EVOLVING TOWARDS A SUBSTRATE GENERAL ASYMMETRIC AZIRIDINATION REACTION AND ITS APPLICATION IN THE ENANTIOSELECTIVE SYNTHESIS OF SPHINGANINES AND PHYTOSPHINGOSINES

By

Munmun Mukherjee

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ABSTRACT

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The research in this dissertation involves methodology development and total synthesis of 'sphingoid bases'. In terms of methodology, a substrate general aziridination has been realized. This was done by the introducing MEDAM group as the most general *N*-protecting group for the aziridination reaction. This lead to the broadening of the substrate scope, which includes imines, prepared from electron rich and electron deficient aromatic aldehydes, and also from 1°, 2° and 3° aliphatic aldehydes. Thereafter, an unprecedented catalyst-controlled aziridination reaction of chiral aldehydes was developed and then subsequently applied towards the syntheses of natural and unnatural isomers of phytosphingosines. These natural products are involved in nearly all aspects of cell regulation including differentiation, proliferation, adhesion, signal transduction and neuronal repair. In addition, new strategies towards ring opening of aziridines were developed which were utilized in the enantioselective synthesis of *threo*-sphinganines. The enantioselective syntheses of the *erythro*-sphinganines were achieved *via* Lewis acid mediated ring expansion of the *N*-Boc protected *cis*-aziridines.

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To,

My Parents and Teachers

ACKNOWLEDGEMENTS

Life is full of experiences and challenges. So far, graduate school has been the most challenging period of my life, which started six years ago upon my arrival to a different country thousand miles away from my own land and loved ones. It is very difficult to pursue a career in an unfamiliar environment unless one gets support from people surrounding oneself. I consider myself lucky to be part of the MSU Chemistry graduate program as its friendly environment helped me to grow as a scientist. I feel very fortunate to have Professor W. D. Wulff as my Ph.D advisor. It's very difficult for me to express my gratitude for him in few words. His intellect and tremendous knowledge in chemistry helped me in every stage of my graduate life. I must admit that, till date, I have not came across a person who has so much patience as he has. In last six years, I have never seen him angry or irritated irrespective of the situation. Apart from chemistry, I also learnt a lot about life from his calm and composed nature. He provided us the most conducive environment to grow as an independent researcher and always encouraged us to pursue our own ideas. Wine is another interesting addition to my life in Prof. Wulff's group. I will always miss our group gathering or post-group meeting wine party.

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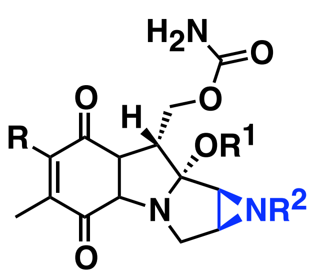
CHAPTER 1

AZIRIDINE: AN IMPORTANT MOTIF IN ORGANIC SYNTHESIS

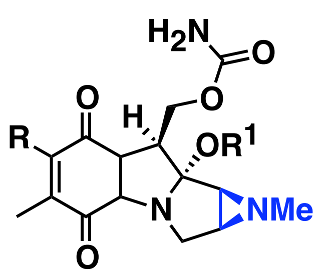
1.1 Biologically important alkaloids containing an aziridine core

Aziridines are highly valuable saturated three-membered heterocyclic compounds containing one nitrogen atom. The presence of the aziridine ring in natural and synthetic compounds is responsible for their anticancer, antimicrobial and antibacterial activity against selected cancer cell lines, microorganisms and pathogenic bacteria. The study to determine their mode of action has revealed that the electrophilic nature of the aziridine ring plays an important role in the mechanism at the molecular level.

Figure 1.1 Aziridines in natural products. " For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this dissertation."

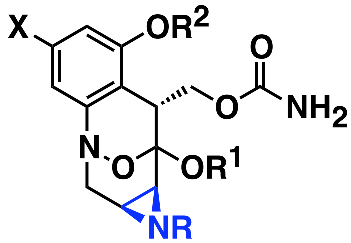


Mitomycin A, R = OMe, R^1, R^2 = H
Mitomycin F, R = OMe, R^1, R^2 = Me
Mitomycin C, R = NH_2, R^1= Me, R^2 = H
Porfiromycin, R = NH_2, R^1, R^2 = Me



Mitomycin B, R = OMe, R^1 = H
Mitomycin J, R = OMe, R^1 = Me
Mitomycin D, R = NH_2, R^1 = H
Mitomycin E, R = NH_2, R^1 = Me

Figure 1.1 (cont'd)

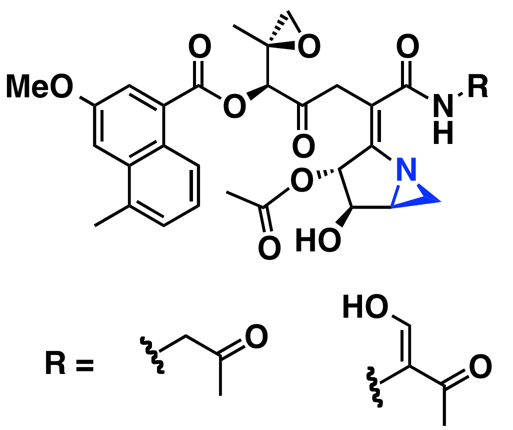


FR 073317 R = R^1 = Ac, R^2 = Me, X = CHO

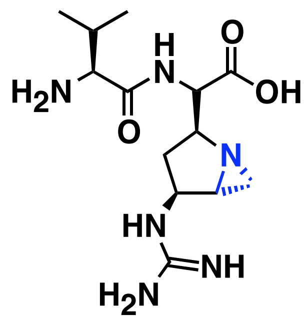
FR 70496 R = Ac, R^1 = H, R^2 = Me, X = CHO

FR 66979 R = R^1 = R^2 = H, X = CH_2OH

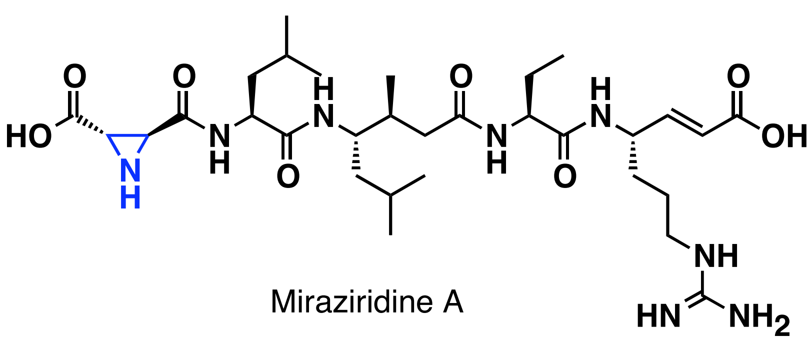
FR 900482 R = R^1 = R^2 = H, X = CHO



Azinomycin A Azinomycin B



Ficellomycin

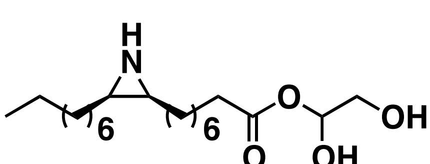


Miraziridine A

A few of the natural products containing an aziridine core are outlined in Figure 1.1. Mitomycins are the first known natural products containing an aziridine ring. Synthetic organic chemists have dedicated a substantial effort towards the synthesis of the Mitomycins, a class of very potent antibacterial and anticancer compounds.[1] The natural products FR-900482 and FR-66979 are structurally related to mitomycin C and exhibits similar antitumor and antibiotic activities.[2] These natural products were isolated from *Streptomyces sandaensis* [2b,3] and they show less toxicity than mitomycins in clinical cancer chemotherapeutics. In 1976 ficellomycin was isolated from *Streptomyces ficellus.*[4] It exhibits *in vivo* effectiveness against *Staphylococcus aureus* infections in mice and inhibits the growth of Gram-positive bacteria *in vitro*. The SS pharmaceutical company in Japan has reported the isolation of azinomycin A and B from *Streptomyces griseofuscus* in 1986.[5] These compounds display significant *in vivo* antitumor activity with potent *in vitro* cytotoxicities.[6] Miraziridine A was found to inhibit the cysteine protease cathepsin B and was isolated from a marine sponge.[7]

In addition to the naturally occurring aziridines, synthetic aziridine containing compounds have been shown to be promising candidates for the development of new drugs for several diseases. Some biologically important synthetically prepared compounds containing the aziridine core are listed in Figure 1.2.[8]

Figure 1.2 Biologically important aziridines



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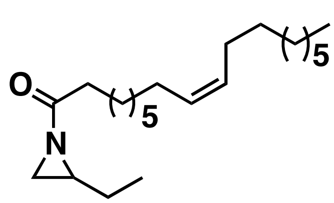

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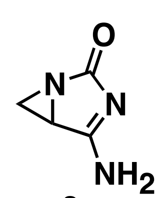
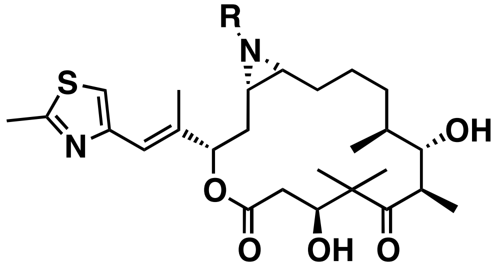


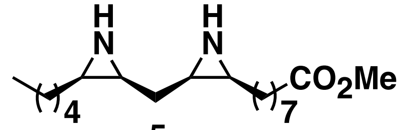
3

Figure 1.2 (cont'd)

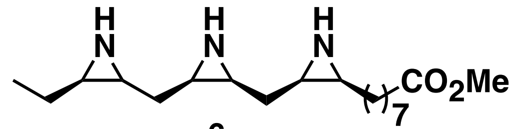


4

(R = H, CH_2CH_2OH, CONHEt, COPh, CH_2Ph)



5



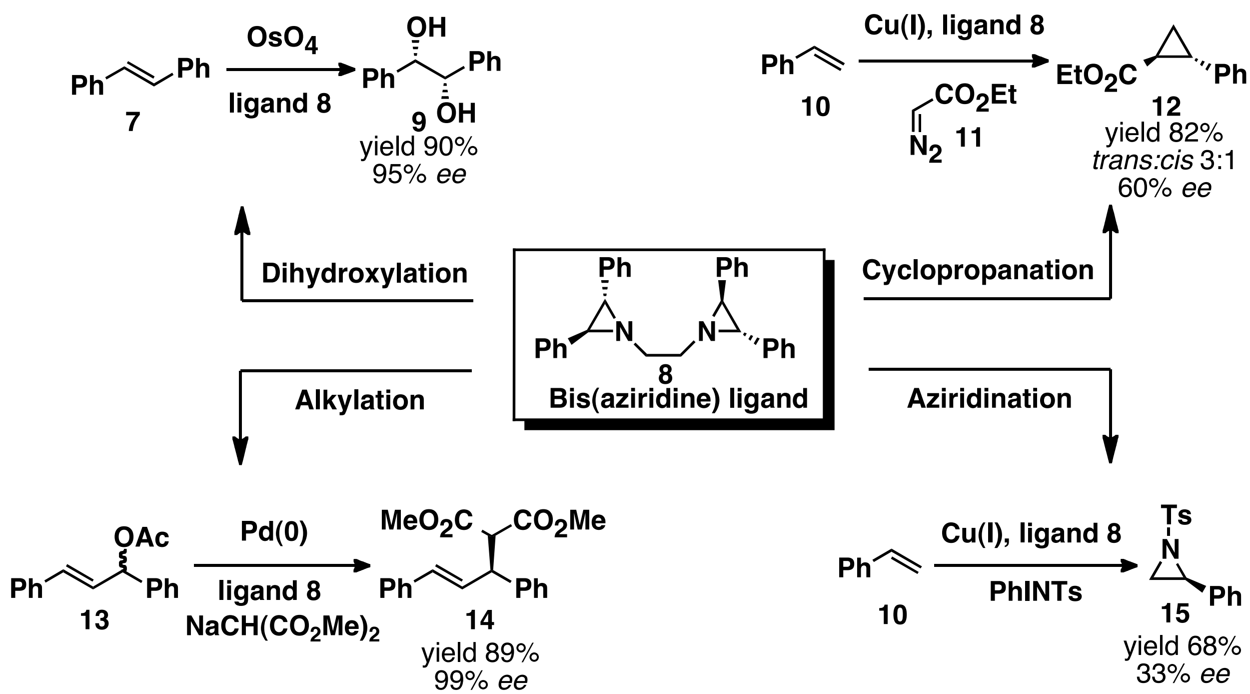
6

Synthetic monoglyceride **1** display antimicrobial activity against Gram-positive bacteria and yeasts.[9] Synthetically prepared 2-ethyl-1-oleoyl-aziridine **2** exhibits a wide spectrum of antimicrobial and antifungal activity. The immunosuppressant Imexon **3** selectively suppresses B-lymphocyte activation and can be used in the treatment of plasma cell or B-cell leukemias or neoplasias. The aziridine analogues **4** of epothiloneA show cytotoxicity against cancer cell lines. Bis-aziridines **5** (all diastereomers) and tris-aziridines **6** (all diastereomers) derived from linolenic acid exhibits cytotoxic and antimicrobial activity. Useful neuroprotective as well as antitumor-promoting effects are the other important properties of these aziridines. There are many more interesting examples of naturally occurring, synthetic or semi-synthetic compounds with aziridinyl scaffold with clinical utility, which have been well reviewed by Ismail et al. in 2009.[8]

1.2 Aziridines as chiral ligands

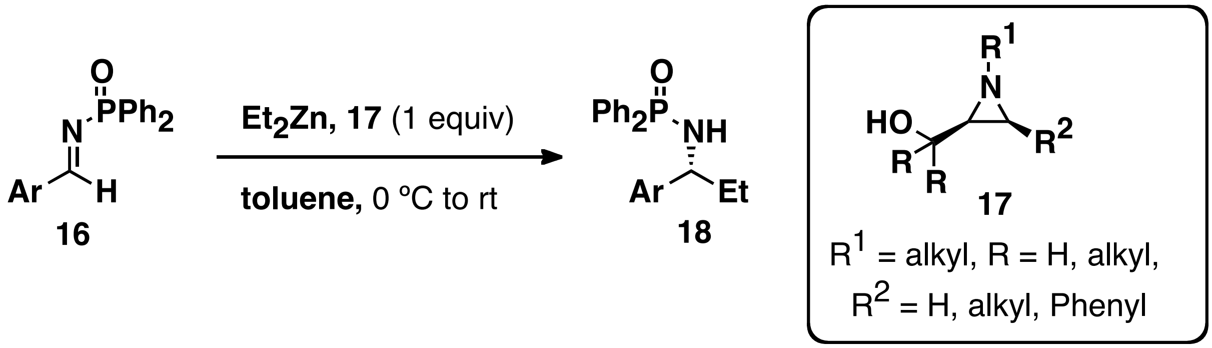
Tanner and Andersson demonstrated the use of C_2-symmetric bis-aziridines **8** and its derivatives as chiral ligands in various asymmetric transformations (Scheme 1.1) with good to moderate selectivity.[10] The transition metal mediated transformations involve both stoichiometric and catalytic use of these ligands.

Scheme 1.1 C_2-Symmetric bis-aziridine **8** as chiral ligands in different asymmetric transformations

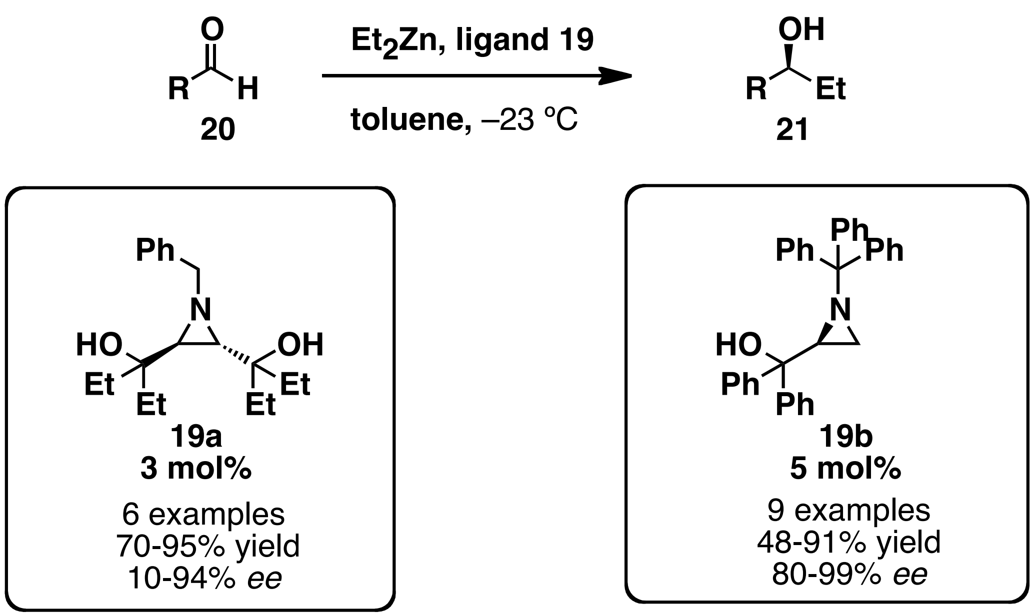


The asymmetric addition of diethyl zinc to the imine **16**[11] or the aldehyde **20**[12] showcases another use of chiral aziridine ligands in asymmetric transformations (Scheme 1.2 and Scheme 1.3).

Scheme 1.2 Aziridino alcohol **17** as chiral ligand in asymmetric addition of diethyl zinc to the imine **16**

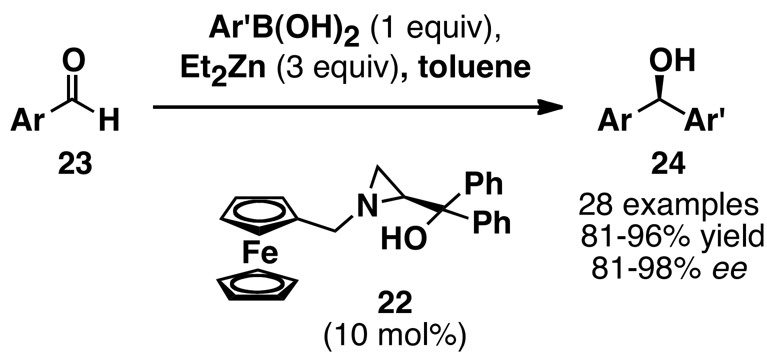


Scheme 1.3 Aziridino alcohol **19** as chiral ligand in asymmetric addition of diethyl zinc to the aldehyde **20**



Wang and coworkers reported the use of chiral ferrocenyl aziridino alcohol **22** in the catalytic asymmetric alkylation of aldehyde **23** (Scheme 1.4).[13]

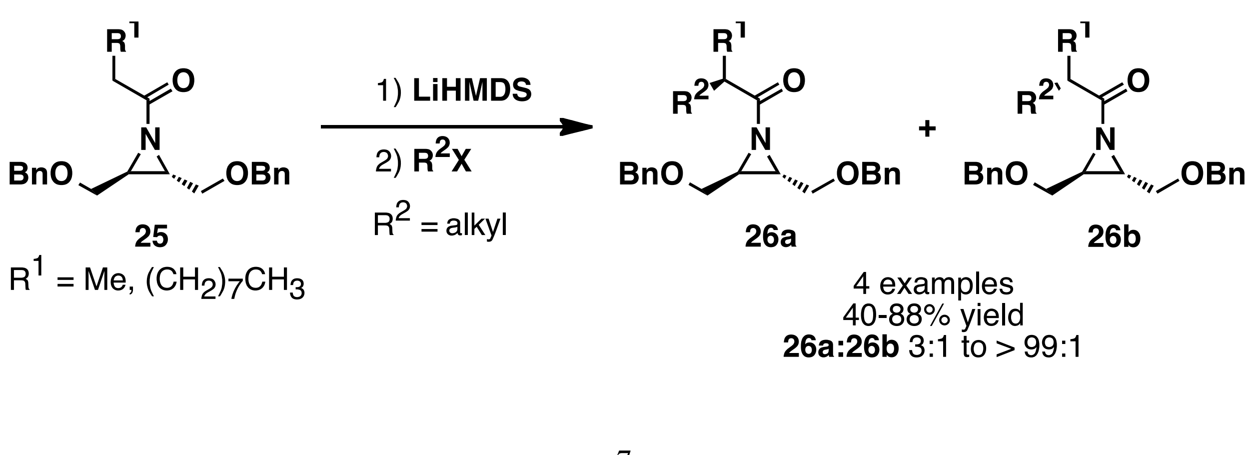
Scheme 1.4 Chiral ferrocenyl aziridino alcohol in the catalytic asymmetric alkylation of aldehydes



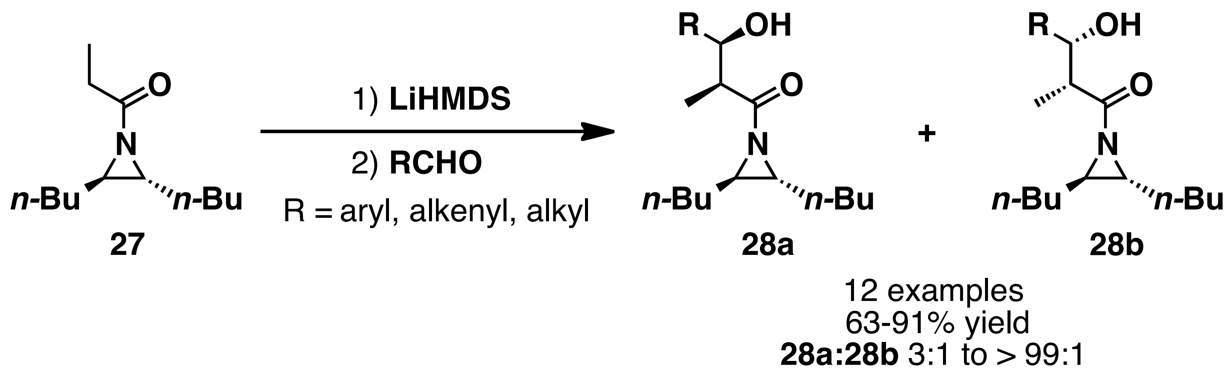
1.3 Aziridines as chiral auxiliaries

The utility of C_2-symmetric aziridines as auxiliaries for asymmetric alkylation (Scheme 1.5) and aldol reactions (Scheme 1.6) of amide enolates was demonstrated by Tanner and coworkers.[14]

Scheme 1.5 C_2-Symmetric aziridine as auxiliary for asymmetric alkylation



Scheme 1.6 C_2-Symmetric aziridine as auxiliary for asymmetric *syn*-aldol reaction

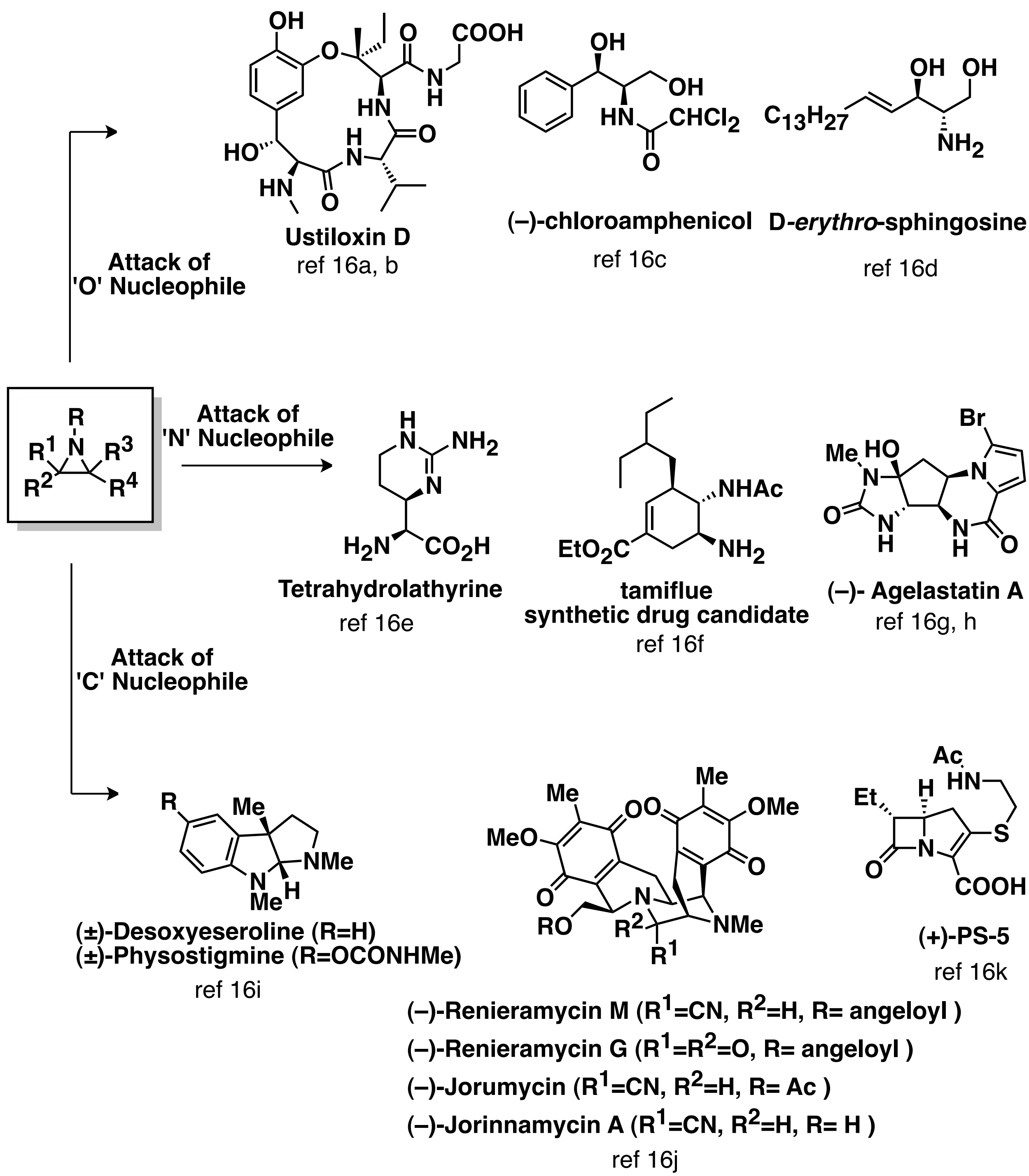


1.4 Synthesis of natural products *via* aziridine intermediates

Aziridines have become important building blocks in synthetic chemistry, especially for nitrogen-containing bioactive natural compounds. The usefulness of these three membered heterocycle is greatly associated with its ability to undergo nucleophilic ring opening to release the ring strain.

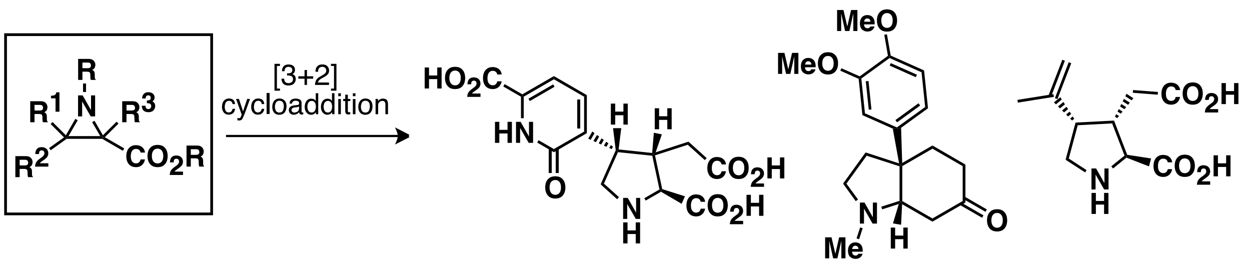
A wide array of nucleophiles can be used. In most of the cases the regio- and stereoselctivity of the ring opening is predictable, which plays an important role in designing a synthetic plan. Although the reaction condition and substrates play major role in stereochemical outcome, often the regioselectivity is governed by steric congestion. In general, the nucleophile attacks the less congested terminus and an *anti* attack (S_N2) determines the stereoselectivity of the ring opening. Till date many authors have extensively reviewed the nucleophilic ring opening of the aziridine ring.[15] Along the same line, the synthetic potential of aziridine ring opening reactions has been well established in the synthesis of complex natural products. Some representative examples are shown in Figure 1.3.[16]

Figure 1.3 Natural products *via* nucleophilic ring opening of aziridine intermediates



The ring strain of the aziridine ring makes it a potential substrate for [3+2] cycloaddition to obtain cyclic adducts. Aziridine esters are used as a precursor of azomethine ylides. Subsequently, they are reacted with olefin substrates. This serves as the key step in many natural product syntheses. A few examples are listed in Figure 1.4.[17]

Figure 1.4 Natural products *via* azomethine ylides derived from aziridines

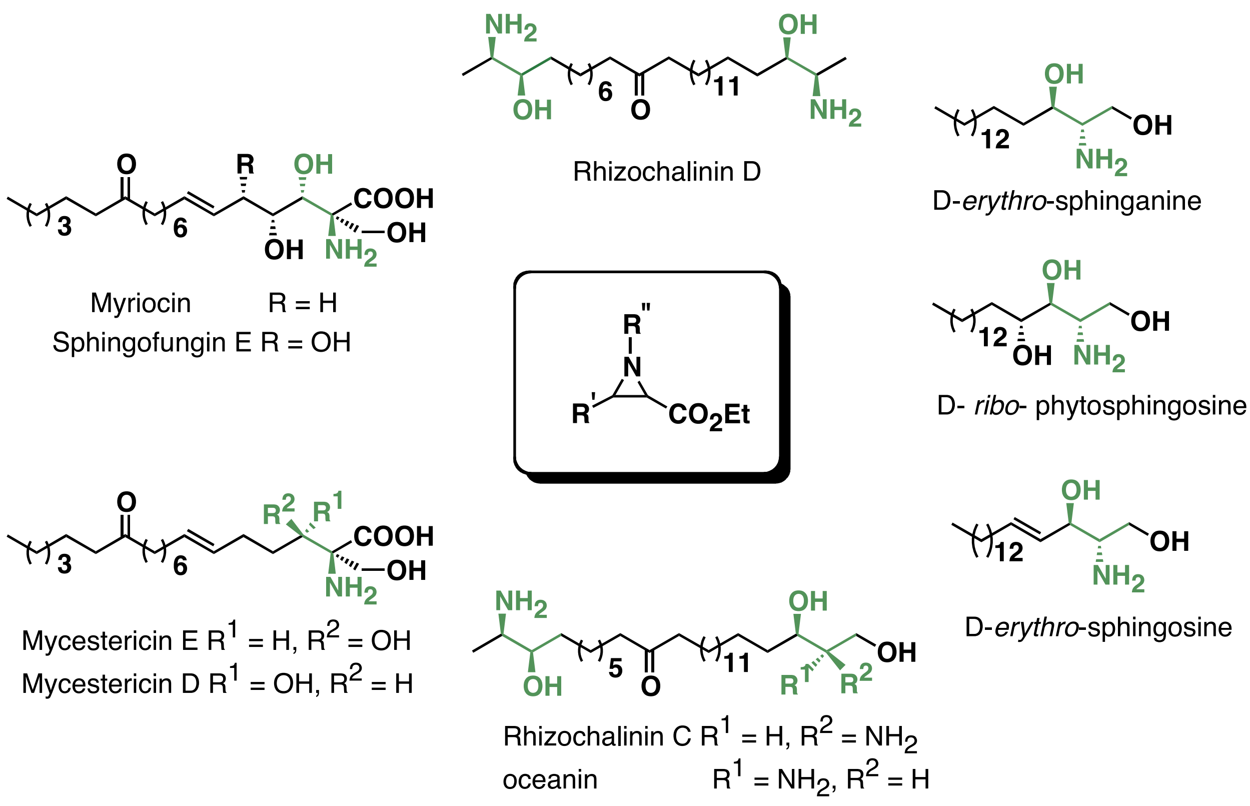


Acromelic acid A
ref 17a
(–)-Mesembrine
ref 17b
(–)-Kainic acid
ref 17c

1.5 Aziridines as the precursor for 1,2-amino alcohols

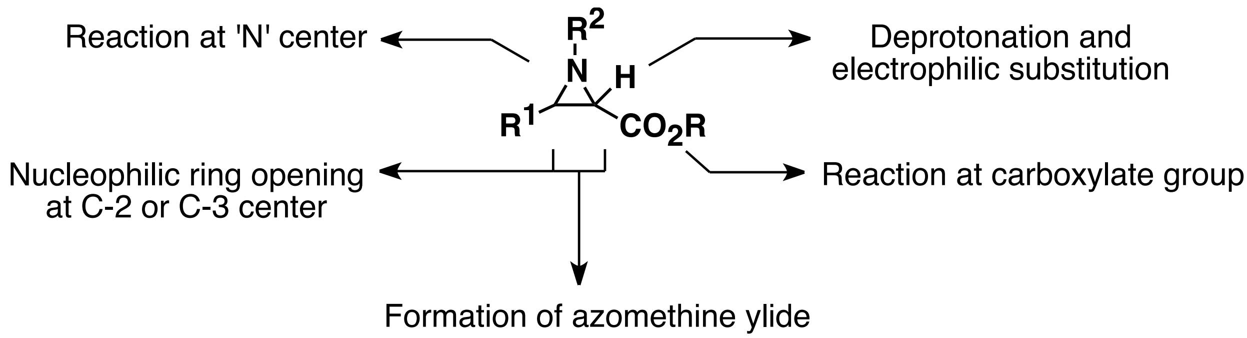
The use of aziridines as an intermediate in natural product synthesis has attracted considerable attention over last two decades. Nonetheless, aziridines, "the epoxides' ugly cousins", [18] have received little interest compared to that for epoxides. The aziridine ring has been used as an efficient precursor of 1,2-amino alcohols and other polyfunctionalized scaffolds. The 1,2-amino alcohol functionality is present in a structurally related family of compounds known as sphingoid bases, where are often termed as 'long-chain bases'.[19] This family of amino alcohols is known to contain hundreds of different molecules.[19b] The synthesis of such sphingoid bases can be planned *via* regio- and stereo-selective ring opening of the aziridine 2-carboxylates (Figure 1.5).

Figure 1.5 Possible approach towards naturally occurring 'Long chain bases' from aziridine 2-carboxylate



In addition to ring opening reactions other multi-dimensional reactivity patterns of aziridine 2-carboxylates (Figure 1.6) makes them versatile synthetic intermediates in organic synthesis.

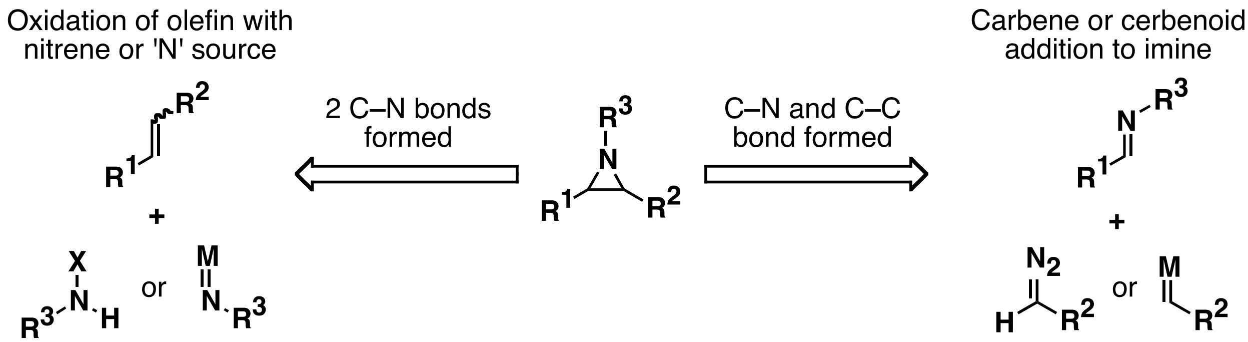
Figure 1.6 Different reactions of aziridine-2-carboxylate



1.6 Catalytic asymmetric synthesis of aziridines

As a result of their importance in synthesis, a lot of effort has been directed towards the preparation aziridines in last two decades. Most effort has been focused on synthesizing chiral aziridines from chiral substrates.[15c,20] Synthesis of aziridines *via* catalytic asymmetric reactions offer a more general method since it is not tied to the chiral pool and two general approaches have been taken (Scheme 1.7).[15c,21] One of them involves oxidation of alkenes i.e. the addition of a nitrene to the alkene precursor.[22] The other approach is the addition of a carbene or carbenoid to an imine. A summary of the extensive study in the field of asymmetric aziridination has been described in several excellent reviews over last few years.[15c,18,20-21,23]

Scheme 1.7 Approaches towards catalytic asymmetric aziridination



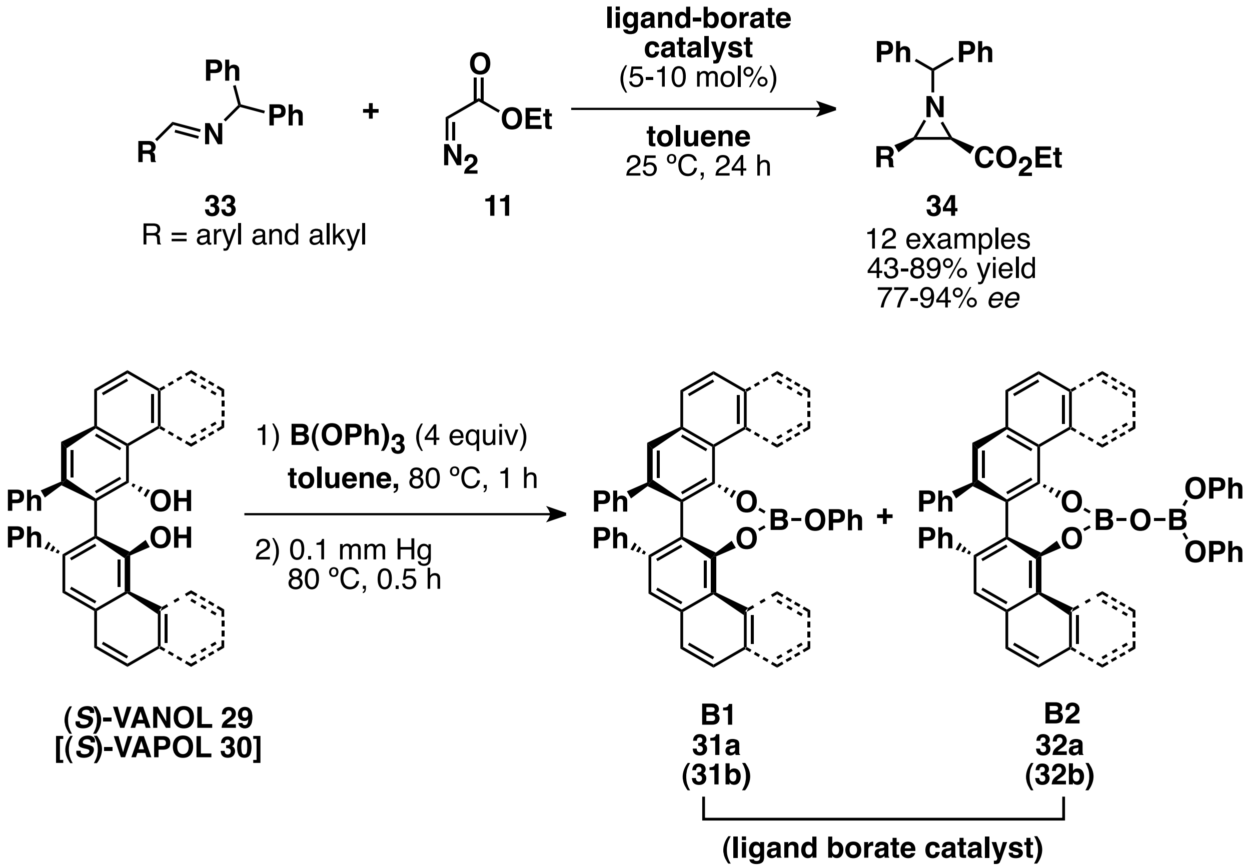
The Wulff group has pioneered the second approach that involves catalytic asymmetric aziridination of imines with carbenoids (*viz* diazoacetaes or diazoacetamides) in the presence of a Brønsted acid catalyst and the contributions of the Wulff group are summarized below.

1.7 Brønsted acid catalyzed asymmetric Aziridination reaction

In 2000, our group reported a very general catalytic asymmetric *cis*-aziridination reaction with high yields and enantioselectivities.[24] In this reaction enantiopure aziridines **34** were prepared by the reaction between the imines **33** and stabilized diazo compounds in presence of the catalyst prepared from the VAPOL **30** or VANOL **29** ligand and $B(OPh)_3$.

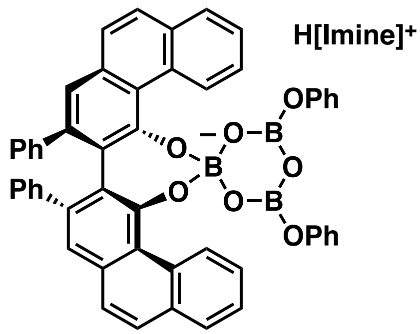
In 2008 the aziridination reaction with benzhydryl imines **33** was reexamined under new reaction conditions (Scheme 1.8).[25] Improved yield and asymmetric induction was observed.

Scheme 1.8 The Wulff-*cis* aziridination with benzhydryl imines



Based on the preliminary studies on catalyst structure,[26] it was thought that the active catalyst in the aziridination reaction was a Lewis acid, specifically a mixture of meso-borate **31** (B1) and pyroborate **32** (B2). Interestingly, when VAPOL **30** and $B(OPh)_3$ are mixed together at room temperature there is no reaction even after 24 h.[27] However, there is immediate formation of a boroxinate catalyst **35** after addition of imine to the mixture of VAPOL and $B(OPh)_3$.[27] Gang Hu, a previous group member, was able to obtained a crystal structure of the active catalyst.[27] The catalyst **35** exists as an ion-pair consisting of a boroxinate anion and an iminium cation resulting from protonation of the imine (Figure 1.7). So the actual catalyst is a chiral Brønsted acid in the Wulff aziridination reaction.

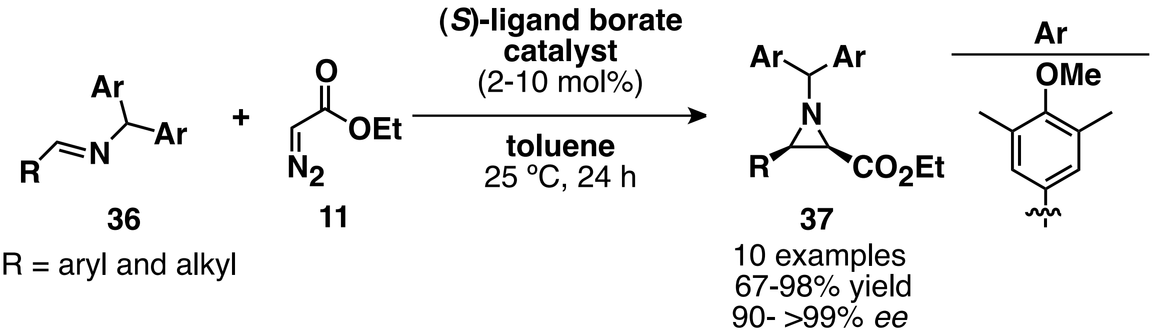
Figure 1.7 (*S*)-VAPOL boroxinate catalyst for the Wulff aziridination reaction



35
(S)-VAPOL-B3 catalyst

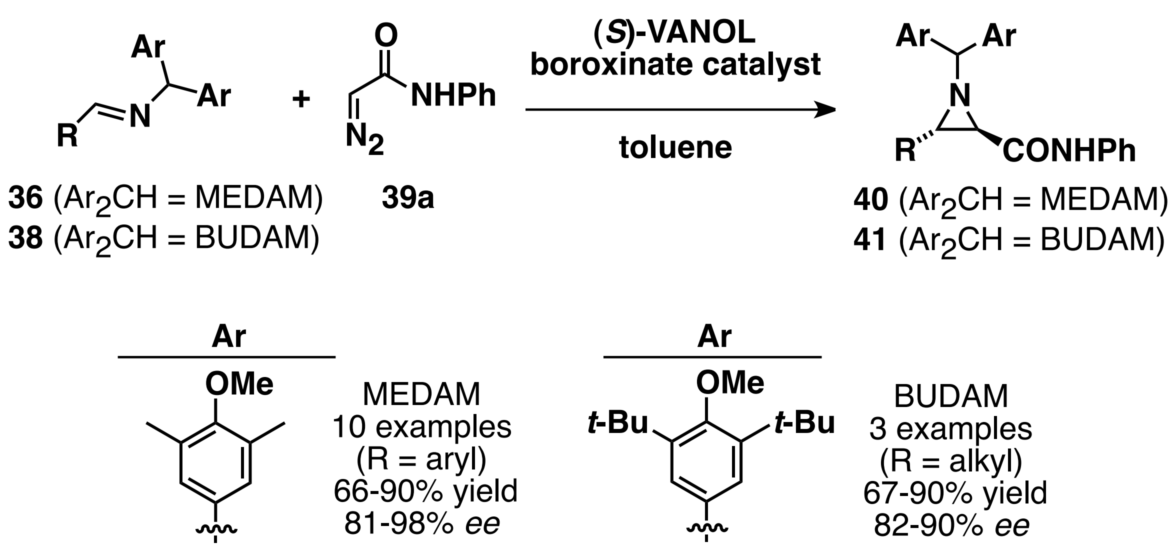
The aziridination reaction with the *N*-benzhydryl imine **33** gives acceptable asymmetric induction with aromatic substrates (90-94% ee) but they fail to give satisfactory results with aliphatic imines (78-87% ee, Scheme 1.8). After an extensive search of *N*-protecting group, it was delightful to find that the MEDAM group gave high inductions with both classes of substrates (Scheme 1.9).[28] A considerable amount of the work in this thesis has been focused on the study of aziridination reaction of *N*-MEDAM imines **36** and is discussed in Chapter 2.

Scheme 1.9 The Wulff-*cis* aziridination with *N*-MEDAM imines **36**

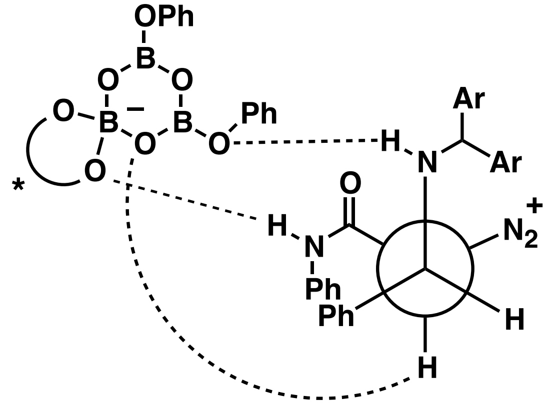


In 2010, another group member, Aman Desai, demonstrated a method for synthesizing *trans*-aziridines with high yields and enantioselectivities using the boroxinate catalyst (Scheme 1.10).[29] In this *trans*-aziridination reaction, diazo acetamides were used instead of diazo esters. The switch in the diastereoselectivity was explained as the outcome of an H-bonding interaction of the diazo acetamide with the boroxinate catalyst [30].

Scheme 1.10 The Wulff *trans*-aziridination reaction



Scheme 1.10 (cont'd)



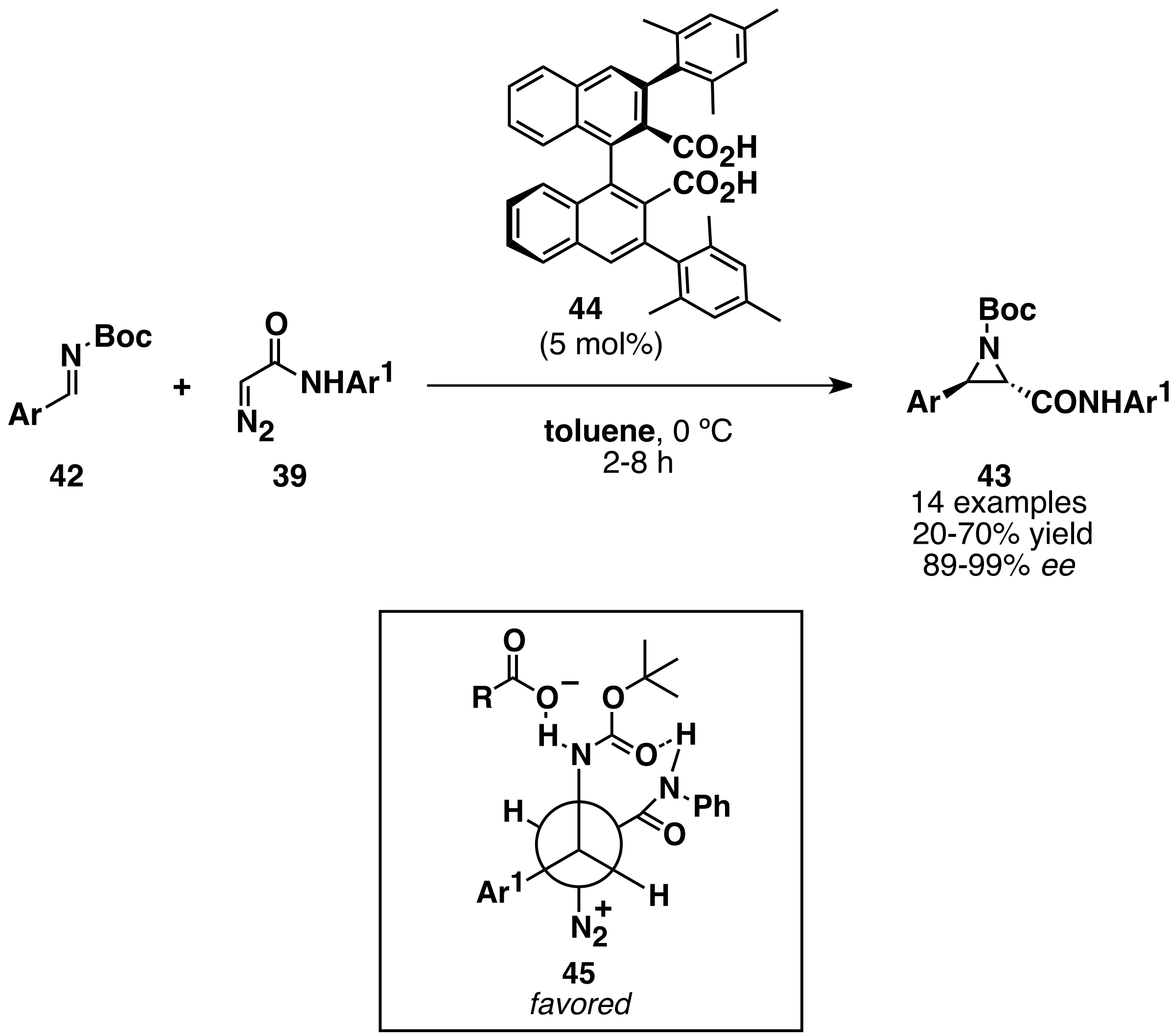
H-bonding and charge stabilization

Thus, the Wulff aziridination system is the only universal catalytic asymmetric aziridination method where the same imine substrate and same catalyst can be used to generate either *cis* or *trans* aziridines.

Over the past few years an enormous amount of work has been carried out in the Wulff group towards addressing different aspects of the aziridination protocol. Not only has it been possible to increase the scope of the reaction methodology but also significant contributions towards mechanistic understanding and to applications of the reaction methodology towards total synthesis have been made in our group. In addition to the Wulff's aziridination system, three other groups have reported Brønsted acid catalyzed asymmetric aziridination reactions.

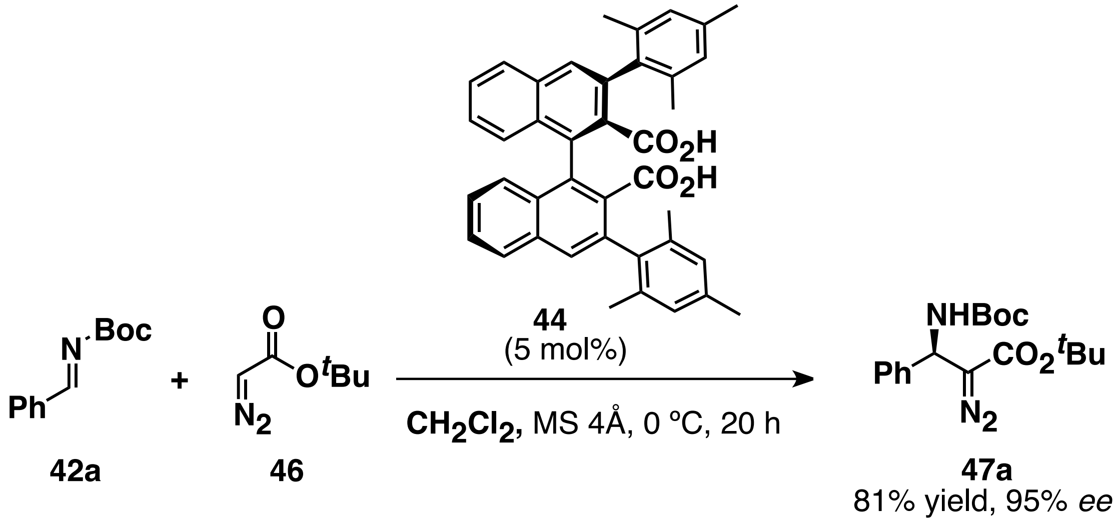
In 2008, Maruoka reported the first *trans*-selective chiral Brønsted acid catalyzed aziridination which involved the *N*-Boc imines **42** with diazo acetamides **39** (Scheme 1.11).[31]

Scheme 1.11 BINOL dicarboxylic acid catalyzed *trans*-aziridination with diazoacetamide



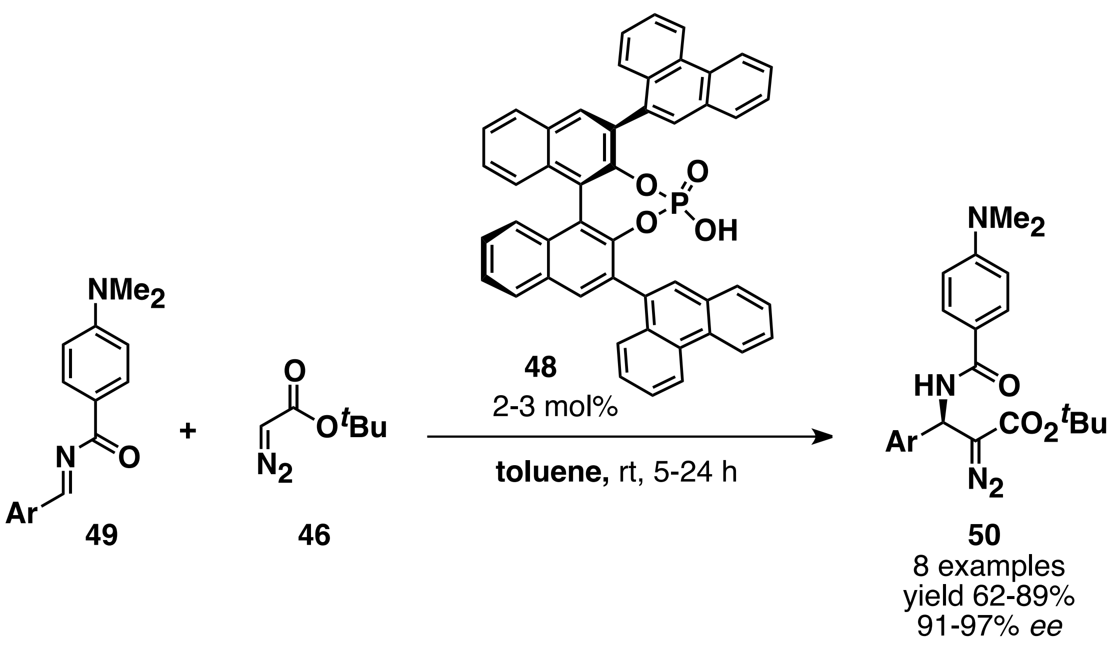
The *trans*- selectivity was explained with the help of a proposed transition state **45** where hydrogen bonding between the Boc group of the imine and the diazoacetamide *N*-H bond plays a major role. Interestingly, they were able to perform an asymmetric alkylation reaction of diazo compounds with the same BINOL dicarboxylic acid catalyst **44** when they substituted the diazo acetamide with a diazo acetate (Scheme 1.12).[32]

Scheme 1.12 BINOL dicarboxylic acid catalyzed asymmetric alkylation of diazoester **46**

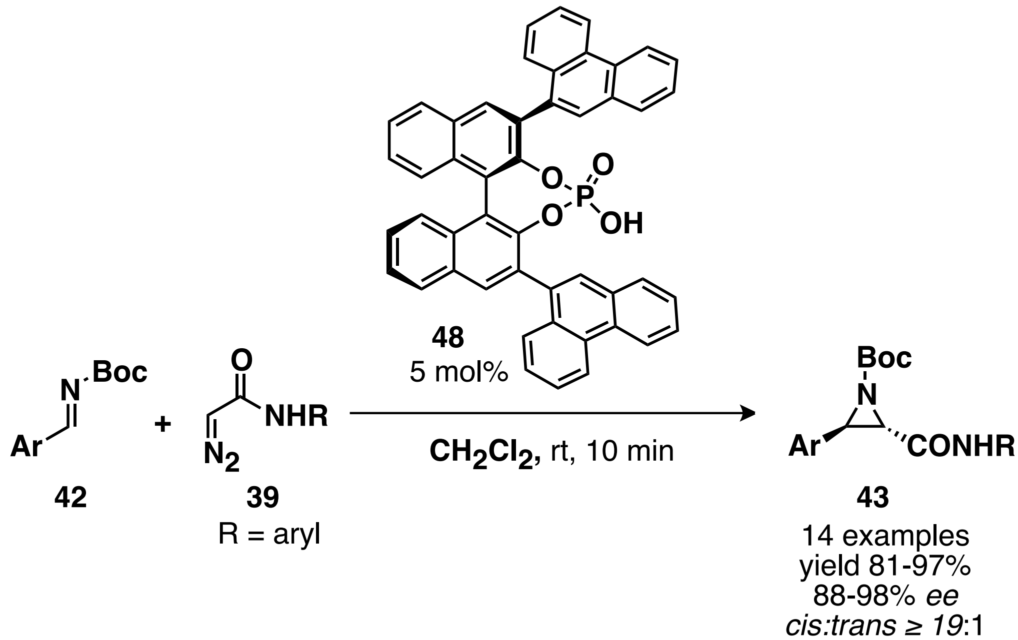


In 2005, Terada and coworkers reported alkylation of diazo acetates utilizing chiral BINOL phosphoric acid **48** (Scheme 1.13).[33] Later, Zhong and coworkers used the same chiral BINOL phosphoric acid **48** for *trans*-aziridinaton reaction with diazoacetamides (Scheme 1.14).[34]

Scheme 1.13 BINOL phosphoric acid catalyzed asymmetric alkylation with a diazoester **46**

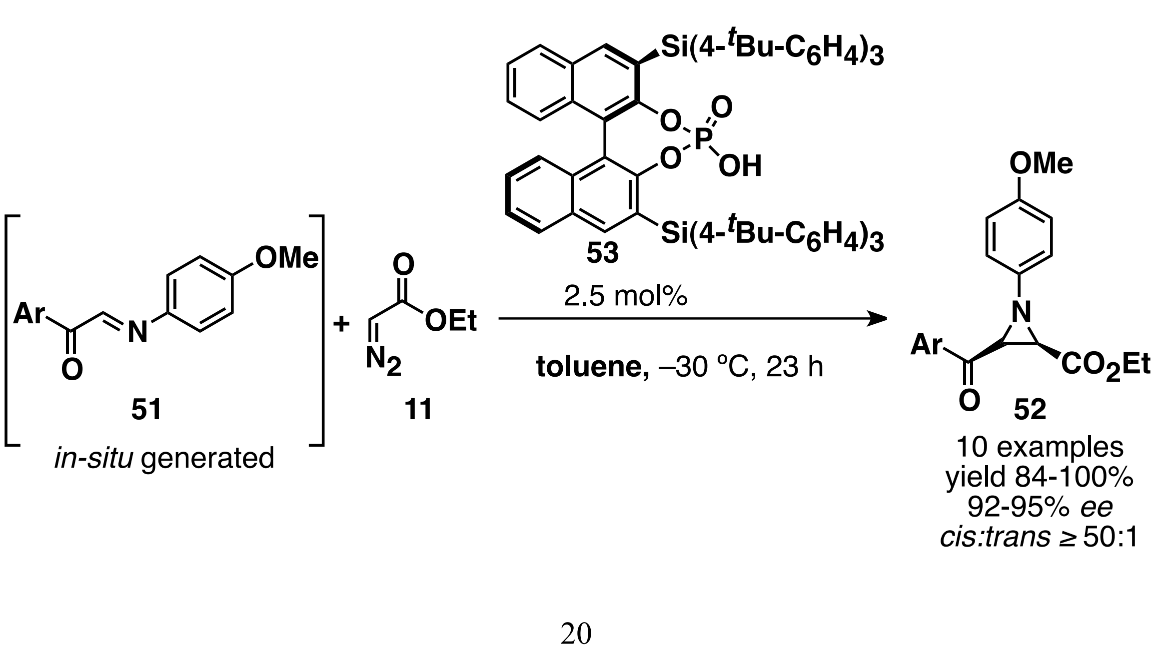


Scheme 1.14 BINOL phosphoric acid catalyzed *trans*-aziridination with diazoacetamides **39**



In 2009 Akiyama reported a Brønsted acid catalyzed asymmetric *cis*-aziridination reaction between *in-situ* formed activated imines **51** and ethyl diazoacetate **11** in the presence of the chiral BINOL phosphoric acid **53** (Scheme 1.15).[35] The scope of the reaction is limited to the activated imine substrates made only from aryl glyoxal derivatives.

Scheme 1.15 BINOL phosphoric acid catalyzed asymmetric *cis*-aziridination reaction



1.8 Conclusions

The ability of aziridines to undergo various regio- and stereo-selective reactions, makes these strained three-membered heterocycle an invaluable motif in organic synthesis. The synthetic potential of aziridines has attracted considerable attention of the scientific community towards the preparation of stereo- and enantioselective aziridinyl core.

In past few years our group has made significant progress in different aspects of catalytic asymmetric aziridination methodology. However, certain goals such as substrate generality, procedure simplification and application to total synthesis remained elusive prior to the research described in this thesis. The aim of this work was to attain the above-mentioned objectives and the results are described in detail in subsequent chapters.

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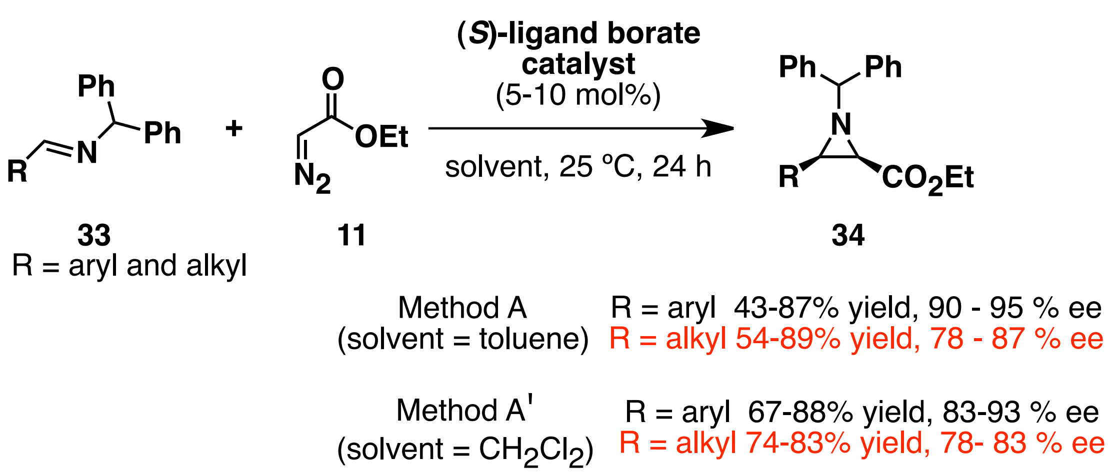
CHAPTER 2

EVOLUTION OF A SUBSTRATE GENERAL CATALYIC ASYMMETRIC AZIRIDINATION REACTION WITH *N*-MEDAM IMINES

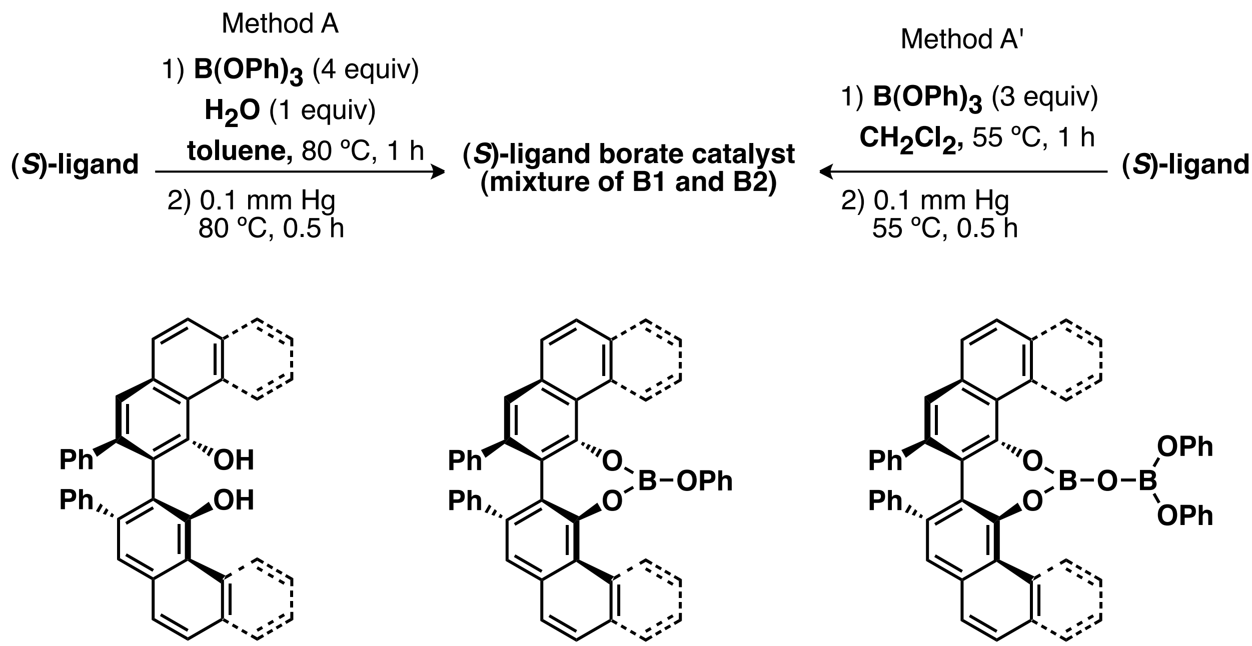
2.1 Introduction

Over the last decade, the Wulff group has developed a very efficient catalytic asymmetric aziridination reaction that is based on the reaction of imines with stabilized diazo compounds.[1] A catalyst prepared from either the VAPOL **30** or VANOL **29** ligand and $B(OPh)_3$ mediates the reaction. In early studies, it was determined that *N*-benzhydryl group in imine **33** was the optimal '*N'* protecting group in the Wulff's *cis*-aziridination reaction.[2]

Scheme 2.1 Asymmetric aziridination with benzhydryl imines **33**.



Scheme 2.1 (cont'd)



(*S*)-VANOL 29
[(*S*)-VAPOL 30]

B1
31a for VANOL
(31b for VAPOL)

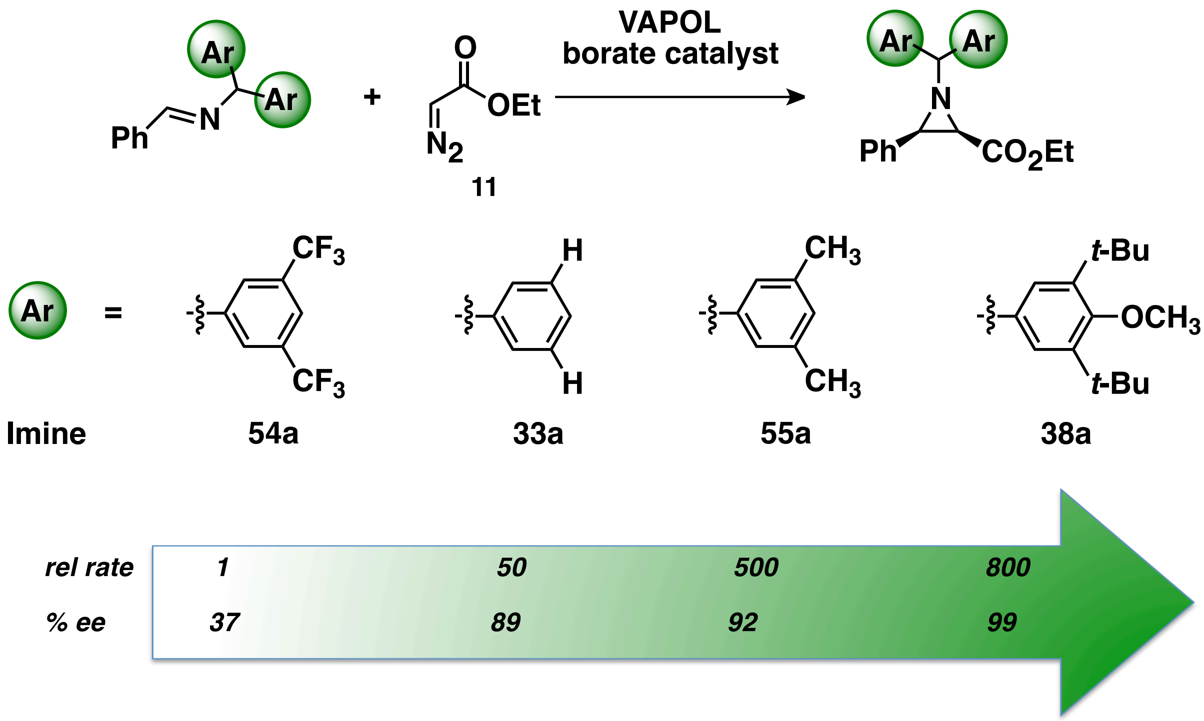
B2
32a for VANOL
(32b for VAPOL)

The aziridination reaction is highly diastereoselective furnishing *cis*-2, 3-disubstituted aziridines **34** with high yields and good to moderate enantioselectivity (Scheme 2.1).[2] The aromatic aziridines could be crystallized to afford optically pure (≥ 99% ee) aziridines,[2c] the aliphatic imines afforded corresponding aziridines with moderate ee (78-87% ee). The optical purity of the aziridines, which are not solid, cannot be enhanced by crystallization. A considerable amount of effort has been made towards extending the substrate generality of our aziridination protocol. There are several factors that were identified that could potentially contribute to the asymmetric induction, and these include the method for catalyst preparation, the nature of the ligand and the nature of the *N*-substituent on the imines. During mechanistic studies, it was found that the catalyst preparation (Method A', Scheme 2.1) lead to the formation of a mixture of mesoborate B1 (**31**) and pyroborate B2 (**32**). Also, a new procedure was developed (Method A in Scheme 2.1) for catalyst preparation that gave a higher ratio of B2 (**32**) to B1 (**31**). It was found that the catalyst enriched in B2 gave higher asymmetric induction and the results were reproducible, which was not the case for Method A' (Scheme 2.1). Employing different *N*- protecting groups on the imine provides a convenient handle for reaction optimization. A comprehensive study regarding variation of the *N*-protecting group is discussed below.

2.2 Study towards developing a universal *N*-protecting group

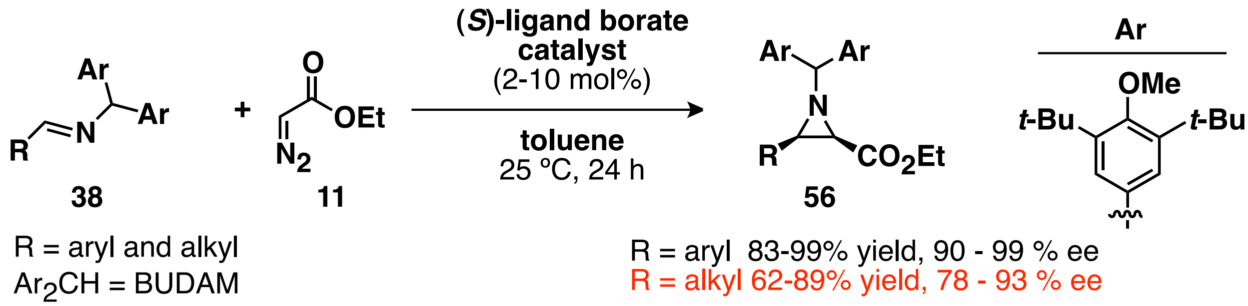
In a study designed for mapping the active site of the chemzyme[3] in the aziridination reaction, a clearer picture concerning the correlation between the shape, size and electronic nature of the *N*-substituent on the imine substrate and the rates and enantioselectivities of the reaction was revealed. The extensive study of the effect of changing the conformation, electronics, and sterics of the two-phenyl groups on the benzhydryl group lead to the identification of the tetra-tert-butyldianisylmethyl (BUDAM) group (imine **38a**) as the optimal *N*-substituent for a high yielding aziridination reaction with near-perfect asymmetric induction (Scheme 2.2).[3]

Scheme 2.2 Relative rates and asymmetric inductions for the aziridinations of *N*-diarylmethylimines



With the VAPOL derived catalyst, the reactions of BUDAM imines **38** from aromatic aldehydes resulted in 90-99% ee for most substrates whereas their benzhydryl analogues gave only 90-95% ee. However, there was no significant difference in the asymmetric induction between BUDAM or benzhydryl imines derived from aliphatic aldehydes. The asymmetric induction with *N*-BUDAM protecting group was in the range of 78-93% (Scheme 2.3) giving greater than 90% ee (93% ee) with only the ethyl imine.

Scheme 2.3 Catalytic asymmetric aziridination with *N*-BUDAM imines **38**.



At this point, the goal was to find a universal *N*-protecting group, which would provide high asymmetric induction in the aziridination reaction irrespective of the substrate. During the studies directed toward the mapping of the active site of the catalyst, the tetra-methyldiphenylmethyl (MEDPM) group was examined as one of the *N*-protecting group.[3] In the subsequent studies, Zhenjie Lu a former group member, found that the aliphatic imine **55i** derived from cyclohexane carboxaldehyde and imine **55j** derived from pivaldehyde underwent asymmetric aziridination with significantly enhanced inductions as compared to the benzhydryl[2c] and BUDAM[3] imines (Table 2.1).

Table 2.1 Catalytic asymmetric aziridination with alkyl imines **33**, **38** and **55**

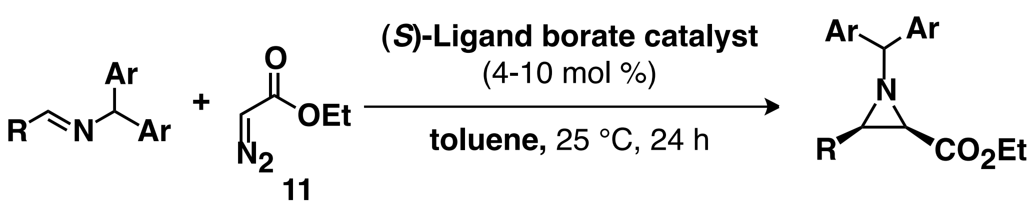
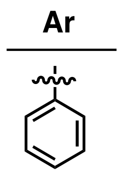
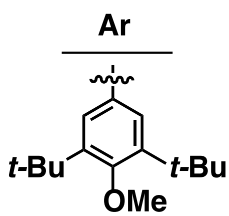


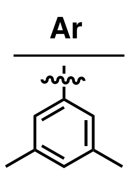
Table 2.1 (cont'd)



R	Imine	Ligand (mol%)	aziridine	% Yield	% ee
Cy	**33i**	(*S*)-VAPOL (5)	**34i**	73	81
Cy	**33i**	(R)-VANOL (5)	**34i**	79	–82
t-Bu	**33j**	(*S*)-VAPOL (5)	**34j**	72	87
t-Bu	**33j**	(*R*)-VANOL (5)	**34j**	89	–85



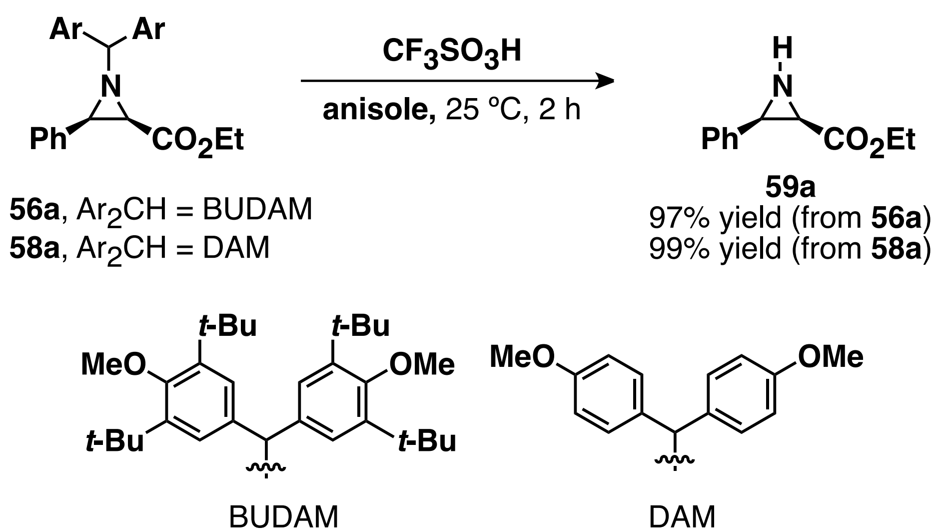
R	Imine	Ligand (mol%)	aziridine	% Yield	% ee
Cy	**38i**	(*S*)-VAPOL (4)	**56i**	89	89
Cy	**38i**	(*S*)-VANOL (4)	**56i**	87	84
t-Bu	**38j**	(*S*)-VAPOL (10)	**56j**	60	78
t-Bu	**38j**	(*S*)-VANOL (10)	**56j**	76	80



R	Imine	Ligand (mol%)	aziridine	% Yield	% ee
Cy	**55i**	(*S*)-VAPOL (4)	**57i**	87	91
Cy	**55i**	(*S*)-VANOL (4)	**57i**	93	92
t-Bu	**55j**	(*S*)-VAPOL (10)	**57j**	94	96
t-Bu	**55j**	(*S*)-VANOL (10)	**57j**	94	96

Although, the MEDPM imines **55i** and **55j** exhibit higher asymmetric induction in the aziridination reaction with aliphatic imines, the applicability of *N*-MEDPM aziridines **57** was found to be limited due to unsatisfactory results form the acid cleavage of the *N*-protecting group from aziridines.[4] In previous studies, it was established that the benzhydryl protecting groups with *p*-methoxy groups such as BUDAM and DAM[5] could be readily cleaved from aziridines by acid without ring opening (Scheme 2.4). Hence, it was thought to install the methoxy group at the *pare* position of the *N*-MEDPM protecting group. This led us to target the tetra-methyl dianisylmethyl (MEDAM) group as a *N*-protecting group in the aziridination reaction.

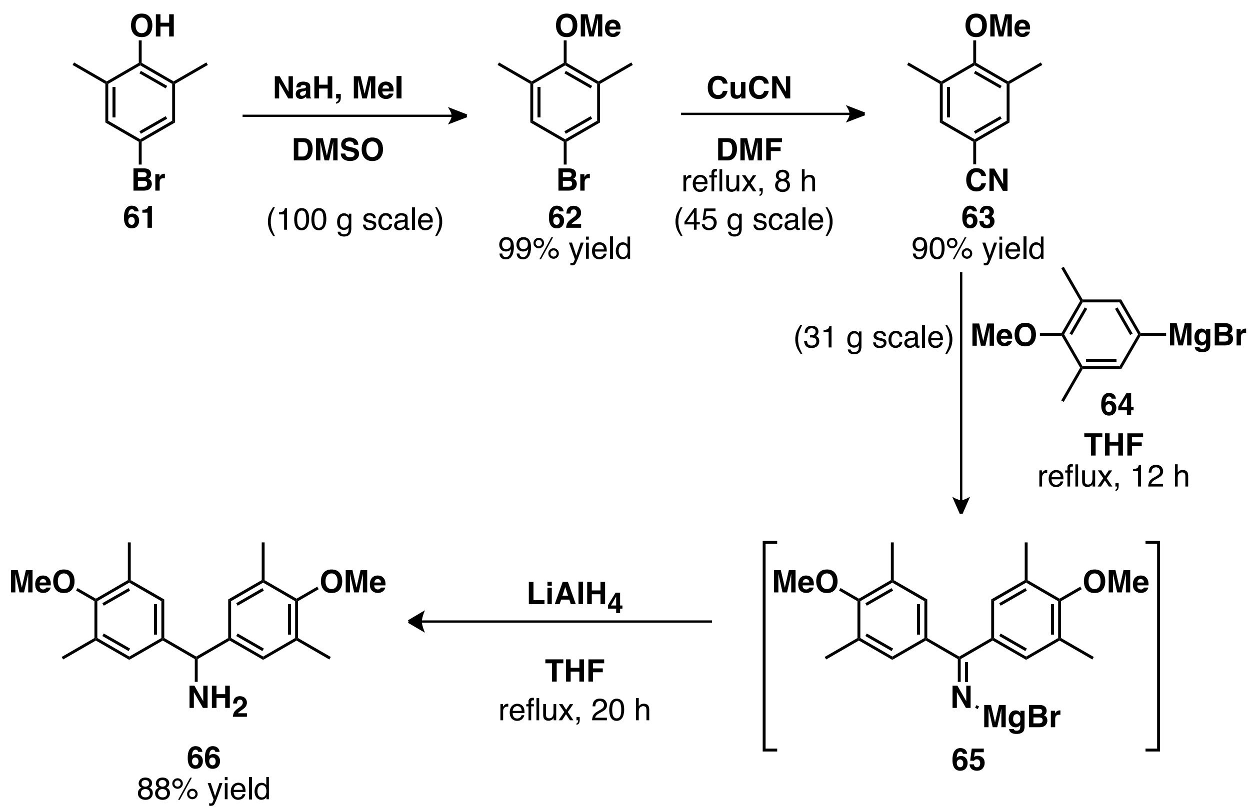
Scheme 2.4 Acid catalyzed deprotection of *N*-protected aziridines **56a** and **58a**



2.3 MEDAM group: a universal protecting group

The tetra-methyldianisylmethyl (MEDAM) amine **66** (Scheme 2.5) was prepared and the aziridination reaction with imines **36** derived from **66** was then evaluated. Imine **36a** prepared from MEDAM amine **66** and benzaldehyde had been previously evaluated in the aziridination reaction but not with imines from aliphatic aldehydes and other aromatic aldehydes.[3] The synthesis of tetra-methyldianisylmethyl (MEDAM) amine **66** shown in Scheme 2.5 follows that previously reported and was scaled up to 100 g on the commercially available phenol **61**.[6] The large scale preparation begins with the synthesis of the the bromide **62** from the inexpensive 4-bromo-2,6-dimethylphenol **61**. The nitrile **63** can be obtained from the bromide **62** by the Shechter modification of the Rosenmund-Van Braun reaction.[7] The key step in the synthesis of amine **66** involves the reaction of the nitrile **63** with the *in-situ* generated Grignard reagent **64**.

Scheme 2.5 Large scale synthesis of MEDAM amine **66** [6]



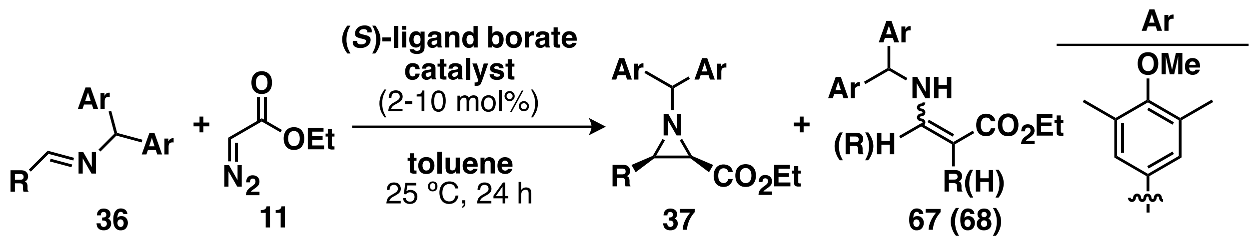
The subsequent *in-situ* reduction of the resulting imine intermediate **65** provides the amine **66** in 88% yield from the nitrile **63**. Yu Zhang, a former group member, developed the small-scale synthesis of the MEDAM amine **66**. The synthesis was then scaled up from original small-scale synthesis by Yu Zhang and the concentration of the reaction in each step was increased to minimize the solvent waste and to simply the overall process. The entire process of preparation of MEDAM amine **66** was carried out efficiently without the use of any column chromatography purification. At this point, the project was taken over by another group member, Anil Gupta. The modifications that he made in the reaction sequence are as follows: a) commercially available bromide **62** was used, b) the nitrile **63** was made from 56 mmol of bromide **62**, c) the nitrle **63** was used in the Grignard reaction without any purification and d) MEDAM amine• HCl salt was made using dry HCl gas instead of a 12M HCl solution during the purification of final product **66**.

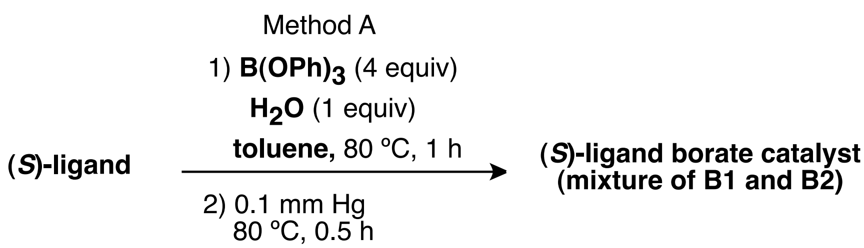
2.4 Catalytic asymmetric aziridination with MEDAM imine 36

During the investigation of the scope of the aziridination reactions with MEDAM imines **36** (Table 2.2) the catalyst was formed following method A.[6] The catalyst, was prepared by heating the mixture of ligand with 4 equiv of $B(OPh)_3$ and 1 equiv water at 80 ºC for an hour. Further, it was exposed to the high vacuum to remove the volatiles. Catalyst formation was then followed by the addition of imine **36** and ethyl diazoacetate **11** and toluene. Later, it was found that the addition of water is not necessary during the catalyst preparation, as commercial $B(OPh)_3$ has enough water to form the catalyst.[6]

The aziridination reaction with the MEDAM imines prepared from aryl aldehydes afforded *cis*-aziridines **37** with high asymmetric induction (98% ee to ≥ 99% ee) with the VAPOL catalyst. The VANOL catalyst produced slightly lower inductions (~ 97% ee) for the same imines. The MEDAM imine **36b** made from *o*-tolualdehyde resulted in aziridine **37b** with a higher *cis*-selectivity (Table 2.2, entry 4 and 5) than the corresponding benzhydryl imine.[2c] To our delight, the MEDAM imines **36** prepared from aliphatic aldehydes shows essentially the same levels of asymmetric induction as those observed for the corresponding MEDPM imines (Table 2.2, entries 23-28 *vs.* Table 2.1, entries 9-12).

Table 2.2 Asymmetric aziridination with MEDAM imines **36**[a].





entry	imine[b]	R	ligand	catalyst (mol%)	%yield cis-**37**[c]	%ee *cis*-**37**[d]	cis/trans[e]	%yield 67(68)[f]
1	**36a**	Ph	(*S*)-VAPOL	5	98	99.8	>50:1	2.0(1.9)
2	**36a**	Ph	(*R*)-VANOL	5	94	–97	>50:1	2.1(1.8)
3	**36a**	Ph	(*R*)-BINOL	5	72	–38	17:1	14(10)
4	**36b**	2-MeC_6H_4	(*S*)-VAPOL	3	91	98	33:1	4.5(2.7)
5	**36b**	2-MeC_6H_4	(*R*)-VANOL	5	90	–97	50:1	2.7(2.7)

Table 2.2 (cont'd)

6	**36c**	4-MeC_6H_4	(*S*)-VAPOL	5	95	99.5	>50:1	3.8(0.9)
7	**36c**	4-MeC_6H_4	(*R*)-VANOL	5	94	–97	>50:1	3.6(2.7)
8	**36d**	4-$MeOC_6H_4$	(*S*)-VAPOL	3	85	98	50:1	1.0(1.0)
9	**36d**	4-$MeOC_6H_4$	(*R*)-VANOL	5	83	–96	33:1	3.3(4.0)
10[g]	**36e**	4-BrC_6H_4	(*S*)-VAPOL	2	89	99.5	>50:1	1.0(1.0)
11	**36e**	4-BrC_6H_4	(*S*)-VAPOL	3	95	99.6	>50:1	2.0(1.9)
12	**36e**	4-BrC_6H_4	(*S*)-VAPOL	5	97	99.5	>50:1	1.0(1.0)
13	**36e**	4-BrC_6H_4	(*R*)-VANOL	5	95	–97	>50:1	1.2(1.4)
14	**36f**	4-$NO_2C_6H_4$	(*S*)-VAPOL	5	96	99.7	>50:1	1.2(2.0)
15	**36f**	4-$NO_2C_6H_4$	(*R*)-VANOL	5	95	–97	>50:1	1.0(1.9)
16	**36k**	*n*-hexyl	(*S*)-VAPOL	3	67	90	nd	nd
17	**36h**	*n*-propyl	(*S*)-VAPOL	10	64	93	nd	5.3(8.0)
18[h]	**36h**	*n*-propyl	(*S*)-VAPOL	10	72	97	nd	3.0(1.5)
19	**36h**	*n*-propyl	(*R*)-VANOL	10	73	–94	nd	1.0(1.5)
20[h]	**36h**	*n*-propyl	(*R*)-VANOL	10	75	–95	nd	1.0(1.0)

Table 2.2 (cont’d)

21[h,i]	**38h**	*n*-propyl	(*S*)-VAPOL	10	69	95	nd	10.3(4.4)
22[h,i]	**38h**	*n*-propyl	(*R*)-VANOL	10	75	–93	nd	nd(5.3)
23	**36i**	cyclohexyl	(*S*)-VAPOL	3	98	91	>50:1	nd
24[h]	**36i**	cyclohexyl	(*S*)-VAPOL	3	94	91	nd	1.0(3.0)
25	**36i**	cyclohexyl	(*R*)-VANOL	3	95	–91	>50:1	nd
26	**36j**	*ter*t-butyl	(*S*)-VAPOL	3	95	94	>50:1	nd
27	**36j**	*ter*t-butyl	(*R*)-VANOL	3	97	–96	>50:1	nd
28[h]	**36j**	*ter*t-butyl	(*R*)-VANOL	10	95	–96	nd	1.0(3.0)

[a] For all reactions with 5 and 10 mol% catalyst, the catalyst was prepared by Method A. For all reactions with 2 and 3 mol% catalyst, the catalyst was prepared by Method A without water. Unless otherwise specified, all reactions were carried out with 1.0 mmol of **36** at 0.5 M in toluene with 1.2 equiv of **11** at 25 °C and went to completion in 24 h. [b] All imines were purified by crystallization except **36h**, **36k** and **38h** which were oils and were used without purification. Imine **36k** was prepared by method 1 and **36h** and **38h** were prepared by method 2 given in the experimental section for chapter 2. [c] Isolated yield of *cis*-**37** after chromatography on silica gel. [d] Determined on purified *cis*-**37** by HPLC on a CHIRAL CEL OD-H column. [e] Ratio

Table 2.2 (cont'd)

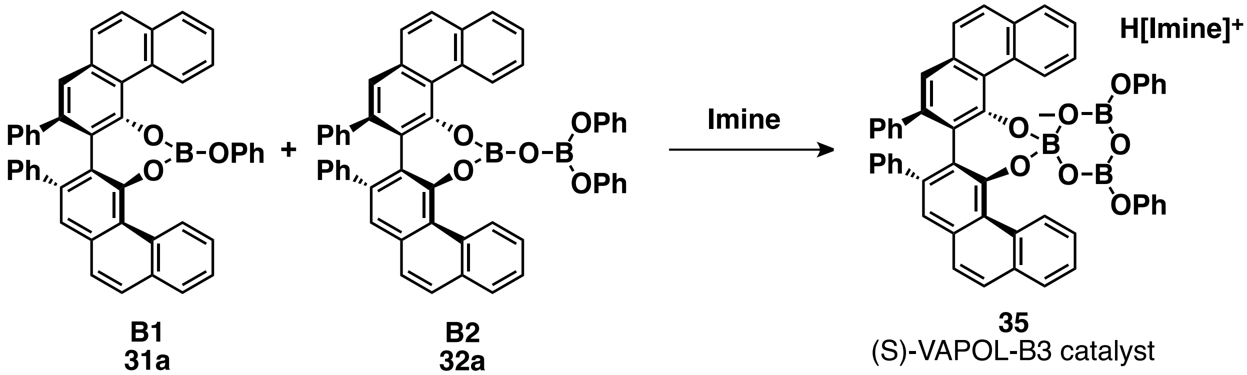
determined by integration of the methine protons of the *cis*- and *trans*-aziridines in the ^{1}H NMR spectrum of the crude reaction mixture. nd = not determined. [f] Determined by integration of the NH signals of **67** and **68** relative to the methine proton of *cis*-**37** in the ^{1}H NMR spectrum of the crude reaction mixture. [g] Reaction went to 97% completion. [h] Reaction performed at 0 °C for 24 h. [i] Imine prepared from BUDAM amine (see experimental section for chapter 2) and the product was aziridine **56h**.

There was no improvement in asymmetric induction as a result of lowering the temperature to 0 ºC for either the cyclohexyl or *tert*-butyl substrates (entries 24 and 28). Most importantly, the asymmetric aziridination of imines from primary aliphatic aldehydes (entries 16-22) with the MEDAM protecting group occurred with good yields and excellent asymmetric inductions. In this case, the asymmetric induction could be improved by lowering the temperature to 0 ºC (entries 17 *vs*. 18 and 19 *vs*. 20). A slightly lower induction was observed for the BUDAM imine **38h** at this temperature (entries 20 *vs*. 22 and 21 *vs*. 18).

2.5 Simplification of the aziridination protocol

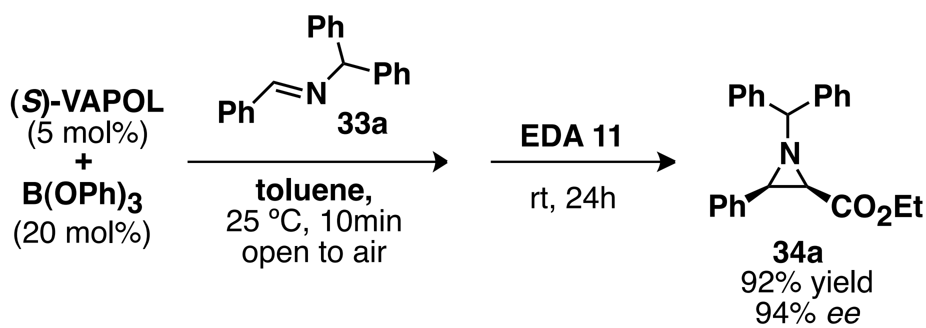
In the continuing effort to gain a mechanistic rationale for the asymmetric induction observed for catalysts generated from VANOL **29** and VAPOL **30**, a major breakthrough was the identification of the active boron-ligand complex B3 **35.**[8] A previous group member, Gang Hu, was able to obtain a crystal structure of the active catalyst **35** which is a complex consisting of a protonated imine and a chiral counteranion in the form of a VAPOL boroxinate.[8b] Evidence was also obtained which shows that the actual catalyst **35** was formed upon the addition of an imine to a mixture of pyroborate B2 **32** and mesoborate B1 **31**.

Scheme 2.6 Formation of the boroxinate (B3) catalyst **35**



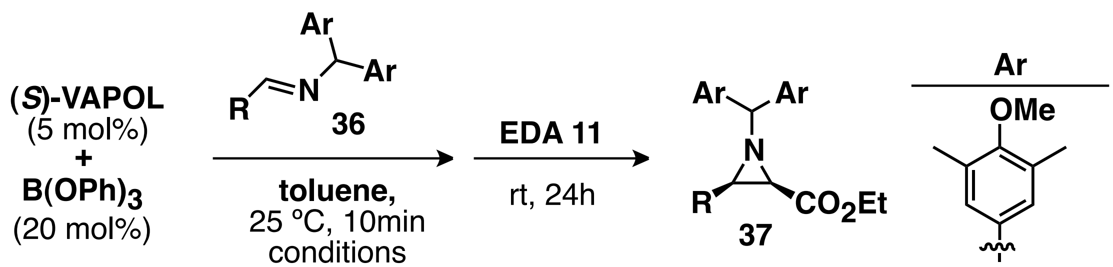
Therefore, it was thus envisioned that the active catalyst B3 **35** could be generated *in situ* directly from VAPOL rather than making it *via* B2 **32** and B1 **31**. Consequently, a simplified procedure (Method B, Scheme 2.7) was found.[8b]

Scheme 2.7 Catalytic asymmetric aziridination reaction with benzhydryl imine **33a** with Method B



One of the aims of the current work was to simply the protocol of the catalytic AZ reaction. Hence, the MEDAM imines **36** were subjected to method B with 5 mol% catalyst loading. All imines but one (imine **36e**, Table 2.3, entry 6) went to completion. All the imines went to completion when the reaction was done under argon atmosphere (Table 2.3, entries 2, 4, 8). Imine **36e** went almost to the completion (95 % conversion, Table 2.3, entry 6). Unfortunately, the result with **36e** was not reproducible (Table 2.3, entry 6).

Table 2.3 Asymmetric aziridination with MEDAM imine **36** with Method B [a]



entry	Imine [b]	R	conditions	conversion(%) [c]	% yield *cis*-**37** [d]	% ee *cis*-**37** [e]
1	**36a**	Ph	Open to air	100	92	98
2	**36a**	Ph	Under argon	100	93	98
3	**36d**	4-$MeOC_6H_4$	Open to air	100	78	82
4	**36d**	4-$MeOC_6H_4$	Under argon	100	82	84
5	**36e**	4-BrC_6H_4	Open to air	100	89	97
6	**36e**	4-BrC_6H_4	Under argon	58-95	51—87	97
7	**36f**	4-$NO_2C_6H_4$	Open to air	100	53	96
8	**36f**	4-$NO_2C_6H_4$	Under argon	100	95	96

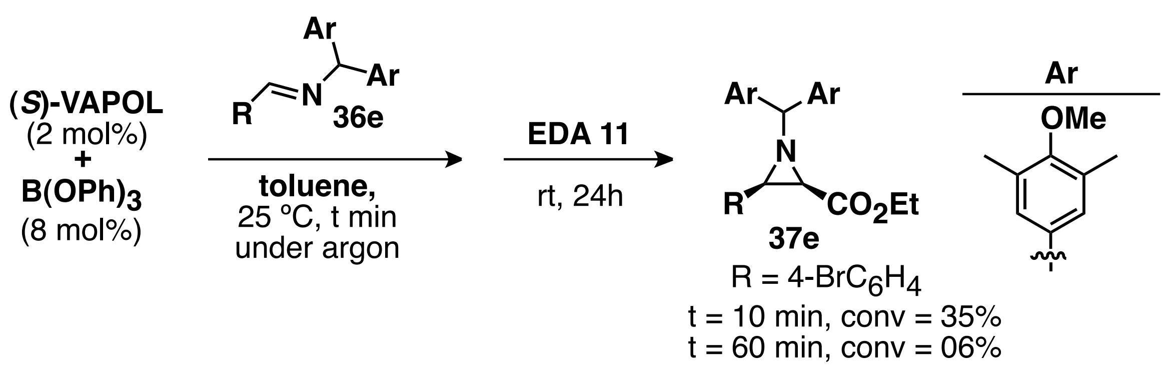
[a] Unless otherwise specified, all reactions were carried out with 1.0 mmol of **36** at 0.5 M in toluene with 1.2 equiv of **11** at 25 °C following Method B with 5 mol % catalyst. [b] All imines

Table 2.3 (cont'd)

were purified by crystallization. [c] Conversion was determined by integration of the methine protons of the *cis*-aziridines relative to the *Sp2* CH proton of unreacted imine in the ^{1}H NMR spectrum of the crude reaction mixture. [d] Isolated yield of *cis*-**37** after chromatography on silica gel. [e] Determined on purified *cis*-**37** by HPLC on a CHIRAL CEL OD-H column.

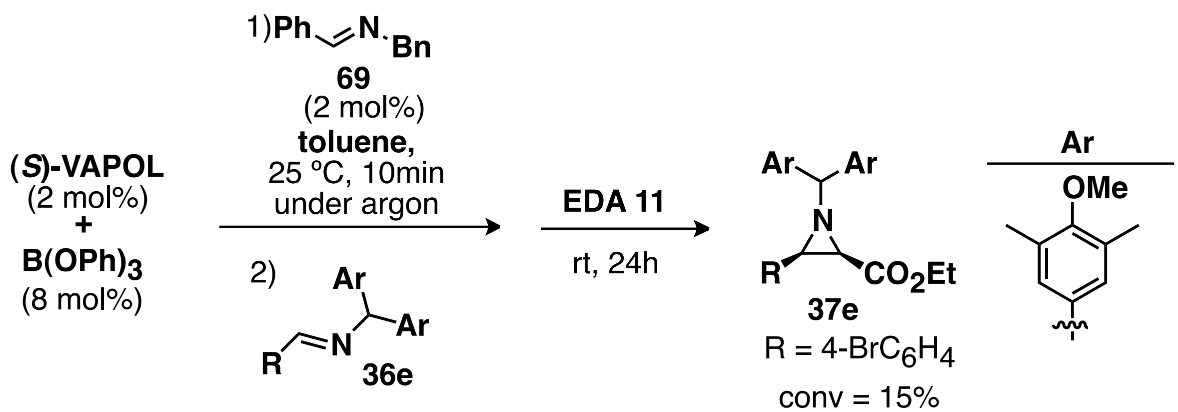
In order to observe the effect of lowering the catalyst loading on the conversion of imine to aziridine, imine **36e** was subjected to method B (under argon) using 2 mol% of VAPOL derived catalyst. As expected, based on the results in table 2.3, only a 35 % conversion was observed (Scheme 2.9). Up until now, the catalyst was allowed to form for 10 min. It was then thought to increase this time period up 1 h. However, an even lower conversion (6%) was observed for imine **36e** (Scheme 2.8). This may have happened due to the decomposition of the catalyst during the extended time.

Scheme 2.8 Asymmetric aziridination with MEDAM imine **36e** with Method B



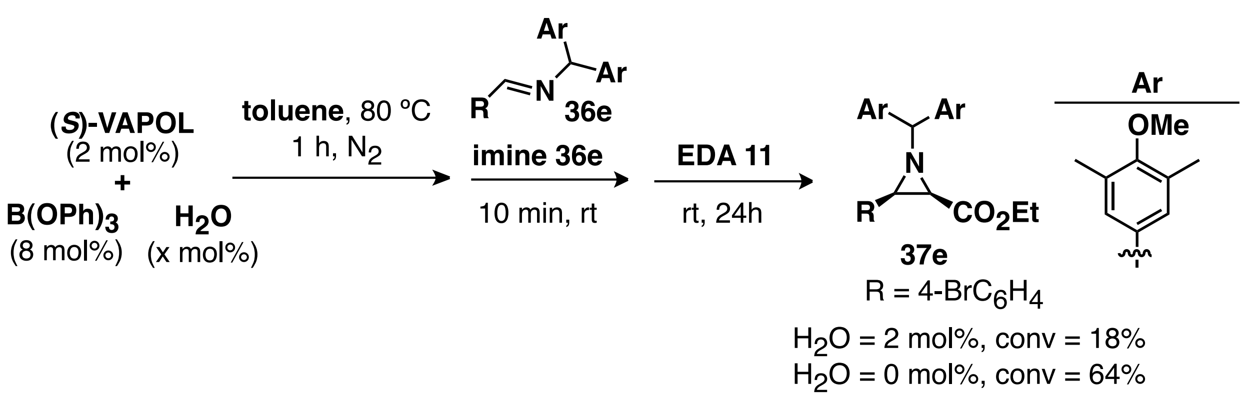
Previously, Gang Hu observed that the benzyl imine **69** forms the boroxinate catalyst readily with VAPOL and $B(OPh)_3$.[9] Thus, we thought to use the same imine in a catalytic amount to generate the B3 catalyst **35** for use in the turnover of the MEDAM imine **36e**. Unfortunately, this resulted in a low conversion to aziridine **37e** (15%, Scheme 2.9). The presence of aziridine derived from imine **69** could not be confirmed from the messy crude NMR.

Scheme 2.9 Asymmetric aziridination with MEDAM imine **36e** with Method B'

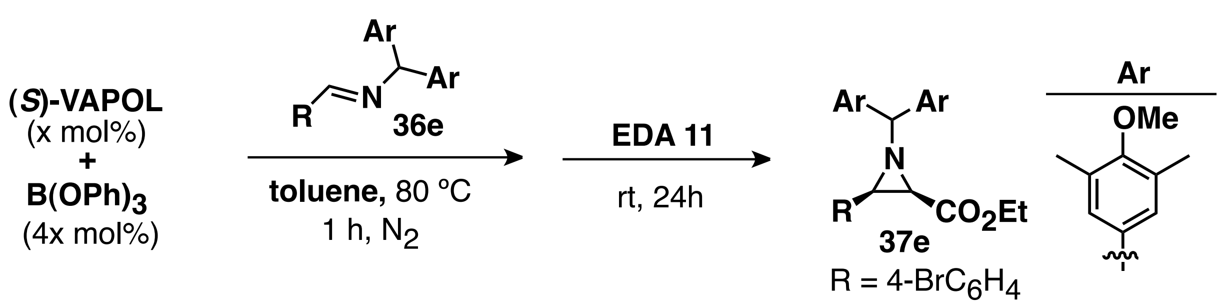


Given the less than satisfactory results with the *in situ* catalyst formation for imine **36e** outlined in Scheme 2.8 (Method B), a variation of this method (Method C) which involved heating the ligand with $B(OPh)_3$ before adding the imine was examined (Scheme 2.10). The only difference between Method C and Method A (Table 2.2) is that the volatiles were not removed under reduced pressure after the heating procedure. Very low conversion (18%) to **37e** was observed. However, when water was excluded, an improved conversion of 64% was observed. This increase in conversion suggested that it is necessary to employ the high temperature and the exclusion of water for the generation of an effective catalyst system. As we know that the generation of the active catalyst occurs only after the addition of imine, the next protocol involved heating the ligand, $B(OPh)_3$ and imine altogether (Method D, Scheme 2.11). As with Method C the removal of volatiles after catalyst formation was not employed. The reaction of imine **36e** with Method D with 2 mol% catalyst loading gave an 86 % conversion. Finally, an increase in the catalyst loading to 3 mol% (Method D) gave 100 % conversion affording aziridine **36e** in 94% yield and 99 % ee (Scheme 2.11).

Scheme 2.10 Catalytic asymmetric aziridination with MEDAM imine **36e** with Method C



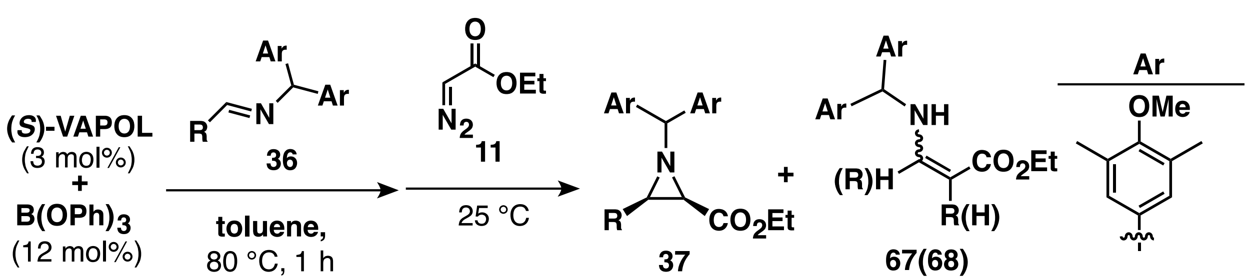
Scheme 2.11 Catalytic asymmetric aziridination with MEDAM imine **36e** with Method D



x	conv (%)	% y	% ee
2	86	–	–
3	100	94	99

Henceforth, Method D became the protocol of choice to re-evaluate the aziridination reaction with MEDAM imines **36** with a simplified catalyst preparation procedure. The catalyst was generated by heating VAPOL with $B(OPh)_3$ and the imine **36** in toluene at 80 °C for 1 h. The procedure is experimentally far easier to perform and the results for several aryl imines are (Table 2.4) comparable with that shown in Table 2.2 (Method A). It is to be noted that the asymmetric inductions for the MEDAM imines of aliphatic aldehydes dropped off slightly (2-4% ee) with Method D (Table 2.4) compared to Method A (Table 2.2). The minimum reaction times for the aziridination reaction were determined for all nine MEDAM imine substrates (Table 2.5) with 3 mol% of the catalyst.

Table 2.4 Catalytic asymmetric aziridination with MEDAM imine **36** with Method D[a]



entry	imine[b]	R	time (h)	%yield cis-**37**[c]	%ee *cis*-**37**[d]	cis/trans[e]	%yield 67(68)[f]
1[g]	**36a**	Ph	3	94	99	>50:1	3.8(1.9)
2	**36a**	Ph	0.25	93	98.5	>50:1	2.5(2.0)
3[h]	**36a**	Ph	24	94	95.5	50:1	2.8(2.8)
4[i]	**36a**	Ph	24	≤15	nd	nd	nd

Table 2.4 (cont'd)

5 [j]	**36b**	2-MeC_6H_4	24	87	96	33:1	5.0(3.2)
6	**36c**	4-MeC_6H_4	0.5	94	99	>50:1	3.0(1.2)
7 [k]	**36d**	4-$MeOC_6H_4$	24	83	97	50:1	1.2(2.1)
8	**36e**	4-BrC_6H_4	2	94	99	>50:1	1.5(1.9)
9	**36f**	4-$NO_2C_6H_4$	0.75	95	99	>50:1	1.2(2.0)
10 [l]	**36k**	*n*-hexyl	24	64	86	nd	10(0)
11	**36i**	cyclohexyl	3	96	89	50:1	nd
12 [m]	**36j**	*tert*-butyl	24	93	92	50:1	nd

[a] Unless otherwise specified, all reactions went to completion and were performed with 3 mol% catalyst prepared (Method D) by heating 3 mol% of (*S*)-VAPOL with 12 mol% $B(OPh)_3$ and 1 mmol of imine **36** as a 0.5 M solution in toluene at 80 °C for 1 h. The flask was cooled to room temperature and then 1.2 equiv of EDA (**11**) was added and the mixture stirred for the indicated time. nd = not determined. [b] All imines were purified by crystallization except **36k** which was an oil and was used without purification. Imine **36k** was prepared by method 1 described in the experimental section for chapter 2. [c] Isolated yield after column chromatography on silica gel. [d] Determined on purified *cis*-**37** by HPLC on a CHIRAL CEL OD-H column. [e] Ratio determined by integration of the methine protons of the *cis*- and *trans*-aziridines in the ^{1}H NMR spectrum of

Table 2.4 (cont'd)

the crude reaction mixture. nd = not determined. [f] Determined by integration of the NH signals of **67** and **68** relative to the methine proton of *cis*-**37** in the ^{1}H NMR spectrum of the crude reaction mixture. [g] A separate reaction with 1 mol% catalyst and 5 mmol of 36a and went to 67% completion in 0.5 h. [h] 100 mol% PhOH was added just prior to EDA (**11**); this reaction was allowed to run for 24 h, and no attempt was made to determine the minimum reaction time but the reaction did go to completion in 24 h. [i] 100 mol% H_2O was added just prior to EDA (**11**). Reaction only went to 15% completion in 24 h. No further purification was carried out. [j] 94% conversion after 12 h. [k] Reaction went to 97% completion. [l] Reaction only went to 87% completion. [m] 20% conversion after 2 h, 44% conversion after 8 h, and 98% conversion after 24 h.

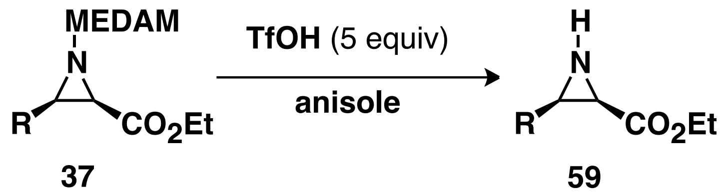
With the exception of the *p*-methoxyphenyl imine **36d** and *o*-methylphenyl imine **36b**, which required 24 h to go to 97% and 94% completion respectively (entries 5 and 7, Table 2.4), the reactions of the aryl imines were all complete within 15-120 min. The secondary and tertiary alkyl imines **36i** and **36j** required 3 – 24 h to reach to completion in the aziridination reaction. The *n*-hexyl-substituted imine **36k** was slower than the cyclohexyl imine **36i** and this may be due to the fact that the imine **36k** was an oil and was not purified by crystallization. The effects of the added phenol and water on the aziridination reaction of the MEDAM imine **36a** were examined. The addition of 100 mol% phenol just prior to the addition of ethyl diazoacetate does not effect the yield of the reaction and only a slight drop in asymmetric induction was observed (entry 3, Table 2.4). This suggests that the removal of phenol during catalyst preparation in Method A does not have a significant benefit on the aziridination reaction. The reaction went to only 15% completion after 24 h when 100 mol% water was added to the reaction mixture which suggests that the catalyst may have been effected (entry 4, Table 2.4).

2.6 Deprotection of MEDAM group

The nucleophilic opening of the aziridines usually requires an electron-withdrawing group on the nitrogen. Hence, the ability to remove the MEDAM protecting group from the nitrogen in the aziridines **37** would be important for their applications in organic synthesis. The protocol for the deprotection of MEDAM group involves treatment with 5 equiv of triflic acid in anisole. This deprotection protocol was previously developed for the cleavage of DAM aziridines **58**.[5]

To our delight, the deprotection of the phenyl-substituted MEDAM aziridine **37a** proceeded smoothly under this standard procedure to give the *N*-H aziridine **59a** in 95% yield. The attempted deprotection of electron rich *p*-methoxyphenyl aziridine **37d** and *p*-methylphenyl aziridine **37c** resulted in complex mixtures of various products. Interestingly, the cleavage of 2-methyl substituted aryl aziridine **37b** proceeded smoothly to give a 97% yield of the *N*-H aziridine **59b**. The aziridines **37e** and **37f** with electron poor phenyl substituents gave 96% and 97% yields of the corresponding *N*-H aziridines upon deprotection of the MEDAM group (entry 5 and 6 in Table 2.5). The alkyl substituted aziridines required heating to 65 ºC to liberate the *N*-H aziridines (entry 7–9 Table 2.5) and gave good to excellent yields.

Table 2.5 Deprotection of MEDAM aziridines **37** [a]

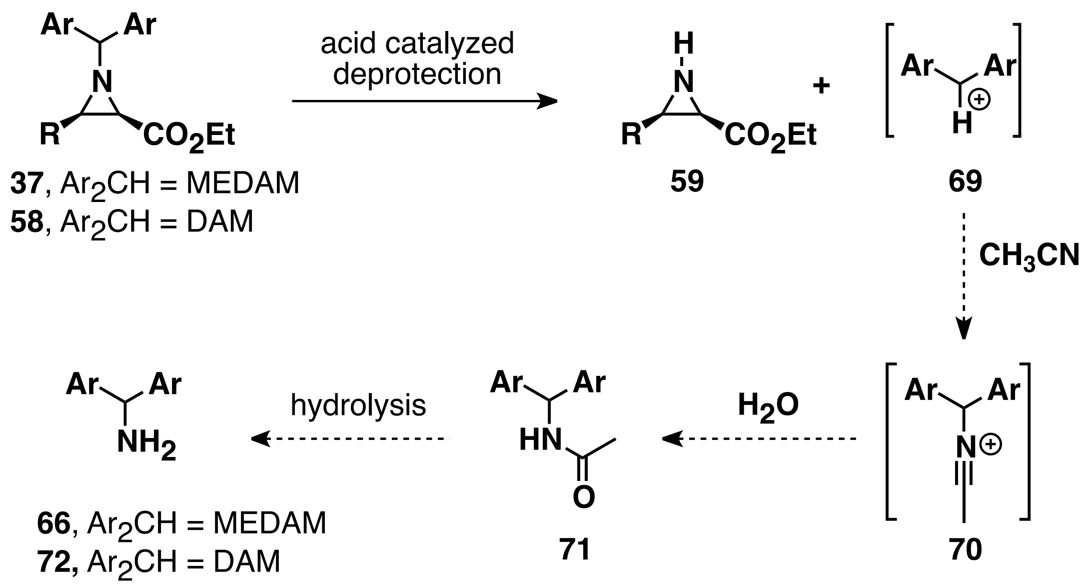


entry	aziridine	R	time (h)	temp (ºC)	% yield **59**[b]
1	**37a**	Ph	2	25	95
2	**37b**	2-MeC_6H_4	1	25	97
3	**37c**	4-MeC_6H_4	1	25	_[c]
4	**37d**	4-$MeOC_6H_4$	1	25	_[c]
5	**37e**	4-BrC_6H_4	1	25	96
6	**37f**	4-$NO_2C_6H_4$	1	25	97
7	**37h**	*n*-propyl	1	65	73[d]
8	**37i**	cyclohexyl	0.5	65	90
9	**37j**	*tert*-butyl	0.7	65	88

[a] Unless otherwise specified, all reactions went to completion and were performed with 5 equivalent of triflic acid **60** and 0.5 mmol of aziridine **37** as a 0.15 M solution in anisole at the indicated temperature for the indicated time. The reactions were quenched with saturated aq. Na_2CO_3 solution. [b] Isolated yield after chromatography on silica gel. [c] Mixtures of products observed including ring-opened products. [d] The NMR yield was 76% with Ph_3CH as internal standard.

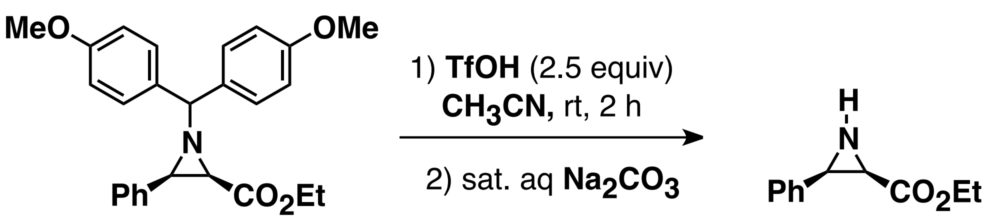
In the deprotection of the dianysylmethyl group from aziridines, the solvent anisole acts as a nucleophile to trap the dianisylmethyl cation generated during the course of the reaction. Hence, it might be possible to intercept the reaction with another nucleophile to trap the dianisylmethyl cations. The aim of the present work is to trap the substituted dianisylmethyl-cation **69** with a nucleophile so that the resulting product could be transformed to substituted-dianysylmethyl amine. In this way, it would be possible to recover the MEDAM amine **66**. It was then thought to perform the reaction using acetonitrile as solvent following the Ritter reaction protocol.[10] It was expected that acetonitrile would serve as a nucleophilic trap for the cation **69** to produce corresponding acetamide **71** upon hydrolysis (scheme 2.12).

Scheme 2.12 Proposed Protocol for trapping of dianisyl cation **69** with acetonitrile



The *N*-DAM aziridine **58a** was used as a model system for the optimization of this proposed deprotection protocol. It was envisioned that these conditions with little variations would be general to all of the *N*-MEDAM aziridines **37**. A series of experiments were carried out to study the effects of the concentration of reaction, equivalents of triflic acid **60**, the temperature and the reaction time on the yield of aziridine **59**. The optimized reaction conditions were found to be the use of 2.5 equivalents of triflic acid, 2 h reaction time and room temperature with 0.2 M concentration of **58a** (Scheme 2.13). Although the *N*-H aziridine **59a** was obtained with 92% yield, no *N*-DAM acetamide **71** was observed. This result could be explained to be the result of an equilibrium between dianisylmethyl cation **69** and **70** (Scheme 2.14) and the selective reaction of **69** with water during the reaction quench.

Scheme 2.13 Deprotection of DAM aziridine **58a** in acetonitrile

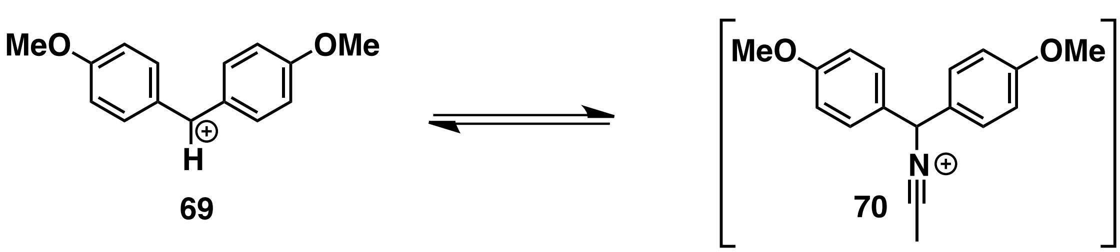


58a
(0.2 M)

59a
92% yield

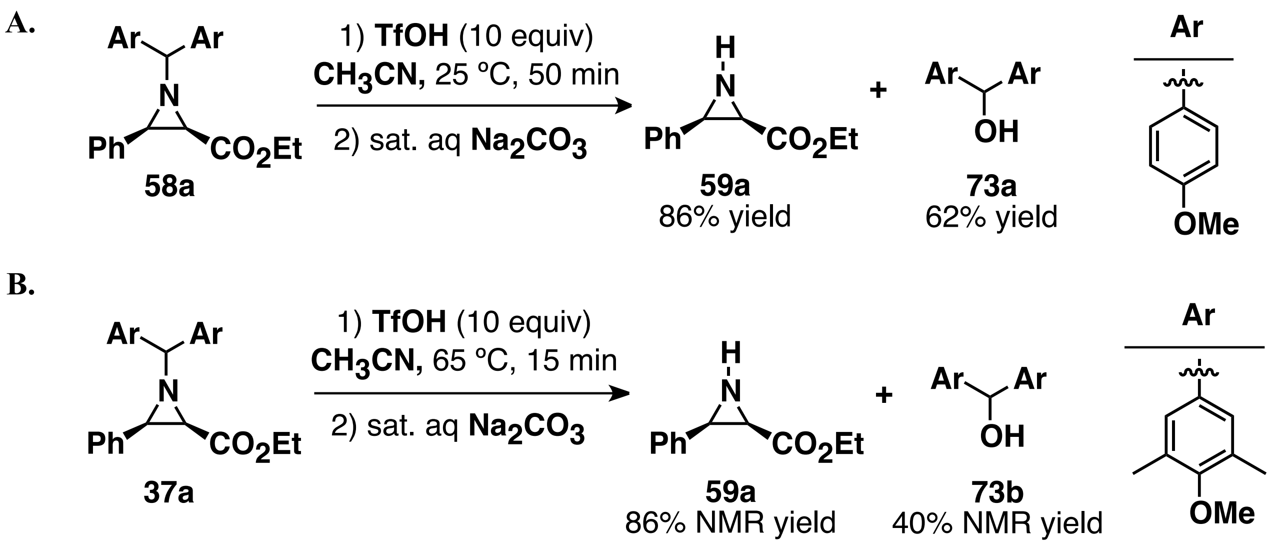
Although the carbonium ion **69** is relatively stable, the electrophilic reactivity of the carbocation might not be high.[11] Additionally, it is possible that the dianisyl cation **69** could decompose *via* self-polymerization.

Scheme 2.14 Equilibrium between cation **69** and **70**



If in fact the cations **69** and **70** are not being intercepted, it may perhaps be necessary to use a more nucleophilic solvent. Mayr and coworkers studied the rate of decomposition of different substituted benzhydryl cations in different solvent medium,[11] According to their study, 20% water (v/v) in acetonitrile could be the optimum solvent combination. A series of experiments were performed in acetonitrile water (4:2 v/v) medium to study the effects of the concentration of triflic acid, the temperature and the reaction time on the formation of the desired products. In all the experiments performed, a slow decomposition of initially formed *N*-H aziridine was observed with time. However, 4,4′-dimethoxybenzhydrol **73a** was obtained as one of the major product of the reaction. These observations suggested that acid promoted ring opening of the aziridine was occurring in presence of water. Dry acetonitrile was then used as the solvent to avoid the ring opening of aziridine. After several attempts, the optimum reaction condition was found to be the use of 10 equiv of triflic acid **60** at room temperature at 0.1M concentration of **58a**, which gave the aziridine **59a** and benzhydrol **73a** was 86% and 62% isolated yields respectively (Scheme 2.15). The alcohol **73a** was possibly formed due to the trapping of cation **69** with water during the reaction quench. However, when the deprotection of *N*-MEDAM aziridine **37a** was carried out using the same reaction conditions, the reaction was incomplete even after 2 h. However, at elevated temperature (65 ºC) the reaction went to completion after 15 min and afforded the *N*-H aziridine **59a** and benzhydrol **73b** in 88% and 40% NMR yields respectively (Scheme 2.15). It must be noted that water was acting as a nucleophile to trap the 4,4′-dimethoxybenzhydryl cation **69** in all of the above deprotection experiments during the work up procedure. In order to attain the dianisyl amine directly, nucleophilic amines could possibly be employed instead of oxygen nucleophile and this should be the subject of future experiments.

Scheme 2.15 Deprotection of *N*-protected aziridines and trapping of dianisyl cation with water. (A) Deprotection of *N*-DAM aziridine **58a** (B) Deprotection of *N*-MEDAM aziridine **37a**



2.7 Conclusions

A summary of the results of the asymmetric inductions for the catalytic asymmetric aziridination with the VANOL-derived catalyst are plotted in Figure 2.1 for nine different imine substrates against four different *N*-substituents on the imine. A similar plot with VAPOL-derived catalyst is presented in Figure 2.2. The data in Figures 2.1 and 2.2 are taken from the present work (MEDAM) and from previous work (Bh, DAM and BUDAM). The AZ reactions were carried out in toluene at room temperature except for the imines derived from *n*-butanal which were done at 0 ºC. Also, the reactions of DAM imines with VANOL-derived catalyst were performed in carbon tetrachloride.[5] Similar trends are observed for both the VANOL and VAPOL ligands. The six aromatic substrates with benzhydryl[2c] and DAM[5] protecting group gave an average induction of 89% ee and 94% ee, respectively. The aromatic substrates with

MEDAM[6] and BUDAM[3] protecting groups gave the highest inductions with an average of 99% ee and 98% ee, respectively. It is clear from both figures that the MEDAM substituent is the most effective protecting group for the aliphatic imines. The average induction for the 1º, 2º and 3º aliphatic imines with the MEDAM protecting group is 94% ee with both the VAPOL and VANOL-derived catalysts. In contrast, the aliphatic imines gave an average induction of 85% ee for benzhydryl, 79% ee for DAM and 87% ee for the BUDAM protecting group, which is clearly not as effective as the *N*-MEDAM substituent.

Figure 2.1 Distribution of the asymmetric inductions with the protecting group for the VANOL derived catalyst

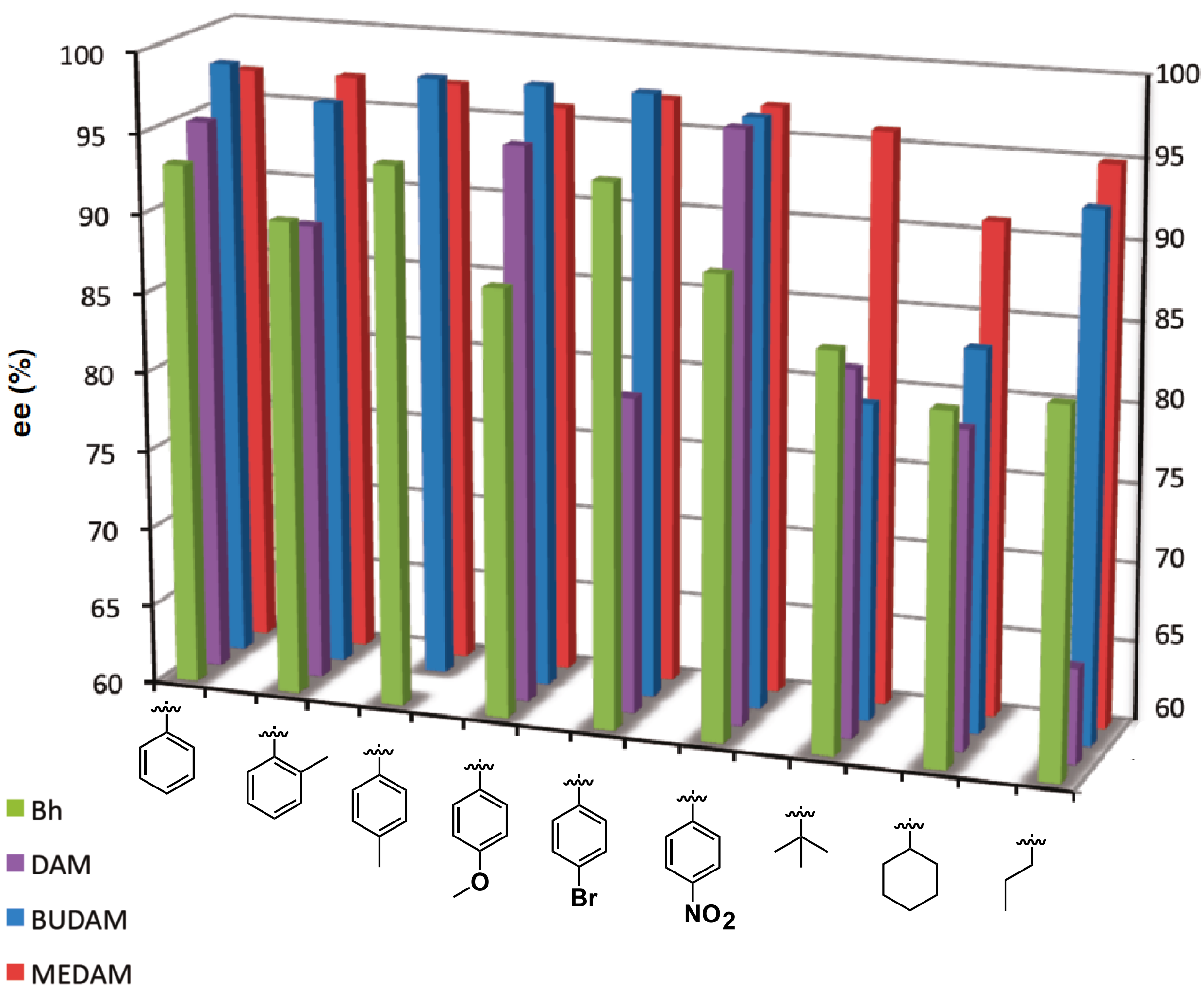
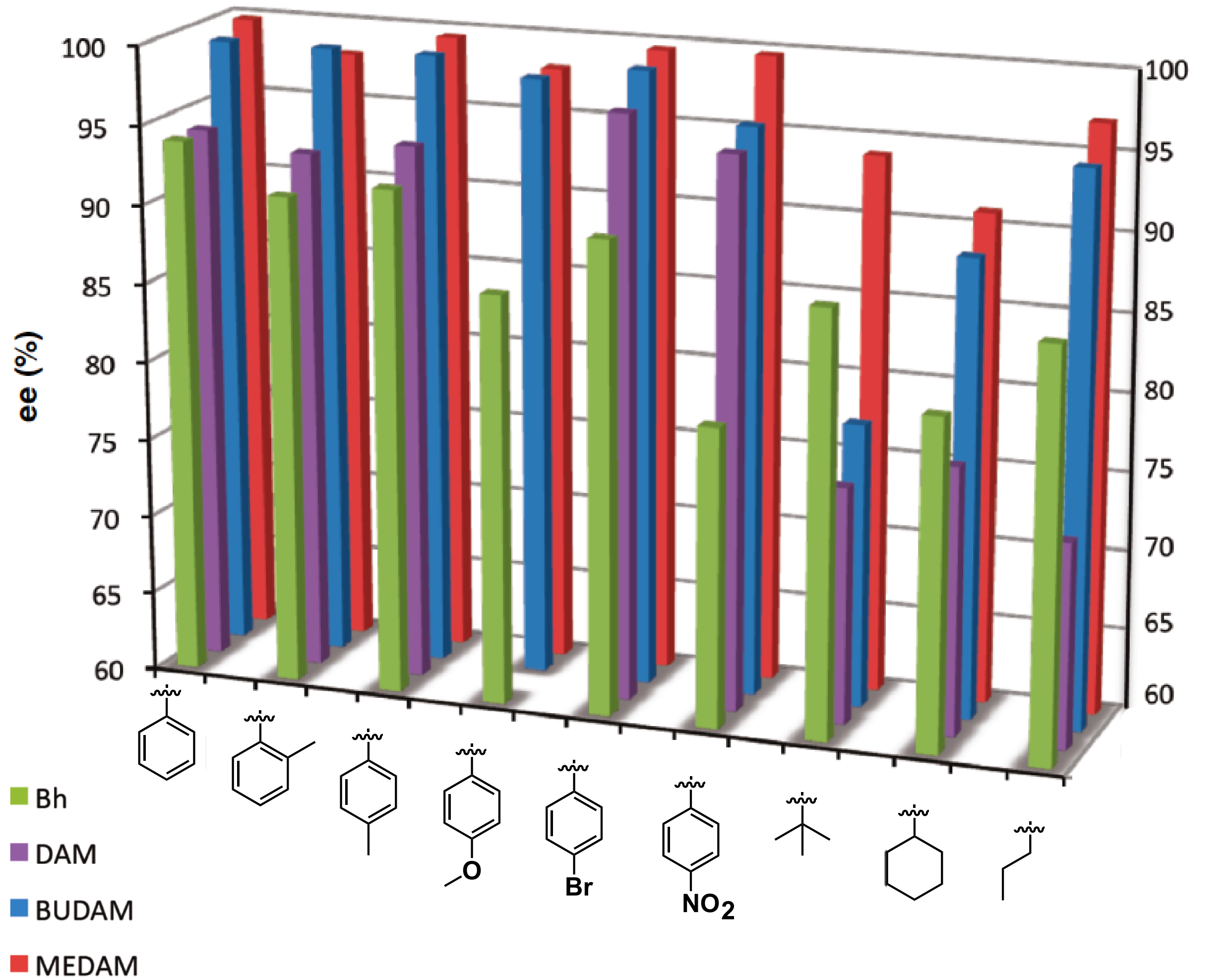


Figure 2.2 Distribution of the asymmetric inductions with the protecting group for the VAPOL derived catalyst



The results from the above comparisons clearly indicate that for the catalytic asymmetric aziridination reaction of imines with ethyl diazoacetate, the best *N*-substituent is the MEDAM substituent. Later, another group member Anil Gupta developed a multi-component *cis*-aziridination protocol utilizing MEDAM amine as one of the components.[12] Further, the MEDAM substituent also proved to be the protecting group of choice for the *trans*-aziridination reaction as well.[13]

APPENDIX

2.8 Experimental procedure

2.8.1 General information

All reactions were carried out in flame-dried glassware under an atmosphere of argon or nitrogen unless otherwise indicated. Triethylamine, dichloromethane and acetonitrile were distilled over calcium hydride under nitrogen. Tetrahydrofuran, dioxane and ether were distilled from sodium and benzophenone. Toluene was distilled from sodium under nitrogen. Hexanes and ethyl acetate were ACS grade and used as purchased.

Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were recorded in KBr matrix (for solids) and on NaCl disc (for liquids) on a Nicolet IR/42 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on a Varian 300 MHz or VXR-500 MHz spectrometer using $CDCl_3$ as solvent (unless otherwise noted) with the residual solvent peak as the internal standard (^{1}HNMR: 7.24 ppm, ^{13}CNMR: 77 ppm). Chemical shifts were reported in parts per million. Low-resolution Mass Spectrometry and High Resolution Mass Spectrometry were performed in the Department of Chemistry at Michigan State University. Analytical thin-layer chromatography (TLC) was performed on Silicycle silica gel plates with F-254 indicator. Visualization was by short wave (254 nm) and long wave (365 nm) ultraviolet light, or by staining with phosphomolybdic acid in ethanol or with potassium permanganate. Column chromatography was performed with silica gel 60 (230 – 450 mesh).

HPLC analyses were peformed using a Varian Prostar 210 Solvent Delivery Module with a Prostar 330 PDA Detector and a Prostar Workstation. Chiral HPLC data for the aziridines were obtained using a CHIRALCEL OD-H column, CHIRALPAK AD column and PIRKLE COVALENT (R, R) WHELK-O 1 column.

Optical rotations were obtained on a Perkin-Elmer 341 polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0 decimeter cell with a total volume of 1.0 mL. Specific rotations are reported in degrees per decimeter at 20 °C and the concentrations are given in gram per 100 mL in ethyl acetate unless otherwise noted.

All reagents were purified by simple distillation or crystallization with simple solvents unless otherwise indicated. Ethyl diazoacetate **11**, triphenylborate, *p*-toluenesulfonic acid, triflic acid and benzhydrylamine (distilled prior to use) obtained from Aldrich Chemical Co., Inc. and used as received. 4-Bromo-2,6-dimethylphenol (99%) was obtained from Alfa Aesar and used as received. VAPOL and VANOL were made according to published procedure.[14] These ligands are also commercially available from Aldrich Chemical Co., Inc and Strem Chemicals. Bis-(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine (BUDAM amine **60**)[3] was made according to the published procedure.

Acronyms used for *N*-protecting groups.

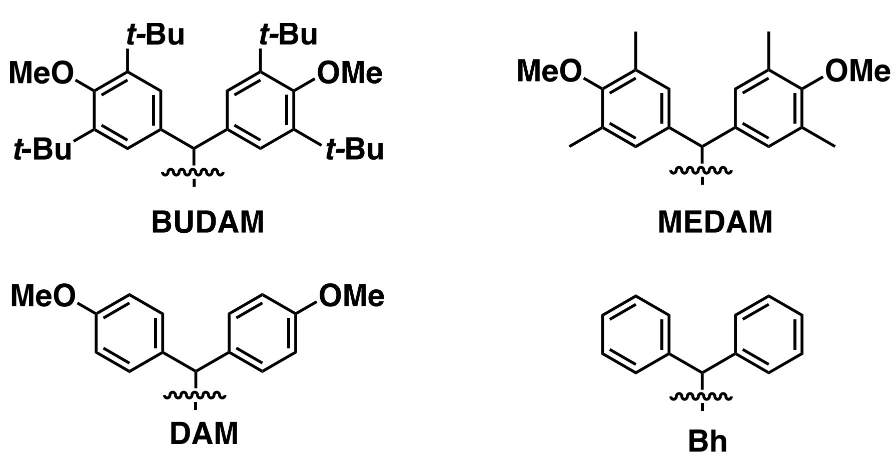
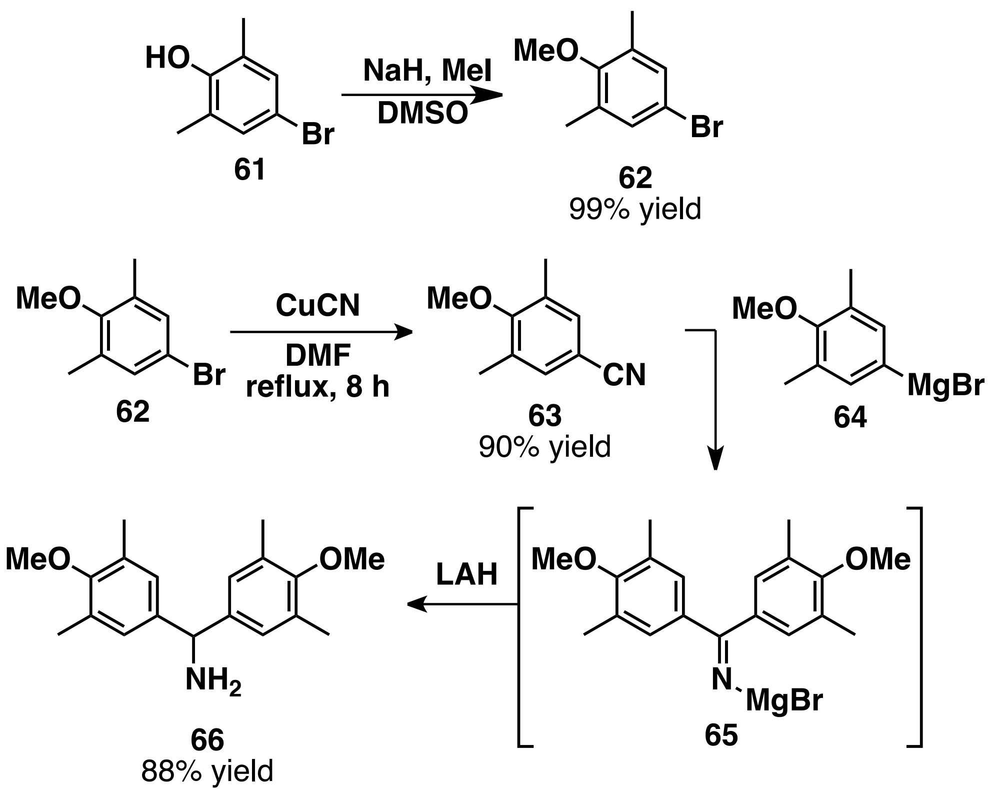


Figure 2.3. Homemade Schlenk flask: The Schlenk flask was prepared from a single-necked 25 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve.

2.8.2 Synthesis of MEDAM Amine 66



5-bromo-2-methoxy-1, 3-dimethylbenzene 62[15,16]**:** A 2-L three-necked round-bottomed flask, equipped with an overhead mechanical stirrer and sealed with rubber septum at the other two necks, was flame-dried and cooled under nitrogen. DMSO (1.2 L, stored over 4Å MS) was added through one of the necks using a glass funnel. Thereafter, sodium hydride (47.4 g, 1200 mmol, 60% dispersion in mineral oil) was added using a powder funnel. During addition, a continuous flow of nitrogen was maintained at the other neck using a needle attached directly to the nitrogen source. The source of nitrogen was then changed to a nitrogen-filled balloon. The flask was then transferred to an ice bath and stirred vigorously at 120 rpm. The stirring must be turned on before the flask was submerged into the 0 ºC bath (vigorous stirring is required in order to avoid DMSO freezing at 0 ºC). This was followed by the slow addition of 4-bromo-2, 6-dimethylphenol **61** (100 g, 497 mmol) in portions (~ 10 g each time) using a powder funnel, over a period of 40 min. The resulting suspension was stirred at 0 °C for 15 min. One of the rubber septums was then replaced by 250-mL pressure-equalizing addition funnel fitted with a nitrogen balloon through the rubber septum at the top of the funnel. Iodomethane (126.9 mL, 289.3 g, 2038 mmol) was then added *via* addition funnel over a period of 25 min. The mixture was stirred at 0 ºC (ice-bath) for 15 min. The reaction mixture was then allowed to gradually warm up to room temperature (~ 2 h), and stirred at room temperature for an additional 3 h. The reaction mixture was cooled to 0 °C, and diluted with hexanes (345 mL). The mixture was then poured into a 4 L Erlenmeyer flask containing hexanes (425 mL) at 0 ºC, the mixture was stirred with a mechanical stirrer at 100 rpm while slowly adding water (425 mL) over a period of 30 min and the mixture was then stirred until two layers appeared. The organic layer was separated using a 6 L separatory funnel, and the aqueous layer was extracted with hexanes (170 mL × 3).

The combined organic layer was then washed with water (300 mL × 3), dried over $MgSO_4$ and concentrated by rotary evaporation to give the crude product **62** as a light yellow liquid. The crude product was purified by simple short-path distillation. The crude product was transferred to a 250-mL, round-bottomed flask equipped with a magnetic stir bar. The product is distilled under vacuum through a straight 12-cm air condenser, which is topped with a short-path distillation assembly. The product bumps during distillation. The desired product **62** was collected in the 80-83 °C fraction (1 mm Hg, oil bath temp ~ 120 °C) and obtained as a colorless liquid in 99% yield (105.7 g, 492 mmol).

Spectral Data for **62**: Colorless liquid; **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 2.15 (s, 6H), 3.83 (s, 3H), 7.08 (s, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 15.06, 60.72, 126.61, 131.80, 113.22, 155.51. These spectral data match those previously reported for this compound.[17]

4-methoxy-3,5-dimethylbenzonitrile 63[7]: A 2-L three-necked round-bottomed flask, equipped with a stir bar and an air condenser (25 mm × 350 mm) followed by a water condenser (17 mm × 220 mm) and sealed with rubber septums at all three necks including the reflux condenser, was flame-dried and cooled under nitrogen. To this flask was added 5-bromo-2-methoxy-1, 3-dimethylbenzene **62** (33.4 mL, 45 g, 209 mmol) and anhydrous DMF (450 mL, freshly distilled and stored over 4Å MS) using a 60 mL syringe. This was followed by the addition of CuCN (22.5 g, 251 mmol) through one of the necks utilizing a powder funnel. During addition, a continuous flow of nitrogen was maintained at the other neck using a needle attached directly to nitrogen source. The same nitrogen source was then used to purge the reaction mixture with nitrogen under the surface of the solution for 15 min. The source of nitrogen was then changed to a nitrogen-filled balloon on the top of the condenser attached via needle through a rubber septum stopper. Thereafter, the rubber septums at the other two necks were replaced by Teflon stoppers. The mixture was then heated to reflux in an oil bath (180 ºC) for 8 h. During the refluxing, the solid CuCN dissolved after approximately 2 h and a light green precipitate of CuBr was observed which further dissolves to give a brown colored solution over the course of time. The reaction mixture was then cooled gradually to room temperature and after cooling down, it was a dark green solution with a small amount of a light green precipitate of a copper salt at the bottom of the flask. The reaction mixture was then slowly poured into a 4 L Erlenmeyer flask containing an aqueous solution of ethylene diamine (90 mL ethylene diamine in 2240 mL water) at 0 ºC (ice-bath). The resulting reaction mixture was then allowed to warm gradually to room temperature. Benzene (680 mL) was added and the resulting mixture was stirred at room temperature for 20 min and then transferred directly into a 6 L separatory funnel. The top organic layer was separated. The aqueous layer was then extracted with benzene (250 mL × 4). The combined organic layer was washed with an aqueous 1.2 M NaCN solution (350 mL), and then with water (400 mL × 2). After drying over $MgSO_4$ the volatiles were removed by rotary evaporation to afford the crude product as an off-white solid (32 g). The crude product was purified by crystallization (using hot hexanes, ~ 40 mL) to afford the final product **63** as white solid (mp 48-49 °C) in 90 % yield (30.3 g, 188 mmol, a combine yield of two crops).

Spectral Data for **63**: **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ 2.26 (s, 6H), 3.72 (s, 3H), 7.29 (s, 2H); **^{13}C-NMR** ($CDCl_3$, 75 MHz) δ 15.93, 59,73, 107.25, 118.99, 132.46, 132.70, 160.75; IR (thin film) 2960vs, 2225vs, 1014s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 161 M^{+} (80), 145 (100), 116 (24); Anal calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.67; H, 6.87; N, 8.58. These spectral data match those previously reported for this compound.[3]

***Bis*-(2,6-di-methyl-4-methoxyphenyl)methineamine 66[18]:** A 1-L three necked round-bottomed flask, equipped with a stir bar and a reflux condenser (33 mm × 470 mm) and sealed with rubber septum at all three necks including reflux condenser, was flame-dried and cooled under nitrogen. To this flask was added magnesium (13.0 g, 534.7 mmol, 2.8 equiv, 20 mesh) through one of the necks utilizing a powder funnel. Next, anhydrous THF (450 mL, freshly distilled) and a few crystals of iodine were added. During addition, a continuous flow of nitrogen was maintained at the other neck using a needle attached directly to a nitrogen source. The source of nitrogen was then changed to a nitrogen-filled balloon on the top of the condenser via a needle through a rubber septum stopper. Then 5-bromo-2-methoxy-1,3-dimethylbenzene **62** (33.4 mL, 45 g, 209 mmol, 1.1 equiv) was added using a 60 mL syringe. Thereafter, the rubber septums at the other two necks were replaced by Teflon stoppers. The mixture was then heated to reflux in an oil bath (78 ºC) for 4 h. The resulting clear grey solution was allowed to cool down to room temperature. One of the Teflon stoppers was then replaced by a rubber septum. The mixture was then transferred *via* cannula to a flame-dried 2-L three-necked round-bottomed flask equipped with a refluxing condenser under nitrogen. Meanwhile, to a flame-dried 1L round-bottomed flask, filled with nitrogen, was added 4-methoxy-3, 5-dimethylbenzonitrile **63** (30.6 g, 190 mmol, 1.0 equiv) and THF (400 mL, freshly distilled). This solution was then transferred *via* cannula to the 2-L three-necked round-bottomed flask containing the freshly prepared Grignard reagent over a period of 20 min at room temperature. The resulting mixture was heated to reflux in an oil bath (78 ºC) for 7 h under nitrogen, then allowed to cool down to room temperature, and then to 0 ºC (ice-bath). Meanwhile, a suspension of $LiAlH_4$ (8 g, 210 mmol) in

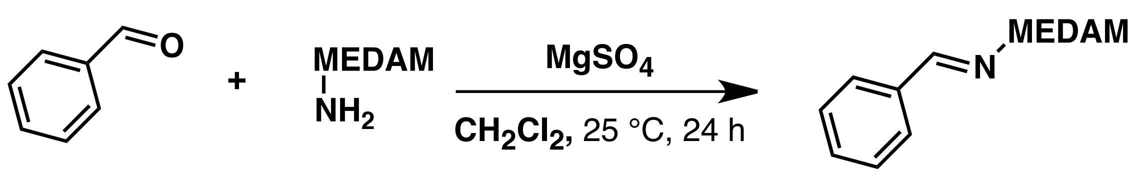
THF (200 mL, freshly distilled) was prepared in a flame-dried 500 mL flask filled with nitrogen and pre-cooled at 0 ºC. Next, the LAH suspension was transferred to 2-L three-necked round-bottomed flask containing *in-situ* generated imine **65** *via* cannula at 0 ºC. The ice bath was then removed, and the resulting greenish yellow reaction mixture was heated to reflux in an oil bath (78 ºC) for 20 h under nitrogen. The reaction flask was cooled down to room temperature, and carefully quenched by the slow addition of water (8 mL), then 3.75 M NaOH solution (8 mL), and water (24 mL) over a period of 10 min. The resulting suspension was filtered through a Celite (503) pad into a 2 L round bottom flask and washed with ether until no amine was left (monitored by TLC analysis on silica gel, appearance of red spot upon visualization with phosomolybidic acid indicates the presence of amine). The total volume of the ether mixture was reduced to around 500 mL using rotatory evaporation and then it was transferred to 2 L Erlenmeyer flask. Conc. HCl (~ 50 mL, 12 M, precooled to 0 ºC) was added portion-wise (~ 5 mL each time) till the pH ~ 2 (determined by pH paper) resulting in the appearance of a yellowish white precipitate. During the addition, continuous stirring is recommended. The yellow colored organic layer was discarded by decanting. The white solid was washed with ether (200 mL × 2) and organic layer was discarded by decanting. It was then followed by the addition of the ether (400 mL). To this mixture was added 6 M NaOH (~ 100 mL) in portions (~ 10 mL each time) till the pH~12. During addition, the mixture was stirred for approximately 20 min until the entire solid dissolved. The reaction mixture was then transferred to 2 L separatory funnel. The organic layer was separated and aqueous layer was washed with ether (200 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to afford a pale-yellow solid (52 g). The crude amine **66** was crystallized from hot hexanes (~ 60 mL) to afford white crystalline solid (mp 59-61 °C) in 88% yield (50 g, 167.2

mmol, a combined yield of several crops).

Spectral Data for **66**: **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ 1.73 (s, 2H), 2.26 (s, 12H), 3.69 (s, 6H), 5.00 (s, 1H), 7.01 (s, 4H); **^{13}C-NMR** ($CDCl_3$, 75 MHz) δ 16.10, 58.77, 59.50, 126.96, 130.56, 140.88, 155.65; IR (thin film) 3376m, 3306m, 2943vs, 1493s cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 299 M^+ (35), 298 (54), 283 (47), 268 (94), 163 (100); Anal calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 75.89; H, 8.54; N, 4.62. These spectral data match those previously reported for this compound.[3]

2.8.3 General Procedure for the synthesis of MEDAM aldimines 36 and BUDAM imine 38h – Illustrated for the synthesis of *N*-phenylmethylidene-*bis*(4-methoxy-3,5-dimethylphenyl)methylamine 36a.

All liquid aldehydes were distilled before use and the solid aldehydes were used as purchased from Aldrich. All imines **36a-j** could be purified by crystallization except **36h, 36k** and **38h**.

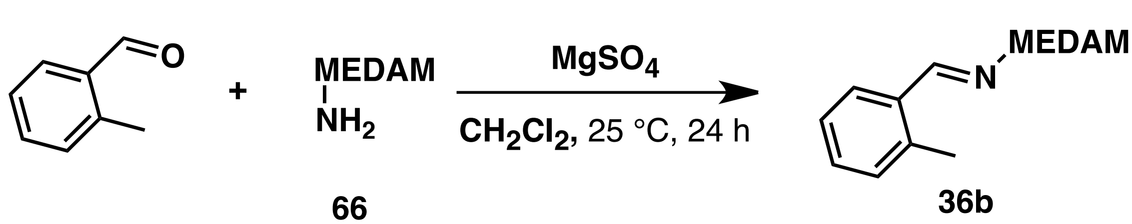


66 **36a**

***N*-phenylmethylidene-*bis*(4-methoxy-3,5-dimethylphenyl)methylamine 36a[3]:** To a 50 mL flame-dried round bottom flask filled with argon was added bis(2,6-di-methyl-4-

methoxyphenyl)methylamine **66** (1.49 g, 5.00 mmol), $MgSO_4$ (1.0 g, 8.4 mmol, freshly flame-dried) and dry CH_2Cl_2 (15 mL). After stirring for 10 min, benzaldehyde (0.54 g, 5.05 mmol, 1.01 equiv) was added. The reaction mixture was stirred at room temperature for 24 h. 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 as an off-white solid. Crystallization (1: 9 CH_2Cl_2/hexanes) and collection of the first crop afforded **36a** as a white solid (mp 144-146 °C) in 90% isolated yield (1.74 g, 4.5 mmol).

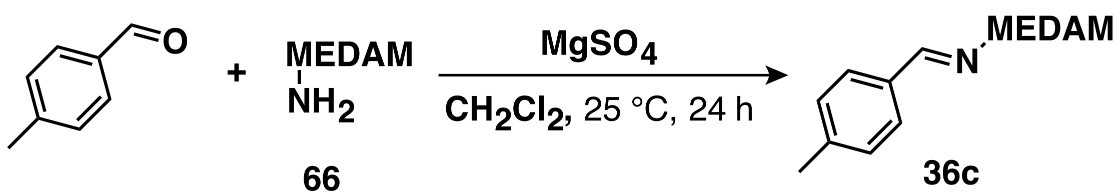
Spectral data for **36a**: **^{1}H-NMR** ($CDCl_3$, 500 MHz) δ 2.24 (s, 12H), 3.66 (s, 6H), 5.35 (s, 1H), 6.99 (s, 4H), 7.39-7.41 (m, 3H), 7.80-7.82 (m, 2H), 8.35 (s, 1H); **^{13}C-NMR** ($CDCl_3$, 125 MHz) δ 16.22, 59.59, 77.41, 127.86, 128.46, 128.49, 130.61, 130.63, 136.45, 139.22, 155.84, 160.28; IR (thin film) 2944w, 1643vs, 1483vs cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 387 M+ (3), 283 (100), 40 (17); Anal calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.42; H, 7.24; N, 3.55. These spectral data match those previously reported for this compound.[3]



***N*-(*o*-tolylbenzylidene)-bis(4-methoxy-3, 5-dimethylphenyl)methylamine 36b:** Imine **36b** was prepared from *o*-tolualdehyde according to the procedure described above for imine **36a**.

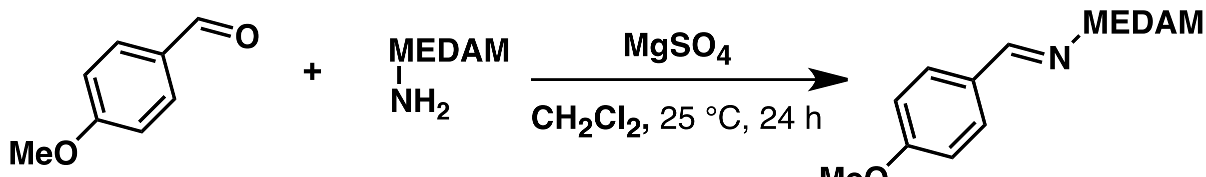
Crystallization (1:10 CH_2Cl_2/hexanes) and collection of the first crop afforded **36b** as white solid crystals (mp 75-76 ºC) in 75% isolated yield (1.50 g, 3.75 mmol).

Spectral data for **36b**: ^{1}**H-NMR** ($CDCl_3$, 500 MHz) δ 2.24 (s, 12H), 2.51 (s, 3H), 3.67 (s, 6H), 5.33 (s, 1H), 7.01 (s, 4H), 7.15 (d, 1H, *J* = 7.3 Hz), 7.22-7.24 (m, 1H), 7.26 (dd, 1H, *J* = 1.7, 7.3 Hz), 7.98 (dd, 1H, *J* = 1.7, 7.6 Hz), 8.65 (s, 1H); ^{13}**C-NMR** ($CDCl_3$, 125 MHz) δ 16.22, 19.58, 59.59, 78.26, 126.03, 127.78, 128.34, 130.15, 130.62, 130.78, 134.34, 137.81, 139.48, 155.81, 158.99. IR (thin film): 2942vs, 1483vs, 1220vs cm^{-1}; HRMS (ESI-TOF) *m/z* 402.2434 [(M+H^{+}); calcd. for $C_{27}H_{32}NO_2$: 402.2433].



***N*-(*p*-tolylbenzylidene)-bis(4-methoxy-3,5-dimethylphenyl)methylamine 36c:** Imine **36c** was prepared from *p*-tolualdehyde according to the procedure described above for imine **36a**. Crystallization (1:10 CH_2Cl_2/hexanes) and collection of the first crop afforded **36c** as white solid crystals (mp 138.5-139 ºC) in 92% isolated yield (1.85 g, 4.60 mmol).

Spectral data for **36c:** ^{1}**H-NMR** ($CDCl_3$, 500 MHz) δ 2.24 (s, 12H), 2.37 (s, 3H), 3.67 (s, 6H), 5.34 (s, 1H), 6.99 (s, 4H), 7.19 (d, 2H, *J* = 8.1 Hz), 7.71 (d, 2H, *J* = 8.4 Hz), 8.32 (s, 1H); ^{13}**C-NMR** ($CDCl_3$, 125 MHz) δ 16.22, 21.51, 59.59, 77.36, 127.87, 128.46, 129.18, 130.59, 134.10, 139.33, 140.88, 155.78, 160.21; IR (thin film) 2943vs, 1483vs, 1219vs cm^{-1}; HRMS (ESI-TOF) *m/z* 402.2425 [(M+H^{+}); calcd. for $C_{27}H_{32}NO_2$: 402.2433].

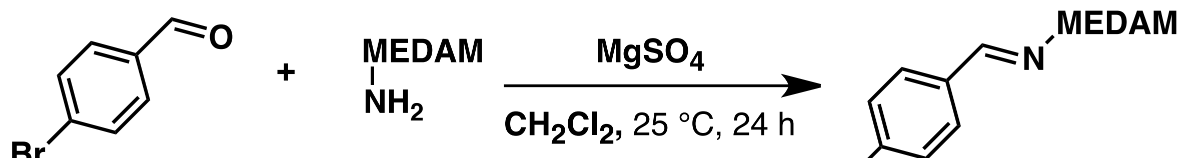


66

36d

***N*-(4-methoxybenzylidene)-bis(4-methoxy-3,5-dimethylphenyl)methylamine 36d:** Imine **36d** was prepared from *p*-methoxybenzaldehyde according to the procedure described above for imine **36a**. Crystallization (1:10 CH_2Cl_2/hexanes) and collection of the first crop afforded **36d** as white solid crystals (mp 119-120 ºC) in 85% isolated yield (1.40 g, 3.40 mmol).

Spectral data for **36d**: **^{1}H-NMR** ($CDCl_3$, 500 MHz) δ 2.24 (s, 12H), 3.67 (s, 6H), 3.82 (s, 3H), 5.32 (s, 1H), 6.91 (d, 2H, *J* = 8.5 Hz), 6.99 (s, 4H), 7.76 (d, 2H, *J* = 9.0 Hz), 8.29 (s, 1H); **^{13}C-NMR** ($CDCl_3$, 125 MHz) δ 16.21, 55.34, 59.59, 77.30, 113.85, 127.87, 129.47, 130.03, 130.57, 139.45, 155.78, 159.57, 161.63; IR (thin film) 2936vs, 1606vs, 1483vs, 1251vs cm^{-1}; HRMS (ESI-TOF) *m/z* 418.2382 [(M+H^{+}); calcd. for $C_{27}H_{32}NO_3$: 418.2382].

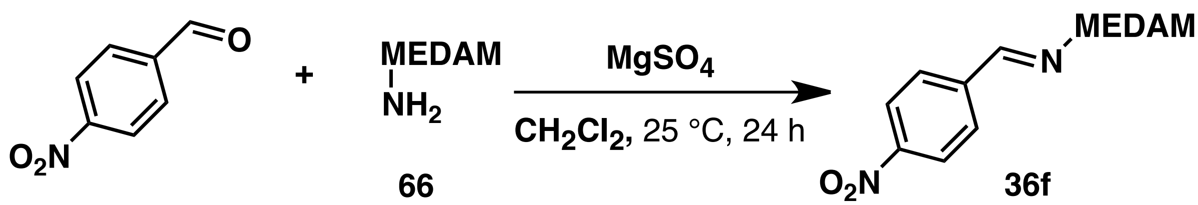


66

36e

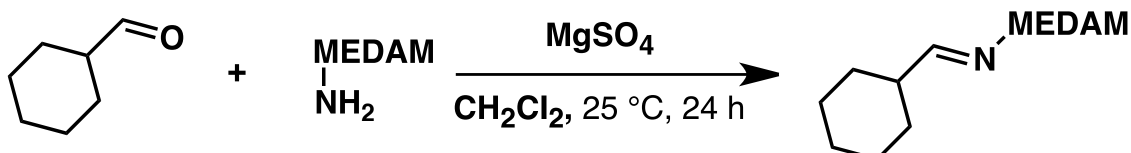
***N*-(4-Bromobenzylidene)-bis(4-methoxy-3,5-dimethylphenyl)methylamine 36e:** Imine **36e** was prepared from *p*-bromobenzaldehyde according to the procedure described above for imine **36a**. Crystallization (1:10 CH_2Cl_2/hexanes) and collection of the first crop afforded **36e** as white solid crystals (mp 156-157 ºC) in 93% isolated yield (2.20 g, 4.65 mmol).

Spectral data for **36e**: ^{1}**H-NMR** ($CDCl_3$, 500 MHz) δ 2.25 (s, 12H), 3.68 (s, 6H), 5.35 (s, 1H), 6.99 (s, 4H), 7.53 (d, 2H, *J* = 8.0 Hz), 7.69 (d, 2H, *J* = 8.5 Hz), 8.29 (s, 1H); ^{13}**C-NMR** ($CDCl_3$, 125 MHz) δ 16.23, 59.59, 77.39, 125.03, 127.79, 129.89, 130.72, 131.71, 135.30, 138.97, 155.91, 159.05; IR (thin film) 2941vs, 1483vs, 1221vs, 1011vs cm^{-1}; HRMS (ESI-TOF) *m/z* 466.1374 [(M+H^{+}); calcd. for $C_{26}H_{29}NO_2{}^{79}Br$: 466.1382].



***N*-(4-Nitrobenzylidene)-bis(4-methoxy-3,5-dimethylphenyl)methylamine 36f:** Imine **36f** was prepared from *p*-nitrobenzaldehyde according to the procedure described above for imine **36a**. Crystallization (1:3 CH_2Cl_2/hexanes) and collection of the first crop afforded **36f** as pale yellow solid crystals (mp 139-140 ºC) in 92% isolated yield (2.00 g, 4.62 mmol).

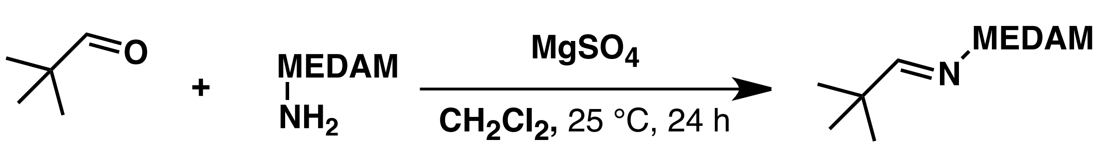
Spectral data for **26f**: ^{1}**H-NMR** ($CDCl_3$, 500 MHz) δ 2.25 (s, 12H), 3.68 (s, 6H), 5.41 (s, 1H), 6.99 (s, 4H), 7.98 (d, 2H, *J* = 9.0 Hz), 8.25 (d, 2H, *J* = 8.7 Hz), 8.42 (s, 1H); ^{13}**C-NMR** ($CDCl_3$, 125 MHz) δ 16.24, 59.61, 77.64, 123.78, 127.75, 129.13, 130.9, 138.51, 141.83, 149.07, 156.08, 158.03; IR (thin film) 2943vs, 1522s, 1344s, 1221s cm^{-1}; HRMS (ESI-TOF) *m/z* 433.2127 [(M+H^+); calcd. for $C_{26}H_{29}N_2O_4$: 433.2127].



66 **36i**

***N*-Cyclohexylmethylidene-*bis*(3,5-dimethyl-4-methoxyphenyl)methylamine 36i:** Imine **36i** was prepared from cyclohexanecarbaldehyde according to the procedure described above for imine **36a**. Crystallization (1: 60 EtOAc/hexanes) and collection of the first crop afforded **36i** as white solid crystals (mp 108-109 ºC) in 71% isolated yield (1.40 g, 3.55 mmol).

Spectral data for **36i**: **^{1}H-NMR** ($CDCl_3$, 300 MHz) 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** ($CDCl_3$, 75 MHz) δ 16.19, 25.42, 26.01, 29.79, 43.51, 59.59, 77.44, 127.74, 130.49, 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)



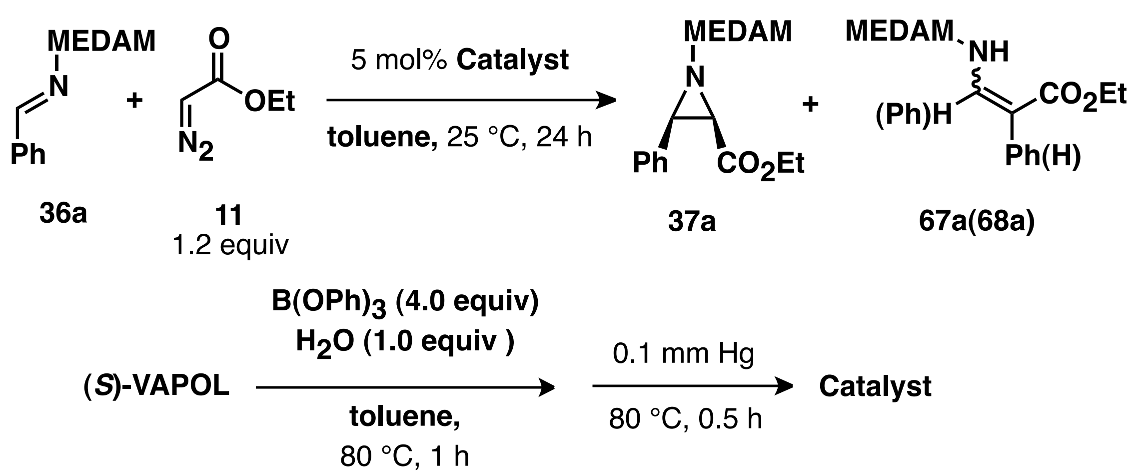
66 **36j**

***N*-(1,1′-dimethylethylidene)-bis(4-methoxy-3,5-dimethylphenyl)methylamine 36j:** Imine **36j** was prepared according to the procedure described above for imine **36a**. Crystallization (1: 100 CH_2Cl_2/hexanes) and collection of the first crop afforded **36j** as white solid crystals (mp 90-91 ºC) in 85% isolated yield (1.56 g, 4.25 mmol).

Spectral data for **36j**: **^{1}H-NMR** ($CDCl_3$, 300 MHz) 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** ($CDCl_3$, 75 MHz) δ 16.22, 27.04, 36.33, 59.59, 76.75, 127.71, 130.41, 139.63, 155.62, 171.11; 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)

See page 18, 21 and 26 for synthesis of Imines **36h**, **38h** and **36k** respectively.

2.8.4 General Procedure for the synthesis of MEDAM aziridines 37 and BUDAM aziridine 56h (*via* Method A) - Illustrated for the synthesis of (2*R*,3*R*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate 37a



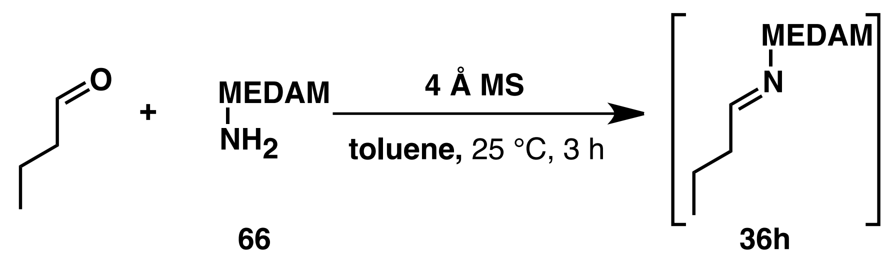
(2*R*,3*R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate 37a: To a 25 mL flame-dried home-made Schlenk flask (Figure 2.3) equipped with a stir bar and flushed with argon was added (*S*)-VAPOL (27 mg, 0.05 mmol) and $B(OPh)_3$ (58 mg, 0.2 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valve to dissolve the two reagents and this was followed by the addition of water (0.9 μL, 0.05 mmol). The flask was sealed by closing the Teflon valve, and then placed in an 80 ºC (oil bath) for 1 h. After 1 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles are removed completely, a full vacuum is applied and is maintained for a period of 30 min at a temperature of 80 ºC (oil bath). The flask was then allowed to cool to room temperature and opened to argon through the side arm of the Schlenk flask.

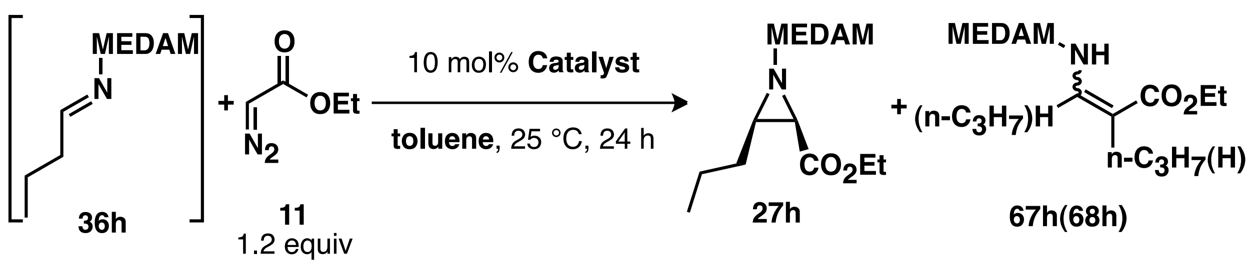
To the flask containing the catalyst was first added the aldimine **36a** (387 mg, 1.0 mmol) and then dry toluene (2 mL) under an argon flow through side arm of the Schlenk flask. The reaction mixture was stirred for 5 min to give a light orange solution. To this solution was rapidly added ethyl diazoacetate (EDA) **11** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. Immediately upon addition of ethyl diazoacetate the reaction mixture became an intense yellow, which changed to light yellow towards the completion of the reaction. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2) and the rinse was added to the 100 mL round bottom flask. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as an off-white solid.

A measure of the extent to which the reaction went to completion was estimated from the ^{1}H NMR spectrum of the crude reaction mixture by integration of the aziridine ring methine protons relative to either the imine methine proton or the proton on the imine carbon. The *cis/trans* ratio was determined by comparing the ^{1}H NMR integration of the ring methine protons for each aziridine in the crude reaction mixture. The *cis* (J = 7-8 Hz) and the *trans* (J = 2-3 Hz) coupling constants were used to differentiate the two isomers. The yields of the acyclic enamine side products **67a** and **68a** were determined by ^{1}H NMR analysis of the crude reaction mixture by integration of the *N*-H proton relative to the that of the *cis*-aziridine methine protons with the aid of the isolated yield of the *cis*-aziridine. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure aziridine **37a** as a white solid (mp 107-108 ºC on 99.8% ee material) in 98% isolated yield (396 mg, 0.98 mmol); *cis/trans*: >50:1. Enamine side products: 2 % yield of **67a** and 1.9% yield of **68a.** The optical purity of **37a** was determined to be 99.8% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.26 min (major enantiomer, **37a**) and R_t = 12.52 min (minor enantiomer, *ent*-**37a**). The AZ reaction of imine **36a** with (*R*)-VANOL gave *ent*-**37a** in 94% yield with 97% ee and cis/trans of >50:1. Performing the reaction with (*R*)-BINOL gave *ent*-**37a** in 72% yield with 38% ee and cis/trans of >17:1.

Spectral data for **37a**: R_f = 0.42 (1:9 EtOAc/hexane). **^{1}H-NMR** ($CDCl_3$, 500 MHz) δ 0.98 (t, 3H, J = 7.1 Hz), 2.18 (s, 6H), 2.24 (s, 6H), 2.55 (d, 1H, J = 6.8 Hz), 3.10 (d, 1H, J = 6.6 Hz), 3.62 (s, 3H), 3.66 (s, 1H), 3.68 (s, 3H) 3.87-3.97 (m, 2H), 7.09 (s, 2H), 7.18 (s, 2H), 7.21-7.24 (m, 3H), 7.36 (d, 2H, J = 7.3 Hz); **^{13}C-NMR** (CDCl$_3$, 125 MHz) δ 14.01, 16.16, 16.22, 46.26, 48.20, 59.52, 59.58, 60.47, 77.04, 127.21, 127.41, 127.70, 127.80,127.85, 130.59, 130.60, 135.33, 137.79, 137.96, 155.95, 156.10, 168.01; IR (thin film) 2961 vs, 1750 vs, 1414 vs, 1202 vs cm^{-1}; Mass spectrum: *m/z* (% rel intensity) 473 M+ (0.27), 284(78), 283 (100), 268 (34), 253 (20), 237 (11), 210(10), 117 (18), 89 (11); Anal calcd for $C_{30}H_{35}NO_4$: C, 76.08; H, 7.45; N, 2.96. Found: C, 76.31; H, 7.28; N, 2.82; $[\alpha]_D^{23}$ +41.3 (c 1.0, EtOAc) on 99% ee material (HPLC). These spectral data match those previously reported for this compound.[3]

MEDAM aziridines **37b-h** were also prepared according to Method A utilizing 5-10 mol% catalyst loading. These results including the yields and optical purity for all of MEDAM aziridines **37** are given in Table 2.2 in Chapter 2.





(*E*)-*N*-butylidene-1,1-bis(4-methoxy-3,5-dimethylphenyl)methanamine 36h: To a 10 mL flame-dried round bottom flask filled with argon was added bis(4-methoxy-3,5-

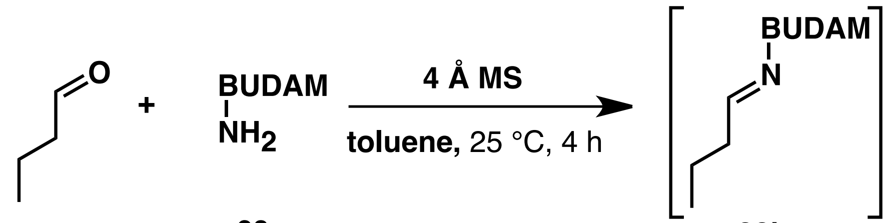
dimethylphenyl)methanamine **66** (299 mg, 1.00 mmol), 4Å MS (250 mg, freshly dried) and dry toluene (1.5 mL). After stirring for 10 min, butanal (78 mg, 1.05 mmol, freshly distilled) was added. The reaction mixture was stirred at room temperature for 3 h. The resulting imine **36h** was used without further purification.

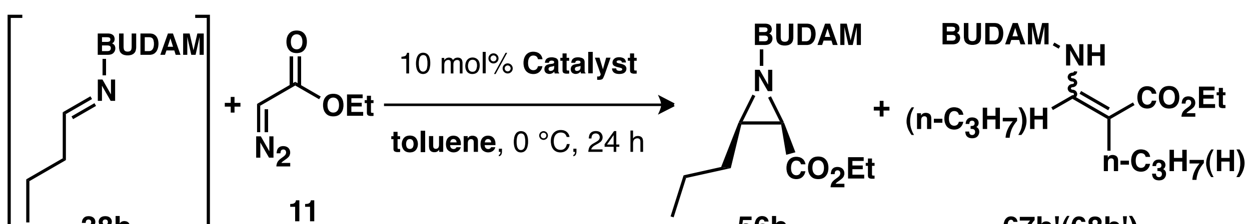
Spectral data for **36h**: ^{1}**H-NMR** ($CDCl_3$ 500 MHz) δ 0.94 (t, 3H, *J* = 7.3 Hz), 1.58 (sextet, 2H, *J* = 7.3 Hz), 2.23 (s, 12H), 2.28-2.32 (m, 2H), 3.67 (s, 6H), 5.09 (s, 1H), 6.92 (s, 4H), 7.75 (t, 1H, *J* = 4.9 Hz); ^{13}**C-NMR** (125 MHz, $CDCl_3$) δ 13.81, 16.17, 19.50, 37.84, 59.59, 77.71, 127.75, 130.55, 139.24, 155.73, 164.88.

(*2R,3R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-propylaziridine-2-carboxylate 37h: To a 25 mL flame-dried home-made Schlenk flask (see Figure 2.3) equipped with a stir bar and flushed with argon was added (*S)*-VAPOL (54 mg, 0.1 mmol) and $B(OPh)_3$ (116 mg, 0.4 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valuve to dissolve the two reagents and this was followed by the addition of water (1.8 μL, 0.1 mmol). The flask was sealed by closing the Teflon valve, and then placed in an 80 ºC oil bath) for 1 h. After 1 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 80 ºC (oil bath). The flask was then allowed to cool to room temperature and opened to argon through side arm of the Schlenk flask.

The toluene solution of imine **36h** (354 mg, 1.0 mmol, prepared as described above) was then directly transferred from the reaction flask in which it was prepared to the flask containing the catalyst utilizing a filter syringe (Corning® syringe filters, Aldrich) to remove the 4Å Molecular Sieves. The flask, which had imine **36h**, was then rinsed with toluene (0.5 mL) and the rinse was transferred to the flask containing the catalyst under argon flow through side-arm of the Schlenk flask. The reaction mixture was stirred for 5 min to give a light yellow solution. To this solution was rapidly added ethyl diazoacetate (EDA) **11** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2) and the rinse was added to the 100 mL round bottom flask. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as a pale yellow semi solid. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 4:2:0.1 hexanes/CH_2Cl_2/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37h** as a semi solid in 64 % isolated yield (281 mg, 0.64 mmol); *cis/trans*: not determined. Enamine side products: 15.3 % yield of **67h** and 8.3 % yield of **68h**. The optical purity of **37h** was determined to be 93% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 4.73 min (major enantiomer, **37h**) and R_t = 5.68 min (minor enantiomer, *ent*-**37h**). The AZ reaction of imine **36h** with (*S*)-VAPOL at 0 °C gave **37h** in 72% yield with 97% ee. With (*R*)-VANOL, *ent*-**37h** was obtained in 73% yield with 94% ee (at room temperature) and 75% yield and 95% ee (at 0 °C). For the reaction at 0 °C, the catalyst was precooled to 0 °C followed by the addition of the imine solution and EDA at 0 °C.

Spectral data for **37h**: R_f = 0.28 (4:2:0.1 hexanes/CH_2Cl_2/EtOAc); **^{1}H-NMR** ($CDCl_3$, 500 MHz) δ 0.72 (t, 3H, J = 7.6 Hz), 0.98-1.08 (m, 1H), 1.11-1.20 (m, 1H), 1.23 (t, 3H, J = 7.1 Hz), 1.38-1.45 (m, 1H), 1.49-1.55 (m, 1H), 1.95 (q, 1H, J = 6.6 Hz), 2.18 (d, 1H, J = 6.8 Hz) 2.22 (s, 12H), 3.39 (s, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 4.12-4.23 (m, 2H), 6.99 (s, 2H), 7.07 (s, 2H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 13.57, 14.33, 16.09, 16.16, 20.33 29.93, 43.53, 46.76, 59.56, 59.60, 60.64, 77.32, 127.41, 128.07, 130.44, 130.47, 137.75, 138.18, 155.81, 156.12, 169.69; IR (thin film) 2957vs, 1744s, 1483s, 1221s, 1182vs cm^{-1}; HRMS (ESI-TOF) *m/z* 440.2817 [(M+H$^+$); calcd. for $C_{27}H_{38}NO_4$: 440.2801]; $[\alpha]_D^{23}$ +95.3 (c 1.0, EtOAc) on 97 % ee material (HPLC).





(*E*)-*N*-butylidene-1,1-bis(3,5-di-tert-butyl-4-methoxyphenyl)methanamine 38h: To a 10 mL flame-dried round bottom flask filled with argon was added bis-(3,5-di-*tert*-butyl-4-methoxyphenyl)methanamine **60** (468 mg, 1.00 mmol), 4Å MS (250 mg, freshly dried) and dry toluene (1.5 mL). After stirring for 10 min, butanal (78 mg, 1.05 mmol, freshly distilled) was added. The reaction mixture was stirred at room temperature for 4 h. The resulting imine 3**8h** was used without further purification.

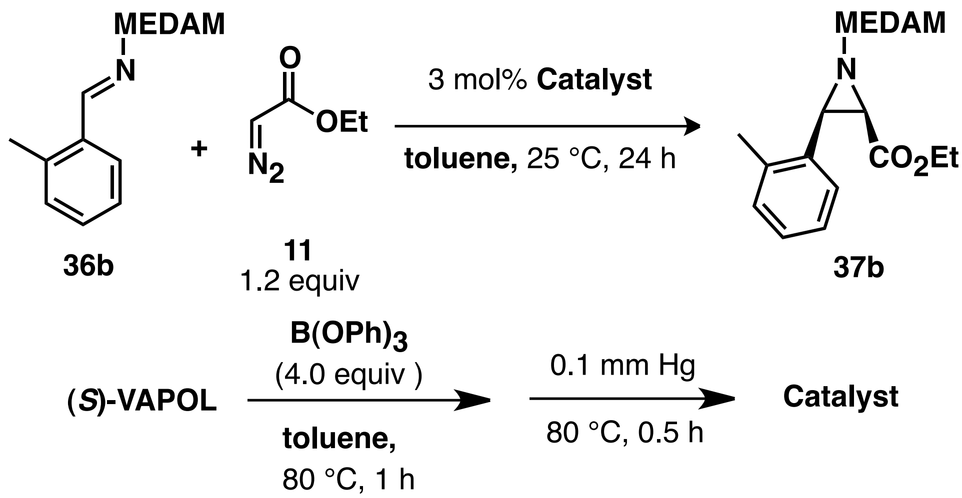
Spectral data for **38h**: ^{1}**H-NMR** ($CDCl_3$ 500 MHz) δ 0.98 (t, 3H, *J* = 7.3 Hz), 1.35 (s, 36H), 1.63 (sextet, 2H, *J* = 7.3 Hz), 2.31-2.35 (m, 2H), 3.64 (s, 6H), 5.22 (s, 1H), 7.05 (s, 4H), 7.87 (t, 1H, *J* = 4.9 Hz)

(*2R,3R*)-ethyl-1-(bis(3,5-di-tert-butyl-4-methoxyphenyl)methyl)-3-propylaziridine-2-carboxylate 56h: To a 25 mL flame-dried home-made Schlenk flask (see Figure 2.3) equipped with a stir bar and flushed with argon was added (*S*)-VAPOL (54 mg, 0.1 mmol) and $B(OPh)_3$ (116 mg, 0.4 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valve to dissolve the two reagents and this was followed by the addition of water (1.8 µL, 0.1 mmol). T he flask was sealed by closing the Teflon valve, and then placed in an 80 ºC oil bath for 1 h. After 1 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 80 ºC (oil bath). The flask was then allowed to cool to 0 ºC and opened to argon through side arm of the Schlenk flask.

The toluene solution of imine **38h** (522 mg, 1.0 mmol, prepared as described above) was then directly transferred from the reaction flask in which it was prepared to the flask containing the catalyst utilizing a filter syringe (Corning® syringe filters, Aldrich) to remove the 4Å Molecular Sieves. The flask, which had imine **38h**, was then rinsed with toluene (0.5 mL) and the rinse was transferred to the flask containing the catalyst under argon flow through the side arm of the Schlenk flask. The reaction mixture was stirred for 5 min to give a light yellow solution. To this solution was rapidly added ethyl diazoacetate (EDA) **11** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. The reaction was dilluted by addition of hexane (6 mL) at 0 ºC. The reaction mixture was then warmed to room temperature and transferred to a 100 mL round bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2) and the rinse was added to the 100 mL round bottom flask. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as a pale yellow semi solid. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 4:2:0.1 hexanes/CH_2Cl_2/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **56h** as a semi solid in 69 % isolated yield (419 mg, 0.69 mmol); *cis/trans*: not determined. Enamine side products: 10.3 % yield of **67h'** and 4.4 % yield of **68h'**. The optical purity of **56h** was determined to be 95% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 7.46 min (major enantiomer **56h**) and R_t = 6.60 min (minor enantiomer, *ent*-**56h**). The AZ reaction of imine **38h** with (*R*)-VANOL gave *ent*-**56h** in 75% yield with 93% ee.

Spectral data for **56h**: R_f = 0.23 (2:1 hexane/CH_2Cl_2); **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ 0.82 (t, 3H, *J* = 7.5 Hz), 1.31 (t, 3H, *J* = 7.1 Hz), 1.50-1.74 (m, 2H), 1.45 (s, 18h), 1.46 (s, 18h) 1.55-1.73 (m, 2H), 2.15 (q, 1H, *J* = 6.6 Hz), 2.36 (d, 1H, *J* = 6.6 Hz), 3.68 (s, 1H), 3.70 (s, 3H), 3.72 (s, 3H), 4.12-4.29 (m, 2H), 7.22 (s, 2H), 7.36 (s, 2H); **^{13}C-NMR** ($CDCl_3$, 75 MHz) δ 13.68, 14.39, 20.57, 29.94, 32.13, 32.18, 35.75, 35.79, 43.39, 47.28, 60.69, 64.09, 64.14, 77.57, 125.60, 126.24, 136.39, 137.00, 142.88, 142.92, 158.29, 158.69, 169.96; IR (thin film) 2961vs, 1747s, 1448s, 1221s, 1182 vs cm^{-1}; HRMS (ESI-TOF) *m/z* 608.4665 [(M+H^{+}); calcd. for $C_{39}H_{62}NO_4$: 608.4679]; $[\alpha]_D^{23}$ –61.6 (c 1.0, EtOAc) on 93 % ee material (HPLC) of *ent*-**56h.**

2.8.5 General Procedure for the synthesis of MEDAM aziridines 37 (*via* Method A, without water) - Illustrated for the synthesis of (2*R*, 3*R*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(*o*-tolyl)aziridine-2-carboxylate 37b.

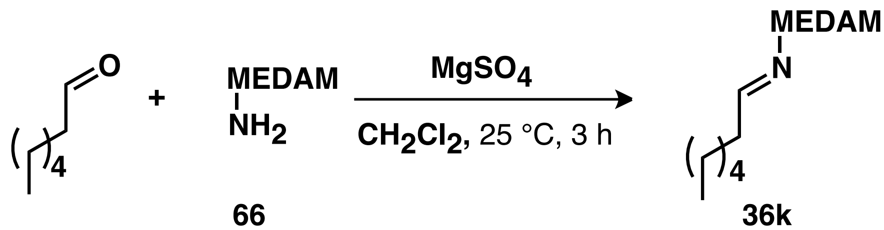


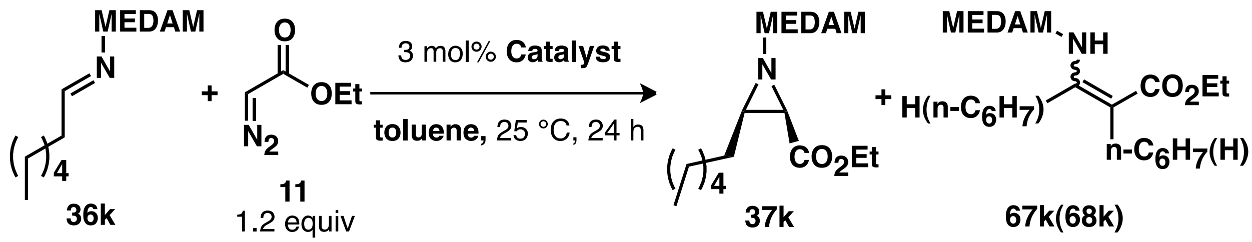
(2*R*,3*R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(*o*-tolyl)aziridine-2-carboxylate 37b: Imine **36b** (401.5 mg, 1.0 mmol) was reacted according to the general Method A described above with (*S*)-VAPOL as ligand with the following differences: a) water was excluded during the preparation of the catalyst and b) 3 mol % catalyst loading was utilized. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37b** as a white solid (mp 59-60 ºC on 98% ee material) in 91 % isolated yield (444 mg, 0.91 mmol); *cis/trans*: 33:1. Enamine side products: 4.5 % yield of **67b** and 2.7 % yield of **68b**. The optical purity of **37b**

was determined to be 98% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.45 min (major enantiomer, **37b**) and R_t = 12.21 min (minor enantiomer, *ent*-**37b**). The AZ reaction of imine **36b** with (*R*)-VANOL (*via* Method A and 5 mol% catalyst loading) gave *ent*-**37b** in 90% yield with 97% ee and *cis/trans* of 50:1.

Spectral data for **37b**: R_f = 0.38 (1:9 EtOAc/hexane). **^{1}H-NMR** ($CDCl_3$, 500 MHz) δ 0.89 (t, 3H, *J* = 7.1 Hz), 2.20 (s, 6H), 2.24 (s, 6H), 2.26 (s, 3H), 2.61 (d, 1H, *J* = 6.8 Hz), 3.08 (d, 1H, *J* = 6.6 Hz), 3.62 (s, 3H), 3.66 (s, 1H), 3.68 (s, 3H), 3.88 (q, 2H, *J* = 7.1 Hz), 7.01 (d, 1H, *J* = 6.6 Hz), 7.06-7.09 (m, 2H), 7.13 (s, 2H), 7.18 (s, 2H), 7.53 (d, 1H, *J* = 6.3 Hz); **^{13}C-NMR** ($CDCl_3$, 125 MHz) δ 13.90, 16.16, 16.22, 18.76, 45.55, 47.15, 59.53, 59.59, 60.36, 77.34, 125.28, 127.05, 127.33, 127.95, 128.62, 129.08, 130.61, 130.63, 133.45, 136.03, 137.85, 138.01, 155.92, 156.18, 168.16; IR (thin film) 2937vs, 1749s, 1485s, 1221s, 1192vs cm^{-1}; HRMS (ESI-TOF) *m/z* 488.2801 [(M+H$^+$); calcd. for $C_{31}H_{38}NO_4$: 488.2801]; $[\alpha]_D^{23}$ +46.4 (*c* 1.0, EtOAc) on 97% ee material (HPLC).

MEDAM aziridines **37d, 37e, 37i, 37j** and **37k** were also prepared according to the Method A (without water) utilizing 2-3 mol% catalyst loading. The results regarding the yields and optical purity for all of MEDAM aziridines **37** are given in Table 2.2 in Chapter 2.





(*E*)-*N*-heptylidene-1,1-bis(4-methoxy-3,5-dimethylphenyl)methanamine 36k: To a 10 mL flame-dried round bottom flask filled with argon was added bis(4-methoxy-3,5-dimethylphenyl)methanamine **66** (299 mg, 1.0 mmol), $MgSO_4$ (200 mg, 1.7 mmol, freshly flame-dried) and dry CH_2Cl_2 (3 mL). After stirring for 10 min, heptanal (120 mg, 1.05 mmol, freshly distilled) was added. The reaction mixture was stirred at room temperature for 3 h. The reaction mixture was filtered through Celite and the Celite bed was washed with CH_2Cl_2 (1 mL × 3) and then the filtrate was concentrated by rotary evaporation to give the crude imine as a pale yellow viscous oil which was dried under high vacuum (~ 0.2 mm Hg) for 1 h to remove any excess aldehyde, 100% crude yield. The resulting imine **36k** was used without further purification.

Spectral data for **36k:** ^{1}**H-NMR** ($CDCl_3$, 300 MHz) 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

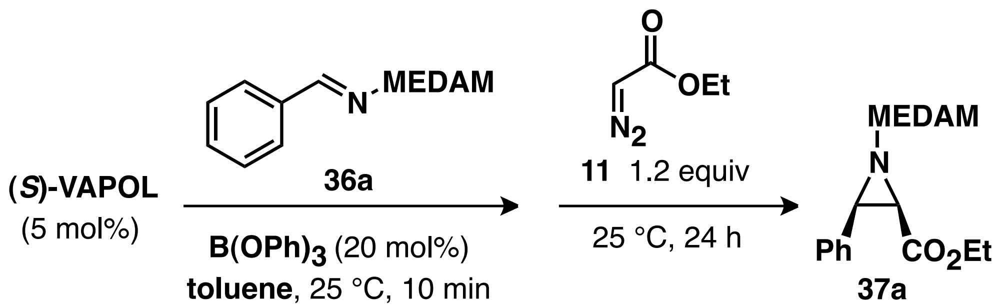
(t, 1H, J = 5.0 Hz); **^{13}C-NMR** ($CDCl_3$, 75 MHz) δ 13.97, 16.14, 22.55, 26.02, 28.94, 31.59, 35.87, 59.56, 77.68, 127.74, 130.53, 139.21, 155.71, 165.03

(*2R,3R*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-hexylaziridine-2-carboxylate 37k: To a 25 mL flame-dried home-made Schlenk flask (see Figure 2.3) equipped with a stir bar and flushed with argon was added (*S)*-VAPOL (16 mg, 0.03 mmol) and $B(OPh)_3$ (35 mg, 0.12 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valve to dissolve the two reagents. The flask was sealed by closing the Teflon valve, and then placed in an 80 ºC oil bath for 1 h. After 1 h, a vacuum (0.5 mm Hg) was carefully applied by slightly opening the Teflon valve to remove the volatiles. After the volatiles were removed completely, a full vacuum was applied and maintained for a period of 30 min at a temperature of 80 ºC (oil bath). The flask was then allowed to cool to room temperature and opened to argon through the side arm of the Schlenk flask.

Meanwhile, to the flask containing imine **36k** (396 mg, 1.0 mmol, prepared as described above) was added dry toluene (1.5 mL) and the resultant toluene solution of imine **36k** was then directly transferred from the reaction flask in which it was prepared to the flask containing the catalyst. The flask, which had imine **26k**, was then rinsed with toluene (0.5 mL) and the rinse was transferred to the flask containing the catalyst under argon flow through the side arm of the Schlenk flask. The reaction mixture was stirred for 5 min to give a light yellow solution. To this solution was rapidly added ethyl diazoacetate (EDA) **11** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2) and the rinse was added to the 100 mL round bottom flask. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as a pale yellow semi solid. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 4:2:0.1 hexanes / CH_2Cl_2 /EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37k** as a semi solid in 67 % isolated yield (323 mg, 0.67 mmol); *cis/trans*: not determined. Enamine side products: not determined. The optical purity of **37k** was determined to be 90% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.27 min (major enantiomer, **37k**) and R_t = 11.17 min (minor enantiomer, *ent*-**37k**).

Spectral data for **37k**: R_f = 0.30 (4:2 hexane/CH_2Cl_2); **^{1}H-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 *sp3* 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); $[\alpha]_D^{23}$ +78.3 (c 1.0, CH_2Cl_2) on 90 % ee material (HPLC).

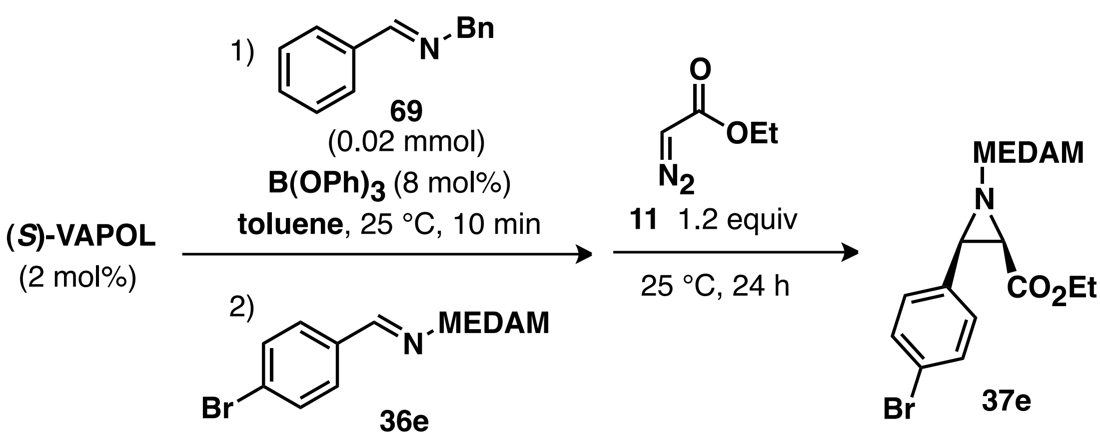
2.8.6 General Procedure for the synthesis of MEDAM aziridines 37 (*via* Method B) - Illustrated for the synthesis of (2*R*,3*R*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate 37a.



(2*R*,3*R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate 37a: To a 25 mL flame-dried round bottom flask equipped with a stir bar and flushed with argon was added (*S)*-VAPOL (27 mg, 0.05 mmol) and $B(OPh)_3$ (58 mg, 0.20 mmol) and aldimine **36a** (387 mg, 1.0 mmol). Dry toluene (2 mL) was added to dissolve the reagents. The reaction mixture was stirred for 10 min at room temperature under argon atmosphere. To this solution was rapidly added ethyl diazoacetate (EDA) **11** (124 μL, 1.2 mmol). The resulting mixture was stirred for 24 h at room temperature. Immediately upon addition of ethyl diazoacetate the reaction mixture became an intense yellow, which changed to light yellow towards the completion of the reaction. The reaction was diluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2) and the rinse was added to the 100 mL round bottom flask. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as an off-white solid. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37a** as a white solid in 93 % isolated yield (440 mg, 0.93 mmol); *cis/trans*: >50:1. The optical purity of **37a** was determined to be 98.0 % *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.26 min (major enantiomer, **37a**) and R_t = 12.52 min (minor enantiomer, *ent*-**37a**).

MEDAM aziridines **37d, 37e** and **37k** were also prepared according to the Method B (both under argon and open to air condition) utilizing 5 mol% catalyst loading. The results regarding the yields and optical purity for all of MEDAM aziridines **37** are given in Table 2.3 in Chapter 2.

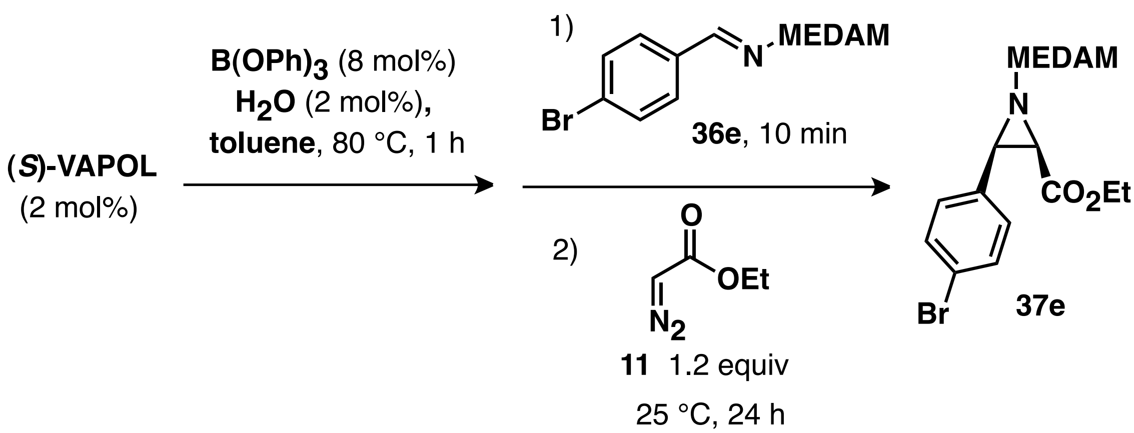
2.8.7 Procedure for the synthesis of MEDAM aziridines 37e (*via* Method B').



To a 25 mL flame-dried round bottom flask equipped with a stir bar and flushed with argon was added (*S)*-VAPOL (11 mg, 0.02 mmol) and $B(OPh)_3$ (23 mg, 0.08 mmol) and aldimine **69** (5 mg, 0.02 mmol). Dry toluene (2 mL) was added to dissolve the reagents. The reaction mixture was stirred for 10 min at room temperature under argon atmosphere. To this solution was rapidly added aldimine **36e** (466 mg, 1.0 mmol) and ethyl diazoacetate (EDA) **11** (124 μL, 1.2

mmol). The resulting mixture was stirred for 24 h at room temperature. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2) and the rinse was added to the 100 mL round bottom flask. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude mixture as yellow solid. The NMR yield of **37e** was 15% using Ph_3CH as internal standard.

2.8.8 Procedure for the synthesis of MEDAM aziridines 37e (*via* Method C).

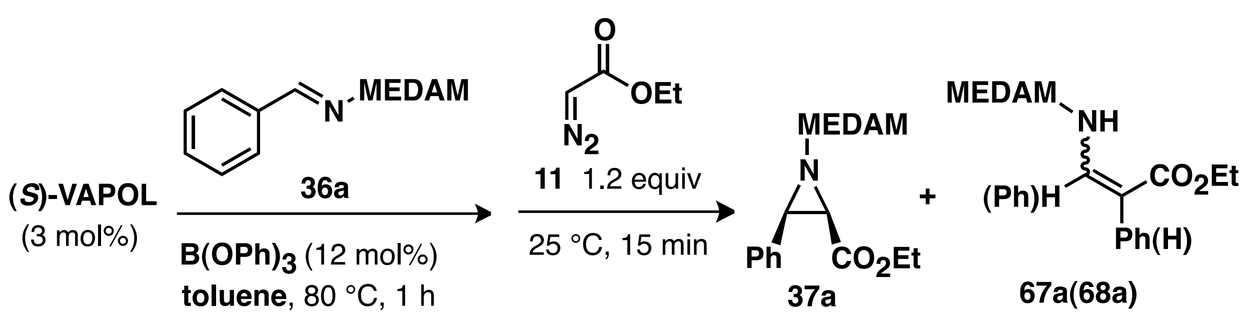


To a 25 mL flame-dried home-made Schlenk flask (see Figure 2.3) equipped with a stir bar and flushed with argon was added (*S)*-VAPOL (11 mg, 0.02 mmol) and $B(OPh)_3$ (23 mg, 0.08 mmol) and water (0.36 µL, 0.02 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valve to dissolve the reagents. The flask was sealed by closing the Teflon valve, and then placed in an 80 ºC oil bath for 1 h. The catalyst mixture was then allowed to cool to room temperature and opened to argon through the side arm of the Schlenk flask. To this solution was added aldimine **36e** (466 mg, 1.0 mmol) and the resulting mixture was stirred for 10 min at room temperature. To the reaction mixture was added ethyl diazoacetate (EDA) **11** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2) and the rinse was added to the 100 mL round bottom flask. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as yellow solid. The NMR yield of **37e** was 18% using Ph_3CH as internal standard.

The above reaction procedure was repeated without water

Imine **36e** (466 mg, 1.0 mmol) was reacted according to the general Method C described above with (*S*)-VAPOL as ligand except water was excluded during the preparation of the catalyst. The NMR yield of **37e** was 64% using Ph_3CH as internal standard.

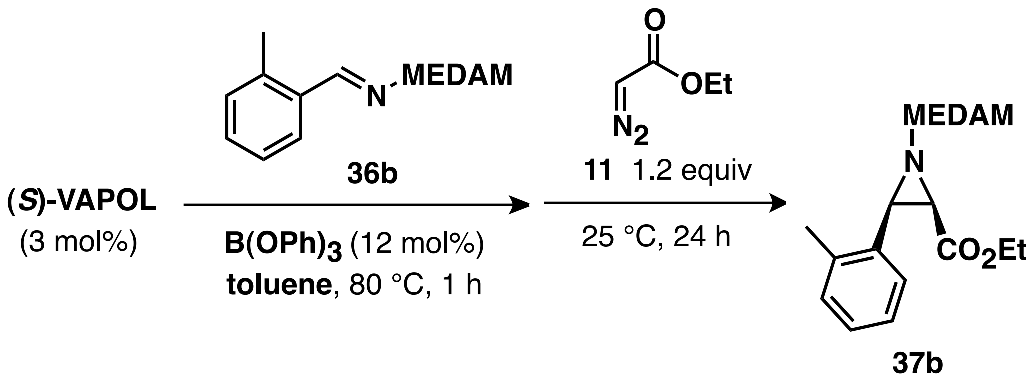
2.8.9 General Procedure for the synthesis of MEDAM aziridines 37 (*via* Method D) - Illustrated for the synthesis of (2*R*,3*R*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate 37a.



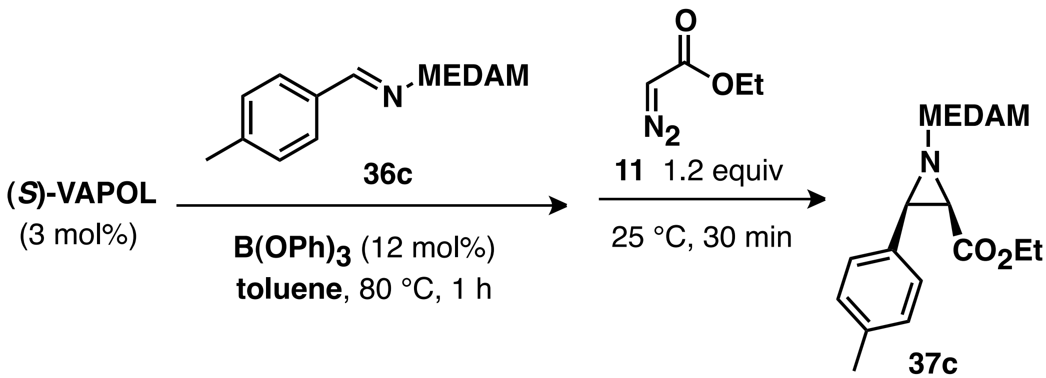
(2*R*,3*R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-carboxylate 37a: To a 25 mL flame-dried home-made Schlenk flask (see Figure 2.3) equipped with a stir bar and flushed with argon was added (*S)*-VAPOL (16 mg, 0.03 mmol) and $B(OPh)_3$ (35 mg, 0.12 mmol) and aldimine **36a** (387 mg, 1.0 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (2 mL) was added through the top of the Teflon valve to dissolve the reagents. The flask was sealed by closing the Teflon valve, and then placed in an 80 ºC oil bath for 1 h. The catalyst mixture was then allowed to cool to room temperature and opened to argon through the side arm of the Schlenk flask. To this solution was rapidly added ethyl diazoacetate (EDA) **11** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 15 min at room temperature. Immediately upon addition of ethyl diazoacetate the reaction mixture became an intense yellow, which changed to light yellow towards the completion of the reaction. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2) and the rinse was added to the 100 mL round bottom flask. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as an off-white solid. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37a** as a white solid (mp 107-108 ºC on 99.8% ee material) in 93 % isolated yield (440 mg, 0.93 mmol); *cis/trans*: >50:1. Enamine side products: 2.5 % yield of **67a** and 2.0% yield of **68a**. The optical purity of **37a** was determined to be 98.5 % *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-

propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.26 min (major enantiomer, **37a**) and R_t = 12.52 min (minor enantiomer, *ent*-**37a**).

Spectral data for **37a**: See page 17

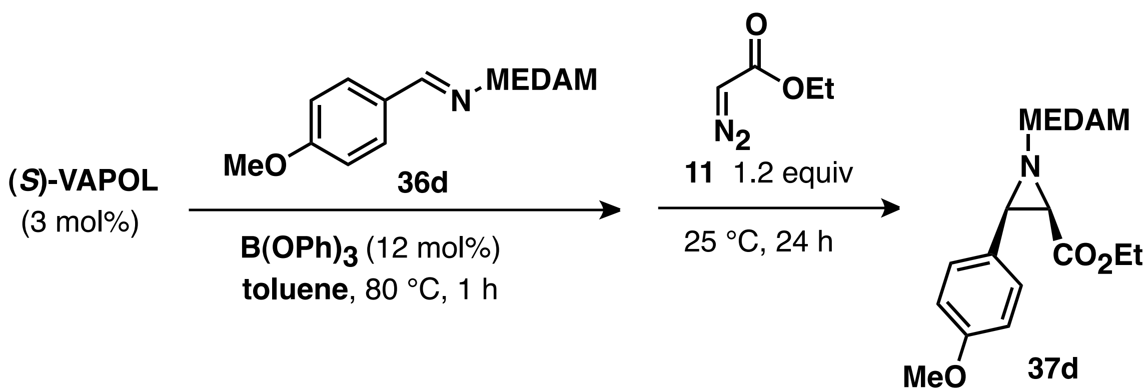


(2*R*,3*R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(*o*-tolyl)aziridine-2-carboxylate 37b: Imine **36b** (401.5 mg, 1.0 mmol) was reacted according to the general Method D described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37b** as a white solid (mp 59-60 ºC on 98% ee material) in 87 % isolated yield (424 mg, 0.87 mmol); *cis/trans*: 33:1. Enamine side products: 5.0 % yield of **67b** and 3.2 % yield of **68b**. The optical purity of **37b** was determined to be 96% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.45 min (major enantiomer, **37b**) and R_t = 12.21 min (minor enantiomer, *ent*-**37b**).



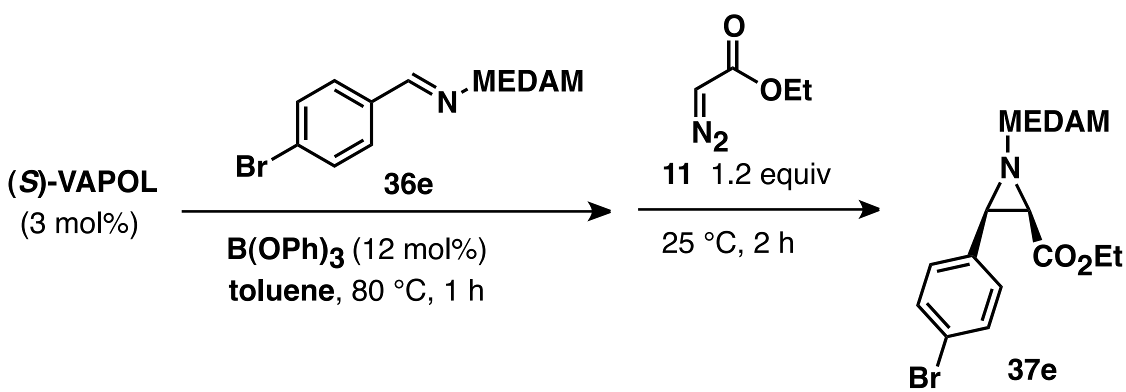
(*2R,3R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(p-tolyl)aziridine-2-carboxylate 37c: Imine **36c** (401.5 mg, 1.0 mmol) was reacted according to the general Method D described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37c** as a white solid (mp 116-117 ºC on 99.5% ee material) in 94 % isolated yield (458 mg, 0.94 mmol); *cis/trans*: >50:1. Enamine side products: 3.0 % yield of **67c** and 1.2 % yield of **68c**. The optical purity of **37c** was determined to be 99% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.22 min (major enantiomer, **37c**) and R_t = 11.62 min (minor enantiomer, *ent*-**37c**).

Spectral data for **37c**: R_f = 0.30 (1:9 EtOAc/hexanes). **^{1}H-NMR** ($CDCl_3$, 500 MHz) δ 1.01 (t, 3H, *J* = 7.1 Hz), 2.18 (s, 6H), 2.24 (s, 6H), 2.26 (s, 3H), 2.52 (d, 1H, *J* = 6.6 Hz), 3.07 (d, 1H, *J* = 6.8 Hz), 3.62 (s, 3H), 3.64 (s, 1H), 3.68 (s, 3H) 3.93 (dq, 2H, *J* = 3.2 Hz, 7.1 Hz), 7.02 (d, 2H, *J* = 7.8 Hz), 7.08 (s, 2H), 7.17 (s, 2H), 7.24 (d, 2H, *J* = 8.0 Hz); **^{13}C-NMR** ($CDCl_3$, 125 MHz) δ 14.05, 16.16, 16.22, 21.11, 46.20, 48.21, 59.52, 59.58, 60.44, 77.11, 127.43, 127.72, 127.81, 128.41, 130.54, 130.57, 132.28, 136.78, 137.86, 138.00, 155.93, 156.08, 168.10; IR (thin film) 2978vs, 1748s, 1483s, 1221s, 1190vs cm^{-1}; HRMS (ESI-TOF) *m/z* 488.2806 [(M+H$^+$); calcd. for $C_{31}H_{38}NO_4$: 488.2801]; $[\alpha]_D^{23}$ +29.4 (*c* 1.0, EtOAc) on 99.8 % ee material (HPLC).



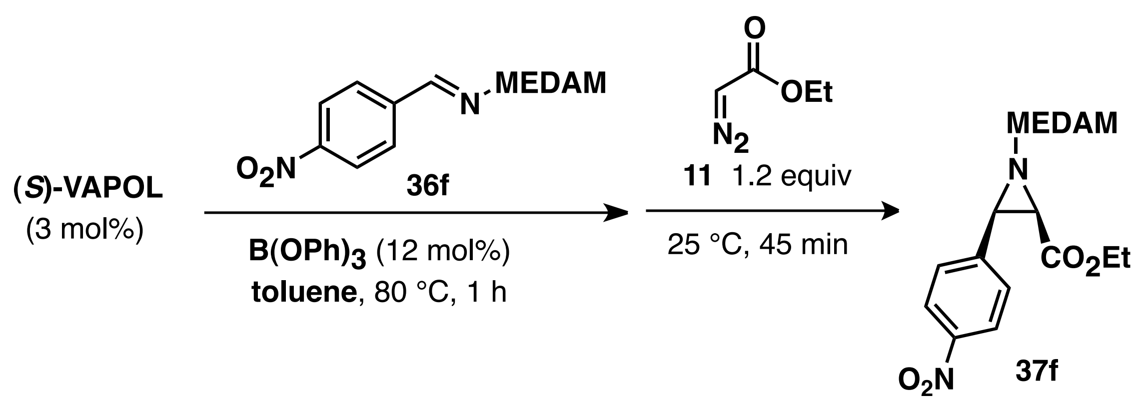
(*2R,3R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-methoxyphenyl)aziridine-2-carboxylate 37d: Imine **36d** (417.5 mg, 1.0 mmol) was reacted according to the general Method D described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 9:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37d** as a white solid (mp 56-57 ºC on 98 % ee material) in 83 % isolated yield (418 mg, 0.83 mmol); *cis/trans*: >50:1. Enamine side products: 1.2 % yield of **67d** and 2.1 % yield of **68d**. The optical purity of **37d** was determined to be 97% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 12.07 min (major enantiomer, **27d**) and R_t = 19.20 min (minor enantiomer, *ent*-**37d**).

Spectral data for **37d**: R_f = 0.28 (1:9 EtOAc/hexane). **^{1}H-NMR** ($CDCl_3$, 500 MHz) δ 1.02 (t, 3H, *J* = 7.1 Hz), 2.19 (s, 6H), 2.24 (s, 6H), 2.51 (d, 1H, *J* = 6.8 Hz), 3.06 (d, 1H, *J* = 6.8 Hz), 3.63 (s, 3H), 3.65 (s, 1H), 3.68 (s, 3H), 3.74 (s, 3H), 3.89-3.99 (m, 2H), 6.77 (d, 2H, *J* = 9.5 Hz), 7.09 (s, 2H), 7.18 (s, 2H), 7.29 (d, 2H, *J* = 8.8 Hz); **^{13}C-NMR** ($CDCl_3$, 125 MHz) δ 14.08, 16.16, 16.21, 46.20, 47.89, 55.19, 59.52, 59.57, 60.45, 77.05, 113.18, 127.43, 127.79, 128.93, 130.55, 130.57, 137.83, 138.01, 155.93, 156.07, 158.86, 168.14 (one *sp2* carbon not located); IR (thin film) 2942vs, 1743s, 1514s, 1250s, 1180vs cm^{-1}; HRMS (ESI-TOF) *m/z* 504.2744 [(M+H^+); calcd. for $C_{31}H_{38}NO_5$: 504.2750]; $[\alpha]_D^{23}$ –25 (*c* 1.0, EtOAc) on 96 % ee material (HPLC) on *ent*-**37d**.



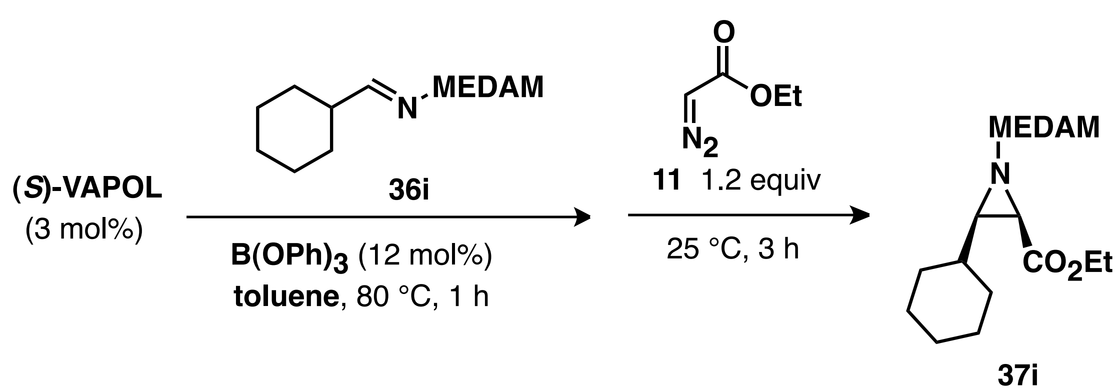
(*2R,3R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-bromophenyl)aziridine-2-carboxylate 37e: Imine **36e** (466.4 mg, 1.0 mmol) was reacted according to the general Method D described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 5:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37e** as a white solid (mp 145-146 ºC on 99.6 % ee material) in 94 % isolated yield (519 mg, 0.94 mmol); *cis/trans*: >50:1. Enamine side products: 1.5 % yield of **67e** and 1.9 % yield of **68e**. The optical purity of **37e** was determined to be 99% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 8.41 min (major enantiomer, **37e**) and R_t = 11.96 min (minor enantiomer, *ent*-**37e**).

Spectral data for **37e**: R_f = 0.32 (1:9 EtOAc/hexane). ^{1}**H-NMR** ($CDCl_3$, 500 MHz) δ 1.02 (t, 3H, *J* = 7.1 Hz), 2.18 (s, 6H), 2.24 (s, 6H), 2.56 (d, 1H, *J* = 6.6 Hz), 3.03 (d, 1H, *J* = 6.8 Hz), 3.62 (s, 3H), 3.66 (s, 1H), 3.68 (s, 3H), 3.89-3.98 (m, 2H), 7.06 (s, 2H), 7.16 (s, 2H), 7.26 (d, 2H, *J* = 8.5 Hz), 7.35 (d, 2H, *J* = 8.5 Hz); ^{13}**C-NMR** ($CDCl_3$, 125 MHz) δ 14.08, 16.18, 16.23,46.35, 47.54, 59.55, 59.59, 60.64, 121.23, 127.35, 127.68, 129.62, 130.69, 130.83, 134.37, 137.57, 137.76, 156.01, 156.17, 167.69 (one sp^2 and one sp^3 carbon not located); IR (thin film) 2942vs, 1745vs, 1485vs, 1221vs cm^{-1}; HRMS (ESI-TOF) *m/z* 552.1733 [(M+H^+); calcd. for $C_{30}H_{35}NO_4{}^{79}Br$: 552.1749]; $[\alpha]_D^{23}$ +12.8 (*c* 1.0, EtOAc) on 99% ee material (HPLC).



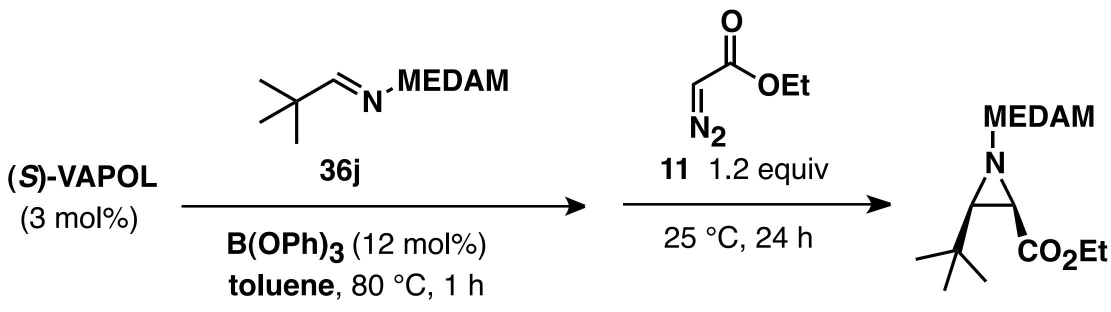
(*2R,3R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(4-nitrophenyl)aziridine-2-carboxylate 37f: Imine **36f** (432.5 mg, 1.0 mmol) was reacted according to the general Method D described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 5:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37f** as a white solid (mp 174-175 ºC on 99.7% ee material) in 95 % isolated yield (493 mg, 0.95 mmol); *cis/trans*: >50:1. Enamine side products: 1.2 % yield of **67f** and 2.0 % yield of **68f**. The optical purity of **37f** was determined to be 99% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 17.12 min (major enantiomer, **37f**) and R_t = 27.13 min (minor enantiomer, *ent*-**37f**).

Spectral data for **37f**: R_f = 0.30 (1:9 EtOAc/hexane). ^{1}**H-NMR** ($CDCl_3$, 500 MHz) δ 1.02 (t, 3H, *J* = 7.1 Hz), 2.18 (s, 6H), 2.25 (s, 6H), 2.68 (d, 1H, *J* = 6.8 Hz), 3.15 (d, 1H, *J* = 6.8 Hz), 3.62 (s, 3H), 3.68 (s, 3H), 3.71 (s, 1H), 3.93 (dq, 2H, *J* = 2.2, 7.1 Hz), 7.06 (s, 2H), 7.16 (s, 2H), 7.57 (d, 2H, *J* = 8.8 Hz), 8.10 (d, 2H, *J* = 8.8 Hz); ^{13}**C-NMR** ($CDCl_3$, 125 MHz) δ 14.08, 16.19, 16.24, 46.81, 47.26, 59.55, 59.59, 60.85, 76.89, 122.98, 127.26, 127.59, 128.81, 130.81, 130.86, 137.25, 137.48, 142.82, 147.28, 156.13, 156.28, 167.20; IR (thin film) 2984 vs, 1745 vs, 1603 s, 1522 vs, 1221 vs cm^{-1}; HRMS (ESI-TOF) *m/z* 519.2505 [$(M+H^+)$; calcd. for $C_{30}H_{35}N_2O_6$: 519.2495]; $[\alpha]_D^{23} - 4.8$ (*c* 1.0, EtOAc) on 99.8% ee material (HPLC).



(*2R,3R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-cyclohexylaziridine-2-carboxylate 37i: Imine **36i** (393.5 mg, 1.0 mmol) was reacted according to the general Method D described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 2:1 hexanes/CH_2Cl_2 as eluent, gravity column) afforded pure *cis*-aziridine 3**27i** as a white solid (mp 47-49 ºC on 91% ee material) in 96 % isolated yield (461 mg, 0.96 mmol); *cis/trans*: 50:1. Enamine side products: not determined. The optical purity of **37i** was determined to be 89% *ee* by HPLC analysis (CHIRALCEL OD column, 99:1 hexane/2-propanol at 223 nm, flow-rate: 0.7 mL/min): retention times; R_t = 10.06 min (major enantiomer, **37i**) and R_t = 12.37 min (minor enantiomer, *ent*-**37i**).

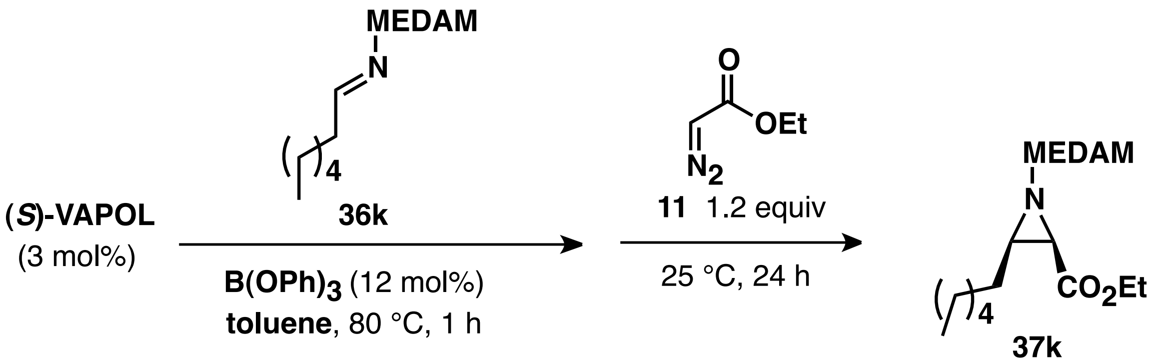
Spectral data for **37i**: R_f = 0.21 (2:1 hexane/CH_2Cl_2); **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ 0.46-0.57 (m, 1H), 0.87-1.19 (m, 4H), 1.21 (t, 3H, *J* = 7.1 Hz), 1.22-1.32 (m, 2H), 1.40-1.60 (m, 4H), 1.71-1.76 (m, 1H), 2.16 (m, 1H), 2.19 (s, 6H), 2.20 (s, 6H), 3.35 (s, 1H), 3.60 (s, 3H), 3.63 (s, 3H), 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); $[\alpha]_D^{23}$ +107.4 (c 1.0, CH_2Cl_2) on 89 % ee material (HPLC).



37j

(*2R,3R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-*t*-butylaziridine-2-carboxylate 37j: Imine **36j** (367.5 mg, 1.0 mmol) was reacted according to the general Method D described above with (*S*)-VAPOL as ligand. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 50:1 hexanes/EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37j** as a semi solid in 93% isolated yield (422 mg, 0.93 mmol); *cis/trans*: 50:1. Enamine side products: not determined. The optical purity of **37j** was determined to be 92% *ee* by HPLC analysis (CHIRALCEL OD column, 99:1 hexane/2-propanol at 226 nm, flow-rate: 1.0 mL/min): retention times; R_t = 6.8 min (major enantiomer, **37j**) and R_t = 10.55 min (minor enantiomer, *ent*-**37j**).

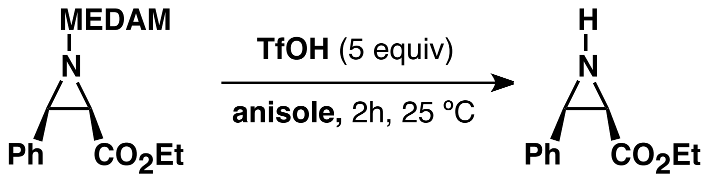
Spectral data for **37j**: R_f = 0.28 (1:2 hexane/CH_2Cl_2); **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ 0.72 (s, 9H), 1.29 (t, 3H, J = 7.1 Hz), 1.70 (d, 1H, J = 7.3 Hz), 2.11 (d, 1H, J = 7.2 Hz), 2.24 (s, 6H), 2.26 (s, 6H), 3.38 (s, 1H), 3.63 (s, 3H), 3.66 (s, 3H), 4.05-4.26 (m, 2H), 7.04 (s, 2H), 7.30 (s, 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 *sp2* 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); $[\alpha]_D^{23}$ +110.0 (c 1.0, CH_2Cl_2) on 94 % ee material (HPLC).



(*2R,3R*)-ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-hexylaziridine-2-carboxylate 37k: To a 25 mL flame-dried home-made Schlenk flask (see Figure 2.3) equipped with a stir bar and flushed with argon was added (*S)*-VANOL (16 mg, 0.3 mmol) and $B(OPh)_3$ (35 mg, 0.12 mmol). Meanwhile, to the flask containing imine **36k** (396 mg, 1.0 mmol, see page 80 for its synthesis) was added dry toluene (1.5 mL) and the resultant toluene solution of imine **36k** was then directly transferred from the reaction flask in which it was prepared to the flask containing the ligand and $B(OPh)_3$. The flask, which had imine **36k**, was then rinsed with toluene (0.5 mL) and the rinse was transferred to the flask containing the ligand and $B(OPh)_3$ under argon flow through the side-arm of the Schlenk flask. The flask was sealed by closing the Teflon valve, and then placed in an 80 ºC oil bath for 1 h. The catalyst mixture was then allowed to cool to room temperature and opened to argon through the side arm of the Schlenk flask. To this solution was rapidly added ethyl diazoacetate (EDA) **11** (124 μL, 1.2 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 24 h at room temperature. The reaction was diluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round bottom flask. The reaction flask was rinsed with dichloromethane (5 mL X 2) and the rinse was added to the 100 mL round bottom flask. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 5 min to afford the crude aziridine as a pale yellow semi solid. Purification of the crude aziridine by silica gel chromatography (35 mm × 400 mm column, 4:2:0.1 hexanes / CH_2Cl_2 /EtOAc as eluent, gravity column) afforded pure *cis*-aziridine **37k** as a semi solid in 64 % isolated yield (308 mg, 0.64 mmol); *cis/trans*: not determined. Enamine side products: 10 % yield of **67k** and 0 % yield of **68k**. The optical purity of **37k** was determined to be 86% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.27 min (major enantiomer, **37k**) and R_t= 11.17 min (minor enantiomer, *ent*-**37k**).

Spectral data for **37k**: R_f = 0.30 (4:2 hexane/CH_2Cl_2); **^{1}H-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 *sp3* 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); $[\alpha]_D^{23}$ +78.3 (c 1.0, CH_2Cl_2) on 90 % ee material (HPLC).

2.8.10 General Procedure for the deprotection of *N*-MEDAM aziridines 37 to give N-H aziridines 59 - Illustrated for the synthesis of (2*R*,3*R*)-ethyl 3-phenylaziridine-2-carboxylate 59a:

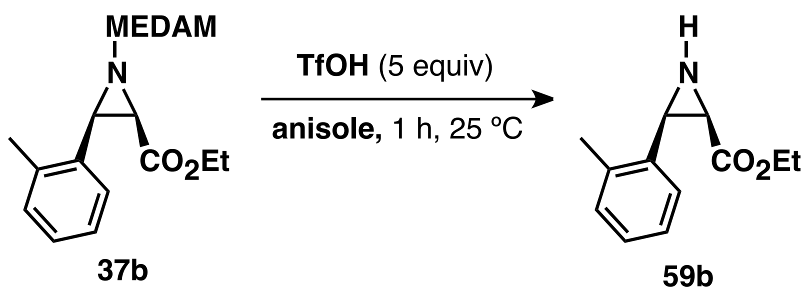


37a **59a**

(2*R*,3*R*)-ethyl 3-phenylaziridine-2-carboxylate 59a: To a 25 mL flame-dried round bottom flask filled with argon was added aziridine **37a** (237 mg, 0.5 mmol, 99% ee) and anisole (5.4 mL, freshly distilled) at room temperature. The flask was cooled to 0 ºC and triflic acid (200 μL, 2.5 mmol) was added. The ice-bath was removed and the reaction mixture was stirred for 2 h. The reaction mixture was quenched by addition of saturated aqueous Na_2CO_3 solution until the pH was greater than 9. After addition of ether (3 mL) and water (1 mL), the organic layer was separated and the water layer was extracted with ether (5 mL × 3). The combined organic layer was washed with saturated aqueous NaCl solution (10 mL × 3) and dried over anhydrous $MgSO_4$. The ether was removed by rotary evaporation and most of the anisole was removed by high vacuum for a short period of time (~ 15 min) leaving an off-white sticky residue. Exposure to high vacuum for extended periods results in loss of **59a** to sublimation. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether / hexanes as eluent) afforded **59a** as a white solid (mp 58-59 ºC) in 95% isolated yield (91 mg, 0.475 mmol). The optical purity of **59a** was determined to be 99% *ee* by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexane/2-

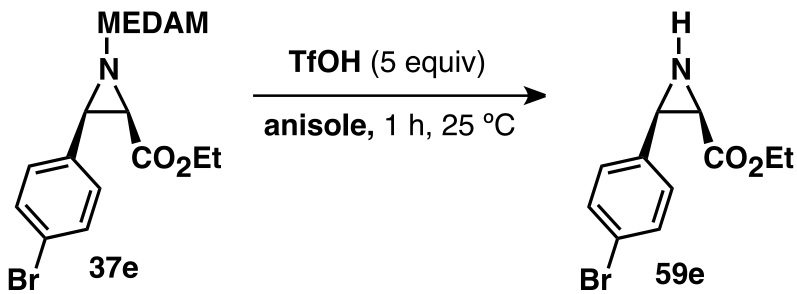
propanol at 228nm, flow-rate: 1.0 mL/min): retention times; R_t = 3.99 min (major enantiomer, **12a**) and R_t = 3.47 min (minor enantiomer, *ent*-**59a**).

Spectral data for **59a**: R_f = 0.13 (1:1 Et_2O/hexane); **^{1}H-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-NMR** ($CDCl_3$, 75 MHz) δ 13.90, 29.65, 37.14, 61.07, 127.47, 127.62, 128.01, 134.80, 169.02; $[\alpha]_D^{23}$ −12.4 (*c* 1.0, EtOAc) on 99% ee material (HPLC). These spectral data match those previously reported for this compound.[5]



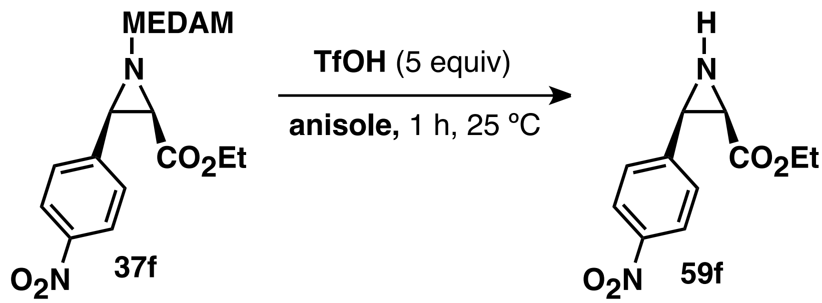
(*2R,3R*)-ethyl 3-(*o*-tolyl)aziridine-2-carboxylate 59b: Aziridine **37b** (244 mg, 0.5 mmol, 99 % ee) was reacted according to the general method described above except that the reaction time was 1 h. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether / hexanes as eluent) afforded **59b** as a white solid (mp 84.5-85.5 ºC) in 97% isolated yield (100 mg, 0.485 mmol). The optical purity of **59b** was determined to be 99% *ee* by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexane/2-propanol at 228nm, flow-rate: 0.7 mL/min): retention times; R_t = 6.4 min (major enantiomer, **59b**) and R_t = 5.5 min (minor enantiomer, *ent*-**59b**).

Spectral data for **12b**: R_f=0.11 (1:1 Et_2O/hexane); ^{1}**H-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-NMR** ($CDCl_3$, 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; $[\alpha]_D^{23}$ –96.9 (*c* 1.0, EtOAc) on 99% ee material (HPLC). These spectral data match those previously reported for this compound.[5]



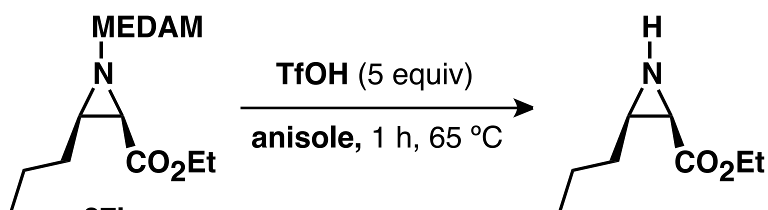
(*2R,3R*)-ethyl 3-(4-bromophenyl)aziridine-2-carboxylate 59e: Aziridine **37e** (276 mg, 0.5 mmol, 99.5 % ee) was reacted according to the general method described above except that the reaction time was 1 h. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether / hexanes as eluent) afforded **59e** as a white solid (mp 78.5-79 ºC) in 96% isolated yield (130 mg, 0.48 mmol). The optical purity of **59e** was determined to be 99.5% *ee* by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexane/2-propanol at 228nm, flow-rate: 0.7 mL/min): retention times; R_t = 8.24 min (major enantiomer, **59e**) and R_t = 7.07 min (minor enantiomer, *ent*-**59e**).

Spectral data for **59e**[5]: R_f = 0.12 (1:1 Et_2O/hexane); **^{1}H-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-NMR** ($CDCl_3$, 75 MHz) δ 13.88, 37.05, 38.98, 61.06, 121.45, 129.18, 130.98, 133.85, 168.62; $[\alpha]_D^{23}$ +11.92 (*c* 1.0, EtOAc) on 99.5% ee material (HPLC). These spectral data match those previously reported for this compound.[5]



(2*R*,3*R*)-ethyl 3-(4-nitrophenyl)aziridine-2-carboxylate 59f: Aziridine **37f** (259 mg, 0.5 mmol, 97 % ee) was reacted according to the general method described above except that the reaction time was 1 h. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether / hexanes as eluent) afforded **59f** as a white solid (mp 89-90.5 ºC) in 97% isolated yield (115 mg, 0.485 mmol). The optical purity of **59f** was determined to be 97% *ee* by HPLC analysis (CHIRALCEL OD-H column, 90:10 hexane/2-propanol at 228nm, flow-rate: 0.7 mL/min): retention times; R_t = 13.75 min (major enantiomer, **59f**) and R_t = 11.92 min (minor enantiomer, *ent*-**59f**).

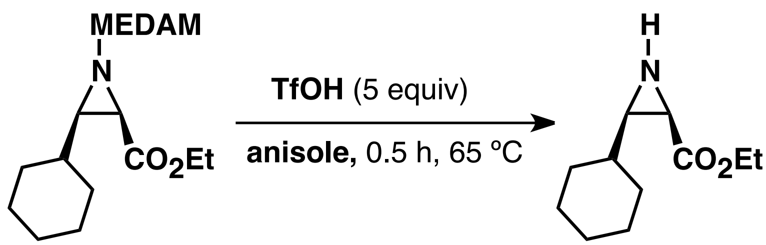
Spectral data for **59f**: R_f = 0.07 (1:1 Et_2O/hexane); ^{1}**H-NMR** ($CDCl_3$, 300 MHz) δ 1.01 (t, 3H, *J* = 7.1 Hz), 1.80 (br, s, 1H), 3.13 (d, 1H, *J* = 6.3 Hz), 3.56 (d, 1H, *J* = 6.6 Hz), 3.92-3.97 (m, 2H), 7.54 (d, 2H, *J* = 8.3 Hz), 8.15 (d, 2H, *J* = 8.8 Hz); ^{13}**C-NMR** ($CDCl_3$, 75 MHz) δ 13.80, 29.45, 37.39, 61.09, 122.94, 128.55, 142.58, 147.08, 168.08; $[\alpha]_D^{23}$ –15.6 (*c* 1.0, EtOAc) on 97% ee material (HPLC). These spectral data match those previously reported for this compound.[5]



37h → **59h**

(2*R*,3*R*)-ethyl 3-propylaziridine-2-carboxylate 59h: Aziridine **37h** (220 mg, 0.5 mmol, 93% ee) was reacted according to the general method described above except that the reaction time was 1 h, the reaction temperature was 65 ºC and an air condenser was utilized. Purification by silica gel chromatography (18 mm × 230 mm, 1:3 ether / pentane as eluent) afforded **59h** as a light yellow liquid in 72% isolated yield (57 mg, 0.36 mmol). The optical purity of **59h** was determined to be 93% *ee* by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 5.06 min (major enantiomer, **59h**) and R_t = 5.88 min (minor enantiomer, *ent*-**59h**). The yield of **59h** was determined to be 76% by ^{1}H NMR analysis of the crude reaction mixture with Ph_3CH as internal standard.

Spectral data for **59h**: R_f = 0.13 (1:1 Et_2O/hexane); ^{1}**H-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-NMR** ($CDCl_3$, 75 MHz) δ 13.46, 13.99, 20.73, 29.60, 34.27, 38.31, 60.97, 170.73. These spectral data match those previously reported for this compound.[5]

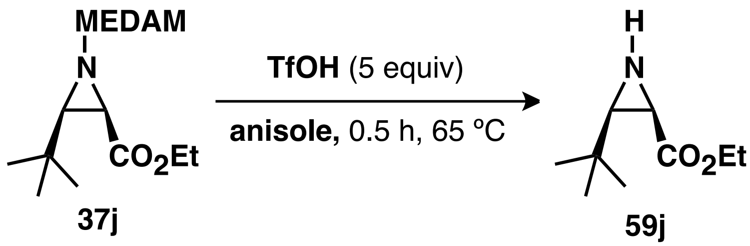


37i 59i

(2*R*,3*R*)-ethyl 3-(4-nitrophenyl)aziridine-2-carboxylate 59i: Aziridine **37i** (240 mg, 0.5 mmol, 99 % ee) was reacted according to the general method described above except that the reaction time was 0.5 h, the reaction temperature was 65 ºC and an air condenser was utilized. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether / hexanes as eluent) afforded **59i** as a white solid (mp 58-59 ºC) in 90% isolated yield (89 mg, 0.45 mmol). The optical purity of **59i** was determined to be 99% *ee* by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexane/2-propanol at 228nm, flow-rate: 1.0 mL/min): retention times; R_t = 3.99 min (major enantiomer, **59i**) and R_t = 3.47 min (minor enantiomer, *ent*-**59i**).

Spectral data for **59i**: R_f = 0.19 (1:1 Et_2O/hexane); ^{1}**H-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-NMR** ($CDCl_3$, 75 MHz) δ

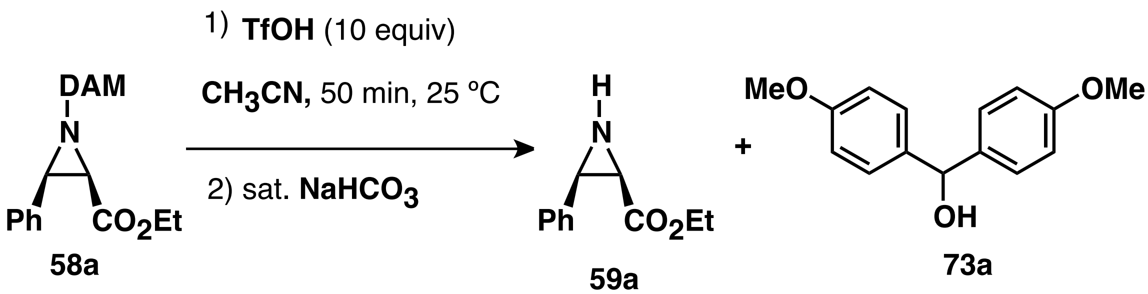
14.14, 25.39, 25.40, 26.01, 30.84, 31.61, 34.24, 36.91, 43.98, 61.06, 170.95; $[\alpha]_D^{23}$ –62.3 (*c* 1.0, EtOAc) on 99% ee material (HPLC). These spectral data match those previously reported for this compound.[5]



(2*R*,3*R*)-ethyl 3-(*tert*-butyl)aziridine-2-carboxylate 59j: Aziridine **37j** (227 mg, 0.5 mmol, 99 % ee) was reacted according to the general method described above except that the reaction time was 0.5 h, the reaction temperature was 65 ºC and an air condenser was utilized. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether / hexanes as eluent) afforded **59j** as colorless oil in 88% isolated yield (75 mg, 0.44 mmol). The optical purity of **59j** was determined to be 97% *ee* by HPLC analysis (CHIRALCEL OD-H column, 99:1 hexane/2-propanol at 228nm, flow-rate: 1.0 mL/min): retention times; R_t = 9.95 min (major enantiomer, **59j**) and R_t= 8.38 min (minor enantiomer, *ent*-**59j**).

Spectral data for **59j**: R_f = 0.10 (1:1 Et_2O/hexane); **^{1}H-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-NMR** ($CDCl_3$, 75 MHz) δ 14.00, 27.42, 31.46, 35.25, 47.36, 60.98, 170.20; $[\alpha]_D^{23}$ –23.7 (*c* 1.0, EtOAc) on 97% ee material (HPLC). These spectral data match those previously reported for this compound.[5]

2.8.11 Procedure for the deprotection of aziridines 58a and 37a and trapping of dianisyl cation to give *N*-H aziridines 59a and alcohol 73.

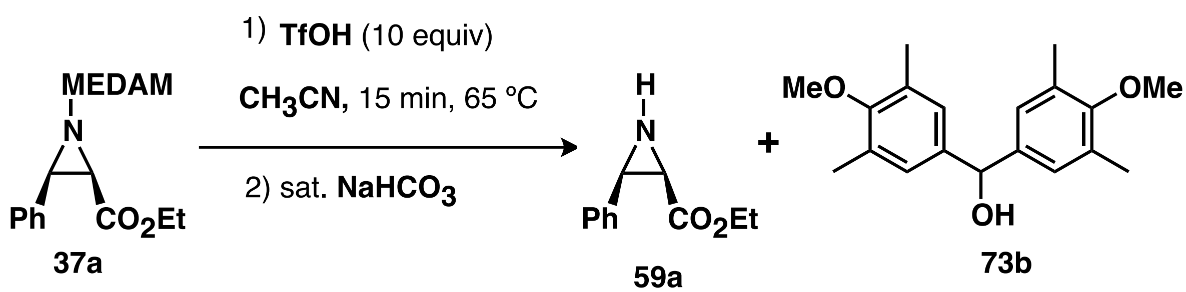


(2*R*,3*R*)-ethyl 3-phenylaziridine-2-carboxylate 59a: To a 25 mL flame-dried round bottom flask filled with argon was added aziridine **58a** (209 mg, 0.5 mmol, 98% ee) and acetonitrile (5.0 mL, freshly distilled) at room temperature. The flask was cooled to 0 ºC and triflic acid (400 μL, 5.0 mmol) was added. The ice-bath was removed and the reaction mixture was stirred for 50 min at room temperature. The reaction mixture was quenched by addition of saturated aqueous Na_2CO_3 solution until the pH was greater than 9. After addition of ether (3 mL) and water (1 mL), the organic layer was separated and the water layer was extracted with ether (5 mL × 3). The combined organic layer was washed with saturated aqueous NaCl solution (10 mL × 3) and dried over anhydrous $MgSO_4$. The ether was removed by rotary evaporation and most of the anisole was removed by high vacuum for a short period of time (~ 15 min) leaving an off-white sticky residue. Exposure to high vacuum for extended periods results in loss of **59a** to sublimation. Purification by silica gel chromatography (18 mm × 230 mm, 1:1 ether / hexanes as eluent) afforded **59a** as a white solid (mp 58-59 ºC) in 86% isolated yield (82 mg, 0.43 mmol) and bis(4-methoxyphenyl)methanol **73a** in 62 % yield (76 mg, 0.31 mmol) as white solid (mp

69-70 ºC). The optical purity of **59a** was determined to be 99% *ee* by HPLC analysis (CHIRALCEL OD-H column, 98:2 hexane/2-propanol at 228nm, flow-rate: 1.0 mL/min): retention times; R_t = 3.99 min (major enantiomer, **12a**) and R_t = 3.47 min (minor enantiomer, *ent*-**59a**).

Spectral data for **59a**: R_f = 0.13 (1:1 Et_2O/hexane); **^{1}H-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-NMR** ($CDCl_3$, 75 MHz) δ 13.90, 29.65, 37.14, 61.07, 127.47, 127.62, 128.01, 134.80, 169.02; $[\alpha]_D^{23}$ −12.4 (*c* 1.0, EtOAc) on 99% ee material (HPLC). These spectral data match those previously reported for this compound.[5]

Spectral data for **73a:** R_f = 0.42 (1:3 EtOAc/hexanes); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 2.08 (d, 1H, *J* = 2.3 Hz), 3.76 (s, 6H), 5.76 (d, 1H, *J* = 2.3 Hz), 6.84 (d, 4H, *J* = 9.0 Hz), 7.25 (d, 4H, *J* = 8.8 Hz); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 55.22, 75.30, 113.79, 127.76, 136.47, 158.91.



The *N*-MEDAM aziridine **37a** (95 mg, 0.2 mmol) was reacted with triflic acid (160 μL, 2.0 mmol 10.0 equiv) in acetonitrile / water medium following the procedure described above for the reaction of *N*-DAM aziridine **58a** except the reaction temperature was 65 ºC. The reaction resulted *N*-H aziridine **59a** and alcohol **73b** in 86% yield and 40% yield respectively as determined by ^{1}H NMR with Ph_3CH as internal standard.

Spectral data for **73b:** **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.26 (d, *J* = 1.8 Hz, 1H), 2.27 (s, 12H), 3.70 (s, 6H), 5.62 (s, 1H), 7.01 (s, 4H).

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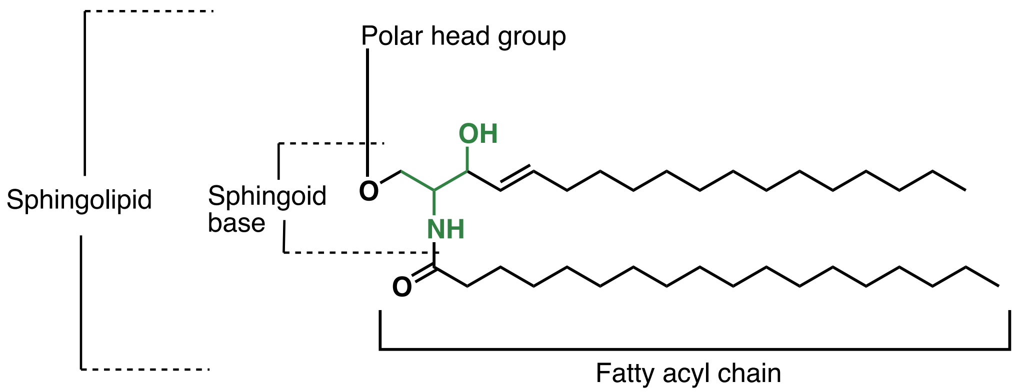
CHAPTER 3

APPLICATION OF THE CATALYIC ASYMMETRIC AZIRIDINATION REACTION: SYNTHESIS OF ALL FOUR ISOMERS OF SPHINGANINE

3.1 Biological properties of sphinganies

The sphingolipids are essential components of the plasma membrane of eukaryotic cells. They are most abundant in mammalian cells.[1] They are also found in plants,[2] marine organisms,[3] bacteria and fungi[4] . They play an important role in many physiological processes including molecular and cellular recognition, signal transduction and modulation of immune response.[5] The error in their metabolism is associated with several diseases including diabetes,[6] cancer,[7] Alzheimer's disease,[8] infection by microorganisms,[9] heart disease[10] and many others. Structurally, sphingolipids consist of three distinct subunits (Figure 3.1), a) the hydrophilic headgroup which can be a saccharide, phosphate or sulfate and which is predominantly located on the external surface of the membrane. b) The lipophilic fatty acyl chain that acts as a membrane membrane anchor. c) The sphingoid base to which the fatty acyl chain is linked *via* an amide bond.

Figure 3.1 Subunits of sphingolipids



The sphingoid bases are often called 'long-chain bases'[11] and are known to contain hundreds of different amino alcohols.[12] The sphingosines **76**, sphinganines **74** (dihydrosphingosines) and phytosphingosines **75** (Figure 3.2) are the most common long-chain structural constituents of sphingolipids. Despite their structural diversity, naturally occurring sphingoid bases share a common (2*S*,3*R*)-D-*erythro* amino alcohol moiety as shown in Figure 3.2A.

Figure 3.2 A list of: (A) naturally occurring sphingoid bases. (B) Unnatural isomers of sphinganine **74**

(A)

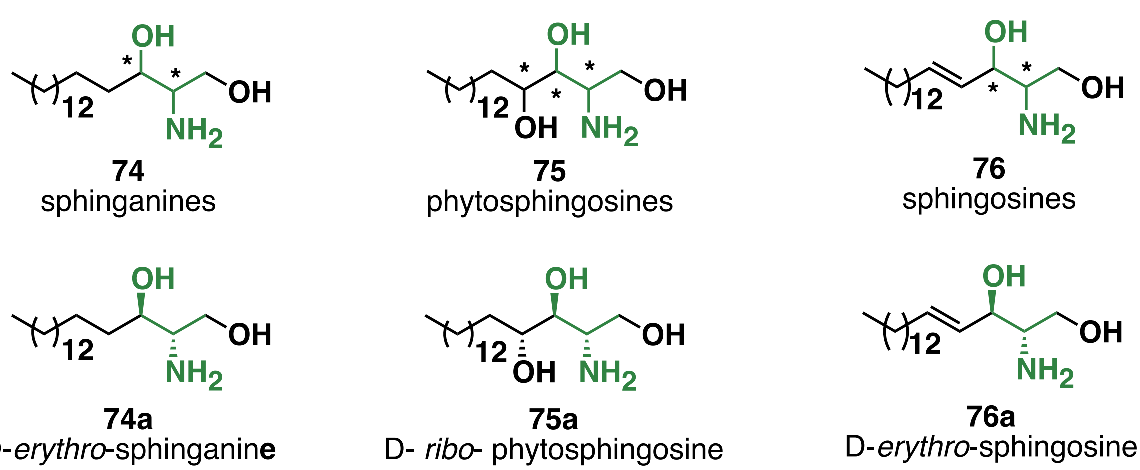
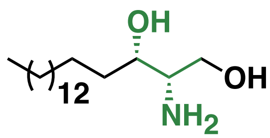
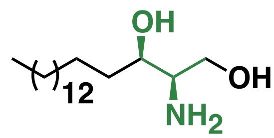


Figure 3.2 (cont'd)

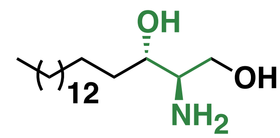
(B)



74b
L-*threo*-sphinganine



74c
D-*threo*-sphinganine



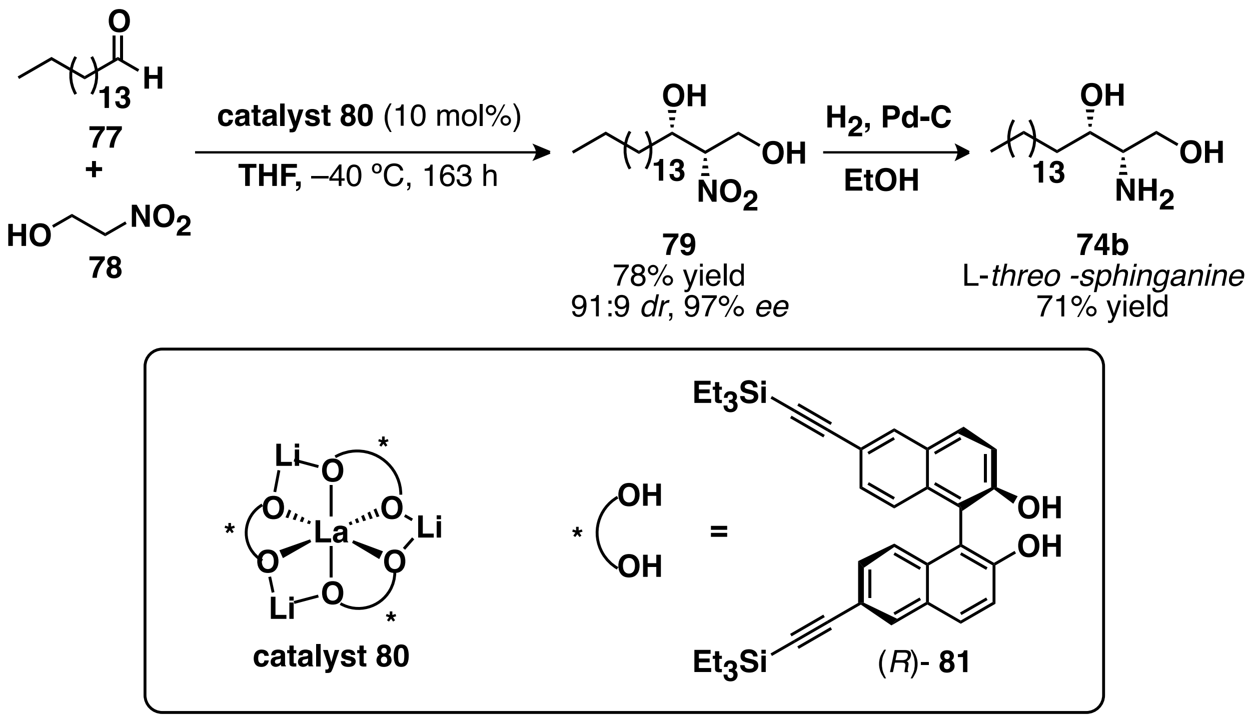
74d
L-*erythro*-sphinganine

However, it has been found that stereochemistry plays a vital role in their biological activities. For example, the L-*threo* isomer of sphinganine, which is also known as safingol **74b** (Figure 3.2B), is an antipsoriatic and antineoplastic drug[13] and has the ability of inhibiting protein kinase C[14]. Since, the biological activity can be heavily dependent on the stereochemistry, all four isomers of sphingosines and sphiganines have been previously synthesized and their biological activity has been investigated.[11a,12]

3.2 Previous approaches towards the synthesis of sphinganines

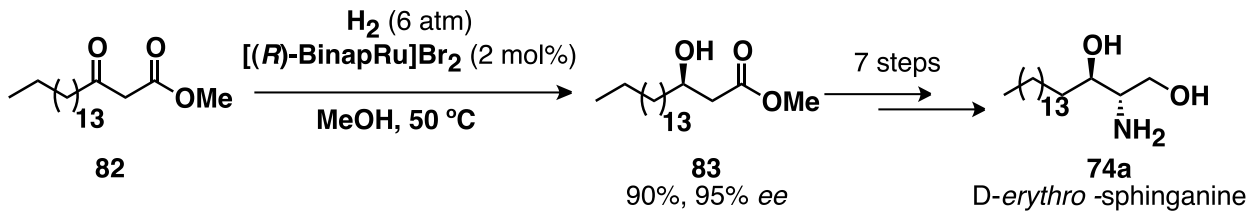
Approaches to the preparation of sphinganines has been recently reviewed by Howell *et. al.* in 2004,[15] which covers the period starting from the first synthesis in 1951 up to 2004. After 2004 many other syntheses of sphinganines have been reported.[16] The early reports of sphinganine syntheses were non-selective and involved separation of diastereomers and resolution of enantiomers from mixtures. Until now very few syntheses of sphinganines involving asymmetric catalytic reactions have been reported. In 1995, Shibasaki *et. al.* reported the shortest synthesis (two steps from hexadecanal) of sphinganine, which involves an asymmetric catalytic nitro aldol reaction (Henry reaction) as the key step (Scheme 3.1)[17].

Scheme 3.1 L-*threo*-sphinganine **74b** synthesis *via* asymmetric catalytic nitro aldol reaction



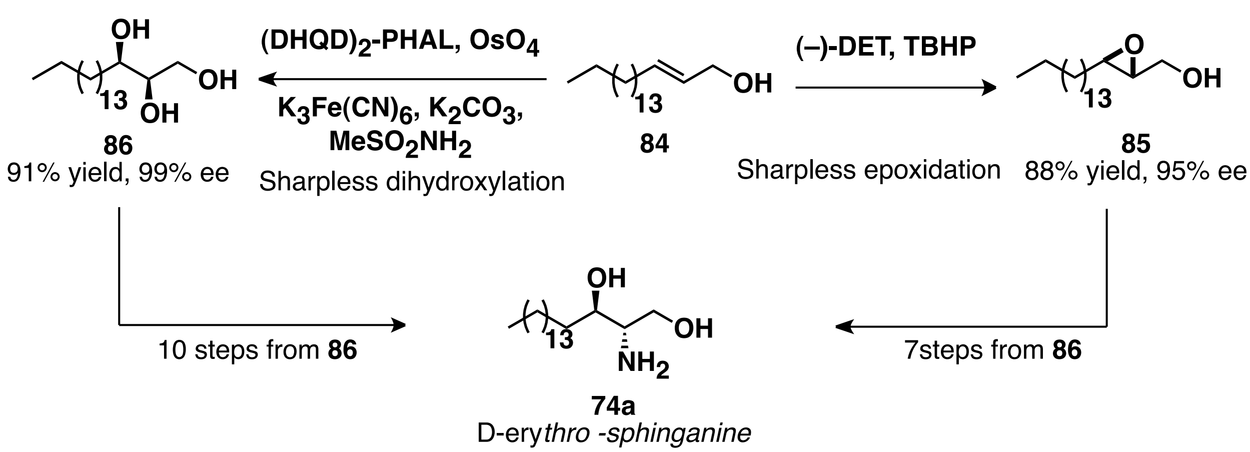
This reaction resulted in very good diastereoselectivity (91:9) and good asymmetric induction (97% ee). The reaction is limited since it only useful for producing one diastereomer and because very long reaction times are required (163 h or ~ 7 days). Later, it was found that this method was impractical to perform on large scale (100 g).[16l] Recently, in 2010 another synthesis of sphinganine was reported which involves catalytic asymmetric hydrogenation of *β*-ketoester **82**[16k] (Scheme 3.2). However, this synthesis is not amenable to both diastereomers.

Scheme 3.2 D-*erythro*-sphinganine **74a** synthesis *via* asymmetric catalytic hydrogenation



The Sharpless asymmetric dihydroxylation and Sharpless asymmetric epoxidation are the most successful catalytic asymmetric approaches towards the synthesis of sphinganines (Scheme 3.3).[15] However, the syntheses of all four isomers of sphinganines were not demonstrated by these methods.

Scheme 3.3 D-*erythro*-sphinganine **74a** synthesis *via* Sharpless asymmetric dihydroxylation and epoxidation

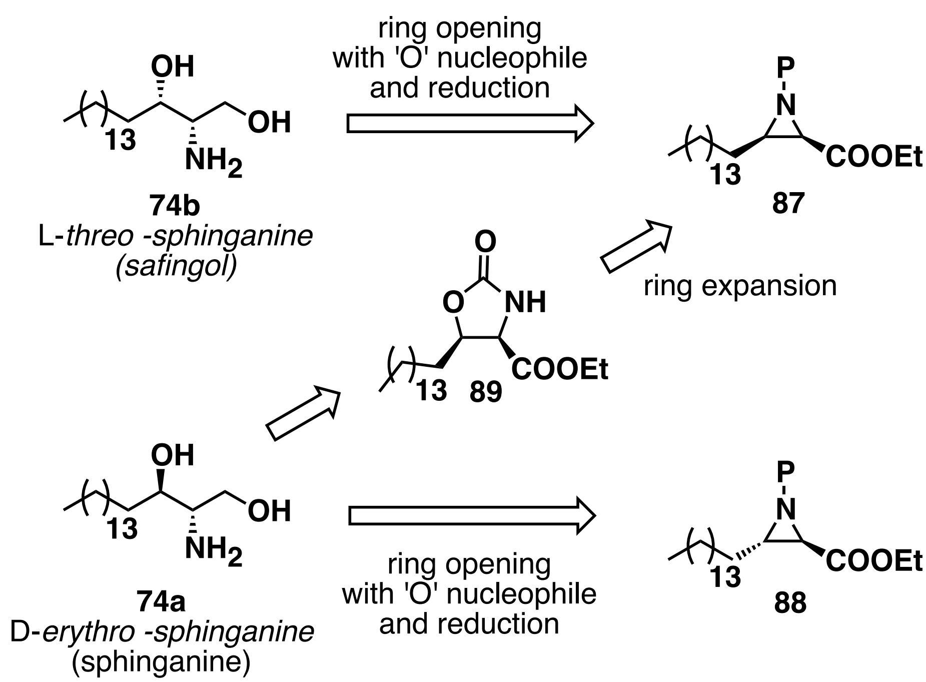


The aim of the present work is to synthesize all four isomers of sphinganines *via* the catalytic asymmetric aziridination reaction.

3.3 Retro-synthetic analysis of sphinganines

A retro-synthetic analysis of the four stereoisomers of sphinganines is presented in Scheme 3.4. The synthesis of *threo*-isomer **74b** and its enantiomer could be possible *via* the ring opening of the appropriate *cis*-aziridines **87** with an oxygen nucleophile. Similarly the ring opening of appropriate *trans*-aziridine **88** with an oxygen nucleophile should lead to the *erythro*-isomer **74a** and its enantiomer. Alternatively, the synthesis of the *erythro*-isomer can be planned *via* the ring expansion of *N*-Boc-protected aziridines to the oxazolidinone **89**. Subsequent hydrolysis of oxazolidinone **89** and reduction of the corresponding ester should give the *erythro*- isomer **74a**.

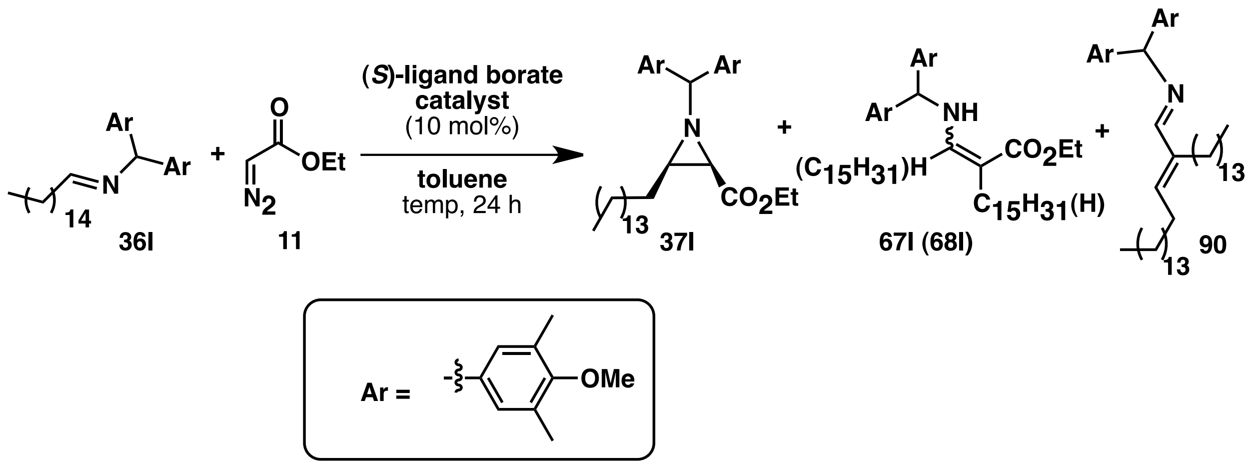
Scheme 3.4 Retro-synthetic analysis*:* *erythro*-sphinganine and *threo*-sphinganine



3.4 Synthesis of aziridine 37l *via* catalytic asymmetric *cis*-aziridination

The requisite aziridine **37l** was synthesized from *N*-MEDAM imine **36l** (Table 3.1) derived from hexadecanal **77**.

Table 3.1 Asymmetric aziridination with alkyl imine **36l** [a]



entry	ligand	temp(ºC)	% yield *cis*-**37l**[c]	% ee *cis*-**37l**[d]	% yield **67l (68l)**[e]	% yield **90**[f]
1	(*R*)-VANOL	25	40	–88	nd	20
2	(*S*)-VAPOL	25	40	88	0 (4)	18
3[b]	(*S*)-VAPOL	0	60	90	5 (4)	10

[a] Unless otherwise specified, all reactions were carried out with 1.0 mmol of **36l** at 0.5 M in toluene with 1.2 equiv of **11** at 25 °C and went to completion in 24 h. The ligand-borate catalyst was prepared by heating the mixture of the ligand and 4 equiv of commercial B(OPh)$_3$ at 80 ºC for an hour followed by the subsequent removal of volatiles on exposure to vacuum. [b] imine **36l** was directly transferred to the catalyst through filter syringe (see experimental for Chapter 3) [c]

Table 3.1 (cont'd)

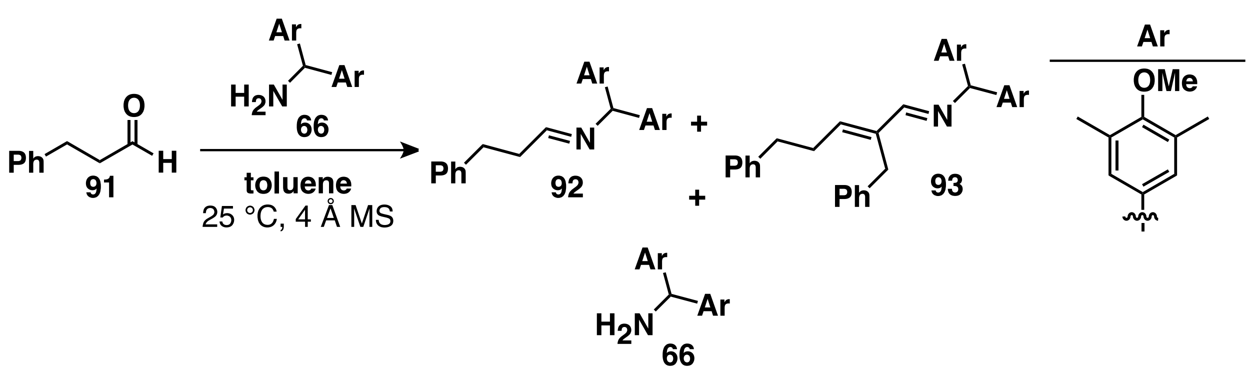
Isolated yield of *cis*-**37l** after chromatography on silica gel. [d] Determined on purified *cis*-**37l** by HPLC on a PIRKLE COVALENT (R, R) WHELK-O1 column. [e] Determined by integration of the NH signals of **67l** and **68l** relative to the methine proton of *cis*-**37l** in the ^{1}H NMR spectrum of the crude reaction mixture. [f] Determined by integration of the γ *sp2* C-H signal of the conjugated imine **90** relative to the methine proton of *cis*-**37l** in the ^{1}H NMR spectrum of the crude reaction mixture.

The reaction with isolated impure imine **36l** in the presence of both VAPOL and VANOL derived catalysts resulted in poor yield (40%) and moderate asymmetric induction (88% ee) at room temperature (Table 3.1, entries 1 and 2). It was found that the imines derived from aliphatic aldehydes tend to decompose while kept under vacuum. To minimize the decomposition of imine **36l**, the imine was directly transferred without being isolated to a flask containing the ligand borate catalyst with the help of a filter syringe. With this method an improved yield (60%) and asymmetric induction (90% ee) was observed (Table 3.1 entry 3) at 0 ºC. In all these reactions substantial amounts of the conjugated imine **90** was formed which is a self-condensation product of imine **36l** (similar to the reaction shown in Scheme 3.5). This mixture of species produced in this process appears to stop the reaction probably due to binding of one or more of these species to the active catalyst. This imposes a serious limitation on the utilization of the aziridination reaction with aliphatic imines.

3.5 Synthesis of aziridine starting material *via* multi-component catalytic asymmetric *cis*-aziridination

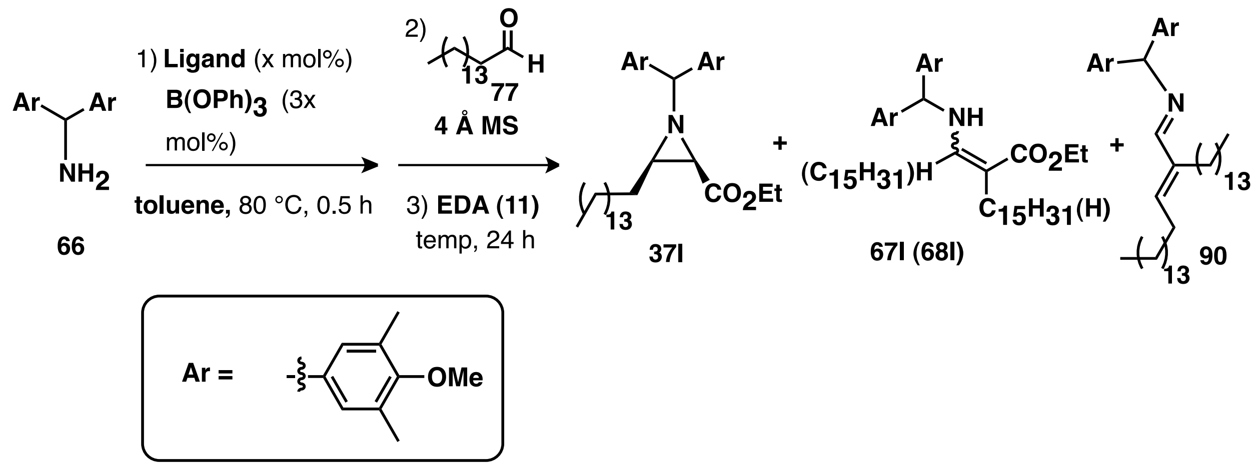
In the process of dealing with this problem with aliphatic imines, a multi-component catalytic asymmetric aziridination reaction was developed by Anil Gupta, a current group member.[18] The obvious advantage of this multi-component protocol is that the imine preparation step can be avoided. Moreover, the process of aziridination became more operationally simplified. The scope of the aziridination reaction is now broadened to include the unstable imines that cannot be purified. In many cases no aziridine product was observed when the aziridination was attempted starting from pre-formed imines derived from unbranched aliphatic aldehydes. It was found in these cases, that the imines couldn't be generated in a clean fashion. For example, treatment of aldehyde **91** with MEDAM amine **66** generates conjugated imine **93** long before complete formation of imine **92** can be realized (Scheme 3.5).[18]

Scheme 3.5 Self-condensation of imine **91**



The multi-component aziridination reaction provides an effective solution to the long-standing problem with imines derived from unbranched aliphatic aldehydes encountered in two-component methods. The multi-component aziridination protocol was employed to synthesize the requisite aziridine **37l** for the synthesis of sphinganines (Table 3.2).

Table 3.2 Multi-component catalytic asymmetric aziridination with hexadecanal **77** [a]



entry	ligand	catalyst x mol%	Temp (ºC)	equiv **11**	% yield **37l** [b]	% ee **37l** [c]	% yield **67l (68l)** [e]	% yield **90** [f]
1	(*S*)-VAPOL	10	0	1.2	70	95	9.0 (6.0)	6.0
2	(*S*)-VAPOL	10	–10	1.2	80	96	nd	< 1.0
3 [d]	(*S*)-VAPOL	10	–10	2.0	85	95	0.0 (3.0)	< 1.0
4 [g]	(*S*)-VAPOL	10	–10	2.0	90	96	1.0 (1.0)	< 1.0
5 [g]	(*S*)-VAPOL	5	–10	2.0	85	96	1.7 (1.7)	< 1.0
6 [g]	(*S*)-VAPOL	10	–20	2.0	85	95	nd	< 1.0
7 [g]	(*S*)-VANOL	10	–10	2.0	85	95	1.7 (nd)	< 1.0

[a] Unless otherwise specified, all reactions were performed with 0.5 mmol amine **66** (0.5 M in

Table 3.2 (cont'd)

toluene) and 1.05 equiv of *n*-hexadecanal **77** and 1.2 equiv EDA **11** and went to 100% completion. Before adding the aldehyde and EDA **11** a solution of amine **66** with x mol% ligand and 3x mol% $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen. nd = not determined. [b] Isolated yield after chromatography on silica gel. [c] Determined on purified *cis*-**37l** by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. [d] The scale of the reaction was 4.5 mmol. [e] Determined by integration of the NH signals of **67l** and **68l** relative to the methine proton of *cis*-**37l** in the ^{1}H NMR spectrum of the crude reaction mixture. [f] Determined by integration of the γ *sp2* C-H signal of the conjugated imine **90** relative to the methine proton of *cis*-**37l** in the ^{1}H NMR spectrum of the crude reaction mixture. [g] concentration of the reaction was 0.2M in amine **66** and the aldehyde **77** was added in as a solution in toluene.

There is a significant enhancement in both yield (70%) and asymmetric induction (95% ee) observed when the aziridination reaction was performed *via* the multi-component protocol with the VAPOL derived catalyst keeping the other variables constant (Table 3.2 entry 1 *vs* Table 3.1 entry 3). The yield of the reaction could be further improved to 80% - 85% by lowering the temperature from 0 ºC to –10 ºC and by increasing the amount of ethyl diazoacetate **11** from 1.2 equiv to 2.0 equiv (Table 3.2, entries 2 and 3). There is a slight increase in yield (90%) observed after diluting the reaction mixture from 0.5M to 0.2 M in concentration (Table 3.2, entries 3 *vs.* 4). There was no significant effect observed on the reaction when the temperature was decreased to –20 ºC (Table 3.2, entry 6). The VANOL derived catalyst shows essentially the same reactivity and asymmetric induction (Table 3.2, entry 7) as the VAPOL derived catalyst.

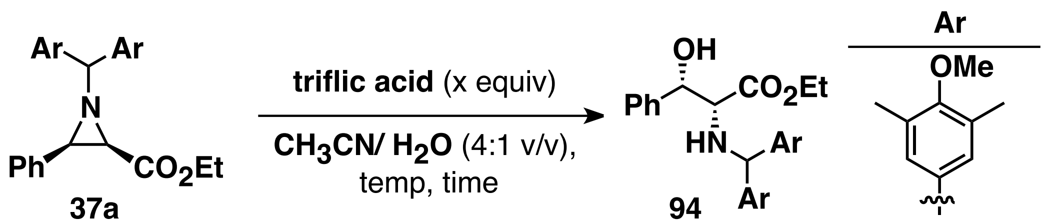
Moreover, the catalyst loading can be decreased to 5 mol% without any detrimental effect on the asymmetric induction (Table 3.2, entry 5). Further, the optical purity of the aziridine **37l** (96% ee) can be improved to 98% ee by single crystallization from hexanes (80% yield).

3.6 Ring opening of *cis*-aziridine with oxygen nucleophile

It was mentioned in the retro synthetic analysis of sphinganines that isomers **74b** and its enantiomer with relative *syn*-stereochemistry should be possible *via* ring opening of the appropriate *cis*-aziridine with oxygen nucleophile.

The phenyl aziridine **37a** was used as the model system to study the ring opening of the *N*-MEDAM aziridines with oxygen nucleophiles. In previous studies of trapping the MEDAM cation (Chapter 2) with water, it was observed that in an acidic medium water cause opening of the aziridine ring. Encouraged by this observation, the ring opening of aziridine **37a** was examined in the presence of water in a highly acidic medium.

Table 3.3 Ring opening of aziridine **37a** with water in acidic medium [a]



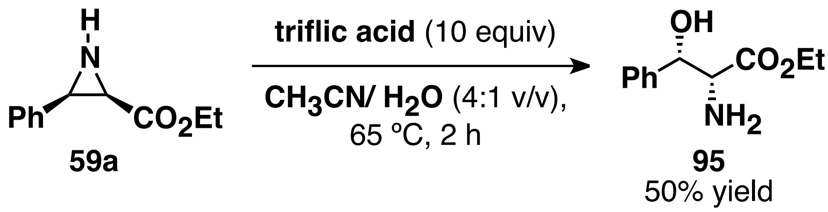
entry	conc (M)	triflic acid (x equiv)	temp (ºC)	time (h)	% yield **94** (NMR) [b]
1	0.2	10	50	4	50
2 [c]	0.2	5	25	24	nd
3 [c]	0.4	5	25	24	nd
4	0.4	5	50	4	60

Table 3.3 (cont'd)

[a] Unless otherwise specified, all reactions were performed with 0.2 mmol aziridine **37a** and triflic acid in acetonitrile water mixture (4:1 v/v) and went to 100% completion. nd = not determined. [b] NMR yield with Ph_3CH as internal standard. [c] the reaction was not complete after 24 h.

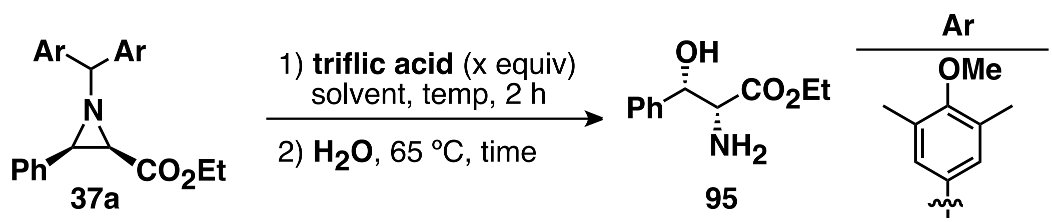
The aziridine **37a** was treated with 10 equiv of triflic acid in an acetonitrile and water (4:1 v/v) mixture at 50 ºC (Table 3.3, entry 1). As expected, ring opening with water was observed giving a 50 % yield of **94** as determined by ^{1}H NMR. The NMR yield was determined using Ph_3CH as internal standard. Some unidentified products were observed along with the ring-opened product. The reaction at room temperature was found to be incomplete even after 24 h when 5 equiv of triflic acid was employed (Table 3.3, entry 2). A similar observation was made when the concentration was increased to 0.4 M (Table 3.3, entry 3). The reaction went to completion at 50 ºC in the presence of 5 equiv of triflic acid giving a 60 % yield of **94** as determined by ^{1}H NMR at 0.4 M (in aziridine **37a**) concentration (Table 3.3, entry 4). At this point it was thought to modify the ring opening reaction conditions so as to effect the removal of the *N*-MEDAM group in a single step to produce the amino alcohol **95** with a free amine group. As a model reaction, the ring opening of the *N*-H aziridine **59a** was performed at 65 ºC in the presence of 10 equiv of triflic acid in acetonitrile-water (4:1 v/v) medium (Scheme 3.6). The reaction resulted in a 50% isolated yield of β-hydroxy-α-amino ester **95**. The lower yield for **95** compared to **94** could possibly be accounted for by the higher solubility of hydroxy amine **95** in water.

Scheme 3.6 Ring opening of *N*-H aziridine **59a** with water in acidic medium



The protocol was changed to reacting the aziridine **37a** with triflic acid in a dry solvent to deprotect the MEDAM group and then a workup with water to open the *N*-H aziridine ring. This led to amino alcohol **95** in 50% yield as determined by ^{1}H NMR (Table 3.4 entry 1). Similar results were observed when the solvent was changed to anisole (Table 3.4, entry 2).

Table 3.4 Ring opening of aziridine **37a** with water in acidic medium *via* deprotection of *N*-MEDAM group[a]

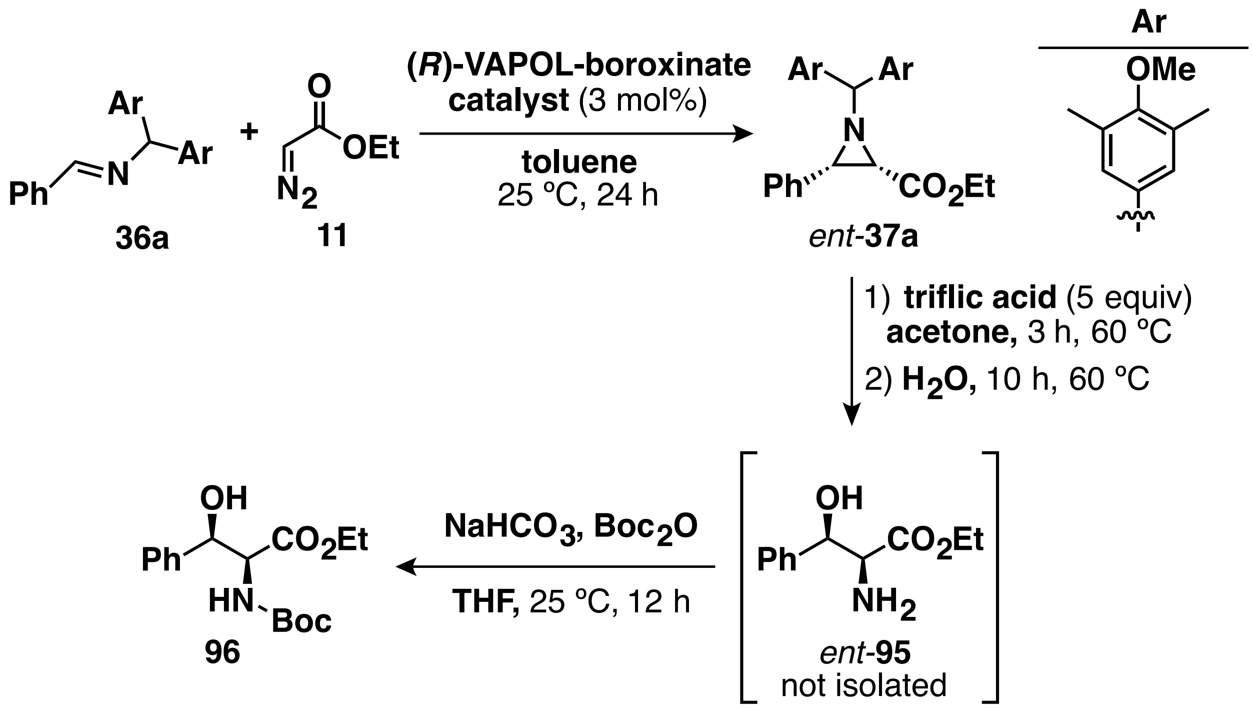


entry	solvent	triflic acid (x equiv)	temp (ºC)	time (h)	% yield **95** [b]
1	acetonitrile	10	65	3	50
2	anisole	5	25	5	55

[a] Unless otherwise specified, the first step of all reactions were performed with 0.2 mmol aziridine **37a** and triflic acid in dry solvent. In the following step water was added (solvent: water 4:1 v/v) and the reactions went to 100% completion. [b] NMR yield with Ph_3CH as internal standard.

To maximize the solubility of the β-hydroxy-α-amino ester **95** in organic solvent, it was thought to protect the free amine group with Boc. After a few attempts to optimize to the yield of the final product **96**, it was found that acetone is the optimum solvent for the deprotection followed by exposure to water to effect ring opening of the aziridine **37a** (Table 3.5).

Table 3.5 Synthesis of *N*-Boc-β-hydroxy-α-amino ester **96** from imine **36a** without isolation of intermediates [a]



Entry	Condition	Reaction scale (mmol)	% Yied **96** [b]
1	Pure **37a** used	2.0	(66) [d] 70 [c]
2	Crude **37a** used	5.0	63 [d]
3	Crude **37a** used	5.0	60 [e]

[a] Unless otherwise specified, the first step of all reactions were performed with aziridine **37a** (0.05 M) and 5 equiv of triflic acid in acetone. In the following step water was added (acetone:

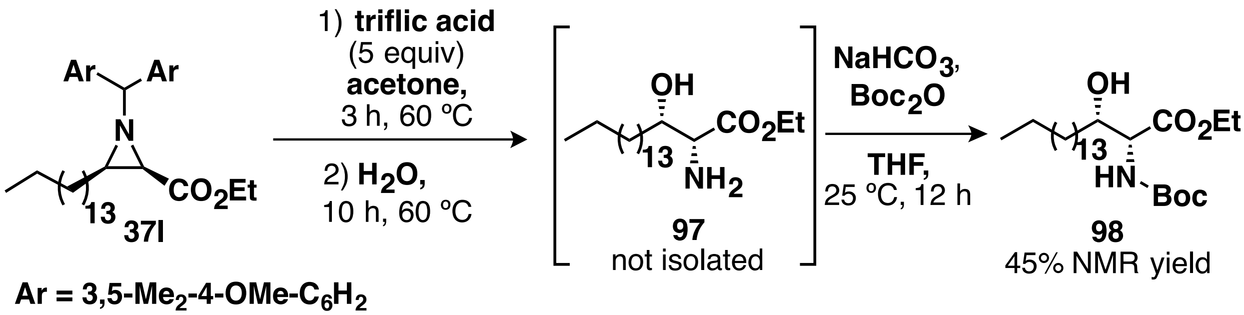
Table 3.5 (cont'd)

water 5:1 v/v) and the reactions went to 100% completion. After 10 h the volume of the reaction mixture was reduced to half of its original volume under reduced pressure and solid $NaHCO_3$ was added followed by Boc_2O. [b] Isolated yield after purification by column chromatography. [c] the yield was calculated from pure aziridine **37a**. [d] the yield was calculated from pure imine **36a**. [e] yield was calculated from amine **66** (aziridine **37a** was synthesized following the multi-component aziridination protocol)

Further, it was envisioned that the crude aziridine *ent*-**37a** could also be subjected to the deprotection and ring opening sequence mediated by triflic acid and water. This process would directly yield the optically pure *N*-Boc-*β*-hydroxy-*α*-amino ester **96** without any isolation and purification of intermediates. The *N*-MEDAM aziridine *ent*-**37a** was synthesized from preformed MEDAM imine **36a**[19] and also following the multi-component protocol starting from MEDAM amine **66** and benzaldehyde.[18] The unpurified aziridines obtained from these two different procedures were then separately subjected to triflic acid deprotection, a water induced ring opening, and a Boc protection sequence**,** without isolation of any intermediate isolations, to afford the pure *N*-Boc-*β* -hydroxyl-*α*-amino ester **96** in a 63% overall yield from imine **36a** (Table 3.5, entry 2) and 60% overall yield from amine **66** (Table 3.5, entry 3) respectively.

The same deprotection/ring opening protocol was applied to aziridine **37l** (Scheme 3.7) as a key step in the synthesis of sphinaganine **74b** (Figure 3.2B). Unfortunately, the aziridine **37l** failed to give a satisfactory yield (45%, NMR yield) of the *β*-hydroxyl-*α*-amino ester **98**.

Scheme 3.7 Synthesis of *N*-Boc-β-hydroxy-α-amino ester **98** from aziridine **37l**



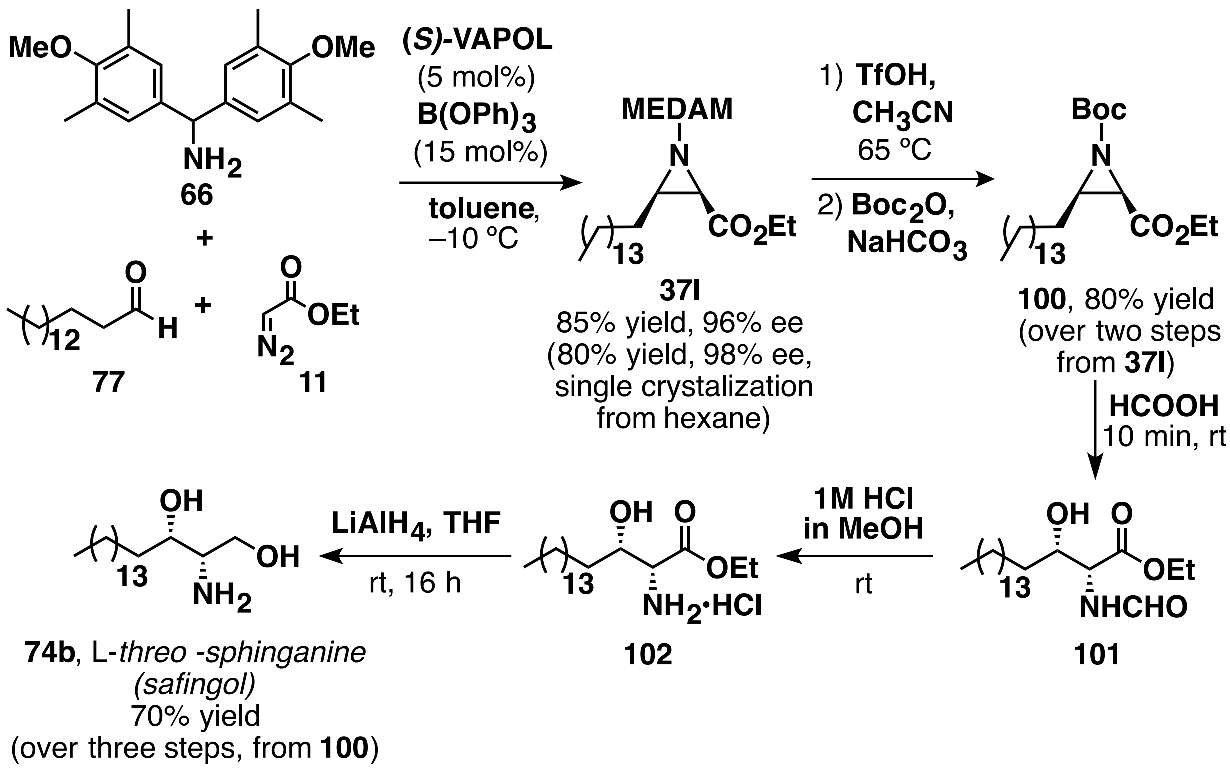
In general, aliphatic aziridines show a lower reactivity toward ring opening reactions with oxygen containing nucleophiles compared to aromatic substituted aziridines. Therefore, it was thought to activate the aziridine ring by introducing an electron-withdrawing group on the nitrogen of the aziridine and this will be described in the next section.

3.7 Synthesis of D and L-*threo*-sphinganines

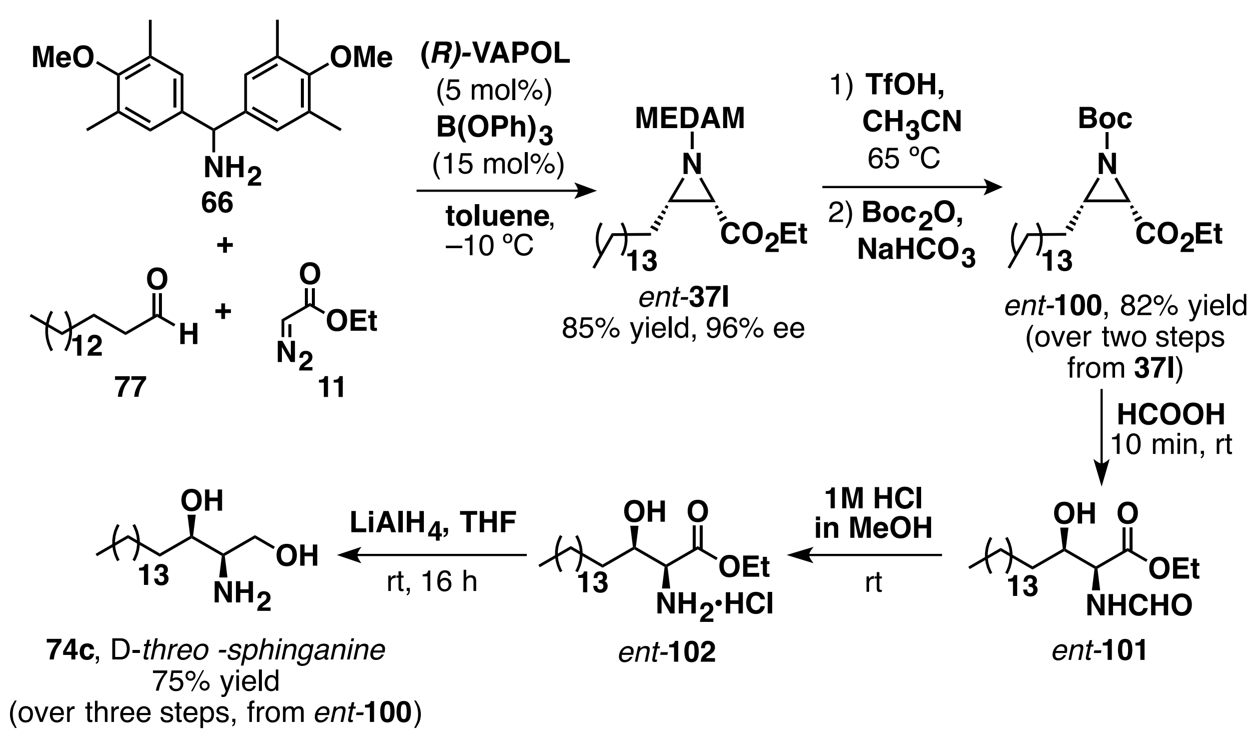
The *N*-MEDAM group was deprotected from aziridine **37l** with triflic acid in actonitrile and the *N*-H aziridine was protected with Boc without purifying the intermediate to give the *N*-Boc aziridine **100** in 80% yield in two-steps from **37l** (Scheme 3.8A). To our delight, the *N*-Boc aziridine **100** underwent ring opening reaction in a clean fashion when treated with formic acid (88% by volume) to give the *N*-formyl amino alcohol **101**. The formamide group in the ring-opened crude product **101** was hydrolyzed with HCl in methanol to afford β -hydroxyl-α-amino ester •HCl salt **102**. The crude salt **102** was finally reduced by $LiAlH_4$ to L-*threo*-sphinganine **74b** with 70% yield over three steps from aziridine **100** (Scheme 3.8A). The same route was followed for synthesis of the D-*threo*-sphinganine **74c** starting from aziridine *ent*-**37l** and the yields are given in Scheme 3.8B. It must be noted that the presence of free amine and hydroxyl groups makes the sphinganines **74b** and **74c** very polar. The final purification of the molecule by column chromatography is troublesome, as the product tends to stick to the silica gel.

Scheme 3.8 (A) synthesis of L-*threo*-sphinganine **74b** (B) synthesis of D-*threo*-sphinganine **74c**

(A)

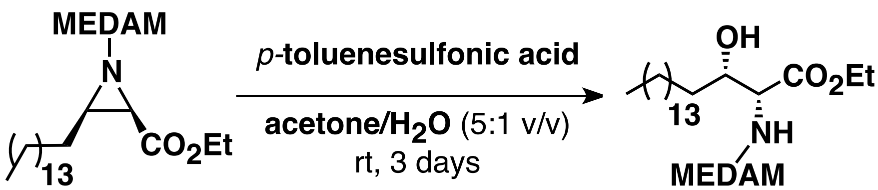


(B)



The essence of any synthesis lies in the ease of isolation and purification of its intermediates and final product. It is always desirable to have simplified isolation procedures of the products of high yielding reactions. In order to attain the above-mentioned goal, an alternative synthetic route to *threo*-spinganine was designed involving protected amine intermediates (Scheme 3.10). It was realized that the ring opening of aziridine **37l** could be possible without deprotecting the *N*-MEDAM group to afford **103** in 80% yield as determined by ^{1}H NMR in presence of *p*-toluenesulfonic acid in an acetone / water mixture (Scheme 3.9). The NMR yield was calculated by using Ph_3CH as internal standard.

Scheme 3.9 Ring opening of aziridine **37l** with water



37l

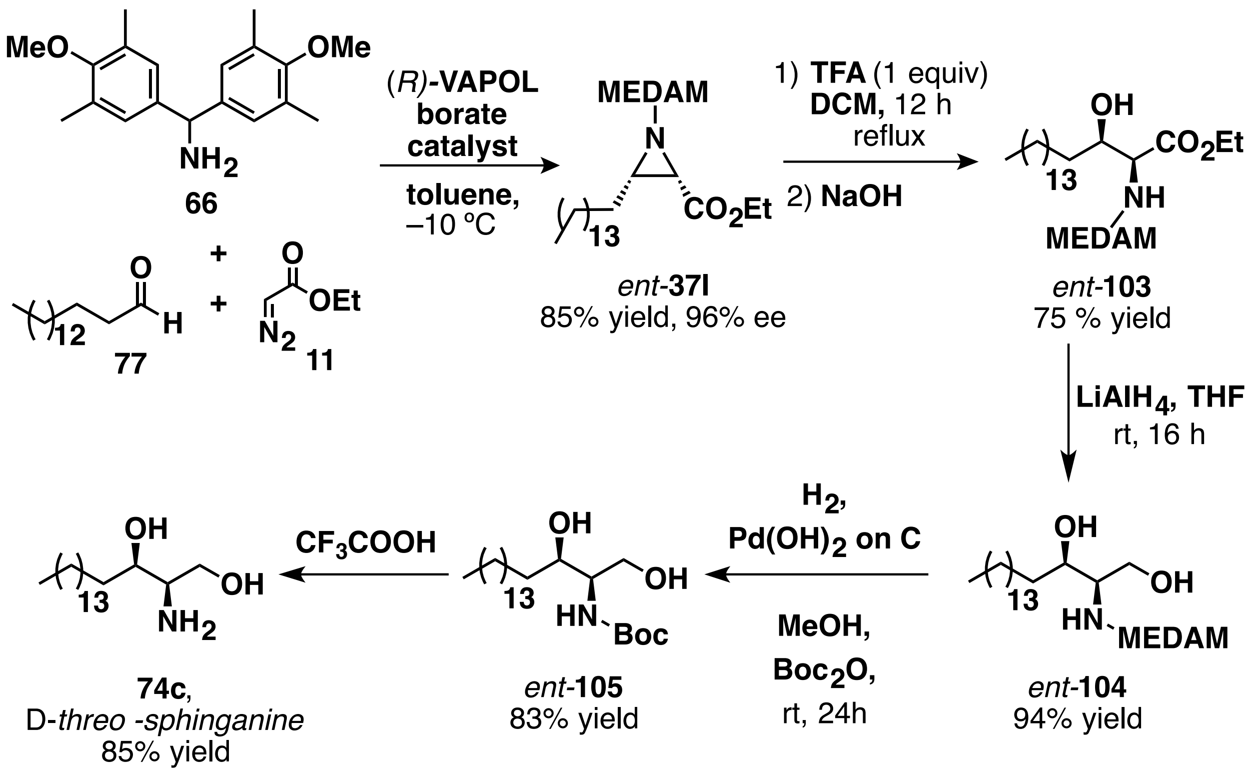
103
80 % NMR yield

To accelerate the rate of the above mentioned reaction, the reaction was performed at 65 ºC. Although the reaction was complete in 36 h, a decrease in the yield of **103** (50% as determined by ^{1}H NMR) was observed at 65 ºC. Finally, acceptable yield (75%) of *ent*-**103** was obtained when the ring opening was performed in refluxing dichloromethane in the presence of 1 equiv of trifluoroacetic acid followed by treatment with base (Scheme 3.10).[20] The MEDAM protected β-hydroxyl-α-amino ester *ent*-**103** was then reduced to corresponding β-hydroxyl-α-amino alcohol *ent*-**104** in 94% isolated yield (Scheme 3.10A). The presence of the bulky MEDAM group on nitrogen makes the intermediates less polar, so monitoring the reaction by

TLC and isolation and purification of the products became easier. Finally, the MEDAM group was cleaved by hydrogenolysis in the presence of Boc anhydride to afford *N*-Boc-D-*threo*-spinganine *ent*-**105** in 85% isolated yield. The presence of Boc group in the final product increases the product stability as compared to the corresponding free amine.

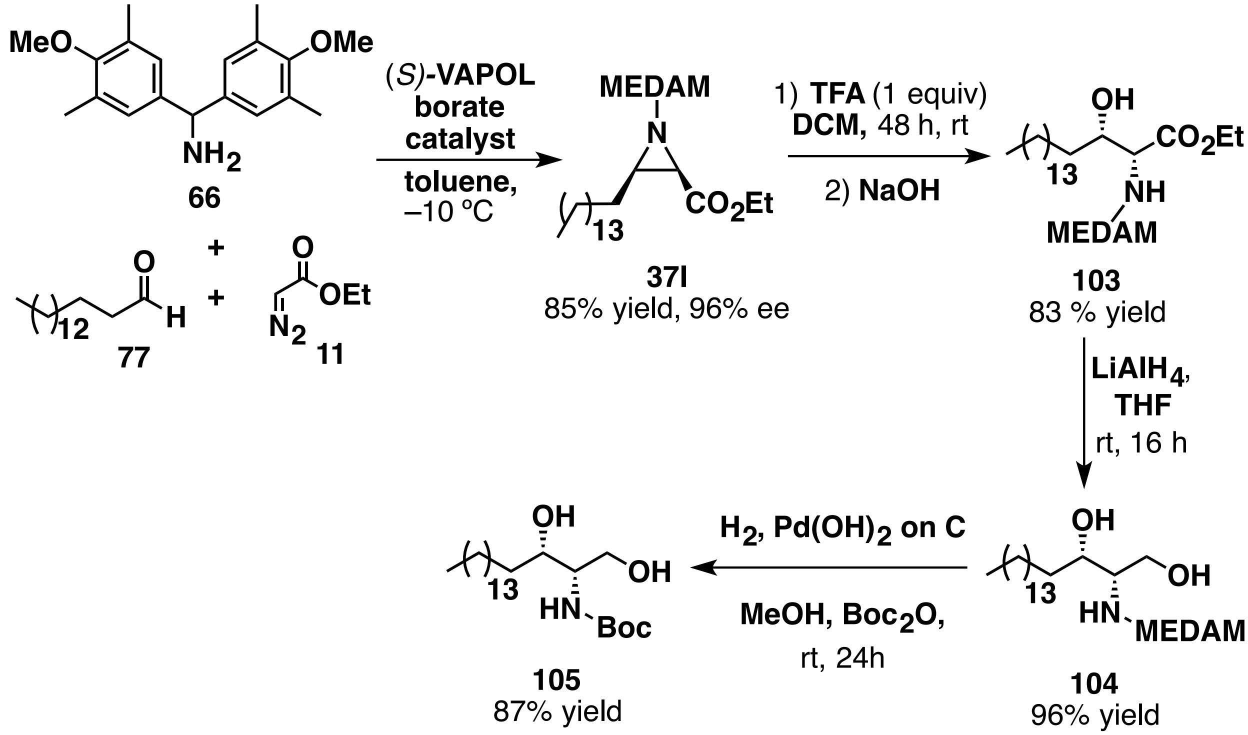
Scheme 3.10 (A) Synthesis of D-*threo*-sphinganine **74c** (B) Synthesis of *N*-Boc-L-*threo*-sphinganine **105**

(A)



Scheme 3.10 (cont'd)

(B)



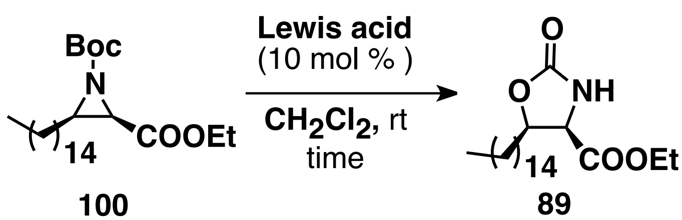
The Boc group was easily removed following the reported procedure in presence of trifluoroacetic acid[21] and the pure sphinganine **74c** was obtained by simple filtration of the reaction mixture. The same route was followed for synthesis of the *N*-Boc-L-*threo*-spinganine **105** starting from aziridine **37l** and the yields are given in Scheme 3.10B.

3.8 Synthesis of *erythro*-sphinganine

The *erythro*-sphinganine synthesis from *cis*- aziridine involves ring expansion of the *N*-carbamoyl aziridine **100** to oxazolidinone **89** (Table 3.6). Although this Lewis acid mediated ring expansion reaction has been reported with retention[22] we had previously observed that aziridines with aryl groups in the 3-position can give mixtures of *cis*- and *trans*- oxazolidinone isomers.[23]

The ring expansion reaction of aziridine **100** with a primary alkyl group at 3-position was tested under the influence of several different Lewis acids (Table 3.6). To our delight, the ring expansion of *N*-Boc aziridine **100** with $Sc(OTf)_3$ resulted in the oxazolidinone **89** in 90% isolated yield (93% NMR yield) with complete retention of configuration (Table 3.6, entry 1). The reactions with the Lewis acids $Cu(OTf)_2$ and $Yb(OTf)_3$ were very slow and resulted in the formation of oxazolidinone **89** in 60% and 70% NMR yields respectively (Table 3.6, entries 2 and 3). Reaction in presence of $BF_3•OEt_2$ resulted in a complex mixture of unidentified products (Table 3.6, entry 4).

Table 3.6 Screening of Lewis acids for the ring expansion of aziridine **100** [a]



Entry	Lewis acid	Time (h)	% Yield **89** [b]
1	$Sc(OTf)_3$	20	93 (90) [c]
2	$Cu(OTf)_2$	48	60
3	$Yb(OTf)_3$	48	70
4 [d]	$BF_3•OEt_2$	48	nd [e]

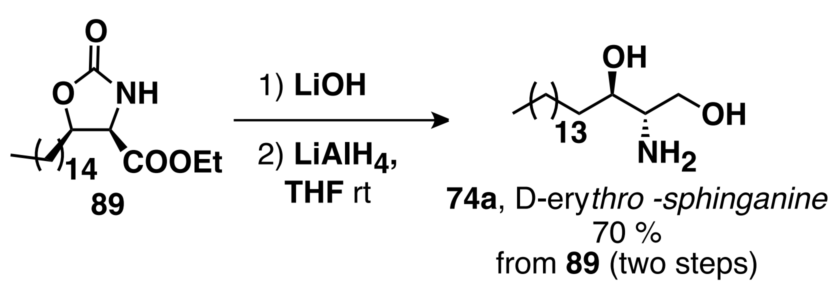
Table 3.6 (cont'd)

[a] Unless otherwise specified all reactions were performed with 0.2 mmol of aziridine **100** (0.2 M) and 10 mol % of Lewis acid in 1 mL of dichoromethane. [b] Determined from ^{1}H NMR spectra of the crude reaction mixture with Ph_3CH as internal standard. nd = not determined. [c] Yield in parenthesis is isolated yield of 90%. [d] 50 mol % catalyst used. [e] A complex mixture of unidentified products obtained.

The oxazolidinone **89** was hydrolyzed with lithium hydroxide and the resulting crude mixture was reduced with lithium aluminum hydride to the *erythro*- sphinganine **74a** in 65 % yield over two steps (Scheme 3.11A). The same route was followed for synthesis of the L-*erythro*-spinganine **74d** starting from aziridine *ent*-**100** and the yields are given in Scheme 3.11B.

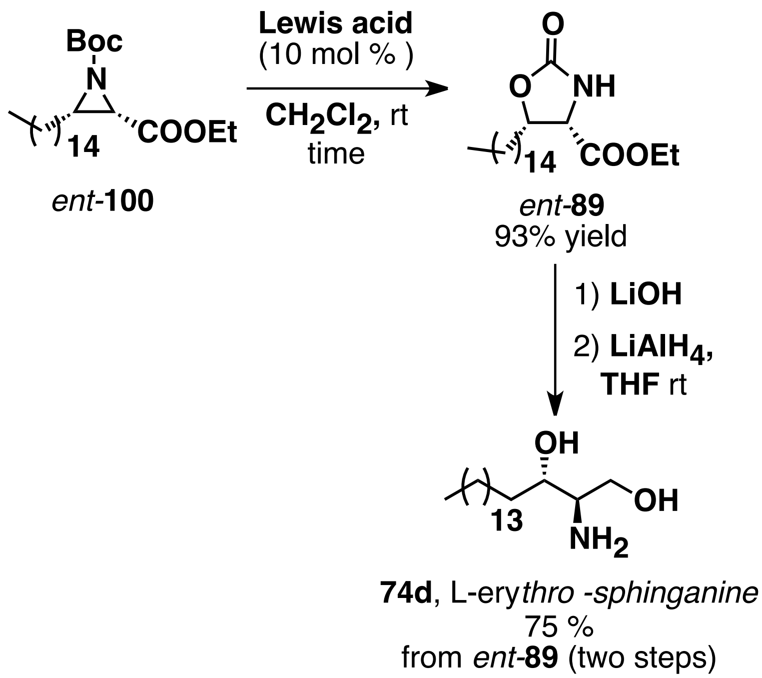
Scheme 3.11 (A) synthesis of D-*erythro*-sphinganine **74a** (B) synthesis of L-*erythro*-sphinganine **74d**

(A)



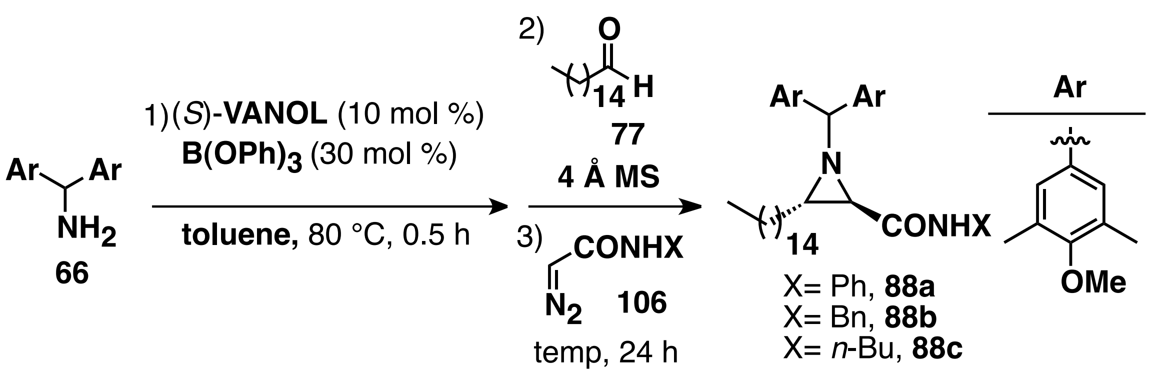
Scheme 3.11 (cont'd)

(B)



As discussed earlier in retro-synthetic analysis, the *erythro*-sphinganine **74a** and its enantiomer can alternatively be synthesized *via* ring opening of *trans*-aziridine **88** (Scheme 3.4). To this end, the multi-component *trans*-aziridination reaction involving *n*-hexadecanel **77** and different diazoacetamide was studied (Table 3.7). Finally, we were able to find suitable conditions for multi-component *trans*-aziridination reaction with *n*-hexadecanal **77** with some optimization. Anil Gupta, a current group member, initiated this study where he used diazoacetamide **106c** (Table 3.7, entry 7). A screening of other diazoacetamides was performed as a part of this doctoral research. The yield and asymmetric induction of the *trans*-aziridination reaction with aldehyde **77** was found to be largely dependent on the diazoacetamide **106**. The phenyl diazoacetamide **106a** resulted in the corresponding *trans*-aziridine **88a** with 35% yield and 57% ee at –20 ºC in presence of the *(S)*-VANOL derived catalyst (Table 3.7, entry 1). There was not much improvement in the results when the reaction temperature was increased to 0 ºC (Table 3.7, entry 2). An improved yield and asymmetric induction was observed with benzyl diazoacetamide **106b**. The benzyl diazoacetamide **106b** resulted in the formation of the corresponding *trans*-aziridine **88b** in 55% yield and 88% ee at 0 ºC in presence of the (*S*)-VANOL derived catalyst (Table 3.7, entry 4). Although there was no significant change in yield observed when the reaction temperature was changed to –20 ºC or to 25 ºC, there was a drop in the asymmetric induction observed in both cases (Table 3.7, entries 3 and 5).

Table 3.7 Multi-component catalytic asymmetric *trans*-aziridination with secondary diazoacetamide **106** [a]



entry	X	temp (ºC)	% yield *trans*-**88** [b]	% ee *trans*-**88** [c]
1	Ph (**106a**)	–20	35	57
2		0	43 [d]	nd
3		–20	50	82
4	Bn (**106b**)	0	55	88
5		25	60	83
6		–40	65	90
7 [e]		–20	65	92

Table 3.7 (cont'd)

8	*n*-Bu (**106c**)	–10	70	93
9		0	60	90
10		25	62	87

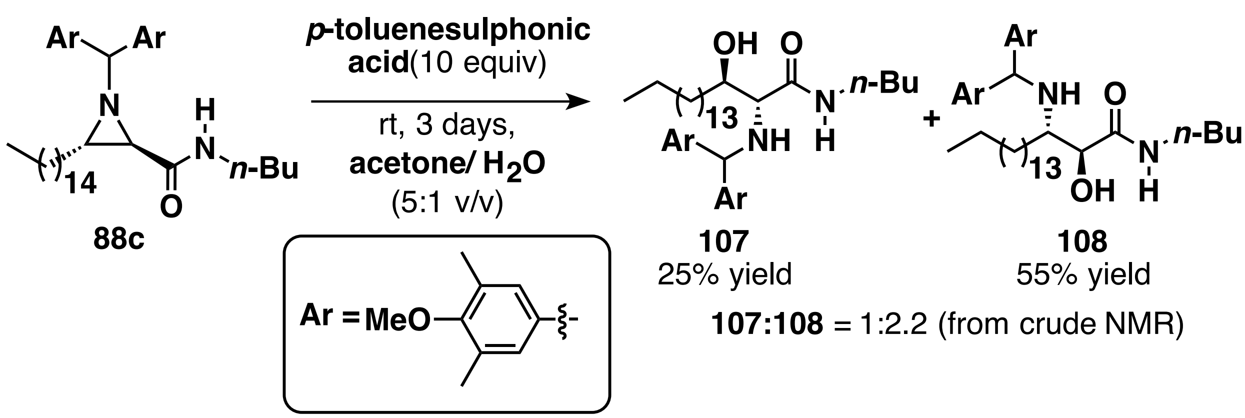
[a] Unless otherwise specified, all reactions were performed with 0.5 mmol amine **66** (0.2 M in toluene) and 1.05 equiv of *n*-hexadecanal **77** and 1.2 equiv diazoacetamide **106** and went to 100% completion. Before adding the aldehyde and EDA **11** a solution of amine **66** with 10 mol% ligand and 30 mol% $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen. nd = not determined. [b] Isolated yield after chromatography on silica gel. [c] Determined on purified *trans*-**88** by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. [d] Determined from ^{1}H NMR spectra of the crude reaction mixture with Ph_3CH as internal standard. [e] Reaction performed by Anil Gupta.

The *n*-butyl diazoacetamide **106c** proved to be the optimum diazo component for the multi-component *trans*-aziridination reaction with hexadecanal **77**. The reaction with *n*-butyl diazoacetamide **106c** resulted in the *trans*-aziridine **88c** in 70% yield and 93% ee at –10 ºC (Table 3.7, entry 8). No significant effect on yield or enantioselectivity of the reaction was observed when the temperature of the reaction was lowered to –20 ºC or –40 ºC (Table 3.7, entries 6 and 7). However, a slight drop in yield and enantioselectivity (62% yield, 87% ee) was observed at room temperature (Table 3.7, entry 10).

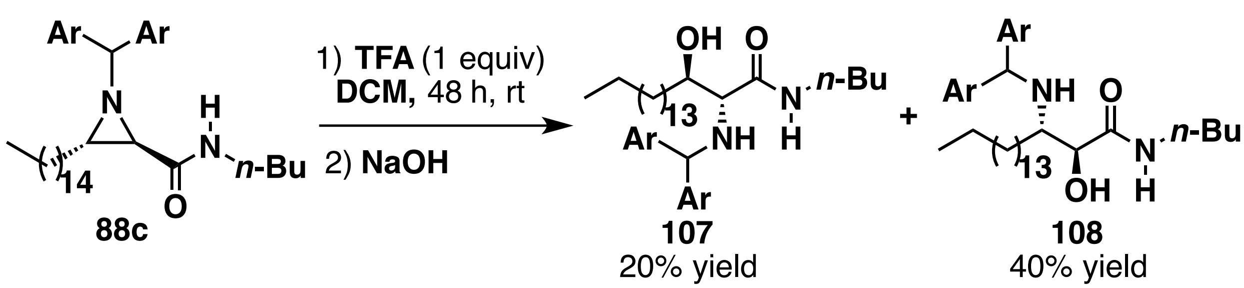
The ring opening of the *trans*-aziridine **88c** with water was tried in the presence of *p*-toluenesulfonic acid in an acetone / water mixture. The nucleophilic attack on the *trans*-aziridine was not regioselective as it was in the case for *cis*-aziridnes. The reaction resulted in a 2:1 ratio of C-2 opened product **108** and C-3 opened product **107** (Scheme 3.12A). A similar observation was made when the ring opening reaction of *trans*-aziridine **88c** was performed in dichloromethane in presence of 1 equiv of trifluoroacetic acid followed by treatment with base (Scheme 3.12B).

Scheme 3.12 (A) Ring opening of *trans*-aziridine **88c** with water in acidic medium (B) Ring opening of *trans*-aziridine **88c** with TFA

(A)



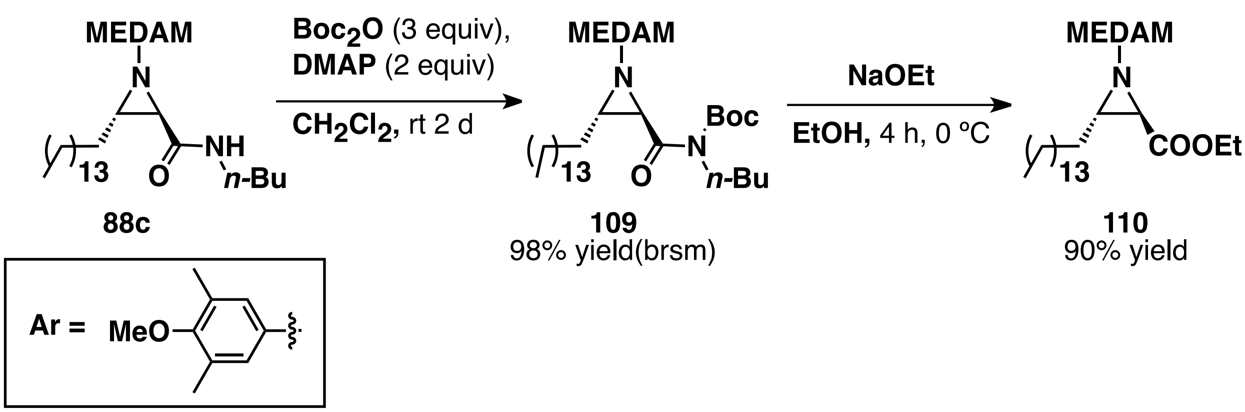
(B)



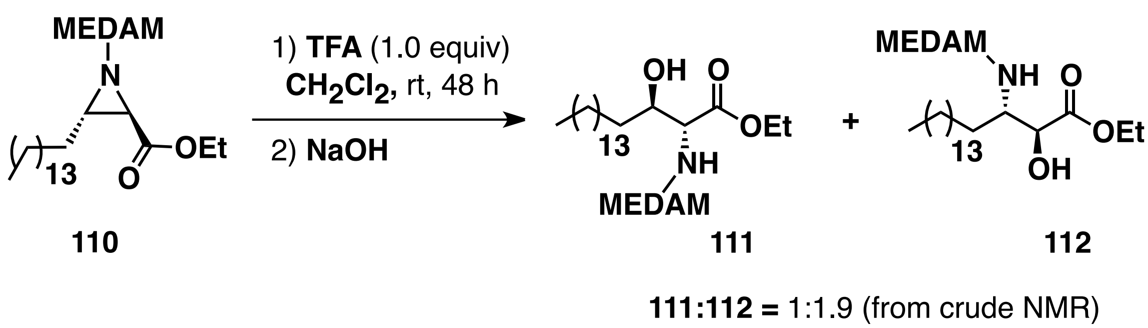
It would be interesting to see whether changing the amide group to carboxylate ester group can solve the regioselectivity issue in this ring opening of the *trans*-aziridine. The amide group in *trans*-aziridine **88c** was converted to corresponding ethyl ester **109** (Scheme 3.13A). The ring opening reaction of *trans*-aziridine **109** was performed in dichloromethane in presence of 1 equiv of trifluoroacetic acid followed by treatment with base (Scheme 3.13B). Unfortunately, the ring opening of *trans*-aziridine **109** was not regioselective as the reaction resulted C-2 opened product **111** and C-3 opened product **110** in 2:1 ratio (Scheme 3.13B).

Scheme 3.13 (A) Synthesis of *trans*-aziridine **110** (B) Ring opening of *trans*-aziridine **110** with TFA

(A)



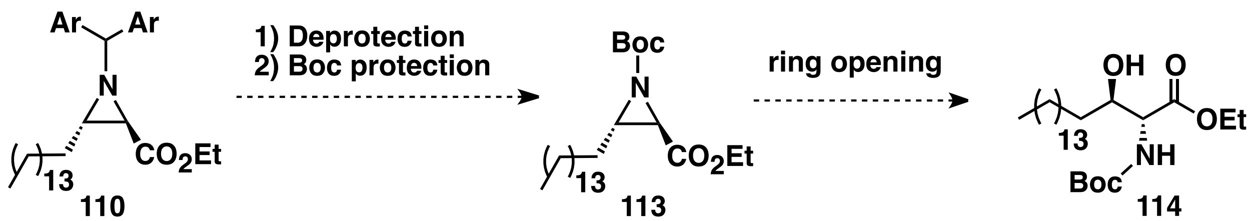
(B)



At this point, the only solution to this regioselectivity issue is to activate the *trans*-

aziridine ring by introducing an electron-withdrawing group on the nitrogen of aziridine ring and this should be the subject of future experiments (Scheme 3.14).[24]

Scheme 3.14 Proposed solution for regioselective Ring opening of *trans*-aziridine



3.9 Study towards synthesis of mycestericin E

After the successful completion of the syntheses of the sphinganines, we envisioned to plan the synthesis of a more complex molecule mycestericin E. The proposed synthetic route to mycestericin E would be similar to that of sphinganines involving the Wulff catalytic asymmetric aziridination reaction as the key component of the strategy.

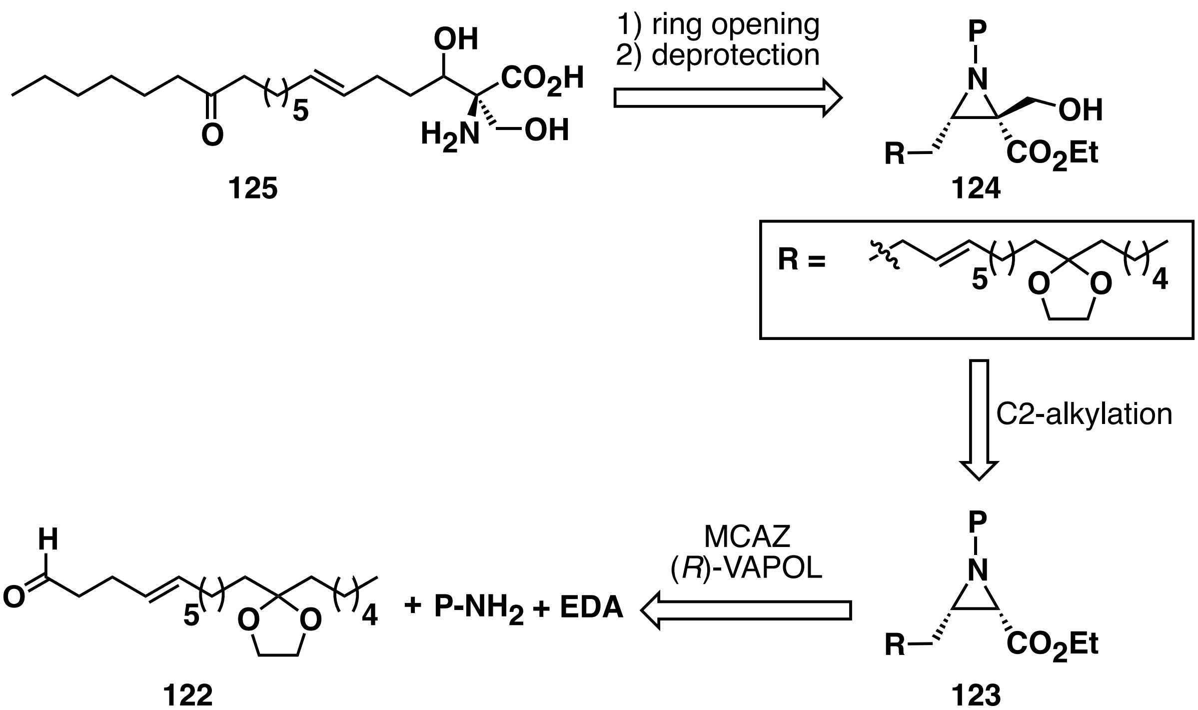
The mycestericin family includes eight members isolated from Mycelia sterilia and which share immunosuppressant activity.[25] There have been a few total syntheses of the mycestericins reported with none of them particularly efficient.[26] Most have involved starting from the chiral pool or a combination of chemical and enzymatic steps.

3.10 Retro-synthetic analysis of mycestericin E

A retro-synthetic analysis of the mycestericin E **125** is presented in Scheme 3.15. The synthesis of mycestericin E **125** could be possible *via* the ring opening of the appropriate *cis*-aziridines **124** with an oxygen nucleophile. The aziridine **124** could be possible to synthesize *via*

C2 alkylation of aziridine **123** with formaldehyde. A multi-component aziridination reaction of aldehyde **122** would yield aziridine **123** in presence of (*R*)-VAPOL or (*R*)-VANOL derived catalyst.

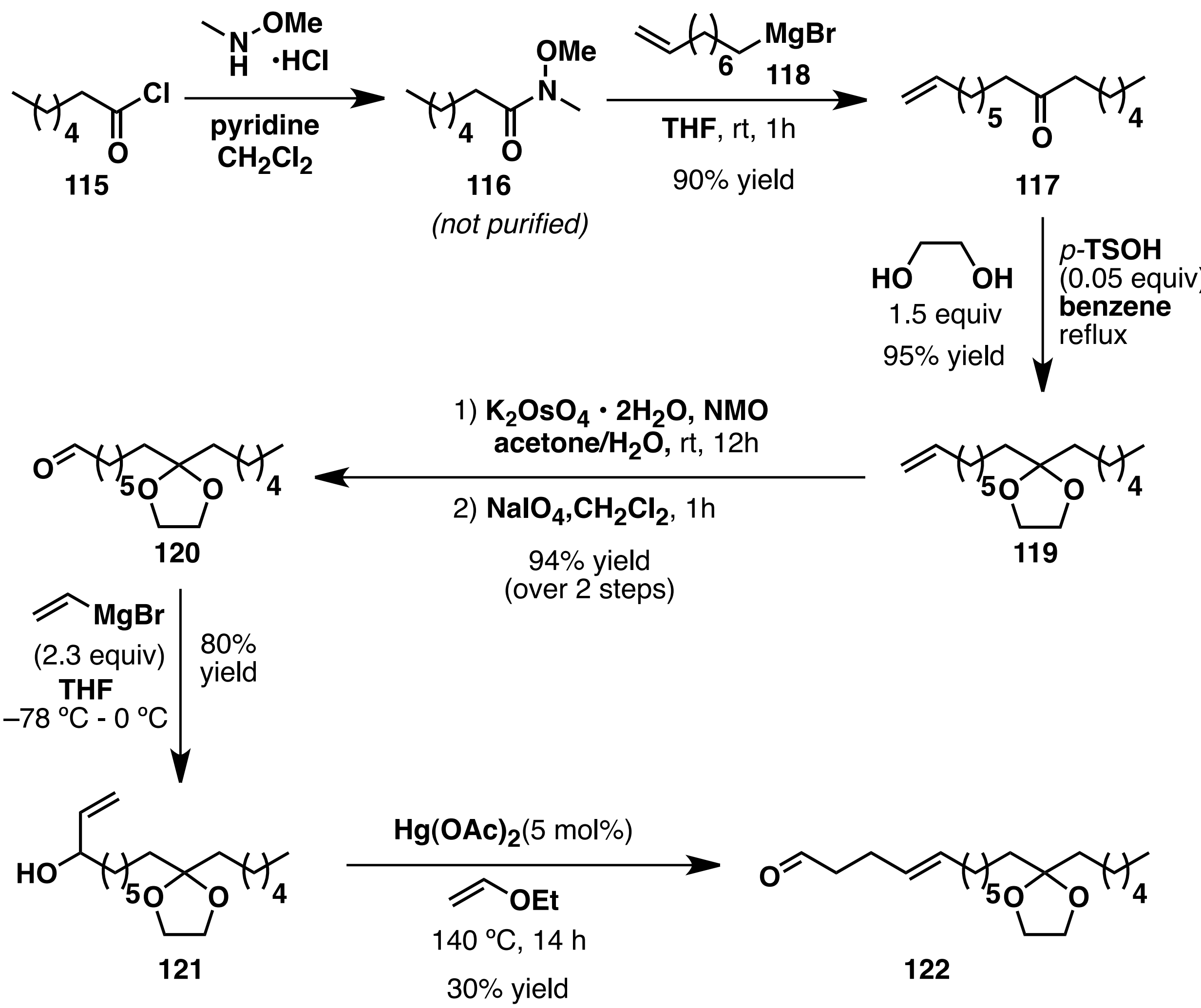
Scheme 3.15 Retro-Synthetic analysis of mycestericin E



3.11 Synthesis of aziridine 123 *via* multi-component aziridination reaction

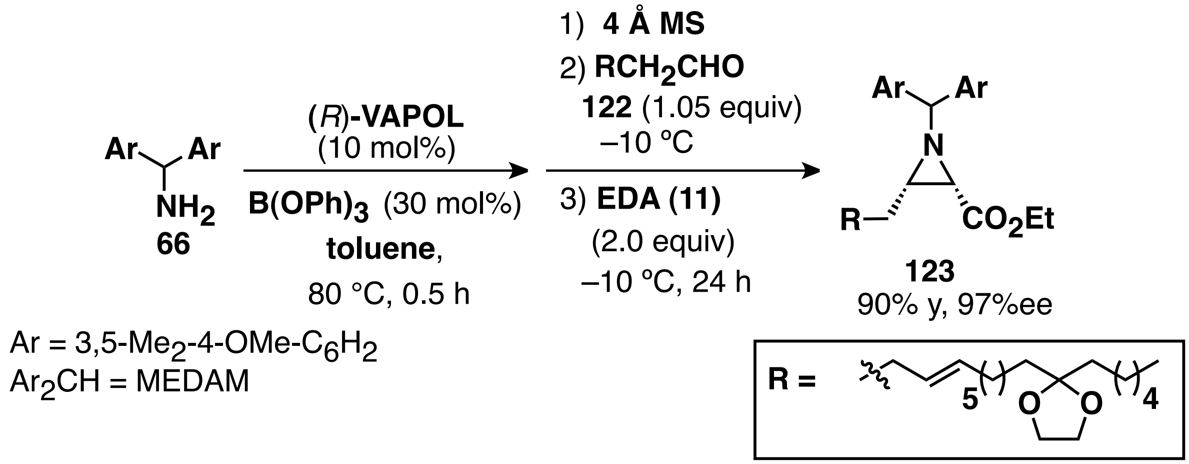
The aldehyde **122** was synthesized from aldehyde **120** which was prepared from the commercial available acid chloride **115** *via* a known procedure involving 5 steps in 80% overall yield (Scheme 3.16).[27] Addition of vinyl Grignard to **120** proceeds in 80% yield but the subsequent Claisen rearrangement only gives aldehyde **122** in 30% yield. The low yield can be attributed to the incompatibility of aldehyde **122** to the high temperatures associated with the enol ether Claisen.

Scheme 3.16 Synthesis of aldehyde **122**



The multi-component aziridination of aldehyde **122** with the (*R*)-VAPOL derived catalyst gives aziridine **123** in 90% yield and 97% ee (Scheme 3.17). The asymmetric induction was not confirmed due to unavailability of authenticate sample of *ent*-**123.** The final stages of mycestericin E synthesis involve the alkylation of aziridine **123** with formaldehyde and subsequent ring opening of the resulting aziridine and this should be the subject of future experiments.

Scheme 3.17 Synthesis of aziridine **123**



3.12 Conclusions

The synthesis of 1,2-amino alcohols and sphingoid bases can be planned *via* regio- and stereo- selective ring opening of the aziridine 2-carboxylates as described in this work. There is a very extensive list of reports on the synthesis of sphingoid bases but very few involve catalytic asymmetric methods. Moreover, this work demonstrates the application of a catalytic asymmetric method to the synthesis of all isomers of a sphingoid base. This approach should help to make aziridines more attractive intermediates in synthesis of chiral amines that constitute an important class of compounds for pharmaceuticals, bioactive materials or small molecule synthesis.

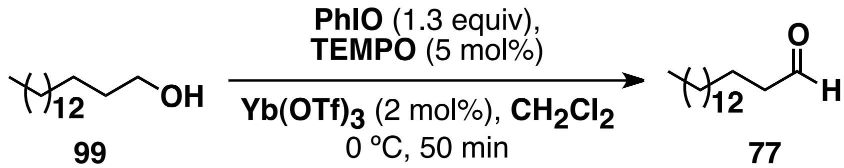
APPENDIX

3.13 Experimental procedure

3.13.1 General information

Same as Chapter 2.

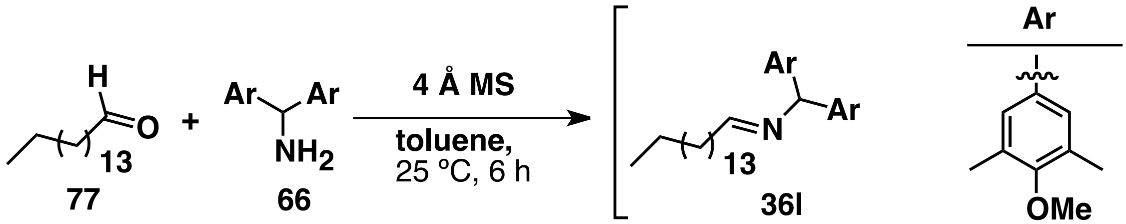
3.13.2 Preparation of hexadecanal 77[28]

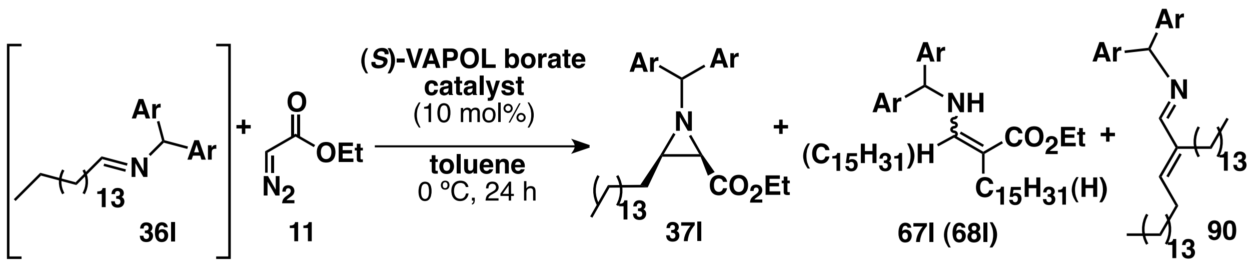


To a 100 mL flame-dried round bottom flask equipped with a stir bar was added 1-hexadecanol **99** (1.21 g, 5.00 mmol). Dry CH_2Cl_2 (20 mL) was added to dissolve **99**. To the resulting solution were added TEMPO (32 mg, 0.25 mmol) and PhIO (1.43 g, 6.50 mmol). The suspension was cooled to 0 °C and $Yb(OTf)_3$ (62.5 mg, 0.10 mmol) was added. The reaction mixture was stirred at 0 °C for 50 min (until the alcohol was no longer detectable by TLC). The yellow cloudy solution was filtered through Celite pad and concentrated under reduced pressure. Purification of the crude aldehyde by silica gel chromatography (30 mm × 300 mm column, 5:1 hexanes / dichloromethane as eluent, flash column) afforded pure aldehyde **77** as a white solid (mp 36-38 ºC) in 75 % isolated yield (0.90 mg, 3.75 mmol).

Spectral data for **77**: R_f = 0.5 (1:3 hexanes/DCM). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.30-1.25 (m, 24H), 1.62 (quintet, *J* = 7.3 Hz, 2H), 2.41 (td, *J* = 7.4, 1.9 Hz, 2H), 9.76 (t, *J* = 1.8 Hz, 1H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.09, 22.10, 22.68, 29.17, 29.35, 29.42, 29.57, 29.63, 29.64, 29.65, 29.67, 29.68, 31.92, 43.91 (1 *sp3* carbon not located), 202.85.

3.13.3 Asymmetric catalytic aziridination of imine 36l to synthesize *cis*-aziridine 37l (Procedure A)





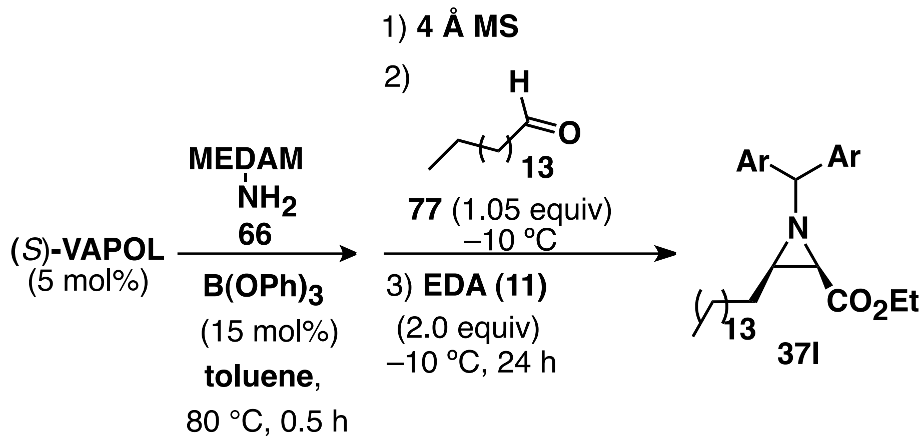
(*E*)-*N*-Hexadecylidene-1,1-bis(4-methoxy-3,5-dimethylphenyl)methanamine 36l: To a 10 mL flame-dried round bottom flask filled with argon was added bis(4-methoxy-3,5-dimethylphenyl)methanamine **66** (299 mg, 1 mmol), 4Å MS (250 mg, freshly dried) and dried toluene (1.5 mL). After stirring for 10 min, hexadecanal **77** (253 mg, 1.05 mmol) was added. The reaction mixture was stirred at room temperature for 6 h. The resulting imine **36l** was used without further purification.

(*2R,3R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-pentadecylaziridine-2-carboxylate 37l: To a 10 mL flame-dried home-made Schlenk flask, prepared from a single necked 25 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, flushed with argon was added (*S)*-VAPOL (54 mg, 0.1 mmol) and

$B(OPh)_3$ (116 mg, 0.4 mmol) . Under an argon flow, dry toluene (2 mL) was added to dissolve the two reagents. The flask was sealed, and then placed in an oil bath at 80 ºC for 1 h. After 1 hour, a vacuum (0.5 mm Hg) was applied carefully to remove the volatiles. The vacuum is maintained for a period of 30 min at a temperature of 80 ºC. The flask was then filled with argon and the catalyst mixture was cooled to 0 ºC. The imine **36l** (1 mmol, crude and non-isolated) was then directly transferred from the reaction flask (of imine) to the flask containing the catalyst utilizing the filter syringe (Corning® syringe filters, Aldrich). The flask, which had imine **36l**, then rinsed with toluene (0.5 mL) and transferred to the flask containing the catalyst. The reaction mixture was stirred for 5 min at 0 ºC to give a light orange solution. To this solution was rapidly added EDA **11** (124 μL, 1.2 mmol) and the resulting mixture was stirred for 24 h at 0 ºC. The reaction was diluted by addition of hexane (6 mL). The reaction mixture was then transferred to a 100 mL round bottom flask. The reaction flask was rinsed with dichloromethane (5 mL × 2) and the rinse was added to the 100 mL round bottom flask. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as pale yellow semi solid. Purification of the crude aziridine by silica gel chromatography (30 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded pure aziridine **37l** as a semi solid in 60% isolated yield (365 mg, 0.60 mmol); *cis/trans*: not determined. Enamine side products: 5% yield of **67l** and 4% yield of **68l**. Imine condensation product: 10% yield of **90**. The optical purity of **37l** was determined to be 90% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O1column, 99.5:0.5 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 18.26 min (major enantiomer, **37l**) and R_t = 33.43 min (minor enantiomer, *ent*-**37l**).

Spectral data for **37l**: R_f = 0.31 (2:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.0 Hz, 3H), 1.14-1.28 (m, 2H), 1.43-1.50 (m, 29H), 1.93 (q, *J* = 6.5 Hz, 1H), 2.18 (d, *J* = 6.5 Hz, 1H) 2.22 (s, 12H), 3.38 (s, 1H), 3.65 (s, 3H), 3.67 (s, 3H), 4.12-4.23 (m, 2H), 6.99 (s, 2H), 7.07 (s, 2H); ^{13}**C NMR** (126 MHz, $CDCl_3$) δ 14.09, 14.34, 16.11, 16.16, 22.68, 27.24, 27.96, 29.18, 29.35, 29.51, 29.61, 29.62, 29.65, 29.68, 31.92, 43.56, 47.01, 59.57, 59.58, 60.64, 77.35, 127.41, 128.10, 130.42, 130.47, 137.78, 138.18, 155.81, 156.15, 169.69 (3 *Sp3* carbon not located); IR (thin film) 2925vs, 1746s, 1484s, 1221s, 1183vs cm-1; HRMS (ESI-TOF) *m/z* 608.4683 [(M+H+); calcd. for $C_{39}H_{62}NO_4$: 608.4679]; $[\alpha]_D^{20}$ +59.0 (c 1.0, EtOAc) on 98 % ee material (HPLC).

3.13.4 Asymmetric catalytic multi-component aziridination of aldehyde 77 to synthesize *cis*-aziridine 37l (Procedure B)



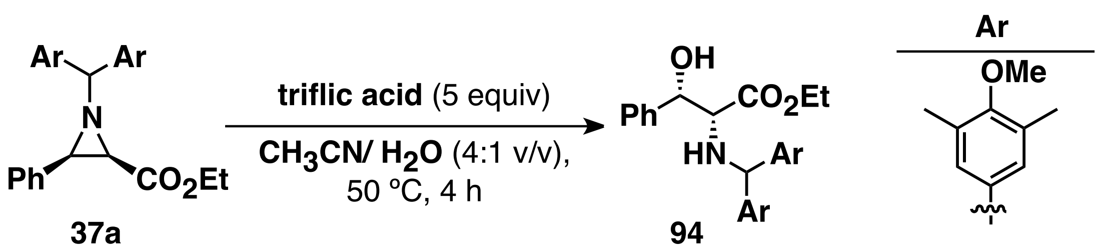
(*2R,3R*)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-pentadecylaziridine-2-carboxylate 37l: To a 25 mL flame-dried Schlenk flask equipped with a stir bar and filled with argon was added (*S)*-VAPOL (14 mg, 0.025 mmol), $B(OPh)_3$ (22 mg, 0.075 mmol) and amine

66 (149.7 mg, 0.500 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (1 mL) was added. The flask was sealed by closing the Teflon valve, and then placed in an oil bath (80 ºC) for 0.5 h. The flask was then allowed to cool to room temperature and open to argon through side arm of the Schlenk flask. To the flask containing the catalyst was added the 4Å Molecular Sieves (150 mg, freshly flame-dried). The flask was then allowed to cool to –10 ºC and a solution of aldehyde **77** (126 mg, 0.525 mmoL, 1.05 equiv) in toluene (1.0 mL) was added to the reaction mixture. The flask containing aldehyde **77** was washed with another 0.5 mL of dry toluene and solution was transferred to the reaction mixture. To the resulting reaction mixture was added ethyl diazoacetate (EDA) **11** (104 µL, 1.0 mmoL, 2.0 equiv). The resulting mixture was stirred for 24 h at –10 ºC. The reaction was dilluted by addition of hexane (6 mL). The reaction mixture was then filtered through a silica gel plug to a 250 mL round bottom flask. The reaction flask was rinsed with EtOAc (20 mL × 3) and the rinse was filtered through the same silica gel plug. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as yellow colored viscous oil.

Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded pure aziridine **37l** as a white solid (mp 41–42 ºC on 96% ee material) in 85% isolated yield (258 mg, 0.425 mmol); *cis/trans*: not determined. Enamine side products: 1.7% yield of **67l** and 1.7% yield of **68l**. Imine condensation product: >1% yield of **90**. The optical purity of **37l** was determined to be 96% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O1column, 99.5:0.5 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 18.26 min (major enantiomer, **37l**) and R_t = 33.43 min (minor enantiomer, *ent*-**37l**). Aldehyde **77** was reacted according to the general Procedure B described above with (*R*)-VAPOL as ligand to afford aziridine *ent*-**37l** with 96% ee.

The chemically pure aziridine **37l** (200 mg, 0.33 mmol, 96% ee) was placed in a 10 mL round bottom flask. An air condenser with a nitrogen balloon was attached to the round bottom flask. Hexanes (0.5 mL) was added to the flask and the mixture was brought to boil with a heat gun as the flask was swirled. The flask with the clear solution was cooled to room temperature and then kept at the refrigerator. The aziridine **37l** crystallized out. The first crop was collected (160 mg, 0.264 mmol, 80% recovery) and determined to be 98% ee (mp 42–43 ºC) by HPLC (see condition above).

3.13.5 Ring opening of aziridine *cis*-37a with water

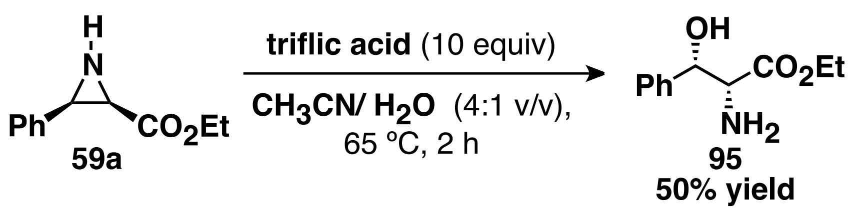


(2*R*, 3*S*)-Ethyl 2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-3-hydroxy-3-phenylpropanoate 94:

To a solution of the aziridine **37a** (95 mg, 0.2 mmol, 99% ee) in an acetonitrile / water (0.5 mL, 4:1 v/v) mixture was added trifluoromethanesulfonic acid (88 μL, 1.0 mmol, 5.0 equiv) at room temperature. The flask was then equipped with an air condenser and a nitrogen balloon at the top of the condenser through a rubber septum. The solution was stirred at 50 ºC for 4 h under nitrogen atmosphere. The reaction mixture was cooled to 0 ºC and was added to a saturated aq. Na_2CO_3 solution. The water layer was extracted with ethyl acetate (4 × 5 mL). The combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The yield of **94** was 60% as determined by ^{1}H NMR with Ph_3CH as internal standard.

Spectral data for **94** (from crude ^{1}H NMR): **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.02 (t, *J* = 7.1 Hz, 3H), 2.22 (s, 6H), 2.24 (s, 6H), 3.39 (d, *J* = 6.9 Hz, 1H), 3.68 (s, 3H), 3.69 (s, 3H), 3.97 (q, *J* = 7.1 Hz, 2H), 4.60 (s, 1H), 4.77 (d, *J* = 6.9 Hz, 1H), 6.90 (s, 2H), 6.91 (s, 2H), 7.32-7.27 (m, 5H), (OH and NH protons were not located).

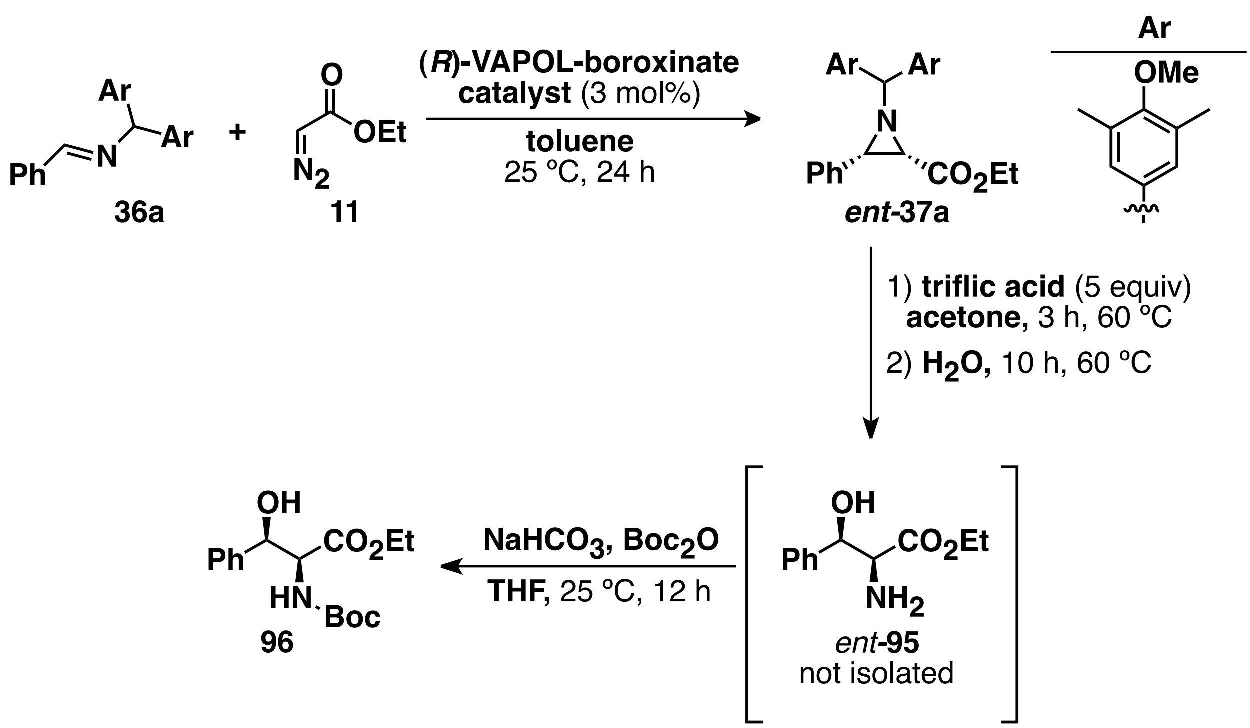
2.13.1 **Ring opening of aziridine *cis*-59a with water**



To a solution of the aziridine **59a** (38 mg, 0.2 mmol) in an acetonitrile / water mixture (1.0 mL, 4:1 v/v) was added trifluoromethanesulfonic acid (177 μL, 2.0 mmol, 10.0 equiv) at room temperature. The flask was then equipped with an air condenser and a nitrogen balloon at the top of the condenser through a rubber septum. The solution was stirred at 65 ºC for 2 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature and diluted with 5 mL of water. The water layer was washed with diethyl ether (5mL). To the water layer was added saturated aq. Na_2CO_3 solution until pH ~ 9. The resulting water layer was extracted with ethyl acetate (4 × 5 mL). The combined organic layer (ethyl acetate extract) was dried with $MgSO_4$. Upon concentration of the organic layer under reduced pressure afforded **95** as white solid with 50% yield of the crude product. The product was dissolved in 2 M HCl in methanol (1 mL) and the resulting mixture was evaporated under reduced pressure. The hyrochloride salt of **95** gave $[\alpha]_D^{20}$ +29.3 (c 1.0, H_2O) [Lit[29] reported $[\alpha]_D^{20}$ +32.6 (c 1.0, H_2O)].

Spectral data for **95**: **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.16 (t, *J* = 7.1 Hz, 3H), 2.29-2.62 (m, 3H), 3.63 (d, *J* = 4.4 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.87 (d, *J* = 4.8 Hz, 1H), 7.27-7.38 (m, 5H); $[\alpha]_D^{20}$ +15.0 (c 0.5, $CHCl_3$).

3.13.6 Ring opening of aziridine *cis*-37a with water



(2S, 3S)-Ethyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-phenylaziridine-2-

carboxylate *ent*-37a:

To a 25 mL flame-dried homemade Schlenk flask equipped with a stir bar and flushed with argon was added (*R*)-VAPOL (81 mg, 0.15 mmol) and $B(OPh)_3$ (174 mg, 0.60 mmol) and aldimine **36a** (1.94 g, 5 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (10 mL) was added through the top of the Teflon valve to dissolve the reagents. The flask was sealed by closing the Teflon valve and then placed in an 80 ºC oil bath for 1 h. The catalyst mixture was then allowed to cool to room temperature and opened to argon through the side arm of the Schlenk flask. To this solution was rapidly added ethyl diazoacetate (EDA) **11** (622 μL, 6.0 mmol) followed by closing the Teflon valve. The resulting mixture was stirred for 1 h at room temperature. Immediately upon addition of ethyl diazoacetate the reaction mixture became an intense yellow, which changed to light yellow towards the completion of the reaction. The reaction was diluted by addition of hexane (30 mL). The reaction mixture was then transferred to a 500 mL round-bottom flask. The reaction flask was rinsed with dichloromethane (30 mL × 2), and the rinse was added to the 500 mL round-bottom flask. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.1 mmHg) for 2 h to afford the crude aziridine as an off-white solid. The crude aziridine was used in the next step without any further purification.

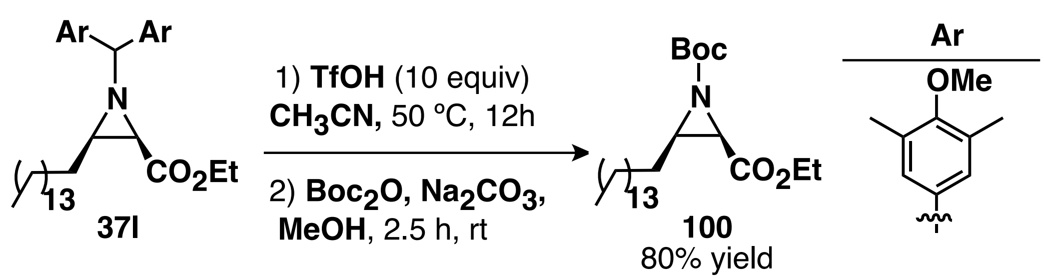
(2*S*, 3*R*)-Ethyl-2-((tert-butoxycarbonyl)amino)-3-hydroxy-3-phenylpropanoate 96:

To a solution of the crude aziridine *ent*-**37a** obtained above in acetone (250 mL) was added trifluoromethanesulfonic acid (2.21 mL, 25 mmol, 5.0 equiv) at room temperature. The flask was then equipped with an air condenser and a nitrogen balloon at the top of the condenser through a rubber septum. The solution was stirred at 60 ºC for 3 h under nitrogen atmosphere. The reaction was monitored by TLC. To the solution was then added water (50 mL), and the resulting mixture was stirred at 60 ºC for 10 h. The solution was then cooled to room temperature, and the volume was reduced to half by rotary evaporation. Water (200 mL) was added to the resulting mixture. The mixture was washed with ether (40 mL × 3). To the water layer was added solid sodium bicarbonate until pH ~ 9. To the resulting mixture was added THF (85 mL) and di-*tert* -butyl dicarbonate (1.75 g, 8.5 mmol, 1.6 equiv). The mixture was stirred at room temperature for 12 h. The mixture was then extracted with ethyl acetate (100 mL × 4). The combined organic layer was washed with saturated aqueous NaCl solution (40 mL × 2) and dried over anhydrous $MgSO_4$. The ethyl acetate was removed by rotary evaporation. Purification by flash silica gel chromatography (1:2 ether/hexanes as eluent) afforded **96** as colorless oil in 63% isolated yield (975 mg, 3.15 mmol).

Spectral data for **96**: R_f = 0.49 (2:1 Et_2O/hexanes); **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.32 (br s, 9H), 2.79 (br s, 1H), 4.17 (q, *J* = 7.3 Hz, 2H), 4.49 (brd, *J* = 7.1 Hz, 1H), 5.16-5.19 (m, 1H), 5.28 (brs, 1H), 7.25-7.37 (m, 5H); **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 14.05, 28.14, 59.51, 61.67, 74.15, 80.03, 126.06, 128.02, 128.34, 139.80, 170.83 (one *sp2* carbon not located); $[\alpha]_D^{20}$ −7.0 (c 1.1, EtOH).

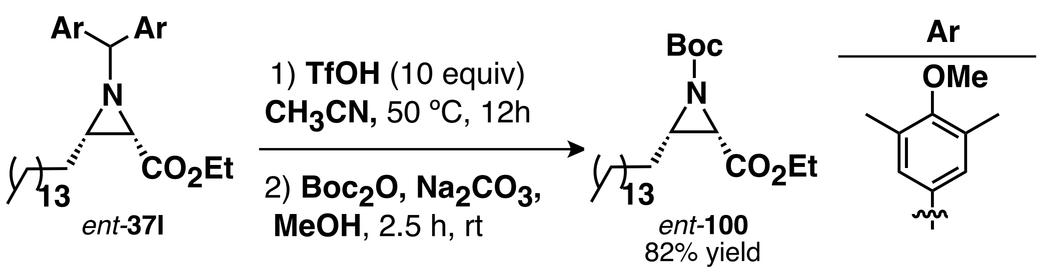
3.13.7 Enantioselective synthesis of L-*threo*-sphinganine 74b and D-*threo*-sphinganine 74c *via* route I

3.13.7.1 Synthesis of *N*-Boc aziridine 100 and *ent*-100



(2*R*,3*R*)-1-*tert*-Butyl 2-ethyl 3-pentadecylaziridine-1,2-dicarboxylate 100: To a 50 mL flame-dried round bottom flask equipped with a stir bar and an air condenser with a rubber septum and a nitrogen balloon at the top, was added aziridine **37l** (304 mg, 0.50 mmol, 98% ee material). Dry acetonitrile (15 mL) was added to dissolve **37l**. Thereafter, triflic acid (450 μL, 5 mmol, 10 equiv) was added slowly to the reaction flask. The flask was placed in a oil (50 ºC) bath and the reaction mixture was stirred for 12 h under nitrogen atmosphere. The flask was then allowed to cool to room temperature and the reaction mixture was added to a saturated aq. Na_2CO_3 (20 mL). The water layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layer was washed with distilled water (2 × 10 mL) followed by brine (2 × 10 mL). The resulting organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude reaction mixture as white solid. To the solution of the crude reaction mixture in methanol (5 mL) solid $NaHCO_3$ (193 mg, 2.3 mmol, 4.6 equiv) and Boc_2O (250 mg, 1.14 mmol, 2.3 equiv) was added. The resulting reaction mixture was stirred for 2.5 h at room temperature under nitrogen atmosphere. The reaction mixture was diluted with diethyl ether (20 mL) and filtered through Celite-pad to a 100 mL round bottom flask. The Celite-pad was washed with ether (3 × 15 mL). The resulting solution was concentrated under reduced pressure followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude *N*-Boc aziridine **100** as a light yellow liquid. Purification of the crude aziridine **100** by silica gel chromatography (20 mm × 300 mm column, 10:1 hexanes/EtOAc as eluent, flash column) afforded pure ester **100** as a colorless liquid in 80 % isolated yield over two steps (170 mg, 0.4 mmol).

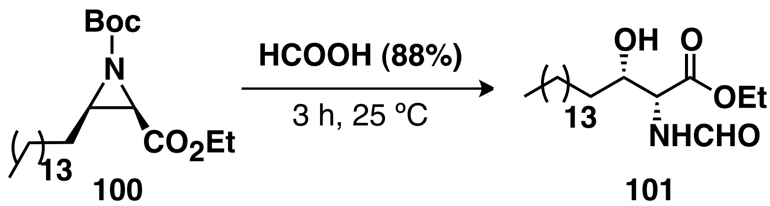
Spectral data for **100** R_f = 0.24 (1:9 EtOAc / hexanes); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.87 (t, J = 6.7 Hz, 3H), 1.34-1.26 (m, 29H), 1.44 (s, 9H), 1.63-1.56 (m, 2H), 2.64-2.57 (m, 1H), 3.09 (d, J = 6.7 Hz, 1H), 4.28-4.17 (m, 2H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 14.07, 14.21, 22.65, 26.94, 27.37, 27.81, 29.04, 29.32, 29.50, 29.51, 29.59, 29.62, 29.64, 29.65, 31.89, 39.83, 43.59, 61.34, 81.84 (2 *sp3* carbon not located), 160.77, 167.63; IR (thin film) 2926vs, 2855vs, 1755s, 1738s, 1298s, 1159vs cm^{-1}; HRMS (ESI-TOF) *m/z* 426.3604 [(M+H^{+}); calcd. for $C_{25}H_{48}NO_4$: 426.3583]; $[\alpha]_D^{20}$ +43.0 (c 1.0, CH_2Cl_2) on 98 % ee material.



(2*S*, 3*S*)**-1-*tert*-Butyl 2-ethyl 3-pentadecylaziridine-1,2-dicarboxylate** *ent*-**100:** The *N*-Boc aziridine *ent*-**100** was synthesized from aziridine *ent*-**37l** (608 mg, 1.0 mmol, 96% ee material) following the procedure described above for the synthesis of *N*-Boc aziridine **100**. Purification of the crude aziridine *ent*-**100** by silica gel chromatography (30 mm×300 mm column, 10:1 hexanes/EtOAc as eluent, flash column) afforded pure *ent*-**100** as a colorless liquid in 82 % isolated yield (349 mg, 0.82 mmol).

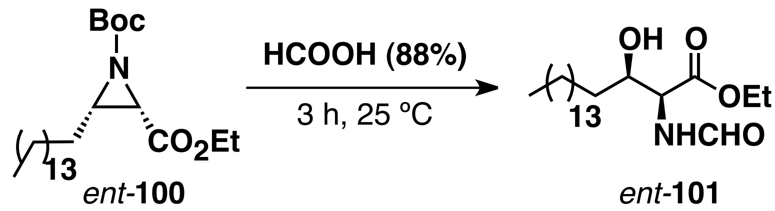
The ^{1}H NMR data matched that for **100** given above. $[\alpha]_D^{20}$ –39.0 (c 1.0, CH_2Cl_2) on 96 % ee material.

3.13.7.2 Ring opening of *N*-Boc aziridine 100 and *ent*-100



(2*R*,3*S*)-ethyl 2-formamido-3-hydroxyoctadecanoate 101: To a 10 mL oven-dried round bottom flask equipped with a stir bar was added *N*-Boc aziridine **100** (85 mg, 0.2 mmol, 98% ee material) and formic acid (2 mL, 88% by volume). The flask was fitted with a rubber septum and a nitrogen balloon. The resulting solution was stirred at room temperature for 3 h under nitrogen atmosphere. Thereafter, the reaction mixture was concentrated under reduced pressure to afford crude **101** as white solid. Purification of the crude **101** by silica gel chromatography (20 mm × 150 mm column, 3:1 hexanes/EtOAc as eluent, flash column) afforded pure **101** as a colorless solid (mp 81-82 ºC) in 98 % isolated yield (73 mg, 0.196 mmol).

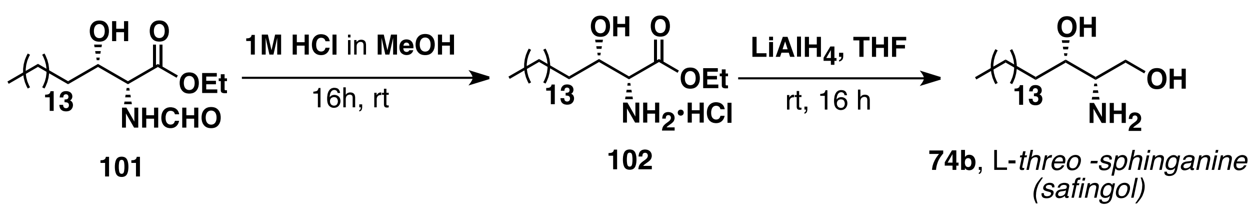
Spectral data for **101:** R_f = 0.05 (1:2 EtOAc / hexanes); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.24-1.30 (m, 29H), 1.44-1.49 (m, 2H), 2.81 (brs, 1H), 4.13 (td, *J* = 6.7, 2.0 Hz, 1H), 4.18-4.26 (m, 2H), 4.70 (dd, *J* = 9.2, 1.9 Hz, 1H), 6.67 (d, *J* = 9.1 Hz, 1H), 8.29 (s, 1H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.10, 14.12, 22.67, 25.56, 29.34, 29.40, 29.49, 29.55, 29.62, 29.64, 29.66, 31.91, 33.80, 54.53, 61.89, 71.88 (3 *sp3* carbon not located), 161.25, 170.81; IR (thin film) 3269 br, 2918vs, 2851vs, 1730s, 1705s, 1541s, 1286s cm-1; HRMS (ESI-TOF) *m/z* 372.3131 [(M+H$^+$); calcd. for $C_{21}H_{42}NO_4$: 372.3114]; $[\alpha]_D^{20}$ –10.7 (c 1.0, CH_2Cl_2) on 98 % ee material.



(2S,3R)-Ethyl 2-formamido-3-hydroxyoctadecanoate *ent*-101: The formamidohydroxy ester *ent*-**101** was synthesized from *N*-Boc aziridine *ent*-**100** (85 mg, 0.2 mmol, 96% ee material) following the procedure described above for the synthesis of **101**. The crude *ent*-**101** (mp 81-82 ºC) was used in the next reaction without further purification.

The ^{1}H NMR data matched that for **101** given above. $[\alpha]_D^{20}$ +9.2 (c 1.0, CH_2Cl_2) on 96 % ee material.

3.13.7.3 Synthesis of L-*threo*-sphinganine 74b and D-*thero*-sphinganine 74c *via* reduction of ester

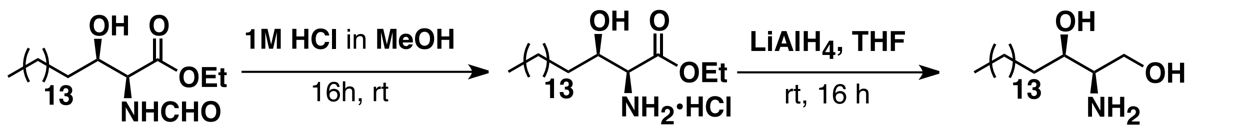


(2R,3S)-ethyl 2-amino-3-hydroxyoctadecanoate hydrochloride 102: To a oven dried 10 mL round bottom flask equipped with a stir bar was added ethyl 2-formamido-3-hydroxyoctadecanoate **101** (63 mg, 0.17 mmol). Methanol (1.0 mL) and HCl methanol mixture (0.6 mL, 1 M solution in methanol) was added to the flask. The flask was fitted with a rubber septum and a nitrogen balloon. The resulting turbid reaction mixture was stirred vigorously under room temperature for 16 h (monitored by TLC) under nitrogen atmosphere. A clear solution of the reaction mixture was observed after 1 h of stirring at room temperature. Upon completion, the reaction mixture was concentrated under reduced pressure to afford crude ethyl 2-amino-3-hydroxyoctadecanoate hydrochloride **102** as white solid. The crude **102** was used in the next reaction without further purification.

Spectral data for **102:** ^{1}**H-NMR** (300MHz, DMSO-d6): δ 0.85 (t, *J* = 6.6 Hz, 3H), 1.17-1.30 (m, 29H), 1.37-1.48 (m, 2H), 3.89-3.92 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 5.63 (d, *J* = 5.7 Hz, 1H), 8.36 (s, 3H); ^{13}**C-NMR** (75 MHz, $CDCl_3$): δ 13.98, 14.11, 22.68, 29.37, 29.67, 29.70, 29.73, 29.76, 31.92, 58.33, 62.95, 69.90, (7 *Sp3* carbon not located), 168.35.

L-*threo*-sphinganine 74b: To an ice-cooled suspension of $LiAlH_4$ (18 mg, 0.48 mmol) in freshly distilled THF (2 mL) under nitrogen was injected a solution of crude ester **102** in THF (1 mL). The reaction mixture was stirred at room temperature for 16 h. After being diluted with 10 mL of dry THF and chilled in an ice-water bath, the reaction mixture was filtered through a pad of silica gel (~ 8 g) slurry in hexane in a sintered glass funnel (2 cm × 6 cm) to remove the salt and the excess $LiAlH_4$ by gentle suction. It was found that this workup procedure was very efficient for small-scale reactions. The pad was washed with $CHCl_3$/MeOH/concentrated NH_4OH 130:25:4 to collect the product. The resulting solution was concentrated under reduced pressure to afford crude L-*threo*-sphinganine **74b** as white solid. Purification of the crude **74b** by silica gel chromatography (20 mm × 120 mm column, 130:25:4 $CHCl_3$/MeOH/concentrated NH_4OH as eluent, flash column) afforded pure **74b** as a white solid. The product was dissolved in $CHCl_3$ and passed through a Cameo filter to remove the dissolved silica gel. Upon concentration of the resulting solution afforded **74b** in 70% isolated yield (36.2 mg, 0.12 mmol) from **101.** (mp 98-101 ºC)

Spectral data for **74b** R_f = 0.27 (130:25:4 $CHCl_3$/MeOH/concentrated NH_4OH); **^{1}H-NMR** (500 MHz, CD_3OD): δ 0.90 (t, *J* = 6.9 Hz, 4H), 1.23-1.40 (m, 26H), 1.43-1.53 (m, 3H), 2.69 (brs, 1H), 3.49 (dd, *J* = 10.8, 6.7 Hz, 1H), 3.53-3.56 (m, 1H), 3.62 (dd, *J* = 10.7, 4.6 Hz, 1H). **^{13}C-NMR** (126 MHz, CD_3OD): δ 14.40, 23.70, 26.92, 30.44, 30.53, 30.75, 33.04, 34.90, 57.95, 64.55, 72.26 (7 *sp3* carbon not located); $[\alpha]_D^{20}$ −12.3 (c 0.3, 1:10 MeOH/ $CHCl_3$)



ent-**101** *ent*-**102** **74c**, D-*threo -sphinganine*

(2*S*,3*R*)-Ethyl 2-amino-3-hydroxyoctadecanoate hydrochloride ***ent*-102:** The ester *ent*-**102** was synthesized from crude *ent*-**101** following the procedure described above for the synthesis of **102**. The crude *ent*-**102** was used in the next reaction without further purification.

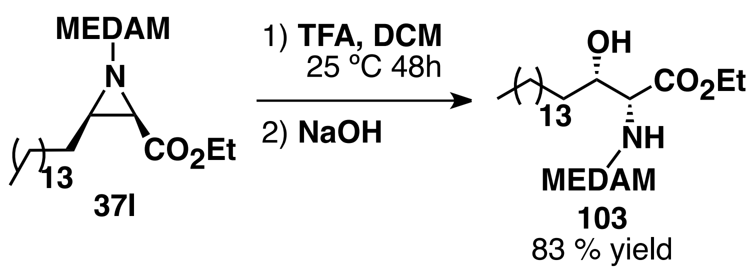
The ^{1}H NMR data matched that for **102** given above.

D-*threo*-sphinganine 74c: The ester D-*threo*-sphinganine **74c** was synthesized from crude *ent*-**102** following the procedure described above for the synthesis of **74b**. Purification of the crude **74c** by silica gel chromatography (20 mm × 120 mm column, 130:25:4 $CHCl_3$/MeOH/concentrated NH_4OH as eluent, flash column) afforded pure **74c** as a white solid (99-101 ºC) in 75% isolated yield (45 mg, 0.15 mmol) in three steps starting from *ent*-**100**.

Spectral data for **74c** R_f = 0.27 (130:25:4 $CHCl_3$/MeOH/concentrated NH_4OH); **^{1}H-NMR** (500 MHz, CD_3OD): δ 0.90 (t, J = 6.9 Hz, 4H), 1.24-1.42 (m, 26H), 1.43-1.53 (m, 3H), 2.67 (brs, 1H), 3.44-3.49 (m, 1H), 3.51-3.56 (m, 1H), 3.61 (dd, J = 10.7, 4.9 Hz, 1H). **^{13}C-NMR** (126 MHz, CD_3OD): δ 14.40, 23.70, 26.92, 30.44, 30.53, 30.75, 33.04, 34.90, 57.95, 64.55, 72.26 (7 *sp3* carbon not located); $[\alpha]_D^{20}$ +12.1 (c 0.3, 1:10 MeOH/ $CHCl_3$)

3.13.8 Enantioselective synthesis of L-*threo*-sphinganine 74b and D-*threo*-sphinganine 74c *via* route II

3.13.8.1 Ring opening of *N*-MEDAM aziridine 37l and *ent*-37l

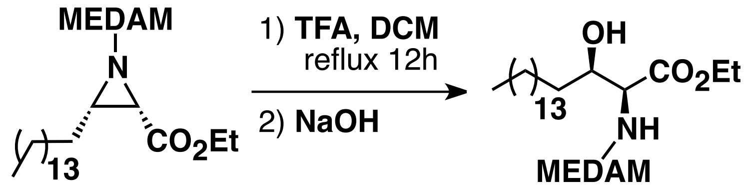


(2*R*, 3*S*)-Ethyl 2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-3-hydroxyoctadecanoate 103:

To a 10 mL flame-dried round bottom flask equipped with a stir bar and a rubber septum with a nitrogen balloon at the top, was added aziridine **37l** (304 mg, 0.50 mmol, 96% ee material). Dry CH_2Cl_2 (1.0 mL) was added to dissolve **37l**. Thereafter, trifluoroacetic acid (38.2 μL, 0.5 mmol, 1.0 equiv) was added to the reaction flask. The resulting reaction mixture was stirred at room temperature for 48 h (monitored by TLC). The reaction mixture was concentrated under reduced pressure to afford colorless viscous oil. The crude product was dissolved in ethanol (2 mL). To the solution was added a sodium hydroxide (20 mg, 0.5 mmol, 1 equiv) solution in ethanol water mixtre (1.25 mL, 2:1 EtOH/H_2O). The resulting mixture was stirred for 20 min (monitored by TLC) at room temperature until the compound with R_f = 0.67 (2:1 hexnanes/Et_2O) disappeared. Upon completion, 15 mL water was added to the reaction flask and the water layer was extracted with ether (4 × 20 mL). The combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude reaction mixture as colorless oil. Purification of the crude **103** by silica gel chromatography (20 mm × 150 mm column, 3:1 hexanes/Et_2O as eluent, flash column) afforded pure ester **103** as a colorless viscous liquid in 83% isolated yield over two steps (260 mg, 0.415 mmol). The optical purity of **103** was determined to be 96% *ee* by HPLC analysis (CHIRALCEL OD-H column, 94:6 hexane/2-propanol at 222nm, flow-rate: 0.5 mL/min): retention times; R_t = 4.92 min (major enantiomer, **103**) and R_t = 5.89 min (minor enantiomer, *ent*-**103**).

Spectral data for **103** R_f = 0.35 (1:1 Et_2O / hexanes) **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.25-1.30 (m, 29H), 1.43-1.48 (m, 2H), 2.24 (s, 6H), 2.25 (s, 6H), 3.06 (d, *J* = 5.7 Hz, 1H), 3.64-3.60 (m, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.57 (s, 1H), 6.96 (s, 2H), 6.99 (s, 2H) (NH and OH proton not located). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.10, 14.32, 16.19, 16.26, 22.68, 25.62, 29.35, 29.58, 29.62, 29.64, 29.65, 29.67, 29.67, 29.69, 31.92, 33.79 (2 *sp3* carbon not located), 59.57, 59.58, 60.90, 63.71, 64.80, 72.44, 127.43, 127.85, 130.70, 130.79, 137.34, 139.22, 156.04, 156.07, 174.08. IR (thin film) 3466br, 2926vs, 2855s 1734s, 1484s, 1221s, 1142s cm-1; HRMS (ESI-TOF) *m/z* 626.4800 [(M+H+); calcd. for

$C_{39}H_{64}NO_5$: 626.4784]; $[\alpha]_D^{20}$ +19.5 (c 1.0, CH_2Cl_2) on 96% ee material.



ent-**37l**

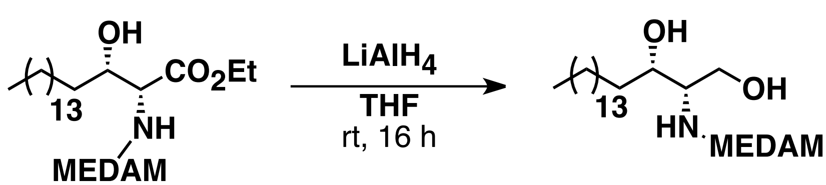
ent-**103**
75 % yield

(2*S*, 3*R*)-Ethyl 2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)-3-hydroxyoctadecanoate *ent*-103:

The *ent*-**103** was synthesized from aziridine *ent*-**37l** (304 mg, 0.50 mmol, 96% ee material) following the procedure described above for the synthesis of **103** except the reaction mixture was refluxed for 32 h in CH_2Cl_2. Purification of the crude *ent*-**103** by silica gel chromatography (20 mm × 150 mm column, 3:1 hexanes/Et_2O as eluent, flash column) afforded pure ester *ent*-**103** as a colorless viscous liquid in 75% isolated yield over two steps (235 mg, 0.375 mmol).

The ^{1}H NMR data matched that for **103** given above. $[\alpha]_D^{20}$ –20.2 (c 1.0, CH_2Cl_2) on 96% ee material.

3.13.8.2 Reduction of terminal ester in 104 and *ent*-104



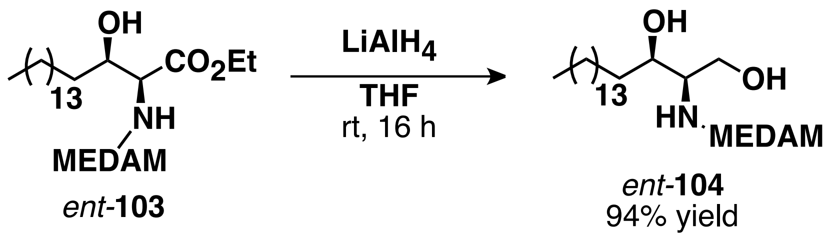
103

104
96% yield

(2*S*, 3*S*)-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)octadecane-1,3-diol 104: To a

10 mL flame-dried round bottom flask equipped with a stir bar and a rubber septum with a nitrogen balloon at the top, was added $LiAlH_4$ (11.4 mg, 0.3 mmol, 1.5 equiv) and dry THF (0.5 mL). the suspension was cooled to 0 ºC in ice water bath. To the LAH suspension was added a solution of **103** (125 mg, 0.2 mmol, 96% ee material) in dry THF (1 mL). The resulting reaction mixture was stirred at room temperature for 16 h (monitored by TLC). Upon completion, the reaction mixture was cooled to 0 ºC. To the reaction mixture was added 0.3 mL water. The reaction mixture was filtered through Celite-pad to a 250 mL round bottom flask. The Celite-pad was washed with ethyl acetate (5 × 15 mL). The resulting solution was concentrated under reduced pressure followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude **104** as a light yellow liquid. Purification of the crude **104** by silica gel chromatography (20 mm × 150 mm column, 3:1 hexanes/EtOAc as eluent, flash column) afforded pure ester **104** as a colorless liquid in 96 % isolated yield (111 mg, 0.19 mmol).

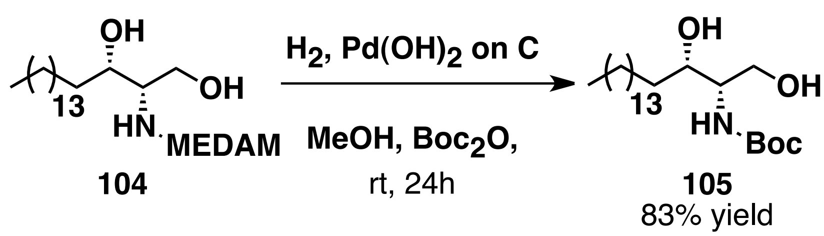
Spectral data for **104** R_f = 0.06 (1:1 Et_2O / hexanes) **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 4H), 1.26 (s, 26H), 1.56-1.44 (m, 2H), 2.25 (s, 12H), 2.47 (td, J = 4.2, 3.0 Hz, 1H), 3.58 (dd, J = 11.2, 2.8 Hz, 1H), 3.66-3.67 (m, 1H), 3.68 (m, 6H), 3.77 (dd, J = 11.2, 4.0 Hz, 1H), 4.76 (s, 1H), 7.01 (s, 2H), 7.02 (s, 2H) (NH and OH proton not located). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.10, 16.23, 16.26, 22.68, 25.88, 29.35, 29.64, 29.65, 29.68, 29.69, 29.73, 31.92, 34.44 (4 *sp3* carbon not located), 58.75, 59.59, 59.61, 62.35, 63.99, 73.59, 127.42, 127.68, 130.72, 130.79, 138.51, 139.53, 155.97 (one *sp2* carbon not located). IR (thin film) 3395br, 2924vs, 2855s, 1483s, 1221s, 1142s cm-1; HRMS (ESI-TOF) *m/z* 584.4685 [(M+H^+); calcd. for $C_{37}H_{62}NO_4$: 584.4679]; $[\alpha]_D^{20}$ +12.5 (c 1.0, CH_2Cl_2) on 96% ee material.



(2*S*, 3*S*)-2-((bis(4-methoxy-3,5-dimethylphenyl)methyl)amino)octadecane-1,3-diol *ent*-104: The 2-amino-1,3-diol *ent*-**104** was synthesized from ester *ent*-**103** (125 mg, 0.2 mmol, 96% ee material) following the procedure described above for the synthesis of **103**. Purification of the crude *ent*-**104** by silica gel chromatography (20 mm × 150 mm column, 3:1 hexanes/EtOAc as eluent, flash column) afforded pure ester *ent*-**104** as a colorless liquid in 94 % isolated yield (109 mg, 0.188 mmol).

The ^{1}H NMR data matched that for **104** given above. $[\alpha]_D^{20}$ −12.0 (c 1.0, CH_2Cl_2) on 96% ee material.

3.13.8.3 Reductive deprotection of *N*-MEDAM group



tert-**Butyl ((2*S*, 3*S*)-1,3-dihydroxyoctadecan-2-yl)carbamate 105:** To a flame dried 25 mL round bottom flask filled with N_2 was added the aziridine (90 mg, 0.15 mmol), MeOH (1.5 mL), Pearlman's catalyst (20% $Pd(OH)_2$ on carbon, moisture *ca* 60%, 27 mg, 0.016 mmol, 0.10 equiv) and $(Boc)_2O$ (66 mg, 0.3 mmol, 2.00 equiv). The flask was equipped with a vacuum transfer adapter connected with vacuum and a H_2 balloon. The valve to vacuum was opened for a few seconds and then switched to the H_2 balloon. This process was repeated 3 additional times. The suspension was stirred at room temperature under a H_2 ballon for 24 hours. Then the mixture was filtered through a Celite pad on a sintered glass funnel and the Celite pad was washed with ethyl acetate (3 × 15 mL). The filtrate was concentrated by rotary evaporation. Purification of the crude **105** by silica gel chromatography (20 mm × 150 mm column, 1:1 hexanes/EtOAc as eluent, flash column) afforded pure *N*-Boc L-*threo*-sphinganine **105** as a white solid (mp 80-81 ºC) in 83% isolated yield (50 mg, 0.12 mmol).

Spectral data for **105** R_f = 0.12 (1:2 EtOAc / hexanes) **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.0 Hz, 3H), 1.28-1.22 (m, 26H), 1.42 (s, 9H), 1.48-1.45 (m, 2H), 2.75 (brs, 2H), 3.55 (brs, 1H), 3.76 (d, *J* = 4.2 Hz, 2H), 3.87-3.83 (m, 1H), 5.23 (d, *J* = 6.6 Hz, 1H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 14.07, 22.65, 25.55, 28.33, 29.32, 29.53, 29.58, 29.62, 29.65, 29.66, 31.88, 34.16, 54.29, 65.22, 72.86, 79.59, 156.50. (4 *sp3* carbon not located); $[\alpha]_D^{20}$ +20.0 (c 1.0, $CHCl_3$), Lit[30] $[\alpha]_D^{21}$ +19.8 (c 1.0, $CHCl_3$).

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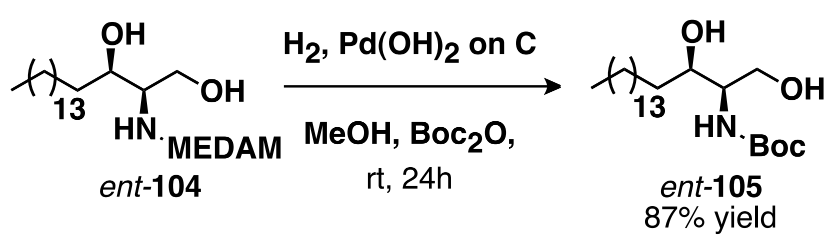
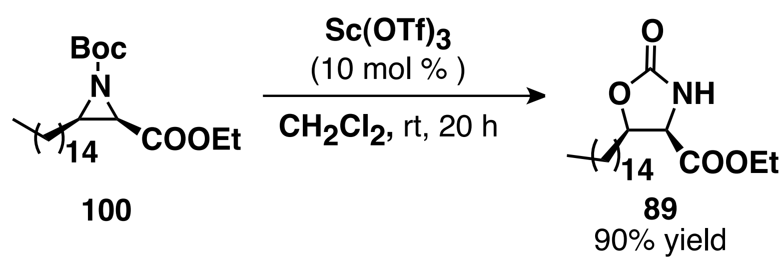


tert-**Butyl ((2*R*, 3*R*)-1,3-dihydroxyoctadecan-2-yl)carbamate** *ent*-**105:** The *N*-Boc D-*threo*-sphinganine *ent*-**105** was synthesized from *ent*-**104** following the procedure described above for the synthesis of **105**. Purification of the crude *ent*-**105** by silica gel chromatography (20 mm × 150 mm column, 1:1 hexanes/EtOAc as eluent, flash column) afforded pure ester *ent*-**105** as a white solid (mp 81 ºC) in 87% isolated yield (52 mg, 0.13 mmol).

Spectral data for *ent*-**105**: ^{1}**H-NMR** (600 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.0 Hz, 3H), 1.28-1.22 (m, 26H), 1.42 (s, 9H), 1.49-1.46 (m, 2H), 2.75 (brs, 2H), 3.56 (brs, 1H), 3.76 (d, *J* = 4.2 Hz, 2H), 3.88-3.84 (m, 1H), 5.23 (d, *J* = 6.6 Hz, 1H); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ 14.10, 22.68, 25.61, 28.36, 29.35, 29.59, 29.63, 29.67, 29.70, 31.92, 34.18, 54.39, 65.04, 72.66, 79.64, 156.58, (5 *sp3* carbon not located); $[\alpha]_D^{20}$ –20.6 (c 1.0, $CHCl_3$).

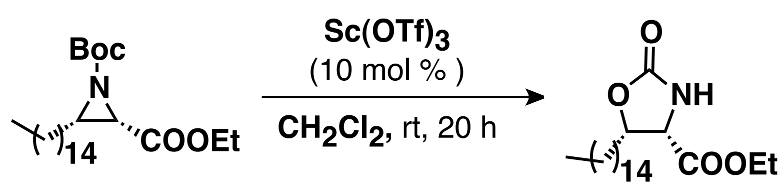
3.13.9 Enantioselective synthesis of D-*erythro*-sphinganine 74a and L-*erythro*-sphinganine 74d

3.13.9.1 Lewis acid catalyzed ring expansion of *N*-Boc aziridine 100 and *ent*-100



(4*R*, 5*R*)-Ethyl 2-oxo-5-pentadecyloxazolidine-4-carboxylate 89: To a 10 mL flame-dried round bottom flask equipped with a stir bar and a rubber septum with a nitrogen balloon at the top, was added *N*-Boc aziridine **100** (85 mg, 0.2 mmol, 98% ee material) and dry CH_2Cl_2 (2 mL). To the resulting solution was added $Sc(OTf)_3$(10 mg, 0.02 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature for 20 h (monitored by TLC) under nitrogen atmosphere. Thereafter, the reaction mixture was filtered through a silica gel plug on a sintered glass funnel. The silica plug was washed with ethyl acetate (3 × 10 mL). The filtrate was concentrated under reduced pressure to afford crude oxazolidinone **89** as white solid. Purification of the crude **89** by silica gel chromatography (20 mm × 150 mm column, 3:1 hexanes/EtOAc as eluent, flash column) afforded pure oxazolidinone **89** as a white solid in 90% isolated yield (66 mg, 0.18 mmol).

Spectral data for **89** R_f = 0.22 (1:2 EtOAc / hexanes). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.25-1.32 (m, 29H), 1.51-1.64 (m, 2H), 4.28-4.23 (m, 2H), 4.37 (d, *J* = 8.4 Hz, 1H), 4.74 (td, *J* = 8.9, 3.9 Hz, 1H), 5.85 (s, 1H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 14.07, 14.08, 14.09, 14.15, 22.67, 25.56, 25.57, 29.16, 29.33, 29.46, 29.57, 29.62, 29.63, 29.65, 30.62, 31.90, 58.10, 61.97, 78.33, 158.91, 169.18. IR (thin film) 2928vs, 2855vs, 1759s, 1737s, 1299s, 1159vs cm^{-1}; HRMS (ESI-TOF) *m/z* 370.2953 [$(M+H^+)$; calcd. for $C_{21}H_{40}NO_4$: 370.2949]; $[\alpha]_D^{20}$ +16.2 (c 1.0, EtOAc) on 98% ee material



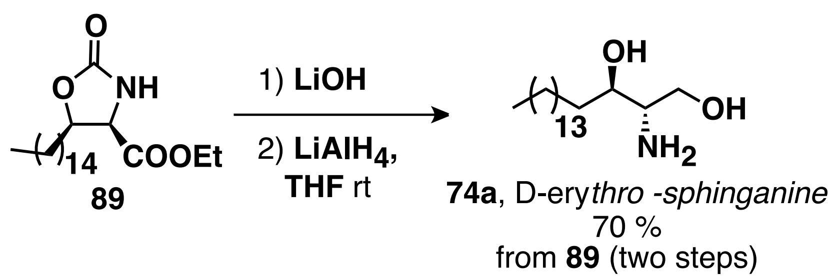
ent-**100**

ent-**89**
93% yield

(4*S*, 5*S*)-Ethyl 2-oxo-5-pentadecyloxazolidine-4-carboxylate *ent*-89: The oxazolidinone *ent*-**89** was synthesized from *ent*-**100** (85 mg, 0.2 mmol, 96% ee material) following the procedure described above for the synthesis of **89**. Purification of the crude **89** by silica gel chromatography (20 mm × 150 mm column, 3:1 hexanes/EtOAc as eluent, flash column) afforded pure oxazolidinone *ent*-**89** as a white solid in 93% isolated yield (69 mg, 0.186 mmol).

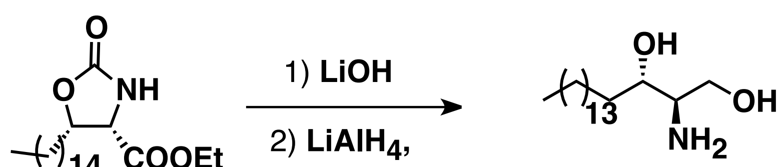
The ^{1}H NMR data matched that for **89** given above. $[\alpha]_D^{20}$ –15.7 (c 1.0, EtOAc).

3.13.9.2 Synthesis of D- and L-*erythro*-sphinganines



D-*erythro*-sphinganine 74a: To a 10 mL oven-dried round bottom flask equipped with a stir bar and a rubber septum with a nitrogen balloon at the top was added oxazolidinone **89** (72 mg, 0.2 mmol) and ethanol (2.5 mL). To the resulting solution was added lithium hydroxide (39 mg, 1.6 mmol, 8 equiv). The resulting suspension was stirred for 3 h (monitored by TLC) at room temperature under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure. The resulting crude white solid was transferred to a 10 mL flame dried round bottom flask and dry THF (3.0 mL) was added to it. The reaction flask was cooled to 0 ºC and $LiAlH_4$ (23 mg, 0.6 mmol, 3.0 equiv) was added to the reaction flask. The reaction mixture was stirred at room temperature for 24 h (monitored by TLC) under nitrogen atmosphere. Upon completion, the reaction mixture was cooled to 0 ºC. To the reaction mixture was added 0.4 mL water. The reaction mixture was filtered through Celite-pad to a 250 mL round bottom flask. The Celite-pad was washed with 130:25:4 $CHCl_3$/MeOH/concentrated NH_4OH mixture (5 × 15 mL). The resulting solution was concentrated under reduced pressure followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude **74a** as white solid. Purification of the crude **74a** by silica gel chromatography (20 mm × 120 mm column, 130:25:4 $CHCl_3$/MeOH/concentrated NH_4OH as eluent, flash column) afforded pure **74a** as a white solid. The product was dissolved in $CHCl_3$ and passed through a Cameo filter to remove the dissolved silica gel. Upon concentration of the resulting solution afforded D-*erythro*-sphinganine **74a** in 70% isolated yield over two steps from **89** (42 mg, 0.14 mmol).

Spectral data for **74a:** R_f = 0.25 (130:25:4 $CHCl_3$/MeOH/concentrated NH_4OH); **^{1}H-NMR** (500 MHz, CD_3OD): δ 0.89 (t, J = 7.0 Hz, 3H), 1.24-1.42 (m, 26H), 1.43-1.53 (m, 3H), 2.69 (brs, 1H), 3.45-3.49 (m, 1H), 3.50-3.55 (m, 1H), 3.59-3.63 (m, 1H); **^{13}C-NMR** (126 MHz, CD_3OD): δ 15.44, 24.73, 27.96, 31.47, 31.56, 31.78, 34.07, 35.93, 58.98, 65.59, 73.29 (7 *Sp3* C not located); $[\alpha]_D^{20}$ −1.9 (c 1.0, pyridine)



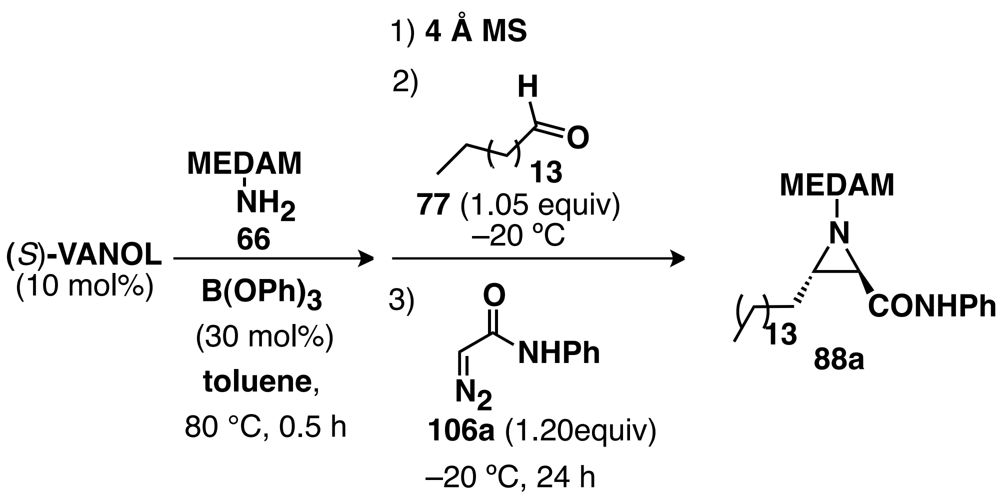
74d, L-ery*thro -sphinganine*
75 %
over two steps

L-***erythro*-sphinganine 74d:** The L-*erythro*-sphinganine **74d** was synthesized from *ent*-**89** (72 mg, 0.2 mmol) following the procedure described above for the synthesis of **74a**. Purification of the crude **74d** by silica gel chromatography (20 mm × 150 mm column, 130:25:4 $CHCl_3$/MeOH/concentrated NH_4OH as eluent, flash column) afforded pure L-*erythro*-sphinganine **74d** as a white solid in 75% isolated yield (45 mg, 0.15 mmol) over two steps from oxazolidinone *ent*-**89**.

Spectral data for **74d:** ^{1}**H-NMR** (500 MHz, CD_3OD): δ 0.89 (t, J = 7.0 Hz, 3H), 1.23-1.41 (m, 26H), 1.43-1.54 (m, 3H), 2.80 (brs, 1H), 3.45-3.49 (m, 1H), 3.50-3.56 (m, 1H), 3.59-3.63 (m, 1H); ^{13}**C-NMR** (126 MHz, CD_3OD): δ 16.44, 25.73, 28.96, 32.47, 32.56, 32.78, 35.07, 36.93, 59.98, 66.59, 74.29 (7 *Sp3* C not located); $[\alpha]_D^{20}$ +2.1 (c 1.0, pyridine)

3.13.10 Asymmetric catalytic multi-component *trans*-aziridination of aldehyde 77 to synthesize *trans*-aziridine 88 (Procedure B)

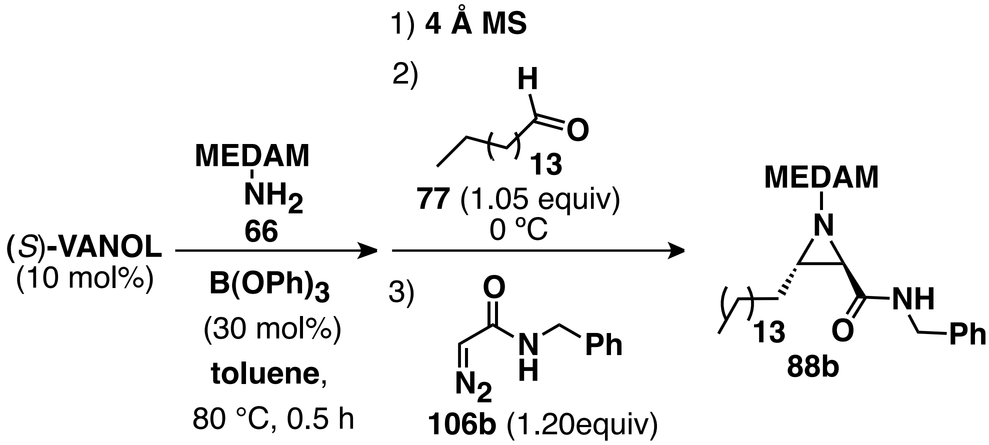
3.13.10.1 Asymmetric catalytic multi-component *trans*-aziridination of aldehyde 77 with diazoacetamide 106a



(2*R*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-pentadecyl-*N*-phenylaziridine-2-carboxamide 88a: Aldehyde **77** was reacted with 2-diazo-*N*-phenylacetamide **106a** (97 mg, 0.6 mmol, 1.2 equiv) according to the general aziridination Procedure B described above with (*S*)-VANOL (22 mg, 0.05 mmol, 10 mol%) as ligand at –20 ºC, to afford *trans*- aziridines **88a**. Purification of the crude aziridine by silica gel chromatography (30 mm × 300 mm column, 3:1 hexanes/Et_2O as eluent, gravity column) afforded *trans*- aziridines **88a** as colorless viscous liquid in 35% isolated yield (114 mg, 0.175 mmol). The optical purity of **88a** was determined to be 57% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O1column, 90:10 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 5.20 min (major enantiomer, **88a**) and R_t = 16.03 min (minor enantiomer, *ent*-**88a**).

Spectral data for **88a:** R_f = 0.37 (1:1 Et_2O / hexanes). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.19-1.32 (m, 26H), 1.53-1.63 (m, 2H), 2.17 (d, *J* = 2.9 Hz, 1H), 2.22 (s, 6H), 2.29 (s, 6H), 2.45 (ddd, *J* = 7.7, 5.1, 2.8 Hz, 1H), 3.65 (s, 3H), 3.71 (s, 3H), 4.19 (s, 1H), 7.01 (s, 2H), 7.12 (s, 2H), 7.31 (t, *J* = 7.9 Hz, 3H), 7.47-7.49 (m, 2H), 8.53 (s, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.10, 16.28, 16.32, 22.67, 26.13, 28.06, 29.27, 29.34, 29.46, 29.49, 29.64, 29.68, 31.91, 45.24, 47.52, 59.53, 59.62, 67.59, (4 *sp3* carbon not located), 119.43, 123.99, 126.86, 127.62, 128.95, 130.67, 130.99, 137.56, 138.28, 138.37, 155.92, 156.23, 168.55. IR (thin film) 3317br, 2926vs, 2855vs, 1684s, 1444s, 1223s cm^{-1}; HRMS (ESI-TOF) *m/z* 655.4865 [(M+H^+); calcd. for $C_{43}H_{63}N_2O_3$: 655.4839]; $[\alpha]_D^{20}$ +13.0 (c 1.0, CH_2Cl_2) on 57% ee material.

3.13.10.2 Asymmetric catalytic multi-component *trans*-aziridination of aldehyde 77 with diazoacetamide 106b

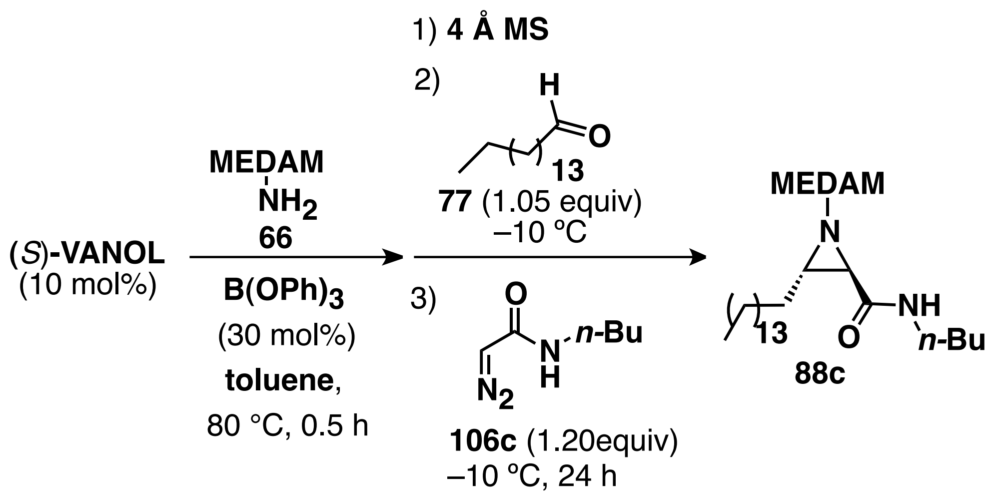


(2*R*,3*S*)-*N*-benzyl-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-pentadecylaziridine-2-carboxamide 88b: Aldehyde **77** was reacted with *N*-benzyl-2-diazoacetamide **106b** (105 mg, 0.6 mmol, 1.2 equiv) according to the general aziridination Procedure B described above with (*S*)-VANOL (22 mg, 0.05 mmol, 10 mol%) as ligand at 0 ºC, to afford *trans*- aziridines **88b**. Purification of the crude aziridine by silica gel chromatography (30 mm × 300 mm column, 5:1 hexanes/Et_2O as eluent, gravity column) afforded *trans*- aziridines **88b** as colorless viscous liquid in 55% isolated yield (184 mg, 0.275 mmol). The optical purity of **88b** was determined to be 88% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O1column, 90:10 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 6.01 min (major enantiomer, **88b**) and R_t = 10.14 min (minor enantiomer, *ent*-**88b**).

Aldehyde **77** was reacted with **106b** according to the general Procedure B described above in presence of (*S*)-VANOL as ligand at different temperature in toluene. The results are represented in Table 3.7 (Chapter 3).

Spectral data for **88b:** R_f = 0.28 (1:1 Et_2O / hexanes). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.19-1.33 (m, 26H), 1.52-1.57 (m, 2H), 2.15 (d, *J* = 2.8 Hz, 1H), 2.18 (s, 6H), 2.22-2.26 (m, 7H), 3.68 (s, 3H), 3.69 (s, 3H), 4.13 (s, 1H), 4.20 (dd, *J* = 15.2, 4.9 Hz, 1H), 4.59 (dd, *J* = 15.2, 7.3 Hz, 1H), 6.93-6.97 (m, 3H), 7.06 (s, 2H), 7.13-7.12 (m, 2H), 7.28-7.33 (m, 3H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.06, 16.17, 16.21, 22.64, 26.02, 28.09, 29.27, 29.31, 29.43, 29.47, 29.61, 29.65, 31.88, 42.50, 44.76, 47.39, 59.50, 59.54, 67.66, (4 *sp3* carbon not located), 126.89, 127.06, 127.18, 127.66, 128.59, 130.48, 130.75, 138.33, 138.39, 138.45, 155.77, 156.10, 170.62; IR (thin film) 3306br, 2926vs, 2855vs, 1649s, 1483s, 1221s, 1136s cm-1; HRMS (ESI-TOF) *m/z* 669.5004 [(M+H+); calcd. for $C_{44}H_{65}N_2O_3$: 669.4995]; $[\alpha]_D^{20}$ −15.5 (c 1.0, CH_2Cl_2) on 83% ee material.

3.13.10.3 Asymmetric catalytic multi-component *trans*-aziridination of aldehyde 77 with diazoacetamide 106c



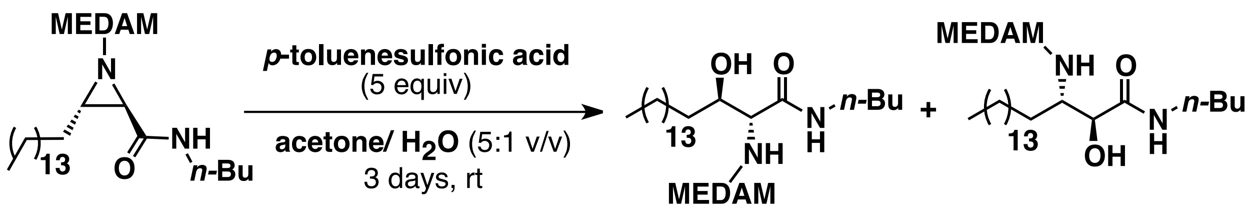
(2*R*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-*N*-butyl-3-pentadecylaziridine-2-carboxamide 88c: Aldehyde **77** was reacted with *N*-butyl-2-diazoacetamide **106c** (85 mg, 0.6 mmol, 1.2 equiv) according to the general aziridination Procedure B described above with (*S*)-VANOL (22 mg, 0.05 mmol, 10 mol%) as ligand at –10 ºC, to afford *trans*- aziridines **88c**. Purification of the crude aziridine by silica gel chromatography (30 mm × 300 mm column, 5:1 hexanes/Et_2O as eluent, gravity column) afforded *trans*- aziridines **88c** as colorless viscous liquid in 70% isolated yield (222 mg, 0.35 mmol). The optical purity of **88c** was determined to be 93% *ee* by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O1column, 90:10 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 5.09 min (major enantiomer, **88c**) and R_t = 8.84 min (minor enantiomer, *ent*-**88c**).

Aldehyde **77** was reacted with **106c** according to the general Procedure B described above in presence of (*S*)-VANOL as ligand at different temperature in toluene. The results are represented in Table 3.7 (Chapter 3).

Spectral data for **88c:** R_f = 0.26 (1:1 Et_2O / hexanes). **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 5.7 Hz, 3H), 0.90 (t, *J* = 6.0 Hz, 3H), 1.20-1.29 (m, 30H), 1.42 (dd, *J* = 14.5, 7.4 Hz, 2H), 1.48-1.53 (m, 1H), 2.04 (d, *J* = 2.9 Hz, 1H), 2.21 (s, 6H), 2.27 (s, 6H), 2.99 (dtd, *J* = 13.3, 6.8, 5.2 Hz, 1H), 3.34 (dq, *J* = 13.6, 6.9 Hz, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 4.10 (s, 1H), 6.63 (dd, *J* = 7.1, 5.0 Hz, 1H), 6.94 (s, 2H), 7.07 (s, 2H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 13.71, 14.04, 16.14, 16.22, 19.85, 22.62, 26.03, 28.06, 29.25, 29.29, 29.41, 29.44, 29.58, 29.59, 29.63, 31.81, 31.86, 38.23, 44.79, 47.29, 59.44, 59.52, 67.54, (3 sp3 carbon not located), 126.88, 127.60, 130.45, 130.63, 138.53, 138.55, 155.76, 156.04, 170.45; IR (thin film) 3312br, 2926vs, 2855vs, 1647s, 1484s, 1221s, 1143s cm-1; HRMS (ESI-TOF) *m/z* 635.5151 [(M+H$^+$); calcd. for $C_{41}H_{67}N_2O_3$: 635.5152]; $[\alpha]_D^{20}$ –22.0 (c 1.0, CH_2Cl_2) on 93% ee material.

3.13.11Ring opening of *trans*-aziridine

3.13.12 Ring opening of *trans*-aziridine 88c with water



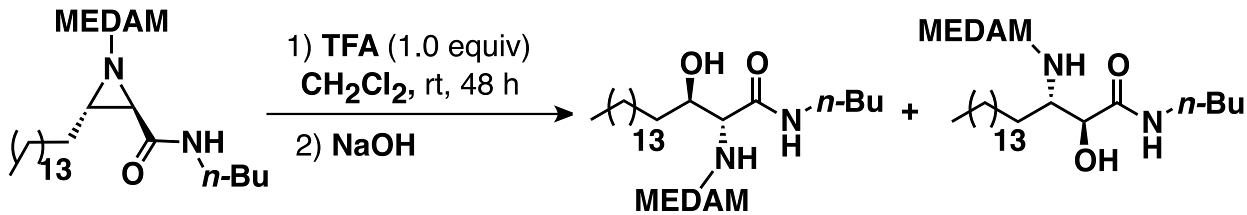
88c **107** **108**

To an oven dried 10 mL round bottom flask flushed with nitrogen was added *trans*-aziridine **88c** (75 mg, 0.12 mmol, 90% ee) and acetone (0.82 mL). To the resulting solution was added *p*-toluenesulfonic acid (114 mg, 0.6 mmol, 5.0 equiv) and water (0.18 mL). The reaction mixture was stirred at room temperature for 3 days (monitored by TLC) under nitrogen atmosphere. The reaction mixture was diluted with water (10 mL) and the water layer was extracted with ethyl acetate (4 × 10 mL). The combined water layer was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the crude aziridine by silica gel chromatography (20 mm × 200 mm column, 4:1 hexanes/EtOAc as eluent, flash column) afforded *C3* ring opened product **107** in 28% (22 mg, 0.034 mmol) yield as colorless viscous liquid and *C2* ring opened product **108** in 53% yield (41 mg, 0.064 mmol) colorless viscous liquid.

Spectral data for **107:** R_f = 0.54 (1:2 EtOAc / hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H), 1.23-1.28 (m, 30H), 1.45-1.50 (m, 2H), 2.24 (s, 6H), 2.25 (s, 6H), 2.93 (brs, 1H), 2.99 (d, J = 5.0 Hz, 1H), 3.24-3.29 (m, 2H), 3.68 (s, 3H), 3.69 (s, 3H), 3.76-3.80 (m, 1H), 4.57 (s, 1H), 6.66 (t, J = 5.8 Hz, 1H), 6.96 (s, 2H), 6.97 (s, 2H), (OH proton not located). ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ 13.71, 14.08, 16.20, 16.22, 20.09, 22.66, 25.84, 29.33, 29.56, 29.59, 29.61, 29.63, 29.65, 29.66, 29.67, 31.67, 31.90, 33.51, 38.82, 59.55, 59.58, 63.90, 64.79, 72.73, (three *sp3* carbon not located), 127.52, 127.59, 130.80, 130.94, 156.06, 156.11, 169.03; IR (thin film) 3339br, 2926vs, 2855vs, 1653s, 1485s, 1221s, 1142vs cm-1; HRMS (ESI-TOF) *m/z* 653.5281 [(M+H+); calcd. for $C_{41}H_{69}N_2O_4$: 653.5257]; $[\alpha]_D^{20}$ +3.0 (c 1.0, CH_2Cl_2).

Spectral data for **108:** R_f = 0.31 (1:2 EtOAc / hexanes); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H), 1.19-1.30 (m, 30H), 1.45-1.50 (m, 2H), 2.24 (s, 6H), 2.26 (s, 6H), 2.94-2.97 (m, 1H), 3.15-3.22 (m, 1H), 3.28-3.35 (m, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 4.01 (d, J = 4.5 Hz, 1H), 4.67 (s, 1H), 6.90-6.93 (m, 3H), 6.94 (s, 2H), (OH and NH protons not located); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ 13.69, 14.09, 16.22, 16.23, 20.08, 22.67, 25.78, 28.66, 29.34, 29.58, 29.64, 29.65, 29.68, 31.62, 31.91, 38.53, 57.68, 59.60, 63.32, 70.82, 127.49, 127.51, 130.78, 130.94, 138.36, 138.51, 156.00, 156.09, 171.90, (6 *sp3* carbon not located) ; IR (thin film) 3327br, 2926vs, 2855vs, 1647s, 1483s, 1221s, 1140s cm-1; HRMS (ESI-TOF) *m/z* 653.5254 [(M+H$^+$); calcd. for $C_{41}H_{69}N_2O_4$: 653.5257]; $[\alpha]_D^{20}$ –6.0 (c 1.0, CH_2Cl_2).

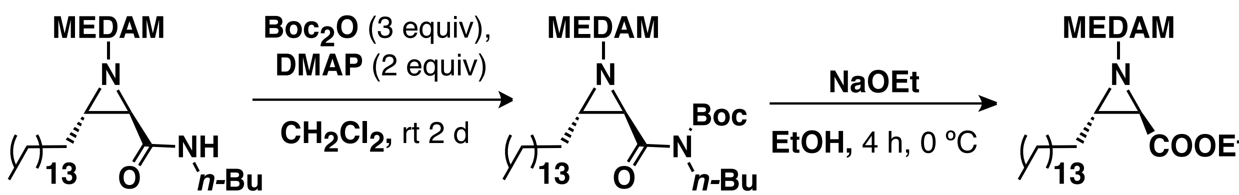
3.13.13 Ring opening of *trans*-aziridine 88c with TFA



88c 107 108

The ring opening reaction of *trans*-**88c** (127 mg, 0.2 mmol) was performed following the procedure described above for the synthesis of **103** from *cis*-aziridine **37l**. Purification of the crude mixture by silica gel chromatography (20 mm × 200 mm column, 4:1 hexanes/EtOAc as eluent, flash column) afforded afforded *C3* ring opened product **107** in 20% (26 mg, 0.04 mmol) yield as colorless liquid and *C2* ring opened product **108** in 40% yield (52 mg, 0.08 mmol) colorless liquid.

3.13.14 Synthesis of *trans*-aziridine 2- carboxylate 110



tert-**Butyl ((2*R*, 3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-pentadecylaziridine-2-carbonyl)(butyl)carbamate 109:** To an flame dried 10 mL round bottom flask flushed with nitrogen was added *trans*-aziridine **88c** (317 mg, 0.5 mmol) and dichloromethane (2 mL). To the resulting solution was added DMAP (120 mg, 1.0 mmol, 2.0 equiv) and Boc_2O (327 mg, 1.5 mmol, 3.0 equiv). The reaction mixture was stirred for 2 days at room temperature under nitrogen atmosphere. Thereafter, the reaction mixture was concentrated under reduced pressure to afford crude dark yellow oil. Purification of the crude mixture by silica gel chromatography (20 mm × 200 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded **109** in 60% (220 mg, 0.3 mmol) yield as colorless viscous liquid and 38% starting material *trans*-aziridine **88c** (120 mg, 0.19 mmol) was recovered.

Spectral data for **109:** R_f = 0.45 (1:2 Et_2O / hexanes); ^{1}**H-NMR** (600 MHz, $CDCl_3$): δ 0.85-0.89 (m, 6H), 1.16-1.29 (m, 32H), 1.41 (s, 9H), 2.19 (s, 7H), 2.24 (s, 6H), 2.44-2.46 (m, 1H), 3.36-3.40 (m, 1H), 3.46-3.49 (m, 1H), 3.63 (s, 3H), 3.67 (s, 3H), 4.42 (s, 1H), 7.00 (s, 2H), 7.10 (s, 2H); ^{13}**C-NMR** (151 MHz, $CDCl_3$): δ 13.78, 14.09, 16.14, 16.17, 20.04, 22.68, 27.06, 27.87, 29.24, 29.35, 29.54, 29.59, 29.65, 29.67, 29.69, 30.49, 31.92, 32.59, 44.04, 44.83, 47.68, 59.44, 59.55, 67.40, 82.63, (three *sp3* carbon not located), 127.88, 128.30, 129.79, 130.24, 138.37, 139.40, 152.61, 155.56, 155.85, 170.86.

(2*R*, 3*S*)-Ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-pentadecylaziridine-2-carboxylate 110:

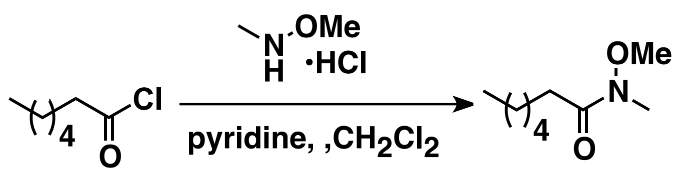
To a flame dried 25 mL round bottom flask flushed with nitrogen was added ethanol (2 mL) and metallic sodium (10 mg, 0.44 mmol, 2.2 equiv). The mixture was stirred for 10 min until sodium was completely dissolved in ethanol. Thereafter, the reaction flask was placed into ice water bath and stirred for another 10 min. To the reaction flask was added a solution of **109** (147 mg, 0.2 mmol) in ethanol (1 mL). The resulting mixture was stirred for 4 h at 0 ºC. To the reaction mixture was added sat. aq. NH_4Cl (5 mL) and brine (10 mL). The aqueous layer was extracted with ether (4 × 10 mL). The combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the crude mixture by neutral alumina chromatography

(20 mm × 200 mm column, 4:2:0.1 hexanes/DCM/Et_2O as eluent, gravity column) afforded **110** in 90% yield (109 mg, 0.18 mmol) as colorless viscous liquid.

Spectral data for **110:** R_f = 0.32 (2:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.1 Hz, 3H), 1.21-1.30 (m, 28H), 2.22 (s, 6H), 2.25 (s, 6H), 2.34-2.37 (m, 1H), 2.54 (d, *J* = 2.9 Hz, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 3.88-4.00 (m, 2H), 4.61 (s, 1H), 7.01 (s, 2H), 7.05 (s, 2H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 13.85, 14.11, 16.14, 16.17, 22.69, 27.01, 29.18, 29.36, 29.53, 29.59, 29.63, 29.66, 29.69, 31.92, 32.47, 41.77, 47.61, 59.53, 59.57, 60.66, 67.28, (three *sp3* carbon not located), 127.62, 128.24, 130.11, 130.40, 138.30, 139.02, 155.61, 155.98, 169.53; IR (thin film) 2930vs, 1748s, 1490s, 1218s, 1186vs cm^{-1}; HRMS (ESI-TOF) *m/z* 608.4685 [(M+H^+); calcd. for $C_{39}H_{62}NO_4$: 608.4679]

3.13.15 Synthesis of aldehyde 122

3.13.15.1 Synthesis of Weinreb amide 116

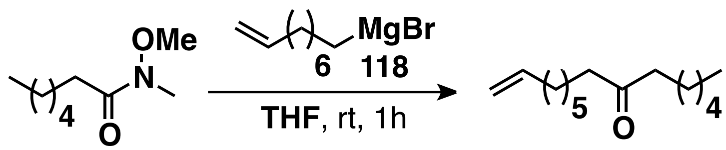


115 **116**

***N*-Methoxy-*N*-methylheptanamide 116:** To an oven dried 500 mL round bottom flask was added *N*,*O*-dimethylhydroxylamine hydrochloride (7.0 g, 71.8 mmol, 1.07 equiv) and dichloromethane (100 mL). To the mixture was added pyridine (14 mL, 150.8 mmol, 2.25 equiv). the resulting reaction mixture was cooled to 0 ºC. To the reaction flask was added heptanoyl chloride **115** (10.4 mL, 67.2 mmol). The reaction mixture was allowed to warm to room temperature over 2 h. The reaction mixture was diluted with EtOAc (200 mL). The organic layer was washed with 2 N HCl (2 × 100 mL), sat. aq. $NaHCO_3$ (2 × 100 mL) and brine (50 mL). The combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford the Weinreb amide **116** as colorless oil in 95% (11.2 g, 63.8 mmol) crude yield. The crude product was used for subsequent reaction without any further purification.

Spectral data for **116** **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.78-0.81 (m, 3H), 1.22 (brs, 6H), 1.52-1.56 (m, 2H), 2.33 (t, J = 7.4 Hz, 2H), 3.09 (s 3H), 3.60 (s, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 13.72, 22.25, 24.30, 28.82, 31.31, 31.64, 31.91, 60.90, 174.82.

3.13.15.2 Synthesis of ketone 117

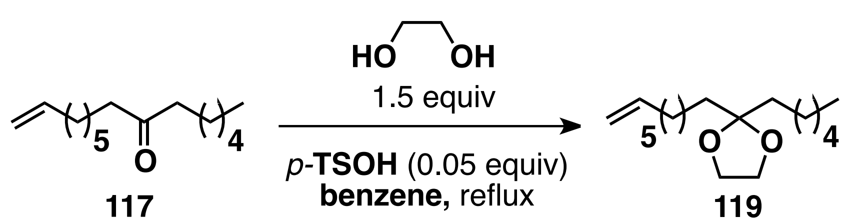


116 **117**

Pentadec-14-en-7-one 117:[27] To a flame dried 100 mL round bottom flask flushed with nitrogen and equipped with a stir bar was added Mg (130 mg, 5.5 mmol, 1.2 equiv) and dry THF (3 mL). To the slurry was added a few drops of 8-bromo-1-octene to initiate the formation of Grignard reagent **118** and the remainder of the 8-bromo-1-octene (950 mg, 5.0 mmol, 1.1 equiv) solution in THF (5.5 mL) was added slowly at room temperature. The mixture was stirred vigorously at room temperature. After most of the Mg had disappeared the mixture was cooled to 0 ºC and a solution of amide **116** (780 mg, 4.5 mmol) in THF (4.5 mL) was slowly added to the Grignard **118**. The mixture was warmed to room temperature and stirred for 40 min at room temperature. Thereafter, the reaction mixture was poured to 10% aq $NaHSO_4$ (15 mL). The aqueous layer was extracted with ether (3 × 25 mL). The combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. Purification of the crude mixture by silica gel chromatography (30 mm × 200 mm column, 20:1 hexanes/Et_2O as eluent, flash column) afforded **117** in 90% yield (909 mg, 4.05 mmol) as colorless viscous liquid.

Spectral data for **117** R_f = 0.34 (1:20 EtOAc / hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.84 (t, J = 6.8 Hz, 3H), 1.17-1.30 (m, 10H), 1.30-1.38 (m, 2H), 1.50-1.56 (m, 4H), 1.99 (q, J = 6.8 Hz, 2H), 2.34 (t, J = 7.4 Hz, 4H), 4.88 (dd, J = 10.2, 1.5 Hz, 1H), 4.94 (dd, J = 17.0, 1.5 Hz, 1H), 5.75 (ddt, J = 17.0, 10.2, 6.8 Hz, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.10, 23.71, 23.86, 23.89, 28.80, 28.90, 29.00, 29.20, 31.71, 33.82, 42.80, 43.00, 114.31, 139.00, 211.50. These spectral data matched those previously reported compound.[27]

3.13.15.3 Synthesis of 119 *via* protection of ketone

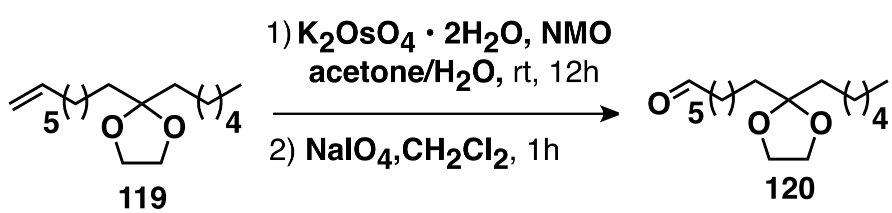


2-hexyl-2-(oct-7-en-1-yl)-1,3-dioxolane 119: To a flame dried 50 mL round bottom flask was added enone **117** (1.06g, 4.74 mmol), ethylene glycol (462 μL; 6.68 mmol, 1.41 equiv), and *p*-toluenesulphonic acid (46.0 mg, 0.24 mmol, 0.05 equiv). To the mixture was added dry benzene

(28 mL). The stirring mixture was heated at reflux under Dean-Stark conditions for 18 hours. The cooled mixture was quenched with sat. aq. $NaHCO_3$ (10mL) and extracted with diethyl ether (3 × 25 mL). The combined organic phase was dried with $MgSO_4$ and concentrated *in vacuo* giving the corresponding crude cyclic acetal **119**. Purification of the crude mixture by silica gel chromatography (30 mm × 200 mm column, 20:1 hexanes/Et_2O as eluent, flash column) afforded **119** in 95% yield (1.21 g, 4.05 mmol) as colorless viscous liquid.

Spectral data for **119:** R_f = 0.42 (1:20 EtOAc / hexanes); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.38-1.26 (m, 16H), 1.61-1.56 (m, 4H), 2.07-1.99 (m, 2H), 3.92 (s, 4H), 4.92 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 5.02-4.95 (m, 1H), 5.81 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H).. **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 14.20, 22.69, 23,92, 24.00, 29.01, 29.21, 29.79, 29.90, 32.01, 33.92, 37.26, 37.29, 65.00, 112.01, 114.31, 139.30. These spectral data matched those previously reported compound.[27]

3.13.15.4 Synthesis of aldehyde 120



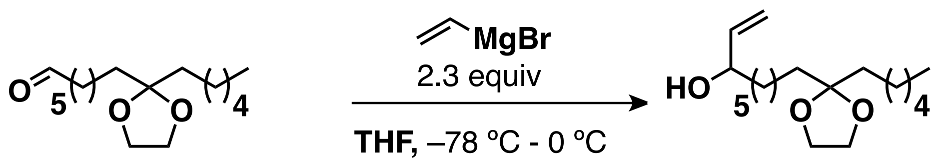
8-(2-hexyl-1,3-dioxolan-2-yl)octane-1,2-diol: To a 500 mL round bottom flask flushed with nitrogen was added acetal **119** (1.20 g, 4.45 mmol) and NMO (1.81 g, 13.4 mmol, 3.0 equiv).

The mixture was dissolved in acetone (170 mL). To the resulting solution was added water (17 mL). Thereafter, $K_2OsO_2{\bullet}2H_2O$ (161 mg, 0.44 mmol, 0.1 equiv) was added in one portion to a stirring solution. The mixture was stirred for 20 h at room temperature under nitrogen atmosphere. The reaction was quenched with sodium sulphite (1.90 g; 15.1 mmol) and water (50 mL), and stirred for 30 minutes. The mixture was filtered to remove the solid, and acetone was removed *in vacuo*. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The combined organic phase dried with $MgSO_4$ and upon concentration *in vacuo* affords yellow oil in 100% crude yield (crude weight 1.44g). The crude product was used in next reaction without any further purification.

Spectral data for **8-(2-hexyl-1,3-dioxolan-2-yl)octane-1,2-diol:** **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.27-1.35 (m, 15H), 1.43-1.44 (m, 3H), 1.56-1.60 (m, 4H), 1.95 (s, 2H), 3.43 (dd, *J* = 11.0, 7.6 Hz, 1H), 3.65 (dd, *J* = 11.0, 3.1 Hz, 1H), 3.68-3.72 (m, 1H), 3.92 (s, 4H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.02, 22.51, 23.71, 25.52, 29.53, 29.61, 29.80, 31.80, 33.01, 37.02, 37.11, 64.82, 66.59, 72.21, 111.80, (one *sp3* carbon not located). These spectral data matched those previously reported compound.[27]

7-(2-hexyl-1,3-dioxolan-2-yl)heptanal 120: To oven dried 50 mL round bottom flask was added prepared crude diol (605 mg, 2.0 mmol) and DCM (17 mL). To the stirred solution was added $NaIO_4$ on silica (4.11 g, 14.6 wt%, 2.8 mmol) in one portion. The heterogeneous mixture was stirred vigorously for 2 h. The mixture was filtered through a sintered glass funnel to a 250 mL round bottom flask. The reaction flask was washed with DCM (3 × 15 mL) and filtered through the same funnel. The filtrate was concentrated under reduced pressure. Purification of the crude mixture by silica gel chromatography (30 mm × 200 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded aldehyed **120** in 94% yield (508 mg, 1.18 mmol) as colorless oil. Spectral data for **120** R_f = 0.36 (1:5 Et_2O / hexanes). **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.82 (t, *J* = 6.7 Hz, 3H), 1.11-1.40 (m, 14H), 1.40-1.64 (m, 6H), 2.36 (dt, *J* = 7.3, 1.8 Hz, 1H), 3.89 (s, 4H), 9.70 (t, *J* = 2.0 Hz, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 13.98, 21.98, 22.53, 23.55, 23.76, 29.07, 29.56, 31.77, 37.00, 37.13, 43.79, 64.82, (one *sp3* carbon not located), 111.77, 202.54. These spectral data matched those previously reported compound.[27]

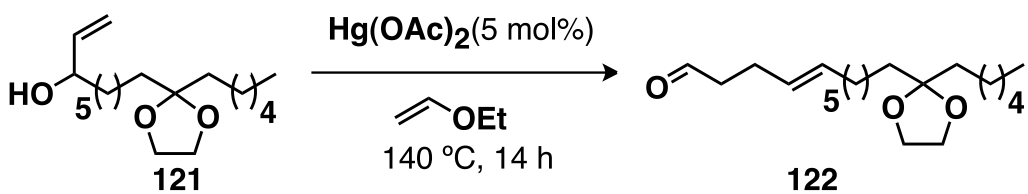
3.13.15.5 Synthesis of 121



9-(2-hexyl-1, 3-dioxolan-2-yl)non-1-en-3-ol 121: To a flame dried 100 mL three neck round bottom flask flushed with nitrogen and equipped with a stir bar and an addition funnel in one of the side neck was added Mg (290 mg, 12.0 mmol, 2.40 equiv) and dry THF (4 mL). the flask was cooled to 0 ºC. To the slurry was slowly added vinyl bromide (0.82 mL, 11.6 mmol, 2.32 equiv) solution in THF (2 mL) *via* the addition funnel. The mixture was warmed to room temperature and stirred for 1 h at room temperature under nitrogen atmosphere. the freshly prepared vinyl Grignard reagent was cooled to –78 ºC and to the reaction flask was slowly added a solution of aldehyde **120** (1.30 g, 5.0 mmol) in THF (2 mL). The resulting mixture was stirred for 1 h at –78 ºC then warmed to 0 ºC over a period of 20 min. The reaction mixture was poured slowly to the sat. aq. NH_4Cl (30 mL) at 0 ºC. The mixture was extracted with diethyl ether (4 × 25 mL). The combined organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. Purification of the crude mixture by silica gel chromatography (30 mm × 200 mm column, 9:1 to 1:1 hexanes/EtOAc as eluent, flash column) afforded **121** in 80% yield (1.20 mg, 4.0 mmol) as colorless oil.

Spectral data for **121** R_f = 0.08 (1:9 EtOAc / hexanes); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.8 Hz, 3H), 1.28-1.37 (m, 18H), 1.56-1.61 (m, 5H), 3.92 (s, 4H), 4.07-4.09 (m, 1H), 5.10 (ddd, *J* = 10.4, 1.6, 1.2 Hz, 1H), 5.18-5.25 (m, 1H), 5.86 (ddd, *J* = 17.2, 10.4, 6.2 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 13.97, 22.49, 23.64, 23.69, 25.16, 29.39, 29.49, 29.74, 31.72, 36.82, 36.89, 36.96, 64.74, 73.03, 111.76, 114.31, 141.28; IR (thin film) 3441 br, 2934vs, 2858s, 1716s, 1458s, 1082vs $cm^{-1.}$

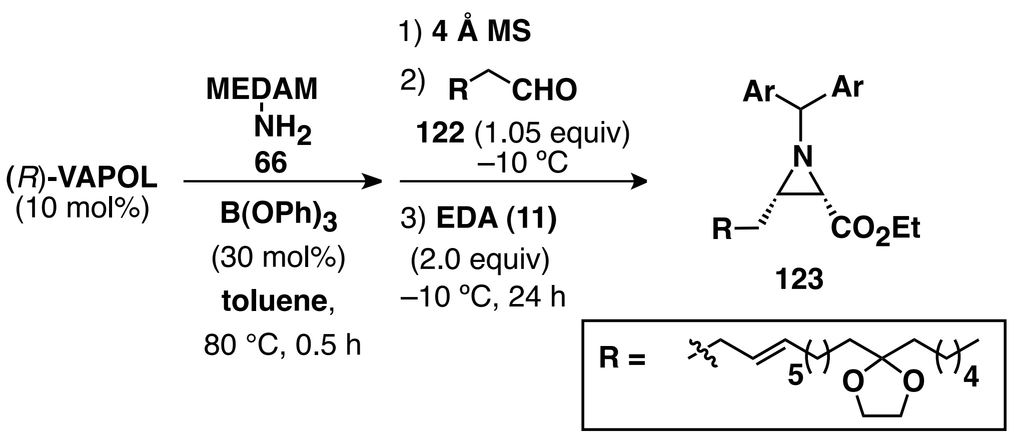
3.13.15.6 Synthesis of aldehyde 122 *via* Claisen rearrangement



(*E*)-11-(2-hexyl-1,3-dioxolan-2-yl)undec-4-enal 122: To a 25 mL flame-dried Schlenk flask equipped with a stir bar and filled with nitrogen was added was added alcohol **121** (128 mg, 0.864 mmol), $Hg(OAc)_2$ (14 mg, 0.043 mmol, 5 mol%) and ethyl vinyl ether (3 mL). The flask was sealed and was place in a oil bath at 140 ºC. The reaction mixture was heated for 14 h. Thereafter, the reaction mixture was cooled to room temperature and was concentrated under reduced pressure. Purification of the crude mixture by silica gel chromatography (30 mm × 200 mm column, 9:1 hexanes/EtOAc as eluent, flash column) afforded **122** in 30% yield (84 mg, 0.260 mmol) as colorless oil.

Spectral data for **122** R_f = 0.28 (1:9 EtOAc / hexanes); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.22-1.40 (m, 18H), 1.50-1.60 (m, 2H), 1.95 (m, 2H), 2.28-2.40 (m, 2H), 2.46 (t, *J* = 7.0 Hz, 2H), 3.95 (s, 4H), 5.11-5.40 (m, 2H), 9.75 (t, *J* = 7.0 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 14.01, 22.51, 23.70, 23.73, 25.08, 28.99, 29.22, 29.53, 29.68, 31.74, 32.36, 37.05, 43.44, 64.78, 111.77, (two *sp3* carbon not located), 127.57, 131.92, 202.31; IR (thin film) 2930vs, 2855s, 1728s, 1458s, 1082vs cm^{-1}; HRMS (ESI-TOF) *m/z* 325.2739 [$(M+H^+)$; calcd. for $C_{20}H_{37}O_3$: 325.2737]

3.13.16 Multi-component catalytic asymmetric aziridination reaction of aldehyde 122 in presence of (*R*)-VAPOL



(2*S*,3*S*)-Ethyl1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*E*)-10-(2-hexyl-1,3-dioxolan-2-yl)dec-3-en-1-yl)aziridine-2-carboxylate 123: Aldehyde **123** (34 mg, 0.105 mmol, 1.05 equiv) was reacted with EDA **11** (21 μL, 0.2 mmol, 2.00 equiv) and MEDAM amine **66** (30 mg, 0.1 mmol) according to the general aziridination Procedure B described above with (*R*)-VAPOL as ligand at –10 ºC, to afford *cis*- aziridines **123**. Purification of the crude aziridine by silica gel chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/DCM/Et_2O as eluent, gravity column) afforded *cis*- aziridines **123** as colorless viscous liquid in 90% isolated yield (62 mg, 0.09 mmol). The optical purity of **123** was determined to be 97% *ee* (tentative due to unavailability of authenticate sample of *ent*-**123**) by HPLC analysis (PIRKLE COVALENT (R, R) WHELK-O1column, 99.5:0.5 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 20.26 min (major enantiomer, **123**) and R_t = 30.03 min (minor enantiomer, *ent*-**123**).

Spectral data for **123:** ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.9 Hz, 3H), 1.24-1.33 (m, 19H), 1.57-1.60 (m, 8H), 1.85-1.88 (m, 2H), 1.98 (q, *J* = 6.3 Hz, 1H), 2.20 (d, *J* = 6.8 Hz, 1H), 2.23 (s, 6H), 2.24 (s, 6H), 3.40 (s, 1H), 3.67 (s, 3H), 3.68 (s, 3H), 3.92 (s, 4H), 4.15-4.22 (m, 2H), 5.08-5.21 (m, 2H), 7.03 (s, 2H), 7.09 (s, 2H); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ 14.06, 14.34, 16.12, 16.16, 22.58, 23.81, 23.82, 27.86, 29.17, 29.45, 29.60, 29.81, 30.09, 31.82, 32.53, 37.16, 43.47, 46.40, 59.56, 59.59, 60.66, 64.86, 77.30, 111.87, (two *sp3* carbon not located), 127.34, 128.05, 128.87, 130.45, 130.46, 131.04, 137.80, 138.25, 155.79, 156.16, 169.65; IR (thin film) 2930vs, 1746s, 1484s, 1458s, 1224s, 1185vs cm^{-1}; HRMS (ESI-TOF) *m/z* 691.4809 [(M+H^{+}); calcd. for $C_{43}H_{66}NO_6$: 691.4812].

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CHAPTER 4

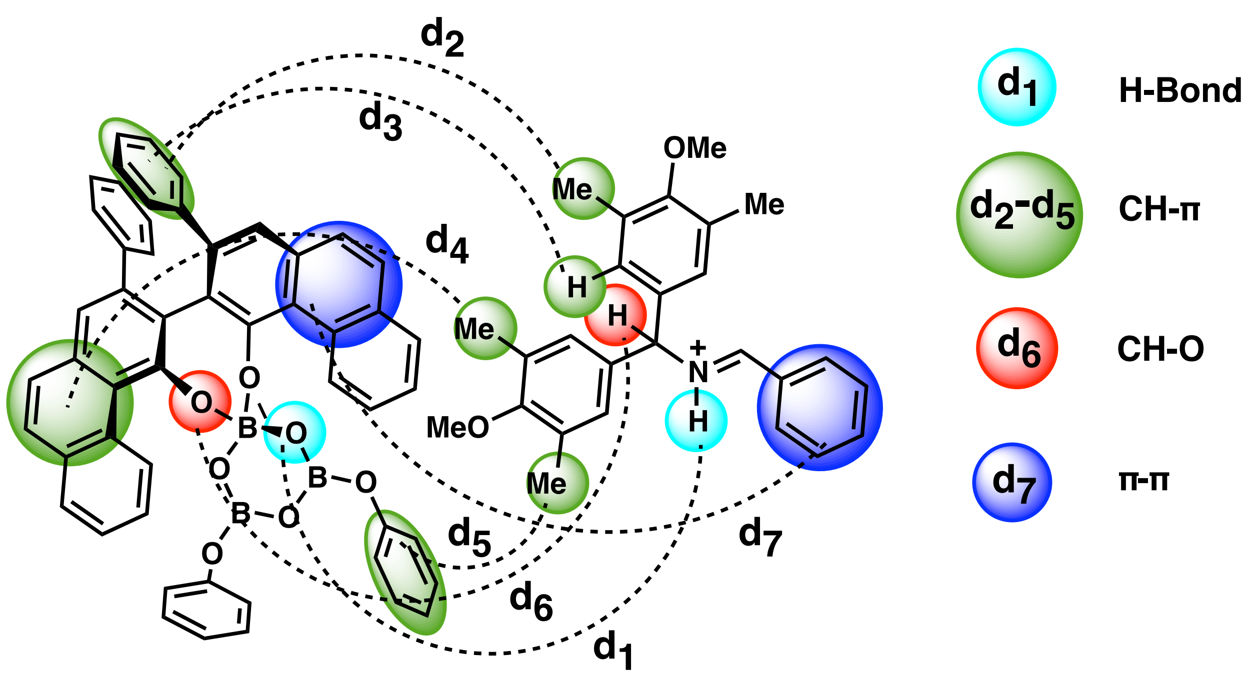
THE EFFECT OF CHIRAL SUBSTRATES IN THE CATALYIC ASYMMETRIC AZIRIDINATION REACTION

4.1 Introduction

The effect of a chiral center on a prochiral reaction center within the same molecule has always been a point of interest in organic synthesis. The interaction of a chiral substrate with a chiral ligand can give rise to three possibilities: a) substrate controlled reaction and b) catalyst controlled reaction c) synergistically controlled by both substrate and catalyst.[1] In the substrate-controlled reaction, there is the strong probability of a matched/mismatched relationship between the chiral catalyst and chiral substrate. This presents an opportunity for a possible kinetic resolution of a racemic substrate. In the catalyst controlled reaction, the stereochemistry of the newly formed chiral centers is independent of the pre-installed chiral centers in the substrate. By a simple change of the enantiomer of the catalyst, the catalyst-controlled reaction can yield different diastereomers with high a diastereomeric ratio from the same substrate. In the present work we found that the Wulff's aziridination reaction is primarily a catalyst controlled reaction.

The Wulff group has developed a general catalytic asymmetric aziridination reaction that is based on the reaction of achiral imines with stabilized diazo compounds.[2] The crystal structure of the active catalyst in this aziridination reaction reveals several non-covalent interactions between the boroxinate anion and the iminium cation (Figure 4.1). The strongest interaction is the hydrogen bonding between the protonated imine and the boroxinate anion. In addition, several CH–π interactions (Figure 4.1, d_2-d_5) were observed. These CH–π interactions are between the methyl on the MEDAM protecting group and the aromatic regions of the chiral ligand (Figure 4.1, d_2 and d_4) or the phenyl group of the phenol component (Figure 4.1, d_5). Another CH–π interaction is between the ortho hydrogen of the MEDAM group and the phenyl ring of the ligand (d_3). One of the most important non-covalent interactions is a π–π stacking interaction between the protonated benzylidine iminium moiety and the phenanthren rings of the VAPOL ligand (Figure 4.1, d_7).

Figure 4.1 Different interactions in the active catalyst structure



iminium-boroxinate complex

At this point it was thought that it would be interesting to study the aziridination of chiral imines of type **127** (Figure 4.2A) to see the different diastereomeric mixtures that would result from the reactions with each enantiomers of the catalyst. Thus, this in effect would be replacing the phenyl group of the imine in Figure 4.1 with a chiral fragment. This would result in the loss of the π–π interaction. Hence, this would serve two purposes: a) give an insight into the possible interactions of the chiral segment with the ligand giving possible matched/ mismatched cases; b) allow making complex organic molecules with more than two chiral centers provided that the aziridination reaction is well behaved in the case of chiral substrates. The former case also presents an additional possibility of no influence of the chiral segment on the reaction, which would fall into the category of catalyst -controlled reactions. The aim for the current project was to screen different chiral aldehydes to observe the impact of chiral substrates in the aziridination reaction with chiral boroxinate catalysts.

4.2 Proposed model and the predicted stereochemical outcome for the AZ reaction of α-chiral imines

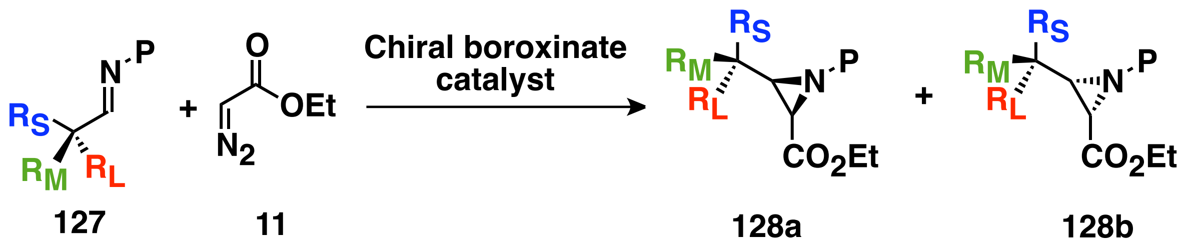
Assuming that the chiral imines **127** will react with EDA **11** in presence of the chiral boroxinate catalysts derived from VAPOL or VANOL to provide aziridines (Figure 4.2A), a prediction of the stereochemical outcome of these aziridination reactions was made with the help of the Felkin-Anh model[3] and the crystal structure of a substrate-catalyst complex in Wulff's aziridination reaction (Figure 4.2B-4.2D).

Figure 4.2 (A) Proposed catalytic asymmetric aziridination reaction with chiral imines **127**. (B) Projected approach of the nucleophile to chiral imine **127** using Felkin-Anh model for Re-face attack of the nucleophile (favored). (C) Projected approach of the nucleophile to chiral imine **127** using Felkin-Anh model for *Si*-face attack of the nucleophile (unfavored). (D) the *X*-ray

Figure 4.2 (cont'd)

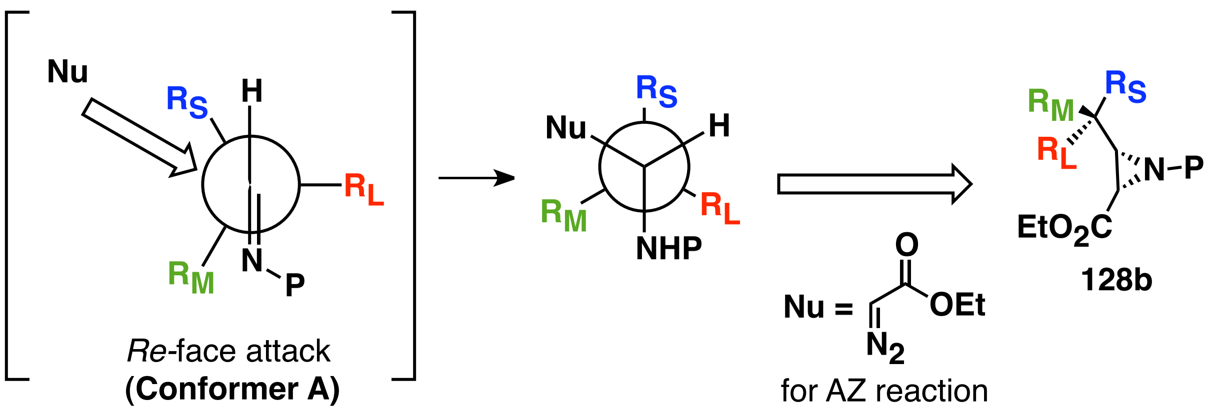
crystal structure of active catalyst consisting of an iminium cation (from achiral imine **36a**) and the boroxinate anion (from (*S*)-VAPOL). The boroxinate anion is green in color and the iminium cation is in traditional color.

(A)



R_L = large group
R_M = medium group
R_S = small group

(B)



(C)

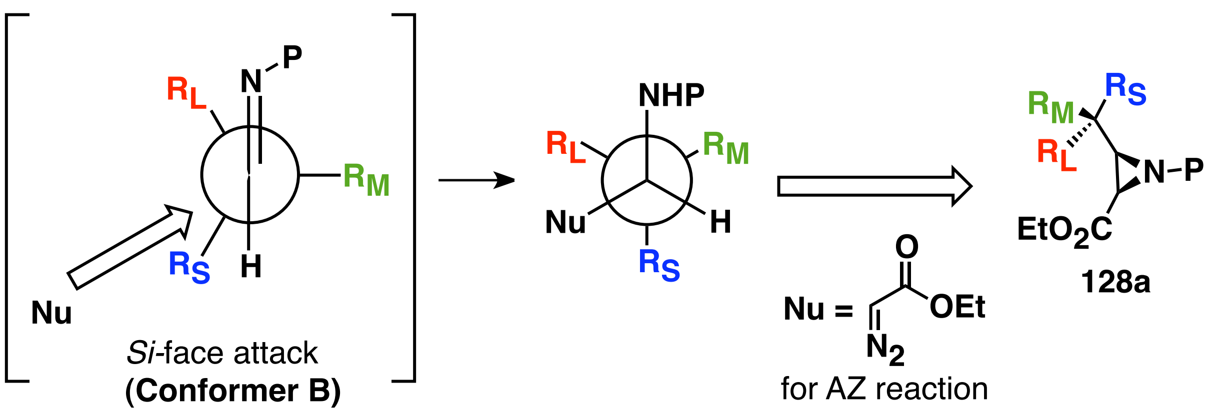
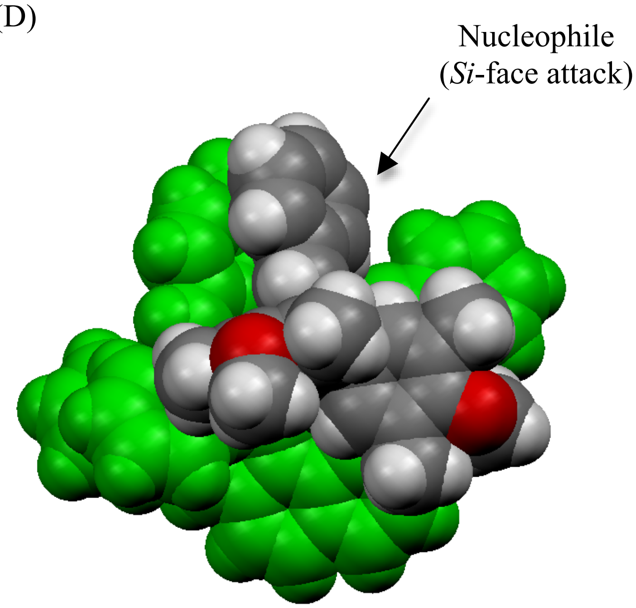
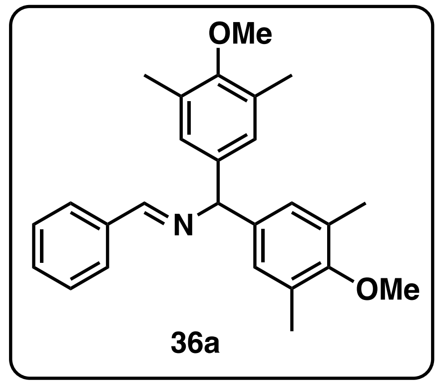


Figure 4.2 (cont'd)

(D)



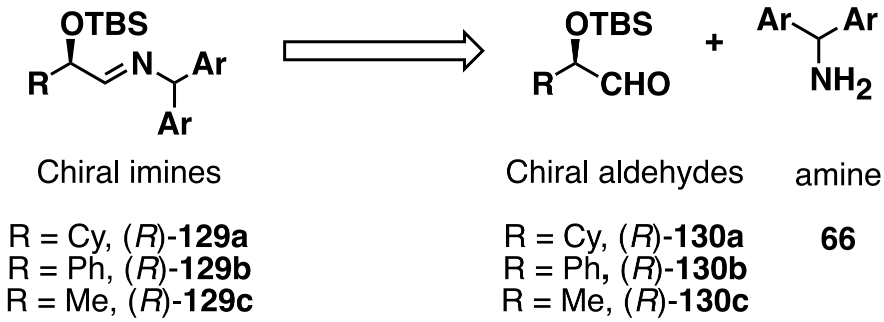


In Figure 4.2B, the *Re*-face attack of the nucleophile (EDA) along the Bürgi-Dunitz angle would be more favorable, leading to the aziridine of type **128b**. On the other hand, in Figure 4.2C, *Si*-face attack along the Bürgi-Dunitz angle would not be expected to be as likely since conformer B of the imine would be expected to be less stable than conformer A. Therefore the less favorable *Si*-face attack of nucleophile will lead to the aziridine of type **128a** as the minor product. The crystal structure of imine-boroxinate complex (Figure 4.2D) suggests that for imine **36a** (achiral imine), a *Si*-face approach of nucleophile should be favorable when the ligand is (*S*)-VAPOL and this is in fact the experimentally observed outcome for the non-chiral imines. Assuming a similar interaction between the chiral imine **127** and the chiral boroxinate catalyst, it can be predicted that the *Si*-face approach would be favored in case of the (*S*)-VAPOL catalyst. This is in turn suggests that *Re*-face approach would be most befitting the case of a (*R*)-VAPOL catalyst. Hence a matched case would be generated when imine **127** with the configuration shown in **127** in Figure 4.2A and when the conformation shown in Figure 4.2B interacts with the (*R*)-VAPOL catalyst to favor *Re*-face attack resulting in aziridine **128b**. In case of the (*S*)-VAPOL derived catalyst, the conformer of imine **127** shown in Figure 4.2C will be the one expected to most often undergo nucleophilic attack under catalyst control. It must be pointed out that the *Si*-face attack is less favored for imine **127** due to the arrangements of the groups around the chiral center which should lead to a mismatched substrate catalyst pair. This situation will give rise to a substrate controlled reaction. If the size of R_M and R_L are comparable then nucleophilic attack from both faces of the imine **127** are equally favorable in the absence of any chiral catalyst. This would lead to attack governed by the stereochemistry of the catalyst. In other words, the reaction will be catalyst controlled resulting in aziridine **128a** or **128b** depending on the chirality of the catalyst. The stereochemical outcomes of the reactions discussed in the subsequent sections are in well agreement with the model discussed above (Figure 4.2). In addition to the model proposed in Figure 4.2 with simple Felkin-Ahn considerations, other types of factors including non-covalent and H-bonding interactions between catalyst and the substrates might also govern the stereochemical outcome of the aziridination reaction with chiral imines.

4.3 Synthesis of Chiral aldehydes

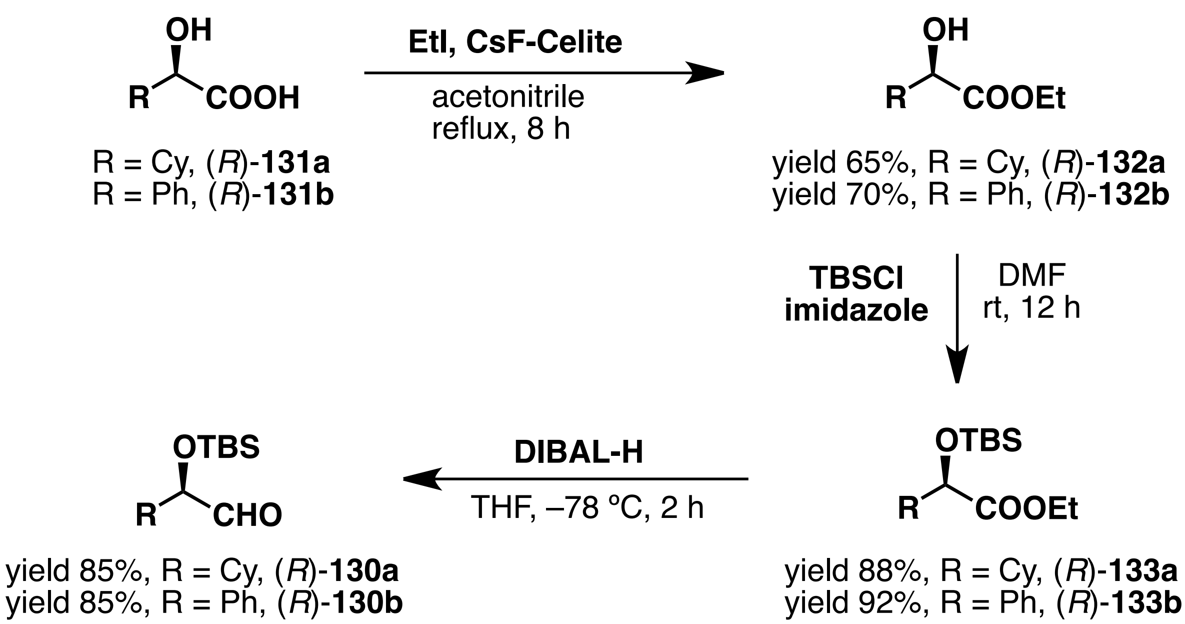
During the investigation of the behavior of the aziridination reactions with chiral imines, it was thought to study the α-chiral imines **129** by varying the ‘R’ group at the α position to include 1º and 2º aliphatic groups as well as an aromatic group (Scheme 4.1). The chiral imines (*R*)-**129** can be synthesized from the corresponding chiral aldehydes (*R*)-**130**.

Scheme 4.1 Chiral imines (*R*)-**129** for aziridination reaction



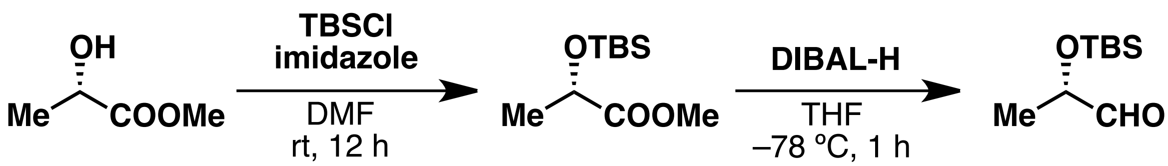
The chiral aldehydes (*R*)-**130a** and (*R*)-**130b** were synthesized following the same synthetic route starting from the corresponding α-hydroxy acids (*R*)-**131a** and (*R*)-**131b** (Scheme 4.2). The esterification reaction of the α-hydroxy acids (*R*)-**109** with ethyliodide in the presence of CsF-Celite afforded the corresponding α-hydroxy esters (*R*)-**132**. The hydroxy group in the esters (*R*)-**132** was protected with a *t*-butyldimethylsilyl group. This was followed by the reduction of the TBS protected esters (*R*)-**133** to corresponding aldehydes (*R*)-**107** with DIBAL-H at –78 ºC (yields of each step are given in Scheme 4.2).

Scheme 4.2 Synthesis of chiral aldehyde (*R*)-**130a** and (*R*)-**130b**



The aldehyde (*S*)-**130c** was synthesized from the commercially available (*S*)-methyl lactate **134** (Scheme 4.3). The hydroxy group in (*S*)-**134** was converted to the corresponding *t*-butyldimethylsilyl ether (*S*)-**135** upon reaction with *t*-butyldimethylsilyl chloride and imidazole in 85% yield. The aldehyde (*S*)-**130c** was synthesized by reducing the methyl ester (*S*)-**135** with DIBAL-H in 75% yield (Scheme 4.3).

Scheme 4.3 Synthesis of chiral aldehyde (*S*)-**130c**

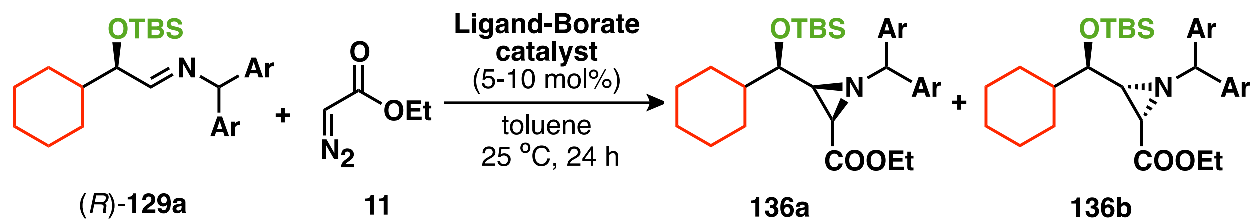


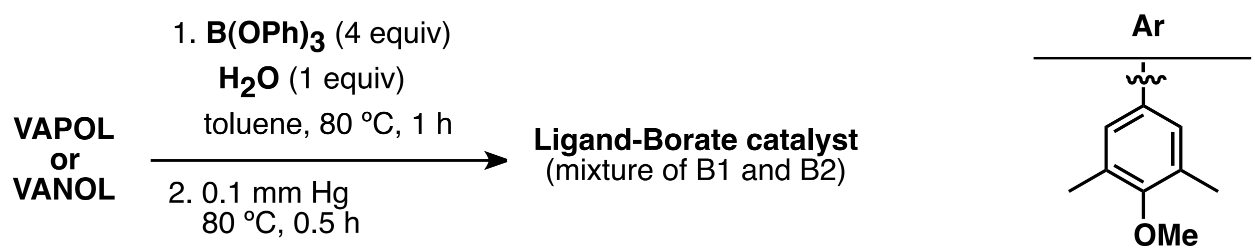
(*S*)-**134** (*S*)-**135** yield 85% (*S*)-**130c** yield 75%

4.4 Aziridination reaction with chiral imine (*R*)-129a: a substrate controlled reaction

The aziridination reactions with chiral imine (*R*)-**129a** were performed using 5-10 mol% catalyst. The pre-catalyst or the ligand borate catalyst (Table 4.1) was prepared by heating the mixture of ligand with 4 equiv of commercial $B(OPh)_3$ at 80 ºC for an hour followed by the subsequent removal of volatiles on exposure to vacuum. This was then followed by the addition of chiral imine (*R*)-**129a** and ethyl diazoacetate **11** and toluene and the resulting mixture was stirred for 24 h at 25 ºC. A diastereomeric mixture of two *cis*-aziridines **136a** and **136b** was obtained. There is a strong matched and mismatched relationship between the chiral imine (*R*)-**129a** and the chiral catalyst was observed. In particular, the reaction of imine (*R*)-**129a** with the catalyst derived from (*R*)-ligand resulted in favorable matched case with the selective formation of **136b** (Table 4.1). In presence of 5 mol% of (*R*)-VANOL and (*R*)-VAPOL derived catalyst the aziridination reaction of (*R*)-**129a** and EDA **11** at room temperature resulted in a mixture of diastereomers **136a** and **136b** with 1:8 and 1:18 diastereomeric ratio, respectively, in favor of **136b** (Table 4.1, entries 1 and 3). The combined yield of the *cis*-aziridnies was 80 and 85% in case of (*R*)-VAPOL and (*R*)-VANOL catalysts respectively.

Table 4.1 Aziridination reaction of chiral imine (*R*)-**129a** in presence of chiral catalyst [a]





entry	ligand	catalyst (mol%)	dr (**136a : 136b**) [d]	% yield (**136a + 136b**) [c]
1	(*R*)-VAPOL	5	1 : 18	80
2	(*S*)-VAPOL	10	2 : 1	30
3	(*R*)-VANOL	5	1 : 8	85
4	(*S*)-VANOL	10	2 : 1	40
5 [b]	$Yb(OTf)_3$	10	1 : 10	25

[a] Unless otherwise specified, all reactions were carried out with 0.5 mmol of (*R*)-**129a** (0.5 M in

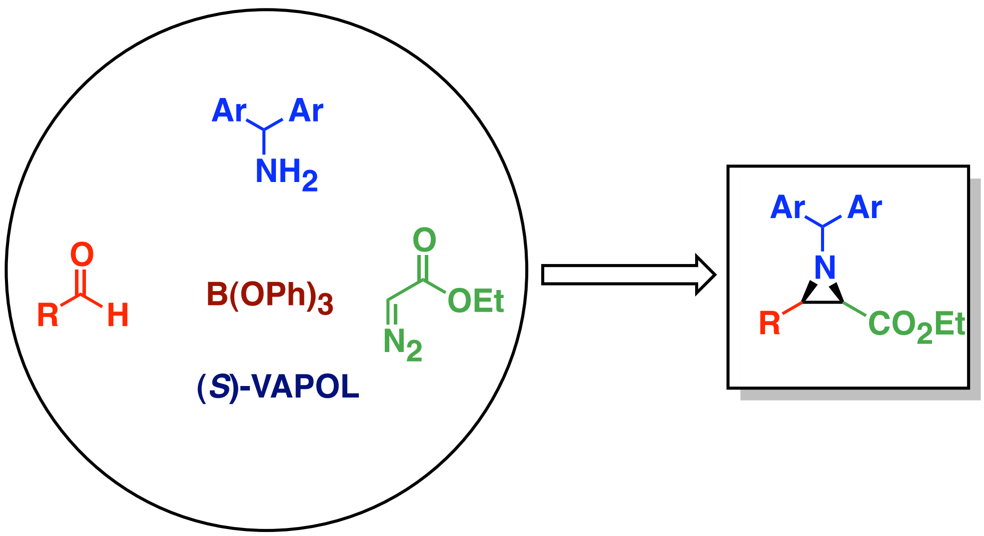
Table 4.1 (cont'd)

toluene) with 1.2 equiv of **11** at 25 °C and went to completion in 24 h. The ligand-borate catalyst was prepared by heating a mixture of the ligand and 4 equiv of commercial $B(OPh)_3$ at 80 ºC for an hour followed by the subsequent removal of volatiles upon exposure to vacuum. [b] The catalyst used for the reaction is $Yb(OTf)_3$. The catalyst was added to a solution of imine in toluene followed by EDA addition. [c] Isolated combined yield of *cis*-**136a** and **136b** after chromatography on silica gel. [d] Determined on crude mixture by HPLC on a PIRKLE COVALENT (R, R) WHELK-O1 column and further confirmed by the ^{1}H NMR spectrum of the crude reaction mixture.

Interestingly, a strong mismatched case was observed in the aziridination reaction of the imine (*R*)-**129a** and EDA **11** at room temperature in presence of 10 mol% of (*S*)-VANOL and (*S*)-VAPOL derived catalyst. Both reactions resulted in a mixture of **136a** and **136b** in a 2:1 diastereomeric ratio with 30-40% yield (Table 4.1, entries 2 and 4). The reaction in the presence of a non-chiral catalyst $Yb(OTf)_3$ shows a strong preference for the diastereomer **136b** (Table 4.1, entry 5).

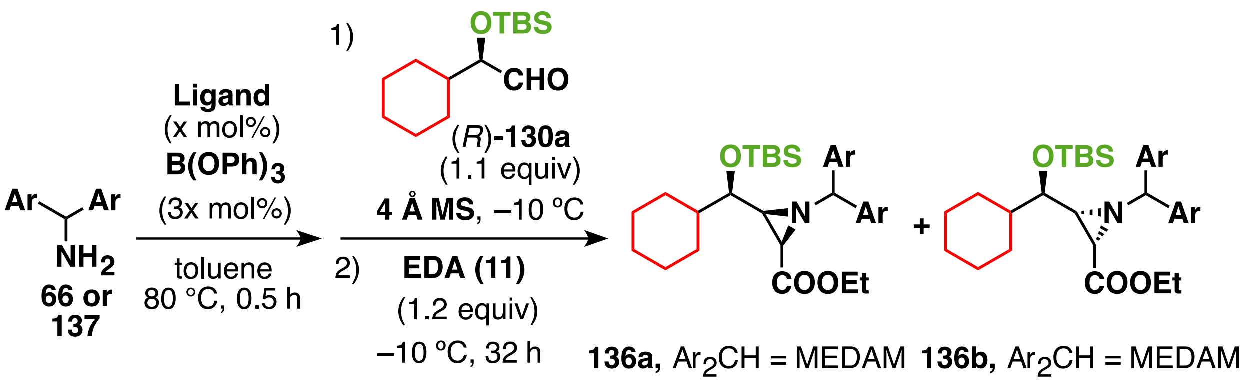
During the course of this work, a multi-component aziridination reaction was developed in our group by Anil Gupta (Scheme 4.4).[4] An obvious advantage of this multi-component protocol is that the imine preparation step can be avoided thus prevented loss of material during purification, usually by crystallization. Moreover, the process of aziridination becomes much more simple to perform. Therefore, we decided to utilize the multi-component aziridination reaction to study the effect of chiral aldehydes on the aziridination reaction. In order to compare the results obtained from the two-step method (Table 4.1), the multi-component aziridination reaction was performed with the chiral aldehyde (*R*)-**130a**, MEDAM amine **66** and EDA **11** in presence of the (*S*) and (*R*) isomers of VAPOL and VANOL derived catalysts. The results are presented in Table 4.2.

Scheme 4.4 Multi-component asymmetric aziridination reaction



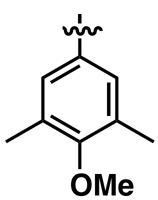
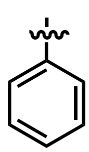
As expected, the aziridination reaction of aldehyde (*R*)-**130a**, at –10 ºC, in the presence of 10 mol% (*R*)-VANOL and (*R*)-VAPOL derived catalysts resulted in the *cis*-aziridine **136b** with > 99:1 diastereomeric ratio in 80% and 85% yield, respectively (Table 4.2, entries 2 and 5). The catalyst loading for the reaction with (*R*)-VAPOL can be reduced to 5 mol% without any detrimental effect on yield or diastereomeric ratio (Table 4.2, entry 3). The mismatched pair of aldehyde (*R*)-**130a** with the (*S*)-VAPOL catalyst resulted in a 1.1:1 diastereomeric ratio of **136a** and **136b** in 30% combined yield in the aziridination reaction at –10 ºC (Table 4.2, entry 1). Similarly, the (*S*)-VANOL catalyst resulted in a 1.5:1 diastereomeric ratio of **136a** and **136b** in only a 15% combined yield at –10 ºC (Table 4.2, entry 4).

Table 4.2 Multi-component aziridination reaction of chiral aldehyde (*R*)-**130a** in presence of a chiral boroxinate catalyst [a]



136a, Ar_2CH = MEDAM **136b,** Ar_2CH = MEDAM

136a', Ar_2CH = Bh **136b',** Ar_2CH = Bh

entry	Ar	ligand	catalyst (mol%)	dr **136a:136b** [c]	% yield **(136a + 136b)** [b]
1[d]		(*S*)-VAPOL	10	1.1:1(1:1)	30
2		(*R*)-VAPOL	10	<1:>99(1:99)	85
3		(*R*)-VAPOL	5	<1:>99(1:99)	83
4[d]		(*S*)-VANOL	10	1.5:1(2:1)	15
5		(*R*)-VANOL	10	<1:>99(1:99)	80
6[d, e, f]		(*S*)-VAPOL	10	nd	nd
7[f]		(*R*)-VAPOL	10	1:>99(1:99)	80

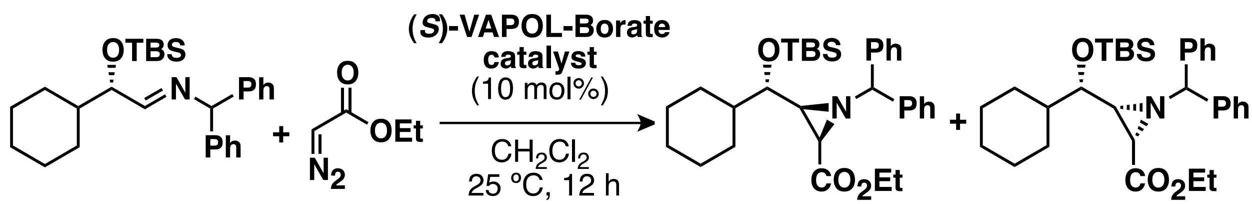
[a] Unless otherwise specified, all reactions were performed with 0.2 mmol amine **66** (0.4 M in toluene) and 1.1 equiv of (*R*)-**130a** and 1.2 equiv EDA **11**, and went to 100% completion. Before adding the aldehyde and EDA **11** a solution of amine **66** with x mol% ligand and 3x

Table 4.2 (cont'd)

mol% commercial $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen. nd = not determined. [b] Isolated combined yield of **136a** and **136b** after chromatography on silica gel. [c] Determined on crude reaction mixture by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. Diastereomeric ratio in parentheses is for the purified inseparable mixture of **136a** and **136b** by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. [d] Reaction did not go for completion even after 32 h. [e] No aziridine was observed after 32 h. The only product was the imine (*R*)-**129a**. [f] The amine component in the reaction is benzhydryl amine **137** and the aziridines are **136a'** and **136b'**.

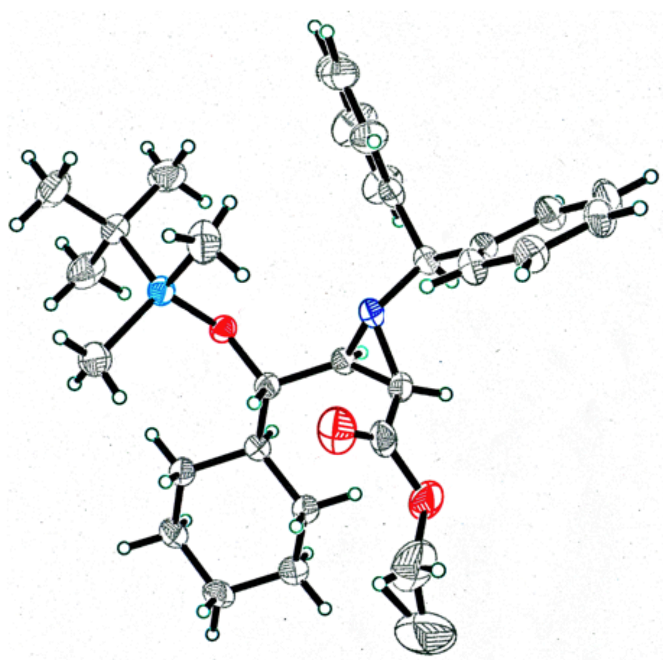
Commercially available benzhydryl amine **137** was examined in the multi-component aziridination reaction with the aldehyde (*R*)-**130a** in the presence of both (*R*) and (*S*)-VAPOL catalysts. Matched and mismatched interactions between substrate and ligand were observed that were similar to that with MEDAM amine **66**. The reaction in the presence of the (*R*)-VAPOL catalyst resulted in **136b'** with > 99:1 diastereomeric ratio in 80% yield (Table 4.2, entry 7). In the mismatched case with the (*S*)-VAPOL catalyst, no aziridine was observed (Table 4.2, entry 6). The stereochemical outcome of the aziridination reaction is confirmed with the help of a crystal structure of *ent*-**136b'** (Scheme 4.5) obtained by Dr Reddy, a former group member. The aziridine *ent*-**136b'** was the major diastereomer with 1:27 diastereomeric ratio in the reaction of the imine (*S*)-**129a'** with EDA **11** in the presence of the catalyst derived from (*S*)-VAPOL.[5] As expected in this case, the (*S*)-enantiomer of the imine formed a matched pair with the catalyst derived from (*S*)-ligand. The diastereoselectivity of the aziridination reactions with (*R*)-**130a** in the presence of (*R*) or (*S*) ligand derived catalyst is in well agreement with the model explained in Figure 4.2, where R_L = Cy, R_M = OTBS and R_S = H.

Scheme 4.5 Aziridination reaction with (*S*)-**129a'** and the ORTEP diagram of the crystal structure of the major diastereomer *ent*-**136b'**[5]

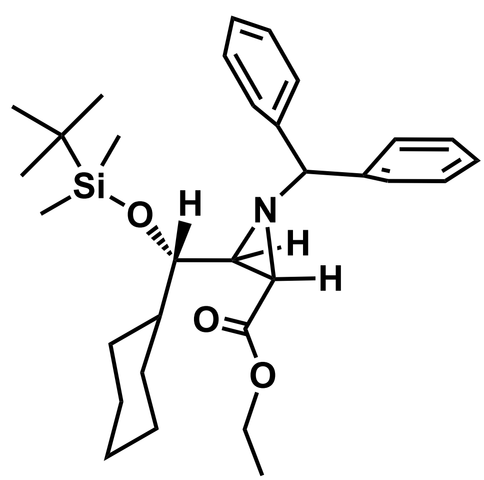


(*S*)-**129a'** **11** *ent*-**136b'** *ent*-**136a'**

dr (*ent*-**136b'**:*ent*-**136a'**) = 27:1
85% yield



ORTEP diagram of *ent*-**136b'**

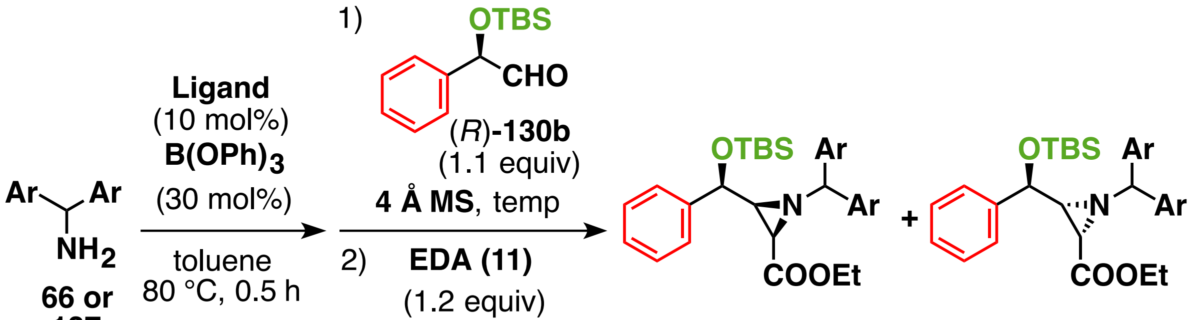


ent-**136b'**

4.5 Aziridination reaction with chiral aldehyde (*R*)-130b: a catalyst controlled reaction

In contrast to the chiral aldehyde (*R*)-**130a**, the aldehyde (*R*)-**130b** reacted via a catalyst controlled aziridination reaction. The multi-component aziridination reaction of aldehyde (*R*)-**130b** with MEDAM amine **66**, at –10 ºC, in the presence of 10 mol% (*R*)-VAPOL catalyst afforded the *cis*-aziridine **138b** with 99:1 diastereomeric ratio in 90% yield (Table 4.3 entry 6). Similarly, the reaction in presence of the (*R*)-VANOL catalyst afforded the *cis*-aziridine **138b** with 98:2 diastereomeric ratio in 85% yield at –10 ºC (Table 4.3 entry 8). Surprisingly, by a simple change to the (*S*)-enantiomer of the ligand, the aziridination reaction yielded the diastereomeric *cis*-aziridine **138a** as the major diastereomer. The ratio of **138a** to **138b** is 98:2 for both (*S*)-VAPOL catalyst and (*S*)-VANOL catalyst at –10 ºC (Table 4.3, entries 5 and 7) in 90% and 85% yield respectively. Although, an increase in the reaction temperature to 0 ºC or to room temperature has no detrimental effect on yield of the aziridines **138a** and **138b**, a slight drop in the diastereomeric ratio was observed with both enantiomers of VAPOL at the elevated temperatures. The diastereomeric ratio of **138a** to **138b** at 0 ºC is 97:3 with the (*S*)-VAPOL catalyst, while the (*R*)-VAPOL catalyst afforded the aziridines with 1:99 diastereomeric ratio (Table 4.3, entries 3 and 4). At the room temperature, the diastereomeric ratio of **138a** to **138b** decreases to 95.7:4.3 with the (*S*)-VAPOL catalyst and 3:97 with the (*R*)-VAPOL catalyst (Table 4.3, entries 1 and 2). Switching the amine component to benzhydryl amine **137** also resulted in a catalyst-controlled reaction with aldehyde (*R*)-**130b**. While the reaction of aldehyde (*R*)-**130b** with benzhydryl amine at –10 ºC afforded the mixture of *cis*-aziridines **138a'** and **138b'** with <1:>99 diastereomeric ratio in the presence of the (*R*)-VAPOL catalyst in 60% yield, a diastereomeric ratio of 15:1 was observed with the (*S*)-VAPOL catalyst in 65% yield (Table 4.3, entries 10 and 9).

Table 4.3 Multi-component aziridination of aldehyde (*R*)-**130b** in the presence of chiral catalyst[a]



138a, Ar_2CH = MEDAM **138b,** Ar_2CH = MEDAM

138a', Ar_2CH = Bh **138b'**, Ar_2CH = Bh

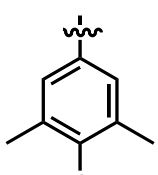
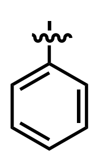
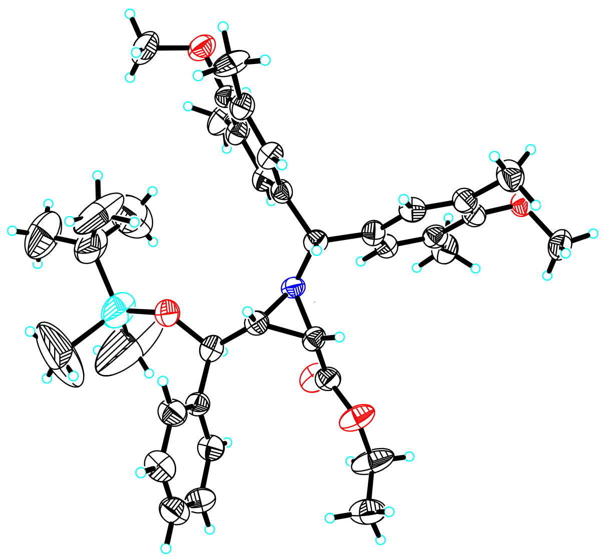
entry	Ar	ligand	temp (°C)	dr **138a:138b** [c]	% yield **(138a + 138b)** [b]
1		(*S*)-VAPOL	25	95.7:4.3(96:4)	90
2		(*R*)-VAPOL	25	3:97(3:97)	90
3		(*S*)-VAPOL	0	97:3(98:2)	90
4		(*R*)-VAPOL	0	1:99(1:99)	92
5		(*S*)-VAPOL	–10	98:2(99:1)	90
6		(*R*)-VAPOL	–10	1:99(1:99)	90
7		(*S*)-VANOL	–10	98:2(99:1)	85
8		(*R*)-VANOL	–10	2:98(1:99)	85
9[d]		(*S*)-VAPOL	–10	<1:>99(1:99)	65
10[d]		(*R*)-VAPOL	–10	17:1(17:1)	50

Table 4.3 (cont'd)

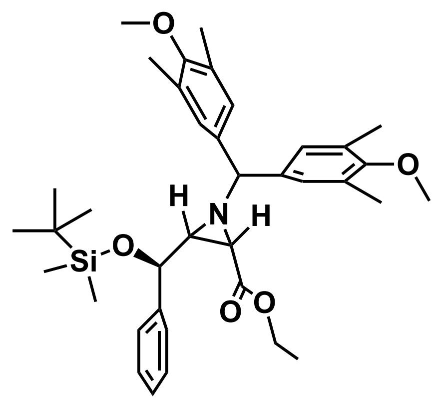
[a] Unless otherwise specified, all reactions were performed with 0.2 mmol amine **66** (0.4 M in toluene) and 1.1 equiv of (*R*)-**130b** and 1.2 equiv EDA **11** and went to 100% completion. Before adding the aldehyde and the EDA **11**, a solution of amine **66** with 10 mol% ligand and 30 mol% commercial $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen. [b] Isolated combined yield of **138a** and **138b** after chromatography on neutral alumina. [c] Determined on a sample prepared by passing the crude reaction mixture through a silica plug. Determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. Diastereomeric ratio in parentheses is for purified inseparable mixture of **138a** and **138b** and was determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. [d] The amine component in the reaction is benzhydryl amine **137** and the aziridines are **138a'** and **138b'**.

The study of other chiral aldehydes in the presence of the chiral boroxinate catalysts was taken forward with MEDAM amine **66** since it gives aziridines with both higher yields and diastereoselectivity. The diastereoselectivity of the aziridination reactions with (*R*)-**130b** in the presence of (*R*) or (*S*) ligand derived catalyst is in well agreement with the model explained in Figure 4.2, where R_L = Ph, R_M = OTBS and R_S = H. The stereochemical outcome of the aziridination reaction is confirmed with the help of a crystal structure of **138b** (Figure 4.3).

Figure 4.3 The *X*-ray crystal structure of **138b**



ORTEP diagram of **138b**

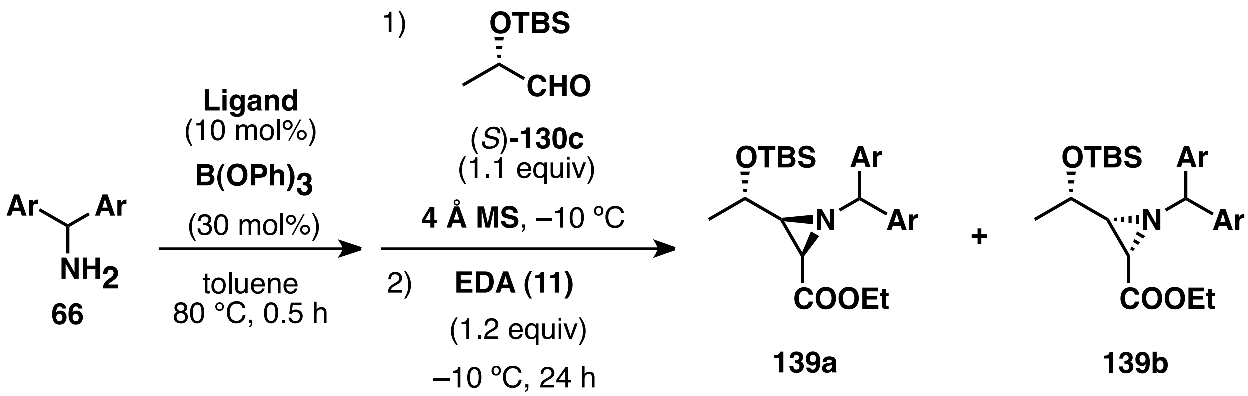


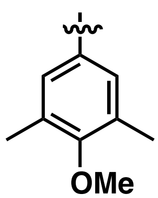
138b

4.6 Aziridination reaction with chiral aldehyde (*S*)-130c: a catalyst controlled reaction

Another case of a catalyst controlled process was observed for the aziridination reaction of aldehyde (*S*)**-130c** with MEDAM amine **66** and EDA **11** in presence of the VANOL and VAPOL boroxinate catalysts.

Table 4.4 Multi-component aziridination reaction of chiral aldehyde (*S*)-**130c** in the presence of chiral boroxinate catalyst: a catalyst controlled case [a]



entry	Ar	ligand	dr **139a:139b** [c]	% yield **139a:139b** [b]
1		(*S*)-VAPOL	91:9(90:10)	85
2		(*R*)-VAPOL	4:96(1:99)	87
3		(*R*)-VANOL	5:95(1:99)	82

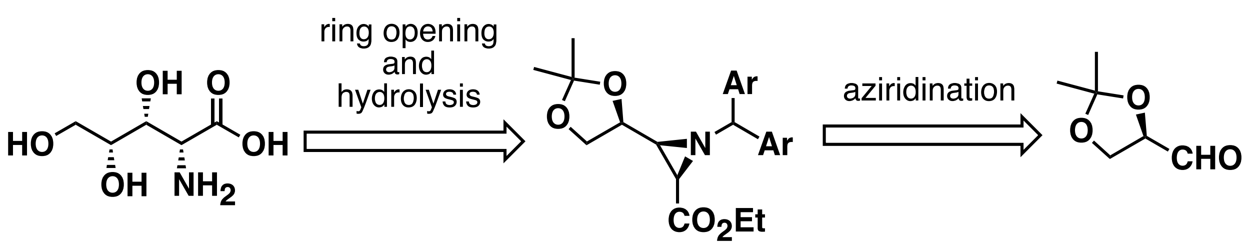
[a] Unless otherwise specified, all reactions were performed with 0.2 mmol amine **66** (0.4 M in toluene) and 1.1 equiv of (*S*)-**130c** and 1.2 equiv EDA **11** and went to 100% completion. Before adding the aldehyde and the EDA **11** a solution of amine **66** with 10 mol% ligand and 30 mol% commercial $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen. [b] Isolated combined yield of **139a** and **139b** after chromatography on neutral alumina. [c] Determined on a sample prepared by passing the crude reaction mixture through a silica plug. Determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. Diastereomeric ratio in parentheses is for purified inseparable mixture of **139a** and **139b** and was determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column.

The reaction in the presence of (*R*)-VAPOL and (*R*)-VANOL derived catalyst afforded the *cis*-aziridines **139a** and **139b** with diastereomeric ratio of 4:96 and 5:95 respectively with high yields (Table 4.4, entry 2 and 3). The reaction in the presence of (*S*)-VAPOL derived catalyst resulted in aziridine **139a** as the major product. The (*S*)-VAPOL catalyst gave a 91:9 mixture of **139a** and **139b** in 85% combined yield.

4.7 Aziridination reaction with the acetonide of glyceraldehyde (*R*)-140: a catalyst controlled reaction

The acetonide of glyceraldehyde (*R*)-**140** was the next substrate of choice for the aziridination reaction as the resulting aziridine **141a** can be a potential substrate for the synthesis of (–)-polyoxamic acid. The ring opening of the aziridine **141a** followed by hydrolysis of the ring opened product can lead to (–)-polyoxamic acid, which is the enantiomer of the natural occurring (+)-polyoxamic acid (Scheme 4.6). The (+)-polyoxamic acid should be obtainable from the aldehyde (*S*)-**140** in a similar fashion. Polyoxamic acid inhibits chitin synthetase of *Candida albicans*, a human pathogen.[6] There have been many syntheses reported in the literature for polyoxamic acid.[7]

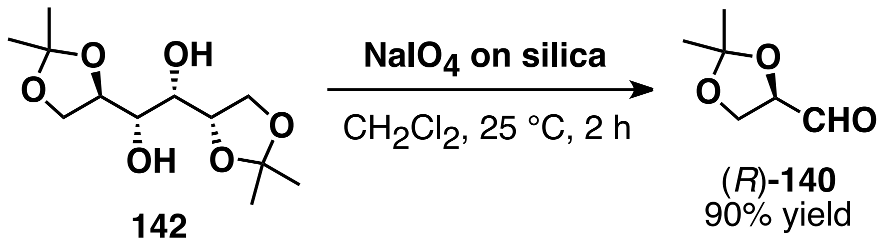
Scheme 4.6 Possible synthetic route for (–)-polyoxamic acid



(–)-polyoxamic acid **141a** (*R*)-**140**

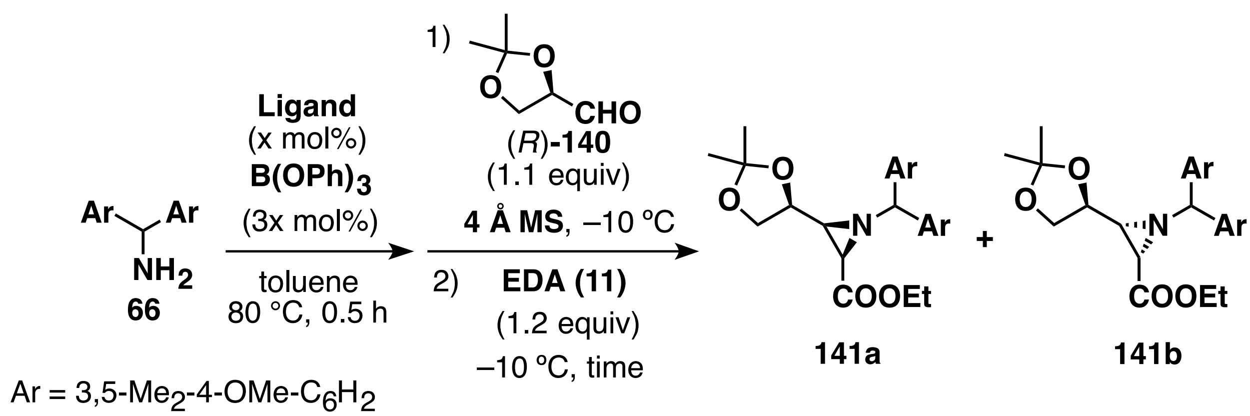
The acetonide of glyceraldehyde (*R*)-**140** was synthesized in 90% yield by oxidative cleavage of the diacetonide of D-mannose **142** with sodium periodate (Scheme 4.7).[8]

Scheme 4.7 Synthesis of (*R*)-**140** *via* oxidative cleavage of the diacetonide of D-mannose **142**



The aziridination reaction with the acetonide of glyceraldehyde (*R*)-**140**, MEDAM amine **66** and EDA **11** in the presence of 10 mol% (*R*)-VAPOL boroxinate catalyst resulted in aziridines **141a** and **141b** with 1:21 diastereomeric ratio in 83% yield at –10 ºC (Table 4.5, entry 2). The catalyst loading can be decreased to 5 mol% without any detrimental effect on yield or diasteremeric ratio (Table 4.5, entry 3). The reaction of the same aldehyde (*R*)-**140** in the presence of the (*S*)-VAPOL boroxinate catalyst afforded aziridine **141a** as the major diastereomer with an 86:14 ratio in 80% total yield.

Table 4.5 Multi-component aziridination reaction of the chiral aldehyde (*R*)-**140** in the presence of a chiral boroxinate catalyst[a]



entry	ligand	Catalyst (x mol%)	Conc. ('C' M)	time (h)	dr **141a:141b**[c]	%yield **141a:141b**[b]
1	(*R*)-VAPOL	10	0.1	24	5:95(5:95)	85
2	(*R*)-VAPOL	10	0.2	24	4.5:95.5(4:96)	83
3 [e]	(*R*)-VAPOL	5	0.2	24	5:95(5:95)	85
4	(*S*)-VAPOL	10	0.2	24	86:14(86:14)	80
5 [e]	(*S*)-VAPOL	5	0.4	5	86:14(86:14)	80
6 [d]	(*S*)-VAPOL	5	1.0	5	85:15(86:14)	80
7 [e]	(*S*)-VANOL	10	0.4	5	85:15(86:14)	75

[a] Unless otherwise specified, all reactions were performed with 0.2 mmol amine **66** with the indicated concentration in toluene and 1.1 equiv of (*R*)-**140** and 1.2 equiv EDA **11** and went to 100% completion. Before adding the aldehyde and the EDA **11**, a solution of amine **66** with x mol% ligand and 3x mol% commercial $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen.

[b] Isolated combined yield of **141a** and **141b** after chromatography on neutral alumina.

Table 4.5 (cont'd)

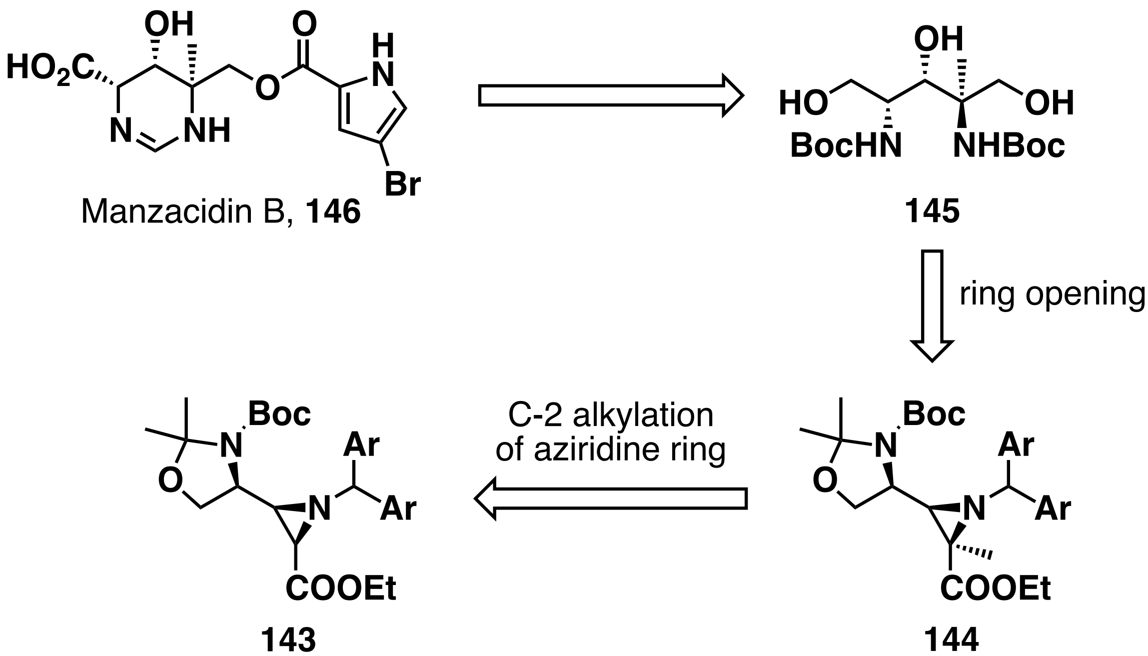
[c] Determined on a sample prepared by passing the crude reaction mixture through a silica plug. Determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. Diastereomeric ratio in parentheses is for purified inseparable mixture of **141a** and **141b** and was determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. [d] The reaction was performed with 1.0 mmol of amine **66**. [e] The reaction was performed with 0.5 mmol of amine **66**.

The reaction in the presence of 10 mol% (*S*)-VAPOL boroxinate catalyst resulted in aziridines **141a** and **141b** with 86:14 diastereomeric ratio in 80% yield at –10 ºC (Table 4.5, entry 4). The reaction concentration does not have substantial effect on the outcome of the reaction with either of the enantiomers of the VAPOL catalyst (Table 4.5, entries 1, 5 and 6). The aziridination reaction of aldehyde (*R*)-**140** in presence of (*S*)-VANOL afforded an 85:15 diastereomeric ratio of aziridines **141a** and **141b** in 75% yield.

4.8 Aziridination reaction with Garner's aldehyde (*S*)-147: a catalyst controlled reaction

Manzacidin B **146**, a biologically important marine natural product has been synthesized from the amino alcohol **145** (Scheme 4.8).[9] We envisioned that amino alcohol **145** might be synthesized *via* ring opening of the aziridine **144** which in turn, can be synthesized *via* alkylation of aziridine **143** (Scheme 4.8). It would be possible to synthesize the aziridine **143** from the (*R*)-Garner aldehyde provided that the aziridination reaction is well behaved in presence of a carbamate group and the resulting aziridine is produced with a high diastereomeric ratio.

Scheme 4.8 Possible synthetic route for Manzacidin B **146**



To our delight commercially available Garner's aldehyde (*S*)-**147** afforded the *cis*-aziridine **143a** with 99% diastereomeric excess in the presence of the (*S*)-VAPOL catalyst. Also, the *cis*-aziridine **143b** can be obtained in the presence of the (*R*)-VAPOL catalyst with >99 % diastereomeric excess (Table 4.6 entries 1 and 2).

Table 4.6 Multi-component aziridination reaction of Garner's aldehyde (*S*)-**147** in the presence of a chiral boroxinate catalyst[a]

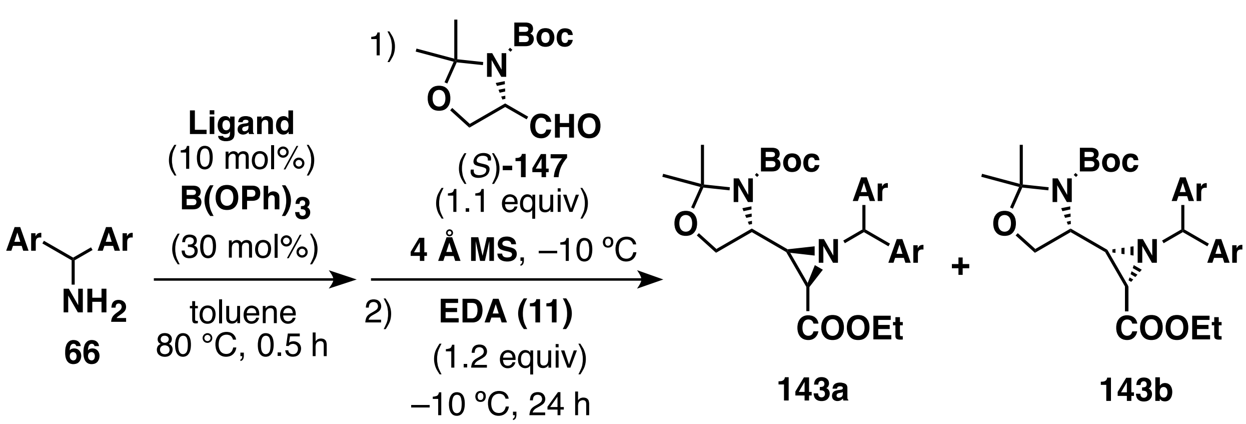
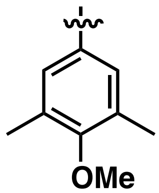


Table 4.6 (cont'd)

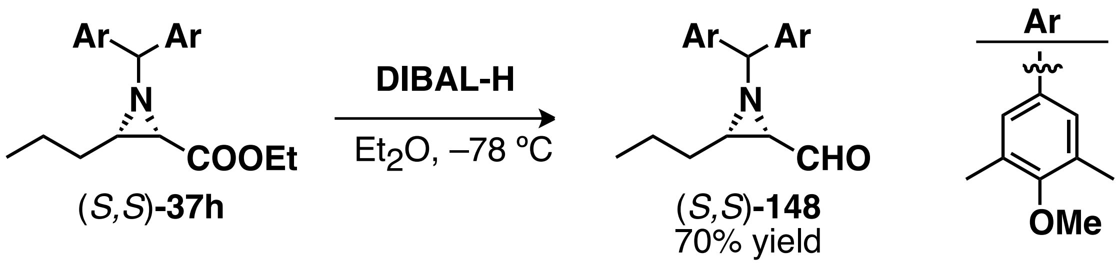
entry	Ar	ligand	dr **143a:143b** [c]	% yield **143a:143b** [b]
1		(*S*)-VAPOL	99.4:0.6(99.5:0.5)	70
2		(*R*)-VAPOL	0.3:99.7(0.3:99.7)	60

[a] Unless otherwise specified, all reactions were performed with 0.2 mmol amine **66** (0.4 M in toluene) and 1.1 equiv of (*S*)-**147** and 1.2 equiv EDA **11** and went to 100% completion. Before adding the aldehyde and the EDA **11**, a solution of amine **66** with 10 mol% ligand and 30 mol% commercial $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen. [b] Isolated combined yield of **143a** and **143b** after chromatography on neutral alumina. [c] Determined on a sample prepared by passing the crude reaction mixture through a silica plug. Determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. Diastereomeric ratio in parentheses is for purified inseparable mixture of **143a** and **143b** and was determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column.

4.9 Aziridination reaction with aziridine 2-carboxaldehyde (*S, S*)-148: a catalyst controlled reaction

The polyaziridines are of interest because it might be possible that they could participate in an aziridine cascadein mucg the same way that polyepoxides can be involved in epoxide cascades.[10] Access to polyaziridines can be thought to be possible by employing aziridine carboxaldehydes in the aziridination reaction. The aziridine carboxaldehyde (*S,S*)-**148** can be synthesized from aziridine-2-carboxylate (*S,S*)-**37h** by DIBAL-H reduction (Scheme 4.9).

Scheme 4.9 Synthesis of aziridine 2-carboxaldehyde (*S,S*)-**148**



The aziridine carboxaldehyde (*S,S*)-**148** produces the diaziridine **149a** with 99% diastereomeric excess in the presence of the (*S*)-VAPOL catalyst and **149b** with 99% diastereomeric excess in the presence of the (*R*)-VAPOL catalyst with excellent yields (Table 4.7, entries 1 and 2).

Table 4.7 Multi-component aziridination reaction of aziridine 2-carboxaldehyde (*S,S*)-**148** in the presence of a chiral boroxinate catalyst[a]

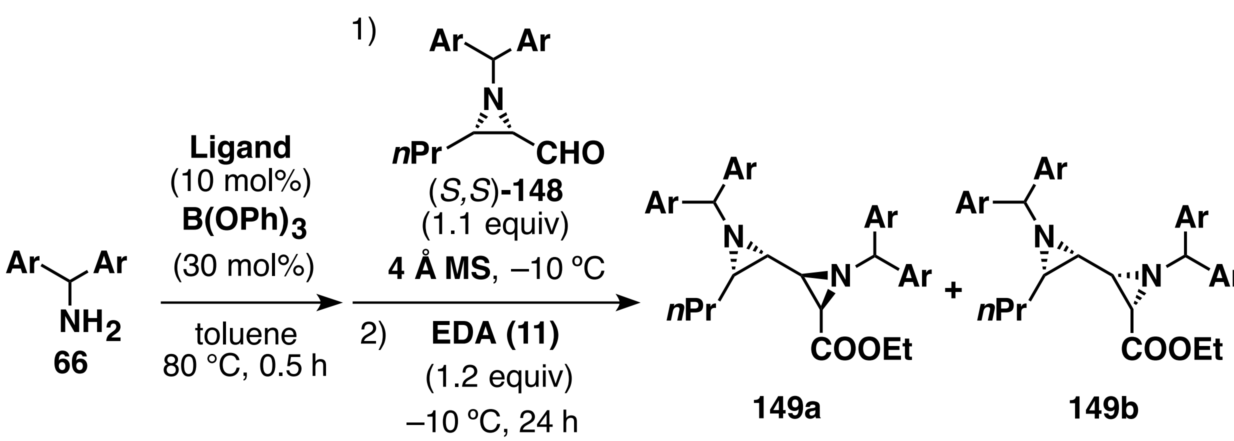
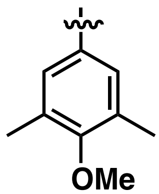


Table 4.7 (cont'd)

entry	Ar	ligand	dr **149a:149b** [c]	% yield **149a:149b** [b]
1		(*S*)-VAPOL	>99:1 (>99:1)	84
2		(*R*)-VAPOL	<1:>99 (<1:>99)	80

[a] Unless otherwise specified, all reactions were performed with 0.2 mmol amine **66** (0.4 M in toluene) and 1.1 equiv of (*S,S*)-**148** and 1.2 equiv EDA **11** and went to 100% completion. Before adding the aldehyde and the EDA **11**, a solution of amine **66** with 10 mol% ligand and 30 mol% commercial $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen. [b] Isolated combined yield of **149a** and **149b** after chromatography on neutral alumina. [c] Determined on a sample prepared by passing the crude reaction mixture through a silica plug. Determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. Diastereomeric ratio in parentheses is for purified inseparable mixture of **149a** and **149b** and was determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column.

4.10 Aziridination reaction with 2-phenylpropanal (*S*)-150: The problem of racemization of the corresponding intermediate imine (*S*)-152 and its solution

In all of the above cases no racemization of the *α*- chiral center was observed during the multi-component aziridination reaction. However, in the case of 2-phenylpropanal (*S*)-**150**, a substantial amount of racemization was observed during the reaction. The multi-component aziridination reaction with (*S*)-**150** resulted in all four possible stereoisomers of the *cis*-aziridine product (Table 4.8). Interestingly the extent of racemization was found to be largely dependent on the concentration of the reaction mixture.

The aziridination reaction of intermediate imine (*S*)-**152** in the presence of the (*S*)-VAPOL catalyst should result in the *cis*-aziridine **151a** and similarly (*R*)-**152** should give the *cis*-aziridine *ent*-**151b**. Due to the racemization of the imine (*S*)-**152**, the reaction in the presence of the (*S*)-VAPOL catalyst would result a substantial amount of aziridine *ent*-**151b** that would decrease the diastereomeric ratio, since **151a** and *ent*-**151b** have diastereomeric relationship. In all the cases, the reaction of (*S*)-**152**, in the presence of the (*S*)-VAPOL catalyst results in **151a**, as the major diastereomer and *ent*-**151b** as the minor diastereomer (Table 4.8, entries 1-5). Although the imine (*S*)-**152** cannot be observed, it is considered to be forming in-situ in the reaction. The ee of the imine (*S*)-**152** can be calculated by 100*[(r-1)/(r+1)] where r = (**151a**+**151b**)/(*ent*-**151a**+*ent*-**151b**)

Table 4.8 Multi-component aziridination reaction of 2-phenylpropanal (*S*)-**150** in the presence of a chiral boroxinate catalyst[a]

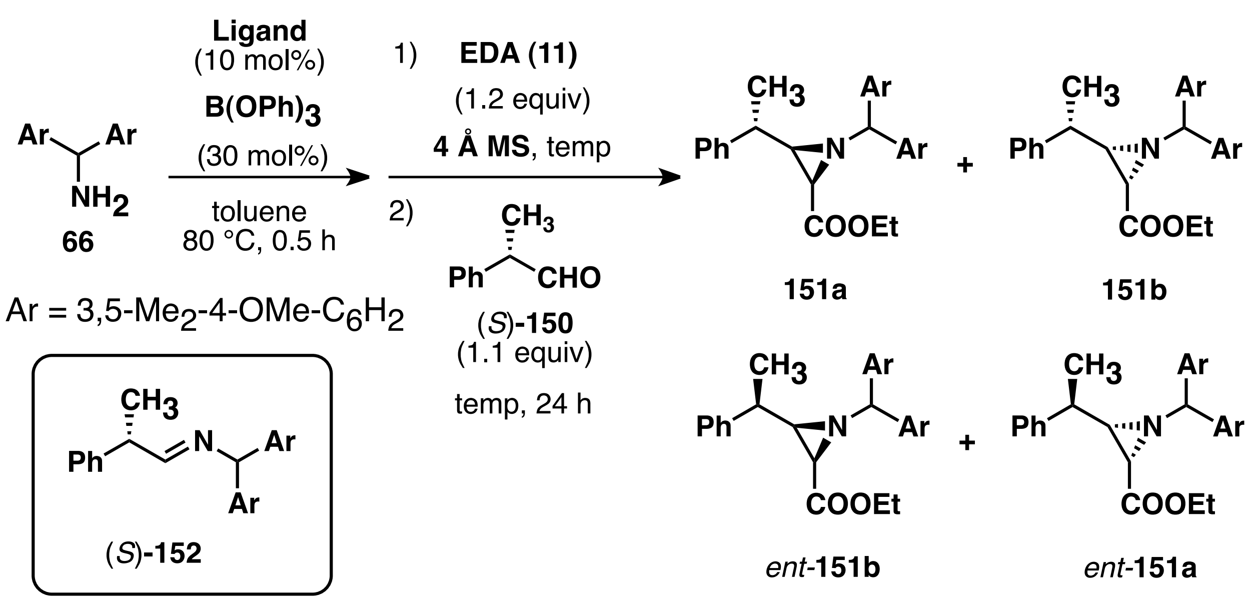


Table 4.8 (cont'd)

entry	ligand	temp (ºC)	Conc. ('C' M)	dr[e] (**151a**+*ent*-**151a**:**151b**+*ent*-**151b**)	% ee **151a**[b]	% ee **151b**[b]	% ee (*S*)-**152**[c]	%yield[d]
1	(*S*)-VAPOL	25	0.4	9:1	95	–83	77	85
2	(*S*)-VAPOL	–10	0.4	11:1	96.4	–86	81	85
3	(*S*)-VAPOL	–10	0.1	13.5:1	96.4	–81	85	95
4	(*S*)-VAPOL	–10	0.04	24:1	99	–80	91.4	92
5	(*S*)-VAPOL	–10	0.01	23:1	99.2	–59	92	90
6	(*R*)-VAPOL	–10	0.4	1:3.5	–35	99.5	69	90
7	(*R*)-VAPOL	–10	0.04	1:5	43	99.9	93	90
8[f]	(*R*)-VAPOL	–10	0.4	11:1	–95.6	83	–80	87

[a] Unless otherwise specified, all reactions were performed with 0.2 mmol amine **66** ('C' M in toluene) and 1.1 equiv of (*S*)-**150** and 4.0 equiv EDA **11** and went to 100% completion. Before adding the aldehyde and the EDA **11**, a solution of amine **66** with 10 mol% ligand and 30 mol% commercial $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen. [b] Determined on a sample prepared by passing the crude reaction mixture through a silica plug. Determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. [c] Determined on a sample prepared by passing the crude reaction mixture through a silica plug. Determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. % ee of the imine (*S*)-**152** = 100*[(r-1)/(r+1)] where r = (**151a**+**151b**)/(*ent*-**151a**+*ent*-**151b**). [d] Isolated combined yield of **151a** and **151b** after

Table 4.8 (cont'd)

chromatography on neutral alumina. [e] The diastereomeric ratio was determined both from the ^{1}H NMR spectrum and HPLC spectrum of crude reaction mixture and the value was comparable with the HPLC data. From HPLC the calculated dr was as follows: dr = (**151a**+*ent*-**151a**):(**151b**+*ent*-**151b**). [f] the reaction was performed with (*R*)-**150.**

At 0.4 M (in **66**) concentration, both the diastereoselection and the extent of racemization were found to be independent of temperature (room temperature *vs* –10 ºC, entry 1 *vs* 2). However, the diastereomeric ratio of **151a** to **151b** (including the corresponding enantiomers) increases from 11:1 to ~14:1 (Table 4.8, entry 3) when the reaction mixture was diluted from 0.4 M to 0.1 M concentration. Further, dilution of the reaction mixture to 0.04 M concentration resulted in a diastereomeric ratio of **151a** to **151b** (including the corresponding enantiomers) of 24:1 (Table 4.8, entry 4). This resulted in the formation of aziridine **151a** with 99% ee, *ent*-**151b** with 80% ee and from these results the imine (*S*)-**152** is calculated to have 91.4% ee. No further improvement was obtained on diluting the reaction mixture to 0.01 M in **66** (entry 5 *vs.* entry 4). The aziridination reaction of (*S*)-**150** in the presence of the (*R*)-VAPOL catalyst results in the maximum racemization of the intermediate imine (*S*)-**152**. The reaction resulted in the formation of aziridine **151b** with 99.5% ee and *ent*-**151a** with 35% ee as the major diastereomers. The diastereomeric ratio of **151a** to **151b** (including the corresponding enantiomers) is calculated to be 1:3.5 (entry 6). The dilution shows similar effect on the racemization of *in situ* formed imine (*S*)-**152** when aziridination reaction was performed with (*R*)-VAPOL derived catalyst at 0.04 M concentration (entry7). The diastereomeric ratio of **151a** to **151b** (including the corresponding enantiomers) is calculated to be 1:5 (Table 4.8, entry 7). The reaction resulted aziridine **151a** with 43% ee, **151b** with 99.9% ee and from these results the imine (*S*)-**152** is calculated to have 93% ee. The HPLC standard sample was prepared by reacting the aldehyde (*R*)-**150** with EDA in the presence of (*R*)-VAPOL derived catalyst (entry 8). The reaction resulted aziridine *ent*-**151a** with 95.6% ee, **151b** with 83% ee and from these results the imine (*R*)-**152** is calculated to have 80% ee. The aziridination reactions with (*S*)-**150** in the presence of (*S*)-VAPOL derived catalyst resulted in better diastereoselectivity. The fact is in well agreement with the model explained in Figure 4.2, where R_L = Ph, R_M = CH_3 and R_S = H.

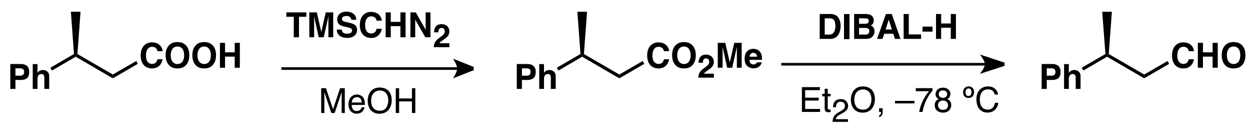
Based on the above discussion, it seems like the rate of racemization of imine (*S*)-**152** decreases with a decrease in concentration of the reaction mixture. This could possibly due to the fact that aziridination reaction and racemization are first and second order reaction respectively, with respect to the imine (*S*)-**152**. Hence, there would be a greater impact of dilution on the racemization as compared to the aziridination reaction.

4.11 Aziridination reaction of chiral aldehydes with a *β*-chiral center: catalyst controlled reaction

Interestingly, there was no racemization observed of the *β*-chiral center in the aziridination reaction with 3-phenylbutanal (*S*)-**155** and 3-((*tert*-butyldimethylsilyl)oxy)butanal (*R*)-**159**. Both aldehydes were found to react under a catalyst controlled process.

The 3-phenylbutanal (*S*)-**155** was synthesized by reducing the methyl 3-phenylbutanoate (*S*)-**154** with DIBAL-H (Scheme 4.10). The methyl 3-phenylbutanoate (*S*)-**154** was obtained by methylation of 3-phenylbutanoic acid (*S*)-**153** with trimethylsilyldiazomethane.

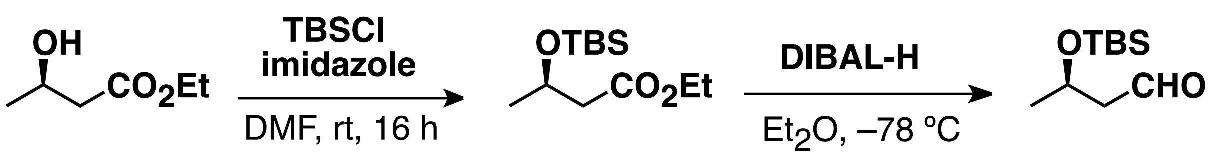
Scheme 4.10 Synthesis of 3-phenylbutanal (*S*)-**155**



(*S*)-**153** (*S*)-**154** 94% yield (*S*)-**155** 75% yield

Protection of the hydxoxy group in the ethyl 3-hydroxybutanoate (*R*)-**134** with *tert*-butyldimethylsilyl group followed by reduction of ethyl ester (*R*)-**135** afforded the corresponding 3-((*tert*-butyldimethylsilyl)oxy)butanal (*R*)-**136** (Scheme 4.11).

Scheme 4.11 Synthesis of 3-((*tert*-butyldimethylsilyl)oxy)butanal (*R*)-**136**



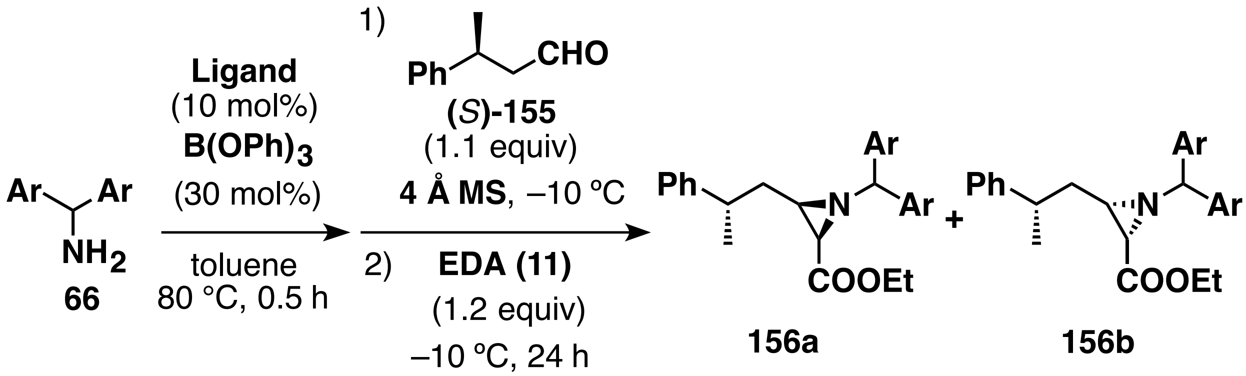
(*R*)-**157** (*R*)-**158** 85% yield (*R*)-**159** 80% yield

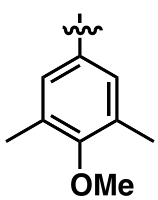
According to the model described in Figure 4.2, the aziridination reaction with (*S*)-**155** and (*R*)-**159** should result in better diastereoselectivity in the presence of the (*R*)-VAPOL derived catalyst, the same observations were made when the respective reactions were performed.

The aziridination reaction with aldehyde (*R*)-**155**, MEDAM amine **66** and EDA **11** in the presence of 10 mol% (*S*)-VAPOL boroxinate catalyst resulted in aziridines **156a** and **156b** with a 94:6 diastereomeric ratio in 80% yield at –10 ºC (Table 4.9, entry 1). The reaction in the presence of the (*R*)-VAPOL derived catalyst resulted in aziridine **156b** as the major product.

The (*R*)-VAPOL catalyst resulted mixture of **156a** and **156b** with a diastereomeric ratio of <1:>99 and in 85% combined yield (Table 4.9, entry 2).

Table 4.9 Multi-component aziridination reaction of 3-phenylbutanal (*S*)-**155** in the presence of a chiral boroxinate catalyst: a catalyst controlled case [a]



entry	Ar	ligand	dr **156a:156b** [c]	% yield **156a:156b** [b]
1		(*S*)-VAPOL	94:6(94:6)	80
2		(*R*)-VAPOL	<1:>99 (1:99)	85

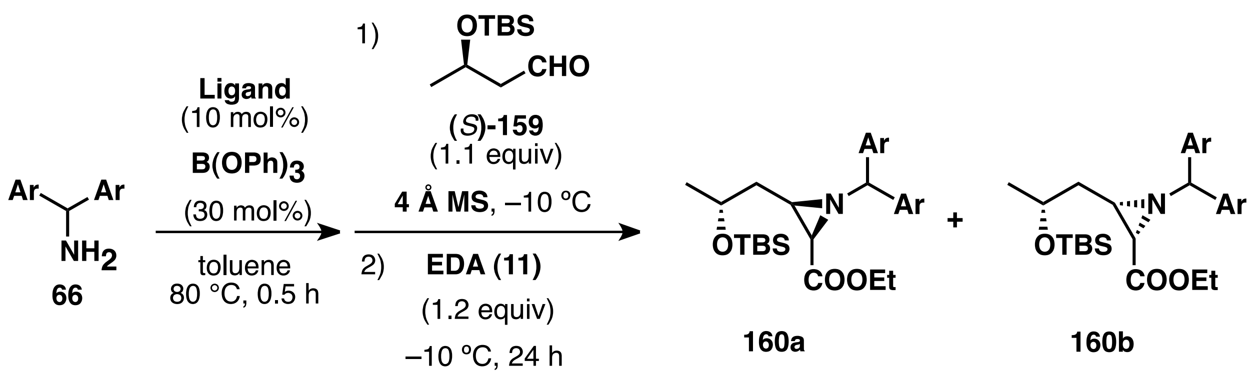
[a] Unless otherwise specified, all reactions were performed with 0.2 mmol amine **66** (0.4 M in toluene) and 1.1 equiv of (*S*)-**155** and 1.2 equiv EDA **11** and went to 100% completion. Before adding the aldehyde and the EDA **11**, a solution of amine **66** with 10 mol% ligand and 30 mol% $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen. [b] Isolated combined yield of **156a** and **156b** after chromatography on neutral alumina. [c] Determined on a sample prepared by passing the crude reaction mixture through a silica plug. Determined by HPLC on PIRKLE

Table 4.9 (cont'd)

COVALENT (R, R) WHELK-O1 column. Diastereomeric ratio in parentheses is for purified inseparable mixture of **156a** and **156b** and was determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column.

In a similar catalyst controlled reaction, the aldehyde (*R*)-**159**, in the presence of the (*S*)-VAPOL catalyst resulted in aziridines **160a** and **160b** in a 98:2 diastereomeic ratio and in 83% yield (Table 4.10, entry 1). The reaction with the same aldehyde (*R*)-**159** in the presence of the (*R*)-VAPOL catalyst resulted in aziridines **160a** and **160b** in a 1:99 diastereomeic ratio and in 85% yield (Table 4.10, entry 2).

Table 4.10 Multi-component aziridination reaction of aldehyde (*R*)-**159** in the presence of a chiral boroxinate catalyst: a catalyst controlled case [a]



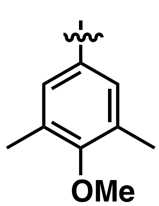
entry	Ar	ligand	dr **160a:160b** [c]	% yield **160a:160b** [b]
1		(*S*)-VAPOL	98:2(97:3)	83
2		(*R*)-VAPOL	1:99 (1:99)	85

Table 4.10 (cont'd)

[a] Unless otherwise specified, all reactions were performed with 0.2 mmol amine **66** (0.4 M) and 1.1 equiv of (*R*)-**159** and 1.2 equiv EDA **11** and went to 100% completion. Before adding the aldehyde and the EDA **11**, a solution of amine **66** with 10 mol% ligand and 30 mol% $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen. [b] Isolated combined yield of **160a** and **160b** after chromatography on neutral alumina. [c] Determined on a sample prepared by passing the crude reaction mixture through a silica plug. Determined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. Diastereomeric ratio in parentheses is for purified inseparable mixture of **160a** and **160b** by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column.

4.12 Conclusions

In this work we have realized that all chiral aldehydes but the cyclohexyl substituted aldehyde (*R*)-**130a** prefer to undergo a catalyst controlled doubly diastereoselective process, where the absolute stereochemistry of the newly formed stereocenters are the function of the catalyst and are independent on any pre-installed chiral centers present at the *α*- or *β*- position in the aldehyde. A variety of functional groups are well tolerated in this aziridination reaction, leading to the controlled synthesis of both diastereomers of complex molecules staring from the same substrate. This protocol has the potential to be used in the synthesis of natural and unnatural diastereomers of many natural products such as phytosphingosine (detailed discussion in Chapter 5), polyoxamic acid, manzacidin B, etc. Finally, this work adds to the not so common examples of catalyst controlled reaction in the field of organic synthesis. Many important catalytic asymmetric reactions do not offer high catalyst control over a broad range of substrates.

APPENDIX

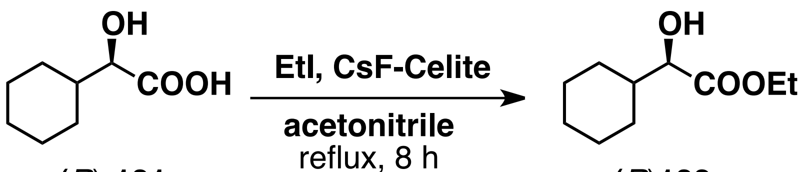
4.13 Experimental procedure

4.13.1 General information

Same as Chapter 2.

4.13.2 Synthesis of chiral aldehydes

4.13.1.1 Esterification of (*R*)-131a

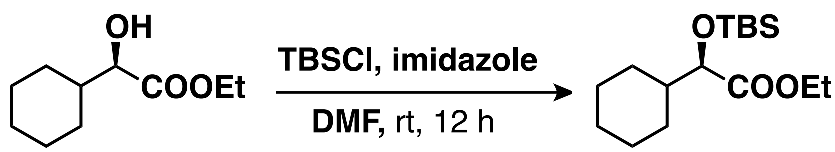


(*R*)-**131a** (*R*)**132a**

(*R*)-ethyl 2-cyclohexyl-2-hydroxyacetate 132a:[11] To a 250 mL flame-dried round bottom flask equipped with a stir bar and a condenser with a rubber septum and a nitrogen balloon at the top, was added (*R*)-hexahydromandelic acid (*R*)-**131a** (0.80g, 5 mmol). Dry acetonitrile (120 mL) was added to dissolve the acid (*R*)-**131a**. Thereafter, CsF-celite (2.6 g) and iodoethane (0.8 mL, 12.5 mmol) was added. The flask was placed in an oil (185 ºC) bath and the reaction mixture was refluxed for 8 h. The flask was then allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the residue was diluted with ethyl acetate (15 mL). The mixture was filtered through a Celite-pad to a 100 mL round bottom flask. The Celite-pad was washed with another 20 mL of ethyl acetate. The resulting solution was concentrated under reduced pressure followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude ester (*R*)-**132a** as a light yellow solid. Purification of the crude ester by silica gel chromatography (30 mm × 300 mm column, 20:1 hexanes/EtOAc as eluent, flash column) afforded pure ester (*R*)-**132a** as a white solid (mp 39–40 ºC) in 65 % isolated yield (605 mg, 3.25 mmol).

Spectral data for (*R*)-**132a** R_f = 0.34 (1:20 EtOAc / hexanes) **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.17-1.28 (m, 5H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.44-1.45 (m, 1H), 1.64-1.79 (m, 5H), 2.65 (d, *J* = 6.3 Hz, 1H), 4.00 (dd, *J* = 6.2, 3.5 Hz, 1H), 4.25 (qd, *J* = 7.1, 1.3 Hz, 2H); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 14.26, 26.01, 26.05, 26.27, 26.34, 29.09, 42.01, 61.51, 74.82, 174.88. $[\alpha]_D^{20}$ –17.8 (c 1.54, $CHCl_3$). Lit[12] $[\alpha]_D^{25}$ + 17.7 (c 1.54, $CHCl_3$) on 100% ee material, for *S*-configuration.

4.13.2.1 TBS protection of *α*-hydroxy ester (*R*)-132a



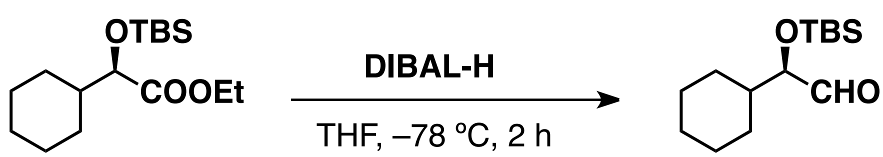
(*R*)-**132a** (*R*)-**133a**

(*R*)-Ethyl 2-(*tert*-butyldimethylsilyloxy)-2-cyclohexylacetate (*R*)-133a: To a 25 mL flame dried round bottom flask equipped with stir bar and filled with nitrogen was added (*R*)-ethyl 2-cyclohexyl-2-hydroxyacetate **(*R*)-132a** (0.5 g, 2.68 mmol). Dry DMF (15 mL, freshly distilled and stored on activated 4 Å MS) was added to dissolve the ester. The resulting solution was cooled to 0 ºC. To the reaction flask was added Imidazole (0.22g, 3.22 mmol, 1.2 equiv) and *tert*-butyldimethylsilylchloride (0.48g, 3.22 mmol, 1.2 equiv). The flask was fitted with a rubber septum and a nitrogen balloon. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was diluted by addition of hexanes (15 mL). Thereafter, brine (10 mL) was added to the resulting mixture. The organic layer was separated, and the aqueous layer was extracted with hexanes (10 mL × 3). The combined organic layer was then dried over $MgSO_4$

and concentrated under reduced pressure to afford the crude product **(*R*)-133a** as a colorless liquid. Purification of the crude by silica gel chromatography (30 mm × 300 mm column, 100:1 hexanes/EtOAc as eluent, flash column) afforded pure ester **(*R*)-133a** as a colorless liquid in 85 % isolated yield (685 mg, 2.28 mmol).

Spectral data for **(*R*)-133a:** R_f = 0.68 (1:20 EtOAc / hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.90 (s, 9H), 1.08-1.23 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.53-1.55 (m, 1H), 1.62-1.74 (m, 5H), 3.93 (d, *J* = 5.2 Hz, 1H), 4.17 (qd, *J* = 7.1, 2.9 Hz, 2H); **^{13}C-NMR** (126 MHz, CDCl3): δ –5.39, –5.01, 14.23, 18.26, 25.93, 26.12, 26.21, 27.42, 29.32, 42.38, 60.32, 76.81, (one *Sp3* carbon not located), 173.41.

4.13.2.2 Synthesis of aldehyde (*R*)-130a

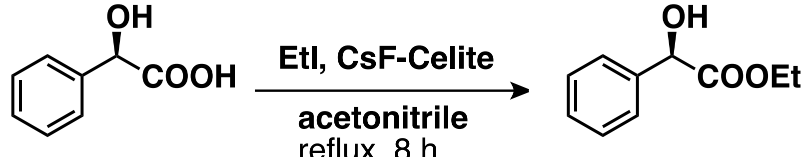


(*R*)-**133a** (*R*)-**130a**

(*R*)-2-(*tert*-butyldimethylsilyloxy)-2-cyclohexylacetaldehyde (*R*)-130a: To a 100 mL flame dried round bottom flask equipped with stir bar and filled with nitrogen was added **(*R*)-133a** (0.6 g, 2.0 mmol). Dry diethyl ether (10 mL) was added to dissolve the ester **(*R*)-133a**. The flask was fitted with a rubber septum and a nitrogen balloon. The solution was cooled to –78 ºC. To the reaction flask was added DIBAL-H (4 mL, 1 M solution in hexanes, 2 equiv) over a period of 2 minutes. The resulting reaction mixture was then stirred for 2 h at –78 °C. To the reaction was added methanol and water mixture (0.5 mL, 1:1 v/v), followed by diethyl ether (10 mL) at –78 °C. The resulting mixture was allowed to warm to room temperature. Thereafter, saturated potassium sodium tartrate solution (10 mL) was added to the reaction flask. The resulting cloudy reaction mixture was stirred for 4 h at room temperature until clear biphasic mixture was obtained. The organic layer was separated and the aqueous layer was extracted with diethyl ether (10 mL × 3). The combined organic layer was washed with saturated brine solution (10 mL) then dried over $MgSO_4$ and concentrated under reduced pressure to give the crude aldehyde **(*R*)-130a** as a colorless liquid. Purification of the crude by silica gel chromatography (20 mm × 300 mm column, 20:1 hexanes/Et_2O as eluent, flash column) afforded pure aldehyde **(*R*)-130a** as a colorless liquid in 85 % isolated yield (0.40 g, 1.70 mmol).

Spectral data for **(*R*)-130a:** R_f = 0.31 (1:20 EtOAc / hexanes) **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.05 (s, 3H), 0.06 (s, 3H), 0.93 (s, 9H), 1.12-1.26 (m, 5H), 1.61-1.76 (m, 6H), 3.70 (dd, *J* = 5.1, 2.2 Hz, 1H), 9.59 (d, *J* = 2.2 Hz, 1H); **^{13}C-NMR** ($CDCl_3$, 126 MHz) δ –4.82, –4.34 18.45, 26.00, 26.20, 26.37, 26.43, 27.53, 29.23, 41.39, 82.01, 205.11. ^{1}H-NMR and ^{13}C-NMR data are in good agreement with literature reported value.[13]

4.13.2.3 Esterification of (*R*)-131b

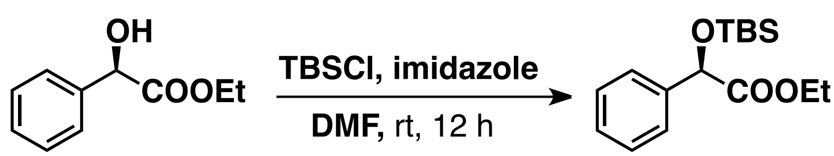


(*R*)-131b (*R*)132b

(*R*)-ethyl 2-hydroxy-2-phenylacetate 110b: (*R*)-hexahydromandelic acid (*R*)-**131b** (760 mg, 5 mmol) was reacted according to the procedure described for the synthesis of ester (*R*)-**131a** above with CsF-celite (2.6 g) and iodoethane (0.8 mL, 12.5 mmol) in dry acetonitrile (120 mL). Purification of the crude ester by silica gel chromatography (30 mm×300 mm column, 4:1 hexanes/EtOAc as eluent, flash column) afforded pure ester (*R*)-**132b** as a white solid (mp 33–34 ºC) in 70 % isolated yield (631 mg, 3.5 mmol).

Spectral data for (*R*)-**132b:** $R_f = 0.16$ (1:4 EtOAc / hexanes) **^{1}HNMR** (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 3.51 (d, J = 6.0 Hz, 1H), 4.17-4.26 (m, 2H), 5.16 (d, J = 6.0 Hz, 1H), 7.33-7.44 (m, 5H); **^{13}CNMR** (126 MHz, $CDCl_3$) δ 13.92, 62.05, 72.82, 126.43, 128.21, 128.44, 138.34, 173.52; $[\alpha]_D^{20}$ −135.3 (c 3.0, $CHCl_3$); Lit $[\alpha]_D^{20}$ −134 (c 3.0, $CHCl_3$) (Sigma Aldrich).

4.13.2.4 TBS protection of *α*-hydroxy ester (*R*)-132b



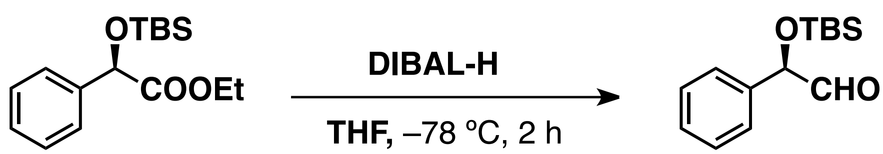
(*R*)**132b** (*R*)**133b**

(*R*)-ethyl 2-((*tert*-butyldimethylsilyl)oxy)-2-phenylacetate (*R*)-133b: The ester **(*R*)-132b** (901 mg, 5.0 mmol) was reacted according to the procedure described for the synthesis of **(*R*)-133a** above with Imidazole and *tert*-butyldimethylsilylchloride in dry DMF (15 mL). Purification of the crude ester by silica gel chromatography (30 mm×300 mm column, 50:1 hexanes/Et_2O as eluent, flash column) afforded pure ester **(*R*)-133b** as a colorless liquid in 92 % isolated yield

(1.35 g, 4.6 mmol).

Spectral data for **(*R*)-133b:** R_f = 0.23 (3:1 hexanes / CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 4.15 (q, *J* = 7.1 Hz, 2H), 5.23 (s, 1H), 7.50 - 7.27 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) –6.01, –5.88, 14.05, 18.33, 25.69, 61.00, 74.45, 126.30, 127.97, 128.24, 139.24, 172.13; $[\alpha]_D^{20}$ –38.3 (c 1.50,$CHCl_3$). Lit [14] $[\alpha]_D^{20}$ +38.8 (c 1.52, $CHCl_3$ *S*-isomer).

4.13.2.5 Synthesis of aldehyde (*R*)-130b



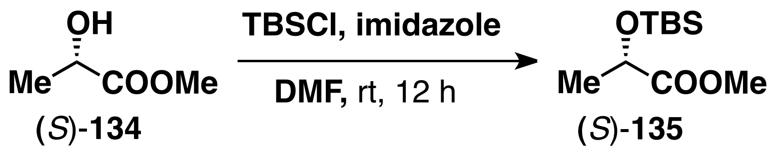
(*R*)133b (*R*)130b

(*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2-phenylacetaldehyde (*R*)-130b: The ester **(*R*)-133b** (581 mg, 2.0 mmol) was reacted according to the procedure described for the synthesis of aldehyde **(*R*)-130a** above with DIBAL-H (4.0 mL, 1 M solution in hexanes, 2 equiv) in dry diethyl ether. Purification of the crude aldehyde by silica gel chromatography (30 mm×300 mm column, 25:1 hexanes / Et_2O as eluent, flash column) afforded pure aldehyde **(*R*)-130b** as a colorless liquid in 85 % isolated yield (423 mg, 1.70 mmol).

Spectral data for **(*R*)-130b:** R_f = 0.35 (1:1 CH_2Cl_2 / hexanes); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.12 (s, 3H), 0.95 (s, 9H), 5.01 (d, *J* = 2.1 Hz, 1H), 7.30-7.41 (m, 5H), 9.51 (d, *J* =

2.2 Hz, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$) δ -4.66, -4.54, 16.27, 25.71, 80.00, 126.40, 128.33, 128.69, 136.60, 199.40; $[\alpha]_D^{20}$ –40.1 (c 0.600, ethanol). Lit[15] $[\alpha]_D^{22}$ –39.5° (c 0.612, ethanol).

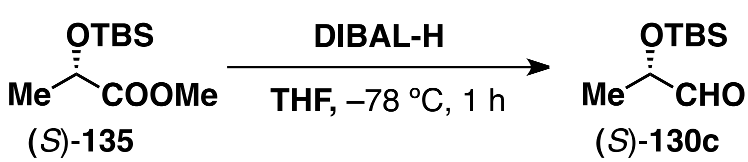
4.13.2.6 TBS protection of *α*-hydroxy ester (*S*)-134



(*S*)-methyl 2-((*tert*-butyldimethylsilyl)oxy)propanoate (*S*)-135: The (*S*)-methyl lactate **(*S*)-134** (520 mg, 5.0 mmol) was reacted according to the procedure described for the synthesis of **(*R*)-133a** above with Imidazole and *tert*-butyldimethylsilylchloride in dry DMF (15 mL). Purification of the crude ester by silica gel chromatography (30 mm×300 mm column, 100:1 hexanes/Et_2O as eluent, flash column) afforded pure ester **(*S*)-135** as a colorless liquid in 85% isolated yield (928 mg, 4.25 mmol).

Spectral data for **(*S*)-135:** R_f = 0.55 (1:9 EtOAc / hexanes; **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 1.40 (d, *J* = 6.7 Hz, 3H), 3.72 (s, 3H), 4.33 (q, *J* = 6.7 Hz, 1H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ –5.02, –4.73, 18.51, 21.56, 25.91, 51.96, 68.50, 174.42; $[\alpha]_D^{20}$ –28.0 (c 0.900, $CHCl_3$). Lit[16] $[\alpha]_D^{26}$ –26.7 (c 0.860, $CHCl_3$).

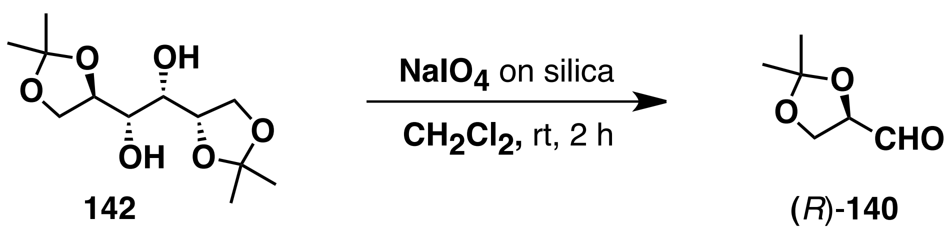
4.13.2.7 Synthesis of aldehyde (*S*)-130c



(*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanal (*S*)-130c: The ester **(*S*)-135** (437 mg, 2.0 mmol) was reacted according to the procedure described for the synthesis of aldehyde **(*R*)-130a** above with DIBAL-H (4 mL, 1 M solution in hexanes, 2.0 equiv) in dry diethyl ether. Purification of the crude aldehyde by silica gel chromatography (20 mm×300 mm column, 50:1 hexanes/Et_2O as eluent, flash column) afforded pure aldehyde **(*S*)-130c** as colorless liquid in 75 % isolated yield (282 mg, 1.5 mmol).

Spectral data for **(*S*)-130c:** R_f = 0.54 (1:6 EtOAc / hexanes) **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.28 (d, *J* = 6.8 Hz, 3H), 4.09 (qd, *J* = 6.8, 1.0 Hz, 1H), 9.61 (d, *J* = 1.0 Hz, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ –4.91, –4.82, 18.22, 18.54, 25.69, 73.80, 204.21; $[\alpha]_D^{20}$ +12.3 (c 1.96, $CHCl_3$). Lit[17] $[\alpha]_D^{25}$ +12.1 (c 1.96, $CHCl_3$).

4.13.2.8 Synthesis of aldehyde (*R*)-140

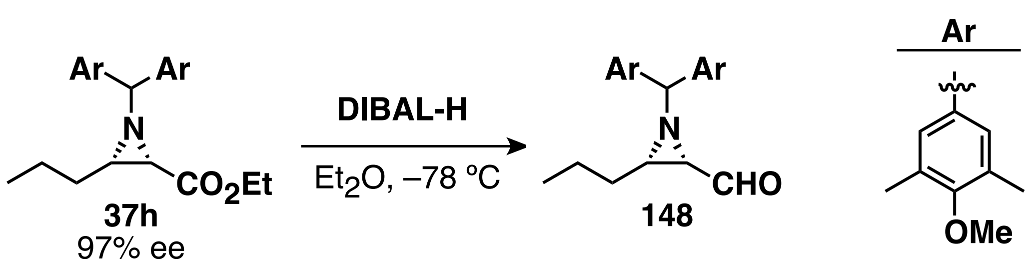


(*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (*R*)-140: To a solution of 1,2,5,6-diisopropylidene-(D)-mannitol **142** (5.0 g, 19.0 mmol) in dichloromethane (50 mL) were added $NaIO_4$ on silica (8.0 g adsorbed on 20 g silica, 38.0 mmol, 2.0 equiv), and the mixture was stirred for 1.5 h (monitored by TLC) at room temperature under nitrogen atmosphere. The reaction mixture was filtered through Celite-pad to a 250 mL round bottom flask and the Celite-pad was washed with dichloromethane (2 × 30 mL). Solvent was evaporated and the residue was purified by distillation under reduced pressure (26 °C, 9 mm Hg) to afford aldehyde **(*R*)-140** as colorless oil in 90% yield (1.17 g, 9.0 mmol).

Preparation of $NaIO_4$ on silica gel: $NaIO_4$ (8.0 g, 38.0 mmol) was dissolved in 10 mL of warm water (temp ~ 70 ºc) and 20 g silica gel was added to the solution. The mixture was stirred vigorously until the silica gel appeared to be free flowing.

Spectral data for **(*R*)-140**: **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.42 (s, 3H), 1.48 (s, 3H), 4.07-4.20 (m, 2H), 4.38 (ddd, *J* = 7.2, 5.0, 2.1 Hz, 1H), 9.72 (d, *J* = 1.9 Hz, 1H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 25.11, 26.22, 65.56, 79.82, 111.25, 201.80; $[\alpha]_D^{20}$ + 53.8 (c 2.0, $CHCl_3$). Lit[8] $[\alpha]_D^{20}$ + 53.8 (c 2.0, $CHCl_3$).

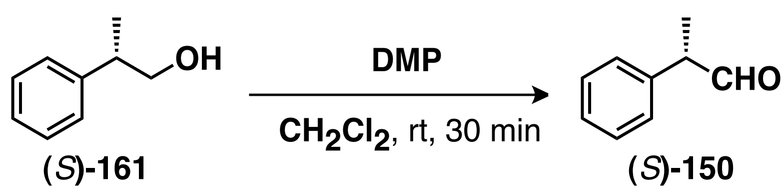
4.13.2.9 Synthesis of aldehyde 148



(2*S*,3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-propylaziridine-2-carbaldehyde 148: The aziridine 2-carboxylate **37h** (527 mg, 1.2 mmol) was reacted according to the procedure described for the synthesis of aldehyde (*R*)-**130a** above with DIBAL-H (2.4 mL, 1 M solution in hexanes, 1.2 equiv) in dry diethyl ether (4 mL) at –78 ºC. Purification of the crude aldehyde by silica gel chromatography (30 mm×300 mm column, 4:1 hexanes/Et_2O as eluent, flash column) afforded pure aldehyde **148** as a colorless liquid in 70 % isolated yield (332 mg, 0.84 mmol).

Spectral data for **148:** $R_f = 0.31$ (2:1:0.2 hexanes/ CH_2Cl_2/ Et_2O); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.80 (t, *J* = 7.3 Hz, 3H), 1.12-1.18 (m, 1H), 1.22-1.29 (m, 1H), 1.50-1.57 (m, 1H), 1.63-1.70 (m, 1H), 2.11-2.20 (m, 2H), 2.25 (s, 6H), 2.29 (s, 6H), 3.49 (s, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 7.03 (s, 2H), 7.06 (s, 2H), 9.44 (d, *J* = 5.6 Hz, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 13.51, 16.15, 16.19, 20.65, 31.34, 48.89, 49.86, 59.54, 59.60, 76.86, 127.26, 127.72, 130.63, 130.70, 137.42, 138.04, 156.02, 156.16, 201.03; IR (thin film) 2959vs, 2930vs, 1719s, 1483s, 1221s, 1140s cm-1; HRMS (ESI-TOF) *m/z* 418.2343 [(M+Na$^+$); calcd. for $C_{25}H_{34}NO_3$: 418.2358]; $[\alpha]_D^{20}$ –85.0 (c 1.0, CH_2Cl_2).

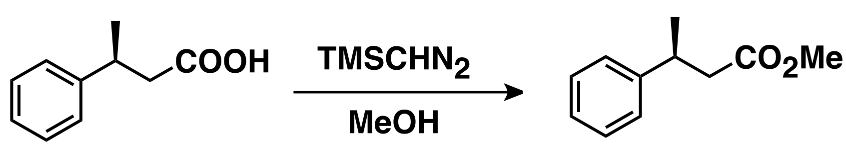
4.13.2.10 Synthesis of (*S*)-2-phenylpropanal (*S*)-150



(*S*)-2-phenylpropanal (*S*)-150: To a flame dried 25 mL round bottom flask flush with nitrogen and equipped with a stir bar was added the (*S*)-**161** (149.8 μL, 1.1 mmol) and freshly distilled CH_2Cl_2 (5.5 mL). To the resulting clear solution was added Dess-Martin periodinane (560 mg, 1.32 mmol, 1.2 equiv). The turbid reaction mixture was stirred for 30 min at room temperature under nitrogen atmosphere. Thereafter, a buffer solution made from dissolving NaH_2PO_4 (262 mg) and Na_2HPO_4 (366 mg) in 2.5 mL water, was added to the reaction mixture. The resulting mixture was stirred for 5 min at room temperature. The turbid mixture was filtered through a Celite pad to a 100 mL round bottom flask. The reaction flask was washed with CH_2Cl_2 (3 × 10 mL) and passed through the same Celite pad. The resulting organic layer was washed with sat. aq. $NaHCO_3$ (2× 10 mL) and then with brine (2 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvents were removed in *vacuo*. Purification of the crude by silica gel chromatography (20 mm × 150 mm column, 9:1 hexanes/Et_2O as eluent, flash column) afforded pure **(*S*)-150** as a colorless liquid in 70 % isolated yield (103 mg, 0.77 mmol).

Spectral data for **(*S*)-150:** R_f = 0.14 (1:1 DCM / hexanes) **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.45 (d, *J* = 7.1 Hz, 3H), 3.64 (qd, *J* = 7.1, 1.3 Hz, 1H), 7.21-7.23 (m, 2H), 7.29-7.32 (m, 1H), 7.37-7.40 (m, 2H), 9.69 (d, *J* = 1.5 Hz, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.61, 53.02, 127.52, 128.30, 129.08, 137.76, 201.03; $[\alpha]_D^{20}$ +290.0 (c 0.45, benzene) Lit[18] $[\alpha]_D^{20}$ +314.6 (c 0.45, benzene)

4.13.2.11 Synthesis of (*S*)-methyl 3-phenylbutanoate (*S*)-154

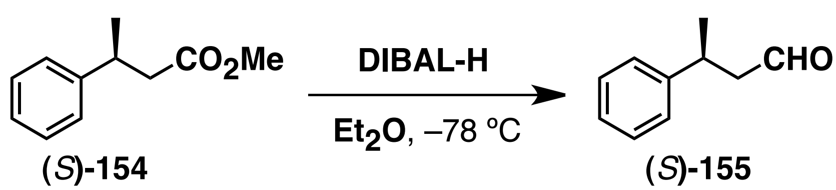


(*S*)-153 **(*S*)-154**

(*S*)-methyl 3-phenylbutanoate (*S*)-154: To a 100 mL flame dried round bottom flask equipped with stir bar and filled with nitrogen was added (*S*)-3-phenylbutanoic acid **(*S*)-153** (0.65 g, 4.0 mmol). Methanol (50 mL) was added to dissolve the acid **(*S*)-154**. The flask was fitted with a rubber septum and a nitrogen balloon. The solution was cooled to 0 ºC. To the reaction flask was added (trimethylsilyl)diazomethane (2 M in hexanes, 6 mL, 12.0 mmol) over a period of 2 minutes. The resulting mixture was warmed to room temperature and stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure. Purification of the crude methyl ester by silica gel chromatography (20 mm×150 mm column, 1:1 hexanes/Et_2O as eluent, flash column) afforded pure ester **(*S*)-154** as a colorless liquid in 94 % isolated yield (0.67 g, 3.76 mmol).

Spectral data for **(*S*)-154:** R_f = 0.21 (1:9 EtOAc / hexanes) **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.32 (d, *J* = 7.0 Hz, 3H), 2.57 (dd, *J* = 15.2, 8.2 Hz, 1H), 2.65 (dd, *J* = 15.2, 6.9 Hz, 1H), 3.30 (sextet, *J* = 7.3 Hz, 1H), 3.63 (s, 3H), 7.25-7.21 (m, 3H), 7.33-7.30 (m, 2H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 21.69, 36.37, 42.66, 51.38, 126.33, 126.63, 128.43, 145.63, 172.73; $[\alpha]_D^{20}$ +43.7, (c 1.0, benzene). Reported for (*R*)-isomer $[\alpha]_D^{20}$ −44, (c 1.0, benzene) (Sigma Aldrich).

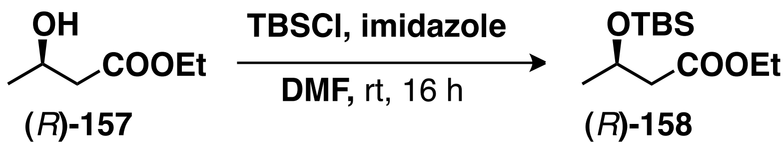
4.13.2.12 Synthesis of (*S*)-3-phenylbutanal (*S*)-155



(*S*)-3-Phenylbutanal (*S*)-155: To a 100 mL flame dried round bottom flask equipped with stir bar and filled with nitrogen was added **(*S*)-154** (0.58 g, 3.0 mmol). Dry diethyl ether (10 mL) was added to dissolve the ester **(*S*)-154**. The flask was fitted with a rubber septum and a nitrogen balloon. The solution was cooled to –78 ºC. To the reaction flask was added DIBAL-H (6 mL, 1 M solution in hexanes) over a period of 2 minutes. The resulting reaction mixture was then stirred for 1 h at –78 °C. To the reaction was added methanol and water mixture (1.0 mL, 1:1 v/v), followed by diethyl ether (15 mL) at –78 °C. The resulting mixture was allowed to warm to room temperature. Thereafter, saturated potassium sodium tartrate solution (15 mL) was added to the reaction flask. The resulting cloudy reaction mixture was stirred for 4 h at room temperature until clear biphasic mixture was obtained. The organic layer was separated and the aqueous layer was extracted with diethyl ether (15 mL × 3). The combined organic layer was washed with saturated brine solution (10 mL) then dried over $MgSO_4$ and concentrated under reduced pressure to give the crude aldehyde **(*S*)-155** as a colorless liquid. Purification of the crude by silica gel chromatography (20 mm × 300 mm column, 50:1 hexanes/Et_2O as eluent, flash column) afforded pure aldehyde **(*S*)-155** as a colorless liquid in 75 % isolated yield (333 g, 2.25 mmol).

Spectral data for **(*S*)-155:** R_f = 0.31 (1:6 Et_2O / hexanes); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ 1.33 (d, *J* = 7.0 Hz, 3H), 2.66 (ddd, *J* = 16.6, 7.7, 2.2 Hz, 1H), 2.76 (ddd, *J* = 16.6, 6.8, 1.8 Hz, 1H), 3.36 (dt, *J* = 14.3, 7.1 Hz, 1H), 7.22-7.24 (m, 3H), 7.30-7.33 (m, 2H), 9.71 (t, *J* = 2.0 Hz, 1H); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ 22.13, 34.28, 51.70, 126.50, 126.72, 128.64, 145.42, 201.80; $[\alpha]_D^{20}$ –39.5 (c 0.2, Et_2O). Lit[19] $[\alpha]_D^{25}$ –38.0 (c 0.2, Et_2O).

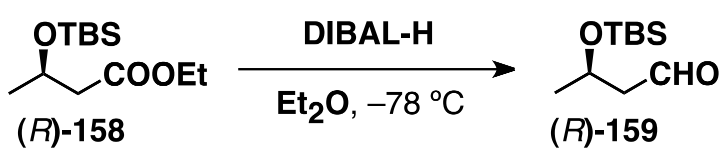
4.13.2.13 Synthesis of ester (*R*)-158



(*R*)-Ethyl 3-((*tert*-butyldimethylsilyl)oxy)butanoate (*R*)-158: The ester **(*R*)-157** (0.90 mL, 7.0 mmol) was reacted according to the procedure described for the synthesis of **(*R*)-133a** above with Imidazole (0.72g, 10.5 mmol, 1.5 equiv) and *tert*-butyldimethylsilylchloride (1.60 g, 10.5 mmol, 1.5 equiv) in dry DMF (15 mL). Purification of the crude ester by silica gel chromatography (30 mm×300 mm column, 50:1 hexanes/Et_2O as eluent, flash column) afforded pure ester **(*R*)-158** as a colorless liquid in 85 % isolated yield (1.47 g, 5.95 mmol).

Spectral data for **(*R*)-158** $R_f = 0.31$ (1:20 EtOAc / hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.16 (d, J = 6.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 2.43 (dd, J = 14.5, 7.6 Hz, 1H), 2.43 (dd, J = 14.5, 7.6 Hz, 1H), 4.14-4.05 (m, 2H), 4.28-4.22 (m, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ –5.08, –4.56, 14.15, 17.90, 23.88, 25.69, 44.93, 60.16, 65.81, 171.54; $[\alpha]_D^{20}$ –26.3 (c 1.0, CH_2Cl_2). Lit[20] $[\alpha]_D^{25}$ –25.5 (c 1.0, CH_2Cl_2).

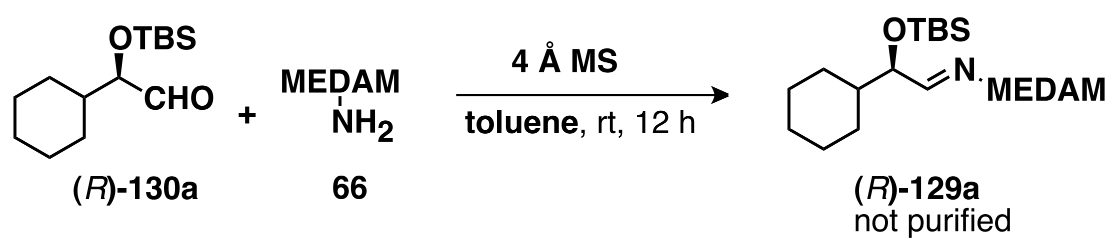
4.13.2.14 Synthesis of aldehyde (*R*)-159



(R)-3-((*tert*-butyldimethylsilyl)oxy)butanal (R)-159: The ester **(R)-158** (0.49 g, 2.0 mmol) was reacted according to the procedure described for the synthesis of aldehyde **(S)-155** above with DIBAL-H (4 mL, 1 M solution in hexanes, 2.0 equiv) in dry diethyl ether (7 mL) at –78 ºC. Purification of the crude aldehyde **136** by silica gel chromatography (30 mm×300 mm column, 25:1 hexanes//Et_2O as eluent, flash column) afforded pure aldehyde **(R)-159** as a colorless liquid in 80 % isolated yield (0.32 g, 1.6 mmol).

Spectral data for **(R)-159:** R_f = 0.41 (1:1 CH_2Cl_2 / hexanes); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.04 (s, 3H), 0.83 (s, 9H), 1.19 (d, J = 6.2 Hz, 3H), 2.38-2.55 (m, 2H), 4.32 (sextet, J = 6.0 Hz, 1H), 9.75 (t, J = 2.3 Hz, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ –5.03, –4.47, 17.87, 24.08, 25.65, 52.90, 64.48, 202.02; $[\alpha]_D^{20}$ –11.6 (c 1.0, CH_2Cl_2). Lit[20] $[\alpha]_D^{25}$ –11.3 (c 1.0, CH_2Cl_2).

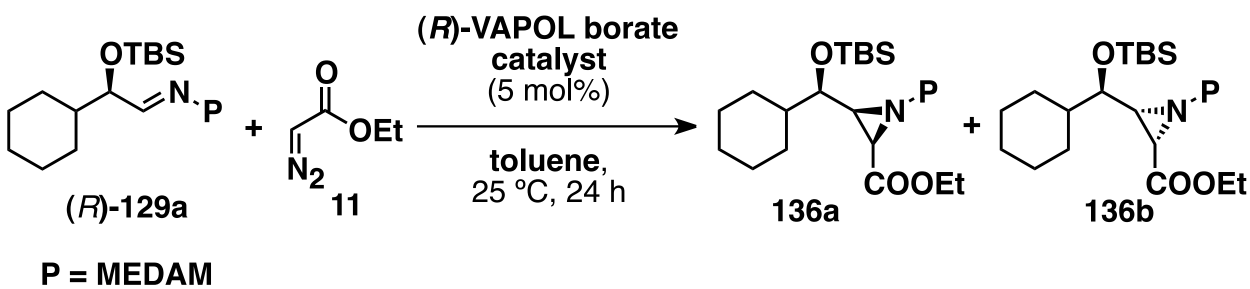
4.13.3 Synthesis of chiral imine (R)-129a



(R,E)-N-(2-((*tert*-butyldimethylsilyl)oxy)-2-cyclohexylethylidene)-1,1-bis(4-methoxy-3,5-dimethylphenyl)methanamine (R)-129a: To a 50 mL flame-dried round bottom flask filled with argon was added bis(4-methoxy-3,5-dimethylphenyl)methanamine **66** (1.25 g, 4.17 mmol), 4Å MS (4 g, freshly dried) and dried toluene (15 mL). After stirring for 10 min, aldehyde **(R)-130a** (1.12 mg, 4.38 mmol, 1.05 equiv) was added. The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was filtered through Celite pad to a 100 mL round bottom flask. The reaction flask was rinsed with ether (2 × 20 mL) and the rinse was filtered through the same Celite pad. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 4 h to afford the crude imine as colorless viscous oil. The resulting imine **(*R*)-129a** was used without further purification.

Spectral data for **(*R*)-129a:** ^{1}**H-NMR** (300 MHz, $CDCl_3$): δ –0.14 (s, 3H), –0.01 (s, 3H), 0.82 (s, 9H), 0.97-1.26 (m, 6H), 1.58-1.84 (m, 5H), 2.23 (s, 6H), 2.24 (s, 6H), 3.68 (s, 3H), 3.70 (s, 3H), 3.96 (t, J = 6.2 Hz, 1H), 5.17 (s, 1H), 6.88 (s, 2H), 6.90 (s, 2H), 7.55 (d, J = 6.2 Hz, 1H); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ –4.88, –4.45, 16.08, 16.13, 18.12, 25.79, 26.06, 26.13, 26.49, 28.18, 28.85, 43.07, 59.59, 59.62, 76.91, 78.71, 127.12, 127.81, 128.19, 130.48, 138.36, 138.66, 155.73, 155.87, 166.82.

4.13.4 Asymmetric catalytic aziridination of imine (*R*)-129a (Procedure A)

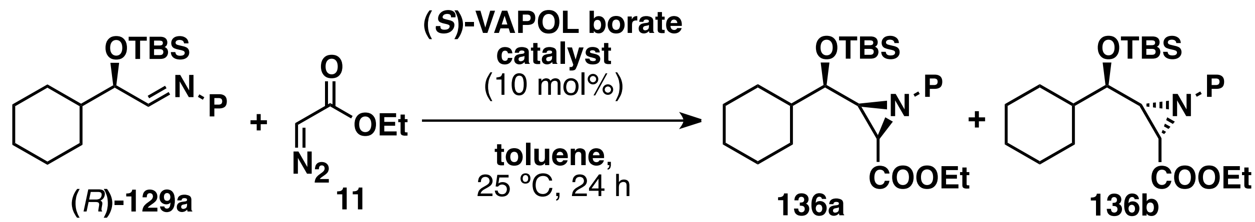


(2*S*, 3*R*)-Ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*R*)-((*tert*-butyldimethylsilyl)oxy) (cyclohexyl)methyl)aziridine-2-carboxylate 136b:

To a 10 mL flame-dried home-made Schlenk flask, prepared from a single necked 25 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, flushed with argon was added (*S)*-VAPOL (14 mg, 0.025 mmol, 5 mol%) and $B(OPh)_3$ (29 mg, 0.100 mmol, 20 mol%). Under an argon flow, dry toluene (2 mL) was added to dissolve the two reagents. The flask was sealed, and then placed in an 80 ºC for 1 h. After 1 hour, a vacuum (0.5 mm Hg) was applied carefully to remove the volatiles. The vacuum is maintained for a period of 30 min at a temperature of 80 ºC. The flask was then filled with argon and the catalyst mixture was cooled to room temperature. The solution of imine **(*R*)-129a** (0.5 mmol, crude) in dry toluene (1.0 mL) was then transferred to the flask containing the catalyst. The reaction mixture was stirred for 5 min at room temperature to give a light orange solution. To this solution was rapidly added EDA **11** (62 μL, 0.6 mmol, 1.2 equiv) and the resulting mixture was stirred for 24 h at room temperature. The reaction was diluted by addition of hexane (6 mL). The reaction mixture was then filtered through a silica gel plug to a 100 mL round bottom flask. The reaction flask was rinsed with EtOAc (20 mL × 3) and the rinse was filtered through the same silica gel plug. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as yellow colored viscous oil. Purification of the crude aziridine by neutral alumina chromatography (30 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **136b** and **136a** as a white solid (mp 48-50 ºC on > 99:1 dr material) in 80 % isolated yield (250 mg, 0.4 mmol).

The diastereomeric ratio of **136b** and **136a** was determined to be 94.7:5.3 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 10.73 min (minor diastereomer, **136a**) and R_t = 13.51 min (major diastereomer, **136b**).

Imine (*R*)-**129a** was reacted according to the general Procedure A described above with (*R*)-VANOL as ligand to afford aziridines **136b** and **136a** with 8:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **136a** and **136b** as a white solid in 85 % isolated yield (265 mg, 0.425 mmol).



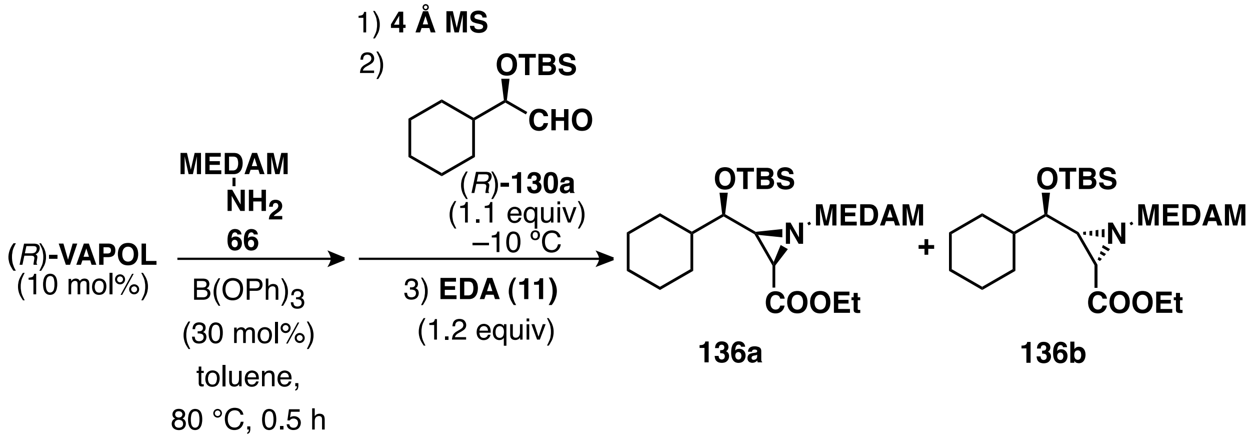
P = MEDAM

Imine (*R*)-**129a** was reacted according to the general Procedure A described above with (*S*)-VAPOL as ligand to afford aziridines **136a** and **136b** with 2:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **136a** and **136b** as a viscous liquid in 30 % isolated yield (94 mg, 0.15 mmol).

Imine (*R*)-**129a** was reacted according to the general Procedure A described above with (*S*)-VANOL as ligand to afford aziridines **136a** and **136b** with 2:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **136a** and **136b** as a white solid in 40 % isolated yield (126 mg, 0.20 mmol).

4.13.5 Asymmetric catalytic multi-component aziridination reaction of aldehyde (*R*)-130a in presence of chiral catalyst (Procedure B)

4.13.5.1 Multi-component aziridination reaction of aldehyde (*R*)-130a and MEDAM amine 66 in presence of (*R*)-ligand (VAPOL/VANOL)



(2*S*, 3*R*)-Ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*R*)-((*tert*-butyldimethylsilyl)oxy) (cyclohexyl)methyl)aziridine-2-carboxylate 136b:

To a 10 mL flame-dried home-made Schlenk flask, prepared from a singlenecked 25 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, equipped with a stir bar and filled with argon was added *(R)*-VAPOL (11 mg, 0.02 mmol), $B(OPh)_3$ (17 mg, 0.06 mmol) and amine **66** (60 mg, 0.2 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (0.5 mL) was added. The flask was sealed by closing the Teflon valve, and then placed in an oil bath (80 ºC) for 0.5 h. The flask was then allowed to cool to room temperature and open to argon through side arm of the Schlenk flask. To the flask containing the catalyst was added the 4Å Molecular Sieves (50 mg, freshly flame-dried). The flask was then allowed to cool to –10 ºC and aldehyde (*R*)-**130a** (56.4 mg, 0.22 mmoL, 1.1 equiv) was added to the reaction mixture. To this solution was rapidly added ethyl diazoacetate (EDA) **11** (25 μL, 0.24 mmoL, 1.2 equiv). The resulting mixture was stirred for 32 h at –10 ºC. The reaction was dilluted by addition of hexane (3 mL). The reaction mixture was then filtered through a silica gel plug to a 100 mL round bottom flask. The reaction flask was rinsed with EtOAc (10 mL × 3) and the rinse was filtered through the same silica gel plug. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as yellow colored viscous oil. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **136b** and **136a** as a white solid (mp 48-50 ºC on 99:1 dr material) in 85 % isolated yield (106 mg, 0.17 mmol).

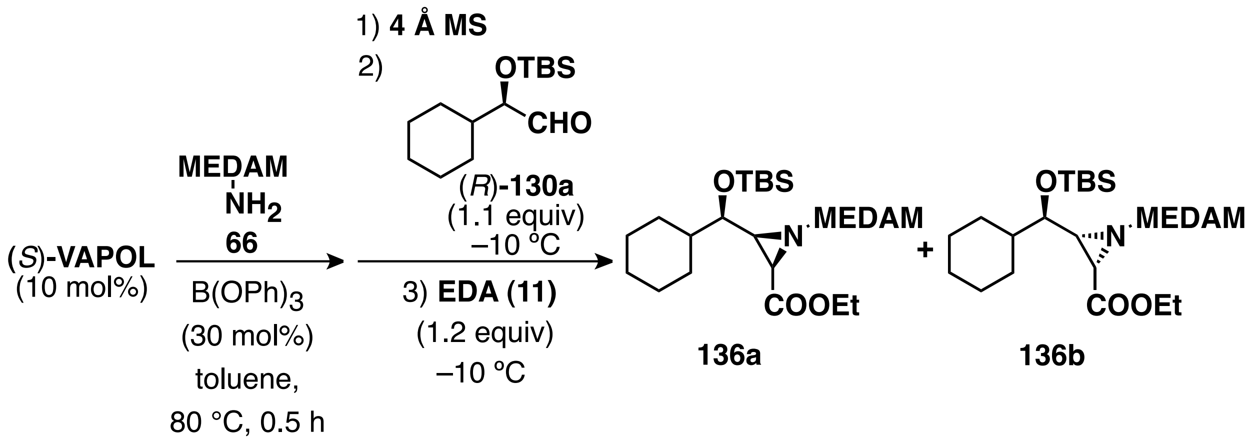
The diastereomeric ratio of **136b** and **136a** was determined to be 94.7:5.3 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 10.73 min (minor diastereomer, **136a**) and R_t = 13.51 min (major diastereomer, **136b**).

Aldehyde (*R*)-**130a** was reacted according to the general Procedure B described above with (*R*)-VANOL (9 mg, 0.02 mmol), as ligand to afford aziridines **136b** and **136a** with >99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **136b** and **136a** as a white solid in 80 % isolated yield (100 mg, 0.16 mmol).

Spectral data for **136b**: R_f = 0.17 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (300 MHz, $CDCl_3$):

δ –0.30 (s, 3H), –0.03 (s, 3H), 0.72 (s, 9H), 0.98-1.18 (m, 6H), 1.28 (t, J = 7.1 Hz, 3H), 1.55-1.73 (m, 5H), 2.04 (d, J = 6.9 Hz, 1H), 2.21-2.25 (m, 13H), 3.52 (dd, J = 8.5, 3.8 Hz, 1H), 3.63 (s, 1H), 3.67 (s, 3H), 3.70 (s, 3H), 4.18 (qd, J = 7.1, 1.7 Hz, 2H), 6.92 (s, 2H), 6.96 (s, 2H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ –4.64, –4.40, 14.35, 16.16, 16.19, 17.96, 25.91, 26.57, 26.63, 26.65, 27.72, 28.78, 41.72, 44.05, 50.94, 59.39, 59.59, 60.63, 73.50, 76.97, 127.96, 129.05, 130.22, 130.34, 137.45, 137.63, 155.69, 156.04, 170.34; IR (thin film) 2930vs, 2855s, 1744s, 1483s, 1257s, 1221s, 1186vs, 1146vs, 1018vs cm^{-1}; HRMS (ESI-TOF) *m/z* 624.4054 [(M+H$^+$); calcd. for $C_{37}H_{58}NO_5Si$: 624.4084]; $[\alpha]_D^{20}$ –90.4 (c 1.0, CH_2Cl_2) on >99:1 dr material (HPLC).

4.13.5.2 Multi-component aziridination reaction of aldehyde (*R*)-130a in presence of (*S*)-ligand (VAPOL/VANOL)

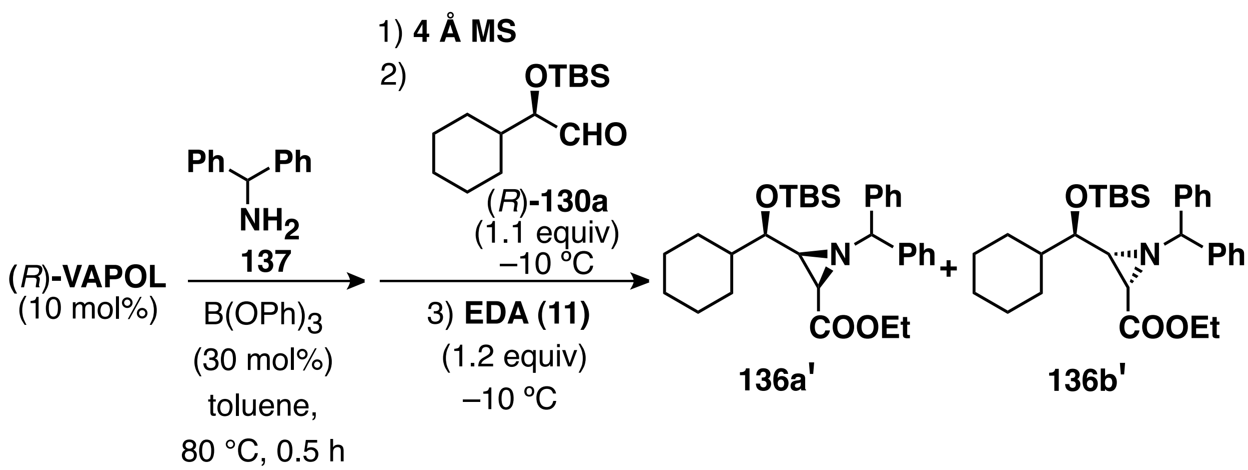


Aldehyde (*R*)-**130a** was reacted according to the general Procedure B described above with (*S*)-VAPOL as ligand to afford aziridines **136a** and **136b** with 1.1:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **136a** and **136b** as a white solid in 30 % isolated yield (37 mg, 0.06 mmol).

Aldehyde (*R*)-**130a** was reacted according to the general Procedure B described above with (*S*)-VANOL as ligand to afford aziridines **136a** and **136b** with 1.5:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **136a** and **136b** as a white solid in 15 % isolated yield (19 mg, 0.03 mmol).

Spectral data for **136a**: R_f = 0.17 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}**H-NMR** (300 MHz, $CDCl_3$): δ –0.07 (s, 3H), –0.06 (s, 3H), 0.85 (s, 9H), 0.91-1.18 (m, 6H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.57-1.86 (m, 5H), 2.14 (d, *J* = 6.4 Hz, 1H), 2.21-2.23 (m, 13H), 3.42 (s, 1H), 3.54 (d, *J* = 8.1 Hz, 1H), 3.67 (s, 3H), 3.68 (s, 3H), 4.05-4.31 (m, 2H), 7.03 (s, 4H); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ –4.00, –3.50, 14.38, 16.17, 16.20, 18.03, 26.20, 26.62, 26.65, 27.65, 28.90, 29.57, 41.82, 44.09, 50.95, 59.38, 59.59, 60.66, 73.55, 77.02, 128.03, 129.05, 130.26, 130.38, 137.45, 137.65, 155.78, 156.09, 170.48.

4.13.5.3 Multi-component aziridination reaction of aldehyde (*R*)-130a and benzhydryl amine 137 in presence of (*R*)-VAPOL

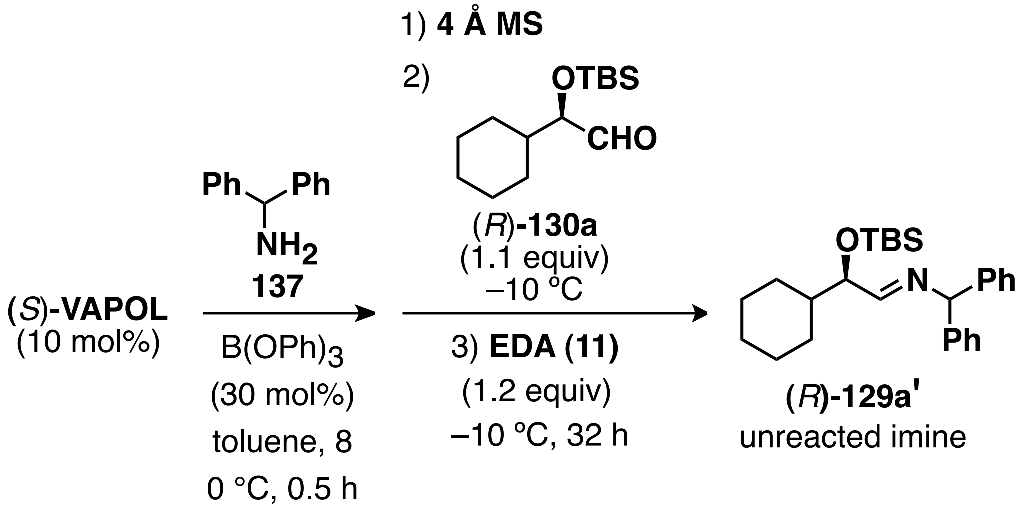


(2*S*, 3*R*)-Ethyl 1-benzhydryl-3-((*R*)-((*tert*-butyldimethylsilyl)oxy)(cyclohexyl)methyl) aziridine-2-carboxylate 136b':

Aldehyde (*R*)-**130a** was reacted according to the general Procedure B described above with (*R*)-VAPOL as ligand except the benzhydryl amine **137** (34.5 µL, 0.2 mmol) was used to afford aziridines **136b'** and **136a'** with >99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **136b'** and **136a'** as a white solid (mp 105-106 ºC on > 99:1 dr material) in 80 % isolated yield (81 mg, 0.16 mmol).

Spectral data for **136b'**: R_f = 0.32 (4:2:0.1 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ –0.21 (s, 3H), –0.02 (s, 3H), 0.75 (s, 9H), 0.99-1.18 (m, 5H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.56-1.75 (m, 6H), 2.13 (d, *J* = 6.8 Hz, 1H), 2.28 (dd, *J* = 8.7, 6.8 Hz, 1H), 3.54 (dd, *J* = 8.7, 4.3 Hz, 1H), 4.03 (s, 1H), 4.11-4.24 (m, 2H), 7.17-7.37 (m, 10H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ –4.64, –4.03, 14.27, 18.11, 26.03, 26.55, 26.60, 26.64, 28.01, 28.46, 41.56, 44.08, 49.34, 60.69, 73.35, 76.61, 127.12, 127.18, 128.23, 128.26, 128.61, 141.36, 142.14, 170.05 (one S*p2* carbon not located); IR (thin film) 2928vs, 2855s, 1745s, 1453s, 1190vs, 1065s cm^{-1}; HRMS (ESI-TOF) *m/z* 508.3250 [(M+H^+); calcd. for $C_{31}H_{46}NO_3Si$: 508.3247]; $[\alpha]_D^{20}$ –84.9 (c 1.0, CH_2Cl_2) on >99:1 dr material (NMR).

4.13.5.4 Multi-component aziridination reaction of aldehyde (*R*)-130a and benzhydryl amine 137 in presence of (*S*)-VAPOL

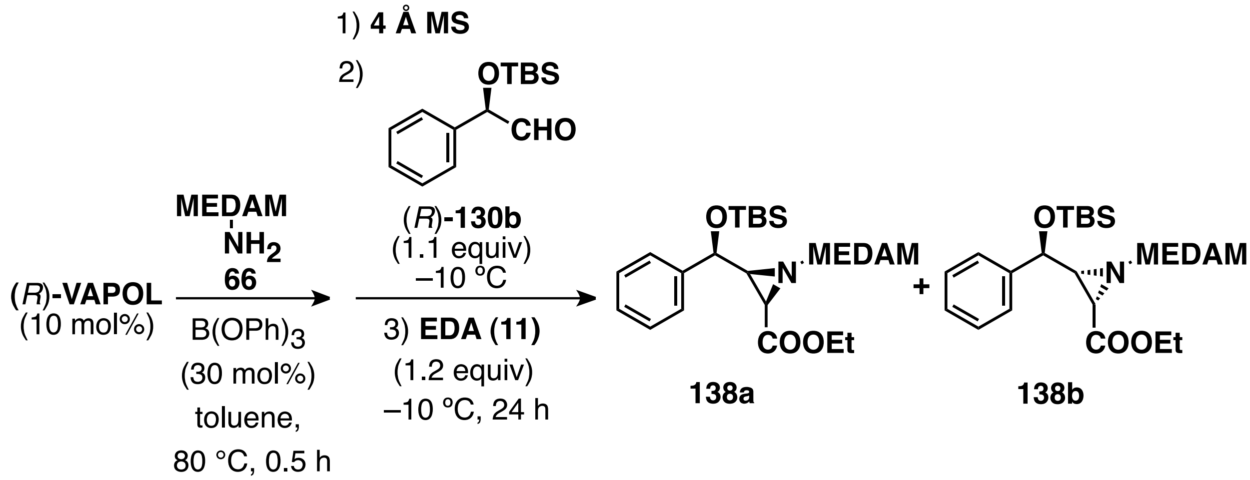


Aldehyde (*R*)-**130a** was reacted according to the general Procedure B described above with (*S*)-VAPOL as ligand except the benzhydryl amine **137** (34.5 μL, 0.2 mmol) was used. However, no aziridine was observed in this case. Instead, *in situ* formed imine (*R*)-**129a'** was observed.

Spectral data for (*R*)-**129a'**: **^{1}H-NMR (**300MHz, $CDCl_3$): δ –0.30 (3H, s), –0.16 (3H, s), 0.66 (9H, s), 0.82-1.12 (5H, m), 1.34-1.72 (6H, m), 3.83 (1H, t, J = 6.30 Hz), 5.24 (1H, s), 7.02 – 7.24 (10 H, m), 7.49 (1H, d, J = 6.30 Hz). (^{1}H NMR data determined from the crude reaction mixture)

4.13.6 Asymmetric catalytic multi-component aziridination reaction of aldehyde (*R*)-130b in presence of chiral catalyst (Procedure B)

4.13.6.1 Multi-component aziridination reaction of aldehyde (*R*)-130b and MEDAM amine 66 in presence of (*R*)-ligand (VAPOL/VANOL)



(2*S*, 3*R*)-Ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*R*)-((*tert*-butyldimethylsilyl) oxy)(phenyl)methyl)aziridine-2-carboxylate 138b:

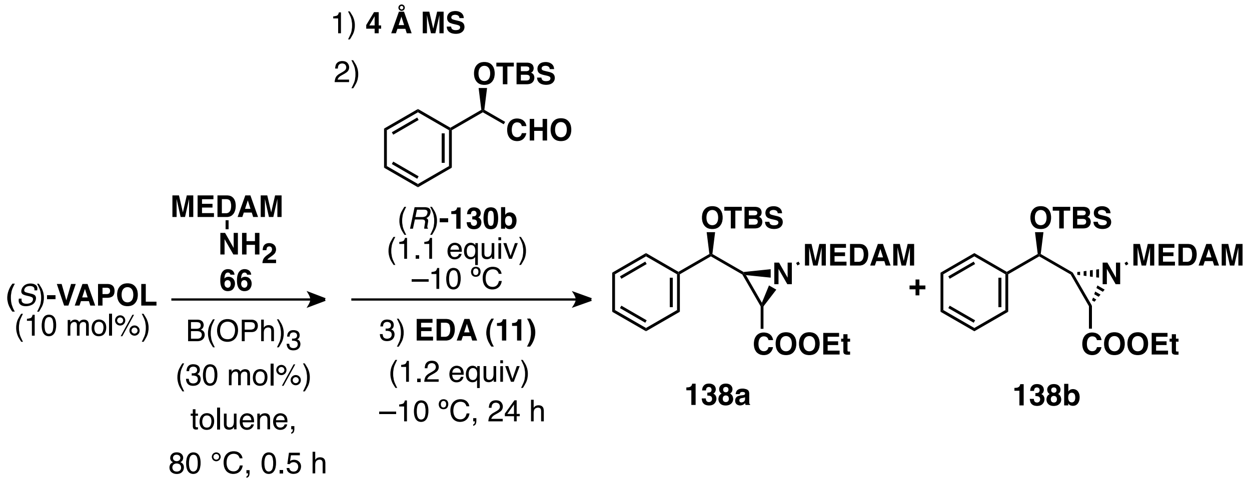
Aldehyde (*R*)-**130b** was reacted according to the general Procedure B described above with (*R*)-VAPOL as ligand to afford aziridines **138b** and **138a** with 99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **138b** and **138a** as a white solid (mp 139-140 ºC on 99:1 dr material) in 90 % isolated yield (111 mg, 0.18 mmol).

The diastereomeric ratio of **138b** and **138a** was determined to be 99:1 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99:1 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 8.49 min (minor diastereomer, **138a**) and R_t = 17.92 min (major diastereomer, **138b**).

Aldehyde (*R*)-**130b** was reacted according to the general Procedure B described above with (*R*)-VANOL (9 mg, 0.02 mmol), as ligand to afford aziridines **138b** and **138a** with 99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **138b** and **138a** as a white solid in 85 % isolated yield (105 mg, 0.17 mmol).

Spectral data for **138b**: R_f = 0.23 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ –0.26 (s, 3H), –0.23 (s, 3H), 0.60 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H), 1.99 (d, *J* = 7.0 Hz, 1H), 2.23 (s, 6H), 2.26 (s, 6H), 2.43 (t, *J* = 7.5 Hz, 1H), 3.49 (s, 1H), 3.68 (s, 3H), 3.70 (s, 3H), 4.06 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.70 (d, *J* = 7.9 Hz, 1H), 7.05 (s, 4H), 7.21-7.28 (m, 5H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ –5.12, –5.07, 14.12, 16.17, 16.24, 17.84, 25.55, 41.68, 55.25, 59.40, 59.54, 60.63, 73.40, 77.65, 126.54, 127.23, 127.47, 128.03, 128.63, 130.35, 130.44, 137.97, 138.20, 142.67, 155.64, 156.15, 169.78; IR (thin film) 2955vs, 2928vs, 1742vs, 1483s, 1221s, 1188vs, 1140s cm^{-1}; HRMS (ESI-TOF) *m/z* 618.3631 [(M+H$^+$); calcd. for $C_{37}H_{52}NO_5Si$: 618.3615]; $[\alpha]_D^{20}$ –92.6 (c 1.0, CH_2Cl_2) on 99:1 dr material (HPLC).

4.13.6.2 Multi-component aziridination reaction of aldehyde (*R*)-130b and MEDAM amine 66 in presence of (*S*)-ligand (VAPOL/VANOL)



(2*R*, 3*S*)-Ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*R*)-((*tert*-butyldimethylsilyl) oxy)(phenyl)methyl)aziridine-2-carboxylate 138a:

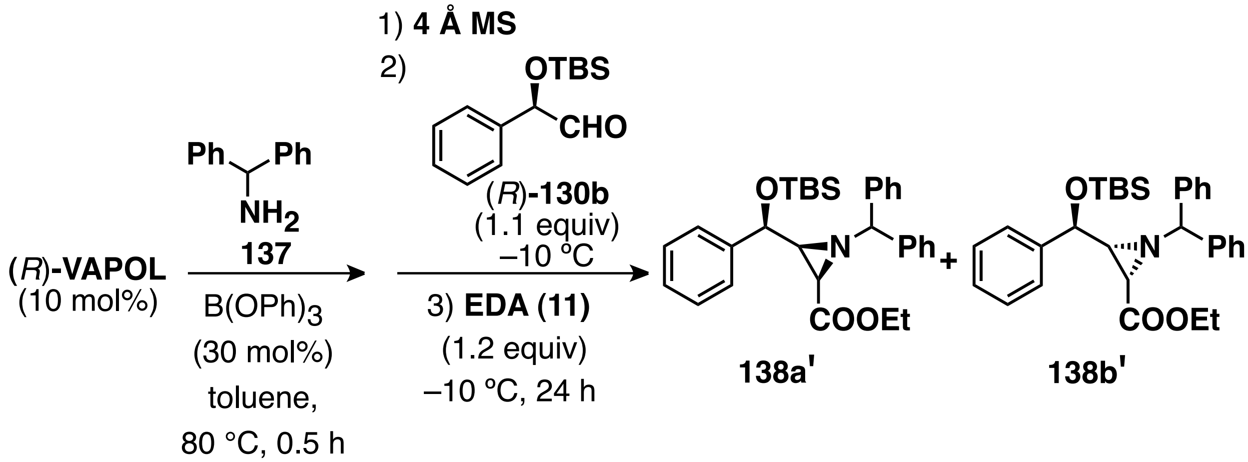
Aldehyde (*R*)-**130b** was reacted according to the general Procedure B described above with (*S*)-VAPOL as ligand to afford aziridines **138a** and **138b** with 98:2 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **138a** and **138b** as a white solid (mp 49-50 ºC on >99:1 dr material) in 90 % isolated yield (111 mg, 0.18 mmol).

The diastereomeric ratio of **138a** and **138b** was determined to be 98:2 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99:1 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 8.30 min (major diastereomer, **138a**) and R_t = 18.48 min (minor diastereomer, **138b**).

Aldehyde (*R*)-**130b** was reacted according to the general Procedure B described above with (*S*)-VANOL (9 mg, 0.02 mmol), as ligand to afford aziridines **138a** and **138b** with 98:2 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **138a** and **138b** as a white solid in 85 % isolated yield (105 mg, 0.17 mmol).

Spectral data for **138a**: R_f = 0.23 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ –0.33 (s, 3H), –0.09 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.79 (s, 9H), 2.01 (s, 6H), 2.21 (s, 6H), 2.28 (d, *J* = 6.4 Hz, 1H), 2.40 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.32 (s, 1H), 3.59 (s, 3H), 3.67 (s, 3H), 4.16 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.29 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.61 (d, *J* = 8.2 Hz, 1H), 6.51 (s, 2H), 6.99 (s, 2H), 7.00-7.01 (m, 3H), 7.11 (dd, *J* = 6.6, 2.9 Hz, 2H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 14.18, 15.25, 16.03, 16.13, 17.92, 25.63, 25.63, 42.92, 54.13, 59.25, 59.55, 60.82, 65.82, 72.33, 126.49, 126.91, 127.14, 127.23, 128.07, 129.69, 130.39, 136.99, 137.66, 142.32, 155.61, 155.63, 169.56; IR(thin film) 2955vs, 2930vs, 1742s, 1483s, 1221s, 1188vs, 1147s cm^{-1}; HRMS (ESI-TOF) *m/z* 618.3641 [$(M+H^+)$; calcd. for $C_{37}H_{52}NO_5Si$: 618.3615]; $[\alpha]_D^{20}$ +107.0 (c 1.0, CH_2Cl_2) on 99:1 dr material (HPLC).

4.13.6.3 Multi-component aziridination reaction of aldehyde (*R*)-130b and benzhydryl amine 137 in presence of (*R*)-VAPOL



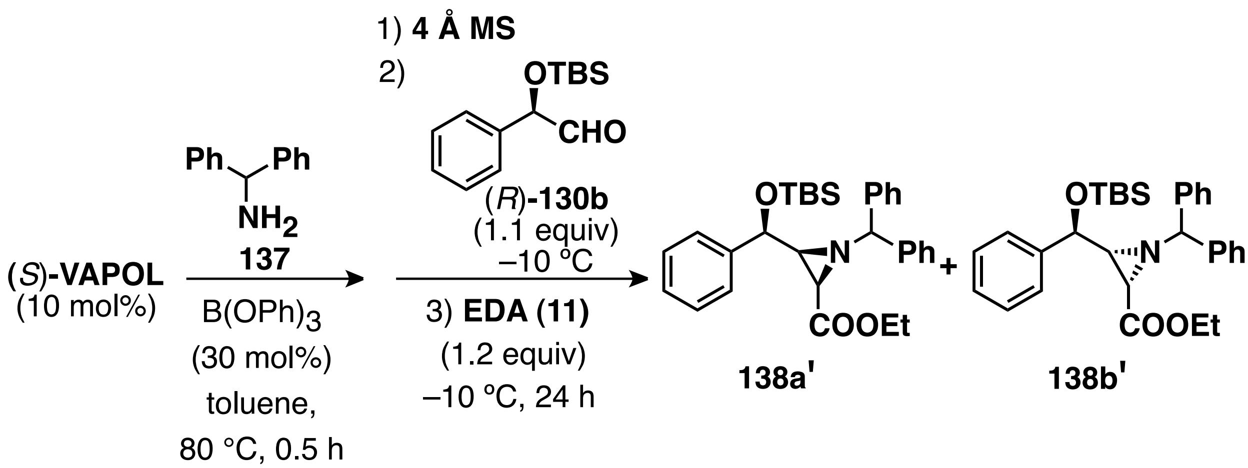
(2*S*, 3*R*)-Ethyl 1-benzhydryl-3-((*R*)-((*tert*-butyldimethylsilyl)oxy)(phenyl)methyl)aziridine-2-carboxylate 138b':

Aldehyde (*R*)-**130a** was reacted according to the general Procedure B described above with (*R*)-VAPOL as ligand except the benzhydryl amine **137** (34.5 µL, 0.2 mmol) was used to afford aziridines **138b'** and **138a'** with 17:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **138b'** and **138a'** as a white solid (mp 93-97 ºC on 17:1 dr material) in 65 % isolated yield (65 mg, 0.13 mmol).

The diastereomeric ratio of **139b'** and **139a'** was determined to be 17:1 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 6.43 min (minor diastereomer, **139a'**) and R_t = 11.47 min (major diastereomer, **139b'**).

Spectral data for **138b'**: R_f = 0.20 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ –0.24 (s, 3H), –0.21 (s, 3H), 0.63 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H), 2.09 (d, J = 7.0 Hz, 1H), 2.49 (dd, J = 8.0, 7.0 Hz, 1H), 3.79 (s, 1H), 4.14-4.07 (m, 2H), 4.74 (d, J = 8.0 Hz, 1H), 7.19-7.30 (m, 11H), 7.42-7.45 (m, 4H); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ –4.95, –4.80, 14.07, 17.98, 25.76, 41.68, 54.57, 60.72, 73.31, 77.85, 126.51, 126.97, 127.29, 127.33, 127.54, 128.08, 128.29, 128.36, 128.40, 142.36, 142.57, 142.66, 169.59; IR (thin film) 2933vs, 1730vs, 1454s, 1256s, 1199vs cm^{-1}; HRMS (ESI-TOF) *m/z* 502.2765 [$(M+H^{+})$; calcd. for $C_{31}H_{40}NO_3Si$: 502.2777]; $[\alpha]_D^{20}$ –70.5 (c 1.0, CH_2Cl_2) on 17:1 dr material (HPLC).

4.13.6.4 Multi-component aziridination reaction of aldehyde (*R*)-130b and benzhydryl amine 137 in presence of (*S*)-VAPOL



(2*R*, 3*S*)-ethyl 1-benzhydryl-3-((*R*)-((*tert*-butyldimethylsilyl)oxy)(phenyl)methyl)aziridine-2-carboxylate 138a':

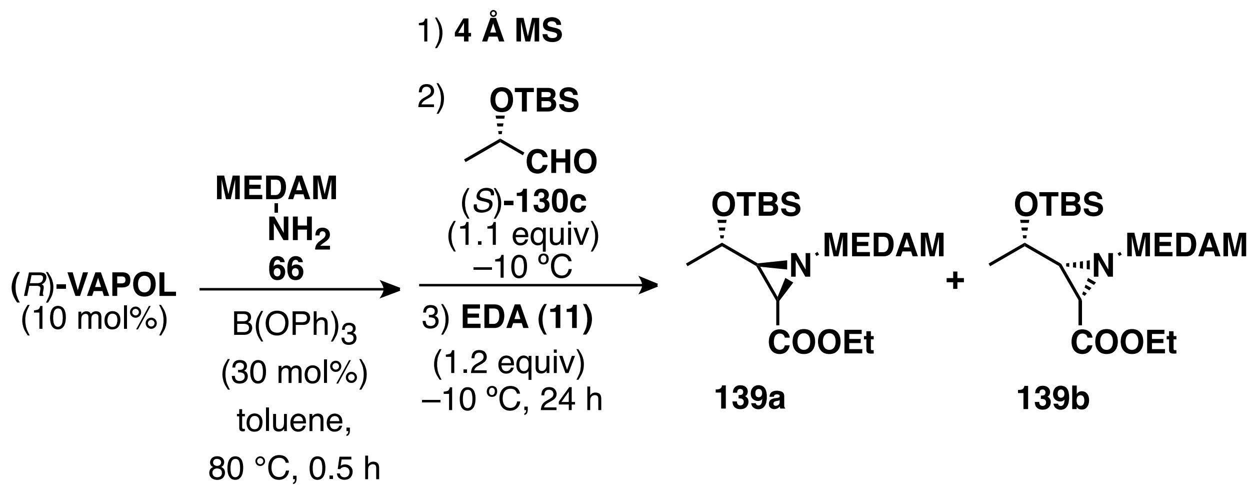
Aldehyde (*R*)-**130a** was reacted according to the general Procedure B described above with (*S*)-VAPOL as ligand except the benzhydryl amine **137** (34.5 µL, 0.2 mmol) was used to afford aziridines **138a'** and **138b'** with 99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **138a'** and **138b'** as a white solid (mp 126-131 ºC on 99:1 dr material) in 50 % isolated yield (50 mg, 0.10 mmol).

The diastereomeric ratio of **139a'** and **139b'** was determined to be 99:1 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 6.44 min (major diastereomer, **139a'**) and R_t = 11.76 min (minor diastereomer, **139b'**).

Spectral data for **138a'**: R_f = 0.20 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ –0.33 (s, 3H), –0.10 (s, 3H), 0.78 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H), 2.35 (d, *J* = 6.4 Hz, 1H), 2.44 (t, *J* = 7.2 Hz, 1H), 3.58 (s, 1H), 4.12-4.28 (m, 2H), 4.62 (d, *J* = 7.9 Hz, 1H), 6.84-7.13 (m, 10H), 7.24 (t, *J* = 7.3 Hz, 3H), 7.36 (d, *J* = 7.4 Hz, 2H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ –5.10, –4.61, 14.11, 17.95, 25.66, 42.93, 53.86, 60.88, 72.22, 77.75, 126.64, 126.76, 126.89, 127.05, 127.12, 127.52, 127.74, 127.87, 128.28, 141.37, 142.35, 142.40, 169.37; IR (thin film) 2932vs, 1728vs, 1454s, 1252s, 1198vs cm^{-1}; HRMS (ESI-TOF) *m/z* 502.2761 [(M+H^+); calcd. for $C_{31}H_{40}NO_3Si$: 502.2777]; $[\alpha]_D^{20}$ +105.3 (c 1.0, CH_2Cl_2) on 99:1 dr material (HPLC).

4.13.7 Asymmetric catalytic multi-component aziridination reaction of aldehyde (*S*)-130c in presence of chiral catalyst (Procedure B)

4.13.7.1 Multi-component aziridination reaction of aldehyde (*S*)-130c and MEDAM amine 66 in presence of (*R*)-ligand (VAPOL/VANOL)



(2*S*, 3*R*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*S*)-1-((*tert*-butyldimethyl silyl)oxy)ethyl)aziridine-2-carboxylate 139b:

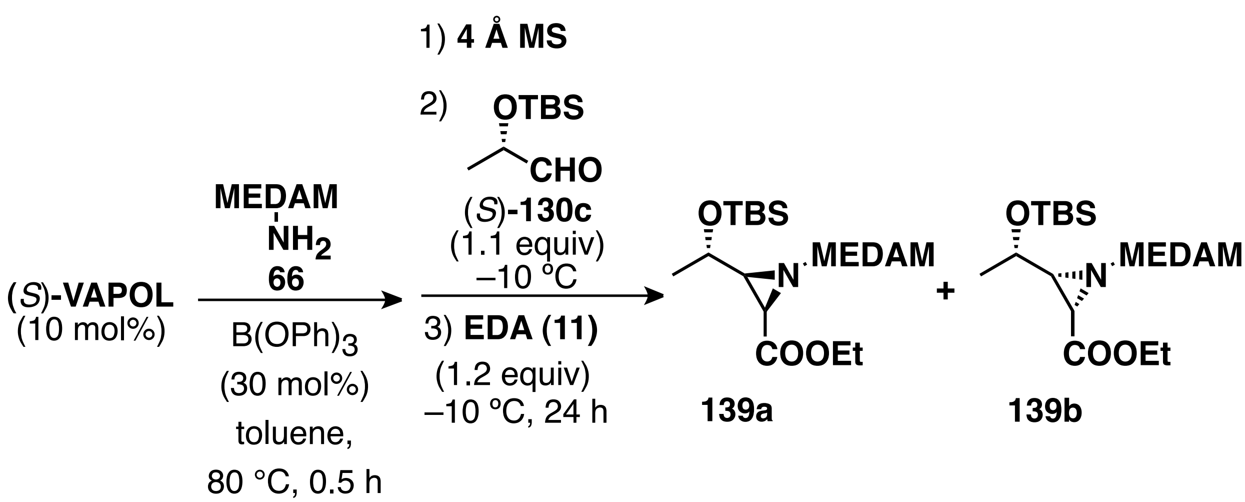
Aldehyde (*S*)-**130c** was reacted according to the general Procedure B described above with (*R*)-VAPOL as ligand to afford aziridines **139b** and **139a** with 96:4 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **139b** and **139a** as a sticky solid in 87 % isolated yield (97 mg, 0.174 mmol).

The diastereomeric ratio of **139b** and **139a** was determined to be 96:4 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 12.36 min (minor diastereomer, **139a**) and R_t = 13.94 min (major diastereomer, **139b**).

Aldehyde (*S*)-**130c** was reacted according to the general Procedure B described above with (*R*)-VANOL (9 mg, 0.02 mmol), as ligand to afford aziridines **139b** and **139a** with 95:5 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **139b** and **139a** as a sticky solid in 82 % isolated yield (91 mg, 0.164 mmol).

Spectral data for **139b**: R_f= 0.37 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ –0.06 (s, 3H), –0.04 (s, 3H), 0.71 (d, J = 6.2 Hz, 3H), 0.82 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H), 2.06 (dd, J = 8.2, 6.5 Hz, 1H), 2.22-2.24 (m, 13H), 3.45 (s, 1H), 3.66 (s, 3H), 3.70 (s, 3H), 3.72-3.81 (m, 1H), 4.06-4.28 (m, 2H), 6.95 (s, 2H), 7.07 (s, 2H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ –4.91, –4.34, 14.15, 16.05, 16.16, 17.84, 22.18, 25.70, 43.47, 53.01, 59.59, 59.64, 60.78, 66.12, (one *sp3* carbon not located), 127.16, 128.66, 130.43, 130.53, 137.48, 137.76, 155.76, 156.42, 169.50; IR (thin film) 2957vs, 2930vs, 1744s, 1483s, 1221s, 1194vs cm^{-1}; HRMS (ESI-TOF) *m/z* 556.3470 [(M+H^+); calcd. for $C_{32}H_{50}NO_5Si$: 556.3458]; $[\alpha]_D^{20}$ –93.3 (c 0.6, CH_2Cl_2) on 99:1 dr material (HPLC).

4.13.7.2 Multi-component aziridination reaction of aldehyde (*S*)-130c and MEDAM amine 66 in presence of (*S*)-VAPOL



(2*R*, 3*S*)-Ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*S*)-1-((*tert*-butyldimethyl silyl)oxy)ethyl)aziridine-2-carboxylate 139a:

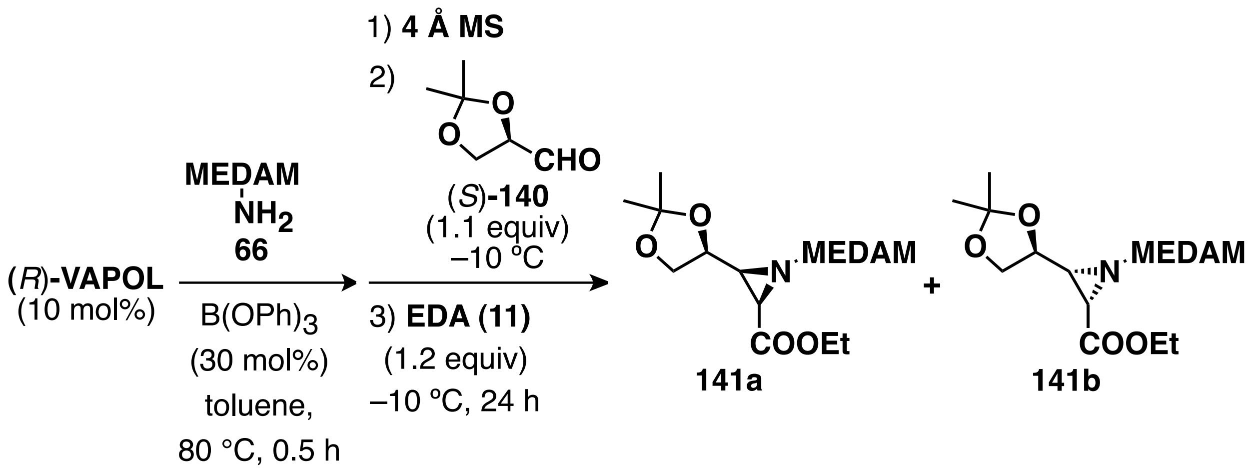
Aldehyde (*S*)-**130c** was reacted according to the general Procedure B described above with (*S*)-VAPOL as ligand to afford aziridines **139a** and **139b** with 91:9 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **139a** and **139b** as a sticky solid in 85 % isolated yield (94 mg, 0.17 mmol).

The diastereomeric ratio of **139b** and **139a** was determined to be 91:9 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 11.63 min (major diastereomer, **139a**) and R_t = 13.67 min (minor diastereomer, **139b**).

Spectral data for **139a**: R_f = 0.14 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ –0.33 (s, 3H), –0.02 (s, 3H), 0.70 (s, 9H), 1.05 (d, *J* = 6.3 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 2.07 (d, *J* = 7.1 Hz, 1H), 2.14-2.19 (m, 1H), 2.22 (s, 6H), 2.23 (s, 6H), 3.42 (s, 1H), 3.66 (s, 3H), 3.68 (s, 3H), 3.75-3.84 (m, 1H), 4.11-4.26 (m, 2H), 6.96 (s, 2H), 7.04 (s, 2H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ –5.13, –5.00, 14.32, 16.18, 17.93, 21.52, 25.69, 41.53, 54.44, 59.38, 59.57, 60.71, 67.51, 77.78, (one *sp3* carbon not located), 127.28, 128.76, 130.35, 130.40, 137.87, 138.15, 155.63, 156.14, 169.80; IR (thin film) 2928vs, 2956s, 1746s, 1484s, 1221s, 1188vs, 1097s cm^{-1}; HRMS (ESI-TOF) *m/z* 556.3475 [(M+H^+); calcd. for $C_{32}H_{50}NO_5Si$: 556.3458]; $[\alpha]_D^{20}$ +69.8 (c 0.6, CH_2Cl_2) on 12:1 dr material (HPLC).

4.13.8 Asymmetric catalytic multi-component aziridination reaction of aldehyde (*R*)-140 in presence of chiral catalyst (Procedure B)

4.13.8.1 Multi-component aziridination reaction of aldehyde (*R*)-140 and MEDAM amine 66 in presence of (*R*)-VAPOL



(2*S*, 3*R*)-Ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine-2-carboxylate 141b:

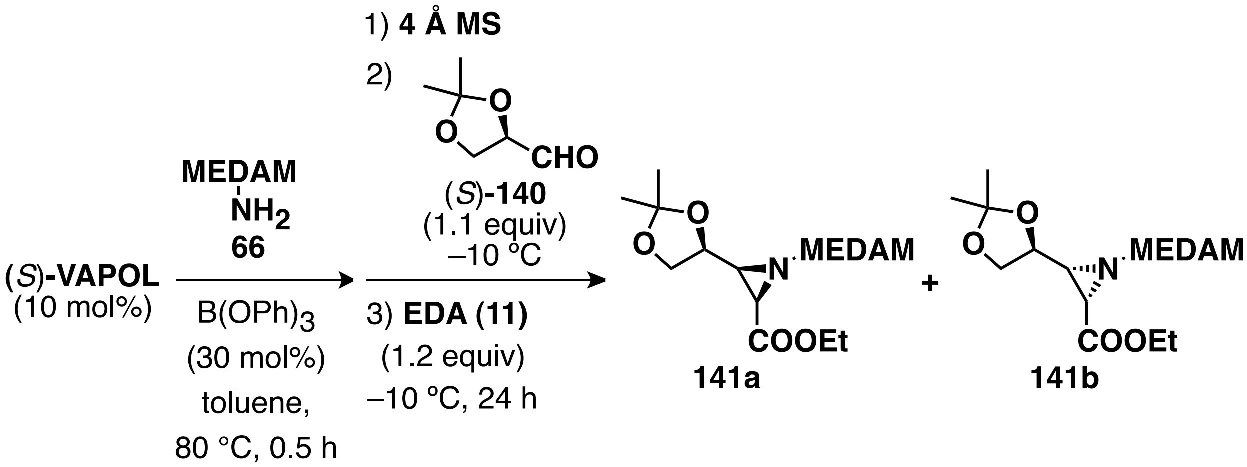
Aldehyde (*R*)-**140** was reacted according to the general Procedure B described above with (*R*)-VAPOL as ligand except before adding the aldehyde **(*R*)-140** to the reaction mixture 0.5 mL dry toluene was added (0.2 M concentration) to afford aziridines **141b** and **141a** with 95.5:4.5 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 2:1 hexanes/Et_2O as eluent, flash column) afforded inseparable mixture of aziridines **141b** and **141a** as a viscous liquid in 83 % isolated yield (83 mg, 0.166 mmol).

The diastereomeric ratio of **141b** and **141a** was determined to be 95.5:4.5 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 98:2 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 16.88 min (minor diastereomer, **141a**) and R_t = 31.23 min (major diastereomer, **141b**).

Aldehyde (*R*)-**140** was reacted according to the general Procedure B described above with (*R*)-VAPOL at different concentration in toluene at –10 ºC. The results are represented in Table 4.5 (Chapter 4).

Spectral data for **141b**: R_f = 0.25 (2:1 hexanes/Et_2O); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.22-1.26 (m, 6H), 1.28 (s, 3H), 2.13 (dd, *J* = 8.0, 7.0 Hz, 1H), 2.23-2.24 (m, 12H), 2.27 (d, *J* = 6.8 Hz, 1H), 3.58 (s, 1H), 3.65-3.70 (m, 7H), 3.92 (dd, *J* = 8.3, 6.5 Hz, 1H), 4.10-4.24 (m, 3H), 7.05 (s, 2H), 7.09 (s, 2H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.16, 16.01, 16.11, 25.36, 26.59, 41.42, 48.13, 59.49, 59.51, 60.96, 66.97, 75.01, 76.26, 109.40, 127.79, 128.19, 130.13, 130.45, 137.05, 137.30, 155.94, 169.02, (one *sp2* carbon not located); IR (thin film) 2986vs, 2938vs, 1744s, 1485s, 1221s, 1190vs, 1149s cm^{-1}; HRMS (ESI-TOF) *m/z* 498.2857 [(M+H+); calcd. for $C_{29}H_{40}NO_6$: 498.2858]; $[\alpha]_D^{20}$ –32.2 (c 1.0, CH_2Cl_2) on 20:1 dr material (^{1}H NMR).

4.13.8.2 Multi-component aziridination reaction of aldehyde (*R*)-140 and MEDAM amine 66 in presence of (*S*)-VAPOL



(2*R*, 3*S*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)aziridine-2-carboxylate 141a:

Aldehyde (*R*)-**140** was reacted according to the general Procedure B described above with (*S*)-VAPOL as ligand except before adding the aldehyde **(*R*)-140** to the reaction mixture 0.5 mL dry toluene was added (0.2 M concentration) to afford aziridines **141a** and **141b** with 86:14 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 2:1 hexanes/Et_2O as eluent, flash column) afforded inseparable mixture of aziridines **141b** and **141a** as a viscous liquid in 80 % isolated yield (80 mg, 0.16 mmol).

The diastereomeric ratio of **141a** and **141b** was determined to be 86:14 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 98:2 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 16.64 min (major diastereomer, **141a**) and R_t = 30.26 min (minor diastereomer, **141b**).

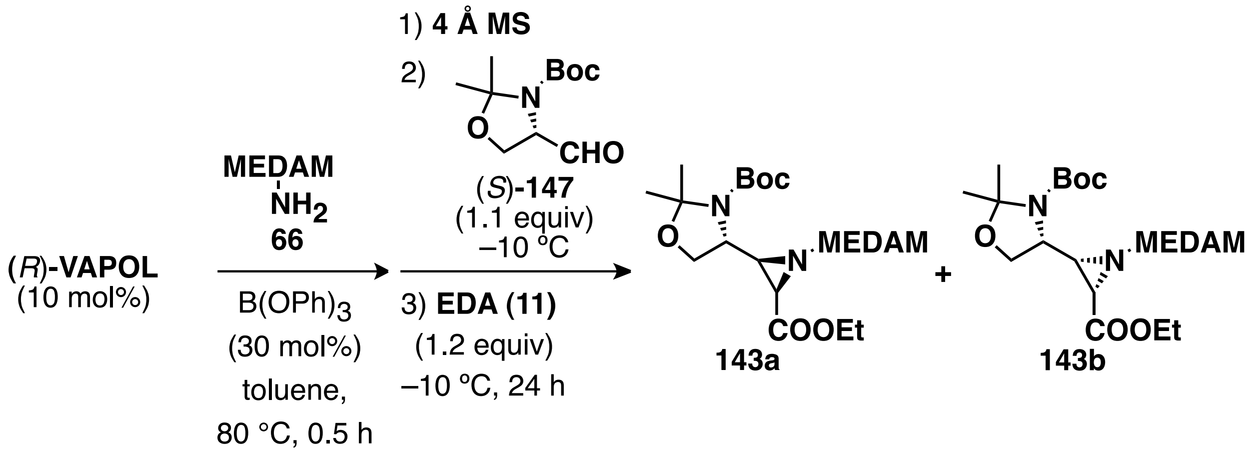
Aldehyde (*R*)-**140** was reacted according to the general Procedure B described above with (*S*)-VAPOL at different concentration in toluene at –10 ºC. The results are represented in Table 4.5 (Chapter 4).

Spectral data for **141a**: R_f = 0.25 (2:1 hexanes/Et_2O); ^{1}**H-NMR** (300 MHz, $CDCl_3$): δ 1.24-1.29 (m, 6H), 1.34 (s, 3H), 2.05-2.10 (m, 1H), 2.23-2.24 (m, 12H), 2.38 (d, *J* = 6.5 Hz, 1H), 3.05 (dd, *J* = 8.5, 6.1 Hz, 1H), 3.48 (s, 1H), 3.67 (s, 3H), 3.68 (s, 3H), 3.80 (dd, *J* = 8.4, 6.3 Hz, 1H), 4.13-4.06 (m, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 6.97 (s, 2H), 7.06 (s, 2H); ^{13}**C-NMR** (151 MHz, $CDCl_3$): δ 14.20, 16.11, 16.18, 25.20, 26.68, 42.71, 47.60, 59.58, 59.68, 61.01, 68.09, 73.28, 76.70, 109.30, 127.08, 127.93, 130.65, 130.78, 137.23, 137.74, 155.93, 156.47, 168.89; IR (thin film) 2988vs, 2938vs, 1746s, 1485s, 1220s, 1194vs, 1149s cm^{-1}; HRMS (ESI-TOF) *m/z* 498.2856

[(M+H+); calcd. for $C_{29}H_{40}NO_6$: 498.2858]; $[\alpha]_D^{20}$ +62.3 (c 1.0, CH_2Cl_2) on >99:1 dr material (^{1}H NMR).

4.13.9 Asymmetric catalytic multi-component aziridination reaction of aldehyde (*S*)-147 in presence of chiral catalyst (Procedure B)

4.13.9.1 Multi-component aziridination reaction of aldehyde (*S*)-147 and MEDAM amine 66 in presence of (*R*)-VAPOL



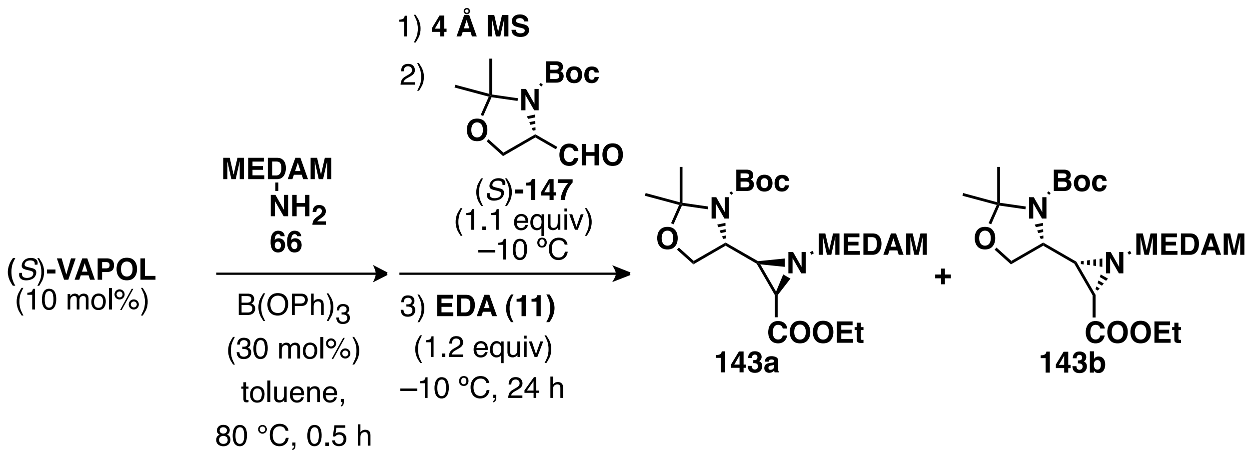
(*R*)-*tert*-Butyl 4-((2*S*, 3*S*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(ethoxycarbonyl) aziridin-2-yl)-2,2-dimethyloxazolidine-3-carboxylate 143b:

Aldehyde (*S*)-**147** was reacted according to the general Procedure B described above with (*R*)-VAPOL as ligand to afford aziridines **143b** and **143a** with >99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 2:1 hexanes/Et_2O as eluent, flash column) afforded inseparable mixture of aziridines **143b** and **143a** as a viscous liquid in 60 % isolated yield (72 mg, 0.12 mmol).

Spectral data for **143b**: R_f = 0.29 (2:1 hexane/Et_2O); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.24-1.27 (m, 5H), 1.35-1.34 (m, 4H), 1.41 (s, 9H), 2.14 (t, *J* = 6.9 Hz, 1H), 2.21 (s, 13H), 3.45 (s, 1H), 3.65-3.68 (s, 8H), 3.88 (td, *J* = 6.6, 2.2 Hz, 1H), 4.26-4.16 (m, 2H), 6.93 (s, 2H), 7.02 (s, 2H);

^{13}C-NMR (126 MHz, $CDCl_3$): δ 14.17, 16.08, 16.18, 28.41, 43.91, 48.59, 54.65, 59.60, 59.65, 60.72, 66.66, 79.81, 93.45, 102.86, 127.27, 128.49, 130.53, 130.70, 137.25, 137.73, 151.96, 155.81, 156.52, 169.18(one *Sp3* carbon not located); IR (thin film) 2979s, 2932s, 1742s, 1699vs, 1484s, 1387vs, 1223vs, 1190s cm^{-1}; HRMS (ESI-TOF) *m/z* 597.4229 [$(M+H^+)$; calcd. for $C_{34}H_{49}N_2O_7$: 597.4230]; $[\alpha]_D^{20}$ –90.5 (c 1.0, CH_2Cl_2) on >99:1 dr material

4.13.9.2 Multi-component aziridination reaction of aldehyde (*R*)-147 and MEDAM amine 66 in presence of (*S*)-VAPOL



(*R*)-*tert*-Butyl 4-((2*R*, 3*R*)-1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-(ethoxycarbonyl) aziridin-2-yl)-2,2-dimethyloxazolidine-3-carboxylate 143a:

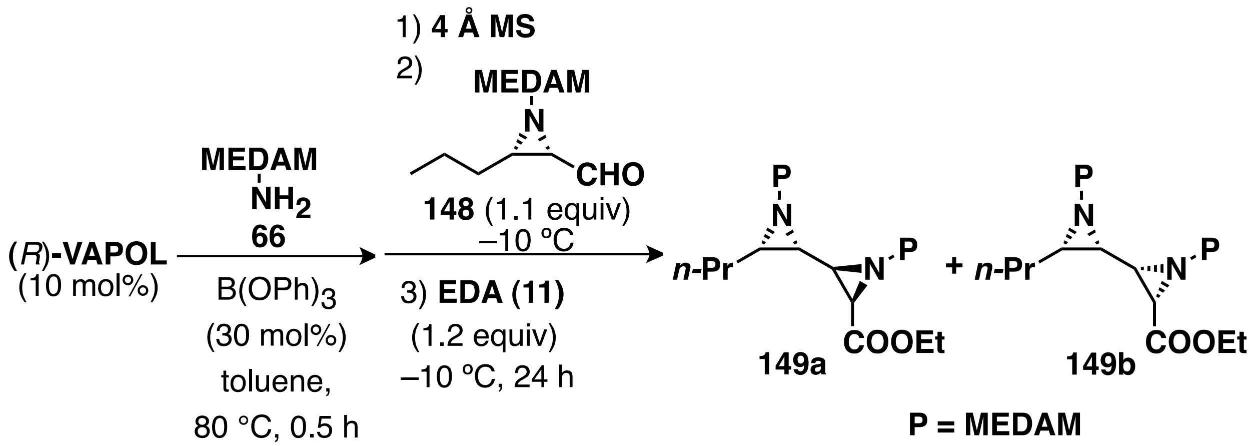
Aldehyde (*S*)-**147** was reacted according to the general Procedure B described above with (*S*)-VAPOL as ligand to afford aziridines **143a** and **143b** with >99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 2:1 hexanes/Et_2O as eluent, flash column) afforded inseparable mixture of aziridines **143a** and **143b** as a sticky solid in 70 % isolated yield (83 mg, 0.14 mmol).

The diastereomeric ratio of **143a** and **143b** was determined to be 99.4:0.6 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 98:2 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 16.26 min (major diastereomer, **143a**) and R_t = 18.98 min (minor diastereomer, **143b**).

Spectral data for **143a**: R_f = 0.29 (2:1 hexanes / Et_2O); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.26-1.23 (m, 4H), 1.30 (s, 2H), 1.41 (brs, 12H), 2.16-2.15 (m, 1H), 2.20 (s, 7H), 2.23 (s, 6H), 3.63 (s, 3H), 3.67 (s, 4H), 3.70 (dd, *J* = 9.2, 5.8 Hz, 1H), 4.08-4.03 (m, 1H), 4.15 (qd, *J* = 7.1, 1.5 Hz, 2H), 6.90 (s, 2H), 7.12 (s, 2H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.16, 16.07, 16.18, 28.35, 28.47, 43.52, 47.00, 56.38, 59.46, 59.55, 60.77, 64.85, 79.61, 93.89, 127.65, 128.15, 130.40, 130.62, 137.12, 137.85, 155.82, 168.75. (two *Sp2* and one *Sp3* carbon not located); IR (thin film) 2980s, 2936s, 1748s, 1698vs, 1484s, 1383vs, 1221vs, 1184vs cm^{-1}; HRMS (ESI-TOF) *m/z* 597.4225 [(M+H^+); calcd. for $C_{34}H_{49}N_2O_7$: 597.4230]; $[\alpha]_D^{20}$ +70.3 (c 1.0, CH_2Cl_2) on >99:1 dr material.

4.13.10 Asymmetric catalytic multi-component aziridination reaction of aldehyde 148 in presence of chiral catalyst (Procedure B)

4.13.10.1 Multi-component aziridination reaction of aldehyde 148 and MEDAM amine 66 in presence of (*R*)-VAPOL



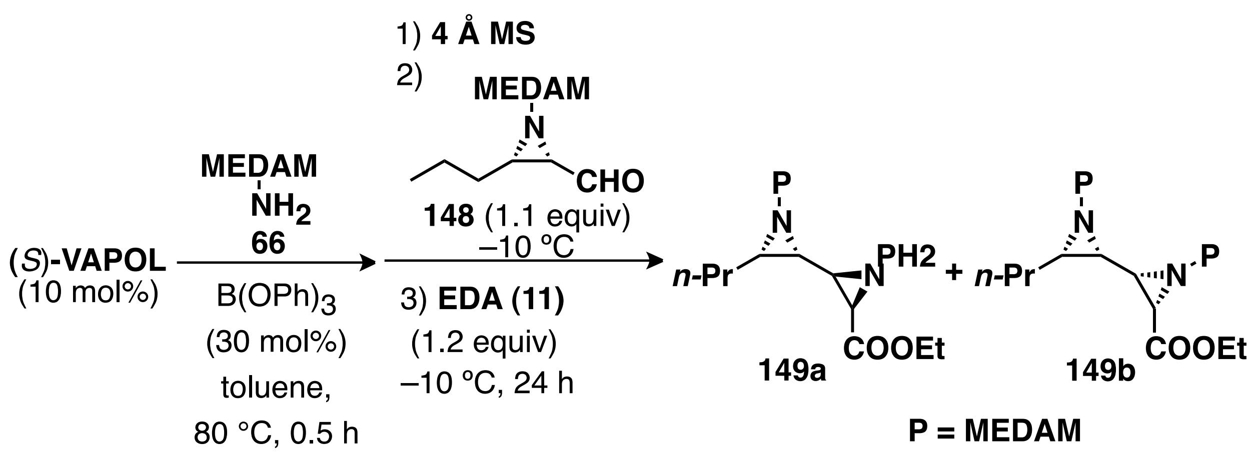
(2*S*, 2'*S*, 3*S*, 3'*S*)-Ethyl 1,1'-bis(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3'-propyl-[2,2'-biaziridine]-3-carboxylate 149b:

Aldehyde **148** was reacted according to the general Procedure B described above with (*R*)-VAPOL as ligand to afford aziridines **149b** and **149a** with >99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **149b** and **149a** as a white solid (mp 79-82 ºC on > 99:1 dr material) in 80 % isolated yield (122 mg, 0.16 mmol).

The diastereomeric ratio of **149b** and **149a** was determined to be 99.5:0.5 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.7:0.3 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 16.30 min (minor diastereomer, **149a**) and R_t = 19.75 min (major diastereomer, **149b**).

Spectral data for **149b**: R_f = 0.29 (2:1 hexanes/Et_2O); ^{1}**H-NMR** (300 MHz, $CDCl_3$): δ 0.49 (t, J = 6.5 Hz, 2H), 0.55-0.64 (m, 2H), 0.68-0.77 (m, 2H), 1.00 (t, J = 7.1 Hz, 3H), 1.50-1.56 (m, 1H), 1.80 (dd, J = 8.7, 6.7 Hz, 1H), 2.01-2.06 (m, 1H), 2.20-2.28 (m, 26H), 3.28 (s, 1H), 3.45 (s, 1H), 3.64 (brs, 6H), 3.66-3.67 (m, 6H), 3.69-3.84 (m, 2H), 6.87 (s, 2H), 6.97 (s, 4H), 7.04 (s, 2H); ^{13}**C-NMR** (75 MHz, $CDCl_3$): δ 13.69, 13.87, 15.99, 16.04, 16.05, 16.10, 20.39, 29.84, 41.35, 42.78, 43.31, 45.42, 59.43, 59.46, 59.50, 59.52, 60.47, 77.21, 77.36, 127.09, 127.11, 128.12, 128.38, 130.04, 130.20, 130.45, 137.52, 137.58, 138.04, 138.97, 155.37, 155.72, 155.88, 156.29, 168.92 (one *sp2* carbon not located); IR (thin film) 2955vs, 1736s, 1483s, 1221s, 1190vs, 1138s cm^{-1}; HRMS (ESI-TOF) *m/z* 763.4703 [$(M+H^{+})$; calcd. for $C_{48}H_{63}N_2O_6$: 763.4686]; $[\alpha]_D^{20}$ –62.8 (c 1.0, CH_2Cl_2) on >99:1 dr material (HPLC).

4.13.10.2 Multi-component aziridination reaction of aldehyde 148 and MEDAM amine 66 in presence of (*S*)-VAPOL



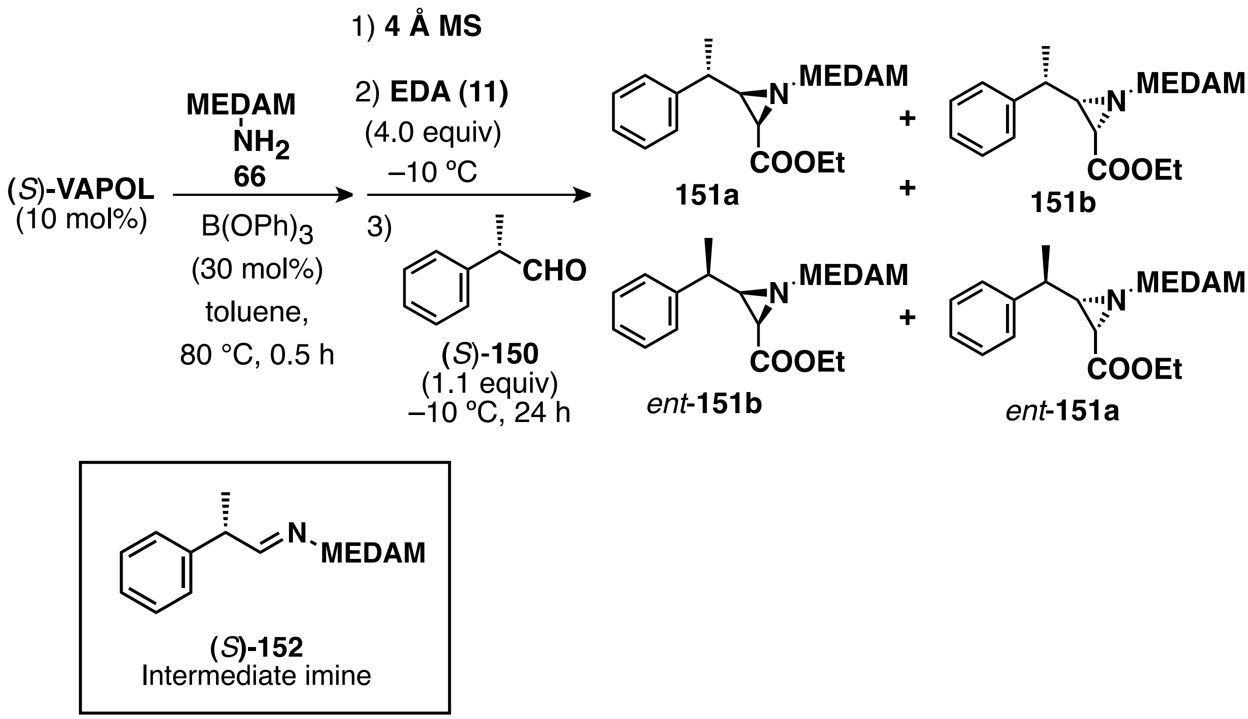
(2*R*, 2'*S*, 3*R*, 3'*S*)-ethyl 1,1'-bis(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3'-propyl-[2,2'-biaziridine]-3-carboxylate 149a:

Aldehyde **148** was reacted according to the general Procedure B described above with (*S*)-VAPOL as ligand to afford aziridines **149a** and **149b** with >99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **149a** and **149b** as a white solid (mp 67-70 ºC on >99:1 dr material) in 84 % isolated yield (129 mg, 0.164 mmol).

Spectral data for **149a**: R_f = 0.29 (2:1 hexanes/Et_2O); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.61 (t, *J* = 7.2 Hz, 3H), 0.75-1.02 (m, 2H), 1.07-1.28 (m, 5H), 1.50-1.57 (m, 1H), 2.01 (dd, *J* = 6.5, 5.3 Hz, 1H), 2.05 (s, 12H), 2.11-2.15 (m, 1H), 2.21-2.26 (m, 13H), 3.45 (s, 1H), 3.63 (s, 3H), 3.64 (s, 3H), 3.65 (s, 3H), 3.67 (s, 3H), 3.82 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 6.85 (s, 2H), 6.91 (s, 2H), 6.95 (s, 4H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 13.67, 14.22, 15.92, 16.03, 16.13, 20.36, 31.22, 40.43, 41.67, 43.75, 45.57, 59.44, 59.46, 59.50, 59.56, 60.62, 75.06, 77.17, (one *Sp2* carbon not located), 127.10, 127.12, 128.19, 128.48, 129.92, 130.17, 130.19, 130.42, 137.17, 137.20, 137.87, 139.12, 155.34, 155.63, 155.89, 155.91, 169.78; IR (thin film) 2955vs, 1743s, 1483s, 1221s, 1186vs, 1140s cm^{-1}; HRMS (ESI-TOF) *m/z* 763.4706 [(M+H^+); calcd. for $C_{48}H_{63}N_2O_6$: 763.4686]; $[\alpha]_D^{20}$ –97.6 (c 1.0, CH_2Cl_2) on >99:1 dr material (NMR).

4.13.11 Asymmetric catalytic multi-component aziridination reaction of aldehyde (*S*)-150 in presence of chiral catalyst (Procedure C)

4.13.11.1 Multi-component aziridination reaction of aldehyde (*S*)-150 and MEDAM amine 66 in presence of (*S*)-VAPOL



To a 25 mL flame-dried home-made Schlenk flask, equipped with a stir bar and filled with argon was added (*S)*-VAPOL (11 mg, 0.02 mmol), $B(OPh)_3$ (17 mg, 0.06 mmol) and amine **66** (60 mg, 0.2 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (0.5 mL) was added. The flask was sealed by closing the Teflon valve, and then placed in an oil bath (80 ºC) for 0.5 h. The flask was then allowed to cool to room temperature and open to argon through side arm of the Schlenk flask. To the flask containing the catalyst was added the 4Å Molecular Sieves (50 mg, freshly flame-dried). The flask was then allowed to cool to –10 ºC and 4.5 mL dry toluene was added to the flask. To the resulting reaction mixture was added ethyl diazoacetate (EDA) **11** (83 µL, 0.80 mmoL, 4.0 equiv). To this solution was rapidly added aldehyde (*S*)-**150** (29.5 mg, 0.22 mmoL, 1.1 equiv). The resulting mixture was stirred for 24 h at –10 ºC. The reaction was dilluted by addition of hexane (3 mL). The reaction mixture was then filtered through a silica gel plug to a 100 mL round bottom flask. The reaction flask was rinsed with EtOAc (10 mL × 3) and the rinse was filtered through the same silica gel plug. The resulting solution was then concentrated *in vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as yellow colored viscous oil. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 6:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **151b**, **151a**, *ent*-**151b** and *ent*-**151a** as a white solid (mp 46-51 ºC on 23:1 dr material) in 92% isolated yield (92 mg, 0.184 mmol).

The ratio of **151b**, **151a**, *ent*-**151b** and *ent*-**151a** was determined to be 0.37: 95.40: 3.49 :0.74 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 14.90 min (*ent*-**151b**), R_t = 15.79 min (**151a**), R_t = 21.82 min (**151b**), R_t = 26.25 min (*ent*-**151a**). Comparing the HPLC data following results were determined: dr = 24:1 [(**151a** + *ent*-**151a)** : **(151b** + *ent*-**151b**)]; % ee **151a** = 99% ee; % ee *ent*-**151b =** 80% ee ; %ee imine (*S*)-**152** = 91.4%ee Although, there was no imine **152** left unreacted in the reaction mixture the % ee of (*S*)-**152** was determined from the ratio [(**151a + 151b)** : **(***ent*-**151b** + *ent*-**151b**)].

Aldehyde (*S*)-**150** was reacted according to the general Procedure C described above with (*S*)-VAPOL at different concentration in toluene at –10 ºC. The results are represented in Table 4.8 (Chapter 4).

Aldehyde (*R*)-**150** was reacted according to the general Procedure C described above with (*S*)-

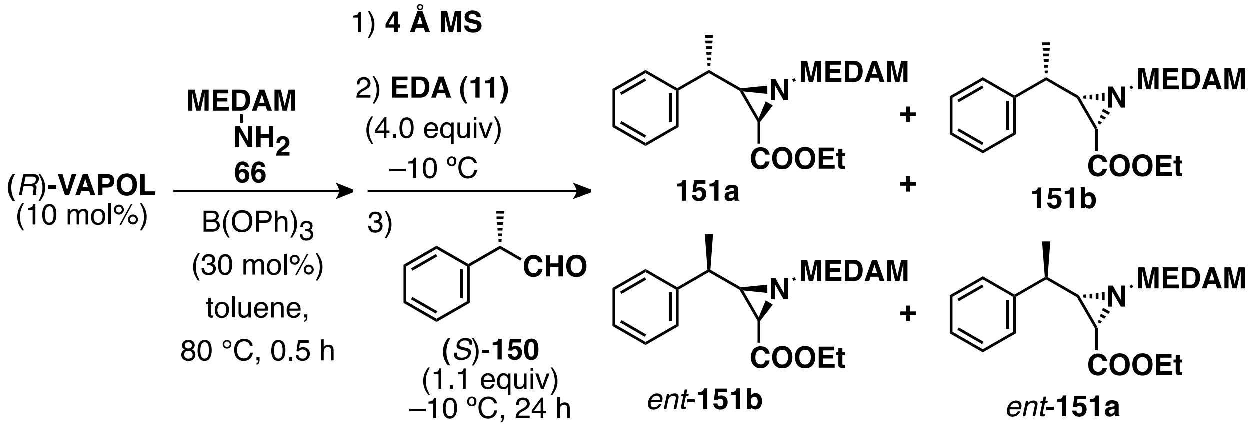
VAPOL except the concentration of the reaction was 0.4 M in amine **66** at –10 ºC. The results are represented in Table 4.8, entry 8 (Chapter 4). Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 6:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **151b**, **151a**, *ent*-**151b** and *ent*-**151a** as a sticky solid in 92% isolated yield (92 mg, 0.184 mmol).

The ratio of **151b**, **151a**, *ent*-**151b** and *ent*-**151a** was determined to be 7.88: 2.02: 0.71: 89.38 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 15.52 min (*ent*-**151b**), R_t = 16.90 min (**151a**), R_t = 22.56 min (**151b**), R_t = 26.65 min (*ent*-**151a**). Comparing the HPLC data following results were determined: dr = 11:1 [(**151a** + *ent*-**151a)** : **(151b** + *ent*-**151b**)]; % ee **151b =** 83% ee ; % ee of *ent*-**151a** = 95.6% ee; % ee imine (*S*)-**152** = 80% ee. Although, there was no imine **152** left unreacted in the reaction mixture the % ee of (*S*)-**152** was determined from the ratio [(**151a** + **151b)** : (*ent*-**151b** + *ent*-**151b**)].

Spectral data for **151a**: R_f = 0.11 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.90 (d, *J* = 7.0 Hz, 3H), 1.10 (t, *J* = 7.1 Hz, 3H), 2.14 (dd, *J* = 9.4, 6.8 Hz, 1H), 2.20 (d, *J* = 6.8 Hz, 1H), 2.26 (s, 6H), 2.28 (s, 6H), 2.81-2.87 (m, 1H), 3.47 (s, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 4.07 (q, *J* = 7.1 Hz, 2H), 7.07 (s, 2H), 7.10 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.14 (s, 2H), 7.16-7.19 (m, 1H), 7.23-7.27 (m, 2H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.06, 16.10, 16.17, 19.96, 38.14, 44.02, 52.85, 59.56, 59.65, 60.60, 77.44, 126.29, 127.00, 127.23, 128.29, 128.53, 130.49, 130.53, 137.51, 138.10, 144.11, 155.78, 156.37, 169.47; IR (thin film) 2932vs, 1742s, 1485s, 1221s, 1188vs, 1148s cm^{-1}; HRMS (ESI-TOF) *m/z* 502.2978 [(M+H$^+$); calcd. for $C_{32}H_{40}NO_4$:

502.2957]; $[\alpha]_D^{20}$ +108.9 (c 0.6, CH_2Cl_2) on 23:1 dr material (NMR, entry 5, Table 4.8, Chapter 4).

4.13.11.2 Multi-component aziridination reaction of aldehyde (*S*)-150 and MEDAM amine 66 in presence of (*R*)-VAPOL



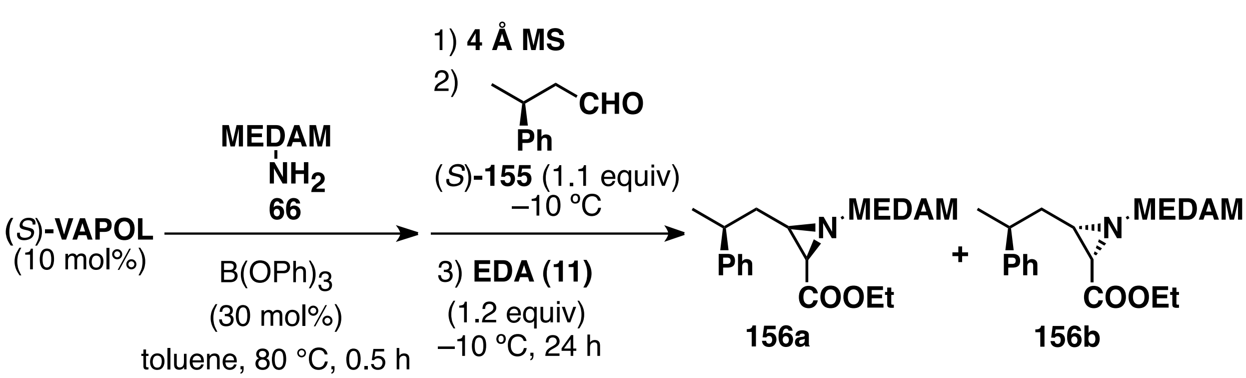
Aldehyde (*S*)-**150** was reacted according to the general Procedure C described above with (*R*)-VAPOL at –10 ºC. The results are represented in Table 4.8, entry7 (Chapter 4). Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 6:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **151b**, **151a**, *ent*-**151b** and *ent*-**151a** as a sticky solid in 90% isolated yield (90 mg, 0.18 mmol).

The ratio of **151b**, **151a**, *ent*-**151b** and *ent*-**151a** was determined to be 83.16: 10.71: 0.05: 6.07 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min). Comparing the HPLC data following results were determined: dr = 1:5 [(**151a** + *ent*-**151a)** : **(151b** + *ent*-**151b**)]; % ee *ent*-**151b =** 99.9% ee ; % ee of **151a** = 43% ee; % ee imine (*S*)-**152** = 93% ee. Although, there was no imine **152** left unreacted in the reaction mixture the % ee of (*S*)-**152** was determined from the ratio [(**151a + 151b)** : **(***ent*-**151b** + *ent*-**151b**)].

Spectral data for **151b**: R_f = 0.11 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 1.15 (d, J = 7.2 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.02 (s, 6H), 2.19 (dd, J = 6.4, 3.1 Hz, 1H), 2.22 (s, 6H), 2.26 (d, J = 6.8 Hz, 1H), 2.80-2.86 (m, 1H), 3.33 (s, 1H), 3.61 (s, 3H), 3.67 (s, 3H), 4.23-4.30 (m, 2H), 6.63 (s, 2H), 6.96-7.00 (m, 5H), 7.04 (s, 2H).; **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.37, 16.02, 16.15, 19.21, 38.37, 42.99, 53.46, 59.32, 59.55, 60.77, 77.52, 125.78, 126.93, 127.22, 127.60, 127.99, 129.84, 130.40, 137.46, 137.78, 143.95, 155.70, 169.70 (one *sp2* carbon not located); IR (thin film) 2932vs, 1741s, 1483s, 1221s, 1186vs, 1148s cm^{-1}; HRMS (ESI-TOF) *m/z* 502.2976 [(M+H$^+$); calcd. for $C_{32}H_{40}NO_4$: 502.2957]; $[\alpha]_D^{20}$ –73.9 (c 0.6, CH_2Cl_2) on 4:1 dr material (NMR, entry 6, Table 4.8, Chapter 4).

4.13.12 Asymmetric catalytic multi-component aziridination reaction of aldehyde (*S*)-155 in presence of chiral catalyst (Procedure B)

4.13.12.1 Multi-component aziridination reaction of aldehyde (*S*)-155 and MEDAM amine 66 in presence of (*S*)-VAPOL



156a

156b

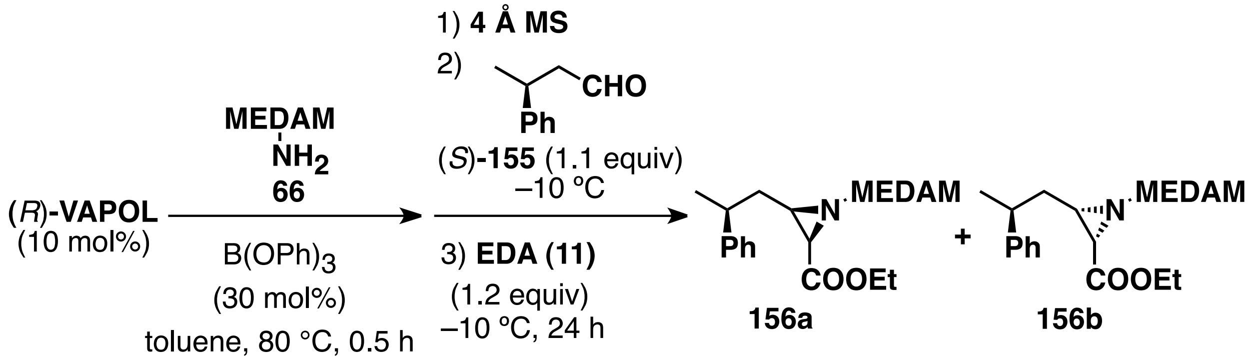
(2*R*, 3*R*)-Ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*S*)-2-phenylpropyl) aziridine-2-carboxylate 156a:

Aldehyde (*S*)-**155** was reacted according to the general Procedure B described above with (*S*)-VAPOL as ligand to afford aziridines **156a** and **156b** with 94:6 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **156a** and **156b** as a sticky solid in 80 % isolated yield (82 mg, 0.16 mmol).

The diastereomeric ratio of **156a** and **156b** was determined to be 94:6 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99:1 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 17.68 min (major diastereomer, **156a**) and R_t = 32.01 min (minor diastereomer, **156b**).

Spectral data for **156a**: R_f= 0.10 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.14 (d, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.73-1.83 (m, 2H), 2.07 (d, *J* = 6.3 Hz, 1H), 2.22-2.25 (m, 7H), 2.31 (s, 6H), 2.43-2.53 (m, 1H), 3.30 (s, 1H), 3.67 (s, 3H), 3.73 (s, 3H), 4.13-4.20 (m, 2H), 6.68 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.06 (s, 2H), 7.07 (s, 2H), 7.12-7.20 (m, 3H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 14.28, 16.15, 23.17, 36.39, 38.40, 43.13, 45.44, 59.54, 59.65, 60.72, 77.25, (one *sp3* carbon not located) 125.83, 127.08, 128.06, 128.18, 130.48, 130.61, 137.91, 138.44, 146.09, 155.68, 156.24, 169.66 (one *sp2* carbon not located); IR (thin film) 2957vs, 2930vs, 1742s, 1483s, 1221s, 1186vs cm^{-1}; HRMS (ESI-TOF) *m/z* 516.3119 [($M+H^+$); calcd. for $C_{33}H_{42}NO_4$: 516.3114]; $[\alpha]_D^{20}$ +70.6 (c 1.0, CH_2Cl_2) on 94:6 dr material (HPLC).

4.13.12.2 Multi-component aziridination reaction of aldehyde (*S*)-155 and MEDAM amine 66 in presence of (*R*)-VAPOL



(2*S*, 3*S*)-Ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*S*)-2-phenylpropyl) aziridine-2-carboxylate 156b:

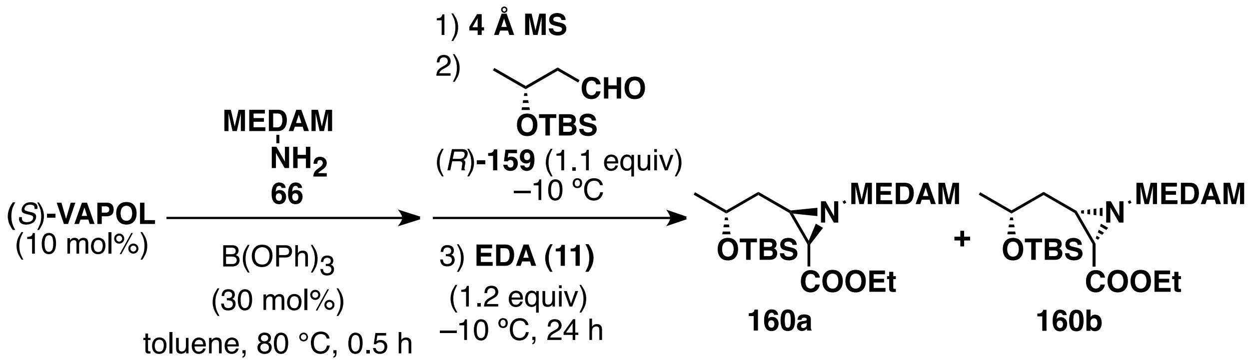
Aldehyde (*S*)-**155** was reacted according to the general Procedure B described above with (*R*)-VAPOL as ligand to afford aziridines **156b** and **156a** with >99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **156b** and **156a** as a white solid (mp 101-102 ºC on 99:1 dr material) in 85 % isolated yield (88 mg, 0.17 mmol).

The diastereomeric ratio of **156b** and **156a** was determined to be 99.4:0.6 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99:1 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 18.49 min (minor diastereomer, **156a**) and R_t = 31.04 min (major diastereomer, **156b**).

Spectral data for **156b**: R_f = 0.10 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 1.02 (d, *J* = 6.9 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.71-1.81 (m, 1H), 1.85-1.97 (m, 2H), 2.22-2.54 (m, 13H), 2.45-2.55 (m, 1H), 3.40 (s, 1H), 3.68 (s, 3H), 3.69 (s, 3H), 4.20 (qd, *J* = 7.1, 2.3 Hz, 2H), 7.02 (s, 2H), 7.08 (s, 2H), 7.10-7.28 (m, 5H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ 14.34, 16.13, 16.17, 21.29, 35.73, 37.96, 43.44, 45.49, 59.56, 59.60, 60.72, 77.07, 125.93, 126.78, 127.32, 127.95, 128.31, 130.49, 137.66, 138.17, 146.99, 155.76, 156.09, 169.65 (one *sp2* carbon not located); IR (thin film) 2959vs, 2930vs, 1744s, 1483s, 1221s, 1183vs cm^{-1}; HRMS (ESI-TOF) *m/z* 516.3120 [$(M+H^+)$; calcd. for $C_{33}H_{42}NO_4$: 516.3114]; $[\alpha]_D^{20}$ –20.0 (c 1.0, CH_2Cl_2) on 99:1 dr material (HPLC).

4.13.13 Asymmetric catalytic multi-component aziridination reaction of aldehyde (*R*)-159 in presence of chiral catalyst (Procedure B)

4.13.13.1 Multi-component aziridination reaction of aldehyde (*R*)-159 and MEDAM amine 66 in presence of (*S*)-VAPOL



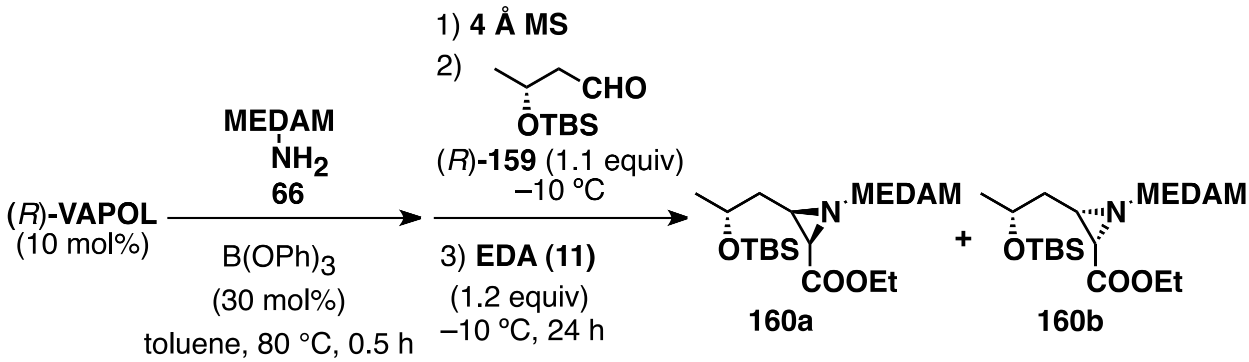
(2*R*, 3*R*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)propyl)aziridine-2-carboxylate 160a:

Aldehyde (*R*)-**159** was reacted according to the general Procedure B described above with (*S*)-VAPOL as ligand to afford aziridines **160a** and **160b** with 98:2 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **160a** and **160b** as a viscous liquid in 83 % isolated yield (94 mg, 0.16 mmol).

The diastereomeric ratio of **160a** and **160b** was determined to be 98:2 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 20.28 min (major diastereomer, **160a**) and R_t = 29.15 min (minor diastereomer, **160b**).

Spectral data for **160a**: R_f = 0.13 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); ^{1}**H-NMR** (300 MHz, $CDCl_3$): δ 0.00 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 0.88 (d, J = 6.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.56 (ddd, J = 13.6, 6.7, 6.7 Hz, 1H), 1.78 (ddd, J = 13.6, 6.7, 6.7 Hz, 1H), 2.07 (q, J = 6.5 Hz, 1H), 2.19 (d, J = 6.8 Hz, 1H), 2.24 (s, 12H), 3.42 (s, 1H), 3.56 (q, J = 6.3 Hz, 1H), 3.68 (s, 3H), 3.69 (s, 3H), 4.25-4.13 (m, 2H), 6.99 (s, 2H), 7.08 (s, 2H); ^{13}**C-NMR** (75 MHz, $CDCl_3$): δ –4.81, –4.55, 14.33, 16.16, 16.19, 18.05, 23.22, 25.84, 37.72, 43.12, 44.14, 59.57, 60.65, 67.15, 77.26, (one sp3 carbon not located), 127.36, 128.03, 130.47, 130.50, 137.72, 138.06, 155.77, 156.12, 169.62; IR (thin film) 2957vs, 2930vs, 1746s, 1483s, 1223s, 1184vs, 1145s cm^{-1}; HRMS (ESI-TOF) *m/z* 570.3634 [(M+H$^+$); calcd. for $C_{33}H_{52}NO_5Si$: 570.3615]; $[\alpha]_D^{20}$ +38.5 (c 1.0, CH_2Cl_2) on 97:3 dr material (HPLC).

4.13.13.2 Multi-component aziridination reaction of aldehyde (*R*)-159 and MEDAM amine 66 in presence of (*R*)-VAPOL



(2*S*, 3*S*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*R*)-2-((*tert*-butyldimethylsilyl)oxy)propyl)aziridine-2-carboxylate 160b:

Aldehyde (*R*)-**159** was reacted according to the general Procedure B described above with (*S*)-VAPOL as ligand to afford aziridines **160b** and **160a** with 99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **160b** and **160a** as a viscous liquid in 85 % isolated yield (97 mg, 0.17 mmol).

The diastereomeric ratio of **160b** and **160a** was determined to be 99:1 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99.5:0.5 hexane/2-propanol at 222nm, flow-rate: 0.7 mL/min): retention times; R_t = 20.83 min (minor diastereomer, **160a**) and R_t = 28.04 min (major diastereomer, **160b**).

Spectral data for **160b**: R_f= 0.13 (4:1:0.2 hexanes/CH_2Cl_2/Et_2O); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ –0.21 (s, 3H), –0.10 (s, 3H), 0.80 (s, 9H), 1.04 (d, *J* = 6.2 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.77-1.59 (m, 2H), 2.16-2.24 (m, 14H), 3.43 (s, 1H), 3.68 (s, 6H), 3.70-3.76 (m, 1H), 4.17 (q, *J* =

7.1 Hz, 2H), 7.07 (s, 2H), 7.08 (s, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$): δ –5.21, –4.64, 14.29, 16.11, 16.16, 17.92, 23.75, 25.78, 37.63, 43.10, 44.34, 59.51, 59.54, 60.66, 67.11, 77.34, 127.23, 127.72, 130.48, 130.50, 138.03, 138.23, 155.75, 155.99, 169.71; IR (thin film) 2955vs, 2930vs, 2856s, 1746s, 1483s, 1221s, 1183vs, 1140s cm^{-1}; HRMS (ESI-TOF) *m/z* 570.3632 [(M+H$^+$); calcd. for $C_{33}H_{52}NO_5Si$: 570.3615]; $[\alpha]_D^{20}$ –33.5 (c 1.0, CH_2Cl_2) on 99:1 dr material (HPLC).

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CHAPTER 5

STUDIES TOWARDS THE ASYMMETRIC SYNTHESIS OF PHYTOSPHINGOSINES

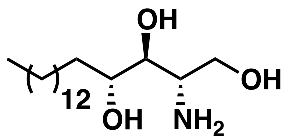
5.1 Introduction

Recent findings have shown that the Wulff's catalytic asymmetric aziridination reaction is primarily a catalyst-controlled process in the case of chiral aldehydes, leading to an easy access to complex organic molecules with multiple chiral centers (Chapter 4). These finding inspired us to plan a synthesis of all four diasereomers of phytosphingosine **75** starting from the *α*-oxygenated chiral aldehyde **192** (Scheme 5.6) using the Wulff catalytic asymmetric aziridination reaction as the key step.

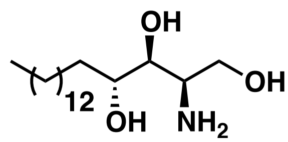
5.2 Biological activity and previous syntheses of phytosphingosines

The most abundant naturally occurring isomer of phytosphingosine is the D-*ribo* isomer **75a** (Figure 5.1). The phytosphingosines **75** are one of the major 'long-chain base' components of glycosphingolipids and were isolated from mushrooms in 1911.[1] It is widely distributed as one of the molecular species of sphingolipids in microorganisms, in plants, and in many mammalian tissues such as brain, hair, kidney,[2] skin,[3] liver,[4] uterus,[5] and intestine,[6] and in blood plasma.[7]

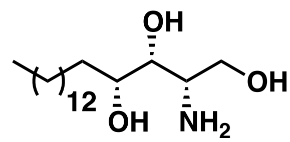
Figure 5.1 Family of phytosphingosines **75**



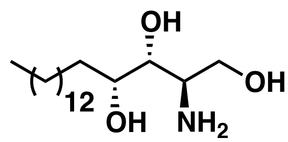
75a
D-*ribo*- phytosphingosine



75b
L-*arabino*- phytosphingosine



75c
D-*xylo*- phytosphingosine



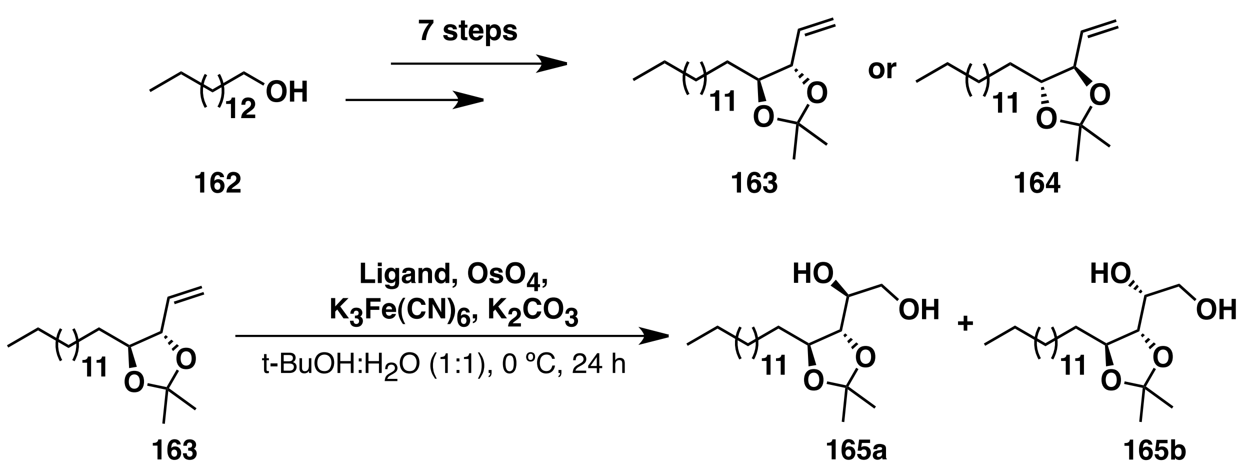
75d
L- *lyxo*-phytosphingosine

A great deal of effort has been made by the scientific community towards the synthesis of phytosphingosines for their use in biochemical, biophysical, and pharmacological studies.[8] Inspired by the fact that various unnatural isomers of sphinganines and sphingosines have different vital biological properties, scientists have been attracted towards the synthesis and biological testing of all eight isomers of phytosphingosines **75**. Recently, there are two reports describing the synthesis of ceramide library that includes the synthesis of all eight isomers of phytosphingosines.[9] Most common approaches towards the synthesis of phytosphingosines involve nature's chiral pool such as amino acids or carbohydrates as the source of chirality.[8,10]

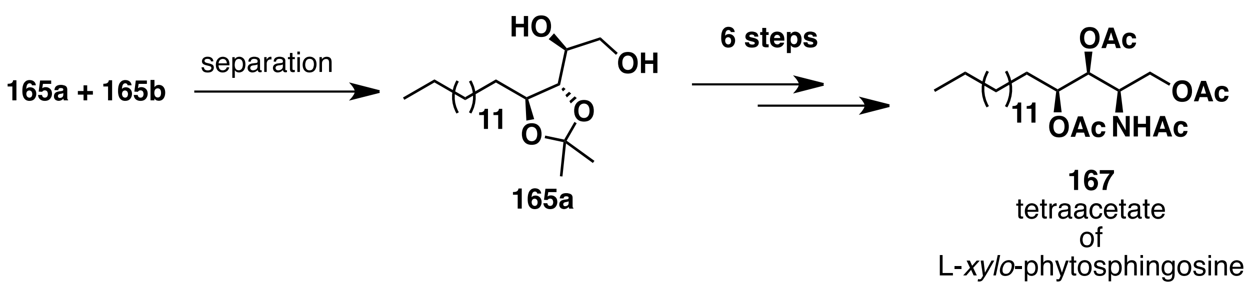
Until now, there are very few syntheses of phytosphingosine that involve asymmetric catalytic reactions as the key step. In 2003, the synthesis of isomers of *xylo*-phytosphingosine acetates was reported using double stereodifferentiation in Sharpless asymmetric dihydroxylation reaction (Scheme 5.1).[11] The key substrates **163** and **164** were each made in 99% ee *via* the

Sharpless asymmetric dihydroxylation of a trans-α,β- unsaturated ester. The enantiomers **163** and **164** were each subjected to Sharpless asymmetric dihydroxylation with both $(DHQD)_2$AQN and $(DHQ)_2$PHAL based catalyst but strong catalyst control was not observed preventing clean access to four of eight stereoisomers of phytosphingosines. The reaction of **163** with $(DHQD)_2$AQN catalyst provided **165a** with 6:1 selectivity, and after separation, a route to L-*xylo*-phytosphingosine. Similarly, the reaction of **164** provided **166a** as a 5.5:1 mixture of diastereomers, and after separation, a route to D-*xylo*-phytosphingosine.

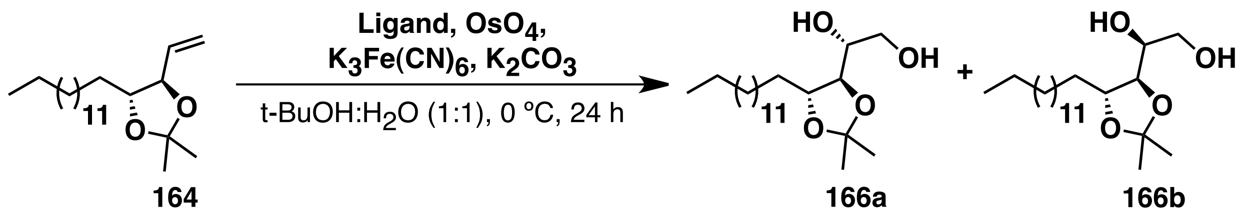
Scheme 5.1 Synthesis of *xylo*-phytosphingosine derivative *via* Sharpless asymmetric dihydroxylation



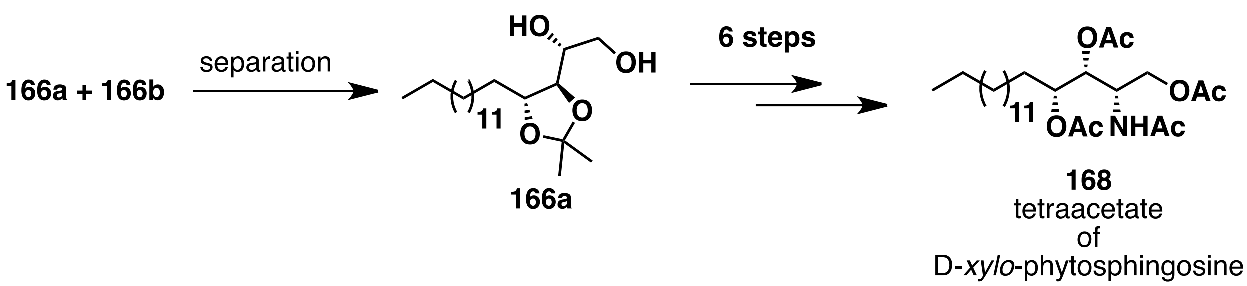
Ligand	165a:165b	% yield
$(DHQ)_2$PHAL	1:2	89
$(DHQD)_2$PHAL	5:1	92



Scheme 5.1 (cont'd)



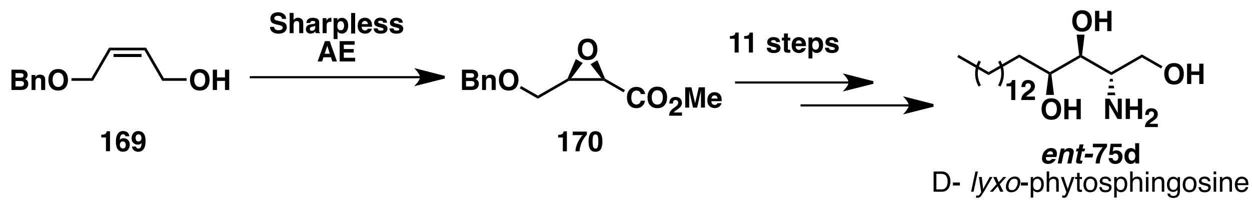
Ligand	166a:166b	% yield
$(DHQ)_2PHAL$	5.5:1	70
$(DHQD)_2PHAL$	1:2	92



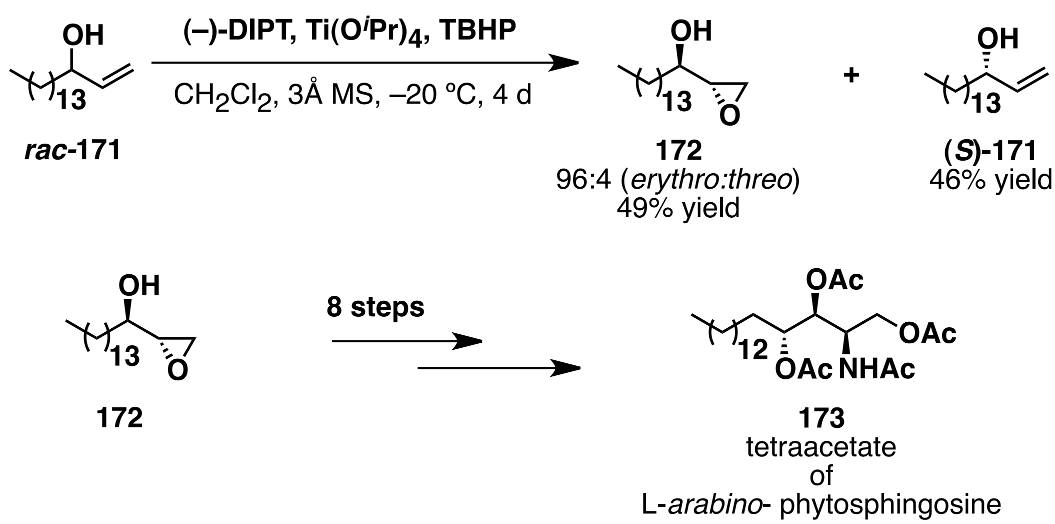
There is a separate report where Sharpless asymmetric epoxidation has been used as the key step for the synthesis of D-*lyxo*-phytosphingosine (Scheme 5.2A).[12] The synthesis of other isomers of phytosphingosine were not described in this report. Further, L-*arabino*-phytosphingosine has been prepared using Sharpless's kinetic resolution of allylic alcohols as the key step (Scheme 5.2B).[13] A synthesis of L-*xylo*-phytosphingosine was also achieved from the allylic alcohol (*S*)-**171**.

Scheme 5.2 Synthesis of phytosphingosines *ent*-**75d** and its derivative **173** *via* (A) Sharpless asymmetric epoxidation (B) Sharpless kinetic resolution

(A)



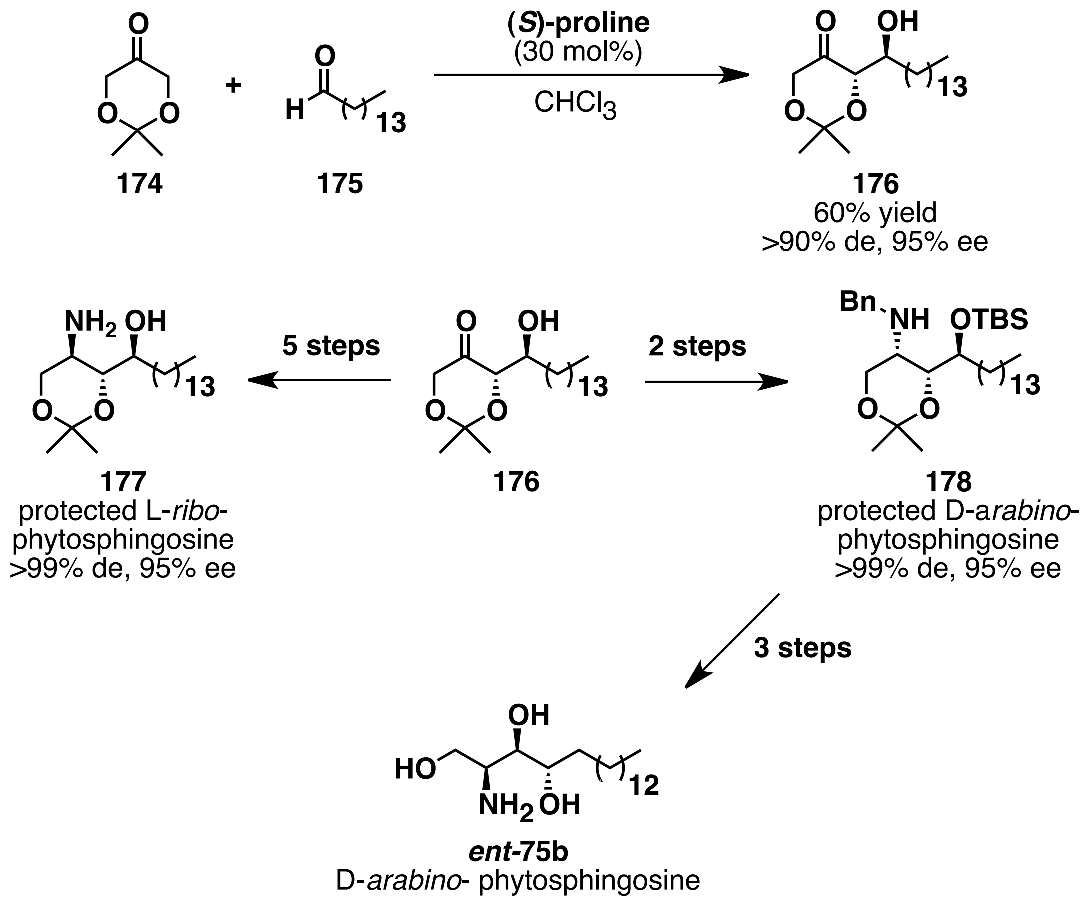
(B)



The organocatalytic asymmetric synthesis of D-*arabino*- and L-*ribo*-phytosphingosine was reported by Enders *et. al* employing (*S*)-proline-catalyzed diastereo and enantioselective aldol reaction of 2,2-dimethyl-1,3-dioxan-5-one **174** and pentadecanal **175** as the key step

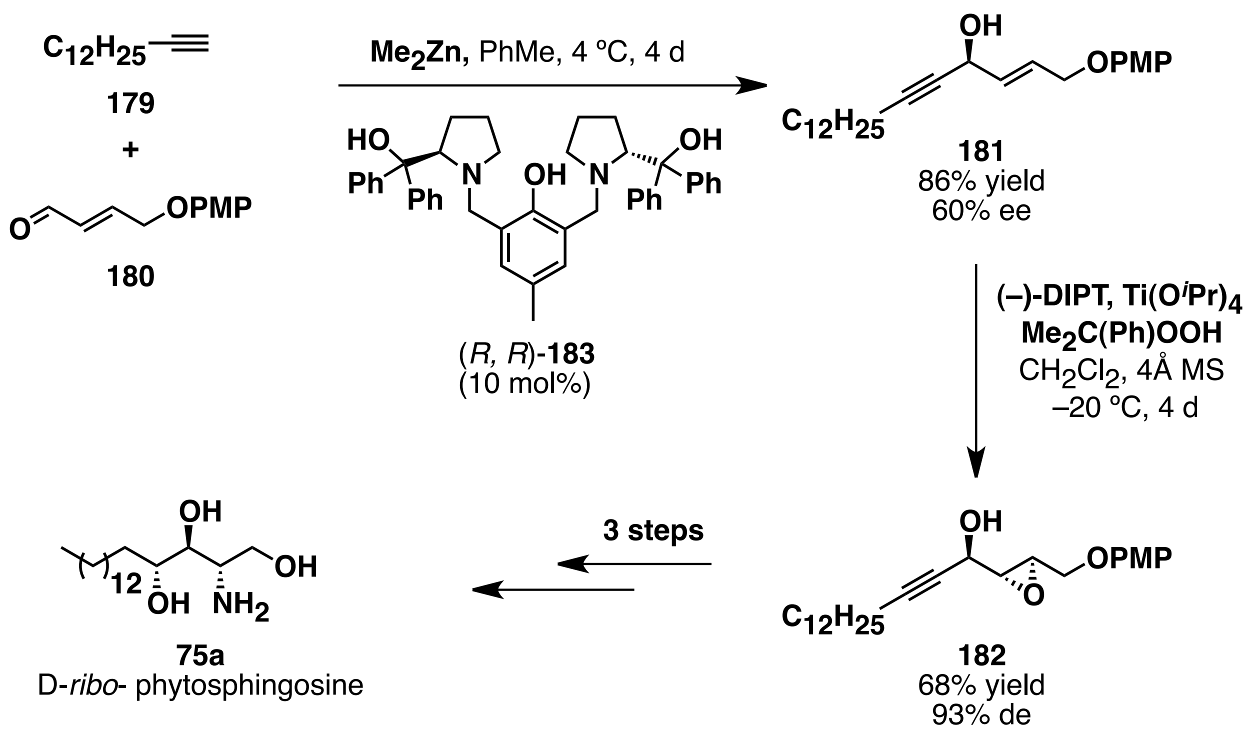
(Scheme 5.3).[14] This approach should allow access to only four of the eight stereoisomers of the phytosphingosines since the aldol reaction will give only the *anti* adduct.

Scheme 5.3 Synthesis of phytosphingosines *ent*-**75d** and its derivative **177** and **178** *via* organocatalytic aldol reaction



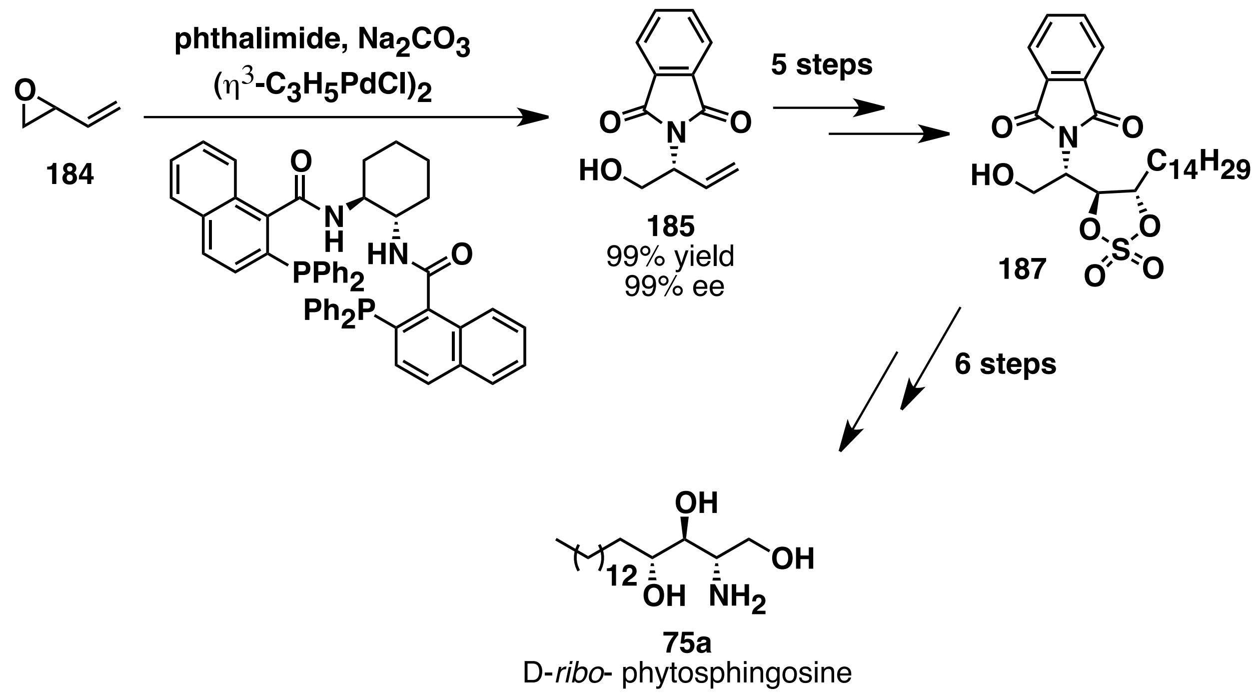
Bittman and coworkers employed a combination of Trost asymmetric alkynylation reaction and then optical purity enhancement by partial kinetic resolution *via* Sharpless asymmetric epoxidation for an asymmetric synthesis of D-*ribo*-phytosphingosine **75a**.[15] The stereochemistry determining steps involve the prophenol (*R,R*)-**183** catalyzed alkynylation of unsaturated aldehyde **180** resulting in the allylic propargylic alcohol (*S*)-**181** in 60% ee. This was followed by the Shapless asymmetric epoxidation to afford epoxy alcohol *anti*-**182** in 93% de. The synthesis of other isomers of phytosphingosine was not reported.

Scheme 5.4 Synthesis of D-*ribo*-phytosphingosine **75a** *via* Trost asymmetric alkynylation reaction and Sharpless asymmetric epoxidation



Llaveria *et. al* made the chiral synthon **185** for the synthesis of D-*ribo*-phytosphingosine **75a** by a palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) from the racemic butadiene monoepoxide **184** (Scheme 5.5).[16]

Scheme 5.5 Synthesis of D-*ribo*-phytosphingosine **75a** *via* palladium-catalyzed dynamic kinetic asymmetric transformation from the racemic epoxide **184**

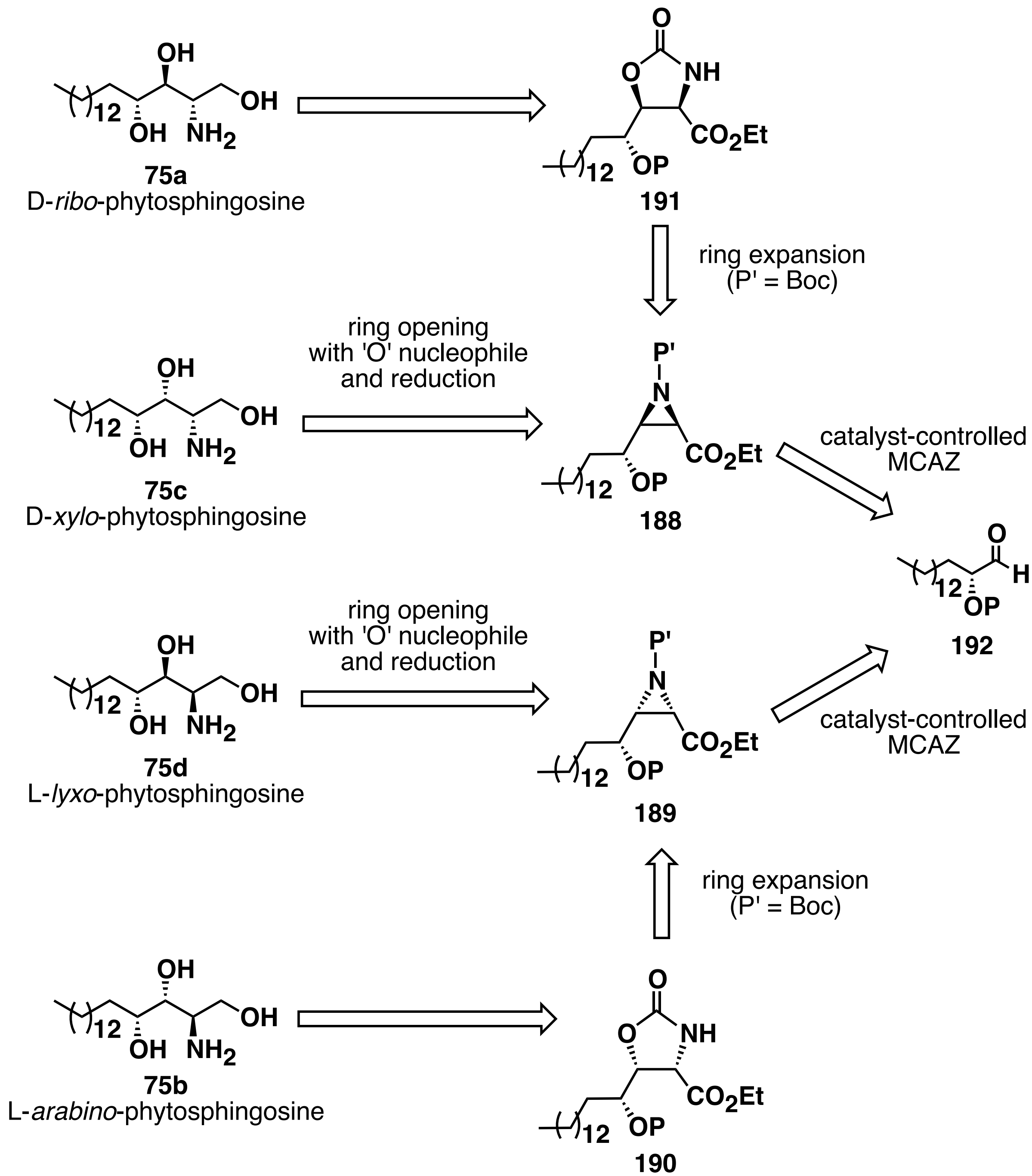


All of the previous approaches are limited to the synthesis of certain diastereomers only. In all cases, the previous methods were unable to cleanly provide all diastereomers of the phytosphingosines with high selectivity. The aim of the present work is to devise a common protocol for the synthesis of four diastereomers of the phytosphingosines. To attain the objective, we envisioned to utilize the catalyst controlled aziridination reaction starting from aldehyde **192** (Scheme 5.6).

5.3 Retro-synthetic analysis of phytosphingosines

A retro-synthetic analysis of the phytosphingosines is presented in Scheme 5.6. The synthesis of D-*xylo*-phytosphingosine **75c** and L-*lyxo*-phytosphingosine **75d** is projected *via* ring opening of the corresponding diastereomers of the *cis*-aziridines **188** and **189**, respectively, with an oxygen nucleophile.

Scheme 5.6 Retro-synthetic analysis: D-*ribo*-phytosphingosine **75a**, D-*xylo*-phytosphingosine **75b**, L-*arabino*-phytosphingosine **75c** and L-*lyxo*-phytosphingosine**75d**

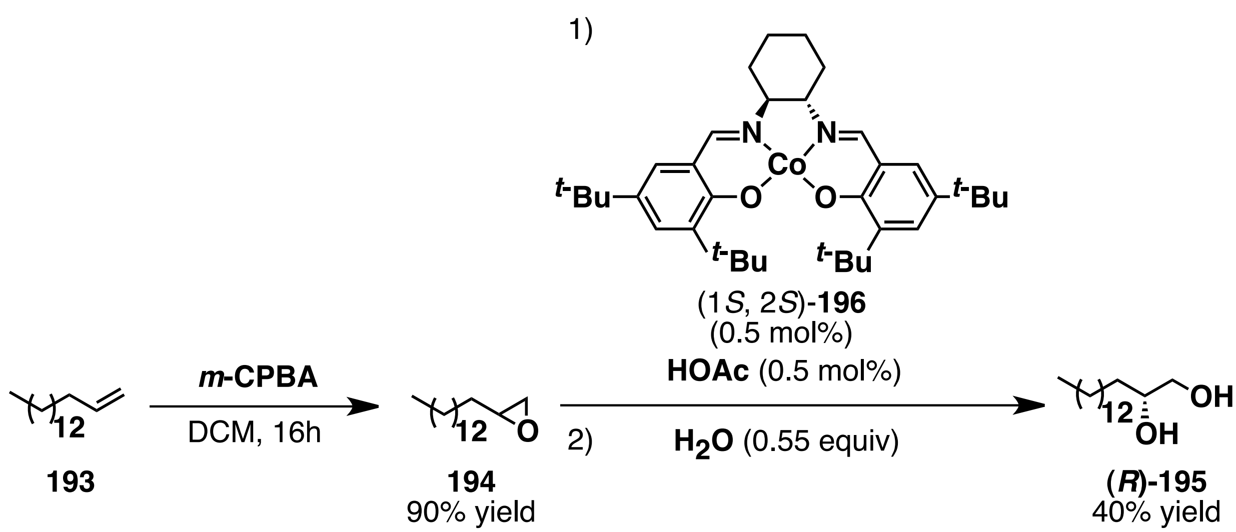


The synthesis of D-*ribo*-phytosphingosine **75a** could be achieved *via* the ring expansion of *N*-Boc (P' = Boc) protected aziridine **188** with retention of configuration to the oxazolidinone **191**. A similar approach was demonstrated for the synthesis of *erythro*-sphinganines **74a** and **74d** in the Chapter 3. Subsequent hydrolysis of the oxazolidinone **191** and the reduction of the corresponding ester would give the D-*ribo*-phytosphingosine **75a**. In a similar fashion, the L-*arabino*- phytosphingosine **75b** could be possible *via* the ring expansion of *N*-Boc (P' = Boc) protected aziridine **189** to oxazolidinone **190**. A multi-component aziridination reaction (MCAZ) of chiral aldehyde **192** would yield aziridines **188** and **189** in the presence of the (*S*)-VAPOL catalyst and the (*R*)-VAPOL catalyst respectively, assuming the reaction would behave in a catalyst-controlled manner as was demonstrated for related chiral aldehydes (see Chapter 4).

5.4 Synthesis of chiral aldehyde (*R*)-192 *via* hydrolytic kinetic resolution of *rac*-epoxide

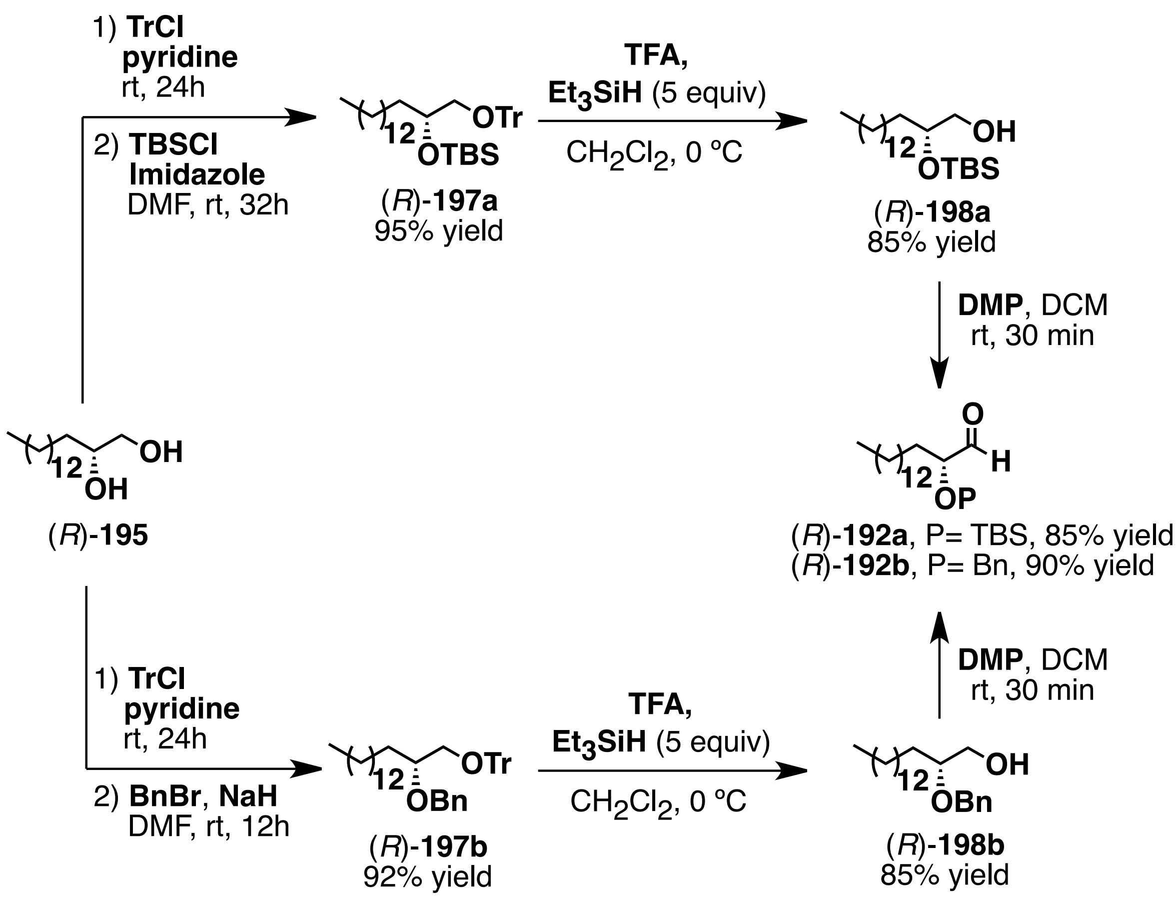
The chiral aldehyde (*R*)-**192a** and (*R*)-**192b** were synthesized starting from 1-hexadecene following the synthetic route shown in Schemes 5.7 and 5.8.

Scheme 5.7 Synthesis of optically pure 1,2- diol (*R*)-**195** by hydrolytic kinetic resolution



The reaction of 1-hexadecene **193** with *m*CPBA afforded the corresponding epoxide **194** in 90% yield. The hydrolytic kinetic resolution of the racemic epoxide **194** resulted in optically pure (> 99% ee) (*R*)-hexadecane-1,2-diol (*R*)-**195** in 40% yield (Scheme 5.7). Stepwise protection of the terminal hydroxyl group as trityl and the internal hydroxyl group as *tert*-butyldimethylsilyl afforded the bis-protected alcohol (*R*)-**197a** in 90% yield over two steps. Similarly, the stepwise protection of the terminal hydroxyl group as trityl and internal hydroxyl group as benzyl afforded the bis-protected alcohol (*R*)-**197b** that was used for the next step without further purification (Scheme 5.8).

Scheme 5.8 Synthesis of optically pure aldehydes (*R*)-**192a** and (*R*)-**192b**



Subsequent mono deprotection of the terminal trityl ether under reductive conditions resulted in the mono protected alcohol (*R*)-**198a** and (*R*)-**198b** from alcohols (*R*)-**197a** and (*R*)-**197b**, respectively, in high yields. The aldehydes (*R*)-**192a** and (*R*)-**192b** was obtained *via* the oxidation of the alcohols (*R*)-**198a** and (*R*)-**198b**, respectively, with Dess-Martin periodinane and used immediately after purification by column chromatography.

5.5 Synthesis of aziridine precursor *via* multi-component catalytic asymmetric aziridination reaction of chiral aldehyde (*R*)-192.

As expected from the previous studies presented in Chapter 4, the catalytic asymmetric aziridination reaction with the aldehyde (*R*)-**192** proceeds under a catalyst-controlled process.

Table 5.1 Multi-component aziridination reaction of chiral aldehyde (*R*)-**192** in the presence of a chiral boroxinate catalyst [a]

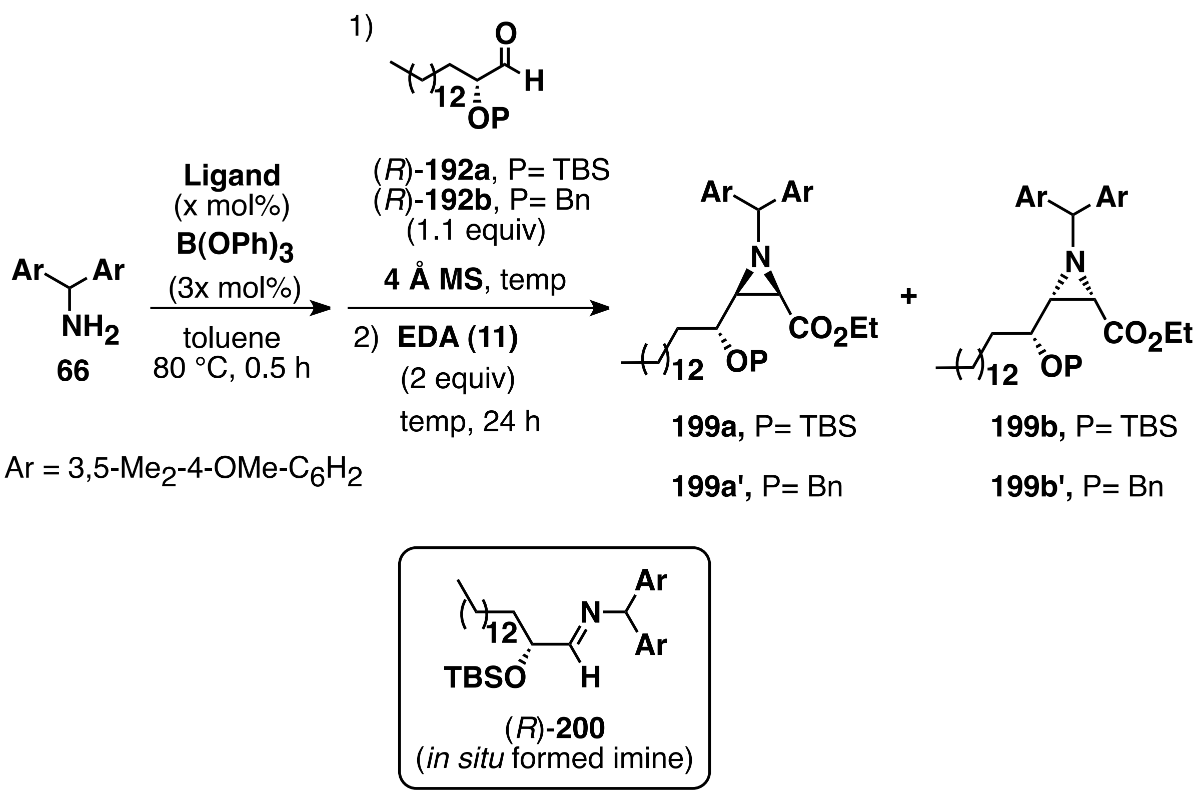


Table 5.1 (cont'd)

entry	P	temp (ºC)	ligand	Catalyst loading (x mol%)	dr **(199a:199b)** [c]	% yield **(199a + 199b)** [b]
1[d]	Bn	–10	(*S*)-VAPOL	10	82:18(82:18)	90
2[d]		–10	(*R*)-VAPOL	10	<1:>99(<1:>99)	95
3	TBS	–10	(*S*)-VAPOL	10	90:10(90:10)	85
4		–10	(*S*)-VAPOL	5	90:10(90:10)	88
5		–10	(*R*)-VAPOL	10	<1:>99(<1:>99)	92
6		–10	(*R*)-VAPOL	5	<1:>99(<1:>99)	94
7		–10	(*S*)-VANOL	5	88:12(90:10)	80
8		–10	(*R*)-VANOL	5	1:99(1:99)	85
9		0	(*S*)-VAPOL	5	89:11(90:10)	80
10		0	(*R*)-VAPOL	5	<1:>99(<1:>99)	94
11[e]		–30	(*S*)-VAPOL	10	nd	nd
12[f]		–30	(*R*)-VAPOL	5	<1:>99(<1:>99)	90

[a] Unless otherwise specified, all reactions were performed with 0.2 mmol amine **66** (0.2 M in toluene) and 1.1 equiv of (*R*)-**192** and 2.0 equiv EDA **11** and went to 100% completion. Prior to the addition of the aldehyde and the EDA **11**, a solution of amine **66** with x mol% ligand and 3x

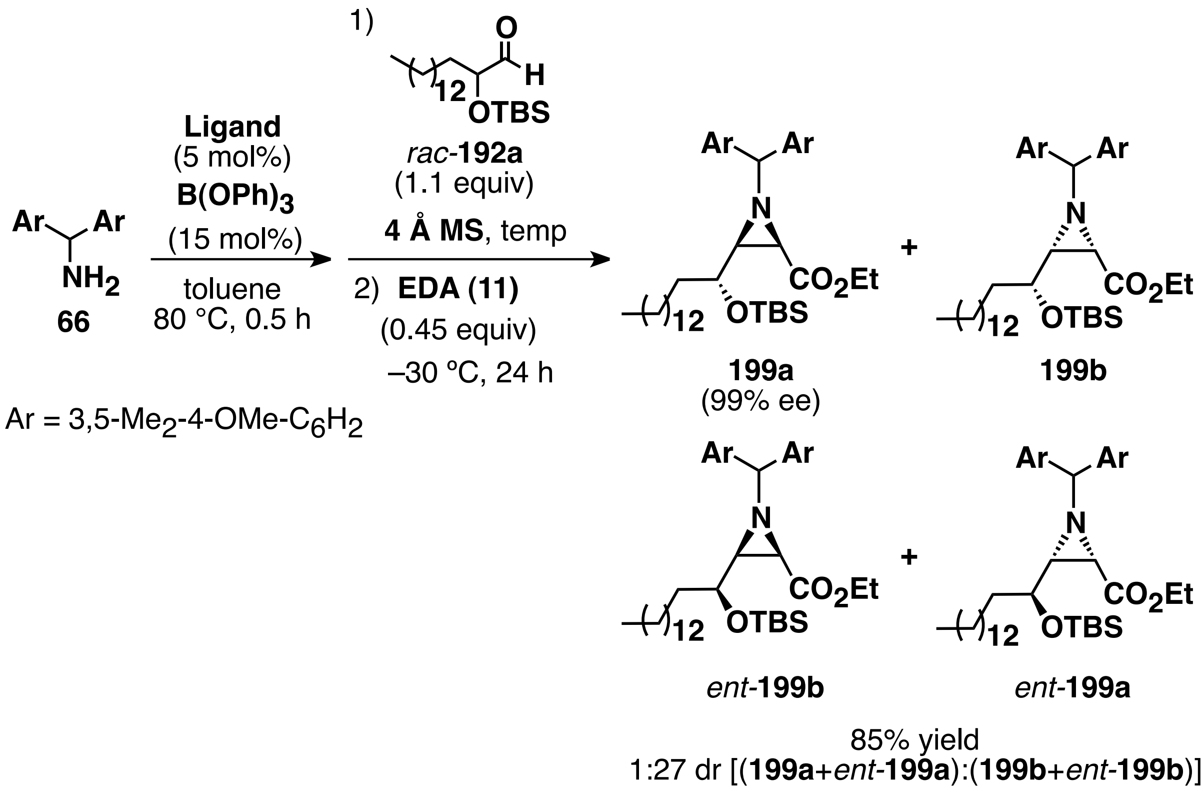
Table 5.1 (cont'd)

mol% commercial $B(OPh)_3$ was stirred for 30 min at 80 °C under nitrogen. nd = not determined. All reactions with 5 mol% catalyst loading are performed with 0.5 mmol **66** (0.2 M in toluene). [b] Isolated combined yield of **199a** and **199b** after chromatography on silica gel. [c] Determined on a sample prepared by passing the crude reaction mixture through a silica plug. Determined by using PIRKLE COVALENT (R, R) WHELK-O1 column. Diastereomeric ratio in parentheses is for the purified inseparable mixture of **199a** and **199b** and was deterimined by HPLC on PIRKLE COVALENT (R, R) WHELK-O1 column. [d] The product aziridines are **199a'** and **199b'**. [e] Reaction was incomplete even after 48 h based on the crude ^{1}HNMR analysis. The ratio of major diastereomer and unreacted *in situ* formed imine (*R*)-**200** is 1.0:2.5. [f] 1.2 equiv EDA used.

The aziridination reaction of the (*R*)-**192b** (P = CH_2Ph), with a benzyl ether at the *α*-position, in the presence of 10 mol% (*S*)-VAPOL boroxinate catalyst at –10 ºC resulted in *cis*-aziridines **199a'** and **199b'** with an 82:18 diastereomeric ratio and in 90% yield (Table 5.1, entry 1). The aziridination reaction of (*R*)-**192b** in the presence of 10 mol% (*R*)-VAPOL boroxinate catalyst at –10 ºC gave aziridine **199b'** as major the diastereomer with a 1:99 diastereomeric ratio in 95% yield (Table 5.1, entry 2). In order to see the effect of the protecting group on the diastereomeric ratio of the product, the hydroxyl protecting group at the *α*- position in aldehyde was changed to *tert*-butyldimethylsilyl group. The aziridination reaction of the (*R*)-**192a** (P = TBS) in the presence of 10 mol% (*S*)-VAPOL boroxinate catalyst at –10 ºC resulted in *cis*-aziridines **199a** and **199b** in a 90:10 diastereomeric ratio (Table 5.1, entry 3). The reaction with

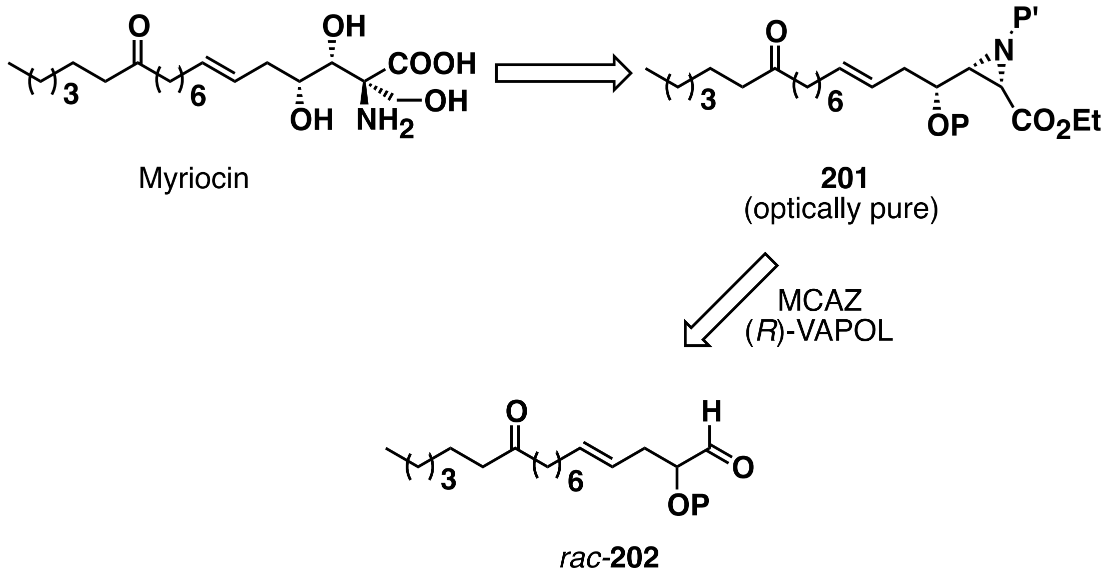
10 mol% (*R*)-VAPOL boroxinate catalyst at –10 ºC resulted in *cis*-aziridines **199a** and **199b** with an <1:>99 diastereomeric ratio and in 92% yield (Table 5.1, entry 5). It was important to find that the catalyst loading could be decreased to 5 mol% without any detrimental effect on the yield or the diastereomeric ratio (entries 4 and 6). The aziridination reaction of (*R*)-**192a** (P = TBS) in the presence of 5 mol% (*S*)-VANOL boroxinate catalyst at –10 ºC resulted in *cis*-aziridines **199a** and **199b** with an 88:12 diastereomeric ratio and in 80% yield (Table 5.1, entry 7). Similarly, with 5 mol% (*R*)-VANOL boroxinate catalyst at –10 ºC, *cis*-aziridines **199a** and **199b** were obtained in a 1:99 diastereomeric ratio and in 85% yield (Table 5.1, entry 8). An increase in the temperature of the reaction to 0 ºC does not show any significant effect either on the yield or the diastereoselectivity of the aziridination reaction (Table 5.1, entries 9 and 10). In the case of the aziridination reaction of aldehyde (*R*)-**192a** with 5 mol% (*R*)-VAPOL boroxinate catalyst, no effect on the yield or the diastereomeric ratio was observed when the reaction temperature was decreased to –30 ºC. The reaction resulted in *cis*-aziridine **199a** and **199b** with a <1:>99 diastereomeric ratio and in 90% yield (entry 12). Interestingly, the reaction of aldehyde (*R*)-**192a** in the presence of 10 mol% of (*S*)-VAPOL boroxinate catalyst at –30 ºC was not completed even after 48 h (entry 11). A substantial amount of unreacted imine (*R*)-**200** could be observed in the crude reaction mixture by ^{1}H NMR analysis. This observation suggests that there is a significant rate difference between the aziridination reactions of aldehyde (*R*)-**192a** with the (*R*)-VAPOL and (*S*)-VAPOL derived boroxinate catalysts at –30 ºC. This suggests that there might be a possibility of a kinetic resolution of racemic aldehyde **192a**. Encouraged by this observation, the aziridination reaction of the aldehyde *rac*-**192a** was performed in the presence of the (*R*)-VAPOL boroxinate catalyst (Scheme 5.9).

Scheme 5.9 Aziridination reaction with *rac*-**168a** in the presence of the (*R*)-VAPOL catalyst



The aziridination reaction of the aldehyde *rac*-**192a** with MEDAM amine **66** and EDA **11** (0.45 equiv) in the presence of 5 mol% (*R*)-VAPOL boroxinate catalyst resulted in *cis*-aziridine **199b** as the major diastereomer. The reaction resulted in *cis*-aziridines **199a** and **199b** with a 1:27 diastereomeric ratio and in 35% combined yield. The asymmetric induction of **199a** was determined to be 99% ee. It must be noted that the ee was determined by the integration of the peaks having same UV absorption pattern in the chiral HPLC. However, the ee could not confirmed due to the unavailability of the authentic sample of *ent*-**199a**. This observation provides an opportunity to synthesize complex molecules such as Myriocin *via* aziridination of the racemic aldehyde **202** (Scheme 5.10), where the synthesis of the chiral aldehyde might be otherwise troublesome.

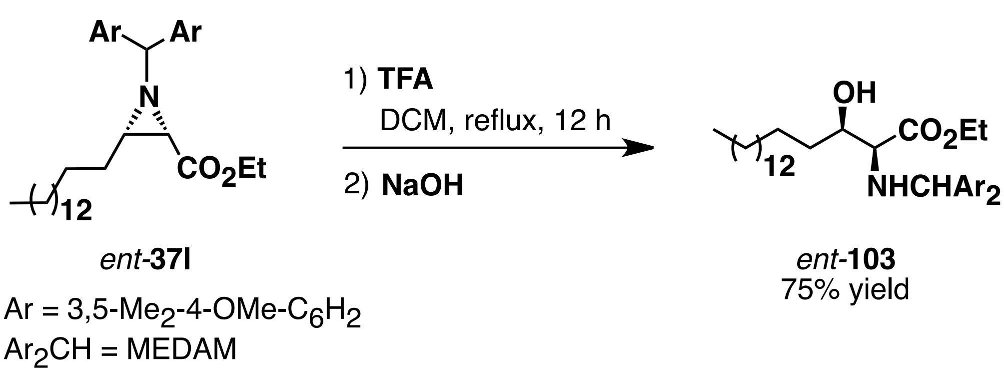
Scheme 5.10 Proposed synthesis of Myriocin *via* aziridination of *rac*-**202** in the presence of the (*R*)-VAPOL catalyst.



5.6 Studies towards the synthesis of phytosphingosines 75

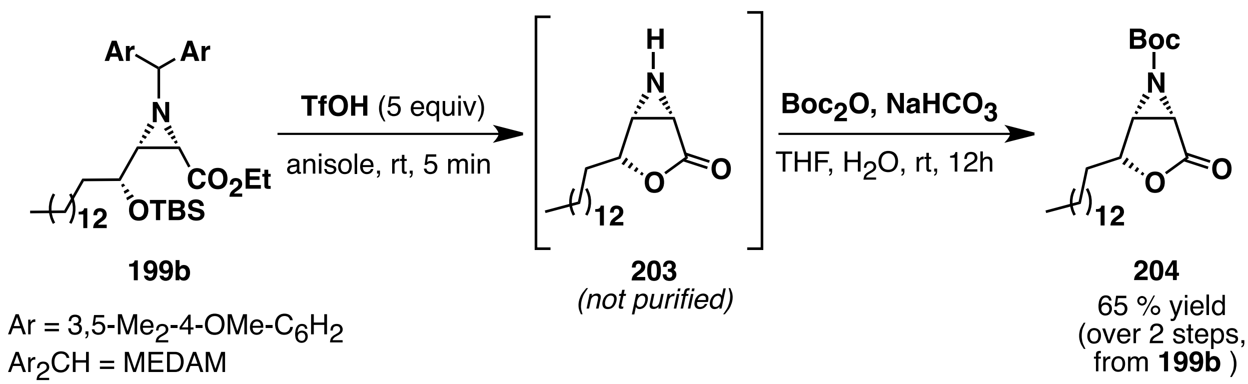
We have shown previously (Chapter 3) that the ring opening of the aziridine *ent*-**37l** was achieved in high yield using TFA (Scheme 5.11). However, the ring opening of aziridine **199b** in the presence of TFA resulted complex mixture of unidentified products, which were no separated or characterized.

Scheme 5.11 Ring opening of aziridine *ent*-**37l** with TFA



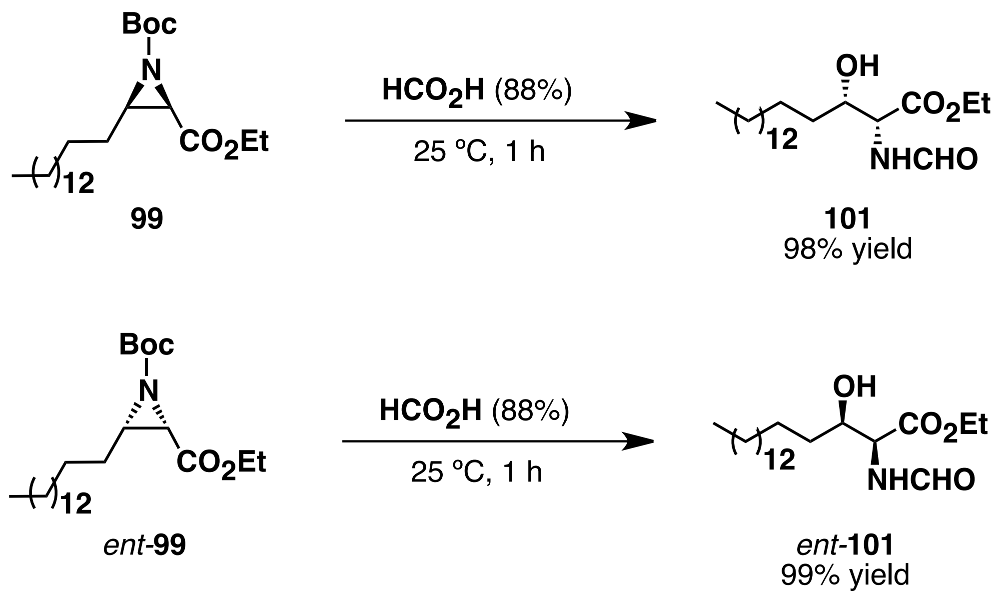
In the planned synthesis of the L-*lyxo*-phytosphingosine **75d**, it was thought to activate the aziridine by replacing the *N*-MEDAM group with an electron withdrawing *N*-Boc group. Surprisingly, the acid catalyzed deprotection of the *N*-MEDAM group in anisole resulted in the formation of the *γ*-lactone fused aziridine **203** (Scheme 5.12). The formation of the *γ*-lactone might be facilitated by the deprotection of the TBS group in acidic medium, as lactone ring formation is expected to be entropically favorable over the ring opened *γ*- hydroxy ester form. The aziridine **203** was not purified but instead directly treated with Boc anhydride under basic condition to afford Boc-protected aziridine **204** in 65% yield.

Scheme 5.12 Deprotection of *N*-MEDAM group and subsequent protection with Boc_2O.



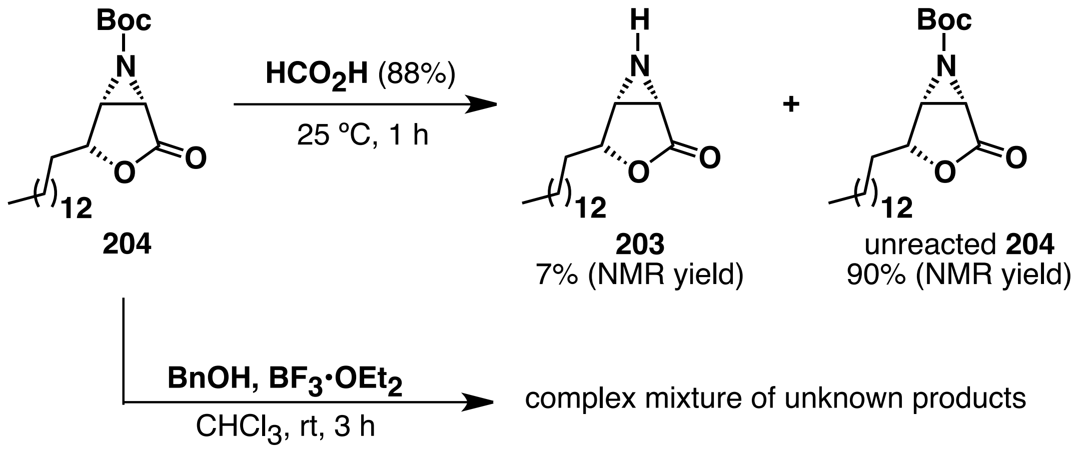
During the synthesis of *threo*-sphinganines **74b** and **74c** (Chapter 3), the reaction of the *N*-Boc aziridines **100** and *ent*-**100** with formic acid resulted in the ring-opened products **101** and *ent*-**101**, respectively, in quantitative yields (Scheme 5.13).

Scheme 5.13 Ring opening of *N*-Boc aziridines **101** and *ent*-**101** with formic acid



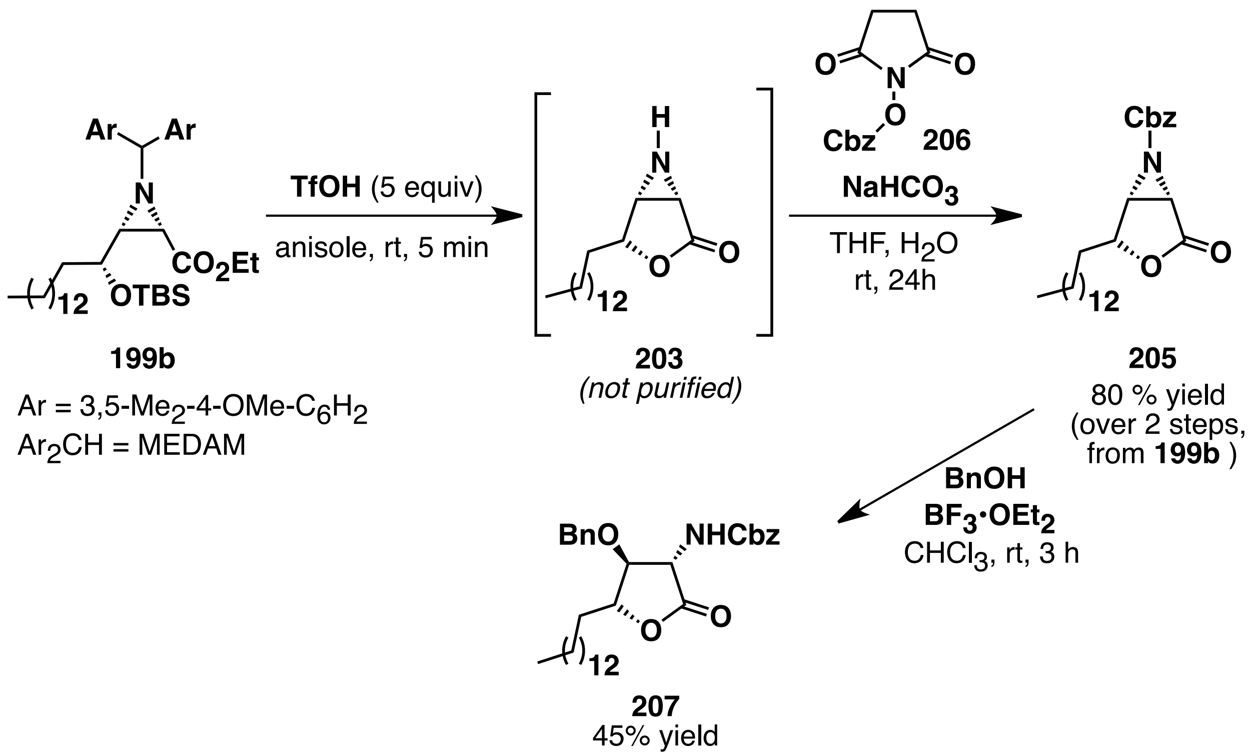
However, no ring-opened product was observed when the same protocol was applied to the lactone fused *N*-Boc aziridine **204**. Instead, a very small amount of *N*-H aziridine **203** was observed after 1 h (Scheme 5.13). The reason for the failure of the ring opening of **204** using formic acid is not known yet. However, there are examples of the ring opening of lactone fused aziridines using alcohol as the nucleophile.[17] Therefore, the *N*-Boc aziridine **204** was subjected to the ring opening conditions in presence of benzyl alcohol and BF_3•OEt_2 in $CHCl_3$ at 25 ºC. Unfortunately, the reaction resulted in a complex mixture of unknown products, which was not further pursued.

Scheme 5.14 Reaction of *N*-Boc aziridine **204** with formic acid



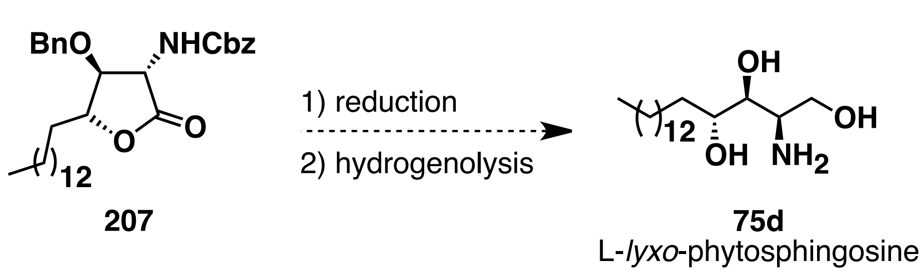
In 1995, Dodd and coworkers demonstrated that in the presence of BF_3•OEt_2, ring opening of *N*-Cbz protected 2,3-aziridino--lactones by alcohols occurs regioselectively at C-3.[17] Hence, it was thought to replace the Boc group with a Cbz group to affect the ring opening reaction. The *N*-Cbz aziridine **205** was synthesized by reacting the crude *N*-H aziridine **203** in presence of *N*-(benzyloxycarbonyloxy)succinimide **206** under basic condition (Scheme 5.15). The ring opening reaction of *N*-Cbz aziridine **205** with benzyl alcohol in presence of BF_3•OEt_2 resulted in the corresponding lactone **207** with 45% yield (Scheme 5.15).[18] The difference in the reactions of **204** and **205** with benzyl alcohol and is BF_3•OEt_2 quite unexpected.

Scheme 5.15 Cbz protection and subsequent ring opening



Although, the aziridine **207** was obtained in 45% yield, it may be possible to improve the yield by employing different Lewis acids and oxygen nucleophiles although this has not yet been explored. Nonetheless, the lactone **207** is likely to provide a direct access to the synthesis of L-*lyxo*-phytosphingosine **75d** by reduction followed by hydrogenolytic cleavage of the '*N*' and '*O*' protecting groups (Scheme 5.16).

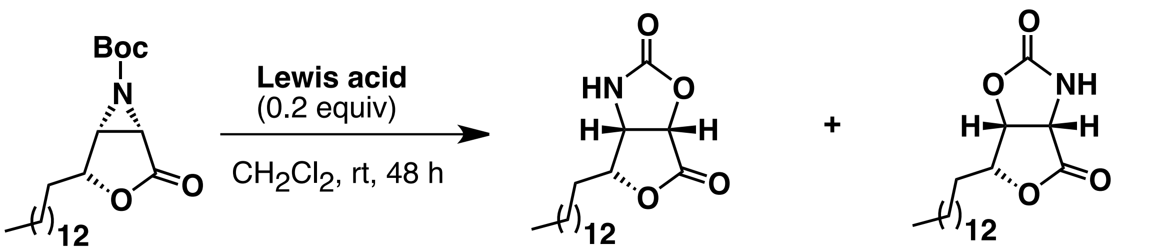
Scheme 5.16 Proposed synthesis of L-*lyxo*-phytosphingosine **75d** from lactone **207**



In an effort to develop a synthesis of L-*arabino*-phytosphingosine **75b**, the *N*-Boc aziridine **204** was subjected to ring expansion conditions in the presence of Lewis acids (see Chapter 3, Table 3.6). To our surprise, the ring expansion in the presence of either scandium triflate or tin (II) triflate resulted in the undesired regioisomer of the lactone-fused oxazolidinone **204** as the major product (Scheme 5.17A). However, it must be remembered that the ring expansion of the aziridines without pre-installed lactone functionality resulted in the desired *C3-N* bond cleavage of the aziridine ring.[19]

Scheme 5.17 (A) Ring expansion of *N*-Boc aziridine **204** to oxazolidinones **208** and **209**. (B) possible rational for the formation of **208**

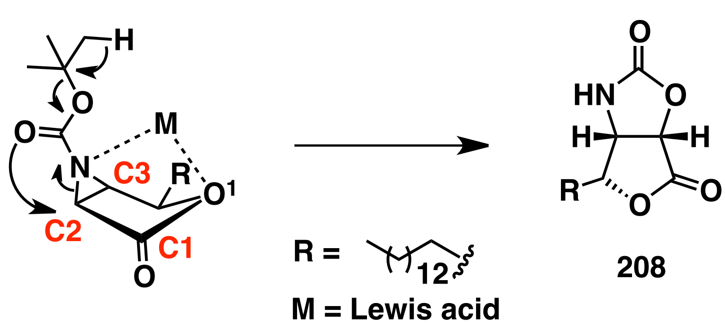
A



204 **208** **209**

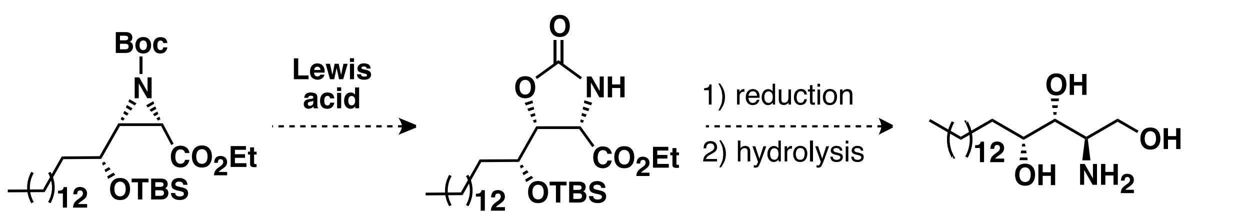
Lewis acid	208:209	combined yield (%)
$Sc(OTf)_3$	10:1	65
$Sn(OTf)_2$	7:1	60

B



This reversal in the regioselectivity in the ring-expansion of **204** might be due to the coordination of the Lewis acid with the O[1] oxygen in the lactone ring, which facilitates the cleavage of the *C2-N* bond instead of the *C3-N* bond resulting in the regio-isomer **208** (Scheme 5.17B). Presently, this project is on hold due to time constraints. However, if the explanation for the reversal in regioselectivity is correct and if *N*-Boc aziridine **210** can be accessed by some means, then subsequent Lewis acid mediated ring expansion to **211** may be possible following a protocol reported for a similar aziridine.[20] The synthesis of the L-*arabino*-phytosphingosine **75b** could be possible via reduction of ester functionality and hydrolysis of the oxazolidinone ring in **211** (Scheme 5.18).

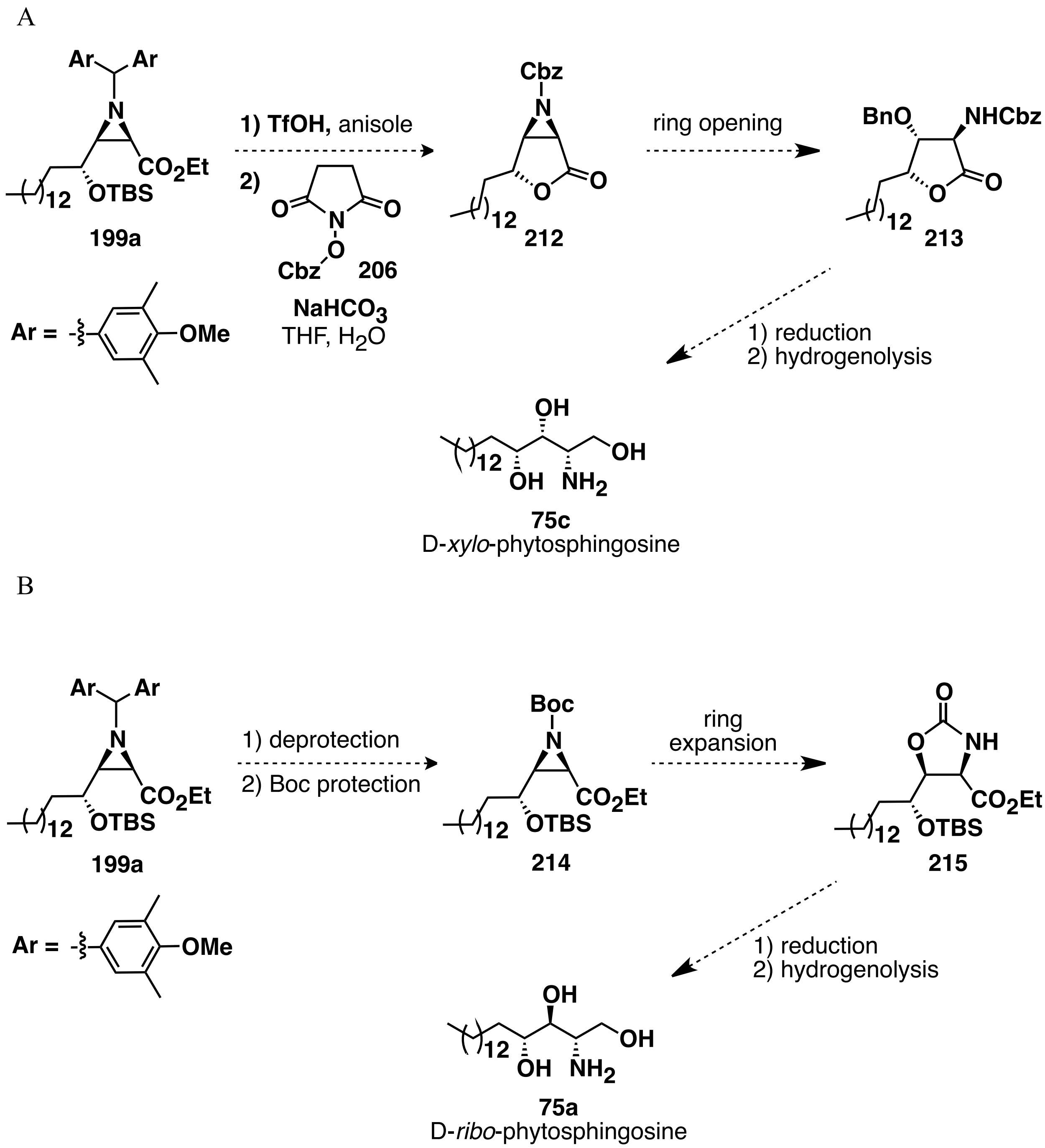
Scheme 5.18 Possible solution to synthesize the required regio-isomer of oxazolidinone **211** by ring expansion of the *N*-Boc aziridine **210**



210 **211** **75b** L-*arabino*-phytosphingosine

Following similar strategies as discussed above, D-*ribo*-phytosphingosine **75a** could be synthesized *via* ring opening of the *N*-Cbz aziridine **212**. The synthesis of D-*xylo*-phytosphingosine **75c** could be possible *via* the ring expansion of the *N*-Boc aziridine **214** to oxazolidinone **215** (Scheme 5.19).

Scheme 5.19 Possible synthetic route to (A) D-*ribo*-phytosphingonine and (B) D-*xylo*-phytosphingonine from aziridine **199a**.



5.7 Conclusions

This chapter describes a study directed to the application of the Wulff catalytic asymmetric aziridination reaction to phytosphingosines. The syntheses of all four diastereomers of phytosphingosine were attempted using the aziridination reaction as the key step. Although, the asymmetric syntheses are not completed, the key premise has been established with the demonstration that the aziridination of the chiral aldehyde (*R*)-**192** is catalyst-controlled giving high absolute stereocontrol with either (*R*)- or (*S*)-VAPOL or VANOL catalysts. Thus, these initial efforts have defined direct and stereoselective route to all four diastereomers. Hopefully, based on the advances made in this project, these targets can be realized in the near future.

APPENDIX

5.8 Experimental procedure

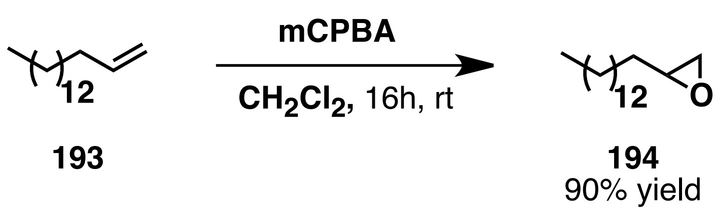
5.8.1 General information

Same as Chapter 2.

1-hexadecene **193**, 3-chloroperoxybenzoic acid was obtained from Alfa Aesar and used as received. The catalyst (1*S*, 2*S*)-**196** was was obtained from Strem Chemicals and used as received.

5.8.2 Synthesis of chiral aldehyde (*R*)-192

5.8.2.1 Epoxidation of 1-hexadecene

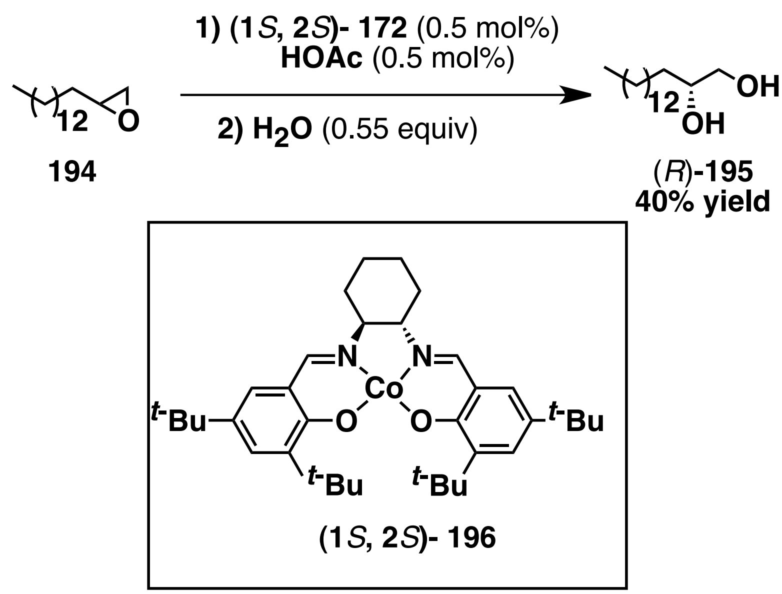


2-Tetradecyloxirane 194: To an oven dried 500 mL round bottom flask was added 1-hexadecene **193** (14.3 mL, 50 mmol) and freshly distilled dichloromethane (250 mL). The solution was cooled to 0 °C. To the solution was added 3-Chloroperoxybenzoic acid (77%, remainder 3-chlorobenzoic acid and water), (15.0 g, 65 mmol, 1.3 equiv) was added in one portion. After 10 min, the resulting suspension was warmed to room temperature and was stirred at that temperature for 16 h. The reaction mixture was then diluted with hexanes (600 mL) and filtered through a Celite pad to a 1L round bottom flask, in order to remove undissolved 3-chlorobenzoic acid from the reaction mixture. The filtrate was washed sequentially with saturated aqueous sodium bicarbonate solution (1 × 800 mL), saturated aqueous sodium bisulfite solution (1 × 800 mL), saturated aqueous sodium bicarbonate solution (1 × 800 mL) and brine (1

× 800 mL). The organic layer was then isolated, dried over $MgSO_4$, concentrated under reduced pressure to afford crude epoxide **194** as colorless oil. The epoxide **194** was purified by simple distillation under reduced pressure (bp 93 ºC at 0.1 Hg) to afford **194** as colorless oil in 90% yield (10.82 g, 45 mmol).

Spectral data for **194**: ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.30-1.33 (m, 26H), 2.46 (dd, *J* = 5.1, 2.8 Hz, 1H), 2.74 (dd, *J* = 5.0, 4.0 Hz, 1H), 2.90 (tdd, *J* = 5.5, 3.9, 2.7 Hz, 1H); ^{13}**C-NMR** (151 MHz, $CDCl_3$): δ 14.11, 22.69, 25.97, 29.36, 29.45, 29.56, 29.64, 29.65, 29.67, 29.68, 29.70, 31.93, 32.50, 47.13, 52.41 (one *sp3* carbon not located). The spectral data matched with those for the reported compound.[21]

5.8.2.2 Hydrolytic kinetic resolution of 2-tetradecyloxirane 194

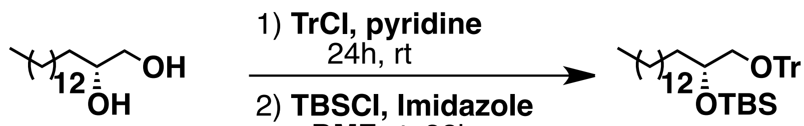


(*R*)-Hexadecane-1,2-diol (*R*)-195: To a 50 mL round bottom flask (1*S*, 2*S*)-**196** (151 mg, 0.25 mmol), toluene (1.3 mL), and acetic acid (28.8 μL, 0.50 mmol, 2.0 equiv to catalyst) was added.

The mixture was stirred while open to the air for 1 h at room temperature. The solvent was removed by rotary evaporation, and the brown residue was dried under vacuum (0.05 mm Hg) for 2h. To the reaction flask, 2-tetradecyloxirane (12.02 g, 50.0 mmol) was added in one portion, and the stirred mixture was cooled in an ice-water bath. Water (495.5 μL, 27.5 mmol, 0.55 equiv) was slowly added to the reaction mixture. Thereafter, the ice-water bath was removed and the reaction mixture was vigorously stirred at room temperature for 12 h. Hexanes (10 mL) were added to the thick slurry and the mixture was filtered through a sintered glass funnel under mild vacuum. The solid precipitate was washed with ice-cold hexanes (4 × 20 mL). The hexanes washing removes the left over chiral epoxide **194**. The light reddish white solid (*R*)-**195** was crystallized from EtOAc/hexanes (1:3) mixture. The first crop was collected with 35% yield (4.52 g, 17.5 mmol) of (*R*)-**195** as an off-white flaky solid (mp 83-84 ºC). The mother liquor was concentrated and again crystallized from EtOAc/hexanes (1:3) mixture. The second crop was collected with 5% yield (646 mg, 2.5 mmol) of (*R*)-**195** (mp 83-84 ºC).

Spectral data for (*R*)-**195**: **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.30-1.26 (m, 24H), 1.41-1.43 (m, 2H), 1.80 (t, *J* = 5.7 Hz, 1H), 1.94 (d, *J* = 4.3 Hz, 1H), 3.44 (ddd, *J* = 10.9, 7.5, 5.0 Hz, 1H), 3.75-3.63 (m, 2H).; **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 14.10, 22.68, 25.55, 29.35, 29.55, 29.59, 29.65, 29.66, 29.68, 29.69, 31.91, 33.19, 66.82, 72.34 (two *sp3* carbon not located). $[\alpha]_D^{20}$ +9.5 (c 1.0 EtOH).

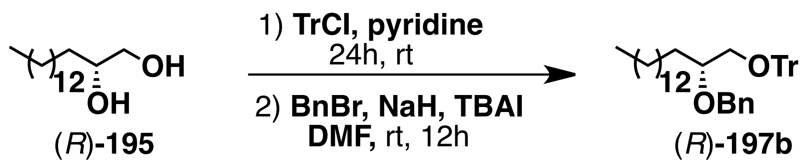
5.8.2.3 Bis-protection of (*R*)-hexadecane-1,2-diol (*R*)-195



(*R*)-**195** (*R*)-**197a**

(*R*)-*tert*-Butyldimethyl((1-(trityloxy)hexadecan-2-yl)oxy)silane (*R*)-197a: To an oven dried 100 mL round bottom flask equipped with a stir bar and a rubber septum with a nitrogen balloon at the top, was added 1,2-diol (*R*)-**195** (1.03 g, 4.0 mmol) and pyridine (22 mL). The mixture was stirred at room temperature to get a clear solution. Thereafter, the flask was transferred to an ice water bath and stirred for another 10 min at 0 ºC. To the reaction mixture was added triphenylmethyl chloride (2.34 g, 8.4 mmol, 2.1 equiv) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 24 h at room temperature under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to afford a pale yellow solid. The crude solid was dissolved in freshly distilled DMF (10 ml) under nitrogen atmosphere. To the clear solution was added imidazole (544 mg, 8.0 mmol, 2.0 equiv) and TBSCl (1.2 g, 8.0 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 32 h under nitrogen atmosphere. Upon completion, the reaction mixture was diluted with hexanes (30 mL) and brine (50 mL) was added to the flask. The organic layer was separated and the aqueous layer was extracted with ether (4 × 20 mL). The combined organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude reaction mixture. Purification of the crude by silica gel chromatography with a rubber septum and a nitrogen balloon at the top (30 mm × 300 mm column, 50:1 hexanes/Et_2O as eluent) afforded pure (*R*)-**197a** as a colorless liquid in 95 % isolated yield (2.34 g, 3.8 mmol) over two steps from (*R*)-**195**.

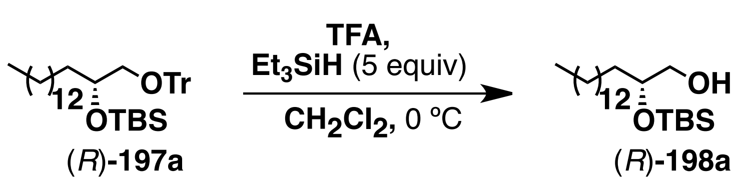
Spectral data for (*R*)-**197a:** R_f = 0.70 (1:16 Et_2O / hexanes) **^{1}H-NMR** (300 MHz, $CDCl_3$): δ –0.03 (s, 3H), –0.01 (s, 3H), 0.84-0.89 (m, 12H), 1.18-1.33 (m, 24H), 1.39-1.45 (m, 1H), 1.60-1.67 (m, 1H), 2.96 (dd, J = 9.2, 5.8 Hz, 1H), 3.05 (dd, J = 9.2, 5.2 Hz, 1H), 3.76 (quintet, J = 5.7 Hz, 1H), 7.19-7.32 (m, 9H), 7.46 (dd, J = 8.3, 1.4 Hz, 6H). **^{13}C-NMR** (151 MHz, $CDCl_3$): δ –4.75, –4.39, 14.12, 18.12, 22.70, 24.96, 25.89, 29.37, 29.60, 29.67, 29.69, 29.70, 29.79, 31.93, 34.97, 67.66, 71.77, 86.37, (three *sp3* carbon not located), 126.82, 127.66, 128.78, 144.31; IR (thin film) 2926vs, 2855s, 1464s, 1448s, 1257s, 1076 s cm^{-1}; HRMS (ESI-TOF) *m/z* 615.4603 [(M+H^+); calcd. for $C_{41}H_{63}O_2Si$: 615.4597]; $[\alpha]_D^{20}$ +9.0 (c 1.0, CH_2Cl_2).



(*R*)-(((2-(Benzyloxy)hexadecyl)oxy)methanetriyl)tribenzene (*R*)-197b: To an oven dried 100 mL round bottom flask equipped with a stir bar and a rubber septum with a nitrogen balloon at the top, was added 1,2-diol (*R*)-**195** (517 mg, 2.0 mmol) and pyridine (11 mL). The mixture was stirred at room temperature to get a clear solution. Thereafter, the flask was transferred to an ice water bath and stirred for another 10 min at 0 ºC. To the reaction mixture was added triphenylmethyl chloride (1.17 g, 4.2 mmol, 2.1 equiv) at 0 ºC. The reaction mixture was warmed to room temperature and stirred for 24 h at room temperature under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to afford pale yellow solid. The crude solid was dissolved in freshly distilled DMF (10 ml) under nitrogen atmosphere. The reaction mixture was cooled to 0 ºC. To the clear solution was added sodium hydride (160 mg, 4.0 mmol, 2.0 equiv) and the resulting suspension was stirred at 0 ºC for 10 min. Thereafter, to the reaction flask was added benzyl bromide (475 μL, 4.0 mmol, 2.0 equiv) and TBAI (74 mg, 0.2 mmol, 0.1 equiv). The reaction mixture was warmed to room temperature and stirred at room temperature for 16 h under nitrogen atmosphere. Upon completion, the reaction mixture was cooled to 0 ºC and diluted with hexanes (20 mL) and brine (50 mL) was added to the flask. The organic layer was separated and the aqueous layer was extracted with ether (4 × 20 mL). The combined organic layer was washed with water (1 × 20 mL) and brine (1 × 20 mL). The resulting organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude reaction mixture. The crude was dissolved in ether (5 mL) and the solution was filtered through a silica gel plug. The silica gel plug was washed with hexanes (3 × 50 mL). The resulting solution was concentrated under reduced pressure and the mixture was used for the next step without further purification.

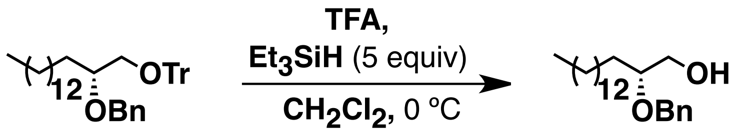
Spectral data for (*R*)-**197b**: ^{1}**H-NMR** (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 4H), 1.18-1.30 (m, 24H), 1.50-1.56 (m, 2H), 3.14 (dd, *J* = 9.9, 4.1 Hz, 1H), 3.22 (dd, *J* = 9.9, 5.7 Hz, 1H), 3.57-3.52 (m, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 7.38-7.23 (m, 20H). The spectral data was extracted from the crude ^{1}H NMR of (*R*)-**197b**.

5.8.2.4 De-protection of trityl ether in (*R*)-197



(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)hexadecan-1-ol (*R*)-198a: To a flame dried 100 mL round bottom flask flush with nitrogen and equipped with a stir bar was added the trityl ether (*R*)-**197a** (615 mg, 1.0 mmol) and freshly distilled CH_2Cl_2 (10 mL). The resulting clear solution was cooled to 0 °C. Triethylsilane (581 mg, 5.0 mmol) was added and the solution was stirred for 10 min after which TFA (153µL, 2.0 mmol) was added dropwise at 0 °C until the yellow color stopped reappearing. The reaction mixture was quenched immediately by the addition of sat. aq. $NaHCO_3$-solution (30 mL) at 0 ºC. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed in *vacuo*. Purification of the crude by silica gel chromatography with a rubber septum and a nitrogen balloon at the top of the column (30 mm × 150 mm column, 20:1 hexanes/Et_2O as eluent) afforded pure (*R*)-**198a** as a colorless liquid in 85 % isolated yield (317 mg, 0.85 mmol).

Spectral data for (*R*)-**198a**: R_f = 0.12 (16:1 hexanes / Et_2O); ^{1}**H-NMR** (300 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.86-0.91 (m, 12H), 1.30-1.21 (m, 24H), 1.44-1.51 (m, 2H), 1.85 (t, *J* = 6.3 Hz, 1H), 3.40-3.49 (m, 1H), 3.56 (ddd, *J* = 11.0, 6.3, 3.6 Hz, 1H), 3.72 (qd, *J* = 5.9, 3.6 Hz, 1H); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ –4.56, –4.43, 14.11, 22.69, 25.34, 25.86, 29.35, 29.56, 29.57, 29.65, 29.67, 29.69, 29.78, 31.93, 33.98, 66.30, 72.96, (three *sp3* carbon not located); IR (thin film) 3400 br, 2926vs, 2855s, 1464s, 1255s, 1109 s cm^{-1}; HRMS (ESI-TOF) *m/z* 373.3499 [(M+H^+); calcd. for $C_{22}H_{49}O_2Si$: 373.3502]; $[\alpha]_D^{20}$ –6.5 (c 1.0, CH_2Cl_2).

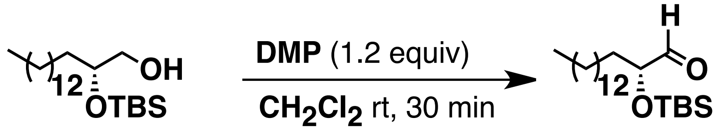


(*R*)-**197b** (*R*)-**198b**

(*R*)-2-(Benzyloxy)hexadecan-1-ol (*R*)-198b: The (*R*)-**198b** was synthesized from trityl ether (*R*)-**197b** (709 mg, 1.2 mmol) following the procedure described above for the synthesis of (*R*)-**198a**. Purification of the crude by silica gel chromatography with a rubber septum and a nitrogen balloon at the top of the column (30 mm × 150 mm column, 20:1 hexanes/Et_2O as eluent) afforded pure (*R*)-**198b** as a colorless solid (mp 35-36 ºC) in 80 % isolated yield (335 mg, 0.96 mmol).

Spectral data for (*R*)-**198b**: $R_f = 0.12$ (10:1 hexanes / EtOAc); ^{1}**H-NMR** (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.26-1.36 (m, 24H), 1.46-1.67 (m, 2H), 1.90-1.94 (m, 1H), 3.47-3.57 (m, 2H), 3.66-3.73 (m, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 7.27-7.37 (m, 5H); ^{13}**C-NMR** (126 MHz, $CDCl_3$): δ 14.10, 22.67, 25.37, 29.35, 29.53, 29.58, 29.64, 29.66, 29.67, 29.78, 30.78, 31.91 (2 *sp3* carbon not located), 64.27, 71.48, 79.81, 127.70, 127.75, 128.43, 138.47; IR (thin film) 3422 br, 2926vs, 2855 vs, 1466s, 1350s cm^{-1}; HRMS (ESI-TOF) *m/z* 371.2925 [(M+Na$^+$); calcd. for $C_{23}H_{40}O_2Na$: 371.2926]; $[\alpha]_D^{20}$ –11.8 (c 1.0, CH_2Cl_2).

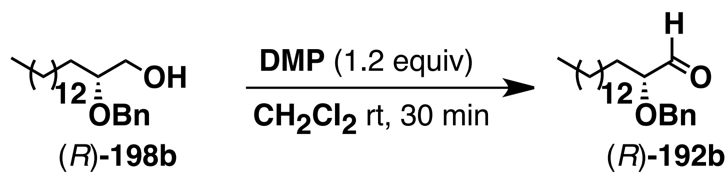
5.8.2.5 Oxidation of alcohol (*R*)-198 to aldehyde (*R*)-192



(*R*)-**198a** (*R*)-**192a**

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)hexadecanal (*R*)-192a: To a flame dried 25 mL round bottom flask flush with nitrogen and equipped with a stir bar was added the (*R*)-**198a** (410 mg, 1.1 mmol) and freshly distilled CH_2Cl_2 (5.5 mL). To the resulting clear solution was added Dess-Martin periodinane (560 mg, 1.32 mmol, 1.2 equiv). The turbid reaction mixture was stirred for 30 min at room temperature under nitrogen atmosphere. Thereafter, a buffer solution made from dissolving NaH_2PO_4 (262 mg) and Na_2HPO_4 (366 mg) in 2.5 mL water, was added to the reaction mixture. The resulting mixture was stirred for 5 min at room temperature. The turbid mixture was filtered through a Celite pad to a 100 mL round bottom flask. The reaction flask was washed with CH_2Cl_2 (3 × 10 mL) and passed through the same Celite pad. The resulting organic layer was washed with sat. aq. $NaHCO_3$ (2× 10 mL) and then with brine (2 × 10 mL). The organic layer was dried over $MgSO_4$ and the solvents were removed in *vacuo*. Purification of the crude by silica gel chromatography (20 mm × 150 mm column, 10:1 hexanes/Et_2O as eluent, flash column) afforded pure (*R*)-**192a** as a colorless liquid in 85 % isolated yield (346 mg, 0.935 mmol).

Spectral data for (*R*)-**192a**: R_f = 0.50 (16:1 hexanes / Et_2O); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.92 (s, 9H), 1.22-1.41 (m, 24H), 1.57-1.65 (m, 2H), 3.96 (ddd, *J* = 6.9, 5.6, 1.5 Hz, 1H), 9.59 (d, *J* = 1.8 Hz, 1H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ –4.93, –4.62, 14.10, 18.20, 22.69, 25.75, 29.36, 29.43, 29.45, 29.53, 29.62, 29.66, 29.68, 29.69, 31.93, 32.64, 77.71, (two *sp3* carbon not located), 204.32; IR (thin film) 2928 vs, 2855 vs, 1738s, 1464s, 1253s cm^{-1}; HRMS (ESI-TOF) *m/z* 371.3346 [(M+H^{+}); calcd. for $C_{22}H_{49}O_2Si$: 371.3345]; $[\alpha]_D^{20}$ +18.6 (c 1.0, CH_2Cl_2).

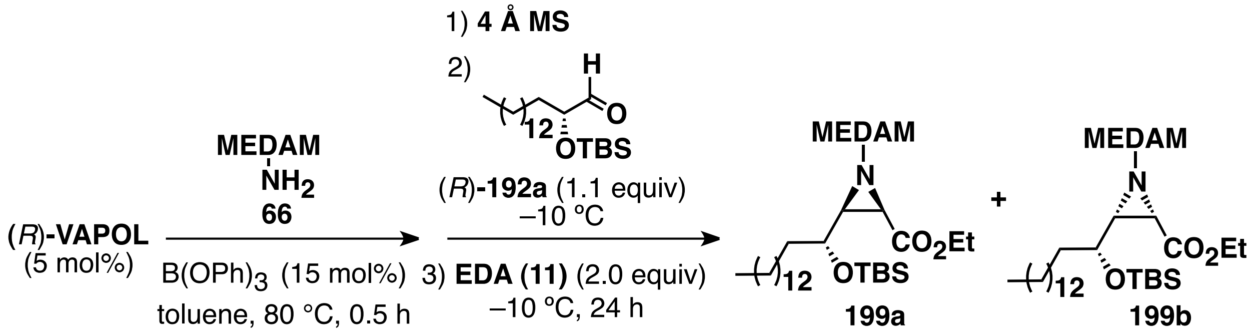


(*R*)-2-(Benzyloxy)hexadecanal (*R*)-192b: The (*R*)-**192b** was synthesized from (*R*)-**198b** (348 mg, 1.0 mmol) following the procedure described above for the synthesis of (*R*)-**192a**. Purification of the crude by silica gel chromatography (30 mm × 150 mm column, 20:1 hexanes/Et_2O as eluent, flash column) afforded pure (*R*)-**192b** as a colorless liquid in 90 % isolated yield (312 mg, 0.90 mmol).

Spectral data for (*R*)-**192b**: R_f = 0.26 (10:1 hexanes / Et_2O); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.28-1.30 (m, 22H), 1.35-1.46 (m, 2H), 1.65-1.70 (m, 2H), 3.75 (td, *J* = 6.4, 2.1 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 7.30-7.36 (m, 5H), 9.65 (d, *J* = 2.2 Hz, 1H).

5.8.3 Multi-component asymmetric aziridination reaction of aldehyde (*R*)-192

5.8.3.1 Multi-component asymmetric aziridination reaction of aldehyde (*R*)-192a



(2*S*,3*R*)-Ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*R*)-1-((*tert*butyldimethylsilyl) oxy)pentadecyl)aziridine-2-carboxylate 199b:

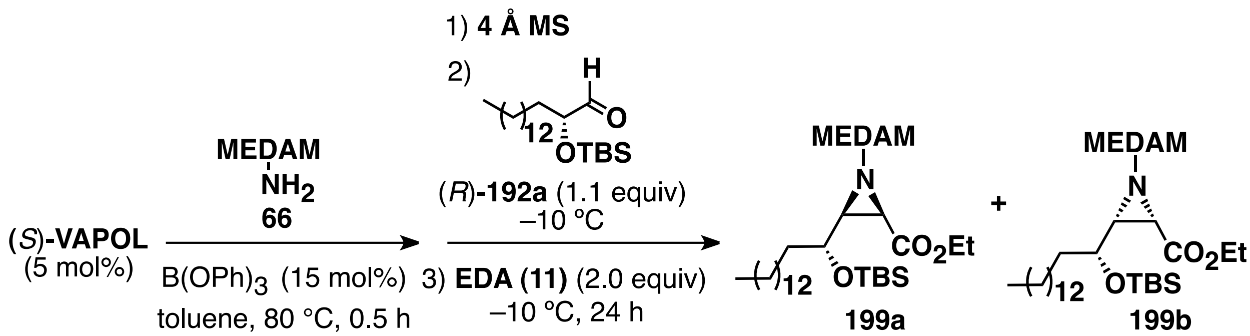
To a 10 mL flame-dried home-made Schlenk flask, prepared from a singlenecked 25 mL pear-shaped flask that had its 14/20 glass joint replaced with a high vacuum threaded Teflon valve, equipped with a stir bar and filled with argon was added (*R)*-VAPOL (14 mg, 0.025 mmol, 5 mol%), $B(OPh)_3$ (22 mg, 0.075 mmol, 15 mol%) and amine **66** (149 mg, 0.5 mmol). Under an argon flow through the side arm of the Schlenk flask, dry toluene (1.0 mL) was added. The flask was sealed by closing the Teflon valve, and then placed in an oil bath (80 ºC) for 0.5 h. The flask was then allowed to cool to room temperature and open to argon through side arm of the Schlenk flask. To the flask containing the catalyst was added the 4Å Molecular Sieves (120 mg, freshly flame-dried) and dry toluene (1.5 mL). The flask was then allowed to cool to –10 ºC and aldehyde (*R*)-**192a** (204 mg, 0.55 mmoL, 1.1 equiv) was added to the reaction mixture. To this solution was rapidly added ethyl diazoacetate (EDA) **11** (68 μL, 0.6 mmoL, 1.2 equiv). The resulting mixture was stirred for 24 h at –10 ºC. The reaction was diluted by addition of hexane (3 mL). The reaction mixture was then filtered through a silica gel plug to a 250 mL round bottom flask. The reaction flask was rinsed with EtOAc (20 mL × 3) and the rinse was filtered through the same silica gel plug. The resulting solution was then concentrated in *vacuo* followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine as yellow colored viscous oil.

Purification of the crude aziridine by neutral alumina chromatography (30 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **199b** and **199a** as colorless oil in 94 % isolated yield (347 mg, 0.47 mmol).

The diastereomeric ratio of **199b** and **199a** was determined to be >99:1 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.26 min (major diastereomer, **199b**) and R_t = 12.52 min (minor diastereomer, **199a**).

Aldehyde (*R*)-**192a** was reacted, according to the multi-component aziridination protocol described above, with (*R*)-VANOL (11 mg, 0.025 mmol, 5 mol%), as ligand to afford aziridines **199b** and **199a** with 99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (30 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **199b** and **199a** as a colorless liquid in 85 % isolated yield (314 mg, 0.425 mmol).

Spectral data for **198b**: R_f = 0.65 (2:1 hexanes/Et_2O); **^{1}H-NMR** (300 MHz, $CDCl_3$): δ –0.35 (s, 3H), –0.02 (s, 3H), 0.88 (t, *J* = 6.7 Hz, 3H), 0.70 (s, 9H), 1.21-1.37 (m, 29H), 2.05 (d, *J* = 7.0 Hz, 1H), 2.16-2.18 (m, 1H), 2.21 (s, 6H), 2.22 (s, 6H), 3.48 (s, 1H), 3.66-3.73 (m, 7H), 4.22-4.11 (m, 2H), 6.95 (s, 2H), 7.00 (s, 2H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ –4.91, –4.82, 14.10, 14.32, 16.17, 16.19, 17.94, 22.68, 24.17, 25.79, 29.35, 29.51, 29.57, 29.64, 29.67, 29.68, 30.03, 31.92, 36.24, 41.59, 53.23, 59.38, 59.58, 60.68, 70.44, 77.61, (one *sp3* carbon not located), 127.51, 128.86, 130.33, 130.39, 137.81, 138.01, 155.66, 156.11, 170.05; IR (thin film) 2928vs, 2855vs, 1747s, 1485s, 1221s, 1184vs cm^{-1}; HRMS (ESI-TOF) *m/z* 738.5476 [(M+H$^+$); calcd. for $C_{45}H_{76}NO_5Si$: 738.5493].



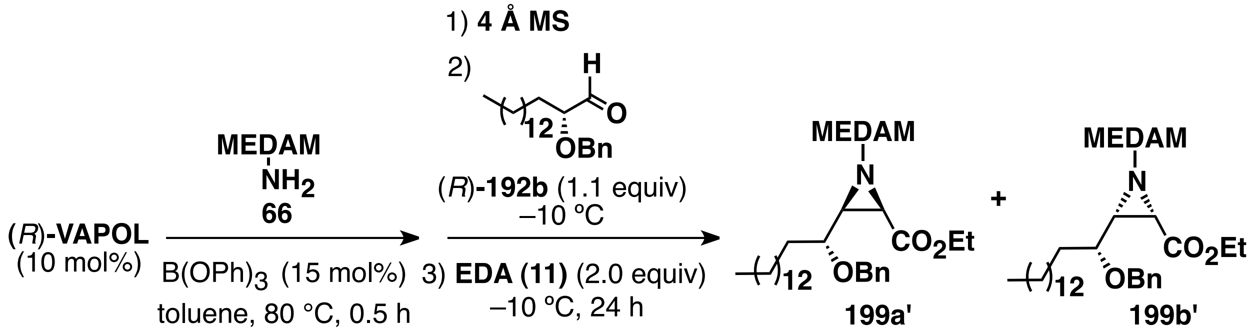
(2*R*,3*S*)-ethyl 1-(bis(4-methoxy-3,5-dimethylphenyl)methyl)-3-((*R*)-1-((*tert*butyldimethylsilyl)oxy)pentadecyl)aziridine-2-carboxylate 198a:

Aldehyde (*R*)-**192a** (204 mg, 0.55 mmoL, 1.1 equiv) was reacted according to the multi-component aziridination protocol described above, with (*S*)-VAPOL (14 mg, 0.025 mmol, 5 mol%) as ligand to afford aziridines **199a** and **199b** with 90:10 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (30 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **199a** and **199b** as colorless oil in 88 % isolated yield (325 mg, 0.44 mmol).

Aldehyde (*R*)-**192a** (204 mg, 0.55 mmoL, 1.1 equiv) was reacted according to the multi-component aziridination protocol described above with (*S*)-VANOL (11 mg, 0.025 mmol, 5 mol%), as ligand to afford **199a** and **199b** with 88:12 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 4:2:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **199a** and **199b** as colorless liquid in 80 % isolated yield (295 mg, 0.4 mmol).

Spectral data for **199a**: R_f = 0.65 (2:1 hexanes/Et_2O); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ –0.05 (s, 3H), –0.03 (s, 3H), 0.85 (s, 9H), 0.90 (t, *J* = 7.0 Hz, 3H), 1.22-1.30 (m, 29H), 2.13-2.15 (m, 1H), 2.21-2.24 (m, 13H), 3.44 (s, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 3.71-3.74 (m, 1H), 4.09-4.28 (m, 2H), 6.99 (s, 2H), 7.07 (s, 2H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ –4.65, –4.56, 14.08, 14.14, 16.08, 16.13, 18.00, 22.67, 23.74, 25.77, 25.78, 29.34, 29.58, 29.60, 29.63, 29.65, 29.68, 29.94, 31.91, 35.90, 43.34, 51.96, 59.47, 59.54, 60.74, 69.01, 77.73, (one *sp3* carbon not located), 127.01, 128.55, 130.41, 130.50, 137.69, 137.77, 155.71, 156.43, 169.70; IR (thin film) 2928vs, 2855vs, 1744s, 1483s, 1221s, 1186vs cm^{-1}; HRMS (ESI-TOF) *m/z* 738.5490 [(M+H^+); calcd. for $C_{45}H_{76}NO_5Si$: 738.5493]; $[\alpha]_D^{20}$ +36.0 (c 1.0, CH_2Cl_2).

5.8.3.2 Multi-component asymmetric aziridination reaction of aldehyde (*R*)-192b

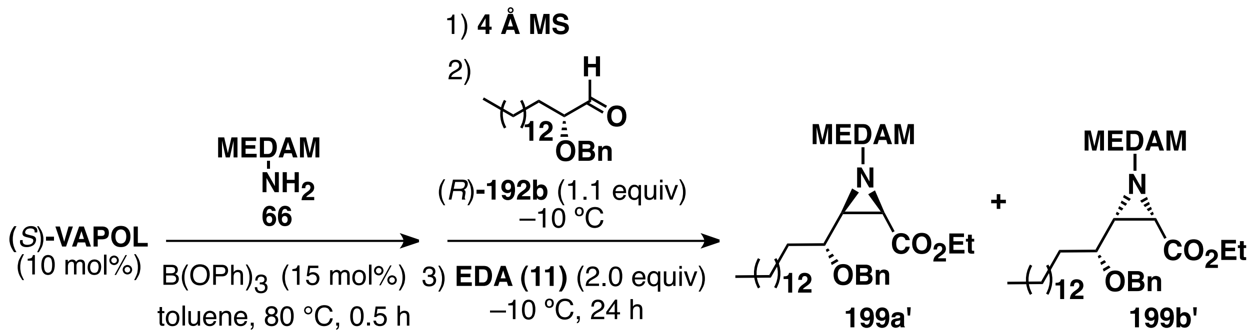


(2*S*,3*R*)-Ethyl 3-((*R*)-1-(benzyloxy)pentadecyl)-1-(bis(4-methoxy-3,5-dimethylphenyl) methyl)aziridine-2-carboxylate 198b':

Aldehyde (*R*)-**192b** (76 mg, 0.22 mmoL, 1.1 equiv) was reacted according to the multi-component aziridination protocol described above, with (*R*)-VAPOL (11 mg, 0.02 mmol, 10 mol%) as ligand to afford aziridines **199b'** and **199a'** with >99:1 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 1:1:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **199b'** and **199a'** as colorless oil in 95 % isolated yield (136 mg, 0.19 mmol).

The diastereomeric ratio of **199b'** and **199a'** was determined to be >99:1 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 6.25 min (major diastereomer, **199b'**) and R_t = 14.62 min (minor diastereomer, **199a'**).

Spectral data for **199b'**: R_f = 0.25 (1:1 hexanes/CH_2Cl_2); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.20-1.29 (m, 27H), 1.35-1.41 (m, 1H), 1.47-1.54 (m, 1H), 2.14 (d, *J* = 7.1 Hz, 1H), 2.17 (s, 6H), 2.24-2.29 (m, 7H), 3.45 (td, J = 8.8, 2.3 Hz, 1H), 3.49 (s, 1H), 3.51 (s, 3H), 3.70 (s, 3H), 3.96 (d, J = 11.6 Hz, 1H), 4.08 (d, J = 11.6 Hz, 1H), 4.23-4.16 (m, 2H), 6.98-6.97 (m, 2H), 7.06 (s, 2H), 7.11 (s, 2H), 7.24-7.16 (m, 3H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.06, 14.28, 16.10, 16.15, 22.63, 25.17, 29.30, 29.34, 29.44, 29.54, 29.60, 29.62, 29.63, 29.64, 31.87, 33.44, 40.76, 51.62, 59.33, 59.52, 60.83, 71.33, 77.37, 77.74, (one *sp3* carbon not located), 126.95, 127.17, 127.33, 127.90, 128.67, 130.52, 130.67, 137.49, 137.82, 139.13, 155.73, 156.47, 169.46; IR (thin film) 2926vs, 2855vs, 1746s, 1484s, 1223s, 1188vs cm^{-1}; HRMS (ESI-TOF) *m/z* 714.5110 [(M+H$^+$); calcd. for $C_{46}H_{68}NO_5$: 714.5097]; $[\alpha]_D^{20}$ –52.6 (c 1.0, CH_2Cl_2).



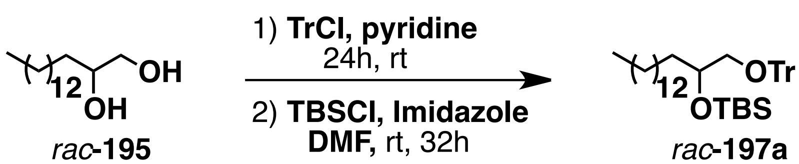
(2*R*,3*S*)-Ethyl 3-((*R*)-1-(benzyloxy)pentadecyl)-1-(bis(4-methoxy-3,5-dimethylphenyl) methyl)aziridine-2-carboxylate 199a':

Aldehyde (*R*)-**192b** (76 mg, 0.22 mmoL, 1.1 equiv) was reacted according to the multi-component aziridination protocol described above in presence of (*S*)-VAPOL (11 mg, 0.02 mmol, 10 mol%) as ligand to afford aziridines **199a'** and **199b'** with 82:18 diastereomeric ratio. Purification of the crude aziridine by neutral alumina chromatography (20 mm × 150 mm column, 1:1:0.1 hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **199a'** and **199b'** as colorless oil in 90 % isolated yield (128 mg, 0.18 mmol).

Spectral data for **199a'**: R_f = 0.25 (1:1 hexanes/CH_2Cl_2); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.9 Hz, 3H), 1.18-1.30 (m, 29H), 2.13-2.15 (m, 1H), 2.23 (s, 6H), 2.25 (s, 6H), 2.36 (d, *J* = 6.5 Hz, 1H), 3.40 (td, *J* = 8.0, 2.6 Hz, 1H), 3.47 (s, 1H), 3.66 (s, 3H), 3.70 (s, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.28 (d, *J* = 11.2 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 6.96 (s, 2H), 7.09 (s, 2H), 7.32-7.23 (m, 5H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.09, 14.28, 16.09, 16.17, 22.67, 24.63, 29.33, 29.35, 29.53, 29.62, 29.64, 29.65, 29.69, 29.88, 31.90, 31.91, 33.18, 43.81, 49.50, 59.54, 59.58, 60.89, 71.21, 76.39, 77.44, 127.16, 127.41, 127.46, 128.23, 128.63, 130.50, 130.55, 137.39, 137.58, 138.68, 155.81, 156.52, 169.68; IR (thin film) 2926vs, 2855vs, 1741s, 1483s, 1223s, 1188vs cm^{-1}; HRMS (ESI-TOF) *m/z* 714.5094 [(M+H^+); calcd. for $C_{46}H_{68}NO_5$: 714.5097]; $[\alpha]_D^{20}$ +36.9 (c 1.0, CH_2Cl_2).

5.8.4 Synthesis of racemic aldehyde *rac*-192a

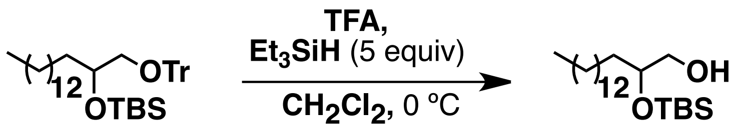
5.8.4.1 Bis-protection of 1,2-diol *rac*-195



***tert*-Butyldimethyl((1-(trityloxy)hexadecan-2-yl)oxy)silane *rac*-197a:** Bis protected 1,2-diol *rac*-**197a** was synthesized from 1,2-diol *rac*-**195** following the procedure described above for the synthesis of (*R*)-**197a**. Purification of the crude by silica gel chromatography with a rubber septum and a nitrogen balloon at the top (30 mm × 300 mm column, 50:1 hexanes/Et_2O as eluent) afforded pure *rac*-**197a** as a colorless liquid in 90 % isolated yield (2.21 g, 3.6 mmol) over two steps from *rac*-**195**.

Spectral data was identical to (*R*)-**195.**

5.8.4.2 Synthesis of *rac*-198a via mono de-protection of *rac*-197a

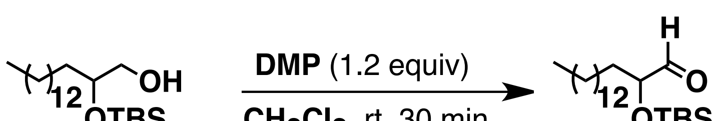


rac-**197a** *rac*-**198a**

2-((*tert*-butyldimethylsilyl)oxy)hexadecan-1-ol *rac*-198a: The *rac*-**198a** was synthesized from trityl ether *rac*-**197a** (615 mg, 1.0 mmol) following the mono deprotection procedure described above for the synthesis of (*R*)-**198a**. Purification of the crude by silica gel chromatography with a rubber septum and a nitrogen balloon at the top of the column (30 mm × 150 mm column, 20:1 hexanes/Et_2O as eluent) afforded pure *rac*-**198a** as a colorless liquid in 80 % isolated yield (298 mg, 0.80 mmol).

Spectral data was identical to (*R*)-**198a**.

5.8.4.3 Oxidation of *rac*-198a to aldehyde *rac*-192a

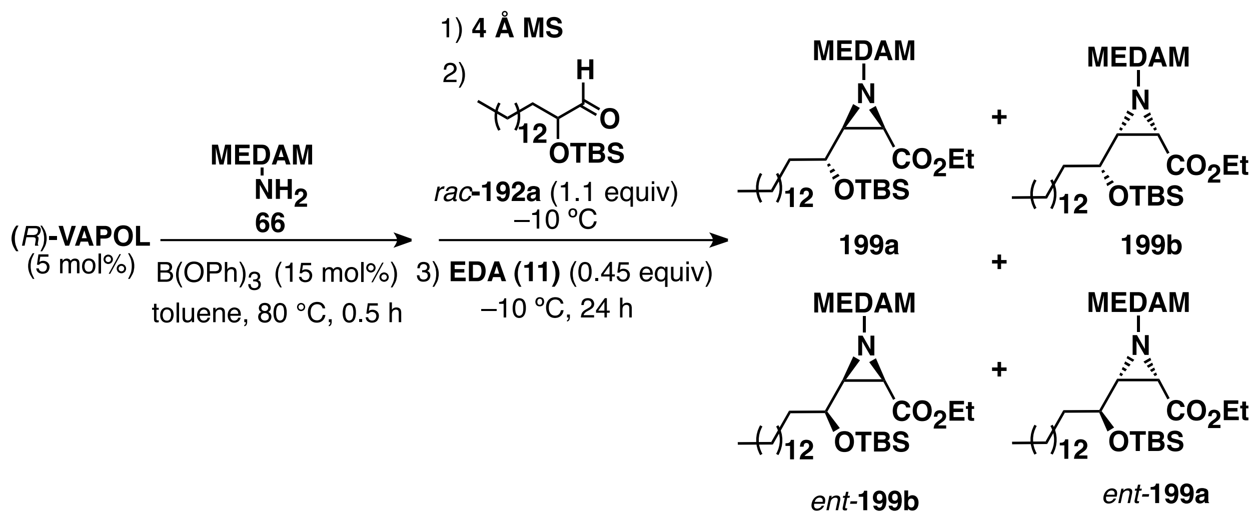


rac-**198a** *rac*-**192a**

2-((*tert*-butyldimethylsilyl)oxy)hexadecanal ***rac*-192a:** The aldehyde *rac*-**192a** was synthesized from *rac*-**198a** (261 mg, 0.7 mmol) following the procedure described above for the synthesis of (*R*)-**192a**. Purification of the crude by silica gel chromatography (30 mm × 150 mm column, 10:1 hexanes/Et_2O as eluent, flash column) afforded pure *rac*-**192b** as a colorless liquid in 90 % isolated yield (233 mg, 0.63 mmol).

Spectral data was identical to (*R*)-**192a.**

5.8.5 Multi-component asymmetric aziridination of racemic aldehyde *rac*-192a

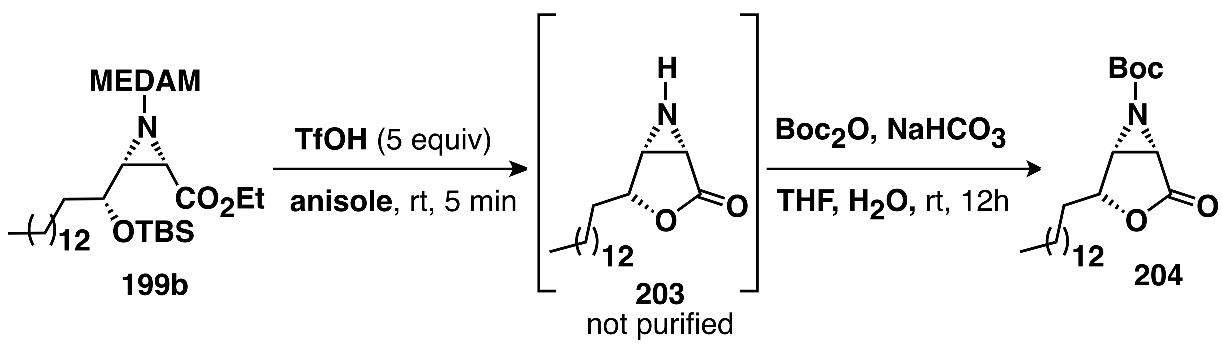


Aldehyde *rac*-**192a** (204 mg, 0.55 mmoL, 1.1 equiv) was reacted according to the multi-component aziridination protocol described above, with (*S*)-VAPOL (14 mg, 0.025 mmol, 5 mol%) as ligand to afford aziridines **199a**, **199b**, *ent*-**199a** and *ent*-**199b**. The diastereomeric ratio determined form crude ^{1}H NMR was 27:1 (**199b**+*ent*-**199b**:**199a**+*ent*-**199a**). Purification of the crude aziridine by neutral alumina chromatography (30 mm × 150 mm column, 4:2:0.1

hexanes/CH_2Cl_2/Et_2O as eluent, gravity column) afforded inseparable mixture of aziridines **199a** and **199b** and their enantiomers as colorless oil in 35 % isolated yield (129 mg, 0.175 mmol). The enantiomeric excess of either **199a** or **199b** was not confirmed, due to unavailability of authenticate sample of *ent*-**199a** or *ent*-**199b**.

The diastereomeric ratio of **199b** and **199a** was determined to be 96.6:3.4 by HPLC analysis of crude reaction mixture (PIRKLE COVALENT (R, R) WHELK-O 1 column, 99:1 hexane/2-propanol at 226nm, flow-rate: 0.7 mL/min): retention times; R_t = 9.26 min (major diastereomer, **199b**) and R_t = 12.52 min (minor diastereomer, **199a**). $[\alpha]_D^{20}$ –68.3 (c 1.0, CH_2Cl_2).

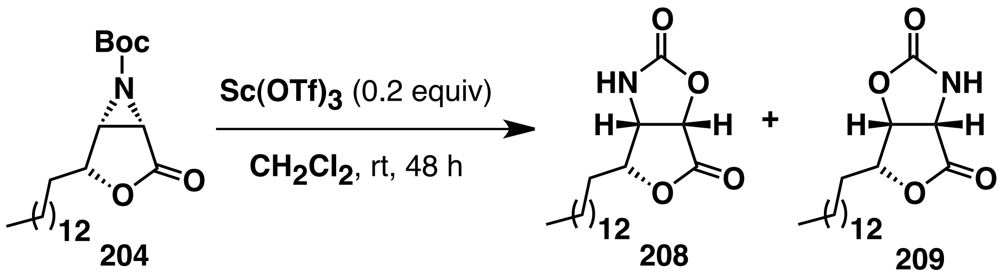
5.8.6 Synthesis of *N*-Boc aziridine 204



(1*S*,4*R*,5*R*)-*tert*-Butyl 2-oxo-4-tetradecyl-3-oxa-6-azabicyclo[3.1.0]hexane-6-carboxylate 204: To a 50 mL flame-dried round bottom flask flushed with nitrogen and equipped with a stir bar was added aziridine **199b** (700 mg, 0.95 mmol, > 99:1 dr material). Dry anisole (9.5 mL) was added to dissolve **199b**. Thereafter, triflic acid (420 μL, 4.75 mmol, 5 equiv) was added slowly to the reaction flask. The reaction mixture was stirred for 5 min under nitrogen atmosphere at room temperature. Upon completion, the gel like reaction mixture was place on ice bath and saturated aq. Na_2CO_3 (20 mL) and ether (10 mL) was added to the reaction flask. The mixture was stirred for 5 min at room temperature. The organic layer was separated and the water layer was extracted with ethyl acetate (4 × 25 mL). The resulting organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude reaction mixture as white solid. To the solution of the crude reaction mixture in THF (9.5 mL) solid $NaHCO_3$ (199 mg, 2.37 mmol, 2.5 equiv), Boc_2O (415 mg, 1.90 mmol, 2.0 equiv) and water (1.9 mL, 1:5 v/v H_2O / THF) was added. The resulting reaction mixture was stirred for 12 h at room temperature under nitrogen atmosphere. The reaction mixture was diluted with diethyl ether (40 mL) and the organic layer was washed with brine (1 × 10 mL). The resulting organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude reaction mixture as white solid. Purification of the crude lactone fused *N*-Boc aziridine **204** by silica gel chromatography (30 mm × 300 mm column, 5:1 to 1:1 hexanes/Et_2O as eluent, flash column) afforded pure **204** as a white solid (mp 79-80 ºC) in 65% isolated yield over two steps (244 mg, 0.617 mmol) from **199b**.

Spectral data for **204:** R_f = 0.46 (1:2 EtOAc / hexanes) **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.23-1.32 (m, 24H), 1.47 (s, 9H), 1.89-1.76 (m, 2H), 3.46 (d, *J* = 4.4 Hz, 1H), 3.58 (dd, *J* = 4.4, 2.7 Hz, 1H), 4.47 (td, *J* = 7.1, 2.7 Hz, 1H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 14.11, 22.68, 25.05, 27.78, 29.33, 29.35, 29.43, 29.50, 29.62, 29.65, 29.67, 29.69, 30.26, 31.92, 38.72, 42.60, 79.80, 83.20, (one *sp3* carbon not located), 158.73, 169.59; IR (thin film) 2920vs, 2851vs, 1788vs, 1724vs, 1468s, 1294s, 1197vs cm^{-1}; HRMS (ESI-TOF) *m/z* 396.3096 [$(M+H^+)$; calcd. for $C_{23}H_{42}NO_4$: 396.3114]; $[\alpha]_D^{20}$ –34.2 (c 1.0, CH_2Cl_2).

5.8.7 Lewis acid catalyzed ring expansion of *N*-Boc aziridine 204



To a 10 mL flame-dried round bottom flask equipped with a stir bar and a rubber septum with a nitrogen balloon at the top, was added *N*-Boc aziridine **204** (40 mg, 0.1 mmol) and dry CH_2Cl_2 (1 mL). To the resulting solution was added $Sc(OTf)_3$(10 mg, 0.02 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature for 48 h under nitrogen atmosphere. Thereafter, the reaction mixture was filtered through a silica gel plug on a sintered glass funnel. The silica plug was washed with ethyl acetate (3 × 10 mL). The filtrate was concentrated under reduced pressure to afford crude product as white solid. Purification of the crude by silica gel chromatography (20 mm × 150 mm column, 1:1 hexanes/EtOAc as eluent, flash column) afforded mixture of oxazolidinone **208** and **209** (10:1 mixture from ^{1}HNMR) as a white solid in 65% combined yield (22 mg, 0.065 mmol).

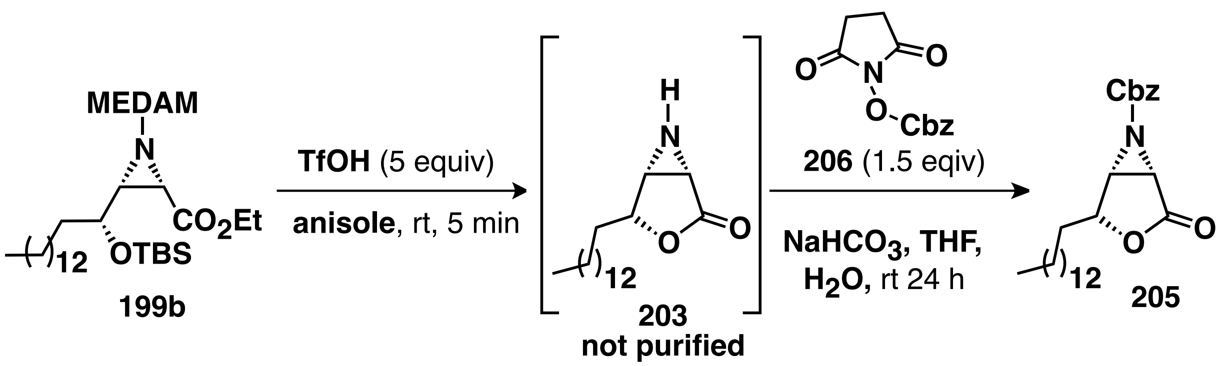
The N-Boc aziridine **204** was reacted with $Sn(OTf)_2$ (8 mg, 0.02 mmol, 0.2 equiv) according the procedure described above. Purification of the crude by silica gel chromatography (20 mm × 150 mm column, 1:1 hexanes/EtOAc as eluent, flash column) afforded mixture of oxazolidinone **208** and **209** (7:1) as a white solid in 60% combined yield (20 mg, 0.060 mmol).

Spectral data for **208:** R_f = 0.11 (1:1 EtOAc / hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$): δ 0.88 (t,

J = 7.0 Hz, 3H), 1.26-1.39 (m, 24H), 1.61-1.67 (m, 1H), 1.84-1.91 (m, 1H), 4.49 (ddd, J = 8.6, 5.2, 4.4 Hz, 1H), 4.61 (ddd, J = 7.6, 4.3, 1.6 Hz, 1H), 5.15 (d, J = 7.6 Hz, 1H), 5.97 (br s, 1H).

Spectral data for **209**: ^{1}**H-NMR** (500 MHz, $CDCl_3$): δ 4.45 (dd, J = 7.4, 0.7 Hz, 1H), 4.67-4.64 (m, 1H), 5.21 (dd, J = 7.4, 4.4 Hz, 1H), 5.84 (s, 1H) (other *sp3* H's are not located due to overlap the major regio-isomer **208** H's peaks).

5.8.8 Synthesis of *N*-Cbz aziridine 205



(1*S*,4*R*,5*R*)-benzyl 2-oxo-4-tetradecyl-3-oxa-6-azabicyclo[3.1.0]hexane-6-carboxylate 205: To a 50 mL flame-dried round bottom flask flushed with nitrogen and equipped with a stir bar was added aziridine **199b** (143 mg, 0.2 mmol, > 99:1 dr material). Dry anisole (3.0 mL) was added to dissolve **199b**. Thereafter, triflic acid (88 μL, 1.0 mmol, 5 equiv) was added slowly to the reaction flask. The reaction mixture was stirred for 5 min under nitrogen atmosphere at room temperature. Upon completion, the gel like reaction mixture was place on ice bath and saturated aq. Na_2CO_3 (10 mL) and ether (10 mL) was added to the reaction flask. The mixture was stirred for 5 min at room temperature. The organic layer was separated and the water layer was extracted with ethyl acetate (4 × 10 mL). The resulting organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude reaction mixture as white solid. To the solution of the crude reaction mixture in THF (2.0 mL) solid $NaHCO_3$ (42 mg, 0.5 mmol, 2.5 equiv), Cbz-OSu **206** (374 mg, 0.3 mmol, 1.5 equiv) and water (0.4 mL, 1:5 v/v H_2O / THF) was added. The resulting reaction mixture was stirred for 24 h at room temperature under nitrogen atmosphere. The reaction mixture was diluted with diethyl ether (20 mL) and the organic layer was washed with brine (1 × 5 mL). The resulting organic layer was dried with $MgSO_4$ and concentrated under reduced pressure to afford the crude reaction mixture as white solid. Purification of the crude lactone fused *N*-Cbz aziridine **205** by silica gel chromatography (30 mm × 300 mm column, 5:1 to 1:2 hexanes/Et_2O as eluent, flash column) afforded pure **205** as a white solid (mp 67-68 ºC) in 80% isolated yield over two steps (69 mg, 0.16 mmol) from **199b**.

Spectral data for **205** R_f = 0.36 (1:2 EtOAc / hexanes) **^{1}H-NMR** (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 6.7 Hz, 3H), 1.26-1.38 (m, 22H), 1.41-1.50 (m, 2H), 1.73-1.90 (m, 2H), 3.55 (d, *J* = 4.4 Hz, 1H), 3.65 (dd, *J* = 4.4, 2.8 Hz, 1H), 4.48 (td, *J* = 7.0, 2.7 Hz, 1H), 5.16 (s, 2H), 7.39-7.34 (m, 5H); **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 14.08, 22.65, 25.02, 29.28, 29.32, 29.37, 29.46, 29.58, 29.62, 29.65, 29.66, 30.32, 31.89, 38.77, 42.87, 69.16, 79.67, (one *sp3* carbon not located), 128.26, 128.64, 128.66, 134.83, 159.84, 169.09; IR (thin film) 2920vs, 2851s, 1780s, 1720s, 1469s, 1273s cm^{-1}; HRMS (ESI-TOF) *m/z* 430.2860 [(M+H$^+$); calcd. for $C_{26}H_{40}NO_4$: 430.2957]; $[\alpha]_D^{20}$ –26.8 (c 1.0, CH_2Cl_2).

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