Hz), 4.03 (s, 1H), 6.55 (d, 2H, *J* = 8.0 Hz), 7.11-7.13 (m, 1H), 7.19-7.38 (m, 11H), 7.48-7.54 (m, 4H), 7.67 (d, 2H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.85, 48.08, 77.22, 121.01, 125.41, 126.88, 127.05, 127.18, 127.21, 127.30, 127.56, 127.68, 128.28, 128.93, 134.45, 141.98, 142.06, 149.98, 166.31(one sp^2 carbon not located); IR (thin film) 1757s, 1491m, 1200s, 1165s, 1060m, 748m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 405 M^+ (0.07), 238 (63), 182 (15), 167 (100), 151 (25), 133 (24), 116 (31), 89 (25). Anal. calcd for $C_{28}H_{23}NO_2$: C, 82.94; H, 5.72; N, 3.45. Found: C, 82.50; H, 5.45; N, 3.38; Specific rotation: $[\alpha]^{23}_D$ +28.0 (*c* 1.0 in EtOAc) on 96% ee material (HPLC).



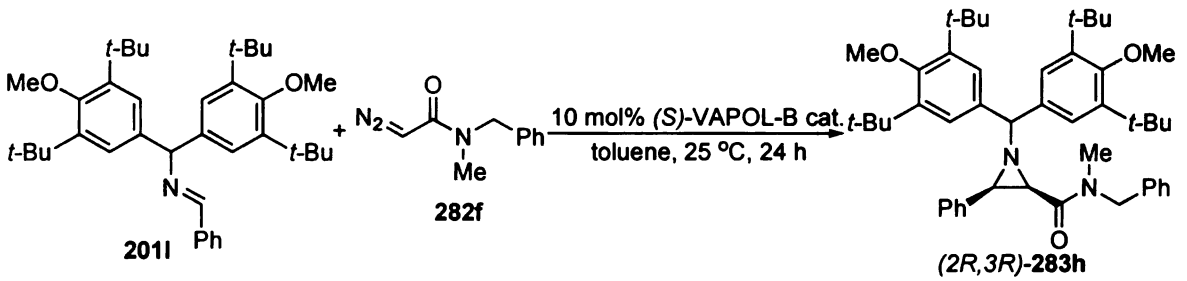
(*2R, 3R*) *Cis-N*-benzhydryl-3-phenyl-2-aziridinyl-N-benzyl-N-methyl-carboxylamide 283f. The procedure for the preparation of aziridine **283a** was followed from imine **35d** (271 mg, 1 mmol) and diazo amide **282f** (200 mg, 1.05 mmol). Purification by silica gel chromatography (25 mm × 550 mm column, 1:5 EtOAc/hexanes as eluent) gave aziridine **283f** as a white solid (mp. 179-180 °C) in 14% isolated yield (61 mg, 0.14 mmol). An optical purity of 88% ee was determined by HPLC analysis (Chiralcel OD-H column, 95:5 hexane/*i*PrOH at 225nm, flow-rate: 0.7 mL/min). Retention times: R_t = 18.30 min for *(2R,3R)*-**283f** and R_t = 26.44 min for *(2S,3S)*-**283f**. The compound **283f** appeared as a mixture of two rotamers in the ^{1}H NMR spectrum at the room temperature in a 2.5 : 1 molar ratio.

Spectral data for the major rotamer of *(2R,3R)*-**283f**: R_f = 0.15 (1:5 EtOAc/ Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.72 (s, 3H), 2.81 (d, 1H, *J* = 6.6 Hz), 3.17 (d, 1H, *J* = 6.8 Hz), 3.68 (d, 1H, *J* = 15.1 Hz), 4.01 (s, 1H), 5.02 (d, 1H, *J* = 14.9 Hz), 6.47 (d, 2H, *J* = 6.9 Hz), 7.01-7.52 (m, 16H), 7.78 (d, 2H, *J* = 7.1 Hz); mass spectrum, *m/z* (% rel intensity) 432 M^+ (0.06), 284 (5), 265 (100), 194 (7), 181 (9), 167 (72), 152 (31), 188 (30), 91 (100), 77 (18), 65 (18), 42(14). Specific rotation: $[\alpha]^{23}_D$ +71.2 (*c* 1.0 in CH_2Cl_2) on 88% ee material (HPLC).



(*2R, 3R*) *Cis*-*N*-bis(3,5-dimethylphenyl)methyl-3-phenyl-2-aziridinyl-*N*-be nzyl-*N*-methyl-carboxylamide 283g. The procedure for the preparation of aziridine **283a** was followed with imine **201k** (163 mg, 0.5 mmol) except that the toluene was used as solvent, and the catalyst was prepared with *(S)*-VAPOL (27 mg, 0.05 mmol), H_2O (0.9 μL, 0.05 mmol), $B(OPh)_3$ (60 mg, 0.2 mmol) at 80 °C for 1 h, and then at 0.5 mm Hg at 80 °C for 0.5 h. Purification by silica gel chromatography (25 mm × 400 mm column, 20:20:1 hexanes/CH_2Cl_2/EtOAc as the first eluent to remove the strong UV absorption fraction and then 1:3 Et_2O/hexanes as the second eluent) gave aziridine **283g** as a white solid (mp. 168-169 °C) in 66% isolated yield (161 mg, 0.33 mmol). The compound **283g** appeared as a mixture of two rotamers in the ^{1}H NMR spectrum at the room temperature in a 3 : 1 molar ratio. The optical purity of **283g** was determined to be 97% ee by HPLC analysis (Chiralcel OD-H column, 90:10 hexane/*i*PrOH at 228nm, flow-rate: 0.7 mL/min). Retention times: R_t = 11.77 min *(2S, 3S)*-**283g** and R_t = 15.84 min *(2R,3R)*-**283g**.

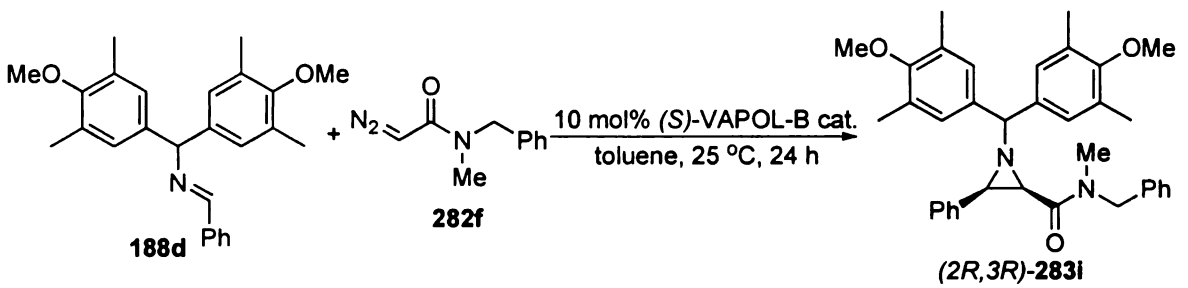
Spectral data for the major rotamer of **283g**: R_f = 0.45 (1:3 EtOAc/ Hexane); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 6H), 2.38 (s, 6H), 2.79 (s, 3H), 2.81 (d, 1H, *J* = 6.8 Hz), 3.17 (d, 1H, *J* = 6.8 Hz), 3.80 (d, 1H, *J* = 14.9 Hz), 3.89 (s, 1H), 5.01 (d, 1H, *J* = 14.9 Hz), 6.54 (d, 2H, *J* = 7.3 Hz), 6.82 (s, 1H), 6.92 (s, 1H), 7.09-7.15 (m, 2H), 7.22 (s, 2H), 7.31-7.33 (m, 3H), 7.46 (s, 2H), 7.49-7.51 (m, 3H); ^{13}C ($CDCl_3$, 75 MHz) δ 21.26, 21.40, 33.15, 47.37, 47.99, 50.16, 78.24, 125.27, 126.68, 127.10, 127.36, 128.03, 128.19, 128.51, 128.64, 128.74, 128.76, 135.74, 136.70, 137.57, 137.69, 142.54, 142.84, 165.74; IR (thin film) 2919s, 1659vs, 1452s, 731s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 488 M^+ (0.04), 340 (5), 265 (100), 239 (10), 223 (75), 208 (33), 193 (62), 178 (15), 120 (22), 91 (100), 65 (16), 42 (25). Anal. calcd for $C_{34}H_{36}N_2O$: C, 83.57; H, 7.43; N, 5.73. Found: C, 83.20; H, 7.90; N, 5.52. Specific rotation: $[\alpha]^{23}_D$ +58.3 (*c* 1.0 in CH_2Cl_2) on 97% ee *(2R,3R)*-**283g** (HPLC).



(*2R, 3R*) *Cis*-*N*-bis(3,5-di-tert-butyl-4-methoxylphenyl)methyl-3-phenyl-2-aziridinyl-*N*-benzyl-*N*-methyl-283h. The procedure described for the preparation of aziridine **283a** was followed with imine **2011** (277 mg, 0.5 mmol) except that the toluene was used as solvent, and the catalyst was prepared with *(S)*-VAPOL (27 mg, 0.05 mmol), H_2O (0.9 μL, 0.05 mmol), $B(OPh)_3$ (60 mg, 0.2 mmol) at 80 °C for 1 h, and then at 0.5 mm Hg at 80 °C for 0.5 h. The crude aziridine **283h** was purified by silica gel chromatography (25 mm × 400 mm column, 1:20:20 EtOAc/CH_2Cl_2/hexanes as the first eluent to remove the strong UV absorption fraction, then changed to 1:3 Et_2O/hexanes as the second eluent).

The aziridine **283h** was obtained as a white solid (mp. 169-170 °C) in 40% isolated yield (145 mg, 0.2 mmol). The compound **283h** appeared as a mixture of two rotamers in the ^{1}H NMR spectrum at the room temperature in a 3 : 1 molar ratio. The optical purity of **283h** was determined to be 93% ee by HPLC analysis (Chiralcel OD-H column, 90:10 hexane/*i*PrOH at 228nm, flow-rate: 0.7 mL/min). Retention times: R_t = 8.45 min *(2S, 3S)*-**283g** and R_t = 9.94 min *(2R,3R)*-**283g**.

Spectral data for the major rotamer of **283h**: R_f = 0.65 (1:3 EtOAc/hexanes); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.34 (s, 18H), 1.47 (s, 18H), 2.80 (s, 3H), 2.87 (d, 1H, *J* = 6.8 Hz), 3.16 (d, 1H, *J* = 6.7 Hz), 3.63 (s, 3H), 3.70 (s, 3H), 3.95 (s, 1H), 3.98 (d, 1H, *J* = 14.9 Hz), 4.82 (d, 1H, *J* = 14.9 Hz), 6.57 (d, 2H, *J* = 7.0 Hz), 7.08-7.13 (m, 3H), 7.30-7.33 (m, 3H), 7.41 (s, 2H), 7.54-7.56 (m, 2H), 7.62 (s, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 32.02, 32.19, 33.29, 35.66, 35.84, 47.71, 48.23, 50.24, 63.87, 63.97, 77.62, 125.46, 125.81, 126.74, 126.92, 127.16, 127.40, 127.61, 128.09, 128.23, 136.72, 136.80, 137.07, 142.82, 142.99, 158.03, 158.12, 165.73; IR (thin film) 2961vs, 1663s, 1414s, 1221s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 716 M^+ (0.36), 451 (26), 265 (29), 120 (14), 118 (13), 91 (100), 58 (84), 42 (24). Specific rotation: $[\alpha]^{23}_D$ +14.3 (*c* 1.0 in CH_2Cl_2) on 97% ee *(2R,3R)*-**283g** (HPLC).



(*2R, 3R*) *Cis*-*N*-bis(3,5-dimethyl-4-methoxylphenyl)methyl-3-phenyl-2-aziridinyl-*N*-benzyl-*N*-methyl-carboxylamide 30. The procedure for the preparation of aziridine **283h** was followed from imine **188d** (193.6 mg, 0.5 mmol) and *(S)*-VAPOL (54 mg, 0.1

mmol), H_2O (1.8 μL, 0.1 mmol), $B(OPh)_3$ (116 mg, 0.4 mmol). Purification by silica gel chromatography (25 mm × 400 mm column, 1:20:20 EtOAc/CH_2Cl_2/hexanes as the initial eluent until the strong UV absorption fraction eluted and then 1:2 Et_2O/hexanes was used as eluent) gave aziridine **283i** as a white solid (mp. 164-165 °C) in 77% isolated yield (213 mg, 0.39 mmol). Compound **283i** appeared as a mixture of two rotamers in the ^1H NMR spectrum at the room temperature in a 3 : 1 molar ratio. An optical purity of 98% ee was determined by HPLC analysis (Chiralcel OD column, 90:10 hexane/*i*PrOH at 222nm, flow-rate: 1.0 mL/min). Retention times: R_t = 13.80 min for *(2S,3S)*-**283i** and R_t = 18.80 min for *(2R, 3R)*-**283i**.

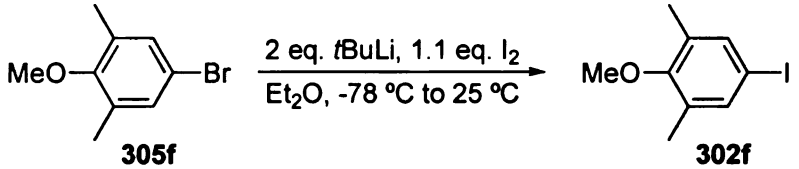
Spectral data for the major rotamer of *(2R,3R)*-**283i**: R_f = 0.28 (1:3 EtOAc/ Hexane); ^1H-NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 6H), 2.31 (s, 6H), 2.76 (d, 1H, *J* = 6.8 Hz), 2.77 (s, 3H), 3.12 (d, 1H, *J* = 6.8 Hz), 3.65 (s, 3H), 3.72 (s, 3H), 3.78 (s, 1H), 3.79 (d, 1H, *J* = 14.4 Hz), 4.98 (d, 1H, *J* = 14.9 Hz), 6.51 (d, 2H, *J* = 7.2 Hz), 7.05-7.12 (m, 3H), 7.18 (s, 2H), 7.26-7.30 (m, 3H), 7.42 (s, 2H), 7.45-7.47 (m, 2H); ^{13}C ($CDCl_3$, 125 MHz) δ 16.15, 16.24, 33.21, 47.41, 48.10, 50.21, 59.47, 59.55, 77.41, 126.73, 127.15, 127.39, 127.72, 127.73, 127.92, 127.97, 128.09, 128.23, 130.43, 130.51, 135.80, 136.69, 137.94, 138.29, 155.87, 165.80; IR (thin film) 2928vs, 1659vs, 1483s, 1221s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 548 M^+ (0.05), 400 (7), 283 (100), 265 (33), 253 (9), 120 (11), 91 (100), 43 (11). Specific rotation: $[\alpha]^{23}_D$ +51.6 (*c* 1.0 in CH_2Cl_2) on 98% ee material (HPLC).

^1H-NMR (C_6D_6, 500 MHz, 25 °C) (major rotamer): δ 2.08 (s, 6H), 2.19 (s, 3H), 2.32 (s, 6H), 2.42 (d, 1H, *J* = 6.7 Hz), 2.82 (d, 1H, *J* = 6.7 Hz), 3.15 (s, 3H), 3.30 (s, 3H), 3.48 (d, 1H, *J* = 15.0 Hz), 3.77 (s, 1H), 5.00 (d, 1H, *J* = 14.9 Hz), 6.42 (d, 2H, *J* = 7.8 Hz), 6.93-6.95 (m, 4H), 7.05 (t, 2H, *J* = 7.9 Hz), 7.41 (s, 2H), 7.52 (d, 2H, *J* = 7.7 Hz), 7.90 (s, 2H).

^{1}H-NMR (C_6D_6, 500 MHz, 25 °C) (minor rotamer): δ 2.06 (s, 6H), 2.27 (s, 6H), 2.40 (s, 3H), 2.60 (d, 1H, *J* = 6.7 Hz), 2.76 (d, 1H, *J* = 6.6 Hz), 3.14 (s, 3H), 3.25 (s, 3H), 3.68 (s, 1H), 3.86 (d, 1H, *J* = 16.1 Hz), 4.19 (d, 1H, *J* = 16.1 Hz), 6.53-6.55 (m, 2H), 6.97-7.00 (m, 4H), 7.10 (t, 2H, *J* = 7.7 Hz), 7.35 (s, 2H), 7.56 (d, 2H, *J* = 7.7 Hz), 7.77 (s, 2H).

The ^{1}H-NMR at 80 °C gave only one compound, ^{1}H-NMR (C_6D_6, 500 MHz, 80 °C): δ 2.07 (s, 6H), 2.26 (s, 6H), 2.33 (s, 3H), 2.52 (s, 1H), 2.85 (d, 1H, *J* = 6.2 Hz), 3.23 (s, 3H), 3.35 (s, 3H), 3.78 (s, 2H), 4.74 (s, 1H), 6.57 (s, 2H), 6.94-6.99 (m, 1H), 6.97-7.01 (m, 1H), 7.06 (t, 2H, *J* = 7.2 Hz), 7.13 (s, 2H), 7.32 (s, 2H), 7.48 (d, 2H, *J* = 7.3 Hz), 7.73 (s, 2H).

General procedure for the synthesis of aryl iodide – illustrated for the preparation of 3,5-dimethyl-4-methoxyiodobenzene 302f.



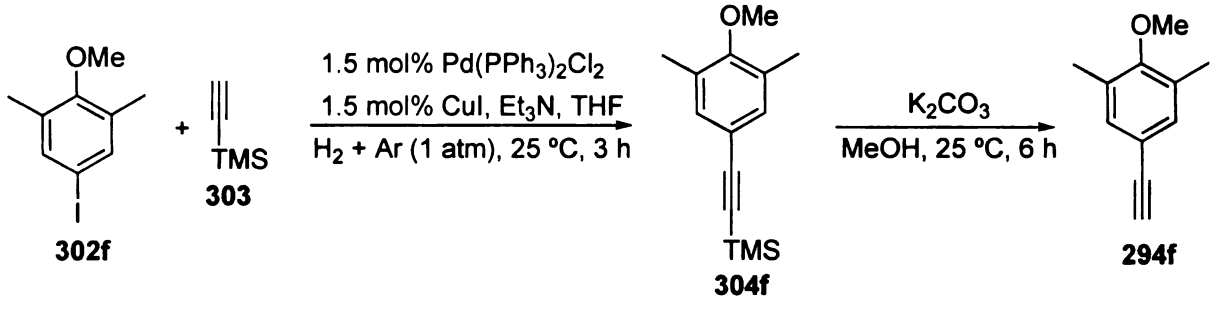
305f **302f**

To a 1 L flame-dried flask filled with argon was added bromide **305f** (21.2 g, 100 mmol) and Et_2O (250 mL). The mixture was stirred until the bromide was dissolved at room temperature and then the flask was submerged into a -78 °C bath, followed by slow addition of *t*-BuLi (143 mL, 200 mmol, 1.4 M in hexanes) and then the solution was stirred at -78 °C for 1h. At the same time, to a flame-dried 250 mL flask iodine (27.7 g, 110 mmol) was dissolved in Et_2O (150 mL). The iodine solution was then cooled to -78 °C and transferred to the aryllithium solution via cannula under the protection of argon to give a light yellow solution, which turned to a white slurry after the mixture was allowed to warm up gradually to room temperature and stir for an additional 2 h (the white slurry changed to light yellow slurry). The reaction was quenched by pouring the reaction mixture slowly into a 5% $Na_2S_2O_3$ solution (200 mL, aq.) to give a white slurry in the

organic layer, which changed to clear after stirring for 20 minutes. After extraction with Et_2O (100 mL × 3), the combined organic layer was washed with H_2O (100 mL × 2), then NaCl (aq. sat.) and dried over Na_2SO_4. Removal of the solvent by rotary evaporation afforded the crude product as an off-white solid. The ^1H NMR spectrum of the crude **302f** was clean, and it was used in the next step without purification.

Spectral data for **302f**: R_f = 0.3 (hexane). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.21 (s, 6H), 3.67 (s, 3H), 7.32 (s, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 15.68, 59.70, 87.57, 133.48, 137.48, 157.00; IR (thin film) 2937m, 1473vs, 1215s, 1013s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 262 M^+ (100), 247 (66), 120 (9), 103 (9), 92 (33), 91 (50), 77 (10).

General procedure for the synthesis of aryl acetylenes – illustrated for the Preparation of 3,5-dimethyl-4-methoxyphenylacetylene 294f.

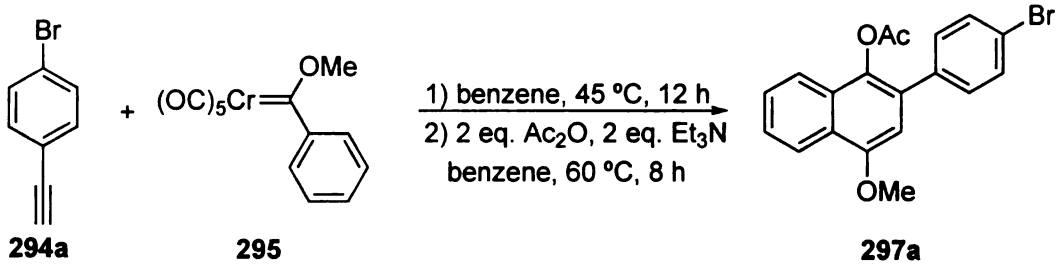


To a 250 mL flame-dried flask filled with argon was added the crude iodide **302f** (5.2 g, ~20 mmol), $Pd(PPh_3)_2Cl_2$ (210 mg, 0.3 mmol) and CuI (57 mg, 0.3 mmol). The flask was then connected to vacuum and then filled with argon and this was repeated for three times. The flask was connected to a vacuum, then opened to a balloon filled with a mixture of H_2 and Ar (10-40% H_2 in Ar) for a few seconds. This was repeated three times and on the last cycle, the flask was opened to the balloon. Following the addition of Et_2O (20 mL, mmol) and THF (100 mL), the reaction mixture was stirred at room temperature for 5 minutes and then trimethylsilyl acetylene **303** (3.2 mL, 22 mmol) was added slowly over one minute. The reaction mixture was stirred for 3 h to give a greenish slurry and

after removal of most of the solvent by rotary evaporation, the residue was treated with 150 mL $NaHCO_3$ (aq. sat.) and 150 Et_2O and the resulting mixture was extracted with Et_2O (50 mL × 3). The combined organic phase was washed with H_2O (100 mL × 2), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product as dark brown liquid, which was roughly purified by passing through a short column (20 mm × 100 mm, neutral Al_2O_3, hexanes as eluent) to give the partially purified product **304f** as a yellow liquid. It was then taken up in 60 mL MeOH and treated with K_2CO_3 (8 g, 60 mmol). The reaction mixture was stirred at room temperature for 4 h to give complete conversion as monitored by TLC. To the reaction mixture was added 200 mL H_2O and this was followed by extraction with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude **294f** as light yellow liquid. Purification by silica gel chromatography (25 mm × 300 mm, hexanes as eluent) afforded **294f** (2.5 g, 16 mmol) as light yellow liquid in 78% overall yield from **305f**.

Spectral data for **294f**: R_f = 0.25 (hexane). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 6H), 3.00 (s, 1H), 3.74 (s, 3H), 7.20 (s, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 15.85, 59.64, 75.91, 83.62, 117.29, 131.07, 132.64, 157.67; IR (thin film) 3291s, 2106m, 1479s, 1226vs, 1013s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 161 M^+ +1(20), 160 M^+ (100), 145 (90), 128 (12), 116 (19), 115 (75), 102 (12), 91 (40), 77 (11), 63 (11), 51 (11).

General procedure for the synthesis of naphthalenes 297– illustrated for the preparation of 2-(4-bromophenyl)-4-methoxynaphthalenyl acetate 297a.

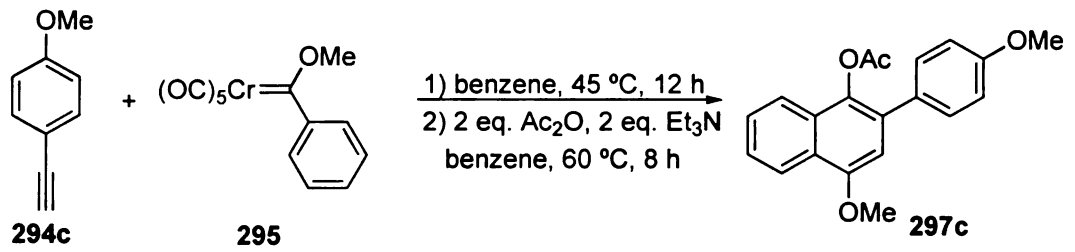


294a **295** **297a**

To a 25 mL flame-dried Schlenk flask flushed with argon was added carbene complex **295** (312 mg, 1 mmol), acetylene **294a** (234 mg, 1.3 mmol) (prepared following the same procedure as described for the preparation of **294f** from 4-bromo-1-iodobenzene **302a**) and benzene (5 mL). The stopcock was sealed, and the flask was then placed in a liquid nitrogen bath. After 30 minutes, a vacuum (0.5 mm Hg) was applied carefully and maintained for 3 minutes while the flask was still in the liquid nitrogen bath, the flask was then sealed and the bath was removed and the flask was then allowed to warm up to room temperature. The flask was returned to the liquid nitrogen bath with the stopcock sealed. This process was repeated for three times and the flask was filled with argon at room temperature on the last cycle and then the stopcock was sealed. The flask was put into a 45 °C bath and the contents were stirred for 20 h. The flask was then removed from the bath and cooled to room temperature. Ac_2O (189 μL, 2 mmol) and Et_3N (278 μL, 2 mmol) were added under a stream of argon, the stopcock was then sealed and the reaction mixture was stirred at 60 °C for 12 h. The flask was then cooled to room temperature and the stopcock was then opened to air and the mixture was stirred for another 4 h. The precipitate was removed by fast filtration, the filtrate was collected and concentrated. Purification by silica gel chromatography (18 mm × 230 mm column, 1:15 EtOAc/hexanes as eluent) gave the product **297a** as a light yellow solid (mp. 136 – 137 °C) in 65% yield (240 mg, 0.65 mmol).

Spectral data for **297a**: R_f = 0.33 (1: 9 EtOAc / Hexanes). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.27 (s, 3H), 4.04 (s, 3H), 6.82 (s, 1H), 7.48 (d, 2H, *J* = 7.6 Hz), 7.58-7.65 (m, 4H), 7.85 (d, 1H, *J* = 7.8 Hz), 8.37 (d, 1H, *J* = 7.8 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 20.53, 55.62, 104.94, 121.16, 121.68, 122.34, 125.72, 125.83, 127.45, 127.78, 129.47, 130.60, 131.43, 136.54, 137.25, 153.51, 169.29; IR (thin film) 1763vs, 1366m, 1204vs cm^{-1}; mass spectrum, *m/z* (% rel intensity) 372 M^+ (6, ^{81}Br), 370 M^+ (6, ^{79}Br), 330 (86, ^{81}Br),

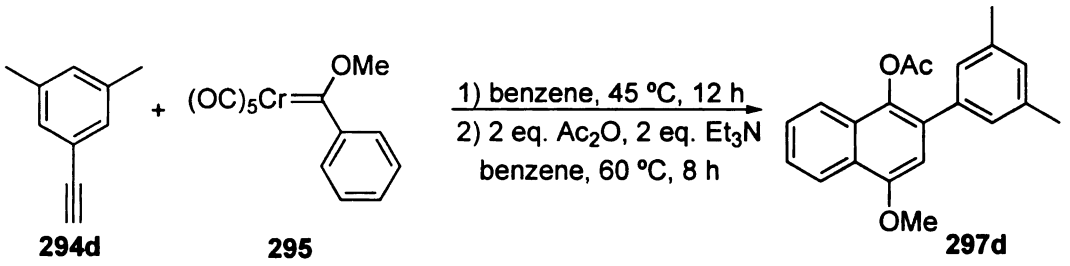
328 (79, ^{79}Br), 315 (60, ^{81}Br), 313 (56, ^{79}Br), 248 (32), 233 (38), 205 (57), 189 (14), 176 (68), 151 (12), 104 (55), 83 (38), 75 (100), 57 (12), 49 (16), 43 (48).



294c **295** **297c**

2-(4-methoxylphenyl)-4-methoxynaphthalenyl acetate 297c. The procedure for the synthesis of **297a** was followed except for the following difference. The carbene complex **295** (3.12 g, 10 mmol) and benzene (40 mL) were added to a flame-dried 100 mL flask, and the resulting solution was purged with argon for 5 minute with a needle under the surface. At the same time, the acetylene **294c** (1.72 g, 13 mmol) (prepared following the same procedure as described for the preparation of **294f** from 4-methoxy-1-iodobenzene **302c**) was dissolved in dry benzene (10 mL) in a flame-dried flask, and the solution was added to the carbene solution via slow addition by syringe pump at 45 °C over 10 minutes. Purification by silica gel chromatography (25 mm × 400 mm column, 1:9 EtOAc/hexanes as eluent) gave the product **297c** as light yellow solid (mp. 121 – 122 °C) in 42% yield (1.35 g, 4.2 mmol).

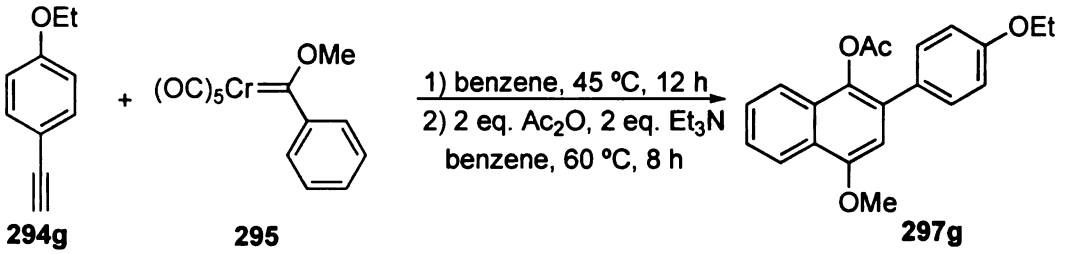
Spectral data for **297c**: R_f = 0.45 (1: 3 EtOAc / Hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.27 (s, 3H), 3.90 (s, 3H), 4.05 (s, 3H), 6.87 (s, 1H), 7.05-7.06 (m, 2H), 7.56-7.61 (m, 4H), 7.83 (s, 1H), 8.35 (s, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 20.59, 55.17, 55.62, 105.64, 113.79, 121.09, 122.29, 125.44, 127.28, 127.90, 130.08, 130.36, 130.67, 136.58, 153.36, 159.00, 169.51 (one sp^2 carbon not located); IR (thin film) 1761vs, 1611s, 1510vs, 1251vs, 1205vs cm^{-1}; mass spectrum, *m/z* (% rel intensity) 322 M^+ (11), 280 (100), 165 (10), 104 (17), 75 (9), 43 (9).



294d **295** **297d**

2-(3,5-dimethylphenyl)-4-methoxynaphthalenyl acetate 297d. The procedure for the synthesis of **297c** was followed for the reaction of carbene complex **295** (3.12 g, 10 mmol), acetylene **294d** (1.91 g, 13 mmol) (prepared following the same procedure as described for the preparation of **294f** from 3,5-dimethyl-1-iodobenzene **302d**). Purification by silica gel chromatography (25 mm × 400 mm column, 1:15 EtOAc/hexanes as eluent) gave the product **297d** as light yellow solid (mp. 139-141 °C) in 67% yield (2.16 g, 6.7 mmol).

Spectral data for **297d**: R_f = 0.35 (1: 9 EtOAc / Hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 2.44 (s, 6H), 4.06 (s, 3H), 6.87 (s, 1H), 7.07 (s, 1H), 7.22 (s, 2H), 7.55-7.62 (m, 2H), 7.82 (d, 1H, *J* = 8.3 Hz), 8.33 (d, 1H, *J* = 8.1 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 20.64, 21.32, 55.71, 105.69, 121.21, 122.33, 125.54, 126.71, 127.28, 127.91, 129.11, 130.86, 136.63, 137.79, 138.27, 153.37, 169.58 (one sp^2 carbon not located); IR (thin film) 1761vs, 1597s, 1383s, 1201vs cm^{-1}; mass spectrum, *m/z* (% rel intensity) 320 M^+ (6), 278 (100), 263 (27), 245 (11), 104 (11), 76 (11), 42 (10).



294g **295** **297g**

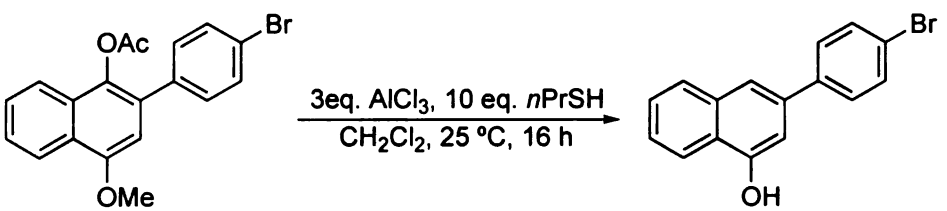
2-(4-ethoxylphenyl)-4-methoxynaphthalenyl acetate 297g. The procedure for the synthesis of **297c** was followed for the reaction of acetylene **294g** (1.09 g, 7.5 mmol) (prepared following the same procedure as described for the preparation of **294f** from 4-

ethoxyl-1-iodobenzene **302g**) and carbene complex **295** (1.6 g, 5 mmol). Purification by silica gel chromatography (25 mm × 300 mm column, 1:9 EtOAc/hexanes as eluent) gave the product **297g** as a light yellow solid (mp. 123 – 124 °C) in 47% yield (0.79 g, 2.3 mmol).

Spectral data for **297g**: R_f = 0.3 (1: 5 EtOAc / Hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (t, 3H, *J* = 7.1 Hz), 2.23 (s, 3H), 4.04 (s, 3H), 4.11 (q, 2H, *J* = 7.1 Hz), 6.82 (s, 1H), 7.00 (d, 2H, *J* = 8.8 Hz), 7.48 (d, 2H, *J* = 8.8 Hz), 7.47-7.58 (m, 2H), 7.77 (d, 1H, *J* = 7.8 Hz), 8.29 (d, 1H, *J* = 7.8 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 14.85, 20.70, 55.74, 63.48, 105.74, 114.39, 121.14, 122.36, 125.49, 127.32, 127.96, 130.13, 130.48, 130.60, 136.64, 153.42, 158.44, 169.62 (one sp^2 carbon not located); IR (thin film) 1761s, 1516s, 1206vs cm^{-1}; mass spectrum, *m/z* (% rel intensity) 336 M^+ (22), 294 (100), 279 (40), 251 (10), 221 (7), 165 (10), 105 (8).

General procedure for the synthesis of naphthols 301 – illustrated for the preparation of 3-(4-bromophenyl)naphthol 301a.

Method A: Deprotection from the intermediate 297a

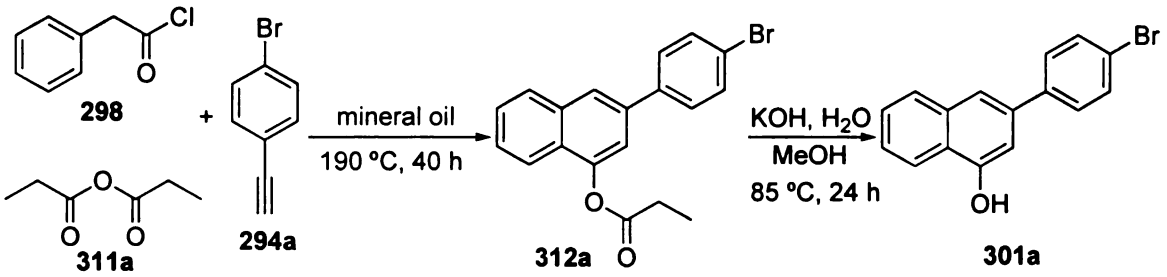


297a **301a**

To a 25 mL flame-dried flask flushed with argon was added acetate **297a** (0.624 g, 1.68 mmol) and CH_2Cl_2 (8 mL), followed by $AlCl_3$ (0.66 g, 5 mmol) at 0 °C to give a red slurry. This was followed by the slow addition of *n*-PrSH (1.4 mL, 17 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for 16 h. The reaction was quenched by slow addition of a pH = 7 buffer. The organic layer was collected, and the aqueous layer (should be colorless, if not, it should be neutralized with $NaHCO_3$) was

extracted with CH_2Cl_2 (10 mL × 3). The combined organic layer was then washed with $NaHCO_3$ (aq. sat.), followed by extraction with CH_2Cl_2 (10 mL × 3). The combined organic extract was washed with NaCl (aq. sat.) and concentrated under reduced pressure to give the crude product as a brown solid. Purification by silica gel chromatography (25 mm × 350 mm column, 1:1:8 EtOAc/CH_2Cl_2/hexanes as eluent) gave the product **301a** as a light yellow solid in 66% yield (333 mg, 1.1 mmol).

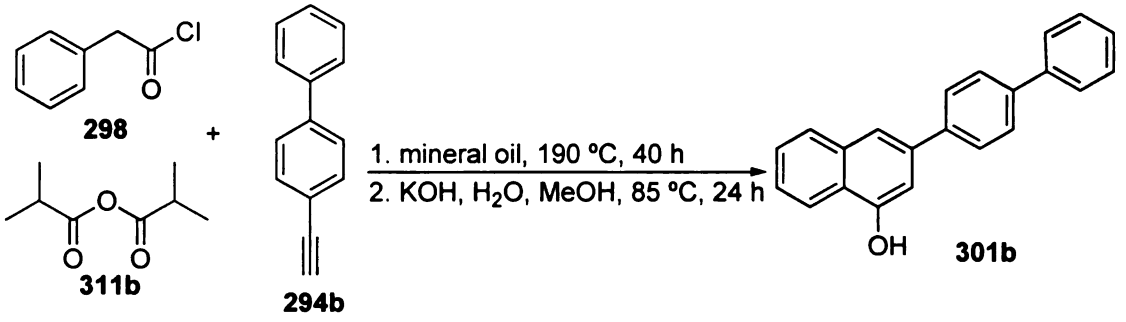
Method B: Preparation of 301 via ketene insertion procedure.



To a 25 mL flame-dried three neck flask equipped with a cooling condenser and flushed with argon was added acetylene **294a** (0.9 g, 5 mmol), phenylacetyl chloride **298** (1.5 mL, 10 mmol), propionic anhydride **311a** (1.3 mL, 10 mmol) and 3 mL mineral oil. An inert atmosphere was maintained by a nitrogen flow across the top of the condenser, and the flask was set into a 190 °C bath, the reaction mixture was stirred at that temperature for 40 h. The reaction mixture was then cooled to room temperature and roughly purified by silica gel chromatography (20 mm × 300 mm column, 1: 9 EtOAc/ hexanes as eluent, R_f = 0.4 (1:9 EtOAc/hexanes)) to remove most of the polar impurities. The partially purified compound **312a** was then dissolved in 10 mL MeOH and 10 H_2O, and then KOH (1.1 g, 20 mmol) was added. The mixture was put into an 85 °C bath and stirred for 24 h. Upon completion, most of the MeOH was removed under reduced pressure, and then EtOAc (20 mL) was added to the residue and the red aqueous layer was slowly treated with 20% HCl solution until a colorless or light yellow

solution just appeared. The aqueous layer was extracted with EtOAc (20 mL × 3) and the combined organic layer was washed with NaCl (aq. sat.), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product **301a** as brown sticky solid. Purification by silica gel chromatography (25 mm × 350 mm column, 1:1:8 EtOAc/CH_2Cl_2/hexanes as eluent) gave the product **301a** as a light yellow solid (mp. 162-163 °C) in 45% yield (670 mg, 2.3 mmol).

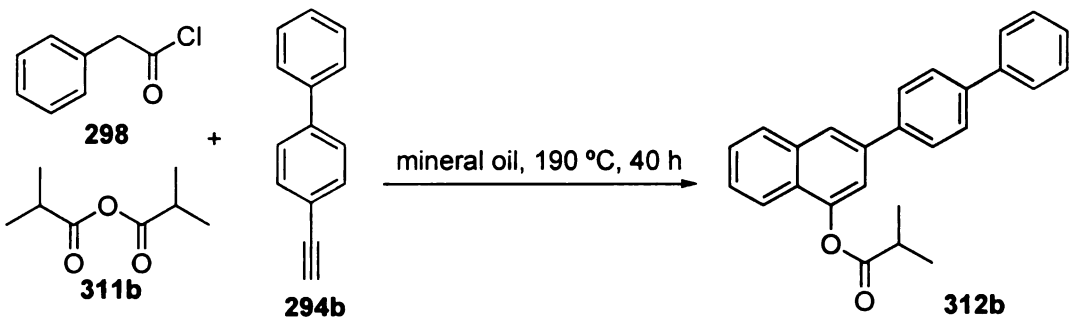
Spectral data for **301a**: R_f = 0.22 (1:1:8 EtOAc/CH_2Cl_2/hexanes). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.31 (s, 1H), 7.05 (d, 1H, *J* = 1.5 Hz), 7.52-7.63 (m, 7H), 7.88 (dd, 1H, *J* = 1.6, 7.9 Hz), 8.18 (dd, 1H, *J* = 1.2, 8.1 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 107.97, 118.72, 121.44, 121.71, 123.66, 125.58, 127.09, 128.03, 128.84, 131.92, 134.91, 137.63, 139.82, 151.84; IR (thin film) 3231br vs, 1603m, 1400s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 300 M^+ (62, ^{81}Br), 298 M^+ (100, ^{79}Br), 191 (31), 189 (84), 163 (12), 109 (23), 95 (58), 82 (20), 62 (12).



3-(4-phenylphenyl)naphthol 301b. The same procedure for the synthesis of **301a** using method B was followed except for the following differences. Starting from acetylene **294b** (1.55 g, 8.7 mmol) (prepared following the same procedure as described for the preparation of **294f** from 4-phenyl-1-iodobenzene **302b**), phenylacetyl chloride **298** (2.1 mL, 17 mmol), isobutyric anhydride **311b** (2.9 mL, 17 mmol) and 7 mL mineral oil. Purification by silica gel chromatography (25 mm × 400 mm column, 1:1:8

EtOAc/CH_2Cl_2/hexanes as eluent) gave the product **301b** as a light yellow solid (mp. 162-163 °C) in 61% yield (1.57 g, 5.3 mmol).

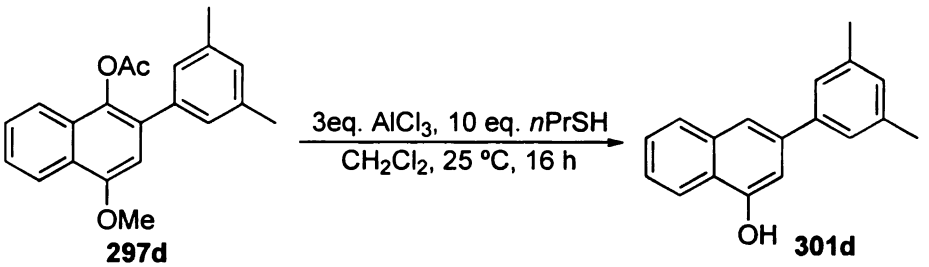
Spectral data for **301b**: R_f = 0.3 (1:1:8 EtOAc/CH_2Cl_2/hexanes). ^1H NMR ($CDCl_3$, 300 MHz) δ 5.35 (s, 1H), 7.11 (d, 1H, *J* = 1.5 Hz), 7.37 (t, 1H, *J* = 7.3 Hz), 7.45-7.51 (m, 4H), 7.52-7.54 (m, 2H), 7.64-7.70 (m, 3H), 7.73-7.75 (m, 2H), 7.87 (d, 1H, *J* = 8.5 Hz), 8.18 (d, 1H, *J* = 8.3 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 108.20, 118.66, 121.48, 123.60, 125.39, 126.96, 127.04, 127.40, 127.54, 127.62, 128.05, 128.85, 134.98, 138.31, 139.71, 140.27, 140.61, 151.74; IR (thin film) 3323br s, 1597m, 1576m, 1402s, 831s, 764s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 297 M^++1 (18), 296 M^+ (100), 295 M^+-1 (10), 267 (13), 148 (14), 126 (10), 120 (13).



3-(4-phenylphenyl)naphthalenyl isobutyrate 312b After the first step of the reaction described above for **301b**, partial of the crude intermediate was taken and purified to give compound **312b** as a light yellow solid (mp. 146.5-147.5 °C) for characterization, the following hydrolysis step was omitted.

Spectral data for **312b**: R_f = 0.6 (1:1:8 EtOAc/CH_2Cl_2/hexanes). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46 (d, 6H, *J* = 6.9 Hz), 3.01-3.05 (m, 1H), 7.34-7.37 (m, 1H), 7.46 (t, 2H, *J* = 7.6 Hz), 7.50 (t, 2H, *J* = 7.4 Hz), 7.54 (s, 1H), 7.65 (d, 2H, *J* = 8.0 Hz), 7.69 (d, 2H, *J* = 8.5 Hz), 7.78 (d, 2H, *J* = 8.1 Hz), 7.85 (d, 1H, *J* = 7.6 Hz), 7.91 (d, 1H, *J* = 7.6 Hz), 7.97 (s, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 19.21, 34.46, 117.67, 121.04, 123.49, 126.11, 126.42,

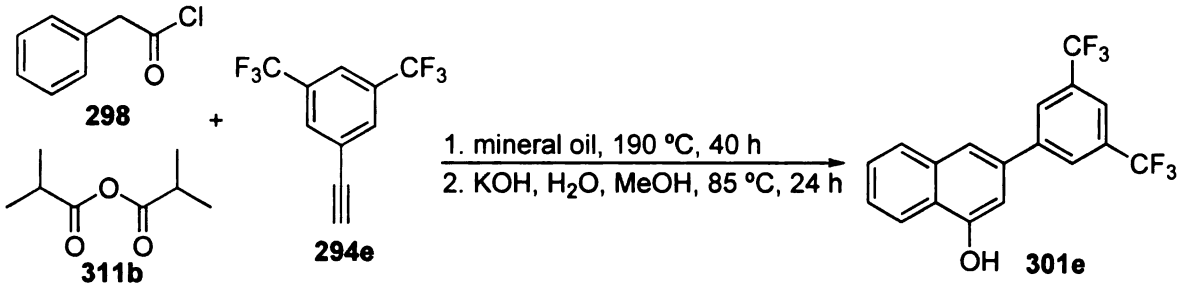
126.84, 127.07, 127.42, 127.58, 127.75, 128.40, 128.83, 134.87, 138.05, 139.21, 140.48, 140.61, 147.18, 175.52; IR (thin film) 1753vs, 1116vs cm^{-1}; mass spectrum, *m/z* (% rel intensity) 366 M^+ (15), 366 M^+-1 (13), 266 (14), 189 (12), 165 (14), 70 (13), 43 (54).



297d **301d**

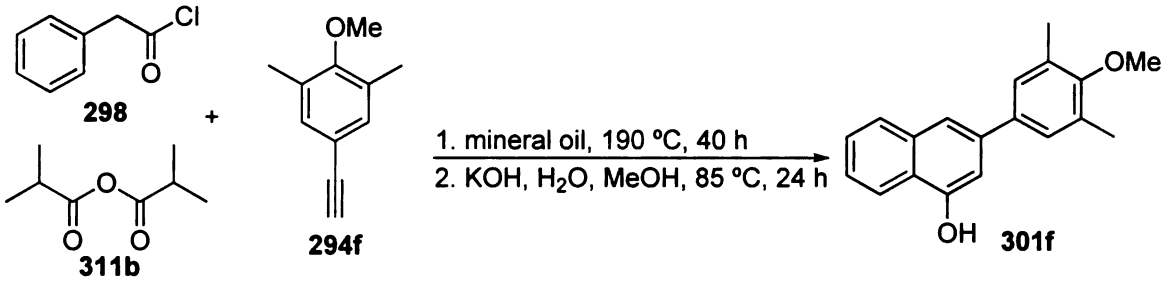
3-(3,5-dimethylphenyl)naphthol 301d. The procedure for the synthesis of **301a** using method A was followed for the reaction of acetate **297d** (2.16 g, 6.7 mmol). Purification by silica gel chromatography (25 mm × 400 mm column, 1:1:20 EtOAc/CH_2Cl_2/hexanes as eluent) gave the product **301d** as a light yellow solid (mp. 103 – 104 °C) in 75% yield (1.2 g, 5 mmol).

Spectral data for **301d**: R_f = 0.35 (1:1:8 EtOAc/CH_2Cl_2/hexanes). ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 6H), 5.25 (s, 1H), 7.01 (s, 1H), 7.07 (d, 1H, *J* = 1.6 Hz), 7.29 (s, 2H), 7.45-7.51 (m, 2H), 7.63 (s, 1H), 7.84 (dd, 1H, *J* = 1.2, 7.8 Hz), 8.15 (dd, 1H, *J* = 1.6, 8.0 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 21.42, 108.53, 118.70, 121.40, 123.46, 125.18, 125.21, 126.79, 127.98, 129.10, 134.94, 138.32, 139.13, 140.86, 151.55; IR (thin film) 3403br vs, 1634m, 1595vs, 1400s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 249 M^++1 (16), 248 M^+ (100), 215 (20), 101 (14).



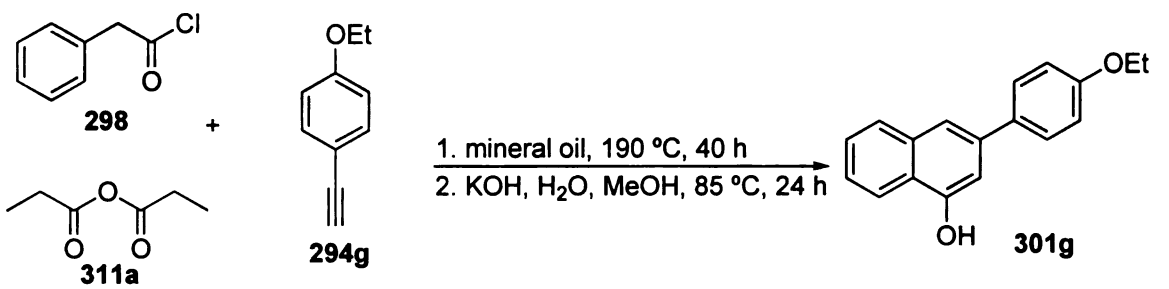
3-(3,5-bistrifluoromethylphenyl)naphthol 301e. The procedure for the synthesis of **301b** using method B was followed for the reaction of acetylene **294e** (3.32 g, 13.9 mmol) (prepared following the same procedure as described for the preparation of **294f** from 3,5-bis(trifluoromethyl)-1-iodobenzene **302e**), phenylacetyl chloride **298** (3.4 mL, 27 mmol), and isobutyric anhydride **311b** (4.6 mL, 27 mmol) in 10 mL mineral oil. Purification by silica gel chromatography (25 mm × 400 mm column, 1:1:20 EtOAc/CH_2Cl_2/hexanes as eluent) gave the product **301e** as a yellow solid (mp. 82-84 °C) in 51% yield (2.52 g, 7.2 mmol).

Spectral data for **301e**: R_f = 0.18 (1:1:20 EtOAc/CH_2Cl_2/hexanes). ^1H NMR ($CDCl_3$, 500 MHz) δ 5.62 (s, 1H), 7.02 (t, 1H, *J* = 1.3 Hz), 7.52-7.57 (m, 2H), 7.64 (s, 1H), 7.87 (s, 1H), 7.88 (d, 1H, *J* = 6.8 Hz), 8.08 (s, 2H), 8.19 (dd, 1H, *J* = 0.7, 7.3 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 107.45, 119.40, 121.58, 123.40 (q, *J* = 273 Hz, CF_3), 124.19, 126.28, 127.25, 127.28, 127.48, 128.21, 132.10 (q, *J* = 33 Hz), 134.80, 135.65, 142.99, 152.38; IR (thin film) 3420br s, 1599m, 1371s, 1277vs, 1177s, 1132s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 357 M^++1 (20), 356 M^+ (85), 355 M^+-1 (100), 327 (35), 259 (34), 238 (17), 189 (18), 178 (24), 153 (12), 129 (20), 119 (27), 115 (59), 94 (13), 89 (14).



3-(3,5-dimethyl-4-methoxylphenyl)naphthol 301f. The procedure for the synthesis of **301b** using method B was followed for the reaction of acetylene **294f** (3.24 g, 20 mmol), phenylacetyl chloride **298** (5.4 mL, 40 mmol), and isobutyric anhydride **311b** (6.8 mL, 40 mmol) in 5 mL mineral oil. Purification by silica gel chromatography (25 mm × 400 mm column, 1:1:8 EtOAc/CH_2Cl_2/hexanes as eluent) gave the product **301f** as a light yellow solid (mp. 154.5 – 155.5 °C) in 65% yield (3.6 g, 13 mmol).

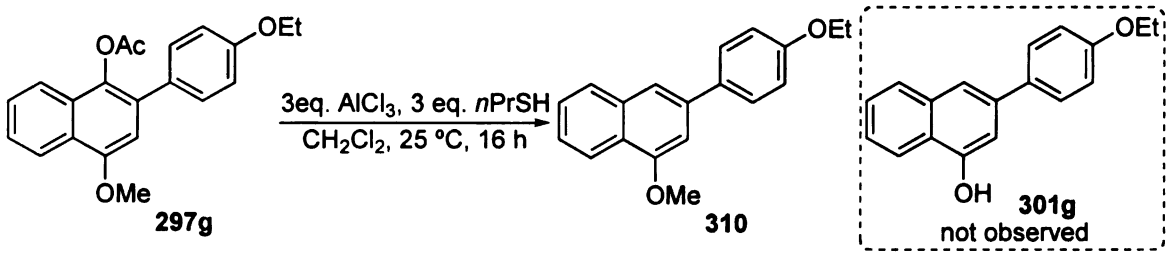
Spectral data for **301f**: R_f = 0.24 (1:1:8 EtOAc/CH_2Cl_2/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.36 (s, 6H), 3.79 (s, 3H), 5.58 (br, s, 1H), 6.98 (d, 1H, *J* = 1.5 Hz), 7.30 (s, 2H), 7.43-7.50 (m, 2H), 7.57 (s, 1H), 7.81 (d, 1H, *J* = 7.8 Hz), 8.15 (d, 1H, *J* = 8.1 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 16.29, 59.84, 108.39, 118.30, 121.45, 123.39, 125.06, 126.78, 127.76, 127.90, 131.17, 134.95, 136.57, 138.68, 151.65, 156.53; IR (thin film) 3343br,s, 1489s, 1462s, 1229s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 279 M^+ +1 (23), 278 M^+ (100), 263 (88), 202 (8), 132 (6).



3-(4-ethoxylphenyl)naphthol 301g. The procedure for the synthesis of **301b** using method B was followed for the reaction of acetylene **294g** (1.69 g, 11.6 mmol),

phenylacetyl chloride **298** (3.1 mL, 23 mmol), propionic anhydride **311a** (3 mL, 23 mmol) and 3 mL mineral oil. Purification by silica gel chromatography (25 mm × 300 mm column, 1:1:8 EtOAc/CH_2Cl_2/hexanes as eluent) gave the product **301g** as a light yellow solid (mp. 145.5 – 146.5 °C) in 61% yield (1.8 g, 7 mmol).

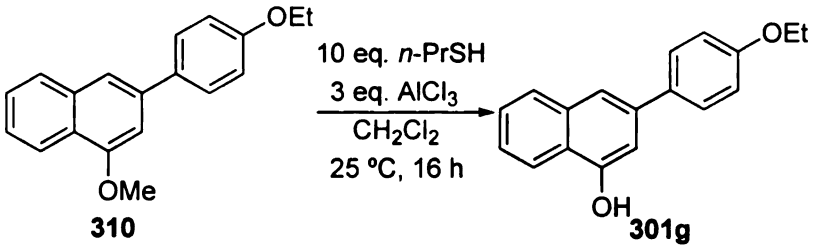
Spectral data for **301g**: R_f = 0.22 (1:1:8 EtOAc/CH_2Cl_2/hexanes). ^1H NMR ($CDCl_3$, 500 MHz) δ 1.44 (t, 3H, *J* = 7.0 Hz), 4.08 (q, 2H, *J* = 7.0 Hz), 5.24 (s, 1H), 6.98 (d, 2H, *J* = 8.7 Hz), 7.05 (d, 1H, *J* = 1.5 Hz), 7.42-7.50 (s, 2H), 7.58 (s, 1H), 7.59 (d, 2H, *J* = 8.8 Hz), 7.82 (d, 1H, *J* = 7.8 Hz), 8.13 (d, 1H, *J* = 8.3 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 14.85, 63.58, 108.24, 114.85, 117.95, 121.41, 123.25, 124.98, 126.80, 127.86, 128.27, 133.27, 135.04, 138.56, 151.69, 158.66; IR (thin film) 3353br, s, 1580m, 1510s, 1404vs cm^{-1}; mass spectrum, *m/z* (% rel intensity) 265 M^+ +1 (21), 264 M^+ (100), 236 (51), 207 (16), 178 (7).



3-(4-ethoxylphenyl)-1-methoxynaphthalene 310. The procedure for the synthesis of **301a** using method A was followed except for the following differences. The reaction was performed with acetate **297g** (336 g, 1 mmol), $AlCl_3$ (0.4 g, 3 mmol) and *n*-PrSH (0.25 mL, 3 mmol). Purification by silica gel chromatography (18 mm × 300 mm column, 1:20 EtOAc/hexanes as eluent) gave the product **310** as a white solid (mp. 105 – 106 °C) in 77% yield (214 mg, 0.77 mmol). The desired product **301g** was not observed.

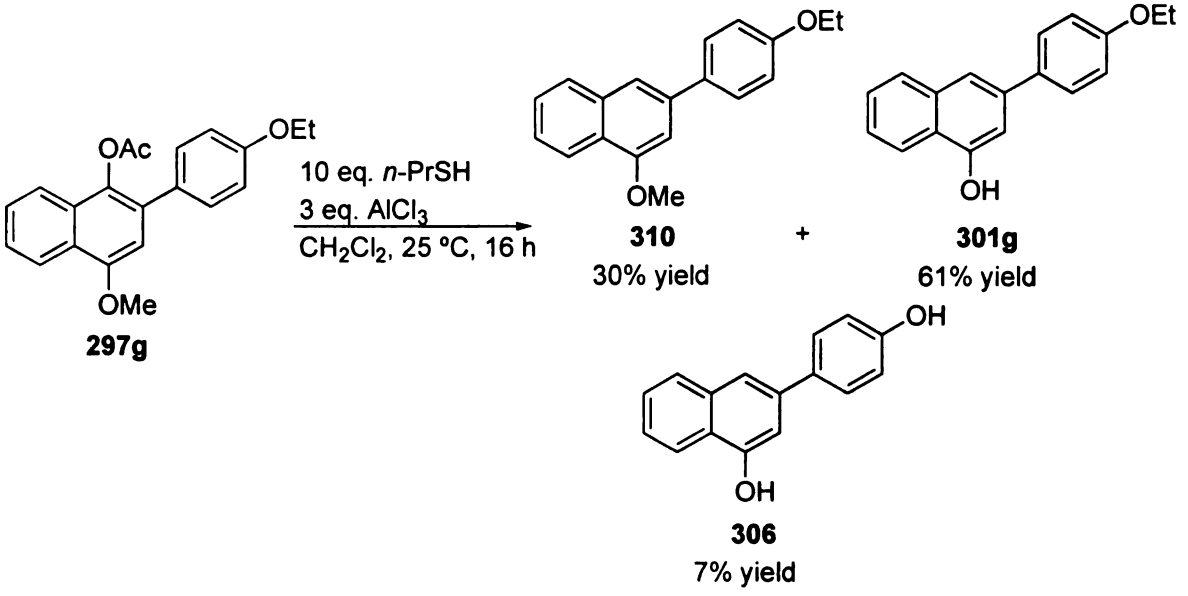
Spectral data for **310**: R_f = 0.55 (1:9 EtOAc/hexanes). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (t, 3H, *J* = 7.1 Hz), 4.11 (s, 3H), 4.15 (q, 2H, *J* = 7.1 Hz), 7.05 (d, 2H, *J* = 7.7 Hz), 7.07 (s, 1H), 7.46-7.57 (m, 2H), 7.62 (s, 1H), 7.68 (d, 2H, *J* = 8.8 Hz), 7.87 (d, 1H, *J* =

8.8 Hz), 8.28 (d, 1H, J = 8.0 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 14.86, 55.57, 63.55, 103.68, 114.80, 117.64, 121.87, 124.50, 124.93, 126.76, 127.62, 128.38, 133.98, 134.68, 138.57, 155.74, 158.62; IR (thin film) 1510s, 1504vs, 1246vs, 1230s, 1113s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 279 M^+ +1 (42), 278 M^+ (100), 249 (55), 235 (15), 221 (11), 207 (30), 189 (13), 179 (21), 125 (10).



310 **301g**

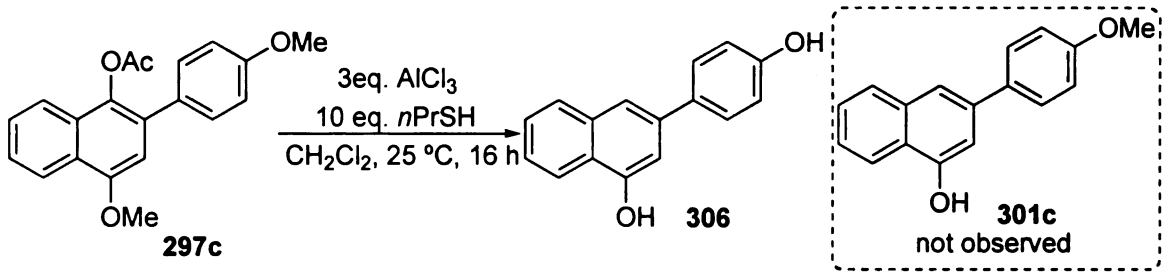
Deprotection of compound 310. The procedure for the synthesis of **301a** using method A was followed for the reaction of compound **310** (28 mg, 0.1 mmol). Purification by silica gel chromatography (15 mm × 200 mm column, 1:5 EtOAc/hexanes as eluent) gave the product **301g** as a light yellow solid in 37% yield (10 mg, 0.04 mmol).



297g

Deprotection of compound 297g. The procedure for the synthesis of **301a** using method A was followed for the reaction of acetate **297g** (200 mg, 0.59 mmol).

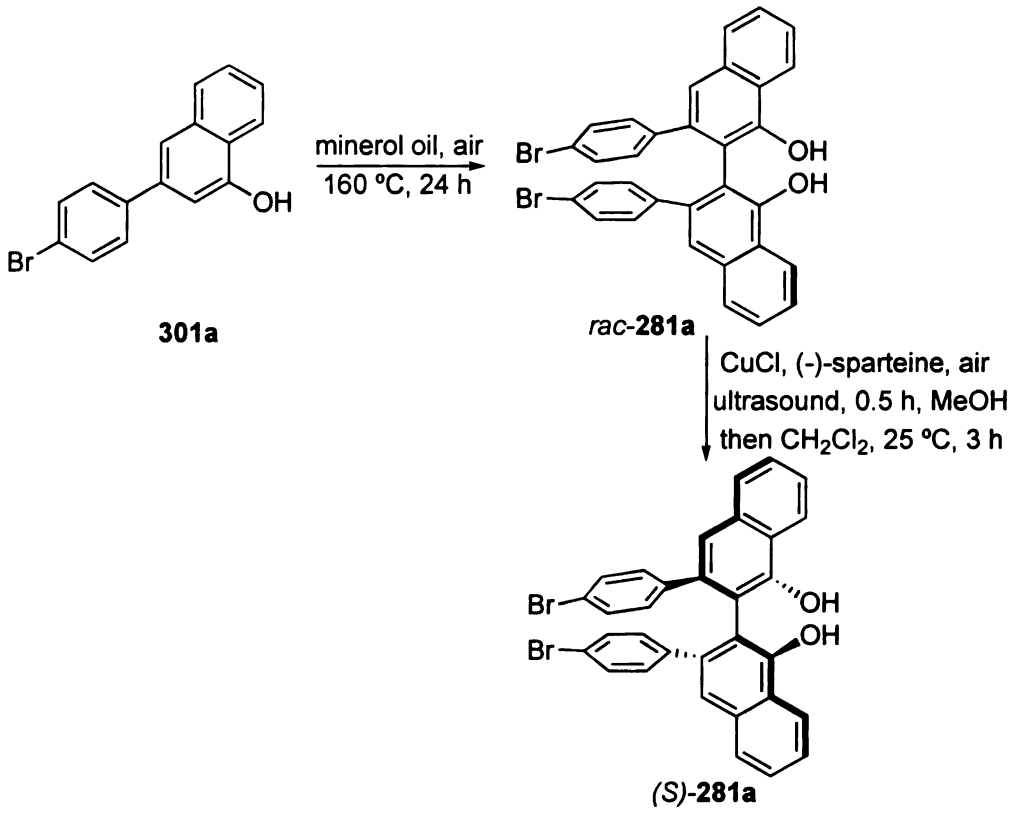
Purification by silica gel chromatography (25 mm × 300 mm column, 1:1:8 EtOAc/CH_2Cl_2/hexanes as eluent) gave the product **301g** as a light yellow solid in 66% yield (105 mg, 0.4 mmol), compound **310** as a white solid in 30% yield (57 mg, 0.2 mmol) (see spectra data above) and compound **306** in 7% yield (19 mg, 8 mmol).



3-(4-hydroxylphenyl)naphthol 306. The procedure for the synthesis of **301a** using method A was followed for the reaction of acetate **297c** (1.31 g, 4 mmol). Purification by silica gel chromatography (25 mm × 300 mm column, 1:5:5 EtOAc/CH_2Cl_2/hexanes as eluent) gave the product **306** as a white solid (mp. 189.5 – 190.5 °C) in 80% yield (760 mg, 3.2 mmol). The desired product **301c** was not observed.

Spectral data for **306**: R_f = 0.15 (1:3 EtOAc/hexanes). ^1H NMR (CD_3COCD_3, 300 MHz) δ 3.05 (br s, 1H), 6.95 (d, 2H, *J* = 8.3 Hz), 7.20 (s, 1H), 7.35-7.42 (m, 1H), 7.45-7.48 (m, 1H), 7.53-7.61 (m, 3H), 7.84 (d, 1H, *J* = 8.3 Hz), 8.21 (d, 1H, *J* = 8.3 Hz), 8.78 (br s, 1H); ^{13}C ($CDCl_3$, 75 MHz) δ 108.15, 116.52, 116.94, 122.78, 124.70, 125.13, 127.31, 128.54, 128.99, 133.28, 136.18, 139.80, 154.28, 158.01; IR (thin film) 3357br vs, 1686m, 1601s, 1510vs, 1402s, 1262s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 238 M^++2 (4), 237 M^++1 (27), 236 M^+ (100), 178 (11), 95 (11).

General procedure for the synthesis of chiral *(S)*-281 – illustrated by the preparation of *(S)*-bis(3-(4-bromophenyl))-2,2'-binaphthol 281a.



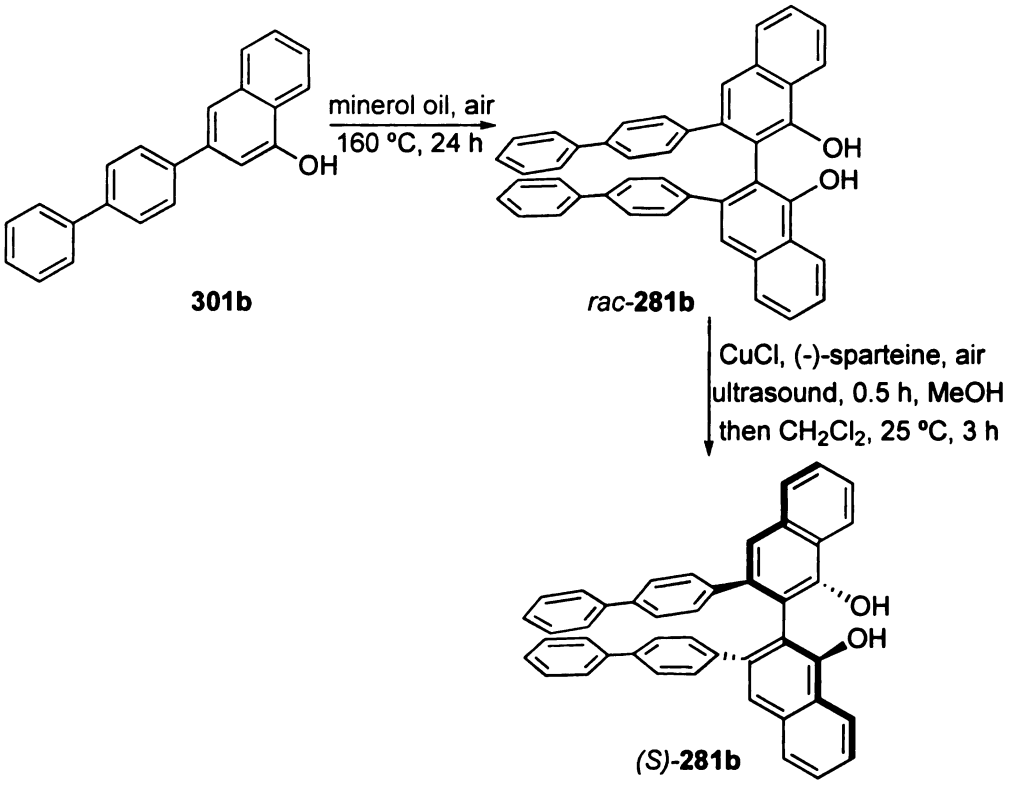
Thermally induced oxidative coupling of the monomer 301a: To a 25 mL flame-dried three neck flask equipped with a cooling condenser was added naphthol **301a** (331 mg, 1.1 mmol) and 1 mL of mineral oil. Oxygen was introduced by an air flow across the top of the condenser with a rate of one bubble per three seconds. The flask was set into a 160 °C oil bath and the contents were stirred at that temperature for 24 h. After cooling down to room temperature, the crude reaction mixture was mixed with 5 mL CH_2Cl_2 and 3 g silica gel and then the solvent was then removed to give an evenly mixed sample that was ready for dry loading onto a silica gel column (25 mm × 350 mm column, 1:2:20 EtOAc/CH_2Cl_2/hexanes as eluent) and upon elution gave the product **281a** as a light yellow solid in 56% yield (187 mg, 0.3 mmol).

Deracemization of racemic 281a: To a 50 mL round bottom flask was added 15 mL MeOH, CuCl (85 mg, 0.85 mmol) and (-)-sparteine (380 mg, 1.7 mmol) under an atmosphere of air. The reaction mixture was sonicated in an ultrasonic water bath for 30

minutes with a needle in the septum to maintain exposure to air. The temperature of the ultrasonic bath was maintained at or below 25 °C by the addition of ice to the water in the bath. The flask was then removed and sealed with a septum, purged with argon, which was introduced by a needle under the surface for 60 minutes. At the same time, to a 150 mL flame-dried flask was added racemic **281a** (300 mg, 0.5 mmol) and 50 mL CH_2Cl_2, the resulting solution was purged with argon for 60 minutes. The green Cu(II)-sparteine solution was then transferred via cannula to the solution of racemic **281a** under an atmosphere of argon and then the combined mixture was sonicated for 15 more minutes and then allowed to stir at room temperature for 3 h under a positive pressure of argon maintained by a slow flow through the head space of the flask, which was covered with aluminum foil. The reaction was quenched by slow addition of 10 mL $NaHCO_3$ (aq. sat.) and most of the solvent was removed under reduced pressure. The residue was then extracted with CH_2Cl_2 (5 mL × 3) and the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel chromatography (18 mm × 350 mm column, 1:9 EtOAc/hexanes as eluent) gave the product *(S)*-**281a** as a light yellow foam-like solid (mp. 103 – 105 °C) in 92% yield (276 mg, 0.45 mmol). The optical purity of **281a** was determined to be >99% ee by HPLC analysis (Chiralcel OD-H column, 98:2 hexane/*i*PrOH at 254nm, flow-rate: 0.7 mL/min). Retention times: R_t = 19.02 min for *(R)*-**281a** and R_t = 23.50 min for *(S)*-**281a**.

Spectral data for *(S)*-**281a**: R_f = 0.3 (1:9 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.82 (s, 2H), 6.49 (d, 4H, *J* = 8.5 Hz), 7.09 (d, 4H, *J* = 8.5 Hz), 7.30 (s, 2H), 7.57–7.63 (m, 4H), 7.78–7.80 (m, 2H), 8.33–8.35 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 112.00, 121.10, 122.12, 122.79, 123.02, 126.10, 127.76, 127.88, 130.48, 130.65, 134.58, 139.05, 139.16, 150.47; IR (thin film) 3509br, s, 1570m, 1409s, 1385m cm^{-1}; mass spectrum, *m/z* (% rel intensity) 598 M^+ (34, ^{81}Br), 596 M^+ (100, ^{81}Br + ^{79}Br), 594 (47, ^{79}Br), 389 (11, ^{81}Br),

387 (10, ^{79}Br), 331 (9, Br^{81}), 329 (9, Br^{79}), 302 (16), 299 (23), 297 (28), 269 (16), 258 (23), 218 (27), 208 (30), 202 (20), 194 (37), 187 (37), 174 (13), 164 (14), 149 (18), 117 (24), 90 (14). Specific rotation: $[\alpha]^{23}_{D}$ –188.2 (*c* 1.0 in CH_2Cl_2) on >99% ee material (HPLC).

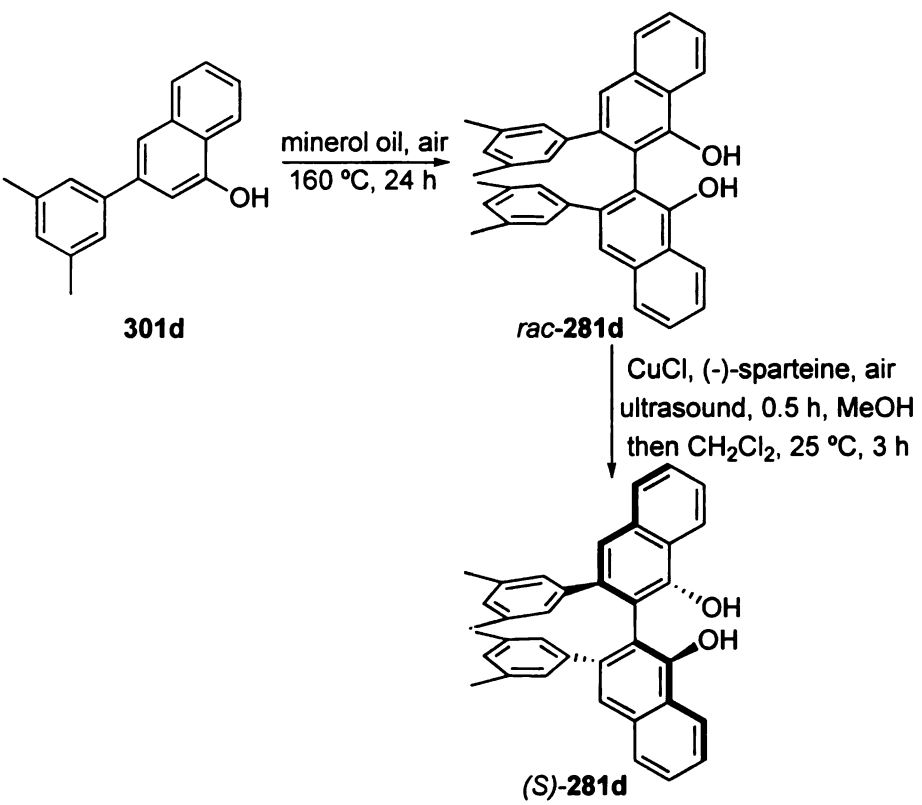


301b *rac*-**281b** *(S)*-**281b**

***(S)*-bis(3-(4-phenylphenyl))-2,2'-binaphthol 281b**. The procedure for the synthesis of *(S)*-**281a** was followed for the thermal coupling of monomer **301b** (596 mg, 2 mmol). Purification by silica gel chromatography (25 mm × 300 mm column, 1:1:40 EtOAc/CH_2Cl_2/hexanes as eluent) gave the racemic product **281b** as a light yellow solid in 40% yield (236 mg, 0.4 mmol), which was set for the deracemization step. After the deracemization, the final product was purified by silica gel chromatography (18 mm × 300 mm column, 1:9 EtOAc/hexanes as eluent) to give *(S)*-**281b** as a light yellow foam-like solid (mp. 122-124 °C) in 91% yield (215 mg, 0.73 mmol). The optical purity of **281b** was determined to be >99% ee by HPLC analysis (Chiralcel OD-H column, 95:5

hexane/*i*PrOH at 254nm, flow-rate: 0.7 mL/min). Retention times: R_t = 13.21 min for *(R)*-**281b** and R_t = 20.69 min for *(S)*-**281b**.

Spectral data for *(S)*-**281b**: R_f = 0.3 (1:9 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.92 (s, 2H), 6.75 (d, 4H, *J* = 8.3 Hz), 7.25 (d, 4H, *J* = 8.3 Hz), 7.32–7.35 (m, 2H), 7.40–7.44 (m, 6H), 7.54 (d, 4H, *J* = 7.1 Hz), 7.59–7.63 (m, 4H), 7.83–7.85 (m, 2H), 8.41–8.42 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 112.64, 122.07, 122.84, 123.01, 125.76, 126.11, 126.90, 127.23, 127.60, 127.75, 128.72, 129.34, 134.66, 139.24, 139.27, 140.21, 140.64, 150.40; IR (thin film) 3511br, m, 1570m, 1487s, 1383s cm^{-1}; mass spectrum, *m/z* (% rel intensity) 591 M^+ +1 (38), 590 M^+ (100), 436 (9), 307 (12), 267 (32), 252 (12), 218 (10), 151 (14), 90 (13). Specific rotation: $[\alpha]^{23}_D$ –169.2 (*c* 1.0 in CH_2Cl_2) on >99% ee material (HPLC).

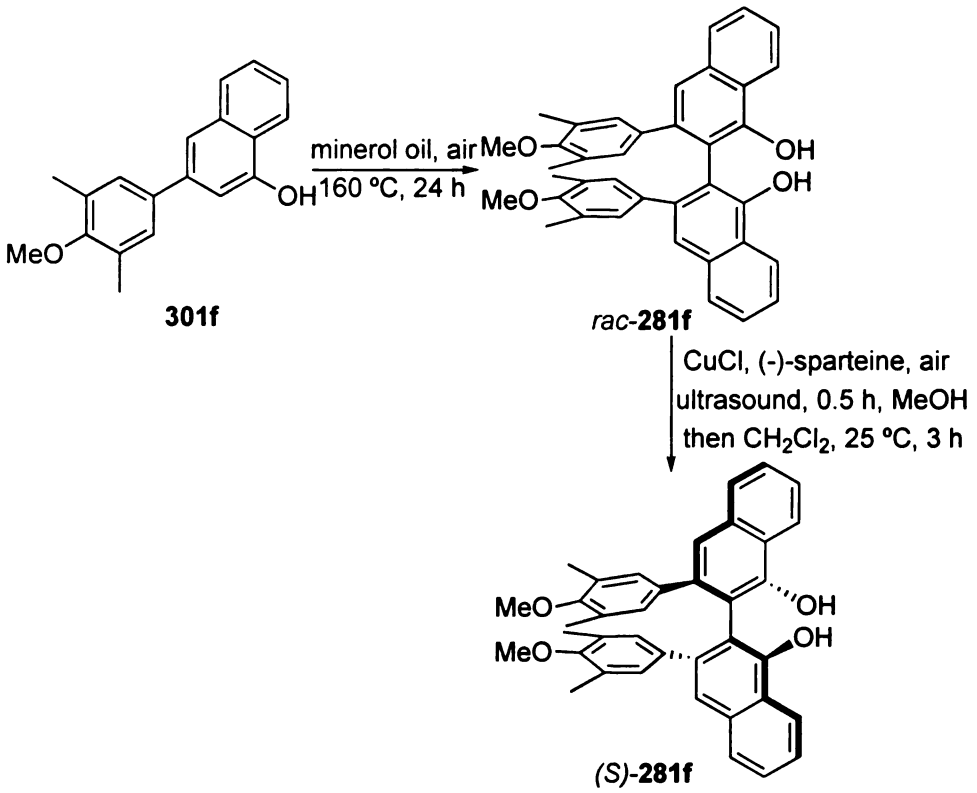


301d *rac*-**281d** *(S)*-**281d**

***(S)*-bis(3-(3,5-dimethylphenyl))-2,2'-binaphthol 281d**. The procedure for the synthesis of *(S)*-**281a** was followed for the thermal coupling of the monomer **301d** (248 mg, 1

mmol). Purification by silica gel chromatography (25 mm × 300 mm column, 1:1:40 EtOAc/CH_2Cl_2/hexanes as eluent) gave the racemic product **281d** as a light yellow solid in 69% yield (171 mg, 0.35 mmol), which was set for the deracemization step. After deracemization, the final product was purified by silica gel chromatography (18 mm × 300 mm column, 1:18 EtOAc/hexanes as eluent) to give *(S)*-**281d** as a light yellow foam-like solid (mp. 74 – 76 °C) in 89% yield (152 mg, 0.6 mmol). The optical purity of **281d** was determined to be >99% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/*i*PrOH at 254nm, flow-rate: 0.7 mL/min). Retention times: R_t = 8.58 min for *(R)*-**281d** and R_t = 18.96 min for *(S)*-**281d**.

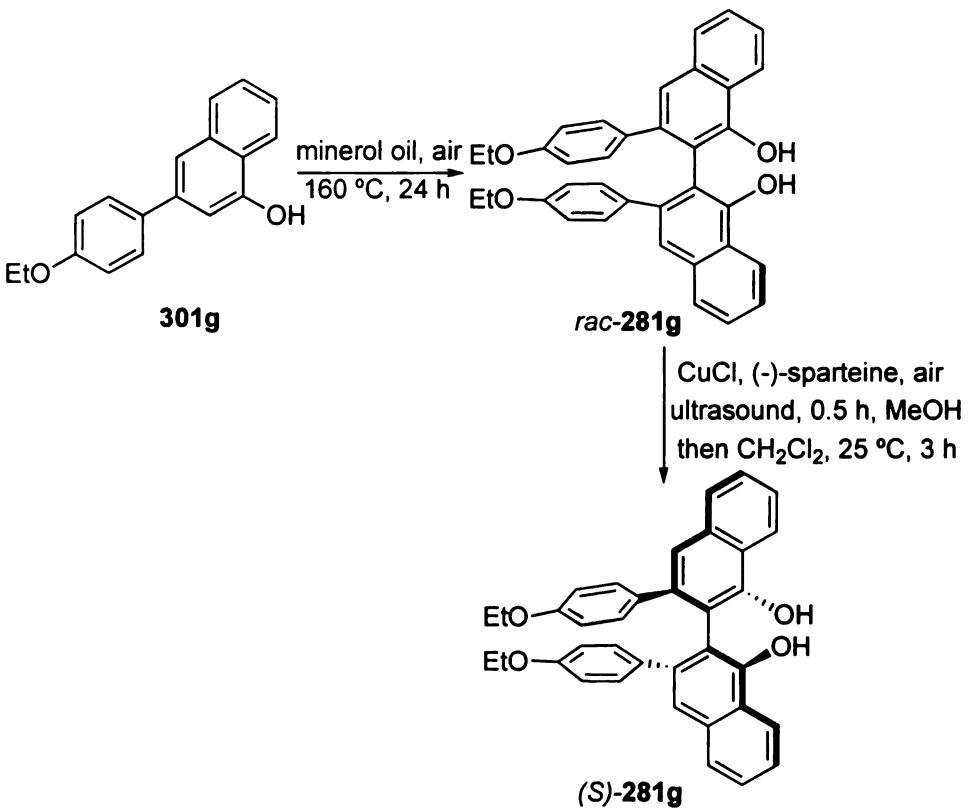
Spectral data for *(S)*-**281d**: R_f = 0.45 (1:9 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.01 (s, 12H), 5.85 (s, 2H), 6.35 (s, 4H), 6.72 (s, 2H), 7.32 (s, 2H), 7.52-7.56 (m, 4H), 7.76-7.77 (m, 2H), 8.34-8.36 (m, 2H); ^{13}C ($CDCl_3$, 75 MHz) δ 21.05, 113.09, 121.55, 122.64, 122.77, 125.43, 126.82, 127.29, 127.52, 128.16, 134.51, 136.54, 140.13, 141.00, 150.43; IR (thin film) 3515br, m, 1581s, 1576vs, 1385vs cm^{-1}; mass spectrum, *m/z* (% rel intensity) 494 M^+ (30), 494 M^+–1 (100), 375 (10), 262 (14), 247 (58), 218 (23), 202 (19), 189 (11), 149 (11), 133 (10), 104 (11), 94 (14), 83 (22), 75 (14), 68 (26), 56 (25), 43 (34). Specific rotation: $[\alpha]^{23}_D$ –200.4 (*c* 1.0 in CH_2Cl_2) on >99% ee material (HPLC).



***(S)*-bis(3-(3,5-dimethyl-4-methoxylphenyl))-2,2'-binaphthol 281f**. The procedure for the synthesis of *(S)*-**281a** was followed for the thermal coupling of monomer **301f** (1.1 g, 4 mmol). Purification by silica gel chromatography (35 mm × 400 mm column, 1:1:20 EtOAc/CH_2Cl_2/hexanes as eluent) gave the racemic product **281f** as a light yellow solid in 67% yield (735 mg, 1.34 mmol), which was set for the deracemization step. After deracemization, the product was purified by silica gel chromatography (25 mm × 300 mm column, 1:1:8 EtOAc/CH_2Cl_2/hexanes as eluent) to give *(S)*-**281f** as a light yellow solid (mp. 206-207 °C) in 93% yield (683 mg, 1.24 mmol). The optical purity of **281f** was determined to be >99% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/*i*PrOH at 254nm, flow-rate: 0.5 mL/min). Retention times: R_t = 26.22 min for *(R)*-**281f** and R_t = 29.74 min for *(S)*-**281f**.

Spectral data for *(S)*-**281f**: R_f = 0.35 (1:1:8 EtOAc/CH_2Cl_2/hexanes). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.94 (s, 12H), 3.61 (s, 6H), 5.78 (s, 2H), 6.32 (s, 4H), 7.29 (s, 2H), 7.52-7.54

(m, 4H), 7.76 (d, 2H, J = 8.9 Hz), 8.31 (d, 2H, J = 8.9 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 15.84, 59.69, 113.05, 121.48, 122.62, 122.70, 125.46, 127.37, 127.51, 129.41, 129.44, 134.53, 135.73, 140.41, 150.38, 155.92; IR (thin film) 3512br,s, 2928s, 1487vs, 1224vs cm^{-1}; mass spectrum, *m/z* (% rel intensity) 555 M^+ +1 (41), 554 M^+ (100), 277 (32), 248 (9), 202 (12), 149 (27), 135 (12); Specific rotation: $[\alpha]^{23}_D$ –235.6 (*c* 1.0 in CH_2Cl_2) on >99% ee material (HPLC).



***(S)*-bis(3-(4-ethoxylphenyl))-2,2'-binaphthol 281g**. The procedure for the synthesis of *(S)*-**281a** was followed for thermal coupling of monomer **301g** (528 g, 2 mmol). Purification by silica gel chromatography (25 mm × 400 mm column, 1:1:8 EtOAc/CH_2Cl_2/hexanes as eluent) gave the racemic product **281g** as a light yellow solid in 60% yield (316 mg, 0.6 mmol), which was set for the deracemization step. After deracemization, the product was purified by silica gel chromatography (25 mm × 300 mm column, 1:1:8 EtOAc/CH_2Cl_2/hexanes as eluent) to give *(S)*-**281g** as light yellow

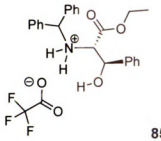
foam-like solid (mp. 202-203 °C) in 55% yield (173 mg, 0.33 mmol). The optical purity of **281g** was determined to be >99% ee by HPLC analysis (Chiralcel OD-H column, 99:1 hexane/*i*PrOH at 254nm, flow-rate: 0.5 mL/min). Retention times: R_t = 32.14 min for *(R)*-**281g** and R_t = 36.82 min for *(S)*-**281g**.

Spectral data for *(S)*-**281g**: R_f = 0.27 (1:1:8 EtOAc/CH_2Cl_2/hexanes). ^1H NMR (C_3D_6O, 300 MHz) δ 1.33 (t, 6H, *J*= 7.1 Hz), 3.89 (q, 4H, *J* = 7.1 Hz), 5.76 (s, 2H), 6.49 (d, 4H, *J* = 8.8 Hz), 6.59 (d, 4H, *J* = 8.8 Hz), 7.30 (s, 2H), 7.49-7.56 (m, 4H), 7.75 (d, 2H, *J* = 7.5 Hz), 8.31 (d, 2H, *J* = 7.6 Hz); ^{13}C ($CDCl_3$, 75 MHz) δ 14.78, 63.27, 112.91, 113.48, 121.77, 122.71, 122.77, 125.41, 127.41, 127.58, 129.95, 132.68, 134.62, 140.35, 150.24, 157.79; IR (thin film) 3515br,s, 2926s, 1570m, 1467vs, 1225vs cm^{-1}; mass spectrum, *m/z* (% rel intensity) 527 M^+ +1 (37), 526 M^+ (100), 406 (9), 276 (9), 263 (35), 235 (24), 207 (18), 189 (17), 165 (15), 135 (15), 121 (23), 107 (16); Specific rotation: $[\alpha]^{23}_D$ –140.8 (*c* 1.0 in CH_2Cl_2) on >99% ee material (HPLC).

APPENDICES

Crystallographic data of Selected Compounds

Figure A.1 ORTEP Drawing of the Trifluoroacetate Salt of Compound 85



85

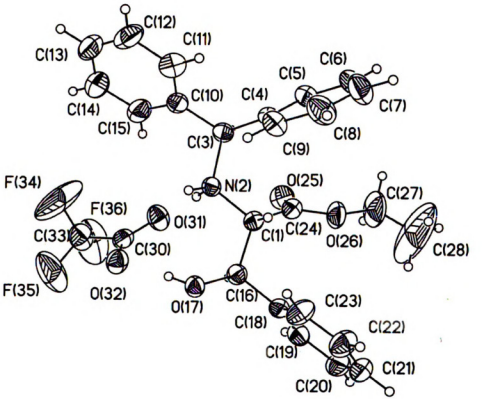


Table A.1.1. Crystal data and structure refinement for the trifluoroacetate salt of **85**

Identification code	wf041305
Empirical formula	C26 H26 F3 N O5
Formula weight	489.48
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.6523(19) A
	b = 11.259(2) A
	c = 12.919(3) A
	alpha = 113.04(3) deg.
	beta = 100.21(3) deg.
	gamma = 101.66(3) deg.
Volume	1213.0(4) A^3
Z	2
Density (calculated)	1.340 Mg/m^3
Absorption coefficient	0.107 mm^-1
F(000)	512
Crystal size	0.4 x 0.25 x 0.1 mm
Theta range for data collection	1.79 to 28.32 deg.
Index ranges	-12<=h<=12, -14<=k<=14, -17<=l<=17
Reflections collected / unique	10037 / 5537 [R(int) = 0.0442]
Completeness to theta = 28.32	91.7%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5537 / 0 / 328
Goodness-of-fit on F^2	0.946
Final R indices [I>2sigma(I)]	R1 = 0.0668, wR2 = 0.1660
R indices (all data)	R1 = 0.1725, wR2 = 0.2037
Largest diff. peak and hole	0.805 and -0.518 e.A^-3

Table A.1.2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for the trifluoroacetate salt of **85**

	x	y	z	U(eq)	Occ.
C(1)	5502(3)	2689(3)	-953(3)	32(1)	1
N(2)	4688(3)	2767(3)	-53(2)	29(1)	1
C(3)	3471(3)	1482(3)	-308(3)	33(1)	1
C(4)	2703(3)	693(3)	-1611(3)	34(1)	1
C(5)	2642(4)	-654(3)	-2173(3)	42(1)	1
C(6)	1996(4)	-1396(4)	-3383(3)	55(1)	1
C(7)	1427(4)	-776(4)	-4008(3)	60(1)	1
C(8)	1467(4)	564(4)	-3459(3)	57(1)	1
C(9)	2099(4)	1287(3)	-2255(3)	42(1)	1
C(10)	2489(4)	1880(3)	479(3)	36(1)	1
C(11)	997(4)	1687(4)	61(3)	50(1)	1
C(12)	142(4)	2022(4)	821(4)	59(1)	1
C(13)	765(5)	2567(4)	2011(4)	64(1)	1
C(14)	2253(5)	2756(4)	2445(4)	67(1)	1
C(15)	3086(4)	2410(4)	1678(3)	52(1)	1
C(16)	6927(3)	3902(3)	-439(3)	33(1)	1
O(17)	6606(2)	5143(2)	113(2)	34(1)	1
C(18)	7606(3)	3884(3)	-1408(3)	32(1)	1
C(19)	8979(4)	3698(3)	-1393(3)	40(1)	1
C(20)	9568(4)	3650(3)	-2307(3)	49(1)	1
C(21)	8790(4)	3774(3)	-3235(3)	50(1)	1
C(22)	7436(4)	3953(4)	-3261(3)	53(1)	1
C(23)	6837(4)	4023(4)	-2347(3)	46(1)	1
C(24)	5905(4)	1385(3)	-1387(3)	38(1)	1
O(25)	6318(3)	908(2)	-747(2)	48(1)	1
O(26)	5790(3)	911(2)	-2519(2)	55(1)	1
C(27)	6288(6)	-277(4)	-3025(4)	88(2)	1
C(28)	6666(14)	-376(8)	-4006(9)	266(7)	1
C(30)	6878(3)	4828(4)	2677(3)	36(1)	1
O(31)	6714(3)	3602(2)	2100(2)	47(1)	1
O(32)	6747(2)	5683(2)	2320(2)	44(1)	1
C(33)	7287(5)	5350(4)	4004(3)	56(1)	1
F(34)	6191(3)	5107(5)	4357(2)	203(3)	1
F(35)	8007(4)	6646(3)	4593(2)	122(1)	1
F(36)	8268(4)	4873(3)	4413(2)	118(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table A.1.3. Bond lengths [A] and angles [deg] for the trifluoroacetate salt of **85**

C(1)-N(2)	1.499(4)	C(1)-C(24)	1.511(4)
C(1)-C(16)	1.551(4)	N(2)-C(3)	1.544(4)
C(3)-C(10)	1.514(4)	C(3)-C(4)	1.514(4)
C(4)-C(9)	1.379(4)	C(4)-C(5)	1.386(4)
C(5)-C(6)	1.396(5)	C(6)-C(7)	1.372(5)
C(7)-C(8)	1.382(5)	C(8)-C(9)	1.387(5)
C(10)-C(15)	1.382(5)	C(10)-C(11)	1.385(5)
C(11)-C(12)	1.382(5)	C(12)-C(13)	1.374(6)
C(13)-C(14)	1.385(6)	C(14)-C(15)	1.373(5)
C(16)-O(17)	1.425(3)	C(16)-C(18)	1.508(4)
C(18)-C(19)	1.382(4)	C(18)-C(23)	1.387(4)
C(19)-C(20)	1.385(5)	C(20)-C(21)	1.370(5)
C(21)-C(22)	1.359(5)	C(22)-C(23)	1.387(5)
C(24)-O(25)	1.203(4)	C(24)-O(26)	1.321(4)
C(26)-C(27)	1.460(4)	C(27)-C(28)	1.349(8)
C(30)-O(32)	1.238(4)	C(30)-O(31)	1.245(4)
C(30)-C(33)	1.523(5)	C(33)-F(34)	1.246(5)
C(33)-F(36)	1.309(5)	C(33)-F(35)	1.313(5)
N(2)-C(1)-C(24)	110.6(2)	N(2)-C(1)-C(16)	110.9(2)
C(24)-C(1)-C(16)	109.2(2)	C(1)-N(2)-C(3)	117.5(2)
C(10)-C(3)-C(4)	116.1(3)	C(10)-C(3)-N(2)	108.7(2)
C(4)-C(3)-N(2)	110.6(2)	C(9)-C(4)-C(5)	119.3(3)
C(9)-C(4)-C(3)	121.9(3)	C(5)-C(4)-C(3)	118.8(3)
C(4)-C(5)-C(6)	120.3(3)	C(7)-C(6)-C(5)	119.3(4)
C(6)-C(7)-C(8)	121.0(4)	C(7)-C(8)-C(9)	119.1(4)
C(4)-C(9)-C(8)	120.9(3)	C(15)-C(10)-C(11)	117.6(3)
C(15)-C(10)-C(3)	118.8(3)	C(11)-C(10)-C(3)	123.5(3)
C(12)-C(11)-C(10)	121.0(4)	C(13)-C(12)-C(11)	120.3(4)
C(12)-C(13)-C(14)	119.5(4)	C(15)-C(14)-C(13)	119.5(4)
C(14)-C(15)-C(10)	122.1(4)	O(17)-C(16)-C(18)	111.0(2)
O(17)-C(16)-C(1)	110.4(2)	C(18)-C(16)-C(1)	109.2(2)
C(19)-C(18)-C(23)	118.9(3)	C(19)-C(18)-C(16)	121.0(3)
C(23)-C(18)-C(16)	120.1(3)	C(18)-C(19)-C(20)	120.1(3)
C(21)-C(20)-C(19)	120.4(3)	C(22)-C(21)-C(20)	120.0(3)
C(21)-C(22)-C(23)	120.5(3)	C(18)-C(23)-C(22)	120.1(3)
O(25)-C(24)-O(26)	126.7(3)	O(25)-C(24)-C(1)	122.6(3)
O(26)-C(24)-C(1)	110.6(3)	C(24)-O(26)-C(27)	116.1(3)
C(28)-C(27)-O(26)	111.4(5)	O(32)-C(30)-O(31)	128.9(3)
O(32)-C(30)-C(33)	115.3(3)	O(31)-C(30)-C(33)	115.8(3)
F(34)-C(33)-F(36)	107.9(4)	F(34)-C(33)-F(35)	108.9(4)
F(36)-C(33)-F(35)	98.8(4)	F(34)-C(33)-C(30)	112.3(3)
F(36)-C(33)-C(30)	113.9(3)	F(35)-C(33)-C(30)	114.1(3)

Symmetry transformations used to generate equivalent atoms:

Table A.1.4. Anisotropic displacement parameters (A^2 x 10^3) for the trifluoroacetate salt of **85**

	U11	U22	U33	U23	U13	U12
C(1)	35(2)	30(2)	31(2)	15(2)	12(2)	8(2)
N(2)	32(2)	29(2)	25(2)	12(1)	7(1)	6(1)
C(3)	39(2)	25(2)	37(2)	16(2)	13(2)	8(1)
C(4)	35(2)	28(2)	35(2)	14(2)	11(2)	4(1)
C(5)	45(2)	31(2)	44(2)	14(2)	12(2)	6(2)
C(6)	58(3)	34(2)	53(3)	6(2)	13(2)	2(2)
C(7)	68(3)	52(3)	38(2)	7(2)	2(2)	8(2)
C(8)	61(3)	52(3)	45(2)	20(2)	-1(2)	8(2)
C(9)	46(2)	35(2)	39(2)	15(2)	5(2)	10(2)
C(10)	41(2)	28(2)	41(2)	17(2)	16(2)	10(2)
C(11)	45(2)	54(2)	55(2)	26(2)	16(2)	13(2)
C(12)	43(2)	69(3)	79(3)	38(3)	35(2)	22(2)
C(13)	72(3)	52(3)	78(3)	25(2)	53(3)	16(2)
C(14)	75(3)	69(3)	49(3)	17(2)	33(2)	7(2)
C(15)	50(2)	61(3)	43(2)	22(2)	19(2)	10(2)
C(16)	34(2)	31(2)	34(2)	15(2)	11(2)	12(2)
O(17)	43(1)	28(1)	32(1)	14(1)	14(1)	12(1)
C(18)	34(2)	27(2)	36(2)	14(2)	13(2)	8(1)
C(19)	38(2)	34(2)	41(2)	12(2)	9(2)	10(2)
C(20)	40(2)	45(2)	63(3)	18(2)	28(2)	15(2)
C(21)	57(3)	44(2)	50(2)	18(2)	30(2)	12(2)
C(22)	57(3)	66(3)	46(2)	34(2)	19(2)	17(2)
C(23)	41(2)	64(2)	53(2)	39(2)	20(2)	23(2)
C(24)	39(2)	34(2)	40(2)	14(2)	17(2)	9(2)
O(25)	51(2)	41(1)	59(2)	24(1)	20(1)	21(1)
O(26)	84(2)	34(1)	48(2)	10(1)	38(2)	19(1)
C(27)	144(5)	51(3)	82(3)	17(3)	70(3)	48(3)
C(28)	527(19)	147(7)	321(12)	143(8)	366(14)	212(10)
C(30)	31(2)	44(2)	33(2)	17(2)	10(2)	8(2)
O(31)	58(2)	42(2)	36(1)	16(1)	6(1)	14(1)
O(32)	56(2)	46(1)	37(1)	22(1)	18(1)	19(1)
C(33)	79(3)	52(3)	36(2)	22(2)	14(2)	15(2)
F(34)	77(2)	406(7)	39(2)	61(3)	19(2)	-32(3)
F(35)	207(3)	69(2)	46(2)	8(1)	6(2)	14(2)
F(36)	167(3)	125(3)	50(2)	36(2)	-12(2)	61(2)

The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

Table A.1.5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for the trifluoroacetate salt of **85**

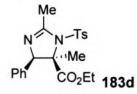
	x	y	z	U(eq)	Occ.
H(1A)	4860	2713	-1619	38	1
H(2A)	4240(30)	3530(30)	80(20)	34(8)	1
H(2B)	5340(30)	2980(30)	590(30)	29(9)	1
H(3A)	3963	906	-77	39	1
H(5A)	3033	-1067	-1744	50	1
H(6A)	1951	-2302	-3760	66	1
H(7A)	1008	-1265	-4815	73	1
H(8A)	1075	975	-3890	68	1
H(9A)	2116	2185	-1878	50	1
H(11A)	564	1327	-742	61	1
H(12A)	-860	1878	525	70	1
H(13A)	192	2807	2522	77	1
H(14A)	2684	3114	3248	81	1
H(15A)	4083	2536	1976	62	1
H(16A)	7629	3805	149	39	1
H(17)	6640(40)	5280(30)	860(30)	57(11)	1
H(19A)	9510	3606	-769	48	1
H(20A)	10497	3532	-2290	58	1
H(21A)	9189	3736	-3848	60	1
H(22A)	6908	4029	-3896	63	1
H(23A)	5917	4163	-2364	55	1
H(27A)	7131	-219	-2452	106	1
H(27B)	5505	-1084	-3212	106	1
H(28A)	6974	-1171	-4323	398	1
H(28B)	7462	409	-3817	398	1
H(28C)	5832	-436	-4574	398	1

Table A.1.6. Torsion angles [deg] for the trifluoroacetate salt of **85**

C(24) C(1) N(2) C(3)	-44.0(4)	C(16) C(1) N(2) C(3)	-165.2(3)
C(1) N(2) C(3) C(10)	-162.3(3)	C(1) N(2) C(3) C(4)	-33.7(4)
C(10) C(3) C(4) C(9)	71.0(4)	N(2) C(3) C(4) C(9)	-53.5(4)
C(10) C(3) C(4) C(5)	-110.8(3)	N(2) C(3) C(4) C(5)	124.8(3)
C(9) C(4) C(5) C(6)	1.0(5)	C(3) C(4) C(5) C(6)	-177.4(3)
C(4) C(5) C(6) C(7)	0.2(5)	C(5) C(6) C(7) C(8)	-0.9(6)
C(6) C(7) C(8) C(9)	0.2(6)	C(5) C(4) C(9) C(8)	-1.6(5)
C(3) C(4) C(9) C(8)	176.7(3)	C(7) C(8) C(9) C(4)	1.0(5)
C(4) C(3) C(10) C(15)	169.9(3)	N(2) C(3) C(10) C(15)	-64.7(4)
C(4) C(3) C(10) C(11)	-7.0(4)	N(2) C(3) C(10) C(11)	118.4(3)
C(15) C(10) C(11) C(12)	0.4(5)	C(3) C(10) C(11) C(12)	177.4(3)
C(10) C(11) C(12) C(13)	0.6(6)	C(11) C(12) C(13) C(14)	-1.2(6)
C(12) C(13) C(14) C(15)	0.7(6)	C(13) C(14) C(15) C(10)	0.3(6)
C(11) C(10) C(15) C(14)	-0.9(5)	C(3) C(10) C(15) C(14)	-178.0(3)
N(2) C(1) C(16) O(17)	-50.5(3)	C(24) C(1) C(16) O(17)	-172.5(2)
N(2) C(1) C(16) C(18)	-172.8(2)	C(24) C(1) C(16) C(18)	65.1(3)
O(17) C(16) C(18) C(19)	121.9(3)	C(1) C(16) C(18) C(19)	-116.1(3)
O(17) C(16) C(18) C(23)	-59.7(4)	C(1) C(16) C(18) C(23)	62.3(4)
C(23) C(18) C(19) C(20)	-0.1(5)	C(16) C(18) C(19) C(20)	178.3(3)
C(18) C(19) C(20) C(21)	-0.5(5)	C(19) C(20) C(21) C(22)	0.3(5)
C(20) C(21) C(22) C(23)	0.6(5)	C(19) C(18) C(23) C(22)	1.0(5)
C(16) C(18) C(23) C(22)	-177.4(3)	C(21) C(22) C(23) C(18)	-1.2(6)
N(2) C(1) C(24) O(25)	-39.4(4)	C(16) C(1) C(24) O(25)	82.9(4)
N(2) C(1) C(24) O(26)	143.1(3)	C(16) C(1) C(24) O(26)	-94.7(3)
O(25) C(24) O(26) C(27)	-3.2(5)	C(1) C(24) O(26) C(27)	174.2(3)
C(24) O(26) C(27) C(28)	-156.3(7)	O(32) C(30) C(33) F(34)	98.4(5)
O(31) C(30) C(33) F(34)	-81.2(5)	O(32) C(30) C(33) F(36)	-138.6(4)
O(31) C(30) C(33) F(36)	41.8(5)	O(32) C(30) C(33) F(35)	-26.2(5)
O(31) C(30) C(33) F(35)	154.2(4)		

Symmetry transformations used to generate equivalent atoms:

Figure A.2 ORTEP Drawing of Compound 183d



183d

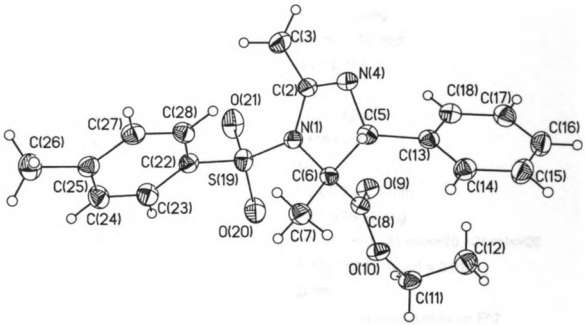


Table A.2.1 Crystal data and structure refinement for **183d**

Identification code	wf122006
Empirical formula	C21 H24 N2 O4 S
Formula weight	400.48
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Orth.
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 8.1942(16) A
	b = 15.052(3) A
	c = 15.877(3) A
	alpha = 90 deg.
	beta = 90 deg.
	gamma = 90 deg.
Volume	1958.2(7) A^3
Z	4
Density (calculated)	1.358 Mg/m^3
Absorption coefficient	0.196 mm^-1
F(000)	848
Crystal size	1.0 x 0.7 x 0.5 mm
Theta range for data collection	1.86 to 28.27 deg.
Index ranges	-10<=h<=10, -20<=k<=20, -21<=l<=20
Reflections collected / unique	22865 / 4720 [R(int) = 0.0147]
Completeness to theta = 28.27	99.1%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4720 / 0 / 265
Goodness-of-fit on F^2	0.793
Final R indices [I>2sigma(I)]	R1 = 0.0260, wR2 = 0.0840
R indices (all data)	R1 = 0.0275, wR2 = 0.0861
Absolute structure parameter	0.03(4)
Largest diff. peak and hole	0.194 and -0.343 e.A^-3

Table A.2.2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for **183d**

	x	y	z	U(eq)	Occ.
N(1)	10427(1)	3248(1)	2851(1)	24(1)	1
C(2)	12092(1)	3421(1)	3040(1)	27(1)	1
C(3)	13460(2)	2856(1)	2729(1)	39(1)	1
N(4)	12322(1)	4096(1)	3505(1)	30(1)	1
C(5)	10742(1)	4514(1)	3707(1)	24(1)	1
C(6)	9386(1)	3929(1)	3264(1)	22(1)	1
C(7)	8414(2)	4493(1)	2643(1)	31(1)	1
C(8)	8308(1)	3459(1)	3925(1)	23(1)	1
O(9)	8669(1)	2773(1)	4266(1)	30(1)	1
O(10)	6974(1)	3938(1)	4082(1)	28(1)	1
C(11)	5877(1)	3600(1)	4738(1)	31(1)	1
C(12)	6467(2)	3862(1)	5602(1)	42(1)	1
C(13)	10579(1)	4655(1)	4650(1)	24(1)	1
C(14)	9791(2)	5413(1)	4951(1)	29(1)	1
C(15)	9713(2)	5581(1)	5815(1)	35(1)	1
C(16)	10407(2)	4988(1)	6384(1)	37(1)	1
C(17)	11183(2)	4225(1)	6086(1)	33(1)	1
C(18)	11270(2)	4061(1)	5221(1)	28(1)	1
S(19)	9675(1)	2515(1)	2190(1)	28(1)	1
O(20)	7997(1)	2383(1)	2412(1)	42(1)	1
O(21)	10754(2)	1764(1)	2170(1)	43(1)	1
C(22)	9728(1)	3011(1)	1183(1)	25(1)	1
C(23)	8702(2)	2657(1)	572(1)	32(1)	1
C(24)	8765(2)	2992(1)	-242(1)	33(1)	1
C(25)	9846(1)	3672(1)	-464(1)	27(1)	1
C(26)	9959(2)	4008(1)	-1353(1)	35(1)	1
C(27)	10842(2)	4024(1)	167(1)	29(1)	1
C(28)	10795(1)	3699(1)	986(1)	28(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table A.2.3. Bond lengths [A] and angles [deg] for **183d**

N(1)-C(2)	1.4209(14)	N(1)-C(6)	1.4861(13)
N(1)-S(19)	1.6426(10)	C(2)-N(4)	1.2688(16)
C(2)-C(3)	1.4915(16)	N(4)-C(5)	1.4744(14)
C(5)-C(13)	1.5181(15)	C(5)-C(6)	1.5825(14)
C(6)-C(7)	1.5260(15)	C(6)-C(8)	1.5436(15)
C(8)-O(9)	1.2033(14)	C(8)-O(10)	1.3328(13)
O(10)-C(11)	1.4676(13)	C(11)-C(12)	1.5072(19)
C(13)-C(18)	1.3935(15)	C(13)-C(14)	1.3953(16)
C(14)-C(15)	1.3960(18)	C(15)-C(16)	1.391(2)
C(16)-C(17)	1.3940(19)	C(17)-C(18)	1.3976(17)
S(19)-O(20)	1.4331(10)	S(19)-O(21)	1.4346(10)
S(19)-C(22)	1.7649(12)	C(22)-C(28)	1.3906(15)
C(22)-C(23)	1.3894(16)	C(23)-C(24)	1.3887(18)
C(24)-C(25)	1.3984(17)	C(25)-C(27)	1.3961(16)
C(25)-C(26)	1.5027(17)	C(27)-C(28)	1.3893(17)
C(2)-N(1)-C(6)	109.30(8)	C(2)-N(1)-S(19)	128.25(8)
C(6)-N(1)-S(19)	121.99(7)	N(4)-C(2)-N(1)	114.39(10)
N(4)-C(2)-C(3)	122.50(11)	N(1)-C(2)-C(3)	123.11(11)
C(2)-N(4)-C(5)	109.71(10)	N(4)-C(5)-C(13)	110.62(9)
N(4)-C(5)-C(6)	106.40(8)	C(13)-C(5)-C(6)	117.03(9)
N(1)-C(6)-C(7)	113.48(9)	N(1)-C(6)-C(8)	108.24(8)
C(7)-C(6)-C(8)	113.28(9)	N(1)-C(6)-C(5)	100.19(8)
C(7)-C(6)-C(5)	110.14(9)	C(8)-C(6)-C(5)	110.76(9)
O(9)-C(8)-O(10)	125.62(10)	O(9)-C(8)-C(6)	123.92(10)
O(10)-C(8)-C(6)	110.40(9)	C(8)-O(10)-C(11)	116.55(9)
O(10)-C(11)-C(12)	111.04(10)	C(18)-C(13)-C(14)	119.30(11)
C(18)-C(13)-C(5)	121.08(10)	C(14)-C(13)-C(5)	119.55(10)
C(15)-C(14)-C(13)	120.38(11)	C(16)-C(15)-C(14)	120.17(12)
C(17)-C(16)-C(15)	119.68(12)	C(16)-C(17)-C(18)	120.08(12)
C(13)-C(18)-C(17)	120.38(11)	O(20)-S(19)-O(21)	119.17(7)
O(20)-S(19)-N(1)	107.22(6)	O(21)-S(19)-N(1)	108.17(6)
O(20)-S(19)-C(22)	107.78(6)	O(21)-S(19)-C(22)	107.31(6)
N(1)-S(19)-C(22)	106.56(5)	C(28)-C(22)-C(23)	120.55(11)
C(28)-C(22)-S(19)	122.33(9)	C(23)-C(22)-S(19)	117.06(9)
C(24)-C(23)-C(22)	119.26(11)	C(23)-C(24)-C(25)	121.53(11)
C(27)-C(25)-C(24)	117.86(11)	C(27)-C(25)-C(26)	120.68(11)
C(24)-C(25)-C(26)	121.45(11)	C(28)-C(27)-C(25)	121.44(10)
C(27)-C(28)-C(22)	119.35(11)		

Symmetry transformations used to generate equivalent atoms:

Table A.2.4. Anisotropic displacement parameters (A^2 x 10^3) for **183d**

U11	U22	U33	U23	U13	U12			
N(1)		22(1)	25(1)	26(1)	-5(1)	0(1)	0(1)	
C(2)		23(1)	34(1)	24(1)	1(1)	1(1)	1(1)	
C(3)		31(1)	50(1)	35(1)	-4(1)	3(1)	12(1)	
N(4)		21(1)	40(1)	30(1)	-5(1)	2(1)	-3(1)	
C(5)		24(1)	22(1)	26(1)	1(1)	0(1)	-3(1)	
C(6)		21(1)	22(1)	22(1)	0(1)	0(1)	1(1)	
C(7)		30(1)	34(1)	27(1)	7(1)	-1(1)	5(1)	
C(8)		21(1)	24(1)	24(1)	0(1)	-2(1)	-1(1)	
O(9)		30(1)	27(1)	33(1)	7(1)	2(1)	2(1)	
O(10)		21(1)	31(1)	32(1)	7(1)	4(1)	2(1)	
C(11)		22(1)	37(1)	33(1)	4(1)	5(1)	-2(1)	
C(12)		38(1)	55(1)	32(1)	1(1)	7(1)	-10(1)	
C(13)		21(1)	24(1)	27(1)	0(1)	0(1)	-4(1)	
C(14)		29(1)	28(1)	32(1)	-1(1)	1(1)	0(1)	
C(15)		37(1)	34(1)	36(1)	-7(1)	5(1)	0(1)	
C(16)		39(1)	44(1)	28(1)	-5(1)	4(1)	-5(1)	
C(17)		33(1)	37(1)	28(1)	6(1)	-2(1)	-4(1)	
C(18)		27(1)	25(1)	32(1)	2(1)	-1(1)	-1(1)	
S(19)		35(1)	24(1)	26(1)	-2(1)	1(1)	-6(1)	
O(20)		41(1)	53(1)	32(1)	-3(1)	4(1)	-24(1)	
O(21)		69(1)	23(1)	38(1)	-3(1)	-3(1)	6(1)	
C(22)		25(1)	24(1)	26(1)	-3(1)	2(1)	-2(1)	
C(23)		33(1)	31(1)	33(1)	-4(1)	0(1)	-10(1)	
C(24)		34(1)	35(1)	30(1)	-6(1)	-4(1)	-7(1)	
C(25)		26(1)	26(1)	29(1)	-3(1)	2(1)	4(1)	
C(26)		42(1)	33(1)	30(1)	2(1)	-2(1)	3(1)	
C(27)		26(1)	27(1)	33(1)	0(1)	2(1)	-4(1)	
C(28)		27(1)	28(1)	30(1)	-3(1)	-2(1)	-6(1)	

The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

Table A.2.5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for **183d**

	x	y	z	U(eq)	Occ.
H(3A)	14477	3089	2932	58	1
H(3B)	13462	2856	2124	58	1
H(3C)	13320	2260	2931	58	1
H(5A)	10728	5100	3439	29	1
H(7A)	7593	4133	2379	46	1
H(7B)	9135	4726	2221	46	1
H(7C)	7902	4975	2938	46	1
H(11A)	5818	2958	4701	37	1
H(11B)	4789	3836	4649	37	1
H(12A)	5735	3630	6020	63	1
H(12B)	6504	4498	5644	63	1
H(12C)	7540	3624	5693	63	1
H(14A)	9315	5808	4574	35	1
H(15A)	9196	6091	6011	42	1
H(16A)	10353	5099	6959	44	1
H(17A)	11643	3825	6465	39	1
H(18A)	11793	3553	5026	33	1
H(23A)	7982	2202	708	38	1
H(24A)	8072	2758	-650	39	1
H(26A)	8970(20)	3915(13)	-1613(13)	47(5)	1
H(26B)	10840(20)	3663(12)	-1618(13)	52(5)	1
H(26C)	10200(30)	4612(13)	-1334(14)	52(5)	1
H(27A)	11551	4486	36	34	1
H(28A)	11471	3939	1398	34	1

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